# Synthesis of α-Aminocyclopropylphosphonic Acids

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**Abstract:** A convenient, general approach to α-aminocyclopropylphosphonic acids via reduction and hydrolysis of α-nitrocyclopropylphosphonates is described. A number of the title compounds were synthesized in excellent yields.

**Key words:** aminophosphonic acids, bioisosteres, cyclopropanes, reduction, hydrolysis

Bioisosteric replacement is known to be one of the most powerful instruments in medicinal chemistry.[1] This method is used to modify lead compounds to improve pharmacological properties and therefore to create more effective drugs and prodrugs. For a carboxylic group there are a number of bioisosteres known in the literature, for example sulfonamide, tetrazole, sulfonate or phosphonate.[1c] Special interest in the phosphonic acid group[2] is associated, among other issues, with its tetrahedral structure and thereby related possible action as a 'transition-state analogue'.[2d] This is why bioisosteric phosphonic acid analogues of such important compounds as amino acids are finding increasing interest.

Restriction of conformational flexibility has also proven effective in drug design to improve various characteristics of biologically active substances.[3] In particular, introduction of the cyclopropane ring into amino acids leads to structures selective in binding with different subtypes of receptors[3d] (Figure 1).

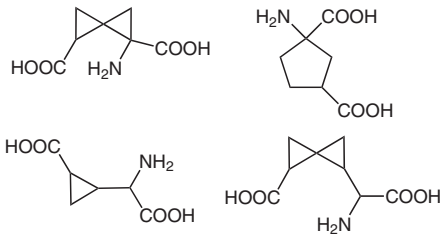



**Figure 1** Examples of conformationally constrained amino acids

Cyclopropyl α-amino acids have been objects of intense interest in our laboratory for a long time.[4] Previously, we have elaborated convenient approaches to a number of polyspirocyclic cyclopropyl amino acids, as well as conformationally restricted glutamate analogues.[4e,f] Investigation of synthetic routes to the bioisosteric analogues, aminocyclopropylphosphonic acids, is a logical continuation of this work. We have already reported the synthesis of a number of bioisosteric glycine analogues containing small rings.[5] Working further in this area, we turned our attention to α-aminocyclopropylphosphonic acids (Figure 2) given that only a few methods for their synthesis have been described as yet.[6] Moreover, a general approach to this class of compounds is lacking and needs to be developed.

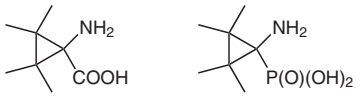
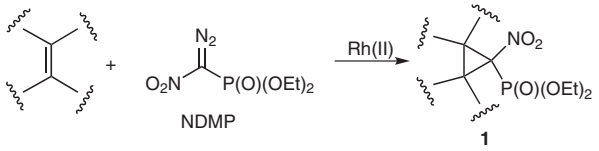



**Figure 2** A cyclopropyl amino acid and the bioisosteric phosphonic acid analogue

Recently, we reported a useful method for the synthesis of structurally diverse α-nitrocyclopropylphosphonates **1** via the rhodium(II)-catalyzed [1+2]-cycloaddition reaction of diethyl [nitro(diazo)methyl]phosphonate (NDMP) with various olefins (Scheme 1).[7] The obtained adducts seem to be useful synthetic precursors of the corresponding α-aminocyclopropylphosphonic acids. Herein, we present a convenient procedure which allows the target α-aminophosphonic acids bearing a cyclopropane moiety to be obtained.




**Scheme 1** Synthesis of α-nitrocyclopropylphosphonates **1**

The first and most challenging step in the synthetic protocol is the reduction of the nitro group. Crucial here is to choose appropriate reduction conditions allowing transformation of the nitro group to an amine without affecting the labile spiroconjugated cyclopropane fragment, which can undergo ring-opening reactions.[4d] To the best of our knowledge, there are no prior examples of nitro reduction in compounds bearing a phosphonate group at the α-position. As reported previously, for nitrocyclopropane-[8] and nitrospiropentanecarboxylates[4d] the best results are obtained when the reduction system zinc–acetic acid–isopropyl alcohol is applied. We investigated the behavior

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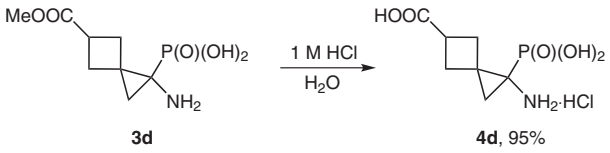
of α-nitrocyclopropylphosphonates[7] **1a–f** under these conditions and obtained the corresponding α-aminocyclopropylphosphonates **2a–f** in high yields (Table 1). It is essential that the spirocondensed cyclopropane fragments remain untouched during the reaction and that the diethoxyphosphoryl fragment does not affect the process.

The best method for cleavage of a diethoxyphosphoryl group is treatment of the phosphonate with trimethylsilyl halides.[6d] This procedure replaces continuous boiling with concentrated acids, unacceptable for the sensitive spirocondensed cyclopropane moiety. We found that heating aminophosphonates **2a–f** with excess trimethylsilyl bromide in dichloromethane, followed by treatment of the reaction mixture with propylene oxide in ethanol, leads to the target α-aminocyclopropylphosphonic acids **3a–f** in excellent yields. In the case of [1-amino-5-(methoxycarbonyl)spiro[2.3]hex-1-yl]phosphonic acid (**3d**), it was also important to saponify the methyl ester group due to its inertness towards trimethylsilyl bromide. Hydrolysis was successfully completed after stirring for 5 minutes with dilute aqueous hydrochloric acid, and the final aminophosphonic acid was isolated in the hydrochloride form **4d** in quantitative yield (Scheme 2). This compound is of great interest as a conformationally restricted bioisosteric analogue of glutamic acid.

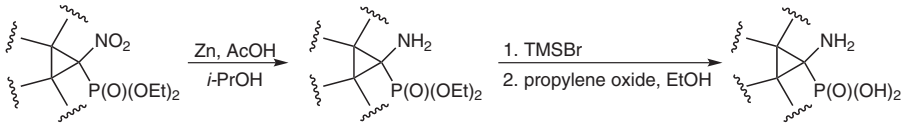
To conclude, we have elaborated a general synthetic approach to α-aminocyclopropylphosphonic acids, a class of bioisosteric analogues of conformationally restricted natural and nonnatural amino acids. The method allows the target compounds to be obtained under mild conditions in excellent yields.

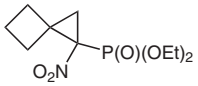
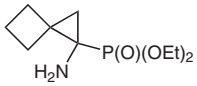
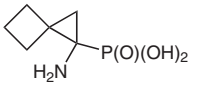
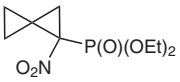
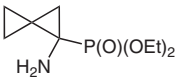
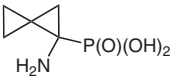
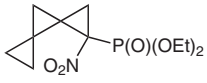
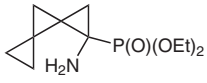
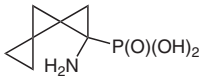
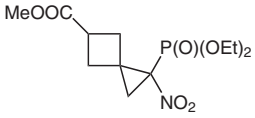
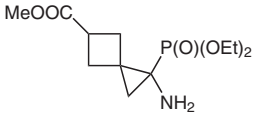
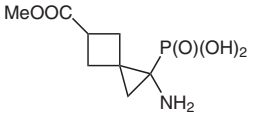
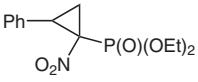
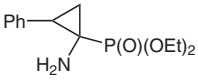
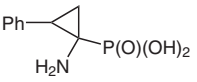
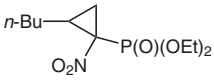
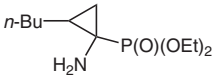
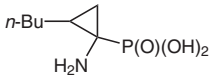



**Scheme 2** Hydrolysis of compound **3d**

All reactions were performed in flame-dried glassware under a slight positive pressure of argon using freshly distilled, anhydrous solvents. Compounds obtained as mixtures of diastereoisomers were not separated into the single isomers. $^1$H, $^{13}$C and $^{31}$P NMR spectra were recorded at r.t. on a Bruker Avance 400 spectrometer at 400.13, 100.61 and 161.98 MHz, respectively. The $^1$H and $^{13}$C chemical shifts (δ) were measured in ppm with respect to the solvent, $CDCl_3$ ($^1$H: δ = 7.27 ppm; $^{13}$C: δ = 77.13 ppm), DMSO-$d_6$ ($^1$H: δ = 2.54 ppm; $^{13}$C: δ = 40.45 ppm) or $D_2O$ ($^1$H: δ = 4.79 ppm; $^{13}$C: δ = 1.47 ppm for $CH_3CN$ as external standard). The $^{31}$P chemical shifts are given relative to 85% $H_3PO_4$ (as external standard, δ = 0 ppm). The NMR spectra of aminophosphonic acids **3a–c**,**e**,**f** and **4d** were registered at pH 3 in $D_2O$ and those of compound **3d** were registered in DMSO-$d_6$. The coupling constants in the $^1$H NMR spectra were measured using selective heteronuclear $^1$H–{$^{31}$P} decoupling. Mass spectra were recorded on a Bruker Daltonics Ultraflex MALDI-TOF spectrometer in positive mode, using 1,8,9-trihydroxyanthracene as a matrix. Melting points were determined on an Electrothermal 9100 capillary apparatus and are uncorrected. All reagents, except commercial products of satisfactory quality, were

**Table 1** Synthesis of α-Aminocyclopropylphosphonates and -phosphonic Acids




| Entry | Nitrophosphonate **1** | Aminophosphonate **2** | Yield[a] (%) | Aminophosphonic acid **3** | Yield[b] (%) |
|---|---|---|---|---|---|
| **a** |  |  | 86 |  | 95 |
| **b** |  |  | 91 |  | 94 |
| **c** |  |  | 89 |  | 92 |
| **d** |  |  | 85 |  | 82 |
| **e** |  |  | 81 |  | 93 |
| **f** |  |  | 91 |  | 87 |

[a] Yield of crude product.
[b] Yield after recrystallization.

purified by literature procedures prior to use. α-Nitrocyclopropylphosphonates **1a–f** were obtained as reported.[7]

### α-Aminocyclopropylphosphonates 2 by the Reduction of α-Nitrocyclopropylphosphonates 1; General Procedure

To a stirred soln of a nitro compound **1** (1 mmol) and glacial AcOH (0.6 g, 10 mmol) in *i*-PrOH (20 mL) was added Zn powder (1.3 g, 20 mmol) in small portions over 30 min. The resulting mixture was stirred for 3 h, the reaction was quenched with sat. aq $K_2CO_3$ (resulting in a soln at pH 10), and the mixture was stirred for 15 min then filtered. The precipitate was washed with $CH_2Cl_2$ (2 × 5 mL). The filtrate was extracted with $CH_2Cl_2$ (3 × 10 mL); the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure to yield amine **2** of satisfactory purity (>90%). The obtained amines were used without further purification.

### Diethyl (1-Aminospiro[2.3]hex-1-yl)phosphonate (2a)

Yield: 200 mg (86%); orange oil.

$^1$H NMR ($CDCl_3$): δ = 0.69–0.72 (m, 1 H, $CH_2$), 1.17–1.22 (m, 1 H, $CH_2$), 1.25–1.29 (m, 6 H, 2 × $OCH_2CH_3$), 1.85–2.12 (m, 4 H, 2 × $CH_2$), 2.25 (br s, 2 H, $NH_2$), 2.31–2.45 (m, 2 H, $CH_2$), 3.95–4.09 (m, 4 H, 2 × $OCH_2CH_3$).

$^{13}$C NMR ($CDCl_3$): δ = 16.22 (*c*-Bu-$CH_2$), 16.26 (d, $^3J_{C,P}$ = 7 Hz, $OCH_2CH_3$), 16.32 (d, $^3J_{C,P}$ = 7 Hz, $OCH_2CH_3$), 25.20 (*c*-Bu-$CH_2$), 26.87 (*c*-Pr-$CH_2$), 28.37 (d, $^3J_{C,P}$ = 4 Hz, *c*-Bu-$CH_2$), 31.39 ($C_{spiro}$), 32.69 [d, $^1J_{C,P}$ = 218 Hz, $C(NH_2)PO(OEt)_2$], 62.01 (d, $^2J_{C,P}$ = 7 Hz, $OCH_2CH_3$), 62.11 (d, $^2J_{C,P}$ = 7 Hz, $OCH_2CH_3$).

$^{31}$P NMR ($CDCl_3$): δ = 27.01.

MS (MALDI-TOF): *m*/*z* = 234 $[M + 1]^+$.

### Diethyl (1-Aminospiro[2.2]pent-1-yl)phosphonate (2b)

Yield: 199 mg (91%); yellow oil.

$^1$H NMR ($CDCl_3$): δ = 0.82–0.91 (m, 2 H, *c*-Pr-$CH_2$), 0.94–0.98 (m, 1 H, *c*-Pr-$CH_2$), 1.01–1.06 (m, 1 H, *c*-Pr-$CH_2$), 1.10–1.12 (m, 1 H, *c*-Pr-$CH_2$), 1.28 (dt, $^3J_{H,H}$ = 7.1 Hz, $^4J_{P,H}$ = 0.5 Hz, 3 H, $OCH_2CH_3$), 1.30 (dt, $^3J_{H,H}$ = 7.1 Hz, $^4J_{P,H}$ = 0.5 Hz, 3 H, $OCH_2CH_3$), 1.54–1.59 (m, 1 H, *c*-Pr-$CH_2$), 2.61 (br s, 2 H, $NH_2$), 4.04–4.15 (m, 4 H, 2 × $OCH_2CH_3$).

$^{13}$C NMR ($CDCl_3$): δ = 3.32 (*c*-Pr-$CH_2$), 6.85 (d, $^3J_{C,P}$ = 4 Hz, *c*-Pr-$CH_2$), 16.49 (d, $^3J_{C,P}$ = 7 Hz, $OCH_2CH_3$), 16.54 (d, $^3J_{C,P}$ = 6 Hz, $OCH_2CH_3$), 20.09 (*c*-Pr-$CH_2$), 20.14 ($C_{spiro}$), 32.85 [d, $^1J_{C,P}$ = 208 Hz, $C(NH_2)PO(OEt)_2$], 61.80 (d, $^2J_{C,P}$ = 7 Hz, $OCH_2CH_3$), 62.09 (d, $^2J_{C,P}$ = 6 Hz, $OCH_2CH_3$).

$^{31}$P NMR ($CDCl_3$): δ = 27.28.

MS (MALDI-TOF): *m*/*z* = 220 $[M + 1]^+$.

### Diethyl (1-Aminodispiro[2.0.2.1]hept-1-yl)phosphonate (2c)

Yield: 218 mg (89%); mixture of isomers (A/B = 67:33); yellow oil.

$^1$H NMR ($CDCl_3$): δ = 0.69–0.75 (m, 1 H + 1 H, *c*-Pr-$CH_2$, isomers A and B), 0.78–0.88 (m, 2 H + 2 H, *c*-Pr-$CH_2$, isomers A and B), 0.97–1.01 (m, 1 H, *c*-Pr-$CH_2$, isomer A), 1.02–1.08 (m, 1 H + 1 H, *c*-Pr-$CH_2$, isomers A and B), 1.11–1.14 (m, 1 H, *c*-Pr-$CH_2$, isomer B), 1.19–1.25 (m, 1 H + 2 H, *c*-Pr-$CH_2$, isomers A and B), 1.27–1.33 (m, 6 H + 6 H, 2 × $OCH_2CH_3$, isomers A and B), 1.38–1.39 (m, 1 H, *c*-Pr-$CH_2$, isomer A), 1.42–1.46 (m, 1 H, *c*-Pr-$CH_2$, isomer B), 1.57–1.61 (m, 1 H, *c*-Pr-$CH_2$, isomer A), 2.45 (br s, 2 H + 2 H, $NH_2$, isomers A and B), 4.13–4.23 (m, 4 H + 4 H, 2 × $OCH_2CH_3$, isomers A and B).

$^{13}$C NMR ($CDCl_3$): δ = 3.43 (*c*-Pr-$CH_2$, isomer A), 4.67 (*c*-Pr-$CH_2$, isomer A), 5.22 (*c*-Pr-$CH_2$, isomer B), 9.48 (*c*-Pr-$CH_2$, isomer B), 12.73 (*c*-Pr-$CH_2$, isomer A), 12.79 (*c*-Pr-$CH_2$, isomer B), 14.96 (d, $^3J_{C,P}$ = 5 Hz, $C_{spiro}$, isomer B), 16.08 ($C_{spiro}$, isomer A), 16.16 (d, $^3J_{C,P}$ = 6 Hz, 2 × $OCH_2CH_3$, isomer B), 16.21 (d, $^3J_{C,P}$ = 6 Hz, 2 × $OCH_2CH_3$, isomer A), 18.88 (*c*-Pr-$CH_2$, isomers A and B), 22.84 ($C_{spiro}$, isomer A), 24.93 ($C_{spiro}$, isomer B), 32.55 [d, $^1J_{C,P}$ = 209 Hz, $C(NH_2)PO(OEt)_2$, isomer B], 34.20 [d, $^1J_{C,P}$ = 205 Hz, $C(NH_2)PO(OEt)_2$, isomer A], 61.48 (d, $^2J_{C,P}$ = 6 Hz, 2 × $OCH_2CH_3$, isomer A), 61.71 (d, $^2J_{C,P}$ = 6 Hz, 2 × $OCH_2CH_3$, isomer B).

$^{31}$P NMR ($CDCl_3$): δ = 26.45 (isomer A), 26.90 (isomer B).

MS (MALDI-TOF): *m*/*z* = 246 $[M + 1]^+$.

### Methyl 1-Amino-1-(diethoxyphosphoryl)spiro[2.3]hexane-5-carboxylate (2d)

Yield: 247 mg (85%); mixture of isomers (A/B = 64:36); orange oil.

$^1$H NMR ($CDCl_3$): δ = 0.60–0.64 (m, 1 H, *c*-Pr-$CH_2$, isomer A), 0.65–0.70 (m, 1 H, *c*-Pr-$CH_2$, isomer B), 1.12–1.17 (m, 1 H + 1 H, *c*-Pr-$CH_2$, isomers A and B), 1.18–1.23 (m, 6 H + 6 H, 4 × $OCH_2CH_3$, isomers A and B), 1.79 (br s, 2 H + 2 H, $NH_2$, isomers A and B), 2.19–2.31 (m, 2 H + 2 H, *c*-Bu-$CH_2$, isomers A and B), 2.44–2.58 (m, 2 H + 2 H, *c*-Bu-$CH_2$, isomers A and B), 3.00–3.05 (m, 1 H, *c*-Bu-CH, isomer A), 3.10–3.14 (m, 1 H, *c*-Bu-CH, isomer B), 3.55 (s, 3 H, $COOCH_3$, isomer B), 3.57 (s, 3 H, $COOCH_3$, isomer A), 3.95–4.03 (m, 4 H + 4 H, 4 × $OCH_2CH_3$, isomers A and B).

$^{13}$C NMR ($CDCl_3$): δ = 16.35 (d, $^3J_{C,P}$ = 6 Hz, 4 × $OCH_2CH_3$, isomers A and B), 24.54 (*c*-Pr-$CH_2$, isomer A), 24.84 (*c*-Pr-$CH_2$, isomer B), 27.09 (d, $^2J_{C,P}$ = 4 Hz, $C_{spiro}$, isomer B), 27.47 ($C_{spiro}$, isomer A), 28.59 (*c*-Bu-$CH_2$, isomer A), 29.35 (*c*-Bu-$CH_2$, isomer B), 31.15 (d, $^3J_{C,P}$ = 5 Hz, *c*-Bu-$CH_2$, isomer A), 32.00 (d, $^3J_{C,P}$ = 5 Hz, *c*-Bu-$CH_2$, isomer B), 32.73 (*c*-Bu-CH, isomer B), 33.13 (*c*-Bu-CH, isomer A), 33.70 [d, $^1J_{C,P}$ = 205 Hz, $C(NH_2)PO(OEt)_2$, isomer B], 33.97 [d, $^1J_{C,P}$ = 206 Hz, $C(NH_2)PO(OEt)_2$, isomer A], 51.47 ($COOCH_3$, isomer B), 51.56 ($COOCH_3$, isomer A), 61.68 (d, $^2J_{C,P}$ = 6 Hz, 2 × $OCH_2CH_3$, isomer B), 61.77 (d, $^2J_{C,P}$ = 6 Hz, 2 × $OCH_2CH_3$, isomer A), 175.29 (*C*OOMe, isomer B), 175.60 (*C*OOMe, isomer A).

$^{31}$P NMR ($CDCl_3$): δ = 26.37 (isomer B), 26.51 (isomer A).

MS (MALDI-TOF): *m*/*z* = 292 $[M + 1]^+$.

### Diethyl (1-Amino-2-phenylcyclopropyl)phosphonate (2e)

Yield: 218 mg (81%); mixture of isomers (A/B = 65:35); brown oil.

$^1$H NMR ($CDCl_3$): δ = 1.09 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, $OCH_2CH_3$, isomer B), 1.15 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, $OCH_2CH_3$, isomer B), 1.19–1.32 (m, 1 H + 1 H, *c*-Pr-$CH_2$, isomers A and B), 1.33–1.41 (m, 6 H, 2 × $OCH_2CH_3$, isomer A), 1.61–1.75 (m, 1 H + 1 H, *c*-Pr-CH, isomers A and B), 1.87 (br s, 2 H + 2 H, $NH_2$, isomers A and B), 2.50–2.56 (m, 1 H, *c*-Pr-CH, isomer B), 2.67–2.75 (m, 1 H, *c*-Pr-CH, isomer A), 3.65–3.81 (m, 4 H, 2 × $OCH_2CH_3$, isomer B), 4.13–4.23 (m, 4 H, 2 × $OCH_2CH_3$, isomer A), 7.20–7.32 (m, 5 H + 5 H, Ar-CH, isomers A and B).

$^{13}$C NMR ($CDCl_3$): δ = 16.36 (d, $^3J_{C,P}$ = 6 Hz, 2 × $OCH_2CH_3$, isomer B), 16.62 (d, $^3J_{C,P}$ = 6 Hz, 2 × $OCH_2CH_3$, isomer A), 17.64 (*c*-Pr-$CH_2$, isomer A), 18.12 (d, $^2J_{C,P}$ = 3 Hz, *c*-Pr-$CH_2$, isomer B), 27.42 (d, $^2J_{C,P}$ = 1 Hz, *c*-Pr-CH, isomer A), 31.93 (d, $^2J_{C,P}$ = 3 Hz, *c*-Pr-CH, isomer B), 33.54 [d, $^1J_{C,P}$ = 210 Hz, $C(NH_2)PO(OEt)_2$, isomer A], 35.78 [d, $^1J_{C,P}$ = 206 Hz, $C(NH_2)PO(OEt)_2$, isomer B], 61.60 (d, $^2J_{C,P}$ = 7 Hz, $OCH_2CH_3$, isomer B), 61.67 (d, $^2J_{C,P}$ = 7 Hz, $OCH_2CH_3$, isomer B), 62.29 (d, $^2J_{C,P}$ = 7 Hz, $OCH_2CH_3$, isomer A), 62.37 (d, $^2J_{C,P}$ = 7 Hz, $OCH_2CH_3$, isomer A), 126.64 (Ar-CH, isomer B), 126.75 (Ar-CH, isomer A), 127.79 (2 × Ar-CH, isomer B), 128.14 (2 × Ar-CH, isomer A), 129.28 (2 × Ar-CH, isomer A), 129.70 (2 × Ar-CH, isomer B), 135.30 (Ar-C, isomer A), 136.40 (d, $^3J_{C,P}$ = 4 Hz, Ar-C, isomer B).

$^{31}$P NMR ($CDCl_3$): δ = 25.77 (isomer B), 27.63 (isomer A).

MS (MALDI-TOF): *m*/*z* = 270 $[M + 1]^+$.

**Diethyl (1-Amino-2-butylcyclopropyl)phosphonate (2f)**
Yield: 227 mg (91%); mixture of isomers (A/B = 62:38); yellow oil.

$^1$H NMR ($CDCl_3$): δ = 0.80–0.85 (m, 3 H + 3 H, 2 × $CH_2CH_2CH_3$, isomers A and B), 0.85–0.90 (m, 2 H + 2 H, $CH_2$, isomers A and B), 1.13–1.25 (m, 4 H + 4 H, 4 × $CH_2$, isomers A and B), 1.26–1.29 (m, 6 H + 6 H, 4 × $OCH_2CH_3$, isomers A and B), 1.32–1.35 (m, 1 H, *c*-Pr-H, isomer B), 1.40–1.50 (m, 2 H + 2 H, *c*-Pr-H, isomers A and B), 1.59–1.66 (m, 1 H, *c*-Pr-H, isomer A), 2.01 (br s, 2 H + 2 H, $NH_2$, isomers A and B), 4.00–4.11 (m, 4 H + 4 H, 4 × $OCH_2CH_3$, isomers A and B).

$^{13}$C NMR ($CDCl_3$): δ = 14.02 ($CH_2CH_2CH_3$, isomer A), 16.41 (d, $^3J_{C,P}$ = 6 Hz, $OCH_2CH_3$, isomer B), 16.45 (d, $^3J_{C,P}$ = 6 Hz, 2 × $OCH_2CH_3$, isomer A), 16.51 (d, $^3J_{C,P}$ = 6 Hz, $OCH_2CH_3$, isomer B), 17.96 (2 × $CH_2CH_2CH_3$, isomer B), 19.83 (d, $^2J_{C,P}$ = 4 Hz, *c*-Pr-$CH_2$, isomer B), 22.27 ($CH_2$, isomer B), 22.36 ($CH_2$, isomer A), 22.55 (d, $^2J_{C,P}$ = 3 Hz, *c*-Pr-$CH_2$, isomer A), 25.21 ($CH_2$, isomer B), 26.11 ($CH_2$, isomer A), 27.86 (d, $^2J_{C,P}$ = 4 Hz, *c*-Pr-CH, isomer A), 28.07 (d, $^2J_{C,P}$ = 3 Hz, *c*-Pr-CH, isomer B), 31.10 [d, $^1J_{C,P}$ = 207 Hz, $C(NH_2)PO(OEt)_2$, isomer A], 31.75 ($CH_2$, isomer A), 31.79 ($CH_2$, isomer B), 32.45 [d, $^1J_{C,P}$ = 203 Hz, $C(NH_2)PO(OEt)_2$, isomer B], 61.57 (d, $^2J_{C,P}$ = 7 Hz, $OCH_2CH_3$, isomer B), 61.80 (d, $^2J_{C,P}$ = 7 Hz, $OCH_2CH_3$, isomer B), 61.95 (d, $^2J_{C,P}$ = 6 Hz, 2 × $OCH_2CH_3$, isomer A).

$^{31}$P NMR ($CDCl_3$): δ = 28.87 (isomer B), 29.30 (isomer A).

MS (MALDI-TOF): *m*/*z* = 250 $[M + 1]^+$.

**α-Aminocyclopropylphosphonic Acids 3 by the Cleavage of α-Aminocyclopropylphosphonates 2; General Procedure**
To a refluxing soln of an amine **2** (1 mmol) in $CH_2Cl_2$ (3 mL), a soln of TMSBr (0.765 g, 5 mmol) in $CH_2Cl_2$ (2 mL) was added dropwise with stirring. The mixture was refluxed for 3 h and then concentrated under reduced pressure. The residue was dissolved in EtOH (2 mL), and propylene oxide (5 mL) was added with stirring. The precipitated aminophosphonic acid **3** was collected by filtration and recrystallized (boiling EtOH) to obtain pure product as a white solid.

**(1-Aminospiro[2.3]hex-1-yl)phosphonic Acid (3a)**
Yield: 168 mg (95%); mp 250–252 °C.

$^1$H NMR ($D_2O$): δ = 1.49 (dd, $^2J_{H,H}$ = 6.9 Hz, $^3J_{P,H}$ = 6.1 Hz, 1 H, *c*-Pr-$CH_2$), 1.66 (dd, $^2J_{H,H}$ = 6.9 Hz, $^3J_{P,H}$ = 13.3 Hz, 1 H, *c*-Pr-$CH_2$), 2.22–2.42 (m, 4 H, 2 × *c*-Bu-$CH_2$), 2.59–2.64 (m, 1 H, *c*-Bu-$CH_2$), 2.71–2.78 (m, 1 H, *c*-Bu-$CH_2$).

$^{13}$C NMR ($D_2O$): δ = 16.68 (t, $^1J_{C,H}$ = 139 Hz, *c*-Bu-$CH_2$), 22.19 (t, $^1J_{C,H}$ = 164 Hz, *c*-Pr-$CH_2$), 26.46 (t, $^1J_{C,H}$ = 138 Hz, *c*-Bu-$CH_2$), 28.28 (t, $^1J_{C,H}$ = 138 Hz, *c*-Bu-$CH_2$), 29.46 ($C_{spiro}$), 35.16 [d, $^1J_{C,P}$ = 205 Hz, $C(NH_2)PO(OH)_2$].

$^{31}$P NMR ($D_2O$): δ = 14.71.

Anal. Calcd for $C_6H_{12}NO_3P$: C, 40.68; H, 6.83; N, 7.91. Found: C, 40.77; H, 7.06; N, 7.85.

**(1-Aminospiro[2.2]pent-1-yl)phosphonic Acid (3b)**
Yield: 153 mg (94%); mp 235 °C (dec).

$^1$H NMR ($D_2O$): δ = 0.95–1.01 (m, 3 H, *c*-Pr-$CH_2$), 1.06–1.13 (m, 1 H, *c*-Pr-$CH_2$), 1.45 (dd, $^2J_{H,H}$ = 6.1 Hz, $^3J_{P,H}$ = 4.3 Hz, 1 H, *c*-Pr-$CH_2$), 1.59 (dd, $^2J_{H,H}$ = 6.1 Hz, $^3J_{P,H}$ = 10.6 Hz, 1 H, *c*-Pr-$CH_2$).

$^{13}$C NMR ($D_2O$): δ = 4.44 (*c*-Pr-$CH_2$), 6.60 (d, $^3J_{C,P}$ = 3.7 Hz, *c*-Pr-$CH_2$), 16.10 (*c*-Pr-$CH_2$), 18.05 (d, $^2J_{C,P}$ = 4.0 Hz, $C_{spiro}$), 33.99 [d, $^1J_{C,P}$ = 201 Hz, $C(NH_2)PO(OH)_2$].

$^{31}$P NMR ($D_2O$): δ = 13.56.

Anal. Calcd for $C_5H_{10}NO_3P$: C, 36.82; H, 6.18; N, 8.59. Found: C, 36.74; H, 6.25; N, 8.45.

**(1-Aminodispiro[2.0.2.1]hept-1-yl)phosphonic Acid (3c)**
Yield: 174 mg (92%); mixture of isomers (A/B = 78:22); mp 240 °C (dec).

$^1$H NMR ($D_2O$): δ = 0.66–0.70 (m, 1 H, *c*-Pr-$CH_2$, isomer B), 0.74–0.77 (m, 1 H, *c*-Pr-$CH_2$, isomer A), 0.82–1.00 (m, 3 H + 3 H, *c*-Pr-$CH_2$, isomers A and B), 1.26 (A of AB, $^2J_{H,H}$ = 4.4 Hz, 1 H, *c*-Pr-$CH_2$, isomer A), 1.28–1.30 (m, 1 H + 1 H, *c*-Pr-$CH_2$, isomers A and B), 1.30–1.32 (m, 1 H, *c*-Pr-$CH_2$, isomer B), 1.37–1.40 (m, 1 H, *c*-Pr-$CH_2$, isomer B), 1.41–1.43 (m, 1 H, *c*-Pr-$CH_2$, isomer B), 1.43 (B of AB, $^2J_{H,H}$ = 4.4 Hz, 1 H, *c*-Pr-$CH_2$, isomer A), 1.56–1.60 (m, 1 H, *c*-Pr-$CH_2$, isomer A).

$^{13}$C NMR ($D_2O$): δ = 4.72 (*c*-Pr-$CH_2$, isomer A), 4.99 (*c*-Pr-$CH_2$, isomer B), 5.04 (*c*-Pr-$CH_2$, isomer A), 5.63 (*c*-Pr-$CH_2$, isomer B), 10.54 (*c*-Pr-$CH_2$, isomer B), 12.95 (d, $^3J_{C,P}$ = 4 Hz, *c*-Pr-$CH_2$, isomer A), 14.12 (2 × $C_{spiro}$, isomers A and B), 15.27 (*c*-Pr-$CH_2$, isomer B), 15.36 (*c*-Pr-$CH_2$, isomer A), 21.97 (d, $^2J_{C,P}$ = 3 Hz, $C_{spiro}$, isomer A), 22.68 ($C_{spiro}$, isomer B), 34.40 [d, $^1J_{C,P}$ = 198 Hz, $C(NH_2)PO(OH)_2$, isomer B], 35.80 [d, $^1J_{C,P}$ = 195 Hz, $C(NH_2)PO(OH)_2$, isomer A].

$^{31}$P NMR ($D_2O$): δ = 11.41 (isomer B), 11.76 (isomer A).

Anal. Calcd for $C_7H_{12}NO_3P$: C, 44.45; H, 6.39; N, 7.41. Found: C, 44.24; H, 6.60; N, 7.28.

**[1-Amino-5-(methoxycarbonyl)spiro[2.3]hex-1-yl]phosphonic Acid (3d)**
Yield: 193 mg (82%); mixture of isomers (A/B = 70:30); mp 255 °C (dec).

$^1$H NMR (DMSO-$d_6$): δ = 0.91–1.02 (m, 1 H + 1 H, *c*-Pr-$CH_2$, isomers A and B), 1.33–1.46 (m, 1 H + 1 H, *c*-Pr-$CH_2$, isomers A and B), 2.24–2.50 (m, 2 H + 2 H, *c*-Bu-$CH_2$, isomers A and B), 2.63–2.76 (m, 2 H + 2 H, *c*-Bu-$CH_2$, isomers A and B), 2.90–2.98 (m, 1 H + 1 H, *c*-Bu-CH, isomers A and B), 3.70 (s, 3 H, $COOCH_3$, isomer A), 3.72 (s, 3 H, $COOCH_3$, isomer B).

$^{13}$C NMR: Not recorded, owing to insufficient solubility.

$^{31}$P NMR (DMSO-$d_6$): δ = 9.00 (isomer B), 9.83 (isomer A).

Anal. Calcd for $C_8H_{14}NO_5P$: C, 40.86; H, 6.00; N, 5.96. Found: C, 40.89; H, 6.09; N, 5.86.

**(1-Amino-2-phenylcyclopropyl)phosphonic Acid (3e)**
Yield: 198 mg (93%); mixture of isomers (A/B = 72:28); mp 248–250 °C.

$^1$H NMR ($D_2O$): δ = 1.60–1.72 (m, 2 H + 1 H, *c*-Pr-$CH_2$, isomers A and B), 1.84–1.91 (m, 1 H, *c*-Pr-$CH_2$, isomer B), 2.85–2.94 (m, 1 H + 1 H, *c*-Pr-CH, isomers A and B), 7.27–7.45 (m, 5 H + 5 H, Ar-CH, isomers A and B).

$^{13}$C NMR ($D_2O$): δ = 14.00 (*c*-Pr-$CH_2$, isomer A), 14.39 (*c*-Pr-$CH_2$, isomer B), 25.94 (*c*-Pr-CH, isomer A), 28.10 (*c*-Pr-CH, isomer B), 34.62 [d, $^1J_{C,P}$ = 196 Hz, $C(NH_2)PO(OH)_2$, isomer A], 35.62 [d, $^1J_{C,P}$ = 198 Hz, $C(NH_2)PO(OH)_2$, isomer B], 127.96 (Ar-CH, isomer B), 128.86 (2 × Ar-CH, isomer B), 129.00 (Ar-CH, isomer A), 129.70 (2 × Ar-CH, isomer A), 129.96 (2 × Ar-CH, isomer B), 130.57 (2 × Ar-CH, isomer A), 132.85 (Ar-C, isomer A), 134.96 (d, $^3J_{C,P}$ = 4 Hz, Ar-C, isomer B).

$^{31}$P NMR ($D_2O$): δ = 11.63 (isomer B), 12.95 (isomer A).

Anal. Calcd for $C_9H_{12}NO_3P$: C, 50.71; H, 5.67; N, 6.57. Found: C, 50.85; H, 5.59; N, 6.33.

**(1-Amino-2-butylcyclopropyl)phosphonic Acid (3f)**
Yield: 168 mg (87%); mixture of isomers (A/B = 50:50); mp 263–264 °C.

$^1$H NMR ($D_2O$): δ (isomers A and B) = 0.81–0.84 (m, 2 H), 0.84 (m, 3 H, $CH_2CH_2CH_3$), 0.86 (m, 3 H, $CH_2CH_2CH_3$), 1.01–1.08 (m, 2 H), 1.20–1.49 (m, 6 H + 6 H), 1.50–1.58 (m, 1 H), 1.67–1.75 (m, 1 H).

$^{13}$C NMR ($D_2O$): δ (isomers A and B) = 13.74 (q, $^1J_{C,H}$ = 125 Hz, $CH_2CH_2CH_3$), 13.92 (q, $^1J_{C,H}$ = 125 Hz, $CH_2CH_2CH_3$), 15.64 (t, $^1J_{C,H}$ = 165 Hz, *c*-Pr-$CH_2$), 16.52 (t, $^1J_{C,H}$ = 165 Hz, *c*-Pr-$CH_2$), 21.41 (d, $^1J_{C,H}$ = 162 Hz, *c*-Pr-CH), 21.55 (t, $^1J_{C,H}$ = 126 Hz, 2 × $CH_2$, isomers A and B), 24.85 (d, $^1J_{C,H}$ = 160 Hz, *c*-Pr-CH), 26.28 (t, $^1J_{C,H}$ = 128 Hz, 2 × $CH_2$, isomers A and B), 31.29 (t, $^1J_{C,H}$ = 128 Hz, $CH_2$), 32.31 (t, $^1J_{C,H}$ = 128 Hz, $CH_2$), 33.84 [d, $^1J_{C,P}$ = 195 Hz, $C(NH_2)PO(OH)_2$], 33.99 [d, $^1J_{C,P}$ = 196 Hz, $C(NH_2)PO(OH)_2$].

$^{31}$P NMR ($D_2O$): δ (isomers A and B) = 12.85, 14.18.

Anal. Calcd for $C_7H_{16}NO_3P$: C, 43.52; H, 8.35; N, 7.25. Found: C, 43.72; H, 8.57; N, 7.30.

**1-Amino-1-phosphonospiro[2.3]hexane-5-carboxylic Acid Hydrochloride (4d)**

Methyl ester **3d** (118 mg, 0.5 mmol) was dissolved in 1 N aq HCl (2.5 mL, 2.5 mmol) and the mixture was stirred for 5 min. Concentration under reduced pressure gave **4d** as a white solid; yield: 122 mg (95%).

Mixture of isomers (A/B = 73:27); mp 259–261 °C (dec).

$^1$H NMR ($D_2O$): δ = 1.05 (dd, $^2J_{H,H}$ = 7.2 Hz, $^3J_{P,H}$ = 5.7 Hz, 1 H, *c*-Pr-$CH_2$, isomer A), 1.10 (dd, $^2J_{H,H}$ = 7.1 Hz, $^3J_{P,H}$ = 5.7 Hz, 1 H, *c*-Pr-$CH_2$, isomer B), 1.26 (dd, $^2J_{H,H}$ = 7.2 Hz, $^3J_{P,H}$ = 12.4 Hz, 1 H, *c*-Pr-$CH_2$, isomer A), 1.33 (dd, $^2J_{H,H}$ = 7.1 Hz, $^3J_{P,H}$ = 12.3 Hz, 1 H, *c*-Pr-$CH_2$, isomer B), 2.24–2.32 (m, 2 H, *c*-Bu-$CH_2$, isomer A), 2.36–2.40 (m, 2 H, *c*-Bu-$CH_2$, isomer B), 2.48–2.53 (m, 1 H, *c*-Bu-$CH_2$, isomer A), 2.54–2.59 (m, 1 H, *c*-Bu-$CH_2$, isomer B), 2.65–2.70 (m, 1 H, *c*-Bu-$CH_2$, isomer B), 2.71–2.76 (m, 1 H, *c*-Bu-$CH_2$, isomer A), 3.20–3.27 (m, 1 H, *c*-Bu-CH, isomer A), 3.31–3.38 (m, 1 H, *c*-Bu-CH, isomer B).

$^{13}$C NMR ($D_2O$): δ = 21.18 (t, $^1J_{C,H}$ = 164 Hz, 2 × *c*-Pr-$CH_2$, isomers A and B), 25.00 ($C_{spiro}$, isomer B), 25.52 ($C_{spiro}$, isomer A), 28.65 (t, $^1J_{C,H}$ = 138 Hz, *c*-Bu-$CH_2$, isomer A), 29.29 (t, $^1J_{C,H}$ = 138 Hz, *c*-Bu-$CH_2$, isomer B), 31.07 (dt, $^3J_{C,P}$ = 4 Hz, $^1J_{C,H}$ = 139 Hz, *c*-Bu-$CH_2$, isomer A), 31.74 (dt, $^3J_{C,P}$ = 4 Hz, $^1J_{C,H}$ = 140 Hz, *c*-Bu-$CH_2$, isomer B), 32.72 (d, $^1J_{C,H}$ = 142 Hz, *c*-Bu-CH, isomer B), 33.43 (d, $^1J_{C,H}$ = 141 Hz, *c*-Bu-CH, isomer A), 35.53 [d, $^1J_{C,P}$ = 194 Hz, $C(NH_2)PO(OH)_2$, isomer B], 35.98 [d, $^1J_{C,P}$ = 193 Hz, $C(NH_2)PO(OH)_2$, isomer A], 179.65 (COOH, isomer B), 180.22 (COOH, isomer A).

$^{31}$P NMR ($D_2O$): δ = 10.78 (isomer A), 10.87 (isomer B).

Anal. Calcd for $C_7H_{13}ClNO_5P$: C, 32.64; H, 5.09; N, 5.44. Found: C, 32.63; H, 5.17; N, 5.25.

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