Synthesis of Enantiomerically Pure (1*S*,2*S*)-1-Aminocyclopropanephosphonic Acids from (2*S*)-Methylcyclopropanone Acetal

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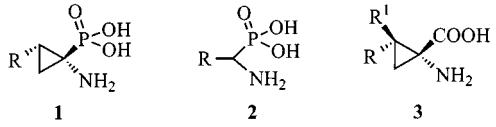
Keywords: Cyclopropanes / Amino acids / Phosphorus / Asymmetric synthesis / Phosphonates / Small ring systems

A one-pot reaction of methylcyclopropanone acetal (2*S*)-**4b** with chiral amines and a trialkyl phosphite has been devised, by means of which the amino phosphonate esters **8** are obtained with excellent diastereoselectivities. Catalytic hydrogenolysis and hydrolysis of these phosphonates gives (1*S*,2*S*)-1-amino-2-methylcyclopropanephosphonic acid **1b** in good overall yield and with excellent enantiomeric excess.

Introduction

1-Aminophosphonic acids serve as important surrogates for 1-aminocarboxylic acids, the fundamental building blocks of peptides and proteins. In the last few years, 1-aminocyclopropanecarboxylic acid (ACC) and its derivatives have attracted particular attention owing to their biological activities.[1] The phosphonic acid analogues of α-amino acids are finding increasing interest[2] by virtue of the fact that, due to the tetrahedral structure of the phosphonic acid moiety, they act as "transition-state analogues".[3] Thus, several α-aminophosphonic acids are known to act as enzyme inhibitors[2,4] (glutamine synthetase, neutral endopeptidase, etc.[5,6]), herbicides (glyphosate), and as antibacterial agents (alafosfalin),[7] fungicides, plant growth regulators, etc.

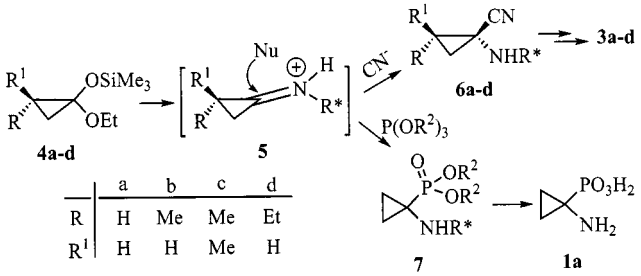
In spite of this broad spectrum of biological activities, the aminophosphonic acids **1** have not received the same attention as the acyclic aminophosphonic acids **2** and aminocyclopropanecarboxylic acids **3** (Scheme 1).



Scheme 1

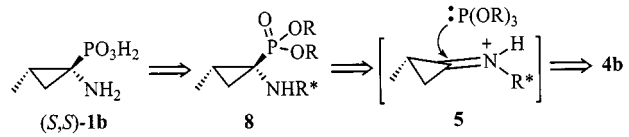
As far as we are aware, only a few methods for the synthesis of compounds of this class have been described. These methods involve a double alkylation of aminomethyl phosphonate anion equivalents with 1,2-dibromomethane,[8,9] or of the diethyl isocyanomethyl phosphonate anion with epoxides,[10a] require many steps,[10b] and only very rarely furnish optically active products.[10b,10c]

We have previously reported simple and convenient syntheses of 1-aminocyclopropanecarboxylic acid **3a** (ACC: R = R′ = H),[11] (*S*)- and (*R*)-methanovalines **3c** (R = R′ = Me),[12a] *allo*-norcoronamic acids **3b** (R′ = H, R = CH_3), and *allo*-coronamic acids **3d** (R′ = H, R = Et)[12b] using an asymmetric Strecker reaction starting from alkylcyclopropanone acetal **4** and proceeding via the aminonitrile **6**. We have recently applied the same methodology for the preparation of 1-aminocyclopropanephosphonic acid **1a** (an ACC analogue) from cyclopropanone acetal **4a** in three steps via the amino phosphonate **7**. The product was obtained in good overall yield (Scheme 2).[13]



Scheme 2

In order to obtain alkylaminophosphonic acids **1b** (analogues of **3b**) through the corresponding amino phosphonates **8**, we decided to study the asymmetric addition of phosphites to cyclopropanone acetal (2*S*)-**4b** in the presence of various amines. These reactions involve the iminium species **5** as intermediates. Such well-known additions of di- or trialkyl phosphite derivatives to imines[14] or oxazolines[15] have been developed for the synthesis of α-amino phosphonates (Scheme 3).



Scheme 3

Synthesis of 1-Amino-2-methylcyclopropane Phosphonates

The cyclopropanone acetal (2*S*)-**4b** was obtained in two steps from commercially available methyl (*S*)-3-hydroxy-2-

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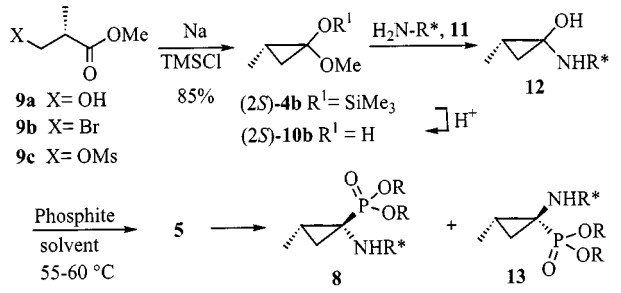
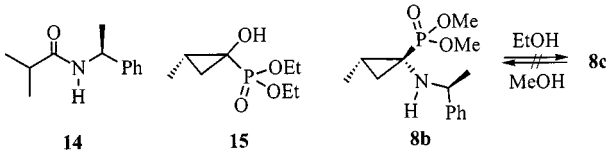
methylpropionate **9a**. The corresponding bromide (+)-**9b**, formed by reaction of **9a** with Ph_3P/CBr_4 [16a] or by treatment of mesylate **9c** with NaBr/acetone,[16b] was found to undergo a sodium-induced cyclization in the presence of Me_3SiCl under sonication at room temperature, thereby affording the desired acetal (2*S*)-**4b**. Subsequent methanolysis of the latter afforded the hemiacetal **10b** in quantitative yield (Scheme 4).[17]



Scheme 4

The reactions were carried out using a one-pot procedure. The hemiacetal **10b**, generated in situ from the acetal (2*S*)-**4b** by alcoholysis in the presence of a catalytic amount of an acid (TMSCl or AcOH),[18] reacted with amines **11** to give the aminols **12**. Under the acidic conditions, the latter were converted into the iminium intermediates **5**, which then underwent phosphite addition to furnish diastereoisomeric amino phosphonates **8** and **13** (Scheme 4). Our results are summarized in Table 1.

Thus, reactions of the hemiacetal **10b** under the conditions of Procedure A [55 °C in ROH in the presence of benzylamine (**11a**·HCl) or (*S*)-α-methylbenzylamine (**11b**·HCl) and trialkyl phosphite] gave the amino phosphonates **8a−c** and **13a−c** in yields of 48−80% as mixtures of diastereoisomers in an 88:12 ratio (entries 1−4). Furthermore, we were delighted to find that treatment of the acetal (2*S*)-**4b** according to Procedure B [in the presence of (*S*)-α-methylbenzylamine (**11b**) and 4 equiv. of AcOH[19] in ethanol] afforded the amino phosphonates **8c** and **13c** in 82% yield as a mixture of diastereoisomers in an 87:13 ratio (entries 5−9 compared to entries 1−4). Inversion of the absolute configuration of the amine **11b** had no effect on the selectivity (entries 7 and 8). Under other conditions investigated, no detectable products were obtained (entries 10 and 11). In further experiments, only the ring-opened amide **14** (7% yield; entry 12) or the hydroxy phosphonate intermediate **15** (70%) as an 80:20 *trans*/*cis* mixture (entry 13) were obtained (Scheme 5).



Scheme 5

It is well known[20] that on heating triethyl phosphite in methanol some trimethyl phosphite is produced. This equilibrium prohibited both the transformation of **8b** into **8c** by heating in EtOH at 55 °C and the transformation of **8c** into **8b** by heating in MeOH (Scheme 5). However, after increased reaction times, more ring-opened amide **14** was formed from the hydroxyamine intermediate **13** (2−8% yield, Table 1, entries 1−4).

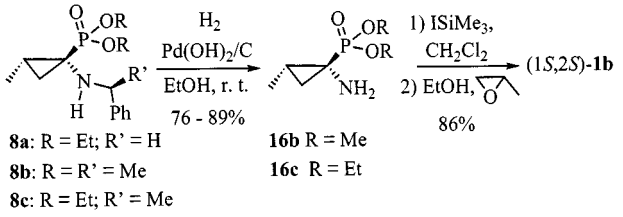
The major phosphonates **8a−c** could easily be separated from the minor diastereoisomers **13a−c** by chromatography on silica gel. Subsequent hydrogenolysis of **8a−c** in the presence of a catalytic amount of Pearlman's catalyst [20% $Pd(OH)_2$] in ethanol afforded the free amino phosphonates **16b**,**c** in yields of 76−89%. Treatment of the latter with trimethylsilyl iodide in dichloromethane, followed by the addition of propylene oxide in ethanol, led to enantiomerically pure (1*S*,2*S*)-(+)-1-amino-2-methylcyclopropanephosphonic acid **1b** (86% yield, m.p. 220−222 °C (dec.) [ref.[10a]: m.p. 224−225 °C (dec.) for racemic **1b**]; $[\alpha]_D^{20} = +34$ (c = 1, H_2O) (Scheme 6).

The enantiomeric excess of product **1b**, as confirmed by ^{19}F and ^{31}P NMR analysis of the corresponding Mosher amide,[21] was found to be 98%. The same value (*ee* = 98%) was determined for the corresponding phosphate **16** using a chiral column (GC, Cydex B, 110 °C, 1 bar).

Table 1. Preparation of amino phosphonates **8** and **13** from acetal (2*S*)-**4b**

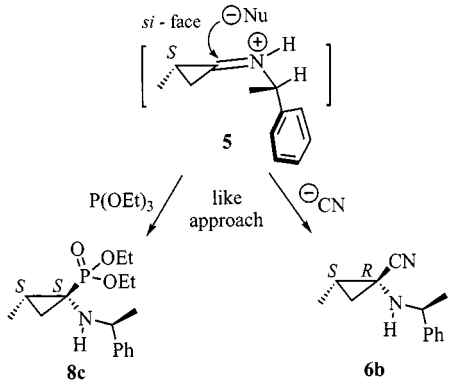
Entry	Amine, H_2N-R^* R*	**11**·H^+	Procedure, Conditions[a]	Time (h)	Yld. (%)	Product (*ds* ratio)
1	CH_2Ph	**11a**	A, $P(OEt)_3$	140	62	**8a**:**13a** (88:12)
2	$CH(CH_3)Ph$	(*S*)-**11b**	A, $P(OMe)_3$ [b]	65	48	**8b**:**13b** (73:27)
3	$CH(CH_3)Ph$	(*S*)-**11b**	A, $P(OEt)_3$	68	80	**8c**:**13c** (87:13)
4	$CH(CH_3)Ph$	(*S*)-**11b**	C, $P(OEt)_3$ [c]	65	54	**8c**:**13c** (82:18)
5	CH_2Ph	**11a**	B, $P(OEt)_3$	22	69	**8a**:**13a** (86:14)
6	$CH(CH_3)Ph$	(*S*)-**11b**	B, $P(OMe)_3$ [b]	21	67	**8b**:**13b** (80:20)
7	$CH(CH_3)Ph$	(*S*)-**11b**	B, $P(OEt)_3$	22	82	**8c**:**13c** (87:13)
8	$CH(CH_3)Ph$	(*R*)-**11b**	B, $P(OEt)_3$	22	82	**8d**:**13d** (87:13)
9	$CH(CH_3)Naph$	(*R*)-**11c**	B, $P(OEt)_3$	20	60	**8e**:**13e** (86:14)
10	$CH(CH_3)Ph$	(*S*)-**11b**	A, $P(OPh)_3$ [d]	160	nr[e]	
11	$CH(CH_3)Ph$	(*S*)-**11b**	A, $HPO(OMe)_2$	166	nr[e]	
12	$CH(CH_3)Ph$	(*S*)-**11b**	B, $P(OiPr)_3$ [f]	46	–	**14** (7%)
13	SO_2-*p*-Tol	**11d**	B, $P(OEt)_3$	46	–	**15** (70%)

[a] Procedure A: reactions carried out with amine·HCl in EtOH at 55 °C; Procedure B: reactions carried out with amine in the presence of 4 equiv. of AcOH at 55 °C; Procedure C: reaction carried out under sonication – [b] In MeOH. – [c] Reaction carried out under sonication. – [d] In phenol. – [e] No reaction. [f] In *i*-propanol. –



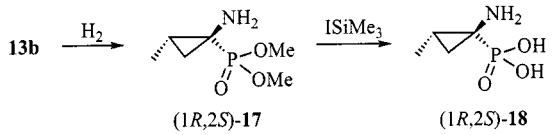
Scheme 6

We have previously reported[12b] that nucleophilic attack of the cyanide anion on the iminium intermediate **5** takes place from the less hindered face (*si*-face) opposite the methyl group on the cyclopropane with a relative *like* approach,[22] thereby affording **6b** as the major product. Similarly, attack of phosphite on the same iminium species **5** with *like* approach can be expected to give **8c** as the major product (Scheme 7).



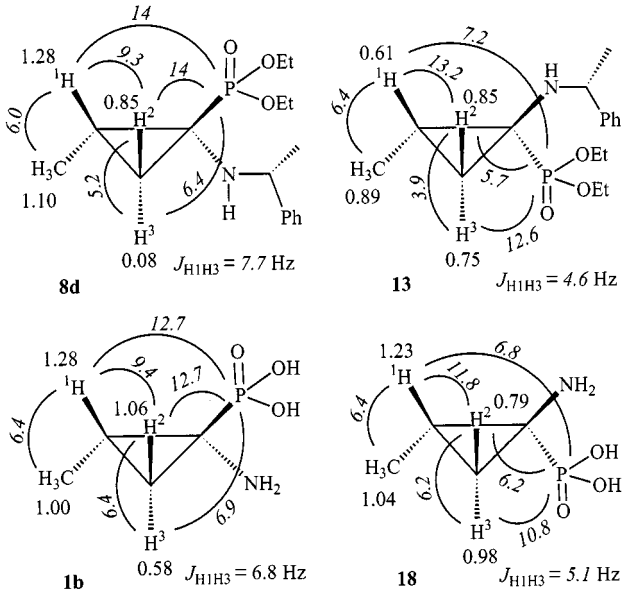
Scheme 7

To confirm the configuration of the product, we studied the proton chemical shifts and coupling constants of the resulting phosphonates **8** and **13**. Thus, in the ^{1}H NMR spectrum, the H^3 proton of **8d** resonates at $\delta = 0.08$, whereas in **13d** it appears at $\delta = 0.75$ due to the deshielding effect of the phosphonate in a *syn* configuration. Such a deshielding effect is also in evidence for the H^3 proton in the free amine **1b** ($\delta = 0.58$) as compared to that in **18** ($\delta = 0.98$), which was prepared from the minor diastereomer **13b** via **17** (Scheme 8).



Scheme 8

Moreover, the ^{1}H-^{31}P coupling constants were measured as $^3J_{P/cis\text{-}2\text{-}H} = {}^3J_{P/cis\text{-}3\text{-}H} = 12-14$ Hz and $^3J_{P/trans\text{-}3\text{-}H} = 4.9-7.2$ Hz for all the *trans*-amino phosphonates **8**. These values are in agreement with those reported by Schöllkopf[10a] for similar products ($^3J_{PH\text{-}cis} = 11.7$ Hz, $^3J_{PH\text{-}trans} = 5.9$ Hz). Moreover, Dolhaine and Hägele[23] have reported values of $^3J_{PH\text{-}cis} = 12.70$ Hz and $^3J_{PH\text{-}trans} = 7.12$ Hz for dimethyl 1-bromo-1-cyclopropane phosphonate. By analogy, we assume that the configuration in the present case is *trans* and consequently the absolute configuration at C-1 of the amino phosphonate must be (*S*). In agreement with the proposed *trans* attack of the phosphite on the iminium intermediate **5** with a *like* approach, the (*S*,*S*)-amino phosphonates **8** are generated as the major products. These conclusions were corroborated by the ^{13}C NMR spectra, where coupling constants between P and CH_3-*cis* of $^3J_{PC} = 3.4$ Hz were measured (Scheme 9).



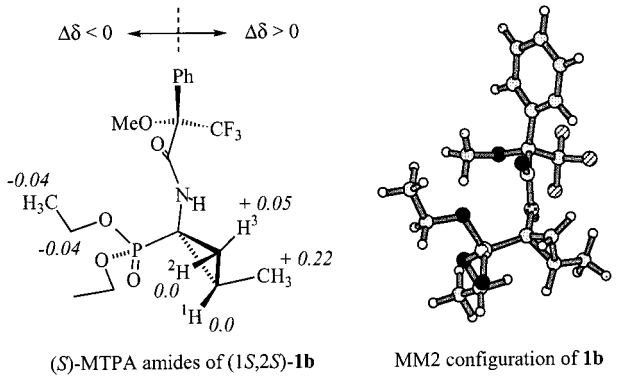
Scheme 9. Chemical shifts and coupling constants (*in italics*)

Unfortunately, we were unable to confirm these conclusions by X-ray crystallographic analyses since the compounds could not be obtained in crystalline form.

On the other hand, following Mosher derivatization,[24] the resulting (*R*)- and (*S*)-methoxy-α-trifluoromethylphenylacetic acid amides (MTPA) showed positive chemical shift differences ($\Delta\delta = \delta_S - \delta_R$) for the 3-$H^3$ and 2-CH_3 protons located on the right side of the MTPA plane and negative values for the O−CH_2 and CH_3 protons located on the left side of the phosphonates. The protons 3-H^2 and 2-H^1 were found to reside virtually in the plane of the MTPA moiety, thus their δ values were nearly equal ($\Delta\delta \approx 0$ ppm). Furthermore, the Δδ values were found to be proportional to the distance between the protons and the MTPA moiety. The optimized structure obtained by molecular mechanics (MM2) calculations on the (*S*)-MTPA amide of (1*S*,2*S*)-**1b** was wholly consistent with these results (Figure 1).

This absolute configuration was also confirmed by ^{31}P NMR and ^{19}F NMR spectroscopy.[25] A negative value ($\Delta\delta = -0.03$) was calculated for the phosphorus (left side), while a positive value ($\Delta\delta = \delta_S - \delta_R = 0.17$) was found for the fluorine (right side), indicating an (*S*) configuration at C-1.

In summary, we have developed an easy and efficient three-step synthesis of enantiomerically pure 1-amino-2-methylcyclopropanephosphonic acid (1*S*,2*S*)-**1b** from readily available methylcyclopropanone acetal (2*S*)-**4b**. The desired product has been obtained in good yield and with high enantiomeric excess. This method involves highly diastereoselective *trans* attack of the iminium intermediate **5**. Investi-



(*S*)-MTPA amides of (1*S*,2*S*)-**1b** MM2 configuration of **1b**

Figure 1. $\Delta\delta = (\delta_S - \delta_R)$ for (*R*)- and (*S*)-MTPA amides of **1b** by ^{1}H NMR spectroscopy at 250 MHz

gations into the synthesis of other cyclic aminophosphonic acids and efforts to improve the diastereoselective phosphite approach are currently in progress in our laboratory.

Experimental Section

General: Except where otherwise indicated, all reactions were carried out under argon with magnetic stirring. − Di- and triethyl phosphite were distilled at reduced pressure and stored under argon. − R_f values refer to TLC on 0.25 mm silica gel plates (Merck F_{254}). − Flash chromatography (FC) was performed on silica gel 60 (0.040−0.063 mm). − Yields refer to chromatographically and spectroscopically pure compounds, except where noted otherwise. − IR spectra were recorded on a Perkin−Elmer 682 spectrophotometer. − Melting points were determined on a Mettler FP51 capillary melting point apparatus and are uncorrected. − ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 250 spectrometer with samples in $CDCl_3$ or D_2O with the solvent signal as an internal standard (δ = 7.24 and 4.60, respectively). ^{31}P NMR spectra were recorded at 101.25 MHz and chemical shifts are quoted relative to internal 85% H_3PO_4 (δ = 0). ^{19}F NMR spectra were recorded at 235.35 MHz and δ_F values are quoted relative to internal CF_3COOH (δ_δ = −77). − Mass spectra were recorded on a Nermag R-10 coupled with an OK 1 DP 125 gas chromatograph. − High-resolution mass spectra were recorded on a MAT 95 S. − Specific rotations were measured at 20 °C on a Perkin−Elmer 341 polarimeter. − Enantiomeric excesses were determined on a Fisons 9130 GC equipped with a Cydex B (SGE) chiral column (25 m, 110 °C, 1 bar). − Elemental analyses were performed by the Microanalytical Service Laboratory of the CNRS at Gif-sur-Yvette (France).

General Procedure A: To a solution of 2-methylcyclopropanone acetal (2*S*)-**4b**[17] (870 mg, 5.00 mmol) in EtOH (10 mL) was added one drop of TMSCl. After stirring for 5 min (complete formation of hemiacetal **10b**), (*R*)-α-methylbenzylamine (*R*)-**11b**·HCl (1.18 g, 7.50 mmol) was added, followed by $P(OEt)_3$ (1.25 g, 1.31 mL, 7.50 mmol). The mixture was stirred and heated at 55 °C for 3−6 days. It was then concentrated in vacuo conc. aq. ammonia (2 mL) was added, and the resulting mixture was filtered through a 5 cm pad of silica gel eluting with diethyl ether (100 mL). The filtrate was concentrated in vacuo to give the crude phosphonates **8** and **13** as an 88:12 diastereoisomeric mixture. Purification by FC on silica gel (EtOAc/CH_2Cl_2, 2:8) gave pure (1*S*,2*S*)-**8**.

General Procedure B: To a solution of cyclopropanone acetal (2*S*)-**4b** (870 mg, 5.00 mmol) in EtOH (10 mL) was added one drop of TMSCl. After stirring for 5 min, (*R*)-α-methylbenzylamine (*R*)-**11b** (910 mg, 7.50 mmol), AcOH (1.2 mL, 3 equiv.), and $P(OEt)_3$ (1.25 g, 1.31 mL, 7.50 mmol) were added sequentially. The resulting mixture was stirred and heated at 55 °C for 22 h. Workup according to Procedure A furnished enantiomerically pure (1*S*,2*S*)-**8** after FC.

Diethyl (1*S*,2*S*)-1-(Benzylamino)-2-methylcyclopropanephosphonate (8a). − Procedure A: Reaction of chiral acetal (2*S*)-**4b** (525 mg, 3.00 mmol), TMSCl (cat. amt.), benzylamine·HCl (**11a**·HCl, 650 mg, 4.50 mmol), EtOH (10 mL), and $P(OEt)_3$ (500 mg, 3.60 mmol) for 6 days at 55 °C gave, after standard workup, 1.2 g of an 88:12 diastereomeric mixture of crude phosphonates **8a** and **13a**. Purification by FC (2 times) afforded 465 mg (52%) of (1*S*,2*S*)-**8a** as the major phosphonate and 90 mg (10%) as a mixture of **8a** and **13a** (in a 40:60 ratio).

(1*S*,2*S*)-8a, Major Isomer: $[\alpha]_D^{20}$ = +4.2 (*c* = 1, $CHCl_3$). − R_f = 0.44 (EtOAc/CH_2Cl_2, 15:85). − IR (neat): $\tilde{\nu}$ = 3684 cm^{-1} (NH), 3620 (NH), 1219 (P=O), 1045 (P−O). − ^{1}H NMR ($CDCl_3$): δ = 7.36−7.12 (m, 5 H), 4.16 (dq, $^2J_{PH}$ = 4.9 Hz, *J* = 7.3 Hz, 2 H), 4.12 (dq, $^2J_{PH}$ = 4.9 Hz, *J* = 7.3 Hz, 2 H), 3.96 (d, AB syst. $\Delta\nu_{AB}$ = 27.3 Hz, J_{AB} = 13.2 Hz, $^3J_{PH}$ = 2.4 Hz, 2 H_{Bzl}), 1.67 (br. s, NH), 1.56−1.35 (m, 1 H_{cycle}), 1.35 (t, *J* = 7.3 Hz, 3 H), 1.33 (t, *J* = 7.3 Hz, 3 H), 1.36−1.17 (m, 1 H_{cycle}), 1.25 (d, *J* = 5.9 Hz, 3 H), 0.52 (ddd, *J* = 4.9 Hz, *J* = 7.2 Hz, *J* = 7.3 Hz, 1 H_{cycle}). − ^{13}C NMR ($CDCl_3$): δ = [6 arom. C: 140.8 (s), 128.1 (2 C), 127.8 (2 C), 126.7 (1 C)], 61.7 (d, $^2J_{PC}$ = 6.2 Hz, 1 C), 61.6 (d, $^2J_{PC}$ = 6.2 Hz, 1 C), 51.7 (1 C), 36.5 (d, *J* = 200.6 Hz, C-1), 18.6 (d, $^2J_{PC}$ = 5.3 Hz, C-3), 18.3 (C-2), 16.5 (d, $^3J_{PC}$ = 2.8 Hz, 1 C), 16.4 (d, $^3J_{PC}$ = 2.8 Hz, 1 C), 11.6 (1 C). − ^{31}P NMR ($CDCl_3$): δ = 29.46. − MS (70 eV); *m*/*z* (%): 298 (6) [M^+ + 1], 297 (4) [M^+], 160 (36), 159 (34), *92* (100), 91 (72). − HRMS: *m*/*z* = 297.1493 (calcd. for $C_{15}H_{24}NO_3P$: 297.1493).

(1*R*,2*S*)-13a, Minor Isomer: R_f = 0.4 (EtOAc/CH_2Cl_2, 15:85). − ^{1}H NMR ($CDCl_3$): δ = 7.40−7.15 (m, 5 H), 4.17 (q, *J* = 6.9 Hz, 2 H), 4.14 (q, *J* = 6.9 Hz, 2 H), 4.20−4.05 (m, 1 H), 4.04 (dd, *J* = 2.5 Hz, *J* = 7.3 Hz, 1 H_{Bzl}), 3.91 (dd, *J* = 1.5 Hz, *J* = 7.3 Hz, 1 H_{Bzl}), 1.80 (br. s, 1 H), 1.36 (t, *J* = 6.9 Hz, 3 H), 1.35 (t, *J* = 6.9 Hz, 3 H), 1.31 (d, *J* = 5.9 Hz, 3 H), 1.40−1.10 (m, 2 H_{cycle}), 1.00 (m, 1 H_{cycle}).

Procedure B: Reaction of chiral acetal (2*S*)-**4b** (525 mg, 3.00 mmol), TMSCl (cat. amt.), benzylamine (480 mg, 4.50 mmol), EtOH (6 mL), AcOH (540 mg, 9.00 mmol), and $P(OEt)_3$ (750 mg, 4.50 mmol) for 22 h at 55 °C gave, after standard workup, 1.3 g of an 86:14 diastereomeric mixture of the crude phosphonates **8a** and **13a**. Purification by FC afforded 470 mg (53%) of (1*S*,2*S*)-**8a** as the major phosphonate and 140 mg (16%) as a mixture of **8a** and **13a**. The spectral data proved identical to those reported above.

Dimethyl (1*S*,2*S*,1′*S*)-2-Methyl-1-[(1′-methylbenzyl)amino]cyclopropane Phosphonate (8b). − Procedure B: Reaction of chiral acetal (2*S*)-**4b** (525 mg, 3.00 mmol), TMSCl (cat. amt.), α-methylbenzylamine (*S*)-**11b** (545 mg, 4.50 mmol), MeOH (6 mL), AcOH (540 mg, 9.00 mmol), and $P(OMe)_3$ (560 mg, 0.53 mL, 4.50 mmol) for 21 h at 55 °C gave, after standard workup, 1.5 g of an 80:20 diastereomeric mixture of the crude phosphonates **8b** and **13b**. Tedious purification by FC (2 times) afforded 425 mg (50%) of (1*S*,2*S*)-**8b** as the major phosphonate, along with 12% of the minor product (1*R*,2*S*)-**13b** and 145 mg (17%) as a mixture.

(1*S*,2*S*)-8b: R_f = 0.23 (EtOAc/CH_2Cl_2, 15:85). − IR (neat): $\tilde{\nu}$ = 3645 cm^{-1} (NH), 3470 (NH), 1245 (P=O), 1030 (P−O). − ^{1}H NMR ($CDCl_3$): δ = 7.40−7.13 (m, 5 H), 4.25 (dq, $^4J_{PH}$ = 3.2 Hz, *J* = 6.6 Hz, 1 H), 3.72 (d, $^3J_{PH}$ = 3.7 Hz, 3 H), 3.67 (d, $^3J_{PH}$ =

3.7 Hz, 3 H), 1.87 (br. s, NH), 1.50−1.15 (m, 2 H_{cycle}), 1.31 (d, J = 6.6 Hz, 3 H), 1.09 (d, J = 5.9 Hz, 3 H), 0.69 (ddd, $J_{PH\ trans}$ = 5.9 Hz, J = 8.1 Hz, J = 3.9 Hz, 1 H_{cycle}). − ^{13}C NMR ($CDCl_3$): δ = [6 arom. C: 146.9 (s), 128.2 (2 C), 126.8 (1 C), 126.6 (2 C)], 56.3 (1 C), 52.8 (d, $^2J_{PC}$ = 6.6 Hz, 1 C), 52.4 (d, $^2J_{PC}$ = 6.6 Hz, 1 C), 34.2 (d, $^1J_{PC}$ = 201.6 Hz, C-1), 23.6 (1 C), 19.6 (d, $^2J_{PC}$ = 2.3 Hz, C-3), 17.3 (d, $^4J_{PC}$ = 3.8 Hz, C-2), 11.8 (C-4). − ^{31}P NMR ($CDCl_3$): δ = 31.89 and 32.36 for the minor (1*R*,2*S*)-**13b**. − MS (70 eV): *m*/*z* (%) = 283 (1) [M^+], 173 (44), *105* (100), 104 (24), 79 (30). − HRMS: *m*/*z* = 283.1346 (calcd. for $C_{14}H_{22}NO_3P$: 283.1337).

Procedure A: Reaction of acetal **4b** (3 mmol) for 3 days with heating furnished 410 mg (48%) of a 73:27 diastereomeric mixture of phosphonates **8b** and **13b**, along with 35 mg (6%) of the ring-opened amide **14**.

Amide 14: R_f = 0.51 (EtOAc/CH_2Cl_2, 15:85). − IR (neat): $\tilde{\nu}$ = 3306 cm^{-1} (NH), 1645 (C=O), 1546, 1240. − ^{1}H NMR ($CDCl_3$): δ = 7.40−7.20 (m, 5 H), 5.68 (br. d, J = 6.9 Hz, 1 H_{amide}), 5.13 (dq, J = 6.9 Hz, J = 6.9 Hz, 1 H), 2.33 (sept., J = 6.9 Hz, 1 H), 1.46 (d, J = 6.9 Hz, 3 H), 1.15 (d, J = 6.9 Hz, 3 H), 1.12 (d, J = 6.9 Hz, 3 H).

Diethyl (1*S*,2*S*,1′*S*)-2-Methyl-1-[(1′-methylbenzyl)amino]cyclopropane Phosphonate (8c). − Procedure B: Reaction of chiral acetal (2*S*)-**4b** (870 mg, 5.00 mmol), TMSCl (cat. amt.), (*S*)-α-methylbenzylamine (*S*)-**11b** (910 mg, 7.50 mmol), EtOH (10 mL), AcOH (0.9 mL, 15.00 mmol), and $P(OEt)_3$ (1.25 g, 1.31 mL, 7.50 mmol) for 22 h at 55 °C gave, after standard workup, 2.5 g of an 87:13 diastereomeric mixture of the crude phosphonates **8c** and **13c**. Purification by FC (2 times) afforded 795 mg (51%) of (1*S*,2*S*)-**8c** as the major phosphonate and 480 mg (31%) as a mixture of **8c** and **13c**.

(1*S*,2*S*)-8c, Major Isomer: $[\alpha]_D^{20}$ = −17 (c = 1, $CHCl_3$). − R_f = 0.31 (EtOAc/CH_2Cl_2, 15:85). − IR (neat): $\tilde{\nu}$ = 3472 cm^{-1}, 3312, 1243 (P=O), 1027 (P−O). − ^{1}H NMR ($CDCl_3$): δ = 7.40−7.10 (m, 5 H), 4.35 (dq, J = 6.8 Hz, $^4J_{PH}$ = 3.4 Hz, 1 H), 4.12 (dq, J = 7 Hz, $^3J_{PH}$ = 1 Hz, 2 H), 4.04 (dq, J = 7 Hz, $^3J_{PH}$ = 1 Hz, 2 H), 1.76 (br. s, 1 H, NH), 1.46−1.20 (m, 2 H_{cycle}), 1.31 (d, J = 6.8 Hz, 3 H), 1.30 (t, J = 7 Hz, 3 H), 1.28 (t, J = 7 Hz, 3 H), 1.08 (d, J = 5.8 Hz, 3 H), 0.67 (ddd, J_{PH} = 5.9 Hz, J = 3.9 Hz, J = 7.8 Hz, 1 H_{cycle}). − ^{13}C NMR ($CDCl_3$): δ = [6 arom. C: 147.0 (s), 128.1 (2 C), 126.8 (2 C), 126.7 (1 C)], 61.7 (d, $^2J_{PC}$ = 6.7 Hz, 1 C), 61.4 (d, $^2J_{PC}$ = 6.7 Hz, 1 C), 56.1 (1 C), 34.6 (d, $^1J_{PC}$ = 200 Hz, C-1), 23.3 (1 C), 19.7 (d, $^2J_{PC}$ = 2.9 Hz, C-3), 17.1 (d, J = 3.8 Hz, C-2), 16.5 (d, $^3J_{PC}$ = 5.7 Hz, 1 C), 16.35 (d, $^3J_{PC}$ = 5.7 Hz, 1 C), 11.8 (C-4). − ^{31}P NMR ($CDCl_3$): δ = 29.51. − MS (70 eV): *m*/*z* (%) = 311 (2) [M^+], 173 (84), 144 (37), 131 (24), *105* (100), 104 (28), 77 (23). − HRMS: *m*/*z* = 311.1649 (calcd. for $C_{16}H_{26}NO_3P$: 311.1650).

(1*R*,2*S*)-13c, Minor Isomer (from a Mixture): ^{1}H NMR ($CDCl_3$): δ = 7.40−7.10 (m, 5 H), 4.33 (dq, J = 7 Hz, $^4J_{PH}$ = 2.5 Hz, 1 H), 4.15 (dq, J = 7 Hz, $^3J_{PH}$ = 3 Hz, 2 H), 4.07 (dq, J = 7 Hz, $^3J_{PH}$ = 3 Hz, 2 H), 1.84 (br. s, NH), 1.50−1.15 (m, 12 H and 1 H_{cycle}), 1.00−0.90 (m, 1 H_{cycle}), 0.90−0.78 (m, 1 H_{cycle}).

Procedure A: Reaction of acetal **4b** (3 mmol) for 3 days with heating furnished 750 mg (80%) of an 87:13 diastereomeric mixture of pure phosphonates **8c** and **13c**, along with 28 mg (5%) of amide **14**.

Diethyl (1*S*,2*S*,1′*R*)-2-Methyl-1-[(1′-methylbenzyl)amino]cyclopropane Phosphonate (8d). − Procedure B: Reaction of chiral acetal **4b** (870 mg, 5.00 mmol), TMSCl (cat. amt.), (*R*)-α-methylbenzylamine (*R*)-**11b** (910 mg, 7.50 mmol), EtOH (10 mL), AcOH (0.9 mL, 15.00 mmol), and $P(OEt)_3$ (1.18 g, 7.50 mmol) for 22 h at 55−60 °C gave, after standard workup, 2.8 g of an 87:13 diastereomeric mixture of the crude phosphonates **8d** and **13d**. Purification by FC (2 times) afforded 1.01 g (65%) of (1*S*,2*S*)-**8d** as the major phosphonate, along with 108 mg (7%) of (1*R*,2*S*)-**13d** containing 10% of **8d** and 155 mg (10%) as a mixture of **8d** and **13d**.

(1*S*,2*S*)-8d, Major Isomer: $[\alpha]_D^{20}$ = +58 (c = 1, $CHCl_3$). − R_f = 0.3 (EtOAc/CH_2Cl_2, 15:85). − IR (neat): $\tilde{\nu}$ = 3500 cm^{-1} (NH), 1266 (P=O), 1070 (P−O). − ^{1}H NMR ($CDCl_3$): δ = 7.34−7.10 (m, 5 H), 4.29 (dq, $^4J_{PH}$ = 2.8 Hz, J = 6.7 Hz, 1 H), 4.14 (dq, $^3J_{PH}$ = 4.0 Hz, J = 6.7 Hz, 2 H), 4.10 (dq, $^3J_{PH}$ = 4.0 Hz, J = 6.7 Hz, 2 H), 1.92 (br. s, 1 H, NH), 1.33 (t, J = 6.7 Hz, 3 H), 1.31 (t, J = 6.7 Hz, 3 H), 1.28 (dddd, J_{cis} = 9.3 Hz, J_{trans} = 7.7 Hz, J = 6.0 Hz, $J_{PH\ cis}$ = 14 Hz, 1 H_{cycle}), 1.29 (d, J = 6.7 Hz, 3 H), 1.10 (d, J = 6.0 Hz, 2-CH_3), 0.85 (ddd, J = 14 Hz, J = 9.3 Hz, J = 5.2 Hz, 1 H_{cycle}), 0.08 (ddd, J = 7.7 Hz, J = 5.2 Hz, J_{PH} = 6.4 Hz, 1 H_{cycle}). − ^{13}C NMR ($CDCl_3$): δ = [6 arom. C: 147.4 (s), 128.1 (2 C), 127.0 (2 C), 126.6 (1 C)], 61.9 (d, $^2J_{PC}$ = 7.2 Hz, 1 C), 61.6 (d, $^2J_{PC}$ = 7.2 Hz, 1 C), 56.1 (1 C), 35.8 (d, $^1J_{PC}$ = 200.6 Hz, C-1), 25.4 (1 C), 17.7 (d, $^2J_{PC}$ = 4.8 Hz, C-2), 16.7 (d, $^2J_{PC}$ = 5.1 Hz, 1 C), 16.6 (d, $^2J_{PC}$ = 1.5 Hz, C-3), 16.5 (d, $^2J_{PC}$ = 5.1 Hz, 1 C), 11.9 (1 C). − ^{31}P NMR ($CDCl_3$): δ = 29.88. − MS (70 eV): *m*/*z* (%) = 312 (1) [M^+ + 1], 311 (2.5) [M^+], 173 (93), 172 (28), 144 (40), *105* (100), 104 (49), 103 (28). − HRMS: *m*/*z* = 311.1653 (calcd. for $C_{16}H_{26}NO_3P$: 311.1650). − $C_{16}H_{26}NO_3P$: (311.1650): calcd. C 61.72, H 8.42, N 4.50; found C 61.55, H 8.34, N 4.51.

(1*R*,2*S*)-13d, Minor Isomer: R_f = 0.28 (EtOAc/CH_2Cl_2, 15:85). − ^{1}H NMR ($CDCl_3$): δ = 7.40−7.10 (m, 5 H), 4.25 (dq, $^4J_{PH}$ = 2.5 Hz, J = 6.8 Hz, 1 H), 4.20−4.00 (m, 4 H), 2.05 (br. s, NH), 1.36 (t, J = 6.9 Hz, 3 H), 1.33 (t, J = 6.9 Hz, 3 H), 1.26 (d, J = 6.8 Hz, 3 H), 9.89 (d, J = 6.4 Hz, 3 H), 0.85 (ddd, $J_{PH\ trans}$ = 5.7 Hz, $J_{PH\ cis}$ = 13.2 Hz, J = 3.9 Hz, 1 H_{cycle}), 0.75 (ddd, $J_{PH\ cis}$ = 12.6 Hz, J = 4.6 Hz, J = 3.9 Hz, 1 H_{cycle}), 0.61 (dddd, $J_{PH\ trans}$ = 7.2 Hz, J_{cis} = 13.2 Hz, J_{trans} = 4.6 Hz, J = 6.4 Hz, 1 H_{cycle}).

Diethyl (1*S*,2*S*,1′*S*)-2-Methyl-1-[(1′-naphthylethyl)amino]cyclopropane Phosphonate (8e). − Procedure B: Reaction of chiral acetal **4b** (525 mg, 3.00 mmol), TMSCl (cat. amt.), (*R*)-1-(1-naphthyl)ethylamine (*R*)-**11c** (770 mg, 4.50 mmol), EtOH (6 mL), AcOH (0.72 mL, 12.00 mmol), and $P(OEt)_3$ (750 mg, 4.5 mmol) for 20 h at 55 °C gave, after standard workup, 2.0 g of an 86:14 diastereomeric mixture of the crude phosphonates **8e** and **13e**. Purification by FC (2 times) afforded 430 mg (40%) of (1*S*,2*S*)-**8e** as the major phosphonate and 215 mg (20%) as a mixture of **8e** and **13e**.

(1*S*,2*S*)-8e, Major Isomer: $[\alpha]_D^{20}$ = +79 (c = 1, $CHCl_3$). − R_f = 0.35 (EtOAc/CH_2Cl_2, 15:85). − IR (neat): $\tilde{\nu}$ = 3460 cm^{-1}, 3290, 1240 (P=O), 1026 (P−O). − ^{1}H NMR ($CDCl_3$): δ = 8.40−8.15 (m, 1 H), 7.80 (br. d, J = 8.0 Hz, 1 H), 7.69 (br. d, J = 8.0 Hz, 2 H), 7.57−7.33 (m, 3 H), 5.14 (m, 1 H, C*H*−N), 4.30−4.00 (m, 4 H), 1.89 (br. s, 1 H), 1.48 (d, J = 7.0 Hz, 3 H), 1.36 (t, J = 7.0 Hz, 3 H), 1.35 (t, J = 7.0 Hz, 3 H), 1.50−1.10 (m, 1 H_{cycle}), 1.19 (d, J = 6.0 Hz, 3 H, 2-CH_3), 0.86 (ddd, J = 5.0 Hz, J = 6.1 Hz, J_{cis} = 14.0, 1 H_{cycle}), 0.15 (m, 1 H_{cycle}). − ^{13}C NMR ($CDCl_3$): δ = [10 arom. C: 143.2, 133.9, 130.9, 128.8, 126.9, 125.5 (2 C), 125.2, 124.3, 123.4], 62.0 (d, $^2J_{PC}$ = 6.7 Hz, 1 C), 61.7 (d, $^2J_{PC}$ = 6.7 Hz, 1 C), 36.6 (d, $^1J_{PC}$ = 199.7 Hz, C-1), 24.7 (1 C), 18.1 (d, $^2J_{PC}$ = 5.2 Hz, C-2), 16.7 (d, $^3J_{PC}$ = 4.8 Hz, 1 C), 16.5 (d, $^3J_{PC}$ = 4.8 Hz, 1 C), 16.5 (C-3), 12.0 (1 C, 2-CH_3). − ^{31}P NMR ($CDCl_3$): δ = 29.93. − MS (70 eV): *m*/*z* (%) = 362 (1) [M^+ + 1], 361 (1.3) [M^+], 224 (68), 223 (75), 206 (75), 180 (41), *155* (100), 153 (37). − HRMS: *m*/*z* = 361.1805 (calcd. for $C_{20}H_{28}NO_3P$: 361.1807). − ^{31}P NMR ($CDCl_3$): δ = 29.71 for the minor **13e**.

Diethyl (2*S*)-1-Hydroxy-2-methylcyclopropane Phosphonate (15). − Procedure A: Reaction of chiral acetal **4b** (250 mg, 2.00 mmol),

TMSCl (cat. amt.), *p*-toluenesulfonamide **11d** (515 mg, 3.00 mmol), EtOH (5 mL), AcOH (0.36 mL, 6.00 mmol), and $P(OEt)_3$ (470 mg, 3.00 mmol) for 46 h at 55 °C gave, after standard workup and FC, only 290 mg (70%) of an 80:20 *trans*:*cis* mixture of by-products (2*S*)-**15**.

Major Isomer *trans*-15: R_f = 0.12 (EtOAc/CH_2Cl_2, 15:85). − ^{1}H NMR ($CDCl_3$): δ = 4.15 (q, *J* = 7.1 Hz, 2 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 3.10 (br. s, 1 H), 1.40−1.10 (m, 2 H_{cycle}), 1.32 (t, *J* = 7.1 Hz, 6 H), 1.18 (d, *J* = 5.5 Hz, 3 H, 2-CH_3), 0.60−0.48 (m, 1 H_{cycle}). − ^{13}C NMR ($CDCl_3$): δ = 62.3 (d, $^2J_{PC}$ = 6.2 Hz, 2 C), 51.2 (d, $^1J_{PC}$ = 226.4 Hz, C-1), 18.4 (C-3), 16.6 (d, $^2J_{PC}$ = 2.9 Hz, C-2), 16.3 (d, $^3J_{PC}$ = 5.3 Hz, 2 C), 10.9 (C-4). − ^{31}P NMR ($CDCl_3$): δ = 25.12. − MS (70 eV): *m*/*z* (%) = 208 (4) [M^+], 138 (32), 111 (63), 83 (46), *82* (100), 65 (42).

Minor Isomer *cis*-15: R_f = 0.12 (EtOAc/CH_2Cl_2, 15:85). − ^{13}C NMR ($CDCl_3$): δ = 62.1 (d, $^2J_{PC}$ = 6.2 Hz, 2 C), 52.9 (d, $^1J_{PC}$ = 226.4 Hz, C-1), 21.0 (C-2), 20.5 (C-3), 16.3 (d, $^3J_{PC}$ = 5.3 Hz, 2 C), 13.4 (d, $^3J_{PC}$ = 2.9 Hz, C-4). − ^{31}P NMR ($CDCl_3$): δ = 24.74. − MS (70 eV): *m*/*z* (%) = 138 (38), 111 (60), 83 (54), *82* (100), 65 (47); parent ion peak not observed.

Dimethyl (1*S*,2*S*)-1-Amino-2-methylcyclopropane Phosphonate (16b). − Procedure C: A mixture of phosphonate adducts **8b** and **13b** (88:12 ratio) (565 mg, 2.00 mmol), obtained as described above, was dissolved in absolute EtOH (12 mL) and 20% $Pd(OH)_2$/C (Pearlman's catalyst, 180 mg) was added. The flask was connected to a hydrogenation apparatus equipped with a graduated burette containing water that allowed the uptake of hydrogen to be monitored. TLC control showed that under 1 atm. H_2 at room temperature the reaction was complete within 3 h. The mixture was then degassed under a stream of argon, filtered through Celite, and the collected solid was washed with EtOH (3 × 10 mL). The combined filtrate and washings were concentrated and the residue was subjected to FC (eluent 2% → 20% MeOH/CH_2Cl_2) to afford **16b** (215 mg, 60%) as a colourless oil, 36 mg (10%) as a mixture of **16b** and **17**, and 22 mg (6%) of (1*R*,2*S*)-**17** as a minor product.

(1*S*,2*S*)-16b: $[\alpha]_D^{20}$ = +27.8 (*c* = 1, $CHCl_3$). − R_f = 0.45 (MeOH/CH_2Cl_2, 1:9). − IR ($CDCl_3$): ν̃ = 3690 cm^{-1}, 3607, 3404, 1245 (P=O), 1040 (P−O). − ^{1}H NMR ($CDCl_3$): δ = 3.71 (d, $^3J_{PH}$ = 4.4 Hz, 3 H, OMe), 3.67 (d, $^3J_{PH}$ = 4.4 Hz, 3 H, OMe), 1.51 (br. s, NH_2), 1.40−1.05 (m, 2 H_{cycle}), 1.11 (d, *J* = 5.4 Hz, 3 H, 2-CH_3), 0.36 (ddd, *J* = 7.4 Hz, *J* = 7.3 Hz, $^3J_{PH}$ = 4.9 Hz, 1 H_{cycle}). − ^{13}C NMR ($CDCl_3$): δ = 52.8 (d, $^2J_{PC}$ = 6.7 Hz, 1 C), 52.6 (d, $^2J_{PC}$ = 6.7 Hz, 1 C), 30.3 (d, $^1J_{PC}$ = 207.3 Hz, C-1), 18.9 (C-3), 16.5 (d, $^3J_{PC}$ = 3.3 Hz, C-2), 11.0 (C-4). − ^{31}P NMR ($CDCl_3$): δ = 31.72. − MS (70 eV): *m*/*z* (%) = 280 (3) [M^+ + 1], 179 (19) [M^+], 164 (37), 93 (33), *70* (100), 69 (84), 68 (77). − HRMS: *m*/*z* = 179.0708 (calcd. for $C_6H_{14}NO_3P$: 179.0711).

Dimethyl (1*R*,2*S*)-1-Amino-2-methylcyclopropane Phosphonate (17): R_f = 0.43 (MeOH/CH_2Cl_2, 1:9). − ^{1}H NMR ($CDCl_3$): δ = 3.80 (d, $^3J_{PH}$ = 3 Hz, 3 H), 3.74 (d, $^3J_{PH}$ = 3 Hz, 3 H), 1.76 (br. s, 2 H), 1.29 (d, *J* = 6.3 Hz, 3 H), 1.40−1.10 (m, 1 H_{cycle}), 1.00 (m, 1 H_{cycle}), 0.92 (m, 1 H_{cycle}). − ^{13}C NMR ($CDCl_3$): δ = 52.6 (d, $^2J_{PC}$ = 6.5 Hz, 1 C), 52.5 (d, $^2J_{PC}$ = 6.5 Hz, 1 C), 32.2 (d, $^1J_{PC}$ = 203.3 Hz, C-1), 22.0 (d, $^2J_{PC}$ = 2.8 Hz, C-2), 21.1 (C-3), 13.8 (d, $^3J_{PC\ cis}$ = 3.7 Hz, C-4).

Diethyl (1*S*,2*S*)-1-Amino-2-methylcyclopropane Phosphonate (16c) (from Phosphonate 8c). − Procedure C: Reaction of phosphonate **8c** (622 mg, 2.00 mmol), EtOH (10 mL), and 20% $Pd(OH)_2$/C (200 mg) under H_2 (1 atm.) for 3.5 h followed by FC gave 340 mg (82%) of (1*S*,2*S*)-**16c** as a colourless oil. − $[\alpha]_D^{20}$ = +24.4 (*c* = 1, $CHCl_3$). − R_f = 0.45 (MeOH/CH_2Cl_2, 1:9). − IR (neat): ν̃ = 3624 cm^{-1} (NH), 1240 (P=O), 1030 (P−O). − ^{1}H NMR ($CDCl_3$): δ = 4.10 (dq, $^2J_{PH}$ = 3.4 Hz, *J* = 6.9 Hz, 2 H), 4.07 (dq, $^2J_{PH}$ = 3.4 Hz, *J* = 6.9 Hz, 2 H), 1.57 (br. s, 2 H), 1.42−1.14 (m, 2 H_{cycle}), 1.31 (t, *J* = 6.9 Hz, 3 H), 1.30 (t, *J* = 6.9 Hz, 3 H), 1.17 (d, *J* = 6.4 Hz, 3 H), 0.41 (ddd, *J* = 6.4 Hz, *J* = 4.4 Hz, *J* = 7.3 Hz, 1 H_{cycle}). − ^{13}C NMR ($CDCl_3$): δ = 61.9 (d, $^2J_{PC}$ = 6.2 Hz, 1 C), 61.8 (d, $^2J_{PC}$ = 6.2 Hz, 1 C), 30.9 (d, *J* = 205.9 Hz, C-1), 19.0 (C-3), 16.7 (d, ^2J = 3.3 Hz, C-2), 16.42 (d, $^3J_{PC}$ = 5.0 Hz, 1 C), 16.41 (d, $^3J_{PC}$ = 5.0 Hz, 1 C), 11.1 (1 C). − ^{31}P NMR ($CDCl_3$): δ = 29.28. − MS (70 eV): *m*/*z* (%) = 208 (9) [M^+ + 1], 207 (25) [M^+], 111 (42), 93 (54), 83 (48), 82 (50), *70* (100), 68 (82). − HRMS: *m*/*z* = 207.1020 (calcd. for $C_8H_{18}NO_3P$: 207.1024).

See ref.[10a] for details of racemic **16c**: ^{1}H NMR ($CDCl_3$): δ = 4.30−3.95 (m, 4 H, OCH_2CH$_3$), 1.64 (s, 2 H), 1.36 (t, *J* = 7.0 Hz, 6 H, OCH$_2$CH_3), 1.10−1.50 (m, 5 H, 2 H_{cycle} and CH_3), 0.30−0.60 (m, 1 H_{cycle}). − ^{31}P NMR ($CDCl_3$): δ = 29.72 (referenced to external H_3PO_4).

16c from Phosphonate 8a. − Procedure C: Reaction of phosphonate **8a** (300 mg, 1.00 mmol), EtOH (5 mL), and 20% $Pd(OH)_2$/C (90 mg) under H_2 (1 atm) for 3 h followed by FC gave 185 mg (89%) of (1*S*,2*S*)-**16c** as a colourless oil. − $[\alpha]_D^{20}$ = +24.0 (*c* = 1, $CHCl_3$). The spectral data proved identical to those listed above.

(1*S*,2*S*)-1-Amino-2-methylcyclopropanephosphonic Acid (1b): Trimethylsilyl iodide (0.6 g, 3 mmol) was added dropwise to a stirred solution of the diethyl phosphonate **16c** (207 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) and stirring was continued at room temperature for 30 min. The volatiles were then removed in vacuo and a mixture of EtOH (5 mL) and propylene oxide (1 mL) was added with stirring. Once precipitation of the pure aminophosphonic acid **1b** was complete, it was filtered off and recrystallized from ε.H_2O, MeOH/Et_2O to afford 130 mg (86%) as a white solid, which was dried under high vacuum. − $[\alpha]_D^{20}$ = +34 (*c* = 1, H_2O), $[\alpha]_D^{20}$ = +45 (*c* = 0.2, H_2O); m.p. 220−222 °C (dec.) [ref.:[10a] m.p. 224−225 °C (dec.)]. − R_f = 0.41 (H_2O/MeOH, 1:9). − IR (KBr): ν̃ = 3600−3100 cm^{-1} (OH and NH_3^+), 1190 (P=O), 1050 (P−O). − ^{1}H NMR (D_2O): δ = 1.28 (dddd, J_{cis} = 9.4 Hz, J_{trans} = 6.8 Hz, *J* = 6.4 Hz, $^3J_{PH\ cis}$ = 12.7 Hz, 1 H, 2-H), 1.06 (ddd, J_{cis} = 9.4 Hz, J_{gem} = 6.4 Hz, $^3J_{PH\ cis}$ = 12.7 Hz, 1 H), 1.00 (d, *J* = 6.4 Hz, 3 H, 2-CH_3), 0.58 (ddd, J_{trans} = 6.8 Hz, J_{gem} = 6.4 Hz, $^3J_{PH\ trans}$ = 6.9 Hz, 1 H). − ^{13}C NMR (D_2O): δ = 33.6 (d, $^1J_{PC}$ = 192.5 Hz, C-1), 16.0 (C-3), 14.8 (C-2), 10.9 (C-4). − ^{31}P NMR ($CDCl_3$): δ = 13.36. − $C_4H_{10}NO_3P$ (151.1029): calcd. C 31.80, H 6.67, N 9.27; found C 31.88, H 6.32, N 8.88.

See ref.[10a] for details of racemic **1b**: ^{1}H NMR (D_2O, pH 4): δ = 1.60−1.02 (m, 5 H, 2 H_{cycle} and CH_3), 0.80−0.58 (m, 1 H_{cycle}). − ^{13}C NMR (D_2O/NaOD, pH 7): δ = 41.14 (d, *J* = 181.2 Hz, C-1), 22.42 (d, *J* = 2 Hz, C-3), 20.71 (C-2), 17.52 (*C*H$_3$). − ^{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) (referenced to external H_3PO_4).

(1*R*,2*S*)-1-Aminocyclopropanephosphonic Acid (18): Treatment of the minor product **17** according to the procedure used for **1b** afforded 10 mg (80%) of **18**: $[\alpha]_D^{20}$ = +22.8 (*c* = 0.5, H_2O); m.p. 234−236 °C (dec.). − R_f = 0.41 (H_2O/MeOH, 1:9). − ^{1}H NMR (D_2O): δ = 1.23 (dddd, J_{cis} = 11.8 Hz, J_{trans} = 5.1 Hz, *J* = 6.4 Hz, $^3J_{PH\ trans}$ = 6.8 Hz, 1 H, 2-H), 1.04 (d, *J* = 6.4 Hz, 3 H, 2-CH_3), 0.98 (ddd, J_{trans} = 5.1 Hz, J_{gem} = 6.2 Hz, $^3J_{PH\ cis}$ = 10.8 Hz, 1 H), 0.79 (ddd, J_{cis} = 11.8 Hz, J_{gem} = 6.2 Hz, $^3J_{PH\ trans}$ = 6.2 Hz, 1 H). − ^{13}C NMR (D_2O): δ = 34.0 (d, $^1J_{PC}$ = 191.6 Hz, C-1), 17.9 (C-3), 16.7 (C-2), 12.6 (d, $^3J_{PC\ cis}$ = 3.4 Hz, C-4). − ^{31}P NMR ($CDCl_3$): δ = 11.48.

General Procedure for the Preparation of Mosher Amides of Aminophosphonic Acid 1b: (*R*)-MTPA-Amide of (1*S*,2*S*)-1b: To a stirred suspension of **1b** (5 mg, 0.024 mmol) in THF (1 mL) was added (*S*)-(+)-Mosher's acid chloride (5.5 μL, 0.029 mmol, 1 equiv.) and propylene oxide (10 μL, 0.14 mmol, 5 equiv.). The resulting mixture was heated to reflux for 1 h, allowed to cool to room temperature, and the solvents were completely evaporated. FC ($EtOAc/CH_2Cl_2$, 1:3 → 2:3) of the residue afforded 9 mg (ca. 90%) of the pure (*R*)-MTPA amide of (1*S*,2*S*)-**1b** as a solid [(*R*)-MTPA-**1b**]. – ^1H NMR ($CDCl_3$): δ = 7.57–7.42 (m, 2 H), 7.42–7.30 (m, 3 H), 6.74 (br. s, 1 H_{amide}), 4.32–4.00 (m, 2 H), 4.12 (dq, $^3J_{PH}$ = 6.8 Hz, *J* = 7.2 Hz, 2 H), 3.51 (q, $^5J_{FH}$ = 1.7 Hz, 3 H, OCH_3), 1.68 (m, 1 H_{cycle}), 1.62 (m, 1 H_{cycle}), 1.27 (t, *J* = 7.2 Hz, 6 H), 0.95 (d, *J* = 5.9 Hz, 3 H), 0.86 (m, 1 H_{cycle}). – ^{13}C NMR ($CDCl_3$): δ = 167.2 [6 arom. C: 132.8, 129.5, 128.4 (2 C), 127.3 (2 C)], 123.5 (q, $^1J_{FC}$ = 289.7 Hz, CF_3), 84.1 (q, $^2J_{FC}$ = 28.6 Hz, *C*CF_3), 62.8 (d, $^2J_{PC}$ = 5.4 Hz, O*C*H_2CH_3), 62.2 (d, $^2J_{PC}$ = 6.0 Hz, O*C*H_2CH_3), 55.2 (OCH_3), 29.4 (d, $^1J_{PC}$ = 218.0 Hz, C-1), 18.9 (C-3), 17.8 (C-2), 16.3 (d, $^3J_{PC}$ = 6.4 Hz, OCH_2CH_3), 16.2 (d, $^3J_{PC}$ = 6.7 Hz, OCH_2CH_3), 12.3 (C-4). – ^{31}P NMR ($CDCl_3$): δ = 24.21. – ^{19}F NMR ($CDCl_3$): δ = –68.19.

(*S*)-MTPA-Amide of (1*S*,2*S*)-1b: Prepared according to the same procedure as described above from (1*S*,2*S*)-**1b** (7 mg, 0.034 mmol) (*R*)-(–)-Mosher's acid chloride (7.5 μL, 0.04 mmol), and propylene oxide (10 μL, 0.14 mmol, 5 equiv.). After evaporation of the solvent and subsequent FC ($EtOAc/CH_2Cl_2$, 1:3 → 2:3) of the residue, the amide (13 mg, 90%) was obtained as a solid [(*S*)-MTPA-**1b**]. – ^1H NMR ($CDCl_3$): δ = 7.63–7.46 (m, 2 H), 7.46–7.30 (m, 3 H), 7.00 (br. s, H amide), 4.29–4.00 (m, 2 H), 4.09 (dq, $^3J_{PH}$ = 6.8 Hz, *J* = 7.2 Hz, 2 H), 3.37 (q, $^5J_{FH}$ = 1.5 Hz, OCH_3), 1.67 (m, 1 H_{cycle}), 1.61 (m, 1 H_{cycle}), 1.22 (t, *J* = 7.2 Hz, 6 H), 1.13 (d, *J* = 5.9 Hz, 3 H), 0.91 (m, 1 H_{cycle}). – ^{13}C NMR ($CDCl_3$): δ = 167.2, [6 arom. C: 132.2, 129.5, 128.4 (2 C), 128.0 (2 C)], 123.7 (q, $^1J_{CF}$ = 289.7 Hz, CF_3), 84.2 (q, $^2J_{CF}$ = 20.5 Hz, *C*CF_3), 62.8 (d, $^2J_{PC}$ = 5.3 Hz, 1 C), 62.3 (d, $^2J_{PC}$ = 6.0 Hz, 1 C), 55.1 (OCH_3), 29.4 (d, $^1J_{PC}$ = 217.8 Hz, C-1), 18.8 (C-3), 17.6 (C-2), 16.3 (OCH_2CH_3), 16.2 (OCH_2CH_3), 12.5 (C-4). – ^{31}P NMR ($CDCl_3$): δ = 24.18. – ^{19}F NMR ($CDCl_3$): δ = –68.36.

[1] For a recent review, see: [1a]C. Stammer, *Tetrahedron* **1990**, *46*, 2231–2254. – [1b]I. Wagner, H. Musso, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 816–828. – [1c]A. Alami, M. Calmes, R. Jacquier, *Bull. Soc. Chim. Fr.* **1993**, *130*, 5–24. – [1d]J. M. Jimenez, J. Rife, R. M. Ortuño, *Tetrahedron: Asymmetry* **1996**, *7*, 537–558.

[2] For a comprehensive review, see: B. Dhawan, D. Redmore, *Phosphorus and Sulfur Relat. Elem.* **1987**, *32*, 119–144.

[3] [3a] R. Wolfenden, *Annu. Rev. Biophys. Bioeng*. **1976**, *5*, 271–306; *Chem. Abst.* **1976**, *85*, 73952b. – [3b] N. E. Jacobsen, P. A. Bartlett, *J. Am. Chem. Soc.* **1981**, *103*, 654–657.

[4] [4a] B. Kafarski, B. Lejczak, *Phosphorus, Sulfur and Silicon* **1991**, *63*, 193–215. – [4b] J. Bird, R. C. De Mello, G. P. Harper, D. J. Hunter, E. H. Karran, R. E. Markwell, A. J. Miles-Williams, S. S. Rahman, R. W. Ward, *J. Med. Chem.* **1994**, *37*, 158–169.

[5] S. De Lombaert, L. Blanchard, J. Tan, Y. Sakane, C. Berry, R. D. Ghai, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 145–150.

[6] S. De Lombaert, L. Blanchard, C. Berry, R. D. Ghai, A. J. Trapani, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 151–154.

[7] F. R. Atherton, C. H. Hassall, R. W. Lambert, *J. Med. Chem.* **1986**, *29*, 29–40 and references cited therein.

[8] [8a] P. L. Diel, L. Maier, *Phosphorus Sulfur* **1984**, *20*, 313–321. – [8b] M. D. Erion, C. T. Walsh, *Biochemistry* **1987**, *26*, 3417–3425.

[9] For an α-aminophosphonic acid, see: P. P. McCleery, B. Tuck, *J. Chem. Soc., Perkin Trans. 1* **1989**, 1319–1329.

[10] For a substituted α-aminocyclopropanephosphonic acid, see: – [10a] U. Groth, L. Lehmann, L. Richter, U. Schöllkopf, *Liebigs Ann. Chem*. **1993**, 427–431. – [10b] S. Yamazaki, T. Takada, Y. Moriguchi, S. Yamabe, *J. Org. Chem.* **1998**, *63*, 5919–5928. – [10c] A. Hercouet, M. Le Corre, B. Carboni, *Tetrahedron Lett.* **2000**, *41*, 197–199, appeared after submission of our manuscript.

[11] A. Fadel, *Tetrahedron* **1991**, *47*, 6265–6274.

[12] [12a] A. Fadel, *Synlett* **1993**, 503–505. – [12b] A. Fadel, A. Khesrani, *Tetrahedron: Asymmetry* **1998**, *9*, 305–320 and references cited therein.

[13] A. Fadel, *J. Org. Chem.* **1999**, *64*, 4953–4955.

[14] [14a] A. N. Pudovik, J. V. Konovalova, *Synthesis* **1979**, 81–96. – [14b] D. Seebach, R. Charczuk, C. Gerber, P. Renaud, H. Berner, H. Schneider, *Helv. Chim. Acta* **1989**, *72*, 401–425. – [14c] T. Oshikawa, M. Yamashita, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3177–3181. – [14d] S. Shatzmiller, B.-Z. Dolitzky, R. Meirovich, R. Neidlein, C. Weik, *Liebigs Ann. Chem.* **1991**, 161–164. – [14e] H. Kunz, S. Laschat, *Synthesis* **1992**, 90–95. – [14f] A. B. Smith, III, K. M. Yager, C. M. Taylor, *J. Am. Chem. Soc.* **1995**, *117*, 10879–10888 and references cited therein. – [14g] H. Gröger, Y. Saida, H. Sasai, K. Yamaguchi, J. Martens, M. Shibasaki, *J. Am. Chem. Soc*. **1998**, *120*, 3089–3103. – [14h] C. Stevens, A. Verbeke, N. De Kimpe, *Synlett* **1998**, 180–182.

[15] C. Maury, Q. Wang, T. Gharbaoui, M. Chiadni, A. Tomas, J. Royer, H. P. Husson, *Tetrahedron* **1997**, *53*, 3627–3636.

[16] [16a] E. Nakamura, H. Oshino, I. Kuwajima, *J. Am. Chem. Soc*. **1986**, *108*, 3745–3755. – [16b] V. Atlan, S. Racouchot, M. Rubin, C. Bremer, J. Ollivier, A. de Meijere, J. Salaün, *Tetrahedron: Asymmetry* **1998**, *9*, 1131–1135.

[17] A. Fadel, J.-L. Canet, J. Salaün, *Synlett* **1990**, 89–91, see also ref.[12b].

[18] The ethanolysis of acetal **4b** to give the hemiacetal **10b** is much slower in the presence of AcOH (3 h) than with a catalytic amount of TMSCl (5 min).

[19] When the same reaction was carried out in AcOH solution, only a 30% yield of product **8c** was isolated after 23 h at 55 °C.

[20] F. W. Hoffmann, R. J. Ess, R. P. Usinger, *J. Am. Chem. Soc*. **1956**, *78*, 5817–5821.

[21] H. S. Mosher, J. A. Dale, D. L. Dull, *J. Org. Chem.* **1969**, *34*, 2543–2549.

[22] D. Seebach, V. Prelog, *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 654–660.

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

[24] I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.

[25] G. R. Sullivan, J. A. Dale, H. S. Mosher, *J. Org. Chem.* **1973**, *38*, 2143–2147.

Received November 26, 1999
[O99677]