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Preparation of enantiomerically pure (1*S*,2*S*)-1-aminocyclopropanephosphonic acid from methylcyclopropanone acetal via spirophosphonate intermediates

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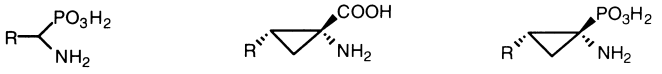
Abstract

An easy and efficient one-pot reaction from readily available methylcyclopropanone acetal (2*S*)-**4b** gave the spirophosphonates **8a**–**b** with excellent diastereoselectivity. These phosphonates, after catalytic hydrogenolysis and hydrolysis, furnished the enantiomerically pure (1*S*,2*S*)-1-amino-2-methylcyclopropanephosphonic acid **3b** (analogue of (1*R*,2*S*)-*allo*-norcoronamic acid). © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

The biologically active phosphonic acids **1** analogues of α-amino acids are finding increasing interest,[1–4] due to the tetrahedral structure of phosphonic acid moiety, since they act as 'transition-state analogues'.[5,6] In recent years, 1-aminocyclopropanecarboxylic acids **2** (ACCs) have attracted special attention owing to their use as enzyme inhibitors as well as their incorporation in strained peptides.[7,8] However, the aminocyclopropanephosphonic acids **3** did not receive the same attention compared to the acyclic aminophosphonic acids **1** and aminocyclopropanecarboxylic acids **2** (Scheme 1).



1 **2** **3**

Scheme 1.

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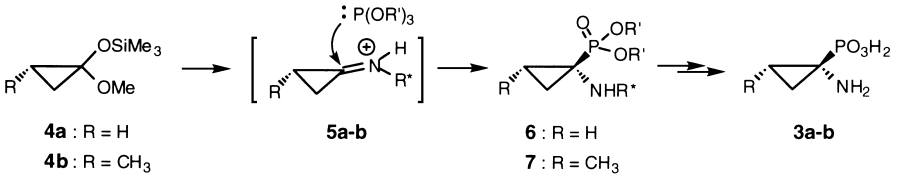
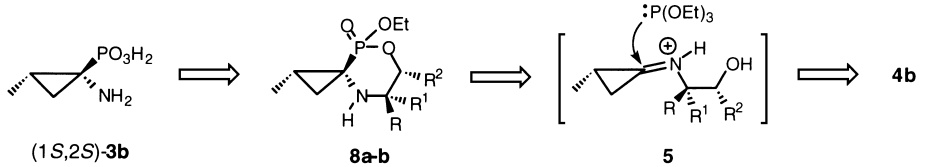
To our knowledge only a few methods for the synthesis of this class of compounds **3** have been described in either racemic[9] or optically active form.[10]

We have previously reported a simple and convenient synthesis of 1-aminocyclopropanephosphonic acid (ACC analogue) **3a** (R = H), in three steps, from cyclopropanone acetal **4a**.[11] Similarly, for the preparation of optically active amino acids **2**,[12] we have recently used the same methodology to synthesize (1*S*,2*S*)-1-aminocyclopropanephosphonic acid **3b** [analogue of (1*R*,2*S*)-*allo*-norcoronamic acid **2b** (R = CH_3)]. This sequence occurred in three steps from the acetal (2*S*)-**4b**, via the iminium **5b** and aminophosphonates **7** in good overall yield (Scheme 2).[13]



Scheme 2.

In order to obtain alkylaminophosphonic acid (1*S*,2*S*)-**3b**, via the cyclic phosphonates **8a**–**b**, we decided in connection with our ongoing program to study the asymmetric addition of triethyl phosphite to the acetal (2*S*)-**4b**. These reactions should occur in the presence of 2-hydroxyamines **9a**–**b** via the iminium intermediate **5** (Scheme 3).



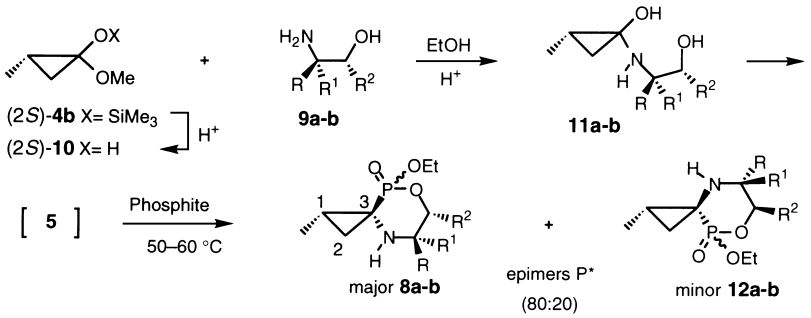
Scheme 3.

2. Results and discussion

The synthesis of (1*S*,2*S*)-1-amino-2-methylcyclopropanephosphonic acid **3b** was carried out starting from the cyclopropanone acetal (2*S*)-**4b**. This latter was easily obtained in two steps from commercially available (*S*)-3-hydroxy-2-methylpropionate.[14] Thus, in a one-pot procedure, the hemiacetal **10** formed in situ from acetal (2*S*)-**4b** by acidic ethanolysis (EtOH, cat. TMSCl) reacted under acidic conditions with amines **9a**–**b** to give, via aminols **11a**–**b**,[†] the iminium intermediate **5**.[‡] The latter underwent phosphite addition to directly furnish a diastereoisomeric mixture of cyclic aminophosphonates **8** and **12** (Scheme 4). Our results are summarized in Table 1.

[†] A spiroamino acetal cannot be obtained by heating **11a**: A. Fadel, unpublished results.

[‡] The formation of a linked phosphite with the hydroxyl group of the amine moiety in **5**, then an intramolecular addition of the resulting phosphite on the iminium function, cannot be excluded.



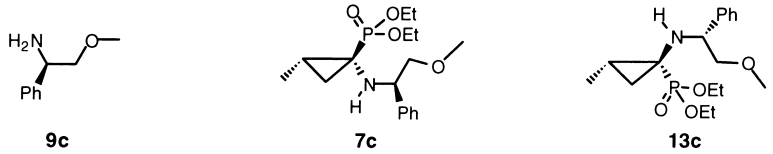
Scheme 4.

Table 1
Preparation of spiroaminophosphonates **8** and **12** from acetal (2*S*)-**4b**

	amine **9**				condition*	time	yield	
entry	R	R^1	R^2	**9**	AcOH	(h)	(%)	product (ds ratio)
1	Ph	H	H	(*R*)-**9a**	3 equiv.	113	65	**8a : 12a** (89 :11)
2	Ph	H	H	(*R*)-**9a**	2 equiv.	42	71	**8a : 12a** (89 :11)
3	H	Me	Ph	**9b**	2 equiv.	90	36	**8b : 12b** (78 :22)

* All reactions of acetal (2*S*)-**4b** were carried out in the presence of 1.5 equiv. of amine **9**, 1.5 equiv. of $P(OEt)_3$ and AcOH in EtOH at 55°C.

The use of triethyl phosphite and amine **9a** gave a mixture of spirophosphates **8a** and **12a** in good yields with the *trans* isomers as the major products (ratio, 89:11) (Table 1, entries 1 and 2). With (–)-norephedrine **9b** under the same conditions, the yield and mixture ratios were lower (entry 3). These compounds **8a**, **8b**, **12a** and **12b**, obtained as a mixture of epimers at the phosphorus atom in an 80:20 (P^*_{major}:P^*_{minor}) ratio, were easily separated by flash chromatography. We observed that the protected hydroxyl amine **9c** gave, under the same conditions, the expected phosphonates **7c** and **13c** (85:15 ratio) in 39% yield, and the cyclic phosphonate **8a** (3% yield). The latter was probably formed by cyclization of **7c** under reaction conditions (Scheme 5).

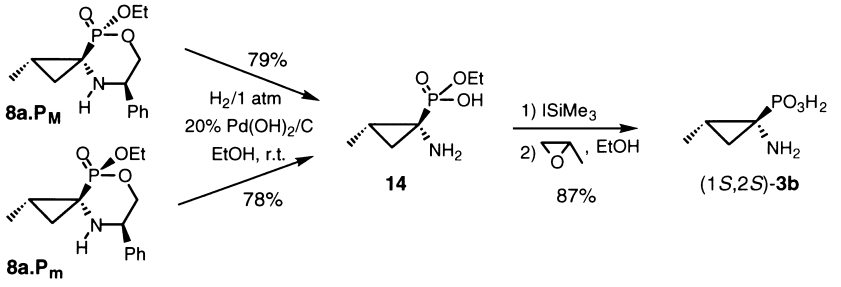


Scheme 5.

Assignment of the stereochemistry of these different compounds was based on $^3J_{P–H}$ coupling constants between the cyclopropane proton H-C_1 and the phosphorus atom. The observed values ($^3J_{PH} = 12.8$ Hz) were in agreement with reported values for the *cis* configuration,[9] and with our previously reported results.[13] These conclusions were supported by ^{13}C NMR spectra of the *cis* **12a** by the coupling constants between P and CH_3-C_1 ($^3J_{PC\,cis} = 5.2$ Hz). Thus, we assigned the *S* configuration on C_3 for the major **8a**–**b** and *R* for the minor **12a**–**b**. The phosphorus atom

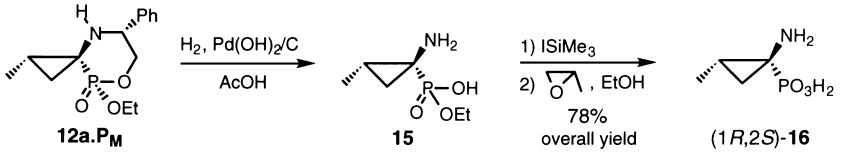
configuration was arbitrarily assigned from the optimized energy determined by molecular mechanics (MM2) calculations of **8** and **12** with *R* configuration for the major epimers.

After separation the major **8a**.$\mathbf{P_M}$ and the minor epimer **8a**.$\mathbf{P_m}$, which were assigned the same configuration *S* at C_3, were hydrogenolyzed separately to give the same compound **14** ($[\alpha]_D^{20} = +26.3$ (*c* 1, MeOH)) in 79% yield. Such epimerization on the phosphorus atom has already been reported by Royer et al. upon hydrogenolysis of cyclic aminophosphonate.[15] This monoester was treated by trimethylsilyl iodide then with propylene oxide in ethanol to lead to enantiomerically pure (1*S*,2*S*)-(+)-1-amino-2-methylcyclopropanephosphonic acid **3b** (87% yield, mp = 220–222°C, $[\alpha]_D^{20} = +34$ (*c* 1, H_2O), $[\alpha]_D^{20} = +45$ (*c* 0.2, H_2O)). These values are in agreement with our previously reported results,[13] and with the literature[10b] for the enantiomer (1*R*,2*R*)-**3b**: mp = 245°C (decomp.), $[\alpha]_D^{20} = -46.4$ (*c* 0.2, H_2O). Its enantiomeric excess, determined from ^{19}F NMR analysis of the corresponding Mosher amide,[13,16] was found to be 98% (Scheme 6).



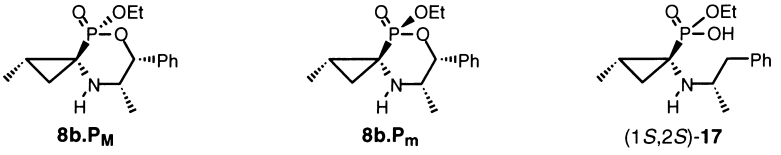
Scheme 6.

Probably the minor **12a**.$\mathbf{P_M}$, isolated by chromatography, was hydrogenolyzed into the monoester **15**, which was treated by $ISiMe_3$ followed by propylene oxide to furnish the *cis*-aminophosphonic acid ((1*R*,2*S*)-**16**, $[\alpha]_D^{20} = +23$ (*c* 0.5, H_2O)) (Scheme 7).



Scheme 7.

In the same way, the major **8b**.$\mathbf{P_M}$ and **8b**.$\mathbf{P_m}$, when hydrogenolyzed separately, gave the same monoester **17** in 86% yield (Scheme 8).



Scheme 8.

3. Conclusion

From the readily available methylcyclopropanone acetal (2*S*)-**4b**, we have developed an easy and efficient three-step synthesis of enantiomerically pure (1*S*,2*S*)-1-amino-2-methylcyclopropanephosphonic acid **3b**. This latter was obtained from the interesting cyclic phosphonate **8a**–**b** in high overall yield. This approach should constitute an efficient way for the synthesis of a wide variety of aminocyclopropanephosphonic acids.

4. Experimental

For general experimental information, see Fadel[11] or Fadel and Tesson.[13]

4.1. General procedure

To a solution of cyclopropanone acetal (2*S*)-**4b** (520 mg, 3 mmol) in EtOH (6 mL) was added one drop of TMSCl. After 5 min of stirring, chiral amine (*R*)-**9a** (550 mg, 4.5 mmol), AcOH (360 mg, 6 mmol), and $P(OEt)_3$ (750 mg, 4.5 mmol) were added successively. The mixture was stirred and heated at 55°C for 42 h. The reaction mixture was concentrated under vacuum, concentrated ammonia (2 mL) was added, and then the mixture was filtered through a 5 cm pad of silica gel and eluted with ether (60 mL). The filtrate was concentrated under vacuum to give crude phosphonates **8a** and **12a** obtained as two diastereoisomers in an 89:11 ratio. Purification by flash chromatography (FC) twice (eluent, EtOAc:CH_2Cl_2, 1:9→1:1, or ether) afforded 410 mg (49%) of (1*S*,2*S*)-**8a**.$\mathbf{P_M}$ as the major *trans*.major phosphorus atom, 80 mg (9.6%) of (1*S*,2*S*)-**8a**.$\mathbf{P_m}$ as the major *trans*.minor phosphorus atom, 39 mg (4.6%) of (1*R*,2*S*)-**12a**.$\mathbf{P_M}$ as the minor *cis*.major phosphorus atom, and 70 mg (8%) as a mixture.

4.1.1. (1S,3S,4S*,7R)-4-Ethoxy-1-methyl-7-phenyl-5-oxa-8-aza-4-phospha-spiro[2.5]octane 4-oxide 8a.P_M

$[\alpha]_D^{20} = +55.4$ (*c* 1, $CHCl_3$); $R_f = 0.22$ (ether); $R_T = 43.40$ min [Cydex B, 170°C (5 min) +1°C/min→180°C (1 h), 1 bar]; IR (neat): 3440, 3265, 1260 (P=O), 1046 (P–O); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 7.54$–7.16 (m, 5H), 4.60–4.28 (m, 2H), 4.21 (dq, $^3J_{PH} = 1$ Hz, $J = 7.3$ Hz, 2H), 4.30–4.00 (m, 1H, C*H*-N), 2.05 (br s, NH), 1.80–1.50 (m, $1H_{cycle}$), 1.39 (t, $J = 7.3$ Hz, 3H), 1.50–1.00 (m, $1H_{cycle}$), 1.25 (d, $J = 5.9$ Hz, 3H, CH_3-C_1), 0.46 (ddd, $J = 5.4$ Hz, $J_{PH\ trans} = 6.8$ Hz, $J = 8.3$ Hz, $1H_{cycle}$); ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ = [6 arom. C: 137.2, 128.7 (2C), 128.1, 126.4 (2C)], 70.0 (d, $^2J_{PC} = 9.0$ Hz, O-CH_2-CH), 61.5 (d, $^2J_{PC} = 6.7$ Hz, 1C), 58.8 (d, $^3J_{PC} = 5.3$ Hz, *C*H-N), 34.8 (d, $^1J_{PC} = 193.5$ Hz, C_3), 17.5 (C_1), 17.4 (C_2), 16.5 (d, $^3J_{PC} = 5.3$ Hz, CH_3-CH_2-O), 10.6 (CH_3-C_1); ^{31}P NMR ($CDCl_3$, 101.25 MHz): $\delta = 18.61$; MS (70 eV); *m*/*z* (%): 282 (M^++1, 6), 281 (M^+, 31), 252 (19), 171 (12), *104* (100), 103 (48); HRMS *m*/*z*: 281.1183 (calcd for $C_{14}H_{20}NO_3P$: 281.1180).

4.1.2. (1S,3S,4R*,7R)-4-Ethoxy-1-methyl-7-phenyl-5-oxa-8-aza-4-phospha-spiro[2.5]octane 4-oxide 8a.P_m

$[\alpha]_D^{20} = +32.6$ (*c* 0.75, $CHCl_3$); $R_f = 0.18$ (ether); $R_T = 38.42$ min [Cydex B, 170°C (5 min) +1°C/min→180°C (1 h), 1 bar]; IR (neat): 3435, 3265, 1260 (P=O), 1046 (P–O); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 7.40$–7.20 (m, 5H), 4.70 (ddd, $J = 4.4$ Hz, $J = 9.7$ Hz, $J_{ab} = 14.4$ Hz, 1H), 4.47 (ddd,

$J = 3.7$ Hz, $J = 11.4$ Hz, $J_{ab} = 14.4$ Hz, 1H), 4.30–4.10 (m, 2H and C*H*-N), 2.32 (br s, NH), 1.55–1.00 (m, $2H_{cycle}$), 1.31 (t, $J = 7.2$ Hz, 3H), 1.23 (d, $J = 5.8$ Hz, 3H, CH_3-C_1), 0.39 (ddd, $J = 5.9$ Hz, $J = 6.7$ Hz, $J = 8.4$ Hz, $1H_{cycle}$); ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ = [6 arom. C: 137.8, 128.7 (2C), 128.0, 126.9 (2C)], 75.3 (d, $^2J_{PC} = 6.7$ Hz, O-*C*H_2-CH), 62.6 (d, $^2J_{PC} = 6.7$ Hz, O-*C*H_2), 58.6 (d, $^3J_{PC} = 5.2$ Hz, *C*H-N), 35.0 (d, $^1J_{PC} = 193.5$ Hz, C_3), 18.2 (C_1), 17.5 (C_2), 16.6 (d, $^3J_{PC} = 5.2$ Hz, O-CH_2-*C*H_3), 10.9 (*C*H_3-C_1); ^{31}P NMR ($CDCl_3$, 101.25 MHz): $\delta = 19.86$; MS (70 eV); *m*/*z* (%): 282 (M^++1, 3), 281 (M^+, 15), 252 (12), 156 (11), 105 (13), *104* (100), 103 (31).

*4.1.3. (1*S*,3*R*,4*R**,7*R*)-4-Ethoxy-1-methyl-7-phenyl-5-oxa-8-aza-4-phospha-spiro[2.5]octane 4-oxide **12a**.P_M*

$[\alpha]_D^{20} = +57$ (*c* 1.45, $CHCl_3$); $R_f = 0.28$ (ether); $R_T = 41.27$ min [Cydex B, 170°C (5 min) +1°C/min→180°C (1h), 1 bar]; ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 7.44$–7.15 (m, 5H), 4.54–4.10 (m, 5H, CH_2-O, CH_2-O and N-C*H*), 2.15 (br s, NH), 1.41 (t, $J = 7.2$ Hz, CH_3-CH_2-O), 1.34 (d, $J = 5.8$ Hz, CH_3-C_1), 1.40–1.10 (m, $2H_{cycle}$), 1.10–0.96 (m, $1H_{cycle}$); ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ = [6 arom. C: 137.0, 128.8 (2C), 128.2, 126.5 (2C)], 76.8 (C_6), 61.3 (d, $^2J_{PC} = 6.2$ Hz, O-*C*H_2-CH_3), 58.1 (d, $^3J_{PC} = 4.8$ Hz, *C*H-N), 37.1 (d, $^1J_{PC} = 192.5$ Hz, C_3), 21.9 (C_1), 20.2 (d, $^2J_{PC} = 3.8$ Hz, C_2), 16.6 (d, $^3J_{PC} = 5.4$ Hz, O-CH_2-*C*H_3), 13.8 (d, $^3J_{PC\ cis} = 5.2$ Hz, *C*H_3-C_1);
^{31}P NMR ($CDCl_3$, 101.25 MHz): $\delta = 17.43$.

*4.1.4. (1*S*,3*S*,4*S**,6*R*,7*S*)-4-Ethoxy-1,7-dimethyl-6-phenyl-5-oxa-8-aza-4-phospha-spiro[2.5]octane 4-oxide **8b**.P_M*

Following the procedure: Chiral acetal (2*S*)-**4b** (350 mg, 2 mmol), TMSCl (cat.), norephedrine (1*R*,2*S*)-**9b** (450 mg, 3 mmol), EtOH (7 mL) and $P(OEt)_3$ (500 mg, 3 mmol) gave, after heating at 55°C for 90 h and the usual work up, 500 mg of crude cyclic phosphonates as a mixture of **8b** and **12b** in a 78:22 ratio. Purification by FC (twice) afforded 115 mg (19.5%) of (1*S*,3*S*)-**8b**.$\mathbf{P_M}$ as the major *trans*.major phosphorous atom, 32 mg (5.5%) of (1*S*,3*S*)-**8b**.$\mathbf{P_m}$ as major *trans*.minor phosphorus atom, 32 mg (5.5%) of (1*S*,3*R*)-**12b**.$\mathbf{P_M}$ as minor *cis*.major phosphorus atom, and 25 mg (4%) as a mixture.

*4.1.4.1. Data for (1*S*,3*S*)-**8b**.P_M.* $[\alpha]_D^{20} = +40.4$ (*c* 1, $CHCl_3$); mp = 142.0–146.0°C; $R_f = 0.24$ (EtOAc:CH_2Cl_2, 15:85); IR (neat): 3296 (NH), 1248 (P=O), 1195, 1053 (P–O); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 7.42$–7.18 (m, 5H), 5.55 (dd, $J = 2.0$ Hz, $^3J_{PH} = 2.5$ Hz, H-C_6), 4.24–3.95 (m, 2H, CH_2-O), 3.01 (dq, $J = 2.0$ Hz, $J = 7.4$ Hz, 1H-C_7), 2.35 (br s, NH), 1.78–1.53 (m, H-C_1), 1.29 (t, $J = 7.4$ Hz, 3H), 1.40–1.15 (m, 1H-C_2), 1.12 (d, $J = 6.3$ Hz, 3H, CH_3-C_1), 0.90 (d, $J = 7.4$ Hz, 3H, CH_3-C_7), 0.31 (ddd, $J = 5.2$ Hz, $J = 6.8$ Hz, $J = 8.8$ Hz, 1H-C_2); ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ = [6 arom. C: 137.8 (d, $^3J_{PC} = 5.2$ Hz, 1C), 128.3 (2C), 127.6 (1C), 124.9 (2C)], 87.5 (d, $^2J_{PC} = 8.6$ Hz, C_6), 61.3 (d, $^2J_{PC} = 6.7$ Hz, 1C), 53.3 (d, $^3J_{PC} = 4.7$ Hz, C_7), 31.4 (d, $^1J_{PC} = 188.2$ Hz, C_3), 19.9 (d, $^3J_{PC} = 5.8$ Hz, 1C), 16.5 (C_2), 16.45 (d, $^2J_{PC} = 5.2$ Hz, C_1), 12.2 (*C*H_3-C_7), 10.8 (*C*H_3-C_1); ^{31}P NMR ($CDCl_3$, 101.25 MHz): $\delta = 21.36$; MS (EI), *m*/*z* (%): 296 (M^++1, 5), 295 (M^+, 5), *178* (100), 118 (82), 117 (71), 97 (52), 91 (56); HRMS, *m*/*z*: 295.1344 (calcd for $C_{15}H_{22}NO_3P$: 295.1337); anal. calcd for $C_{15}H_{22}NO_3P$: C, 61.01; H, 7.51; N, 4.74. Found: C, 60.73; H, 7.68; N, 4.52.

*4.1.5. (1*S*,3*S*,4*R**,6*R*,7*S*)-4-Ethoxy-1,7-dimethyl-6-phenyl-5-oxa-8-aza-4-phospha-spiro[2.5]octane 4-oxide **8b**.P_m*

$[\alpha]_D^{20} = -12.1$; $[\alpha]_{365}^{20} = -30$ (*c* 0.35, $CHCl_3$); $R_f = 0.07$ (EtOAc:CH_2Cl_2, 15:85); IR (neat): 3300 (NH), 1245 (P=O), 1195, 1053 (P–O); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 7.45$–7.15 (m, 5H), 5.83

(dd, $J=3.4$ Hz, $^3J_{PH}=3.9$ Hz, 1H-C_6), 4.17 (dq, $^3J_{PH}=8.3$ Hz, $J=7.3$ Hz, 2H), 3.25 (dq, $J=3.4$ Hz, $J=6.8$ Hz, 1H-C_7), 2.24 (br s, NH), 1.55–1.00 (m, 2H *c*-propyl), 1.33 (t, $J=7.3$ Hz, 3H), 1.17 (d, $J=6.0$ Hz, 3H, CH_3-C_1), 0.85 (d, $J=6.8$ Hz, 3H, CH_3-C_7), 0.45 (ddd, $J=4.9$ Hz, $J=6.8$ Hz, $J=8.3$ Hz, 1H-C_2); ^{13}C NMR ($CDCl_3$, 62.86 MHz): $\delta=$[6 arom. C: 137.6 (d, $^3J_{PC}=5.5$ Hz, 1C), 128.3 (2C), 127.6 (1C), 125.4 (2C)], 84.5 (d, $J_{PC}=6.9$ Hz, C_6), 62.5 (d, $^2J_{PC}=6.6$ Hz, 1C), 53.4 (d, $^3J_{PC}=4.1$ Hz, C_7), 33.0 (d, $^1J_{PC}=188.6$ Hz, C_3), 19.0 (d, $^3J_{PC}=2.6$ Hz, 1C), 18.0 (C_2), 16.6 (d, $^2J_{PC}=5.3$ Hz, C_1), 13.0 (CH$_3$-C_7), 12.1 (CH$_3$-C_1); ^{31}P NMR ($CDCl_3$, 101.25 MHz): $\delta=22.99$; MS (70 eV); *m*/*z* (%): 296 (M^++1, 2), 295 (M^+, 4), 178 (93), 177 (21), *118* (100), 117 (69), 97 (44), 91 (27); HRMS *m*/*z*: 295.1340 (calcd for $C_{15}H_{22}NO_3P$: 295.1337).

4.1.6. (1S,3R,4R,6R,7S)-4-Ethoxy-1,7-dimethyl-6-phenyl-5-oxa-8-aza-4-phospha-spiro[2.5]octane 4-oxide* ***12b*.P_M**

From a mixture we can read: $R_f=0.15$ (EtOAc:CH_2Cl_2, 15:85); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta=$7.45–7.15 (m, 5H), 5.58 (dd, $J=2.4$ Hz, $J=2.3$ Hz, 1H-C_6), 4.30–4.03 (m, 2H), 3.15 (dq, $J=2.3$ Hz, $J=7.3$ Hz, 1H-C_7), 1.56 (br s, NH), 1.40–1.30 (m, 1H$_{c\text{-propyl}}$), 1.33 (t, $J=6.8$ Hz, 3H), 1.32 (d, $J=6.3$ Hz, 3H, CH_3-C_1), 1.30–0.90 (m, 2H$_{c\text{-propyl}}$), 0.98 (d, $J=7.3$ Hz, 3H, CH_3-C_7); ^{13}C NMR ($CDCl_3$, 50.29 MHz): $\delta=$[6 arom. C: 137.8 (d, $^3J_{PC}=5.0$ Hz, 1C), 128.4 (2C), 127.7 (1C), 125.0 (1C)], 87.2 (d, $^2J_{PC}=9.0$ Hz, C_6), 61.0 (d, $^2J_{PC}=7.1$ Hz, 1C), 54.6 (d, $^3J_{PC}=3.9$ Hz, C_7), 32.3 (d, $^1J_{PC}=196.9$ Hz, C_3), 22.8 (d, $^2J_{PC}=4.0$ Hz, C_2), 19.1 (1C), 16.6 (d, $^2J_{PC}=5.9$ Hz, C_1), 13.8 (d, $^3J_{PC\ cis}=5.9$ Hz, CH$_3$-C_1), 11.2 (CH$_3$-C_7).

4.2. Diethyl (1S,2S,1′R)-1-(2-methoxy-1-phenylethylamino)-2-methylcyclopropanephosphonate ***7c***

Following the procedure: acetal **4b** (2 mmol) and amine **9c** (616 mg, 3 mmol) gave, after FC (twice), 185 mg (27%) of **7c**, 18 mg (3%) of spirophosphonate **8a**.$\mathbf{P_M}$ and 37 mg (5.2%) as a mixture of **7c**, **8a**.$\mathbf{P_M}$ and minor **13c**. $[\alpha]_D^{20}=-38.7$ (*c* 1, $CHCl_3$); $R_f=0.23$ (EtOAc:CH_2Cl_2, 1:1); $R_T=24.37$ min [Cydex B, 170°C (5 min) +1°C/min→180°C (1 h), 1 bar]; IR (neat): 3430 (NH), 1240 (P=O), 1030 (P–O); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta=$7.45–7.15 (m, 5H), 4.20 (m, 1H), 4.13–3.77 (m, 4H), 3.60–3.25 (m, 2H), 3.29 (s, 3H), 2.10 (br s, NH), 1.53–1.05 (m, 2H$_{cycle}$), 1.23 (t, $J=7.3$ Hz, 3H), 1.21 (t, $J=7.3$ Hz, 3H), 0.98 (d, $J=6.6$ Hz, CH_3-C_2), 0.60 (m, 1H$_{c\text{-propyl}}$); ^{13}C NMR ($CDCl_3$, 62.86 MHz): $\delta=$[6 arom. C: 142.5 (1C), 127.9 (2C), 127.8 (2C), 127.0 (1C)], 77.0 (CH$_2$-CH-N), 61.65 (d, $^3J_{PH}=6.2$ Hz, 1C), 61.6 (d, $^3J_{PH}=6.2$ Hz, 1C), 60.3 (CH-N), 58.8 (CH$_3$-O), 35.8 (d, $^1J_{PC}=207.8$ Hz, C_1), 18.8 (C_3), 18.4 (d, $^2J_{PC}=4.3$ Hz, C_2), 16.4 (1C), 16.3 (1C), 11.9 (CH$_3$-C_2); ^{31}P NMR ($CDCl_3$, 101.25 MHz): $\delta=28.93$; MS (70 eV); *m*/*z* (%): 341 (M^+, 1), 296 (27), 295 (29), 172 (87), 171 (41), *103* (100), 102 (38), 91 (36); HRMS *m*/*z*: 341.1753 (calcd for $C_{17}H_{28}NO_4P$: 341.1756); anal. calcd for $C_{17}H_{28}NO_4P$: C, 59.81; H, 8.27; N, 4.01. Found: C, 59.62; H, 7.48; N, 4.23.

4.3. Ethyl (1S,2S)-1-amino-2-methylcyclopropanephosphonate ***14***

Following a reported procedure:[11] cyclic phosphonate **8a**.$\mathbf{P_M}$ (197 mg, 0.7 mmol), EtOH (4 mL) and 20% $Pd(OH)_2$/C (Pearlman's catalyst, 90 mg) under H_2 (1 atm) gave, after 6 h and FC (eluent 50:50, MeOH:EtOAc), 99 mg (79%) of (1*S*,2*S*)-**14** as a white solid. $[\alpha]_D^{20}=+26.3$ (*c* 1, MeOH); mp = 169.7°C (decomp.); $R_f=0.21$ (MeOH:CH_2Cl_2, 1:1); IR (neat): ^{1}H NMR (D_2O, HOD, 4.6 ppm, 250 MHz): $\delta=3.74$ (dq, $^3J_{PH}=6.7$ Hz, $J=7.1$ Hz, 2H), 1.30–1.03 (m, 1H), 1.03 (t, $J=7.1$ Hz, 3H), 1.03–0.80 (m, 1H$_{cycle}$), 0.95 (d, $J=6.3$ Hz, 3H), 0.39 (ddd, $J_{trans}=6.6$ Hz,

J_{gem} = 6.4 Hz, $^3J_{PH\ trans}$ = 6.8 Hz, 1H); ^{13}C NMR (D_2O, 82.86 MHz): δ = 61.5 (d, $^2J_{PC}$ = 5.7 Hz, 1C), 32.1 (d, $^1J_{PC}$ = 195.4 Hz, C_1), 16.7 (C_3), 16.1 (d, $^2J_{PC}$ = 5.2 Hz, C_2), 14.9 (1C), 10.9 (1C); ^{31}P NMR (D_2O, 101.25 MHz): δ = 19.29.

4.4. *Ethyl (1*S*,2*S*,1′*S*)-2-methyl-1-(1′-methyl-2-phenylethylamino)cyclopropanephosphonate **17***

Following a reported procedure:[11] cyclic phosphonate **8b**.$\mathbf{P_M}$ (60 mg, 0.2 mmol), AcOH (2 mL) and 20% $Pd(OH)_2$/C (25 mg), under H_2 (1 atm) gave, after 4 h and FC (eluent 20:80, MeOH:CH_2Cl_2), 51 mg (86%) of (1*S*,2*S*)-**17**. $[\alpha]_D^{20}$ = +13.7 (*c* 0.9, MeOH); IR (neat): 3600–3200 (NH_3^+, OH), 2750 (P–OH), 1602, 1216 (P=O), 1052 (P–O); ^{1}H NMR (d_4-MeOH, 4.78 ppm, 200 MHz): δ = 7.30–7.00 (m, 5H), 4.28–4.02 (m, 1H), 3.85 (dq, $^3J_{PH}$ = 7.2 Hz, *J* = 7.3 Hz, 2H), 3.21 (dd, *J* = 3.8 Hz, *J* = 12.6 Hz, $1H_{benzyl}$), 2.43 (dd, *J* = 10.5 Hz, *J* = 12.6 Hz, $1H_{benzyl}$), 1.67 (m, 1H-C_2), 1.44–1.20 (m, $1H_{c\text{-propyl}}$), 1.20 (d, *J* = 6.4 Hz, 3H, C*H*$_3$-C_2), 1.10 (t, *J* = 7.3 Hz, 3H, C*H*$_3$-CH_2-O), 1.07 (d, *J* = 7.0 Hz, 3H), 0.58 (ddd, *J* = 6.2 Hz, *J* = 6.4 Hz, *J* = 6.6 Hz, $1H_{cycle}$); ^{13}C NMR (d_4-MeOH, 49 ppm, 62.86 MHz): δ = [6 arom. C: 138.1 (1C), 130.4 (2C), 129.8 (2C), 128.1 (1C)], 61.9 (d, $^2J_{PC}$ = 6 Hz, 1C), 57.5 (*C*H-N), 40.9 (1C, benzyl), 39.0 (d, $^1J_{PC}$ = 190.0 Hz, C_1), 17.8 (1C), 17.3 (d, $^2J_{PC}$ = 6.1 Hz, C_2), 17.0 (1C), 16.4 (C_3), 12.1 (*C*H$_3$-C_2); ^{31}P NMR (d_4-MeOH, 101.25 MHz): δ = 12.53.

4.5. *(1*S*,2*S*)-1-Amino-2-methylcyclopropanephosphonic acid **3b***

Trimethylsilyl iodide (300 mg, 1.5 mmol) was added dropwise to a stirred solution of the monoethyl phosphonate **14** (90 mg, 0.50 mmol) in CH_2Cl_2 (5 mL), and stirring was continued at room temperature for 30 min. Organic solvents were removed under vacuum, and a mixture of EtOH (3 mL) was added with stirring. After complete precipitation, the pure aminophosphonic acid **3b** was filtered off, giving after crystallization from (ε.H_2O, MeOH/Et_2O) 65 mg (86%) as a white solid (dried under high vacuum). $[\alpha]_D^{20}$ = +34 (*c* 1, H_2O), $[\alpha]_D^{20}$ = +45 (*c* 0.2, H_2O) [lit.[10b] for an enantiomer (1*R*,2*R*)-**3b** $[\alpha]_D^{20}$ = –46.4 (*c* 0.2, H_2O); mp = 220–222°C (decomp.), lit.[9] mp = 224–225°C (decomp.)]; R_f = 0.41 (H_2O:MeOH, 1:9); IR (KBr): 3600–3100 (OH and NH_3^+), 1190 (P=O), 1050 (P–O); ^{1}H NMR (D_2O, 250 MHz): δ = 1.28 (dddd, J_{cis} = 9.4 Hz, J_{trans} = 6.8 Hz, *J* = 6.4 Hz, $^3J_{PH\ cis}$ = 12.7 Hz, 1H-C_2), 1.06 (ddd, J_{cis} = 9.4 Hz, J_{gem} = 6.4 Hz, $^3J_{PH\ cis}$ = 12.7 Hz, 1H), 1.00 (d, *J* = 6.4 Hz, 3H, CH_3-C_2), 0.58 (ddd, J_{trans} = 6.8 Hz, J_{gem} = 6.4 Hz, $^3J_{PH\ trans}$ = 6.9 Hz, 1H); ^{13}C NMR (D_2O, 62.86 MHz): δ = 33.6 (d, $^1J_{PC}$ = 192.5 Hz, C_1), 16.0 (C_3), 14.8 (C_2), 10.9 (*C*H$_3$-C_2); ^{31}P NMR (D_2O, 101.25 MHz): δ = 13.36; anal. calcd for $C_4H_{10}NO_3P$ (151.1029): C, 31.80; H, 6.67; N, 9.27. Found: C, 31.88; H, 6.32; N, 8.88.

4.6. *(1*R*,2*S*)-1-Amino-2-methylcyclopropanephosphonic acid **16***

From minor **12a** following the procedure used for (1*S*,2*S*)-**3b**, we obtained 10 mg (78% overall yield) of (1*S*,2*S*)-**16**. $[\alpha]_D^{20}$ = +23 (*c* 0.5, H_2O); mp = 234–236°C (decomp.); R_f = 0.41 (H_2O:MeOH, 1:9); ^{1}H NMR (D_2O, 250 MHz): δ = 1.23 (dddd, J_{cis} = 11.8 Hz, J_{trans} = 5.1 Hz, *J* = 6.4 Hz, $^3J_{PH\ trans}$ = 6.8 Hz, 1H-C_2), 1.04 (d, *J* = 6.4 Hz, 3H, CH_3-C_2), 0.98 (ddd, J_{trans} = 5.1 Hz, J_{gem} = 6.2 Hz, $^3J_{PH\ cis}$ = 10.8 Hz, 1H), 0.79 (ddd, J_{cis} = 11.8 Hz, J_{gem} = 6.2 Hz, $^3J_{PH\ trans}$ = 6.2 Hz, 1H); ^{13}C NMR (D_2O, 62.86 MHz): 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*H$_3$-C_2); ^{31}P NMR (D_2O, 101.25 MHz): δ = 11.48; in agreement with our previously reported data.[13]

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