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RUTHENIUM TETROXIDE OXIDATION OF *N*-ACYL CYCLIC AMINE-2-PHOSPHONIC ACID DIESTERS

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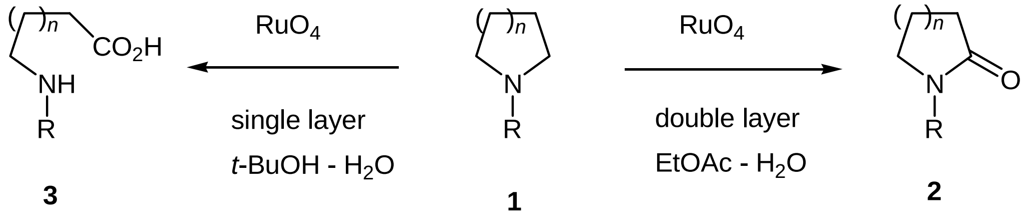
Abstract - The utility of the ruthenium tetroxide (RuO_4) oxidation of *N*-acyl cyclic amine-2-phosphonic acid esters was investigated. The oxidation of the *N*-protected cyclic amines (**4**, **5**) having a phosphono diester group under the standard double layer condition of ethyl acetate-water using a catalytic amount of RuO_2 and excess $NaIO_4$ produce the corresponding lactams in good yields. The obtained lactam phosphono diesters (**6**, **7**) were readily converted into the ω-amino-ω-phosphonocarboxylic acids (**10**, **11**).

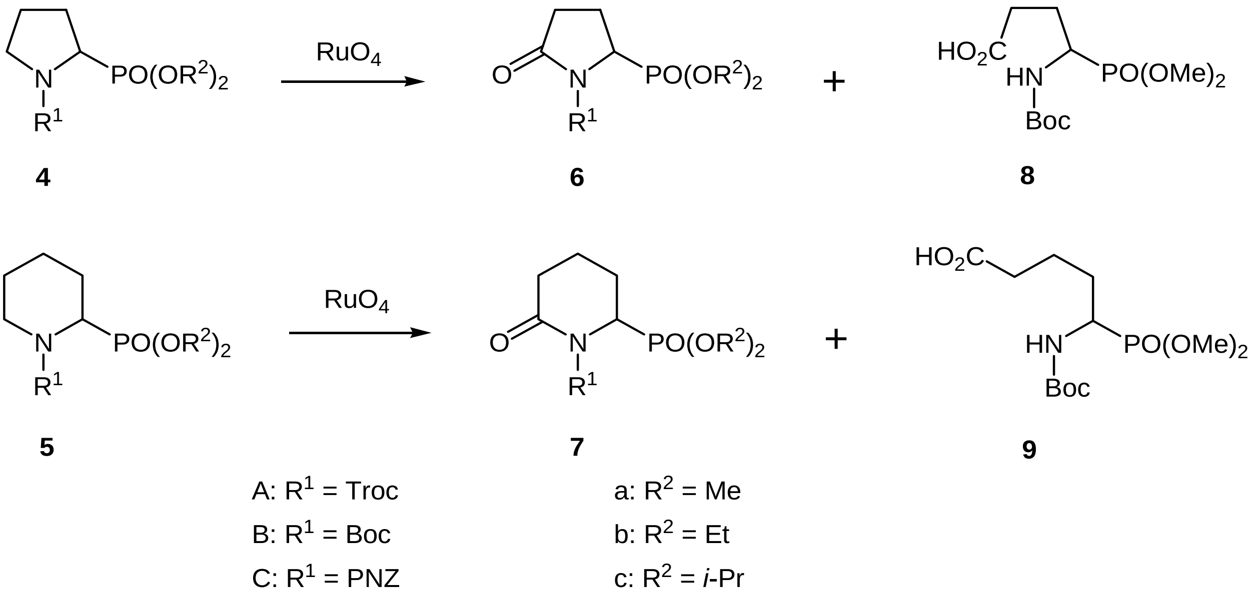
α-Aminophosphonic acids, 'phosphorous analogues' of naturally occurring α-amino acids, in which the carboxylic acid group is replaced by a phosphonic acid group, have attracted attention[1] because they have potent activity with a wide range of biological activities[2,3] as antibiotics, enzyme, inhibitors,[3] pharmacological agents,[4] antiviral agents,[5] and herbicides.[6] Thus, the chemistry of the α-aminophosphonic acids has been reviewed and a large number of compounds have been prepared.[1,7] In spite of the impressive development of the acyclic α-aminophosphonic acids, only a small effort regarding the synthesis of the cyclic amine-2-phosphonic acids containing a pyrrolidine- or piperidine-ring, have been made to date. We have been deeply interested in the chemistry (synthesis,



Scheme 1

structure and physical properties and reactions) of amino acids, especially the chemical conversions of the amino acids[8] and related compounds including the natural products[9] by the RuO_4 oxidation under the standard double layer condition of ethyl acetate-water in recent years. We previously described the facile chemical conversion of cyclic α-amino acids to cyclic α-aminophosphonic acids.[10] In addition, we focused on the formation of ω-amino acids from cyclic *N*-acylamines by the RuO_4 oxidation in a miscible aqueous solution containing *tert*-butanol (the so-called "single layer method") (Scheme 1).[11] As part of our continuing studies, this report deals with the practical synthetic route for the five- and six-membered lactamphosphonic acids from the corresponding cyclic amine-2-phosphonic acids by the RuO_4 oxidation, and the conversion of the obtained phosphonic acid diesters into the corresponding free ω-amino-ω-phosphonocarboxylic acids by acidic hydrolysis.

The RuO_4 oxidation of the pyrrolidine phosphono dimethyl ester (**4Aa**) protected on the nitrogen atom with a trichloroethoxycarbonyl (Troc) group was carried out at room temperature according to our standard method using a catalytic amount of RuO_2 hydrate and an excess of 10% $NaIO_4$ in a double layer system of ethyl acetate-water. The reaction smoothly proceeded under the stated conditions and the desired lactam (**6Aa**) was produced in 78% yield as the sole product (Table 1, entry 1). The results obtained using the *N*-protected and ethyl and isopropyl diester substrates are also summarized in Table 1. The phosphono diethyl (**4Ab**) and diisopropyl esters (**4Ac**) were similarly oxidized at only the C-5 position to afford the corresponding lactams (**6Ab**, **6Ac**) in 56 and 67% yields, respectively (entries 2, 3). When the *N*-*tert*-butoxycarbonyl (Boc) phosphono dimethyl ester (**4Ba**) was oxidized under the same conditions, the reaction was completed within 5 h, and the corresponding lactam (**6Ba**) and the ring opening aminocarboxylic acid (**8**) were formed in 53 and 19% yields, respectively (entry 4). In the case of the similar oxidation of the *N*-(*p*-nitrobenzyl)oxycarbonyl (PNZ) phosphono dimethyl ester (**4Ca**), the corresponding product (**6Ca**) was obtained in 46% yield (entry 5). This oxidation was also successfully



Scheme 2

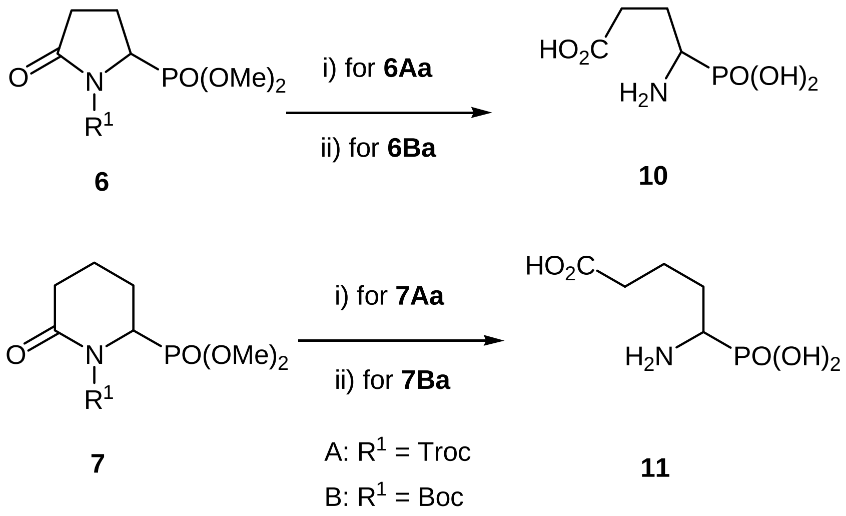
Table 1. RuO_4 Oxidation of *N*-Protected Cyclic Amine Phosphonic Acid Diesters

Entry	Comp.	*n*	R^1	R^2	$RuO_2 \cdot xH_2O$ (g)	Time (h)	Product Yield (%)	Recovery Yield (%)
1	**4Aa**	1	Troc	Me	0.12	54	**6Aa** (78)	-
2	**4Ab**	1	Troc	Et	0.12	47	**6Ab** (56)	-
3	**4Ac**	1	Troc	*i*-Pr	0.12	50	**6Ac** (67)	-
4	**4Ba**	1	Boc	Me	0.12	5	**6Ba** (53) **8** (19)	-
5	**4Ca**	1	PNZ	Me	0.12	46	**6Ca** (46)	-
6	**5Aa**	2	Troc	Me	0.12	336	**7Aa** (49)	31
7	**5Aa**	2	Troc	Me	1.20	96	**7Aa** (67)	-
8	**5Ab**	2	Troc	Et	1.20	65	**7Ab** (76)	-
9	**5Ac**	2	Troc	*i*-Pr	1.20	85	**7Ac** (82)	-
10	**5Ba**	2	Boc	Me	0.12	20	**7Ba** (40) **9** (11)	-

applied to the construction of the six-membered lactam phosphono diester framework. A similar treatment of the *N*-Troc piperidine phosphono dimethyl esters (**5Aa**) with RuO_4 using the double layer system resulted in the carbonylation at the C-6 position to give the piperidinone derivative (**7Aa**) in 49% yield. In spite of the long reaction time, such as 14 days, the starting material (**5Aa**) was recovered in 31% yield (entry 6). However, the use of 10 times excess of the catalyst (RuO_2 hydrate) increased the efficiency to 67% yield without recovery of the starting material (entry 7). Both the diethyl (**5Ab**) and diisopropyl ester

(**5Ac**) also produced **7Ab** and **7Ac** under these conditions in good yields (entries 8, 9). In the case of the oxidation of the *N*-Boc piperidine phosphono diesters (**5Ba**), the ring opening product (**9**) was also obtained in 11% yield together with the desired piperidinones (**7Ba**, 40% yield) (entry 10). Both the five- and six-membered cyclic *N*-Boc amine phosphono diesters (**4Ba, 5Ba**) were oxidized to give the corresponding lactams (**6Ba**, **7Ba**) and the ring opening carboxylic acids (**8**, **9**). The treatment of the isolated lactams (**6Ba**, **7Ba**) under these oxidation conditions never produced the aminocarboxylic acids (**8**, **9**). This suggests that **8** and **9** are not the hydrolysis products of the lactams. The mechanism for the formation of the aminocarboxylic acids (**8**, **9**) in this RuO_4 oxidation reaction of the cyclic *N*-Boc amines have been described in a previous report.[11]

Next, the transformations from the lactam phosphonates (**6**, **7**) to the *ω*-phosphono carboxylic acids (**10**, **11**) were carried out. The deprotection of the *N*-Troc phosphonates (**6Aa**, **7Aa**) with zinc dust in acetic acid at room temperature, followed by the hydrolysis with refluxing 6N HCl produced the corresponding *ω*-amino-*ω*-phosphonocarboxylic acids (**10**, **11**) in 87 and 76% yields, respectively. When the *N*-Boc derivatives (**6Ba**, **7Ba**) were treated with 6N HCl, both reactions involving the deprotection and acidic hydrolysis proceeded to directly give the desired acids **10** and **11** in good yields.



Reagents and Conditions: i, 1) Zn dust, AcOH, room temp., 3 days, 2) 6N HCl, reflux, 12 h.
ii, 6N HCl, reflux, 12 h.

Scheme 3

In summary, we conclude that the RuO_4 oxidation is useful for oxidizing *N*-protected cyclic amine phosphono dimethyl esters by introducing the imide carbonyl function, and the conversion of the obtained phosphonic acid diesters into the corresponding free ω-amino-ω-phosphonocarboxylic acids. Further investigation of the chemical conversion of the amino acids using the RuO_4 oxidation as the key reaction is now in progress.

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro melting point hot stage apparatus and are uncorrected. IR spectra were determined with a Horiba FT-720 spectrometer. Mass spectra (MS) and HRMS were recorded on a JEOL JMS-DX300 instrument. NMR spectra were determined with a JEOL EX-90A (90 MHz) or a JEOL JNM-GSX 400 (400 MHz) spectrometer in $CDCl_3$ using tetramethylsilane or 1,4-dioxane (H, δ 3.70 ppm, C, δ 67.40 ppm) as internal standard. Microanalyses were performed in the Microanalytical Laboratory in this Faculty.

Starting Cyclic Amine-2-phosphonic Acid Esters

N-Protected cyclic amine-2-phosphonic acid esters (**4**, **5**) were prepared by the reported methods.[10]

General Procedure for the RuO_4 Oxidation of *N*-Protected Cyclic Amine-2-phosphonic Acid Esters

A solution of a substrate (**4** or **5**, 12 mmol) to be oxidized in EtOAc (40 mL) was added to a mixture of $RuO_2 \cdot x$hydrate (120 mg) and 10% aqueous $NaIO_4$ (120 mL). The reaction mixture was vigorously stirred in a sealed flask at room temperature until disappearance of the starting materials. The layers were separated, and the aqueous layer was extracted with EtOAc (40 mL x 3). The combined organic layer was stirred with 2-propanol (2 mL) to decompose the RuO_4 for 2-3 h and filtered off. The filtrate was washed with brine (40 mL x 2) and dried over anhydrous Na_2SO_4. The organic solvent was evaporated in vacuo to leave a residue, which was purified by silica gel chromatography using EtOAc -hexane (3:1) as an eluent to give **6** or **7**. Compounds **8** and **9** were obtained from the later part of $CHCl_3$-MeOH (10:1) as an eluent.

2,2,2-Trichloroethyl 2-Dimethylphosphono-5-oxopyrrolidine-1-carboxylate (6Aa)

Colorless oil. IR (neat) 1806, 1768, 1738 cm^{-1} (C=O). EI-MS *m/z*: 368, 370, 372, 374 (MH^+). ^{1}H-NMR δ: 1.80-3.20 (4H, m, 3- and 4-H_2), 3.80 and 3.83 (each 3H, d_p, $^3J_{HP}$ = 10.6 Hz, Me x 2), 4.17-4.97 (1H, m, 2-H), 4.81 and 5.02 (each 1H, d, J = 11.9 Hz, $COOCH_2$). ^{13}C-NMR δ: 20.53 (t), 31.45 (t), 52.67 (dd_p, $^1J_{cp}$ = 160.5 Hz), 53.24 (qd_p, $^2J_{cp}$ = 7.4 Hz), 53.64 (qd_p, $^2J_{cp}$ = 6.7 Hz), 75.42 (t), 94.31 (s), 149.56 (s), 172.60 (s). EI-HR-MS *m/z*: 367.9621 (Calcd for $C_9H_{14}NO_6P$: 367.9625).

2,2,2-Trichloroethyl 2-Diethylphosphono-5-oxopyrrolidine-1-carboxylate (6Ab)

Colorless oil. IR (neat) 1806, 1768, 1740 cm^{-1} (C=O). EI-MS *m/z*: 396, 398, 400, 402 (MH^+). ^{1}H-NMR δ: 1.34 (6H, t, *J* = 7.0 Hz, -CH_2*CH_3* x 2), 2.32-2.56 and 2.84-2.94 (3H, m and 1H, m, 3- and 4-H_2), 4.13-4.24 (4H, m, -*CH_2*CH_3 x 2), 4.58-4.61 (1H, m, 2-H), 4.79 and 5.01 (each 1H, d, *J* = 12.0 Hz, -$COOCH_2$). ^{13}C-NMR δ: 16.46 (qd_p, $^3J_{CP}$ = 4.6 Hz), 20.60 (t), 31.59 (t), 53.21 (dd_p, $^1J_{cp}$ = 160.2 Hz), 62.93 (td_p, $^2J_{cp}$ = 7.6 Hz), 63.18 (td_p, $^2J_{cp}$ = 6.1 Hz), 75.50 (t), 94.31 (s), 149.65 (s), 172.75 (s). EI-HR-MS *m/z*: 395.9949 (Calcd for $C_{11}H_{18}NO_6Cl_3P$: 395.9938).

2,2,2-Trichloroethyl 2-Diisopropylphosphono-5-oxopyrrolidine-1-carboxylate (6Ac)

Colorless oil. IR (neat) 1808, 1768, 1740 cm^{-1} (C=O). EI-MS *m/z*: 424, 426, 428, 430 (MH^+). ^{1}H-NMR δ: -OCH(*CH_3*)$_2$ x 2 [1.33 (6H, d, *J* = 6.2 Hz), 1.34 (3H, d, *J* = 5.9 Hz), 1.35 (3H, d, *J* = 5.9 Hz)], 2.25-2.57 and 2.83-2.97 (3H, m and 1H, m, 3- and 4-H_2), 4.50-4.59 (1H, m, 2-H), 4.70-4.77 (2H, m, -C*H*(CH_3)$_2$ x 2), 4.76 and 5.03 (each 1H, d, *J* = 11.7 Hz, -$COOCH_2$). ^{13}C-NMR δ: 20.63 (td_p, $^2J_{cp}$ = 2.0 Hz), 23.91 and 24.00 (each qd_p, $^3J_{cp}$ = 4.7 Hz), 24.08 (qd_p, $^3J_{cp}$ = 5.4 Hz), 31.60 (t), 53.97 (dd_p, $^1J_{cp}$ = 162.5 Hz), 71.98 (dd_p, $^2J_{cp}$ = 7.4 Hz), 72.13 (dd_p, $^2J_{cp}$ = 7.4 Hz), 75.42 (t), 94.37 (s), 149.41 (s), 173.01 (s). EI-HR-MS *m/z*: 424.0258 (Calcd for $C_{13}H_{22}NO_6Cl_3P$: 424.0251).

2,2,2-Trichloroethyl 2-Dimethylphosphono-6-oxopiperidine-1-carboxylate (7Aa)

Colorless oil. IR (neat) 1790, 1732 cm^{-1} (C=O). EI-MS *m/z*: 381, 383, 385, 387 (M^+). ^{1}H-NMR δ: 1.85-1.91, 2.04-2.30, 2.34-2.39, 2.51-2.60 and 2.71-2.78 (1H, m, 2H, m, 1H, m, 1H, m, 1H, m, 3- 4- and 5-H_2), 3.78 and 3.81 (each 3H, d_p, $^3J_{HP}$ = 10.6 Hz, Me x 2), 4.86-5.00 (1H, m, 2-H), 4.85 and 4.95 (each 1H, d, *J* = 12.1 Hz, $COOCH_2$). ^{13}C-NMR δ: 18.90 (t), 23.19 (t), 34.29 (t), 51.34 (dd_p, $^1J_{cp}$ = 155.6 Hz), 53.15 (qd_p, $^2J_{cp}$ = 7.6 Hz), 53.46 (qd_p, $^2J_{cp}$ = 6.1 Hz), 76.05 (t), 94.35 (s), 152.38 (s), 170.54 (s). EI-HR-MS *m/z*: 380.9698 (Calcd for $C_{10}H_{15}NO_6Cl_3P$: 380.9703).

2,2,2-Trichloroethyl 2-Diethylphosphono-6-oxopiperidine-1-carboxylate (7Ab)

Colorless oil. IR (neat) 1790, 1730 cm^{-1} (C=O). EI-MS *m/z*: 409, 411, 413, 415 (M^+). ^{1}H-NMR δ: 1.32 and 1.33 (each 3H, t, *J* = 7.1 and 7.5 Hz, -OCH_2*CH_3* x 2), 1.63-3.02 (6H, m, 3- 4- and 5-H_2), 3.94-4.38 (4H, m, O*CH_2*CH_3 x 2), 4.75-5.08 (1H, m, 2-H), 4.80 and 4.98 (each 1H, d, *J* = 11.9 Hz, $COOCH_2$). ^{13}C-NMR δ: 16.38 (qd_p, $^3J_{cp}$ = 5.4 Hz), 18.74 and 18.86 (t), 23.09 (t), 34.31 (t), 51.57 (dd_p, $^1J_{cp}$ = 156.5 Hz), 62.85 (td_p, $^2J_{cp}$ = 7.4 Hz), 62.95 (td_p, $^2J_{cp}$ = 6.7 Hz), 75.84 (t), 94.40 (s), 152.28 (s), 170.63 (s).

EI-HR-MS *m/z*: 409.0006 (Calcd for $C_{12}H_{19}NO_6Cl_3P$: 409.0016).

2,2,2-Trichloroethyl 2-Diisopropylphosphono-6-oxopiperidine-1-carboxylate (7Ac)

Colorless oil. IR (neat) 1790, 1730 cm^{-1} (C=O). EI-MS *m/z*: 437, 439, 441, 443 (M^+). ^{1}H-NMR δ: 1.31, 1.32, 1.34 and 1.35 (3H, d, J = 6.2 Hz, 3H, d, J = 6.2 Hz, 3H, d, J = 6.2 Hz, 3H, d, J = 5.9 Hz, -OCH(CH_3)$_2$ x 2), 1.78-1.90, 1.97-2.18, 2.23-2.24, 2.47-2.61, 2.71-2.83 (1H, m, 1H, m, 2H, m, 1H, m, 1H, m, 3- 4- and 5-H_2), 4.67-4.97 (3H, m, 2-H and -OCH(CH_3)$_2$ x 2), 4.82 and 4.93 (each 1H, d, J = 11.9 Hz, $COOCH_2$). ^{13}C-NMR δ: 18.66 (t), 23.06 (t), 23.85 (qd_p, ^3J_cp = 6.1 Hz), 24.01 (qd_p, ^3J_cp = 4.6 Hz, 24.17 (qd_p, ^3J_cp = 3.0 Hz), 34.34 (t), 52.18 (dd_p, ^1J_cp = 160.2 Hz), 72.00 (dd_p, ^2J_cp = 7.6 Hz), 76.02 (t), 94.40 (s), 152.17 (s), 170.81 (s). EI-HR-MS *m/z*: 437.0309 (Calcd for $C_{14}H_{23}NO_6Cl_3P$: 437.0329).

1-*tert*-Butyl 2-Dimethylphosphono-5-oxopyrrolidine-1-carboxylate (6Ba)

Colorless needles, mp 81-82 °C (from *i*-propyl ether). IR (KBr) 1744, 1720 cm^{-1} (C=O). EI-MS *m/z*: 293 (M^+). ^{1}H-NMR δ: 1.55 (9H, s, *t*-Bu), 2.23-2.50 and 2.76-2.88 (3H, m and 1H, m, 3- and 4-H_2), 3.79 and 3.81 (each 3H, d_p, ^3J_HP = 10.6 and 11.9 Hz, Me x 2), 4.51-4.75 (1H, m, 2-H). ^{13}C-NMR δ: 20.30 (t), 27.90 (q), 31.98 (t), 52.72 (dd_p, ^1J_CP = 160.3 Hz), 53.08 (qd_p, ^2J_CP = 6.7 Hz), 53.45 (qd_p, ^2J_CP = 5.8 Hz), 83.71 (s), 149.58 (s), 173.17 (s). *Anal*. Calcd for $C_{11}H_{20}NO_6P$: C, 45.05; H, 6.87; N, 4.78. Found: C, 44.90; H, 6.87; N, 4.71.

4-*tert*-Butoxycarbonylamino-4-(dimethylphosphono)butanoic acid (8)

Colorless oil. IR (neat) 3319, 2979 (NH, OH), 1712 cm^{-1} (C=O). EI-MS *m/z*: 311 (M^+). ^{1}H-NMR δ: 1.33-1.59 (9H, m, *t*-Bu), 1.81-1.99, 2.09-2.23 and 2.39-2.57 (1H, m, 1H, m, 2H, m, 2- and 3-H_2), 3.79 (6H, d_p, ^3J_HP = 10.6 Hz, Me x 2), 4.09-4.23 (1H, m, 4-H), 5.37 and 5.75 (0.2H and 0.8H, each d, J = 10.6 Hz, NH), 7.91-9.13 (1H, br, COOH). ^{13}C-NMR δ: 24.96 (td_P, ^2J_CP = 4.6 Hz), 28.26 (q), 30.31 (td_P, ^3J_CP = 13.7 Hz), 46.00 (dd_P, ^1J_CP = 157.2 Hz), 53.20 (qd_P, ^2J_CP = 7.7 Hz), 53.72 (qd_P, ^2J_CP = 6.1 Hz), 80.28 (s), 155.60 and 155.66 (each s), 176.26 (s). EI-HR-MS *m/z*: 311.1132 (Calcd for $C_{11}H_{22}NO_7P$: 311.1134).

1-*tert*-Butyl 2-Dimethylphosphono-6-oxopiperidine-1-carboxylate (7Ba)

Colorless needles, mp 102-103 °C (from *i*-propyl ether). IR (KBr) 1718 cm^{-1} (C=O). EI-MS *m/z*: 308 (MH^+). ^{1}H-NMR δ: 1.54 (9H, s, *t*-Bu), 1.77-1.86, 1.96-2.13, 2.15-2.25, 2.27-2.35, 2.44-2.52 and 2.66-2.73 (1H, m, 1H, m, 1H, m, 1H, m, 1H, m and 1H, m, 3-, 4- and 5-H_2), 3.77 and 3.79 (each 3H, d_p, ^3J_HP = 10.6 and 10.7 Hz, Me x 2), 4.83-4.89 (1H, m, 2-H). ^{13}C-NMR δ: 18.71 (t, ^2J_CP = 2.9 Hz), 23.08 (t), 27.92 (q), 34.00 (t), 50.42 (dd$_p$, $^1J_{CP}$ = 155.5 Hz), 53.09 (qd$_P$, $^2J_{CP}$ = 7.7 Hz), 53.22 (qd$_P$, $^2J_{CP}$ = 5.8 Hz), 83.62 (s), 152.30 (s), 170.98 (s). *Anal*. Calcd for $C_{12}H_{22}NO_6P$: C, 46.90; H, 7.22; N, 4.56. Found: C, 46.63; H, 7.24; N, 4.52.

5-*tert*-Butoxycarbonylamino-5-(dimethylphosphono)pentanoic acid (9)

Colorless oil. IR (neat) 3296, 2964 (NH, OH), 1716, 1704 cm^{-1} (C=O). EI-MS *m/z*: 326 (MH$^+$). ^{1}H-NMR δ: 1.17-2.12 (4H, m, 3-and 4-H$_2$), 1.46 (9H, s, *t*-Bu), 2.12-2.63 (2H, m, 2-H$_2$), 3.78 (6H, d$_P$, $^3J_{HP}$ = 10.5 Hz, Me x 2), 4.00-4.47 (1H, m, 5-H), 5.40 (1H, br d, *J* = 10.5 Hz, NH), 6.92 (1H, br, COOH). EI-HR-MS *m/z*: 326.1375 (Calcd for $C_{12}H_{25}NO_7P$: 326.1369).

4-Nitrobenzyl 2-Dimethylphosphono-5-oxopyrrolidine-1-carboxylate (6Ca)

Colorless oil. IR (neat) 1796, 1760, 1734 cm^{-1} (C=O). EI-MS *m/z*: 373 (MH$^+$), ^{1}H-NMR δ: 2.31-2.56 and 2.83-2.93 (3H, m, 1H, m, 3- and 4-H$_2$), 3.77 (3H, d$_p$, $^3J_{HP}$ = 11.0 Hz, Me), 3.79 (3H, d$_p$, $^3J_{HP}$ = 10.6 Hz, Me), 4.59-4.62 (1H, m, 2-H), 5.42 (2H, s, -COOCH$_2$), 7.66 (2H, d, *J* = 8.8 Hz, Ar-H), 8.22 (2H, d, *J* = 8.8 Hz, Ar-H). ^{13}C-NMR δ: 20.49 (t), 31.76 (t), 52.66 (dd$_p$, $^1J_{cp}$ = 160.2 Hz), 53.11 (qd$_p$, $^2J_{cp}$ = 6.1 Hz), 53.58 (qd$_p$, $^2J_{cp}$ = 6.1 Hz), 67.02 (t), 123.79 (d), 128.20 (d), 142.43 (s), 147.77 (s), 151.03 (s), 172.89 (s). EI-HR-MS *m/z*: 373.0805 (Calcd for $C_{14}H_{18}N_2O_8P$: 373.0801).

Transformation from 6Aa to 4-Amino-4-phosphonobutylic acid (10)

Activated zinc dust (*ca*. 600 mg) was added to a solution of *N*-troc dimethyl ester (**6Aa**, 1 mmol) in AcOH (6 mL). The suspended mixture was stirred at rt for 3 days and then filtered off. Zinc dust was washed with AcOH (2 mL), and the combined AcOH was concentrated *in vacuo*. 6N HCl (6 mL) was added to the resulting residue. The mixture was refluxed for 12 h and then evaporated. The obtained residue was dissolved in H_2O (2 mL), and the aqueous solution was chromatographed on ion-exchange resin (Dowex 1 x 8, acetate form) with H_2O as an eluent. The aqueous eluate was evaporated to give the crude amino acid (**10**), which was recrystallized from H_2O-EtOH. Yield 87%, colorless prisms, mp 140-140 ˚C (decomp.) (lit: mp 167-169 ˚C (decomp.),[12] mp 174-175 ˚C[13]). This compound was identical (in terms of IR, ^{1}H- and ^{13}C-NMR) with the authentic sample.

Transformation from 6Ba to ω-Amino-ω-phosphonocarboxylic Acid (10)

A mixture of *N*-Boc dimethyl ester (**6Ba**, 1 mmol) in 6N HCl (6 mL) was refluxed for 12 h and then evaporated. The obtained residue was dissolved in H_2O (2 mL), and the aqueous solution was chromatographed on ion-exchange resin (Dowex 1 x 8, acetate form) with H_2O as an eluent. The aqueous eluate was evaporated to give the crude amino acid (**10**), which was recrystallized from H_2O-EtOH. Yield 94%.

Transformation from 7Aa to 5-Amino-5-phosphonopentanoic acid (10)

Activated zinc dust (*ca*. 600 mg) was added to a solution of *N*-troc dimethyl ester (**7Aa**, 1 mmol) in AcOH (6 mL). The suspended mixture was stirred at rt for 3 days and then filtered off. Zinc dust was washed with AcOH (2 mL), the combined AcOH was concentrated *in vacuo*. 6N HCl (6 mL) was added to the resulting residue. The mixture was refluxed for 12 h and then evaporated. The obtained residue was dissolved in H_2O (2 mL) and stored in a refrigerator for 2 days to give the crude amino acid (**11**), which was recrystallized from H_2O-EtOH. Yield 76%, colorless prisms, mp 208-209 ˚C (lit.[13] mp 220-221 ˚C). This compound was also identical (in terms of IR, ^{1}H- and ^{13}C-NMR) with the authentic sample.

Transformation from 7Ba to ω-Amino-ω-phosphonocarboxylic Acid (11)

A mixture of *N*-Boc dimethyl ester (**7Ba**, 1 mmol) in 6N HCl (6 mL) was refluxed for 12 h and then evaporated. The obtained residue was dissolved in H_2O (2 mL) and stored in a refrigerator for 2 days to give the crude amino acid (**11**), which was recrystallized from H_2O-EtOH. Yield 68%.

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REFERENCES AND NOTES

1. V. P. Kukhar and H. R. Hudson, “Aminophosphonic and Aminophosphinic Acids Chemistry and Biological Activity”, John Wiley & Sons, LTD, 2000.
2. F. R. Atherton, C. H. Hassall, and R. W. Lambert, *J. Med. Chem.*, 1986, **29**, 29.
3. S. De Lombaert, L. Blanchard, L. B. Stamford, J. Tan, E. M. Wallace, Y. Satoh, J. Fitt, D. Hover, D. Simonsbergen, J. Moliterni, N. Marcopoulos, and P. Savage, *J. Med. Chem.*, 2000, **43**, 488 and references cited therein.
4. J. Bird, C. R. De Mello, P. G. Harper, J. D. Hunter, H. E. Karran, E. R. Markwell, J. A. Miles-Williams, S. S. Rahman, and W. R. Ward, *J. Med. Chem.*, 1994, **37**, 158.

5. G. Lavielle, P. Hautefaye, C. Schaeffer, J. A. Boutin, C. A. Cudennec, and A. Pierre, *J. Med. Chem.*, 1991, **34**, 1998; N. P. Camp, P. C. D. Hawkins, and P. B. Hichcock, *Bioorg. Med. Chem. Lett.*, 1992, **2**, 1047.

6. S. Tada, M. Hatano, Y. Nakayama, S. Volrath, D. Guyer, E. Ward, and D. Ohta, *Plant Physiol.*, 1995, **109**, 153; P. Kafarski and B. Lejczak, *Phosphorous, Sulfur Silicon Relat. Elem.*, 1991, **63**, 193.

7. Edg. Alonso, Edu. Alonso, A. Soíis, and C. del Pozo, *Synlett.*, 2000, 698; K. S. Kim, E. Y. Hurh, J. N. Youn, and J. I. Park, *J. Org. Chem.*, 1999, **64**, 9272; C. Maury, T. Gharbaoui, J. Royer, and H. P. Husson, *J. Org. Chem.*, 1996, **61**, 3687.

8. S. Yoshifuji, Y. Arakawa, and Y. Nitta, *Chem. Pharm. Bull.*,1985, **33**, 5042; S. Yoshifuji, K. Tanaka, T. Kawai, and Y. Nitta, *Chem. Pharm. Bull.*,1985, **33**, 5515; S. Yoshifuji, K. Tanaka, T. Kawai, and Y. Nitta, *Chem. Pharm. Bull.*, 1986, **34**, 3873; S. Yoshifuji, K. Tanaka, and Y. Nitta, *Chem. Pharm. Bull.*, 1985, **33**, 1749; K. Tanaka, S. Yoshifuji, and Y. Nitta, *Chem. Pharm. Bull.*,1987, **35**, 364; S. Yoshifuji, K. Tanaka, and Y. Nitta, *Chem. Pharm. Bull.*, 1987, **35**, 2994.

9. S. Yoshifuji, H. Matsumoto, K. Tanaka, and Y. Nitta, *Tetrahedron Lett.*, 1980, **21**, 2963; K. Tanaka, S. Yoshifuji, and Y. Nitta, *Chem. Pharm. Bull.*,1986, **34**, 3879; M. Kaname and S. Yoshifuji, *Tetrahedron Lett.*, 1992, **33**, 8103; S. Yoshifuji and M. Kaname, *Chem. Pharm. Bull.*,1995, **43**, 1302; S. Yoshifuji and M. Kaname, *Chem. Pharm. Bull.*, 1995, **43**, 1617.

10. M. Kaname, H. Mashige, and S. Yoshifuji, *Chem. Pharm. Bull.*, 2001, **49**, 531.

11. M. Kaname, S. Yoshifuji, and H. Sashida, *Tetrahedron Lett.*, 2008, **49**, 2786.

12. J. Oleksyszyn, E. Gruszecka, P. Kafarski, and P. Mastalerz, *Monatsh. Chem.*, 1982, **113**, 59.

13. P. J. Diel and L. Maier, *Phosphorous, Sulfur Silicon Relat. Elem.*, 1987, **29**, 201.