Stereocontrolled Reduction of 2-(*p*-Tolylsulfinyl)cycloalkanones under Basic Conditions: π-Facial Selection in Cyclic Systems Directed by a Chiral Side Chain

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Reduction of a 2-(*p*-tolylsulfinyl)cycloalkanone with sodium borohydride in methanol-triethylamine is accompanied by rapid epimerization at C_2. Under the conditions employed here, the π-facial selectivity of the reduction is directed by the side chain chirality and, among four possible isomers of the corresponding cycloalkanol, one isomer is given with high selectivities up to 85%.

Stereofacial control in nucleophilic additions to cycloalkanones has been recognized as a significant problem for stereoselective construction of cyclic systems.[1] Although the π-facial selection is often controlled by the stereochemistry contained in the cyclic system itself, there are few reports which deal with the selection affected by stereochemistry of the side chain. This may be attributable to the presence of an additional chiral center at the position bonding to this side chain, the configuration of which must be controlled in advance.[2] Recently, an efficient 1,3-asymmetric induction was realized in $NaBH_4$ reduction of α-substituted β-keto sulfoxides under basic conditions: the chirality of the sulfinyl group controls the hydride attack on the β-carbonyl group regardless of the stereochemistry of C_α which rapidly epimerizes under the reaction conditions.[3] This paper describes that the 1,3-stereochemical control accompanied by C_α-epimerization is successfully applied to cyclic systems, i.e., reduction of 2-(*p*-tolylsulfinyl)cycloalkanones with $NaBH_4$ under basic conditions provides a unique method for facial selection directed by the side chain.

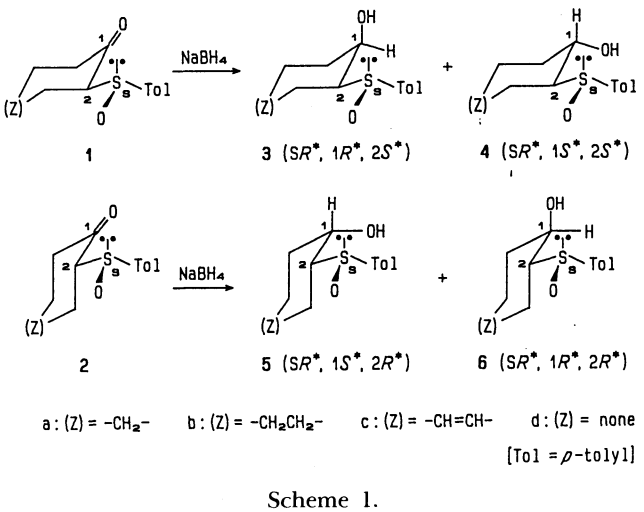
Results and Discussion

When a diastereomeric mixture of 2-(*p*-tolylsulfinyl)cyclohexanone (**1a** : **2a**=54 : 46) was reduced with $NaBH_4$ in methanol (Scheme 1),[4] four possible diastereomers (**3a—6a**) of 2-(*p*-tolylsulfinyl)cyclohexanol were formed in a moderately selective manner (**3a** : **4a** : **5a** : **6a**=48 : 12 : 31 : 9). Preferable formation of **3a** and **5a** (total 79%) predicts that this reduction is mainly directed by the stereochemistry of C_2 since **3a** and **5a** have the same stereochemical relationship between C_1 and C_2. Hence, the chirality of the sulfinyl group seems to less reflect on the new chiral center developing on C_1.

In striking contrast, predominant formation of **3a** (72%) was observed when the reaction was carried out under basic conditions (in a 1 : 1 mixture of MeOH-NEt_3).[5] In addition, it is noteworthy that two major isomers (**3a** and **6a**; their total yield 85%) have the same stereochemical relationship between C_1 and S (hereafter, the position of the sulfur atom is represented by a symbol "S"). Thus, the π-facial selection is strongly directed by the side chain chirality.

The same phenomena were observed for the $NaBH_4$ reduction of other 2-(*p*-tolylsulfinyl)cycloalkanones (**1b—d** and **2b—d**) under the basic conditions. The results are summarized in Table 1. In any case, one diastereomer (**3a—d**) is predominantly formed with high selectivities up to 85%.

Under the basic conditions, the C_2 of **1** and **2** might epimerize rapidly during the reduction. In fact, brief treatment of pure **1a**[6] with a 1 : 1 mixture of triethylamine and MeOH (1 h/room temperature) produces **1a** and **2a** in a ratio of 57 : 43. This rapid epimerization allows $NaBH_4$ to attack preferentially from the most favorable face among four possible ones (axial and equatorial faces[7] of **1** and **2**). In this case, the attack from the equatorial face of **1** giving **3** is predominant. Worthy of comment is that the configuration of **3** is in good accordance with that of the major isomer produced in the reduction of acyclic α-sulfinyl ketones.[3] Thus, the reduction of α-sulfinyl ketones might occur via similar stereochemical course in both acyclic and cyclic systems. This is in sharp contrast with the usual addition of a nucleophile to a carbonyl group.[8]



Scheme 1.

Table 1. Stereoselective Reduction of **1** and **2** with $NaBH_4$[a)]

Substrates	(Ratio)	Solvent	Reduction products[b)]	
			Total yield/%	**3**: **4**: **5**: **6**
1a+**2a**	(54:46)	MeOH-NEt_3 (1:1)	98	72: 6: 9:13
1a+**2a**	(54:46)	MeOH	99	48:12:31: 9
1a		MeOH	100	65:27: 6: 2
1b+**2b**	(52:48)	MeOH-NEt_3 (1:1)	97	85: 1:10: 4
1b+**2b**	(52:48)	MeOH	94	58: 2:35: 5
1c+**2c**	(53:47)	MeOH-NEt_3 (1:1)	95	75: 4:16: 5
1c+**2c**	(53:47)	MeOH	95	48: 6:38: 8
1d+**2d**	(78:22)	MeOH-NEt_3 (1:1)	92	84: 3:12: 1
1d+**2d**	(78:22)	MeOH	91	78: 4:16: 2

a) Carried out with $NaBH_4$ (1.2—2.0 mol equiv) at 0 °C for ca. 2 h. b) Determined by HPLC analysis (see Experimental section).

Relative configurations of the diastereomers **3**—**6** were assigned as follows. Reduction of 2-(*p*-tolylthio)-cyclohexanone with $NaBH_4$ gave *cis*- and *trans*-2-(*p*-tolylthio)cyclohexanols.[11] In oxidation of *cis*-2-(*p*-tolylthio)cyclohexanol with *m*-chloroperbenzoic acid (*m*-CPBA), a 30:70 mixture of **3a** and **5a** was given. On the other hand, *m*-CPBA oxidation of *trans*-2-(*p*-tolylthio)cyclohexanol resulted in formation of **4a** and **6a** (78:22). Thermolysis of optically active (*SR*)-**3a**, obtainable from a mixture of (*SR*)-**1** and (*SR*)-**2a**,[13] produced (*R*)-2-cyclohexenol. From these facts, the configurations of **3a** and **5a** were assigned to be *SR**, *1R** and *SR**,*1S**,*2R**, respectively.

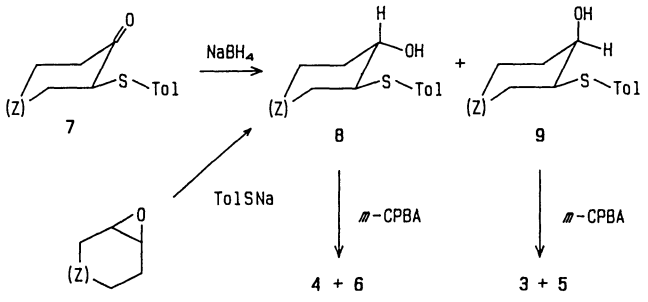
Since **3a** and **4a** were predominantly given by reduction of one diastereomer (**1a**) in MeOH (Table 1),[15] **4a** has *SR**,*1S**,*2S** configuration. Consequently, the configuration of the final isomer (**6a**) was assigned to be *SR**,*1R**,*2R**.

The stereochemical structure of **5c** was determined by X-ray crystallography. The molecular structure is shown in Fig. 1, which exhibits that **5c** has *SR**,*1S**, *2R** configuration. The configuration of the isomer **3c** was determined to be *SR**,*1R**,*2S**, because both **3c** and **5c** gave the same sulfone (**7**) on oxidation with *m*-CPBA. The structures of the minor products (**4c** and **6c**) were tentatively estimated as depicted in Scheme 1.

Oxidation of *trans*-2-(*p*-tolylthio)cycloheptanol with *m*-CPBA gave **4b** and **6b** in a ratio of 84:16, whereas a 14:86 mixture of **3b** and **5b** was produced by oxidation of *cis*-2-(*p*-tolylthio)cycloheptanol. By considering the analogy between **1b** and **1a** (or **1c**), the configurations of **3b**—**6b** were assigned.

It was also found that *cis*-2-(*p*-tolylthio)cyclopentanol was oxidized with *m*-CPBA to yield **3d** and **5d** (20:80), while the similar oxidation of *trans*-2-(*p*-tolylthio)cyclopentanol resulted in formation of **4d** and **6d** (80:20). By comparision of these facts with oxidation behavior of the corresponding cyclohexanols, the stereochemical structures of **3d**, **4d**, **5d**, and **6d** were tentatively estimated.

In conclusion, a diastereomeric mixture of 2-(*p*-tolylsulfinyl)cycloalkanones can produce (*SR**,*1R**, *2S**)-2-(*p*-tolylsulfinyl)cycloalkanols on reduction with $NaBH_4$ in MeOH-Et_3N, which provides one example for facial selection directed by the side chain.



Scheme 2.

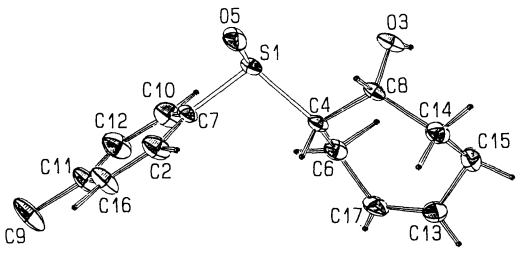


Fig. 1. An ORTEP drawing of **5c**.

Experimental

Melting points were determined on a hot-stage microscope apparatus (Yanagimoto) and are uncorrected. ^1H NMR spectra were obtained on Hitachi R-600 (60 MHz), and JEOL JNM-GSX 270 (270 MHz) spectrometers. Infrared spectra were determined with a JASCO A-200 spectrometer. Optical rotations were measured on a JASCO DIP-181 polarimeter. High pressure liquid chromatography (HPLC) analyses were performed with a Hitachi 638-30 using UV detector (270 nm).

2-(*p*-Tolylthio)cycloalkanones. 2-(*p*-Tolylthio)cyclohexanone, 2-(*p*-tolylthio)cyclopentanone, and 2-(*p*-tolylthio)-cycloheptanone are prepared by reaction of an enolate ion of the corresponding cycloalkanones with di-*p*-tolyl disulfide according to the reaction conditions reported for preparing 2-(phenylthio)cycloalkanones.[16]

2-(*p*-Tolylthio)cyclopentanone: A colorless oil; ^{1}H NMR ($CDCl_3$) δ=1.78—2.22 (4H, m), 2.22—2.46 (2H, m), 2.33 (3H, s), 3.49 (1H, t, J=7.9 Hz), 7.10 (2H, d, J=7.9 Hz), and 7.37 (2 H, d, J=7.9 Hz); IR (neat) 1740 cm^{-1}. Found: C, 69.79; H, 6.81%. Calcd for $C_{12}H_{14}OS$: C, 69.86; H, 6.83%.

2-(*p*-Tolylthio)cyclohexanone: A colorless oil; ^{1}H NMR ($CDCl_3$) δ=1.57—2.29 (7H, m), 2.32 (3H, s), 2.91 (1H, m), 3.75 (1H, dt, J=1.3 and 5.6 Hz), 7.10 (2H, d, J=7.9 Hz), and 7.31 (2H, d, J=7.9 Hz); IR (neat) 1710 cm^{-1}. Found: C, 70.53; H, 7.16%. Calcd for $C_{13}H_{16}OS$: C, 70.86; H, 7.31%.

2-(*p*-Tolylthio)cycloheptanone: A colorless oil; ^{1}H NMR ($CDCl_3$) δ=1.23—1.66 (4H, m), 1.71—2.03 (3H, m), 2.16—2.43 (2H, m), 2.32 (3H, s), 2.77 (1H, ddd, J=3.0, 11.9, and 13.2 Hz), 3.67 (lH, dd, J=5.6 and 10.6 Hz), 7.10 (2H, d, J=7.9 Hz), and 7.30 (2 H, d, J=7.9 Hz); IR (neat) 1705 cm^{-1}. Found: C, 71.53; H, 7.74%. Calcd for $C_{14}H_{18}OS$: C, 71.75; H, 7.74%.

Preparation of 2-(*P*-Tolylsulfinyl)cyclohexanone (1 and 2). A Typical Procedure. *m*-Chloroperbenzoic acid (*m*-CPBA) (1.7 g, 9.9 mmol) was added portionwise to a dichloromethane (25 ml) solution of 2-(*p*-tolylthio)cyclohexanone (2.1 g, 9.6 mmol) at 0 °C. After being stirred for an hour at 0 °C and for 3 h at room temperature, the mixture was treated with 20 wt% aqueous K_2CO_3 (40 ml). The aqueous layer was separated and extracted with dichloromethane (40 ml× 2). The organic layers are combined, dried over anhydrous $MgSO_4$, concentrated, and subjected to column chromatography (silica gel, benzene-ethyl acetate 6 : 1) to give 2-(*p*-tolylsulfinyl)cyclohexanone (a 6 : 4 mixture of **1a** and **2a**) as an oil which soon crystallized. This was identical with an authentic sample (**1a** : **2a**=6 : 4) which was prepared by intramolecular cyclization of 1-(*p*-tolylsulfinyl)-6-iodo-2-hexanone.[14]

Recrystallization of this diastereomeric mixture from diethyl ether-hexane gave **1a** in a pure form: colorless crystals; mp 99—100 °C: ^{1}H NMR ($CDCl_3$) δ=1.50—1.76 (2H, m), 1.76—2.15 (3H, m), 2.15—2.42 (2H, m), 2.41 (3H, s), 2.42—2.60 (1H, m), 3.37 (1H, ddd, J=1.0, 4.6, and 9.6 Hz), 7.31 (2H, d, J=7.9 Hz), and 7.51 (2H, d, J=7.9 Hz); IR (KBr) 1710 and 1038 cm^{-1}. Found: C, 66.25; H, 6.83%. Calcd for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82%.

2-(*p*-Tolylsulfinyl)cycloheptanone (1b and 2b): Colorless crystals; 73% yield; mp 104—120 °C (a 52 : 48 diastereomeric mixture); ^{1}H NMR ($CDCl_3$) δ=1.15—1.65 (4H, m), 1.75—2.10 (4H, m), 2.12—2.28 (1H, m), 2.35—2.53 (1H, m), 2.41 (3H, s), 3.49 and 3.78 (major) [total 1H, dd (J=4.3 and 11.2 Hz) and dd (J=4.3 and 11.9 Hz), respectively], 7.31 (major) and 7.33 (total 2H, d (J=7.9 Hz) and d (J=7.9 Hz), respectively), 7.47 and 7.52 (major) (total 2H, d (J=7.9 Hz) and d (J=7.9 Hz), respectively); IR (KBr) 1700, 1030 cm^{-1}, for the diastereomer mixture. Found: C, 67.17; H, 7.31%. Calcd for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.24%.

2-(*p*-Tolylsulfinyl)cyclopentanone (1d and 2d): A pale yellow oil; 98% yield (a 78 : 22 diastereomer mixture); ^{1}H NMR ($CDCl_3$) δ=1.70—1.95 (3H, m), 2.05—2.60 (3H, m), 2.41 (3H, s), 3.27 (major) and 3.76 [total 1H, t (J=8.57 Hz) and dd (J=5.77 and 9.07 Hz), respectively], 7.32 (2H, d, J=7.9 Hz), and 7.48 (2H, d, J=7.9 Hz); IR (neat) 1740, 1050, and 1035 cm^{-1}. Found: C, 64.57; H, 6.34%. Calcd for $C_{12}H_{14}O_2S$: C, 64.83; H, 6.34%.

2-(*p*-Tolylsulfinyl)-4-cyclohepten-1-one (1c and 2c): This compound was obtained by a different method from the above one: the reaction of the dianion of (*p*-tolylsulfinyl)acetone with *cis*-1,4-dichloro-2-butene followed by treatment with sodium hydride in DMF.[14]

Reduction of 2-(*p*-Tolylsulfinyl)cyclohexanone (1 and 2) with Sodium Borohydride. (a) Reduction in Methanol: Sodium borohydride (30 mg, 0.81 mmol) was added to a solution involving a 54 : 46 mixture of **1a** and **2a** (118 mg, 0.50 mmol) in methanol (5 ml) under ice-cooling. After 2 h at 0 °C, water (20 ml) was added and the mixture was extracted with dichloromethane (10 ml×3). The extract was dried ($MgSO_4$), concentrated under reduced pressure, and subjected to column chromatography on silica gel using hexane-ethyl acetate (1 : 2) as an eluent to give 2-(*p*-tolylsulfinyl)cyclohexanol (117 mg, 99% yield, a mixture of four diastereomers (**3a** : **4a** : **5a** : **6a**=48 : 12 : 31 : 9) as a viscous oil. Found: C, 65.50; H, 7.63%. Calcd for $C_{13}H_{16}O_2S$: C, 65.51; H, 7.61%.

The diastereomer ratio was estimated by HPLC analysis.[17] Retention time (t_R): **3a**, 20 min; **4a**, 31 min; **5a**, 36 min; **6a**, 34 min. In the ^{1}H NMR (270 MHz) of this mixture, the C_1-protons of **3a**, **4a**, **5a**, and **6a** appeared at δ=4.43 (broad s), 3.88 (dt, J=4.7 and 10.4 Hz), 4.32 (broad s), and 4.10 (dt, J=4.6 and 9.9 Hz), respectively.

A single isomer (**1a**) (236 mg, 1.0 mmol) was treated with sodium borohydride (75 mg, 2.0 mmol) in a similar manner to that described above to give a mixture of **3a**, **4a**, **5a**, and **6a** (238 mg, 100% yield), the ratio of which was determined by HPLC analysis to be 65 : 27 : 6 : 2. Found: C, 65.49; H, 7.62%. Calcd for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61%.

(b) Reduction in Methanol-Triethylamine: A diastereomeric mixture (54 : 46) of **1a** and **2a** (50 mg, 0.21 mmol) was dissolved in methanol-triethylamine (1 : 1, 4 ml). Sodium borohydride (10 mg, 0.26 mmol) was added to this solution at 0 °C. After 2 h at 0 °C, brine (20 ml) and water (10 ml) were added and the mixture was extracted with dichloromethane (20 ml×1, 10 ml×3). The extract was dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and subjected to column chromatography on silica gel using benzene-ethyl acetate (2 : 1) as an eluent to give 2-(*p*-tolylsulfinyl)cyclohexanol (49 mg, 98% yield) as a viscous oil. The diastereomeric ratio (**3a** : **4a** : **5a** : **6a**) was estimated by HPLC analysis to be 72 : 6 : 9 : 13.

From this diastereomeric mixture, **3a** was isolated in a pure form by recrystallization from diethyl ether-hexane: colorless crystals; mp 109—112 °C: ^{1}H NMR ($CDCl_3$) δ=1.07—1.29 (1H, m), 1.32—1.51 (2H, m), 1.62—2.11 (4H, m), 2.43 (3H, s), 2.47 (1H, ddd, J=2.3, 5.0 and 14.6 Hz), 3.32 (1H, broad s, OH), 4.43 (1H, broad), 7.34 (2H, d, J=7.9 Hz), and 7.47 (2H, d, J=7.9 Hz); IR (KBr) 1705 and 1025 cm^{-1}. Found: C, 65.48; H, 7.65%. Calcd for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61%.

Similarly, a diastereomeric mixture of (*SR*)-2-(*p*-tolylsulfinyl)cyclohexanone (**1a** and **2a**)[8] (435 mg, 1.84 mmol) was treated with sodium borohydride (104 mg, 2.76 mmol) in methanol-triethylamine (1 : 1, 14 ml) to give a mixture of **3a**, **4a**, **5a**, and **6a** having *R* configuration on the sulfur atom (412 mg, 94%) in a ratio of 72 : 6 : 9 : 13. Recrystallization from diethyl ether-hexane gave (1*R*,2*S*,*SR*)-**3a** in a pure form: colorless crystals; mp 117—117.5 °C; $[\alpha]_D^{22}$ +173.5 (*c* 1, $CHCl_3$) (lit,[18] $[\alpha]_D^{22}$ +174 (*c* 1, $CHCl_3$)). The ^{1}H NMR and IR spectra of this compound were in complete accordance with those of racemic **3a**.

Reduction of 2-(*p*-Tolylsulfinyl)cycloheptanone (1b and 2b). A diastereomeric mixture (52 : 48) of **1b** and **2b** was subjected to the $NaBH_4$ reduction in methanol in a similar

manner described in reduction of **1a** and **2a** to give a 58:2:35:5 mixture of **3b**, **4b**, **5b**, and **6b** (66 mg: 94% yield) as a colorless solid. Found: C, 66.60; H, 7.81%. Calcd for $C_{14}H_{20}O_2S$: C, 66.63; H, 7.99%.

The diastereomeric ratio was determined by a HPLC analysis[17] (t_R: **3b**, 38 min; **4b**, 59 min; **5b**, 62 min; **6b**, 55 min). The ^1H NMR (270 MHz) of this mixture exhibited the C_1-protons of **3b**, **4b**, **5b**, and **6b** at δ=4.63 (1H, diffused t, J=2.6 Hz), 4.25—4.35 (m), 4.12 (diffused q, J=7.3 Hz), and 4.43 (diffused s), respectively.

Reduction of a 52:48 mixture of **1b** and **2b** in methanol-triethylamine was performed in an analogous manner described in reduction of a mixture of **1a** and **2a**. The total yield of **3b**, **4b**, **5b**, and **6b** was 97%, and its diastereomer ratio was determined by the HPLC analysis to be 85:1:10:4. Recrystallization of this mixture from diethyl ether-hexane gave **3b** in a pure form: colorless crystals; mp 122—123 °C: ^1H NMR ($CDCl_3$) δ=1.20—1.83 (8H, m), 1.92—2.13 (2H, m), 2.42 (3H, s), 2.61 (1H, ddd, J=1.7, 3.6, and 10.9 Hz), 2.73 (1H, broad s, OH), 4.63 (1H, diffused t), 7.33 (2H, d, J=8.2 Hz), and 7.47 (2H, d, J=8.2 Hz); IR (KBr) 3340, 1010, and 990 cm^{-1}. Found: C, 66.80; H, 7.97%. Calcd for $C_{14}H_{20}O_2S$: C, 66.63; H, 7.99%.

Reduction of 2-(*p*-Tolylsulfinyl)-4-cyclohepten-1-one (1c and 2c). In a similar manner described in reduction of **1a** and **2a**, a 53:47 mixture of **1c** and **2c** was reduced with $NaBH_4$ in methanol to give a 48:6:38:8 mixture of **3c**, **4c**, **5c**, and **6c** (95% yield) as a colorless solid; mp 147—169 °C. Found: C, 67.15; H, 7.24%. Calcd for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.24%.

The diastereomeric ratio was determined by a HPLC analysis[17] (t_R: **3c**, 29 min; **4c**, 45 min; **5c**, 53 min; **6c**, 48 min). The ^1H NMR (270 MHz) of this mixture exhibited the C_1-protons of **3c**, **4c**, **5c**, and **6c** at δ=4.66 (broad d, J=4.9 Hz), 4.23 (diffused dt, J=4.3 and 8.6 Hz), 4.46 (diffused s), and 4.27—4.76 (m), respectively.

Pure **5c** was isolated by recrystallization of this mixture from diethyl ether-hexane: mp 158—172 °C: ^1H NMR ($CDCl_3$) δ=1.36—1.52 (1H, m), 1.80—1.97 (2H, m), 2.28—2.40 (1H, m), 2.44 (3H, s), 2.52 (1H, ddd, J=1.7, 2.0, and 11.5 Hz), 2.50—2.63 (1H, m), 3.10 (1H, m), 4.34 (1H, broad d, J=1.7 Hz, OH), 4.46 (1H, diffused s), 5.70—5.82 (1H, m), 5.85—5.97 (1H, m), 7.36 (2H, d, J=7.9 Hz), and 7.54 (2H, d, J=7.9 Hz); IR (KBr) 3275, 1018, and 1005 cm^{-1}. Found: C, 67.15; H, 7.21%. Calcd for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.24%.

A 53:47 mixture of **1c** and **2c** was reduced in methanol-triethylamine (1:1) according to the method described in reduction of **1a** and **2a** in methanol-triethylamine. Chromatography of the crude product gave a 75:4:16:5 mixture of **3c**, **4c**, **5c**, and **6c** (95% yield). Recrystallization of this mixture from diethyl ether-hexane gave pure **3c**: colorless crystals; mp 162—168 °C: ^1H NMR ($CDCl_3$) δ=1.55 (1H, diffused t, J=4.9 Hz), 1.83—2.10 (3H, m), 2.40—2.65 (1H, m), 2.43 (3H, s), 2.56 (diffused dt, J=11.9 and 1.8 Hz), 2.87 (1H, diffused t, J=12.2 Hz), 3.10 (1H, broad s, OH), 5.58—5.70 (1H, m), 5.76—5.90 (1H, m), 7.35 (2H, d, J=7.9 Hz), and 7.48 (2H, d, J=7.9 Hz); IR (KBr) 3275, 1082, and 1015 cm^{-1}. Found: C, 67.10; H, 7.09%. Calcd for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.24%.

Recrystallization of a mixture of **1c** and **2c** from diethyl ether-hexane gave almost pure **1c**. When **1c** (15 mg, 0.060 mmol) was reduced with $NaBH_4$ (3.0 mg, 0.79 mmol) in methanol under ice-cooling, a mixture (15 mg) of **3c**, **4c**, and **5c** was produced. The HPLC analysis of this mixture showed that the product ratio was 87:10:3.

Reduction of 2-(*p*-Tolylsulfinyl)cyclopentanone (1d and 2d). A 78:22 mixture of **1d** and **2d** was subjected to the $NaBH_4$ reduction in methanol in a similar manner described in reduction of **1a** and **2a** to give a 78:4:16:2 mixture of **3d**, **4d**, **5d**, and **6d** in 91% yield as a colorless solid. Found: C, 64.28; H, 7.21%. Calcd for $C_{12}H_{16}O_2S$: C, 64.25; H, 7.19%.

The retention times of **3d**, **4d**, **5d**, and **6d** on an HPLC analysis[17] (the eluent: MeOH-H_2O 35:65) were 44 min, 63 min, 66 min, and 57 min, respectively. The ^1H NMR (270 MHz) of this mixture exhibited the C_1-protons of **3d**, **4d**, **5d**, and **6d** at δ=4.53 (diffused q, J=4.6 Hz), 4.18—4.24 (m), 4.58—4.66 (m), and 4.45 (diffused s), respectively.

When a 78:22 mixture of **1d** and **2d** was reduced with $NaBH_4$ in methanol-triethylamine, total yield of **3d**, **4d**, **5d**, and **6d** was 92%. Its diastereomer ratio was determined by the HPLC analysis to be 84:3:12:1. Recrystallization of this mixture from diethyl ether-hexane gave **3d** in a pure form: colorless crystals; mp 110—111 °C: ^1H NMR ($CDCl_3$) δ=1.39—1.65 (2H, m), 1.70—2.02 (3H, m), 2.21—2.38 (1H, m), 2.41 (3H, s), 2.95 (1H, dt, J=5.6 and 8.6 Hz), 3.12 (1H, broad s, OH), 4.53 (1H, diffused q, J=4.6 Hz), 7.31 (2H, d, J=7.9 Hz), and 7.50 (2H, d, J=7.9 Hz); IR (KBr) 3320, 1020, and 1006 cm^{-1}. Found: C, 64.23; H, 7.12%. Calcd for $C_{12}H_{16}O_2S$: C, 64.25; H, 7.19%.

Thermolysis of (*SR*,1*R*,2*S*)-3a. A mixture of (*SR*,1*R*,2*S*)-**3a** (104 mg, 0.44 mmol) and calcium carbonate (160 mg, 1.60 mmol) was heated at 60 Torr#/180 °C in a glass tube oven (Sibata GTO-250RS). The fraction was trapped in a collecting vessel cooled with Dry Ice, and was further distilled under reduced pressure (oven temperature: 120 °C/60 Torr) to give (*R*)-2-cyclohexen-1-ol (32 mg, 75% yield): $[\alpha]_D^{20}$ +115.3° (*c* 0.76, $CHCl_3$) (lit,[18] $[\alpha]_D^{23}$ +67.9 (*c* 0.60, $CHCl_3$)).

Oxidation of 3c and 5c. To a solution of **3c** (137 mg, 0.55 mmol) in dichloromethane (3 ml), was added *m*-CPBA (104 mg, 0.60 mmol) and the resulting mixture was stirred under ice-cooling for 2 h. After addition of aqueous K_2CO_3 solution (20 wt%, 5 ml), the mixture was extracted with dichloromethane (5 ml×2). The combined organic layers were dried ($MgSO_4$), evaporated, and subjected to column chromatography on silica gel using benzene-ethyl acetate (4:1) to afford a sulfone (126 mg: 86% yield): colorless crystals; mp 103—105 °C (from diethyl ether-hexane); ^1H NMR ($CDCl_3$) δ=1.38 (1H, diffused t, J=12 Hz), 1.80—2.03 (2H, m), 2.32—2.74 (2H, m), 2.47 (3H, s), 2.93 (1H, diffused d, J=3.3 Hz), 2.90—2.98 (1H, m), 3.29 (1H, t, J=1.8 Hz, OH),[19] 4.55 (1H, diffused s), 5.65—5.79 (1H, m), 5.82—5.98 (1H, m), 7.39 (2H, d, J=7.9 Hz), and 7.78 (2H, d, J=7.9 Hz); IR (KBr) 3450, 1280, 1160, and 1075 cm^{-1}. Found: C, 63.01; H, 6.81%. Calcd for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81%.

Similarly, **5c** was oxidized with *m*-CPBA to give a sulfone derivative which was identified (by TLC, IR, and ^1H NMR) with the sulfone derived from **3c**.

Reduction of 2-(*p*-Tolylthio)cyclohexanone. A Typical Procedure. Sodium borohydride (121 mg, 3.21 mmol) was added portionwise to a dichloromethane-methanol (1:2, 15 ml) solution of 2-(*p*-tolylthio)cyclohexanone (426 mg, 1.94 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C and 11 h at room temperature. Water (10 ml) was added and the whole was extracted with dichloromethane (20 ml×1, 10

1 Torr=133.322 Pa.

ml×3). The extract was dried over anhydrous $MgSO_4$, condensed under reduced pressure, and subjected to column chromatography (silica gel, benzene-hexane 1:1—2:1) to give *cis*- and *trans*-2-(*p*-tolylthio)cyclohexanols (218 mg and 163 mg, respectively; 88% total yield). *cis*-2-(*p*-Tolylthio)cyclohexanol: a colorless oil; ^{1}H NMR ($CDCl_3$) δ=1.20—1.55 (3H, m), 1.58—1.92 (5H, m), 2.33 (3H, s), 2.49 (1H, broad s, OH), 3.25 (1H, dt, J=2.6 and 5.3 Hz), 3.83 (1H, dt, J=3.0 and 6.4 Hz), 7.11 (2H, d, J=7.9 Hz), and 7.35 (2H, d, J=7.9 Hz); IR (neat) 3450 cm^{-1}. Found: C, 70.04; H, 8.17%. Calcd for $C_{13}H_{18}OS$: C, 70.22; H, 8.15%.

trans-2-(*p*-Tolylthio)cyclohexanol was identified by comparison of its IR and ^{1}H NMR spectra with those of an authentic sample which was prepared by the reaction of cyclohexene oxide with sodium *p*-toluenethiolate.[12]

***cis*- and *trans*-2-(*p*-Tolylthio)cyclopentanols:** These were obtained in a ratio of 65:35 (90% total yield) by reduction of 2-(*p*-tolylthio)cyclopentanone with $NaBH_4$) in methanol. The stereochemistry of *trans*-2-(*p*-tolylthio)cyclopentanol was confirmed by an alternative synthesis of the trans isomer.[12] *cis*-2-(*p*-Tolylthio)cyclopentanol: a colorless oil; ^{1}H NMR ($CDCl_3$) δ=1.55—1.82 (3H, m), 1.82—1.92 (2H, m), 1.97—2.13 (1H, m), 2.32 (3H, s), 2.63 (1H, broad s, OH), 3.39 (1H, ddd, J=4.0, 8.6, and 10.9 Hz), 4.03 (1H,diffused t), 7.10 (2H, d, J=7.9 Hz), and 7.33 (2H, d, J=7.9 Hz); IR (neat) 3400 cm^{-1}. Found: C, 68.85; H, 7.79%. Calcd for $C_{12}H_{16}OS$: C, 69.18; H, 7.74%.

***cis*- and *trans*-2-(*p*-Tolylthio)cycloheptanols:** Similar reduction of 2-(*p*-tolylthio)cycloheptanone gave these compounds in 65% and 31% yields, respectively. *cis*-2-(*p*-Tolylthio)cycloheptanol: a colorless oil; ^{1}H NMR ($CDCl_3$) δ=1.28—1.65 (5H, m), 1.65—2.00 (5H, m), 2.33 (3H, s), 2.55 (1H, broad s, OH), 3.33 (1H, dt, J=3.0 and 9.6 Hz), 3.83 (1H, dt, J=3.0 and 6.4 Hz), 7.11 (2H, d, J=7.6 Hz) and 7.35 (2H, d, J=7.6 Hz); IR (neat) 3450 cm^{-1} Found: C, 70.97; H, 8.46%. Calcd for $C_{14}H_{20}OS$: C, 71.13; H, 8.52%.

***trans*-2-(*p*-Tolylthio)cyclohexanol:** A colorless oil; ^{1}H NMR ($CDCl_3$) δ=1.32—1.80 (7H, m), 1.90—2.15 (3H, m), 2.34 (3H, s), 2.90 (1H, dt, J=3.0 and 9.2 Hz), 2.92 (1H, broad s, OH), 3.52 (1H, ddd, J=3.6, 7.9, and 9.2 Hz), 7.12 (2H, d, J=7.9 Hz), and 7.35 (2H, d, J=7.9 Hz); IR (neat) 3375 cm^{-1}. Found: C, 71.36; H, 8.54%. Calcd for $C_{14}H_{20}OS$: C, 71.13; H, 8.52%.

Oxidation of 2-(*p*-Tolylthio)cyclohexanol with *m*-CPBA. A Typical Procedure: A dichloromethane (5 ml) solution of *cis*-2-(*p*-tolylthio)cyclohexanol (86.7 mg, 0.391 mmol) was cooled at 0 °C. To this solution was added *m*-CPBA (70 mg, 0.40 mmol) and the mixture was stirred for 1 h at 0 °C and for 2 h at room temperature. An aqueous solution (20 wt%, 10 ml) of K_2CO_3 was added and the whole was stirred for a while. The aqueous layer was separated and extracted with dichloromethane (10 ml×2). The organic layers were combined, dried over anhydrous $MgSO_4$, condensed under reduced pressure, and subjected to column chromatography on silica gel using benzene-ethyl acetate (6:1) as an eluent to give a mixture of **3a** and **5a** (82 mg, 88%) in a ratio of 30:70, which was determined by the HPLC analysis.

Similarly, *trans*-2-(*p*-tolylthio)cyclohexanol (89 mg, 0.40 mmol) was treated with *m*-CPBA (70 mg, 0.41 mmol) (1 h at

Table 2. Atomic Positional and Thermal Parameters for **5C**

Atom	*x*	*y*	*z*	*B*
S 1	0.2189(2)	0.2207(2)	0.8257(1)	3.70
C 2	0.4724(7)	0.2238(5)	1.1419(6)	4.40
O 3	−0.1311(4)	0.1123(4)	0.5656(4)	4.30
C 4	0.0536(5)	0.1540(5)	0.8506(5)	3.00
O 5	0.2899(4)	0.0848(5)	0.7587(4)	5.40
C 6	−0.0261(6)	0.2879(5)	0.9255(6)	3.90
C 7	0.3766(6)	0.3075(5)	1.0436(5)	3.40
C 8	−0.0707(6)	0.0387(5)	0.6892(5)	3.30
C 9	0.7792(9)	0.5285(8)	1.5558(7)	8.20
C10	0.4069(7)	0.4622(6)	1.1066(6)	4.60
C11	0.6322(7)	0.4515(6)	1.3722(6)	4.90
C12	0.5359(7)	0.5320(6)	1.2716(7)	5.20
C13	−0.2651(6)	0.1582(6)	0.9180(6)	4.40
C14	−0.2169(6)	−0.0341(5)	0.6901(6)	4.10
C15	−0.3388(6)	0.0691(6)	0.7280(6)	4.50
C16	0.6014(7)	0.2971(6)	1.3086(6)	5.10
C17	−0.1270(6)	0.2530(6)	1.0035(6)	4.20

Table 3. Bond Distances of **5C**

Atom 1 Atom 2	Distance/Å	Atom 1 Atom 2	Distance/Å
S1-C4	1.990(6)	C7-C10	1.400(7)
S1-O5	1.550(4)	C8-C14	1.647(9)
S1-C7	1.836(4)	C9-C11	1.608(7)
C2-C7	1.407(7)	C10-C12	1.433(6)
C2-C16	1.446(6)	C11-C12	1.396(8)
O3-C8	1.426(6)	C11-C16	1.398(8)
C4-C6	1.584(7)	C13-C15	1.523(7)
C4-C8	1.572(5)	C13-C17	1.405(8)
C6-C17	1.593(10)	C14-C15	1.626(9)

Table 4. Bond Angles of **5C**

Atom 2-Atom 1-Atom 3	Angle/°	Atom 2-Atom 1-Atom 3	Angle/°
C4-S1-O5	109.7(2)	O3-C8-C14	107.6(4)
C4-S1-C7	103.9(2)	C4-C8-C14	118.2(4)
O5-S1-C7	101.0(2)	C7-C10-C12	118.8(5)
C7-C2-C16	120.2(4)	C9-C11-C12	122.8(5)
S1-C4-C6	112.1(4)	C9-C11-C16	118.6(5)
S1-C4-C8	110.0(4)	C12-C11-C16	118.6(4)
C6-C4-C8	109.5(4)	C10-C12-C11	122.4(5)
C4-C6-C17	115.6(4)	C15-C13-C17	122.3(6)
S1-C7-C2	122.2(3)	C8-C14-C15	120.8(4)
S1-C7-C10	117.7(4)	C13-C15-C14	109.2(4)
C2-C7-C10	119.9(4)	C2-C16-C11	120.1(5)
O3-C8-C4	106.8(4)	C6-C17-C13	128.0(5)

Table 5. Torsional Angles of **5C**

Atom 3-Atom 1-Atom 2-Atom 4	Angle/°
O5-S1-C4-C6	−178.8(3)
O5-S1-C4-C8	−56.7(4)
C7-S1-C4-C6	74.0(4)
C7-S1-C4-C8	−163.9(3)
C4-S1-C7-C2	77.9(5)
C4-S1-C7-C10	−106.7(4)
O5-S1-C7-C2	−35.7(5)
O5-S1-C7-C10	139.7(4)
C16-C2-C7-S1	175.9(4)
C16-C2-C7-C10	0.6(8)
C7-C2-C16-C11	−0.6(9)
S1-C4-C6-C17	−164.4(4)
C8-C4-C6-C17	73.2(5)
S1-C4-C8-O3	−59.9(4)
S1-C4-C8-C14	178.8(3)
C6-C4-C8-O3	63.7(5)
C6-C4-C8-C14	−57.6(5)
C4-C6-C17-C13	−67.2(7)
S1-C7-C10-C12	−175.7(4)
C2-C7-C10-C12	−0.2(8)
O3-C8-C14-C15	−57.3(6)
C4-C8-C14-C15	63.6(6)
C7-C10-C12-C11	−0.3(9)
C9-C11-C12-C10	178.7(6)
C16-C11-C12-C10	0.3(9)
C9-C11-C16-C2	−178.4(6)
C12-C11-C16-C2	0.1(9)
C17-C13-C15-C14	56.9(7)
C15-C13-C17-C6	1.2(9)
C8-C14-C15-C13	−74.6(6)

0 °C and 2 h at room temperature) to give a mixture of **4a** and **6a** (86 mg, 90%) in a ratio of 78:22, which was determined by the HPLC analysis.

Oxidation of 2-(*p*-Tolylthio)cycloheptanols: The cis isomer gave a mixture of **3b** and **5b** (92% yield) in a ratio of 14:86, while the trans isomer gave a mixture of **4b** and **6b** (83% yield) in a ratio of 84:16.

Oxidation of 2-(*p*-Tolylthio)cyclopentanols: The cis isomer gave a mixture of **3d** and **5d** (85% yield) in a ratio of 20:80, while the trans isomer gave a mixture of **4d** and **6d** (84% yield) in a ratio of 80:20.

X-Ray Crystallography of 5c. Crystal data are as follows: $C_{14}H_{18}O_2S$, F.W.=250.35, triclinic, space group, $P\bar{1}$, a=8.942(2) Å, b=9.592(5) Å, c=9.404(3) Å; α=108.53(5)°, β=118.01(2)°, γ=87.25(4)°; V=670.20 Å^3; D_x=1.116 g cm^{-3}, Z=2. A computer program UNICS III[20] PRG. MULTAN 80[21] run on a HITACHI M680 at Tokyo University was employed for the analysis. The intensity data were collected in the region $3° \leqq 2\theta \leqq 120°$ at a scan rate 4° min^{-1}. 2233 independent reflections with $F(0) > 3\sigma(F_o)$ were used for a structure analysis. The final refined R value was 0.0682. Atomic positional and thermal parameters, bond distances, bond angles, and torsional angles are summarized in Tables 2—5.

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