

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

Ken-ichi Tanaka,* Hirokazu Suzuki, and Hiroyuki Sawanishi

Faculty of Pharmaceutical Science, Hokuriku University, Ho-3, Kanagawa-machi, Kanazawa 920-11, Japan

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 C₂ 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}

(-)-Cucurbitine³ 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 inhibit⁴ 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).

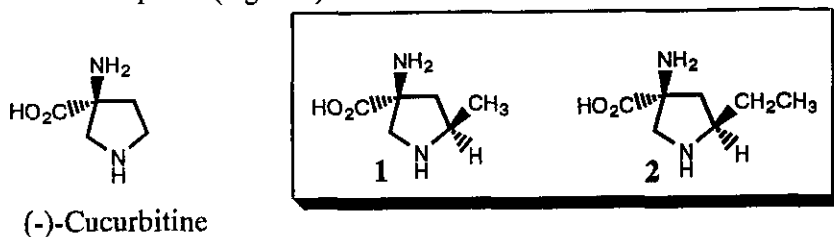
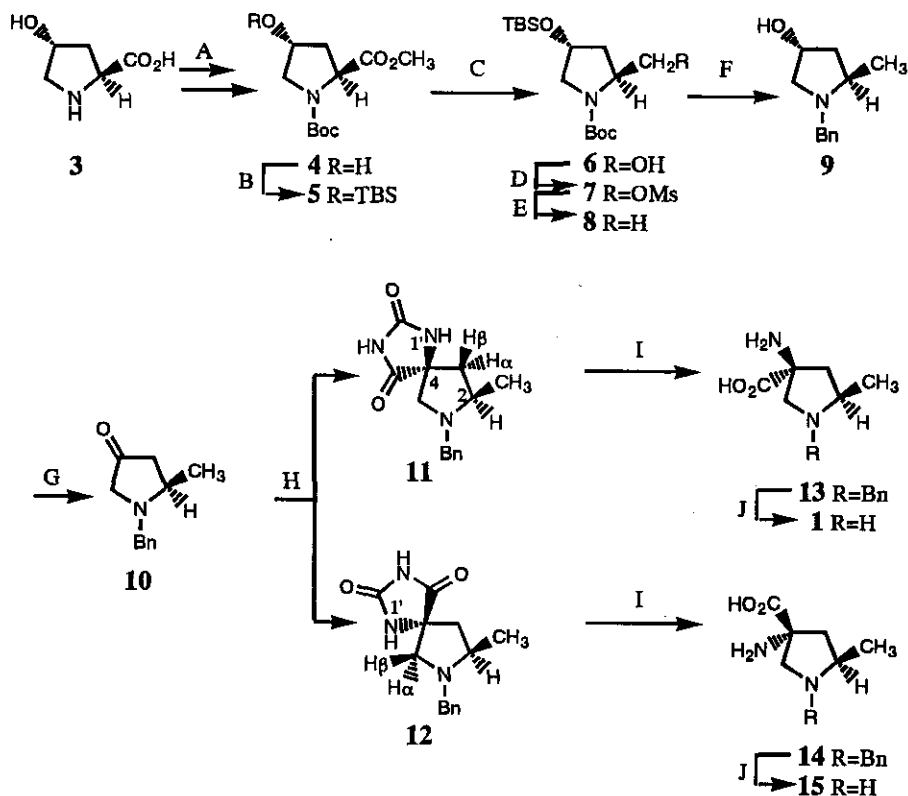


Figure 1

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-oxoproline 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

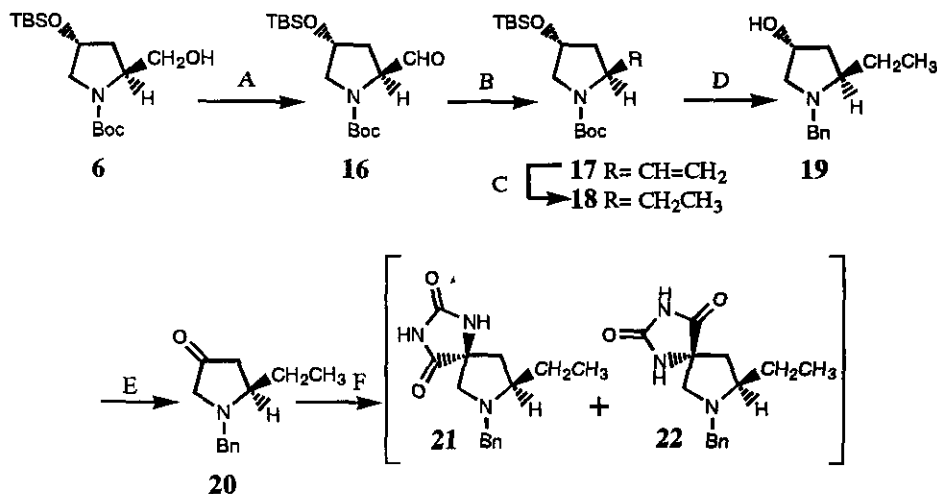
Reagent and conditions: A. i) SOCl_2 , MeOH, reflux, ii) Boc_2O , Et_3N , CH_2Cl_2 , room temperature; B. TBSCl, imidazole, DMF, 0°C ; C. LiBH_4 , dry THF, 0°C ; D. MeSO_2Cl , Et_3N , CH_2Cl_2 , 0°C ; E. LiEt_3BH (Super-Hydride), dry THF, 0°C ; F. i) *p*-TsOH, MeOH, ii) BnCl , Et_3N , CH_2Cl_2 , reflux; G. $(\text{COCl})_2$, DMSO, dry CH_2Cl_2 , -78°C , then Et_3N ; H. $(\text{NH}_4)_2\text{CO}_3$, KCN, 60% aq. MeOH, $55\text{--}60^\circ\text{C}$; I. 6*N* HCl, in a sealed tube, 130°C ; J. 20% $\text{Pd}(\text{OH})_2/\text{C}$, 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*-toluenesulfonic acid in MeOH followed by *N*-benzylation with benzyl chloride and triethylamine (Et_3N) in CH_2Cl_2 to give *N*-benzyl derivative (**9**) in 68% yield, and then the Swern oxidation⁸ of **9** afforded the corresponding ketone (**10**) in 88% yield. The Bucherer-Bergs reaction⁹ 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 spirohydantoin (**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 (SiO₂; CHCl₃/MeOH=50/1, v/v). The stereostructures of the newly formed stereogenic centers at C₄-position in both **11** and **12** were assigned by NOE measurements in their 400 MHz ¹H-nmr spectra. Thus, for the compound (**11**), irradiation of the C₂-CH₃ (1.24 ppm) produced an enhancement of the signals due to both the C₃-H_β (1.69 ppm) and N₁-H (6.86 ppm), and irradiation of the C₃-H_α (2.57 ppm) gave no enhancement of the signal due to the N₁-H. For the compound (**12**), irradiation of the C₂-CH₃ (1.23 ppm) gave no enhancement of the signal due to the N₁-H (6.31 ppm), but irradiation of the C₅-H_α (2.46 ppm) produced an enhancement of the signal due to both the C₂-H (2.88-3.00 ppm) and N₁-H. Accordingly, the C₂-CH₃ and N₁-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**)

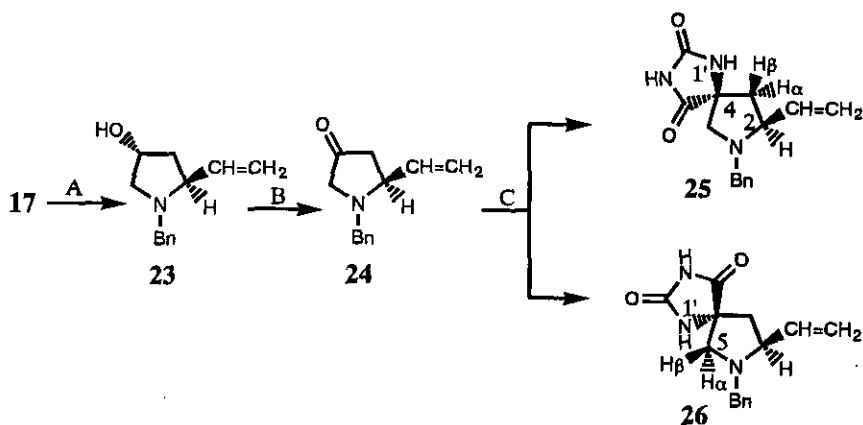


Scheme 2

Reagents and conditions: A. SO₃-pyridine, Et₃N, dry DMSO, 0°C; B. MePPh₃Br, NaH (60% mineral oil dispersion), dry THF, room temperature; C. 10% Pd/C-H₂, EtOH; D. i) *p*-TsOH, MeOH, room temperature, ii) BnCl, Et₃N, CH₂Cl₂, reflux; E. (COCl)₂, dry DMSO, dry CH₂Cl₂, -78°C, then Et₃N; F. (NH₄)₂CO₃, 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 (SO₃)-pyridine complex in dimethyl sulfoxide (DMSO) at 0°C according to the Parikh-Doehring procedure¹⁰ 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 spirohydantoin (**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-spirohydantoin (**25** and **26**) by alternative route to investigate the separable possibility of the diastereoisomers, as shown in Scheme 3.



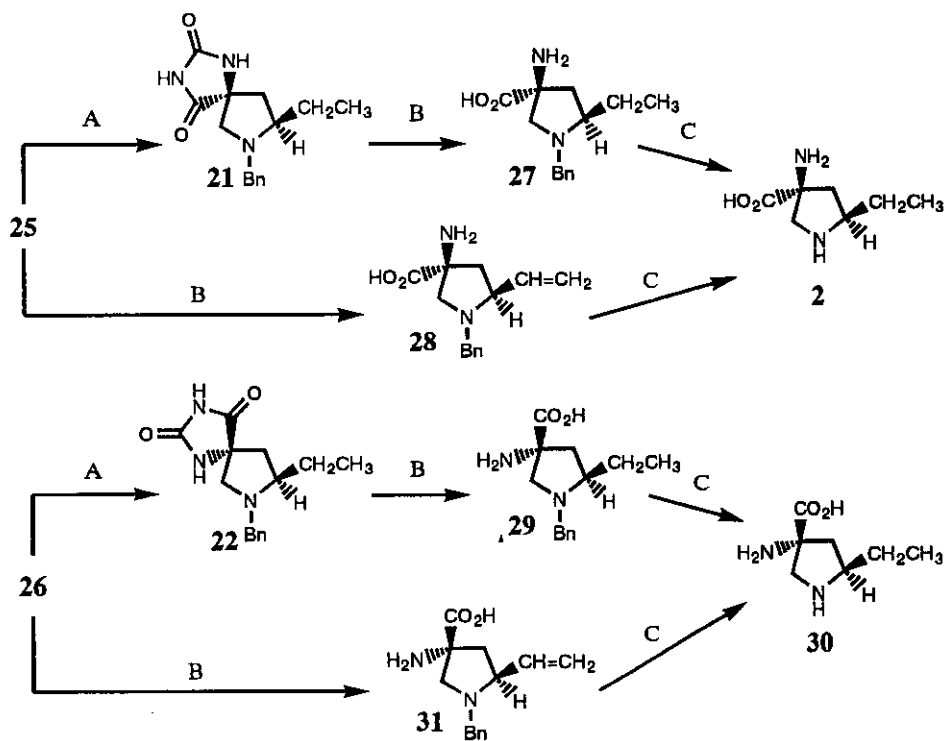
Scheme 3

Reagents and conditions: A. i) *p*-TsOH, MeOH, room temperature, ii) BnCl, Et₃N, CH₂Cl₂, reflux; B. (COCl)₂, dry DMSO, dry CH₂Cl₂, -78°C, then Et₃N; C. (NH₄)₂CO₃, 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 spirohydantoin (**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 (SiO₂; CHCl₃/MeOH=100/1, v/v). The stereostructures of the newly formed stereogenic centers at the C₄-position in both **25** and **26** were assigned by NOE measurements in their 400 MHz ¹H-nmr spectra. Thus, for the compound (**25**), irradiation of the C₃-H_β (1.76 ppm) produced an enhancement of the signal due to the N₁-H (7.20 ppm), and irradiation of the C₃-H_α (2.35 ppm) produced no enhancement of the signal due to the N₁-H, which suggested that the C₃-H_β and N₁-H are of the same side of the molecule. For the compound (**26**), irradiation of the C₅-H_α (2.32 ppm) produced an enhancement of both the signals due to the N₁-H (7.20 ppm) and C₂-H (3.20-3.39 ppm), whereas irradiation of the C₅-H_β (3.12 ppm) produced no enhancement of both the signals due to the N₁-H and C₂-H, which suggested that the C₅-H_β and N₁-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% $\text{Pd}(\text{OH})_2/\text{C}$ 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% $\text{Pd}(\text{OH})_2/\text{C}$ 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**).

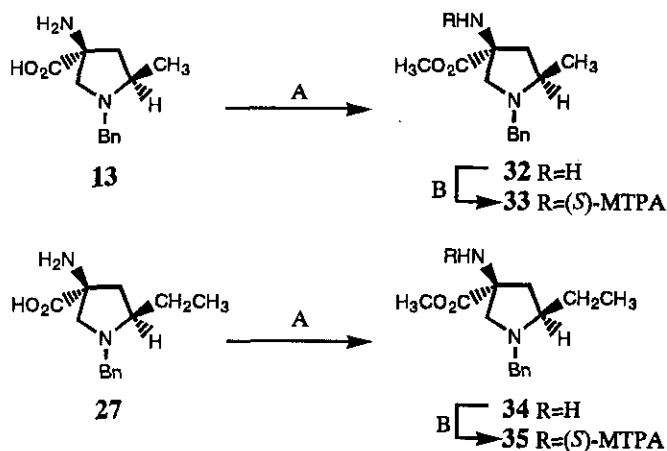


Scheme 4

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

The enantiomeric purities of **1** and **2** were determined to be more than 95% by 400 MHz ^1H -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 pyridine¹¹ 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 literature.^{6a}



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. ^1H - 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 abbreviations 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 F254. 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 material was purchased from Sigma Chemical Co. Methyl (2*S*,4*R*)-1-*tert*-butoxycarbonyl-4-[(*tert*-butyldimethylsilyl)oxy]prolinolate (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 8⁷ (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 Et₃N (28.5 g, 0.28 mol) were added to the mixture of the resulting residue in CH₂Cl₂ (100 ml) and the mixture was refluxed for 12 h. 1M aqueous NaOH solution was added the reaction mixture, the mixture was extracted with CH₂Cl₂. The extract was washed, dried over anhydrous Na₂SO₄. 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. [α]_D²⁰ -115.5° (c=0.97, MeOH). Ms m/z: 191 (M⁺). Ir (film): 3480, 1620 cm⁻¹. ¹H-Nmr (CDCl₃) δ : 1.15 (3H, d, J=6.23 Hz, CH₃), 1.71-1.88 (2H, m, C₃-H), 1.92 (1H, br s, OH), 2.15 (1H, dd, J=10.26, 4.76 Hz, C₅-H), 2.75-2.85 (1H, m, C₂-H), 3.24 (1H, dd, J=10.26, 6.23 Hz, C₅-H), 3.26 and 4.01 (each 1H, each d, J=13.19 Hz, CH₂Ph), 4.29-4.32 (1H, m, C₄-H), 7.29 (5H, m, Ph). ¹³C-Nmr (CDCl₃) δ : 18.59 (CH₃), 43.73 (C₃), 57.49 (C₂), 57.64 (C₅), 62.67 (CH₂Ph), 69.40 (C₄), 126.91, 128.20, 128.95, 138.98 (Ph). High resolution ms m/z: Calcd C₁₂H₁₇NO (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 CH₂Cl₂ (30 ml) was added dropwise to a stirred solution of oxalyl chloride (2.5 g, 20 mmol) in dry CH₂Cl₂ (15 ml) at -78°C under nitrogen. After 15 min, a solution of 9 (3.5 g, 18 mmol) in dry CH₂Cl₂ (30 ml) was added slowly, and stirring was continued for 30 min at -78°C. After addition of Et₃N (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 CH₂Cl₂. The extract was washed with brine and dried over anhydrous Na₂SO₄. 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. [α]_D²⁰ -188.9° (c=0.92, MeOH). Ms m/z: 189 (M⁺). Ir (film): 1760 cm⁻¹. ¹H-Nmr (CDCl₃) δ : 1.32 (3H, d, J=6.23 Hz, CH₃), 2.11 (1H, dd, J=17.95, 9.90 Hz, C₃-H β), 2.47 (1H, dd, J=17.95, 6.20 Hz, C₃-H α), 2.62 (1H, d, J=17.22 Hz, C₅-H), 2.91-2.97 (1H, m, C₂-H), 3.20 (1H, d, J=17.22 Hz, C₅-H), 3.25 and 4.16 (each 1H, each d, J=13.19 Hz, CH₂Ph), 7.29 (5H, m, Ph). ¹³C-Nmr (CDCl₃) δ : 18.32 (CH₃), 45.99 (C₃), 57.02 (C₂), 57.15 (C₅), 61.74 (CH₂Ph), 127.20, 128.37, 128.63, 137.98 (Ph), 213.12 (CO). High resolution ms m/z: Calcd C₁₂H₁₅NO (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 Na₂SO₄. 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 [CHCl₃/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. ¹H-Nmr (CDCl₃) δ: 1.24 (3H, d, J=6.23 Hz, CH₃), 1.69 (1H, dd, J=13.55, 9.16, C₃-H_β), 2.57 (1H, dd, J=13.55, 6.23 Hz, C₃-H_α), 2.66 (1H, d, J=10.26 Hz, C₅-H), 2.69-2.75 (1H, m, C₂-H), 2.89 (1H, d, J=10.26 Hz, C₅-H), 3.19 and 4.11 (each 1H, each d, J=13.19 Hz, CH₂Ph), 6.86 (1H, br s, N₁-H), 7.29 (5H, m, Ph), 9.78 (1H, br s, N₃-H). ¹³C-Nmr (CDCl₃) δ: 18.45 (CH₃), 44.78 (C₃), 56.91 (C₅), 59.40 (C₂), 63.15 (CH₂Ph), 65.96 (C₄), 127.42, 128.42, 129.08, 137.44 (Ph), 155.59 (C₂-CO), 177.23 (C₄-CO). *Anal.* Calcd for C₁₄H₁₇N₃O₂: 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. ¹H-Nmr (CDCl₃) δ: 1.23 (3H, d, J=6.23 Hz, CH₃), 2.10-2.16 (2H, m, C₃-H₂), 2.46 (1H, d, J=10.62 Hz, C₅-H_α), 2.88-3.00 (1H, m, C₂-H), 3.32 (1H, d, J=10.62 Hz, C₅-H_β), 3.41 and 3.98 (each 1H, each d, J=13.19 Hz, CH₂Ph), 6.31 (1H, br s, N₁-H), 7.29 (5H, m, Ph), 8.42 (1H, br s, N₃-H). ¹³C-Nmr (CDCl₃) δ: 17.03 (CH₃), 45.08 (C₃), 55.88 (C₅), 57.93 (C₂), 62.12 (CH₂Ph), 66.36 (C₄), 127.21, 128.39, 128.63, 137.46 (Ph), 156.18 (C₂-CO), 176.59 (C₄-CO). *Anal.* Calcd for C₁₄H₁₇N₃O₂: C, 64.85; H, 6.61; N, 16.21. Found: C, 64.82; H, 6.78; N, 16.24.

(2R,4S)-4-Amino-1-benzyl-4-carboxy-2-methylpyrrolidine Dihydrochloride (13). A solution of **11** (0.8 g, 3 mmol) in 6N 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, 2N HCl). Fast atom bombardment ms m/z: 234 (M⁺). Ir (KBr): 3432, 300-2200, 1598, 1388 cm⁻¹. ¹H-Nmr (D₂O) δ: 1.53 (3H, d, J=6.23 Hz, CH₃), 2.16 (1H, dd, J=14.29, 12.09 Hz, C₃-H_β), 2.87 (1H, dd, J=14.29, 6.23 Hz, C₃-H_α), 3.64 and 3.95 (each 1H, each d, J=13.92 Hz, C₅-H₂), 4.00-4.10 (1H, m, C₂-H), 4.32 (1H, d, 13.19 Hz, CH₂Ph), 7.54 (5H, m, Ph). ¹³C-Nmr (D₂O) δ: 17.08 (CH₃), 44.78 (C₃), 59.67 (C₅), 61.77 (CH₂Ph), 63.21 (C₄), 66.93 (C₂), 132.03, 132.19, 132.96, 133.28 (Ph), 175.75 (CO₂H). *Anal.* Calcd for C₁₃H₁₈N₂O₂ (2HCl): C, 50.82; H, 6.56; N, 9.11. Found: C, 50.75; H, 6.34; N, 8.89.

(2R,4S)-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 H₂ 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 2N 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, 2N HCl). Fast atom bombardment ms m/z: 144 (M⁺). Ir (KBr): 3452, 3000-2150, 1640, 1396 cm⁻¹. ¹H-Nmr (D₂O) δ: 1.49 (3H, d, J=6.23 Hz, CH₃), 2.05 (1H, dd, J=13.56, 11.72 Hz, C₃-H_β), 2.77 (1H, dd, J=13.56, 6.60 Hz, C₃-H_α), 3.65 and 3.90 (each 1H, each d, J=12.82 Hz, C₅-H₂), 4.09-4.15 (1H, m, C₂-H). ¹³C-Nmr (D₂O) δ: 18.82 (CH₃), 44.18 (C₃), 53.94 (C₅), 59.34 (C₂), 65.24 (C₄), 176.48 (CO₂H). *Anal.* Calcd for C₆H₁₂N₂O₂ (2HCl·H₂O): C, 30.65; H, 6.86; N, 11.91. Found: C, 30.46; H, 6.75; N, 11.79.

(2R,4R)-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). $[\alpha]^{23}_D -41.9^\circ$ ($c=0.66$, 2*N* HCl). Fast atom bombardment *m/z*: 234 (M^+). Ir (KBr): 3364, 3100-2200, 1642, 1400 cm^{-1} . $^1\text{H-Nmr}$ (D_2O) δ : 1.62 (3H, d, $J=6.23$ Hz, CH_3), 2.58 (1H, dd, $J=15.02$, 11.72 Hz, $\text{C}_3\text{-H}_\alpha$), 2.81 (1H, dd, $J=15.02$, 6.96 Hz, $\text{C}_3\text{-H}_\beta$), 3.61 and 4.03 (each 1H, each d, $J=13.92$ Hz, $\text{C}_5\text{-H}_2$), 3.95-4.04 (1H, m, $\text{C}_2\text{-H}$), 4.34 (1H, d, $J=13.19$ Hz, CH_2Ph), 7.55 (5H, m, Ph). $^{13}\text{C-Nmr}$ (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 $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_2$ (2HCl): C, 50.82; H, 6.56; N, 9.11. Found: C, 50.62; H, 6.29; N, 9.10.

(2R,4R)-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. $[\alpha]^{20}_D -16.9^\circ$ ($c=0.85$, 2*N* HCl). Fast atom bombardment *m/z*: 144 (M^+). Ir (KBr): 3450, 3100-2200, 1640, 1392 cm^{-1} . $^1\text{H-Nmr}$ (D_2O) δ : 1.52 (3H, d, $J=6.23$ Hz, CH_3), 2.47 (1H, dd, $J=15.02$, 11.36 Hz, $\text{C}_3\text{-H}_\alpha$), 2.73 (1H, dd, $J=15.02$, 6.59, $\text{C}_3\text{-H}_\beta$), 3.65 and 4.13 (each 1H, each d, $J=13.19$ Hz, $\text{C}_5\text{-H}_2$), 4.11-4.14 (1H, m, $\text{C}_2\text{-H}$). $^{13}\text{C-Nmr}$ (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 $\text{C}_6\text{H}_{12}\text{N}_2\text{O}_2$ ($2\text{HCl}\cdot\text{H}_2\text{O}$): C, 30.65; H, 6.86; N, 11.91. Found: C, 30.52; H, 6.66; N, 11.77.

(2S,4R)-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 mixture 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. $[\alpha]^{20}_D -35.2^\circ$ ($c=1.2$, MeOH). *Ms m/z*: 330 (M^+). Ir (film): 1742, 1702 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3) δ : 0.04-0.07 (6H, m, $\text{Si}(\text{CH}_3)_2$), 0.87 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 1.43 and 1.48 (9H, each s, $\text{OC}(\text{CH}_3)_3$, rotamers), 1.92-2.10 (2H, m, $\text{C}_3\text{-H}_2$), 3.48-4.37 (2H, m, $\text{C}_5\text{-H}_2$), 4.21-4.37 (2H, m, $\text{C}_2\text{-}$ and $\text{C}_4\text{-H}$), 9.50 (1H, br s, CHO).

(2R,4R)-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. $[\alpha]^{20}_D -13.4^\circ$ ($c=0.8$, MeOH). *Ms m/z*: 328 (M^+). Ir (film): 1718 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3) δ : 0.04-0.07 (6H, m, $\text{Si}(\text{CH}_3)_2$), 0.87 (9H, s, $\text{SiC}(\text{CH}_3)_3$), 1.44 (9H, s, $\text{OC}(\text{CH}_3)_3$), 1.70-1.78 (1H, m, $\text{C}_3\text{-H}$), 1.92-2.00 (1H, m, $\text{C}_3\text{-H}$), 3.37-3.46 (2H, m, $\text{C}_5\text{-H}_2$), 4.22-4.38 (2H, m, $\text{C}_2\text{-}$

and C₄-H), 4.95-5.10 (2H, m, =CH₂), 5.74-5.82 (1H, m, CH=). High resolution ms m/z: Calcd C₁₇H₃₃NO₃Si (M⁺) 327.2229. Found: 327.2212.

(2R,4R)-1-tert-Butoxycarbonyl-4-(tert-butylidimethylsilyloxy)-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 H₂ (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. $[\alpha]_{\text{D}}^{19}$ -36.8° (c=1.50, MeOH). Ms m/z: 329 (M⁺). Ir (film): 1718 cm⁻¹. ¹H-Nmr (CDCl₃) δ: 0.04-0.07 (6H, m, Si(CH₃)₂), 0.87 (9H, s, SiC(CH₃)₃), 0.90-1.06 (3H, m, CH₂CH₃), 1.44 (9H, s, OC(CH₃)₃), 1.60-2.04 (4H, m, C₃-H₂, CH₂CH₃), 3.37-3.45 (2H, m, C₅-H₂), 3.95-4.50 (2H, m, C₂- and C₄-H). High resolution ms m/z: Calcd C₁₇H₃₅NO₃Si (M⁺) 329.2386. Found: 329.2365.

(2R,4R)-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). $[\alpha]_{\text{D}}^{17}$ -108.5° (c=0.96, MeOH). Ms m/z: 205 (M⁺). Ir (film): 3352 cm⁻¹. ¹H-Nmr (CDCl₃) δ: 0.88 (3H, t, J=7.70 Hz, CH₂CH₃), 1.08-2.24 (4H, m, C₃-H₂, CH₂CH₃), 2.45 (1H, br s, OH), 2.60-3.30 (2H, m, C₂-H, C₅-H, CH₂Ph), 3.90-4.40 (2H, m, C₄-H, CH₂Ph), 7.29 (5H, m, Ph). High resolution ms m/z: Calcd C₁₃H₁₉NO (M⁺) 205.1466. Found: 205.1448.

(2R)-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)]. $[\alpha]_{\text{D}}^{20}$ -200.0° (c=0.86, MeOH). Ms m/z: 203 (M⁺). Ir (film): 1760 cm⁻¹. ¹H-Nmr (CDCl₃) δ: 0.97 (3H, t, J=7.70 Hz, CH₂CH₃), 1.56 (2H, m, CH₂CH₃), 2.15 (1H, dd, J=17.95, 9.89 Hz, C₃-H_β), 2.46 (1H, dd, J=17.95, 6.59 Hz, C₃-H_α), 2.62 and 3.23 (each 1H, each d, J=17.22 Hz, C₅-H₂), 2.79-2.88 (1H, m, C₂-H), 3.25 and 4.20 (each 1H, J=13.19 Hz, CH₂Ph), 7.29 (5H, m, Ph). ¹³C-nmr (CDCl₃) δ: 9.62 (CH₃), 25.12 (CH₂CH₃), 42.98 (C₃), 57.48 (C₅), 62.15 (CH₂Ph), 63.05 (C₂), 127.23, 128.39, 128.60, 138.06 (Ph), 213.24 (CO). High resolution ms m/z: Calcd C₁₃H₁₇NO (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.

(2R,4R)-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)]. $[\alpha]_{\text{D}}^{24}$ -90.4° (c=1.20, MeOH). Ms m/z: 203 (M⁺). Ir (film): 3388 cm⁻¹. ¹H-Nmr (CDCl₃) δ: 1.75 (1H, br s, OH), 1.85-1.94 (2H, m, C₃-H₂), 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, CH₂Ph), 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, =CH₂), 5.25 (1H, dd, J=17.04, 1.84 Hz, =CH₂), 5.68-5.78 (1H, m, CH=), 7.29 (5H, m, Ph). ¹³C-Nmr (CDCl₃) δ: 42.46 (C₃), 57.64 (C₅), 62.04 (CH₂Ph), 66.22 (C₂), 69.78 (C₄), 117.21 (=CH₂), 126.85, 128.20, 128.87, 139.05 (Ph), 139.95 (CH=). High resolution ms m/z: Calcd C₁₃H₁₇NO (M⁺) 203.1310. Found: 203.1302.

(2R)-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)]. $[\alpha]^{24}_{\text{D}} -160.2^{\circ}$ ($c=0.80$, MeOH). Ms m/z : 201 (M^+). Ir (film): 1762 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3) δ : 2.31 (1H, dd, $J=17.96, 10.25\text{ Hz}$, $\text{C}_3\text{-H}_\beta$), 2.52 (1H, dd, $J=17.96, 6.23\text{ Hz}$, $\text{C}_3\text{-H}_\alpha$), 2.63 and 3.27 (each 1H, each d, $J=17.22\text{ Hz}$, $\text{C}_5\text{-H}_2$), 3.22 and 4.17 (each 1H, each d, $J=13.19\text{ Hz}$, CH_2Ph), 3.33-3.37 (1H, m, $\text{C}_2\text{-H}$), 5.29 (1H, dd, $J=9.90, 1.84\text{ Hz}$, $=\text{CH}_2$), 5.37 (1H, dd, $J=17.04, 1.84\text{ Hz}$, $=\text{CH}_2$), 5.80-5.90 (1H, m, $\text{CH}=\text{}$), 7.29 (5H, m, Ph). $^{13}\text{C-Nmr}$ (CDCl_3) δ : 44.73 (C_3), 57.49 (C_5), 60.89 (CH_2Ph), 65.56 (C_2), 118.88 ($=\text{CH}_2$), 127.26, 128.41, 128.67, 137.88 (Ph), 212.51 (CO). High resolution ms m/z : Calcd $\text{C}_{13}\text{H}_{15}\text{NO}$ (M^+) 201.1153. Found: 201.1139.

(2R,4S)-1-Benzyl-2-ethenylpyrrolidine-4-spiro-5'-hydantoin (25) and its **(2R,4R)-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 [$\text{CHCl}_3/\text{MeOH}$ (100/1, v/v)].

Less polar 25: mp $247\text{-}248^{\circ}\text{C}$ as colorless needles (from AcOEt-isopropyl ether). $[\alpha]^{23}_{\text{D}} -85.4^{\circ}$ ($c=0.92$, MeOH). Ms m/z : 271 (M^+). Ir (KBr): 3228, 1774, 1724 cm^{-1} . $^1\text{H-Nmr}$ ($\text{DMSO-}d_6$) δ : 1.76 (1H, dd, $J=13.19, 9.16\text{ Hz}$, $\text{C}_3\text{-H}_\beta$), 2.35 (1H, dd, $J=13.19, 6.23\text{ Hz}$, $\text{C}_3\text{-H}_\alpha$), 2.50 and 2.83 (each 1H, each d, $J=9.89\text{ Hz}$, $\text{C}_5\text{-H}$), 3.03-3.10 (1H, m, $\text{C}_2\text{-H}$), 3.14 and 3.93 (each 1H, each d, $J=13.56\text{ Hz}$, CH_2Ph), 5.20 (1H, dd, $J=9.90, 1.84\text{ Hz}$, $=\text{CH}_2$), 5.31 (1H, dd, $J=17.04, 1.84\text{ Hz}$, $=\text{CH}_2$), 5.72-5.84 (1H, m, $\text{CH}=\text{}$), 7.20 (1H, br s, $\text{N}_1\text{-H}$), 7.29 (5H, m, Ph), 8.34 (1H, br s, $\text{N}_3\text{-H}$). $^{13}\text{C-Nmr}$ ($\text{DMSO-}d_6$) δ : 42.69 (C_3), 56.19 (C_5), 62.23 (CH_2Ph), 65.21 (C_4), 67.05 (C_2), 117.97 ($=\text{CH}_2$), 126.73, 128.03, 128.35, 138.38 (Ph), 139.18 ($\text{CH}=\text{}$), 156.17 ($\text{C}_2\text{-CO}$), 177.64 ($\text{C}_4\text{-CO}$). Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.53; H, 6.42; N, 15.40.

More polar 26: mp $208\text{-}209^{\circ}\text{C}$ as colorless needles (from AcOEt-isopropyl ether). $[\alpha]^{24}_{\text{D}} -92.3^{\circ}$ ($c=0.96$, MeOH). Ms m/z : 271 (M^+). Ir (KBr): 3240, 1772, 1724 cm^{-1} . $^1\text{H-Nmr}$ ($\text{DMSO-}d_6$) δ : 1.97 (1H, dd, $J=13.19, 6.23\text{ Hz}$, $\text{C}_3\text{-H}_\alpha$), 2.02 (1H, dd, $J=13.19, 9.16\text{ Hz}$, $\text{C}_3\text{-H}_\beta$), 2.32 (1H, d, $J=10.2\text{ Hz}$, $\text{C}_5\text{-H}_\alpha$), 3.12 (1H, d, $J=10.2\text{ Hz}$, $\text{C}_5\text{-H}_\beta$), 3.20-3.39 (1H, m, $\text{C}_2\text{-H}$), 3.21 and 3.90 (each 1H, each d, $J=13.19\text{ Hz}$, CH_2Ph), 5.21 (1H, dd, $J=9.90, 1.84\text{ Hz}$, $=\text{CH}_2$), 5.29 (1H, dd, $J=17.04, 1.84\text{ Hz}$, $=\text{CH}_2$), 5.70-5.80 (1H, m, $\text{CH}=\text{}$), 7.20 (1H, br s, $\text{N}_1\text{-H}$), 7.29 (5H, m, Ph), 8.24 (1H, br s, $\text{N}_3\text{-H}$). $^{13}\text{C-Nmr}$ ($\text{DMSO-}d_6$) δ : 43.48 (C_3), 56.16 (C_5), 61.80 (CH_2Ph), 64.99 (C_4), 66.54 (C_2), 118.00 ($=\text{CH}_2$), 126.69, 128.06, 128.18, 138.14 (Ph), 138.90 ($\text{CH}=\text{}$), 156.04 ($\text{C}_2\text{-CO}$), 177.60 ($\text{C}_4\text{-CO}$). Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.20; H, 6.32; N, 15.35.

(2R,4S)-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 $255\text{-}256^{\circ}\text{C}$. $[\alpha]^{26}_{\text{D}} -78.3^{\circ}$ ($c=0.84$, 2N HCl). Ms m/z : 273 (M^+). Ir (KBr): 3276, 3224, 1774, 1746 cm^{-1} . $^1\text{H-Nmr}$ ($\text{DMSO-}d_6$) δ : 0.88 (3H, t, $J=7.70\text{ Hz}$, CH_3), 1.36-1.40 and 1.74-1.84 (each 1H, each m, CH_2CH_3), 1.64 (1H, dd, $J=13.19, 9.16\text{ Hz}$, $\text{C}_3\text{-H}_\beta$), 2.32 (1H, dd, $J=13.19, 7.32\text{ Hz}$, $\text{C}_3\text{-H}_\alpha$), 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 (CH_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.

(2R,4S)-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.

(2R,4S)-4-Amino-4-carboxy-2-ethylpyrrolidine Dihydrochloride (2). The same treatment 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 285-289°C (decomp.). $[\alpha]^{20}_D -7.9^\circ$ ($c=0.60$, 2N HCl). Fast atom bombardment ms m/z : 158 (M^+). Ir (KBr): 3464, 3000-2200, 1648, 1348 cm^{-1} . 1H -Nmr (D_2O) δ : 1.03 (3H, t, $J=7.70$ Hz, CH_3), 1.82-1.90 (2H, m, CH_2CH_3), 2.06 (1H, dd, $J=13.92$, 11.72 Hz, $C_3-H\beta$), 2.78 (1H, dd, $J=13.92$, 6.60 Hz, $C_3-H\alpha$), 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 (CH_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.

(2R,4S)-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). $[\alpha]^{24}_D -59.2^\circ$ ($c=0.81$, 2N HCl). Ir (KBr): 3500, 3200-2200, 1634, 1396 cm^{-1} . 1H -Nmr (D_2O) δ : 2.52 (1H, dd, $J=14.65$, 12.10 Hz, $C_3-H\beta$), 3.08 (1H, dd, $J=14.65$, 6.23 Hz, $C_3-H\alpha$), 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 1H -nmr spectra, and $[\alpha]_D$ value of this sample were identical with those recorded for the sample obtained from **27**.

(2R,4R)-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). $[\alpha]^{26}_D -91.1^\circ$ ($c=0.72$, 2N HCl). Ms m/z : 273 (M^+). Ir (KBr): 3216, 1774, 1742 cm^{-1} . 1H -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, CH_2CH_3), 1.89 (1H, dd, $J=13.19$, 9.89 Hz, $C_3-H\alpha$), 1.96 (1H, dd, $J=13.19$, 6.60 Hz, $C_3-H\beta$), 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 (CH_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

(C₄-CO). *Anal.* Calcd for C₁₅H₁₉N₃O₂: 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.). $[\alpha]_D^{20}$ -3.7° (c=0.76, 2*N* HCl). Ir (KBr): 3448, 3200-2200, 1648, 1394 cm⁻¹. ¹H-Nmr (D₂O) δ: 1.03 (3H, t, J=7.70 Hz, CH₃), 1.29-1.42 and 1.79-1.90 (each 1H, each m, CH₂CH₃), 2.34 (1H, dd, J=14.66, 12.99 Hz, C₃-H_α), 2.62 (1H, dd, J=14.66, 6.96 Hz, C₃-H_β), 3.54 and 3.97 (each 1H, each d, J=13.19 Hz, C₅-H₂), 3.83-4.94 (1H, m, C₂-H). ¹³C-Nmr (D₂O) δ: 12.80 (CH₃), 27.28 (CH₂CH₃), 42.30 (C₃), 52.95 (C₅), 54.92 (C₂), 64.25 (C₄), 176.38 (CO). *Anal.* Calcd for C₇H₁₄N₂O₂ (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). $[\alpha]_D^{23}$ -23.0° (c=0.30, 2*N* HCl). Ir (KBr): 3432, 3200-2200, 1652, 1386 cm⁻¹. ¹H-Nmr (D₂O) δ: 2.80-2.85 (2H, m, C₃-H₂), 3.67 and 4.06 (each 1H, each d, J=13.92 Hz, C₅-H₂), 4.31 and 4.68 (each 1H, each d, J=13.19 Hz, CH₂Ph), 4.44-4.54 (1H, m, C₂-H), 5.79 (1H, dd, J=10.26, 1.52 Hz, =CH₂), 5.83 (1H, dd, J=16.84, 1.52 Hz, =CH₂), 5.90-6.02 (1H, m, CH=), 7.53 (5H, m, Ph). ¹³C-Nmr (D₂O) δ: 42.06 (C₃), 58.89 (C₅), 60.71 (CH₂Ph), 62.65 (C₄), 71.59 (C₂), 130.36 (=CH₂), 131.30, 132.13, 133.24, 133.30 (Ph), 173.77 (CO). *Anal.* Calcd for C₁₄H₁₈N₂O₂ (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 treatment 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 ¹H-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 NaHCO₃ and extracted with AcOEt. The extract was washed with brine and dried over anhydrous Na₂SO₄. 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⁺). ¹H-Nmr (CDCl₃) δ: 1.23 (3H, d, J=5.86 Hz, CH₃), 1.45-1.54 (1H, m, C₃-H_β), 2.04 (2H, br s, NH₂), 2.50 and 2.74 (each 1H, each d, J=9.52 Hz, C₅-H₂), 2.60-2.70 (2H, m, C₂-H and C₃-H_α), 3.13 and 4.07 (each 1H, each d, J=13.19 Hz, CH₂Ph), 3.70 (3H, s, CO₂CH₃), 7.31 (5H, m, Ph). ¹³C-Nmr (CDCl₃) δ: 19.25 (CH₃), 47.51 (C₃), 52.34 (CO₂CH₃), 57.32 (C₅), 59.72 (C₂),

61.80 (C₄), 66.76 (CH₂Ph), 126.95, 128.34, 128.79, 138.95 (Ph), 176.05 (CO₂CH₃). High resolution ms m/z: Calcd C₁₄H₂₀N₂O₂ (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⁺). ¹H-Nmr (CDCl₃) δ: 0.94 (3H, t, J=7.33 Hz, CH₃), 1.40-1.58 (2H, m, CH₂CH₃), 1.76-1.88 (1H, m, C₃-H_β), 1.98 (2H, br s, NH₂), 2.51 and 2.75 (each 1H, each d, J=9.52 Hz, C₅-H₂), 2.48-2.58 (1H, m, C₂-H), 2.63 (1H, dd, J=13.19, 8.06 Hz, C₃-H_α), 3.13 and 4.08 (each 1H, each d, J=12.82 Hz, CH₂Ph), 3.71 (3H, s, CO₂CH₃), 7.30 (5H, m, Ph). ¹³C-Nmr (CDCl₃) δ: 9.85 (CH₃), 26.04 (CH₂CH₃), 44.53 (C₃), 52.35 (CO₂CH₃), 57.42 (C₅), 61.78 (C₄), 65.37 (C₂), 66.58 (CH₂Ph), 126.96, 128.26, 128.73, 139.03(Ph), 175.90 (CO₂CH₃). High resolution ms m/z: Calcd C₁₅H₂₂N₂O₂ (M⁺) 262.1681. Found: 262.1653.

Preparation of (2R,4S)-1-Benzyl-4-[(S)-2-methoxy-2-(trifluoromethyl)phenylacetyl-amino]-4-methoxycarbonyl-2-methylpyrrolidine [(S)-MTPA Amide of **32] (**33**) and (2R,4S)-1-Benzyl-2-ethyl-4-[(S)-2-methoxy-2-(trifluoromethyl)phenylacetyl-amino]-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 ¹H-nmr analysis of this MTPA amide. Ms m/z: 464 (M⁺). ¹H-Nmr (CDCl₃) δ: 1.11 (3H, d, J=5.86 Hz, C₂-CH₃), 1.67 (1H, dd, J=13.92, 8.06 Hz, C₃-H_β), 2.67 and 2.99 (each 1H, each d, J=10.62 Hz, C₅-H₂), 2.85 (1H, dd, J=13.92, 8.06 Hz, C₃-H_α), 3.17 and 4.01 (each 1H, each d, J=13.19 Hz, Ph), 3.46 (3H, s, OCH₃), 3.69 (3H, s, CO₂CH₃), 7.10 (1H, br s, NHCO), 7.23-7.56 (10H, m, Ph x 2). High resolution ms m/z: Calcd C₂₄H₂₇N₂O₄F₃ (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 ¹H-nmr analysis of this MTPA amide. Ms m/z: 478 (M⁺). ¹H-Nmr (CDCl₃) δ: 0.84 (3H, t, J=7.70 Hz, CH₂CH₃), 1.62-1.80 (3H, m, CH₂CH₃ and C₃-H_β), 2.55-2.64 (1H, m, C₃-H_α), 2.63 and 2.98 (each 1H, each d, J=10.26 Hz, C₅-H₂), 2.80 (1H, dd, J=13.92, 8.80 Hz, C₂-H), 3.16 and 4.02 (each 1H, each d, J=13.19 Hz, CH₂Ph), 3.47 (3H, d, J=1.47 Hz, OCH₃), 3.69 (3H, s, CO₂CH₃), 7.06 (1H, br s, NHCO), 7.20-7.60 (10H, m, Ph x 2). High resolution ms m/z: Calcd C₂₅H₂₉N₂O₄F₃ (M⁺) 478.2079. Found: 478.2060.

REFERENCES

- (a) G. Massiot and C. Delaude, "The Alkaloids," Vol. 27, ed. by A. Brossi, Academic Press, New York, 1986, Chapter 3; (b) A. Numata and T. Ibuka, "The Alkaloids," Vol. 31, ed. by A. Brossi, Academic Press, New York, 1987, Chapter 6.
- (a) R. M. Williams, "Synthesis of Optically Active α-Amino Acids," Vol. 7 of Organic Chemistry Series, ed. by J. E. Baldwin and P. D. Magnus, Pergamon Press, Oxford, 1989; (b) R. O. Duthaler, *Tetrahedron*, 1994, **50**, 1539.

3. S-T. Fang, L-C. Li, C-I. Niu, and K-F. Ts'eng, *Sci. Sinica*, 1961, **10**, 845.
4. S. H. Shiao, B. J. Shao, Y. H. Ho, Y. C. Yang, and C. P. Mao, *Sci. Sinica*, 1962, **11**, 1527.
5. (a) T-C. Sun, S-H. Lo, S-W. Chao, and J-Y. Chi, *Sci. Sinica*, 1961, **10**, 852; (b) H. J. Monteiro, *J. Chem. Soc., Chem. Commun.*, 1973, 2. (c) Y. Morimoto and K. Achiwa, *Chem. Pharm. Bull.*, 1987, **35**, 3845; (d) O. Mamoun, H. Benhaoua, R. D.-Bougout, and D. Danion, *Synth. Commun.*, 1995, **25**, 1295.
6. (a) K. Tanaka and H. Sawanishi, *Tetrahedron: Asymmetry*, 1995, **6**, 1641; (b) K. Tanaka, H. Iwabuchi, and H. Sawanishi, *Tetrahedron: Asymmetry*, (in press).
7. T. Rosen, D. T. W. Chu, I. M. Lico, P. B. Fernande, K. Marsh, L. Shen, V. G. Cepa, and A. G. Pernet, *J. Med. Chem.*, 1988, **31**, 1598.
8. A. J. Mancuso, S.-L. Huang, and D. Swern, *J. Org. Chem.*, 1978, **43**, 2480.
9. (a) J. T. Edward and C. Jitrangsri, *Can. J. Chem.*, 1975, **53**, 3339; (b) G. G. Trigaro, C. Arendano, E. Santos, J. T. Edward, and S. C. Wong, *Can. J. Chem.*, 1979, **57**, 1456.
10. (a) J. R. Parikh and W. von E. Doering, *J. Am. Chem. Soc.*, 1967, **89**, 5505; (b) Y. Hamada and T. Shioiri, *Chem. Pharm. Bull.*, 1982, **30**, 1921; (c) Y. Hamada, M. Shibata, T. Sugiura, S. Kato, and T. Shioiri, *J. Org. Chem.*, 1987, **52**, 1252.
11. J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.

Received, 31st August, 1995