Asymmetric Synthesis of 4-Phenyl-1,5-diazacyclooctan-2-one Using Optically Active Vinyl Sulfoxides

Nobuhiro Itoh, Haruo Matsuyama,* Masato Yoshida, Nobumasa Kamigata, and Masahiko Iyoda

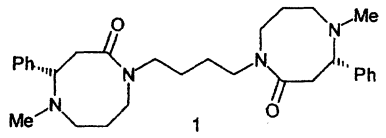
Department of Chemistry, Faculty of Science, Tokyo Metropolitan University, Hachioji, Tokyo 192-03

(Received March 24, 1995)

Both enantiomers of (*S*)- and (*R*)-4-phenyl-1,5-diazacyclooctan-2-ones (**7**) were synthesized stereoselectively with good optical purity by the asymmetric conjugate addition of pyrazolidine to optically active vinyl sulfoxides, *t*-butyl (*E*)-2-[(*R*)- and (*S*)-*p*-tolylsulfinyl]cinnamates, respectively. Starting from **7**, a synthesis of optically active homaline was achieved.

Homaline (**1**),[1,2] isolated from the leaves of *Homalium pronyense*, has a structure incorporating the naturally occurring polyamine, spermine, along with two dihydrocinnamoyl residues, and the 1,5-diazacyclooctan-2-one system is unique among natural products. Although synthesis of optically active (*S*,*S*)-(−)-**1** through a translactamization process involving the optically active β-lactam, (*S*)-(−)-4-phenylazetidin-2-one, has been reported,[3,4] no report on the synthetic approach to both (*S*,*S*)-(−)-**1** and (*R*,*R*)-(+)-**1** has been shown.

Recently, enantiomerically pure vinyl sulfoxides have proved to be useful reagents in asymmetric syntheses.[5] We report here the asymmetric synthesis of 4-phenyl-1,5-diazacyclooctan-2-one (**7**), which is a key intermediate in the synthesis of natural homaline (**1**), using optically active vinyl sulfoxides. Our synthetic approach to **7** involves the conjugate addition-cyclization reaction of pyrazolidine (**5**) to optically active vinyl sulfoxides, *t*-butyl 2-[(*S*)- and (*R*)-*p*-tolylsulfinyl]cinnamates (**4**), followed by successive reduction of the *p*-tolylsulfinyl group of the adduct with SmI_2[6] and reductive cleavage of the N–N bond of 4-phenyl-1,5-diazabicyclo[3.3.0]-octan-2-one (**6**).



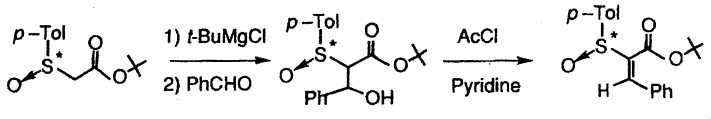
1

Chart 1.

Results and Discussion

Synthesis of *t*-Butyl 2-(*p*-Tolylsulfinyl)-cinnamate (4). The efficient synthesis of optically active *t*-butyl 2-(*p*-tolylsulfinyl)cinnamate (**4**) was established by using a modification of Andersen's method and Solladie's procedure (Scheme 1).[7,8]

The aldol-type reaction of α-carbanion of *t*-butyl (*R*)-(+)-2-(*p*-tolylsulfinyl)acetate (**2**) (o.p. 100%) with benzaldehyde produced *t*-butyl 3-hydroxy-3-phenyl-2-[(*R*)-*p*-tolylsulfinyl]propionate (**3**). Using *t*-butylmagnesium chloride as a base, the reaction took place easily to give the mixture of two diastereoisomers of (S*R*)-**3** in 87% yield (in the ratio of 5.1/1.0). Solladie reported that the structures of these diastereoisomers prepared from ester (*R*)-(+)-**2** were identified as (S*R*, 2*R*,3*R*) for the major isomer and to be (S*R*,2*R*,3*S*) for the minor isomer.[8] The conversion of **3** into vinyl sulfoxide **4** was investigated under reaction conditions for converting the hydroxy group of **3** to an acetoxy group. The acetylation reaction of alcohol **3** was done as described by Solladie. Under these reaction conditions, the elimination of acetic acid from *t*-butyl 3-acetoxy-3-phenyl-2-[(*S*)-*p*-tolylsulfinyl]propionate proceeded



(*R*)-(+)-2 (*S*)-(-)-2 | (*R*)-(+)-3 (*S*)-(-)-3 | (*S*,*E*)-(+)-4 (*R*,*E*)-(-)-4

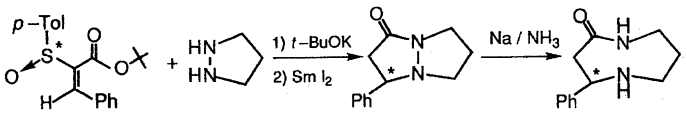
Scheme 1.

spontaneously and vinyl sulfoxide **4** was obtained as a major product, although Solladie did not describe the preparation of **4** in the acetylation of **3**.[8] The two isomers of vinyl sulfoxide (*S*)-**4** were obtained, and the ratio of *E*-**4**/*Z*-**4** was measured as 40/1 by separation using a silica-gel column chromatography. The major isomer of (*S*)-**4**, which was obtained in 91% e.e., could be purified by recrystallization to give the mostly pure vinyl sulfoxide (*S*)-**4** (99% e.e.) which was identified as the *E*-configuration.[9] Inversely, under the reaction conditions of acetylation of *t*-butyl 3-hydroxy-3-phenyl-2-[(*S*)-*p*-tolylsulfinyl]propionate (**3**) the major isomer of *t*-butyl (*R*)-(−)-2-(*p*-tolylsulfinyl)cinnamate (**4**), which was obtained in 93% e.e., could be purified by recrystallization to give mostly pure (*R*,*E*)-**4** (98% e.e.). The enantiomeric excess of (*E*)-**4** was measured by an HPLC measurement using an optically active column (Daicel Chiralpak AS).

Conjugate Addition-Cyclization Reaction of Cyclic Hydrazine 5 to Vinyl Sulfoxides 4. If the chiral bicyclic lactam **6** is obtained by the conjugate addition-cyclization reaction of pyrazolidine (**5**) to chiral *t*-butyl 2-(*p*-tolylsulfinyl)cinnamate (**4**), 4-phenyl-1,5-diazacyclooctan-2-one (**7**) can be synthesized according to the procedure shown in Scheme 2.[10]

The conjugate addition-cyclization reaction of pyrazolidine (**5**) to **4** proceeded smoothly under the basic conditions using potassium *t*-butoxide as a base in THF at room temperature and the bicyclic lactam **6** was obtained by successive reduction of *p*-tolylsulfinyl group of the bicyclic adduct with samarium(II) iodide[6] in situ. On the other hand, in the absence of potassium *t*-butoxide in THF, only the conjugate addition of pyrazolidine (**5**) to vinyl sulfoxide (*S*)-**4** took place and no cyclization product (*R*)-**6** was obtained after treatment of the addition product with samarium(II) iodide[6] in situ (Entry 6 in Table 1). The enantiomeric excess of bicyclic lactam **6** was 75—87% by an HPLC measurement using an optically active column (Daicel Chiralpak AS). The results are summarized in Table 1. A catalytic amount of potassium *t*-butoxide is sufficient for the cyclization reaction, and the conjugate addition-cyclization reaction of **5** to (*S*,*E*)-**4** and (*R*,*E*)-**4** proceeded smoothly to give (*R*)-(+)-**6** (82% e.e.) and (*S*)-(−)-**6** (87% e.e.) in 57 and 66% yields, respectively (Entries 1 and 2). When an equimolar amount of potassium *t*-butoxide was used, the optical purity of (*S*)-**6** was 75% e.e. and the chemical yield was 58% (Entry 3). The conjugate addition-cyclization reaction of pyrazolidine (**5**) to vinyl sulfoxide (*S*,*E*)-**4** was also examined in methanol as a solvent. The cyclization reaction did not proceed smoothly and the optical purity and chemical yield of (*R*)-(+)-**6** were decreased to 65% e.e. and 29%, respectively (Entry 4). The enantiomeric excess of the conjugate addition reaction of **5** to (*S*,*E*)-**4** in methanol under several conditions was 41—65% (Entries 4 and 5) and it was lower than that of the reaction examined in THF.

Reaction Mechanism. On the basis of the stereochemistry of bicyclic lactam (*R*)-**6** obtained from vinyl sulfoxide (*S*,*E*)-**4**, the mechanism of asymmetric conjugate addition can be explained as follows. The preferred non-chelate conformation of sulfoxide (*S*,*E*)-(+)-**4** may be expected to be that one in which the dipoles of the carbonyl and sulfinyl groups are oriented in opposite



Scheme 2.

Table 1. Conjugate Addition-Cyclization of Pyrazolidine (**5**) to Vinyl Sulfoxides **4**[a]

Entry	Sulfoxide	Solvent	*t*-BuOK (Molar amount)	Product	Yield[b] %	$[\alpha]_D$[c] deg.	e.e.[d] %
1	(*S*)-**4**	THF	0.1	(*R*)-**6**	57	+186	82
2	(*R*)-**4**	THF	0.1	(*S*)-**6**	66	−177	87
3	(*R*)-**4**	THF	1.0	(*S*)-**6**	58	−153	75
4	(*S*)-**4**	MeOH	1.0	(*R*)-**6**	29	+165	65
5	(*S*)-**4**	MeOH	0.1	(*R*)-**6**	19	+105	41
6	(*S*)-**4**	THF	0	(*R*)-**6**	0[e]		

a) The optical purity of vinyl sulfoxides **4** was determined by an HPLC analysis using a chiral column (Chiralpak AS; hexane/ethanol=9/1). (*S*)-**4**: $[\alpha]_D$ +241° (*c* 0.9, $CHCl_3$), 98% e.e.; (*R*)-**4**: $[\alpha]_D$ −243° (*c* 1.0, $CHCl_3$), 99% e.e. b) Isolated yield. c) Measured in $CHCl_3$ at 25 °C. d) Determined by a HPLC using a chiral column (Chiralpak AS; hexane/ethanol=7/3). e) The conjugate addition of **5** to **4** took place to give the acyclic adduct in 65% yield.

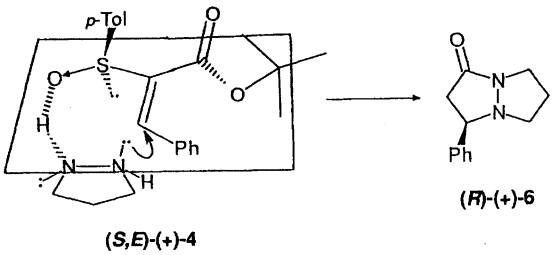
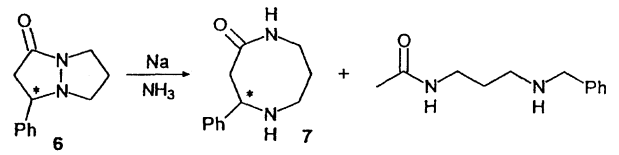


Fig. 1. Proposed mechanism in the conjugate addition of **5** to (*S*,*E*)-(+)-**4**.

directions, as shown in Fig. 1.[11] The sulfinyl oxygen atom is repelled the carbonyl group of *t*-butyl ester and placed near the plane formed from the phenyl group and carbon–carbon double bond, and the tolyl group on sulfur is directed above the plane. Thus, the rear side of the plane shown in Fig. 1 is not sterically crowded and it is expected that pyrazolidine (**5**) attacks the *β*-carbon of the double bond of vinyl sulfoxide (*S*,*E*)-(+)-**4** from the rear side of the plane (*si*-face), and in the presence of *t*-butoxide as a base successive cyclization of hydrazine with the bulky *t*-butyl ester group takes place to afford bicyclic lactam (*R*)-(+)-**6** by successive reduction of the *p*-tolylsulfinyl group of the bicyclic adduct with samarium(II) iodide. From these reasons, bicyclic lactam (*R*)-(+)-**6** was formed from the reaction of vinyl sulfoxide (*S*,*E*)-(+)-**4** with pyrazolidine (**5**), and inversely (*S*)-(−)-**6** was prepared from the reaction of vinyl sulfoxide (*R*,*E*)-(−)-**4** with **5**.

Synthesis of Optically Active 4-Phenyl-1,5-diazacyclooctan-2-one (7). The reductive cleavage of N–N bond of optically active bicyclic lactam **6** with sodium in liquid ammonia afforded 4-phenyl-1,5-diazacyclooctan-2-one (**7**) (Scheme 3). First using a large excess (15 molar amounts) of sodium, a further cleavage reaction of the eight-membered ring took place to give *N*-(3-benzylaminopropyl)acetamide (65%) and **7** (27%), but the mechanism of this side-reaction has not been clarified. When reductive cleavage of N–N bond of (*S*)-(−)-**6** (87% e.e.) with sodium (3.0 molar amounts) in liquid ammonia for 1 h afforded eight-membered azalactam (*S*)-(−)-**7** (87% e.e.) in 99% yield and the asymmetric carbon of (*S*)-(−)-**6** could be retained during the reduction process.[10]

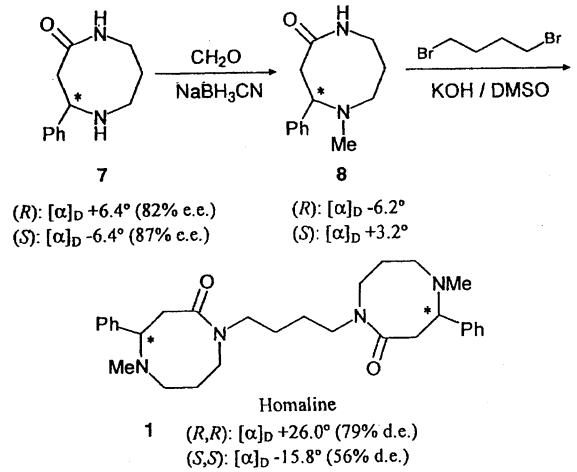
Similarly, (*R*)-(+)-**7** (82% e.e.) was obtained from the reductive cleavage of the N–N bond of (*R*)-(+)-**6** (82% e.e.) in 79% yield.[10] Starting from the optically active **7**, a synthesis of chiral homaline (**1**) was achieved



15 molar amounts of Na: 27% yield
3.0 molar amounts of Na: 99% yield

65% yield

Scheme 3.

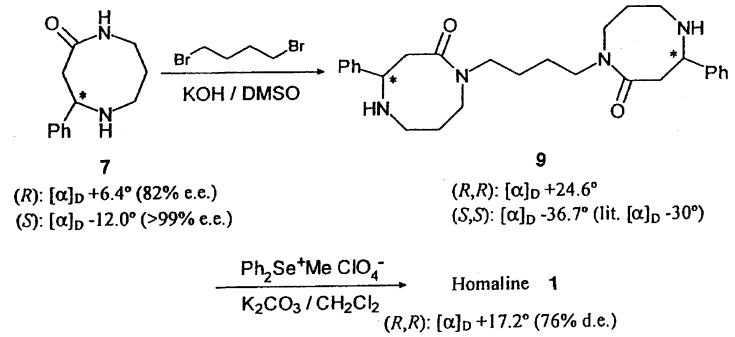


Scheme 4.

as shown in Scheme 4.[4]

N-Methylation of (*R*)-4-phenyl-1,5-diazacyclooctan-2-one [(*R*)-**7**] (82% e.e.) with CH_2O and $NaBH_3CN$ gave (*R*)-(−)-5-methyl-4-phenyl-1,5-diazacyclooctan-2-one [(*R*)-**8**] in 98% yield.[4] A double alkylation of (*R*)-**8** with 1,4-dibromobutane and powdered potassium hydroxide in dimethyl sulfoxide (DMSO) (20 °C, 12 h) gave (+)-homaline (**1**) in 12% yield. The isomeric ratio of (+)-homaline (**1**) was (*R*,*R*) : (*S*,*S*) : *meso*(*R*,*S*)= 89.3 : 2.2 : 8.5 by HPLC measurement using an optically active column (Chiralpak AS), and the diastereomeric excess of (*R*,*R*)-**1** (79% d.e.) was calculated by $[(R,R)-(S,S)-(R,S)/(R,R)+(S,S)+(R,S)]\times 100\%$. Similarly, (−)-homaline (**1**) was synthesized in 38% yield by a double alkylation of (*S*)-**8**, which was derived from *N*-methylation (CH_2O and $NaBH_3CN$) of (*S*)-**7** (87% e.e.), with 1,4-dibromobutane. The isomeric ratio of (−)-homaline (**1**) was (*R*,*R*) : (*S*,*S*) : *meso*(*R*,*S*)=2.7 : 78.1 : 19.2, and the diastereomeric excess of (−)-homaline (**1**) (56% d.e.) was calculated. While *N*-methylation of (*R*)-**7** [or (*S*)-**7**] with CH_2O and $NaBH_3CN$ gave (*R*)-**8** [or (*S*)-**8**] in good yield, partial racemization took place under these reaction conditions.[3] Although Crombie et al. reported a double alkylation of racemic **8** with 1,4-dibromobutane, our synthesis of **1** is the first example of a double alkylation of optically active 5-methyl-4-phenyl-1,5-diazacyclooctan-2-one (**8**).[4]

On the other hand, a double alkylation of (*R*)-**7** (82% e.e.) with 1,4-dibromobutane and powdered potassium hydroxide in DMSO (20 °C, 1 h) gave didemethylhomaline, 1,1′-(1,4-butanediyl)bis[(*R*)-4-phenyl-1,5-diazacyclooctan-2-one] [(*R*,*R*)-**9**] in 53% yield. The *N*-methylation of (*R*,*R*)-(+)-**9** with 5 molar amounts of methyldiphenylselenonium perchlorate (Ph_2Se^+Me ClO_4^-) in the presence of potassium carbonate (3 molar amounts) in dichloromethane at room temperature for 24 h gave homaline (*R*,*R*)-(+)-**1** (76% d.e.) in 43% yield without significant racemization at the benzylic carbon atoms (Scheme 5).[12] Synthetic homaline (**1**) was characterized by comparing its spectroscopic



Scheme 5.

data with those of natural (−)-homaline[3,4] and was in good agreement with natural (−)-homaline in all spectroscopic data.

The optically pure (*S*)-(−)-**7** [[α]$_D$ −12.0° (*c* 1.4, $CHCl_3$); >99% e.e.] was obtained by resolution of diastereomers derived from (*S*)-(−)-**7** (87% e.e.) and (*R*,*R*)-(+)-tartaric acid. Using a similar procedure to that shown in Scheme 5, didemethylhomaline (*S*,*S*)-**9** [[α]$_D$ −36.7° (*c* 1.3, $CHCl_3$); >99% e.e.] was prepared in 68% yield using optically pure (*S*)-(−)-**7**. Wasserman et al.[3] and Crombie et al.[4] reported independently the synthesis of natural (−)-homaline (**1**) using (*S*,*S*)-**9** [lit,[3] [α]$_D$ −30.0° (*c* 1.3, $CHCl_3$); >99% e.e.], so this procedure is a formal synthesis of (−)-homaline (**1**).

In summary, the conjugate addition-cyclization of pyrazolidine (**5**) to optically active vinyl sulfoxides **4** proceeded smoothly in THF at room temperature in the presence of potassium *t*-butoxide as a base. The diastereoselectivity of the conjugate addition was good (75—87%) and optically active bicyclic lactam **6** was obtained. Optically active 4-phenyl-1,5-diazacyclooctan-2-one (**7**), which is a key intermediate for the synthesis of homaline, could be synthesized by the reductive cleavage of N–N bond of optically active bicyclic lactam **6**. This is the first example of asymmetric synthesis of (*S*)-(−)- and (*R*)-(+)-4-phenyl-1,5-diazacyclooctan-2-ones (**7**).

Experimental

Melting points were measured with Yamato MP-21 and Yanaco MP-500D melting point apparatuses, and are uncorrected. Infrared spectra were recorded on Hitachi 260-10 and Perkin–Elmer 1600 series FTIR spectrometers. NMR spectra were recorded on JEOL JNM-PMX 60SI (60 MHz ^{1}H NMR) and JEOL JNM-EX 400 (400 MHz ^{1}H and 100 MHz ^{13}C NMR) spectrometers using tetramethylsilane as an internal standard. The mass and high-resolution mass spectra were measured with JEOL JMS-DX 300 and JEOL JMS-AX 505W mass spectrometers with a JEOL JMA 5000 mass data system at an ionizing voltage of 70 eV. Optical rotations were measured with a JASCO DIP-140 digital polarimeter in a 0.1 dm cell at 25 °C. The enantiomeric excess of optically active compounds was measured by HPLC (Hitachi 655) using a chiral column (Daicel Chemical, Chiralpak AD and Chiralpak AS, 0.46 cm ϕ×25 cm). Preparative HPLC was done using Kusano CPS-HS-221-05 and CPS-223L-1 C.I.G. pre-packed columns with a Kusano KPW-20 micro pump and Shodex RI SE-52 RI detector system. Gel permeation liquid chromatography (GPLC) was done with a JAI LC-08 (or LC-908) liquid chromatography with Jaigel-1H columns (20 mm×600 mm×2) using chloroform as eluent. Thin layer chromatography was done with a Merck Kiesel gel (Merck Art. 5554). Column chromatography was done with Wakogel C-200, Daisogel IR-60 (60/210 mesh), and Kanto silica gel (100/200 mesh).

All solvents were dried and purified by the usual procedures: Ether and THF were distilled from sodium diphenylketyl; methanol and ethanol were distilled from dimethoxy- or diethoxymagnesium; dichloromethane, acetonitrile, *N*,*N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) were distilled from calcium hydride.

Preparation of *t*-Butyl 2-(*p*-Tolylsulfinyl)acetate (2). *t*-Butyl acetate (13.6 ml, 101 mmol) was added dropwise to LDA solution (prepared from 9.6 ml (69 mmol) of diisopropylamine and 69 mmol of butyllithium in 300 ml of dry-THF) at −78 °C; 1.5 molar amounts of *t*-butyl acetate to LDA was used, because diisopropylamide anion attacked (1*R*,3*R*,4*S*)-*p*-menth-3-yl (*S*)-(−)-*p*-toluensulfinate to give *N*,*N*-diisopropyl(*p*-tolylsulfinyl)amine when LDA was remained in solution. After stirring was continued for 1 h at −78 °C, (1*R*,3*R*,4*S*)-*p*-menth-3-yl (*S*)-(−)-*p*-toluenesulfinate [[α]$_D$ −199° (*c* 1.0, acetone), lit,[7] [α]$_D$ −198° (*c* 1.0, acetone)]; 10 g, 34 mmol) in dry-THF (50 ml) was added dropwise to the solution. Then the solution was warmed to 0 °C and stirred for 1 h. The reaction was quenched with saturated ammonium chloride solution (100 ml) and the product was extracted with ether. After the ether solution was dried and concentrated, *t*-butyl (*R*)-(+)-2-(*p*-tolylsulfinyl)acetate (**2**) (8.36 g, 33 mmol) was obtained in 97% yield as a pale yellow oil by the purification using silica-gel column chromatography (hexane/ethyl acetate=4/1 as eluent).

Similarly, the stereoisomer (*S*)-(−)-**2** (19.4 g, 76 mmol) was prepared from the reaction of (1*S*,3*S*,4*R*)-*p*-menth-3-yl (*R*)-(+)-*p*-toluenesulfinate [[α]$_D$ +199° (*c* 1.0, acetone); 24 g, 82 mmol] with α-carbanion of *t*-butyl acetate; yield 93%.

***t*-Butyl (*R*)-(+)-2-(*p*-Tolylsulfinyl)acetate (2):** R_f=0.28 (hexane/ethyl acetate=2/1 as eluent); IR (neat) 1725 (C=O), 1160 (C–O), 1055 cm^{-1} (S=O); ^{1}H NMR ($CDCl_3$) δ=1.40 (s, 9 H, methyl of *t*-butyl), 2.42 (s, 3 H, methyl of *p*-tolyl), 3.59 and 3.79 (ABq, *J*=13.7 Hz, 2 H, CH_2), 7.34 and 7.59 (ABq, *J*=8.0 Hz, 4 H, aromatic H); MS *m*/*z* (rel intensity) 254 (M^+; 6), 198 (20), 140 (12), 139 (100), 91 (15), 77 (5), 57 (35); [α]$_D$ +150° (*c* 2.3, EtOH), o.p. 100% [lit,[8] [α]$_D$ +149° (*c* 2.3, EtOH); o.p. 100%], [α]$_D$ +118° (*c* 1.8, $CHCl_3$).

***t*-Butyl (*S*)-(−)-2-(*p*-Tolylsulfinyl)acetate (2):** IR (neat) 1734 (C=O), 1158 (C–O), 1049 cm^{-1} (S=O); ^1H NMR ($CDCl_3$) δ=1.40 (s, 9 H, methyl of *t*-butyl), 2.42 (s, 3 H, methyl of *p*-tolyl), 3.59 and 3.79 (ABq, J=12.4 Hz, 2 H, CH_2), 7.34 and 7.59 (ABq, J=8.0 Hz, 4 H, aromatic H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ=21.4, 27.8, 62.6, 83.1, 124.5, 130.0, 140.0, 142.3, 163.9; MS *m/z* (rel intensity) 254 (M^+; 8), 139 (100), 57 (26); $[\alpha]_D$ −113° (*c* 1.5, $CHCl_3$; o.p. 96%).

Preparation of *t*-Butyl 3-Hydroxy-3-phenyl-2-(*p*-tolylsulfinyl)propionate (3). In a 300 ml, three-necked round-bottomed flask with a magnetic stirrer, a thermometer, and a 250 ml pressure equalizing dropping funnel were placed *t*-butyl (*R*)-(+)-2-(*p*-tolylsulfinyl)acetate (**2**) (3.7 g, 14.56 mmol) and dry THF (100 ml), and the solution was cooled down to −78 °C under nitrogen. To the 1.63 M (1 M=1 mol dm^{-3}) solution of *t*-butylmagnesium chloride (22.0 mmol) in dry THF (13.5 ml) was added dropwise, and the mixture was stirred for 1 h. Then benzaldehyde (4.6 ml, 45 mmol) was added at −78 °C. After stirring was continued for 1 h, the reaction solution was treated with saturated ammonium chloride (30 ml), and the product was extracted with three 100 ml portions of ether. After the solution was dried and concentrated, the product was purified by silica-gel column chromatography (hexane/ethyl acetate=3/1 as eluent). *t*-Butyl 3-hydroxy-3-phenyl-2-[(*R*)-(*p*-tolylsulfinyl)propionate] (**3**) (4.36 g, 12.1 mmol) was obtained in 83% yield as a white solid (ratio of the products: (S*R*,2*R*,3*R*)/(S*R*,2*R*,3*S*)=5.1/1.0); yield of (S*R*,2*R*,3*R*): 3.65 g (10.1 mmol); yield of (S*R*,2*R*,3*S*): 0.71 g (2.0 mmol).

Similarly, the stereoisomer (*S*)-(−)-**3** (25.9 g, 72 mmol) was prepared from the reaction of *t*-butyl 2-[(*S*)-*p*-tolylsulfinyl]acetate (**2**) (19.4 g, 76 mmol), *t*-butylmagnesium chloride, and benzaldehyde; yield, 94%.

***t*-Butyl (2*R*,3*R*)-(+)-3-Hydroxy-3-phenyl-2-[(*R*)-*p*-tolylsulfinyl]propionate (3):** R_f=0.20 (hexane/ethyl acetate=2/1 as eluent); mp 105—106 °C; IR ($CHCl_3$)3440 (O–H), 1715 (C=O), 1145 cm^{-1} (S=O); ^1H NMR ($CDCl_3$) δ=1.22 (s, 9 H, methyl of *t*-butyl), 2.41 (s, 3 H, methyl of *p*-tolyl), 3.68 (d, J=6.4 Hz, 1 H, CH–O), 5.11 (d, J=6.4 Hz, S–CH), 7.25—7.40 (m, 8 H, OH and aromatic H), 7.53 (d, J=7.6 Hz, 2 H, aromatic H of tolyl); MS *m/z* (rel intensity) 361 (M^+; 1), 305, 198 (7), 165 (8), 147 (9), 139 (54), 105 (57), 77 (89), 65 (37), 56 (100); $[\alpha]_D$ +201° (*c* 1.4, $CHCl_3$), recrystallized compound from hexane/ether).

***t*-Butyl (2*R*,3*S*)-(+)-3-Hydroxy-3-phenyl-2-[(*R*)-*p*-tolylsulfinyl]propionate (3):** R_f=0.27 (hexane/ethyl acetate=2/1 as eluent); ^1H NMR ($CDCl_3$) δ=0.92 (s, 9 H, methyl of *t*-butyl), 2.39 (s, 3 H, methyl of *p*-tolyl), 3.76 (d, J=9.3 Hz, 1 H, CH–O), 4.34 (broad s, 1 H, OH), 5.43 (d, J=9.3 Hz, 1 H, S–CH), 7.20—7.56 (m, 5 H, phenyl), 7.28 and 7.46 (ABq, J=7.6 Hz, 4 H, aromatic H of tolyl); $[\alpha]_D$ +171° (*c* 1.23, $CHCl_3$).

***t*-Butyl (2*S*,3*S*)-(−)-3-Hydroxy-3-phenyl-2-[(*S*)-*p*-tolylsulfinyl]propionate (3):** R_f=0.21 (hexane/ethyl acetate=2/1); IR ($CHCl_3$) 3383 (O–H), 1720 (C=O), 1148 (S=O), 1049 cm^{-1} (S=O); ^1H NMR ($CDCl_3$) δ=1.23 (s, 9 H, methyl of *t*-butyl), 2.42 (s, 3 H, methyl of *p*-tolyl), 3.69 (d, J=6.0 Hz, 1 H, CH–O), 5.10 (d, J=6.0 Hz, 1 H, S–CH), 7.25—7.40 (m, 8 H, OH and aromatic H), 7.53 (d, J=8.0 Hz, 2 H, aromatic H of tolyl); MS *m/z* (rel intensity) 361 (M^+; 1), 105 (100), 57 (22); $[\alpha]_D$ −184° (*c* 1.7, $CHCl_3$).

***t*-Butyl (2*S*,3*R*)-(−)-3-Hydroxy-3-phenyl-2-[(*S*)-*p*-tolylsulfinyl]propionate (3):** IR ($CHCl_3$) 3384 (O–H), 1719 (C=O), 1140 (S=O), 1041 cm^{-1} (S=O); ^1H NMR ($CDCl_3$) δ=0.91 (s, 9 H, methyl of *t*-butyl), 2.41 (s, 3 H, methyl of *p*-tolyl), 3.76 (d, J=9.4 Hz, 1 H, CH–O), 5.09 (broad s, 1 H, OH), 5.44 (d, J=9.4 Hz, 1 H, S–CH), 7.20—7.56 (m, 7 H, aromatic H), 7.61 (d, J=8.4 Hz, 2 H, aromatic H of tolyl); MS *m/z* (rel intensity) 361 (M^+; 1), 139 (100), 57 (33).

Preparation of *t*-Butyl 2-(*p*-Tolylsulfinyl)cinnamate (4). To a dry-ether (500 ml) solution of *t*-butyl 3-hydroxy-3-phenyl-2-[(*S*)-*p*-tolylsulfinyl]propionate (**3**) (18 g, 50 mmol) and pyridine (5.0 ml, 62 mmol) in a 1000-ml three-necked flask with a magnetic stirrer and a septum, acetyl chloride (4.7 ml, 66 mmol) were added dropwise by syringe at room temperature. If a large excess of acetyl chloride were used, Pummerer rearrangement took place, and *t*-butyl 3-acetoxy-2-(*p*-tolylthio)cinnamate and *t*-butyl 2,3-diacetoxy-3-phenyl-2-(*p*-tolylthio)propionate were obtained. During addition of acetyl chloride, white solid of pyridinium hydrochloride precipitated, and the temperature of solution increased to ether-reflux temperature. After stirring was continued for 2 h, the reaction mixture was dissolved in 200 ml ether and washed successively with 100 ml of water, 100 ml of 10% hydrochloric acid solution, and 100 ml of 10% sodium hydrogencarbonate solution. The organic layer was then dried over magnesium sulfate, filtered, and evaporated. From the organic residue, 10.4 g (30 mmol) of *t*-butyl (*R*)-(−)-2-(*p*-tolylsulfinyl)cinnamate (**4**) (ratio of isomers; *E*-**4**/*Z*-**4**=40/1) was obtained in 61% yield by the purification using silica-gel column chromatography (hexane/ethyl acetate=3/1 as eluent); yield of *E*-**4**: 10.15 g (29.7 mmol); yield of *Z*-**4**: 0.25 g (0.74 mmol). (*R*,*E*)-(−)-isomer of vinyl sulfoxide **4** could be purified by recrystallization from hexane as colorless needles.

Similarly, (*S*,*E*)-(+)-**4** (6.4 g, 18.7 mmol) was obtained from the reaction of (*SR*)-(+)-**3** (8.5 g, 23.6 mmol) with acetyl chloride and pyridine in dry ether; yield, 79%.

***t*-Butyl (*S*,*E*)-(+)-2-(*p*-Tolylsulfinyl)cinnamate (4):** R_f=0.45 (hexane/ethyl acetate=2/1); mp 111.5 °C; IR (KBr) 1695 (C=O), 1620 (C=C), 1595, 1365, 1235, 1150, 1085, 1065 cm^{-1} (S=O); IR (CCl_4) 1720, 1705 (C=O), 1620 (C=C), 1493, 1394, 1369, 1232, 1150, 1086, 1062 cm^{-1} (S=O); ^1H NMR ($CDCl_3$) δ=1.22 (s, 9 H, methyl of *t*-butyl), 2.38 (s, 3 H, methyl of *p*-tolyl), 7.28 and 7.62 (ABq, J=8.0 Hz, 4 H, aromatic H of tolyl), 7.26—7.66 (m, 5 H, phenyl), 7.61 (s, 1 H, =CH); MS *m/z* (rel intensity) 342 (M^+; 3), 294 (51), 238 (63), 225 (14), 213 (13), 193 (18), 147 (13), 140 (56), 139 (31), 119 (11), 102 (27), 91 (38), 77 (18), 57 (100). HRMS Found: *m/z* 342.1300. Calcd for $C_{20}H_{22}O_3S$: M, 342.1290. Found: C, 69.80; H, 6.77%. Calcd for $C_{20}H_{22}O_3S$: C, 70.14; H, 6.47%. $[\alpha]_D$ +219° (*c* 1.1, $CHCl_3$) (91% e.e.); $[\alpha]_D$ +241° (*c* 0.9, $CHCl_3$, recrystallized compound from hexane); the enantiomeric purity (99% e.e.) was calculated from an HPLC measurement using an optically active column (Daicel Chiralpak AS); retention time: t_R=14.2 min: 0.6% (*R*-form); t_R=19.2 min: 99.4% (*S*-form); eluent: hexane/ethanol=9/1; flow rate: 1 ml min^{-1}; detection: UV 254 nm).

***t*-Butyl (*R*,*E*)-(−)-2-(*p*-Tolylsulfinyl)cinnamate (4):** Mp 112.0 °C; IR (KBr) 1706 (C=O), 1602, 1492, 1368, 1277, 1257, 1157, 1085, 1054 cm^{-1} (S=O); ^1H NMR ($CDCl_3$) δ=1.22 (s, 9 H, methyl of *t*-butyl), 2.38 (s, 3 H,

methyl of *p*-tolyl), 7.27 and 7.62 (ABq, J=8.0 Hz, 4 H, aromatic H of tolyl), 7.26—7.61 (m, 5 H, phenyl), 7.61 (s, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ=21.5 (methyl of tolyl), 27.6 (methyl of *t*-butyl), 83.2 (saturated carbon of *t*-butyl), 126.8 and 128.3 (*o*- and *m*-carbon of tolyl), 130.0 (*p*-carbon of phenyl), 130.0 and 133.1 (*o*- and *m*-carbon of phenyl), 137.4 (=CH), 138.1, 139.7 (aromatic C), and 142.5 (aromatic *C*-CH), 162.3 (CO); MS *m/z* (rel intensity) 342 (M^+; 1), 57 (100). HRMS Found: *m/z* 342.1323. Calcd for $C_{20}H_{22}O_3S$: M, 342.1290. Found: C, 69.88; H, 6.75%. Calcd for $C_{20}H_{22}O_3S$: C, 70.14; H, 6.47%. $[\alpha]_D$ −224° (*c* 1.7, $CHCl_3$) (93% e.e.), $[\alpha]_D$ −243° (*c* 1.0, $CHCl_3$, recrystallized compound from hexane); the enantiomeric purity (98% e.e.) was calculated from an HPLC measurement using an optically active column (Daicel Chiralpak AS); retention time: t_R=15.7 min: 99.0% (*R*-form); t_R=21.7 min: 1.0% (*S*-form); eluent: hexane/ethanol 9/1; flow rate: 1 ml min^{-1}; detection: UV 254 nm).

***t*-Butyl (*S,Z*)-(−)-2-(*p*-Tolylsulfinyl)cinnamate (4):** IR (neat) 1706 (C=O), 1156 cm^{-1} (S=O); ^{1}H NMR ($CDCl_3$) δ=1.25 (s, 9 H, methyl of *t*-butyl), 2.40 (s, 3 H, methyl of tolyl), 7.26—7.73 (m, 9 H, aromatic H), 8.25 (s, 1 H, =CH); MS *m/z* (rel intensity) 342 (M^+; 5), 239 (100), 57 (74); $[\alpha]_D$ −167° (*c* 0.6, $CHCl_3$).

***t*-Butyl (*R,Z*)-(+)-2-(*p*-Tolylsulfinyl)cinnamate (4):** IR (neat) 1706 (C=O), 1157 cm^{-1} (S=O); ^{1}H NMR ($CDCl_3$) δ=1.25 (s, 9 H, methyl of *t*-butyl), 2.40 (s, 3 H, methyl of *p*-tolyl), 7.26—7.72 (m, 9 H, aromatic H), 8.25 (s, 1 H, =CH); MS *m/z* (rel intensity) 342 (M^+; 7), 239 (100), 57 (88); $[\alpha]_D$ +204° (*c* 0.7, $CHCl_3$).

Pyrazolidine (5): Bp 138 °C; 46 °C/25 Torr, 1 Torr= 133.322 Pa; IR (neat) 3270 cm^{-1} (N–H); ^{1}H NMR ($CDCl_3$) δ=1.90 (quint, J=7.2 Hz, 2 H), 2.93 (t, J=7.2 Hz, 4 H), 3.14—3.52 (broad s, 2 H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ=28.1, 48.7; MS *m/z* (rel intensity) 72 (M^+; 100), 57 (76).

Conjugate Addition Reaction of Pyrazolidine (5) to *t*-Butyl 2-(*p*-Tolylsulfinyl)cinnamate (4) in the Presence of Potassium *t*-Butoxide as a Base. Pyrazolidine (**5**) (104 mg, 1.44 mmol) was added to a dry-THF (5 ml) solution of *t*-butyl (*R,E*)-(−)-2-(*p*-tolylsulfinyl)-cinnamate (**4**) (100 mg, 0.29 mmol) and a catalytic amount of potassium *t*-butoxide (3.3 mg, 0.029 mmol) in a 50-ml three-necked flask, and the mixture was stirred for 4 h at room temperature under nitrogen. After reaction mixture was cooled down to ice-water temperature, samarium(II) iodide in THF (0.1 M; 17.4 ml, 1.74 mmol) and methanol (0.5 ml) were added, and stirring was continued for 30 min. Afterwards, the reaction mixture was treated with saturated sodium carbonate solution (10 ml), and the product was extracted with dichloromethane (100 ml×3). After the organic layer was dried and evaporated, the residue was purified by gel permeation liquid chromatograpy (chloroform as eluent), and (*S*)-(−)-4-phnenyl-1,5-diazabicyclo[3.3.0]octan-2-one (**6**) (39 mg, 0.19 mmol) was obtained in 66% yield. The optical purity of (*S*)-(−)-**6** (87% e.e.) was calculated from HPLC measurement using an optically active column (Daicel Chiralpak AS).

Similarly, (*R*)-(+)-**6** (34 mg, 0.17 mmol, 82% e.e.) was obtained in 57% yield from the reaction of (*S,E*)-(+)-**4** (100 mg, 0.29 mmol) with pyrazolidine (**5**) (104 mg, 1.44 mmol).

The conjugate addition reactions of pyrazolidine (**5**) to vinyl sulfoxides **4** were examined under several conditions. In a dry-THF (5 ml) solution, the conjugate addition-cyclization reaction of **5** (1.0 g, 13.9 mmol) to (*R,E*)-(−)-**4** (1.0 g, 2.9 mmol) took place in the presence of potassium *t*-butoxide (327 mg, 2.9 mmol), and (*S*)-(−)-**6** (341 mg, 1.69 mmol, $[\alpha]_D$ −153° (*c* 1.1, $CHCl_3$), 75% e.e.) was obtained in 58% yield. In methanol solution (5 ml), conjugate addition-cyclization reaction of **5** (1.45 mmol) to (*S,E*)-(+)-**4** (100 mg, 0.29 mmol) took place in the presence of potassium *t*-butoxide (33 mg, 0.29 mmol) at room temperature for 4 h, and (*R*)-(+)-**6** (17 mg, 0.084 mmol, $[\alpha]_D$ +165° (*c* 0.7, $CHCl_3$), 65% e.e.) was obtained in 29% yield. Similarly, (*R*)-(+)-**6** ($[\alpha]_D$ +105° (*c* 1.0, $CHCl_3$), 41% e.e.) was obtained in 19% yield by the conjugate addition-cyclization of **5** with (*S,E*)-(+)-**4** (100 mg, 0.29 mmol) in the presence of potassium *t*-butoxide (3.3 mg, 0.029 mmol) in methanol (5 ml) at room temperature for 4 h. These results are summarized in Table 1.

***(S)*-(−)-4-Phenyl-1,5-diazabicyclo[3.3.0]octan-2-one (6):** R_f=0.49 (chloroform/methanol=19/1); IR (neat) 1650 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=2.32—2.42 (m, 2 H, C–CH_2–C), 2.44 (q, J=8.3 Hz, 1 H, N–CH–C), 2.97 (d, J=9.8 Hz, 2 H, CH_2CO), 3.21 (t, J=8.3 Hz, 1 H, N–CH–C), 3.35 (ddd, J=11.2, 8.3, 4.9 Hz, CO–N–CH–C), 3.75 (dt, J=11.2, 7.8 Hz, 1 H, CO–N–CH–C), 4.11 (t, J=9.8 Hz, 1 H, N–CH–Ph), 7.25—7.45 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ=27.5 (N–C–CH_2–C–N), 39.5 ($CONCH_2$), 43.9 (CH_2CO), 53.3 (NCH_2), 69.0 (NCHPh), 126.9, 128.1, 128.8 (aromatic CH), 139.1 (aromatic *C*-CH), 165.9 (C=O); MS *m/z* (rel intensity) 202 (M^+; 67), 159 (9), 131 (12), 104 (100), 77 (10). HRMS Found: *m/z* 202.1079. Calcd for $C_{12}H_{14}N_2O$: M, 202.1106; $[\alpha]_D$ −177° (*c* 1.9, $CHCl_3$) (87% e.e.); the enantiomeric purity (87% e.e.) was determined by an HPLC measurement using an optically active column (Daicel Chiralpak AS; retention time: t_R=19.9 min: 93.7% (*S*-form); t_R=33.4 min: 6.3% (*R*-form); eluent: hexane/ethanol=7/3; flow rate: 1 ml min^{-1}; detection: UV 254 nm).

***(R)*-(+)-4-Phenyl-1,5-diazabicyclo[3.3.0]octan-2-one (6):** IR (neat) 1665 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=2.34—2.41 (m, 2 H, C–CH_2–C), 2.44 (q, J=8.3 Hz, 1 H, N–CH–C), 2.97 (d, J=9.8 Hz, 2 H, CH_2CO), 3.21 (t, J=8.3 Hz, 1 H, N–CH–C), 3.35 (ddd, J=11.2, 8.3, 4.9 Hz, CO–N–CH–C), 3.75 (dt, J=11.2, 7.8 Hz, 1 H, CO–N–CH–C), 4.11 (t, J=9.8 Hz, 1 H, N–CH–Ph), 7.30—7.42 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ=27.5 (N–C–CH_2–C–N), 39.3 ($CONCH_2$), 43.9 (CH_2CO), 53.2 (NCH_2), 69.0 (NCHPh), 126.9, 128.1, 128.7 (aromatic CH), 139.0 (aromatic *C*-CH), 165.8 (C=O); GC-MS *m/z* (rel intensity) 202 (M^+; 44), 159 (9), 131 (11), 104 (100), 77 (15). HRMS Found: *m/z* 202.1123. Calcd for $C_{12}H_{14}N_2O$: M, 202.1106. $[\alpha]_D$ +186° (*c* 1.1, $CHCl_3$) (82% e.e.); the enantiomeric purity (82% e.e.) was calculated from an HPLC measurement using an optically active column (Daicel Chiralpak AS; retention time: t_R=20.4 min: 9.1% (*S*-form); t_R=31.8 min: 90.9% (*R*-form); eluent: hexane/ethanol=7/3; flow rate: 1 ml min^{-1}; detection: UV 254 nm).

Synthesis of 4-Phenyl-1,5-diazacyclooctan-2-one (7). Into a 300-ml three-necked flask fitted with a Dewar condenser, ammonia gas was added until about 100 ml of liquid ammonia was collected at −78 °C under nitrogen. Then the dry-THF (5 ml) solution of (*S*)-(−)-4-phenyl-1,5-diazabicyclo[3.3.0]octan-2-one (**6**) (365 mg, 1.8 mmol,

$[\alpha]_D$ −177° (*c* 1.9, $CHCl_3$), 87% e.e.) and sodium metal (124 mg, 5.4 mmol) were added; if a large excess (15 molar amounts) of sodium metal were added, the ring cleavage product of eight-membered ring of **7**, *N*-(3-benzylaminopropyl)acetamide was obtained as a side-reaction product. After the mixture was stirred for 1 h, ammonium chloride was added till the dark blue color of the solution disappeared. Then a Dewar condenser and a cooling bath were removed, and liquid ammonia was evaporated. The residue was dissolved in 50 ml of dichloromethane and 10 ml of water, and the product was extracted with dichloromethane (50 ml×3). After the organic solution was dried over anhydrous sodium sulfate, the solution was concentrated. The product was purified by silica-gel column chromatography (chloroform/methanol=19/1 as eluent), and (*S*)-(−)-4-phenyl-1,5-diazacyclooctan-2-one (**7**) [363 mg, 1.8 mmol, $[\alpha]_D$ −6.4° (*c* 0.9, $CHCl_3$)] was obtained in 99% yield.

Similarly, (*R*)-(+)-**7** (35 mg, 0.17 mmol, $[\alpha]_D$ +6.4° (*c* 1.2, $CHCl_3$)) was prepared in 79% yield by the reduction of N–N bond of (*R*)-(+)-**6** [44 mg, 0.22 mmol, $[\alpha]_D$ +186° (*c* 0.9, $CHCl_3$), 82% e.e.] with sodium metal (15 mg, 0.65 mmol) in liquid ammonia.

(*S*)-(−)-4-Phenyl-1,5-diazacyclooctan-2-one (7): R_f=0.32 (chloroform/methanol=19/1); IR (neat) 3100—3700 (N–H), 1640 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.56—1.67 (m, 1 H, N–C–CH–C–NCO), 1.67—1.78 (m, 1 H, N–C–CH–C–NCO), 2.23 (broad s, 1 H, NH), 2.43 (dd, *J*=12.8, 1.6 Hz, 1 H, CHCO), 2.54 (ddd, *J*=14.4, 12.2, 3.8 Hz, 1 H, NCH–C–C–NCO), 2.91 (dd, *J*=12.8, 10.8 Hz, 1 H, CHCO), 3.15—3.26 (m, 2 H, NCH–C–CH–NCO), 3.82 (td, *J*=12.6, 3.6 Hz, 1 H, N–C–C–CHNCO), 4.02 (dd, *J*=10.8, 1.6 Hz, 1 H, NCHPh), 6.89 (broad s, 1 H, CONH), 7.21—7.40 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ=34.2 (N–C–CH_2–C–N), 39.4 ($CONCH_2$), 44.1 (CH_2CO, NCH_2–C–C–NCO), 64.0 (NCHPh), 126.4, 127.5, 128.6 (aromatic CH), 144.7 (aromatic *C*–CH), 176.5 (C=O); GC-MS *m/z* (rel intensity) 204 (M^+; 32), 145 (32), 132 (100), 118 (78), 105 (38), 91 (48), 77 (16). HRMS Found: *m/z* 204.1219. Calcd for $C_{12}H_{16}N_2O$: M, 204.1264. $[\alpha]_D$ −6.4° (*c* 0.9, $CHCl_3$) (87% e.e.); though the enantiomeric purity of **7** could not be found by HPLC measurement using optically active columns, the enantiomeric purity (87% e.e.) was estimated based on the purity of starting material **6** (87% e.e.), because the chemical yield of **7** was 99%. For the synthesis of 9-phenyl-1,6-diazacyclononan-7-one, the asymmetric carbon could be retained during the reductive cleavage of N–N bond of optically active bicyclic lactam, 9-phenyl-1,6-diazabicyclo[4.3.0]nonan-2-one.[10]

(*R*)-(+)-4-Phenyl-1,5-diazacyclooctan-2-one (7): IR (neat) 3350 (N–H), 1640 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.54—1.63 (m, 1 H, N–C–CH–C–NCO), 1.63—1.77 (m, 1 H, N–C–CH–C–NCO), 2.31 (broad s, 1 H, NH), 2.43 (dd, *J*=11.7, 1.5 Hz, 1 H, CHCO), 2.56 (ddd, *J*=15.2, 11.7, 3.4 Hz, 1 H, NCH–C–C–NCO), 2.92 (dd, *J*=11.7, 10.7 Hz, 1 H, CHCO), 3.15—3.30 (m, 2 H, NCH–C–CHNCO), 3.86 (td, *J*=13.4, 3.4 Hz, 1 H, N–C–C–CHNCO), 4.03 (dd, *J*=10.7, 1.5 Hz, 1 H, NCHPh), 6.35 (broad s, 1 H, CONH), 7.22—7.41 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ=34.2 (N–C–CH_2–C–NCO), 39.5 ($CONCH_2$), 44.0 (CH_2CO), 44.1 (NCH_2–C–C–NCO), 64.0 (NCHPh), 126.5, 127.6, 128.7 (aromatic CH), 144.5 (aromatic *C*–CH), 176.3 (C=O); MS *m/z* (rel intensity) 204 (M^+; 100), 145 (18), 132 (61), 118 (74), 105 (31), 91 (31), 77 (14). HRMS Found: *m/z* 204.1259. Calcd for $C_{12}H_{16}N_2O$: M, 204.1264. $[\alpha]_D$ +6.4° (*c* 1.2, $CHCl_3$) (82% e.e.); the enantiomeric purity (82% e.e.) was estimated based on the purity of starting material **6** (82% e.e.) because the chemical yield of **7** was 79%.[10]

***N*-(3-*N*-Benzylaminopropyl)acetamide, Ring Cleavage Product of 7:** IR (neat) 3450 and 3300 (N–H), 1655 (C=O), 1520 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ=1.69 (q, *J*=6.6 Hz, 2 H, CON–C–CH_2–C–N), 1.91 (s, 3 H, CH_3CON), 2.72 (t, *J*=6.6 Hz, 2 H, NCH_2), 2.92 (broad s, 1 H, NH), 3.30 (q, *J*=6.6 Hz, 2 H, $CONCH_2$), 3.71 (s, 2 H, NCH_2Ph), 7.31 (s, 5 H, Ph), 7.10—7.50 (m, 1 H, CONH); ^1H NMR ($CDCl_3$+D_2O, 60 MHz) δ=1.65 (q, *J*=6.6 Hz, 2 H, CO–N–C–CH_2–C–N), 1.91 (s, 3 H, CH_3CO–N), 2.70 (d, *J*=6.6 Hz, 2 H, NCH_2), 3.30 (t, *J*=6.6 Hz, 2 H, $CONCH_2$), 3.71 (s, 2H, N–CH_2Ph), 7.31 (s, 5 H, Ph); MS *m/z* 206 (M^+), 188, 120, 115, 106. HRMS Found: *m/z* 206.1412. Calcd for $C_{12}H_{18}N_2O$: M, 206.1420.

Resolution of 4-Phenyl-1,5-diazacyclooctan-2-one (7). (*S*)-(−)-4-Phenyl-1,5-diazacyclooctan-2-one (**7**) [368 mg, 1.8 mmol, $[\alpha]_D$ −6.4° (*c* 1.3, $CHCl_3$), 87% e.e.] and (*R*,*R*)-(+)-tartaric acid (270 mg, 1.8 mmol) were dissolved in methanol (10 ml) at room temperature for 3 h. After the solvent was evaporated in vacuo, the salts of diastereoisomers were recrystallized from ethanol. Optically pure **7** [142 mg, 0.70 mmol, 39% yield, $[\alpha]_D$ −12.0° (*c* 1.4, $CHCl_3$), >99% e.e.][4] was obtained by the purification using silica-gel chromatography (chloroform/methanol=19/1) after treatment of diastereoisomers (432 mg) obtained from the mother liquor with 0.1 M sodium hydroxide solution (1 ml) and extraction with chloroform. On the other hand, from the crystals of diastereoisomers (273 mg), **7** [$[\alpha]_D$ −3.2° (*c* 1.4, $CHCl_3$), 114 mg, 31% yield] was obtained by treatment with 0.1 M sodium hydroxide solution (1 ml) and extraction with chloroform.

Synthesis of 5-Methyl-4-phenyl-1,5-diazacyclooctan-2-one (8). To an acetonitrile (6 ml) solution of (*R*)-(+)-4-phenyl-1,5-diazacyclooctan-2-one (**7**) [105 mg, 0.51 mmol, $[\alpha]_D$ +6.4° (*c* 1.2, $CHCl_3$), 82% e.e.] and 37% aqueous solution of formaldehyde (85 mg, 1.05 mmol) in a 20 ml round-bottomed flask, sodium cyanoborohydride (86 mg, 1.34 mmol) was added at room temperature. After the mixture was stirred for 1 h, acetic acid (0.05 ml) was added to the solution, and stirring was continued for 1 h. Then 0.05 ml of acetic acid was added, and the solution was stirred for another 30 min. The reaction solution was treated with 0.1 M sodium hydroxide solution (5 ml), and the product was extracted with dichloromethane (30 ml×3). After the organic solution was dried and concentrated, (*R*)-(−)-5-methyl-4-phenyl-1,5-diazacyclooctan-2-one (**8**) (109 mg, 0.50 mmol) was obtained in 98% yield by the purification using HPLC (silica-gel column, chloroform/methanol=99/1 as eluent).

Similarly, (*S*)-(+)-**8** (71 mg, 0.33 mmol) was obtained in 57% yield from the *N*-methylation of (−)-(*S*)-**7** [117 mg, 0.57 mmol, $[\alpha]_D$ −6.4° (*c* 0.9, $CHCl_3$), 87% e.e.] with formaldehyde (0.4 ml, 5.0 mmol).

(*R*)-(−)-5-Methyl-4-phenyl-1,5-diazacyclooctan-2-one (8): R_f=0.19 (chloroform/methanol=19/1); ^1H NMR ($CDCl_3$) δ=1.72—1.91 (m, 2 H, N–C–CH_2–C–N), 2.39 (s, 3 H, NCH_3), 2.55 (dd, *J*=13.0, 3.0 Hz, 1 H, CHCO), 2.66—

2.76 (m, 1 H, NCH–C–C–NCO), 3.23 (dd, J=13.0, 11.6 Hz, 1 H, CHCO), 3.15—3.28 (m, 1 H, NCH–C–C–NCO), 3.34—3.45 (m, 1 H, N–C–C–CHNCO), 3.55—3.68 (m, 1 H, N–C–C–CHNCO), 4.18 (dd, J=11.6, 2.8 Hz, 1 H, NCHPh), 6.50 (broad s, 1 H, CONH), 7.30—7.41 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ=31.4 (N–C–CH_2–C–N), 38.8 (CH_2CO), 42.2 ($CONCH_2$), 44.3 (NCH_3), 51.7 (NCH_2), 67.8 (NCHPh), 127.9, 128.2, 128.8 (aromatic CH), 138.7 (aromatic *C*–CH), 175.8 (C=O); MS m/z (rel intensity) 218 (M^+; 100), 203 (2), 189 (2), 174 (9), 159 (21), 146 (38), 132 (92), 118 (51), 104 (34); $[\alpha]_D$ −6.2° (*c* 0.9, $CHCl_3$).

(*S*)-(+)-5-Methyl-4-phenyl-1,5-diazacyclooctan-2-one (8): IR (neat) 3300 (N–H), 1650 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=1.60—1.80 (m, 2 H, N–C–CH_2–C–N), 2.34 (s, 3 H, NCH_3), 2.49 (dd, J=12.8, 3.6 Hz, 1 H, CHCO), 2.58 (ddd, J=15.2, 7.0, 3.0 Hz, 1 H, NCH–C–C–NCO), 3.07 (ddd, J=15.2, 8.4, 2.4 Hz, 1 H, NCH–C–C–NCO), 3.12 (dd, J=12.8, 11.6 Hz, 1 H, CHCO), 3.28—3.37 (m, 1 H, N–C–C–CHNCO), 3.52—3.63 (m, 1 H, N–C–C–CH–NCO), 4.09 (dd, J=11.6, 3.6 Hz, 1 H, NCHPh), 6.72 (broad s, 1 H, CONH), 7.24—7.36 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ=32.3 (N–C–CH_2–C–N), 39.6 (CH_2CO), 42.5 ($CONCH_2$), 43.9 (NCH_3), 50.9 (NCH_2), 67.3 (NCHPh), 127.3, 127.6, 128.4 (aromatic CH), 141.0 (aromatic *C*–CH), 176.6 (C=O); MS m/z (rel intensity) 218 (M^+; 99), 203 (3), 189 (2), 174 (11), 159 (27), 146 (42), 132 (100), 118 (66), 104 (48). HRMS Found: m/z 218.1390. Calcd for $C_{13}H_{18}N_2O$: M, 218.1420. $[\alpha]_D$ +3.2° (*c* 0.5, $CHCl_3$).

Synthesis of 1,1′-(1,4-Butanediyl)bis(5-methyl-4-phenyl-1,5-diazacyclooctan-2-one) (Homaline) (1). In a 10 ml three-necked flask, powdered potassium hydroxide (56 mg, 1.0 mmol) and dry dimethyl sulfoxide (1 ml) were placed, and the mixture was stirred for 10 min. To the mixture, the dry dimethyl sulfoxide (1 ml) solution of (*S*)-(+)-5-methyl-4-phenyl-1,5-diazacyclooctan-2-one (**8**) [59 mg, 0.27 mmol, $[\alpha]_D$ +3.2° (*c* 0.5, $CHCl_3$)] and 1,4-dibromobutane (29 mg, 0.13 mmol) were added and the stirring was continued for 12 h. The reaction solution was treated with water (2 ml) and the product was extracted with dichloromethane (50 ml×3). The organic layer was dried over magnesium sulfate and filtered. After the filtrate was concentrated, the product was purified by gel permeation liquid chromatography (chloroform as eluent), and (*S*,*S*)-homaline (**1**) (25 mg, 0.051 mmol) was obtained in 38% yield.

Similarly, (*R*,*R*)-(+)-homaline (**1**) (5 mg, 0.022 mmol) was prepared in 12% yield by a double alkylation of [(*R*)-(−)-**8** (39 mg, 0.18 mmol, $[\alpha]_D$ −6.2° (*c* 0.9, $CHCl_3$)] with 1,4-dibromobutane (18 mg, 0.083 mmol) and powdered potassium hydroxide in dry dimethyl sulfoxide (1 ml) for 12 h. Diastereoisomers of 1,1′-(1,4-butanediyl)bis(5-methyl-4-phenyl-1,5-diazacyclooctan-2-one) (**1**)[4] (61 mg, 0.124 mmol) was prepared in 49% yield according to the method described above by a double alkylation of (*R*,*S*)-**8** (111 mg, 0.51 mmol) with 1,4-dibromobutane (54 mg, 0.25 mmol): In a 10 ml three-necked flask, powdered potassium hydroxide (112 mg, 2.0 mmol) and dry dimethyl sulfoxide (1 ml) were placed, and the mixture was stirred for 5 min. To the mixture, a dry dimethyl sulfoxide (1 ml) solution of 5-methyl-4-phenyl-1,5-diazacyclooctan-2-one (**8**) (111 mg, 0.51 mmol) and 1,4-dibromobutane (54 mg, 0.25 mmol) were added and the stirring was continued for 12 h. The reaction solution was treated with water (2 ml) and the product was extracted with dichloromethane (50 ml×3). The organic layer was dried over magnesium sulfate and filtered. After the filtrate was concentrated, the product was purified by gel permeation liquid chromatography (chloroform as eluent), and diastereoisomers of 1,1′-(1,4-butanediyl)bis(5-methyl-4-phenyl-1,5-diazacyclooctan-2-one) (61 mg, 0.124 mmol) was obtained in 49% yield.

Diastereoisomers of 1,1′-(1,4-Butanediyl)bis(5-methyl-4-phenyl-1,5-diazacyclooctan-2-one) (Homaline) (1):[4] R_f=0.21 (ether/methanol=9/1); ^{1}H NMR ($CDCl_3$) δ=1.54—1.68 (m, 4 H, 2×CH_2, N–C–CH_2CH_2–C–N), 1.76—1.84 (m, 4 H, 2×CH_2, N–C–CH_2–C–NCO), 2.31 (s, 6 H, 2×NCH_3), 2.52—2.68 (m, 4 H, 2×CHCO, 2×NCH–C–C–NCO), 3.00—3.16 (m, 4 H, 2×NCH–C–C–NCO, NCH–C–C–CHN), 3.23—3.40 (m, 4 H, 2×CHCO, 2×N–C–C–CHNCO), 3.68—3.87 (m, 2 H, NCH–C–C–CHN), 3.87—4.02 (m, 2 H, N–C–C–CHNCO), 4.05 (d, J=11.2 Hz, 2 H, 2×PhCHN), 7.27—7.36 (m, 10 H, 2×Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ=25.4 (N–C–CH_2–CH_2–C–N), 29.2 (N–C–CH_2–C–NCO), 41.0 (CH_2CO), 44.0 (NCH_3), 45.7 and 46.0 (NCH_2–C–C–NCO), 47.7 (N–C–C–CH_2NCO), 51.9 (NCH_2–C–C–CH_2N), 68.1 and 68.8 (PhCHN), 127.6, 127.7, 128.5 (aromatic CH), 140.9 (aromatic *C*–CH), 173.1 (C=O); MS m/z (rel intensity) 490 (M^+; 100), 475 (13), 448 (5), 422 (11), 399 (5), 289 (18), 259 (26), 247 (23), 230 (43), 159 (73), 146 (37), 132 (52). HRMS Found: m/z 490.3343. Calcd for $C_{30}H_{42}N_4O_2$: M, 490.3311; the proportion of (±)-natural homaline (*R*,*R*/*S*,*S*) to the (*R*,*S*)-(*meso*)-form was 47 : 53, and it was calculated by measurement of an HPLC using an optically active column (Daicel Chiralpak AS; retention time: r.t.=27.3 min: 27.7% (*S*,*S*-form); 35.6 min: 53.1% (*R*,*S*-form); 43.3 min: 19.2% (*R*,*R*-form); eluent: hexane/ethanol=9/1; flow rate: 1 ml min^{-1}; detection: UV 254 nm).

(*S*,*S*)-(−)-1,1′-(1,4-Butanediyl)bis[5-methyl-4-phenyl-1,5-diazacyclooctan-2-one] (Homaline) (1): ^{1}H NMR ($CDCl_3$) δ=1.51—1.68 (m, 4 H, 2×CH_2, N–C–CH_2–CH_2–C–N), 1.68—1.88 (m, 4 H, 2×CH_2, N–C–CH_2–C–NCO), 2.28 (s, 6 H, 2×NCH_3), 2.55 (dd, J=13.2, 2.8 Hz, 2 H, 2×CHCO), 2.48—2.61 (m, 2 H, 2×NCH–C–C–NCO), 2.94—3.08 (m, 4 H, 2×NCH–C–C–NCO, NCH–C–C–CHN), 3.21 (dd, J=13.2, 11.8 Hz, 2 H, 2×CHCO), 3.34 (dt, J=15.2, 3.2 Hz, 2 H, 2×N–C–C–CHNCO), 3.68—3.95 (m, 4 H, 2×N–C–C–CHNCO, NCH–C–C–CHN), 4.01 (dd, J=11.8, 2.8 Hz, 2 H, 2×PhCHN), 7.24—7.36 (m, 10 H, 2×Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ=25.3 (N–C–CH_2CH_2–C–N), 29.6 (N–C–CH_2–C–NCO), 41.1 (CH_2CO), 43.8 (NCH_3), 45.7 (NCH_2–C–C–NCO), 47.8 (N–C–C–CH_2NCO), 51.4 (NCH_2–C–C–CH_2N), 68.4 (PhCHN), 127.3, 127.6, 128.4 (aromatic CH), 141.6 (aromatic *C*–CH), 173.3 (C=O); MS m/z (rel intensity) 490 (M^+; 100), 475 (18), 447 (7), 422 (15), 399 (7), 371 (8), 330 (12), 302 (12), 259 (31), 159 (71), 132 (43); $[\alpha]_D$ −15.8° (*c* 1.1, $CHCl_3$) (56% d.e.); the enantiomeric purity of (*S*,*S*)-**1** (56% d.e.) was from this calculation: $100\times[(S,S)-(R,R)-(R,S)]/[(S,S)+(R,R)+(R,S)]$; optically active column (Daicel Chiralpak AS; retention time: t_R=26.9 min: 78.1% (*S*,*S*-form); t_R=35.7 min: 19.2% (*R*,*S*-form); t_R=43.6 min: 2.7% (*R*,*R*-form); eluent: hexane/ethanol=9/1; flow rate: 1 ml min^{-1}; detection: UV 254 nm).

(*R*,*R*)-(+)-1,1′-(1,4-Butanediyl)bis(5-methyl-4-

phenyl-1,5-diazacyclooctan-2-one) (Homaline) (1): IR ($CHCl_3$) 1630 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ = 1.48—1.90 (m, 8 H, 4×CH_2, N–C–CH_2–CH_2–C–N, N–C–CH_2–C–N), 2.28 (s, 6 H, 2×NCH_3), 2.50 (dd, J = 13.2, 2.8 Hz, 2 H, 2×CHCO), 2.49—2.58 (m, 2 H, 2×NCH–C–C–NCO), 2.90—3.22 (m, 4 H, 2×NCH–C–C–NCO, NCH–C–C–CHN), 3.21 (dd, J = 13.2, 11.8 Hz, 2 H, 2×CHCO), 3.33 (dt, J = 15.2, 3.2 Hz, 2 H, 2×N–C–C–CHNCO), 3.64—3.87 (m, 4 H, 2×N–C–C–CHNCO, NCH–C–C–CHN), 4.01 (dd, J = 11.8, 2.8 Hz, 2 H, PhCHN), 7.21—7.41 (m, 10 H, 2×Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 25.7 (N–C–CH_2CH_2–C–N), 29.6 (N–C–CH_2–C–N), 41.1 (CH_2CO), 43.8 (NCH_3), 45.7 (NCH_2–C–C–NCO), 47.8 (N–C–C–CH_2NCO), 51.4 (NCH_2–C–C–CH_2N), 68.4 (PhCHN), 127.3, 127.6, 128.4 (aromatic CH), 140.6 (aromatic *C*–CH), 173.3 (C=O); MS m/z (rel intensity) 490 (M^+; 100), 475 (14), 448 (5), 422 (10), 399 (5), 371 (6), 330 (9), 302 (9), 259 (24), 159 (64), 132 (39). HRMS Found: m/z 490.3269. Calcd for $C_{30}H_{42}N_4O_2$: M, 490.3311. $[\alpha]_D$ +26.0° (c 0.26, $CHCl_3$) (78.6% d.e.); the enantiomeric purity of (*R,R*)-**1** (79% d.e.) was found according to the following calculation: $100\times[(R,R)-(S,S)-(R,S)]/[(R,R)+(S,S)+(R,S)]$; optically active column (Daicel Chiralpak AS; retention time: t_R=27.2 min: 2.2% (*S,S*-form); t_R=35.2 min: 8.5% (*R,S*-form); t_R=41.8 min: 89.3% (*R,R*-form); eluent: hexane/ethanol=9/1; flow rate: 1 ml min^{-1}; detection: UV 254 nm).

Synthesis of 1,1′-(1,4-Butanediyl)bis(4-phenyl-1,5-diazacyclooctan-2-one) (9). In a 10-ml three-necked flask, powdered potassium hydroxide (45 mg, 0.80 mmol) and dry dimethyl sulfoxide (0.5 ml) were placed, and the mixture was stirred for 5 min. A dry dimethyl sulfoxide (0.5 ml) solution of (*S*)-(−)-4-phenyl-1,5-diazacyclooctan-2-one (**7**) [34 mg, 0.17 mmol, $[\alpha]_D$ −12.0° (c 1.4, $CHCl_3$); >99% e.e.][4] and 1,4-dibromobutane (7.0 μl, 0.059 mmol) were added and the mixture was stirred for 2 h. Then the reaction mixture was treated with water (2 ml) and the product was extracted with dichloromethane (30 ml×3). After the solution was dried and evaporated, the product was purified by HPLC on silica-gel column (chloroform/methanol=99/1 as eluent), and (*S,S*)-(−)-1,1′-(1,4-butanediyl)bis(4-phenyl-1,5-diazacyclooctan-2-one) (**9**) (18 mg, 0.039 mmol) was obtained in 47% yield (conversion yield was 68%).

Similarly, (*R,R*)-(+)-1,1′-(1,4-butanediyl)bis(4-phenyl-1,5-diazacyclooctan-2-one) (**9**) (41 mg, 0.089 mmol) was obtained in 44% yield (conversion yield was 53%) by a double alkylation of (*R*)-(+)-**7** [83 mg, 0.41 mmol, $[\alpha]_D$ +6.4° (c 2.3, $CHCl_3$); 82% e.e.] with 1,4-dibromobutane (20 μl, 0.17 mmol) and powdered potassium hydroxide (90 mg, 1.61 mmol) in dry dimethyl sulfoxide (2 ml) for 2 h. (*R*)-(+)-**7** (17 mg, 21%) was recovered.

(*S,S*)-(−)-1,1′-(1,4-Butanediyl)bis(4-phenyl-1,5-diazacyclooctan-2-one) (9): R_f = 0.31 (chloroform/methanol = 19/1); IR ($CHCl_3$) 3300 (N–H), 1621 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ = 1.18 (s, 2 H, NH), 1.43—2.08 (m, 8 H, 4×CH_2, NC–CH_2–CH_2–C–N and 2×N–C–CH_2–C–N), 2.31 (ddd, J = 15.0, 11.9, 3.2 Hz, 2 H, 2×NCH–C–C–NCO), 2.43 (d, J = 12.8 Hz, 2 H, 2×CHCO), 2.93 (dd, J = 12.4, 11.2 Hz, 2 H, 2×CHCO), 2.81—2.98 (m, 2 H, NCH–C–C–CHN), 3.10 (dd, J = 15.0, 3.2 Hz, 2 H, 2×NCH–C–C–NCO), 3.19 (dd, J = 15.4, 3.4 Hz, 2 H, 2×N–C–C–CHNCO), 3.75—3.84 (m, 2 H, NCH–C–C–CHN), 3.95 (d, J = 9.6 Hz, 2 H, 2×PhCHN), 4.04 (dd, J = 15.4, 12.2 Hz, 2 H, N–C–C–CHNCO), 7.14—7.33 (m, 10 H, 2×Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 25.2 (N–C–CH_2CH_2–C–N), 31.4 (N–C–CH_2–C–NCO), 44.2 (NCH_2–C–C–NCO), 44.8 (NCH_2–C–C–CH_2N), 45.0 (N–C–C–CH_2NCO), 45.3 (CH_2CO), 64.7 (PhCHN), 126.4, 127.5, 128.6 (aromatic CH), 144.8 (aromatic *C*–CH), 173.0 (C=O); MS m/z (rel intensity) 462 (M^+; 52), 318 (26), 245 (46), 145 (64), 132 (67), 118 (100), 104 (45), 91 (79); $[\alpha]_D$ −36.7° (c 0.9, $CHCl_3$) (lit,[3] $[\alpha]_D$ −30.0° (c 1.3, $CHCl_3$)).

(*R,R*)-(+)-1,1′-(1,4-Butanediyl)bis(4-phenyl-1,5-diazacyclooctan-2-one) (9):[3,4] ^1H NMR ($CDCl_3$) δ = 1.52—1.71 (m, 6 H, NC–CH_2–CH_2–C–N and 2×N–C–CH–C–N), 1.71—1.83 (m, 2 H, 2×N–C–CH–C–N), 1.96 (s, 2 H, 2×NH), 2.37 (ddd, J = 15.0, 11.2, 3.6 Hz, 2 H, 2×NCH–C–C–NCO), 2.50 (dd, J = 12.8, 1.6 Hz, 2 H, 2×CHCO), 2.99 (dd, J = 12.8, 12.0 Hz, 2 H, 2×CHCO), 2.88—3.04 (m, 2 H, NCH–C–C–CHN), 3.16 (dd, J = 15.0, 2.8 Hz, 2 H, 2×NCH–C–C–NCO), 3.26 (dd, J = 14.6, 3.6 Hz, 2 H, 2×N–C–C–CHNCO), 3.78—3.91 (m, 2 H, NCH–C–C–CHN), 4.02 (dd, J = 12.0, 1.6 Hz, 2 H, 2×PhCHN), 4.12 (ddd, J = 15.8, 12.2, 3.6 Hz, 2 H, 2×N–C–C–CHNCO), 7.25 (t, J = 6.6 Hz, 2 H, aromatic *para*-CH), 7.32 (dd, J = 8.0, 6.6 Hz, 4 H, aromatic *meta*-CH), 7.38 (d, J = 8.0 Hz, 4 H, aromatic *ortho*-CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 25.2 (N–C–CH_2CH_2–C–N), 31.4 (N–C–CH_2–C–NCO), 44.2 (NCH_2–C–C–NCO), 44.8 (NCH_2–C–C–CH_2N), 45.0 (N–C–C–CH_2NCO), 45.5 (CH_2CO), 64.7 (PhCHN), 126.4 (aromatic *ortho*-CH), 127.5 (aromatic *para*-CH), 128.6 (aromatic *meta*-CH), 144.9 (aromatic *C*–CH), 173.0 (C=O); MS m/z (rel intensity) 462 (M^+; 100), 419 (6), 371 (10), 344 (19), 318 (48), 302 (21), 288 (11), 245 (54), 145 (56), 132 (39), 118 (43). HRMS Found: m/z 462.3027. Calcd for $C_{28}H_{38}O_2N_4$: M, 462.3027. $[\alpha]_D$ +24.6° (c 1.3, $CHCl_3$).

Synthesis of (*R,R*)-(+)-1,1′-(1,4-Butanediyl)bis(5-methyl-4-phenyl-1,5-diazacyclooctan-2-one) (1) by the *N*-Methylation of 7 with Methyl(diphenyl)selenonium Perchlorate. To a dry dichloromethane (5 ml) solution of (*R,R*)-(+)-1,1′-(1,4-butanediyl)bis(4-phenyl-1,5-diazacyclooctan-2-one) (**9**) [24 mg, 0.052 mmol, $[\alpha]_D$ +24.6° (c 1.3, $CHCl_3$)] and methyl(diphenyl)selenonium perchlorate[12] (91 mg, 0.26 mmol) in a 20 ml round-bottomed flask, potassium carbonate (22 mg, 0.16 mmol) was added and the mixture was stirred for 1 d at room temperature. The reaction mixture was filtered, and the filtrate was concentrated. After the residue was purified by silica-gel column chromatography (chloroform/methanol=1/1 as eluent), (*R,R*)-homaline (**1**) (11 mg, 0.022 mmol, $[\alpha]_D$ +17.2° (c 0.3, $CHCl_3$), 76% d.e.) was obtained in 43% yield.

(*R,R*)-(+)-1,1′-(1,4-Butanediyl)bis(5-methyl-4-phenyl-1,5-diazacyclooctan-2-one) (Homaline) (1): ^1H NMR ($CDCl_3$) δ = 1.61—1.85 (m, 8 H, 4×CH_2, N–C–CH_2–CH_2–C–N, N–C–CH_2–C–N), 2.34 (s, 6 H, 2×NCH_3), 2.56—2.62 (m, 4 H, 2×NCH–C–C–NCO, 2×CHCO), 3.03—3.38 (m, 8 H, NCH–C–C–CHN, 2×CHCO, 2×NCH–C–CHNCO), 3.74—4.04 (m, 4 H, 2×N–C–C–CHNCO, NCH–C–C–CHN), 4.09 (dd, J = 11.8, 2.8 Hz, 2 H, PhCHN), 7.27—7.36 (m, 10 H, 2×Ph). HRMS Found: m/z 490.3370, Calcd for $C_{30}H_{42}N_4O_2$: M, 490.3311. $[\alpha]_D$ +17.2° (c 0.26, $CHCl_3$) (76% d.e.); optically active column (Daicel Chiralpak AS); retention time: t_R=25.7 min: 2.3% (*S,S*-form); t_R=32.9 min: 9.5% (*R,S*-form); t_R=39.4

min: 88.2% (*R,R*-form); eluent: hexane/ethanol=9/1; flow rate: 1 ml min^{-1}; detection: UV 254 nm).

References

1) M. Pais, R. Sarfati, F. -X. Jarreau, and R. Goutarel, *Tetrahedron*, **29**, 1001 (1973), and references cited therein; natural homaline, $[\alpha]_D^{24}$ −34° (*c* 1, $CHCl_3$).

2) M. Pais, R. Sarfati, and F. -X. Jarreau, *Bull. Soc. Chim. Fr.*, **1973**, 331.

3) H. H. Wasserman, G. D. Berger, and K. R. Cho, *Tetrahedron Lett.*, **23**, 465 (1982); H. H. Wasserman and G. D. Berger, *Tetrahedron*, **39**, 2459 (1983).

4) L. Crombie, R. C. F. Jones, Ab. Rasid Mat-Zin, and S. Osborne, *J. Chem. Soc., Chem. Commun.*, **1983**, 960; L. Crombie, D. Haigh, R. C. F. Jones, and Ab. Rasid Mat-Zin, *J. Chem. Soc., Perkin Trans. 1*, **1993**, 2047; optically active (*S*)-**7**, $[\alpha]_D$ −10.7° (*c* 0.65, $CHCl_3$), was prepared by the transamidation reaction starting from (*S*)-(−)-4-phenylazetidin-2-one.

5) S. G. Pyne, P. Bloem, and R. Griffith, *Tetrahedron*, **45**, 7013 (1989), and references cited therein.

6) For an SmI_2 reduction of sulfoxides, see: Y. Arai, M. Matsui, and T. Koizumi, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 1233.

7) K. K. Andersen, W. Gaffield, N. E. Papanikolaou, J. W. Foley, and R. I. Perkins, *J. Am. Chem. Soc.*, **86**, 5637 (1964); G. Solladie, *Synthesis*, **1981**, 185, and references cited there in.

8) C. Mioskowski and G. Solladie, *Tetrahedron*, **36**, 227 (1980).

9) The stereochemistry of *E*-configuration of (*S*)-(+)- and (*R*)-(−)-**4** was identified in comparison of the optical rotation of **4** with that of methyl (*S,E*)-(+)-2-(*p*-tolylsulfinyl)cinnamate, $[\alpha]_D$ +219° (*c* 1.0, $CHCl_3$) (o.p. 93%) which was prepared by one-pot α-lithiation of (*R,E*)-2-phenylvinyl *p*-tolyl sulfoxide, $[\alpha]_D$ +153° (*c* 1.0, $CHCl_3$) (o.p. 93%), followed by carboxylation and esterification with methyl iodide in 64% yield: J. Fawcett, S. House, P. R. Jenkins, N. J. Lawrence, and D. R. Russell, *J. Chem. Soc., Perkin Trans. 1*, **1993**, 67; S. House, P. R. Jenkins, J. Fawcett, and D. R. Russel, *J. Chem. Soc., Chem. Commun.*, **1987**, 1844; G. H. Posner, J. P. Mallamo, and K. Miura, *J. Am. Chem. Soc.*, **103**, 2886 (1981). Methyl (*R,E*)-(−)-2-(*p*-tolylsulfinyl)-cinnamate, $[\alpha]_D$ −224° (*c* 1.0, $CHCl_3$) (o.p. 96%) was also prepared from (*S,E*)-2-phenylvinyl *p*-tolyl sulfoxide, $[\alpha]_D$ −158° (*c* 1.0, $CHCl_3$) (o.p. 96%). H. Matsuyama, N. Itoh, and N. Kamigata, *Chem. Lett.*, **1990**, 1547.

10) For the synthesis of 9-phenyl-1,6-diazacyclononan-7-one, see: H. H. Wasserman, R. P. Robinson, and H. Matsuyama, *Tetrahedron Lett.*, **21**, 3493 (1980); H. Matsuyama, M. Kobayashi, and H. H. Wasserman, *Heterocycles*, **26**, 85 (1987). The stereochemistry of asymmetric carbon atom could be retained during reductive cleavage of N–N bond of optically active bicyclic lactam, 9-phenyl-1,6-diazabicyclo[4.3.0]nonan-7-one, see: N. Itoh, H. Matsuyama, M. Yoshida, N. Kamigata, and M. Iyoda, *Heterocycles*, **41**, 415 (1995).

11) B. M. Trost, T. N. Salzmann, and K. Hiroi, *J. Am. Chem. Soc.*, **98**, 4887 (1976).

12) *N*-Alkylation of amines utilizing alkylselenonium salts, see: K. Umemura, H. Matsuyama, and N. Kamigata, *Bull. Chem. Soc. Jpn.*, **63**, 2593 (1990).