ASYMMETRIC SYNTHESES OF (2*R*,4*S*)-4-AMINO-4-CARBOXY-2-METHYLPYRROLIDINE AND (2*R*, 4*S*)-4-AMINO-2-CARBOXY-2-ETHYL-PYRROLIDINE AS NOVEL 2-ALKYL-SUBSTITUTED (-)-CUCURBITINE ANALOGUES

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Abstract---Asymmetric syntheses of (2*R*,4*S*)-4-amino-4-carboxy-2-methylpyrrolidine (**1**) and (2*R*,4*S*)-4-amino-4-carboxy-2-ethylpyrrolidine (**2**) as 2-alkyl-substituted (-)-cucurbitine analogues, have been achieved without disturbing C_2 stereogenic center through a route including a diastereoselective Bucherer-Bergs reaction of 2-methyl- and 2-ethenyl-4-oxopyrrolidines (**10**) and (**24**), easily derived from *trans*-4-hydroxy-*L*-proline.

Chiral, non-racemic pyrrolidines are common structural subunits found in many natural and synthetic products with biological activity.[1] The biological activities of pyrrolidines depend on their substitution pattern, functionalization, and absolute configuration. Consequently, a variety of synthetic methods for chiral pyrrolidines continue to be reported.[1,2]

(-)-*Cucurbitine*[3] *containing the (S)-α-amino acid function at the* 3-position in the pyrrolidine ring is a naturally occurring non-proteinogenic amino acid, which has been isolated from the seeds of several species of *Cucurbitaceae*, and has been known to inhibit [4] the growth of immature *Schistosoma japonicum*. So far, a few reports on the synthesis of Cucurbitine are found in literature.[5] Only one asymmetric synthesis of (-)- and (+)-one has been reported by Morimoto and Achiwa.[5c] However, 2-alkyl-substituted cucurbitines have not been reported (Figure 1).

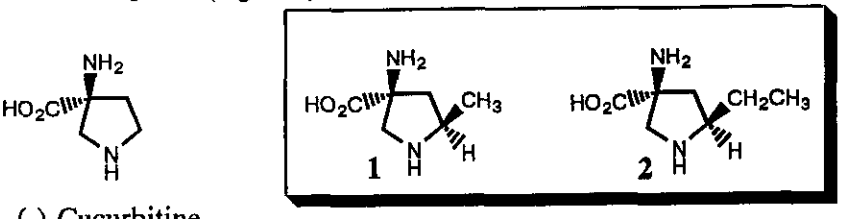
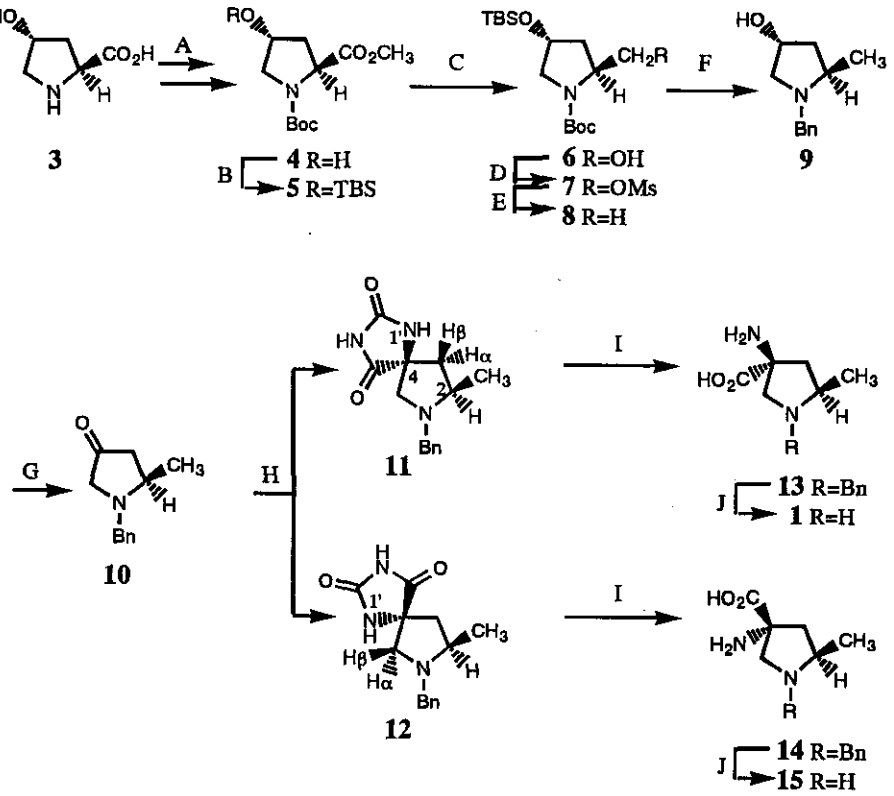


Figure 1

Our interest in this field has been focused on the construction of α-amino acid function on the pyrrolidine ring in connection with the synthesis of biologically active non-proteinogenic amino acid, and for this

purpose we have employed a Bucherer-Bergs reaction of 4-oxoprolinate derivatives leading to the stereoselective construction of α-amino acid function.[6] Herein, we report a full detail of the syntheses of (2*R*,4*S*)-4-amino-4-carboxy-2-methylpyrrolidine (**1**) and (2*R*,4*S*)-4-amino-4-carboxy-2-ethylpyrrolidine (**2**) and their C4-enantiomers (**15**) and (**30**) as novel 2-alkyl-substituted cucurbitine analogues by employing our synthetic methodology described above.

Preparation of 2-Methyl Cucurbitine Analogues (1, 15) We initially pursued the synthesis of (2*R*,4*S*)-(**1**) as shown in Scheme 1.



Scheme 1

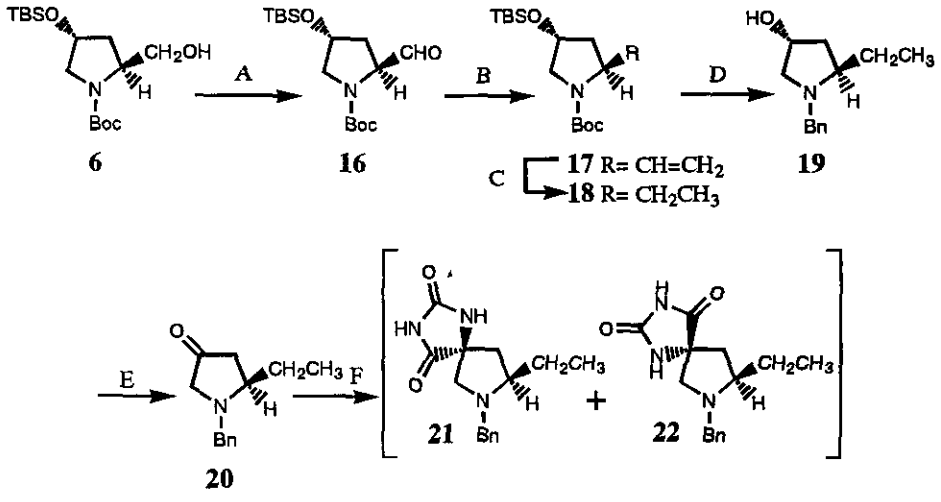
Reagent and conditions: A. i) $SOCl_2$, MeOH, reflux, ii) Boc_2O, Et_3N, CH_2Cl_2, room temperature; B. TBSCl, imidazole, DMF, 0°C; C. $LiBH_4$, dry THF, 0°C; D. $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0°C; E. $LiEt_3BH$ (Super-Hydride), dry THF, 0°C; F. i) *p*-TsOH, MeOH, ii) BnCl, Et_3N, CH_2Cl_2, reflux; G. $(COCl)_2$, DMSO, dry CH_2Cl_2, -78°C, then Et_3N; H. $(NH_4)_2CO_3$, KCN, 60% aq.MeOH, 55-60°C; I. 6*N* HCl, in a sealed tube, 130°C; J. 20% $Pd(OH)_2/C$, 5% AcOH, then 2*N* HCl.

At the outset, the key intermediate spirohydantoin (**11**) was prepared from *trans*-4-hydroxy-*L*-proline (**3**). **3** was converted to 1-*tert*-butoxycarbonyl-2-methylpyrrolidine (**8**) *via* **4**, **5**, **6**, and **7** according to the reported methods.[7] Next, the simultaneous removal of both the *N*- and *O*-protections of **8** by acidic hydrolysis with *p*-toluensulfonic acid in MeOH followed by *N*-benzylation with benzyl chloride and triethylamine (Et3N) in CH_2Cl_2 to give *N*-benzyl derivative (**9**) in 68% yield, and then the Swern oxidation[8] of **9** afforded the corresponding ketone (**10**) in 88% yield. The Bucherer-Bergs reaction[9] of **10**

with potassium cyanide (2 molar eq.) and ammonium carbonate (5 molar eq.) *in 60% aqueous* MeOH at 60°C for 24 h afforded a mixture of diastereomeric spirohydantoins (**11**) and (**12**) in a ratio of 80:20 respectively, in 70% yield. These isomers (**11**) and (**12**) could be cleanly separated by flash chromatography (SiO_2; $CHCl_3$/MeOH=50/1, v/v). The stereostructures of the newly formed stereogenic centers at C_4-position in both **11** and **12** were assigned by NOE measurements in their 400 MHz ^{1}H-nmr spectra. *Thus, for the compound* (**11**), *irradiation* of the C_2-CH_3 (1.24 ppm) produced an enhancement of the signals due to both the C_3-Hβ (1.69 ppm) and $N_{1'}$-H (6.86 ppm), and irradiation of the C_3-Hα (2.57 ppm) gave no enhancement of the signal due to the $N_{1'}$-H. For the compound (**12**), *irradiation of the* C_2-CH_3 (1.23 ppm) gave no enhancement of the signal due to the $N_{1'}$-H (6.31 ppm), but irradiation of the C_5-Hα (2.46 ppm) produced an enhancement of the signal due to both the C_2-H (2.88-3.00 ppm) and $N_{1'}$-H. Accordingly, the C_2-CH_3 and $N_{1'}$-H in **11** and **12** were assigned to have *cis*- and *trans*-configurations, respectively.

Subsequently, the target amino acid (**1**) was prepared by acidic hydrolysis of **11** with 6*N* HCl at 130°C in a sealed tube for 24 h followed by hydrogenolysis of the resulting *N*-benzylamino acid (**13**) with 20% $Pd(OH)_2$/C in 54 % overall yield from **11**. By employing the reaction pathway similar to that described above, **12** was converted into the amino acid (**15**) *via* **14** in 53% overall yield from **12**.

Preparation of 2-Ethyl Cucurbitine Analogues (2, 30)

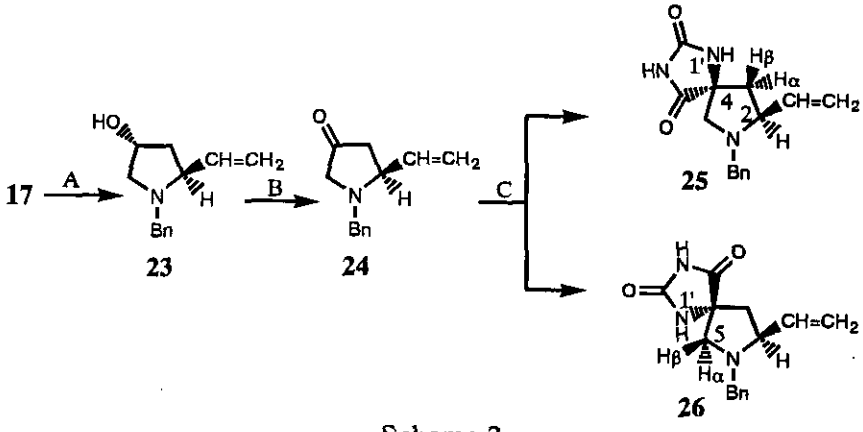


Scheme 2

Reagents and conditions: A. SO_3-pyridine, Et_3N, dry DMSO, 0°C; B. $MePPh_3Br$, NaH (60% mineral oil dispersion), dry THF, room temperature; C. 10% Pd/C-H_2, EtOH; D.i) *p*-TsOH, MeOH, room temperature, ii) BnCl, Et_3N, CH_2Cl_2, reflux; E. $(COCl)_2$,dry DMSO, dry CH_2Cl_2, -78°C, then Et_3N; F. $(NH_4)_2CO_3$, KCN, 60% aq. MeOH, 55-60°C.

We next proceeded to prepare (2*R*,4*S*)-**2**. Our first approach was based on the synthesis of the key intermediate 2-ethyl-spirohydantoin (**21**) as shown in Scheme 2. Thus, oxidation of alcohol (**6**) with sulfur trioxide (SO_3)-pyridine complex in dimethyl sulfoxide (DMSO) at 0°C according to the Parikh-Doehring procedure[10] gave the aldehyde (**16**) in 85% yield without detectable racemization, and which was

used immediately without purification for the next reaction. **16** was then converted to the alkene (**17**) by means of the Wittig reaction with methylenetriphenylphosphorane in 90% yield. The catalytic hydrogenation of **17** with 10% Pd/C gave the ethyl compound (**18**) quantitatively. Next, the simultaneous removal of both the *N*- and *O*-protection of **18** followed by *N*-benzylation gave **19** in 67% yield according to the similar procedure obtained **9** from **8**. The Swern oxidation of **19** afforded the ketone (**20**) in 88% yield. The Bucherer-Bergs reaction of **20** gave a mixture of diastereomeric spirohydantoins (**21**+ **22**) in 60% yield, but which could not be unfortunately separated by chromatographic methods. We therefore discontinued this route. Next, we turned our attention to the synthesis of 2-ethenyl-spirohydantoins (**25** and **26**) by alternative route to investigate the separable possibility of the diastereoisomers, as shown in Scheme 3.



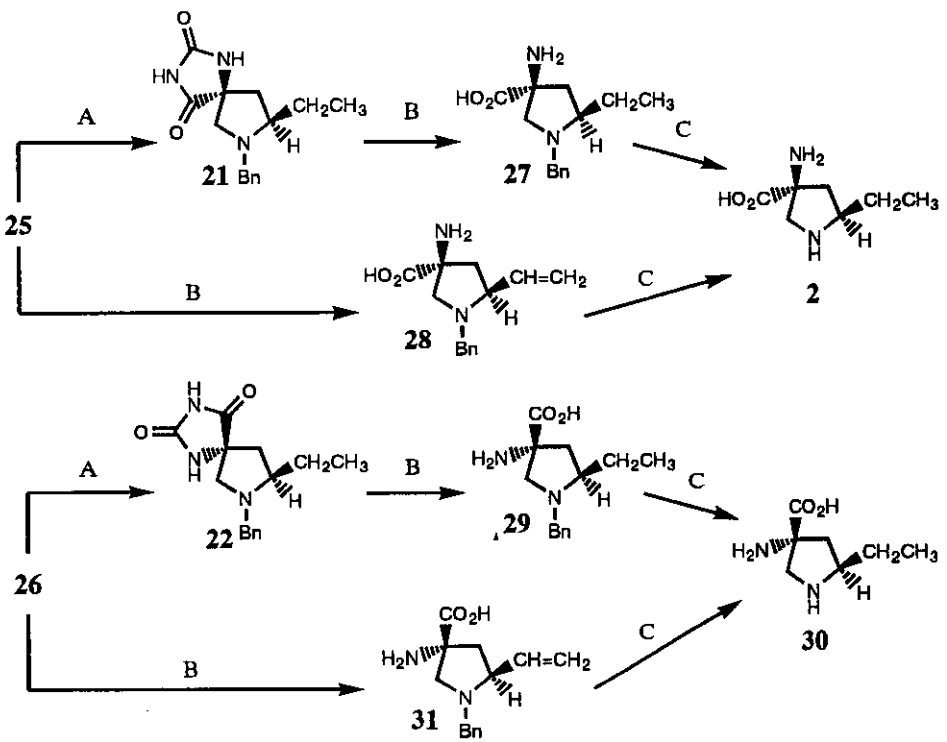
Scheme 3

Reagents and conditions: A. i) *p*-TsOH, MeOH, room temperature, ii) BnCl, Et_3N, CH_2Cl_2, reflux; B. $(COCl)_2$, dry DMSO, dry CH_2Cl_2, -78°C, then Et_3N; C. $(NH_4)_2CO_3$, KCN, 60% aq. MeOH, 55-60°C.

Thus, the simultaneous deprotection of both the TBS and Boc groups of **17** followed by *N*-benzylation gave **23** in 61% overall yield from **17**. The Swern oxidation of **23** afforded the ketone (**24**) in 88% yield, then the Bucherer-Bergs reaction of **24** in a similar manner to that described above gave a mixture of diastereomeric spirohydantoins (**25**) and (**26**) in a ratio of 84:16 respectively, in 78% yield. These isomers (**25**) and (**26**) could be cleanly separated by flash chromatography (SiO_2; $CHCl_3$/MeOH=100/1, v/v). The stereostructures of the newly formed stereogenic centers at the C_4-position in both **25** and **26** were assigned by NOE measurements in their 400 MHz ^{1}H-nmr spectra. Thus, for the compound (**25**), irradiation of the C_3-Hβ (1.76 ppm) produced an enhancement of the signal due to the $N_{1'}$-H (7.20 ppm), and irradiation of the C_3-Hα (2.35 ppm) produced no enhancement of the signal due to the $N_{1'}$-H, which suggested that the C_3-Hβ and $N_{1'}$-H are of the same side of the molecule. For the compound (**26**), irradiation of the C_5-Hα (2.32 ppm) produced an enhancement of both the signals due to the $N_{1'}$-H (7.20 ppm) and C_2-H (3.20-3.39 ppm), whereas irradiation of the C_5-Hβ (3.12 ppm) produced no enhancement of both the signals due to the $N_{1'}$-H and C_2-H, which suggested that the C_5-Hβ and $N_{1'}$-H are of the

opposite side of the molecule. Based on these spectral features, the stereostructures of **25** and **26** could be rigorously assigned as pictured in Scheme 3.

Subsequently, the target amino acid (**2**) was prepared from **25** by the two different pathway as shown in Scheme 4. Thus, initially the catalytic hydrogenation of **25** with PtO_2 in EtOH followed by hydrolysis with 6*N* HCl gave the *N*-benzylamino acid (**27**) in 65% overall yield from **25**. Finally, the debenzylation of **27** with 20% $Pd(OH)_2/C$ in 5% AcOH afforded **2** in 88% yield. An alternative route was to obtain initially the 2-ethenylamino acid (**28**) by acid hydrolysis from **25**, and then the debenzylation and hydrogenation of the resulting **28** with 10% $Pd(OH)_2/C$ was simultaneously carried out to give **2** in 54% overall yield from **25**. By employing the reaction pathway similar to that described for the preparation of **2** from **25**, **26** was converted to the **30** *via* 2-ethyl-spirohydantoin (**22**) or *N*-Benzyl-2-ethenyl derivative (**31**).

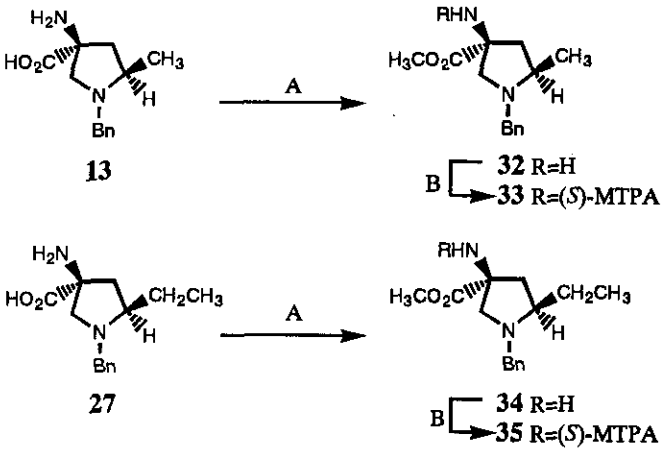


Scheme 4

Reagents and conditions: A. PtO_2-H_2, EtOH; B. 6*N* HCl, in a sealed tube, 130°C; C. 20% $Pd(OH)_2/C$-H_2, 5% AcOH, then 2*N* HCl.

The enantiomeric purities of **1** and **2** were determined to be more than 95% by 400 MHz ^{1}H-nmr analysis of (*S*)-2-methoxy-2-(trifluoromethyl)phenylacetyl (MTPA) amides (**33**) and (**35**) derived respectively from **13** and **27** *via* 2-step sequence involving esterification with $SOCl_2$ in MeOH and acylation with (*S*)-MTPA chloride in pyridine[11] as shown in Scheme 5.

In conclusion, the first asymmetric syntheses of the title compounds (**1**) and (**2**) have been achieved in highly enantiomeric purity starting from *trans*-4-hydroxy-*L*-proline *via* the diastereoselective Bucherer-Bergs reaction of 2-alkyl-4-oxopyrrolidines (**10**) and (**24**). The stereoselectivity observed for the reaction of **10** and **24** is compatible with the mechanism reported in our previous literture.[6a]



13 **27**

Scheme 5

Reagents and conditions: A. $SOCl_2$, MeOH, reflux; B. (*S*)-MTPACl, pyridine, room temperature.

EXPERIMENTAL

General Notes. Melting points were measured on a Yanaco MP-S3 micromelting 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 spectrophotometer. ^{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 $CDCl_3$ and DMSO-d_6 solutions, or from 3-trimethylsilyl-1-propanesulfonic acid sodium salt as internal standard in D_2O solutions. The following abbreviation are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Mass (ms) spectra 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 *N*,*N*-dimethylformamide were distilled from calcium hydride under N_2 atmosphere. The *trans*-4-hydroxy-*L*-proline as chiral starting meterial was purchased from Sigma Chemical Co. **Methyl (2*S*,4*R*)-1-*tert*-butoxycarbonyl-4-[(*tert*-butyldimethylsilyl)oxy]prolinate** (**5**), **(2*R*,4*R*)-1-*tert*-butoxycarbonyl-4-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxymethylpyrrolidine** (**6**), **(2*R*,4*R*)-1-*tert*-butoxycarbonyl-4-[(*tert*-butyldimethylsilyl)oxy]-2-(methylsulfonyl)-methylpyrrolidine** (**7**), and **(2*R*,4*R*)-1-*tert*-**

butoxycarbonyl-4-[(*tert*-butyldimethylsilyl)-oxy]-2-methylpyrrolidine (8) were prepared from *trans*-4-hydroxy-*L*-proline (**3**) according to the reported methods.[7]

(2*R*,4*R*)-1-Benzyl-4-hydroxy-2-methylpyrrolidine (9). A solution of **8**[7] (15.0 g, 47 mmol) in MeOH (100 ml) was stirred at room temperature, and *p*-toluenesulfonic acid (35.8 g, 0.19 mol) was added portionwise. After the solution was stirred for 6 h, the mixture was concentrated *in vacuo* to give a residue. Benzyl chloride (11.9 g, 94 mmol) and Et_3N (28.5 g, 0.28 mol) were added to the mixture of the resulting residue in CH_2Cl_2 (100 ml) and the mixture was refluxed for 12 h. 1M aqueous NaOH solution was added the reaction mixture, the mixture was extracted with CH_2Cl_2. The extract was washed, dried over anhydrous Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography [AcOEt/MeOH (20/1, v/v)] to give **9** (6.1 g, 68%) as a colorless oil. $[\alpha]^{20}_D$ -115.5° (c=0.97, MeOH). Ms m/z: 191 (M^+). Ir (film): 3480, 1620 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.15 (3H, d, J=6.23 Hz, CH_3), 1.71-1.88 (2H, m, C_3-H), 1.92 (1H, br s, OH), 2.15 (1H, dd, J=10.26, 4.76 Hz, C_5-H), 2.75-2.85 (1H, m, C_2-H), 3.24 (1H, dd, J=10.26, 6.23 Hz, C_5-H), 3.26 and 4.01 (each 1H, each d, J=13.19 Hz, CH_2Ph), 4.29-4.32 (1H, m, C_4-H), 7.29 (5H, m, Ph). ^{13}C-Nmr ($CDCl_3$) δ: 18.59 (CH_3), 43.73 (C_3), 57.49 (C_2), 57.64 (C_5), 62.67 (CH_2Ph), 69.40 (C_4), 126.91, 128.20, 128.95, 138.98 (Ph). High resolution ms m/z: Calcd $C_{12}H_{17}NO$ (M^+) 191.1310. Found: 191.1301.

(2*R*)-1-Benzyl-2-methyl-4-oxopyrrolidine (10). A solution of DMSO (3.1 g, 39 mmol) in dry CH_2Cl_2 (30 ml) was added dropwise to a stirred solution of oxalyl chloride (2.5 g, 20 mmol) in dry CH_2Cl_2 (15 ml) at -78°C under nitrogen. After 15 min, a solution of **9** (3.5 g, 18 mmol) in dry CH_2Cl_2 (30 ml) was added slowly, and stirring was continued for 30 mim at -78°C. After addition of Et_3N (9.1 g, 90 mmol), the mixture was gradually warmed up to room temperature. The mixture was quenched with water and aqueous layer was separated and extracted with CH_2Cl_2. The extract was washed with brine and dried over anhydrous Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography [AcOEt/n-Hexane (1/2,v/v)] to give **10** (3.0 g, 88%) as a colorless oil. $[\alpha]^{20}_D$ -188.9° (c=0.92, MeOH). Ms m/z: 189 (M^+). Ir (film): 1760 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.32 (3H, d, J=6.23 Hz, CH_3), 2.11 (1H, dd, J=17.95, 9.90 Hz, C_3-Hβ), 2.47 (1H, dd, J=17.95, 6.20 Hz, C_3-Hα), 2.62 (1H, d, J=17.22 Hz, C_5-H), 2.91-2.97 (1H, m, C_2-H), 3.20 (1H, d, J=17.22 Hz, C_5-H), 3.25 and 4.16 (each 1H, each d, J=13.19 Hz, CH_2Ph), 7.29 (5H, m, Ph). ^{13}C-Nmr ($CDCl_3$) δ: 18.32 (CH_3), 45.99 (C_3), 57.02 (C_2), 57.15 (C_5), 61.74 (CH_2Ph), 127.20, 128.37, 128.63, 137.98 (Ph), 213.12 (CO). High resolution ms m/z: Calcd $C_{12}H_{15}NO$ (M^+) 189.1153. Found: 189.1140.

(2*R*,4*S*)-1-Benzyl-2-methylpyrrolidine-4-spiro-5'-hydantoin (11) and Its **(2*R*,4*R*)-Isomer (12).** Ammonium carbonate (4.8 g, 0.05 mol) and potassium cyanide (1.3 g, 0.02 mol) were added to a solution of **10** (2.0 g, 0.01 mol) in 60% aqueous MeOH (60 ml). The mixture was heated at 55°C-60°C for 24 h and the solvent was removed *in vacuo*. The residue was diluted with water, and the mixture was extracted with AcOEt. The extract was washed with brine, and then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (AcOEt) to give (**11** + **12**) (1.8 g, 70%) as a mixture of two diastereoisomers. This mixture was further separated by flash column chromatography [$CHCl_3$/MeOH (50/1, v/v)] to give **11** as a less polar product and **12** as a more polar product in a ratio of 80:20.

Less polar 11: mp 211-212°C as colorless prisms (from AcOEt). $[\alpha]^{17}_D$ -138.6° (c=0.98, MeOH). Ms m/z: 259 (M^+). Ir (KBr): 3236, 1776, 1740 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.24 (3H, d, J=6.23 Hz, CH_3), 1.69 (1H, dd, J=13.55, 9.16, C_3-Hβ), 2.57 (1H, dd, J=13.55, 6.23 Hz, C_3-Hα), 2.66 (1H, d, J=10.26 Hz, C_5-H), 2.69-2.75 (1H, m, C_2-H), 2.89 (1H, d, J=10.26 Hz, C_5-H), 3.19 and 4.11 (each 1H, each d, J=13.19 Hz, CH_2Ph), 6.86 (1H, br s, $N_{1'}$-H), 7.29 (5H, m, Ph), 9.78 (1H, br s, $N_{3'}$-H). ^{13}C-Nmr ($CDCl_3$) δ: 18.45 (CH_3), 44.78 (C_3), 56.91 (C_5), 59.40 (C_2), 63.15 (CH_2Ph), 65.96 (C_4), 127.42, 128.42, 129.08, 137.44 (Ph), 155.59 ($C_{2'}$-CO), 177.23 ($C_{4'}$-CO). *Anal.* Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.21. Found: C, 64.88; H, 6.85; N, 16.40.

More polar 12: mp 198-199°C as colorless needles (from AcOEt-isopropyl ether). $[\alpha]^{17}_D$ -115.8° (c=0.86, MeOH). Ms m/z: 259 (M^+). Ir (KBr): 3200, 1780, 1742 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.23 (3H, d, J=6.23 Hz, CH_3), 2.10-2.16 (2H, m, C_3-H_2), 2.46 (1H, d, J=10.62 Hz, C_5-Hα), 2.88-3.00 (1H, m, C_2-H), 3.32 (1H, d, J=10.62 Hz, C_5-Hβ), 3.41 and 3.98 (each 1H, each d, J=13.19 Hz, CH_2Ph), 6.31 (1H, br s, $N_{1'}$-H), 7.29 (5H, m, Ph), 8.42 (1H, br s, $N_{3'}$-H). ^{13}C-Nmr ($CDCl_3$) d: 17.03 (CH_3), 45.08 (C_3), 55.88 (C_5), 57.93 (C_2), 62.12 (CH_2Ph), 66.36 (C_4), 127.21, 128.39, 128.63, 137.46 (Ph), 156.18 ($C_{2'}$-CO), 176.59 ($C_{4'}$-CO). *Anal.* Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.21. Found: C, 64.82; H, 6.78; N, 16.24.

(2*R*,4*S*)-4-Amino-1-benzyl-4-carboxy-2-methylpyrrolidine Dihydrochloride (13). A solution of **11** (0.8 g, 3 mmol) in 6*N* HCl (20 ml) was heated at 130°C for 24 h in a sealed tube. After cooling, the mixture was concentrated *in vacuo*. The white residue was dissolved in water (10 ml) and purified by Amberlite XAD-4 ion exchange column chromatography (water, then MeOH) to give **13** (0.73 g, 64%) as colorless needles, mp 182-183°C (from 70% aqueous EtOH). $[\alpha]^{23}_D$ -64.9° (c=0.84, 2*N* HCl). Fast atom bombardment ms m/z: 234 (M^+). Ir (KBr): 3432, 300-2200, 1598, 1388 cm^{-1}. ^{1}H-Nmr (D_2O) δ: 1.53 (3H, d, J=6.23 Hz, CH_3), 2.16 (1H, dd, J=14.29, 12.09 Hz, C_3-Hβ), 2.87 (1H, dd, J=14.29, 6.23 Hz, C_3-Hα), 3.64 and 3.95 (each 1H, each d, J=13.92 Hz, C_5-H_2), 4.00-4.10 (1H, m, C_2-H), 4.32 (1H, d, 13.19 Hz, CH_2Ph), 7.54 (5H, m, Ph). ^{13}C-Nmr (D_2O) δ: 17.08 (CH_3), 44.78 (C_3), 59.67 (C_5), 61.77 (CH_2Ph), 63.21 (C_4), 66.93 (C_2), 132.03, 132.19, 132.96, 133.28 (Ph), 175.75 (CO_2H). *Anal.* Calcd for $C_{13}H_{18}N_2O_2$ (2HCl): C, 50.82; H, 6.56; N, 9.11. Found: C, 50.75; H, 6.34; N, 8.89.

(2*R*,4*S*)-4-Amino-4-carboxy-2-methylpyrrolidine Dihydrochloride (1). A mixture of **13** (0.5 g, 1.3 mmol) and 20% $Pd(OH)_2$/C (0.1 g) in 5% AcOH (20 ml) was stirred under H_2 atmosphere (3 atm) at room temperature for 5 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The white residue was dissolved in 2*N* HCl (10 ml) and the mixture was concentrated *in vacuo* to give **1** (0.24 g, 84%) as a white solid. Recrystallization of the solid from 70% aqueous EtOH afforded an analytical sample as colorless needles, mp 263-267°C (decomp.). $[\alpha]^{25}_D$ -74.8° (c=0.54, 2*N* HCl). Fast atom bombardment ms m/z: 144 (M^+). Ir (KBr): 3452, 3000-2150, 1640, 1396 cm^{-1}. ^{1}H-Nmr (D_2O) δ: 1.49 (3H, d, J=6.23 Hz, CH_3), 2.05 (1H, dd, J=13.56, 11.72 Hz, C_3-Hβ), 2.77 (1H, dd, J=13.56, 6.60 Hz, C_3-Hα), 3.65 and 3.90 (each 1H, each d, J=12.82 Hz, C_5-H_2), 4.09-4.15 (1H, m, C_2-H). ^{13}C-Nmr (D_2O) d: 18.82 (CH_3), 44.18 (C_3), 53.94 (C_5), 59.34 (C_2), 65.24 (C_4), 176.48 (CO_2H). *Anal.* Calcd for $C_6H_{12}N_2O_2$ (2HCl· H_2O): C, 30.65; H, 6.86; N, 11.91. Found: C, 30.46; H, 6.75; N, 11.79.

(2*R*,4*R*)-4-Amino-1-benzyl-4-carboxy-2-methylpyrrolidine Dihydrochloride (14). The same treatment of **12** (0.4 g, 1.5 mmol) as described for the preparation of **13** from **11** gave **14** (0.37 g, 65%) as colorless needles, mp 195-197 (decomp.) (from 70% aqueous EtOH). $[\alpha]^{23}_D$ -41.9° (c=0.66, 2*N* HCl). Fast atom bombardment ms m/z: 234 (M+). Ir (KBr): 3364, 3100-2200, 1642, 1400 cm^{-1}. ^{1}H-Nmr (D_2O) δ: 1.62 (3H, d, J=6.23 Hz, CH_3), 2.58 (1H, dd, J=15.02, 11.72 Hz, C3-Hα), 2.81 (1H, dd, J=15.02, 6.96 Hz, C_3-Hβ), 3.61 and 4.03 (each 1H, each d, J=13.92 Hz, C_5-H_2), 3.95-4.04 (1H, m, C_2-H), 4.34 (1H, d, J=13.19 Hz, CH_2Ph), 7.55 (5H, m, Ph). ^{13}C-Nmr (D_2O) δ: 16.65 (CH_3), 43.63 (C_3), 58.50 (C_5), 61.37 (CH_2Ph), 62.40 (C_4), 65.33 (C_2), 131.10, 132.18, 133.12, 133.60 (Ph), 174.09 (CO_2H). *Anal.* Calcd for $C_{13}H_{18}N_2O_2$ (2HCl): C, 50.82; H, 6.56; N, 9.11. Found: C, 50.62; H, 6.29; N, 9.10.

(2*R*,4*R*)-4-Amino-4-carboxy-2-methylpyrrolidine Dihydrochloride (15). The same treatment of **14** (0.2 g, 0.5 mmol) as described for the preparation of **1** from **13** gave **15** (97 mg, 83%) as a hygroscopic solid. $[\alpha]^{20}_D$ -16.9° (c=0.85, 2*N* HCl). Fast atom bombardment ms m/z: 144 (M^+). Ir (KBr): 3450, 3100-2200, 1640, 1392 cm^{-1}. ^{1}H-Nmr (D_2O) δ: 1.52 (3H, d, J=6.23 Hz, CH_3), 2.47 (1H, dd, J=15.02, 11.36 Hz, C_3-Hα), 2.73 (1H, dd, J=15.02, 6.59, C_3-Hβ), 3.65 and 4.13 (each 1H, each d, J=13.19 Hz, C_5-H_2), 4.11-4.14 (1H, m, C_2-H). ^{13}C-Nmr (D_2O) δ: 18.32 (CH_3), 43.51 (C_3), 54.70 (C_5), 58.75 (C_2), 65.23 (C_4), 174.49 (CO_2H). *Anal.* Calcd for $C_6H_{12}N_2O_2$ (2HCl·H_2O): C, 30.65; H, 6.86; N, 11.91. Found: C, 30.52; H, 6.66; N, 11.77.

(2*S*,4*R*)-1-*tert*-Butoxycarbonyl-4-(*tert*-butyldimethylsilyloxy)prolinal (16). Sulfur trioxide-pyridine complex (17.8 g, 112 mmol) was added portionwise to a stirred solution of **6** (9.5 g, 28 mmol) and Et_3N (19.7 g, 195 mmol) in dry DMSO (50 ml) under N_2 at 0°C and the mixture was stirred at the same temperature for 1 h. An ice-water was added to the reaction mixtutre and the mixture was extracted with AcOEt. The extract was washed successively with 5% aqueous citric acid, water, saturated aqueous $NaHCO_3$, and brine and then dried over anhydrous Na_2SO_4. Concentration of the solvent *in vacuo* gave **16** (8.0 g, 85%) as a colorless oil, which was used without further purification. $[\alpha]^{20}_D$ -35.2° (c=1.2, MeOH). Ms m/z: 330 (M^+). Ir (film): 1742, 1702 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.04-0.07 (6H, m, $Si(CH_3)_2$), 0.87 (9H, s, $SiC(CH_3)_3$), 1.43 and 1.48 (9H, each s, $OC(CH_3)_3$, rotamers), 1.92-2.10 (2H, m, C_3-H_2), 3.48-4.37 (2H, m, C_5-H_2), 4.21-4.37 (2H, m, C_2- and C_4-H), 9.50 (1H, br s, CHO).

(2*R*,4*R*)-1-*tert*-Butoxycarbonyl-4-(*tert*-butyldimethylsilyloxy)-2-ethenylpyrrolidine (17). A solution of methyltriphenylphosphonium bromide (8.1 g, 23 mmol) in dry THF (30 ml) was added to a stirred mixture of NaH (60% mineral oil dispersion) (0.9 g, 23 mmol) in dry THF (10 ml) under N_2 at room temperature, and the mixture was stirred at the same temperature for 1 h. A solution of **16** (6.2 g, 19 mmol) in dry THF (15 ml) was added dropwise to the mixture and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into an ice water and extracted with AcOEt. The extract was washed with brine and dried over anhydrous Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography [n-Hexane/AcOEt (10/1, v/v)] to give **17** (5.5 g, 90%) as a colorless oil. $[\alpha]^{20}_D$ -13.4° (c=0.8, MeOH). Ms m/z: 328 (M^+). Ir (film): 1718 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.04-0.07 (6H, m, $Si(CH_3)_2$), 0.87 (9H,s, $SiC(CH_3)_3$), 1.44 (9H, s, $OC(CH_3)_3$), 1.70-1.78 (1H, m, C_3-H), 1.92-2.00 (1H, m, C_3-H), 3.37-3.46 (2H, m, C_5-H_2), 4.22-4.38 (2H, m, C_2-

and C4-H), 4.95-5.10 (2H, m, $=CH_2$), 5.74-5.82 (1H, m, CH=). High resolution ms m/z: Calcd $C_{17}H_{33}NO_3Si$ (M^+) 327.2229. Found: 327.2212.

(2*R*,4*R*)-1-*tert*-Butoxycarbonyl-4-(*tert*-butyldimethylsilyloxy)-2-ethylpyrrolidine (18). A mixture of **17** (3.8 g, 12 mmol) and 10% Pd/C (0.3 g) in EtOH (30 ml) was stirred at room temperature under H_2 (2 atm) for 5 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography [n-Hexane/AcOEt (10/1,v/v)] to give **18** (3.7 g, 97%) as a colorless oil. $[\alpha]^{19}_D$ -36.8° (c=1.50, MeOH). Ms m/z: 329 (M^+). Ir (film): 1718 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.04-0.07 (6H, m, $Si(CH_3)_2$), 0.87 (9H, s, $SiC(CH_3)_3$), 0.90-1.06 (3H, m, CH_2CH_3), 1.44 (9H, s, $OC(CH_3)_3$), 1.60-2.04 (4H, m, C3-H_2, CH_2CH_3), 3.37-3.45 (2H, m, C5-H_2), 3.95-4.50 (2H, m, C2- and C4-H). High resolution ms m/z: Calcd $C_{17}H_{35}NO_3Si$ (M^+) 329.2386. Found: 329.2365.

(2*R*,4*R*)-1-Benzyl-4-hydroxy-2-ethylpyrrolidine (19). The same treatment of **18** (3.3 g, 10 mmol) as described for the preparation of **9** from **8** gave **19** (1.4 g, 67%) as a colorless oil after purification by column chromatography (AcOEt). $[\alpha]^{17}_D$ -108.5° (c=0.96, MeOH). Ms m/z: 205 (M^+). Ir (film): 3352 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, t, J=7.70 Hz, CH_2CH_3), 1.08-2.24 (4H, m, C3-H_2, CH_2CH_3), 2.45 (1H, br s, OH), 2.60-3.30 (2H, m, C2-H, C5-H, CH_2Ph), 3.90-4.40 (2H, m, C4-H, CH_2Ph), 7.29 (5H, m, Ph). High resolution ms m/z: Calcd $C_{13}H_{19}NO$ (M^+) 205.1466. Found: 205.1448.

(2*R*)-1-Benzyl-2-ethyl-4-oxopyrrolidine (20). The same treatment of **19** (0.55 g, 2.7 mmol) as described for the preparation of **10** from **9** gave **20** (0.48 g, 88%) as a colorless oil after purification by column chromatography [n-Hexane/AcOEt (3/1,v/v)]. $[\alpha]^{20}_D$ -200.0° (c=0.86, MeOH). Ms m/z: 203 (M^+). Ir (film): 1760 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.97 (3H, t, J=7.70 Hz, CH_2CH_3), 1.56 (2H, m, CH_2CH_3), 2.15 (1H, dd, J=17.95, 9.89 Hz, C3-Hβ), 2.46 (1H, dd, J=17.95, 6.59 Hz, C3-Hα), 2.62 and 3.23 (each 1H, each d, J=17.22 Hz, C5-H_2), 2.79-2.88 (1H, m, C2-H), 3.25 and 4.20 (each 1H, J=13.19 Hz, CH_2Ph), 7.29 (5H, m, Ph). ^{13}C-nmr ($CDCl_3$) δ: 9.62 (CH_3), 25.12 (CH_2CH_3), 42.98 (C3), 57.48 (C5), 62.15 (CH_2Ph), 63.05 (C2), 127.23, 128.39, 128.60, 138.06 (Ph), 213.24 (CO). High resolution ms m/z: Calcd $C_{13}H_{17}NO$ (M^+) 203.1310. Found: 203.1296.

Bucherer-Bergs Reaction of 20. Treatment of **20** (0.3 g, 1.5 mmol) under the same conditions as described for the preparation of **11** and **12** from **10** gave **(21+ 22)** (0.24 g, 60%) as a mixture of two diastereoisomers after purification by column chromatography (AcOEt). This mixture could not be separated by column chromatography methods.

(2*R*,4*R*)-1-Benzyl-4-hydroxy-2-ethenylpyrrolidine (23). The same treatment of **17** (6.8 g, 32 mmol) as described for the preparation of **19** from **18** gave **23** (3.9 g, 61%) as a colorless oil after purification by column chromatography [AcOEt/MeOH (10/1, v/v)]. $[\alpha]^{24}_D$ -90.4° (c=1.20, MeOH). Ms m/z: 203 (M^+). Ir (film): 3388 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.75 (1H, br s, OH), 1.85-1.94 (2H, m, C3-H_2), 2.16 (1H, dd, J=10.26, 4.40 Hz, C5-H), 3.17-3.23 (1H, m, C2-H), 3.21 and 4.01 (each 1H, each d, J=12.82 Hz, CH_2Ph), 3.28 (1H, dd, J=10.26, 6.23 Hz, C5-H), 4.32-4.37 (1H, m, C4-H), 5.16 (1H, dd, J=9.90, 1.84 Hz, $=CH_2$), 5.25 (1H, dd, J=17.04, 1.84 Hz, $=CH_2$), 5.68-5.78 (1H, m, CH=), 7.29 (5H, m, Ph). ^{13}C-Nmr ($CDCl_3$) δ: 42.46 (C3), 57.64 (C5), 62.04 (CH_2Ph), 66.22 (C2), 69.78 (C4), 117.21 ($=CH_2$), 126.85, 128.20, 128.87, 139.05 (Ph), 139.95 (CH=). High resolution ms m/z: Calcd $C_{13}H_{17}NO$ (M^+) 203.1310. Found: 203.1302.

(2*R*)-1-Benzyl-2-ethenyl-4-oxopyrrolidine (24). The same treatment of **23** (2.1 g, 10 mmol) as described for the preparation of **10** from **9** gave **24** (1.8 g, 88%) as a colorless oil after purification by column chromatography [Benzene/AcOEt (5/1, v/v)]. $[\alpha]^{24}_D$ -160.2° (c=0.80, MeOH). Ms m/z: 201 (M^+). Ir (film): 1762 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 2.31 (1H, dd, J=17.96, 10.25 Hz, C_3-Hβ), 2.52 (1H, dd, J=17.96, 6.23 Hz, C_3-Hα), 2.63 and 3.27 (each 1H, each d, J=17.22 Hz, C_5-H_2), 3.22 and 4.17 (each 1H, each d, J=13.19 Hz, CH_2Ph), 3.33-3.37 (1H, m, C_2-H), 5.29 (1H, dd, J=9.90, 1.84 Hz, =CH_2), 5.37 (1H, dd, J=17.04, 1.84 Hz, =CH_2), 5.80-5.90 (1H, m, CH=), 7.29 (5H, m, Ph). ^{13}C-Nmr ($CDCl_3$) δ: 44.73 (C_3), 57.49 (C_5), 60.89 (CH_2Ph), 65.56 (C_2), 118.88 (=CH_2), 127.26, 128.41, 128.67, 137.88 (Ph), 212.51 (CO). High resolution ms m/z: Calcd $C_{13}H_{15}NO$ (M^+) 201.1153. Found: 201.1139.

(2*R*,4*S*)-1-Benzyl-2-ethenylpyrrolidine-4-spiro-5'-hydantoin (25) and Its **(2*R*,4*R*)-Isomer (26).** Treatment of **24** (0.3 g, 1.5 mmol) under the same conditions as described for the preparation of **11** and **12** from **10** gave **25** as a less polar product and **26** as a more polar product in a ratio of 84 : 16 in 78% yield, after purification by flash column chromatography [$CHCl_3$/MeOH (100/1, v/v)].

Less polar 25: mp 247-248°C as colorless needles (from AcOEt-isopropyl ether). $[\alpha]^{23}_D$ -85.4° (c=0.92, MeOH). Ms m/z: 271 (M^+). Ir (KBr): 3228, 1774, 1724 cm^{-1}. ^{1}H-Nmr (DMSO-d_6) δ: 1.76 (1H, dd, J=13.19, 9.16 Hz, C_3-Hβ), 2.35 (1H, dd, J=13.19, 6.23 Hz, C_3-Hα), 2.50 and 2.83 (each 1H, each d, J=9.89 Hz, C_5-H), 3.03-3.10 (1H, m, C_2-H), 3.14 and 3.93 (each 1H, each d, J=13.56 Hz, CH_2Ph), 5.20 (1H, dd, J=9.90, 1.84 Hz, =CH_2), 5.31 (1H, dd, J=17.04, 1.84 Hz, =CH_2), 5.72-5.84 (1H, m, CH=), 7.20 (1H, br s, $N_{1'}$-H), 7.29 (5H, m, Ph), 8.34 (1H, br s, $N_{3'}$-H). ^{13}C-Nmr (DMSO-d_6) δ: 42.69 (C_3), 56.19 (C_5), 62.23 (CH_2Ph), 65.21 (C_4), 67.05 (C_2), 117.97 (=CH_2), 126.73, 128.03, 128.35, 138.38 (Ph), 139.18 (CH=), 156.17 ($C_{2'}$-CO), 177.64 ($C_{4'}$-CO). *Anal.* Calcd for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.53; H, 6.42; H, 15.40.

More polar 26: mp 208-209°C as colorless needles (from AcOEt-isopropyl ether). $[\alpha]^{24}_D$ -92.3° (c=0.96, MeOH). Ms m/z: 271 (M^+). Ir (KBr): 3240, 1772, 1724 cm^{-1}. ^{1}H-Nmr (DMSO-d_6) δ: 1.97 (1H, dd, J=13.19, 6.23 Hz, C_3-Hα), 2.02 (1H, dd, J=13.19, 9.16 Hz, C_3-Hβ), 2.32 (1H, d, J=10.2 Hz, C_5-Hα), 3.12 (1H, d, J=10.2 Hz, C_5-Hβ), 3.20-3.39 (1H, m, C_2-H), 3.21 and 3.90 (each 1H, each d, J=13.19 Hz, CH_2Ph), 5.21 (1H, dd, J=9.90, 1.84 Hz, =CH_2), 5.29 (1H, dd, J=17.04, 1.84 Hz, =CH_2), 5.70-5.80 (1H, m, CH=), 7.20 (1H, br s, $N_{1'}$-H), 7.29 (5H, m, Ph), 8.24 (1H, br s, $N_{3'}$-H). ^{13}C-Nmr (DMSO-d_6) δ: 43.48 (C_3), 56.16 (C_5), 61.80 (CH_2Ph), 64.99 (C_4), 66.54 (C_2), 118.00 (=CH_2), 126.69, 128.06, 128.18, 138.14 (Ph), 138.90 (CH=), 156.04 ($C_{2'}$-CO), 177.60 ($C_{4'}$-CO). *Anal.* Calcd for $C_{15}H_{17}N_3O_2$: C,66.40; H, 6.32; N, 15.49. Found: C, 66.20; H, 6.32; N, 15.35.

(2*R*,4*S*)-1-Benzyl-2-ethylpyrrolidine-4-spiro-5'-hydantoin (21). A mixture of **25** (0.3 g, 1.1 mmol) and PtO_2 (50 mg) in EtOH (20 ml) was stirred under H_2 at room temperature for 3 h. The catalyst was filtered off and filtrate was concentrated *in vacuo* to give **21** (0.29 g, 97%) as a white solid. Recrystallization of the solid from AcOEt afforded an analytical sample as colorless needles, mp 255-256°C. $[\alpha]^{26}_D$ -78.3° (c=0.84, 2*N* HCl). Ms m/z: 273 (M^+). Ir (KBr): 3276, 3224, 1774, 1746 cm^{-1}. ^{1}H-Nmr (DMSO-d_6) δ: 0.88 (3H, t, J=7.70 Hz, CH_3), 1.36-1.40 and 1.74-1.84 (each 1H, each m, $C\underline{H_2}CH_3$), 1.64 (1H, dd, J=13.19, 9.16 Hz, C_3-Hβ), 2.32 (1H, dd, J=13.19, 7.32 Hz, C_3-Hα), 2.44

and 2.80 (each 1H, each d, J=10.25 Hz, C_5-H_2), 2.49-2.52 (1H, m, C_2-H), 3.15 and 4.04 (each 1H, each d, J=13.19 Hz, CH_2Ph), 7.22 (1H, br s, $N_{1'}$-H), 7.30 (5H, m, Ph), 8.24 (1H, br s, $N_{3'}$-H). ^{13}C-Nmr (DMSO-d_6) δ: 9.71 (CH_3), 25.06 ($\underline{C}H_2CH_3$), 41.55 (C_3), 56.56 (C_5), 63.31 (CH_2Ph), 64.63 (C_2), 64.96 (C_4), 126.63, 127.97, 128.35, 138.79 (Ph), 156.21 ($C_{2'}$-CO), 177.84 ($C_{4'}$-CO). *Anal.* Calcd for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.78; H, 6.93; N, 15.22.

(2*R*,4*S*)-4-Amino-1-benzyl-4-carboxy-2-ethylpyrrolidine Dihydrochloride (27). The same treatment of **21** (0.3 g, 1 mmol) as described for the preparation of **13** from **11** gave **27** (0.23 g, 67%) as a white solid, which was used to next reaction without purification.

(2*R*,4*S*)-4-Amino-4-carboxy-2-ethylpyrrolidine Dihydrochloride (2). The same treatement of **27** (0.22 g, 0.68 mmol) as described for the preparation of **1** gave **2** (0.14 g, 88%) as a white solid. Recrystallization of the solid from 70% aqueous EtOH afforded an analytical sample as colorless needles, mp 285-289C (decomp.). $[\alpha]^{20}_D$ -7.9° (c=0.60, 2*N* HCl). Fast atom bomberdment ms m/z: 158 (M^+). Ir (KBr): 3464, 3000-2200, 1648, 1348 cm^{-1}. ^{1}H-Nmr (D_2O) δ: 1.03 (3H, t, J=7.70 Hz, CH_3), 1.82-1.90 (2H, m, $C\underline{H}_2CH_3$), 2.06 (1H, dd, J=13.92, 11.72 Hz, C_3-Hβ), 2.78 (1H, dd, J=13.92, 6.60 Hz, C_3-Hα), 3.63 and 3.90 (each 1H, each d, J=12.82 Hz, C_5-H_2), 3.92-3.97 (1H, m, C_2-H). ^{13}C-Nmr (D_2O) δ: 12.78 (CH_3), 27.38 ($\underline{C}H_2CH_3$), 42.50 (C_3), 53.65 (C_5), 60.13 (C_2), 64.93 (C_4), 176.24 (CO). *Anal.* Calcd for $C_7H_{14}N_2O_2$ (2HCl): C, 36.37; H, 6.97; N, 12.12. Found: C, 36.10; H, 6.74; N, 11.95.

(2*R*,4*S*)-4-Amino-1-benzyl-4-carboxy-2-ethenylpyrrolidine Dihydrochloride (28). The same treatment of **25** (1.0 g, 3.7 mmol) as described for the preparation of **13** gave **28** (0.74 g, 63%) as colorless needles, mp 224-226°C (from 70% aqueous EtOH). $[\alpha]^{24}_D$ -59.2° (c=0.81, 2*N* HCl). Ir (KBr): 3500, 3200-2200, 1634, 1396 cm^{-1}. ^{1}H-Nmr (D_2O) δ: 2.52 (1H, dd, J=14.65, 12.10 Hz, C_3-Hβ), 3.08 (1H, dd, J=14.65, 6.23 Hz, C_3-Hα), 3.82 and 4.12 (each 1H, each d, J=13.92 Hz, C_5-H_2), 4.35 and 4.69 (each 1H, each d, J=13.19 Hz, CH_2Ph), 4.50-4.55 (1H, m, C_2-H), 5.71 (1H, dd, J=10.26, 1.52 Hz, $=CH_2$), 5.78 (1H, dd, J=16.84, 1.52 Hz, $=CH_2$), 5.93-6.05 (1H, m, CH=), 7.53 (5H, m, Ph). ^{13}C-Nmr (D_2O) δ: 42.06 (C_3), 59.06 (C_5), 59.95 (CH_2Ph), 62.18 (C_4), 72.06 (C_5), 129.66 ($=CH_2$), 130.01, 131.24, 131.77, 132.65 (Ph), 133.24 (CH=), 173.07 (CO). *Anal.* Calcd for $C_{14}H_{18}N_2O_2$ (2HCl): C, 52.67; H, 6.31; N, 8.77. Found: C, 52.46; H, 6.02; N, 8.55.

Preparation of 2 from 28. The same treatment of **28** (0.21 g, 0.65 mmol) as described for the preparation of **1** gave **2** (0.13 g, 86%). The ir and ^{1}H-nmr spectra, and $[\alpha]_D$ value of this sample were identical with those recorded for the sample obtained from **27**.

(2*R*,4*R*)-1-Benzyl-2-ethylpyrrolidine-4-spiro-5'-hydantoin (22). The same treatment of **26** (0.3 g, 1 mmol) as described for the preparation of **21** from **25** gave **22** (0.29 g, 97%) as colorless needles, mp 216-217°C (from AcOEt-isopropyl ether). $[\alpha]^{26}_D$ -91.1° (c=0.72, 2*N* HCl). Ms m/z: 273 (M^+). Ir (KBr): 3216, 1774, 1742 cm^{-1}. ^{1}H-Nmr (DMSO-d_6) δ: 0.87 (3H, t, J=7.70 Hz, CH_3), 1.30-1.40 and 1.70-1.82 (each 1H, each m, $C\underline{H}_2CH_3$), 1.89 (1H, dd, J=13.19, 9.89 Hz, C_3-Hα), 1.96 (1H, dd, J=13.19, 6.60 Hz, C_3-Hβ), 2.33 and 3.11 (each 1H, each d, J=10.25 Hz, C_5-H_2), 2.65-2.73 (1H, m, C_2-H), 3.24 and 4.01 (each 1H, each d, J=13.19 Hz, CH_2Ph), 7.22 (1H, br s, $N_{1'}$-H), 7.29 (5H, m, Ph), 8.25 (1H, br s, $N_{3'}$-H). ^{13}C-Nmr (DMSO-d_6) δ: 9.66 (CH_3), 24.53 ($\underline{C}H_2CH_3$), 42.03 (C_3), 56.38 (C_5), 62.85 (CH_2Ph), 64.00 (C_2), 64.85 (C_4), 126.58, 128.01, 128.16, 139.05 (Ph), 156.11 ($C_{2'}$-CO), 177.81

($C_{4'}$-CO). *Anal.* Calcd for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.88; H, 6.95; N, 15.18.

(2*R*,4*R*)-4-Amino-1-benzyl-4-carboxy-2-ethylpyrrolidine Dihydrochloride (29). The same treatment of **22** (0.2 g, 0.7 mmol) as described for the preparation of **27** from **21** gave **29** (0.15 g, 65%) as a white solid, which was used without further purification.

(2*R*,4*R*)-4-Amino-4-carboxy-2-ethylpyrrolidine Dihydrochloride (30). The same treatment of **29** (0.15 g, 0.4 mmol) as described for the preparation of **2** from **27** gave **30** (92 mg, 86%) as a white solid. Recrystallization of the solid from 70% aqueous EtOH afforded an analytical sample as colorless scales, mp 258-260°C (decomp.). $[\alpha]^{20}_D$ -3.7° (c=0.76, 2*N* HCl). Ir (KBr): 3448, 3200-2200, 1648, 1394 cm^{-1}. ^{1}H-Nmr (D_2O) δ: 1.03 (3H, t, J=7.70 Hz, CH_3), 1.29-1.42 and 1.79-1.90 (each 1H, each m, $C\underline{H}_2CH_3$), 2.34 (1H, dd, J=14.66, 12.99 Hz, C_3-Hα), 2.62 (1H, dd, J=14.66, 6.96 Hz, C_3-Hβ), 3.54 and 3.97 (each 1H, each d, J=13.19 Hz, C_5-H_2), 3.83-4.94 (1H, m, C_2-H). ^{13}C-Nmr (D_2O) δ: 12.80 (CH_3), 27.28 ($\underline{C}H_2CH_3$), 42.30 (C_3), 52.95 (C_5), 54.92 (C_2), 64.25 (C_4), 176.38 (CO). *Anal.* Calcd for $C_7H_{14}N_2O_2$ (2HCl): C, 36.37; H, 6.97; N, 12.12. Found: C, 36.16; H, 6.82; N, 11.98.

(2*R*,4*R*)-4-Amino-1-benzyl-4-carboxy-2-ethenylpyrrolidine Dihydrochloride (31). The same treatment of **26** (0.3 g, 1 mmol) as described for the preparation of **28** from **25** gave **31** (0.23 g, 65%) as colorless needles, mp 201-204°C (decomp.)(from 70% aqueous EtOH). $[\alpha]^{23}_D$ -23.0° (c=0.30, 2*N* HCl). Ir (KBr): 3432, 3200-2200, 1652, 1386 cm^{-1}. ^{1}H-Nmr (D_2O) δ: 2.80-2.85 (2H, m, C_3-H_2), 3.67 and 4.06 (each 1H, each d, J=13.92 Hz, C_5-H_2), 4.31 and 4.68 (each 1H, each d, J=13.19 Hz, CH_2Ph), 4.44-4.54 (1H, m, C_2-H), 5.79 (1H, dd, J=10.26, 1.52 Hz, =CH_2), 5.83 (1H, dd, J=16.84, 1.52 Hz, =CH_2), 5.90-6.02 (1H, m, CH=), 7.53 (5H, m, Ph). ^{13}C-Nmr (D_2O) δ: 42.06 (C_3), 58.89 (C_5), 60.71 (CH_2Ph), 62.65 (C_4), 71.59 (C_2), 130.36 (=CH_2), 131.30, 132.13, 133.24, 133.30 (Ph), 173.77 (CO). *Anal.* Calcd for $C_{14}H_{18}N_2O_2$ (2HCl): C, 52.67; H, 6.31; N, 8.77. Found: C, 52.43; H, 6.11; N, 8.50.

Preparation of 30 from 31. The same treatement of **31** (0.12 g, 0.37 mmol) as described for the preparation of **2** from **28** gave **30** (76 mg, 88%) as a hygroscopic solid. The ir and ^{1}H-nmr spectra, and $[\alpha]_D$ value of this sample were identical with those recorded for the sample obtained from **29**.

Preparation of (2*R*,4*S*)-4-Amino-1-benzyl-4-methoxycarbonyl-2-methylpyrrolidine (32) and (2*R*,4*S*)-4-Amino-1-benzyl-2-ethyl-4-methoxycarbonylpyrrolidine (34). a) Preparation of **32** : Thionyl chloride (26 µl, 0.33 mmol) was added to a mixture of **13** (110 mg, 0.3 mmol) in MeOH (5 ml), and then the solution was refluxed for 3 h. The reaction mixture was concentrated *in vacuo* and the residue was diluted with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The extract was washed with brine and dried over anhydrous Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by short column chromatography [AcOEt/n-Hexane (2/1,v/v)] to give **32** (63 mg, 85%) as a colorless oil. Ms m/z: 248 (M^+). ^{1}H-Nmr ($CDCl_3$) δ: 1.23 (3H, d, J=5.86 Hz, CH_3), 1.45-1.54 (1H, m, C_3-Hβ), 2.04 (2H, br s, NH_2), 2.50 and 2.74 (each 1H,each d, J=9.52 Hz, C_5-H_2), 2.60-2.70 (2H, m, C_2-H and C_3-Hα), 3.13 and 4.07 (each 1H, each d, J=13.19 Hz, CH_2Ph), 3.70 (3H, s, CO_2CH_3), 7.31 (5H, m, Ph). ^{13}C-Nmr ($CDCl_3$) δ: 19.25 (CH_3), 47.51 (C_3), 52.34 (CO_2CH_3), 57.32 (C_5), 59.72 (C_2),

61.80 (C_4), 66.76 (CH_2Ph), 126.95, 128.34, 128.79, 138.95 (Ph), 176.05 ($\underline{C}O_2CH_3$). High resolution ms m/z: Calcd $C_{14}H_{20}N_2O_2$ (M^+) 248.1525. Found: 248.1519.

b) Preparation of **34** : Treatment of **27** (100 mg, 0.3 mmol) under the same condition as described for the preparation of **32** gave **34** (54 mg, 82%) as a colorless oil. Ms m/z: 262 (M^+). ^{1}H-Nmr ($CDCl_3$) δ: 0.94 (3H, t, J=7.33 Hz, CH_3), 1.40-1.58 (2H, m, $C\underline{H}_2CH_3$), 1.76-1.88 (1H, m, C_3-Hβ), 1.98 (2H, br s, NH_2), 2.51 and 2.75 (each 1H, each d, J=9.52 Hz, C_5-H_2), 2.48-2.58 (1H, m, C_2-H), 2.63 (1H, dd, J=13.19, 8.06 Hz, C_3-Hα), 3.13 and 4.08 (each 1H, each d, J=12.82 Hz, CH_2Ph), 3.71 (3H, s, CO_2CH_3), 7.30 (5H, m, Ph). ^{13}C-Nmr ($CDCl_3$) δ: 9.85 (CH_3), 26.04 ($\underline{C}H_2CH_3$), 44.53 (C_3), 52.35 ($CO_2\underline{C}H_3$), 57.42 (C_5), 61.78 (C_4), 65.37 (C_2), 66.58 (CH_2Ph), 126.96, 128.26, 128.73, 139.03(Ph), 175.90 ($\underline{C}O_2CH_3$). High resolution ms m/z: Calcd $C_{15}H_{22}N_2O_2$ (M^+) 262.1681. Found: 262.1653.

Preparation of (2*R*,4*S*)-1-Benzyl-4-[(*S*)-2-methoxy-2-(trifluoromethyl)phenylacetylamino]-4-methoxycarbonyl-2-methylpyrrolidine [(*S*)-MTPA Amide of 32] (33) and (2*R*,4*S*)-1-Benzyl-2-ethyl-4-[(*S*)-2-methoxy-2-(trifluoromethyl)phenylacetylamino]-4-methoxycarbonylpyrrolidine [(*S*)-MTPA Amide of 34] (35). a) Preparation of **33** : (*S*)-2-Methoxy-2-(trifluoromethyl)phenylacetyl chloride [(*S*)-MTPACl] (86 mg, 0.26 mmol) was added to a stirred solution of **32** (60 mg, 0.24 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 [AcOEt/n-Hexane (2/1,v/v)] to give **33** (89 mg, 82 %) as a single compound. The enantiomeric excess of **33** was more than 95% based on ^{1}H-nmr analysis of this MTPA amide. Ms m/z: 464 (M^+). ^{1}H-Nmr ($CDCl_3$) δ: 1.11 (3H, d, J=5.86 Hz, C_2-CH_3), 1.67 (1H, dd, J=13.92, 8.06 Hz, C_3-Hβ), 2.67 and 2.99 (each 1H, each d, J=10.62 Hz, C_5-H_2), 2.85 (1H, dd, J=13.92, 8.06 Hz, C_3-Hα), 3.17 and 4.01 (each 1H, each d, J=13.19 Hz, Ph), 3.46 (3H, s, OCH_3), 3.69 (3H, s, CO_2CH_3), 7.10 (1H, br s, NHCO), 7.23-7.56 (10H, m, Ph x 2). High resolution ms m/z: Calcd $C_{24}H_{27}N_2O_4F_3$ (M^+) 464.1922. Found: 464.1908.

b) Preparation of **35** : The same treatment of **34** (50 mg, 0.2 mmol) as described for the preparation of **33** gave **35** (73 mg, 80%) as a single compound. The enantiomeric excess of **35** was more than 95% based on ^{1}H-nmr analysis of this MTPA amide. Ms m/z: 478 (M^+). ^{1}H-Nmr ($CDCl_3$) δ: 0.84 (3H, t, J=7.70 Hz, $CH_2C\underline{H}_3$), 1.62-1.80 (3H, m, $C\underline{H}_2CH_3$ and C_3-Hβ), 2.55-2.64 (1H, m, C_3-Hα), 2.63 and 2.98 (each 1H, each d, J=10.26 Hz, C_5-H_2), 2.80 (1H, dd, J=13.92, 8.80 Hz, C_2-H), 3.16 and 4.02 (each 1H, each d, J=13.19 Hz, CH_2Ph), 3.47 (3H, d, J=1.47 Hz, OCH_3), 3.69 (3H, s, CO_2CH_3), 7.06 (1H, br s, NHCO), 7.20-7.60 (10H, m, Ph x 2). High resolutiom ms m/z: Calcd $C_{25}H_{29}N_2O_4F_3$ (M^+) 478.2079. Found: 478.2060.

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