A Practical Optical Resolution of (Arylsulfinyl)acetones and Its Application to the Synthesis of 2-(Arylsulfinyl)cycloalkanones

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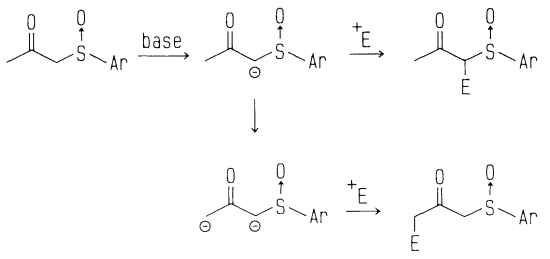
Racemic (arylsulfinyl)acetones (**1**) were efficiently resolved by formation of their oxazolidine derivatives with (*R*)- or (*S*)-2-amino-2-phenylethanol followed by chromatography on Florisil–MgO and the subsequent hydrolysis to give (*S*)- or (*R*)-**1**, respectively. Further, derivation of **1** to optically active 2-(*p*-tolylsulfinyl)-cyclohexanone and 2-(*p*-tolylsulfinyl)-4-cycloheptenone is described.

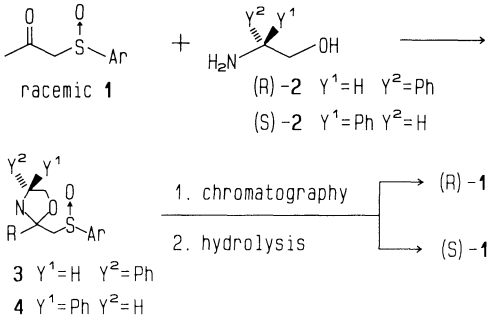
Optically active α-(arylsulfinyl) ketones have proved to be one of the most valuable chiral building blocks for asymmetric syntheses of alcohols,[1] α-hydroxy aldehydes,[2] β-hydroxy ketones,[3] epoxides,[4] γ-substituted γ-lactones,[5] and 4-aryl-3-(*p*-methoxyphenylsulfonyl)-1,4-dihydropyridines,[6] and 3-substituted cycloalkanones.[7] In spite of their potential utilities, these asymmetric syntheses seem to be limited in practical use, mainly due to a multistep preparation of the optically active α-(arylsulfinyl) ketones: Acylation of (*R*)-(methyl *p*-tolyl sulfoxide), obtainable from the reaction of methylmagnesium iodide with *l*-menthyl *p*-toluenesulfinate, has been employed frequently.[1a–d,8] Alternatively, the direct reaction of *l*-menthyl *p*-toluenesulfinate with the enolate ion of a ketone was also reported.[9] Since *l*-menthyl *p*-toluenesulfinate must be synthesized by the reaction of *p*-toluenesulfinyl chloride and *l*-menthyl alcohol followed by repeating recrystallization and epimerization,[10] both of these methods are too tedious to be practical.

For preparing many kinds of optically active α-(arylsulfinyl) ketones, our attention was paid to the utilization of chiral (arylsulfinyl)acetones (**1**) as a versatile intermediate, because the monoanion and dianion of racemic **1** were known to react with various electrophiles to afford a variety of α-(arylsulfinyl) ketones.[11]



Scheme 1.

Here we wish to disclose a practical method for optical resolution of (arylsulfinyl)acetones (**1**), which is achieved by easy formation of an oxazolidine (**3** or **4**) from **1** and (*R*)- or (*S*)-2-amino-2-phenylethanol (**2**), followed by column chromatography on Florisil–MgO. In order to demonstrate the usefulness of



Scheme 2.

optically active **1a**, we further investigated the reaction conditions for deriving **1a** into (R_s)-(*p*-tolylsulfinyl)-cyclohexanone and (S_s)-2-(*p*-tolylsulfinyl)-4-cycloheptenone, the result of which is also described in the present article.

Results and Discussion

Optical Resolution of (Arylsulfinyl)acetones. At first, we found that racemic (*p*-tolylsulfinyl)acetone (**1a**) afforded an oxazolidine derivative (**3a**) by simply stirring **1a** and (*R*)-**2** in ethanol or dichloromethane at room temperature. Thus, an ethanolic solution (3 ml) of racemic (*p*-tolylsulfinyl)acetone (**1a**) (1.0 mmol) and (*R*)-**2** (1.1 mmol) was stirred for 24 h at room temperature. After removal of the solvent under a reduced pressure, the ^{1}H NMR analysis of the residue showed quantitative formation of an oxazolidine (**3a**), which consisted of four diastereomers in the ratio of ca. 2:2:1:1.[12] Without any purification, the crude oxazolidine (**3a**) was subjected to column chromatography (φ 18 mm×290 mm) using benzene–ethyl acetate (9:1) as an eluent. As an adsorbent, we chose 70-fold excess (to **3a** in weight) of Florisil–MgO (70:30, 82:18, and 100:0),[13] prepared by mechanical mixing and subsequent calcination at 200 °C for 2 h. Since **3a** underwent partial hydrolysis during elution, all of the fractions contained **1a** along with **3a**. It was shown by the HPLC analysis that the earlier fractions consisted mainly of **1a** and, as the chromatography proceeded, the content of **3a** increased. The mixture of **1a** and **3a**

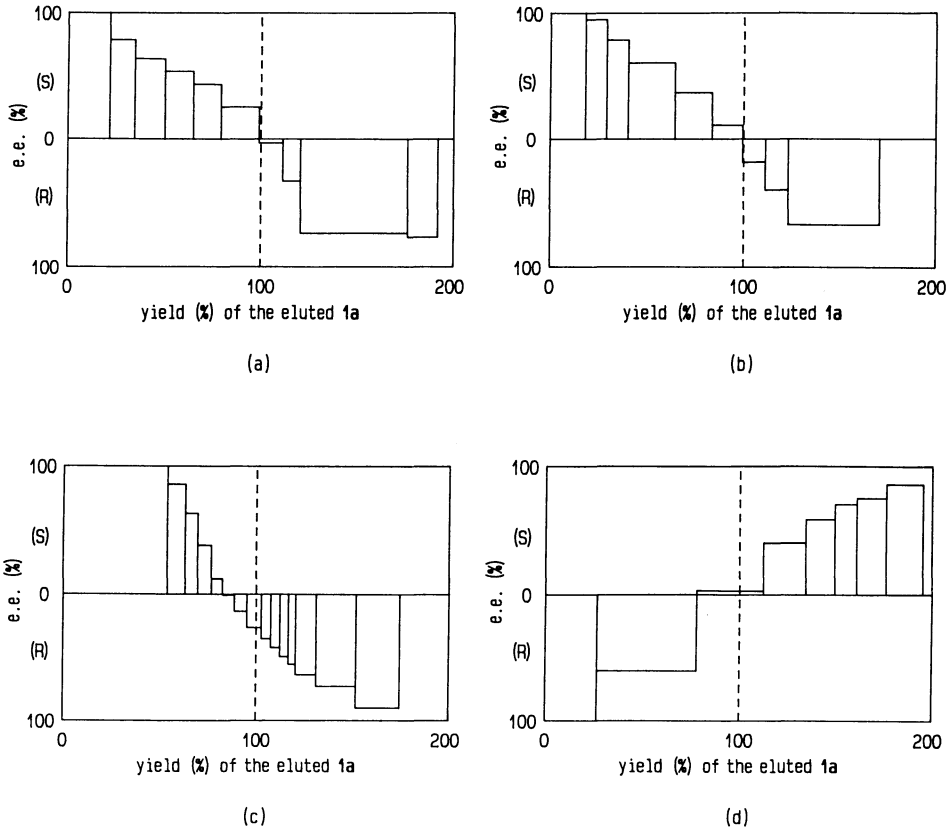
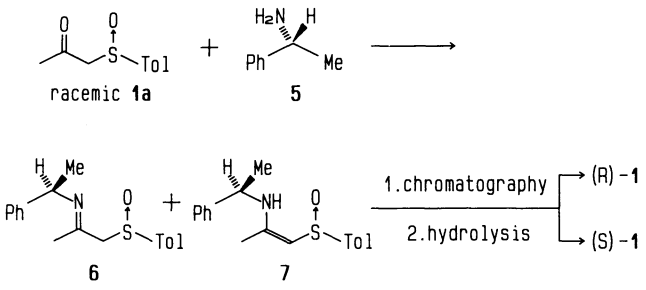


Fig. 1. Chromatography of the oxazolidines: (a) **3a** on Florisil; (b) **3a** on Florisil–MgO (82:18); (c) **3a** on Florisil–MgO (70:30); (d) the oxazolidine derived from **1a** and (*S*)-2-amino-3-methyl-1-butanol on Florisil–MgO (70:30).

in each fraction was treated with silica gel to hydrolyze the involved **3a** to **1a**. This procedure made it possible to isolate **1a** as a sole product. The enantiomeric excess (e.e.) of **1a** of each fraction was determined by HPLC using a column with a chiral stationary phase (Daisel Chiral-cell OB). The results are summarized in Fig. 1, where the ordinate exhibits the e.e. value and the abscissa does integration of the yield of **1a** in each fraction, based on its one enantiomer. Hereafter, the yields of (*R*)- and (*S*)-**1** based on a half of the amount of the used racemic **1** are utilized. Among the adsorbents examined herein, a 70:30 mixture of Florisil and MgO gave the best result: All the fractions containing (*S*)-**1a** with >99% e.e. were combined and concentrated. The yield of (*S*)-**1a** with >99% e.e. amounted to 54%. A parallel experiment using (*S*)-**2** instead of (*R*)-**2** gave (*R*)-**1a** with >99% e.e. in a comparable yield. The present technique can be suitably applied to a large-scale resolution of **1a**. Thus, the oxazolidine (**4a**), produced from **1a** (10 mmol) and (*S*)-**2** (12 mmol), was eluted through the column (ϕ 45 mm×300 mm) packed with 250 g of Florisil–MgO (70:30) by the use of benzene–ethyl acetate (6:1) as an eluent. Hydrolysis of the fractions containing **1a** with a high enantiomeric excess gave (*R*)-**1a** of >99% e.e. in 48% yield together with (*R*)-**1a** (11% yield) of 98% e.e. It should be noted that the column could be regenerated for reuse by washing with methanol and then with benzene.

The separation mechanism of the present system seems to be quite different from that of the usual chromatography. During elution, the oxazolidine (**3a** or **4a**) is partially hydrolyzed to form **1a**, which is less polar than the oxazolidine and, consequently, is more preferably eluted. Therefore, preferential elution of (*S*)-**1a** on chromatography of **3a** derived from (*R*)-**2** might suggest that the (S_s)-isomers of **3a** is more susceptive to hydrolysis than the (R_s)-isomers.

(*R*)-2-Amino-1-butanol and (*S*)-2-amino-3-methyl-1-butanol also reacted with **1a** to produce the corresponding oxazolidines, but the subsequent chromatography on Florisil–MgO (70:30) resulted in less effective resolution: when (*S*)-2-amino-3-methyl-1-butanol was utilized almost optically pure (*R*)-**1a** (>99% e.e.) was obtained in 27% yield. In the case of (*R*)-2-amino-1-butanol, **1a** was not isolated in an optically pure form. Further, we utilized (*R*)-1-phenylethylamine (**5**) instead of **2**. In the reaction of **5** with **1a**, formation of an imine (**6**) and an enamine (**7**) was observed by the ^{1}H NMR analysis of a crude product. Chromatography of the crude product on Florisil–MgO (70:30) using benzene–ethyl acetate



Scheme 3.

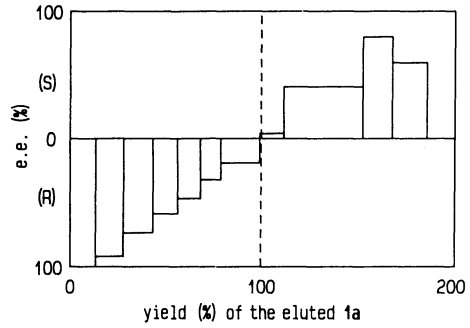


Fig. 2. Chromatography of a mixture of **6** and **7** on Florisil-MgO (70:30).

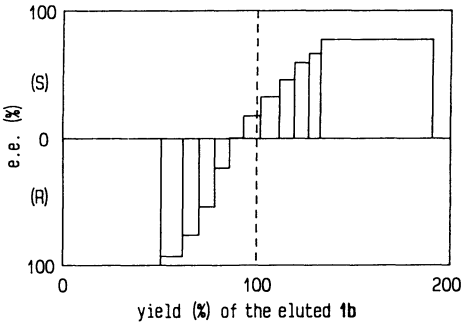
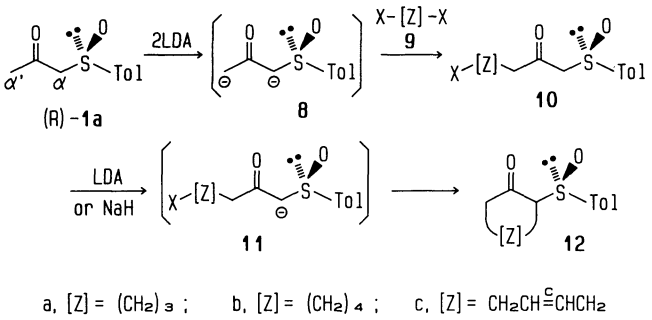


Fig. 3. Chromatography of **4b** on Florisil-MgO (70:30).



Scheme 4.

(9:1) gave **1a** with >99% e.e. in 13% yield.

In conclusion, chromatography of the oxazolidine (**3a** or **4a**) on Florisil-MgO (70:30) has proved to be most efficient for the optical resolution of **1a**. Recently, (*R*)-(*p*-methoxyphenylsulfinyl)acetone (**1b**) was found to be a good precursor of (*S*)-4-(*m*-chlorophenyl)-3-(*p*-methoxyphenylsulfonyl)-1,4-dihydropyridine, a potent cardiovascular drug.[6] We applied the present technique to an optical resolution of racemic (*p*-methoxyphenylsulfinyl)acetone (**1b**). Like **1a**, **1b** reacted with (*S*)-**2** to quantitatively form the corresponding oxazolidine (**4b**), which was subjected to column chromatography on Florisil-MgO (70:30) using benzene-ethyl acetate (9:1). At the initial stage, we obtained pure (*R*)-**1b** with >99% e.e. in 51% yield (Fig. 3): mp 75.5—77.0 °C (lit,[6] mp 56—58 °C); $[\alpha]_D^{21}$ +231° (*c* 0.75, MeOH) (lit,[6] $[\alpha]_D$ +168°).

Derivation of (*R*$_S$)-2-(*p*-Tolylsulfinyl)cycloalkanones from 1a. Since optically active **1a** are now in hand, their conversion into useful chiral compounds are particularly of interest. As well-known, successive treatment of racemic α-(phenylsulfinyl) ketones with sodium hydride and butyllithium gives the corresponding dianion, which reacts with various electrophiles to give α′-substituted products.[1f,11,14] By applying this chemistry of α-(phenylsulfinyl) ketones to the optically active **1**, we investigated a short-step synthesis of (*R*$_S$)-2-(*p*-tolylsulfinyl)cycloalkanones, which are novel precursors of optically active cyclic compounds, as outlined in Scheme 4. This route may be complementary to the conventional way leading to chiral 2-(*p*-tolylsulfinyl)cycloalkanones which are prepared by the reaction of *l*-menthyl *p*-toluenesulfinate with the enolate of a cycloalkanone.[9]

By the use of racemic **1a**, we first tested the possibility of the reaction paths depicted in Scheme 4. Treatment of **1a** with lithium diisopropylamide (LDA) (2.2 mol equiv) in tetrahydrofuran (THF) at −78 °C to room temperature generated the corresponding dianion (**8**).[15] After addition of excess amount (3 mol equiv) of 1,ω-dihaloalkane (**9**), the resulting mixture was stirred for 10—30 min to give an α′-substituted product (**10**). Reaction of the dianion (**8**) with **9a** (X=Br), **9a** (X=I), and **9b** (X=I) gave the corresponding **10** in 41%, 49%, and 60% yields, respectively. In contrast, treatment of the dianion (**8**) with 1,2-diiodoethane (**9**, X=I) did not give the corresponding **10**, but 1-iodo-3-(*p*-tolylsulfinyl)propanone (54% yield). Next, intramolecular cyclization of **10** to **12** was examined. LDA (1.1 mol equiv) was added to a 0.04 M# THF solution of **10** at −78 °C, and the resulting mixture was stirred at −15 °C to room temperature. In the case of **10a** (X=I), a smooth cyclization took place at −15 °C for 20 h to give **12a** in 51% yield. The reaction of **10a** (X=Br) was so slow that **12a** was produced in 27% yield even after stirring at room temperature for 10 h. However, cyclization of **10b** (X=I) did not form the expected **12b**, but a de-

1 M=1 mol dm^{-3}.

hydroiodinated product, 1-(*p*-tolylsulfinyl)-6-hepten-2-one. Consequently, the synthetic path depicted in Scheme 4 was shown to be suitable to the preparation of **12a**. Starting from (*R*)-**1a**, we obtained (R_s)-**12a** as a 64:36 mixture of two diastereomers: $[\alpha]_D$ +215° (*c* 0.80, $CHCl_3$).[16]

Further, we found that optically active 2-(*p*-tolylsulfinyl)-4-cycloheptenone (**12c**), which seems to be a good synthetic precursor of optically active cycloheptanone derivatives, was synthesized according to the reaction path of Scheme 4: Treatment of the dianion (**8**), generated from (*S*)-**1a**, with *cis*-1,4-dichloro-2-butene (**9c**) in THF at −78 °C for 30 min gave 7-chloro-1-(*p*-tolylsulfinyl)-5-hepten-2-one (**10c**) in 72% yield. Sodium hydride (2 equiv) was added to a THF solution of the thus-obtained **10c** under ice-cooling, and the reaction mixture was stirred at room temperature for 2 h. By the usual workup and subsequent chromatography on silica gel, (S_s)-**12c** was obtained in 74% yield as a 52:48 mixture of two diastereomers.

Thus, (*R*)- or (*S*)-**1a** was shown to provide a new and novel method for preparing optically active 2-(*p*-tolylsulfinyl)cyclohexanone (**12a**) and 2-(*p*-tolylsulfinyl)-4-cycloheptenone (**12c**).

Experimental

Melting points were determined on a hot-stage microscope apparatus (Yanagimoto) and are uncorrected. ^{1}H NMR spectra were obtained on Hitachi R-600 (60 MHz), JEOL JNM-GSX 270 (270 MHz), and JEOL JNM-GSX 500 (500 MHz) spectrometers. Infrared spectra were determined with a JASCO A-200 spectrometer. Optical rotations were measured on a JASCO polarimeter. The adsorbent for chromatography of the oxazolidines (**3** or **4**) was prepared by mechanically mixing Florisil (Wako; 100—200 mesh) and MgO (Merck Art. 5866) followed by being dried in a microwave oven (30 min) and then in an oven (200 °C/2 h). (*R*)-**2** and (*S*)-**2** were prepared by reduction of (*R*)-phenylglycine (Tokyo Kasei) and (*S*)-phenylglycine (Aldrich), respectively, with lithium aluminium hydride in THF and purified by recrystallization from dichloromethane–hexane. Their enantiomeric excesses were determined to be 100% by measuring ^{1}H NMR of their diacetyl derivatives, which were obtained by acetylation with acetic anhydride and pyridine, in the presence of Eu(hfc)$_3$ (0.4 mol equiv).

Preparation of (Arylsulfinyl)acetone (1). The starting materials, racemic **1a** and **1b**, were obtained by oxidation of the corresponding (arylthio)acetone with sodium periodate in ethanol–water (1:1). **1a**: colorless crystals; mp 44.5—45.5 °C (from hexane–diethyl ether) (lit,[17] mp 44—47 °C). **1b**: colorless crystals; mp 69.5—71.0 °C (from hexane–diethyl ether); ^{1}H NMR ($CDCl_3$) δ=2.23 (3H, s), 3.78 (1H, d, J=13.5 Hz), 3.87 (1H, d, J=13.5 Hz), 3.86 (3H, s), 7.04 (2H, d, J=8.9 Hz), and 7.59 (2H, d, J=8.9 Hz); IR (KBr) 1711, 1032, and 1020 (sh) cm^{-1}. Calcd for $C_{10}H_{12}O_3S$: C, 56.60; H, 5.70%. Found: C, 56.65; H, 5.69%.

Optical Resolution of 1. A Typical Procedure. A solution of **1a** (196 mg, 1.0 mmol) and (*R*)-**2** (151 mg, 1.1 mmol) in absolute ethanol (2 ml) was stirred at room temperature for 15 h under an atmosphere of nitrogen. After evaporation, the residue was chromatographed through a column (ϕ 17.5 mm×290 mm) packed with a 70:30 mixture (70 fold excess in weight) of Florisil (16.1 g) and MgO (6.9 g). A 9:1 mixture of benzene and ethyl acetate was eluted and 80-ml fractions were collected. Finally, ethyl acetate was eluted to completely recover **1a** and **3a**. Each fraction was evaporated in vacuo and the residue was subjected to short-path column chromatography on silica gel using benzene–ethyl acetate (1:1) as an eluent. The result was summarized in Table 1 and Fig. 1c. The fractions 23, 24, and 25 involved the oxazolidine (**3a**), which was hydrolyzed by treatment with silica gel in dichloromethane. The enantiomeric excess (e.e.) was analyzed by HPLC with a chiral stationary phase (Daisel Chiral-cell OB) using 2-propanol–hexane (1:2) as an eluent (flow rate: 0.7 ml min^{-1}). Under these conditions, the retention times of (*S*)-**1a** and (*R*)-**1a** were about 13 min and 17 min, respectively. The obtained (*S*)-**1a** and (*R*)-**1a** were identified by comparison of their physical properties (IR and ^{1}H NMR) with those of racemic **1a**. Specific optical rotations of (*S*)-**1a** and (*R*)-**1a** were $[\alpha]_D^{22}$ −269° (*c* 1.00, acetone) and $[\alpha]_D^{22}$ +269° (*c* 1, acetone) (lit,[18] $[\alpha]_D$ +255.0° (*c* 1.00, acetone)).

Table 1. Chromatography of **3a** on Florisil–MgO (70:30)

Fraction	Eluent[a]	Vol/ml	**1a**/mg	E.e./%
1—11	A	80×11	52.8	100 (*S*)
12	A	80	9.1	86 (*S*)
13	A	80	6.4	63 (*S*)
14	A	80	7.0	38 (*S*)
15	A	80	5.6	12 (*S*)
16	A	80	5.9	1 (*R*)
17	A	80	6.5	14 (*R*)
18	A	80	7.3	27 (*R*)
19	A	80	5.0	36 (*R*)
20	A	80	4.7	43 (*R*)
21	A	80	4.3	50 (*R*)
22	A	80	3.7	56 (*R*)
23	A	250	10.4	64 (*R*)
24	B	80	20.5	73 (*R*)
25	B	200	22.2	90 (*R*)

a) A: PhH–AcOEt (9:1); B: AcOEt.

Except for the use of (*S*)-2-amino-3-methyl-1-butanol (1.1 mmol) and (*R*)-1-phenylethylamine (1.1 mmol) instead of **2** (1.1 mmol), the same procedure was repeated and the results were depicted in Figs. 1d and 2. It was shown by ^{1}H NMR analysis that reaction of **1a** with (*R*)-1-phenylethylamine in ethanol gave a mixture which consisted of **6** and **7** in the ratio of ca. 1:1. The signals at δ=3.6—3.9 which consisted mainly of an AB quartet at 3.67 and 3.76 (J=13.0 Hz) and a singlet at δ=3.80 were assigned to those of **6** (mainly two isomers). The olefinic protons of **7** (two isomers) appeared at δ=4.83 (s) and 4.95 (s) in a relative intensity of 7:5.

In a similar manner, (*p*-methoxyphenylsulfinyl)acetone (**1b**) was resolved and the result is depicted in Fig. 3. The (*R*)- and (*S*)-**1b** were identified by comparison of their physical properties (IR and ^{1}H NMR) with those of racemic **1b**. Pure (*R*)-**1b** (>99.5% e.e. by HPLC): colorless crystals;

mp 75.5—77.0 °C (diethyl ether-hexane) (lit,[6] mp 56—58 °C); $[\alpha]_D^{21}$ +231° (*c* 0.75, MeOH) (lit,[6] $[\alpha]_D$ +168° (MeOH); no comment on its e.e.).

Reaction of the Dianion (8) with 1,3-Dibromopropane (9a, X=Br). (a) Dianion Formation Using 2 Equiv of LDA: To a solution of **1a** (589 mg, 3.00 mmol) in THF (20 ml), was added a THF solution of LDA, prepared by the action of butyllithium (6.60 mmol/4.26 ml of hexane) and diisopropylamine (1.2 ml, 8.6 mmol) in THF (10 ml), at −78 °C under an atmosphere of nitrogen. The resulting mixture was stirred at the same temperature for 30 min and then at room temperature for 1 h. After the mixture was again cooled to −78 °C, **9a** (X=Br) (0.94 ml, 9.0 mmol) was added and the reaction mixture was stirred at the same temperature for 30 min. The mixture was poured into a saturated aqueous solution (20 ml) of ammonium chloride, followed by extraction with diisopropyl ether (IPE) (20 ml×3). The combined extracts were dried ($MgSO_4$), evaporated, and subjected to column chromatography on silica gel using benzene-ethyl acetate (4:1) as an eluent to give **10a** (X=Br) (390 mg: 41% yield) along with the unchanged **1a** (186 mg). **10a** (X=Br): colorless crystals; mp 107—108 °C (from diethyl ether-hexane); ^{1}H NMR ($CDCl_3$) δ=1.60—1.73 (2H, m), 1.73—1.87 (2H, m), 2.42 (3H, s), 2.50 (1H, dt, *J*=18.5 and 6.9 Hz), 2.55 (1H, dt, *J*=18.5 and 6.6 Hz), 3.36 (2H, t, *J*=6.6 Hz), 3.75 (1H, d, *J*=13.2 Hz), 3.81 (1H, d, *J*=13.2 Hz), 7.34 (2H, d, *J*=7.9 Hz), and 7.52 (2H, d, *J*=7.9 Hz); IR (KBr) 1705 and 1035 cm^{-1}. Calcd for $C_{13}H_{17}BrO_2S$: C, 49.21; H, 5.40%. Found: C, 49.27; H, 5.38%.

(b) Dianion Formation Using NaH and Butyllithium: To a solution of **1a** (498 mg, 2.54 mmol) in THF (20 ml) and hexamethylphosphoric triamide (2 ml), was added NaH (60% dispersion in an oil) (156 mg, 3.90 mmol) under ice-cooling under N_2 atmosphere, and then the resulting mixture was stirred at room temperature for 1 h. After the mixture was cooled to −78 °C, a 1.55 M hexane solution (1.97 ml) of butyllithium (3.05 mmol) was added and the mixture was stirred at room temperature for 1 h. After **9a** (X=Br) (0.94 ml, 9.0 mmol) was added at −78 °C, the reaction mixture was stirred at the same temperature for 1 h. The workup similar to that described in (a) and column chromatography on silica gel gave **10a** (X=Br) (322 mg: 40% yield) along with the unchanged **1a** (63 mg).

In the manner analogous to that described in (a), the reaction of **1a** (316 mg, 1.61 mmol) with **9a** (X=I) (0.56 ml, 4.8 mmol) afforded **10a** (X=I) (246 mg: 42% yield) together with **1a** (105 mg). **10a** (X=I): colorless crystals; mp 101—106 °C (from diethyl ether-hexane); ^{1}H NMR ($CDCl_3$) δ=1.59—1.69 (2H, m), 1.69—1.82 (2H, m), 2.43 (3H, s), 2.49 (1H, dt, *J*=18.5 and 6.9 Hz), 2.51 (1H, dt, *J*=18.5 and 6.9 Hz), 3.13 (2H, t, *J*=6.6 Hz), 3.75 (1H, d, *J*=13.2 Hz), 3.81 (1H, d, *J*=13.2 Hz), 7.35 (2H, d, *J*=7.9 Hz), and 7.53 (2H, d, *J*=7.9 Hz); IR (KBr) 1710 and 1035 cm^{-1}. Calcd for $C_{13}H_{17}IO_2S$: C, 42.86; H, 4.70%. Found: C, 42.89; H, 4.72%.

Similarly, **9b** (X=I) reacted with **1a** to give the corresponding **10b** (X=I) in 60% yield: colorless crystals; mp 73.5—75.0 °C (from diethyl ether-hexane); ^{1}H NMR ($CDCl_3$) δ=1.28—1.42 (2H, m), 1.49—1.63 (2H, m), 1.73—1.85 (2H, m), 2.43 (3H, s), 2.48 (1H, dt, *J*=18.5 and 7.3 Hz), 2.52 (1H, dt, *J*=18.5 and 7.3 Hz), 3.16 (2H, t, *J*=6.9 Hz), 3.75 (1H, d, *J*=13.2 Hz), 3.83 (1H, d, *J*=13.2 Hz), 7.35 (2H, d, *J*=7.9 Hz), and 7.53 (2H, d, *J*=7.9 Hz); IR (KBr) 1705 and 1030 cm^{-1}. Calcd for $C_{14}H_{19}IO_2S$: C, 44.45; H, 5.06%. Found: C, 44.63; H, 5.06%.

Reaction of the Dianion (8) with 1,2-Diiodoethane (9, X=I). To a THF solution (5 ml) of the dianion (**8**) prepared from **1a** (500 mg, 2.55 mmol) and LDA (2.2 equiv), was added a solution of **9** (X=I) (2.22 g, 7.88 mmol) in THF (5 ml) at −78 °C, and the reaction mixture was stirred at the same temperature for 5 min. The mixture was poured into a saturated aqueous solution (20 ml) of ammonium chloride, followed by extraction with IPE (20 ml×1) and dichloromethane (10 ml×4). The combined extracts were washed with 5% aqueous solution of $Na_2S_2O_3$, dried ($MgSO_4$), evaporated, and subjected to column chromatography on silica gel using benzene-ethyl acetate (6:1) as an eluent to give a colorless oil (477 mg) which was too unstable to be completely identified. Its ^{1}H NMR spectrum exhibited the signals which were in accordance with those of 1-iodo-3-(*p*-tolylsulfinyl)-2-propanone: ^{1}H NMR ($CDCl_3$) δ=2.45 (3H, s), 4.00 (1H, d, *J*=13.5 Hz), 4.03 (1H, d, *J*=13.5 Hz), 4.17 (2H, s), 7.39 (2H, d, *J*=9.0 Hz), and 7.55 (2H, d, *J*=9.0 Hz).

Intramolecular Cyclization of 10a (X=I). A Typical Procedure. A THF solution (10 ml) of LDA, prepared from butyllithium (1.26 mmol/0.81 ml of hexane) and diisopropylamine (0.23 ml), was dropwise added to a solution of **10a** (379 mg, 1.04 mmol) in THF (20 ml) at −78 °C under N_2 atmosphere over 5 min. After being stirred at the same temperature for 30 min and then at −15 °C for 20 h, the mixture was poured into a saturated aqueous solution (20 ml) of ammonium chloride, followed by extraction with IPE (15 ml×3). The combined extracts were dried ($MgSO_4$) and evaporated. The oily residue was separated by column chromatography on silica gel using benzene-ethyl acetate (4:1) as an eluent to give **12a** (125 mg: 15% yield) which was shown by HPLC analysis to consist of two diastereomers in the ratio of 6:4. **12a**: colorless crystals; mp 105—115 °C: ^{1}H NMR ($CDCl_3$) δ=1.20—2.10 (6H, broad m), 2.30—2.80 (2H, m), 2.42 (3H, s), 3.00—3.70 (1H, m), 7.30 (2H, d, *J*=9.0 Hz), and 7.51 (2H, d, *J*=9.0 Hz); IR (KBr) 1710 and 1035 cm^{-1}. Calcd for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82%. Found: C, 66.25; H, 6.83%.

This compound was identified with the product derived from oxidation of 2-(*p*-tolylthio)cyclohexanone[19] with *m*-chloroperbenzoic acid in dichloromethane by comparison of their IR and ^{1}H NMR spectra.

In a similar manner, (R_s)-**12a** was prepared by the cyclization of (R_s)-**10a**: colorless crystals which was shown by HPLC to consist of two diastereomers (64:36); mp 110—118 °C; $[\alpha]_D^{22}$ +215° (*c* 0.80, $CHCl_3$).[16]

Synthesis of (S_s)-12c. To a solution of (*S*)-**1a** (234 mg, 1.19 mmol) in THF (5 ml), was added a THF solution of LDA, prepared by the action of butyllithium (2.86 mmol/1.92 ml of hexane) and diisopropylamine (0.48 ml) in THF (3 ml), at −78 °C under an atmosphere of nitrogen. The resulting mixture was stirred at the same temperature for 30 min and then at room temperature for 1 h. After the mixture was again cooled to −78 °C, **9c** (X=Cl) (464 mg, 2.38 mmol) was added and the reaction mixture was stirred at the same temperature for 30 min. The mixure was poured into a saturated aqueous solution (5 ml) of ammonium chloride, followed by extraction with IPE (5 ml×3). The combined extracts were dried ($MgSO_4$), evaporated, and subjected to column chromatography on silica gel using

benzene–ethyl acetate (1:1) as an eluent to give (*S*)-**10c** (X=Cl) (246 mg: 72% yield): colorless crystals; mp 59.5—60.5 °C (from diethyl ether–hexane); $[\alpha]_D^{22}$ −181° (*c* 1.00, $CHCl_3$). The IR and ^1H NMR of this compound was in complete accordance with those of racemic **10c**: colorless crystals; mp 65—66 °C (from diethyl ether–hexane); ^1H NMR ($CDCl_3$) δ=2.10—2.90 (4H, m), 2.42 (3H, s), 4.08 (2H, d, *J*=6.0 Hz), 5.35—5.85 (2H, broad s), 7.35 (2H, d, *J*=8.4 Hz), and 7.57 (2H, d, *J*=8.4 Hz); IR (KBr) 1705 and 1025 cm^{-1}. Calcd for $C_{14}H_{17}O_2ClS$: C, 59.04; H, 6.01%. Found: C, 59.24; H, 6.00%.

To a DMF solution (2 ml) of (*S*)-**10c** (87 mg, 0.31 mmol), was added NaH (60% dispersion in an oil, 15 mg, 0.37 mmol) under ice-cooling, and then the resulting mixture was stirred at room temperature for 2 h. The mixture was poured into a saturated aqueous solution (3 ml) of ammonium chloride and extracted with IPE (5 ml×3). The combined extracts were dried ($MgSO_4$), evaporated, and subjected to column chromatography on silica gel using hexane–ethyl acetate (1:1) as an eluent to give (S_s)-**12c** (56 mg: 74% yield) which was shown by HPLC analysis to consist of two diastereomers in the ratio of 52:48. An analytical sample (its diastereomeric ratio: 72:28) of (S_s)-**12c** was obtained by recrystallization from diethyl ether: colorless crystals; mp 95.5—100.5 °C; $[\alpha]_D^{20}$ −246° (*c* 0.75, $CHCl_3$). The IR and ^1H NMR of this compound was identical to those of racemic **11c**: mp 95—96 °C: ^1H NMR ($CDCl_3$) δ=2.10—3.20 (6H, m), 2.49 (3H, s), 3.72 (1H, dd, *J*=4.8 and 11.4 Hz), 5.28 (2H, broad s), 7.38 (2H, d, *J*=8.4 Hz), and 7.58 (2H, d, *J*=8.4 Hz); IR (KBr) 1705 and 1025 cm^{-1}. Calcd for $C_{14}H_{16}O_2S$: C, 67.71; H, 6.49%. Found: C, 67.74; H, 6.57%.

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12) In a separate run, the oxazolidine of optically pure (*R*)- or (*S*)-**1a** with (*R*)-**2** showed two sets of ^1H NMR signals with a relative intensity of ca. 2:1 (see Experimental section).

13) Silica gel is not suitable because it adsorbs the amino part of **3a** too tightly to cause smooth hydrolysis of **3a**. MgO was also shown not to be effective as an adsorbent for separation of **3a**.

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15) By the conventional way using sodium hydride and butyllithium as bases in THF,[11] the dianion (**8**) was also generated and subsequent treatment with **9a** (X=Br) gave the corresponding **10** in 41% yield (see Experimental section).

16) For a 75:25 diastereomeric mixture of (R_s)-**12a**, its $[\alpha]_D^{20}$ was reported to be +258° (*c* 1, $CHCl_3$).[9b]

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