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Optically Active Seleninate Esters: Isolation, Absolute Configuration, Racemization Mechanism, and Transformation into Chiral Selenoxide

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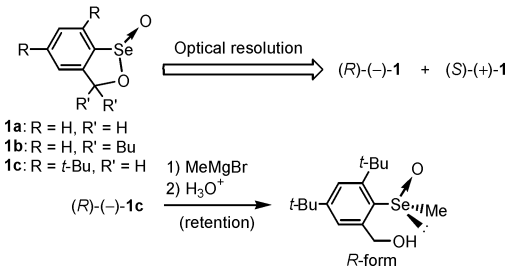

Optically active seleninate esters were obtained for the first time by chromatographic resolution on an optically active column. The absolute configurations of the optically active seleninate esters were determined by comparing their chiroptical properties with those of two analogous sulfinate esters, the absolute configuration of one of which is known and that of the other was determined by X-ray crystallographic analysis. The optically active seleninate esters were found to racemize in solution. Kinetic studies of the racemization, the oxygen exchange reaction with $H_2{}^{18}O$, and theoretical studies clarified that the racemization of the optically active seleninate esters in solution proceeded via an achiral hypervalent selenurane intermediate that was formed by the reaction with water. The reaction of the optically active seleninate ester and the sulfinate ester having bulky substituents with Grignard reagents was found to proceed with the retention of stereochemistry to give an optically active selenoxide and sulfoxides, respectively.

Introduction

Tricoordinated chalcogen compounds have pyramidal structures around the chalcogen atoms.[1,2] Therefore, chiral centers exist on the chalcogen atoms of the compounds if the substituents differ from each other. Chiral sulfur compounds have been well studied,[1] and chiral selenium and tellurium compounds, such as oxides, onium salts, ylides, and imides, have been isolated and their properties determined in the last few decades.[2] Recently, we have isolated optically active seleninic acids[3] and seleninamides,[4] and determined their properties. However, there have been no reports on chiral seleninate esters, whereas chiral sulfinate esters, such as *l*-menthyl *p*-toluenesulfinate, are well-known and utilized as precursors of chiral sulfoxides.[5,6] The reason for the lack of

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(1) For books, see: (a) Metzner, P.; Thuillier, A. *Sulfur Reagents in Organic Synthesis*; Academic Press: London, UK, 1993. (b) *The Chemistry of Sulphones and Sulphoxides*; Patai, S., Rappoport, Z., Stirling, M., Eds.; Wiley: New York, 1988. (c) *The Chemistry of the Sulphonium Group*; Stirling, C. J., Patai, S., Eds.; Wiley: New York, 1981. (d) Mikolajczyk, M.; Dorabowicz, J. *Topics in Stereochemistry*; Allinger, N., Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1982; Vol. 13, p 333.

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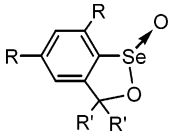
study may be that acyclic seleninate esters are unstable toward hydrolysis.[7] By contrast, cyclic seleninate esters are stable toward hydrolysis.[8]

We examined the optical resolution of cyclic seleninate esters **1** by means of liquid chromatography on an optically active column, and isolated the optically active seleninate esters for the first time. We describe herein the isolation of the optically active seleninate esters, the determination of their absolute configurations, the stability toward racemization, and the transformation into a chiral selenoxide.

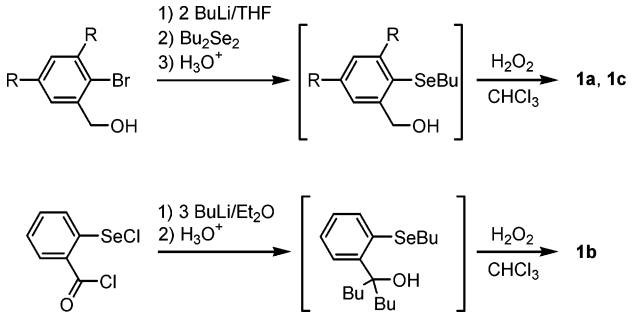


1a: R = H, R' = H
1b: R = H, R' = Bu
1c: R = *t*-Bu, R' = H

Results and Discussion

Preparation and Optical Resolution of Seleninate Esters. Seleninate esters **1a** and **1c** were prepared from bromobenzyl alcohol derivatives via selenides in yields of 59% and 46%, respectively (Scheme 1). Seleninate ester **1b** was prepared from 2-(chloroseleno)benzoyl chloride in 43% yield.

SCHEME 1



When a racemic sample of seleninate ester **1a** was subjected to HPLC on a chiral column (4.6 × 250 mm) packed with amylose carbamate derivative−silica gel at an analytical scale with 2-propanol as the eluent, two peaks corresponding to two enantiomers were observed on the chromatogram (Figure 1). That the intensity between the two peaks was not reduced to the baseline on the chromatogram is an indication that the resolution and the racemization of the seleninate ester occurred competitively in the column. In the cases of **1b** and **1c** possessing alkyl substituents at the benzyl position or the ortho position, respectively, two distinct peaks of the enantiomers were observed, showing that the racemization of the seleninate esters may be suppressed by the alkyl substituents.

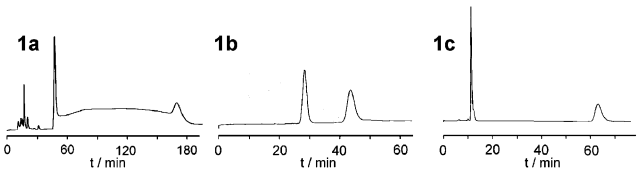


FIGURE 1. Chromatographic resolution of racemic seleninate esters **1a**−**c** on an optically active column (Daicel Chiralpak AS) by means of HPLC at an analytical scale. Eluent: 2-propanol for **1a**; hexane/2-propanol (4/1) for **1b**; hexane/2-propanol (1/1) for **1c**. Flow rate: 0.3 mL min^{-1} for **1a**; 1.0 mL min^{-1} for **1b**; 0.5 mL min^{-1} for **1c**.

The optical resolution of **1a**−**c** at a preparative scale was examined on a larger column of the same type (10 × 250 mm). In the cases of **1b** and **1c**, the first-eluted and second-eluted fractions containing the enantiomers were collected, respectively, and the enantiomeric excess of each enantiomer was determined by HPLC analysis. As a result, optically active seleninate esters (+)-**1b** {$[\alpha]^{27}_{D}$ +72 (*c* 0.016, hexane/2-propanol = 4/1); $[\alpha]^{27}_{435}$ +132 (*c* 0.016, hexane/2-propanol = 4/1)} and (−)-**1c** {$[\alpha]^{27}_{D}$ −174 (*c* 0.583, 2-propanol); $[\alpha]^{27}_{435}$ −338 (*c* 0.583, 2-propanol)} were obtained from the first-eluted fractions in 60% and 100% ee, respectively; and (−)-**1b** {$[\alpha]^{27}_{D}$ −24 (*c* 0.0085, hexane/2-propanol = 4/1); $[\alpha]^{27}_{435}$ −59 (*c* 0.0085, hexane/2-propanol = 4/1)} and (+)-**1c** {$[\alpha]^{27}_{D}$ +175 (*c* 0.437, 2-propanol); $[\alpha]^{27}_{435}$ +338 (*c* 0.437, 2-propanol)} were obtained from the second-eluted fractions in 19% and 100% ee, respectively. The enantiomers of **1c** did not racemize during the concentration of the eluates under reduced pressure, whereas those of **1b** racemized partially during the concentration. Therefore, the specific rotation of the enantiomers of **1b** was measured without concentration of the eluates. In the case of **1a**, optical resolution could not be accomplished at the preparative scale because the complete racemization of **1a** occurred until the time of the elution. Therefore, a small amount of **1a** was subjected to the chiral column for analysis (4.6 × 250 mm), and the first-eluted and second-eluted fractions containing the enantiomers were collected. The enantiomer in the first-eluted fraction showed positive optical rotation and that in the second-eluted fraction showed negative optical rotation, although the enantiomeric excesses of the enantiomers could not be determined due to the rapid racemization in solution.

Chiroptical Properties and Absolute Configurations of Optically Active Seleninate Esters. Each (+)-isomer of seleninate esters **1a** and **1b** showed three negative Cotton effects at around 270, 265, and 240 nm on the circular dichroism spectrum, and each (−)-isomer showed positive Cotton effects in the same region, as shown in Figure 2. On the other hand, optically active seleninate ester (+)-**1c** showed a negative Cotton effect at 245 nm and (−)-**1c** showed a positive Cotton effect in the same region. The Cotton effect at around 240 nm was common to the circular dichroism spectra of **1a**−**c**, although there was a slight difference in shape between the circular dichroism spectra of **1a**,**b** and that of **1c**.

The absolute configurations of the optically active seleninate esters were assigned by comparing their chiroptical properties with those of the optically active sulfinate esters of known configuration. The racemic samples of sulfinate esters **2a** and **2b** were subjected to

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(8) (a) Lindgren, B. *Chem. Scr.* **1980**, *16*, 24. (b) Kawashima, T.; Ohno, F.; Okazaki, R. *J. Am. Chem. Soc.* **1993**, *115*, 10434. (c) Back, T. G.; Moussa, Z. *J. Am. Chem. Soc.* **2003**, *125*, 13455.

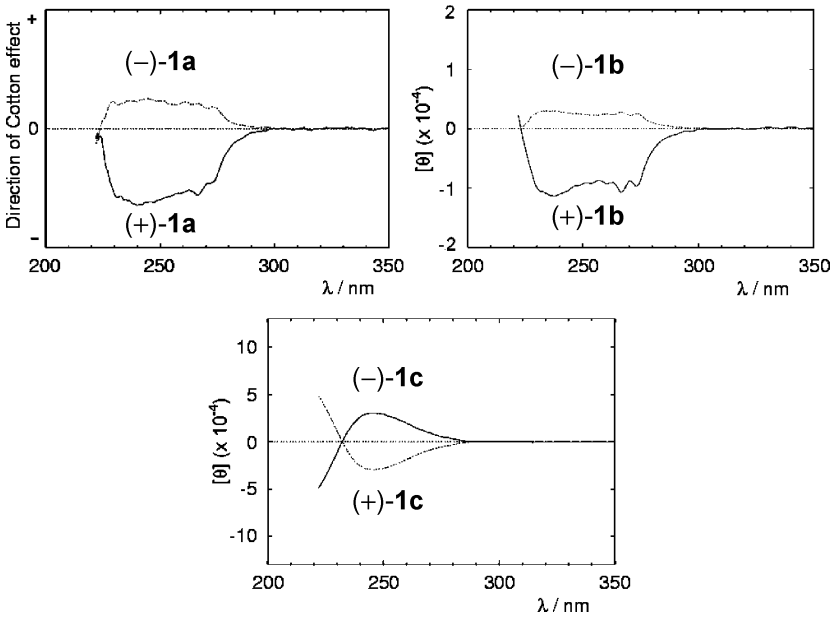


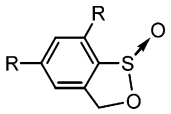
FIGURE 2. Circular dichroism spectra of optically active seleninate esters **1a**−**c**. Solvent: 2-propanol for **1a**; hexane/2-propanol (4/1) for **1b**; 2-propanol for **1c**.

TABLE 1. Chiroptical Properties and Absolute Configurations of Optically Active Seleninate Esters (1a−c) and Sulfinate Esters (2a,b)

	order of elution	ee (%)	$[\alpha]_D$	$[\alpha]_{435}$	Cotton effect/nm (sign)	abs config
1a	first		+[a]	+[a]	272 (−), 266 (−), 242 (−)[a]	*S*
	second		−[a]	−[a]	273 (+), 267 (+), 240 (+)[a]	*R*
1b	first	60	+72 (*c* 0.016)[b]	+132 (*c* 0.016)[b]	273 ([θ] −9.74 × 10^3)[b]	*S*
					266 ([θ] −1.07 × 10^4)	
					237 ([θ] −1.13 × 10^4)	
	second	19	−24 (*c* 0.0085)[b]	−59 (*c* 0.0085)[b]	274 ([θ] 2.53 × 10^3)[b]	*R*
					266 ([θ] 2.75 × 10^3)	
					237 ([θ] 2.98 × 10^3)	
1c	first	100	−174 (*c* 0.583)[a]	−338 (*c* 0.583)[a]	245 ([θ] 3.04 × 10^4)[a]	*R*
	second	100	+175 (*c* 0.473)[a]	+338 (*c* 0.473)[a]	246 ([θ] −2.99 × 10^4)[a]	*S*
2a	first	100	−230 (*c* 0.136)[a]	−441(*c* 0.136)[a]	273 ([θ] 3.58 × 10^3)[a]	*R*
					266 ([θ] 4.31 × 10^3)	
					223 ([θ] 3.50 × 10^4)	
2b	first	100	−185 (*c* 0.522)[a]	−368 (*c* 0.522)[a]	232 ([θ] 1.32 × 10^4)[a]	*R*

[a] In 2-propanol. [b] In hexane/2-propanol (4/1).

chromatography on the chiral column, and (−)-**2a** {$[\alpha]^{28}_D$ −220 (*c* 0.137, chloroform); $[\alpha]^{27}_D$ −230 (*c* 0.136, 2-propanol); $[\alpha]^{27}_{435}$ −441 (*c* 0.136, 2-propanol)} and (−)-**2b** {$[\alpha]^{28}_D$ −185 (*c* 0.522, 2-propanol); $[\alpha]^{28}_{435}$ −368 (*c* 0.522, 2-propanol)} were obtained from the first-eluted fractions in optically pure forms. The absolute configuration of (−)-**2a** was found to be *R* because Pirkle and co-workers reported that (*S*)-**2a** showed positive specific rotation in chloroform.[9] Sulfinate ester (*R*)-(−)-**2a** showed positive Cotton effects at 273, 266, and 223 nm on the circular dichroism spectrum and those Cotton effects corresponded well with those of seleninate ester (−)-**1a**. Therefore, on the basis of the similarity in chiroptical properties between (*R*)-(−)-**2a** and (−)-**1a**, the absolute configuration of optically active seleninate ester (−)-**1a** was assigned to be *R* and that of (+)-**1a** to be *S* (Table 1). Similarly, the absolute configuration of seleninate ester (−)-**1b**, the Cotton effects of which corresponded well with that of (*R*)-(−)-**2a**, was assigned to be *R*, and that of (+)-**1b** to be *S*.



2a: R = H
2b: R = *t*-Bu

On the other hand, sulfinate ester (−)-**2b** showed a positive Cotton effect at 232 nm on the circular dichroism spectrum, which corresponded well with that of seleninate ester (−)-**1c**. The absolute configuration of (−)-**2b** could be determined by X-ray crystallographic analysis, whereas the X-ray analysis of (+)-**1c** or (−)-**1c** could not be performed because they were not deposited as crystals despite a number of recrystallization attempts with various solvents. The crystal structure of (−)-**2b** showed that the absolute configuration around the sulfur atom

(9) Pirkle, W. H.; Hoekstra, S. *J. Am. Chem. Soc.* **1976**, *98*, 1832.

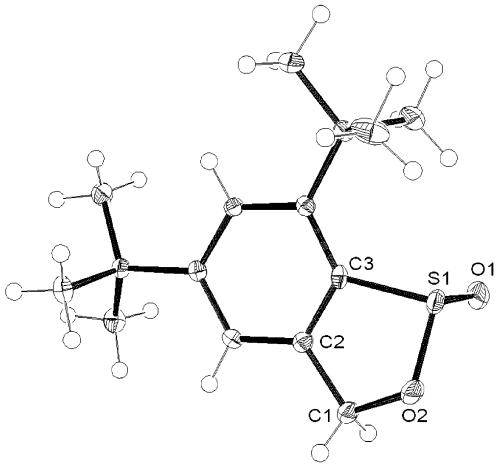


FIGURE 3. X-ray structure of (*R*)-(−)-**2b**. Selected bond lengths (Å) and bond angles (deg): S1−O1 1.472(1), S1−O2 1.6311(9), S1−C3 1.803(1), O1−S1−O2 108.52(5), O1−S1−C3 106.03(6), O2−S1−C3 91.50(5).

TABLE 2. First-Order Rate Constants and Half-Lives for Racemization of Optically Active Seleninate Esters 1a−c[a]

run	compd	solvent	$k_1 \times 10^4$ (s^{-1})	$t_{1/2}$
1	(*S*)-(+)-**1a**	2-propanol	108	1.07 min
2	(*S*)-(+)-**1b**	dichloromethane	0.0357	2.25 d
3	(*S*)-(+)-**1b**	2-propanol	1.07	107 min
4	(*S*)-(+)-**1b**	2-propanol/H_2O (4/1)	196	0.589 min
5	(*S*)-(+)-**1b**	2-propanol/D_2O (4/1)	41.8	2.76 min
6	(*R*)-(−)-**1c**	dichloromethane	A[b]	
7	(*R*)-(−)-**1c**	2-propanol	A[b]	
8	(*R*)-(−)-**1c**	2-propanol/H_2O (4/1)	A[b]	

[a] In 10^{-4}−10^{-5} M solutions at 25 ± 1 °C. [b] A: No racemization was observed after 2 days.

is *R*, as shown in Figure 3. Therefore, based on the similarity in chiroptical properties to those of (*R*)-(−)-**2b**, the absolute configuration of seleninate ester (−)-**1c** was determined to be *R* and that of (+)-**1c** to be *S*.

Stability of Optically Active Seleninate Esters. Optically active seleninate ester (*R*)-(−)-**1c** did not racemize in the solid state or in 2-propanol at room temperature. By contrast, optically active (*S*)-(+)-**1a** and (*S*)-(+)-**1b** racemized in 2-propanol at room temperature. Therefore, the kinetics for the racemization of the optically active seleninate esters was examined under various conditions to clarify the racemization mechanism. The racemization of (*S*)-(+)-**1a** and (*S*)-(+)-**1b** showed a good linear relationship with first-order rate plots in all cases. The first-order rate constants and the half-lives for the racemization of the seleninate esters are summarized in Table 2.

Nonsubstituted seleninate ester (*S*)-(+)-**1a** racemized most rapidly among optically active seleninate esters **1a−c** in 2-propanol (runs 1, 3, and 7). In the case of (*S*)-(+)-**1b**, the rate constant in 2-propanol (1.07×10^{-4} s^{-1}) is much larger than that in dichloromethane (3.57×10^{-6} s^{-1}), which is a hydrophobic solvent, and is much smaller than that in 2-propanol containing water (1.96×10^{-2} s^{-1}), indicating that a small amount of water remaining in the solvents may cause the racemization of the optically active seleninate esters (runs 2−4). Two possible mechanisms involving water are proposed for the racemization. One involves the formation of achiral selenurane **A** (Scheme 2, path a), and the other involves the formation of seleninic acid **B** that racemizes rapidly in solution[3] (path b). The rate constant for the racemization of (*S*)-(+)-**1b** in 2-propanol/H_2O (4/1) is approximately 5 times as large as that in 2-propanol/D_2O (4/1) (runs 4 and 5), showing that there is a primary kinetic isotope effect in the racemization and the rate-controlling step is the protonation of seleninate esters by water. The atomic charge (−0.614) on the oxygen atom of the Se=O moiety of **1a** estimated by MO calculations (MP2/6-31+(d)) is smaller than that (−0.416) on the oxygen atom of the Se−OCH_2 moiety, indicating that protonation to the oxygen atom of the Se=O is preferable. If the racemization were to proceed via path a, the racemization would be suppressed by disturbing the access of the water to the oxygen atom of the Se=O moiety. In fact, seleninate ester (*R*)-(−)-**1c** having a bulky substituent at the ortho position was stable toward racemization even in the presence of water (run 8). These results indicate that the racemization proceeds via path a, not path b.

The ^1H NMR spectrum of **1a** was measured in CD_3OD containing D_2O (100 equiv) to confirm the formation of selenurane **A**. However, only the signals of **1a** were observed. Thus, the oxygen exchange reaction was examined by using $H_2{}^{18}O$ to check whether selenurane **A** is formed in the presence of water. When seleninate ester **1b** was dissolved in 2-propanol/$H_2{}^{18}O$ (4/1, 95 atom %^{18}O) and allowed to stand for 2 h, an ion peak corresponding to **1b**, one oxygen atom of which was substituted by an ^{18}O atom, was observed on the MS spectrum, indicating that addition and elimination of water via selenurane **A** occurred.

Vertex inversion is also a first-order racemization mechanism of tricoordinated optically active chalcogen compounds.[10] However, the activation energy for the vertex inversion of **1a** was estimated to be 79 kcal mol^{-1} by MO calculations (MP2/6-31+(d)), which is too high for the racemization to occur at room temperature.

Therefore, the racemization of the optically active seleninate esters is concluded to proceed via an achiral hypervalent selenurane that is formed by the addition of water to seleninate ester (Scheme 2, path a).

In the case of optically active seleninate ester (*R*)-(−)-**1c**, a decrease of the ellipticity at around 245 nm on the circular dichroism spectrum was observed in 2-propanol/HCl(aq) or 2-propanol/NaOH(aq) (Table 3), whereas

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SCHEME 2. Possible Racemization Mechanisms of Optically Active Seleninate Esters

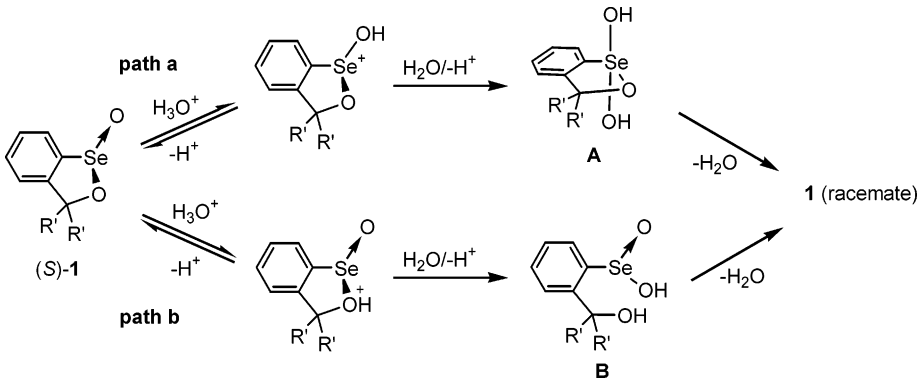
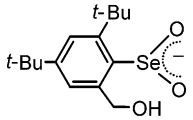


TABLE 3. First-Order Rate Constants and Half-Lives for Racemization or Decomposition of Optically Active Seleninate Ester (*R*)-(−)-1c under Acidic or Basic Conditions[a]

solvent	$k_1 \times 10^5$ (s^{-1})	$t_{1/2}$ (min)
2-propanol/0.1 M HCl (4/1)	9.64	120
2-propanol/1 M HCl (4/1)	A[b]	
2-propanol/0.1 M NaOH(aq) (4/1)	1130	1.02

[a] In 4×10^{-5} M at 28 °C. [b] A: Complete racemization occurred within 1 min.

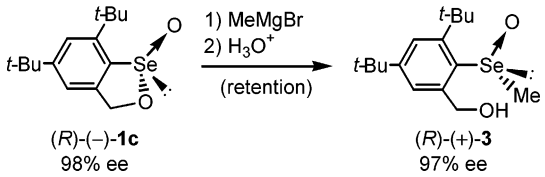
no racemization occurred in the presence of neutral water, as stated above. ^{1}H NMR studies of **1c** were performed in CD_3OD containing 1 M HCl (2 equiv) or 0.1 M NaOH(aq) (1.7 equiv) to check whether each reaction is racemization or decomposition. Under acidic conditions, only the signals of **1c** were observed, indicating that the decrease of the ellipticity is due to the racemization of (*R*)-(−)-**1c**. Under basic conditions, the signals of **1c** were not observed at all, and only a set of signals of a decomposed compound was observed. Moreover, the unequivalent signals of the benzylic protons {5.6 (1H, d) and 5.8 (1H, d) ppm} of **1c** become equivalent {5.3 (2H, s) ppm}. Seleninate ester **1c** was regenerated together with the disappearance of the decomposed compound by neutralizing the solution with hydrochloric acid. These results indicate that **1c** is decomposed to seleninate anion **C** via the attack of the hydroxide anion on the selenium atom under basic conditions and the decrease of the ellipticity is due to the decomposition of (*R*)-(−)-**1c**.



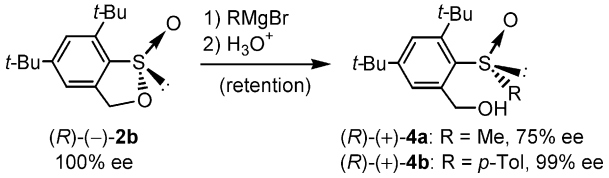
C

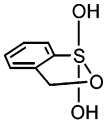
Optically active sulfinate ester (*R*)-(−)-**2a** was stable toward racemization in the solid state or in 2-propanol/H_2O (4/1) at room temperature, whereas corresponding seleninate ester (*S*)-(+)-**1a** was very unstable toward racemization in solution. The difference in stability between the optically active sulfinate ester and the seleninate ester is explained by the ability to form the hypervalent chalcogenurane, which is the intermediate for the racemization. The energy difference from **2a** and water to hypervalent sulfurane **D** was estimated to be 40.4 kcal mol^{-1} by MO calculations (MP2/6-31+(d)), whereas that from **1a** to selenurane **A** was 16.7 kcal mol^{-1}. These results show that the seleninate ester forms an achiral selenurane more readily and is more unstable toward racemization than the sulfinate ester.

SCHEME 3



SCHEME 4



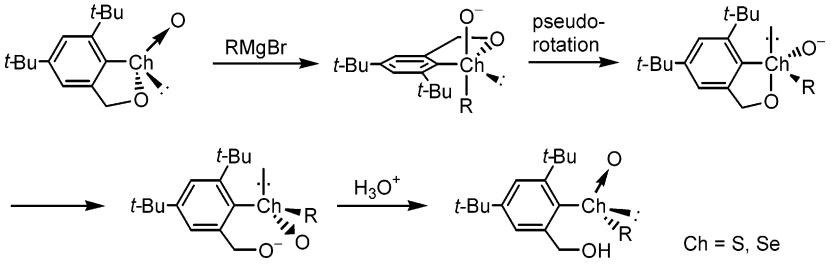


D

Transformation of Optically Active Seleninate Ester into Optically Active Selenoxide. It is well-known that the reaction of sulfinate esters with Grignard or organolithium reagents gives optically active sulfoxides with inversion of the stereochemistry.[5,6] However, there is no study concerning the stereochemistry on the reaction of seleninate esters with organometallic reagents. Therefore, the reaction of optically active seleninate ester **1c** with methylmagnesium bromide was attempted. As a result, 97% ee of selenoxide (+)-**3** was obtained from 98% ee of (*R*)-(−)-**1c** (Scheme 3), and recrystallization afforded optically pure (+)-**3** {$[\alpha]^{29}_D$ +15 (*c* 0.052, 2-propanol), $[\alpha]^{29}_{435}$ +39 (*c* 0.052, 2-propanol)}. Pirkle and co-workers reported that (*R*)-2-(hydroxymethyl)phenyl methyl sulfoxide showed positive optical rotation.[9] Thus, the absolute configuration of selenoxide (+)-**3** was determined to be *R*. This result indicates that the reaction proceeded with retention of the configuration.

The reaction of optically active sulfinate ester (*R*)-(−)-**2b** with Grignard reagents was also examined to check whether the stereochemistry is a property specific to the seleninate ester. As a result, 75% ee of sulfoxide (+)-**4a**

SCHEME 5. Plausible Mechanism of the Reaction of Chalcogeninate Esters Having Bulky Substituents with Grignard Reagents



and 99% ee of sulfoxide (+)-**4b** were obtained by the reaction of optically pure (*R*)-(−)-**2b** with methylmagnesium bromide and *p*-tolylmagnesium bromide in yields of 28% and 44%, respectively (Scheme 4). The absolute configuration of (+)-**4a** was determined to be *R* in a manner similar to (*R*)-(+)-**3**, and that of (+)-**4b** was determined to be *R* because (*S*)-**4b**, which was prepared by the reaction of (*S*)-*l*-menthyl *p*-toluenesulfinate with an organolithium reagent with inversion of stereochemistry, showed negative specific rotation. Thus, the reaction of sulfinate ester (*R*)-(−)-**2b** with Grignard reagents was found to proceed with retention of the configuration. Taken together, the stereochemistry of the reaction is not a property peculiar to seleninate esters but is due to the prevention of the attack of Grignard reagents on the chalcogen atom from the backside of the Ch-OCH_2 bond by the bulky *tert*-butyl group at the ortho position. The reaction probably proceeded via the pseudorotation of a chalcogenurane (Scheme 5).

Conclusion

The isolation of optically active seleninate esters was accomplished for the first time by chromatographic resolution on an optically active column and their absolute configurations were determined. It was found that the optically active seleninate esters racemize in solution and the racemization could be suppressed by bulky substituents. Kinetic studies of the racemization, the oxygen exchange reaction with $H_2{}^{18}O$, and theoretical studies clarified that the racemization of the optically active seleninate esters proceeds via an achiral hypervalent selenurane intermediate that is formed by the reaction with a small amount of water in the solvents. The difference in stability between the optically active sulfinate esters and the seleninate esters is due to the ability to form the hypervalent chalcogenurane. The stereospecific transformation from optically active seleninate and sulfinate esters with steric restriction into chiral chalcogen oxides was accomplished, and the reactions were found to proceed with retention of the stereochemistry, different from those of acyclic chalcogeninates.

Experimental Section

General. Tetrahydrofuran (THF) and ether were distilled from sodium benzophenone ketyl before use. Dichloromethane, hexane, and 2-propanol were distilled from CaH_2 before use.

General Procedure for the Preparation of Seleninate Esters 1a and 1c. To a THF (5 mL) solution of bromobenzyl alcohol derivative (5.00 mmol) was slowly added butyllithium (11.2 mmol) at −78 °C, then the solution was stirred for 40 min until it reached −10 °C. A THF (5 mL) solution of dibutyl diselenide[11] was added to the mixture, which was then stirred for 40 h at room temperature. HCl (1 M, 5 mL) was added to the mixture and the organic components were extracted with ether (3 × 40 mL), washed with brine (50 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (hexane/ethyl acetate) afforded the crude selenide. To a chloroform (20 mL) solution of the selenide was added 30% hydrogen peroxide (1.13 mL, 11.0 mmol), and the mixture was stirred vigorously for 16 h at room temperature. The organic layer of the mixture was dried over anhydrous sodium sulfate. Removal of the solvent and purification of the residue by silica gel column chromatography (hexane/ethyl acetate) afforded the products.

3*H*-2,1-Benzoxaselenole 1-Oxide (1a). Yield 59%; mp 133−135 °C (colorless needles from chloroform/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 (1H, d, J = 13.8 Hz), 5.95 (1H, d, J = 13.8 Hz), 7.45−7.48 (2H, m), 7.57 (1H, t, J = 7.64 Hz), 7.88 (1H, d, J = 7.64 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 78.1, 122.5, 125.6, 128.9, 131.8, 143.3, 147.9; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 1345; MS (EI, 30 eV) *m/z* 202 (M^+, ^{80}Se), 200 (M^+, ^{78}Se), 186 ($M^+ - O$, ^{80}Se), 184 ($M^+ - O$, ^{78}Se), 157, 106, 78; IR (KBr) 3078, 2859, 1435, 1200, 976, 861 (Se=O), 838, 773, 555 cm^{-1}; UV (2-propanol) λ_{max} 263 (ϵ 1.38 × 10^3), 220 (sh, ϵ 9.25 × 10^3), 200 (ϵ 1.99 × 10^4) nm; Anal. Calcd for $C_7H_6O_2Se$: C, 41.81; H, 3.01. Found: C, 41.64; H, 3.01.

5,7-Di-*tert*-butyl-3*H*-2,1-benzoxaselenole 1-Oxide (1c). Yield 46%; mp 118−119 °C (colorless powder); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (9H, s), 1.51 (9H, s), 5.55 (1H, d, J = 13.7 Hz), 5.94 (1H, d, J = 13.7 Hz), 7.31 (1H, s), 7.50 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.1, 32.5, 35.1, 36.8, 77.4, 117.0, 124.4, 143.8, 144.1, 149.6, 155.6; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 1347; MS (EI, 30 eV) *m/z* 298 ($M^+ - O$, ^{80}Se), 296 ($M^+ - O$, ^{78}Se), 282, 280, 203; IR (KBr) 2955, 1589, 1482, 1397, 1366, 988, 877 (Se=O), 594 cm^{-1}; UV (2-propanol) λ_{max} 267 (sh, ϵ 1.16 × 10^3), 227 (sh, ϵ 8.82 × 10^3), 201 (ϵ 4.05 × 10^4) nm; UV (dichloromethane) λ_{max} 264 (sh, ϵ 1.36 × 10^3), 226 (ϵ 1.36 × 10^3) nm. Anal. Calcd for $C_{15}H_{22}O_2Se$: C, 57.51; H, 7.08. Found: C, 57.47; H, 6.80.

3,3-Dibutyl-3*H*-2,1-benzoxaselenole 1-Oxide (1b). To an ether (30 mL) solution of 2-(chloroseleno)benzoyl chloride[12] (1.27 g, 5.00 mmol) was slowly added butyllithium (16.0 mmol) at −20 °C, then the mixture was stirred for 3.5 h until it reached room temperature. HCl (1 M, 15 mL) and brine (15 mL) were added to the mixture, and the organic components in the mixture were extracted with dichloromethane (3 × 30 mL), washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. To a chloroform (30 mL) solution of the residue was added 30% hydrogen peroxide (1.03 mL, 10.0 mmol) and the mixture was stirred vigorously for 16 h at room temperature. The organic layer of the mixture was dried over anhydrous magnesium sulfate. Removal of the solvent and purification of the residue by silica gel column chromatography (hexane/ethyl acetate)

(11) Syper, L.; Mlochowski, J. *Synthesis* **1984**, 439.
(12) Kamigata, N.; Iizuka, H.; Izuoka, A.; Kobayashi, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2179.

afforded the products (669 mg). Yield 43%; mp 38−39 °C (colorless needles from hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.71 (1H, m), 0.80 (3H, t, J = 7.18 Hz), 0.84 (3H, t, J = 7.48 Hz), 1.07 (1H, m), 1.10−1.33 (5H, m), 1.49 (1H, m), 1.79 (1H, td, J = 12.8, 4.45 Hz), 1.94 (2H, t, J = 8.23 Hz), 2.05 (1H, td, J = 13.0, 4.45 Hz), 7.22 (1H, d, J = 7.60 Hz), 7.51 (1H, dd, J = 7.60, 7.36 Hz), 7.59 (1H, d, J = 7.60, 7.36 Hz), 7.73 (1H, d, J = 7.60 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 13.9, 22.6, 22.7, 25.5, 25.8, 40.8, 42.8, 101.0, 123.8, 125.2, 129.2, 132.1, 147.9, 148.2; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 1323; MS (EI, 30 eV) m/z 314 (M^+, ^{80}Se), 312 (M^+, ^{78}Se), 298, 296, 280, 278, 257, 255, 241, 209; MS (FAB) m/z 315 ($M^+ + 1$, ^{80}Se), 313 ($M^+ + 1$, ^{78}Se); IR (KBr) 2956, 1464, 852 (Se=O), 666 cm^{-1}; UV (2-propanol) λ_{max} 264 (ϵ 8.15 × 10^2), 201 (ϵ 1.54 × 10^4) nm; UV (hexane/2-propanol = 4/1) λ_{max} 265 (ϵ 1.25 × 10^3), 257 (ϵ 1.26 × 10^3), 200 (ϵ 2.23 × 10^4) nm; UV (dichloromethane) λ_{max} 265 (ϵ 1.25 × 10^3), 225 (ϵ 3.04 × 10^3) nm. Anal. Calcd for $C_{15}H_{22}O_2Se$: C, 57.51; H, 7.08. Found: C, 57.02; H, 6.77.

Optical Resolution of Seleninate Esters 1b and 1c. A racemic sample of **1b** or **1c** (10−20 mg) in eluent (0.5 mL) was charged to a chiral column packed with amylase carbamate derivative−silica gel (Daicel Chiralpak AS; 10 × 250 mm) and eluted with hexane containing 20 (for **1b**) or 50 (for **1c**) vol % of 2-propanol at a flow rate of 1.5 mL min^{-1}. The eluates containing about 3−9 mg of optically active seleninate esters were collected from the first eluted portions and second portions, respectively. In the case of **1b**, the optical rotations and the circular dichroism spectra were measured in the eluates because concentration of the eluates caused racemization. The chemical structures of **1b** and **1c** were confirmed by ^{1}H NMR spectra after concentration.

Compound (*R*)-(−)-1c. 100% ee; mp 84−86 °C; $[\alpha]^{27}_D$ −174 (c 0.583, 2-propanol); $[\alpha]^{27}_{435}$ −338 (c 0.583, 2-propanol); CD (2-propanol) 245 ($[\theta]$ 3.04 × 10^4) nm. ^{1}H and ^{13}C NMR spectra were almost the same as those of the racemic sample.

Compound (*S*)-(+)-1c. 100% ee; mp 84−86 °C; $[\alpha]^{27}_D$ +175 (c 0.473, 2-propanol); $[\alpha]^{27}_{435}$ +338 (c 0.473, 2-propanol); CD (2-propanol) 246 ($[\theta]$ −2.99 × 10^4) nm. ^{1}H and ^{13}C NMR spectra were almost the same as those of the racemic sample.

3*H*-2,1-Benzoxathiole 1-Oxide (2a).[9] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57 (1H, d, J = 13.4 Hz), 6.00 (1H, d, J = 13.4 Hz), 7.49 (1H, d, J = 7.60 Hz), 7.53 (1H, t, J = 7.60 Hz), 7.60 (1H, t, J = 7.60 Hz), 7.78 (1H, d, J = 7.60 Hz); UV (2-propanol) λ_{max} 265 (ϵ 5.24 × 10^2), 214 (sh, ϵ 7.44 × 10^3), 200 (ϵ 1.06 × 10^4) nm.

5,7-Di-*tert*-butyl-3*H*-2,1-benzoxathiole 1-Oxide (2b). To a THF (5 mL) solution of 2-bromo-3,5-di-*tert*-butylbenzyl alcohol[13] (916 mg, 3.06 mmol) was slowly added butyllithium (6.3 mmol) at −78 °C, and the solution was stirred for 1.5 h until it reached −10 °C, then the mixture was cooled to −60 °C. To the mixture was added THF (15 mL), then the solution was bubbled with sulfur dioxide and quenched by 1 M HCl (10 mL), and the organic components were extracted with ether (3 × 40 mL), washed with brine (20 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was washed with hexane and dissolved in THF (5 mL) containing concentrated hydrochloric acid (3 mL), and the solution was stirred for 2 days at room temperature. The solution was neutralized by saturated sodium hydrocarbonate solution, and the organic components were extracted with dichloromethane (20 mL × 3), washed with brine (20 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (hexane/ethyl acetate) afforded **2b**. Yield 58%; mp 98−99 °C (colorless prisms from hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (9H, s), 1.53 (9H, s), 5.45 (1H, d, J = 13.4 Hz), 5.95 (1H, d, J = 13.4 Hz), 7.30 (1H, s), 7.48 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.3, 32.3, 35.3, 36.9, 77.0, 116.1, 124.2, 138.8, 143.6, 147.8, 155.5; MS (EI, 30 eV) m/z 266 (M^+), 250 ($M^+ - O$), 233, 203, 161; IR (KBr) 2955, 1596, 1482, 1397, 1366, 1230, 1202, 1118 (S=O), 964, 946, 901, 880, 722, 681 cm^{-1}; UV (2-propanol) λ_{max} 270 (ϵ 4.65 × 10^2), 221 (sh, ϵ 8.47 × 10^3), 202 (ϵ 2.54 × 10^4) nm. Anal. Calcd for $C_{15}H_{22}O_2S$: C, 67.63; H, 8.32. Found: C, 67.54; H, 8.10.

Optical Resolution of Sulfinate Esters 2a and 2b. A racemic sample of **2a** or **2b** (15−20 mg) in eluent (0.5 mL) was charged to a chiral column packed with amylase carbamate derivative−silica gel (Daicel Chiralpak AS; 10 × 250 mm) and eluted with hexane containing 25 vol % of 2-propanol at a flow rate of 1.5 mL min^{-1}. The eluates containing about 7−10 mg of optically active sulfinate esters were collected from the first eluted portions.

Compound (*R*)-(−)-2a. 100% ee; colorless oil; $[\alpha]^{28}_D$ −220 (c 0.137, chloroform); $[\alpha]^{27}_D$ −230 (c 0.136, 2-propanol); $[\alpha]^{27}_{435}$ −441 (c 0.136, 2-propanol); CD (2-propanol) 273 ($[\theta]$ 3.58 × 10^3), 266 ($[\theta]$ 4.31 × 10^3), 223 ($[\theta]$ 3.50 × 10^4) nm. The ^{1}H NMR spectrum was almost the same as that of the racemic sample.

Compound (*R*)-(−)-2b. 100% ee; mp 116−118 °C (colorless prisms from 2-propanol); $[\alpha]^{28}_D$ −185 (c 0.522, 2-propanol); $[\alpha]^{28}_{435}$ −368 (c 0.522, 2-propanol); CD (2-propanol) 232 ($[\theta]$ 1.32 × 10^4) nm. The ^{1}H NMR spectrum was almost the same as that of the racemic sample.

X-ray Crystallographic Analysis of (*R*)-(−)-2b. Crystal data for (*R*)-(−)-**2b**: $C_{15}H_{22}O_2S$, M_r = 266.40; orthorhombic, space group $P2_12_12_1$, a = 9.566(2) Å, b = 10.902(3) Å, c = 14.003(4) Å, V = 1460.3(7) Å^3, Z = 4, T = 103 K, D_c = 1.212 gcm^{-3}, μ = 2.14 cm^{-1}, Mo $K\alpha$ 0.71075 Å. A prismatic crystal with dimensions of 0.38 × 0.24 × 0.12 mm^3 was used for the data collection. Of the 14388 reflections that were collected, 3305 were unique (R_{int} = 0.026). An empirical absorption correction was applied that resulted in transmission factors ranging from 0.88 to 1.00. The data were corrected for Lorentz and polarization effects. Final refinement with 252 parameters against 3305 reflections gave R = 0.026, $R_1(I > 2\sigma(I))$ = 0.024, wR = 0.0059, and $\Delta\rho_{min}$ = −0.33, $\Delta\rho_{max}$ = 0.40 eÅ^{-3}. The flack absolute structure parameter was −0.01(5).

Kinetic Studies on Racemization of Optically Active Seleninate Esters. Kinetic studies of optically active seleninate esters were examined in 10^{-4}−10^{-5} M solutions. The rates of racemization were calculated on the basis of their circular dichroism spectra and were plotted to the first-order rate equation.

General Procedure for Reaction of 1c with Methylmagnesium Bromide. To a THF (2 mL) solution of **1c** (0.1 mmol) was slowly added methylmagnesium bromide (0.1 mmol) at −50 °C, and the mixture was stirred for 15 min. Brine (5 mL) was added to the mixture, and the organic components were extracted with dichloromethane (15 mL × 3), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Recrystallization of the residue by dichloromethane/hexane afforded the products.

4,6-Di-*tert*-butyl-2-hydroxymethylphenyl Methyl Selenoxide (3, racemate). Yield 30%; mp 132 °C (colorless powder from dichloromethane/hexane; dec); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (9H, s), 1.50 (9H, s), 2.94 (3H, s), 4.48 (1H, dd, J = 10.4, 12.5 Hz), 5.40 (1H, dd, 4.30, 12.5 Hz), 6.39 (1H, dd, 4.30, 10.5 Hz), 7.39 (1H, s), 7.46 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.0, 32.8, 34.3, 34.9, 37.2, 64.8, 123.6, 129.5, 137.9, 145.3, 150.5, 154.6; ^{77}Se NMR (95 MHz, $CDCl_3$) δ 860; MS (EI, 30 eV) m/z 314 ($M^+ - O$, ^{80}Se), 312 ($M^+ - O$, ^{78}Se), 298, 296, 280, 266, 203, 119; IR (KBr) 3221 (OH), 2962, 1070, 808 (Se=O), 792 cm^{-1}; UV (2-propanol) λ_{max} 256 (sh, ϵ 3.08 × 10^3), 229 (sh, ϵ 9.70 × 10^3), 202 (ϵ 3.09 × 10^4) nm. Anal. Calcd for $C_{16}H_{26}O_2Se$: C, 58.35; H, 7.96. Found: C, 58.07; H, 7.72.

Compound (*R*)-(+)-3. Yield 6%; 100% ee; mp 130 °C (colorless powder from dichloromethane/hexane; dec); $[\alpha]^{29}_D$ +15 (c 0.052, 2-propanol); $[\alpha]^{29}_{435}$ +39 (c 0.052, 2-propanol); CD (2-propanol) 260 ($[\theta]$ 2.68 × 10^4), 231 ($[\theta]$ −3.80 × 10^4) nm. The ^{1}H NMR spectrum was almost the same as that of the racemic sample.

(13) Kimura, S.; Bill, E.; Weyhermüller, T.; Wieghardt, K. *J. Am. Chem. Soc.* **2001**, *123*, 6025.

General Procedure for Reaction of 2b with Grignard Reagents. To a THF (1 mL) solution of **2b** (0.1 mmol) was slowly added Grignard reagents (1 mmol) at 0 °C. After the mixture was stirred for 4 h, saturated ammonium chloride solution (5 mL) was added to the mixture, and the organic components were extracted with dichloromethane (3 × 5 mL), washed with brine (10 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (hexane/ethyl acetate) and/or GPC afforded the products.

4,6-Di-*tert*-butyl-2-hydroxymethylphenyl Methyl Sulfoxide (4a, racemate). Yield 32%; mp 152−153 °C (colorless prisms from chloroform/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (9H, s), 1.50 (9H, s), 3.03 (3H, s), 4.49 (1H, dd, J = 11.2, 12.5 Hz), 4.95 (1H, dd, J = 3.90, 11.2 Hz), 5.54 (1H, dd, J = 3.90, 12.5 Hz), 7.37 (1H, s), 7.46 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.1, 32.8, 35.2, 37.3, 40.1, 64.4, 123.8, 129.5, 139.2, 143.4, 149.3, 154.6; MS (EI, 30 eV) *m/z* 266 (M^+ − O), 264, 248, 218, 175; IR (KBr) 3402 (OH), 2964, 1044, 1025 (S=O), 948, 881 cm^{-1}; UV (2-propanol) λ_{max} 266 (ϵ 2.11 × 10^3), 226 (sh, ϵ 9.37 × 10^3), 201 (ϵ 3.13 × 10^4) nm. Anal. Calcd for $C_{16}H_{26}O_2S$: C, 68.04; H, 9.28. Found: C, 67.44; H, 8.74.

Compound (*R*)-(+)-4a. Yield 28%; 75% ee; mp 110−121 °C (colorless powder); $[\alpha]^{28}_D$ +88.1 (*c* 0.110, 2-propanol); $[\alpha]^{28}_{435}$ +248 (*c* 0.110, 2-propanol); CD (2-propanol) 263 ([θ] 3.33 × 10^4), 229 ([θ] −3.19 × 10^4) nm. The ^{1}H NMR spectrum was almost the same as that of the racemic sample.

4,6-Di-*tert*-butyl-2-hydroxymethylphenyl 4-Methylphenyl Sulfoxide (4b, racemate). Yield 42%; mp 180 °C (colorless powder; dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (9H, s), 1.60 (9H, s), 2.38 (3H, s), 3.99 (1H, dd, J = 11.2, 12.7 Hz), 4.65 (1H, dd, J = 3.32, 12.7 Hz), 4.97 (1H, dd, J = 3.32, 11.2 Hz), 7.24 (2H, d, J = 8.54 Hz), 7.29 (2H, d, J = 8.54 Hz), 7.34 (1H, s), 7.55 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 31.1, 33.3, 35.3, 37.4, 64.1, 123.2, 125.3, 129.5, 129.6, 138.2, 140.2, 140.9, 144.8, 152.0, 155.6; MS (EI, 30 eV) *m/z* 342 (M^+ − O), 340, 325, 309, 105; IR (KBr) 3386 (OH), 2962, 1030 (S=O), 972, 814 cm^{-1}. Anal. Calcd for $C_{22}H_{30}O_2S$: C, 73.70; H, 8.43. Found: C, 73.79; H, 8.39.

Compound (*R*)-(+)-4b. Yield 44%; 99% ee; mp 149 °C (colorless powder; dec); $[\alpha]^{27}_D$ +124 (*c* 0.369, 2-propanol); $[\alpha]^{27}_{435}$ +358 (*c* 0.369, 2-propanol). ^{1}H and ^{13}C NMR spectra were almost the same as those of the racemic sample.

Compound (*S*)-(−)-4b. To a THF (2 mL) solution of 2-bromo-3,5-di-*tert*-butylbenzyl alcohol (155 mg, 0.500 mmol) was slowly added butyllithium (1.1 mmol) at −78 °C, then the solution was allowed to warm to 0 °C during stirring, and the mixture was cooled again to −60 °C. To the mixture was added a THF (2 mL) solution of (*S*)-*l*-menthyl *p*-toluenesulfinate (147 mg, 0.500 mmol),[14] and the solution was stirred for 1.5 h until it reached room temperature. To the solution was added saturated ammonium chloride solution (5 mL), and the organic components were extracted with ethyl acetate (10 mL × 3), washed with brine (20 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification of the residue afforded (*S*)-(−)-**4b** (63 mg). Yield 35%; 88% ee; mp 144 °C (colorless powder; dec); $[\alpha]^{27}_D$ −116 (*c* 0.344, 2-propanol); $[\alpha]^{27}_{435}$ −290 (*c* 0.344, 2-propanol). ^{1}H and ^{13}C NMR spectra were almost the same as those of the racemic sample.

Oxygen Exchange Reaction of 1b with $H_2{}^{18}O$. To a 2-propanol solution (160 μl) of **1b** (3.1 mg, 10 μmol) was added $H_2{}^{18}O$ (95 atom %^{18}O, 40 mg, 200 equiv), and the solution was allowed to stand for 2 h. The solvent was removed under reduced pressure, and the residue was dissolved in *m*-nitrobenzyl alcohol. Then, the MS (FAB) spectrum was measured. The ratio of the seleninate ester containing ^{18}O was determined to be 37% based on the peak intensities on the MS spectrum. The ratio is rather lower than the theoretical value (95%). The reason is probably that the oxygen exchange reaction of **1b** with water in air or in the solvent occurred during preparation of the sample.

Theoretical Study. Geometries were optimized with use of the MP2[15] method with the 6-31+(d) basis set. All calculations were performed by using the Gaussian98[16] program. The energies are corrected for zero-point vibrational energies, using a scaling factor of 0.9670[17] at the standard state (298.15 K, 1 atm). Vibrational frequency analysis of the geometry of the transition state of vertex inversion of **1a** showed one imaginary frequency that corresponds to the vertex inversion mode, clearly indicating the real saddle-point in the reaction pathway.

Supporting Information Available: X-ray crystallographic data (CIF format) and Cartesian coordinates and computed total energies and complete ref 16. This material is available free of charge via the Internet at http://pubs.acs.org.

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