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Synthetic Studies on Quinocarcin and Its Related Compounds. 3.[1, 2] Synthesis of 5-Substituted- and 3,5-Disubstituted-2-formyl-pyrrolidine Derivatives, the Key D-Ring Fragments of Enantiomeric Pairs of Quinocarcin and 10-Decarboxyquinocarcin

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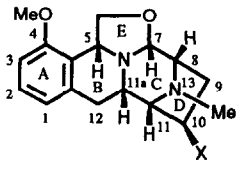
Key words: quinocarcin, 10-decarboxyquinocarcin, D-ring fragment, 5-substituted-2-formylpyrrolidine, 3,5-disubstituted-2-formylpyrrolidine, glutamic acid, pyroglutamic acid

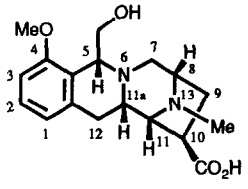
Abstract: *The title synthesis was accomplished by employing each enantiomer of glutamic acid and pyroglutamic acid as chiral starting materials and featuring formation of an N-protected aminal, substitution of the methoxy group with a cyanide anion, and reduction of the cyanide function to an aldehyde as common key steps.*

(–)-Quinocarcin (**1**), a natural secondary metabolite produced by *Streptomyces melanovinaceus* along with pharmacologically inactive quinocarcinol (**3**), exhibits prominent antitumor activity. It has been also reported that the more stable 7-cyano congener, DX-52-1 (**4**), retains significant antitumor activity of **1**.[2a]

As described in the preceding papers,[2] we have succeeded in developing efficient synthetic schemes to enantiomeric pairs of the ABE and ABC ring systems of **1**. Based on the results accumulated in these model studies, we next embarked on the total synthesis of enantiomeric pairs of **1** and 10-decarboxyquinocarcin (**2**) (the ABCDE ring system of **1**).[1c,d]



1 : X=CO_2H
2 : X=H



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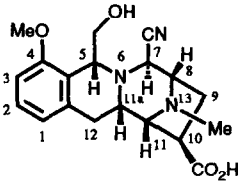

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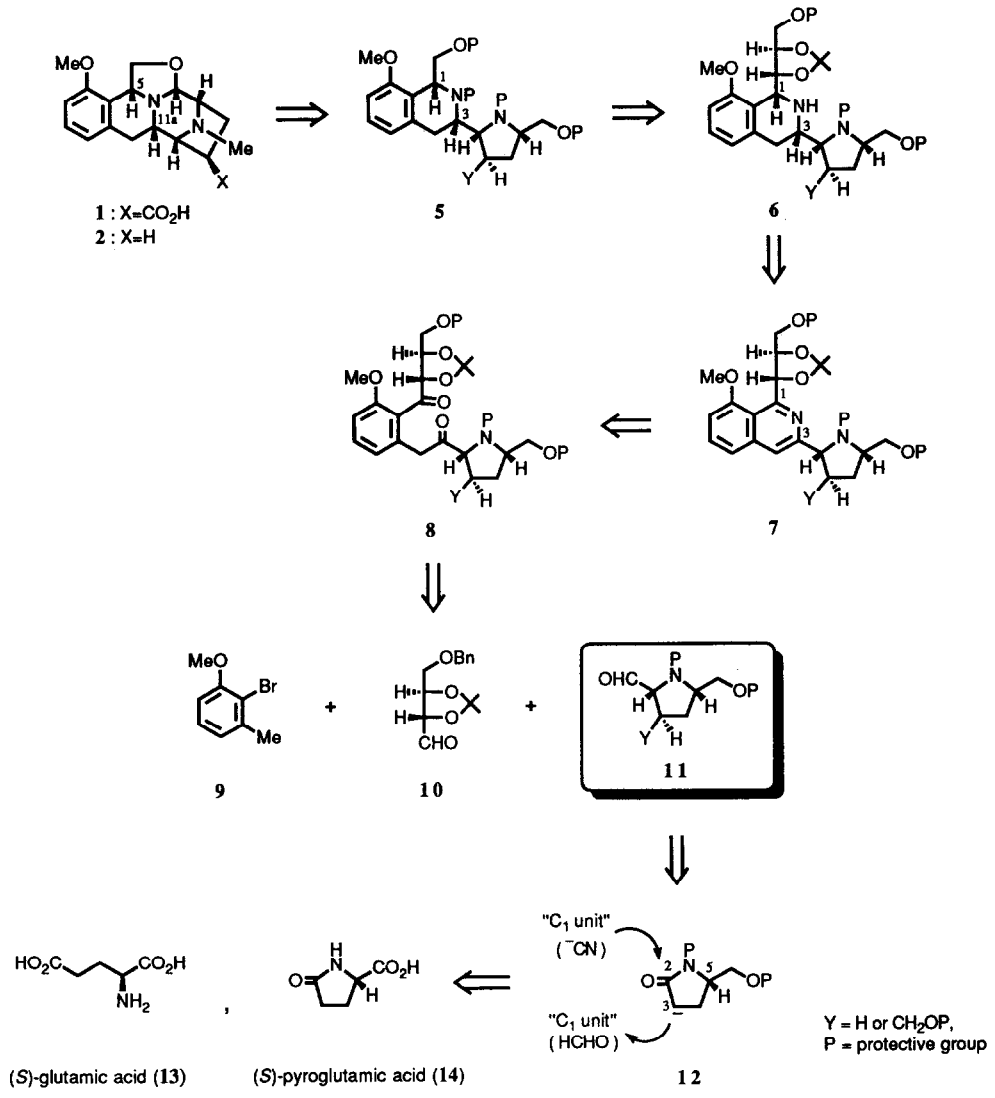
Synthetic Plan

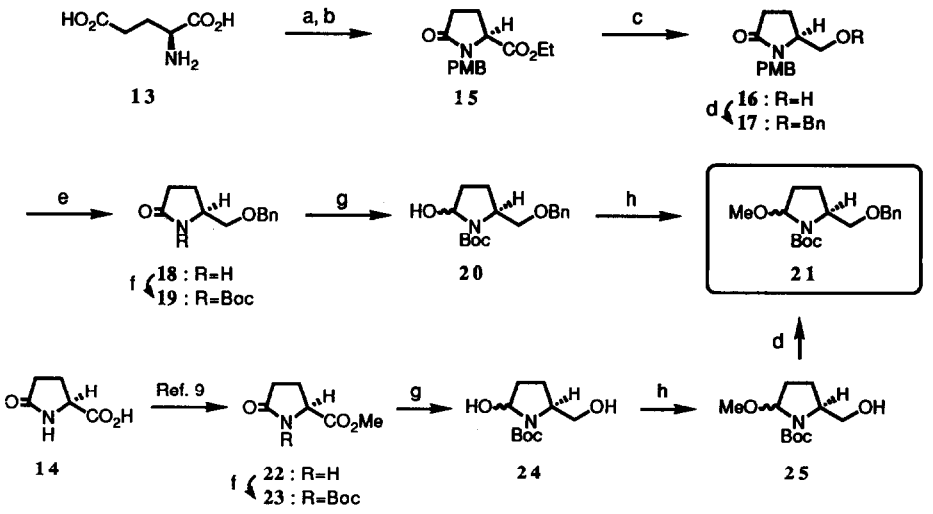
Our approach to **1** and **2** is shown in the antithetic format in **Scheme 1**. The most critical step in this contemplated scheme is envisaged to be the diastereoselective reduction of 1,3-disubstituted isoquinoline derivative **7** to control requisite asymmetric centers at the C5 and C11a positions in **1** and **2** simultaneously in

Scheme 1



a single step. The reduction product **6** could be transformed to the key intermediate **5** possessing the requisite carbon framework and functional groups with correct absolute stereochemistries, by proper functional group manipulations. The key substrate **7** for the diastereoslective reduction might be accessible from the anisole **9**, the threose **10**, and the 2-formylpyrrolidine **11** through diketone **8**. To realize this synthetic scheme, our efforts were first focused on exploiting an efficient synthetic route to **11** since the preparation methods of **9** and **10** have already established.[2] The key feature of the explored synthesis of **11** consists of introducing a one-carbon unit into the C2 and C3 positions of lactam **12** in a stereoselective manner under an influence of the asymmetric center (C5 position) involved in **12**. This was anticipated to be readily accessible from (*S*)-

Scheme 2



reagents and conditions : a) *p*-anisaldehyde, $NaBH_4$, 2M NaOH, rt, 43% b) $SOCl_2$, EtOH, reflux, 88% c) $NaBH_4$, LiCl, EtOH-THF(2:1v/v), rt, 95% d) BnBr, NaH, DMF, rt, 96% for **17**, 92% for **21** e) CAN, MeCN-H_2O(10:1v/v), rt, 83% f) Boc_2O, DMAP, Et_3N, MeCN, rt, 98% for **19**, 100% for **22** g) DIBAL, THF, -78°C for **19**, -78→0°C for **23** h) PPTS, MeOH, rt, 92% for **21** from **19**, 76% for **25** from **23**

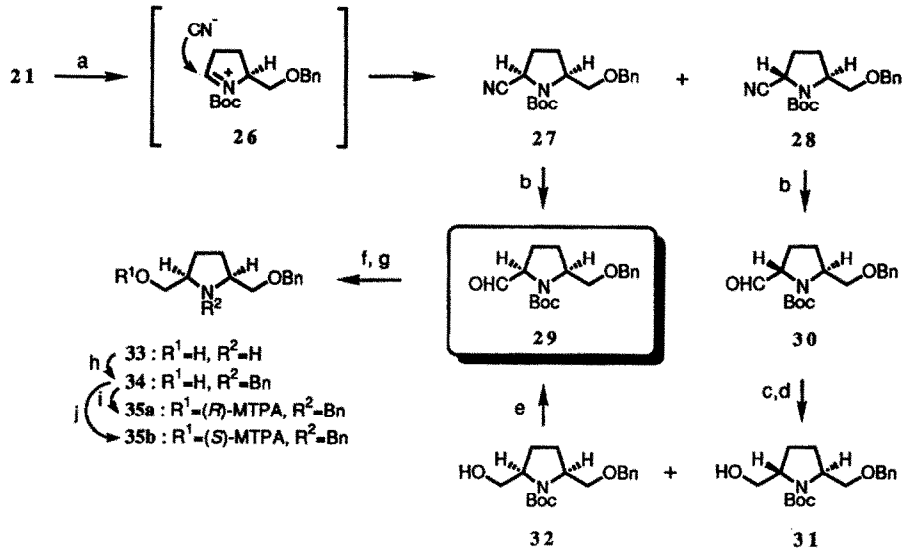
glutamic acid (**13**) or (*S*)-pyroglutamic acid (**14**). In the third part of this series of papers, we wish to disclose full details of the facile and efficent synthesis of an enantiomeric pair of **11**, the key D-ring fragments required for the total synthesis of enantiomeric pairs of **1** and **2**. The explored synthetic route utilized each enatiomer of **13** and **14** as a chiral starting material.[1c] The accompanying paper details the total synthesis of **1** and **2** which features this novel synthetic strategy.[4]

Results and Discussion

1. Synthesis of 5-Substituted-2-formylpyrrolidines 29 and *ent*-29, the Key D-Ring Fragments for an Enantiomeric Pair of 10-Decarboxyquinocarcin (2 and *ent*-2)

We initially pursued the synthesis of 5-substituted-2-formylpyrrolidine **29** corresponding to **11** (Y=H) as shown in **Scheme 2** and **Scheme 3**. At the outset, the key intermediate **21** was prepared from commercially available (*S*)-glutamic acid (**13**). Thus, protection of the amino group[5] in **13** followed by simultaneous lactam and ester formation[6] provided ethyl ester **15**. Reduction of **15** with lithium borohydride[7] afforded the alcohol **16**, whose hydroxy group was protected to furnish benzyl ether **17**. Exchange of the *N*-protecting group yielded carbamate **19**[8] *via* lactam **18**. Reduction of **19** with diisobutylaluminium hydride (DIBAL) followed by treatment of the resulting hemiaminal **20** with pyridinium *p*-toluenesulfonate (PPTS) in methanol provided the desired 2-methoxypyrrolidine **21** as an epimeric mixture. After experimentation, it was found that **21** could be prepared more readily starting from commercially available (*S*)-pyroglutamic acid (**14**). Thus, protection of the amino group in the methyl ester **22** derived from **14** according to the reported method[9] furnished *N*-protected lactam **23** in a quantitative yield. After reduction of **23** with DIBAL, treatment of the

Scheme 3



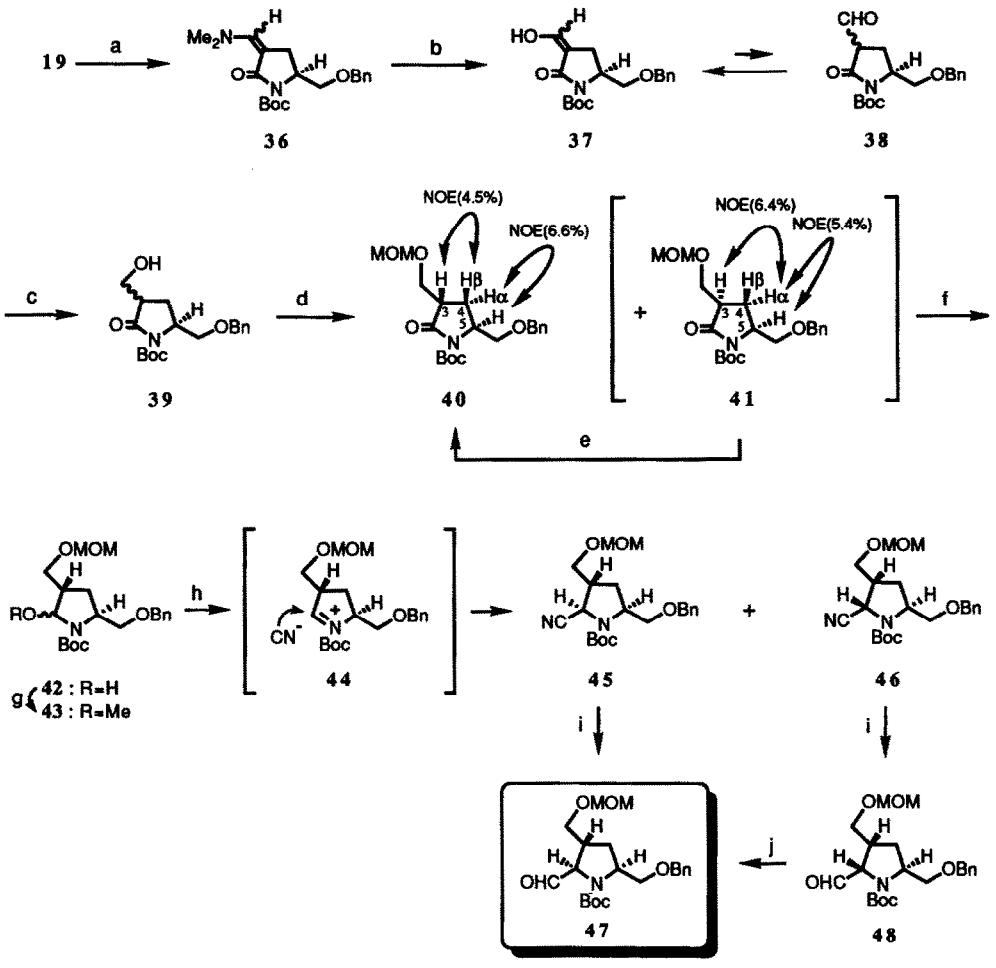
reagents and conditions : a) TMSCN, BF_3•Et_2O, CH_2Cl_2, -78°C, 95%(27:28=31:69) b) DIBAL, toluene, -78°C, 66% for **29**, 63% for **30** c) K_2CO_3, MeOH, reflux, 100% d) $NaBH_4$, MeOH, rt, 97%(31:32=22:78) e) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; Et_3N, 97% f) $NaBH_4$, MeOH, rt g) TMSBr, CH_2Cl_2, rt h) BnBr, aq $NaHCO_3$, CH_2Cl_2, rt, 89%(3 steps) i) (*R*)-MTPACl, Py, rt, 92%, j) (*S*)-MTPACl, Py, rt, 94 %

resulting alcohol **24** with acidic methanol provided the *N*-protected aminal **25**, whose hydroxy group was further benzylated to give **21**.

Next, the conversion of **21** to **29** was investigated as shown in **Scheme 3**. Thus, nucleophilic addition of a cyanide anion to the reactive *N*-acyliminium ion **26** generated *in situ* from **21** was best achieved by employing trimethylsilyl cyanide in the presence of boron trifluoride etherate in dichloromethane at -78°C, giving rise to a mixture of the *cis*-2-cyanopyrrolidine **27** and its *trans*-isomer **28** in a ratio of 31:69 in 95% yield.[10] These pyrrolidine derivatives (**27** and **28**) could be cleanly separated by column chromatography on silica gel. In the case of using other Lewis acids such as stanic chloride[10,11a] and titanium tetrachrolide[11b,c], poor yields (23-37%) of the mixture of **27** and **28** were obtained. The stereochemistries of both isomers **27** and **28** were unambiguously established as depicted by combination of X-ray diffraction analysis of **28**[12] and spectroscopic properties of **27** and **28**. Finally, reduction of **27** with DIBAL provided **29**. On the other hand, **28** was similarly reduced with DIBAL to afford the *trans*-2-formylpyrrolidine **30**, which could be transformed to the thermodynamically more stable isomer **29** by following 4-step sequence. Thus, epimerization of **30** with potassium carbonate in refluxing methanol followed by reduction of the resulting inseparable aldehydes **29** and **30** with sodium borohydride afforded the diastereomeric alcohols **31** and **32** in a ratio of 27:73. Separation of this mixture by column chromatography on silica gel followed by Swern oxidation of the desired *cis*-alcohol **32** provided **29**.

The optical purity of **29** was determined to be more than 95% ee by comparison of the 400 MHz ^{1}H-NMR spectra of (*R*)-and (*S*)-MTPA esters **35a** and **35b** derived from **29** by 4-step sequence involving reduction, removal of the Boc group, *N*-benzylation, and acylation with (*R*)-and (*S*)-MTPA chloride.[13]

Scheme 4

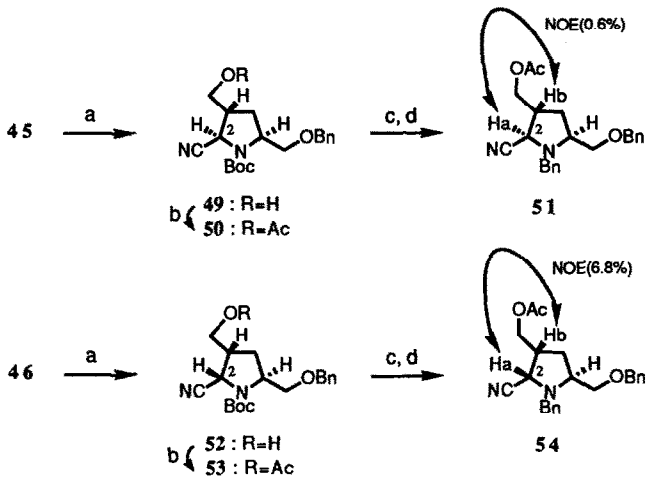


reagents and conditions : a) $(Me_2N)_2CHO^tBu$, 75°C b) HCl, THF, rt, 88%(2 steps) c) $NaBH_3CN$, THF-EtOH-AcOH(5:1:1), -10°C, 81% d) MOMCl, $^iPr_2EtN$, CH_2Cl_2, rt, 93%(**40**:**41**=88:12) e) DBU, benzene, reflux, 100%(**40**:**41**=83:17) f) DIBAL, THF, -78°C g) PPTS, MeOH, rt, 92%(2 steps) h) TMSCN, BF_3•Et_2O, CH_2Cl_2, -78°C, 95%(**45**:**46**=27:73) i) DIBAL, toluene, -78°C, 63% for **47**, 61% for **48** j) K_2CO_3, MeOH, reflux, 100%

By employing (*R*)-glutamic acid (*ent*-**13**) and (*R*)-pyroglutamic acid (*ent*-**14**) instead of their (*S*)-isomers (**13** and **14**), the enantiomeric 5-substituted-2-formylpyrrolidine derivative (*ent*-**29**) required for the total synthesis of *ent*-**2** was prepared in a similar manner to that described above.

2. Synthesis of 3,5-Disubstituted-2-formylpyrrolidine 47 and *ent*-47, the Key D-Ring Fragments for an Enantiomeric Pair of Quinocarcin (1 and *ent*-1)

Scheme 5



reagents and conditions : a) *p*-TsOH, $CHCl_3$-MeOH(3:1), rt, 95% for **49**, 93% for **52** b) Ac_2O, DMAP, Py, rt, 99% for **50**, 98% for **53** c) TMSBr, CH_2Cl_2, rt d) BnBr, aq.$NaHCO_3$, CH_2Cl_2, rt, 79% for **51**(2 steps), 79% for **54**(2 steps)

We next addressed on the synthesis of 3,5-disubstituted-2-formylpyrrolidine **47** corresponding to **11** (Y=CH_2OP) required for the total synthesis of **1** as shown in **Scheme 4**. In order to introduce a hydroxymethyl group into the C3 position of **19**, it was first treated with Bredereck reagent[14,15] providing enamine **36**. Acidic hydrolysis of **36** followed by chemoselective reduction of the resulting enol **37** with sodium cyanoborohydride in acidic media at -10°C, afforded alcohol **39** as an inseparable epimeric mixture, presumably *via* aldehyde tautomer **38**.[15] This mixture could be readily separated by column chromatography on silica gel after protection of the hydroxy group in **39** with methoxymethyl group, giving rise to a mixture of desired *trans*-methoxymethyl ether **40** and undesired *cis*-isomer **41** in a ratio of 88:12. Epimerization of **41** to the thermodynamically more stable **40** was effected by treating with 1,8-diazabicyclo-[5,4,0]undec-7-ene (DBU) in refluxing benzene, providing a mixture of **40** and **41** in a ratio of 83:17 in a quantitative yield.

The stereostructures of both **40** and **41** were proven by NOE measurements in their 400 MHz ^{1}H-NMR spectra. Thus, NOE between the signals due to C3-H and C4-Hβ and that between the signals due to C5-H and C4-Hα in **40** were found to be 4.5% and 6.6%, respectively. On the other hand, NOE between the signals due to C3-H and C4-Hα and that between the signals due to C5-H and C4-Hα in **41** were recorded as 6.4% and 5.4%, respectively. Accordingly, the C3-H and C5-H in **40** and **41** were assigned to have *trans*- and *cis*-configurations, respectively.

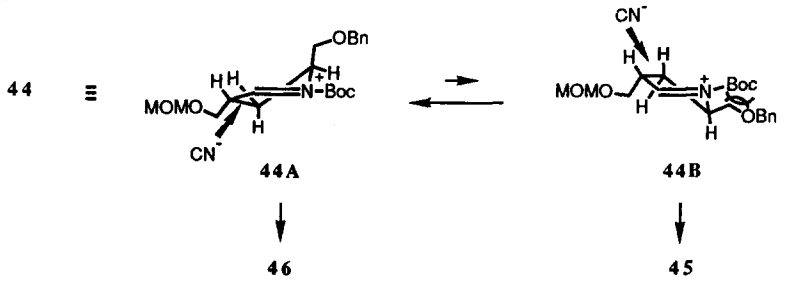
By employing the reaction sequence similar to that described for the preparation of **27** and **28** from **19**, **40** was converted to 2,5-*cis*-3-substituted-2-formylpyrrolidine **45** and its 2,5-*trans*-isomer **46** in a ratio of 27:73 *via* 3-substituted-2-hydroxypyrrolidine **42** and 3-substituted-2-methoxypyrrolidine **43**. Separation of these diastereomers (**45** and **46**) could be effectively accomplished by employing column chromatography on silica gel. The stereostructures of both **45** and **46** were rigorously confirmed by the 400 MHz ^{1}H-NMR spectral analysis of the compounds derived from **45** and **46**, respectively (*vide infra*). To complete the synthesis of **47**, **45** was reduced with DIBAL yielding desired **47**. On the other hand, **46** was similarly reduced to give the

2,5-*trans*-3,5-disubstituted-2-formylpyrrolidine **48**, which smoothly converged to **47** by base-catalyzed epimerization in a quantitative yield.

In order to determine the stereostructure of both **45** and **46**, they were converted to the corresponding *N*-benzylpyrrolidine derivatives **51** and **54**, respectively, as shown in **Scheme 5**. Thus, selective deprotection of the methoxymethyl group in **45** followed by acetylation of the resulting alcohol **49** provided acetate **50**. The *N*-protecting group of **50** was exchanged to afford *N*-benzylpyrrolidine **51**. On the other hand, **46** was transformed to **54** in the same manner as described above. NOE between Ha and Hb in the 400 MHz ^{1}H-NMR spectrum of **51** and that between Ha and Hb in **54** were found to be 0.6% and 6.8%, respectively. Based on these observations, the stereostructures of both **45** and **46** were unambiguously assigned as pictured.

The stereoselectivity observed for the nucleophilic addition of a cyanide anion to iminium ion **44** can be explained by the preferred transition state conformation of **44** as shown in **Figure 1**. Thus, the conformer **44A** is expected to be more favored than the other conformer **44B** which has $A^{1,2}$-strain between the *tert*-butoxycarbonyl (Boc) and the benzyloxymethyl groups.[16] The attack of a cyanide anion might occur preferentially from the *re*-face of **44A** under an influence of stereoelectronic effect,[17] giving rise to **46** as a major product.

Figure 1



The enantiomeric 3,5-disubstituted-2-formylpyrrolidine derivative (*ent*-**47**) required for the total synthesis of *ent*-**1** was prepared in a similar manner to that described above by employing (*R*)-glutamic acid (*ent*-**13**) instead of its (*S*)-isomer (**13**).

Conclusion

As described above, we have succeeded in establishing facile and efficient routes to enantiomeric pairs of 5-substituted- and 3,5-disubstituted-2-formylpyrrolidines **29**, *ent*-**29**, **47**, and *ent*-**47**, the key D-ring fragments of enantiomeric pairs of **1** and **2**, by employing each enantiomer of glutamic acid (**13** and *ent*-**13**) and pyroglutamic acid (**14** and *ent*-**14**) as chiral starting materials. The explored synthetic routes feature introducing a one-carbon unit into the C2 and C3 positions of lactam **19** in a stereoselective manner. Successful total synthesis of enantiomeric pairs of **1** and **2** utilizing **29**, *ent*-**29**, **47**, and *ent*-**47** as key D-ring fragments is the subject of the accompanying paper.[4]

Experimental

General. All melting points were determined with a Yamato MP-21 micro melting point apparatus and are uncorrected. Measurements of optical rotations were performed with a Horiba SEPA-200 automatic digital polarimeter. ^{1}H-NMR spectra were measured with a Hitachi R-90H (90 MHz) and a Brucker AM-400 (400 MHz) spectrometer.The chemical shifts were expressed in ppm using tetramethylsilane (δ=0) and/or residual solvents such as chloroform (δ=7.25) and benzene (δ=7.20) as internal standards. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Infrared (IR) spectral measurements were carried out with a JASCO A-202 and a JASCO FT/IR-5300 spectrometer. Low resolution mass (MS) spectra were taken with a Hitachi RMU-6MG spectrometer, and high resolution mass (HRMS) spectra were obtained on a Hitachi M-80A spectrometer. Routine monitoring of reactions was carried out using Merck 60 F254 silica gel, glass-supported TLC plates. Flash column chromatography was performed with indicated solvents on Wakogel C-300. Solvents and commercial reagents were dried and purified before use. Methanol and ethanol were distiled from sodium; ether, tetrahydrofuran, and toluene were distilled from sodium benzophenone ketyl; dichloromethane, benzene, and *N,N*-dimethylformamide were distilled from calcium hydride under argon.

(*S*)-5-Ethoxycarbonyl-1-(4-methoxybenzyl)-2-pyrrolidinone (15) and Its Enantiomer (*ent*-15)

a) Preparation of **15**: *p*-Anisaldehyde (167 ml, 1.4 mol) was added to a stirred solution of (*S*)-glutamic acid **13** (200 g, 1.4 mol) in 2M sodium hydroxide (1200 ml) at room temperature. After 20 min, sodium borohydride (15.6 g, 0.41 mol) was added in small portions at 0°C, and stirring was continued for 1.5 h at room temperature. Another *p*-anisaldehyde (167 ml, 1.4 mol) was added to the above mixture, and after 20 min, another sodium borohydride (15.6 g, 0.41 mol) was added at 0°C. The resulting mixture was stirred for 2 h at room temperature and then washed with ether (3 x 800 ml). The aqueous layer was acidified to pH 3 with 37% aqueous hydrochloric acid at 0°C, liberating a white precipitate, which was collected by filtration and dried *in vacuo* at 50°C to give (*S*)-*N*-(4-methoxybenzyl)glutamic acid (156 g, 43%) as a white solid. This material was directly used for the next reaction without further purification.

Thionyl chloride (196 ml, 2.7 mol) was added dropwise to a stirred suspension of (*S*)-*N*-(4-methoxybenzyl)glutamic acid (156 g, 0.59 mol) in ethanol (1400 ml) at room temperature, and the mixture was refluxed for 3 h. After cooling, the mixture was neutralized with saturated ethanolic sodium hydroxide and filtrated through a pad of celite. The filtrate was concentrated *in vacuo* to give a residue, which was purified by column chromatography (hexane-ethyl acetate, 1:1) to give **15** (142 g, 88%) as a colorless oil. $[\alpha]D^{20}$ +35.1°(c 1.00, CHCl3). IR (neat): 3500, 3000, 2950, 2870, 1740, 1695, 1615, 1590, 1515, 1440, 1415, 1300, 1250, 1200, 1180, 1115, 1030 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.25 (3H, t, J=7.1 Hz, CH2C*H3*), 2.02-2.10 (1H, m, C4-H), 2.22 (1H, ddd, J=18.7, 13.2, 9.2 Hz, C4-H), 2.40 (1H, ddd, J=16.8, 9.6, 3.8 Hz, C3-H), 2.51-2.61 (1H, m, C3-H), 3.79 (3H, s, ArO*Me*), 3.94 (1H, dd, J=9.2, 3.5 Hz, C5-H), 3.94 (1H, d, J=14.7 Hz, NC*H*2Ar), 4.08-4.21 (2H, m, C*H*2CH3), 4.95 (1H, d, J=14.7 Hz, NC*H*2Ar), 6.84 (2H, d, J=8.3 Hz, aromatic protons), 7.14 (2H, d, J=8.3 Hz, aromatic protons). EIMS m/z: 277 (M^+), 204 [(M-CO2Et)$^+$], 121, 78. HRMS calcd for C15H19NO4 (M^+): 277.1313. Found: 277.1316.

b) Preparation of *ent*-**15**: The same treatments of (*R*)-glutamic acid (*ent*-**13**) (200g, 1.4 mol) as described for the preparation of **15** from **13** gave *ent*-**15** (122 g, 83%) as a colorless oil *via* (*R*)-*N*-(4-methoxybenzyl)glutamic acid (142 g, 39%). $[\alpha]D^{20}$ -35.4°(c 1.46, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **15**.

(*S*)-5-Hydroxymethyl-1-(4-methoxybenzyl)-2-pyrrolidinone (16) and Its Enantiomer (*ent*-16)

a) Preparation of **16**: Lithium chloride (30.0 g, 0.70 mol) and sodium borohydride (27.0 g, 0.70 mol) were successively added to a stirred solution of **15** (99.8 g, 0.36 mol) in ethanol-tetrahydrofuran (2:1) (1500 ml) at room temperature. After 2 h, the mixture was neutralized with 20% aqueous acetic acid and extracted with ethyl acetate (2500 ml). The extract was washed with aqueous sodium hydrogen carbonate and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 1:5) to give **16** (80.0 g, 95%) as a colorless oil. $[\alpha]D^{20}$ +73.2°(c 1.05, CHCl3). IR (neat): 3400, 2950, 2860, 1660, 1615, 1520, 1460, 1420, 1305, 1250, 1180, 1105, 1030 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.70 (1H, br s, OH), 1.95-2.10 (2H, m, C4-H2), 2.38 (1H, ddd, J=17.1, 10.1, 5.9 Hz, C3-H), 2.55 (1H, ddd, J=17.1, 9.5, 7.1 Hz, C3-H), 3.50 (1H, dd, J=11.7, 3.2 Hz, C*H*2OH), 3.52-3.58 (1H,m, C5-H), 3.74 (1H,dd, J=11.7, 3.2 Hz, C*H*2OH), 3.79 (3H, s, ArO*Me*), 4.25 (1H, d, J=14.9 Hz, NC*H*2Ar), 4.70 (1H, d, J=14.9 Hz, NC*H*2Ar), 6.85 (2H, d, J=8.6 Hz, aromatic protons), 7.21 (2H, d, J=8.6 Hz, aromatic protons). EIMS m/z: 235 (M^+), 204 [(M-CH2OH)$^+$], 121, 78. HRMS calcd for C13H17NO3 (M^+): 235.1207. Found: 235.1195.

b) Preparation of *ent*-**16**: The same treatments of *ent*-**15** (100g, 0.36 mol) as described for the preparation of **16** from **15** gave *ent*-**16** (78.1 g, 92%) as a colorless oil. $[\alpha]D^{20}$ -71.9°(c 1.06, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **15**.

(*S*)-5-Benzyloxymethyl-1-(4-methoxybenzyl)-2-pyrrolidinone (17) and Its Enantiomer (*ent*-17)

a) Preparation of **17**: Sodium hydride (60% dispersion in mineral oil, 26.0 g, 0.65 mol) was added in small portions to a stirred solution of **16** (127 g, 0.54 mol) in dry *N,N*-dimethylformamide (500 ml) at 0°C. After 30 min, benzyl bromide (77.0 ml, 0.65 mol) was added slowly, and stirring was continued for 1 h at room temperature under argon. The reaction was quenched with saturated aqueous ammonium chloride (50 ml), and the mixture was diluted with ethyl acetate (1500 ml). The organic layer was washed with water and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 4:1→ 1:1) to give **17** (169 g, 96%) as a colorless oil. $[\alpha]D^{20}$ +40.0°(c 1.01, CHCl3). IR (neat): 3475, 2925, 2860, 1730, 1680, 1610, 1590, 1505, 1450, 1410, 1360, 1300, 1240, 1205, 1170, 1105, 1030

cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.82-1.91 (1H, m, C4-H), 1.98-2.10 (1H, m, C4-H), 2.36 (1H, ddd, J=16.9, 10.0, 5.2 Hz, C3-H), 2.49-2.60 (1H, m, C3-H), 3.41 (1H, dd, J=9.9, 4.5 Hz, C*H*2OBn), 3.46 (1H, dd, J=9.9, 3.9 Hz, C*H*2OBn), 3.57-3.64 (1H, m, C5-H), 3.78 (3H, s, ArO*Me*), 4.01 (1H, d, J=14.8 Hz, NC*H*2Ar), 4.41 (1H, d, J=12.0 Hz, OC*H*2Ph), 4.46 (1H, d, J=12.0 Hz, OC*H*2Ph), 4.85 (1H, d, J=14.8 Hz, NC*H*2Ar), 6.81 (2H, d, J=8.7 Hz, aromatic protons), 7.12 (2H, d, J=8.7 Hz, aromatic protons), 7.25-7.39 (5H, m, aromatic protons). EIMS m/z: 325 (M^+), 204 [(M-CH2OBn)$^+$], 121, 91. HRMS calcd for C20H23NO3 (M^+): 325.1675. Found: 325.1654.

b) Preparation of *ent*-**17**: The same treatments of *ent*-**16** (115 g, 0.49 mol) as described for the preparation of **17** from **16** gave *ent*-**17** (149 g, 94%) as a colorless oil. [α]D^{20} -40.7°(c 0.86, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **17**.

(*S*)-5-Benzyloxymethyl-2-pyrrolidinone (18) and Its Enantiomer (*ent*-18)

a) Preparation of **18**: Ammonium cerium (IV) nitrate (CAN) (700 g, 1.3 mol) was added in small portions to a stirred solution of **17** (83.5 g, 0.26 mol) in acetonitrile-water (10:1) (1600 ml) at room temperature. After 2 h, the mixture was diluted with ethyl acetate (2300 ml), and the organic layer was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (ethyl acetate-methanol, 15:1) to give **18** (43.7 g, 83%) as a pale yellow oil. [α]D^{20} +62.1°(c 1.01, CHCl3). IR (neat): 3225, 2900, 1700, 1505, 1460, 1420, 1390, 1320, 1260, 1215, 1120 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.69-1.79 (1H, m, C4-H), 2.15-2.25 (1H, m, C4-H), 2.29-2.39 (2H, m, C3-H2), 3.32 (1H, dd, J=9.2, 8.2 Hz, C*H*2OBn), 3.49 (1H, dd, J=9.2, 3.9 Hz, C*H*2OBn), 3.83-3.91 (1H, m, C5-H), 4.53 (2H, s, OC*H*2Ph), 6.05 (1H, br s, NH), 7.27-7.39 (5H, m, aromatic protons). EIMS m/z: 206 [(M+H)$^+$], 205 (M^+), 114 [(M-Bn)$^+$], 84 [(M-CH2OBn)$^+$]. HRMS calcd for C12H15NO2 (M^+): 205.1102. Found: 205.1106.

b) Preparation of *ent*-**18**: The same treatments of *ent*-**17** (80.0 g, 0.25 mol) as described for the preparation of **18** from **17** gave *ent*-**18** (45.5 g, 86%) as a colorless oil. [α]D^{20} -58.8°(c 0.91, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **18**.

(*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonyl-2-pyrrolidinone (19) and Its Enantiomer (*ent*-19)

a) Preparation of **19**: Di-*tert*-butyl dicarbonate (107 g, 0.49 mol) was added to a stirred solution of **18** (50 g, 0.24 mol) in triethylamine-acetonitrile (3:1) (800 ml) containing 4-dimethylaminopyridine (2.98 g, 25 mmol) at room temperature. After 3 h, the mixture was diluted with ethyl acetate (2500 ml). The organic layer was washed successively with 3% aqueous hydrochloric acid, saturated sodium hydrogen carbonate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1→ 3:1) to give **19** (72.9 g, 98%) as a pale yellow oil. [α]D^{20} -77.0°(c 1.00, CHCl3). IR (neat): 3000, 2950, 2900, 1790, 1750, 1715, 1485, 1450, 1370, 1350, 1310, 1290, 1250, 1150, 1110 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.49 (9H, s, ^{t}Bu), 1.99-2.17 (2H, m, C4-H2), 2.39 (1H, ddd, J=17.6, 9.5, 2.3 Hz, C3-H), 2.72 (1H, ddd, J=17.6, 11.1, 9.8 Hz, C3-H), 3.57 (1H, dd, J=9.6, 2.9 Hz, C*H*2OBn), 3.67 (1H, dd, J=9.6, 4.9 Hz, C*H*2OBn), 4.24-4.29 (1H, m, C5-H), 4.52 (2H, s, OC*H*2Ph), 7.27-7.37 (5H, m, aromatic protons). EIMS m/z: 306 [(M+H)$^+$], 205 [(M-Boc+H)$^+$], 143, 91, 84, 57. HRMS calcd for C17H24NO4 [(M+H)$^+$]: 306.1704. Found: 306.1726.

b) Preparation of *ent*-**19**: The same treatments of *ent*-**18** (65.3 g, 0.32 mol) as described for the preparation of **19** from **18** gave *ent*-**19** (93.3 g, 96%) as a colorless oil. [α]D^{20} -78.2°(c 1.02, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **19**.

(*S*)-1-*tert*-Butoxycarbonyl-5-methoxycarbonyl-2-pyrrolidinone (23) and Its Enantiomer (*ent*-23)

a) Preparation of **23**: Treatments of (*S*)-5-methoxycarbonyl-2-pyrrolidinone[9] (**22**) (100 g, 0.67 mol) in a similar manner to that described for the preparation of **19** from **18** gave **23** (170 g, 100%) as a white solid after purification by column chromatography (hexane-ethyl acetate, 1:1). Recrystallization from hexane-ethyl acetate gave an analytical sample of **23** as colorless prisms, mp 72.5-73.5 °C and [α]D^{20} -30.4°(c 1.00, CHCl3). IR (neat): 3000, 1790, 1750, 1720, 1380, 1320, 1260, 1150, 1080, 1020 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.49 (9H, s, ^{t}Bu), 1.99-2.08 (1H, m, C4-H), 2.26-2.38 (1H, m, C4-H), 2.49 (1H, ddd, J=17.5, 9.4, 3.6 Hz, C3-H), 2.58-2.69 (1H, m, C3-H), 3.79 (3H, s, CO2Me), 4.62 (1H, dd, J=9.4, 3.3 Hz, C5-H). EIMS m/z: 228 [(M-Me)$^+$], 184 [(M-CO2Me)$^+$], 142 [(M-Boc)$^+$], 84, 57. HRMS calcd for C10H14NO5 [(M-Me)$^+$]: 228.0870. Found: 228.0860. *Anal.* Calcd for C11H17NO5: C, 54.31; H, 7.04; N, 5.76%. Found: C, 54.43; H, 7.03; N, 5.71%.

b) Preparation of *ent*-**23**: The same treatments of (*R*)-5-methoxycarbonyl-2-pyrrolidinone[9] (*ent*-**22**) (92.3 g, 0.62 mol) as described for the preparation of **23** from **22** gave *ent*-**23** (141.2 g, 98%) as a white solid. Recrystallization from hexane-ethyl acetate gave an analytical sample of *ent*-**23** as colorless prisms, mp 72.0-73.5 °C and [α]D^{20} +33.8°(c 1.05, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **23**.

(5*S*)-1-*tert*-Butoxycarbonyl-5-hydroxymethyl-2-methoxypyrrolidinone (25) and Its Enantiomer (*ent*-25)

a) Preparation of **25**: Diisobutylaluminium hydride in hexane (1.0 M solution, 580 ml, 0.58 mol) was added dropwise to a stirred solution of **23** (42.5 g, 0.17 mol) in dry tetrahydrofuran (900 ml) at –78°C under argon. After 1 h, the mixture was gradually warmed up to 0°C and further stirred for 2 h. The reaction was quenched with 25% aqueous sodium hydroxide (25 ml) at 0°C, and the mixture was diluted with ethyl acetate (1000 ml). The resulting mixture was filtered through a pad of celite, and the filtrate was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave (5*S*)-1-*tert*-butoxycarbonyl-2-hydroxy-5-hydroxymethylpyrrolidines (**24**) (38.4 g), which was dissolved in methanol (450 ml). The methanolic solution of **24** was treated with a catalytic amount of pyridinium *p*-toluenesulfonate (5.50 g, 22 mmol) for 12 h at room temperature. The mixture

was diluted with ethyl acetate (1500 ml). The organic layer was washed successively with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 2:1) to give **25** (30.7 g, 76%, 2 steps) as a mixture of two diastereomers. This material was directly used for the next step without separation. In a small scale experiment, this mixture was further separated by column chromatography (ethyl acetate-hexane, 5:1→ 2:1) to give pure samples of less polar and more polar **25** in a ratio of 69: 31.

Less polar 25: colorless oil. $[\alpha]D^{20}$ -44.4°(c 1.16, CHCl3). IR (neat): 3500, 3450, 2950, 1790, 1750, 1700, 1680, 1450, 1390, 1370, 1330, 1260, 1170, 1120, 1090, 1050 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.45 (9H, br s, ^{t}Bu), 1.75 (2H, br s, C4-H2), 1.90 (1H, br dd, J=14.7, 7.8 Hz, C3-H), 2.06 (1H, br ddd, J=14.7, 10.7, 2.8 Hz, C3-H), 3.33 (3H, br s, OMe), 3.55 (1H, br dt, J=15.8, 6.1 Hz, C*H*2OH), 3.76 (1H, br d, J=10.4 Hz, C*H*2OH), 4.01-4.08 (1H, m, C5-H), 4.30 (1H, br s, OH), 5.18 (1H, br s, C2-H). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening was observed for this ^{1}H-NMR spectrum. EIMS m/z: 200 [(M-OMe)$^+$], 144 [(M-OMe-^{t}Bu)$^+$], 100 [(M-OMe-Boc+H)$^+$], 68, 57. HRMS calcd for C10H18NO3 [(M-OMe)$^+$]: 200.1285. Found: 200.1280.

More polar 25: colorless oil. $[\alpha]D^{20}$ -39.0°(c 1.18, CHCl3). IR (neat): 3450, 2990, 2950, 2900, 2850, 1700, 1680, 1480, 1450, 1390, 1370, 1330, 1310, 1250, 1170, 1120, 1080, 1010 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.50 (9H, br s, ^{t}Bu), 1.71-1.96 (3H, m, C4-H2 and C3-H), 2.16-2.29 (1H, m, C3-H), 3.34 (3H, br s, OMe), 3.52-3.77 (1H, m, C*H*2OH), 3.96 (1H, br s, C5-H), 4.08 (1H, br s, OH). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening was observed for this ^{1}H-NMR spectrum. EIMS m/z: 200 [(M-OMe)$^+$], 144 [(M-OMe-^{t}Bu)$^+$], 100 [(M-OMe-Boc+H)$^+$], 68, 57. HRMS calcd for C10H18NO3 [(M-OMe)$^+$]: 200.1285. Found: 200.1282.

b) Preparation of *ent*-**25**: The same treatments of *ent*-**23** (51.5 g, 0.21 mol) as described for the preparation of **25** from **23** gave *ent*-**25** (38.7 g, 79%, 2 steps) as a mixture of two diastereomers *via ent*-**24**. Separation of this mixture by column chromatography (ethyl acetate-hexane, 5:1→ 2:1) gave pure samples of less polar and more polar *ent*-**25** in a ratio of 69: 31.

Less polar *ent*-25: colorless oil. $[\alpha]D^{20}$ +42.4°(c 1.30, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for less polar **25**.

More polar *ent*-25: colorless oil. $[\alpha]D^{20}$ +37.5°(c 0.71, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for more polar **25**.

(5*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonyl-2-methoxypyrrolidine (21) and Its Enantiomer (*ent*-21)

a) Preparation of **21** from **19**: Diisobutylaluminium hydride in hexane (1.0 M solution, 221 ml, 0.22 mol) was added dropwise to a stirred solution of **19** (45.0 g, 0.15 mol) in dry tetrahydrofuran (550 ml) at -78°C under argon. After 1 h, the reaction was quenched with 25% aqueous sodium hydroxide (20 ml) at -78°C, and the mixture was allowed to warm up to room tempreture. The resulting mixture was diluted with ethyl acetate (1000 ml) and filtered through a pad of celite, and the filtrate was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave (5*S*)-5-benzyloxymethyl-1-*tert*-butoxycarbonyl-2-hydroxypyrrolidine (**20**) (43.9 g), which was dissolved in methanol (500 ml). The methanolic solution of **20** was treated with a catalytic amount of pyridinium *p*-toluenesulfonate (5.27 g, 21 mmol) for 3 h at room temperature. The mixture was diluted with ethyl acetate (1500 ml). The organic layer was washed successively with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 4:1) to give **21** (43.6 g, 92%, 2 steps) as a mixture of two diastereomers. This material was directly used for the next step without further separation. In a small scale experiment, this mixture was further separated by column chromatography (ethyl acetate-hexane, 10:1→ 4:1) to give pure samples of less polar and more polar **21** in a ratio of 71: 29.

Less polar 21: colorless oil. $[\alpha]D^{20}$ -51.8°(c 0.96, CHCl3). IR (neat): 2980, 2940, 1700, 1480, 1440, 1380, 1370, 1320, 1250, 1190, 1160, 1090, 1080 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.42 (1.8H, br s, ^{t}Bu), 1.45 (7.2H, br s, ^{t}Bu), 1.72-1.85 (1H, m, C4-H), 1.86-1.95 (1H, m, C4-H), 1.95-2.08 (1H, m, C3-H), 2.08-2.25 (1H, m, C3-H), 3.30 (2.3H, br s, OMe), 3.34 (0.7H, br s, OMe), 3.49-3.68 (1H, m, C*H*2OBn), 3.92-4.13 (2H, m, C*H*2OBn and C5-H), 4.51 (0.4H, br dd, J=6.0, 5.8 Hz, OC*H*2Ph), 4.55 (1.6H, br dd, J=6.0, 5.8 Hz, OC*H*2Ph), 5.22 (0.8H, br s, C2-H), 5.43 (0.2H, br s, C2-H), 7.25-7.38 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening was observed for this ^{1}H-NMR spectrum. EIMS m/z: 290 [(M-OMe)$^+$], 233 [(M-OMe-^{t}Bu)$^+$], 200 [(M-CH2OBn)$^+$], 190 [(M-OMe-Boc+H)$^+$], 144, 100, 91, 68, 57. HRMS calcd for C17H24NO3 [(M-OMe)$^+$]: 290.1754. Found: 290.1741.

More polar 21: colorless oil. $[\alpha]D^{20}$ -56.0°(c 1.13, CHCl3). IR (neat): 2990, 2950, 2880, 1700, 1480, 1450, 1380, 1370, 1330, 1250, 1170, 1120, 1080 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.41 (1.8H, br s, ^{t}Bu),1.44 (7.2H, br s, ^{t}Bu), 1.73-1.84 (1H, m, C4-H), 1.86-1.97 (1H, m, C4-H), 1.97-2.10 (1H, m, C3-H), 2.10-2.24 (1H, m, C3-H), 3.30 (2.3H, br s, OMe), 3.34 (0.7H, br s, OMe), 3.49-3.68 (1H, m, C*H*2OBn), 3.92-4.13 (2H, m, C*H*2OBn and C5-H), 4.50 (0.4H, br dd, J=6.0, 5.8 Hz, OC*H*2Ph), 4.57 (1.6H, br dd, J=6.0, 5.8 Hz, OC*H*2Ph), 5.22 (0.8H, br s, C2-H), 5.44 (0.2H, br s, C2-H), 7.25-7.38 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening was observed for this ^{1}H-NMR spectrum. EIMS m/z: 290 [(M-OMe)$^+$], 233 [(M-OMe-^{t}Bu)$^+$], 200 [(M-CH2OBn)$^+$], 190 [(M-OMe-Boc+H)$^+$], 144, 100, 91, 68, 57. CIMS (isobutane): 322 [(M+H)$^+$]. HRMS calcd for C17H24NO3 [(M-OMe)$^+$]: 290.1755. Found: 290.1763.

b) Preparation of **21** from **25**: Treatments of **25** (30.0 g, 0.13 mol) in a similar manner to that described for the preparation of **17** from **16** gave **21** (38.4 g, 92%) as a mixture of two diastereomers after purification by column chromatography (hexane-ethyl acetate, 4:1). This material was directly used for the next reaction. Further separation of this mixture by column chromatography

(ethyl acetate-hexane, 10:1→ 4:1) gave pure samples of less product and more polar **21** in a ratio of 71: 29 both as a colorless oil. The IR, ^{1}H-NMR, and mass spectra of these samples were identical with those recorded in a).

c) Preparation of *ent*-**21** from *ent*-**19**: The same treatments of *ent*-**19** (38.3 g, 0.13 mol) as described for the preparation of **21** from **19** gave *ent*-**21** (36.2 g, 90%, 2 steps) as a mixture of two diastereomers *via ent*-**20**. Separation of this mixture by column chromatography (ethyl acetate-hexane, 5:1→ 2:1) gave pure samples of less polar and more polar **21** in a ratio of 71: 29.

Less polar *ent*-21: colorless oil. $[\alpha]D^{20}$ +52.9°(c 1.02, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for less polar **21**.

More polar *ent*-21: colorless oil. $[\alpha]D^{20}$ +54.4°(c 1.03, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for more polar **21**.

d) Preparation of *ent*-**21** from *ent*-**25**: The same treatments of *ent*-**25** (32.9 g, 0.14 mol) as described for the preparation of **21** from **25** gave *ent*-**21** (43.4 g, 95%) as a mixture of two diastereomers. Separation of this mixture by column chromatography (ethyl acetate-hexane, 10:1→ 4:1) gave pure samples of less polar and more polar *ent*-**21** in a ratio of 69: 31 both as a colorless oil. The IR, ^{1}H-NMR, and mass spectra of these samples were identical with those recorded for less polar and more polar **21**, respectively.

(2*R*,5*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonyl-2-cyanopyrrolidine (27), Its (2*S*,5*S*)-Isomer (28), Its (2*S*,5*R*)-Isomer (*ent*-27), and Its (2*R*,5*R*)-Isomer (*ent*-28)

a) Preparation of **27** and **28**: Trimethylsilyl cyanide (21.8 ml, 0.16 mol) and boron trifluoride etherate (40.0 ml, 0.16 mmol) were added successively to a stirred solution of **21** (35.0 g, 0.11 mol) in dry dichloromethane (300 ml) at -78°C under argon. After 1 h, the reaction was quenched with saturated aqueous sodium bicarbonate (20 ml) at -78°C, and the mixture was allowed to warm up to room temperature. The resulting mixture was diluted with ethyl acetate (800 ml), and the organic layer was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was separated by column chromatography (hexane-ethyl acetate, 6:1) to give **27** (10.0 g, 29%) as a more polar product and **28** (22.7 g, 66%) as a less polar product.

27: colorless oil. $[\alpha]D^{20}$ +19.8°(c 1.05, CHCl3). IR (neat): 2990, 2950, 2880, 2230, 1700, 1480, 1450, 1380, 1340, 1310, 1250, 1160, 1110, 1060, 1020 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.44 (4H, br s, ^{t}Bu),1.50 (5H, br s, ^{t}Bu), 2.06 (0.4H, br s, C4-H), 2.16 (1.6H, br s, C4-H), 2.26 (0.6H, br s, C3-H), 2.35 (0.4H, br s, C3-H), 3.48 (0.8H, br s, C*H*2OBn), 3.65 (1.2H, br s, C*H*2OBn), 3.95 (0.4H, br s, C5-H), 4.07 (0.6H, br s, C5-H), 4.45 (1H, br s, C2-H), 4.53 (1H, d, J=11.9 Hz, OC*H*2Ph), 7.25-7.39 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 290 [(M-CN)$^+$], 260 [(M-^{t}Bu+H)$^+$], 215 [(M-Boc)$^+$], 190, 153, 95, 57. CIMS (isobutane): 317 [(M+H)$^+$]. HRMS calcd for C14H16N2O3 [(M-^{t}Bu+H)$^+$]: 260.1160. Found: 260.1169.

28: colorless prisms. mp 77-78 °C (ether-hexane). $[\alpha]D^{20}$ -124°(c 0.81, CHCl3). IR (neat): 2990, 2950, 2880, 2240, 2220, 1710, 1490, 1480, 1450, 1380, 1300, 1260, 1170, 1120, 1020 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.43 (4H, br s, ^{t}Bu), 1.45 (5H, br s, ^{t}Bu), 1.92-2.02 (0.4H, m, C4-H), 2.06-2.18 (1.6H, m, C4-H), 2.19-2.46 (2H, m, C3-H2), 3.33-3.68 (2H, m, C*H*2OBn), 3.98 (0.4H, br s, C5-H), 4.11 (0.6H, br dd, J=14.3, 7.1 Hz, C5-H), 4.41-4.59 (3H, m, OC*H*2Ph and C2-H), 7.25-7.38 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 290 [(M-CN)$^+$], 260 [(M-^{t}Bu)$^+$], 215 [(M-Boc)$^+$], 190, 154, 95, 57. CIMS (isobutane): 317 [(M+H)$^+$]. HRMS calcd for C17H24NO3 [(M-CN)$^+$]: 290.1755. Found: 290.1794. *Anal.* Calcd for C18H24N2O3: C, 68.33; H, 7.65; N, 8.85%. Found: C, 68.45; H, 7.72; N, 8.84%. **28** was further characterized by single-crystal X-ray diffraction analysis.[12]

b) Preparation of *ent*-**27** and *ent*-**28**: The same treatments of *ent*-**21** (29.3 g, 91 mmol) as described for the preparation of **27** and **28** from **21** gave *ent*-**27** (7.79 g, 27%) as a more polar product and *ent*-**28** (19.6 g, 68%) as a less polar product.

***ent*-27**: colorless oil. $[\alpha]D^{20}$ -19.7°(c 0.80, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **27**.

***ent*-28** : colorless prisms. mp 77.5-78 °C (ether-hexane). $[\alpha]D^{20}$ +121°(c 0.98, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **28**.

(2*R*,5*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonyl-2-formylpyrrolidine (30) and Its Enantiomer (*ent*-30)

a) Preparation of **30**: Diisobutylaluminium hydride in toluene (1.0 M solution, 104 ml, 0.10 mol) was added dropwise to a stirred solution of **28** (22.0 g, 69 mmol) in dry toluene (540 ml) at -78°C under argon. After 1 h, the mixture was quenched with 25% aqueous sodium hydroxide (30 ml) at -78°C, and the mixture was gradually warmed up to room temperature. The resulting mixture was diluted with ethyl acetate (600 ml) and filtered through a pad of celite. The filtrate was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 5:1) to give **30** (14.0 g, 63%) as a colorless oil. $[\alpha]D^{20}$ -91.8°(c 1.58, CHCl3). IR (neat): 2950, 2850, 1740, 1710, 1590, 1480, 1460, 1380, 1370, 1250, 1210, 1170, 1110, 1030 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.41 (4.5H, br s, ^{t}Bu),1.42 (4.5H, br s, ^{t}Bu), 1.85-2.05 (3H, m, C4-H2 and C3-H), 2.11-2.23 (0.5H, m, C3-H), 2.23-2.35 (0.5H, m, C3-H), 3.46 (0.5H, br dd, J=9.2, 7.1 Hz, C*H*2OBn), 3.56 (0.5H, br dd, J=9.2, 3.1 Hz, C*H*2OBn), 3.58-3.66 (1H, m, C*H*2OBn), 4.07 (0.5H, br td, J=7.1, 3.0 Hz, C2-H or C5-H), 4.16 (0.5H, br dt, J=9.7, 1.6 Hz, C2-H or C5-H), 4.17-4.25 (0.5H, m, C2-H or C5-H), 4.29 (0.5H, br dt, J=9.7, 1.6 Hz, C2-H or C5-H), 4.50 (1H, d, J=12.0 Hz, OC*H*2Ph), 4.54 (1H, d, J=12.0 Hz, OC*H*2Ph), 7.24-7.38 (5H, m, aromatic protons), 9.53 (0.5H, d, J=1.9 Hz, CHO), 9.58 (0.5H, d, J=1.9 Hz, CHO). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR

spectrum. EIMS m/z: 320 [(M+H)$^+$], 290 [(M-CHO)$^+$], 190 [(M-CHO-Boc+H)$^+$], 142, 91, 57. HRMS calcd for C17H24NO3 [(M-CHO)$^+$]: 290.1754. Found: 290.1762.

b) Preparation of *ent*-**30**: The same treatments of *ent*-**28** (19.3 g, 61 mmol) as described for the preparation of **30** from **28** gave *ent*-**30** (11.9 g, 62%) as a colorless oil. [α]D^{20} +91.5°(c 0.75, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **30**.

(2*S*,5*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonyl-2-hydroxymethylpyrrolidine (31), Its (2*R*,5*S*)-Isomer (32), Its (2*R*,5*R*)-Isomer (*ent*-31), and Its (2S,5*R*)-Isomer (*ent*-32)

a) Preparation of **31** and **32**: A solution of **30** (13.5 g, 42 mmol) in methanol (680 ml) containing potassium carbonate (29.2 g, 0.21 mol) was heated at reflux for 2 h. After cooling, sodium borohydride (1.60 g, 42 mmol) was added in small portions to the above mixture, and stirring was continued for 30 min at room temperature. The resulting mixture was neutralized with 3% aqueous hydrochloric acid and extracted with ethyl acetate (950 ml). The extract was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which were separated by column chromatography (hexane-ethyl acetate, 5:1→ 1:1) to give **32** (10.3 g, 76%) as a less polar product and **31** (2.85 g, 21%) as a more polar product.

31: colorless oil. [α]D^{20} -54.9°(c 1.10, CHCl3). IR (neat): 3450, 2990, 2950, 2890, 1740, 1690, 1670, 1480, 1450, 1400, 1370, 1340, 1310, 1250, 1170, 1110, 1050 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.41 (6H, br s, ^{t}Bu), 1.47 (3H, br s, ^{t}Bu), 1.55-1.86 (2H, m, C3-H2 or C4-H2), 1.91-2.18 (2H, m, C3-H2 or C4-H2), 3.36 (1H, br t, J=11.1 Hz, C*H*2OBn), 3.46-3.64 (2H, m, C*H*2OH), 3.70 (1H, br dd, J=11.1, 7.2 Hz, C*H*2OBn), 3.90-4.08 (2H, m, C2-H and C5-H), 4.24 (1H, br s, OH), 4.51 (2H, br s, OC*H*2Ph), 7.26-7.38 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 322 [(M+H)$^+$], 290 [(M-CH2OH)$^+$], 264 [(M-^{t}Bu)$^+$], 190[(M+H-CH2OH-Boc)$^+$], 144, 100, 91, 57. HRMS calcd for C17H24NO3 [(M-CH2OH)$^+$]: 290.1754. Found: 290.1759.

32: colorless oil. [α]D^{20} -30.3°(c 1.10, CHCl3). IR (neat): 3450, 3000, 2950, 2890, 1740, 1690, 1670, 1480, 1450, 1400, 1370, 1340, 1300, 1250, 1170, 1110, 1050, 1030 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.43 (9H, br s, ^{t}Bu), 1.78 (3H, br s, C3-H or C4-H), 1.84-2.17 (3H, m, C3-H2 and/or C4-H2), 3.42-3.56 (3H, m, C*H*2OBn and OH), 3.78 (1H, br s, C2-H or C5-H), 3.91-4.05 (2H, m, C*H*2OH), 4.51 (1H, br d, J=12.4 Hz, OC*H*2Ph), 4.58 (1H, br d, J=12.4 Hz, OC*H*2Ph), 4.71 (1H, br s, C2-H or C5-H), 7.26-7.39 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 322 [(M+H)$^+$], 290 [(M-CH2OH)$^+$], 265 [(M-^{t}Bu+H)$^+$], 220 [(M-Boc)$^+$], 190 [(M+H-CH2OH-Boc)$^+$], 144, 100, 91, 57. HRMS calcd for C17H24NO3 [(M-CH2OH)$^+$]: 290.1754. Found: 290.1754.

b) Preparation of *ent*-**31** and *ent*-**32**: The same treatments of *ent*-**30** (11.7 g, 37 mmol) as described for the preparation of **31** and **32** from **30** gave *ent*-**32** (8.33 g, 73%) as a less polar product and *ent*-**31** (2.59 g, 22%) as a more polar product.

ent-**31**: colorless oil. [α]D^{20} +54.4°(c 1.30, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **31**.

ent-**32**: colorless oil. [α]D^{20} +30.0°(c 1.28, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **32**.

(2*R*,5*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonyl-2-formylpyrrolidine (29) and Its Enatiomer (*ent*-29)

a) Preparation of **29** from **27**: Treatments of **27** (9.50 g, 30 mmol) under the same conditions as described for the preparation of **30** from **28** gave **29** (6.33 g, 66%) as a colorless oil after purification by column chromatography (hexane-ethyl acetate, 5:1). [α]D^{20} -10.4°(c 1.27, CHCl3). IR (neat): 3000, 2950, 2890, 1740, 1700, 1480, 1450, 1390, 1370, 1310, 1290, 1250, 1170, 1100, 1070, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.40 (4.5H, br s, ^{t}Bu),1.42 (4.5H, br s, ^{t}Bu), 1.83 (1H, br dd, J=12.7, 7.6 Hz, C3-H), 1.89-2.15 (3H, m, C4-H2 and C3-H), 3.40-3.56 (1H, m, C*H*2OBn), 3.56-3.67 (1H, m, C*H*2OBn), 3.81-4.22 (2H, m, C2-H and C5-H), 4.43-4.56 (2H, m, OC*H*2Ph), 7.24-7.38 (5H, m, aromatic protons), 9.33 (0.5H, br s, CHO), 9.45 (0.5H, br s, CHO). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 320 [(M+H)$^+$], 290 [(M-CHO)$^+$], 220[(M-Boc)$^+$], 190 [(M-CHO-Boc+H)$^+$], 149, 91, 57. HRMS calcd for C17H24NO3 [(M-CHO)$^+$]: 290.1754. Found: 290.1748.

b) Preparation of **29** from **32**: Dimethyl sulfoxide (22.3 ml, 0.31 mol) in dry dichloromethane (20 ml) was added dropwise to a stirred solution of oxalyl chloride (13.7 ml, 0.16 mol) in dry dichloromethane (100 ml) at -78°C under argon. After 10 min, a solution of **32** (10.1 g, 31 mmol) in dry dichloromethane (20 ml) was added slowly, and stirring was continued for 15 min at -78°C. After addition of triethylamine (43.8 ml, 0.31 mol), the mixture was gradually warmed up to -25°C and further stirred for 30 min. The mixture was diluted with water (15 ml) and extracted with ethyl acetate (350 ml). The extract was washed successively with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1→ 3:1) to give **29** (9.74 g, 97%) as a colorless oil. [α]D^{20} -9.9°(c 1.21, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this material were identical with those recorded in a).

c) Preparation of *ent*-**29** from *ent*-**27**: The same treatments of *ent*-**27** (7.73 g, 24 mmol) as described for the preparation of **30** from **27** gave *ent*-**29** (5.07 g, 65%) as a colorless oil. [α]D^{20} +9.7°(c 1.20, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **29**.

d) Preparation of *ent*-**29** from *ent*-**32**: The same treatments of *ent*-**32** (8.28 g, 26 mmol) as described for the preparation of **29** from **32** gave *ent*-**29** (8.15 g, 99%) as a colorless oil. $[\alpha]D^{20}$ +9.5°(c 0.97, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **29**.

[(2*R*,5*S*)-1-Benzyl-5-benzyloxymethylpyrroridin-2-yl]methyl (*R*)-α-methoxy-α-(trifluoromethyl) phenylacetate [(*R*)-MTPA Ester of 34] (35a) and [(2*R*,5*S*)-1-Benzyl-5-benzyloxymethylpyrroridin-2-yl]methyl (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetate [(*S*)-MTPA Ester of 34] (35b)

a) Preparation of **35a**: Sodium borohydride (16.6 mg, 0.44 mmol) was added to a stirred solution of **29** (127mg, 0.40mmol) in methanol (4 ml) at room temperature. After 10 min, the mixture was diluted with ethyl acetate (60ml). The organic layer was washed with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave (2*R*,5*S*)-5-benzyloxymethyl-1-*tert*-butoxycarbonyl-2-hydroxymethylpyrrolidine (125mg), which was dissolved in dichloromethane (4 ml). The dichloromethane solution was treated with bromotrimethylsilane (0.525ml, 2.0mmol) for 2 h at room temperature. The mixture was concentrated *in vacuo* to give (2*R*,5*S*)-5-benzyloxymethyl-2-hydroxymethylpyrrolidine (**33**) (83mg). Benzyl bromide (0.947ml, 8.0mmol) was added to a stirred suspension of crude **33** (83.7mg) in dichloromethane (3 ml) covered with saturated aqueous sodium hydrogen carbonate (2 ml) at room temperature. After 20 h, the mixture was diluted with ethyl acetate (60ml). The organic layer was washed with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1→ 2:1) to give (2*R*,5*S*)-1-benzyl-5-benzyloxymethyl-2-hydroxymethylpyrrolidine (**34**) (110 mg, 89%, 3 steps) as a colorless oil. (*R*)-α-Methoxy-α-(trifluoromethyl) phenylacetyl chloride [(*R*)-MTPACl] (34.0 μl, 0.18 mmol) was added to a stirred solution of **34** (47 mg, 0.15 mmol) in pyridine (0.5 ml) at room temperature. After 15 min, the mixture was diluted with ethyl acetate (40ml) and the organic layer was washed with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 2:1) to give **35a** (73.0mg, 92%) as a colorless oil. ^{1}H-NMR (400 MHz, C6D6): δ 1.41-1.51 (1H, m, C4-H), 1.51-1.60 (1H, m, C4-H), 1.68-1.79 (1H, m, C3-H), 1.88-1.97 (1H, m, C3-H), 3.07 (1H, dd, J=9.3, 3.5 Hz, C*H*2OBn), 3.08-3.17 (2H, m, C2-H and C5-H), 3.26 (1H, dd, J=9.3, 3.5 Hz, C*H*2OBn), 3.42 (3H, d, J=1.1 Hz, OMe), 3.63 (1H, d, J=14.2 Hz, NC*H*2Ph), 3.85 (1H, d, J=14.2 Hz, NC*H*2Ph), 3.98 (1H, dd, J=11.1, 3.5 Hz, C*H*2OMTPA), 4.15 (1H, dd, J=11.1, 5.4 Hz, C*H*2OMTPA), 4.19 (2H, s, OC*H*2Ph), 7.10-7.30 (13H, m, aromatic protons), 7.70-7.75 (2H, m, aromatic protons).

b) Preparation of **35b**: **34** (63.0 mg, 0.20 mmol) was acylated with (*S*)-α-methoxy-α-(trifluoromethyl) phenylacetyl chloride [(*S*)-MTPACl] in the same manner as described for the preparation of **35a** from **34** gave **35b** (100 mg, 94%) as a colorless oil. ^{1}H-NMR (400 MHz, C6D6): δ 1.40-1.50 (1H, m, C4-H), 1.52-1.58 (1H, m, C4-H), 1.72-1.80 (1H, m, C3-H), 1.88-1.95 (1H, m, C3-H), 3.04 (1H, dd, J=9.3, 3.5 Hz, C*H*2OBn), 3.12-3.18 (2H, m, C2-H and C5-H), 3.22 (1H, dd, J=9.3, 3.5 Hz, C*H*2OBn), 3.37 (3H, d, J=1.1 Hz, OMe), 3.58 (1H, d, J=14.2 Hz, NC*H*2Ph), 3.84 (1H, d, J=14.2 Hz, NC*H*2Ph), 3.96 (1H, dd, J=11.1, 3.5 Hz, C*H*2OMTPA), 4.16 (1H, dd, J=11.1, 5.4 Hz, C*H*2OMTPA), 4.18 (2H, s, OC*H*2Ph), 7.05-7.27 (13H, m, aromatic protons), 7.65-7.70 (2H, m, aromatic protons).

Comparision of the ^{1}H-NMR spectra of **35a** and **35b** obviously disclosed that the optical purity of **29** is more than 95% ee.

(*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonyl-3-*N*,*N*-dimethylaminomethylidene-2-pyrrolidinone (36) and Its Enantiomer (*ent*-36)

a) Preparation of **36**: A stirred solution of **19** (24.0 g, 79 mmol) in *tert*-butoxybis(dimethylamino)methane[14] (Bredereck reagent) (54.8 ml, 0.31 mol) was heated at 75°C for 3 h under argon. After cooling, the mixture was diluted with ethyl acetate (300 ml), and the organic layer was washed with water and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave **36** (26.8 g, 99%) as an orange-yellow oil. This material was immediately used for the next reaction without further purification to avoid decomposition. IR (neat): 2970, 2920, 2855, 1760, 1695, 1615, 1450, 1365, 1335, 1270, 1250, 1205, 1155, 1120 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl3): δ 1.49 (9H, s, ^{t}Bu), 2.62-3.20 (2H, m, C4-H2), 3.03 (6H, s, NMe2), 3.22-3.86 (2H, m,C*H*2OBn), 4.02-4.47 (1H, m, C5-H), 4.57 (2H, s, OC*H*2Ph), 7.16 (1H, dd, J=3.8, 1.8 Hz, C*H*NMe2), 7.34 (5H, s, aromatic protons). EIMS m/z: 360 (M^+), 260 [(M-C4H8)$^+$], 259 [(M-Boc)$^+$], 216, 139, 91, 57. HRMS calcd for C20H28N2O4 (M^+): 360.2047. Found: 360.2052.

b) Preparation of *ent*-**36**: The same treatments of *ent*-**19** (36.0 g, 0.12 mol) as described for the preparation of **36** from **19** gave *ent*-**36** (27.5 g, 97%) as an orange-yellow oil. This material was immediately used for the next reaction without further purification to avoid decomposition. The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **36** .

(*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonyl-3-hydroxymethylidene-2-pyrrolidinone (37) and Its (*R*)-Enantiomer (*ent*-37)

a) Preparation of **37**: 1M Hydrochloric acid (90.0 ml, 90 mmol) was added dropwise to a stirred solution of **36** (26.2 g, 76 mmol) in tetrahydrofuran (300 ml) at room temperature. After 1 h, the mixture was neutralized with saturated aqueous sodium hydrogen carbonate and diluted with ethyl acetate (800 ml). The organic layer was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 3:1) to give **37** (25.4 g, 89%) as a pale yellow caramel. $[\alpha]D^{20}$ -50.8°(c 1.20, CHCl3). IR (neat): 3320, 2975, 2930, 2860, 1775, 1720, 1685, 1450, 1365, 1300, 1250, 1250, 1145, 1005 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl3): δ 1.48 (9H, br s, ^{t}Bu), 2.02-2.96 (2H, m, C4-H2), 3.17-3.92 (3H, m, C*H*2OBn and OH), 4.03-4.40 (1H, m, 5-H), 4.40-4.62 (2H, m, OC*H*2Ph), 7.31 (5H, s, aromatic

protons), 9.44-9.76 (1H, m, CH=C*H*OH). EIMS m/z: 277 [(M-C4H8)$^+$], 233 [(M-Boc+H)$^+$], 205, 142, 127, 112, 91, 57. CIMS (isobutane) m/z: 334 [(M+H)$^+$]. HRMS calcd for C14H15NO5 [(M-C4H8)$^+$]: 277.0948. Found: 277.0948.

b) Preparation of *ent*-**37**: The same treatments of *ent*-**36** (27.2 g, 75 mmol) as described for the preparation of **37** from **36** gave *ent*-**37** (21.4 g, 85%) as a pale yellow caramel. [α]D^{20} +51.1°(c 1.28, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **37**.

(*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonyl-3-hydroxymethyl-2-pyrrolidinone (39) and Its Enantiomer (*ent*-39)

a) Preparation of **39**: Sodium cyanoborohydride (14.3 g, 0.23 mol) was added in small portions to a stirred solution of **37** (25.2 g, 76 mmol) in tetrahydrofuran-ethanol-acetic acid (5:1:1) (350 ml) at -10°C. After 2 h, the mixture was neutralized with saturated aqueous sodium hydrogen carbonate and diluted with ethyl acetate (650 ml). The organic layer was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 2:1→ 1:1) to give **39** (20.5 g, 81%) as a mixture of two diastereomers as a colorless oil. IR (neat): 3410, 2970, 2925, 2855, 1775, 1705, 1450, 1365, 1305, 1275, 1255, 1150, 1100 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.49 (9H, s, ^{t}Bu), 1.86 (0.2H, ddd, J=12.5, 7.2, 5.3 Hz, C4-H), 2.01 (0.8H, dt, J=12.7, 9.0 Hz, C4-H), 2.11 (0.8H, ddd, J=12.7, 9.0, 2.9 Hz, C4-H), 2,31 (0.2H, ddd, J=12.5, 11.2, 9.1 Hz, C4-H), 2.72-3.05 (2H, m, C3-H and OH), 3.57 (0.8H, dd, J=9.7, 2.8 Hz, C*H*2OBn), 3.60 (0.2H, dd, J=9.5, 2.7 Hz, C*H*2OBn), 3.69 (0.8H, dd, J=9.7, 4.8 Hz, C*H*2OBn), 3.71 (0.8H, dd, J=11.3, 6.5 Hz, C*H*2OH), 3.74 (0.2H, dd, J=9.5, 5.0 Hz, C*H*2OBn), 3.82 (0.2H, br s, C*H*2OH), 3.84 (0.2H, br s, C*H*2OH), 3.89 (1H, dd, J=11.3, 4.5 Hz, C*H*2OH), 4.18-4.27 (1H, m, C5-H), 4.52 (2H, s, OC*H*2Ph), 7.25-7.38 (5H, m, aromatic protons). Based on the intensity of signals, the ratio of epimers was caluculated as 4:1. EIMS m/z: 235 [(M-Boc+H)$^+$], 234 [(M-Boc)$^+$], 188, 173, 144, 129, 114, 91, 57. CIMS (isobutane) m/z: 336 (M+H). HRMS calcd for C13H17NO3 [(M-Boc+H)$^+$]: 235.1207. Found: 235.1217. Since separation of this epimeric mixture was found to be very difficult, it was directly subjected to the next reaction.

b) Preparation of *ent*-**39**: The same treatments of *ent*-**37** (21.2 g, 64 mmol) as described for the preparation of **39** from **37** gave *ent*-**39** (17.7 g, 83%) as an inseparable mixture of two diastereomers as a colorless oil, which was directly used for the next step. The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **39**.

(3*S*,5*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonyl-3-methoxymethoxymethyl-2-pyrrolidinone (40), Its (3*R*,5*S*)-Isomer (41), and (3*R*,5*R*)-Isomer (*ent*-40), and Its (3*S*,5*R*)-Isomer (*ent*-41)

a) Preparation of **40** and **41**: Chloromethyl methyl ether (24.0 ml, 0.32 mol) was added to a stirred solution of **39** (20.3 g, 61 mmol) in dry dichloromethane (520 ml) containing *N*,*N*-diisopropylethylamine (75.4 ml, 0.43 mol) at room temperature under argon. After 12 h, the mixture was diluted with dichloromethane (500 ml). The organic layer was washed successively with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was separated by column chromatography (hexane-ethyl acetate, 10:1→ 4:1) to give **40** (23.5 g, 82%) as a less polar product and **41** (3.20 g, 11%) as a more polar product.

40: colorless oil. [α]D^{20} -42.4° (c 0.93, CHCl3). IR (neat): 2975, 2930, 2880, 1780, 1745, 1710, 1450, 1365, 1305, 1275, 1250, 1150, 1110, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.48 (9H, s, ^{t}Bu), 2.14-2.18 (1H, m, C4-H), 2.18-2.24 (1H, m, C4-H), 2.98-3.08 (1H, m, C3-H), 3.35 (3H, s, OMe), 3.58 (1H, dd, J=9.6, 2.8 Hz, C*H*2OBn), 3.68 (1H, dd, J=9.6, 4.5 Hz, C*H*2OBn), 3.72 (1H, dd, J=9.8, 3.6 Hz, C*H*2OMOM), 3.82 (1H, dd, J=9.8, 3.6 Hz, C*H*2OMOM), 4.21-4.27 (1H, m, C5-H), 4.51 (2H, s, OC*H*2Ph), 4.60 (1H, d, J=6.5 Hz, OC*H*2OMe), 4.62 (1H, d, J=6.5 Hz, OC*H*2OMe), 7.26-7.37 (5H, m, aromatic protons). EIMS m/z: 279 [(M-Boc+H)$^+$], 248 [(M-Boc-OMe+H)$^+$]. CIMS (isobutane) m/z: 380 (M+H). HRMS calcd for C15H21NO4 [(M-Boc+H)$^+$]: 279.1468. Found: 279.1467.

41: colorless oil. [α]D^{20} -45.9° (c 1.02, CHCl3). IR (neat): 2975, 2930, 2880, 1780, 1745, 1710, 1450, 1365, 1305, 1275, 1250, 1150, 1110, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.48 (9H, s, ^{t}Bu), 2.14-2.18 (1H, m, C4-H), 2.18-2.24 (1H, m, C4-H), 2.98-3.08 (1H, m, C3-H), 3.35 (3H, s, OMe), 3.58 (1H, dd, J=9.6, 2.8 Hz, C*H*2OBn), 3.68 (1H, dd, J=9.6, 4.5 Hz, C*H*2OBn), 3.72 (1H, dd, J=9.8, 3.6 Hz, C*H*2OMOM), 3.82 (1H, dd, J=9.8, 3.6 Hz, C*H*2OMOM), 4.21-4.27 (1H, m, C5-H), 4.51 (2H, s, OC*H*2Ph), 4.60 (1H, d, J=6.5 Hz, OC*H*2OMe), 4.62 (1H, d, J=6.5 Hz, OC*H*2OMe), 7.26-7.37 (5H, m, aromatic protons). EIMS m/z: 279 [(M-Boc+H)$^+$], 248 [(M-Boc-OMe+H)$^+$], 234, 173, 126, 91, 57. CIMS (isobutane) m/z: 380 (M+H). HRMS calcd for C15H21NO4 [(M-Boc+H)$^+$]: 279.1469. Found: 279.1481.

b) Preparation of *ent*-**40** and *ent*-**41**: The same treatments of *ent*-**39** (17.5 g, 52 mmol) as described for the preparation of **40** and **41** from **39** gave *ent*-**40** (16.6 g, 84%) as a less polar product and *ent*-**41** (2.77 g, 14%) as a more polar product.

ent-**40**: colorless oil. [α]D^{20} +39.8° (c 0.63, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **40**.

ent-**41**: colorless oil. [α]D^{20} +43.9° (c 1.02, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **41**.

Epimerization of 41 to 40 and that of *ent*-41 to *ent*-40

A solution of **41** (3.11 g, 8.2 mmol) in dry benzene (10 ml) containing 1,8-diazabicyclo-[5,4,0]undec-7-ene (DBU) (6.80 ml, 45 mmol) was heated at reflux for 20 h. After cooling, the mixture was diluted with ethyl acetate (50 ml). The organic layer was washed successively with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was separated by column chromatography (hexane-ethyl

acetate, 7:1→ 4:1) to give less polar **40** (2.57 g, 83%) and more polar **41** (0.53 g, 17%) both as a colorless oil. The IR, ^{1}H-NMR, and mass spectra of these materials were identical with those described for authentic **40** and **41**, respectively.

Treatments of *ent*-**41** (2.76g, 7.3 mmol) under the same conditions as described for the epimerization of **41** to **40** gave less polar *ent*-**40** (2.26 g, 82%) and more polar *ent*-**41** (0.47 g, 17%) both as a colorless oil. The IR, ^{1}H-NMR, and mass spectra of these materials were identical with those recorded for authentic **40** and **41**, respectively.

(3*S*,5*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonyl-2-methoxy-3-methoxymethoxymethylpyrrolidine (43) and Its Enantiomer (*ent*-43)

a) Preparation of **43**: Treatments of **40** (22.5 g, 59 mmol) in a similar manner to that described for the preparation of **21** from **19** gave **43** (21.6 g, 92%, 2 steps) as a mixture of two diastereomers *via* (3*S*,5*S*)-5-benzyloxymethyl-1-*tert*-butoxycarbonyl-2-hydroxy-3-methoxymethoxymethylpyrrolidine (**42**) after purification by column chromatography (hexane-ethyl acetate, 9:1). This material was directly used for the next reaction without further separation.

42: colorless oil. IR (neat): 3450, 2970, 2925, 2880, 1690, 1475, 1450, 1385, 1365, 1305, 1255, 1185, 1150, 1105, 1040 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl3): δ 1.45 (9H, s, ^{t}Bu), 1.60-2.32 (2H, m, C4-H2), 2.32-2.68 (1H, m, C3-H), 3.38 (3H, s, OMe), 3.39-3.83 (5H, m, C*H*2OBn, C*H*2OMOM, and OH), 3.83-4.28 (1H, m, C5-H), 4.59 (2H, s, OC*H*2Ph), 4.63 (2H, s, OC*H*2OMe), 4.31 (1H, br s, C2-H), 7.32 (5H, s, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening was observed for this ^{1}H-NMR spectrum. EIMS m/z: 363 [(M-H2O)$^+$], 263 [(M-H2O-Boc+H)$^+$], 202, 160, 91, 57. HRMS calcd for C20H29NO5 [(M-H2O)$^+$]: 363.2043. Found: 363.2041.

43: colorless oil. IR (neat): 2970, 2930, 2880, 1700, 1495, 1475, 1450, 1385, 1370, 1335, 1305, 1255, 1170, 1110, 1085, 1045 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.45 (9H, br s, ^{t}Bu), 1.76-2.04 (2H, m, C4-H), 2.15 (1H, br dt, J=13.2, 7.6Hz, C4-H), 2.44 (1H, br ddd, J=15.2, 7.6, 1.9 Hz, C3-H), 3.25-3.90 (4H, m, C*H*2OBn and C*H*2OMOM), 3.35 (3H, s, MOM), 3.36 (1.3H, s, C2-OMe), 3.48 (1.7H, s, C2-OMe), 3.92-4.19 (1H, m, C5-H), 4.51-4.64 (4H, m, OC*H*2OMe and OC*H*2Ph), 5.15 (1H, br s, C2-H), 7.28-7.35 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 364 [(M-OMe)$^+$], 264 [(M-OMe-Boc+H)$^+$], 218, 202, 174, 142, 91, 57. HRMS calcd for C20H30NO5 [(M-OMe)$^+$]: 364.2122. Found: 364.2109.

b) Preparation of *ent*-**43**: The same treatments of *ent*-**40** (18.6 g, 49 mmol) as described for the preparation of **43** from **40** gave *ent*-**43** (16.9 g, 87%, 2 steps) as a mixture of two diastereomers *via ent*-**42**.

ent-**42**: colorless oil. The IR, ^{1}H-NMR, and mass spectra of this material were identical with those recorded for **42**.

ent-**43**: colorless oil. The IR, ^{1}H-NMR, and mass spectra of this material were identical with those recorded for **43**.

(2*R*,3*R*,5*S*)-5-Benzyloxymethyl-2-cyano-1-*tert*-butoxycarbonyl-3-methoxymethoxymethylpyrrolidine (45), Its (2*S*, 3*R*, 5*S*)-Isomer (46), Its (2*S*, 3*S*,5*R*)-Isomer (*ent*-45), and Its (2*R*,3*S*,5*R*)-Isomer (*ent*-46)

a) Preparation of **45** and **46**: Treatments of **43** (21.2 g, 54 mmol) in a similar manner to that described for the preparation of **27** and **28** from **21** gave **45** (5.44 g, 26%) as a more polar product and **46** (14.4 g, 69%) as a less polar product after separation by column chromatography (hexane-ethyl acetate, 9:1→ 4:1).

45: colorless oil. [α]D^{20} +2.0° (c 2.08, CHCl3). IR (neat): 2980, 2930, 2880, 2230, 1700, 1475, 1450, 1380, 1370, 1300, 1255, 1165, 1150, 1110, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.43 (2.7H, br s, ^{t}Bu), 1.51 (6.3H, s, ^{t}Bu), 1.94 (1H, br s, C4-H), 2.14 (1H, br s, C4-H), 3.04 (1H, br s, C3-H), 3.36 (3H, s, OMe), 3.48 (1H, br t, J=6.7 Hz, C*H*2OBn), 3.55-3.68 (3H, m, C*H*2OBn and C*H*2OMOM), 4.02 (0.3H, br s, C5-H), 4.12 (0.7H, br s, C5-H), 4.33 (0.7H, br s, C2-H), 4.48 (0.3H, br s, C2-H), 4.57 (1H, d, J=12.2 Hz, OC*H*2Ph), 4.57 (1H, d, J=12.2 Hz, OC*H*2Ph), 4.61 (1H, d, J=7.7 Hz, OC*H*2OMe), 4.67 (1H, d, J=7.7 Hz, OC*H*2OMe), 7.27-7.38 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 334 [(M-C4H8)$^+$], 289 [(M-Boc)$^+$], 263 [(M-Boc-CN)$^+$], 169, 137, 91, 57. CIMS (isobutane) m/z: 391 (M+H). HRMS calcd for C17H22N2O5 [(M-C4H8)$^+$]: 334.1527. Found: 334.1545.

46: colorless oil. [α]D^{20} -70.1° (c 1.07, CHCl3). IR (neat): 2970, 2930, 2875, 2230, 1700, 1475, 1450, 1375, 1330, 1300, 1275, 1265, 1250, 1165, 1120, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.42 (3H, br s, ^{t}Bu), 1.52 (6H, s, ^{t}Bu), 1.79-1.97 (1H, m, C4-H), 2.02-2.12 (1H, m, C4-H), 2.89-3.08 (1H, m, C3-H), 3.39 (3H, s, OMe), 3.52-3.68 (3H, m, C*H*2OBn and C*H*2OMOM), 3.74 (1H, dd, J=10.0, 5.3 Hz, C*H*2OMOM), 3.98 (0.3H, br s, C5-H), 4.12 (0.7H, br s, C5-H), 4.48 (1H, d, J=12.1 Hz, OC*H*2Ph), 4.52 (1H, d, J=12.1 Hz, OC*H*2Ph), 4.58-4.68 (1H, m, C2-H), 4.63 (1H, d, J=7.5 Hz, OC*H*2OMe), 4.66 (1H, d, J=7.5 Hz, OC*H*2OMe), 7.26-7.38 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 334 [(M-C4H8)$^+$], 289 [(M-Boc)$^+$], 263 [(M-Boc-CN)$^+$], 169, 137, 91, 57. CIMS (isobutane) m/z: 391 (M+H). HRMS calcd for C17H22N2O5 [(M-C4H8)$^+$]: 334.1526. Found: 334.1510.

b) Preparation of *ent*-**45** and *ent*-**46**: The same treatments of *ent*-**43** (16.7 g, 42 mmol) as described for the preparation of **45** and **46** from **43** gave *ent*-**45** (3.96 g, 24%) as a more polar product and *ent*-**46** (11.5 g, 70%) as a less polar product.

ent-**45**: colorless oil. [α]D^{20} -2.3° (c 2.08, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this material were identical with those recorded for **45**.

ent-**46**: colorless oil. [α]D^{20} +69.2° (c 1.07, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this material were identical with those recorded for **46**.

(2*S*,3*R*,5*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonyl-2-formyl-3-methoxymethoxymethylpyrrolidine (48) and Its Enantiomer (*ent*-48)

a) Preparation of **48**: Treatments of **46** (14.1 g, 36 mmol) in a similar manner to that described for the preparation of **30** from **28** gave **48** (8.67 g, 61%) as a colorless oil after purification by column chromatography (hexane-ethyl acetate, 10:1→ 3:1). $[\alpha]D^{20}$ -24.8° (c 0.79, CHCl3). IR (neat): 2970, 2925, 2880, 1730, 1695, 1475, 1450, 1375, 1360, 1250, 1165, 1160, 1110, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.39 (5.4H, s, ^{t}Bu), 1.41 (3.6H, s, ^{t}Bu), 1.93-2.07 (2H, m, C4-H2), 2.91-3.09 (1H, m, C3-H), 3.34 (3H, s, OMe), 3.45-3.66 (4H, m, C*H*2OBn and C*H*2OMOM), 4.10-4.16 (0.4H, m, C5-H), 4.24 (0.6H, dd, J=9.3, 2.9 Hz, C2-H), 4.26-4.31 (0.6H, m, C5-H), 4.38 (0.6H, dd, J=9.3, 2.2 Hz, C2-H), 4.51 (1H, d, J=12.5 Hz, OC*H*2Ph), 4.53 (1H, d, J=12.5 Hz, OC*H*2Ph), 4.55 (1H, d, J=5.1 Hz, OC*H*2OMe), 4.57 (1H, d, J=5.1 Hz, OC*H*2OMe), 7.27-7.38 (5H, m, aromatic protons), 9.56 (0.6H, d, J=2.9 Hz, CHO), 9.62 (0.4H, d, J=2.9 Hz, CHO). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 364 [(M-CHO)$^+$], 264 [(M-CHO-Boc+H)$^+$], 202, 172, 91, 57. CIMS (isobutane) m/z: 394 [(M+H)$^+$]. HRMS calcd for C20H30NO5 [(M-CHO)$^+$]: 364.2122. Found: 364.2135.

b) Preparation of *ent*-**48**: The same treatments of *ent*-**46** (11.4 g, 29 mmol) as described for the preparation of **48** from **46** gave *ent*-**48** (7.58 g, 66%) as a colorless oil. $[\alpha]D^{20}$ +23.2° (c 1.14, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this material were identical with those recorded for **48**.

(2*R*,3*R*,5*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonyl-2-formyl-3-methoxymethoxymethylpyrrolidine (47) and Its Enantiomer (*ent*-47)

a) Preparation of **47** from **45**: Treatments of **45** (5.32 g, 14 mmol) in the same manner as described for the preparation of **29** from **27** gave **47** (3.38 g, 63%) as a colorless oil after purification by column chromatography (hexane-ethyl acetate, 8:1→ 3:1). $[\alpha]D^{20}$ -18.1° (c 1.43, CHCl3). IR (neat): 2970, 2925, 2880, 1730, 1695, 1475, 1450, 1380, 1360, 1255, 1170, 1150, 1135, 1110, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.42 (9H, s, ^{t}Bu), 1.96 (1H, br dd, J=19.8, 11.2 Hz, C4-H), 2.11 (1H, br dd, J=11.2, 6.7 Hz, C4-H), 2.58-2.73 (1H, m, C3-H), 3.35 (3H, s, OMe), 3.47-3.61 (4H, m, C*H*2OBn and C*H*2OMOM), 3.65-3.74 (0.6H, m, C5-H), 3.84 (0.4H, br dd, J=8.6, 2.7 Hz, C5-H), 3.98-4.08 (0.6H, m, C2-H), 4.20 (0.4H, br s, C2-H), 4.53 (2H, s, OC*H*2Ph), 4.61 (2H, s, OC*H*2OMe), 7.27-7.38 (5H, m, aromatic protons), 9.42 (0.6H, br d, J=2.7 Hz, CHO), 9.52 (0.4H, br s, CHO). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 364 [(M-CHO)$^+$], 264 [(M-CHO-Boc+H)$^+$], 202, 172, 91, 57. CIMS (isobutane) m/z: 394 [(M+H)$^+$]. HRMS calcd for C20H30NO5 [(M-CHO)$^+$]: 364.2122. Found: 364.2093.

b) Preparation of **47** from **48**: A solution of **48** (8.52 g, 22 mmol) in methanol (350 ml) containing potassium carbonate (15.0 g, 0.11 mol) was heated at reflux for 2 h. After cooling, the mixture was diluted with ethyl acetate (700 ml), and the organic layer was washed successively with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 3:1) to give **47** (8.52 g, 100%) as a colorless oil. $[\alpha]D^{20}$ -18.3° (c 1.23, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this material were identical with those described for **47**.

c) Preparation of *ent*-**47** from *ent*-**45**: The same treatments of *ent*-**45** (3.95 g, 10 mmol) as described for the preparation of **47** from **45** gave *ent*-**47** (2.47 g, 62%) as a colorless oil. $[\alpha]D^{20}$ +18.2° (c 0.99, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this material were identical with those recorded for **47**.

d) Preparation of *ent*-**47** from *ent*-**48**: The same treatments of *ent*-**48** (7.56 g, 19 mmol) as described for the preparation of **47** from **48** gave *ent*-**47** (7.48 g, 99%) as a colorless oil. $[\alpha]D^{20}$ +17.9° (c 1.09, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this material were identical with those recorded for **47**.

(2*R*,3*R*,5*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonyl-2-cyano-3-hydroxymethylpyrrolidine (49) and Its (2*S*, 3*R*, 5*S*)-Isomer (52)

a) Preparation of **49**: *p*-Toluenesulfonic acid monohydrate (60.2mg, 0.32 mmol) was added to a stirred solution of **45** (88.3 mg, 0.23 mmol) in chloroform-methanol (3:1) (3 ml) at room temperature. After 3 h, the mixture was diluted with ethyl acetate (30 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 2:1→ 1:1) to give **49** (74.4 mg, 95%) as a colorless oil. $[\alpha]D^{20}$ +6.3° (c 1.70, CHCl3). IR (neat): 3460, 2970, 2930, 2870, 2240, 1700, 1480, 1430, 1390, 1370, 1300, 1260, 1160, 1120, 1090 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.51 (9H, br s, ^{t}Bu), 1.65 (1H, br s, OH), 1.93 (1H, br s, C4-H), 2.11 (1H, br s, C4-H), 2.98 (1H, br s, C3-H), 3.55-3.67 (1H, m, C*H*2OH), 3.60 (1H, d, J=6.3 Hz, C*H*2OBn), 3.63 (1H, d, J=6.3 Hz, C*H*2OBn), 3.73-3.82 (1H, m, C*H*2OH), 4.02 (0.3H, br s, C5-H), 4.13 (0.7H, br s, C5-H), 4.37 (0.7H, br s, C2-H), 4.47 (0.3H, br s, C2-H), 4.53 (1H, d, J=12.1 Hz, OC*H*2Ph), 4.59 (1H, d, J=12.1 Hz, OC*H*2Ph), 7.25-7.38 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 290 [(M-C4H8)$^+$], 245 [(M-Boc)$^+$], 183, 125, 91, 57. CIMS (isobutane) m/z: 347 (M+H). HRMS calcd for C15H18N2O4 [(M-C4H8)$^+$]: 290.1265. Found: 290.1240.

b) Preparation of **52**: The same treatments of **46** (78.6 mg, 0.20 mmol) as described for the preparation of **49** from **45** gave **52** (64.8 mg, 93%) as a colorless oil after purification by column chromatography (hexane-ethyl acetate, 2:1). $[\alpha]D^{20}$ -73.6° (c 1.70, CHCl3). IR (neat): 3460, 2970, 2930, 2870, 2240, 1700, 1470, 1430, 1380, 1320, 1250, 1160, 1130, 1110, 1070, 1020 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.52 (9H, br s, ^{t}Bu), 1.63 (1H, br s, OH), 1.77-1.98 (1H, m, C4-H), 2.02-2.15 (1H, m, C4-H), 2.96 (1H, br s, C3-H), 3.42-3.67 (2H, m, C*H*2OBn), 3.78-3.94 (2H, m, C*H*2OH), 3.98 (0.3H, br s, C5-H), 4.13 (0.7H, br s, C5-

H), 4.37 (0.7H, br s, C2-H), 4.47 (0.3H, br s, C2-H), 4.49 (1H, d, J=12.1 Hz, OC*H*2Ph), 4.54 (1H, d, J=12.1 Hz, OC*H*2Ph), 4.64 (2H, br d, J=7.6 Hz, C2-H), 7.25-7.38 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 290 [(M-C4H8)$^+$], 245 [(M-Boc)$^+$], 219 [(M-Boc-CN)$^+$], 183, 125, 91, 57. CIMS (isobutane) m/z: 347 (M+H). HRMS calcd for C15H18N2O4 [(M-C4H8)$^+$]: 290.1266. Found: 290.1290.

(2*R*,3*R*,5*S*)-3-Acetoxymethyl-5-benzyloxymethyl-1-*tert*-butoxycarbonyl-2-cyanopyrrolidine (50) and Its (2*S*, 3*R*, 5*S*)-Isomer (53)

a) Preparation of **50**: Acetic anhydride (0.198 ml, 2.1 mmol) was added to a stirred solution of **49** (72.5 mg, 0.21 mmol) in pyridine (1 ml) containing a catalytic amount of 4-dimethylaminopyridine (5.10 mg, 42 μmol) at room temperature. After 2 h, the mixture was diluted with ethyl acetate (40 ml). The organic layer was washed successively with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 3:1) to give **50** (79.2 mg, 99%) as a colorless oil. [α]D^{20} +3.5° (c 1.30, CHCl3). IR (neat): 2970, 2930, 2860, 2250, 1740, 1700, 1490, 1450, 1380, 1360, 1300, 1230, 1160, 1140, 1120, 1030 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.43 (3H, br s, ^{t}Bu), 1.51 (6H, br s, ^{t}Bu), 1.84 (1H, br s, C4-H), 2.11 (3H, s, Ac), 2.16 (1H, br s, C4-H), 3.16 (1H, br s, C3-H), 3.48-3.68 (2H, m, C*H*2OBn), 4.02 (1.4H, br s, C2-H and C5-H), 4.14 (0.6H, br s, C2-H or C5-H), 4.22 (1.4H, br dd, J=11.4, 4.8 Hz, C*H*2OAc), 4.38 (0.6H, br s, C*H*2OAc), 4.54 (1H, d, J=12.1 Hz, OC*H*2Ph), 4.59 (1H, d, J=12.1 Hz, OC*H*2Ph), 7.24-7.38 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 332 [(M-C4H8)$^+$], 287 [(M-Boc)$^+$], 261 [(M-Boc-CN)$^+$], 181, 167, 91, 57. CIMS (isobutane) m/z: 389 (M+H). HRMS calcd for C17H20N2O5 [(M-C4H8)$^+$]: 332.1370. Found: 332.1370.

b) Preparation of **53**: The same treatments of **52** (63.1 mg, 0.18 mmol) as described for the preparation of **50** from **49** gave **53** (69.3 mg, 98%) as a colorless oil after purification by column chromatography (hexane-ethyl acetate, 4:1). [α]D^{20} -46.8° (c 1.50, CHCl3). IR (neat): 2970, 2930, 2860, 2240, 1740, 1700, 1490, 1470, 1450, 1370, 1360, 1330, 1300, 1270, 1240, 1170, 1120, 1090, 1060, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.42 (3H, br s, ^{t}Bu), 1.52 (3H, br s, ^{t}Bu), 1.52 (3H, br s, ^{t}Bu), 1.86-2.02 (1H, m, C4-H), 2.05-2.18 (1H, br s, C4-H), 2.09 (3H, s, Ac), 3.06 (1H, br s, C3-H), 3.46-3.57 (1.6H, m, C*H*2OBn), 3.66 (0.4H, br dd, J=9.8, 5.5 Hz, C*H*2OBn), 3.98 (0.4 H, br s, C*H*2OAc), 4.06-4.17 (1.6 H, m, C*H*2OAc), 4.42 (1H, br dd, J=11.4, 5.1 Hz, C5-H), 4.49 (1H, d, J=12.3 Hz, OC*H*2Ph), 4.53 (1H, d, J=12.3 Hz, OC*H*2Ph), 4.58 (0.6 H, br d, J=7.4 Hz, C2-H), 4.65 (0.4 H, br d, J=7.4 Hz, C2-H), 7.24-7.38 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 332 [(M-C4H8)$^+$], 331[(M-^{t}Bu)$^+$], 287 [(M-Boc)$^+$], 261 [(M-Boc-CN)$^+$], 181, 167, 91, 57. CIMS (isobutane) m/z: 389 (M+H). HRMS calcd for C17H20N2O5 [(M-C4H8)$^+$]: 332.1370. Found: 332.1350.

(2*R*,3*R*,5*S*)-3-Acetoxymethyl-1-benzyl-5-benzyloxymethyl-2-cyanopyrrolidine (51) and Its (2*S*, 3*R*, 5*S*)-Isomer (54)

a) Preparation of **51**: Bromotrimethylsilane (0.124ml, 0.94 mmol) was added to a stirred solution of **50** (73.2 mg, 0.19 mmol) in dichloromethane (3 ml) at room temperature under argon. After 2 h, the mixture was concentrated *in vacuo* to give (2*R*,3*R*,5*S*)-3-acetoxymethyl-5-benzyloxymethyl-2-cyanopyrrolidine (54mg), which was dissolved in dichloromethane (3ml) covered with saturated aqueous sodium hydrogen carbonate (2ml). The mixture was treated with benzyl bromide (0.448ml, 3.8 mmol) for 28 h at room temperature. The mixture was diluted with ethyl acetate (60ml), and the organic layer was washed with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 5:1→ 1:1) to give **51** (56.3 mg, 79%, 2 steps) as a colorless oil. [α]D^{20} -9.2° (c 0.13, CHCl3). IR (neat): 2920, 2850, 2240, 1740, 1490, 1450, 1360, 1330, 1230, 1150, 1100, 1070, 1060, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.67-1.76 (1H, m, C4-H), 1.92-2.00 (1H, m, C4-H), 2.05 (3H, s, Ac), 2.75-2.86 (1H, m, C3-H), 3.16-3.26 (1H, m, C5-H), 3.32 (1H, dd, J=9.5, 6.3 Hz, C*H*2OBn), 3.38 (1H, d, J=7.2 Hz, C2-H), 3.41 (1H, dd, J=9.5, 5.0 Hz, C*H*2OBn), 3.93 (1H, d, J=14.1 Hz, NC*H*2Ph), 3.95 (1H, dd, J=11.3, 8.1 Hz, C*H*2OAc), 4.06 (1H, d, J=14.1 Hz, NC*H*2Ph), 4.14 (1H, dd, J=11.3, 5.2 Hz, C*H*2OAc), 4.47 (2H, s, OC*H*2Ph), 7.26-7.38 (10H, m, aromatic protons). EIMS m/z: 378 (M$^+$), 352[(M-CN)$^+$], 257, 197, 149, 91, 43. CIMS (isobutane) m/z: 379 (M+H). HRMS calcd for C23H26N2O3 (M$^+$): 378.1941. Found: 378.1923.

b) Preparation of **54**: The same treatments of **53** (65.7 mg, 0.17 mmol) as described for the preparation of **51** from **50** gave **54** (50.5 mg, 79%) as a colorless oil after purification by column chromatography (hexane-ethyl acetate, 5:1→ 3:2). [α]D^{20} -56.3° (c 0.16, CHCl3). IR (neat): 2920, 2840, 2230, 1740, 1490, 1450, 1360, 1230, 1150, 1100, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.83-1.97 (1H, m, C4-H2), 2.00 (3H, s, Ac), 2.62-2.74 (1H, m, C3-H), 3.12-3.19 (1H, m, C5-H), 3.45 (1H, dd, J=9.6, 5.4 Hz, C*H*2OBn), 3.55 (1H, dd, J=9.5, 5.0 Hz, C*H*2OBn), 3.68 (1H, d, J=13.4 Hz, NC*H*2Ph), 3.82 (1H, d, J=6.0 Hz, C2-H), 4.03 (1H, dd, J=11.5, 10.0 Hz, C*H*2OAc), 4.21 (1H, d, J=13.4 Hz, NC*H*2Ph), 4.35 (1H, dd, J=11.5, 10.0 Hz, C*H*2OAc), 4.57 (2H, s, OC*H*2Ph), 7.28-7.38 (10H, m, aromatic protons). EIMS m/z: 378 (M$^+$), 352[(M-CN)$^+$], 257, 197, 172, 149, 91, 43. CIMS (isobutane) m/z: 379 (M+H). HRMS calcd for C23H26N2O3 (M$^+$): 378.1942. Found: 378.1958.

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