Efficient Synthesis of Substituted Cyclic α-Aminophosphonates

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Abstract: The addition of diethyl phosphite to cyclic imines bearing alkyl, aryl, or heteroaryl substituents at the α-position in diethyl ether at room temperature presents an efficient route to substituted cyclic α-aminophosphonates. The application of boron trifluoride–diethyl ether complex as a catalyst significantly accelerates the reaction.

Key words: diethyl phosphonate, cyclic imines, addition reactions, α-aminophosphonates

α-Aminophosphonates have attracted constant attention over several decades because of the high and diverse biological activity determining their practical applications, and there have been ongoing searches for and investigations of novel structures of this type.[1] Being analogous to amino acids, they have been found to be useful for a number of applications, e.g. as antibiotics,[2] enzyme inhibitors,[3] anticancer agents,[4] and herbicides.[5] These α-aminophosphonate compounds are also of undoubted interest as ligands in homogeneous[6] or organic[7] catalysis.

Cyclic or heterocyclic rings introduced into the molecular skeleton increase the rigidity and modify the electronic effects of these compounds. Thus, many cyclic α-aminophosphonic acids bearing an exocyclic amino group have been prepared, mostly in racemic series.[8] However, among the α-aminophosphonates synthesized, those containing nitrogen as a ring heteroatom are scarce. The synthetic routes to such products are limited mostly to the addition of hydrophosphoryl compounds to triazine derivatives,[9] lactam alkylation using dialkyl phosphite sodium salts[10] or multistep asymmetric synthesis[11] for unsubstituted five- and six-membered compounds, and some procedures developed for aziridinylphosphonates.[12] The synthesis of diethyl 2-methyl- and 2-phenylpyrrolidin-2-ylphosphonates, used as precursors for phosphorylated nitrones, has also been reported.[13]

Cyclic imines with various aliphatic or aromatic substituents at the α-position can be easily prepared according to literature procedures[14] from cheap, commercially available starting materials, and these imines open up broad synthetic possibilities. We have demonstrated their application in the synthesis of biologically and synthetically attractive molecules, such as derivatives of indole, pyrazole, isoxazole, amino acids, and seminatural peptides.[15]

Taking into account that the most convenient approach to build phosphonate P–C–N systems generally comprises the addition of dialkyl phosphites[16–20] or alkali metal phosphides[21] to the carbon–nitrogen double bond of Schiff bases, we believe that the phosphorylation of substituted cyclic imines may be an advantageous strategy to obtain α-substituted cyclic α-aminophosphonates.

In this paper, we report the effective synthesis of cyclic α-aminophosphonates with different ring sizes on the basis of the above-mentioned methodology.

Depending on the structure and electrophilicity of a Schiff base, dialkyl phosphites are known to add to its carbon–nitrogen double bond under thermal,[16a,b] ultrasonic,[16c] or microwave[18] initiation and in the presence of strong bases[17] or Lewis acids.[18,20] We found, however, that the addition of diethyl phosphite to substituted five-, six-, and seven-membered cyclic imines **1a–e**, **2a** and **2b**, and **3** proceeded smoothly in diethyl ether at room temperature without any catalyst to afford the corresponding α-aminophosphonates **4a–e**, **5a** and **5b**, and **6**, respectively (Scheme 1). The reaction rate was much higher in the case of alkyl-substituted derivatives. For such substrates, the reaction was complete in approximately 30 hours at ambient conditions. In the case of aryl- or heteroaryl-substituted imines **1c–e**, **2b**, and **3**, the reaction was complete within 3–5 days. After workup, the crude phosphonates were isolated in good yields with purity higher than 95% according to their corresponding ^{1}H and ^{31}P NMR spectra.

Our attempts to accelerate the reaction using microwave or thermal initiation resulted in the formation of a complex product mixture. When room-temperature ionic liquids 1-butyl-3-methylimidazolium tetrafluoroborate and hexafluorophosphate ([bmim]BF_4 and [bmim]PF_6, respectively) were used as activating reaction media, in a similar manner to the synthesis of α-aminophosphonates via the Kabachnik–Fields reaction,[22] the increase in the conversion rate was negligible (ca. 5–9% for the same period of time). No significant influence of the anionic nature of the reaction medium using ionic liquids was observed.

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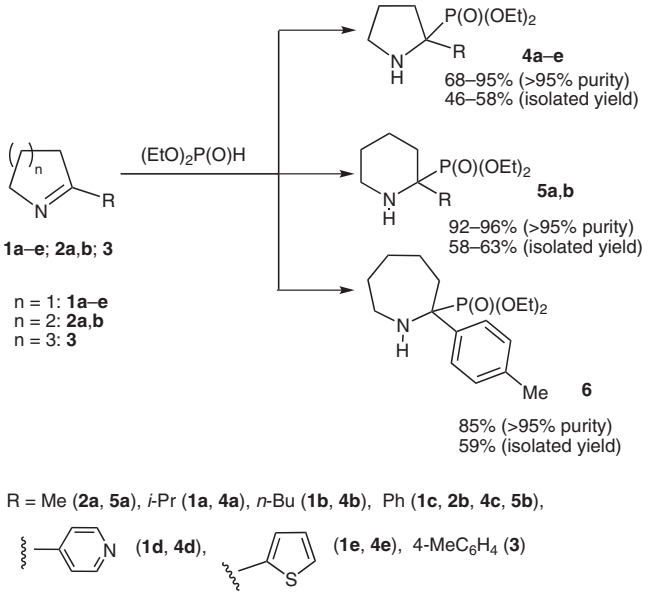
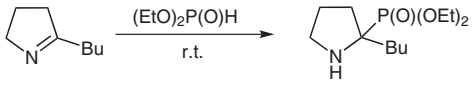


Scheme 1 *Reaction conditions*: Et_2O or THF as solvent, r.t.; without catalyst, 30 h to 5 d; with $BF_3{\cdot}OEt_2$ (20 mol%) as catalyst, 12–24 h.

The catalyst of choice for the synthesis was boron trifluoride–diethyl ether complex ($BF_3{\cdot}OEt_2$) (20 mol%), and using this catalyst the reaction was complete over 12–24 hours depending on the substituent R and ring size of the starting imine in either diethyl ether or tetrahydrofuran. A comparison of the reaction rates using the different catalytic systems in the synthesis of cyclic α-aminophosphonate **4b** are shown in Table 1.

Table 1 Influence of a Catalyst on the Reaction Rate

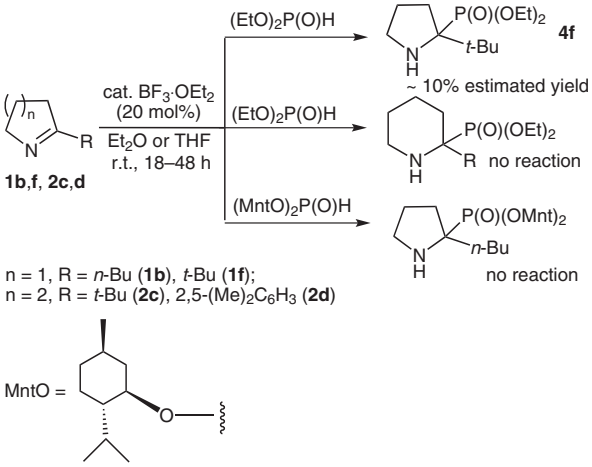


Entry	Reaction conditions	Time (h)	Yield (%) of **4b**[a]
1	Et_2O, without catalyst	6	35
		24	66
2	[bmim]BF_4	6	32
		24	75
3	[bmim]PF_6	6	33
		24	71
4	Et_2O, 20 mol% $BF_3{\cdot}OEt_2$	6	54
		12	95

[a] Yield according to ^{31}P NMR spectroscopic data.

Excluding solid (2-pyridin-4-ylpyrrolidin-2-yl)phosphonate **4d**, α-aminophosphonates **4**–**6** are all yellowish oils and water soluble. It should be noted that these compounds are inclined to form stable hydrates and solvate with chloroform; in the case of compound **6** such a $CHCl_3$ solvate, for example, could be destroyed only after prolonged drying in vacuo (1 mmHg, 4–5 h) at approximately 100 °C. The formation of strong solvates with chloroform acting as a proton donor for α-aminophosphonates has been previously reported.[23]

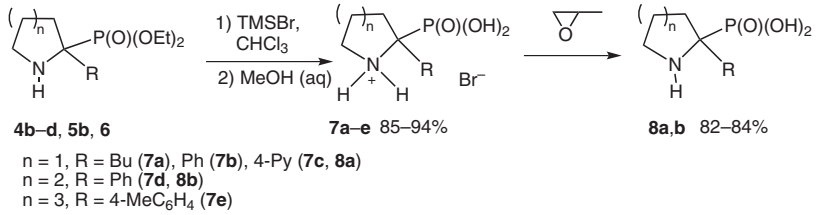
The reaction is very sensitive to the steric conditions of both the starting cyclic imine and dialkyl phosphite. For example, when the substituent at the 2-position of the substrate was a *tert*-butyl group, the yield of product (2-*tert*-butylpyrrolidin-2-yl)phosphonate **4f** did not exceed about 10% according to the ^{31}P NMR spectroscopic data of the reaction mixture. The result was the same even after a prolonged reaction time and using a catalyst. 6-*tert*-Butyl-2,3,4,5-tetrahydropyridine (**2c**) did not undergo phosphorylation either using the above conditions or at elevated temperatures. The introduction of an *ortho*-methyl group on the phenyl substituent of the six-membered cyclic imine substrate **2d** inhibited the reaction as well. Moreover, we failed to perform the reaction of **1b** using chiral dimenthyl phosphonate (Scheme 2).



Scheme 2

The α-aminophosphonates obtained can be easily converted into their corresponding α-aminophosphonic acids via reaction with trimethylsilyl bromide in chloroform, followed by treatment with aqueous methanol (Scheme 3). Because the cyclic aminophosphonic acids easily undergo quaternization with hydrogen bromide formed as a result of the hydrolysis of trimethylsilyl bromide, they are isolated as the corresponding hydrobromides **7**. Further treatment with propylene oxide affords the free amino acids **8**, as illustrated using (2-pyridin-4-ylpyrrolidin-2-yl)- and (2-phenylpiperidin-2-yl)phosphonic acid hydrobromide (**7c**) and (**7d**), respectively (Scheme 3). Naturally, the isolation of the intermediate hydrobromides is an optional step. The high melting points of acids **8a** and **8b** and the presence of an absorption band at around 1628 cm^{-1} in their IR spectra are characteristic[24] of ammonium species $>NH_2^+$, which allows one to suggest that these compounds exist as their corresponding zwitterions.

To conclude, we have developed a simple and convenient approach to synthesize α-alkyl-, α-aryl-, and α-heteroaryl-substituted cyclic α-aminophosphonates via diethyl phos-



Scheme 3

phite addition to readily available cyclic imines and have elucidated the benefits and limitations of this reaction.

The NMR spectra were recorded with Bruker Avance 300 (^{1}H, 300.13; ^{31}P, 121.49; and ^{13}C, 75.47 MHz) and Avance 400 (^{1}H, 400.13; ^{31}P, 161.97; and ^{13}C, 100.61 MHz) spectrometers using residual proton signals of the deuterated solvent as an internal standard (^{1}H and ^{13}C) and H_3PO_4 as an external standard (^{31}P). The ^{13}C NMR spectra were registered using the JMODECHO mode; the signals for the C atom bearing odd and even numbers of protons have opposite polarities. The IR spectra were recorded in a thin layer on a Fourier transform spectrometer Magna-IR750 (Nicolet) (resolution 2 cm^{-1}, 128 scans). Mass spectrometry was performed on a tandem Finnigan LCQ Advantage instrument using positive mode. Analytical TLC was performed with Merck silica gel 60 F_{254} plates. Visualization was accomplished using UV light or by spraying with $Ce(SO_4)_2$ soln in 5% H_2SO_4. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. The starting cyclic imines **1a–f**, **2a–d**, and **3** were obtained according to known procedures.[14] Other reactants were purchased from Aldrich and used without further purification.

Diethyl Pyrrolidin-2-ylphosphonates, Piperidin-2-ylphosphonates, and Hexahydro-1*H*-azepin-2-ylphosphonates 4–6; General Procedure

To a solution of the appropriate cyclic imine **1**–**3** (5 mmol) and diethyl phosphite (0.83 g, 6 mmol) in anhyd Et_2O or THF (ca. 2 mL) was slowly added $BF_3{\cdot}OEt_2$ (0.14 g, 1 mmol) via syringe. The mixture was stirred at r.t. over 12–24 h while monitoring the course of the reaction using ^{31}P NMR spectroscopy or TLC. Then, CH_2Cl_2 (10 mL) was added and the mixture was extracted with dil HCl (10 mL). The organic layer was discarded, the aqueous layer was adjusted to pH 10 with 20% NaOH, and this mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried (Na_2SO_4), and CH_2Cl_2 was removed by evaporation in vacuo to give the crude target phosphonates **4**–**6** in 68–96% yield with >95% purity according to NMR spectroscopic data. Analytically pure samples were obtained using silica gel column chromatography ($CHCl_3$–EtOH, 100:6). It should be noted that the column chromatography resulted in a large loss of the compounds because of their high affinity to silica gel; TLC purification gave better results. However, for the synthesis of the corresponding phosphonic acids, crude compounds **4**–**6** can be successfully used without further purification.

Diethyl (2-Isopropylpyrrolidin-2-yl)phosphonate (4a)

Obtained in Et_2O as reaction solvent. Yield: 0.9 g (72%, crude), 0.61 g (49%, after column chromatography), 0.79 g (63%, after TLC purification); oil.

IR (KBr): 961, 1028 and 1055 (P–O–C), 1097, 1228 (P=O), 1391, 1444, 1471, 2974, 2908, 2977 (NH), 3360, 3442 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 and 1.00 [both d, $^3J_{H,H}$ = 6.8 Hz, 3 H + 3 H, $(CH_3)_2CH$], 1.27 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H, 2 CH_3CH_2O), 1.62–2.18 (m, 6 H, CH + NH + 2 cyclic CH_2), 2.92–3.03 (m, 2 H, NCH_2), 4.04–4.17 (m, 4 H, 2 OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.23 and 16.31 (both d, $^3J_{P,C}$ = 6.6 Hz, CH_3CH_2O), 17.56 [d, $^3J_{P,C}$ = 7.5 Hz, $(CH_3)_2CH$], 18.23 [d, $^3J_{P,C}$ = 4.4 Hz, $(CH_3)_2CH$], 26.06 (d, $^3J_{P,C}$ = 3.1 Hz, C-4), 29.40 ($^2J_{P,C}$ = 2.1 Hz, CH), 34.31 (d, $^3J_{P,C}$ = 9.8 Hz, C-3), 47.17 (d, $^3J_{P,C}$ = 5.2 Hz, C-5), 61.25 (d, $^2J_{P,C}$ = 7.7 Hz, OCH_2), 62.15 (d, $^2J_{P,C}$ = 7.7 Hz, OCH_2), 66.29 (d, $^1J_{P,C}$ = 158.3 Hz, C-2).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 30.6.

Anal. Calcd for $C_{11}H_{24}NO_3P{\cdot}H_2O$: C, 49.43; H, 9.80; N, 5.24; P, 11.34. Found: C, 49.49; H, 9.86; N, 5.24; P, 11.10.

Diethyl (2-Butylpyrrolidin-2-yl)phosphonate (4b)

Obtained in Et_2O as reaction solvent. Yield: 1.25 g (95%, crude), 1.13 g (86%, after TLC purification), 0.71 g (54%, after column chromatography); viscous oil.

IR (KBr): 957, 1029 and 1057 (P–O–C), 1235 (P=O), 2934, 2958 (NH), 3318 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3), 1.33 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H, 2 CH_3CH_2O), overlapped with 1.28–1.48 [m, 4 H, $CH_3(CH_2)_2$], 1.62–2.00 (m, 5 H), 2.11–2.26 (m, 1 H, cyclic CH_2), 3.09–3.23 (m, 2 H, NCH_2), 4.10–4.21 (m, 4 H, 2 OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.09 (CH_3), 16.66 (d, $^3J_{P,C}$ = 4.2 Hz, CH_3CH_2O), 23.35 (CH_3CH_2), 25.60 (d, $^3J_{P,C}$ = 2.8 Hz, $CH_3CH_2CH_2$), 26.27 (d, $^3J_{P,C}$ = 5.6 Hz, C-4), 32.34 (C-3), 36.30 (d, $^2J_{P,C}$ = 5.6 Hz, $PCCH_2$), 47.53 (d, $^3J_{P,C}$ = 5.6 Hz, C-5), 62.89 (d, $^2J_{P,C}$ = 8.4 Hz, OCH_2), 63.18 (d, $^2J_{P,C}$ = 7.0 Hz, OCH_2), 64.04 (d, $^1J_{P,C}$ = 160.0 Hz, C-2).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 28.9.

ESI-MS: *m*/*z* (%) = 263 (18) (M^+), 126 (100) $[M - P(O)(OEt)_2]^+$.

Anal. Calcd for $C_{12}H_{26}NO_3P$: C, 54.74; H, 9.95; N, 5.32; P, 11.76. Found: C, 54.73; H, 9.80; N, 5.17; P, 11.72.

Diethyl (2-Phenylpyrrolidin-2-yl)phosphonate (4c)[13b]

Obtained in THF as reaction solvent. Yield: 1.22 g (86%, crude), 0.76 g (54%, after column chromatography), 1.02 g (72%, after TLC purification); viscous yellowish oil.

IR (KBr): 961, 1026 and 1053 (P–O–C), 1241 (P=O), 1600 (Ar), 2978 (NH) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14 and 1.22 (both t, $^3J_{H,H}$ = 7.1 Hz, 3 H + 3 H, 2 CH_3CH_2O), 1.60–1.72 (m, 1 H, cyclic CH_2), 1.86–1.95 (m, 1 H, cyclic CH_2), 2.18–2.32 (m, 2 H, NH + cyclic CH_2), 2.48–2.61 (m, 1 H, cyclic CH_2), 2.91–2.98 (m, 1 H, NCH_2), 3.16–3.23 (m, 1 H, NCH_2), 3.72–3.82 (m, 1 H, OCH_2), 3.84–3.93 (m, 1 H, OCH_2), 3.94–4.03 (m, 2 H, OCH_2), 7.20–7.26 (m, 1 H, CH_{Ar}), 7.28–7.34 (m, 2 H, 2 CH_{Ar}), 7.55–7.59 (m, 2 H, 2 CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.48 (d, $^3J_{P,C}$ = 4.2 Hz, CH_3CH_2O), 25.30 (d, $^3J_{P,C}$ = 7.1 Hz, C-4), 32.34 (C-3), 46.66 (d, $^3J_{P,C}$ = 8.4 Hz, C-5), 62.61 (d, $^2J_{P,C}$ = 7.0 Hz, OCH_2), 62.98 (d, $^2J_{P,C}$ = 7.1 Hz, OCH_2), 67.08 (d, $^1J_{P,C}$ = 150.3 Hz, C-2), 127.12 (d, $^5J_{P,C}$ = 2.8 Hz, C-4 in Ph), 127.58 (d, $^3J_{P,C}$ = 4.3 Hz, C-2 in Ph), 127.96 (d, $^4J_{P,C}$ = 2.8 Hz, C-3 in Ph), 141.19 (*ipso*-C in Ph).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 27.58.

ESI-MS: *m*/*z* (%) = 146 (100) $[M - P(O)(OEt)_2]^+$.

Anal. Calcd for $C_{14}H_{22}NO_3P$: C, 59.35; H, 7.83; N, 4.94; P, 10.93. Found: C, 59.52; H, 7.85; N, 4.90; P, 11.06.

Diethyl (2-Pyridin-4-ylpyrrolidin-2-yl)phosphonate (4d)
Obtained in THF as reaction solvent. Yield: 0.97 g (68%, crude), 0.65 g (46%, after column chromatography); white solid; mp 64–65 °C.

IR (KBr): 967, 1021 and 1055 (P–O–C), 1231 (P=O), 1593 (Ar), 2927 and 2981 (NH), 3328 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 and 1.24 (both t, $^3J_{H,H}$ = 7.1 Hz, 3 H + 3 H, 2 CH_3CH$_2$O), 1.52–1.73 (m, 1 H, cyclic CH_2), 1.80–2.00 (m, 1 H, cyclic CH_2), 2.12–2.28 (m, 1 H, cyclic CH_2), 2.40 (br, 1 H, NH), 2.40–2.65 (m, 1 H, cyclic CH_2), 2.83–2.97 (m, 1 H, NCH_2), 3.14–3.25 (m, 1 H, NCH_2), 3.80–4.18 (m, 4 H, 2 OCH_2), 7.54 (br, 2 H, py), 8.55 (br, 2 H, py).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.59 (d, $^3J_{P,C}$ = 5.6 Hz, CH_3CH$_2$O), 25.47 (d, $^3J_{P,C}$ = 7.0 Hz, C-4), 36.41 (C-3), 46.91 (d, $^3J_{P,C}$ = 8.4 Hz, C-5), 63.12 (d, $^2J_{P,C}$ = 7.0 Hz, OCH_2), 63.40 (d, $^2J_{P,C}$ = 7.1 Hz, OCH_2), 66.70 (d, $^1J_{P,C}$ = 149.1 Hz, C-2), 122.83 (CH in py), 149.58 (CHN in py), 151.38 (d, $^2J_{P,C}$ = 2.8 Hz, *ipso*-C in py).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 27.1.

ESI-MS: *m*/*z* = 146 (100) $[M - P(O)(OEt)_2]^+$.

Anal. Calcd for $C_{13}H_{21}N_2O_3P$: C, 54.92; H, 7.45; N, 9.85; P, 10.90. Found: C, 54.97; H, 7.58; N, 10.02; P, 10.21.

Diethyl [2-(2-Thienyl)pyrrolidin-2-yl]phosphonate (4e)
Obtained in Et_2O as reaction solvent. Yield: 1.04 g (72%, crude), 0.84 g (58%, after column chromatography); yellowish oil.

IR (KBr): 965, 1023 and 1053 (P–O–C), 1237 (P=O), 1433, 1611, 2861, 2976, 3071, 3457 and 3466 (br) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 and 1.26 (both t, $^3J_{H,H}$ = 7.1 Hz, 3 H + 3 H, 2 CH_3CH$_2$O), 1.72–1.83 (m, 1 H, cyclic CH_2), 1.83–1.94 (m, 1 H, cyclic CH_2), 2.22–2.39 (br m, 2 H, NH + cyclic CH_2), 2.42–2.54 (m, 1 H, cyclic CH_2), 3.03–3.16 (m, 2 H, NCH_2), 3.83–3.94 and 3.95–4.16 (both m, 1 H + 3 H, 2 OCH_2), 6.97 (dd, $^3J_{H,H}$ = $^4J_{P,H}$ = 4.88 Hz, 1 H, =CH), 7.07 (apparent dt, *J* = 4.88, 1.21 Hz, 1 H, =CH), 7.17 (br d, $^3J_{H,H}$ = 4.88 Hz, 1 H, =CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.38 (d, $^3J_{P,C}$ = 5.5 Hz, CH_3CH$_2$O), 25.38 (d, $^3J_{P,C}$ = 8.3 Hz, C-4), 37.70 (C-3), 47.03 (d, $^3J_{P,C}$ = 9.0 Hz, C-5), 63.27 (d, $^2J_{P,C}$ = 7.1 Hz, OCH_2), 63.78 (d, $^2J_{P,C}$ = 7.0 Hz, OCH_2), 66.70 (d, $^1J_{P,C}$ = 158.5 Hz, C-2), 124.59, 124.79 (d, $^2J_{P,C}$ = 5.5 Hz), 127.37, 128.93 (d, $^3J_{P,C}$ = 9.0 Hz).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 25.4.

Anal. Calcd for $C_{12}H_{20}NO_3PS$: C, 49.81; H, 6.97; P, 10.71. Found: 49.84; H, 6.59; P, 10.41.

Diethyl (2-Methylpiperidin-2-yl)phosphonate (5a)
Obtained in Et_2O as reaction solvent. Yield: 1.08 g (92%, crude), 0.68 g (58%, after column chromatography), 0.92 g (78%, after TLC purification); yellowish oil.

IR (KBr): 957, 1029 and 1058 (P–O–C), 1096, 1238 (P=O), 1367, 1391, 1443, 2867, 2933 (NH), 2978, 3300, 3478 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.27–1.32 (m, 9 H, CH_3), 1.42–1.58 (m, 4 H, 2 cyclic CH_2), 1.70 (br, 1 H, NH), 1.80–1.89 (m, 2 H, cyclic CH_2), 2.75–2.83 (m, 1 H, NCH_2), 2.91–2.97 (m, 1 H, NCH_2), 4.10–4.18 (m, 4 H, 2 OCH_2).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.00 and 16.05 (both d, $^3J_{P,C}$ = 2.3 Hz, CH_3CH$_2$O), 19.14 (d, $^3J_{P,C}$ = 8.8 Hz, C-4), 20.02 (CH_3), 25.34 (C-3), 30.56 (C-5), 40.33 (d, $^3J_{P,C}$ = 9.9 Hz, C-6), 52.38 (d, $^1J_{P,C}$ = 154.0 Hz, C-2), 61.55 (d, $^2J_{P,C}$ = 7.3 Hz, OCH_2), 61.61 (d, $^2J_{P,C}$ = 7.1 Hz, OCH_2).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 30.6.

Anal. Calcd for $C_{10}H_{22}NO_3P{\cdot}0.5H_2O$: C, 49.17; H, 9.49; P, 12.68. Found: C, 49.07; H, 8.77; P, 12.38.

Diethyl (2-Phenylpiperidin-2-yl)phosphonate (5b)
Obtained in THF as reaction solvent. Yield: 1.43 g (96%, crude), 0.94 g (63%, after column chromatography); yellowish oil.

IR (KBr): 964, 1025 (P–O–C), 1062, 1236 (P=O), 2864, 2934, 2980, 3322 (br), 3456 (br) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 and 1.20 (both t, $^3J_{H,H}$ = 7.0 Hz, 3 H + 3 H, 2 CH_3CH$_2$O), 1.23–1.40 (m, 1 H, cyclic CH_2), 1.40–1.54 (m, 2 H, cyclic CH_2), 1.60–1.67 (m, 1 H, cyclic CH_2), 2.09–2.22 (m overlapped with br s, 2 H, cyclic CH_2 + NH), 2.51–2.56 (m, 1 H, cyclic CH_2), 2.59–2.68 (m, 1 H, NCH_2), 2.82–2.86 (m, 1 H, NCH_2), 3.71–3.83 and 3.84–4.02 (both m, 1 H + 3 H, 2 OCH_2), 7.23–7.28 (m, 1 H, CH_{Ar}), 7.37 (t, $^3J_{H,H}$ = 7.8 Hz, 2 H, 2 CH_{Ar}), 7.53–7.57 (m, 2 H, 2 CH_{Ar}).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.33 (d, $^3J_{P,C}$ = 4.8 Hz, CH_3CH$_2$O), 19.66 (d, $^3J_{P,C}$ = 11.8 Hz, C-4), 26.42 (C-3), 29.74 (C-5), 40.61 (d, $^3J_{P,C}$ = 13.1 Hz, C-6), 60.39 (d, $^1J_{P,C}$ = 154.3 Hz, C-2), 62.75 (d, $^2J_{P,C}$ = 7.6 Hz, OCH_2), 63.08 (d, $^2J_{P,C}$ = 7.6 Hz, OCH_2), 126.87 ($^5J_{P,C}$ = 3.4 Hz, C-4 in Ph), 128.25, 128.78 (d, $^3J_{P,C}$ = 4.8 Hz, C-2 in Ph), 136.48 ($^2J_{P,C}$ = 7.6 Hz, *ipso*-C in Ph).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 25.23.

Anal. Calcd for $C_{15}H_{24}NO_3P$: C, 60.59; H, 8.14; N, 4.71; P, 10.42. Found: C, 60.49; H, 8.14; N, 4.69; P, 10.05.

Diethyl [2-(4-Tolyl)hexahydro-1*H*-azepin-2-yl]phosphonate (6)
Obtained in Et_2O as reaction solvent. Yield: 1.38 g (85%, crude), 0.96 g (59%, after column chromatography); yellow oil.

IR (KBr): 961, 1026 and 1055 (P–O–C), 1236 (P=O), 2854, 2925, 2979, 3373 (br) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 and 1.24 (both t, $^3J_{H,H}$ = 7.0 Hz, 3 H + 3 H, 2 CH_3CH$_2$O), 1.29–1.37 (m, 1 H, cyclic CH_2), 1.47–1.64 (m, 3 H, cyclic CH_2), 1.73–1.82 (m, 1 H, cyclic CH_2), 2.07 (br, 1 H, NH), 2.14–2.24 (m, 2 H, cyclic CH_2), 2.31 (d, *J* = 1.9 Hz, 3 H, CH_3), 2.57–2.73 (m, 1 H + 1 H, cyclic CH_2 + NCH_2), 3.05–3.12 (m, 1 H, NCH_2), 3.62–3.73, 3.79–3.88, and 3.93–4.04 (all m, 1 H + 1 H + 2 H, 2 OCH_2), 7.13 (d, $^3J_{H,H}$ = 8.4 Hz, 2 CH_{Ar}), 7.46 (dd, $^3J_{H,H}$ = 8.4 Hz, $^4J_{P,H}$ = 2.5 Hz, 2 CH_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.38 (d, $^3J_{P,C}$ = 4.8 Hz, CH_3CH$_2$O), 20.93 (CH_3), 23.18 (d, $^3J_{P,C}$ = 23.8 Hz, C-4), 29.99 (C-5), 32.88 (C-6), 36.05 (C-3), 43.57 (d, $^3J_{P,C}$ = 11.8 Hz, C-7), 62.44 (d, $^2J_{P,C}$ = 7.6 Hz, OCH_2), 62.96 (d, $^2J_{P,C}$ = 7.6 Hz, OCH_2), 63.03 (d, $^1J_{P,C}$ = 148.8 Hz, C-2), 126.50 (*ipso*-C in Ph), 127.84 (d, $^3J_{P,C}$ = 4.8 Hz, C-2 in Ph), 128.59, 138.37 ($C_{Ar}CH_3$).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 27.66.

Anal. Calcd for $C_{17}H_{28}NO_3P{\cdot}0.25CHCl_3$: C, 58.32; H, 8.02; N, 3.94; P, 8.72. Found: C, 58.72; H, 7.97; N, 3.90; P, 8.88.

Pyrrolidin-2-yl-, Piperidin-2-yl-, and Hexahydro-1*H*-azepin-2-ylphosphonic Acid Hydrobromides 7 and the Corresponding Free Acids 8; General Procedure
A solution of TMSBr (0.72 g, 5 mmol) in $CHCl_3$ (2 mL) was added dropwise to a solution of the appropriate aminophosphonate (2 mmol) in $CHCl_3$ (2 mL). The mixture was allowed to stir at r.t. overnight, then the solvent was removed under reduced pressure (rotor evaporator) and the residue was dissolved in MeOH (5 mL). Hydrobromides **7b–e** were precipitated from MeOH as light-yellow solids, collected by filtration, and dried in vacuo. Because hydrobromide **7a** represented a very hydroscopic material, it was additionally converted into the corresponding *tert*-butylammonium

salt by treatment with an excess of *t*-BuNH$_2$ (0.3 g, 4 mmol), followed by recrystallization (MeCN).

To obtain free acids **8**, propylene oxide (0.5 mL) was added to a solution of isolated hydrobromide **7c** or crude product **7d** (2 mmol) in EtOH (5 mL) at r.t., and the mixture was stirred overnight. The solvent was then evaporated to half of the initial volume of the mixture, Et$_2$O was added (2 mL), and the precipitated acid was collected by filtration and dried in vacuo.

(2-Butylpyrrolidin-2-yl)phosphonic Acid *tert*-Butylammonium Salt Hydrobromide (7a)
Yield: 0.61g (85%); light-yellow crystalline solid; mp 145–146 °C.

^{1}H NMR (300 MHz, D$_2$O): δ = 0.75 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH$_3$), 1.22 (s, 9 H, CH$_3$ in *t*-Bu), overlapped with 1.15–1.39 [m, 4 H, CH$_3$(C*H*$_2$)$_2$], 1.62–1.76 [m, 2 H, CH$_3$(CH$_2$)$_2$C*H*$_2$], 1.86–2.02 (m, 3 H, cyclic CH$_2$), 2.04–2.19 (m, 1 H, cyclic CH$_2$), 3.22 (t, $^3J_{H,H}$ = 6.3 Hz, 2 H, NCH$_2$).

^{13}C NMR (75 MHz, D$_2$O): δ = 13.59 (*C*H$_3$CH$_2$), 22.90 (CH$_3$*C*H$_2$), 24.39 (d, $^3J_{P,C}$ = 5.6 Hz, CH$_3$CH$_2$*C*H$_2$), 26.43 (d, $^3J_{P,C}$ = 4.2 Hz, C-4), 27.10 [C(*C*H$_3$)$_3$], 31.83 (C-3), 34.92 [CH$_3$(CH$_2$)$_2$*C*H$_2$], 46.80 (C-5), 52.27 [*C*(CH$_3$)$_3$], 68.04 (d, $^1J_{P,C}$ = 142.0 Hz, C-2).

^{31}P NMR (121 MHz, D$_2$O): δ = 16.6.

Anal. Calcd for C$_{12}$H$_{29}$N$_2$O$_3$P·HBr: C, 39.90; H, 8.37; N, 7.75. Found: C, 39.99; H, 8.24; N, 7.82.

(2-Phenylpyrrolidin-2-yl)phosphonic Acid Hydrobromide (7b)
Yield: 0.57 g (92%); light-brown solid; mp 116 °C.

^{1}H NMR (300 MHz, D$_2$O): δ = 1.73–1.98 (m, 1 H, cyclic CH$_2$), 1.99–2.26 (m, 1 H, cyclic CH$_2$), 2.28–2.74 (m, 2 H, cyclic CH$_2$), 3.12–3.31 (m, 1 H, NCH$_2$), 3.32–3.53 (m, 1 H, NCH$_2$), 7.26 (br m, 5 H, C$_6$H$_5$).

^{13}C NMR (75 MHz, D$_2$O): δ = 22.50 (d, $^3J_{P,C}$ = 4.2 Hz, C-4), 32.96 (C-3), 46.01 (C-5), 70.75 (d, $^1J_{P,C}$ = 140.1 Hz, C-2), 127.02 (d, $^3J_{P,C}$ = 4.2 Hz, C-2 in Ph), 128.83 (d, $^5J_{P,C}$ = 2.8 Hz, C-4 in Ph), 129.10 (C-3 in Ph), 136.16 (d, $^2J_{P,C}$ = 2.8 Hz, *ipso*-C in Ph).

^{31}P NMR (121 MHz, D$_2$O): δ = 14.3.

Anal. Calcd for C$_{10}$H$_{14}$NO$_3$P·HBr: C, 38.98; H, 4.91; N, 4.55. Found: C, 39.21; H, 5.01; N, 4.39.

(2-Pyridin-4-ylpyrrolidin-2-yl)phosphonic Acid Hydrobromide (7c)
Yield: 0.58 g (94%); light-brown solid; mp 214–215 °C (MeCN–EtOH, 8:2).

^{1}H NMR (400 MHz, D$_2$O): δ = 2.05–2.18 (m, 1 H, cyclic CH$_2$), 2.35–2.46 (m, 1 H, cyclic CH$_2$), 2.53–2.67 (m, 1 H, cyclic CH$_2$), 2.90–3.01 (m, 1 H, cyclic CH$_2$), 3.50–3.57 (m, 1 H, NCH$_2$), 3.68–3.75 (m, 1 H, NCH$_2$), 8.07 (d, $^3J_{H,H}$ = 7.0 Hz, 2 H, py), 8.83 (d, $^3J_{H,H}$ = 7.0 Hz, 2 H, py).

^{13}C NMR (75 MHz, D$_2$O): δ = 22.52 (C-4), 33.01 (C-3), 46.60 (C-5), 71.74 (d, $^1J_{P,C}$ = 125.0 Hz, C-2), 125.72 (CH in py), 141.51 (CHN in py), 158.33 (*ipso*-C in py).

^{31}P NMR (121 MHz, D$_2$O): δ = 9.5.

Anal. Calcd for C$_9$H$_{13}$N$_2$O$_3$P·HBr·H$_2$O: C, 33.05; H, 4.93; N, 8.56. Found: C, 33.73; H, 4.67; N, 8.25.

[2-(4-Tolyl)hexahydro-1*H*-azepin-2-yl]phosphonic Acid Hydrobromide (7e)
Yield: 0.63 g (90%); white solid; mp 123–124 °C [recrystallized (pentane) after complete evaporation of the solvent from the mixture].

^{1}H NMR (400 MHz, D$_2$O): δ = 1.79–1.88 (m, 4 H, 2 cyclic CH$_2$), 1.95–2.04 (m, 2 H, cyclic CH$_2$), 2.45 (s, 3 H, CH$_3$), 3.30–3.34 (m, 2 H, cyclic CH$_2$), 3.95–3.98 (m, 2 H, NCH$_2$), 7.47 (d, $^3J_{H,H}$ = 8.4 Hz, 2 CH$_{Ar}$), 7.75 (d, $^3J_{H,H}$ = 6.0 Hz, 2 CH$_{Ar}$).

^{31}P NMR (121 MHz, D$_2$O): δ = 3.00.

Anal. Calcd for C$_{13}$H$_{20}$NO$_3$P·0.25HBr: C, 53.93; H, 7.05; N, 4.84. Found: C, 53.81; H, 6.68; N, 4.70.

(2-Pyridin-4-ylpyrrolidin-2-yl)phosphonic Acid (8a)
Yield: 0.47 g (82%); yellowish solid; mp 243–244 °C.

IR (KBr): 564, 895, 920, 1011, 1069, 1100, 1204 (P=O), 1425, 1606, 1628 (>NH$_2^+$), 2396, 2444, 2773, 2937, 2979 cm^{-1}.

^{1}H NMR (400 MHz, D$_2$O): δ = 1.92–2.10 (m, 1 H, cyclic CH$_2$), 2.25–2.43 (m, 1 H, cyclic CH$_2$), 2.44–2.61 (m, 1 H, cyclic CH$_2$), 2.80–2.95 (m, 1 H, cyclic CH$_2$), 3.40–3.51 (m, 1 H, NCH$_2$), 3.61–3.76 (m, 1 H, NCH$_2$), 7.73 (s, 2 H, py), 8.60 (s, 2 H, py).

^{13}C NMR (101 MHz, D$_2$O): δ = 22.47 (C-4), 33.00 (C-3), 46.10 (C-5), 71.34 (d, $^1J_{P,C}$ = 124.0 Hz, C-2), 123.38 (CH in py), 141.5 (CHN in py), 153.25 (d, $^2J_{P,C}$ = 12.3 Hz, *ipso*-C in py).

^{31}P NMR (162 MHz, D$_2$O): δ = 9.65.

Anal. Calcd for C$_9$H$_{13}$N$_2$O$_3$P·0.5H$_2$O: C, 45.57; H, 5.95; N, 11.81. Found: C, 45.16; H, 5.42; N, 11.74.

(2-Phenylpiperidin-2-yl)phosphonic Acid (8b)
Yield: 0.40 g (84%); white solid; mp 253–254 °C.

IR (KBr): 575, 943, 1044, 1066, 1088, 1172, 1222 (P=O), 1446, 1462, 1629 (>NH$_2^+$), 2321, 2455, 2574, 2687, 2737, 2939 cm^{-1}.

^{1}H NMR (300 MHz, D$_2$O): δ = 1.41–1.58 (m, 1 H, cyclic CH$_2$), 1.60–1.88 (m, 3 H, cyclic CH$_2$), 2.16–2.27 (m, 1 H, cyclic CH$_2$), 2.66–2.75 (m, 1 H, cyclic CH$_2$), 2.93–3.14 (m, 1 H, NCH$_2$), 3.18–3.28 (m, 1 H, NCH$_2$), 7.34–7.52 (m, 5 H, 5 CH$_{Ar}$).

^{13}C NMR (75 MHz, HCl–DMSO-d_6): δ (HCl salt) = 17.30 (d, C-4, $^3J_{P,C}$ = 7.7 Hz), 21.38 (C-3), 26.91 (C-5), 41.16 (d, $^3J_{P,C}$ = 13.1 Hz, C-6), 60.39 (d, C-2, $^1J_{P,C}$ = 146.5 Hz), 127.91 (CH$_{Ar}$), 128.42 (*p*-C in Ph), 129.06 (CH$_{Ar}$), 131.33 (*ipso*-C in Ph).

^{31}P NMR (121 MHz, D$_2$O): δ = 12.4.

Anal. Calcd for C$_{11}$H$_{16}$NO$_3$P·0.5H$_2$O: C, 52.80; H, 6.85; N, 5.60. Found: C, 52.51; H, 6.61; N, 5.26.

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