Synthesis of New (3-Aminopyrrolidin-3-yl)phosphonic Acid – A Cucurbitine Analogue – and (3-Aminotetrahydrothiophen-3-yl)phosphonic Acid via Phosphite Addition to Heterocyclic Hydrazones

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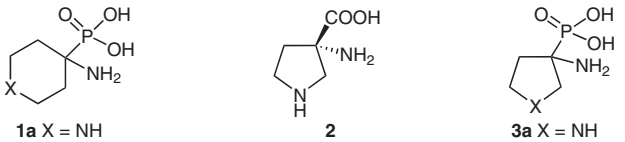
Abstract: Hydrazones were prepared by condensation of carbocyclic and heterocyclic ketones with benzoyl- and tosylhydrazines. These hydrazones underwent nucleophilic addition with phosphite to provide efficiently (3-hydrazinopyrrolidin-3-yl)-, (3-hydrazinotetrahydrothiophen-3-yl)-, (3-hydrazinotetrahydrofuran-3-yl)-, and (1-hydrazinocyclopentyl)phosphonates. Cleavage of the hydrazine N–N bonds followed by acidic hydrolysis of the phosphonate functions of the (3-aminoheterocyclopentyl)phosphonates gave the new (3-aminopyrrolidin-3-yl)- and (3-aminotetrahydrothiophen-3-yl)phosphonic acids. This synthesis was achieved in a four-step sequence from the appropriate ketones.

Key words: phosphonic acids, heterocycles, amines, cucurbitine analogue, nucleophilic additions

Several α-aminophosphonic acids show activity as enzyme inhibitors, antibacterials, herbicides, or plant growth regulators.[1] 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,[2] serine protease[3]). Thus, in recent years, many cyclic α-aminophosphonic acids have been prepared,[4–11] and when from cycloalkanones, mainly by Mannich-type reactions.[12]

Very few examples of heterocyclic α-aminophosphonic acids **1** or the corresponding phosphonates have been reported; only the 4-aminobutyric acid (GABA)[13] analogue **1a**,[14] the tetrahydropyranylphosphonate derivative of **1b**,[15] and tetrahydrothiopyranylphosphonate derivative of **1c** are described (Figure 1).[16] In all these synthetic approaches, the Kabatschnick–Fields reaction[15a] was used from heterocyclohexanones, to provide α-aminophosphonates in moderate to good yields.

(–)-Cucurbitine (**2**; Figure 1), isolated from the seeds of several species of Cucurbitaceae, has been used as an antiallergenic agent for the preparation of cosmetics and pharmaceuticals. Despite its interesting biological activity,[17] only few syntheses have been described, in which the Bucherer–Bergs reaction is used to introduce the α-amino acid moiety.[18,19] In contrast, (3-aminopyrrolidin-3-yl)phosphonic acid (**3a**) (a cucurbitine analogue) and tetrahydrofuranyl- and tetrahydrothiophenylphosphonic acid analogues **3b** and **3c** are still unknown (Figure 1).



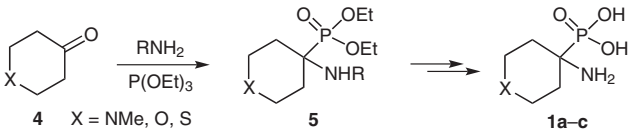
1a X = NH
1b X = O
1c X = S

2
(–)-cucurbitine

3a X = NH
3b X = O
3c X = S

Figure 1 Heterocyclic α-aminocarboxylic and phosphonic acids

We previously reported a simple and convenient synthesis of 1-aminocyclopropanephosphonic acids [aminocyclopropanecarboxylic acid (ACC) analogues], in three steps, starting from cyclopropanone hemiacetals and proceeding via aminophosphonates.[8] Furthermore, we have very recently reported, in racemic series, an efficient three-step synthesis of new heterocyclic α-aminophosphonic acids **1a–c** in good yields from readily available ketones **4** via aminophosphonates **5** (Scheme 1).[20] We also applied the same sequence to obtain (3-aminopiperidin-3-yl)phosphonic acids from the corresponding cyclic ketones.[20]



4 X = NMe, O, S

5

1a–c

Scheme 1

Herein, we report our efforts towards the synthesis of phosphonocucurbitine **3a** and related compounds **3b**,**c** (Figure 1). We decided to first apply our methodology involving the addition of a phosphite to iminium intermediate **6** as a key step (Scheme 2). Unfortunately, we realized that for the five-membered-ring heterocyclic ketones **7–9** (X = NCO_2Et, O, or S), the failure of formation of iminiums **6** limited the formation of the corresponding aminophosphonates **10–12** (Scheme 2). Attempts to isolate and characterize such imine intermediates (corresponding to iminiums **6**) also failed (Scheme 2).[20]

In addition, we tried different conditions for the phosphite additions to 3-pyrrolidinone **7** [$P(OEt)_3$, $HP(OEt)_2$ under acidic conditions, or $LiP(O)(OEt)_2$ under basic conditions] (Scheme 2).[21] However, none of these conditions

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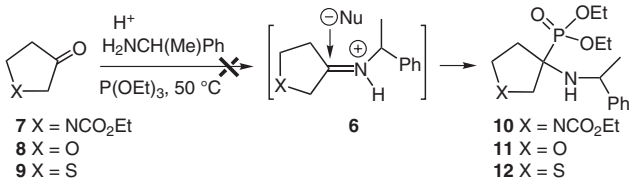
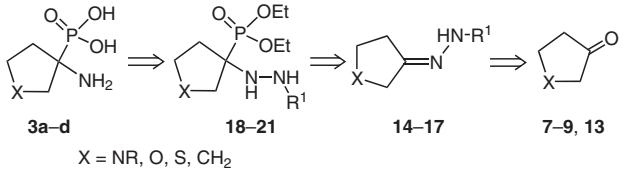


Scheme 2



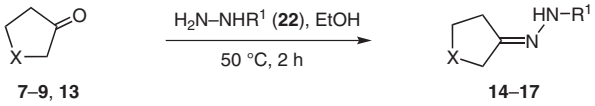
Scheme 3

gave the corresponding aminophosphonate **10**. Microwave[22] or solvent- and catalyst-free[23] reactions also failed.

Therefore, knowing that hydrazones are much more stable than their corresponding imines, we decided to investigate their reactivity. Such hydrazones are readily available from heterocyclic and carbocyclic ketones **7**–**9** and **13** (Scheme 3). Addition of phosphite to hydrazones **14**–**17** should[24] give the desired aminophosphonates **18**–**21**, precursors of aminophosphonic acids **3a**–**d** (Scheme 3).

Hydrazone formation was carried out under mild conditions. Ketones **7**[25] and **8**,[26] as well as commercially available ketones **9** and **13**, reacted with tosylhydrazine **22a** and benzoylhydrazine **22b** in ethanol at 50 °C, to give the desired *E*/*Z*-configured hydrazones **14**–**17** in good yields (72–89%) (Scheme 4, Table 1). The thus obtained hydrazones **14**–**17** were used in the next step without further purification.

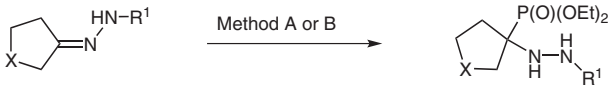
The standard reactions (Scheme 5) of pyrrolidin-3-one hydrazones **14a**,**b** with diethyl phosphite, used as solvent and reagent, in the presence of 0.3 equivalents trifluo-



Scheme 4

romethanesulfonic acid, were carried out at 0 °C for one hour, and then the mixtures were warmed slowly to room temperature for four hours (method A); this gave the corresponding hydrazinophosphonates **18a**,**b** in good yields (60–96%) (Table 2, entries 1 and 3). Conducting the same reaction with tetrahydrofuran-3-one hydrazone **15b** or tetrahydrothiophen-3-one hydrazone **16b** gave hydrazinophosphonates **19b** or **20b**, respectively, in lower yields (Table 2, entries 5 and 7).

On the other hand, the reactions of benzoylhydrazones **14b**, **15b**, and **16b** with triethyl phosphite (1.1 equiv) in the presence of 0.5 equivalents trifluoromethanesulfonic acid in dichloromethane at room temperature for 18–24 hours (method B), furnished the expected hydrazinophosphonates **18b**, **19b**, and **20b**, respectively, in slightly increased yields (Table 2, entries 4, 6 and 8). Likewise, cyclopentanone hydrazones **17a**[27a] and **17b**,[27b] by methods A and B, respectively, gave hydrazinophosphonates **21a** and **21b**, respectively, in the same yields obtained for the pyrrolidine derivatives (Table 2, cf. entries 1 and 9; and entries 4 and 10).



Scheme 5

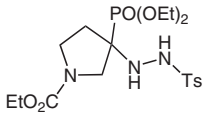
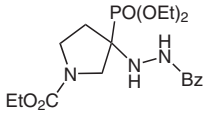
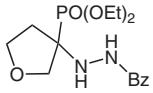
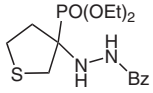
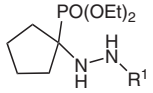
We next tried to obtain the aminophosphonates starting from other imine analogues (such as oximes or phosphinimides), which are known to be easily cleaved in the final sequence affording free amines. Thus, imine **23**, prepared from cyclopentanone oxime and chlorodiphenylphosphine,[28] reacted with triethyl phosphite to give the desired aminophosphonate **24** in low yield and with a mixture of unidentified products (Scheme 6). Similarly, the addition of diethoxyphosphorylpotassium in the presence of three equivalents of boron trifluoride–diethyl ether complex to the easily prepared carbocyclic and heterocyclic oximes **25a** and **25b**[29] yielded the expected aminophosphonates **26a** and **26b**, respectively, in only 30% and 24% yields, respectively, with 30–55% recovered starting materials (Scheme 6). Finally, optically active hydrazone **27**, prepared from (*R*)-(+)-1-amino-2-(methoxymethyl)pyrroli-

Table 1 Preparation of Hydrazones **14**–**17** from Ketones **7**–**9** and **13**[a]

Entry	Ketone **7**–**9**	X	Hydrazine **22**	R^1	Hydrazone **14**–**17**	Yield (%)
1	**7**	NCO_2Et	**22a**	Ts	**14a**	82
2	**7**	NCO_2Et	**22b**	Bz	**14b**	89
3	**8**	O	**22b**	Bz	**15b**	74
4	**9**	S	**22b**	Bz	**16b**	84
5	**13**	CH_2	**22a**	Ts	**17a**	88
6	**13**	CH_2	**22b**	Bz	**17b**	72

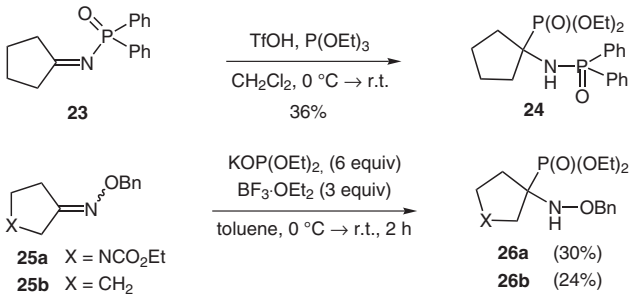
[a] See Scheme 4. Reaction conditions: ketone **7**, **8**, **9**, or **13**, hydrazine **22a** or **22b** (1 equiv), EtOH, 50 °C, 2 h.

Table 2 Preparation of Hydrazinophosphonates **18**–**21** from Hydrazones **14**–**17**[a]

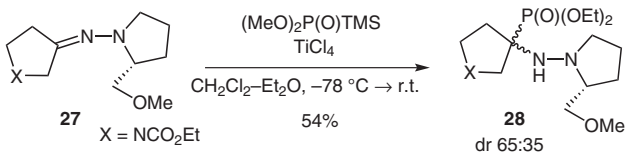
Entry	X	R^1	Hydrazone	Conditions[a]	Phosphonate **18**–**21**	Yield (%)
1	NCO_2Et	Ts	**14a**	A	**18a** 	96
2	NCO_2Et	Ts	**14a**	A[b]	**18a**	–[c]
3	NCO_2Et	Bz	**14b**	A	**18b** 	60
4	NCO_2Et	Bz	**14b**	B	**18b**	68
5	O	Bz	**15b**	A	**19b** 	29
6	O	Bz	**15b**	B	**19b**	37
7	S	Bz	**16b**	A	**20b** 	34
8	S	Bz	**16b**	B	**20b**	40
9	CH_2	Ts	**17a**	A	**21a** R^1 = Ts, R^1 = Bz 	90
10	CH_2	Bz	**17b**	B	**21b**	61

[a] See Scheme 5. Reaction conditions: Method A: hydrazone, $HP(O)(OEt)_2$ (excess), TfOH (0.3 equiv), 0 °C to r.t., 4 h; Method B: hydrazone, $P(OEt)_3$ (1.1 equiv), TfOH (0.5 equiv), CH_2Cl_2, 0 °C, 1 h, then r.t., 18–24 h.
[b] $ZnBr_2$ in DMF was used instead of TfOH.
[c] No reaction took place.

dine (RAMP) and heterocyclic ketone **7**, reacted with a phosphonate in the presence of titanium(IV) chloride to provide an inseparable diastereomeric mixture of aminophosphonates **28** in moderate yield (Scheme 7). Because of these unsatisfactory results, aminophosphonates **24**, **26a**, **26b**, and **28** are not used for the next steps.

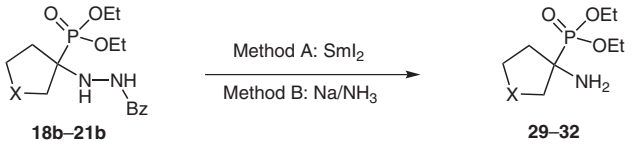


Scheme 6



Scheme 7

We then subjected (benzoylhydrazino)phosphonates **18b–21b** to cleavage of the hydrazine N–N bonds (Scheme 8, Table 3). Reaction of hydrazinophosphonate **18b** under the mild conditions of 2.2 equivalents samarium(II) iodide in tetrahydrofuran–methanol[30] at 0 °C resulted in cleavage of the N–N bond, affording free aminophosphonate **29** in low yield (Table 3, entry 1). Although the reaction as monitored by TLC gave the desired aminophosphonate **29** cleanly, the workup and purification on silica gel seem to be the limiting step for this reaction. Use of hexamethylphosphoramide as cosolvent, known to increase the reduction power of the samarium(II) iodide solution towards functional groups,[31] did not improve the yield (20%). Attempt to cleave the N–N bond of tosylhydrazine **18a** under the same conditions (SmI_2, MeOH) failed. The best result was obtained when the cleavage reaction of **18b** was carried out with sodium/ammonia in ethanol,[32] giving the free amine **29** in 55% yield (Table 3, entry 2). Unexpectedly, this reduction step required 35 equivalents of sodium for complete N–N bond cleavage. Furthermore, other reduction agents, such as Raney nickel/hydrogen in ethanol,[32] hydrogen/palladium(II) hydroxide/carbon in acetic acid, hydrogen/platinum(IV) oxide in acetic acid,[33a] zinc/acetic acid/trifluoroacetic acid,[33b] sodium borohydride/nickel(II)



Scheme 8

Table 3 Cleavage of the N–N Bonds of Hydrazines **18b**–**21b**[a]

Entry	Hydrazine	X	Conditions[a]	Yield (%)	Product
1	**18b**	NCO_2Et	A: SmI_2	20	**29**
2	**18b**	NCO_2Et	B: Na/NH_3	55	**29**
3	**19b**	O	A: SmI_2	dec[b]	**30**
4	**20b**	S	A: SmI_2	50	**31**
5	**21b**	CH_2	A: SmI_2	32	**32**
6	**21b**	CH_2	B: Na/NH_3	15	**32**

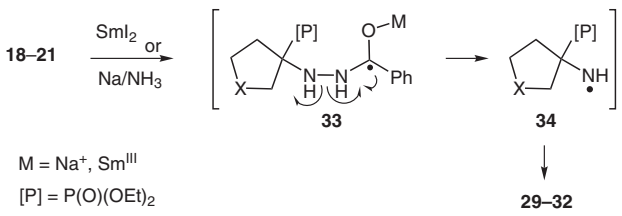
[a] See Scheme 8. Reaction conditions: Method A: SmI_2 (2.2 equiv), THF, MeOH, 0 °C to r.t., 1 h; Method B: Na (35 equiv), liquid NH_3, THF–EtOH, –50 °C to r.t., 1 h.
[b] Decomposition.

chloride in ethanol,[33c] and sodium bis(2-methoxyethoxy)aluminum hydride in toluene at reflux,[33d] did not cleave hydrazinophosphonates **18**.

Cleavage of (benzoylhydrazino)phosphonate **19b** (a furan derivative) under the same conditions afforded a mixture of degradation products (Table 3, entry 3). In contrast, the tetrahydrothiophene derivative **20b** and cyclopentyl derivative **21b** reacted with samarium(II) iodide to furnish the desired free aminophosphonates **31** and **32** in the acceptable yields of 50% and 32%, respectively (Table 3, entries 4 and 5). In addition, **21b** was reduced by sodium/ammonia or tributylstannane to give **32** in 15% yield (Table 3, entry 6) or to form degradation products, respectively.

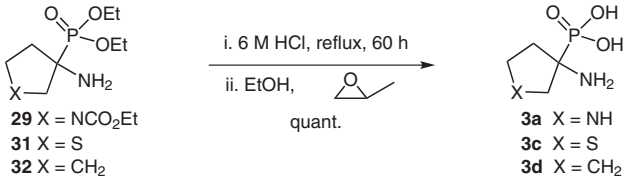
These results are probably explained by the formation of the radical **33** in the presence of samarium(II) iodide or sodium/ammonia, which by fragmentation gives radical **34** (Scheme 9). By hydrogen abstraction, free amines **29**–**32** form (Scheme 9). Although we were not able to isolate any byproducts, the possible ring-opening rearrangement of heterocyclic radical **34** cannot be excluded.

Subsequent phosphonate hydrolysis and methoxycarbonyl group deprotection of **29** was accomplished simultaneously in six molar hydrochloric acid at reflux, to give



Scheme 9 Proposed mechanism of N–N bond reduction

the new amino acid hydrochloride **3a**·2HCl (a cucurbitine analogue) quantitatively (Scheme 10). Hydrolysis of aminophosphonates **31** and **32** with six molar hydrochloric acid at reflux, followed by treatment with propylene oxide, provided the new (3-aminotetrahydrothiophen-3-yl)phosphonic acid (**3c**) and (1-aminocyclopentyl)phosphonic acid (**3d**),[9b] in quantitative yields (Scheme 10). Additionally, hydrolysis of **32** was also achieved with trimethylsilyl iodide, followed by treatment with propylene oxide.[34]



Scheme 10

In summary, we have developed an easy and efficient four-step synthesis of new (3-amino-3-heterocyclopentyl)phosphonic acids **3a** and **3c** and (aminocyclopentyl)phosphonic acid **3d**. Thus, starting from readily available 3-heterocyclic ketones **7**–**9** and commercially available cyclopentanone (**13**), we have demonstrated that the hydrazones formed from these ketones undergo nucleophilic addition of phosphites to give the heterocyclic aminophosphonates **18**–**21** in good to acceptable yields. Subsequent cleavage of the N–N bonds with sodium/liquid ammonia or samarium(II) iodide was accomplished in acceptable yields. Finally, acid hydrolysis of the phosphonate functions provided amino-substituted phosphonic acids in quantitative yields. This new approach to the synthesis of aminophosphonates from five-membered heterocyclic ketones and hydrazines constitutes an interesting and useful alternative to our previously reported method on six-membered-ring heterocycles.[20] This series of experiments confirms that the reactivity of five-membered-ring compounds is very often different from that of the six-membered analogues.

All reactions were carried out under an argon atmosphere and under magnetic stirring. *rac*-α-Methylbenzylamine, tosylhydrazine (**22a**), benzoylhydrazine (**22b**), RAMP, AcOH, TfOH, cyclopentanone (**13**), dihydrothiophen-3-one (**9**), TFA, BF_3·OEt_2, $Pd(OH)_2$/C (20%), $P(OEt)_3$, $HP(OEt)_2$, $(MeO)_2P(O)TMS$, KHMDS, and propylene oxide were purchased from Aldrich. Dihydropyrrolidin-3-one **7**,[25] dihydrofuran-3-one (**8**),[26] and SmI_2[35] were prepared by literature procedures. $P(OEt)_3$ and $HP(OEt)_2$ were distilled under reduced pressure and stored over 4-Å molecular sieves under argon. DMF, toluene, DMSO, HMPA, and CH_2Cl_2 were freshly distilled over CaH_2 under argon before use. TLC (source of reported R_f) was carried out on 0.25-mm silica gel plates (Merck F254). Flash chromatography 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. ^1H and ^{13}C NMR spectra were measured on a Bruker DRX250 (^1H, 250 MHz; ^{13}C, 62.9 MHz) or Bruker AC360 (^1H,

360 MHz; ^{13}C, 90.56 MHz) spectrometer. Chemical shifts δ are reported relative to the solvent resonance (^1H: $CDCl_3$, δ = 7.27; D_2O, δ = 4.8; ^{13}C: $CDCl_3$, δ = 77.16). ^{31}P NMR spectra were recorded on a Bruker AM250 (101.25 MHz) spectrometer, and chemical shifts δ are reported relative to internal 85% H_3PO_4 (δ = 0). HRMS was carried out on a Finnigan MAT 95S spectrometer. All new compounds were determined to be >95% pure by ^1H NMR spectroscopy.

Hydrazones 14–17; General Procedure

A procedure published by Shapiro was followed.[27a] Tosylhydrazine (**22a**; 1.115 g, 6 mmol) or benzoylhydrazine (**22b**; 817 mg, 6 mmol) was added to a soln of one of ketones **7–9** or **13** (6 mmol) in EtOH (8 mL). The mixture was heated at 50 °C for 12–24 h. After cooling to r.t., the mixture was concentrated in vacuo to dryness, and the solid residue was filtered and washed with Et_2O; this afforded hydrazones **14–17** as white solids; yields: 72–89%. Hydrazones **14a**, **14b**, **15b**, **16b**, **17a**, and **17b** thus obtained were used in the next step without further purification.

Ethyl (*Z*/*E*)-3-(Tosylhydrazono)pyrrolidine-1-carboxylate (14a)

Yield: 82%; mp 161 °C; R_f = 0.61 (EtOAc–PE, 70:30).

IR (neat): 3442, 3054, 2985, 1694, 1674, 1600, 1435, 1385, 1167, 1034, 1010 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ (*E*/*Z* or *Z*/*E*, 60:40) = 1.24 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3), 2.44 (s, 3 H, C$H_{3\ tolyl}$), 2.54 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, 4-H, *E* or *Z*), 2.71 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, 4-H, *Z* or *E*), 3.50–3.76 (m, 2 H, 5-H), 3.90–4.07 (m, 2 H, 2-H), 4.12 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH_2O), 7.33 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, H_{arom}), 7.47 (br s, 1 H, NH, *Z* or *E*), 7.68 (s, 1 H, NH, *E* or *Z*), 7.83 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, H_{arom}).

^1H NMR (250 MHz, DMSO-d_6): δ (*E*/*Z*) = 1.63 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3), 2.30 (s, 3 H, $CH_{3\ tolyl}$), 2.43–2.72 (sharp m, 2 H, 4-H), 3.29–3.62 (m, 2 H, 5-H, *Z*/*E*), 3.85/4.04 (s, 2 H, 2-H, *E*/*Z*), 4.02 (q, $3J_{H,H}$ = 7.0 Hz, 2 H, CH_2O), 7.40 (d, $3J_{H,H}$ = 8.0 Hz, 2 H), 7.74 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H), 10.37/10.42 (s, 1 H, NH, *Z*/*E*).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.8 (CH_3), 21.8 ($CH_{3\ tolyl}$), 30.8/31.6 (C-4, *E*/*Z*), 43.9 (C-5, *E*), 44.3 (C-5, *Z*), 46.4 (C-2, *Z*), 49.6 (C-2, *E*), 61.7 (CH_2O, *Z*), 61.9 (CH_2O, *E*), [6 C_{arom}: 128.2 (2 CH), 129.9 (2 CH), 135.2 (C-SO_2), 144.6 (C)], 153.3 (OCON), 159.6 (*C*=N).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 14.6 (CH_3), 21.0 ($CH_{3\ tolyl}$), 27.6/30.1 (C-4, *E*/*Z*), 43.4/44.1 (C-5, *Z*/*E*), 46.9/49.1 (C-2, *E*/*Z*), 60.6/60.7 (CH_2O, *E*/*Z*), [6 C_{arom}: 127.4 (2 CH), 129.5 (2 CH), 136.2 (C–SO_2), 143.3 (C)], 154.0/154.1 (OCON, *E*/*Z*), 160.2/160.4 (*C*=N, *E*/*Z*).

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{19}O_4N_3NaS$: 348.0988; found: 348.0994.

Ethyl (*Z*/*E*)-3-(2-Benzoylhydrazono)pyrrolidine-1-carboxylate (14b)

Yield: 89%; white solid; mp 118.2 °C; R_f = 0.30 (MeOH–Et_2O–aq NH_3, 10:90:0.5).

IR (KBr): 3680, 3195, 3007, 1708, 1640, 1602, 1578, 1544, 1430, 1112 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ (*E*/*Z*, 6:4) = 1.29/1.28 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3), 2.74 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, 4-H, *E*), 2.95 (m, 2 H, 4-H, *Z*), 3.65–3.76 (m, 2 H, 5-H, *Z*), 3.79 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, 5-H, *E*), 3.80–3.40 (m, 2 H, 2-H), 4.19 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH_2O), 7.33–7.54 (m, 3 H, H_{arom}), 7.76 (d, $^3J_{H,H}$ = 7.6 Hz, 2 H, H_{arom}), 9.27/9.41 (br s, 1 H, NH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ (*Z*/*E* or *E*/*Z*, 70:30) = 14.7 (CH_3), 31.0/31.6 (C-4, *E*/*Z*), 43.6/44.3 (C-5, *E*/*Z*), 46.4/49.6 (C-2, *Z*/*E*), 61.5/61.6 (CH_2O, *E*/*Z*), [6 C_{arom}: 127.6 (2 CH), 128.5 (2 CH), 132.0 (CH), 133.0 (C)], 154.9 (COON), 159.5 (C=N), 164.4 (N*C*OPh).

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{17}O_3N_3Na$: 298.1162; found: 298.1160.

Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 60.85; H, 6.13; N, 14.94.

N′-[(*E*/*Z*)-Dihydrofuran-3(2*H*)-ylidene]benzohydrazide (15b)

Yield: 74%; mp 159 °C; R_f = 0.29 (MeOH–Et_2O–NH_3, 5:95:0.5).

IR (neat): 3195, 2955, 1635, 1600, 1576, 1530, 1300, 1137, 1044 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ (*E*/*Z*) = 2.64 (t, $^3J_{H,H}$ = 6.7 Hz, 2 H, 4-H, *E*), 2.86 (m, 2 H, 4-H, *Z*), 4.07 (t, $^3J_{H,H}$ = 6.7 Hz, 2 H, 5-H, *Z*), 4.16 (t, $^3J_{H,H}$ = 6.7 Hz, 2 H, 5-H, *E*), 4.38 (br s, 2 H, 2-H, *Z*), 4.42 (br s, 2 H, 2-H, *E*), 7.30–7.63 (m, 3 H, H_{arom}), 7.63–8.00 (m, 2 H, H_{arom}), 8.20 (s, 1 H, NH, *Z*), 8.59 (s, 1 H, NH, *E*).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ (*E*/*Z*) = 27.9 (C-4, *E*), 32.7 (C-4, *Z*), 66.0 (C-2, *Z*), 67.9 (C-5, *E*/*Z*), 69.8 (C-2, *E*), [6 C_{arom}: 127.3/127.5 (CH, *Z*/*E*), 128.9 (2 CH, *E*/*Z*), 132.3 (2 CH, *E*/*Z*), 133.1 (C, *E*/*Z*)], 150.1/153.9 (C-3, *E*/*Z*), 168.4/166.0 (CON, *E*/*Z*).

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{12}N_2O_2Na$: 227.0791; found: 227.0795.

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92, N, 13.72. Found: C, 64.33; H, 5.84; N, 13.82.

N′-[(*E*/*Z*)-Dihydrothiophen-3(2*H*)-ylidene]benzohydrazide (16b)

Yield: 84%; white solid; mp 191.0 °C; R_f = 0.39 (MeOH–Et_2O–aq NH_3, 5:95:0.5).

IR (film): 3210, 3048, 3003, 1650, 1640, 1600, 1578, 1530, 1286, 907 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ (*E*/*Z*) = 2.74 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, 4-H, *E*), 2.90–3.04 (m, 4 H, 2 4-H, *Z*, and 2 5-H, *E*), 3.07 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, 5-H, *Z*), 3.52 (app s, 2 H, 2-H, *Z*), 3.68 (br s, 2 H, 2-H, *E*), 7.40–7.57 (m, 3 H, H_{arom}), 7.75–7.81 (m, 2 H, H_{arom}), 8.63 (s, 1 H, NH, *Z*), 8.74 (s, 1 H, NH, *E*).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ (*E*/*Z*) = 28.4 (C-5, *E*), 29.1 (C-4, *E*), 29.6 (C-5, *Z*), 30.0 (C-2, *Z*), 36.4 (C-4, *Z*), 37.4 (C-2, *E*), [6 C_{arom}: 127.4 (CH), 128.8 (2 CH), 132.2 (2 CH), 133.2 (C)], 152.5/155.7 (C-3, *E*/*Z*), 163.3/168.3 (CON, *E*/*Z*).

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{12}N_2OSNa$: 243.0563; found: 243.0570.

Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72. Found: C, 59.61; H, 5.47; N, 12.56.

N′-Cyclopentylidene-4-toluenesulfonohydrazide (17a)

Compound **17a** was prepared according to the procedure in ref. 27a.

Yield: 88%; white solid.

^1H NMR (360 MHz, $CDCl_3$): δ (*E*/*Z*) = 1.64–1.77 (m, 2 H, 4-H), 1.77–1.90 (m, 2 H, 3-H), 2.14 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, 5-H), 2.37 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, 2-H), 2.44 (s, 3 H, CH_3), 7.04 (s, 1 H, NH), 7.32 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, H_{arom}), 7.86 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, H_{arom}).

Analytical data were in accord with the literature values.[27a]

N′-Cyclopentylidenebenzohydrazide (17b)

Yield: 72%; mp 150.1 °C; R_f = 0.45 (MeOH–Et_2O–aq NH_3, 10:90:0.5).

^1H NMR spectral data were in accord with the literature values,[27b] but ^{13}C NMR data were not previously reported.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.70–1.88 (m, 2 H, 4-H), 1.88–2.05 (m, 2 H, 3-H), 2.29–2.40 (m, 2 H, 5-H), 2.45–2.75 (m, 2 H, 2-H), 7.35–7.62 (m, 3 H, H_{arom}), 7.63–7.96 (m, 2 H, H_{arom}), 8.51 (br s, 1 H, NH).

^{13}C NMR (90.56 MHz, $CDCl_3$): δ = 24.8 (C-4), 24.9 (C-3), 27.5 (C-5), 33.7 (C-2), [6 C_{arom}: 127.3 (CH), 128.8 (2 CH), 131.9 (2 CH), 133.8 (C)], 155.5 (C-1), 167.7 (CON).

Hydrazinophosphonates 18–21 by Method A; General Procedure

TfOH (55 μL, 0.6 mmol, 0.3 equiv) was added to a soln of a hydrazone **14**–**17** (2 mmol) in $HP(O)(OEt)_2$ (2.06 mL, 16 mmol, 8 equiv) at 0 °C. The mixture was warmed to r.t. over 4 h, and then concentrated to dryness in vacuo. The residue was mixed with sat. aq $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were dried ($MgSO_4$), filtered, and then concentrated in vacuo to give the crude phosphonate. Purification by flash chromatography (silica gel, MeOH–Et_2O, 5:95) gave pure hydrazinophosphonates **18**–**21**; yields: 29–96%.

Hydrazinophosphonates 18–21 by Method B; General Procedure

$P(OEt)_3$ (380 μL, 2.2 mmol) and TfOH (76 μL, 0.5 equiv) were added successively to a soln of a hydrazone **14**–**17** (2 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The mixture was then stirred at r.t. for 12–24 h. After addition of sat. aq $NaHCO_3$ (5 mL), the reaction mixture was extracted with CH_2Cl_2 (2 × 30 mL). The organic layer was dried, filtered, and concentrated under vacuum. The resulting residue was purified by flash chromatography (silica gel); this gave pure hydrazinophosphonates **18**–**21**; yields: 37–68%.

Diethyl [1-(Ethoxycarbonyl)-3-(2-tosylhydrazino)pyrrolidin-3-yl]phosphonate (18a)

Prepared by Method A.

Yield: 96%; colorless viscous oil; R_f = 0.33 (MeOH–Et_2O–aq NH_3, 5:95:0.5).

IR (neat): 3437, 3560, 3121, 2982, 1693, 1682, 1428, 1330, 1230, 1160, 1050 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ (two rotamers a/b) = 1.15–1.40 (m, 9 H, $CH_{3\ carbamate}$ + 2 C$H_3$$CH_2$OP), 1.90–2.40 (m, 2 H, 4-H), 2.43 (s, 3 H, $CH_{3\ tolyl}$), 3.20–3.61 (m, 4 H, 2 2-H and 2 5-H), 3.91/3.96 (s, 1 H, NH), 4.00–4.25 (m, 6 H, CH_2OCO and 2 CH_2OP), 6.87/6.91 (s, 1 H, NHTs), 7.30 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, H_{arom}), 7.75/7.76 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, H_{arom}).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.8 ($CH_{3\ carbamate}$), 16.5 (2 CH_3CH_2OP), 21.6 ($CH_{3\ tolyl}$), 30.5 (d, $^2J_{P,C}$ = 2.0 Hz, C-4), 44.3 (C-5), 50.2/51.7 (d, $^2J_{P,C}$ = 6.5 Hz, C-2), 61.1 (CH_2OCO), 63.1 (2 CH_2OP), 65.1/64.6 (d, $^1J_{P,C}$ = 164.9 Hz, C-3), [6 C_{arom}: 128.3 (2 CH), 129.4 (2 CH), 134.6 (C-SO_2), 143.9 (C)], 154.9 (COON).

^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 25.11; (101.25 MHz, DMSO-d_6): δ (two rotamers) = 24.97/25.11.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{30}N_3NaO_7PS$: 486.1434; found: 486.1433.

Anal. Calcd for $C_{18}H_{30}N_3O_7PS$: C, 46.64; H, 6.52; N, 9.07. Found: C, 46.64; H, 6.56; N, 8.73.

Diethyl [3-(2-Benzoylhydrazino)-1-(ethoxycarbonyl)pyrrolidin-3-yl]phosphonate (18b)

Prepared by Method B.

Yield: 68%; colorless viscous oil; R_f = 0.42 (MeOH–Et_2O–aq NH_3, 10:90:0.5).

IR (neat): 3445, 3268, 3061, 2925, 1694, 1682, 1603, 1580, 1428, 1232, 1051, 1024, 970 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$, 300 K): δ (two rotamers a/b) = 1.13–1.31 (m, 3 H, CH_3), 1.31–1.50 (m, 6 H, 2 CH_3), 2.07–2.32 (m, 2 H, 4-H), 3.45–3.75 (m, 4 H, 2 5-H and 2 2-H), 4.00–4.37 (m, 6 H, 2 CH_2OP and CH_2O), 5.23/5.33 (dd, $^3J_{H,H}$ = 6.5 Hz, $^3J_{P,H}$ = 6.6 Hz, 1 H, NH), 7.30–7.60 (m, 3 H, H_{arom}), 7.80 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, H_{arom}), 8.80 (d, $^3J_{H,H}$ = 6.5 Hz, 1 H, NH).

^{1}H NMR (360 MHz, DMSO-d_6, 300 K): δ = 1.14 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3), 1.25 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3), 1.26 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3), 2.10–2.30 (m, 2 H), 3.37–3.70 (m, 4 H), 3.99 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH_2O), 4.03–4.17 (m, 4 H, 2 CH_2OP), 5.58 (dd, $^3J_{H,H}$ = 6.1 Hz, $^3J_{P,H}$ = 7.0 Hz, 1 H, NH), 7.43–7.58 (m, 3 H, H_{arom}), 7.79 (d, $^3J_{H,H}$ = 7.2 Hz, 2 H, H_{arom}), 9.78 (d, $^3J_{H,H}$ = 6.1 Hz, 1 H, NH).

^{13}C NMR (90.56 MHz, $CDCl_3$): δ (rotamers a/b) = 14.5 ($CH_{3\ carbamate}$), 16.3 (2 CH_3CH_2OP), 29.2/29.4 (C-4, a/b), 44.1/44.2 (d, *J* = 8.5 Hz, C-5, a/b), 50.5/51.2 (d, *J* = 6.7 Hz, C-2, a/b), 61.0 (CH_2OCO, a), 61.3 (d, *J* = 5.6 Hz, CH_2OCO, b), 62.8/63.0 (d, $^2J_{P,C}$ = 6.6 Hz, CH_2OP, a/b), 63.3/63.6 (d, $^2J_{P,C}$ = 5.8 Hz, CH_2OP, a/b), 64.9 (d, $^1J_{P,C}$ = 171.6 Hz, C-3, a), 65.7 (d, $^1J_{P,C}$ = 172.9 Hz, C-3, b), [6 C_{arom}: 126.8 (2 CH), 128.4 (2 CH), 132.7 (CH), 132.1/132.6 (C, a/b)], 154.6/154.9 (C, a/b), 165.9 (CON).

^{31}P NMR (101.25 MHz, $CDCl_3$): δ [two rotamers (a/b, 70:30)] = 23.64/23.95.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{28}N_3NaO_6P$: 436.1608; found: 436.1615.

Anal. Calcd for $C_{18}H_{28}N_3O_6P$: C, 52.30; H, 6.83; N, 10.16. Found: C, 51.83; H, 6.91; N, 9.86.

Diethyl [3-(Benzoylhydrazino)]tetrahydrofuran-3-yl]phosphonate (19b)

Prepared by Method B.

Yield: 37%; colorless oil; R_f = 0.35 (MeOH–Et_2O–aq NH_3, 5:95:0.5).

IR (neat): 3479, 3298, 3057, 2983, 1682, 1602, 1581, 1521, 1277, 1216, 1048, 1020, 968 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.34 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H, 2 C$H_3$$CH_2$O), 2.03–2.35 (m, 2 H, 4-H), 3.79–4.00 (m, 3 H, 2 5-H and 2-H), 4.00–4.38 (m, 5 H, 2 CH_2OP and 2-H), 5.48 (dd, $^3J_{P,H}$ = 28.5 Hz, $^3J_{H,H}$ = 8.2 Hz, 1 H, NH), 7.32–7.65 (m, 3 H, H_{arom}), 7.75–7.95 (m, 2 H, H_{arom}), 8.85 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, HNCO).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.6 (2 CH_3CH_2O), 31.5 (d, $^2J_{P,C}$ = 4.6 Hz, C-4), 63.0 (d, $^2J_{P,C}$ = 7.2 Hz, CH_2OP), 63.8 (d, $^2J_{P,C}$ = 6.9 Hz, CH_2OP), 67.5 (d, $^1J_{P,C}$ = 174.0 Hz, C-3), 67.9 (d, $J_{P,C}$ = 9.9 Hz, C-2 or C-5), 72.8 (d, $J_{P,C}$ = 7.2 Hz, C-5 or C-2), [6 C_{arom}: 126.9 (2 CH), 128.7 (2 CH), 131.9 (CH), 132.3 (C)], 165.6 (CON).

^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 24.57.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{23}N_2O_5PNa$: 365.1237; found: 365.1244.

Diethyl [3-(Benzoylhydrazino)tetrahydrothiophen-3-yl]phosphonate (20b)

Prepared by Method B.

Yield: 40%; colorless oil; R_f = 0.79 (MeOH–Et_2O–aq NH_3, 10:90:0.5).

IR (neat): 3445, 3261, 3062, 2928, 1659, 1603, 1580, 1447, 1278, 1049, 1025, 972 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.23–1.48 (m, 6 H, 2 CH_3), 1.88–2.18 (m, 1 H, 4-H), 2.46–2.68 (m, 1 H, 4-H), 2.88–3.02 (m, 2 H, 2-H), 3.15–3.35 (m, 2 H, 5-H), 4.10–4.40 (m, 4 H, 2 CH_2O), 5.83 (dd, $^3J_{P,H}$ = 32.5 Hz, $^3J_{H,H}$ = 8.8 Hz, 1 H, NH), 7.35–7.70 (m, 3 H, H_{arom}), 7.75–7.95 (m, 2 H, H_{arom}), 8.84 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, NH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.6 (CH_3), 16.7 (CH_3), 29.9 (C-4), 33.4 (d, $^2J_{P,C}$ = 8.6 Hz, C-2), 36.8 (C-5), 62.9 (CH_2O), 64.3 (CH_2O), 69.6 (d, $^1J_{P,C}$ = 170.1 Hz, C-3), [6 C_{arom}: 126.9 (2 CH), 128.8 (2 CH), 131.9 (CH), 134.0 (C)], 166.4 (CON).

^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 24.45.

ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{15}H_{23}N_2NaO_4PS$: 381.1008; found: 381.1009.

Anal. Calcd for $C_{15}H_{23}N_2O_4PS$: C, 50.27; H, 6.47; N, 7.82. Found: C, 50.32; H, 6.51; N, 8.14.

Diethyl [1-(2-Tosylhydrazino)cyclopentyl]phosphonate (21a)
Prepared by Method A.

Yield: 90%; white solid; mp 121.5 °C; R_f = 0.27 (MeOH–CH_2Cl_2–aq NH_3, 5:95:0.5).

IR (film): 3425, 3300, 3150, 2958, 1596, 1439, 1330, 1220, 1162, 1041, 1022, 966 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 1.34 (t, $^3J_{H,H}$ = 7.2 Hz, 6 H, 2 CH_3CH_2O), 1.40–1.90 (m, 8 H_{cycle}), 2.44 (s, 3 H, $CH_{3\ tolyl}$), 3.71 (s, 1 H, NH), 4.00–4.20 (m, 4 H, 2 CH_2OP), 6.49 (s, 1 H, $HNSO_2$), 7.31 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, H_{arom}), 7.79 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, H_{arom}).

^{13}C NMR (90.56 MHz, $CDCl_3$): δ = 16.3 (CH_3CH_2O), 16.4 (CH_3CH_2O), 21.3 ($CH_{3\ tolyl}$), 24.1 (C-4), 24.2 (C-3), 32.37 (C-5), 32.43 (C-2), 62.2 (d, $^2J_{P,C}$ = 6.8 Hz, 2 CH_2OP), 66.0 (d, $^1J_{P,C}$ = 148.3 Hz, C-1), [6 C_{arom}: 128.1 (2 CH), 129.1 (2 CH), 135.0 (C-CH_3), 143.4 (C-SO_2)].

^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 30.15.

Anal. Calcd for $C_{16}H_{27}N_2O_5PS$: C, 49.22; H, 6.97; N, 7.17. Found: C, 49.26; H, 7.12; N, 7.17.

Diethyl [1-(Benzoylhydrazino)cyclopentyl]phosphonate (21b)
Prepared by Method B.

Yield: 61%; colorless oil; R_f = 0.70 (MeOH–Et_2O–aq NH_3, 10:90:0.5).

IR (neat): 3480, 3274, 3061, 2977, 1652, 1603, 1580, 1455, 1225, 1049, 1026, 968 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 1.32 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H, 2 CH_3CH_2O), 1.66 (sharp m, 2 H, H_{cycle}), 1.68–2.10 (m, 6 H, H_{cycle}), 4.07–4.24 (m, 4 H, 2 CH_2OP), 5.01 (dd, $^3J_{H,H}$ = 7.0 Hz, $^3J_{P,H}$ = 27.0 Hz, 1 H, NH), 7.30–7.50 (m, 3 H, H_{arom}), 7.70–7.90 (m, 2 H, H_{arom}), 8.90 (d, $^3J_{H,H}$ = 7.0 Hz, 1 H, NH).

^{13}C NMR (90.56 MHz, $CDCl_3$): δ = 16.6 (2 CH_3CH_2O), 24.6 (C-3), 24.7 (C-4), 32.4 (C-2 and C-5), 63.0 (d, $^2J_{P,C}$ = 7.3 Hz, 2 CH_2OP), 67.1 (d, $^1J_{P,C}$ = 167.0 Hz, C-1), [6 C_{arom}: 126.9 (2 CH), 128.7 (2 CH), 131.7 (CH), 132.7 (C)], 165.5 (CON).

^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 28.81.

HRMS data could not be obtained.[36]

***N*-Cyclopentylidene-*P*,*P*-diphenylphosphinic Amide (23)**
Cyclopentanone oxime was prepared by a general procedure from cyclopentanone (**13**; 555 mg, 6.6 mmol), H_2NOH·HCl (459 mg, 6.6 mmol), and K_2CO_3 (912 mg, 6.6 mmol) in EtOH (10 mL). This gave crude cyclopentanone oxime, which was used without further purification; yield: 643 mg (98%).

Phosphinic amide **23** was prepared according to a literature procedure.[28] A soln of crude cyclopentanone oxime (640 mg, 6.46 mmol) in CH_2Cl_2 (10 mL) was cooled to –78 °C and then successively treated with Et_3N (1.012 mL, 7.26 mmol) and Ph_2PCl (1.60 g, 7.26 mmol). The mixture was stirred at –78 °C to r.t. for 3 h. Sat. aq NH_4Cl (10 mL) was added to the reaction mixture, which was then extracted with CH_2Cl_2 (3 × 70 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification (silica gel, CH_2Cl_2–PE, 20:80) afforded amide **23**.

Yield: 1.39 g (76%); viscous oil; R_f = 0.24 (Et_2O–PE, 80:20).

IR (neat): 3230, 3057, 1699, 1635, 1591, 1438, 1184, 1125 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.70 (m, 4 H, 2 H-C-3 and 2 H-4), 2.54–2.60 (m, 4 H, 2 H-2 and 2 H-5), 7.29–7.38 (m, 6 H, H_{arom}).

^{13}C NMR (90.56 MHz, $CDCl_3$): δ = 24.3 (C-3 and C-4), 38.5 (C-2 or C-5), 38.7 (C-5 or C-2), [12 C_{arom}: 128.0 (2 CH), 128.2 (2 CH), 131.1 (CH), 131.2 (CH), 131.3 (2 CH),131.4 (2 CH), 133.3 (C) 135.0 (C)], 202.8 (d, $^2J_{P,C}$ = 10.2 Hz, C-1).

^{31}P NMR (121.49 MHz, $CDCl_3$): δ = 19.39.

Diethyl {1-[(Diphenylphosphoryl)amino]cyclopentyl}phosphonate (24)
Prepared by Method B (as for preparation of phosphonates **18**–**21**) from amide **23**.

Yield: 36% (triple purification on silica gel from a mixture of unidentified products); colorless oil; R_f = 0.40 (MeOH–Et_2O–aq NH_3, 5:95).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, J = 7.0 Hz, 6 H, CH_3), 1.46–1.70 (m, 2 H), 1.70–1.88 (m, 2 H), 1.88–2.18 (m, 4 H), 3.35 (dd, $^2J_{P,H}$ = 8.4 Hz, $^3J_{P,H}$ = 3.0 Hz, 1 H, NH), 4.17 (q, J = 7.0 Hz, 2 H), 4.20 (q, J = 7.0 Hz, 2 H), 7.12–7.58 (m, 6 H), 7.59–8.08 (m, 4 H).

^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 21.28 (d, $^3J_{P,P}$ = 25.3 Hz, POPh$_2$), 30.12 [d, $^3J_{P,P}$ = 25.3 Hz, PO(OEt)$_2$].

1-(Ethoxycarbonyl)pyrrolidin-3-one *O*-Benzyloxime (25a)
O-Benzyloxime **25a** was prepared by a general procedure from pyrrolidinone **7** (353 mg, 2.25 mmol), H_2NOBn·HCl (358 mg, 2.25 mmol), and K_2CO_3 (310 mg, 2.25 mmol) in EtOH (10 mL). Purification by chromatography (silica gel, Et_2O–PE, 90:10) gave an *E*/*Z* mixture of oxime **25a**.

Yield: 380 mg (64%); colorless oil.

^1H NMR (250 MHz, $CDCl_3$): δ (*E*/*Z*, 70:30) = 1.27 (t, J = 7.0 Hz, 3 H, *E*/*Z*), 2.72/2.80 (t, J = 7.5 Hz, 2 H, *E*/*Z*), 3.55/3.70 (m, 2 H, *E*/*Z*), 4.01/4.26 (m, 2 H, *E*/*Z*), 4.16 (t, J = 7.0 Hz, 2 H, CH_2CH$_3$, *E*/*Z*), 5.10/5.11 (s, 2 H, H_{Bn}, *E*/*Z*), 7.36 (br s, 5 H, *E*/*Z*).

Diethyl {3-[(Benzyloxy)amino]-1-(ethoxycarbonyl)pyrrolidin-3-yl}phosphonate (26a)
BF_3·OEt_2 (300μL, 3 eq, 2.463 mmol) was added to a soln of oxime **25a** (215 mg, 0.821 mmol) in toluene at 0 °C. After the mixture had stirred for 10 min, a soln of KP(O)(OEt)$_2$ [prepared from HP(O)(OEt)$_2$ (640 μL, 4.92 mmol) and a soln of KHMDS (9.84 mL, 4.92 mmol) in toluene (1 mL)] was added. The mixture was stirred at r.t. for 24 h. Sat. aq $NaHCO_3$ (5 mL) was added to the mixture, which was then extracted with EtOAc (3 × 70 mL). The organic layer was concentrated and purified by chromatography (silica gel, MeOH–Et_2O–NH_3, 2:98:0.5); this gave starting oxime **25a** (120 mg, 55%) and phosphonate **26a**.

Yield: 100 mg (30%); colorless oil; R_f = 0.66 (MeOH–Et_2O–aq NH_3, 10:90:0.5).

^1H NMR (250 MHz, $CDCl_3$): δ = 1.02/1.36 (m, 9 H, 3 CH_3), 1.84–2.02 (m, 1 H, H-4), 2.02–2.38 (m, 1 H, H-4), 3.30–3.77 (m, 4 H, 2 H-2 and 2 H-5), 3.93–4.26 (m, 6 H, 2 CH_2OP and CH_2OOC), 4.68 (br s, 2 H, CH_2ON), 5.94 (d, $^3J_{P,H}$ = 10.5 Hz, 1 H, HNO), 7.32 (br s, 5 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ (two rotamers) = 14.9 (CH_3CH_2OCO), 16.4 (CH_3CH_2OP), 16.5 (CH_3CH_2OP), 29.8/30.1 (C-4), 44.6/44.9 (d, $^3J_{P,C}$ = 8.4 Hz, C-5), 50.1/50.5 (d, $^2J_{P,C}$ = 11.0 Hz, C-2), 61.2 (CH_3CH_2OCO), 62.4/62.6 (d, $^2J_{P,C}$ = 5.6 Hz, CH_2OP), 65.7/64,9 (d, $^1J_{P,C}$ = 152.0 Hz, C-3), 77.7 (CH_2Ph), [6 C_{arom}: 128.1 (CH), 128.4 (2 CH), 128.8 (2 CH), 137.0 (C)], 155.6 (COO).

^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 26.0.

Diethyl {1-[(Benzyloxy)amino]cyclopentyl}phosphonate (26b)
Phosphonate **26b** was prepared from benzyloxime **25b**[29] by the procedure described above for the preparation of **26a**.

Yield: 24%; colorless oil; R_f = 0.74 (MeOH–Et_2O–aq NH_3, 5:95:0.5).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.0 Hz, 6 H, CH_3), 1.62/1.84 (m, 6 H, H_{Bn}), 1.91–2.08 (m, 2 H, 1 H-2 and 1 H-5), 4.04–4.24 (m, 4 H, CH_2OP), 4.74 (s, 2 H, CH_2ON), 5.81–5.90 (br s, 1 H, NH), 7.31–7.39 (m, 5 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.4 (d, $^3J_{P,C}$ = 5.8 Hz, 2 CH_3CH_2OP), 25.1 (C-3), 25.2 (C-4), 32.4 (d, $^2J_{P,C}$ = 4.5 Hz, C-2 and C-5), 61.8 (d, $^2J_{P,C}$ = 6.8 Hz, 2 CH_2OP), 67.8 (d, $^1J_{P,C}$ = 148.4 Hz, C-1), 77.3 (CH_2ON), [6 C_{arom}: 127.7 (2 CH), 128.2 (2 CH), 128.5 (CH), 137.5 (C)].

^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 31.07.

(*R*)-*N*-[1-(Ethoxycarbonyl)pyrrolidin-3-ylidene]-2-(methoxymethyl)pyrrolidin-1-amine (27)
Pyrrolidin-1-amine **27** was prepared by a general procedure from pyrrolidinone **7** (277 mg, 1.76 mmol) and RAMP (235 μL, 1.76 mmol) in EtOH (4 mL) at 50 °C for 2 h. After purification by chromatography (silica gel, MeOH–Et_2O, 2:98) an *E*/*Z* mixture of hydrazone **27** was obtained.

Yield: 300 mg (63%); R_f = 0.66 and 0.53 (*Z*/*E*), (MeOH–Et_2O–aq NH_3, 10:90:0.5).

IR (neat): 2974, 2926, 2875, 1705, 1625, 1424, 1113 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 7.0 Hz, 3 H, *Z*), 1.28 (t, *J* = 7.0 Hz, 3 H, *E*), 1.38–1.64 (m, 1 H), 1.64–1.97 (m, 3 H), 2.14–2.64 (m, 2 H), 3.01–3.47 (m, 5 H), 3.18/3.19 (s, 3 H, OCH_3, *Z*/*E*), 3.47–3.80 (m, 2 H), 3.80–3.95 (m, 2 H), 4.00 (q, *J* = 7.0 Hz, 2 H, CH_2O, *Z*), 4.01 (q, *J* = 7.0 Hz, 2 H, CH_2O, *E*).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.6 (CH_3), 22.4 (C-4 $_{RAMP}$), 26.3/26.6 (C-3 $_{RAMP}$, *E*/*Z*), 28.5/29.1 (C-4, *Z*), 31.0/31.8 (C-4, *E*), 43.1/44.4 (C-5, *E*/*Z*), 47.0/47.3 (C-2, *Z*), 49.7 (C-2, *E*), 54.0/54.5 (C-5 $_{RAMP}$, *E*/*Z*), 59.0 (C-2 $_{RAMP}$), 61.0 (CH_2OCO), 66.3 (CH_3O), 75.1/75.6 (CH_2OCH_3, *E*/*Z*), 154.9 (COO), 159.9 (C=N).

Dimethyl ((*R*/*S*)-1-(Ethoxycarbonyl)-3-{[(*R*)-2-(methoxymethyl)pyrrolidin-1-yl]amino}pyrrolidin-3-yl)phosphonate (28)
A soln of hydrazone **27** (122 mg, 0.453 mmol) in CH_2Cl_2 (2.3 mL) was added to a 1 M soln of $TiCl_4$ in CH_2Cl_2 (906 μL) at –78 °C. After the mixture had stirred for 15 min at –78 °C, Et_2O (200 μL) was added, and 15 min later, $(MeO)_2P(O)TMS$ (130 μL, 0.680 mmol) was added. The stirred reaction mixture was warmed slowly from –78 °C to r.t. over 3 h. After hydrolysis with a sat. aq soln of KF/NH_4Cl, the mixture was extracted with CH_2Cl_2 (3 × 50 mL). Concentration of the organic layer and purification (silica gel, MeOH–Et_2O, 10:90) gave an inseparable diastereomeric mixture of hydrazinophosphonates **28**.

Yield: 100 mg (54%); colorless oil; R_f = 0.33 (MeOH–Et_2O–aq NH_3, 10:90:0.5).

^{1}H NMR (360 MHz, $CDCl_3$, 320 K): δ (diastereomers a/b, 65:35) = 1.27/1.28 (t, *J* = 7.2 Hz, 6 H, CH_3, a/b), 1.48–1.65 (m, 1 H, H_{RAMP}), 1.65–1.83 (m, 1 H, H_{RAMP}), 1.83–2.00 (m, 1 H, H_{RAMP}), 2.17–2.37 (m, 2 H, H-4), 2.37–2.64 (m, 1 H), 2.64–2.88 (m, 1 H), 3.00 (s, 1 H, NH), 3.25–3.40 (m, 1 H), 3.32/3.35 (s, OCH_3, b/a), 3.40–3.68 (m, 5 H), 3.68–3.95 (m, 1 H), 3.78 (s, 3 H, CH_3OP, b), 3.80 (s, 3 H, CH_3OP, a), 3.81 (s, 3 H, CH_3OP, b), 3.83 (s, 3 H, CH_3OP, a), 4.15/4.16 (q, *J* = 7.2 Hz, 2 H, CH_2OCO, a/b).

^{31}P NMR (121.49 MHz, $CDCl_3$): δ (297 K) = 29.49/29.40 (b/a); δ (320 K) = 29.31 (a and b).

Free Aminophosphonate 29 by Cleavage of the Hydrazine N–N Bond with Sodium/Ammonia[32] (Method B)
Liquid NH_3 (4 mL) was condensed into a soln of hydrazinophosphonate **18b** (0.6 mmol) in THF (1 mL) and absolute EtOH (1 mL) cooled to –78 °C. Then Na (485 mg, 35 equiv) was added in small portions. The mixture was warmed to –50 °C and stirred at this temperature for 1 h. Then the reaction mixture was degassed at r.t. with argon to remove the excess liquid NH_3. The resulting residue was quenched with solid NH_4Cl (1 g) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, MeOH–Et_2O–aq NH_3, 10:90:0.5); this provided free aminophosphonate **29**.

Yield: 97 mg (55%).

Free Aminophosphonates 29–32 by Cleavage of the Hydrazine N–N Bond with Samarium(II) Iodide[30] (Method A); General Procedure
A 1.2 M soln of SmI_2 in THF (3.6 mmol) was added to a soln of one of the hydrazinophosphonates **18b**–**21b** (0.43 mmol) in MeOH (3 mL) at 0 °C. The mixture was stirred for 20 min at the same temperature and then concentrated under reduced pressure to remove the solvents. The residue was extracted with 1 M HCl (2 × 5 mL) and the aqueous layers were washed with Et_2O (8 mL), made alkaline with 1 M aq NaOH, and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O (2 × 1 mL) and brine (2 × 2 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, MeOH–Et_2O–aq NH_3, 10:90:0.5); this afforded free aminophosphonates **29**, **31**, and **32**; yields: 20–50%.

Diethyl [3-Amino-1-(ethoxycarbonyl)pyrrolidin-3-yl]phosphonate (29)
The cleavage of the hydrazine N–N bond was achieved by Method B (Na/NH_3 method).

Yield: 55%; colorless oil; R_f = 0.15 (MeOH–Et_2O–aq NH_3, 10:90:0.5).

IR (neat): 3460, 3382, 3051, 2982, 1695, 1428, 1232, 1048, 1023, 966 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ (two conformers a/b) = 1.24 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3CH_2OCO), 1.35 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3CH_2OP), 1.36 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3CH_2OP), 1.51 (br s, 2 H, NH_2), 1.70–1.84 (m, 1 H, 4-H), 2.17–2.37 (m, 1 H, 4-H), 3.29 (ABX, *J* = 2.5 Hz, J_{AB} = 11.2 Hz, 1 H, 2-H, a), 3.38 (ABX, *J* = 1.5 Hz, $J_{A,B}$ = 11.2 Hz, 1 H, 2-H, b), 3.52–3.67 (m, 2 H, 5-H), 3.70 (ABX, $J_{A,B}$ = 11.2 Hz, *J* = 8.3 Hz, 1 H, 2-H, a), 3.75 (dd, $J_{A,B}$ = 11.2 Hz, 7.9 Hz, 1 H, 2-H, b), 4.04–4.24 (m, 6 H, 3 CH_2O).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ (two conformers a/b) = 14.9 (CH_3 $_{carbamate}$), 16.7 (CH_3CH_2OP), 16.8 (CH_3CH_2OP), 34.0/34.7 (C-4, a/b), 44.3/44.6 (d, $^3J_{P,C}$ = 9.3 Hz, C-5, a/b), 54.8/55.2 (d, $^2J_{P,C}$ = 13.4 Hz, C-2, a/b), 57.2/58.3 (d, $^1J_{P,C}$ = 161.2 Hz, C-3, a/b), 61.3 (CH_2OCO), 62.8 (CH_2OP), 62.9 (CH_2OP), 155.1/155.3 (COO, a/b).

^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 27.03.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{23}N_2NaO_5P$: 317.1237; found: 317.1239.

Diethyl (3-Aminotetrahydrothiophen-3-yl)phosphonate (31)
The cleavage of the hydrazine N–N bond was achieved by Method A (SmI_2 method).

Yield: 50%; pale yellow oil; R_f = 0.26 (MeOH–Et_2O–aq NH_3, 5:95:0.5).

IR (neat): 3420, 3290, 3049, 2925, 1445, 1395, 1238, 1163, 1021, 970 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.38 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H, CH_3), 1.60 (br s, 2 H, NH_2), 2.03–2.33 (m, 2 H, 4-H), 2.72 (ddd, *J* = 11.0, 1.5, 1.5 Hz, 1 H, 2-H), 3.02 (ddd, *J* = 2.5, 7.2, 9.8, Hz, 1 H, 5-H), 3.14 (ddd, *J* = 7.2, 9.8, 10.7 Hz, 1 H, 5-H), 3.32 (dd, $^3J_{H,H}$ = 11.0 Hz, $^3J_{P,H}$ = 7.5 Hz, 1 H, 2-H), 4.21 (dq, $^3J_{P,H}$ = 1.8 Hz, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH_2O), 4.24 (dq, $^3J_{P,H}$ = 1.8 Hz, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH_2O).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.6 (d, $^3J_{P,C}$ = 5.5 Hz, 2 CH_3), 29.3 (d, $^2J_{P,C}$ = 16.2 Hz, C-4), 39.5 (d, $^3J_{P,C}$ = 7.5 Hz, C-5), 40.3 (d, $^2J_{P,C}$ = 10.3 Hz, C-2), 62.8 (d, $^2J_{P,C}$ = 7.2 Hz, 2 CH_2O), 71.6 (d, $^1J_{P,C}$ = 177.1 Hz, C-3).

^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 27.41.

HRMS data could not be obtained.[36]

Diethyl (1-Aminocyclopentyl)phosphonate (32)

The cleavage of the hydrazine N–N bond was achieved by Method A (SmI_2 method).

Yield: 32%; pale yellow oil; R_f = 0.29 (MeOH–Et_2O–aq NH_3, 10:90:0.5).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.35 (t, $^3J_{H,H}$ = 7.0 Hz, 6 H, CH_3), 1.40–1.65 (m, 4 H, 2 H_{cycle} and NH_2), 1.65–1.80 (m, 2 H_{cycle}), 1.80–2.00 (m, 2 H_{cycle}), 2.00–2.20 (m, 2 H_{cycle}), 4.17 (dq, $^3J_{P,H}$ = 7.2 Hz, $^3J_{H,H}$ = 7.0 Hz, 4 H, CH_2O).

Analytical data were in accord with the literature values.[9b]

(3-Aminopyrrolidin-3-yl)phosphonic Acid Dihydrochloride (3a·2HCl)

A soln of diethyl phosphonate **29** (59 mg, 0.2 mmol) in 6 M aq HCl (3 mL) was heated at reflux for 12 h. The solvent was evaporated under reduced pressure. The residue was dissolved in MeOH (2 mL), and then the soln was concentrated again, to afford the crude aminophosphonic acid hydrochloride salt **3a**·2HCl.

Yield: 100%; mp 280 °C (dec); R_f = 0.66 (MeOH–1.4 M aq NH_4OH, 1:1).

IR (KBr): 3431, 2963, 1526, 1446, 1403, 1215, 1080, 915 cm^{-1}.

^{1}H NMR (250 MHz, D_2O): δ = 2.30–2.55 (m, 1 H, 4-H), 2.59–2.85 (m, 1 H, 4-H), 3.54–3.82 (m, 3 H, 2-H and 2 5-H), 3.89 (dd, $^3J_{P,H}$ = 12.5, $^3J_{H,H}$ = 13.2 Hz, 1 H, 2-H).

^{13}C NMR (62.9 MHz, D_2O): δ = 32.1 (C-4), 45.5 (d, $^3J_{P,C}$ = 5.2 Hz, C-5), 50.9 (d, $^2J_{P,C}$ = 3.7 Hz, C-2), 58.4 (d, $^1J_{P,C}$ = 148.0 Hz, C-3).

^{31}P NMR (101.25 MHz, D_2O): δ = 11.71.

HRMS data could not be obtained.[36]

(3-Aminotetrahydrothiophen-3-yl)phosphonic Acid (3c)

Aminophosphonic acid·hydrochloride **3c**·HCl, obtained by the procedure described above to prepare **3a·2HCl**, was dissolved in a minimum amount of EtOH (1.5 mL); an excess of propylene oxide (5 mL) was added dropwise to this soln, which was stirred at r.t. for 1 h. The volatile compounds were removed by evaporation in vacuo.

Yield: 100%; mp 186 °C; R_f = 0.28 (aq NH_3/EtOH/H_2O, 20:30:3).

IR (KBr): 3385, 2941, 1538, 1448, 1408, 1175, 1078, 1001, 935 cm^{-1}.

^{1}H NMR (250 MHz, D_2O): δ = 2.24–2.38 (m, 2 H, 4-H), 2.82–2.98 (m, 2 H, 5-H and 2-H), 2.98–3.13 (ddd, $J_{H,H}$ = 6.0, 5.5 Hz, $J_{A,B}$ = 11.5 Hz, 1 H, 5-H), 3.29 (dd, $^3J_{P,H}$ = 6.5 Hz, $^3J_{H,H}$ = 13.0 Hz, 1 H, 2-H).

^{13}C NMR (62.9 MHz, D_2O): δ = 28.7 (d, $^2J_{P,C}$ = 11.7 Hz, C-4), 37.1 (C-5), 38.3 (d, $^2J_{P,C}$ = 2.0 Hz, C-2), 65.9 (d, $^1J_{P,C}$ = 136.1 Hz, C-3).

^{31}P NMR (101.25 MHz, D_2O): δ = 11.25.

^{31}P NMR (101.25 MHz, $CDCl_3$): δ = 12.43.

HRMS data could not be obtained.[36]

(1-Aminocyclopentyl)phosphonic Acid (3d)

Hydrolysis of aminophosphonate with TMSI according to our previously reported method:[8b] TMSI (150 mg, 107 μL, 0.75 mmol) was added dropwise to a stirred soln of diethyl phosphonate **32** (55 mg, 0.25 mmol) in CH_2Cl_2 (3 mL) and stirring was continued at r.t. for 6 h. The volatiles were then removed in vacuo and a mixture of EtOH (2 mL) and an excess of propylene oxide (1 mL) were added, followed by stirring for 18 h. Once precipitation of pure aminophosphonic acid was complete, it was collected by filtration and dried under high vacuum.

Yield: 40 mg (100%); white solid; mp 243.5 °C (crystallized from H_2O–EtOH); R_f = 0.45 (aq NH_3–MeOH, 20:80).

^{1}H NMR (360 MHz, D_2O): δ = 1.70–1.90 (m, 6 H, H_{cycle}), 2.10–2.38 (m, 2 H, H_{cycle}).

Analytical data were in accord with the literature values.[9b]

References

(1) (a) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193. (b) Maier, L. *Phosphorus Sulfur Relat. Elem.* **1983**, *14*, 295. (c) Baylis, E. K.; Campbell, C. D.; Dingwall, J.-G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2845. (d) Maier, L. *Phosphorus, Sulfur Silicon Relat. Elem.* **1990**, *53*, 43. (e) Hudson, H. R.; Pianka, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1996**, *109-110*, 345.

(2) Peyman, A.; Budt, K. H.; Spanig, J.; Ruppert, D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1720.

(3) Cheng, L.; Goodwin, C. A.; Scully, M. F.; Kakkar, V. V.; Claeson, G. *Tetrahedron Lett.* **1991**, *32*, 7333.

(4) Kukhar, V. P.; Hudson, H. R. *Aminophosphonic and Aminophosphinic Acids*; Wiley: New York, **2000**.

(5) For recent enantioselective synthesis of α-aminophosphonic acids, see: (a) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161. (b) Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **1998**, *9*, 1279; and references cited therein.

(6) (a) Vercruysse, K.; Dejugnat, C.; Munoz, A.; Etemad-Moghadam, G. *Eur. J. Org. Chem.* **2000**, 281; and references cited therein. (b) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102; and references cited therein.

(7) For recent synthesis of cyclopropyl aminophosphonic acids, see: Yamazaki, S.; Takada, T.; Imanishi, T.; Moriguchi, Y.; Yamabe, S. *J. Org. Chem.* **1998**, *63*, 5919; and references cited therein.

(8) For synthesis of chiral nonracemic cyclopropyl aminophosphonic acids, see: (a) Fadel, A. *J. Org. Chem.* **1999**, *64*, 4953. (b) Fadel, A.; Tesson, N. *Eur. J. Org. Chem.* **2000**, 2153. (c) Fadel, A.; Tesson, N. *Tetrahedron: Asymmetry* **2000**, *11*, 2023. (d) Tesson, N.; Dorigneux, B.; Fadel, A. *Tetrahedron: Asymmetry* **2002**, *13*, 2267.

(9) (a) Hercouet, A.; Le Corre, M.; Carboni, B. *Tetrahedron Lett.* **2000**, *41*, 197. (b) For cyclobutyl and cyclopentyl derivatives, see: Guéguen, C.; About-Jaudet, E.; Collignon, N.; Savignac, P. *Synth. Commun.* **1996**, *26*, 4131.

(10) For cyclopentyl derivatives, see: (a) Ranu, B. C.; Hajra, A. *Green Chem.* **2002**, *4*, 551. (b) Wieczorek, J. C.; Gancarz, R.; Bielecki, K.; Grzys, E.; Sarapuk, J. *Phosphorus, Sulfur Silicon Relat. Elem.* **2001**, *174*, 119. (c) Stoikov, I. I.; Repejkov, S. A.; Antipin, I. S.; Konovalov, A. I. *Heteroat. Chem.* **2000**, *11*, 518.

(11) (a) Wieczorek, J. S.; Gancarz, R.; Bielecki, L.; Grzys, E.; Sarapuk, J. *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *166*, 111. (b) Matveera, E. D.; Podrugina, T. A.; Tishkovskaya, E. V.; Tomilova, L. G.; Zefirov, N. S. *Synlett* **2003**, 2321. (c) Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Synthesis* **2004**, 2692.

(12) For microwave assistance, see: Kabachnick, M. M.; Zobnina, E. V.; Belatskaya, I. P. *Synlett* **2005**, 1393; and references cited therein.
(13) GABA-related drugs have shown promising properties as antiepileptic, antispastic, and antidepressive agents: Fonnum, F. In *Psychopharmacology*, Vol. 18; Meltzer, H., Ed.; Raven: New York NY, **1987**, 173–182.
(14) (a) Tukanova, S. K.; Dzhiembaev, B. Z.; Butin, B. M. *Zh. Obshch. Khim.* **1991**, *61*, 1118; *Chem. Abstr.* **1992**, *116*, 6637. (b) Gancarz, R.; Latajka, R.; Halama, A.; Kafarski, P. *Magn. Reson. Chem.* **2000**, *38*, 867. (c) For aminophosphonic acid derivatives of substituted piperidines and tetrathiophenes, see: Bosyakov, Y. G.; Maishinova, G. T.; Logunov, A. P.; Revenko, G. P. *Izv. Nats. Akad. Nauk. Resp. Kaz., Ser. Khim.* **1993**, *6*, 72; *Chem. Abstr.* **1995**, *123*, 112161.
(15) For aminophosphonates of substituted tetrahydropyrans, see: (a) Kabatschnick, M. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1967**, 1362. (b) Kabatschnick, M. I. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1967**, 1379. (c) For unsubstituted tetrahydropyran derivatives, see ref. 16a.
(16) (a) Tukanova, S. K.; Dzhiembaev, B. Z.; Khalilova, S. F.; Butin, B. M. *Zh. Obshch. Khim.* **1993**, *63*, 938; *Chem. Abstr.* **1993**, *119*, 250038. (b) Kiyashev, D. K.; Turisbekova, L. K.; Sadykov, T. S.; Erzhanov, K. B.; Nurakhov, D. B. *Izv. Akad. Nauk Kaz. SSR, Ser. Khim.* **1990**, *6*, 82; *Chem. Abstr.* **1991**, *114*: 122537. (c) See ref. 14c.
(17) (a) Fang, S. D.; Li, L. G.; Niu, G.; Tseng, K. F. *Sci Sin.* **1961**, *10*, 845. (b) Shiao, S. H.; Shao, B. J.; Ho, Y. H.; Yang, Y. C.; Mao, C. P. *Sci Sin.* **1962**, *11*, 1527.
(18) (a) Sun, T. T.; Loh, S. H.; Chow, S. W.; Kyi, Z. Y. *Sci Sin.* **1961**, *10*, 852. (b) Monteiro, H. J. *J. Chem. Soc., Chem. Commun.* **1973**, 2. (c) Morimoto, Y.; Achiwa, K. *Chem. Pharm. Bull.* **1987**, *35*, 3845. (d) Mamoun, O.; Benhaoua, H.; Danion-Bougot, R.; Danion, D. *Synth. Commun.* **1995**, *25*, 1295. (e) Williams, R. M.; Fegley, G. J. *Tetrahedron Lett.* **1992**, *33*, 6755. (f) Paik, S.; Kwak, H. S.; Park, T. H. *Bull. Korean Chem. Soc.* **2000**, *21*, 131.
(19) For the synthesis of cucurbitine derivatives, see: Tanaka, K.-I.; Suzuki, H.; Sawanishi, H. *Heterocycles* **1996**, *43*, 205.
(20) (a) Rabasso, N.; Louaisil, N.; Fadel, A. *Tetrahedron* **2006**, *62*, 7445. (b) Louaisil, N.; Rabasso, N.; Fadel, A. *Synthesis* **2007**, 289.
(21) For a review, see: Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003; and references cited therein.
(22) Kaboudin, B.; Rahmani, A. *Synthesis* **2003**, 2705.
(23) Chandrasekhar, S.; Narsihmulu, C.; Sultana, S. S.; Saritha, B.; Prakash, S. J. *Synlett* **2003**, 505.
(24) Additions of phosphites to hydrazones have been reported rarely, see: (a) Inokawa, S.; Nakatsukasa, Y.; Horisaki, M.; Yamashita, M.; Yosida, H.; Ogata, T. *Synthesis* **1977**, 179. (b) Yamashita, M.; Takeuchi, J.; Nakatani, K.; Oshikawa, T.; Inokawa, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 377. (c) Yamamoto, H.; Hanaya, T.; Kawamoto, H.; Inokawa, S. *Chem. Lett.* **1989**, 121.
(25) (a) Wu, Y.-H.; Gould, W. A.; Lobeck, W. G. Jr.; Roth, H. R.; Feldkamp, R. F. *J. Med. Chem.* **1962**, *5*, 752. (b) Yadav, J. S.; Sarkar, S.; Chandrasekhar, S. *Tetrahedron* **1999**, *55*, 5449.
(26) Ketone **8** was prepared from its corresponding alcohol by use of the Dess–Martin oxidation reagent.
(27) (a) Lipton, M. F.; Shapiro, R. H. *J. Org. Chem.* **1978**, *43*, 1409. (b) Okimoto, M.; Chiba, T. *J. Org. Chem.* **1990**, *55*, 1070.
(28) Krzyzanowska, B.; Stec, W. J. *Synthesis* **1982**, 270.
(29) Kim, S.; Yoon, J.-Y. *J. Am. Chem. Soc.* **1997**, *119*, 5982.
(30) (a) Ogawa, C.; Sugiura, M.; Kobayashi, S. *J. Org. Chem.* **2002**, *67*, 5359. (b) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266.
(31) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132.
(32) (a) Denmark, S. E.; Nicaise, O.; Edwards, J. P. *J. Org. Chem.* **1990**, *55*, 6219. (b) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253. (c) Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron* **2001**, *57*, 5393.
(33) (a) Bournaud, C.; Bonin, M.; Micouin, L. *Org. Lett.* **2006**, *8*, 3041. (b) Mellor, J. M.; Smith, N. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2927. (c) Brown, C. A.; Brown, H. C. *J. Am. Chem. Soc.* **1963**, *85*, 1003. (d) Bertelson, R. C.; Glanz, K. D. *J. Org. Chem.* **1972**, *37*, 2207.
(34) For hydrolysis with TMSI, see the experimental section
(35) (a) Girard, P.; Namy, J.-L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693. (b) Wipf, P.; Wenkatraman, S. *J. Org. Chem.* **1993**, *58*, 3455.
(36) Unfortunately, HRMS could not be carried out despite use of various kinds of methods, including ESI, EI, or CI.