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Enantiomeric purity enrichment of (*R*)-tetrahydrothiophene-3-ol sulfonyl derivatives by crystallization

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ABSTRACT

(*R*)-Tetrahydrothiophene-3-ol sulfonyl derivatives **3**–**19** were prepared by introduction of various sulfonyl groups at the hydroxyl group of (*R*)-tetrahydrothiophene-3-ol **1** with low enantiomeric purity (68–74% ee). Crystallization was applied to improve their enantiomeric purity. Improvement in enantiomeric purity depended on the introduced sulfonyl group. The enantiomeric purity of enantiomeric sulfonyl derivatives was improved to more than 90% ee by simple crystallization without using seed crystals. These products from crystallization provided not only higher %ee crystals but also a higher %ee mother liquor. The enantiomeric purity of diastereomeric sulfonyl derivatives was improved remarkably, and the product of the derivative **18** provided the mother liquor with 100% de. Crystallization of these sulfonyl derivatives showed a novel and interesting feature that mother liquors with high enantiomeric purity were obtained in many cases.

1. Introduction

(*R*)-Tetrahydrothiophene-3-ol **1** and its sulfonyl derivatives are useful key intermediates in the synthesis of penem-based antibiotics.[1] We previously reported on bioconversion, which involves an enantioselective reduction from tetrahydrothiophene-3-one **2** to (*R*)-**1** and development of a crystallization process which leads to (*R*)-**1** with high enantiomeric purity (99% ee).[2] The enantiomeric purity of (*R*)-**1** was improved by simple cooling and crystallization from organic solvents. However, (*R*)-**1** is a viscous liquid at room temperature, which needs crystallization equipment that is not common for scale-up. Therefore, in order to obtain crystals at room temperature, we prepared derivatives by the introduction of various sulfonyl groups at the hydroxyl group of the (*R*)-**1** (Fig. 1), which makes the crystallization easy to scale-up at room temperature. In addition, the derivatives are expected to show the same features as (*R*)-**1**, which improve their enantiomeric purity by crystallization.

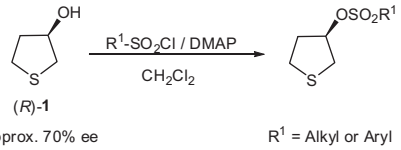

Figure 1. General method for preparing various sulfonyl derivatives from (*R*)-**1**.

On the other hand, resolution by crystallization is generally classified into preferential crystallization,[3] fractional crystallization via diastereomeric formation,[4] diastereoselective host–guest inclusion complexation,[5] and preferential enrichment.[6] Resolution via diastereomeric formation has a wide range of applications, and is widely known as the most effective method. Preferential crystallization is a resolution method which utilized spontaneous crystallization from a conglomerate, and has the feature that crystals with high enantiomeric purity are crystallized preferentially. Thus, in spite of this effective method, the target conglomerates are estimated to be less than 10% of all racemates. In contrast, preferential enrichment shows an opposite phenomenon as compared with preferential crystallization. However few papers have reported that the mother liquor is obtained with high enantiomeric purity by crystallization.

Herein we report the preparation of various sulfonyl derivatives from (*R*)-**1** with low enantiomeric purity, and the enantiomeric purity enrichment by the crystallization using these derivatives. These derivatives led to an improvement in enantiomeric purity due to the introduction of the sulfonyl group. In many cases, the phenomenon of enantiomeric purity enrichment showed the interesting feature that mother liquors with high enantiomeric purity were obtained with similar preferential enrichment.[6]

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2. Results and discussion

2.1. Preparation of sulfonyl derivatives

Optically active (*R*)-**1** (68–74% ee) was prepared as the initial starting material via biocatalytic reduction of **2** (Fig. 2).[2] For evaluation of the enantiomeric purity by HPLC analysis, racemic **1** was also prepared by a reductive reaction, which used the borane tetrahydrofuran complex solution (BH_3·THF). The preparation of various sulfonyl derivatives from (*R*)-**1** was performed by the general method shown in Figure 1 whereby the substrate, sulfonyl chloride and 4-(dimethylamino)pyridine (DMAP) reacted in dichloromethane (CH_2Cl_2). The sulfonyl derivatives **3**–**19** prepared are shown in Figure 3.

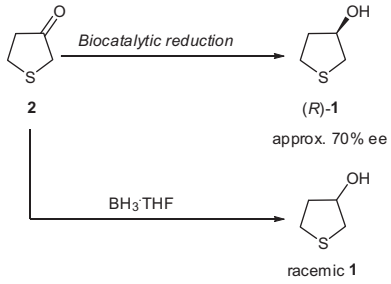


Figure 2. Preparation of racemic and optically active (*R*)-**1** by reductive reaction of tetrahydrothiophene-3-one **2**.

2.2. Evaluation of the enantiomeric purity by crystallization of enantiomeric sulfonyl derivatives 3–17

Crystallization experiments were performed by using *p*-toluenesulfonyl derivative (*R*)-**3** with 68.5% ee as the starting material. Crystallization was conducted in a mixed solvent system of ethyl acetate (EtOAc)/hexane at low temperature. The effect of the amount of hexane added as an ineffective solvent was examined as shown in Table 1.

In this derivative (*R*)-**3**, enantiomeric purity enrichment was observed by simple crystallization and the 'mother liquor' was obtained with 90.7% ee (entry 3). In contrast, crystals with low enantiomeric purity were obtained and this result showed the phenomenon opposite to the crystallization of (*R*)-**1**. The melting points were measured for both the initial material and the obtained crystals. The results showed that higher enantiomerically pure compounds had relatively lower melting points, and a general correlation between enantiomeric purity and the melting point was suggested.

Next, crystallization experiments were performed using derivatives **4**–**17**, and the behavior of the enantiomeric purity enrichment was investigated. The anti-solvent crystallization was mainly adopted using the mixed solvent system of EtOAc/hexane, while cooling crystallization was conducted using EtOAc or methanol (MeOH) as the solvent. The experimental results are shown in Table 2.

Many of the derivatives improved the enantiomeric purity by simple crystallization. Unfortunately, since four sulfonyl derivatives, methane **4**, 2-propane **5**, butane **6**, and benzene **7**, formed oily substances at room temperature, crystallization experiments were not performed. In addition, the separation conditions by HPLC could not be found for the derivatives **11** and **13**, and therefore enantiomeric purity was not evaluated.

Four derivatives, **8**, **10**, **14**, and **16**, produced the 'mother liquor' with higher enantiomeric purity as a result of precipitation of the crystals with lower enantiomeric purity. The products with higher enantiomeric purity were found to have lower melting points. For example, 2-naphthalene (*R*)-**16** with 73% ee produced the mother liquors with 94.2% ee (mp 59–65 °C) and crystals with 65.7% ee (mp 64–66 °C), respectively (entry 13-2). These results were reproduced with *p*-toluenesulfonyl derivative **3** which gave the mother with a higher %ee. This phenomenon was the same as the feature of preferential enrichment.[6]

On the other hand, only dansyl (5-(dimethylamino)naphthalene) **17** produced 'crystals' with higher enantiomeric purity (entry 14). In this case, the higher %ee product had a higher melting point. This result was opposite to those of compounds which produced a

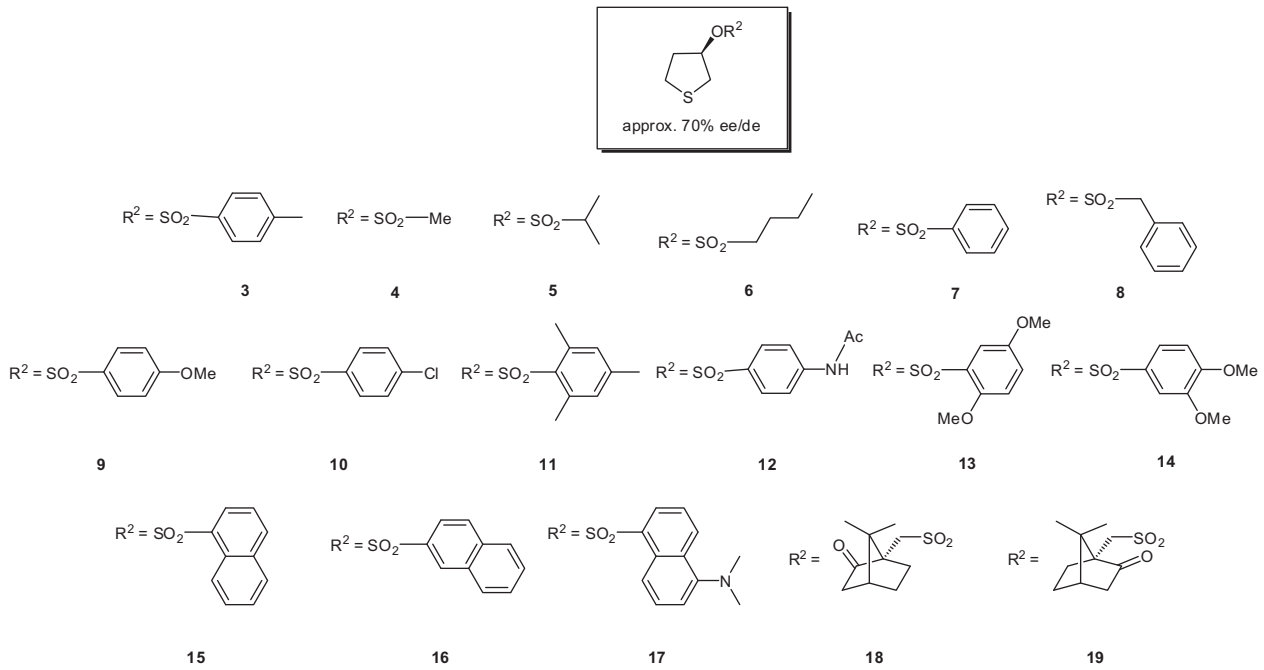


Figure 3. List of sulfonyl derivatives.

Table 1
Evaluation of the enantiomeric purity by crystallization of *p*-toluenesulfonyl derivative **3**

Entry	Initial material			Crystallization condition		Product[b]	Result		
	Derivative	ee[a] (%)	Mp (°C)	Solvent system (v/w)	Temperature (°C)		Yield[c] (%)	ee[a] (%)	Mp (°C)
1	(*R*)-**3**	68.5	37–42	EtOAc/hexane (2/2)	5	Crystals	31	33.1	50–52
						Mother liquor	68	83.5	—
2				EtOAc/hexane (2/4)	5	Crystals	37	39.7	48–51
						Mother liquor	61	87.4	—
3				EtOAc/hexane (2/6)	5	Crystals	50	49.2	46–50
						Mother liquor	48	90.7	—

[a] Determined by HPLC analysis: Chiralpak AD, hexane/2-PrOH (95/:5).
[b] Mother liquor was concentrated by an evaporator.
[c] Recovery based on the amount of derivative (*R*)-**3** as the initial material.

Table 2
Evaluation of the enantiomeric purity by crystallization of the derivatives **4**–**17**

Entry	Initial material		Crystallization condition		Product[a]	Result			HPLC analysis	
	Derivative	ee (%)	Solvent system (v/w)	Temperature (°C)		Yield[b] (%)	ee (%)	Mp (°C)	Column[c]	Eluent[d]
1	(*R*)-**4**		Oil at room temperature							
2	(*R*)-**5**		Oil at room temperature							
3	(*R*)-**6**		Oil at room temperature							
4	(*R*)-**7**		Oil at room temperature							
5-1	(*R*)-**8**	72	EtOAc/hexane (4.5/11)	Heating→rt	Crystals	56	68.2	—	AS-H	80/20
					ML[e]	32	*81.3*	83–90		
5-2		68	EtOAc/MeOH/hexane (7/0.2/10)	rt→5	Crystals	67	66.7	93–95		
					ML[e]	27	*85.4*	—		
5-3		68	MeOH (8)	Heating→rt	Crystals	73	63.5	91–94		
					ML[e]	23	*90.0*	—		
6-1	(*R*)-**9**	74	EtOAc/hexane (2/4)	rt	Crystals	30	73.6	50–52	OJ	75/25
					ML[e]	64	75.0	50–53		
6-2		74	EtOAc/hexane (2/6)	rt	Crystals	68	74.1	49–51		
					ML[e]	19	75.6	49–52		
7	(*R*)-**10**	72	EtOAc/hexane (2/10)	rt→5	Crystals	38	60.3	92–94	OJ-H	60/40
					ML[e]	42	*81.0*	—		
8	(*R*)-**11**	—							Not separated	
9-1	(*R*)-**12**	72	EtOAc (10)	Heating→rt	Crystals	62	68.9	133–135	OJ-H	60/40
					ML[e]	33	75.0	—		
		72	MeOH (8)	Heating→rt	Crystals	65	70.3	133–135		
					ML[e]	31	76.2	—		
10	(*R*)-**13**	—							Not separated	
11-1	(*R*)-**14**	69	EtOAc (5)	Heating→5	Crystals	53	61.8	87–90	OD-H	85/15
					ML[e]	38	75.4	—		
11-2		69	MeOH (8)	Heating→rt	Crystals	85	67.8	88–89		
					ML[e]	12	*82.3*	—		
12-1	(*R*)-**15**	72	EtOAc/hexane (2/4)	rt	Crystals	52	75.2	62–65	AS-H	90/10
					ML[e]	38	71.6	—		
12-2		72	EtOAc/hexane (2/6)	rt	Crystals	69	73.7	64–66		
					ML[e]	28	70.7	61–64		
12-2[f]		72	EtOAc/hexane (2/6)	rt	Crystals	64	74.6	62–65		
					ML[e]	27	70.6	—		
12-3		72	EtOAc (2)	Heating→0	Crystals	33	74.6	63–66		
					ML[e]	58	72.5	62–66		
13-1	(*R*)-**16**	73	EtOAc/hexane (2/4)	rt	Crystals	52	62.2	68–70	OJ	60/40
					ML[e]	35	*91.5*	56–61		
13-2		73	EtOAc/hexane (2/6)	rt	Crystals	75	*65.7*	64–66		
					ML[e]	15	*94.2*	59–65		
13-2[f]		73	EtOAc/hexane (2/6)	rt	Crystals	65	66.5	67–70		
					ML[e]	28	*93.4*	58–64		
13-3		73	EtOAc (2)	Heating→0	Crystals	33	59.0	65–70		
					ML[e]	51	*84.9*	61–62		
14	(*R*)-**17**	71	EtOAc/hexane (10/25)	rt	Crystals	52	*84.9*	104–106	OD	90/10
					ML[e]	44	56.8	92–100		

[a] Mother liquor was concentrated by an evaporator.
[b] Recovery based on the amount of the initial material.
[c] Chiralcel or Chiralpak.
[d] Hexane/2-PrOH.
[e] Mother liquor.
[f] Reproducibility experiment.

high %ee mother liquor. In other derivatives **9**, **12**, and **15**, there was almost no change of enantiomeric purity and thus a melting point. The results of the reproducibility experiment (entries 12-2 and 13-2) are also shown in Table 2. The results showed the same crystallization pattern.

2.3. Evaluation of the enantiomeric purity by crystallization of the diastereomeric sulfonyl derivatives 18 and 19

Crystallization experiments were also performed for the diastereomeric sulfonyl derivatives **18** and **19**, and the enantiomeric purity evaluated. In order to investigate the effect of the enantiomeric purity enrichment via diastereomer formation, both enantiomers of the 10-camphorsulfonic acid, widely utilized as a resolving reagent, were selected. The experimental results are shown in Table 3.

In the crystallization of **18**, the dissolution operation was carried out using EtOAc by heating. Hexane was then added at room temperature. In the crystallization of **19**, MeOH was added to the EtOAc to accelerate the dissolution. Both diastereomers **18** and **19** also produced the "mother liquor" with higher enantiomeric purity as a result of the precipitation of the crystals with lower enantiomeric purity. The purity of diastereomer (*R*)-(−)-**19** was improved from 73% to 87.8% de (entry 2), while that of the diastereomer (*R*)-(+)-**18** was improved remarkably from 72% to 97.7% de (entry 1). Unlike the results of enantiomeric sulfonyl derivatives that an increase in enantiomeric purity led to a decrease in recovery, these diastereomers improved both the enantiomeric purity and recovery. The melting points are also shown in Table 3. These products also showed that the compounds with high enantiomeric purity had relatively lower melting points.

The solubility data of the compounds shown in Table 3 in EtOAc, MeOH, and acetone were also investigated (Table 4). As presumed, the solubility had a large effect on the enantiomeric purity, and low %ee products showed low solubility in the solvents. It was surmised that the solubility of these derivatives in EtOAc was lower than 0.5 g/100 mL. From these solubility data, recrystallization was performed using the EtOAc which had the largest difference in compound solubility (Fig. 4).

Recrystallization of these diastereomers increased the enantiomeric purity. Compound (*R*)-(+)-**18** produced the mother liquor with 100% de [the (*S*)-isomer was not detected], and (*R*)-(−)-**19** produced the mother liquor with 94.6% de. Although the purity of (*R*)-(+)-**18** was improved from 72% to 100% de by repeating the crystallization, it was expected that further optimization would lead to same results by crystallizing only once.

2.4. Features of the enantiomeric purity enrichment in sulfonyl derivatives

A summary of the enantiomeric purity enrichment by crystallization is shown in Figure 5. Enantiomeric purity enrichment was mainly observed with the mother liquor, and this phenomenon was similar to preferential enrichment.[6] A mechanism for the preferential enrichment is proposed as a symmetry-breaking phenomenon induced by phase transition between polymorphisms, that is, those compounds require the existence of two or more polymorphisms. Our compounds do not have hydroxyl groups or amino groups, which generally act as a hydrogen-bond donor except for derivatives **1** and **12**, and it seems that the formation of hydrogen-bonded networks is difficult.

On the other hand, intermolecular and intramolecular nonbonded interactions between a divalent sulfur (S) atom and an oxygen (O) atom have been reported.[7] We considered that these nonbonded S–O interactions affected the phenomenon of enantiomeric purity enrichment. In the derivatives which produced a high %ee mother liquor, a racemic compound which consists of a pair of (*R*)- and (*S*)-enantiomers is stabilized by intermolecular nonbonded S–O interactions, and possibly the high %ee mother liquor was obtained due to the precipitation of this racemic compound. In contrast, the derivatives which produced high %ee crystals have a hydroxyl group or a dimethyl group. A racemic conglomerate, which composed of a mixture of homochiral (*R*)- and (*S*)-crystals was stabilized by one or more interactions, and possibly high purity crystals deposited. Since the derivatives, which did not have any change of enantiomeric purity, did not form a stable conformation by an interaction, a racemic mixed crystal which composed of a random alignment of two enantiomers was possibly obtained.

Table 3
Evaluation of the enantiomeric purity by crystallization of the derivatives **18** and **19**

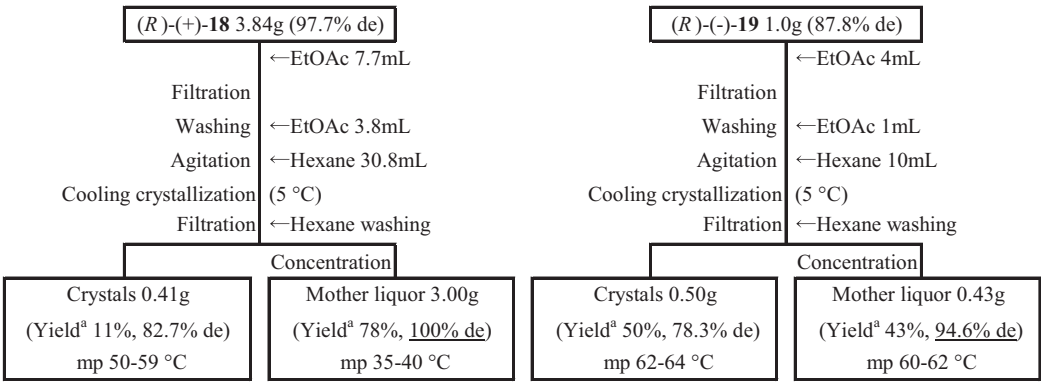
Entry	Initial material		Crystallization condition		Product[b]	Result		
	Derivative	de[a] (%)	Solvent system (v/w)	Temperature (°C)		Yield[c] (%)	de[a] (%)	Mp (°C)
1	(*R*)-(+)-**18**	72	EtOAc/hexane (5/10)	Heating→5	Crystals	28	20.0	96–100
					Mother liquor	70	*97.7*	38–44
2	(*R*)-(−)-**19**	73	EtOAc/MeOH/hexane (6/0.2/12)	Heating→rt	Crystals	14	6.3	96–98
					Mother liquor	83	*87.8*	62–66

[a] Determined by HPLC analysis: Chiralpak AS-H, hexane/2-PrOH (80/20).
[b] Mother liquor was concentrated by an evaporator.
[c] Recovery based on the amount of the initial material.

Table 4
Solubility of the derivatives (*R*)-(+)-**18** and (*R*)-(−)-**19** by the difference in enantiomeric purity

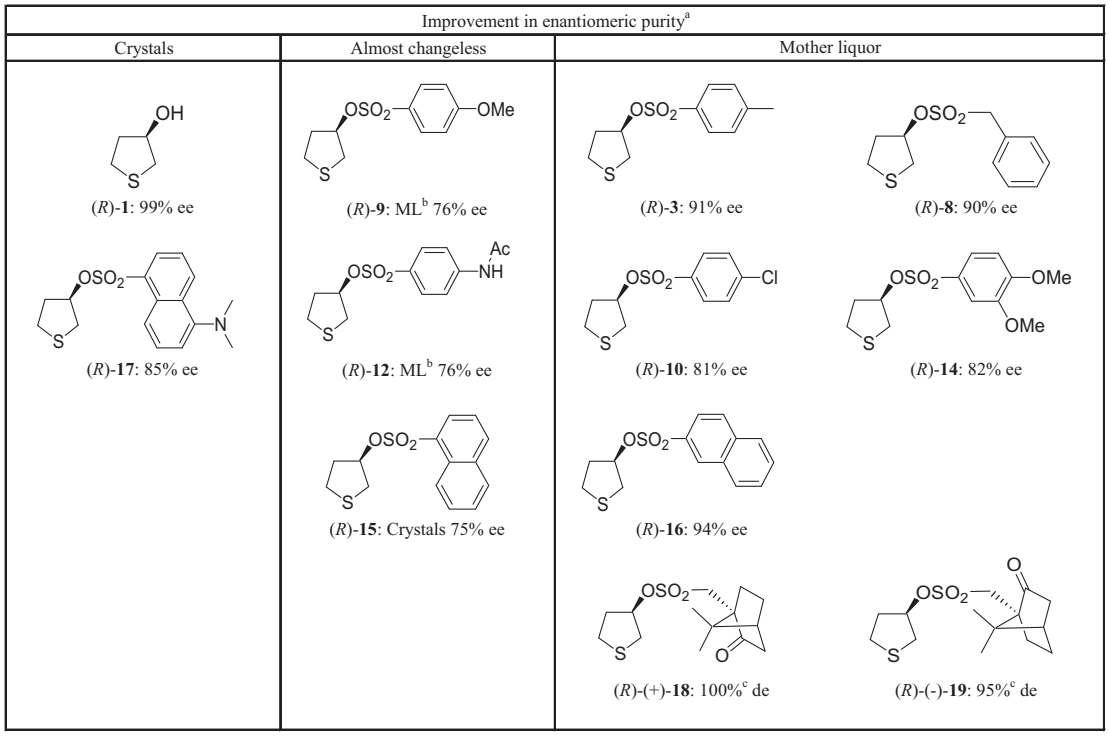
Derivative	de (%)	Solubility[a] (g/100 mL, rt)			Mp (°C)
		EtOAc	MeOH	Acetone	
(*R*)-(+)-**18**	20.0	<0.5	1	5	96–00
	97.7	25	8	25	38–44
(*R*)-(−)-**19**	6.3	<0.5	1	10	96–98
	87.8	13	3	25	62–66

[a] Visual evaluation.



[a] Recovery based on the amount of the initial material

Figure 4. Recrystallization of (*R*)-(+)-**18** and (*R*)-(−)-**19** from an EtOAc/hexane system.



[a] Initial enantiomeric purity before crystallization was approximately 70% ee/de

[b] Mother liquor

[c] Crystallization was repeated twice

Figure 5. Summary of the enantiomeric purity enrichment by crystallization.

Although an investigation of this phenomenon is currently in progress, these results tentatively show the importance of molecular conformations in crystal formation.

3. Conclusion

Various sulfonyl derivatives **3**–**19** were prepared from (*R*)-**1** with low enantiomeric purity (68–74% ee). The enantiomeric purity enrichment by crystallization was investigated using these derivatives. The enantiomeric purity changed depending on the sulfonyl group introduced. As a result, we succeeded in obtaining an (*R*)-enantiomeric derivative with 94% ee and (*R*)-diastereomeric derivative with 100% de. Many of these derivatives produced the "mother liquor" with high enantiomeric purity, and this showed a phenomenon opposite to preferential crystallization similar to (*R*)-**1**. The phenomenon of enantiomeric purity enrichment was most probably due to nonbonded S–O interactions, which contributed to the stabilization of the molecular conformation in crystal formation. These sulfonyl derivatives including those of **18** and **19** can be converted into the key intermediate (*S*)-3-(acetylthio)thiolane 1(*R*)-oxide via an S_N2 reaction via a similar protocol as reported in the literature.[1b,8]

4. Experimental

4.1. Materials and methods

Reagents and solvents were obtained from commercial sources. ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 500 spectrometer. Enantiomeric purities were determined by HPLC system with a UV detector. HPLC condition: Chiralpak or Chiralcel column (4.6 mm × 250 mm; Daicel Corporation) kept at 30 °C, elu-

tion is hexane/2-propanol system at a flow rate of 1 mL/min and detection at 210 or 254 nm. Selected column and mobile phase ratio are shown in Tables 1–3. Optical rotations were measured on a Rudolph AUTOPOL V automatic polarimeter. Melting points were determined with a Yanaco MP instrument and are uncorrected.

Compound (*R*)-**1** with about 70% ee as an initial starting material was prepared as described in a previous report:[2] $[\alpha]_D^{20}$ = +22.8 (*c* 0.56, MeOH) for 72.8% ee; $[\alpha]_D^{20}$ = +30.3 (*c* 0.57, MeOH) for 98.7% ee {lit.[9] $[\alpha]_D^{23}$ = +14.6 (*c* 1, MeOH) for 100% ee, (*R*)-enantiomer}; HPLC analysis: Chiralpak AS-H column, mobile phase: hexane/2-PrOH = 96:4, column temperature: 30 °C, flow rate: 1 mL/min, detection: 210 nm, t_R (retention time) = 14.9 min for (*R*)-**1**, 13.7 min for (*S*)-**1**; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.65–4.61 (m, 1H), 3.03–2.82 (m, 4H), 2.19–2.14 (m, 1H), 1.90 (d, *J* = 6.0, 1H), 1.91–1.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 74.61, 39.86, 38.03, 28.14. Racemic **1** as an initial starting material for HPLC analysis was prepared as follows. Tetrahydrothiophene-3-one **2** (5.1 g, 50 mmol) was dissolved in THF (50 mL) and cooled to 5 °C. To this solution was added dropwise 1 M BH_3–THF (50 mL, 50 mmol) at 5 °C, and the mixture was stirred overnight at room temperature. After monitoring that the reaction was complete by TLC (hexane/EtOAc 1:1), the reaction mixture was cooled again to 5 °C, and MeOH (5 mL) was slowly added at 5 °C. Then, EtOAc (50 mL) and 25% Rochelle salt solution (50 mL) were added, and reaction mixture was vigorously stirred for 30 min. The two layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). All organic layers were dried (Na_2SO_4), and evaporated in vacuum to yield racemic **1** (5.04 g, 97%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.63 (br s, 1H), 3.03–2.82 (m, 4H), 2.22–2.14 (m, 1H), 2.09 (d, *J* = 6.0, 1H), 1.91–1.84 (m, 1H).

4.2. Preparation and crystallization

4.2.1. (*R*)-3-[(*p*-Toluenesulfonyl)oxy]tetrahydrothiophene 3 (*R*)-3

To a solution of (*R*)-**1** (10.4 g, 100 mmol) in pyridine (50 mL) was added dropwise a solution of *p*-toluenesulfonyl chloride (19.0 g, 100 mmol) in CH_2Cl_2 (50 mL) at room temperature. The mixture was stirred overnight at room temperature. After monitoring that the reaction was complete by TLC (hexane/EtOAc 1:1), H_2O (5 mL) was added at room temperature. Next, EtOAc (150 mL) and 2 M HCl (150 mL) were added, and the organic layer was separated. This organic layer was washed with 2 M HCl again, and subsequently washed with 5% $NaHCO_3$ and with brine, and dried (Na_2SO_4). The solvent was evaporated in vacuo to provide crude (*R*)-**3**. The crude was purified by silica gel chromatography (hexane/EtOAc 19:1–9:1, stepwise) to yield (*R*)-**3** (15.8 g, 68.5% ee, 61%) as a white solid: mp 37–42 °C; $[\alpha]_D^{20}$ = +13.7 (*c* 0.52, MeOH) {lit.[1a] $[\alpha]_D$ = +16.8 (*c* 0.63, MeOH) for (*R*)-enantiomer}; HPLC analysis: Chiralpak AD column, mobile phase: hexane/2-PrOH = 95:5, column temperature: 30 °C, flow rate: 1 mL/min, detection: 254 nm, t_R = 15.3 min for (*R*)-**3**, 16.9 min for (*S*)-**3**; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80 (d, *J* = 8.5, 2H), 7.35 (d, *J* = 8.0, 2H), 5.23–5.20 (m, 1H), 3.01–2.84 (m, 4H), 2.46 (s, 3H), 2.34–2.28 (m, 1H), 1.99–1.92 (m, 1H).

Compound (*R*)-**3** (1.0 g, 68.5% ee) was dissolved in EtOAc (2 mL, 2 v/w) at room temperature. Hexane (2 mL, 2 v/w) was added slowly into the solution, and the mixture was stirred overnight at 5 °C. The precipitated crystals were filtered and washed with hexane to furnish white crystals (0.31 g, 33.1% ee, 31%): mp 50–52 °C. The mother liquor was concentrated by an evaporator to provide a colorless oil (0.83 g, 83.5% ee, 83%).

Compound (*R*)-**3** (1.0 g, 68.5% ee) was dissolved in EtOAc (2 mL, 2 v/w) at room temperature. Hexane (4 mL, 4 v/w) was added slowly into the solution, and the mixture was stirred overnight at 5 °C. The precipitated crystals were filtered and washed with hexane to furnish white crystals (0.37 g, 39.7% ee, 37%): mp 48–51 °C. The mother liquor was concentrated by an evaporator to provide a colorless oil (0.61 g, 87.4% ee, 61%).

Compound (*R*)-**3** (1.0 g, 68.5% ee) was dissolved in EtOAc (2 mL, 2 v/w) at room temperature. Hexane (6 mL, 6 v/w) was added slowly into the solution, and the mixture was stirred overnight at 5 °C. The precipitated crystals were filtered and washed with hexane to furnish white crystals (0.50 g, 49.2% ee, 50%): mp 46–50 °C; $[\alpha]_D^{20}$ = +8.0 (*c* 0.50, MeOH). The mother liquor was concentrated by an evaporator to provide a colorless oil (0.48 g, 90.7% ee, 48%).

4.2.2. (*R*)-3-[(Methanesulfonyl)oxy]tetrahydrothiophene 4 (*R*)-4

Compound (*R*)-**1** (3.0 g, 28.8 mmol) was dissolved in CH_2Cl_2 (30 mL) and cooled to 5 °C. To this solution were added DMAP (5.28 g, 43.2 mmol) and methanesulfonyl chloride (3.96 g, 34.6 mmol) at 5 °C, and the mixture was stirred overnight at room temperature. After monitoring that the reaction was complete by TLC (hexane/EtOAc 1:1), 1 M HCl (15 mL) was added. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). All organic layers were washed with brine, and dried (Na_2SO_4). The solvent was evaporated in vacuum to provide crude (*R*)-**4**. The crude was purified by silica gel chromatography (hexane/EtOAc 2:1-1:1, stepwise) to yield (*R*)-**4** (4.59 g, 87%) as a pale yellow oil: $[\alpha]_D^{20}$ = +15.8 (*c* 0.50, MeOH) {lit.[1a] $[\alpha]_D$ = +19.9 (*c* 0.174, MeOH) for the (*R*)-enantiomer}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.46–5.43 (m, 1H), 3.19–3.09 (m, 2H), 3.05 (s, 3H), 3.04–2.94 (m, 2H), 2.50–2.45 (m, 1H), 2.11–2.04 (m, 1H).

4.2.3. (*R*)-3-[(2-Propanesulfonyl)oxy]tetrahydrothiophene 5 (*R*)-5

Using the same procedure as (*R*)-**4**, (*R*)-**1** (2.08 g, 20 mmol) was treated with DMAP (3.66 g, 30 mmol) and 2-propanesulfonyl chloride (2.99 g, 21 mmol), and gave crude (*R*)-**5**. The crude mixture was purified by silica gel chromatography (hexane/EtOAc 9:1–4:1, stepwise) to yield (*R*)-**5** (2.50 g, 59%) as a colorless oil: $[\alpha]_D^{20}$ = +17.2 (*c* 0.48, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.46–5.43 (m, 1H), 3.31–3.26 (m, 1H), 3.18–3.10 (m, 2H), 3.04–2.93 (m, 2H), 2.50–2.45 (m, 1H), 2.09–2.02 (m, 1H), 1.43 (d, *J* = 7.5, 6H).

4.2.4. (*R*)-3-[(Butanesulfonyl)oxy]tetrahydrothiophene 6 (*R*)-6

Using the same procedure as (*R*)-**4**, (*R*)-**1** (2.08 g, 20 mmol) was treated with DMAP (3.66 g, 30 mmol) and butanesulfonyl chloride (3.29 g, 21 mmol), and gave crude (*R*)-**6**. The crude was purified by silica gel chromatography (hexane/EtOAc 9:1–4:1, stepwise) to yield (*R*)-**6** (2.90 g, 65%) as a colorless oil: $[\alpha]_D^{20}$ = +15.2 (*c* 0.49, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.44–5.42 (m, 1H), 3.18–3.10 (m, 4H), 3.04–2.93 (m, 2H), 2.48–2.44 (m, 1H), 2.09–2.04 (m, 1H), 1.88–1.82 (m, 2H), 1.48 (q, *J* = 7.5, 2H), 0.97 (t, *J* = 7.5, 2H).

4.2.5. (*R*)-3-[(Benzenesulfonyl)oxy]tetrahydrothiophene 7 (*R*)-7

Using the same procedure as (*R*)-**4**, (*R*)-**1** (2.08 g, 20 mmol) was treated with DMAP (3.66 g, 30 mmol) and benzenesulfonyl chloride (3.89 g, 22 mmol), and gave crude (*R*)-**7**. The crude was purified by silica gel chromatography (hexane/EtOAc 9:1–4:1, stepwise) to yield (*R*)-**7** as a colorless oil: $[\alpha]_D^{20}$ = +13.3 (*c* 0.53, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93 (d, *J* = 8.0, 2H), 7.67 (t, *J* = 7.5, 1H), 7.57 (t, *J* = 8.0, 2H), 5.27–5.24 (m, 1H), 3.03–2.85 (m, 4H), 2.35–2.31 (m, 1H), 2.00–1.94 (m, 1H).

4.2.6. (*R*)-3-[(Benzylsulfonyl)oxy]tetrahydrothiophene 8 (*R*)-8

Using the same procedure as (*R*)-**4**, (*R*)-**1** (2.0 g, 19.2 mmol) was treated with DMAP (3.52 g, 28.8 mmol) and benzylsulfonyl chloride (4.38 g, 23.0 mmol), and gave (*R*)-**8** (4.83 g, 97%) as a white solid: HPLC analysis: Chiralpak AS-H column, mobile phase: hex-

ane/2-PrOH = 80:20, column temperature: 30 °C, flow rate: 1 mL/min, detection: 210 nm, t_R = 19.4 min for (*R*)-**8**, 21.2 min for (*S*)-**8**; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 (s, 5H), 5.18–5.16 (m, 1H), 4.37 (s, 2H), 3.03–2.84 (m, 4H), 2.31–2.27 (m, 1H), 1.94–1.87 (m, 1H).

Next, EtOAc (20 mL, 4.5 v/w) was added to (*R*)-**8** (4.44 g, 72% ee), and was heated until it dissolved. To this solution was added dropwise hexane (50 mL, 11 v/w), and the mixture was stirred overnight at room temperature. The precipitated crystals were filtered and washed with hexane to furnish white crystals (2.78 g, 68.2% ee, 56%): mp 93–95 °C; $[\alpha]_D^{20}$ = +9.5 (*c* 0.50, MeOH). The mother liquor was concentrated by an evaporator to provide a pale brown solid (1.61 g, 81.3% ee, 32%): mp 83–90 °C; $[\alpha]_D^{20}$ = +11.1 (*c* 0.52, MeOH).

Compound (*R*)-**8** (1.0 g, 68% ee) was dissolved in EtOAc (7 mL, 7 v/w) and MeOH (0.2 mL, 0.2 v/w) at room temperature. To this solution was added dropwise hexane (10 mL, 10 v/w), and the mixture was stirred overnight at 5 °C. The precipitated crystals were filtered and washed with hexane to furnish white crystals (0.67 g, 66.7% ee, 67%). The mother liquor was concentrated by an evaporator to provide a pale brown solid (0.27 g, 85.4% ee, 27%).

Next, MeOH (8 mL, 8 v/w) was added to (*R*)-**8** (1.0 g, 68% ee), and heated until it dissolved. This solution was stirred overnight at room temperature, and the precipitated crystals were filtered to furnish white crystals (0.73 g, 63.5% ee, 73%): mp 91–94 °C. The mother liquor was concentrated by an evaporator to provide a pale brown solid (0.23 g, 90.0% ee, 23%).

4.2.7. (*R*)-3-[(4-Methoxybenzenesulfonyl)oxy]tetrahydrothiophene 9 (*R*)-9

Using the same procedure as (*R*)-**4**, (*R*)-**1** (2.08 g, 20 mmol) was treated with DMAP (3.66 g, 30 mmol) and 4-methoxybenzenesulfonyl chloride (4.55 g, 22 mmol), and gave (*R*)-**9** (2.30 g, 74.3% ee, 42%) as a white solid: mp 50–52 °C; $[\alpha]_D^{20}$ = +12.1 (*c* 0.51, MeOH); HPLC analysis: Chiralcel OJ column, mobile phase: hexane/2-PrOH = 75:25, column temperature: 30 °C, flow rate: 1 mL/min, detection: 254 nm, t_R = 18.4 min for (*R*)-**9**, 16.8 min for (*S*)-**9**; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 (d, *J* = 9.0, 2H), 7.01 (d, *J* = 9.0, 2H), 5.22–5.19 (m, 1H), 3.89 (s, 3H), 2.99–2.84 (m, 4H), 2.34–2.29 (m, 1H), 1.99–1.92 (m, 1H).

Compound (*R*)-**9** (1.0 g, 74.3% ee) was dissolved in EtOAc (2 mL, 2 v/w) at room temperature. To this solution was added dropwise hexane (4 mL, 4 v/w), and the mixture was stirred overnight at room temperature. The precipitated crystals were filtered and washed with hexane to furnish white crystals (0.30 g, 73.6% ee, 30%): mp 50–52 °C. The mother liquor was concentrated by an evaporator to provide a white solid (0.64 g, 75.0% ee, 64%): mp 50–53 °C.

Compound (*R*)-**9** (0.3 g, 74.3% ee) was dissolved in EtOAc (0.6 mL, 2 v/w) at room temperature. To this solution was added dropwise hexane (1.8 mL, 6 v/w), and the mixture was stirred overnight at room temperature. The precipitated crystals were filtered and washed with hexane to furnish white crystals (0.20 g, 74.1% ee, 68%): mp 49–51 °C. The mother liquor was concentrated by an evaporator to provide a white solid (0.06 g, 75.6% ee, 19%): mp 49–52 °C.

4.2.8. (*R*)-3-[(4-Chlorobenzenesulfonyl)oxy]tetrahydrothiophene 10 (*R*)-10

Using the same procedure as (*R*)-**4**, (*R*)-**1** (2.0 g, 19.2 mmol) was treated with DMAP (3.52 g, 28.8 mmol) and 4-chlorobenzenesulfonyl chloride (4.85 g, 23.0 mmol), and gave (*R*)-**10** (5.18 g, 97%) as a pale orange solid: HPLC analysis: Chiralcel OJ-H column, mobile phase: hexane/2-PrOH = 60:40, column temperature: 30 °C, flow rate: 1 mL/min, detection: 210 nm, t_R = 11.6 min for (*R*)-**10**, 10.0 min for (*S*)-**10**; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.87 (d, *J* = 9.0, 2H), 7.55 (d, *J* = 8.5, 2H), 5.28–5.25 (m, 1H), 3.05–2.87 (m, 4H), 2.37–2.31 (m, 1H), 2.02–1.95 (m, 1H).

Compound (*R*)-**10** (5.18 g, 72% ee) was dissolved in EtOAc (10 mL, 2 v/w) at room temperature. Hexane (50 mL, 10 v/w) was added slowly into the solution, and the mixture was stirred overnight at 5 °C. The precipitated crystals were filtered and washed with hexane to furnish white crystals (2.04 g, 60.3% ee, 38%): mp 92–94 °C; $[\alpha]_D^{20}$ = +10.0 (*c* 0.49, MeOH). The mother liquor was concentrated by an evaporator to provide a pale orange oil (2.24 g, 81.0% ee, 42%).

4.2.9. (*R*)-3-[(2,4,6-Trimethylbenzenesulfonyl)oxy]tetrahydrothiophene 11 (*R*)-11

Using the same procedure as (*R*)-**4**, (*R*)-**1** (2.08 g, 20 mmol) was treated with DMAP (3.66 g, 30 mmol) and 2,4,6-trimethylbenzenesulfonyl chloride (4.81 g, 22 mmol), and gave (*R*)-**11** (2.91 g, 51%) as a white solid: mp 57–58 °C; $[\alpha]_D^{20}$ = +14.6 (*c* 0.52, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.98 (s, 2H), 5.22–5.19 (m, 1H), 3.02–2.85 (m, 4H), 2.64 (s, 6H), 2.37–2.32 (m, 1H), 2.32 (s, 3H), 1.99–1.92 (m, 1H).

4.2.10. (*R*)-3-[(4-Acetamidebenzenesulfonyl)oxy]tetrahydrothiophene 12 (*R*)-12

Using the same procedure as (*R*)-**4**, (*R*)-**1** (2.08 g, 20 mmol) was treated with DMAP (3.66 g, 30 mmol) and 4-acetamidebenzenesulfonyl chloride (5.14 g, 22 mmol), and gave (*R*)-**12** (4.21 g, 72.2% ee, 70%) as a white solid: mp 133–134 °C; $[\alpha]_D^{20}$ = +11.7 (*c* 0.52, MeOH); HPLC analysis: Chiralcel OJ-H column, mobile phase: hexane/2-PrOH = 60:40, column temperature: 30 °C, flow rate: 1 mL/min, detection: 210 nm, t_R = 10.0 min for (*R*)-**12**, 8.5 min for (*S*)-**12**; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 (d, *J* = 9.0, 2H), 7.72 (d, *J* = 8.5, 2H), 5.23–5.20 (m, 1H), 3.02–2.85 (m, 4H), 2.34–2.28 (m, 1H), 2.23 (s, 3H), 1.99–1.92 (m, 1H).

Next EtOAc (10 mL, 10 v/w) was added to (*R*)-**12** (1.0 g, 72.2% ee), and heated until it dissolved. This solution was stirred overnight at room temperature, and the precipitated crystals were filtered to furnish white crystals (0.62 g, 68.9% ee, 62%): mp 133–135 °C. The mother liquor was concentrated by an evaporator to provide a colorless oil (0.33 g, 75.0% ee, 33%).

Next, MeOH (8 mL, 8 v/w) was added to (*R*)-**12** (1.0 g, 72.2% ee), and heated until it dissolved. This solution was stirred overnight at room temperature, and the precipitated crystals were filtered to furnish white crystals (0.65 g, 70.3% ee, 65%): mp 133–135 °C. The mother liquor was concentrated by an evaporator to provide a colorless oil (0.31 g, 76.2% ee, 31%).

4.2.11. (*R*)-3-[(2,5-Dimethoxybenzenesulfonyl)oxy]tetrahydrothiophene 13 (*R*)-13

Using the same procedure as (*R*)-**4**, (*R*)-**1** (2.08 g, 20 mmol) was treated with DMAP (3.66 g, 30 mmol) and 2,5-dimethoxybenzenesulfonyl chloride (4.97 g, 21 mmol), and gave (*R*)-**13** as a white solid: mp 106–108 °C;$[\alpha]_D^{20}$ = +14.4 (*c* 0.52, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.47 (d, *J* = 3.5, 1H), 7.14 (dd, *J* = 9.0, 3.0, 1H), 6.99 (d, *J* = 9.5, 1H), 5.39–5.36 (m, 1H), 3.93 (s, 3H), 3.82 (s, 3H), 3.05–2.97 (m, 3H), 2.91–2.87 (m, 1H), 2.43–2.37 (m, 1H), 2.02–1.95 (m, 1H).

4.2.12. (*R*)-3-[(3,4-Dimethoxybenzenesulfonyl)oxy]tetrahydrothiophene 14 (*R*)-14

Using the same procedure as (*R*)-**4**, (*R*)-**1** (2.08 g, 20 mmol) was treated with DMAP (3.66 g, 30 mmol) and 3,4-dimethoxybenzenesulfonyl chloride (4.97 g, 21 mmol), and gave (*R*)-**14** (4.20 g, 68.6% ee, 69%) as a white solid: mp 87–88 °C; $[\alpha]_D^{20}$ = +10.6 (*c* 0.52, MeOH); HPLC analysis: Chiralcel OD-H column, mobile phase: hexane/2-PrOH = 85:15, column temperature: 30 °C, flow rate: 1 mL/min, detection: 210 nm, t_R = 14.5 min for

(*R*)-**14**, 15.5 min for (*S*)-**14**; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55 (dd, J = 8.5, 2.5, 1H), 7.34 (d, J = 2.5, 1H), 6.97 (d, J = 8.5, 1H), 5.22–5.19 (m, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 2.99–2.88 (br m, 4H), 2.35–2.30 (m, 1H), 2.00–1.93 (m, 1H).

Next, EtOAc (5 mL, 5 v/w) was added to (*R*)-**14** (1.0 g, 68.6% ee), and heated until it dissolved. This solution was stirred overnight at 5 °C, and the precipitated crystals were filtered to furnish white crystals (0.53 g, 61.8% ee, 53%): mp 87–90 °C. The mother liquor was concentrated by an evaporator to provide a colorless oil (0.38 g, 75.4% ee, 38%).

Next, MeOH (8 mL, 8 v/w) was added to (*R*)-**14** (1.0 g, 68.6% ee), and heated until it dissolved. This solution was stirred overnight at room temperature, and the precipitated crystals were filtered to furnish white crystals (0.85 g, 67.8% ee, 85%): mp 88–89 °C. The mother liquor was concentrated by an evaporator to provide a colorless oil (0.12 g, 82.3% ee, 12%).

4.2.13. (*R*)-3-[(1-Naphthalenesulfonyl)oxy]tetrahydrothiophene 15 (*R*)-15

Using the same procedure as (*R*)-**4**, (*R*)-**1** (2.0 g, 19.2 mmol) was treated with DMAP (3.52 g, 28.8 mmol) and 1-naphthalenesulfonyl chloride (5.21 g, 23.0 mmol), and gave crude (*R*)-**15**. The crude was purified by silica gel chromatography (hexane/EtOAc 3:1–2:1, stepwise) to yield (*R*)-**15** (4.86 g, 72.4% ee, 86%) as a white solid: mp 62–64 °C; $[\alpha]_D^{20}$ = +18.6 (*c* 0.50, MeOH); HPLC analysis: Chiralpak AS-H column, mobile phase: hexane/2-PrOH = 90:10, column temperature: 30 °C, flow rate: 1 mL/min, detection: 254 nm, t_R = 19.6 min for (*R*)-**15**, 21.3 min for (*S*)-**15**; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.59 (d, J = 8.5, 1H), 8.31 (d, J = 7.5, 1H), 8.15 (d, J = 8.5, 1H), 7.97 (d, J = 8.0, 1H), 7.72 (t, J = 8.5, 1H), 7.64 (t, J = 7.0, 1H), 7.58 (t, J = 8.0, 1H), 5.19–5.16 (m, 1H), 2.90–2.80 (br, 4H), 2.25–2.19 (m, 1H), 1.89–1.82 (m, 1H).

Compound (*R*)-**15** (1.0 g, 72.4% ee) was dissolved in EtOAc (2 mL, 2 v/w) at room temperature. To this solution was added dropwise hexane (4 mL, 4 v/w), and the mixture was stirred overnight at room temperature. The precipitated crystals were filtered and washed with hexane to furnish white crystals (0.52 g, 75.2% ee, 52%): mp 62–65 °C. The mother liquor was concentrated by an evaporator to provide a white solid (0.38 g, 71.6% ee, 38%).

Compound (*R*)-**15** (1.0 g, 72.4% ee) was dissolved in EtOAc (2 mL, 2 v/w) at room temperature. To this solution was added dropwise hexane (6 mL, 6 v/w), and the mixture was stirred overnight at room temperature. The precipitated crystals were filtered and washed with hexane to furnish white crystals (0.69 g, 73.7% ee, 69%): mp 64–66 °C; $[\alpha]_D^{20}$ = +19.3 (*c* 0.50, MeOH). The mother liquor was concentrated by an evaporator to provide a white solid (0.28 g, 70.7% ee, 28%): mp 61–64 °C. Reproducibility experiment: white crystals (0.64 g, 74.6% ee, 64%): mp 62–65 °C, a white solid from the mother liquor (0.27 g, 70.6% ee, 27%).

EtOAc (2 mL, 2 v/w) was added to (*R*)-**15** (1.0 g, 72.4% ee), and heated until it dissolved. This solution was stirred overnight at 0 °C, and the precipitated crystals were filtered to furnish white crystals (0.33 g, 74.6% ee, 33%): mp 63–66 °C. The mother liquor was concentrated by an evaporator to provide a white solid (0.58 g, 72.5% ee, 58%): mp 62–66 °C.

4.2.14. (*R*)-3-[(2-Naphthalenesulfonyl)oxy]tetrahydrothiophene 16 (*R*)-16

Using the same procedure as (*R*)-**4**, (*R*)-**1** (5.0 g, 48.1 mmol) was treated with DMAP (11.8 g, 96.2 mmol) and 2-naphthalenesulfonyl chloride (16.4 g, 72.2 mmol), and gave crude (*R*)-**16**. The crude was purified by silica gel chromatography (hexane/EtOAc 3:1) to yield (*R*)-**16** (8.22 g, 72.7% ee, 58%) as a pale yellow solid: HPLC analysis: Chiralcel OJ column, mobile phase: hexane/2-PrOH = 60:40, column temperature: 30 °C, flow rate: 1 mL/min, detection: 254 nm, t_R = 12.8 min for (*R*)-**16**, 10.9 min for (*S*)-**16**; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.51 (s, 1H), 8.02–7.86 (m, 4H), 7.71–7.64 (m, 2H), 5.29–5.27 (m, 1H), 2.97–2.86 (br m, 4H), 2.35–2.32 (m, 1H), 1.99–1.93 (m, 1H).

Compound (*R*)-**16** (1.0 g, 72.7% ee) was dissolved in EtOAc (2 mL, 2 v/w) at room temperature. To this solution was added dropwise hexane (4 mL, 4 v/w), and the mixture was stirred overnight at room temperature. The precipitated crystals were filtered and washed with hexane to furnish pale yellow crystals (0.52 g, 62.2% ee, 52%): mp 68–70 °C. The mother liquor was concentrated by an evaporator to provide a pale yellow solid (0.35 g, 91.5% ee, 35%): mp 56–61 °C.

Compound (*R*)-**16** (3.0 g, 72.7% ee) was dissolved in EtOAc (6 mL, 2 v/w) at room temperature. To this solution was added dropwise hexane (18 mL, 6 v/w), and the mixture was stirred overnight at room temperature. The precipitated crystals were filtered and washed with hexane to furnish pale yellow crystals (2.26 g, 65.7% ee, 75%): mp 64–66 °C; $[\alpha]_D^{20}$ = +10.6 (*c* 0.50, MeOH). The mother liquor was concentrated by an evaporator to provide a pale yellow solid (0.44 g, 94.2% ee, 15%): mp 59–65 °C; $[\alpha]_D^{20}$ = +13.5 (*c* 0.50, MeOH). Reproducibility experiment: pale yellow crystals (0.65 g, 66.5% ee, 65%): mp 67–70 °C, a pale yellow solid from the mother liquor (0.28 g, 93.4% ee, 28%): mp 58–64 °C; $[\alpha]_D^{20}$ = +13.6 (*c* 0.50, MeOH).

Next, EtOAc (1.4 mL, 2 v/w) was added to (*R*)-**16** (0.68 g, 72.7% ee), and was heated until it dissolved. This solution was stirred overnight at 0 °C, and the precipitated crystals were filtered to furnish pale yellow crystals (0.23 g, 59.0% ee, 33%): mp 65–70 °C. The mother liquor was concentrated by an evaporator to provide a pale yellow solid (0.35 g, 84.9% ee, 51%): mp 61–62 °C.

4.2.15. (*R*)-3-[(5-(Dimethylamino)naphthalene-1-sulfonyl)oxy] tetrahydrothiophene 17 (*R*)-17

Using the same procedure as (*R*)-**4**, (*R*)-**1** (2.08 g, 20 mmol) was treated with DMAP (3.66 g, 30 mmol) and 5-(dimethylamino)naphthalene-1-sulfonyl chloride (6.74 g, 25 mmol), and gave crude (*R*)-**17**. The crude was purified by silica gel chromatography (hexane/EtOAc 9:1–5:1, stepwise) to yield (*R*)-**17** (5.00 g, 71.4% ee, 74%) as a light yellow solid: mp 100–104 °C; $[\alpha]_D^{20}$ = +16.7 (*c* 0.50, MeOH); HPLC analysis: Chiralcel OD column, mobile phase: hexane/2-PrOH = 90:10, column temperature: 30 °C, flow rate: 1 mL/min, detection: 254 nm, t_R = 7.7 min for (*R*)-**17**, 8.4 min for (*S*)-**17**; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.61 (d, J = 8.5, 1H), 8.29 (d, J = 7.5, 1H), 8.23 (d, J = 9.0, 1H), 7.60 (dd, J = 8.0, 7.5, 1H), 7.55 (dd, J = 7.5, 7.5, 1H), 7.21 (d, J = 7.5, 1H), 5.18–5.15 (m, 1H), 2.94–2.85 (m, 3H), 2.90 (s, 3H), 2.89 (s, 3H), 2.82–2.78 (m, 1H), 2.26–2.21 (m, 1H), 1.90–1.83 (m, 1H).

Compound (*R*)-**17** (1.0 g, 71.4% ee) was dissolved in EtOAc (10 mL, 10 v/w) at room temperature. To this solution was added dropwise hexane (25 mL, 25 v/w), and the mixture was stirred overnight at room temperature. The precipitated crystals were filtered and washed with hexane to furnish light yellow crystals (0.52 g, 84.9% ee, 52%): mp 104–106 °C; $[\alpha]_D^{20}$ = +19.9 (*c* 0.50, MeOH). The mother liquor was concentrated by an evaporator to provide a yellow solid (0.44 g, 56.8% ee, 44%): mp 92–100 °C; $[\alpha]_D^{20}$ = +13.2 (*c* 0.50, MeOH).

4.2.16. (*R*)-3-[((+)-10-Camphorsulfonyl)oxy]tetrahydrothiophene 18 (*R*)-(+)-18

Using the same procedure as (*R*)-**4**, (*R*)-**1** (2.0 g, 19.2 mmol) was treated with DMAP (3.52 g, 28.8 mmol) and (+)-10-camphorsulfonyl chloride (5.77 g, 23.0 mmol), and gave crude (*R*)-(+)-**18** (6.36 g, 72% de, quant.) as a yellow solid: HPLC analysis: Chiralpak AS-H column, mobile phase: hexane/2-PrOH = 80:20, column temperature: 30 °C, flow rate: 1 mL/min, detection: 210 nm, t_R = 20.9 min for (*R*)-(+)-**18**, 19.1 min for (*S*)-(+)-**18**; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.49–5.46 (m, 1H), 3.63 (d, J = 15.0, 1H), 3.17 (d,

J = 3.5, 2H), 3.04 (d, J = 15.0, 1H), 3.02–2.92 (m, 2H), 2.51–2.37 (m, 3H), 2.14 (t, J = 4.5, 1H), 2.11–2.03 (m, 2H), 1.96 (d, J = 18.5, 1H), 1.72–1.65 (m, 1H), 1.48–1.43 (m, 1H), 1.12 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 214.36, 83.38, 58.02, 48.25, 48.02, 42.72, 42.51, 37.10, 36.89, 28.21, 26.90, 24.88, 19.80, 19.71.

Next, EtOAc (32 mL, 5 v/w) was added to (*R*)-(+)-**18** (6.36 g, 72% de), and heated until it dissolved. To this solution was added dropwise hexane (64 mL, 10 v/w), and the mixture was stirred overnight at 5 °C. The precipitated crystals were filtered and washed with hexane to furnish white crystals (1.71 g, 20.0% de, 28%): mp 96–100 °C; $[\alpha]_D^{20}$ = +34.5 (*c* 0.50, MeOH). The mother liquor was concentrated by an evaporator to provide a yellow solid (4.26 g, 97.7% de, 70%): mp 38–44 °C; $[\alpha]_D^{20}$ = +46.6 (*c* 0.50, MeOH). This yellow solid (3.84 g) was dissolved in EtOAc (11.5 mL, 3 v/w) at room temperature. Hexane (30.8 mL, 8 v/w) was then added slowly into the solution, and the mixture was stirred overnight at 5 °C. The precipitated crystals were filtered off and washed with hexane to furnish white crystals (0.41 g, 82.7% de, 11%): mp 50–59 °C; $[\alpha]_D^{20}$ = +44.4 (*c* 0.50, MeOH). The mother liquor was concentrated by an evaporator to provide a yellow solid (3.00 g, 100% de, 78%): mp 35–40 °C; $[\alpha]_D^{20}$ = +45.8 (*c* 0.50, MeOH).

4.2.17. (*R*)-3-[((−)-10-Camphorsulfonyl)oxy]tetrahydrothiophene 19 (*R*)-(−)-19

Using the same procedure as (*R*)-**4**, (*R*)-**1** (2.0 g, 19.2 mmol) was treated with DMAP (3.52 g, 28.8 mmol) and (−)-10-camphorsulfonyl chloride (5.77 g, 23.0 mmol), and gave crude (*R*)-(−)-**19** (6.58 g, 73% de, quant.) as a pale yellow solid: HPLC analysis: Chiralpak AS-H column, mobile phase: hexane/2-PrOH = 80:20, column temperature: 30 °C, flow rate: 1 mL/min, detection: 210 nm, t_R = 19.0 min for (*R*)-(−)-**19**, 16.5 min for (*S*)-(−)-**19**; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.49–5.46 (m, 1H), 3.64 (d, J = 15.0, 1H), 3.19–3.11 (m, 2H), 3.04 (d, J = 15.0, 1H), 3.04–2.93 (m, 2H), 2.52–2.37 (m, 3H), 2.13 (t, J = 4.5, 1H), 2.11–2.03 (m, 2H), 1.96 (d, J = 18.5, 1H), 1.71–1.65 (m, 1H), 1.48–1.43 (m, 1H), 1.12 (s, 3H), 0.89 (s, 3H).

Next, EtOAc (40 mL, 6 v/w) and MeOH (1.4 mL, 0.2 v/w) were added to (*R*)-(−)-**19** (6.58 g, 73% de), and were heated until it dissolved. To this solution was added dropwise hexane (80 mL, 12 v/w), and the mixture was stirred overnight at room temperature. The precipitated crystals were filtered off and washed with hexane to furnish white crystals (0.87 g, 6.3% de, 14%): mp 96–98 °C; $[\alpha]_D^{20}$ = −30.8 (*c* 0.49, MeOH). The mother liquor was concentrated by an evaporator to provide a white solid (5.10 g, 87.8% de, 83%): mp 62–66 °C; $[\alpha]_D^{20}$ = −17.0 (*c* 0.51, MeOH). This white solid (1.0 g) was dissolved in EtOAc (5 mL, 5 v/w) at room temperature. Hexane (10 mL, 10 v/w) was added slowly into the solution, and the mixture was stirred overnight at 5 °C. The precipitated crystals were filtered and washed with hexane to furnish white crystals (0.50 g, 78.3% de, 50%): mp 62–64 °C; $[\alpha]_D^{20}$ = −17.9 (*c* 0.50, MeOH). The mother liquor was concentrated by an evaporator to provide a white solid (0.43 g, 94.6% de, 43%): mp 60–62 °C; $[\alpha]_D^{20}$ = −15.7 (*c* 0.50, MeOH).

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