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

HIROSHI TAKAHASHI,* YASUHIRO CHIDA, KIMIO HIGASHIYAMA, and HIRAKU ONISHI

Institute of Medicinal Chemistry, Hoshi University, Ebara, Shinagawa-ku, Tokyo 142, Japan

(Received February 12, 1985)

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 (1R,1′R)- and (1S,1′R)-1-alkyl- and 1-cycloalkyl-N-2′-hydroxy-1′-phenylethyl-2-phenylethylamines (3a; 3b, 3d, 3e). The absolute configurations of (1R,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 (1R,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.

\[ \text{MeNH}_{\text{HO}} \quad \xrightarrow{\text{RCHO}} \quad \text{Me} \quad \xrightarrow{\text{R'MgX}} \quad \text{Me} \quad \xrightarrow{\text{OH}} \]

\[(S) \quad \xrightarrow{\text{RCHO}} \quad (2S, 4S) \quad \xrightarrow{\text{R'MgX}} \quad (1S, 1'S) \text{ or } (1R, 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, (2R,4R)- and (2S,4R)-2, may be formed, depending on the configuration of the asymmetric center at the 2-position. However, the 400 MHz proton nuclear magnetic
resonance (1H-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 nuclear magnetic resonance (13C-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 configurations39 and the absolute configuration was assumed to be (2S,4R) for the reasons described later.

The reactions of (2S,4R)-2-methyl- and (2S,4R)-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, (1R,1′R) and (1S,1′R), by 1H-NMR spectrometric analysis. The product ratios were estimated and the data are summarized in Table I. The reactions of (2S,4R)-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 (1R,1′R)- and (1S,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](chart2.png)
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 $-16.3^\circ$. The absolute configuration of this compound was elucidated as $R$ by comparison of the above value with that of an authentic sample. Consequently, the original compound was proved to be $(1R,1'R)$. The absolute configuration of 3b was assumed to be the same.

The $\alpha$-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 (2S,4R)-2-isopropyl- and (2S,4R)-2-cyclohexyl-N-methyl-4-phenyl-1,3-
TABLE II. Crystal Data

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>C_{23}H_{31}NO</td>
</tr>
<tr>
<td>Formula weight</td>
<td>337.49</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Cell dimensions (Å)</td>
<td>a = 12.773 (2)</td>
</tr>
<tr>
<td></td>
<td>b = 6.693 (3)</td>
</tr>
<tr>
<td></td>
<td>c = 11.891 (2)</td>
</tr>
<tr>
<td>Cell volume (Å³)</td>
<td>1006.1 (5)</td>
</tr>
<tr>
<td>Space group</td>
<td>P2_1</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>D_e (g cm⁻³)</td>
<td>1.11</td>
</tr>
<tr>
<td>μ (Mo Kα) (cm⁻¹)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

![Atomic Numbering of (1R,1'R)-3e](image1)

![Stereoscopic Drawings of the Structure of (1R,1'R)-3e](image2)

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

<table>
<thead>
<tr>
<th>Atom</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>B_{eq} (Å²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>5472</td>
<td>3531</td>
<td>450</td>
<td>5.3</td>
</tr>
<tr>
<td>N</td>
<td>3795</td>
<td>3122</td>
<td>1667</td>
<td>4.1</td>
</tr>
<tr>
<td>C(1)</td>
<td>3681</td>
<td>4265</td>
<td>2703</td>
<td>4.0</td>
</tr>
<tr>
<td>C(2)</td>
<td>4420</td>
<td>3352</td>
<td>3739</td>
<td>5.3</td>
</tr>
<tr>
<td>C(3)</td>
<td>5578</td>
<td>3409</td>
<td>3500</td>
<td>5.4</td>
</tr>
<tr>
<td>C(4)</td>
<td>6127</td>
<td>5260</td>
<td>3632</td>
<td>6.7</td>
</tr>
<tr>
<td>C(5)</td>
<td>7217</td>
<td>5266</td>
<td>3388</td>
<td>9.3</td>
</tr>
<tr>
<td>C(6)</td>
<td>7643</td>
<td>3634</td>
<td>3027</td>
<td>10.1</td>
</tr>
<tr>
<td>C(7)</td>
<td>7113</td>
<td>1765</td>
<td>2948</td>
<td>7.9</td>
</tr>
<tr>
<td>C(8)</td>
<td>6021</td>
<td>1587</td>
<td>3167</td>
<td>6.7</td>
</tr>
<tr>
<td>C(9)</td>
<td>2538</td>
<td>4569</td>
<td>2945</td>
<td>5.1</td>
</tr>
<tr>
<td>C(10)</td>
<td>2459</td>
<td>6531</td>
<td>3614</td>
<td>6.1</td>
</tr>
<tr>
<td>C(11)</td>
<td>1290</td>
<td>6956</td>
<td>3779</td>
<td>7.4</td>
</tr>
<tr>
<td>C(12)</td>
<td>819</td>
<td>5225</td>
<td>4361</td>
<td>8.5</td>
</tr>
<tr>
<td>C(13)</td>
<td>924</td>
<td>3308</td>
<td>3729</td>
<td>9.0</td>
</tr>
<tr>
<td>C(14)</td>
<td>2118</td>
<td>2831</td>
<td>3627</td>
<td>8.6</td>
</tr>
<tr>
<td>C(15)</td>
<td>3371</td>
<td>1109</td>
<td>1574</td>
<td>5.3</td>
</tr>
<tr>
<td>C(16)</td>
<td>3643</td>
<td>4410</td>
<td>623</td>
<td>4.3</td>
</tr>
<tr>
<td>C(17)</td>
<td>4409</td>
<td>3538</td>
<td>-180</td>
<td>3.9</td>
</tr>
<tr>
<td>C(18)</td>
<td>2520</td>
<td>4499</td>
<td>-24</td>
<td>4.6</td>
</tr>
<tr>
<td>C(19)</td>
<td>2080</td>
<td>2935</td>
<td>-662</td>
<td>6.3</td>
</tr>
<tr>
<td>C(20)</td>
<td>1022</td>
<td>3095</td>
<td>-1263</td>
<td>8.0</td>
</tr>
<tr>
<td>C(21)</td>
<td>478</td>
<td>4899</td>
<td>-1243</td>
<td>7.6</td>
</tr>
<tr>
<td>C(22)</td>
<td>952</td>
<td>6428</td>
<td>-615</td>
<td>7.4</td>
</tr>
<tr>
<td>C(23)</td>
<td>1988</td>
<td>6278</td>
<td>19</td>
<td>5.2</td>
</tr>
</tbody>
</table>

\[ B_{eq} = \frac{4}{3} \sum_{i} \sum_{j} \beta_{ij} a_i \cdot a_j \]
oxazolidines (2d, 2e) with benzylmagnesium chloride gave mixtures of (1R,1'R)- and (1S,1'R)-1-alkyl-N-2'-hydroxy-1'-phenylethyl-N-methyl-2-phenylethylamines (3d, 3e). The product ratios were estimated by 1H-NMR spectrometric analysis; the results are summarized in Table I. The reactions of (2S,4R)-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 1H-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 torsion angles for nonhydrogen atoms are give in Tables IV and V.

The structure of this compound (3e) was determined as (1R,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 (1R,1'R) by analogy with 3e. The above
TABLE V. Torsion Angles (°) of (1R,1'R)-3e with Their Standard Deviations in Parentheses

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D(^a)</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(9)</td>
<td>-C(1)</td>
<td>-C(2)</td>
<td>-C(3)</td>
<td>-171.1</td>
<td>(11)</td>
<td>C(10)</td>
<td>-C(9)</td>
</tr>
<tr>
<td>N</td>
<td>-C(1)</td>
<td>-C(2)</td>
<td>-C(3)</td>
<td>58.6</td>
<td>(14)</td>
<td>C(9)</td>
<td>-C(10)</td>
</tr>
<tr>
<td>C(2)</td>
<td>-C(1)</td>
<td>-C(2)</td>
<td>-C(9)</td>
<td>81.5</td>
<td>(14)</td>
<td>C(9)</td>
<td>-C(10)</td>
</tr>
<tr>
<td>C(2)</td>
<td>-C(1)</td>
<td>-C(9)</td>
<td>-C(14)</td>
<td>-40.2</td>
<td>(16)</td>
<td>C(11)</td>
<td>-C(12)</td>
</tr>
<tr>
<td>N</td>
<td>-C(1)</td>
<td>-C(9)</td>
<td>-C(10)</td>
<td>-151.4</td>
<td>(11)</td>
<td>C(12)</td>
<td>-C(13)</td>
</tr>
<tr>
<td>N</td>
<td>-C(1)</td>
<td>-C(9)</td>
<td>-C(14)</td>
<td>86.9</td>
<td>(14)</td>
<td>C(1)</td>
<td>-N</td>
</tr>
<tr>
<td>C(2)</td>
<td>-C(1)</td>
<td>-N</td>
<td>-C(15)</td>
<td>70.2</td>
<td>(14)</td>
<td>C(1)</td>
<td>-N</td>
</tr>
<tr>
<td>C(2)</td>
<td>-C(1)</td>
<td>-N</td>
<td>-C(16)</td>
<td>-148.1</td>
<td>(10)</td>
<td>C(15)</td>
<td>-N</td>
</tr>
<tr>
<td>C(9)</td>
<td>-C(1)</td>
<td>-N</td>
<td>-C(15)</td>
<td>-58.4</td>
<td>(15)</td>
<td>C(15)</td>
<td>-N</td>
</tr>
<tr>
<td>C(9)</td>
<td>-C(1)</td>
<td>-N</td>
<td>-C(16)</td>
<td>83.2</td>
<td>(13)</td>
<td>N</td>
<td>-C(16)</td>
</tr>
<tr>
<td>C(1)</td>
<td>-C(2)</td>
<td>-C(3)</td>
<td>-C(4)</td>
<td>77.8</td>
<td>(16)</td>
<td>C(18)</td>
<td>-C(16)</td>
</tr>
<tr>
<td>C(1)</td>
<td>-C(2)</td>
<td>-C(3)</td>
<td>-C(8)</td>
<td>-102.6</td>
<td>(15)</td>
<td>N</td>
<td>-C(16)</td>
</tr>
<tr>
<td>C(2)</td>
<td>-C(3)</td>
<td>-C(4)</td>
<td>-C(5)</td>
<td>-179.4</td>
<td>(14)</td>
<td>N</td>
<td>-C(16)</td>
</tr>
<tr>
<td>C(8)</td>
<td>-C(3)</td>
<td>-C(4)</td>
<td>-C(5)</td>
<td>1.0</td>
<td>(24)</td>
<td>C(17)</td>
<td>-C(16)</td>
</tr>
<tr>
<td>C(2)</td>
<td>-C(3)</td>
<td>-C(8)</td>
<td>-C(7)</td>
<td>179.6</td>
<td>(14)</td>
<td>C(17)</td>
<td>-C(16)</td>
</tr>
<tr>
<td>C(4)</td>
<td>-C(3)</td>
<td>-C(8)</td>
<td>-C(7)</td>
<td>-0.8</td>
<td>(23)</td>
<td>C(16)</td>
<td>-C(18)</td>
</tr>
<tr>
<td>C(3)</td>
<td>-C(4)</td>
<td>-C(5)</td>
<td>-C(6)</td>
<td>2.2</td>
<td>(27)</td>
<td>C(23)</td>
<td>-C(18)</td>
</tr>
<tr>
<td>C(4)</td>
<td>-C(5)</td>
<td>-C(6)</td>
<td>-C(7)</td>
<td>-5.5</td>
<td>(32)</td>
<td>C(16)</td>
<td>-C(18)</td>
</tr>
<tr>
<td>C(5)</td>
<td>-C(6)</td>
<td>-C(7)</td>
<td>-C(8)</td>
<td>5.6</td>
<td>(31)</td>
<td>C(19)</td>
<td>-C(18)</td>
</tr>
<tr>
<td>C(6)</td>
<td>-C(7)</td>
<td>-C(8)</td>
<td>-C(3)</td>
<td>-2.3</td>
<td>(25)</td>
<td>C(18)</td>
<td>-C(19)</td>
</tr>
<tr>
<td>C(1)</td>
<td>-C(9)</td>
<td>-C(10)</td>
<td>-C(11)</td>
<td>175.3</td>
<td>(11)</td>
<td>C(19)</td>
<td>-C(20)</td>
</tr>
<tr>
<td>C(14)</td>
<td>-C(9)</td>
<td>-C(10)</td>
<td>-C(11)</td>
<td>-59.7</td>
<td>(16)</td>
<td>C(20)</td>
<td>-C(21)</td>
</tr>
<tr>
<td>C(1)</td>
<td>-C(9)</td>
<td>-C(14)</td>
<td>-C(13)</td>
<td>-176.3</td>
<td>(13)</td>
<td>C(21)</td>
<td>-C(22)</td>
</tr>
</tbody>
</table>

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

\[\text{Ph} \quad \text{MgCl}\]
\[\text{H} \quad \text{Ph} \quad \text{O} \quad \text{Me} \quad \text{N} \quad \text{H} \]
\[\text{R} = \text{a, Me; b, Et; d, (CH}_3\text{)}\text{2CH}_2^-\; \text{e, c-} \text{C}_6\text{H}_4^-\]

**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, 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 (1R,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-oxazolines, which are easily obtained from commercially available (R)-phenylglycine.

Experimental

The 1H-NMR spectra were obtained with a JEOL JNM-FX100 and/or JNM-GX400 spectrometers. The 13C-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 CHCl3 (10 ml), and the mixture was stirred in the presence of anhydrous MgSO4 (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.

(2S,4R)-2, N-Dimethyl-4-phenyl-1,3-oxazoline (2a): Yield, 1.52 g (86%); bp 86–87 °C/7 mm Hg. [α]D = −153.8° (c = 0.70, n-hexane). MS m/z: Cl, 178 (M+); EI, 162 (base peak, M+ - CH3). 1H-NMR (CDCl3) δ: 1.38 (3H, d, J = 5.1 Hz, CH3CH2), 2.16 (3H, s, NCH3), 3.51 (1H, dd, J = 7.1, 8.8 Hz, OCH2CH3), 3.70 (1H, dd, J = 7.1, 8.8 Hz, OCH2CH3), 4.06 (1H, q, J = 5.1 Hz, OCH2CH3), 4.14 (1H, t, J = 7.1 Hz, PhCH2CH3). 13C-NMR (CDCl3) δ: 19.6 (q, CH3CH2), 36.0 (q, NCH3), 3Jc-H = 4.6 Hz), 70.3 (d, NCH3), 72.9 (t, OCH3), 94.3 (d, NCHO).

(2S,4R)-2-Ethyl-N-methyl-4-phenyl-1,3-oxazoline (2b): Yield, 1.67 g (87%); bp 105–106 °C/5 mm Hg. [α]D = −120.9° (c = 0.59, n-hexane). MS m/z: Cl, 192 (M+); EI, 162 (base peak, M+ - CH3). 1H-NMR (CDCl3) δ: 1.04 (3H, t, J = 7.3 Hz, CH3CH2), 1.62 (1H, ddq, J = 6.0, 7.3, 14.6 Hz, CH2CH2CH3), 1.78 (1H, ddq, J = 2.5, 7.3, 14.6 Hz, CH2CH2CH3), 2.16 (3H, s, NCH3), 3.55 (1H, dd, J = 7.3, 9.0 Hz, OCH2CH3), 3.65 (1H, dd, J = 7.3, 9.0 Hz, OCH2CH3), 3.99 (1H, dd, J = 2.6, 6.0 Hz, NCH2CH2CH3), 4.14 (1H, t, J = 7.3 Hz, OCH2CH3). 13C-NMR (CDCl3) δ: 81.1 (q, CH3CH2), 36.4 (t, CH3CH2), 36.3 (q, NCH3), 3Jc-H = 4.6 Hz), 70.3 (d, NCH3), 73.3 (t, OCH3), 98.6 (d, NCHO).

(2S,4R)-2-Benzyl-N-methyl-4-phenyl-1,3-oxazoline (2e): Yield, 2.05 g (81%); bp 161 °C/2.5 mm Hg. [α]D = −53.0° (c = 0.81, n-hexane). MS m/z: Cl, 254 (M+); EI, 162 (base peak, M+ - CH3CH2). 1H-NMR (CDCl3) δ: 1.97 (3H, s, NCH3), 2.93 (2H, d, J = 4.6 Hz, PhCH2CH3), 3.29 (1H, dd, J = 6.8, 8.8 Hz, OCH2CH3), 3.52 (1H, dd, J = 6.8, 8.8 Hz, OCH2CH3), 3.91 (1H, t, J = 6.8 Hz, PhCH2CH3), 4.16 (1H, t, J = 4.6 Hz, OCH3).

(2S,4R)-2-Isopropyl-N-methyl-4-phenyl-1,3-oxazoline (2d): Yield, 1.73 g (84%); bp 110–111 °C/6 mm Hg. [α]D = 103.4° (c = 1.04, n-hexane). MS m/z: Cl, 206 (M+); EI, 162 (base peak, M+ - CH3). 1H-NMR (CDCl3) δ: 1.03 (3H, d, J = 7.0 Hz, CH3CH2), 1.05 (3H, d, J = 7.0 Hz, CH3CH2), 1.88 (1H, double septet J = 2.4, 7.0 Hz, CH2CH2CH3), 2.17 (3H, s, NCH3), 3.56 (1H, dd, J = 3.1, 12.6 Hz, OCH2CH3), 3.60 (1H, dd, J = 3.1, 12.6 Hz, OCH2CH3), 3.93 (1H, d, J = 2.4 Hz, NCH2CH2CH3), 4.13 (1H, t, J = 3.1 Hz, OCH2CH3). 13C-NMR (CDCl3) δ: 15.0 (q, CH2CH3), 18.7 (q, CH3CH2), 30.9 (d, CH3CH2), 36.8 (q, NCH3), 3Jc-H = 4.6 Hz), 70.3 (d, NCH3), 73.8 (t, OCH3), 101.6 (d, NCHO).

(2S,4R)-2-Cyclohexyl-N-methyl-4-phenyl-1,3-oxazoline (2e): Yield, 2.18 g (89%); bp 146 °C/3 mm Hg. [α]D = −72.0° (c = 0.74, n-hexane). MS m/z: Cl, 246 (M+); EI, 162 (base peak, M+ - CH3). 1H-NMR (CDCl3) δ: 1.99 (3H, s, NCH3), 3.35 (1H, dd, J = 6.8, 9.2 Hz, OCH2CH3), 3.58 (1H, dd, J = 6.8, 9.2 Hz, OCH2CH3), 3.87 (1H, d, J = 4.0 Hz, OCH3), 4.00 (1H, t, J = 6.8 Hz, PhCH2CH3). 13C-NMR (CDCl3) δ: 25.3 (t, cyclohexyl), 26.1 (t, cyclohexyl), 26.6 (t, cyclohexyl), 29.2 (t, cyclohexyl), 36.6 (q, NCH3), 3Jc-H = 4.8 Hz), 40.9 (d, cyclohexyl), 70.0 (d, NCH3), 73.5 (t, OCH3), 101.0 (d, NCHO).

General Procedure for the Reaction of (2S,4R)-2-Substituted N-Methyl-4-phenyl-1,3-oxazolines (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 MgSO4 and concentrated under reduced pressure. The residue was chromatographed on silica gel with CH2Cl2 to give a mixture of two diastereomers as a colorless oil. The ratio of the isomers was estimated by 1H-NMR (100 and/or 400 MHz) spectrometric analysis. The major product was isolated by recrystallization on silica gel.

(1R,1'R)-N-2'-Hydroxy-1'-phenethyl-1,N-dimethyl-2-phenylethylamine (3a) (major product): MS m/z: CI, 270 (M-H+). 1H-NMR (CDCl3) δ: 0.72 (3H, d, J = 6.3 Hz, CH3CH2), 2.39 (3H, s, NCH3), 2.48 (1H, dd, J = 7.3, 13.1 Hz, PhCH2CH2), 2.72 (1H, dd, J = 7.2, 13.1 Hz, PhCH2CH2). (1R,1'R)-3a·HCl: mp 199—200°C, [α]D −55.0° (c 0.61, ethanol).

(1R,1'R)-1-Ethyl-N-2'-hydroxy-1'-phenethyl-N-methyl-2-phenylethylamine (3b) (major product): MS m/z: CI, 284 (M-H+); EI, 254 (M+ - CH2CH2), 192 (base peak, M+ - CH2CH2), 1H-NMR (CDCl3) δ: 0.80 (3H, t, J = 7.3 Hz, CH3CH2), 2.34 (3H, s, NCH3), 2.47 (1H, dd, J = 6.7, 13.3 Hz, PhCH2CH2), 2.55 (1H, dd, J = 7.7, 13.3 Hz, PhCH2CH2), 3.55 (1H, dd, J = 4.4, 10.3 Hz, OCH2CH2), 3.73 (1H, dd, J = 8.3, 10.3 Hz, OCH2CH2), 3.78 (1H, dd, J = 4.4, 8.3 Hz, NCH3). (1R,1'R)-3b·HCl: mp 200—202°C, [α]D −35.1° (c 0.64, ethanol).

(1R,1'R)-N-2'-Hydroxy-1'-phenethyl-N-isopropyl-N-methyl-2-phenylethylamine (3d) (major product): MS m/z: CI, 298 (M-H+); EI, 254 (M+ - CH3), 206 (base peak, M+ - CH2CH2), 1H-NMR (CDCl3) δ: 0.81 (3H, d, J = 6.6 Hz, CH3CH2), 0.94 (3H, d, J = 6.8 Hz, CH3CH2), 2.35 (3H, s, NCH3), 2.61 (1H, dd, J = 5.9, 13.9 Hz, PhCH2CH2), 2.66 (1H, dd, J = 8.3, 13.9 Hz, PhCH2CH2), 2.81 (1H, dd, J = 4.4, 5.9, 8.3 Hz, CH3CH2), 3.41 (1H, dd, J = 4.9, 10.5 Hz, OCH2CH2), 3.58 (1H, dd, J = 4.9, 8.3 Hz, NCH3), 3.68 (1H, dd, J = 8.3, 10.5 Hz, OCH2CH2). (1R,1'R)-3d·HCl: mp 215—217°C, [α]D +16.0° (c = 0.66, ethanol). (1S,1'R)-3d·HCl: mp 146—166°C, [α]D +10.5° (c = 0.55, ethanol). (1S,1'R)-3e·HCl: mp 197—199°C, [α]D −32.4° (c = 0.57, ethanol).

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

Intensity data were collected by using the 2θ/ω scan technique for 2θ ≤ 10° and with an average scan rate of 4°/min. In total, 2108 independent reflections with 0 < 2θ ≤ 50° were collected, and 1059 satisfying the condition Fobs ≥ 3σ(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.

\((R)-1\text{-Cyclohexyl-}N\text{-methyl-}2\text{-phenylethylamine (}4e\text{)}\) — A solution of \((1R,1' R)-3e\) (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\(_2\)C\(_6\)H\(_5\)). \(^1\)H-NMR (CD\(_6\)D\(_6\)) \(\delta:\) 2.17 (3H, s, NCH\(_3\)), 2.43 (1H, dt, \(J = 4.4, 8.6\) Hz, CH\(_2\)CHCH), 2.49 (1H, dd, \(J = 8.6, 13.2\) Hz, PhCH\(_2\)CH), 2.64 (1H, dd, \(J = 4.4, 13.2\) Hz, PhCH\(_2\)CH).

The free amine was treated with hydrogen chloride in methanol to give the hydrochloride. This product was recrystallized from CH\(_2\)Cl\(_2\) 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).

Acknowledgment We are grateful to Mrs. M. Yuyama, Miss T. Tanaka, and Mrs. T. Ogata of Hoshi University for \(^1\)H- and \(^13\)C-NMR spectra, mass spectra, and elemental analysis.

References