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Practical Enantioselective Synthesis of Endothelin Antagonist S-1255 by Dynamic Resolution of 4-Methoxychromene-3-carboxylic Acid Intermediate

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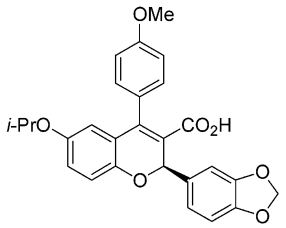
A practical multikilogram-scale synthesis of enantiomerically pure S-1255 (**1**), a potent and orally active ET_A receptor antagonist, is described. Utilizing readily available starting materials and reagents, the entire sequence of reactions starting from 2,5-dihydroxyacetophenone **8** proceeded under mild conditions to give **1** in an excellent chemical yield (8 steps, 41% overall yield) and in a high enantiopurity (98% ee). The crucial step of the synthesis is a dynamic resolution of key intermediate **16**. (*R*)-Methoxy acid (*R*)-**16** having 97−99% ee was obtained in 83−84% yield from racemic **16** as a crystalline (1*S*,2*R*)-(+)-norephedrine or (+)-cinchonine salt by the dynamic resolution comprising concurrent crystallization and in situ racemization. A mechanism of the dynamic resolution through a ring-opened zwitterionic intermediate is discussed. In the final synthetic step, an effective carbon−carbon bond formation between the C4 carbon and the *p*-anisyl group was accomplished by a conjugate addition−elimination reaction of Grignard reagent **3** to (*R*)-**16** to give **1** having 98% ee. Owing to high efficiencies of functional group transformations, carbon−carbon bond formations, and the dynamic resolution, the synthesis required no chromatographic purification and was amenable to a multikilogram-scale preparation. Several kilograms of **1** for clinical trials were successfully prepared by this process.

Introduction

Endothelins (ET), endogenous vasoconstrictive peptides consisting of 21 amino acids, have been implicated in various cardiovascular disorders.[1] Three isopeptides, ET-1, ET-2, and ET-3, have been identified, which exert the biological actions by binding the G-protein-coupled receptors, ET_A and ET_B. Because of a promising therapeutic potential of an ET_A receptor antagonist, a number of peptide and nonpeptide ET_A receptor antagonists have been developed for treating various cardiovascular diseases.[2]

In a previous paper,[3] we have reported a synthesis, the biology, and the structure−activity relationships (SAR) of a novel ET_A receptor antagonist, S-1255 (**1**), which is an optically active 2*H*-chromene-3-carboxylic acid bearing substituted phenyl groups on the 2- and 4-positions. The absolute configuration of the 2-position was determined to be *R* by X-ray analysis.[3] In a discovery route, **1** was prepared in 10 steps from 2,5-dihydroxyacetophenone **8** and in overall yield of 5%.[3] Although this route facilitated the SAR studies and led to a rapid optimization of lead derivatives, it had several drawbacks for a multikilogram-scale preparation of **1**. The most serious problem resided in the optical resolution of the racemic **1** (*rac*-**1**) in the last step, where the yield was as low as 25% and no practical method for recycling the undesired (*S*)-isomer by racemization was available. The original route also required several expensive reagents such as a palladium complex in the Suzuki coupling reaction, and chromatographic purification was used in most of the reaction steps.

Since identification of **1** as a promising drug candidate, we have investigated a more efficient enantioselective synthesis of **1** that is amenable to a multikilogram-scale preparation to supply a sufficient amount of **1** for



S-1255 (**1**)

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(1) Yanagisawa, M.; Kurihara, H.; Kimura, S.; Tomobe, Y.; Kobayashi, M.; Mitsui, Y.; Yasaki, Y.; Goto, K.; Masaki, T. *Nature* **1988**, *332*, 411.

(2) Wu, C. *Exp. Opin. Ther. Patents* **2000**, *10*, 1653 and references therein.

(3) Ishizuka, N.; Matsumura, K.; Sakai, K.; Yamamori, T.; Mihara, S.; Fujimoto, M. *J. Med. Chem.* **2002**, *10*, 2041.

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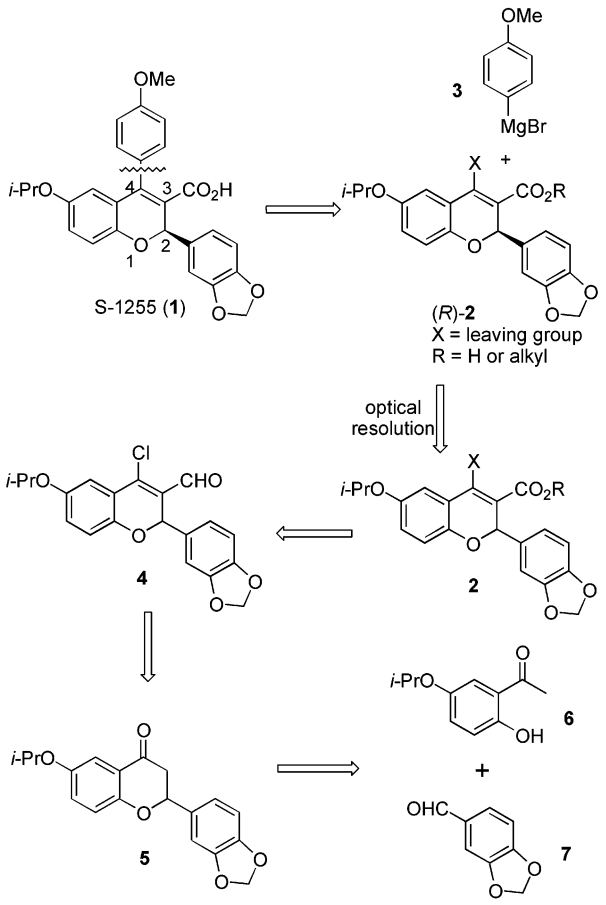
SCHEME 1



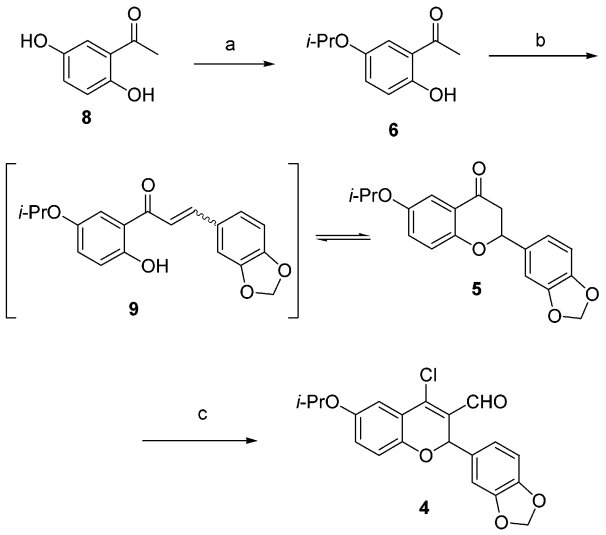
toxicological and clinical studies. In this paper, we report the development of a practical multikilogram-scale synthesis of S-1255 (**1**) via a new dynamic resolution of the key intermediate **16**, and the mechanism of the dynamic resolution is discussed.

Results and Discussion

Retrosynthesis. Our retrosynthetic analysis of **1** is shown in Scheme 1. The retrosynthetic disconnection of the alkenyl−aryl bond at the 4-position furnished chromene (*R*)-**2** having a leaving group X at the 4-position. The conjugate addition−elimination reaction of Grignard reagent **3** to (*R*)-**2** was planned for this alkenyl−aryl bond formation. (*R*)-**2** would be prepared by an optical resolution of racemic carboxylic acid **2** (R = H) via a diastereomeric salt with an optically active amine. The racemic **2** could be synthesized from aldehyde **4** via chromanone **5**, which could be prepared by the coupling of piperonal **7** with 2-hydroxy-5-isopropoxyacetophenone **6** that could be readily available from inexpensive 2,5-dihydroacetophenone **8**. An efficient optical resolution of the racemic **2** (R = H) with facile racemization of the unwanted (*S*)-**2** (R = H) should be developed.

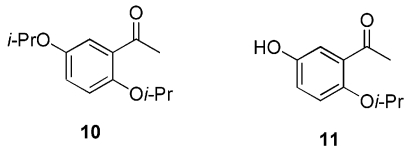
Synthesis of Chloroaldehyde 4. As shown in Scheme 2, commercially available 2,5-dihydroxyacetophenone **8** was treated with 2-bromopropane and K_2CO_3 in refluxing MeCN. Simple filtration and concentration of the reaction mixture gave 5-isopropoxy-2-hydroxyacetophenone **6** containing 2% of **8** and 9% of 2,5-diisopropoxy compound **10** (HPLC). 2-Isopropoxy compound **11** also was detected in

SCHEME 2[a]



[a] Reagents and conditions: (a) *i*-PrBr, K_2CO_3, MeCN, reflux; (b) **7**, 2 N NaOH, MeOH, rt, 78% (2 steps); (c) $POCl_3$, DMF, rt, 99%.

a small amount when other alkylation conditions were used. This crude material of **6** was used for the next reaction without further purification. The regioselective isopropylation on the 5-position can be explained by an intramolecular hydrogen bonding between the 1-acetyl oxygen and the 2-hydroxy hydrogen, which retards the alkylation of the 2-hydroxy group.

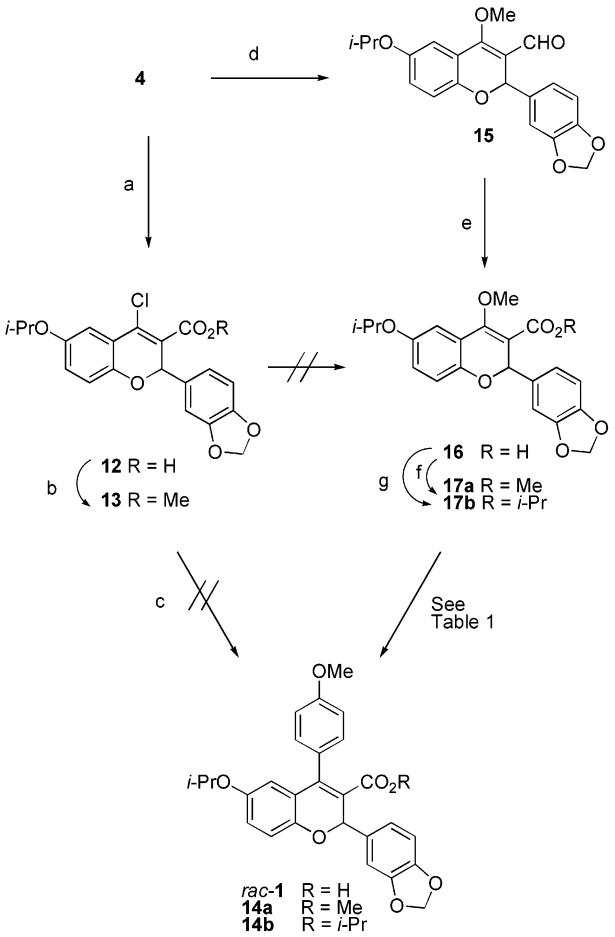


Synthesis of chromanone **5** from **6** was conducted under conventional basic conditions.[4] Stirring of a MeOH solution of crude **6**, piperonal **7**, and 2 N NaOH at room temperature followed by collection of the precipitated crystals by filtration gave **5** containing 4% of chalcone **9** in 78% overall yield from **8**. The choice of the solvent proved to be crucial for this reaction. When EtOH or MeCN was used as the solvent, none of the crystals were precipitated out and a complex mixture of **5**, **9**, and aldol products was obtained. These results show that chromanone **5** is in equilibrium with chalcone **9** in the reaction solution,[5] and crystallization of **5** from MeOH (not from EtOH or MeCN) shifts the equilibrium to give **5** in good yield.

The next step involving formylation of chromanone **5** at the 3-positon and a concurrent enol chlorination at the 4-position to form chloroaldehyde **4** was accomplished in a single step by a Vilsmeier−Haack-type reaction.[6] Reaction of **5** with $POCl_3$ in DMF at room temperature, followed by addition of H_2O and collection of the precipitates, gave **4** in 99% yield and 95% purity.

(4) Reichel, L.; Müller, K. *Chem. Ber.* **1941**, *74*, 1741.
(5) Draper, R. W.; Radha, B. H.; Iyer, R. V.; Li, X.; Lu, Y.; Rahman, M.; Vater, E. J. *Tetrahedron* **2000**, *56*, 1811.
(6) Litkei, G.; Patonay, T.; Szilágyi, L.; Dinya, Z. *Org. Prep. Proced. Int.* **1991**, *23*, 741.

SCHEME 3[a]

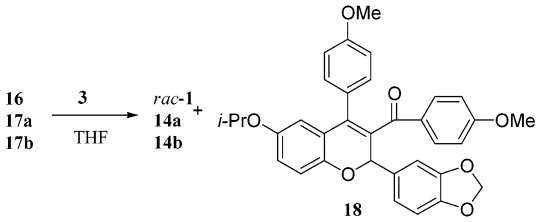


[a] Reagents and conditions: (a) $NaClO_2$, NH_2SO_3H, toluene, H_2O, 0 °C, 91%; (b) MeI, K_2CO_3, DMF, rt, 100%; (c) **3**, THF, 0 °C or **3**, CuI, THF, 0 °C; (d) 28% NaOMe, MeOH, reflux; (e) $NaClO_2$, NaH_2PO_4, DMSO, H_2O (pH 5), 25 °C, 69% (2 steps); (f) MeI, K_2CO_3, DMF, rt, 88%; (g) *i*-PrBr, K_2CO_3, DMF, rt, 96%.

Synthesis of Racemic S-1255 (*rac*-1). Carbon−Carbon Bond Formation at the C4 Position. Conversion of chloroaldehyde **4** into S-1255 (**1**) requires oxidation of the formyl group to the carboxylic acid at the 3-position, substitution of chlorine with the *p*-anisyl group at the 4-position, and introduction of the chirality at the 2-position. To optimize the oxidation and substitution conditions, synthesis of the racemic **1** (*rac*-**1**) was initially examined. Having failed in the reaction of **4** with Grignard reagent **3** under a variety of conditions, we next tried the Grignard reaction of 3-carboxy derivatives (Scheme 3). Chloroaldehyde **4** was treated with $NaClO_2$ in the presence of NH_2SO_3H as an HOCl scavenger[7] to give chloro acid **12** in 91% yield. The esterification of **12** with MeI afforded methyl ester **13** in quantitative yield. The conjugate addition−elimination reaction of **12** or **13** with Grignard reagent **3** was then examined to form the carbon−carbon bond at the 4-position giving compound *rac*-**1** or **14a**. But, the reaction for **12** or **13** failed, giving unchanged starting materials or 1,2-addition product. The addition of CuI to the reaction mixture was also ineffective.

(7) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888.

TABLE 1. Addition−Elimination Reaction of 16 or 17 with Grignard Reagent 3

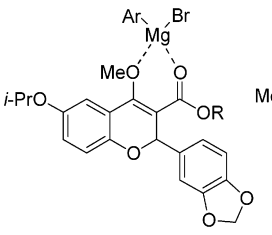


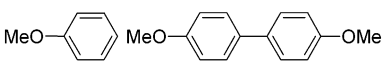
		conditions			yield (%)[a]		
entry	reactant	**3** (equiv)	*T* (°C)	time (h)	**16** or **17**	*rac*-**1** or **14**	**18**
1	**16**	3.0	0	2	6	81	0
2	**16**	4.0	0	2	0	87 (84[b])	0
3	**17a**	1.1	0	3	34	57	9
4	**17a**	3.0	0	0.5	0	64[c]	30[c]
5	**17b**	3.0	0	0.5	0	82	9
6	**17b**	3.0	−78	4	4	64	18

[a] Determined by HPLC analysis of the crude reaction mixture unless otherwise stated. The yield was presented as an area percentage of the compound peak relative to the total area of all the peaks integrated. [b] Isolated yield after recrystallization. [c] Isolated yield after chromatography.

As the methoxy group has been known to be a better leaving group than the chloro group for this type of Grignard reaction,[8,9] we determined to try the reaction for methoxy acid **16** and methoxy esters **17**. Preparation of these compounds is shown in Scheme 3. The reaction of chloro acid **12** or chloro ester **13** with NaOMe to give **16** or **17a** was unsuccessful, recovering unchanged **12** and **13**. Alternatively, the reaction of chloroaldehyde **4** with NaOMe proceeded smoothly to give methoxyaldehyde **15**, which was isolated by aqueous workup and used for the next step without further purification. Oxidation of **15** with an acidic reagent of $NaClO_2$−NH_2SO_3H resulted in decomposition of the starting material **15**, whereas mild $NaClO_2$−DMSO oxidation in a weakly acidic medium[10] gave highly pure methoxy acid **16** (HPLC, 99% purity) in 69% overall yield from **4** after aqueous workup and crystallization from toluene. The esterification of **16** with MeI or 2-bromopropane with K_2CO_3 as the base and DMF as the solvent provided methyl ester **17a** or isoporpyl ester **17b**, respectively, in good yield.

The results of the conjugate addition−elimination reaction with Grignard reagent **3** are summarized in Table 1. The reaction of 4-methoxy acid **16** with **3** proceeded smoothly to give *rac*-**1** in excellent yields (entries 1 and 2). Coordination of the methoxy group and the carbonyl group on the metal center of **3** would be responsible for this smooth substitution.[9] To complete the reaction, 4.0 equiv of the Grignard reagent was required (entry 2 vs entry 1). Although the crude product of *rac*-**1**





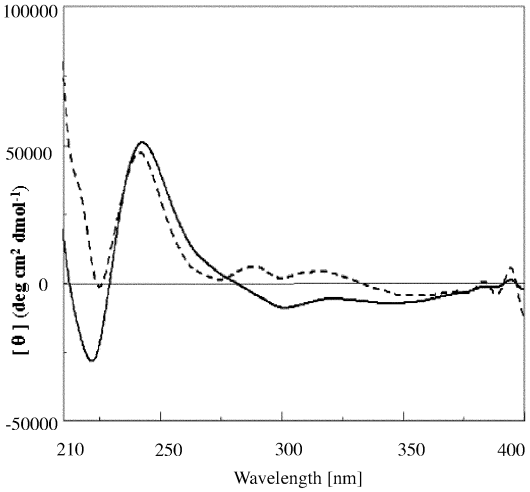


FIGURE 1. CD spectra of (*R*)-(+)-**16** (a solid line) and **1** (a dotted line) in MeOH.

was contaminated with anisole **19** and homodimer **20** arising from the Grignard reagent, these byproducts were readily removed by the simple acid−base extraction method. The overall yield of *rac*-**1** from chloroaldehyde **4** was 58% in three steps, in which no chromatographic purification was required. Thus, an efficient synthetic route applicable to a multikilogram-scale production of **1** was established.

The reaction for methoxy esters **17** was also examined to minimize the amount of Grignard reagent **3** (Table 1, entries 3 to 6). The reaction of methyl ester **17a** with 1.1 equiv of **3** resulted in recovery of **17a** and formation of ketone **18**, excessive addition byproduct (entry 3). When 3.0 equiv of **3** was used, the starting material **17a** was completely consumed, but the formation of **18** was significantly increased (entry 4). The use of **17b** having a bulkier isopropyl group in an attempt to avoid the formation of **18** was not fruitful (entries 5 and 6). In addition, the protection of the carboxyl group (**17** vs **16**) is not beneficial from the viewpoint of brevity.

Dynamic Resolution of Methoxy Acid 16. Our attention was next directed to the enantioselective synthesis of S-1255 (**1**) via the resolution of methoxy acid **16**, the precursor of *rac*-**1**, using optically active amines. A conventional optical resolution of **16** by the diastereomeric salt formation with (1*S*,2*R*)-(+)-norephedrine ((+)-NE) in MeOH/MeCN (1/1) gave (+)-**16**·(+)-NE salt (**22**) in 42% yield and 99% ee.

The absolute configuration of the salt **22** obtained was determined from a CD spectrum of a pure sample (100% ee) of free acid (+)-**16** prepared from **22** by the method in the next section, followed by recrystallization from acetone/isopropyl ether. Compound (+)-**16** exhibits a positive Cotton effect around 240 nm arising from the styrene chromophore similar to that of **1** (Figure 1), indicating that both compounds have the same stereochemistry.[11] Because the absolute configuration of **1** already has been assigned to be *R* on the basis of the single-crystal X-ray structure,[3] that of (+)-**16** is reasonably assigned to be *R*. This conclusion was further supported by the experimental result that (+)-**16** was converted into **1** by the reaction with **3** (vide infra), which should rationally proceed with retention of configuration at the 2-position.

As the maximum theoretical yield of the desired (*R*)-salt **22** in the above conventional resolution is only 50%, the resolution conditions should be modified to improve the yield of **22**. Two important observations for the modification were found during the conventional resolution. First, the unwanted (*S*)-**16**·(+)-NE salt (**21**) in the filtrate was rapidly epimerized by heating to give a 1:1 mixture of (*S*)-salt **21** and (*R*)-salt **22**. Second, the desired (*R*)-salt **22** is less soluble in many organic solvents, whereas (*S*)-salt **21** is more soluble and tends to remain in solution or as an oil in a concentrated solution. These observations suggested that a dynamic resolution of methoxy acid **16** could be achieved by modifying the resolution conditions. A dynamic resolution is a methodology in which a racemic or diastereomeric compound is transformed into a single stereoisomer by a preferential crystallization of one stereoisomer coupled with an in situ racemization of the other, thereby offering the potential of 100% conversion to the desired stereoisomer.[12]

The optimal condition for the dynamic resolution of **16** with (+)-NE was first investigated. The first crop of the desired (*R*)-salt **22** was isolated in 54% yield and 96% ee by heating a solution of acid **16** and (+)-NE in MeOH at 40 °C (Scheme 4). The yield of over 50% indicated that the dynamic resolution occurred. To recycle the unwanted (*S*)-salt **21** in filtrate through racemization, the filtrate was heated under reflux conditions. After concentration, the mixture was stirred at 40 °C to give the second crop (22% yield, 99% ee). A similar resolution−racemization process was repeated by using the second filtrate to give the third crop (8% yield, 99% ee). Thus, (*R*)-salt **22** of 97% ee was isolated in 84% total yield. The fourth crop (6% yield, 99% ee) obtained in a similar manner was contaminated with chromanone **5**, which presumably formed by a hydrolysis of the vinylic methoxy moiety at the 4-position in **16** followed by decarboxylation of the resulting 4-oxo-3-carboxylic acid.

While carrying out a multikilogram-scale preparation of **1** by this method, several optically active amines other than (+)-NE were screened for the dynamic resolution. (+)-Cinchonine was found to be the most suitable. After a solution of acid **16** and an equimolar amount of (+)-cinchonine in MeOH/*i*-PrOH (1/1) was stirred at 70 °C and then at 45 °C, the precipitates were collected to give

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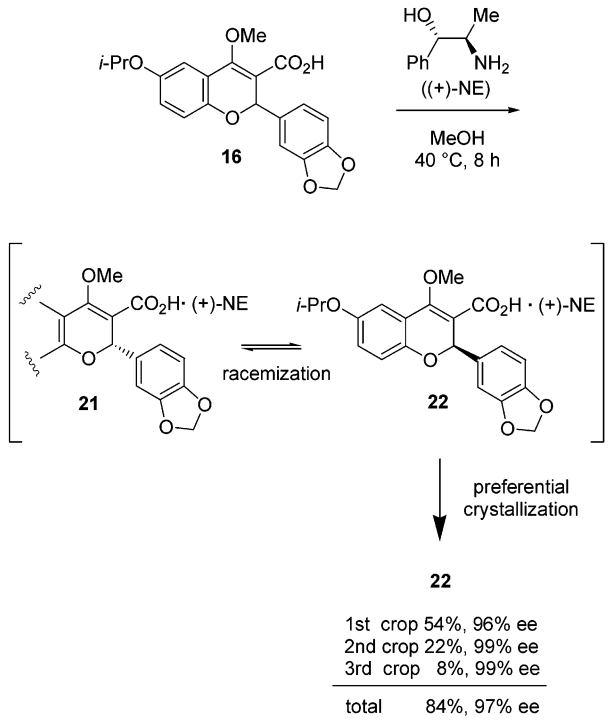
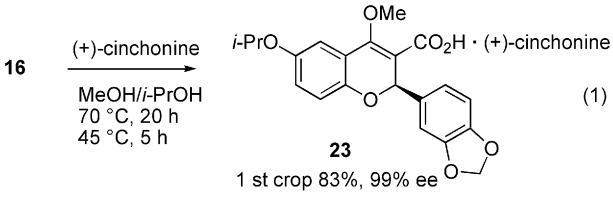
SCHEME 4



the desired (*R*)-**16**·(+)-cinchonine salt (**23**) in 83% yield and 99% ee (eq 1). It was significant that **23** was obtained



(1)

in excellent yield in a single crystallization step without recycling the (*S*)-isomer. Among a number of dynamic resolutions reported,[12] our method especially using (+)-cinchonine exceeds others in several respects: excellent yield and high enantiopurity of the product, the mild conditions, the simple operation, the use of an inexpensive resolving reagent, and no requirement of an auxiliary to accelerate the racemization.

Although the dynamic resolution of *rac*-**1** with some chiral amines[13] was also attempted under several conditions, the yield of **1** did not exceed 50% owing to a sluggish racemization of the antipode of **1** under the resolution conditions.

A facile racemization of (*R*)- and (*S*)-**16** under the resolution conditions is crucial for our successful dynamic resolution. To clarify the mechanism of the dynamic resolution, the racemization rates of **1** and (*R*)-**16** were compared in MeOH at 40 °C in the presence or absence of Et_3N, NaOH, or H_2SO_4 (Figure 2). The order of the racemization rate was found to be **1** < (*R*)-**16** < (*R*)-**16**/Et_3N = (*R*)-**16**/NaOH < (*R*)-**16**/H_2SO_4. These data indicate that the existence of the methoxy group at the 4-position (**1** vs (*R*)-**16**) and the formation of the carboxylate anion at the 3-position (addition of base) play crucial roles in the racemization.

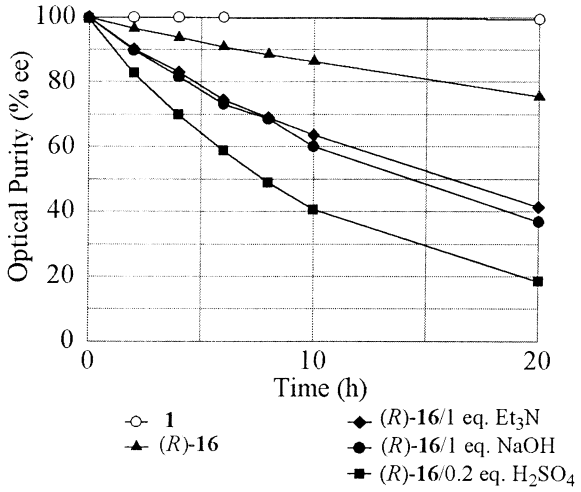


FIGURE 2. Racemization rates of **1** and (*R*)-**16** in MeOH at 40 °C.

The racemization of **16** can be explained by a mechanism via the ring-opened zwitterionic intermediate (Figure 3, A−D) as reported in the C2 epimerization of a 2*H*-chromene compound.[14] The existence of the zwitterionic intermediate is supported by an experimental result that the C2 proton of (*R*)-**16** was not exchanged with deuterium when its (+)-NE salt **22** was refluxed in CD_3OD. This indicates the O1−C2 bond cleavage in a racemizing process and denies the double bond isomerization mechanism involving protonation−deprotonation on C3−C4 and isomerized C2−C3 olefins of **16** in CD_3OD. Both the electron-donating mesomeric effect of the C4 methoxy group ($\sigma_R = -0.58$,[15] B) and the electron-donating inductive effect of the C3 carboxylate anion ($\sigma_I = -0.19$,[15] C) will stabilize the C2 carbocation in the zwitterionic intermediate, facilitating the racemization of **16**. This proposed racemization mechanism can explain the successful dynamic resolution of methoxy acid **16** with (+)-NE or (+)-cinchonine.

The racemization rate was also enhanced by the addition of a catalytic amount of H_2SO_4. In this case, protonation at the O1 atom prompts the O1−C2 bond cleavage, leading to the rate enhancement of the racemization (Figure 3, D).

Synthesis of Enantiomerically Pure S-1255 (1). Liberation of free acid (*R*)-**16** from (+)-NE salt **22** was carried out by using aqueous H_3PO_4 buffered with NaH_2PO_4 at pH 4 to minimize the acid decomposition of (*R*)-**16** (Scheme 5). Crude acid (*R*)-**16** obtained in 97% ee was used for the next step without further purification. (+)-NE was easily recovered from the aqueous layer by treatment with aqueous NaOH followed by toluene extraction.

The reaction of (*R*)-**16** with Grignard reagent **3** was accomplished by using a procedure similar to that

(13) (1*S*,2*R*)-(+)-Norephedrine, (+)-cinchonine, (−)-cinchonidine, (*R*)-(+)-α-methylbenzylamine, (*R*)-(+)-α-amino-ϵ-caprolactam, and (*R*)-(+)-1-(1-naphthyl)ethylamine were examined.

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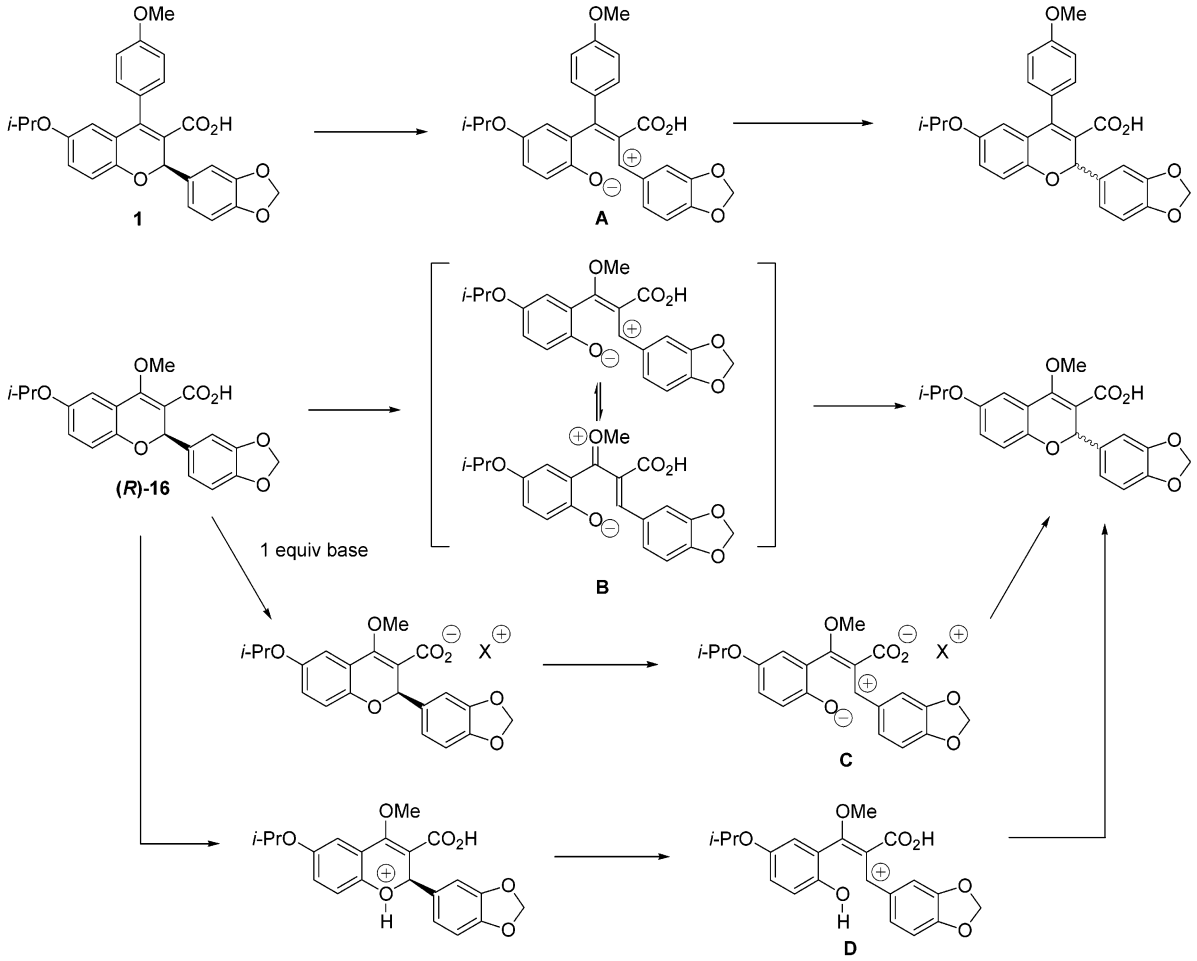
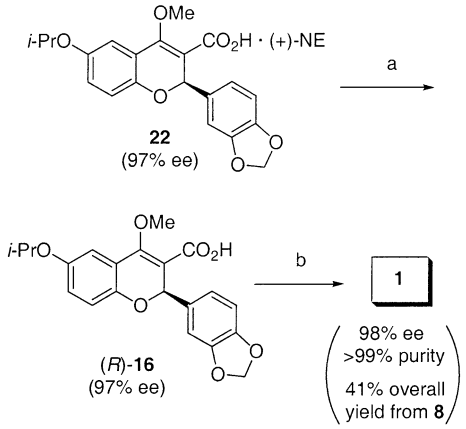


FIGURE 3. Proposed racemization mechanism.

SCHEME 5[a]



[a] Reagents and conditions: (a) H_3PO_4, NaH_2PO_4, EtOAc, H_2O (pH 4); (b) 4.0 equiv of **3**, THF, 0 °C, 92% (2 steps).

employed for the synthesis of *rac*-**1**. The reaction proceeded cleanly without racemization at the C2 position. After workup for removing anisole **19** and dimer **20**, the product was crystallized from MeOH/H_2O (1/1) with stirring at room temperature to give the crude **1**. Recrystallization of the crude **1** from MeOH/H_2O (4/1) at room temperature gave purified **1** having 98% ee and >99% purity in 92% yield (41% overall yield from **8**). Although **1** was prepared on a kilogram scale via the (*R*)-**16**·(+)-NE salt (**22**), it is obvious that the (*R*)-**16**·(+)-cinchonine salt (**23**) obtained more simply can be equally used for the kilogram-scale synthesis of **1**.

Conclusion

We have established the practical multikilogram-scale synthesis of S-1255 (**1**), which provides a shorter route and higher overall yield than the original synthesis (8 steps and 41% overall yield vs 10 steps and 5% overall yield). To achieve the efficient enantioselective synthesis, the highly efficient dynamic resolution of the key intermediate **16** with (+)-NE or (+)-cinchonine as the resolving reagent was newly developed. A mechanistic investigation has shown that the methoxy group at the 4-positon as well as the carboxylate anion at the 3-position play important roles in the successful dynamic resolution. The formation of the carbon−carbon bond between the C4 atom and the *p*-anisyl group was successfully accomplished by the addition−elimination reaction of (*R*)-**16** with Grignard reagent **3** without loss of enantiopurity. The short-step synthesis of **1** described herein required no chromatographic purification and thus can be easily applicable to the kilogram-scale preparation. In fact, this process has been scaled up in the pilot plant to make over 10 kg of compound **1** for clinical evaluations.

Experimental Section

General Methods. Chromatography was done on silica gel (70−230 mesh). Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, and signals are given in ppm with TMS as an internal standard. *J* values are given in hertz. Optical rotations were measured in a 10-cm cell. HPLC analysis was performed under the following conditions. Condition A: Cosmosil 5C18R AR 4.6 mm × 150 mm; solvent, MeCH/H_2O/TFA; flow rate, 1.0 mL/min; detection, 254 nm. Condition B: CHIRALCEL OJ-R 4.6 mm × 150 mm; solvent, MeCN/H_2O/TFA or MeCN/0.2 M H_3PO_4−KH_2PO_4 (pH 2.2); flow rate, 0.5 mL/min; detection, 286 nm. HPLC results are presented as an area percent of the peak for a particular compound relative to the total area of all the peaks integrated.

5-Isopropoxy-2-hydroxyacetophenone (6). A mixture of 2,5-dihydroxyacetophenone **8** (1.52 kg, 10.0 mol), 2-bromopropane (3.08 kg, 25.0 mol), K_2CO_3 (325 mesh, 3.46 kg, 25.0 mol), and MeCN (15.2 L) was stirred under reflux for 10 h. An insoluble material was removed by filtration and the filtrate was concentrated under reduced pressure. Toluene (6 L) was added to the residue and the resulting suspension was concentrated to 4 L. An insoluble material was removed by filtration and the filtrate was concentrated under reduced pressure to give crude **6** (2.00 kg) as a dark brown oil, which contained 2% of **8** and 9% of dialkoxy compound **10** (HPLC). This crude product was used in the next reaction without further purification. Analytically pure samples of **6** and **10** were obtained by silica gel chromatography (EtOAc/hexane, 1/5). **6**: Yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.32 (6H, d, J = 6.1), 2.60 (3H, s), 4.34−4.52 (1H, m), 6.89−7.23 (3H, m). ^{13}C NMR ($CDCl_3$) δ 22.4, 27.1, 71.9, 117.7, 119.3, 119.7, 126.5, 149.9, 156.9, 204.1. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.97; H, 7.43. **10**: Yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.30 (6H, d, J = 6.0), 1.37 (6H, d, J = 6.0), 2.62 (3H, s), 4.44−4.61 (2H, m), 6.87 (1H, d, J = 9.0), 6.98 (1H, dd, J = 3.3 and 9.0), 7.26 (1H, d, J = 3.3). ^{13}C NMR ($CDCl_3$) δ 22.4, 22.5, 32.5, 71.1, 71.5, 115.7, 116.6, 122.7, 129.9, 151.5, 151.8, 200.0. Anal. Calcd for $C_{14}H_{20}O_3$·0.1H_2O: C, 70.62; H, 8.55. Found: C, 70.32; H, 8.44. HPLC, condition A (MeCN/H_2O/TFA (75/25/0.1)): t_R **8**, 1.8 min; t_R **6**, 3.0 min; t_R **10**, 4.0 min.

2-(Benzo[1,3]dioxol-5-yl)-6-isopropoxychroman-4-one (5). To a stirred mixture of crude **6** (2.00 kg), piperonal (1.35 kg, 9.00 mol), and MeOH (2.25 L) was added 2 N NaOH (9.00 L, 18.0 mol) at room temperature, and the stirring was continued for 2 days. The precipitated product was collected by filtration, washed with H_2O (60 L), and air dried to give **5** (2.54 kg, 78% yield from **8**) as yellow crystals, which contained 4% of chalcone **9** (HPLC). An analytically pure sample of **5** was obtained by recrystallization from acetone/isopropyl ether. Mp 125−126 °C. ^{1}H NMR ($CDCl_3$) δ 1.33 (6H, d, J = 6.1), 2.76−3.11 (2H, m), 4.44−4.62 (1H, m), 5.34 (1H, dd, J = 3.2, 13.0), 5.99 (2H, s), 6.81−7.36 (6H, m). ^{13}C NMR ($CDCl_3$) δ 22.3, 22.3, 44.9, 71.0, 79.8, 101.6, 107.0, 108.6, 110.4, 119.6, 120.2, 121.0, 127.2, 132.9, 148.1, 148.2, 152.5, 156.1, 192.2. Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 70.16; H, 5.46. **9**: Yellow crystals. Mp 164−166. ^{1}H NMR ($CDCl_3$) δ 1.34 (6H, d, J = 5.7), 4.43−4.51 (1H, m), 6.04 (2H, s), 6.86 (1H, d, J = 8.1), 6.96 (1H, d, J = 9.0), 7.12−7.18 (3H, m), 7.39−7.44 (2H, m), 7.84 (1H, d, J = 15.3), 12.44 (1H, s). ^{13}C NMR ($CDCl_3$) δ 22.5, 72.0, 102.0, 107.0, 109.0, 117.1, 118.3, 119.4, 120.2, 126.0, 126.1, 129.3, 145.6, 148.7, 149.8, 150.5, 158.1, 193.3. Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.59; H, 5.42. HPLC, condition A ((MeCN/H_2O/TFA (75/25/0.1)): t_R **5**, 3.8 min; t_R **9**, 5.6 min.

2-(Benzo[1,3]dioxol-5-yl)-4-chloro-6-isopropoxy-2*H*-chromene-3-carbaldehyde (4). Phosphoryl oxychloride (2.68 kg, 17.5 mol) was added dropwise to DMF (6.85 L) with stirring at 0 °C over 1.5 h and the mixture was additionally stirred at room temperature for 30 min. To the resulting mixture was added chromanone **5** (2.28 kg, 7.00 mol) in one portion. The reaction mixture was stirred at room temperature for 24 h and then poured into a mixture of NaOAc (7.18 kg, 12.5 mol), EtOAc (1.37 L), and ice−water (27.4 L). The resulting precipitate was collected by filtration, washed with H_2O (55 L), and air dried to give **4** (2.58 kg, 99%) as yellow crystals: Mp 126−127 °C. ^{1}H NMR ($CDCl_3$) δ 1.33 (6H, d, J = 6.0), 4.38−4.57 (1H, m), 5.90 (2H, s), 6.23 (1H, s), 6.60−7.26 (6H, m), 10.26 (1H, s). ^{13}C NMR ($CDCl_3$) δ 22.4, 22.5, 71.3, 75.0, 101.4, 107.8, 108.4, 113.1, 118.6, 120.8, 121.1, 123.2, 127.3, 132.0, 144.0, 148.0, 148.1, 148.9, 152.8, 188.2. Anal. Calcd for $C_{20}H_{17}ClO_5$: C, 64.44; H, 4.60; Cl, 9.51. Found: C, 64.36; H, 4.53; Cl, 9.28. HPLC, condition A ((MeCN/H_2O/TFA (75/25/0.1)): t_R 5.5 min.

2-(Benzo[1,3]dioxol-5-yl)-4-chloro-6-isopropoxy-2*H*-chromene-3-carboxylic Acid (12). A solution of NH_2SO_3H (57.6 g, 593 mmol) in H_2O (346 mL) was added to a stirred solution of chloroaldehyde **4** (92.0 g, 247 mmol) in toluene (1.38 L). Thereto was added dropwise a solution of $NaClO_2$ (55.9 g, 618 mmol) in H_2O (346 mL) over 1 h at 0 °C, and stirring was continued for 20 min at the same temperature. The reaction was quenched successively with aqueous 24% Na_2SO_3 (131 g) and aqueous 5.5% NaOH (740 g). After removing the toluene layer, the aqueous layer was acidified with concentrated HCl to pH 2. The resultant precipitate was collected by filtration, washed with H_2O, and air dried to give **12** (87.5 g, 91%) as yellow crystals: mp 177 °C. ^{1}H NMR ($CDCl_3$) δ 1.33 (6H, d, J = 6.0), 4.36−4.54 (1H, m), 5.91 (2H, s), 6.25 (1H, s), 6.26−7.26 (6H, m). ^{13}C NMR ($CDCl_3$) δ 22.4, 22.5, 71.2, 76.5, 101.5, 108.2, 108.4, 114.0, 118.3, 120.2, 121.6, 121.9, 122.1, 131.7, 139.4, 147.8, 148.0, 148.2, 152.7, 168.8. Anal. Calcd for $C_{20}H_{17}ClO_6$: C, 61.78; H, 4.41; Cl. 9.12. Found: C, 61.84; H, 4.12; Cl, 8.84.

Methyl 2-(Benzo[1,3]dioxol-5-yl)-4-chloro-6-isopropoxy-2*H*-chromene-3-carboxylate (13). A mixture of chloro acid **12** (7.00 g, 18.0 mmol), MeI (3.83 g, 27.0 mmol), K_2CO_3 (3.73 g, 27.0 mmol), and DMF (70 mL) was stirred at room temperature for 3 h. The reaction mixture was poured into ice−water and extracted with toluene, and the extract was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/3) to give **13** (7.25 g, 100%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.31 (6H, d, J = 6.3), 3.78 (3H, s), 4.42−4.49 (1H, m), 5.91 (2H, s), 6.23 (1H, s), 6.674−6.72 (2H, m), 6.78−6.84 (3H, m), 7.22 (1H, d, J = 2.7). ^{13}C NMR ($CDCl_3$) δ 22.4, 22.5, 52.5, 71.2, 76.8, 101.4, 108.2, 108.3, 113.9, 118.0, 121.3, 121.5, 121.6, 121.9, 131.9, 136.2, 147.4, 148.0, 148.1, 152.7, 164.3. Anal. Calcd for $C_{21}H_{19}ClO_6$·0.1EtOAc: C, 62.44; H, 4.85; Cl, 8.61. Found: C, 62.13; H, 4.81; Cl, 8.67.

2-(Benzo[1,3]dioxol-5-yl)-6-isopropoxy-4-methoxy-2*H*-chromene-3-carbaldehyde (15). Chloroaldehyde **4** (2.42 kg, 6.50 mol) was added portionwise to a stirred mixture of NaOMe (28 wt % solution in MeOH, 1.38 kg, 7.15 mol) and methanol (7.3 L). After being stirred at 40 °C for 1.5 h, the reaction mixture was allowed to cool to room temperature and then poured into a mixture of EtOAc (24 L) and ice−water (24 L). The organic layer was separated and an aqueous layer was extracted with EtOAc (6 L). After each layer was washed with brine (24 L), the organic layer and the extract were combined and concentrated. Toluene (2.4 L) was added to the residue, and the resulting suspension was concentrated to remove EtOAc. This procedure was repeated twice to give crude **15** (2.68 kg), which was used for the next step without further purification. An analytically pure sample of **15** was obtained by recrystallization from acetone/isopropyl ether. Yellow crystals. Mp 82−83 °C. ^{1}H NMR ($CDCl_3$) δ 1.32 (6H, d, J = 6.0), 4.06 (3H, s), 4.35−4.53 (1H, m), 5.88 (2H, s), 6.24 (1H, s), 6.64−7.26 (6H, m), 10.21 (1H, s). ^{13}C NMR ($CDCl_3$) δ 22.4, 22.5, 64.0, 71.2, 74.1, 101.3, 107.9, 108.2, 111.2, 118.5, 118.9, 119.1, 121.0, 122.5, 133.0, 147.8, 147.8, 150.8, 152.5, 165.0, 186.9. Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.42; H, 5.50. HPLC, condition A ((MeCN/H_2O/TFA (75/25/0.1)): t_R 3.5 min.

2-(Benzo[1,3]dioxol-5-yl)-6-isopropoxy-4-methoxy-2*H*-chromene-3-carboxylic Acid (16). A solution of NaH_2PO_4 (1.95 kg, 16.3 mol) in H_2O (4.9 L) was added to a stirred solution of crude **15** (2.68 kg) in DMSO (29 L) at room temperature over 15 min. Thereto was added a solution of $NaClO_2$ (80% purity, 1.91 kg, 16.9 mol) in H_2O (7.64 L) in 10 portions over 3.5 h at a rate to keep the temperature at 25 °C. After being stirred at room temperature for 20 min, the mixture was poured into H_2O (57.5 L) and the resulting precipitate was collected by filtration. The crystals obtained were dissolved in EtOAc (21 L), and the resulting solution was washed with brine (5 L × 2). After evaporation of the solvent, toluene (4 L) was added to the residue, and the suspension was concentrated to remove EtOAc. Toluene (4 L) was added and the resulting suspension was allowed to stand at 0 °C for 1.5 h. The precipitated product was collected, washed with cold toluene (2 L), and air dried to give **16** (1.73 kg, 69% yield from **4**) as yellow crystals: Mp 134 °C. ^{1}H NMR ($CDCl_3$) δ 1.31 (3H, d, J = 6.1), 1.32 (3H, d, J = 6.1), 4.01 (3H, s), 4.34−4.52 (1H, m), 5.89 (2H, s), 6.25 (1H, s), 6.65−6.92 (6H, m). ^{13}C NMR ($CDCl_3$) δ 21.8, 21.9, 62.0, 70.7, 75.3, 100.8, 107.6, 107.7, 109.6, 110.9, 117.5, 118.5, 120.8, 121.2, 131.8, 147.3, 147.4, 150.0, 152.0, 159.6, 165.2. Anal. Calcd for $C_{21}H_{20}O_7$: C, 65.62; H, 5.24. Found: C, 65.53; H; 5.39. HPLC, condition A ((MeCN/H_2O/TFA (75/25/0.1)): t_R 2.6 min.

Methyl 2-(Benzo[1,3]dioxol-5-yl)-6-isopropoxy-4-methoxy-2*H*-chromene-3-carboxylate (17a). To a stirred solution of methoxy acid **16** (7.00 g, 18.2 mmol) in DMF (70 mL) were added MeI (3.87 g, 27.3 mmol) and K_2CO_3 (3.77 g, 27.3 mmol), and the stirring was continued for 1.5 h at room temperature. The mixture was poured into ice−water and extracted with EtOAc, and the extract was concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/4) to give **17a** (6.40 g, 88%) as pale yellow crystals: Mp 112 °C. ^{1}H NMR ($CDCl_3$) δ 1.30 (6H, d, J = 6.0), 3.77 (3H, s), 3.95 (3H, s), 4.37−4.48 (1H, m), 5.89 (2H, s), 6.16 (1H, s), 6.65−7.03 (6H, m). ^{13}C NMR ($CDCl_3$) δ 22.4, 22.5, 52.1, 62.2, 71.1, 76.3, 101.3, 108.2, 108.3, 108.6, 111.6, 118.2, 120.2, 121.1, 121.4, 133.3, 147.8, 149.3, 152.4, 160.2, 164.8. Anal. Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.28; H, 5.51. HPLC, condition A ((MeCN/H_2O/TFA (75/25/0.1)): t_R 5.9 min.

Isopropyl 2-(Benzo[1,3]dioxol-5-yl)-6-isopropoxy-4-methoxy-2*H*-chromene-3-carboxylate (17b). To a stirred solution of methoxy acid **16** (3.00 g, 7.80 mmol) in DMF (30 mL) were added 2-bromopropane (1.92 g, 15.6 mmol) and K_2CO_3 (2.16 g, 15.6 mmol), and the stirring was continued for 17 h at 50 °C. The mixture was poured into ice−water and extracted with EtOAc, and the extract was concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/4) to give **17b** (3.20 g, 96%) as pale yellow crystals: mp 77−78 °C. ^{1}H NMR ($CDCl_3$) δ 1.18−1.32 (12H, m), 3.94 (3H, s), 4.37−4.50 (1H, m), 5.05−5.18 (1H, m), 5.89 (2H, s), 6.15 (1H, s), 6.65−7.26 (6H, m). ^{13}C NMR ($CDCl_3$) δ 22.1, 22.3, 22.4, 22.5, 62.1, 68.3, 71.1, 76.6, 101.3, 108.1, 108.3, 109.8, 111.5, 118.1, 120.3, 120.9, 121.4, 133.6, 147.7, 149.3, 152.4, 159.4, 163.9. Anal. Calcd for $C_{24}H_{26}O_7$: C, 67.59; H, 6.15. Found: C, 67.20; H, 6.24. HPLC, condition A ((MeCN/H_2O/TFA (75/25/0.1)): t_R 6.1 min.

Reaction of Methoxy Acid 16 with Grignard Reagent 3 (*rac*-1, Table 1, entry 2). A solution of 4-bromoanisole (18.7 g, 100 mmol) in THF (15 mL) was added dropwise to a stirred mixture of Mg (2.43 g, 100 mmol), I_2 (2 crystals), and THF (15 mL), and then the resulting mixture was refluxed for 2.5 h. After cooling to room temperature, the mixture was diluted with THF to a total volume of 100 mL. A portion (20.8 mL, 20.8 mmol) of this Grignard reagent was added dropwise to a stirred solution of **16** (2.00 g, 5.20 mmol) in THF (14 mL) at −30 °C. After the reaction mixture was stirred at 0 °C for 2 h, ice and 2 N HCl (13 mL) were successively added. The resulting mixture was extracted with EtOAc, and the extract was washed with H_2O and concentrated. The residue was dissolved in toluene (50 mL), and 1 N NaOH (10 mL) and H_2O (20 mL) were added with stirring. The aqueous layer was separated and washed with toluene. After being acidified with 35% HCl, the aqueous layer was extracted with EtOAc. The extract was washed with H_2O, dried with Na_2SO_4, and concentrated. The residue was crystallized from EtOAc/toluene/isopropyl ether to give *rac*-**1** (2.02 g, 84%) as yellow crystals: Mp 179−181 °C. ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, d, J = 6.0), 1.18 (3H, d, J = 6.0), 3.87 (3H, s), 4.19 (1H, m), 5.91 (2H, s), 6.15 (1H, s), 6.25 (1H, m), 6.69−6.74 (3H, m), 6.87−6.97 (4H, m), 7.15−7.19 (2H, br). ^{13}C NMR ($CDCl_3$) δ 22.2, 22.4, 55.6, 70.8, 74.9, 101.3, 108.3, 108.4, 113.9, 116.4, 117.9, 120.2, 120.3, 121.5, 125.1, 128.6, 130.3, 132.8, 147.5, 147.9, 152.1, 159.7, 170.3. Anal. Calcd for $C_{27}H_{24}O_7$: C, 70.43; H, 5.25. Found: C, 70.28; H, 5.30. HPLC, condition A ((MeCN/H_2O/TFA (75/25/0.1)): t_R 5.4 min.

(*R*)-2-(Benzo[1,3]dioxol-5-yl)-6-isopropoxy-4-methoxy-2*H*-chromene-3-carboxylic Acid (1*S*,2*R*)-(+)-Norephedrine Salt (22). Dynamic Resolution with (1*S*,2*R*)-(+)-Norephedrine. (1*S*,2*R*)-(+)-Norephedrine (617 g, 4.08 mol) was added to a stirred mixture of methoxy acid **16** (1.57 kg, 4.08 mol) and MeOH (6.56 L). The resulting slurry was dissolved on heating at 70 °C and then stirred at 40 °C for 8 h. After cooling to 0 °C, the precipitate was collected by filtration and washed with cold MeOH (3 L) to give the first crop of salt **22** as crystals (1.18 kg, 54%, 96% ee). The filtrate was diluted with MeOH to 15 L, refluxed for 4 h, concentrated to 3.4 kg, stirred at 40 °C for 8 h, and cooled to 0 °C. The precipitate formed was filtered off and washed with cold MeOH (1.5 L) to give the second crop (473 g, 22%, 99% ee). The filtrate was again diluted with MeOH to 4 L, refluxed for 7 h, concentrated to 1.8 kg, stirred at 40 °C for 3 h, and cooled to 0 °C. The precipitate was filtrated off and washed with cold MeOH (1 L) to give the third crop (170 g, 8%, 99% ee). These three crops were combined to give **22** (1.82 kg, 84%, 97% ee) as colorless crystals: Mp 158−161 °C. ^{1}H NMR (DMSO-d_6) δ 0.87 (3H, d, J = 6.6), 1.21 (6H, d, J = 6.2), 3.25−3.36 (1H, m), 3.89 (3H, s), 4.35−4.53 (1H, m), 4.86 (1H, d, J = 3.2), 5.93 (2H, s), 6.04 (1H, s), 6.67−7.35 (11H, m). ^{13}C NMR (DMSO-d_6) δ 12.8, 22.8, 22.9, 52.7, 61.2, 70.7, 72.4, 77.8, 101.7, 108.5, 108.7, 110.9, 117.4, 117.8, 118.3, 121.9, 122.8, 126.7, 127.8, 128.9, 135.4, 142.6, 147.5, 147.7, 148.1, 150.5, 152.3, 169.7. $[\alpha]^{22}_D$ +51.0 (*c* 1.00, MeOH). Anal. Calcd for $C_{30}H_{33}NO_8$: C, 67.18; H, 6.21; N, 2.62. Found: C, 67.25; H, 6.27; N, 2.91. HPLC, condition B (MeCN/0.2 M H_3PO_4−KH_2PO_4 (50/50)): t_R **22**, 11.3 min; t_R (*S*)-salt **21**, 13.1 min.

(*R*)-2-(Benzo[1,3]dioxol-5-yl)-6-isopropoxy-4-methoxy-2*H*-chromene-3-carboxylic Acid Cinchonine Salt (23). Dynamic Resolution with (+)-Cinchonine. (+)-Cinchonine (>98% purity, 800 mg, 2.71 mmol) was added to a mixture of **16** (1.00 g, 2.60 mmol), MeOH (5 mL), and *i*-PrOH (5 mL). The resulting slurry was dissolved on heating at 70 °C and stirred at 70 °C for 20 h and then at 45 °C for 5 h. The precipitate was collected by filtration, washed with *i*-PrOH (5 mL), and air dried to give **23** (1.47 g, 83%, 99% ee) as colorless crystals: Mp 178−180 °C. ^{1}H NMR (DMSO-d_6) δ 1.22 (6H, d, J = 6.0), 1.58 (2H, br), 1.78 (1H, br), 2.03−2.10 (1H, m), 2.34−2.42 (1H, m), 2.73−2.83 (1H, m), 2.93−3.01 (2H, m), 3.19−3.26 (1H, m), 3.42−3.49 (1H, m), 3.94 (3H, s), 4.43−4.51 (1H, m), 5.11−5.17 (2H, m), 5.75−5.77 (1H, m), 5.93−5.94 (2H, m), 6.02−6.11 (1H, m), 6.12 (1H, s), 6.70−6.93 (6H, m), 7.54−7.62 (2H, m), 7.72−7.77 (1H, m), 8.04 (1H, d, J = 8.4), 8.31 (1H, s, J = 8.4), 8.87 (1H, d, J = 4.5). ^{13}C NMR (DMSO-d_6) δ 21.6, 22.7, 22.7, 25.4, 28.2, 39.1, 48.4, 49.3, 60.6, 61.8, 69.4, 70.6, 77.0, 101.7, 108.4, 108.4, 111.0, 113.5, 116.0, 118.0, 119.4, 119.5, 121.6, 121.8, 124.5, 126.1, 127.1, 129.6, 130.3, 134.6, 140.4, 147.6, 147.7, 148.3, 148.4, 149.6, 150.7, 152.3, 154.3, 168.1. $[\alpha]^{26}_D$ +98.7 (*c* 1.01, MeOH). Anal. Calcd for $C_{40}H_{42}N_2O_8 \cdot 0.5H_2O$: C, 69.85; H, 6.30; N, 4.07. Found: C, 69.88; H, 6.13; N, 4.06. The enantiopurity was determined by HPLC with the same conditions as for **22**.

(*R*)-2-(Benzo[1,3]dioxol-5-yl)-6-isopropoxy-4-methoxy-2*H*-chromene-3-carboxylic Acid ((*R*)-16). Salt **22** (1.61 kg,

3.00 mol) was suspended in a mixture of aqueous 1 M NaH_2PO_4 (7.5 L) and EtOAc (16 L). Thereto was added dropwise aqueous 10% H_3PO_4 (3.5 L) with stirring over 10 min at 20 °C. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 L). After each layer was washed with H_2O, the organic layer and the extract were combined and concentrated. Toluene (7 L) was added to the residue, and the resulting suspension was concentrated to remove the remaining EtOAc to afford crude (*R*)-**16** (1.20 kg, 97% ee) as yellow crystals, which contained 7% of toluene. This crude product was used in the next reaction without further purification. An analytically pure sample of (*R*)-**16** (100% ee) was obtained by recrystallization from acetone/isopropyl ether: Mp 136−137 °C. ^{1}H NMR ($CDCl_3$) δ 1.31 (3H, d, J = 6.1), 1.32 (3H, d, J = 6.1), 4.01 (3H, s), 4.34−4.52 (1H, m), 5.89 (2H, s), 6.25 (1H, s), 6.65−6.92 (6H, m). ^{13}C NMR ($CDCl_3$) δ 21.8, 21.9, 62.0, 70.7, 75.3, 100.8, 107.6, 107.7, 109.6, 110.9, 117.5, 118.5, 120.8, 121.2, 131.8, 147.3, 147.4, 150.0, 152.0, 159.6, 165.2. $[\alpha]^{24}_D$ +42.6 (*c* 1.00, MeOH). Anal. Calcd for $C_{21}H_{20}O_7$: C, 65.42; H, 5.24. Found: C, 65.45; H, 5.28. The enantiopurity was determined by HPLC with the same conditions as for **22**.

Recycle of (1*S*,2*R*)-(+)-Norephedrine. The aqueous layer containing (1*S*,2*R*)-(+)-norephedrine phosphate obtained in the previous step was concentrated and then added portionwise to aqueous 25% NaOH over 45 min, and the resulting mixture was stirred at 35 °C for 2 h. The resultant slurry was filtered to remove Na_3PO_4, and the filtrate was mixed with toluene (4.3 L). The organic layer was separated, dried with Na_2SO_4, and concentrated. Hexane (4 L) was added to the residue and the precipitate was collected by filtration to give (1*S*,2*R*)-(+)-norephedrine (390 g, 86%) as colorless crystals: Mp 51 °C. $[\alpha]^{24}_D$ +41.5 (*c* 5.00, 1 N HCl) (reported in the Aldrich catalog: mp 51−54 °C; $[\alpha]^{20}_D$ +40 (*c* 7, 1 N HCl)).

(*R*)-2-(Benzo[1,3]dioxol-5-yl)-6-isopropoxy-4-(4-methoxyphenyl)-2*H*-chromene-3-carboxylic Acid (1). A solution of 4-bromoanisole (2.25 kg, 12.0 mol) in THF (5 L) was added dropwise to a stirred mixture of Mg (292 g, 12.0 mol), I_2 (1.00 g, 3.93 mmol), and THF (1 L) at a rate to keep the temperature at 40−45 °C, and the stirring was continued at 40 °C for 3 h. The Grignard reagent was added dropwise to a solution of crude (*R*)-**16** (1.20 kg, 97% ee) in THF (7.5 L) at −35 °C, and the stirring was continued at 0 °C for 2 h. To the reaction mixture was added dropwise 6 N HCl (0.5 L) over 30 min under ice cooling, and the resulting mixture was poured into a stirred mixture of 6 N HCl (1.7 L), ice−water (4.4 L), and EtOAc (8 L). The organic layer was separated, and the aqueous layer was extracted with EtOAc (6 L). After each layer was washed with brine (12 L × 2), the organic layer and extract were combined and concentrated. Toluene (1.5 L) was added to the residue, and the resulting suspension was concentrated to remove EtOAc. The residue was dissolved in toluene (13.5 L) and mixed with H_2O (3 L). To the resulting mixture was added dropwise 0.5 N NaOH (9 L) at 25 °C. The basic aqueous layer was separated and the organic layer was extracted with 0.25 N NaOH (6 L). After each layer was washed with toluene (6 L), the basic aqueous layer and the basic extract were combined. Thereto, 35% HCl (0.23 L), EtOAc (12 L), and 35% HCl (0.3 L) were successively added with stirring. The organic layer was separated, and the aqueous layer was extracted with EtOAc (6 L). After each layer was washed with H_2O (9 L), the organic layer and the extract were combined and concentrated. The residue was dissolved in MeOH (8.7 L) on heating at 50 °C, allowed to cool to room temperature, and then mixed with H_2O (6.5 L). After the mixture was left standing at room temperature for 1 h, the precipitated crystals were filtered off and washed with cold MeOH/H_2O (1/1, 4.7 L) to give crude **1** (1.34 kg, 97%, 98% ee) as pale yellow crystals.

Purification of S-1255. The crude **1** (3.50 kg, 7.60 mol) was dissolved in MeOH (28 L) on heating, and the solution was allowed to cool to room temperature and mixed with H_2O (7 L) at 25 °C. The precipitated crystals were collected by filtration, washed with cold MeOH/H_2O (4/1, 3 L), and air dried to give pure **1** as pale yellow crystals (3.34 kg, 95% yield, 98% ee, >99% purity): Mp 170−172 °C. ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, d, J = 6.2), 1.18 (3H, d, J = 6.2), 3.87 (3H, s), 4.09−4.27 (1H, m), 5.90 (2H, s), 6.14 (1H, s), 6.24−7.18 (10H, m). ^{13}C NMR ($CDCl_3$) δ 21.8, 22.0, 55.2, 70.5, 74.6, 101.0, 108.0, 108.1, 113.6, 116.2, 117.7, 120.0, 120.1, 121.3, 124.9, 128.5, 130.1, 132.6, 147.4, 147.7, 152.0, 159.5, 170.6. $[\alpha]^{24}_D$ +178.8 (*c* 1.00, MeOH). Anal. Calcd for $C_{27}H_{24}O_7$: C, 70.43; H, 5.25. Found: C, 70.20; H, 5.23. HPLC, condition A ((MeCN/H_2O/TFA (55/45/0.1)): t_R 16.9 min. HPLC, condition B (MeCN/H_2O/TFA (68/32/0.1)): t_R **1**, 6.3 min; t_R (*S*)-form, 12.9 min.

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Supporting Information Available: Experimental details for reactions of **17a** and **17b** with **3** (Table 1, entries 4 and 5), melting point, ^{1}H and ^{13}C NMR, analytical data, and HPLC data for **11**, ^{1}H NMR spectra of **6**, **13**, and **23** which supplement the elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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