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Asymmetric Syntheses of All Four Isomers of 4-Amino-4-carboxyproline: Novel Conformationally Restricted Glutamic Acid Analogues

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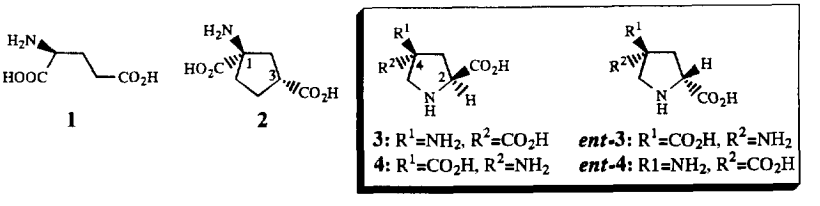
Abstract: Asymmetric syntheses of all four isomers of 4-amino-4-carboxyprolines, *i.e.* (2*S*,4*S*)-**3**, (2*S*,4*R*)-**4**, and their corresponding enantiomers, as novel conformationally restricted analogues of glutamic acid, were performed from *trans*-4-hydroxy-*L*-proline as a homochiral starting material. The key step was the spirohydantoin ring formation by employing the Bucherer-Bergs reaction of 4-oxoproline derivatives. These structures were determined by NMR studies.

Introduction

L-Glutamic acid (*L*-Glu) is one of the major excitatory neurotransmitters in the mammalian central nervous system. Several conformationally restricted analogues of Glu have been recently developed for use either for the elucidation of the conformational requirements for receptor binding of the excitatory amino acid[1], particularly the most studied *N*-methyl-*D*-aspartate (NMDA) receptor, or as conformational probes of the active sites of the vitamine K-dependent carboxylase after incorporation into peptide substrates[2]. Therefore the asymmetric synthesis of such analogues of Glu has been the subject of extensive interest. Among them, (1*R*,3*R*)-1-amino-1,3-dicarboxycyclopentane (**2**) have been characterized as an NMDA receptor agonist.[1b] We focused our attention on the synthesis of novel glutamic acid analogues **3** and **4** with restricted conformational flexibility, in which the C4 ring carbon atom of **2** was replaced by nitrogen atom as shown in **Figure 1**.

We report here the syntheses of all four stereoisomers of 4-amino-4-carboxyprolines [(2*S*,4*S*)-**3**, (2*S*, 4*R*)-**4**, *ent*-(2*R*,4*R*)-**3**, and *ent*-(2*R*,4*S*)-**4**], from *trans*-4-hydroxy-*L*-proline (**5**) as a homochiral starting material.

Figure 1

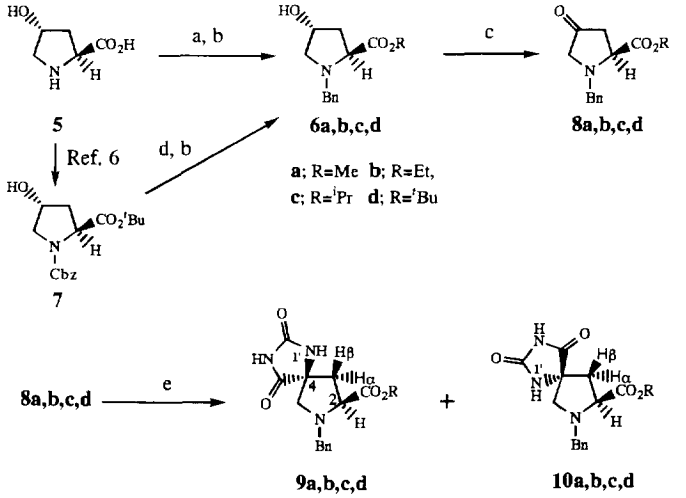


Results and Discussion

Our approach is based on spirohydantoin formation by Bucherer-Bergs reaction of 4-oxoproline derivatives followed by hydrolysis as shown in **Scheme 1** and **Scheme 3**. The required 4-oxoproline derivatives **8a-c** were prepared in 3-step sequence of reactions involving esterification with appropriate alcohols

in the presence of thionyl chloride, *N*-benzylation, and Swern oxidation[4] of the resulting alcohols **6** from **5** according to the method of Rosen *et al.*[5] *tert*-Butyl ester **8d** was obtained in 3 steps from the known *N*-Cbz derivative **7**[6]. The removal of the Cbz group from **7** by hydrogenolysis followed by *N*-benzylation gave **6d**, then Swern oxidation[4] of **6d** afforded **8d**. Treatment of **8a** with potassium cyanide and ammonium carbonate in the Bucherer-Bergs reaction afforded a mixture of diastereomeric spirohydantoins **9a** and **10a** in a ratio of 75: 25 respectively, in 70% yield. These spirohydantoin derivatives **9a** and **10a** could be cleanly separated by flash chromatography (SiO_2; $CHCl_3$/MeOH: 50/1). Similarly, treatment of **8b-d** under the Bucherer-Bergs reaction gave the diastereomers **9b-d** and **10b-d**. These results are summarized in **Table 1**.

Scheme 1



Reagents: a) ROH, $SOCl_2$, reflux, 3h; b) BnCl, TEA, CH_2Cl_2, reflux, 6h; c) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, then TEA; d) 10% Pd-C/H_2, MeOH; e) $(NH_4)_2CO_3$, KCN, ROH-H_2O (for **8a,b,c**) or DMF-H_2O (for **8d**), 55°C-60°C, 24h.

Table 1. Diastereoselevtivity of the Bucherer-Bergs reaction of 4-oxoproline derivatives **8**

Starting Material	Isomeric Ratio[a]			Comb.Yield
	9	:	**10**	(%)
8a	75	:	25	70
8b	78	:	22	75
8c	84	:	16	72
8d	96	:	4	74

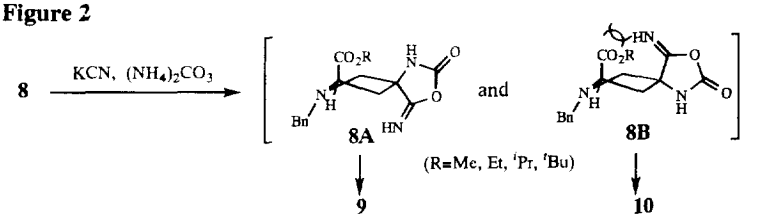
a) The ratio was determined by isolation, after flash chromatography.

Increasing the steric bulkiness of the ester groups in **8** led to an increase of the diastereoselectivity in the reaction. The stereoselectivity could be explained by Edward and Jitransgri's mechanism[3a] as shown in **Figure 2**. Thus, the intermediate **8A** would be thermodynamically more favorable than that of **8B** due to steric repulsion between the C=NH and the ester groups. Therefore the diastereomer **9** derived from **8A** may be obtained as a major product.

The stereostructures of the stereogenic center newly formed at C_4 in both **9** and **10** were assigned by NOE

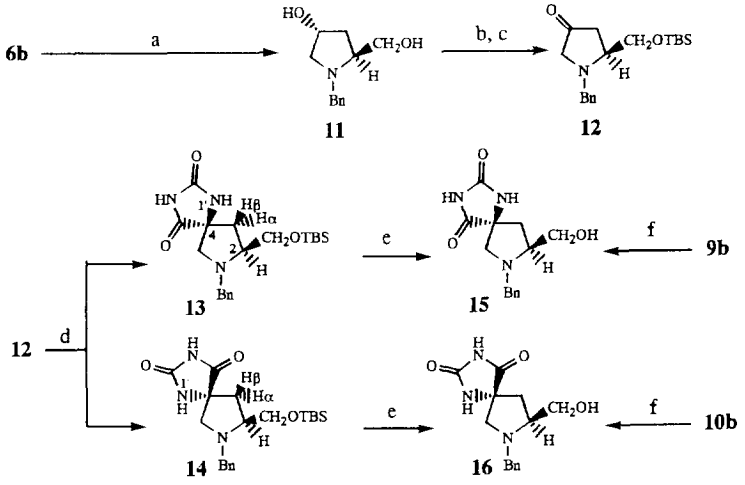
measurements in their 400 MHz ^{1}H-NMR spectra. Thus, for the compounds **9**, irradiation of the C_2-H produced an enhancement of the C_3-Hα and irradiation of the $N_{1'}$-H gave an enhancement of the C_3-Hβ and no enhancement of the C_3-Hα, which suggested that the C_3-Hβ and $N_{1'}$-H are of the same side of the molecule. For the compounds **10**, irradiation of the C_2-H gave an enhancement of the C_3-Hα and irradiation of the $N_{1'}$-H gave an enhancement of the C_3-Hα and no enhancement of the C_3-Hβ, which suggested that the C_3-Hβ and $N_{1'}$-H are of the opposite side of the molecule.

Figure 2



Next, in order to confirm that no epimerization at C_2 of both **9b** and **10b** had occured during the Bucherer-Bergs reaction, they were converted to the corresponding 2-hydroxymethylpyrrolidine derivatives **15** and **16**, respectively (**Scheme 2**). The selective reduction of the ethoxycarbonyl group in **9b** with sodium borohydride in THF/MeOH (5/1)[7] afforded the corresponding alcohol **15** in 76% yield, $[\alpha]_D^{20}$ -50.2 (c=0.9, 2*N* HCl). Similar reduction of **10b** afforded the corresponding **16** in 79% yield, $[\alpha]_D^{20}$ -48.4 (c=0.9, 2*N* HCl). These resulting alcohols **15** and **16** were identified with $[\alpha]_D$ values of authentic samples prepared in enantiomerically pure form by the alternate route as shown in **Scheme 2**.

Scheme 2

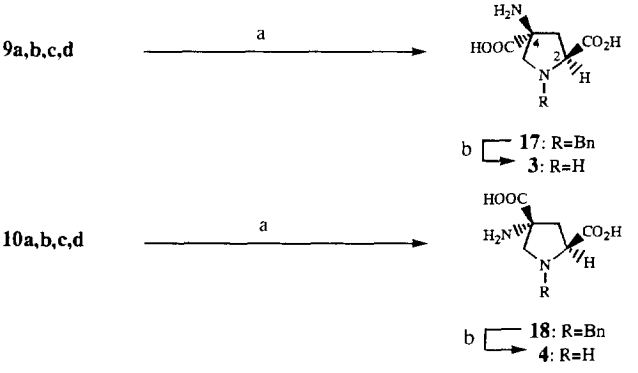


Reagents: a) $LiBH_4$, THF, rt, 10h; b) TBSCl, TEA, 4-DMAP, CH_2Cl_2, -10°C; c) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, then TEA; d) $(NH_4)_2CO_3$, KCN, DMF-H_2O, 55-C~60°C, 24h; e) Bu_4NF, THF, rt., 3h; f) $NaBH_4$, THF/MeOH (5/1), 55°C, 1h.

The syntheses of authentic 2-hydroxymethylpyrrolidine detivatives **15** and **16** were easily achieved from ethyl 1-benzyl-4-hydroxyprolinate **6b** *via* 5-step sequence as follows: 1) reduction of **6b** with lithium borohydride in THF (84% yield), 2) selective protection of primary hydroxy group of **11** as the *tert*-

butyldimethylsilyl (TBS) chloride in the presence of triethylamine (TEA) and a catalytic amount of 4-dimethylaminopyridine (4-DMAP) in CH_2Cl_2[8] at -10°C (82% yield), 3) Swern oxidation (85%), 4) Bucherer-Bergs reaction with potassium cyanide and ammonium carbonate [spirohydantoin derivatives **13** and **14** in a ratio of 8:1 with 69% yield respectively after flash chromatography (SiO_2; $CHCl_3$/MeOH=50/1)], and 5) deprotection of TBS ether of **13** with tetrabutylammonium fluoride in THF. The desired authentic alcohol derivative **15** was obtained in 79% yield, $[\alpha]_D^{18}$ -50.4 (c=1.02, 2*N* HCl), whereas **14** was similarly deprotected with tetrabutylammonium fluoride to afford the **16** in 80% yield, $[\alpha]_D^{18}$ -48.6 (c=0.55, 2*N* HCl). Attempts to direct confirm the stereostructures of the asymmetric centers at the C_4- positions in **15** and **16** were unsuccessful; however, their immediate precursors, silyl ether spirohydantoin derivatives **13** and **14** were assigned by NOE measurements in their 400 MHz ^{1}H-NMR spectra. Thus, NOE between the signals due to C_2-H at 2.95-3.01 ppm and C_3-Hα at 2.59 ppm and that between the signals due to C_3-Hβ at 1.93 ppm and N_1-H at 6.51 ppm in **13** were found to be 6.8% and 2.5%, respectively, whereas NOE between the signals due to C_2-H at 3.14-3.19 ppm and C_3-Hα at 2.15 ppm and that between the signals due to C_3-Hα at 2.15 ppm and N_1-H at 6.89 ppm in **14** were recorded as 5.8% and 2.4%, respectively. Accordingly, the stereostructures of **13** and **14** could be rigorously assigned as depicted in **Scheme 2**. At this stage, no racemization at the C_2 position in both **9b** and **10b** under the Bucherer-Bergs reaction had taken place on the basis of these results ($[\alpha]_D$ values and NOE measurements). Thus, absolute configurations of these compounds **9a-d** and **10a-d** were unambiguously determined as (2*S*,4*S*)-**9** and (2*S*,4*R*)-**10**, respectively.

Scheme 3



Reagents: a) 6*N* HCl, 130°C in a sealded tube, 24h; b) 20% $Pd(OH)_2$-C/H_2, MeOH, 3 atm.

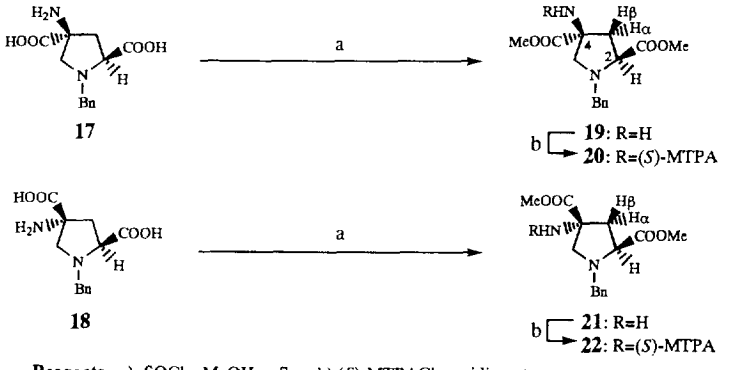
Finally, the acidic hydrolysis of both the spirohydantoins (2*S*,4*S*)-**9** and (2*S*,4*R*)-**10** with 6*N* HCl at 130°C in a sealded tube for 24 hours followed by hydrogenolysis of the resulting *N*-benzyl amino acids **17** and **18** with 20% $Pd(OH)_2/C$[9] , afforded the target free amino acids (2*S*,4*S*)-**3** and (2*S*,4*R*)-**4**, respectively after ion exchange chromatography on Dowex 50W x 8 (**Scheme 3**).

The enantiomeric purities of both **3** and **4** were determined to be more than 95% ee by 400 MHz ^{1}H-NMR analyses of (*S*)-MTPA amides **20** and **22** derived respectively from **17** and **18** *via* 2-step sequence involving esterification and acylation with (*S*)-MTPA chloride in pyridine[10] as shown in **Sheme 4**. Furthermore, the

stereostructures of both **20** and **22** were confirmed on the basis of NOE experiments in their 400MHz ^{1}H-NMR spectra.

Thus, NOE between the signals due to C_2-H and C_3-Hα and that between the signals due to C_3-Hβ and NH in **20** were found to be 13.5% and 4.3%, respectively. On the other hand, NOE between the signals due to C_2-H and C_3-Hα and that between the signals due to C_3-Hα and NH in **22** were recorded as 12.5% and 3.8%, respectively, thus confirming that the C_2-H and NH in **20** and **22** were assigned to have *trans*- and *cis*-configurations, respectively. No epimerization of the C_2 stereogenic centers in both **17** and **18** had occured during the hydrolysis described above.

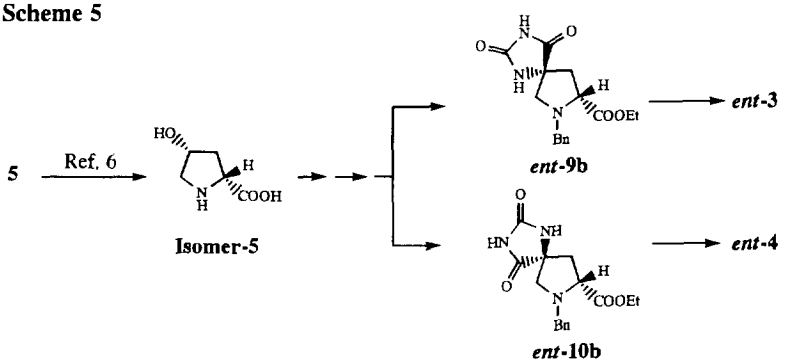
Scheme 4



Reagents: a) $SOCl_2$, MeOH, reflux, b) (*S*)-MTPACl, pyridine, rt.

Each of the enantiomeric 4-amino-4-carboxyprolines (***ent*-3** and ***ent*-4**) were obtained in the same reaction sequence as described above *via* the key intermediates ***ent*-9b** and ***ent*-10b** by employing *cis*-4-hydroxy-*D*-proline (**Isomer-5**) easily converted from *trans*-4-hydroxy-*L*-proline (**5**) by the literture method[6] as shown in **Scheme 5**.

Scheme 5



In conclusion, the syntheses of all four isomers of 4-amino-4-carboxyprolines (**3**, **4**, ***ent*-3**, and ***ent*-4**) with high enantiomeric purity (e.e.>95 %) have been performed by employing the Bucherer-Bergs reaction as the key reaction, from *trans*-4-hydroxy-*L*-proline as a homochiral starting material.

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 $CDCl_3$ and DMSO-d_6 solutions, or from 3-(trimethylsilyl)-1-propanesulfonic 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), quartet (q), septet (sept), 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}. 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.

Synthesis of Methyl (2*S*,4*R*)-1-Benzyl-4-hydroxyprolinate (**6a**)[5], *tert*-Butyl (2*S*,4*R*)-1-Benzyloxycarbonyl-4-hydroxyprolinate (**7**)[6], and *cis*-4-hydroxy-*D*-proline (**isomer-5**)[6] were prapared according to literture procedure.

Ethyl (2*S*,4*R*)-1-Benzyl-4-hydroxyprolinate (6b) and Its (2*R*,4*R*)-Isomer (6b)

a) Preparation of **6b**: Thionyl chloride (20.2 g, 0.17 mol) was added dropwise to a mixture of *trans*-4-hydroxy-*L*-proline (**5**) (20.0 g, 0.15 mol) in ethanol (200 ml) at 0°C. The solution was refluxed for 6h and cooled to room temperature. The solution was diluted with ether, and the resulting white solid was filtered, washed with ether and dried *in vacuo* to yield ethyl (2S,4R)-4-hydroxyprolinate hydrochloride (25.6 g, 86 %). This material was directly used for the next reaction without further purification. Benzyl chloride (9.8 g, 0.078 mol) was added to a mixture of the Ethyl (2S,4*R*)-4-hydroxyprolinate hydrochloride (10.3 g, 0.053 mol) and triethylamine (12.1 g, 0.12 mol) in dichloromethane (80 ml). The reaction mixture was refluxed for 6h. After cooling, 1M aqueous sodium hydroxide was added to the mixture. The mixture was extracted with dichloromethane (100ml). The extract was washed with brine, dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane/ethyl acetate:1/2) to give **6b** (9.1 g, 70 %), as a colorless oil: $[\alpha]_D^{23}$ -65.0 (c 1.07, MeOH). IR (neat): 3400, 1737. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.23 (3H, t, J=7.32, $CH_2\underline{CH_3}$), 2.05 (1H, ddd, J=3.30, 8.06, 13.20, C_3-H), 2.22 (1H, ddd, J=7.30, 7.70, 13.20, C_3-H), 2.36-2.52 (1H, br s, OH), 2.44 (1H, dd, J=4.03, 9.89, C_5-H), 3.29 (1H, dd, J=5.50, 9.89, C_5-H), 3.57 (1H, d, J=7.70, 8.06, C_2-H), 3.63 and 3.90 (2H, each d, J=12.82, $\underline{CH_2}$Ph), 4.11 (2H, q, J=7.32, $\underline{CH_2}CH_3$), 4.38-4.45 (1H, m, C_4-H), 7.30 (5H, m, Ph). EIMS m/z: 249 (M^+). HRMS: calcd for $C_{14}H_{19}NO_3$ (M^+): 249.1364. Found: 249.1370.

b) Preparation of **Isomer-6b**: The same treatment of (2*R*,4*R*)-Isomer **5** hydrochloride[6] (5.0 g, 0.03 mol) as described for the preparetion of **6b** from **5** gave **Isomer-6b** (4.7 g, 63 %, 2 steps) as a colorless oil. $[\alpha]_D^{22}$ +76.2 (c 1.20, MeOH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.23 (3H, t, J=7.32, $CH_2\underline{CH_3}$), 1.98 (1H, ddd, J=1.40, 4.00, 14.20, C_3-H), 2.25 (1H, ddd, J=5.82, 10.00, 14.20, C_3-H), 2.34-2.55 (1H, br s, OH), 2.38

(1H, dd, J=4.00, 10.00, C_5-H), 3.02 (1H, dd, J=1.40, 10.00, C_5-H), 3.32 (1H, dd, 4.00, 10.00, C_2-H), 3.74 and 3.85 (1H, d, J=12.82, $C\underline{H}_2$Ph), 4.10 (2H, q, J=7.32, $C\underline{H}_2CH_3$), 4.25-4.40 (1H, m, C_4-H), 7.30 (5H, m, Ph).

Isopropyl (2*S*,4*R*)-1-Benzyl-4-hydroxyprolinate (6c)

The same treatment of **5** (5.0 g, 0.038 mol) as described for the preparetion of **6b** from **5**, except for the use of isopropanol instead of ethanol, gave **6c** (6.3 g, 63 %, 2 steps) as a colorless oil. $[\alpha]_D^{22}$ -66.5 (c 1.16, MeOH). IR (neat): 3440, 1730. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.23 (6H, d, J=6.23, $(C\underline{H}_3)_2$), 2.05 (1H, ddd, J=3.30, 8.06, 13.56, C_3-H), 2.08-2.20 (1H, br s, OH), 2.22 (1H, ddd, J=7.30, 7.70, 13.56, C_3-H), 2.44 (1H, dd, J=3.66, 9.89, C_5-H), 3.28 (1H, dd, J=5.86, 9.89, C_5-H), 3.54 (1H, t, J=7.70, C_2-H), 3.63 and 3.93(2H, each d, J=12.82, $C\underline{H}_2$Ph), 4.39-4.46 (1H, m, C_4-H), 5.01 (1H, sept, J=6.23, $C\underline{H}(CH_3)_2$), 7.31 (5H, m, Ph). EIMS m/z: 263 (M^+). HRMS: calcd for $C_{15}H_{21}NO_3$ (M^+): 263.1520. Found: 263.1515.

***tert*-Butyl (2*S*,4*R*)-1-Benzyl-4-hydroxyprolinate (6d)**

A mixture of *tert*-Butyl (2*S*,4*R*)-1-Benzyloxycarbonyl-4-hydroxyprolinate[6] **7** (4.5 g, 0.014 mol) and 10% palladium on carbon (0.3 g) in methanol (60 ml) was stirred for 10h at room temperature under H_2 atmosphere (1 atm). The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give *tert*-Butyl (2*S*,4*R*)-4-hydroxyprolinate (2.4 g) as a colorless oil. This product was directly used for the next reaction without purification. Benzyl chloride (2.4 g, 0.019 mol) was added to a mixture of the *tert*-Butyl (2S,4R)-4-hydroxyprolinate (2.4 g, 0.013 mol) and triethylamine (1.6 g, 0.015 mol) in dichloromethane (50 ml). The reaction mixture was refluxed for 6h. After cooling, 1M aqueou sodium hydroxide was added to the mixture. The mixture was extracted with dichloromethane (60 ml). The extract was washed with brine, dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane/ethyl acetate:1/1) to give **6d** (2.4 g, 68 %) as a colorless oil. $[\alpha]_D^{22}$ -65.3 (c 1.05, MeOH), IR (neat): 3440, 1730. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.44 (9H, s, $(CH_3)_3$), 2.01 (1H, ddd, J=3.30, 8.06, 13.19, C_3-H), 2.20 (1H, ddd, J=7.30, 7.70, 13.19, C_3-H), 2.35-2.55 (1H, br s, OH), 2.41 (1H, dd, J=4.03, 9.89, C_5-H), 3.24 (1H, dd, J=5.50, 9.89, C_5-H), 3.47 (1H, dd, J=7.70, 8.06, C_2-H), 3.62 and 3.95 (2H, each d, J=12.82, $C\underline{H}_2$Ph), 4.36-4.44 (1H, m, C_4-H), 7.31 (5H, m, Ph). EIMS m/z: 277 (M^+). HRMS: calcd for $C_{16}H_{23}NO_3$ (M^+): 277.1678. Found: 277.1665.

Methyl (2*S*)-1-Benzyl-4-oxoprolinate (8a)

Following the reported procedure,[5] a solution of dimethyl sulfoxide (3.9 g, 0.049 mol) in dry dichloromethane (15 ml) was added dropwise to a stirred solution of oxalyl chloride (3.2 g, 0.025 mol) in dry dichloromethane (20 ml) at -78°C under N_2 atmosphere. After 15 min, a solution of **6a**[5] (5.4 g, 0.023 mol) in dry dichloromethane (30 ml) was added slowly, and stirring was continued for 30 min at -78°C. After addition of triethylamine (11.6 g, 0.11 mol), the mixture was gradually warmed up to room temperature. The mixture was quenched with water (10 ml) and aqueous layer was separated and extracted with dichloromethane (80 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 (hexane/ethyl acetate: 1/1) to give **8a** (2.7 g, 86 %) as a white solid, colorless needles, mp 49-50°C (isopropyl ether). $[\alpha]_D^{22}$ -47.8 (c 0.80, MeOH). IR (KBr): 1756, 1725. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.58 (1H, dd, J=5.50, 17.95, C_3-Hβ), 2.74 (1H, dd, J=7.70, 17.95, C_3-Hα), 3.01 and 3.39 (2H, each dd, J=17.22, C_5-H_2), 3.65 (3H, s, OCH_3), 3.76 and 3.98 (2H, each d, J=13.19, $C\underline{H}_2$Ph), 3.84 (1H, dd, J=5.50, 7.70, C_2-H), 7.31 (5H, m, Ph).

Ethyl (2*S*)-1-Benzyl-4-oxoprolinate (8b) and Its (2*R*)-Enantiomer (*ent*-8b)

a) Preparation of **8b**: The same treatment of **6b** (4.5 g, 0.018 mol) as described for the preparetion of **8a** from **6a** gave **8b** (4.1 g, 92 %) as a colorless oil. $[\alpha]_D^{24}$ -49.3 (c 1.02, MeOH). IR (neat): 1755, 1728. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.29 (3H, t, J=7.33, $CH_2\underline{CH_3}$) 2.55 (1H, dd, J=5.50, 17.95, C_3-Hβ), 2.70 (1H, dd, J=7.70, 17.95, C_3-Hα), 3.00 and 3.35 (2H, each d, J=17.22, C_5-H_2), 3.74 and 3.95 (2H, each d, J=13.19, $C\underline{H_2}$Ph), 3.82 (1H, dd, J=5.50, 7.70, C_2-H), 4.20 (2H, q, J=7.33, $C\underline{H_2}CH_3$), 7.31 (5H, m, Ph). EIMS m/z: 247 (M^+). HRMS: calcd for $C_{14}H_{17}NO_3$ (M^+): 247.1208. Found: 247.1216.

b) Preparetion of ***ent*-8b**: The same treatment of ***ent*-6b** (5.2 g, 0.02 mol) as described for the preparetion of **8a** from **6a** gave ***ent*-8b** (4.6 g, 90 %) as a colorless oil. $[\alpha]_D^{22}$ +48.8 (c 1.02, MeOH). The IR and ^{1}H-NMR spectra of this sample were identical with those recorded for **8b**.

Isopropyl (2*S*)-1-Benzyl-4-oxoprolinate (8c)

The same treatment of **6c** (6.2 g, 0.023 mol) as described for the preparetion of **8a** from **6a** gave **8c** (5.3 g, 86 %) as a colorless oil. $[\alpha]_D^{24}$ -51.6 (c 0.95, MeOH). IR (neat): 1768, 1732. EIMS m/z: 261 (M^+). HRMS: calcd for $C_{15}H_{19}NO_3$ (M^+): 261.1365. Found: 261.1342. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.19 and 2.20 (6H, each d, J=6.60, $CH(C\underline{H_3})_2$), 2.48 (1H, dd, J=5.50, 17.95 C_3-Hβ), 2.68 (1H, dd, J=7.70, 17.95, C_3-Hα), 2.98 and 3.33 (2H, each d, J=17.22, C_5-H_2), 3.74 (1H, dd, J=5.50, 7.70, C_2-H), 3.82 and 3.95 (2H, each d, J=13.19, $C\underline{H_2}$Ph), 4.85 (1H, sept, J=6.60, $C\underline{H}(CH_3)_2$), 7.32 (5H, m, Ph).

***tert*-Butyl (2*S*)-1-Benzyl-4-oxoprolinate (8d)**

The same treatment of **6d** (2.8 g, 0.01 mol) as described for the preparetion of **8a** from **6a** gave **8d** (2.4 g, 88 %) as a colorless oil. $[\alpha]_D^{23}$ -42.7 (c 1.02, MeOH). IR (neat): 1766, 1730. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.50 (1H, dd, J=5.13, 17.95, C_3-Hβ), 2.66 (1H, dd, J=7.70, 17.95, C_3-Hα), 3.00 and 3.31 (2H, each d, J=17.22, C_5-H_2), 3.73 (1H, dd, J=5.13, 7.70, C_2-H), 3.75 and 3.97 (2H, each d, J=13.19, $C\underline{H_2}$Ph), 7.32 (5H, m, 5H). EIMS m/z: 275 (M^+). HRMS: calcd for $C_{16}H_{21}NO_3$ (M^+): 275.1521. Found: 275.1509.

(2*S*,4*S*)-1-Benzyl-2-methoxycarbonylpyrrolidine-4-spiro-5'-hydantoin (9a) and Its (2S, 4R)-Isomer (10a)

Ammonium carbonate (5.76 g, 0.06 mol) and potassium cyanide (1.56 g, 0.024 mol) were added to a solution of **8a** (2.95 g, 0.012 mol) in methanol/water (1/1) (60 ml). The mixture was heated at 55°C-60°C for 24h and the solvent was removed *in vacuo*. The residue was diluted with water (20 ml), and the mixture was extracted with ethyl acetate (80 ml). The extract was washed with brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* give a residue, which was purified by column chromatography (hexane/ethyl acetate:2/1) to give **(9a+10a)** (2.68 g, 70 %) as a mixture of two diastereoisomers. This mixture was further separated by flash column chromatography (chloroform/methanol:50/1) to give **9a** as a less polar product and **10a** as a more polar product in a ratio of 75: 25.

Less polar 9a: colorless needles. mp 187-188°C (ethyl acetate/isopropyl ether). $[\alpha]_D^{25}$ -65.3 (c 1.32, MeOH), IR (KBr): 3304, 3224, 1780, 1740, 1724. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.10 (1H, dd, J=8.42, 13.19, C_3-Hβ), 2.51 (1H, dd, J=8.06, 13.19, C_3-Hα), 2.70 and 2.94 (2H, each d, J=10.26, C_5-H_2), 3.47 (1H, dd, J=8.06, 8.53, C_2-H), 3.49 and 3.97 (2H, each d, J=13.56, $C\underline{H_2}$Ph), 7.25 (1H, br s, N_1'H), 7.32 (5H, m, Ph), 8.21 (1H, s, N_3'H). ^{13}C-NMR (90 MHz, DMSO-d_6): δ 41.23 (t, C_3), 51 71 (q, OCH_3), 57.31 (t, C_5), 61. 47 (t, $\underline{C}H_2$Ph), 64.44 (d, C_3), 65.24 (s, C_4), 127.02, 128.12, 128.61, and 137.93 (Ph), 156.04 (s, C_2' CO), 172.06 (s, CO_2), 177.32 (s, C_4' CO). EIMS m/z: 303 (M^+). *Anal.* Calcd for $C_{15}H_{17}N_3O_4$: C, 59.39; H, 5.65; N, 13.86. Found: C, 59.20; H, 5.46; N, 13.64.

More polar 10a: colorless needles. mp 164-165°C (ethyl acetate/isopropyl ether). $[\alpha]_D^{25}$ -31.4 (c 1.10, MeOH). IR (neat): 3300, 3224, 1780, 1740. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.36 (1H, dd, J=8.06, 13.92, C_3-Hα), 2.61 (1H, dd, J=6.70, 13.92, C_3-Hβ), 2.75 and 3.46 (2H, each d, J=10.26, C_5-H_2), 3.70 (3H, s, OCH_3), 3.79 (1H, dd, J=6.70, 8.06, C_2-H), 3.80 and 3.93 (2H, each d, J=13.19, C$\underline{H_2}$Ph), 7.12 (1H, br s, N_1'H), 7.27 (5H, m, Ph), 9.40 (1H, s, N_3'H). ^{13}C-NMR (90 MHz, DMSO-d_6): δ 40.81 (t, C_3), 51.87 (q, OCH_3), 55.56 (t, C_5), 60.83 (t, $\underline{C}H_2$Ph), 62.72 (d, C_2), 67.31 (s, C_4), 127.37, 128.39, 128.64, 137.68 (Ph), 157.12 (s, C_2'CO), 172.59 (s, CO_2), 175.40 (s, C_4'CO). EIMS m/z: 303 (M^+). *Anal.* Calcd for $C_{15}H_{17}N_3O_4$: C, 59.39; H, 5.65; N, 13.86. Found: C, 59.16; H, 5.40; N, 13.62.

(2*S*,4*S*)-1-Benzyl-2-ethoxycarbonylpyrrolidine-4-spiro-5'-hydantoin (9b) , Its (2*S*,4*R*)-Isomer (10b), Its (2*R*,4*R*)-Isomer (*ent*-9b), and Its (2*R*,4*S*)-Isomer (*ent*-10b)

a) Preparetion of **9b** and **10b**: Treatment of **8b** (3.0 g, 0.012 mol) under the same conditions as described for the preparation of **9a** and **10a** from **8a** , except for the use of ethanol/water (2/1) (60 ml) instead of methanol/water, gave **9b** as a less polar product and **10b** as a more polar product in a ratio of 78:22 with 75% yield, after flash column chromatography (chloroform/methanol:50/1).

Less polar 9b: colorless needles. mp 107-108°C (ethyl acetate/isopropyl ether). $[\alpha]_D^{26}$ -62.8 (c 1.24, MeOH). IR (KBr): 3250, 1788, 1724. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.24 (3H, t, J=6.96, $CH_2C\underline{H_3}$), 2.14 (1H, dd, J=4.40, 13.92, C_3-Hβ), 2.71 (1H, dd, J=9.52, 13.92, C_3-Hα), 2.98 and 3.03 (2H, each d, J=9.53, C_5-H_2), 3.54 (1H, dd, J=4.40, 9.52, C_2-H), 3.66 and 3.94 (2H, each d, J=13.19, C$\underline{H_2}$Ph), 4.13 (2H, q, J=6.96, C$\underline{H_2}$CH$_3$), 6.80 (1H, br s, N_1'H), 7.31 (5H, m, Ph), 9.17 (1H, s, N_3'H). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 14.13 (q, $CH_2\underline{C}H_3$), 40.03 (t, C_3), 57.72 (t, C_5), 61.31 (t, OCH_2), 62.06 (t, $\underline{C}H_2$Ph), 63.93 (d, C_2), 67.21 (s, C_4), 127.52, 128.39, 128.87, and 137.14 (Ph), 155.88 (s, C_2'CO), 173.25 (s, CO_2), 175.32 (s, C_4'CO). EIMS m/z: 317 (M^+). *Anal.* Calcd for $C_{16}H_{19}N_3O_4$: C, 60.55; H, 6.04; N, 13.24. Found: C, 60.26; H, 6.24; N, 13.24.

More polar 10b: colorless needles. mp 94-96°C (ethyl acetate/isopropyl ether). $[\alpha]_D^{26}$ -29.5 (c 1.14, MeOH). IR (KBr): 3460, 3250, 1784, 1730. ^{1}H-NMR (400MHz, $CDCl_3$): δ 1.28 (3H, t, J=6.96, $CH_2C\underline{H_3}$), 2.36 (1H, dd, J=8.79, 13.92, C_3-Hα), 2.63 (1H, dd, J=6.22, 13.92, C_3-Hβ), 2.77 and 3.50 (2H, each d, J=9.53, C_5-H_2), 3.78 (1H, dd, J=6.22, 8.79, C_2-H), 3.83 and 3.95 (2H, each d, J=13.19, C$\underline{H_2}$Ph), 4.19 (2H, q, J=6.96, C$\underline{H_2}$CH$_3$), 6.77 (1H, br s, N_1'H), 7.31 (5H, m, Ph), 8.98 (1H, s, N_3'H). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 14.25 (q, $CH_2\underline{C}H_3$), 40.91 (t, C_3), 55.42 (t, C_5), 60.85 (t, OCH_2), 60.92 (t, $\underline{C}H_2$Ph), 62.67 (d, C_2), 67.39 (s, C_4), 127.39, 128.41, 128.64, 137.76 (Ph), 156.91 (s, C_2'CO), 172.12 (s, CO_2), 175.22 (s, C_4'CO). EIMS m/z: 317 (M^+). *Anal.* Calcd for $C_{16}H_{19}N_3O_4$: C, 60.55; H, 6.04; N, 13.24. Found: C, 60.30; H, 5.90; N, 13.02.

b) Preparetion ***ent*-9b** and ***ent*-10b**: The same treatment of ***ent*-8b** (1.5 g, 6 mmol) as described for the preparetion of **9b** and **10b** from **8b** gave ***ent*-9b** as a less polar product and ***ent*-10b** as a more polar product in a ratio of 75:25 with 75% yield, after flash column chromatography (chloroform/methanol:50/1).

Less polar *ent*-9b: colorless needles. mp 105-106°C (ethyl acetate/isopropyl ether). $[\alpha]_D^{26}$ +62.9 (c 1.10, MeOH). The IR and ^{1}H-NMR spectra of this sample were identical with those recorded for **9b**.

More polar *ent*-10b: colorless needles. mp 94-96°C (ethyl acetate/isopropyl ether). $[\alpha]_D^{26}$ +28.8 (c 1.00, MeOH). The IR and ^{1}H-NMR spectra of this sample were identical with those recorded for **10b**.

(2*S*,4*S*)-1-Benzyl-2-isopropoxycarbonylpyrrolidine-4-spiro-5'-hydantoin (9c) and Its (2*S*,4*R*)-Isomer (10c)

Treatment of **8c** (1.8 g, 6.8 mmol) under the same conditions as described for the preparation of **9a** and **10a** from **8a**, except for the use of isopropanol/water (1/1) (60 ml) instead of methanol/water, gave **9c** as a less polar product and **10c** as a more polar product in a ratio of 84:16 with 72% yield, after flash column chromatography (chloroform/methanol:70/1).

Less polar 9c: colorless viscous oil. $[\alpha]_D^{20}$ -52.6 (c 0.65, MeOH). IR (neat): 3250, 1778, 1740. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.22 and 1.23 (6H, each d, J=6.23, $(CH_3)_2$), 2.12 (1H dd, J=4.03, 13.92, C_3-Hβ), 2.71 (1H, dd, J=9.53, 13.92, C_3-Hα), 2.98 and 3.52 (2H, each d, J=9.53, C_5-H_2), 3.52 (1H, dd, J=4.03, 9.53, C_2-H), 3.65 and 3.94 (2H, each d, J=13.19, CH_2Ph), 5.02 (1H, sept, J=6.23, CH(CH_3)$_2$), 6.66 (1H, br s, N_1'H), 7.30 (5H, m, Ph), 8.69 (1H, s, N_3'H). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 21.70 and 21.21 (each q, $(CH_3)_2$), 39.98 (t, C_3), 57.68 (t, C_5), 62.09 (t, CH_2Ph), 63.97 (d, C_2), 67.40 (s, C_4), 69.07 (d, CH(CH_3)$_2$), 127.55, 128.45, 128.80, 137.28 (Ph), 155.34 (s, C_2'CO), 172.85 (s, CO_2), 174.92 (s, C_4'CO). EIMS m/z: 331 (M^+). HRMS: calcd for $C_{17}H_{21}N_3O_4$ (M^+): 331.1532. Found: 331.1526.

More polar 10c: colorless needles, mp 162-163°C (ethyl acetate/isopropyl ether). $[\alpha]_D^{20}$ -38.2 (c 1.03, MeOH). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.23 and 1.25 (6H, each d, J=6.23, $(CH_3)_2$), 2.34 (1H, dd, J=8.06, 13.56, C_3-Hα), 2.59 (1H, dd, J=6.60, 13.56, C_3-Hβ), 2.74 and 3.47 (2H, each d, J=9.90, C_5-H_2), 3.75 (1H, dd, J=6.60, 8.06, C_2-H), 3.81 and 3.96 (2H, each d, J=13.19, CH_2Ph), 5.06 (1H, sept, J=7.23, CH(CH_3)$_2$), 7.17 (1H, br s, N_1'H), 7.30 (5H, m, Ph), 9.44 (1H, s, N_3'H). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 21.81 and 21.85 (each q, $(CH_3)_2$), 40.91 (t, C_3), 55.39 (t, C_5), 60.91 (t, CH_2Ph), 62.86 (d, C_2), 67.44 (s, C_4), 68.55 (d, CH(CH_3)$_2$), 127.31, 128.39, 128.61, 137.95 (Ph), 157.22 (s, C_2'CO), 171.71 (s, CO_2), 175.38 (s, C_4'CO). EIMS m/z: 331 (M^+). *Anal.* Calcd for $C_{17}H_{21}N_3O_4$: C, 61.62; H, 6.39; N, 12.68. Found: C, 61.67; H, 6.37; N, 12.67.

(2*S*,4*S*)-1-Benzyl-2-*tert*-butoxycarbonylpyrrolidine-4-spiro-5'-hydantoin (9d) and Its (2*S*,4*R*)-Isomer (10d)

Treatment of **8d** (0.8 g, 2.9 mmol) under the same conditions as described for the preparation of **9a** and **10a** from **8a**, except for the use of *N*,*N*-dimethylformamide/water (1/1) (60 ml) instead of methanol/water, gave **9d** and **10d** in a ratio of 96:4 with 74% yield after flash column chromatography (chloroform/methanol: 100/1).

Less polar 9d: colorless needles, mp 147-148°C (ethyl acetate/isopropyl ether). $[\alpha]_D^{22}$ -67.8 (c 0.92, MeOH). IR (KBr): 3250, 1776, 1745. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.44 (9H, s, $(CH_3)_3$), 2.10 (1H, dd, J=3.67, 13.55, C_2-Hβ), 2.67 (1H, dd, J=9.52, 13.55, C_3-Hα), 2.97 and 3.00 (2H, each d, J=9.53, C_5-H_2), 3.46 (1H, dd, J=3.67, 9.52, C_2-H), 3.65 and 3.96 (2H, each d, J=13.19, CH_2Ph), 6.65 (1H, br s, N_1'H), 7.31 (5H, s, Ph), 8.87 (1H, s, N_3'H). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 28.01 (q, $(CH_3)_3$), 39.90 (t, C_3), 57.71 (t, C_5), 62.14 (t, CH_2Ph), 64.60 (d, C_2), 67.46 (s, C_4), 82.08 (s, C(CH_3)$_3$), 127.49, 128.47, 128.83, 137.49 (Ph), 155.57 (s, C_2'CO), 172.67 (s, CO_2), 175.16 (s, C_4'CO). EIMS m/z: 345 (M^+). *Anal.* Calcd for $C_{18}H_{23}N_3O_4$: C, 62.59; H, 6.71; N, 12.17. Found: C, 62.44; H, 6.58; N, 12.05.

More polar 10d: colorless needles, mp 184-186°C (ethyl acetate/isopropyl ether). $[\alpha]_D^{23}$ -35.8 (c 0.5, MeOH). IR (KBr): 3250, 1770, 1742. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.49 (9H, s, $(CH_3)_3$), 2.34 (1H, dd, J=8.06, 13.91, C_3-Hα), 2.61 (1H, dd, J=6.23, 13.91, C_3-Hβ), 2.75 and 3.48 (2H, each d, J=9.89, C_5-H_2), 3.70 (1H, dd, J=6.23, 8.06, C_2-H), 3.87 and 3.95 (2H, each d, J=13.19, CH_2Ph), 6.64 (1H, br s, N_1'H),

7.31 (5H, m, Ph), 8.85 (1H, s, N_3'H). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 28.15 (q, $(CH_3)_3$), 41.07 (t, C_3), 55.01 (t, C_5), 60.76 (t, $\underline{C}H_2Ph$), 63.18 (d, C_2), 67.59 (s, C_4), 81.81 (s, $\underline{C}(CH_3)_3$), 127.38, 128.46, 128.60, 138.07 (Ph), 156.55 (s, C_2'CO), 171.46 (s, CO_2), 174.82 (s, C_4'CO). EIMS m/z: 345 (M^+). *Anal.* Calcd for $C_{18}H_{23}N_3O_4$: C, 62.59; H, 6.71; N, 12.17. Found: C, 62.38; H, 6.52; N, 12.00.

(2*S*,4*R*)-1-Benzyl-4-hydroxy-2-hydroxymethylpyrrolidine (11)

A solution of **6b** (6.6 g, 0.026 mol) in dry tetrahydrofuran (30 ml) was added dropwise to a stirred mixture of lithium borohydride (11.3 g, 0.52 mol) in dry tetrahydrofuran (50 ml) at room temperature. After 10h, the mixture was cooled to 0°C with stirring and water (15 ml) was added carefully. The resulting white granular precipitate was removed by suction through a celite, and the filtrate was concentrated in vacuo. Water (30 ml) was added, and the mixture was extracted with ethyl acetate (80 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 (chloroform/methanol:10/1) to give **11** (4.6 g, 84 %) as a colorless oil. $[\alpha]_D^{22}$ -79.8 (c 1.12, MeOH). IR (neat): 3410, 2840, 1610. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.81 (1H, ddd, J=4.03, 8.06, 13.19, C_3-H), 2.08 (1H, ddd, J=7.30, 7.70, 13.19, C_3-H), 3.34 (1H, dd, J=5.50, 10.25, C_5-H), 2.72 and 2.88 (2H, each br s, OH x 2), 2.98-3.07 (1H, m, C_2-H), 3.20 (1H, dd, J=5.50, 10.25 , C_5-H), 3.39 (1H, dd, J=1.40, 10.99, CH_2O), 3.45 and 3.95 (2H, each d, J=12.82, $C\underline{H}_2Ph$), 3.63 (1H, dd, J=3.70, 10.99, CH_2O), 4.24-4.32 (1H, m, C_4-H), 7.31 (5H, m, Ph). EIMS m/z: 207 (M^+). HRMS: calcd for $C_{12}H_{17}NO_2$ (M^+): 207.1261. Found: 207.1248.

(2*S*)-1-Benzyl-2-[(*tert*-butyldimethylsilyloxy)methyl]-4-oxopyrrolidine (12)

Following the reported procedure,[8] triethylamine (1.4 g, 13 mmol), 4-dimethylaminopyridine (0.058 g, 0.4 mmol) and *tert*-butyldimethylsilyl chloride (2.2 g, 14 mmol) were successively added to a stirred solution of **11** (2.5 g, 12 mmol) in dichloromethane (20 ml) at -10°C. After 6h, the mixture was quenched with brine (20 ml) and 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 (hexane/ethyl acetate:1/1) to give (2*S*)-1-Benzyl-2-[(*tert*-butyldimethylsilyloxy)-methyl]-4-hydroxypyrrolidine (3.2 g, 82 %) as a colorless oil. This material was used for the next reaction. A solution of dimethyl sulfoxide (1.5 g, 19.1 mmol) in dry dichloromethane (15 ml) was added dropwise to a stirred solution of oxalyl chloride (1.2 g, 9.5 mmol) in dry dichloromethane (20 ml) at -78°C under N_2 atmosphere. After 15 min, a solution of the compound (2.8 g, 8.7 mmol) obtained above in dry dichloromethane (20 ml) was added slowly and the mixture was stirred for 30 min at -78°C. After addition of triethylamine (4.4 g, 43 mmol), the mixture was gradually warmed up to room temperature. The mixture was diluted with water (15 ml) and 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 (hexane/ethyl acetate: 4/1) to give **12** (2.4 g, 85%) as a coloeless oil. $[\alpha]_D^{19}$ -43.9 (c 1.02, MeOH). IR (neat): 1762, 1610. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.05 and 0.06 (6H, each s, $Si(CH_3)_2$), 0.90 (9H, s, $(CH_3)_3$), 2.35 (1H, dd, J=9.53, 17.96, C_3-H), 2.56 (1H, dd, J=6.25, 17.96, C_3-H), 2.70 and 3.25 (2H, each d, J=17.22, C_5-H_2), 3.20-3.32 (1H, m, C_2-H), 3.52 and 4.20 (2H, each d, J=13.19, $C\underline{H}_2Ph$), 3.64 (1H, dd, J=5.86, 10.25, CH_2O), 3.75 (1H, dd, J=5.12, 10.25, CH_2O), 7.31 (5H, m, Ph). ^{13}C-NMR (90 MHz, $CDCl_3$): δ -5.47 (q, $Si(CH_3)_2$), 18.13 (s, SiC), 25.80 (q, $(CH_3)_3$), 41.55 (t, C_3), 58.06 (t, C_5), 61.67 (d, C_2), 61.90 (t, $\underline{C}H_2Ph$), 65.02 (t, CH_2O),

127.15, 128.34, 128.45, 138.22 (Ph), 213.12 (s, CO). EIMS m/z: 319 (M^+). HRMS: calcd for $C_{18}H_{29}NO_2Si$: 319.1967. Found: 319.1945.

(2*S*,4*S*)-1-Benzyl-2-[(*tert*-butyldimethylsilyloxy)methyl]pyrrolidine-4-spiro-5'-hydantoin (13) and Its (2*S*,4*R*)-Isomer (14)

Treatment of **12** (1.6 g, 5 mmol) under the same conditions as described for the preparation of **9a** and **10a** from **8a** except for the use of *N*,*N*-dimethylformamide/water (1/1) (60 ml) instead of methanol/water, gave **13** (1.2 g, 62 %) as a less polar product and **14** (0.15 g, 7.7 %) as a more polar product.

Less polar 13: colorless needles. mp 146-146°C (isopropyl ether). $[\alpha]_D^{18}$ -54.7 (c 1.27, MeOH). IR (KBr): 3272, 1778, 1730. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.10 and 1.12 (6H, each s, $Si(CH_3)_2$), 0.93 (9H, s, $(CH_3)_3$), 1.93 (1H, dd, J=4.03 13.55, C_3-Hβ), 2.59 (1H, dd, J=9.89, 13.55, C_3-Hα), 2.77 and 2.98 (2H, each d, J=9.53, C_5-H_2), 2.95-3.01 (1H, m, C_2-H), 3.47 and 4.05 (2H, each d, J=13.19, $C\underline{H}_2Ph$), 3.58 and 3.65 (2H, each d, J=3.30, 10.62, CH_2O), 6.51 (1H, br s, N_1'H), 7.29 (5H, m, Ph), 8.79 (1H, s, N_3'H). ^{13}C-NMR (90 MHz, $CDCl_3$): δ -5.39 (q, $Si(CH_3)_2$), 18.49 (s, $\underline{C}(CH_3)_3$), 26.01 (q, $(CH_3)_3$), 37.78 (t, C_3), 58.02 (t, C_5), 62.92 (t, $\underline{C}H_2Ph$), 63.66 (d, C_2), 64.39 (t, CH_2O), 66.85 (s, C_4), 127.27, 128.39, 128.61, 138.30 (Ph), 155.79 (s, C_2'CO), 175.43 (s, C_4'CO). EIMS m/z: 389 (M^+). *Anal.* Calcd for $C_{20}H_{31}N_3O_3Si$: C, 61.66; H, 8.02; N, 10.79. Found: C, 61.55; H, 7.85; N, 10.72.

More polar 14: colorless needles. mp 141-142°C (isopropyl ether). $[\alpha]_D^{20}$ -53.3 (c 1.20, MeOH). IR (KBr): 3272, 1778. 1736, 1724. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.05 and 0.07 (6H, each s, $Si(CH_3)_2$), 0.89 (9H, s, $(CH_3)_3$), 2.15 (1H, dd, J=6.96, 13.55, C_3-Hα), 2.28 (1H, dd, J=8.06, 13.55, C_3-Hβ), 2.61 and 3.34 (2H, each d, J=10.25, C_5-H_2), 3.14-3.19 (1H, m, C_2-H), 3.65 (1H, dd, J=5.86, 10.25, CH_2O), 3.68 and 4.05 (2H, each d, J=13.55, $C\underline{H}_2Ph$), 3.78 (1H, dd, J=5.86, 10.26, CH_2O), 6.89 (1H, br s, N_1'H), 7.30 (5H, m, Ph), 9.17 (1H, s, N_3'H). ^{13}C-NMR (90 MHz, CDCl3): δ -5.41 (q, Si(CH3)2, 18.20 (s, $\underline{C}(CH_3)_3$), 25.88 (q, $(CH_3)_3$), 40.53 (t, C_3), 57.21 (t, C_5), 62.40 (t, $\underline{C}H_2Ph$), 63.46 (d, C_2), 64.96 (t, CH_2O), 67.05 (s, C_4), 127.11, 128.35, 128.44, 138.67 (Ph), 156.83 (s, C_2'CO), 176.16 (s, C_4'CO). EIMS m/z: 389 (M^+). *Anal.* Calcd for $C_{20}H_{31}N_3O_3Si$: C, 61.66; H, 8.02; N, 10.79. Found: C, 61.45; H, 7.90; N, 10.65.

(2*S*,4*S*)-1-Benzyl-2-hydroxymethylpyrrolidine-4-spiro-5'-hydantoin (15)

a) Preparation of authentic **15** from **13**: A 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran (6 ml) was added dropwise to a stirred solution of **13** (1.6 g, 4 mmol) in tetrahydrofuran at 0°C for 1h and at room temperature for 3h. The solution was quenched with brine (5 ml) and then concentrated *in vacuo*. A 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 (chloroform/methanol:10/1) to give **15** (0.97 g, 86 %) as a white solid. Recrystallization from methanol/isopropyl ether gave an analytical authentic sample of **15** as a colorless needles, mp 219-221°C. $[\alpha]_D^{18}$ -50.4 (c 1.02, 2*N* HCl). IR (KBr): 3332, 3190, 1736, 1720. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.81 (1H, dd, J=6.96, 13.55, C_3-Hβ), 2.33 (1H, dd, J=8.80, 13.55, C_3-Hα), 2.53 and 2.97 (2H, each d, J=9.52, C_5-H_2), 2.76-2.82 (1H, m, C_2-H), 3.32 and 4.10 (2H, each d, J=13.55, $C\underline{H}_2Ph$), 3.48-3.52 (2H, m, CH_2O), 4.35-4.39 (1H, m, OH), 7.21 (1H, br s, N_1'H), 7.33 (5H, m, Ph), 8.19 (1H, s, N_3'H). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 40.08 (t, C_3), 57.33 (t, C_5), 62.48 (t, $\underline{C}H_2Ph$), 63.07 (t, CH_2O), 64.23 (d, C_2), 65.61 (s, C_4), 126.64, 127.94, 128.37, 138.80 (Ph), 156.08 (s, C_2'CO), 177.01 (s, C_4'CO). EIMS m/z: 275 (M^+). *Anal.* Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 61.01; H, 6.15; N, 15.26.

b) Preparation of **15** from **9b**: Methanol (1.5 ml) was added dropwise to a stirred mixture of **9b** (0.6 g, 1.8 mmol) and sodium borohydride (0.2 g, 5.3 mmol) in tetrahydrofuran (6 ml) at 55°C. After 1h, water (2 ml) was added to the reaction mixture. Most of the organic solvent was removed *in vacuo*. Water (5 ml) was added, 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* gave a residue, which was purified by column chromatography (chloroform/methanol:10/1) to give unchanged **9b** (0.1 g) and **15** (0.32 g, 75 %) as a white solid. Recrystallization from methanol/isopropyl ether gave an analytical sample of **15** as a colorless needles, mp 219-221°C. $[\alpha]_D^{20}$ -50.2 (c 0.9, 2*N* HCl). This product was identical by IR and ^{1}H-NMR (400 MHz) spectra with authentic **15** obtained above.

(2*S*,4*R*)-1-Benzyl-2-hydroxymethylpyrrolidine-4-spiro-5'-hydantoin (16)

a) Preparation of authentic **16** from **14**: Treatment of **14** (0.52 g, 1.3 mol) under the same condition as described for the praparation of authentic **15** from **13** gave **16** (0.28 g, 80 %) as a white solid. Recrystallization from methanol/isopropyl ether gave an analytical authentic sample of **16** as a colorless needles, mp 214-215°C. $[\alpha]_D^{20}$ -48.6 (c 0.55, 2*N* HCl). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.90-2.10 (2H, m, C_3-H_2), 2.42 and 3.12 (2H, each d, J=9.52, C_5-H_2), 2.90-3.02 (1H, m, C_2-H), 3.42 and 4.09 (2H, each d, J=13.92, $C\underline{H}_2$Ph), 3.52-3.60 (2H, m, CH_2O), 4.50 (1H, br s, OH), 7.22 (1H, br s, N_1'H), 7.31 (5H, m, Ph), 8.30 (1H, s, N_3'H). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 40.28 (t, C_3), 57.42 (t, C_5), 62.82 (t, CH_2O and $\underline{C}H_2$Ph), 64.32 (d, C_2), 65.33 (s, C_4), 126.60, 127.99, 128.82, 138.92 (Ph), 156.68 (s, C_3'CO), 178.29 (s, C_4'CO). *Anal.* Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 60.90; H, 6.02; N, 15.06.

b) Preparetion of **16** from **10b**: The same treatment of **10b** (0.52 g,1.6 mmol) as described for the preparetion of **15** from **9b** gave unchanged **10b** (0.11 g) and **16** [0.25 g, 72 %, $[\alpha]_D^{20}$ -48.4 (c 0.9, 2*N* HCl)] as a colorless needles, mp 214-215°C. This product was identical by IR and ^{1}H-NMR (400 MHz) spectra with authentic **16** obtained above.

General Procedure for the Hydrolysis of 9, *ent*-9b, 10, and *ent*-10b

A solution of **9** (1.5 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 (10 ml) and purified by Dowex 50W x 8 (50-100 mesh) ion exchange column chromatography (water, then 5% aqueous ammonia) to give **17** (63% from **9a**; 65% from **9b**; 62% from **9c**; 67% from **9d**).

(2*S*,4*S*)-4-Amino-1-benzyl-4-carboxyproline (17): colorless needles. (70% aqueous ethanol). mp 208-210°C. $[\alpha]_D^{21}$ -68.5 (c 0.73, 2*N* HCl). IR (KBr): 3436, 3100-2200, 1634, 1400, 1385 cm^{-1}. ^{1}H-NMR (400 MHz, D_2O): δ 2.29 (1H, dd, J=9.52, 14.29, C_3-Hβ), 2.98 (1H, dd, J=8.42, 14.29, C_3-Hα), 3.68 and 3.76 (2H, each d, J=12.82, C_5-H_2), 4.15 (1H, dd, J=8.42, 9.52, C_2-H), 4.26 and 4.50 (2H, each d, J=12.82, $C\underline{H}_2$Ph), 7.48 (5H, m, Ph). ^{13}C-NMR (90 MHz, D2O): δ 41.67 (t, C_3), 61.43 (t,C_5), 62.37 (t, $\underline{C}H_2$Ph), 65.47 (s, C_4), 70.93 (d, C_2), 131 87, 132.41, 133.09, 133.72 (Ph), 175.60 (s), 175.90 (s). FABMS m/z: 264 (M^+). *Anal.* Calct for $C_{13}H_{16}N_2O_4$ (H_2O): C, 55.31; H, 6.43; N, 9.92. Found: C, 55.16; H, 6.42; N, 9.79.

***ent*-17**: Treatment of ***ent*-9b** (0.4 g,1.2 mmol) under the same conditions as described for the general procedure gave ***ent*-17** (0.21 g, 64 %) as a colorless needles. mp 208-209°C. $[\alpha]_D^{22}$ +67.0° (c 1.02, 2*N* HCl)). The IR and ^{1}H-NMR spectra of this sample were identical with those recorded for **17**.

(2S,4*R*)-4-Amino-1-benzyl-4-carboxyproline (18)

Treatment of **10** (1.5 mmol) under the same conditions as described for the general procedure gave **18** (62% from **10a**; 65% from **10b**; 64% from **10c**; 68% from **10d**) as a colorless powder after recrystallization from 60% aqueous ethanol. mp 220-222°C. $[\alpha]_D^{21}$ -45.8 (c 0.65, 2*N* HCl). IR (KBr): 3440, 3000-2200, 1636, 1395 cm-1. ^{1}H-NMR (400 MHz, D_2O): δ 2.56 (1H, dd, J=9.52, 14.29, C_3-Hα), 2.65 (1H, dd, J=9.16, 14.29, C_3-Hβ), 3.33 and 3.84 (2H, each d, J=12.82, C_5-H_2), 4.19 (1H, dd, J=9.16, 9.52, C_2-H), 4.25 and 4.58 (2H, each d, J=12.82, CH_2Ph), 7.50 (5H, m, Ph). ^{13}C-NMR (90 MHz, D_2O): δ 41.48 (t, C_3), 60.61 (t, C_5), 61.81 (t, CH_2Ph), 63.93 (s, C_4), 69.18 (d, C_2), 131.88, 132.00, 132.55, 133.12 (Ph),175.41 (s), 177.57 (s). FABMS m/z: 264 (M^+). *Anal.* Calcd for $C_{13}H_{16}N_2O_4$ (H_2O): C, 55.31; H, 6.43; N, 9.92. Found: C, 55.20; H, 6.42; N, 9.80.

***ent*-18:** The same treatment of ***ent*-10b** (0.34 g, 1.0 mmol) as described for the general preparetion gave ***ent*-18** (0.19 g, 68 %) as a colorless needles. mp 219-220°C. $[\alpha]_D^{22}$ +44.2 (c 0.55, 2*N* HCl). The IR and ^{1}H-NMR spectra of this sample were identical with those recorded for **18**.

(2*S*,4*S*)-4-Amino-4-carboxyproline (3) and Its (2*R*,4*R*)-Enantiomer (*ent*-3)

a) Preparation of **3**: A mixture of **17** (0.82 g, 3.1 mmol) and 20% palladium hydroxide on carbon (0.2 g) in 5% acetic acid (20 ml) was stirred for 10h 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 (8 ml) and purified by Dowex 50W x 8 (50-100 mesh) ion exchange column chromatography (water, then 5% aqueous ammonia) to give **3** (0.45 g, 83 %) as a white solid. Recrystallization from 70% aqueous ethanol gave an analytical sample of **3** as a colorless needles, mp >300°C. $[\alpha]_D^{22}$ +25.5 (c 0.52, H_2O). IR (KBr): 3450, 3300-2200, 1642, 1574 cm-1. ^{1}H-NMR (400 MHz, D_2O): δ 2.38 (1H, dd, J=8.80, 14.29, C_3-Hβ), 2.94 (1H, dd, J=8.80, 14.29, C_3-Hα), 3.67 and 3.92 (2H, each d, J=12.82, C_5-H_2), 4.49 (1H, t, J=8.80, C_2-H). ^{13}C-NMR (90 MHz, D_2O): δ 40.46 (t, C_3), 54.05 (t, C_5), 63.87 (d, C_2), 65.55 (s, C_4), 175.58 (s), 175.64 (s). FABMS m/z: 174 (M^+). *Anal.* Calcd for $C_6H_{10}N_2O_4$ (1/2 H_2O): C, 39.34; H, 6.05; N, 15.29. Found: C, 39.10; H, 5.92; N, 15.02.

b) Preparation of ***ent*-3** from ***ent*-17**: The same treatment of ***ent*-17** (0.65 g, 2.4 mmol) as described for the preparetion of **3** from **17** gave ***ent*-3** (0.32 g, 76 %) as a colorless needles. mp >300°C. $[\alpha]_D^{22}$ -24.8 (c 0.65, H_2O). The IR and ^{1}H-NMR spectra of this sample were identical with those recorded for **3**.

(2*S*,4*R*)-4-Amino-4-carboxyproline (4) and Its (2*R*,4*S*)-Enantiomer (*ent*-4)

a) Praparation of **4**: Treatment of **18** (0.35 g, 1.3 mmol) under the same conditions as described for the preparation of **3** from **17** gave **4** (0.17 g, 74 %) as a colorless prisms after recrystallization from 60% aqueous ethanol. mp >300°C. $[\alpha]_D^{21}$ -37.3 (c 0.46, H_2O). IR (KBr): 3530, 3300-2200, 1648, 1598 cm-1. ^{1}H-NMR (400 MHz, D_2O): δ 2.55-2.68 (2H, m, C_3-H_2), 3.52 and 3.92 (2H, each d, J=12.82, C_5-H_2), 4.42 (1H, t, J=8.80, C_2-H). ^{13}C-NMR (90 MHz, D_2O): δ 41.42 (t, C_3), 55.61 (t, C_5), 63.28 (d, C_2), 66.22 (s, C_4), 176.08 and 177.32 (each s, CO). FABMS m/z:174 (M^+). *Anal.* Calcd for $C_6H_{10}N_2O_4$ (1/2 H_2O): C, 39.34; H, 6.05; N, 15.29. Found: C, 39.06; H, 5.82; N, 15.02.

b) Preparation of ***ent*-4** from ***ent*-18**: The same treatment of ***ent*-18** (0.45 g, 1.7 mmol) as described for the preparetion of **3** from **17** gave ***ent*-4** (0.25 g, 83 %) as a colorless prisms. mp >300°C. $[\alpha]_D^{22}$ +36.8 (c 0.55, H_2O). The IR and ^{1}H-NMR spectra of this sample were identical with those recorded for **4**.

Methyl (2*S*,4*S*)-4-Amino-1-benzyl-4-methoxycarbonylprolinate (19) and Its Isomer (2S, 4*R*)-(21)

a) Preparation of **19**: Thionyl chloride (0.12 g, 1 mmol) was added dropwise to a mixtute of **17** (0.24 g, 0.8 mmol) in methanol (10 ml) at 0°C, and then the solution was refluxed for 6h. The reaction mixture was concentrated *in vacuo* and the residue was diluted with saturated aqueous sodium carbonate and extracted with ethyl acetate (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 (hexane/ethyl acetate:1/2) to give **19** (0.18 g, 73 %) as a colorless oil. $[\alpha]_D^{22}$ -70.9 (c 1.10, MeOH), IR (neat): 3380, 3040, 3000, 1740. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.99 (1H, ddd, J=1.0, 5.50, 13.55, C3-Hβ), 2.04 (2H, br s, NH_2), 2.78 (1H, dd, J=9.53, 13.55, C3-Hα), 2.82 and 2.90 (2H, each d, J=9.53, C5-H_2), 3.45 (1H, dd, J=5.50, 9.53, C2-H), 3.58 and 3.97 (2H, each d, J=13.19, CH_2Ph), 3.67 and 3.73 (6H, each s, OCH_3 x 2), 7.32 (5H, m, Ph). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 42.69 (t, C3), 52.00 and 52.53 (each q, CH_3 x 2), 58.02 (t, C5), 63.01 (s, C4), 64.34 (d, C2), 64.96 (t, CH_2Ph), 127.28, 128.28, 128.98, and 137.81 (Ph), 173.82 and 174.59 (each s, CO_2). EIMS m/z: 292 (M^+). HRMS: calcd for $C_{15}H_{20}N_2O_4$ (M^+): 292.1423. Found: 292.1409.

b) Preparetion of **21**: Treatment of **18** (0.18 g, 0.6 mmol) under the same condition as described for the praparation of **19** from **17** gave **21** (0.14 g, 78 %) as a colorless oil. $[\alpha]_D^{21}$ -61.9 (c 0.70, MeOH). IR (neat): 3384, 3032, 3004, 1736. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.74 (2H, br s, NH_2), 2.07 (1H, dd, J=7.32, 12.82, C3-Hβ), 2.48 and 3.52 (2H, each d, J=9.89, C5-H_2), 2.62 (1H, dd, J=8.43, 12.82, C3-Hα), 3.68 and 4.03 (2H, each d, J=13.19, CH_2Ph), 3.69 and 3.71 (6H, each s, OCH_3 x 2), 3.77 (1H, dd, J=7.32, 8.43, C2-H), 7.30 (5H, m, Ph). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 42.22 (t, C3), 51.80 and 52.50 (each q, CH_3 x 2), 58.37 (t, C5), 62.91 (s, C4), 64.03 (d, C2), 64.44 (t, CH_2Ph), 127.17, 128.28, 128.88, and 138.29 (Ph), 173.54 and 175.62 (each s, CO). EIMS m/z: 292 (M^+). HRMS: calcd for $C_{15}H_{20}N_2O_4$ (M^+): 292.1423. Found: 292.1410.

Methyl (2*S*,4*S*)-1-Benzyl-4-[(*S*)-2-methoxy-2-(trifluoromethyl)phenylacetylamino]-4-methoxycarbonylprolinate [(*S*)-MTPA Amide of 19] (20) and Its (2*S*,4*R*)-Isomer [(*S*)-MTPA Amide of 21] (22)

a) Preparation of **20**: (*S*)-2-Methoxy-2-(trifluoromethyl) phenylacetyl chloride [(*S*)-MTPACl] (97 mg, 0.29 mmol) was added to a stirred solution of **19** (70 mg, 0.2 mmol) in pyridine (2 ml) at room temperature for 1h. The reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography (hexane/ethyl acetate:1/2) to give **20** (93 mg, 77 %) of MTPA amide as a single compound. The enantiomeric excess of **17** was >95% based on ^{1}H-NMR analysis of this MTPA amide. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.22 (1H, ddd, J=1.10, 4.39, 13.92, C3-Hβ), 2.72 (1H, dd, J=9.89, 13.92, C3-Hα), 3.05 (1H, d, J=9.89, C5-H), 3.24 (1H, dd, J=1.10, 9.89, C5-H), 3.47 (3H, d, J=1.47, OCH3), 3.52 (1H, dd, J=4.39, 9.82, C2-H), 3.59 and 3.70 (6H, each s, OCH_3 x 2), 3.64 and 4.00 (2H, each d, J=13.19, CH_2Ph), 7.20-7.60 (10H, m, Ph x 2), 7.79 (1H, br s, NHCO).

b) Preparation of **22**: The same treatment of **18** (52 mg, 0.17 mmol) as described for the preparation **20** from **17** gave **22** (68 mg, 75 %) of MTPA amide as a single compound. The enantiomeric excess of **18** was >95% based on ^{1}H-NMR analysis of this MTPA amide. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.51 (1H, dd, J=8.42, 13.92, C3-Hα), 2.83 and 3.49 (2H, each d, J=10.26, C5-H_2), 2.91 (1H, dd, J=6.96, 13.92, C3-Hβ), 3.39 (3H, d, J=1.10, OCH3), 3.70 (6H, s, OCH_3 x 2), 3.72 and 3.98 (2H, each d, J=13.19, CH_2Ph), 3.75 (1H, dd, J=6.96, 8.42, C2-H), 7.19 (1H, br s, NHCO), 7.20-7.62 (10H, m, Ph x 2).

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