Syntheses of α-Aminophosphonic Acids, VI[1]

Synthesis of Diastereomerically Pure 1-Aminocyclopropylphosphonic Acids

Ulrich Groth*, Lutz Lehmann, Lutz Richter[+], and Ulrich Schöllkopf*

Institut für Organische Chemie der Universität Göttingen,
Tammanstraße 2, W-3400 Göttingen, Germany

Received December 10, 1992

Key Words: α-Aminophosphonic acids / Cyclopropanation, diastereoselective / Isocyanides

The lithium or potassium derivative of diethyl isocyanomethylphosphonate (**1**) reacts with epoxides in the presence of boron trifluoride–diethyl ether to provide the diethyl 3-hydroxy-1-isocyanoalkylphosphonates *rac*-**3**. The corresponding mesylates *rac*-**4** undergo a base-mediated cyclization to the diethyl 1-isocyanocyclopropylphosphonates *rac*-**5**. Acidic hydrolysis affords the diethyl 1-aminocyanocyclopropylphosphonates *rac*-**6**, which upon treatment with trimethylsilyl iodide yield the 1-aminocyclopropylphosphonic acids *rac*-**7**. A base-mediated cycloalkylation of **1** with dibromoalkanes **10** gives the diethyl 1-isocyanocycloalkylphosphonates **11**, which are suitable precursors for the achiral 1-aminocycloalkylphosphonic acids.

In the last few years, 1-aminocyclopropanecarboxylic acid (ACC) and its derivatives have attracted special attention due to their biological activity[2]. The outstanding properties of the cyclopropyl group seem to be responsible for the selective inhibition of enzymes by many cyclopropyl amino acids. The best known cyclopropyl amino acid is the achiral 1-amino-1-cyclopropanecarboxylic acid itself, the biosynthetic precursor of ethylene, which is responsible for the ripening of fruits[3]. Other cyclopropane derivatives are widespread among various classes of natural products, such as fatty acids, terpenes, steroids and amino acids. A replacement of the carboxylic group of ACC by a phosphonic group would yield aminocyclopropylphosphonic acids.

α-Aminophosphonic acids, the phosphonic acid analogues of α-amino acids, are finding increasing interest[4] because of their potential or proven biological activity[5]. Due to the tetrahedral structure of the phosphonic acid moiety, they act as "transition-state analogues"[6] and thus serve as models for enzyme reactions[7] or as components in enzyme inhibitors[8,11a].

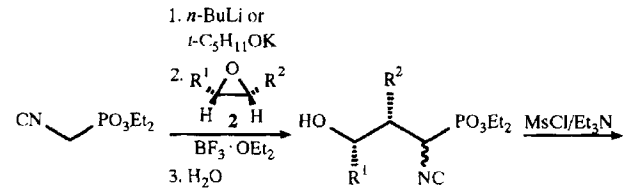
Recently, we reported on the asymmetric synthesis of enantiomerically and diastereomerically pure cyclopropyl amino acids[9] and phosphonic acid analogues of glutamic acid and proline[10].

In order to combine the outstanding properties of the cyclopropyl and phosphonic acid moiety, we were interested in the synthesis of aminocyclopropylphosphonic acids[11]. Although a few methods for the preparation of this class of compounds have been described[12], a general method is still lacking.

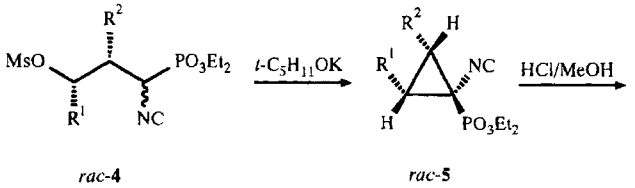
Diethyl isocyanomethylphosphonate[13] (**1**) can be deprotonated either with *n*-butyllithium or potassium *tert*-pentoxide. Upon addition of a 1:1 mixture of boron trifluoride–diethyl ether and epoxides **2**, the diethyl 3-hydroxy-1-isocyanoalkylphosphonates *rac*-**3** were obtained after aqueous workup as a mixture of diastereomers at C-1 in 45–55% yield. In many cases, only one diastereomer was detectable by ^{1}H-, ^{13}C- and ^{13}P-NMR spectroscopical analysis. The nucleophilic attack exclusively takes place at the less substituted carbon atom of the expoxide with inversion of the configuration. The 3-hydroxy-1-isocyanoalkylphosphonates *rac*-**3** are precursors of the phosphonic acid analogues of homoserine, which could serve as "transition-state analogues" for homoserines[6].

The diethyl 3-hydroxy-1-isocyanoalkylphosphonates *rac*-**3** were transformed into the mesylates *rac*-**4** with methanesulfonyl chloride in the presence of triethylamine in almost quantitative yield. Upon treatment with potassium *tert*-pentoxide, the mesylates *rac*-**4** underwent a base-mediated, S_N2-type cyclization to afford the diethyl 1-isocyano-1-cyclopropylphosphonates *rac*-**5**. Due to the considerably large difference in size between the isocyano and the bulky diethoxyphosphoryl group, solely the diastereomers with *cis* orientation of R^1, R^2 and NC were formed. Upon acidic hydrolysis with hydrochloric acid in methanol, the diethyl 1-amino-1-cyclopropylphosphonates *rac*-**6** were obtained in 73–78% yield. Treatment of the diethyl 1-amino-1-cyclopropylphosphonates *rac*-**6** with trimethylsilyl iodide in dichloromethane and subsequent addition of ethanol and propylene oxide yielded the crystalline and diastereomerically pure 1-amino-1-cyclopropylphosphonic acids *rac*-**7**, which were obtained analytically pure without further purification. The relative configuration at C-1 and C-2 of 1-amino-2-methyl-1-cyclopropylphosphonic acid (*rac*-**7a**) was assigned by ^{31}P-NMR spectroscopy to be *trans*. The $^{1}H^{31}P$ coupling constants were determined to be $^{3}J_{P/cis\text{-}2\text{-}H}$ = 11.4 Hz, $^{3}J_{P/cis\text{-}3\text{-}H}$ = 11.4 Hz and $^{3}J_{P/trans\text{-}3\text{-}H}$ = 5.9 Hz. Dolhaine and Hägele[14] reported for dimethyl 1-bromo-1-cyclopropylphosphonate $^{3}J_{P/cis\text{-}2\text{-}H}$ = 12.70 Hz and

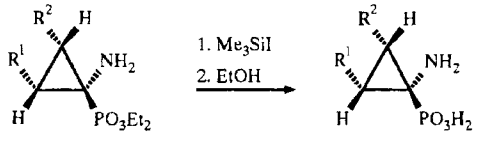
[+] Present address: Genentech Inc., Department of Bioorganic Chemistry MS 18, 460 Point San Bruno Boulevard, South San Francisco, CA 94080, USA.



1 *rac*-3



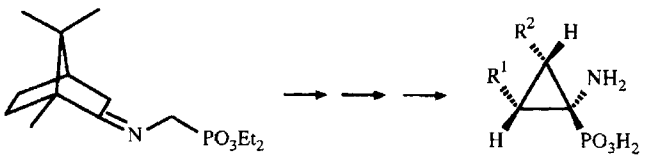
rac-4 *rac*-5



rac-6 *rac*-7

2–7	R^1	R^2	3	Yield (%) of 4	5	6	7
a	CH_3	H	52	>95	71	77	86
b	C_2H_5	H	59	>95	74	78	90
c	$(CH_2)_4$		45	>95	74	73	87
d	CH_3	CH_3	48	–	–	–	–

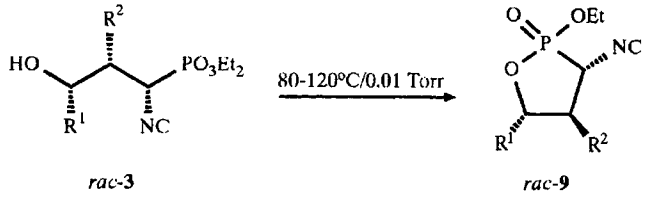
$^3J_{P/trans\text{-}2\text{-}H}$ = 7.12 Hz. In analogy we assume the relative configuration at C-1 and C-2 of the 1-amino-1-cyclopropylphosphonic acids *rac*-**7b** and **c** to be *trans*.



8 **7**

Enantio- and diastereomerically pure 1-amino-1-cyclopropylphosphonic acids **7** should be accessible by using the (+)-camphor derivative **8**[1] and/or enantiomerically pure epoxides[15].

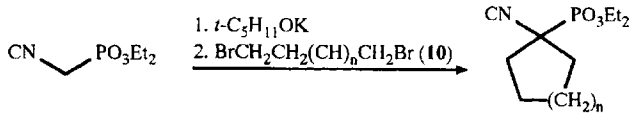
In contrast to the diethyl 3-hydroxy-1-isocyanoalkylphosphonates *rac*-**3a** and **b**, the diethyl 3-hydroxy-1-isocyanoalkylphosphonates *rac*-**3c** and **d** could not be purified by bulb-to-bulb distillation. Upon heating, *rac*-**3c** and **d** underwent an intramolecular transesterification to afford the 2-ethoxy-3-isocyano-1,2-oxaphospholan-2-ones *rac*-**9**. The relative configuration at C-3 and C-5 of *rac*-**9b** was assigned to be *trans* due to the $^3J_{H/H}$ coupling constant of 11.5 Hz. In analogy, we assume the same configuration for *rac*-**9a**. Consequently, the major diastereomers of the diethyl 3-



rac-3 *rac*-9

3	9	R^1	R^2	Yield of 9 (%)	d.e. of 9 (%)
c	**a**	$(CH_2)_4$		40	76
d	**b**	CH_3	CH_3	42	68

hydroxy-1-isocyanoalkylphosphonates *rac*-**3c** and **d** must possess the *all syn* configuration.



1 **11**

10, 11	n	Yield of 11 (%)
a	1	60
b	2	62
c	3	35

Using the same starting material **1** and a similar method, we were able to prepare the achiral diethyl 1-isocyanocycloalkylphosphonates **11**. Upon treatment of diethyl isocyanomethylphosphonate (**1**) with two equivalents of potassium *tert*-pentoxide and one equivalent of the dibromoalkanes **10**, the diethyl 1-isocyanocycloalkylphosphonates **11** were obtained in 35–62% yield. Compounds **11** are suitable precursors for the synthesis of 1-aminocycloalkylphosphonic acids, which should be obtained as described above by acidic hydrolysis and subsequent dealkylation of **11**.

Financial support by the *Stiftung Volkswagenwerk* and the *Fonds der Chemischen Industrie* is gratefully acknowledged. We thank the *BASF AG* for providing valuable starting materials.

Experimental

Infrared (IR) spectra were recorded with a Perkin-Elmer 298 spectrometer. – NMR spectra were measured with a Varian XL 200 or a VXR 200 spectrometer for ^1H and ^{13}C NMR and a Bruker WP 250 spectrometer for ^{31}P NMR. Chemical shifts are given in δ values by using tetramethylsilane or dioxane as an internal standard for ^1H and ^{13}C NMR and orthophosphoric acid (85%) as an external standard for ^{31}P NMR. – Melting points are uncorrected. – TLC analyses were performed on Polygram Sil G/UV_{254} silica gel plates. Silica gel (240–400 mesh) from Merck was used for flash chromatography. – Combustion analyses were carried out by the microanalytical laboratory of the University of Göttingen. – All reactions were carried out under nitrogen or argon. All reagents were purified and dried if necessary prior to use. – Diethyl isocyanomethylphosphonate (**1**) was prepared as described previously[13].

Diethyl 3-Hydroxy-1-isocyanoalkylphosphonates rac-3. – General Procedure, Method A: To a stirred solution of **1** (2.66 g, 15.0 mmol) in THF (20 ml), *n*-butyllithium (16.0 mmol, 10 ml of a 1.6 N solution in hexane) was added dropwise at −70°C. After stirring at −70°C for 15 min, a precooled solution of the epoxide **2** (15.5 mmol) and $BF_3 \cdot Et_2O$ (15.5 mmol) in THF (50 ml), which had been prepared by addition of boron trifluoride–diethyl ether (15.5 mmol) to a solution of the epoxide **2** in THF (45 ml) at −70°C, was added dropwise, and stirring was continued at −70°C for 20 min. Then a phosphate buffer solution (20 ml, pH = 7) was added, and the mixture was allowed to warm up to room temp. within 15 min. The organic solvents were removed in vacuo, water (20 ml) was added to the residue and the mixture was extracted with three portions of diethyl ether (40 ml each). The combined organic layers were dried with $MgSO_4$, the solvent was removed in vacuo, and the crude products *rac*-**3** were purified by bulb-to-bulb distillation.

General Procedure, Method B: To a stirred solution of **1** (2.66 g, 15.0 mmol) in dichloromethane (40 ml), potassium *tert*-pentoxide (16.0 mmol, 9 ml of a 1.8 N solution in toluene) was added dropwise at −70°C. After stirring at −70°C for 15 min, a solution of the epoxide **2** (15.5 mmol) in dichloromethane (5 ml) and then $BF_3 \cdot Et_2O$ (15.5 mmol) were added dropwise, and stirring was continued at −70°C for 20 min. Then a phosphate buffer solution (20 ml, pH = 7) was added, and the mixture was allowed to warm up to room temp. within 15 min. The organic solvents were removed in vacuo, water (20 ml) was added to the residue, and the mixture was extracted with three portions of diethyl ether (40 ml each). The combined organic layers were dried with $MgSO_4$, the solvent was removed in vacuo, and the crude products *rac*-**3** were purified by bulb-to-bulb distillation or flash chromatography (silica gel, 70 g).

Diethyl 3-Hydroxy-1-isocyanobutylphosphonate (*rac*-**3a**): According to method B, 2.66 g (15.0 mmol) of diethyl isocyanomethylphosphonate (**1**), 0.90 g (15.5 mmol) of 1,2-propylene oxide and 1.95 ml (15.5 mmol) of $BF_3 \cdot EtO_2$ were used to yield 1.83 g (52%) of *rac*-**3a** after bulb-to-bulb distillation. – B.p. 125–130°C/0.01 Torr; d.e. 45%, determined by ^{31}P NMR spectroscopy. – IR (neat): $\tilde{\nu}$ = 3600–3200 (OH), 2140 (N≡C), 1250 (P=O), 1040 cm^{-1} (P–O). – ^1H NMR ($CDCl_3$): δ = 1.26 and 1.29 (2d, *J* = 6 Hz, 3H, CH_3), 1.40 (t, *J* = 7 Hz; 6H, OCH_2CH_3), 1.65–2.20 (m; 2H, CH_2), 2.70 (s; 1H, OH), 3.90–4.46 (m; 6H, OCH_2CH_3, CH–NC and C*H*–OH). – ^{31}P NMR ($CDCl_3$): δ = 17.51 (minor diastereomer), 17.71 (major diastereomer).

$C_9H_{18}NO_4P$ (235.2) Calcd. C 45.96 H 7.71
Found C 45.91 H 7.78

Diethyl 3-Hydroxy-1-isocyanopentylphosphonate (*rac*-**3b**): According to method A, 2.66 g (15.0 mmol) of diethyl isocyanomethylphosphonate (**1**), 1.12 g (15.5 mmol) of 1,2-epoxybutane and 1.95 ml (15.5 mmol) of $BF_3 \cdot Et_2O$ were used to yield 2.21 g (59%) of *rac*-**3b** after bulb-to-bulb distillation. – B.p. 150–155°C/0.01 Torr; d.e. 38%, determined by ^{31}P NMR spectroscopy. – IR (neat): $\tilde{\nu}$ = 3600–3200 (OH), 2130 (N≡C), 1250 (P=O), 1020 cm^{-1} (P–O). – ^1H NMR ($CDCl_3$): δ = 0.99 (t, *J* = 6 Hz, 3H, CH_3), 1.41 (t, *J* = 7 Hz; 6H, OCH_2CH_3), 1.40–1.65 (m; 2H, CH_2), 1.75–2.20 (m; 2H, CH_2), 2.38 (s; 1H, OH), 3.60–4.00 (m; 1H, C*H*–OH), 4.05–4.42 (m; 5H, OCH_2CH_3 and CH–NC). – ^{31}P NMR ($CDCl_3$): δ = 17.59 (minor diastereomer), 17.84 (major diastereomer).

$C_{10}H_{20}NO_4P$ (249.3) Calcd. C 48.19 H 8.09
Found C 48.43 H 7.96

Diethyl 1-(2-Hydroxycyclohexyl)-1-isocyanomethylphosphonate (*rac*-**3c**): According to method B, 2.66 g (15.0 mmol) of diethyl isocyanomethylphosphonate (**1**), 1.52 g (15.5 mmol) of cyclohexene oxide and 1.95 ml (15.5 mmol) of $BF_3 \cdot Et_2O$ were used. After removal of organic solvents at 95°C/0.01 Torr for 30 min and flash chromatography with diethyl ether/methanol (50:1) 1.86 g (45%) of *rac*-**3c** was obtained; R_f = 0.81; d.e. 94%, determined by ^{31}P-NMR spectroscopy. – IR (neat): $\tilde{\nu}$ = 3600–3200 (OH), 2140 (N≡C), 1250 (P=O), 1030 cm^{-1} (P–O). – ^1H NMR ($CDCl_3$): δ = 1.35 (t, *J* = 7 Hz, 6H, OCH_2CH_3), 1.35–2.40 (m; 9H, aliph. H), 2.60 (s; 1H OH), 3.15–3.33 (m; 1H, C*H*–OH), 3.95–4.40 (m, 4H, OCH_2CH_3), 4.50–4.70 (m, 1H, CH–NC). – ^{31}P NMR ($CDCl_3$): δ = 17.72 (major diastereomer), 18.23 (minor diastereomer).

$C_{12}H_{22}NO_4P$ (275.3) Calcd. C 52.36 H 8.06
Found C 52.34 H 8.09

Diethyl 3-Hydroxy-1-isocyano-2-methylbutylphosphonate (*rac*-**3d**): According to method B, 2.66 g (15.0 mmol) of diethyl isocyanomethylphosphonate (**1**), 1.12 g (15.5 mmol) of *cis*-2,3-epoxybutane and 1.95 ml (15.5 mmol) of $BF_3 \cdot Et_2O$ were used to yield 1.79 g (48%) of *rac*-**3d** after flash chromatography with ethyl acetate; R_f = 0.54; d.e. 97%, determined by ^{31}P-NMR spectroscopy. – IR (neat): $\tilde{\nu}$ = 3600–3200 (OH), 2135 (N≡C), 1250 (P=O), 1020 cm^{-1} (P–O). – ^1H NMR ($CDCl_3$): δ = 1.13 and 1.27 (2d, *J* = 6 Hz, 6H, CH_3), 1.40 (t, *J* = 7 Hz; 6H, OCH_2CH_3), 1.70–2.20 (m; 1H, C*H*CH_3), 2.64 (s; 1H, OH), 3.40–3.76 (m; 1H, C*H*–OH), 4.00–4.45 (m; 4H, OCH_2CH_3), 4.50–4.80 (m; 1H, CH–NC). – ^{31}P NMR ($CDCl_3$): δ = 17.47 (minor diastereomer) 17.89 (major diastereomer).

$C_{10}H_{20}NO_4P$ (249.3) Calcd. C 48.19 H 8.09
Found C 47.98 H 8.04

Preparation of the Mesylates rac-4. – General Procedure: To a stirred solution of the alcohols *rac*-**3a–c** (5.0 mmol) and triethylamine (0.80 g, 8.0 mmol) in dichloromethane (20 ml), methanesulfonyl chloride (0.47 ml, 6.0 mmol) was added dropwise with stirring at −10°C, and stirring was continued at −5°C for 30 min. The crude mixture was washed with 30 ml portions of ice/water, 2% hydrochloric acid, a saturated aqueous $NaHCO_3$ solution and a saturated aqueous NaCl solution. The organic layer was dried with $MgSO_4$ and the solvent removed in vacuo. The sensitive mesylates *rac*-**4a–c** were directly submitted to reaction with potassium *tert*-pentoxide without further purification.

Diethyl 1-Isocyano-1-cyclopropylphosphonates rac-5. – General Procedure: To a stirred solution of the mesylates *rac*-**4a–c** (5.0 mmol) in dichloromethane (20 ml), potassium *tert*-pentoxide (5.4 mmol, 3 ml of a 1.8 N solution in toluene) was added dropwise with stirring at −70°C, and stirring was continued at −70°C for 3 h and at 0°C for 2 h. A phosphate buffer solution (20 ml, pH = 7) was added, and the mixture was allowed to warm up to room temp. within 5 min. The organic solvents were removed in vacuo, water (20 ml) was added to the residue, and the mixture was extracted with three portions of diethyl ether (40 ml each). The combined organic layers were dried with $MgSO_4$, the solvent was removed in vacuo, and the crude products *rac*-**5** were purified by bulb-to-bulb distillation.

Diethyl (1a,2β)-1-Isocyano-2-methyl-1-cyclopropylphosphonate (*rac*-**5a**): 1.18 g (5.0 mmol) of the alcohol *rac*-**3a** was used to yield 0.77 g (71%) of *rac*-**5a** after bulb-to-bulb distillation. – B.p. 90–95°C/0.01 Torr; d.e. >95%, only one diastereomer detectable by ^{13}C- and ^{31}P-NMR spectroscopy. – IR (neat): $\tilde{\nu}$ = 3090 (cyclopropyl C–H), 2120 (N≡C), 1260 (P=O), 1020 cm^{-1} (P–O). – ^1H NMR ($CDCl_3$): δ = 0.97–1.12 (m; 1H, cyclopropyl H), 1.32–1.52 (m; 9H, OCH_2CH_3 and CH_3), 1.54–1.90 (m; 2H, cyclopropyl H), 4.15–4.34 (m; 4H, OCH_2CH_3). – ^{13}C NMR ($CDCl_3$): δ = 13.05 (2-CH_3), 16.34 (d, *J* = 6 Hz,, OCH_2CH_3), 18.86 (C-2), 21.34 (d,

J = 1.6 Hz, C-3), 63.65 (d, J = 6.1 Hz, OCH_2CH_3), 63.76 (d, J = 6.6 Hz, OCH_2CH_3), 157.57 (N≡C); C-1 was not detectable. – ^{31}P NMR ($CDCl_3$): δ = 17.62.

$C_9H_{16}NO_3P$ (217.2) Calcd. C 49.77 H 7.42
Found C 49.91 H 7.31

Diethyl (1a,2β)-2-Ethyl-1-isocyano-1-cyclopropylphosphonate (*rac*-**5b**): 1.25 g (5.0 mmol) of the alcohol *rac*-**3b** was used to yield 0.86 g (74%) of *rac*-**5b** after bulb-to-bulb distillation. – B.p. 100–105°C/0.01 Torr; d.e. >95%, only one diastereomer detectable by ^{13}C- and ^{31}P-NMR spectroscopy. – IR (neat): $\tilde{\nu}$ = 3070 (cyclopropyl C–H), 2120 (N≡C), 1250 (P=O), 1020 cm^{-1} (P–O). – ^1H NMR ($CDCl_3$): δ = 0.85–1.20 (m; 4H, cyclopropyl H and CH_3), 1.25–1.85 (m; 10H, OCH_2CH_3 and CH_2), 4.00–4.40 (m; 4H, OCH_2CH_3). – ^{13}C NMR ($CDCl_3$): δ = 12.77 (CH_3), 16.37 (d, J = 6 Hz,, OCH_2CH_3), 20.45 (d, J = 1.2 Hz, C-3), 21.96 (CH_2), 25.89 (C-2), 63.75 (d, J = 6.2 Hz, OCH_2CH_3), 157.37 (N≡C); C-1 was not detectable. – ^{31}P NMR ($CDCl_3$): δ = 17.64.

$C_{10}H_{18}NO_3P$ (231.2) Calcd. C 51.94 H 7.85
Found C 51.81 H 7.99

Diethyl (1a,6a,7a)-7-Isocyanobicyclo[4.1.0]hept-7-ylphosphonate (*rac*-**5c**): 1.38 g (5.0 mmol) of the alcohol *rac*-**3c** was used to yield 0.95 g (74%) of *rac*-**5c** after bulb-to-bulb distillation. – B.p. 105–110°C/0.01 Torr; d.e. >95%, only one diastereomer detectable by ^{31}P-NMR spectroscopy. – IR (neat): $\tilde{\nu}$ = 2120 (N≡C), 1260 (P=O), 1020 cm^{-1} (P–O). – ^1H NMR ($CDCl_3$): δ = 1.35 (dt; $J_{H/H}$ = 7 Hz, $J_{P/H}$ = 1 Hz; 6H, OCH_2CH_3), 1.40–2.20 (m; 10H, aliph. H), 3.95–4.35 (m; 4H, OCH_2CH_3). – ^{13}P NMR ($CDCl_3$): δ = 18.39.

$C_{12}H_{20}NO_3P$ (257.3) Calcd. C 56.02 H 7.84
Found C 55.83 H 7.84

Diethyl 1-Amino-1-cyclopropylphosphonates rac-**6**. – *General Procedure:* A solution of concentrated hydrochloric acid (0.7 ml, 4.5 mmol) in methanol (20 ml) was added with stirring to the diethyl 1-isocyano-1-cyclopropylphosphonates *rac*-**5a–c** (3.0 mmol), and stirring was continued at room temp. for 48 h. The organic solvents were removed in vacuo and water (6 ml) and then a saturated $NaHCO_3$ solution were added to the residue until pH = 7. The mixture was extracted with three portions of $CHCl_3$ (20 ml each), and the combined organic layers were dried with $MgSO_4$. The solvent was removed in vacuo, and the crude products *rac*-**6** were purified by flash chromatography (silica gel, 20 g; diethyl ether/methanol, 20:1).

Diethyl (1a,2β)-1-Amino-2-methyl-1-cyclopropylphosphonate (*rac*-**6a**): 0.65 g (3.0 mmol) of *rac*-**5a** was used to yield 0.48 g (77%) of *rac*-**6a**; R_f = 0.45; d.e. >95%, only one diastereomer detectable by ^{31}P-NMR spectroscopy. – IR (neat): $\tilde{\nu}$ = 3600–3200 (NH_2), 3070 (cyclopropyl C–H), 1230 (P=O), 1030 cm^{-1} (P–O). – ^1H NMR ($CDCl_3$): δ = 0.30–0.60 (m; 1H, cyclopropyl H), 1.10–1.50 (m; 5H, cyclopropyl H and CH_3), 1.36 (t, J = 7 Hz; 6H, OCH_2CH_3), 1.64 (s; 2H, NH_2), 3.95–4.30 (m; 4H, OCH_2CH_3). – ^{31}P NMR ($CDCl_3$): δ = 29.72.

$C_8H_{18}NO_3P$ (207.2) Calcd. C 46.37 H 8.76
Found C 46.40 H 8.87

Diethyl (1a,2β)-1-Amino-2-ethyl-1-cyclopropylphosphonate (*rac*-**6b**): 0.69 g (3.0 mmol) of *rac*-**5b** was used to yield 0.52 g (78%) of *rac*-**6b**; R_f = 0.43; d.e. >95%, only one diastereomer detectable by ^{31}P-NMR spectroscopy. – IR (neat): $\tilde{\nu}$ = 3600–3200 (NH_2), 3080 (cyclopropyl C–H), 1240 (P=O), 1030 cm^{-1} (P–O). – ^1H NMR ($CDCl_3$): δ = 0.40–0.60 (m; 1H, cyclopropyl H), 1.02 (t, J = 6 Hz; 3H, CH_3), 1.34 (t; J = 7 Hz; 6H, OCH_2CH_3), 1.10–1.75 (m; 4H, CH_2), 1.60 (s; 2H, NH_2), 3.90–4.30 (m; 4H, OCH_2CH_3). – ^{31}P NMR ($CDCl_3$): δ = 29.64.

$C_9H_{20}NO_3P$ (221.2) Calcd. C 48.86 H 9.11
Found C 48.67 H 9.10

Diethyl (1a,6a,7a)-7-Aminobicyclo[4.1.0]hept-7-ylphosphonate (*rac*-**6c**): 0.77 g (3.0 mmol) of *rac*-**5c** was used to yield 0.54 g (73%) of *rac*-**6c**; R_f = 0.48; d.e. >95%, only one diastereomer detectable by ^{31}P-NMR spectroscopy. – IR (neat): $\tilde{\nu}$ = 3600–3200 (NH_2), 1240 (P=O), 1020 cm^{-1} (P–O). – ^1H NMR ($CDCl_3$): δ = 1.30 (t, J = 7 Hz; 6H, OCH_2CH_3), 1.35 (s; 2H, NH_2), 1.20–2.10 (m; 10H, aliph. H), 3.85–4.25 (m; 4H, OCH_2CH_3). – ^{31}P NMR ($CDCl_3$): δ = 30.30.

$C_{11}H_{22}NO_3P$ (254.3) Calcd. C 53.43 H 8.97
Found C 53.55 H 8.91

1-Amino-1-cyclopropylphosphonic Acids rac-**7**. – *General Procedure:* Trimethylsilyl iodide (1.2 g, 6.0 mmol) was added dropwise at 0°C with stirring to a solution of the diethyl 1-amino-1-cyclopropylphosphonates *rac*-**6** (2.0 mmol) in dichloromethane (20 ml), and stirring was continued at room temp. for 30 min. Organic solvents were removed in vacuo, and a mixture of ethanol (10 ml) and propylene oxide (1 ml) was added with stirring. After the precipitation was complete, the analytically pure aminophosphonic acids *rac*-**7** were filtered off.

(1a,2β)-1-Amino-2-methyl-1-cyclopropylphosphonic Acid (rac-**7a**): 0.41 g (2.0 mmol) of the ester *rac*-**6a** was used to yield 0.26 g (86%) of *rac*-**7a**. M.p. 224–225°C (decomp.); d.e. >95%, only one diastereomer detectable by ^{13}C- and ^{31}P-NMR spectroscopy. – IR (KBr): $\tilde{\nu}$ = 3600–2200 (OH and NH_3^+), 1170 (P=O), 1080 cm^{-1} (P–O). – ^1H NMR (D_2O, pH = 4): δ = 0.58–0.80 (m; 1H, cyclopropyl H), 1.02–1.60 (m; 5H, cyclopropyl H and CH_3). – ^{13}C NMR (D_2O/NaOD, pH = 7): δ = 17.52 (2-CH_3), 20.71 (C-2), 22.42 (d, J = 2 Hz; C-3), 41.14 (d, J = 181.2 Hz; C-1). – ^{31}P NMR (D_2O, pH = 4): δ = 13.75 ($^3J_{P/cis\text{-}2\text{-}H}$ and $^3J_{P/cis\text{-}3\text{-}H}$ = 11.4 Hz, $^3J_{P/trans\text{-}3\text{-}H}$ = 5.9 Hz).

$C_4H_{10}NO_3P$ (151.1) Calcd. C 31.80 H 6.67
Found C 31.95 H 6.61

(1a,2β)-1-Amino-2-ethyl-1-cyclopropylphosphonic Acid (*rac*-**7b**): 0.44 g (2.0 mmol) of the ester *rac*-**6b** was used to yield 0.30 g (90%) of *rac*-**7b**. – M.p. 231–233°C (decomp.); d.e. >95%, only one diastereomer detectable by ^{13}C- and ^{31}P-NMR spectroscopy. – IR (KBr): $\tilde{\nu}$ = 3600–2200 (OH and NH_3^+), 1180 (P=O), 1090 cm^{-1} (P–O). – ^1H NMR (D_2O, pH = 4): δ = 0.60–0.85 (m; 1H, cyclopropyl H), 0.97 (t, J = 7 Hz; 3H, CH_3), 1.08–1.62 (m; 4H, aliph. CH_2). – ^{13}C NMR (D_2O, pH = 4): δ = 13.94 (CH_3), 15.79 (d, J = 2.2 Hz; C-3), 20.85 (CH_2), 23.28 (C-2), 34.79 (d, J = 192.4 Hz; C-1). – ^{31}P NMR (D_2O, pH = 4): δ = 13.59.

$C_5H_{12}NO_3P$ (165.1) Calcd. C 36.37 H 7.32
Found C 36.28 H 7.30

(1a,6a,7a)-7-Aminobicyclo[4.1.0]hept-7-ylphosphonic Acid (*rac*-**7c**): 0.49 g (2.0 mmol) of the ester *rac*-**6c** was used to yield 0.33 g (87%) of *rac*-**7c**. M.p. 205–206°C (decomp.); d.e. >95%, only one diastereomer detectable by ^{13}C- and ^{31}P-NMR spectroscopy. – IR (KBr): $\tilde{\nu}$ = 3600–2200 (OH and NH_3^+), 1170 (P=O), 1060 cm^{-1} (P–O). – ^1H NMR (D_2O/NaOD, pH = 8): δ = 0.75–2.25 (m; aliph. H). – ^{13}C NMR (D_2O/NaOD, pH = 7): δ = 21.69 (d, J = 1.1 Hz; CH), 22.99 (d, J = 1.6 Hz; CH_2), 26.97 (d, J = 0.8 Hz; CH_2), 44.23 (d, J = 178.9 Hz; C-7). – ^{31}P NMR (D_2O/NaOD, pH = 7): δ = 14.23.

$C_7H_{14}NO_3P$ (191.2) Calcd. C 43.98 H 7.38
Found C 43.89 H 7.41

8-Ethoxy-9-isocyano-7-oxa-8-phosphabicyclo[4.3.0]nonan-8-one (*rac*-**9a**): The crude alcohol *rac*-**3c**, which was obtained from 2.66 g (15.0 mmol) of diethyl isocyanomethylphosphonate (**1**), was heated at 120°C for 30 min. The resulting crude bicyclic *rac*-**9a** was purified by flash chromatography (silica gel, 70 g; ethyl acetate) to yield 1.38 g (40%, based on **1**) of *rac*-**9a**; R_f = 0.80; d.e. 76%, after one recrystallization from diethyl ether/petroleum ether diastereomerically pure according to ^{31}P-NMR spectroscopical analysis. – M.p. 117°C. – IR (KBr): $\tilde{\nu}$ = 2130 cm^{-1} (N≡C). – ^{1}H NMR ($CDCl_3$): δ = 1.40 (t, *J* = 7 Hz, 3H, OCH_2CH_3), 1.10–2.40 (m; 9H, aliph. H), 3.41–3.81 (m; 2H, CH–O and CH–N≡C), 4.10–4.21 (m; 2H OCH_2CH_3). – ^{31}P NMR ($CDCl_3$): δ = 28.24.

$C_{10}H_{16}NO_3P$ (229.2) Calcd. C 52.40 H 7.04
Found C 52.44 H 6.96

2-Ethoxy-3-isocyano-4,5-dimethyl-1,2-oxaphospholan-2-one (*rac*-**9b**): The crude alcohol *rac*-**3d**, which was obtained from 2.66 g (15.0 mmol) of diethyl isocyanomethylphosphonate (**1**), was heated at 80°C for 30 min. The resulting crude *rac*-**9b** was purified by flash chromatography (silica gel, 70 g; ethyl acetate) to yield 1.28 g (42%, based on **1**) of *rac*-**9b**; R_f = 0.75; d.e. 68%, determined by ^{31}P-NMR spectroscopy. – IR (neat): $\tilde{\nu}$ = 2140 cm^{-1} (N≡C). – ^{1}H NMR ($CDCl_3$): δ = 1.25 (d, *J* = 6 Hz, 3H, 5-CH_3), 1.30–1.60 (m; 6H, OCH_2CH_3 and 4-CH_3), 2.25–2.55 (m; 1H 4-H), 3.59 (dd, $J_{H/H}$ = 11.5 Hz, $J_{P/H}$ = 14 Hz; 1H, CH–N≡C), 3.80–4.15 (m; 1H, 5-H), 4.15–4.50 (m: 2H, OCH_2CH_3). – ^{31}P NMR ($CDCl_3$): δ = 25.27 (major diastereomer), 26.83 (minor diastereomer).

$C_8H_{14}NO_3P$ (203.2) Calcd. C 47.29 H 6.95
Found C 47.04 H 6.86

Diethyl 1-Isocyano-1-cycloalkylphosphonates **11**. – *General Procedure:* To a stirred solution of 0.89 g (5.0 mmol) of diethyl isocyanomethylphosphonate (**1**) in dichloromethane (20 ml), potassium *tert*-pentoxide (12.0 mmol, 6.5 ml of a 1.8 N solution in toluene) was added dropwise with stirring at –70°C, and stirring was continued at –70°C for 15 min. A solution of the dibromoalkane **10** (5.0 mmol) in dichloromethane (3 ml) was added dropwise, and stirring was continued at –70°C for 30 min and at room temp. for 4 h. Water (15 ml) was added, and the aqueous layer was extracted twice with dichloromethane (10 ml each). The combined organic layers were dried with $MgSO_4$, the solvent was removed in vacuo, and the crude products **11** were purified by flash chromatography (silica gel, 70 g; diethyl ether/methanol, 100:1).

Diethyl 1-Isocyano-1-cyclopentylphosphonate (**11a**): 0.89 g (5.0 mmol) of diethyl isocyanomethylphosphonate (**1**) and 1.08 g (5.0 mmol) of 1,4-dibromobutane (**10a**) were used to yield 0.69 g (60%) of **11a**; R_f = 0.42. – IR (neat): $\tilde{\nu}$ = 2120 (N≡C), 1260 (P=O), 1020 cm^{-1} (P–O). – ^{1}H NMR ($CDCl_3$): δ = 1.37 (dt, $J_{H/H}$ = 7 Hz, $J_{P/H}$ = 1 Hz; 6H,OCH_2CH_3), 1.60–2.40 (m; 8H, aliph. H), 4.00–4.45 (m: 4H, OCH_2CH_3). – ^{13}C NMR ($CDCl_3$): δ = 16.09 (d, *J* = 5.5 Hz; OCH_2CH_3), 23.49 (d, *J* = 10.9 Hz; CH_2), 36.81 (d, *J* = 1.4 Hz; CH_2), 62.30 (d, *J* = 160 Hz; C-1), 63.59 (d, *J* = 7.3 Hz; OCH_2CH_3), 157.52 (N≡C). – ^{31}P NMR ($CDCl_3$): δ = 20.49.

$C_{10}H_{18}NO_3P$ (231.2) Calcd. C 51.94 H 7.85
Found C 51.77 H 7.74

Diethyl 1-Isocyano-1-cyclohexylphosphonate (**11b**): 0.89 g (5.0 mmol) of diethyl isocyanomethylphosphonate (**1**) and 1.15 g (5.0 mmol) of 1,4-dibromopentane (**10b**) were used to yield 0.76 g (62%) of **11b**; R_f = 0.39. – IR (neat): $\tilde{\nu}$ = 2120 (N≡C), 1250 (P=O), 1020 cm^{-1} (P–O). – ^{1}H NMR ($CDCl_3$): δ = 1.40 (t, *J* = 7 Hz, 6H, OCH_2CH_3), 1.40–2.20 (m; 10H, aliph. H), 4.10–4.40 (m: 4H, OCH_2CH_3). – ^{13}C NMR ($CDCl_3$): δ = 15.94 (d, *J* = 5.5 Hz; OCH_2CH_3), 19.72 (d, *J* = 10.5 Hz; CH_2), 24.02 (d, *J* = 1.1 Hz; CH_2), 30.64 (d, *J* = 1.9 Hz; CH_2), 57.50 (d, *J* = 160 Hz; C-1), 63.49 (d, *J* = 7.3 Hz; OCH_2CH_3), 157.81 (N≡C). – ^{31}P NMR ($CDCl_3$): δ = 19.58.

$C_{11}H_{20}NO_3P$ (245.3) Calcd. C 53.87 H 8.22
Found C 53.98 H 8.32

Diethyl 1-Isocyano-1-cycloheptylphosphonate (**11c**): 0.89 g (5.0 mmol) of diethyl isocyanomethylphosphonate (**1**) and 1.22 g (5.0 mmol) of 1,4-dibromohexane (**10c**) were used to yield 0.45 g (35%) of **11c**; R_f = 0.43. – IR (neat): $\tilde{\nu}$ = 2120 (N≡C), 1250 (P=O), 1020 cm^{-1} (P–O). – ^{1}H NMR ($CDCl_3$): δ = 1.35 (t, *J* = 7 Hz, 6H, OCH_2CH_3), 0.80–2.20 (m; 12H, aliph. H), 4.05–4.40 (m: 4H, OCH_2CH_3). – ^{13}C NMR ($CDCl_3$): δ = 16.49 (d, *J* = 5.5 Hz; OCH_2CH_3), 22.28 (d, *J* = 11.2 Hz; CH_2), 27.76 (CH_2), 34.93 (d, *J* = 1.6 Hz; CH_2), 61.75 (d, *J* = 158 Hz; C-1), 64.19 (d, *J* = 7.6 Hz; OCH_2CH_3), 158.73 (N≡C). – ^{31}P NMR ($CDCl_3$): δ = 21.13.

$C_{12}H_{22}NO_3P$ (259.3) Calcd. C 55.59 H 8.55
Found C 55.51 H 8.48

[1] For Part V see: U. Groth, L. Richter, U. Schöllkopf, *Liebigs Ann. Chem.* **1992**, 903–909.

[2] [2a] C. Stammer, *Tetrahedron* **1990**, *46*, 2231–2254. – [2b] D. Aitken, J. Royer, H.-P. Husson, *J. Org. Chem.* **1990**, *55*, 2814–2820 – [2c] J. Salaun, J. Marguerite, B. Karkour, *J. Org. Chem.* **1990**, *55*, 4276–4281. – [2d] N. de Kimpe, P. Sulmon, P. Brunet, *J. Org. Chem.* **1990**, *55*, 5777–5784, and references cited therein.

[3] M. C. Pirrung, *J. Am. Chem. Soc.* **1983**, *105*, 7207–7209.

[4] Review on the synthesis of optically active α-aminophosphonic acids: B. Dhawan, D. Redmore, *Phosphorus Sulfur* **1987**, *32*, 119–144.

[5] [5a] K. Issleib, *Nachr. Chem. Tech.* **1987**, *35*, 1037–1042. – [5b] E. W. Petrillo, E. R. Spitzmiller, *Tetrahedron Lett.* **1979**, 4929–4930. – [5c] E. Gruszecka, M. Soroka, P. Mastalerz, *Pol. J. Chem.* **1979**, *53*, 937–939.

[6] R. Wolfenden, *Annu. Rev. Biophys. Bioeng.* **1976**, *5*, 271–306.

[7] P. A. Bartlett, W. B. Kezer, *J. Am. Chem. Soc.* **1984**, *106*, 4282–4283.

[8] [8a]N. E. Jacobsen, P. A. Bartlett, *J. Am. Chem. Soc.* **1981**, *103*, 654–657. – [8b] L. Kupczyk-Subotkowska, P. Mastalerz, *Int. J. Pept. Protein Res.* **1983**, *21*, 485–490.

[9] [9a] U. Groth, U. Schöllkopf, T. Tiller, *Liebigs Ann. Chem.* **1991**, 857–860. – [9b] U. Groth, W. Halfbrodt, U. Schöllkopf, *Liebigs Ann. Chem.* **1992**, 351–355.

[10] [10a]U. Groth, L. Richter, U. Schöllkopf, *Tetrahedron* **1992**, *48*, 117–122. – [10b] See ref.[1].

[11] [11a] E. L. Dulaney, *J. Antibiot.* **1970**, *23*, 567–568. – [11b] K. Prajer, J. Rachon, *Z. Chem.* **1975**, *15*, 209–215. – [11c] T. Kametani, *Heterocycles* **1981**, *16*, 1205–1242.

[12] P. L. Diel, L. Maier, *Phosphorus Sulfur* **1984**, *20*, 313–321.

[13] J. Rachon, U. Schöllkopf, T. Wintel, *Liebigs Ann. Chem.* **1981**, 709–718.

[14] H. Dolhaine, G. Hägele, *Phosphorus Sulfur* **1978**, *4*, 123–124.

[15] R. Gull, U. Schöllkopf, *Synthesis* **1985**, 1052–1055.

[256/92]