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Practical Synthesis of Novel Cardioprotective Drug, CP-060*S*

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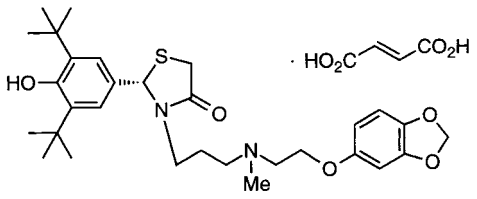
Abstract:

A practical synthesis of a novel cardioprotective drug, CP-060*S*, is described. Key intermediate (*S*)-7, a chiral carboxylic acid, was prepared from 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde 2 by employing thiazolidinone cyclocondensation followed by selective crystallization from a diastereomeric salt mixture which was prepared by treating racemic 7 with (*S*)-(−)-*N*-benzyl-α-methylbenzylamine 11. Racemization of the (*R*)-7-rich mixture, obtained from the mother liquid, by treatment with NaOH solution and subsequent resolution gave a second crop of (*S*)-7. Resolving agent 11 was efficiently recovered from the resolution process and pure enough for recycling use. Chiral acid (*S*)-7 was converted to the corresponding methyl ester (*S*)-14, which was reduced with $NaBH_4-CaCl_2$ to give alcohol intermediate (*S*)-4. Subsequent mesylation, amination, and salt formation with fumaric acid afforded CP-060*S* as pure enantiomer (99.8% ee) without any column chromatography.

Introduction

CP-060*S*, (*S*)-(−)-2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]-amino]propyl]-1,3-thiazolidin-4-one hydrogen fumarate (Figure 1), is a novel Ca^{2+} antagonist possessing both Ca^{2+} overload inhibition and antioxidant activity.[1,2] On the basis of this combined action, it was expected that CP-060*S* would show cardioprotective effect against ischemic heart injuries. Actually, CP-060*S* showed potent cardioprotective activity in various experimental models.[3−6] Extensive pharmacological and toxicological evaluation of CP-060*S* is currently being investigated.

The previous synthetic method reported by us[2] was based on optical resolution of racemic 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)-phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one **1** using chiral preparative HPLC as shown in Scheme 1. The initial scale-up campaign has been carried out through a similar route in which racemic **1** was optically resolved via diastereomeric salt formation with a chiral acid.[7] Those previous methods are not economical enough for providing sufficient quantity of the compound for preclinical studies and industrial preparation in the future. In this paper, we report a new synthetic route which includes a three-component cyclocondensation of aldehyde **2**, β-alanine, and α-mercaptoacetic acid, which offers quick access to the racemic carboxylic acid intermediate **7** as well as efficient selective crystallization from the diastereomeric salt mixture of the early stage intermediate **7**.



CP-060*S* ((*S*)-**1** hydrogen fumarate)

Figure 1.

Results and Discussion

Preparation of Racemic Carboxylic Acid 7. In the previous synthesis,[2] we prepared thiazolidinone **4** by condensation of aldehyde **2** with 3-aminopropanol to give an imine **3**, followed by treatment with α-mercaptoacetic acid. However, when **2** was treated with β-alanine instead of 3-aminopropanol under the same conditions, the corresponding imine could not be detected. On the other hand, direct condensation of **2**, β-alanine, and α-mercaptoacetic acid proceeded to give the desired thiazolidinone **7** in 55% yield along with dithioacetal **8** in 25% yield as the major byproduct as shown in Scheme 2. Since the purification of **7** requires column chromatography to remove **8**, this method is not suitable for large-scale synthesis. We speculated that the byproduct **8** was formed by direct condensation of aldehyde **2** with α-mercaptoacetic acid, whereas thiazolidinone **7** was formed by stepwise reaction via an imine derivative as intermediate. To make the stepwise reaction exclusive, β-alanine was initially activated by the method of Birkofer et al.[8] Thus, treatment of β-alanine with 2.2 equiv each of TMSCl and Et_3N in toluene at 50 °C gave the *N*,*O*-bissilylated intermediate **9** which, without isolation, was treated with aldehyde **2** to give the imine **10**. Further treatment of this imine with α-mercaptoacetic acid afforded the desired thiazolidinone carboxylic acid **7** without formation of **8** as shown in Scheme 3. The other improvement of this process

(1) Kato, T.; Ozaki, T.; Tamura, K.; Suzuki, Y.; Akima, M.; Ohi, N. *J. Med. Chem.* **1998**, *41*, 4309−4316.
(2) Kato, T.; Ozaki, T.; Tamura, K.; Suzuki, Y.; Akima, M.; Ohi, N. *J. Med. Chem.* **1999**, *42*, 3134−3146.
(3) Adachi, Y.; Suzuki, Y.; Homma, N.; Fukazawa, M.; Tamura, K.; Nishie, I.; Kuromaru, O. *Eur. J. Pharmacol.* **1999**, *367*, 267−273.
(4) Koga, T.; Fukazawa, M.; Suzuki, Y.; Akima, M.; Adachi, Y.; Tamura, K.; Kato, T.; Kuromaru, O. *Br. J. Pharmacol.* **1998**, *123*, 1409−1417.
(5) Suzuki, Y.; Tamura, K.; Akima, M.; Adachi, Y.; Fukazawa, M.; Kato, T. *J. Cardiovasc. Pharmacol.* **1998**, *31*, 400−407.
(6) Sugiyama, A.; Hashimoto, K. *J. Cardiovasc. Pharmacol.* **1999**, *33*, 70−77.
(7) Kato, T.; Ozaki, T.; Ohi, N. *Tetrahedron: Asymmetry* **1999**, *10*, 3963−3968.
(8) Birkofer, L.; Schramm, J. *Liebigs Ann. Chem.* **1975**, 2195−2200.

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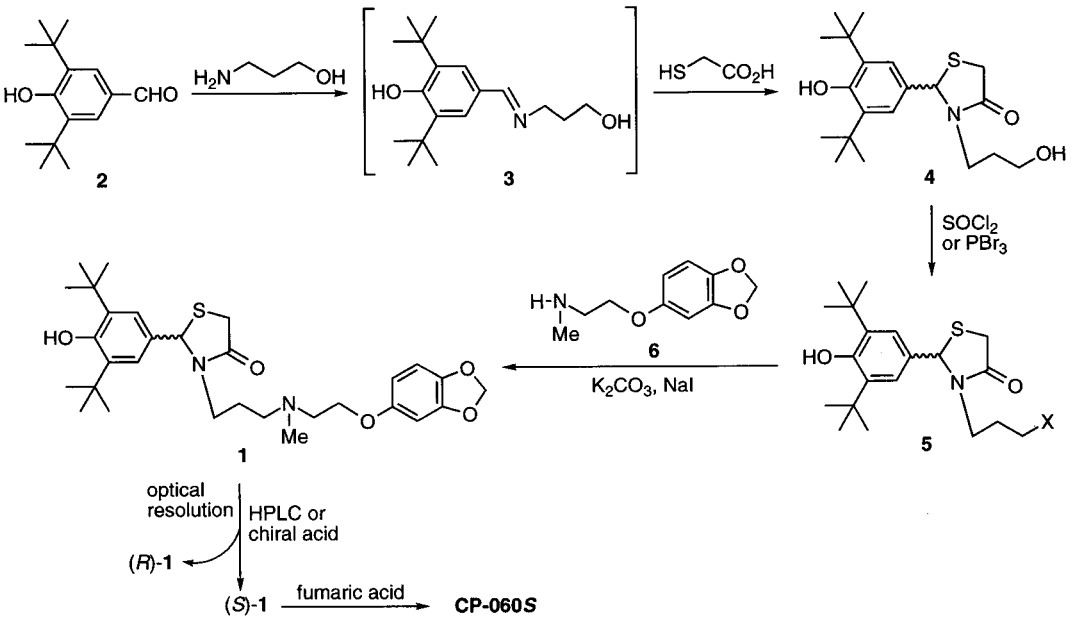
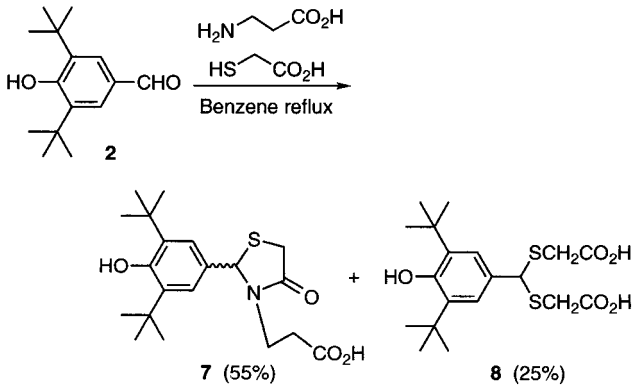
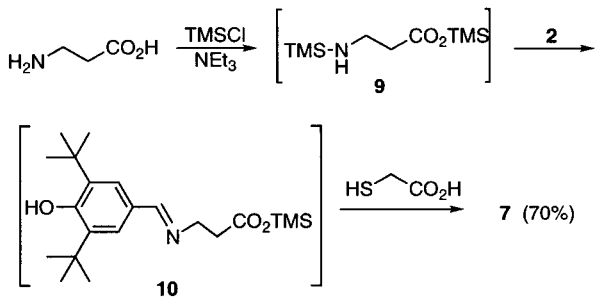
Scheme 1. **Previous synthetic route to CP-060*S***



Scheme 2. **Initial synthesis of racemic 7**



Scheme 3. **Improved synthesis of racemic 7**



is use of toluene instead of toxic benzene as solvent. The crude precipitate was obtained by an aqueous quench, followed by recrystallization from AcOEt−hexane. **7** was obtained in 70% yield from aldehyde **2** without column chromatography.

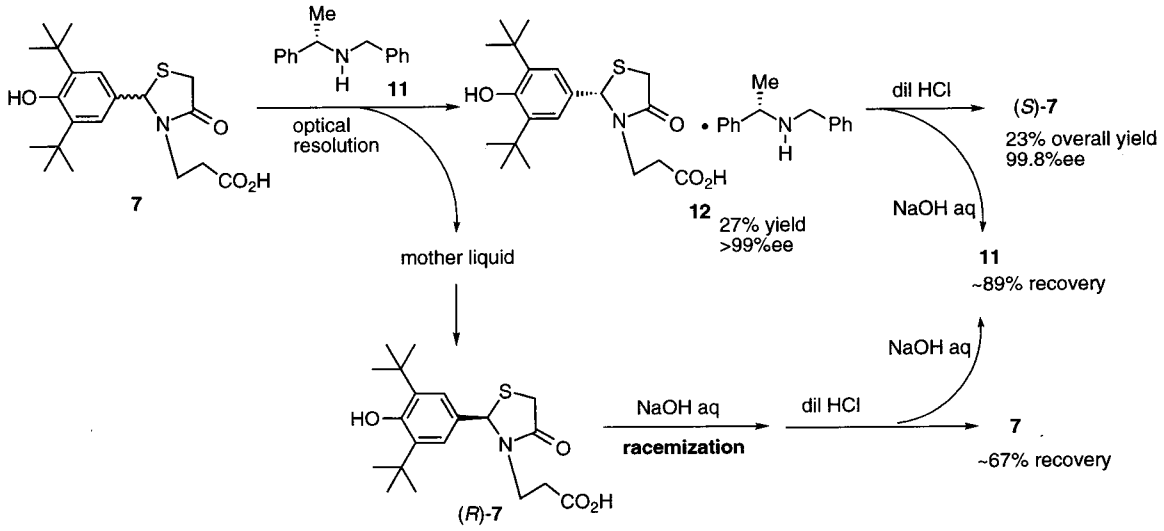
Optical Resolution of 7. Having developed a practical synthesis of racemic carboxylic acid **7**, we next tried an efficient optical resolution of **7**. Initially, we focused on the resolution of **7** using common reagents (phenethylamine, alkaloids, etc.) reported by Wilen.[9] Among these trials, crystals were obtained from (−)-brucine salt; however, the crystals contained the undesired enantiomer (*R*)-**7** (91% ee). The desired enantiomer (*S*)-**7** was enriched in the mother liquid (61% ee). Then many commercially available chiral amines were examined and we eventually found (*S*)-(−)-*N*-benzyl-α-methylbenzylamine **11** as a suitable resolving agent to form a crystalline salt with (*S*)-**7**. A resolution was carried out on a more than 500 g scale so that only 0.6 equiv of resolving agent **11** was needed. Although the optical purity of the first obtained precipitate was 96% de, recrystallization of the precipitate from *i*-PrOH/*i*-Pr_2O improved it to >99% de. After neutralization with dilute hydrochloric acid, colorless crystals of (*S*)-**7** (99.8% ee) were obtained in 23% yield based on racemic **7**.

Recycling of the Mother Liquid. Although the optical resolution method mentioned above is satisfactory concerning optical purity, the isolated yield of (*S*)-**7** needed to be improved from both economic and environmental points of view. As a method to recover racemic **7** from the (*R*)-**7**-rich mother liquid, racemization of chiral **7** was investigated. First, we presumed that the racemization could occur under basic conditions, because of the high acidity of the proton at the 2-position adjacent to the S, N, and aromatic ring. As expected, treatment of (*R*)-**7** with aqueous NaOH solution at room temperature gave racemic **7** (<1% ee, 67% recovery) as shown in Scheme 4. The recovered racemic **7** was optically resolved by the same procedure as above. Theoretically, the conversion yield from racemic **7** to (*S*)-**7** was improved to about 70% by this resolution and racemization cycle. Furthermore, the resolving agent **11** could also be recovered from the combined aqueous acidic extracts by treatment with NaOH solution, extraction, and distillation. The recovery yield was 89% based on the starting compound **11**.

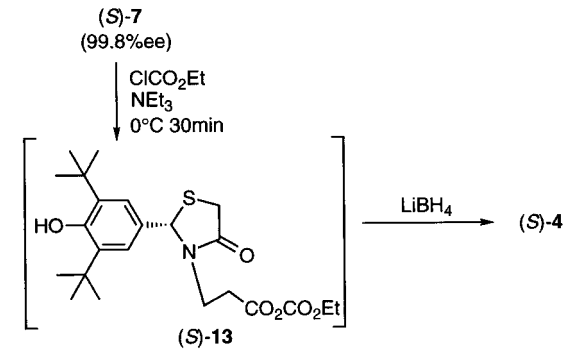
Reduction of Chiral Carboxylic Acid (*S*)-7. With the chiral carboxylic acid (*S*)-**7** in hand, we next investigated the reduction to the corresponding alcohol (*S*)-**4**. Initially the

(9) Wilen, S. H. *Top. Stereochem.* **1971**, *6*, 107−176.

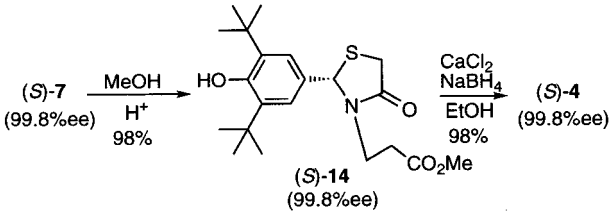
Scheme 4. **Optical resolution of 7 and recycling of the mother liquid**



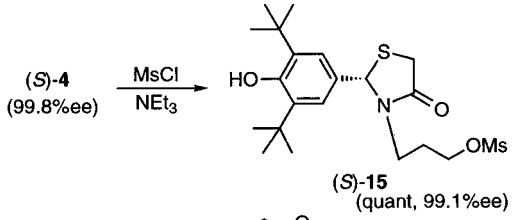
Scheme 5. **Reduction of carboxylic acid (*S*)-7**

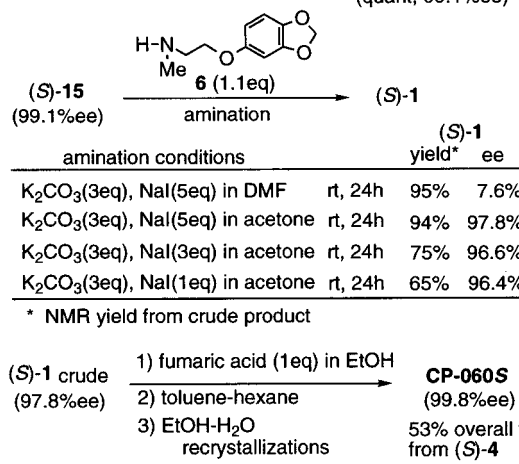


reduction conditions	(*S*)-4 yield	ee
$LiBH_4$ (2.0eq) –45°C, 20min	92%	61.0%
$LiBH_4$ (1.2eq) –45°C, 20min	93%	87.8%
$LiBH_4$ (0.9eq) 0°C, 20min	91%	93.8%
$LiBH_4$ (0.7eq) 0°C, 20min	74%	96.0%



Scheme 6. **Conversion of (*S*)-4 to CP-060*S***





amination conditions		(*S*)-1 yield*	ee
K_2CO_3(3eq), NaI(5eq) in DMF	rt, 24h	95%	7.6%
K_2CO_3(3eq), NaI(5eq) in acetone	rt, 24h	94%	97.8%
K_2CO_3(3eq), NaI(3eq) in acetone	rt, 24h	75%	96.6%
K_2CO_3(3eq), NaI(1eq) in acetone	rt, 24h	65%	96.4%

* NMR yield from crude product

reduction of the corresponding mixed anhydride (*S*)-**13** obtained by treatment with ethyl chloroformate was studied. The reduction by using $LiBH_4$ proceeded well, but the obtained (*S*)-**4** was not optically pure. Racemization seems to occur by basic action of $LiBH_4$. Despite extensive effort, we could not find reduction conditions without causing racemization. Next, we investigated the reduction via the corresponding methyl ester (*S*)-**14**. Esterification of (*S*)-**7** in refluxing MeOH in the presence of a catalytic amount of sulfuric acid gave (*S*)-**14** in good yield. Subsequent reduction of (*S*)-**14** with $NaBH_4-CaCl_2$ in EtOH proceeded smoothly to give (*S*)-**4** in excellent yield as shown in Scheme 5. The advantages of this method are both that the reaction proceeds in excellent yields without racemization and that the work-up procedure is facile.

Mesylation, Amination, and Salt Formation. Mesylation of chiral alcohol (*S*)-**4** gave the corresponding mesylate (*S*)-**15** in quantitative yield. Crude (*S*)-**15** was directly reacted with amine **6** in the presence of K_2CO_3 and NaI to give (*S*)-**1** as shown in Scheme 6. In the amination step severe racemization occurred in DMF. However, the use of acetone in place of DMF suppressed racemization. Our attempts to decrease the amount of NaI resulted in lower yield of (*S*)-**1**. Although racemization could not be avoided completely during the amination step, enantiomerically pure CP-060*S* (99.8% ee) was finally obtained by recrystallization after salt formation with fumaric acid.

Conclusions

Enantiomerically pure CP-060*S* was efficiently synthe-

sized by a chromatography-free process in which racemic carboxylic acid **7** was optically resolved by selective crystallization from a diastereomeric salt mixture. Racemic **7** was efficiently recovered from the mother liquid by treatment with NaOH. Chiral amine **11**, the resolving agent, was also recovered from the resolution process. This process is economical enough for industrial preparation of CP-060*S*.

Experimental Section

General. Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured with a JEOL JNM-EX270 spectrometer (270 MHz) or a Varian Mercury-300 spectrometer (300 MHz) with TMS as an internal standard. Optical rotation was determined on a Horiba SEPA-200 high sensitive polarimeter. Analytical HPLC was performed using a Shimadzu LC-6AD pump and a SPD-10A UV-detector operated at 280 nm. The chiral stationary phase columns (Chiralcel OD and OD-H) were purchased from Daicel Chemical Industries.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(2-carboxylethyl)-1,3-thiazolidin-4-one (7). To a suspension of powdered β-alanine (380 g, 4.27 mol) in toluene (4 L) at 50 °C were added NEt_3 (1.19 L, 8.53 mol) and TMSCl (1.08 L, 8.53 mol) over 45 min, and the mixture was stirred for 1 h at the same temperature. 3,5-Di-*tert*-butyl-4-hydroxybenzaldehyde **2** (507 g, 2.16 mol) and toluene (1 L) were added to the reaction mixture and stirred for 4.5 h at 80 °C and overnight at 50 °C. After the solution cooled to 40 °C, α-mercaptoacetic acid (297 mL, 4.27 mol) was added dropwise, and the resulting mixture was stirred for 7 h at 80 °C and overnight at ambient temperature. The mixture was poured into 1 N HCl (4 L) and stirred for 1 h. The precipitate thus formed was collected by filtration, washed with H_2O (1 L) and dried under ambient conditions. The crude product was dissolved in hot AcOEt (230 mL), and then hexane (500 mL) was added, causing the product to crystallize. After the mixture stirred overnight at ambient temperature, the precipitate was filtered, washed with AcOEt/hexane (1:2, 1.7 L), and dried, affording 571 g of **7** (70% yield from **2**) as colorless crystals: mp 164−165 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (18H, s), 2.3−2.5 (1H, m), 2.66 (1H, dt, J = 16.5, 7.5 Hz), 3.16 (1H, dt, J = 13.8, 7.5 Hz), 3.6−3.9 (3H, m), 5.35 (1H, s), 5.66 (1H, s), 7.10 (2H, s). Anal. Calcd for $C_{20}H_{29}NO_4S$: C, 63.30; H, 7.70; N, 3.69. Found: C, 63.15; H, 7.66; N, 3.73.

Optical Resolution of 7. A mixture of racemic **7** (568 g, 1.5 mol), (*S*)-(−)-*N*-benzyl-α-methylbenzylamine **11** (190 g, 0.9 mol) and *i*-PrOH (1.08 L) was heated until all of the solid material dissolved. To the mixture was added *i*-Pr_2O (2.27 L), and then it was seeded with small amount (∼10 mg) of salt **12** (99.8% ee) and aged for 2 days at 0 °C. The solid was collected, and the filter cake was washed with *i*-Pr_2O (1.6 L) and then dried under vacuum to give 269 g of **12** as a white solid. The optical purity of the free acid was 96.1% ee. Recrystallization from a mixture of *i*-PrOH (670 mL) and *i*-Pr_2O (1.35 L) gave 237 g of optically pure **12** with 99.6% ee (27% from racemic **7**): mp 121−124 °C; ^{1}H NMR (CD_3OD) δ 1.42 (18H, s), 1.61 (3H, d, J = 6.9 Hz), 2.23 (1H, ddd, J = 15.3, 8.7, 6.0 Hz), 2.47 (1H, ddd, J = 15.3, 9.0, 6.6 Hz), 3.02 (1H, ddd, J = 15.3, 8.7, 6.9 Hz), 3.6−3.8 (3H, m), 3.78 and 3.96 (2H, ABq, J = 12.9 Hz), 4.25 (1H, q, J = 6.9 Hz), 5.84 (1H, s), 7.16 (2H, s), 7.2−7.4 (10H, m).

The above salt **12** was suspended in AcOEt (1.2 L) and 1 N HCl (1.2 L) was added. The mixture was stirred at ambient temperature and extracted with AcOEt, washed again with 0.5 N HCl (1 L × 4), H_2O (1 L × 3), dried over Na_2SO_4, and concentrated under reduced pressure to ∼300 mL. Hexane (100 mL) was added causing the product to crystallize. After aging for 2 days at 0 °C the crystals were filtered, washed with hexane (100 mL), and dried, affording 128 g of (*S*)-**7** (99.8% ee) as colorless crystals (23% from racemic **7**): mp 157−159 °C. The ^{1}H NMR spectrum of (*S*)-**7** was the same as that of racemic **7**. The optical purity of (*S*)-**7** was analyzed by chiral HPLC [column: Chiralcel OD-H; mobile phase: hexane/*i*-PrOH/TFA (85:15:0.2); flow rate: 0.4 mL/min]. The retention times are 15.2 and 17.1 min for the *R* and *S* enantiomers, respectively.

Recycling from the Mother Liquid. All of the filtrates obtained from the optical resolution mentioned above were combined and concentrated under reduced pressure. The residue was dissolved in hot MeOH (1 L), and the solution of NaOH (119 g, 2.96 mol) in H_2O (350 mL) was added. The mixture was stirred for 2 h at room temperature and cooled to 0 °C. Then 2 N HCl (2 L) was added, and the precipitate was filtered, washed with H_2O (5 L), and dried at 60 °C to give 379 g of racemic **7** (<1% ee) as colorless crystals (67% recovered). The recovered **7** (379 g) could also be resolved in the same way as mentioned above to give 107 g of (*S*)-**7** (99.5% ee, 28% yield).

All of the acidic filtrates obtained on the neutralization of **12** and on the recycling of **7** after racemization were combined, and NaOH was added until pH = 9. The white suspension was extracted with toluene, and the organic layer was dried with K_2CO_3, concentrated under reduced pressure, and distilled to give 169 g of **11** as a colorless oil (89% recovered).

(*S*)-(−)-2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[2-(methoxycarboxyl)ethyl]-1,3-thiazolidin-4-one ((*S*)-14). To a suspension of (*S*)-**7** (121 g, 318 mmol) in MeOH (360 mL) was added a catalytic amount of sulfuric acid (0.48 mL) and the mixture was heated at reflux for 1.5 h. After the mixture cooled to 0 °C, saturated $NaHCO_3$ (480 mL), H_2O (480 mL) and a small amount (∼10 mg) of (*S*)-**14** (99.8% ee) were added causing the product to crystallize. After the mixture stirred for 1 h at 0 °C, the crystals were filtered, washed with H_2O (200 mL), and dried, affording 123 g (98% yield) of (*S*)-**14** (99.8% ee) as colorless crystals: mp 100−102 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (18H, s), 2.36 (1H, ddd, J = 16.2, 7.5, 6.0 Hz), 2.63 (1H, dt, J = 16.2, 7.5 Hz), 3.14 (1H, dt, J = 14.1, 7.5 Hz), 3.65 (3H, s), 3.5−3.8 (3H, m), 5.33 (1H, s), 5.65 (1H, s), 7.10 (2H, s). The optical purity of (*S*)-**14** was analyzed by chiral HPLC [column: Chiralcel OD; mobile phase: hexane/*i*-PrOH (80:20); flow rate: 0.7 mL/min]. The retention times are 9.0 and 13.9 min for the *R* and *S* enantiomers, respectively.

(*S*)-(−)-2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-(3-hydroxypropyl)-1,3-thiazolidin-4-one ((*S*)-4). To a suspension of $NaBH_4$ (23.7 g, 627 mmol) in EtOH (630 mL) powdered $CaCl_2$ (34.8 g, 313 mmol) was added over a period of 10 min at 0 °C and then (*S*)-**14** (123 g, 313 mmol) was added over 20 min. After the mixture stirred for 2 h at 0 °C, the reaction mixture was poured into ice-cooled 1 N HCl (2 L) and seeded with a small amount (∼10 mg) of (*S*)-**4** (99.8% ee), causing the product to crystallize. After the mixture stirred for 2 h at 0 °C, the crystals were filtered, washed with H_2O (200 mL), and dried, affording 122 g (98% yield) of (*S*)-**4** (99.8% ee) as colorless crystals: mp 107−109 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (18H, s), 1.2−1.6 (2H, m), 3.0−3.2 (1H, m), 3.3−3.6 (4H, m), 3.70 and 3.83 (2H, ABq, J = 16.0 Hz), 5.39 (1H, s), 5.54 (1H, s), 7.11 (2H, s). The optical purity of (*S*)-**4** was analyzed by chiral HPLC [column: Chiralcel OD; mobile phase: hexane/*i*-PrOH (80:20); flow rate: 0.7 mL/min]. The retention times are 7.3 and 8.1 min for the *R* and *S* enantiomers, respectively.

(*S*)-(−)-2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-(methanesulfonyloxy)propyl]-1,3-thiazolidin-4-one ((*S*)-15). To a solution of (*S*)-**4** (105 g, 287 mmol) in THF (287 mL) were added NEt_3 (52.0 mL, 373 mmol) and methanesulfonyl chloride (26.7 mL, 345 mmol) over 15 min at 0 °C and then stirred for 15 min at ambient temperature. The reaction mixture was poured into ice-cooled H_2O (500 mL) and extracted with AcOEt. The organic layers were washed successively with 0.1 N HCl (200 mL), H_2O (200 mL), saturated $NaHCO_3$ (200 mL), H_2O (200 mL), and saturated NaCl (200 mL), then dried over Na_2SO_4, and concentrated under reduced pressure to afford 136 g of (*S*)-**15** as an oil. The crude product was used without further purification in the next reaction.

(*S*)-(−)-2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]-propyl]-1,3-thiazolidin-4-one Hydrogen Fumarate (CP-060*S*). To a solution of (*S*)-**15** (136 g, 287 mmol) in acetone (478 mL) were added HCl-salt of **6** (73.1 g, 316 mmol), K_2CO_3 (119 g, 861 mmol), and NaI (215 g, 1.43 mol). The mixture was stirred for 17 h at ambient temperature. The reaction mixture was poured into ice-cooled H_2O (1.2 L) and extracted with AcOEt. The organic extracts were washed with H_2O (200 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford 168 g of crude product as a brown oil. To the solution of this oil (168 g) in EtOH (100 mL) was added a hot solution of fumaric acid (27.9 g, 240 mmol) in EtOH (760 mL). After the mixture stirred for 15 min at ambient temperature, the mixture was concentrated under reduced pressure. The residue was dissolved in toluene (630 mL), and hexane (210 mL) was added. After being seeded with a small amount (∼10 mg) of CP-060*S* (99.8% ee), the mixture was stirred overnight at ambient temperature, and then the precipitate was filtered. The filter cake was washed with AcOEt−hexane (10:3, 500 mL × 4) and dried under vacuum to give 126 g of crude CP-060*S*. The crude material was dissolved in EtOH (230 mL), and H_2O (230 mL) was added. The mixture was stirred for 1.5 h at ambient temperature to form a crystalline product. The product was filtered, washed with H_2O (100 mL), and dried at 60 °C, affording 100 g of CP-060*S* (99.8% ee) as colorless crystals (53% yield from (*S*)-**4**): mp 143−144 °C; ^{1}H NMR (DMSO-d_6) δ 1.36 (18H, s), 1.5−1.8 (2H, m), 2.18 (3H, s), 2.3−2.5 (2H, m), 2.6−2.8 (3H, m), 3.3−3.5 (1H, m), 3.63 and 3.75 (2H, ABq, J = 15.7 Hz), 3.95 (2H, t, J = 5.6 Hz), 5.4 (3H, brs), 5.78 (1H, s), 5.94 (2H, s), 6.32 (1H, dd, J = 8.3, 2.6 Hz), 6.58 (1H, d, J = 2.6 Hz), 6.60 (2H, s), 6.77 (1H, d, J = 8.3 Hz), 7.10 (2H, s). Anal. Calcd for $C_{30}H_{42}N_2O_5S\cdot C_4H_4O_4$: C, 61.99; H, 7.04; N, 4.25; S, 4.87. Found: C, 61.77; H, 7.10; N, 3.90; S 4.91. The optical purity of CP-060*S* was analyzed by chiral HPLC [column: Chiralcel OD; mobile phase: hexane/*i*-PrOH (80:20); flow rate: 0.7 mL/min]. The retention times are 10.2 and 12.0 min for the *R* and *S* enantiomers, respectively.

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