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A new access to substituted tetraethyl *N*-Boc 2-aminoethylidene-1,1-bisphosphonates and phosphonyl-substituted aza-Morita–Baylis–Hillman-type adducts

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This paper is dedicated to Professor Andrzej Zwierzak on the occasion of his 75th birthday

Abstract

A general one-pot synthesis of substituted 2-aminoethylidene-1,1-bisphosphonates has been developed. The protocol involves base-induced addition of sodium tetraethyl methylenebisphosphonate to *N*-Boc imines generated in situ from *N*-Boc-α-amidoalkyl-*p*-tolylsulfones by the action of sodium hydride. The direct and efficient conversion of the title compounds into aza-Morita–Baylis–Hillman-type adducts has been also elaborated.

Keywords: Bisphosphonates; Nucleophilic addition; *N*-Boc imines; α-Amidosulfones; Aza-Morita–Baylis–Hillman-type adducts

1. Introduction

Geminal bisphosphonates are hydrolytically stable analogs of naturally occurring inorganic pyrophosphates and constitute an important class of biologically active compounds. A number of these compounds have found application in treatment of bone diseases such as Paget's disease, myeloma, bone metastases, and osteoporosis[1] (Fig. 1). Recently, bisphosphonates have also been used as antiprotozoan[1f,2] agents and are found to stimulate human γδ T cells.[3]

Current investigations prove that mevalonate pathway enzyme, farnesyl pyrophosphate synthase (FPPS), is a principal molecular target of the bisphosphonates action.[4] Bioactivity of bisphosphonates is determined by the structure of the side-chain as well as the nature of the functional groups connected with the methylenebisphosphonate moiety. Among numerous bisphosphonates the nitrogen-containing derivatives (*N*-BPs) are shown to be the most potent compounds.[1a] Increasing interest in the nitrogen-containing bisphosphonates resulted in the development of different strategies for their synthesis. The standard route to 2-aminoethylidene-1,1-bisphosphonates **6** exploits the Michael-type addition of amines[2a,2b,5] or amides[6] to tetraethyl vinylidenebisphosphonate (**5**) by the method elaborated by Hutchinson and Thornton[5a] (Scheme 1). The addition

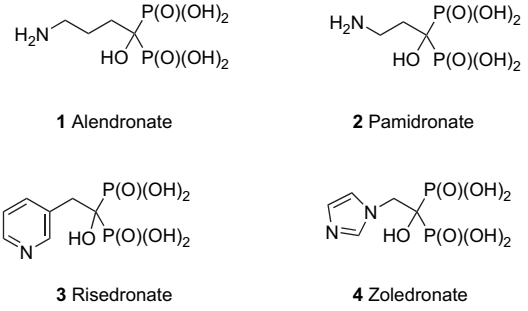

Figure 1. Representative members of the second- and third generation of bisphosphonates **1**–**4** used in treatment of bone diseases (the common names given here refer to their salts).

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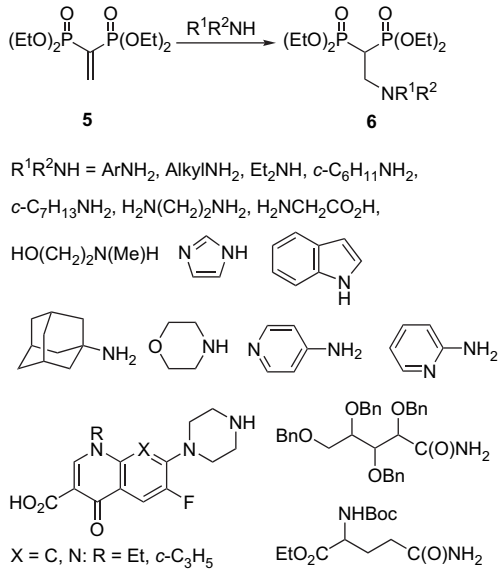
of nitrogen-containing nucleophiles to homologs of the above-mentioned Michael acceptor has not been hitherto reported.



Scheme 1. Preparation of aminoethylidene-1,1-bisphosphonate derivatives **6** from the tetraethyl vinylidenebisphosphonate (**5**) and amine derivatives.

Some *N*-BPs are also available via reductive (Pd/ammonium formate) ring-opening of *N*-(*p*-toluenesulfonyl)-2,2-(diethoxyphosphoryl)aziridine,[5f] or by Curtius rearrangement of 2,2-bis(diethoxyphosphoryl)cyclopropanecarboxylic acid.[7] Another well documented methodology, leading, however, only to 2-amino-1-hydroxyethylidene-1,1-bisphosphonate derivatives, is based on the reaction of the corresponding carboxylic acid with a mixture of phosphorus trichloride and phosphorous acid,[2a,2b,4e,8] followed by hydrolysis. Alternatively, phosphorus oxychloride/phosphorous acid[2a,4b] or phosphorus trichloride/phosphoric acid[1e] system can be applied. In turn, *N*-methyl and *N*,*N*-dimethyl analogs of 2-amino-1-hydroxyethylidene-1,1-bisphosphonate can be obtained via addition of dimethyl phosphite to 2-(*N*-phthaloylamino)acetylphosphonic acid dimethyl ester, followed by hydrolysis with hydrobromic acid and subsequent methylation with formic acid/formaldehyde.[9]

N-Boc-α-amidoalkyl-*p*-tolylsulfones can be considered as a stable and easy to handle equivalents of *N*-Boc imines. Therefore, nucleophilic additions to *N*-Boc imines generated in situ from the α-amidosulfones mentioned above by base-induced elimination have been recently the subject of extensive research.[10]

Herein we report on the synthesis of novel β-functionalized bisphosphonates using *N*-Boc-α-amidoalkyl-*p*-tolylsulfones as imine precursors for the β-aminoalkylation of tetraethyl methylenebisphosphonate. To the best of our knowledge this approach to 2-aminoethylidene-1,1-bisphosphonate derivatives has not been hitherto reported.

2. Results and discussion

We established a new and efficient route to diethyl 2-substituted [2-*tert*-butoxycarbonylamino-1-(diethoxyphosphoryl)-ethyl]phosphonates **11** via addition of sodium tetraethyl methylenebisphosphonate (**9**) to *N*-Boc imines **10**, both generated in situ from tetraethyl methylenebisphosphonate (**7**) and *N*-Boc-α-amidoalkyl-*p*-tolylsulfones **8**, by the action of sodium hydride (Scheme 2).

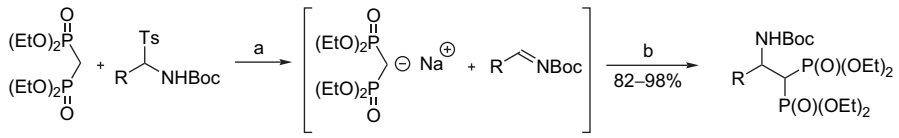
As shown in Scheme 2, the reaction was performed by adding **7** (1 equiv) to the suspension of sodium hydride (2 equiv) in THF at rt, followed by the addition of α-amidosulfones **8** in THF at −20 °C. The reaction was completed within 3 h. The corresponding adducts **11a–j** were isolated in high yields and purity. The reaction was general and a number of diverse alkyl, aryl, or heteroaryl substituted bisphosphonates **11** were obtained in this way. The results are summarized in Table 1.

The reactions of α-amidosulfones **8** with **7** were temperature sensitive and in order to avoid the formation of side-products the temperature regime should be strictly obeyed. When the reactions were carried out at rt diethyl 1-alkenylphosphonates

Table 1
Diethyl 2-substituted [2-*tert*-butoxycarbonylamino-1-(diethoxyphosphoryl)-ethyl]phosphonates **11a–j** prepared

Entry	Product	R	Yield[a] (%)
1	**11a**	Me	92
2	**11b**	Et	90
3	**11c**	*i*-Pr	92
4	**11d**	Bu	93
5	**11e**	*c*-Hex	93
6	**11f**	2-Furyl	82
7	**11g**	Ph	98
8	**11h**	2-Py	87
9	**11i**	3-Py	88
10	**11j**	1-Naphthyl	92

[a] Yields of pure, isolated products.



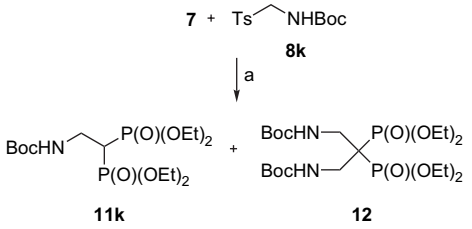
8,10,11	R	8,10,11	R
a	Me	**f**	2-Furyl
b	Et	**g**	Ph
c	*i*-Pr	**h**	2-Py
d	Bu	**i**	3-Py
e	*c*-Hex	**j**	1-Naphthyl

Scheme 2. Reagents and conditions: (a) NaH (2 equiv), −20 °C to −10 °C, 3 h, THF; (b) aq NH_4Cl, −10 °C.

were identified as one of the by-products, as determined by ^{1}H and ^{31}P NMR.

The structure of final products was unequivocally confirmed by NMR, mass spectra, and elemental analyses. Due to anisochronicity of diethoxyphosphoryl groups in **11a–j**, two separate signals could be observed in their proton decoupled ^{31}P NMR spectra, sometimes accompanied (**11c**,**e**) by additional peaks of rotamers.

Unfortunately, under the conditions mentioned above the α-amidosulfone **8k**, derived from formaldehyde, afforded the mixture of mono- and bis-adducts **11k** and **12** in 1:4 ratio (^{31}P NMR, δ_P=21.67 and 23.28, respectively), together with starting compound **7** (Scheme 3). Attempted synthesis of pure **11k** failed.

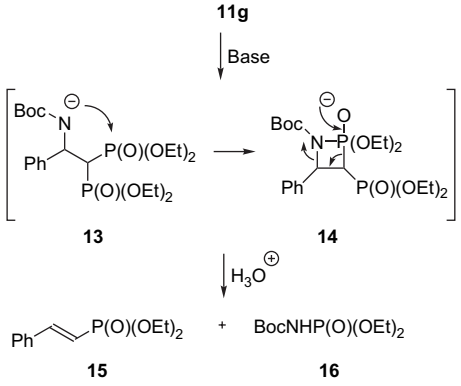


Scheme 3. Reagents and conditions: (a) NaH (2 equiv), −20 °C to −10 °C, 3 h, THF then satd aq NH_4Cl, −10 °C.

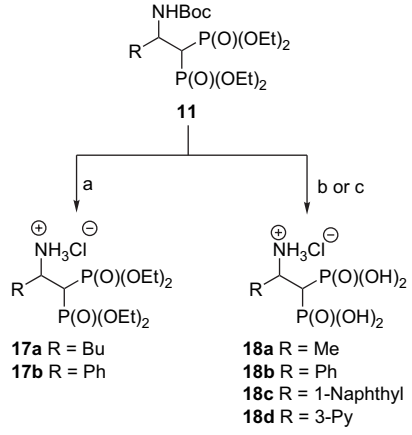
The final aminobisphosphonates **11a–j** are stable compounds and can be stored for unlimited time at rt. They are, however, base sensitive to some extent. Thus, when the solution of pure diethyl [2-*tert*-butoxycarbonylamino-1-(diethoxyphosphoryl)-ethyl]phosphonate (**11g**, R=Ph) in THF is subjected to the action of stoichiometric amount of sodium hydride for 12 h at rt, partial rearrangement of **11g** occurred, and the mixture of diethyl (*E*)-styrylphosphonate[11] (**15**) (δ_P=20.45) and diethyl *N*-Boc phosphoramidate[12] (**16**) (δ_P=−2.7) accompanied by starting **11g** (δ_P=20.89, 21.25) has been obtained in 1:1:1.5 ratio, as confirmed by ^{1}H and ^{31}P NMR analyses of the reaction mixture. The NMR data of the crude reaction mixture agree with those collected for the original samples of **15**[11] and **16**[12] prepared by an independent way, what confirms the above assumption. This result can also explain the side formation of diethyl 1-alkenylphosphonates in the reactions of α-amidosulfones **8** with **7** carried out at rt. The plausible pathway of this rearrangement is shown in Scheme 4. Thus, the intermediate anion **13**, formed under basic conditions from **11g**, can decompose via transient azaphosphetane **14** to give diethyl (*E*)-styrylphosphonate (**15**) and diethyl *N*-Boc phosphoramidate (**16**) on quenching.

The synthetic versatility of the diethyl [2-*tert*-butoxycarbonylamino-1-(diethoxyphosphoryl)ethyl]phosphonate derivatives **11** was confirmed by the following transformations. As shown in Scheme 5, treatment of the model phosphonates **11d** and **11g** with 3.5 M HCl solution in anhydrous ethanol at rt resulted in the smooth and selective cleavage of the *N*-Boc group[13] to give analytically pure **17a**,**b** in quantitative yields (Table 2, entries 1 and 2).

In turn, aq HCl solution was the reagent of choice for simultaneous Boc group deprotection and the dealkylation of



Scheme 4. A plausible pathway of base-induced rearrangement of bisphosphonate **11g**.



Scheme 5. Reagents and conditions: (a) 3.5 M HCl/AcOEt, rt, 1 h; (b) 20% aq HCl, reflux, 10 h; (c) TMSBr, CH_2Cl_2, rt, 48 h, followed by CH_3OH, rt, 2 h.

Table 2
Aminobisphosphonate hydrochlorides **17a**,**b** and aminobisphosphonic acid hydrochlorides **18a–d** prepared

Entry	Product	R	Yield[a] (%)
1	**17a**	Bu	100[b]
2	**17b**	Ph	100[b]
3	**18a**	Me	50[c]
4	**18b**	Ph	68[c]
5	**18c**	1-Naphthyl	52[c]
6	**18d**	3-Py	35[d]

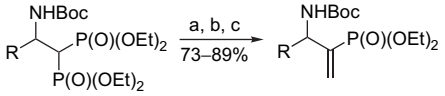
[a] Yields of pure, isolated products.
[b] Obtained by the action of 3.5 M HCl in anhydrous EtOH.
[c] Prepared by the action of 20% aq HCl. The products were isolated after lyophilization as hydrochlorides.
[d] Prepared by the action of TMSBr, followed by methanolysis. The product was isolated after lyophilization as dihydrobromide.

bisphosphonic acid ester functions in **11**. The aminobisphosphonic acid hydrochlorides **18a–c** were prepared by refluxing the mixture of the aminobisphosphonates **11a**,**g**,**j** and 20% aq HCl solution for 10 h (Scheme 5). Analytically pure **18a–c** were obtained in satisfactory yields (50–68%) after their precipitation from the reaction mixture with acetone, followed by redissolving in water and lyophilization (Table 2, entries 3–5). Pyridine derivative **11i** underwent, however, the complete degradation under these hydrolytic conditions. Aminobisphosphonic

acid dihydrobromide **18d** was obtained from **11i** in 35% yield using bromotrimethylsilane[14] in CH_2Cl_2 at rt for 48 h, followed by methanolysis of the intermediate trimethylsilyl esters (entry 6). The structures of the aminobisphosphonates **17a**,**b** and aminobisphosphonic acid **18a–d** were fully confirmed by ^1H, ^{13}C and ^{31}P NMR as well as elemental analyses and mass spectra.

Straightforward conversion of *N*-Boc derivatives **11** to substituted [1-(*tert*-butoxycarbonylamino-methyl)vinyl]phosphonates **19a–f** by Horner–Wadsworth–Emmons (HWE) olefination of formaldehyde[11,15,16] was also accomplished. On account of the base sensitivity of the phosphonates **11** (vide supra), repeated attempts were made to find optimal reaction conditions, under which a side formation of the diethyl 1-alkenylphosphonates could be avoided. As shown in Scheme 6, these transformations were performed using potassium *tert*-butoxide as a base and paraformaldehyde at −10 °C in anhydrous THF. Under these conditions clean conversion of **11** to the desired aminomethylene derivatives **19** took place and the final products **19a–f** were obtained in high yields (73–89%) and in spectroscopic purity. The results are summarized in Table 3. The structures of **19a–f** were unambiguously confirmed by ^1H, ^{13}C and ^{31}P NMR spectroscopies as well as elemental analyses and mass spectra. The HWE reaction was limited to formaldehyde. Attempted olefinations of the higher aldehydes failed. Under the reaction condition mentioned above only the unreacted **11** was present in the reaction mixture on quenching.

The conversion of **11** to **19** established by us is an alternative to the aza-Morita–Baylis–Hillman reaction[17] (aza-MBH reaction) whereby polyfunctional adducts can be prepared in a single step by the nucleophile-catalyzed condensation of *N*-acyl imines with electron-deficient olefins. The aza-MBH adducts have proven to be useful intermediates in organic synthesis.[17]



11a-c,e,g,j

19a R = Me
19b R = Et
19c R = *i*-Pr
19d R = *c*-Hex
19e R = Ph
19f R = 1-Naphthyl

Scheme 6. Reagents and condition: (a) *t*-BuOK (1.2 equiv), THF, −10 °C, 10 min; (b) $(CH_2O)_n$ (8 equiv), −10 °C, 5 h; (c) satd aq NH_4Cl at −10 °C to rt.

Table 3
Aza-Morita–Baylis–Hillman-type adducts **19a–f** prepared

Entry	Product	R	Yield[a] (%)
1	**19a**	Me	73
2	**19b**	Et	87
3	**19c**	*i*-Pr	89
4	**19d**	*c*-Hex	89
5	**19e**	Ph	78
6	**19f**	1-Naphthyl	73

[a] Yields of pure, isolated products.

However, Burger et al. have demonstrated that the aza-MBH reaction of diethyl vinyl phosphonate with *N*-Boc fluoroalkyl substituted imines proceeds slowly, giving unsatisfactory yields of products.[18] Therefore, the number of aza-MBH adducts derived from diethyl vinyl phosphonate is limited[19] and there are only a few alternative routes to their synthesis. The aza-MBH-type adducts have been obtained via the aldol-type reaction of diethyl 2-(*N*,*N*-dimethylamino)ethylphosphonate with trifluoromethyl substituted imines, followed by treatment of the intermediate adducts with *m*-chloroperbenzoic acid.[18] Loreto and collaborates have described the synthesis of α-methylene *N*-(ethoxycarbonyl) β-aminophosphonic esters[20] via aziridination of (1-trimethylsilanylmethyl-vinyl)phosphonic acid esters with ethyl *N*-{[(4-nitrobenzene)sulfonyl]oxy}carbamate, followed by silyl group elimination and aziridine ring-opening. In 2006 Krische et al. have reported a concise approach to the phosphonyl-substituted aza-MBH adducts via phosphine-catalyzed allylic substitution of diethyl 1-substituted [1-(acetylamino-methyl)-vinyl]phosphonates (MBH acetates), employing 4,5-dichlorophthalimide as a nucleophile.[21] Recently, the aza-MBH-type adducts derived from vinyl phosphonates have found application as a building blocks in the synthesis of β-amino-α-hydroxyphosphonates.[20b]

3. Conclusions

The protocol described here provides a new and operationally simple one-pot access to substituted *N*-Boc 2-aminoethylidene-1,1-bisphosphonate derivatives from easily available tetraethyl methylenebisphosphonate and *N*-Boc-α-amidoalkyl-*p*-tolylsulfones. The reaction is general and structurally diverse aminobisphosphonates have been thus obtained under mild conditions and in good yields. The title products are also versatile synthetic intermediates for further transformations, including selective Boc group deprotection, conversion to free aminobisphosphonic acids, and direct synthesis of the aza-Morita–Baylis–Hillman-type adducts.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker Avance DPX 250 instrument at 250.13 MHz for ^1H NMR, 62.90 MHz for ^{13}C NMR, and 101.3 MHz for ^{31}P NMR in $CDCl_3$ solution, using either tetramethylsilane as an internal or 85% H_3PO_4 as an external standard. Positive chemical shifts are downfield from external 85% H_3PO_4 for ^{31}P NMR spectra. Chemical shifts (δ) are indicated in parts per million and coupling constants (J) in hertz. For ^{13}C NMR spectra, the peak assignments were made with the assistance of CH-COSY experiments. Partially overlapped signals are assigned by asterisks (*). Elemental analyses were performed on a Perkin–Elmer PE 2400 Analyzer. High- and low-resolution mass spectra (m/z) were recorded on a Finnigan MAT 95 spectrometer (FAB, glycerol matrix or CI, isobutane). IR spectra were measured on a Specord M80 (Zeiss) instrument and are reported in cm^{-1}.

Melting points were determined in open capillaries and are uncorrected. All reagents were purchased from Fluka and were used without further purification. Tetraethyl methylenebisphosphonate,[22] diethyl (*E*)-styrylphosphonate,[11] diethyl *N*-Boc phosphoramidate,[12] and *N*-Boc α-amidoalkyl-*p*-tolylsulfones[23,24] were prepared as described previously.

4.2. Preparation of substituted tetraethyl N-Boc 2-aminoethylidene-1,1-bisphosphonates **11**; general procedure

A solution of tetraethyl methylenebisphosphonate (**7**, 173 mg, 0.6 mmol) in anhydrous THF (1 mL) was added with stirring to a suspension of NaH (29 mg, 1.2 mmol) in anhydrous THF (1 mL) at rt. The resulting mixture was stirred at rt for 10 min, cooled to −20 °C, and a solution of α-amidosulfones (**8**, 0.6 mmol) in THF (10 mL) was then added dropwise over 30 min. The reaction mixture was stirred at −20 °C for 1 h and at −10 °C for 2 h. The mixture was quenched with satd aq NH_4Cl (10 mL). CH_2Cl_2 (30 mL) was added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (15 mL). The combined organic phases were washed with water (2×10 mL), dried over $MgSO_4$, and evaporated to give spectroscopically pure **11a–j** (Table 1). All impurities were water soluble and remained in the aqueous phase.

4.2.1. Diethyl [2-tert-butoxycarbonylamino-1-(diethoxyphosphoryl)propyl]phosphonate (**11a**)

Yield: 238 mg (92%); colorless oil; [Found: C, 44.46; H, 8.29; N, 3.40. $C_{16}H_{35}NO_8P_2$ requires: C, 44.55; H, 8.18; N, 3.25%]; ν_{max} (film) 3384, 2984, 1712, 1504, 1392, 1368, 1252, 1168, 1024, 968 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 5.78 (d, 1H, *J* 9.7 Hz, N*H*), 4.44–4.38 (m, 1H, C*H*N), 4.30–4.12 (m, 8H, 4×CH_2O), 2.74 (dt, 1H, J_{HP} 26.4 Hz, *J* 2.4 Hz, C*H*P), 1.45 (d, 3H*, *J* 7.4 Hz, CH_3), 1.43 (s, 9H*, 3×CH_3), 1.35 (t, 12H, *J* 7.0 Hz, 4×CH_3); δ_C (63 MHz, $CDCl_3$) 154.3, 79.0, 62.8 (d, $^2J_{CP}$ 6.6 Hz), 62.4 (d, $^2J_{CP}$ 6.4 Hz), 62.2 (d, $^2J_{CP}$ 6.7 Hz), 62.2 (d, $^2J_{CP}$ 6.9 Hz), 44.1, 42.1 (t, $^1J_{CP}$ 130.3 Hz), 27.9, 19.3 (d, $^3J_{CP}$ 6.6 Hz), 15.9 (d, $^3J_{CP}$ 6.2 Hz); δ_P (101 MHz, $CDCl_3$) 22.2, 21.6; *m/z* (CI, isobutane) 432.2 (100, MH^+), 332 (90%).

4.2.2. Diethyl [2-tert-butoxycarbonylamino-1-(diethoxyphosphoryl)butyl]phosphonate (**11b**)

Yield: 240 mg (90%); colorless oil; [Found: C, 45.65; H, 8.46; N, 3.18. $C_{17}H_{37}NO_8P_2$ requires: C, 45.84; H, 8.37; N, 3.14%]; ν_{max} (film) 3400, 2976, 2936, 1716, 1504, 1456, 1393, 1368, 1252, 1168, 1028, 996, 972 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 5.74 (d, 1H, *J* 10.0 Hz, N*H*), 4.25–4.10 (m, 9H, 4×CH_2, C*H*N), 2.73 (dt, 1H, J_{HP} 25.1 Hz, *J* 2.4 Hz, C*H*P), 1.92–1.68 (m, 2H, CH_2), 1.42 (s, 9H, 3×CH_3), 1.35 (t, 12H, *J* 7.0 Hz, 4×CH_3), 0.94 (t, 3H, *J* 7.5 Hz, CH_3); δ_C (63 MHz, $CDCl_3$) 155.0, 78.5, 62.9 (d, $^2J_{CP}$ 6.9 Hz), 62.8 (d, $^2J_{CP}$ 6.8 Hz), 62.2 (d, $^2J_{CP}$ 6.4 Hz), 62.2 (d, $^2J_{CP}$ 6.5 Hz), 50.2, 41.4 (t, $^1J_{CP}$ 130.1 Hz), 28.0, 27.3 (d, $^3J_{CP}$ 8.2 Hz,), 16.0 (d, $^3J_{CP}$ 6.2 Hz), 10.9; δ_P (101 MHz, $CDCl_3$) 22.3, 21.4; *m/z* (CI, isobutane), 446.3 (100, MH^+), 346.2 (20%).

4.2.3. Diethyl [2-tert-butoxycarbonylamino-1-(diethoxyphosphoryl)-3-methyl-butyl]phosphonate (**11c**)

Yield: 254 mg (92%); colorless oil; [Found: C, 47.20; H, 8.70; N, 3.09. $C_{18}H_{39}NO_8P_2$ requires: C, 47.05; H, 8.56; N, 3.05%]; ν_{max} (film) 3384, 2976, 1720, 1612, 1508, 1392, 1368, 1292, 1280, 1252, 1172, 1096, 1088, 1032, 992, 968 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 5.99 (d, 1H, *J* 10.3 Hz, N*H*), 4.30–4.09 (m, 8H*, 4×CH_2O), 4.09–3.87 (m, 1H*, C*H*N), 2.74 (dt, 1H, J_{HP} 26.4 Hz, *J* 2.4 Hz, C*H*P), 2.07–1.92 (m, 1H, C*H*(CH_3)$_2$), 1.43 (s, 9H*, 3×CH_3), 1.44–1.31 (m, 12H*, 4×CH_3), 0.95 (d, 6H, *J* 7.5 Hz, 2×CH_3); δ_C (63 MHz, $CDCl_3$) 155.0, 78.3, 63.3 (d, $^2J_{CP}$ 6.8 Hz), 62.3 (d, $^2J_{CP}$ 7.1 Hz), 62.1 (d, $^2J_{CP}$ 6.79 Hz), 61.7 (d, $^2J_{CP}$ 7.0 Hz), 54.2 (t, $^2J_{CP}$ 5.7 Hz), 39.4 (t, $^1J_{CP}$ 132.4 Hz), 33.4 (dd, $^3J_{CP}$ 1.5, 11.7 Hz), 28.2, 20.0, 19.1, 16.1 (d, $^3J_{CP}$ 6.3 Hz), 16.0 (d, $^3J_{CP}$ 6.9 Hz); δ_P (101 MHz, $CDCl_3$) 22.8, 22.0 (23.0, 22.4, rotamers) (1:1:0.15:0.15); *m/z* (CI, isobutane) 460.3 (100, MH^+), 360.2 (80%).

4.2.4. Diethyl [2-tert-butoxycarbonylamino-1-(diethoxyphosphoryl)hexyl]phosphonate (**11d**)

Yield: 264 mg (93%); colorless oil; [Found: C, 48.36; H, 8.64; N, 3.11. $C_{19}H_{41}NO_8P_2$ requires: C, 48.20; H, 8.73; N, 2.96%]; ν_{max} (film) 3384, 2976, 2872, 1712, 1504, 1392, 1368, 1252, 1168, 1096, 1088, 1032, 992, 968 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 5.72 (d, 1H, *J* 10.0 Hz, N*H*), 4.23–4.13 (m, 9H, 4×CH_2O, C*H*N), 2.73 (dt, 1H, J_{HP} 26.4 Hz, *J* 2.4 Hz, C*H*P), 1.85–1.43 (m, 6H, 3×CH_2), 1.42 (s, H, 3×CH_3), 1.35 (t, 12H, *J* 7.05 Hz, 4×CH_3), 0.90 (distorted t, 3H, *J* 6.5 Hz, CH_3); δ_C (63 MHz, $CDCl_3$) 155.0, 78.6, 62.9 (d, $^2J_{CP}$ 6.6 Hz), 62.3 (d, $^2J_{CP}$ 6.3 Hz), 62.2 (d, $^2J_{CP}$ 6.1 Hz), 62.0 (d, $^2J_{CP}$ 7.0 Hz), 48.6, 41.8 (dd, $^1J_{CP}$ 129.8, 131.5 Hz), 33.9 (d, $^3J_{CP}$ 7.5 Hz), 28.6, 28.1, 22.0, 16.1 (d, $^3J_{CP}$ 6.1 Hz), 13.8; δ_P (101 MHz, $CDCl_3$): 22.1, 21.1; *m/z* (CI, isobutane) 474.3 (100, MH^+), 374.2 (50%).

4.2.5. Diethyl [2-tert-butoxycarbonylamino-2-cyclohexyl-1-(diethoxyphosphoryl)ethyl]phosphonate (**11e**)

Yield: 279 mg (93%); colorless oil; [Found: C, 50.59; H, 8.80; N, 2.94. $C_{21}H_{43}NO_8P_2$ requires: C, 50.49; H, 8.68; N, 2.80%]; ν_{max} (film) 3384, 2976, 2960, 2928, 2856, 1720, 1508, 1448, 1392, 1368, 1288, 1252, 1172, 1024, 992, 964 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 5.97 (d, 1H, *J* 10.5 Hz, N*H*), 4.27–3.95 (m, 9H, 4×CH_2O, C*H*N), 2.83 (dt, 1H, J_{HP} 25.4 Hz, *J* 2.2 Hz, C*H*P), 1.91–1.58 (m, 9H, 4×CH_2, C*H*), 1.82 (s, 9H*, 3×CH_3), 1.48–1.31 (m, 12H, 4×CH_3), 1.25–1.09 (m, 2H, CH_2); δ_C (63 MHz, $CDCl_3$) 154.6, 77.8, 62.9 (d, $^2J_{CP}$ 6.8 Hz), 62.0 (d, $^2J_{CP}$ 6.9 Hz), 61.8 (d, $^2J_{CP}$ 6.9 Hz), 61.2 (d, $^2J_{CP}$ 6.9 Hz), 52.6, 41.8 (d, $^3J_{CP}$ 11.5 Hz), 38.2 (t, $^1J_{CP}$ 132.6 Hz), 30.0, 28.5, 27.8, 25.4, 25.3, 15.7 (d, $^3J_{CP}$ 6.1 Hz); δ_P (101 MHz, $CDCl_3$) 22.9, 22.3 (22.5, 23.2, rotamers) (1:1:0.15:0.15); *m/z* (CI, isobutane) 500.2 (100, MH^+), 400.1 (40%).

4.2.6. Diethyl [2-tert-butoxycarbonylamino-1-(diethoxyphosphoryl)-2-furan-2-yl-ethyl]phosphonate (**11f**)

Yield: 238 mg (82%); pale yellow solid; mp 42–45 °C; [Found: C, 47.09; H, 7.46; N, 3.05. $C_{19}H_{35}NO_9P_2$ requires: C, 47.21; H, 7.30; N, 2.90%]; ν_{max} (film) 3368, 2984, 2928,

1720, 1508, 1392, 1368, 1252, 1168, 1096, 1088, 1024, 992, 972 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.32 (s, $1H_{arom}$), 6.65 (d, 1H, *J* 9.7 Hz, N*H*), 6.28–6.25 (m, $2H_{arom}$), 5.58 (ddt, 1H, J_{HP} 32.4 Hz, *J* 9.7, 2.8 Hz, C*H*N), 4.27–4.11 (m, 6H, 3×CH_2O), 3.89–3.77 (m, 2H, CH_2O), 3.16 (dt, J_{HP} 24.5 Hz, *J* 2.6 Hz, C*H*P), 1.45 (s, 9H, 3×CH_3), 1.39–1.28 (m, 9H, 3×CH_3), 1.11 (t, 3H, *J* 7.5 Hz, CH_3); δ_C (63 MHz, $CDCl_3$) 154.6, 153.1 (d, $^3J_{CP}$ 13.8 Hz), 141.4, 110.2, 106.1, 79.2, 63.4 (d, $^2J_{CP}$ 6.8 Hz), 62.7 (d, $^2J_{CP}$ 6.8 Hz), 62.5 (d, $^2J_{CP}$ 6.8 Hz), 61.7 (d, $^2J_{CP}$ 6.8 Hz), 46.8, 40.7 (t, $^1J_{CP}$ 131.8 Hz), 28.1, 16.2, 16.1 (2×d, $^3J_{CP}$ 6.1 Hz), 15.8 (d, $^3J_{CP}$ 6.7 Hz); δ_P (101 MHz, $CDCl_3$) 21.0, 20.2; *m/z* (CI, isobutane) 484.3 (100, MH^+), 384.2 (60%).

*4.2.7. Diethyl [2-tert-butoxycarbonylamino-1-(diethoxy-phosphoryl)-2-phenyl-ethyl]phosphonate (**11g**)*

Yield: 290 mg (98%); white solid; mp 79–83 °C; [Found: C, 51.18; H, 7.71; N, 2.92. $C_{21}H_{37}NO_8P_2$ requires: C, 51.11; H, 7.56; N, 2.84%]; ν_{max} (film) 3432, 2984, 2936, 1716, 1500, 1392, 1368, 1256, 1168, 1096, 1032, 996, 972 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.40–7.18 (m, $5H_{arom}$), 6.86 (d, 1H, *J* 9.3 Hz, N*H*), 5.68–5.30 (m, 1H, C*H*N), 4.3–4.01 (m, 6H, 3×CH_2O), 3.77–3.40 (m, 2H, CH_2O), 2.95 (dt, J_{HP} 24.5 Hz, *J* 3.0 Hz, C*H*P), 1.43 (s, 9H, 3×CH_3), 1.38 (t, 3H*, *J* 7.1 Hz, CH_3), 1.36 (t, 3H*, *J* 7.2 Hz, CH_3), 1.27, 0.90 (2×t, 6H, *J* 7.05 Hz, 2×CH_3); δ_C (63 MHz, $CDCl_3$) 154.5, 140.5 (d, $^3J_{CP}$ 13.6 Hz), 127.9, 126.8, 126.0, 78.8, 63.2 (d, $^2J_{CP}$ 6.8 Hz), 62.7 (d, $^2J_{CP}$ 6.6 Hz), 62.3 (d, $^2J_{CP}$ 6.4 Hz), 61.3 (d, $^2J_{CP}$ 6.9 Hz), 51.2, 43.7 (t, $^1J_{CP}$ 130.5 Hz), 28.0, 16.1 (d, $^3J_{CP}$ 7.4 Hz), 16.1 (d, $^3J_{CP}$ 6.1 Hz), 16.0 (d, $^3J_{CP}$ 6.1 Hz), 15.4 (d, $^3J_{CP}$ 7.0 Hz); δ_P (101 MHz, $CDCl_3$) 21.3, 20.9; *m/z* (CI, isobutane) 494.3 (90, MH^+), 394.2 (100%).

*4.2.8. Diethyl [2-tert-butoxycarbonylamino-1-(diethoxy-phosphoryl)-2-pyridin-2-yl-ethyl]phosphonate (**11h**)*

Yield: 258 mg (87%); pale yellow oil; [Found: C, 48.49; H, 7.50; N, 5.85. $C_{20}H_{36}N_2O_8P_2$ requires: C, 48.58; H, 7.34; N, 5.67%]; ν_{max} (film) 3888, 3368, 2984, 2952, 2936, 1720, 1592, 1504, 1456, 1440, 1392, 1256, 1164, 1040, 996, 976 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.53–8.51 (m, $1H_{arom}$), 7.69–7.62 (m, $1H_{arom}$), 7.43 (d, $1H_{arom}$, *J* 7.9 Hz), 7.16–7.10 (m, $1H_{arom}$), 6.75 (d, 1H, *J* 9.2 Hz, N*H*), 5.71–5.48 (m, 1H, C*H*N), 4.30–4.07 (m, 6H, 3×CH_2O), 3.84 (dt, 1H*, J_{HP} 24.4 Hz, *J* 2.7 Hz, C*H*P), 3.77–3.59 (m, 2H*, CH_2O), 1.46 (s, 9H, 3×CH_3), 1.37 (t, 6H, *J* 7.1 Hz, 2×CH_3), 1.26 (t, 3H, *J* 7.1 Hz, CH_3), 0.93 (t, 3H, *J* 7.0 Hz, CH_3); δ_C (63 MHz, $CDCl_3$) 159.6 (d, $^3J_{CP}$ 13.6 Hz), 156.1, 148.3, 136.2, 121.5, 119.7, 79.0, 63.2 (d, $^2J_{CP}$ 6.7 Hz), 62.6 (d, $^2J_{CP}$ 6.6 Hz), 62.3 (d, $^2J_{CP}$ 6.5 Hz), 61.3 (d, $^2J_{CP}$ 7.0 Hz), 52.9, 40.2 (t, $^1J_{CP}$ 130.5 Hz), 28.0, 16.0 (d, $^3J_{CP}$ 6.5 Hz), 15.8 (d, $^3J_{CP}$ 6.5 Hz), 15.4 (d, $^3J_{CP}$ 6.7 Hz); δ_P (101 MHz, $CDCl_3$) 22.2, 21.6 (2×d, J_{PP} 5.1 Hz); *m/z* (CI, isobutane) 495.4 (100%, MH^+).

*4.2.9. Diethyl [2-tert-butoxycarbonylamino-1-(diethoxy-phosphoryl)-2-pyridin-3-yl-ethyl]phosphonate (**11i**)*

Yield: 262 mg (88%); white solid; mp 117–120 °C; [Found: C, 48.40; H, 7.49; N, 5.74. $C_{20}H_{36}N_2O_8P_2$ requires: C, 48.58; H, 7.34; N, 5.67%]; ν_{max} (film) 3984, 3432, 2984, 2952, 2896, 1712, 1500, 1468, 1432, 1392, 1368, 1328, 1248, 1208, 1160, 1124, 1104, 1088, 1024, 996, 976 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.62 (s, $1H_{arom.}$), 8.49 (d, $1H_{arom}$, *J* 4.3 Hz), 7.73 (d, $1H_{arom}$, *J* 7.0 Hz), 7.25 (dd, $1H_{arom}$, *J* 7.0, 4.3 Hz), 6.87 (d, *J* 9.3 Hz, N*H*), 5.71–5.56 (m, 1H, C*H*N), 4.29–4.08 (m, 6H, 3×CH_2O), 3.83–3.55 (m, 2H, CH_2O), 2.90 (dt, 1H, J_{HP} 24.5 Hz, *J* 2.6 Hz, C*H*P), 1.43 (s, 9H, 3×CH_3), 1.36 (t, 6H, *J* 7.0 Hz, 2×CH_3), 1.28 (t, 3H, *J* 7.0 Hz, CH_3), 0.95 (t, 3H, *J* 7.0 Hz, CH_3); δ_C (63 MHz, $CDCl_3$) 154.0, 135.7 (d, $^3J_{CP}$ 12.6 Hz), 147.8, 133.5, 122.3, 78.8, 63.2 (d, $^2J_{CP}$ 6.7 Hz), 62.3 (d, $^2J_{CP}$ 6.6 Hz), 62.1 (d, $^2J_{CP}$ 6.4 Hz), 61.0 (d, $^2J_{CP}$ 6.9 Hz), 49.3, 42.9 (t, $^1J_{CP}$ 130.9 Hz), 27.7, 15.7 (d*, $^3J_{CP}$ 6.1 Hz), 15.7 (d*, $^3J_{CP}$ 6.2 Hz), 15.6 (d*, $^3J_{CP}$ 6.1 Hz), 15.0 (d, $^3J_{CP}$ 6.9 Hz); δ_P (101 MHz, $CDCl_3$) 21.0, 20.6; *m/z* (CI, isobutane) 495.4 (100, MH^+), 439.3 (35), 395.3 (40%).

*4.2.10. Diethyl [2-tert-butoxycarbonylamino-1-(diethoxy-phosphoryl)-2-naphthalen-1-yl-ethyl]phosphonate (**11j**)*

Yield: 300 mg (92%); white solid; mp 69–73 °C; [Found: C, 55.51; H, 7.05; N, 2.77. $C_{25}H_{39}NO_8P_2$ requires: C, 55.24; H, 7.23; N, 2.58%]; ν_{max} (film) 3368, 2984, 1720, 1508, 1392, 1368, 1256, 1172, 1024, 972 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.03–7.30 (m, $7H_{arom}$), 7.20 (d, 1H, *J* 9.0 Hz, N*H*), 6.49–6.31 (m, 1H, C*H*N), 4.40–4.03 (m, 6H, 3×CH_2O), 3.44–3.41 (m, 2H, CH_2O), 3.21 (dt, J_{HP} 24.7 Hz, *J* 2.6 Hz, C*H*P), 1.54–1.41 (m, 15H, 5×CH_3), 1.25 (t, 3H, *J* 7.1 Hz, CH_3), 0.66 (t, 3H, *J* 7.1 Hz, CH_3); δ_C (63 MHz, $CDCl_3$) 153.0, 134.5 (d, $^3J_{CP}$ 15.5 Hz), 132.0, 127.3, 127.1, 126.2, 124.7, 123.6, 123.3, 122.2, 120.3, 77.4, 61.9 (d, $^2J_{CP}$ 7.2 Hz), 61.4 (d, $^2J_{CP}$ 6.9 Hz), 60.9 (d, $^2J_{CP}$ 5.8 Hz), 59.6 (d, $^2J_{CP}$ 6.8 Hz), 47.0, 40.1 (t, $^1J_{CP}$ 130.8 Hz), 26.6, 14.5 (d, $^3J_{CP}$ 5.6 Hz), 14.4 (d, $^3J_{CP}$ 6.4 Hz), 13.6 (d, $^3J_{CP}$ 7.3 Hz); δ_P (101 MHz, $CDCl_3$) 21.5, 21.4; *m/z* (CI, isobutane) 544 (100%, MH^+).

*4.3. Preparation of aminobisphosphonate hydrochlorides **17a**,**b**; general procedure*

A mixture of **11** (0.3 mmol) and 3.5 M HCl in anhydrous EtOH (4.5 mL) was stirred for 1 h at rt. Evaporation of the solvent gave spectroscopically pure aminobisphosphonate hydrochlorides **17** in quantitative yields.

*4.3.1. Diethyl [2-amino-1-(diethoxyphosphoryl)hexyl]-phosphonate hydrochloride (**17a**)*

Yield: 123 mg (100%); white solid; mp 120–121 °C; [Found: C, 41.09; H, 8.52; N, 3.51. $C_{14}H_{34}ClNO_6P_2$ requires (409.82): C, 41.03; H, 8.36; N, 3.42%]; ν_{max} (KBr) 3448, 2984, 2872, 1252, 1028, 996, 972 cm^{-1}; δ_H (250 MHz, MeOD) 4.83 (s, NH_3), 4.30–4.18 (m, 8H, 4×CH_2O), 3.90–3.58 (m, 1H, C*H*N), 3.25 (dt, 1H, J_{HP} 25.5 Hz, *J* 2.9 Hz, C*H*P), 2.21–1.37 (m, 6H*, 3×CH_2), 1.38 (t, 6H*, *J* 7.0 Hz, 2×CH_3), 1.37 (t, 6H*, *J* 7.0 Hz, 2×CH_3), 0.97 (t, 3H, *J* 6.9 Hz, CH_3); δ_C (63 MHz, MeOD) 63.4 (d, $^2J_{CP}$ 6.0 Hz), 63.3 (d, $^2J_{CP}$ 7.0 Hz), 48.0 (d, $^2J_{CP}$ 5.7 Hz), 36.8 (t, $^1J_{CP}$ 133.1 Hz),

29.0 (d, $^3J_{CP}$ 5.6 Hz), 25.6, 19.6, 13.8 (d, $^3J_{CP}$ 5.7 Hz), 11.1; δ_P (101 MHz, MeOD) 21.5, 20.1 (2×d, J_{PP} 4.0 Hz); *m/z* (CI, isobutane) 374.2 (18, MH^+-HCl), 357.1 (100%).

4.3.2. Diethyl [2-amino-1-(diethoxyphosphoryl)-2-phenyl-ethyl]phosphonate hydrochloride (**17b**)

Yield: 129 mg (100%); white solid; mp 128–129 °C; [Found: C, 44.62; H, 7.15; N, 3.34. $C_{16}H_{30}ClNO_6P_2$ requires: C, 44.71; H, 7.04; N, 3.26%]; ν_{max} (KBr) 3448, 3088, 3064, 2984, 1584, 1528, 1480, 1440, 1388, 1236, 1160, 1124, 1024 cm^{-1}; δ_H (250 MHz, MeOD) 7.65–7.42 (m, $5H_{arom}$), 4.96–4.83 (m, 1H, C*H*N), 4.83 (s, NH_3), 4.35–3.84 (m, 8H, 4×CH_2O), 3.25 (dt, 1H, J_{HP} 23.9 Hz, J 7.4 Hz, C*H*P), 1.36, 1.31, 1.25, 1.20 (4×t, 12H, J 7.1 Hz, 4×CH_3); δ_C (63 MHz, MeOD) 131.4 (dd, $^3J_{CP}$ 4.1, 8.7 Hz), 128.3, 127.2, 126.2, 63.4 (d, $^2J_{CP}$ 7.0 Hz), 63.3 (d, $^2J_{CP}$ 6.9 Hz), 63.0 (d, $^2J_{CP}$ 7.0 Hz), 50.8, 38.5 (dd, $^1J_{CP}$ 132.7, 129.5 Hz), 13.7 (d, $^3J_{CP}$ 6.0 Hz); δ_P (101 MHz, MeOD) 20.8, 19.5 (2×d, J_{PP} 9.1 Hz); *m/z* (CI, isobutane) 394 (20, MH^+-HCl), 377 (100%).

4.4. Preparation of free aminobisphosphonic acids **18a–d**; general procedure

A mixture of bisphosphonate **11** (0.4 mmol) and 20% aq HCl solution (3 mL) was heated at reflux for 10 h. Then the solution was concentrated under reduced pressure and the residue was co-evaporated with absolute ethanol to remove traces of water and hydrochloric acid. Acetone (1 mL) was then added to the residue and the mixture was left for 24 h at rt. The precipitated solid was collected, redissolved in distilled water (5 mL), and the solution was lyophilized to give crystalline, spectroscopically pure acids **18a–c**.

4.4.1. (2-Amino-1-phosphono-propyl)phosphonic acid hydrochloride (**18a**)

Yield: 53 mg (50%); white solid, mp 240 °C (dec); [Found: C, 14.20; H, 4.85; N, 5.35. $C_3H_{12}ClNO_6P_2\times0.5H_2O$ requires: C, 14.10; H, 4.73; N, 5.48%]; ν_{max} (KBr) 3220, 3134, 3048, 2360, 1640, 1400, 1195, 1061, 987, 965 cm^{-1}; δ_H (250 MHz, D_2O) 4.68 (NH_3), 3.92–3.75 (m, 1H, C*H*N), 2.47 (dt, 1H, $^1J_{HP}$ 24.5 Hz, J 3.3 Hz, C*H*P), 1.45 (d, 3H, J 6.8 Hz, CH_3); δ_C (63 MHz, D_2O) 46.2, 41.6 (t, $^1J_{CP}$ 120.4 Hz), 17.2; δ_P (101 MHz, D_2O) 16.7, 16.2; *m/z* (FAB) 217.9 (50%, $M-H^+-HCl$); HRMS (negative ions, glycerol): $[M-H]^-$, found 217.9991. $C_3H_{10}NO_6P_2$ requires 217.9983.

4.4.2. (2-Amino-2-phenyl-1-phosphono-ethyl)phosphonic acid hydrochloride (**18b**)

Yield: 89 mg (68%); white solid; mp 210 °C (dec); [Found: C, 29.69; H, 4.90; N, 4.55. $C_8H_{14}ClNO_6P_2\times0.5H_2O$ requires: C, 29.42; H, 4.63; N, 4.29%]; ν_{max} (KBr) 3633, 3383, 2922, 2887, 2359, 2341, 1252, 1234, 1173, 1159, 1130, 1061, 1010, 948 cm^{-1}; δ_H (250 MHz, D_2O) 7.49–7.38 (m, $5H_{arom}$), 5.20–4.80 (m, 1H C*H*N), 4.75 (NH_3), 2.86 (dt, 1H, $^1J_{HP}$ 22.0 Hz, J 3.3 Hz, C*H*P); δ_C (63 MHz, D_2O) 135.1, 129.2, 128.8, 127.4, 53.3, 43.2 (br t, $^1J_{CP}$ 120.4 Hz); δ_P (101 MHz, D_2O) 16.0, 15.3; *m/z* (FAB) 280.1 (100%, $M-H^+-HCl$); HRMS (negative ions, glycerol): $[M-H]^-$, found 280.0134. $C_8H_{12}NO_6P_2$ requires 280.0140.

4.4.3. (2-Amino-2-naphthalen-1-yl-1-phosphono-ethyl)-phosphonic acid hydrochloride (**18c**)

Yield: 78 mg (52%); white solid; mp 207 °C (dec); [Found: C, 38.51; H, 4.30; N, 4.81. $C_{12}H_{16}ClNO_6P_2\times0.5H_2O$ requires: C, 38.26; H, 4.55; N, 3.72%]; ν_{max} (KBr) 3401, 2940, 2360, 1170, 1060, 1012, 950 cm^{-1}; δ_H (250 MHz, D_2O) 8.02–7.50 (m, $7H_{arom}$), 5.89–5.74 (m, 1H, C*H*N), 4.75 (NH_3), 3.03–2.91 (m, 1H, C*H*P), δ_C (63 MHz, D_2O) 133.6, 131.0, 129.5, 129.3, 129.1, 127.4, 126.4, 125.2, 123.8, 122.0, 49.0, 44.2 (br t, $^1J_{CP}$ 120.4 Hz); δ_P (101 MHz, D_2O) 16.3, 14.4; *m/z* (FAB) 330.1 (100%, $M-H^+-HCl$); HRMS (negative ions, glycerol): $[M-H]^-$, found 330.0287. $C_{12}H_{14}NO_6P_2$ requires 330.0296.

4.4.4. (2-Amino-1-phosphono-2-pyridin-3-yl-ethyl)-phosphonic acid dihydrobromide (**18d**)

Bromotrimethylsilane (0.65 mL, 0.765 g, 5 mmol) was added at rt to a solution of **11i** (247 mg, 0.5 mmol) in dry CH_2Cl_2 (2 mL). The mixture was stirred at rt for 24 h. Then the second portion of bromotrimethylsilane (0.65 mL, 0.765 g, 5 mmol) was added to the mixture and the reagents were stirred at rt for additional 24 h. Dichloromethane and the excess of bromotrimethylsilane were evaporated under reduced pressure. Anhydrous methanol (4 mL) was added to the residue and the solution was left for 2 h at rt. The solvent was evaporated under reduced pressure, the residue was redissolved in methanol (2 mL) and left for 24 h. The precipitated solid was collected, redissolved in distilled water (5 mL), and the solution was lyophilized to give 87 mg (35%) of spectroscopically pure acid **18d** as a white solid; mp 241 °C (dec); [Found: C, 17.02; H, 4.30; N, 5.91. $C_7H_{14}Br_2N_2O_6P_2\times3H_2O$ requires: C, 16.88; H, 4.05; N, 5.63%]; ν_{max} (KBr) 3426, 3066, 2963, 2906, 2896, 2361, 1160, 1050, 1015, 962 cm^{-1}; δ_H (250 MHz, D_2O) 8.99 (s, $1H_{arom}$), 8.86–8.72 (m, $2H_{arom}$), 8.05 (dd, $1H_{arom}$, J 6.2, 7.42 Hz), 5.18–4.80 (m, 1H, C*H*N), 4.74 (NH_3), 2.75 (distorted t, 1H, $^1J_{HP}$ 20.4 Hz, C*H*P); δ_C (63 MHz, D_2O) 146.5, 141.6, 141.2, 135.5, 127.3, 50.8, 45.4 (br t, $^1J_{CP}$ 120.9 Hz); δ_P (101 MHz, D_2O) 13.0 (br s); *m/z* (FAB) 281.1 (80%, $M-H^+-2HBr$); HRMS (negative ions, glycerol): $[M-H]^-$, found 281.0103. $C_7H_{11}N_2O_6P_2$ requires 281.0092.

4.5. Preparation of aza-Morita–Baylis–Hillman-type adducts **19a–f**; general procedure

A solution of bisphosphonate **11** (0.5 mmol) in anhydrous THF (3 mL) was added dropwise to a solution of *t*-BuOK (67 mg, 0.6 mmol) in THF (2 mL) at −10 °C. The reaction mixture was stirred for 10 min at −10 °C and paraformaldehyde (120 mg, 4 mmol) was then added. Stirring was continued for 5 h at this temperature. The resultant mixture was quenched with satd aq NH_4Cl solution (ca. 5 mL) until neutral pH was reached. The mixture was extracted with CH_2Cl_2 (2×30 mL), the combined organic extracts were washed with water (2×10 mL), and dried over $MgSO_4$. The solvent

was evaporated under reduced pressure and the rest of the volatile material was removed at 35–40 °C/0.1 mmHg to give spectroscopically pure **19a–f** (Table 3).

*4.5.1. Diethyl (2-tert-butoxycarbonylamino-1-methylene-propyl)phosphonate (**19a**)*

Yield: 112 mg (73%); colorless oil; [Found: C, 50.65; H, 8.70; N, 4.32. $C_{13}H_{26}NO_5P$ requires: C, 50.81; H, 8.53; N, 4.56%]; ν_{max} (film) 3296, 2976, 2936, 1712, 1528, 1448, 1392, 1368, 1248, 1172, 1096, 1028, 968 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 6.01 (d, $1H_{vin}$, J_{HP}(cis) 19.8 Hz), 5.94 (d, $1H_{vin}$, J_{HP}(trans) 45.8 Hz), 5.13 (br d, 1H, *J* 8.1 Hz, N*H*), 4.68–4.42 (m, 1H, C*H*N), 4.13–4.06 (m, 4H, 2×CH_2), 1.43 (t, 6H*, *J* 7.1 Hz, 2×CH_3), 1.37 (d, 3H*, *J* 7.0 Hz, CH_3); δ_C (63 MHz, $CDCl_3$) 152.9, 140.1 (d, $^1J_{CP}$ 169.7 Hz), 127.6 (d, $^2J_{CP}$ 7.2 Hz), 77.5, 60.3 (d, $^2J_{CP}$ 8.0 Hz), 60.1 (d, $^2J_{CP}$ 6.0 Hz), 54.1 (d, $^2J_{CP}$ 12.0 Hz), 26.5, 19.5, 14.4 (d, $^3J_{CP}$ 6.5 Hz); δ_P (101 MHz, $CDCl_3$) 17.9; *m/z* (CI, isobutane) 308.1 (100%, MH^+).

*4.5.2. Diethyl (2-tert-butoxycarbonylamino-1-methylene-butyl)phosphonate (**19b**)*

Yield: 140 mg (87%); colorless oil; [Found: C, 52.11; H 8.90; N 4.19. $C_{14}H_{28}NO_5P$ requires: C, 52.33; H, 8.78; N, 4.36%]; ν_{max} (film) 3304, 2976, 2936, 1712, 1528, 1520, 1512, 1456, 1392, 1368, 1240, 1172, 1028, 968 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 6.01 (d, $1H_{vin}$, J_{HP}(cis) 21.8 Hz), 5.90 (d, $1H_{vin}$, J_{HP}(trans) 45.8 Hz), 5.20 (br d, 1H, *J* 11.5 Hz, N*H*), 4.32–3.98 (m, 5H, 2×CH_2, C*H*), 1.81–1.59 (m, 2H, CH_2), 1.43 (s, 9H*, 3×CH_3), 1.50–1.23 (m, 6H*, 2×CH_3), 0.91 (t, 3H, *J* 7.5 Hz, CH_3); δ_C (63 MHz, $CDCl_3$) 153.3, 138.0 (d, $^1J_{CP}$ 168.7 Hz), 128.5 (d, $^2J_{CP}$ 7.2 Hz), 77.1, 60.2 (d, $^2J_{CP}$ 5.7 Hz), 60.0 (d, $^2J_{CP}$ 6.0 Hz), 54.1 (d, $^2J_{CP}$ 12.0 Hz), 26.4, 25.8, 14.4 (d, $^3J_{CP}$ 6.5 Hz), 8.7; δ_P (101 MHz, $CDCl_3$) 18.2; *m/z* (CI, isobutane) 322 (100%, MH^+).

*4.5.3. Diethyl (2-tert-butoxycarbonylamino-3-methyl-1-methylene-butyl)phosphonate (**19c**)*

Yield: 149 mg (89%); colorless oil; [Found: C, 53.88; H, 9.25; N, 4.38. $C_{15}H_{30}NO_5P$ requires: C, 53.72; H, 9.02; N, 4.18%]; ν_{max} (film) 3294, 2976, 1712, 1512, 1456, 1392, 1368, 1248, 1172, 1028, 992, 968 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 6.00 (d, $1H_{vin}$, J_{HP}(cis) 20.6 Hz), 5.88 (d, $1H_{vin}$, J_{HP}(trans) 44.6 Hz), 5.27 (br d, 1H, *J* 9.5 Hz, N*H*), 4.16–4.01 (m, 5H, 2×CH_2, C*H*N), 2.02 (m, 1H, C*H*), 1.43 (s, 9H, 3×CH_3), 1.34, 1.33 (2×t, 6H, *J* 7.1 Hz, 2×CH_3), 0.94 (d, 3H, *J* 6.7 Hz, CH_3), 0.90 (d, 3H, *J* 6.7 Hz, CH_3); δ_C (63 MHz, $CDCl_3$) 153.5, 137.6 (d, $^1J_{CP}$ 168.0 Hz), 130.0 (d, $^2J_{CP}$ 8.2 Hz), 77.1, 60.2 (d, $^2J_{CP}$ 5.5 Hz), 60.0 (d, $^2J_{CP}$ 6.1 Hz), 59.2 (d, $^2J_{CP}$ 12.1 Hz), 29.2, 26.5, 18.3, 16.6, 14.3 (d, $^3J_{CP}$ 6.2 Hz); δ_P (101 MHz, $CDCl_3$) 17.9; *m/z* (CI, isobutane) 336 (100%, MH^+).

*4.5.4. Diethyl [1-(tert-butoxycarbonylamino-cyclohexyl-methyl)-vinyl]phosphonate (**19d**)*

Yield: 167 mg (89%); colorless oil; [Found: C, 57.40; H, 9.36; N, 3.49. $C_{18}H_{34}NO_5P$ requires: C, 57.58; H, 9.13; N, 3.73%]; ν_{max} (film) 3288, 2976, 2960, 2928, 1712, 1504, 1448, 1392, 1368, 1252, 1168, 1024, 968 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 5.99 (d, $1H_{vin}$, J_{HP}(cis) 21.6 Hz), 5.86 (d, $1H_{vin}$, J_{HP}(trans) 45.9 Hz), 5.31 (br d, 1H, *J* 10.2 Hz, N*H*), 4.15–3.99 (m, 5H, 2×CH_2, C*H*N), 2.02 (m, 1H, C*H*), 1.42 (s, 9H*, 3×CH_3), 1.34, 1.33 (2×t, 6H*, *J* 7.0 Hz, 2×CH_3), 1.85–0.91 (m, 11H*, 5×CH_2, C*H*); δ_C (63 MHz, $CDCl_3$) 154.4, 137.9 (d, $^1J_{CP}$ 169.2 Hz), 130.2 (d, $^2J_{CP}$ 8.1 Hz), 78.0, 61.1 (d, $^2J_{CP}$ 5.6 Hz), 60.9 (d, $^2J_{CP}$ 6.0 Hz), 59.4 (d, $^2J_{CP}$ 11.5 Hz), 39.3, 29.7, 28.0, 27.4, 25.3, 24.9, 15.3 (d, $^3J_{CP}$ 6.6 Hz); δ_P (101 MHz, $CDCl_3$) 18.3; *m/z* (CI, isobutane) 376 (100%, MH^+).

*4.5.5. Diethyl [1-(tert-butoxycarbonylamino-phenyl-methyl)-vinyl]phosphonate (**19e**)*

Yield: 144 mg (78%); colorless oil; [Found: C, 58.31; H, 7.85; N, 3.58. $C_{18}H_{28}NO_5P$ requires: C, 58.53; H, 7.64; N, 3.79%]; ν_{max} (film) 3280, 2976, 1712, 1528, 1520, 1512, 1456, 1392, 1368, 1244, 1200, 1168, 1024, 972 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.34–7.25 (m, $5H_{arom}$), 6.17 (d, $1H_{vin}$, J_{HP}(cis) 25.9 Hz), 6.01 (d, $1H_{vin}$, J_{HP}(trans) 49.7 Hz), 5.75 (br s, 1H, N*H*), 5.57 (dd, 1H, J_{HP} 17.1 Hz, *J* 8.1 Hz, C*H*N), 4.88–3.67 (m, 4H, 2×CH_2O), 1.44 (s, 9H, 3×CH_3), 1.26, 1.05 (2×t, 6H, *J* 7.0 Hz, 2×CH_3); δ_C (63 MHz, $CDCl_3$) 154.5, 139.8 (d, $^1J_{CP}$ 171.3 Hz), 139.3 (d, $^3J_{CP}$ 2.5 Hz), 130.6 (d, $^2J_{CP}$ 8.3 Hz), 128.2, 127.3, 126.8, 79.4, 61.8 (d, $^2J_{CP}$ 5.6 Hz), 61.6 (d, $^2J_{CP}$ 5.8 Hz), 57.0 (d, $^2J_{CP}$ 13.3 Hz), 28.1, 15.9 (d, $^3J_{CP}$ 6.7 Hz), 15.7 (d, $^3J_{CP}$ 6.7 Hz); δ_P (101 MHz, $CDCl_3$) 17.1; *m/z* (CI, isobutane) 370 (100%, MH^+).

*4.5.6. Diethyl [1-(tert-butoxycarbonylamino-naphthalen-1-yl-methyl)-vinyl]phosphonate (**19f**)*

Yield: 153 mg (73%); yellow oil; [Found: C, 62.81; H, 7.32; N, 3.53. $C_{22}H_{30}NO_5P$ requires: C, 63.00; H, 7.21; N, 3.34%]; ν_{max} (film) 3288, 2984, 2928, 1708, 1512, 1464, 1456, 1392, 1380, 1368, 1292, 1280, 1244, 1208, 1168, 1024, 992, 968 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.17–7.30 (m, $7H_{arom}$), 6.38 (m, 1H, C*H*N), 6.31 (d, $1H_{vin}$, J_{HP}(cis) 21.7 Hz), 6.00 (d, $1H_{vin}$, J_{HP}(trans) 45.7 Hz), 5.44 (br s, 1H, N*H*), 4.39–3.85 (m, 4H, 2×CH_2O), 1.44 (s, 9H, 3×CH_3), 1.33 (t, 3H, *J* 7.1 Hz, CH_3), 1.00 (t, 3H, *J* 6.8 Hz, CH_3); δ_C (63 MHz, $CDCl_3$) 154.4, 139.8 (d, $^1J_{CP}$ 173.9 Hz), 135.1 (d, $^3J_{CP}$ 3.8 Hz), 133.7, 131.3 (d, $^2J_{CP}$ 8.3 Hz), 130.7, 128.6, 128.4, 126.2, 125.5, 125.4, 124.9, 124.7, 123.2, 79.6, 62.0 (d, $^2J_{CP}$ 5.8 Hz), 61.8 (d, $^2J_{CP}$ 6.1 Hz), 52.6 (d, $^2J_{CP}$ 13.3 Hz), 28.2, 16.1 (d, $^3J_{CP}$ 6.5 Hz), 15.7 (d, $^3J_{CP}$ 6.8 Hz); δ_P (101 MHz, $CDCl_3$) 17.5; *m/z* (CI, isobutane) 420 (100%, MH^+).

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