The Absolute Configuration and Stereoselective Grignard Reaction of *N*-Substituted 4-Phenyl-1,3-oxazolidines

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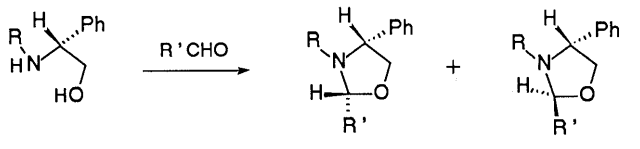
The configuration at the 2-position of 2-(*p*-bromophenyl)-*N*-methyl-4-phenyl-1,3-oxazolidine (2a) was determined by X-ray analysis. The reactions of 2,4-diphenyl- and 2-methyl-4-phenyl-1,3-oxazolidines (2b—d and 2e—g) with methyl and phenylmagnesium bromides were investigated.

Keywords absolute configuration; organomagnesium complex; Grignard reaction; immonium salt intermediate; 1-phenylethylamine; (*R*)-phenylglycinol; 4-phenyl-1,3-oxazolidine; stereoselective reaction; X-ray analysis

Chiral 1,3-oxazolidines are easily obtained by the condensation of (*R*)- and (*S*)-2-hydroxyethylamines with carbaldehydes, and these compounds play an important role in the stereoselective Grignard reaction.[1-3] However, the structures have not been fully elucidated because it was considered difficult to determine them by circular dichroism (CD)[1] and nuclear magnetic resonance (NMR)[2,4] spectral analyses. Initially,[5] the structure of 1,3-oxazolidine synthesized from *l*-ephedrine and *p*-bromobenzaldehyde was reported to have *trans* configuration at the 2-position of the ring. But, this structure was revised to *cis* configuration on the basis of an X-ray analysis.[6] In this paper, we wish to describe the structure of 2-(*p*-bromophenyl)-*N*-methyl-4-phenyl-1,3-oxazolidine (**2a**), and the stereoselective Grignard reaction of **2a** and analogous compounds (**2b—g**).

The *N*-substituted 4-phenyl-1,3-oxazolidines (**2a—g**) were synthesized by the condensation of *N*-substituted (*R*)-phenylglycinols [*N*-methyl (**1a**),[7] *N*-benzyl (**1b**),[8] and *N*-isopropyl (**1c**)[9]] with carbaldehydes (*p*-bromobenzaldehyde, benzaldehyde, and acetaldehyde). These products were shown to consist of mixtures of two diastereomeric isomers; the minor component amounted to less than 5% as judged from the ^{1}H-NMR spectra, except in the case of the *N*-benzyl derivatives (**2c** and **2f**) where the ratios of the major to the minor components were 85 : 15 and 88 : 12. It was not possible to isolate the major product owing to cleavage of the 1,3-oxazolidine ring during column chromatography. The major product in the case of **2a** was purified by recrystallization.



1	R
a	CH_3
b	$CH_2C_6H_5$
c	iso-C_3H_7

2	R	R'
a	CH_3	*p*-Br–C_6H_4
b	CH_3	C_6H_5
c	$CH_2C_6H_5$	C_6H_5
d	iso-C_3H_7	C_6H_5
e	CH_3	CH_3
f	$CH_2C_6H_5$	CH_3
g	iso-C_3H_7	CH_3

Chart 1

The absolute configuration of **2a** was elucidated by X-ray analysis. A colorless columnar crystal of **2a** was used. The atomic numbering of **2a** is shown in Fig. 1, and the crystal data are summarized in Table I.

Stereoscopic drawings of the molecular structure are shown in Fig. 2. 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.

It was determined that the substituent at the 2-position of the ring in **2a** is attached in a *cis* relationship to the phenyl group at the 4-position. The structures of the major products of **2b—g** may be assumed to have the same configuration because the reactions of **1a—c** with carbaldehydes are expected to proceed *via* a similar reaction mechanism. We had tentatively assigned the *trans* configuration to **2e** based on ^{13}C-NMR spectrometric analysis,[2] but the *cis* configuration was clearly indicated for the structures of 4-phenyl-1,3-oxazolidines obtained from (*R*)-phenylglycinols and carbaldehydes in the present work.

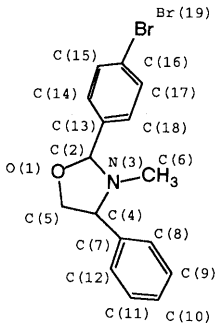


Fig. 1. Atomic Numbering of (2*R*,4*R*)-**2a**

TABLE I. Crystal Data

Chemical formula	$C_{16}H_{16}BrNO$
Formula weight	318.21
Crystal system	Monoclinic
Cell dimensions	a = 11.069 (7) (Å)
	b = 5.985 (3) (Å)
	c = 11.031 (4) (Å)
	β = 92.52 (4) (°)
Cell volume (Å^3)	730.0 (6)
Space group	$P2_1$
Z	2
D_c (g cm^{-3})	1.45

The reaction of **2a** with methylmagnesium bromide (CH_3MgBr) gave a diastereomeric mixture of (1*S*,1′*R*)- and (1*R*,1′*R*)-*N*-2′-hydroxy-1′-phenylethyl-*N*-methyl-1-(*p*-bromophenyl)ethylamines (**3a**). The reaction of **2b—d** with CH_3MgBr gave diastereomeric mixtures of **3b—d**, while the similar reactions of of **2e—g** with phenylmagnesium bromide (C_6H_5MgBr) also gave **3b—d** but in different major–minor product ratios. The structures and the diastereomeric ratios of these products were determined by ^{1}H-NMR analysis (Chart 3 and Table IV).

The absolute configuration at the 1-position of the products was elucidated as follows: (*S*)-*N*-1′-phenyl-1′-ethoxycarbonylmethylidene-1-phenylethylamine (**4**) was synthesized by the condensation of (*S*)-1-phenylethylamine and ethyl phenylglyoxylate, and a mixture of (1*S*,1′*R*)- and (1*S*,1′*S*)-*N*-2′-hydroxy-1′-phenylethyl-1-phenylethylamine (**5**) was obtained by the reduction of **4**, while (1*S*,1′*R*)-**5** was also obtained by the known route.[10] The condensation of

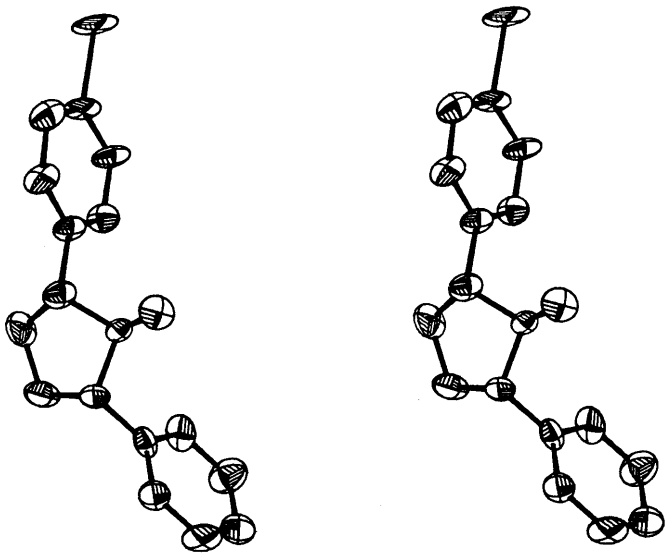


Fig. 2. Stereoscopic Drawings of the Structure of (2*R*,4*R*)-**2a**

TABLE II. Positional and Thermal Parameters of (2*R*,4*R*)-**2a** for Nonhydrogen Atoms with Their Standard Deviations in Parentheses

Atom	*X*	*Y*	*Z*	B_{eq} (Å^2)[a]
O(1)	0.710 (2)	0.872 (4)	0.170 (2)	4.7
C(2)	0.621 (2)	0.725 (1)	0.217 (2)	3.4
N(3)	0.637 (2)	0.750 (5)	0.351 (2)	2.6
C(4)	0.772 (1)	0.746 (3)	0.367 (1)	3.4
C(5)	0.807 (1)	0.904 (3)	0.260 (1)	4.3
C(6)	0.578 (2)	0.573 (4)	0.415 (2)	4.1
C(7)	0.812 (2)	0.841 (5)	0.489 (2)	2.9
C(8)	0.765 (2)	1.042 (4)	0.530 (2)	3.8
C(9)	0.803 (2)	1.132 (6)	0.645 (2)	4.9
C(10)	0.890 (2)	1.025 (4)	0.716 (2)	4.9
C(11)	0.937 (2)	0.813 (4)	0.675 (2)	4.7
C(12)	0.900 (2)	0.723 (4)	0.560 (2)	3.9
C(13)	0.497 (2)	0.801 (4)	0.172 (2)	2.9
C(14)	0.433 (2)	0.658 (7)	0.090 (2)	3.7
C(15)	0.316 (2)	0.730 (5)	0.040 (2)	4.1
C(16)	0.275 (2)	0.930 (5)	0.081 (2)	3.6
C(17)	0.335 (2)	1.075 (4)	0.163 (2)	3.4
C(18)	0.450 (2)	1.015 (5)	0.208 (2)	3.4
Br(19)	0.115 (2)	1.022 (4)	0.023 (2)	5.5

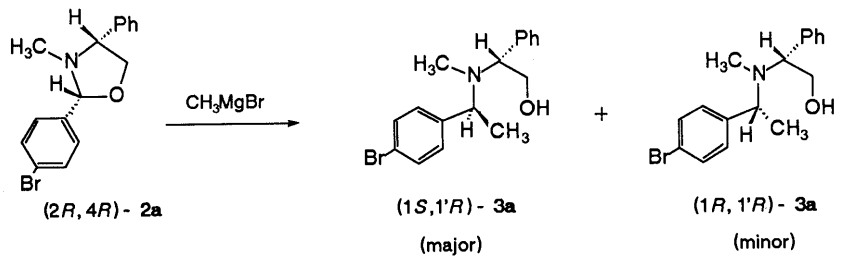
a) $B_{eq}=(4/3)\sum_i\sum_j \beta_{ij}\boldsymbol{a}_i\cdot\boldsymbol{a}_j$.

TABLE III. Bond Distances (Å) and Bond Angles (°) of (2*R*,4*R*)-**2a** for Nonhydrogen Atoms with Their Standard Deviations in Parentheses

Bond distance			
O(1)–C(2)	1.432 (31)	C(9)–C(10)	1.368 (52)
O(1)–C(5)	1.461 (33)	C(10)–C(11)	1.469 (50)
C(2)–C(13)	1.513 (33)	C(11)–C(12)	1.416 (38)
N(3)–C(2)	1.481 (30)	C(13)–C(14)	1.412 (34)
N(3)–C(4)	1.502 (31)	C(14)–C(15)	1.459 (38)
N(3)–C(6)	1.449 (34)	C(15)–C(16)	1.365 (37)
C(4)–C(5)	1.570 (37)	C(17)–C(16)	1.400 (35)
C(7)–C(4)	1.511 (34)	C(18)–C(17)	1.387 (44)
C(7)–C(8)	1.378 (43)	C(18)–C(13)	1.449 (43)
C(7)–C(12)	1.416 (35)	Br(19)–C(16)	1.935 (25)
C(8)–C(9)	1.428 (47)		
Bond angle			
O(1)–C(2)–C(13)	108.6 (19)	C(8)–C(9)–C(10)	120.3 (31)
O(1)–C(5)–C(4)	102.8 (20)	C(9)–C(10)–C(11)	118.3 (34)
C(2)–O(1)–C(5)	109.3 (19)	C(10)–C(11)–C(12)	120.9 (27)
C(2)–N(3)–C(4)	100.5 (17)	C(7)–C(12)–C(11)	118.3 (24)
N(3)–C(2)–O(1)	104.6 (18)	C(2)–C(13)–C(14)	116.8 (21)
N(3)–C(2)–C(13)	111.1 (19)	C(2)–C(13)–C(18)	120.8 (23)
N(3)–C(4)–C(5)	100.8 (19)	C(13)–C(14)–C(15)	118.8 (23)
N(3)–C(4)–C(7)	109.9 (19)	C(14)–C(15)–C(16)	115.4 (24)
C(6)–N(3)–C(2)	111.5 (19)	C(15)–C(16)–C(17)	127.5 (24)
C(6)–C(3)–C(4)	113.5 (19)	C(16)–C(17)–C(18)	118.2 (25)
C(7)–C(4)–C(5)	111.5 (20)	C(17)–C(18)–C(13)	117.7 (28)
C(4)–C(7)–C(8)	121.2 (24)	C(18)–C(13)–C(14)	122.3 (24)
C(4)–C(7)–C(12)	118.3 (21)	Br(19)–C(16)–C(15)	116.4 (19)
C(8)–N(7)–C(12)	120.5 (25)	Br(19)–C(16)–C(17)	116.1 (18)
C(7)–C(8)–C(9)	121.6 (30)		

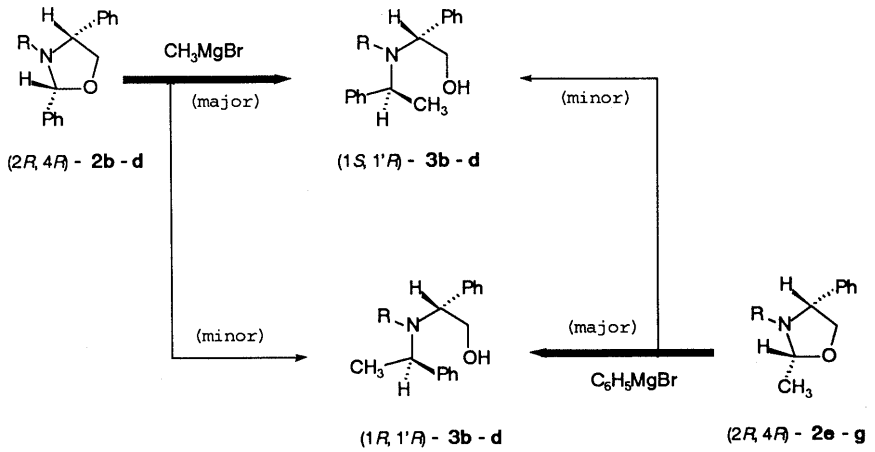
TABLE IV. Diastereoselective Reaction of *N*-Substituted 4-Phenyl-1,3-oxazolidines (**2a—g**) with Grignard Reagents

Substrate	Reagent	Reaction time (h)	Product	Yield (%)	Ratio of (1*S*,1′*R*):(1*R*,1′*R*)
2a	CH_3MgBr	20	**3a**	80.5	66:34
2b	CH_3MgBr	20	**3b**	86.2	66:34
2c	CH_3MgBr	20	**3c**	94.4	84:16
2d	CH_3MgBr	72	**3d**	89.6	97: 3
2e	C_6H_5MgBr	15	**3b**	90.3	22:78
2f	C_6H_5MgBr	15	**3c**	92.1	23:77
2g	C_6H_5MgBr	15	**3d**	89.4	11:88



(2*R*,4*R*)-**2a** → (1*S*,1′*R*)-**3a** (major) + (1*R*,1′*R*)-**3a** (minor)

Chart 2



Compound	R
2b, **2e**, **3b**	CH_3
2c, **2f**, **3c**	$CH_2C_6H_5$
2d, **2g**, **3d**	iso-C_3H_7

Chart 3

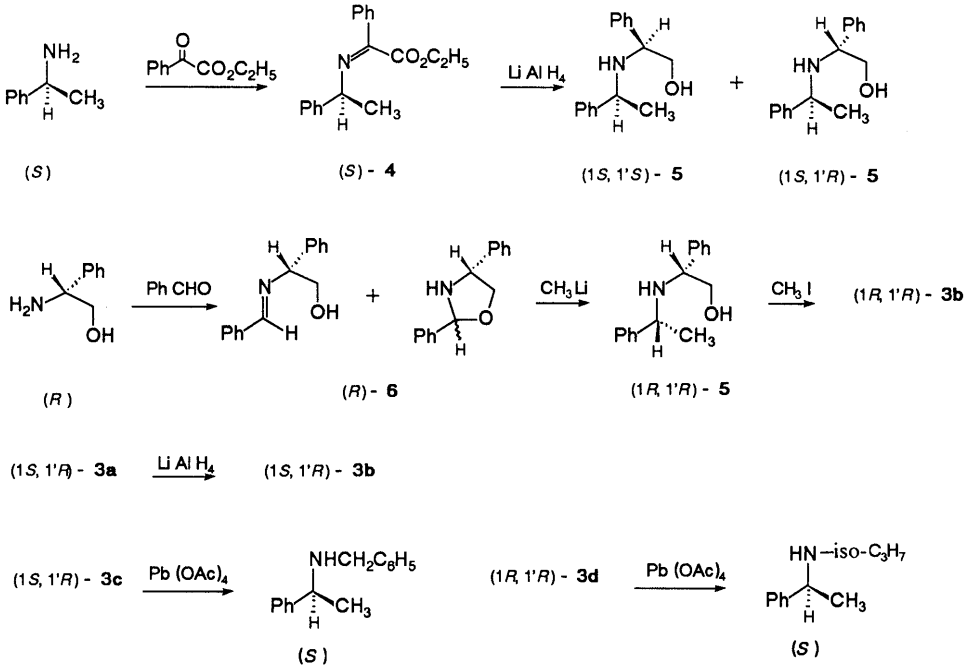


Chart 4

(*R*)-phenylglycinol and benzaldehyde gave a mixture [(*R*)-**6**] of (*R*)-*N*-benzylidene-2-hydroxy-1-phenylethylamine and 2,4-diphenyl-1,3-oxazolidines. The product [(1*R*,1′*R*)-**5**] was derived from the mixture [(*R*)-**6**] and was proved to be identical with (1*S*,1′*S*)-**5** obtained from (*S*)-**4** by ^{1}H-NMR spectral comparison. Thus, the *N*-methylation product of (1*R*,1′*R*)-**5** was identical with the minor product [(1*R*,1′*R*)-**3b**] obtained from **2b**.

The reduction of the mixture of (1*S*,1′*R*)- and (1*R*,1′*R*)-**3a** (ratio, 66 : 34) with lithium aluminum hydride ($LiAlH_4$) gave a mixture of (1*S*,1′*R*)- and (1*R*,1′*R*)-**3b** (ratio, 65 : 35) in 87% yield. On the other hand, the mixture of (1*S*,1′*R*)- and (1*R*,1′*R*)-**3c** (ratio, 84 : 16) gave (*S*)-*N*-benzyl-1-phenylethylamine[11] upon oxidative cleavage with lead tetraacetate, while (1*S*,1′*R*)-**3d** gave (*S*)-*N*-isopropyl-1-phenylethylamine[12] when subjected to the same oxidative cleavage.

The configurations of the major products obtained from **2b**—**d** were the same as those of the minor products obtained from **2e**—**g**, as shown in Chart 3, and so it was considered that the stereoselective Grignard reactions of the *N*-substituted 4-phenyl-1,3-oxazolidines occur by a similar reaction mechanism. Moreover, the stereoselectivity of this reaction was suggested to increase with increasing bulkiness of the *N*-substituent, *i.e.*, methyl < benzyl < isopropyl, as shown in Table IV. Consequently, we propose a possible reaction mechanism in which the Grignard reagent approaches the oxygen atom of the 1,3-oxazolidine ring to give a favorable intermediate immonium salt, and nucleophilic attack occurs from the *si*-face of the carbon–nitro-

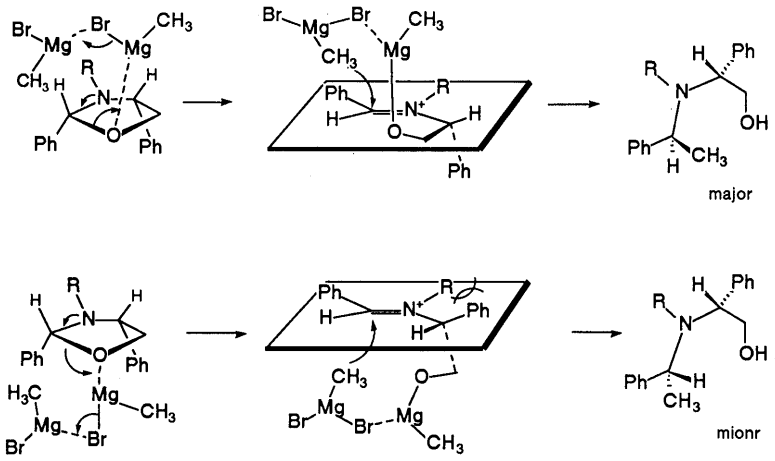


Chart 5

gen double bond as shown in Chart 5.

Experimental

The ^{1}H-NMR spectra were obtained with a JEOL JNM-GSX270 spectrometer, and the mass spectra (MS) were recorded with a JEOL JMS-D300 spectrometer by using the chemical ionization (CI) (isobutane) and the electron impact (EI) 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.

Condensation of (*R*)-1a—c with Benzenecarbaldehydes A mixture of (*R*)-**1a**—**c** (10 mmol) and benzenecarbaldehyde (*p*-bromobenzaldehyde and benzaldehyde, 11 mmol) in benzene (25 ml) was refluxed for 2—30 h using a Dean–Stark trap. The mixture was concentrated under reduced pressure to give 4-phenyl-1,3-oxazolidines (**2a**—**d**).

(2*R*,4*R*)-2-(*p*-Bromophenyl)-*N*-methyl-4-phenyl-1,3-oxazolidine (**2a**): Colorless columns, mp 131.5 °C (from EtOH). Yield, 91%. MS *m/z*: CI, 318 ($M^+ + 1$), 320 ($M^+ + 3$); EI, 162 ($M^+ - C_6H_4Br$, base peak). ^{1}H-NMR ($CDCl_3$) δ: 2.09 (3H, s, NCH_3), 3.75 (1H, dd, J=7.3, 9.2 Hz, $NC\underline{H}CH_2O$), 3.89 (1H, dd, J=7.3, 9.2 Hz, $NCHC\underline{H}_2O$), 4.30 (1H, t, J=7.3 Hz, $NCHC\underline{H}_2O$), 4.79 (1H, s, NCHO), 7.29—7.77 (9H, m, aromatic H). $[\alpha]_D$ −21.8° (c=3.66, $CHCl_3$). *Anal.* Calcd for $C_{16}H_{16}BrNO$: C, 60.39; H, 5.07; N, 4.40. Found: C, 60.39; H, 5.02; N, 4.38.

(2*R*,4*R*)-*N*-Methyl-2,4-diphenyl-1,3-oxazolidine (**2b**): Colorless oil, bp 139.5 °C (0.8 mmHg). Yield, 82.2% (97:3 mixture). MS *m/z*: CI, 240 ($M^+ + 1$); EI, 162 ($M^+ - C_6H_5$, base peak). ^{1}H-NMR ($CDCl_3$) δ: major component: 2.10 (3H, s, NCH_3), 3.75 (1H, dd, J=7.5, 9.0 Hz, $NC\underline{H}CH_2O$), 3.91 (1H, dd, J=7.5, 9.0 Hz, $NCHC\underline{H}_2O$), 4.31 (1H, t, J=7.5 Hz, $NCHC\underline{H}_2O$), 4.83 (1H, s, NCHO), 7.25—7.62 (10H, m, aromatic H). $[\alpha]_D$ −52.1° (c=1.28, *n*-hexane). *Anal.* Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.46; H, 7.11; N, 5.88.

(2*R*,4*R*)-*N*-Benzyl-2,4-diphenyl-1,3-oxazolidine (**2c**): Colorless oil, bp 183 °C (0.4 mmHg). Yield, 85.4% (85:15 mixture). MS *m/z*: CI, 316 ($M^+ + 1$); EI, 238 ($M^+ - C_6H_5$), 91 ($C_7H_7^+$, base peak). ^{1}H-NMR ($CDCl_3$) δ: major component: 3.68 (2H, s, $PhCH_2N$), 3.88 (1H, t, J=7.3 Hz, $NC\underline{H}CH_2O$), 4.03 (1H, t, J=7.3 Hz, $NCHC\underline{H}_2O$), 4.22 (1H, t, J=7.3 Hz, $NCHC\underline{H}_2O$), 5.14 (1H, s, NCHO), 6.95—7.65 (15H, m, aromatic H); minor component: 3.15 (1H, d, J=14.3, $PhCH_2N$), 3.52 (1H, d, J=14.3 Hz, $PhCH_2N$), 4.17 (1H, dd, J=4.4, 7.4 Hz, $NC\underline{H}CH_2O$), 4.38 (1H, dd, J=4.4, 6.4 Hz, $NCHC\underline{H}_2O$), 4.58 (1H, dd, J=6.4, 7.4 Hz, $NCHC\underline{H}_2O$), 5.53 (1H, s, NCHO), 6.95—7.65 (15H, m, aromatic H). $[\alpha]_D$ −34.4° (c=1.28, *n*-hexane). *Anal.* Calcd for $C_{22}H_{21}NO$: C, 83.77; H, 6.71; N, 4.44. Found: C, 83.80; H, 6.72; N, 4.82.

(2*R*,4*R*)-*N*-Isopropyl-2,4-diphenyl-1,3-oxazolidine (**2d**): Colorless oil, bp 148 °C (0.75 mmHg). Yield, 86.5% (95:5 mixture). MS *m/z*: CI, 268 ($M^+ + 1$); EI, 252 ($M^+ - CH_3$, base peak), 190 ($M^+ - C_6H_5$). ^{1}H-NMR ($CDCl_3$) δ: major component: 0.92 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.95 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 3.02 (1H, septet, J=6.6 Hz, $C\underline{H}(CH_3)_2$), 3.77 (1H, dd, J=7.1, 7.5 Hz, $NC\underline{H}CH_2O$), 4.20 (1H, t, J=7.5 Hz, $NCHC\underline{H}_2O$), 4.27 (1H, dd, J=7.1, 7.5 Hz, $NCHC\underline{H}_2O$), 5.44 (1H, s, NCHO), 7.22—7.82 (10H, m, aromatic H). $[\alpha]_D$ −20.8° (c=1.22, *n*-hexane). *Anal.* Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.78; H, 8.09; N, 5.29.

Condensation of (*R*)-1a—c with Acetaldehyde A solution of (*R*)-**1a**—**c** (11 mmol) in CH_2Cl_2 (40 ml) was added dropwise to a stirred solution of acetaldehyde (33 mmol) in CH_2Cl_2 (10 ml) in the presence of anhydrous $MgSO_4$ (2 g) for 10 min. After being stirred at room temperature for 2—18 h, the solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was distilled *in vacuo* to give the corresponding 4-phenyl-1,3-oxazolidine (**2e**—**g**) as a colorless oil.

(2*R*,4*R*)-2,*N*-Dimethyl-4-phenyl-1,3-oxazolidine (**2e**): Colorless oil, bp 63 °C (0.6 mmHg). Yield, 82.2% (98:2 mixture). $[\alpha]_D$ −164.2° (c=1.10, *n*-hexane). This was found to be identical with the compound reported as (2*S*,4*R*)-2,*N*-dimethyl-4-phenyl-1,3-oxazolidine[2] by comparison of the ^{1}H-NMR spectra and the specific rotations [lit.,[2] bp 86—87 °C (7 mmHg); $[\alpha]_D$ −153.8° (c=0.70, *n*-hexane)].

(2*R*,4*R*)-*N*-Benzyl-2-methyl-4-phenyl-1,3-oxazolidine (**2f**): Colorless oil, bp 138.5 °C (1.0 mmHg). Yield, 90.9% (88:12 mixture). MS *m/z*: CI, 254 ($M^+ + 1$); EI, 238 ($M^+ - CH_3$), 91 ($C_7H_7^+$, base peak). ^{1}H-NMR ($CDCl_3$) δ: major component: 1.14 (3H, d, J=5.1 Hz, $CHC\underline{H}_3$), 3.50 (1H, d, J=14.0 Hz, $PhCH_2N$), 3.73 (1H, t, J=7.3 Hz, $NC\underline{H}CH_2O$), 3.87 (1H, d, J=14.0 Hz, $PhCH_2N$), 3.88 (1H, t, J=7.3 Hz, $NCHC\underline{H}_2O$), 4.14 (1H, t, J=7.3 Hz, $NCHC\underline{H}_2O$), 4.39 (1H, q, J=5.1 Hz, NCHO), 7.16—7.48 (10H, m, aromatic H); minor component: 1.28 (3H, d, J=5.5 Hz, $CHC\underline{H}_3$), 3.61 (1H, d, J=14.1 Hz, $PhCH_2N$), 3.71 (1H, J=14.1 Hz, $PhCH_2N$), 3.83 (1H, t, J=7.4 Hz, $NC\underline{H}CH_2O$), 4.16 (1H, t, J=7.4 Hz, $NCHC\underline{H}_2O$), 4.33 (1H, t, J=7.4 Hz, $NCHC\underline{H}_2O$), 4.85 (1H, q, J=5.5 Hz, NCHO), 7.16—7.48 (10H, m, aromatic H). $[\alpha]_D$ −87.3° (c=1.00, *n*-hexane). *Anal.* Calcd for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.56; H, 7.59; N, 5.39.

(2*R*,4*R*)-*N*-Isopropyl-2-methyl-4-phenyl-1,3-oxazolidine (**2g**): Colorless oil, bp 78 °C (0.5 mmHg). Yield, 78.5% (98:2 mixture). MS *m/z*: CI, 206 ($M^+ + 1$); EI, 190 ($M^+ - CH_3$). ^{1}H-NMR ($CDCl_3$) δ: major component: 0.97 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 1.02 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 1.39 (3H, d, J=5.3 Hz, $CHC\underline{H}_3$), 2.97 (1H, septet, J=6.7 Hz, $C\underline{H}(CH_3)_2$), 3.69 (1H, dd, J=5.4, 6.9 Hz, $NC\underline{H}CH_2O$), 4.10 (2H, m, $NCHC\underline{H}_2O$), 4.74 (1H, q, J=5.3 Hz, NCHO), 7.19—7.49 (5H, m, aromatic H). $[\alpha]_D$ −106.4° (c=1.00, *n*-hexane). *Anal.* Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.03; H, 9.58; N, 6.79.

Crystallographic Measurements A single crystal of (2*R*,4*R*)-**2a** was grown in ethanol as a colorless column with dimensions of 0.4 × 0.4 × 0.3 mm. All the measurements were performed on a Rigaku AFC-5 diffractometer using graphite-monochromated Cu K_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, 1445 independent reflections with $0° < 2\theta < 130°$ were collected, and 1031 satisfying the condition $F_O \geq 3\sigma(F)$ were used for calculations.

Structure Analysis and Refinement The structure was solved by the heavy atom method, 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 0.097.

Reaction of (2*R*,4*R*)-2a—d with CH_3MgBr CH_3MgBr (4.8 mmol, 1.6 ml of 3 M solution of ether) was added dropwise to a stirred solution of (2*R*,4*R*)-**2a**—**d** (1.6 mmol) in tetrahydrofuran (THF) (15 ml) at −10 °C under a nitrogen atmosphere. After being stirred at room temperature for 20 h, the reaction mixture was treated with a small amount of water, and the resulting white precipitate was filtered off. The filtrate was dried over

$MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel with *n*-hexane–ether (2 : 1) to give a diastereomeric mixture of (1*S*,1′*R*)- and (1*R*,1′*R*)-**3a—d** as a colorless oil. The experimental data are summarized in Table IV.

Reaction of (2*R*,4*R*)-2e—g with C_6H_5MgBr C_6H_5MgBr (9 mmol, 9 ml of 1 M solution of THF) was added dropwise to a stirred solution of (2*R*,4*R*)-**2e—g** (3 mmol) in THF (15 ml) at −10 °C under a nitrogen atmosphere, and the stirring was continued at room temperature for 20 h. After treatment of the reaction mixture as described for the reaction of (2*R*,4*R*)-**2a—d**, a diastereomeric mixture of (1*R*,1′*R*)- and (1*S*,1′*R*)-**3b—d** was obtained as a colorless oil. The experimental data are summarized in Table IV.

(1*S*,1′*R*)- and (1*R*,1′*R*)-*N*-2′-Hydroxy-1′-phenylethyl-*N*-methyl-1-(*p*-bromophenyl)ethylamine (**3a**): MS *m/z*: CI, 334 ($M^+ + 1$), 336 ($M^+ + 3$); EI, 120 (base peak). ^{1}H-NMR ($CDCl_3$) δ: (1*S*,1′*R*)-**3a**: 1.25 (3H, d, J=6.1 Hz, $CHC\underline{H}_3$), 2.22 (3H, s, NCH_3), 3.50 (1H, dd, J=5.5, 10.4 Hz, $NC\underline{H}CH_2O$), 3.63 (1H, q, J=6.1 Hz, $C\underline{H}CH_3$), 3.80 (1H, dd, J=5.5, 10.4 Hz, $NCHC\underline{H}_2O$), 3.95 (1H, t, J=10.4 Hz, $NCHC\underline{H}_2O$), 7.11—7.53 (9H, m, aromatic H); (1*R*,1′*R*)-**3a**: 1.36 (3H, d, J=6.1 Hz, $CHC\underline{H}_3$), 2.03 (3H, s, NCH_3). 3.63 (1H, q, J=6.1 Hz, $C\underline{H}CH_3$), 3.80 (1H, dd, J=5.5, 10.4 Hz, $NC\underline{H}CH_2O$), 3.93 (1H, t, J=10.4 Hz, $NCHC\underline{H}_2O$), 4.11 (1H, dd, J=5.5, 10.4 Hz, $NCHC\underline{H}_2O$), 7.12—7.53 (9H, m, aromatic H).

(1*S*,1′*R*)- and (1*R*,1′*R*)-*N*-2′-Hydroxy-1′-phenylethyl-*N*-methyl-1-phenylethylamine (**3b**): MS *m/z*: CI, 256 ($M^+ + 1$); EI, 120 (base peak). ^{1}H-NMR ($CDCl_3$) δ: (1*S*,1′*R*)-**3b**: 1.28 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 2.23 (3H, s, NCH_3), 3.49 (1H, dd, J=4.9, 9.8 Hz, $NC\underline{H}CH_2O$), 3.65 (1H, q, J=6.7 Hz, $C\underline{H}CH_3$), 3.85 (1H, dd, J=4.9, 9.8 Hz, $NCHC\underline{H}_2O$), 3.95 (1H, t, J=9.8 Hz, $NCHC\underline{H}_2O$), 7.14—7.41 (10H, m, aromatic H); (1*R*,1′*R*)-**3b**: 1.40 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 2.03 (3H, s, NCH_3), 3.69 (1H, q, J=6.7 Hz, $C\underline{H}CH_3$), 3.72 (1H, dd, J=5.4, 10.4 Hz, $NC\underline{H}CH_2O$), 3.97 (1H, dd, J=8.6, 10.4 Hz, $NCHC\underline{H}_2O$), 4.16 (1H, dd, J=5.4, 8.6 Hz, $NCHC\underline{H}_2O$), 7.22—7.36 (10H, m, aromatic H).

(1*S*,1′*R*)- and (1*R*,1′*R*)-*N*-Benzyl-*N*-2′-hydroxy-1′-phenylethyl-1-phenylethylamine (**3c**): MS *m/z*: CI, 332 ($M^+ + 1$); EI, 105 (base peak). ^{1}H-NMR ($CDCl_3$) δ: (1*S*,1′*R*)-**3c**: 1.28 (3H, d, J=7.0 Hz, $CHC\underline{H}_3$), 3.40 (1H, d, J=16.0 Hz, $PhC\underline{H}_2N$), 3.59 (1H, dd, J=5.8, 11.0 Hz, $NC\underline{H}CH_2O$), 3.84 (1H, dd, J=8.3, 11.0 Hz, $NCHC\underline{H}_2O$), 3.98 (1H, dd, J=5.8, 8.3 Hz, $NCHC\underline{H}_2O$), 4.04 (1H, q, J=7.0 Hz, $C\underline{H}CH_3$), 4.12 (1H, d, J=16.0 Hz, $PhC\underline{H}_2N$), 7.20—7.40 (15H, m, aromatic H); (1*R*,1′*R*)-**3c**: 1.08 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 3.41—3.51 (1H, m, $NC\underline{H}CH_2O$), 3.62 (1H, d, J=13.8 Hz, $PhC\underline{H}_2N$), 3.87—3.95 (2H, m, $NCHC\underline{H}_2O$), 3.98 (1H, d, J=13.8 Hz, $PhC\underline{H}_2N$), 4.15 (1H, q, J=6.8 Hz, $C\underline{H}CH_3$), 7.20—7.41 (15H, m, aromatic H).

(1*S*,1′*R*)-*N*-Isopropyl-*N*-2′-hydroxy-1′-phenylethyl-1-phenylethylamine (**3d**): This compound was isolated from the diastereomeric mixture by column chromatography on silica gel with *n*-hexane–ether (2 : 1) as a crystalline solid. Colorless needles, mp 61.5 °C (from *n*-hexane). MS *m/z*: CI, 284 ($M^+ + 1$); EI, 105 (base peak). ^{1}H-NMR ($CDCl_3$) δ: (1*S*,1′*R*)-**3d**: 0.73 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 1.24 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 1.49 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 3.28 (1H, septet, J=6.7 Hz, $C\underline{H}(CH_3)_2$), 3.75 (1H, dd, J=6.2, 9.7 Hz, $NC\underline{H}CH_2O$), 3.96 (1H, t, J=9.7 Hz, $NCHC\underline{H}_2O$), 4.03 (1H, dd, J=6.2, 9.7 Hz, $NCHC\underline{H}_2O$), 4.23 (q, J=6.7 Hz, $C\underline{H}CH_3$), 7.04—7.30 (10H, m, aromatic H). $[\alpha]_D$ −60.6° (c=3.77, EtOH). *Anal.* Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89: N, 4.94. Found: C, 80.57; H, 9.02; N, 4.90.

(1*R*,1′*R*)-**3d**: This compound was isolated from the diastereomeric mixture as a colorless oil, bp 159 °C (0.6 mmHg). MS *m/z*: CI, 284 ($M^+ + 1$); EI, 105 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 1.09 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 1.25 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 3.37 (1H, septet, J=6.7 Hz, $C\underline{H}(CH_3)_2$), 3.47 (1H, dd, J=5.9, 10.6 Hz, $NC\underline{H}CH_2O$), 3.83 (1H, dd, J=9.3, 10.6 Hz, $NCHC\underline{H}_2O$), 4.06 (1H, dd, J=5.9, 9.3 Hz, $NCHC\underline{H}_2O$), 4.32 (1H, q, J=6.8 Hz, $C\underline{H}CH_3$), 7.19—7.45 (10H, m, aromatic H). $[\alpha]_D$ −31.4° (c=4.60, EtOH). *Anal.* Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.20; H, 8.74; N, 4.96.

(*S*)-*N*-1′-Phenyl-1′-ethoxycarbonylmethylidene-1-phenylethylamine (4) A mixture of (*S*)-1-phenylethylamine (1.55 g, 12.8 mmol) and ethylphenylgloxylate (3.4 g, 19.2 mmol) was stirred at 45—50 °C for 2 h. The reaction mixture was diluted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was distilled *in vacuo* to give (*S*)-**4** (2.07 g, 56%) as a colorless oil, bp 175—179 °C (3.5 mmHg). MS *m/z*: CI, 282 ($M^+ + 1$); EI, 105 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=6.7 Hz, $CH_2C\underline{H}_3$), 1.58 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 4.44 (2H, q, J=6.7 Hz, $C\underline{H}_2CH_3$), 4.64 (1H, q, J=6.7 Hz, $C\underline{H}CH_3$), 7.21—8.33 (10H, m, aromatic H). *Anal.* Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.57; H, 6.47; N, 5.15.

Reduction of (*S*)-4 (*S*)-**4** (2.07 g, 7 mmol) was added dropwise to a stirred suspension of $LiAlH_4$ (0.53 g, 14 mmol) in THF (100 ml), and stirring was continued at room temperature for 20 h. After treatment with a small amount of water, the resulting white precipitate was filtered off. The filtrate was dried over $MgSO_4$ and concentrated under reduced pressure to give a colorless oil (1.45 g, 86%). The diastereomeric mixture was subjected to column chromatography on silica gel with a solution of *n*-hexane–ether (2 : 1) to give (1*S*,1′*S*)-**5** (0.5 g, 30%) from the first fraction and (1*S*,1′*R*)-**5** (0.63 g, 37%) from the second fraction.

(1*S*,1′*S*)-**5**: The ^{1}H-NMR ($CDCl_3$) spectrum of this compound coincided with that of (1*R*,1′*R*)-**5** (*vide infra*). $[\alpha]_D$ +16.0° (c=4.60, $CHCl_3$). (1*S*,1′*R*)-**5**: ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 3.48—3.59 (3H, m, $NC\underline{H}C\underline{H}_2O$), 3.64 (1H, q, J=6.8 Hz, $C\underline{H}CH_3$), 7.18—7.39 (10H, m, aromatic H). $[\alpha]_D$ −167.4° (c=2.42, $CHCl_3$) [lit.,[10] $[\alpha]_D$ −186.3° (c=10, $CHCl_3$)].

(1*R*,1′*R*)-*N*-2′-Hydroxy-1′-phenylethyl-1-phenylethylamine (5) A mixture of (*R*)-phenylglycinol (5.5 g, 40.2 mmol) and benzaldehyde (4.7 g, 44.2 mmol) in benzene (40 ml) was refluxed for 3 h using a Dean–Stark trap. The reaction mixture was washed with brine and dried over $MgSO_4$. The removal of the solvent gave a crystalline solid (7.0 g, 78%). Recrystallization from *n*-hexane–ether gave colorless needles of mp 72—72.5 °C. *Anal.* Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.72; H, 6.71; N, 6.19. This product was confirmed to be a mixture of (*R*)-*N*-benzylidene-2-hydroxy-1-phenylethylamine and 2,4-diphenyl-1,3-oxazolidines by ^{1}H-NMR spectral analysis. The ratio of the mixture was determined to be 85 : 15 by peak-area measurement at δ 8.40 (N=CH) and δ 5.60 and 5.67 (NCHO).

CH_3Li (5.6 mmol, 4 ml of 1.4 M solution in ether) was added dropwise to a stirred solution of the mixture of the imine and 1,3-oxazolidines (0.42 g, 1.87 mmol) in THF (30 ml) at −50 °C under a nitrogen atmosphere. After being stirred at room temperature for 2 h, the reaction mixture was treated with a small amount of water. The resulting white precipitate was filtered off. The filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with CH_2Cl_2–MeOH (99 : 1) to give (1*R*,1′*R*)-**5** (0.4g, 82%) as a colorless oil, bp 149 °C (0.6 mmHg). MS *m/z*: CI, 242 ($M^+ + 1$); EI, 105 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, d, J=6.7 Hz, $CHC\underline{H}_3$), 3.51 (1H, dd, J=7.9, 10.4 Hz, $NC\underline{H}CH_2O$), 3.74 (1H, dd, J=4.9, 7.9 Hz, $NCHC\underline{H}_2O$), 3.78 (1H, q, J=6.7 Hz, $C\underline{H}CH_3$), 3.89 (1H, dd, J=4.9, 10.4 Hz, $NCHC\underline{H}_2O$), 7.19—7.36 (10H, m, aromatic H). $[\alpha]_D$ −16.5° (c=3.50, $CHCl_3$). *Anal.* Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.87; H, 8.12; N, 5.80.

Methylation of (1*R*,1′*R*)-5 CH_3I (1.3 g, 9.1 mmol) and K_2CO_3 (100 mg) were added to a stirred solution of (1*R*,1′*R*)-**5** (0.137 g, 0.57 mmol) in *N*,*N*-dimethylformamide (DMF, 3 ml), and stirring was continued at room temperature for 20 h. The mixture was poured into water (30 ml) and extracted with ether. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on a silica gel column with *n*-hexane–ether (2 : 1) to give (1*R*,1′*R*)-**3b** as a colorless oil (0.11 g, 75%). This product was identical with the minor product obtained by the reaction of (2*R*,4*R*)-**2b** on the basis of ^{1}H-NMR spectral comparison.

Reduction of 3a A solution of a mixture of (1*S*,1′*R*)- and (1*R*,1′*R*)-**3a** (ratio of 66 : 34, 0.267 g, 0.8 mmol) in THF (5 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.1 g, 2.4 mmol) in THF (10 ml) and the stirring was continued at room temperature for 18 h. After treatment with a small amount of water, the resulting white precipitate was filtered off. The filtrate was dried over $MgSO_4$ and concentrated under reduced pressure to give **3b** as a colorless oil (0.18 g, 87%). This product was identical with the mixture of (1*S*,1′*R*)- and (1*R*,1′*R*)-**3b** (ratio of 65 : 35) on the basis of the ^{1}H-NMR spectral comparison.

Oxidation of 3c Lead tetraacetate (1.77 g, 4 mmol) was added to a solution of a mixture of (1*S*,1′*R*)- and (1*R*,1′*R*)-**3c** (ratio of 84 : 16, 0.66 g, 2 mmol) in benzene (40 ml) and the mixture was stirred at room temperature for 23 h. After treatment with a small amount of dilute hydrochloric acid, the reaction mixture was made alkaline with K_2CO_3 saturated aqueous solution, and extracted with benzene. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel with *n*-hexane–ether (2 : 1) to afford an enantiomeric mixture of (*S*)- and (*R*)-*N*-benzyl-1-phenylethylamines (0.28 g, 66.5%). The structure was confirmed by ^{1}H-NMR spectral analysis and the specific rotation was shown to be $[\alpha]_D$ −38.0° (c=3.48, EtOH) [lit.,[11] (*S*)-*N*-benzyl-1-phenylethylamine: $[\alpha]_D$ −56.9° (c=4.50, EtOH)].

Oxidation of (1*S*,1′*R*)-3d Lead tetraacetate (4.07 g, 9.2 mmol) was added to a solution of (1*S*,1′*R*)-**3d** (1.3 g, 4.6 mmol) in benzene (40 ml). The mixture was stirred at room temperature for 20 h and then worked up in the same manner as above to give (*S*)-*N*-isopropyl-1-phenylethylamine (0.44 g, 58.8%). $[\alpha]_D$ −59.7° (c=6.76, EtOH) [lit.,[12] (*S*)-*N*-isopropyl-1-phenylethylamine: $[\alpha]_D$ −59.5° (neat)].

References

1) H. Takahashi, Y. Suzuki, and T. Kametani, *Heterocycles*, **20**, 607 (1983).
2) H. Takahashi, Y. Chida, K. Higashiyama, and H. Onishi, *Chem. Pharm. Bull.*, **33**, 4662 (1985).
3) L. Neelakantan, *J. Org. Chem.*, **36**, 2256 (1971).
4) F. Santiesteban, C. Grimaldo, R. Contreras, and B. Wrackmeyer, *J. Chem. Soc., Chem. Commun.*, **1983**, 1486.
5) L. Neelakantan and J. A. Molin-Case, *J. Org. Chem.*, **36**, 2261 (1971).
6) G. Just, P. Potvin, P. Uggowitzer, and P. Bird, *J. Org. Chem.*, **48**, 2923 (1983).
7) Y. Ito, Y. Amino, M. Nakatsuka, and T. Saegusa, *J. Am. Chem. Soc.*, **105**, 1586 (1983).
8) J. H. Hunt and D. McHale, *J. Chem. Soc.*, **1957**, 2073.
9) A. Ando and T. Shioiri, *J. Chem. Soc., Chem. Commun.*, **1987**, 656.
10) M. B. Eleveld, H. Hogeveen, and E. P. Schudde, *J. Org. Chem.*, **51**, 3635 (1986).
11) S. Terashima, M. Wagatsuma, and S. Yamada, *Chem. Pharm. Bull.*, **18**, 1137 (1970).
12) G. Markl and B. Merkl, *Tetrahedron Lett.*, **24**, 5865 (1983); A. C. Regan and J. Staunton, *J. Chem. Soc., Chem. Commun.*, **1983**, 764.