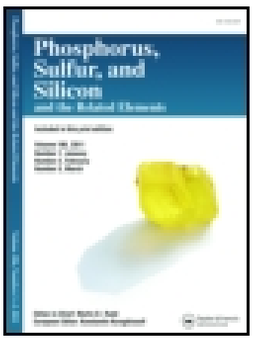

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Conversion of nitriles to 1-aminophosphonic acids and preparation of phosphahomocysteines of high enantiomeric excess

Renzhe Qian[a], Jeannie Horak[b] and Friedrich Hammerschmidt[a,*]

[a]Institute of Organic Chemistry, University of Vienna, Vienna, Austria

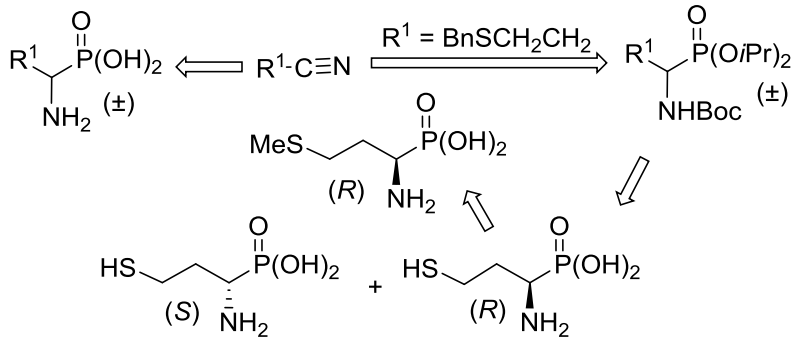
[b]Institute of Pharmaceutical Sciences, Pharmaceutical (Bio-)Analysis, Eberhard-Karls-University Tuebingen, Tuebingen, Germany

Correspondence author: friedrich.hammerschmidt@univie.ac.at

ABSTRACT

A variety of nitriles was reduced to diisobutylaluminum salts of aldimines, to which diisopropyl phosphite was added. The corresponding 1-aminophosphonates were either deprotected to give racemic 1-aminophosphonic acids or reacted with Boc_2O to yield *N*-Boc-protected 1-aminophosphonates. The enantiomers of 2-benzylthio-1-(*t*-butoxycarbonylamino)propylphosphonate were obtained from the racemate by chiral HPLC and converted to phosphonic acid analogs of (*R*)- and (*S*)-homocysteine, (*R*)- and (*S*)-2-aminobutyric acid and (*S*)-methionine, all of ee >97% as determined by chiral HPLC.

Graphical Abstract



Keywords

Nitriles; 1-aminophosphonic acids; phosphahomocysteine; desulfurization; enantiomeric excess; chiral HPLC; 6-aminoquinolyl-*N*-hydroxysuccinimidyl carbamate.

Introduction

Aminophosphonic acids as analogs of amino(carboxylic) acids have interesting chemical and biological properties, which have made them synthetic targets for the last decades.[1] Many, especially the phosphonic acid analogs of proteinogenic amino acids, have been prepared as racemates as well as enantiomers of (*R*)- and (*S*)-configuration of high enantiomeric excess by a multitude of methods.[2] Nevertheless, the synthesis of analogs of certain amino acids has not been described neither in racemic nor enantiomerically pure form, e. g. phosphahomocysteine, the phosphonic acid analogue of homocysteine. We envisaged to test it as a potential inhibitor of phenylalanine ammonia lyase (PAL), an enzyme of central importance in plant metabolism.[3] It contains a 5-methylene-3,5-dihydroimidazol-4-one (MIO) moiety in the active site, post-translationally formed from three amino acid. Its function in the conversion of L-phenylalanine to cinnamic acid and ammonia is still open to debate.[4] (*R*)-Phosphaphenylalanine is a strong inhibitor of PAL.[5] Hence it was reasoned that the SH group of (*R*)-phosphahomocysteine could add to MIO as Michael acceptor and thus irreversibly block it. Surprisingly, this phosphonic acid analog of homocysteine has not been described in the literature to the best of our knowledge. Therefore, a synthesis was developed to obtain phosphahomocysteine as racemate as well as both of its enantiomers.

Results and discussion

First, we aimed at using nitriles as starting materials for the preparation of α-aminophosphonic acids, then *N*-Boc-protected α-aminophosphonic acids and finally the phosphahomocysteines. This approach is reminiscent of the one developed by Kudzin and Majchrzak for simple

aminophosphonic acids.[6] Thus, nitriles **1a-d** were reacted with *i*Bu_2AlH under argon in dry toluene for 2 h at 0°C (Scheme 1). The reaction mixtures containing the intermediate diisobutylaluminum salts **2a-d** of the corresponding imine were cooled to –30°C and diisopropyl phosphite (1.2 equiv.) was added. After allowing the temperature to slowly rise to room temperature, the diisopropyl α-aminophosphonates **3a-d** were extracted with 6 N HCl and refluxed for 4 h. The racemic *α*-aminophosphonic acids (±)-**4a-d** were isolated and purified by cation exchange chromatography and crystallized from water/EtOH. Replacing diethyl phosphite as used in the literature[6] by diisopropyl phosphite increased the yield significantly.

This reaction sequence was applied to easily access phosphaproline (Scheme 2). When ω-bromobutyronitrile (**1e**) was reacted in sequence with DIBAH and diisopropyl phosphite, aminophosphonate (±)-**3e** was evidently formed. Then, heating the reaction mixture for 2 h at 100°C induced its cyclisation with the formation of diisopropyl phosphaproline (±)-**5** possibly complexed with diisobutylaluminum bromide. Deprotection and purification as before furnished racemic phosphaproline (±)-**4e**.[7,8]

Next, we became interested in the preparation of *N*-Boc-protected 1-aminophosphonates from nitriles using this methodology (Scheme 3). Powell et al.[9] found that tris(2-hydroxyethyl)- amine was a good ligand for the aluminum and facilitated isolation of aminoalcohols from reaction mixtures, obtained by using $LiAlH_4$ as reducing agent. Addition of this triol and Boc_2O to the reaction mixture containing the aluminum salts of aminophosphonates (±)-**3f-i**, furnished *N*-Boc-protected aminophosphonates (±)-**6a-d**. The most interesting of the four products was (±)-**6d**, the starting material for racemic and both enantiomeric phosphahomocysteines with at least 98% ee.

The enantiomers of the racemate could be separated by analytical chiral HPLC (Chiralpak IC column) and on a preparative scale on a semi-preparative IC column delivering both enantiomers with 99% ee. In order to determine their absolute configuration, they were converted to 1-aminopropylphosphonic acids of known configuration (Scheme 4).

The phosphonates (±)-, (–)- and (+)-**6d** were deprotected at the nitrogen and phosphorus atom by refluxing 6 M HCl to give salts (±)-, **(+)** and **(–)-7**. Their solutions were neutralized with 2 M NaOH and then desulfurized with Raney-nickel.[10] The three 1-aminopropylphosphonic acids **8** were isolated by cation exchange chromatography. As (–)-**8** has (*R*)-configuration,[11-13] (–)-**6d** has also (*R*)-configuration and (+)-**8** and (+)-**6d** have consequently (*S*)-configuration. The enantiomeric excesses of (*S*)-(+)- and (*R*)-(–)-**8**, the latter before and after crystallization, were 98.3%, 97.0, and 97.4%, respectively, as determined by chiral HPLC (see experimental and supplementary material Table S1 and Figure S1).

It is noteworthy, that two research groups tried to synthesize racemic phosphahomocysteine, but could isolate only the respective disulfide, the phosphahomocystine. Kudzin and Stec[14.15] obtained it in 64-77% yield, when they deprotected *S*-*t*-butyl-, *S*-acetyl- and *S*-(*t*BuO)$_3$Si-phosphahomocsyteine with AcOH/HBr. Tam et al. reported that various attempts, e. g. sodium in liquid ammonia, to deprotect *S*-benzyl- and *S*-4-nitrobenzyl-phosphahomocysteine also afforded only phosphahomocystine.16 We had two options for the deprotection of phosphahomocysteines **6**, which we considered as starting materials for racemic and enantiomeric phosphahomocysteines **9** (Scheme 5). The benzyl group could be removed removed reductively with sodium in liquid ammonia before or after removal of Boc and isopropyl groups with hot 6

M HCl. The first option, transformation of (±)-**6** via (±)-**7,** which has already been described in Scheme 3, into (±)-**9** was tested first. Carefully dried aminophosphonic acid hydrochloride (±)-**7** dissolved in THF was treated with a large excess (5.4 equiv.) of sodium in liquid ammonia under exclusion of air. Nevertheless, the yield of racemic phosphahomocysteine obtained by cation exchange chromatography was only 40%. TLC of the reaction mixture had already revealed that a large portion of starting material was still present. As the low yield was attributed to the insufficient solubility of the salt in liquid ammonia, the two steps of deprotection of (±)-**6d** were interchanged. The benzyl group of the protected phosphahomocysteine (±)-**6d** was reductively removed with 3 equiv. of sodium in liquid ammonia smoothly. The residue after evaporation of the ammonia was immediately refluxed with 6 M HCl. The crude product did not contain *S*-benzyl-phosphahomocsteine as evidenced by TLC. Not surprisingly, cation exchange chromatography furnished 68% of the desired crystalline phosphahomocysteine (±)-**9**. The enantiomers (*R*)-(–)- and (*S*)-(+)-**9** were similarly prepared in 79% and 76% yield, respectively.

Finally, phosphahomocysteine (*R*)-(–)-**9** was treated with 3 equiv. of EtONa/EtOH to generate the respective salt, which reacted rapidly with methyl iodide. (Scheme 6). The phosphamethionine (*R*)-(–)-**10** the phosphonic acid analog of proteinogenic L-methionine was isolated by cation exchange chromatography in 93% yield. Its configuration and specific optical rotation were in agreement with literature data[17,18] which is an independent support for the configurations assigned to (–)- and (+)-**6d**. Importantly, the conversion of (*R*)-(–)-**9** to (*S*)-(+)-**10** is a chemical proof that indeed phosphahomocysteine was obtained and not the corresponding disulfide, which would not undergo this reaction. The enantiomeric excesses of (*R*)-(–)-**8**, before

and after crystallization, were 99.3%, and 99.6%, respectively, as determined by chiral HPLC (see experimental and supplementary material Table S1 and Figure S2).

In summary, a variety of aminophosphonic acids and *N*-Boc-protected aminophosphonates were prepared from nitriles in one pot reactions. The enantiomers of *O,O*-diisopropyl *S*-benzyl-*N*-Boc-phosphahomocysteine were isolated from the racemate by chiral HPLC on a Chiralpak IC column. The configurations of the enantiomers were determined by chemical correlation with (*R*)-(–)- and (*S*)-(+)-1-aminopropylphosphonic acid. Furthermore, the enantiomers were converted to the enantiomers of phosphahomocysteine, which were prepared for the first time. The (*R*)-enantiomer of phosphahomocysteine was methylated to give the phosphonic acid analog of L-methionine. All enantiomers of **6**, **8**, and **9** had ee >97% as determined by HPLC on a quinine-based chiral anion exchanger.

Experimental

^{1}H, ^{13}C (*J*-modulated) and ^{31}P NMR spectra were recorded in $CDCl_3$, toluene-d_8, D_2O, D_2O/NaOD, and D_2O/DCl on a Bruker AV III 400 (^{1}H: 400.27 MHz, ^{13}C: 100.65 MHz, ^{31}P: 162.03 MHz), AV 400 (^{1}H: 400.13 MHz; ^{13}C: 100.61 MHz; ^{31}P: 161.98 MHz) Spectrometer at 25°C. Chemical shifts (δ) are reported in parts per million (ppm) relative to $CDCl_3$ (δ_H 7.24; δ_C 77.00), $C_6D_5CD_2H$ (δ_H 2.09), HDO (δ_H 4.80, and external H_3PO_4 (85%; δ_P 0.00) and coupling constants (*J*) in Hz. Data for ^{1}H NMR spectra are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants, and integration. IR spectra of compounds soluble in CH_2Cl_2 or $CDCl_3$ were recorded on a Perkin-Elmer FT 1600 IR Spectrometer.[19] The solution was applied to a silicon disc and the solvent was

allowed to evaporate before the measurement. IR spectra of the aminophosphonic acids were recorded on a Bruker VERTEX 70 IR Spectrometer as ATR spectra. Optical rotations were measured with a Perkin-Elmer Polarimeter 141 in a 1 dm cell. Analytical HPLC: Shimadzu system comprising components LC-20AT, SIL-20A HT, CTO-20AC, SPD-20A, CMB-20A, column: Chiralpak IC (250 × 4.6 mm, particle size 5 μm, solvent: *n*-heptanes/2-propanol, 10:1; 0.7 mL/min), LC solutions; semi-preparative column: Chiralpak IC, 260 × 20 mm, particle size 5 mm. Melting points were measured on a Leica Galen III Thermovar instrument and are uncorrected. The Supplemental Materials contains sample ^{1}H, ^{13}C and ^{31}P NMR spectra for 6b, 6d and 9, together with chromatoggraphic outputs (Figures S 1 -- S 13, Table S 1)

Cation exchange chromatography was performed on Dowex 50W × 8, H^+, 100-200 mesh. Flash (column) chromatography was performed with silica gel 60 (230-400 mesh) or aluminum oxide (standardized according to Brockmann) and monitored by TLC, carried out on 0.20 mm thick plates, silica gel 60 F_{254}. Spots were visualized by UV and/or dipping the plate into a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (24 g) and $Ce(SO_4)_2\cdot 4H_2O$ (1.0 g) in 10% aqueous H_2SO_4 (500 mL), followed by heating with a heat gun. TLC of aminophosphonic acids was performed on the same silica gel 60 plates as given above, using a mixture of *i*PrOH/H_2O/NH_3 (25%) = 6:3:1 as solvent. Spots were visualized by dipping the dried plate into a solution of ninhydrin (0.2%) in ethanol (96%) and heating with a heat gun.

Dry diethyl ether and THF were refluxed over $LiAlH_4$ and potassium, respectively, and distilled before use. Commercial CH_2Cl_2, EtOAc and hexanes used as solvents were distilled. Cooling at –78°C was done with acetone/dry ice.

Determination of enantiomeric excess of aminophosphonic acids

Analytical determination of enantiomeric access for 6-aminoquinolyl-*N*-hydroxysuccinimidyl carbamate (AQC; AccQ) derivatized phospha amino acids **8** and **10** was performed with an in-house prepared underivatized OH-QN-AX column[20] (150 mm x 4 mm, 5 µm; CSP1) employing as mobile phase 2 M aqueous H_3PO_4/MeOH (1:9, (v/v)), pH 4.0 (adjusted with triethylamine) at a flow rate of 0.5 mL/min and a column temperature of 40°C. For AQC sample derivatization, phospha amino acids (10 µL, 20 mM) were added to 0.2 M borate buffer (70 µL, pH 8.5), followed by AQC-reagent (20 µL, 3 mg/mL in dry CH_3CN). This reaction mixture was immediately heated at 55°C for 10 min on a thermoshaker PHMT with PSC24N from Grant-bio (Cambridgeshire, UK). HPLC-UV-FLD Analysis was performed on a Agilent 1100 binary pump with column oven, autosampler, multi-wavelength detector (MWD) and fluorescence detector (FLD; gain 10; excitation: 254 nm; emission: 395 nm) from Agilent (Waldbronn, Germany). Note that the chiral ligand of OH-QN-AX is per se fluorescence active, which necessitates a thorough column rinse with the mobile phase prior to analysis. Sample injection was only performed after obtaining a stable base line. The (+)-enantiomers of **8** and **10** eluted before the (–)-enantiomers. Due to a slight peak tailing at high sample loading, trace amounts of the (+) enantiomer can be easily separated from the main enantiomer peak, while in the reversed case the impurity peak could disappear under the tailing of the main enantiomer peak. In the latter case, the inverse quinidine-type column could be used, which provides a reversal in elution order. In the present case, the mobile phase flow rate was reduced to 0.5 mL/min to achieve better separation efficiencies. For both racemates, of compound **8** as well as **10**, a separation

factor of 1.14 could be obtained. Chromatographic results are summarized in the Supporting Information in Figures S1, S2 and Table S1.

General procedure A -- Preparation of diisopropyl 1-aminophosphonate (±)-3, followed by conversion to 1-aminoalkylphosphonic acid (±)-4

DIBAH (6.0 mL, 1 M in toluene, 1.2 equiv.) was added dropwise to a stirred solution of nitrile (5 mmol) dissolved in dry toluene (10 mL) at 0°C under argon. After 2 h at 0°C, the reaction mixture was cooled to –30°C. Diisopropyl phosphite (1.0 g, 6.0 mmol, 1.0 mL, 1.2 equiv.) was added and stirring was continued for 18 h, while the solution was allowed to slowly warm to room temperature in the cooling bath. The reaction mixture was extracted with 6 N HCl (3 × 15 mL). The combined acidic solutions were refluxed for 4 h, concentrated under reduced pressure and dried in a vacuum desiccator over KOH for 18 h. The residue was dissolved in water and applied to a column filled with Dowex 50W × 8, H^{+}, 100-200 mesh for cation exchange chromatography. Elution with water gave fractions which were analyzed for 1-aminophosphonic acid by TLC (*i*PrOH/H_2O/NH_3 (25%), 6:3:1). Ninhydrin-positive fractions were pooled and concentrated under reduced pressure to give crystalline products.

(±)-1-Aminoethylphosphonsäure [(±)-4a]

Dry CH_3CN (0.21 g, 5 mmol, 0.26 mL) was transformed into 1-aminophosphonic acid (±)-**4a** (0.48 g, 76%) as colorless crystals, using general procedure A. R_f = 0.28; mp 294-297°C (H_2O/EtOH) (lit.[21]: 283-286°C). The NMR spectra were in agreement with those of the literature.[22]

(±)-1-Amino-2-methylpropylphosphonic acid [(±)-4b]

Isobutyronitrile (0.346 g, 5 mmol, 0.45 mL) was transformed into 1-aminophosphonic acid (±)-**4b** (0.425 g, 56%) as colorless crystals, using general procedure A. R_f = 0.22; mp 281-286°C (H_2O/EtOH) (lit.[21]: 280-281°C). The ^{1}H NMR spectrum was identical to that of (*R*)-**4b** reported in the literature.[23]

^{13}C NMR (100.61 MHz, D_2O/NaOD): δ = 55.4 (d, *J* = 141.9 Hz, CHP), 28.0 (CH), 20.2 (d, *J* = 7.0 Hz, CH_3), 18.2 (d, *J* = 7.0 Hz, CH_3). ^{31}P NMR (162.02 MHz, D_2O/NaOD): δ = 14.1.

(±)-1-Amino-2-chloroethylphosphonic acd [(±)-4c]

Chloroacetonitrile (0.38 g, 5.0 mmol, 0.32 mL) was transformed into 1-aminophosphonic acid (±)-**4c** (0.43 g, 58%) as colorless crystals, using general procedure A. R_f = 0.73; mp 219-222°C (H_2O/EtOH) (lit.[24]: 202-208°C).

IR (ATR): ν = 2363, 1596, 1507, 1167, 1104, 1065, 914 cm^{-1}. ^{1}H NMR (400.13 MHz, D_2O/DCl): δ = 3.84 (X part of ABX system, *J* = 12.6, 9.4, 3.4 Hz, 1H, CHP), 3.63 (A part of ABX system, *J* = 12.6, 9.6, 4.7 Hz, 1H, CH_2Cl), 3.49 (B part of ABX system, *J* = 15.2, 9.6, 3.4 Hz, 1H, CH_2Cl).

^{13}C NMR (100.61 MHz, D_2O/DCl): δ = 50.6 (d, *J* = 130.0 Hz, CHP), 41.8 (CH_2Cl).

^{31}P NMR (162.02 MHz, D_2O/DCl): δ = 11.0.

(±)-1-Amino-3-(methylthio)propylphosphonic acid [(±)-4d]

3-Methylthiopropionitrile[25] (0.51 g, 5.0 mmol, 0.45 mL) was transformed into 1-aminophosphonic acid (±)-**4d**[14,16], (0.81 g, 87%) as colorless crystals, using general procedure A. R_f = 0.35; mp 284-285°C (H_2O/EtOH) (lit[16]: 274-275°C).

^{1}H NMR (400.27 MHz, D_2O): δ = 3.49 (ddd. J = 13.6, 8.0, 5.7 Hz, 1H, CHP), 2.87-2.70 (m, 2H, SCH_2), 2.37-2.22 (m, 1H, CH_2), 2.18 (s, 3H, CH_3), 2.15-2.06 (m, 1H, CH_2).

^{13}C NMR (100.61 MHz, D_2O): δ = 48.0 (d, J = 142.8 Hz, CHP), 29.6 (SCH_2), 27.6 (CH_2), 13.8 (SCH_3).

^{31}P NMR (162.02 MHz, D_2O): δ = 12.8.

(±)-(Pyrrolidin-2-yl)phosphonic acid [(±)-4e]

After reacting 4-bromobutyronitrile (0.74 g, 5.0 mmol, 0.50 mL) with DIBAH and diisopropyl phosphite according to general procedure A, the reaction mixture was heated at 100°C for 2 h. Work up, hydrolysis, and isolation of phosphaproline (±)-**4e** were again performed according to general procedure A. R_f = 0.19; yield: 0.53 g (70%) of colorless crystals; mp 266-268°C (H_2O/EtOH) (lit.[7]: 264-265°C; lit.[8]: 266-267°C). The spectroscopic data were identical to those reported in the literature.[26]

General procedure B -- Preparation of *N*-Boc-protected dialkyl 1-aminophosphonates (±)-6a-d

Nitrile (5.0 mmol), DIBAH (6.0 mmol, in toluene) and diethyl or diisopropyl phosphite (6.0 mmol) were reacted according to general procedure A. After 18 h, when the temperature of the reaction mixture had risen from –30°C to room temperature, a solution of tris(2-

hydroxyethyl)amine (0.97 g, 6.5 mmol, 1.3 equiv.) in dry CH_2Cl_2 (2 mL) was added, followed by a solution of Boc_2O (1.42 g, 6.5 mmol, 1.3 equiv.) in dry CH_2Cl_2 (2 mL). Stirring was continued at room temperature for 18 h. The mixture was concentrated at reduced pressure, taken up in EtOAc, passed through a column (3 × 10 cm) filled with aluminum oxide and using EtOAc as eluens. The eluate was concentrated under reduced pressure and the residue was flash chromatographed (silica gel).

(±)-Diisopropyl 1-(*t*-butoxycarbonylamino)phenylmethylphosphonate [(±)-6a]

Benzonitrile (0.52 g, 5.0 mmol, 5.2 mL) was transformed into (±)-**6a** according to general procedure B. The crude product was flash chromatographed (hexanes/EtOAc, 2:1; R_f = 0.22) to give (±)-**6a** (1.0 g, 54%) as colorless crystals; mp 84-88°C (hexanes).

IR (Si): ν = 3253, 2979, 2935, 1713, 1532, 1386, 1366, 1285, 1236, 1173, 993 cm^{-1}. The NMR spectroscopic data were identical to those of the literature for a product of ee 63%.[27] ^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 21.3 (major conformer: 0.9P), 20.85 (minor: 0.1P).

Anal. calcd for $C_{18}H_{30}NO_5P$ (371.41): C, 58.21; H, 8.14; N, 3.77. Found: C, 58.50; H, 8.11; N, 3.77.

(±)-Diisopropyl 1-(*t*-butoxycarbonylamino)-2-phenylethylphosphonate [(±)-6b]

Phenylacetonitrile (0.59 g, 5.0 mmol, 0.57 mL) was transformed into (±)-**6b** according to general procedure B. The crude product was flash chromatographed (hexanes/EtOAc, 1:1; R_f = 0.58) to give (±)-**6b** (1.04 g, 54%) as colorless crystals; mp 81-82°C (hexanes).

IR (Si): ν = 3261, 3030, 2933, 1717, 1528, 1498, 1387, 1366, 1228, 1175, 1106, 1010 cm^{-1}.

Ratio of conformers A and B in $CDCl_3$: 4:1. ^1H NMR (400.13 MHz, $CDCl_3$): δ = 7.34-7.17 (m, 5H, H_{ar}), 4.86-4.69 (m, 2H, POCH), 4.65 (A: d, *J* = 10.2 Hz, 0.8H, NH), 4.44 (B: br. d, *J* = 6.9 Hz, 0.2H, NH), 4.34-4.24 (A: m, 0.8H, CHP), 4.11-4.00 (B: m, 0.2H, CHP), 3.24 (ddd, *J* = 13.8, 7.3, 4.0 Hz, 1H, CH_2Ph), 2.78 (A: td, *J* = 13.8, 10.0 Hz, 0.8H, CH_2Ph), 2.73-2.57 (B: m, 0.2H, CH_2Ph), 1.38-1.24 (overlapping d, 12H, CH_3), 1.29 (A: s, 7.2H, *t*Bu), 1.14 (B: s, 1.8H, *t*Bu).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 154.9 (C = O), 137.0 (d, *J* = 13.5 Hz, C_{ar}), 129.5 (br. s) and 129.3 (B and A: $2CH_{ar}$),128.3 (br. s) and 128.2 (B and A: $2HC_{ar}$), 126.5 (HC_{ar}), 79.7 (OC), 71.4 (d, *J* = 7.3Hz, POCH), 71.1 (d, *J* = 7.0 Hz, POCH), 48.5 (d, *J* = 158.2 Hz, CHP), 36.5 (CH_2Ph), 28.1 and 27.7 (br. s) (A and B: each 3C, *t*Bu), 24.2 (d, *J* = 3.3 Hz, CH_3), 24.1 (d, *J* = 3.5 Hz, CH_3), 23.9 (d, *J* = 4.5 Hz, CH_3), 23.7 (d, *J* = 5.3 Hz, CH_3).

^{31}P NMR (161.98 MHz, $CDCl_3$):δ = 23.8 (A, 0.8P), 23.1 (B, 0.2P); ratio of conformers A and B in toluene-d_8: 6.7:1.

^1H NMR (400.27 MHz, toluene-d_8, 25°C): δ = 7.24-6.95 (m, 5H, H_{ar}), 5.93 (B: br. d, *J* = 7.0 Hz, 0.13H, NH), 5.69 (A: d, *J* = 10.3 Hz, 0.87H, NH), 4.90-4.60 (m, 2H, POCH), 4.53 (A: tdd, *J* = 17.3, 10.3, 4.3 Hz, 0.87H, CHP), 4.16 (B: br. s, 0.13H, CHP), 3.25 (ddd, *J* = 13.8, 6.9, 4.3 Hz, 1H, CH_2Ph), 2.78 (A: td, *J* = 13.8, 10.4 Hz, 0.87H, CH_2Ph), 2.89 (B: br. s, 0.13H,CH_2Ph), 1.30 (A: 7.83H, *t*Bu), 1.22-1.15 (overlapping d und s of B, 13.17H, CH_3 and *t*Bu).

^1H NMR (400.13 MHz, toluene-d_8, 70°C): δ = 7.18-6.95 (m, 5H, H_{ar}), 4.89 (br. d, *J* = 9.1 Hz, 1H, NH), 4.75-4.55 (m, 2H, POCH), 4.39 (br. s, 1H, CHP), 3.22 (ddd, *J* = 13.9, 8.6, 4.3 Hz, 1H,

CH_2Ph), 2.82 (td, J = 13.9, 10.4 Hz, 1H, CH_2Ph), 1.27 (s, 9H, *t*Bu), 1.19 (d, J = 4.3 Hz, 3H, CH_3), 1.17 (d, J = 4.3 Hz, 6H, CH_3), 1.15 (d, J = 4.3 Hz, 3H, CH_3).

^{31}P NMR (162.00 MHz, toluene-d_8, 25°C): δ = 23.2 (A: 0.85P), 22.7 (B: 0.15P); ratio: 5.7:1.

^{31}PNMR (161.98 MHz, toluene-d_8, 70°C): δ = 23.2.

Anal. calcd for $C_{19}H_{32}NO_5P$ (385.44): C, 59.21; H, 8.37; N, 3.63. Found: C, 59.28; H, 8.33; N, 3.63.

(±)-Diethyl 1-(*t*-butoxycarbonylamino)-2-phenylethylphosphonate [(±)-6c]

Phenylacetonitrile (0.59 g, 5.0 mmol, 0.57 mL) was transformed into (±)-**6c** according to general procedure B, except that diisopropyl phosphite was replaced by diethyl phosphite. The crude product was flash chromatographed (hexanes/EtOAc, 1:1; R_f = 0.32) to give (±)-**6c**[28] (1.0 g, 56%) as colorless crystals; mp 47-49°C.

IR (Si): ν = 3263, 2979, 1713, 1526, 1391, 1366, 1229. 1171, 1029 cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.28-7.15 (m, 5H, H_{ar}), 4.64 (conformer A: br. d, J = 10.1 Hz, 0.83H, NH), 4.41 (B: br. s, 0.17H, NH), 4.32 (A: tdd, J = 15.6, 10.4, 4.6 Hz, 0.83H, CHP), 4.20-4.02 (m, 4H, $POCH_2$ and 0.17H, CHP), 3.19 (ddd, J = 14.0, 8.4, 4.6 Hz, 1H, CH_2Ph), 2.80 (A: td, J = 14.0, 10.4 Hz, 0.83H, CH_2Ph), 2.67 (B: br. s, 0,17H,), 1.35-1.12 (m, 15H, CH_3 and *t*Bu).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 154.9 (d, J = 6.9 Hz, C = O), 137.7 (d, J = 12.9 Hz, C_{ar}), 129.2 ($2CH_{ar}$), 128.3 ($2CH_{ar}$), 126.6 (CH_{ar}), 79.8 (OC), 62.7 (d, J = 7.1 Hz, $POCH_2$), 62.4 (d, J =

6.7 Hz, $POCH_2$), 48.8 (d, J = 156.5 Hz, CHP), 36.2 (d, J = 3.9 Hz, CH_2Ph), 28.1 (A: 3C, *t*Bu), 27.8 (B: 3C, *t*Bu), 16.4 (d, J = 5.7 Hz, CH_3), 16.3 (d, J = 6.1 Hz, CH_3).

^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 25.8 (A: 0.83P), 25.1 (B: 0.17P); ratio of conformers: 4.9:1.

Anal. calcd for $C_{17}H_{28}O_5NP$ (357.38): C, 57.13; H, 7.90; N, 3.92. Found: C, 57.06; H, 7.60; N, 3.93.

(±)-, (–)- and (+)-diisopropyl 3-(benzylthio)-1-(*t*-butoxycarbonylamino)propylphosphonate [(±)-, (–)- and (+)-6d]

3-Benzylthiopropionitrile[29] (0.89 g, 5.0 mmol) was transformed into (±)-**6c** according to general procedure B. The crude product was flash chromatographed (hexanes/EtOAc, 2:1; R_f = 0.27) to give (±)-**6d** (1.55 g 69%) as colorless crystals; mp 56-58°C (hexanes).

Analytical HPLC on Chiralpak IC column: (+)-**6d**: t_R = 14.14 min; (–)-**6d**: t_R = 20.35 min; preparative separation gave (+)-**6d**, $[\alpha]_D^{20}$ = +28.8 (c = 1.06, acetone), and (–)-**6d**, $[\alpha]_D^{27}$ = –29.6 (c = 1.0, acetone) as oils; both with ee >99%.

IR (Si): ν = 3263, 2979, 1713, 1526, 1391, 1366, 1229. 1171, 1029 cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$), ratio of major conformer A/minor conformer B, 0.87:0.13: δ = 7.30-7.17 (m, 5H, H_{ar}), 4.67 (oct, J = 6.3 Hz, 2H, POCH), 4.62 (br. d, J = 10.4 Hz, 0.87H, NH, major conformer A), 4.30 (br. d, J = 7.5 Hz, 0.13H, NH, minor conformer B), 4.11-3.88 (m, 1H, CHP), 3.69 (s, 2H, SCH_2Ph), 2.58-2.38 (m, 2H, SCH_2), 2.19-2.00 (m, 1H, CH_2),1.79-1.61 (m, 1H, CH_2),1.40 (s, 9H, *t*Bu), 1.30 (d, J = 6.3 Hz, 6H, CH_3), 1.28 (d, J = 6.3 Hz, 3H, CH_3), 1.27 (d, J = 6.3 Hz, 3H, CH_3).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 155.2 (d, J = 6.0 Hz, C = O), 138.2 (C_{ar}), 128.8 ($2HC_{ar}$), 128.5 ($2HC_{ar}$), 127.0 (HC_{ar}), 80.0 (C_q), 71.4 (d, J = 7.1 Hz, POCH), 71.2 (d, J = 6.8 Hz, POCH), 47.0 (d, J = 156.8 Hz, CHP), 36.2 (SCH_2Ph), 30.7 (d, J = 4.2 Hz, CH_2), 28.2 (3C, *t*Bu), 27.6 (d, J = 14.8 Hz, CH_2), 24.1 (d, J = 6.2 Hz, POCH), 24.1 (d, J = 6.1 Hz, CH_3), 23.9 (d, J = 4.6 Hz, CH_3), 23.9 (d, J = 4.6 Hz, CH_3).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 23.7 (A: 0.87P), 23.3 (B: 0.13P); ratio of conformers: 0.87:0.13 = 6.7:1.

Anal. calcd for $C_{21}H_{36}O_5NPS$ (445.55): C, 56.61; H, 8.14; N, 3.14. Found: C, 56.38; H, 8.05; N, 3.07.

(±)-, (*R*)-(–)- and (*S*)-(+)-1-aminopropylphosphonic acid [(±)-, (*R*)-(–)- and (*S*)-(+)-8]

A mixture of racemic diisopropyl 3-(benzylthio)-1-(*t*-butoxycarbonylamino)propylphosphonate [(±)-**6d]** (0.80 g, 1.8 mmol) and 6 M HCl (20 mL) was refluxed for 5 h. The solution was concentrated under reduced pressure and stored in a vacuum desiccator over KOH for 20 h. A sample (±)-**7** was withdrawn and investigated by NMR spectroscopy: ^{1}H NMR (400.27 MHz, D_2O/NaOD): δ = 7.53-7.43 (m, 4H, H_{ar}), 7.42-7.34 (m, 1H, H_{ar}), 3.87 (s, 2H, $PhCH_2$), 2.78 (ddd, J = 13.4, 10.2, 4.5 Hz, 1H, CHP), 2.70-2.54 (m, 2H, CH_2S), 2.18-2.04 (m, 1H, CH_2), 1.26-1.60 (m, 1H, CH_2); ^{31}P NMR (162.03 MHz, D_2O/NaOD): δ = 20.6; homogeneous product.[16]

The residue was dissolved in dry ethanol (20 mL) and neutralized with NaOH (1 M) using phenolphthalein as indicator. Freshly prepared moist Raney nickel (2.2 g) was added. After stirring for 19 h at room temperature, more moist Raney nickel[10] (1.2 g; stored at room

temperature over distilled water for 18 h) was added as TLC (*i*PrOH/H_2O/NH_3 (25%), 6:3:1, starting material: R_f = 0.54; product: R_f = 0.24) indicated the presence of some starting material in the reaction mixture. After stirring for another 2 h (TLC monitoring) the mixture was filtered through Celite, which was thoroughly washed with warm water. The filtrate was concentrated under reduced pressure. The residue was purified by cation exchange chromatography (Dowex 50W × 8, H^+, o. d. 1.1 cm × 23 cm; fractions of 8 mL; water as eluens). The ninhydrin-positive fractions (5-11) were pooled and concentrated under reduced pressure to give racemic 1-aminopropylphosphonic acid [(±)-**8]** (0.20 g, 82%) as colorless crystals, which were crystallized from H_2O/EtOH; mp 264°C (dec.) (H_2O/EtOH). The NMR spectra were identical to those of (*S*)-(+)-**8**.

Similarly, protected (–)-*S*-benzyl phosphahomocysteine (–)-**6d** (0.75 g, 1.67 mmol) gave (–)-1-aminopropylphosphonic acid [(*R*)-(–)-**8]** (0.18 g, 77%), ee before crystallization: 97%; after crystallization: 97.4%; mp 265°C (dec.) (H_2O/EtOH) (lit.[30]: 274-275°C); $[\alpha]_D^{17}$ = –17.35 (*c* = 0.83, 1 M NaOH) {lit.[11]: for (*R*)-**8** of 91% ee: $[\alpha]_{578}$ = –19.2 (*c* = 1.0, 1 M NaOH); lit.[12]: for (*R*)-**8** of 63% ee: $[\alpha]_{578}^{25}$ = –13.7 (*c* = 1.0, 1 M NaOH); lit.[13]: for (*R*)-**8** of 76% ee: $[\alpha]_{578}^{25}$ = –21.0 (*c* = 1.0, 1 M NaOH); lit.[30]: for (*R*)-**8**: $[\alpha]_{578}^{20}$ = –22.0 (*c* = 1.0, 1 M NaOH)}.

Similarly, protected (+)-*S*-benzyl phosphahomocysteine (+)-**6d** (0.68 g, 1.53 mmol) gave (+)-1-aminopropylphosphonic acid (0.16 g, 73%), ee 98.3%; mp 267°C (dec.) (H_2O/EtOH) (lit.[30]: 273-274°C); $[\alpha]_D^{17}$ = +17.57 (*c* = 0.70, 1 M NaOH) {lit.[30]: for (*S*)-**8**: $[\alpha]_{578}^{20}$ = +21.0 (*c* = 1.0, 1 M NaOH). The NMR spectra were identical to those of (+)-**8**.

Spectra of (+)-**8**: IR (ATR): ν = br. signal between 3400-2000, 1627, 153, 1463, 1154, 1120, 1016, 916 cm^{-1}.

^{1}H (400.27 MHz, D_2O): δ = 3.23 (ddd, *J* = 13.6, 8.5, 5.8 Hz, 1H, CHP), 2.10-1.94 (m, 1H, CH_2), 1.90-1.72 (m, 1H, CH_2), 1.13 (t, *J* = 7.5 Hz, 3H, CH_3).

^{13}C NMR (100.65 MHz, D_2O): δ = 50.8 (d, *J* = 143.2 Hz, CHP), 21.8 (d, *J* = 1.4 Hz, CH_2), 10.2 (d, *J* = 9.4 Hz, CH_3).

^{31}P NMR (162.03 MHz, D_2O): δ = 13.5.

Initial attempt to prepare (±)-phosphahomocysteine [(±)-9]

A solution of racemic 1-amino-3-(benzylthio)propylphosphonic acid×HCl [(±)-**7**] (0.29 g, 0.97 mmol; see preparation of 1-aminopropylphosphonic acid, carefully dried to remove H_2O) in dry THF (4 mL) was added to liquid ammonia (50 mL, –50°C). Alternatingly, a sodium piece (a total of .0.12 g, 5.26 mmol, 5.4 equiv.) and, when the blue color had been discharged, a small amount of ammonium chloride (total of 0.28 g, 5.26 mmol, 5.4 equiv.) were added. When the last aliquot had been added, ammonia was allowed to evaporate (exclusion of air!), water (5 mL) and HCl (1 mL, 2 M) were added. The solution (TLC: *i*PrOH/H_2O/NH_3 (25%), 6:3:1, starting material: R_f = 0.54; product: R_f = 0.20; much starting material present) was applied to a column (o. d. 1.2 × 20 cm) filled with Dowex 50W × 8, H^+ for cation exchange chromatography (water as eluens, fractions of 10 mL). Ninhydrin-positive fractions were pooled and concentrated to yield phosphahomocysteine [(±)-**9**] (0.066 g, 40%).

(±)-, (*R*)-(–)- and (*S*)-(+)-1-amino-3-mecaptopropylphosphonic acid (phosphahomocysteine) [(±)-, (*R*)-(–)- and (*S*)-(+)-9]

A solution of racemic diisopropyl 3(-benzylthio)-1-(*t*-butoxycarbonylamino)-propylphosphonate [(±)-**6d**] (0.85 g, 1.91 mmol) in dry Et_2O (3 mL) was added to a stirred solution of liquid NH_3 (70 mL, –70°C). Alternatingly, a sodium piece (total of 0.13 g, 5.73 mmol, 3 equiv.) and, when the blue color had been discharged, a small amount of NH_4Cl (total of 0.33 g, 6.11 mmol, 3.2 equiv.) were added. When the last aliquot had been added, ammonia was allowed to evaporate (exclusion of air!). Water (10 mL) and HCl (15 mL, 37%) were added and the mixture was refluxed for 7 h. Concentration of the solution gave a residue (*i*PrOH/H_2O/NH_3 (25%), 6:3:1, starting material: R_f = 0.54; product: R_f = 0.20) The residue was purified by cation exchange chromatography (Dowex 50W × 8, H^+, o. d. 1.8 cm × 23 cm; fractions of 25 mL; water as eluens). Ninhydrin-positive fractions were pooled and concentrated under reduced pressure to leave 1-amino-3-mercaptopropylphosphonic acid [(±)-**9**] (0.17 g, 68%) as crystalline product, which was crystallized from H_2O/*i*PrOH) to give colorless crystals; mp 262°C (dec.).

Similarly, diisopropyl 3-(benzythio)-1-(*t*-butoxycarbonylamino)propylphosphonate [(*R*)-(–)-**6d**] (0.81 g, 1.82 mmol) was converted to phosphahomocysteine [(*R*)-(–)-**9**] (0.25 g, 79%) as colorless crystals; mp. 270°C (dec.) (H_2O/*i*PrOH); $[\alpha]_D^{20}$ = –16.6 (*c* = 1.0, H_2O). The NMR spectra were identical to those of the racemate.

Similarly, diisopropyl 3-(benzythio)-1-(*t*-butoxycarbonylamino)propylphosphonate [(*S*)-(+)-**6d**] (0.64 g, 1.44 mmol) was converted to phosphahomocysteine [(*S*)-(+)-**9**] (0.19 g, 76%) as

colorless crystals; mp. 270°C (dec.) (H_2O/*i*PrOH); $[\alpha]_D^{20}$ = +15.30 (*c* = 1.15, H_2O). The NMR spectra were identical to those of the racemate.

Spectra of (±)-**9**: IR (ATR): ν = br. 3250-1500, 1645, 1620, 1547, 1224, 1149, 1146, 1015, 916 cm^{-1}.

^1H NMR (400.27 MHz, D_2O): δ = 3.59-3.47 (m, 1H, CHP), 2.90-2.79 (m, 1H, CH_2S), 2.79-2.68 (m, 1H, CH_2S), 2.33-2.17 (m, 1H, CH_2), 2.17-2.01 (m, 1H, CH_2).

^{13}C NMR (100.65 MHz, D_2O): δ = 47.6 (d, *J* = 142.7 Hz, CHP), 32.6 (CH_2), 20.6 (d, *J* = 9.9 Hz, CH_2).

3^1P NMR (162.03 MHz, D_2O): δ = 12.8.

Anal. calcd for $C_3H_{10}NO_3PS$ (171.15): C, 21.05; H, 5.89; N, 8.18; O, 28.04; S, 18.73. Found: C, 20.94; H, 5.89; N, 7.87. Found for (*R*)-(–)-**9**: C, 21.38; H, 5.80; N, 8.13; O, 28.00; S, 18.85.

(*R*)-(–)-Phosphamethionine [(*R*)-(–)-10]

Water (4 mL) and EtONa/EtOH (4.75 mL, 2.28 mmol, 3.15 equiv.) were added to phosphahomocysteine [(*R*)-(–)-**9]** (0.12 g, 0.73 mmol) under argon at 0°C, followed by CH_3I (0.80 mL, 1.08 M solution in EtOH, 1.2 equiv.). After stirring for 1 h (TLC in *i*PrOH/H_2O/NH_3 (25%) = 6:3:1, phosphahomocysteine: R_f = 0.10; phosphamethionine: R_f = 0.35; no starting material left) the solution was concentrated (about 1 mL) and the phosphamethionine [(*R*)-(–)-**10]** was isolated by cation exchange chromatography (Dowex 50W × 8, H^+, o. d. 1.1 cm × 22 cm, water as eluens, fractions of 8 mL). Ninhydrin-positive fractions (TLC: *i*PrOH/H_2O/NH_3

(25%), 6:3:1, R_f = 0.35) were pooled and concentrated under reduced pressure to yield crystalline phosphahomocysteine [(*R*)-(–)-**10**] (0.12 g, 93%) which was crystallized from H_2O/EtOH; ee before crystallization: 99.3%; after crystallization: 99.6%; mp 266°C (dec.) [lit.[18]: 265-266°C (dec.)]; crude product: $[\alpha]_D^{17}$ = –29.21 (*c* = 0.76, H_2O); crystallized product: $[\alpha]_D^{17}$ = –29.04 (*c* = 0.83, H_2O) {lit.[18]: $[\alpha]_D^{25}$ = –11.5 (*c* = 1.1, H_2O) for (*R*)-(–)-**10**}; $[\alpha]_D^{17}$ = –43.76 (*c* = 0.77, 0.25 M NaOH) {lit.[31]: $[\alpha]_{578}^{25}$ = –40.4 (*c* = 1.0, 0.25 M NaOH) for (*R*)-(–)-**9**; compare lit.[32]: $[\alpha]_D^{25}$ = +39.0 (*c* 1.1, 0.25 M NaOH) for incorrectly assigned (*R*)-(+)-**9**}.

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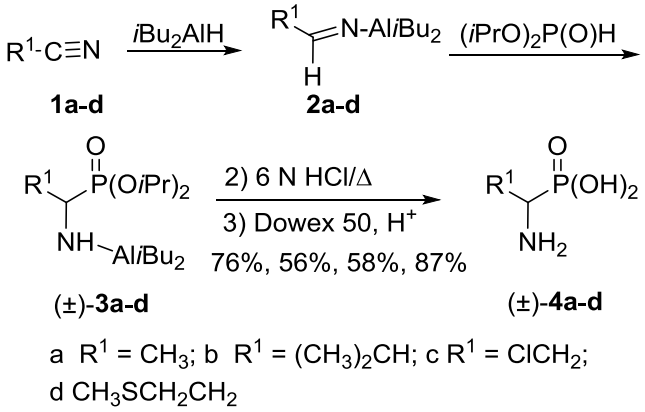
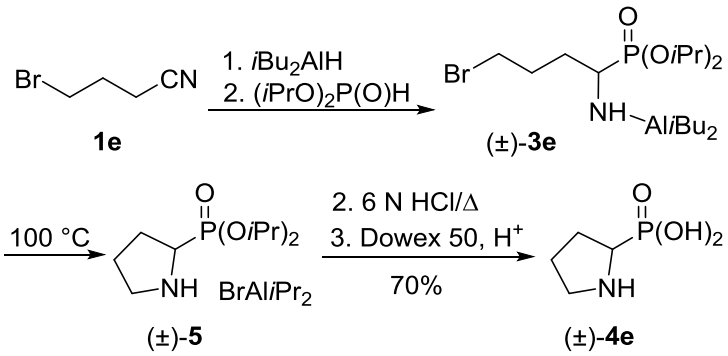
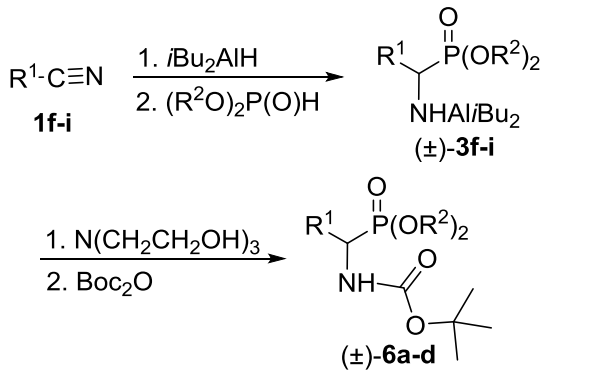


Scheme 1 Conversion of nitriles to aminophosphonic acids (±)-**4a-d**.

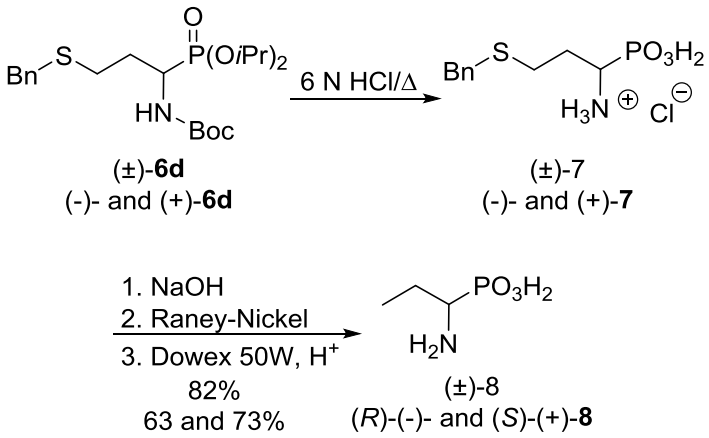


Scheme 2 Conversion of 4-bromobutyronitrile to phosphaproline [(±)-**4e**].



1f, (±)-**3f**, (±)-**6a**, R^1 = Ph, R^2 = *i*Pr, 54%
1g, (±)-**3g**, (±)-**6b,** R^1 = Bn, R^2 = *i*Pr, 54%
1h, (±)-**3h**, (±)-**6c**, R^1 = Bn, R^2 = Et, 56%
1i, (±)-**3i**, (±)-**6d**, R^1 = $BnSCH_2CH_2$, R^2 = *i*Pr, 69%

Scheme 3 Conversion of nitriles to *N*-Boc-protected α-aminophosphonates **6**.

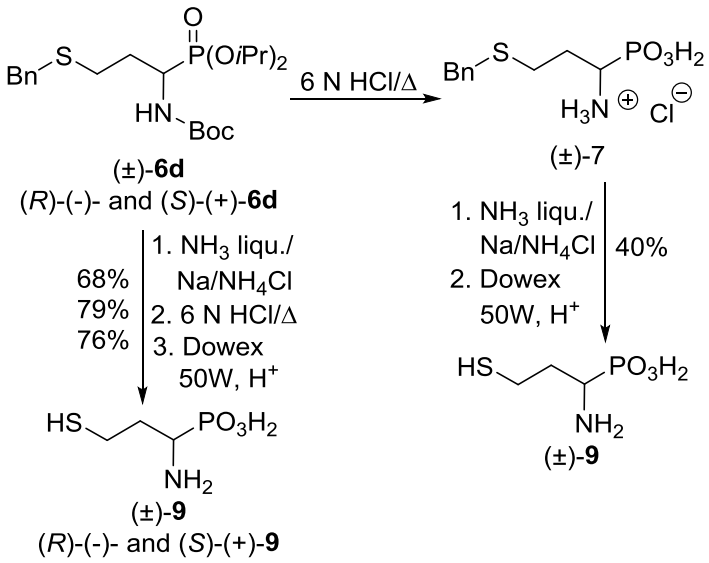


(±)-**6d**
(-)- and (+)-**6d**

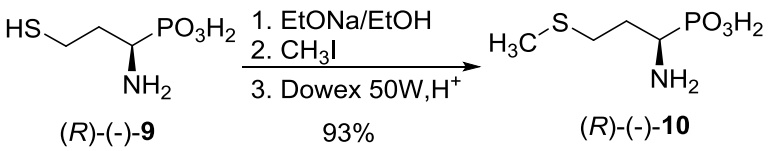
(±)-7
(-)- and (+)-**7**

(±)-8
(*R*)-(-)- and (*S*)-(+)-**8**

Scheme 4 Determination of absolute configuration of (–)- and (+)-**6d**.



Scheme 5 Synthesis of phosphahomocysteines **9** from **6d**.



(*R*)-(-)-**9** 93% (*R*)-(-)-**10**

Scheme 6 Methylation of (*R*)-(–)-**9** to give (*R*)-phosphamethionine.