Chemical Conversion of Cyclic α-Amino Acids to Cyclic α-Aminophosphonic Acids

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The oxidative decarboxylation of cyclic α-amino acids having urethane-type *N*-protecting groups with lead tetraacetate [$Pb(OAc)_4$] gave 2-hydroxy derivatives, which were transformed into the corresponding α-aminophosphonic acid esters by treatment of trialkyl phosphites in the presence of Lewis acids. Deprotection and ester cleavage of the products in the usual manner afforded cyclic α-aminophosphonic acids. The convenient chemical conversion of five- and six-membered cyclic α-amino acids to the corresponding cyclic α-aminophosphonic acids has been accomplished.

Key words α-aminophosphonic acid; α-amino acid; phosphonylation; acyliminium ion; Lewis acid; decarboxylation

α-Aminophosphonic acids are believed to be phosphorus analogs of naturally occurring α-amino acids and have found applications as potent active compounds with a wide range of biological activities as antibiotics,[1] enzyme inhibitors,[2] pharmacological agents,[2b,3] antiviral agents,[4] and herbicides.[5] Their negligible mammalian toxicity, and the fact that they bear a very close chemical resemblance to their amino carboxylic counterparts, make them remarkably important structural units of phosphonopeptides and peptidomimetics.[6] During the last two decades, considerable efforts toward the synthesis of α-aminophosphonic acids have been made.[7] However, a simple and general synthetic method for cyclic amino-type of compounds, such as phosphonic acid analogs of 2-pyrrolidinecarboxylic acid (proline) and 2-piperidinecarboxylic acid, is not relatively known, and most of the reported methods are about acyclic compounds. The cyclic analogues can be viewed as useful tools for the elucidation of conformational requirements of a receptor, since the conformation is easily fixed. Many synthetic routes to α-aminophosphonic acids and their derivatives include a key step of nucleophilic phosphonylation to either performed or *in situ* generated imines (Schiff bases) or iminium ions.[8] Shono[9] and co-workers reported the phosphonylation of *N*-protected 2-methoxyamines using trialkyl phosphites in the presence of Lewis acids. Similar transformation of 2-benzotriazolylpyrrolidine derivatives into pyrrolidine-2-phosphonic acid esters was reported by Katritzky[10] and co-workers. We wish to report herein the convenient conversion of cyclic α-amino acids to cyclic α-aminophosphonic acids through the corresponding *N*-protected 2-hydroxyamines, with which easy generation of acyliminium ions in the presence of Lewis acids would be expected. To our knowledge, only a few studies concerning the chemical conversion of naturally occurring cyclic α-amino acid (proline or proline-containing dipeptide) into the corresponding phosphonic acid analogues have been published,[11,12] and these are not systematic or detailed studies. In this paper, we describe a systematic study on a simple route to a series of phosphonic acid analogues from proline and 2-piperidinecarboxylic acid, as illustrated in Chart 1.

Initially, we examined the transformation of commercially available cyclic α-amino acids (**1**, **2**) into the key intermediates of cyclic *N*-protected 2-hydroxyamines (**5**, **6**). Displacement of the carboxylic acid moiety by hydroxy group or its equivalents such as acetoxy group had been realized by using two methods of oxidative decarboxylation: lead tetraacetate [$Pb(OAc)_4$] oxidation[13] of carboxylic acids and *m*-chloroperbenzoic acid (*m*-CPBA) oxidation[14] of active esters. We applied these methods to *N*-protected amino acids (**3a**—**e**, **4a**—**c**) and their active esters (**3f**, **g**), as summarized in Table1. L-Proline derivatives (**3a**—**e**) having various *N*-protecting groups were oxidized with $Pb(OAc)_4$ to the desired 2-hydroxy compounds (**5a**—**e**) in good yields. *N*-Benzoyl (Bz) product (**5e**) was contaminated with an inseparable equivalent of the ring-opened aldehyde (**11e**) (Chart 2). In the case of the substrates having urethane-type *N*-protecting groups, production of such ring-opened aldehydes was not be detectable, but treatment of the product (**5b**) having *N*-benzyloxycarbonyl (Z) group, as an example, with hydroxylamine afforded the corresponding ring-opened oxime (*N*-Z-4-aminobutanal oxime) in quantitative yield.

Decarboxylation of the esters (**3f**, **g**) using *m*-CPBA gave the corresponding hydroxy compounds (**5b**) in satisfactory yields. In comparison with the $Pb(OAc)_4$ method, however, this method seems to be disadvantageous for our purpose, because esterification of the starting amino acids is necessary. Therefore, oxidation of the 2-piperidinecarboxylic acid derivatives (**4a**—**c**) was achieved with $Pb(OAc)_4$. *N*-Z derivative (**4b**) afforded only the hydroxy compound (**6b**) in high yield, while in the case of two substrates (**4a**, **c**) *N*-protected with trichloroethoxycarbonyl (Troc) or *p*-nitrobenzyloxycarbonyl (PNZ) group, the oxidation products, estimated as the hydroxy compounds, were very unstable and were completely transformed into the enecarbamates (**12a**, **c**) by elimination of H_2O during the purification. Therefore, these products were immediately used for the next step without further purification.

Next, conversion of the 2-hydroxy compounds (**5**, **6**) into the phosphonic acid derivatives (**7**, **8**) was studied. Conditions for the generation of the acyliminium ions and subsequent nucleophilic phosphonylation were examined with *N*-Troc-2-hydroxypyrrolidine (**5a**) as a model substrate. Upon treatment with trialkyl phosphites in the presence of 1 or 1.5 mol equivalent of various Lewis acids in CH_2Cl_2 at room temperature, compound **5a** was transformed into the corresponding 2-phosphonic acid esters (**7aa**—**7ac**) in variable

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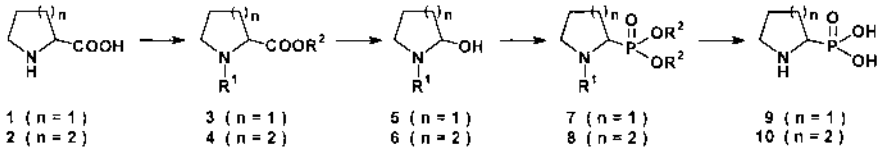

Chart 1

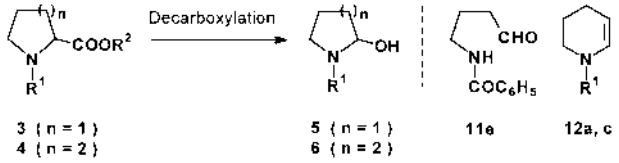

Chart 2

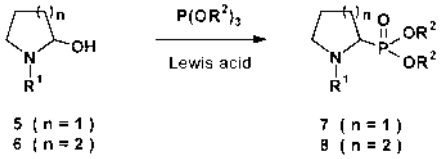

Chart 3

Table 1. Oxidative Decarboxylation of Cyclic α-Amino Acid Derivatives (**3**, **4**)

Entry	Substrate			Reaction[a]		Product	Yield (%)
		R^1	R^2	Method[b]	Time		
1	**3a** (n=1)	Troc	H	A	48 h	**5a**	97
2	**3b**	Z	H	A	48 h	**5b**	93
3	**3c**	PNZ	H	A	48 h	**5c**	Quant.
4	**3d**	Boc	H	A	20 h	**5d**	65
5	**3e**	Bz	H	A	48 h	**5e**[e]	60
6	**3f**	Z	PNP[c]	B	24 h	**5b**	90
7	**3g**	Z	DP[d]	B	24 h	**5b**	62
8	**4a** (n=2)	Troc	H	A	48 h	**12a**	Quant.
9	**4b**	Z	H	A	3 d	**6b**	87
10	**4c**	PNZ	H	A	48 h	**12c**	99

a) Reaction was carried out at room temperature. *b*) Method A: $Pb(OAc)_4$ oxidation. Method B: *m*-CPBA oxidation. *c*) PNP: *p*-nitrophenyl. *d*) DP: 2,5-dioxo-1-pyrrolidinyl. *e*) A mixture of **5e** and the ring-opened aldehyde (**11e**).

Table 2. Phosphonylation of Cyclic 2-Hydroxyamines (**5**, **6**)

Entry	Substrate		Trialkyl phosphite (R^2)	Lewis acid (mole eq)	Product	Yield (%)
		R^1				
1	**5a** (n=1)	Troc	Me	$TiCl_4$ (1.5)	**7aa**	68
2				$BF_3 \cdot OEt_2$ (1.5)		62
3				TMSOTf (1.0)		57
4				TMSOTf (1.5)		87
5			Et		**7ab**	71
6			Isopropyl		**7ac**	55
7	**5b**	Z	Me	TMSOTf (1.5)	**7ba**	67
8	**5c**	PNZ			**7ca**	65
9	**6a** (n=2)	Troc	Me	TMSOTf (1.5)	**8aa**	46
10			Et		**8ab**	66
11			Isopropyl		**8ac**	52
12	**6b**	Z	Me		**8ba**	60

yields. The results are summarized in Table 2. Production of **7aa** by the reaction using a combination of trimethyl phosphite and trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a Lewis acid gave the best yield of 87%. As bulkiness of the alkyl group in trialkyl phosphite increased, yield of the product was reduced. Use of the other substrates having different *N*-protecting groups did not improve for yield of the phosphonylation. Reaction of six-membered cyclic 2-hydroxy compounds (**6a**, **b**) with trialkyl phosphites proceeded smoothly under the same conditions, but moderate yields (46—66%) of the desired products (**8**) were obtained.

All the *N*-protected cyclic α-aminophosphonic acid esters (**7**, **8**) prepared above are new compounds, which were characterized on the basis of their spectral data, especially by observation of C–P spin couplings ($^1J_{CP}$=154.1—163.3 Hz) of the C-2 carbon in ^{13}C-NMR spectra. These *N*-protected derivatives would be very important for the synthesis of peptides and the related compounds containing these aminophosphonic acids. *N-tert*-Butoxycarbonyl (Boc) group is one of the most common amino protecting groups as well as *N*-Z group in the field of amino acid chemistry.[15] However, it is impossible to use the *N*-Boc group in our phospho-

Table 3. Preparation of Cyclic α-Aminophosphonic Acids (**9**, **10**)

Substrate		Method		α-Aminophosphonic acid	Yield (%)[a]
	R^1	Deprotection	Ester cleavage		
7aa (n=1)	Troc	Zn/AcOH	6 N HCl	**9**	80
7ba	Z	H_2/10% Pd–C	6 N HCl	**9**	81
7da	Boc	6 N HCl		**9**	87
8aa (n=2)	Troc	Zn/AcOH	6 N HCl	**10**	82
8ba	Z	H_2/10% Pd–C	6 N HCl	**10**	80
8da	Boc	6 N HCl		**10**	97

a) Yield of salt-free acid.

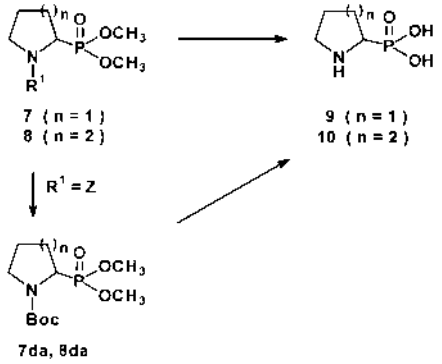

Chart 4

nylation under a Lewis acid catalyst. Therefore, we tried a conversion of the *N*-Z products into the *N*-Boc derivatives by the method developed for that of α-amino acids.[16] The five- and six-membered cyclic *N*-Z compounds (**7ba**, **8ba**) were treated with Boc reagent (Boc_2O) in methanol under hydrogenolytic conditions (Pd-C/H_2) to furnish the expected *N*-Boc derivatives **7da** and **8da** in 97% and 74% yield, respectively (Chart 4).

Finally, the cyclic α-aminophosphonic acids were obtained in a two-step sequence from *N*-protected α-aminophosphonic acid methyl esters (**7**, **8**) in good yields (Table 3). Deprotection of the *N*-protecting groups by the appropriate procedure utilizing in amino acid chemistry[15,17] and hydrochloric acid-catalyzed hydrolysis of the methyl phosphonate moieties followed by desalting to the salt-free aminophosphonic acids were successfully achieved. The structure of target compounds (**9**, **10**) was supported by their analytical and spectral data, which were in accordance with literature data of the compounds (**9**, **10**) synthesized from a different non-amino acids source.[18,19]

Thus, the novel chemical conversion of five- and six-membered cyclic α-amino acids to cyclic α-aminophosphonic acids and their *N*-protected derivatives has been established. The route described in this paper is potentially applicable to the preparation of optical active analogs of these compounds. *N*-Protected cyclic 2-hydroxyamines were used in our approach for the formation of acyliminium ions. More recently, direct formation of the acyliminium ions from *N*-acylated cyclic α-amino acids by the novel oxidation with a combination of (diacetoxyiodo)benzene (DIB) and iodine has been reported by Boto[20] and co-workers, who applied the acyliminium ions to C–C bond formation for alkaloid synthesis.

Experimental

All melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected. MS and HRMS were obtained on a JEOL JMS-DX300 or JMS-SX102A spectrometer. IR spectra were recorded on a Hitachi 270-30 spectrophotometer. ^{1}H-NMR spectra were obtained at 23 °C on a JEOL PMX-60-SI, JNM-EX90A or JNM-GSX-400 spectrometer using tetramethylsilane (TMS, δ 0 ppm) or dioxane (δ 3.70 ppm from TMS) as an internal standard. ^{13}C-NMR spectra were measured on a JEOL JNM-EX90A or JNM-GSX-400 spectrometer using TMS or dioxane (δ 67.4 ppm from TMS) as an internal standard. The following abbreviations are used: m=multiplet, q=quartet, t=triplet, d=doublet, s=singlet, and br=broad, d_p=doublet (H–P or C–P multiplicity). Column chromatography was carried out on silica gel (Kieselgel 60, 70—230 mesh, Merck) or alumina (aluminium oxide 90, 70—230 mesh, Merck).

***N*-Protection of Cyclic α-Amino Acids** All the *N*-protected cyclic α-amino acids were prepared from commercially available amino acids (**1**, **2**) by acylation with di-*tert*-butyl dicarbonate (Boc_2O) or the corresponding acid chlorides under the Shotten-Baumann reaction conditions (dioxane–H_2O, $NaHCO_3$, 0 °C—room temperature).

1-(2,2,2-Trichloroethoxycarbonyl)pyrrolidine-2-carboxylic Acid (**3a**)[21]: Yield quant.

1-(Benzyloxycarbonyl)pyrrolidine-2-carboxylic Acid (**3b**)[22]: Yield 88%.

1-(4-Nitrobenzyloxycarbonyl)pyrrolidine-2-carboxylic Acid (**3c**)[23]: Yield quant.

1-(*tert*-Butoxylcarbonyl)pyrrolidine-2-carboxylic Acid (**3d**)[24]: Yield 84%.

1-Benzoylpyrrolidine-2-carboxylic Acid (**3e**)[25]: Yield quant.

1-(2,2,2-Trichloroethoxycarbonyl)piperidine-2-carboxylic Acid (**4a**): Yield 66%, colorless prisms, mp 117—119 °C (benzene–hexane). MS *m*/*z*: 303 (M^+), 305 (M^++2), 307 (M^++4), 309 (M^++6). IR (KBr) cm^{-1}: 3172 (OH), 1740, 1684 (C=O). ^{1}H-NMR ($CDCl_3$) [60 MHz] δ: [1.15—2.01 (5H, m), 2.01—2.58 (1H, m), C_3-H_2, C_4-H_2, C_5-H_2], 2.75—3.53 (1H, m, C_6-Ha), 3.88—4.40 (1H, m, C_6-Hb), 4.79 (2H, s, OCH_2CCl_3), 4.85—5.16 (1H, m, C_2-H), 10.55 (1H, br s, COOH).

1-(Benzyloxycarbonyl)piperidine-2-carboxylic Acid (**4b**)[26]: Yield 76%.

1-(4-Nitrobenzyloxycarbonyl)piperidine-2-carboxylic Acid (**4c**): Yield 97%, colorless prisms, mp 138—140 °C (65% MeOH–H_2O). MS *m*/*z*: 308 (M^+). IR (KBr) cm^{-1}: 3088 (OH), 1740, 1662 (C=O). ^{1}H-NMR ($CDCl_3$) [60 MHz] δ: 1.80—2.67 (6H, m, C_3-H_2, C_4-H_2, C_5-H_2), 2.67—3.48 (1H, m, C_6-Ha), [3.93—4.17 (0.6H, br), 4.17—4.40 (0.4H, br), C_6-Hb], 4.80—5.17 (1H, br, C_2-H), 5.33 (2H, br s, O<u>C</u>H_2Ar), [7.53 (2H, d, J=9.0 Hz), 8.29 (2H, d, J=9.0 Hz), aromatic protons] 10.90 (1H, br s, COOH).

1-Benzyl 2-(4-Nitrobenzyl) Pyrrolidine-1,2-dicarboxylate (3f)[27] A solution of *N*-Z proline (**3b**) (4.99 g, 20 mmol) in DMF (25 ml) was stirred under cooling at 0 °C. 4-Nitrophenol (3.06 g, 22 mmol) and 1,3-dicyclohexylcarbodiimide (DCC, 4.33 g, 21 mmol) were added to the solution. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 3 h. The yellow suspension of DCU was filtered off and washed with DMF (20 ml). The filtrate was diluted with benzene–MeOH (800 ml—3 ml) and H_2O (700 ml). The solution was transferred to a separatory funnel and the organic layer was separated, washed with H_2O (100 ml×5), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by recrystallization. Yield 62%, colorless needles, mp 94—95 °C (EtOH) (lit.[27] mp 94—96 °C). MS *m*/*z*: 370 (M^+). IR (KBr) cm^{-1}: 1770, 1702 (C=O). ^{1}H-NMR ($CDCl_3$) [60 MHz] δ: 1.78—2.65 (4H, m, C_3-H_2, C_4-H_2), 3.48—3.87 (2H, m, C_5-H_2), 4.42—4.78 (1H, m, C_2-H), 4.89—5.53 (2H, m, O<u>C</u>H_2Ar), [6.78—7.32 (2H, m), 7.40 (5H, s), 8.02—8.45 (2H, m), aromatic protons].

1-Benzyl 2-(2,5-Dioxo-1-pyrrolidinyl) Pyrrolidine-1,2-dicarboxylate (3g)[28] A solution of *N*-Z proline (**3b**) (9.63 g, 38.6 mmol) in DMF (50 ml) was stirred under cooling at 0 °C. *N*-Hydroxysuccinimide (4.44 g, 38.6 mmol) and DCC (8.77 g, 42.5 mmol) were added to the solution. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 24 h. The white suspension of DCU was filtered off and washed with DMF (50 ml×2). The filtrate was concentrated under reduced pressure. The residue was diluted with isoPrOH, the precipitate (DCU) was filtered off and washed with isoPrOH (10 ml). The filtrate was diluted with benzene (350 ml), and washed with H_2O (100 ml×3), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by recrystallization. Yield 84%, colorless needles, mp 88—89.5 °C (benzene–hexane) (lit.[28] mp 90 °C). MS *m/z*: 346 (M^+). IR (KBr) cm^{-1}: 1816, 1786, 1746, 1708 (C=O). ^{1}H-NMR ($CDCl_3$) [60 MHz] δ: 1.72—2.55 (4H, m, C_3-H_2, C_4-H_2), 2.80 (4H, s, $COCH_2CH_2CO$), 3.35—3.75 (2H, m, C_5-H_2), 4.50—4.79 (1H, m, C_2-H), 5.14 and 5.19 (2H (1 : 1), s, O$\underline{C}H_2$Ar), 7.36 (5H, s, aromatic protons).

Oxidative Decarboxylation of *N*-Protected Cyclic α-Amino Acids (3, 4) Method A) Modified Hunsdiecker Reaction using $Pb(OAc)_4$: A solution of an *N*-protected cyclic α-amino acid (**3a**—**e**, **4a**—**c**, 50 mmol) in dry benzene (250 ml) was added to $Pb(OAc)_4$ (1.2 mol eq), and the mixture was vigorously stirred at room temperature. After the reaction was completed, saturated aqueous NaCl (200 ml) was added dropwise to the reaction mixture under ice-cooling. The mixture was vigorously stirred for 30 min to decompose the oxidant, and the precipitate was collected by filtration with Hyflo Super-cel (Celite Co.) and washed with AcOEt (250 ml). The filtrate was transferred to a separatory funnel and the organic layer was separated. The aqueous layer was extracted with AcOEt (250 ml). The combined organic solution was washed successively with saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*.

Method B) *m*-CPBA Oxidation of the Activated Esters (**3f**, **g**): To a solution of the activated ester (**3f**, **g**) (1 mmol) in dioxane (24 ml), 0.1 M aqueous $NaHCO_3$ (12 ml) and 0.1 M aqueous Na_2CO_3 (12 ml), *m*-CPBA (2.0 mmol) was added. The solution was allowed to stand for 3 h at room temperature, and was treated with Na_2CO_3 (370 mg). After the reaction mixture was stirred for 24 h, H_2O (30 ml) was added. The aqueous solution was extracted with $CHCl_3$ (80 ml×3). The combined organic solution was washed with H_2O (50 ml), dried over anhydrous Na_2SO_4, and concentrated *in vacuo.*

2,2,2-Trichloroethyl 2-Hydroxypyrrolidine-1-carboxylate (**5a**): Pale yellow oil. MS *m/z*: 260 ($[M-1]^+$), 262 ($[M+1]^+$), 264 ($[M+3]^+$). IR (neat) cm^{-1}: 3480 (OH), 1724 (C=O). ^{1}H-NMR ($CDCl_3$) [60 MHz] δ: 1.75—2.31 (4H, m, C_3-H_2, C_4-H_2), 2.85—4.01 (3H, m, C_5-H_2, OH), 4.78 (2H, s, OCH_2CCl_3), 5.43—5.83 (1H, m, C_2-H).

Benzyl 2-Hydroxypyrrolidine-1-carboxylate (**5b**): Colorless oil. MS *m/z*: 220 ($[M-1]^+$). IR (neat) cm^{-1}: 3425 (OH), 1705 (C=O). ^{1}H-NMR ($CDCl_3$) [60 MHz] δ: 1.48—2.28 (5H, m, C_3-H_2, C_4-H_2, OH), 3.02—3.82 (2H, m, C_5-H_2), 5.15 (2H, s, O$\underline{C}H_2$Ar), 5.33—5.72 (1H, m, C_2-H), 7.34 (5H, s, aromatic protons). This sample was converted into the corresponding ring-opened oxime (*N*-Z-4-aminobutanal oxime) as follows.

4-(Benzyloxycarbonylamino)butanal Oxime: A mixture of 2-hydroxy compound (**5b**) (664 mg, 3 mmol), hydroxylamine hydrochloride (211 mg, 3 mmol) and sodium acetate (369 mg, 4.5 mmol) in 65% aqueous EtOH (15 ml) was refluxed in an oil bath for 2 h. The reaction solution was concentrated under reduced pressure and the residue was dissolved in H_2O (20 ml). The aqueous solution was extracted with ether (40 ml×2). The ether extracts were combined, washed with H_2O (20 ml), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a white solid (quantitative yield). Recrystallization of the solid from benzene gave pure oxime (519 mg, 73%). White powder, mp 92—93 °C (benzene). (lit.[13b] mp 94—95 °C). MS *m/z*: 236 (M^+). IR (KBr) cm^{-1}: 3316 (OH, NH), 1682 (C=O). ^{1}H-NMR ($CDCl_3$) [400 MHz] δ: 1.55—1.73 (2H, m, C_3-H_2), 2.14—2.25 and 2.30—2.45 (2H (1 : 9), m, C_2-H_2), 3.06—3.27 (2H, m, C_4-H_2), 5.09 (2H, s, O$\underline{C}H_2$Ar), 5.16 and 5.49 (1H (9 : 1), br s, OH), 6.71 (1H, t, J=5.5 Hz, C_1-H), 7.25—7.40 (5H, m, aromatic protons), 8.74—9.50 (1H, br, NH). ^{13}C-NMR ($CDCl_3$) [100 MHz] δ: 22.21 (t, C_3), 26.23 and 26.69 (t, C_2), 40.12 and 40.35 (t, C_4), 66.73 (t, O$\underline{C}H_2$Ar), [128.13 (d), 128.52 (d), 136.51 (s), aromatic carbons], 151.05 and 151.46 (d, C_1), 156.57 (s, COO).

4-Nitrobenzyl 2-Hydroxypyrrolidine-1-carboxylate (**5c**): Colorless oil. MS *m/z*: 266 (M^+). IR (neat) cm^{-1}: 3452 (OH), 1707 (C=O). ^{1}H-NMR ($CDCl_3$) [60 MHz] δ: 1.61—2.32 (4H, m, C_3-H_2, C_4-H_2), 3.16—3.46 (2H, m, C_5-H_2), 4.07—4.66 (1H, br, OH), 5.27 (2H, s, O$\underline{C}H_2$Ar), 5.32—5.72 (1H, m, C_2-H), [7.54 (2H, d, J=8.7 Hz), 8.26 (2H, d, J=8.7 Hz), aromatic protons].

tert-Butyl 2-Hydroxypyrrolidine-1-carboxylate (**5d**): Colorless oil. MS *m/z*: 187 (M^+). IR (neat) cm^{-1}: 3448 (OH), 1706 (C=O). ^{1}H-NMR ($CDCl_3$) [400 MHz] δ: 1.47—1.55 (10H, m, *tert*-butyl protons, OH), 1.72—2.17 (4H, m, C_3-H_2, C_4-H_2), 3.14—3.36 (1H, m, C_5-Ha), 3.40—3.58 (1H, m, C_5-Hb), 5.25—5.57 (1H, m, C_2-H).

1-Benzoyl-2-hydroxypyrrolidine (**5e**) and 4-(benzoylamino)butanal (**11e**): Pale yellow oil was a mixture of **5e** and **11e** (80 : 20). MS *m/z*: 192 (MH^+). IR (neat) cm^{-1}: 3319 (OH, NH), 1722, 1639 (C=O). ^{1}H-NMR ($CDCl_3$) [60 MHz] δ: 1.64—2.41 (4.4H, m, OH, **5e** C_3-H, **5e** C_4-H, **11e** C_3-H), 2.41—2.78 (0.4H, m, **11e** C_2-H), 3.23—4.00 (2H, m, **5e** C_4-H, **11e** C_5-H), 5.03—5.96 (0.8H, m, **5e** C_2-H), 7.23—7.69 (5.2H, m, aromatic protons, NH), 9.79 (0.2H, s, CHO).

2,2,2-Trichloroethyl 1,2,3,4-Tetrahydropyridine-1-carboxylate (**12a**): Pale yellow oil. MS *m/z*: 258 ($[MH]^+$), 260 ($[MH+2]^+$), 262 ($[MH+4]^+$, 264 ($[MH+6]^+$). IR (neat) cm^{-1}: 1726, 1658 (C=O). ^{1}H-NMR ($CDCl_3$) [60 MHz] δ: 1.67—2.33 (4H, m, C_4-H_2, C_5-H_2), 3.17—3.88 (2H, br, C_6-H_2), 4.81 (2H, s, OCH_2CCl_3), 4.82—5.27 (1H, m, C_3-H), 6.87 (1H, d, J=8.4 Hz, C_2-H).

Benzyl 2-Hydroxypiperidine-1-carboxylate (**6b**): Pale yellow oil. MS *m/z*: 235 (M^+). IR (neat) cm^{-1}: 3460 (OH), 1706 (C=O). ^{1}H-NMR ($CDCl_3$) [60 MHz] δ: 1.10—2.23 (7H, m, C_3-H_2, C_4-H_2, C_5-H_2, OH), 2.70—3.47 (1H, m, C_6-Ha), 3.77—4.34 (1H, m, C_6-Hb), 4.72—5.28 (1H, br, C_2-H), 5.18 (2H, br s, O$\underline{C}H_2$-Ar), 7.37 (5H, brs, aromatic protons).

4-Nitrobenzyl 1,2,3,4-Tetrahydropyridine-1-carboxylate (**12c**): Colorless oil. MS *m/z*: 262 (M^+). IR (neat) cm^{-1}: 1709 (C=O). ^{1}H-NMR ($CDCl_3$) [60 MHz] δ: 1.5—2.28 (4H, m, C_4-H_2, C_5-H_2), 3.50—3.78 (2H, m, C_6-H_2), 4.72—5.16 (1H, m, C_3-H), 5.28 (2H, s, O$\underline{C}H_2$Ar), 6.82 (1H, d, J=8.5 Hz, C_2-H), [7.52 (2H, d, J=9.0 Hz), 8.22 (2H, d, J=9.0 Hz), aromatic protons].

Phosphonylation of *N*-Protected Cyclic 2-Hyroxyamines (5, 6) A solution of the *N*-protected cyclic 2-hyroxyamines (**5**, **6**) (10 mmol) in CH_2Cl_2 (60 ml) was treated with trialkyl phosphite (25 mmol) and TMSOTf (or other Lewis acid) (15 mmol) at 0 °C. After 15 min the solution was allowed to warm to room temperature and was stirred for a further 12 h. Water (5 ml) was added dropwise to the reaction mixture under ice-cooling. After the mixture was vigorously stirred for 30 min, it was added to AcOEt (150 ml) and saturated aqueous $NaHCO_3$ (100 ml), and the organic layer (upper layer) was separated. The aqueous layer was extracted with AcOEt (100 ml). The combined organic solution was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo.* The residue was treated on silica gel (AcOEt–hexane) [or alumina ($CHCl_3$–hexane)] by column chromatography to give the phosphonylated compounds (**7**, **8**).

2,2,2-Trichloroethyl 2-(Dimethoxyphosphoryl)pyrrolidine-1-carboxylate (**7aa**): Yield 87%, colorless oil. MS *m/z*: 353 (M^+), 355 (M^++2), 357 (M^++4), 359 (M^++6). IR (neat) cm^{-1}: 1724 (C=O). ^{1}H-NMR ($CDCl_3$) [90 MHz] δ: 1.70—2.67 (4H, m, C_3-H_2, C_4-H_2), 3.34—4.18 (2H, m, C_5-H_2), 3.78 (3H, d_P, J_{HP}=10.6 Hz, OCH_3), 3.81 (3H, d_P, J_{HP}=10.6 Hz, OCH_3), 4.21—4.52 (1H, br, C_2-H), 4.52—5.17 (2H, m, OCH_2CCl_3). ^{13}C-NMR ($CDCl_3$) [22.5 MHz] δ: 23.30 and 24.29 (t, C_3), 26.85 (t, C_4), 46.93 (t, C_5), [52.96 and 53.11 (qd_P, $^2J_{CP}$=6.7 Hz), 54.28 (qd_P, $^2J_{CP}$=6.0 Hz), OCH_3], 53.36 (dd_P, $^1J_{CP}$=161.8 Hz, C_2), 75.07 (t, O$\underline{C}H_2CCl_3$), 95.59 (s, CCl_3), 153.20 (s, C=O). HRMS *m/z* Calcd for $C_9H_{15}NO_5Cl_3P$: 352.9754 (M^+). Found: 352.9761. Calcd for $C_7H_9NO_2Cl_3$: 243.9699 ($M^+-PO(OCH_3)_2$). Found: 243.9707. Calcd for $C_7H_{13}NO_4P$: 206.0582 ($M^+-OCH_2CCl_3$). Found: 206.0569.

Benzyl 2-(Dimethoxyphosphoryl)pyrrolidine-1-carboxylate (**7ba**): Yield 67%, colorless oil. MS *m/z*: 313 (M^+). IR (neat) cm^{-1}: 1710 (C=O). ^{1}H-NMR ($CDCl_3$) [60 MHz] δ: 1.59—2.56 (4H, m, C_3-H_2, C_4-H_2), 3.26—3.73 (2H, m, C_5-H_2), 3.71 (6H, d_P, J_{HP}=10.7 Hz, 2×OCH_3), 4.14—4.49 (1H, m, C_2-H), 5.17 (2H, s, O$\underline{C}H_2$Ar), 7.37 (5H, br s, aromatic protons).

4-Nitrobenzyl 2-(Dimethoxyphosphoryl)pyrrolidine-1-carboxylate (**7ca**): Yield 65%, colorless oil. MS *m/z*: 358 (M^+). IR (neat) cm^{-1}: 1708 (C=O). ^{1}H-NMR ($CDCl_3$) [400 MHz] δ: 1.80—2.39 (4H, m, C_3-H_2, C_4-H_2), 3.30—3.70 (2H, m, C_5-H_2), 3.76 (3H, d_P, J_{HP}=10.6 Hz, OCH_3), 3.80 (3H, d_P, J_{HP}=10.6 Hz, OCH_3), 4.30—4.34 (1H, m, C_2-H), 5.26 (2H, s, O$\underline{C}H_2$Ar), [7.58 (2H, d, J=9.0 Hz), 8.22 (2H, d, J=9.0 Hz), aromatic protons]. ^{13}C-NMR ($CDCl_3$) [100 MHz] δ: 23.42 and 24.44 (t, C_3), 26.82 and 27.75 (t, C_4), 46.84 and 47.15 (t, C_5), 53.36 (dd_P, $^1J_{CP}$=163.3 Hz, C_2), 52.96 (qd_P, $^2J_{CP}$=9.2 Hz, OCH_3), 53.05 (qd_P, $^2J_{CP}$=9.1 Hz, OCH_3), 65.79 (t, O$\underline{C}H_2$Ar), [123.74 (d), 128.08 (d), 144.03 (s), 147.60 (s), aromatic carbons], 154.57 (s, C=O).

2,2,2-Trichloroethyl 2-(Diethoxyphosphoryl)pyrrolidine-1-carboxylate (**7ab**): Yield 71%, colorless oil. MS *m/z*: 381 (M^+), 383 (M^++2), 385 (M^++4), 387 (M^++6). IR (neat) cm^{-1}: 1724 (C=O). ^{1}H-NMR ($CDCl_3$) [400 MHz] δ: 1.32 (3H, t, J=7.3 Hz, $OCH_2C\underline{H}_3$), 1.34 (3H, t, J=7.0 Hz,

$OCH_2C\underline{H}_3$), 1.90—2.40 (4H, m, C_3-H_2, C_4-H_2), 3.45—3.71 (2H, m, C_5-H_2), 4.04—4.27 (4H, m, 2×$OC\underline{H}_2CH_3$), 4.27—4.43 (1H, br, C_2-H), [4.51 (0.3H, d, J=11.0 Hz), 4.70 (0.7H, d, J=11.7 Hz), $OCHaCCl_3$], [4.82 (0.7H, d, J=12.1 Hz), 5.07 (0.3H, d, J=11.7 Hz), $OCHbCCl_3$]. ^{13}C-NMR ($CDCl_3$) [100 MHz] δ: 16.47 (q, $OCH_2\underline{C}H_3$), 23.30 and 24.29 (t, C_3), 26.81 and 27.50 (t, C_4), 46.89 and 47.13 (t, C_5), 53.91 (dd_P, $^1J_{CP}$=163.3 Hz, C_2), [62.39 (td_P, $^2J_{CP}$=6.1 Hz), 62.52 (td_P, $^2J_{CP}$=7.6 Hz), $O\underline{C}H_2CH_3$], 75.09 (t, $O\underline{C}H_2CCl_3$), 95.61 (s, $OCH_2\underline{C}Cl_3$), 153.29 (s, C=O). HRMS *m/z* Calcd for $C_{11}H_{19}NO_5Cl_3P$: 381.0067 (M^+). Found: 381.0076. Calcd for $C_7H_9NO_2Cl_3$: 243.9699 ($M^+-PO(OC_2H_5)_2$). Found: 243.9705. Calcd for $C_9H_{17}NO_4P$: 234.0895 ($M^+-OCH_2CCl_3$). Found: 234.0897.

2,2,2-Trichloroethyl 2-(Diisopropoxyphosphoryl)pyrrolidine-1-carboxylate (**7ac**): Yield 55%, colorless oil. MS *m/z*: 409 (M^+), 411 (M^++2), 413 (M^++4), 415 (M^++6). IR (neat) cm^{-1}: 1728 (C=O). ^{1}H-NMR ($CDCl_3$) [400 MHz] δ: 1.21—1.39 (12H, m, 2×$OCH(C\underline{H}_3)_2$), [1.88—2.00 (1H, m), 2.00—2.20 (1H, m), 2.20—2.37 (2H, m), C_3-H_2, C_4-H_2], 3.47—3.77 (2H, m, C_5-H_2), 4.23—4.35 (1H, m, C_2-H), 4.63—4.80 (2H, m, $OC\underline{H}(CH_3)_2$), [4.33 (0.3H, d, J=11.4 Hz), 4.67 (0.7H, d, J=11.7 Hz), $OCHaCCl_3$], [4.84 (0.7H, d, J=11.7 Hz), 5.12 (0.3H, d, J=11.4 Hz), $OCHbCCl_3$]. ^{13}C-NMR ($CDCl_3$) [100 MHz] δ: 23.82 and 23.95 (t, C_3), 24.14 and 24.17 (qd_P, $^3J_{CP}$=7.7 Hz, $OCH(\underline{C}H_3)_2$), 26.82 and 27.41 (t, C_4), 46.84 and 46.98 (t, C_5), 54.80 (dd_P, $^1J_{CP}$=163.2 Hz, C_2), 71.11 and 71.24 (dd_P, $^2J_{CP}$=7.6 Hz, $O\underline{C}H(CH_3)_2$), 75.09 (t, $O\underline{C}H_2CCl_3$), 95.63 (s, CCl_3), 153.26 (s, C=O). HRMS *m/z* Calcd for $C_{13}H_{23}NO_5Cl_3P$: 409.0380 (M^+). Found: 409.0380. Calcd for $C_7H_9NO_2Cl_3$: 243.9699 (M^+-PO(O-isopropyl)$_2$). Found: 243.9704.

2,2,2-Trichloroethyl 2-(Dimethoxyphosphoryl)piperidine-1-carboxylate (**8aa**): Yield 46%, colorless oil. MS *m/z*: 367 (M^+), 369 (M^++2), 371 (M^++4), 373 (M^++6). IR (neat) cm^{-1}: 1720 (C=O). ^{1}H-NMR ($CDCl_3$) [60 MHz] δ: 1.14—2.47 (6H, m, C_3-H_2, C_4-H_2, C_5-H_2), 3.00—3.60 (1H, m, C_6-Ha), 3.79 (6H, d_P, J_{HP}=10.8 Hz, 2×OCH_3), 3.98—4.44 (1H, m, C_6-Hb), 4.44—5.00 (1H, m, C_2-H), 4.80 (2H, s, OCH_2CCl_3). ^{13}C-NMR ($CDCl_3$) [22.5 MHz] δ: 20.05 and 20.11 (t, C_3), [24.55 (t), 25.06 (t), C_4, C_5], 41.98 (t, C_6), 48.07 (dd_P, $^1J_{CP}$=154.4 Hz, C_2), [52.78 (qd_P, $^2J_{CP}$=6.7 Hz), 52.88 (qd_P, $^2J_{CP}$=7.4 Hz), OCH_3], 75.33 (t, $O\underline{C}H_2CCl_3$), 95.53 (s, $\underline{C}Cl_3$), 150.68 (s, C=O). HRMS *m/z* Calcd for $C_{10}H_{17}NO_5Cl_3P$: 366.9910 (M^+). Found: 366.9898. Calcd for $C_8H_{11}NO_2Cl_3$: 257.9855 ($M^+-PO(OCH_3)2$). Found: 257.9865.

Benzyl 2-(Dimethoxyphosphoryl)piperidine-1-carboxylate (**8ba**): Yield 60%, colorless oil. MS *m/z*: 327 (M^+). IR (neat) cm^{-1}: 1704 (C=O). ^{1}H-NMR ($CDCl_3$) [60 MHz] δ: 1.10—2.27 (6H, m, C_3-H_2, C_4-H_2, C_5-H_2), 2.97—3.52 (1H, m, C_6-Ha), 3.69 (3H, d_P, J_{HP}=10.8 Hz, OCH_3), 3.71 (3H, d_P, J_{HP}=10.8 Hz, OCH_3), 3.93—4.38 (1H, m, C_6-Hb), 4.43—5.00 (1H, m, C_2-H), 5.18 (2H, s, $OC\underline{H}_2Ar$), 7.39 (5H, s, aromatic protons).

2,2,2-Trichloroethyl 2-(Diethoxyphosphoryl)piperidine-1-carboxylate (**8ab**): Yield 66%, colorless oil. MS *m/z*: 395 (M^+), 397 (M^++2), 399 (M^++4), 401 (M^++6). IR (neat) cm^{-1}: 1722 (C=O). ^{1}H-NMR ($CDCl_3$) [90 MHz] δ: 0.92—2.40 (6H, m, C_3-H_2, C_4-H_2, C_5-H_2), 1.32 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 1.33 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 3.07—3.73 (1H, m, C_6-Ha), 3.73—4.47 (5H, m, 2×$OC\underline{H}_2CH_3$, C_6-Hb), 4.47—4.65 (1H, br, C_2-H), 4.65—4.95 (2H, br, $OC\underline{H}_2CCl_3$). ^{13}C-NMR ($CDCl_3$) [22.5 MHz] δ: [16.48 (qd_P, $^3J_{CP}$=6.0 Hz), 16.59 (qd_P, $^3J_{CP}$=5.4 Hz), $OCH_2\underline{C}H_3$], 20.08 and 20.14 (t, C_3), [24.61 (t), 25.18 (t), C_4, C_5], 42.04 (t, C_6), 48.45 (dd_P, $^1J_{CP}$=154.4 Hz, C_2), [62.16 (td_P, $^2J_{CP}$=7.4 Hz), 62.37 (td_P, $^2J_{CP}$=7.4 Hz), $O\underline{C}H_2CH_3$], 75.39 (t, $O\underline{C}H_2CCl_3$), 95.56 (s, CCl_3), 153.80 (s, C=O). HRMS *m/z* Calcd for $C_{12}H_{21}NO_5Cl_3P$: 395.0223 (M^+). Found: 395.0216. Calcd for $C_8H_{11}NO_2Cl_3$: 257.9855 ($M^+-PO(OC_2H_5)_2$). Found: 257.9843.

2,2,2-Trichloroethyl 2-(Diisopropoxyphosphoryl)piperidine-1-carboxylate (**8ac**): Yield 52%, colorless oil. MS *m/z*: 423 (M^+), 425 (M^++2), 427 (M^++4), 429 (M^++6). IR (neat) cm^{-1}: 1722 (C=O). ^{1}H-NMR ($CDCl_3$) [400 MHz] δ: [1.29 (3H, d, J=5.9 Hz), 1.33 (9H, d, J=6.2 Hz), $OCH(C\underline{H}_3)_2$], [1.37—1.53 (1H, m), 1.60—1.89 (3H, m), 1.91—2.20 (2H, m), C_3-H_2, C_4-H_2, C_5-H_2], [3.32 (0.4H, t, J=13.2 Hz), 3.45 (0.6H, t, J=12.8 Hz), C_6-Ha], 4.16 (1H, t, J=13.2 Hz, C_6-Hb), 4.47—5.03 (5H, m, C_2-H, 2×$OC\underline{H}(CH_3)_2$, OCH_2CCl_3). ^{13}C-NMR ($CDCl_3$) [100 MHz] δ: 20.08 (t, C_3), [24.04 (qd_P, $^3J_{CP}$=12.2 Hz), 24.18 (qd_P, $^3J_{CP}$=15.3 Hz), 24.20 (qd_P, $^3J_{CP}$=18.3 Hz), 24.71 (qd_P, $^3J_{CP}$=24.4 Hz), $OCH(\underline{C}H_3)_2$], [25.06 (t), 25.38 (t), C_4, C_5], 42.03 (t, C_6), [49.19 (dd_P, $^1J_{CP}$=157.2 Hz), 49.45 (dd_P, $^1J_{CP}$=154.1 Hz), C_2], [71.09 (dd_P, $^2J_{CP}$=7.1 Hz), 72.01 (dd_P, $^2J_{CP}$=6.1 Hz), $O\underline{C}H(CH_3)_2$], 75.44 (t, $O\underline{C}H_2CCl_3$), 95.54 (s, CCl_3), [153.55 (s), 153.79 (s), C=O]. HRMS *m/z* Calcd for $C_{14}H_{25}NO_5Cl_3P$: 423.0536 (M^+). Found: 423.0528. Calcd for $C_8H_{11}NO_2Cl_3$: 257.9855 (M^+-PO(O-isopropyl)$_2$). Found: 257.9863.

Transformation of Dimethyl *N*-Z-α-Aminophosphonates (7ba, 8ba) to Dimethyl *N*-Boc-α-Aminophosphonates (7da, 8da) A solution of dimethyl *N*-Z-α-aminophosphonate (**7ba**, **8ba**) (12 mmol), Boc_2O (15 mmol), and 10% Pd-C (300 mg), under a hydrogen atmosphere (1 atm) in MeOH (100 ml) was stirred at room temperature for 20 h. The reaction mixture was filtered off and concentrated under reduced pressure to leave a colorless oil, which was separated by column chromatography (SiO_2, 3% MeOH–$CHCl_3$) to give the *N*-Boc analog (**7da**, **8da**).

tert-Butyl 2-(Dimethoxyphosphoryl)pyrrolidine-1-carboxylate (**7da**): Yield 97%, colorless oil. MS *m/z*: 279 (M^+). IR (neat) cm^{-1}: 1700 (C=O). ^{1}H-NMR ($CDCl_3$) [60 MHz] δ: 1.49 (9H, s, *tert*-butyl protons), 1.63—2.80 (4H, m, C_3-H_2, C_4-H_2), 3.30—3.60 (2H, m, C_5-H_2), 3.80 (6H, d_P, J_{HP}=10.5 Hz, 2×OCH_3), 4.11—4.43 (1H, m, C_2-H).

tert-Butyl 2-(Dimethoxyphosphoryl)piperidine-1-carboxylate (**8da**): Yield 74%, colorless oil. MS *m/z*: 293 (M^+). IR (neat) cm^{-1}: 1696 (C=O). ^{1}H-NMR ($CDCl_3$) [60 MHz] δ: 1.49 (9H, s, *tert*-butyl protons), 1.50—2.23 (6H, m, C_3-H_2, C_4-H_2, C_5-H_2), 2.85—3.47 (1H, m, C_6-Ha), 3.78 (6H, d_P, J_{HP}=10.7 Hz, 2×OCH_3), 3.70—4.28 (1H, m, C_6-Hb), 4.40—4.97 (1H, m, C_2-H).

Deprotection of *N*-Protected Derivatives (7, 8) Deprotection of *N*-protected derivatives (**7**, **8**) was achieved as follows.

Deprotection of *N*-Troc Derivatives (**7aa**, **8aa**): Activated zinc powder (1.0 g) was added to a solution of *N*-Troc compound (**5aa**, **6aa**) (2 mmol) in acetic acid (12 ml). The suspension was stirred at room temperature for 3 d and then filtered. The zinc powder was washed with a little acetic acid. The filtrate and the washings were combined and concentrated *in vacuo.* The residue was used for the next step.

Deprotection of *N*-Z Derivatives (**7ba**, **8ba**): A solution of *N*-Z compound (**7ba**, **8ba**) (2 mmol) and 10% Pd-C (30 mg), under hydrogen atmosphere (1 atm) in MeOH–2 N HCl (5 ml—5 ml) was stirred at room temperature for 20 h. The reaction mixture was filtered off and concentrated under reduced pressure to leave a colorless oil of residue, which was used for the next step.

Deprotection of *N*-Boc Derivatives (**7da**, **8da**): Deprotection of *N*-Boc compound (**5da**, **6da**) (2 mmol) was done simultaneously with ester cleavage by acid hydrolysis as described below.

Hydrolysis of Esters and Preparation of Salt-free Cyclic α-Aminophosphonic Acids (9, 10) A solution of the above residue in 6 N HCl (4 ml) was refluxed in an oil bath for 12 h. The reaction solution was concentrated under reduced pressure. The residue from 5-membered cyclic amine derivatives was dissolved in a small amount of H_2O. The aqueous solution was applied to a column of Dowex 50W×4 (50—100 mesh, H^+ form), and eluted with H_2O. Concentration of the eluate to dryness afforded the crude salt-free product as a white solid. Recrystallization of the solid form H_2O gave the pure sample (**9**). The residue from 6-membered cyclic compounds was dissolved in a small amount of EtOH, and treated with propylene oxide (1 ml). Concentration of the treated solution to dryness afforded the crude salt-free amino phosphonic acid as a white solid. Recrystallization of the solid form ether–MeOH gave the pure sample (**10**). Total yields from *N*-protected derivatives (**7**, **8**) are summarized in Table 3.

Pyrrolidine-2-phosphonic Acid (**9**)[18]: Colorless prisms, mp 264—265 °C (H_2O) (lit.[18a] mp 266—267 °C). MS (FAB) *m/z*: 152 (MH^+). IR (KBr) cm^{-1}: 3408 (OH), 2962 (NH), 1136 (P=O), 1068 (P–O). ^{1}H-NMR (D_2O) [400 MHz] δ: [1.88—2.16 (3H, m), 2.16—2.32 (1H, m), C_3-H_2, C_4-H_2], 3.22—3.38 (2H, m, C_5-H_2), 3.52 (1H, dd_P, J=18.8 Hz, J_{HP}=9.3 Hz, C_2-H). ^{13}C-NMR (D_2O) [100 MHz] δ: [24.80 (td_P, $^2J_{CP}$=8.8 Hz, C_3), 27.23 (t), C_4], 47.67 (td_P, $^3J_{CP}$=5.9 Hz, C_5), 56.64 (dd_P, $^1J_{CP}$=143.8 Hz, C_2). *Anal.* Calcd for $C_4H_{10}NO_3P$: C, 31.80; H, 6.67; N, 9.27. Found: C, 31.99; H, 6.41; N, 9.20.

Piperidine-2-phosphonic Acid (**10**)[19]: Colorless needles, mp 268—270 °C (ether–MeOH) (lit.[19a] mp 269—271 °C). IR (KBr) cm^{-1}: 3425 (OH), 2958 (NH), 1130 (P=O), 1076 (P–O). ^{1}H-NMR (D_2O) [400 MHz] δ: [1.48—1.56 (1H, m), 1.56—1.78 (2H, m), 1.78—1.99 (2H, m), 1.99—2.50 (1H, m), C_3-H_2, C_4-H_2, C_5-H_2], [2.90—3.05, (1H, m), 3.05—3.20 (1H, m), C_6-H_2], 3.39 (1H, d_{HP}, J_{HP}=12.5 Hz, C_2-H). ^{13}C-NMR (D_2O) [100 MHz] δ: [22.47 (t), 22.62 (t), 22.81 (t), C_3, C_4, C_5], 46.61 (td_P, $^3J_{CP}$=7.6 Hz, C_6), 55.28 (dd_P, $^1J_{CP}$=141.9 Hz, C_2). *Anal.* Calcd for $C_5H_{12}NO_3P$: C, 36.37; H, 7.32; N, 8.48. Found: C, 36.38; H, 6.96; N, 8.50.

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