[Chem. Pharm. Bull. 33(1) 84—89 (1985)]

Stereoselective Reduction of (*S*)-4-Isopropyl-3-phenacyl-1,3-oxazolidin-2-one by Means of 1,4-Asymmetric Induction: Synthesis of Chiral 2-Amino-1-phenylethanols

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(Received May 1, 1984)

Stereoselective reductions of (*S*)-4-isopropyl-3-phenacyl-1,3-oxazolidin-2-one (**2**) with several complex metal hydrides gave 2-4′-isopropyl-2′-oxo-1′,3′-oxazolidinyl-1-phenylethanol (**3**) and 2-*N*-1′-isopropyl-2′-hydroxyethyl-*N*-methylamino-1-phenylethanol (**4**) in good yields. These products were diastereomeric mixtures and the diastereomer ratios were estimated to be *ca.* 75:25. The asymmetric 2-amino-1-phenylethanols (major products of **3** and **4**) were easily isolated by recrystallization. The absolute configuration of (1*S*,4′*S*)-**3** was determined by X-ray analysis.

The reductions of (*S*)-4-isopropyl-3-phenacyl-1,3-oxazolidine (**6**) with complex metal hydrides gave 2-4′-isopropyl-1′,3′-oxazolidinyl-1-phenylethanol (**7**) and **4** as diastereomeric mixtures (*ca.* 70:30).

Keywords——1,4-asymmetric induction; chiral phenacylamine; chiral phenylethanolamine; 1,3-oxazolidine chiral; 1,3-oxazolidin-2-one; stereoselective reduction; (*S*)-valinol

Chiral heterocyclic compounds can offer high stereoselectivity in their reactions,[1] and we have reported the reactions of chiral (2*S*,4*S*)-2-aryl-4-isopropyl-1,3-oxazolidines, which are easily prepared from (*S*)-valinol and arylaldehydes.[2] Evans *et al.* have proposed that an extremely highly stereoselective 1,4-asymmetric induction occurs at the carbon atom adjacent to the acyl group in (*S*)-3-acyl-4-isopropyl-1,3-oxazolidin-2-ones.[3] In this work, we deal with the stereoselective reduction of (*S*)-4-isopropyl-1,3-oxazolidin-2-one having a phenacyl group at the 3-position by means of 1,4-asymmetric induction. Recently, syntheses of chiral 2-amino-1-phenylethanols from phenacylamines have become increasingly important in the

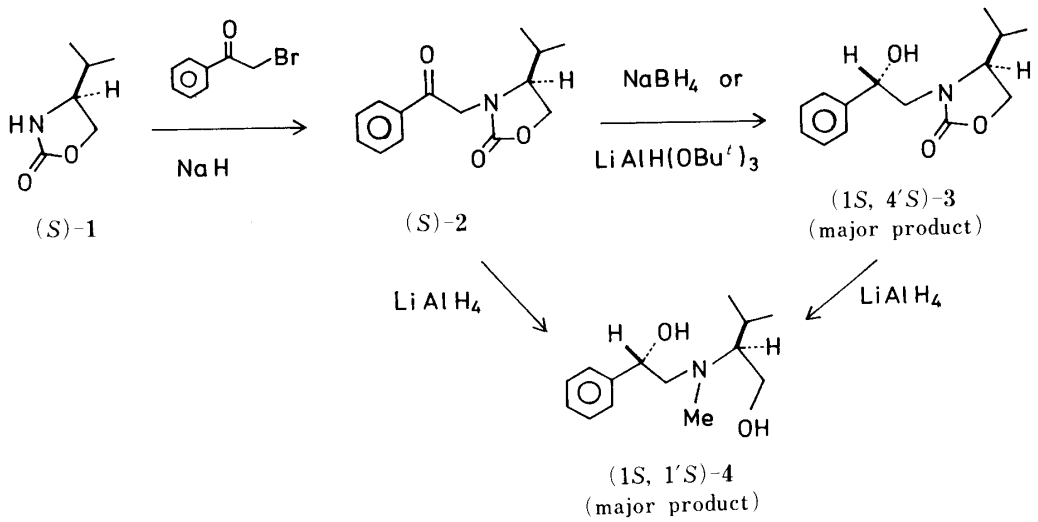

Chart 1

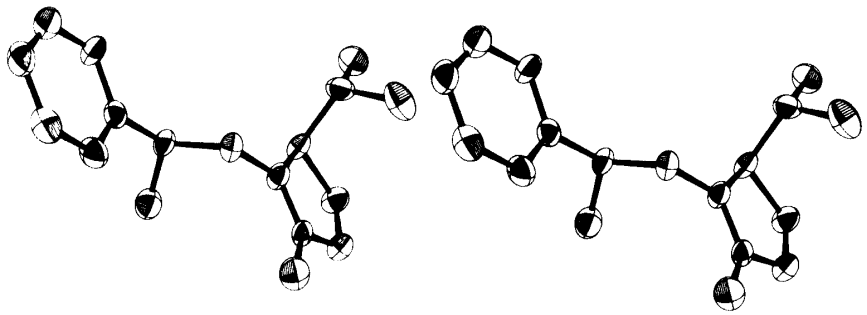

Fig. 1. Stereoscopic Drawings of the Structure of (1*S*,4′*S*)-**3**

design of medicinal agents.[4]

(*S*)-4-Isopropyl-3-phenacyl-1,3-oxazolidin-2-one (**2**) was obtained by condensation of the sodium salt of 4-isopropyl-1,3-oxazolidin-2-one (**1**)[5] with phenacyl bromide. The signals of the methylene protons of the phenacyl group of this compound were observed at δ 4.32 and 5.08 ($J=18.1$ Hz) in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, indicating that the molecule is fixed in a favorable conformation. The structure of this compound was confirmed by mass, infrared (IR), and ^{1}H-NMR spectroscopies.

The carbonyl bond of the phenacyl group was reduced with sodium borohydride and lithium tri-*tert*-butoxyaluminium hydride to give 2-4′-isopropyl-2′-oxo-1′,3′-oxazolidinyl-1-phenylethanol (**3**) in 96 and 94% yields, respectively. These products were confirmed to consist of two diastereomers by observation of the ^{1}H-NMR spectra, in ratios of 83 : 17 and 71 : 29, respectively. The major product was isolated from the mixture of isomers by recrystallization to give colorless needles. Moreover, a single-crystal X-ray analysis of this compound established the configuration of the newly created asymmetric carbon atom at the 1-position; stereoscopic drawings of the molecular structure are shown in Fig. 1. Consequently, the absolute configuration of the major product obtained by the reduction of (*S*)-**2** was defined unequivocally to be (1*S*,4′*S*).

The reduction of (*S*)-4-isopropyl-3-phenacyl-1,3-oxazolidin-2-one (**2**) with lithium aluminium hydride occurred at the two carbonyl bonds of the phenacyl group and the 1,3-oxazolidin-2-one to give 2-*N*-1′-isopropyl-2′-hydroxyethyl-*N*-methylamino-1-phenylethanol (**4**) in 71% yield. This product was confirmed to consist of two diastereomers in a ratio of 72 : 28. The major product was isolated from the mixture by recrystallization, and it was identical with (1*S*,1′*S*)-**4** obtained by the reduction of (1*S*,4′*S*)-**3** with lithium aluminium hydride. Consequently, the absolute configuration of this compound was correlated to the (1*S*,1′S)-family.

In order to investigate the effect of the chiral heterocyclic compounds in 1,4-asymmetric induction, the reduction of (*S*)-4-isopropyl-3-phenacyl-1,3-oxazolidine (**6**) lacking the carbonyl group at the 2-position of the ring was carried out with complex metal hydrides. This compound (**6**) was prepared by condensation of (*S*)-valinol with formaldehyde, followed by reaction with phenacyl bromide, and showed in the ^{1}H-NMR methylene proton signals similar to those of (*S*)-**2**.

The reduction of (*S*)-4-isopropyl-3-phenacyl-1,3-oxazolidine (**6**) with lithium tri-*tert*-butoxyaluminium hydride gave a diastereomeric mixture of 2-4′-isopropyl-1′,3′-oxazolidinyl-1-phenylethanols (**7**) in a ratio of 61 : 39 as determined by ^{1}H-NMR spectroscopy. On the other hand, the reduction with lithium aluminium hydride gave 2-*N*-1′-isopropyl-2′-hydroxyethyl-*N*-methylamino-1-phenylethanol (**4**), and the ratio of diastereomers was estimated to be 75 : 25. The major product of **7** was converted to (1*S*,1′*S*)-**4** by reduction with lithium aluminium hydride, so that the absolute configuration of this compound was clearly

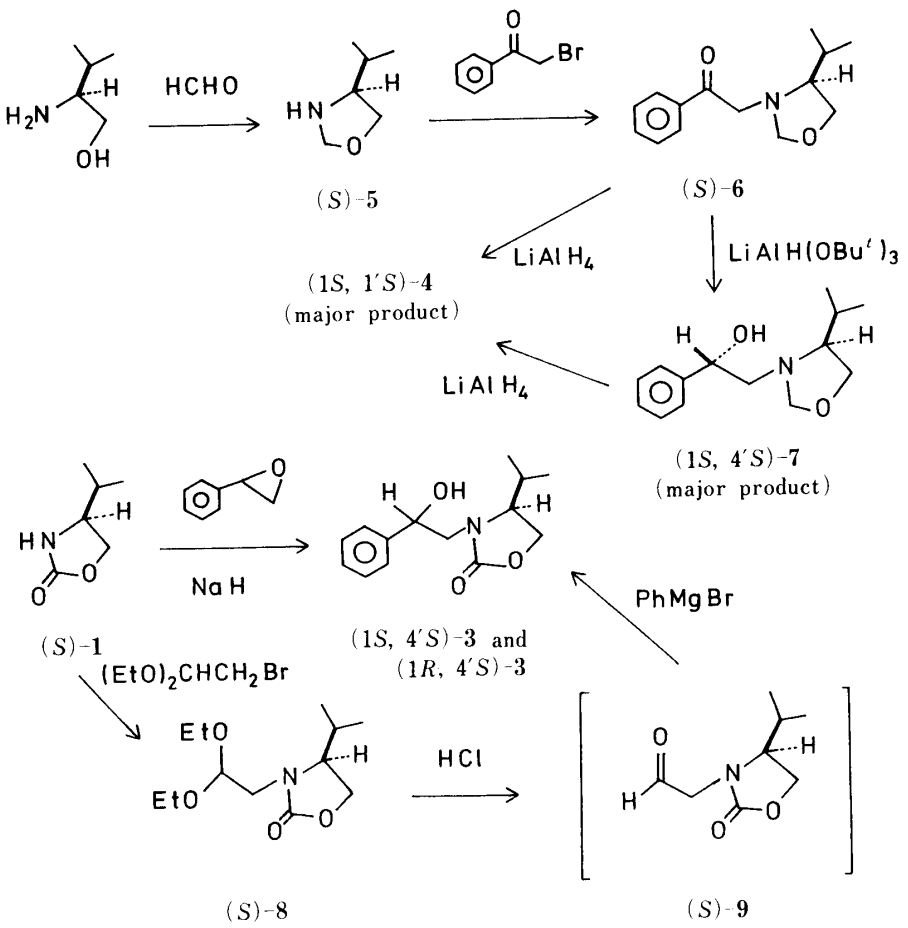

Chart 2

proved to be (1*S*,4′*S*).

We attempted to make use of the chirality of (*S*)-4-isopropyl-1,3-oxazolidin-2-one to synthesize the chiral 2-4′-isopropyl-2′-oxo-1′,3′-oxazolidinyl-1-phenylethanol (**3**). The reaction of sodium (*S*)-4-isopropyl-1,3-oxazolidin-2-onate with 2-phenyloxirane[6] proceeded in low yield to give a mixture of (1*S*,4′*S*)-**3** and (1*R*,4′*S*)-**3** in nearly equal amounts. Next, (*S*)-3-2′,2′-diethoxyethyl-1,3-oxazolidin-2-one (**8**) was prepared by condensation of (*S*)-**1** with 2-bromo-1,1-diethoxyethane. Grignard reaction of 3-formylmethyl-1,3-oxazolidin-2-one (**9**), which was derived from **8**, with phenylmagnesium bromide gave **3**, but this reaction also proceeded to give nearly equal amounts of isomers.

The asymmetric reactions of 3-acyl-4-isopropyl-1,3-oxazolidin-2-ones were found to show extremely high stereoselectivity[3,7] due to the involvement of a chiral chelated intermediate[8] involving the acyl group at the 3-position of the 1,3-oxazolidine ring and the carbonyl group at the 2-position. The reduction of (*S*)-3-phenacyl-4-isopropyl-1,3-oxazolidin-2-one (**2**) with complex metal hydrides proceeded with 66—42% ds (diastereoselectivity),[9] and (*S*)-3-phenacyl-4-isopropyl-1,3-oxazolidine (**6**) gave the product with 50—22% ds in similar reductions. These results suggested that these reactions occur *via* a weak chiral chelate intermediate involving the phenacyl group and the 1,3-oxazolidine moiety.

Experimental

The IR spectra were recorded with a Hitachi 260-10 spectrometer and the ^{1}H-NMR spectra were obtained with a JEOL JNM-FX100 spectrometer. The mass spectra (MS) were recorded with a JEOL JMS-D300 spectrometer by

using the chemical ionization (CI, isobutane) method. The melting points were measured with a Yanagimoto micromelting-point apparatus and are uncorrected. The optical rotations were measured with a Jasco DIP-180 polarimeter.

(*S*)-4-Isopropyl-3-phenacyl-1,3-oxazolidin-2-one (2)——A solution of (*S*)-**1** (2.06 g, 16 mmol) in toluene (50 ml) was slowly added, drop by drop, to a suspension of NaH (0.67 g, 28 mmol) in toluene (80 ml) with vigorous stirring, and the reaction mixture was refluxed for 9 h. A solution of phenacyl bromide (3.4 g, 17 mmol) in toluene (30 ml) was added dropwise to the suspension of the sodium 4-isopropyl-1,3-oxazolidin-2-onate. The reaction mixture was stirred at room temperature for 8 h, refluxed for 5 h, and then concentrated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2 to give (*S*)-**2** as a colorless oil (2.13 g, 54%). IR (film): 1750 (C=O), 1700 (C=O) cm^{-1}. MS *m/z*: 248 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 0.90 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 4.15 (1H, dd, J=5.6 and 7.8 Hz, $OC\underline{H}_2CH$), 4.32 (1H, d, J=18.1 Hz, $COCH_2$), 4.40 (1H, t, J=7.8 Hz, $OC\underline{H}_2CH$), 5.08 (1H, d, J=18.1 Hz, $COCH_2$).

(1*S*,4′*S*)-2-4′-Isopropyl-2′-oxo-1′,3′-oxazolidinyl-1-phenylethanol (3)——(i) Reduction of (*S*)-**2** with $NaBH_4$: $NaBH_4$ (0.15 g, 4 mmol) was added little by little to a stirred solution of (*S*)-**2** (0.49 g, 2 mmol) in methanol (5 ml), and the reaction mixture was stirred at −20——10 °C for 4 h. After addition of dilute acetic acid solution, the whole was extracted with ether and the ethereal solution was dried over anhydrous $MgSO_4$. The removal of the solvent gave a mixture of (1*S*,4′*S*)-**3** and (1*R*,4′*S*)-**3** as a colorless crystalline solid (0.48 g, 96%). The product ratio was estimated to be 83 : 17 by ^{1}H-NMR spectroscopy.

The mixture of isomers was recrystallized from ether to give colorless needles of mp 90—91 °C. This compound was confirmed to consist of the major product, (1*S*,4′*S*)-**3**, by ^{1}H-NMR spectroscopy. IR ($CDCl_3$): 3450 (OH), 1740 (C=O) cm^{-1}. MS m/*z*: 250 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 0.84 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 3.12 (1H, dd, J=4.4 and 14.4 Hz, $NC\underline{H}_2CH$), 3.80 (1H, dd, J=8.3 and 14.4 Hz, $NC\underline{H}_2CH$), 4.04 (1H, dd, J=5.4 and 9.0 Hz, $OC\underline{H}_2CH$), 4.20 (1H, t, J=9.0 Hz, $OC\underline{H}_2CH$), 4.93 (1H, dd, J=4.4 and 8.3 Hz, $OC\underline{H}CH_2$). *Anal.* Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.29; H, 7.75; N, 5.52. $[\alpha]_D^{20}$ +24.5° (*c*=4.0, 95% ethanol).

The minor product of this reaction was (1*R*,4′*S*)-**3**; ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 0.84 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 3.14 (1H, dd, J=8.5 and 14.6 Hz, $NC\underline{H}_2CH$), 3.61 (1H, dd, J=2.9 and 14.6 Hz, $NC\underline{H}_2CH$), 4.03 (1H, dd, J=4.9 and 8.6 Hz, $OC\underline{H}_2CH$), 4.21 (1H, t, J=8.6 Hz, $OC\underline{H}_2CH$), 4.98 (1H, dd, J=2.9 and 8.5 Hz, $OC\underline{H}_2CH_2$).

(ii) Reduction of (*S*)-**2** with $LiAlH(OBu^t)_3$: $LiAlH(OBu^t)_3$ (1.52 g, 6 mmol) was added, little by little, to a stirred solution of (*S*)-**2** (0.49 g, 2 mmol) in THF (10 ml), and the reaction mixture was stirred at −20——10 °C for 9 h. After addition of ether (17 ml), the mixture was treated with a minimum quantity of H_2O, and the whole was dried over anhydrous $MgSO_4$ then concentrated under reduced pressure to give a mixture of (1*S*,4′*S*)-**3** and (1*R*,4′*S*)-**3** (0.47 g, 94%). The product ratio was estimated to be 71 : 29.

Crystallographic Measurements——A single crystal of (1*S*,4′*S*)-**3** was grown in ether as a colorless column with dimensions of 0.2×0.3×0.5 mm. All the measurements were performed on a Rigaku AFC-5 diffractometer using graphite-monochromated Mo*K*α radiation. The unit cell dimensions were determined by least-squares calculation with 20 high-angle reflections.

Intensity data were collected by using the $2\theta/\omega$ scan technique for $3° < 2\theta < 55°$ with an average scan rate of 4 °/min. In total, 1848 independent reflections were collected, and 1015 satisfying the condition $F_0 < 2\sigma(F)$ were used for calculations.

Crystal Data——$C_{14}H_{19}NO_3$. M=249.3. Monoclinic. a=10.494 (3), b=6.313 (3), c=10.438 (4) Å, U=683.2 (5) Å^3, D_c=1.21 g·cm^{-1}, Z=2. μ(Mo*K*α)=0.8 cm^{-1}. Space group $P2_1$.

Structure Analysis and Refinement——The structure was solved by the direct method using MULTAN[10] 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 0.108.

(1*S*,1′*S*)-2-*N*-1′-Isopropyl-2′-hydroxyethyl-*N*-methylamino-1-phenylethanol (4)——Reduction of (*S*)-**2** with $LiAlH_4$: $LiAlH_4$ (0.23 g, 6 mmol) was added, little by little, to a stirred solution of (*S*)-**2** (0.49 g, 2 mmol) in THF (7.5 ml) and the reaction mixture was stirred at −20——10 °C for 9 h. After addition of ether (10 ml), the mixture was treated with a small amount of H_2O. The solid was filtered off, and the filtrate was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2–methanol (93 : 7) and a mixture of (1*S*,1′*S*)-**4** and (1*R*,1′*S*)-**4** was collected from all fractions. A colorless crystalline solid (0.34 g, 72%) was obtained. The ratio of the two isomers was estimated to be 72 : 28 by ^{1}H-NMR spectroscopy. Recrystallization of the mixture from *n*-pentane gave colorless plates of mp 60—61 °C; this product was confirmed to be the major one, (1*S*,1′*S*)-**4**, by ^{1}H-NMR spectroscopy. IR ($CDCl_3$): 3450 (OH) cm^{-1}. MS *m/z*: 238 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.00 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 2.47 (3H, s, NCH_3), 2.7—2.9 (2H, m, ABX Type, $NC\underline{H}_2CH$), 3.42 (1H, dd, J=9.0 and 11.0 Hz, $OC\underline{H}_2CH$), 3.66 (1H, dd, J=4.6 and 11.0 Hz, $OC\underline{H}_2CH$), 4.75 (1H, dd, J=5.4 and 8.0 Hz, $OC\underline{H}CH_2$). *Anal.* Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.81; H, 9.96; N, 5.81. $[\alpha]_D^{20}$ +64.5° (*c*=4.0, 95% ethanol).

The minor product of this reaction was (1*R*,1′*S*)-**4**; ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.94

(3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 2.42 (3H, s, NCH_3), 2.72 (1H, dd, J=9.5 and 13.4 Hz, $NC\underline{H}_2CH$), 3.00 (1H, dd, J=3.7 and 13.4 Hz, $NC\underline{H}_2CH$), 3.38 (1H, dd, J=9.5 and 10.7 Hz, $OC\underline{H}_2CH$), 3.69 (1H, dd, J=4.6 and 10.7 Hz, $OC\underline{H}_2CH$), 4.75 (1H, dd, J=3.7 and 9.5 Hz, $OC\underline{H}CH_2$).

Conversion of (1*S*,4′*S*)-3 into (1*S*,1′*S*)-4——$LiAlH_4$ (0.08 g, 2 mmol) was added, little by little, to a stirred solution of (1*S*,4′*S*)-**3** (0.13 g, 0.5 mmol) in THF (3 ml), and the reaction mixture was stirred at −20——10 °C for 4 h. After treatment with H_2O, the whole was extracted with ether. The ethereal solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give (1*S*,1′*S*)-**4** (0.08 g, 67%), which was identical with an authentic sample.

(*S*)-4-Isopropyl-1,3-oxazolidine (5)——Formaldehyde obtained by heating (180—190 °C) of paraformaldehyde (2.7 g, 90 mmol) was bubbled into a stirred solution of (*S*)-valinol (6.18 g, 60 mmol) in ether (150 ml) on an ice-cold bath using nitrogen as a carrier gas, and the reaction mixture was stirred in the presence of $MgSO_4$ (14 g) for 1 h. After removal of the solid, the mixture was concentrated under reduced pressure and the residue was distilled *in vacuo* to give (*S*)-**5** as a colorless oil, bp 85 °C/80 mmHg, (2.86 g, 42%). IR (film): 3350 (NH) cm^{-1}. MS *m/z*: 116 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.06 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.9 (1H, s, NH), 2.91 (1H, q, J=7.5 Hz, $CH_2C\underline{H}CH$), 3.22 (1H, t, J=7.5 Hz, $OC\underline{H}_2CH$), 3.81 (1H, t, J=7.5 Hz, $OC\underline{H}_2CH$), 4.32 (1H, d, J=6.0 Hz, OCH_2N), 4.53 (1H, d, J=6.0 Hz, OCH_2N).

(*S*)-4-Isopropyl-3-phenacyl-1,3-oxazolidine (6)——A solution of (*S*)-**5** (0.58 g, 5 mmol) in THF (3 ml) was slowly added to a solution of phenacyl bromide (0.59 g, 3 mmol) and triethylamine (0.45 g) in THF (4 ml), and the reaction mixture was stirred on an ice-cold bath for 12 h. After removal of the solid, the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2 to give (*S*)-**6** as a colorless oil (0.36 g, 52%). IR ($CHCl_3$): 1690 (C=O) cm^{-1}. MS *m/z*: 234 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.96 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 3.48 (1H, dd, J=5.9 and 8.5 Hz, $OC\underline{H}_2CH$), 3.94 (1H, d, J=16.6 Hz, $COCH_2N$), 4.02 (1H, dd, J=7.3 and 8.5 Hz, $OC\underline{H}_2CH$), 4.15 (1H, d, J=16.6 Hz, $COCH_2N$), 4.38 (1H, d, J=5.9 Hz, OCH_2N), 4.42 (1H, d, J=5.9 Hz, OCH_2N).

Reaction of (*S*)-6 with $LiAlH(OBu^t)_3$——$LiAlH(OBu^t)_3$ (1.0 g, 4 mmol) was added, little by little, to a stirred solution of (*S*)-**6** (0.47 g, 2 mmol) in THF (24 ml), and the reaction mixture was stirred at −20——10 °C for 9 h. After addition of ether (10 ml), the mixture was treated with a minimum quantity of H_2O. The whole was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2 and a mixture of (1*S*,4′*S*)-**7** and (1*R*,4′*S*)-**7** was collected from all fractions. A colorless oil (0.24 g, 51%) was obtained. The product ratio was estimated to be 61:39 by ^{1}H-NMR spectroscopy. The mixture was re-chromatographed on silica gel with CH_2Cl_2 to give (1*S*,4′*S*)-**7** (major product) as the first fraction and (1*R*,4′*S*)-**7** (minor product) as the second fraction. IR (film): 3500 (OH) cm^{-1}. MS *m/z*: 236 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: (1*S*,4′*S*)-**7**; 0.89 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.04 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 2.50 (1H, dd, J=10. 5 and 12.5 Hz, $NC\underline{H}_2CH$), 3.00 (1H, dd, J=3.2 and 12.5 Hz, $NC\underline{H}_2CH$), 3.48 (1H, dd, J=5.9 and 8.3 Hz, $OC\underline{H}_2CH$), 3.95 (1H, dd, J=7.3 and 8.3 Hz, $OC\underline{H}_2CH$), 4.29 (1H, d, J=5.9 Hz, OCH_2N), 4.45 (1H, d, J=5.9 Hz, OCH_2N), 4.61 (1H, dd, J=3.2 and 10.5 Hz, $(OC\underline{H}CH_2)$. (1*R*,4′*S*)-**7**; 0.92 (3H, d, J=6.4 Hz, $CHC\underline{H}_3$), 1.05 (3H, d, J=6.4 Hz, $CHC\underline{H}_3$), 2.61 (1H, dd, J=9.5 and 12.9 Hz, $NC\underline{H}_2CH$), 2.90 (1H, dd, J=3.7 and 12.9 Hz, $NC\underline{H}_2CH$), 3.47 (1H, dd, J=5.1 and 8.3 Hz, $OC\underline{H}_2CH$), 3.92 (1H, dd, J=6.8 and 8.3 Hz, $OC\underline{H}_2CH$), 4.28 (1H, d, J=6.1 Hz, OCH_2N), 4.31 (1H, d, J=6.1 Hz, OCH_2N), 4.66 (1H, dd, J=3.7 and 9.5 Hz, $OC\underline{H}CH_2$).

Reaction of (*S*)-6 with $LiAlH_4$——$LiAlH_4$ (0.23 g, 6 mmol) was added, little by little, to a stirred solution of (*S*)-**6** (0.47 g, 2 mmol) in THF (7 ml). The reaction mixture was stirred at −20——10 °C for 10 h, and worked-up as described above for the reaction of (*S*)-**2** to give a mixture of (1*S*,1′*S*)-**4** and (1*R*,1′*S*)-**4** (0.31 g, 66%). The product ratio was estimated to be 75:25 by the ^{1}H-NMR spectroscopy, and these compounds were identified by comparison with the diastereomers obtained from (*S*)-**2** by $LiAlH_4$ reduction.

Conversion of (1*S*,4′*S*)-7 into (1*S*,1′*S*)-4——(1*S*,4′*S*)-**7** (0.13 g, 0.5 mmol) was reduced wih $LiAlH_4$ (0.08 g, 2 mmol) in THF (3 ml) to give (1*S*,1′*S*)-**4** (0.09 g, 69%) by a procedure similar to that used for the reduction of (1*S*,4′*S*)-**3** with $LiAlH_4$ as described above.

Condensation of (*S*)-1 with 2-Phenyloxirane——A suspension of sodium (*S*)-4-isopropyl-1,3-oxazolidin-2-onate (7.5 mmol) in toluene (20 ml), which was prepared as described above, was added dropwise to a refluxing solution of 2-phenyloxirane (2.3 g, 19 mmol) in toluene (12 ml). After being refluxed for 6 h, the reaction mixture was concentrated under reduced pressure and treated with dilute HCl. The whole was extracted with ether, and the organic layer was dried over anhydrous $MgSO_4$ then concentrated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2 to give a mixture of (1*S*,4′*S*)-**3** and (1*R*,4′*S*)-**3** (0.29 g, 16%). The amounts of the two isomers were estimated to be nearly equal by ^{1}H-NMR spectroscopy.

(*S*)-3-1′,1′-Diethoxyethyl-4-isopropyl-1,3-oxazolidin-2-one (8)——A solution of (*S*)-**1** (16.8 g, 0.13 mol) and NaH (6.3 g, 0.26 mol) in $[(CH_3)_3N]_3PO$ (150 ml) was stirred at room temperature for 9 h. A solution of 2-bromo-1,1-diethoxyethane (28.6 g, 0.15 mol) in $[(CH_3)_3N]_3PO$ (30 ml) was added dropwise to the solution of the sodium salt of (*S*)-**1**, and the reaction mixture was stirred at room temperature for 8 h. After treatment with a small amount of H_2O, the whole was extracted with ether. The ethereal solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was distilled *in vacuo* to give (*S*)-**8** as a colorless oil, bp 153—155 °C/3 mmHg, (29 g,

90%). IR ($CHCl_3$): 1750 (C=O) cm^{-1}. MS *m/z*: 246 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 0.88 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 1.21 (6H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 2.98 (1H, dd, J=6.6 and 14.4 Hz, $NC\underline{H}_2CH$), 4.64 (1H, dd, J=3.9 and 6.6 Hz, $O(O)C\underline{H}CH_2$).

Reaction of (*S*)-9 with Phenylmagnesium Bromide——A solution of (*S*)-**8** (0.5 g, 2 mmol) in 10% HCl (15 ml) and acetone (5 ml) was stirred at 40—45 °C for 1 h. After removal of the acetone, the whole was extracted with CH_2Cl_2 and the organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in THF (3 ml) and added dropwise to a stirred suspension of phenylmagnesium bromide (4 mmol in 4 ml of THF) under a nitrogen atmosphere. After being stirred at −20—−10 °C for 9 h, the reaction mixture was poured into NH_4Cl solution and the whole was extracted with ether. The ethereal solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2 to give a mixture of (1*S*,4′*S*)-**3** and (1*R*,4′*S*)-**3** (0.33 g, 66%). The amounts of the two isomers were estimated to be nearly equal by ^{1}H-NMR spectroscopy.

Acknowledgement We are grateful to Mrs. M. Yuyama, Miss T. Tanaka, and Mrs. T. Ogata of Hoshi university for mass spectra, ^{1}H-NMR spectra, and elemental analysis.

References and Notes

1) A. I. Meyers and E. D. Mihelich, *Angew. Chem. Int. Ed. Engl.*, **15**, 270 (1976); A. I. Meyers, *Accounts Chem. Research*, **11**, 375 (1978); T. Mukaiyama, *Tetrahedron*, **37**, 4111 (1981).
2) H. Takahashi, Y. Suzuki, and T. Kametani, *Heterocycles*, **20**, 607 (1983); H. Takahashi, Y. Chida, T. Suzuki, H. Onishi, and S. Yanaura, *Chem. Pharm. Bull.*, **32**, 2714 (1984).
3) D. A. Evans, J. Bartroli, and T. L. Shin, *J. Am. Chem. Soc.*, **103**, 2127 (1981); D. A. Evans and L. R. McGee, *ibid.*, **103**, 2876 (1981); D. A. Evans, M. D. Ennis, and D. J. Mathre, *ibid.*, **104**, 1737 (1982).
4) D. Hartley, *Chem. Ind.* (London), **1981**, 551.
5) A. H. Homeyer, U. S. Patent 2399118 (1946) [*Chem. Abstr.*, **40**, 4084 (1946)].
6) F. Sauriol-Lord and T. B. Grindley, *J. Org. Chem.*, **46**, 2831 (1981).
7) D. A. Evans, J. V. Nelson, and T. R. Taber, "Topics in Stereochemistry," Vol. 13, ed. by N. L. Allinger, E. L. Eliel, and S. H. Wilen, John Wiley and Sons, Inc., 1982, pp. 1—115.
8) K. Koga, "Asymmetric Reactions and Processes in Chemistry," ed. by E. L. Eliel and S. Otsuka, American Chemical Society, 1982, pp. 73—81.
9) Diastereoselectivity (% ds) coincides with diastereomeric excess (% d.e.); D. Seebach and V. Prelog, *Angew. Chem. Int. Ed. Engl.*, **21**, 654 (1982).
10) P. Main, M. M. Woolfson, and G. Germin, *Acta Crystallogr.*, **A27**, 368 (1971).