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Asymmetric Synthesis of Structurally Diverse Aminophosphonic Acids by Using Enantiopure *N*-(*p*-Tolylsulfinyl)cinnamaldimines as Reagents

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We have developed new approaches to diverse enantiopure aminophosphonic acids by using enantiomeric (*S*)-*N*-(*p*-tolylsulfinyl)cinnamaldimine (**1**) as a single starting material. The synthetic strategy is based on a highly diastereoselective addition reaction of phosphite anion or α-phosphonate carbanion to a sulfinimine followed by isolation of the major diastereoisomeric α-amino- or β-amino adducts and their further conversion to the desired targets through proper transformation of the cinnamylidene moiety. Both diastereoisomerically pure (S_S,R_C)- and (S_S,S_C)-α-amino adducts **2** and **4** obtained were converted under acidic conditions into the unknown enantiomerically pure (*R*)- and (*S*)-α-amino-β,γ-propenylphosphonic acids **3**. In the same way, the enantiopure (*R*)- and (*S*)-β-amino-γ,δ-butenylphosphonic acids were synthesized from the corresponding (S_S,R_C)- and (S_S,S_C)-β-amino adducts. Starting from the (S_S,R_C)-β-amino adduct a new stereoselective synthesis of (*R*)-2-amino-3-phosphonopropanoic acid (**9**) has been accomplished in three simple steps (tandem ozonolysis/reduction reaction, oxidation reaction and acidic hydrolysis) in an overall 40 % yield. The 3-amino regioisomer of **9** has been prepared from the (S_S,R_C)-α-amino adduct **2** through a two-reaction sequence involving a tandem ozonolysis/reduction reaction and a Mitsunobu cyanation/acidic hydrolysis. The overall yield of this conversion to **11** was 52.5 %. According to our strategy, we have been able to complete the first synthesis of the enantiopure (*R*)-phosphoemeriamine **15**, which is an unknown phosphonic analogue of emeriamine (aminocarnitine). The conversion of the (S_S,R_C)-β-amino adduct **5** into (*R*)-phosphoemeriamine has been accomplished in five simple synthetic steps (ozonolysis/reduction reaction, mesylation reaction, amination reaction, methylation reaction and acidic hydrolysis) in 24 % overall yield. The stereochemistry of the addition of P^{III}-nucleophiles and α-phosphonate carbanion to a chiral sulfinimine is also discussed.

Introduction

Aminophosphonic acids (AP) are important analogues of protein and nonprotein amino acids in which the planar carboxylic group is replaced by a tetrahedral phosphonic acid moiety. As a consequence of this structural change APs mimic the tetrahedral transition state (or intermediate) formed in enzyme-mediated peptide bond cleavage and act as inhibitors of proteolytic enzymes. (e.g. HIV protease, serine protease). The spectrum of biological activities expressed by APs and their conjugates with peptides is very wide. They exhibit antibacterial, anticancer, antiviral and neuroactive properties. Some of them show pesticidal, insecticidal and herbicidal activity and function as plant growth regulators. Therefore, selected APs and their derivatives have found commercial applications in medicine and agriculture. This class of phosphorus compounds still has remarkable potential in medicinal chemistry.[1]

Although a lot of experimental material has been accumulated in the field of chemistry and biology of APs [2,3] there is continued interest in this class of phosphorus compounds focused particularly on the synthesis and bioactivity studies of optically active, enantiopure compounds. The biological activity of APs depends markedly on the absolute configuration of the stereogenic carbon atom connected with the amino group. Therefore, the development of general synthetic methods for the preparation of enantiomerically pure APs has been a challenging task. Currently, the synthetic chemistry of optically active APs encompasses three main directions. The first aims to discover new, original synthetic methodologies. The second is connected with the improvement of existing methods to increase their scope, efficiency and applicability. The final direction is devoted to the synthesis of new structures of aminophosphonic acids, including conformationally constrained ones, and new phosphorus analogues of natural and unnatural amino acids, which, after determination of their bioactivity, may be selected as potential drugs (Scheme 1).

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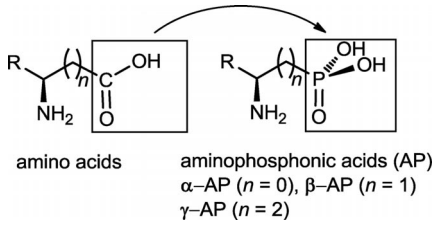
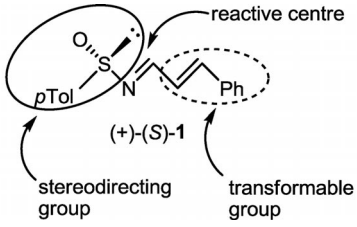


Scheme 1. General structure of amino acids and their corresponding aminophosphonic acids.

In the course of our work in this area we devised a new and general asymmetric synthesis of α- and β-aminophosphonic acids starting from enantiopure *p*-toluenesulfinimines as chiral reagents.[4–7] Recently, we extended this approach to the asymmetric synthesis of γ-aminophosphonic acids. In this case, (+)-(*S*)-*N*-(*p*-tolylsulfinyl)-3-(diethoxyphosphoryl)propanalimine was used for highly diastereoselective generation of the new stereogenic carbon atom bearing the amino group.[8] As a result, a short and efficient synthesis of (+)-(*S*)-2-amino-4-phosphonobutanoic acid was developed. The latter is a phosphonic analogue of glutamic acid and acts as a modulator for the *N*-methyl-D-aspartate receptor site.



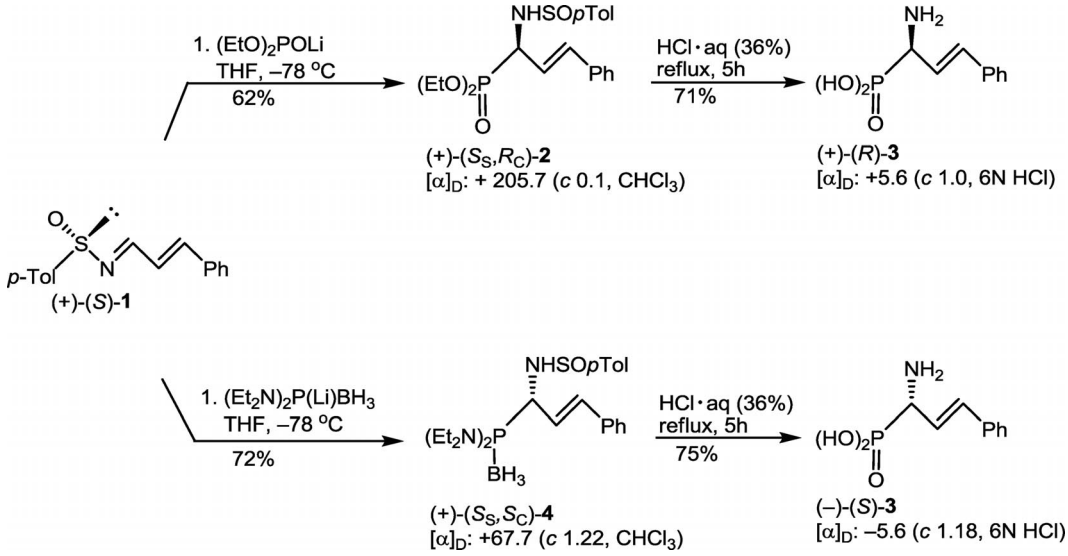
As part of our efforts to develop further the synthesis of enantiopure APs by using the sulfinimine methodology we turned our attention to chiral *N*-(*p*-tolylsulfinyl)cinnamaldimine (**1**). It was obtained by the Davis group[9] but so far has not been exploited as the asymmetric synthesis. An important structural feature of this sulfinimine is that it contains, in addition to a very powerful stereodirecting *p*-tolylsulfinyl group, the cinnamylidene moiety that can be easily transformed into diverse functional groups. In this paper we report the first synthesis of enantiopure unsaturated α-amino- and β-aminophosphonic acids, a new synthesis of enantiopure 2-amino-3-phosphonopropanoic acid (**9**) and its 3-amino regioisomer **11** as well as the first synthesis of (–)-(*R*)-phosphoemeriamine **15**. All these structurally diverse APs were efficiently obtained by using the enantiomers of sulfinimine **1** as reagents.

Results and Discussion

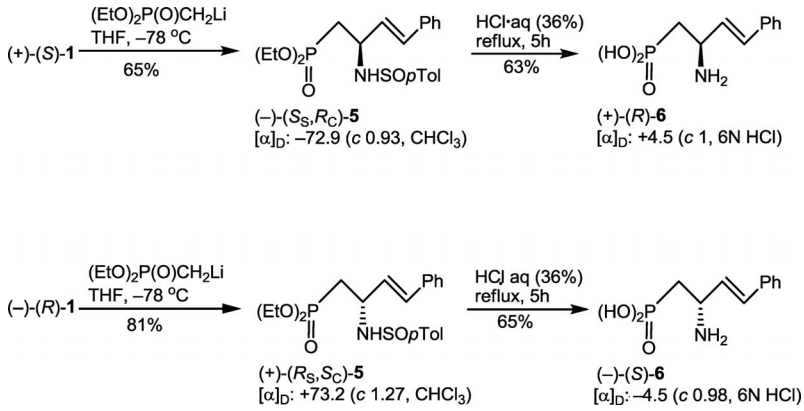
Synthesis of Enantiopure Unsaturated α-Amino- and β-Aminophosphonic Acids

From the outset of this work it was obvious that the addition of phosphite anions and α-phosphonate carbanions to the enantiomers of **1** should produce the corresponding phosphonate adducts that, in turn, could be converted into enantiomerically enriched or pure unsaturated α-amino- and β-aminophosphonic acids. To the best of our knowledge, this group of optically active and enantiopure APs has not been obtained and reported nor their biological properties investigated. It is interesting to note that their precursors i.e. unsaturated aminophosphonates have been obtained by enantioselective hydrophosphonylation of imines but only in an enantiomerically enriched state.[10,11] Therefore, in an extension of our program on the use of chiral sulfinimines in the asymmetric synthesis of APs, and stimulated by a recently published enantioselective multistep synthesis of unsaturated α-aminophosphonates,[12] we disclose our two-step approach to both enantiomers of APs.

The starting (+)-(*S*)- and (–)-(*R*)-sulfinimines **1** with $[\alpha]_D$ = +389 (*c* = 1.43, $CHCl_3$) and $[\alpha]_D$ = –393 (*c* = 1.38, $CHCl_3$), respectively, were prepared according to a described procedure[9] from the corresponding commercially



Scheme 2. Synthesis of enantiopure (1-amino-3-phenylpropen-2-yl)phosphonic acid (**3**).



Scheme 3. Synthesis of enantiopure (2-amino-4-phenyl-buten-3-yl)phosphonic acid (**6**).

available (+)-(*S*)- and (–)-(*R*)-*p*-toluenesulfinamides with $[\alpha]_D$ = +85 and –85. The details of the synthesis of both enantiomers of 1-amino-3-phenylpropen-2-ylphosphonic acid (**3**) are outlined in Scheme 2.

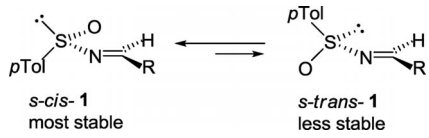
In the first step, lithium diethyl phosphite was added at –78 °C to a tetrahydrofuran (THF) solution of (+)-(*S*)-sulfinimine **1**. The addition product formed in this reaction was found to be a 16:1 mixture of two diastereoisomeric phosphonates **2** as determined by ^{31}P NMR spectroscopy [δ_P = 20.8 ppm (major), δ_P = 21.4 ppm (minor)]. After flash chromatography and crystallization pure, major diastereoisomer (+)-**2** was obtained in 62% yield. In accordance with our previous results[5,7] and rationalization given below the absolute configuration (*R*) was assigned to the newly generated stereogenic α-carbon atom in (+)-**2**. In the next step, phosphonate (+)-**2** was converted efficiently (71% yield) into the corresponding enantiopure α-aminophosphonic acid [(+)-(*R*)-**3**] by heating for 5 h in hydrochloric acid heated to reflux.

To synthesize the (–)-(*S*)-enantiomer of **3** the addition of lithium bis(diethylamino)phosphido–borane complex to the same (+)-(*S*)-sulfinimine **1** was performed. Analytically pure addition product (+)-**4** was obtained in 72% yield. The latter upon similar acidic treatment as described above afforded (–)-(*S*)-**3** with the same value of optical rotation as that of (+)-(*R*)-**3** indicating that it is enantiomerically pure. Hence, the addition of the lithiated diaminophosphane borane complex to (+)-(*S*)-**1** occurred with complete diastereoselectivity but with opposite stereochemical course to that observed for lithium diethyl phosphite.

In a similar way, enantiomerically pure (2-amino-4-phenylbuten-3-yl)phosphonic acids (**6**) were synthesized (see Scheme 3). In this case, however, both enantiomers of sulfinimine **1** were used for the addition reaction with α-phosphonate carbanion.

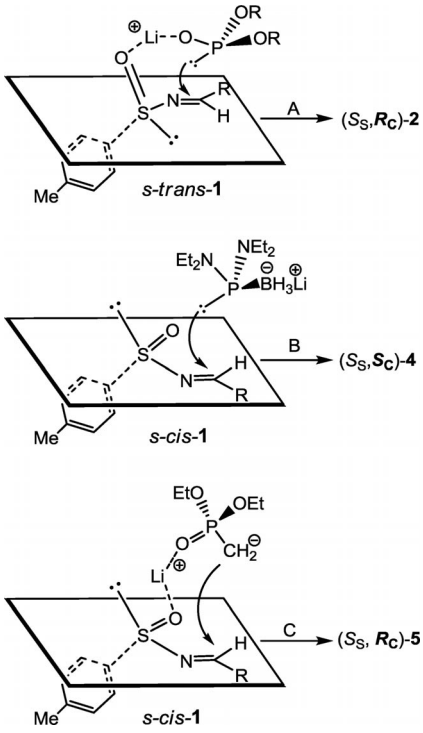
Reaction of (+)-(*S*)-**1** with the lithium salt of diethyl methanephosphonate afforded a mixture of diastereoisomeric adducts in a 9:1 ratio [δ_P = 28.3 ppm (major), δ_P = 27.5 ppm (minor)] from which pure major diastereoisomer (–)-**5** was isolated in 65% yield. The absolute (*R*)-configuration was ascribed to the newly formed stereogenic β-carbon atom in (–)-**5** on the basis of an earlier proposed transition-state model for the addition reaction of α-phosphonate carbanion to chiral sulfinimines.[4,7] Acidic hydrolysis of (–)-(S_S,R_C)-**5** gave corresponding β-aminophosphonic acid (+)-(*R*)-**6** in 63% yield. Starting from (–)-(*R*)-sulfinimine **1** the opposite enantiomer of acid **6** was similarly prepared. Interestingly, the addition reaction of α-phosphonate carbanion to (–)-(*R*)-**1** was highly diastereoselective leading to the formation of a mixture of diastereoisomers in a 38:1 ratio. The overall yield of (–)-(*S*)-**6** from (–)-(*R*)-**1** was 53%.

To conclude this part of the present work we wish to provide a complete explanation of the stereochemical outcomes and very high diastereoselectivities observed in the addition reactions discussed above. Our rationale is based on the consideration of the ground state and reactive structures of both reacting components, i.e. sulfinimine **1** and P- and C-nucleophiles, as well as steric and chelation effects operating there. First, it is necessary to point out that sulfinimine (+)-(*S*)-**1** exists in equilibrium between two most stable conformations *s-cis*-**1** and *s-trans*-**1** (see Scheme 4). According to recent DFT calculations the difference in energy between such conformers of a sulfinimine is about 4 kcal/mol.[13] Therefore, conformer *s-cis*-**1** is more stable than *s-trans*-**1**.



Scheme 4. Conformations of (+)-(*S*)-sulfinimine **1**.

In the case of the addition reactions of lithium dialkyl phosphites, which exist in trivalent phosphorus form with the lithium cation coordinated to the phosphoryl oxygen, the nucleophilic phosphorus atom approaches the conformation *s-trans*-**1** from the diastereotopic π-face occupied by the sulfinyl oxygen atom to allow chelation of the lithium cation by the sulfinyl oxygen atom (Scheme 5, Path A) and stabilization of the cyclic seven-membered transition state formed in this way.[14] This chelation-controlled addition reaction results in the formation of adduct **2** with the (R_C)-configuration as a major diastereoisomer.



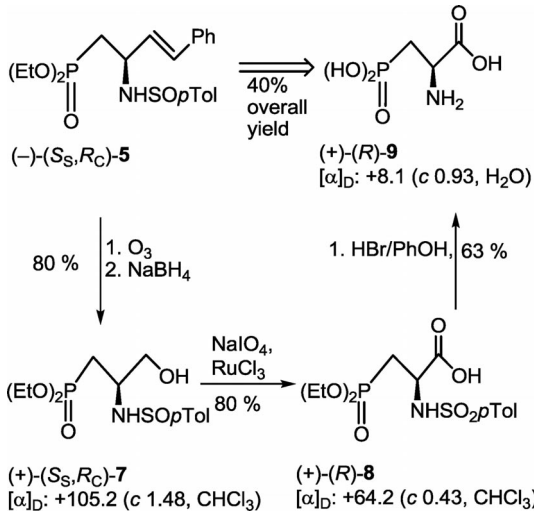
Scheme 5. The proposed transition-state models for the preferred addition of P- and C-nucleophiles to (+)-(*S*)-sulfinimine **1**.

The switchover of diastereoselectivity in the addition reaction of lithium bis(diethylamino)phosphido–borane, $[(Et_2N)_2P(BH_3)Li]$, to (+)-(*S*)-**1** is undoubtedly as result of the peculiar structure of this reagent. Although its exact structure is not known, recent elegant studies by a French-Italian research group showed unequivocally that in the closely related lithium diphenylphosphido–borane, $[Ph_2P(BH_3)Li]$, the lithium cation is bound to the hydrides on the boron.[15] Most probably in our bis(diethylamino) analogue the site of coordination of lithium is the same. Hence, the addition reaction is not controlled by chelation and the phosphido–borane reagent reacts with another conformation of **1**. Among four diastereotopic π-faces formed by *s-trans*-**1** and *s-cis*-**1**, that occupied by the sulfur lone electron pair in the more stable *s-cis*-**1** is the least hindered one. So, approach of lithium aminophosphido–borane takes place from this π-face of *s-cis*-**1** (Scheme 5, Path B). Such a steric course generates the (S_C)-configuration on the α-carbon atom in adduct **4** that is preferentially or exclusively formed.

Finally, the stereochemical course of the addition reaction of a larger α-phosphonate carbanion to (+)-(*S*)-**1** is controlled primarily by steric factors (steric approach control). Hence, nucleophilic attack of the α-phosphonate carbanion occurs from the least hindered π-face of *s-cis*-**1** that is occupied by the sulfur lone electron pair (Scheme 5, Path C) and major adduct **5** is produced with the (*R*)-configuration at the β-carbon atom bearing the amino moiety. As in the case of phosphite anions, stabilization of the eight-membered cyclic transition state may be through coordination of lithium by the sulfinyl and phosphoryl oxygen atoms.

Synthesis of Enantiopure 2-Amino-3-phosphonopropanoic Acid (9) and Its 3-Amino Regioisomer 11

To demonstrate the wide applicability of chiral sulfinimine **1** for the synthesis of various Aps, and encouraged by our efficient asymmetric synthesis of (+)-(*S*)-2-amino-4-phosphonobutanoic acid mentioned above,[8] we decided to develop a new synthesis of 2-amino-3-phosphonopropanoic acid (**9**), which is a phosphonic analogue of aspartic acid. This phosphonic acid is a selective, potent modulator of the metabotropic excitatory amino acids receptor subtype.[16] In accordance with our desire to prepare **9**[17] in a more simple and efficient way, diastereoisomerically pure adduct (–)-**5** was selected for conversion into **9**. As shown in Scheme 6, this conversion was easily accomplished in three steps.



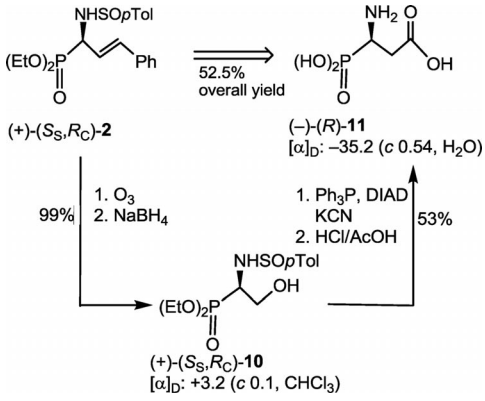
Scheme 6. Synthesis of enantiopure (+)-(*R*)-**9**.

First, ozonolysis of (–)-**5** and subsequent reduction with sodium borohydride gave corresponding alcohol (+)-**7**. Then, the latter was subjected to oxidation with sodium metaperiodate in the presence of ruthenium chloride to afford carboxylic acid (+)-**8** containing a *N*-p-tolylsulfonyl moiety. In the final step, both the amino and phosphonate functions were deprotected under acidic conditions to give desired (+)-**9**. The overall yield of the conversion of (–)-**5** into (+)-**9** was 40%.

Taking into account the fact that the bonds around the stereogenic β-carbon atom are not broken and no racemization occurred during the conversion of (–)-**5** into (+)-**9**, the (*R*)-configuration was assigned to the resulting product. This is in accordance with the literature assignment.[17f]

Having diastereoisomerically pure adduct (+)-**2** with the amino function at the α-carbon atom in hand we were able to convert it into 3-amino-3-phosphonopropanoic acid (**11**), which is a regioisomer of **9** with regard to the position of the amino group. To the best of our knowledge there are only two reports of the asymmetric synthesis of this amino-

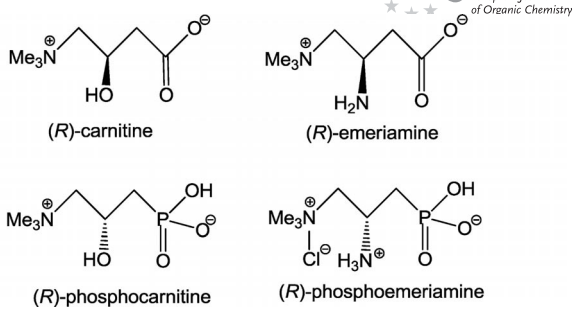
phosphonic acid.[18] Scheme 7 shows the transformation involving a two-step reaction sequence. The synthesis starts with the tandem ozonolysis/sodium borohydride reduction reaction of (+)-(S_S,R_C)-**2** producing corresponding alcohol (+)-(S_S,R_C)-**10** in almost quantitative yield. In the next step, it was converted under Mitsunobu reaction conditions into the corresponding cyanide that, without isolation, was hydrolysed to target acid (–)-(*R*)-**11**. The overall yield for the above conversion was 52.5%.



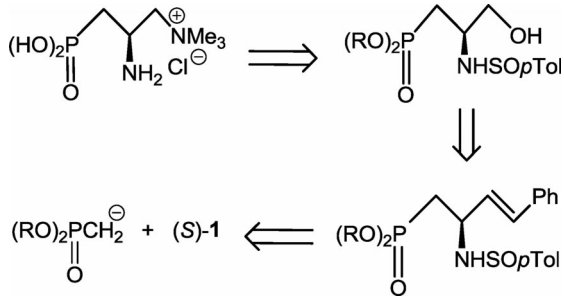
Scheme 7. Synthesis of enantiopure (–)-(*R*)-3-amino-3-phosphonopropanoic acid (**11**).

The First Synthesis of (*R*)-Phosphoemeriamine 15

In the course of searching for new phosphonic analogues of biologically active amino acids, we found that, in contrast to carnitine, the phosphonic analogue of emeriamine is unknown. Emeriamine, also called aminocarnitine, which is derived from carnitine, exhibits interesting pharmacological properties. Emeriamine itself and a few other related compounds inhibit fatty-acid oxidation and reduce hyperglycemia and ketosis.[19]

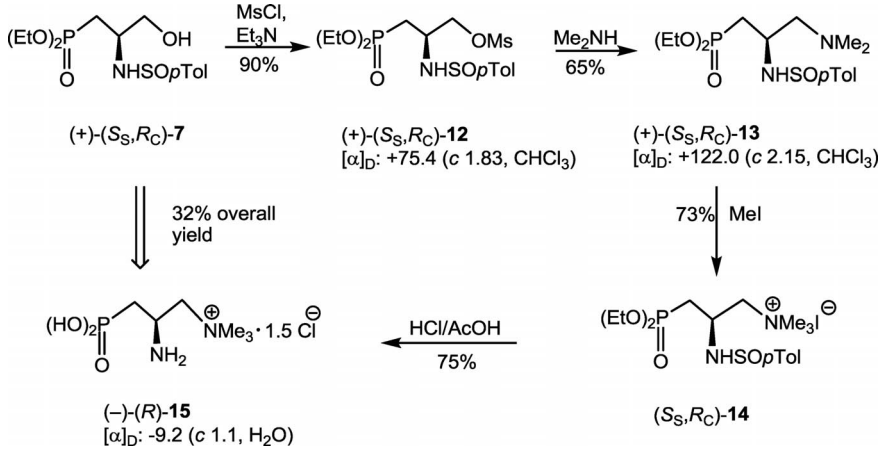


Therefore, in an extension of our work on phosphocarnitine,[20] we decided to synthesize the enantiomers of phosphoemeriamine to study their structure-activity relationships. According to our strategy devised for the synthesis of phosphoemeriamine mediated by sulfinimine (*S*)-**1** and outlined retrosynthetically in Scheme 8, the precursor of (*R*)-phosphoemeriamine would be the corresponding (*R*)-β-amino-γ-hydroxypropanephosphonate. This, in turn, could be obtained from the adduct formed in the addition reaction of α-phosphonate carbanion to (*S*)-**1**.



Scheme 8. Retrosynthetic analysis for the synthesis of (*R*)-phosphoemeriamine.

To our satisfaction, phosphoemeriamine precursor (+)-(S_S,R_C)-**7** was obtained during the synthesis of (+)-(*R*)-aminophosphonic acid (**9**). So, the real synthetic task was its conversion into the desired phosphoemeriamine. We



Scheme 9. Synthesis of enantiopure (–)-(*R*)-phosphoemeriamine **15**.

achieved this goal in four simple steps as shown in Scheme 9.

The hydroxy group in (+)-**7** was mesylated with mesyl chloride in the presence of triethylamine to give mesylate (+)-**12** in 90% yield. Then, the mesyloxy group in the latter was replaced with a dimethylamino group. Upon treatment with methyl iodide, β,γ-diaminopropanephosphonate (+)-**13**, which was formed in 65% yield, gave corresponding phosphonopropyltrimethylammonium iodide **14** isolated after column chromatography in 73% yield. This hygroscopic iodide exhibited correct ^{1}H, ^{13}C and ^{31}P NMR and mass spectra; however, attempts to purify it resulted in slow decomposition, most probably owing to a deethylation reaction taking place at phosphorus. Therefore, iodide **14** was immediately hydrolysed under standard acidic conditions (concd. HCl·aq, AcOH, 5 h reflux temperatures) to afford desired phosphoemeriamine (–)-**15** as white crystals in 75% yield. The overall yield of (–)-**15** from (+)-**7** was 32%. The crystalline product exhibited a sharp melting point and was spectroscopically pure. The presence of a molecular ion [M^+] relating to $C_6H_{18}N_2PO_3$ was confirmed by HRMS. Surprisingly, however, elemental analysis revealed substantial differences between the calculated values for $C_6H_{18}N_2PO_3Cl$ and those found.

To clear this discrepancy, we selected a suitable crystal of (–)-**15** for X-ray diffraction analysis and determined the crystal and molecular structure of phosphoemeriamine.[21] A three-dimensional view of a molecule of (–)-**15** and the atom numbering are shown in Figure 1.

The X-ray diffraction analysis revealed that the absolute configuration at the β-carbon atom C(2) is (*R*) confirming our configurational assignments for the starting material and intermediate products. The trimethylammonium group at C(3) was found to exist in the solid state in two conformations A (major) and B (minor), the disorder ratio is 9:1. The elements that show disorder are three methyl groups that rotate around the C(3)–N(2) bond by 60 degrees. Protonation of nitrogen atom N(1) by the phosphonic acid moiety was clearly visible in the difference Fourier map by the presence of three residual peaks near N(1). The unit cell contains four phosphoemeriamine cations and six chloride ions (Figure 2) from which two chloride ions (labelled as

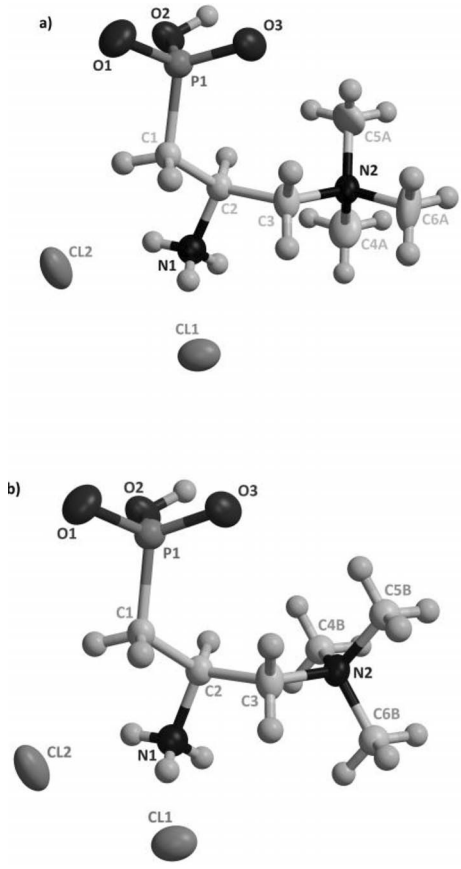


Figure 1. Molecular view of the asymmetric unit of phosphoemeriamine (–)-**15** (two conformations), showing the atom-numbering scheme. The displacement ellipsoids are drawn at the 50% probability level and H atoms are depicted as spheres of arbitrary radii.

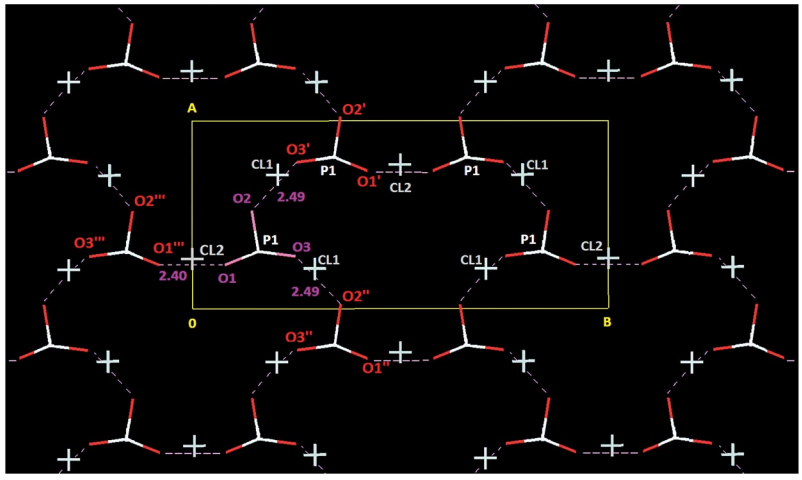


Figure 2. Molecular packing of compound (–)-**15** in the crystal lattice. Only the phosphonic acid fragments and chloride anions are shown for clarity. The phosphonic groups from neighboring molecules are in close contact, marked by the pink dashed lines. Chloride ion CL2 lies in a special position.

CL2) additionally incorporated from the reaction medium occupy a special position in the crystal lattice.

Most probably the chloride ions also stabilize the supramolecular structure formed by the strongly hydrogen-bonded phosphonic acid residues of phosphoemeriamine. It is interesting to point out that the macrocyclic ring consisting of six molecules of **15** is a repeating unit in this structure (Figure 2). With regard to the elemental analysis problem, we learned from the X-ray diffraction data that in one molecule of **15** prepared as above the ratio between the emeriamine cation and the chloride anion is 1:1.5.

Finally we would like to point out that the (*S*)-enantiomer of phosphoemeriamine may be obtained in the same way from adduct (+)-(R_S,S_C)-**5**.

Conclusions

In summary, we have demonstrated that chiral (*S*)-(*p*-tolylsulfinyl)cinnamaldimine is a versatile reagent in the synthesis of structurally diverse enantiopure APs. The easily isolable diastereoisomerically pure α-amino and β-amino adducts formed in a highly diastereoselective addition reaction of P^{III}-nucleophiles and α-phosphonate carbanion to this sulfinimine were converted into the corresponding enantiopure unsaturated α-amino and β-aminophosphonic acids. A new simple synthesis of enantiopure 2-amino-3-phosphonopropanoic acid (**9**; phosphoaspartic acid) was developed by using the β-amino adduct as a starting material. However, based on the diastereoisomerically pure α-amino adduct a stereoselective synthesis of the enantiopure 3-amino regioisomer of **9** has also been developed. The synthetic utility of the β-amino adduct has been shown in the first synthesis of (*R*)-phosphoemeriamine, which is an unknown phosphonic analogue of emeriamine. The synthetic approaches to known aminophosphonic acids compare favourably in terms of the use of simple reagents and transformations with the previously reported syntheses. Finally, it should be pointed out that the diastereoisomerically pure α-amino and β-amino adducts reported herein may be developed not only into chiral APs but also into diverse chiral ligands containing, for example chiral phosphanes. Work in this direction is in progress.

Experimental Section

General: Thin layer chromatography (TLC) was conducted on Silica Gel 60 F_{254} TLC purchased from Merck. Column chromatography was performed with Merck Silica Gel (70–230 mesh). NMR spectroscopic data were recorded at 20 °C with a Bruker AV 200 and Bruker AV III 500 instruments: ^{1}H data at 200 MHz, ^{31}P data at 81 MHz and ^{13}C data at 125 MHz. Mass spectra including HRMS were measured with a Finnigan MAT 95 spectrometer by using the FAB technique. Optical rotation measurements were carried out with a Perkin–Elmer MC 241 photopolarimeter at room temperature (20–22 °C).

(S_S,R_C)-Diethyl [3-Phenyl-1-(*p*-tolylsulfinylamino)propen-2-yl]phosphonate (2): Diethyl phosphite (1.053 g, 7.6 mmol) in THF (10 mL) was cooled under nitrogen to –78 °C and lithium bis(trimethylsilyl)-amide (LiHMDS; 1.2 g, 7.5 mmol) in THF (10 mL) was added. The reaction mixture was stirred at this temperature for 1 h. Then, (+)-(*S*)-sulfinimine **1** (1.345 g, 5 mmol) in THF (25 mL) was added dropwise and stirring was continued for 5 h at –78 °C. The reaction was quenched with an aqueous solution of NH_4Cl (10 mL), extracted with CH_2Cl_2 (3 × 10 mL) and, after separation, the organic layer was dried with $MgSO_4$ and the solvents evaporated. The crude mixture of diastereoisomeric adducts **2** obtained in a 16:1 ratio (^{31}P NMR assay) was purified with flash chromatography (silica gel, CH_2Cl_2/MeOH, 20:1). After crystallization from diethyl ether, a single diastereoisomer of **2** was obtained as a white crystalline solid (1.26 g, 62%). $[\alpha]_D$ = +205.7 (*c* = 0.1, $CHCl_3$), m.p. 104–105 °C. ^{31}P NMR ($CDCl_3$): δ = 20.8 ppm. ^{1}H NMR ($CDCl_3$): δ = 7.65–7.16 (m, 9 H, aromatic), 6.8 (dd, *J* = 15.8, *J* = 4.6 Hz, 1 H, =CHPh), 6.25–6.30 (m, 1 H, CH=CHPh), 4.5 (t, *J* = 8.9 Hz, 1 H, NHCH), 4.36 (dq, *J* = 4.3, *J* = 18.2 Hz, 1 H, CHNH), 4.20–4.00 (m, 4 H, CH_2CH_3), 2.42 (s, 3 H, CH_3), 1.30 (t, *J* = 7.1 Hz, 6 H, CH_3CH_2) ppm. ^{13}C NMR ($CDCl_3$): δ = 141.8, 141.3, 136.1, 135.9, 129.6, 128.6, 128.3, 126.8, 125.6, 121.9, 121.7, 63.3, 53.7 (d, J_{PC} = 156.2 Hz, PCH), 21.4, 16.4 ppm. MS (FAB): *m*/*z* = 408.3 [M + H]. $C_{20}H_{26}NO_4PS$ (407.46): calcd. C 58.99, H 6.38, P 7.62, N 3.44, S 7.86; found C 58.99, H 6.43, P 7.63, N 3.44, S 7.69.

[(*R*)-1-Amino-3-phenylpropen-2-yl]phosphonic Acid (3): Aminophosphonate (+)-**2** (0.27 g, 0.66 mmol) prepared as above was heated to reflux with hydrochloric acid (36% aq. solution, 5 mL) for 5 h. After cooling to room temperature the reaction mixture was extracted with $CHCl_3$ (3 × 5 mL). The aqueous layer was separated and the solvents evaporated. The residue was dissolved in EtOH (5 mL) and propylene oxide was added to pH ≈ 6. The precipitate was filtered off, washed with EtOH and crystallized from H_2O/EtOH (1:1). The white crystals formed were washed with diethyl ether and dried with P_2O_5 to give enantiomerically pure acid (+)-**3** (0.1 g, 71%). $[\alpha]_D$ = +5.6 (*c* = 1, 6 N HCl), m.p. 240–243 °C (decomp.). ^{31}P NMR (D_2O): δ = 12.98 ppm. ^{1}H NMR (D_2O): δ = 6.70–6.40 (m, 5 H, aromatic), 6.09 (dd, *J* = 15.95, *J* = 4.01 Hz, 1 H, =CHPh), 5.40 (dd, *J* = 15.95, *J* = 15.60, *J* = 8.90 Hz, 1 H, CH=CHPh), 3.45 (dd, *J* = 8.90, *J* = 16.30 Hz, 1 H, $CHNH_2$) ppm. ^{13}C NMR (D_2O): δ = 135.60, 133.09, 127.0, 126.9, 124.93, 115.4, 49.0 (d, J_{PC} = 149.5 Hz, PCH) ppm. $C_9H_{12}NO_3P$ (213.17): calcd. C 50.78, H 5.64, N 6.57, P 14.54; found C 50.68, H 5.78, N 6.49, P 14.31.

(S_S,S_C)-[3-Phenyl-1-(*p*-tolylsulfinylamino)propen-2-yl]-bis(diethylamino)phosphane–Borane (4): Bis(diethylamino)chlorophosphane (2.1 g, 10 mmol) in THF (10 mL) was cooled to 0 °C and borane–methyl sulfide complex (5 mL) was added. The reaction mixture was stirred at room temperature for 4 h and the solvent was removed under vacuum affording bis(diethylamino)chlorophosphane–borane complex. It was dissolved in THF (10 mL) and added slowly to lithium naphthalenide prepared from naphthalene (2.56 g, 20 mmol) and cut lithium wire (0.14 g, 20 mmol) at –78 °C. After stirring for 30 min, a solution of (+)-(*S*)-sulfinimine **1** (0.6187 g, 2.3 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred for 4 h at –78 °C. Then, after warming the reaction mixture to room temperature and quenching with an aqueous solution of NH_4Cl, the organic layer was separated. The aqueous phase was extracted with ethyl ether and the combined organic layers were dried with $MgSO_4$ and the solvents evaporated. The crude product was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH, 4:0.1) to afford borane complex (+)-**4** as a white solid (0.76 g, 72%). $[\alpha]_D$ = +67.7 (*c* = 1.22, $CHCl_3$), m.p. 130–132 °C. ^{31}P NMR ($CDCl_3$): δ = 90.74 (m) ppm. ^{1}H NMR ($CDCl_3$): δ = 7.60–6.95 (m, 10 H, =CHPh, aromatic), 5.85–5.75 (m, 1 H, CH=CHPh), 4.90–4.70 (m, 2 H, CHNH), 3.40–3.10 (m, 4 H, CH_2CH_3), 3.10–2.84 (m, 4 H, CH_2CH_3), 2.02 (s, 3 H, CH_3), 1.16

(t, J = 7.0 Hz, 3 H, CH_3CH_2), 0.92 (t, J = 7.0 Hz, 3 H, CH_3CH_2) ppm. ^{13}C NMR ($CDCl_3$): δ = 141.61, 140.51, 133.0, 132.8, 129.1, 128.2, 127.3, 126.2, 126.0, 125.7, 46.1 (d, J_{PC} = 65.13 Hz, PCH), 40.3, 20.9, 14.1, 13.5 ppm. HRMS: calcd. for $C_{24}H_{40}N_3PSOB$ [M + H] 460.4431; found 460.2727. $C_{24}H_{39}BN_3OPS$ (459.44): calcd. C 62.74, H 8.55, N 9.15, S 6.98, P 6.74; found C 62.80, H 8.30, N 9.08, S 6.88, P 6.78.

[(*S*)-1-Amino-3-phenylpropen-2-yl]phosphonic Acid (3): Borane complex (+)-**4** (0.76 g, 1.65 mmol) was heated to reflux with hydrochloric acid (36%, 5 mL) for 5 h. Acid (–)-**3** formed was isolated from the reaction mixture according to the procedure described for the (+)-(*R*)-enantiomer of acid **3** as white crystals (0.35 g, 75%). $[a]_D$ = –5.6 (c = 1.18, 6*N* HCl), m.p. 240–243 °C. ^{31}P NMR (D_2O): δ = 12.94 ppm. $C_9H_{12}NO_3P$ (213.17): calcd. C 50.78, H 5.64, N 6.57, P 14.54; found C 50.43, H 5.61, N 6.55, P 14.26.

(S_S,R_C)-Diethyl [4-Phenyl-2-(*p*-tolylsulfinylamino)buten-3-yl]phosphonate (5): Diethyl methanephosphonate (2.43 g, 16 mmol) in THF (10 mL) was cooled under nitrogen to –78 °C and LiHMDS (16 mmol) in THF (10 mL) was added. The reaction mixture was stirred for 1 h at this temperature. Then, a solution of (+)-(*S*)-sulfinimine **1** (4.3 g, 16 mmol) in THF (25 mL) was added dropwise and the reaction mixture was stirred at –78 °C for 5 h. After this time, the reaction was quenched with an aqueous solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3× 10 mL). The organic layer was dried with $MgSO_4$ and the solvents evaporated. The crude product consisted of two diastereoisomers in a 9:1 ratio [^{31}P NMR assay, δ_P = 28.3 (major), δ_P = 27.5 ppm (minor)] and was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH, 20:1) and crystallized from ethyl ether affording a single diastereoisomer of (–)-**5** as white crystals (4.37g, 65%). $[a]_D$ = –72.9 (c = 0.93, $CHCl_3$), m.p. 75–76 °C. ^{31}P N: δ = MR ($CDCl_3$); δ = 28.3 ppm. ^1H NMR ($CDCl_3$): δ = 7.65–7.16 (m, 9 H, aromatic), 6.4 (d, J = 15.8 Hz, 1 H, =CHPh), 6.10 (dd, J = 15.8, J = 6.5 Hz, 1 H, CH=CHPh), 5.6 (d, J = 6.9 Hz, 1 H, NHCH), 4.3 (dq, J = 6, J = 24 Hz, 1 H, CHNH), 4.1 (q, J = 7.3 Hz, 2 H, CH_2CH_3), 4.0 (q, J = 7.3 Hz, 2 H, CH_2CH_3), 2.31 (s, 3 H, CH_3), 2.44–2.13 (m, 2 H, CH_2P), 1.32 (t, J = 7 Hz, 3 H, CH_3CH_2), 1.22 (t, J = 7 Hz, 3 H, CH_3CH_2) ppm. ^{13}C NMR ($CDCl_3$): δ = 141.1, 136.3, 130.9, 129.6, 128.4, 127.6, 126.4, 126.0, 124.4, 61.8, 48.8, 33.3 (d, J_{PC} = 137.7 Hz, PCH_2), 21.2, 16.4 ppm. HRMS: calcd. for $C_{21}H_{29}O_4PSN$ [M + H] 422.1554; found 422.1555. $C_{21}H_{28}NO_4PS$ (421.49): calcd. C 59.84, H 6.69, P 7.35, N 3.32, S 7.60; found C 59.79, H 6.53, P 7.66, N 3.14, S 8.34.

[(*R*)-2-Amino-4-phenylbuten-3-yl]phosphonic Acid (6): Phosphonate (–)-**5** (0.2 g, 0.47 mmol) was heated to reflux with hydrochloric acid (36% aq., 5 mL) for 5 h. The reaction mixture was cooled to room temperature and extracted with $CHCl_3$ (3× 5 mL). The aqueous layer was separated and the solvents evaporated. The residue was dissolved in EtOH (5 mL) and propylene oxide added to pH ≈ 6. The precipitate was filtered off, washed with EtOH and crystallized from H_2O/EtOH (1:1). The white crystals formed were washed with diethyl ether and dried with P_2O_5 to give pure acid (+)-**6** as white crystals (0.068 g, 63%). $[a]_D$ = +4.5 (c = 1, 6*N* HCl), m.p. 218–228 °C (decomp.). ^{31}P NMR (D_2O): δ = 17.98 ppm. ^1H NMR (D_2O): δ = 7.26–6.11 (m, 5 H, aromatic), 6.58 (d, J = 15.89 Hz, 1 H, =CHPh), 5.99 (dd, J = 15.89, J = 8.6 Hz, 1 H, CH=CHPh), 4.20–3.95 (m, 1 H, C*H*NH_2), 2.08 (dd, J = 19.05, J = 7.12 Hz, 2 H, CH_2P) ppm. ^{13}C NMR (D_2O): δ = 135.8, 135.0, 128.79, 127.0, 126.8, 123.0, 65.8, 49.7, 30.6 (d, J_{PC} = 136.7 Hz, PCH_2) ppm. HRMS: calcd. for $C_{10}H_{15}NPO_3$ [M + H] 228.0786; found 228.0789. $C_{10}H_{14}NO_3P$ (227.20): calcd. C 52.90, H 6.21, N 6.17, P 13.57; found C 52.64, H 6.24, N 6.08, P 14.35.

(R_S,S_C)-Diethyl [4-Phenyl-2-(*p*-tolylsulfinylamino)buten-3-yl]phosphonate (5): According to the procedure described above from diethyl methanephosphonate (3.31 g, 21.8 mmol) dissolved in THF (15 mL) and (–)-(*R*)-sulfinimine **1** (5.86 g, 21.8 mmol) in THF (30 mL), title phosphonate (+)-**5** was obtained (7.42 g, 81%). $[a]_D$ = + 73.2 (c 1.27, $CHCl_3$). $C_{21}H_{28}NO_4PS$ (421.49): calcd. C 59.84, H 6.69, P 7.35, N 3.32, S 7.60; found C 59.79, H 6.38, P 7.89, N 3.45, S 7.36.

[(*S*)-2-Amino-4-phenylbuten-3-yl]phosphonic Acid (6): Acid hydrolysis of phosphonate (+)-**5** (0.45 g, 1.07 mmol) under elaborated standard conditions (36% aq. HCl, reflux, 5 h) afforded acid (–)-**6** as white crystals (0.158 g, 65%). $[a]_D$ = – 4.5 (c 0.98, 6*N* HCl), m.p. 218–228 °C. ^{31}P NMR (D_2O): δ = 17.98 ppm. HRMS: calcd. for $C_{10}H_{15}NPO_3$ [M + H] 228.0788; found 228.0789. $C_{10}H_{14}NO_3P$ (227.20): calcd. C 52.90, H 6.21, N 6.17, P 13.57; found C 52.64, H 6.28, N 6.19, P 13.49.

(S_S,R_C)-Diethyl [3-Hydroxy-2-(*p*-tolylsulfinylamino)propane]phosphonate (7): Methanol (25 mL) was cooled to –78 °C and a steam of ozone was bubbled through until the blue colour of unreacted ozone was noticeable. Then, a solution of aminophosphonate (–)-**5** (1.34 g, 3.18 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise (the reaction mixture remains blue) and stirring was continued for 15 min before dry oxygen was bubbled through the reaction mixture to remove an excess of ozone. Then, $NaBH_4$ (1.2 g, 31.6 mmol) was added at –78 °C and the reaction mixture was stirred for 3 h at this temperature and then for 2 h at room temperature. After extraction with $CHCl_3$ (3× 15 mL), the organic layer was dried with $MgSO_4$ and the solvents evaporated. Column chromatography (silica gel, CH_2Cl_2/MeOH, 20:1) and crystallization from diethyl ether gave desired product (+)-**7** as a white solid (0.89 g, 80%). $[a]_D$ = +105.2 (c = 1.48, $CHCl_3$), m.p. 85–87 °C. ^{31}P NMR ($CDCl_3$): δ = 28.6 ppm. ^1H NMR ($CDCl_3$): δ = 7.60–7.20 (AB syst., 4 H, aromatic), 4.95 (d, J = 9.25 Hz, 1 H, NHCH), 4.15 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 4.05 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 3.94–3.52 (m, 3 H, CHNH, CH_2O), 2.37 (s, 3 H, CH_3), 2.23 (dd, J = 6.20, J = 12.28 Hz, 2 H, CH_2P), 1.33 (t, J = 7.0 Hz, 3 H, CH_3CH_2), 1.29 (t, J = 7.0 Hz, 3 H, CH_3CH_2) ppm. ^{13}C NMR ($CDCl_2$): δ = 141.2, 129.35, 125.8, 65.4, 61.7, 53.0, 29.5 (d, J_{PC} = 139.0 Hz, PCH_2), 21.1, 16.4 ppm. MS (FAB): m/z = 350 [M + H]. $C_{14}H_{24}NO_5PS$ (349.38): calcd. C 48.13, H 6.92, N 4.03, S 9.18, P 8.87; found C 48.11, H 6.98, N 4.00, S 9.18, P 9.10.

(*R*)-3-(Diethoxyphosphoryl)-2-(*p*-tolylsulfonylamino)propanoic Acid (8): To a solution of (+)-**7** (0.467 g, 1.33 mmol) in a mixture of CCl_4 and MeCN (1:1, 8 mL) was added water (8 mL), $RuCl_3$ (3 mg) and $NaIO_4$ (2.29 g, 10.7 mmol). The heterogeneous mixture was stirred for 4 h at room temperature. After this time, water (20 mL) and $CHCl_3$ (20 mL) were added. The organic layer was separated and water layer extracted with $CHCl_3$ (3× 5 mL). The combined organic fraction was dried with $MgSO_4$ and the solvents evaporated. The residue was washed with petroleum ether (3× 5 mL) to give pure product (+)-**8** as white crystals (0.405 g, 80%). $[a]_D$ = +64.2 (c = 0.43, $CHCl_3$), m.p. 125–126 °C. ^{31}P NMR($CDCl_3$): δ = 26.7 ppm. ^1H NMR ($CDCl_3$): δ = 7.59–7.29 (AB, 4 H, aromatic), 5.93 (d, J = 5.9 Hz, 1 H, NHCH), 4.15 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 4.05 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 4.00–3.9 (m, 1 H, CHNH), 2.50 (dd, J = 17.9, J = 5.4 Hz, 2 H, CH_2P), 2.41 (s, 3 H, CH_3), 1.34 (t, J = 7.0 Hz, 3 H, CH_3CH_2), 1.30 (t, J = 7.0 Hz, 3 H, CH_3CH_2) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.6 (C=O), 143.8, 135.9, 129.7, 127.3, 62.8, 50.9, 29.5 (d, J_{PC} = 139.0 Hz, PCH_2), 21.0, 16.2 ppm. HRMS: calcd. for $C_{14}H_{23}NPSO_7$ [M + H] 380.0942; found 380.0933. $C_{14}H_{21}NO_7PS$ (378.36): calcd. C 44.33, H 5.85, N 3.69, P 8.20, S 8.45; found C 44.33, H 5.94, N 3.75, P 8.35, S 8.55.

(*R*)-2-Amino-3-phosphonopropanoic Acid (9): The acid (+)-**8** (0.5 g, 1.32 mmol) prepared as above and phenol (0.37 g, 3.98 mmol) were heated to reflux with hydrobromic acid (40%, 20 mL) for 14 h. After cooling to room temperature, water (30 mL) was added and reaction solution extracted with $CHCl_3$ (15 mL). The aqueous layer was separated and the solvents evaporated. The residue was dissolved in EtOH (10 mL) and propylene oxide was added to pH ≈ 6. The precipitate was filtered off, washed with EtOH (5 mL) and crystallized from H_2O/EtOH (1:1). The white crystals formed were washed with hexane and dried with P_2O_5 to give pure acid (+)-**9** (0.14 g, 63%). $[\alpha]_D$ = +8.1 (*c* = 0.93, H_2O); ref.[17b] α_D: +8.0 (*c* 0.5 , H_2O), m.p. 225–226 °C; ref.[17f] 224–226 °C. ^{31}P NMR (D_2O): δ = 18.1 ppm. ^{1}H NMR (D_2O): δ = 3.90–4.20 (m, 1 H, $CHNH_2$), 2.00–2.40 (m, 2 H, CH_2P) ppm.

(S_S,R_C)-Diethyl [2-Hydroxy-1-(*p*-tolylsulfinylamino)propane]phosphonate (10): According to the procedure described for the synthesis of (+)-**7**, phosphonate (+)-**2** (0.24 g, 0.59 mmol) was subjected to ozonolysis and then reduction with $NaBH_4$ (0.217 g, 5.9 mmol). The crude product was purified by column chromatography (CH_2Cl_2/MeOH, 20:1) and crystallized from diethyl ether affording diastereoisomerically pure hydroxyphosphonate (+)-**10** as a white solid (0.195 g, 99%). $[\alpha]_D$ = +3.2 (*c* = 0.1, $CHCl_3$), m.p. 103–107 °C. ^{31}P NMR ($CDCl_3$): δ = 21.5 ppm. ^{1}H NMR ($CDCl_3$): δ = 7.39–7.59 (AB, 4 H, aromatic), 5.2 (dd, *J* = 8.3, *J* = 10.3 Hz, 1 H, OH), 4.75 (d, *J* = 8.2 Hz, 1 H, NHCH), 4.2–3.8 (m, 5 H, CHP, CH_2CH_3), 3.6–3.2 (m, 2 H, CH_2O), 2.34 (s, 3 H, CH_3), 1.25–1.16 (m, 6 H, CH_3CH_2) ppm. ^{13}C NMR ($CDCl_3$): δ = 141.6, 137.4, 129.4, 126.5, 62.5, 61.5, 53.2 (d, J_{PC} = 150.3 Hz, PCH), 21.1, 16.1 ppm. MS (FAB): *m*/*z* = 336.1 [M + H]. $C_{13}H_{22}NO_5PS$ (335.35): calcd. C 46.56, H 6.61, P 9.24, N 4.1, S 9.56; found C 46.83, H 6.65, P 9.56, N 4.23, S 9.34.

(*R*)-3-Amino-3-phosphonopropanoic Acid (11): Triphenylphosphane (0.2 g, 1.49 mmol) and isopropyl diazocarboxylate (0.3 mL, 1.49 mmol) in CH_2Cl_2 (5 mL) were stirred under nitrogen at 0 °C for 30 min. Then, phosphonate (+)-10 (0.2 g, 0.597 mmol) was added dropwise and stirring was continued for 30 min. After that, KCN (0.2 g, 2.98 mmol) was added and the reaction mixture was stirred under nitrogen at room temperature for 24 h. Addition of water (10 mL) resulted in two layers that were separated. The aqueous layer was extracted with $CHCl_3$ (3× 5 mL) and the combined organic layers were dried with $MgSO_4$ and the solvents evaporated. The crude cyanide formed (δ_p = 20.2 ppm) was used for the next reaction step [heating to reflux with hydrochloric acid (36%, 10 mL) for 5 h]. After cooling to room temperature, the reaction solution was extracted with $CHCl_3$ (3× 5 mL). The aqueous layer was separated and the solvents evaporated. The residue formed was dissolved in EtOH (10 mL) and propylene oxide was added to pH ≈ 6. The precipitate was filtered off, washed with EtOH, and crystallized from H_2O/EtOH (1:1). The crystals formed were washed with diethyl ether and dried with P_2O_5 affording product (–)-**11** (0.053 g, 53%). $[\alpha]_D$ = –35.2 (*c* = 0.54, H_2O); ref.[18a] $[\alpha]_D$ = –32.6 (*c* = 1.0, H_2O). ^{31}P NMR (D_2O): δ = 8.4 ppm. ^{1}H NMR (D_2O): δ = 4.1–3.90 (m, 1 H, CHP), 3.80–3.60 (m, 1 H, CH_2COOH), 3.60–3.40 (m, 1 H, CH_2COOH) ppm.

(S_S,R_C)-Diethyl [3-Mesyloxy-2-(*p*-tolylsulfinylamino)propane]phosphonate (12): To a solution of phosphonate (+)-**7** (0.5 g, 1.43 mmol) and Et_3N (0.288 g, 2.86 mmol) in THF (5 mL) cooled to 0 °C was added dropwise mesyl chloride (0.245 g, 2.15 mmol) and the reaction mixture was stirred at this temperature for 1 h. The reaction progress was monitored by TLC (CH_2Cl_2/MeOH, 20:1). Then, water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3× 5 mL). The organic layer was dried with $MgSO_4$, evaporated and the crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 20:1) giving corresponding mesylate (+)-**12** as a colourless oil (0.55 g, 90%). $[\alpha]_D$ = +75.4 (*c* = 1.83, $CHCl_3$). ^{31}P NMR ($CDCl_3$): δ = 26.7 ppm. ^{1}H NMR ($CDCl_3$): δ = 7.62–7.28 (AB, 4 H, aromatic), 5.25 (d, *J* = 4.92 Hz, 1 H, NHCH), 4.19–4.07 (m, 6 H, CH_2OMs, CH_2CH_3), 3.90–3.75 (m, 1 H, CHNH), 2.97 [s, 6 H, $(CH_3)_2N$] 2.40 (s, 3 H, CH_3), 2.30 (dd, *J* = 6.0, *J* = 12 Hz, 2 H, CH_2P), 1.33 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2), 1.30 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2) ppm. ^{13}C NMR ($CDCl_3$): δ = 141.6, 140.5, 129.5, 125.8, 71.6, 62.6, 47.9, 37.2, 29.3 (d, J_{PC} = 137.8 Hz, PCH_2), 21.2, 16.2 ppm. HRMS: calcd. for $C_{15}H_{27}NPS_2O_2$ [M + H] 428.0962; found 428.0966. $C_{15}H_{26}NO_7PS_2$ (427.47): calcd. C 42.15, H 6.08, N 3.28, S 15.01, P 7.25; found C 42.13, H 6.11, N 3.12, S 14.44, P 6.61.

(S_S,R_C)-Diethyl 3-Dimethylamino-2-[(*p*-tolylsulfinylamino)propane]-phosphonate (13): To a solution of mesylate (+)-**12** (1.49 g, 0.35 mmol) in THF (5 mL), Me_2NH (2 M solution in THF, 9 mL) was added and the reaction mixture was stirred overnight at 40 °C. The solvent was evaporated and CH_2Cl_2 (10 mL) was added. After washing with water (2× 5 mL) the organic layer was separated. The water fraction was extracted with CH_2Cl_2 (2× 5 mL). The combined organic layers were dried with $MgSO_4$. After removal of the solvent and purification by column chromatography pure product (+)-**13** was obtained as a pale yellow oil (0.85 g, 65%). $[\alpha]_D$ = +122.0 (*c* = 2.15, $CHCl_3$). ^{31}P NMR ($CDCl_3$): δ = 28.6 ppm. ^{1}H NMR ($CDCl_3$): δ = 7.62–7.25 (AB, 4 H, aromatic), 5.25 (d, *J* = 5.9 Hz, 1 H, NHCH), 4.08 (q, *J* = 7.0 Hz, 2 H, CH_2CH_3), 4.06 (q, *J* = 7.0 Hz, 2 H, CH_2CH_3), 3.78–3.60 (m, 1 H, CHNH), 2.58–2.39 (m, 2 H, CH_2P), 2.37 (s, 3 H, CH_3), 2.34–2.15 (m, 2 H, CH_2P), 2.09 [s, 6 H, $(CH_3)_2N$], 1.32 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2), 1.3 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2) ppm. ^{13}C NMR ($CDCl_3$): δ = 141.8, 141.15, 129.4, 125.75, 63.3, 61.7, 45.4, 45.1, 30.1 (d, J_{PC} = 138.1 Hz, PCH_2), 21.25, 16.3 ppm. HRMS: calcd. for $C_{16}H_{30}N_2PSO_4$ [M + H] 377.1667; found 377.1664. $C_{16}H_{29}N_2O_4PS$ (376.45): calcd. C 51.56, H 7.71, N 7.44, S 8.51, P 8.24; found C 50.82, H 7.76, N 7.28, S 8.77, P 8.32.

(S_S,R_C)-[3-(Dimethoxyphosphoryl)-2-(*p*-tolylsulfinylamino)propyl]-trimethylammonium Iodide (14): To a solution of (+)-**13** (0.297 g, 0.792 mmol) prepared as above in acetone (10 mL), methyl iodide (0.12 g, 0.95 mmol) was added dropwise under nitrogen. The reaction mixture was stirred at room temperature for 4 h. The acetone was evaporated, water (10 mL) was added and extracted with CH_2Cl_2 (3× 2 mL). The aqueous extract was evaporated and the oily residue was dissolved in CH_2Cl_2 (5 mL). The organic solution was dried with $MgSO_4$ and evaporated to afford the crude product (light brown solid) that after column chromatography (CH_2Cl_2/MeOH, 20:1) gave the desired iodide as a yellowish solid (0.22 g, 73%), m.p. 55–60 °C. ^{31}P NMR ($CDCl_3$): δ = 26.1 ppm. ^{1}H NMR ($CDCl_3$): δ = 7.76–7.31 (AB, 4 H, aromatic), 4.48–4.36 (m, 1 H, NHCH), 4.25–4.00 (m, 4 H, CH_2CH_3), 3.94–3.75 (m, 2 H, CH_2), 3.08 [s, 9 H, $(CH_3)_3N$], 3.10–2.80 (m, 1 H, CHNH), 2.50–2.32 (m, 2 H, CH_2P), 2.43 (s, 3 H, CH_3), 1.37 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2), 1.32 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2) ppm. ^{13}C NMR ($CDCl_3$):δ = 142.6, 140.1, 130.1, 125.5, 67.9, 62.4, 54.8, 43.4 (d, J_{PC} = 118.7 Hz, PCH_2), 21.3, 16.3 ppm. HRMS: calcd. for $C_{17}H_{32}PSNO_4$ [M^+] 391.1823; found 391.1820.

(*R*)-[2-Amino-3-(trimethylammonio)propane]phosphonic Acid Hydrochloride (15): Ammonium salt **14** (0.187 g, 0.48 mmol) was heated to reflux with concd. hydrochloric acid (9 mL) and acetic acid (3 mL) for 5 h. Then, water (10 mL) was added and extracted with CH_2Cl_2 (4× 10 mL). The aqueous layer was evaporated to give the light yellow oil. It was dissolved in EtOH (5 mL) and neu-

tralized with propylene oxide. The white solid formed was filtered off, washed with EtOH (2 × 1 mL) and Et_2O (3 mL) and dried with P_2O_5 affording product (–)-**15** as white crystals (0.07 g, 75%). $[\alpha]_D$ = –9.2 (*c* = 1.1, H_2O), m.p. 237–239 °C. ^{31}P NMR (D_2O): δ = 16.24 ppm. ^1H NMR (D_2O): δ = 4.14–4.00 (m, 1 H, $CHNH_2$), 3.90–3.66 (m, 2 H, CH_2), 3.18 [s, 9 H, $(CH_3)_3N$], 2.11–1.97 (m, 2 H, CH_2P) ppm. ^{13}C NMR (D_2O): δ = 66.4, 52.3, 41.9, 29.9 (*d*, J_{PC} = 129.8 Hz, PCH_2) ppm. HRMS: calcd. for $C_6H_{18}N_2PO_2$ [M^+] 197.1051; found 197.1055. $C_6H_{18}Cl_{15}N_2O_3P$ (250.37): calcd. C 28.81, H 7.26, N 11.21; found C 29.32, H 7.75, N 10.75.

Supporting Information (see footnote on the first page of this article): All ^{31}P, ^1H and ^{13}C NMR spectroscopic data, and MS or HRMS data of synthesized compounds. X-ray crystal structure for compound (–)-**15**.

Acknowledgments

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[21] CCDC-867834 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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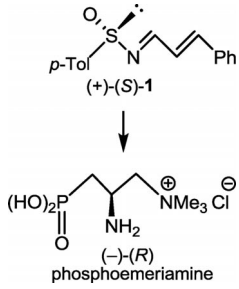
Asymmetric Synthesis

Starting from sulfinimine (+)-(*S*)-**1**, as a single reagent, the synthesis of diverse enantiopure aminophosphonic acids was accomplished. In addition to the synthesis of unsaturated α- and β-aminophosphonic acids, the first synthesis of (–)-(*R*)-phosphoemeriamine and new approaches to (+)-(*R*)-2-amino-3-phosphonopropanoic acid (**8**) and its 3-amino regioisomer **11** are reported.



Keywords: Synthetic methods / Asymmetric synthesis / Diastereoselectivity / Aminophosphonic acids

