Diastereoselective 1,6-Asymmetric Induction to Obtain Chiral 4-Hydroxyethylaminobutanones by Using Methyltitanium Triisopropoxide

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The reactions of (*S*)-4-amino-1-phenylbutanones (3a—e) with methyllithium, methylmagnesium bromide, and methyltitanium triisopropoxide were studied. The reactions of the (*S*)-4-hydroxyethylamino derivatives (3a and 3d) with methyltitanium triisopropoxide gave 4a and 4d by 1,6-asymmetric induction with diastereoselectivities of 78 and 70%.

Keywords methyltitanium triisopropoxide; 1,6-asymmetric induction; diastereoselective reaction; chiral 2-hydroxyethylamine; 1-phenylbutanone; chiral 2-phenyl-2-pentanol; (*S*)-4-isopropyl-1,3-oxazolidine; (*S*)-prolinol; (*S*)-*N*-methylvalinol; (*S*)-4-phenyl-γ-valerolactone

The diastereoselective reaction of carbonyl compounds with organotitanium reagents is known to give 1,3- and 1,4-asymmetrically induced products.[1-3] We have reported the reaction of (*S*)-3-1′,3′-oxazolidino-1-phenylpropanones by using organotitanium triisopropoxides with extremely high diastereoselectivity through 1,5-asymmetric induction.[4] In this paper, we wish to describe the reaction of (*S*)-4-amino-1-phenylbutanones (**3a—e**) with methyllithium, methylmagnesium bromide, and methyltitanium triisopropoxide to give 1,6-asymmetric induction products.

The (*S*)-4-amino-1-phenylbutanones (**3a—e**) were obtained by condensation of 1,1-ethylenedioxy-4-iodo-1-phenylbutane (**1**) and chiral amines [(*S*)-*N*-methylvalinol (**2a**),[5] (*S*)-1-isopropyl-2-methoxy-*N*-methylethylamine (**2b**), (*S*)-4-isopropyl-1,3-oxazolidine (**2c**),[6] (*S*)-2-hydroxymethylpyrrolidine (**2d**),[7] and (*S*)-2-methoxymethylpyrrolidine (**2e**)[7]] in the presence of sodium carbonate, followed by treatment with dilute hydrochloric acid, in yields of 70—75%. The structures of **3a—e** thus obtained were confirmed by infrared (IR), mass (MS), and proton nuclear magnetic resonance (^{1}H-NMR) spectral analyses.

Compounds **3a—e** were allowed to react with methyllithium, methylmagnesium bromide, and methyltitanium triisopropoxide in tetrahydrofuran (THF) at room temperature to give diastereomeric mixtures of the (2*S*,1′*S*)- and (2*R*,1′*S*)-5-amino-2-phenyl-2-pentanols (**4a—e**). The structures of these products were confirmed by ^{1}H-NMR (400 MHz and/or 270 MHz), MS, and IR spectral analyses. The diastereomeric excesses of these isomers were estimated by ^{1}H-NMR (400 MHz) spectrometric analysis.

On the other hand, the synthesis of (2*S*,1′*S*)- and (2*R*,1′*S*)-**4a** was attempted by an alternate route. (*S*)-*N*-2′-Hydroxy-1′-isopropylethyl-*N*-methyl-4-oxopentanamide (**7**) was obtained by condensation of 4-oxopentanoyl chloride (**6**) and (*S*)-*N*-methylvalinol (**2a**), and the reaction of **7** with phenylmagnesium bromide gave a diastereomeric mixture of *N*-2′-hydroxy-1′-isopropylethyl-*N*-methyl-4-hydroxy-4-phenylpentanamide (**8**). The cleavage of the amide bond of **8** proceeded to give 4-phenyl-γ-valerolactone (**9**) and (*S*)-*N*-methylvalinol (**2a**). The configuration of **9** was elucidated to be *S* (major component) by comparison of the specific rotation with that of an authentic sample.[8] On the other hand, the reduction of **8** by lithium aluminum hydride gave **4a**. The configuration of **4a** was determined

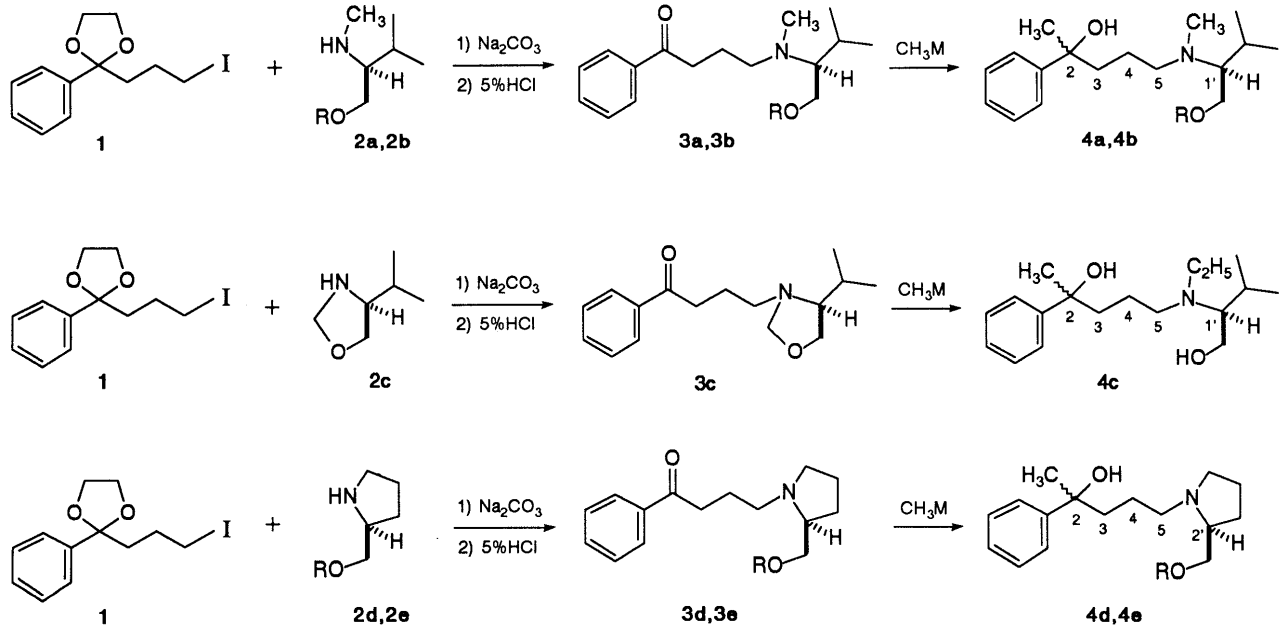

Chart 1

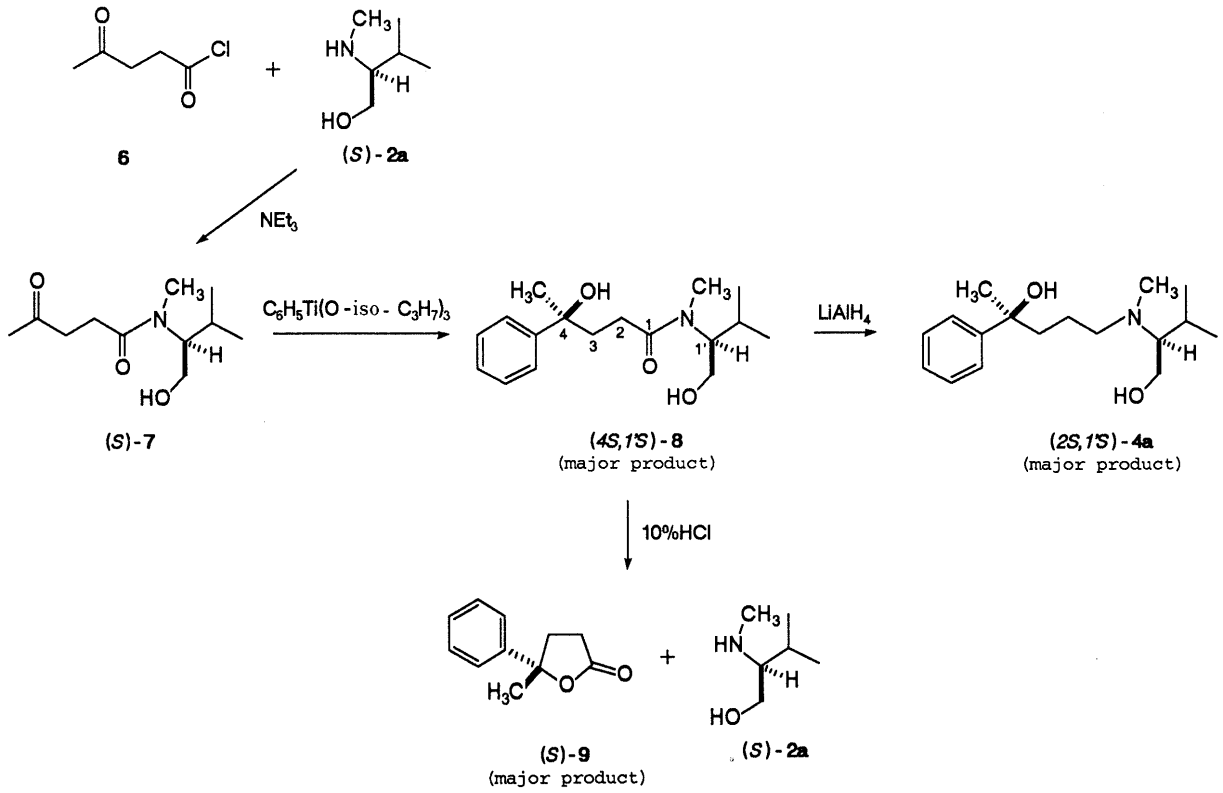

Chart 2

TABLE I. Reaction of (*S*)-4-Amino-1-phenylbutanones (**3a—e**) with Organometallic Reagents at Room Temperature in THF

Compd.	CH_3Li			CH_3MgBr			$CH_3Ti(O\text{-}iso\text{-}C_3H_7)_3$		
	Yield[a] (%)	Ratio of *SS*:*RS*	Recov.[b] (%)	Yield[a] (%)	Ratio of *SS*:*RS*	Recov.[b] (%)	Yield[a] (%)	Ratio of *SS*:*RS*	Recov.[b] (%)
4a	53	55:45	32	63	54:46	20	27	11:89	55
4b	63	51:49	25	53	68:32	25	34	49:51	50
4c	55	56:44	0	52	51:49	0	Trace	24:76	0
4d	56	59:41	30	55	55:45	30	15	15:85	60
4e	57	52:48	30	68	84:16	20	18	45:55	65

a) Isolated yield. *b*) Recovery.

from the ^{1}H-NMR spectrum, and in the case of **4b—e** the configurations were assumed on the basis that the reaction mechanism should be similar.

The reactions using methyllithium and methylmagnesium bromide showed low diastereoselectivity. On the contrary, the reaction of the (*S*)-4-hydroxyethylamino derivatives (**3a** and **3d**) with methyltitanium triisopropoxide proceeded with good diastereoselectivity. The reaction may occur mainly *via* a chiral intermediate involving the carbonyl and hydroxyl groups.

Experimental

The IR spectra were recorded with a Hitachi 260-10 spectrometer and the ^{1}H-NMR spectra were obtained with JEOL JNM-GX400, and/or JNM-GSX270 spectrometers. The MS were recorded with a JEOL JMS-D300 spectrometer by using the electron impact (EI) and the chemical ionization (CI) (isobutane) methods. The melting points were measured with a Yanagimoto micromelting-point apparatus and are uncorrected. The optical rotations were measured at 20—23 °C with a JASCO DIP-360 digital polarimeter. The purification of oily products was accomplished by bulb-to-bulb distillation using a Shibata glass-tube-oven.

1,1-Ethylenedioxy-4-iodo-1-phenylbutane (1) A solution of 4-iodo-1-phenyl-1-butanone[9] (73.3 g) and ethylene glycol (20.0 g) in benzene (450 ml) was refluxed in the presence of *p*-toluenesulfonic acid (0.7 g) for 5 h using a Dean-Stark trap. After cooling, the reaction mixture was washed with sodium carbonate solution and with a saline solution. The organic layer was separated, dried over $MgSO_4$, and concentrated to give colorless crystals (68.0 g, 80%). mp 71 °C. (*n*-hexane). *Anal.* Calcd for $C_{12}H_{15}IO_2$: C, 45.30; H, 4.75. Found: C, 45.59; H, 4.82. ^{1}H-NMR ($CDCl_3$) δ: 1.67—2.33 (4H, m, CCH_2CH_2), 2.97—3.37 (2H, m, ICH_2), 3.68—4.08 (4H, m, OCH_2CH_2O), 7.17—7.55 (5H, m, aromatic H).

(*S*)-1-Isopropyl-2-methoxy-*N*-methylethylamine (2b) A solution of (*S*)-1-isopropyl-2-methoxyethylamine[10] (3.7 g) in ethyl formate (30 ml) was refluxed for 1 h. The removal of the excess ethyl formate gave the *N*-formyl product as a colorless oil. A solution of the *N*-formyl product in THF (95 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (3.8 g) in THF (95 ml), and the stirring was continued at room temperature for 15 h. After treatment with a small amount of water (6 ml), the organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was bulb-to-bulb distilled (oven temperature 60 °C, 25 mmHg) to give a colorless oil (3.1 g, 75%). MS *m/z*: CI, 132 ($M+H^+$); EI, 86 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, d, J=6.7 Hz, $CHCH_3$), 0.94 (3H, d, J=6.7 Hz, $CHCH_3$), 1.86 (1H, double sptet, J=4.9, 6.7 Hz, $CH(CH_3)_2$), 2.35—2.42 (1H, m, NCH), 2.42 (3H, s, NCH_3), 3.27 (1H, dd, J=6.7, 9.4 Hz, OCH_2), 3.35 (3H, s, OCH_3), 3.43 (1H, dd, J=4.2, 9.4 Hz, OCH_2). $[\alpha]_D$ +15.79° (c=1.91, ethanol).

General Procedure for Condensation of 1 with 2a—e A solution of **1** (8.7 g, 26 mmol) and **2a—e** (26 mmol) in benzene (20 ml) was refluxed in the presence of anhydrous Na_2CO_3 (30 g) for 24—30 h. The precipitate was

filtered off and the solvent was evaporated under reduced pressure. A 5% HCl aqueous solution (50 ml) was added to the residue and the mixture was stirred at room temperature for 15 min. After the removal of *n*-hexane-soluble components, the mixture was adjusted to pH 9—10 and extracted with CH_2Cl_2. The organic layer was washed with saline and evaporated under reduced pressure to give **3a—e**.

(*S*)-4-2′-Hydroxy-1′-isopropyl-*N*-methylethylamine-1-phenylbutanone (**3a**): Colorless oil (oven temperature 135 °C, 14 mmHg). Yield, 70%. $[\alpha]_D$ −12.4° (c=1.0, chloroform). *Anal.* Calcd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found: C, 73.00; H, 9.72; N, 5.29. IR ($CHCl_3$): 3370 (OH), 1675 (C=O) cm^{-1}. MS m/z: CI, 264 ($M+H^+$); EI, 147 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.99 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.65—2.15 (3H, m, CCH_2, $C\underline{H}(CH_3)_2$), 2.36 (3H, s, NCH_3), 2.25—2.58 (1H, m, NCH), 2.64—2.86 (2H, m, NCH_2), 3.00 (2H, t, J=7.1 Hz, $O=CCH_2$), 3.20 (1H, t, J=10.3 Hz, OCH_2), 3.57 (1H, dd, J=5.1, 10.3 Hz, OCH_2), 7.29—8.01 (5H, m, aromatic H).

(*S*)-4-1′-Isopropyl-2′-methoxy-*N*-methylethylamino-1-phenylbutanone (**3b**): Colorless oil (oven temperature 194—196 °C, 4 mmHg). *Anal.* Calcd for $C_{17}H_{27}NO_2$: C, 73.60; H, 9.81; N, 5.05. Found: C, 73.59; H, 9.86; N, 4.92. IR ($CHCl_3$): 1670 (C=O) cm^{-1}. MS m/z: 278 ($M+H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (6H, t, J=6.5 Hz, $CH(C\underline{H}_3)_2$), 1.59—2.0 (3H, m, CCH_2, $C\underline{H}(CH_3)_2$), 2.13—2.32 (1H, m, NCH), 2.27 (3H, s, NCH_3), 2.4—2.83 (2H, m, NCH_2), 3.04 (2H, t, J=7.3 Hz, $O=CCH_2$), 3.28 (3H, s, OCH_3), 3.43—3.49 (2H, m, OCH_2), 7.33—8.01 (5H, m, aromatic H).

(*S*)-4-4′-Isopropyl-1′,3′-oxazolidino-1-phenylbutanone (**3c**): Colorless oil (oven temperature 165—170 °C, 4 mmHg). Yield, 72%. IR ($CHCl_3$): 1675 (C=O) cm^{-1}. MS m/z: 262 ($M+H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.96 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.73—2.10 (3H, m, CCH_2, $C\underline{H}(CH_3)_2$), 2.45—2.72 (3H, m, NCH_2, NCH), 3.09 (2H, t, J=7.2 Hz, $O=CCH_2$), 3.40 (1H, dd, J=5.7, 8.2 Hz, OCH_2), 3.91 (1H, dd, J=7.2, 8.2 Hz, OCH_2), 4.23 (1H, d, J=5.6 Hz, NCH_2O), 4.31 (1H, d, J=5.6 Hz, NCH_2O), 7.33—8.01 (5H, m, aromatic H).

(*S*)-4-2′-Hydroxymethylpyrrolidino-1-phenylbutanone (**3d**): Colorless needles. Yield, 75%. mp 71—72 °C (*n*-hexane). $[\alpha]_D$ −60.74 (c=1.05, chloroform). *Anal.* Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.94; H, 8.71; N, 5.66. IR ($CHCl_3$): 3490 (OH), 1675 (C=O) cm^{-1}. MS m/z: 248 ($M+H^+$). ^{1}H-NMR ($CDCl_3$) δ: 1.57—3.25 (13H, m, 4×CCH_2, CH_2NCH_2, NCH), 3.36 (1H, dd, J=3.3, 10.6 Hz, OCH_2), 3.61 (1H, dd, J=3.5, 10.6 Hz, OCH_2), 7.29—8.0 (5H, m, aromatic H).

(*S*)-4-2′-Methyoxymethylpyrrolidino-1-phenylbutanone (**3e**): Colorless oil (oven temperature 185 °C, 14 mmHg). Yield, 73%. $[\alpha]_D$ −72.03° (c=1.19, chloroform). *Anal.* Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.55; H, 9.04; N, 5.33. IR ($CHCl_3$): 1670 (C=O) cm^{-1}. MS m/z: 262 ($M+H^+$). ^{1}H-NMR ($CDCl_3$) δ: 1.53—2.06 (6H, m, 3×CCH_2), 2.19—3.17 (7H, CH_2NCH_2, NCH, $O=CCH_2$), 3.21 (1H, dd, J=6.1, 9.8 Hz, OCH_2), 3.31 (3H, s, OCH_3), 3.35 (1H, dd, J=5.5, 9.8 Hz, OCH_2), 7.42—7.98 (5H, m, aromatic H).

General Procedure for Reaction of 3a—e with Methyllithium CH_3Li (2—3 mmol, 1.43—2.14 ml of 1.4 M solution in ether) was added dropwise to a stirred solution of **3a—e** (1 mmol) in THF (3 ml) at 0 °C under a nitrogen atmosphere. After being stirred at room temperature for 20—21 h, the reaction mixture was treated with a small amount of water, the resulting white precipitate was filtered off, and the filtrate was extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with a solution of CH_2Cl_2 : methanol : NH_4OH = 95 : 4.5 : 0.5. The first fraction gave the starting material and the second fraction gave **4a—e**.

General Procedure for Reaction of 3a—e with Methylmagnesium Bromide CH_3MgBr (2—3 mmol, 0.67—1.0 ml of 3 M solution of ether) was added dropwise to a stirred solution of **3a—e** (1 mmol) in THF (3 ml) at 0 °C under a nitrogen atmosphere, and the stirring was continued at room temperature for 20—21 h. Subsequent treatment as described above gave **4a—e**.

General Procedure for Reaction of 3a—e with Methyltitanium Triisopropoxide CH_3MgBr (9—12 mmol, 3—4 ml of 3 M solution in ether) was slowly added dropwise to a stirred solution of $ClTi(O\text{-iso-}C_3H_7)_3$ (9—12 mmol) in THF (9—12 ml) under a nitrogen atmosphere. The resulting mixture was stirred for 2 h, then added dropwise to a stirred solution of **3a—e** (3 mmol) in THF (9 ml) at 0 °C, and stirring was continued at room temperature under a nitrogen atmosphere for 78—78 h. Subsequent treatment as described above gave **4a—e**.

5-2′-Hydroxy-1′-isopropyl-*N*-methylethylamino-2-phenyl-2-pentanols (**4a**): IR ($CHCl_3$): 3380 (OH), 3030 (OH) cm^{-1}. MS m/z: 280 ($M+H^+$). ^{1}H-NMR ($CDCl_3$) δ: (2*S*,1′*S*)-product; 0.86 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 0.99 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 1.37—2.07 (5H, CCH_2CH_2, $C\underline{H}(CH_3)_2$), 1.56 (3H, s, CCH_3), 2.27 (3H, s, NCH_3), 2.38—2.73 (3H, m, NCH_2, NCH), 3.32 (1H, t, J=10.3 Hz, OCH_2), 3.59 (1H, dd, J=4.5, 10.3 Hz, OCH_2), 7.22—7.48 (5H, m, aromatic H). (2*R*,1′*S*)-product; 0.83 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 0.97 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 1.37—2.07 (5H, m, CCH_2CH_2, $C\underline{H}(CH_3)_2$), 1.53 (3H, s, CCH_3), 2.24 (3H, s, NCH_3), 2.38—2.73 (3H, m, NCH_2, NCH), 3.35 (1H, t, J=10.9 Hz, OCH_2), 3.56 (1H, dd, J=4.3, 10.9 Hz, OCH_2), 7.22—7.48 (5H, m, aromatic H).

5-1′-Isopropyl-2′-methoxy-*N*-methylethylamino-2-phenyl-2-pentanols (**4b**): IR ($CHCl_3$): 2950 (OH) cm^{-1}. MS m/z: 294 ($M+H^+$). ^{1}H-NMR ($CDCl_3$) δ: (2*S*,1′*S*)-product; 0.96 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 1.06 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 1.30—2.07 (5H, m, CCH_2CH_2, $C\underline{H}(CH_3)_2$), 1.47 (3H, s, CCH_3), 2.07 (3H, s, NCH_3), 2.4—2.73 (3H, m, NCH_2, NCH), 3.26 (3H, s, OCH_3), 3.43 (1H, dd, J=3.2, 10.5 Hz, OCH_2), 3.49 (1H, dd, J=5.4, 10.5 Hz, OCH_2), 7.16—7.52 (5H, m, aromatic H). (2*R*,1′*S*)-product; 0.93 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 1.01 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 1.30—2.03 (5H, m, CCH_2CH_2, $C\underline{H}(CH_3)_2$), 1.48 (3H, s, CCH_3), 2.15 (3H, s, NCH_3), 2.4—2.73 (3H, m, NCH_2, NCH), 3.28 (3H, s, OCH_3), 3.45 (1H, dd, J=3.4, 10.5 Hz, OCH_2), 3.50 (1H, dd, J=5.6, 10.5 Hz, OCH_2), 7.16—7.52 (5H, m, aromatic H).

5-*N*-Ethyl-2′-hydroxy-1′-isopropylethylamino-2-phenyl-2-pentanols (**4c**): IR ($CHCl_3$): 3380 (OH), 3020 (OH) cm^{-1}. MS m/z: 234 ($M+H^+$): ^{1}H-NMR ($CDCl_3$) δ: (2*S*,1′*S*)-product; 0.82 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 0.96 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 1.05 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 1.32—2.0 (5H, m, CCH_2CH_2; $C\underline{H}(CH_3)_2$), 1.53 (3H, s, CCH_3), 2.43—2.73 (5H, m, CH_2NCH_2, NCH), 3.27 (1H, t, J=10.5 Hz, OCH_2), 3.55 (1H, dd, J=4.4, 10.5 Hz, OCH_2), 7.18—7.5 (5H, m, aromatic H). (2*R*,1′*S*)-product; 0.82 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.96 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 1.02 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 1.32—2.0 (5H, m, CCH_2CH_2, $C\underline{H}(CH_3)_2$), 1.55 (3H, s, CCH_3), 2.43—2.75 (5H, m, CH_2NCH_2, NCH), 3.18 (1H, t, J=10.5 Hz, OCH_2), 3.54 (1H, dd, J=4.9, 10.5 Hz, OCH_2), 7.18—7.5 (5H, m, aromatic H).

5-2′-Hydroxymethylpyrrolidino-2-phenyl-2-pentanols (**4d**): IR ($CHCl_3$): 3480 (OH), 3030 (OH) cm^{-1}. MS m/z: CI, 264 ($M+H^+$); EI, 114 (base peak). ^{1}H-NMR ($CDCl_3$) δ: (2*S*,2′*S*)-product; 1.47 (3H, s, CCH_3), 1.50—3.12 (13H, m, 4×CCH_2, CH_2NCH_2, NCH), 3.58 (1H, dd, J=5.1, 12.5 Hz, OCH_2), 3.82 (1H, dd, J=3.2, 12.5 Hz, OCH_2), 7.16—7.52 (5H, m, aromatic H). (2*R*,2′*S*)-product; 1.51 (3H, s, CCH_3), 1.56—2.02 (8H, m, 4×CCH_2), 2.2—3.27 (5H, m, CH_2NCH_2, NCH), 3.49 (1H, dd, J=4.4, 11.8 Hz, OCH_2), 3.71 (1H, dd, J=3.2, 11.8 Hz, OCH_2), 7.16—7.52 (5H, m, aromatic H).

5-2′-Methoxymethylpyrrolidino-2-phenyl-2-pentanols (**4e**): IR ($CHCl_3$): 2950 (OH) cm^{-1}. MS m/z: 278 ($M+H^+$). ^{1}H-NMR ($CDCl_3$) δ: (2*S*,2′*S*)-product; 1.48—2.05 (8H, m, 4×CCH_2), 1.53 (3H, s, OCH_3), 2.27—3.23 (5H, m, CH_2NCH_2, NCH), 3.34 (3H, s, OCH_3), 3.28—3.39 (1H, m, OCH_2), 3.48 (1H, dd, J=5.5, 9.2 Hz, OCH_2), 7.21—7.56 (5H, m, aromatic H). (2*R*,2′*S*)-product; 1.44 (3H, s, CCH_3), 1.53—2.08 (8H, m, 4×CCH_2), 2.26—3.2 (5H, m, CH_2NCH_2, NCH), 3.39 (3H, s, OCH_3), 3.37—3.47 (1H, m, OCH_2), 3.59 (1H, dd, J=6.1, 9.8 Hz, OCH_2), 7.15—7.56 (5H, m, aromatic H).

(*S*)-*N*-2′-Hydroxy-1′-isopropylethyl-*N*-methyl-4-oxopentanamide (7) A solution of 4-oxopentanoyl chloride (7.0 g) in CH_2Cl_2 (10 ml) was added dropwise to a stirred CH_2Cl_2 solution (35 ml) of (*S*)-*N*-methylvalinol (5.8 g) in the presence of triethylamine (7.0 g) and the stirring was continued at room temperature for 15 h. The reaction mixture was washed with a saline solution and the organic layer was concentrated under reduced pressure. The residue was chromatographed on a silica gel column with a solution of CH_2Cl_2 : methanol = 15 : 1 to give **7** as a colorless oil (7.9 g, 72%). MS m/z: CI, 216 ($M+H^+$); EI, 86 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 0.97 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 1.94 (1H, dt, J=6.7, 10.4 Hz, $C\underline{H}(CH_3)_2$), 2.20 (3H, s, $O=CCH_3$), 2.60 (2H, t, J=6.1 Hz, $CH_2C\underline{H}_2$), 2.80 (2H, t, J=6.1 Hz, $CH_2C\underline{H}_2$), 2.96 (3H, s, NCH_3), 3.5—4.1 (2H, m, OCH_2).

***N*-2′-Hydroxy-1′-isopropylethyl-*N*-methyl-4-hydroxy-4-phenylpentanamide (8)** C_6H_5MgBr (30 mmol, 30 ml of 1 M solution of THF) was added dropwise to a stirred solution of $ClTi(O\text{-iso-}C_3H_7)_3$ (30 mmol, 30 ml of 1 M solution of toluene) in toluene (30 ml), and stirring was continued at room temperature for 2 h. The resulting mixture was added dropwise to a stirred solution of **7** (2.15 g, 10 mmol) in toluene (20 ml) under a nitrogen atmosphere. After being stirred at room temperature for 2 h, the mixture was treated with a small amount of aqueous solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with a solution of ether : methanol = 40 : 1 to give **8** (1.47 g, 50.2%). The ratio of the two isomers was estimated to be 61 : 39 by ^{1}H-NMR spectrometric

analysis. MS *m/z*: CI, 294 ($M+H^+$); EI, 86 (base peak). ^{1}H-NMR ($CDCl_3$) δ: (4*S*,1′*S*)-product; 0.81 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 0.97 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 1.55 (3H, s, CCH_3), 1.6—1.9 (1H, m, $C\underline{H}(CH_3)_2$), 2.0—2.3 (4H, m, CCH_2CH_2), 2.74 (3H, s, NCH_3), 3.4—4.2 (2H, m, OCH_2), 7.2—7.5 (5H, m, aromatic H). (4*R*,1′*S*)-product; 0.74 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 0.90 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 1.54 (3H, s, CCH_3), 2.73 (3H, s, NCH_3).

Cleavage of 8 A solution of **8** (1.37 g) in methanol (10 ml) was refluxed in the presence of 10% HCl (3 ml) for 20 min. After removal of the solvent, the residue was diluted with water and extracted with ether. The organic layer was dried over anhydrous $Na_2SO_4$and concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column with a solution of *n*-hexane:ether=2:1 to give 4-phenyl-γ-valerolactone (**9**) (0.68 g, 88%). On the other hand, the acidic aqueous layer was made alkaline and extracted with ether. The ethereal solution was dried over anhydrous Na_2SO_4 and concentrated to give **2a** (0.36 g, 68%). Compounds **9** and **2a** were identical with authentic samples by ^{1}H-NMR spectral comparison. The specific rotation of **9** was $[\alpha]_D$ −5.17° (c=8.5, ethanol) [(*S*)-4-phenyl-γ-valerolactone, $[\alpha]_D$ −54.8° (ethanol)].[8,11]

Reduction of 8 A solution of **8** (0.1 g) in THF (2 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.1 g) in THF (6 ml). After being stirred for 1 h, the reaction mixture was treated with a small amount of water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The oily residue was chromatographed on a silica gel column to give **4a**, and the ratio of (2*S*,1′*S*)- and (2*R*,1′*S*)-**4a** was estimated to be 59:41 by ^{1}H-NMR spectrometric analysis.

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