Pergamon

*Tetrahedron: Asymmetry*, Vol. 7, No. 4, pp. 1095-1100, 1996

0957-4166/96 $15.00 + 0.00

S0957-4166(96)00114-0

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

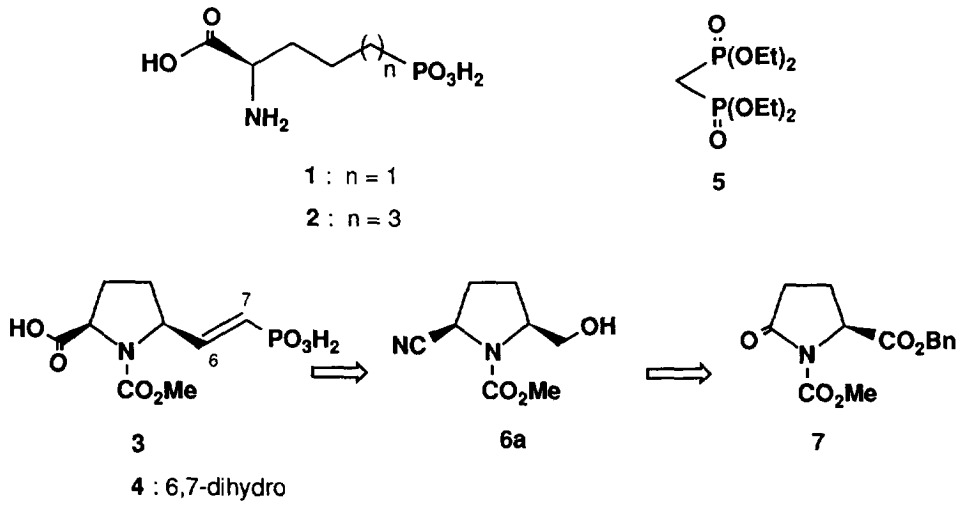
**Nicole Langlois*, Anne Rojas-Rousseau, Oreste Decavallas**

Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette, France

**Abstract** : Conformationally restricted AP7 analogues of 2*R* configuration are readily prepared from (*S*)-pyroglutamic acid. 

(*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]

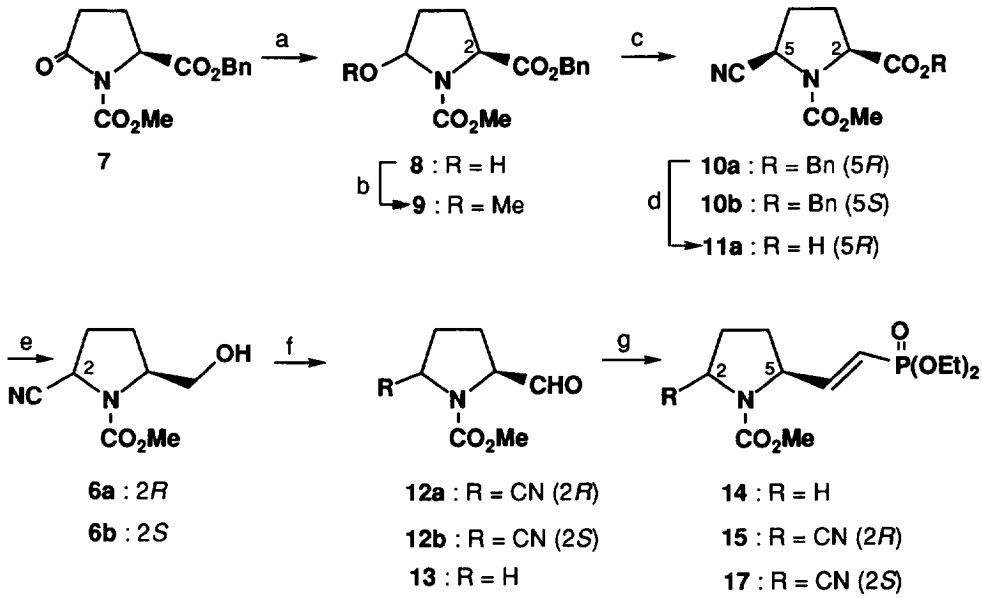
Owing to the versatility of pyroglutamic acid in synthesis,[5-7] we planned to prepare semi-rigid analogues of (*R*)-AP7 **2** from this inexpensive amino acid of (*S*)-configuration. The relative orientation of the functional groups in a folded conformation of these analogues was postulated to be important 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**).



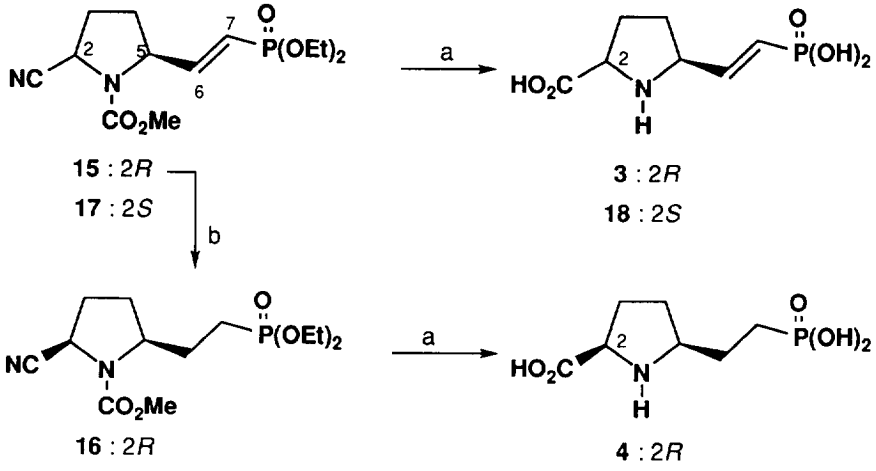

Reagents : a) : DIBAL-H, 95% ; b) : MeOH, TsOH, 100% ; c) : $Me_3SiCN$, $SnCl_4$, 66% ; d) : $H_2$-Pd/C 10%, 100% ; e) : $BH_3$-DMS, 80% ; f) : DMSO, $(COCl)_2$ ; g) : $CH_2[P(O)(OEt)_2]_2$, *n*-BuLi, 66-78%.

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 ; $iPr_2NEt$ (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, $J_{H,P}$ ~ 20, $J_{6,7}$ ~ 17, $J_{5,6}$ ~ 4, H-6), 5.68, 5.62 (2dd, $J_{H,P}$ ~ $J_{6,7}$ ~ 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, $J_{H,P}$ ~ $J_{6,7}$ ~ 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).

## References and Notes


1. a) Watkins, J.C.; Krogsgaard-Larsen, P.; Honoré, H. *Trends Pharmacol. Sci.* **1990**, *11*, 25. b) Kyle, D.J.; Patch, R.J.; Karbon, E.W.; Ferkany, J.W. "NMDA Receptors : Heterogeneity and Agonism", Chap. 6, p. 121 in "Excitatory Amino Acid Receptors", Editors Krogsgaard-Larsen, P.; Hansen, J.J. Ellis Horwood **1992** and references therein.
2. a) Davies, J.; Francis, A.A.; Jones, A.W.; Watkins, J.C. *Neurosci. Lett.*, **1981**, *21*, 77. b) Evans, R.H., Francis, A.A.; Jones, A.W.; Smith, D.A.S.; Watkins, J.C. *Br.J. Pharmacol.* **1982**, *75*, 65.
3. Ornstein, P.L.; Klimbowski, V.J. " Competitive NMDA Receptor Antagonists ", Chap. 8, p. 183 in "Excitatory Amino Acid Receptors", Editors Krogsgaard-Larsen, P.; Hansen, J.J. Ellis Horwood **1992** and references therein.
4. For examples : a) Hutchison, A.J.; Williams, M.; Angst, C.; de Jesus R.; Blanchard, L.; Jackson, R.H.; Wilusz, E.J.; Murphy, D.E.; Bernard, P.S.; Schneider, J.; Campbell, T.; Guida, W.; Sills, M.A. *J. Med. Chem.* **1989**, *32*, 2171. b) Bigge, C.F.; Johnson, G.; Ortwine, D.F.; Drummond, J.T.; Retz, D.M.; Brahce, L.J.; Coughenour, L.L.; Marcoux, F.W.; Probert, Jr, A.W. *J. Med. Chem.* **1992**, *35*, 1371. c) Hamilton, G.S.; Huang, Z.; Yang, X.-J.; Patch, R.J.; Narayanan, B.A.; Ferkany, J.W. *J. Org. Chem.* **1993**, *58*, 7263.
5. We are grateful to UCIB for a gift of (*S*)-pyroglutamic acid.
6. a) Langlois, N.; Rojas, A. *Tetrahedron*, **1993**, *49*, 77. b) Langlois, N.; Favre, F.; Rojas, A. *Tetrahedron Lett.* **1993**, *34*, 4635. c) Panday, S.K.; Griffart-Brunet, D.; Langlois N. *Tetrahedron Lett.* **1994**, *35*, 6673.
7. Rojas, A. PhD Thesis, Paris XI University, Orsay **1994**, order n° 3264.
8. Thaning, M.; Wistrand, L.G. *Acta Chem. Scand.* **1989**, *43*, 290.
9. Walba, D.M.; Thurmes, W.N.; Haltiwanger, R.C. *J. Org. Chem.* **1988**, *53*, 1046.
10. a) Wadworth, W.S. Jr; Emmons, W.D. *J. Am. Chem. Soc.* **1961**, *83*, 1733. b) Waszkuc, W.; Janecki, T.; Bodalski, R. *Synthesis* **1984**, 1025.
11. Ornstein, P.L.; Schauss, J.M.; Chambers, J.W.; Huser, D.L.; Leander, J.D.; Wong, D.T.; Paschal, J.W.; Jones, N.D.; Deeter, J.B. *J. Med. Chem.* **1989**, *32*, 827.
12. Hullar, T.L. *J. Med. Chem.* **1969**, *12*, 58.
13. Aebischer, B.; Frey, P.; Haerter, H.P.; Herrling, P.L.; Mueller, W.; Olverman, H.J.; Watkins, J.C. *Helv. Chim. Acta* **1989**, *72*, 1043.


(*Received in UK* 1 *February* 1996)