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Synthesis of (1*S*,2*S*)- and (1*R*,2*R*)-1-amino-2-methylcyclopropane-phosphonic acids from racemic methylcyclopropanone acetal†

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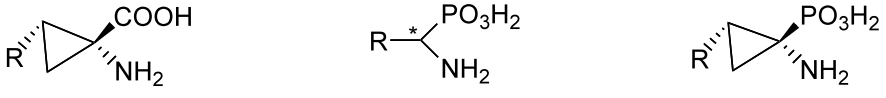
Abstract—An efficient and easy one-pot reaction from readily available racemic alkylcyclopropanone acetals gave the corresponding aminophosphonates with excellent diastereoselectivity. After catalytic hydrogenolysis, and hydrolysis, these *trans*-phosphonates led to enantiopure (+)-1-amino-2-methylcyclopropanephosphonic acid and its antipode (analogues of *allo*-norcoronamic acid).

1. Introduction

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

As far as we are aware, only a few methods for the synthesis of compounds of this class 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, starting from cyclopropanone acetal **4a** and proceeding via the aminophosphonates **6A**.**a**.[11] We have recently applied the same methodology for the preparation of (1*S*,2*S*)-1-aminocyclopropanephosphonic acid **3b** [an analogue of (1*R*,2*S*)-*allo*-norcoronamic acid **1b** (R = CH_3)].[12] This sequence occurred in three steps from acetal (2*S*)-**4b**, proceeding by asymmetric addition of phosphite to the intermediate iminium species **5A** via aminophosphonates **6A**.**b**[13] or spirophosphonates **7a**–**b**.[14] The products were obtained in good overall yields (Scheme 2).

This strategy appeared to be a promising approach for the asymmetric synthesis of various aminophosphonic acids **3**. In order to obtain such acids through the corresponding aminophosphonates **6A**.**b**–**f** and **6C**.**b**–**f**, we decided in connection with our ongoing program,[13]



1 **2** **3**

Scheme 1.

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† Dedicated to Professor Dr. Dieter Seebach in honour of the occasion of his 65th birthday.

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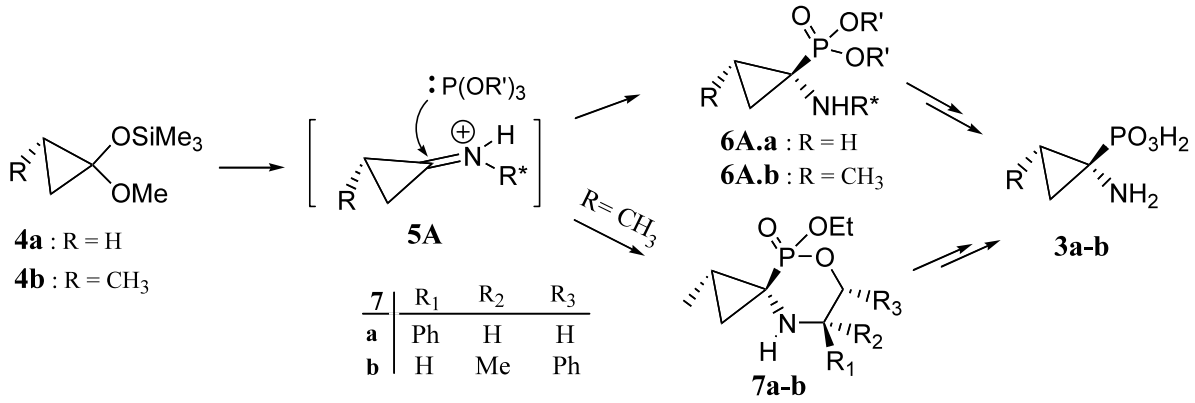


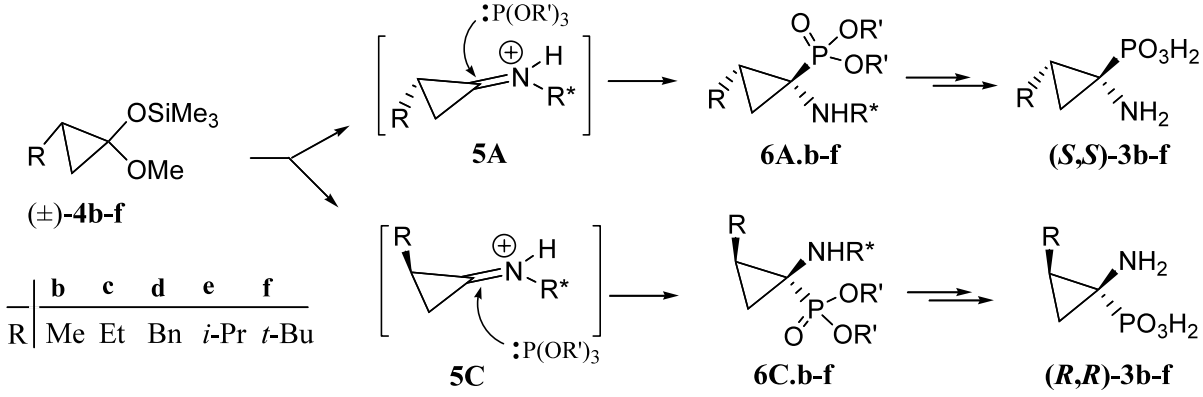
Scheme 2.

to study the asymmetric addition of triethyl phosphite to the inexpensive and readily available racemic acetal (±)-**4**.[12b] We anticipated that this reaction, involving the iminium species **5A** and **5C** as intermediates, should occur in the presence of a chiral amine (Scheme 3).

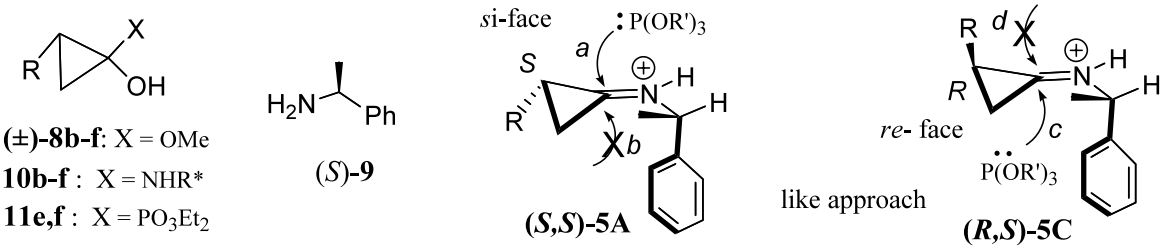
2. Results and discussion

The reactions were carried out using a one-pot procedure. Thus, the hemiacetal (±)-**8b–f**, generated in situ from the acetal (±)-**4b–f** by alcoholysis in the presence of a catalytic amount of an acid (TMSCl or AcOH),[14] reacted with chiral amine (*S*)-**9**, and 3 equiv. of AcOH to give the aminals **10**. Under acidic conditions, the latter were converted into the iminium intermediates (*S*,*S*)-**5A** and (*R*,*S*)-**5C** (Scheme 4), which then underwent triethylphosphite addition in EtOH at 60°C, to furnish the amino phosphonates **6A–D** in good yields (62–80%) as mixtures of diastereoisomers in which the major *trans* products **6A** and **6C** were obtained with high selectivity (*trans*:*cis* ratio of up to 88:12, Table 1, entries 1–4). The selectivity of this one-pot reaction increase to 100:0 for sterically hindered acetal **4f** (R = *t*-Bu) (entry 7). Nevertheless, the low yields from the reactions of bulky acetals were improved by forming the iminium intermediate prior to adding the phosphite, thus preventing the competitive formation of the hydroxy phosphonates **11e,f** (X = PO_3Et_2), giving 56 and 60% yields, respectively, of the major *trans* **6A** and **6C** (entries 6, 8 and 9).

We anticipated that the nucleophilic attack of phosphite on the iminium intermediates (*S*,*S*)-**5A** and (*R*,*S*)-**5C**, would afford one predominant diastereoisomer (path *a* or *c* with a like approach in Scheme 4) of the

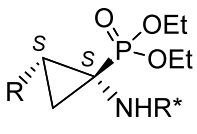


Scheme 3.

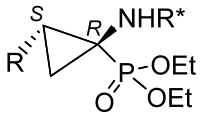


Scheme 4.

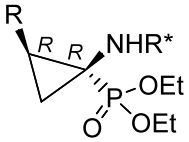
Table 1. Preparation of aminophosphonates **6A–D** from racemic acetals **4***



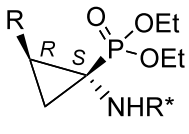
major *trans*
6A.b-f



cis
6B.b-f



major *trans*
6C.b-f



cis
6D.b-f

Run	**4b–f**	Amine **9**	Time (h)	Yield (%)	**6** Diastereomeric ratio[a]		*trans*/*cis*	**6A+6B/6C+6D**
	R					**A:B–C:D**		
1	**b** Me	(*S*)	23	80	**b**	41.8:5.7–46.4:6.1	88.2/11.8	47.5/52.5
2	**b** Me	(*R*)	40	78	**b′**	46.5:6.1–41.5:5.9	88/12	52.6/47.4
3	**c** Et	(*S*)	30	78	**c**	41:9–41:9	82/18	50/50
4	**d** Bn	(*S*)	60	62	**d**	43:7–43:7	86/14	50/50
5	**e** *i*-Pr	(*S*)	49	30[c]	**e**	38:12–38:12	76/24	50/50
6	**e** *i*-Pr	(*S*)	16[b]+20	56	**e**	38:12–38:12	76/24	50/50
7	**f** *t*-Bu	(*S*)	89	14[d]	**f**	50:0–50:0	100/0	50/50
8	**f** *t*-Bu	(*S*)	15[b]+48	42	**f**	50:0–50:0	100/0	50/50
9	**f** *t*-Bu	4 equiv. (*S*)	16[b]+63	60	**f**	50:0–50:0	100/0	50/50

* All reactions of racemic acetal **4** were carried out in the presence of 1.5 equiv. of amine and $P(OEt)_3$ and 3 equiv. of AcOH in EtOH at 55°C.
[a] Diastereoisomeric ratios were measured by GC analysis on a chiral column.
[b] Time allowed for iminium formation before adding phosphite.
[c] In plus 10% of hydroxy phosphonate **11e**.
[d] In plus 55% of **11f**.

four possible isomers.[12b,15] However, only a slight difference in the **6A**:**6C** ratio was observed using (*S*)-**9** and (*R*)-**9**. Thus, the ratio changed from 41.8/46.4 to 46.5/41.5, respectively (Table 1, entries 1 and 2).

We have previously reported[13] that no reaction occurs when bulky phosphites such as $(i\text{PrO})_3\text{P}$ or $(\text{PhO})_3\text{P}$ are used in *i*-PrOH or phenol, respectively (see also Table 2, entries 2 and 5 compared to entry 1). In contrast, in DMSO solvent the triisopropylphosphite gave a mixture of major *trans* isomers **12A** and **12C** in 20% yield (entry 3). Furthermore, by forming the iminium intermediate before adding the bulky phosphite the yield of **12A**/**12C** and **13A**/**13C** could be improved to 40 and 35%, respectively (Table 2, entries 4 and 6).

The major amino phosphonates **6A**.**b–f** and **6C**.**b–f** obtained above were readily isolated from the minor *cis* isomers **6B**.**b–f** and **6D**.**b–f** by chromatography on silica gel. Unfortunately, we were unable to isolate **6A**.**b–f** from **6C**.**b–f** even after exhaustive chromatography, and only in the case of **6C**.**c**/**6A**.**c** the mixture was enriched to 28% d.e.

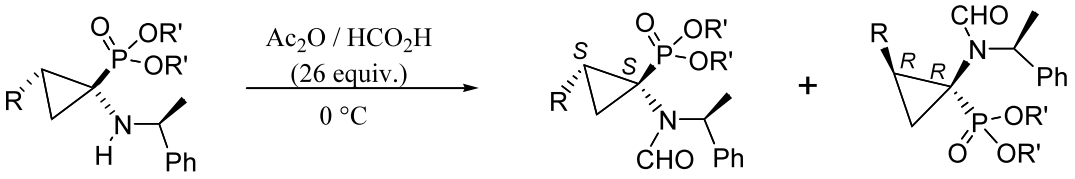
To overcome this problem of separation we selected some mixtures of major *trans* **6A**.**b**/**6C**.**b**, **6A**.**c**/**6C**.**c** and **12A**.**b**/**12C**.**b**. However, it was possible to protect these mixtures, as its formamide derivatives **14A–16A** and **14C–16C** using in situ generated acetic formic anhydride[16] under solvent free conditions (Scheme 5).

Since our goal was to find a practical protocol for preparation of 2-alkyl-1-aminocyclopropanephosphonic acids, it was critical to demonstrate that the *N*-benzyl group could be removed along with the *N*-formamide group under the same conditions. Indeed, the major

Table 2. Preparation of aminophosphonates **X(A–D).b** from racemic acetals **4b**

Run	$P(OR')_3$	Solvent* (equiv.)	Time (h)	Yield (%)	Products (**X(A–D).b**)	Major/minor (**A+C/B+D**)
	(R′)					
1	Et	EtOH	30	78	**6(A–D).b**	88/12
2	*i*-Pr	*i*-PrOH	46	0	**12(A–D).b**	–/–
3	*i*-Pr	DMSO[b]	160	20	**12(A–D).b**	100/0
4	*i*-Pr	DMSO[b]	18[a]+48	40	**12(A–D).b**	100/0
5	Bn	BnOH	53	0	**13(A–D).b**	–/–
6	Bn	DMSO[c]	17[a]+140	35	**13(A–D).b**	>95/5

* All reactions of acetal (±)-**4b** were carried out in the presence of amine (*S*)-**9** (1.5 equiv.), $P(OR')_3$, (1.5 equiv.) and AcOH (3 equiv.) at 55°C.
[a] Time of iminium formation before adding phosphite.
[b] With 2 equiv. of *i*-PrOH.
[c] With 2 equiv. of BnOH.



	time (h)	yield (%)	xA		xC
6A.b/6C.b : R= Me, R'= Et	3	86	**14A**	separable	**14C**
12A.b/12C.b : R= Me, R'= *i*-Pr	10	76	**15A**	separable	**15C**
6A.c/6C.c : R= R'= Et	19	80	**16A**	difficult separation	**16C**

Scheme 5.

trans phosphonates **14A** and **15A**, could be reacted under mild conditions (20% $Pd(OH)_2/C$, and 1 atm H_2, in 2N HCl[17] to effect double deprotection affording 2-methylphosphonates **17A** ($[\alpha]_D=+23.7$ (*c* 1, $CHCl_3$), and **18A** ($[\alpha]_D=+19.5$ (*c* 1.1, $CHCl_3$), in good yield.

Under the same conditions, the isolated **14C**, gave the antipodal ethyl phosphonate (−)-**17C** ($[\alpha]_D=-23.5$ (*c* 1.2, $CHCl_3$)) in 95% yield. Subsequent treatment of the phosphonates (+)-**17A** and (+)-**18A** with trimethylsilyliodide in dichloromethane, followed by the addition of propylene oxide in ethanol, furnished the same enantiopure (1*S*,2*S*)-1-amino-2-methylcyclopropanephosphonic acid (+)-**3b** ($[\alpha]_D=+33.6$ (*c* 1, H_2O)) in yields of 90 and 100%, respectively. To demonstrate the efficiency of this method, we applied the same treatment to (−)-**17C**, which furnished the enantiopure antipodal aminophosphonic acid (−)-**3b** in 91% yield, ($[\alpha]_D=-43.5$ (*c* 0.2, H_2O)) (Scheme 6). These values are in agreement with our previously reported results,[13,14] ($[\alpha]_D=+34$ (*c* 1, H_2O)) and ($[\alpha]_D=+45$ (*c* 0.2, H_2O)) for (+)-**3b**, and with the literature value[10b] for (−)-**3b** ($[\alpha]_D=-46.4$ (*c* 0.2, H_2O)). Its enantiomeric excess, determined from ^{19}F NMR analysis of the corresponding Mosher amide,[18] was found to be >98%.

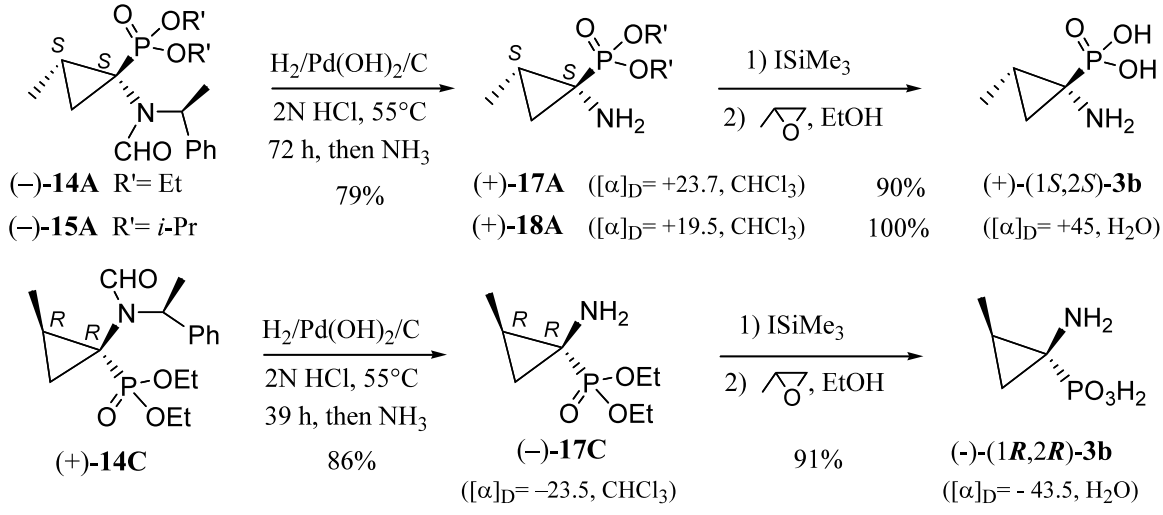
The absolute configuration of these acids, assigned in agreement with our previously reported results[13,14] and with the literature data,[10b] is 1*S*,2*S* for (+)-**3b**, 1*R*,2*R* for (−)-**3b**, and consequently the major *trans* isomers **6A** and **6C** have 1*S*,2*S* and 1*R*,2*R* configuration, respectively. These conclusions were corroborated by the ^{13}C NMR spectra of the *cis*-**6B**.**b**–**c**, by the coupling constants between P and CH_3–C_1 or P and CH_3–CH_2–C_1 ($^3J_{PC\ cis}=3.8$ Hz), were measured.[19]

3. Conclusion

We have developed an easy and efficient three-step synthesis of enantiopure (+)-*trans*-(1*S*,2*S*)-1-amino-2-methylcyclopropanephosphonic acid (+)-**3b** and its antipode (−)-(1*R*,2*R*)-**3b** starting from the readily available racemic alkylcyclopropanone acetals **4b**–**f**. These acids were obtained from separable formamide derivatives (**14** and **15**) of the major *trans* aminophosphonates **6A** and **6C**. This approach should constitute an efficient method for the synthesis of a wide variety of aminocyclopropanephosphonic acids. Efforts to improve the diastereoselective phosphite approach are currently in progress in our laboratory.

4. Experimental

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



Scheme 6.

4.1. General procedure A: Preparation of aminophosphonates according to our reported method[13,14]

To a solution of cyclopropanone acetal **4** (5 mmol) in EtOH (10 mL), was added one drop of TMSCl, after 5 min of stirring, α-methylbenzylamine (*S*)-**9** (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 successively. The mixture was stirred and heated at 55°C for 3–6 days. It was then concentrated under vacuum, concentrated ammonia (2 mL) was added, and then the mixture was filtered through a 5 cm pad of silica gel and eluting with ether (100 mL). The filtrate was concentrated under vacuum to give the crude phosphonates as a mixture of four diastereomers. Purification was done by flash chromatography (FC) on silica gel, (eluent, $EtOAc/CH_2Cl_2$: 10/90 to 40/60).

4.1.1. Diethyl (1*S,2*S**,1′*S*)-2-methyl-1-(1′-methylphenylamino)-cyclopropane-phosphonates: (1*S*,2*S*,1′*S*)-6A.b and (1*R*,2*R*,1′*S*)-6C.b**. *Following procedure A*: reaction of acetal **4b** (5 mmol), EtOH (10 mL), TMSCl (cat.), amine (*S*)-**9** (7.50 mmol), AcOH (15 mmol), and $P(OEt)_3$ (1.31 mL, 7.5 mmol), for 40 h at 55°C gave, after standard work-up 2.50 g of a (41.8:46.4:6.1:5.7) diastereomeric mixture of the crude *trans*/*cis* phosphonates. Purification by FC (twice) afforded 771 mg (60%) of a non separable mixture of *trans* diastereomers (1*S*,2*S*,1′*S*)-**6A**.**b** and (1*R*,2*R*,1′*S*)-**6C**.**b**, along with 224 mg (18%) as a mixture.

4.1.1.1. Data for (1*S*,2*S*,1′*S*)-6A.b major *trans* isomer. (Data obtained from a *trans*/*trans* mixture) ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.67 (ddd, $J_{PH}=5.9$ Hz, $J=3.9$ Hz, $J=7.8$ Hz, $1H_{cycle}$), 1.08 (d, $J=5.8$ Hz, 3H), 1.28 (t, $J=7.0$ Hz, 3H), 1.30 (t, $J=7.0$ Hz, 3H), 1.31 (d, $J=6.8$ Hz, 3H), 1.20–1.46 (m, $2H_{cycle}$), 1.76 (br. s, 1H, NH), 4.04 (dq, $J=7.0$ Hz, $^3J_{PH}=1$ Hz, 2H), 4.12 (dq, $J=7.0$ Hz, $^3J_{PH}=1$ Hz, 2H), 4.35 (dq, $J=6.8$ Hz, $^4J_{PH}=3.4$ Hz, 1H), 7.10–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 11.8 (C_4), 16.35 (d, $^3J_{PC}=5.7$ Hz, 1C), 16.5 (d, $^3J_{PC}=5.7$ Hz, 1C), 17.1 (d, $^2J_{PC}=3.8$ Hz, C_2), 19.7 (d, $^2J_{PC}=2.9$ Hz, C_3), 23.3, 34.6 (d, $^1J_{PC}=200$ Hz, C_1), 56.1, 61.4 (d, $^2J_{PC}=6.7$ Hz, 1C), 61.7 (d, $^2J_{PC}=6.7$ Hz, 1C), [6 arom. C: 126.7, 126.8 (2C), 128.1 (2C), 147.0]; ^{31}P NMR ($CDCl_3$, 101 MHz) δ: 29.51 ppm.

4.1.1.2. Data for (1*R*,2*R*,1′*S*)-6C.b major *trans* isomer. (Data obtained from a *trans*/*trans* mixture) ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.08 (ddd, $J=7.7$ Hz, $J=5.2$ Hz, $J_{PH}=6.4$ Hz, $1H_{cycle}$), 0.85 (ddd, $J=14.0$ Hz, $J=9.3$ Hz, $J=5.2$ Hz, $1H_{cycle}$), 1.10 (d, $J=6.0$ Hz, CH_3-C_2), 1.29 (d, $J=6.7$ Hz, 3H), 1.28 (dddd, $J_{cis}=9.3$ Hz, $J_{trans}=7.7$ Hz, $J=6.0$ Hz, $J_{PH\ cis}=14$ Hz, $1H_{cycle}$), 1.31 (t, $J=6.7$ Hz, 3H), 1.33 (t, $J=6.7$ Hz, 3H), 1.76 (br. s, 1H, NH), 4.10 (dq, $^3J_{PH}=4.0$ Hz, $J=6.7$ Hz, 2H), 4.14 (dq, $^3J_{PH}=4.0$ Hz, $J=6.7$ Hz, 2H), 4.29 (dq, $^4J_{PH}=2.8$ Hz, $J=6.7$ Hz, 1H), 7.10–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 11.9, 16.5 (d, $^2J_{PC}=5.1$ Hz, 1C), 16.6 (d, $^2J_{PC}=1.5$ Hz, C_3), 16.7 (d, $^2J_{PC}=5.1$ Hz, 1C), 17.7 (d, $^2J_{PC}=4.8$ Hz, C_2), 25.4, 35.8 (d, $^1J_{PC}=200.6$ Hz, C_1), 56.1, 61.6 (d, $^2J_{PC}=7.2$ Hz, 1C), 61.9 (d, $^2J_{PC}=7.2$ Hz, 1C), [6 arom. C: 126.6, 127.0 (2C), 128.1 (2C), 147.4]; ^{31}P NMR ($CDCl_3$, 101 MHz) δ: 29.88 ppm.

The spectral data are identical with those already reported by us for (1*S*,2*S*,1′*S*) and the (1*S*,2*S*,1′*R*) antipode, respectively.[13]

4.1.2. Diethyl (1*S,2*S**,1′*S*)-2-ethyl-1-(1′-methylphenylamino)-cyclopropane-phosphonates: (1*S*,2*S*,1′*S*)-6A.c and (1*R*,2*R*,1′*S*)-6C.c**. *Following procedure A*: reaction of acetal **4c** (5 mmol), EtOH (10 mL), TMSCl (cat.), amine (*S*)-**9** (7.50 mmol), AcOH (15 mmol), and $P(OEt)_3$ (1.31 mL, 7.5 mmol), for 30 h at 55°C gave, after standard work-up 2.80 g of a (41:41:9:9) diastereomeric mixture of the crude *trans*/*cis*-phosphonates. Purification by FC (twice) furnished 817 mg (50%) of a non separable mixture of *trans* diastereomers (1*S*,2*S*,1′*S*)-**6A**.**c** and (1*R*,2*R*,1′*S*)-**6C**.**c**, along with 407 mg (28%) as a mixture and 48 mg (3%) of a *cis*-(1*R*,2*S*,1′*S*)-**6B**.**c**/*trans* mixture (in 90:10 ratio).

4.1.2.1. Data for (1*S*,2*S*,1′*S*)-6A.c major *trans* isomer. (Data obtained from a *trans*/*trans* mixture) ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.70–0.85 (m, $1H_{cycle}$), 0.94 (t, $J=6.5$ Hz, 3H), 1.05–1.45 (m, $2H_{cycle}$), 1.31 (t, $J=6.7$ Hz, 3H), 1.33 (d, $J=6.4$ Hz, 3H), 1.34 (t, $J=6.7$ Hz, 3H), 1.54 (dq, $J=6.3$ Hz, $J=6.5$ Hz, 2H), 1.80 (br s, NH), 4.00–4.25 (m, 4H), 4.43 (dq, $J_{PH}=3.5$ Hz, $J=6.4$ Hz, 1H), 7.15–7.40 (m, 5H); MS (70 eV) m/z (%): 325 [M^+] (2.6), *187* (100), 186 (53), 105 (88).

4.1.2.2. Data for (1*R*,2*R*,1′*S*)-6C.c major *trans* isomer. (Data obtained from a *trans*/*trans* mixture) ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.13 (ddd, $J=5.5$ Hz, $J=7.2$ Hz, $J=8.2$ Hz, $1H_{cycle}$), 0.84 (ddd, $J=8.9$ Hz, $J=3.9$ Hz, $J=14.4$ Hz, $1H_{cycle}$), 0.95 (t, $J=6.5$ Hz, 3H), 1.05–1.28 (m, $1H_{cycle}$), 1.33 (d, $J=6.4$ Hz, 3H), 1.36 (t, $J=6.7$ Hz, 3H), 1.39 (t, $J=6.7$ Hz, 3H), 1.52 (dq, $J=6.1$ Hz, $J=6.5$ Hz, 2H), 1.60–2.10 (m, NH), 4.12 (dq, $J_{PH}=2.1$ Hz, $J=6.7$ Hz, 2H), 4.15 (dq, $J_{PH}=2.1$ Hz, $J=6.7$ Hz, 2H), 4.30 (dq, $^4J_{PH}=2.6$ Hz, $J=6.8$ Hz, 1H), 7.15–7.40 (m, 5H); MS (70 eV) m/z (%): 325 [M^+] (2), *187* (100), 186 (54), 105 (95).

4.1.2.3. Data for (1*R*,2*S*,1′*S*)-6B.c isolated minor *cis* isomer. $[\alpha]_D=-17.6$ (c 1, $CHCl_3$) e.e. >98%; ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.00–1.26 (m, $2H_{cycle}$), 1.05 (t, $J=7.4$ Hz, 3H), 1.20–1.30 (m, $1H_{cycle}$), 1.34 (t, $J=7.3$ Hz, 3H), 1.35 (d, $J=6.1$ Hz, 3H), 1.36 (t, $J=7.3$ Hz, 3H), 1.45–1.68 (m, 1H), 1.68–1.90 (m, 1H), 1.90–2.20 (m, NH), 4.14 (dq, $J_{PH}=2.1$ Hz, $J=7.3$ Hz, 2H), 4.16 (dq, $J_{PH}=2.1$ Hz, $J=7.3$ Hz, 2H), 4.34 (dq, $^4J_{PH}=2.9$ Hz, $J=6.1$ Hz, 1H), 7.17–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 13.8 (C_5), 16.5 (d, $^3J_{PC}=6.2$ Hz, 2C), 18.5 (d, $^3J_{PC}=3.8$ Hz, C_4), 21.6 (d, $^2J_{PC}=2.9$ Hz, C_3), 22.2, 30.9 (d, $^2J_{PC}=5.7$ Hz, C_2), 36.9 (d, $J=195.9$ Hz, C_1), 56.2, 61.6 (d, $^2J_{PC}=5.2$ Hz, 2C), [6 arom. C: 126.7 (2C), 127.0, 128.3 (2C), 146.1]; ^{31}P NMR ($CDCl_3$, 101 MHz) δ: 28.80 ppm.

4.1.3. Diethyl (1*S,2*S**,1′*S*)-2-benzyl-1-(1′-methylphenylamino)-cyclopropane-phosphonates: (1*S*,2*S*,1′*S*)-6A.d and (1*R*,2*R*,1′*S*)-6C.d**. *Following procedure A*: reaction

of acetal **4d** (550 mg, 0.88 mmol), EtOH (2 mL), TMSCl (cat.), amine (*S*)-**9** (160 mg, 1.32 mmol), AcOH (150 μL), and $P(OEt)_3$ (230 μL, 1.32 mmol), for 60 h at 55°C gave, after standard work-up 1.030 g of a (43:43:7:7) diastereomeric mixture of the crude *trans* phosphonates. Purification by FC (twice) furnished 171 mg (50%) of a non separable mixture of *trans* diastereomers (1*S*,2*S*,1′*S*)-**6A**.**d** and (1*R*,2*R*,1′*S*)-**6C**.**d**, 4 mg (1%) as oil of *cis*-(1*R*,2*S*,1′*S*)-**6B**.**d**, 10 mg (3%) of *cis*-(1*S*,2*R*,1′*S*)-**6D**.**d**, and 20 mg (6%) as a mixture.

4.1.3.1. Data for (1*S*,2*S*,1′*S*)-6A.d (a) and (1*R*,2*R*,1′*S*)-6C.d (b), major *trans* isomer. R_f = 0.38 (Et_2O); R_T = 35.79 min (**a**) and 36.18 min (**b**) [CPSIL-5CB, 200–240°C, 1.3 bar)]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm) (**a**/**b**): 0.28 (ddd, *J* = 5.9 Hz, *J* = 6.8 Hz, *J* = 8.3 Hz, $1H_{cycle}$ **b**), 0.83–1.00 (m, $1H_{cycle}$ **a**+$1H_{cycle}$ **b**), 1.17 (t, *J* = 7.3 Hz, 3H**a**, CH_3), 1.23 (t, *J* = 7.3 Hz, 3H**b**, CH_3), 1.29 (t, *J* = 7.3 Hz, 3H**a**, CH_3), 1.32 (d, *J* = 6.8 Hz, 3H**b**, CH_3-$C_{1'}$), 1.35 (d, *J* = 6.8 Hz, 3H**a**, CH_3-$C_{1'}$), 1.36 (t, *J* = 7.3 Hz, 3H**b**, CH_3), 1.40–1.48 (m, $1H_{cycle}$ **b**), 1.48–1.62 (m, $1H_{cycle}$ **a**), 1.62–1.81 (m, $1H_{cycle}$ **a**), 2.72–2.95 (m, $2H_{benzyl}$ **b**+$2H_{benzyl}$ **a**), 3.75–4.10 (m, 8H, $4CH_2$-O), 4.31 (dq, *J* = 2.9 Hz, *J* = 6.8 Hz, H-$C_{1'}$**b**), 4.40 (dq, *J* = 3.4 Hz, *J* = 6.4 Hz, H-$C_{1'}$**a**), 7.09–7.40 (m, 10H**a**+10H**b**); ^{13}C NMR ($CDCl_3$, 63 MHz) δ (ppm) (**a**/**b**): 15.1 (C_3**b**), 16.3–16.7 (m, 2*C*H_3**a**+2*C*H_3**b**), 18.8 (C_3**a**), 23.4 (*C*H_3-$C_{1'}$**a**), 23.5 (d, $^2J_{PC}$ = 3.8 Hz, C_2**a**), 24.2 (d, $^2J_{PC}$ = 4.6 Hz, C_2**b**), 25.8 (*C*H_3-$C_{1'}$**b**), 32.8 (C_4**b**), 32.9 (C_4**a**), 35.0 (d, $^1J_{PC}$ = 198.7 Hz, C_1**a**), 36.6 (d, $^1J_{PC}$ = 199.6 Hz, C_1**b**), 56.3 ($C_{1'}$**a**), 56.4 ($C_{1'}$**b**), 61.6–62.2 (m, 4C, 2*C*H_2-O**a**/**b**), [24 arom.C: 125.8 (C**a**/**b**), 126.2 (2C**a**/**b**), 126.7 (C**a**/**b**), 127.0 (2C**a**/**b**), 128.1 (2C**a**/**b**), 128.3 (3C**a**/**b**), 141.3 (C**a**), 141.5 (C**b**), 147.0 (C**b**), 147.4 (C**a**)]; ^{31}P NMR ($CDCl_3$, 101 MHz) δ (ppm): 29.24 (**a**) and 29.75 (**b**); MS (70 eV) *m*/*z* (%): 387 [M^+] (4.2), 250 (35), 249 (87), 192 (51), 131 (41), *105* (100); HRMS *m*/*z* (**a**): 387.1953, (**b**): 387.1958 (calcd for $C_{22}H_{30}NO_3P$: 387.1963).

4.1.3.2. Data for (1*R*,2*S*,1′*S*)-6B.d, minor *cis* isomer. R_f = 0.48 (Et_2O); R_T = 37.67 min [CPSIL-5CB, 200–240°C, 1.3 bar)]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.81–0.94 (m, $1H_{cycle}$), 1.09 (ddd, *J* = 4.9 Hz, *J* = 7.3 Hz, *J* = 12.7 Hz, $1H_{cycle}$), 1.28 (d, *J* = 6.8 Hz, 3H, CH_3-$C_{1'}$), 1.34 (t, *J* = 7.3 Hz, 6H, CH_3), 1.32–1.48 (m, $1H_{cycle}$), 2.84 (dd, *J* = 10.9 Hz, *J* = 14.7 Hz, $1H_{benzyl}$), 3.14 (dd, *J* = 4.4 Hz, *J* = 14.7 Hz, $1H_{benzyl}$), 4.14 (dq, *J* = 2.9 Hz, *J* = 7.3 Hz, CH_2-O), 4.15 (dq, *J* = 7.3 Hz, *J* = 7.3 Hz, CH_2-O), 4.31 (dq, *J* = 2.9 Hz, *J* = 6.8 Hz, H-$C_{1'}$), 7.14–7.32 (m, 10H); ^{31}P NMR ($CDCl_3$, 101 MHz) δ (ppm): 29.44; MS (70 eV) *m*/*z* (%): 387 [M^+] (2.1), 250 (27), 249 (51), 192 (35), 131 (26), *105* (100); HRMS *m*/*z*: 387.1971 (calcd for $C_{22}H_{30}NO_3P$: 387.1963).

4.1.3.3. Data for (1*S*,2*R*,1′*S*)-6D.d, minor *cis*. R_f = 0.31 (EtOAc/CH_2Cl_2 15:85); R_T = 33.84 min [CPSIL-5CB, 200°C+3°C/min, 1.3 bar)]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.78–0.89 (m, $1H_{cycle}$), 1.03–1.14 (m, $1H_{cycle}$), 1.30 (d, *J* = 6.8 Hz, 3H, CH_3-$C_{1'}$), 1.38 (t, *J* = 7.3 Hz, 3H, CH_3), 1.40 (t, *J* = 7.3 Hz, 3H, CH_3), 1.40–1.60 (m, $1H_{cycle}$), 2.50 (dd, *J* = 9.3 Hz, *J* = 14.6 Hz, $1H_{benzyl}$), 2.67 (dd, *J* = 4.9 Hz, *J* = 14.6 Hz, $1H_{benzyl}$), 4.06–4.29 (m, 4H, $2CH_2$-O), 4.29 (dq, $^4J_{PH}$ = 2.5 Hz, *J* = 6.8 Hz, H-$C_{1'}$), 6.78–6.90 (m, 1H), 7.05–7.40 (m, 9H); ^{31}P NMR ($CDCl_3$, 101 MHz) δ (ppm): 30.34; MS (70 eV) *m*/*z* (%): 387 [M^+] (1.7), 249 (24), 192 (33), 144 (21), *105* (100), 91 (33); HRMS *m*/*z*: 387.1957 (calcd for $C_{22}H_{30}NO_3P$: 387.1963).

4.1.4. Diethyl (1*S,2*R**,1′*S*)-2-*iso*-propyl-1-(1′-methyl-phenylamino)-cyclopropane-phosphonates: (1*S*,2*R*,1′*S*)-6A.e and (1*R*,2*S*,1′*S*)-6C.e**. *Following procedure A*: reaction of acetal **4e** (1 mmol), EtOH (2 mL), TMSCl (cat.), amine (*S*)-**9** (170 mg, 1.5 mmol), AcOH (170 μL, 3 mmol), and $P(OEt)_3$ (260 μL, 1.5 mmol), for 49 h at 55°C gave, after standard work-up 850 mg of a (38:38:12:12) diastereomeric mixture of the crude *trans* phosphonates. Purification by FC (three times) furnished 70 mg (20%) of a non separable mixture of *trans* diastereomers (1*S*,2*R*,1′*S*)-**6A**.**e** and (1*R*,2*S*,1′*S*)-**6C**.**e**, 8 mg (2%) of minor *cis*-(1*R*,2*R*,1′*S*)-**6B**.**e** (or (1*S*,2*S*,1′*S*)-**6D**.**e**), 4 mg (1%) of minor *cis*-(1*S*,2*S*,1′*S*)-**6D**.**e** (or (1*R*,2*R*,1′*S*)-**6B**.**e**), 24 mg (7%) as a mixture, and 33 mg (14%) of hydroxyphosphonate **11e**.

4.1.4.1. Data for (1*S*,2*R*,1′*S*)-6A.e and (1*R*,2*S*,1′*S*)-6C.e major *trans* isomer. (Data obtained from a *trans*/*trans* mixture) R_f = 0.43 (Et_2O); R_T = 23.73 min and 25.92 min [CPSIL-5CB, 165°C (5 min)+1°C/min to 180°C (20 min)+3°C/min to 240°C (20 min), 1 bar]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.05–0.17 (m, $1H_{cycle}$), 0.70–0.85 (m, $2H_{cycle}$), 0.91 (d, *J* = 6.8 Hz, 6H, $2CH_3$), 0.99 (d, *J* = 6.4 Hz, 3H, CH_3), 0.88–1.01 (m, 1H), 1.04 (d, *J* = 6.8 Hz, 3H, CH_3), 1.08–1.37 (m, 2H), 1.24–1.44 (m, 18H, $4CH_3$+$2CH_3$-$C_{1'}$), 1.50–1.83 (m, $2H_{cycle}$), 1.87 (br s, 2H, NH), 4.00–4.21 (m, 8H, $4CH_2$-O), 4.30 (dq, *J* = 2.4 Hz, *J* = 6.8 HZ, H-$C_{1'}$), 4.42 (dq, *J* = 3.4 Hz, *J* = 6.4 Hz, H-$C_{1'}$), 7.12–7.41 (m, 10H); ^{13}C NMR ($CDCl_3$, 62.86 MHz) δ (ppm): 14.5(C_3), 16.6 (4C, *C*H_3), 18.0 (d, *J* = 3.2 Hz, C_3), 22.2 (1C, *C*H_3-$C_{1'}$), 22.4 (1C, *C*H_3-C-O), 22.6 (1C, *C*H_3-C-O), 22.65 (1C, *C*H_3-C-O), 23.3 (*C*H_3-$C_{1'}$), 25.9 (*C*H_3-$C_{1'}$), 26.7 (C_4), 26.8 (C_4), 30.9 (br s, C_2), 31.5 (d, *J* = 3.3 Hz, C_2), 32.2 (d, $^1J_{PC}$ = 198.3 Hz, C_1), 36.7 (d, $^1J_{PC}$ = 199.7 Hz, C_1), 56.3 (2C, $C_{1'}$), 61.5–61.8 (m, 4C, 4*C*H_2-O), [12 arom. C: 126.4, 126.5, 126.8 (2C), 126.9 (2C), 128.0 (2C), 128.2 (2C), 147.2, 147.5]; ^{31}P NMR ($CDCl_3$, 101 MHz) δ (ppm): 29.99 and 29.41.

4.1.4.2. Data for (1*R*,2*R*,1′*S*)-6B.e (or *cis*-(1*S*,2*S*,1′*S*)-6D.e) minor *cis* isomer. R_f = 0.48 (Et_2O); R_T = 26.62 min [CPSIL-5CB, 165–240°C, 1 bar]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.77 (ddd, *J* = 4.4 Hz, *J* = 8.8 Hz, *J* = 13.7 Hz, $1H_{cycle}$), 0.82–0.94 (m, $1H_{cycle}$), 0.93 (d, *J* = 6.4 Hz, 3H, CH_3), 1.12 (d, *J* = 6.8 Hz, 3H, CH_3), 1.30 (t, *J* = 7.3 Hz, 3H, CH_3-C-O), 1.33 (t, *J* = 7.3 Hz, 3H, CH_3-C-O), 1.34 (d, *J* = 6.8 Hz, 3H, CH_3-$C_{1'}$), 1.25–1.50 (m, H_4), 1.60–1.85 (m, $1H_{cycle}$), 4.01–4.22 (m, 4H, $2CH_2$-O), 4.30 (dq, *J* = 2.9 Hz, *J* = 6.8 HZ, H-$C_{1'}$), 7.10–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ (ppm):, 16.5 (br s, 2*C*H_3), 18.3(C_3), 22.5 (*C*H-C_2), 22.8 (*C*H_3), 22.9 (*C*H_3), 27.8 (*C*H_3-$C_{1'}$), 37.5 (d, $^1J_{PC}$ = 195.9 Hz, C_1), 37.6 (d, *J* = 7.4 Hz, C_2), 56.0 ($C_{1'}$), 61.4 (d, $^2J_{PC}$ = 6.5 Hz, *C*H_2-O), 61.7 (d, $^2J_{PC}$ = 6.5 Hz, *C*H_2-O), [6 arom. C: 126.6 (2C), 126.9, 128.3 (2C), 147.0]; ^{31}P NMR ($CDCl_3$, 101 MHz) δ (ppm): 29.74; MS (70 eV), *m*/*z* (%): 340 [M^++1] (0.6), 339 [M^+] (0.6), 201 (32), *105* (100), 103 (20); HRMS *m*/*z*: 339.1964 (calcd for $C_{18}H_{30}NO_3P$: 339.1963).

4.1.4.3. Data for (1*S*,2*S*,1′*S*)-6D.e (or *cis*-(1*R*,2*R*,1′*S*)-6B.e) minor *cis* isomer. R_f=0.40 (Et_2O); R_T=24.19 min [CPSIL-5CB, 165–240°C, 1 bar]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.52 (d, J=6.4 Hz, 3H, CH_3), 0.70 (d, J=6.8 Hz, 3H, CH_3), 0.57–0.96 (m, 3H), 1.16–1.29 (m, 1H), 1.24 (d, J=6.8 Hz, 3H, CH_3-$C_{1'}$), 1.36 (t, J=7.3 Hz, 3H), 1.37 (t, J=7.3 Hz, 3H), 1.25–1.50 (m, H_4), 1.60–1.85 (m, $1H_{cycle}$), 4.03–4.22 (m, 4H, $2CH_2$-O), 4.26 (dq, J=2.4 Hz, J=6.8 Hz, H-$C_{1'}$), 7.10–7.38 (m, 5H); ^{31}P NMR ($CDCl_3$, 101 MHz) δ (ppm): 31.19.

4.1.4.4. Data for diethyl *rac-trans*-1-hydroxy-2-*iso*-propyl-cyclopropylphosphonate, 11e. R_f=0.08 (EtOAc/CH_2Cl_2: 15/85); R_T=4.51 min [CPSIL-5CB, 165°C, 1 bar]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.61 (m, with J=5.9 Hz, $1H_{cycle}$), 1.02 (d, J=6.8 Hz, 3H, CH_3), 1.07 (d, J=6.8 Hz, 3H, CH_3), 0.90–1.28 (m, $2H_{cycle}$), 1.33 (t, J=6.8 Hz, 3H), 1.34 (t, J=6.8 Hz, 3H), 1.44–1.60 (m, C$H_{i\mathrm{Pr}}$), 2.35 (br s, OH), 4.15 (dq, J=6.8H, J=6.8H, 2H, CH_2-O), 4.16 (dq, J=6.8 Hz, J=6.8 Hz, 2H, CH_2-O); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm): 16.4 (CH_3-C_4), 16.5 (CH_3-C_4), 17.1 (C_3), 22.3 (CH_3), 22.7 (CH_3), 26.7 (C_4), 30.3 (C_2), 52.5 (d, $^1J_{PC}$=224.4 Hz, C_1), 62.4 (br s, CH_2-O), 62.5 (br s, CH_2-O); ^{31}P NMR ($CDCl_3$, 101 MHz) δ (ppm): 24.84; MS (70 eV), m/z (%): 236 (M^+, 2.5), 139 (29), *138* (100), 111 (64); HRMS m/z: 236.1179 (calcd for $C_{10}H_{21}NO_4P$: 236.1177).

4.2. General procedure B

To a solution of cyclopropanone acetal **4** (1 mmol) in alcohol (2 mL), was added one drop of TMSCl, after stirring for 5 min, amine (*S*)-**9** (1.50 mmol), AcOH (3 mmol) and $MgSO_4$ (100 mg) were added. The mixture was stirred and heated at 55°C for 15–18 h before adding trialkylphosphites (1.5 mmol), then the mixture was heated at 55°C for 3–6 days. After standard work-up as in the procedure A, the residue was purified by FC on silica gel.

4.2.1. Diethyl (1*S,2*R**,1′*S*)-2-*tert*-butyl-1-(1′-phenylethylamino)-cyclopropane-phosphonates: (1*S*,2*R*,1′*S*)-6A.f and (1*R*,2*S*,1′*S*)-6C.f**. *Following procedure B*: reaction of acetal **4f** (3 mmol), TMSCl (cat.), EtOH (6 mL), amine (*S*)-**9** (510 μL, 4.5 mmol), AcOH (6 mmol), $MgSO_4$ (300 mg), then $P(OEt)_3$ (780 μL, 1.5 mmol), for 48 h at 55°C gave, after standard work-up 2.62 g of a (50:50) diastereomeric mixture of the crude *trans* phosphonates. Purification by FC furnished 444 mg (42%) of a non separable mixture of *trans* diastereomers (1*S*,2*R*,1′*S*)-**6A**.**f** and (1*R*,2*S*,1′*S*)-**6C**.**f**.

4.2.1.1. Data for (1*S*,2*R*,1′*S*)-6A.f and (1*R*,2*S*,1′*S*)-6C.f major *trans* isomer. R_T=28.10 min (a) and 30.25 min (b) [CPSIL-5CB, 150–175°C, 1 bar)]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.30 (ddd, J=5.4 Hz, J=8.3 Hz, J=8.3 Hz, $1H_{cycle}$), 0.68 (ddd, J=5.9 Hz, J=10.3 Hz, J=15.4 Hz, $1H_{cycle}$), 0.95 (s, 9H, $3CH_3$), 1.05 (s, 9H, $3CH_3$), 1.21–1.42 (m, 18H, $4CH_3$ and $2CH_3$-$C_{1'}$), 0.86–1.43 (m, $4H_{cycle}$), 3.97–4.21 (m, 8H, $4CH_2$-O), 4.29 (dq, J=2.9 Hz, J=6.4 Hz, H-$C_{1'}$), 4.40 (dq, J=3.9 Hz, J=6.4 Hz, H-$C_{1'}$), 7.13–7.36 (m, 10H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm): 12.3 (C_3), 14.5 (C_3), 16.5 ($4CH_3$), 22.6 (CH_3-$C_{1'}$), 25.1 (CH_3-$C_{1'}$), 29.9 (6C, $CH_{3t\text{-butyl}}$), 30.5 ($2C_4$), 32.1 (C_2), 33.0 (C_2), 35.7 (d, $^1J_{PC}$=192.4 Hz, C_1), 36.9 (d, $^1J_{PC}$=193.4 Hz, C_1), 56.4 ($C_{1'}$), 56.8 ($C_{1'}$), 61.4 (d, $^2J_{PC}$=6.5 Hz, 2 CH_2-O), 61.7 (d, $^2J_{PC}$=6.5 Hz, 2 CH_2-O), [12 arom.C: 126.5 (3C), 126.8, 127.4 (2C), 127.7 (2C), 128.2 (2C), 146.2, 147.1]; ^{31}P NMR ($CDCl_3$, 101 MHz) δ (ppm): 30.06 and 29.30; MS (70 eV) m/z (%) (a): 353 [M^+] (0.9), 215 (76), 192 (31), *105* (100), m/z (b): 353 [M^+] (0.1), 215 (71), 192 (26), *105* (100).

4.2.1.2. Diethyl (1*S,2*R**,1′*S*)-2-*tert*-butyl-1-(1′-phenylethylamino)-cyclopropane-phosphonates: (1*S*,2*R*,1′*S*)-6A.f and (1*R*,2*S*,1′*S*)-6C.f. Method II**. *Following procedure A*: 148 mg (14%) of a mixture of *trans*-(1*S*,2*R*,1′*S*)-**6A**.**f** and (1*R*,2*S*,1′*S*)-**6C**.**f** were obtained along with 412 mg (55%) of hydroxyphosphonate **11f**.

4.2.1.2.1. Data for diethyl rac-trans-*2*-tert-*butyl-1-hydroxy-cyclopropylphosphonate, 11f*. R_f=0.20 (EtOAc/CH_2Cl_2: 15/85); R_T=30.54 min and 31.65 min (two enantiomers) [chiral Cydex B, 120°C, 1 bar]; IR (neat): 3256 (OH), 1215 (P=O), 1033 (P-O); ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.88–0.98 (m, $1H_{cycle}$), 1.13 (s, 9H), 1.10–1.39 (m, $2H_{cycle}$), 1.32 (t, J=7.3 Hz, 6H), 1.83 (br s, OH), 4.18 (dq, J=6.3H, J=6.3H, 4H, $2CH_2$-O); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm):, 13.7 (C_3), 16.3 (CH_3), 16.4 (CH_3), 29.6 ($3CH_{3\ t\mathrm{Bu}}$), 30.4 ($C(CH_3)_3$), 32.2 (C_2), 53.05 (d, $^1J_{PC}$=222.4 Hz, C_1), 62.3 (d, $^2J_{PC}$=5.0 Hz, CH_2-O), 62.4 (d, $^2J_{PC}$=5.0 Hz, CH_2-O); ^{31}P NMR ($CDCl_3$, 101 MHz) δ (ppm): 24.46; MS (70 eV), m/z (%): 250 (M^+] (1.2), 193 (42), 181 (89), *138* (100), 125 (58), 111 (65); HRMS m/z: 250.1332 (calcd for $C_{11}H_{23}O_4P$: 250.1333).

4.3. Procedure C

As for procedure B, but DMSO solvent was used instead of alcohol. After heating at 55°C for 3–6 days, the mixture was concentrated under vacuum, concentrated ammonia (2 mL) was added, then the mixture was extracted with EtOAc (2×50 mL). The organic layer was washed with water (2×4 mL) and concentrated, to give after FC the aminophosphonates.

4.3.1. Diisopropyl (1*S,2*S**,1′*S*)-2-methyl-1-(1′-phenylethylamino)-cyclopropane-phosphonates: (1*S*,2*S*,1′*S*)-12A.b and (1*R*,2*R*,1′*S*)-12C.b**. *Following procedure C*: reaction of acetal **4b** (3 mmol), DMSO (6 mL), TMSCl (cat.), *i*-PrOH (600 μL), amine (*S*)-**9** (545 mg, 4.5 mmol), AcOH (510 μL, 4.5 mmol), $MgSO_4$ (300 mg), then $P(O\text{-}i\mathrm{Pr})_3$ (1.11 mL, 4.5 mmol), for 48 h at 55°C gave, after standard work-up 1.82 g of a (50:50) diastereomeric mixture of the crude *trans* phosphonates. Purification by FC furnished 405 mg (60%) of a non separable mixture of *trans* diastereomers (1*S*,2*S*,1′*S*)-**12A**.**b** and (1*R*,2*R*,1′*S*)-**12C**.**b**.

4.3.1.1. Data for (1*S*,2*S*,1′*S*)-12A.b and (1*R*,2*R*,1′*S*)-12C.b major *trans* isomer. R_f=0.30 ($EtOAc/CH_2Cl_2$ 15:85); R_T=33.62 min (**a**) and 34.82 min (**b**) [CPSIL-

5CB, 120°C, 1 bar)]; IR (neat): 3468 (NH), 1244 (P=O), 1107 (P-O); ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.03 (ddd, $J=4.9$ Hz, $J=6.4$ Hz, $J=7.8$ Hz, $1H_{cycle}$), 0.61 (ddd, $J=4.4$ Hz, $J=5.4$ Hz, $J=6.8$ Hz, $1H_{cycle}$), 0.80 (ddd, $J=5.4$ Hz, $J=9.0$ Hz, $J=14.6$ Hz, $1H_{cycle}$), 1.20–1.36 (m, 33H, $8CH_3$, $2CH_3$-$C_{1'}$ and $3H_{cycle}$), 4.31 (dq, $J=2.4$ Hz, $J=7.3$ Hz, H-$C_{1'}$), 4.39 (dq, $J=2.9$ Hz, $J=6.0$ Hz, H-$C_{1'}$), 4.52–4.78 (m, 4H, 4C*H*-O), 7.05–7.43 (m, 10H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm): 11.9 ($2C_4$), 16.2 (C_3) 17.1 (d, $J=3.7$ Hz, C_2), 17.7 (d, $J=5.5$ Hz, C_2), 19.9 (C_3), 23.2 (CH_3-$C_{1'}$), 24.1 (4 CH_3), 25.4 (CH_3-$C_{1'}$), 35.4 (d, $^1J_{PC}=200.5$ Hz, C_1), 36.7 (d, $^1J_{PC}=201.5$ Hz, C_1), 55.9 ($C_{1'}$), 56.0 ($C_{1'}$), 69.6–70.2 (m, 4C, *C*H-O), [12 arom.C: 126.4 (2C), 126.6 (2C), 126.9 (2C), 127.9 (2C), 128.1 (2C), 147.3, 147.6]; ^{31}P NMR ($CDCl_3$, 101 MHz) δ (ppm): 31.44 and 31.17; MS (70 eV) m/z (%): 339 [M$^+$] (0.3), 174 (29), 173 (74), 150 (27), 144 (30), *105* (100); HRMS m/z: (a) 339.1959, (b): 339.1967 (calcd for $C_{18}H_{30}NO_3P$: 339.1963).

4.3.2. Dibenzyl (1*S,2*S**,1′*S*)-2-methyl-1-(1′-phenylethylamino)-cyclopropane-phosphonates: (1*S*,2*S*,1′*S*)-13A.b and (1*R*,2*R*,1′*S*)-13C.b**. *Following procedure C*: reaction of acetal **4b** (1 mmol), DMSO (2 mL), TMSCl (cat.), *n*-butanol (210 μL), amine (*S*)-**9** (180 mg, 1.5 mmol), AcOH (170 μL, 4.5 mmol), $MgSO_4$ (100 mg), then $P(OBn)_3$ (528 mg, 1.5 mmol), for 5.8 days at 55°C gave, after standard work-up 771 mg of a (50:50) diastereomeric mixture of the crude *trans* phosphonates. Purification by FC furnished 180 mg (45%) of a non separable mixture of *trans* diastereomers (1*S*,2*S*,1′*S*)-**13A**.**b** and (1*R*,2*R*,1′*S*)-**13C**.**b** with 40 mg (10%) of a non identified compound.

4.3.2.1. Data for (1*S*,2*S*,1′*S*)-13A.b and (1*R*,2*R*,1′*S*)-13C.b major *trans* isomer. $R_f=0.32$ (Et_2O/pentane 60:40); $R_T=49.63$ min (**a**) and 52.59 min (**b**) [CPSIL 5CB, 200–240°C, 1.3 bar)]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.11 (m, with $J=7.8$ Hz, $1H_{cycle}$), 0.68 (ddd, $J=4.4$ Hz, $J=5.9$ Hz, $J=7.3$ Hz, $1H_{cycle}$), 0.92 (ddd, $J=4.9$ Hz, $J=8.8$ Hz, $J=14.2$ Hz, $1H_{cycle}$), 1.02 (d, $J=5.9$ Hz, 3H, CH_3), 1.22 (d, $J=6.4$ Hz, 3H, CH_3), 1.28 (d, $J=6.4$ Hz, 3H, CH_3), 1.16–1.51 (m, $3H_{cycle}$) 1.80 (br s, 2NH), 4.29 (dq, $J=2.9$ Hz, $J=6.4$ Hz, H-$C_{1'}$), 4.37 (dq, $J=3.4$ Hz, $J=6.4$ Hz, H-$C_{1'}$), 4.97–5.13 (m, 8H, $4CH_2$-O), 7.02–7.47 (m, 30H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) **a**/**b**: 11.8 ($2C_4$), 16.8 (C_3) 17.4 (d, $J=3.8$ Hz, C_2), 17.9 (d, $J=4.8$ Hz, C_2), 20.0 (d, $J=2.9$ Hz, C_3), 23.3 (CH_3-$C_{1'}$), 25.1 (CH_3-$C_{1'}$), 35.0 (d, $J=198.8$ Hz, C_1), 36.0 (d, $J=200.0$ Hz, C_1), 55.9 ($C_{1'}$), 56.1 ($C_{1'}$), 66.9–67.1 (m, 4C, CH-O), [36 arom.C: 126.1–136.9 (34C), 146.8, 147.1]; ^{31}P NMR ($CDCl_3$, 101 MHz) δ (ppm): 31.44 and 31.17; MS (70 eV) m/z (%): 435 [M$^+$] (0.1), 210 (8), 105 (26), 103 (11), *91* (100); HRMS m/z: 435.1966 (calcd for $C_{26}H_{30}NO_3P$: 435.1963).

4.4. Procedure D: Formylation of aminophosphonates completed according to Ref. 16

To a mixture of the major *trans* aminocyclopropanephosphonates **6A**/**6C**, cooled at 0°C, was added a solution of acetic formic anhydride (26 mmol, 26 equiv.), [generated in situ by heating an equimolar amount of acetic anhydride and formic acid (26 mmol, each)]. The mixture was stirred at 0°C for 3–5 h. Then water (40 mL) was added, the resulting mixture was extracted with CH_2Cl_2 (80 mL). The organic layer was washed with a 10% solution of $NaHCO_3$ (70 mL), dried ($MgSO_4$) then concentrated. The residue was purified by FC on silica gel to give the desired formylated aminophosphonates.

4.4.1. Diethyl 1-[formyl-(1′-phenylethylamino)-2-methyl-cyclopropane-phosphonates: (1*R*,2*R*,1′*S*)-14C and (1*S*,2*S*,1′*S*)-14A. *Following procedure D*: reaction of 200 mg (0.64 mmol) of a non separable mixture of major *trans* (1*R*,2*R*,1′*S*)-**6C**.**b** and (1*S*,2*S*,1′*S*)-**6A**.**b** Ac_2O (1.58 mL, 16.6 mmol) and 0.630 mL of HCOOH, for 3 h at 0°C gave, after work-up, 377 mg of residue. Purification by FC (three times) (eluent, MeOH/Et_2O: 3/97 to 10/90) furnished 72 mg (33%) of (1*R*,2*R*,1′*S*)-**14C** as oil, 65 mg (30%) of (1*S*,2*S*,1′*S*)-**14A** as oil and 55 mg (27%) as a mixture.

4.4.1.1. Data for (1*R*,2*R*,1′*S*)-14C. rotamers (**a**/**b**: 85/15): $[\alpha]_D=+104.7$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.41 (ddd, $J=7.3$ Hz, $J=7.3$ Hz, $J=7.4$ Hz, $1H_{cycle}$ **b**), 0.62 (ddd, $J=7.3$ Hz, $J=7.3$ Hz, $J=7.4$ Hz, $1H_{cycle}$ **a**), 0.85–1.01 (m, $1H_{cycle}$ **b**), 0.93 (d, $J=5.9$ Hz CH_3-C_2 **a**), 0.97 (d, $J=5.9$ Hz, CH_3-C_2 **b**), 1.11–1.25 (m, $1H_{cycle}$ **a**), 1.27 (t, $J=6.8$ Hz, 3H **b**), 1.29 (t, $J=6.8$ Hz, 3H **b**), 1.31 (t, $J=6.8$ Hz, 3H **a**), 1.35 (t, $J=6.8$ Hz, 3H **a**), 1.58–1.72 (m, $1H_{cycle}$ **a**/**b**), 1.72 (d, $J=7.3$ Hz, CH_3-$C_{1'}$ **b**), 1.87 (d, $J=7.3$ Hz, CH_3-$C_{1'}$ **a**), 4.00–4.25 (m, 4H **a** and 4H **b**), 4.42 (q, $J=7.3$ Hz, H–$C_{1'}$ **a**), 4.66 (q, $J=7.3$ Hz, H–$C_{1'}$ **b**), 7.08–7.42 (m, 5H **a** and 5H **b**), 8.15 (s, C*H*O **a**), 8.58 (s, C*H*O **b**); ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 13.2 (C_4 **a**), 13.5 (C_4 **b**), 15.2 (C_3 **b**), 15.9 (C_3 **a**), 16.5–23.6 (m, 2C **a**/**b**), 20.4 (d, $^2J_{PC}=2.9$ Hz, C_2 **a**), 20.9 (CH_3-$C_{1'}$ **a**), 21.4 (d, $^2J_{PC}=2.9$ Hz, C_2 **b**), 24.6 (CH_3-$C_{1'}$ **b**), 39.2 (d, $^1J_{PC}=212.1$ Hz, C_1 **b**), 40.8 (d, $^1J_{PC}=217.8$ Hz, C_1 **a**), 61.1 ($C_{1'}$ **b**), 61.8 (d, $^2J_{PC}=7.1$ Hz, O-CH_2 **b**), 62.6 (d, $^2J_{PC}=5.7$ Hz, 2*C* **a**), 62.8 (d, $^2J_{PC}=7.1$ Hz, O-CH_2 **b**), 63.3 ($C_{1'}$ **a**), [6 arom. C: 125.8 (**a**), 127.1 (2C **a**/**b**), 127.5 (**b**), 128.4 (2C **a**), 128.8 (2C **b**), 142.9 (**b**), 143.1 (**a**)], 163.2 (*C*HO **b**), 166.5 (*C*HO **a**); ^{31}P NMR ($CDCl_3$, 101 MHz) δ: **a**/**b**: 24.78/25.76 ppm.

4.4.1.2. Data for (1*S*,2*S*,1′*S*)-14A: rotamers (a/b: 85/15). $[\alpha]_D=-14.3$ (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.62 (m, $1H_{cycle}$ **a**), 0.75 (m, $1H_{cycle}$ **b**), 0.88 (d, $J=5.9$ Hz, CH_3-C_2 **a**), 0.85–1.05 (m, $1H_{cycle}$ **b**), 0.99 (t, $J=7.3$ Hz, 3H **b**), 1.08 (d, $J=6.4$ Hz, CH_3-C_2 **b**), 1.16 (t, $J=7.3$, Hz, 3H **a**), 1.26 (t, $J=7.3$ Hz, 3H **a**), 1.42 (t, $J=7.3$ Hz, 3H **b**), 1.21–1.44 (m, $1H_{cycle}$ **a**), 1.69 (d, $J=7.3$ Hz, CH_3-$C_{1'}$ **b**), 1.72 (d, $J=7.3$ Hz, CH_3-$C_{1'}$ **a**), 1.60–2.10 (m, $1H_{cycle}$ **a**/**b**), 3.90–4.25 (m, 4H **a** and 4H **b**), 4.68 (q, $J=6.8$ Hz, H–$C_{1'}$ **b**), 5.27 (q, $J=7.3$ Hz, H–$C_{1'}$ **a**), 7.09–7.47 (m, 5H **a** and 5H **b**), 8.18 (s, C*H*O **a**), 8.29 (s, C*H*O **b**); ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 13.0 (C_4 **a**), 13.8 (C_4 **b**), 15.2 (C_3 **b**), 16.0 (C_3 **a**), 15.8–16.2 (m, 2C **b**), 16.2 (d, $^3J_{PC}=8.1$ Hz, CH_3 **a**), 16.3 (d, $^3J_{PC}=6.2$ Hz, CH_3 **a**) 17.5 (CH_3-$C_{1'}$ **a**), 20.2 (d, $^2J_{PC}=3.3$ Hz, C_2 **a**), 21.7 (d, $^2J_{PC}=3.8$ Hz, C_2 **b**), 37.9 (d, $^1J_{PC}=219.2$ Hz, C_1 **a**), 38.4 (d, $^1J_{PC}=214.0$ Hz, C_1 **b**), 54.2 ($C_{1'}$ **a**), 58.8 ($C_{1'}$ **b**), 61.4 (d, $^2J_{PC}=7.0$ Hz, O-CH_2 **b**), 62.5 (d, $^2J_{PC}=3.0$ Hz, O-CH_2 **a**), 62.6 (d, $^2J_{PC}=3.0$ Hz, O-CH_2 **a**), 62.9 (d, $^2J_{PC}=5.2$ Hz, O-CH_2

b), [6 arom. C: 126.7 (2C **b**), 127.1 (**a**), 127.2 (**b**), 127.6 (2C **a**), 127.9 (**a**), 128.3 (2C **b**), 141.3 (**a**), 141.8 (**b**),], 164.1 (*C*HO **b**), 166.8 (*C*HO **a**); ^{31}P NMR ($CDCl_3$, 101 MHz) δ: **a**/**b**: 24.30/25.33 ppm.

4.4.2. Diisopropyl 1-[formyl-(1′-phenylethylamino)-2-methyl-cyclopropane-phosphonates: (1*R*,2*R*,1′*S*)-15C and (1*S*,2*S*,1′*S*)-15A. *Following procedure D*: reaction of a non separable mixture of major *trans* (1*R*,2*R*,1′*S*)-**12C**.**b** and (1*S*,2*S*,1′*S*)-**12A**.**b** (283 mg, 0.83 mmol) with Ac_2O (2.5 mL) and HCOOH (1 mL), for 10 h at 0°C gave, after work-up, 394 mg of residue. Purification by FC (two times) (eluent, MeOH/Et_2O: 15/85 to 50/50) furnished 116 mg (38%) of pure (1*R*,2*R*,1′*S*)-**15C** as oil, 115 mg (38%) of pure (1*S*,2*S*,1′*S*)-**15A** as oil.

4.4.2.1. Data for (1*R*,2*R*,1′*S*)-15C. $[\alpha]_D$ = +118.7 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.61 (ddd, *J* = 5.9 Hz, *J* = 7.7 Hz, *J* = 7.9 Hz, $1H_{cycle}$), 0.95 (d, *J* = 6.3 Hz CH_3), 1.15–1.29 (m, $1H_{cycle}$), 1.34 (d, *J* = 6.3 Hz, 6H), 1.40 (dd, *J* = 6.3 Hz, *J* = 6.3 Hz, 6H), 1.62–1.80 (m, $1H_{cycle}$), 1.80 (d, *J* = 7.3 Hz CH_3), 4.47 (d, *J* = 7.3 Hz, 1H), 4.69 (sept, *J* = 6.3 Hz, C$H_{i\mathrm{Pr}}$), 4.75 (sept, *J* = 6.3 Hz, C$H_{i\mathrm{Pr}}$), 7.12–7.48 (m, 5H), 8.20 (s, C*H*O); ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 13.4 (*C*H_3-C_2), 15.9 (C_3), 20.6 (d, *J* = 3.3 Hz, C_2), 21.0 (*C*H_3-$C_{1'}$), 24.0 (2C), 24.1 (2C), 41.7 (d, $^1J_{PC}$ = 219.4 Hz, C_1), 63.4 ($C_{1'}$), 71.4 (O-*C*H-), 71.5 (O-*C*H-), [6 arom. C: 127.0, 127.2 (2C), 128.5 (2C), 143.4], 166.9 (*C*HO); ^{31}P NMR ($CDCl_3$, 101 MHz) δ: 22.50 ppm.

4.4.2.2. Data for (1*S*,2*S*,1′*S*)-15A. $[\alpha]_D$ = −14.5 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.65 (ddd, *J* = 6.9 Hz, *J* = 7.0 Hz, *J* = 7.2 Hz, $1H_{cycle}$), 0.92 (d, *J* = 6.4 Hz CH_3), 1.18 (d, *J* = 6.3 Hz, CH_3), 1.19 (d, *J* = 6.3 Hz, CH_3), 1.29 (d, *J* = 6.3 Hz, CH_3), 1.30 (d, *J* = 6.3 Hz, CH_3), 1.23–1.43 (m, $1H_{cycle}$), 1.74 (d, *J* = 7.3 Hz, CH_3), 1.67–1.92 (m, $1H_{cycle}$), 4.61 (sept, *J* = 6.3 Hz, C$H_{i\mathrm{Pr}}$), 4.67 (sept, *J* = 6.3 Hz, C$H_{i\mathrm{Pr}}$), 5.24 (q, *J* = 7.3 Hz, 1H), 7.12–7.34 (m, 3H), 7.34–7.52 (m, 2H), 8.20 (s, C*H*O); ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 13.2 (*C*H_3-C_2), 16.1 (C_3), 17.7 (*C*H_3-$C_{1'}$), 20.5 (C_2), 23.8 (d, $^2J_{PC}$ = 4.0 Hz, 2C), 23.9 (d, $^2J_{PC}$ = 4.0 Hz, 2C), 38.9 (d, $^1J_{PC}$ = 221.1 Hz, C_1), 54.6 ($C_{1'}$), 71.3 (d, $^2J_{PC}$ = 6.3 Hz, O-*C*H-), 71.4 (d, $^2J_{PC}$ = 6.3 Hz, O-*C*H-), [6 arom. C: 127.0, 127.7 (2C), 127.9 (2C), 141.3], 167.0 (*C*HO); ^{31}P NMR ($CDCl_3$, 101 MHz) δ: 21.98 ppm.

4.4.3. Diethyl 1-[formyl-(1′-phenylethylamino)-2-ethyl-cyclopropane-phosphonates: (1*R*,2*R*,1′*S*)-16C and (1*S*,2*S*,1′*S*)-16A. *Following procedure D*: reaction of 130 mg (0.4 mmol) of a non separable mixture of major *trans* (1*R*,2*R*,1′*S*)-**6C**.**c** and (1*S*,2*S*,1′*S*)-**6A**.**c**, Ac_2O (980 μL, 10.4 mmol) and HCOOH (390 μL), for 19 h at 0°C gave, after work-up, 187 mg of residue. Purification by FC (three times) (eluent, EtOAc/CH_2Cl_2: 20/80–70/30) afforded only 11 mg (8%) of one diastereomer (1*R*,2*R*,1′*S*)-**16C** (or (1*S*,2*S*,1′*S*)-**16A**), 102 mg (72%) as a mixture of (1*R*,2*R*,1′*S*)-**16C** and (1*S*,2*S*,1′*S*)-**16A**.

4.4.3.1. Data for (1*R*,2*R*,1′*S*)-16C or (1*S*,2*S*,1′*S*)-16A. (**a**/**b** rotamers: 85/15): R_f = 0.38 (EtOAc/CH_2Cl_2 30:70); R_T = 40.50 min [CPSIL-5CB, 180–200°C, 1 bar)]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm) **a**/**b** rotamers: 0.40 (m, with *J* = 7.8 Hz, $1H_{cycle}$ **b**), 0.63 (m, with *J* = 5.4 Hz, *J* = 7.3 Hz, $1H_{cycle}$ **a**), 0.91 (d, *J* = 5.6 Hz, 3H, CH_3-C-C_2 **a**), 0.70–0.96 (m, CH_2-C_2 **a**), 1.33 (t, *J* = 7.3 Hz, 3H, O-C-CH_3 **a**), 1.38 (t, *J* = 7.3 Hz, 3H, O-C-CH_3 **a**), 1.48–1.71 (m, $2H_{cycle}$ **a**), 1.74 (d, *J* = 7.3 Hz, CH_3-$C_{1'}$ **b**), 1.87 (d, *J* = 7.3 Hz, CH_3-$C_{1'}$ **a**), 3.98–4.26 (m, 4H**a**+4H**b**, $2CH_2$-O), 4.43 (q, *J* = 7.3 Hz, H-$C_{1'}$ **a**), 5.67 (q, *J* = 7.3 Hz, H-$C_{1'}$ **b**), 7.07–7.43 (m, 5H**a**+5H**b**), 8.18 (s, N-C*H*O **a**), 8.56 (s, N-C*H*O **b**); ^{31}P NMR ($CDCl_3$, 101 MHz) δ (ppm): 24.68 (**a**) and 25.50 (**b**).

4.5. Procedure E: Hydrogenolysis of formylated aminophosphonates

To a solution of formylated aminophosphonates (0.25 mmol) in EtOH (2 mL), was added 2N HCl (2 mL) and 20% $Pd(OH)_2$/C (Pearlman's catalyst, 80% w/w). 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 50°C for 40–72 h, the reaction was then degassed under a stream of argon, filtered through paper, and the collected solid was washed with EtOH (3×10 mL). The combined filtrate and washings were concentrated and the resulting residue was neutralised with concentrated ammonia (0.2 mL). Purification by FC on silica gel gave the desired aminophosphonate.

4.5.1. Diethyl (1*S*,2*S*)-1-amino-2-methyl-cyclopropane-phosphonate, 17A. *Following procedure E*: reaction of formylated aminophosphonate (1*S*,2*S*,1′*S*)-**14A** (70 mg 0.21 mmol), EtOH (2 mL), 2N HCl (2 mL), $Pd(OH)_2$/C (60 mg), for 50 h at 50°C under H_2 (1 atm) gave, after work-up, and FC (eluent, MeOH/CH_2Cl_2: 4/96) 30 mg (80%) of (1*S*,2*S*)-**17A** as a yellow oil.

4.5.1.1. Data for (1*S*,2*S*)-17A. $[\alpha]_D$ = +24.0 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.41 (ddd, *J* = 6.4 Hz, *J* = 4.4 Hz, *J* = 7.3 Hz, $1H_{cycle}$), 1.17 (t, *J* = 6.4 Hz, 3H), 1.30 (t, *J* = 6.9 Hz, 3H), 1.31 (t, *J* = 6.9 Hz, 3H), 1.14–1.42 (m, $2H_{cycle}$), 1.52 (br s, NH_2), 4.07 (dq,, $^2J_{PH}$ = 3.4 Hz, *J* = 6.9 Hz, 2H), 4.10 (dq,, $^2J_{PH}$ = 3.4 Hz, *J* = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 11.1 (CH_3-C_2), 16.41 (d, $^2J_{PC}$ = 5.0 Hz, 1C), 16.42 (d, $^3J_{PC}$ = 5.0 Hz, 1C), 16.7 (d, $^2J_{PC}$ = 3.3 Hz, C_2), 19.0 (C_3), 30.9 (d, $^1J_{PC}$ = 205.9 Hz, C_1), 61.8 (d, $^2J_{PC}$ = 6.2 Hz, 1C), 61.9 (d, $^2J_{PC}$ = 6.2 Hz, 1C); ^{31}P NMR ($CDCl_3$, 101 MHz) δ: 29.28 ppm; in agreement with those of the enantiopure (1*S*,2*S*) isomer.[13,14]

4.5.2. Diisopropyl (1*S*,2*S*)-1-amino-2-methyl-cyclopropane-phosphonate 18A. *Following procedure E*: reaction of formylated aminophosphonate (1*S*,2*S*,1′*S*)-**15A** (80 mg 0.22 mmol), EtOH (2 mL), 2N HCl (2 mL), $Pd(OH)_2$/C (64 mg), for 72 h at 50°C under H_2 (1 atm) gave, after work-up, and FC (eluent, MeOH/CH_2Cl_2: 4/96) 40 mg (79%) of (1*S*,2*S*)-**18A** as a yellow oil.

4.5.2.1. Data for (1*S*,2*S*)-18A. $[\alpha]_D$ = +19.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.37 (ddd, *J* = 4.4 Hz, *J* = 6.4 Hz, *J* = 6.4 Hz, $1H_{cycle}$), 1.15 (t,

$J=5.9$ Hz, CH_3-C_2, 3H), 1.27 (t, $J=6.4$ Hz, 12H), 1.10–1.45 (m, $2H_{cycle}$), 1.59 (br s, NH_2), 4.61 (sept, $J=6.4$ Hz, CH_{iPro}), 4.64 (sept, $J=6.4$ Hz, CH_{iPro}); ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 11.3 (CH_3-C_2), 16.7 (C_2), 19.0 (C_3), 24.0 (4C), 31.7 (d, $^1J_{PC}=206.1$ Hz, C_1), 70.1 (O-*C*H-), 70.2 (O-*C*H-); ^{31}P NMR ($CDCl_3$, 101 MHz) δ: 27.72 ppm;

4.5.3. Diethyl (1*R*,2*R*)-1-amino-2-methyl-cyclopropane-phosphonate, 17C. *Following procedure E*: reaction of formylated aminophosphonate (1*R*,2*R*,1′*S*)-**14C** (60 mg 0.18 mmol), EtOH (2 mL), 2N HCl (2 mL), $Pd(OH)_2/C$ (48 mg), for 39 h at 50°C under H_2 (1 atm) gave, after work-up, and FC (eluent, $MeOH/CH_2Cl_2$: 4/96 to 6/94) 32 mg (86%) of (1*R*,2*R*)-**17C** as a yellow oil.

4.5.3.1. Data for (1*R*,2*R*)-17C. $[\alpha]_D=-23.5$ (*c* 1.2, $CHCl_3$), all spectral data are identical with those of antipode (+)-**17A**.

4.6. Procedure F: Hydrolysis of aminophosphonates according to our reported method[13]

4.6.1. (1*S*,2*S*)-1-Amino-2-methyl-cyclopropane-phosphonic acid, (+)-3b. *Following procedure F*: reaction of diethyl aminophosphonate (1*S*,2*S*)-**17A** (103 mg, 0.5 mmol), CH_2Cl_2 (5 mL), TMSI (300 mg, 1.5 mmol), then EtOH (2.5 mL) and propylene oxide (1 mL), for 10 h at rt gave, after usual work-up and crystallisation 130 mg (86%) of (1*S*,2*S*)-(+)-**3b** as a white solid.

4.6.1.1. Data for (+)-(1*S*,2*S*)-3b. $[\alpha]_D=+33.6$ (*c* 1, H_2O), $[\alpha]_D=+45.0$ (*c* 0.2, H_2O); ^1H NMR (D_2O, $\delta_{HOD}=4.60$ ppm, 250 MHz) δ: 0.58 (ddd, $J_{trans}=6.8$ Hz, $J=6.4$ Hz, $J_{PH\ trans}=6.9$ Hz, $1H_{cycle}$), 1.00 (d, $J=6.4$ Hz, 3H, CH_3-C_2), 1.06 (ddd, $J_{cis}=9.4$ Hz, $J_{gem}=6.4$ Hz, $^3J_{PH\ cis}=12.7$ Hz, 1H), 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); ^{13}C NMR (D_2O, 63 MHz) δ: 10.9 (C_4), 14.8 (C_2), 16.0 (C_3), 33.6 (d, $^1J_{PC}=192.5$ Hz, C_1); ^{31}P NMR ($CDCl_3$, 101 MHz) δ: 13.36.

4.6.2. (1*S*,2*S*)-1-Amino-2-methyl-cyclopropane-phosphonic acid, (+)-3b. *Following procedure F*: reaction of diisopropyl amino-phosphonate (1*S*,2*S*)-**18A** (35 mg, 0.15 mmol), CH_2Cl_2 (1.5 mL), TMSI (90 mg, 0.45 mmol), then EtOH (1 mL) and propylene oxide (0.5 mL), for 10 h at rt gave, after usual work-up and crystallisation 22 mg (98%) of (1*S*,2*S*)-(+)-**3b** as an amorphous solid. $[\alpha]_D=+33.3$ (*c* 1, H_2O), all spectral data are identical to those noted above.

4.6.3. (1*R*,2*R*)-1-Amino-2-methyl-cyclopropane-phosphonic acid, (−)-3b. *Following procedure F*: reaction of diethyl amino-phosphonate (1*R*,2*R*)-**17C** (20 mg, 0.116 mmol), CH_2Cl_2 (2 mL), TMSI (60 μL, 0.30 mmol), then EtOH (2 mL) and propylene oxide (0.6 mL), for 10 h at 20°C gave, after usual work-up, 14 mg (91%) of (1*R*,2*R*)-(−)-**3b** as an amorphous white solid.

4.6.3.1. Data for (−)-(1*R*,2*R*)-3b. $[\alpha]_D=-43.5$ (*c* 0.2, H_2O), [lit.[10b] $[\alpha]_D=-45.6$ (*c* 0.2, H_2O)], the spectral data are in agreement with those of the antipode (1*S*,2*S*)-(+)-**3a** and with the literature.[10b]

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