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Absolute Structures of Some Naturally Occurring Isopropenyldihydrobenzofurans, Remirol, Remiridiol, Angenomalin, and Isoangenomalin

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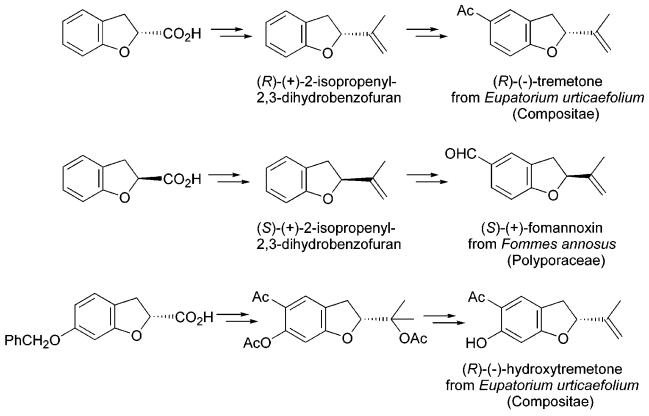
The absolute structures of some naturally occurring chiral 2-isopropenyl-2,3-dihydrobenzofurans, (+)-remirol (**1a**), (+)-remiridiol (**1b**), (+)-angenomalin (**2**), and (+)-isoangenomalin (**3**), were studied by respective chiral synthesis. Kinetic resolutions of racemic 2-isopropenyl-2,3-dihydrobenzofurans, 2-isopropenyl-4,6-dimethoxy-2,3-dihydrobenzofuran (**4**), 4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde (**8**), and 2-isopropenyl-6-(MOM)oxy-2,3-dihydrobenzofuran-5-carbaldehyde (**11c**), by Sharpless dihydroxylation using $(DHQ)_2AQN$ or $(DHQD)_2AQN$ gave the corresponding chiral 2-isopropenyl-2,3-dihydrobenzofurans. Chiral (*S*)-(+)-**4** (99% ee, using $(DHQD)_2AQN$) was converted to natural remirol (*S*)-(+)-**1a** and then to natural remiridiol (*S*)-(+)-**1b**. (*S*)-(+)-**8** (97% ee, using $(DHQD)_2AQN$) was converted to natural angenomalin (*S*)-(+)-**2**. (*R*)-(−)-**11**c (>99% ee, using $(DHQ)_2AQN$), was converted to natural isoangenomalin (*R*)-(+)-**3**. Thus, the absolute structures of natural remirol (+)-**1a** and remiridiol (+)-**1b** and angenomalin (+)-**2** were determined to be *S*, and the structure of natural isoangenomalin (+)-**3** was *R*.

Many 2-isopropenyl-2,3-dihydrobenzofuran derivatives, isolated from various plants, might be derived by an enzymic oxidative cyclization of the corresponding *o*-prenylphenols in plants. However, the existence of *R* and *S*, two types of absolute configurations ((*R*)-(−)-tremetone,[1,2] (*R*)-(−)-hydroxy-tremetone,[3] and (*S*)-(+)-fomannoxin),[2] means that the different asymmetrical cyclization occurs in different kinds of plants. Interested in chemotaxonomy, we have attempted to clarify the relation between the absolute configurations of some natural 2-isopropenyl-2,3-dihydrobenzofurans and the species of the original plant.

Some previous syntheses of chiral 2-isopropenyl-2,3-dihydrobenzofurans,[2,3] as shown in Scheme 1, needed the respective preparation and structural determination of the corresponding chiral 2,3-dihydrobenzofuran-2-carboxylic acids and the conversion to the corresponding chiral 2-isopropenyl-2,3-dihydrobenzofuran.

Recently, some asymmetric oxidative cyclizations of *o*-(2-butenyl)phenols were reported, as shown in Scheme 2. Murahashi et al. already reported the first chiral cyclization of *o*-(2-butenyl)phenol using (+)-(η^3-pinene)-palladium(II) acetate,[5] but they showed nonasymmetric cyclization in *o*-prenylphenol. Recently, Hayashi et al. reported an effective chiral Pd(II) cyclization of *o*-(2,3-dimethyl-2-butenyl)phenol using a chiral ligand, (*S*,*S*)-ip-boxax, giving chiral 2-isopropenyl-2-methyl-2,3-dihydrobenzofuran in 96% ee (75% yield).[6] For a new synthesis of chiral 2-isopropenyl-2,3-dihydrobenzofurans, a similar asymmetric cyclization of *o*-prenylphenol was planned in

SCHEME 1. Previous Structural Determinations of Some Naturally Occurring Chiral Isopropenyldihydrobenzofurans



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(1) Bonner, W. A.; Burke, N. I.; Fleck, W. E.; Hill, R. K.; Joule, J. A.; Sjoberg, B.; Zalkow, J. H. *Tetrahedron* **1964**, *20*, 1419.

(2) Kawase, Y.; Yamaguchi, S.; Inoue, O.; Sannomiya, M.; Kawabe, K. *Chem. Lett*. **1980**, 1581.

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(5) Hosokawa, T.; Ohkata, H.; Moritani, I. *Bull. Chem. Soc. Jpn*. **1975**, *48*, 1533. Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S. *J. Am. Chem. Soc*. **1981**, *103*, 2318. Hosokawa, T.; Okuda, C.; Inui, S.; Murahashi, S. *J. Org. Chem*. **1985**, *15*, 1282. In chiral cyclizations of *o*-(2-butenyl)phenols using (+)-(η^3-pinene)palladium(II) acetate, the trans isomer gave (+)-2-vinyl-2,3-dihydrobenzofuran in 18%ee (81% yield) and the cis isomer gave (−)-enantiomer in 0.7% ee (62% yield).

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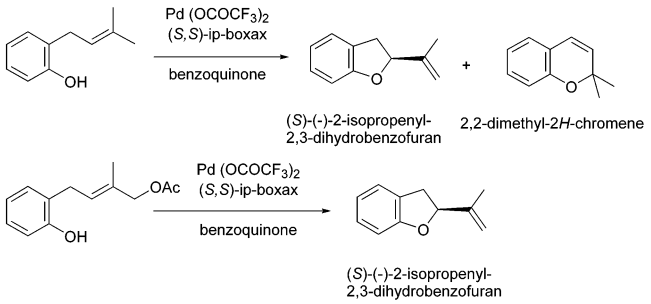
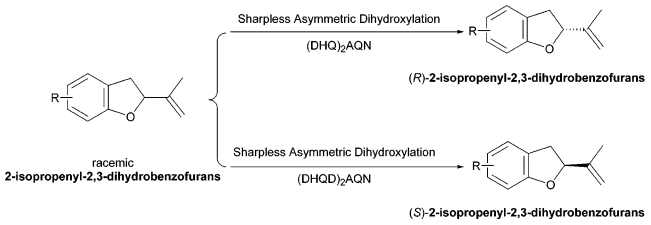
SCHEME 2. Our Chiral Cyclization of *o*-Prenylphenols Using Hayashi's Chiral Ligand



SCHEME 3. New Kinetic Resolution Using Sharpless Asymmetric Dihydroxylation



Hayashi's procedure. However, as shown in Scheme 2, a similar cyclization of *o*-prenylphenol gave a mixture of chiral (*S*)-(−)-2-isopropenyl-2,3-dihydrobenzofuran (15% ee) and 2,2-dimethyl-2*H*-chromene in only 8% yield (ratio 42:58), and the obtained chiral 2-isopropenyl-2,3-dihydrobenzofuran showed only 15% ee.[7]

In our previous studies,[8a−h] some racemic 2-isopropenyl-2,3-dihydrobenzofurans were readily prepared by one-step cyclization of the corresponding phenols with 1,4-dibromo-2-methyl-2-butene. So, for another effective preparation of chiral 2-isopropenyl-2,3-dihydrobenzofurans, some kinetic resolutions of racemic 2-isopropenyl-2,3-dihydrobenzofurans were studied. And finally, the kinetic resolution in Sharpless dihydroxylation using a chiral ligand, $(DHQ)_2AQN$ or $(DHQD)_2AQN$,[9] was found to be the most effective procedure, as shown in Scheme 3. This new procedure is a diastereoselective kinetic resolution of both enantiomeric mixtures recovering an enantiomer, while most of the chiral resolutions using Sharpless dihydroxylation were enantioselective kinetic resolution of an achiral substrate giving a chiral product.

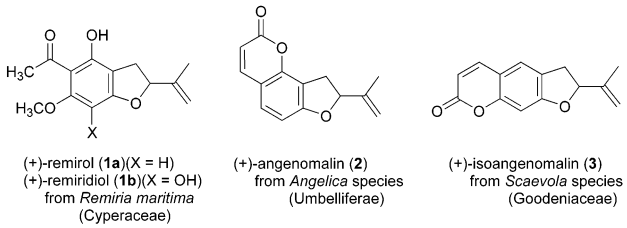


FIGURE 1. Naturally occurring chiral isopropenyldihydrobenzofurans as synthetic targets.

In this paper, we describe chiral synthesis and structural determination of some naturally occurring chiral 2-isopropenyl-2,3-dihydrobenzofuran derivatives, (+)-remirol (**1a**),[10] (+)-remiridiol (**1b**),[11] (+)-angenomalin (**2**),[12] and (+)-isoangenomalin (**3**),[13] shown in Figure 1.

The synthesis of racemic remirol (**1a**) was already reported in our previous paper,[8f] via one-step cyclization of 3,5-dimethoxyphenol with 1,4-dibromo-2-methyl-2-butene giving 2-isopropenyl-4,6-dimethoxy-2,3-dihydrobenzofuran (**4**), acylation with acetic acid−trifluoroacetic anhydride giving 5-acetyl-2-isopropenyl-4,6-dimethoxy-2,3-dihydrobenzofuran (**6**), and selective demethylation with magnesium iodide diethyl etherate giving racemic **1a**. Sharpless asymmetric dihydroxylation of racemic **4** was studied under several conditions, and the results are summarized in Table 1. Racemic **4** was subjected to Sharpless asymmetric dihydroxylation: treatment with $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, and some chiral ligands.[9] As shown in Table 1, chiral ligand $(DHQ)_2AQN$[9] gave (−)-**4** (95% ee) in 26% yield, and chiral ligand $(DHQD)_2AQN$[9] gave (+)-**4** (99% ee) in 14% yield. The absolute structure of (−)-**4**, thus obtained, was determined to be *R*, as shown in Scheme 4, via hydrogenation to (−)-**5**, oxidative cleavage of (−)-**5** with O_3, following methyl esterification with diazomethane, and comparison with authentic (*R*)-(+)-methyl 3-hydroxy-4-methylpentanoate.[14]

Then, both enantiomers, (*R*)-(−)-**4** and (*S*)-(+)-**4**, were subjected to the respective conversion to the corresponding remirols: (1) acylation with acetic acid−trifluoroacetic anhydride and (2) selective demethylation with magnesium iodide etherate. Ketone (*R*)-**6** was obtained from (*R*)-(−)-**4** of 95% ee and was demethylated to give enantiomeric remirol (*R*)-(−)-**1a** (51% ee) after vigorous refluxing with magnesium iodide etherate in benzene for 3 h. The lower optical rotation might show partial racemization, via ring-opening and re-cyclization of the

(6) Uozumi, Y.; Kyouta, H.; Kishi, E.; Kitayama, K.; Hayashi, T. *Tetrahedron* **1996**, *6*, 1603. Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063. Chiral Pd(II) cyclization of *o*-(2,3-dimethyl-2-butenyl)phenol using a chiral ligand, (*S*,*S*)-ip-boxax, gave chiral 2-isopropenyl-2-methyl-2,3-dihydrobenzofuran in 96% ee (75% yield).

(7) As shown in Scheme 2, our similar cyclization of 2-(4-acetoxy-3-methyl-2-buteneyl)phenol treating with Pd(II)−(*S*,*S*)-ip-boxax−1,4-benzoquinone gave chiral (−)-2-isopropenyl-2,3-dihydrobenzofuran in 19% ee (34%).

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(9) Becker, H.; Sharpless, K. B. *Ang. Chem., Int. Ed. Engl*. **1996**, *35*, 448.

(10) Allan, R. D.; Correll, R. L.; Wells, R. J. *Tetrahedron Lett*. **1969**, 4673.

(11) Allan, R. D.; Wells, R. J.; MacLeod, J. K. *Tetrahedron Lett*. **1970**, 3945.

(12) Angenomalin: mp 105−106 °C; $[\alpha]_D$ +39.0. Hata, K.; Kozawa, M.; Ikeshiro, Y. *Yakugaku Zasshi* **1967**, *87*, 1118. Abu-Mustafa et al. isolated majurin (mp 95−96 °C) of the same structure, but there was no describe about the rotation. (Abu-Mustafa, E. A.; El-Bay, F. K. A.; Fayez, M. B. E. *Tetrahedron Lett*. **1971**, 1657.)

(13) -Isoangenomalin (from *Scaevola lobelia*): mp 116−117 °C; $[\alpha]_D$ +7.0. Kikuchi, T.; Yokoi, T.; Umemoto, K.; Shingu, T. *Yakugaku Zasshi* **1974**, *94*, 1616. Bohlmann et al. also isolated the same coumarin (mp 117 °C), no name, from *Scaevola frutescens*, but the rotation was not described. Bohlmann, F.; Jacob, J.; Grenz, M. *Chem. Ber*. **1975**, *108*, 433.

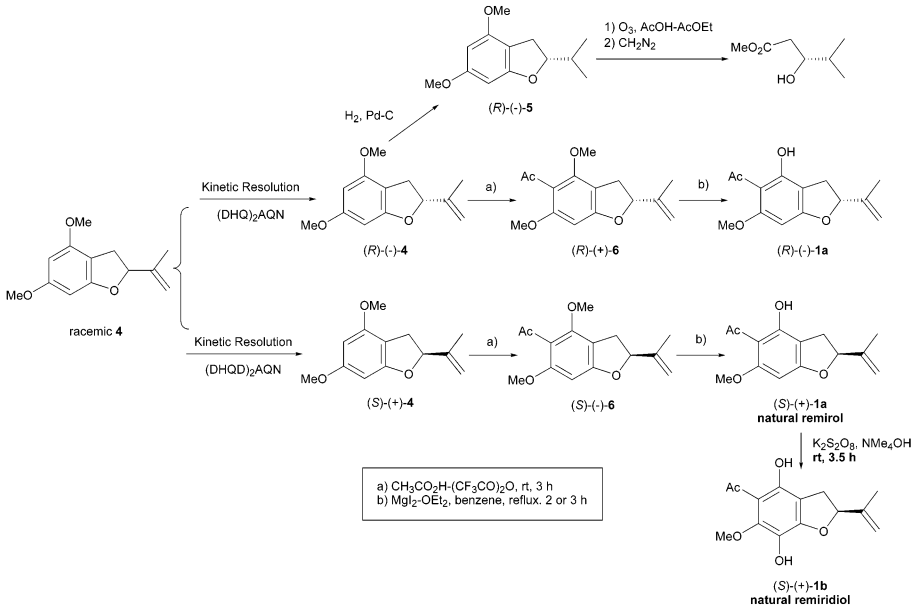
(14) Nakazaki, M.; Arakawa, H. *Bull. Chem. Soc. Jpn*. **1961**, *34*, 1246.

TABLE 1. Kinetic Resolution of Racemic Isopropenyl-2,3-dihydrobenzofurans 4, 8, 11a−c, and 3[a]

racemic substrate	chiral ligand	$K_3[Fe(III)CN_6]$ (reoxidant) (mol)	reaction time	recovered chiral compound
4	$(DHQ)_2PHAL$	3	3 h	(*R*)-(−)-**4** (19% ee, 33%)
4	$(DHQ)_2AQN$	1	1 h	(*R*)-(−)-**4** (67% ee, 40%)
4	$(DHQ)_2AQN$	2	1 h	(*R*)-(−)-**4** (73% ee, 38%)
4	$(DHQ)_2AQN$	3	30 min	(*R*)-(−)-**4** (27% ee, 50%)
4	$(DHQ)_2AQN$	3	1 h	(*R*)-(−)-**4** (95% ee, 26%)
4	$(DHQD)_2AQN$	3	1 h	(*S*)-(+)-**4** (99% ee, 14%)
8	$(DHQ)_2AQN$	3	7 h	(*R*)-(−)-**8** (97% ee, 21%)
8	$(DHQD)_2AQN$	3	11 h	(*S*)-(+)-**8** (97% ee, 19%)
11a	$(DHQ)_2AQN$	3	4 h*	(*R*)-(−)-**11a** (80% ee, 24%)
11a	$(DHQD)_2AQN$	3	4 h*	(*S*)-(+)-**11a** (80% ee, 13%)
3	$(DHQ)_2AQN$	3	4 h*	(*R*)-(+)-**3** (17% ee, 23%)
11b	$(DHQ)_2AQN$	3	7 h	(*R*)-(−)-**11b** (9% ee, 45%)
11c	$(DHQ)_2AQN$	3	5 h	(*R*)-(−)-**11c** (>99% ee, 29%)

[a] Substrate (1 mol), chiral ligand (1% mol), $KOsO_4$ (4% mol), $K_3[Fe(III)CN_6]$ (reoxidant) (3 mol), K_2CO_3 (3 mol), $CH_3SO_2NH_2$ (1 mol); reaction temperature 0 °C (*20 °C).

SCHEME 4. Synthesis and Structural Determination of Natural (+)-Remirol and (+)-Remiridiol



isopropenyl dihydrofuran ring.[15] So, ketone (*S*)-**6**, obtained from (*S*)-(+)-**4** of 99% ee, was subjected to milder demethylation (mild refluxing for 2 h). Obtained (*S*)-(+)-**1a** showed a higher rotation of 57.9° and 87% ee and was identical with natural remirol (+)-**1a**[10] in all spectral data. Remirol (*S*)-(+)-**1a**, thus obtained, was then converted to remiridiol (*S*)-(+)-**1b** by oxidation with potassium persulfate in 15% yield.[16] (*S*)-(+)-**1b**, thus obtained, was also identical with natural remiridiol (+)-**1b**[11] in all spectral data. Thus, both absolute structures of natural remirol (+)-**1a** and remiridiol (+)- **1b** were determined to be *S*.

The synthesis of racemic angenomalin (**2**) was already reported in our previous paper[8g] via one-step cyclization of cyclohexane-1,3-dione with 1,4-dibromo-2-methyl-2-butene to give 2-isopropenyl-2,3,6,7-tetrahydro-4(5*H*)-benzofuranone (**7**), formylation with $HCO_2Et-NaH$ followed by dehydrogenative aromatization with DDQ to give 4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde (**8**), and pyran-ring formation with dimethylacetamide dimethylacetal to give racemic angenomalin (**2**). Racemic **8** was then subjected to Sharpless asymmetric dihydroxylation, treatment with $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, and a chiral ligand $(DHQD)_2AQN$ or $(DHQ)_2AQN$.[9] As shown in Table 1, $(DHQD)_2AQN$ gave (+)-**8** (97% ee) in 26% yield, and $(DHQ)_2AQN$ gave (−)-**8** (78% ee). The absolute structure of (+)-**8**, thus obtained, was similarly determined to be *S*, as shown in Scheme 5, via hydrogenation to (+)-**9**, oxidative cleavage of (+)-**9** with $RuCl_3-NaIO_4$, following methyl esterification with diazomethane, and comparison with authentic (*R*)-(+)-methyl 3-hydroxy-4-methylpentanoate.[14]

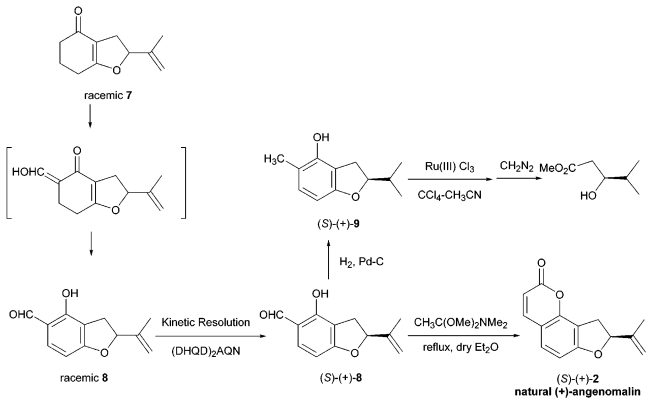
The pyran-ring formations were studied in both enantiomeric salicylaldehydes, (*S*)-(+)-**8** and (*R*)-(−)-**8**, thus obtained, and gave the corresponding coumarins (*S*)-(+)-**2** and (*R*)-(−)-**2**. The coumarin (*S*)-(+)-**2** was identical with natural (+)-angenomalin[12] in all spectral data. Thus, the absolute structure of natural angenomalin was determined to be *S*.

The synthesis of racemic isoangenomalin (**3**) was already reported in our previous paper[8g] via one-step

(15) Partial racemization might be caused by a dihydrofuran ring opening followed by recyclization.

(16) In our previous conversion, a similar oxidation of racemic remirol (**1a**) gave racemic remiridiol (**1b**) in a better yield (53%).

SCHEME 5. Synthesis and Structural Determination of Natural (+)-Angenomalin



cyclization of 3-methoxyphenol with 1,4-dibromo-2-methyl-2-butene to give 2-isopropenyl-6-methoxy-2,3-dihydrobenzofuran (**10**), formylation with *N*-methylformanilide-$POCl_3$ to give 2-isopropenyl-6-methoxy-2,3-dihydrobenzofuran-5-carbaldehyde (**11a**), demethylation with anhydrous magnesium iodide etherate to give 6-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde (**11b**), and pyran-ring formation with with dimethylacetamide dimethylacetal to give racemic isoangenomalin (**3**). Demethylation of chiral methyl ether **11a** might cause partial racemization. So, methyl ether **11a** was then converted to the corresponding MOM ether **11c** by prior demethylation followed by MOM protection. Racemic **11a**−**c** were subjected to Sharpless asymmetric dihydroxylation: treatment with $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, and a chiral ligand $(DHQ)_2AQN$ or $(DHQD)_2$-AQN.[9] As shown in Table 1, kinetic resolution of racemic angenomalin **2** using $(DHQ)_2AQN$ gave (+)-**2**, showing the same (+) rotation as natural angenomalin, and so the same ligand $(DHQ)_2AQN$ was used in the kinetic resolution of racemic salicyl aldehyde **11a**−**c** and gave (−)-**11a** (80% ee), (−)-**11b** (9% ee), and (−)-**11c** (>99% ee) in 24%, 45%, and 29% yields, respectively. Chiral MOM ether (−)-**11c**, thus obtained, was converted to (*R*)-(−)-hydroxytremetone, an enantiomer of natural (−)-hydroxytremetone, as shown in Scheme 6, via Grignard methylation (MeMgBr), oxidation (PDC), and deprotection (concentrated HCl−MeOH), and the absolute configuration of (−)-**11c** was determined to be *R* by comparison with authentic natural (*R*)-(−)-hydroxytremetone.[3]

Salicylaldehyde (*R*)-(−)-**11b**, prepared by deprotection of (*R*)-(−)-**11c**, was then subjected to the pyran-ring formation; refluxing (*R*)-(−)-**11b** with dimethylacetamide dimethylacetal in dry ether gave the corresponding coumarin (*R*)-(+)-**3**. The thus-obtained coumarin (*R*)-(+)-**3** was identical with natural (+)-isoangenomalin.[13] Therefore, the absolute structure of natural (+)-isoangenomalin was determined to be *R*.

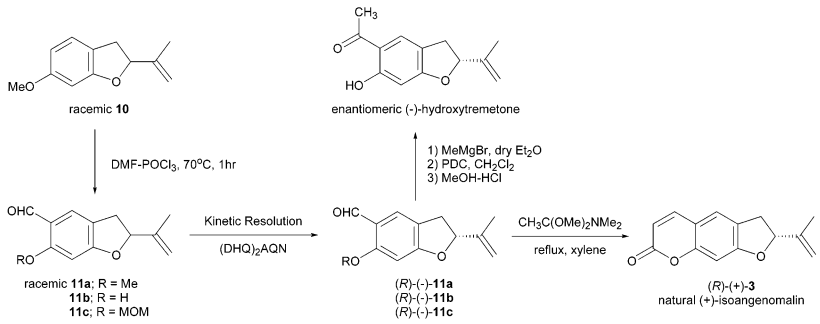
Thus, natural (+)-remirol **1a** and (+)-remiridiol **1b**, isolated from *Remirea maritima* (Cyperaceae), and (+)-angenomalin **2**, isolated from *Angenlica anomala* (Umbelliferae), showed the *S* structures, the same as (+)-fomannnoxin, isolated from *Fommes annosus* (Polyporaceae). (+)-Isoangenomalin **3**, isolated from *Scaevola frutescens* (Goodeniaceae), showed the different *R* structure, like (−)-tremetone and (−)-hydroxytremetone, isolated from *Eupatorium urticaefolium* (Compositae). Thus, both *R* and *S* structures exist in natural plants. This implies that different enzymic cyclization exists in different kinds of plants.

Experimental Section

Methods and Materials. All reactions requiring anhydrous conditions were conducted in flame-dried glassware under an argon atmosphere. Solvents were distilled immediately before use: THF and Et_2O from Na/benzophenone; benzene, pyridine, Et_3N, *N*,*N*-diisopropylethylamine, and DMF from calcium hydride (DMF; under reduced pressure); MeOH from $Mg(OMe)_2$. CH_2Cl_2 was distilled first from P_2O_5 and then from CaH_2. Organic solutions were concentrated by rotary evaporator below 45 °C in vacuo. Analytical TLC was carried out using 0.25 mm Merck silica gel plates (60F-254) using UV light as plates, and column chromatography was performed with 230−400 mesh Merck silica gel 60 for flash chromatography. Melting points were taken on a micro melting point apparatus and are uncorected. IR spectra were obtained in liquid films or KBr disks on an FT/IR spectrometer, and ^{1}H NMR spectra were obtained in $CDCl_3$ solution on a 400 MHz spectrometer. ^{1}H NMR data are reported in ppm (δ) downfield from internal TMS; coupling constants are given in Hz. Elemental analyses were determined on a micro CHN analyzer. Mass spectra were recorded under electron ionization (EI) conditions on a mass spectrometer. Racemic 2-isopropenyl-2,3-dihydrobenzofurans **4**, **8**, and **11a**,**b** were prepared according to the reported procedure,[8f,g] and the optical purities were confirmed by measuring on on HPLC using chiral column OD (eluent; 10% 2-propanol in hexane) prior to the respective optical resolutions.

General Kinetic Resolution of Some 2-Isopropenyl-2,3-dihydrobenzofuran Derivatives by Sharpless Dihydroxylation. To a solution of chiral ligand (0.0050 mmol), potassium hexacyanoferrate(III) (490 mg, 1.5 mmol), potassium carbonate (210 mg, 1.5 mmol), and potassium osmate(IV) dihydrate (0.8 mg, 0.0020 mmol) in *tert*-butyl alcohol (1 mL) and water (1 mL) was added methanesulfonamide (47 mg, 0.50 mmol), and the mixture was cooled to 0 °C. Under cooling at 0 °C, to the cooled mixture was added racemic 2-isopropenyl-2,3-dihydrobenzofuran substrate (0.50 mmol), and the mixture

SCHEME 6. Synthesis and Structural Determination of Natural (+)-Isoangenomalin



was stirred for several hours. After the reaction, the mixture was treated with sodium sulfite (400 mg, 3.1 mmol) and extracted with diethyl ether. The organic layer was washed with 5% aqueous sodium hydroxide solution, 10% hydrochloric acid, and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The oily residue was chromatographed on a silica gel column to afford the corresponding chiral 2-isopropenyl-2,3-dihydrobenzofuran as fractions eluted with 10% ethyl acetate in hexane. The results are summarized in Table 1.

Conversion of (*R*)-(−)-4 to (*R*)-(−)-1a, (−)-Enantiomer of Natural (+)-Remirol. According to the reported procedure,[8f] chiral (*R*)−(−)-**4** (95% ee) was acylated with acetic acid and trifluoroacetic anhydride to give chiral (*R*)−(+)-**6** and then demethylated with magnesium iodide etherate to give chiral (*R*)−(−)-**1a** (12% in two steps) as pale yellow crystals (mp 72−73 °C). The sample was identical with the racemic remirol[8f] and natural (+)-remirol[10] in IR and ^{1}H NMR spectra; however, it showed different (−) rotation, $[\alpha]^{22}_D$ −34.0 (*c* 0.75, EtOH), from that of natural (+)-remirol. Furthermore, the optical purity showed a low 38% ee, despite the use of the starting material of 95% ee. This means the demethylation might have caused partial racemization.[15]

Conversion of Chiral (*S*)-(+)-4 to (*S*)-(+)-1a (Natural (+)-Remirol). According to the reported procedure,[8f] chiral (*S*)-(+)-**4** (>99% ee) was also acylated with acetic acid and trifluoroacetic anhydride to give chiral (*S*)-(−)-**6**; $[\alpha]^{29}_D$ −15.2 (*c* 1.25, $CHCl_3$) and optical purity; 98%ee in HPLC using chiral clomun OD, and no racemization was shown in this step. Chiral (*S*)−(−)-**6** (98% ee) was then demethylated with magnesium iodide etherate for a shorter 2 h reflux to give chiral (*S*)-(+)-**1a**, which was also identical with natural remirol[10] in IR and ^{1}H NMR spectra and showed the (+) rotation, $[\alpha]^{25}_D$ +54.0 (*c* 0.45, EtOH), and the optical purity, 82% ee. A shorter 1 h reflux gave (*S*)-(+)-**1a** in lower yield, but in higher optical purity, $[\alpha]^{25}_D$ +65.0 (*c* 0.45, EtOH) (98% ee).

Conversion of (*S*)-(+)-1a (Natural Remirol) to (*S*)-(+)-1b (Natural (+)-Remiridiol). To a solution of (*S*)-(+)-**1a** (50 mg, 0.201 mmol) (90%ee) in 5% aqueous tetramethylammonium hydroxide solution (2.5 mL) was added an aqueous solution of potassium persulfate (60 mg, 0.22 mmol) in water (3 mL), and the mixture was stirred at room temperature for 10 h. The mixture was neutralized with saturated aqueous sodium bihydrogenphosphate solution and washed with diethyl ether. The aqueous layer was acidified with 10% hydrochloric acid, saturated with sodium chloride, and extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residual oil was purified on a silica gel column to afford (*S*)-(+)-**1b** (8 mg, 15%),[16] which was identical with natural (+)-remiridiol[11] in IR and ^{1}H NMR spectra and showed an optical rotation of $[\alpha]^{25}_D$ +61.4 (*c* 0.35, EtOH) and an optical purity of 87% ee.

Coumarin Ring Formation of Chiral (*S*)-(+)-8 or (*R*)-(−)-11b Giving (*S*)-(+)-2 (Natural (+)-Angenomalin) and (*R*)-(+)-3 (Natural (+)-Isoangenomalin). According to the reported procedure,[8g] chiral salicylaldehyde, (*S*)-(+)-**8** (97% ee) or (*R*)-(−)-**11b** (92% ee), obtained by deprotection of (*R*)-(−)-**11c** (optical purity 92% ee), was treated with *N*,*N*-dimethylacetamide dimethyl acetal to give the corresponding coumarin. The coumarin (*S*)-(+)-**2**, (*S*)-(+)-8-isopropenyl-8,9-dihydrofuro-[2,3-*h*]chromen-2-one, was identical with natural (+)-angenomalin[12] in IR and ^{1}H NMR spectra and showed an optical rotation of $[\alpha]^{23}_D$ +181.0 (*c* 0.50, EtOH) and an optical purity of 99% ee. The other coumarin (*R*)-(+)-**3**, (*R*)-(+)-2-isopropenyl-2,3-dihydrofuro[3,2-*g*]benzopyran-7-one (isoangenomalin), was identical with natural (+)-isoangenomalin[13] in IR and ^{1}H NMR spectra and showed an optical rotation of $[\alpha]^{24}_D$ +7.6 (*c* 1.08, $CHCl_3$) and an optical purity of 92% ee.

Supporting Information Available: Experimental procedures and spectral data for preparation of racemic **11c**, structural determinations of (−)-**4**, (+)-**8**, **and** (−)-**11c**, and the conversion of (*R*)-(−)-**4** to (*R*)-(−)-**1a**, (−)-enantiomer of natural (+)-remirol. This material is available free of charge via the Internet at http://pubs.acs.org.

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