The synthesis of phosphonic acids derived from homocysteine *via* transesterification reactions

Jan Pícha, Miloš Buděšínský, Pavel Fiedler and Jiří Jiráček*

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, v.v.i., Flemingovo nám. 2, 166 10 Prague 6, Czech Republic
E-mail: jiracek@uochb.cas.cz

Dedicated to Professor Paweł Kafarski to honor the achievements within his career

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Abstract

An efficient methodology for the synthesis of S-substituted derivatives of phosphonohomocysteine has been developed. It starts from the corresponding thiols and is based on a synthetic sequence consisting of (i) the Kabachnik-Fields reaction, (ii) the transesterification of the diphenylphosphoryl moiety and (iii) the acidic deprotection of the phosphoryl and amino groups. The proposed synthetic procedures describing syntheses of phosphonohomocysteine precursors with di-*tert*-butylphosphoryl and *tert*-butyloxycarbonylamino groups could be useful for the preparation of novel *S*-substituted phosphonohomocysteine derivatives.

Keywords: Aminophosphonic acid, phosphonohomocysteine, protecting groups, acidolabile groups, transesterification

Introduction

In the course of our search for new inhibitors of betaine-homocysteine *S*-methyltransferases (BHMT[1-3] and BHMT 2[4]) we aimed to synthesize phosphonoanalogues of homocystine and homocysteine. Phosphonic[5] and phosphinic[6] amino acids are well known inhibitors of different metalloenzymes.

The previously published preparation[7] of phosphonohomocystine **3** (Scheme 1) consists of the synthesis of a phosphonohomocysteine intermediate bearing an acidolabile *tert*-butyl *S*-protecting group followed by the acidic hydrolysis of this group and a mild oxidation of the resulting free thiol group. The available literature[7-9] offers several methods for the preparation of phosphonohomocysteine-derived analogues with different *S*-linked unbranched alkyl chains. However, there is no information concerning less stable *S*-linked groups.

The aim of this study was to find the most suitable protecting groups for the phosphoryl and amino moieties of phosphonohomocysteine with regard to the lability of the RS- moiety under acidic conditions. This strategy could facilitate the preparation of phosphonohomocysteine derivatives with different alkyl or aryl substituents on the sulfur atom.

Therefore, we introduced three different hydrocarbon *S*-substituents (Ph, *tert*-butyl, Bn) to create four series of differently protected precursors **2a-c**, **7a-c**, **8a-c** and **9a-c** and examined the stability of their respective C-S bonds under various conditions (Scheme 2).

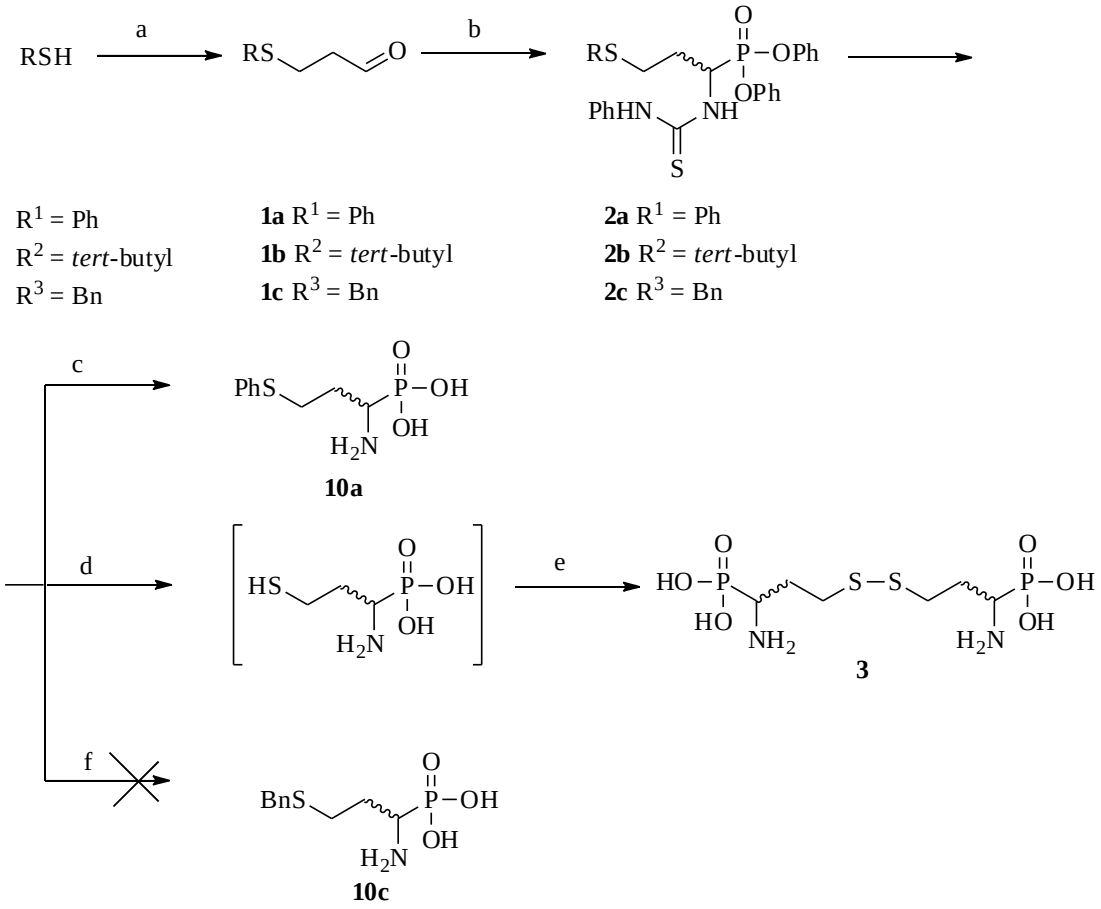
Although at first glance the synthesis of this type of compounds appears trivial, it may be complicated because some important methods used for the synthesis aliphatic aminophosphonic acids are prohibited in the case of sulfur. For example, the use of the catalytic hydrogenation is excluded due to poisoning effect of sulfur, and sulfides tend to be oxidized by some agents to sulfoxides or sulfones.

Our synthetic approach is based on a three-step sequence. The first step consists of four variants of the three-component Kabachnik-Fields reaction:[10] the condensation of (a) aldehydes, benzylcarbamate and triphenylphosphite in glacial acetic acid;[11,12] (b) aldehydes, *N*-phenyl thiourea and triphenylphosphite in glacial acetic acid;[7,13,14] (c) aldehydes, *tert*-butyl carbamate and triphenylphosphite in DCM in the presence of $TiCl_4$;[15] or (d) aldehydes, benzylcarbamate and dimethyl phosphite in acetyl chloride.[16] The second step involves transesterification of the reaction products using potassium tert-butanolate for (a) and (c) or with sodium methanolate for (b) and (d). The third and final synthetic step is the removal of the protecting groups of the phosphoryl and amino moieties.

Results and Discussion

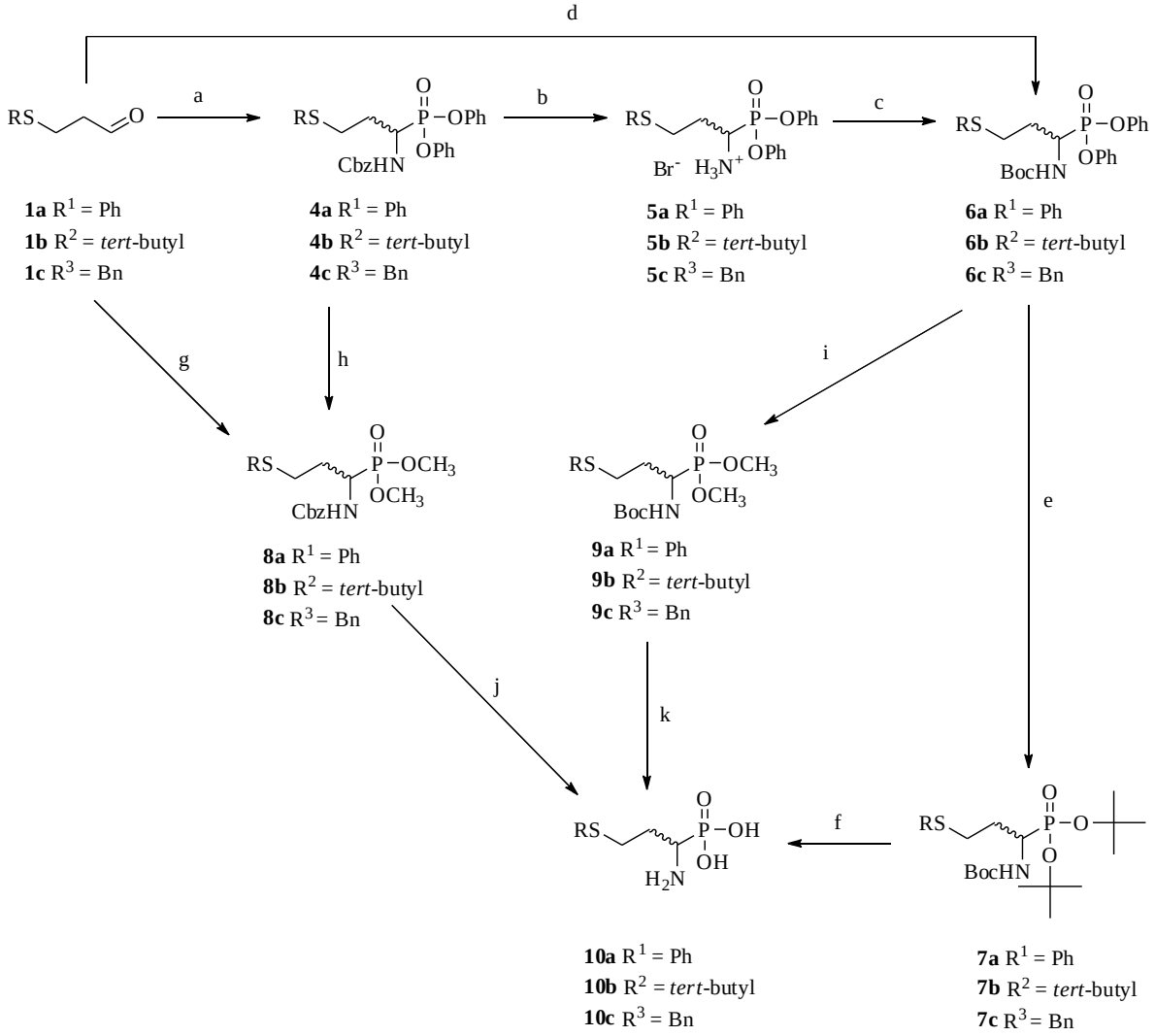
Our initial effort was focused on the synthesis of phosphonic acids starting from aldehydes through 1-phenylthioureido phosphonate intermediates **2**.[7-9] Thus, the Michael addition of thiophenol, tert-butylmercaptan and benzylmercaptan to acrolein afforded the corresponding aldehydes **1a-c** in high yield, and the subsequent condensation with *N*-phenylthiourea and triphenylphosphine in glacial acetic acid gave phosphonate precursors **2a-c** (Scheme 1).

Heating **2a** in concentrated hydrochloric acid furnished the expected free 1-aminophosphonic acid **10a**. As stated in the Introduction, the reflux of analogue **2b** bearing a *tert*-butyl moiety generated the crude phosphonohomocysteine,[13] which, after oxidation with iodine,[7] gave the required phosphonohomocystine **3**. In contrast to Kudzin´s and Stec´s work,[7] the attempt to prepare acid **10c** from **2c** under these harsh conditions led, in our hands, only to a mixture of unknown products.



Scheme 1. Reactions, conditions and yields: (a) acrolein, TEA, dichloromethane, 0°C for 1 h, then rt overnight, R^1 = Ph (79%) for **1a**, R^2 = *tert*-butyl (75%) for **1b**, R^3 = Bn (81%) for **1c**; (b) *N*-phenyl thiourea, triphenyl phosphite, AcOH, 80 °C, 1 h, R^1 = Ph (54%) for **2a**, R^2 = *tert*-butyl (45%) for **2b**, R^3 = Bn (55%) for **2c**; (c) 35% HCl and AcOH, reflux for 12 h, then 1,2-epoxypropane, methanol, (67%) starting from **2a**; (d) 48% HBr and AcOH, reflux 14 h; (e) I_2, methanol and then 1,2-epoxypropane, methanol (65% for two steps starting from **2b**); (f) starting from **2c** under the same conditions as for (c).

The observed lability of the $(CH_3)_3CS$ and BnS moieties during the deprotection of compounds **2b** and **2c** led us to modify the protecting group design to allow the deprotection of the phosphoryl and amino moieties under milder conditions. The diphenyl ester was replaced with the dimethyl or di-*tert*-butyl ester, and the 1-phenylthioureido moiety was changed to the Cbz or Boc moiety. The methodology for the preparation of precursors **7a-c**, **8a-c** and **9a-c** is outlined in Scheme 2.



Scheme 2. Reactions, conditions and yields: (a) benzyl carbamate, triphenylphosphite, AcOH, 80°C, 1h, R^1 = Ph (59%) for **4a**, R^2 = *tert*-butyl (57%) for **4b**, R^3 = Bn (55%) for **4c**; (b) 35% HBr/AcOH, R^1 = Ph (82%) for **5a**, R^2 = *tert*-butyl (78%) for **5b**, R^3 = Bn (75%) for **5c**; (c) Boc_2O, TEA, dichloromethane, 0°C for 1 h, then rt overnight, R^1 = Ph (74%) for **6a**, R^2 = *tert*-butyl (65%) for **6b**, R^3 = Bn (75%) for **6c**; (d) *tert*-butyl carbamate, triphenyl phosphite, $TiCl_4$, dichloromethane, rt, overnight, R_1 = Ph (52%) for **6a**, R^2 = *tert*-butyl (54%) for **6b**, R^3 = Bn (49%) for **6c**; (e) potassium *tert*-butoxide, *tert*-butanol and dioxane, rt, overnight, R^1 = Ph (53%) for **7a**, R^2 = *tert*-butyl (59%) for **7b**, R^3 = Bn (60%) for **7c**; (f) TFA, dimethyl sulfide, DCM, water, rt, overnight, R^1 = Ph (73%) for **10a**, R^2 = *tert*-butyl (68%) for **10b**, R^3 = Bn (75%) for **10c**; (g) benzyl carbamate, dimethyl phosphite, acetyl chloride 0°C for 1 h, then rt overnight, R^1 = Ph (31%) for **8a**, R^2 = *tert*-butyl (45%) for **8b**, R^3 = Bn (40%) for **8c**; (h) sodium methoxide, methanol and dioxane, rt overnight, R^1 = Ph (71%) for **8a**, R^2 = *tert*-butyl (66%) for **8b**, R^3 = Bn (65%) for **8c**; (i) sodium methoxide, methanol and dioxane, rt, overnight, R^1 = Ph (55%) for **9a**, R^2 = *tert*-butyl (64%) for **9b**, R^3 = Bn (57%) for **9c**; (j) 35% HBr/AcOH rt overnight then 1,2-

epoxypropane, methanol, R^1 = Ph (69%) for **10a**, R^2 = *tert*-butyl (trace) for **10b**, R^3 = Bn (62%) for **10c**; (k) TMSBr, acetonitrile, rt for 48 hours, then TFA, dimethyl sulfide, DCM, water, rt, overnight, R^1 = Ph (50%) for **10a**, R^2 = *tert*-butyl (51%) for **10b**, R^3 = Bn (55%) for **10c**.

The Birum-Oleksyszyn condensation[11,12] of aldehydes **1a-c** with triphenyl phosphite and benzyl carbamate afforded Z-protected diphenyl phosphonates **4a-c**, enabling access to the first precursors, dimethylesters **8a-c**, *via* transesterification using sodium methanolate. Cleavage of the benzyloxycarbonyl group from compounds **4a-c** was achieved by treatment with hydrobromic acid in glacial acetic acid to yield the corresponding salts **5a-c**, which were subsequently converted to Boc-protected phosphonates **6a-c** by reaction with triethylamine and Boc anhydride. The three-step synthetic sequence converting compounds **1a-c** into **6a-c** was successfully accomplished by the one-pot reaction of the aldehydes (**1a-c**) with triphenyl phosphite and *tert*-butyl carbamate in the presence of titanium tetrachloride as a Lewis acid.[15] The subsequent transesterification of diphenyl esters **6a-c** was accomplished by using either potassium *tert*-butanoate or sodium methanolate to afford precursors **7a-c** and **9a-c**, respectively. An alternative and straightforward route for the preparation of compounds **8a-8c** was the reaction of benzyl carbamate and dimethyl phosphite with aldehydes **1a-1c**, respectively, in acetyl chloride.[16]

The final deprotection step, the treatment of precursors **8a** and **8c** with 35% HBr/AcOH, furnished **10a** and **10c**, respectively. In the case of compound **8b**, the C-S bond underwent fission and only traces of **10b** were isolated from the reaction mixture. We believe that the stability of the $(CH_3)_3CS$ moiety depends on the temperature during the workup. While debenzyloxycarbonylation of **4b** in 35% HBr/AcOH proceeded smoothly at room temperature and gave a precipitate of **5b** in 78% yield, the reaction from **8b** to **10b** required evaporation of the acids using a rotary evaporator at 60°C and caused the decomposition of the compound scaffold.

The most promising precursors **7a-c** were treated with an acidic cleavage cocktail containing dimethyl sulfide (DMS) as a scavenger and afforded target compounds **10a-c** in yields of approximately 70% after RP-HPLC purification. Alternatively, the two-step deprotection of **9a-c** represents another possibility for the synthesis of **10a-c**. The methyl esters were preferentially demethylated using TMSBr followed by acidic hydrolysis to removed the Boc group. Decreased yields (approximately 50%) were achieved in this case.

Conclusions

From the literature[7-9] and from our experimental results described above, we can deduce the following conclusions: (i) derivatives of phosphonohomocysteine with *S*-linked unbranched alkyl and phenyl substituents are inert towards hot and aqueous strong acids; (ii) BnS derivatives are stable in hydrobromic acid but only under non-aqueous conditions; (iii) the acidolability of

the $(CH_3)_3CS$ moiety in trifluoroacetic acid is significantly reduced; and (iv) the observed order in the stability of the three substituents studied for use on the sulfur atom of phosphonohomocysteine in strong acid solutions is Ph > Bn > *tert*-butyl. We hope that these proposed synthetic procedures describing the syntheses of phosphonohomocysteine precursors with di-*tert*-butylphosphoryl and *tert*-butyloxycarbonylamino groups might be helpful and might serve for the preparation of novel *S*-substituted phosphonohomocysteines.

Experimental Section

General Procedures. The reagents and solvents (Sigma-Aldrich-Fluka) used in this study were of analytical grade. The TLCs were performed on silica gel-coated aluminum plates (Fluka) using the following systems (v/v): chloroform-ethanol 99/1 (S1); chloroform-ethanol 98/2 (S2); chloroform-ethanol 95/5 (S3); chloroform-ethanol 90/10 (S4); isopropyl alcohol - concentrated aqueous ammonia - water 7/1/2 (S5); toluene-ethyl acetate 80/20 (S6). The compounds were visualized by exposure to UV light at 254 nm, by ninhydrin application (amines show a dark blue color), by 1 % $KMnO_4$ application (sulfides show a yellow color) and by application of a 1% (v/v) ethanolic solution of 4-(4-nitrobenzyl)pyridine followed by heating and exposure to gaseous ammonia (the diesters of phosphonic acids show a blue color). Flash chromatography purifications were carried out on silica gel (40-63 μm, Fluka). Preparative RP-HPLC chromatography was carried out using a C18 Luna column (Phenomenex, 250 x 21.2 mm, 10 μm) at a flow rate 9 ml/min. The solvents used were the following: solvent A - 0.1% TFA in water; and solvent B - 80% CH_3CN, 0.1% TFA in water. The following gradients were used: G1: t = 0 min (90% A, 10% B), t = 30 min (30% A, 70% B), t = 31 min (90% A, 10% B); G2: t = 0 min (59% A, 41% B), t = 10 min (59% A, 41% B), t = 30 min (54% A, 46% B), t = 31 min (100% B), t = 34 min (59% A, 41% B). Analytical RP-HPLC chromatography was carried out at a flow rate of 1 ml/min using a C18 Nucleosil column (250 x 4 mm, 5 μm) from Watrex (Praha, CZ) using the same gradients and solvents. The eluted compounds were detected at 218 nm. Melting points were determined on a Boetius block and are uncorrected. ^1H and ^{13}C NMR spectra were measured on a Bruker AVANCE-600 spectrometer (^1H at 600.13 MHz, ^{13}C at 150.9 MHz) in $CDCl_3$, DMSO-d_6, CD_3OD or D_2O solution at 300 K. The 2D-H,H-COSY, 2D-H,C-HSQC and 2D-H,C-HMBC spectra were recorded and used for the structural assignments of proton and carbon signals. IR spectra were recorded on a Bruker IFS 55 Equinox apparatus. HRMS spectra were obtained on a FTMS mass spectrometer LTQ-orbitrap XL (Thermo Fisher, Bremen, Germany) in electrospray ionization mode or, in the case of HRMS (EI) spectra, on a GCT Premier (Waters). The purities of the target compounds were confirmed by elemental analysis (C, H, N), and the experimental values differed from the calculated values by less than 0.4%.

3-(Phenylsulfanyl)propanal (**1a**)**.** Thiophenol (27.5 g; 0.25 mol) in 100 ml dichlormethane was added dropwise over 30 minutes to an ice-cooled and stirred solution of acrolein (14 g; 0.25 mol) and 10 ml of triethylamine in 400 ml dichlormethane. The ice bath was removed and stirring continued overnight at rt. All volatile materials were evaporated *in vacuo* and yellow residue was distilled under reduced pressure. Yield 32.7 g (79%). Colorless liquid, bp 91-95 °C/0.6 - 0.8 torr (lit.[17] 94-99 °C/0.7 torr). R_f = 0.64 (S2). ^{1}H NMR (500 MHz; $CDCl_3$): δ_H 2.77 (2H, td, $^3J_{HH}$ = 7.1 and 1.2 Hz, CH_2-CO), 3.19 (2H, t, $^3J_{HH}$ = 7.1 Hz, CH_2-S), 7.22 (1H$_{arom}$, m, 1CH), 7.31 (2H$_{arom}$, m, 2CH), 7.36 (2H$_{arom}$, m, 2CH), 9.77 (1H, t, $^3J_{HH}$ = 1.2 Hz, CH=O). ^{13}C NMR (125.8 MHz; $CDCl_3$): δ_C 26.39 (1C, S-CH_2), 43.23 (1C, $\underline{C}H_2$-CO), 126.66, 129.09(2), 130.02(2) and 135.04 (6C$_{arom}$, C_6H_5), 200.20 (1C, CH=O). IR (film, ν_{max}, cm^{-1}) 1724 vs (C=O), 1584 m, 1482 s, 1440 s, 692 s (ring). HRMS (EI) calc for $C_9H_{10}OS$ $[M]^+$ 166.0452; found: 166.0451.

3-(*tert*-Butylsulfanyl)propanal (1b). Aldehyde **1b** was prepared in the same fashion as compound **1a** by the reaction of acrolein (16.8 g; 0.3 mol), 2-methyl-2-propanethiol (27.1 g; 0.3 mol) and 10 ml TEA. Yield 32.7 g (75%). Colorless liquid, bp 65-67 °C/7 torr. R_f = 0.76 (S2). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 1.34 (9H, s, $C(CH_3)_3$), 2.72 (2H, m, CH_2-CO), 2.81 (2H, m, CH_2-S), 9.78 (1H, t, $^3J_{HH}$ = 1.3 Hz, CH=O). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 20.64 (1C, S-CH_2), 30.75 (3C, C($\underline{C}H_3)_3$), 42.47 (1C, -$\underline{C}(CH_3)_3$), 43.61 (1C, $\underline{C}H_2$-CO), 200.69 (1C, CH=O). IR (film, ν_{max}, cm^{-1}) 1726 vs (C=O), 1365 s (CH_3), 1165 s ($C(CH_3)_3$). HRMS (EI) calc for $C_7H_{14}OS$ $[M]^+$ 146.0765; found: 146.0768.

3-(Benzylsulfanyl)propanal (1c). Aldehyde **1c** was prepared in the same fashion as compound **1a** by the reaction of acrolein (16.8 g; 0.3 mol), benzylmercaptan (37.2 g; 0.3 mol) and 10 ml of TEA. Yield 44 g (81%). Colorless liquid, bp 94-96 °C/0.4 torr (lit.[18] 96-98 °C/0.3 torr). R_f = 0.76 (S2). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 2.65 (2H, m, CH_2-CO), 2.69 (2H, s, CH_2-S), 3.73 (2H, s, CH_2-S), 7.25 (1H$_{arom}$, m, 1CH), 7.31 (4H$_{arom}$, m, 4CH), 9.70 (1H, t, $^3J_{HH}$ = 1.3 Hz, CH=O). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 23.56 (1C, S-CH_2), 36.45 (1C, S-CH_2), 43.26 (1C, $\underline{C}H_2$-CO), 127.12, 128.55(2), 128.77(2) and 137.89 (6C$_{arom}$, C_6H_5), 200.48 (1C, CH=O). IR ($CHCl_3$, ν_{max}, cm^{-1}) 1724 vs (C=O), 1495 m, 1454 m, 703 s (ring). HRMS (EI) calc for $C_{10}H_{12}OS$ $[M]^+$ 180.0609; found: 180.0617.

Diphenyl [(*R*,*S*)-1-(3-phenylthioureido)-3-(phenylsulfanyl)propyl]phosphonate (2a). Compound **2a** was prepared according to a modified protocol published by Kudzin and Stec[7]. A solution of triphenyl phosphite (13.7 g; 44 mmol), aldehyde **1a** (8 g; 48.4 mmol) and *N*-phenyl thiourea (6.7 g; 44 mmol) in 50 ml of glacial acetic acid was heated for 1 hour at 80°C. The acetic acid was evaporated *in vacuo*, and the residue was dissolved in 100 ml of methanol. The solution was left to stand overnight at -20°C and afforded white crystals, which were removed by filtration and washed with petroleum ether. The pure product was obtained by recrystallization from a mixture of chloroform-methanol. Yield 14 g (59%). White solid, mp 116-119 °C. R_f = 0.73 (S2). ^{1}H NMR (600 MHz; d_6DMSO): δ_H 2.14 (1H, m, C-C$\underline{Ha}$Hb-C), 2.23 (1H, m, C-CHa$\underline{Hb}$-C), 3.06 (1H, ddd, $^2J_{HH}$ = 13.6, $^3J_{HH}$ = 8.2 and 7.3 Hz, S-C$\underline{Ha}$Hb), 3.18 (1H, ddd, $^2J_{HH}$ = 13.6, $^3J_{HH}$ = 8.5 and 4.8 Hz, S-C$\underline{Ha}$Hb), 5.85 (1H, dtd, $^3J_{HP}$ = 17.0, $^3J_{HH}$ = 10.2, 9.8 and 3.6 Hz, N-CH-P), 7.14 (1H$_{arom}$, m, 1CH), 7.17 (4H$_{arom}$, m, 4CH), 7.21 (1H$_{arom}$, m, 1CH), 7.23 (2H$_{arom}$, m,

2CH), 7.33 (2H$_{arom}$, m, 2CH), 7.34 (2H$_{arom}$, m, 2CH), 7.36 (2H$_{arom}$, m, 2CH), 7.39 (4H$_{arom}$, m, 4CH), 7.48 (2H$_{arom}$, m, 2CH), 8.36 (1H, d, $^3J_{HH}$ = 9.8, NH), 9.80 (1H, s, NH). ^{13}C NMR (150.9 MHz; d$_6$DMSO): δ_C 28.83 (1C, d, $^3J_{CP}$ = 15.6 Hz, S-CH$_2$), 30.01 (1C, d, $^2J_{CP}$ = 4.3 Hz, C-CH$_2$-C), 50.02 (1C, d, $^1J_{CP}$ = 156.6 Hz, N-CH-P), 120.68 (2C, d, $^3J_{CP}$ = 3.8 Hz, *ortho*-CH$_{arom}$), 120.78 (2C, d, $^3J_{CP}$ = 3.8 Hz, *ortho*-CH$_{arom}$), 123.32(2), 124.75, 125.67, 125.72, 126.14, 128.61(2), 128.81(2), 129.39(2), 130.14(2) and 130.20(2) (16C, CH$_{arom}$), 135.68 (1C, *ipso*-C$_{arom}$), 139.36 (1C, *ipso*-C$_{arom}$), 149.82 (d, $^2J_{CP}$ = 9.5 Hz, *ipso*-C$_{arom}$), 150.07 (d, $^2J_{CP}$ = 9.6 Hz, *ipso*-C$_{arom}$), 181.89 (1C, N-CS-N). IR (KBr, ν_{max}, cm^{-1}) 3330 m (NH); 1538 vs, 1355 m, 1326 s (HNC=S); 1230 vs (P=O); 1210 vs, 1188 vs, 1163 s (Ph-OP); 954 vs (P-OPh); 1589 m, 1489 vs, 1025 m, 1008 m, 760 s, 690 s (ring). HRMS (ESI) calc for $C_{28}H_{28}O_3N_2PS_2$ $[M+1]^+$ 535.12735; found: 535.12768.

Diphenyl [(*R*,*S*)-1-(3-phenylthioureido)-3-(*tert*-butylsulfanyl)propyl]phosphonate (2b). Phosphonate **2b** was prepared in the same manner as compound **2a** by the reaction of triphenyl phosphite (9.3 g; 30 mmol), aldehyde **1b** (4.8 g; 33 mmol) and *N*-phenyl thiourea (4.6 g; 30 mmol). Yield 7 g (45%). White solid, mp 134-135 °C (lit.[7] 134-135°C). R_f = 0.73 (S2). ^{1}H NMR (600 MHz; d$_6$DMSO): δ_H 1.26 (9H, s, C(CH$_3$)$_3$), 2.09 (1H, m, C-CHaHb-C), 2.19 (1H, m, C-CHaHb-C), 2.66 (1H, ddd, $^2J_{HH}$ = 12.8, $^3J_{HH}$ = 9.1 and 6.9 Hz, S-CHaHb), 2.71 (1H, ddd, $^2J_{HH}$ = 12.8, $^3J_{HH}$ = 9.2 and 5.3 Hz, S-CHaHb), 5.76 (1H, dtd, $^3J_{HP}$ = 17.0, $^3J_{HH}$ = 9.7, 9.7 and 4.0 Hz, N-CH-P), 7.14 (1H$_{arom}$, m, 1CH), 7.20 (2H$_{arom}$, m, 2CH), 7.24 (4H$_{arom}$, m, 4CH), 7.33 (2H$_{arom}$, m, 2CH), 7.41 (4H$_{arom}$, m, 4CH), 7.48 (2H$_{arom}$, m, 2CH), 8.33 (1H, d, $^3J_{HH}$ = 9.7, NH), 9.77 (1H, s, NH). ^{13}C NMR (150.9 MHz; d$_6$DMSO): δ_C 24.35 (1C, d, $^3J_{CP}$ = 14.5 Hz, S-CH$_2$), 30.98 (3C, C(CH$_3$)$_3$), 31.42 (1C, d, $^2J_{CP}$ = 4.0 Hz, C-CH$_2$-C), 42.38 (1C, C(CH$_3$)$_3$), 50.44 (1C, d, $^1J_{CP}$ = 156.0 Hz, N-CH-P), 120.68 (2C, d, $^3J_{CP}$ = 3.7 Hz, *ortho*-CH$_{arom}$), 120.82 (2C, d, $^3J_{CP}$ = 3.8 Hz, *ortho*-CH$_{arom}$), 123.25(2), 124.69, 125.63, 125.72, 128.78(2), 130.12(2) and 130.21(2) (11C, CH$_{arom}$), 139.41 (1C, *ipso*-C$_{arom}$), 149.90 (1C, d, $^2J_{CP}$ = 9.5 Hz, *ipso*-C$_{arom}$), 150.13 (1C, d, $^2J_{CP}$ = 9.6 Hz, *ipso*-C$_{arom}$), 181.81 (1C, N-CS-N). IR (KBr, ν_{max}, cm^{-1}) 3317 s (NH); 1537 vs, 1348 s, 1321 s (HNC=S); 1227 vs (P=O); 1211 vs, 1186 vs, 1163 s (Ph-OP); 958 vs (P-OPh); 1591 s, 1489 vs, 1453 m, 1026 m, 1008 m, 763 s, 689 s (ring); 2961 m (CH$_3$). HRMS (ESI) calc for $C_{26}H_{32}O_3N_2PS_2$ $[M+1]^+$ 515.15865; found: 515.15853.

Diphenyl [(*R*,*S*)-1-(3-phenylthioureido)-3-(benzylsulfanyl)propyl]phosphonate (2c). Phosphonate **2c** was prepared in the same manner as compound **2a** by the reaction of triphenyl phosphite (9.3 g; 30 mmol), aldehyde **1c** (5.4 g; 33 mmol) and *N*-phenyl thiourea (4.6 g; 30 mmol). Yield 9 g (55%). White solid, mp 98-99 °C (lit.[7] 99-100 °C). R_f = 0.37 (S1). ^{1}H NMR (600 MHz; CDCl$_3$): δ_H 1.84 (1H, m, C-CHaHb-C), 2.20 (1H, m, C-CHaHb-C), 2.58 (2H, bt, $^3J_{HH}$ = 7.5 Hz, S-CH$_2$), 3.67 (1H, d, $^2J_{HH}$ = 13.5, S-CHaHb), 3.70 (1H, d, $^2J_{HH}$ = 13.5, S-CHaHb), 5.86 (1H, m, N-CH-P), 7.03 (2H$_{arom}$, m, 2CH), 7.06 (1H, b, NH), 7.10 (1H$_{arom}$, m, 1CH), 7.12 (2H$_{arom}$, m, 2CH), 7.14 (2H$_{arom}$, m, 2CH), 7.16 (1H$_{arom}$, m, 1CH), 7.19 (1H$_{arom}$, m, 1CH), 7.20 (2H$_{arom}$, m, 2CH), 7.22 (3H$_{arom}$, m, 1CH), 7.26 (4H$_{arom}$, m, 4CH), 7.31 (2H$_{arom}$, m, 2CH), 8.52 (1H, b, NH). ^{13}C NMR (150.9 MHz; CDCl$_3$): δ_C 27.34 (1C, d, $^3J_{CP}$ = 14.5 Hz, S-CH$_2$), 30.47 (1C, C-CH$_2$-C), 36.26 (1C, S-CH$_2$), 50.42 (1C, d, $^1J_{CP}$ = 156.1 Hz, N-CH-P), 120.41 (2C, d, $^3J_{CP}$ = 3.9 Hz, *ortho*-

CH_{arom}), 120.57 (2C, d, $^3J_{CP}$ = 4.1 Hz, *ortho*-CH_{arom}), 124.49(2), 124.64, 125.83, 126.35, 126.97, 128.47(3), 128.84(2), 129.27(2), 129.74 and 129.98(2) (16C, CH_{arom}), 138.02 (1C, *ipso*-C_{arom}), 149.40 (1C, d, $^2J_{CP}$ = 10.5 Hz, *ipso*-C_{arom}), 150.08 (1C, d, $^2J_{CP}$ = 10.1 Hz, *ipso*-C_{arom}), 181.88 (1C, N-CS-N). IR (KBr, ν_{max}, cm^{-1}) 3310 s (NH); 1537 vs, 1347 s, 1320 s (HNC=S); 1226 vs (P=O); 1207 vs, 1186 vs, 1162 s (Ph-OP); 958 vs (P-OPh); 1590 s, 1489 vs, 1452 m, 1025 m, 1009 m, 768 s, 689 s (ring). HRMS (ESI) calc for $C_{29}H_{30}O_3N_2PS_2$ $[M+1]^+$ 549.1430; found: 549.1426.

1-(*R*,*S*), 8-(*R*,*S*)-Diamino-4,5-dithiaoctane-1,8-diphosphonic acid (3). Phosphonohomocystine was prepared by acid hydrolysis of **2b** (6 g; 11.7 mmol) as described earlier by Kudzin and Stec[7]. Yield 1.3 g (65%). White solid, mp 267-269 °C (lit.[7] 271-273 °C). R_f = 0.05 (S4). Calcd. for $C_6H_{18}N_2O_6P_2S_2$ (340.3) C 21.18 %, H 5.34%, N 8.23 %. Found: C 21. 27%, H 5.33%, N 8.01%. ^{1}H NMR (600 MHz; D_2O + NaOD): (signals of 2 diatereoisomers overlapped) δ_H 2.07 (1H, m, C-C<u>Ha</u>Hb-C), 2.32 (1H, m, C-CHa<u>Hb</u>-C), 2.87 (1H, m, S-C<u>Ha</u>Hb), 2.99 (1H, m, S-CHa<u>Hb</u>), 3.16 (1H, m, N-CH-P), 7.03 (2H, m, 2CH). ^{13}C NMR (150.9 MHz; D_2O + NaOD): (signals of 2 diatereoisomers ~1:1) δ_C 31.63 and 31.65 (1C, C-<u>C</u>H_2-C), 37.41 and 37.55 (1C, d, $^3J_{CP}$ = 10.0 Hz, S-CH_2), 51.86 and 51.93 (1C, d, $^1J_{CP}$ = 132.4 Hz, N-CH-P). IR (KBr, ν_{max}, cm^{-1}) 2920 vbr, 1628 s, 1535 s (NH_3^+); 1171 vs, 1035 vs (PO_2^-), 928 s (POH). HRMS (ESI) calc for $C_6H_{17}O_6N_2P_2S_2$ $[M-1]^+$ 339.00087; found: 339.00081.

Diphenyl [(*R*,*S*)-1-(benzyloxycarbonylamino)-3-(phenylsulfanyl)propyl]phosphonate (4a). Compound **4a** was prepared according to the procedure described by Vo-Quang *et al*.[19] Benzyl carbamate (20.6 g; 0.14 mol), triphenylphosphite (43.4 g; 0.14 mol) and 3-(phenylsulfanyl)propanal **1a** (24.4 g; 0.15 mol) were stirred for 1.5 hours at 80°C in glacial acetic acid (100 ml). The acetic acid was evaporated *in vacuo*, and the residue was dissolved in 200 ml of methanol. The solution was left to stand overnight at -20°C to afford white crystals, which were removed by filtration and washed with petroleum ether. The pure product was obtained by recrystallisation from a mixture of chloroform-methanol. Yield 43 g (59%). White solid, mp 106-107 °C (lit.[19] 106-107 °C). R_f = 0.27 (S1). ^{1}H NMR (500 MHz; $CDCl_3$): δ_H 2.05 (1H, m, C-C<u>Ha</u>Hb-C), 2.31 (1H, m, C-CHa<u>Hb</u>-C), 2.99 (1H, ddd, $^2J_{HH}$ = 13.2, $^3J_{HH}$ = 8.7 and 7.2 Hz, S-C<u>Ha</u>Hb), 3.11 (1H, ddd, $^2J_{HH}$ = 13.2, $^3J_{HH}$ = 8.9 and 4.8 Hz, S-C<u>Ha</u>Hb), 4.68 (1H, dtd, $^3J_{HP}$ = 17.9, $^3J_{HH}$ = 10.6, 10.2 and 3.8 Hz, N-CH-P), 5.11 (1H, d, $^2J_{HH}$ = 12.2 Hz, C<u>Ha</u>Hb-O), 5.14 (1H, d, $^2J_{HH}$ = 12.2 Hz, CHa<u>Hb</u>-O), 5.34 (1H, bd, $^3J_{HH}$ = 10.2 Hz, NH), 7.06-7.34 (20H_{arom}, m, 20CH). ^{13}C NMR (125.8 MHz; $CDCl_3$): δ_C 30.04 (1C, d, $^2J_{CP}$ = 6.0 Hz, C-<u>C</u>H_2-C), 30.24 (1C, d, $^3J_{CP}$ = 18.9 Hz, S-CH_2), 47.62 (1C, d, $^1J_{CP}$ = 198.4 Hz, N-CH-P), 67.45 (1C, CH_2-O), 120.33 (2C, d, $^3J_{CP}$ = 5.4 Hz, *ortho*-CH_{arom}), 120.47 (2C, d, $^3J_{CP}$ = 5.4 Hz, *ortho*-CH_{arom}), 125.33, 125.45, 126.47, 128.17(2), 128.30(2), 128.55(2), 129.02(2), 129.71, 129.82(2) and 130.01(2) (16C, CH_{arom}), 135.98 and 135.23 (2C, C_{arom}), 149.89 (1C, d, $^2J_{CP}$ = 12.1 Hz, *ipso*-C_{arom}), 150.13 (1C, d, $^3J_{CP}$ = 12.2 Hz, *ipso*-C_{arom}), 155.86 (1C, d, $^3J_{CP}$ = 8.2 Hz, N-CO-O). IR (KBr, ν_{max}, cm^{-1}) 3261 s (NH); 1545 s (CONH); 1715 vs (C=O); 1251 s (P=O); 1196 s (Ph-OP); 955 vs (P-OPh); 1587 m, 1491 s, 1457 m, 1436 m, 1070 m, 1481 s, 765 m, 688 s (ring). HRMS (EI) calc for $C_{29}H_{29}O_5NPS$ $[M+1]^+$ 534.1499; found: 534.1495.

Diphenyl [(*R,S*)-1-(benzyloxycarbonylamino)-3-(*tert*-butylsulfanyl)propyl]phosphonate (4b). Using the procedure as outlined for **4a**, compound **4b** was prepared from benzyl carbamate (18.9 g; 0.125 mol), triphenylphosphite (38.8 g; 0.125 mol) and 3-(*tert*-butylsulfanyl)propanal (**1b**) (20 g; 0.137 mol). The residue was triturated at -20 °C using a mixture of diethyl ether-petroleum ether (200 ml; 1:4) to afford a brown material, which was isolated by filtration and purified by crystallization from a mixture of chloroform-petroleum ether. Yield 36.5 g (57%). White solid, mp 81-83 °C. R_f = 0.46 (S2). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 1.29 (9H, s, $C(CH_3)_3$), 2.03 (1H, m, C-CHaHb-C), 2.28 (1H, m, C-CHaHb-C), 2.63 (1H, ddd, $^2J_{HH}$ = 12.2, $^3J_{HH}$ = 8.7 and 7.2 Hz, S-CHaHb), 2.72 (1H, ddd, $^2J_{HH}$ = 12.2, $^3J_{HH}$ = 9.2 and 5.0 Hz, S-CHaHb), 4.65 (1H, dtd, $^3J_{HP}$ = 17.5, $^3J_{HH}$ = 10.4, 10.4 and 3.7 Hz, N-CH-P), 5.12 (2H, s, O-CH_2), 5.40 (1H, dd, $^3J_{HH}$ = 10.4 and $^3J_{HP}$ = 1.5 Hz, NH), 7.08-7.34 (15H_{arom}, m, 15CH). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 24.47 (1C, d, $^3J_{CP}$ = 15.1 Hz, S-CH_2), 30.68 (1C, d, $^2J_{CP}$ = 4.8 Hz, C-CH_2-C), 30.87 (3C, C(CH_3)$_3$), 42.41 (1C, C(CH_3)$_3$), 47.96 (1C, d, $^1J_{CP}$ = 158.6 Hz, N-CH-P), 67.30 (1C, CH_2-O), 120.33 (2C, d, $^3J_{CP}$ = 4.1 Hz, *ortho*-CH_{arom}), 120.53 (2C, d, $^3J_{CP}$ = 4.1 Hz, *ortho*-CH_{arom}), 125.26, 125.41, 128.11(2), 128.22, 128.50(2), 129.66(2) and 129.79(2) (11C, CH_{arom}), 136.02 (1C, C_{arom}), 149.87 (1C, d, $^2J_{CP}$ = 9.7 Hz, *ipso*-C_{arom}), 150.12 (1C, d, $^3J_{CP}$ = 9.8 Hz, *ipso*-C_{arom}), 155.82 (1C, d, $^3J_{CP}$ = 6.1 Hz, N-CO-O). IR (KBr, ν_{max}, cm^{-1}) 3287 m (NH); 1540 s (CONH); 1723 vs (C=O); 1248 s, 1229 s (P=O); 1218 s, 1206 s, 1189 s, 1163 s (Ph-OP); 950 vs (P-OPh); 1593 m, 1492 vs, 1456 m, 1027 m, 765 s, 689 m, 525 m (ring); 2960 m (CH_3). HRMS (ESI) calc for $C_{27}H_{33}O_5NPS$ $[M+1]^+$ 514.18116; found: 514.18086.

Diphenyl [(*R,S*)-1-(benzyloxycarbonylamino)-3-(benzylsulfanyl)propyl]phosphonate (4c). Using the procedure as outlined for **4a**, compound **4c** was prepared from benzyl carbamate (21.2 g; 0.14 mol), triphenylphosphite (43.4 g; 0.14 mol) and 3-(benzylsulfanyl)propanal (**1c**) (27 g; 0.15 mol). The residue was triturated at -20 °C using a mixture of ethylacetate-petroleum ether to afford a waxy material. Yield 42 g (55%). R_f = 0.30 (S1). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 1.96 (1H, m, C-CHaHb-C), 2.25 (1H, m, C-CHaHb-C), 2.51 (1H, ddd, $^2J_{HH}$ = 13.5, $^3J_{HH}$ = 8.6 and 7.3 Hz, S-CHaHb), 2.59 (1H, ddd, $^2J_{HH}$ = 13.5, $^3J_{HH}$ = 8.6 and 4.7 Hz, S-CHaHb), 4.61 (1H, dtd, $^3J_{HP}$ = 17.5, $^3J_{HH}$ = 10.5, 10.5 and 3.6 Hz, N-CH-P), 5.09 (1H, d, $^2J_{HH}$ = 12.0 Hz, CHaHb-O), 5.11 (1H, d, $^2J_{HH}$ = 12.0 Hz, CHaHb-O), 5.25 (1H, dd, $^3J_{HH}$ = 10.2 and $^3J_{HP}$ = 1.5 Hz, NH), 7.06- 7.34 (20H_{arom}, m, 20CH). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 27.27 (1C, d, $^3J_{CP}$ = 15.1 Hz, S-CH_2), 30.02 (1C, d, $^2J_{CP}$ = 4.7 Hz, C-CH_2-C), 36.11 (1C, S-CH_2), 47.64 (1C, d, $^1J_{CP}$ = 158.7 Hz, N-CH-P), 67.38 (1C, CH_2-O), 120.32 (2C, d, $^3J_{CP}$ = 4.2 Hz, *ortho*-CH_{arom}), 120.54 (2C, d, $^3J_{CP}$ = 4.0 Hz, *ortho*-CH_{arom}), 125.29, 125.46, 127.03, 128.15(2), 128.27, 128.50(2), 128.53, 128.83(3), 129.69(2) and 129.82(2) (16C, CH_{arom}), 136.00 (1C, *ipso*-C_{arom}), 137.96 (1C, *ipso*-C_{arom}), 149.91 (1C, d, $^2J_{CP}$ = 9.7 Hz, *ipso*-C_{arom}), 150.14 (1C, d, $^3J_{CP}$ = 10.0 Hz, *ipso*-C_{arom}), 155.81 (1C, d, $^3J_{CP}$ = 6.2 Hz, N-CO-O). IR (CCl_4, ν_{max}, cm^{-1}) 3432 w, 3261 w (NH); 1535 m, 1491 vs (CONH); 1727 vs (C=O); 1265 s (P=O); 1211 vs, 1189 vs, 1163 s (Ph-OP); 945 vs (P-OPh); 1593 m, 1455 m, 1027 s, 1481 s, 765 m, 697 s, 689 s (ring). HRMS (ESI) calc for $C_{30}H_{30}O_5NNaPS$ $[M+Na]^+$ 570.14745; found: 570.14743.

[3-(Phenylsulfanyl)-1-(*R,S*)-(diphenoxyphosphoryl)propan-1-aminium] bromide (5a). Phosphonate **4a** (26.5 g; 49.7 mmol) was suspended in 50 ml of 30% HBr/AcOH. The reaction mixture was stirred and the solid material disappeared after 30 minutes accompanied by the extensive evolution of CO_2. After standing for 2 hours, crystals of the hydrobromide had formed. They were removed by filtration and washed with diethyl ether. The pure product was obtained by recrystallization from a mixture of methanol-diethyl ether. Yield 19.5 g (82%). White solid, mp 168-170 °C. R_f = 0.77 (S4). ^{1}H NMR (600 MHz; d$_6$DMSO): δ_H 2.23 (1H, m, C-CHaHb-C), 2.27 (1H, m, C-CHaHb-C), 3.24 (1H, ddd, $^2J_{HH}$ = 13.9, $^3J_{HH}$ = 9.2 and 6.7 Hz, S-CHaHb), 3.33 (1H, ddd, $^2J_{HH}$ = 13.9, $^3J_{HH}$ = 9.3 and 5.5 Hz, S-CHaHb), 4.36 (1H, ddd, $^3J_{HP}$ = 14.2, $^3J_{HH}$ = 7.9 and 5.8 Hz, N-CH-P), 7.16- 7.43 (15H$_{arom}$, m, 15CH), 8.94 (3H, bs, NH_3). ^{13}C NMR (150.9 MHz; d$_6$DMSO): δ_C 28.18 (1C, S-CH_2), 28.21 (1C, d, $^2J_{CP}$ = 9.8 Hz, C-CH_2-C), 45.66 (1C, d, $^1J_{CP}$ = 156.7 Hz, N-CH-P), 120.72 (2C, d, $^3J_{CP}$ = 4.4 Hz, *ortho*-CH$_{arom}$), 120.74 (2C, d, $^3J_{CP}$ = 4.2 Hz, *ortho*-CH$_{arom}$), 126.15, 126.19, 126.39, 128.71(2), 129.47(2), 130.32(2) and 130.36(2) (11C, CH$_{arom}$), 134.82 (1C, *ipso*-C$_{arom}$), 149.34 (1C, d, $^2J_{CP}$ = 3.6 Hz, *ipso*-C$_{arom}$), 149.40 (1C, d, $^3J_{CP}$ = 3.5 Hz, *ipso*-C$_{arom}$). IR (KBr, ν_{max}, cm^{-1}) 3100-2400 vs+vbr, 1513 s (NH_3^+); 1252 m, 1234 m (P=O); 1210 s, 1182 vs (Ph-OP); 960 vs, 941 vs (P-OPh); 1588 s, 1487 vs, 1161 s, 1069 m, 1024 m, 769 s, 740 s, 690 s (ring). HRMS (ESI) calc for $C_{21}H_{23}O_3NPS$ $[M+1]^+$ 400.11308; found: 400.11339.

[3-(*tert*-Butylsulfanyl)-1-(*R,S*)-(diphenoxyphosphoryl)propan-1-aminium] bromide (5b). The salt **5b** was prepared in the same manner as **5a** by the reaction of phosphonate **4b** (30 g; 58.4 mmol) with 50 ml of 30% HBr/AcOH. Yield 21 g (78%). White solid, mp 154-155 °C. R_f = 0.82 (S4). ^{1}H NMR (600 MHz; d$_6$DMSO): δ_H 1.25 (9H, s, C(CH_3)$_3$), 2.12 (1H, m, C-CHaHb-C), 2.22 (1H, m, C-CHaHb-C), 2.75 (1H, ddd, $^2J_{HH}$ = 12.9, $^3J_{HH}$ = 10.3 and 5.8 Hz, S-CHaHb), 2.81 (1H, ddd, $^2J_{HH}$ = 12.9, $^3J_{HH}$ = 10.4 and 5.7 Hz, S-CHaHb), 4.26 (1H, ddd, $^3J_{HP}$ = 14.1, $^3J_{HH}$ = 7.4 and 6.0 Hz, N-CH-P), 7.20 (4H$_{arom}$, m, 4CH), 7.27 (2H$_{arom}$, m, 2CH), 7.42 (4H$_{arom}$, m, 4CH). ^{13}C NMR (150.9 MHz; d$_6$DMSO): δ_C 24.28 (1C, d, $^3J_{CP}$ = 9.9 Hz, S-CH_2), 29.73 (1C, C-CH_2-C), 31.19 (3C, C(CH_3)$_3$), 43.08 (1C, C(CH_3)$_3$), 46.24 (1C, d, $^1J_{CP}$ = 156.2 Hz, N-CH-P), 120.93 (2C, d, $^3J_{CP}$ = 4.0 Hz, *ortho*-CH$_{arom}$), 120.98 (2C, d, $^3J_{CP}$ = 4.0 Hz, *ortho*-CH$_{arom}$), 126.52(2), 130.64(2) and 130.66(2) (6C, CH$_{arom}$), 149.63 (2C, d, $^2J_{CP}$ = 9.5 Hz, *ipso*-C$_{arom}$). IR (KBr, ν_{max}, cm^{-1}) 3100-2400 vs +vbr, 1521 m, 1511 m (NH_3^+); 1233 s (P=O); 1207 vs, 1180 vs, 1162 s (Ph-OP); 954 vs (P-OPh);1589 s, 1489 vs, 1456 m, 1025 m, 1009 m, 910 m, 770 s, 689 s (ring); 2960 s (CH_3). HRMS (ESI) calc for $C_{19}H_{27}O_3NPS$ $[M+1]^+$ 380.14438; found: 380.14442.

[3-(benzylsulfanyl)-1-(*R,S*)-(diphenoxyphosphoryl)propan-1-aminium] bromide (5c). The salt **5c** was prepared in the same manner as **5a** by the reaction of phosphonate **4c** (30 g; 54.8 mmol) with 50 ml of 30% of HBr/AcOH. Yield 20.3 g (75%). White solid, mp 197-198 °C. R_f = 0.80 (S4). ^{1}H NMR (600 MHz; d$_6$DMSO): δ_H 2.29 (2H, m, C-CH_2-C), 2.75 (2H, m, S-CH_2), 4.29 (1H, m, N-CH-P), 3.76 (1H, d, $^2J_{HH}$ = 13.2 Hz, S-CHaHb), 3.78 (1H, d, $^2J_{HH}$ = 13.2 Hz, S-CHaHb), 7.22 (5H$_{arom}$, m, 5CH), 7.26 (2H$_{arom}$, m, 2CH), 7.29 (2H$_{arom}$, m, 2CH), 7.32 (2H$_{arom}$, m, 2CH), 7.42 (4H$_{arom}$, m, 4CH), 8.99 (3H, bs, NH_3^+). ^{13}C NMR (150.9 MHz; d$_6$DMSO): δ_C 26.91 (1C, d, $^3J_{CP}$ = 9.9 Hz, S-CH_2), 28.29 (1C, d, $^2J_{CP}$ = 1.3 Hz, C-CH_2-C), 34.88 (1C, S-CH_2), 45.65

(1C, d, $^{1}J_{CP}$ = 156.5 Hz, N-CH-P), 120.68 (2C, d, $^{3}J_{CP}$ = 4.1 Hz, *ortho*-CH_{arom}), 120.75 (2C, d, $^{3}J_{CP}$ = 4.1 Hz, *ortho*-CH_{arom}), 126.05(2), 127.02, 128.57(2), 128.98(2), 130.23(2) and 130.26(2) (11C, CH_{arom}), 138.51 (1C, *ipso*-C_{arom}), 149.41 (d, $^{2}J_{CP}$ = 9.5 Hz, *ipso*-C_{arom}), 149.44 (1C, d, $^{2}J_{CP}$ = 9.5 Hz, *ipso*-C_{arom}). IR (KBr, ν_{max}, cm^{-1}) 3100-2400 vs+vbr, 1521 s (NH_3^+); 1249 s (P=O); 1200 vs, 1175 vs, 1160 vs (Ph-OP); 957 vs, 941 vs (P-OPh); 1587 s, 1486 vs, 1454 s, 1024 m, 1010 s, 770 s, 689 s (ring). HRMS (ESI) calc for $C_{22}H_{25}O_3NPS$ $[M+1]^+$ 414.12873; found: 414.12866.

Diphenyl [(*R*,*S*)-1-(*tert*-butoxycarbonylamino)-3-(phenylsulfanyl)propyl]phosphonate (6a). TEA (2.9 g; 28.3 mmol) was added to a suspension of salt **5a** (13.6 g; 28.3 mmol) in 250 ml of dichloromethane. As soon as the solution clarified (approximately 10 minutes), the reaction flask was immersed in an ice bath, and Boc_2O (6.8 g; 31.1 mmol) in 50 ml of DCM was added dropwise. After stirring for one hour at 0 °C and then overnight at rt, the solvent was removed by rotary evaporator, and the oily residue was purified by flash chromatography on silica gel using a linear gradient of ethyl acetate in toluene as the eluant. The yield from the reaction was 10.5 g (74%).

Alternatively, compound **6a** was prepared according to procedure described by Van der Veken *et al*.[15] Aldehyde **1a** (2 g; 12 mmol), *tert*-butyl carbamate[20] (1.2 g; 10 mmol) and triphenyl phosphite (3.1 g; 10 mmol) were dissolved in 25 ml of dry dichloromethane. $TiCl_4$ (0.1 eq, 0.1 M solution) was added in one portion. The reaction mixture turned dark red and a mild reflux of the solvent was observed due to the exothermic nature of the reaction. After stirring for 24 hr at rt, the dichloromethane was evaporated *in vacuo*, and the residue was purified twice by flash chromatography on silica gel using a linear gradient of ethyl acetate in toluene as the eluant. Yield 2.6 g (52%). White solid, mp 72-74 °C. R_f = 0.47 (S6). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 1.45 (9H, s, $C(CH_3)_3$), 2.03 (1H, m, C-CHaHb-C), 2.32 (1H, m, C-CHaHb-C), 3.01 (1H, ddd, $^{2}J_{HH}$ = 13.5, $^{3}J_{HH}$ = 8.8 and 7.0 Hz, S-CHaHb), 3.13 (1H, ddd, $^{2}J_{HH}$ = 13.5, $^{3}J_{HH}$ = 9.2 and 4.7 Hz, S-CHaHb), 4.62 (1H, dtd, $^{3}J_{HP}$ = 18.2, $^{3}J_{HH}$ = 10.4, 10.4 and 3.8 Hz, N-CH-P), 7.12 ($4H_{arom}$, m, 4CH), 7.17 ($2H_{arom}$, m, 2CH), 7.19 ($1H_{arom}$, m, 1CH), 7.28 ($2H_{arom}$, m, 2CH), 7.30 ($4H_{arom}$, m, 4CH), 7.36 ($2H_{arom}$, m, 2CH), ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 28.24 (3C, $C(CH_3)_3$), 30.27 (1C, C-CH_2-C), 30.23 (1C, d, $^{3}J_{CP}$ = 19.5 Hz, S-CH_2), 47.40 (1C, d, $^{1}J_{CP}$ = 158.3 Hz, N-CH-P), 80.61 (1C, $C(CH_3)_3$), 120.38 (2C, d, $^{3}J_{CP}$ = 4.1 Hz, *ortho*-CH_{arom}), 120.50 (2C, d, $^{3}J_{CP}$ = 4.1 Hz, *ortho*-CH_{arom}), 125.32, 125.43, 126.42, 129.00(2), 129.73(2), 129.83(2) and 129.92(2) (11C, CH_{arom}), 135.31 (1C, *ipso*-C_{arom}), 149.89 (1C, d, $^{2}J_{CP}$ = 9.7 Hz, *ipso*-C_{arom}), 150.20 (1C, d, $^{2}J_{CP}$ = 10.0 Hz, *ipso*-C_{arom}), 155.04 (1C, d, $^{3}J_{CP}$ = 6.9 Hz, N-CO-O). IR (KBr, ν_{max}, cm^{-1}) 3406 m, 3273 s (NH); 1526 s (CONH); 1713 vs (C=O); 1246 vs (P=O); 1212 vs, 1189 vs (Ph-OP); 943 vs (P-OPh); 1591 s, 1440 s, 1291 s, 1071 m, 1025 s, 766 s, 740 s, 690 vs (ring); 1367 s (CH_3), 1163 vs ($C(CH_3)_3$). HRMS (ESI) calc for $C_{26}H_{31}O_5NPS$ $[M+1]^+$ 500.16551; found: 500.16599.

Diphenyl [(*R*,*S*)-1-(*tert*-butoxycarbonylamino)-3-(*tert*-butylsulfanyl)propyl]phosphonate (6b). Phosphonate **6b** was prepared by the reaction of **5b** (18.7 g; 41 mmol), TEA (4.1 g; 41 mmol) and Boc_2O (10.7 g; 49.2 mmol) as described above for **6a**. The yield was 12.6 g (65%).

Phosphonate **6b** was also synthesized using the alternate protocol for **6a** by the reaction of aldehyde **1b** (3.5 g; 24 mmol), *tert*-butyl carbamate[20] (2.3 g; 20 mmol) and triphenyl phosphite (6.2 g; 20 mmol). Yield 5.1 g (54%). Semisolid. R_f = 0.52 (S2). ^{1}H NMR (600 MHz; d_6DMSO): δ_H 1.31 (9H, s, C(CH_3)$_3$), 1.44 (9H, s, C(CH_3)$_3$), 2.00 (1H, m, C-C<u>Ha</u>Hb-C), 2.28 (1H, m, C-CHa<u>Hb</u>-C), 2.65 (1H, ddd, $^2J_{HH}$ = 12.4, $^3J_{HH}$ = 9.2 and 7.4 Hz, S-C<u>Ha</u>Hb), 2.74 (1H, ddd, $^2J_{HH}$ = 12.4, $^3J_{HH}$ = 9.5 and 4.8 Hz, S-C<u>Ha</u>Hb), 4.59 (1H, dtd, $^3J_{HP}$ = 17.6, $^3J_{HH}$ = 10.6, 10.6 and 3.8 Hz, N-CH-P), 4.96 (1H, dd, $^3J_{HH}$ = 10.6 and $^3J_{HP}$ = 1.5 Hz, NH), 7.13 (2H$_{arom}$, m, 2CH), 7.17 (2H$_{arom}$, m, 2CH), 7.19 (2H$_{arom}$, m, 2CH), 7.31 (4H$_{arom}$, m, 4CH). ^{13}C NMR (150.9 MHz; d_6DMSO): δ_C 24.49 (1C, d, $^3J_{CP}$ = 15.0 Hz, S-CH_2), 28.22 (3C, C(<u>C</u>H$_3$)$_3$), 30.92 (3C, C(<u>C</u>H$_3$)$_3$), 42.39 (1C, S-<u>C</u>(CH$_3$)$_3$), 47.28 (1C, d, $^1J_{CP}$ = 158.2 Hz, N-CH-P), 80.46 (1C, O-<u>C</u>(CH$_3$)$_3$), 120.40 (2C, d, $^3J_{CP}$ = 4.1 Hz, *ortho*-CH$_{arom}$), 120.57 (2C, d, $^3J_{CP}$ = 4.1 Hz, *ortho*-CH$_{arom}$), 125.27, 125.41, 129.70(2) and 129.82(2) (6C, CH$_{arom}$), 149.85 (1C, d, $^2J_{CP}$ = 9.7 Hz, *ipso*-C$_{arom}$), 150.25 (1C, d, $^2J_{CP}$ = 9.9 Hz, *ipso*-C$_{arom}$), 155.03 (1C, d, $^3J_{CP}$ = 6.5 Hz, N-CO-O). IR (CCl_4, ν_{max}, cm^{-1}) 3436 w, 3274 w (NH); 1525 m, 1490 vs (CONH); 1721 vs (C=O); 1242 m (P=O); 1213 s, 1190 vs, 1163 vs (Ph-OP); 942 vs (P-OPh); 1594 m, 1457 m, 1026 m, 688 m., (ring); 2976 m, 1457 m, 1392 m, 1367 m (CH_3). HRMS (ESI) calc for $C_{24}H_{34}O_5NNaPS$ $[M+Na]^+$ 502.17875; found: 502.17873.

Diphenyl [(*R*,*S*)-1-(*tert*-butoxycarbonylamino)-3-(benzylsulfanyl)propyl]phosphonate (6c). Phosphonate **6c** was prepared by the reaction of **5c** (20 g; 40.1 mmol), TEA (4.1 g; 40.1 mmol) and Boc_2O (9.6 g; 44.1 mmol) as described above for **6a**. The yield was 15.5 g (75%).

Phosphonate **6c** was also synthesized using the alternate protocol for **6a** by the reaction of aldehyde **1c** (2.5 g; 14 mmol), *tert*-butyl carbamate[20] (1.5 g; 12.8 mmol) and triphenyl phosphite (4 g; 12.8 mmol). Yield 3.2 g (49%). R_f = 0.45 (S2). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 1.43 (9H, s, C(CH_3)$_3$), 1.94 (1H, m, C-C<u>Ha</u>Hb-C), 2.25 (1H, m, C-CHa<u>Hb</u>-C), 2.52 (1H, ddd, $^2J_{HH}$ = 13.2, $^3J_{HH}$ = 9.0 and 7.0 Hz, S-C<u>Ha</u>Hb), 2.61 (1H, ddd, $^2J_{HH}$ = 13.2, $^3J_{HH}$ = 9.4 and 4.6 Hz, S-C<u>Ha</u>Hb), 3.71 (2H, s, S-CH_2), 4.54 (1H, dtd, $^3J_{HP}$ = 13.0, $^3J_{HH}$ = 10.5, 10.5 and 3.5 Hz, N-CH-P), 4.87 (1H, bdd, $^3J_{HH}$ = 10.5, $^3J_{HP}$ = 1.5, 7.12 - 7.32 (15H$_{arom}$, m, 15CH). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 27.35 (1C, d, $^3J_{CP}$ = 15.3 Hz, S-CH_2), 28.24 (3C, C(<u>C</u>H$_3$)$_3$), 30.35 (1C, d, $^2J_{CP}$ = 5.0 Hz, C-<u>C</u>H$_2$-C), 36.18 (1C, S-CH_2), 47.02 (1C, d, $^1J_{CP}$ = 158.3 Hz, N-CH-P), 80.47 (1C, <u>C</u>(CH$_3$)$_3$), 120.38 (2C, d, $^3J_{CP}$ = 4.2 Hz, *ortho*-CH$_{arom}$), 120.57 (2C, d, $^3J_{CP}$ = 4.0 Hz, *ortho*-CH$_{arom}$), 125.27, 125.42, 127.03, 128.52(2), 128.84(2), 129.71(2) and 129.83(2) (11C, CH$_{arom}$), 138.06 (1C, *ipso*-C$_{arom}$), 149.99 (1C, d, $^2J_{CP}$ = 9.4 Hz, *ipso*-C$_{arom}$), 150.28 (1C, d, $^2J_{CP}$ = 9.4 Hz, *ipso*-C$_{arom}$), 154.99 (d, $^3J_{CP}$ = 6.9 Hz, N-CO-O). IR (CCl_4, ν_{max}, cm^{-1}) 3436 w, 3273 m (NH); 1525 m, 1491 vs (CONH); 1719 vs (C=O); 1262 vs (P=O); 1213 vs, 1190 vs, 1163 vs (Ph-OP); 943 vs (P-OPh); 1594 s, 1455 s, 1072 m, 1026 s, 698 s, 688 s (ring); 1367 s (CH_3). HRMS (ESI) calc for $C_{27}H_{32}O_5NNaPS$ $[M+Na]^+$ 536.16310; found: 536.16292.

Di-*tert*-butyl [(*R*,*S*)-1-(*tert*-butoxycarbonylamino)-3-(phenylsulfanyl)propyl]phosphonate (7a). Potassium *tert*-butoxide (7 g; 62.4 mmol) was carefully added to a stirred solution of compound **6a** (10 g; 18.7 mmol) dissolved in 100 ml of anhydrous *tert*-butanol and 100 ml of dry dioxane. The flask was equipped with a calcium dichloride tube and the reaction was allowed to proceed at rt overnight. The solvents were evaporated *in vacuo*, and the residue was taken up in

100 ml of ethyl acetate and washed with 100 ml of water and brine. The organic layer was separated, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel using a linear gradient of ethyl acetate in toluene as the eluant. Yield 3.8 g (53%). Colorless oil, R_f = 0.79 (S3). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 1.455 (9H, s, $C(CH_3)_3$), 1.475 (9H, s, $C(CH_3)_3$), 1.48 (9H, s, $C(CH_3)_3$), 1.75 (1H, m, C-CHaHb-C), 2.19 (1H, m, C-CHaHb-C), 2.98 (1H, ddd, $^2J_{HH}$ = 13.2, $^3J_{HH}$ = 9.5 and 6.7 Hz, S-CHaHb), 3.04 (1H, ddd, $^2J_{HH}$ = 13.2, $^3J_{HH}$ = 9.7 and 5.0 Hz, S-CHaHb), 3.98 (1H, dtd, $^3J_{HP}$ = 17.2, $^3J_{HH}$ = 10.4, 10.0 and 4.1 Hz, N-CH-P), 4.64 (1H, dd, $^3J_{HH}$ = 10.4, $^3J_{HP}$ = 3.6, NH), 7.17 (1H$_{arom}$, m, 1CH), 7.27 (2H$_{arom}$, m, 2CH), 7.35 (2H$_{arom}$, m, 2CH). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 28.24 (3C, $C(CH_3)_3$), 30.15 (3C, d, $^3J_{CP}$ = 3.6, $C(CH_3)_3$), 30.35 (3C, d, $^3J_{CP}$ = 3.6, $C(CH_3)_3$), 30.46 (1C, S-CH_2), 31.13 (1C, d, $^2J_{CP}$ = 3.7 Hz, C-CH_2-C), 49.00 (1C, d, $^1J_{CP}$ = 159.7 Hz, N-CH-P), 79.80 (1C, $C(CH_3)_3$), 82.97 (1C, d, $^2J_{CP}$ = 8.5 Hz, $C(CH_3)_3$), 83.14 (1C, d, $^2J_{CP}$ = 9.8 Hz, $C(CH_3)_3$), 126.00 (1C, *para*-CH$_{arom}$), 128.84 (2C, *meta*-CH$_{arom}$), 128.84 (2C, *ortho*-CH$_{arom}$), 135.99 (1C, *ipso*-C$_{arom}$), 155.35 (1C, d, $^3J_{CP}$ = 6.5 Hz, N-CO-O). IR (CCl_4, ν_{max}, cm^{-1}) 3449 w, 3259 w (NH); 1497 s (CONH); 1718 s (C=O); 1248 m (P=O); 982 vs (C-OP); 1482 m, 1440 m, 691 m (ring); 2981 s, 1369 s (CH_3), 1170 s ($C(CH_3)_3$). HRMS (ESI) calc for $C_{22}H_{39}O_5NPS$ $[M+1]^+$ 460.22811; found: 460.22836.

Di-*tert*-butyl [(*R*,*S*)-1-(*tert*-butoxycarbonylamino)-3-(*tert*-butylsulfanyl)propyl]phosphonate (7b). Using the procedure outlined for **7a**, phosphonate **7b** was prepared from compound **6b** (8 g; 17 mmol) and potassium *tert*-butoxide (7.6 g; 68 mmol). Yield 4.3 g (59%). Semisolid, R_f = 0.67 (S3). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 1.31 (9H, s, $C(CH_3)_3$), 1.45 (9H, s, $C(CH_3)_3$), 1.50 (9H, s, $C(CH_3)_3$), 1.51 (9H, s, $C(CH_3)_3$), 1.68 (1H, m, C-CHaHb-C), 2.15 (1H, m, C-CHaHb-C), 2.59 (1H, ddd, $^2J_{HH}$ = 12.0, $^3J_{HH}$ = 10.2 and 6.5 Hz, S-CHaHb), 2.65 (1H, ddd, $^2J_{HH}$ = 12.0, $^3J_{HH}$ = 10.5 and 4.8 Hz, S-CHaHb), 3.93 (1H, dtd, $^3J_{HP}$ = 16.6, $^3J_{HH}$ = 10.3, 10.2 and 3.8 Hz, N-CH-P), 4.62 (1H, dd, $^3J_{HH}$ = 10.3, $^3J_{HP}$ = 3.2, NH), 7.17 (1H$_{arom}$, m, 1CH), 7.27 (2H$_{arom}$, m, 2CH), 7.35 (2H$_{arom}$, m, 2CH). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 24.92 (1C, d, $^3J_{CP}$ = 14.4, S-CH_2), 28.30 (3C, $C(CH_3)_3$), 30.18 (3C, d, $^3J_{CP}$ = 3.5, $C(CH_3)_3$), 30.37 (3C, d, $^3J_{CP}$ = 3.8, $C(CH_3)_3$), 30.93 (3C, $C(CH_3)_3$), 31.73 (1C, d, $^2J_{CP}$ = 3.6 Hz, C-CH_2-C), 42.14 (1C, $C(CH_3)_3$), 49.43 (1C, d, $^1J_{CP}$ = 159.6 Hz, N-CH-P), 79.65 (1C, $C(CH_3)_3$), 82.86 (1C, d, $^2J_{CP}$ = 8.4 Hz, $C(CH_3)_3$), 83.03 (1C, d, $^2J_{CP}$ = 9.7 Hz, $C(CH_3)_3$), 155.34 (1C, d, $^3J_{CP}$ = 6.4 Hz, N-CO-O). IR (CCl_4, ν_{max}, cm^{-1}) 3450, 3256 w (NH); 1535 w,1497 s (CONH); 1718 vs (C=O); 1259 s, 1248 s (P=O); 981 vs (C-OP); 2980 s, 1393 m, 1369 s (CH_3); 1170 vs ($C(CH_3)_3$). HRMS (ESI) calc for $C_{20}H_{42}O_5NNaPS$ $[M+Na]^+$ 462.24135; found: 462.24132.

Di-*tert*-butyl [(*R*,*S*)-1-(*tert*-butoxycarbonylamino)-3-(benzylsulfanyl)propyl]phosphonate (7c). Using the procedure outlined for **7a**, phosphonate **7c** was prepared from **6c** (3.8 g; 7.4 mmol) and potassium *tert*-butoxide (3.3 g; 29.6 mmol). Yield 2.1 g (60%). Colorless oil, R_f = 0.2 (S2). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 1.44 (9H, s, $C(CH_3)_3$), 1.49 (9H, s, $C(CH_3)_3$), 1.50 (9H, s, $C(CH_3)_3$), 1.63 (1H, m, C-CHaHb-C), 2.15 (1H, m, C-CHaHb-C), 2.47 (1H, ddd, $^2J_{HH}$ = 13.2, $^3J_{HH}$ = 9.6 and 6.8 Hz, S-CHaHb), 2.54 (1H, ddd, $^2J_{HH}$ = 13.2, $^3J_{HH}$ = 10.0 and 4.7 Hz, S-CHaHb), 3.71 (2H, s, S-CH_2), 3.90 (1H, dtd, $^3J_{HP}$ = 16.8, $^3J_{HH}$ = 10.4, 10.4 and 3.6 Hz, N-CH-P),

4.54 (1H, dd, $^3J_{HH}$ = 10.4, $^3J_{HP}$ = 3.3, NH), 7.22 (1H$_{arom}$, m, 1CH), 7.30 (4H$_{arom}$, m, 4CH).^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 27.88 (1C, d, $^3J_{CP}$ = 14.5, S-CH_2), 28.00 (3C, C($\underline{C}H_3)_3$), 30.15 (3C, d, $^3J_{CP}$ = 3.6, C($\underline{C}H_3)_3$), 30.36 (3C, d, $^3J_{CP}$ = 3.6, C($\underline{C}H_3)_3$), 31.09 (d, $^2J_{CP}$ = 3.6 Hz, C-$\underline{C}H_2$-C), 36.17 (1C, S-CH_2), 49.07 (1C, d, $^1J_{CP}$ = 159.7 Hz, N-CH-P), 79.63 (1C, $\underline{C}(CH_3)_3$), 82.47 (1C, d, $^2J_{CP}$ = 8.4 Hz, $\underline{C}(CH_3)_3$), 83.01 (1C, d, $^2J_{CP}$ = 9.9 Hz, $\underline{C}(CH_3)_3$), 126.86 (1C, *para*-CH$_{arom}$), 128.40 (2C, *ortho*-CH$_{arom}$), 128.81 (2C, *meta*-CH$_{arom}$), 138.34 (1C, *ipso*-C$_{arom}$), 155.29 (1C, d, $^3J_{CP}$ = 6.3 Hz, N-CO-O). IR (CCl_4, ν_{max}, cm^{-1}) 3449 m, 3259 w (NH); 1530 m, 1496 vs (CONH); 1718 vs (C=O); 1259 m (P=O); 982 vs (CO-P); 1454 s, 1072 m, 918 m, 691 s (ring); 2981 s, 1393 s, 1370 vs, (CH_3), 1171 vs (C($CH_3)_3$). HRMS (ESI) calc for $C_{23}H_{40}O_5NNaPS$ $[M+Na]^+$ 496.22570; found: 496.22551.

Dimethyl [(*R*,*S*)-1-(benzyloxycarbonylamino)-3-(phenylsulfanyl)propyl]phosphonate (8a). Compound **8a** was prepared using a slight modification of the method developed by Yuan *et al.*[16] A well-stirred mixture of benzylcarbamate (3 g; 20 mmol) and dimethyl phosphite (2.2 g; 20 mmol) in 50 ml of acetyl chloride was cooled in ice bath to -5 °C, and aldehyde **1a** (4.2 g; 25 mmol) was added dropwise over 10 minutes. The reaction mixture was stirred for 1 hour at 0°C and then left to react at rt overnight. The acetyl chloride was evaporated *in vacuo*, and the crude product was purified twice by flash chromatography on silica gel using a linear gradient of ethyl acetate in toluene as the eluant. The yield was 2.5 g (31%).

Alternatively, phosphonate **8a** was prepared as follows. Sodium methoxide (4 g; 74.8 mmol) was carefully added to a stirred solution of compound **4a** (10 g; 18.7 mmol) dissolved in 100 ml of anhydrous methanol and 100 ml of dry dioxane. The flask was equipped with a calcium dichloride tube and the reaction was allowed to proceed at rt overnight. The solvents were evaporated *in vacuo*; the residue was taken up in 100 ml of diethyl ether and washed with 100 ml of water and brine. The organic layer was separated, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel using a linear gradient of ethyl acetate in toluene as the eluant. Yield 5.5 g (71%). Colorless oil, R_f = 0.59 (S3). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 1.89 (1H, m, C-C$\underline{Ha}$Hb-C), 2.13 (1H, m, C-CHa$\underline{Hb}$-C), 2.93 (1H, ddd, $^2J_{HH}$ = 13.4, $^3J_{HH}$ = 9.0 and 7.0 Hz, S-C$\underline{Ha}$Hb), 3.06 (1H, ddd, $^2J_{HH}$ = 13.4, $^3J_{HH}$ = 9.1 and 4.8 Hz, S-C$\underline{Ha}$Hb), 3.69 (3H, d, $^3J_{HP}$ = 10.7, OCH_3), 3.71 (3H, d, $^3J_{HP}$ = 10.7, OCH_3), 4.30 (1H, dtd, $^3J_{HP}$ = 16.8, $^3J_{HH}$ = 10.4, 10.4 and 3.9 Hz, N-CH-P), 5.11 (1H, d, $^2J_{HH}$ = 12.4, O-C$\underline{Ha}$Hb), 5.14 (1H, d, $^2J_{HH}$ = 12.4, O-CHa$\underline{Hb}$), 5.26 (1H, dd, $^3J_{HH}$ = 10.4, $^3J_{HP}$ = 1.9, NH), 7.19 (1H$_{arom}$, m, 1CH), 7.27 (2H$_{arom}$, m, 2CH), 7.32 (1H$_{arom}$, m, 1CH), 7.33 (2H$_{arom}$, m, 2CH), 7.35 (4H$_{arom}$, m, 4CH). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 29.74 (1C, d, $^2J_{CP}$ = 4.2 Hz, C-$\underline{C}H_2$-C), 30.21 (1C, d, $^3J_{CP}$ = 14.3, S-CH_2), 46.34 (1C, d, $^1J_{CP}$ = 156.7 Hz, N-CH-P), 79.63 (1C, $\underline{C}(CH_3)_3$), 53.07 (1C, d, $^2J_{CP}$ = 6.6 Hz, OCH_3), 53.25 (1C, d, $^2J_{CP}$ = 7.1 Hz, OCH_3), 67.26 (1C, OCH_2), 126.32, 128.05(2), 128.23, 128.50(2), 128.94(2) and 129.75(2) (10C, CH$_{arom}$), 135.38 (1C, *ipso*-C$_{arom}$), 136.07 (1C, *ipso*-C$_{arom}$), 155.97 (1C, d, $^3J_{CP}$ = 5.5 Hz, N-CO-O). IR (CCl_4, ν_{max}, cm^{-1}) 3433 w, 3240 m (NH); 1540 m, 1504 m (CONH); 1724 vs (C=O); 1252 s, 1233 s (P=O); 1044 vs (C-OP); 835 m (CO-P); 1481 m, 1455 m, 1440 m, 695 s (ring); 2955 m (CH_3). HRMS (ESI) calc for $C_{19}H_{25}O_5NPS$ $[M+1]^+$ 410.11856; found: 410.11850.

Dimethyl [(*R,S*)-1-(benzyloxycarbonylamino)-3-(*tert*-butylsulfanyl)propyl]phosphonate (8b). Phosphonate **8b** was prepared in the same manner as **8a** by the reaction of benzylcarbamate (3 g; 20 mmol) and dimethyl phosphite (2.2 g; 20 mmol) and aldehyde **1b** (3.7 g; 25 mmol). The yield was 3.5 g (45%).

Phosphonate **8b** was also prepared using the alternative protocol for **8a** by the reaction of sodium methoxide (2.7 g; 51.6 mmol) and phosphonate **4b** (6.6 g; 12.9 mmol). Yield 3 g (66%). Colorless oil, R_f = 0.28 (S2). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 1.29 (9H, s, $C(CH_3)_3$), 1.86 (1H, m, C-CHaHb-C), 2.08 (1H, m, C-CHaHb-C), 2.56 (1H, ddd, $^2J_{HH}$ = 12.1, $^3J_{HH}$ = 9.0 and 7.2 Hz, S-CHaHb), 2.66 (1H, ddd, $^2J_{HH}$ = 12.1, $^3J_{HH}$ = 9.2 and 5.0 Hz, S-CHaHb), 3.72 (3H, d, $^3J_{HP}$ = 10.6, OCH_3), 3.75 (3H, d, $^3J_{HP}$ = 10.6, OCH_3), 4.26 (1H, dtd, $^3J_{HP}$ = 16.5, $^3J_{HH}$ = 10.4, 10.4 and 3.8 Hz, N-CH-P), 5.13 (2H, s, O-CH_2), 5.25 (1H, dd, $^3J_{HH}$ = 10.4, $^3J_{HP}$ = 1.5, NH), 7.30 – 7.36 ($5H_{arom}$, m, 5CH). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 24.58 (1C, d, $^3J_{CP}$ = 14.3, S-CH_2), 30.41 (1C, d, $^2J_{CP}$ = 4.0 Hz, C-CH_2-C), 30.87 (3C, C(CH_3)$_3$), 42.32 (1C, C(CH_3)$_3$), 46.71 (1C, d, $^1J_{CP}$ = 156.4 Hz, N-CH-P), 53.05 (1C, d, $^2J_{CP}$ = 6.6 Hz, OCH_3), 53.22 (1C, d, $^2J_{CP}$ = 7.1 Hz, OCH_3), 67.15 (1C, OCH_2), 128.01 (2C, *meta*-CH_{arom}), 128.16 (1C, *para*-CH_{arom}), 128.46 (2C, *ortho*-CH_{arom}), 136.16 (1C, *ipso*-C_{arom}), 155.93 (1C, d, $^3J_{CP}$ = 5.4 Hz, N-CO-O). IR (CCl_4, ν_{max}, cm^{-1}) 3433 w, 3240 m (NH);1540 m, 1505 s (CONH); 1725 vs (C=O); 1252 s (P=O); 1044 vs (C-OP); 835 m (CO-P); 1458 m, 696 m (ring); 2957 s (CH_3); 1165 m ($C(CH_3)_3$). HRMS (ESI) calc for $C_{17}H_{29}O_5NPS$ $[M+1]^+$ 390.14986; found: 390.14986.

Dimethyl [(*R,S*)-1-(benzyloxycarbonylamino)-3-(benzylsulfanyl)propyl]phosphonate (8c). Phosphonate **8c** was prepared in the same manner as **8a** by the reaction of benzylcarbamate (4 g; 26.5 mmol) and dimethyl phosphite (2.9 g; 26.5 mmol) and aldehyde **1c** (5.7 g; 31.8 mmol). The yield was 4.5 g (40%).

Phosphonate **8c** was also prepared using the alternative protocol for **8a** by the reaction of sodium methoxide (4 g; 73 mmol) and phosphonate **4c** (10 g; 18.2 mmol). Yield 5 g (65%). Colorless oil, R_f = 0.65 (S3). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 1.81 (1H, m, C-CHaHb-C), 2.05 (1H, m, C-CHaHb-C), 2.44 (1H, ddd, $^2J_{HH}$ = 13.4, $^3J_{HH}$ = 8.8 and 7.3 Hz, S-CHaHb), 2.54 (1H, ddd, $^2J_{HH}$ = 13.4, $^3J_{HH}$ = 9.0 and 4.8 Hz, S-CHaHb), 3.38 (3H, d, $^3J_{HP}$ = 10.8, OCH_3), 3.69 (2H, s, S-CH_2), 3.72 (3H, d, $^3J_{HP}$ = 10.8, OCH_3), 4.23 (1H, dtd, $^3J_{HP}$ = 16.5, $^3J_{HH}$ = 10.4, 10.4 and 3.7 Hz, N-CH-P), 5.09 (1H, d, $^2J_{HH}$ = 12.2, O-CHaHb), 5.12 (1H, d, $^2J_{HH}$ = 12.2, O-CHaHb), 5.35 (1H, dd, $^3J_{HH}$ = 10.4, $^3J_{HP}$ = 1.2, NH), 7.22 – 7.34 ($10H_{arom}$, m, 10CH). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 27.30 (1C, d, $^3J_{CP}$ = 14.2, S-CH_2), 29.60 (1C, d, $^2J_{CP}$ = 4.0 Hz, C-CH_2-C), 35.98 (1C, S-CH_2), 46.25 (1C, d, $^1J_{CP}$ = 156.8 Hz, N-CH-P), 52.96 (1C, d, $^2J_{CP}$ = 6.6 Hz, OCH_3), 53.19 (1C, d, $^2J_{CP}$ = 7.1 Hz, OCH_3), 67.10 (1C, OCH_2), 129.91, 127.98(2), 128.14, 128.40(2), 128.42(2) and 128.77 (2) (10C, CH_{arom}), 136.09 (1C, *ipso*-C_{arom}), 138.02 (1C, *ipso*-C_{arom}), 155.90 (1C, d, $^3J_{CP}$ = 5.3 Hz, N-CO-O). IR (CCl_4, ν_{max}, cm^{-1}) 3434 w, 3242 m (NH); 1540 m, 1497 s (CONH); 1724 vs (C=O); 1252 s (P=O); 1043 vs (C-OP); 834 m (CO-P); 1454 m, 698 s (ring). HRMS (ESI) calc for $C_{20}H_{27}O_5NPS$ $[M+1]^+$ 424.13421; found: 424.13409.

Dimethyl [(*R,S*)-1-(*tert*-butoxycarbonylamino)-3-(phenylsulfanyl)propyl]phosphonate (9a). Sodium methoxide (4.3 g; 80 mmol) was carefully added to a stirred solution of compound **6a**

(10 g; 20 mmol) dissolved in 100 ml of anhydrous methanol and 100 ml of dry dioxane. The flask was equipped with a calcium dichloride tube and the reaction was allowed to proceed at rt overnight. The solvents were evaporated *in vacuo*; the residue was taken up in 100 ml of diethyl ether and washed with 100 ml of water and brine. The organic layer was separated, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel using a linear gradient of ethyl acetate in toluene as the eluant. Yield 4.1 g (55%). Colorless oil, R_f = 0.65 (S3). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 1.45 (9H, s, $C(CH_3)_3$), 1.86 (1H, m, C-CHaHb-C), 2.13 (1H, m, C-CHaHb-C), 2.95 (1H, ddd, $^2J_{HH}$ = 13.4, $^3J_{HH}$ = 9.2 and 6.9 Hz, SCHaHb), 3.07 (1H, ddd, $^2J_{HH}$ = 13.4, $^3J_{HH}$ = 9.4 and 4.8 Hz, S-CHaHb), 3.74 (3H, d, $^3J_{HP}$ = 10.6, OCH_3), 3.76 (3H, d, $^3J_{HP}$ = 10.6, OCH_3), 4.24 (1H, dtd, $^3J_{HP}$ = 17.0, $^3J_{HH}$ = 10.5, 10.4 and 4.0 Hz, N-CH-P), 4.84 (1H, dd, $^3J_{HH}$ = 10.5, $^3J_{HP}$ = 1.7, NH), 7.19 (1H$_{arom}$, m, 1CH), 7.28 (2H$_{arom}$, m, 2CH), 7.35 (2H$_{arom}$, m, 2CH). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 28.20 (3C, $C(CH_3)_3$), 29.96 (1C, d, $^2J_{CP}$ = 4.4 Hz, C-CH_2-C), 30.24 (1C, d, $^3J_{CP}$ = 14.4, S-CH_2), 45.27 (1C, d, $^1J_{CP}$ = 156.0 Hz, N-CH-P), 52.97 (1C, d, $^2J_{CP}$ = 6.6 Hz, OCH_3), 53.24 (1C, d, $^2J_{CP}$ = 7.0 Hz, OCH_3), 80.30 (1C, $C(CH_3)_3$), 126.26 (1C, *para*-CH_{arom}), 128.91 (2C, *meta*-CH_{arom}), 129.71 (2C, *ortho*-CH_{arom}), 135.52 (1C, *ipso*-C_{arom}), 155.24 (1C, d, $^3J_{CP}$ = 5.7 Hz, N-CO-O). IR (CCl_4, ν_{max}, cm^{-1}) 3436 w, 3258 m (NH); 1529 m, 1496 s (CONH); 1718 vs (C=O); 1251 s (P=O); 1062 vs, 1045 vs, 1037 vs (C-OP); 834 m (CO-P); 1482 s, 1440 m, 691 m (ring); 2980 m, 1367 s (CH_3); 1171 vs ($C(CH_3)_3$). HRMS (ESI) calc for $C_{16}H_{26}O_5NNaPS$ $[M+Na]^+$ 398.11615; found: 398.11617.

Dimethyl [(*R,S*)-1-(*tert*-butoxycarbonylamino)-3-(*tert*-butylsulfanyl)propyl]phosphonate (9b). Phosphonate **9b** was prepared in the same manner as **9a** by the reaction of compound **6b** (7.3 g; 15.2 mmol) and sodium methoxide (3.3 g; 60.8 mmol). Yield 3.5 g (64%). Colorless oil, R_f = 0.67 (S3). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 1.31 (9H, s, $C(CH_3)_3$), 1.45 (9H, s, $C(CH_3)_3$), 1.82 (1H, m, C-CHaHb-C), 2.08 (1H, m, C-CHaHb-C), 2.58 (1H, ddd, $^2J_{HH}$ = 12.2, $^3J_{HH}$ = 9.2 and 7.3 Hz, S-CHaHb), 2.68 (1H, ddd, $^2J_{HH}$ = 12.2, $^3J_{HH}$ = 9.3 and 4.9 Hz, S-CHaHb), 3.73 (6H, d, $^3J_{HP}$ = 10.5, 2x OCH_3), 4.21 (1H, dtd, $^3J_{HP}$ = 16.6, $^3J_{HH}$ = 10.5, 10.5 and 3.8 Hz, N-CH-P), 4.76 (1H, bd, $^3J_{HH}$ = 10.5, NH). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 24.62 (1C, d, $^3J_{CP}$ = 14.3, S-CH_2), 28.22 (3C, $C(CH_3)_3$), 30.67 (1C, d, $^2J_{CP}$ = 4.2 Hz, C-CH_2-C), 30.92 (3C, $C(CH_3)_3$), 42.29 (1C, $C(CH_3)_3$), 46.10 (1C, d, $^1J_{CP}$ = 155.8 Hz, N-CH-P), 52.98 (1C, d, $^2J_{CP}$ = 6.6 Hz, OCH_3), 53.24 (1C, d, $^2J_{CP}$ = 7.0 Hz, OCH_3), 80.20 (1C, $C(CH_3)_3$), 155.24 (1C, d, $^3J_{CP}$ = 5.4 Hz, N-CO-O). IR (CCl_4, ν_{max}, cm^{-1}) 3437 m, 3259 m (NH); 1529 m, 1497 s (CONH); 1716 vs (C=O); 1251 vs (P=O); 1062 vs, 1046 vs (C-OP); 834 s (CO-P); 2976 s, 1366 vs (CH_3); 1172 vs ($C(CH_3)_3$). HRMS (ESI) calc for $C_{14}H_{30}O_5NNaPS$ $[M+Na]^+$ 378.14745; found: 378.14736.

Dimethyl [(*R,S*)-1-(*tert*-butoxycarbonylamino)-3-(benzylsulfanyl)propyl]phosphonate (9c). Phosphonate **9c** was prepared in the same manner as **9a** by the reaction of compound **6c** (7.3 g; 14.2 mmol) and sodium methoxide (3 g; 56.8 mmol). Yield 3.1 g (57%). Colorless oil, R_f = 0.83 (S3). ^{1}H NMR (600 MHz; $CDCl_3$): δ_H 1.43 (9H, s, $C(CH_3)_3$), 1.77 (1H, m, C-CHaHb-C), 2.06 (1H, m, C-CHaHb-C), 2.46 (1H, ddd, $^2J_{HH}$ = 13.3, $^3J_{HH}$ = 9.0 and 7.2 Hz, S-CHaHb), 2.55 (1H, ddd, $^2J_{HH}$ = 13.3, $^3J_{HH}$ = 9.3 and 4.8 Hz, S-CHaHb), 3.75 (3H, d, $^3J_{HP}$ = 10.6, OCH_3), 3.76 (3H,

d, $^3J_{HP}$ = 10.6, OCH_3), 4.17 (1H, dtd, $^3J_{HP}$ = 16.7, $^3J_{HH}$ = 10.5, 10.5 and 3.8 Hz, N-CH-P), 4.71 (1H, bd, $^3J_{HH}$ = 10.5, NH), 7.23 ($1H_{arom}$, m, 1CH), 7.30 ($4H_{arom}$, m, 4CH). ^{13}C NMR (150.9 MHz; $CDCl_3$): δ_C 27.44 (1C, d, $^3J_{CP}$ = 14.5, S-CH_2), 28.22 (3C, C($\underline{C}H_3)_3$), 30.04 (1C, d, $^2J_{CP}$ = 4.1 Hz, C-$\underline{C}H_2$-C), 36.14 (1C, S-CH_2), 45.76 (1C, d, $^1J_{CP}$ = 156.0 Hz, N-CH-P), 52.95 (1C, d, $^2J_{CP}$ = 6.8 Hz, OCH_3), 53.23 (1C, d, $^2J_{CP}$ = 7.0 Hz, OCH_3), 80.22 (1C, $\underline{C}(CH_3)_3$), 126.98 (1C, *para*-CH_{arom}), 128.48 (2C, *ortho*-CH_{arom}), 128.84 (2C, *meta*-CH_{arom}), 138.16 (1C, *ipso*-C_{arom}), 155.20 (1C, d, $^3J_{CP}$ = 5.3 Hz, N-CO-O). IR (CCl_4, ν_{max}, cm^{-1}) 3437 w, 3260 m (NH); 1529 m, 1496 s (CONH); 1716 vs (C=O); 1250 vs (P=O); 1062 vs, 1045 vs (C-OP); 834 s (CO-P); 1454 s, 1440 m, 699 s (ring); 2980 s, 1367 s (CH_3); 1173 vs ($C(CH_3)_3$). HRMS (ESI) calc for $C_{17}H_{28}O_5NNaPS$ $[M+Na]^+$ 412.13180; found: 412.13169.

[(*R*,*S*)-1-Amino-3-(phenylsulfanyl)propyl]phosphonic acid (10a). From **2a**: Compound **2a** (13 g; 24.3 mmol) was heated for 12 h at reflux with 50 ml of 35% HCl and 50 ml of glacial acetic acid. The solvents were evaporated under reduced pressure, and the resultant oily residue was taken up in 50 ml of methanol. The methanolic solution of the crude product was treated with methyloxirane until a pH of 6 was reached. The product precipitated, was removed by filtration and then washed with methanol and diethyl ether. The yield was 4 g (67%). The product was a white solid, mp 266-268 °C.

From **8a**: Compound **8a** (0.6 g; 1.5 mmol) was stirred for 24 h in 2 ml of 35% of HBr/AcOH. The solvent was evaporated at 60°C *in vacuo*, and the residue was treated with 1,2-epoxypropane in methanol as described above. The yield was 0.25 g (69%).

From **7a**: Compound **7a** (0.3 g; 0.65 mmol) was dissolved in 5 ml of a mixture TFA-DCM-DMS-H_2O (47.5 : 47.5 : 2.5 : 2.5), and the solution was stirred at rt overnight. The volatile liquids (DCM and DMS) were removed by rotary evaporator at 25 °C, and the remaining yellow solution (approximately 2 ml) was lyophilized twice with 5 ml of water. The residue was dissolved in 10 ml of 0.1% aqueous TFA, passed through a filter (Rotilabo 0.22 μm, the compound tends to precipitate from the solution) and subjected to preparative RP-HPLC (G1). Finally, the pure product was lyophilized from water. The yield was 113 mg (73%). The product was a white powder.

From **9a**: TMSBr (1.5 g; 10 mmol) was added to the solution of **9a** (0.4 g; 1 mmol) in 10 ml of anhydrous acetonitrile, and the reaction was allowed to proceed at rt for 48 hours excluded from air and moisture. The reaction was then concentrated under reduced pressure; the residue was dissolved in 5 ml of a mixture TFA-DCM-DMS-H_2O (47.5 : 47.5 : 2.5 : 2.5) and stirred at rt overnight. The isolation of target product **10a** was performed in the same fashion as described for the reaction from **7a** to **10a**. Yield 130 mg (50%). White powder. R_f = 0.35 (S5). Calcd. for $C_9H_{14}NO_3PS$ (247.3) C 43.72 %, H 5.71%, N 5.66 %. Found: C 43.47%, H 5.62%, N 5.52%. ^{1}H NMR (600 MHz; D_2O + NaOD): δ_H 1.72 (1H, m, C-C$\underline{Ha}$Hb-C), 2.10 (1H, m, C-CHa$\underline{Hb}$-C), 2.69 (1H, m, dtd, $^3J_{HP}$ = 11.4, $^3J_{HH}$ = 10.5 and 3.4 Hz, N-CH-P), 3.06 (1H, ddd, $^2J_{HH}$ = 13.0, $^3J_{HH}$ = 9.2 and 7.0 Hz, S-C$\underline{Ha}$Hb), 3.26 (1H, ddd, $^2J_{HH}$ = 13.0, $^3J_{HH}$ = 9.6 and 4.7 Hz, S-C$\underline{Ha}$Hb), 7.29 ($1H_{arom}$, m, 1CH), 7.40 ($2H_{arom}$, m, 2CH), 7.46 ($2H_{arom}$, m, 2CH). ^{13}C NMR (150.9 MHz; D_2O + NaOD): δ_C 33.41 (1C, d, $^3J_{CP}$ = 14.5 Hz, S-CH_2), 34.20 (1C, C-$\underline{C}H_2$-C), 52.14 (1C, d, $^1J_{CP}$ =

137.7 Hz, N-CH-P), 128.94 (1C, *para*-CH_{arom}), 131.39 (2C, *ortho*-CH_{arom}), 132.05 (2C, *meta*-CH_{arom}), 138.37 (1C, *ipso*-C_{arom}). IR (KBr, ν_{max}, cm^{-1}) 3100-2400 vs+vbr, 1535 s (NH_3^+); 1178 s (PO_2^-); 1023 vs (POH); 1585 m, 1481 m, 1439 m, 736 s, 689 s (ring). HRMS (ESI) calc for $C_9H_{13}O_3NPS$ $[M-1]^+$ 246.03592; found: 246.03588.

[(*R*,*S*)-1-Amino-3-(*tert*-butylsulfanyl)propyl]phosphonic acid (10b). From **8b**: The acid **10b** was prepared in the same fashion as **10a** by the reaction of **8b** (0.6 g; 1.4 mmol) and 2 ml of 35% HBr/AcOH. The precipitated oil was separated and subjected to RP-HPLC. Only traces of the product were isolated.

From **7b**: The acid **10b** was prepared in the same fashion as **10a** by the treatment of **7b** (0.5 g; 1.1 mmol) with 5 ml of the cleavage cocktail. RP-HPLC (G2). The yield was 168 mg (68%). The product was a white powder.

From **9b**: The acid **10b** was prepared in the same fashion as **10a** by the reaction of **9b** (0.6 g; 1.7 mmol) and TMSBr (2.6 g; 17 mmol) followed by the treatment of the resulting oil with 5 ml of the cleavage cocktail. Yield 195 mg (51%). White powder. R_f = 0.29 (S5). Calcd. for $C_7H_{18}NO_3PS$ (227.3) C 37.00 %, H 7.98%, N 6.16 %. Found: C 36.76%, H 7.87%, N 5.81%. ^{1}H NMR (600 MHz; D_2O + NaOD): δ_H 1.33 (9H, s, $C(CH_3)_3$), 1.59 (1H, m, C-C<u>Ha</u>Hb-C), 1.97 (1H, m, C-CHa<u>Hb</u>-C), 2.58 (1H, m, td, $^3J_{HP}$ = 11.0, $^3J_{HH}$ = 11.0 and 3.1 Hz, N-CH-P), 2.65 (1H, ddd, $^2J_{HH}$ = 11.8, $^3J_{HH}$ = 9.8 and 6.8 Hz, S-C<u>Ha</u>Hb), 2.85 (1H, ddd, $^2J_{HH}$ = 11.8, $^3J_{HH}$ = 10.2 and 4.8 Hz, S-C<u>Ha</u>Hb). ^{13}C NMR (150.9 MHz; D_2O + NaOD): δ_C 28.64 (1C, d, $^3J_{CP}$ = 14.5 Hz, S-CH_2), 32.88 (3C, C(<u>C</u>H_3)$_3$), 34.99 (1C, <u>C</u>$(CH_3)_3$), 45.32 (1C, C-<u>C</u>H_2-C), 52.76 (1C, d, $^1J_{CP}$ = 137.6 Hz, N-CH-P). IR (KBr, ν_{max}, cm^{-1}) 3100-2400 vs+vbr, 1535 s (NH_3^+); 1170 vs (PO_2^-); 1027 vs (POH); 2962 vs (CH_3). HRMS (ESI) calc for $C_7H_{18}O_3NPS$ $[M-1]^+$ 226.06722; found: 226.06730.

[(*R*,*S*)-1-Amino-3-(benzylsulfanyl)propyl]phosphonic acid (10c). From **8c**: The acid **10c** was prepared in the same fashion as **10a** by the reaction of **8c** (0.6 g; 1.4 mmol) and 2 ml of 35% HBr/AcOH. The yield was 0.23 g (62%). The product was a white solid, mp 264-266 °C (lit.[7] 270-272°C).

From **7c**: The acid **10c** was prepared in the same fashion as **10a** by the treatment of **7c** (0.5 g; 1 mmol) with 5 ml of the cleavage cocktail. RP-HPLC (G2). The yield was 200 mg (75%). The product was a white powder.

From **9c**: The acid **10c** was prepared in the same fashion as **10a** by the reaction of **9c** (0.4 g; 1 mmol) and TMSBr (1.5 g; 10 mmol) followed by the treatment of the residual oil with 5 ml of the cleavage cocktail. Yield 147 mg (55%). White powder. R_f = 0.33 (S5). Calcd. for $C_{10}H_{16}NO_3PS$ (261.3) C 45.97 %, H 6.17%, N 5.36 %. Found: C 45.57%, H 6.02%, N 5.26%.^{1}H NMR (600 MHz; D_2O + NaOD): δ_H 1.64 (1H, m, C-C<u>Ha</u>Hb-C), 2.07 (1H, m, C-CHa<u>Hb</u>-C), 2.60 (1H, m, ddd, $^3J_{HP}$ = 11.2, $^3J_{HH}$ = 10.6 and 3.1 Hz, N-CH-P), 2.55 (1H, ddd, $^2J_{HH}$ = 12.8, $^3J_{HH}$ = 9.4 and 7.0 Hz, S-C<u>Ha</u>Hb), 2.73 (1H, ddd, $^2J_{HH}$ = 12.8, $^3J_{HH}$ = 9.7 and 4.6 Hz, S-C<u>Ha</u>Hb), 3.81 (2H, s, S-CH_2), 7.35 (1H_{arom}, m, 1CH), 7.39 (4H_{arom}, m, 4CH). ^{13}C NMR (150.9 MHz; D_2O + NaOD): δ_C 31.45 (1C, d, $^3J_{CP}$ = 14.7 Hz, S-CH_2), 34.12 (1C, S-CH_2), 37.63 (1C, C-<u>C</u>H_2-C), 52.17 (1C, d, $^1J_{CP}$ = 137.9 Hz, N-CH-P), 129.94 (1C, *para*-CH_{arom}), 131.56 (2C, *ortho*-CH_{arom}), 131.70 (2C, *meta*-CH_{arom}), 141.43 (1C, *ipso*-C_{arom}). IR (KBr, ν_{max}, cm^{-1}) 3200-2400 vs+vbr, 1535

s (NH_3^+); 1177 s (PO_2^-); 1023 vs (POH); 1494 m, 1463 m, 697 m (ring). HRMS (ESI) calc for $C_{10}H_{15}O_3NPS$ $[M-1]^+$ 260.05157; found: 260.05124.

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