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Synthesis of α-amino tetrahydropyranyl-, tetrahydrothiopyranyl-, 4- and 3-piperidinyl-phosphonic acids via phosphite addition to iminium ions☆

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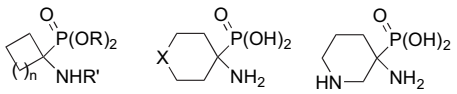
Abstract—α-Amino cyclobutyl-, cyclopentyl-, cyclohexyl- and 4- and 3-heterocyclohexyl-phosphonates were efficiently prepared from carbocyclic and heterocyclic ketones, by nucleophilic addition of phosphite to the iminium ion formed by in situ condensation of these ketones with benzylic amines. Cleavage of the benzyl groups and acidic hydrolysis of the resulting α-amino heterocyclohexyl-phosphonates gave, in a three-step sequence from ketones, new 4- and 3-heterocyclohexyl-phosphonic acids.

1. Introduction

Due to their potential biological activity[1] and their use as building blocks for phosphorus-containing peptide mimetics, derivatives of phosphonic acid analogues of α-amino acids are of considerable current interest. Several α-aminophosphonic acid derivatives show activity as enzyme inhibitors, antibacterials, herbicides, fungicides or plant growth regulators.[2] Other α-aminophosphonic acid derivatives, in particular phosphorus-containing peptide mimetics, have been prepared. These acid derivatives, in which the tetrahedral phosphorus moiety acts as a transition-state analogue of peptide bond cleavage, selectively inhibit peptidases and proteinases (e.g., HIV protease,[3] serine protease[4]). Such an impressive array of applications has recently stimulated considerable effort towards the asymmetric synthesis of α-aminophosphonic acids.[5–7]

In addition, cyclic or heterocyclic rings introduced into the molecular skeleton increase its rigidity and modify electronic effects. Thus in recent years, many cyclic α-aminophosphonic acids **1** (R=H) or -phosphonates **1** (R=alkyl) have been prepared, such as derivatives of α-aminocyclopropylphosphonic acid,[8–10] as well as their cyclobutyl,[10b] cyclopentyl[11] and cyclohexyl analogues.[12] These compounds were prepared either from cycloalkanones or derivatives by Mannich-type reactions,[13] or from cycloalkylphosphonates by electrophilic azidation.[10b]

However, very few examples of heterocyclic α-aminophosphonic acids **2** or the corresponding phosphonates have been reported in the literature; only the 4-aminobutyric acid (GABA)[14] analogue **2a** (X=NH),[15] the pyran phosphonate derivative of **2b** (X=O)[16] and thiopyran phosphonate derivative of **2c** (X=S) are described.[17] Among these synthetic approaches, only one describes a total synthesis and isolation of free α-amino(4-pyrrolidine)phosphonic acid **2a** (X=NH).[15c] In contrast, pyran acid **2b**, thiopyran acid **2c** and especially 3-pyrrolidine acid analogue **3** are still unknown. In all these synthetic approaches, the Kabachnick–Fields reaction[16a] was used from heterocyclohexanones, to provide α-aminophosphonates with moderate to good yields, accompanied, in some cases, with α-hydroxyphosphonate derivatives as byproducts (Scheme 1).



Scheme 1.

We have previously reported a simple and convenient synthesis of 1-aminocyclopropanephosphonic acids **4** (ACC analogues), in three steps, starting from cyclopropanone

☆ Part of this study was previously reported at the Organic Chemistry Symposium at Marseille (GECO 46, September 2005), France.

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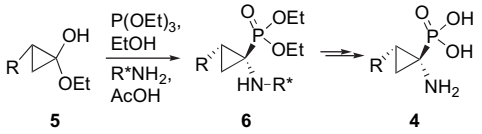
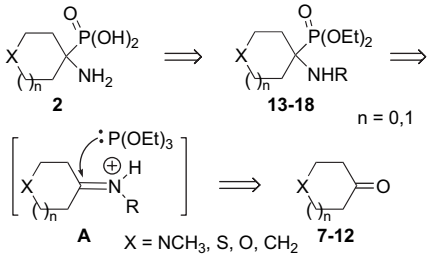
hemi-acetals **5** and proceeding via aminophosphonates **6** (Scheme 2).[9]



Scheme 2.

As part of our ongoing programme in this area, we decided to study the addition of triethyl phosphite to the iminium ions **A** of readily available heterocyclic ketones **7–12**. This one-pot reaction, involving the iminium species **A** as intermediate, should occur in the presence of benzylamine derivatives to give the desired aminophosphonates **13–18** (Scheme 3).



Scheme 3.

2. Results and discussion

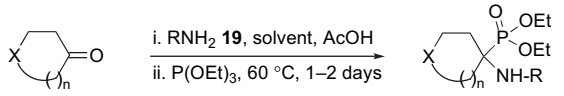
The reactions were carried out using a one-pot procedure. Benzylamine derivatives, α-methylbenzylamine **19a**, benzylamine **19b**, α-phenylglycinol **19c** and *p*-methoxybenzylamine **19d**, were selected for their efficient reaction to form the iminium ions **A**, and in particular for their straightforward cleavage by catalytic hydrogenolysis at the end of the synthetic sequence. In addition, the phenylglycinol derivative can be cleaved by an oxidative degradation with $NaIO_4$, whereas, the *p*-methoxybenzyl group can be cleaved by a DDQ oxidation followed by basic hydrolysis.

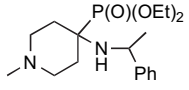
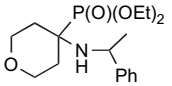
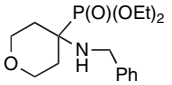
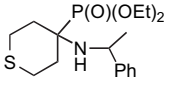
The standard one-pot procedure of ketones **7–12** with amine derivatives **19** was carried out in EtOH in the presence of 2 equiv of AcOH, 1 equiv of $MgSO_4$ and 1.5 equiv of triethyl phosphite at 50–60 °C for 1 day. The commercially available heterocyclic ketones **7–9** were reacted with benzylamine derivatives **19a–d**, to give the iminium ion intermediates **A** before triethyl phosphite addition to furnish aminophosphonates **13–15** in good yields (46–92%) (Table 1, entries 1–7).

By comparison, conducting the same reaction with cyclic ketones (cyclohexanone **10** and cyclobutanone **12**), in EtOH for 1–4 days, gave the corresponding aminophosphonates **16** and **18** in good yields (93% and 50%, respectively) (Table 1, entries 8 and 10). However, lower yields were obtained for aminophosphonates **16–18** in DMSO as a solvent in the presence of $MgSO_4$ at 55 °C for 2 days (Table 1, entries 8–10). These new aminophosphonates **16–18** are of particular interest, since the dibutyl phosphonate analogue of **16**, known as Trakephon®, is a highly efficient herbicide.[12a,b]

On the other hand, the commercially available *N*-Boc-3-piperidone **20a**, in which the heteroatom is in the 3-position to the carbonyl function, underwent a one-pot reaction with amine **19a** to give aminophosphonate **21a**, for the first time, in 54% yield as a mixture of two diastereoisomers. However, with the benzylamine **19b** aminophosphonate **21a′** was

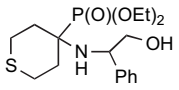
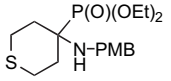
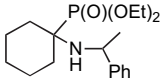
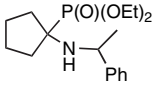
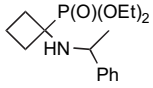
Table 1. Preparation of aminophosphonates **13–18** from ketones **7–12**[a]



Entry	Ketone 7–12			RNH_2 19a–d[b]	Solvent	Time (h)	Yield (%) EtOH (DMSO)[c]	Phosphonates 13–18	
		n	X						
1	**7**	2	N-Me	**19a**	EtOH	18	71 (36)	**13**	
2	**7**	2	N-Me	**19a**	Toluene/CH_3CN[d]	18	30	**13**	
3	**8**	2	O	**19a**	EtOH	30	66	**14a**	
4	**8**	2	O	**19b**	EtOH	22	55	**14b**	
5	**9**	2	S	**19a**	EtOH	18	92	**15a**	

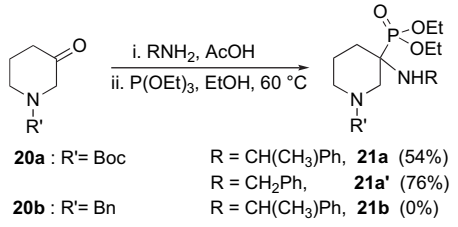
(*continued*)

Table 1. *(continued)*

Entry		Ketone **7–12**		RNH_2 **19a–d**[b]	Solvent	Time (h)	Yield (%) EtOH (DMSO)[c]		Phosphonates **13–18**
		n	X						
6	**9**	2	S	**19c**	EtOH	39	46	**15b**	
7	**9**	2	S	**19d**	EtOH	24	80	**15c**	
8	**10**	2	CH_2	**19a**	EtOH	20	93 (43)	**16**	
9	**11**	1	CH_2	**19a**	DMSO	48	NR[e] (76)	**17**	
10	**12**	0	CH_2	**19a**	EtOH	100	50 (30)	**18**	

[a] Reactions of ketones **7–12** with amines **19** were carried out in the presence of $MgSO_4$.
[b] Amines, **19a**: H_2N–$CH(CH_3)Ph$; **19b**: H_2N–CH_2Ph; **19c**: H_2N–$CH(CH_2OH)Ph$; **19d**: H_2N–$CH_2C_6H_4$–*p*OMe.
[c] Reactions in DMSO were run at 55 °C for 2 days.
[d] The reaction was run with $HP(O)(OEt)_2$ and catalyzed with 5 mol % of Me_2AlCl (Ref. 18).
[e] NR=not run.

obtained in 76% yield. In contrast, the *N*-benzyl-3-piperidone **20b** did not lead to the expected phosphonate **21b**, but to a mixture of degradation products (Scheme 4).

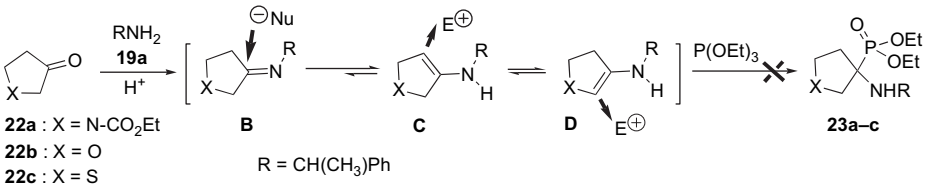


Scheme 4.

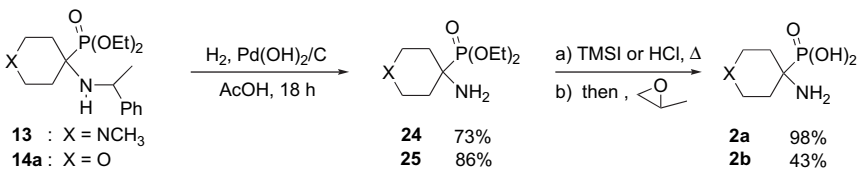
To better understand this behaviour, we attempted to react α-methylbenzylamine **19a** with 3-heterocyclopentanones **22a–c**, but none among them gave the corresponding aminophosphonates **23a–c** under these conditions. We can tentatively explain this by the fact that the iminium intermediate **B** is not favoured, and undergoes a double bond migration to the heterocyclic enamines **C** and **D**, thus preventing the nucleophilic attack of the phosphite on imine **B**. Such migration has already been reported,[19] and could allow electrophilic reaction of enamine **C** or **D** (Scheme 5).[20]

We then submitted the heterocyclic phosphonates **13–15** to the deprotection sequence. The aminophosphonates **13** and **14a** reacted under mild conditions (20% $Pd(OH)_2$/C, and 1 atm H_2) to cleave the benzyl group affording free aminophosphonates **24** and **25**, in a good yield (Scheme 6).

Subsequent hydrolysis of aminophosphonate **24** was accomplished by 6 N HCl solution at reflux for 7 h, followed by



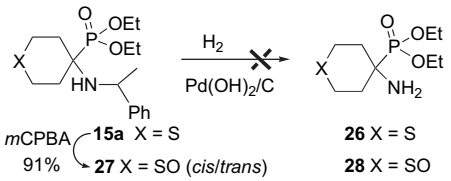
Scheme 5.



Scheme 6.

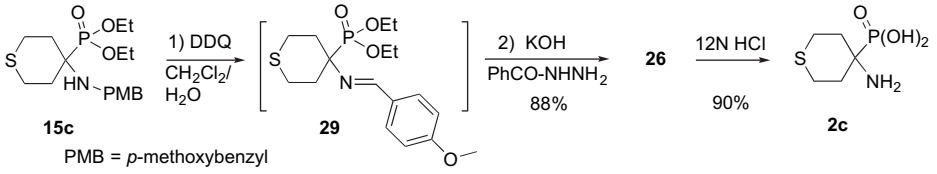
treatment with propylene oxide to provide, the previously unknown *N*-methyl-4-aminopiperidine-phosphonic acid **2a**. Surprisingly, hydrolysis of the phosphonate moiety of **24** with TMSI led only to the formation of byproducts with a small amount of the desired acid **2a**. On the other hand, treatment of aminophosphonate **25** with the trimethylsilyl iodide in dichloromethane followed by the addition of propylene oxide in ethanol furnished, for the first time, aminophosphonic acid **2b** in 43% yield.

N-Benzyl cleavage of **15a** (X=S) was unsuccessful under the same conditions (H_2, $Pd(OH)_2$/C, AcOH), or with other known debenzylation procedures (H_2, Pd/C, HCl; Na/NH_3 liq. or Na/naphthalene). Knowing that the sulfur group could poison the palladium catalyst, we oxidized **15a** by *m*CPBA (1 equiv) to afford a mixture of unseparable sulfoxides **27** (cis/trans: 37/63) in 91% yield. Subsequent hydrogenolysis (H_2, $Pd(OH)_2$/C) of this cis/trans **27** mixture did not furnish the expected free amine **28** (cis/trans), returning the starting sulfoxides unreacted (Scheme 7). Similarly, an attempted cleavage of the phenylglycinol group of **15b** by a known oxidative degradation with $Pb(OAc)_4$[21] did not furnish **26**.



Scheme 7.

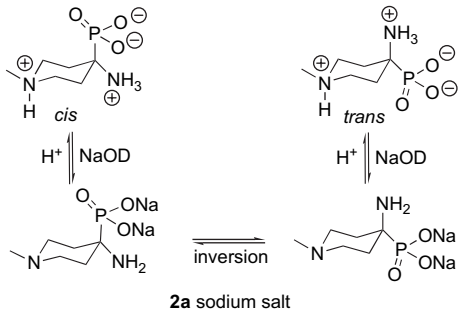
Nevertheless, cleavage of **15c** (Table 1, entry 6) by DDQ (H_2O/CH_2Cl_2: 1/9) at 20 °C,[22] provided, after purification on silica gel, the corresponding free aminophosphonate **26**, accompanied by imine **29** (Scheme 8). However, treatment



Scheme 8.

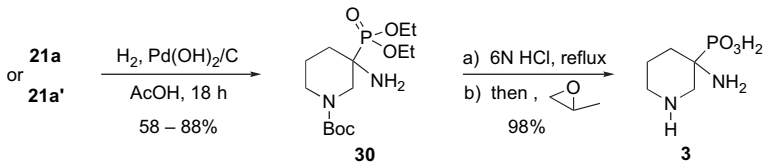
of the reaction mixture with 2 N KOH in the presence of benzoyl hydrazine, to trap the highly reactive *p*-anisaldehyde, furnished exclusively the desired aminophosphonate **26** in 88% yield.

TMSBr followed by propylene oxide treatment gave a mixture of acid **2c** and degradation products. It is worthy of note that the NMR spectra of **2a** in D_2O solution showed two diastereomers, due to the pyramidalization of the nitrogen atom in acidic medium, as previously described by Kafarski.[15c] Deprotection of the ring nitrogen in neutral or basic solution speeds up the nitrogen inversion and makes the whole process faster. Thus, the coalescence of the two singlets in ^{31}P NMR was observed on addition of NaOD to the solution, and forming **2a** sodium salt (Scheme 9, see also Section 4).



Scheme 9.

On the other hand, in the 3-heterocyclic system, cleavage of the benzyl group of compounds **21a** or **21a′** under mild conditions (20% $Pd(OH)_2$/C and 1 atm H_2) furnished the corresponding free amine **30** in good yield 76% or 88%, respectively. Phosphonate hydrolysis and Boc deprotection of **30** were accomplished simultaneously in 6 N aq HCl solution at reflux, to give quantitatively the amino acid hydrochloride **3·2HCl**. Treatment of this amino acid salt with propylene oxide provided for the first time the racemic free aminophosphonic acid **3** in excellent yield. However, the use of TMSI for hydrolysis of **30** was ineffective once more (Scheme 10).



Scheme 10.

Hydrolysis of **26** with 12 N HCl solution at reflux, followed by treatment with propylene oxide provided the new 4-tetrahydrothiopyranylphosphonic acid **2c**, in quantitative yield. We found that hydrolysis of phosphonate **26** with TMSI or

3. Conclusion

We have developed an easy and efficient three-step synthesis of new heterocyclic α-aminophosphonic acids **2** and **3**. Thus,

starting from readily available cyclic and heterocyclic ketones **7**–**12** and **20**, we have demonstrated that the iminium ion formed from these ketones undergoes nucleophilic addition of phosphite to give the cyclic and heterocyclic aminophosphonates **13**–**18** and **21** in good yield. Subsequent hydrogenolysis of the benzyl group (for tetrahydropyran **14** and piperidine derivatives **13** and **21**) and hydrolysis of phosphonate functions were accomplished with good yields. However, deprotection of the *N*-PMB group (for the tetrahydrothiopyran derivative) required oxidation with DDQ. The stable cyclic aminophosphonates **16**–**18**, analogues of the biologically active molecule Trakephon®, were not transformed into their corresponding aminophosphonic acids, but may be performed straightforwardly using a reported method.[9c] We are currently developing an asymmetric version to prepare the homochiral 3-heterocyclic aminophosphonic acids.

4. Experimental

4.1. General

Except where otherwise indicated, all reactions were carried out under argon with magnetic stirring. Di- and triethylphosphite were distilled at reduced pressure and stored under argon (see Table 1). 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. IR spectra were recorded on a Perkin–Elmer (spectrum one) spectrophotometer. Melting points were determined on a Büchi B-545 capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured on a Bruker AM250 (250 MHz) or Bruker AC360 (360 MHz) spectrometer. Chemical shifts were recorded in parts per million from the solvent resonance ($CDCl_3$ at 7.27 ppm and D_2O at 4.8 ppm). ^{13}C NMR spectra were measured on a Bruker AM250 (62.9 MHz), or Bruker AC360 (90.56 MHz) spectrometer. Chemical shifts were recorded in parts per million from the solvent resonance ($CDCl_3$ at 77.16 ppm). ^{31}P NMR spectra were recorded on a Bruker AM250 (101.25 MHz), and chemical shifts were quoted relative to internal 85% H_3PO_4 (δ=0 ppm). Mass spectra were recorded on a Finnigan DSQ-Thermo. High-resolution mass spectra were recorded on a Finnigan MAT 95S. All new compounds were determined to be >95% pure by ^{1}H NMR spectroscopy.

4.2. General procedure A

To a solution of heterocyclic ketones **7**–**12** or **20** (5 mmol) in EtOH (10 mL), was added benzylamine **19** (7.50 mmol), AcOH (600 μL, 10 mmol) and $MgSO_4$ (420 mg, 3.50 mmol). After stirring and heating at 55 °C for 4–5 h, $P(OEt)_3$ (1.25 g, 1.31 mL, 7.50 mmol) was added. The mixture was heated at 55 °C for 1–3 days. It was then concentrated in vacuo, concd aq ammonia (2 mL) was added and the resulting mixture was filtered through a 3 cm pad of silica gel eluting with ethyl acetate (50 mL). The filtrate was concentrated in vacuo to give the crude phosphonate. Purification by flash chromatography (FC) on silica gel (MeOH/CH_2Cl_2: 1/9) gave pure aminophosphonates **13**–**18** or **21**.

4.2.1. Diethyl 4-(1′-methylbenzyl)amino-1-methylpiperidin-4-yl-phosphonate (13). Following procedure A: reaction of *N*-methylpiperidin-4-one **7** (545 mg, 5 mmol), EtOH (10 mL), α-methylbenzylamine **19a** (910 mg, 7.50 mmol), $MgSO_4$ (420 mg), AcOH (600 μL, 10 mmol) and $P(OEt)_3$ (1.25 g, 7.5 mmol) for 18 h at 55 °C gave, after standard work-up and purification by FC (eluent, MeOH/CH_2Cl_2/NH_3: 2/98/1), 1.260 g (71%) of aminophosphonate **13** as a colourless oil. R_f=0.65 (MeOH/CH_2Cl_2: 50/50+2% NH_3 aq). IR (neat) ν: 3449, 3353, 2932, 1235 (P═O), 1050 and 1025 (P–O), 957 cm^{-1}. ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 1.30 (t, J=7.2 Hz, 3H, CH_3–CH_2O), 1.33 (t, J=7.2 Hz, CH_3–CH_2O), 1.33 (d, J=6.8 Hz, 3H, CH_3–$C_{1'}$), 1.42–1.90 (m, 5H, 4H$_{cycle}$ and NH), 1.90–2.20 (m, 2H$_{cycle}$), 2.10 (s, 3H, CH_3N), 2.30–2.60 (m, 2H, 1H–C_2 and 1H–C_6), 4.10 (qd, J=7.2 Hz, $^2J_{PC}$=7.2 Hz, 2H, CH_2OP), 4.13 (qd, J=7.2 Hz, $^2J_{PC}$=7.2 Hz, 2H, CH_2OP), 4.44 (qd, J=6.8 Hz, $^4J_{PH}$=2.5 Hz, 1H–$C_{1'}$), 7.08–7.48 (m, 5H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 16.6 (*C*H_3–CH_2O), 16.7 (*C*H_3–CH_2O), 27.0 (CH_3–$C_{1'}$), 27.9 (d, $^2J_{PC}$=4.1 Hz, C_3 or C_5), 32.6 (s, C_5 or C_3), 46.2 (CH_3N), 49.4 (d, $^3J_{PC}$=12.1 Hz, C_2 or C_6), 49.55 (d, $^3J_{PC}$=9.8 Hz, C_6 or C_2), 52.5 ($C_{1'}$), 54.8 (d, $^1J_{PC}$=143.1 Hz, C_4), 61.7 (d, $^2J_{PC}$=8.0 Hz, *C*H_2OP), 61.9 (d, $^2J_{PC}$=8.0 Hz, *C*H_2OP), [6 arom C: 126.3 (1C), 126.8 (2C), 128.0 (2C), 148.4 (s)]. ^{31}P NMR ($CDCl_3$, 101.25 MHz) δ: 29.51. ES$^+$ MS, *m*/*z*: 377.2 [M+Na]$^+$. HRMS data were not obtained.[23]

4.2.2. Diethyl 4-(1′-methylbenzyl)amino-tetrahydro-2*H*-pyran-4-yl-phosphonate (14a). Following procedure A: reaction of tetrahydropyran-4-one **8** (172 mg, 1.72 mmol), EtOH (4.5 mL), α-methylbenzylamine **19a** (330 μL, 2.68 mmol), $MgSO_4$ (155 mg), AcOH (200 μL, 3.43 mmol) and $P(OEt)_3$ (442 μL, 2.58 mmol) for 30 h at 55 °C furnished, after standard work-up and purification by FC (eluent, MeOH/CH_2Cl_2/NH_3: 2/98/0.5), 387 mg (66%) of tetrahydropyranphosphonate **14a** as a colourless oil. R_f=0.35 (MeOH/CH_2Cl_2: 5/95). IR (neat) ν: 3468, 3333, 1233 (P═O), 1047 and 1026 (P–O), 950. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.37 (t, J=7.0 Hz, 3H, CH_3–CH_2O), 1.40 (t, J=7.0 Hz, CH_3–CH_2O), 1.41 (d, J=6.8 Hz, 3H, CH_3), 1.30–1.70 (m, 3H, 2H$_{cycle}$ and NH), 1.70–1.90 (m, 1H$_{cycle}$), 1.90–2.28 (m, 1H$_{cycle}$), 3.06–3.35 (m, 2H$_{cycle}$, CH_2O), 3.61–3.77 (m, 1H$_{cycle}$, CH_2O), 3.98 (tt, J=10.7 Hz, J=1.9 Hz, 1H$_{cycle}$, CH_2O), 4.16 (qd, J=7.3 Hz, $^3J_{PH}$=7.0 Hz, 2H, CH_2OP), 4.22 (qd, J=7.3 Hz, $^3J_{PH}$=7.0 Hz, 2H, CH_2OP), 4.49 (qd, J=6.8 Hz, $^4J_{PH}$=2.8 Hz, 1H–$C_{1'}$), 7.10–7.25 (m, 1H), 7.25–7.36 (m, 2H), 7.36–7.50 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 16.5 (q, *C*H_3–CH_2O), 16.6 (q, *C*H_3–CH_2O), 26.8 (CH_3-$C_{1'}$), 27.8 (d, $^2J_{PC}$=2.2 Hz, C_3 or C_5), 32.8 (C_5 or C_3), 52.8 ($C_{1'}$), 55.0 (d, $^1J_{PC}$=144.3 Hz, C_4), 61.7 (d, $^2J_{PC}$=7.3 Hz, *C*H_2OP), 61.8 (C_2 or C_6), 61.9 (C_6 or C_2), 62.0 (d, $^2J_{PC}$=7.6 Hz, CH_2OP), [6 arom C: 126.4 (d), 126.6 (d, 2C), 128.1 (d, 2C), 148.0 (s)]. ^{31}P NMR ($CDCl_3$, 101.25 MHz) δ: 28.35. HRMS (ESI, *m*/*z*): calcd mass for $C_{17}H_{28}O_4NPNa$, [M+Na]$^+$: 364.1648. Found: 364.1653.

4.2.3. Diethyl 4-(benzylamino)-tetrahydro-2*H*-pyran-4-yl-phosphonate (14b). Following procedure A: reaction of tetrahydropyran-4-one **8** (200 mg, 2.0 mmol), EtOH (5.0 mL), benzylamine **19b** (325 μL, 2.98 mmol), $MgSO_4$ (180 mg), AcOH (230 μL, 3.96 mmol) and $P(OEt)_3$

(493 μL, 2.97 mmol) for 22 h at 50 °C provided, after standard work-up and purification by FC (eluent, MeOH/CH_2Cl_2/NH_3: 2/98/0.5), 354 mg (55%) of tetrahydropyran-phosphonate **14b** as a colourless oil. R_f=0.42 (MeOH/CH_2Cl_2: 10/90). IR (neat) ν: 3468, 3312, 1240 (P═O), 1047 and 1027 (P–O), 958. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.37 (t, J=7.0 Hz, 6H, CH_3), 1.50–1.70 (m, 2H, 1H–C_3 and 1H–C_5), 1.94–2.17 (m, 3H, 1H–C_3, 1H–C_5 and 1NH), 3.54–3.71 (m, 2H, 1H–C_2 and 1H–C_6), 3.77–3.95 (m, 4H, 2H_{benzyl}, 1H–C_2 and 1H–C_6), 3.95–4.24 (m, 4H, 2CH_2OP), 7.10–7.43 (m, 5H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 16.5 (q, CH_3), 16.6 (q, CH_3), 29.8 (C_3 and C_5), 47.1 (CH_2–N), 53.4 (d, $^1J_{PC}$=146.7 Hz, C_4), 61.6 (d, $^2J_{PC}$=2.7 Hz, 2CH_2OP), 61.8 (C_2 and C_6), [6 arom C: 126.8 (d), 128.0 (2C), 128.2 (2C), 140.8 (s)]. ^{31}P NMR ($CDCl_3$, 101.25 MHz) δ: 27.60. HRMS (ESI, m/z): calcd mass for $C_{16}H_{26}NO_4PNa$, $[M+Na]^+$: 350.1492. Found: 350.1496.

4.2.4. Diethyl 4-(1′-methylbenzyl)amino-tetrahydro-2*H*-thiopyran-4-yl-phosphonate (15a). Following procedure A: reaction of tetrahydrothiopyran-4-one **9** (430 mg, 4.75 mmol), EtOH (12 mL), α-methylbenzylamine **19a** (910 μL, 7.13 mmol), $MgSO_4$ (420 mg, 3.5 mmol), AcOH (520 μL, 9.50 mmol) and P(OEt)$_3$ (1.22 g, 7.13 mmol) for 20 h at 50 °C gave, after standard work-up and purification by FC (eluent, MeOH/CH_2Cl_2/NH_3: 1/99/0.5), 1.560 g (92%) of thiopyran phosphonate **15a** as a colourless oil. R_f=0.57 (MeOH/CH_2Cl_2: 5/95). IR (neat) ν: 3457, 3333, 2982, 1210 (P═O), 1055 and 1026 (P–O), 954. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.38 (t, J=7.0 Hz, 3H, CH_3–CH_2O), 1.39 (t, J=6.8 Hz, 3H, CH_3–$C_{1'}$), 1.40 (t, J=7.0 Hz, 3H, CH_3–CH_2O), 1.67 (br s, 1H, NH), 1.78–2.24 (m, 5H_{cycle}), 2.24–2.50 (m, 2H_{cycle}), 3.28 (tt, J=12.7 Hz, J=2.0 Hz, 1H–C_2 or 1H–C_6), 4.16 (qd, J=7.0 Hz, $^2J_{PH}$=7.0 Hz, 2H, CH_2OP), 4.22 (qd, J=7.0 Hz, $^2J_{PH}$=6.5 Hz, 2H, CH_2OP), 4.46 (qd, J=6.8 Hz, $^4J_{PH}$=2.5 Hz, 1H–$C_{1'}$), 7.14–7.24 (m, 1H), 7.24–7.35 (m, 2H), 7.35–7.50 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 16.5 (CH_3–C–O), 16.6 (CH_3–C–O), 21.5 (d, $^2J_{PC}$=13.7 Hz, C_2 or C_6), 21.7 (d, $^2J_{PC}$=10.6 Hz, C_6 or C_2), 26.8 (CH_3–$C_{1'}$), 29.0 (C_3 or C_5), 33.7 (C_5 or C_3), 52.4 ($C_{1'}$), 56.6 (d, $^1J_{PC}$=141.0 Hz, C_4), 61.7 (d, $^2J_{PC}$=7.5 Hz, CH_2OP), 61.9 (d, $^2J_{PC}$=7.7 Hz, CH_2OP), [6 arom C: 126.5 (d, 2C), 128.2 (d, 3C), 148.1 (s)]. ^{31}P NMR ($CDCl_3$, 101.25 MHz) δ: 28.87. HRMS (ESI, m/z): calcd mass for $C_{17}H_{28}NO_3PSNa$, $[M+Na]^+$: 380.1420. Found: 380.1424.

4.2.5. Diethyl 4-[(1′-hydroxymethyl)benzylamino]tetrahydro-2*H*-thiopyran-4-yl-phosphonate (15b). Following procedure A: reaction of tetrahydrothiopyran-4-one **9** (210 mg, 1.8 mmol), EtOH (4.5 mL), α-hydroxymethylbenzylamine **19c** (370 mg, 2.7 mmol), $MgSO_4$ (162 mg), AcOH (200 μL, 3.62 mmol) and P(OEt)$_3$ (465 μL, 2.70 mmol), for 40 h at 50 °C furnished, after standard work-up and purification by FC (eluent, MeOH/CH_2Cl_2/NH_3: 1/99/0.5), 311 mg (46%) of aminophosphonate **15b** as a colourless oil. R_f=0.45 (MeOH/CH_2Cl_2: 5/95). ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.31 (t, J=7.0 Hz, 3H, CH_3–CH_2O), 1.32 (t, J=7.0 Hz, CH_3–CH_2O), 1.70–2.18 (m, 5H, 2H–C_3, 2H–C_5 and 1H–C_2 or 1H–C_6), 2.18–2.46 (m, 2H, 1H–C_2 and 1H–C_6), 3.20 (br t, J=12.5 Hz, 1H–C_6 or 1H–C_2), 3.42 (dd, J=9.0 Hz, J=11.0 Hz, 1H, CH_2–$C_{1'}$), 3.63 (dd, J=4.2 Hz, J=11.0 Hz, 1H, CH_2–$C_{1'}$), 4.12 (dq, $^3J_{PH}$=7.2 Hz, J=7.0 Hz, 2H, CH_2O), 4.15 (dq, J=7.2 Hz, J=7.0 Hz, 2H, CH_2O), 4.30–4.46 (m, 1H–$C_{1'}$), 7.08–7.50 (m, 5H arom). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 16.5 (CH_3), 16.55 (CH_3), 21.5 (d, $^2J_{PC}$=14.1 Hz, C_2 or C_6), 21.7 (d, $^2J_{PC}$=10.8 Hz, C_6 or C_2), 29.1 (d, $^3J_{PC}$=4.0 Hz, C_3 or C_5), 33.6 (C_5 or C_3), 56.7 (d, $^1J_{PC}$=141.0 Hz, C_4), 58.9 ($C_{1'}$), 61.9 (d, $^2J_{PC}$=8.2 Hz, CH_2O), 62.4 (d, $^2J_{PC}$=8.2 Hz, CH_2O), 68.1 (CH_2OH), [6 arom C: 127.0 (1C), 127.2 (2C), 128.2 (2C), 143.4 (s)]. ^{31}P NMR ($CDCl_3$, 101.25 MHz) δ: 29.58. HRMS (ESI, m/z): calcd mass for $C_{17}H_{28}NO_4PSNa$, $[M+Na]^+$: 396.1369. Found: 396.1363.

4.2.6. Diethyl 4-(4-methoxybenzyl)amino-tetrahydro-2*H*-thiopyran-4-yl-phosphonate (15c). Following procedure A: condensation reaction of tetrahydrothiopyran-4-one **9** (618 mg, 5.39 mmol), EtOH (14 mL), *p*-methoxybenzylamine **19d** (1.04 mL, 8.0 mmol), $MgSO_4$ (480 mg) and AcOH (590 μL, 10.66 mmol) was stirred and heated for 17 h). Then addition of P(OEt)$_3$ (1.37 mL, 8.0 mmol), (24 h at 50 °C) gave, after standard work-up and purification by FC (eluent, MeOH/CH_2Cl_2/NH_3: 2/98/0.5), 1.60 g (80%) of PMB aminophosphonate **15c** as a colourless oil. R_f=0.74 (MeOH/CH_2Cl_2: 10/90). IR (neat) ν: 3463, 3318, 2977, 1510, 1243 (P═O), 1044, 954. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.35 (t, J=7.0 Hz, 3H, CH_3), 1.80 (br s, NH), 2.00–2.24 (m, 4H, 2H–C_3 and 2H–C_5), 2.29 (d, J=12.7 Hz, 2H, 1H–C_2 and 1H–C_6), 3.26 (ddd, J=2.5 Hz, J=12.2 Hz, J=12.7 Hz, 2H, 1H–C_2 and 1H–C_6), 3.83 (s, 3H, OMe), 3.87 (d, $^4J_{PH}$=3.0 Hz, 2H, CH_2–N), 4.14 (dq, $^3J_{PH}$=7.2 Hz, J=7.0 Hz, 2H, CH_2O), 4.17 (dq, $^3J_{PH}$=7.2 Hz, J=7.0 Hz, 2H, CH_2O), 6.87 (like d, J=8.5 Hz, 2H_{aryl}), 7.32 (like d, J=8.5 Hz, 2H_{aryl}). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 16.45 (CH_3), 16.5 (CH_3), 21.2 (C_2 or C_6), 21.4 (C_6 or C_2), 30.5 (C_3 and C_5), 46.0 (CH_2–N), 54.8 (d, $^1J_{PC}$=141.6 Hz, C_4), 55.0 (CH_3O), 61.7 (CH_2O), 61.8 (CH_2O), [6 arom C: 113.6 (2C), 129.1 (2C), 132.7 (s), 158.5 (s)]. ^{31}P NMR ($CDCl_3$, 101.25 MHz) δ: 28.22. HRMS (ESI, m/z): calcd mass for $C_{17}H_{28}NO_4PSNa$, $[M+Na]^+$: 396.1369. Found: 396.1365.

4.2.7. Diethyl 1-[(1′-methylbenzyl)amino]cyclohexane-phosphonate (16). Following procedure A: reaction of cyclohexanone **10** (294 mg, 3 mmol), EtOH (6 mL), α-methylbenzylamine **19a** (410 mg, 4.5 mmol), $MgSO_4$ (250 mg), AcOH (360 μL, 6 mmol) and P(OEt)$_3$ (750 mg, 4.5 mmol), for 20 h at 55 °C furnished, after standard work-up and purification by FC (eluent, ether), 930 mg (93%) of pure aminophosphonate **16** as a colourless oil. R_f=0.40 (MeOH/CH_2Cl_2: 5/95). IR (neat) ν: 3463, 3061, 2932, 1232 (P═O), 1062 and 1025 (P–O), 955. ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 0.92–1.21 (m, 3H_{cycle}), 1.30 (t, J=7.0 Hz, 3H, CH_3), 1.31 (d, J=6.9 Hz, CH_3–$C_{1'}$), 1.325 (t, J=7.0 Hz, 3H, CH_3), 1.38–1.90 (m, 7H_{cycle} and 1NH), 4.10 (qd, J=7.0 Hz, $^3J_{PH}$=7.0 Hz, 2H, CH_2O), 4.12 (qd, J=7.0 Hz, $^3J_{PH}$=7.0 Hz, 2H, CH_2O), 4.37 (qd, J=6.9 Hz, $^4J_{PH}$=2.2 Hz, 1H–$C_{1'}$), 7.00–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 16.35 (CH_3–CH_2O), 16.4 (CH_3–CH_2O), 19.55 (d, $^2J_{PC}$=12.2 Hz, C_2), 19.85 (d, $^2J_{PC}$=9.8 Hz, C_6), 25.3 (C_4), 26.8 (CH_3–C_1), 27.9 (d, $^3J_{PC}$=4.1 Hz, C_5), 32.4 (C_3), 52.2 ($C_{1'}$), 57.1 (d, $^1J_{PC}$=137.6 Hz, C_1), 61.25 (d, $^2J_{PC}$=7.8 Hz, CH_2O), 61.5 (d, $^2J_{PC}$=7.9 Hz, CH_2O), [6 arom C: 125.8, 126.3 (2C), 127.7 (2C), 148.5

(s)]. ^{31}P NMR ($CDCl_3$, 101.25 MHz) δ: 31.21. ES$^+$ MS, *m/z*: 362.2 [M+Na]$^+$. HRMS data were not obtained.[23]

4.2.8. Diethyl 1-[(1′-methylbenzyl)amino]cyclopentanephosphonate (17). Following procedure A, with DMSO as solvent: reaction of cyclopentanone **11** (252 mg, 3 mmol), DMSO (6 mL), α-methylbenzylamine **19a** (545 mg, 4.5 mmol), $MgSO_4$ (250 mg), AcOH (360 μL, 6 mmol) and $P(OEt)_3$ (750 mg, 4.5 mmol), for 48 h at 55 °C furnished, after standard work-up and purification by FC (eluent, EtOAc/hexane: 20/80), 740 mg (76%) of pure aminophosphonate **17** as a colourless oil. R_f=0.47 (EtOAc/CH_2Cl_2: 15/85). ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 1.31 (d, J=6.8 Hz, CH_3–$C_{1'}$), 1.33 (t, J=7.0 Hz, CH_3–CH_2O), 1.36 (t, J=7.0 Hz, CH_3–CH_2O), 1.20–1.50 (m, 2H$_{cycle}$), 1.50–1.70 (m, 4H$_{cycle}$), 1.70–2.10 (m, 3H, 2H$_{cycle}$ and NH), 4.06–4.24 (m, J=7.0 Hz, 4H, CH_2O), 4.32 (qd, J=6.8 Hz, $^4J_{PH}$=2.3 Hz, 1H–$C_{1'}$), 7.10–7.45 (m, 5H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 16.7 (d, $^3J_{PC}$=4.2 Hz, CH_3–CH_2O), 16.75 (d, $^3J_{PC}$=4.2 Hz, CH_3–CH_2O), 24.1 (dd, $^2J_{PC}$=11.1 Hz, d, $^3J_{PC}$=4.2 Hz, C_3), 27.1 (CH_3–$C_{1'}$), 29.7 (C_4), 31.9 (d, $^3J_{PC}$=9.1 Hz, C_2), 37.4 (d, $^3J_{PC}$=7.4 Hz, C_5), 53.4 ($C_{1'}$), 61.6 (d, $^2J_{PC}$=7.7 Hz, CH_2O), 62.0 (d, $^2J_{PC}$=7.5 Hz, CH_2O), 64.5 (d, $^1J_{PC}$=144.0 Hz, C_1), [6 arom C: 126.2 (3C), 128.1 (2C), 149.1 (s)]. ^{31}P NMR ($CDCl_3$, 101.25 MHz) δ: 31.90. ES$^+$ MS, *m/z*: 348.2 [M+Na]$^+$. HRMS data were not obtained.[23]

4.2.9. Diethyl 1-[(1′-methylbenzyl)amino]cyclobutanephosphonate (18). Following procedure A, with DMSO as solvent: reaction of cyclobutanone **12** (210 mg, 3 mmol), DMSO (6 mL), α-methylbenzylamine **19a** (545 mg, 4.50 mmol), $MgSO_4$ (250 mg), AcOH (360 μL, 6 mmol) and $P(OEt)_3$ (750 mg, 4.5 mmol), for 3 days at 55 °C gave, after standard work-up and purification by FC (eluent, EtOAc/petroleum ether, 40/60→60/40), 470 mg (51%) of aminophosphonate **18**. Mp 93.6 °C. R_f=0.30 (EtOAc/CH_2Cl_2: 3/7). IR (neat) ν: 3420, 3320 (NH), 1250 and 1200 (P═O), 1050 (P–O). ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.35 (d, J=6.8 Hz, 3H–$C_{1'}$), 1.36 (t, J=7.1 Hz, CH_3–CH_2O), 1.37 (t, J=7.1 Hz, CH_3–CH_2O), 1.70 (br s, NH), 1.70–2.10 (m, 4H$_{cycle}$), 2.10–2.50 (m, 2H$_{cycle}$), 4.00–4.40 (m, J=7.1 Hz, 4H, CH_2O), 7.10–7.55 (m, 5H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 15.4 (d, $^2J_{PC}$=7.1 Hz, C_4), 16.6 (d, $^3J_{PC}$=2.4 Hz, CH_3–C–O), 16.65 (d, $^3J_{PC}$=2.4 Hz, CH_3–C–O), 26.0 (CH_3), 28.0 (C_3), 30.6 (C_2), 53.5(d, $^3J_{PC}$=5.2 Hz, $C_{1'}$), 57.9 (d, $^1J_{PC}$=147.2 Hz, C_1), 61.9 (d, $^2J_{PC}$=7.6 Hz, CH_2–O), 62.2 (d, $^2J_{PC}$=7.6 Hz, CH_2–O), [6 arom C: 126.4 (2C), 126.5, 128.2 (2C), 148.1 (s)]. ^{31}P NMR ($CDCl_3$, 101.25 MHz) δ: 28.70. MS (*m/z*): 311 (M$^+$, 0.4), 111 (12), 105 (100), 104 (11), 70 (20). HRMS (EI, *m/z*): calcd mass for $C_{16}H_{26}NO_3P$: 311.1650. Found: 311.1653.

4.2.10. Diethyl 1-(*tert*-butyloxycarbonyl)-3-(1-methylbenzyl)amino-piperidin-3-yl-phosphonate (21a). Following procedure A: reaction of *N*-Boc-piperidone **20a** (600 mg, 3 mmol), EtOH (6 mL), α-methylbenzylamine **19a** (410 mg, 4.5 mmol), $MgSO_4$ (250 mg), AcOH (360 μL, 6 mmol) and $P(OEt)_3$ (750 mg, 4.5 mmol), for 14 h at 55 °C furnished, after standard work-up and purification by FC (eluent, MeOH/CH_2Cl_2: 5/95), 680 mg (54%) of piperidinephosphonate **21a** as a mixture of two diastereoisomers in 63/37 ratio. R_f=0.29 (EtOH/petroleum ether: 50/50). IR (neat) ν: 3468, 3979, 2929, 1694 (CON), 1427, 1276, 1245, 1054, 1024, 964. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: two diastereomers **a/b** (63/37): 1.14 (t, J=7.0 Hz, 3H, **b**), 1.20–1.45 (m, 9H, 6H **a/b** CH_3–$C_{1'}$ and CH_3–CH_2–, 1NH **a/b**, and 3H **a**), 1.50 (s, 9H *t*-Bu, **a/b**), 1.45–2.10 (m, 3.4H, 2H–C_5 **a/b**, 1H–C_4 **a/b**, and 1H–C_4, **b**), 2.60 (ddd, J=3.2 Hz, J=12.7 Hz, 0.6H–C_4 **a**), 2.80–3.65 (m, 2H–C_6, **a/b**), 2.65–3.97 (m, 2H–C_2 **a/b**), 3.97–4.22 (m, 4H, CH_2O, **a/b**), 4.22–4.42 (m, 1H–$C_{1'}$, **a/b**), 7.03–7.20 (m, 5H arom, **a/b**). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: two diastereomers **a/b** (63/37): 16.4–16.6 (d, $^3J_{PC}$=5.5 Hz, 2CH_3–CH_2O, **b/a**), 19.4 (d, $^3J_{PC}$=10.4 Hz, C_5, **a**), 20.0 (d, J=8.2 Hz, C_5, **b**), 26.5 (C_4, **a/b**), 27.1 (CH_3–$C_{1'}$, **a/b**), 28.3/28.5 (C(CH_3)$_3$, **b/a**), 43.5/44.6 (C_6, **b/a**), 49.0/50.2 (d, J=9.2 Hz, C_2, **a/b**), 52.3 ($C_{1'}$, **a**), 52.6 ($C_{1'}$, **b**), 56.5 (d, J=145.4 Hz, C_3, **b**), 57.5 (d, J=141.5 Hz, C_3, **a**), 61.7 (OCH_2, **a**), 62.1 (d, J=7.7 Hz, CH_2O, **b**), 79.3 (C(CH_3)$_3$, **a/b**), [6 arom C: 126.3, 126.4 (2C), 128.1 (2C), 148.1/148.7 (s, **a/b**)], 155.1/155.6 (COO, **a/b**). ^{31}P NMR ($CDCl_3$, 101.25 MHz) δ: two diastereoisomers **a/b** (63/37): 27.48/27.78 (**b/a**). HRMS (ESI, *m/z*): calcd mass for $C_{22}H_{37}N_2O_5PNa$, [M+Na]$^+$: 463.2332. Found: 463.2348.

4.2.11. Diethyl 3-benzylamino-1-(*tert*-butyloxycarbonyl)-piperidin-3-yl-phosphonate (21a′). Following procedure A: condensation reaction of 255 mg (1.62 mmol) of ketone **20a**, benzylamine **19b** (174 mg, 1.62 mmol), AcOH (200 μL) and $MgSO_4$ (164 mg) was heated and stirred at 50 °C for 4 h. Then heating with $P(OEt)_3$ (410 μL, 2.43 mmol) at 50 °C overnight, gave after usual work-up and purification by FC (eluent, MeOH/CH_2Cl_2/NH_3: 3/97/0.5), 530 mg (76%) of pure aminophosphonate **21a′** as a colourless oil. R_f=0.65 (MeOH/CH_2Cl_2/NH_3: 5/95/0.5). IR (neat) ν: 3560, 2980, 1693 (CON), 1428, 1276 and 1246 (P═O), 1161, 1028. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.36 (t, J=7.2 Hz, 6H, CH_{3ester}), 1.44 (s, 9H, *t*-Bu), 1.20–2.10 (m, 5H, 4H$_{cycle}$ and NH), 2.40–3.70 (m, 2H$_{cycle}$), 3.87 (d, J=12.2 Hz, 1H$_{benzyl}$), 4.08 (d, J=12.2 Hz, 1H$_{benzyl}$), 4.40–4.90 (m, 5H, 2CH_2O and 1H$_{cycle}$), 7.10–7.50 (5H arom). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 16.6 (d, $^3J_{PC}$=5.2 Hz, CH_{3ester}), 19.5 (d, $^3J_{PC}$=10.0 Hz, C_5), 27.6 (C_4), 28.3 (CH_3)$_3$C), 43.5 (C_6), 47.2 ($CH_{2benzyl}$), 47.8 (C_2), 56.0 (d, $^1J_{PC}$=146.6 Hz, C_3), 61.9 (d, $^2J_{PC}$=7.7 Hz, CH_2O), 62.2 (d, $^2J_{PC}$=7.4 Hz, CH_2O), 79.6 (C(CH_3)$_3$), [6 arom C: 126.7 (1C), 128.0 (2C), 128.1 (2C), 141.0 (s)], 155.2 (CON). ^{31}P NMR ($CDCl_3$, 101.25 MHz) δ: 26.78. HRMS (ESI, *m/z*): calcd mass for $C_{21}H_{35}N_2O_5PNa$, [M+Na]$^+$: 449.2176. Found: 449.2182.

4.3. Diethyl [1-oxido-4-(1′-methylbenzyl)amino-tetrahydro-2*H*-thiopyran-4-yl-phosphonate (27)

To a solution of aminophosphonate **15a** (159 mg, 0.415 mmol) in 2 mL of CH_2Cl_2, was added at 0 °C *m*CPBA (77%, 146 mg, 0.415 mmol). The mixture was stirred at 0 °C for 20 min then 5 mL of saturated solution of $Na_2S_2O_3$/$NaHCO_3$ (1/1) was added, vigorously stirred for 1 h, then extracted with CH_2Cl_2 (3×50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum to furnish 168 mg (100%) of clean sulfoxide **27** as a colourless oil mixture of two isomers (40/60, cis/trans or trans/cis). R_f=0.44 (MeOH/CH_2Cl_2: 10/90). IR (neat) ν: 3447, 3354, 2925, 1266 and 1233 (P═O), 1199, 1163 (S═O), 1029

(P–O), 962. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: (two isomers **a/b**: 40/60): 1.25–1.40 (m, 9H, CH_3, **a/b**), 1.50–1.67 (m, 0.6H–C_3, **b**), 1.67–2.20 (m, 4.4H, $3H_{cycle}$ **a/b** and NH and 1H **a**), 2.25–2.85 (m, 2.6H, 2H **a/b** and 0.6H **b**), 2.90–3.10 (m, 1H, **a/b**), 3.10–3.26 (m, 0.4H, **a**), 4.02–4.24 (m, 4H, CH_2OP, **a/b**), 4.39 (qd, J=6.8 Hz, $^3J_{PH}$=2.3 Hz, 0.4H, H–$C_{1'}$, **a**), 4.46 (qd, J=6.8 Hz, $^3J_{PH}$=2.5 Hz, 0.6H, H–$C_{1'}$, **b**), 7.08–7.40 (m, 5H, **a/b**). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: (two isomers, **a/b**: 40/60): 16.6 (CH_3–CH_2O, **a/b**), 16.7 (CH_3–CH_2O, **a/b**), 17.1 (d, $^2J_{PC}$=6.5 Hz, C_3 or C_5, **b**), 21.8 (d, $^2J_{PC}$=3.2 Hz, C_5 or C_3, **b**), 24.5 (d, $^2J_{PC}$=7.6, C_3 or C_5, **a**), 26.7 (CH_3–$C_{1'}$, **b**), 26.8 (CH_3–$C_{1'}$, **a**), 28.5 (d, $^2J_{PC}$=2.8 Hz, C_5 or C_3, **a**), 39.2 (d, $^3J_{PC}$=10.4 Hz, C_2 or C_6, **b**), 39.5 (d, $^3J_{PC}$=13.8 Hz, C_6 or C_2, **b**), 44.3 (C_2 or C_6, **a**), 44.45 (C_6 or C_2, **a**), 52.7 ($C_{1'}$, **a/b**), 55.1 (d, $^1J_{PC}$ 142.4 Hz, C_4, **a**), 55.3 (d, $^1J_{PC}$=143.1 Hz, C_4, **b**), 62.2 (d, $^2J_{PC}$=7.8 Hz, CH_2OP, **b**), 62.5 (d, $^2J_{PC}$=7.7 Hz, CH_2OP, **a**), [6 arom C: 126.4/126.5 (2C, **b/a**), 126.8/126.9 (1C, **b/a**), 128.5 (2C, **a/b**), 147.3/147.9 (s, **a/b**)]. ^{31}P NMR ($CDCl_3$, 101.25 MHz) δ: (**a/b**: 40/60): 28.44/27.54. HRMS (EI, *m/z*): calcd mass for $C_{17}H_{28}NO_4PSNa$, $[M+Na]^+$: 396.1369. Found: 396.1361.

4.4. Hydrogenolysis: general procedure B

To a solution of aminophosphonates **13**–**18** or **21** (1 mmol) in 5 mL of AcOH, was added 20% $Pd(OH)_2$/C (Pearlman's catalyst, 150 mg (40% 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 for 18 h, the reaction was complete. Then degassed under a stream of argon, filtered through paper and the collected solid was washed with EtOH (2×10 mL). The combined filtrate and washings were concentrated and purified by FC on silica gel (20 g), eluent ($MeOH/CH_2Cl_2/NH_3$: 10/90/0.5) to give free amines **24**–**26** or **30**.

4.4.1. Diethyl 4-amino-1-methylpiperidin-4-yl-phosphonate (24). Following procedure B: reaction of phosphonate **13** (274 mg, 0.773 mmol), AcOH (4 mL) and 20% $Pd(OH)_2$/C (132 mg) under H_2 (1 atm) for 18 h followed by FC ($CH_2Cl_2/MeOH/NH_3$: 90/10/0.5→80/20) gave 140 mg (73%) of aminophosphonate **24** as a colourless oil. R_f=0.20 ($MeOH/CH_2Cl_2$: 10/90). ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.25 (t, J=7.0 Hz, 6H, CH_3–CH_2O), 1.46–1.61 (m, 2H, 1H–C_3 and 1H–C_5), 1.94–2.12 (m, 2H, 1H–C_3 and 1H–C_5), 2.27 (s, 3H, CH_3N), 2.47 (br t, J=11.3 Hz, 1H–C_2 and 1H–C_6), 2.66 (br d, J=11.3 Hz, 2H, 1H–C_2 and 1H–C_6), 3.12 (br s, 2HN), 4.07 (qd, J=7.0 Hz, $^3J_{PH}$=7.0 Hz, 4H, CH_2OP). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 16.5 (d, $^3J_{PC}$=5.3 Hz, $2CH_3$–CH_2O), 30.6 (C_3 and C_5), 45.4 (CH_3-N), 48.7 (d, $^1J_{PC}$=154.9 Hz, C_4), 48.8 (d, $^2J_{PC}$=11.6 Hz, $2CH_2OP$), 62.4 (C_2 or C_6), 62.5 (C_6 or C_2). ^{31}P NMR ($CDCl_3$, 101.25 MHz) δ: 29.50. HRMS (ESI, *m/z*): calcd mass for $C_{10}H_{23}N_2O_3PNa$, $[M+Na]^+$: 273.1339. Found: 273.1349.

4.4.2. Diethyl 4-amino-tetrahydro-2*H*-pyran-4-yl-phosphonate (25). Following procedure B: reaction of phosphonate **14a** (140 mg, 0.410 mmol), AcOH (2.40 mL) and 10% $Pd(OH)_2$/C (70 mg) under H_2 (1 atm) for 18 h followed by FC gave 83 mg (86%) of aminophosphonate **25** as a colourless oil. R_f=0.23 ($MeOH/CH_2Cl_2$: 10/90). IR (neat) ν: 3457, 3380, 2951, 1235 (P=O), 1049 and 1026 (P–O), 959. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.28 (t, J=7.0 Hz, 6H, CH_3), 1.30–1.45 (m, 2H, 1H–C_3 and 1H–C_5), 1.74 (br s, 2HN), 1.90–2.10 (m, 2H, 1H–C_3 and 1H–C_5), 3.62–3.72 (m, $2H_{cycle}$, CH_2O), 3.76–3.88 (m, $2H_{cycle}$, CH_2O), 4.08 (q, J=7.0 Hz, 2H, CH_2OP), 4.11 (q, J=7.0 Hz, 2H, CH_2OP). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 16.5 (d, $^3J_{PC}$=5.2 Hz, $2CH_3$–CH_2O), 31.4 (C_3 and C_5), 49.2 (d, $^1J_{PC}$=155.0 Hz, C_4), 61.7 (C_2), 61.77 (d, $^2J_{PC}$=7.7 Hz, CH_2OP), 61.85 (C_6), 62.4 (d, J=7.7 Hz, CH_2OP). ^{31}P NMR ($CDCl_3$, 101.25 MHz) δ: 28.61. HRMS (ESI, *m/z*): calcd mass for $C_9H_{20}NO_4PNa$, $[M+Na]^+$: 260.1022. Found: 260.1030.

4.4.3. Diethyl 3-amino-1-(*tert*-butyloxycarbonyl)-piperidin-3-yl-phosphonate (30). Following procedure B: reaction of *N*-Boc phosphonate **21a′** (350 mg, 0.82 mmol), AcOH (6 mL) and 20% $Pd(OH)_2$/C (140 mg) under H_2 (1 atm) for 18 h followed by FC (eluent: $MeOH/CH_2Cl_2/NH_3$: 5/93/2), gave 285 mg (88%) of aminophosphonate **30** as a colourless oil. R_f=0.63 (ether). ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.34 (t, J=7.0 Hz, 6H, CH_3–CH_2O), 1.46 (s, 9H, *t*-Bu), 1.40–2.00 (m, 6H, 2H–C_4, 2H–C_5, and NH_2), 2.67–2.90 (m, 1H, 1H–C_6), 3.04–3.32 (m, 1H–C_6), 3.80–4.10 (m, 2H–C_2), 4.05–4.37 (m, 4H, CH_2OP). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 16.7 ($2CH_3$–CH_2O), 19.5 (C_5), 28.5 ((CH_3)$_3$–C), 30.5 (d, $^2J_{PC}$=2.4 Hz, C_4), 51.6 (d, $^1J_{PC}$=155.8 Hz, C_3), 62.8 (C_6), 76.6 (C_2), 77.2 (CH_2OP), 77.6 (CH_2OP), 79.9 (s, $C(CH_3)_3$), 155.7 (COO). ^{31}P NMR ($CDCl_3$, 101.25 MHz) δ: 27.84. HRMS (ESI, *m/z*): calcd mass for $C_{14}H_{29}N_2O_5PNa$, $[M+Na]^+$: 359.1706. Found: 359.1723.

4.5. Diethyl 4-amino-tetrahydro-2*H*-thiopyran-4-yl-phosphonate (26)

To a solution of *N*-PMB aminophosphonate **15c** (240 mg, 0.64 mmol) in 2.5 mL of a mixture of CH_2Cl_2/H_2O (9/1), was added DDQ (16.2 mg, 0.70 mmol). The mixture was stirred at rt for 3 h. Then 350 μL of 2 N KOH solution was added and stirred for 1 h. The reaction mixture was filtered over Celite® and concentrated, and the residue was purified by FC (eluent: $MeOH/CH_2Cl_2/NH_3$ aq: 1/99/0.5) to afford 65 mg (40%) of the free aminophosphonate **26** as a yellow viscous oil accompanied with 120 mg (50%) of imine intermediate **29**. Or treatment of the crude mixture (**26** and **29**) with KOH (2 N) in the presence of benzoyl hydrazine (1 equiv) gave after FC the desired free amine **26** (143 mg, 88%).

4.5.1. Data for free amine (26). R_f=0.42 ($MeOH/CH_2Cl_2$+NH_3: 10/90). IR (neat) ν: 3468, 2980, 1605, 1248, 1026, 965. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.34 (t, J=7.0 Hz, 6H, CH_3), 1.40–1.90 (br s, 2H–N), 1.83–2.01 (m, 2H, 1H–C_3 and 1H–C_5), 2.01–2.22 (m, 2H, 1H–C_3 and 1H–C_5), 2.37 (br d, J=12.7 Hz, 2H, 1H–C_2 and 1H–C_6), 3.13 (dddd, J=2.2 Hz, J=2.2 Hz, J=12.7 Hz, J=12.2 Hz, 2H, 1H–C_2 and 1H–C_6), 4.13 (q, J=7.0 Hz, 2H, CH_2O), 4.16 (q, J=7.0 Hz, 2H, CH_2O). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 16.7 (d, $^3J_{PC}$=5.2 Hz, $2CH_3$), 21.7 (C_2 or C_6), 21.9 (C_6 or C_2), 32.3 (C_3 and C_5), 50.7 (d, J=151.2 Hz, C_4), 62.6 (d, J=7.7 Hz, $2CH_2O$). ^{31}P NMR ($CDCl_3$, 101.25 MHz) δ: 29.36. HRMS (ESI, *m/z*): calcd mass for $C_9H_{20}NO_3PSNa$, $[M+Na]^+$: 276.0794. Found: 276.0800.

4.5.2. (*E*)-Diethyl 3-(4′-methoxybenzylideneamino)tetrahydro-2*H*-thiopyran-4-yl-phosphonate (29). R_f=0.83 (MeOH/CH_2Cl_2+NH_3: 5/95+0.5). IR (neat) ν: 3044, 2982, 1630 (C=N), 1605, 1575, 1512, 1245, 1029, 967. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.30 (t, J=7.0 Hz, 6H, $2CH_3$), 2.20–2.50 (m, 4H, 1H–C_3, 1H–C_5 and 1H–C_2, 1H–C_6), 2.50–2.78 (m, 2H, 1H–C_3 and 1H–C_5), 2.78–3.10 (m, like t, 2H, 1H–C_2 and 1H–C_6), 3.86 (s, 3H, OCH_3), 4.06 (q, J=7.0 Hz, 2H, CH_2O), 4.09 (q, J=7.0 Hz, 2H, CH_2O), 6.95 (d, J=8.7 Hz, $2H_{aryl}$), 7.77 (d, J=8.7 Hz, $2H_{aryl}$), 8.52 (d, $^4J_{PH}$=4.7 Hz, $1H_{imine}$). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 16.6 (d, $^3J_{PC}$=5.5 Hz, $2CH_{3ester}$), 22.3 (C_2), 22.5 (C_6), 32.5 (C_3 and C_5), 55.5 (OCH_3), 61.3 (d, $^1J_{PC}$=146.7 Hz, C_4), 62.9 (d, $^2J_{PC}$=7.2 Hz, $2CH_2O$), [6 arom C: 144.1 (2C), 129.6 (s), 130.0 (2C), 161.1 (*C*–OCH_3)], 163.4 (d, $^3J_{PC}$=10.4 Hz, N=C), ^{31}P NMR ($CDCl_3$, 101.25 MHz) δ: 25.26. HRMS data were not obtained.[23]

4.6. Hydrolysis of aminophosphonates

4.6.1. 4-Amino-1-methylpiperidin-4-yl-phosphonic acid (2a). General procedure C—Hydrolysis of aminophosphonates with HCl: A solution of diethylphosphonate **24** (119 mg, 0.38 mmol) in aq 6 N HCl (3 mL) was heated at reflux for 7 h. The solvent was evaporated under reduced pressure to dryness. The residue was dissolved in 4 mL of CH_2Cl_2, then concentrated to dryness to give the crude aminophosphonic acid·*x*HCl, hydrochloride. The crude hydrochloride aminophosphonic acid·*x*HCl was dissolved in minimum amount of EtOH (3 mL), then to which was added dropwise an excess of propylene oxide (5 mL) and stirring at rt for 18 h. The volatile compounds were removed by evaporation under vacuum, to give 74 mg of phosphonic acid **2a** quantitatively. Mp>250 decomp. IR (KBr) ν cm^{-1}: 3413, 2925, 1617, 1206, 1080, 1057, 923. ^{1}H NMR (D_2O, 360 MHz) δ: two diastereomers **a/b** (in 55/45 ratio): 1.87–2.10 (m, 2H, 1H–C_3 and 1H–C_5, **a**), 2.10–2.25 (m, 2H, 1H–C_3 and 1H–C_5, **b**), 2.25–2.38 (m, 2H, 1H–C_3 and 1H–C_5, **b**), 2.38–2.54 (m, 2H, 1H–C_3 and 1H–C_5, **a**), 2.81/2.83 (s, CH_3, **a/b**), 3.02–3.20 (m, 2H, 1H–C_2 and 1H–C_6, **b**), 3.33–3.65 (m, 6H, 4H **a** and 2H **b**); in (NaOD/D_2O, 250 MHz) δ: 1.28–1.47 (m, 2H, 1H–C_3 and 1H–C_5), 1.67–1.94 (m, 2H, 1H–C_3 and 1H–C_5), 2.06 (s, CH_3), 2.08–2.30 (m, 2H, 1H–C_2 and 1H–C_6), 2.37–2.60 (m, 2H, 1H–C_2 and 1H–C_6). ^{13}C NMR (D_2O, 62.9 MHz) δ: two diastereomers, **a/b** (55/45): 26.4 (C_3 and C_5, **b**), 28.6 (C_3 and C_5, **a**), 43.0 (CH_3, **a/b**), 48.2 (C_2 and C_6, **a**), 48.4 (C_2 and C_6, **b**), 50.2 (d, $^1J_{PC}$=147.2 Hz, C_4, **a**), 50.4 (d, $^1J_{PC}$=141.6 Hz, C_4, **b**), 50.8 (C_2 and C_6, **a**); in (D_2O+NaOD): 31.3 (C_3 and C_5), 44.8 (CH_3), 48.44 (d, $^1J_{PC}$=144.1 Hz, C_4), 49.1 (C_2 or C_6), 49.2 (C_6 or C_2). ^{31}P NMR (D_2O, 101.25 MHz) δ: two diastereomers, **a/b** (55/45): 12.09/12.85 (**a/b**); in (DMSO-d_6): 14.91/15.72 (**b/a**); in (D_2O+NaOD): 23.33 only one. HRMS (ESI, *m/z*): calcd mass for $C_6H_{16}N_2O_3P$, $[M+H]^+$: 195.0893. Found: 195.0899.

4.6.2. 4-Amino-tetrahydro-2*H*-pyran-4-yl-phosphonic acid (2b). Hydrolysis of aminophosphonates with TMSI according to our reported method:[9b] Reaction of diethylphosphonate **25** (62 mg, 0.26 mmol), CH_2Cl_2 (3 mL), TMSI (78 mg, 0.55 mmol), 6 h then EtOH (1.3 mL) and propylene oxide (1 mL), for 18 h at rt gave, after usual work-up, 20 mg (43%) of pure aminophosphonic acid **2b** as a white solid. Mp 237 °C decomp. ^{1}H NMR (D_2O, 250 MHz) δ: 1.60–1.77 (m, 2H, 1H–C_3 and 1H–C_5), 2.01–2.23 (m, 2H, 1H–C_3 and 1H–C_5), 3.60 (ddd, J=2.8 Hz, J=10.3 Hz, J=12.3 Hz, 2H, 1H–C_2 and 1H–C_6), 3.87 (ddd, J=4.7 Hz, J=4.7 Hz, J=12.3 Hz, 2H, 1H–C_2 and 1H–C_6). ^{13}C NMR (D_2O, 62.9 MHz) δ: 30.0 (C_3 and C_5), 52.9 (d, $^1J_{PC}$=138.5 Hz, C_4), 62.4 (C_2 or C_6), 62.5 (C_6 or C_2). ^{31}P NMR (D_2O, 101.25 MHz) δ: 13.31. ES$^+$ MS, *m/z*: 204.1 $[M+Na]^+$. HRMS data were not obtained.[23]

4.6.3. 4-Amino-tetrahydro-2*H*-thiopyran-4-yl-phosphonic acid (2c). Following procedure C: reaction of diethylphosphonate **26** (127 mg, 0.50 mmol), 12 N HCl (2 mL) at reflux for 5 h, then EtOH (2.5 mL) and propylene oxide (2 mL) for 17 h at rt gave, after usual work-up, 92 mg (90%) of aminophosphonic acid **2c**. Mp 242 °C decomp. IR (KBr) ν cm^{-1}: 3338, 3230, 3140, 2920, 1617, 1545, 1203, 1070, 1038, 912. ^{1}H NMR (D_2O, 250 MHz) δ: 1.90–2.14 (m, 2H, 1H–C_3 and 1H–C_5), 2.14–2.35 (m, 2H, 1H–C_3 and 1H–C_5), 2.60–2.85 (m, 4H, 2H–C_2 and 2H–C_6). ^{1}H NMR (D_2O+NaOD, 360 MHz) δ: 1.00–1.32 (m, 4H, 2H–C_3 and 2H–C_5), 1.60–1.80 (m, 2H, 1H–C_2 and 1H–C_6), 2.13–2.34 (m, 2H, 1H–C_2 and 1H–C_6). ^{13}C NMR (D_2O+NaOD, 90.6 MHz) δ: 21.3 (C_2), 21.5 (C_6), 32.0 (C_3 and C_5), 49.0 (d, $^1J_{PC}$=142.6 Hz, C_4). ^{31}P NMR (D_2O, 101.25 MHz) δ: 16.25; in (D_2O+NaOD) δ: 23.13.

Purification of a sample by FC (eluent, EtOH/H_2O/concd NH_4OH: 30/3/10): ^{1}H NMR (D_2O, 360 MHz) δ: 2.06–2.22 (m, 2H), 2.22–2.37 (m, 2H), 2.72–2.91 (m, 4H). ^{31}P NMR (D_2O, 101.25 MHz) δ: 13.78. HRMS data were not obtained.[23]

4.6.4. 3-Amino-piperidin-3-yl-phosphonic acid hydrochloride (3·2HCl). Following procedure C: reaction of *N*-Boc phosphonate **30** (122 mg, 0.36 mmol), 6 N HCl (4 mL) at reflux for 12 h, gave after usual work-up 99 mg (100%) of crude aminophosphonic acid hydrochloride **3·2HCl**. IR (KBr) ν cm^{-1}: 3390, 2926, 1613, 1204, 1153, 1073, 982. ^{1}H NMR (D_2O, 250 MHz) δ: 1.70–2.27 (m, 3H, 2H–C_5 and 1H–C_4), 2.27–2.57 (m, 1H, C_4), 2.92–3.57 (m, 3H, 2H–C_6+1H–C_2), 3.57–3.88 (m, 1H–C_2). ^{1}H NMR (D_2O+NaOD, 250 MHz) δ: 1.20–1.41 (m, 1H–C_5), 1.41–1.64 (m, 2H), 1.64–1.85 (m, 1H–C_4), 2.20–2.44 (m, 1H–C_6), 2.44–2.88 (m, 3H, 2H–C_2 and 1H–C_6). ^{13}C NMR (D_2O, 62.9 MHz) δ: 18.4 (C_5), 27.7 (C_4), 43.5 (C_6), 46.0 (C_2), 50.7 (d, $^1J_{PC}$=138.5 Hz, C_3).

4.6.5. 3-Amino-piperidin-3-yl-phosphonic acid (3). Following procedure C: The crude aminophosphonic acid hydrochloride **3·2HCl** (80 mg) and propylene oxide (5 mL) gave after concentration 74 mg (100%) of free aminophosphonic acid **3** as colourless solid. Mp >250 °C decomp. ^{1}H NMR (D_2O, 250 MHz) δ: 1.60–2.17 (m, 3H, 2H–C_5 and 1H–C_4), 2.17–2.37 (m, 1H–C_4), 2.96 (m, 1H–C_6), 3.13–3.04 (d, J=12.7 Hz, 1H–C_2), 3.32 (m, 1H–C_6), 3.57–3.54 (dd, J=1.5 Hz, J=12.7 Hz, 1H–C_2); in (D_2O+NaOD) δ: 1.22–1.30 (m, 1H–C_5), 1.36–1.58 (m, 2H, 1H–C_5 and 1H–C_4), 1.58–1.80 (m, 1H–C_4), 2.20–2.34 (m, 1H–C_6), 2.42–2.58 (m, 1H–C_2), 2.58–2.78 (m, 2H, 1H–C_6 and 1H–C_6). ^{13}C NMR (D_2O+NaOD, 62.9 MHz) δ: 20.6 (d, $^3J_{PC}$=8.0 Hz, C_5), 30.3 (C_4), 44.7 (C_6), 50.15 (d, $^1J_{PC}$=140.1 Hz, C_3), 50.9 (d, $^2J_{PC}$=5.3 Hz, C_2). ^{31}P NMR

(D_2O, 101.25 MHz) δ: 11.81; in (D_2O+NaOD) δ: 21.97. ES^+ MS, *m/z*: 203.1 $[M+Na]^+$. HRMS data were not obtained.[23]

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