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A CONVENIENT METHOD TO SYNTHESIZE PHOSPHINIC PEPTIDES CONTAINING AN ASPARTYL OR GLUTAMYL AMINOPHOSPHINIC ACID. USE OF THE PHENYL GROUP AS THE CARBOXYL SYNTHON.

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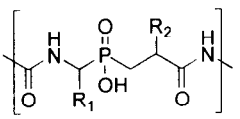
Abstract: Many attempts to synthesize Asp$\Psi(PO_2CH_2)$Ala phosphinic pseudodipeptides by Michael addition of aspartyl aminophosphinic acid to ethyl methacrylate have failed. The preparation of such phosphinic peptides was finally achieved starting from a protected Phe$\Psi(PO_2CH_2)$Ala phosphinic building block. The key step is a mild oxidation of the phenyl group to carboxylic acid by use of the ruthenium trichloride-sodium metaperiodate system.

In the last decade, several studies have demonstrated that the synthesis of phosphinic peptides is a very effective approach to develop highly potent inhibitors of zinc metalloproteases.[1] While many phosphinic peptides, containing in the R_1 and R_2 positions various alkyl and arylalkyl groups, have been successfully prepared,[2] the synthesis of corresponding derivatives bearing functional side chains in R_1 and R_2 was more problematic.



Nevertheless, the synthesis of pseudo-peptides harboring a carboxylic acid side chain at R_1 will have important applications for the development of phosphinic peptide inhibitors of zinc-proteases able to specifically cleave peptide bonds following an aspartic or glutamic residue.[3]

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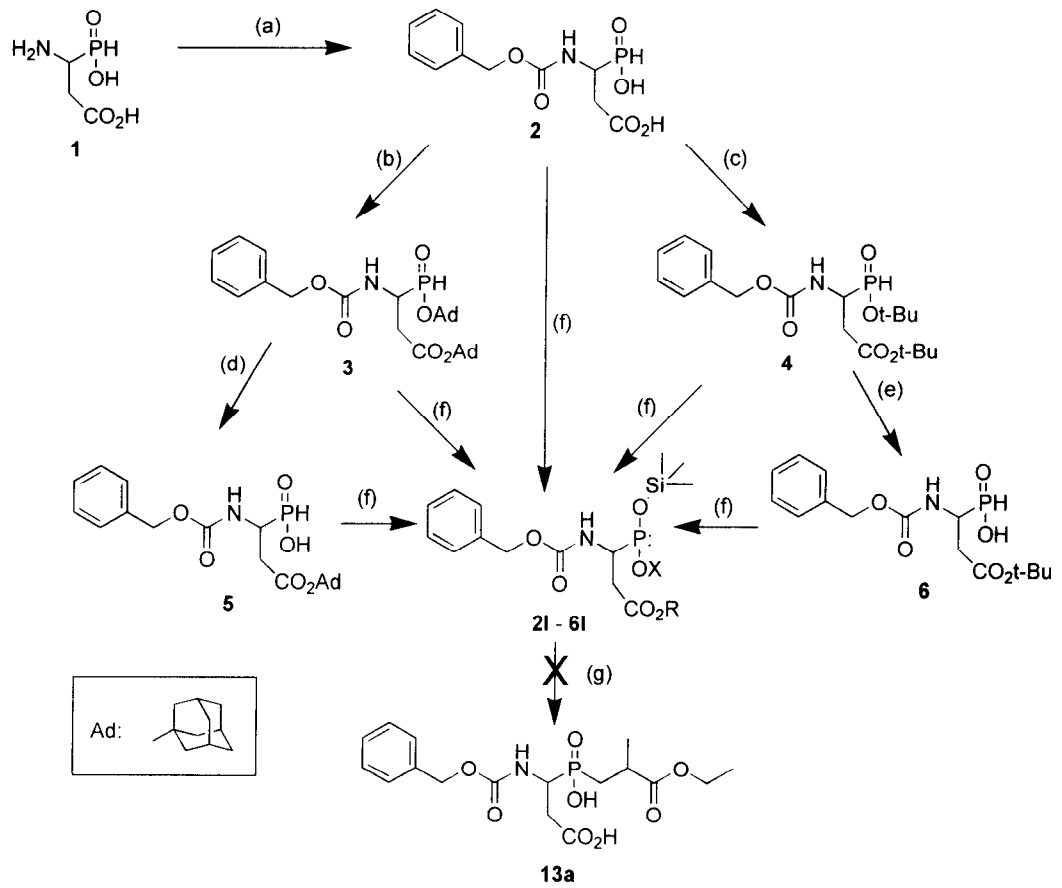
A first attempt to synthesize compound **13a** was based on the Michael addition of ethyl methacrylate to compound **2**[4] using HMDS to form phosphorus (III) intermediate **2I**.[5] This reaction, which was used successfully in many cases to prepare various phosphinic pseudo-dipeptidic blocks,[1c,6] failed in the present case. Other assays, based on the use of milder conditions to perform the Michael addition, employing the TMSCl/i-Pr_2EtN method for phosphorus activation, were also unsuccessful (Scheme 1).[7]



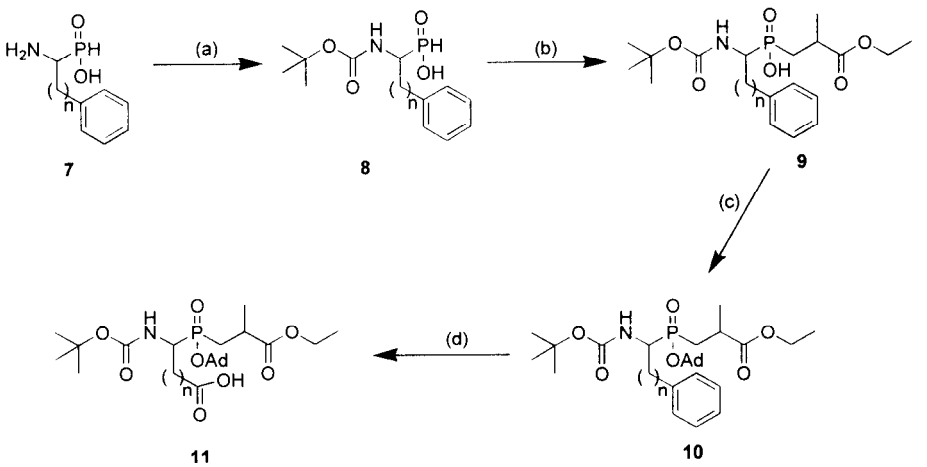
Compound	Intermediate	R	X
2	2I	$-Si(CH_3)_3$	$-Si(CH_3)_3$
3	3I	-Ad	-Ad
4	4I	-t-Bu	-t-Bu
5	5I	-Ad	$-Si(CH_3)_3$
6	6I	-t-Bu	$-Si(CH_3)_3$

Scheme 1: (a) Boc_2O, Et_3N, MeOH, 50°C 3h then rt 24h. (b) AdBr, Ag_2O, $CHCl_3$, reflux, 2h. (c) N,N-dimethylformamide di-tert-butyl acetal, benzene, reflux, 30 min. (d) 5% TFA/CH_2Cl_2, 7h (e) 5% TFA/CH_2Cl_2, 3h. (f) HMDS, 110°C, 1h or TMS-Cl, i-Pr_2EtN, 0°C to rt. (g) $H_2C{=}C(CH_3)COOEt$, 90°C, 3.5h or $H_2C{=}C(CH_3)COOBzl$, 0°C to rt, then EtOH, then deprotection 50% TFA

As the formation of trivalent phosphorus trimethylsilyl ester **2I** can be affected by the presence of a free carboxylic function, the same reactions were performed starting from phosphinic precursors, in which the hydroxyphosphinyl and the carboxylic functions were protected.

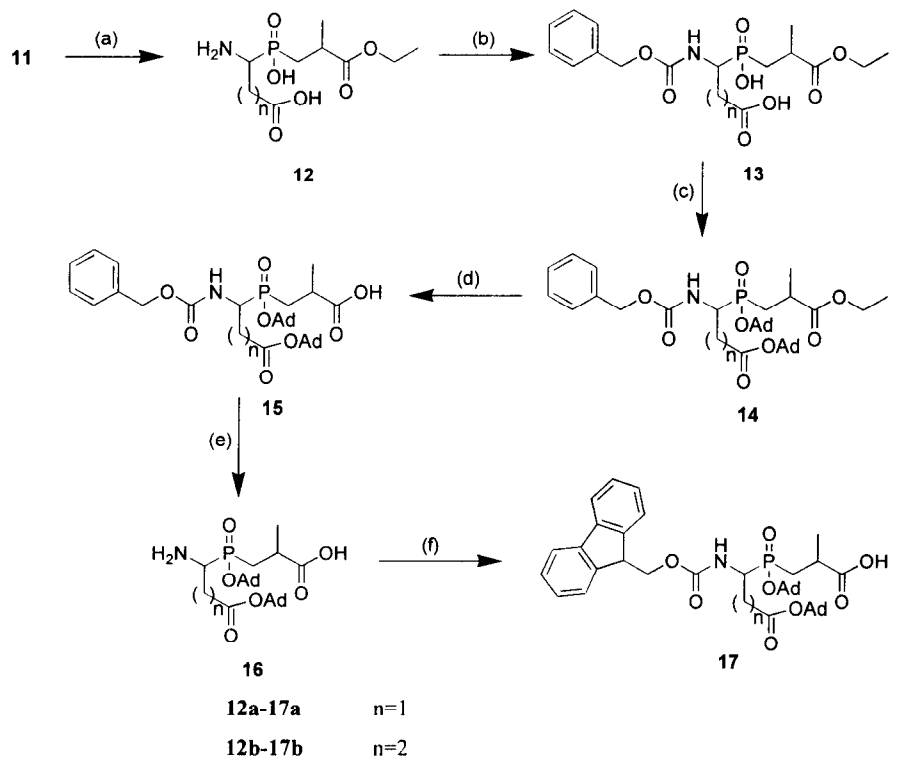
When compound **3** was submitted to Michael addition, using the two methods of activation described above, (Scheme 1, reaction (f)) the expected product was not formed. Unequal sharing of electrons in the phosphorus intermediate, due to the lack of symmetry and/or steric reasons caused by the presence of the adamantyl group, might explain this lack of reactivity. Thus, to maintain the symmetry of the phosphorus intermediate, a tert-butyl group, which is close in structure to the trimethylsilyl group, was used as the protecting group for the acidic functions. Refluxing compound **2** in benzene with N,N-dimethylformamide di-tert butyl acetal,[8] led to the formation of compound **4**. Again,with this starting material, no Michael addition was observed.

In a final attempt, free hydroxyphosphinyl aminophosphinic derivatives, incorporating a carboxylic function protected with either an adamantyl or tert-butyl ester, were prepared (compounds **5** and **6**). Compounds **5** and **6** were obtained from compounds **3** and **4** by selective cleavage of the hydrophosphinyl ester group with 5% TFA/CH_2Cl_2 (Scheme 1). Once again, attempts to perform Michael addition using **5** and **6** as nucleophiles did not proceed.



Scheme 2: (a) Boc_2O, Et_3N, MeOH, 50°C 3h then rt 24h. (b) HMDS, 110°C, 1h then $H_2C{=}C(R_2)COOEt$, 90°C, 3.5h then EtOH 70°C. (c) AdBr, Ag_2O, $CHCl_3$, reflux 2h. (d) $RuCl_3$, $NaIO_4$, CH_3CN, H_2O, rt, 3h.

The reason for these unsuccessful results might be an unexpected role played by the neighboring carboxylate groups (this particular problem is under investigation in our lab). This led us to consider the possibility of introducing the carboxylic acid side chain after the Michael addition. In this respect, compound **10** was chosen, as the phenyl group can be oxidized under mild conditions to a carboxylic acid. The synthetic process which was followed is illustrated in Scheme 2. This strategy requires the replacement of the Cbz- group by tert-butyloxycarbonyl as the protecting group of the aminophosphinic acid. Starting from compound **7**, compound **10** was obtained in three steps following a method previously described.[6] Compounds of type **10** were smoothly transformed to compounds of type **11** using a ruthenium catalyzed oxidative reaction.[9] This transformation proceeds in satisfactory yields within 3 h, also producing a small amount of overoxidized side products. It is worth noting that if the hydroxyphosphinyl group is not protected, overoxidized products are exclusively obtained. Using this method, two phosphinic dipeptides AspΨ(PO_2CH_2)Ala and GluΨ(PO_2CH_2)Ala, compounds **13**, were prepared (Scheme 3).



Scheme 3: (a) 50% TFA/CH_2Cl_2, rt, 3h (b) Cbz-Cl, MgO, H_2O, 4h (c) AdBr, Ag_2O, $CHCl_3$, reflux, 2h. (d) 0.4M NaOH/MeOH then aq. HCl. (e) $HCOONH_4$, 10% Pd/C, MeOH. (f) Fmoc-Cl, 10% Na_2CO_3, dioxan.

Even after saponification of the C-terminal ester of compound **13**, the resulting phosphinic building block cannot be used for the synthesis of longer phosphinic peptides, due to the presence of a free side chain carboxylic group. Convenient building blocks, compatible with conventional solid-phase peptide synthesis, were thus prepared using the pathway described in Scheme 3.

Both carboxylic and hydroxyphosphinyl groups were protected by the adamantyl group. The adamantyl group was chosen as a protecting group, since it can be removed easily under the classical deprotection conditions required by the Fmoc solid-phase peptide synthesis protocol from both carboxylic and phosphinic functions.[6,10] In addition, these esters are quite resistant to acidic conditions, since they remain stable during acidification which follows saponification.[11] After the saponification step, the Cbz group was removed using ammonium formate as a hydrogen donor, in the presence of palladium/carbon catalyst.[12] The final synthons **17** were obtained after the introduction of the Fmoc group to the intermediates **16** in moderate yields.

Although this synthetic strategy to obtain compound **17** consists of 10 steps, affording overall yields of 16%, it is the only method described which can lead to aspartyl or glutamyl phosphinic peptides. This fact gives a boost to the development of various important inhibitors for zinc proteases by parallel or combinatorial chemistry since building blocks **17** are perfect synthons for such an approach.[13]

Experimental part

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, and charring after spraying with a solution of NH_4HSO_4 and ninhydrin spray. The solvents systems used for TLC development were (1) 1-butanol-acetic/acid-water (4:1:1), (2) chloroform/methanol/acetic acid (7:2:1), (3) chloroform/methanol/acetic acid (7:0.5:0.5), (4) chloroform/2-propanol (9.8:0.2), (5) hexane/ethyl acetate/acetic acid (3:3:0.2), (6) chloroform/methanol/acetic acid (7:0.2:0.2). 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. Thus, the R_f values quoted correspond to an average value. Column chromatography was carried out on silica gel (E.Merck, 70-230 mesh). All the compounds were characterized by ^1H, ^{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 resonances corresponding to the different diastereoisomers. Assignment of the NMR signals was achieved using DQ-COSY and DEPT experiments. ^1H, ^{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-NMR chemical shifts are reported on δ scale (in ppm) downfield from 85% H_3PO_4. Mass spectroscopy and analytical data are also provided. Before microanalysis, 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). (*R,S*)-(1-(amino)-2-carboxyethyl)phosphinic

acid was prepared according to the Soroka procedure.[4a] (*R,S*)-(1-(amino)-2-phenylethyl)phosphinic acid and (*R,S*)-(1-(amino)-3-phenylpropyl)phosphinic acid were synthesized according to the Baylis procedure .[14]

(R,S)-3-(N-(benzyloxycarbonyl)amino)-3-hydroxyphosphinyl propanoic acid **2**: The aminophosphinic analogue of aspartic acid **1** (1.53 g, 10 mmol) was dissolved in H_2O (17 ml). To this solution were added Et_2O (5 ml) and magnesium oxide (1.22 g, 30 mmol). The mixture was cooled in an ice water bath and benzyl chloroformate (2.55 g, 2.15 ml, 15 mmol) was added dropwise over a period of 1 h. After the end of the addition, the mixture was stirred at rt for 3 h. Then, the mixture was acidified with 2M HCl to pH 1, and two extractions with AcOEt (2x10 ml) were performed. The combined organic layers were concentrated in vacuo and the residue was treated with a 10% aqueous solution of Na_2CO_3 (10 ml) and Et_2O (5 ml). The aqueous phase was separated, washed with Et_2O (2x5 ml) and acidified with 2M HCl to pH 1. The aqueous phase was extracted with AcOEt (2x10 ml) and the combined organic layers were washed with H_2O (5 ml), dried over Na_2SO_4 and concentrated in vacuo to afford the pure **2** derivative (2.28 g, 90%) as a white solid, m.p. 193-194 °C. TLC R_f(1) 0.47, R_f(2) 0.64; IR ν_{max}(KBr) 3650-3250(br), 3037, 2950, 2392, 1694, 1534, 1438, 1265, 1243, 1182, 1052, 985, 736, 695 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 1.94-2.15 (m, 1H, C*H*HCOOH), 2.24-2.40 (m, 1H, CH*H*COOH), 3.61-3.83 (m, 1H, PC*H*), 4.86 (s, 2H, PhCH_2O), 6.27 (d, 1H, $^1J_{PH}$ = 522 Hz, P*H*), 7.16 (s, 5H, aryl); ^{13}C-NMR (50 MHz, D_2O) δ 33.5 (d, J = 3.6 Hz, *C*H_2COOH), 52.3 (d, J = 101.9 Hz, PCH), 65.5 (PhCH$_2$O), 126.1, 126.8, 127.3, 134.9 (aryl), 156.3 (d, J = 3.1 Hz, *C*ONH), 177.5 (d, J = 15.0 Hz, *C*OOH); ^{31}P-NMR (81 MHz, D_2O) δ 22.02; ESMS *m/z* calcd for $C_{11}H_{15}NO_6P$ $(M+H)^+$ 288.0, found 287.6; Anal. Calcd for $C_{11}H_{14}NO_6P+H_2O$ (287.06); C, 43.43; H, 4.97; N, 4.60. Found: C, 43.63; H, 4.73; N, 4.65.

(R,S)-3-(N-(benzyloxycarbonyl)amino)-3-adamantyloxyphosphinyl propanoic acid, adamantyl ester **3**: Compound **2** (0.14 g, 0.5 mmol) and 1-adamantylbromide (0.26 g, 1.2 mmol) were dissolved in chloroform (10 ml). This reaction mixture was refluxed. Then, silver oxide (2.78 g, 1.2 mmol) was added in five equal portions, over 50 min. This solution was refluxed for an additional 1 h. After, the solvents were removed, the residue was treated with diethylether and filtered through celite. The filtrates were concentrated. The residue was purified by column chromatography using chloroform/isopropanol (9.8:0.2) as eluent. Compound **3** (0.19 g, 70%) was obtained as a colourless gum. TLC R_f(4) 0.78, R_f(5) 0.86; IR ν_{max}(liquid film) 3660-3230(br), 3036, 2976, 2950, 2849, 2388, 1697, 1541, 1437, 1371, 1311, 1265, 1243, 1182, 1126, 1054, 1000, 934, 831, 747, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.53-1.75 (m, 12H, CHCH_2CH of Ad group), 2.01-2.36 (m, 18H, C*H* of Ad group, CCH_2 of Ad group), 2.14-2.31 (m, 1H, C*H*HCOOH), 2.42-2.66 (m, 1H, CH*H*COOH), 4.01-4.23 (m, 1H, PC*H*), 4.86 (s, 2H, PhCH_2O), 6.23 (d, 1H, $^1J_{PH}$ = 552 Hz, P*H*), 7.07 (s, 5H, aryl); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 30.6 (*C*H of Ad in carboxyl group), 30.9 (*C*H of Ad in phosphinyl group), 35.2 (CHCH_2CH of Ad in carboxyl group), 35.6 (CHCH_2CH of Ad in phosphinyl group), 41.3 (COOC*C*H_2), 44.3 (d, J = 3.2 Hz, POC*C*H_2), 33.7 (d, J = 4.4 Hz, *C*H_2COOAd), 48.1 (d, J = 110.1 Hz, PCH), 66.2 (PhCH_2O), 127.7, 127.9, 128.1, 135.7 (aryl), 155.4 (d, J = 5.2 Hz, *C*ONH), 169.4 (d, J = 11.7 Hz, *C*OOAd); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 24.99, 26.31; ESMS *m/z* calcd for $C_{31}H_{43}NO_6P$ $(M+H)^+$ 556.7, found 556.3; Anal. Calcd for $C_{31}H_{42}NO_6P$ (555.7); C, 67.01; H, 7.62; N, 2.52. Found: C, 67.16; H, 7.87; N, 2.57.

(R,S)-3-(N-(benzyloxycarbonyl)amino)-3-tert-butyloxyphosphinyl propanoic acid, tert-butyl ester **4**: A suspension of **2** (0.28 g, 1 mmol) in dry benzene (3 ml) was refluxed. N,N-Dimethylformamide di-tert-butyl acetal (1.92 ml, 8 mmol) was added to the refluxing mixture, dropwise, over a period of 15 min. The mixture was refluxed for an additional 2 h. Then, the mixture was concentrated in vacuo and the oily residue was treated with Et_2O (10 ml) and 5% $NaHCO_3$ (10 ml). The organic layer was separated and two more extractions with Et_2O (2x10 ml) were performed. The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. Compound **4** was obtained after silica gel column chromatography purification, using chloroform/isopropanol (9.7:0.3) as eluent. Compound **4** (0.22 g, 55%) was obtained as a colourless gum. TLC R_f(4) 0.72, R_f(5) 0.79; IR ν_{max}(liquid film) 3660-3230(br), 3031, 2950, 2849, 2389, 1689, 1542, 1431, 1374, 1312, 1272, 1245, 1181, 1126, 1046, 936, 832, 752, 696 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.15 (s, 9H, COOC(CH_3)$_3$), 1.19 (s, 9H, POC(CH_3)$_3$), 2.11-2.34 (m, 1H, C*H*HCOOH), 2.40-2.70 (m, 1H, CH*H*COOH), 3.97-4.18 (m, 1H, PC*H*), 4.84 (s, 2H, PhCH_2O), 6.29 (d, 1H, $^1J_{PH}$ = 560 Hz, P*H*), 7.05 (s, 5H, aryl); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 27.5 (COOC(*C*H$_3$)$_3$), 29.6 (POC(*C*H$_3$)$_3$), 33.6 (d, J = 14.9 Hz, *C*H$_2$COOH), 47.1 (d, J = 112.8 Hz, PCH), 66.2 (PhCH$_2$O), 80.7 (COOC(*C*H$_3$)$_3$), 82.7 (POC(*C*H$_3$)$_3$), 127.6, 128.0, 136.3 (aryl), 155.7 (d, J = 3.8 Hz, *C*ONH), 169.2 (d, J = 13.4 Hz,

$COOC(CH_3)_3$); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 23.59, 24.71; ESMS *m/z* calcd for $C_{19}H_{31}NO_6P$ $(M+H)^+$ 400.6, found 400.2; Anal. Calcd for $C_{19}H_{30}NO_6P$ (399.6); C, 57.13; H, 7.57; N, 3.51. Found: C, 57.42; H, 7.29; N, 3.57.

(R,S)-3-(N-(benzyloxycarbonyl)amino)-3-hydroxyphosphinyl propanoic acid, adamantyl ester **5**: Compound **3** (0.11 g, 0.2 mmol) was dissolved in 5% TFA/CH_2Cl_2 (3 ml) and the reaction mixture was stirred for 7 h. The proper reaction time was determined by ^{31}P NMR in a time-arrayed experiment in which the changes of phosphorus signal were observed in a solution of **3** in 5% TFA/$CDCl_3$ (displacement of the signal downfield at 36.11 ppm). Then, the mixture was evaporated to dryness. Methylene chloride was added to the residue, and the solution was evaporated to dryness. The residue was dissolved in 5% $NaHCO_3$ (10 ml) and the aqueous solution was extracted with Et_2O (2x10 ml). The aqueous phase was ice-cooled and acidified with 1 M aqueous solution of $KHSO_4$ to pH 2.5. Two extractions were performed to the aqueous phase with AcOEt (2x10 ml) and the combined organic layers were dried with Na_2SO_4. The solvent was evaporated and the oily product that was obtained was used in the next step without further purification due to its sensitivity. TLC R_f(2) 0.87, R_f(3) 0.61.

(R,S)-3-(N-(benzyloxycarbonyl)amino)-3-hydroxyphosphinyl propanoic acid, tert-butyl ester **6**: Compound **4** (0.16 g, 0.4 mmol) was dissolved 5% TFA/CH_2Cl_2 (6 ml) and the reaction mixture was stirred for 2 h. The proper reaction time was determined by ^{31}P NMR in a time-arrayed experiment in which the changes of phosphorus signal were observed in a solution of **4** in 5% TFA/$CDCl_3$ (displacement of the signal downfield at 35.94 ppm). Then, the mixture was evaporated to dryness. Methylene chloride was added to the residue, and the solution was evaporated to dryness. The residue was dissolved in 5% $NaHCO_3$ and the aqueous solution was extracted with Et_2O (2x20 ml). The aqueous phase was ice-cooled and acidified with 1 M aqueous solution of $KHSO_4$ to pH 2.5. Two extractions were performed on the aqueous phase with AcOEt (2x10 ml) and the combined organic layers were dried with Na_2SO_4. The solvent was evaporated and the oily product which was obtained was used in the next step without further purification due to its sensitivity. TLC R_f(2) 0.83, R_f(3) 0.54.

(R,S)-(1-(N-(tert-butyloxycarbonyl)amino)-2-phenylethyl) phosphinic acid **8a**: To a solution of (R,S)-((1-amino)-2-phenylethyl) phosphinic acid **7a** (1.85 g, 10 mmol) in Et_3N (10 mmol) and MeOH (100 ml), Boc_2O (3.27 g, 15 mmol) was added. The resulting mixture was stirred at 50 °C over a period of 2 h and then in rt for another 5 h. The reaction mixture was concentrated in vacuo and the residue was treated with 5% aqueous solution of $NaHCO_3$ (10 ml) and Et_2O (10 ml). The aqueous phase was separated, ice-cooled and acidified with 0.5 M HCl to pH 1. Then, ethyl acetate (15 ml) was added and the compound was extracted from the aqueous phase. Two more extractions with ethyl acetate (2x10 ml) were performed and the combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The pure product was afforded in quantitative yield (4.3 g) as a white solid, m.p. 124-125 °C. TLC R_f(2) 0.63, R_f(3) 0.47; IR ν_{max}(KBr) 3540-3240(br), 3028, 3006, 2984, 2930, 2394, 1685, 1522, 1456, 1444, 1369, 1253, 1207, 1197, 1161, 1022, 976, 963, 731, 699 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33 (s, 9H, CCH_3), 2.76-2.99 (m, 1H, PhCH*H*), 3.09-3.27 (m, 1H, PhC*H*H), 4.12-4.22 (m, 1H, PC*H*), 5.03 (br d, 1H, NH), 7.08 (d, 1H, $^1J_{PH}$ = 573 Hz, P*H*), 7.18-7.34 (s, 5H, aryl); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 28.1 (CCH_3), 33.0 (d, J = 3.5 Hz, PhCH_2), 50.6 (d, J = 106.5 Hz, P*C*H), 80.4 (CCH_3) 126.8, 128.5, 129.2, 136.0, 136.2, 134.9 (aryl), 155.5 (d, J = 3.5 Hz, *C*ONH); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 32.52; ESMS *m/z* calcd for $C_{13}H_{21}NO_4P$ $(M+H)^+$ 286.3, found 285.9; Anal. Calcd for $C_{13}H_{20}NO_4P$ (285.3); C, 54.73; H, 7.07; N, 4.91. Found: C, 54.73; H, 7.03; N, 4.85.

(R,S)-(1-(N-(tert-butyloxycarbonyl)amino)-3-phenylpropyl) phosphinic acid **8b**: (R,S)-((1-amino)-3-phenylpropyl) phosphinic acid **7b** was treated as described above. Compound **8b** was obtained in quantitative yield, m.p. 130-131 °C. TLC R_f(2) 0.59, R_f(3) 0.42; IR ν_{max}(liquid film) 3580-3190(br), 3030, 3007, 2987, 2935, 2356, 1685, 1507, 1457, 1444, 1367, 1251, 1207, 1172, 1050, 970, 966, 751, 699 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.54 (s, 9H, CCH_3), 1.79-2.01 (m, 1H, CHCH*H*), 2.06-2.28 (m, 1H, CHC*H*H), 2.65-2.93 (m, 2H, PhCH_2), 3.86-4.07 (m, 1H, PC*H*), 5.09 (br d, 1H, NH), 7.02 (d, 1H, $^1J_{PH}$ = 563 Hz, P*H*), 7.16-7.42 (s, 5H, aryl); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 28.2 (CCH_3), 28.6 ($CHCH_2$), 31.9 (d, J = 11.8 Hz, PhCH_2), 49.0 (d, J = 106.2 Hz, P*C*H), 80.4 (CCH_3) 126.2, 128.5, 129.1, 140.6 (aryl), 155.6 (d, J = 4.1 Hz, *C*ONH); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 32.46; ESMS *m/z* calcd for $C_{14}H_{23}NO_4P$ $(M+H)^+$ 300.1, found 299.9; Anal. Calcd for $C_{14}H_{22}NO_4P$ (299.1); C, 56.18; H, 7.41; N, 4.68. Found: C, 56.13; H, 7.02; N, 4.78.

(R,R,S,S) 2-methyl-3((1-(N-(tert-butyloxycarbonyl)amino)-2-phenylethyl)-hydroxyphosphinyl) propanoic acid, ethylester **9a**: A suspension of compound **8a** (2.35 g, 8 mmol) in hexamethyldisilazane (6.5 g, 8.4 ml, 40 mmol) was heated at 110°C for 1 h, under nitrogen. Then ethyl methacrylate (1.19 g, 1.29 ml, 10.4 mmol) was added dropwise over 15 min. This reaction mixture was stirred for an additional 3 h at 110°C. This mixture was allowed to cool to 70°C and ethanol (25 ml) was added dropwise. After cooling to rt the reaction mixture was concentrated. The residue was treated with 5% aqueous solution of $NaHCO_3$ (20 ml) and Et_2O (15 ml). The aqueous phase was separated, ice-cooled and acidified with 0.5 M HCl to pH 1. Then, ethyl acetate (15 ml) was added and the compound was extracted from the aqueous phase. Two more extractions (2x15 ml) with ethyl acetate were performed and the combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. A white solid was obtained, which was further purified by column chromatography, using chloroform/methanol/acetic acid (7:0.5:0.5) as eluent, to give compound **9a** (3.05 g, **96%**) as a white solid, m.p. 72-73 °C. TLC R_f(2) 0.84, R_f(3) 0.81; IR ν_{max}(liquid film) 3600-3150(br), 3073, 3032, 3007, 2982, 2936, 1736, 1685, 1560, 1509, 1455, 1393, 1369, 1309, 1250, 1164, 1042, 963, 754, 700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33 (t, J = 7.4 Hz, 3H, CH_2CH_3), 1.37 (s, 9H, $C(CH_3)_3$), 1.41 (d, J = 7.2 Hz, 3H, CH_3), 1.70-2.04 (m, 1H, PC*H*H), 2.28-2.53 (m, 1H, PCH*H*), 2.77-3.10 (m, 2H, PhC*H*H, C*H*CO), 3.27-3.45 (m, 1H, PhCH*H*), 4.26-4.41 (m, 1H, PC*H*), 4.23 (q, J = 7.4 Hz, 2H, CH_2CH_3), 5.10 (d, J = 10.4 Hz, 1H, N*H*), 7.28-7.44 (m, 5H, aryl); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 14.1 (CH_2CH_3), 18.9 (d, J = 8.1 Hz, CH_3, I), 19.1 (d, J = 9.8 Hz, CH_3, II), 28.1 ($C(CH_3)_3$), 29.8 (d, J = 91.5 Hz, PCH_2, I), 30.1 (d, J = 91.5 Hz, PCH_2, II), 33.7 (d, J = 5.1 Hz, PhCH_2), 33.7 (d, J = 3.8 Hz, CHCOOEt), 50.1 (d, J = 105.6 Hz, PCH, I), 50.6 (d, J = 105.6 Hz, PCH, II), 60.9 (CH_2CH_3), 80.0 ($C(CH_3)_3$), 126.6, 128.4, 129.2, 136.6, 136.8 (aryl), 155.3 (d, J = 6.3 Hz, OCONH), 175.5 (d, J = 8.2 Hz, COOEt); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 52.09, 53.73; ESMS *m/z* calcd for $C_{19}H_{31}NO_6P$ $(M+H)^+$ 400.4, found 400.1; Anal. Calcd for $C_{19}H_{30}NO_6P$ (399.4); C, 57.13; H, 7.57; N, 3.51. Found: C, 56.98; H, 7.16; N, 3.50.

(R,R,S,S) 2-methyl-3((1-(N-(tert-butyloxycarbonyl)amino)-3-phenylpropyl)-hydroxyphosphinyl) propanoic acid, ethyl ester **9b**: Compound **9b** was obtained in 98% yield as a white solid, m.p. 104-105 °C. TLC R_f(2) 0.85, R_f(3) 0.83; IR ν_{max}(liquid film) 3650-3160(br), 3068, 3024, 3001, 2981, 2932, 1737, 1687, 1559, 1507, 1455, 1394, 1369, 1307, 1247, 1161, 1020, 968, 864, 753, 700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.32 (d, J = 6.7 Hz, 3H, CH_3), 1.54 (s, 9H, $C(CH_3)_3$), 1.75-2.01 (m, 2H, PCHC*H*H, PC*H*H), 2.08-2.40 (m, 2H, PCHCH*H*, PCH*H*), 2.62-3.01 (m, 3H, PhCH_2, C*H*CO), 3.99-4.09 (m, 1H, PC*H*), 4.19 (q, J = 7.1 Hz, 2H, CH_2CH_3), 5.14 (d, J = 10.2 Hz, 1H, N*H*), 7.20-7.41 (m, 5H, aryl); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 14.1 (CH_2CH_3), 18.7 (d, J = 7.7 Hz, CH_3, I), 19.0 (d, J = 9.5 Hz, CH_3, II), 28.3 ($C(CH_3)_3$), 29.4 (PCHCH_2, I), 29.5 (PCHCH_2, II), 29.6 (d, J = 91.8 Hz, PCH_2, I), 29.9 (d, J = 91.8 Hz, PCH_2, II), 32.0 (d, J = 11.3 Hz, PhCH_2), 33.6 (d, J = 3.9 Hz, CHCOOEt), 48.6 (d, J = 105.6 Hz, PCH, I), 49.1 (d, J = 105.6 Hz, PCH, II), 60.8 (CH_2CH_3), 80.1 ($C(CH_3)_3$), 126.0, 128.1, 128.4, 128.4, 140.8 (aryl), 155.5 (d, J = 5.0 Hz, OCONH), 175.3 (d, J = 10.3 Hz, COOEt); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 52.90, 54.11; ESMS *m/z* calcd for $C_{20}H_{33}NO_6P$ $(M+H)^+$ 414.4, found 414.1; Anal. Calcd for $C_{20}H_{32}NO_6P$ (413.4); C, 58.10; H, 7.80; N, 3.39. Found: C, 57.82; H, 7.94; N, 3.57.

(R,R,S,S) 2-methyl-3((1-(N-(tert-butyloxycarbonyl)amino)-2-phenylethyl)-adamantyloxyphosphinyl) propanoic acid, ethylester **10a**: Compound **9a** (2.71 g, 6.8 mmol) and 1-adamantylbromide (1.76 g, 8.2 mmol) were dissolved in chloroform (70 ml). This reaction was refluxed. Then, silver oxide (1.90 g, 8.2 mmol) was added in five equal portions, over 50 min. This solution was refluxed for an additional 2h. then, the solvent was removed, the residue was treated with diethylether and filtered through celite. The filtrates were concentrated. The residue was purified by column chromatography using chloroform/isopropanol (9.8:0.2) as eluent. Compound **10a** (3.45 g, 95%) was obtained as a white foam. TLC R_f(4) 0.66, R_f(5) 0.83; IR ν_{max}(liquid film) 3660-3150(br), 3065, 3028, 2976, 2904, 2853, 1736, 1686, 1560, 1541, 1507, 1457, 1392, 1368, 1353, 1303, 1246, 1174, 1120, 1089, 1051, 992, 933, 850, 814, 755, 698 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20-1.34 (s+d+t, J = 7.1, 7.0 Hz, 15H, $C(CH_3)_3$, CH_3, CH_2CH_3), 1.57-1.78 (m, 7H, PC*H*H, CHCH_2CH of Ad group), 2.03-2.22 (m, 9H, C*H* of Ad group, CCH_2 of Ad group), 2.25-2.47 (m, 1H, PCH*H*), 2.59-2.98 (m, 2H, PhC*H*H, C*H*CO), 3.12-3.39 (m, 1H, PhCH*H*), 4.05-4.24 (m+q, J = 7.0 Hz, 3H, PC*H*, CH_2CH_3), 4.98 (d, J = 10.6 Hz, 1H, N*H*), 7.21-7.31 (m, 5H, aryl); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 14.1 (CH_2CH_3), 19.0 (d, J = 7.5 Hz, CH_3, I), 19.5 (d, J = 8.6 Hz, CH_3, II), 28.0 ($C(CH_3)_3$), 31.7 (d, J = 88.6 Hz, PCH_2, I), 32.0 (d, J = 88.6 Hz, PCH_2, II), 30.9 (CH of Ad group), 33.8 (d, J = 4.4 Hz, CHCOOEt),

34.2 (d, J = 5.9 Hz, $PhCH_2$), 35.6 ($CHCH_2CH$ of Ad group), 44.3 (d, J = 3.2 Hz, CCH_2 of Ad group), 50.9 (d, J = 102.3 Hz, PCH, I), 51.4 (d, J = 102.3 Hz, PCH, II), 60.7 (CH_2CH_3), 79.6 ($C(CH_3)_3$), 83.9 (d, J = 11.3 Hz, POC), 126.4, 128.2, 129.2, 129.5, 132.7, 136.9, 137.0 (aryl), 155.7 (d, J = 7.1 Hz, OCONH), 175.8 (d, J = 8.5 Hz, COOEt); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 47.59, 48.36, 48.72, 48.88; ESMS *m/z* calcd for $C_{29}H_{45}NO_6P$ $(M+H)^+$ 534.6, found 534.3; Anal. Calcd for $C_{29}H_{44}NO_6P$ (533.6); C, 65.27; H, 8.31; N, 2.62. Found: C, 65.44; H, 8.10; N, 2.71.

(R,R,S,S) 2-methyl-3((1-(N-(tert-butyloxycarbonyl)amino)-3-phenylpropyl)-adamantyloxyphosphinyl) propanoic acid, ethylester **10b**: Compound **10b** was obtained in 96% yield as a colourless gum. TLC R_f(4) 0.69, R_f(5) 0.84; IR ν_{max}(liquid film) 3660-3170(br), 3092, 3065, 3028, 2976, 2931, 2860, 1736, 1686, 1560, 1542, 1507, 1459, 1394, 1364, 1357, 1303, 1249, 1171, 1120, 1089, 1054, 989, 934, 851, 814, 752, 701 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.32 (d, J = 6.7 Hz, 3H, CH_3), 1.54 (s, 9H, $C(CH_3)_3$), 1.75-2.01 (m, 2H, PCHC*H*H, PC*H*H), 2.08-2.40 (m, 2H, PCHCH*H*, PCH*H*), 2.62-3.01 (m, 3H, $PhCH_2$, *CH*CO), 3.99-4.09 (m, 1H, PC*H*), 4.19 (q, J = 7.1 Hz, 2H, CH_2CH_3), 5.14 (d, J = 10.2 Hz, 1H, N*H*), 7.20-7.41 (m, 5H, aryl); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 14.1 (CH_2CH_3), 18.7 (d, J = 7.7 Hz, CH_3, I), 19.0 (d, J = 9.5 Hz, CH_3, II), 28.3 ($C(CH_3)_3$), 29.4 (PCHCH_2, I), 29.5 (PCHCH_2, II), 29.6 (d, J = 91.8 Hz, PCH_2, I), 29.9 (d, J = 91.8 Hz, PCH_2, II), 32.0 (d, J = 11.3 Hz, $PhCH_2$), 33.6 (d, J = 3.9 Hz, CHCOOEt), 48.6 (d, J = 105.6 Hz, PCH, I), 49.1 (d, J = 105.6 Hz, PCH, II), 60.8 (CH_2CH_3), 80.1 ($C(CH_3)_3$), 126.0, 128.1, 128.4, 128.4, 140.8 (aryl), 155.5 (d, J = 5.0 Hz, OCONH), 175.3 (d, J = 10.3 Hz, COOEt);); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 47.63, 48.33, 48.77, 48.95; ESMS *m/z* calcd for $C_{30}H_{47}NO_6P$ $(M+H)^+$ 548.7, found 548.3; Anal. Calcd for $C_{30}H_{46}NO_6P$ (547.7); C, 65.79; H, 8.46; N, 2.55. Found: C, 65.69; H, 8.44; N, 2.52.

(R,R,S,S)-3-(N-(tert-butyloxycarbonyl)amino)-3-((2methyl-ethoxyprpionyl)adamantyloxyphosphinyl) propanoic acid **11a**: To a solution of **10a** (2.67 g, 5.0 mmol) in AcOEt (13 ml) and H_2O (130 ml), sodium metaperiodate (2.78 g, 130 mmol) was added. The resulting mixture was stirred vigorously and ruthenium trichloride (46.7 mg, 0.23 mmol) was added. The solution was stirred for 3 h and then H_2O (100 ml) and AcOEt (50 ml) was added to the mixture. The organic layer was separated. Two more extractions with AcOEt (2x30 ml) were performed and the combined organic layers were washed with H_2O (30 ml), dried with Na_2SO_4, and concentrated in vacuo. A solid residue was obtained which was purified by column chromatography using chloroform/methanol/acetic acid (7:0.15:0.15) as eluent, to afford **11a** (1.13 g, 45%) as a white solid, m.p. 78-79 °C. TLC R_f(4) 0.22, R_f(6) 0.64; IR ν_{max}(liquid film) 3600-3130(br), 2979, 2914, 2857, 1736, 1726, 1698, 1559, 1540, 1500, 1459, 1396, 1368, 1356, 1302, 1252, 1163, 1105, 1051, 1004, 935, 854, 815, 756 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.21-1.36 (d+t, J = 7.4, 6.9 Hz, 6H, CH_3, CH_2CH_3), 1.44 (s, 9H, $C(CH_3)_3$), 1.58-1.67 (m, 6H, $CHCH_2CH$ of Ad group), 1.81-2.17 (m, 10H, *CH* of Ad group, CCH_2 of Ad group, PC*H*H), 2.27-2.52 (m, 1H, PCH*H*), 2.56-2.97 (m, 3H, *CH*CO, CH_2CO), 4.14 (q, J = 6.9 Hz, 2H, CH_2CH_3), 4.25-4.52 (m, 1H, PC*H*), 6.08 (d, J = 10.2 Hz, 1H, N*H*); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 14.1 (CH_2CH_3), 19.1 (d, J = 9.1 Hz, CH_3, I), 19.7 (d, J = 10.8 Hz, CH_3, II), 28.3 ($C(CH_3)_3$), 31.2 (*CH* of Ad group), 33.3 (d, J = 82.4 Hz, PCH_2, I), 33.5 (CH_2CO), 33.6 (d, J = 82.4 Hz, PCH_2, II), 33.9 (d, J = 4.2 Hz, *CH*COOEt), 35.6 ($CHCH_2CH$ of Ad group), 44.2 (d, J = 3.4 Hz, CCH_2 of Ad group), 46.3 (d, J = 110.3 Hz, PCH, I), 47.3 (d, J = 110.3 Hz, PCH, II), 60.8 (CH_2CH_3), 80.1 ($C(CH_3)_3$), 84.5 (d, J = 12.3 Hz, POC), 155.0 (d, J = 16.0 Hz, OCONH), 172.9 (d, J = 9.5 Hz, COOH), 175.1 (d, J = 10.7 Hz, COOEt); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 48.97, 49.14, 49.44, 50.33; ESMS *m/z* calcd for $C_{29}H_{45}NO_6P$ $(M+H)^+$ 502.5, found 502.2; Anal. Calcd for $C_{29}H_{44}NO_6P$ (501.5); C, 57.47; H, 8.04; N, 2,79. Found: C, 57.87; H, 8.12; N, 2.76.

(R,R,S,S)-3-(N-(tert-butyloxycarbonyl)amino)-4-((2methyl-ethoxyprpionyl)adamantyloxyphosphinyl) butanoic acid **11b**: Compound **10b** was obtained in 47% yield as a white solid, m.p. 85-86 °C. TLC R_f(4) 0.24, R_f(6) 0.66; IR ν_{max}(liquid film) 3630-3150(br), 2981, 2914, 2856, 1734, 1726, 1696, 1558, 1540, 1503, 1459, 1397, 1369, 1356, 1304, 1252, 1231, 1167, 1102, 1048, 999, 935, 851, 815, 755 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10-1.23 (d+t, J = 7.1, 6.9 Hz, 6H, CH_3, CH_2CH_3), 1.34 (s, 9H, $C(CH_3)_3$), 1.46-1.59 (m, 6H, $CHCH_2CH$ of Ad group), 1.63-1.83 (m, 2H, PC*H*H, PCHCH*H*H), 1.89-2.14 (m, 10H, *CH* of Ad group, CCH_2 of Ad group, PCHCH*H*), 2.18-2.47 (m, 1H, PCH*H*, CH_2CO), 2.62-2.87 (m, 1H, *CH*CO), 3.66-3.93 (m, 1H, PC*H*), 4.03 (q, J = 6.9 Hz, 2H, CH_2CH_3), 5.93 (d, J = 10.1 Hz, 1H, N*H*); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 13.9 (CH_2CH_3), 18.9 (d, J = 8.6 Hz, CH_3, I), 19.6 (d, J = 11.0

Hz, CH_3, II), 28.0 ($C(CH_3)_3$), 30.3 (CH_2CO), 31.0 (CH of Ad group), 31.5 (d, J = 90.1 Hz, PCH_2, I), 31.7 (d, J = 90.1 Hz, PCH_2, II), 34.2 (d, J = 3.0 Hz, CHCOOEt), 35.4 ($CHCH_2CH$ of Ad group), 44.0 (d, J = 3.1 Hz, CCH_2 of Ad group), 49.0 (d, J = 111.6 Hz, PCH, I), 49.3 (d, J = 111.6 Hz, PCH, II), 60.6 (CH_2CH_3), 79.7 ($C(CH_3)_3$), 84.2 (d, J = 10.8 Hz, POC), 155.8 (d, J = 6.3 Hz, OCONH), 175.2 (d, J = 9.9 Hz, COOH), 175.6 (d, J = 10.4 Hz, COOEt); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 49.27, 49.46, 49.57, 50.56; ESMS *m/z* calcd for $C_{25}H_{43}NO_8P$ $(M+H)^+$ 516.6, found 516.3; Anal. Calcd for $C_{25}H_{42}NO_8P$ (515.6); C, 58.24; H, 8.21; N, 2,72. Found: C, 58.23; H, 8.42; N, 2.58.

(R,R,S,S)-3-(N-(benzyloxycarbonyl)amino)-3-((2methyl-ethoxyprpionyl)hydroxyphosphinyl) propanoic acid **13a**: To an ice cooled solution of **11a** (1.00 g, 2.0 mmol) in CH_2Cl_2 (3 ml), a 10:7 TFA/CH_2Cl_2 (17 ml) mixture and H_2O (0.5 ml) was added. The resulting solution was stirred for 3 h at rt. Then, the mixture was concentrated to dryness in vacuo. A mixture of Et_2O/hexane (1:1) was added to the solid residue. The precipitate was filtrated and washed with Et_2O. The salt **12a** which was obtained (0.50 g, 91%) is very hygroscopic and it was used immediately in the next reaction. Compound **12a** (0.45 g, 1.5 mmol) was dissolved in H_2O (4 ml). Magnesium oxide (0.18 g, 4.5 mmol) was added to the mixture. The resulting solution was ice cooled and benzyl chloroformate (0.51 g, 0.43 ml, 3.0 mmol) was added dropwise over a period of 1 h. When the addition was complete, the mixture was acidified with 1 M HCl to pH 1, and two extractions with AcOEt (2x10 ml) were performed. The combined organic layers were concentrated in vacuo and the residue was treated with 5% aqueous solution of $NaHCO_3$ (10 ml) and Et_2O (5 ml). The aqueous phase was separated, washed with Et_2O (2x5 ml) and acidified with 1M HCl to pH 1. The aqeuous phase was extracted with AcOEt (2x10 ml) and the combined organic layers were washed with H_2O (5 ml), dried with Na_2SO_4 and concentrated in vacuo to afford the pure **13a** derivative (0.42 g, 70%) as a white solid, m.p. 129-130 °C. TLC R_f(2) 0.47, R_f(3) 0.18; IR ν_{max}(liquid film) 3660-3170(br), 3073, 3026, 2976, 2920, 2855, 1736, 1718, 1686, 1563, 1519, 1500, 1459, 1371, 1357, 1305, 1267, 1169, 1118, 1089, 1058, 996, 932, 849, 817, 753, 699, 667 cm^{-1}; ^{1}H NMR (200 MHz, D_2O) δ 0.98-1.18 (d+t J = 7.0, 6.6 Hz, 6H, CH_2CH_3, CH_3), 1.34-1.52 (m, 1H, PC*H*H), 1.75-1.95 (m, 1H, PCH*H*), 2.08-2.24 (m, 1H, C*H*HCO), 2.47-2.81 (m, 2H, C*H*CO, CH*H*CO), 3.91-4.08 (m+q, J = 7.0 Hz, 3H, PC*H*, CH_2CH_3), 5.06 (s, 2H, PhCH_2O), 7.25-7.40 (m, 5H, aryl); ^{13}C-NMR (50 MHz, D_2O) δ 11.9 (CH_2CH_3), 16.9 (d, J = 6.6 Hz, CH_3, I), 17.3 (d, J = 9.0 Hz, CH_3, II), 29.4 (d, J = 91.5 Hz, PCH_2, I), 29.6 (d, J = 91.5 Hz, PCH_2, II), 32.9 (CH_2CO), 34.5 (d, J = 4.5 Hz, CHCOOEt), 47.9 (d, J = 103.8 Hz, PCH, I), 48.1 (d, J = 103.8 Hz, PCH, II), 60.5 (CH_2CH_3), 65.5 (PhCH_2O), 126.1, 126.9, 127.4, 135.3 (aryl), 156.5 (d, J = 10.0 Hz, OCONH), 176.9 (d, J = 11.5 Hz, COOH), 178.1 (d, J = 10.3 Hz, COOEt); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 51.48, 51.63; ESMS *m/z* calcd for $C_{17}H_{25}NO_8P$ $(M+H)^+$ 402.3, found 402.0; Anal. Calcd for $C_{17}H_{24}NO_8P$ (401.3); C, 50.87; H, 6.03; N, 3.49. Found: C, 50.48; H, 5.84; N, 3.37.

(R,R,S,S)-3-(N-(benzyloxycarbonyl)amino)-4-((2-methyl-ethoxyprpionyl)hydroxyphosphinyl) butanoic acid **13b**: The salt **12a** was obtained in 94% yield and compound **13a** was obtained in 79% yield as a white solid, m.p. 139-140 °C. TLC R_f(2) 0.50, R_f(3) 0.20; IR ν_{max}(liquid film) 3630-3150(br), 3071, 3017, 2976, 2918, 2849, 1736, 1724, 1685, 1562, 1519, 1497, 1457, 1377, 1359, 1305, 1266, 1172, 1121, 1086, 1056, 1002, 932, 848, 818, 753, 700, 665 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15-1.25 (d+t J = 7.0, 5.6 Hz, 6H, CH_2CH_3, CH_3), 1.62-1.99 (m, 2H, PCHCHH_2, PCH*H*), 2.04-2.51 (m, 4H, CH_2CO, PCHCHH_2, PCH*H*), 2.71-2.92 (m, 1H, C*H*CO), 3.87-4.15 (m+q, J = 7.0 Hz, 3H, PC*H*, CH_2CH_3), 5.08 (s, 2H, PhCH_2O), 7.26-7.37 (m, 5H, aryl); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 14.0 (CH_2CH_3), 18.8 (d, J = 8.6 Hz, CH_3, I), 19.1 (d, J = 9.4 Hz, CH_3, II), 22.8 (d, J = 4.5 Hz, PCHCH_2), 28.8 (d, J = 89.8 Hz, PCH_2, I), 29.5 (d, J = 89.8 Hz, PCH_2, II), 30.3 (CH_2CO), 33.6 (CHCOOEt), 49.3 (d, J = 103.6 Hz, PCH, I), 49.7 (d, J = 103.6 Hz, PCH, II), 61.1 (CH_2CH_3), 67.2 (PhCH_2O), 127.9, 128.1, 128.2, 128.5, 136.1 (aryl), 156.5 (d, J = 4.3 Hz, OCONH), 175.5 (d, J = 9.4 Hz, COOH), 177.0 (d, J = 11.0 Hz, COOEt); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 52.75, 52.89; ESMS *m/z* calcd for $C_{18}H_{27}NO_8P$ $(M+H)^+$ 416.3, found 416.0; Anal. Calcd for $C_{18}H_{26}NO_8P \cdot 2H_2O$ (451.3); C, 48.11; H, 6.28; N, 3.12. Found: C, 48.33; H, 6.55; N, 3.09.

(R,R,S,S)-2-methyl-3-((3-(N-(benzyloxycarbonyl)amino)adamantyloxypropionyl)adamantyloxyphosphinyl) propanoic acid, ethylester **14a**: Compound **13a** (0.40 g, 1.0 mmol) and 1-adamantylbromide (0.52 g, 2.4 mmol) were dissolved in chloroform (10 ml). This reaction was refluxed. Then, silver oxide (0.93 g, 4.0 mmol) was added in five equal portions, over 50 min. This solution was refluxed for an additional 1h. Then, the solvent was removed, the residue was treated with diethylether and filtered through celite. The

filtrates were concentrated. The residue was purified by column chromatography using chloroform/isopropanol (9.8:0.2) as eluent. Compound **14a** (0.66 g, 98%) was obtained as a colourless gum. TLC R_f(4) 0.65, R_f(5) 0.79; IR ν_{max}(liquid film) 3670-3120(br), 3070, 3022, 2976, 2923, 2861, 1736, 1718, 1686, 1561, 1520, 1501, 1459, 1371, 1355, 1309, 1253, 1113, 1091, 1052, 997, 936, 849, 813, 755, 697, 668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.24 (d, J = 6.5 Hz, 3H, CH_3), 1.26 (t, 7.2 Hz, 3H, CH_2CH_3), 1.56-1.69 (m, 13H, $CHCH_2CH$ of Ad groups, $PCHH$), 1.78-1.91 (m, 1H, $PCHH$), 1.99-2.22 (m, 18H, CH of Ad groups, CCH_2 of Ad groups), 2.29-2.53 (m, 1H, $CHHCO$), 2.63-2.97 (m, 2H, $CHCO$, $CHHCO$), 4.14 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.27-4.55 (m, 1H, PCH), 5.14 (s, 2H, $PhCH_2O$), 5.58 (d, J = 10.0 Hz, 1H, NH), 7.23-7.42 (m, 5H, aryl); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 14.2 (CH_2CH_3), 19.1 (d, J = 8.6 Hz, CH_3, I), 19.7 (d, J = 6.2 Hz, CH_3, II), 30.8 (CH of Ad in carboxyl group), 31.2 (CH of Ad in phosphinyl group), 31.52 (d, J = 91.5 Hz, PCH_2, I), 32.03 (d, J = 91.5 Hz, PCH_2, II), 32.9 (CH_2CO), 34.4 (d, J = 4.1 Hz, $CHCOOEt$), 35.7 ($CHCH_2CH$ of Ad in carboxyl group), 36.1 ($CHCH_2CH$ of Ad in phosphinyl group), 41.1 ($COOCCH_2$), 44.3 (d, J = 3.3 Hz, $POCCH_2$), 47.6 (d, J = 108.7 Hz, PCH, I), 48.4 (d, J = 108.7 Hz, PCH, II), 60.8 (CH_2CH_3), 67.0 ($PhCH_2O$), 81.6 ($COOC$), 84.0 (d, J = 10.2 Hz, POC), 128.1, 128.5, 128.6, 136.0 (aryl), 155.5 (d, J = 8.6 Hz, $OCONH$), 176.3 (d, J = 9.9 Hz, $COOAd$), 175.4 (d, J = 10.1 Hz, $COOEt$); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 46.82, 47.22, 47.56; ESMS calcd for $C_{37}H_{53}NO_8P$ $(M+H)^+$ 670.8, found *m/z* 670.4; Anal. Calcd for $C_{37}H_{52}NO_8P$ (669.8); C, 66.35; H, 7.82; N, 2.09. Found: C, 66.77; H, 8.12; N, 1.86.

(R,R,S,S)-4-(N-(benzyloxycarbonyl)amino)-4-((2-methyl-ethoxypropionyl)adamantyloxyphoshinyl) butanoic acid, adamantylester **14b**: Compound **14b** was obtained in 96% yield as a colourless gum. TLC R_f(4) 0.69, R_f(5) 0.81; IR ν_{max}(liquid film) 3660-3170(br), 3073, 3023, 2981, 2923, 2862, 1735, 1718, 1685, 1560, 1519, 1500, 1459, 1371, 1355, 1309, 1251, 1115, 1089, 1058, 996, 934, 850, 814, 752, 699, 667 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.19 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.24 (d, J = 7.4 Hz, 3H, CH_3), 1.45-1.71 (m, 13H, $CHCH_2CH$ of Ad groups, $PCHH$), 1.88-1.73 (m, 2H, $PCHCHH_2$, $PCHH$), 1.92-2.16 (m, 18H, CH of Ad groups, CCH_2 of Ad groups), 2.20-2.41 (m, 4H, CH_2CO, $PCHCHH_2$, $PCHH$), 2.64-2.93 (m, 1H, $CHCO$), 3.79-4.01 (m, 1H, PCH), 4.09 (q, J = 7.2 Hz, 2H, CH_2CH_3), 5.08 (s, 2H, $PhCH_2O$), 5.60 (d, J = 10.1 Hz, 1H, NH), 7.23-7.36 (m, 5H, aryl); δ 14.0 (CH_2CH_3), 19.0 (d, J = 8.8 Hz, CH_3, I), 19.5 (d, J = 10.5 Hz, CH_3, II), 23.8 (d, J = 4.0 Hz, $PCHCH_2$), 31.9 (CH_2CO), 31.5 (d, J = 90.1 Hz, PCH_2, I), 31.8 (d, J = 90.1 Hz, PCH_2, II), 30.6 (CH of Ad in carboxyl group), 31.0 (CH of Ad in phosphinyl group), 34.3 (d, J = 3.8 Hz, $CHCOOEt$), 35.5 ($CHCH_2CH$ of Ad in carboxyl group), 36.0 ($CHCH_2CH$ of Ad in phosphinyl group), 41.1 ($COOCCH_2$), 44.2 (d, J = 3.5 Hz, $POCCH_2$), 49.4 (d, J = 107.6 Hz, PCH, I), 50.6 (d, J = 107.6 Hz, PCH, II), 60.7 (CH_2CH_3), 66.8 ($PhCH_2O$), 80.4 ($COOC$), 83.5 (d, J = 9.7 Hz, POC), 127.8, 127.9, 127.9, 128.4, 136.2 (aryl), 156.2 (d, J = 6.2 Hz, $OCONH$), 171.7 (d, J = 6.5 Hz, $COOAd$), 175.5 (d, J = 9.6 Hz, $COOEt$); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 46.95, 47.18, 47.71, 47.92; ESMS calcd for $C_{38}H_{55}NO_8P$ $(M+H)^+$ 684.8, found *m/z* 684.5; Anal. Calcd for $C_{38}H_{54}NO_8P$ (683.8); C, 66.74; H, 7.96; N, 2.05. Found: C, 66.74; H, 8.28; N, 1.89.

(R,R,S,S)-2-methyl-3-((3-(N-(benzyloxycarbonyl)amino)adamantyloxypropionyl) adamantyloxyphosphinyl) propanoic acid **15a**: To a stirred solution of **14a** (0.53 g, 0.8 mmol) in methanol (5 ml), a 4 M aqueous solution of NaOH (0.9 ml) was added dropwise. The reaction mixture was stirred for 2h. Then the solvent was removed and the residue was diluted with water and acidified with 0.5 M HCl in an ice water bath. This aqueous solution was extracted with AcOEt (2x10 ml) and the combined organic layers were dried over Na_2SO_4 and concentrated to give **15a** (0.44 g, 85%) as a white solid, m.p. 69-70 °C. TLC R_f(4) 0.28, R_f(5) 0.75; IR ν_{max}(liquid film) 3670-3130(br), 3071, 3026, 2976, 2924, 2861, 1736, 1726, 1686, 1563, 1518, 1502, 1459, 1369, 1356, 1309, 1271, 1114, 1086, 1052, 981, 932, 846, 813, 757, 697, 663 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.28 (d, J = 7.7 Hz, 3H, CH_3), 1.56-1.73 (m, 13H, $CHCH_2CH$ of Ad groups, $PCHH$), 1.62-1.88 (m, 1H, $PCHH$), 1.90-2.22 (m, 18H, CH of Ad groups, CCH_2 of Ad groups), 2.28-2.53 (m, 1H, $CHHCO$), 2.58-3.02 (m, 2H, $CHCO$, $CHHCO$), 4.27-4.63 (m, 1H, PCH), 5.14 (s, 2H, $PhCH_2O$), 6.50 (d, J = 9.3 Hz, 1H, NH), 7.24-7.42 (m, 5H, aryl); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 19.1 (d, J = 8.9 Hz, CH_3, I), 19.6 (d, J = 9.4 Hz, CH_3, II), 30.8 (CH of Ad in carboxyl group), 31.2 (CH of Ad in phosphinyl group), 31.52 (d, J = 88.8 Hz, PCH_2, I), 32.2 (d, J = 88.8 Hz, PCH_2, II), 32.7 (CH_2CO), 34.0 (d, J = 4.1 Hz, $CHCOOEt$), 35.6 ($CHCH_2CH$ of Ad in carboxyl group), 36.1 ($CHCH_2CH$ of Ad in phosphinyl group), 41.1 ($COOCCH_2$), 44.3 (d, J = 3.4 Hz, $POCCH_2$), 47.3 (d, J = 110.1 Hz, PCH, I), 48.2 (d, J = 110.1 Hz, PCH, II), 66.9 ($PhCH_2O$), 81.6 ($COOC$), 84.2 (d, J = 10.0 Hz, POC), 128.1, 128.4, 128.6, 128.9, 136.3 (aryl), 155.9 (d, J = 6.6 Hz, $OCONH$), 176.0 (d, J = 9.3

Hz, *C*OOAd), 177.9 (d, J = 9.8 Hz, *C*OOH); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 48.01, 48.57, 49.94, 50.27; ESMS *m/z* calcd for $C_{35}H_{49}NO_8P$ $(M+H)^+$ 642.7, found 642.4; Anal. Calcd for $C_{35}H_{48}NO_8P$ (641.7); C, 65.51; H, 7.54; N, 2.18. Found: C, 65.99; H, 7.81; N, 1.93.

(R,R,S,S)-2-methyl-3-((4-(N-(benzyloxycarbonyl)amino)adamantyloxybutyroyl) adamantyloxyphosphinyl) propanoic acid **15b**: Compound **15b** was obtained in 88% yieldas a white solid, m.p. 76-77 °C. TLC R_f(4) 0.31, R_f(5) 0.78; IR ν_{max}(liquid film) 3610-3160(br), 3068, 3019, 2982, 2923, 2856, 1736, 1715, 1687, 1561, 1518, 1500, 1459, 1370, 1357, 1279, 1253, 1188, 1115, 1085, 1051, 994, 934, 845, 814, 759, 698, 666 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.14 (d, J = 6.8 Hz, 3H, C*H*$_3$), 1.44-1.72 (m, 13H, CHC*H*$_2$CH of Ad groups, PC*H*H), 1.88-1.74 (m, 2H, PCHCH*H*$_2$, PCH*H*), 1.92-2.16 (m, 18H, C*H* of Ad groups, CC*H*$_2$ of Ad groups), 2.26-2.49 (m, 4H, C*H*$_2$CO, PCHCH*H*$_2$, PCH*H*), 2.65-2.91 (m, 1H, C*H*CO), 3.78-4.12 (m, 1H, PC*H*), 5.09 (s, 2H, PhC*H*$_2$O), 6.38 (d, J = 10.3 Hz, 1H, N*H*), 6.98-7.41 (m, 5H, aryl); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 19.0 (d, J = 10.0, *C*H$_3$, I), 19.8 (d, J = 13.2 Hz, *C*H$_3$, II), 23.0 (d, J = 3.6 Hz, PCHCH$_2$), 32.3 (*C*H$_2$CO), 31.1 (d, J = 87.2 Hz, PCH$_2$, I), 31.6 (d, J = 87.2 Hz, PCH$_2$, II), 30.6 (*C*H of Ad in carboxyl group), 31.0 (*C*H of Ad in phosphinyl group), 34.5 (d, J = 3.6 Hz, *C*HCOOEt), 35.4 (CH*C*H$_2$CH of Ad in carboxyl group), 36.0 (CH*C*H$_2$CH of Ad in phosphinyl group), 41.1 (COOC*C*H$_2$), 44.1 (d, J = 2.9 Hz, POC*C*H$_2$), 49.4 (d, J = 112.9 Hz, P*C*H, I), 50.2 (d, J = 112.9 Hz, P*C*H, II), 66.9 (PhCH$_2$O), 80.6 (COO*C*), 84.6 (d, J = 10.0, PO*C*), 127.7, 127.9, 128.1, 128.2, 128.3, 136.3 (aryl), 159.6 (d, J = 6.4 Hz, OCONH), 171.9 (d, J = 8.9 Hz, *C*OOAd), 178.2 (d, J = 8.4 Hz, *C*OOH); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 49.04, 49.53, 49.64, 50.31; ESMS *m/z* calcd for $C_{36}H_{51}NO_6P$ $(M+H)^+$ 656.8, found 656.4; Anal. Calcd for $C_{36}H_{50}NO_8P$ (655.8); C, 65.94; H, 7.69; N, 2.14. Found: C, 66.11; H, 7.53; N, 1.80.

(R,R,S,S)-2-methyl-3-((3-(N-(9-fluorenylmethylcarboxyl)amino)adamantyloxypropionyl) adamantyloxyphosphinyl) propanoic acid **17a**: To a solution of methanol (4 ml), containing compound **15a** (0.38 g, 0.6 mmol) and ammonium formate (0.15 g, 2.4 mmol), 10% Pd/C (0.15 g) was added. After 12 min at rt, the catalyst was removed by filtration through celite, and the filtrate was evaporated to dryness. Methylenechloride was added to the residue, and the solution was evaporated to dryness. This procedure was repeated twice. The residue, compound **16a**, was dissolved in 10% Na_2CO_3 (2 ml). The reaction mixture was concentrated in vacuo until half of the volume was removed, and then water (1 ml) and dioxane (1.5 ml) were added. The mixture was ice-cooled and a solution of Fmoc-Cl (0.19 g, 0.72 mmol) in dioxane (1.5 ml) was added dropwise over a period of 1 h. After the solution was stirred for 2 h at 4°C and 4 h at rt, the reaction mixture was diluted with water (15 ml), cooled in an ice-water bath, and acidified to pH 2 with 2 M HCl. The solid product which was precipitated was quickly taken up by diethylether, and the organic layer was rinsed with water, dried over Na_2SO_4, and evaporated to dryness to give the crude product **15a** which was purified by silica column chromatography using chloroform/methanol (9.7:0.3) as eluent. The pure product **15a** (0.23 g, 53%) was obtained as a white solid, m.p. 84-84 °C. TLC R_f(4) 0.33, R_f(5) 0.79; IR ν_{max}(liquid film) 3630-3140(br), 3069, 3020, 2980, 2926, 2862, 1736, 1717, 1684, 1562, 1532, 1505, 1459, 1373, 1355, 1312, 1209, 1109, 1048, 991, 935, 852, 814, 769, 744, 667, 621 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (d, J = 6.5 Hz, 3H, C*H*$_3$), 1.49-1.75 (m, 13H, CHC*H*$_2$CH of Ad groups, PC*H*H), 1.79-2.23 (m, 19H, C*H* of Ad groups, CC*H*$_2$ of Ad groups, PCH*H*), 2.31-2.49 (m, 1H, C*H*HCO), 2.55-3.00 (m, 2H, C*H*CO, CH*H*CO), 4.15-4.54 (m, 4H, CHC*H*$_2$O, C*H*CH$_2$O, PC*H*), 6.36 (d, J = 10.1 Hz, 1H, N*H*), 7.25-7.80 (m, 5H, aryl); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 19.4 (d, J = 10.1 Hz, *C*H$_3$, I), 20.0 (d, J = 12.7 Hz, *C*H$_3$, II), 30.7 (*C*H of Ad in carboxyl group), 31.2 (*C*H of Ad in phosphinyl group), 32.7 (d, J = 88.2 Hz, PCH$_2$, I), 33.1 (d, J = 88.2 Hz, PCH$_2$, II), 33.1 (*C*H$_2$CO), 34.7 (d, J = 4.1 Hz, *C*HCOOH), 35.6 (CH*C*H$_2$CH of Ad in carboxyl group), 36.1 (CH*C*H$_2$CH of Ad in phosphinyl group), 41.2 (COOC*C*H$_2$), 44.3 (d, J = 3.1 Hz, POC*C*H$_2$), 47.0 (*C*HCH$_2$O), 47.8 (d, J = 104.9 Hz, P*C*H, I), 48.3 (d, J = 104.9 Hz, P*C*H, II), 67.6 (CH*C*H$_2$O), 81.8 (COO*C*), 84.8 (d, J = 11.0 Hz, PO*C*), 119.8, 119.9, 125.0, 125.2, 127.0, 127.1, 127.7, 141.1, 143.8 (aryl), 156.2 (d, J = 6.2 Hz, O*C*ONH), 169.3 (d, J = 13.8 Hz, *C*OOAd) 178.0 (d, J = 9.0 Hz, *C*OOH); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 47.73, 48.29, 48.88; ESMS *m/z* calcd for $C_{42}H_{53}NO_8P$ $(M+H)^+$ 730.2, found 729.8; Anal. Calcd for $C_{42}H_{52}NO_8P+0.5H_2O$ (738.8); C, 68.27; H, 7.17; N, 1.89. Found: C, 68.51; H, 7.29; N, 2.12.

(R,R,S,S)-2-methyl-3-((4-(N-(9-fluorenylmethylcarboxyl)amino)adamantyloxybutyroyl)adamantyloxyphosphinyl) propanoic acid **17b**: Compound **17b** was obtained in 65% yield as a white solid, m.p. 90-91 °C. TLC R_f(4) 0.81, R_f(5) 0.36; IR ν_{max}(liquid film)

3650-3120(br), 3073, 3021, 2982, 2923, 2866, 1736, 1719, 1687, 1561, 1535, 1509, 1459, 1370, 1355, 1279, 1208, 1115, 1042, 993, 934, 855, 815, 763, 743, 667, 621 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.23 (d, J = 7.44 Hz, 3H, CH_3), 1.48-1.74 (m, 13H, $CHCH_2CH$ of Ad groups, $PCHH$), 1.92-1.75 (m, 2H, $PCHCHH_2$, $PCHH$), 1.97-2.18 (m, 18H, CH of Ad groups, CCH_2 of Ad groups), 2.27-2.56 (m, 4H, CH_2CO, $PCHCHH_2$, $PCHH$), 2.72-2.99 (m, 1H, $CHCO$), 3.88-4.12 (m, 1H, PCH), 4.16-4.46 (m, 3H, $CHCH_2O$, $CHCH_2O$), 5.99 (d, J = 9.8 Hz, 1H, NH), 7.23-7.79 (m, 5H, aryl); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 19.1 (d, J = 9.3 Hz, CH_3, I), 19.9 (d, J = 19.9 Hz, CH_3, II), 29.6 (d, J = 5.0 Hz, $PCHCH_2$), 30.8 (CH of Ad in carboxyl group), 30.8 (d, J = 83.8 Hz, PCH_2, I), 31.4 (CH of Ad in phosphinyl group), 31.4 (d, J = 83.8 Hz, PCH_2, II), 32.1 (CH_2CO), 34.4 (d, J = 4.6 Hz, $CHCOOH$), 35.4 ($CHCH_2CH$ of Ad in carboxyl group), 35.9 ($CHCH_2CH$ of Ad in phosphinyl group), 41.2 ($COOCCH_2$), 44.2 (d, J = 2.9 Hz, $POCCH_2$), 46.9 ($CHCH_2O$), 49.2 (d, J = 108.0 Hz, PCH, I), 50.0 (d, J = 108.0 Hz, PCH, II), 67.4 ($CHCH_2O$), 80.5 ($COOC$), 84.7 (d, J = 10.3 Hz, POC), 119.7, 124.9, 125.3, 127.0, 127.5, 141.1, 143.7 (aryl), 156.8 (d, J = 6.7 Hz, OCONH), 171.8 (d, J = 5.7 Hz, $COOAd$), 178.2 (d, J = 8.3 Hz, $COOH$); ^{31}P-NMR (81 MHz, $CDCl_3$) δ 49.07, 49.53, 49.46, 50.33; ESMS m/z calcd for $C_{43}H_{55}NO_8P$ $(M+H)^+$ 744.9, found 744.6; Anal. Calcd for $C_{43}H_{54}NO_8P$ (743.9); C, 69.43; H, 7.32; N, 1.88. Found: C, 69.41; H, 7.71; N, 1.85.

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