Efficient Alternative Synthetic Route to Diltiazem *via* (2*R*,3*S*)-3-(4-Methoxyphenyl)glycidamide

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An effective new route to diltiazem, a representative coronary vasodilator, through (−)-(2*R*,3*S*)-3-(4-methoxyphenyl)glycidamide [(−)-2] has been achieved. The glycidamide (−)-2 was prepared in 43% overall yield by a combination of the enzymatic resolution of methyl (±)-(2*RS*,3*SR*)-3-(4-methoxyphenyl)glycidate [(±)-1] with lipase and the following amidation of (−)-1 with ammonia. A one-pot synthesis through the treatment of (−)-2 with 2-aminothiophenol and a following ring closing reaction efficiently gave a key intermediate of diltiazem synthesis, (2*S*,3*S*)-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one [*cis*-(+)-5] in 80% overall yield.

Key words diltiazem; glycidamide; addition reaction; ring closing reaction

Diltiazem[1] (+)-**6** is a remarkable calcium antagonist and used as a safe and effective drug for the treatment of hypertension and angina pectoris. For the synthesis of diltiazem, many processes[2] have been extensively investigated, and at present diltiazem is mainly manufactured by the route using the optically active methyl glycidate (−)-**1** and the amino ester *threo*-(+)-**3** (Chart 1). This route is simple and efficient because of the short reaction steps including a one-pot synthesis.[3,4] However, (−)-**1** is quite irritating and harmful to skin,[5] and thus careful operations are required particularly in industrial production.

During our synthetic study of diltiazem, we found that the methyl glycidate (−)-**1** can be easily converted into the glycidamide (−)-**2** with ammonia. Compound (−)-**2** was proved to be far less irritating than (−)-**1** according to a sensitization test using guinea pigs. The racemic glycidamide (±)-**2** is already found in patents,[6] whereas, to our knowledge, optically active (−)-**2** is not known. We expected that (−)-**2** would be a more favorable synthetic intermediate for diltiazem. In general, however, it is more difficult to prepare the 1,5-benzothiazepine derivative, *cis*-(+)-**5**, from the amino amide, *threo*-(+)-**4**, than that from the amino ester, *threo*-(+)-**3**. This situation prompted us to examine in detail the synthesis of *cis*-(+)-**5** *via* ring closing reaction of *threo*-(+)-

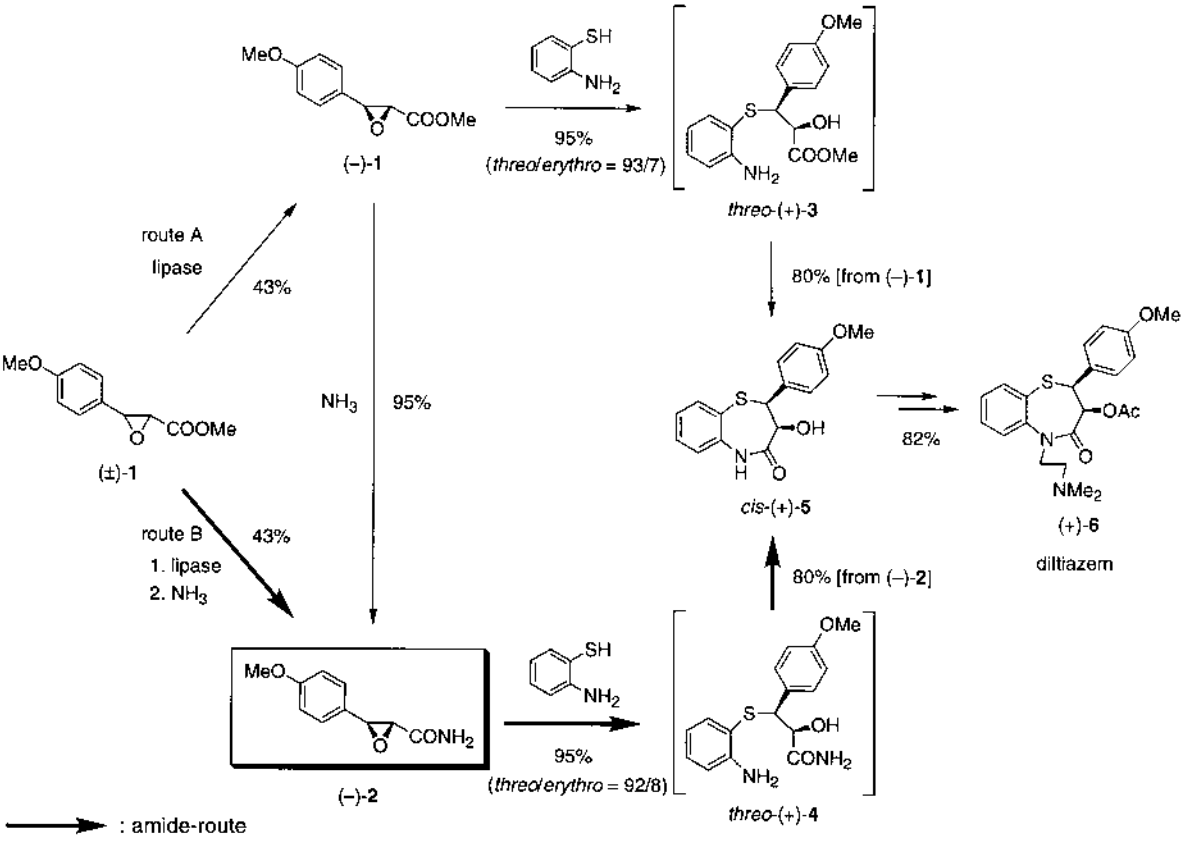

Chart 1

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Table 1. Preparation of (−)-**2** by the Amidation of (−)-**1** with Ammonia[a)]

Solvent (quantity)[b)]	NH_3 (eq)	Reaction conditions		Crystallization conditions		(−)-**2**[c)]	
		Temperature	Time (h)	Temperature	Additional solvent	Isolated yield (%)	Chemical purity (%)[d)]
Toluene (11)	28% NH_3/H_2O (10)	r.t.	4	r.t.	—	60	95
Toluene (11)	15% NH_3/MeOH (10)	r.t.	15	Ice cooled	Toluene[e)]	86	95
DMF (1.5)	28% NH_3/H_2O (10)	r.t.	2	r.t.	—	85	>99
MeOH (1.9)	28% NH_3/H_2O (10)	r.t	5	r.t.	—	80	>99
MeOH (−)	22% NH_3/MeOH (6)	15 °C	2.5	Ice cooled	H_2O	95	99

a) Condition: (−)-**1** (10 mmol). *b*) Multiples of (−)-**1** [solvent: ml/(−)-**1**: g]. *c*) In all cases, optical purities were >99%. *d*) Determined by HPLC analysis. *e*) MeOH was evaporated and then toluene was added.

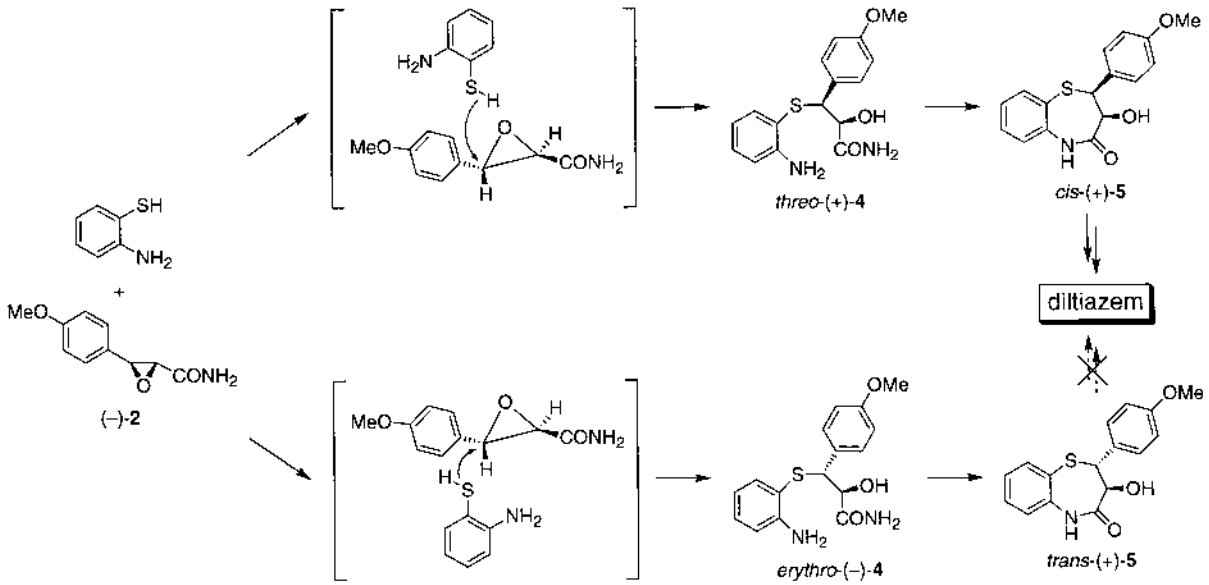

Chart 2

4, which is prepared by the epoxy opening reaction of (−)-**2** with 2-aminothiophenol. We report here an alternative amide-route to diltiazem.

Results and Discussion

Preparation of the Glycidamide To prepare the optically active glycidamide (−)-**2**, we examined the amidation of methyl (−)-(2*R*,3*S*)-3-(4-methoxyphenyl)glycidate [(−)-**1**] (Table 1). We initially employed toluene as a solvent and attempted the amidation of (−)-**1** with NH_3 under various reaction conditions. Anhydrous NH_3 gas was bubbled into the toluene solution of (−)-**1**, but no amidation occurred. In NH_3/toluene/H_2O or NH_3/toluene/MeOH, although the desired amidation proceeded, the reaction was very slow and accompanied by side reactions. Moreover, it was difficult to filter the crystals of (−)-**2** precipitated from these solutions, because they were pasty and very fine. On the other hand, in NH_3/MeOH or NH_3/*N*, *N*-dimethylformamide (DMF), the reaction proceeded smoothly and (−)-**2** could be obtained as more suitable crystals for the collection by filtration. After completion of the reaction, addition of a large amount of water was found to increase the yield of (−)-**2** owing to its insolubility in water. As a result, the enantiomerically pure glycidamide (−)-**2** was obtained in nearly quantitative yield by amidation in NH_3/MeOH.

Next, we examined the successive procedures for the preparation of (−)-**2** by a combination of the enzymatic resolution of (±)-**1** and the amidation of (−)-**1** (route B). The enzymatic resolution was carried out using lipase SM according to a previously reported procedure,[3)] and optically pure (−)-**1** in the toluene solution was determined to be 45.3% yield based on (±)-**1** by HPLC analysis. After toluene was evaporated, the amidation of (−)-**1** with 20% NH_3/MeOH was performed at 15 °C for 2.5 h. To the mixture, a large amount of ice water was added and (−)-**2** was allowed to crystallize for 2 h in an ice-cold bath. After filtration and dryness, (−)-**2** of >99% e.e. was obtained in 43% overall yield. These successive procedures (route B) are almost equal to the present ester-route (route A) in terms of yield and operative ease.

Reaction of the Glycidamide with 2-Aminothiophenol (AP) In the present diltiazem synthesis, an iron catalyst is found to be very effective in the reaction of the glycidate (−)-**1** with AP. Accordingly, we examined the effect of various metal catalysts on the reaction of the glycidamide (−)-**2** with AP (Table 2). In this reaction, two major products are generated, *threo*-(+)-**4**, *cis*-opening product of the epoxy ring, and *erythro*-(−)-**4**, *trans*-opening product (Chart 2). *Threo*-(+)-**4**, which would be converted into the desired *cis*-(+)-**5** by the subsequent ring closing reaction, results from

Table 2. Effect of Catalyst on the Reaction of (−)-**2** with AP[a]

Catalyst	**4**	
	Conversion (%)[b]	*threo*/*erythro*[b]
None	36	83/17
$FeCl_3$ (anhydrous)	**84**	**91/ 9**
$FeSO_4 \cdot 7H_2O$	**85**	**91/ 9**
$Fe(NO_3)_3 \cdot 9H_2O$	**84**	**90/10**
$CaCl_2$	71	13/87
$MnCl_2 \cdot 4H_2O$	56	76/24
$BaCl_2 \cdot 2H_2O$	45	14/86
$PdCl_2$	39	84/16
$Cu(AcO)_2$	34	83/17
$NiCl_2 \cdot 6H_2O$	31	84/16
$Zn(AcO)_2 \cdot 2H_2O$	29	76/24
$ZnCl_2$	28	74/26
$VOSO_4 \cdot 4H_2O$	27	86/14
KI	25	41/59
$ZrCl_4$	24	83/17
$SnCl_4$	19	79/21
CoF_3	19	82/18
$TiCl_4$	18	67/33

a) Conditions: (−)-**2** (5 mmol), AP (5.5 mmol), catalyst (5×10^{-4} mmol), xylene (10 ml), reflux, 5 min. *b*) Determined by HPLC analysis.

Table 3. Effect of Solvent on the Reaction of (−)-**2** with AP[a]

Solvent (quantity)[b]	AP addition period (s)	Reaction temp. (°C)	**4**	
			Conversion (%)[c]	*threo*/*erythro*[c]
Toluene (10)	<30	110	77	92/ 8
Mesitylene (10)	<30	165	79	90/10
Xylene (10)	<30	140	84	91/ 9
Xylene (20)	<30	140	91	91/ 9
Chlorobenzene (5)	<30	130	84	92/ 8
Chlorobenzene (10)	<30	130	89	92/ 8
Chlorobenzene (15)	<30	130	91	92/ 8
Chlorobenzene (20)	<30	130	95	92/ 8

a) Conditions: (−)-**2** (5 mmol), AP (6 mmol), $FeCl_3 \cdot 6H_2O$ (5×10^{-4} mmol), 5 min.*b*) Multiples of (−)-**2** [solvent: ml/(−)-**2**: g]. *c*) Determined by HPLC analysis.

the attack of the thiol group from the same side of the epoxy oxygen. In contrast, the attack of the thiol group from the opposite side gives *erythro*-(−)-**4**; this is the origin of unwanted *trans*-(+)-**5**. Hence, it is important to obtain *threo*-(+)-**4** in higher ratio in this ring-opening reaction.

The glycidamide (−)-**2** and AP were reacted under reflux in xylene with or without a catalyst. Under a non-catalytic condition, although desired *threo*-(+)-**4** was produced predominantly, conversion into **4** was no more than 36%. Addition of an iron catalyst, for example, $FeSO_4 \cdot 7H_2O$ dramatically increased the conversion to 85% and improved the *threo*/*erythro* ratio to 91/9. A family of iron compounds, $FeCl_3$ and $Fe(NO_3)_3 \cdot 9H_2O$ had an equally high effect, whereas the other various metals did not have as much effect as iron (Table 2). The coordination of iron with both the sulfur atom of AP and the oxygen atom of the epoxy ring may facilitate the *cis*-opening of the epoxy ring. Previously, Hashiyama *et al*. presented similar discussion in the reaction of the methyl glycidate (±)-**1** with 2-nitrothiophenol.[7]

Next, solvent effect on the reaction of (−)-**2** with AP was examined (Table 3). Chlorobenzene was more favorable than hydrocarbon solvents, namely toluene, xylene, and mesitylene, by reason of the higher conversion into **4**. In addition, the concentration of the reaction components affected the conversion: as the quantity of the solvent increased, the conversion into **4** became higher. With respect to the *threo*/*erythro* ratios of **4**, they were almost the same among these solvents. Under optimum conditions, **4** was produced in >90% yield and 92/8 *threo*/*erythro* ratio.

Table 4. Effect of Reaction Temperature and Addition Period of AP on the Reaction of (−)-**2** with AP[a]

Solvent (quantity)[b]	AP addition period	Reaction temp. (°C)	**4**	
			Conversion (%)[c]	*threo*/*erythro*[c]
Chlorobenzene (10)	<30 s	90—100	64	93/ 7
Chlorobenzene (10)	5 min	100—110	83	93/ 7
Chlorobenzene (10)	<30 s	100—110	87	93/ 7
Chlorobenzene (10)	5 min	130	79	90/10
Chlorobenzene (10)	<30 s	130	89	92/ 8

a) Conditions: (−)-**2** (5 mmol), AP (6 mmol), $FeCl_3 \cdot 6H_2O$ (5×10^{-4} mmol), 5 min. *b*) Multiples of (−)-**2** [solvent: ml/(−)-**2**: g]. *c*) Determined by HPLC analysis.

Table 5. Effect of Acid Catalyst on the Ring Closing Reaction[a]

Catalyst (eq)	Reaction time (h)	*cis*-(+)-**5**[b]	
		Isolated yield (%) [from (−)-**2**]	Chemical purity (%)[c]
None	24	52[c]	
Phosphoric acid (1.0)	40	—[d]	—
Sulfuric acid (0.2)	29	80	93
Methanesulfonic acid (0.3)	38	79	98
p-Toluenesulfonic acid (0.2)	32	79	100

a) Conditions: **4** (92/8 mixture of *threo*/*erythro* isomers, 20 mmol), chlorobenzene (77 ml), reflux. *b*) In all cases, optical purities were >99%. *c*) Determined by HPLC analysis. *d*) After the completion of the reaction chemically pure *cis*-(+)-**5** could not be isolated from the reaction mixture.

Table 4 shows the effects of the reaction temperature and the addition period of AP. At the reaction temperature of 90—100 °C, the conversion of **2** into **4** was moderate, whereas at >100 °C it rose to >80%. Also, the addition period of AP affected the reaction, and when it was added to (−)-**2** in chlorobenzene within 30 s, the conversion into **4** was higher. The *threo*/*erythro* ratios of **4** were nearly constant (93/7) under all these reaction conditions.

Ring Closing Reaction Regarding the intramolecular cyclization of amide to the lactam *cis*-(+)-**5**, there is a report that an imide carrying (−)-4-isopropyl-2-oxazolizinone was treated with trimethylaluminum.[8] However, the cyclization of a simple amide like *threo*-(+)-**4** has not been previously reported, and in the above example, corrosive and highly flammable trimethylaluminum was used. We investigated the reaction from *threo*-(+)-**4** to *cis*-(+)-**5** using a cheap and safe catalyst. As mentioned above, when (−)-**2** was reacted with AP in chlorobenzene in the presence of $FeCl_3 \cdot 6H_2O$, a 92/8 mixture of *threo*-(+)-**4**/*erythro*-(−)-**4** was obtained in >90% yield. In order to complete the successive procedures, the mixture in chlorobenzene was used for the subsequent ring closing reaction without isolation.

The effect of acid catalysts on the cyclization reaction is summarized in Table 5. In the absence of a catalyst, the re-

Table 6. Effect of Divided Addition of Acid Catalyst and Concentration on the Ring Closing Reaction[a)]

Entry	Catalyst (eq×times)	Solvent, chlorobenzene quantity[b)]	Distillation of chlorobenzene	Reaction time (h)	*cis*-(+)-**5**[c)] Isolated yield (%) [from (−)-**2**]
1	*p*-Toluenesulfonic acid (0.2×1)	13	Not dist.	32	79.0
2	*p*-Toluenesulfonic acid (0.05×5)	10	Dist.	24	80.6
3	Methanesulfonic acid (0.04×5)	4	Not dist.	13	79.0

a) Conditions: **4** (92/8 mixture of *threo*/*erythro* isomers, 10—80 mmol), reflux. *b*) Multiples of **4** [solvent: ml/**4**: g]. *c*) In all cases, chemical and optical purities were >99%.

action was very slow even at the reflux temperature in chlorobenzene. Phosphoric acid, sulfuric acid, methanesulfonic acid, and *p*-toluenesulfonic acid effectively promoted the reaction. However, in cases of phosphoric acid and sulfuric acid, isolation and purification of *cis*-(+)-**5** by a simple crystallization procedure were difficult because of the contamination with these acids. On the contrary, in cases of methanesulfonic acid and *p*-toluenesulfonic acid, these acids were readily removed from the reaction mixture by refluxing in MeOH, and chemically pure *cis*-(+)-**5** was obtained in nearly 80% yield. By this procedure, *trans*-(+)-**5** originated from *erythro*-(−)-**4**, an undesired product for diltiazem synthesis, was removed effectively. From *cis*-(+)-**5**, diltiazem can be readily prepared in high yield through the following *N*-alkylation[2b,9)] and *O*-acetylation.[9)]

Table 6 shows the effect of the divided addition of the acid catalysts and the reaction components concentration. When 0.2 eq of *p*-toluenesulfonic acid was added all at once at the beginning of the reaction, the completion of the reaction needed no less than 32 h reflux in chlorobenzene. However, the reaction time was reduced to 24 h in the case of divided addition of the catalyst (0.05 eq×5 times) and distillation of the solvent during the reaction. Furthermore, when the solution was concentrated to fourfold of **4** in advance and then the cyclization was performed with divided addition of methanesulfonic acid (0.04 eq×5 times), the reaction was completed in 13 h. In short, the reaction time could be reduced from 32 h to 13 h by the divided addition of the sulfonic acid catalysts and increase of the reaction concentration.

Conclusion

Optically active glycidamide (−)-**2** is prepared in 43% overall yield by successive procedures composed of the enzymatic resolution of the racemic methyl glycidate (±)-**1** with lipase and the following amidation of (−)-**1** with ammonia. From (−)-**2**, the 1,5-benzothiazepine derivative *cis*-(+)-**5**, a key intermediate of diltiazem, is efficiently prepared in 80% yield by the addition and the ring closing reaction in a one-pot manner. Combining these procedures, we have developed a practical new process for manufacturing diltiazem. This proposed amide-route is safer to human skin and thus more advantageous for industrial application than the ester-route.

Experimental

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. Flash column chromatography was carried out on E. Merck Silica gel 60 (230—400 mesh). A conversion from (±)-**1** to (−)-**1** and the optical purity of (−)-**1** were analyzed by chiral HPLC. [column: Daicel Chiralcel OD 4.6×250 mm; mobile phase: *n*-hexane/2-propanol=95/5; flow rate: 1.0 ml/min; detection: UV 254 nm; temperature: 35 °C]. The chemical and optical purities of (−)-**2** were analyzed by chiral HPLC. [column: Daicel Chiralcel OJ 4.6×250 mm; mobile phase: *n*-hexane/EtOH=80/20; flow rate: 1.0 ml/min; detection: UV 254 nm; temperature: 35 °C]. Conversions from (−)-**2** to *threo*-(+)-**4** and *erythro*-(−)-**4** were analyzed by reversed-phase HPLC. [column: Waters Puresil 5 μm C18 120 Å 4.6×150 mm; mobile phase: CH_3CN/10 mM KH_2PO_4 (pH 3)=30/70; flow rate: 1.0 ml/min; detection: UV 254 nm; temperature: 40 °C]. The chemical purity of *cis*-(+)-**5** was analyzed by reversed-phase HPLC. [column: Waters Puresil 5 μm C18 120 Å 4.6×150 mm; mobile phase: CH_3CN/10 mM KH_2PO_4 (pH 3)=50/50; flow rate: 0.5 ml/min; detection: UV 250 nm; temperature: 40 °C]. The optical purity of *cis*-(+)-**5** 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].

Preparation of (−)-(2*R*,3*S*)-3-(4-Methoxyphenyl)glycidamide [(−)-2] (Table 1) To a solution of methyl (−)-(2*R*,3*S*)-3-(4-methoxyphenyl)glycidate[3)] [(−)-**1**] (2.08 g, 10 mmol) in a solvent was added NH_3 solution under cooling. The reaction mixture was stirred under the conditions indicated. Precipitated crystals were collected by filtration and dried at 40 °C to give (−)-**2**.

Preparation of (−)-2 by Successive Procedures of the Enzymatic Resolution of (±)-1 and the Amidation of (−)-1 To a solution of (±)-**1**[2b)] (165 g, 0.792 mol) in toluene (750 ml) were added a pH (8.3—8.6) adjusted solution of KH_2PO_4 (18 g, 0.132 mol) in water (225 ml), $CaCl_2$ (60 mg), and lipase SM (800 mg, esterase activity: 2.6—3.2×10^4 units). The mixture was vigorously stirred for 4 h at 30 °C and then sodium lauryl sulfate (78 mg) was added to destroy emulsion. The aqueous layer was removed and the toluene solution was washed twice with a pH (6.2—6.4) adjusted solution of $NaHSO_3$ (22.5 g) in water (480 ml), once with water (480 ml), once with 1% aqueous solution of $NaHCO_3$ (450 ml), and three times with water (480 ml×3). The organic layer was dried over $MgSO_4$ and (−)-**1** in toluene was determined by chiral HPLC. [936.3 g, content of (−)-**1**: 74.9 g, 45.3%, optical purity >99%].

The above solution of (−)-**1** in toluene (467.7 g, content of (−)-**1**: 37.4 g, 0.18 mol) was concentrated to 51 g. To the solution was added 20 wt.% NH_3 in MeOH (91.8 g, 1.08 mol) under cooling, and then the solution was stirred for 2.5 h at 15 °C. Cold water (184 ml) was added and the mixture was stirred for an additional 2 h in an ice bath. Precipitated crystals were collected by filtration, washed with cold MeOH/water (1/1, 25 ml), and dried overnight at 40 °C to give (−)-**2** (32.9 g, 95.3%, chemical purity >99%, optical purity >99%). A sample for analytical use was prepared by recrystallization from MeOH/H_2O (1/1); mp 142—144 °C; $[\alpha]_D^{25}$ −163.5° (c=1.0, MeOH); IR (KBr, cm^{-1}) 3385, 1642, 1517, 1247; ^{1}H-NMR (DMSO-d_6) δ: 3.49 (d, 1H, J=1.9 Hz), 3.75 (s, 3H), 3.96 (d, 1H, J=1.9 Hz), 6.94 (d, 2H, J=8.7 Hz), 7.27 (d, 2H, J=8.7 Hz), 7.41 (s, 1H), 7.56 (s, 1H); MS (SI-MS) *m/z* 194 [(M+H)$^+$]. *Anal*. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.17; H, 5.55; N, 7.30.

Effect of Catalyst on the Reaction of (−)-2 with AP (Table 2) A suspension of (−)-**2** (0.966 g, 5 mmol) in xylene (10 ml) was stirred and heated under N_2. Immediately after reflux, a mixture of AP (0.689 g, 5.5 mmol) and a catalyst (5×10^{-4} mmol) in MeOH (0.1 ml) was added within 30 s. The reaction mixture was refluxed for 5 min and then cooled to room temperature. The conversion and the *threo*/*erythro* ratio of **4** were analyzed by HPLC.

Effect of Solvent, Temperature, and Addition Period of AP on the Reaction of (−)-2 with AP (Table 3, 4) A suspension of (−)-**2** (0.966 g, 5 mmol) in a solvent was stirred under N_2. Immediately after the mixture was heated to the temperature indicated, a mixture of AP (0.750 g, 6.0 mmol) and $FeCl_3\cdot6H_2O$ (0.14 mg, 5×10^{-4} mmol) in MeOH (0.1 ml) was added over the period indicated. The reaction mixture was stirred for 5 min and then cooled to room temperature. The conversion and the *threo*/*erythro* ratio of **4** were analyzed by HPLC.

Isolation of (2*S*,3*S*)-3-(2-Aminophenylthio)-2-hydroxy-3-(4-methoxyphenyl)propionamide [*threo*-(+)-4] A suspension of (−)-**2** (1.93 g, 10 mmol) in xylene (15 ml) was stirred and heated under N_2. Immediately after reflux, a mixture of AP (1.38 g, 11 mmol) and $FeSO_4\cdot7H_2O$ (0.28 mg, 10×10^{-4} mmol) in MeOH (0.2 ml) was added within 30 s. The reaction mixture was refluxed for 5 min and then cooled to room temperature. After the solvent was evaporated under reduced pressure, the residue was dissolved in EtOH (3 ml) and water (3 ml), and then stirred at 0 °C. Precipitated crystals were collected by filtration, washed with cold EtOH/water (1/1), and dried at 50 °C to yield *threo*-(+)-**4** (2.23 g, 70.1%): mp 110—112 °C; $[\alpha]_D^{25}$ +506° (c=1.0, MeOH); IR (KBr) cm^{-1}: 3456, 1609, 1511, 1480, 1253; ^{1}H-NMR (DMSO-d_6) δ: 3.70 (s, 3H), 4.11 (dd, 1H, J=3.5, 6.5 Hz), 4.44 (d, 1H, J=3.5 Hz), 5.35 (s, 2H), 6.02 (d, 1H, J=6.5 Hz), 6.25—7.28 (m, 8H), 7.39 (s, 2H); MS (SI-MS) *m/z* 319 [(M+H)$^+$]. *Anal*. Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80. Found: C, 60.12; H, 5.64; N, 8.94.

Preparation of the Authentic Sample. (2*S*,3*R*)-3-(2-Aminophenylthio)-2-hydroxy-3-(4-methoxyphenyl)propionamide [*erythro*-(−)-4] By referring to a previous paper,[10] *erythro*-(−)-**4** was prepared through *erythro*-(−)-**3**. To a solution of (−)-**1** (2.08 g, 10 mmol) in MeOH (20 ml) at room temperature were added $NaHCO_3$ (84 mg, 1 mmol) and AP (1.38 g, 11 mmol). After the solution was stirred overnight, water was added and then the mixture was extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give crude *erythro*-(−)-**3** (3.5 g) as a yellow viscous oil.

Erythro-(−)-**3** (3.5 g) was dissolved in MeOH (10 ml) and 20 wt.% NH_3/MeOH (8.5 g, 100 mmol) was added. The reaction mixture was stirred at room temperature for 4 d and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography with a *n*-hexane/AcOEt gradient (30/70 to 0/100) to give *erythro*-(−)-**4** (0.48 g, 15.1%) as a yellowish crystal. A sample for analytical use was prepared by recrystallization from EtOH/H_2O (1/2); mp 113—115 °C; $[\alpha]_D^{25}$ −182.3° (c=1.0, MeOH); IR (KBr) cm^{-1}: 3457, 1670, 1609, 1511, 1250; ^{1}H-NMR (DMSO-d_6) δ: 3.70 (s, 3H), 4.10 (dd, 1H, J=3.6, 5.8 Hz), 4.37 (d, 1H, J=3.6 Hz), 5.38 (s, 2H), 5.96 (d, 1H, J=5.8 Hz), 6.40—7.25 (m, 8H), 7.03 (s, 2H); MS (SI-MS) *m/z* 319 [(M+H)$^+$]. *Anal*. Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80. Found: C, 60.28; H, 5.57; N, 8.66.

Effect of Acid Catalyst on the Ring Closing Reaction (Table 5) A suspension of (−)-**2** (3.86 g, 20 mmol) in chlorobenzene (77 ml) was stirred and heated under N_2. Immediately after reflux, a mixture of AP (2.75 g, 22 mmol) and $FeCl_3\cdot6H_2O$ (0.54 mg, 20×10^{-4} mmol) in MeOH (0.2 ml) was added within 30 s. The reaction mixture was refluxed for 5 min to give a 92/8 mixture of *threo*-(+)-**4**/*erythro*-(−)-**4** in chlorobenzene in 95% yield. An acid catalyst was added and the mixture was refluxed for a further 29—40 h. After the reaction mixture was cooled to room temperature, the solvent was evaporated under reduced pressure. To the residue, MeOH (10—25 ml) was added, and the mixture was refluxed for 1 h and then cooled in an ice bath. Precipitated crystals were collected by filtration, washed with cold MeOH and dried to give *cis*-(+)-**5**.

Effect of Divided Addition of Catalyst and Concentration on the Ring Closing Reaction. Representative Procedure (Table 6, Entry 2) A suspension of (−)-**2** (15.46 g, 80 mmol) in chlorobenzene (232 ml) was stirred and heated under N_2. Immediately after reflux, a mixture of AP (11.02 g, 88 mmol) and $FeCl_3\cdot6H_2O$ (2.16 mg, 80×10^{-4} mmol) in MeOH (0.1 ml) was added within 30 s, and the resulting solution was refluxed for 5 min to give a 92/8 mixture of *threo*-(+)-**4**/*erythro*-(−)-**4** in chlorobenzene in 95% yield. The reaction mixture was refluxed for a further 24 h with addition of five portions of *p*-toluenesulfonic acid (0.76 g×5, total 20 mmol) and with distillation of the solvent (the amount of distilled chlorobenzene: 165 ml). After the mixture was cooled to room temperature, the residual solvent was evaporated under reduced pressure. To the residue, MeOH (90 ml) was added, and the mixture was refluxed for 1 h and then cooled in an ice bath. Precipitated crystals were collected by filtration, washed with cold MeOH (40 ml) and dried at 50°C to give *cis*-(+)-**5** [19.43 g, 80.6% from (−)-**2**]. The properties and spectral data of *cis*-(+)-**5** were completely identical with those reported in previous papers.[2]

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