Asymmetric Synthesis of (*R*)- and (*S*)-α-Amino-3-piperidinylphosphonic Acids via Phosphite Addition to Iminium Ions

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Abstract: α-Amino-3-piperidinylphosphonates were conveniently prepared from 3-piperidinone, by nucleophilic addition of phosphite to the iminium ion formed by in situ condensation of this ketone with chiral benzylic amines. Subsequent deprotection of *N*-Boc group, cleavage of the benzyl groups and acidic hydrolysis of the resulting α-amino-3-piperidinylphosphonates gave, in a four-step sequence from piperidinone, the enantiopure α-amino-3-piperidinylphosphonic acids. The absolute configuration has been established by X-ray crystal structure analysis of the *N*-(4-nitrobenzoyl)aminophosphonate derivative.

Key words: amino acids, heterocycles, piperidines, asymmetric synthesis, addition reaction

In recent years, due to their potential biological activity[1] and their use as building blocks for peptide mimetics, α-aminophosphonic acids are of considerable current interest.[2] Cyclic or heterocyclic rings introduced into the molecular skeleton increase its rigidity and modify electronic effects. Thus, many cyclic α-aminophosphonic acids have been prepared.[3–7] However, very few examples of heterocyclic acids **1** or the corresponding phosphonates presented in the literature have been reported in racemic series.[8–12] In all the synthetic approaches to introduce the aminophosphonate moiety, the Kabachnick–Fields reaction[10a] was used starting from heterocyclohexanones, to provide α-aminophosphonates with moderate to good yields. In contrast, enantiopure 3-piperidine acid **2** is still unknown (Figure 1).

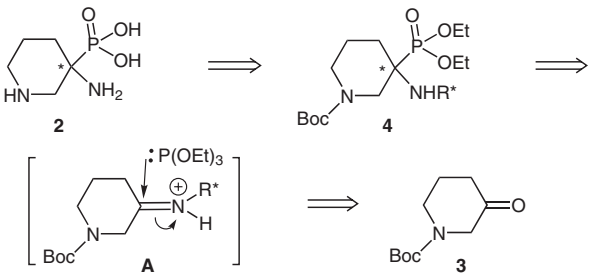
1a X = NH, NMe
1b X = O
1c X = S

2

Figure 1 Heterocyclic α-aminopiperidinylphosphonic acids

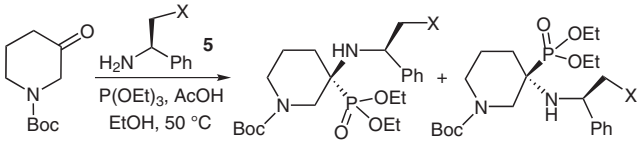
In the course of our work on the asymmetric synthesis of cyclic analogues of α-aminophosphonic acids,[4] we have previously reported a simple and convenient synthesis of 1-aminocyclopropanephosphonic acids [aminocyclopropanecarboxylic acid (ACC) analogues], in three steps, starting from cyclopropanone hemiacetals. Furthermore, we have very recently reported, in racemic series, an efficient three step synthesis of new heterocyclic α-aminophosphonic acids **1a–c** and **2** from readily available heterocyclic ketones in good yields.[12]

We decided to study the selectivity in the addition of trialkyl phosphite to the iminium ions **A**, readily available from 3-piperidinone **3**. This one-pot reaction should occur in the presence of chiral benzylamine derivatives to give the desired aminophosphonates **4**, precursors of aminophosphonic acid **2** (Scheme 1).



Scheme 1

The standard one-pot procedure[4,12] for the reaction of ketone **3** with chiral amine **5a** (X = H) was carried out in EtOH in the presence of 2 equivalents of AcOH, 0.8 equivalent of $MgSO_4$ and 1.5 equivalents of triethyl phosphite at 50 °C for 17 hours. The aminophosphonates **6** were obtained in good yield (75%) as an inseparable mixture of two diastereoisomers **6A/6B** in a 40:60 ratio as shown by their ^{31}P NMR spectra (δ_{6A}/δ_{6B} = 27.44/27.74). The use of chiral amine **5b** (X = OMe) did not change the diastereoisomeric ratio (^{31}P NMR, δ_{7A}/δ_{7B} = 27.56/27.30) of the resulting inseparable mixture of aminophosphonates **7A/7B** (55% yield) (Scheme 2).



3 X = H (**5a**) **6A** (40:60) **6B**
X = OMe (**5b**) **7A** (40:60) **7B**

Scheme 2 Preparation of aminophosphonates **6** and **7** from ketone **3**.

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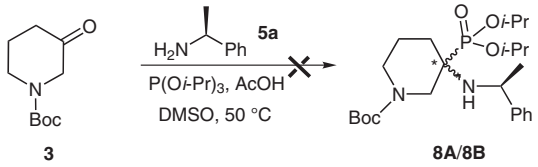
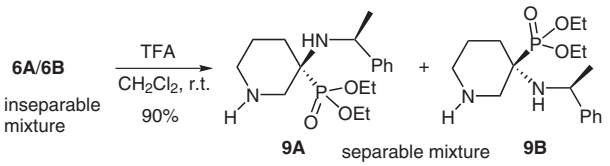
We have previously reported that a bulky phosphite reacted with iminium ion in DMSO to enhance the selectivity of addition reaction.[4d] Thus we treated ketone **3** with chiral amine **5a** under the same conditions as above, by using triisopropyl phosphite in DMSO instead of $P(OEt)_3$ in EtOH to obtain aminophosphonates **8A** or **8B**. However, neither was formed (Scheme 3).



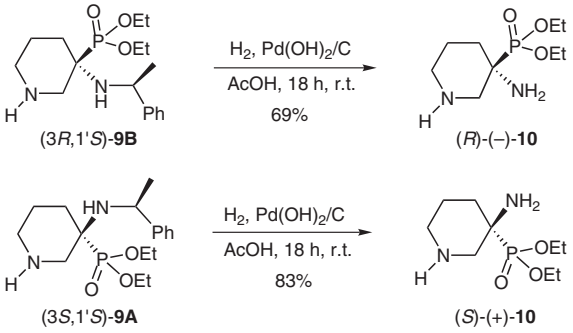
Scheme 3

We found that the chromatographic separation of diastereoisomers **6A/6B** from each other was not possible. Conversely, the cleavage of the *N*-Boc protecting group with trifluoroacetic acid (TFA) at room temperature allowed each diastereoisomer **9A** and **9B** to be separated on silica gel column (Scheme 4).



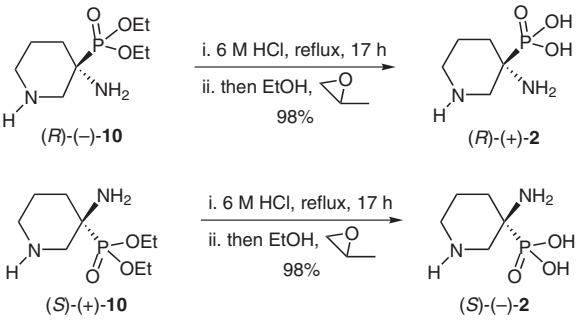
Scheme 4

We then submitted the heterocyclic phosphonates **9B** and **9A** to a deprotection sequence. These phosphonates reacted under mild conditions [20% $Pd(OH)_2$/C and 1 atm H_2] to cleave the benzyl groups affording free diaminophosphonates (*R*)-**10** and (*S*)-**10**, in good yields (Scheme 5).



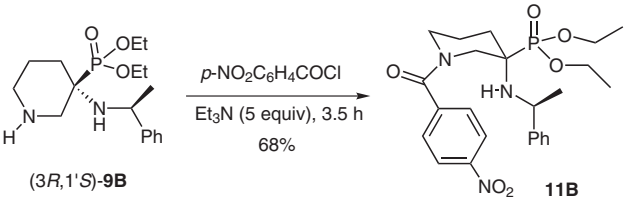
Scheme 5

Phosphonate hydrolysis of (*R*)-**10** and (*S*)-**10** was accomplished in aqueous 6 M HCl solution at reflux, followed by treatment with propylene oxide to provide the enantiopure diaminophosphonic acid (*R*)-(+)-**2** and (*S*)-(–)-**2**, in quantitative yield {$[\alpha]_D$ +2.4 (*c* = 0.25, 1 M NaOH) for (*R*)-**2**} (Scheme 6).



Scheme 6

To determine the absolute configuration of these isomers, we have protected the major isomer with 4-nitrobenzoyl chloride in the presence of Et_3N to give **11B** in good yield (Scheme 7). Suitable crystals of **11B** were analyzed by X-ray crystallography,[13] which showed a (3*R*,1′*S*)-absolute configuration (Figure 2). Moreover, in the X-ray structure two conformers in which the phosphonate group at C-3 occupies an equatorial position were observed. By comparison, the absolute configuration for the major isomer should be (3*R*,1′*S*)-**9B** and must be (3*S*,1′*S*)-**9A** for the minor isomer.



Scheme 7

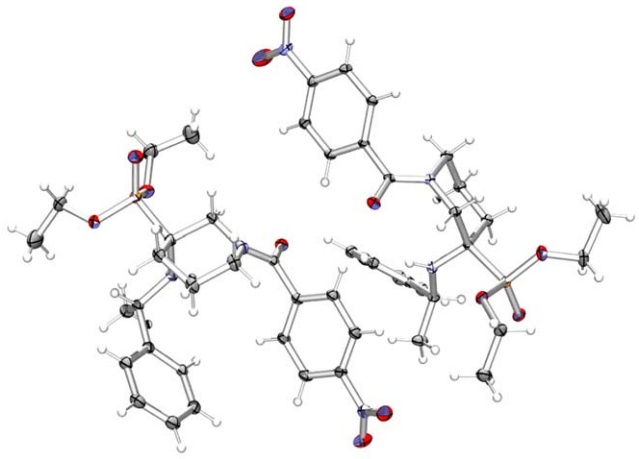


Figure 2 ORTEP plot of X-ray crystal structure of (3*R*,1′*S*)-**11B**

In summary, we have developed an easy and efficient four step synthesis of enantiopure (*R*)- and (*S*)-α-amino-3-piperidinylphosphonic acids **2**. Thus, starting from commercially available *N*-Boc 3-piperidinone **3**, we have demonstrated that this iminium ion **A** formed from the ketone **3** and chiral amine **5** undergoes an asymmetric nucleophilic addition of phosphite to give a major α-aminopiperidinylphosphonate. Good separation of the

major diastereoisomer required deprotection of the *N*-Boc group. Subsequent cleavage of the benzyl group and acidic hydrolysis of the resulting α-aminophosphonate provided the optically active (*R*)- and (*S*)-α-aminophosphonic acids in good yields. Efforts to improve the diastereoselective phosphite approach are currently in progress in our laboratory.

All reactions were carried out under argon with magnetic stirring. (*S*)-α-Methylbenzylamine (**5a**), (*R*)-α-(methoxymethyl)benzylamine (**5b**), AcOH, *N*-Boc-piperidin-3-one (**3**), trifluoroacetic acid (TFA), $Pd(OH)_2/C$ (20%), 4-nitrobenzoyl chloride, $P(OEt)_3$, and $P(Oi\text{-}Pr)_3$ were purchased from Aldrich. $P(OEt)_3$, and $P(Oi\text{-}Pr)_3$ were distilled under reduced pressure and stored on molecular sieves 4 Å under argon. Et_3N, DMSO and CH_2Cl_2 were freshly distilled over CaH_2 under argon before use. R_f values refer to values obtained by TLC on 0.25 mm silica gel plates (Merck F254). Flash chromatography (FC) was performed on silica gel 60 (0.040–0.063 mm). Yields are reported for chromatographically and spectroscopically pure compounds, unless otherwise noted. IR spectra were recorded on a Perkin-Elmer (spectrum one) spectrophotometer. Melting points were determined on a Büchi B-545 capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DRX250 (250 MHz) or Bruker AC360 (360 MHz) spectrometer. Chemical shifts were recorded in parts per million from the solvent resonance ($CDCl_3$ at 7.27 ppm and D_2O at 4.8 ppm). ^{13}C NMR spectra were recorded on a Bruker DRX250 (62.9 MHz), or Bruker AC360 (90.56 MHz) spectrometer. Chemical shifts are reported in parts per million from the solvent resonance ($CDCl_3$ at 77.16 ppm). ^{31}P NMR spectra were recorded on a Bruker AM250 (101.25 MHz), and chemical shifts are quoted relative to internal 85% H_3PO_4 (δ = 0). High-resolution mass spectra were recorded on a Finnigan MAT 95S spectrometer. All new compounds were determined to be >95% pure by ^{1}H NMR spectroscopy.

Aminophosphonates 6A/6B; General Procedure

To a solution of *N*-Boc-piperidin-3-one **3** (862 mg, 4.33 mmol) in EtOH (10 mL), was added (*S*)-α-methylbenzylamine (**5a**; 6.50 mmol), AcOH (500 μL, 8.67 mmol) and $MgSO_4$ (390 mg, 3.25 mmol). After stirring and heating at 50 °C for 5 h, $P(OEt)_3$ (1.08 g, 1.13 mL, 6.50 mmol) was added. The mixture was heated at 50 °C for 17 h. It was then concentrated in vacuo and concd aq ammonia (1 mL) was added to the residue. The resulting mixture was purified by flash chromatography on silica gel (MeOH–CH_2Cl_2, 10:90) to afford 1.43 g (75%) of pure aminophosphonates **6A/6B** as an inseparable mixture of two diastereoisomers in a 40:60 ratio as determined from its ^{31}P NMR spectrum. The spectral data given are for the **6A/6B** diastereoisomeric mixture.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 7.0 Hz, 1.2 H, CH_3, **A**), 0.85–1.45 (m, 8.8 H, CH_3CHN, CH_3CH_2, and 1 HN, **A/B**, and CH_3, **B**), 1.50 (s, 9 H, *t*-C_4H_9, **A/B**), 1.45–2.10 (m, 3.4 H, 2 H-5 and H-4 **A/B**, and H-4, **A**), 2.60 (ddd, *J* = 3.2, 12.7, 12.7 Hz, 0.6 H, H-4, **B**), 2.80–3.65 (m, 2 H-6, **A/B**), 3.65–3.97 (m, 2 H-2, **A/B**), 3.97–4.22 (m, 4 H, 2 CH_2O, **A/B**), 4.22–4.42 (m, 1 H, CHN, **A/B**), 7.03–7.20 (m, 5 H_{arom}, **A/B**).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 16.4/16.6 (d, $^3J_{P,C}$ = 5.5 Hz, 2 *C*H_3CH_2O, **A/B**), 19.4 (d, $^3J_{P,C}$ = 10.4 Hz, C-5, **B**), 20.0 (d, *J* = 8.2 Hz, C-5, **A**), 26.5 (C-4, **A/B**), 27.1 (*C*H_3CHN, **A/B**), 28.3/28.5 [C(*C*H_3)$_3$, **A/B**], 43.5/44.6 (C-6, **A/B**), 49.0/50.2 (d, *J* = 9.2 Hz, C-2, **B/A**), 52.3 (CHN, B), 52.6 (CHN, **A**), 56.5 (d, *J* = 145.4 Hz, C-3, **A**), 57.5 (d, *J* = 141.5 Hz, C-3, **B**), 61.7 (2 CH_2O, **B**), 62.1 (d, *J* = 7.7 Hz, 2 CH_2O, **A**), 79.3 [*C*(CH_3)$_3$, **A/B**], [6 arom: 126.3 (CH), 126.4 (2 CH), 128.1 (2 CH), 148.1/148.7 (C, **A/B**)], 155.1/155.6 (COO, **A/B**).

^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 27.44/27.74.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{37}N_2O_5P$ + Na: 463.2332; found: 463.2348.

Aminophosphonates 7A/7B

The aminophosphonates **7A/7B** were prepared following the procedure used for the preparation of **6A/6B**. *N*-Boc-piperidin-3-one **3** (208 mg, 1.045 mmol) was reacted in EtOH (3 mL) with (*S*)-methoxymethylbenzylamine (**5b**; 215 mg, 1.57 mmol), AcOH (115 μL, 2.09 mmol), $MgSO_4$ (94 mg, 0.78 mmol) and $P(OEt)_3$ (270 μL, 1.57 mmol) at 50 °C for 24 h. Standard work-up and flash chromatography on silica gel (MeOH–CH_2Cl_2, 5:95) gave 270 mg (55%) of aminophosphonates **7A/7B** as an inseparable mixture of two diastereoisomers in a 40:60 ratio as determined from its ^{31}P NMR spectrum. The spectral data given are for **7A/7B** diastereoisomeric mixture.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 6.9 Hz, 1.2 H, CH_3, **A**), 0.85–1.75 (m, 8.2 H, CH_3, 2 H-5, and 1 H-4 **A/B**, and CH_3 **B**, 1 H-4 **A**), 1.53 (s, 9 H, *t*-C_4H_9, **A/B**), 1.75–2.10 (m, 0.6 H, **B**), 2.10–2.52 (m, 1 HN), 2.66 (dd, *J* = 7.5, 7.5, 0.6 H, H-6, **B**), 3.27 (s, 1.2 H, OCH_3, **A**), 3.37 (s, 1.8 H, OCH_3, **B**), 2.79–3.70 (m, 3.4 H, 1 H-6, CH_2OMe **A/B**, and 1 H-6 **A**), 3.70–4.70 (m, 7 H, 2 H-2, 2 CH_2O and CHN, **A/B**), 7.10–7.50 (m, 5 H_{arom}, **A/B**).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 16.5/16.7 (d, $^3J_{P,C}$ = 3.7 Hz, 2 *C*H_3CH_2O, **A/B**), 19.2 (C-5, **A**), 20.1 (d, $^3J_{P,C}$ = 5.6 Hz, C-5, **B**), 26.8 (C-4, **B**), 28.4 [C(*C*H_3)$_3$, **A/B**], 29.8 (C-4, **A**), 43.7/44.8 (C-6, **B/A**), 49.0/50.7 (C-2, **A/B**), 55.5/57.0 (d, $^1J_{P,C}$ = 143.7 Hz, C-3, **A/B**), 56.2/57.0 (CHN, **B/A**), 58.9/59.0 (OCH_3, **A/B**), 61.8/61.9 (d, *J* = 6.5 Hz, 2 CH_2OP, **B**), 62.2/62.3 (s, 2 CH_2OP, **A**), 76.8/78.0 (*C*H_2OMe, **A/B**), 78.4/79.4 [*C*(CH_3)$_3$, **A/B**], [6 arom: 126.9/127.2 (CH), 127.8/127.4 (2 CH), 128.0/128.5 (2 CH), 143.8/143.2 (C)], 154.1/154.7 (COO, **A/B**).

^{3} ^{1}P NMR (101.25 MHz, C_6D_6): δ = 27.56/27.30.

Aminophosphonates 9

To a solution of the inseparable mixture of **6A/6B** (1.430 g, 3.25 mmol) in CH_2Cl_2 (40 mL), was added TFA (7.2 mL) and the mixture was stirred at r.t. for 3 h. An aq sat. solution of $NaHCO_3$ (30 mL) was added and the mixture was extracted with EtOAc. The organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography (MeOH–CH_2Cl_2–aq NH_3, 5:95:0.5) gave **9A** (430 mg, 39%) and **9B** (560 mg, 51%) as light yellow oils.

(3*S*,1′*S*)-Diethyl 3-(1′-Methylbenzyl)aminopiperidin-3-ylphosphonate (9A)

$[\alpha]_D$ –62.6 (*c* = 0.65, $CHCl_3$); R_f = 0.46 (MeOH–CH_2Cl_2–aq NH_3, 10:90:0.5).

IR (neat): 3665, 3324, 2980, 1266, 1230, 1056, 1024, 960 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.33–1.48 (m, 9 H, 3 CH_3), 1.50–1.80 (m, 4 H, 2 HN and 2 H-5), 1.81–2.03 (m, 2 H-4), 2.46 (ddd, *J* = 3.0, 11.5, 14.0 Hz, 1 H-6), 2.77 (dd, *J* = 2.7, 14.0 Hz, 1 H-2), 2.72–2.88 (m, 1 H-6), 2.92 (ddd, *J* = 2.0, 5.0, 14.0 Hz, 1 H-2), 4.07–4.28 (m, 4 H, 2 CH_2O), 4.45 (qd, *J* = 6.5 Hz, $^4J_{P,H}$ = 2.7 Hz, 1 CHN), 7.15–7.50 (m, 5 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.8 (2 *C*H_3CH_2O), 20.8 (d, $^2J_{P,C}$ = 7.3 Hz, C-5), 26.9 (*C*H_3CHN), 31.0 (C-4), 45.7 (C-6), 47.4 (d, $^2J_{P,C}$ = 9.1 Hz, C-2), 52.8 (CHN), 56.3 (d, $^1J_{P,C}$ = 136.7 Hz, C-3), 61.7 (d, $^2J_{P,C}$ = 7.7 Hz, CH_2O), 62.1 (d, $^2J_{P,C}$ = 7.8 Hz, CH_2O), [6 arom: 126.4 (2 CH), 126.9 (CH), 128.7 (2 CH), 148.3 (C)].

^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 29.47.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{29}N_2O_3P$ + Na: 363.1808; found: 363.1811.

(3*R*,1′*S*)-Diethyl 3-(1′-Methylbenzyl)aminopiperidin-3-ylphosphonate (9B)

$[\alpha]_D$ –74.0 (*c* = 0.60, $CHCl_3$); R_f = 0.40 (MeOH–CH_2Cl_2–aq NH_3, 10:90:0.5).

IR (neat): 3665, 3450, 3347, 2980, 1232 (P=O), 1056, 1024, 961 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 0.96–1.10 (m, 2 H-5), 1.27 (t, *J* = 7.2 Hz, 3 H, C$H_3$$CH_2O$), 1.29 (d, *J* = 6.8 Hz, 3 H, CH_3CHN), 1.30 (t, *J* = 7.2 Hz, 3 H, C$H_3$$CH_2O$), 1.65–1.84 (m, 2 H-4), 1.90–2.40 (br s, 2 HN), 2.56 (ddd, *J* = 7.2, 7.2, 13.5 Hz, 1 H-6), 2.75–2.95 (m, 2 H, H-6 and H-2), 3.07 (dd, *J* = 3.2, 13.7 Hz, 1 H-2), 4.08–4.15 (m, 4 H, 2 CH_2O), 4.41 (dq, $^4J_{P,H}$ = 2.2 Hz, *J* = 6.8 Hz, 1 CHN), 7.15–7.47 (m, 5 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.5 (*C*$H_3$$CH_2O$), 16.6 (*C*$H_3$$CH_2O$), 20.0 (d, $^3J_{P,C}$ = 9.4 Hz, C-5), 26.3 (d, $J_{P,C}$ = 3.4 Hz, C-4), 26.8 (*C*H_3CHN), 45.4 (C-6), 52.0 (d, $^2J_{P,C}$ = 6.8 Hz, C-2), 52.6 (CHN), 57.3 (d, $^1J_{P,C}$ = 140.7 Hz, C-3), 61.6 (d, $^2J_{P,C}$ = 7.7 Hz, CH_2O), 62.0 (d, $^2J_{P,C}$ = 7.7 Hz, CH_2O), [6 arom: 126.3 (CH), 126.4 (2 CH), 128.1 (2 CH), 148.1 (C)].

^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 29.04.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{29}N_2O_3P$ + Na: 363.1808; found: 363.1812.

Diaminophosphonate 10

To a solution of aminophosphonate **9A** or **9B** (1 mmol) in AcOH (5 mL), was added 20% $Pd(OH)_2$/C (Pearlman's catalyst, 150 mg). The mixture was stirred at r.t. under H_2 (1 atm) for 18 h, then degassed under a stream of argon, filtered and the collected solid was washed with EtOH. The combined filtrate and washings were concentrated and purified by chromatography (silica gel, eluent: MeOH–CH_2Cl_2–aq NH_3, 5:95:0.5) to give the free diaminophosphonate **10** as yellow oils.

(*R*)-(–)-Diethyl 3-Aminopiperidin-3-ylphosphonate [(*R*)-10]

$[\alpha]_D$ –3.4 (*c* = 0.60, $CHCl_3$).

IR (neat): 3370, 3297 (NH), 2933, 1228 (P=O), 1055, 1024 (P–O), 963 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.2 Hz, 6 H, CH_3), 1.40–1.55 (m, 1 H-5), 1.55–1.78 (m, 5 H, 3 HN, 1 H-4 and 1 H-5), 1.78–2.10 (m, 1 H-4), 2.62 (ddd, *J* = 3.2, 10.5, 13.0 Hz, 1 H-6), 2.79 (ddd, *J* = 1.5, 8.5, 13.1 Hz, 1 H-2), 2.94 (br d, *J* = 13.0 Hz, 1 H-6), 3.02 (dd, *J* = 3.2, 13.1 Hz, 1 H-2), 4.14 (dq, $^3J_{P,H}$ = 1.7 Hz, *J* = 7.2 Hz, 2 H, CH_2OP), 4.17 (mq, *J* = 7.2 Hz, 2 H, CH_2OP).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.5 (CH_3), 16.6 (CH_3), 20.8 (d, $^2J_{P,C}$ = 8.6 Hz, C-5), 30.4 (C-4), 46.2 (C-6), 50.6 (d, $^1J_{P,C}$ = 151.2 Hz, C-3), 51.5 (d, $^2J_{P,C}$ = 5.6 Hz, C-2), 62.2 (d, $^2J_{P,C}$ = 7.3 Hz, CH_2O), 62.3 (d, $^2J_{P,C}$ = 7.5 Hz, CH_2O).

^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 29.41.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_9H_{21}N_2O_3P$ + Na: 259.1182; found: 259.1193.

(*S*)-(+)-Diethyl 3-Aminopiperidin-3-ylphosphonate [(*S*)-10]

$[\alpha]_D$ +3.4 (*c* = 0.60, $CHCl_3$).

(*R*)-(+)-3-Aminopiperidin-3-ylphosphonic Acid [(*R*)- 2]

Hydrolysis of phosphonate (*R*)-**10** was carried out with aq 6 M HCl according to our previously reported method;[12] $[\alpha]_D$ +2.4 (*c* = 0.25, aq 1 M NaOH); mp >250 °C (dec.).

^1H NMR (250 MHz, D_2O): δ (two conformers) = 1.60–2.17 (m, 3 H, 2 H-5 and 1 H-4), 2.17–2.37 (m, 1 H-4), 2.97–3.13 (m, 1 H-6), 3.17/3.26 (d, *J* = 12.7 Hz, 1 H-2), 3.24–3.42 (m, 1 H-6), 3.63/3.66 (dd, *J* = 1.5, 12.7 Hz, 1 H-2).

^{13}C NMR (D_2O + NaOD, 62.9 MHz): δ = 20.6 (d, $^3J_{P,C}$ = 8.0 Hz, C-5), 30.3 (C-4), 44.7 (C-6), 50.15 (d, $^1J_{P,C}$ = 140.1 Hz, C-3), 50.9 (d, $^2J_{P,C}$ = 5.3 Hz, C-2).

^{31}P NMR (101.25 MHz, D_2O): δ = 11.80.

MS (ESI$^+$): *m*/*z* = 203.1 $[M + Na]^+$.

All spectral data were identical with those reported for the racemic compound.[12]

(*S*)-(–)-3-Aminopiperidin-3-ylphosphonic Acid [(*S*)-2]

$[\alpha]_D$ –2.4 (*c* = 0.25, aq 1 M NaOH).

(+)-Diethyl 3-(1′-Methylbenzyl)amino-1-(4-nitrobenzoyl)piperidin-3-ylphosphonate (11B)

To a solution of major phosphonate **9B** (75 mg, 0.220 mmol) in CH_2Cl_2 (2 mL), was added Et_3N (155 μL, 5 equiv) and 4-nitrobenzoyl chloride (43 mg, 0.232 mmol) at 0 °C. The mixture was stirred at 0 °C for 3.5 h. After dilution with Et_2O (10 mL), the mixture was washed with H_2O, then with brine. The organic layer was dried ($MgSO_4$) and concentrated under vacuo. The residue was purified by flash chromatography on silica gel (eluent, EtOAc–pentane–aq NH_3, 50:50:0.5) to provide 73 mg (68%) of (+)-**11B** as a viscous oil. Crystallization from MeOH–Et_2O gave suitable crystals; mp 95 °C; $[\alpha]_D$ +12.7 (*c* = 1.00, $CHCl_3$).

IR (neat): 3467, 3360 (NH), 2980, 1645, 1634 (C=O), 1286, 1238 (P=O), 1055, 1024 (P–O), 963 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ [two conformers (a/b = 75:25)] = 1.00–1.20 (m, 1 H-5, a/b), 1.40 (d, *J* = 6.9 Hz, 3 H, CH_3CHN, a/b), 1.41 (t, *J* = 7.0 Hz, 3 H, CH_3-CH_2O, a/b), 1.44 (t, *J* = 7.0 Hz, 3 H, C$H_3$$CH_2O$, a/b), 1.50–1.88 (m, 2 H, 1 H-5 and HN, a/b), 1.88–2.05 (m, 1 H-4, a/b), 2.80–3.00 (m, 1 H-4, a/b), 3.30 (dd, *J* = 2.2, 14.0 Hz, 2 H-6, a), 3.56 (dd, *J* = 2.7, 14.0 Hz, 2 H-6, b), 3.98–4.13 (m, 1 H-2), 4.13–4.30 (m, 4 H, 2 CH_2O), 4.37 (qd, *J* = 6.9 Hz, $^3J_{P,H}$ = 2.2 Hz, 1 CHN), 4.45 (dd, *J* = 7.2, 13.5 Hz, 1 H-2), 7.12–7.36 (m, 5 H_{phenyl}), 7.53 (d, *J* = 8.6 Hz, 2 H_{arom}), 8.23 (d, *J* = 8.3 Hz, 2 H_{arom}).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ [two conformers (a/b = 75:25)] = 16.6/16.7 (*C*$H_3$$CH_2O$, b/a), 16.75 (*C*$H_3$$CH_2O$, a/b), 19.1/20.2 (d, $^2J_{P,C}$ = 11.0 Hz, C-5, b/a), 26.2/26.5 (C-4, b/a), 26.7/27.1 (*C*H_3CHN, a/b), 42.9/47.7 (C-6, b/a), 47.9/53.8 (d, *J* = 9.8 Hz, C-2, a/b), 52.5/53.0 (CHN, a/b), 57.1 (d, $^1J_{P,C}$ = 142.0 Hz, C-3, a/b), 62.4 (d, $^2J_{P,C}$ = 8.3 Hz, CH_2OP, a/b), 62.5 (d, *J* = 8.3 Hz, CH_2OP, a/b), [12 arom: 123.8 (2 CH, a/b), 126.5 (2 CH, a/b), 126.6/126.8 (CH, a/b), 127.8/128.4 (2 CH, a/b), 128.2/128.7 (2 CH, a/b), 142.5 (s, a/b), 148.2 (s, a/b), 148.7 (s, a/b)], 168.9 (CON, a/b).

^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 26.98.

HRMS (ES): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{32}N_3O_6P$ + Na: 512.1921; found: 512.1921.

X-ray Crystal Structure Analysis of (+)-(3*R*,1′*S*)-Phosphonate 11B[13]

Colorless crystal of 0.10 × 0.08 × 0.07 mm. $C_{24}H_{32}N_3O_6P$, *M* = 489.50: triclinic system, space group *P*1 (No 1), *Z* = 2, with *a* = 8.4002 (6), *b* = 10.3126 (6), *c* = 14.5471 (10) Å, *α* = 83.474 (2), *β* = 77.733 (2), *γ* = 81.702 (2)°, *V* = 1214.02 (14) A^3, *d* = 1.339 g cm^{-3}, F(000) = 520, λ: = 0.71073 Å (Mo-Kα), *μ* = 0.158 mm^{-1}, 17403 reflections measured ($-14 \le h \le 14$, $-10 \le k \le 18$, $-25 \le l \le 25$) on a Bruker X8 diffractometer. The structure was solved and refined with SHELXL-97.[14] Hydrogen atom riding, refinement converged to *R*(*gt*) = 0.0453 for the 14768 reflections having $I > 2\sigma(I)$, and *wR* (*gt*) = 0.1163, Goodness-of-Fit *S* = 1.044, residual electron density: –0.510 and 0.816 $eÅ^{-3}$.

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