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Asymmetric α-Substituted Phenethylamines. V.[1] Synthesis of Chiral 1-Alkyl-2-phenylethylamines *via* Grignard Reaction of 4-Phenyl-1,3-oxazolidines

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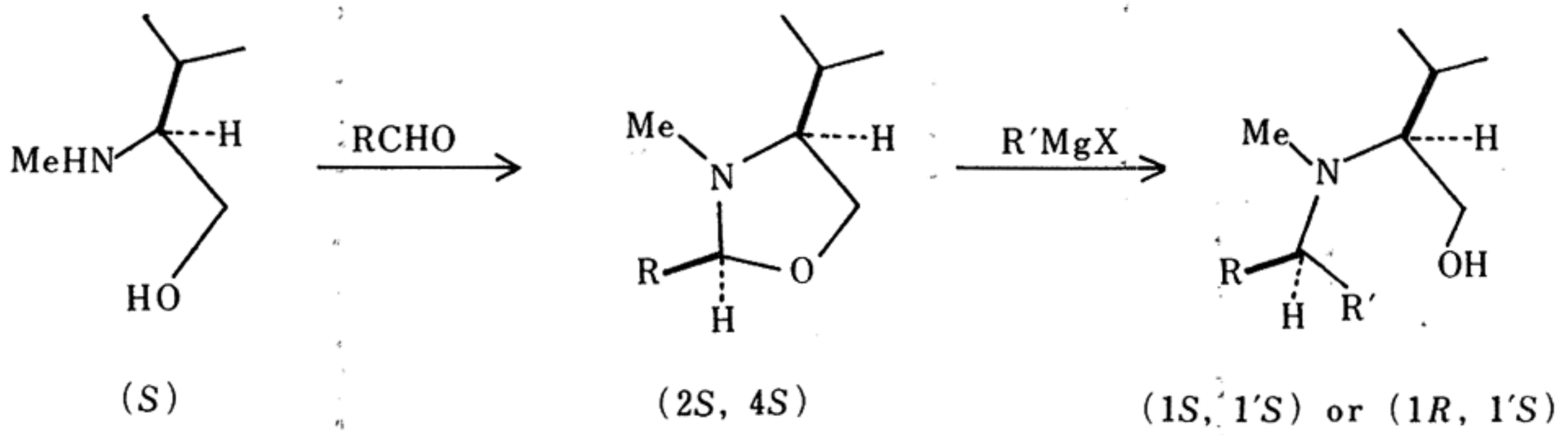
Chiral *N*-methyl-4-phenyl-1,3-oxazolidines (**2a—e**) having a methyl, ethyl, benzyl, isopropyl, and cyclohexyl group at the 2-position of the 1,3-oxazolidine ring were synthesized. Reactions of **2a—e** with Grignard reagents gave (1*R*,1′*R*)- and (1*S*,1′*R*)-1-alkyl- and 1-cycloalkyl-*N*-2′-hydroxy-1′-phenylethyl-2-phenylethylamines (**3a**, **3b**, **3d**, **3e**). The absolute configurations of (1*R*,1′*R*)-**3a** and -**3e** were determined.

(*R*)-1-Methyl- and (*R*)-1-cyclohexyl-2-phenylethylamines (**4a**, **4e**) were obtained in high yield by hydrogenolysis of (1*R*,1′*R*)-**3a** and -**3e**.

Keywords——absolute configuration; 1-alkyl-2-phenylethylamine; asymmetric reaction; Grignard reaction; *N*-methyl-1,3-oxazolidine; 2-aminophenylethanol; (*R*)-phenylglycine; stereoselective reaction; X-ray analysis

4-Isopropyl-1,3-oxazolidines, which are asymmetric heterocyclic compounds derived from (*S*)-valinol, show characteristically high stereoselectivity in various respects. We have suggested that the configuration at the 2-position of 1,3-oxazolidines is induced by the chirality of the asymmetric carbon atom at the 4-position, and the attack of Grignard reagents at the 2-position of these compounds occurs with high diastereoselectivity. In this work, optically pure (*R*)- and (*S*)-α-substituted phenethylamines were synthesized from (*S*)-valinol by reaction with aldehydes followed by Grignard reagents, as shown in Chart 1.[2] We describe here the synthesis and reactions of new chiral 4-phenyl-1,3-oxazolidines, which differ in properties from the 4-isopropyl derivatives.



(*S*) (2*S*, 4*S*) (1*S*, 1′*S*) or (1*R*, 1′*S*)

Chart 1

Chiral *N*-methyl-4-phenyl-1,3-oxazolidines (**2a—e**) having a methyl, ethyl, benzyl, isopropyl, and cyclohexyl group at the 2-position of the 1,3-oxazolidine ring were synthesized from (*R*)-2-*N*-methylamino-2-phenylethanol (**1**) with various aldehydes in high yields. Two diastereomers, (2*R*,4*R*)- and (2*S*,4*R*)-**2**, may be formed, depending on the configuration of the asymmetric center at the 2-position. However, the 400 MHz proton nuclear magnetic

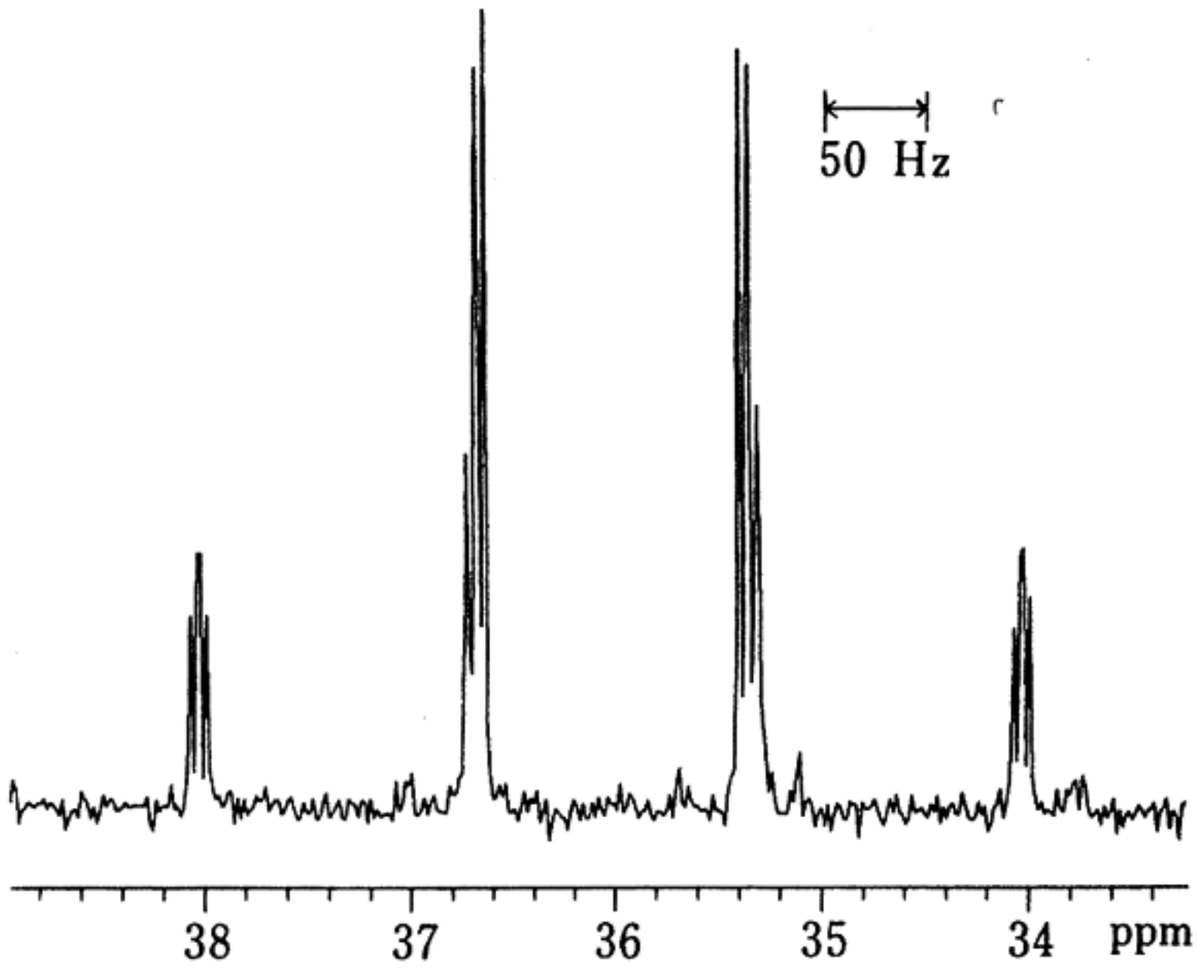


Fig. 1. Proton-Coupled ^{13}C-NMR Spectrum Showing the *N*-Methyl Carbon Signal of (2*S*,4*R*)-**2a**

resonance (^{1}H-NMR) spectra of these products showed that only one isomer was present. An investigation of the structure of these 1,3-oxazolidines (**2a**, **2b**, **2d**, **2e**) was attempted by 100.53 MHz carbon-13 nulcear magnetic resonance (^{13}C-NMR) spectroscopy. The coupling constants ($^3J_{C-H}$) between the carbon atom of the *N*-methyl group and hydrogen atoms at the 2- and 4-positions of the 1,3-oxazolidine ring were observed as $^3J_{C-H}=4.6$—4.8 Hz at δ 36.0—36.8 in every compound. These experimental results suggested similar configurations[3] and the absolute configuration was assumed to be (2*S*,4*R*) for the reasons described later.

The reactions of (2*S*,4*R*)-2-methyl- and (2*S*,4*R*)-2-ethyl-*N*-methyl-4-phenyl-1,3-oxazolidines (**2a**, **2b**) with benzylmagnesium chloride in tetrahydrofuran (THF) gave colorless oily products, 1-methyl- and 1-ethyl-*N*-2′-hydroxy-1′-phenylethyl-*N*-methyl-2-phenylethylamines (**3a**, **3b**), which were elucidated to consist of two diastereomers, (1*R*,1′*R*) and (1*S*,1′*R*), by ^{1}H-NMR spectrometric analysis. The product ratios were estimated and the data are summarized in Table I. The reactions of (2*S*,4*R*)-2-benzyl-*N*-methyl-4-phenyl-1,3-oxazolidine (**2c**) with methyl- and ethylmagnesium bromide gave 1-methyl- and 1-ethyl-*N*-2′-hydroxy-1′-phenylethyl-*N*-methyl-2-phenylethylamines (**3a**, **3b**) as diastereomeric mixtures of (1*R*,1′*R*)- and (1*S*,1′*R*)-isomers. The major products of these reactions were identical with the minor components obtained from the reactions of **2a** and **2b**, as shown in Chart 2.

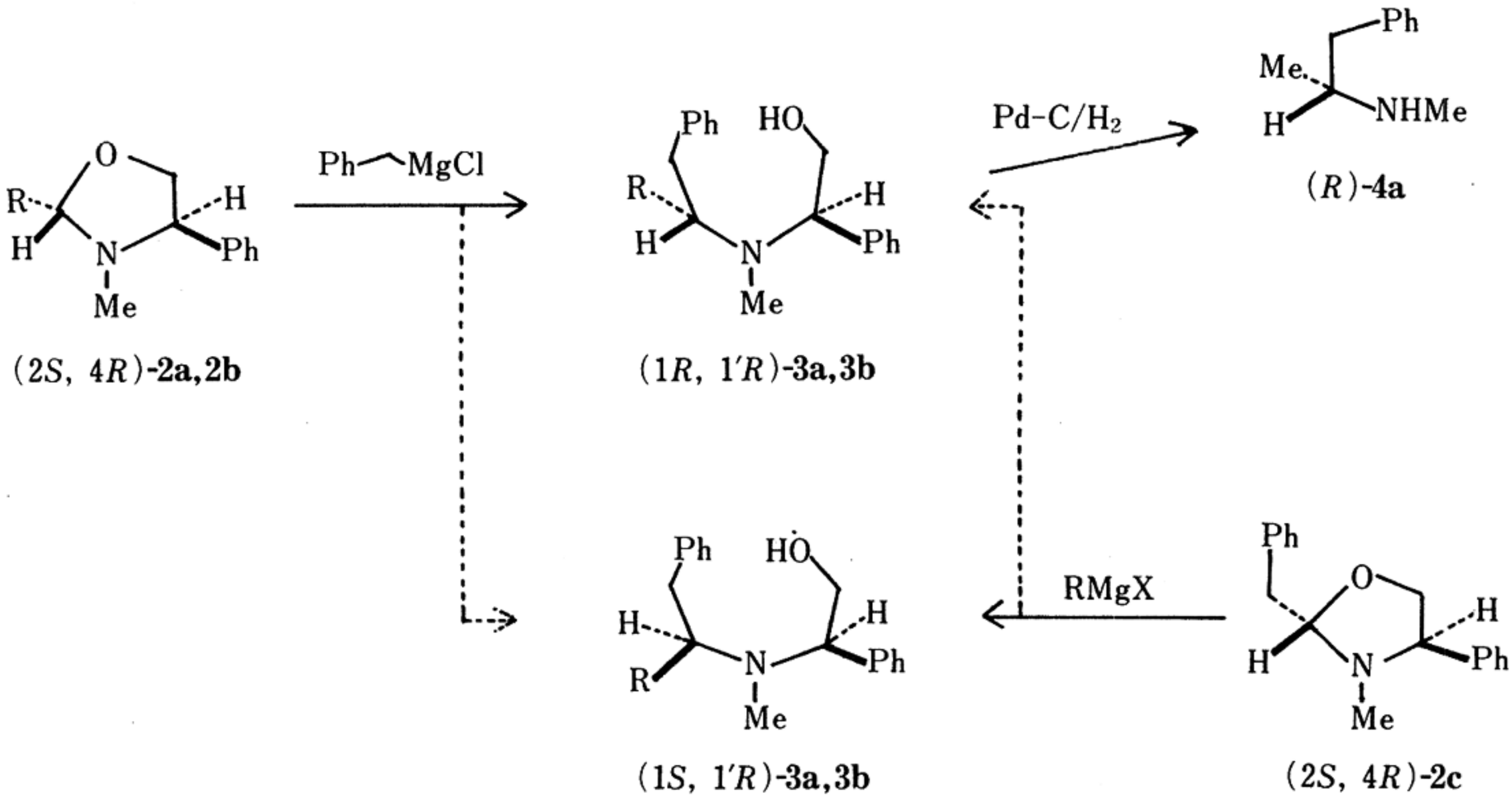


Chart 2

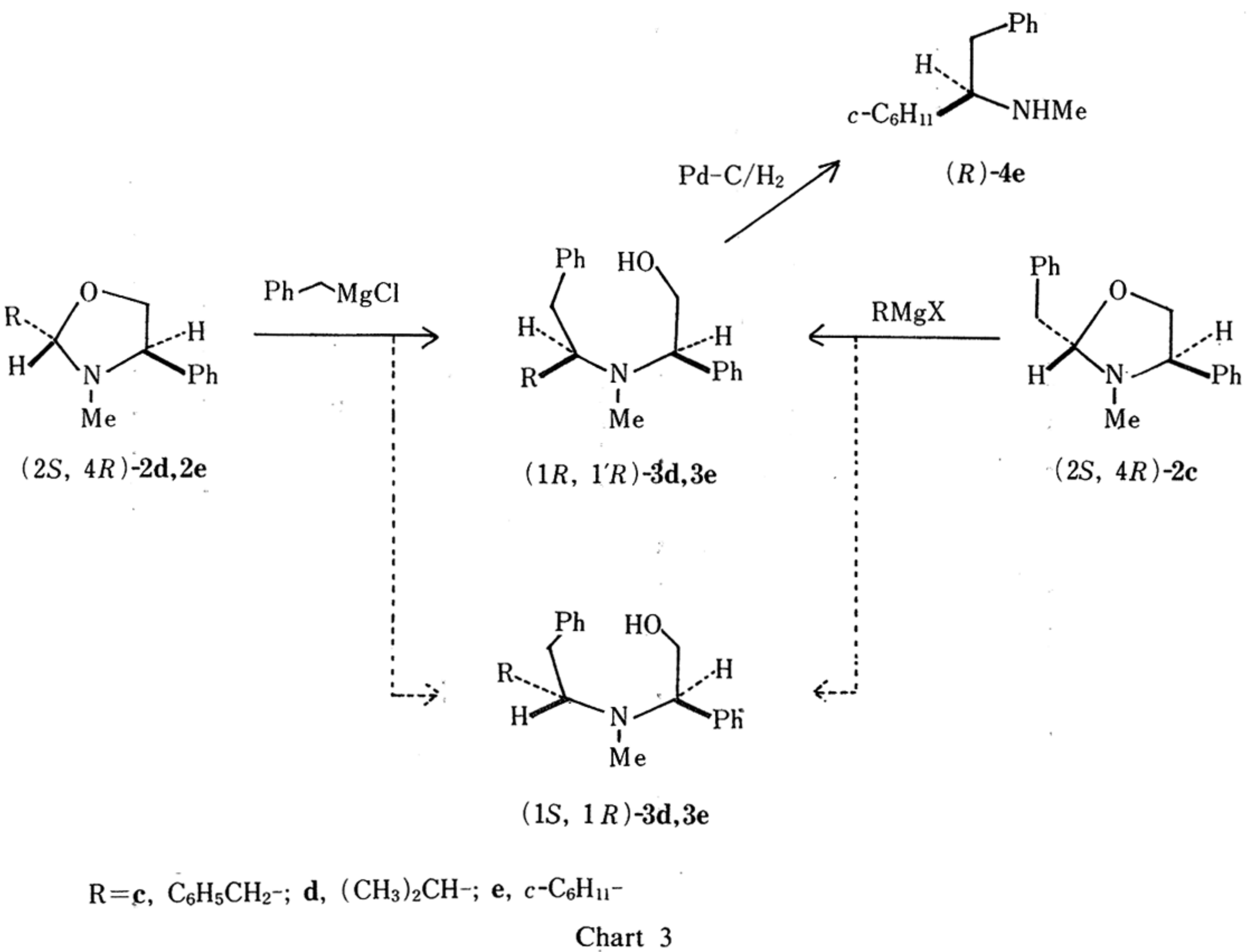
TABLE I. Stereoselective Reaction of 2-Substituted *N*-Methyl-4-phenyl-1,3-oxazolidines (**2a—e**) with Grignard Reagents

Compd. No.	R	R′MgX R′	Compd. No.	Yield (%)	Ratio of (1*R*,1′*R*):(1*S*,1′*R*)
2a	Me	$C_6H_5CH_2$–	**3a**	86	80:20
2c	$C_6H_5CH_2$–	Me	**3a**	40	19:81
2b	Et	$C_6H_5CH_2$–	**3b**	87	75:25
2c	$C_6H_5CH_2$–	Et	**3b**	80	39:61
2d	$(CH_3)_2CH$–	$C_6H_5CH_2$–	**3d**	85	61:39
2c	$C_6H_5CH_2$–	$(CH_3)_2CH$–	**3d**	81	76:24
2e	*c*-C_6H_{11}–	$C_6H_5CH_2$–	**3e**	88	75:25
2c	$C_6H_5CH_2$–	*c*-C_6H_{11}–	**3e**	92	74:26

In order to determine the absolute configuration of the asymmetric carbon atom created by this reaction, the major product obtained from **2a** and benzylmagnesium chloride was hydrogenolyzed with a Pd–carbon catalyst to give 2-*N*-methylamino-1-phenylpropane (**4a**) in good yield. This free amine was converted to colorless crystals of the hydrochloride of **4a**, which showed a specific rotation of $-16.3°$. The absolute configuration of this compound was elucidated as *R* by comparison of the above value with that of an authentic sample.[4] Consequently, the original compound was proved to be (1*R*,1′*R*). The absolute configuration of **3b** was assumed to be the same.

The α-substituted phenethylamines having (*R*)- and (*S*)-configuration were synthesized from (*R*)-2-*N*-methylamino-2-phenylethanol (**1**). The reaction mechanism of **2a** and **2b** with Grignard reagents should be similar to that of **2c**.

The reactions of (2*S*,4*R*)-2-isopropyl- and (2*S*,4*R*)-2-cyclohexyl-*N*-methyl-4-phenyl-1,3-



R=**c**, $C_6H_5CH_2$–; **d**, $(CH_3)_2CH$–; **e**, *c*-C_6H_{11}–

Chart 3

TABLE II. Crystal Data

Chemical formula	$C_{23}H_{31}NO$
Formula weight	337.49
Crystal system	Monoclinic
Cell dimensions (Å)	$a = 12.773$ (2)
	$b = 6.693$ (3)
	$c = 11.891$ (2)
Cell volume (Å^3)	1006.1 (5)
Space group	$P2_1$
Z	2
D_c (g cm^{-3})	1.11
μ (Mo K_α) (cm^{-1})	0.6

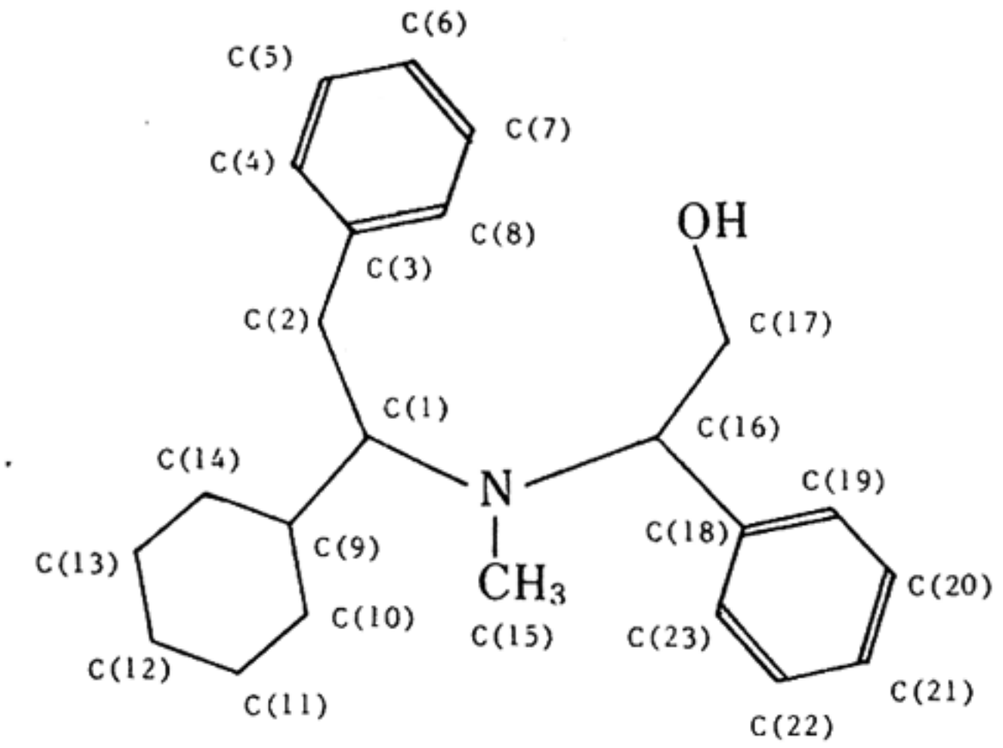


Fig. 2. Atomic Numbering of (1*R*,1′*R*)-**3e**

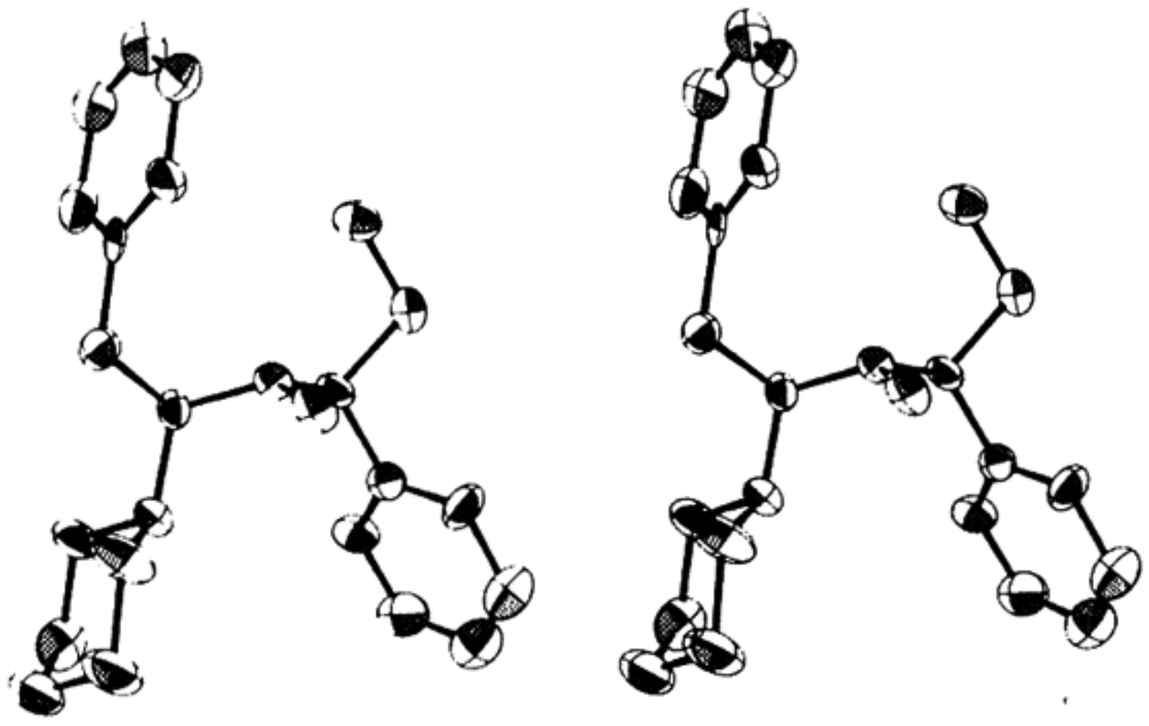


Fig. 3. Stereoscopic Drawings of the Structure of (1*R*,1′*R*)-**3e**

TABLE III. Positional ($\times 10^4$) and Thermal Parameters of (1*R*,1′*R*)-**3e** for Nonhydrogen Atoms with Their Standard Deviations in Parentheses

Atom	*X*	*Y*	*Z*	B_{eq} (Å^2)[a]
O	5472 (6)	3531 (18)	450 (7)	5.3
N	3795 (7)	3122 (17)	1667 (8)	4.1
C(1)	3681 (9)	4265 (20)	2703 (9)	4.0
C(2)	4420 (10)	3352 (29)	3739 (10)	5.3
C(3)	5578 (10)	3409 (30)	3500 (8)	5.4
C(4)	6127 (12)	5260 (28)	3632 (12)	6.7
C(5)	7217 (14)	5266 (36)	3388 (14)	9.3
C(6)	7643 (13)	3634 (46)	3027 (14)	10.1
C(7)	7113 (13)	1765 (35)	2948 (13)	7.9
C(8)	6021 (12)	1587 (32)	3167 (11)	6.7
C(9)	2538 (10)	4569 (25)	2945 (10)	5.1
C(10)	2459 (11)	6531 (26)	3614 (13)	6.1
C(11)	1290 (14)	6956 (26)	3779 (15)	7.4
C(12)	819 (14)	5225 (32)	4361 (15)	8.5
C(13)	924 (13)	3308 (39)	3729 (16)	9.0
C(14)	2118 (14)	2831 (28)	3627 (15)	8.6
C(15)	3371 (11)	1109 (23)	1574 (12)	5.3
C(16)	3643 (9)	4410 (22)	623 (10)	4.3
C(17)	4409 (9)	3538 (20)	−180 (9)	3.9
C(18)	2520 (10)	4499 (23)	−24 (9)	4.6
C(19)	2080 (11)	2935 (27)	−662 (12)	6.3
C(20)	1022 (14)	3095 (32)	−1263 (15)	8.0
C(21)	478 (13)	4899 (30)	−1243 (14)	7.6
C(22)	952 (13)	6428 (32)	−615 (14)	7.4
C(23)	1988 (10)	6278 (24)	19 (12)	5.2

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

TABLE IV. Bond Distances (Å) and Bond Angles (°) of (1*R*,1′*R*)-**3e** for Nonhydrogen Atoms with Their Standard Deviations in Parentheses

O –C(17)	1.453 (15)	C(9) –C(14)	1.557 (24)
N –C(1)	1.475 (16)	C(10)–C(11)	1.560 (24)
N –C(15)	1.451 (19)	C(11)–C(12)	1.517 (27)
N –C(16)	1.501 (16)	C(12)–C(13)	1.512 (32)
C(1)–C(2)	1.565 (18)	C(13)–C(14)	1.579 (25)
C(1)–C(9)	1.542 (18)	C(16)–C(17)	1.574 (19)
C(2)–C(3)	1.546 (18)	C(16)–C(18)	1.529 (17)
C(3)–C(4)	1.422 (26)	C(18)–C(19)	1.365 (21)
C(3)–C(8)	1.424 (27)	C(18)–C(23)	1.375 (21)
C(4)–C(5)	1.462 (25)	C(19)–C(20)	1.440 (22)
C(5)–C(6)	1.319 (35)	C(20)–C(21)	1.395 (28)
C(6)–C(7)	1.419 (36)	C(21)–C(22)	1.357 (27)
C(7)–C(8)	1.460 (23)	C(22)–C(23)	1.430 (21)
C(9)–C(10)	1.546 (23)		
C(1) –N –C(15)	117.8 (10)	C(10)–C(9) –C(14)	108.3 (12)
C(1) –N –C(16)	112.1 (10)	C(9) –C(10)–C(11)	110.7 (12)
C(15)–N –C(16)	117.9 (10)	C(10)–C(11)–C(12)	111.6 (14)
N –C(1)–C(2)	109.5 (11)	C(11)–C(12)–C(13)	110.8 (16)
N –C(1)–C(9)	115.7 (10)	C(12)–C(13)–C(14)	111.6 (16)
C(2)–C(1)–C(9)	112.7 (10)	C(9) –C(14)–C(13)	107.3 (15)
C(1)–C(2)–C(3)	109.3 (11)	N –C(16)–C(17)	105.7 (10)
C(2)–C(3)–C(4)	118.1 (16)	N –C(16)–C(18)	116.1 (11)
C(2)–C(3)–C(8)	117.3 (16)	C(17)–C(16)–C(18)	109.2 (9)
C(4)–C(3)–C(8)	124.6 (13)	O –C(17)–C(16)	107.7 (9)
C(3)–C(4)–C(5)	116.7 (17)	C(16)–C(18)–C(19)	122.1 (13)
C(4)–C(5)–C(6)	120.8 (20)	C(16)–C(18)–C(23)	116.6 (12)
C(5)–C(6)–C(7)	122.4 (17)	C(19)–C(18)–C(23)	121.3 (12)
C(6)–C(7)–C(8)	121.3 (19)	C(18)–C(19)–C(20)	120.0 (16)
C(3)–C(8)–C(7)	114.0 (17)	C(19)–C(20)–C(21)	119.4 (17)
C(1)–C(9)–C(10)	109.9 (12)	C(20)–C(21)–C(22)	118.5 (16)
C(1)–C(9)–C(14)	113.9 (13)	C(21)–C(22)–C(23)	122.9 (18)
		C(18)–C(23)–C(22)	117.7 (14)

oxazolidines (**2d**, **2e**) with benzylmagnesium chloride gave mixtures of (1*R*,1′*R*)- and (1*S*,1′*R*)-1-alkyl-*N*-2′-hydroxy-1′-phenylethyl-*N*-methyl-2-phenylethylamines (**3d**, **3e**). The product ratios were estimated by ^{1}H-NMR spectrometric analysis; the results are summarized in Table I. The reactions of (2*S*,4*R*)-**2c** with isopropyl- and cyclohexylmagnesium halides were attempted in order to prepare the minor components of the former reactions. However, the major products of these reactions were identical with the major components obtained from **2d** and **2e**, respectively, based on a comparison of their ^{1}H-NMR (400 MHz) spectra in deuteriochloroform and hexadeuteriobenzene solutions.

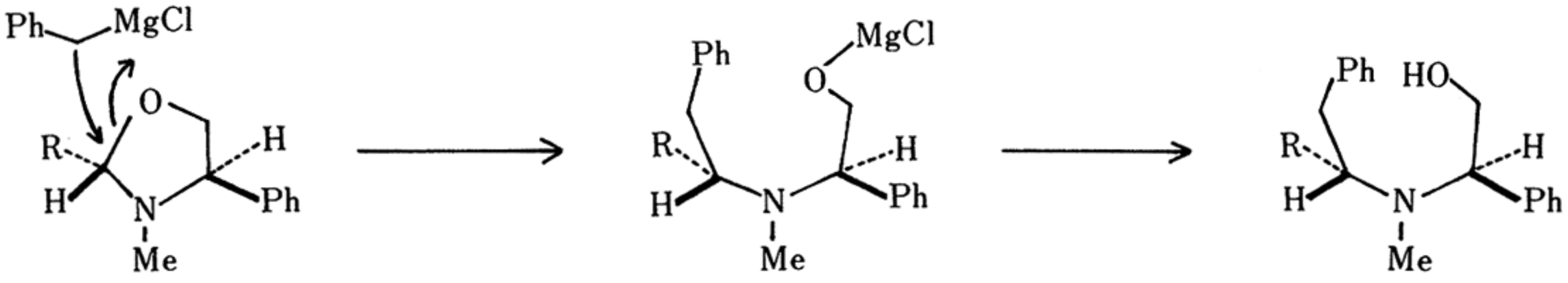
In order to establish the absolute configuration of the newly created asymmetric carbon atom, the structure of the major product of **3e** was elucidated by X-ray analysis. The atomic numbering of **3e** is shown in Fig. 2, and the crystal data are summarized in Table II. Stereoscopic drawings of the molecular structure are shown in Fig. 3. The positional and thermal parameters with their standard deviations are listed in Table III. The intramolecular bond distances, bond angles, and tosion angles for nonhydrogen atoms are give in Tables IV and V.

The structure of this compound (**3e**) was determined as (1*R*,1′*R*)-1-cyclohexyl-*N*-2′-hydroxy-1′-phenylethyl-*N*-methyl-2-phenylethylamine. The absolute configuration of the major component of **3d** was assumed to be (1*R*,1′*R*) by analogy with **3e**. The above

TABLE V. Torsion Angles (°) of (1*R*,1′*R*)-**3e** with Their Standard Deviations in Parentheses

A	B	C	D[a]		A	B	C	D[a]	
C(9)	–C(1)–	C(2)	–C(3)	−171.1 (11)	C(10)–	C(9)	–C(14)–	C(13)	61.0 (16)
N	–C(1)–	C(2)	–C(3)	58.6 (14)	C(9)	–C(10)–	C(11)–	C(12)	56.1 (18)
C(2)	–C(1)–	C(9)	–C(10)	81.5 (14)	C(10)–	C(11)–	C(12)–	C(13)	−54.5 (20)
C(2)	–C(1)–	C(9)	–C(14)	−40.2 (16)	C(11)–	C(12)–	C(13)–	C(14)	58.0 (21)
N	–C(1)–	C(9)	–C(10)	−151.4 (11)	C(12)–	C(13)–	C(14)–	C(9)	−61.4 (19)
N	–C(1)–	C(9)	–C(14)	86.9 (14)	C(1)	–N	–C(16)–	C(17)	146.2 (10)
C(2)	–C(1)–	N	–C(15)	70.2 (14)	C(1)	–N	–C(16)–	C(18)	−96.5 (12)
C(2)	–C(1)–	N	–C(16)	−148.1 (10)	C(15)–	N	–C(16)–	C(17)	−72.2 (13)
C(9)	–C(1)–	N	–C(15)	−58.4 (15)	C(15)–	N	–C(16)–	C(18)	49.1 (15)
C(9)	–C(1)–	N	–C(16)	83.2 (13)	N	–C(16)–	C(17)–	O	−56.1 (12)
C(1)	–C(2)–	C(3)	–C(4)	77.8 (16)	C(18)–	C(16)–	C(17)–	O	178.3 (10)
C(1)	–C(2)–	C(3)	–C(8)	−102.6 (15)	N	–C(16)–	C(18)–	C(19)	−73.2 (16)
C(2)	–C(3)–	C(4)	–C(5)	−179.4 (14)	N	–C(16)–	C(18)–	C(23)	110.0 (13)
C(8)	–C(3)–	C(4)	–C(5)	1.0 (24)	C(17)–	C(16)–	C(18)–	C(19)	46.2 (17)
C(2)	–C(3)–	C(8)	–C(7)	179.6 (14)	C(17)–	C(16)–	C(18)–	C(23)	−130.6 (12)
C(4)	–C(3)–	C(8)	–C(7)	−0.8 (23)	C(16)–	C(18)–	C(19)–	C(20)	−179.5 (14)
C(3)	–C(4)–	C(5)	–C(6)	2.2 (27)	C(23)–	C(18)–	C(19)–	C(20)	−2.9 (23)
C(4)	–C(5)–	C(6)	–C(7)	−5.5 (32)	C(16)–	C(18)–	C(23)–	C(22)	177.6 (13)
C(5)	–C(6)–	C(7)	–C(8)	5.6 (31)	C(19)–	C(18)–	C(23)–	C(22)	0.8 (21)
C(6)	–C(7)–	C(8)	–C(3)	−2.3 (25)	C(18)–	C(19)–	C(29)–	C(21)	3.8 (25)
C(1)	–C(9)–	C(10)–	C(11)	175.3 (11)	C(19)–	C(20)–	C(21)–	C(22)	−2.6 (27)
C(14)–	C(9)–	C(10)–	C(11)	−59.7 (16)	C(20)–	C(21)–	C(22)–	C(23)	0.5 (27)
C(1)	–C(9)–	C(14)–	C(13)	−176.3 (13)	C(21)–	C(22)–	C(23)–	C(18)	0.5 (25)

a) Looking from B to C. The clockwise rotation of bond C–D with reference to bond B–A is given.



R=**a**, Me; **b**, Et; **d**, $(CH_3)_2CH$–; **e**, *c*-C_6H_{11}–

Chart 4

experimental results suggest that the reaction mechanism of **2d** and **2e** with Grignard reagents differs from that of **2c**.

The Grignard reactions of 2-methyl- and 2-cyclohexyl-*N*-methyl-4-phenyl-1,3-oxazolidine (**2a, 2e**) were examined in order to elucidate the reaction mechanism. The reaction

of **2a** with an equimolar amount of benzylmagnesium chloride gave **3a** in almost 100% yield as determined by gas chromatography. However, the reaction of **2e** with equimolar benzylmagnesium chloride gave **3e** in almost 50% yield, while the reaction with a 2-fold molar excess of Grignard reagent gave **3e** in almost 100% yield. Consequently, it was considered that in the former reaction one molecule of Grignard reagent approaches the oxygen atom and attacks the carbon atom at the 2-position, while in the later reaction one molecule is used for cleavage of the 1,3-oxazolidine ring and another attacks the carbon–nitrogen double bond of the intermediate immonium salt,[5] because the 1,3-oxazolidine ring of **2e** is assumed to cleave easily, as shown in Chart 4.

Moreover, the carbon–nitrogen bond adjacent to the phenyl group of (1*R*,1′*R*)-**3e** was cleaved by hydrogenolysis with Pd–carbon catalyst in acetic acid solution to give (*R*)-1-cyclohexyl-*N*-methyl-2-phenylethylamine (**4e**) in high yield. This free amine was converted to colorless crystals of the hydrochloride of **4e**. Thus, a new synthetic route to asymmetric 1-alkyl-2-phenylethylamines was established *via* chiral *N*-methyl-4-phenyl-1,3-oxazolidines, which are easily obtained from commercially available (*R*)-phenylglycine.

Experimental

The ^{1}H-NMR spectra were obtained with a JEOL JNM-FX100 and/or JNM-GX400 spectrometers. The ^{13}C-NMR spectra were obtained at 100.53 MHz with a JNM-GX400 spectrometer. The mass spectra (MS) were recorded with a JEOL JMS-D300 spectrometer by using the electron impact (EI) and chemical ionization (CI) (isobutane) methods. The melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. The optical rotations were measured with a Jasco DIP-360 digital polarimeter.

General Procedure for the Condensation of (*R*)-2-*N*-Methylamino-2-phenylethanol (1) with Aldehyde——An aldehyde (10 mmol) was added dropwise over about 5 min to a stirred solution of **1** (1.51 g, 10 mmol) in CH_2Cl_2 (10 ml), and the mixture was stirred in the presence of anhydrous $MgSO_4$ (2 g) at room temperature for 1 h. After removal of the solid, the reaction mixture was concentrated and the residue was distilled *in vacuo* to give a colorless oil.

(2*S*,4*R*)-2,*N*-Dimethyl-4-phenyl-1,3-oxazolidine (**2a**): Yield, 1.52 g (86%); bp 86—87 °C/7 mmHg. $[\alpha]_D$ −153.8° (c=0.70, *n*-hexane). MS *m/z*: CI, 178 ($M\cdot H^+$); EI, 162 (base peak, $M^+ - CH_3$), ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, d, J=5.1 Hz, $CHC\underline{H}_3$), 2.16 (3H, s, NCH_3), 3.51 (1H, dd, J=7.1, 8.8 Hz, $OC\underline{H}_2CH$), 3.70 (1H, dd, J=7.1, 8.8 Hz, $OC\underline{H}_2CH$), 4.06 (1H, q, J=5.1 Hz, $OC\underline{H}CH_3$), 4.14 (1H, t, J=7.1 Hz, $PhC\underline{H}CH_2$). ^{13}C-NMR ($CDCl_3$) δ: 19.6 (q, $CH\underline{C}H_3$), 36.0 (q, NCH_3, $^3J_{C-H}$=4.6 Hz), 70.3 (d, NCH), 72.9 (t, OCH_2), 94.3 (d, NCHO).

(2*S*,4*R*)-2-Ethyl-*N*-methyl-4-phenyl-1,3-oxazolidine (**2b**): Yield, 1.67 g (87%); bp 105—106 °C/5 mmHg. $[\alpha]_D$ −120.9° (c=0.59, *n*-hexane). MS *m/z*: CI, 192 ($M\cdot H^+$); EI, 162 (base peak, $M^+ - C_2H_5$). ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 1.62 (1H, ddq, J=6.0, 7.3, 14.6 Hz, $CHC\underline{H}_2CH_3$), 1.78 (1H, ddq, J=2.5, 7.3, 14.6 Hz, $CHC\underline{H}_2CH_3$), 2.16 (3H, s, NCH_3), 3.55 (1H, dd, J=7.3, 9.0 Hz, $OC\underline{H}_2CH$), 3.65 (1H, dd, J=7.3, 9.0 Hz, $OC\underline{H}_2CH$), 3.99 (1H, dd, J=2.6, 6.0 Hz, $NC\underline{H}CH_2CH_3$), 4.14 (1H, t, J=7.3 Hz, $NC\underline{H}CH_2O$). ^{13}C-NMR ($CDCl_3$) δ: 8.1 (q, $CH_2\underline{C}H_3$), 26.4 (t, $\underline{C}H_2CH_3$), 36.3 (q, NCH_3, $^3J_{C-H}$=4.6 Hz), 70.3 (d, NCH), 73.3 (t, OCH_2), 98.6 (d, NCHO).

(2*S*,4*R*)-2-Benzyl-*N*-methyl-4-phenyl-1,3-oxazolidine (**2c**): Yield, 2.05 g (81%); bp 161 °C/2.5 mmHg. $[\alpha]_D$ −53.0° (c=0.81, *n*-hexane). MS *m/z*: CI, 254 ($M\cdot H^+$); EI, 162 (base peak, $M^+ - CH_2C_6H_5$). ^{1}H-NMR (C_6D_6) δ: 1.97 (3H, s, NH_3), 2.93 (2H, d, J=4.6 Hz, $PhC\underline{H}_2CH$), 3.29 (1H, dd, J=6.8, 8.8 Hz, $OC\underline{H}_2CH$), 3.52 (1H, dd, J=6.8, 8.8 Hz, $OC\underline{H}_2CH$), 3.91 (1H, t, J=6.8 Hz, $PhC\underline{H}CH_2$), 4.16 (1H, t, J=4.6 Hz, OCHN).

(2*S*,4*R*)-2-Isopropyl-*N*-methyl-4-phenyl-1,3-oxazolidine (**2d**): Yield, 1.73 g (84%); bp 110—111 °C/6 mmHg. $[\alpha]_D$ −103.4° (c=1.04, *n*-hexane). MS *m/z*: CI, 206 ($M\cdot H^+$); EI, 162 (base peak, $M^+ - C_3H_7$). ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, d, J=7.0 Hz, $CHC\underline{H}_3$), 1.05 (3H, d, J=7.0 Hz, $CHC\underline{H}_3$), 1.88 (1H, double septet J=2.4, 7.0 Hz, $CHC\underline{H}(CH_3)_2$), 2.17 (3H, s, NCH_3), 3.56 (1H, dd, J=3.1, 12.6 Hz, $OC\underline{H}_2CH$), 3.60 (1H, dd, J=3.1, 12.6 Hz, $OC\underline{H}_2CH$), 3.93 (1H, d, J=2.4 Hz, $NC\underline{H}CH$), 4.13 (1H, t, J=3.1 Hz, $NC\underline{H}CH_2$). ^{13}C-NMR ($CDCl_3$) δ: 15.0 (q, $CH\underline{C}H_3$), 18.7 (q, $CH\underline{C}H_3$), 30.9 (d, $CH_3\underline{C}H$), 36.8 (q, NCH_3, $^3J_{C-H}$=4.6 Hz), 70.3 (d, NCH), 73.8 (t, OCH_2), 101.6 (d, NCHO).

(2*S*,4*R*)-2-Cyclohexyl-*N*-methyl-4-phenyl-1,3-oxazolidine (**2e**): Yield, 2.18 g (89%); bp 146 °C/3 mmHg. $[\alpha]_D$ −72.0° (c=0.74, *n*-hexane). MS *m/z*: CI, 246 ($M\cdot H^+$); EI, 162 (base peak, $M^+ - C_6H_{11}$). ^{1}H-NMR (C_6H_6) δ: 1.99 (3H, s, NCH_3), 3.35 (1H, dd, J=6.8, 9.2 Hz, $OC\underline{H}_2CH$), 3.58 (1H, dd, J=6.8, 9.2 Hz, $OC\underline{H}_2CH$), 3.87 (1H, br s, OCHN), 4.00 (1H, t, J=6.8 Hz, $PhC\underline{H}CH_2$). ^{13}C-NMR ($CDCl_3$) δ: 25.3 (t, cyclohexyl C), 26.1 (t, cyclohexyl C), 26.6 (t, cyclohexyl C), 29.2 (t, cyclohexyl C), 36.6 (q, NCH_3, $^3J_{C-H}$=4.8 Hz), 40.9 (d, cyclohexyl C), 70.0 (d, NCH), 73.5 (t, OCH_2), 101.0 (d, NCHO).

General Procedure for the Reaction of (2*S*,4*R*)-2-Substituted *N*-Methyl-4-phenyl-1,3-oxazolidines (2a, 2b, 2d, 2e)

with Benzylmagnesium Chloride——A suspension of benzylmagnesium chloride (30 mmol in 30 ml of THF) was added, drop by drop, to a stirred solution of *N*-methyl-4-phenyl-1,3-oxazolidine (**2a**, **2b**, **2d**, **2e**) (10 mmol) in THF (10—30 ml) under a nitrogen atmosphere. After being stirred at room temperature for 3—4 h, the reaction mixture was treated with a small amount of water, the resulting white precipitate was filtered off, and the mixture was extracted with ether. The ethereal solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2 to give a mixture of two diastereomers as a colorless oil. The ratio of the isomers was estimated by ^{1}H-NMR (100 and/or 400 MHz) spectrometric analysis. The major product was isolated by rechromatography on silica gel.

(1*R*,1′*R*)-*N*-2′-Hydroxy-1′-phenylethyl-1,*N*-dimethyl-2-phenylethylamine (**3a**) (major product): MS *m/z*: CI, 270 ($M\cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.72 (3H, d, J=6.3 Hz, $CHC\underline{H}_3$), 2.39 (3H, s, NCH_3), 2.48 (1H, dd, J=7.3, 13.1 Hz, $PhC\underline{H}_2CH$), 2.72 (1H, dd, J=7.2, 13.1 Hz, $PhC\underline{H}_2CH$). (1*R*,1′*R*)-**3a**·HCl: mp 199—200 °C, $[\alpha]_D$ −55.0° (c=0.61, ethanol).

(1*R*,1′*R*)-1-Ethyl-*N*-2′-hydroxy-1′-phenylethyl-*N*-methyl-2-phenylethylamine (**3b**) (major product): MS *m/z*: CI, 284 ($M\cdot H^+$); EI, 254 ($M^+ - C_2H_5$), 192 (base peak, $M^+ - CH_2C_6H_5$). ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 2.34 (3H, s, NCH_3), 2.47 (1H, dd, J=6.7, 13.3 Hz, $PhC\underline{H}_2CH$), 2.55 (1H, dd, J=7.7, 13.3 Hz, $PhC\underline{H}_2CH$), 3.55 (1H, dd, J=4.4, 10.3 Hz, $OC\underline{H}_2CH$), 3.73 (1H, dd, J=8.3, 10.3 Hz, $OC\underline{H}_2CH$), 3.78 (1H, dd, J=4.4, 8.3 Hz, $NC\underline{H}CH_2$). (1*R*,1′*R*)-**3b**·HCl: mp 200—202 °C, $[\alpha]_D$ −35.1° (c=0.64, ethanol).

(1*R*,1′*R*)-*N*-2′-Hydroxy-1′-phenylethyl-1-isopropyl-*N*-methyl-2-phenylethylamine (**3d**) (major product): MS *m/z*: CI, 298 ($M\cdot H^+$); EI, 254 ($M^+ - C_3H_7$), 206 (base peak, $M^+ - CH_2C_6H_5$). ^{1}H-NMR ($CDCl_3$) δ: 0.81 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.94 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 2.35 (3H, s, NCH_3), 2.61 (1H, dd, J=5.9, 13.9 Hz, $PhC\underline{H}_2CH$), 2.66 (1H, dd, J=8.3, 13.9 Hz, $PhC\underline{H}_2CH$), 2.81 (1H, ddd, J=4.4, 5.9, 8.3 Hz, $CH_2C\underline{H}CH$), 3.41 (1H, dd, J=4.9, 10.5 Hz, $OC\underline{H}_2CH$), 3.58 (1H, dd, J=4.9, 8.3 Hz, $NC\underline{H}CH_2$), 3.68 (1H, dd, J=8.3, 10.5 Hz, $OC\underline{H}_2CH$). (1*R*,1′*R*)-**3d**·HCl: mp 215—217 °C, $[\alpha]_D$ +16.0° (c=0.66, ethanol). (1*S*,1′*R*)-**3d**, (minor product): ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.88 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 2.37 (3H, s, NCH_3).

(1*R*,1′*R*)-1-Cyclohexyl-*N*-2′-hydroxy-1′-phenylethyl-*N*-methyl-2-phenylethylamine (**3e**) (major product): MS *m/z*: CI, 338 ($M\cdot H^+$); EI, 254 ($M^+ - C_6H_{11}$), 246 (base peak, $M^+ - CH_2C_6H_5$). ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s, NCH_3), 2.62 (1H, dd, J=5.6, 13.9 Hz, $PhC\underline{H}_2CH$), 2.67 (1H, dd, J=8.3, 13.9 Hz, $PhC\underline{H}_2CH$), 2.77 (1H, ddd, J=4.2, 5.6, 8.3 Hz, $CHC\underline{H}CH_2$), 3.43 (1H, dd, J=4.9, 10.6 Hz, $OC\underline{H}_2CH$), 3.58 (1H, dd, J=4.9, 8.2 Hz, $PhC\underline{H}CH_2$), 3.68 (1H, dd, J=8.2, 10.6 Hz, $OC\underline{H}_2CH$). This product was recrystallized from *n*-heptane to give colorless needles of mp 77—78 °C. *Anal.* Calcd for $C_{23}H_{31}NO$: C, 81.85; H, 9.26; N, 4.15. Found: C, 81.66; H, 9.25; N, 4.03. (1*R*,1′*R*)-**3e**·HCl: mp 164—166 °C, $[\alpha]_D$ +10.5° (c=0.55, ethanol). (1*S*,1′*R*)-**3e**, (minor product): ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s, NCH_3).

General Procedure for the Reaction of (2*S*,4*R*)-2-Benzyl-*N*-methyl-4-phenyl-1,3-oxazolidine (2c) with Grignard Reagent——A suspension of Grignard reagent ($C_6H_{11}MgCl$, $(CH_3)_2CHMgBr$, MeMgBr, EtMgBr) (30 mmol in 30 ml of THF) was slowly added, drop by drop, to a stirred solution of **2c** (2.53 g, 10 mmol) in THF (10—30 ml) under a nitrogen atmosphere. After being stirred at room temperature for 3—4 h, the reaction mixture was worked up as described above to give a colorless oil. The ratio of the two diastereomers was estimated by ^{1}H-NMR (100 and/or 400 MHz) spectrometric analysis. The major product was isolated by rechromatography on silica gel.

(1*S*,1′*R*)-*N*-2′-Hydroxy-1′-phenylethyl-1,*N*-dimethyl-2-phenylethylamine (**3a**) (major product): MS *m/z*: CI, 270 ($M\cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 2.21 (3H, s, NCH_3), 2.49 (1H, dd, J=6.8, 13.4 Hz, $PhC\underline{H}_2CH$), 2.72 (1H, dd, J=7.8, 13.4 Hz, $PhC\underline{H}_2CH$). (1*S*,1′*R*)-**3a**·HCl: mp 206—208 °C, $[\alpha]_D$ +21.1 (c=0.55, ethanol).

(1*S*,1′*R*)-1-Ethyl-*N*-2′-hydroxy-1′-phenylethyl-*N*-methyl-2-phenylethylamine (**3b**) (major product): ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 2.27 (3H, s, NCH_3). (1*S*,1′*R*)-**3b**·HCl: mp 197—199 °C, $[\alpha]_D$ −32.4° (c=0.57, ethanol).

(*R*)-2-*N*-Methylamino-1-phenylpropane (4a)——A solution of (1*R*,1′*R*)-**3a** (0.16 g, 0.6 mmol) in glacial acetic acid (5 ml) was treated with 10% Pd–carbon (80 mg), and the mixture was shaken in a hydrogen atomosphere at room temperature for 12 h under a pressure of 6.0 kg/cm^2. The catalyst was then filtered off and the filtrate was concentrated under reduced pressure. The residue was treated with Na_2CO_3 aqueous solution and extracted with ether. After evaporation of the solvent, the residue was chromatographed on silica gel with CH_2Cl_2 to give a colorless oil (81.5 mg, 92%). The structure of this compound was confirmed by MS and ^{1}H-NMR spectroscopy.

The free amine was treated with hydrogen chloride in methanol to give the hydrochloride. mp 171—173 °C. $[\alpha]_D$ −16.3° (c=0.52, water).

Crystallographic Measurements——A single crystal of (1*R*,1′*R*)-**3e** was grown in *n*-heptane solution as a colorless column with dimensions of 0.5 × 0.4 × 0.2 mm. All the measurements were performed on a Rigaku AFC-5 diffractometer using graphite-monochromated MoK_α radiation. The unit cell dimensions were determined by least-squares calculation with 18 high-angle reflections.

Intensity data were collected by using the $2\theta/\omega$ scan technique for 2θ<50.5° with an average scan rate of 4°/min. In total, 2108 independent reflections with 0<2θ<50.5° were collected, and 1059 satisfying the condition $F_0 \geqq 3\sigma(F)$ were used for calculations.

Structure Analysis and Refinement——The structure was solved by the direct method using MULTAN[6] and the Rigaku crystallographic package RASA-II. The structure was refined by the block-diagonal least-squares method with anisotropic thermal parameters for all non-hydrogen atoms. The *R* factor was finally reduced to 0.113.

(*R*)-1-Cyclohexyl-*N*-methyl-2-phenylethylamine (4e)——A solution of (1*R*,1′*R*)-**3e** (3.38 g, 10 mmol) in glacial acetic acid (100 ml) was treated with 10% Pd–carbon (1 g), and the mixture was treated as described for the hydrogenolysis of **3a** to give a colorless oil (2.1 g, 95%). MS *m/z*: CI, 218 ($M \cdot H^+$); EI, 126 (base peak, $M^+ - CH_2C_6H_5$). ^{1}H-NMR (C_6D_6) δ: 2.17 (3H, s, NCH_3), 2.43 (1H, dt, J=4.4, 8.6 Hz, $CH_2C\underline{H}CH$), 2.49 (1H, dd, J=8.6, 13.2 Hz, $PhC\underline{H}_2CH$), 2.64 (1H, dd, J=4.4, 13.2 Hz, $PhC\underline{H}_2CH$).

The free amine was treated with hydrogen chloride in methanol to give the hydrochloride. This product was recrystallized from CH_2Cl_2 to give colorless needles of mp 239—241 °C. *Anal.* Calcd for $C_{15}H_{23}N \cdot HCl$: C, 70.98; H, 9.53; N, 5.52. Found: C, 71.00, H, 9.73; N, 5.44. $[\alpha]_D^{25}$ +8.4° (c=0.38, ethanol).

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