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First practical resolution of a 3-(4-methoxyphenyl)glycidic acid ester by preferential crystallization and synthesis of diltiazem

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Abstract

Among the various esters of 3-(4-methoxyphenyl)glycidic acid, 4-chloro-3-methylphenyl ester (±)-**3** was found to exist as a conglomerate, and could be alternately resolved into (+)- and (−)-**3** of >98% ee by a preferential crystallization procedure. Furthermore, a 1,5-benzothiazepine derivative, (+)-**6**, a significant intermediate of diltiazem, was prepared in one pot in 76% overall yield through the treatment of enantiomerically pure (−)-**3** with 2-aminothiophenol followed by a ring closing reaction.

1. Introduction

Optically active glycidic acid esters are efficient synthetic sources, because epoxides are useful electrophilic building blocks for making new bonds.[1] As such, an epoxide, methyl (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate (−)-**1** has been recently utilized to manufacture the coronary vasodilator, diltiazem (+)-**7**,[2] due to the minimum number of reaction steps and the reduction of raw materials. Since optically active (−)-**1** and its ester derivatives are such significant compounds, their economical preparations have been tried using diastereomeric[3] and enzymatic[4] resolutions, asymmetric aldol[5] and Darzens[6] reactions, and asymmetric reductions[7] and epoxidations.[8] However, there is no report on the successful alternate resolution of (±)-**1** by a preferential crystallization procedure, except for one that was achieved under very limited conditions.[9]

Resolution via preferential crystallization is known to be practical and cost-effective in that it requires no chiral reagent or enzyme, and can be applied to industrial scale preparations.[10] Therefore, we investigated the resolution of 3-(4-methoxyphenyl)glycidic acid ester derivatives using this procedure,

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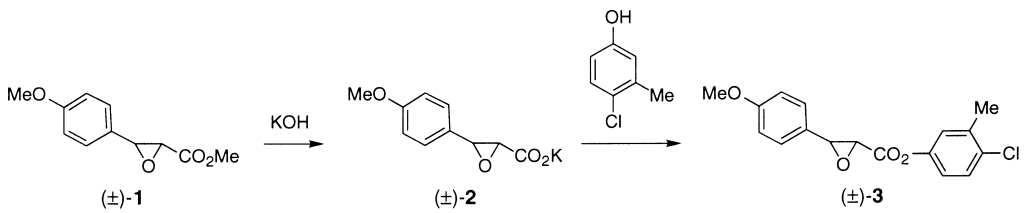
and fortunately found that the 4-chloro-3-methylphenyl ester (±)-**3** can be alternately resolved. In addition, we examined the synthesis of diltiazem from enantiomerically pure (−)-**3**, and also succeeded in an effective one-pot synthesis. The present paper reports the first practical resolution of the racemic glycidic acid ester (±)-**3** and the efficient synthesis of diltiazem.

2. Results and discussion

2.1. Search for a conglomerate glycidic acid ester

(±)-**1** itself is not a conglomerate appropriate for preferential crystallization, because the infrared spectrum of (±)-**1** is different from that of (+)- or (−)-**1**. Consequently, (±)-**1** can not be successfully resolved by this method. For this reason, we searched for a conglomerate ester derivative of (±)-**1** and prepared various racemic and optically active esters according to reported procedures. The hydrolysis of the methyl ester **1** provided the potassium salt **2** in >90% yield,[11] which was then reacted with another alcohol in the presence of the 2-chloropyridinium salt and triethylamine to form an ester derivative in about 50% yield[12] (Scheme 1). As a result, most of the aliphatic ester derivatives were oily substances, while half of the aromatic esters formed good crystals which have a high melting point.



(±)-**1** (±)-**2** (±)-**3**

Scheme 1. Synthesis of the racemic glycidic acid ester

Next, the glycidic acid substituted phenylesters were examined as to whether they were conglomerate crystals using a standard screening method.[10] Of approximately 30 esters tested, only the 3-(4-methoxyphenyl)glycidic acid 4-chloro-3-methylphenyl ester (±)-**3** was found to exist as a conglomerate. Table 1 shows the properties of the racemic and optically active **3**. The melting point of (−)-**3** is higher than that of (±)-**3**, the solubility of (−)-**3** in both THF and DMF is half that of (±)-**3**, and the infrared spectra of (−)- and (±)-**3** are identical. These results suggest that (±)-**3** has typical conglomerate crystals and can be resolved into its enantiomers by preferential crystallization.

2.2. Resolution of the glycidic acid ester by preferential crystallization

First, we employed THF as the solvent and attempted the resolution of (±)-**3**. A supersaturated solution of (±)-**3** including a small excess of (−)-**3** was prepared by heating, and then cooled to 30°C. A small number of seeds of (−)-**3** was added and the stirred solution was allowed to crystallize for 20 min. The

Table 1
Properties of (±)- and (−)-**3**

	mp (°C)	$[\alpha]_D^{25}$ (*c* 1, THF)	solubility[a] (g/100 ml)		IR spectrum
			THF	DMF	
(±)-**3**	123–124	0	14.0	13.0	identical
(−)-**3**	139–141	− 193.4	6.7	6.9	

a) 25 °C.

Table 2
Successive alternate resolution of (±)-**3** by preferential crystallization in THF[a)]

run	amount of (±)-**3** added (g)	composition of the solution		separated crystals		degree of resolution[d)] (%) (R)
		(±)-**3** (g) (A)	excess (+)-**3** or (−)-**3**[b)] (g) (B)	yield (g) (C)	optical purity[c)] (%) (D)	
1	—	8.58	0.40 (−)	0.51 (−)	100	2.5
2	0.22	8.58	0.11 (+)	0.35 (+)	98	5.4
3	0.48	8.58	0.24 (−)	0.42 (−)	99	4.2
4	0.36	8.58	0.18 (+)	0.49 (+)	99	7.0
5	0.62	8.58	0.31 (−)	0.64 (−)	91	6.3
6	0.62	8.58	0.28 (+)	0.61 (+)	99	7.5

a) Resolutions were carried out at 25 °C on a 50 ml scale using 3 mg of seed crystals. *b*) Values were calculated from an analysis of the separated crystals. *c*) Determined by comparison of the specific rotation of the separated crystals with that of the enantiomerically pure ones. *d*) R = (C·D/100–B–0.03)·(2/A)·100.

Table 3
Successive alternate resolution of (±)-**3** by preferential crystallization in DMF[a)]

run	amount of (±)-**3** added (g)	composition of the solution		separated crystals		degree of resolution[d)] (%) (R)
		(±)-**3** (g) (A)	excess (+)-**3** or (−)-**3**[b)] (g) (B)	yield (g) (C)	optical purity[c)] (%) (D)	
1	—	8.10	0.31 (−)	0.62 (−)	91	6.2
2	2.26	9.18	0.25 (+)	0.72 (+)	94	9.2
3	1.23	9.12	0.42 (−)	0.92 (−)	86	8.1
4	1.80	9.47	0.37 (+)	0.82 (+)	90	7.8
5	2.25	10.36	0.37 (−)	1.09 (−)	74	8.4
6	2.38	11.16	0.44 (+)	0.88 (+)	87	5.8

a) Resolutions were carried out at 25 °C on a 50 ml scale using 3 mg of seed crystals. *b*) Values were calculated from an analysis of the separated crystals. *c*) Determined by comparison of the specific rotation of the separated crystals with that of the enantiomerically pure ones. *d*) R = (C·D/100–B–0.03)·(2/A)·100.

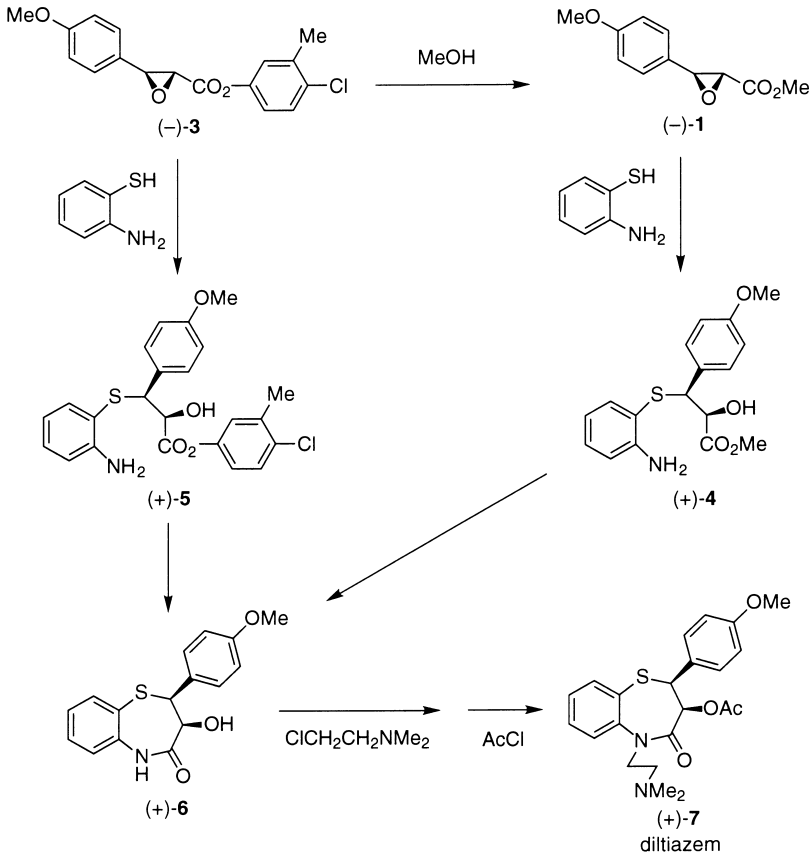
weight of (−)-**3** obtained after filtration was more than that of the (−)-**3** introduced in excess at the beginning of the experiment and the ee was almost 100%. To the mother liquor, (±)-**3** was then added in order that the quantity of (±)-**3** in the solution could be recovered. The mixture was heated until the solid was completely dissolved and then cooled to 30°C. After the solution had been seeded with (+)-**3** and stirred for 20 min, the precipitated (+)-**3** was collected in a similar manner. These cycles of the procedure were carried out six times to yield (+)- and (−)-**3** of >91% ee with a 2.5–7.5% degree of resolution (Table 2).

In the same manner as already described, alternate resolutions were done in DMF solvent, and (+)- and (−)-**3** of 74–94% ee could be repeatedly obtained in a 6–9% degree of resolution (Table 3). Crude (+)- and (−)-**3** could be easily purified into enantiomerically pure **3** by recrystallization.

In this way, we succeeded in the successive alternate resolution of (±)-**3** in both THF and DMF solvents. The degree of resolution is slightly low, but it might be improved by a detailed examination of the resolution conditions.

2.3. Synthesis of diltiazem

Since (−)-**3** is a new compound, diltiazem has not been previously prepared from it. With respect to the preparation, we planned two routes as indicated in Scheme 2.



Scheme 2. Synthesis of diltiazem

Table 4
Synthesis of (−)-**1** from (−)-**3** by transesterification[a)]

entry	catalyst (equiv)	reaction temperature (°C)	reaction time (h)	(−)-**1** isolated yield (%)
1	—	rt	48	0[b)]
2	—	65	0.5	22
3	NaOH (0.01)	rt	0.5	51
4	NaOMe (0.01)	rt	3.0	71
5[c)]	NaOMe (0.1)	50–60	0.5	32

a) Conditions: (−)-**3** (1.57 mmol), MeOH (30 ml). *b*) (−)-**3** was quantitatively recovered. *c*) MeOH (15 ml) was used.

We first investigated the transesterification of (−)-**3** to (−)-**1**, because diltiazem is presently manufactured in high yield through the key intermediate (−)-**1**.[13] As shown in Table 4, without a catalyst, the reaction did not rapidly proceed even at the elevated temperature. Conversely, a catalytic amount of base accelerated the reaction and (−)-**1** could be isolated in 71% yield after 3 h at room temperature. From (−)-**1**, another intermediate, (+)-**6**, with >99% ee was obtained in 80% yield, similar to a previous report.[13]

Second, we explored the more straightforward route from (−)-**3** to (+)-**6**. Initially, we attempted the reaction of 2-aminothiophenol with (−)-**3** using chlorobenzene or xylene as a solvent, and $FeCl_3 \cdot 6H_2O$ as the catalyst[14] (Table 5). In all cases, the cyclization product (+)-**6** was recognized as well as (+)-**5**.

Table 5
Reaction of (−)-**3** with 2-aminothiophenol[a)]

entry	solvent	catalyst	reaction temperature (°C)	reaction time	conversion (%)[b)]	
					(+)-**5**	(+)-**6**
1	chlorobenzene	$FeCl_3 \cdot 6H_2O$	100	2 h	6	2
2	xylene	$FeCl_3 \cdot 6H_2O$	100	2 h	3	2
3	chlorobenzene	$FeCl_3 \cdot 6H_2O$	110	2 h	22	24
4	chlorobenzene	none	132	30 min	81	12
5	chlorobenzene	$FeCl_3 \cdot 6H_2O$	132	5 min	86	7
6	chlorobenzene	$FeCl_3 \cdot 6H_2O$	132	30 min	71	21
7	xylene	none	140	30 min	25	7
8	xylene	$FeCl_3 \cdot 6H_2O$	140	5 min	82	9

a) Conditions: (–)-**3** (1.0 mmol), 2-aminothiophenol (1.1 mmol), $FeCl_3 6H_2O$ (1×10^{-4} mmol), chlorobenzene or xylene (5 ml). *b*) Determined by HPLC analysis.

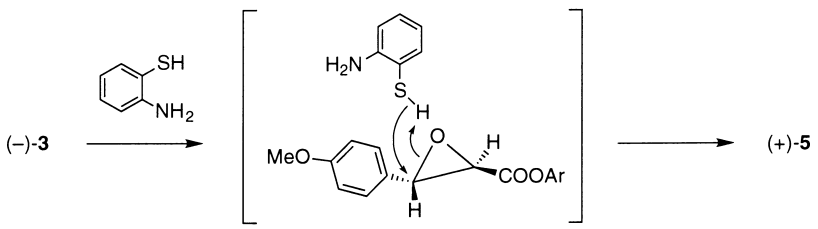


Fig. 1.

When the reaction was conducted at 100 or 110°C, the conversions into the two products were low. In contrast, at the reflux temperatures of chlorobenzene or xylene, the total conversion into (+)-**5** and (+)-**6** exceeded 90%. As for the catalyst, it was effective in xylene, but did not affect the conversions in chlorobenzene. Eventually, (+)-**5** could be isolated in 72% yield under the conditions indicated in run 5. In this case, the *cis*-opening of the epoxy ring, that is, attack of the thiol group on the C-3 position from the same side of the epoxy oxygen is predominant, and thereby the *threo* isomer (+)-**5** stereoselectively forms (Fig. 1).[15] Next, we examined the intramolecular cyclization reaction of (+)-**5** into the 1,5-benzothiazepine derivative (+)-**6**. Fortunately, the enantiomerically pure (+)-**6** was easily obtained almost quantitatively by refluxing for 1 h in chlorobenzene with a catalytic amount of methanesulfonic acid.

A one-pot synthesis is very attractive, in particular, for industrial scale operations, because two reactions are performed in the same reactor and thus transferring contents to another vessel between the two reactions is unnecessary.[13] Therefore, we finally attempted to complete the successive procedure from (−)-**3** to (+)-**6**. The ester (−)-**3** was reacted with 2-aminothiophenol in chlorobenzene at reflux temperature for 30 min to give the intermediate (+)-**5**. Without being isolated, (+)-**5** was cyclized in the presence of methanesulfonic acid in the same vessel to give enantiomerically pure (+)-**6** in 76% overall yield. From (+)-**6**, diltiazem is readily prepared in high yield through *N*-alkylation[6c,16] and *O*-acetylation.[6c]

In conclusion, we have succeeded in the first practical resolution of the 3-phenylglycidic acid ester by preferential crystallization, and developed effective procedures for the diltiazem synthesis. Epoxides are generally reactive and susceptible to cleavage, and thus they are more difficult to be resolved. This successive alternate resolution might be regarded as a rare case.

3. Experimental section

Melting points are uncorrected. Optical rotations were measured on a Perkin–Elmer model 243 polarimeter. IR spectra were recorded on a Perkin–Elmer 1600 series FT-IR. ^{1}H-NMR spectra were measured at 200 MHz on a Bruker AC-200 instrument and chemical shifts are reported relative to the tetramethylsilane (TMS) reference. Mass spectra were measured at 70 eV in the EI mode on a Hitachi M-2000A mass spectrometer. Elemental analyses were performed on a Perkin–Elmer 2400 CHN analyzer. All of the solvents and reagents were commercial products used without further purification. An analytical TLC was performed on E. Merck precoated silica gel 60 F_{254} plates. Conversions from (−)-**3** to (+)-**5** and (+)-**6** were analyzed by reverse-phase HPLC [column: Waters Puresil 5 μm C_{18} 120 Å 4.6×150 mm; mobile phase: CH_3CN/10 mM KH_2PO_4 (pH 3)=60/40; flow rate: 1.0 mL/min; detection: UV 254 nm; temperature: 40°C]. The optical purities of (+)- and (−)-**3** were determined by a comparison of the optical rotation with that of the optically pure compounds. The optical purity of (+)-**6** was analyzed by chiral HPLC [column: Daicel Chiralcel OD 4.6×250 mm; mobile phase: *n*-hexane/EtOH=85/15; flow rate: 0.5 mL/min; detection: UV 250 nm; temperature: 35°C].

3.1. *Potassium (±)-(2*RS*,3*SR*)-3-(4-methoxyphenyl)glycidate (±)-**2***

(±)-**2** was prepared according to the reported procedure.[11] To a solution of 85% potassium hydroxide (15.0 g, 0.227 mol) in EtOH (90 ml) was added a solution of methyl (±)-(2*RS*,3*SR*)-3-(4-methoxyphenyl)glycidate (±)-**1**[16] (30.0 g, 0.144 mol) in EtOH (480 ml) under ice-cooling. After the reaction mixture had been stirred for 3 h at room temperature, precipitated crystals were collected by filtration, washed with EtOH (100 ml), and dried to give (±)-**2** (31.9 g, 95.4%).

3.2. *(±)-(2*RS*,3*SR*)-3-(4-Methoxyphenyl)glycidic acid 4-chloro-3-methylphenyl ester (±)-**3***

(±)-**3** was prepared according to the reported procedure.[12] A mixture of (±)-**2** (40.7 g, 0.175 mol) and triethylamine (17.7 g, 0.175 mol) in DMF (200 ml) was stirred at 40°C. To the mixture were added a solution of 4-chloro-3-methylphenol (25.0 g, 0,175 mol) in DMF (100 ml) and a 1 M solution of 2-chloro-1-methylpyridinium methyl sulfate in CH_2Cl_2 (193 ml) and then it was stirred for 30 min. The reaction mixture was extracted with AcOEt, and the extract was washed with water and brine. After the extract had been dried over $MgSO_4$, it was concentrated under reduced pressure. Precipitated crystals were collected by filtration, washed with cold AcOEt, and dried to give (±)-**3** (28.1 g, 50.3%): mp 123–124°C; IR (KBr, cm^{-1}) 1750, 1612, 1517, 1476; ^{1}H-NMR ($CDCl_3$) δ: 2.38 (s, 3H), 3.71 (d, *J*=1.7 Hz, 1H), 3.83 (s, 3H), 4.19 (d, *J*=1.7 Hz, 1H), 6.9–7.4 (m, 7H); MS *m/z* 318 (M^+).

3.3. *(+)-(2*S*,3*R*)-3-(4-Methoxyphenyl)glycidic acid 4-chloro-3-methylphenyl ester (+)-**3***

(+)-**3** was prepared from (+)-**1**[17] according to the above procedures: yield from (+)-**2** 50.0%; mp 138–140°C; $[\alpha]_D^{25}$ +192.3 (*c* 1.0, THF); MS *m/z* 318 (M^+); the IR and ^{1}H-NMR spectra of the product were identical with those of (±)-**3**.

3.4. *(−)-(2*R*,3*S*)-3-(4-Methoxyphenyl)glycidic acid 4-chloro-3-methylphenyl ester (−)-**3***

(−)-**3** was prepared from (−)-**1**[4c] by using 2 equiv. of 4-chloro-3-methylphenol and 2 equiv. of 2-chloro-1-methylpyridinium methyl sulfate, according to the above procedures: yield from (−)-**2** 81.6%;

mp 139–141°C; $[\alpha]_D^{25}$ −193.4 (*c* 1.0, THF); MS *m/z* 318 (M^+). Anal. calcd for $C_{17}H_{15}ClO_4$: C 64.06; H 4.74. Found: C 64.07; H 4.59. The IR and ^{1}H-NMR spectra of the product were identical with those of (±)-**3**.

3.5. Optical resolution of (±)-3 by preferential crystallization in THF (Table 2)

(A) (±)-**3** (8.58 g) and (−)-**3** (0.40 g) were completely dissolved in THF (50 ml) by heating. After the solution had been cooled to 30°C, the solution was seeded with crystals of (−)-**3** (3 mg). The mixture was stirred for 20 min while being cooled to 25°C. Precipitated crystals were collected by filtration, washed with cold THF, and dried to give (−)-**3** (0.51 g): $[\alpha]_D^{25}$ −193 (*c* 1.0, THF); 100% ee. The IR and ^{1}H-NMR spectra of the product were identical with those of (±)-**3**.

(B) The amount of the mother liquor obtained by the above mentioned step (A) was adjusted to 50 ml. To the solution, (±)-**3** (0.22 g) was added, which was completely dissolved by heating. After the solution had been cooled to 30°C, it was seeded with crystals of (+)-**3** (3 mg). The mixture was stirred for 20 min while being cooled to 25°C. Precipitated crystals were collected by filtration, washed with cold THF, and dried to give (+)-**3** (0.35 g): $[\alpha]_D^{25}$ +190 (*c* 1.0, THF); 98% ee. The IR and ^{1}H-NMR spectra of the product were identical with those of (±)-**3**. Subsequently, (+)- and (−)-**3** were obtained by repeated resolutions (4 times) in the same manner as already described.

3.6. Optical resolution of (±)-3 by preferential crystallization in DMF (Table 3)

(A) (±)-**3** (8.10 g) and (−)-**3** (0.31 g) were completely dissolved in DMF (50 ml) by heating. After the solution had been cooled to 30°C, it was seeded with crystals of (−)-**3** (3 mg). The mixture was stirred for 20 min while being cooled to 25°C. Precipitated crystals were collected by filtration, washed with cold DMF, and dried to give (−)-**3** (0.62 g): $[\alpha]_D^{25}$ −176 (*c* 1.0, THF); 91% ee. The IR and ^{1}H-NMR spectra of the product were identical with those of (±)-**3**.

(B) To the mother liquor obtained by the above mentioned step, (A), was added (±)-**3** (2.26 g), which was completely dissolved by heating. After the solution had been cooled to 30°C, the solution was seeded with crystals of (+)-**3** (3 mg). The mixture was stirred for 20 min while being cooled to 25°C. Precipitated crystals were collected by filtration, washed with cold DMF, and dried to give (+)-**3** (0.72 g): $[\alpha]_D^{25}$ +181 (*c* 1.0, THF); 94% ee. The IR and ^{1}H-NMR spectra of the product were identical with those of (±)-**3**. Subsequently, (+)- and (−)-**3** were obtained by repeated resolutions (4 times) in the same manner as already described. The amount of DMF increased to 69 ml in the final crystallization.

3.7. General procedure for the synthesis of (−)-1 from (−)-3 by transesterification (Table 4)

A suspension of (−)-**3** (0.5 g, 1.57 mmol) in MeOH (30 ml) with or without a catalyst was stirred under the conditions indicated in Table 4. The solvent was evaporated under reduced pressure, the residue was dissolved in diethyl ether (10 ml), and the solution was then seeded with a small amount of (−)-**1**. Precipitated crystals were collected by filtration, washed with diethyl ether, and dried to give (−)-**1**. A sample for analytical use was prepared by recrystallization from MeOH: mp 87–88°C; $[\alpha]_D^{20}$ −207.1 (*c* 1.0, MeOH); IR (KBr) cm^{-1}: 1750, 1520, 1450, 1210; ^{1}H-NMR (DMSO-d_6) δ: 3.73 (s, 3H), 3.76 (s, 3H), 3.82 (d, 1H, *J*=1.9 Hz), 4.10 (d, 1H, *J*=1.9 Hz), 6.94 (d, 2H, *J*=10 Hz), 7.29 (d, 2H, *J*=10 Hz); MS *m/z* 208 (M^+).

3.8. General procedure for the synthesis of (+)-**5** and (+)-**6** (Table 5)

A suspension of (−)-**3** (319 mg, 1.0 mmol) in chlorobenzene (5 ml) or xylene (5 ml) was heated to 100–140°C. 2-Aminothiophenol (138 mg, 1.1 mmol) with or without $FeCl_3 \cdot 6H_2O$ (0.027 mg, 1.0×10^{-4} mmol) in MeOH (0.1 ml) was added. The resulting mixture was stirred under the conditions indicated in Table 5 and then cooled to room temperature. The conversions into (+)-**5** and (+)-**6** were analyzed by HPLC.

3.9. (+)-(2S,3S)-3-(2-Aminophenylthio)-2-hydroxy-3-(4-methoxyphenyl)propionic acid 4-chloro-3-methylphenyl ester (+)-**5**

A suspension of (−)-**3** (319 mg, 1.0 mmol) in chlorobenzene (5 ml) was heated to reflux temperature. 2-Aminothiophenol (138 mg, 1.1 mmol) with $FeCl_3 \cdot 6H_2O$ (0.027 mg, 1.0×10^{-4} mmol) in MeOH (0.1 ml) was added. The resulting mixture was refluxed for 5 min and then cooled to room temperature. Precipitated crystals were collected by filtration, washed with chlorobenzene, and dried to give a crude product (320 mg, 72.1%), which was recrystallized from AcOEt to give (+)-**5** (160 mg, 36.0%): mp 160–162°C; $[\alpha]_D^{20}$ +242 (*c* 0.5, DMF); IR (KBr) cm^{-1}: 1735, 1610, 1510, 1480; ^{1}H-NMR (DMSO-d_6) δ: 2.26 (s, 3H), 3.72 (s, 3H), 4.42 (d, *J*=6.7 Hz, 1H), 4.61 (t, *J*=6.7 Hz, 1H), 5.36 (s, 2H), 6.60 (d, 1H), 6.31–7.41 (m, 11H); MS (SIMS) *m/z* 444 (M^+). Anal. calcd for $C_{23}H_{22}ClNO_4S$: C 62.23; H 4.99; N 3.16. Found: C 62.35; H 4.85; N 3.06.

3.10. (+)-(2S,3S)-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (+)-**6**

A suspension of (+)-**5** (1.33 g, 3.0 mmol) in chlorobenzene (6 ml) was heated to 110°C. Methanesulfonic acid (5.6 mg, 0.058 mmol) was added and the resulting mixture was refluxed for 1 h. After the reaction mixture had been cooled to room temperature, precipitated crystals were collected by filtration, washed with chlorobenzene, and dried to give (+)-**6** (0.85 g, 94.0%): mp 199–200°C; $[\alpha]_D^{25}$ +109.0 (*c* 0.5, DMF); IR (KBr) cm^{-1}: 1680, 1510, 1475, 1250; ^{1}H-NMR (DMSO-d_6) δ: 3.76 (s, 3H), 4.29 (dd, 1H, *J*=6.4 Hz, 6.6 Hz), 4.74 (d, 1H, *J*=6.4 Hz), 5.05 (d, 1H, *J*=6.6 Hz), 6.87–7.62 (m, 8H), 10.31 (s, 1H); MS *m/z* 301 (M^+).

3.11. One-pot synthesis of (+)-**6** from (−)-**3**

A suspension of (−)-**3** (3.19 g, 10 mmol) in chlorobenzene (50 ml) was heated to reflux temperature. 2-Aminothiophenol (1.38 g, 11 mmol) with $FeCl_3 \cdot 6H_2O$ (0.27 mg, 10×10^{-4} mmol) in MeOH (0.1 ml) was added, and the resulting mixture was refluxed for 30 min. Methanesulfonic acid (19 mg, 0.2 mmol) was added and the solution was refluxed for an additional 1 h. After the reaction mixture had been cooled to room temperature, the solvent was evaporated under reduced pressure and the residue was triturated in MeOH (20 ml). Precipitated crystals were collected by filtration, washed with MeOH and dried to give (+)-**6** (2.30 g, 76.3%): mp 203–205°C; $[\alpha]_D^{20}$ +114.4 (*c* 0.5, DMF); 100% ee; MS *m/z* 301 (M^+). Anal. calcd for $C_{16}H_{15}NO_3S$: C 63.77; H 5.02; N 4.65. Found: C 63.83; H 4.93; N 4.55. The IR and ^{1}H-NMR spectra of the product were identical with those reported above.

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