Organometallic Reactions Characteristic of Chiral Heterocyclic Compounds: Synthesis and Stereoselective Grignard Reaction of Chiral 4-Oxa-7,7a-diazaperhydroindans

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New heterocyclic compounds, 6-phenyl-4-oxa-7,7a-diazaperhydroindans (5 and 6), were synthesized by condensation of chiral 2-hydroxyethylhydrazines prepared from (*R*)-phenylglycinol with γ-chlorobutyraldehyde. The stereoselective Grignard reaction of 5 and 6 proceeded to give chiral 2-substituted 1-[*N*-(2-hydroxy-1-phenylethyl)amino]pyrrolidines (7a—d and 8a—d). The structures of these products were determined by comparison with authentic samples, and the reaction mechanism is proposed to involve an intermediate iminium salt.

Keywords 1-aminopyrrolidine; chiral iminium intermediate; chiral 2-substituted pyrrolidine; chiral heterocyclic compound; Grignard reaction; 4-oxa-7,7a-diazaperhydroindan; (*R*)-phenylethylhydrazine; (*R*)-phenylglycinol; stereoselective reaction; X-ray analysis

We have recently reported the syntheses and stereoselective organometallic reactions of 1,3-oxazolidines[1] and 5-oxa-7,8a-diazaperhydroazulen-8-ones.[2] In this paper, we wish to describe the synthesis and stereoselective reactions of compounds having a new ring system, *i.e.*, chiral 7-alkyl-6-phenyl-4-oxa-7,7a-diazaperhydroindans (**5** and **6**).

The synthesis of (*R*)-*N*-alkyl-2-hydroxy-1-phenylethylhydrazines (**3** and **4**) was achieved by *N*-amination of (*R*)-*N*-alkyl-2-hydroxy-1-phenylethylamines (**1**[1,3] and **2**[1,4]), and the new heterocyclic compounds (**5** and **6**) were synthesized by condensation of **3** and **4** with γ-chlorobutyraldehyde in 80% and 66% yields, respectively. Compound **5** was found to consist exclusively of one isomer by proton nuclear magnetic resonance (^{1}H-NMR) spectral (270 MHz) analysis.

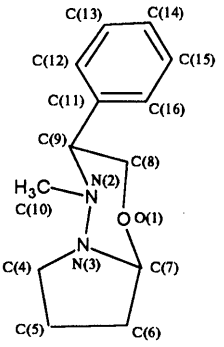


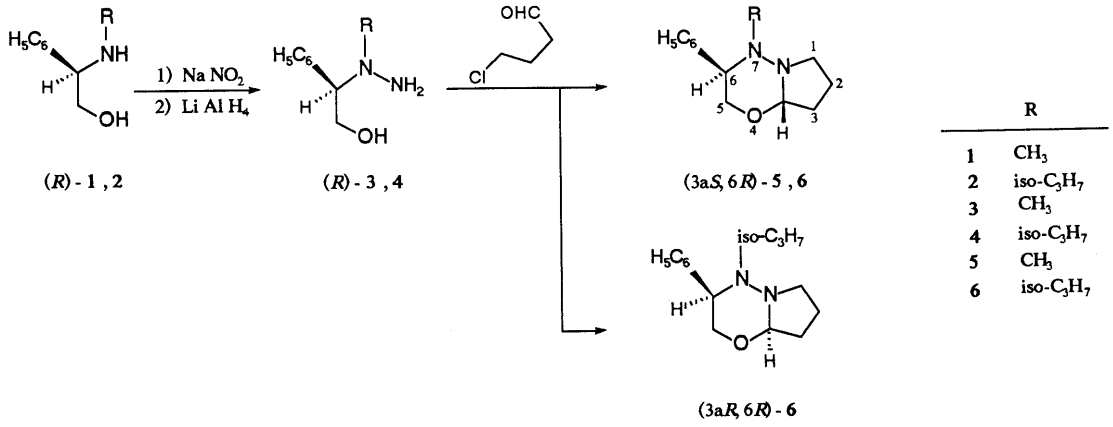
Fig. 1. Atomic Numbering of (3a*S*,6*R*)-**3a**

The absolute configuration of a newly created asymmetric carbon atom at the 3a-position of the heterocyclic ring of **5** was established by X-ray analysis. The atomic numbering is shown in Fig. 1, and the crystal data are summarized in Table I. The positional and thermal parameters with their standard deviations are listed in Table II. The intramolecular bond distances and bond angles for nonhydrogen atoms are given in Table III. Stereoscopic drawings of the molecular structure are shown in Fig. 2. It was determined that the hydrogen atom at the 3a-position of the ring is attached in a *cis* relationship to the phenyl group at the 6-position.

On the other hand, **6** was obtained as a mixture of two isomers, and the ratio of the major to the minor components was estimated as 55:45 by ^{1}H-NMR spectral analysis. Diastereomerically pure **6** could not be isolated from the

TABLE I. Crystal Data

Chemical formula	$C_{13}H_{18}N_2O$
Formula weight	218.30
Crystal system	Orthorhombic
Cell dimensions	a= 7.050 (2) (Å)
	b=25.586 (6) (Å)
	c= 6.641 (5) (Å)
Cell volume (Å^3)	1197.9 (10)
Space group	$P2_12_12_1$
Z	4
D_c (g cm^{-3})	1.12



R	
1	CH_3
2	iso-C_3H_7
3	CH_3
4	iso-C_3H_7
5	CH_3
6	iso-C_3H_7

Chart 1

TABLE II. Positional and Thermal Parameters of (3a*S*,6*R*)-**3a** for Nonhydrogen Atoms with Their Standard Deviations in Parentheses

Atom	*X*	*Y*	*Z*	B_{eq} (Å^2)[a]
O(1)	0.973 (1)	0.1014 (3)	0.418 (1)	2.6
N(2)	0.871 (1)	0.1386 (2)	0.537 (1)	2.4
N(3)	0.680 (1)	0.0634 (2)	0.307 (1)	3.5
C(4)	0.856 (1)	0.0861 (4)	0.245 (1)	3.3
C(5)	1.092 (2)	0.0166 (4)	0.335 (2)	5.4
C(6)	0.975 (2)	0.0404 (4)	0.148 (2)	4.7
C(7)	0.997 (1)	0.1571 (4)	0.697 (2)	3.5
C(8)	0.369 (1)	0.1851 (4)	1.001 (2)	3.6
C(9)	0.485 (1)	0.1470 (4)	0.901 (1)	3.2
C(10)	0.577 (1)	0.1594 (3)	0.719 (1)	2.5
C(11)	0.619 (1)	0.1175 (3)	0.613 (1)	2.7
C(12)	0.352 (1)	0.2348 (4)	0.915 (2)	3.4
C(13)	0.444 (1)	0.2471 (4)	0.736 (2)	3.8
C(14)	1.040 (1)	0.0523 (3)	0.521 (2)	3.5
C(15)	0.578 (1)	0.1000 (4)	0.425 (2)	3.6
C(16)	0.558 (1)	0.2097 (3)	0.635 (2)	3.2

a) $B_{eq}=(4/3)\sum_i\sum_j \beta_{ij}\boldsymbol{a}_i\boldsymbol{a}_j$.

TABLE III. Bond Distances (Å) and Bond Angles (°) of (3a*S*,6*R*)-**3a** for Nonhydrogen Atoms with Their Standard Deviations in Parentheses

Bond distance (Å)			
O(1)–C(7)	1.432 (13)	C(6)–C(7)	1.573 (16)
O(1)–C(8)	1.416 (12)	C(8)–C(9)	1.543 (14)
N(2)–N(3)	1.428 (10)	C(9)–C(11)	1.514 (13)
N(2)–C(9)	1.469 (12)	C(11)–C(12)	1.407 (13)
N(2)–C(10)	1.463 (12)	C(11)–C(16)	1.409 (13)
N(3)–C(4)	1.506 (13)	C(12)–C(13)	1.419 (15)
N(3)–C(7)	1.470 (13)	C(13)–C(14)	1.393 (15)
C(4)–C(5)	1.580 (18)	C(14)–C(15)	1.397 (15)
C(5)–C(6)	1.613 (19)	C(15)–C(16)	1.435 (14)
Bond angle (°)			
C(7)–O(1)–C(8)	109.3 (8)	O(1)–C(8)–C(9)	112.3 (8)
N(3)–N(2)–C(9)	112.3 (7)	N(2)–C(9)–C(8)	106.0 (7)
N(3)–N(2)–C(10)	108.2 (7)	N(2)–C(9)–C(11)	111.1 (7)
C(9)–N(2)–C(10)	113.3 (7)	C(8)–C(9)–C(11)	107.9 (8)
N(2)–N(3)–C(4)	117.5 (7)	C(9)–C(11)–C(12)	121.0 (8)
N(2)–N(3)–C(7)	109.3 (7)	C(9)–C(11)–C(16)	118.8 (8)
C(4)–N(3)–C(7)	108.2 (7)	C(12)–C(11)–C(16)	120.2 (8)
N(3)–C(4)–C(5)	101.5 (9)	C(11)–C(12)–C(13)	119.0 (9)
C(4)–C(5)–C(6)	105.4 (10)	C(12)–C(13)–C(14)	121.0 (10)
C(5)–C(6)–C(7)	103.8 (9)	C(13)–C(14)–C(15)	120.7 (10)
O(1)–C(7)–N(3)	111.3 (8)	C(14)–C(15)–C(16)	118.9 (9)
O(1)–C(7)–C(6)	106.1 (8)	C(11)–C(16)–C(15)	120.3 (9)
N(3)–C(7)–C(6)	102.7 (8)		

mixture by column chromatography. It was considered that the two diastereomeric isomers are equilibrated during column chromatography owing to the cleavage of the carbon–oxygen bond of the 4-oxa-7,7a-diazaperhydroindan ring, since cleavage of the carbon–oxygen bond of the chiral 1,3-oxazolidine ring during column chromatography been reported.[1]

The Grignard reaction of diastereomerically pure 7-methyl-6-phenyl-4-oxa-7,7a-diazaperhydroindan (**5**) with methyl, ethyl, benzyl, and phenylmagnesium halides gave diastereomeric mixtures of 1-[*N*-(2-hydroxy-1-phenylethyl)-*N*-methylamino]pyrrolidine (**7a—d**) in 81—88% yields. On the other hand, a diastereomeric mixture of 7-isopropyl-6-phenyl-4-oxa-7,7a-diazaperhydroindan (**6**) gave diastereomerically pure 1-[*N*-(2-hydroxy-1-phenylethyl)-*N*-isopropylamino]pyrrolidines (**8a—d**) in the same reaction, in

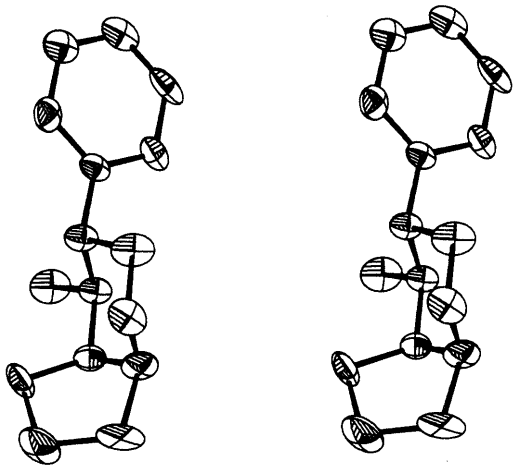


Fig. 2. Stereoscopic Drawings of the Structure of (3a*S*,6*R*)-**3a**

TABLE IV. Reaction of 7-Alkyl-6-phenyl-4-oxa-7,7a-diazaperhydroindans (**5** and **6**) with Grignard Reagent at 0 °C for 12 h

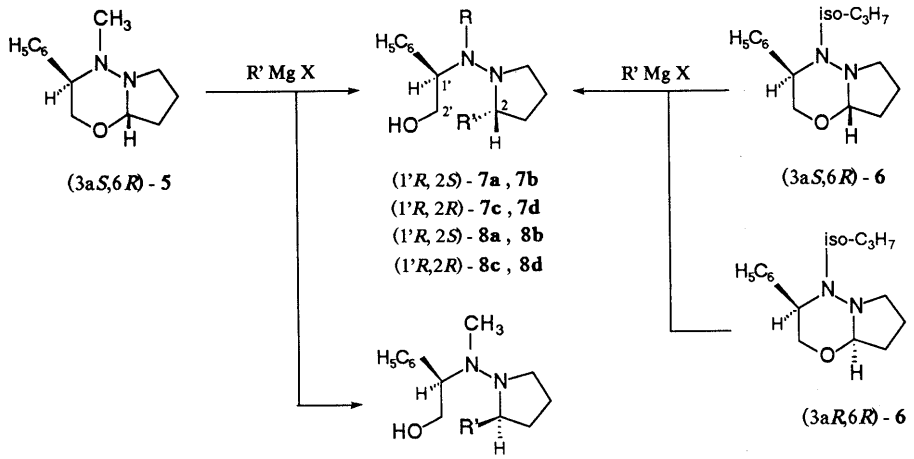
Reactant	Reagent (eq mol)	Solvent	Product	Yield[a] (%)	Ratio of[b] (1′*R*,2*R*):(1′*R*,2*S*)
5[c]	CH_3MgBr	(3) Et_2O–THF	**7a**	83	75:25
5[c]	C_2H_5MgBr	(3) Et_2O–THF	**7b**	86	58:42
5[c]	$C_6H_5CH_2MgCl$	(4) THF	**7c**	88	46:54
5[c]	C_6H_5MgBr	(4) THF	**7d**	81	25:75
6[d]	CH_3MgBr	(3) Et_2O–THF	**8a**	81	— : >98
6[d]	C_2H_5MgBr	(3) Et_2O–THF	**8b**	80	— : >98
6[d]	$C_6H_5CH_2MgCl$	(4) THF	**8c**	82	>98 : —
6[d]	C_6H_5MgBr	(4) Et_2O–THF	**8d**	62	>98 : —

a) Isolated yield. b) Estimated by ^{1}H-NMR (270 MHz) spectral analysis. c) Diastereomerically pure compound was used. d) Diastereomeric mixture (ratio, 55:45) was used.

62—82% yields, as shown in Chart 2. Thus, it was found that the stereoselectivity of these Grignard reactions does not correlate with the configuration at the 3a-position of 4-oxa-7,7a-diazaperhydroindans. The ratios of the major to the minor components of **7a—d** were estimated by ^{1}H-NMR spectral analysis, and **8a—d** were confirmed to consist of a single isomer by ^{1}H-NMR spectral analysis. These experimental data are summarized in Table IV.

The absolute configurations at the 2-position of **8c**, **7a**, and **7c** were elucidated as follows. (*R*)-2-Benzylpyrrolidine (**9**)[5] was converted to (*R*)-1-amino-2-benzylpyrrolidine (**10**), and (*R*)-2-benzyl-1-isopropylaminopyrrolidine (**11**) was obtained by *N*-isopropylation of (*R*)-**10**. Alternatively, (*R*)-**11** was also obtained by hydrogenolysis of **8c** using a palladium–carbon catalyst. Both products were identical on ^{1}H-NMR spectral and specific rotation comparisons. Consequently, the absolute configuration of **8c** was determined as (1′*R*,2*R*), and those of **8a**, **8b**, and **8d** were deduced to be the same as that of **8c**, form a in Chart 2, on the assumption that these compounds might have been formed by a similar reaction mechanism.

(*R*)-2-Methylpyrrolidine hydrochloride (**12**)[6] was converted to (*R*)-1-amino-2-methylpyrrolidine (**13**), followed by condensation of ethyl phenylglyoxylate to give 1-(α-ethoxycarbonylbenzylideneamino)-2-methylpyrrolidines (**14**). Reduction of **14** with lithium aluminum hydride gave



7	R	R'
a	CH_3	CH_3
b	CH_3	C_2H_5
c	CH_3	$CH_2C_6H_5$
d	CH_3	C_6H_5

8	R	R'
a	iso - C_3H_7	CH_3
b	iso-C_3H_7	C_2H_5
c	iso-C_3H_7	$CH_2C_6H_5$
d	iso-C_3H_7	C_6H_5

Chart 2

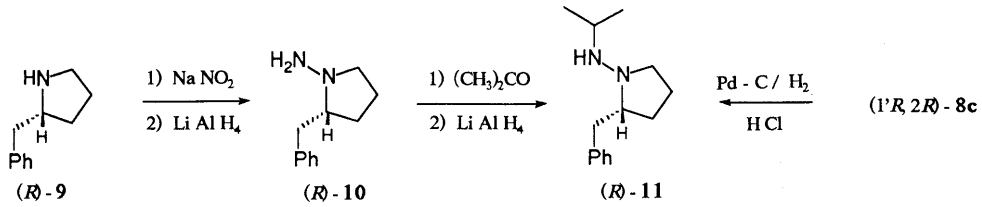


Chart 3

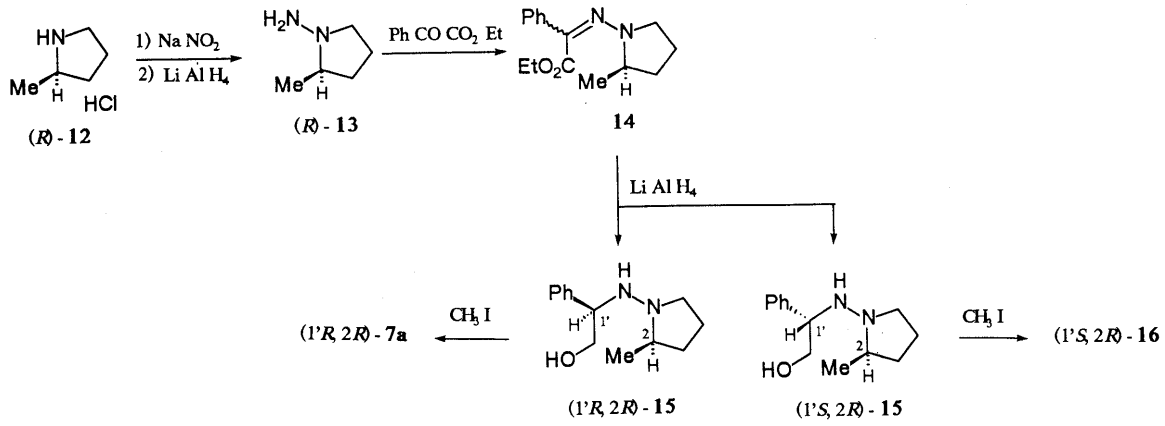


Chart 4

a mixture of (1′*R*,2*R*)- and (1′*S*,2*R*)-1-[*N*-(2-hydroxy-1-phenylethyl)amino]-2-methylpyrrolidines (**15**), and the diastereomerically pure compound was isolated by column chromatography on silica gel. Compounds (1′*R*,2*R*)-**15** and (1′*S*,2*R*)-**15** were converted to the *N*-methyl products [(1′*R*,2*R*)-**7a** and (1′*S*,2*R*)-**16**]. Then, the ^{1}H-NMR spectra and specific rotations of **7a** (ratio of diastereomers, 75 : 25), (1′*R*,2*R*)-**7a**, and (1′*S*,2*R*)-**16** were compared with each other. The specific rotation of (1′*R*,2*S*)-**7a** may be estimated as $[\alpha]_D + 111.7°$ if (1′*R*,2*S*)-**7a** is the minor component, whereas it is $[\alpha]_D + 31.9°$ if (1′*R*,2*S*)-**7a** is the major component. Consequently, it was concluded that (1′*R*,2*S*)-**7a** is the minor component, since the specific rotation of (1′*S*,2*R*)-**16** was $[\alpha]_D - 121.8°$.

Similarly, the condensation of (*R*)-**10** with ethyl phenylglyoxylate gave a mixture of 2-benzyl-1-[*N*-(α-ethoxycarbonylbenzylidene)amino]pyrrolidines (**17**), which was converted to a mixture of 2-benzyl-1-[*N*-(2-hydroxy-1-phenylethyl)amino]pyrrolidines (**18**) by reduction with lithium aluminum hydride. The diastereomerically pure

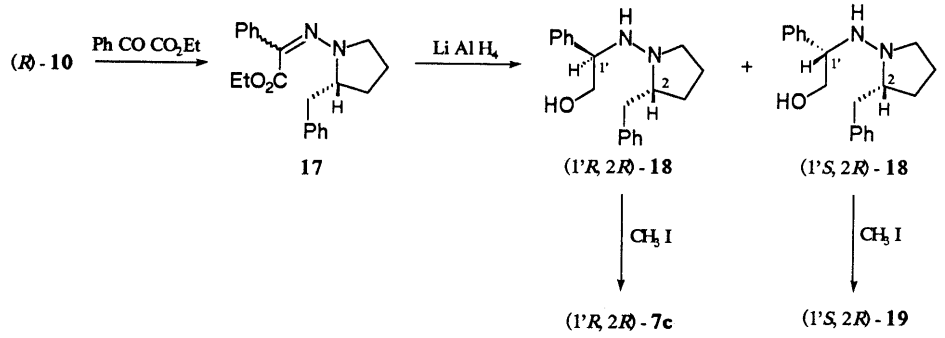


Chart 5

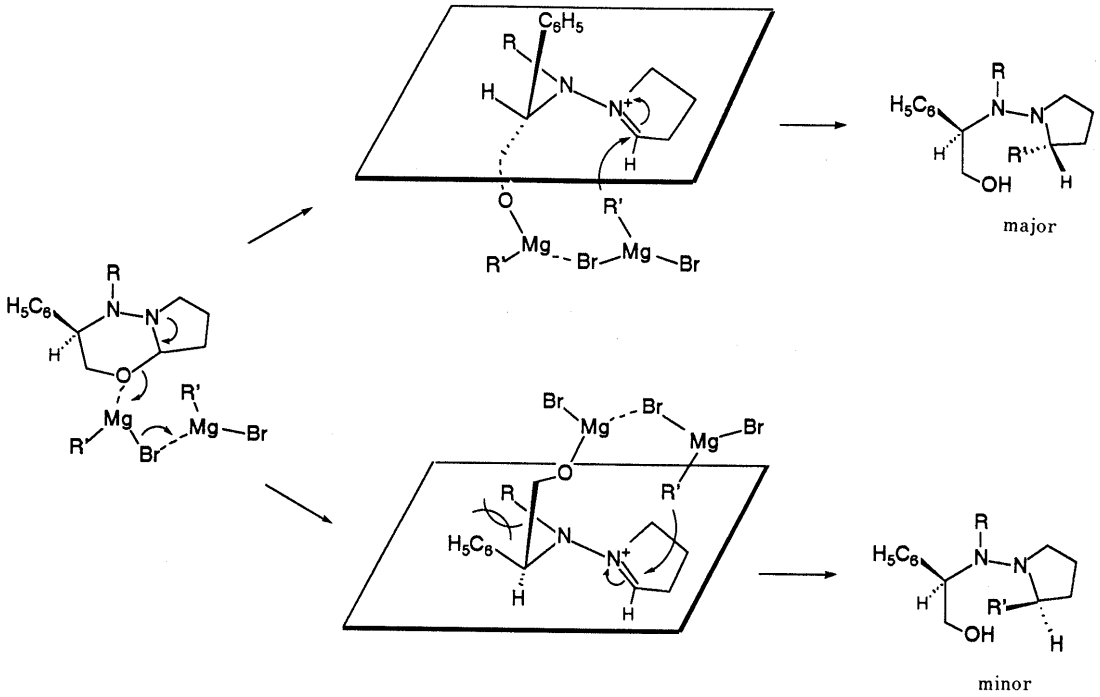


Chart 6

compound was isolated by column chromatography on silica gel. Compounds (1′*R*,2*R*)-**18** and (1′*S*,2*R*)-**18** were converted to (1′*R*,2*R*)-**7c** and (1′*S*,2*R*)-**19**, respectively. The ^{1}H-NMR spectra and the specific rotations of **7c** (ratio of diastereomers, 54:46), (1′*R*,2*R*)-**7c**, (1′*S*,2*R*)-**19** were compared with each other, and the configuration of the minor component of **7c** may be assumed as (1′*R*,2*R*).

We have reported the stereoselective Grignard reaction of 3-alkyl-4-phenyl-1,3-oxazolidines prepared from (*R*)-*N*-alkylphenylglycinol, and proposed a possible reaction mechanism, *i.e.*, the Grignard reagent approaches the oxygen atom of the 1,3-oxazolidine ring to give a favorable intermediate iminium salt, and nucleophilic attach occurs from the *si*-face of the carbon–nitrogen double bond of the intermediate.[1] Thus, it was considered that the Grignard reaction of 7-alkyl-6-phenyl-4-oxa-7,7a-diazaperhydroindans (**5** and **6**) prepared from (*R*)-*N*-alkylphenylglycinol occurs by a similar reaction mechanism to that of 3-alkyl-4-phenyl-1,3-oxazolidines, as shown in Chart 6. Furthermore, the extremely highly diastereoselective reaction presumably proceeded by nucleophilic attack from the *si*-face of the intermediate in the *N*-isopropyl compound (**6**), because steric hindrance is considered to occur between the isopropyl group at the *N*-position and the phenyl group at the 1′-position.

Experimental

The ^{1}H-NMR spectra were obtained with a JEOL JNM-GSX270 spectrometer. The mass spectra (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 micro melting point apparatus and are uncorrected. The optical rotations were measured at 20—23°C with a JASCO DIP-360 digital polarimeter.

(*R*)-*N*-(2-Hydroxy-1-phenylethyl)-*N*-methylhydrazine (3a) An aqueous solution of $NaNO_2$ (2.76 g, 40 mmol) in H_2O (6 ml) was added dropwise to a suspension of (*R*)-*N*-(2-hydroxy-1-phenylethyl)-*N*-methylamine (**1**)[3] (3.02 g, 20 mmol) in H_2O (6 ml) with vigorous stirring on an ice-cold bath, and then acetic acid (1.80 g, 30 mmol) was added. The mixture was stirred at room temperature for 4 h, the whole was extracted with ether, and the ethereal solution was dried over Na_2SO_4 and concentrated under reduced pressure to give the *N*-nitroso compound as a colorless oil. The *N*-nitroso compound was slowly added to a stirred suspension of $LiAlH_4$ (1.14 g, 30 mmol) in tetrahydrofuran (THF) (60 ml), and the mixture was refluxed for 3 h. After treatment with a small amount of water, the resulting white precipitate was filtered off, and the filtrate was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was distilled *in vacuo* to give a colorless oil (2.66 g, 80%), bp 165—170 °C (1.2 mmHg). $[\alpha]_D$ −40.0° (c=1.98, EtOH). MS *m/z*: Calcd for $C_9H_{14}N_2O$, 166.1103 (M^+); Found, 166.1101. EI, 166 (M^+), 135 ($M^+ - CH_2OH$); CI, 167 ($M^+ + 1$),

135 ($M^+ - CH_2OH$), 121 ($M^+ - CH_3NNH_2$). ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s, NCH_3), 3.2—3.3 (2H, br s, NH_2), 3.56 (1H, dd, J=2.4, 8.6 Hz, $NCHCH_2O$), 3.69 (1H, dd, J=2.4, 11.0 Hz, $NCHCH_2O$), 4.15 (1H, dd, J=8.6, 11.0 Hz, $NCHCH_2O$), 4.8—5.1 (1H, br s, OH), 7.36—7.48 (5H, m, aromatic H).

(*R*)-*N*-(2-Hydroxy-1-phenylethyl)-*N*-isopropylhydrazine (4) *N*-Amination of (*R*)-*N*-(2-hydroxy-1-phenylethyl)-*N*-isopropylamine (**2**)[4] (3.59 g, 20 mmol) was achieved in a similar manner to that described for the preparation of (*R*)-**3** to give (*R*)-**4** (2.37 g, 61%) as a colorless oil, bp 146—150 °C (1.3 mmHg). $[\alpha]_D$ −24.7° (c=1.40, EtOH). MS *m/z*: Calcd for $C_{11}H_{18}N_2O$, 194.1413 (M^+); Found, 194.1408. EI, 194 (M^+), 163 ($M^+ - CH_2OH$); CI, 195 ($M^+ + 1$), 163 ($M^+ - CH_2OH$). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, d, J=6.7 Hz, $CHCH_3$), 1.00 (3H, d, J=6.7 Hz, $CHCH_3$), 1.5—1.7 (2H, br s, NH_2), 2.82 (1H, septet, J=6.7 Hz, $CH(CH_3)_2$), 3.54 (1H, dd, J=2.4, 11.0 Hz, $NCHCH_2O$), 3.80 (1H, dd, J=2.4, 8.5 Hz, $NCHCH_2O$), 4.0—4.1 (1H, br s, OH), 4.02 (1H, dd, J=8.5, 11.0 Hz, $NCHCH_2O$), 7.21—7.35 (5H, m, aromatic H).

(3a*S*,6*R*)-7-Methyl-6-phenyl-4-oxa-7,7a-diazaperhydroindan (5) A solution of (*R*)-**3** (3.32 g, 20 mmol) in CH_2Cl_2 (20 ml) was added dropwise to a solution of γ-chlorobutyraldehyde (2.34 g, 22 mmol) in CH_2Cl_2 (30 ml) in the presence of anhydrous $MgSO_4$ (6 g), and the reaction mixture was stirred at room temperature for 1 h. The precipitate was filtered off and the solvent was evaporated under reduced pressure. The residue thus obtained was dissolved in benzene (40 ml) and the solution was refluxed in the presence of K_2CO_3 (6 g) for 24 h. After removal of the solid, the reaction mixture was concentrated under pressure and the residue was subjected to column chromatography on silica gel with a solution of ether–hexane (1 : 1) to give (3a*S*,6*R*)-**5** (3.49 g, 80%). Colorless columns, mp 79 °C (hexane). $[\alpha]_D$ −193.9° (c=1.10, EtOH). *Anal.* Calcd for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31; N, 12.83. Found: C, 71.64; H, 8.45; N, 12.80. MS *m/z*: EI, 218 (M^+); CI, 219 ($M^+ + 1$). ^{1}H-NMR ($CDCl_3$) δ: 1.67—2.10 (4H, m, CH_2CH_2), 2.32 (3H, s, NCH_3), 2.93 (1H, dt, J=2.4, 8.5 Hz, NCH_2CH_2), 3.30 (1H, q, J=8.5 Hz, NCH_2CH_2), 3.61—3.83 (3H, m, $NCHCH_2$), 4.86 (1H, d, J=3.7 Hz, NCHO), 7.26—7.39 (5H, m, aromatic H).

Diastereomeric Mixture of 7-Isopropyl-6-phenyl-4-oxa-7,7a-diazaperhydroindans (6) The condensation of (*R*)-**4** (20 mmol) with γ-chlorobutyraldehyde (2.34 g, 22 mmol) gave a diastereomeric mixture of **6** (3.25 g, 66%) as a colorless oil in a similar manner to the preparation of (3a*S*,6*R*)-**5**, bp 67—70°C (1.3 mmHg). The ratio of the major to the minor components was estimated as 55 : 45 by ^{1}H-NMR spectrometric analysis. MS *m/z*: EI, 246 (M^+), 203 ($M^+ - C_3H_7$); CI, 247 ($M^+ + 1$). ^{1}H-NMR ($CDCl_3$) δ: Major component; 0.86 (3H, d, J=6.7 Hz, $CHCH_3$), 1.09 (3H, d, J=6.7 Hz, $CHCH_3$), 1.58—2.08 (4H, m, CH_2CH_2), 2.99 (1H, septet, J=6.7 Hz, $CH(CH_3)_2$), 3.12 (1H, q, J=8.5 Hz, NCH_2), 3.26 (1H, dt, J=3.7, 8.5 Hz, NCH_2), 3.62—3.88 (2H, m, $NCHCH_2O$), 4.18—4.25 (1H, m, $NCHCH_2O$), 4.80 (1H, d, J=3.1 Hz, NCHO), 7.22—7.46 (5H, m, aromatic H). Minor component; 1.02 (6H, d, J=6.1 Hz, $CH(CH_3)_2$), 2.73 (1H, septet, J=6.1 Hz, $CH(CH_3)_2$), 2.78 (1H, dt, J=3.1, 7.9 Hz, NCH_2), 3.40 (1H, q, J=7.9 Hz, NCH_2), 5.07 (1H, d, J=3.7 Hz, NCHO), 7.22—7.46 (5H, m, aromatic H).

Crystallographic Measurements A single crystal of (3a*S*,6*R*)-**5** was grown in hexane solution as a colorless column with dimensions of 0.4 × 0.3 × 0.4 mm. All the measurements were performed on a Rigaku AFC-5 diffractometer using graphite-monochromated CuK_α radiation. The unit cell dimensions were determined by least-squares calculation with 24 high-angle reflections.

Intensity data were collected by using the $2\theta/\omega$ scan technique with an average scan rate of 4°/min. In total, 1248 independent reflections with $0° < 2\theta < 130°$ were collected, of which 1183 that satisfied the condition $F_0 > 3\sigma(F)$ were used for calculations.

Structure Analysis and Refinement The structure was solved by the direct method using MULTAN[7] and the Rigaku crystallographic package RASA-II. The structure was refined by the block-diagonal least-squares technique with anisotropic thermal factors for all nonhydrogen atoms. The *R* factor was finally reduced to 0.102.

General Procedure for the Reaction of (3a*S*,6*R*)-5 with Grignard Reagents Grignard reagent (CH_3MgBr or C_2H_5MgBr, 3 mmol; $C_6H_5CH_2MgCl$ or C_6H_5MgBr, 4 mmol) was added dropwise to a stirred solution of (3a*S*,6*R*)-**5** (0.22 g, 1 mmol) in THF (2 ml) at 0 °C under a nitrogen atmosphere. After being stirred at 0 °C for 12 h, the reaction mixture was treated with a small amount of water. The resulting white precipitate was filtered off, and the filtrate was diluted with CH_2Cl_2 (10 ml). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give a colorless oily residue. The ratios of the major to the minor components were estimated by ^{1}H-NMR spectrometric analysis. The residues were subjected to column chromatography on silica gel with a solution of ether–hexane (1 : 1) to give the corresponding diastereomeric mixture of **7a—d** as a colorless oil. The experimental data are summarized in Table IV.

1-[*N*-(2-Hydroxy-1-phenylethyl)-*N*-methylamino]-2-methylpyrrolidine (**7a**): CH_3MgBr (1 ml of a 3 M solution in ether) was used. Specific rotation of this mixture (ratio, 75 : 25) was $[\alpha]_D$ +22.0° (c=1.12, EtOH). ^{1}H-NMR ($CDCl_3$) δ: Major component, (1′*R*,2*R*); 1.36 (3H, d, J=6.1 Hz, CH_2CHCH_3), 1.69—1.90 (4H, m, CH_2CH_2), 2.02 (3H, s, NCH_3), 2.74 (1H, dq, J=2.6, 6.1 Hz, $CHCH_3$), 2.80 (1H, q, J=9.2 Hz, NCH_2), 3.05 (1H, dt, J=3.7, 9.2 Hz, NCH_2), 3.48 (1H, dd, J=2.0, 11.5 Hz, $NCHCH_2O$), 3.72 (1H, dd, J=2.0, 9.2 Hz, $NCHCH_2O$), 3.98 (1H, dd, J=9.2, 11.5 Hz, $NCHCH_2O$), 6.3—6.5 (1H, br s, OH), 7.24—7.32 (5H, m, aromatic H). Minor component, (1′*R*,2*S*); 1.31 (3H, d, J=6.1 Hz, $CHCH_3$), 2.24 (3H, s, NCH_3), 2.74—2.92 (2H, m, CH_3CHCH_3 and NCH_2), 3.05—3.10 (1H, m, NCH_2), 3.60 (1H, dd, J=2.0, 10.8 Hz, $NCHCH_2O$), 3.94 (1H, dd, J=2.0, 9.0 Hz, $NCHCH_2O$), 4.04 (1H, dd, J=9.0, 10.8 Hz, $NCHCH_2O$), 7.22—7.31 (5H, m, aromatic H).

2-Ethyl-1-[*N*-(2-hydroxy-1-phenylethyl)-*N*-methylamino]pyrrolidine (**7b**): C_2H_5MgBr (1 ml of a 3 M solution in ether) was used. ^{1}H-NMR ($CDCl_3$) δ: Major component, (1′*R*,2*R*); 0.98 (3H, t, J=7.3 Hz, CH_2CH_3), 1.34—1.95 (4H, m, CH_2CH_2), 1.97—2.01 (2H, m, CH_2CH_3), 2.03 (3H, s, NCH_3), 2.64—2.81 (2H, m, NCH_2, $CHCH_2CH_3$), 2.84—2.92 (1H, m, NCH_2), 3.47 (1H, t, J=9.8 Hz, $NCHCH_2O$), 3.73 (1H, dd, J=2.4, 9.8 Hz, $NCHCH_2O$), 3.90—4.07 (1H, m, $NCHCH_2O$), 6.4 (1H, br s, OH), 7.23—7.31 (5H, m, aromatic H). Minor component, (1′*R*,2*S*); 0.92 (3H, t, J=7.3 Hz, CH_2CH_3), 2.20—2.29 (2H, m, CH_2CH_3), 2.25 (3H, s, NCH_3), 3.02—3.09 (1H, m, NCH_2), 3.63 (1H, t, J=6.1 Hz, $NCHCH_2O$), 3.90—4.07 (2H, m, $NCHCH_2O$), 5.9 (1H, br s, OH), 7.23—7.31 (5H, m, aromatic H).

2-Benzyl-1-[*N*-(2-hydroxy-1-phenylethyl)-*N*-methylamino]pyrrolidine (**7c**): $C_6H_5CH_2MgCl$ (4 ml of a 1 M solution in THF) was used. Specific rotation of this mixture (ratio, 54 : 46) was $[\alpha]_D$ +10.0° (c=1.32, EtOH). ^{1}H-NMR ($CDCl_3$) δ: Major component, (1′*R*,2*S*); 1.41—1.81 (4H, m, CH_2CH_2), 2.10 (3H, s, NCH_3), 2.55 (1H, dd, J=10.1, 13.4 Hz, $PhCH_2$), 2.76—2.86 (1H, m, NCH_2), 2.99—3.07 (1H, m, NCH_2), 3.09—3.14 (1H, m, $PhCH_2CH$), 3.52 (1H, dd, J=1.8, 11.8 Hz, $NCHCH_2O$), 3.70 (1H, dd, J=3.7, 13.4 Hz, $PhCH_2$), 3.73 (1H, dd, J=1.8, 9.2 Hz, $NCHCH_2O$), 4.05 (1H, dd, J=9.2, 11.6 Hz, $NCHCH_2O$), 6.3 (1H, br s, OH), 7.19—7.36 (10H, m, aromatic H). Minor component, (1′*R*,2*R*); 1.21—1.78 (4H, m, CH_2CH_2), 2.38 (3H, s, NCH_3), 2.58 (1H, dd, J=10.7, 13.4 Hz, $PhCH_2$), 2.69—2.79 (1H, m, NCH_2), 2.86—2.94 (1H, m, NCH_2), 3.19—3.29 (1H, m, $PhCH_2CH$), 3.39 (1H, dd, J=3.7, 13.4 Hz, $PhCH_2$), 3.68 (1H, dd, J=2.4, 10.4 Hz, $NCHCH_2O$), 3.97 (1H, dd, J=2.4, 9.5 Hz, $NCHCH_2O$), 4.08 (1H, dd, J=9.5, 10.4 Hz, $NCHCH_2O$), 7.18—7.36 (10H, m, aromatic H).

1-[*N*-(2-Hydroxy-1-phenylethyl)-*N*-methylamino]-2-phenylpyrrolidine (**7d**): C_6H_5MgBr (4 ml of a 1 M solution in THF) was used. ^{1}H-NMR ($CDCl_3$) δ: Major component, (1′*R*,2*S*); 1.92—2.15 (4H, m, CH_2CH_2), 2.10 (3H, s, NCH_3), 2.89 (1H, q, J=8.5 Hz, NCH_2), 3.14 (1H, dt, J=3.7, 8.5 Hz, NCH_2), 3.25 (1H, d, J=7.3 Hz, $PhCH$), 3.63 (1H, dd, J=4.3, 8.3 Hz, $NCHCH_2O$), 3.78—3.84 (2H, m, $NCHCH_2O$), 5.5 (1H, br s, OH), 6.93—7.25 (10H, m, aromatic H). Minor component, (1′*R*,2*R*); 1.92—2.15 (4H, m, CH_2CH_2), 2.41 (3H, s, NCH_3), 2.45—2.53 (1H, m, NCH_2), 3.33 (1H, dd, J=3.7, 8.7 Hz, $NCHCH_2O$), 3.71—3.81 (2H, m, $NCHCH_2O$), 5.9 (1H, br s, OH), 6.93—7.25 (10H, m, aromatic H).

General Procedure for the Reaction of a Diastereomeric Mixture of 6 with Grignard Reagents Grignard reagent (CH_3MgBr or C_2H_5MgBr, 3 mmol; $C_6H_5CH_2MgCl$ or C_6H_5MgBr, 4 mmol) was added dropwise to a stirred solution of the diastereomeric mixture (ratio, 55 : 45) of **6** (0.25 g, 1 mmol) in THF (2 ml) at 0°C under a nitrogen atmosphere. After being stirred at 0 °C for 12 h, the reaction mixture was worked up in a similar manner to that employed in the reaction of (3a*S*,6*R*)-**5** to give the corresponding product (**8a—d**) as a colorless crystaline solid. The experimental data are summarized in Table IV.

(1′*R*,2*S*)-1-[*N*-(2-Hydroxy-1-phenylethyl)-*N*-isopropylamino]-2-methylpyrrolidine (**8a**): CH_3MgBr (1 ml of a 3 M solution in ether) was used. Colorless plates, mp 109—110 °C (hexane). $[\alpha]_D$ +64.9° (c=0.82, EtOH). *Anal.* Calcd for $C_{16}H_{26}N_2O$: C, 73.24; H, 9.99; N, 10.68. Found: C, 73.54; H, 10.15; N, 10.68. MS *m/z*: CI, 263 ($M^+ + 1$), 121 ($M^+ - PhCHCH_2OH$). ^{1}H-NMR ($CDCl_3$) δ: 0.60 (3H, d, J=6.7 Hz, $CHCH_3$), 1.08 (3H, d, J=6.7 Hz, $CHCH_3$), 1.38 (3H, d, J=6.1 Hz, $CHCH_3$), 1.62—1.92 (4H, m, CH_2CH_2), 2.63 (1H, q, J=8.6 Hz, NCH_2), 2.83 (1H, ddq, J=1.8, 14.0, 6.1 Hz, CH_3CHCH_2), 3.07 (1H, septet, J=6.7 Hz, $CH(CH_3)_2$), 3.17 (1H,

dt, J=8.6, 3.7 Hz, NCH_2), 3.34 (1H, m, $NCHCH_2O$), 3.94 (1H, dd, J=8.6, 11.6 Hz, $NCHCH_2O$), 4.15 (1H, dd, J=1.8, 8.6 Hz, $NCHCH_2O$), 5.9 (1H, br s, OH), 7.19—7.39 (5H, m, aromatic H).

(1′*R*,2*S*)-2-Ethyl-1-[*N*-(2-hydroxy-1-phenylethyl)-*N*-isopropylamino]-pyrrolidine (**8b**): C_2H_5MgBr (1 ml of a 3 M solution in ether) was used. Colorless columns, mp 123—124 °C (ether–hexane). $[\alpha]_D$ +71.8° (c=0.94, EtOH). *Anal.* Calcd for $C_{17}H_{28}N_2O$: C, 73.86; H, 10.21; N, 10.14. Found: C, 74.11; H, 10.57; N, 10.15. MS *m/z*: CI, 277 (M^++1), 155 (M^+−$PhCHCH_2OH$). ^{1}H-NMR ($CDCl_3$) δ: 0.60 (3H, d, J=7.3 Hz, $CHCH_3$), 0.97 (3H, t, J=7.3 Hz, CH_2CH_3), 1.08 (3H, d, J=7.3 Hz, $CHCH_3$), 1.35 (2H, m, CH_2CH_3), 1.60—1.89 (4H, m, CH_2CH_2), 2.37 (1H, m, CH_3CH_2CH), 2.65 (1H, q, J=9.2 Hz, NCH_2), 3.09 (1H, septet, J=7.3 Hz, $CH(CH_3)_2$), 3.19 (1H, dt, J=9.2, 3.1 Hz, NCH_2), 3.33 (1H, dd, J=2.4, 11.6 Hz, $NCHCH_2O$), 3.93 (1H, dd, J=9.1, 11.6 Hz, $NCHCH_2O$), 4.16 (1H, dd, J=2.4, 9.1 Hz, $NCHCH_2O$), 5.9 (1H, br s, OH), 7.20—7.39 (5H, m, aromatic H).

(1′*R*,2*R*)-2-Benzyl-1-[*N*-(2-hydroxy-1-phenylethyl)-*N*-isopropylamino]-pyrrolidine (**8c**): $C_6H_5CH_2MgCl$ (4 ml of a 1 M solution in THF) was used. Colorless columns, mp 106—106.5 °C (ether–hexane). $[\alpha]_D$ +28.7° (c=1.03, EtOH). *Anal.* Calcd for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93; N, 8.28. Found: C, 78.21; H, 9.13; N, 8.30. MS *m/z*: CI, 339 (M^++1), 217 (M^+−$PhCHCH_2OH$). ^{1}H-NMR ($CDCl_3$) δ: 0.72 (3H, d, J=6.7 Hz, $CHCH_3$), 1.13 (3H, d, J=6.7 Hz, $CHCH_3$), 1.43—1.75 (4H, m, CH_2CH_2), 2.47 (1H, dd, J=10.4, 12.8 Hz, $PhCH_2$), 2.70 (1H, q, J=8.6 Hz, NCH_2), 2.98 (1H, m, $PhCH_2CH$), 3.18 (1H, septet, J=6.7 Hz, $CH(CH_3)_2$), 3.23 (1H, dt, J=8.6, 4.3 Hz, NCH_2), 3.39 (1H, dd, J=2.4, 11.6 Hz, $NCHCH_2O$), 3.86 (1H, d, J=10.4 Hz, $PhCH_2$), 4.03 (1H, dd, J=9.2, 11.6 Hz, $NCHCH_2O$), 4.22(1H, dd, J=2.4, 9.2 Hz, $NCHCH_2O$), 5.8 (1H, br s, OH), 7.18—7.43 (10H, m, aromatic H).

(1′*R*,2*R*)-1-[*N*-(2-Hydroxy-1-phenylethyl)-*N*-isopropylamino]-2-phenylpyrrolidine (**8d**): C_6H_5MgBr (4 ml of a 1 M solution in THF) was used. Colorless plates, mp 63—64 °C (hexane). $[\alpha]_D$ +114.3° (c=1.45, EtOH). MS *m/z*: Calcd for $C_{12}H_{28}N_2O$: 324.2202 (M^+); Found: 324.2202. CI, 325 (M^++1), 203 (M^+−$PhCHCH_2OH$). ^{1}H-NMR ($CDCl_3$) δ: 0.50 (3H, d, J=6.7 Hz, $CHCH_3$), 1.10 (3H, d, J=6.7 Hz, $CHCH_3$), 1.89—2.17 (4H, m, CH_2CH_2), 2.82 (1H, q, J=8.5 Hz, NCH_2), 3.05 (1H, t, J=9.2 Hz, $PhCH$), 3.20—3.30 (3H, m, NCH_2, $CH(CH_3)_2$, and $NCHCH_2O$), 3.82 (1H, dd, J=4.3, 8.5 Hz, $NCHCH_2O$), 4.04 (1H, dd, J=2.4, 8.5 Hz, $NCHCH_2O$), 5.3 (1H, br s, OH), 6.80—7.47 (10H, m, aromatic H).

(*R*)-1-Amino-2-benzylpyrrolidine (10) (*R*)-2-Benzylpyrrolidine (**9**)[5] (3.2 g, 20 mmol) was converted into the *N*-nitroso compound by treatment with $NaNO_2$ and acetic acid, and the product was reduced with $LiAlH_4$ as described for the preparation of (*R*)-**3** to give (*R*)-**10** (2.5 g, 70%). Colorless oil, bp 119—120 °C (3 mmHg). $[\alpha]_D$ +64.5° (c=1.25, EtOH). MS *m/z*: CI, 177 (M^++1), 85 (M^+−$PhCH_2$). ^{1}H-NMR ($CDCl_3$) δ: 1.45—1.86 (4H, m, CH_2CH_2), 2.26—2.42 (2H, m, NCH_2), 2.54 (1H, dd, J=9.3, 13.1 Hz, $PhCH_2$), 2.9 (2H, br s, NH_2), 3.17 (1H, dd, J=4.3, 13.1 Hz, $PhCH_2$), 3.27—3.34 (1H, m, $PhCH_2CH$), 7.16—7.31 (5H, m, aromatic H).

(*R*)-2-Benzyl-1-isopropylaminopyrrolidine (11) i) From (*R*)-**10**: A solution of (*R*)-**10** (0.18 g, 1 mmol) in acetone (10 ml) was refluxed for 3 h, and then the solvent was removed. A solution of the residue in THF (1 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.038 g, 1 mmol) in THF (10 ml), and the reaction mixture was refluxed for 20 h. A small amount of water was added, and the resulting white precipitate was filtered off. The filtrate was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel with a solution of ether–hexane (1 : 3) to give (*R*)-**11** (0.17 g, 78%) as a colorless oil. $[\alpha]_D$ +101.1° (c=1.00, EtOH). MS *m/z*: Calcd for $C_{14}H_{22}N_2$: 218.1782 (M^+); Found: 218.1744. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, d, J=6.1 Hz, $CHCH_3$), 1.07 (3H, d, J=6.1 Hz, $CHCH_3$), 1.37—1.79 (1H, m, CH_2CH_2), 2.0 (1H, br s, NH), 2.08—2.18 (1H, m, NCH_2), 2.38 (1H, dd, J=9.8, 13.1 Hz, $PhCH_2$), 2.50—2.60 (1H, m, NCH_2), 3.04 (1H, septet, J=6.1 Hz, $CH(CH_3)_2$), 3.29 (1H, dd, J=3.7, 13.1 Hz, $PhCH_2$), 3.44—3.51 (1H, m, $PhCH_2CH$), 7.13—7.29 (5H, m, aromatic H).

ii) From (1′*R*,2*R*)-**8c**: A solution of (1′*R*,2*R*)-**8c** (0.18 g, 0.5 mmol) in methanol (5 ml) was treated with 10% Pd–carbon (0.91 g) and concentrated HCl (0.5 ml), and the mixture was shaken in a hydrogen atmosphere at room temperature for 3 h under a pressure of 3 kg/cm^2. The catalyst was then filtered off and the filtrate was concentrated under reduced pressure. The phenylethanol thus prepared was extracted into ether, and the residual solution was made alkaline with 1 N NaOH aqueous solution and extracted with ether. The ethereal solution was concentrated and the residue was subjected to column chromatography on silica gel with a solution of ether–hexane (1 : 3) to give (*R*)-**11** (0.04 g, 39%). $[\alpha]_D$ +96.1° (c=1.27, EtOH). This compound was identical with (*R*)-**11** prepared from (*R*)-**10** on the basis of ^{1}H-NMR spectral comparison.

(*R*)-1-Amino-2-methylpyrrolidine (13) (*R*)-2-Methylpyrrolidine hydrochloride (**12**)[6] (2.4 g, 20 mmol) was converted into the *N*-nitroso compound by treatment with $NaNO_2$ and acetic acid, and the product was reduced with $LiAlH_4$ as described for the preparation of (*R*)-**3** to give (*R*)-**13** (1.3 g, 65%). Colorless oil, bp 62—67 °C (62 mmHg). $[\alpha]_D$ −35.7° (c=1.23, EtOH). MS *m/z*: CI, 101 (M^++1). ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, d, J=6.1 Hz, $CHCH_3$), 1.36—2.02 (4H, m, CH_2CH_2), 2.17 (1H, dq, J=9.2, 6.1 Hz, $CHCH_3$), 2.30 (1H, q, J=9.2 Hz, NCH_2), 2.9 (2H, br s, NH_2), 3.27 (1H, dt, J=9.2, 3.1 Hz, NCH_2).

1-(α-Ethoxycarbonylbenzylideneamino)-2-methylpyrrolidines (14) A mixture of (*R*)-**13** (1.0 g, 10 mmol) and ethyl phenylglyoxylate (2.0 g, 11 mmol) was stirred at 60 °C for 2 h, and the reaction mixture was diluted with CH_2Cl_2 (20 ml). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel with a solution of ether–hexane (1 : 3) to give a mixture of two isomers as a pale yellow oil (2.5 g, 95%; 62 : 38 mixture), which was unstable at room temperature. ^{1}H-NMR ($CDCl_3$) δ: Major component; 1.11 (3H, d, J=6.1 Hz, $CHCH_3$), 1.40 (3H, t, CH_2CH_3), 1.56—1.97 (4H, m, CH_2CH_2), 2.13—2.25 (1H, m, NCH_2), 2.95—2.99 (1H, m, NCH_2), 3.01—3.73 (1H, m, $CHCH_3$), 4.38 (2H, q, J=6.7 Hz, CH_2CH_3), 7.41—8.07 (5H, m, aromatic H). Minor component; 1.29 (3H, t, J=7.3 Hz, CH_2CH_3), 1.33 (3H, d, J=6.1 Hz, $CHCH_3$), 1.35—2.01 (4H, m, CH_2CH_2), 2.59 (1H, q, J=7.9 Hz, NCH_2), 2.77 (1H, dt, J=7.9, 4.3 Hz, NCH_2), 3.80 (1H, sextet, J=6.1 Hz, $CHCH_3$), 4.24 (2H, q, J=7.3 Hz, CH_2CH_3), 7.23—7.45 (5H, m, aromatic H).

(1′*R*,2*R*)- and (1′*S*,2*R*)-1-[*N*-(2-Hydroxy-1-phenylethyl)amino]-2-methylpyrrolidines (15) A solution of the mixture of two isomers of **14** (2.3 g, 9 mmol) in THF (10 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.7 g, 18 mmol) in THF (20 ml), and stirring was continued at room temperature for 20 h. The reaction mixture was worked up with a small amount of water, and the resulting precipitate was filtered off. The filtrate was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel with CH_2Cl_2. The first fraction gave (1′*R*,2*R*)-**15** (0.61 g, 28%) as a colorless oil. $[\alpha]_D$ −23.9° (c=1.30, EtOH). MS *m/z*: CI, 221 (M^++1), 189 (M^+−CH_2OH). ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, d, J=6.1 Hz, $CHCH_3$), 1.61—1.99 (4H, m, CH_2CH_2), 2.03 (1H, q, J=9.2 Hz, NCH_2), 2.43—2.51 (1H, m, NCH_2), 2.5—2.6 (1H, br s, NH or OH), 2.8—3.0 (1H, br s, NH or OH), 3.68 (1H, dd, J=1.8, 4.2 Hz, $NCHCH_2O$), 3.73—3.79 (1H, m, $CHCH_3$), 3.91 (1H, dd, J=4.2, 9.2 Hz, $NCHCH_2O$), 4.28 (1H, dd, J=1.8, 9.2 Hz, $NCHCH_2O$), 7.23—7.38 (5H, m, aromatic H).

The second fraction gave (1′*S*,2*R*)-**15** (0.42 g, 19%) as a pale yellow oil. $[\alpha]_D$ −162.2° (c=0.20, EtOH). MS *m/z*: CI, 221 (M^++1), 189 (M^+−CH_2OH). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, d, J=6.7 Hz, $CHCH_3$), 1.38—2.01 (4H, m, CH_2CH_2), 2.8—2.9 (2H, br, NH and OH), 2.66—2.76 (1H, m, NCH_2), 2.73 (1H, q, J=8.5 Hz, NCH_2), 3.12—3.20 (1H, m, $CHCH_3$), 3.72 (1H, dd, J=3.1, 10.4 Hz, $NCHCH_2O$), 3.94 (1H, dd, J=8.6, 10.4 Hz, $NCHCH_2O$), 4.32 (1H, dd, J=3.1, 8.6 Hz, $NCHCH_2O$), 7.23—7.38 (5H, m, aromatic H).

Preparation of (1′*R*,2*R*)-7a CH_3I (2.27 g, 16 mmol) and anhydrous K_2CO_3 (0.2 g) were added to a solution of (1′*R*,2*R*)-**15** (0.22 g, 1 mmol) in *N*,*N*-dimethylformamide (DMF, 4 ml). After being stirred at room temperature for 20 h, the reaction mixture was poured into water and extracted with ether. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure, and the residue was subjected to column chromatography on silica gel with a solution of ether–hexane (1 : 3) to give (1′*R*,2*R*)-**7a** (0.16 g, 68%) as a colorless oil. $[\alpha]_D$ −7.9° (c=0.44, EtOH). This compound was identical with the major component [(1′*R*,2*R*)] of **7a** on the basis of ^{1}H-NMR spectral comparison.

Preparation of (1′*S*,2*R*)-16 (1′*S*,2*R*)-**15** (0.22 g, 1 mmol) gave (1′*S*,2*R*)-**16** (0.18 g, 77%) as a colorless oil in a similar manner to that described for the preparation of (1′*R*,2*R*)-**7a**. $[\alpha]_D$ −121.8° (c=1.21, EtOH). This compound was identical with the minor component [(1′*R*,2*S*)] of **7a** on the basis of ^{1}H-NMR spectral comparison.

2-Benzyl-1-(α-ethoxycarbonylbenzylideneamino)pyrrolidines (17) (*R*)-**10** (1.8 g, 10 mmol) was condensed with ethyl phenylglyoxylate (2.0 g, 11 mmol) to give a pale yellow oil (2.0 g, 86%) in a similar manner to that employed in the preparation of (*R*)-**14**. This product was a mixture of two isomers (ratio, 64 : 36) and was unstable at room temperature. ^{1}H-NMR ($CDCl_3$) δ: Major component; 1.31 (3H, t, J=7.3 Hz, CH_2CH_3), 1.44—1.80 (4H, m, CH_2CH_2), 2.54—2.75 (2H, m, NCH_2), 2.82 (1H, dd, J=9.6, 13.4 Hz, $PhCH_2$), 3.29 (1H, dd, J=3.7, 13.4 Hz, $PhCH_2$), 3.98—4.05 (1H, m, $PhCH_2CH$), 4.22 (1H, dq, J=11.0, 7.3 Hz, CH_2CH_3),

4.31 (1H, dq, J=11.0, 7.3 Hz, CH_2CH_3), 7.19—7.34 (10H, m, aromatic H). Minor component; 1.37 (3H, t, J=7.0 Hz, CH_2CH_3), 1.54—1.89 (4H, m, CH_2CH_2), 2.78 (1H, dd, J=9.2, 13.4 Hz, $PhCH_2$), 3.02—3.11 (1H, m, NCH_2), 3.30 (1H, dd, J=4.3, 13.4 Hz, $PhCH_2$), 3.35—3.44 (1H, m, NCH_2), 3.82—3.91 (1H, m, $PhCH_2CH$), 4.31—4.41 (2H, m, CH_2CH_3), 7.18—7.35 (10H, m, aromatic H).

(1′*R*,2*R*)- and (1′*S*,2*R*)-2-Benzyl-1-[*N*-(2-hydroxy-1-phenylethyl)amino]-pyrrolidines (18) A solution of the mixture of two isomers of **17** (3.0 g, 8.9 mmol) was reduced with $LiAlH_4$ (0.7 g, 18 mmol) in a similar manner to that employed in the preparation of (1′*R*,2*R*)- and (1′*S*,2*R*)-**15**. The first fraction gave (1′*S*,2*R*)-**18** (1.05 g, 40%) as a colorless oil. $[\alpha]_D$ +56.9° (c=1.18, EtOH). MS m/z: CI, 297 (M^++1), 205 (M^+−$PhCH_2$), 175 (M^+−$PhCHCH_2OH$). ^{1}H-NMR ($CDCl_3$) δ: 1.5—1.6 (2H, br, NH and OH), 1.43—1.81 (4H, m, CH_2CH_2), 2.03—2.13 (1H, m, NCH_2), 2.55 (1H, dd, J=9.8, 12.2 Hz, $PhCH_2$), 2.16—2.66 (1H, m, NCH_2), 3.67 (1H, dd, J=3.1, 12.2 Hz, $PhCH_2$), 3.69 (1H, dd, J=2.4, 11.0 Hz, $NCHCH_2O$), 3.80—3.87 (1H, m, $PhCH_2CH$), 4.00 (1H, dd, J=9.2, 11.0 Hz, $NCHCH_2O$), 4.34 (1H, dd, J=2.4, 9.2 Hz, $NCHCH_2O$), 7.18—7.41 (10H, m, aromatic H).

The second fraction gave (1′*R*,2*R*)-**18** (1.02 g, 39%) as colorless needles, mp 107—108 °C (ether–hexane). $[\alpha]_D$ +124.6° (c=1.24, EtOH). MS m/z: CI, 297 (M^++1), 265 (M^+−CH_2OH). ^{1}H-NMR ($CDCl_3$) δ: 1.6—1.8 (2H, m, NH and OH), 1.41—1.80 (4H, m, CH_2CH_2), 2.51 (1H, dd, J=10.1, 12.8 Hz, $PhCH_2$), 2.65—2.75 (1H, m, NCH_2), 2.81—2.92 (1H, m, NCH_2), 3.30 (1H, dd, J=4.3, 12.8 Hz, $PhCH_2$), 3.74 (1H, dd, J=3.1, 10.4 Hz, $NCHCH_2O$), 3.90 (1H, dd, J=8.9, 10.4 Hz, $NCHCH_2O$), 4.27 (1H, dd, J=3.1, 8.9 Hz, $NCHCH_2O$), 7.14—7.39 (10H, m, aromatic H).

Preparation of (1′*R*,2*R*)-7c CH_3I (2.27 g, 16 mmol) and anhydrous K_2CO_3 (0.2 g) were added to a solution of (1′*R*,2*R*)-**18** (0.30 g, 1 mmol) in DMF (4 ml) in a similar manner to that described for the preparation of (1′*R*,2*R*)-**7a** to give (1′*R*,2*R*)-**7c** (0.21 g, 69%) as a colorless oil. $[\alpha]_D$ +22.0° (c=0.07, EtOH). This compound was identical with the minor component [(1′*R*,2*R*)] of **7c** on the basis of ^{1}H-NMR spectral comparison.

Preparation of (1′*S*,2*R*)-19 (1′*S*,2*R*)-**18** (0.30 g, 1 mmol) gave (1′*S*,2*R*)-**19** (0.16 g, 53%) as a colorless oil in the same manner as employed in the preparation of (1′*R*,2*R*)-**7c**. $[\alpha]_D$ −5.9° (c=0.06, EtOH). This compound was identical with the major component [(1′*R*,2*S*)] of **7c** on the basis of ^{1}H-NMR spectral comparison.

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