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Synthesis of Homochiral 4-Amino-4-carboxy-2-phosphonomethylpyrrolidines *via* a Diastereoselective Bucherer-Bergs Reaction of 4-Oxopyrrolidine Derivative: Novel Conformationally Restricted AP 5 Analogues

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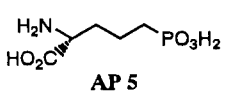
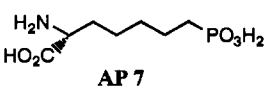
Abstract: Asymmetric synthesis of 4-amino-4-carboxy-2-phosphonomethylpyrrolidines **1** and **2**, which can be viewed as novel conformationally restricted analogues of 2-amino-5-phosphonopentanoic acid (AP 5) incorporated into the pyrrolidine ring, was achieved from *trans*-4-hydroxy-*L*-proline as a homochiral starting material using the diastereoselective Bucherer-Bergs reaction of (2*S*)-1-benzyl-2-[(diisopropylphosphonyl)methyl]-4-oxopyrrolidine **12**.

Extensive synthetic work is currently being undertaken in the field of *N*-methyl-*D*-aspartate (NMDA) receptor antagonists. Among them, (*R*)-2-Amino-5-phosphonopentanoic acid (AP 5) and (*R*)-2-amino-7-phosphonoheptanoic acid (AP 7) are known to be potent and selective prototypical NMDA antagonists[1] (**Figure 1**).

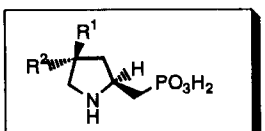
Figure 1



AP 5



AP 7



1 R^1=NH_2, R^2=CO_2H
2 R^1=CO_2H, R^2=NH_2

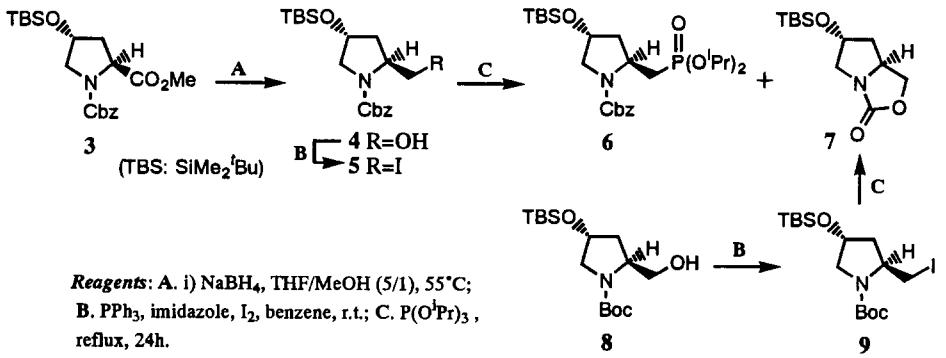
The introduction of conformational restrictions into the acyclic ω-phosphono-α-amino acids such as AP 5 and AP 7 is one of the most interesting subjects to enhance their potency to NMDA receptor antagonist activity. Thus, this strategy is based on the incorporation of aromatic[2], heterocyclic[3] (*i.e.*, piperidine, piperazine, and isoquinoline), and cycloalkanoic[4] rings in addition to unsaturation[2b,3b] into acyclic ω-phosphono-α-amino acids. On the other hand, the active form of AP 5 and AP 7 analogues has been shown usually[1], but not always[2d], to have the (*R*)-configuration at the α-amino acid center.

As part of a project directed toward the synthesis of novel conformationally restricted non-proteinogenic amino acids, we were interested in preparing AP 5 analogues incorporated into the pyrrolidine ring. In a previous paper we reported the syntheses of four isomers of 4-amino-4-carboxyproline in highly enantiomeric purities *via* the Bucherer-Bergs reactions of (2*S*)- or (2*R*)-4-oxoprolinates easily derived from *trans*-4-hydroxy-*L*-proline.[5]

In the present paper, we report the further exploitation of this methodology for the synthesis of enantiopure 4-amino-4-carboxy-2-phosphonomethylpyrrolidines **1** and **2**, which can be viewed as novel conformationally restricted analogues of AP 5.

The key substance for our approach to the synthesis of **1** and **2**, the spirohydantoins **13** and **14**, were prepared from methyl 1-benzyloxycarbonyl prolinate **3**, easily prepared from *trans*-4-hydroxy-*L*-proline without racemization[6], *via* 2-(phosphonomethyl)pyrrolidine derivative **6** in a six-step sequence in shown **Scheme 1** and **Scheme 2**. Thus, **3** was reduced with $NaBH_4$ in THF/MeOH (5/1)[7] to give the alcohol **4**. For use in the next Michaelis-Arbuzov reaction, treatment of **4** with imidazole, triphenylphosphine, and iodine in benzene at room temperature[8] afforded the iodide **5** in 75% yield. Previous studies have shown that the diastereoselectivity of the Bucherer-Bergs reaction of the 4-oxoprolinate derivatives is dependent on the steric bulkiness of C_2-substituent groups.[5] Therefore, the Michaelis-Arbuzov reaction of **5** with triisopropyl phosphite having a sterically bulky alkyl group was carried out without use of solvent under reflux for 24 h to give the corresponding phosphonate **6** in 64% yield along with a 15% yield of known cyclic carbamate **7**[9]. Whereas, the treatment of Boc iodide **9** derived from **8** under the same condition afforded only a 35% yield of **7**. This cyclic carbamate formation can be explained by intramolecular attack of the carbonyl oxygen of the Cbz group on the alkyl iodide to form the intermediate and subsequent attack of triisopropyl phosphite on the benzylic position of the intermediate afforded **7** in shown **Figure 2**.[10] In the case of Boc derivative **9**, pyrolytic cyclization[11] should proceeds predominantly to afford **7**.

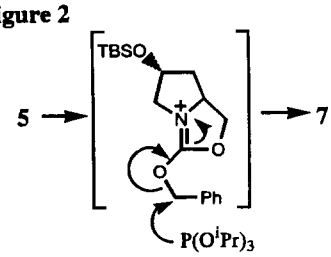
Scheme 1



Reagents: **A.** i) $NaBH_4$, THF/MeOH (5/1), 55°C; **B.** PPh_3, imidazole, I_2, benzene, r.t.; **C.** $P(O^iPr)_3$, reflux, 24h.

Next, simultaneous removal of both the *N*- and *O*-protections of **6** by hydrogenolysis in the presence of *p*-toluenesulfonic acid followed by *N*-benzylation to give **10** in 63% yield over the two steps. At this stage, the possible racemization at the C_2 stereogenic center was concerned under the thermal treatment required in the step for **6** from **5**. Thererfore, we decided to determine the enantiomeric excess of **10**. Thus the treatment of **10** with (*S*)-MTPA chloride in pyridine[11] gave the corresponding (*S*)-MTPA ester **11**. The enantiomeric excess of **11** was determined to be more than 95% ee by the 400 MHz ^{1}H-NMR spectra analysis.

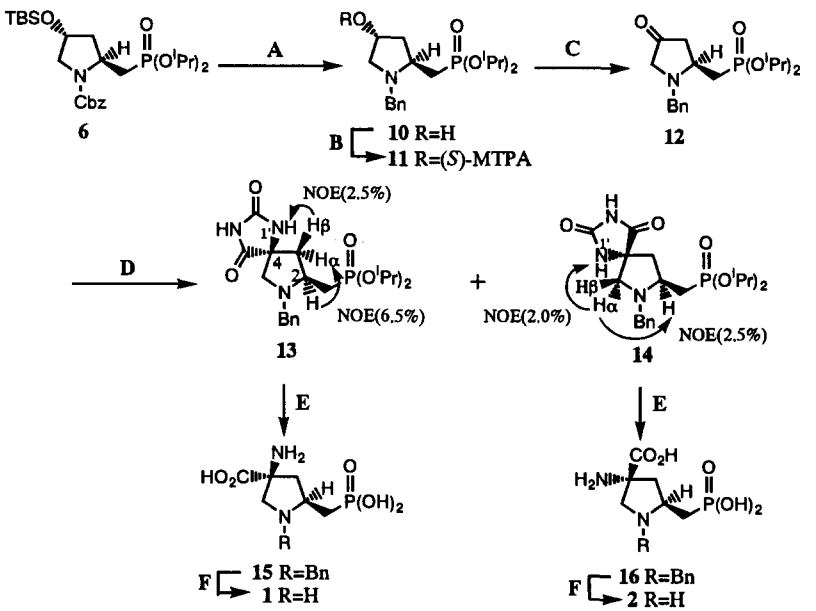
Figure 2



The Swern oxidation[12] of **10** gave the ketone **12** in 85% yield. The Bucherer-Bergs reaction of **12** with ammonium carbonate and potassiumu cyanide in 60% aqueous ethanol gave the spirohydantoins (2*S*,4*S*)-**13** and (2*S*,4*R*)-**14** as pure diastereoisomers in the ratio of 84:16, respectively in 75% yield, after purification by flash chromatography (SiO_2, chloroform/methanol: 50/1). The stereostructures of the newly formed stereogenic centers at C_4 position of these isomers **13** and **14** were assigned by NOE experiments, as indicated

in **Scheme 2**. Thus, NOEs between the signals due to C_2-H and C_3-Hα and that between the signals due to C_3-Hβ and N_1'H in **13** were found to be 6.5% and 2.5%, respectively, and no NOE between the signal due to C_3-Hα and N_1'H was observed. On the other hand, NOEs between the signals due to C_5-Hα and N_1'H and that between the signals due to C_5-Hα and C_2-H in **14** were recorded as 2.0% and 2.5%, respectively, and no NOE between the signal due to C_5-Hβ and N_1'H was observed. According, the C_3-Hβ and N_1'H in **13** and **14** were assigned to have *cis*-and *trans*-configurations, respectively. The absolute configurations of **13** and **14** were unambiguously determined as (2*S*,4*S*)-**13** and (2*S*,4*R*)-**14**, respectively. Finally, hydrolysis of **13** and **14** with 6*N* HCl followed by hydrogenolysis with 20% palladium hydroxide on carbon in 5% aqueous acetic acid gave the desired free ω-phosphono-α-amino acids **1** and **2**, respectively, after purification by ion exchange resin (Dowex 50W x 8) (**Schme 2**). The diastereomeric purities of each of **1** and **2** were confirmed by 400 MHz ^{1}H-NMR spectra (d.e.>95%).

Scheme 2



Reagents: **A**. i) 10% Pd-C/H_2, *p*-TsOH, MeOH, ii) BnCl, Et_3N, CH_2Cl_2, reflux,10h; **B**. (*S*)-MTPA chloride, pyridine, r.t ; **C**.$(COCl)_2$, DMSO, CH_2Cl_2, -78°C, then Et_3N; **D**.$(NH_4)_2CO_3$, KCN, 60% aq. EtOH, 55°C, 24h; **E**. 6*N* HCl, 130°C in a sealded tube, 24h; **F**. 20% $Pd(OH)_2$-C/H_2, 5% AcOH, 3 atm.

The synthetic strategy outlined above would be equally applicable for the synthesis of ***ent*-1** and ***ent*-2**, starting with *cis*-4-hydroxy-*D*-proline. The methodology we have established for producing the α-amino acid moiety at C_4 position in the 2-substituted pyrrolidine ring without disturbing C_2 stereogenic center is thus particularly versatile.

Experimental

General. Melting points were measured on a Yanaco MP-S3 micro melting point apparatus and uncorrected. Optical rotations were measured with a JASCO DIP-370 automatic digital polarimeter. Infrared

(IR) spectra were recorded with a Hitachi 270-30 spectrometer. ^{1}H- and ^{13}C-NMR spectra were measured with a JNM- GSX400 (400 MHz) or a JNM-EX90 (90 MHz) spectrometer. The chemical shifts were expressed in ppm (δ) downfield from tetramethylsilane as internal standard in $CDCl_3$ solutions, or from 3-(trimethylsilyl)-1-propane-sulfonic acid sodium salt as internal standard in D_2O solutions. Coupling constants were expressed in Hz. The following abbreviation are used: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). Electron impact mass spectra (EIMS), high resolution mass spectra (HRMS) and fast atom bombardment mass spectra (FABMS) were obtained with JMS DX-300 spectrometer. Routine monitoring of reactions was carried out using Merck TLC aluminium sheet silica gel 60 F_{254}. Column chromatography was performed on Merck silica gel, 70-230 mesh. Flash column chromatography was performed with indicated solvents on Merck silica gel, 230-400 mesh. Solvents and commercial reagents were dried and purified before use. Methanol and ethanol were distilled from sodium; tetrahydrofuran was distilled from sodium benzophenone ketyl; dichloromethane and dimethyl sulfoxide were distilled from calcium hydride under N_2 atmosphere. The *trans*-4-hydroxy-*L*-proline as a chiral starting meterial was purchased from Sigma Chemical Co. **(2*S*,4*R*)-1-Benzyloxycarbonyl-4-[(*tert*-butyldimethylsilyl)oxy]-2-(methoxycarbonyl)pyrrolidine 3** and **(2*S*,4*R*)-1-*tert*-Butoxycarbonyl-4-[(*tert*-butyldimethylsilyl)oxy]-2-(hydroxymethyl)pyrrolidin 8** were prepared from *trans*-4-hydroxy-*L*-proline according to the reported method.[9]

(2*S*,4*R*)-1-Benzyloxycarbonyl-4-[(*tert*-butyldimethylsilyl)oxy]-2-(hydroxymethyl)pyrrolidine 4. Methanol (8 ml) was added dropwise to a stirred mixture of **3**[9] (7.2 g, 18 mmol) and sodium borohydride (1.4 g, 36 mmol) in tetrahydrofuran (40 ml) at 55°C. After 1 h, water (5 ml) was added to the reaction mixture. Most of the organic solvent was removed *in vacuo*. Water (10 ml) was added and the mixture was extracted with ethyl acetate (60 ml). The extract was washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (ethyl acetate/n-hexane: 2/1) to give **4** (5.7 g, 85%) as a colorless viscous oil. $[\alpha]^{24}_D$ -45.6 (c 0.98, MeOH). IR (neat): 3452, 1720. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.03-0.09 [6H, m, $Si(CH_3)_2$], 0.86 (9H, s, $SiC(CH_3)_3$), 1.60-1.70 (1H, m, C_3-H), 1.94-2.03 (1H, m, C_3-H), 3.40-3.80 (5H, m, C_5-H_2, CH_2OH, and OH), 4.10-4.22 (1H, m, C_2-H), 4.56-4.72 (1H, m, C_4-H), 5.10-5.20 (2H, m, CH_2Ph), 7.29 (5H, m, Ph). ^{13}C-NMR (90MHz, $CDCl_3$): δ -4.89 and -4.80 ($Si(CH_3)_2$), 17.95 ($SiC(CH_3)_3$), 25.69 ($SiC(CH_3)_3$), 37.93 (C_3), 56.02 (C_5), 59.65 (C_2), 66.61 and 66.70 (CH_2OH, rotamers), 67.28 (CH_2Ph), 69.78 (C_4), 127.81, 128.07 128.53, and 136.50 (Ph), 157.41 (CO_2). EIMS m/z: 365 (M^+). HRMS: calcd for $C_{19}H_{31}NO_4Si$: 365.2022. Found: 365. 2008.

(2*S*,4*R*)-1-Benzyloxycarbonyl-4-[(*tert*-butyldimethylsilyl)oxy]-2-(iodomethyl)pyrrolidine 5. A mixture of **4** (3.1 g, 8.4 mmol), triphenylphosphine (5.5 g, 21 mmol), imidazole (1.4 g, 21 mmol), and iodine (2.1 g, 17 mmol) in benzene (40 ml) was stirred at room temperature. After 1 h, water (10 ml) was added to the reaction mixture and aqueous layer was separated, and extracted with benzene (40 ml). The extract was washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (benzene) to give **5** (3.0 g, 75%) as a pale yellow oil. $[\alpha]^{24}_D$ -57.7 (c 1.21, MeOH). IR (neat): 1708. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.03-0.07 (6H, m, $Si(CH_3)_2$), 0.85 (9H, s, $SiC(CH_3)_3$), 1.84-1.94 (1H, m, C_3-H), 1.97-2.14 (1H, m, C_3-H), 3.36-3.74 (4H, m, C_5-H_2, CH_2I), 3.88-4.00 (1H, m, C_2-H), 4.34-4.40 (1H, m, C_4-H), 5.06-5.20 (2H, m, CH_2Ph), 7.30 (5H, m, Ph). ^{13}C-NMR (90 MHz, $CDCl_3$): δ -4.82 and -4.76 ($Si(CH_3)_2$), 12.92 and 13.00 (CH_2I, rotamers), 17.95 ($SiC(CH_3)_3$), 25.70 ($SiC(CH_3)_3$), 41.39 and 42.17 (C_3, rotamers), 55.98 and 56.02 (C_5, rotamers),

56.35 and 56.41 (C_2, rotamers), 66.79 and 67.14 (CH_2Ph, rotamers), 69.52 and 69.90 (C_4, rotamers), 127.68, 127.82, 127.93, 128.04, 128.48, and 127.57 (Ph, rotamers), 155.29 (CO_2). EIMS m/z: 475 (M^+). HRMS: calcd for $C_{19}H_{30}NO_3SiI$: 475.1040. Found: 465.1022.

Arbuzov Reaction of 5. **5** (4.1 g, 8.6 mmol) was dissolved in triisopropyl phosphite (8.9 g, 43 mmol) and refluxed under nitrogen atmosphere for 24 h. The reaction mixture was distillated *in vacuo* to remove unreacted triisopropyl phosphite. The residue was purified by column chromatography (ethyl acetate/n-hexane:1/1) to give (2*S*,4*R*)-1-benzyloxycarbonyl-4-[(*tert*-butyldimethylsilyl)oxy]-2-[(diisopropylphosphono)-methyl]-pyrrolidine **6** (2.8 g, 64%) and (5*S*,7*R*)-1-aza-7-(*tert*-butyldimethylsilyl)oxy-3-oxabicyclo[3,3,0]-octan-2-one **7**[9] (0.33 g, 15%).

6: colorless viscous oil. $[\alpha]^{20}_D$ -25.7 (c 1.10, MeOH). IR (neat): 1706, 1248, 1008. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.04-0.07 (6H, m, $Si(CH_3)_2$), 0.86 (9H, s, $SiC(CH_3)_3$), 1.08-1.30 (12H, m, $CH(C\underline{H}_3)_2$ x 2), 1.65-1.78 (1H, m, C_3-H), 1.97-2.15 (2H, m, CH_2P), 2.40-2.50 (1H, m, C_3-H), 3.42-3.52 (2H, m, C_5-H_2), 4.08-4.18 (1H, m, C_2-H), 4.32-4.40 (1H, m, C_4-H), 4.50-4.60 (2H, m, $C\underline{H}(CH_3)_2$ x 2), 5.10-5.22 (2H, m, CH_2Ph), 7.29 (5H, m, Ph). ^{13}C-NMR (90 MHz, $CDCl_3$): δ -4.86 and -4.77 ($Si(CH_3)_2$), 17.94 ($SiC(CH_3)_3$), 23.55, 23.71, 23.82, and 23.98 (each d, ^{3}Jc,p=4.4, $OCH(\underline{C}H_3)_2$), 24.04 and 25.70 ($Si(CH_3)_3$, rotamers), 31.41 (d, ^{1}Jc,p=135, CH_2P), 40.75 and 41.49 (C_3, rotamers), 51.96 and 52.51 (C_2, rotamers), 54.82 and 55.04 (C_5, rotamers), 66.54 and 66.93 (CH_2Ph, rotamers), 70.10 and 70.16 (each d, ^{2}Jc,p=7.4, $OCH(CH_3)_2$), 71.91 and 71.97 (C_4, rotamers), 127.68, 127.93, 128.32, 128.45, 129.85, 129.93, 136.65, and 136.89 (Ph, rotamers), 155.10 (CO_2). EIMS m/z: 513 (M^+). HRMS: calcd for $C_{25}H_{44}NO_6SiP$: 513.2676. Found: 513.2684.

7: $[\alpha]^{23}_D$ -40.6 (c 1.30, MeOH]. colorless plates. mp 93-94°C (from isopropyl ether). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.06 (6H, s, $Si(CH_3)_2$), 0.81 (9H, s, $SiC(CH_3)_3$), 1.54 (1H, ddd, J=12.45, 10.25, 5.30, C_6-H), 1.95 (1H, m, C_6-H), 2.97 (1H, dd, J=12.25, 1.60, C_5-H), 3.80 (1H, dd, J=12.19, 5.35, C_8-H), 4.18 (2H, m, C_7- and C_8-H), 4.47 (2H, m, C_4-H_2). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 17.95 ($SiC(CH_3)_3$), 25.71 ($SiC(\underline{C}H_3)_3$), 40.98 (C_6), 56.17 (C_8), 57.82 (C_5), 67.22 (C_4), 72.99 (C_7), 161.58 (CO). *Anal.* Calcd for $C_{12}H_{23}NO_3Si$: C, 55.99; H, 9.00; N, 5.44. Found: C, 55.89; H, 8.87; N, 5.45.

(2*S*,4*R*)-1-*tert*-Butoxycarbonyl-4-[(*tert*-butyldimethylsilyl)oxy]-2-(iodomethyl)pyrrolidine 9. The same treatment of **8**[9] (6.1 g, 18 mmol) as described for the preparation of **5** gave **9** (6.5 g, 80%) as a pale yellow oil. $[\alpha]^{21}_D$ -51.9 (c 1.50, MeOH). IR (neat): 1698, 1394, 1256, 1166. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.04-0.07 (6H, m, $Si(CH_3)_2$), 0.87 (9H, s, $SiC(CH_3)_3$), 1.47 (9H, s, $OC(CH_3)_3$), 1.81-2.13 (2H, m, C_3-H_2), 3.35-3.57 (4H, m, C_5-H_2 and CH_2I), 3.63-4.03 (1H, m, C_2-H), 4.20-4.50 (1H, m, C_4-H). EIMS m/z: 442 (M^++ 1).

Arbuzov Reaction of 9. Following the same procedure described for the Arbuzov reaction of **5**, treatment of **9** (2.5 g, 5.6 mmol) gave only **7** (0.51 g, 35%). The IR and ^{1}H-NMR spectra of this sample were identical with those recorded for **7** obtained above.

(2*S*,4*R*)-1-Benzyl-2-[(diisopropylphosphonyl)methyl]-4-hydroxypyrrolidine 10. A mixture of **6** (3.0 g, 5.8 mmol), *p*-toluenesulfonic acid (2.4 g, 12 mmol), and 10% paradium on carbon (0.4 g) in methanol (50 ml) was stirred under H_2 atmosphere at room temperature for 3 h. The catalyst was filted off and the filtrate was concentrated *in vacuo* to give a residue. Benzyl chloride (1.1 g, 8.6 mmol) and triethylamine (2.3 g, 22 mmol) was added to the mixture of the resulting residue in dichloromethane (100 ml) and the mixture was refluxed for 12 h. 1M aqueous NaOH solution was added to the mixture, the mixture was extracted with dichloromethane (60 ml). The extract was washed with brine and dried over Na_2SO_4.

Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (ethyl acetate/methanol: 10/1) to give **10** (1.3 g, 63%) as a pale yellow oil. $[\alpha]^{20}_D$ -59.5 (c 1.10, MeOH). IR (neat): 3396, 1240, 1218, 1012, 988. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.30-1.34 (12H, m, $CH(C\underline{H}_3)_2$ x 2), 1.70-1.82 (1H, m, C_3-H), 1.92-2.06 (1H, m, C_3-H), 2.09-2.40 (4H, m, C_5-H, CH_2P, and OH), 3.04-3.13 (1H, m, C_2-H), 3.18-3.23 (1H, m, C_5-H), 3.34 and 3.35 (1H, each d, J=13.19, CH_2Ph), 3.99 and 4.00 (1H, each d, J=13.19, CH_2Ph), 4.35-4.60 (3H, m, C_4-H and $C\underline{H}(CH_3)_3$ x 2), 7.29 (5H, m, Ph). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 24.16 and 24.36 ($CH(\underline{C}H_3)_2$), 32.56 (d, ^{1}Jc,p=139.16, CH_2P), 42.57 (C_3), 57.96 (C_2), 58.30 (C_5), 62.16 (CH_2Ph), 68.94 (C_4), 70.31 and 70.45 (each d, ^{2}Jc,p=7.4, $O\underline{C}H(CH_3)_2$), 127.29, 128.56, 129.20, and 139.30 (Ph). EIMS m/z: 355 (M^+). HRMS: calcd for $C_{18}H_{30}NO_4P$: 355.1912. Found: 355.1901.

(2*S*,4*R*)-1-Benzyl-2-[(diisopropylphosphonyl)methyl]-4-[(*S*)-2-methoxy-2-(trifluoromethyl)phenylacetoxy]pyrrolidine 11. (*S*)-2-Methoxy-2-(trifluoromethyl)phenylacetyl chloride [(*S*)-MTPACl] (0.08g, 0.24 mmol) was added to a stirred solution of **10** (0.08 g, 0.22 mmol) in pyridine (3 ml) at room temperature for 1 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by short column chromatography (ethyl acetate/n-hexane: 3/1) to give **11** (0.10 g, 82%) of MTPA ester as a single compound. The enantiomeric excess of **11** was more than 95% based on ^{1}H-NMR analysis of this MTPA ester. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.30-1.33 (12H, m, $CH(C\underline{H}_3)_2$ x 2), 1.72-1.84 (1H, m, C_3-H), 2.06-2.13 (1H, m, C_3-H), 2.18-2.46 (3H, m, C_5-H, CH_2P), 2.98-3.06 (1H, m, C_2-H), 3.25 (1H, d, J=13.19, CH_2Ph), 3.30-3.40 (1H, m, C_5-H), 3.53 (3H, d, J=1.1, OCH_3), 3.98 (1H, d, J=13.19, CH_2Ph), 5.30-5.42 (3H, m, $C\underline{H}(CH_3)_2$ x 2 and C_4-H), 7.20-7.50 (10H, m, Ph x 2). EIMS m/z: 571 (M^+). HRMS: calcd for $C_{28}H_{37}NO_6PF_3$: 571.2310. Found: 571.2298.

(2*S*)-1-Benzyl-2-[(diisopropylphosphonyl)methyl]-4-oxopyrrolidine 12. A solution of dry dimethyl sulfoxide (0.73 g, 9.4 mmol) in dry dichloromethane (5 ml) was added dropwise to a stirred solution of oxalyl chloride (0.60 g, 4.7 mmol) in dry dichloromethane (5 ml) at -78°C under N_2 atmosphere. After 15 min, a solution of **10** (1.53 g, 4.3 mmol) in dry dichloromethane (8 ml) was added slowly, and stirring was continued for 30 min at -78°C. After addition of triethylamine (2.1 g, 21 mmol), the mixture was gradually warmed up to room temperature. The mixture was quenched with water (3 ml) and aqueous layer was separated and extracted with dichloromethane (30 ml). The extract was washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (ethyl acetate/methanol: 20/1) to give **12**(1.3 g, 85%) as a pale yelloe oil. $[\alpha]^{23}_D$ -107.6 (c 1.03, MeOH). IR (neat): 1760, 1246, 1008, 984. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.29-1.33 (12H, m, $CH(C\underline{H}_3)_2$ x 2), 1.85 and 1.90 (1H, each dd, J=15.02, 10.25, C_3-Hβ), 2.35 (1H, dd, J=18.32, 9.52, CH_2P), 2.42 and 2.48 (1H, each dd, J=15.02, 6.02, C_3-Hα), 2.70 (1H, d, J=17.60, C_5-H), 2.76 (1H, dd, J=18.32, 6.60, CH_2P), 3.20 (1H, d, J=17.60, C_5-H), 3.22-3.31 (1H, m, C_2-H), 3.30 (1H, d, J=13.19, CH_2Ph), 4.10-4.22 (3H, m, CH_2Ph and $C\underline{H}(CH_3)_2$ x 2), 7.29 (5H, m, Ph). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 24.16 and 24.36 ($CH(\underline{C}H_3)_2$), 32.06 (d, ^{1}Jc,p=139.2, CH_2P), 44.88 (C_3), 56.54 (C_2), 57.90 (C_5), 61.88 (CH_2Ph), 70.26 and 70.38 (each d, ^{2}Jc,p=7.4, $\underline{C}H(CH_3)_2$ x 2), 127.48, 128.54, 129.12, and 139.20 (Ph), 212.20 (CO). EIMS m/z: 353 (M^+). HRMS: calcd for $C_{18}H_{28}NO_4P$: 352.1756. Found: 352.1782.

(2*S*,4*S*)-1-Benzyl-2-[(diisopropylphosphonyl)methyl]pyrrolidine-4-spiro-5'-hydantoin 13 and **(2*S*,4*R*)-Isomer 14.** Ammonium carbonate (1.15 g, 12 mmol) and potassium cyanide (0.31 g, 4.7 mmol) were added to a solution of **12** (0.84 g, 2.4 mmol) in 60% aqueous ethanol (40 ml). The mixture was heated at 55°C for 24h and the solvent was removed *in vacuo*. The residue was diluted with water (15 ml), and

the mixture was extracted with ethyl acetate (40 ml). The extract was washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* give a residue, which was purified by column chromatography (chloroform/methanol: 10/1) to give **(13+14)** (0.75 g, 75%) as a mixture of two diastereoisomers. This mixture was further separated by flash column chromatography (chloroform/methanol: 50:1) to give **13** as a less polar product and **14** as a more polar product in a ratio of 84:16.

Less polar 13: colorless viscous oil. $[\alpha]^{23}_D$ -77.4 (c 0.56, MeOH). IR (neat): 3400, 3250, 1776, 1728, 1120, 1080. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.30-1.34 (12H, m, $CH(C\underline{H}_3)_2$ x 2), 2.02 (1H, dd, J=14.29, 6.59, C_3-Hβ), 2.10-2.25 (2H, m, CH_2P), 2.64 (1H, d, J=9.52, C_5-H), 2.71 (1H, dd, J=14.29, 9.15, C_3-Hα), 2.90 (1H, d, J=9.52, C_5-H), 2.94-3.06 (1H, m, C_2-H), 3.30 (1H, d, J=13.19, CH_2Ph), 4.06 (1H, d, J=13.19, CH_2Ph), 4.66-4.76 (2H, m, $C\underline{H}(CH_3)_2$ x 2), 7.29 (5H, m, Ph), 7.52 (1H, br s, $N_{1'}$-H), 9.35 (1H, br s, $N_{3'}$-H). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 24.04 and 24.13 (each d, ^{3}Jc,p=4.4, $CH(\underline{C}H_3)_2$ x 2), 31.45 (d, ^{1}Jc,p=140.8, CH_2Ph), 42.44 (C_3), 56.69 (C_5), 57.93 (C_2), 62.47 (CH_2Ph), 66.53 (C_4), 70.53 (d, ^{2}Jc,p=7.4, $C\underline{H}(CH_3)_2$ x 2), 127.37, 128.42, 128.83, and 137.37 (Ph), 156.46 ($C_{2'}$-CO), 176.31 ($C_{4'}$-CO). EIMS m/z: 423 (M^+). HRMS: calcd for $C_{20}H_{30}N_3O_5P$: 423.1923. Found: 423.1942.

More polar 14: colorless viscous oil. $[\alpha]^{23}_D$ -68.4 (c 0.80, MeOH). IR (neat): 3460, 3250, 1776, 1730, 1110, 1080. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.25-1.35 (12H, m, $CH(C\underline{H}_3)_2$ x 2), 1.85-2.25 (2H, m, CH_2P), 2.31 (1H, dd, J=13.19, 9.15, C_3-Hα), 2.39 (1H, dd, J=13.19, 6.23, C_3-Hβ), 2.51 (1H, d, J=10.62, C_5-Hα), 3.30 (1H, d, J=10.62, C_5-Hβ), 3.40 (1H, d, J=13.56, CH_2Ph), 3.99 (1H, d, J=13.56, CH_2Ph), 4.04-4.12 (1H, m, C_2-H), 4.60-4.78 (2H, m, $C\underline{H}(CH_3)_2$ x 2), 7.29 (5H, m, Ph), 7.57 (1H, br s, $N_{1'}$-H), 9.92 (1H, br s, $N_{3'}$-H). EIMS m/z: 423 (M^+). HRMS: calcd for $C_{20}H_{30}N_3O_5P$: 423.1923. Found: 423.1905.

Acid Hydrolysis of 13 and 14.

a) Preparation of **(2*S*,4*S*)-4-Amino-1-benzyl-4-carboxy-2-(phosphonomethyl)pyrrolidine 15**: A solution of **13** (0.82 g, 1.9 mmol) in 6*N* HCl (20 ml) was heated at 130°C for 24h in a sealed tube. After cooling, the mixture was concentrated *in vacuo*. The white residue was dissolved in water (8 ml) and purified by Dowex 50W x 8 (50-100 mesh) ion exchange column chromatography (water, then 5% aqueous ammonia) to give **15** (0.38 g, 63%) as a white solid. Recrystallization from 70% aqueous ethanol gave an analytical sample of **15** as a colorless needles, mp 205-207°C. $[\alpha]^{23}_D$ -54.6 (c 1.0, 2*N* HCl). IR (KBr): 3450, 3000-2100, 1640, 1400, 1135, 1110, 1038. ^{1}H-NMR (400 MHz, D_20): δ 1.92-2.03 (2H, m, CH_2P), 2.22 (1H, dd, J=14.25, 12.09, C_3-Hβ), 2.38 (1H, dd, J=14.25, 9.89, C_3-Hα), 3.35 (1H, d, J=12.82, C_5-H), 3.42 (1H, d, J=12.82, C_5-H), 3.67-3.80 (1H, m, C_2-H), 3.87 (1H, d, J=13.19, CH_2Ph), 4.53 (1H, d, J=13.19, CH_2Ph), 7.45 (5H, m, Ph). ^{13}C-NMR (90 MHz, D_2O): δ 31.40 (d, ^{1}Jc,p=124.7, CH_2P), 43.41 (C_3), 59.27 (C_5), 62.13 (CH_2Ph), 65.72 (C_2), 131.85, 132.69, 135.47, and 135.50 (Ph), 176.84 (CO_2H). FABMS m/z: 315 (M^++ 1). *Anal.* Calcd for $C_{13}H_{19}N_2O_5P$ ($2H_2O$): C, 44.57; H, 6.62; N, 7.99. Found: C,44.61; H, 6.48; N, 7.70.

b) Preparation of **(2*S*,4*R*)-4-Amino-1-benzyl-4-carboxy-2-(phosphonomethyl)pyrrolidine 16**: The same treatment of **14** (0.35 g, 0.8 mmol) as described for the preparation of **15** gave **16** (0.17 g, 60%) as a white solid. Recrystallization from 70% aqueous ethanol gave an analytical sample of **16** as a colorless needles, mp 218-220°C. $[\alpha]^{23}_D$ -45.3 (c 1.0, 2*N* HCl). IR (KBr): 3450, 3100-2100, 1640, 1400, 1070. ^{1}H-NMR (400 MHz, D_2O): δ 1.93-2.05 (1H, m, CH_2P), 2.38-2.45 (1H, m, CH_2P), 2.53 (1H, dd, J=15.02, 11.72, C_3-Hα), 2.75 (1H, dd, J=15.02, 6.59, C_3-Hβ), 3.22 (1H, d, J=13.19, C_5-H), 3.72 (1H, d, J=13.19, C_5-H), 3.75-3.82 (1H, m, C_2-H), 4.08 (1H, d, J=13.19, CH_2Ph), 4.52 (1H, d, J=13.19, CH_2Ph), 7.42 (5H, m, Ph). ^{13}C-NMR (90 MHz, D_2O): δ 32.18 (d, ^{1}Jc,p=129, CH_2Ph), 43.86 (C_3), 58.47 (C_2),

62.00 (CH_2Ph), 63.81 (C_4), 65.34 (C_2), 132.00, 132.38, 133.24, and 133.43 (Ph), 176.94 (CO_2H). FABMS m/z: 315 (M^++ 1). *Anal.* Calcd for $C_{13}H_{19}N_2O_5P$ ($2H_2O$): C, 44.57; H, 6.62; N, 7.99. Found: C,44.35; H, 6.34; N, 7.78.

Hydrogenolysis of 15 and 16

a) Preparation of **(2*S*,4*S*)-4-Amino-4-carboxy-2-(phosphonomethyl)pyrrolidine 1**: A mixture of **15** (0.45 g, 1.3 mmol) and 20% palladium hydroxide on carbon (0.08 g) in 5% acetic acid (20 ml) was stirred for 5h at room temperature under H_2 atmosphere (3 atm). The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The white residue was dissolved in water (5 ml) and purified by Dowex 50W x 8 (50-100 mesh) ion exchange column chromatography (water, then 5% aqueous ammonia) to give **1** (0.24 g, 83%) as a white solid. Recrystallization from 70% aqueous ethanol gave an analytical sample of **1** as a colorless needles, mp 156-158°C. $[\alpha]^{25}_D$ -15.9 (c 0.93, H_2O). IR (KBr): 3490, 3030, 3000-2100, 1614, 1404, 1168, 1120. ^{1}H-NMR (400 MHz, D_2O): δ 1.97-2.20 (2H, m, CH_2P), 2.28 (1H, dd, J=13.56, 11.32, C_3-Hβ), 2.84 (1H, dd, J=13.56, 6.96, C_3-Hα), 3.67 (1H, d, J=12.82, C_5-H), 3.85 (1H, d, J=12.82, C_5-H), 4.10-4.26 (1H, m, C_2-H). ^{13}C-NMR (90 MHz, D_2O): δ 32.78 (d, ^{1}Jc,p=126.2, CH_2P), 43.33 (d, ^{3}Jc,p=5.8, C_3), 54.00 (C_5), 59.87 (C_2), 65.33 (C_4), 176.56 (CO_2H). FABMS m/z: 225 (M^++ 1). *Anal.* Calcd for $C_6H_{13}N_2O_5P$ (H_2O): C, 30.00; H, 5.45; N, 11.66. Found: C, 29.78; H, 5.35; N, 11.46.

b) Preparation of **(2*S*,4*R*)-4-Amino-4-carboxy-2-(phosphonomethyl)pyrrolidine 2**: The same treatment of **16** (0.15 g, 0.4 mmol) as described for the preparation of **1** gave **2** (75 mg, 78%) as a white solid. Recrystallization from 70% aqueous ethanol gave an analytical sample of **2** as a colorless needles, mp >300°C. $[\alpha]^{20}_D$ -14.3 (c 0.30, H_2O). IR (KBr): 3460, 3148, 1644, 1396, 1060. ^{1}H-NMR (400 MHz, D_2O): δ 1.90-2.12 (2H, m, CH_2P), 2.39 (1H, dd, J=14.65, 11.36, C_3-Hα), 2.63 (1H, dd, J=14.65, 6.59, C_3-Hβ), 3.49 (1H, d, J=13.19, C_5-H), 3.89 (1H, d, J=13.19, C_5-H), 4.06-4.20 (1H, m, C_2-H). ^{13}C-NMR (90 MHz, D_2O): δ 33.96 (d, ^{1}Jc,p=126.1, CH_2P), 44.75 (d, ^{3}Jc,p=8.8, C_3), 55.30 (C_5), 59.52 (C_2), 66.73 (C_4), 176.95 (CO_2H). FABMS m/z: 225 (M^++ 1). *Anal.* Calcd for $C_6H_{13}N_2O_5P$ (H_2O): C, 30.00; H, 5.45; N, 11.66. Found: C, 29.84; H, 5.28; N, 11.58.

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