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Optical Resolution and Chiral Synthesis of Methyl 6,7-Dichloro-2,3-dihydrobenzo[*b*]furan-2-carboxylate

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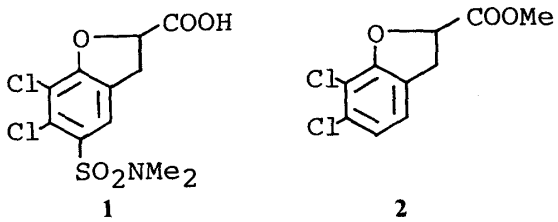
Optical isomers of methyl 6,7-dichloro-2,3-dihydrobenzo[*b*]furan-2-carboxylate (**2**) were prepared by means of both optical resolution and chiral synthesis. The resolution of the carboxylic acid **3** was achieved in a practical and efficient way *via* the *l*- and *d*-menthyl esters, which were directly converted to enantiomers of **2**. Chiral synthesis of **2** was attained with high optical yield *via* acid-catalyzed cyclization of the β-hydroxysulfide **10** derived from optically active glycidyl phenyl sulfide **13**. The optical resolution method was considered to be better for large-scale preparation from the economical and operational viewpoints.

Keywords——methyl 6,7-dichloro-2,3-dihydrobenzo[*b*]furan-2-carboxylate; optical resolution; (*R*)-4-phenyl-2-oxazolidone; menthol; chiral synthesis; glycidyl phenyl sulfide; β-hydroxysulfide; episulfonium ion; S-8666

While studying the uricosuric diuretic antihypertensive, S-8666[1] (**1**), we resolved the optical isomers of **1** using the L-proline *tert*-butyl ester and found that they have different biological activities. However, this method of resolution did not supply the enantiomers in substantial quantities. In order to develop a practical preparative method for the optical isomers of **1**, we tried optical resolution and chiral synthesis of methyl 6,7-dichloro-2,3-dihydrobenzo[*b*]furan-2-carboxylate (**2**), the key intermediate in the synthesis of **1**.



1 **2**

Chart 1

Optical Resolution

For the purpose of the configurational assignment of each enantiomer of **1**, resolution of the carboxylic acid **3** was carried out through the sequence outlined in Chart 2. A mixture of diastereomers **6a** and **6b** was prepared by the reaction of the acid chloride **4** with the lithium salt of (*R*)-4-phenyl-2-oxazolidone (**5**).[2] Separation of this mixture was readily effected by column chromatography to afford a more polar diastereomer **6a** and a less polar one **6b**. The absolute configuration at the 2-position of the dihydrobenzofuran moiety of **6a** was determined to be *R* on the basis of the X-ray analysis of **6a**.[3] Subsequently, **6a** and **6b** were individually treated with alcoholic potassium hydroxide in tetrahydrofuran (THF) to give **3a** and **3b** in 85% and 80% yields, respectively. The absence of racemization during the alkaline hydrolysis was ascertained by hydrolysis of **6a** under acidic conditions, which gave **3a** showing

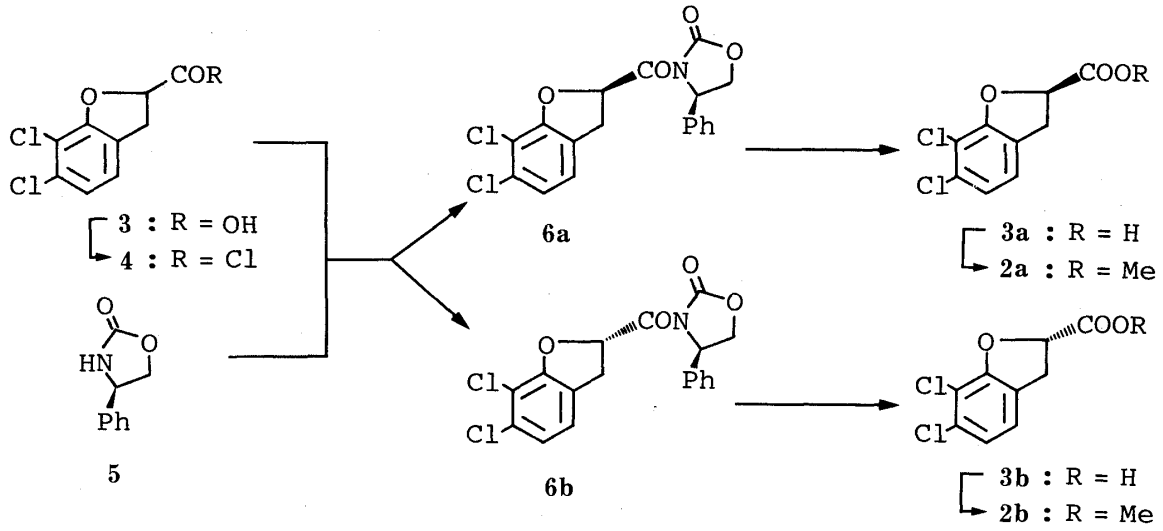


Chart 2

the same specific rotation as that obtained by the alkaline hydrolysis. Next, **3a** and **3b** were converted to the methyl esters **2a** and **2b**, respectively, by treatment with diazomethane.

Individual treatment of **2a** and **2b** with chlorosulfonic acid and thionyl chloride in dichloromethane (CH_2Cl_2) afforded intermediary sulfonyl chlorides, which were then allowed to react with dimethylamine in acetone to give **7a** and **7b** in 88% and 90% yields, respectively (Chart 3). Hydrolysis of **7a** and **7b** with an equimolar amount of sodium hydroxide in acetonitrile (CH_3CN) gave **1a** and **1b** in 94% and 93% yields, respectively. The carboxylic acid **1a** derived from **2a** with *R*-configuration proved to be dextrorotatory.

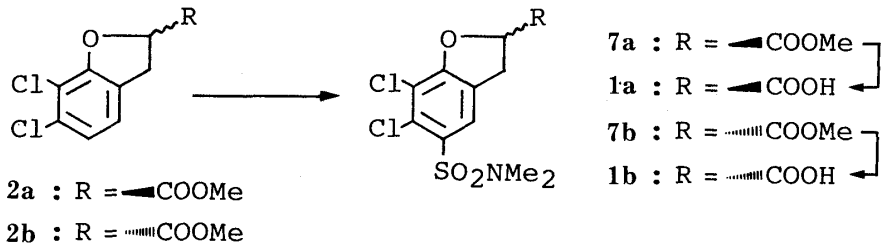
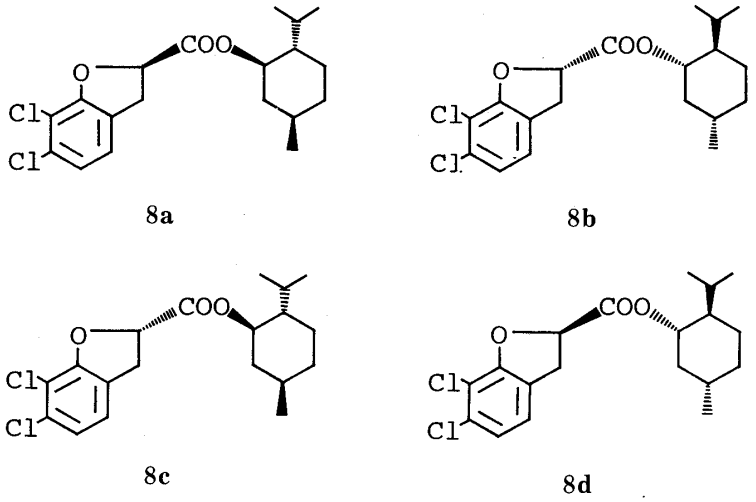


Chart 3

We were thus able to assign the configurations of the optical isomers of **1**. However, a simpler resolution method using a less expensive resolving agent was desired for a large-scale preparation. Menthol was selected as the first choice for the agent, because both *l*- and *d*-menthols are readily available and comparatively inexpensive. First, resolution of **3** using naturally occurring *l*-menthol was tried. Heating **3** with *l*-menthol in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) or concentrated sulfuric acid (H_2SO_4) gave the *l*-menthyl ester **8** in high yield as a mixture of two diastereomers **8a** and **8c** (Chart 4). Although this mixture afforded a single spot in thin-layer chromatography, one diastereomer **8a** crystallized easily while the other, **8c**, did not. Thus, crystals of **8a** could be separated by filtration and purified by recrystallization from hexane. The resulting mother liquor contained a small amount of **8a** and all of the uncrystalline diastereomer **8c**. Heating **8a** in methanol in the presence of a catalytic amount of concentrated H_2SO_4 or *p*-TsOH gave the optically active methyl ester **2a** in 93% yield. The absolute configuration of **2a** was assigned as *R* from its specific rotation.

Similarly, **3** was converted to a diastereomeric mixture of *d*-menthyl esters **8b** and **8d**



8a 8b

8c 8d

Chart 4

using *d*-menthol. In this case, the diastereomer **8b**, which is an antipode of the crystalline *l*-menthyl ester **8a**, was separated as crystals from the diastereomeric mixture in 39% yield, and similar methanolysis of **8b** gave **2b** with the *S*-configuration in 92% yield.

The methyl esters **2a** and **2b** were individually hydrolyzed with an equimolar amount of aqueous sodium hydroxide in CH_3CN to give **3a** and **3b** in 95% and 98% yields, respectively. The crystalline menthyl esters **8a** and **8b** were also quantitatively hydrolyzed to **3a** and **3b**, respectively, in a similar manner. However, the optical purities of the hydrolysis products **3a** and **3b** from **8a** and **8b** were slightly lower than those from **2a** and **2b**.

On the basis of the above results, we tried to resolve **3** by sequential use of *l*- and *d*-menthols as outlined in Chart 5. (In the chart, the ester derived from the (*R*)-carboxylic acid **3a** and *l*-menthol is abbreviated as (*R*)-COO-men^l.) The racemic carboxylic acid **3** would be converted into the *l*-menthyl esters **8a** and **8c**, and **8a** would be separated and converted to **2a**. Then the resulting mother liquor would be hydrolyzed to the carboxylic acid which should be rich in **3b**. Next, this carboxylic acid **3** would be converted to the *d*-menthyl esters **8b** and **8d**, and **8b** would be separated and converted to **2b**. Based on this scheme, the resolution of 61.5 g

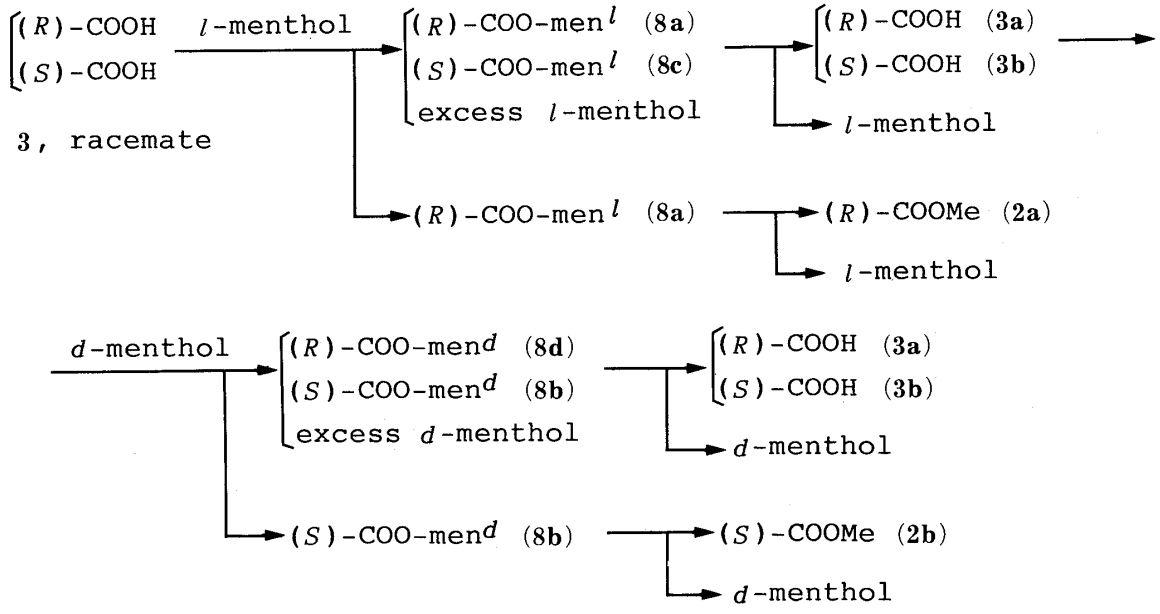


Chart 5

of **3** was tried, and 25.4 g (39%) of **2a** and 27.0 g (41%) of **2b** as well as 7.3 g (12%) of **3** were obtained. Furthermore, *l*- and *d*-menthols were recovered in high yield.

These experimental results showed that the method for resolution of **3** using menthols is characterized by the following points. 1) Each step of the procedure produces a high yield, and the products can be easily isolated with high levels of purity by crystallization. 2) Both *l*- and *d*-menthols can be recovered with a high yield and purity. 3) Both *l*- and *d*-menthols are easily available and comparatively inexpensive. Therefore, this method is suitable for large-scale resolution of the racemic carboxylic acid **3**.

Chiral Synthesis

Murahashi *et al.*[4] have reported the asymmetric synthesis of 2,3-dihydrobenzo[*b*]furan-2-carboxylic acids *via* enantioselective cyclization of 2-(*trans*-2-butenyl)phenols using a palladium(II) complex-bearing pinanyl ligand. However, as the enantioselectivities of this cyclization were not high (<26% ee), induction of chirality by this type of cyclization seemed to be difficult. As a practical approach, chiral synthesis of **2** *via* incorporation of a small chiral fragment was planned.

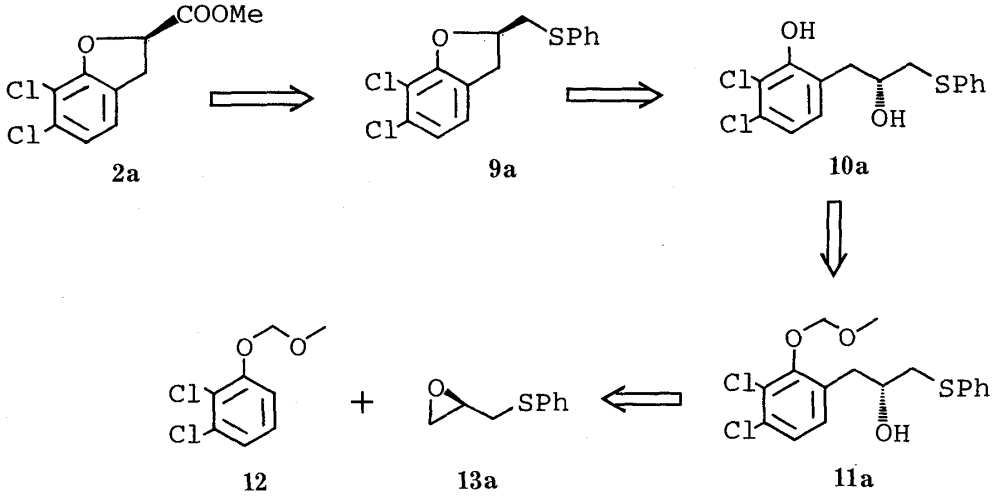


Chart 6

The retrosynthetic route for the (*R*)-ester **2a**, shown in Chart 6, is characterized by the acid-catalyzed cyclization of a β-hydroxysulfide **10a** to a dihydrobenzofuran derivative **9a**. We expected **10a** to be derived from a methoxymethyl ether **12** and the optically active glycidyl phenyl sulfide **13a** and that the conversion of **9a** into **2a** might be carried out according to Fortes' method,[5] *i.e.*, α-dichlorination of sulfide followed by methanolysis without loss of optical purity. Using the racemic glycidyl phenyl sulfide **13**, we examined the feasibility of the synthetic route outlined in Chart 6.

As shown in Chart 7, the methoxymethyl ether **12** was treated with butyl lithium in ether then with **13**, which was prepared from epibromohydrin and thiophenol, in the presence of copper(I) iodide to give **11** in 63% yield. Direct conversion of **11** into **9** was attempted, but the yield of **9** was poor. Next, stepwise conversion of **11** into **9** was tried. Heating **11** with a catalytic amount of concentrated H_2SO_4 in ethanol gave **10** in quantitative yield. Cyclization of **10** proceeded smoothly by heating in benzene in the presence of a catalytic amount of concentrated H_2SO_4 and gave **9** in 89% yield. Treatment of **9** with 2.3 eq of sulfuryl chloride in CH_2Cl_2 gave the α-dichlorosulfide **14**. The reaction mixture was concentrated, then the crude **14** was dissolved without purification in methanol containing an equimolar amount of water and the solution was stirred at room temperature to afford **2** in 82% yield.

Recently Fujisawa *et al.*[6] reported the preparation of (*S*)-glycidyl phenyl sulfide **13b** *via*

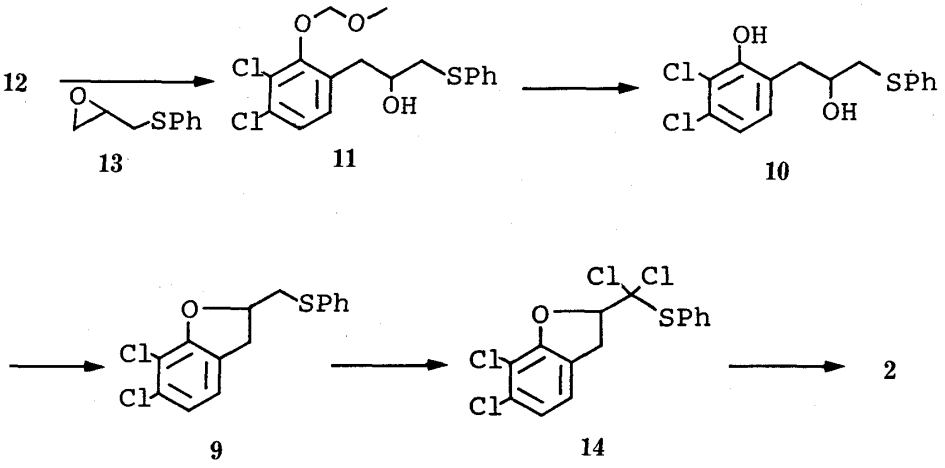


Chart 7

(*S*)-3-(phenylthio)-1,2-propanediol **16b**, which was obtained by enantioselective reduction of 1-hydroxy-3-phenylthio-2-propanone with baker's yeast, and demonstrated the utility of **13b** as a chiral building block. As we needed both enantiomers of **13**, we tried to prepare them from 1,2-*O*-isopropylidene-*sn*-glycerol (**15**)[7,8] according to the sequence outlined in Chart 8. Conversion of **15** into the (*R*)-glycidyl sulfide **13a** was carried out as follows. The primary hydroxy group of **15** was displaced with a phenylthio group by treatment of **15** with tributylphosphine and diphenyl disulfide in benzene,[9] and the resulting sulfide was hydrolyzed to give the 1,2-diol **16a** in 83% yield by heating in 1 N hydrochloric acid and tetrahydrofuran. Subsequently, **16a** was converted to **13a** in 73% yield according to the method of Fujisawa *et al.*[6] except that the intermediary primary tosylate was not isolated.

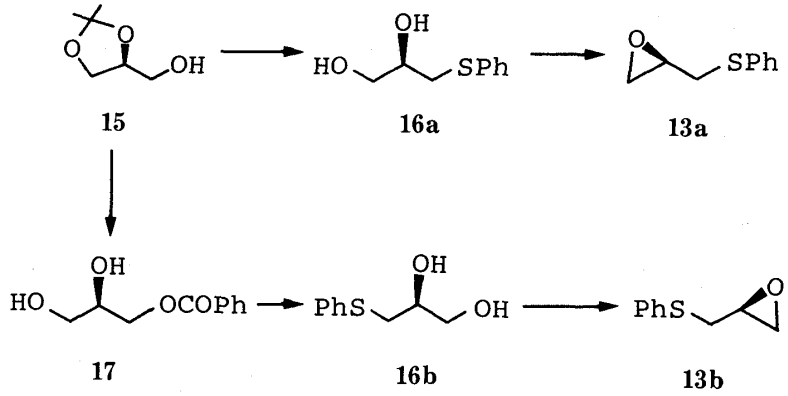


Chart 8

To prepare the (*S*)-enantiomer **13b**, the hydroxy group of **15** was esterified with benzoyl chloride in CH_2Cl_2 in the presence of triethylamine, and the resulting benzoate was treated with 1 N hydrochloric acid in acetone to give the 1,2-diol **17** in 63% yield. The primary hydroxy group of **17** was selectively displaced by a phenylthio group, and the resulting sulfide was treated with aqueous sodium hydroxide in methanol to give **16b** in 80% yield. Conversion of **16b** to the (*S*)-glycidyl sulfide **13b** was carried out by the same procedure as used for the *R*-enantiomer **16a**.

The melting point of **16b** obtained here differed greatly from that of **16b** they reported, and the specific rotations for **16b** and **13b** were slightly different from the reported values. However, since the specific rotations of the *R*-enantiomers **16a** and **13a** showed the same absolute values as those of the *S*-enantiomers **16b** and **13b** obtained here, respectively, and the

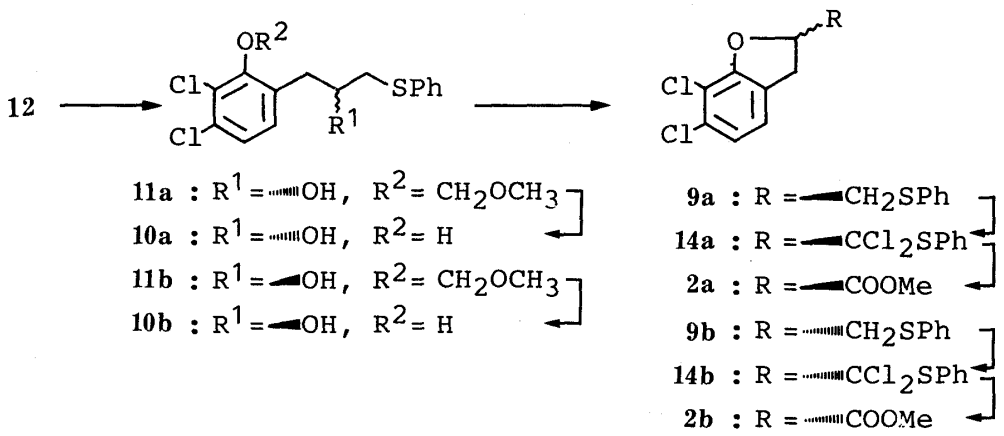


Chart 9

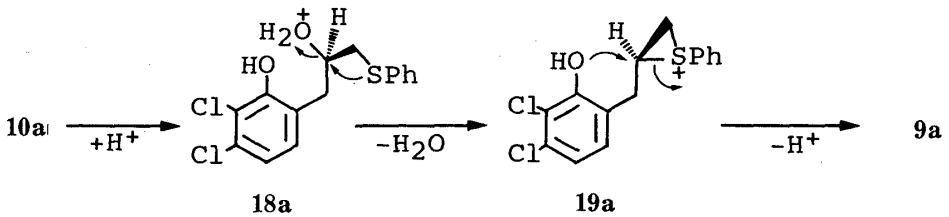
melting point of **16a** agreed with that of **16b**, the optical purities of **13a** and **13b** were not further examined.

Chiral synthesis of **2** using **13a** and **13b** is shown in Chart 9. Starting from **12** and **13a**, the synthesis of **9a** was carried out *via* **11a** under the conditions used for the preparation of the racemate **9**. However, the sulfide **9a** thus obtained did not crystallize and its purification was difficult, whereas the racemic sulfide **9** crystallized easily. Consequently, the optical yield and the absolute configuration of **9a** were not determined at this stage. Chlorination and methanolysis of **9a** were carried out as in the case of the racemate **9** to afford **2a** in 82% yield. The absolute configuration of **2a** obtained here was determined to be *R* from its specific rotation, which agreed with that of **2a** obtained by the optical resolution described above. Consequently, the optical yield of **2a** seemed to be almost 100% ee.

Similarly, synthesis of **2** using the (*S*)-glycidyl sulfide **13b** was carried out, and **2b** with the *S*-configuration was obtained. In this case also, the specific rotation of the **2b** synthesized here agreed with that of the **2b** obtained by optical resolution.

Although the optical yields of **2a** and **2b** were determined to be almost 100% ee, the enantiomeric integrity of **2a** and **2b** obtained here was further confirmed by enantiomeric separation by high-performance liquid chromatography (HPLC) with a chiral stationary phase. The optical purities of **11a**, **11b** and the sulfides **9a**, **9b** were determined by similar HPLC analysis. Each enantiomer was optically pure and each step of the synthesis had proceeded without loss of optical purity. The absolute configurations of **9a** and **9b** were determined to be identical with those of **2a** and **2b**, respectively, since the α-dichlorination and methanolysis of **9** would not affect the configuration of the asymmetric center at the β-position with respect to the sulfur atom.

Thus, both enantiomers of **2** were synthesized in an enantiomerically pure form from the optically active glycidyl phenyl sulfides **13a** and **13b** with retention of configuration. These results suggested that the cyclization of **10** to **9** would proceed according to the mechanism illustrated in Chart 10. That is to say, initial protonation of **10a** to **18a** would be followed by



18a 19a

Chart 10

backside participation of the neighboring sulfur atom to yield an episulfonium ion **19a** with inversion of the configuration. Subsequently, nucleophilic displacement of **19a** by the internal phenolic hydroxy group from the backside would give **9a** with inversion of the configuration. Consequently, this cyclization would proceed with retention of the configuration of the asymmetric carbon center. The stereospecific integrity observed in this cyclization suggests that the intermediate episulfonium ion **19a** is a strongly bridged species having little positive charge on its carbon atoms. Clearly, **19a** retained its chirality under the conditions of the cyclization. Similar cyclization of *β*-hydroxysulfides *via* an episulfonium ion with complete retention of the configuration has been reported by Williams and Phillips.[10]

Conclusion

For the purpose of large-scale preparation of the optical isomers of **2**, optical resolution and chiral synthesis of **2** were examined. The optical resolution of the carboxylic acid **3** was done by using *l*- and *d*-menthols, and both enantiomers of the ester **2** were obtained in enantiomerically pure form. The chiral synthesis of **2** was carried out using **13a** and **13b** as chiral building blocks. From both the economical and operational points of views, we concluded that the optical resolution method using menthols was more suitable for large-scale preparation of the optically active ester **2**.

Experimental

Melting points were determined on a Yanagimoto hot plate micro melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded on a Hitachi 260-10 infrared spectrophotometer. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian EM-390 spectrometer in $CDCl_3$ unless otherwise noted. Chemical shifts are reported as δ values with respect to Me_4Si used as an internal standard. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Silica gel 60 (E. Merck, 0.063—0.200 mm) was used for column chromatography. Organic extracts were dried over $MgSO_4$. HPLC was performed on a Shimadzu LC-3A high-performance liquid chromatograph equipped with a Shimadzu SPD-2A detector (set at 254 nm).

Resolution of the Optical Isomers of 3——A solution of **3** (3.9 g, 16.7 mmol) and $SOCl_2$ (3.7 ml, 50.7 mmol) in benzene (17 ml) was heated at reflux for 2 h. The resulting solution was concentrated *in vacuo*. In order to remove the remaining $SOCl_2$, the residue was diluted with benzene and concentrated *in vacuo* (3 times) to give 4.18 g (99%) of **4**. On the other hand, BuLi in hexane (1.5 M, 11.7 ml) was added dropwise to a cooled (−78 °C) solution of **5**[2] (2.87 g, 17.6 mmol) in anhydrous THF (50 ml) with stirring under an N_2 atmosphere. The resulting solution was stirred for 1 h at −78——40 °C. A solution of **4** prepared above (4.18 g) in THF (25 ml) was added dropwise over a period of 5 min to the reaction mixture at −38 °C with stirring. After the addition was completed, stirring was continued at −10——5 °C for 1 h and at 5—15 °C for 3 h. The reaction mixture was treated with a small amount of saturated aqueous NH_4Cl and then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with water, giving a white precipitate, which was collected by filtration and suspended in water. The resulting suspension was acidified with dilute HCl, and extracted with Et_2O to give 0.95 g (24%) of **3**. The CH_2Cl_2 layer was washed with water, dried, and passed through a column of silica gel (6 g) to give 5.5 g of a mixture of diastereomers. Chromatography of this mixture on silica gel with CH_3CN–CH_2Cl_2 (1 : 39, v/v) as the eluant gave 2.06 g (33%) of **6a** and 2.22 g (35%) of **6b**. Single crystals of **6a** for X-ray analysis were prepared by recrystallization from dioxane. **6a**: Colorless needles, mp 188—189 °C ($CHCl_3$). *Anal.* Calcd for $C_{18}H_{13}Cl_2NO_4$: C, 57.16; H, 3.46; Cl, 18.75; N, 3.70. Found: C, 57.15; H, 3.49; Cl, 18.78; N, 3.75. $[\alpha]_D^{24}$ +3.1° (c=1.01, $CHCl_3$). ^{1}H-NMR δ: 3.32 (1H, dd, J=18, 6 Hz, 3′-H), 3.80 (1H, dd, J=18, 11 Hz, 3′-H), 4.35 (1H, dd, J=10, 4 Hz, 5-H), 4.76 (1H, t, J=10 Hz, 5-H), 5.40 (1H, dd, J=9, 4 Hz, 4-H), 6.26 (1H, dd, J=11, 6 Hz, 2′-H), 6.95 (2H, s, 4′- and 5′-H), 7.36 (5H, s, Ph). **6b**: Colorless needles, mp 117—118 °C (benzene). *Anal.* Calcd for $C_{18}H_{13}Cl_2NO_4$: C, 57.16; H, 3.46; Cl, 18.75; N, 3.70. Found: C, 57.41; H, 3.69; Cl, 18.66; N, 3.60. $[\alpha]_D^{24}$ −250.2° (c=1.00, $CHCl_3$). ^{1}H-NMR δ: 3.10 (1H, dd, J=18, 7 Hz, 3′-H), 3.82 (1H, dd, J=18, 11 Hz, 3′-H), 4.35 (1H, dd, J=10, 4 Hz, 5-H), 4.80 (1H, t, J=9.5 Hz, 5-H), 5.43 (1H, dd, J=9.5, 4 Hz, 4-H), 6.25 (1H, dd, J=11, 7 Hz, 2′-H), 6.90 (2H, s, 4′- and 5′-H), 7.33 (5H, s, Ph).

Alkaline Hydrolysis of 6a——A solution of KOH in EtOH (0.378 N, 9.46 ml) was added to an ice-cooled solution of **6a** (1.38 g, 3.65 mmol) in THF (57 ml) and EtOH (7 ml). The resulting solution was stirred at 0—3 °C for 10 min, and the precipitated potassium salts were collected by filtration, washed with CH_2Cl_2, and suspended in water and Et_2O. The resulting suspension was acidified to pH 2 with 1 N HCl under ice-cooling. The ethereal layer was separated, washed with brine, dried, and concentrated *in vacuo* to give 0.72 g (85%) of **3a**. **3a**: Colorless needles, mp 169—170 °C (1,2-dichloroethane). *Anal.* Calcd for $C_9H_6Cl_2O_3$: C, 46.38; H, 2.59; Cl, 30.43. Found: C, 46.40; H, 2.75;

Cl, 30.59. $[\alpha]_D^{22}$ +76.9° (c=1.00, acetone). ^{1}H-NMR (acetone-d_6) δ: 3.45 (1H, ddm, J=16.2, 6.8 Hz, 3-H), 3.76 (1H, ddm, J=16.2, 10.0 Hz, 3-H), 5.45 (1H, dd, J=10.0, 6.8 Hz, 2-H), 7.05 (1H, d, J=8.1 Hz, 5-H), 7.20 (1H, d, J=8.1 Hz, 4-H), 9.2—10.4 (1H, br, COOH).

Alkaline Hydrolysis of 6b——Similar hydrolysis of **6b** (1.22 g, 3.2 mmol) gave 0.60 g (80%) of **3b**. **3b**: Colorless needles, mp 169—170 °C (1,2-dichloroethane). *Anal.* Calcd for $C_9H_6Cl_2O_3$: C, 46.38; H, 2.59; Cl, 30.43. Found: C, 46.33; H, 2.76; Cl, 30.71. $[\alpha]_D^{23}$ −78.0° (c=1.00, acetone). The ^{1}H-NMR spectrum of **3b** agreed with that of **3a**.

Acidic Hydrolysis of 6a——Compound **6a** (100 mg, 0.26 mmol) was dissolved in a solution of H_2SO_4 in dioxane–water (9 : 1, v/v) (2 N, 1 ml) and the resulting solution was heated overnight at 90—95 °C. The reaction mixture was alkalized with aqueous $NaHCO_3$ and washed with Et_2O. The aqueous layer was acidified with dilute HCl and extracted with Et_2O. Drying of the ethereal extract and concentration *in vacuo* gave 62 mg (quantitative yield) of **3a**. **3a**: Colorless needles, mp 169—170 °C (1,2-dichloroethane). $[\alpha]_D^{22}$ +76.9° (c=1.0, acetone).

Methyl (*R*)-6,7-Dichloro-2,3-dihydrobenzo[*b*]furan-2-carboxylate (2a)——A solution of **3a** (464 mg, 2.0 mmol) in Et_2O was treated with a solution of CH_2N_2 in Et_2O at room temperature. The resulting solution was concentrated *in vacuo* to give 492 mg (quantitative yield) of **2a**, mp 80—81 °C (hexane). $[\alpha]_D^{23}$ +71.8° (c=1.02, acetone). ^{1}H-NMR δ: 3.39 (1H, dd, J=16.3, 7.0 Hz, 3-H), 3.63 (1H, dd, J=16.3, 9.8 Hz, 3-H), 3.80 (3H, s, CH_3), 5.32 (1H, dd, J=9.8, 7.0 Hz, 2-H), 6.99 (2H, s, 4- and 5-H).

Methyl (*S*)-6,7-Dichloro-2,3-dihydrobenzo[*b*]furan-2-carboxylate (2b)——Similar methylation of **3b** with CH_2N_2 gave **2b**, mp 80—81 °C (hexane). $[\alpha]_D^{23}$ −73.7° (c=1.01, acetone). The ^{1}H-NMR spectrum of **2b** agreed with that of **2a**.

Methyl (*R*)-6,7-Dichloro-5-(*N*,*N*-dimethylsulfamoyl)-2,3-dihydrobenzo[*b*]furan-2-carboxylate (7a)——Chlorosulfonic acid (1.0 g, 12.2 mmol) was added dropwise to a solution of **2a** (1.0 g, 4.05 mmol) in CH_2Cl_2 (10 ml) at room temperature and the resulting solution was heated with $SOCl_2$ (1.2 g, 10.1 mmol) at 40 °C for 1 h. The reaction mixture was poured onto ice and the resulting mixture was extracted with AcOEt (70 ml). The organic extracts were washed with water, dried, and concentrated *in vacuo*. The residual oil was diluted with acetone (10 ml) and cooled at −30 °C. A 50% aqueous solution of dimethylamine (1.3 g, 14.5 mmol) was added, and the resulting solution was stirred at −30——10 °C for 2 h. The solvent was evaporated off *in vacuo*, and the residue was dissolved in AcOEt and water. The AcOEt layer was separated, washed with water, dried, and concentrated *in vacuo*. The residue was chromatographed on silica gel (12.5 g) with CH_2Cl_2 as the eluant to give an oil, which, when crystallized by treatment with Et_2O, gave 1.26 g (88%) of **7a** as colorless crystals, mp 99—100 °C (Et_2O). *Anal.* Calcd for $C_{12}H_{13}Cl_2NO_5S$: C, 40.69; H, 3.70; Cl, 20.02; N, 3.95; S, 9.05. Found: C, 40.56; H, 3.67; Cl, 20.02; N, 3.85; S, 8.95. $[\alpha]_D^{23}$ +16.7° (c=2.00, acetone). ^{1}H-NMR δ: 2.85 (6H, s, $N(CH_3)_2$), 3.45 (1H, dd, J=16.5, 7.5 Hz, 3-H), 3.75 (1H, dd, J=16.5, 10.5 Hz, 3-H), 3.81 (3H, s, $COOCH_3$), 5.42 (1H, dd, J=10.5, 7.5 Hz, 2-H), 7.85 (1H, br s, 4-H).

Methyl (*S*)-6,7-Dichloro-5-(*N*,*N*-dimethylsulfamoyl)-2,3-dihydrobenzo[*b*]furan-2-carboxylate (7b)——Similar treatment of **2b** (1.0 g, 4.05 mmol) through the reaction sequence described for the synthesis of **7a** gave 1.29 g (90%) of **7b** as colorless crystals, mp 100—101 °C (Et_2O). *Anal.* Calcd for $C_{12}H_{13}Cl_2NO_5S$: C, 40.69; H, 3.70; Cl, 20.02; N, 3.95; S, 9.05. Found: C, 40.51; H, 3.69; Cl, 20.11; N, 3.88; S, 8.97. $[\alpha]_D^{23}$ −17.4° (c=2.00, acetone). The ^{1}H-NMR spectrum of **7b** agreed with that of **7a**.

(*R*)-6,7-Dichloro-5-(*N*,*N*-dimethylsulfamoyl)-2,3-dihydrobenzo[*b*]furan-2-carboxylic acid (1a)——A solution of **7a** (708 mg, 2.0 mmol) in CH_3CN (5 ml) and 1 N NaOH (2.1 ml, 2.1 mmol) was stirred at room temperature for 20 min, and then concentrated *in vacuo*. The resulting mixture was acidified with 10% H_2SO_4 and extracted with AcOEt. The organic extracts were washed with water, dried, and concentrated *in vacuo*. Treatment of the residue with AcOEt–hexane gave 641 mg (94%) of **1a** as colorless crystals, mp 135—136 °C (AcOEt–hexane). *Anal.* Calcd for $C_{11}H_{11}Cl_2NO_5S$: C, 38.84; H, 3.26; Cl, 20.84; N, 4.12; S, 9.43. Found: C, 38.93; H, 3.35; Cl, 20.92; N, 4.03; S, 9.25. $[\alpha]_D^{21}$ +18.9° (c=2.00, acetone). ^{1}H-NMR (acetone-d_6) δ: 2.83 (6H, s, $N(CH_3)_2$), 3.53 (1H, ddd, J=16.0, 7.0, 1.0 Hz, 3-H), 3.86 (1H, ddd, J=16.0, 10.0, 1.0 Hz, 3-H), 5.55 (1H, dd, J=10.0, 7.0 Hz, 2-H), 5.70—6.80 (1H, br, COOH), 7.86 (1H, t, J=1.0 Hz, 4-H).

(*S*)-6,7-Dichloro-5-(*N*,*N*-dimethylsulfamoyl)-2,3-dihydrobenzo[*b*]furan-2-carboxylic acid (1b)——Hydrolysis of **7b** (708 mg, 2.0 mmol), carried out by using the procedure described for the synthesis of **1a**, gave 633 mg (93%) of **1b** as colorless crystals, mp 135—136 °C (AcOEt–hexane). *Anal.* Calcd for $C_{11}H_{11}Cl_2NO_5S$: C, 38.84; H, 3.26; Cl, 20.84; N, 4.12; S, 9.43. Found: C, 39.07; H, 3.29; Cl, 20.69; N, 4.02; S, 9.37. $[\alpha]_D^{21}$ −19.0° (c=2.00, acetone). The ^{1}H-NMR spectrum of **1b** agreed with that of **1a** except for the signal of the proton of COOH which appeared at δ 7.10—8.20 (1H, br).

(1*R*,3*R*,4*S*)-*p*-Menth-3-yl (*R*)-6,7-Dichloro-2,3-dihydrobenzo[*b*]furan-2-carboxylate (8a)——A mixture of **3** (10.0 g, 42.9 mmol), *l*-menthol (8.05 g, 51.5 mmol), and a catalytic amount of *p*-TsOH in benzene was refluxed for 6.5 h with separation of water as the benzene azeotrope. The reaction mixture was concentrated and the residue was diluted with Et_2O, washed with water and brine, dried, and concentrated *in vacuo*. Chromatography of the residue on silica gel with CH_2Cl_2–hexane (1 : 1, v/v) as the eluant gave 17.3 g of a mixture of **8a** and **8c**, which crystallized upon standing. Washing of this mixture with cold pentane gave 6.61 g (41%) of **8a** as colorless crystals, mp 112—113.5 °C (hexane). *Anal.* Calcd for $C_{19}H_{24}Cl_2O_3$: C, 61.46; H, 6.52; Cl, 19.10. Found: C, 61.53; H, 6.43; Cl, 19.38. $[\alpha]_D^{22}$ +2.4° (c=1.01, acetone). IR (Nujol): 1740, 1600 cm^{-1}. ^{1}H-NMR δ: 0.7—2.2 (18H, m, protons of menthyl group), 3.33 (1H,

dd, $J=16.0$, 6.9 Hz, 3-H), 3.63 (1H, dd, $J=16.0$, 10.0 Hz, 3-H), 4.76 (1H, tdm, $J=10.0$, 4.5 Hz, COOCH), 5.27 (1H, dd, $J=10.0$, 6.9 Hz, 2-H), 6.99 (2H, s, 4- and 5-H).

(1*S*,3*S*,4*R*)-*p*-Menth-3-yl (*S*)-6,7-Dichloro-2,3-dihydrobenzo[*b*]furan-2-carboxylate (8b)——Esterification of **3** (2.00 g, 8.53 mmol) with *d*-menthol (1.61 g, 10.3 mmol), carried out in a similar manner, gave 1.25 g (39%) of **8b** as colorless crystals, mp 111—112.5 °C (hexane). *Anal.* Calcd for $C_{19}H_{24}Cl_2O_3$: C, 61.46; H, 6.52; Cl, 19.10. Found: C, 61.34; H, 6.36; Cl, 19.11. $[\alpha]_D^{22}$ −2.7° ($c=1.01$, acetone). The ^{1}H-NMR spectrum of **8b** agreed with that of **8a**.

Methanolysis of 8a——A mixture of **8a** (410 mg, 1.10 mmol) and a catalytic amount of *p*-TsOH in MeOH was heated at reflux for 20 h. The reaction mixture was concentrated and the residue was dissolved in AcOEt; this solution was washed with water and brine, dried, and concentrated *in vacuo*. Chromatography of the residue on silica gel with CH_2Cl_2–hexane (2 : 1, v/v) as the eluant gave 252 mg (93%) of **2a** as colorless crystals and 140 mg (81%) of *l*-menthol. **2a**: mp 81—82 °C (Et_2O–hexane). *Anal.* Calcd for $C_{10}H_8Cl_2O_3$: C, 48.61; H, 3.26; Cl, 28.70. Found: C, 48.48; H, 3.38; Cl, 28.56. $[\alpha]_D^{23}$ +71.3° ($c=1.00$, acetone). IR (Nujol): 1750, 1600, 1585 cm^{-1}. *l*-Menthol: $[\alpha]_D^{22}$ −50.3° ($c=10.0$, EtOH).

Methanolysis of 8b——Similar methanolysis of **8b** (512 mg, 1.38 mmol) gave 315 mg (92%) of **2b** as colorless crystals and 176 mg (82%) of *d*-menthol. **2b**: mp 81.5—82 °C (Et_2O–hexane). *Anal.* Calcd for $C_{10}H_8Cl_2O_3$: C, 48.61; H, 3.26; Cl, 28.70. Found: C, 48.41; H, 3.32; Cl, 28.80. $[\alpha]_D^{23}$ −72.3° ($c=1.01$, acetone). *d*-Menthol: $[\alpha]_D^{22}$ +50.0° ($c=10.0$, EtOH).

Hydrolysis of 2a——A 10% NaOH solution (0.3 ml, 0.83 mmol) was added to a solution of **2a** ($[\alpha]_D^{23}$ +71.3°, 170 mg, 0.69 mmol) in CH_3CN (4 ml). The resulting mixture was stirred at room temperature for 3.5 h and concentrated *in vacuo*. The residue was dissolved in water. This solution was washed with CH_2Cl_2, acidified with 10% HCl, and extracted with AcOEt. The organic extract was washed with water and brine, dried, and concentrated *in vacuo*. Washing of the resultant solid with hexane gave 153 mg (95%) of **3a** as colorless crystals, mp 173—174 °C (1,2-dichloroethane). *Anal.* Calcd for $C_9H_6Cl_2O_3$: C, 46.38; H, 2.59; Cl, 30.43. Found: C, 46.02; H, 2.72; Cl, 30.70. $[\alpha]_D^{22}$ +77.9° ($c=1.01$, acetone).

Hydrolysis of 2b——Similar hydrolysis of **2b** ($[\alpha]_D^{23}$ −72.3°, 244 mg, 0.99 mmol) gave 226 mg (98%) of **3b** as colorless crystals, mp 172.5—174 °C (1,2-dichloroethane). *Anal.* Calcd for $C_9H_6Cl_2O_3$: C, 46.38; H, 2.59; Cl, 30.43. Found: C, 46.15; H, 2.82; Cl, 30.62. $[\alpha]_D^{22}$ −78.3° ($c=1.01$, acetone).

Hydrolysis of 8a——A 10% NaOH solution (1.1 ml, 2.67 mmol) was added to a solution of **8a** ($[\alpha]_D^{23}$ +1.8°, 826 mg, 2.22 mmol) in CH_3CN (12 ml), and the resulting mixture was stirred at room temperature for 17 h. The precipitated sodium salts were collected, washed with CH_3CN, and suspended in water. The resulting suspension was acidified with 10% HCl and extracted with AcOEt. The CH_3CN washings were combined with the filtrate and concentrated *in vacuo*. The residue was dissolved in water and extracted with Et_2O. The aqueous layer was acidified with 10% HCl and extracted with AcOEt. The AcOEt extracts were washed with water and brine, dried, and concentrated to give 515 mg (quantitative yield) of **3a**, mp 167—170 °C. The ethereal extract was washed with water and brine, dried, and concentrated *in vacuo* to give 331 mg (95%) of *l*-menthol. **3a**: mp 160—173 °C (1,2-dichloroethane). *Anal.* Calcd for $C_9H_6Cl_2O_3$: C, 46.38; H, 2.59; Cl, 30.43. Found: C, 46.16; H, 2.80; Cl, 30.40. $[\alpha]_D^{22}$ +72.8° ($c=1.01$, acetone).

Hydrolysis of 8b——Similar hydrolysis of **8b** ($[\alpha]_D^{22}$ −2.7°, 605 mg, 1.63 mmol) gave 376 mg (99%) of **3b** as colorless crystals and 246 mg (97%) of *d*-menthol. **3b**: mp 167—169 °C (crude), mp 160—172 °C (1,2-dichloroethane). *Anal.* Calcd for $C_9H_6Cl_2O_3$: C, 46.38; H, 2.59; Cl, 30.43. Found: C, 46.46; H, 2.84; Cl, 30.42. $[\alpha]_D^{22}$ −72.2° ($c=1.02$, acetone).

Separation of Optical Isomers of 3

Esterification of 3 with *l*-Menthol——A mixture of **3** (61.5 g, 0.264 mol), *l*-menthol (49.5 g, 0.316 mol), and concentrated H_2SO_4 (10 drops) in benzene was heated at reflux for 4.5 h with separation of water as the benzene azeotrope. The reaction mixture was concentrated and the residue was diluted with Et_2O (500 ml), washed with aqueous $NaHCO_3$, water, and brine, dried, and concentrated *in vacuo*. The resultant pale yellow solid (117.5 g) was dissolved in hexane (150 ml) with heating and then left standing at room temperature. The precipitated crystals were collected by filtration and washed with hexane to give 35.8 g (mp 111.5—113 °C) of **8a**. The hexane washings were combined with the filtrate and concentrated. The residue was dissolved in pentane and cooled with a dry ice-acetone bath. The precipitates were collected, washed with cold pentane, and recrystallized from hexane to give 4.77 g (mp 111.5—113 °C) of **8a**. The mother liquor and the washings were combined and used for the next hydrolysis. The total yield of **8a** was 40.6 g (41.4%). **8a**: Colorless crystals, mp 112.5—114 °C (hexane). *Anal.* Calcd for $C_{19}H_{24}Cl_2O_3$: C, 61.46; H, 6.52; Cl, 19.10. Found: C, 61.53; H, 6.43; Cl, 19.38. $[\alpha]_D^{22}$ +2.4° ($c=1.01$, acetone).

Hydrolysis of the Mother Liquor——The mother liquor (64.4 g) obtained in the synthesis of **8a** was dissolved in CH_3CN (300 ml). After addition of a solution of NaOH (7.62 g, 0.189 mol) in water (100 ml), the resulting mixture was stirred for 6 h at room temperature. The precipitated sodium salts were collected, washed with CH_3CN, and suspended in water. The resulting suspension was acidified with 10% HCl and extracted with AcOEt. On the other hand, the filtrate and the washings were combined and concentrated *in vacuo*. The residue was dissolved in water, washed with Et_2O, acidified with 10% HCl, and extracted with AcOEt. The AcOEt extracts were combined, washed with brine, dried, and concentrated. The resultant solid was washed with hexane to give 35.4 g (57.5% from racemic **3**)

of **3** which was rich in **3b**, mp 161—164 °C. The Et_2O washings were washed with brine, dried, and concentrated *in vacuo*, and the residue was sublimed under reduced pressure (3 mmHg, bath temperature 50—60 °C) to give 30.4 g (61.4%) of *l*-menthol.

Esterification with *d*-Menthol——The carboxylic acid **3** thus obtained (35.4 g, 0.152 mmol) was condensed with *d*-menthol (28.5 g, 0.182 mol) in the presence of a catalytic amount of *p*-TsOH using a procedure similar to that described for the preparation of **8a** to give 44.3 g (45% from racemic **3**) of **8b**, mp 112.5—114 °C (hexane). $[\alpha]_D^{23}$ −2.8° (c = 1.01, acetone). The mother liquor (17.3 g) was used for the following hydrolysis.

Hydrolysis of the Mother Liquor of 8b——A solution of the mother liquor of **8b** (17.3 g) in CH_3CN (120 ml) and 1 N NaOH (40 ml) was stirred at room temperature for 8 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in water and Et_2O. The aqueous layer was further extracted with Et_2O and the ethereal extracts were combined, washed with brine, dried, and concentrated *in vacuo* to give 9.58 g (33.6%) of *d*-menthol. The aqueous layer was acidified with 10% HCl and extracted with AcOEt. The AcOEt extracts were washed with brine, dried, and concentrated. The white solid left was washed with hexane and gave 7.32 g (12% from racemic **3**) of a mixture of **3a** and **3b**, mp 140—160 °C.

Methanolysis of 8a——A mixture of **8a** (40.1 g, 0.108 mol) and concentrated H_2SO_4 (10 drops) in MeOH (400 ml) was heated at reflux for 30 h. The reaction mixture was concentrated and the residue was dissolved in AcOEt. The resulting solution was washed with aqueous $NaHCO_3$, water, and brine, dried, and concentrated *in vacuo*. Recrystallization of the resulting white solid (50 g) from hexane gave 25.5 g (95% from **8a**, 39% from racemic **3**) of **2a**. Sublimation of the mother liquor gave 16.0 g (95%) of *l*-menthol. **2a**: mp 81—82 °C (benzene–hexane). $[\alpha]_D^{23}$ +71.3° (c = 1.01, acetone).

Methanolysis of 8b——Similar methanolysis of **8b** (42.8 g, 0.115 mol) gave 27.0 g (95% from **8b**, 41% from racemic **3**) of **2b**, mp 81—82 °C (benzene–hexane). $[\alpha]_D^{23}$ −71.5° (c = 1.02, acetone).

2,3-Dichlorophenyl Methoxymethyl Ether (12)——A mixture of 2,3-dichlorophenol (16.3 g, 0.10 mol), chloromethyl methyl ether (9.7 g, 0.12 mol), K_2CO_3 (27.6 g, 0.20 mol), and CH_3CN (150 ml) was heated at 50—60 °C for 40 min and concentrated *in vacuo*. The residue was suspended in CH_2Cl_2, washed with water, dried over Na_2SO_4, and concentrated *in vacuo* to give 20.8 g (100%) of **12** as a pale yellow oil. ^{1}H-NMR δ: 3.52 (3H, s, OCH_3), 5.24 (2H, s, OCH_2O), 7.13 (3H, s, arom. H).

(Phenylthiomethyl)oxirane (13)——A solution of thiophenol (303 mg, 2.75 mmol) in CH_3CN was added dropwise to a stirred mixture of epibromohydrin (452 mg, 3.30 mmol) and K_2CO_3 (456 mg, 3.30 mmol) in CH_3CN. The resulting mixture was stirred at room temperature for 2 h and heated at reflux for 30 min. The insoluble salts were collected by filtration and washed with CH_3CN. The washings were combined with the filtrate, and the resultant solution was concentrated. The residue (482 mg) was chromatographed on silica gel with CH_2Cl_2–hexane (3 : 1, v/v) as the eluant to give 373 mg (82%) of **13** as a colorless oil. ^{1}H-NMR δ: 2.49 (1H, dd, J = 4.8, 2.5 Hz, 1H of OCH_2), 2.6—3.3 (4H, m, 1H of OCH_2, $OCHCH_2Ph$), 7.1—7.5 (5H, m, Ph).

1-[3,4-Dichloro-2-(methoxymethoxy)phenyl]-3-(phenylthio)-2-propanol (11)——Butyl lithium in hexane (1.3 N, 0.82 ml, 1.07 mmol) was added to an ice-cooled solution of **12** (223 mg, 1.07 mmol) in Et_2O (3 ml) under an N_2 atmosphere, and the resulting mixture was stirred at room temperature for 1 h. Copper(I) iodide (102 mg, 0.54 mmol) was added under ice-cooling, and the resultant mixture was stirred at room temperature for 30 min. After addition of a solution of **13** (178 mg, 1.07 mmol) in Et_2O (2 ml) to the reaction mixture, stirring was continued for 75 min at room temperature. A small amount of aqueous NH_4Cl was added to the reaction mixture, which was stirred at room temperature for some time. The reaction mixture was diluted with AcOEt, washed with water and brine, dried, and concentrated *in vacuo*. Chromatography of the residue on silica gel with AcOEt–hexane (1 : 2, v/v) gave 255 mg (64%) of **11** as a colorless viscous oil. ^{1}H-NMR δ: 2.7—3.1 (5H, m, $ArCH_2$, CH_2SPh, OH), 3.57 (3H, s, CH_3), 3.8—4.2 (1H, m, CHOH), 5.07 (2H, s, OCH_2O), 7.0—7.5 (7H, m, arom. H).

2,3-Dichloro-6-[2-hydroxy-3-(phenylthio)propyl]phenol (10)——A catalytic amount of concentrated H_2SO_4 was added to a solution of **11** (421 mg, 1.13 mmol) in EtOH, and the resulting solution was heated at reflux for 2 h. The reaction mixture was concentrated, and the residue was diluted with AcOEt, washed with aqueous $NaHCO_3$, water, and brine, dried, and concentrated *in vacuo* to give 376 mg (quantitative yield) of **10** as a pale yellow oil, which was used for the next step without further purification. ^{1}H-NMR δ: 2.6—3.3 (4H, m, $ArCH_2$ and CH_2SPh), 3.35 (1H, br s, CHOH), 3.8—4.1 (1H, m, CHOH), 6.90 (2H, s, 4- and 5-H), 7.2—7.5 (5H, m, Ph), 7.93 (1H, s, ArOH).

6,7-Dichloro-2-(phenylthiomethyl)-2,3-dihydrobenzofuran (9)——A catalytic amount of concentrated H_2SO_4 was added to a solution of **10** (376 mg, 1.1 mmol) in benzene (10 ml), and the resulting solution was heated at reflux for 30 min with separation of water as the benzene azeotrope. The reaction mixture was concentrated, and the residue was diluted with AcOEt, washed with aqueous $NaHCO_3$, water, and brine, dried, and concentrated *in vacuo*. Chromatography of the residue on silica gel with CH_2Cl_2–hexane (1 : 2, v/v) as the eluant gave 314 mg (89%) of **9** as colorless crystals, mp 69—69.5 °C. ^{1}H-NMR δ: 3.09 (1H, dd, J = 13.5, 8.1 Hz, 1H of CH_2SPh), 3.12 (1H, dd, J = 16.1, 7.0 Hz, 3-H), 3.40 (1H, dd, J = 16.1, 8.7 Hz, 3-H), 3.44 (1H, dd, J = 13.5, 4.5 Hz, 1H of CH_2SPh), 5.04 (1H, m, 2-H), 6.93 (2H, s, 4- and 5-H), 7.1—7.5 (5H, m, Ph).

Methyl 6,7-Dichloro-2,3-dihydrobenzo[*b*]furan-2-carboxylate (2)——A solution of SO_2Cl_2 (0.75 g, 5.59 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a stirred solution of **9** (756 mg, 2.43 mmol) in CH_2Cl_2 (10 ml). The resulting

mixture was stirred at room temperature for 1 h and then concentrated. The resulting yellow viscous oil (0.96 g) was suspended in MeOH (10 ml) and water (0.05 ml). The mixture was stirred at room temperature for 18 h and then concentrated *in vacuo*. The residue was dissolved in AcOEt, washed with aqueous $NaHCO_3$, water, and brine, then dried and concentrated. The crystalline residue was filtered and washed with hexane to give 529 mg of **2**, which was recrystallized from benzene to give 492 mg (82%) of **2a** as colorless crystals, mp 116—118 °C. *Anal.* Calcd for $C_{10}H_8Cl_2O_3$: C, 48.61; H, 3.26; Cl, 28.70. Found: C, 48.27; H, 3.31; Cl, 28.76.

1,2-*O*-Isopropylidene-*sn*-glycerol (**15**) was prepared from D-mannitol according to refs. 7 and 8.

(*R*)-3-(Phenylthio)-1,2-propanediol (16a)——Tributylphosphine (28.1 g, 0.139 mol) was added dropwise over a period of 45 min to a mixture of **15** (15.3 g, 0.116 mol), diphenyl disulfide (30.4 g, 0.139 mol), and benzene (3 ml). The resulting mixture was stirred at room temperature for 1 h and then chromatographed on silica gel (300 g). Elution with CH_2Cl_2–hexane (1 : 10, v/v) provided thiophenol, which was discarded. Continued elution with AcOEt–hexane (1 : 5, v/v) gave 23.7 g (91%) of an intermediate sulfide as a colorless oil. ^{1}H-NMR δ: 1.32 and 1.41 (each 3H, s, CH_3), 2.90 (1H, dd, J=13.4, 7.7 Hz, 1H of C$\underline{H}_2$SPh), 3.22 (1H, dd, J=13.4, 4.9 Hz, 1H of C$\underline{H}_2$SPh), 3.71 (1H, dd, J=8.0, 5.7 Hz, 1H of OCH_2), 3.9—4.4 (2H, m, 1H of OCH_2, OCH), 7.1—7.5 (5H, m, Ph). This oil was dissolved in THF (88 ml) and 1 N HCl (44 ml), and the resulting mixture was heated at reflux for 40 min. The reaction mixture was concentrated, and the residue was dissolved in AcOEt. The resultant solution was washed with saturated aqueous $NaHCO_3$. The washing was extracted with AcOEt, and the AcOEt extract was combined with the organic layer. The resulting solution was washed with brine, dried, and concentrated *in vacuo*. The residual solid (18.6 g) was recrystallized from benzene to give 17.8 g (83%) of **16a** as colorless crystals, mp 82.5—83.5 °C. *Anal.* Calcd for $C_9H_{12}O_2S$: C, 58.67; H, 6.56; S, 17.40. Found: C, 58.75; H, 6.54; S, 17.29. $[\alpha]_D^{23}$ −24.6° (c=1.00, EtOH). ^{1}H-NMR δ: 3.01 (2H, d, J=6 Hz, C$\underline{H}_2$SPh), 2.3—3.4 (2H, br, 2×OH), 3.4—4.0 (3H, m, OCH_2, OCH), 7.1—7.5 (5H, m, Ph).

(*R*)-(Phenylthiomethyl)oxirane (13a)——A solution of *p*-TsCl (2.29 g, 12.0 mmol) in CH_2Cl_2 (12 ml) was added to an ice-cooled solution of **16a** (1.84 g, 10.0 mmol) in pyridine (18 ml), and the resulting solution was stirred at room temperature for 13.5 h. The solvent was evaporated off *in vacuo*, and the residue was dissolved in AcOEt, washed with 10% HCl, water, and brine, dried, and concentrated to give a colorless viscous oil (3.62 g). A solution of NaOH in MeOH (1.03 M, 8.74 ml, 9.0 mmol) was added to a cooled (−10—−20 °C) solution of the oil in MeOH (10 ml), and the resulting mixture was stirred for 4 h at that temperature. The reaction mixture was concentrated, and the residue was dissolved in AcOEt, washed with water and brine, dried, and concentrated. Chromatography of the residue on silica gel with AcOEt–hexane (1 : 3, v/v) as the eluant gave 1.21 g (73%) of **13a** as a colorless oil, which was distilled under reduced pressure, bp 85—87 °C (0.2 mmHg). *Anal.* Calcd for $C_9H_{10}OS$: C, 65.03; H, 6.06; S, 19.29. Found: C, 64.77; H, 6.03; S, 19.03. $[\alpha]_D^{24}$ +29.5° (c=1.07, $CHCl_3$). The ^{1}H-NMR spectrum of **13a** agreed with that of the racemate **13**.

3-*O*-Benzoyl-*sn*-glycerol (17)——A solution of benzoyl chloride (17.2 g, 0.122 mol) in CH_2Cl_2 (50 ml) was added over a period of 25 min to an ice-cooled solution of **15** (14.75 g, 0.11 mol) and Et_3N (22.5 g, 0.222 mol) in CH_2Cl_2 (100 ml) with stirring. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with Et_2O, washed with water, dilute HCl, water, and brine, dried, and concentrated *in vacuo*. The remaining brown oil (26.4 g) was dissolved in acetone (60 ml) and 1 N HCl (180 ml), and the mixture was stirred for 1.5 h at room temperature. The reaction mixture was washed with hexane to remove the excess benzoyl chloride and then concentrated. The residue was saturated with NaCl and extracted with AcOEt. The organic extracts were washed with brine, dried, and concentrated *in vacuo*. Recrystallization of the residual brown solid (16.7 g) from Et_2O gave 10.7 g of **17** as colorless crystals, mp 65—66 °C. Chromatography of the mother liquor on silica gel with AcOEt–hexane (1 : 1 then 3 : 1, v/v) gave 3.1 g of **17**. Total yield of **17**: 13.8 g (63%). *Anal.* Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.09; H, 6.20. $[\alpha]_D^{23}$ −19.0° (c=1.00, EtOH). IR (Nujol): 3600—3100, 1700 cm^{-1}. ^{1}H-NMR δ: 3.34 (2H, br s, 2×OH), 3.6—3.8 (2H, m, C$\underline{H}_2$OH), 4.06 (1H, m, C$\underline{H}$OH), 4.38 (2H, d, J=5.4 Hz, CH_2OCO), 7.2—7.7 (3H, m, 3H of Ph), 8.03 (2H, dm, J=8 Hz, 2H of Ph).

(*S*)-3-(Phenylthio)-1,2-propanediol (16b)——Tributylphosphine (13.6 g, 67.1 mmol) was added dropwise to a mixture of **17** (12.0 g, 61.0 mmol), diphenyl disulfide (14.7 g, 67.1 mmol), and benzene (9 ml). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was chromatographed on silica gel (250 g). Elution with CH_2Cl_2–hexane (1 : 10, v/v) gave thiophenol, which was discarded. Continued elution with AcOEt–hexane (1 : 2, v/v) gave 14.9 g (85%) of an intermediate sulfide as colorless crystals, mp 62.5—63.5 °C (benzene–hexane). *Anal.* Calcd for $C_{16}H_{16}O_3S$: C, 66.64; H, 5.59; S, 11.12. Found: C, 66.62; H, 5.66; S, 10.97. $[\alpha]_D^{23}$ −10.7° (c=1.00, $CHCl_3$). IR (Nujol): 3550—3100, 1690 cm^{-1}. ^{1}H-NMR δ: 2.95 (1H, dm, J=4.5 Hz, OH), 3.04 (1H, dd, J=13.8, 6.9 Hz, 1H of C$\underline{H}_2$SPh), 3.22 (1H, dd, J=13.8, 5.5 Hz, 1H of C$\underline{H}_2$SPh), 3.9—4.2 (1H, m, C$\underline{H}$OH), 4.40 (2H, J=4.7 Hz, CH_2OCO), 7.1—7.7 (8H, m, SPh, 3H of COPh), 8.01 (2H, dm, J=8 Hz, 2H of COPh). This sulfide (13.7 g, 47.4 mmol) was dissolved in MeOH (100 ml) and 1 N NaOH (50 ml), and the resulting mixture was stirred at room temperature for 45 min. The reaction mixture was concentrated, and the residue was dissolved in AcOEt. This solution was washed with water, and the washing was extracted with AcOEt. The AcOEt extract was combined with the organic layer, washed with brine, dried, and concentrated *in vacuo*, leaving a white solid (9.91 g). Recrystallization of the residue from benzene gave 8.19 g (94%) of **16b** as colorless crystals, mp 82—83 °C (benzene). [lit.[6] mp 89—90 °C (benzene)] *Anal.* Calcd for $C_9H_{12}O_2S$: C, 58.67; H, 6.56; S, 17.40. Found: C, 58.55; H, 6.57; S, 17.23. $[\alpha]_D^{23}$ +23.6° (c=1.01, EtOH) [lit.[6] $[\alpha]_D^{23}$

+20.7° (c=0.997, EtOH)]. The ^{1}H-NMR spectrum of **16b** agreed with that of **16a**.

(*S*)-(Phenylthiomethyl)oxirane (13b)——**13b** was prepared from **16b** (3.69 g, 20.0 mmol) by a procedure similar to that used for the preparation of **13a**. This gave 2.49 g (75%) of **13b** as a colorless oil, which was distilled under reduced pressure, bp 89—90 °C (0.15 mmHg) [lit.[6] bp 120 °C (0.55 mmHg)]. *Anal.* Calcd for $C_9H_{10}OS$: C, 65.03; H, 6.06; S, 19.29. Found: C, 64.91; H, 6.15; S, 19.20. $[\alpha]_D^{24}$ −31.5° (c=1.01, $CHCl_3$) [lit.[6] $[\alpha]_D^{23}$ −34.1° (c=1.06, $CHCl_3$)]. The ^{1}H-NMR spectrum of **13b** agreed with that of the racemate **13**.

(*R*)-1-[3,4-Dichloro-2-(methoxymethoxy)phenyl]-3-(phenylthio)-2-propanol (11a)——Starting from **12** (2.51 g, 12.1 mmol) and **13a** (2.01 g, 12.1 mmol), synthesis of **11a** was carried out by using a procedure similar to that described for the synthesis of the racemate **11**, and 2.77 g (61%) of **11a** was obtained as a colorless viscous oil. The ^{1}H-NMR spectrum of **11a** agreed with that of the racemate **11**. Analysis of **11a** by HPLC on a Chiralcel OD column (4.6 i.d. × 250 mm, Daicel Chem. Ind.) with hexane–2-propanol (9 : 1, v/v) as a mobile phase at a flow rate of 0.5 ml/min showed a single peak at the retention time of 19.8 min.

(*R*)-6,7-Dichloro-2-(phenylthiomethyl)-2,3-dihydrobenzofuran (9a)——A solution of **11a** (2.72 g, 7.29 mmol) and concentrated H_2SO_4 (2 drops) in EtOH (25 ml) was heated at reflux for 45 min and then concentrated. The residue was dissolved in AcOEt, washed with water and brine, dried, and concentrated *in vacuo* to give a pale-brown oil (2.42 g). A solution of the oil and concentrated H_2SO_4 (2 drops) in benzene (40 ml) was refluxed for 30 min and then concentrated *in vacuo*. The residue was worked up similarly to give a pale brown oil (2.22 g). Chromatography of the oil on silica gel with CH_2Cl_2–hexane (1 : 2, v/v) gave 2.16 g (95%) of **9a** as a colorless viscous oil. The ^{1}H-NMR spectrum of **9a** agreed well with that of the racemate **9**. Analysis of **9a** by HPLC on a Chiralcel OB column (4.6 i.d. × 250 mm, Daicel Chem. Ind.) with hexane–2-propanol (9 : 1, v/v) as a mobile phase at a flow rate of 1.0 ml/min showed a single peak at the retention time of 12.4 min.

Methyl (*R*)-6,7-Dichloro-2,3-dihydrobenzo[*b*]furan-2-carboxylate (2a)——A solution of SO_2Cl_2 (2.10 g, 15.6 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a stirred solution of **9a** (2.11 g, 6.77 mmol) in CH_2Cl_2 (20 ml). The resulting mixture was refluxed for 35 min and then concentrated. The resulting yellow viscous oil (2.90 g) was suspended in MeOH (30 ml) and water (0.15 ml). The mixture was stirred at room temperature for 18 h and then concentrated *in vacuo*. The residue was dissolved in AcOEt, washed with aqueous $NaHCO_3$, water, and brine, dried, and concentrated. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 5 then 1 : 3, v/v) as the eluant to give 1.45 g of **2a**, which was recrystallized from benzene–hexane to give 1.36 g (82%) of **2a** as colorless crystals, mp 82—82.5 °C. *Anal.* Calcd for $C_{10}H_8Cl_2O_3$: C, 48.61; H, 3.26; Cl, 28.70. Found: C, 48.37; H, 3.04; Cl, 28.96. $[\alpha]_D^{23}$ +71.3° (c=1.01, acetone). Analysis of **2a** by HPLC on a Chiralcel OD column (4.6 i.d. × 250 mm, Daicel Chem. Ind.) with hexane–2-propanol (9 : 1, v/v) as a mobile phase at a flow rate of 0.5 ml/min showed a single peak at the retention time of 15.4 min.

(*S*)-1-[3,4-Dichloro-2-(methoxymethoxy)phenyl]-3-(phenylthio)-2-propanol (11b)——Compound **11b** was prepared from **12** and **13b** in a similar manner to the racemate **11**. Yield 64%. The ^{1}H-NMR spectrum of **11b** agreed with that of the racemate **11**. Analysis of **11b** by HPLC under the same conditions as used for **11a** showed a single peak at the retention time of 21.5 min.

(*S*)-6,7-Dichloro-2-(phenylthiomethyl)-2,3-dihydrobenzofuran (9b)——Compound **9b** was prepared from **11b** as described for the *R*-enantiomer **9a**. Yield 91%. The ^{1}H-NMR spectrum of **9b** agreed with that of **9a**. Analysis of **9b** by HPLC under the same conditions as used for **9a** showed a single peak at the retention time of 18.9 min.

Methyl (*S*)-6,7-Dichloro-2,3-dihydrobenzo[*b*]furan-2-carboxylate (2b)——Compound **2b** was prepared from **9b** by the same procedure as described for the *R*-enantiomer **2a**. Yield 86%. Colorless crystals, mp 82—82.5 °C (benzene–hexane). $[\alpha]_D^{23}$ −72.5° (c=1.01, acetone). Analysis of **2b** by HPLC under the conditions described for **2a** showed a single peak at the retention time of 14.1 min.

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References and Notes

1) H. Harada, Y. Matsushita, M. Yodo, M. Nakamura, and Y. Yonetani, *Chem. Pharm. Bull.*, **35**, 3195 (1987).
2) J. J. Plattner, A. K. L. Fung, J. A. Parks, R. J. Pariza, S. R. Crowley, A. G. Pernet, P. R. Bunnell, and P. W. Dodge, *J. Med. Chem.*, **27**, 1016 (1984).
3) M. Shiro, unpublished results.
4) T. Hosokawa, C. Okuda, and S. Murahashi, *J. Org. Chem.*, **50**, 1282 (1985).
5) C. C. Fortes, H. C. Fortes, and D. C. R. G. Goncalves, *J. Chem. Soc., Chem. Commun.*, **1982**, 857.
6) T. Fujisawa, T. Itoh, M. Nakai, and T. Sato, *Tetrahedron Lett.*, **1985**, 771.
7) G. J. F. Chittenden, *Carbohydr. Res.*, **84**, 350 (1980).
8) H. Eibl, *Chem. Phys. Lipids*, **28**, 1 (1981).
9) W. H. Pirkle and P. L. Rinaldi, *J. Org. Chem.*, **44**, 1025 (1979); I. Nakagawa and T. Hata, *Tetrahedron Lett.*, **1975**, 1409.
10) D. R. Williams and J. G. Phillips, *Tetrahedron*, **42**, 3013 (1986).