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Diastereoselective Syntheses of (2*R*,3*R*,5*R*)- and (2*S*,3*S*,5*S*)-3-Hydroxy-5-methyl-2-pyrrolidinecarboxylic Acid as a Component of Actinomycin Z_1

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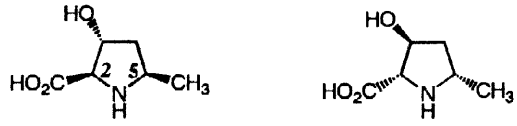
Abstract: A novel diastereoselective syntheses of both (2*R*,3*R*,5*R*)-**1** and its enantiomer (2*S*,3*S*,5*S*)-**1** were accomplished by employing *trans*-selective nucleophilic addition of cyanide to 3-benzoyloxy-*N*-acyliminium ions as the key step, starting from *trans*-4-hydroxy-*L*-proline.

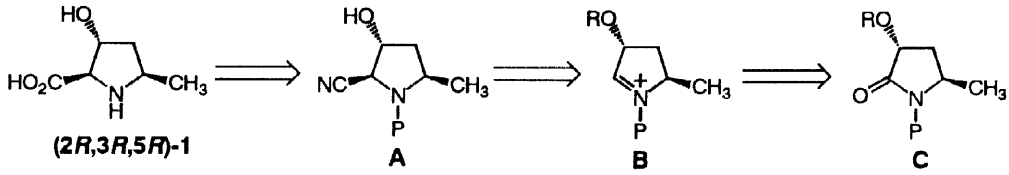
Keywords: Unusual amino acids; Asymmetric synthesis; Stereoselection; *N*-Acyliminium ion; Lactam synthesis.

An unusual amino acid, 3-hydroxy-5-methyl-2-pyrrolidinecarboxylic acid (**1**) was found as a minor component of a peptide antibiotic actinomycin Z_1 produced by *Streptomyces fradiae*.[1] After the syntheses of the four diastereoisomers of **1**, the relative stereochemistry of this compound was elucidated to be 2,3-*trans* and 2,5-*cis* configuration based on analyses of ^{1}H-NMR coupling constants by Mauger *et al.*[2] The absolute configuration (2*S*,3*S*,5*S* or 2*R*,3*R*,5*R*) and biological activities of the natural amino acid (**1**), however, remain unknown due to their sort supply from natural sources. Consequently, the development of efficient and stereoselective methods to produce such amino acid in an enantiomerically pure form is crucial. To our knowledge, only two reports on the synthesis of **1** are found in literature, one of the four racemic diastereoisomers,[2] and another of the optically active forms,[3] which were prepared by [3+2] dipolar cycloaddition starting from *L*-vinylglycine.



(2*R*,3*R*,5*R*)-**1** (2*S*,3*S*,5*S*)-**1**

Figure 1



(2*R*,3*R*,5*R*)-**1** **A** **B** **C**

Scheme 1

In continuing our studies in the asymmetric synthesis of novel unusual α-amino acids containing pyrrolidine ring,[4] we report herein the novel diastereoselective syntheses of both (2*R*, 3*R*, 5*R*)-**1** and its enantiomer (2*S*,3*S*,5*S*-**1**) starting from *trans*-4-hydroxy-*L*-proline. Our synthetic strategy for (2*R*, 3*R*, 5*R*)-**1** is illustrated in **Scheme 1**. Thus, the carboxyl group of α-amino acid moiety of (*R*)-configuration can be

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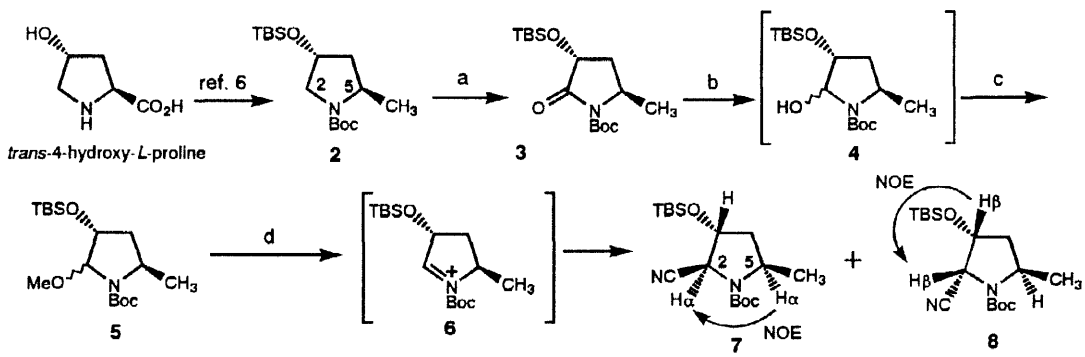
obtained through the *trans*-nucleophilic addition of cyanide anion to the C_3-substituent group of *N*-acyliminium ion intermediate **B** derived from homochiral lactam **C**, followed by acidic hydrolysis of both cyano and protecting groups. In connection with the reaction of *N*-acylpyrrolidine 2-iminium ions,[5] Wistrand has reported that the stereoselectivity of nucleophilic addition of cyanide anion to the *N,O*-diprotected 3-hydroxypyrrolidine-2-iminium ions can be controlled by the nature of the *O*-protecting group at the C_3-position.[5a] On the other hand, Shono and Matsumura have reported that the degree of stereoselectivity depends on both the steric bulkiness of *N*-protecting groups and the nature of the substituents of the pyrrolidine ring.[6] We therefore investigated the reaction of *N*-acyliminium ion **B** with different *N,O*-diprotecting groups in order to enhance the desired *trans* selectivity.

Results and Discussion

1. Synthesis of (2*R*,3*R*,5*R*)-1

First, for the synthesis of (2*R*, 3*R*, 5*R*)-**1**, nucleophilic addition of cyanide to *N*-acyliminium ion **6** with sterically bulky *O*-*tert*-butyldimethylsilyl (*O*-TBS) group at C_3-position was examined as shown in **Scheme 2.** Thus, ruthenium tetroxide (RuO_4) oxidation[7] of **2** easily prepared from *trans*-4-hydroxy-*L*-proline,[8] followed by chemoselective partial reduction of the resulting lactam **3** with $LiEt_3BH$ in tetrahydrofuran at -78°C led to a diastereomeric mixture of hemiaminal **4** and subsequent treatment of **4** with pyridinium *p*-toluenesulfonate (PPTS) in methanol gave the corresponding 2-methoxypyrrolidine **5** as a mixture of diastereoisomers. **5** was directly converted into 2-cyanopyrrolidines (**7** and **8**) by treatment with trimethylsilyl cyanide (TMSCN) in the presence of boron trifluoride etherate in dichloromethane at -78°C[5a,d] and the desired 2,3-*trans*-2-cyanopyrrolidine **7** as a minor product and the undesirable its *cis*-isomer **8** as a major product were isolated in a ratio of 30:70 in 84% combined yield. 2-Cyanopyrrolidines **7** and **8** could be cleanly separated by column chromatography on silica gel.

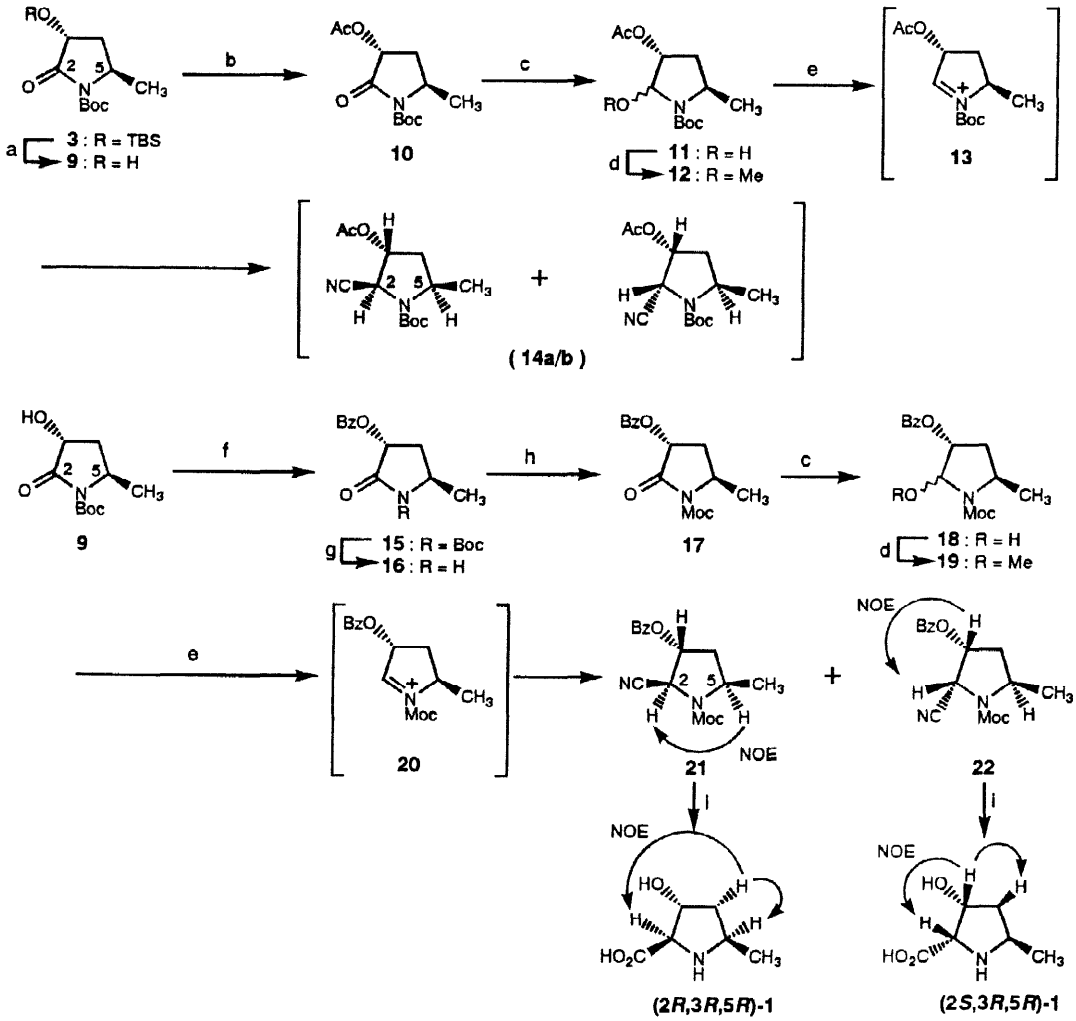
The stereochemistries of the newly formed stereogenic centers at C_2 position of these isomers **7** and **8** were assingned by NOE experiments, as indicated in **Scheme 2.** Thus, for the compound **7**, irradiation of the C_5-H resulted in enhancement of the the signal due to the C_2-H and irradiation of the C_3-H gave no enhancement of the signal due to the C_2-H. For the compound **8**, irradiation of the C_3-H resulted in enhancement of the signal due to the C_2-H. Accordingly, the C_2-H and C_3-H in **7** and **8** were assigned to have *trans*- and *cis*-configurations, respectively.



Reagents and Conditions : a) RuO_2 • H_2O,10% aq. $NaIO_4$, AcOEt, 88% b) $LiEt_3BH$,THF,-78°C c) PPTS, MeOH, r.t., 75%, 2 steps d) TMSCN, BF_3 • Et_2O, CH_2Cl_2, -78°C, 84% (7:8=30:70)

Scheme 2

Next, we decided to exchange both the *N*- and *O*-protecting groups of the intermediate **6** and investigated stereoselectivities of the reactions using resulting alternative *O*-acetyl (Ac)-*N*-Boc iminium ion **13** and *O*-benzoyl (Bz)-*N*-methoxycarbonyl (Moc) iminium ion **20**, respectively, as shown in **Scheme 3**. Thus, after removal of TBS protecting group of **3** with *n*-Bu_4NF, sequential acetylation of the resulting alcohol **9** afforded *O*-Ac protected lactam **10**. By employing the reaction sequence similar to that described for the preparation of **7** and **8** from **3**, **10** was converted to 2-cyanopyrrolidines (**14a/b**) in 70% yield (3 steps), as an inseparable diastereomeric mixture (**14a**:**14b**=58:42 by 400MHz ^{1}H-NMR analysis) *via* 2-hydroxypyrrolidine **11** and 2-methoxypyrrolidine **12**. The diastereoselectivity was not improved. As a further exchange of both *N*- and *O*-protecting groups of **13**, *O*-Bz-*N*-Moc lactam **17** was preparared from the alcohol **9** *via* 3-step sequence as follows: 1) benzoylation of **9**, 2) deprotection of *N*-Boc group of **15**, and 3) *N*-protection of **16** with methyl chlorocarbonate (MocCl) in the presence of lithium bis(trimethylsilyl)amide ($LiN(TMS)_2$) as base at -15°C.[9]



Reagents and Conditions : a) *n*-Bu_4NF, THF, r.t., 92% b) Ac_2O, pyridine, 0°C~r.t., 95% c) $LiEt_3BH$, THF, -78°C d) PPTS, MeOH, r.t., 82% for **12** (2 steps), 80% for **19** (2 steps) e) TMSCN, $BF_3 \cdot Et_2O$, CH_2Cl_2, -78°C, 85% (**14a**:**14b**=58:42), 82% (**21**:**22**=72:28) f) BzCl, pyridine, 0°C~r.t., 82% g) TFA, CH_2Cl_2, r.t., 90% h) MocCl, $LiN(TMS)_2$, THF, -15°C, 86% i) 6M HCl, 115°C; Dowex 50w x 8, 75~78%

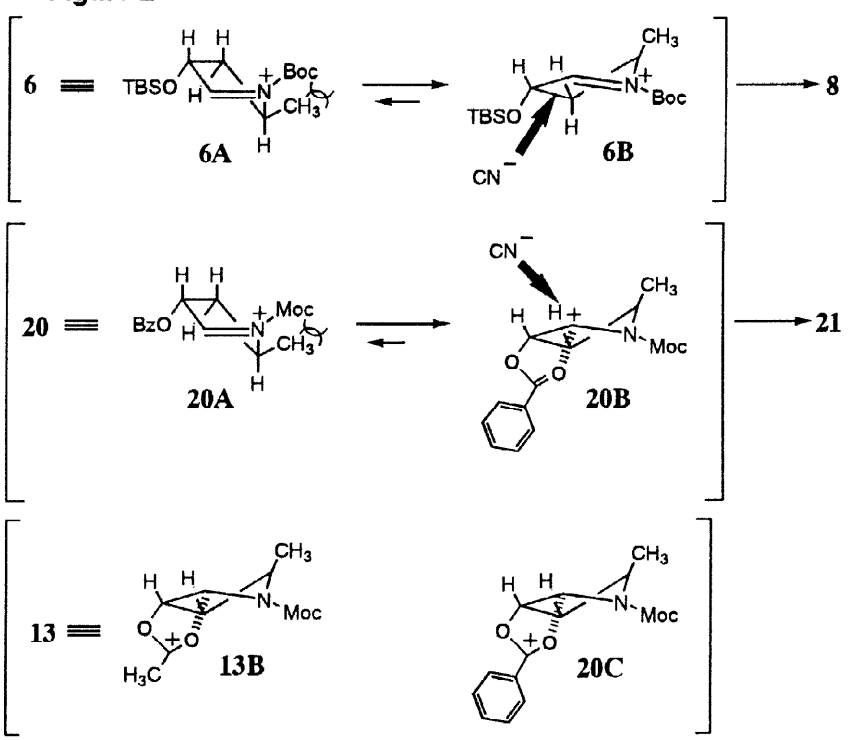
Scheme 3

The same reaction sequence for the preparation of **7** and **8** from **3** was applied to **17**, giving rise to the desired 2,3-*trans*-2-cyanopyrrolidine **21** and its *cis*-isomer **22** in a ratio of 72: 28 in 82% combined yield, *via* 2-hydroxypyrrolidine **18** and 2-methoxypyrrolidine **19**.

The stereochemistries of the stereogenic center at C_2 in both **21** and **22** were proven by NOE measurements in their 400 MHz ^{1}H-NMR spectra. Thus, for the compound **21**, irradiation of the C_5-H resulted in enhancement of the signal due to the C_2-H and irradiation of the C_3-H gave no enhancement of the signal due to the C_2-H. For the compound **22**, irradiation of the C_3-H resulted in enhancement of the signal due to the C_2-H and irradiation of the C_5-H gave no enhancement of the signal due to the C_2-H. Accordingly, C_2-H and C_3-H in **21** and **22** were assigned to have *trans*- and *cis*-configurations, respectively. Thus, absolute configurations of these compounds **21** and **22** were unambiguously determined as (2*R*,3*R*,5*R*)-**21** and (2*S*,3*R*,5*R*)-**22**, respectively.

The stereoselectivity observed for the nucleophilic addition of a cyanide anion to iminium ions **6** and **20** can be explained by the preferred transition state conformations of **6** and **20** as shown in **Figure 2**. Thus, the conformers **6B** and **20B** is expected to be more favored than the other conformers **6A** and **20A** which have $A^{1,2}$-strain between the *N*-protecting groups (Boc and Moc) and the methyl groups. The improved *trans*-selectivity in the case of the *O*-Bz-*N*-Moc iminium ion intermediate **20** can be explained by the known ability of the carbonyl oxygen of the benzoyloxy group to bridge to ajacent cationic center (transition state **20B**),[6a,10] and hence a cyanide anion may approach the cation center preferentially from the opposite side to the benzoyl group. Also, good *trans*-selectivity in the case of *O*-Bz iminium ion intermediate **20** than the case of the *O*-Ac intermediate **13** can be explainable by both of the stability of the benzylic cation of the transition state **20C** and the steric bulkiness of the phenyl ring. Whereas a less satisfactory diastereoselectivity in the case of the *O*-TBS-

Figure 2

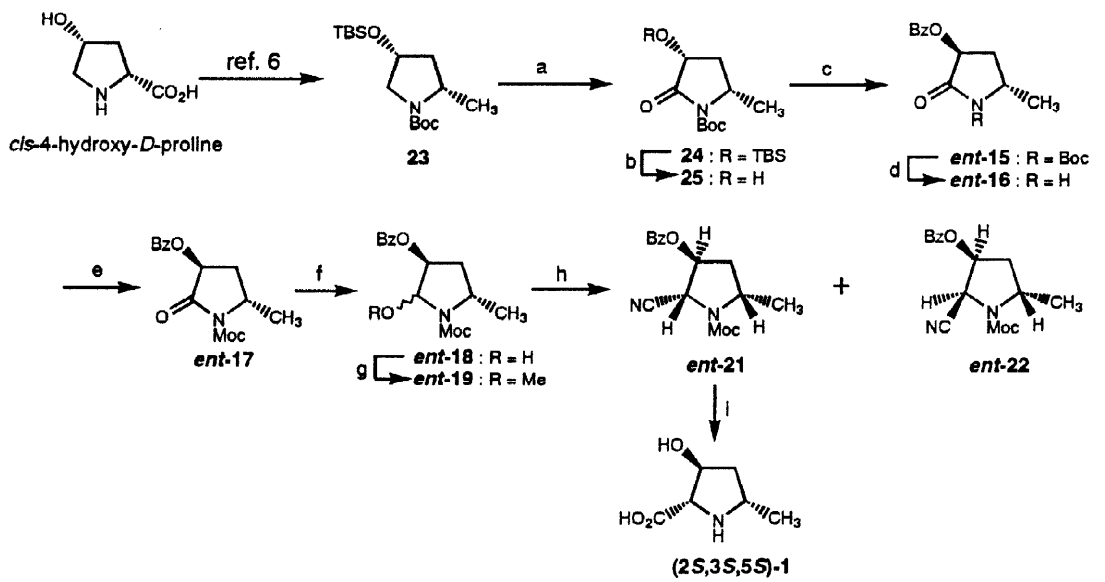


N-Boc iminium ion intermediate **6** can be explained by assuming that the attack of a cyanide anion occur preferentially from the same side of *O*-TBS group of **6** under an influence of stereoelectronic effect[5d,11] (transition state **6B**), giving rise to undesirable **8** as a major product . Finally, the acidic hydrolysis of both **21** and **22** with 6M HCl at 110°C for 24h afforded the target free amino acids (2*R*, 3*R*, 5*R*)-**1**, $[\alpha]_D^{25}$ +18.6° (c 1.02, H_2O); lit.[3] $[\alpha]_D$ +18° (c 0.32, H_2O), in 75% yield, and its isomer (2*S*,3*R*,5*R*)-**1**, $[\alpha]_D^{20}$ -85.1° (c 0.70, H_2O), in 78% yield, respectively, after ion-exchange chromatography on Dowex 50W x 8 (**Scheme 3**).

The stereochemical assignment of (2*R*, 3*R*, 5*R*)-**1** and (2*S*,3*R*,5*R*)-**1** were made on the basis of NOE experiments. Thus, for the compound (2*R*, 3*R*, 5*R*)-**1**, irradiation of the C_4-Hα (δ 2.18) resulted in enhancements both of the the signals due to the C_2- and C_5-H (δ 3.98-4.10) and irradiation of the C_3-H (δ 4.64-4.77) gave no enhancement of the signal due to the C_2-H. For the compound (2*S*,3*R*,5*R*)-**1**, irradiation of the C_3-H (δ 4.70) resulted in enhancements both of the signals due to the C_2-H (δ 4.24) and C_4-H (δ 1.91). Accordingly, C_2-H and C_4-H in (2*R*,3*R*,5*R*)-**1** and (2*S*,3*R*,5*R*)-**1** were assigned to have *trans*- and *cis*-configurations, respectively. No epimerization of the C_2 stereogenic centers in both (2*R*,3*R*,5*R*)-**1** and (2*S*,3*R*,5*R*)-**1** had occured during the hydrolysis described above. The structure was confirmed by the reported (2*R*,3*R*,5*R*)-**1**, whose ^{1}H- and ^{13}C- NMR spectra data were in good agreement with the literature data[3] of its enantiomer (2*S*,3*S*,5*S*)-**1**.

2. Synthesis of (2*S*,3*S*,5*S*)-1

For the synthesis of (2*S*,3*S*,5*S*)-**1**, the intermediate (3*R*,5*S*)-*N*-Boc-3-hydroxylactam **25** derived from (3*R*,5*S*)-**23**,[12] was submitted to the Mitsunobu inversion[13] followed by exchange *N*-Boc protecting group with *N*-Moc group to give *ent*-**17**. Conversion of *ent*-**17** to *ent*-**21** was achieved by the procedure similar to that described above, and the *ent*-**21** was hydrolyzed to afford the target free amino acid (2*S*,3*S*,5*S*)-**1**,



Reagents and Conditions : a) RuO_2 • xH_2O, 10% aq. $NaIO_4$, AcOEt, 92% b) *n*-Bu_4NF, THF, r.t., 88% c) PPh_3, DEAD, $PhCO_2H$, 0°C~r.t., 85% d) TFA, CH_2Cl_2, r.t., 90% e) MocCl, $LiN(TMS)_2$, THF, -15°C~r.t., 82% f) $LiEt_3BH$, THF, -78°C g) PPTS, MeOH, r.t., 85%, 2 steps h) TMSCN, BF_3 • Et_2O, CH_2Cl_2, -78°C, 84% (*ent*-**21**: *ent*-**22**=80:20) I) 6M HCl, 115°C; Dowex 50w x 8, 70%

Scheme 4

$[\alpha]$ $^{24}_{D}$ -17.6° (c 0.80, H_2O); lit.[3] $[\alpha]_D$ -17° (c 0.50, H_2O), in 70% yield, whose spectra data were in good agreement with the literature data[3] of (2*S*,3*S*,5*S*)-**1**.

In summary, a novel diastereoselective syntheses of (2*R*,3*R*,5*R*)-**1** and its enantiomer (2*S*,3*S*,5*S*)-**1** were accomplished by employing the *trans*-selective nucleophilic addition of cyanide anion to the 3-benzoyloxy-*N*-acyliminium ions as the key step, starting from *trans*-4-hydroxy-*L*-proline.

Experimental

General. Melting points were measured on a Yanaco MP-S3 micro melting point apparatus and uncorrected. Optical rotations were measured with a JASCO DIP-370 automatic digital polarimeter. Infrared (IR) spectra were recorded with a Hitachi 270-30 spectrometer. ^{1}H- and ^{13}C-NMR spectra were measured with a JNM- GSX400 (400 MHz) or a JNM-EX90 (90 MHz) spectrometer. The chemical shifts were expressed in ppm (δ) downfield from tetramethylsilane as internal standard in $CDCl_3$ solutions, or from 3-(trimethylsilyl)-1-propane-sulfonic acid sodium salt as internal standard in D_2O solutions. The following abbreviation are used: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). Electron impact mass spectra (EIMS) and high resolution mass spectra (HRMS) were obtained with JMS DX-300 spectrometer. Routine monitoring of reactions was carried out using Merck TLC aluminium sheet silica gel 60 F_{254}. Column chromatography was performed on Merck silica gel, 70-230 mesh. Usual workup means that organic layer was dried over magnesium sulfate, and evaporated *in vacuo*. The *trans*-4-hydroxy-*L*-proline as a chiral starting meterial was purchased from Sigma Chemical Co.

Material. (3*R*,5*R*)-1-(*tert*-Butoxycarbonyl)-4-(*tert*-butyldimethylsilyl)oxy-2-methylpyrrolidine (2) and Its (3*R*,5*S*)-Isomer (23) were prepared from *trans*-4-hydroxy-*L*-proline according to the reported method.[8] *cis*-4-Hydroxy-*D*-proline was preparaed from *trans*-4-hydroxy-*L*-proline according to the reported method.[12]

(3*R*,5*R*)-1-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsilyl)oxy-5-methyl-2-pyrrolidinone (3) and Its (3*R*,5*S*)-Isomer (24)

a) Preparation of **3** from **2**: A solution of **2** (10.8 g, 26 mmol) in ethyl acetate (80 ml) was added to a mixture of $RuO_2 \cdot xH_2O$ (0.4 g) and 10% aqueous $NaIO_4$ (120 ml). The solution was stirred vigorously for 3 h at room temperature. The layer was separated and the aqueous layer was extracted with ethyl acetate (80 ml). The extract was treated with 2-propanol (0.2 ml). Black-colored RuO_2 which precipitated from the solution was filtered off and the filtrate was washed with brine, and usual workup gave a residue which was purified by column chromatography (hexane: ethyl acetate=6:1) to give **3** (7.6 g, 88%) as a colorless oil. $[\alpha]^{23}_{D}$ +13.4° (c 1.04, MeOH). IR (neat): 1798, 1768, 1726 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 0.13, 0.18 (6H, each s, $Si(CH_3)_2$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.31 (3H, d, J=6.23 Hz, CH_3), 1.53 (9H, s, $C(CH_3)_3$), 2.03-2.14 (2H, m. C_4-H_2), 4.15-4.24 (1H, m, C_5-H), 4.45 (1H, t, J=8.80 Hz, C_3-H_2). ^{13}C-NMR ($CDCl_3$): δ -5.28, -4.44, 18.29, 20.58, 25.75, 28.04, 36.04, 49.67, 70.23, 82.95, 150.05, 172.81. HRMS: calcd for $C_{16}H_{32}NO_4Si$ $(M+H)^+$: 330.2100. Found: 330.2088.

b) Preparation of **24** from **23**: Treatment of **23** (8.6 g, 27 mmol) in the same manner as described for the preparation of **3** from **2** gave **24** (8.3 g, 92%) as a colorless oil. $[\alpha]^{25}_D$ +43.3° (c 1.10, MeOH). IR (neat): 1794, 1764, 1726 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 0.13, 0.15 (6H, each s, $Si(CH_3)_2$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.42 (3H, d, J=6.23 Hz, CH_3), 1.53 (9H, s, $OC(CH_3)_3$), 1.50-1.62 (1H, m, C_4-Hα), 2.37 (1H, ddd, J=13.19, 7.33, 1.02 Hz, C_4-Hβ), 3.98-4.80 (1H, m, C_5-H), 4.22 (1H, dd, J=7.69, 6.23 Hz, C_3-H). ^{13}C-NMR ($CDCl_3$): δ −5.25, −4.53, 18.19, 21.75, 25.72, 28.07, 35.79, 51.34, 71.27, 82.92, 150.24, 172.87. HRMS: calcd for $C_{16}H_{32}NO_4Si$ $(M+H)^+$: 330.2100. Found: 330.2082.

(3*R*,5*R*)-1-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsilyl)oxy-5-methyl-2-methoxy-pyrrolidine (5)

Lithium triethylborohydride in THF (1.0 M solution, 14.4 ml, 14.4 mmol) was added to a solution of **3** (4.0 g, 12 mmol) in THF (50 ml) at -78°C under nitrogen atmosphere. After 30 min, the reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was allowed to warm up to room temperature. The mixture was extracted with ethyl acetate (80 ml). Usual workup afforded (3*R*,5*R*)-1-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsilyl)oxy-2-hydroxy-5-methylpyrrolidine (**4**) (3.85 g), which was dissolved in methanol (50 ml). The methanolic solution of **4** was treated with a catalytic amount of pyridinium *p*-toluenesulfonate (0.25 g, 1.0 mmol) for 12h at room temperature. The mixture was diluted with ethyl acetate. The organic layer was washed successively with 10% aqueous citric acid, saturated aqueous $NaHCO_3$, and brine. Usual workup followed by column chromatography (hexane: ethyl ether=6:1) gave **5** (3.1 g, 75%, 2 steps) as a mixture of two diastereomers. This material was directly used for the next step without separation. IR (neat): 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 0.05, 0.06 (6H, m, $Si(CH_3)_2$), 0.85 (9H, s, $SiC(CH_3)_3$), 1.27 (3H, br d, J=6.25 Hz, CH_3), 1.48 (9H, br s, $OC(CH_3)_3$), 1.72-2.02 (2H, m, C_4-H_2), 3.31, 3.34 (3H, each s, OCH_3), 3.88-4.02 (1H, m, C_5-H), 4.82-4.98 (1H, m, C_3-H). ^{13}C-NMR ($CDCl_3$): δ −4.88, −4.82, −4.67, 17.89, 21.65, 21.73, 22.18, 22.27, 25.48, 25.63, 28.20, 28.40, 40.01, 40.12, 40.55, 40.68, 52.63, 54.57, 54.70, 54.78, 54.85, 73.90, 74.49, 79.54, 79.57, 79.63, 95.09, 155.24, 155.26. HRMS calcd for $C_{17}H_{36}NO_4Si$ $(M+H)^+$: 346.2414. Found: 346.2408.

(2*R*,3*R*,5*R*)-1-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsilyl)oxy-2-cyano-5-methyl-pyrrolidine (7) and Its (2*S*,3*R*,5*R*)-Isomer (8)

Trimethylsilyl cyanide (1.50 ml, 11mmol) and boron trifluoride etherate (1.40 ml, 11 mmol) were added successively to a stirred solution of **5** (2.6 g, 7.5 mmol) in dry dichloromethane (20 ml) at -78°C under nitrogen. After 1.5 h, the reaction was quenched with saturated Na_2CO_3 (8 ml) at -78°C, and the mixture was allowed to warm up to room temperature. The mixture was extracted with dichloromethane (60 ml). Usual workup followed by column chromatography (hexane: ethyl acetate=5:1) gave **7** (0.65 g, 25%) as a more polar product and **8** (1.5 g, 59%) as a less polar product.

7: colorless oil. $[\alpha]^{25}_D$ +6.6° (c 0.94, MeOH). IR (neat): 2220, 1698 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 0.06–0.10 (6H, m, $Si(CH_3)_2$), 0.93 (9H, s, $SiC(CH_3)_3$), 1.21 (3H, d, J=6.23 Hz, CH_3), 1.51 (9H, s, $OC(CH_3)_3$), 1.80-

1.92 (1H, m, C4-Hβ), 2.16-2.32 (1H, m, C4-Hα), 3.92-4.10 (2H, m, C2-, C5-H), 4.47-4.56 (1H, m, C3-H). ^{13}C-NMR ($CDCl_3$): δ -4.95, -4.82 ($Si(CH_3)_2$), 17.98 ($SiC(CH_3)_3$), 21.22, 21.86 (CH_3), 25.54 ($SiC(CH_3)_3$), 28.20 ($OC(CH_3)_3$), 39.42 (C4), 53.71 (C5), 54.13 (C4), 69.69 (C3), 81.50 ($OC(CH_3)_3$), 116.19 (CN), 156.62 (C=O). HRMS calcd for $C_{17}H_{32}N_2O_3Si$ (M^+): 340.2182. Found: 340.2172.

8: colorless prisms. mp 77-78°C (ethyl acetate-isopropyl ether). $[\alpha]^{25}_D$ -34.1° (c 1.15, MeOH). IR (KBr): 2220, 1712 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 0.06-0.10 (6H, m, $Si(CH_3)_2$), 0.93 (9H, s, $SiC(CH_3)_3$), 1.20 (3H, d, J=6.23 Hz, CH_3), 1.51 (9H, s, $OC(CH_3)_3$), 1.80-1.90 (1H, m, C4-Hβ), 2.17-2.30 (1H, m, C4-Hα), 3.88-4.10 (2H, m, C2-, C5-H), 4.45-4.56 (1H, m, C3-H). ^{13}C-NMR ($CDCl_3$): δ -4.93, -4.80 ($Si(CH_3)_2$), 17.99 ($SiC(CH_3)_3$), 21.19 , 21.25 (CH_3), 25.63 ($SiC(CH_3)_3$, 28.36 ($OC(CH_3)_3$), 39.85 (C4). 51.48 (C5), 54.13 (C2), 69.48 (C3), 81.30 ($OC(CH_3)_3$), 116.13 (CN), 155.98 (C=O). Anal. Calcd for $C_{17}H_{32}N_2O_3Si$: C, 59.96; H, 9.47; N, 8.22. Found: C, 59.86; H, 9.38; N, 8.04.

(3*R*,5*R*)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-5-methyl-2-pyrrolidinone (9) and Its (3*R*,5*S*)-Isomer (25)

a) Preparation of **9** from **3**: Tetra-*n*-butylammonium fluoride (TBAF) in THF (1.0 M solution, 20 ml, 20.0 mmol) was added dropwise to a stirred solution of **3** (5.5 g, 16.7 mmol) in THF (60 ml) at room temperature for 3 h. The reaction mixture was concentrated, and the residue was purified by column chromatography (ethyl acetate: benzene=2:1) to give **9** (3.3 g, 92%) as a colorless solid. Recrystallization from ethyl acetate: isopropyl ether gave an analytical sample of **9** as colorless prisms, mp 112-113°C. $[\alpha]^{24}_D$ +4.6° (c 1.19, MeOH). IR (KBr): 3620-3200, 1786, 1748 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.33 (3H, d, J=6.23 Hz, CH_3), 1.54 (9H, s, $OC(CH_3)_3$), 2.05-2.24 (2H, m, C4-H_2), 3.30-3.54 (1H, br s, OH), 4.20-4.29 (1H, m, C5-H), 4.50 (1H, dd, J=11.36, 8.43 Hz, C3-H). ^{13}C-NMR ($CDCl_3$): δ 20.43, 28.01, 34.58, 50.53, 69.18, 83.46, 149.54, 174.94. EIMS m/z: 215 (M^+). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.68; H, 7.84; N, 6.50.

b) Preparation of **25** from **24**: Treatment of **24** (6.9 g, 20.9 mmol) in the same manner as described for the preparation of **9** from **3** gave **25** (3.9 g, 88%) as a colorless solid. Recrystallization from ethyl acetate: isopropyl ether gave an analytical sample of **25** as colorless prisms, mp 97-98°C. $[\alpha]^{25}_D$ +75.1° (c 1.22, MeOH). IR (KBr): 3420-3200, 1788, 1695 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.43 (3H, d, J=6.23 Hz, CH_3), 1.53 (9H, s, $OC(CH_3)_3$), 1.56-1.66 (1H, m, C4-Hα), 2.52-2.62 (1H, m, C4-Hβ), 3.62 (1H, br s, OH), 3.96-4.05 (1H, m, C5-H), 4.33 (1H, t, J=8.43 Hz, C3-H). ^{13}C-NMR ($CDCl_3$): δ 21.79, 28.02, 34.52, 51.07, 69.93, 83.37, 149.85, 175.10. Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.72; H, 7.78; N, 6.46.

(3*R*,5*R*)-3-Acetoxy-1-(*tert*-butoxycarbonyl)-5-methyl-2-pyrrolidinone (10)

Alcohol **9** (2.5 g, 12 mmol) was dissolved in a mixture of acetic anhydride (30 ml) and dry pyridine (30 ml) at 0°C, and the solution was stirred at room temperature for 20 h. The solvents were removed *in vacuo* and the residue was dissolved in ethyl acetate (50 ml). The solution was washed succesively with 10% aqueous citric acid, saturated aqueous $NaHCO_3$, and brine. Usual workup followed by column chromatography (hexane: ethyl

acetate=2:1) gave **10** (2.8 g, 95%) as a colorless oil. $[\alpha]^{24}_D$ +25.7° (c 1.16, MeOH). IR (neat): 1798, 1754, 1724 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.37 (3H, d, J=6.23 Hz, CH_3), 1.54 (9H, s, $OC(CH_3)_3$), 2.15 (3H, s, $COCH_3$), 2.17 (1H, ddd, J=12.45, 10.99, 8.79 Hz, C_4-Hβ), 2.26 (1H, ddd, J=12.45, 8.43, 2.20, C_4-Hα), 4.26-4.34 (1H, m, C_5-H), 5.54 (1H, dd, J=10.99, 8.43 Hz, C_3-H). ^{13}C-NMR ($CDCl_3$): δ 20.55, 27.99, 32.53, 50.24, 69.97, 83.53, 149.60, 169.17, 170.01. HRMS calcd for $C_{12}H_{19}NO_5$ (M^+): 257.1263. Found: 257.1248.

(3*R*,5*R*)-3-Acetoxy-1-(*tert*-butoxycarbonyl)-2-methoxy-5-methylpyrrolidine (12)

Treatment of **10** (2.4 g, 9.3 mmol) in a similar manner to that described for the preparation of **5** from **3** gave **12** (2.1 g, 82%, 2 steps) as a mixture of two diastereomers *via* (3*R*, 5*R*)-3-acetoxy-1-(*tert*-butoxycarbonyl)-2-hydroxy-5-methylpyrrolidine (**11**) after purification by column chromatography (hexane: ethyl acetate=3:1). This material was directly used for the next reaction without further separation.

12: colorless oil. IR (neat): 1745, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.28-1.33 (3H, m, CH_3), 1.50 (9H, s, $OC(CH_3)_3$, 2.01 (3H, s, $COCH_3$), 1.90-2.20 (2H, m, C_4-H_2), 3.37 (3H, br s, OCH_3), 3.88-4.10 (1H, m, C_5-H), 4.93-5.10 (1H, m, C_3-H). HRMS calcd for $C_{13}H_{24}NO_5$ $(M+H)^+$: 274.1655. Found: 274.1642.

(2*R*,3*R*,5*R*)-3-Acetoxy-1-(*tert*-butoxycarbonyl)-2-cyano-5-methylpyrrolidine and Its (2*S*,3*R*,5*R*)-Isomer (14a/b)

Treatment of **12** (0.8 g, 2.9 mmol) in a similar manner to that described for the preparation of **7** and **8** from **5** gave **14a/b** (0.67 g, 85%, **a**:**b**=58:42) as a mixture of two diastereomers after purification by column chromatography (hexane: ethyl acetate=3:1). colorless oil. $[\alpha]^{21}_D$ +8.0° (c 1.60, MeOH). IR (neat): 2240, 1754, 1716 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.24, 1.39 (total 3H, each d, J=6.23 Hz, CH_3), 1.51 (9H, s, $OC(CH_3)_3$), 2.08, 2.17 (total 3H, each s, $COCH_3$), 2.00-2.45 (2H, m, C_4-H_2), 3.97-4.15 (1H, m, C_5-H), 4.50-4.75 (1H, m, C_2-H), 5.20-5.35 (1H, m, C_3-H). HRMS calcd for $C_{13}H_{21}N_2O_4$ $(M+H)^+$: 269.1501. Found: 269.1492.

(3*R*,5*R*)-3-Benzoyloxy-1-(*tert*-butoxycarbonyl)-5-methyl-2-pyrrolidinone (15) and Its Enantiomer (*ent*-15)

a) Preparation of **15** from **9**: To a stirred solution of alcohol **9** (3.1 g, 14.4 mmol) in dry pyridine (50 ml) was added benzoyl chloride (2.4 g, 17.3 mmol) at 0°C and the mixture was stirred at room temperature for 20 h. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate (50 ml). The solution was washed succesively with 10% aqueous citric acid, saturated aqueous $NaHCO_3$, and brine. Usual workup followed by column chromatography (hexane: ethyl acetate=4:1) gave **15** (3.7 g, 82%) as a colorless solid. Recrystallyzation from petroleum ether gave an analytical sample of **15** as colorless needles, mp 86-87°C. $[\alpha]^{20}_D$ -6.9° (c 1.56, MeOH). IR (KBr): 1794, 1768, 1726, 1598 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.42 (3H, d, J=6.60 Hz, CH_3), 1.56 (9H, s, $OC(CH_3)_3$), 2.28 (1H, ddd, J=12.45, 10.99, 8.79 Hz, C_4-Hβ), 2.39 (1H, ddd, J=12.45, 8.43, 1.10

Hz, C_4-Hα), 4.30-4.42 (1H, m, C_5-H), 5.76 (1H, dd, J=10.99, 8.43 Hz, C_3-H), 7.40-8.12 (5H, m, aromatic-H). ^{13}C-NMR ($CDCl_3$): δ 20.65, 28.02, 32.80, 50.30, 70.47, 83.60, 128.41, 129.14, 130.01, 133.49, 149.70, 165.64, 169.09. EIMS m/z: 319 (M^+). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.93: H, 6.63; N, 4.39. Found: C, 63.77; H, 6.60; N, 4.40.

b) Preparation of *ent*-**15** from **25**: To a stirred solution of alcohol **24** (3.5 g, 16.2 mmol) in THF (80 ml) was added benzoic acid (3.9 g, 32.5 mmol) followed by PPh_3 (8.5 g, 32.5 mmol). The solution was then cooled to 0°C, and a solution of diethyl azodicarboxylate (DEAD, 5.6 g, 32.5 mmol) in THF (20 ml) was added dropwise. The reaction mixture was stirred for 1 h at 0°C, and 15 h at room temperature. The reaction mixture was concentrated *in vacuo* to give a thick yellow oil residue. The residue was dissolved in dichloromethane (100 ml) and the solution was washed with saturated aqueous $NaHCO_3$ and brine. Usual workup followed by column chromatography (hexane: ethyl acetate=4:1) gave *ent*-**15** (4.4 g, 85%) as a colorless oil. $[\alpha]^{25}_D$ +6.7° (c 1.60, MeOH). The IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra of this material were identical with those recorded for **15**.

(3*R*,5*R*)-3-Benzoyloxy-5-methyl-2-pyrrolidinone (16) and Its Enantiomer (*ent*-16)

a) Preparation of **16** from **15**: Trifluoroacetic acid (5 ml) was added to a stirred solution of **15** (2.5g, 7.8 mmol) in dichloromethane (20 ml) at 0°C. The reaction mixture was stirrede for 2 h at room temperature and then the solvent was evaporated *in vacuo*. The residue was dissolved in ethyl acetate (50 ml) and the solution was washed with saturated aqueous $NaHCO_3$ and brine. Usual workup gave **16** (1.54 g, 90%) as a colorless solid. Recrystallyzation from ethyl acetate: isopropyl ether gave an analytical sample of **16** as colorless needles, mp 154-155°C. $[\alpha]^{20}_D$ +42.5° (c 1.27, MeOH). IR (KBr): 3240, 1730, 1714, 1676, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.30 (3H, d, J=6.23 Hz, CH_3), 2.30 (1H, ddd, J=13.92, 8.43, 8.06 Hz, C_4-Hβ), 2.35 (1H, ddd, J=13.92, 6.59, 1.47 Hz, C_4-Hα), 3.89-3.98 (1H, m, C_5-H), 5.59 (1H, dd, J=8.06, 6.59 Hz, C_3-H), 7.38 (1H, br s, NH), 7.43-8.13 (5H, m, aromatic-H). ^{13}C-NMR ($CDCl_3$): δ 22.70, 35.95, 47.49, 71.12, 128.38, 129.44, 129.94, 133.34, 165.93, 173.20. EIMS m/z: 220 $(M+H)^+$. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.68; H, 6.00; N, 6.26.

b) Preparation of *ent*-**16** from *ent*-**15**: Treatment of *ent*-**15** (4.2 g, 13.1 mmol) in the same manner as described for the preparation of **16** from **15** gave *ent*-**16** (2.6 g, 90%) as colorless needles. mp 154-155°C (ethyl acetate:isopropyl ether). $[\alpha]^{22}_D$ -41.8° (c 1.20, MeOH). The IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra of this material were identical with those recorded for **16**.

(3*R*,5*R*)-3-Benzoyloxy-1-methoxycarbonyl-5-methyl-2-pyrrolidinone (17) and Its Enantiomer (*ent*-17)

a) Preparation of **17** from **16**: Lithium bis(trimethylsilyl)amide ($LiN(TMS)_2$) in THF (1.0 M solution, 8.2 ml, 8.2 mmol) was added to a solution of **16** (1.5 g, 6.8 mmol) in dry THF (30 ml) under nitrogen at -15°C, and the reaction mixture was stirred for 30 min. Then methyl chlorocarbonate (0.78 g, 8.2 mmol) was added to the reaction mixture. After stirring for 1 h at -15°C and the reaction mixture was allowed to warm up to room temperature. The reaction was quenched with saturated NH_4Cl solution (10 ml) and the mixture was extracted

with ethyl acetate (50 ml). Usual workup followed by column chromatography (chloroform: methanol=30:1) gave **17** (1.6 g, 86%) as a colorless solid. Recrystallization from ethyl acetate: isopropyl ether gave an analytical sample of **17** as colorless needles, mp 129-130°C. $[\alpha]^{22}_D$ -20.4° (c 0.82, MeOH). IR (KBr): 1768, 1720, 1604 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.44 (3H, d, J=6.60 Hz, CH_3), 2.31 (1H, ddd, J=12.46, 10.99, 10.62 Hz, C_4-Hβ), 2.42 (1H, ddd, J=12.46, 8.43, 1.73 Hz, C_4-Hα), 3.91 (3H, s, OCH_3), 4.38-4.47 (1H, m, C_5-H), 5.76 (1H, dd, J=10.62, 8.43 Hz, C_3-H), 7.40-8.10 (5H, m, aromatic-H). ^{13}C-NMR ($CDCl_3$): δ 20.58, 32.91, 50.59, 53.78, 70.41, 128.47, 129.05, 130.00, 133.58, 151.92, 165.57, 168.95. EIMS m/z: 277 (M^+). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.44; H, 5.32; N, 4.85.

b) Preparation of *ent*-**17** from *ent*-**16**: Treatment of *ent*-**16** (2.2 g, 10.0 mmol) in the same manner as described for the preparetion of **16** from **15** gave *ent*-**17** (2.3 g, 82%) as colorless needles. mp 128-129°C (ethyl acetate: isopropyl ether). $[\alpha]^{25}_D$ +20.8° (c 1.12, MeOH). The IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra of this material were identical with those recorded for **17**.

(3*R*,5*R*)-3-Benzoyloxy-2-methoxy-1-methoxycarbonyl-5-methylpyrrolidine (19) and Its Enantiomer (*ent*-19)

a) Preparetion of **19**: Treatment of **17** (1.5 g, 5.4 mmol) in a similar manner to that described for the preparation of **5** from **3** gave **19** (1.27 g, 80%) as a mixture of diastereomers. This material was directly used for the next reaction without separation. In a small scale experiment, this diastereomers was further separated by column chromatography (benzene: ethyl acetate=3:1) to give pure samples of more polar **19** and less polar **19** in a ratio of 75: 25.

More polar 19: colorless needles (ethyl acetate: isopropyl ether), mp 128-129°C. $[\alpha]^{24}_D$ -12.5° (c 1.02, MeOH). IR (KBr): 1768, 1720, 1608 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.44 (3H, d, J=6.23 Hz, CH_3), 2.33 (1H, ddd, J=12.43, 10.62, 8.43 Hz, C_4-H), 2.43 (1H, ddd, J=12.43, 8.43, 1.10 Hz, C_4-H), 3.91 (3H, s, OCH_3), 3.87-3.98 (1H, m, C_5-H), 4.36-4.45 (1H, m, C_2-H), 5.77 (1H, dd, J=10.62, 8.43 Hz, C_3-H), 7.42-8.08 (5H, m, aromatic-H). EIMS m/z: 262 $(M\text{-}OCH_3)^+$. Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.33; H, 6.42; N, 4.58.

Less polar 19: colorless oil. $[\alpha]^{24}_D$ +7.6° (c 0.88, MeOH). IR (neat): 1765, 1718, 1606 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.24 (3H, d, J=6.59 Hz, CH_3), 2.06-2.14 (1H, m, C_4-H), 2.21-2.30 (1H, m, C_4-H), 3.76 (3H, s, OCH_3), 3.98-4.08 (1H, m, C_5-H). 4.60-4.68 (1H, m, C_2-H), 5.37-5.42 (1H, m, C_3-H), 7.42-8.16 (5H, m, aromatic-H). HRMS calcd for $C_{14}H_{16}NO_4$ $(M\text{-}OCH_3)^+$: 262.1079. Found: 269.1060.

b) Preparation of *ent*-**19** from *ent*-**17**: The same treatment of *ent*-**17** (2.1 g, 7.5 mmol) as described for the preparation of **19** from **17** gave *ent*-**19** (1.9 g, 85%, 2 steps) as a mixture of two diastereomers *via* *ent*-**18**. This material was directly used for the next reaction without separation. In a small scale experiment, this diastereomers was further separated by column chromatography (benzene: ethyl acetate=3:1) to give pure samples of more polar *ent*-**19** and less polar *ent*-**19** in a ratio of 74:26.

More polar *ent*-19: colorless needles, mp 128-129°C (ethyl acetate: isopropyl ether). $[\alpha]^{25}_D$ +12.3° (c 1.22, MeOH). The IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra of this material were identical with those recorded for more polar **19**.

Less polar *ent*-19: colorless oil. $[\alpha]^{25}_D$ -7.4° (c 0.76, MeOH). The IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra of this material were identical with those recorded for less polar **19**.

(2*R*,3*R*,5*R*)-3-Benzoyloxy-2-cyano-1-methoxycarbonyl-5-methylpyrrolidine (21), Its (2*S*,3*R*,5*R*)-Isomer (22), Its (2*S*,3*S*,5*S*)-Isomer (*ent*-21) and Its (2*R*,3*S*,5*S*)-Isomer (*ent*-22)

a) Preparation of **21** and **22**: Treatment of **19** (1.2 g, 4.1 mmol) in a similar manner to that described for the preparation of **7** and **8** from **5** gave **21** (0.70 g, 59%) as a more polar product and **22** (0.27 g, 23%) as a less polar product after separation by column chromatography (hexane: ethyl acetate=5:1).

21: colorless needles (ethyl acetate:petroleum ether), mp 86-87°C. $[\alpha]^{21}_D$ -37.5° (c 1.32, MeOH). IR (KBr): 2220, 1725, 1603 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.47 (3H, s, CH_3), 2.24 (1H, br s, C_4-Hβ), 2.48-2.58 (1H, m, C_4-Hα), 3.78 (3H, s, OCH_3), 4.22 (1H, br s, C_5-H), 4.76 (1H, br s, C_2-H), 5.60 (1H, br s, C_3-H), 7.38-8.02 (5H, m, aromatic-H). ^{13}H-NMR ($CDCl_3$): δ 20.57, 20.60 (CH_3), 38.40, 38.43 (C_4), 53.21 (OCH_3), 53.68, 53.83 (C_5), 53.88, 58.95 (C_2), 75.38 (C_3), 116.62 (CN), 128.63, 128.76, 129.81, 133.88 (aromatic-C), 165.41 (C=O). EIMS m/z: 288 (M^+). Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.38; H, 5.40; N, 9.66.

22: colorless oil. $[\alpha]^{21}_D$ -49.7° (c 0.97, MeOH). IR (neat): 2220, 1732, 1603 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.33 (3H, s, CH_3), 2.25 (1H, br s, C_4-Hβ), 2.47-2.60 (1H, m, C_4-Hα), 3.81 (3H, s, OCH_3), 4.21 (1H, br s, C_5-H), 5.05 (1H, d, J=3.96 Hz, C_2-H), 5.02-5.12 (1H, m, C_3-H), 7.43-8.20 (5H, m, aromatic-H). ^{13}H-NMR ($CDCl_3$): δ 20.83, 20.87 (CH_3), 35.57, 36.52 (C_4), 51.04, 51.16 (C_5), 51.52, 51.67 (C_2), 53.20 (OCH_3), 69.33, 70.04 (C_3), 115.10 (CN), 128.54, 128.66, 129.98, 133.91 (aromatic-C), 165.70 (C=O). HRMS calcd for $C_{15}H_{16}N_2O_4$ (M^+): 288.1110. Found: 288.1098.

b) Preparetion of *ent*-**21** and *ent*-**22**: The same treatment of *ent*-**19** (1.6 g, 5.5 mmol) as described for the preparation of **21** and **22** from **19** gave *ent*-**21** (1.05 g, 67%) as a more polar product and *ent*-**22** (0.26 g, 17%) as a less polar product.

ent-**21**: colorless needles, mp 87-88°C (ethyl acetate: petroleum ether). $[\alpha]^{25}_D$ +37.8° (c 1.14, MeOH). The IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra of this material were identical with those recorded for **21**.

ent-**22**: colorless oil. $[\alpha]^{25}_D$ +49.6° (c 0.88, MeOH). The IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra of this material were identical with those recorded for **22**.

(2*R*,3*R*,5*R*)-3-Hydroxy-5-methyl-2-pyrrolidinecarboxylic acid [(2*R*,3*R*,5*R*)-1], Its (2*S*,3*R*,5*R*)-Isomer [(2*S*,3*R*,5*R*)-1], and (2*S*,3*S*,5*S*)-Isomer [(2*S*,3*S*,5*S*)-1]

a) Preparation of (2*R*,3*R*,5*R*)-**1**: A solution of **21** (0.7 g, 2.4 mmol) in 6M HCl (30 ml) was heated at 115°C for 24 h and then the solvent was evaporated *in vacuo*. The residue was dissolved in water (2 ml) and purified by Dowex 50W x 8 (50-100 mash) ion exchange column chromatography (water then 5% aqueous ammonia) to give (2*R*,3*R*,5*R*)-**1** (0.26 g, 75%) as a white solid. Recrystallization from 70% aqueous ethanol gave an analytical sample of (2*R*,3*R*,5*R*)-**1** as colorless needles, mp 252-253°C. $[\alpha]^{21}_D$ +17.8° (c 0.88, H_2O); [lit.[3] $[\alpha]_D$ +18° (c 0.32, H_2O)]. IR (KBr): 3280, 2850-2200, 1636, 1570 cm^{-1}. ^{1}H-NMR (D_2O): δ 1.49 (3H, d, J=6.60 Hz, CH_3),

1.74 (1H, ddd, J=14.28, 11.72, 4.39 Hz, C_4-Hβ), 2.18 (1H, ddd, J=14.28, 5.87, 1.02 Hz, C_4-Hα), 3.98-4.10 (2H, m, C_2-, C_5-H), 4.64-4.72 (1H, m, C_3-H). ^{13}H-NMR ($CDCl_3$): δ 19.70 (CH_3), 41.96 (C_4), 58.32 (C_5), 72.16 (C_2), 76.93 (C_3), 174.38 (C=O). Anal. Calcd for $C_6H_{11}NO_3$: C, 49.64; H, 7.64; N, 9.65. Found: C, 49.40; H, 7.74; N, 9.56.

b) Preparation of (2*S*,3*R*,5*R*)-**1**: The same treatment of **22** (0.65 g, 2.2 mmol) as described for the preparation of (2*R*,3*R*,5*R*)-**1** from **21** gave (2*S*,3*R*,5*R*)-**1** (0.25 g, 78%) as colorless needles, mp 286-288°C (70% aqueous ethanol). $[\alpha]^{20}_D$ -85.1° (c 0.70, H_2O). IR (KBr): 3332, 3100-2180, 1652, 1624, 1590, 1436, 1412 cm^{-1}. ^{1}H-NMR (D_2O): δ 1.43 (3H, d, J=6.60 Hz, CH_3), 1.91 (1H, ddd, J=14.28, 11.73, 4.03 Hz, C_4-Hβ), 2.28 (1H, ddd, J=14.28, 5.86, 1.72 Hz, C_4-Hα), 4.05-4.16 (1H, m, C_5-H), 4.24 (1H, d, J=4.39 Hz, C_2-H), 4.70 (1H, t, J=4.03 Hz, C_3-H). ^{13}H-NMR ($CDCl_3$): δ 19.62 (CH_3), 44.02 (C_4), 57.68 (C_5), 69.59 (C_2), 73.94 (C_3), 173.26 (C=O).

c) Preparation of (2*S*,3*S*,5*S*)-**1** from *ent*-**21**: The same treatment of *ent*-**21** (0.80 g, 2.8 mmol) as described for the preparation of (2*R*,3*R*,5*R*)-**1** from **21** gave (2*S*,3*S*,5*S*)-**1** (0.28 g, 70%) as colorless needles, mp 252-253°C [lit.[3] mp 247-249°C (decomp.)]. $[\alpha]^{21}_D$ -17.6° (c 0.80, H_2O), [lit.[3] $[\alpha]_D$ -17° (c 0.50, H_2O)]. The IR, ^{1}H-NMR, and ^{13}C-NMR spectra of this material were identical with those recorded for (2*R*,3*R*,5*R*)-**1**.

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