Highly Diastereoselective Reaction of (3a*S*,6*R*)-5-Oxa-7,8a-diazaperhydroazulen-8-ones with Diethylzinc

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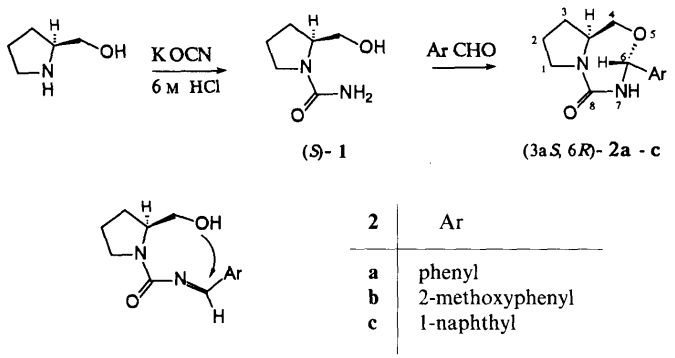
New chiral heterocyclic compounds, (3a*S*,6*R*)-5-oxa-7,8a-diazaperhydroazulen-8-ones (2a—c), were synthesized and their absolute configurations were determined by X-ray analysis. The reaction of (3a*S*,6*R*)-2a—c with diethylzinc proceeded under mild conditions with extremely high diastereoselectivity.

Keywords absolute configuration; alkylation; chiral heterocyclic compound; diastereoselective reaction; diethylzinc; oxadiazaperhydroazulene; (*S*)-prolinol-*N*-carbamoyl; 1-pyrrolidinecarboxamide; triethylaluminum; X-ray analysis

Reactions with dialkylzinc are generally limited to carbaldehydes owing to the weak nucleophilicity of the reagent.[1] In this paper, we wish to describe a highly diastereoselective reaction of the diethylzinc reagent leading to the alkylation of (3a*S*,6*R*)-5-oxa-7,8a-diazaperhydroazulen-8-ones under mild reaction conditions.[2]

The reaction of (*S*)-prolinol with potassium cyanate[3] gave (*S*)-1-carbamoyl-2-hydroxymethylpyrrolidine (**1**) in 95% yield. The new heterocyclic compounds, (3a*S*,6*R*)-5-oxa-7,8a-diazaperhydroazulen-8-ones (**2a—c**), were obtained by the condensation of (*S*)-**1** with carbaldehydes (benzaldehyde, *o*-anisaldehyde, and 1-naphthaldehyde) in 53—64% yields. Two diastereomeric forms could be formed, considering the configuration of the groups at the 6-position of the ring, but these products (**2a—c**) were established to



2	Ar
a	phenyl
b	2-methoxyphenyl
c	1-naphthyl

Chart 1

TABLE I. Crystal Data

Chemical Formula	$(C_{13}H_{16}N_2O_2)\times 2$
Formula weight	464.55
Crystal system	Monoclinic
Cell dimensions	$a=11.661$ (4) (Å)
	$b=18.429$ (18) (Å)
	$c=5.753$ (2) (Å)
	$\beta=97.33$ (3) (°)
Cell volume (Å^3)	1226.2 (13)
Space group	$P2_1$
Z	2
D_c (g cm^{-3})	1.26

TABLE II. Positional ($\times 10^4$) and Thermal Parameters of (3a*S*,6*R*)-**2a** for Nonhydrogen Atoms with Their Standard Deviations in Parentheses

Atom	X	Y	Z	B_{eq} (Å^2)[a]
C(1)	4870 (10)	1300 (10)	3590 (40)	6.2
C(2)	5380 (20)	510 (10)	3920 (60)	11.9
C(3)	4670 (20)	−0 (10)	2130 (40)	7.1
C(3a)	3470 (10)	369 (8)	1770 (30)	4.4
C(4)	2940 (20)	240 (10)	−850 (40)	6.6
O(5)	1748 (9)	474 (6)	−1120 (20)	5.0
C(6)	1630 (10)	1289 (8)	−1090 (30)	3.5
N(7)	1773 (8)	1566 (6)	1310 (20)	2.8
C(8)	2860 (10)	1679 (8)	2580 (20)	3.1
N(8a)	3685 (9)	1171 (7)	2320 (20)	3.5
O(9)	3015 (8)	2179 (5)	3890 (20)	3.5
C(10)	380 (10)	1421 (8)	−2140 (20)	3.1
C(11)	180 (10)	1830 (10)	−4190 (20)	3.9
C(12)	−930 (10)	1950 (10)	−5290 (30)	4.4
C(13)	−1840 (10)	1640 (10)	−4280 (30)	4.7
C(14)	−1660 (10)	1270 (10)	−2140 (30)	5.2
C(15)	−540 (10)	1140 (10)	−1060 (30)	4.5
C(1′)	9120 (10)	3640 (10)	7910 (30)	4.7
C(2′)	8930 (10)	4060 (10)	5630 (40)	6.2
C(3′)	9760 (10)	4710 (10)	5890 (30)	5.6
C(3a′)	10830 (10)	4406 (8)	7560 (30)	3.9
C(4′)	11860 (10)	4300 (10)	6210 (30)	5.2
O(5′)	12894 (7)	4154 (6)	7830 (20)	4.1
C(6′)	12880 (10)	3432 (8)	8740 (20)	3.0
N(7′)	12144 (8)	3361 (6)	10670 (20)	2.9
C(8′)	10390 (10)	3292 (8)	10250 (30)	3.5
N(8a′)	10399 (9)	3700 (7)	8420 (20)	3.2
O(9′)	10430 (8)	2908 (6)	11450 (20)	3.9
C(10′)	14120 (10)	3274 (8)	9720 (20)	3.1
C(11′)	14800 (10)	2890 (10)	8350 (30)	4.2
C(12′)	16010 (10)	2760 (10)	9210 (40)	5.8
C(13′)	16460 (10)	3040 (10)	11390 (30)	5.2
C(14′)	15760 (10)	3430 (10)	12740 (30)	5.2
C(15′)	14600 (10)	3562 (9)	11970 (30)	4.2

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

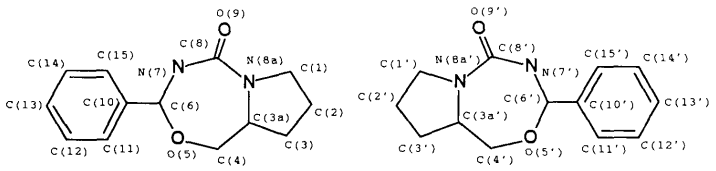


Fig. 1. Atomic Numbering of (3a*S*,6*R*)-**2a**

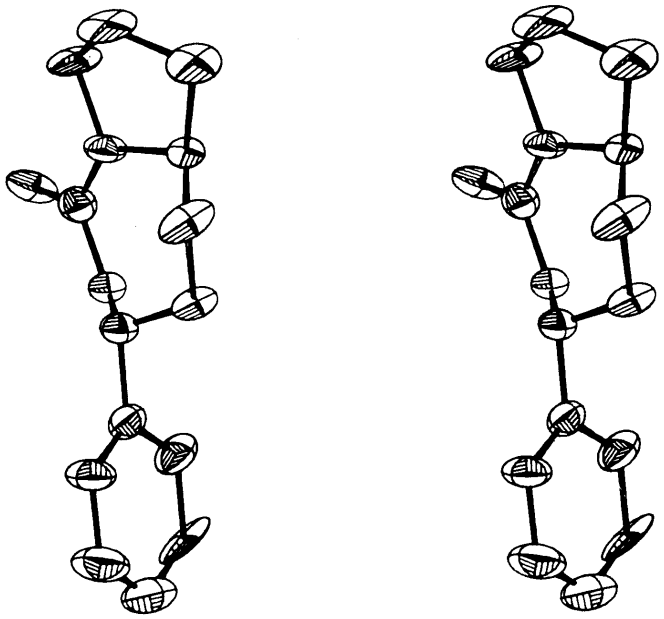


Fig. 2. Stereoscopic Drawings of the Structure of (3a*S*,6*R*)-**2a**

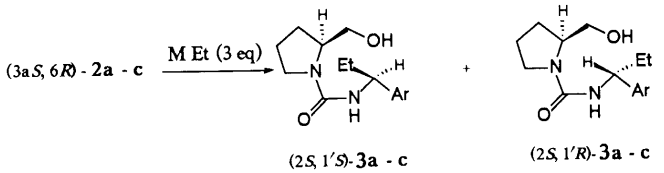


Chart 2

consist exclusively of one isomer by proton nuclear magnetic resonance (^{1}H-NMR) spectral (270 MHz) analysis.

The absolute configuration of the newly created asymmetric carbon at the 6-position of the ring was elucidated by X-ray analysis. A colorless columnar crystal of **2a** was used. The atomic numbering is shown in Fig. 1, and the crystal data are summarized in Table I.

Stereoscopic drawings of the molecular structure are shown in Fig. 2. The positional and thermal parameters with their standard deviations are listed in Table II. The intramolecular bond distances and bond angles for nonhydrogen atoms are given in Table III.

In the structure of **2a**, the hydrogen atom at the 6-position of the ring is attached *trans* with respect to the hydrogen atom at the 3a-position. Consequently, the ring closure was considered to proceed by attack of the hydroxyl group on the *re*-face of the imine intermediate. The structures of **2b** and **2c** are assumed to have the same configuration, because the compounds are expected to be produced through a similar reaction mechanism.

The reaction of (3a*S*,6*R*)-**2a**—**c** with diethylzinc gave *N*-1′-arylpropyl-2-hydroxymethyl-1-pyrrolidinecarboxamides (**3a**—**c**) in 87—92% yields by the attack of the reagent on the carbon atom at the 6-position of the ring. These products could consist of two diastereomers since the new asymmetric center was created at the 1′-position of **3a**—**c**. However, no minor component was formed in the reactions of **2b** and **2c** as far as could be ascertained from the ^{1}H-NMR spectra of the products, whereas **2a** gave a minor product in only 6% yield. The minor products were obtained by the use of triethylaluminum and ethylmagnesium bromide, and the ^{1}H-NMR spectra of these products were measured.

The reaction using triethylaluminum reagent proceeded with diastereoselectivities (d.s.) of 24—62%, while the reaction with ethylmagnesium bromide proceeded with very low stereoselectivities (4—30% d.s.). The experimental results are summarized in Table IV. The stereoselectivities of these reactions were slightly increased by decreasing the temperature to −50 °C, and using dichloromethane as the solvent. The structures of the major and minor products were confirmed by ^{1}H-NMR spectrometric analysis. These results are summarized in Tables V and VI.

The absolute configuration at the 1′-position of **3a**—**c** was elucidated as follows. Compounds **3a**—**c** obtained from (3a*S*,6*R*)-**2a**—**c** and diethylzinc gave (*S*)-1-aryl-*N*-methylpropylamines (**4a**—**c**) along with (*S*)-prolinol on reduction with sodium bis(2-methoxyethyl)aluminum hydride (Red-

Table III. Bond Distances (Å) and Bond Angles (°) of (3a*S*,6*R*)-**2a** for Nonhydrogen Atoms with Their Standard Deviations in Parentheses

Bond distance			
C(1)–C(2)	1.575 (42)	C(1′)–C(2′)	1.511 (20)
C(1)–N(8a)	1.493 (25)	C(1′)–N(8a′)	1.483 (22)
C(2)–C(3)	1.569 (43)	C(2′)–C(3′)	1.543 (29)
C(3)–C(3a)	1.543 (30)	C(3′)–C(3a′)	1.576 (25)
C(3a)–C(4)	1.578 (28)	C(3a′)–C(4′)	1.534 (24)
C(3a)–N(8a)	1.526 (22)	C(3a′)–N(8a′)	1.497 (20)
C(4)–O(5)	1.443 (24)	C(4′)–O(5′)	1.448 (21)
O(5)–C(6)	1.509 (20)	O(5′)–C(6′)	1.434 (18)
C(6)–N(7)	1.467 (19)	C(6′)–N(7′)	1.490 (19)
C(6)–C(10)	1.529 (21)	C(6′)–C(10′)	1.518 (20)
N(7)–C(8)	1.387 (18)	N(7′)–C(8′)	1.403 (20)
C(8)–N(8a)	1.364 (19)	C(8′)–N(8a′)	1.380 (20)
C(8)–O(9)	1.194 (18)	C(8′)–O(9′)	1.191 (19)
C(10)–C(11)	1.392 (23)	C(10′)–C(11′)	1.387 (23)
C(10)–C(15)	1.414 (23)	C(10′)–C(15′)	1.440 (22)
C(11)–C(12)	1.378 (25)	C(11′)–C(12′)	1.447 (28)
C(12)–C(13)	1.403 (26)	C(12′)–C(13′)	1.402 (29)
C(13)–C(14)	1.405 (27)	C(13′)–C(14′)	1.386 (29)
C(14)–C(15)	1.385 (27)	C(14′)–C(15′)	1.392 (27)
Bond angle			
C(2)–C(1)–N(8a)	103.6 (19)	C(2′)–C(1′)–N(8a′)	99.5 (15)
C(1)–C(2)–C(3)	107.7 (24)	C(1′)–C(2′)–C(3′)	107.2 (17)
C(2)–C(3)–C(3a)	102.7 (20)	C(2′)–C(3′)–C(3a′)	102.4 (15)
C(3)–C(3a)–C(4)	107.5 (16)	C(3′)–C(3a′)–C(4′)	110.4 (14)
C(3)–C(3a)–N(8a)	106.3 (15)	C(3′)–C(3a′)–N(8a′)	104.0 (13)
C(4)–C(3a)–N(8a)	112.7 (10)	C(4′)–C(3a′)–N(8a′)	112.3 (13)
C(3a)–C(4)–O(5)	108.0 (15)	C(3a′)–C(4′)–O(5′)	110.0 (14)
C(4)–O(5)–C(6)	112.7 (13)	C(4′)–O(5′)–C(6′)	111.4 (12)
O(5)–C(6)–N(7)	110.9 (12)	O(5′)–C(6′)–N(7′)	113.1 (11)
O(5)–C(6)–C(10)	103.7 (12)	O(5′)–C(6′)–C(10′)	105.0 (11)
N(7)–C(6)–C(10)	107.6 (12)	N(7′)–C(6′)–C(10′)	108.8 (11)
C(6)–N(7)–C(8)	121.9 (12)	C(6′)–N(7′)–C(8′)	122.8 (12)
N(7)–C(8)–N(8a)	116.8 (12)	N(7′)–C(8′)–N(8a′)	115.4 (13)
N(7)–C(8)–O(9)	120.2 (13)	N(7′)–C(8′)–O(9′)	120.7 (14)
N(8a)–C(8)–O(9)	122.9 (13)	N(8a′)–C(8′)–O(9′)	123.9 (14)
C(1)–N(8a)–C(3a)	111.7 (13)	C(1′)–N(8a′)–C(3a′)	111.8 (12)
C(1)–N(8a)–C(8)	117.6 (13)	C(1′)–N(8a′)–C(8′)	116.9 (13)
C(3a)–N(8a)–C(8)	126.0 (13)	C(3a′)–N(8a′)–C(8′)	126.0 (12)
C(6)–C(10)–C(11)	117.8 (13)	C(6′)–C(10′)–C(11′)	118.5 (14)
C(6)–C(10)–C(15)	120.8 (13)	C(6′)–C(10′)–C(15′)	120.3 (13)
C(11)–C(10)–C(15)	121.4 (14)	C(11′)–C(10′)–C(15′)	121.1 (14)
C(10)–C(11)–C(12)	121.0 (16)	C(10′)–C(11′)–C(12′)	119.3 (16)
C(11)–C(12)–C(13)	117.8 (17)	C(11′)–C(12′)–C(13′)	119.0 (18)
C(12)–C(13)–C(14)	121.5 (17)	C(12′)–C(13′)–C(14′)	120.6 (19)
C(13)–C(14)–C(15)	120.3 (18)	C(13′)–C(14′)–C(15′)	122.1 (19)
C(10)–C(15)–C(14)	117.7 (16)	C(10′)–C(15′)–C(14′)	117.9 (16)

Table IV. Reaction of (3a*S*,6*R*)-**2a**—**c** with $ZnEt_2$, $AlEt_3$ and EtMgBr at 0 °C for 3 h

Reactant	Reagent	Solvent	Product	Yield[a] (%)	Ratio of isomers[b] (2*S*,1′*S*) : (2*S*,1′*R*)
2a	$ZnEt_2$	Toluene	**3a**	92	93 : 7
2b	$ZnEt_2$	Toluene	**3a**	87	100 : 0
2c	$ZnEt_2$	Toluene	**3c**	91	100 : 0
2a	$AlEt_3$	Toluene	**3a**	88	81 : 19
2b	$AlEt_3$	Toluene	**3b**	85	62 : 38
2c	$AlEt_3$	Toluene	**3c**	90	79 : 21
2a	EtMgBr	THF	**3a**	89	35 : 65
2b	EtMgBr	THF	**3b**	86	37 : 63
2c	EtMgBr	THF	**3c**	95	42 : 58

a) Isolated yield. *b*) Estimated by ^{1}H-NMR (270 MHz) spectral analysis.

Table V. Reaction of (3a*S*,6*R*)-**2a**—**c** with $AlEt_3$ and EtMgBr at −50 °C

Reactant	Reagent	Solvent	Time (h)	Product	Yield[a] (%)	Ratio of isomers[b] (2*S*,1′*S*) : (2*S*,1′*R*)
2a	$AlEt_3$	Toluene	48	**3a**	86	91 : 9[c]
2b	$AlEt_3$	Toluene	48	**3b**	82	82 : 18
2c	$AlEt_3$	Toluene	48	**3c**	74	89 : 11[c]
2a	EtMgBr	THF	24	**3a**	72	59 : 41
2b	EtMgBr	THF	24	**3b**	71	57 : 43
2c	EtMgBr	THF	24	**3c**	80	61 : 39

a) Isolated yield. *b*) Estimated by ^{1}H-NMR (270 MHz) spectral analysis. *c*) Estimated with a ^{1}H-NMR (400 MHz) spectrometer.

Table VI. Reaction of (3a*S*,6*R*)-**2a**—**c** with $AlEt_3$ in CH_2Cl_2

Reactant	Temp. (°C)	Time (h)	Product	Yield[a] (%)	Ratio of isomers[b] (2*S*,1′*S*) : (2*S*,1′*R*)
2a	0	3	**3a**	79	83 : 17
2b	0	3	**3b**	86	76 : 24
2c	0	3	**3c**	81	88 : 12
2a	−50	48	**3a**	77	92 : 8[c]
2b	−50	48	**3b**	79	77 : 23
2c	−50	48	**3c**	78	90 : 10[c]

a) Isolated yield. *b*) Estimated by ^{1}H-NMR (270 MHz) spectral analysis. *c*) Estimated with a ^{1}H-NMR (400 MHz) spectrometer.

Al) in toluene. The structures of these products were confirmed by mass spectrum (MS) and ^{1}H-NMR spectral analyses, and the specific rotations of **4a**, **4b**, and **4c** were −36.7°, −18.1°, and −54.5°, respectively. On the other hand, (*R*)-*N*-methyl-1-phenylpropylamine was produced from (*R*)-1-phenylpropylamine[4] (the compound of $[\alpha]_D$ +19.7° was used) by formylation with ethyl formate *in situ via* reduction with lithium aluminum hydride, and the specific rotation of this compound was +36.1°. Consequently, the absolute configuration of (2*S*,1′*S*)-**3a** was determined. The configurations of **3b** and **3c** obtained from **2b** and **2c** with diethylzinc may also be assumed to be (2*S*,1′*S*) because these compounds are expected to be produced through a similar reaction mechanism.

The use of an equimolar amount of diethylzinc for (3a*S*,6*R*)-**2a** resulted in recovery of the starting material, while the reaction with 2 equimolar amounts of the reagent gave (2*S*,1′*S*)-**3a** in about 90% yield. Thus, it was considered that 1 molar amount of diethylzinc exchanges the proton of the NH group, and the second diethylzinc approaches the oxygen atom of (3a*S*,6*R*)-**2a** and cleaves the

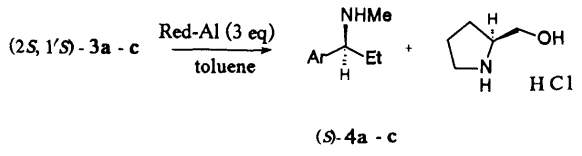


Chart 3

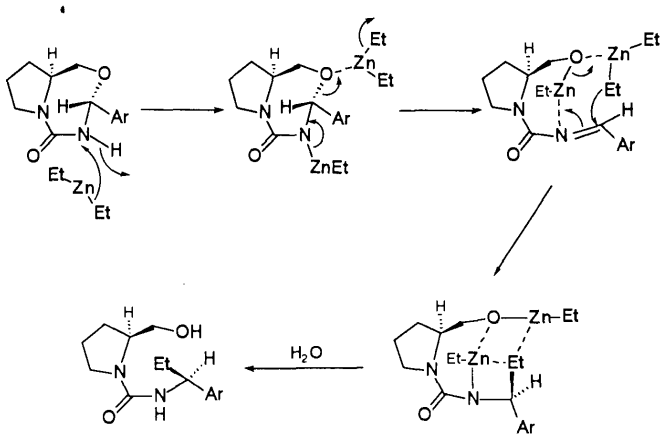


Chart 4

carbon–oxygen bond to form a favorable chiral imine intermediate, then nucleophilic attack occurs from the *si*-face of the carbon–nitrogen double bond as shown in Chart 4.

Experimental

The ^{1}H-NMR spectra were obtained with JEOL JNM-GSX270 and/or JEOL JNM-GX400 spectrometers and the MS were recorded with a JEOL JMS-D300 spectrometer by using the chemical ionization (isobutane) method. The infrared (IR) spectra were recorded with a Hitachi 200-10 spectrometer. The melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. The optical rotations were measured at 26—28 °C with a JASCO DIP-360 digital polarimeter.

(*S*)-1-Carbamoyl-2-hydroxymethylpyrrolidine (1) Potassium cyanate (20.4 g, 252 mmol) was added to a stirred solution of (*S*)-prolinol (21.2 g, 210 mmol) in 6 M hydrochloric acid aqueous solution (42 ml), and stirring was continued at room temperature for 12 h. After removal of the precipitate, the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2CH_2–MeOH (3 : 1) solution, dried over Na_2SO, and concentrated *in vacuo* to give colorless plates (28.7 g, 95%). mp 89—90 °C (from acetone). *Anal.* Calcd for $C_6H_{12}N_2O_2$: C, 49.98; H, 8.39; N, 19.43. Found: C, 49.81; H, 8.24; N, 19.38. IR ($CHCl_3$): 3540, 3440, 3350, 1630 (C=O) cm^{-1}. MS *m/z*: 145 ($M^+ + 1$). ^{1}H-NMR ($CDCl_3$) δ: 1.56—2.10 (4H, m, CH_2CH_2), 3.35—3.50 (2H, m, NCH_2), 3.57 (1H, dd, J=8.5, 11.0 Hz, NCHC$\underline{H}_2$O), 3.65 (1H, dd, J=3.1, 11.0 Hz, NCHC$\underline{H}_2$O), 4.06—4.09 (1H, m, NC$\underline{H}$CH$_2$O), 4.8 (3H, br, NH_2 and OH).

General Procedure for the Reaction of (*S*)-1 with Aromatic Carbaldehydes An aromatic carbaldehyde (benzaldehyde, *o*-anisaldehyde, or 1-naphthaldehyde, 45 mmol) and *p*-toluenesulfonic acid monohydrate (0.01 g) were added to a solution of (*S*)-**1** (4.3 g, 30 mmol) in toluene (42 ml), and the mixture was refluxed for 3—48 h using a Dean-Stark trap. The reaction mixture was made alkaline with saturated aqueous Na_2CO_3 solution, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel with a solution of AcOEt–hexane (5 : 1) to give the corresponding (3a*S*,6*R*)-**2a**—**c** as a colorless crystalline solid.

(3a*S*,6*R*)-6-Phenyl-5-oxa-7,8a-diazaperhydroazulen-8-one (**2a**): Colorless columns, mp 140 °C (AcOEt–hexane). Yield, 4.5 g (64%). *Anal.* Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.04. Found: C, 67.00; H, 6.91; N, 11.85. $[\alpha]_D$ −75.6° (c=1.52, EtOH). IR ($CHCl_3$): 3440 (NH), 1640 (C=O) cm^{-1}. MS *m/z*: 232 ($M^+ + 1$). ^{1}H-NMR ($CDCl_3$) δ: 1.52—2.22 (4H, m, CH_2CH_2), 3.29—3.38 (1H, m, NCH_2), 3.36 (1H, dd, J=9.8, 11.6 Hz, NCHC$\underline{H}_2$O), 3.76—3.82 (1H, m, NC$\underline{H}$CH$_2$O), 3.89—3.97 (1H, m, NCH_2), 4.08 (1H, dd, J=1.8, 11.6 Hz, NCHC$\underline{H}_2$O), 4.97 (1H, br, NH),

5.40 (1H, d, J=2.4 Hz, NCHO), 7.33—7.48 (5H, m, aromatic H).

(3a*S*,6*R*)-6-(2-Methoxyphenyl)-5-oxa-7,8a-diazaperhydroazulen-8-one (**2b**): Colorless needles, mp 141—142 °C (AcOH–hexane). Yield, 4.8 g (61%). *Anal.* Calcd for $C_{14}H_{18}N_2O_2$: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.34; H, 7.04; N, 10.62. $[\alpha]_D$ −140.9° (c=1.33, EtOH). IR ($CHCl_3$): 3440 (NH), 1640 (C=O) cm^{-1}. MS m/z: 263 (M^++1). ^{1}H-NMR ($CDCl_3$) δ: 1.55—2.20 (4H, m, CH_2CH_2), 3.30—3.40 (1H, m, NCH_2), 3.36 (1H, dd, J=9.8, 12.2 Hz, NCHC$\underline{H}_2$O), 3.75—3.82 (1H, m, NC$\underline{H}$CH$_2$O), 3.85 (3H, s, OCH_3), 3.89—3.98 (1H, m, NCH_2), 4.06 (1H, dd, J=2.5, 12.2 Hz, NCHC$\underline{H}_2$O), 4.93 (1H, br, NH), 5.74 (1H, d, J=2.4 Hz, NCHO), 6.89—7.56 (4H, m, aromatic H).

(3a*S*,6*R*)-6-(1-Naphthyl)-5-oxa-7,8a-diazaperhydroazulen-8-one (**2c**): Colorless needles, mp 184—185 °C (AcOH–hexane). Yield, 4.5 g (53%). *Anal.* Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.39; H, 6.45; N, 9.92. $[\alpha]_D$ −81.9° (c=1.51, EtOH). IR ($CHCl_3$): 3440 (NH), 1640 (C=O) cm^{-1}. MS m/z: 283 (M^++1). ^{1}H-NMR ($CDCl_3$) δ: 1.58—2.27 (4H, m, CH_2CH_2), 3.35—3.45 (1H, m, NCH_2), 3.45 (1H, dd, J=1.8, 12.2 Hz, NCHC$\underline{H}_2$O), 3.89—4.04 (2H, m, NCH_2, NC$\underline{H}$CH$_2$O), 4.18 (1H, dd, J=2.4, 12.2 Hz, NCHC$\underline{H}_2$O), 5.12 (1H, br, NH), 5.95 (1H, d, J=2.5 Hz, NCHO), 7.26—8.30 (7H, m, aromatic H).

Crystallographic Measurements A single crystal of (3a*S*,6*R*)-**2a** was grown in AcOH–hexane solution as a colorless column with dimensions of 0.5×0.4×0.4 mm. All the measurements were performed on a Rigaku AFC-5 diffractometer using graphite-monochromated Cu$K\alpha$ radiation. The unit cell dimensions were determined by least-squares calculation with 24 high-angle reflections.

Intensity data were collected by using the 2 θ/ω scan technique with an average scan rate of 4°/min. In total, 2394 independent reflections with $0° < 2\theta < 130°$ were collected, of which 2039 that satisfied the condition $F_O \geq 3\sigma(F)$ were used for calculations.

Structure Analysis and Refinement The structure was solved by the direct method using MULTAN[5] and the Rigaku crystallographic package RASA-II. The structure was refined by the block-diagonal least-squares technique with anisotropic thermal factors for all nonhydrogen atoms. The R factor was finally reduced to 0.119.

General Procedure for the Reaction of (3a*S*,6*R*)-2a—c with Diethylzinc $ZnEt_2$ (3 mmol, 3 ml of a 1 M solution in hexane) was added dropwise to a stirred solution of one of (3a*S*,6*R*)-**2a—c** (1 mmol) in toluene (2 ml) at 0 °C under a nitrogen atmosphere. After being stirred at 0 °C for 3 h, the reaction mixture was treated with a small amount of water. The resulting white precipitate was filtered off, and the filtrate was diluted with CH_2Cl_2 (10 ml). The organic layer was dried over Na_2SO_4, and evaporated under reduced pressure. The residue was analyzed by ^{1}H-NMR (270 MHz) spectrometry, and the experimental data are summarized in Table IV.

General Procedure for the Reaction of (3a*S*,6*R*)-2a—c with Triethylaluminum $AlEt_3$ (3 mmol, 3 ml of a 1 M solution in hexane) was added dropwise to a stirred solution of one of (3a*S*,6*R*)-**2a—c** (1 mmol) in toluene or CH_2Cl_2 (2 ml) at 0 or −50 °C under a nitrogen atmosphere for 3 or 48 h. The reaction mixture was worked up in a similar manner to that used in the reaction with $ZnEt_2$, and the residue was analyzed by ^{1}H-NMR (270 MHz and/or 400 MHz) spectrometry. The experimental data are summarized in Tables IV—VI.

General Procedure for the Reaction of (3a*S*,6*R*)-2a—c with Ethylmagnesium Bromide EtMgBr (3 mmol, 1 ml of a 3 M solution in ether) was added dropwise to a stirred solution of one of (3a*S*,6*R*)-**2a—c** (1 mmol) in tetrahydrofuran (THF) (2 ml) at 0 or −50 °C under a nitrogen atmosphere for 3 or 24 h. The reaction mixture was worked up in a similar manner to that used in the reaction with $ZnEt_2$, and the residue was analyzed by ^{1}H-NMR (270 MHz) spectrometry. The experimental data are summarized in Tables IV and V.

(2*S*,1′*S*)-2-Hydroxymethyl-*N*-1′-phenylpropyl-1-pyrrolidinecarboxamide (**3a**): Colorless needles, mp 87—88 °C (hexane–ether). *Anal.* Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.72; H, 8.68; N, 10.72. $[\alpha]_D$ −51.4° (c=0.30, EtOH). MS m/z: 263 (M^++1). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 1.53—2.02 (4H, m, CH_2CH_2), 1.81 (2H, quintet, J=7.3 Hz, $CHC\underline{H}_2CH_3$), 3.34 (2H, dd, J=4.3, 6.1 Hz, NCHC$\underline{H}_2$O), 3.49—3.67 (2H, m, NCH_2), 4.03—4.10 (1H, m, NC$\underline{H}$CH$_2$O), 4.75 (1H, dt, J=7.3, 14.7 Hz, NHC$\underline{H}$CH$_2$), 4.89 (1H, br, OH), 4.92 (1H, J=14.7 Hz, NH), 7.16—7.36 (5H, m, aromatic H); (2*S*,1′*R*)-**3a** (minor product), 0.88 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 1.76—2.00 (4H, m, CH_2CH_2), 1.85 (2H, quintet, J=7.3 Hz, $CHC\underline{H}_2CH_3$), 4.04—4.12 (1H, m, NC$\underline{H}$CH$_2$O), 4.76 (1H, dt, J=7.3, 14.6 Hz, NHC$\underline{H}$CH$_2$), 4.96 (2H, br, OH, NH), 7.21—7.37 (5H, m, aromatic H).

(2*S*,1′*S*)-2-Hydroxymethyl-*N*-1′-(2-methoxyphenyl)-1-pyrrolidinecarboxamide (**3b**): Colorless plates, mp 89—91 °C (hexane–ether). *Anal.* Calcd for $C_{16}H_{24}N_2O_3$: C, 65.72; H, 8.24; N, 9.58. Found: C, 65.68; H, 8.31; N, 9.62. $[\alpha]_D$ −100.8° (c=0.94, EtOH). MS m/z: 293 (M^++1). ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 1.82 (2H, quintet, J=7.3 Hz, $CHC\underline{H}_2CH_3$), 1.85—2.00 (4H, m, CH_2CH_2), 3.27 (1H, dt, J=1.2, 7.3 Hz, NCHC$\underline{H}_2$O), 3.39 (1H, dt, J=1.2, 7.3 Hz, NCHC$\underline{H}_2$O), 3.50—3.67 (2H, m, NCH_2), 3.87 (3H, s, OCH_3), 4.04—4.11 (1H, m, NC$\underline{H}$CH$_2$O), 4.85 (1H, dt, J=7.3, 9.2 Hz, NHC$\underline{H}$CH$_2$), 5.39 (1H, d, J=1.2 Hz, $CH_2O\underline{H}$), 5.64 (1H, d, J=9.2 Hz, N$\underline{H}$CH), 6.91—7.26 (4H, m, aromatic H); (2*S*,1′*R*)-**3b** (minor product), 0.84 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 1.53—2.05 (4H, m, CH_2CH_2), 1.81 (2H, quintet, J=7.3 Hz, $CHC\underline{H}_2CH_3$), 3.88 (3H, s, OCH_3), 4.07—4.15 (1H, m, NC$\underline{H}$CH$_2$O), 4.86 (1H, dt, J=7.3, 8.5 Hz, NHC$\underline{H}$CH$_2$), 5.34 (1H, br, OH), 5.71 (1H, d, J=8.5 Hz, N$\underline{H}$CH), 6.89—7.27 (4H, m, aromatic H).

(2*S*,1′*S*)-2-Hydroxy-*N*-1′-(1-naphthyl)-1-pyrrolidinecarboxamide (**3c**): Colorless needles, mp 116—118 °C (hexane–ether). *Anal.* Calcd for $C_{19}H_{24}N_2O_2$: C, 73.04; H, 7.74; N, 8.97. Found: C, 73.01; H, 7.69; N, 8.94. $[\alpha]_D$ +35.5° (c=0.68, EtOH). MS m/z: 313 (M^++1). ^{1}H-NMR ($CHCl_3$) δ: 0.98 (3H, t, J=7.3 Hz, $CHC\underline{H}_3$), 1.82—1.95 (4H, m, CH_2CH_2), 2.02 (2H, quintet, J=7.3 Hz, $CHC\underline{H}_2CH_3$), 3.23—3.38 (1H, m, NCH_2), 3.32 (1H, dd, J=7.3, 10.9 Hz, NCHC$\underline{H}_2$O), 3.51—3.68 (1H, m, NCH_2), 3.64 (1H, dd, J=3.7, 10.9 Hz, NCHC$\underline{H}_2$O), 4.06—4.13 (1H, m, NC$\underline{H}$CH$_2$O), 4.89 (1H, d, J=14.7 Hz, N$\underline{H}$CH), 4.93 (1H, br, OH), 5.64 (1H, dt, J=7.3, 14.7 Hz, NHC$\underline{H}$CH$_2$), 7.43—8.23 (7H, m, aromatic H); (2*S*,1′*R*)-**3c** (minor product), 0.97 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 1.81—2.10 (4H, m, CH_2CH_2), 2.01 (2H, quintet, J=7.3 Hz, $CHC\underline{H}_2CH_3$), 4.08—4.13 (1H, m, NC$\underline{H}$CH$_2$O), 4.99 (2H, br, OH, NH), 5.63 (1H, dt, J=7.3, 14.7 Hz, NHC$\underline{H}$CH$_2$), 7.43—8.24 (7H, m, aromatic H).

General Procedure for the Reduction of (2*S*,1′*S*)-3a—c with Red-Al Red-Al (7.5 ml of a 2 M solution in toluene) was added dropwise to a stirred solution of one of (2*S*,1′*S*)-**3a—c** (5 mmol) in toluene (15 ml) at −50 °C under a nitrogen atmosphere. After being stirred at room temperature for 24 h, the reaction mixture was treated with a small amount of water. The resulting white precipitate was filtered off, and the filtrate was diluted with CH_2Cl_2 (10 ml). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was bulb-to-bulb distilled to give a colorless oil. The product was subjected to column chromatography on silica gel with a solution of CH_2Cl_2–MeOH (3 : 1) to give (*S*)-*N*-methyl-1-arylpropylamine (**4a—c**), and (*S*)-prolinol hydrochloride was obtained by extraction from the silica gel used in the column chromatography with a dilute hydrochloric acid solution in yields of 58—63%.

(*S*)-*N*-Methyl-1-phenylpropylamine (**4a**): Yield, 0.47 g (63%). Colorless oil, bp 109 °C (20 mmHg). $[\alpha]_D$ −36.7° (c=2.63, EtOH). MS m/z: 150 (M^++1). ^{1}H-NMR ($CDCl_3$) δ: 0.81 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 1.55 (1H, br, NH), 1.55—1.69 (1H, m, $CHC\underline{H}_2CH_3$), 1.71—1.83 (1H, m, $CHC\underline{H}_2CH_3$), 2.28 (3H, s, NCH_3), 3.36 (1H, dd, J=6.1, 7.9 Hz, NC$\underline{H}$CH$_2$), 7.20—7.36 (5H, m, aromatic H).

(*S*)-*N*-Methyl-1-(2-methoxyphenyl)propylamine (**4b**): Yield, 0.51 g (57%). Colorless oil, bp 107 °C (11 mmHg). $[\alpha]_D$ −18.1° (c=3.71, EtOH). MS m/z: 180 (M^++1). ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 1.73 (2H, dq, J=6.1, 7.3 Hz, $CHC\underline{H}_2CH_3$), 1.77 (1H, br, NH), 2.26 (3H, s, NCH_3), 3.77 (1H, t, J=7.3 Hz, NC$\underline{H}$CH$_2$), 3.82 (3H, s, OCH_3), 6.85—7.26 (4H, m, aromatic H).

(*S*)-*N*-Methyl-1-(1-naphthyl)propylamine (**4c**): Yield, 0.65 g (65%). Colorless oil, bp 162 °C (9 mmHg). $[\alpha]_D$ −54.5° (c=1.73, EtOH). MS m/z: 200 (M^++1). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 1.61 (1H, br, NH), 1.89 (2H, dq, J=6.1, 7.3 Hz, $CHC\underline{H}_2CH_3$), 2.35 (3H, s, NCH_3), 4.32 (1H, t, J=6.1 Hz, NC$\underline{H}$CH$_2$), 7.25—8.25 (7H, m, aromatic H).

(*R*)-*N*-Methyl-1-phenylpropylamine (4a) (*R*)-1-Phenylpropylamine, bp 93 °C (18 mmHg), $[\alpha]_D$ +19.7° (neat) [lit.,[4] bp 98 °C (23 mmHg) $[\alpha]_D$ +21.1° (neat)] (4.05 g, 30 mmol), was dissolved in ethyl formate (30 ml). The solution was refluxed for 72 h, then the solvent was evaporated off under reduced pressure. The residue was added dropwise to a stirred suspension of $LiAlH_4$ (2.28 g, 60 mmol) in THF (50 ml) and the mixture was refluxed for 3 h, then treated with a small amount of water. The resulting white precipitate was filtered off. The filtrate was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was distilled *in vacuo*, bp 106 °C (18 mmHg), to give a colorless oil (3.71 g, 83%). This compound was identical with (*S*)-*N*-methyl-1-phenylpropylamine (**4a**) on the basis of ^{1}H-NMR spectral comparison, and the specific rotation was $[\alpha]_D$ +36.1° (c=2.62, EtOH).

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