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Synthesis of Conformationally Constrained Analogues of (*R*)-2-amino-7-phosphonoheptanoic Acid

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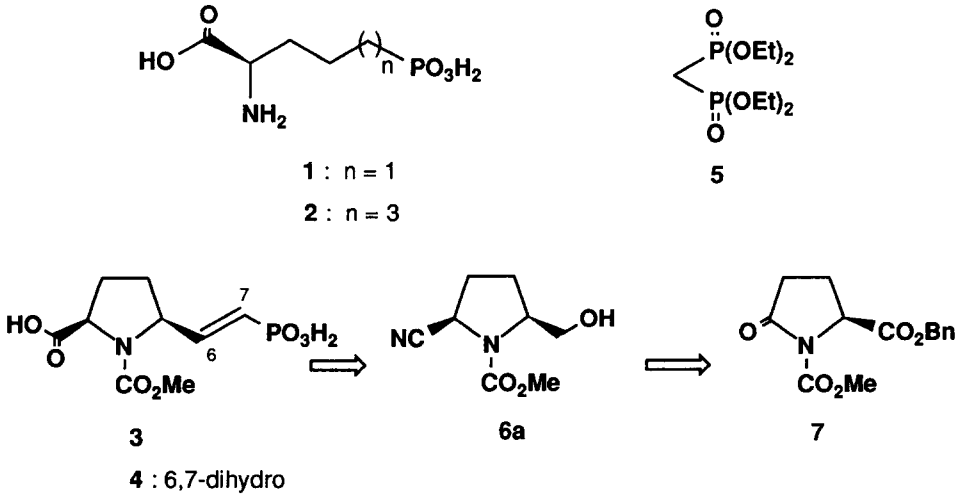
Abstract : Conformationally restricted AP7 analogues of 2*R* configuration are readily prepared from (*S*)-pyroglutamic acid. Copyright © 1996 Elsevier Science Ltd

(*S*)-Glutamic acid is one of the major excitatory neurotransmitters in the mammalian central nervous system. The excitatory amino acid (EAA) receptors play a key role in certain neurodegenerative processes and therefore the synthesis of conformationally constrained analogues of EAA has been extensively developed, particularly NMDA receptor ligands.[1] Among them, several analogues of the potent and selective NMDA receptor antagonists D-AP5 **1** ((*R*)-2-amino-5-phosphonopentanoic acid) and D-AP7 **2** ((*R*)-2-amino-7-phosphonoheptanoic acid)[2] have received recently much interest. Most of the compounds which exhibit enhanced affinity for NMDA receptor, possess in their structure a ring or/and an unsaturation restricting their conformational mobility.[3,4]

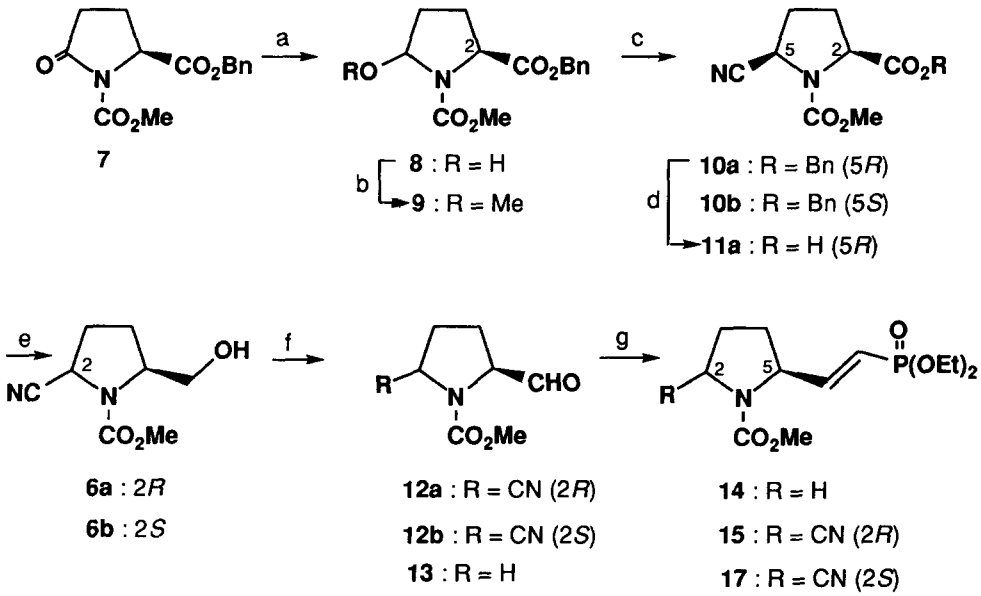
Owing to the versatility of pyroglutamic acid in synthesis,[5-7] we planned to prepare semi-rigid analogues of (*R*)-AP7 **2** from this inexpensive amino acid of (*S*)-configuration. The relative orientation of the functional groups in a folded conformation of these analogues was postulated to be important for the biological activity. Therefore based on this rationale the *cis* amino diacids **3** and **4** were designed as main target molecules.[7] The retrosynthetic pathway is depicted in Scheme 1.



Scheme 1

Thus, the carboxyl group of α-amino acid moiety of (*R*)-configuration can be obtained through the *cis* addition of cyanide to suitable 1-methoxycarbonyl-5-pyrrolinium ions[8] derived from (*S*)-pyroglutamates, followed by hydrolysis of the cyano group. The phosphonate function is introduced through a Horner-Wadsworth-Emmons variant of the Wittig reaction involving tetraethyl methylenediphosphonate **5** and an aldehyde prepared from (2*R*, 5*S*)-2-cyano-5 hydroxymethyl-1-methoxycarbonylpyrrolidine **6a**.

Taking advantage of our previous work in this area,[6] (*S*)-benzyl pyroglutamate **7** was partially reduced by DIBAL-H into α-hydroxy carbamates **8** in 95% yield. The α-methoxy derivatives **9** were quantitatively obtained from **8** as a mixture of diastereomers by treatment with methanol in acidic medium. They were directly converted into the 2,5-cyano esters **10** using Me_3SiCN in the presence of $SnCl_4$ and the major 2,5-*cis* diastereomer **10a** was isolated in 66% yield. Hydrogenolysis of **10a** to the carboxylic acid **11a** (H_2-Pd/C 10%) and subsequent reduction of the carboxylic acid with BH_3-DMS (80% in two steps, Scheme 2), led to (2*R*, 5*S*)-2-cyano-5-hydroxymethyl-1-methoxycarbonylpyrrolidine **6a**.[6a] The Swern oxidation of **6a** (DMSO, $(COCl)_2$), in modified conditions using diisopropylethylamine as base instead of triethylamine,[6b,9] provided the aldehyde **12a** without epimerization (only one diastereomer could be detected, which appeared to be different on TLC from the Swern oxidation product of the *trans* cyano alcohol **6b**).



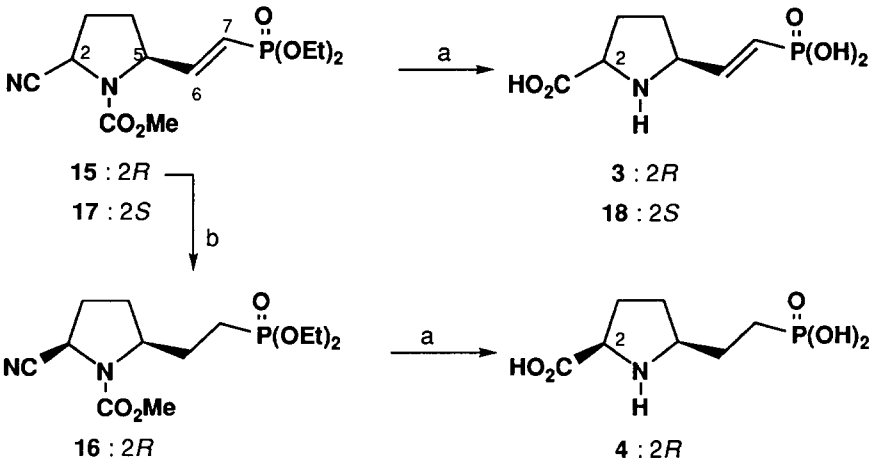
Reagents : a) : DIBAL-H, 95% ; b) : MeOH, TsOH, 100% ; c) : Me_3SiCN, $SnCl_4$, 66% ; d) : H_2-Pd/C 10%, 100% ; e) : BH_3-DMS, 80% ; f) : DMSO, $(COCl)_2$; g) : $CH_2[P(O)(OEt)_2]_2$, *n*-BuLi, 66-78%.

Scheme 2

Few examples of Horner-Wadsworth-Emmons reactions are described with tetra-alkyl methylenediphosphonates such as **5**, and they are generally carried out with the sodium salt.[4c,10-11] (2*S*)-*N*-methoxycarbonyl prolinal **13** was used as a model to compare the results obtained with sodium and lithium salts in THF, respectively at 0°C and -10°C (Scheme 2). The lithium salt generated with *n*-BuLi at -30°C gave **14** in better yield (78%) as compared to the sodium salt generated with NaH at 0°C (68%). The formation of only one stereoisomer was observed and its E geometry was demonstrated by the characteristic coupling constant between the ethylenic protons in NMR (17 Hz).[10b,12] Using the same procedure, the crude 2,5-*cis* cyanoaldehyde **12a** was treated with the lithio anion of tetraethyl methylenediphosphonate **5** to afford the (E)-*cis* cyanophosphonate **15** as the sole detectable product ; thus, the presence of the nitrile function did not give

rise to any by-products. The compound **15** was isolated in 68% overall yield from the primary alcohol **6a** (Scheme 2).

The hydrogenation of **15** (H_2-Pd/C 10%) led rapidly to the saturated ethyl phosphonate **16** in high yield (96%). The cyano and protective groups of **15** and **16** were hydrolysed in the same step to afford respectively the carboxylic and phosphonic amino diacids **3** and **4** after treatment with propylene oxide[4a] (Scheme 3).



Reagents : a) : 6N HCl, Δ, 24h, propylene oxide, EtOH, 90-99% ; b) : H_2-Pd/C 10%, 96%.

Scheme 3

This simple synthetic scheme has also been extended to the *trans* (2*S*,5*S*)-2-cyano-5-hydroxymethyl-1-methoxycarbonylpyrrolidine **6b**, prepared more efficiently from (*S*)-pyroglutaminol, as previously described.[6a] It led to the (E)-*trans* diethyl cyanophosphonate **17** (66% after two steps) precursor of the phosphonic acid **18**. As the (*R*)-configuration of the amino acid center is generally preferred for the antagonists of NMDA receptor related to AP5 or AP7,[13] these last results would be applicable to the synthesis of the enantiomer (2*R*,5*R*) amino diacid **ent-18** and its derivatives from (*R*)-pyroglutaminol.

Thus, this work could give access to the four diastereomers of 5-(2-phosphonoethen-1-yl)-2-pyrrolidinecarboxylic acids, illustrating new potential of pyroglutamic acid for synthesis. Starting from (2*S*)-α-methoxycarbamates **9**, the stereoselectivity of the introduction of the cyano group allowed the efficient preparation of phosphono-(2*R*)-α-aminoacids, conformationally restrained analogues of (*R*)-AP7, which could provide further insight into the structural requirements for activity at the NMDA receptor.

EXPERIMENTAL

Optical rotations were measured on a Perkin-Elmer 241 ; the concentrations in $CHCl_3$ solution (unless otherwise indicated) were given in g/100 mL. IR spectra (ν cm^{-1}, $CHCl_3$) were recorded on a Nicolet 205 (FT). ^1H NMR spectra were obtained ($CDCl_3$ unless otherwise indicated, Me_4Si, δ = 0 ppm) from Bruker AC200, AC250, AM300 ; coupling constants *J* values are given in Hertz (s, d, t, dd, and m indicate singlet, doublet, triplet, doublet of doublets, and multiplet respectively). ^{13}C NMR spectra were recorded on AC250 (62.5 MHz) or AM300 (75.0MHz). Mass spectra and high resolution mass spectra were respectively measured on an AEI MS50 and on a Kratos MS80 spectrometer. Flash chromatography was performed on silica gel (SDS 230-400 mesh) and preparative thin layer chromatography on silica gel (Merck HF 254 + 366). Usual workup means that organic layer was dried over magnesium sulfate, filtered, and evaporated under vacuum.

(2*S*)-Benzyl-5-methoxy-1-methoxycarbonyl-2-pyrrolidinecarboxylates 9.

To a stirred solution of (*S*)-benzyl-1-methoxycarbonylpyroglutamate (4.80 g, 17.3 mmol) in anhydrous THF (44 mL), was added DiBAL-H (1M in hexane, 31.2 mL) at -78°C under argon. After being stirred for 15 min, the reaction was quenched by addition of saturated aqueous solution of NH_4Cl and aqueous solution of Na_2CO_3 (10% w/v) and extracted with dichloromethane. Usual workup afforded **8** (4.60 g, 95%). IR : 3335, 1709, 1456. ^1H NMR (300 MHz) : 7.38 (bs, 5H, H-Ar), 5.63 (m, 1H), 5.22 (s, 2H, $C\underline{H}_2Ph$), 4.45, 4.33 (2m, 1H), 3.77, 3.58 (2s, 3H, OCH_3), 2.30-1.88 (m, 5H, H_2-3, H_2-4, OH). ^{13}C NMR (75.0 MHz) : 171.26 (CO), 154.11 (N-CO_2), 128.4 (CH, Ar), 82.98-82.24 (C-5), 67.21 (OCH_2), 59.56-59.26 (C-2), 53.02-52.74 (OCH_3), 32.70-32.27, 28.13-27.30 (C-3, C-4). MS (m/z) : 279 ($M^{+\cdot}$), 261, 144 (100%), 91.

A solution of *p*-toluenesulfonic acid in anhydrous methanol (0.1%, 110 mL) was added to the α-hydroxycarbamates **8** (3.49 g, 12.5 mmol) and the mixture was stirred at room temperature (RT) until completion of the reaction. After the addition of an aqueous solution of 10% Na_2CO_3, The α-methoxycarbamates **9** were extracted with CH_2Cl_2 in quantitative yield (3.65 g). IR : 3389, 3089, 2950, 1722, 1450. ^1H NMR (200 MHz splitted signals) : 7.35 (bs, 5H, H-Ar), 5.34 (m), 5.19, 5.15 (H-5, CH_2Ph), 4.49 (m, 1H, H-2), 3.76, 3.62, 3.52, 3.42, 3.34 (5s, 2 x OCH_3), 2.40 (m), 2.19 (m), 1.97 (m), 1.77 (m) : H_2-3 and H_2-4. MS (m/z) : 293 ($M^{+\cdot}$), 261, 216, 158 (100%), 91.

(2*S*,5*R*)-Benzyl-5-cyano-1-methoxycarbonyl-2-pyrrolidinecarboxylate 10a.

To α-methoxycarbamates **9** (1.65 g, 5.63 mmol) at -40°C under argon was added a solution of $SnCl_4$ in anhydrous CH_2Cl_2 (5% v/v, 4.0 mL) and Me_3SiCN (1.49 mL, 11.2 mmol) under stirring. After 2 h at -40°C, an aqueous solution of Na_2CO_3 (10%, 15 mL) was added to the reaction mixture and the products were extracted with CH_2Cl_2. Usual workup followed by flash chromatography on silicagel (heptane-ether-methanol 4:1:0.1) afforded **10b** (434 mg, 27%) and **10a** (1.07 g; 66%) as colorless oils. **10a** : $[\alpha]_D^{20}$ = +18 (c = 0.9). IR : 2957, 2260, 1745 (sh), 1722. ^1H NMR (200 MHz) : 7.38 (bs, 5H, H-Ar), 5.23 (2H, CH_2Ph), 4.71, 4.64 (2m, 1H, H-5 or H-2), 4.49, 4.38 (2m, 1H, H-2 or H-5), 3.81, 3.58 (2s, 3H, OCH_3), 2.32 (m, 4H, H_2-3, H_2-4). ^{13}C NMR (75.0 MHz) : 170.9 (CO), 153.9 (N-CO_2), 135.4 (qC, Ar), 128.5 (CH, Ar), 118.0 (CN), 67.22 (OCH_2), 59.77-59.42 (CH), 53.53-53.27 (OCH_3), 48.14-47.57 (CH), 30.71, 29.76 and 28.68 (C-3, C-4). MS (m/z) : 288 ($M^{+\cdot}$), 261, 153 (100%), 91, 68. Anal. calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found : C, 62.53; H, 5.60; N, 9.69.

(2*S*,5*R*)-5-cyano-1-methoxycarbonyl-2-pyrrolidinecarboxylic acid 11a.

Hydrogenolysis of (2*S*,5*R*)-benzyl-5-cyano-1-methoxycarbonyl-2-pyrrolidinecarboxylate **10a** (950 mg, 3.3 mmol) in methanol (80 mL) with H_2 (1 atm) in the presence of Pd/C 10% (30 mg) for 2h, followed by filtration and evaporation of the solvent under vacuum, led to the acid **11a** (654 mg, 100%). $[\alpha]_D^{20}$ = +25 (c = 0.19). ^1H NMR (300 MHz) : 10.10 (OH), 4.66, 4.43 (2m, 2H, H-5, H-2), 3.82, 3.77 (2s, OCH_3), 2.32 (m, 4H, H_2-3, H_2-4). ^{13}C NMR (75.0 MHz) : 176.7 (CO_2H), 154.73 (N-CO_2), 118.51 (CN), 60.7 (C-2), 53.85-53.47 (OCH_3), 48.23-47.86 (C-5), 30.80, 29.85-28.83 (C-3, C-4). MS (m/z) : 198 ($M^{+\cdot}$), 172, 153.

(2*R*,5*S*)-2-cyano-5-hydroxymethyl-1-methoxycarbonylpyrrolidine 6a and aldehyde 12a.

BH_3-DMS (2M in THF, 6.0 mL) was added at RT under argon to a stirred solution of *cis*-cyano acid **11a** (595 mg, 3.0 mmol) in anhydrous THF (15.0 mL). After stirring for 5h, methanol was added and the mixture was stirred for 1h at RT before extraction with CH_2Cl_2. Usual workup afforded (2*R*, 5*S*)-2-cyano-5-hydroxymethyl-1-methoxycarbonylpyrrolidine **6a** (445 mg, 80%).

To a solution of oxalyl chloride (0.42 mL) in anhydrous CH_2Cl_2 (6.4 mL) stirred at -30°C was added dropwise DMSO (0.67 mL, 8.66 mmol). After stirring for 30 min. at -30°C, a solution of the primary alcohol **6a** (395 mg, 2.15 mmol) in CH_2Cl_2 (11.5 mL) was added dropwise and the mixture was stirred for 1.5 h at the same temperature ; iPr_2 NEt (2.30 mL) was then added and the mixture was stirred for 10 min at -30°C and 30 min at 0°C before the addition of a pH 5.6 buffer, followed by extraction with EtOAc (3 x 160 mL). The organic phases were washed 3 times with H_2O (3 x 20 mL) and usual workup provided the aldehyde **12a** (395

mg), which was used without purification. IR : 2366, 1702, 1456, 1390. ^{1}H NMR (300 MHz) : 9.57 (d, 1H, CHO), 4.78, 4.66, 4.27, 4.18 (4 m, 2H, H-2, H-5), 3.84, 3.77 (2s, 3H, OCH_3), 2.30 (m, 4H, H_2-3, H_2-4).

(2*S*)-2-[2-(diethylphosphono)ethen-1-yl]-1-methoxycarbonylpyrrolidine 14.

n-BuLi (1.4 M in hexane, 0.75 mL) was added to a stirred solution of tetraethyl methylenediphosphonate **5** (317 mg, 1.1 mmol) in anhydrous THF (3.0 mL) under argon at -30°C. After being stirred for 30 min at -30°C, a solution of crude aldehyde **13** (157 mg, 1.0 mmol) in THF (4.0mL) was added dropwise and the mixture was stirred at -10°C for 80 min. Saturated aqueous solution of NH_4Cl was added to the mixture before extraction with EtOAc. Purification of the crude product by flash chromatography on silicagel (EtOAc-MeOH 99:1) afforded the conjugate phosphonate **14** (227 mg, 78%). $[\alpha]_D^{20}$ = -66 (c = 0.7). IR : 1700, 1642, 1463, 1390. ^{1}H NMR (250 MHz) : 6.63 (ddd, 1H, $J_{H,P}$ = 22, $J_{6,7}$ = 17, $J_{2,6}$ = 5, H-6), 5.66 (m, 1H, H-7), 4.47 (m, 1H, H-2), 4.07 (m, 4H, 2 x OCH_2), 3.66 (2s, 3H, OCH_3), 3.43 (m, 2H, H_2-5), 2.07, 1.86 (2m, 4H, H_2-3, H_2-4), 1.34 (t, 6H, 2 x CH_3). MS (m/z) : 292 (M + 1), 291 ($M^{+\cdot}$), 246, 232, 154 (100%), 128.

(2*R*,5*S*)-2-cyano-5-[2-(diethylphosphono)ethen-1-yl]-1-methoxycarbonylpyrrolidine 15.

The compound **15** was prepared using the same general procedure. To a solution of tetraethyl methylenediphosphonate **5** (606 mg, 2.10 mmol) in anhydrous THF (6 mL) under argon was added *n*-BuLi (1.4 M, 1.5 mL) at -30°C. After being stirred for 30 min at -30°C, a solution of crude aldehyde **12a** (370 mg, 2.0 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at -10°C for 80 min. Saturated aqueous solution of NH_4Cl was added and the mixture was extracted with EtOAc. The crude product (680 mg) was purified by chromatography on silicagel (EtOAc-MeOH 93:7) to give the cyanophosphonate **15** (438 mg, 68%). $[\alpha]_D^{20}$ = +11 (c = 1.2). IR : 1715, 1642, 1456, 1370. ^{1}H NMR (300 MHz) : 6.69 (ddd, 1H, $J_{H,P}$ = 22, $J_{6,7}$ = 18, $J_{5,6}$ = 5, H-6), 5.84 (dd, 1H, $J_{H,P} \sim J_{6,7}$ = 18, H-7), 4.59 (m, 2H, H-2, H-5), 4.09 (m, 4H, 2 x OCH_2), 3.78 (bs, 3H, OCH_3), 2.27 (m, 3H), 2.03 (m, 1H) : H_2-3 and H_2-4, 1.34 (dt, 6H, J = 7, 2 x CH_3). ^{13}C NMR (62.5 MHz) : 150.0 (C-6), 119.7-116.7 (C-7), 118.6 (CN), 62.0-61.9 (OCH_2), 60.4-60.0 (C-5), 53.3 (OCH_3), 47.9 (C-2), 30.0-29.4 (C-3, C-4), 16.3 (CH_3). MS (m/z) : 316 ($M^{+\cdot}$), 289, 257, 179 (100%). HRMS calcd for $C_{13}H_{21}N_2O_5P$: 316.1187, found 316.1189 ; calcd for $C_{12}H_{20}NO_5P$: 289.1079, found 289.1052; cald for $C_9H_{11}N_2O_2$: 179.0794, found 179.0817.

(2*R*,5*S*)-2-cyano-5-[2-(diethylphosphono)ethyl]-1-methoxycarbonyl pyrrolidine 16. Hydrogenation of 15.

The phosphonate **15** (285 mg, 0.9 mmol) was hydrogenated in methanol (28 mL) over Pd/C 10% (15 mg) for 3.5 h. Usual treatment gave the compound **16** (276 mg, 96%). $[\alpha]_D^{20}$ = +19 (c = 0.7). ^{1}H NMR (250 MHz) : 4.63 (m, 1H, H-2), 4.10 (m, 4H, 2 x OCH_2), 3.96 (m, 1H, H-5), 3.78 (s, 3H, OCH_3), 2.23, 2.13, 1.81 (3m, 8H, H_2-3, H_2-4, H_2-6, H_2-7), 1.33 (t, 6H, 2 x CH_3). MS (m/z) : 318 (($M^{+\cdot}$), 292, 265, 259, 166, 153, 152 (100%), 125. HRMS calcd for $C_{13}H_{23}N_2O_5P$: 318.1345, found 318.1348.

(2*R*,5*S*)-5-(2-phosphonoethen-1-yl)-2-pyrrolidinecarboxylic acid 3.

A solution of 2,5-cyanophosphonate **15** (238 mg, 0.75 mmol) in 6N HCl (10 mL) was heated under reflux for 24 h to afford **3** as hydrochloride, after evaporation to dryness. This product in EtOH (1.38 mL) was treated with propylene oxide (0.33 mL) to give **3** (149 mg, 90%). $[\alpha]_D^{20}$ = +15 (c = 0.4, H_2O). ^{1}H NMR (300 MHz, D_2O) : 6.43 (ddd, 1H, $J_{6,7}$ = 17, H-6), 6.16 (dd, 1H, $J_{H,P}$ = 16, $J_{6,7}$ = 17, H-7), 4.22 (m, 2H, H-2, H-5), 2.25-1.92 (4H, H_2-3, H_2-4). ^{13}C NMR (75.0 MHz, D_2O, δ dioxane = 67.8 ppm) : 173.54 (CO), 139.20-139.13 (C-6), 131.20-128.89 (C-7), 63.47-63.16 (C-5), 61.40 (C-2), 30.14-28.77 (C-3, C-4). (FAB)MS : 222 $(M + 1)^+$.

(2*R*5*S*)-5-(2-phosphonoethyl)-pyrrolidine-2-carboxylic acid 4.

Ethylphosphonate **16** (191 mg, 0.6 mmol) was hydrolyzed with 6N HCl as described above to give the amino diacid **4** after treatment with propylene oxide (126 mg, 94%). $[\alpha]_D^{20}$ = +30 (c = 0.85, H_2O). ^{1}H NMR

(250 MHz, D_2O) : 4.14 (m, 1H, H-2), 3.65 (m, 1H, H-5), 2.20 (m, 2H, H_2-6), 2.01 (m, 2H, H_2-7), 1.68, 1.15 (4H, H_2-3, H_2-4). (FAB)MS : 224 $(M+1)^+$.

(2*S*,5*S*)-2-cyano-5-[2-(diethylphosphono)ethen-1-yl)-1-methoxycarbonylpyrrolidine 17.

The aldehyde **12b** was prepared from (2*S*,5*S*)-2-cyano-5-hydroxymethyl-1-methoxycarbonyl pyrrolidine **6b**[6a] , as described for **12a** (90% yield). This aldehyde was treated with the lithium salt of tetraethyl methylenediphosphonate **5** as described above to afford the unsaturated phosphonate **17** (66% yield). $[\alpha]_D^{22}$ = -104 (c = 1.6). IR : 2997, 1709, 1457, 1384. ^1H NMR (300 MHz) : 6.60 (ddd, 1H, $J_{H,P} \sim 20$, $J_{6,7} \sim 17$, $J_{5,6} \sim 4$, H-6), 5.68, 5.62 (2dd, $J_{H,P} \sim J_{6,7} \sim 17$, H-7), 4.63, 4.58 (2m, H-2, H-5), 4.05 (m, 4H, 2x OCH_2), 3.78, 3.73 (2s, OCH_3), 2.43 (m, 1H,), 2.25 (m, 2H), 2.00 (m, 1H) : H_2-3 and H_2-4, 1.33 (dt, 6H, J = 6.8, 2 x CH_3). Splitting of signals (conformers) disapeared in C_6D_6 at 60°C. ^{13}C NMR (75.0 MHz) : 149.83-149.42 (C-6), 119.2-116.6 (C-7), 118.2 (CN), 61.90 (OCH_2), 59.24-58.94-58.62 and 48.18-47.69 (C-5, C-2), 53.20 (OCH_3), 30.23, 29.30, 28.12 (C-3, C-4), 16.5 (CH_3). HRMS cald for $C_{13}H_{21}N_2O_5P$: 316.1188, found 316.1201.

(2*S*,5*S*)-5-(2-phosphonoethen-yl)-2-pyrrolidinecarboxylic acid 18.

Acid hydrolysis of **17** (403 mg, 1.27 mmol) with 6N HCl (17 mL) under the conditions described for **15** to give the diacid **18** after treatment with propylene oxide (279 mg, 99%). mp > 250°C. $[\alpha]_D^{27}$ = - 58.5 (c = 0.99, H_2O). ^1H NMR (300 MHz, D_2O) : 6.42 (ddd, 1H, H-6), 6.18 (dd, 1H, $J_{H,P} \sim J_{6,7} \sim 16$, H-7), 4.36 (m, 2H, H-2, H-5), 2.52, 2.31, 2.12, 1.95 (4m, 4H, H_2-3, H_2-4). ^{13}C NMR (75.0 MHz, D_2O) : 173.70 (CO), 138.71 (C-6), 131.43-129.11 (C-7), 63.34-63.03, 60.91 (C-5, C-2), 31.13 and 29.33 (C-3, C-4).

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