A Useful Synthesis of 1-Aminocyclopropanephosphonic Acid from Cyclopropanone Acetal†

Antoine Fadel*

Laboratoire des Carbocycles (Associé au CNRS), Institut de Chimie Moléculaire d'Orsay, Bât. 420, Université de Paris-Sud, 91405 Orsay, France

Received January 13, 1999

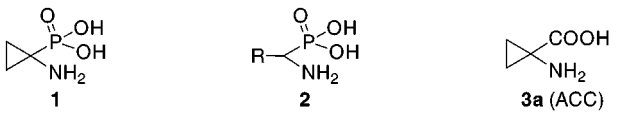
1-Aminophosphonic acids serve as important surrogates for 1-aminocarboxylic acids, the fundamental building blocks of peptides and proteins. The phosphonic acid analogues of α-amino acids are finding increasing interest,[1] due to the tetrahedral structure of the phosphonic acid moiety, they act as "transition-state analogues".[2] Thus several α-aminophosphonic acids are known as enzyme inhibitors [1,3] (glutamine synthetase, neutral endopeptidase, etc.[4,5]), herbicides (glyphosate), antibacterial reagents (alafosfalin), fungicides, plant growth regulators, etc.

In the past few years, 1-aminocyclopropanecarboxylic acid (ACC) and its derivatives have attracted special attention due to their biological activity.[6] Despite this large spectrum of biological activity, the aminocyclopropanephosphonic acid **1** did not receive the same attention as compared to the acylic aminophosphonic acids **2** and aminocyclopropanecarboxylic acid **3a** (ACC) (Scheme 1).

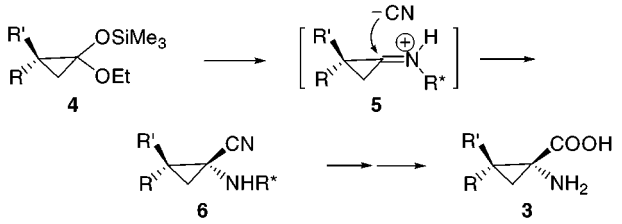
To our knowledge only a few methods for the synthesis of this class of compounds **1** have been described. These methods imply a double alkylation of aminomethylphosphonate anion equivalents with 1,2-dibromoethane,[7,8] or diethyl isocyanomethylphosphonate anion using epoxides[9a] and multistep transformation.[9b] These syntheses give moderate yield and are tedious preparations; furthermore, a general method is still lacking.

We have recently reported a simple and convenient synthesis of 1-aminocyclopropanecarboxylic acid **3a** (ACC) from cyclopropanone acetal **4a** (R = R′ = H) which underwent a one-pot Strecker reaction, via the iminium intermediate **5**, in good overall yield (Scheme 2).[10]

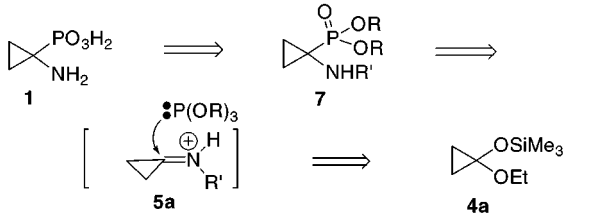
Scheme 1



Scheme 2



Scheme 3



The same methodology was also adopted to prepare (*S*)- and (*R*)-1-amino-2,2-dimethylcyclopropanecarboxylic acids (methanovaline) (**3**; R = R′ = CH_3) using an asymmetric Strecker reaction from dimethylcyclopropanone acetal **4** (R = R′ = CH_3),[11a] and *allo*-norcoronamic acids **3** (R = CH_3, R′ = H) and *allo*-coronamic acids **3** (R = Et, R′ = H), from corresponding acetal **4**.[11b]

To obtain aminophosphonic acid **1** analogue of ACC **3a**, via the corresponding aminophosphonate **7**, we decided to study the addition of phosphites to the same iminium intermediate **5a** (R = R′ = H), generated by reaction of the cyclopropanone acetal **4a** with an amine, in a one-pot reaction (Scheme 3). Such well-known addition of di- or trialkyl phosphite derivatives to imine [12] or oxazoline,[13] was developed for the synthesis of α-aminophosphonates.

Synthesis of α-Aminocyclopropanephosphonates. The cyclopropanone acetal **4a** is commercially available or prepared from ethyl *β*-chloropropanoate by sodium-induced cyclization in the presence of trimethylsilyl chloride under sonication conditions at room temperature.[14] Subsequent methanolysis of the latter afforded the hemiacetal **9** in quantitative yield (Scheme 4).[10]

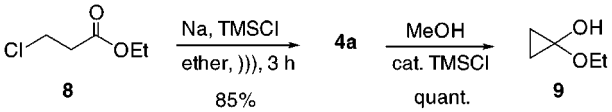
* To whom correspondence should be addressed. Tel: +33/1/69157252. Fax: +33/1/69156278. E-mail: antfadel@icmo.u-psud.fr.

† Part of this study was previously communicated at the Organic Chemistry symposium (GECO 39), Sept 1998, at La Bourboule (France).

(1) For a comprehensive review, see: Dhawan, B.; Redmore, D. *Phosphorus Sulfur Relat. Elem.* **1987**, *32*, 119.
(2) Wolfenden, R. *Annu. Rev. Biophys. Bioeng.* **1976**, *5*, 271.
(3) Kafarski, B.; Lejczak B. *Phosphorus, Sulfur Silicon* **1991**, *63*, 193.
(4) De Lombaert, S.; Blanchard, L.; Tan, J.; Sakane, Y.; Berry, C.; Ghai, R. D. *Biorg. Med. Chem. Lett.* **1995**, *5*, 145.
(5) De Lombaert, S.; Blanchard, L.; Berry, C.; Ghai, R. D.; Trapani, A. J. *Biorg. Med. Chem. Lett.* **1995**, *5*, 151.
(6) For an recent review see: (a) Stammer, C. *Tetrahedron* **1990**, *46*, 2254. (b) Wagner, I.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816. (c) Alami, A.; Calmes, M.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1993**, *130*, 5. (d) Jimenez, J. M.; Rife, J.; Ortuno, R. M. *Tetrahedron: Asymmetry* **1996**, *7*, 537.
(7) (a) Diel, P. L.; Maier, L. *Phosphorus Sulfur* **1984**, *20*, 313. (b) Erison, M. D.; Walsh, C. T. *Biochemistry* **1987**, *26*, 3417.
(8) For an α-aminocyclopropanephosphonic acid: McCleery, P. P.; Tuck, B. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1319.
(9) For substituted α-aminocyclopropanephosphonic acids; racemic syntheses: (a) Groth, U.; Lehmann, L.; Richter, L.; Schöllkopf, U. *Liebigs Ann. Chem.* **1993**, 427; enantiopure: (b) Yamazaki, S.; Takada, T.; Moriguchi, Y.; Yamabe, S. *J. Org. Chem.* **1998**, *63*, 5919.
(10) Fadel, A. *Tetrahedron* **1991**, *47*, 6265.
(11) (a) Fadel, A. *Synlett* **1993**, 503. (b) Fadel, A.; Khesrani, A. *Tetrahedron: Asymmetry* **1998**, *9*, 305 and references therein.
(12) (a) Pudovik, A. N.; Konovalova, I. V. *Synthesis* **1979**, 81. (b) Seebach, D.; Charczuk, R.; Gerber, C.; Renaud, P. *Helv. Chim. Acta* **1989**, *72*, 401. (c) Oshikawa, T.; Yamashita, M. *Bull. Chem. Soc. Jpn* **1989**, *62*, 3177. (d) Shatzmiller, S.; Dolitzky, B.-Z.; Meirovich, R.; Neidlein, R.; Weik, C. *Liebigs, Ann. Chem.* **1991**, 161. (e) Kunz, H.; Laschat, S. *Synthesis* **1992**, 90. (f) Smith, A. B., III; Yager, K. M.; Taylor, C. M. *J. Am. Chem. Soc.* **1995**, *117*, 10879 and references therein. (g) Gröger, H.; Saida, Y.; Sasai, H.; Yamaguchi, K.; Martens, J.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 3089. (h) Stevens, C.; Verbake, A.; De Kimpe, N. *Synlett* **1998**, 180.
(13) Maury, C.; Wang, Q.; Gharbaoui, T.; Chiadni, M.; Tomas, A.; Royer, J.; Husson, H. P. *Tetrahedron* **1997**, *53*, 3627.
(14) (a) Salaün, J.; Marguerite, J. *Org. Synth.* **1984**, *63*, 149. (b) Fadel, A.; Canet, J.-L.; Salaün, J. *Synlett* **1990**, 89.

10.1021/jo990064w CCC: $18.00
Published on Web 06/03/1999

Scheme 4



Scheme 5

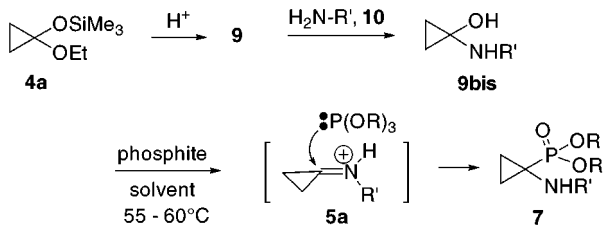


Table 1. Addition of Trialkyl Phosphite to Iminium 5a Derived from Acetal 4a

entry	amine R′	amine **10**·HCl	procedure, conditions	time (d)	product (yield, %)
1	CH_2Ph	**10a**	B, $P(OEt)_3$[a]	3	**7a** (68)
2	CH(Me)Ph	(*R*)-**10b**	B, $P(OEt)_3$[a]	3	**7b** (68)
3	CH(Me)Ph	(*R*)-**10b**	B, $P(OEt)_3$[b]	4	**7b** (87)
4	CH(Me)Ph	**10b**	B, $P(OMe)_3$[c]	3	**7c** (71)
5	CH(Me)Ph	**10b**	B, $HPO(OR)_2$[d]	3	**7c** (0)
6	CH(Me)Ph	(*R*)-**10b**[e]	A, $P(OEt)_3$	1	**7b** (95)

[a] Procedure B: reactions carried out with amine·HCl in EtOH. [b] In EtOH−THF(1:1). [c] In MeOH. [d] In MeOH (R = Me), in EtOH (R = Et). [e] Procedure A: reaction carried out with amine in the presence of 4 equiv of AcOH in EtOH.

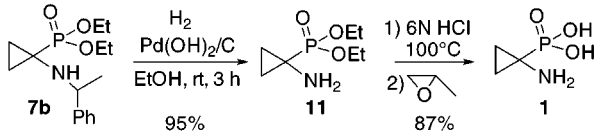
The cyclopropanone acetal **4a** by reaction in ethanol with different amine **10** and trialkyl phosphite led to the aminocyclopropanephosphonates **7** in a one-pot procedure, via **9bis** and **5a** intermediates. In effect, the hemiacetal **9** formed in situ from the acetal **4a** under reaction conditions (ROH, cat. TMSCl or AcOH)[15] gave with amine **10** the aminol **9bis**, which under acidic conditions led to the iminium intermediate **5a**. The latter underwent phosphite addition to furnish aminophosphonates **7** (Scheme 5). We chose benzylamine types **10** to remove at the end of the synthetic sequence the benzyl group by hydrogenolysis. Our results are reported in Table 1.

Thus, the hemiacetal **9** formed in situ from the acetal **4a** under reaction conditions gave, following procedure B [55 °C in EtOH, in the presence of benzylamine (**10a**·HCl) or (*R*)-α-phenylethylamine (**10b**·HCl), and triethyl phosphite], the aminophosphonate **7a** or **7b** in 68 and 88%, respectively (entries 1, 2). In a mixture of EtOH/THF (1:2), the reaction addition (procedure B) was much more slower (entry 3). On the other hand, reaction addition of trimethyl phosphite did not improve the yield nor the time reaction (entry 4). Moreover, we were delighted to find that the acetal **4a** following procedure A [in the presence of (*R*)-α-phenylethylamine (**10b**) and 4 equiv of AcOH[16] in absolute ethanol], underwent the one-pot addition of triethyl phosphite at 55 °C within 23 h to afford the aminophosphonate **7b** in 95% yield (entry 6). Other conditions such as utilization of diethyl phosphite in EtOH, dimethyl phosphite in MeOH, or its sodium salt ($NaP(O)(OMe)_2$) in THF) were investigated. These reagents did not furnish any detectable product, even after several days at room temperature (entry 5). We found, as previously reported for aminocarboxylic acid synthesis (Scheme 2),[10,11] that methylbenzylamine gave a better yield than benzylamine. The use of (*R*)-α-phenylethylamine **10b** following procedure A or B gave the expected enantiomerically pure product (*R*)-**7b** without racemization (entries 2, 6).

(15) The methanolysis of acetal **4a** into the hemiacetal **9** under reaction conditions, in the presence of AcOH (procedure A) is much more slower 3 h are necessary for complete transformation, than with cat. TMSCl in MeOH (5 min).

(16) If the same reaction was carried out in AcOH as solvent, only 30% yield of product **7b** was isolated after 23 h at 55 °C.

Scheme 6



Subsequent hydrogenolysis of the phosphonate **7b** in the presence of a catalytic amount of Pearlman's catalyst (20% $Pd(OH)_2$) on activated carbon in absolute ethanol (20 °C, 3 h) afforded after flash chromatography the free aminophosphonate **11** in 95% yield as colorless crystals (mp 120.5 °C).

The latter, upon acidic hydrolysis in 6 N hydrochloric acid (100 °C, 16 h) or by treatment with trimethylsilyl iodide in dichloromethane, and subsequent addition of ethanol and propylene oxide, led to pure 1-aminocyclopropanephosphonic acid **1** as a white solid (87% yield, mp 251 °C (decomp; lit.:[7] 255 °C) (Scheme 6).

In summary, we have developed an easy and efficient three-step synthesis of 1-aminocyclopropanephosphonic acid **1** from a commercially or readily available cyclopropanone acetal **4a** in high overall yield (77%). This new method is based on a one-pot reaction of acetal **4a** with amine and phosphite to provide the aminophosphonates **7**. The synthesis, by this methodology of asymmetric aminocyclopropanephosphonic acids derivatives, is currently under investigation in our laboratory.

Experimental Section

General Methods. For general information see ref 11b. Except as otherwise indicated, reactions were carried out under argon, with magnetic stirring. Di- and triethyl phosphite were distilled at reduced pressure and stored under argon. Yields refer to chromatographically and spectroscopically pure compounds, except as noted. ^{13}C chemical shift in D_2O is relative to internal reference. ^{31}P NMR spectra were recorded at 101.25 MHz. ^{31}P chemical shifts are relative to internal reference (85% H_3PO_4 δ = 0 ppm). Mass spectra were recorded at an ionizing voltage of 70 eV by EI. Elemental analyses were performed by the Microanalytical Service Laboratory of CNRS at Gif (France).

(1′*R*)-Diethyl 1-[(1′-Methylbenzyl)amino]cyclopropanephosphonate 7b. General Procedure A. To a solution of cyclopropanone acetal **4a**[14] (870 mg, 5 mmol) in EtOH (10 mL) was added one drop of TMSCl. After 5 min of stirring, (*R*)-methylbenzylamine **10b** (910 mg, 7.5 mmol), AcOH (1.2 mL, 4 equiv), and $P(OEt)_3$ (1.25 g, 1.31 mL, 7.5 mmol) were successively added. The mixture was stirred and heated at 55 °C for 23 h. The reaction mixture was concentrated under vacuum, concd ammonia (2 mL) was added, and then the mixture was filtered through 5 cm-pad of silica gel and eluted with ether (100 mL). The filtrate was concentrated under vacuum to give 1.47 g of practically pure aminophosphonate (*R*)-**7b**. Purification by FC over silica gel ($EtOAc/CH_2Cl_2$ 2/8) gave pure (*R*)-**7b** (1.41 g, 95%): R_f = 0.18 ($EtOAc/CH_2Cl_2$ 15/85); $[\alpha]^{20}_D$ +52.5 (*c* 1, $CHCl_3$); IR (film, cm^{-1}) 3600−3320 (NH), 1260 (P=O), 1060 (P−O); ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.40−7.17 (m, 5H), 4.38 (dq, *J* = 7 Hz, $^4J_{PH}$ = 2 Hz, 1H), 4.17 (dq, *J* = 6.4 Hz, $^3J_{PH}$ = 2 Hz, 2H), 4.13 (dq, *J* = 6.4 Hz, $^3J_{PH}$ = 2.8 Hz, 2H), 2.20−1.80 (br s, 1H, NH), 1.39 (t, *J* = 6.4 Hz, 6H), 1.34 (d, *J* = 7 Hz, 3H), 1.19−

1.00 (m, $1H_{cycle}$), 0.96−0.70 (m, $2H_{cycle}$), 0.60−0.45 (m, $1H_{cycle}$); ^{13}C NMR (62.86 MHz, $CDCl_3$) δ (ppm) [6 arom C: 146.6 (1C), 128.0 (2C), 126.6 (3C)], 61.75 (d, $^2J_{PC}$ = 6 Hz, 1C), 61.65 (d, $^2J_{PC}$ = 6 Hz, 1C), 55.8 (1C), 31.7 (d, $^1J_{PC}$ = 200 Hz, C_1), 24.2 (1C), 16.4 (d, $^3J_{PC}$ = 5.7 Hz, 2C), 13.35 (d, $^2J_{PC}$ = 4.8 Hz, C_2), 11.1 (d, $^2J_{PC}$ = 3.8 Hz, C_3); ^{31}P NMR (101.25 MHz, $CDCl_3$) δ (ppm) 28.85; EI-MS *m*/*z* (rel int) 297 (M^+, 0.65), 159 (84), 105 (100); HRMS (EI) *m*/*z* 297.1478 (calcd for $C_{15}H_{24}NO_3P$ 297.1493). Anal. Calcd for $C_{15}H_{24}NO_3P$: C, 60.59; H, 8.14; N, 4.71. Found: C, 60.34; H, 8.11; N, 4.83.

(1′*R*)-Diethyl 1-[(1′-Methylbenzyl)amino]cyclopropanephosphonate 7b. General Procedure B. To a solution of cyclopropanone acetal **4a** (870 mg, 5 mmol) in EtOH (10 mL) was added one drop of TMSCl. After 5 min of stirring (complete formation of hemiacetal **9**) were added successively (*R*)-methylbenzylamine **10b**·HCl(1.18 g, 7.5 mmol) and $P(OEt)_3$ (1.25 g, 1.31 mL, 7.5 mmol). The mixture was stirred and heated at 55 °C for 3 days. The workup following procedure A furnished after FC enantiomerically pure (*R*)-**7b** (1.3 g, 88%). The spectral data were identical with those reported above.

Diethyl 1-(Benzylamino)cyclopropanephosphonate 7a. Following Procedure B. Acetal **4a** (870 mg, 5 mmol), TMSCl (cat.), benzylamine·HCl (1.07 g, 7.5 mL), EtOH (10 mL), and $P(OEt)_3$ (1.18 g, 7.5 mmol) gave, after heating at 55 °C for 3 days, usual workup, and FC, 960 mg (68%) of pure amino phosphonate **7a**: R_f = 0.17 (EtOAc/CH_2Cl_2 15/85); IR (film, cm^{-1}) 3600−3300 (NH), 1255 (P═O), 1060 (P−O); ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.37−7.14 (m, 5H), 4.15 (dq, ^3J = 7.4 Hz, 4H), 3.96 (d, J = 2.2 Hz, 2H benzyl), 1.95 (br.s, 1H, NH), 1.35 (t, J = 7.4 Hz, 6H), 1.21−1.05 (m, $2H_{cycle}$), 0.93−0.80 (m, $2H_{cycle}$); ^{13}C NMR (62.86 MHz, $CDCl_3$) δ (ppm) [6 arom C: 140.4 (s), 128.1 (2C), 127.8 (2C), 126.7 (1C)], 61.7 (d, $^2J_{PC}$ = 6.7 Hz, 2C), 51.4 (1C), 33.1 (d, $^1J_{PC}$ = 201.6 Hz, C_1), 16.4 (d, $^3J_{PC}$ = 5.7 Hz, 2C), 12.8 (d, $^2J_{PC}$ = 4.4 Hz, C_2 and C_3); ^{31}P NMR (101.25 MHz, $CDCl_3$) δ (ppm) 28.48; EI-MS *m*/*z* (rel int) 283 (M^+, 12), 145 (72), 91 (100); HRMS (EI) *m*/*z* 283.1330 (calcd for $C_{14}H_{22}NO_3P$: 283.1337). Anal. Calcd for $C_{14}H_{22}NO_3P$: C, 59.35; H, 7.83; N, 4.94. Found: C, 59.02; H, 7.83; N, 4.92.

Dimethyl 1-[(1′-Methylbenzyl)amino]cyclopropanephosphonate *rac*-7c. Following Procedure B. Acetal **4a** (870 mg, 5 mmol), TMSCl (cat.), methylbenzylamine·HCl (1.18 g, 7.5 mmol), MeOH (10 mL), and $P(OMe)_3$ (930 mg, 0.9 mL, 7.5 mmol) gave, after heating at 55 °C for 3 days, usual workup, and FC, 955 mg (71%) of pure aminophosphonate *rac*-**7c**: R_f = 0.18 (EtOAc/CH_2Cl_2, 15/85); IR (film, cm^{-1}) 3600−3340 (NH); 1270 (P═O); 1060 (P−O); ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.38−7.15 (m, 5H), 4.30 (dq, J = 7.4 Hz, $^1J_{PH}$ = 2.8 Hz, 1H), 3.80 (d, $^3J_{PH}$ = 4.2 Hz, 3H), 3.76 (d, $^3J_{PH}$ = 4.2 Hz, 3H), 2.12−1.80 (br, s, 1H, NH), 1.30 (d, J = 6.7 Hz, 3H), 1.17 (m, $1H_{cycle}$), 0.94 (m, $2H_{cycle}$), 0.62−0.45 (m, $1H_{cycle}$); ^{13}C NMR (62.86 MHz, $CDCl_3$) δ (ppm) [6 arom C: 146.4 (s, 1C), 128.0 (2C), 126.7 (1C), 126.6 (2C)], 55.9 (1C), 52.6 (d, $^2J_{PC}$ = 7.4 Hz, 1C), 52.5 (d, $^2J_{PC}$ = 7.4 Hz, 1C), 31.1 (d, $^1J_{PC}$ = 200.6 Hz, C_1), 13.2 (d, $^2J_{PC}$ = 4.3 Hz, C_2), 11.2 (d, $^2J_{PC}$ = 3.8 Hz, C_3); ^{31}P NMR (101.25 MHz, $CDCl_3$) δ (ppm) 31.86; EI-MS *m*/*z* (rel int) 269 (M^+, 0.9), 159 (72), 105 (100); HRMS (EI) *m*/*z* 269.1167 (calcd for $C_{13}H_{20}NO_3P$: 269.1180). Anal. Calcd for $C_{13}H_{20}NO_3P$: C, 57.99; H, 7.49; N, 5.20. Found: C, 59.92; H, 7.62; N, 4.42.

Diethyl 1-Aminocyclopropanephosphonate 11. Phosphonate adduct **7b** (1.19 g, 4 mmol) was dissolved in absolute EtOH (25 mL), and 20% $Pd(OH)_2/C$ (Pearlman's catalyst, 300 mg) was added. The flask was connected to a hydrogenation apparatus equipped with a graduated buret containing water to monitor uptake of hydrogen. Monitored by TLC, the reaction was complete under H_2 (1 atm) at room temperature within 3 h, degassed under a current of argon, filtered through Celite, and washed with EtOH (3 × 10 mL). Concentration and FC (eluent 8 → 30% MeOH/CH_2Cl_2) afforded **11** (735 mg, 95%) as a white solid. Recrystallization from CH_2Cl_2/ether gave 700 mg (91% yield) of **11** as colorless crystals: R_f = 0.23 (MeOH/CH_2Cl_2 1/9); mp 120.5 °C; IR ($CHCl_3$, cm^{-1}) 3570−3380 (NH_2), 1250 (P═O), 1060 (P−O); ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 8.60 (br, s, 2H), 4.25 (br, q, 4H), 1.53 (m, $2H_{cycle}$), 1.40 (br, t, 6H), 1.35 (m, $2H_{cycle}$), [lit.[7] in $CDCl_3$, 4.15 (q, 4H), 2.10 (s, 2H), 1.35 (t, 6H), 0.90 (m, 4H)]; ^{13}C NMR (62.86 MHz, $CDCl_3$) δ (ppm) 67.7 (d, $^2J_{PC}$ = 6.2 Hz, 2*C*H_2O), 26.7 (d, $^1J_{PC}$ = 213 Hz, C_1), 16.3 (d, $^3J_{PC}$ = 5.7 Hz, 2*C*H_3), 9.5 (C_2 and C_3); ^{31}P NMR (101.25 MHz, $CDCl_3$) δ (ppm) 18.99; EI-MS *m*/*z* (rel int) 193 (M^+, 8), 82 (62), 56 (100); HRMS (EI) *m*/*z* 193.0861 (calcd for $C_7H_{16}NO_3P$: 193.0867). Anal. Calcd for $C_7H_{16}NO_3P$: C, 43.52; H, 8.35; N, 7.25. Found: C, 43.85; H, 8.55; N, 7.60.

1-Aminocyclopropanephosphonic Acid 1. Hydrolysis with 6 N HCl. A solution of diethyl phosphonate **11** (385 mg, 2 mmol) in aqueous 6 N HCl (10 mL) was heated at reflux for 20 h. The solvent was evaporated under reduced pressure to dryness. The residue was dissolved in minimum amount of EtOH, then to which was added dropwise an excess of propylene oxide while heating. The volatile compounds were removed by evaporation under vacuum, and the residue was recrystallized from H_2O/EtOH to afford 240 mg (87%) of **1** as a white solid (dried under high vacuum): mp 251 °C (lit.[7] 255 °C); IR (cm^{-1}, Nujol) 3345 (NH_2, OH), 1260 (P═O), 1050 (P−O); ^1H NMR (250 MHz, D_2O) δ (HOD, 4.80 ppm) 1.29−0.92 (m, $4H_{cycle}$), [lit.[8] D_2O, 1.05−1.30 (m, 4H)]; ^{13}C NMR (62.86 MHz, D_2O) δ (ppm) 29.6 (d, $^1J_{CP}$ = 193.5 Hz, C_1), 9.2 (C_2 and C_3), [lit.[7] (D_2O/NaOD, pH = 11), δ = 30.9 ($^1J_{CP}$ = 193.5 Hz, C_1), 11.8 (C_2 and C_3); ^{31}P NMR (101.25 MHz, D_2O) δ (ppm) 12.70, [lit.[7] (D_2O/NaOD, pH = 11), δ = 11.8 ppm; lit.[8] in D_2O, δ = 15.9 ppm external reference H_3PO_4].

Hydrolysis with Me_3SiI. Trimethylsilyl iodide (1.2 g, 6 mmol) was added dropwise at 0 °C to a stirred solution of the diethyl phosphonate **11** (385 mg, 2 mmol) in CH_2Cl_2 (20 mL), and stirring was continued at room temperature for 30 min. Organic solvents were removed under vacuum, and a mixture of EtOH (10 mL) and propylene oxide (1 mL) was added with stirring. After complete precipitation, the pure aminophosphonic acid **1** was filtered off, giving 245 mg (89%) as a white solid: mp 250 °C. The spectral data are identical with those reported above.

JO990064W