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.

Keywords: amino acids, heterocycles, piperidines, asymmetric synthesis, addition reaction

In recent years, due to their potential biological activity and their use as building blocks for peptide mimetics, α-amino phosphonic acids are of considerable current interest. Cyclic or heterocyclic rings introduced into the molecular skeleton increase its rigidity and modify electronic effects. Thus, many cyclic α-amino phosphonic acids have been prepared. However, very few examples of heterocyclic acids 1 or the corresponding phosphonates presented in the literature have been reported in racemic series. In all the synthetic approaches to introduce the aminophosphonate moiety, the Kabachnick–Fields reaction 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).

![Figure 1 Heterocyclic α-aminopiperidinylphosphonic acids](image)

In the course of our work on the asymmetric synthesis of cyclic analogues of α-amino phosphonic acids, we have previously reported a simple and convenient synthesis of 1-amino cyclopropanecarboxylic 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-amino phosphonic acids 1a–c and 2 from readily available heterocyclic ketones in good yields.

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 Preparation of aminophosphonate](image)

The standard one-pot procedure 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 MgSO4 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 31P NMR spectra (δ6A/δ6B = 27.44/27.74). The use of chiral amine 5b (X = OMe) did not change the diastereoisomeric ratio (31P NMR, δ6A/δ6B = 27.56/27.30) of the resulting inseparable mixture of aminophosphonates 7A/7B (55% yield) (Scheme 2).

![Scheme 2 Preparation of aminophosphonates 6 and 7 from ketone 3](image)
We have previously reported that a bulky phosphite reacted with iminium ion in DMSO to enhance the selectivity of addition reaction.\(^4\) Thus we treated ketone 3 with chiral amine 5a under the same conditions as above, by using trisopropyl phosphite in DMSO instead of P(OEt)\(_3\) in EtOH to obtain aminophosphonates 8A or 8B. However, neither was formed (Scheme 3).

![Scheme 3](image)

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](image)

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](image)

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).

To determine the absolute configuration of these isomers, we have protected the major isomer with 4-nitrobenzoyl chloride in the presence of Et\(_3\)N to give 11B in good yield (Scheme 7). Suitable crystals of 11B were analyzed by X-ray crystallography,\(^1\) which showed a (3R,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 (3R,1’S)-9B and must be (3S,1’S)-9A for the minor isomer.

![Scheme 6](image)

![Scheme 7](image)

In summary, we have developed an easy and efficient four step synthesis of enantiopure (R)- and (S)-\(\alpha\)-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 phosphate to give a major \(\alpha\)-aminopiperidinylphosphonate. Good separation of the
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)-methoxybenzylamine (5b; 215 mg, 1.57 mmol). AcOH (115 μL, 2.09 mmol), MgSO4 (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–CH2Cl2, 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 31P NMR spectrum. The spectral data given are for 7A/7B diastereoisomeric mixture.

1H NMR (250 MHz, CDCl3): δ = 1.17 (t, J = 6.9 Hz, 1 H, CH3, A), 0.85–1.75 (m, 8.2 H, CH3, CH2, C-2, CH3, B), 2.60 (ddd, J = 3.2, 12.7, 12.7 Hz, 0.6 H, H-4, B), 2.80–3.65 (2 H, H-6, A), 3.65–3.97 (2 H, H-2, A), 3.97–4.22 (m, 4 H, 2 CH2O, A/B), 4.22–4.42 (2 H, 1 CH3, CH2O, A/B), 7.03–7.20 (m, 5 H, arom, A/B).

13C NMR (250 MHz, CDCl3): δ = 114.6/146.4 (d, JPC = 5.5 Hz, 2 CH2O, A/B), 194.1 (d, JPC = 10.4 Hz, C-5, B), 20.0 (d, J = 8.2 Hz, C-5, A), 26.5 (C-4, A/B), 27.1 (CH3, CH2N, A/B), 28.3/28.5 (C(CH3)3, A/B), 43.5/44.6 (C-6, A/B), 49.0/50.2 (d, J = 9.2 Hz, C-2, A/B), 52.3 (CH2, B), 52.6 (CH2, A), 56.5 (d, J = 14.5 Hz, C-3, A), 57.5 (d, J = 141.5 Hz, C-3, B), 61.7 (2 CH2O, B), 62.1 (d, J = 7.7 Hz, 2 CH2O, A), 79.3 (C(CH3)3, A/B), [6 arom: 126.3 (CH), 126.4 (2 CH), 128.1 (2 CH), 148.1/148.7 (C, A/B)].

31P NMR (101.25 MHz, CDCl3): δ = 27.44/27.74.


Asymmetric Synthesis of (R)- and (S)-α-Amino-3-piperidinylphosphonic Acids

To a solution of the inseparable mixture of 6A/6B (1.430 g, 3.25 mmol) in CH2Cl2 (40 mL), was added TFA (7.2 mL) and the mixture was stirred at r.t. for 3 h. An aq sat. solution of NaHCO3 (50 mL) was added and the mixture was extracted with EtOAc. The organic layers were combined, dried (MgSO4), filtered and concentrated in vacuo. Purification by flash chromatography (MeOH–CH2Cl2–aq NH3, 5:95:0.5) gave 9A (430 mg, 39%) and 9B (560 mg, 51%) as yellow oils.

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

1H NMR (400 MHz, CDCl3, δ = 6.26 (c = 0.65, CHCl3), δ: 0.46 (MeOH–CH2Cl2–aq NH3, 10:90:0.5).

IR (neat): 3566, 3324, 2980, 1266, 1230, 1056, 1024, 960 cm−1.

1H NMR (250 MHz, CDCl3): δ = 1.33–1.48 (m, 9 H, 3 CH3), 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 (ddd, J = 2.7, 14.0 Hz, 1 H-2), 2.72–2.88 (m, 1 H, H-6), 2.92 (ddd, J = 2.0, 5.0, 14.0 Hz, 1 H-2), 4.07–4.28 (m, 4 H, 2 CH2O), 4.45 (qd, J = 6.5 Hz, 2JPC = 2.7 Hz, 1 CHN), 7.15–7.50 (m, 5 H).

13C NMR (62.9 MHz, CDCl3): δ = 16.8/16.4 (d, JPC = 5.5 Hz, 2 CH2O, A/B), 20.3 (d, J = 8.2 Hz, C-5, A), 26.5 (C-4, A/B), 27.1 (CH3, CH2N, A/B), 28.3/28.5 (C(CH3)3, A/B), 43.5/44.6 (C-6, A/B), 49.0/50.2 (d, J = 9.2 Hz, C-2, A/B), 52.3 (CH2, B), 52.6 (CH2, A), 56.5 (d, J = 14.5 Hz, C-3, A), 57.5 (d, J = 141.5 Hz, C-3, B), 61.7 (2 CH2O, B), 62.1 (d, J = 7.7 Hz, 2 CH2O, A), 79.3 (C(CH3)3, A/B), [6 arom: 126.3 (CH), 126.4 (2 CH), 128.1 (2 CH), 148.1/148.7 (C, A/B)].

31P NMR (101.25 MHz, CDCl3): δ = 29.47.

Diaminophosphonate 10

To a solution of aminophosphonic 9A or 9B (1 mmol) in AcOH (5 mL), was added 20% Pd(OH)_2/C (Palladin’s catalyst, 150 mg). The mixture was stirred at rt 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 flash chromatography on silica gel (eluent: MeOH–CH₂Cl₂–aq NH₃, 5:95:0.5) to give the free diaminophosphonate 10 as yellow oils.

(R)-(−)-Diaminophosphonic acid [(R)-10]


(S)-(−)-Diaminophosphonic acid [(S)-10]


X-ray Crystal Structure Analysis of (R)-(3R,1’S)-Phosphonic Acid 11B

Colorless crystal of 0.10 × 0.08 × 0.07 mm. C₃H₅N₂O₃P, M = 489.50: triclinic system, space group P1 (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) Å³, d = 1.339 g cm⁻³, F(000) = 520, λ = 0.71073 Å (Mo-Kα), μ = 0.158 mm⁻¹, 17403 reflections measured (−14 ≤ h ≤ 14, −10 ≤ k ≤ 18, −25 ≤ l ≤ 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 > 2σ(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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References


(13) Crystallographic data for compound (+)-1B has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 614693. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk.