Oxidative Homocoupling of Chiral 3-Arylpropanoic Acid Derivatives. Application to Asymmetric Synthesis of Lignans

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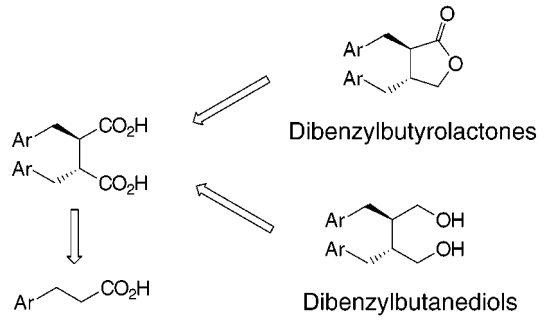
The oxidative homocouplings of lithium enolates of (4*S*)-3-(3-arylpropanoyl)-4-isopropyl-2-oxazolidinones and (4*R*,5*S*)-1-(3-arylpropanoyl)-3,4-dimethyl-5-phenyl-2-imidazolidinones gave the corresponding *R*,*R*-dimers stereoselectively with $TiCl_4$, $PhI(OAc)_2$, or $CuCl_2$ as an oxidant. The stereoselectivity can be explained by a radical coupling mechanism. Optically active dibenzylbutyrolactone lignans, such as (−)-hinokinin and (−)-dimethylmatairesinol, and dibenzylbutanediol lignans, such as (−)-dihydrocubebin and (−)-dimethylsecoisolariciresinol, were synthesized from the major *R*,*R*-dimers. The oxidative coupling of (4*R*,5*S*)-1-(3-arylpropanoyl)-3,4-dimethyl-5-phenyl-2-imidazolidinones with LDA−I_2 gave *R*,*S*-dimers mainly, and this result can be explained by an S_N2 mechanism.

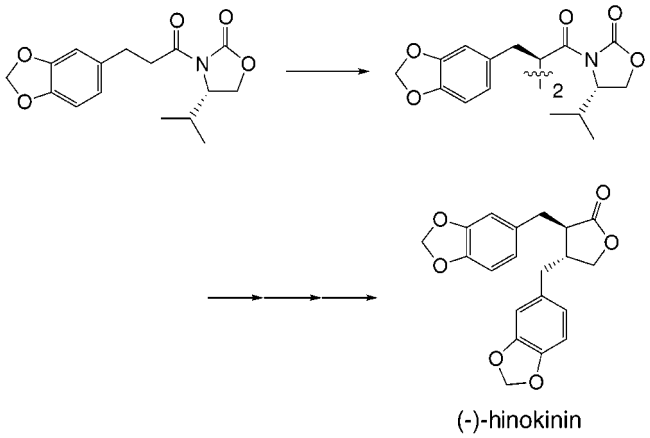
Introduction

Dibenzylbutyrolactones, such as (−)-hinokinin and (−)-enterolactone, and dibenzylbutanediols, such as (−)-dihydrocubebin and (−)-enterodiol, are one of the classes of lignans and attract considerable interest due to their biological activities.[1] Recently, a number of strategies for the asymmetric synthesis of these classes of lignans have been reported.[2] Optically active 3,4-dibenzylsuccinic acids are useful precursors of dibenzylbutyrolactone and dibenzylbutanediol lignans (Scheme 1). Oxidative homocoupling of 3-phenylpropanoic acids is an effective method for the synthesis of 3,4-dibenzylsuccinic acids.[3] We have reported the first asymmetric synthesis of 3,4-dibenzylsuccinic acids by the oxidative homocoupling of (4*S*)-3-(3-arylpropanoyl)-4-isopropyl-2-oxazolidinones with LDA−$TiCl_4$ and its application to the synthesis of (−)-hinokinin (Scheme 2).[4] After that, Helmchen's group reported the oxidative coupling of (4*S*,5*R*)-1-(3-arylpropanoyl)-3,4-dimethyl-5-phenyl-2-imidazolidinones and the synthesis of *ent*-hinokinin from the adducts.[5] Herein we report full details of our study on the stereoselective oxidative homocoupling of optically active 3-arylpropanoic acid derivatives.[6,7] We also present the asymmetric synthesis of dibenzylbutyrolactone and dibenzylbutanediol lignans from the obtained enantiomerically pure adducts.

Scheme 1



Scheme 2



Results and Discussion

Oxidative Homocoupling of (4*S*)-3-(3-Arylpropanoyl)-4-isopropyl-2-oxazolidinones. We have already reported that the oxidative homocoupling of chiral 3-(arylacetyl)-2-oxazolidinones took place stereospecifi-

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10.1021/jo991317o CCC: $19.00
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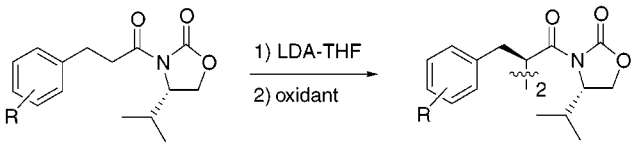
Table 1. Oxidative Coupling of Chiral 3-(3-Arylpropanoyl)-2-oxazolidinones 1



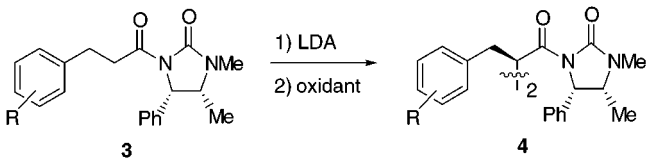
run	1	oxidant	2	% yield of 2[a]	*R,R*:*R,S* of 2[b]
1	**1a**	$TiCl_4$	**2a**	67	85:15
2	**1a**	$PhI(OAc)_2$	**2a**	69	85:15
3	**1a**	$CuCl_2$[c]	**2a**	55	80:20
4	**1a**	I_2[c]	**2a**	38	57:43
5	**1b**	$TiCl_4$	**2b**	55	85:15
6	**1b**	$PhI(OAc)_2$	**2b**	69	78:22
7	**1b**	$CuCl_2$[c]	**2b**	42	75:25
8	**1c**	$TiCl_4$	**2c**	43	86:14
9	**1c**	$PhI(OAc)_2$	**2c**	80	83:17
10	**1c**	$CuCl_2$[c]	**2c**	51	78:22
11	**1d**	$TiCl_4$	**2d**	71	87:13
12	**1d**	$PhI(OAc)_2$	**2d**	81	85:15
13	**1d**	$CuCl_2$[c]	**2d**	41	83:17

[a] Isolated yields. [b] Determined by ^{1}H NMR analysis. [c] In the presence of DMPU.

cally by treatment with an amine−$TiCl_4$ couple.[4,8] Unfortunately, 3-(3-arylpropanoyl)-2-oxazolidinones **1** did not react with the amine−$TiCl_4$ couple probably due to the low basicity of the amine. Therefore, LDA was employed as a base in place of the amine to generate lithium enolates of **1**. The results of the oxidative homocoupling of **1a**−**d** with several LDA−oxidant couples are shown in Table 1. The oxidative homocoupling of the lithium enolates of (4*S*)-4-isopropyl-3-(3-phenylpropanoyl)-2-oxazolidinone (**1a**) with $TiCl_4$ gave the dimer **2a** in 67% yield and *R,R*:*R,S* = 85:15 selectivity (run 1). A similar result was obtained with $PhI(OAc)_2$ as an oxidant (run 2). The reactions with $CuCl_2$ and I_2 proceeded in the presence of DMPU as an additive, although the yields and selectivities were low (runs 3 and 4). Aryl-substituted substrates **1b**−**d** were also subjected to the oxidative homocoupling (runs 5−13). Generally, $PhI(OAc)_2$ as an oxidant gave the best yields of **2**, while $TiCl_4$ resulted in the best *R,R*-selectivities of **2**. The absolute configurations of the major isomers of **2b**−**d** were determined to be *R,R* by their transformation to the known compounds as described below. The *R,R*-configuration of the major isomer of **2a** was assigned by the correlation of its ^{1}H NMR spectrum with those of (*R,R*)-**2b**−**d**.

Oxidative Homocoupling of (4*R*,5*S*)-1-(3-Arylpropanoyl)-3,4-dimethyl-5-phenyl-2-imidazolidinones. Helmchen's group has reported that the LDA−$TiCl_4$ couple gave the best results for the oxidative homocoupling of (4*S*,5*R*)-3,4-dimethyl-1-(3-(3,4-methylenedioxyphenyl)propanoyl)-5-phenyl-2-imidazolidinone.[5] We examined the oxidative coupling of (4*R*,5*S*)-1-(3-arylpropanoyl)-3,4-dimethyl-5-phenyl-2-imidazolidinones **3a**−**d** with several LDA−oxidant couples, similarly to the above-described reactions of **1**. According to the results summarized in Table 2, it was found that the LDA−$CuCl_2$ or LDA−$TiCl_4$ couple gave the best *R,R*-

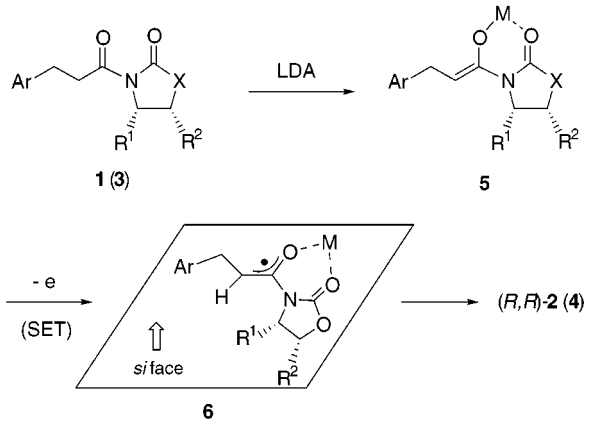
Table 2. Oxidative Coupling of Chiral 1-(3-Arylpropanoyl)-2-imidazolidinones 3



run	3	oxidant	4	% yield of 2[a]	*R,R*:*R,S* of 2[b]
1	**3a**	$TiCl_4$	**4a**	55	>98:2
2	**3a**	$PhI(OAc)_2$	**4a**	79	74:26
3	**3a**	$CuCl_2$[c]	**4a**	52	>98:2
4	**3a**	I_2[c]	**4a**	76	40:60
5	**3b**	$TiCl_4$	**4b**	52	84:16
6	**3b**	$PhI(OAc)_2$	**4b**	82	74:26
7	**3b**	$CuCl_2$[c]	**4b**	63	92:8
8	**3b**	I_2[c]	**4b**	80	30:70
9	**3c**	$TiCl_4$	**4c**	43	87:13
10	**3c**	$PhI(OAc)_2$	**4c**	78	81:19
11	**3c**	$CuCl_2$[c]	**4c**	52	88:12
12	**3c**	I_2[c]	**4c**	65	11:89
13	**3d**	$TiCl_4$	**4d**	48	92:8
14	**3d**	$PhI(OAc)_2$	**4d**	78	77:23
15	**3d**	$CuCl_2$[c]	**4d**	45	92:8
16	**3d**	I_2[c]	**4d**	57	25:75

[a] Isolated yields. [b] Determined by ^{1}H NMR analysis. [c] In the presence of DMPU.

Scheme 3



selectivities and the LDA−$PhI(OAc)_2$ couple afforded the best yields of the adducts **4**. It is noted that *R,S*-isomers of **4** were formed mainly with the LDA−I_2 couple. In all cases, the formation of *S,S*-isomers of **4** could not be detected by ^{1}H NMR spectra of the crude products. The absolute configurations of (*R,R*)-**4b**−**d** were confirmed by their transformation to the known compounds (vide infra). The stereoconfiguration of (*R,R*)-**4a** was assigned by the correlation of its ^{1}H NMR spectrum with those of (*R,R*)-**4b**−**d**.

Reaction Mechanism of Oxidative Homocoupling. The *R,R*-selectivity in the oxidative homocouplings of **1** and **3** can be explained by a radical coupling mechanism[9] (Scheme 3). It is well-known that the treatment of 3-acyl-2-oxazolidinones or 1-acyl-2-imidazolidinones with LDA affords Li-chelated (*Z*)-enolates.[10] In the reaction of **1** or **3** with LDA−$TiCl_4$, it is likely that the initially formed lithium enolate (**5**, M = Li) is trans-

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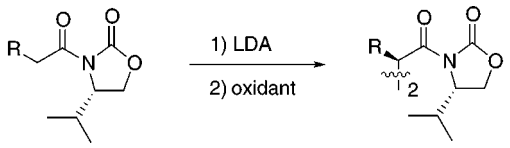
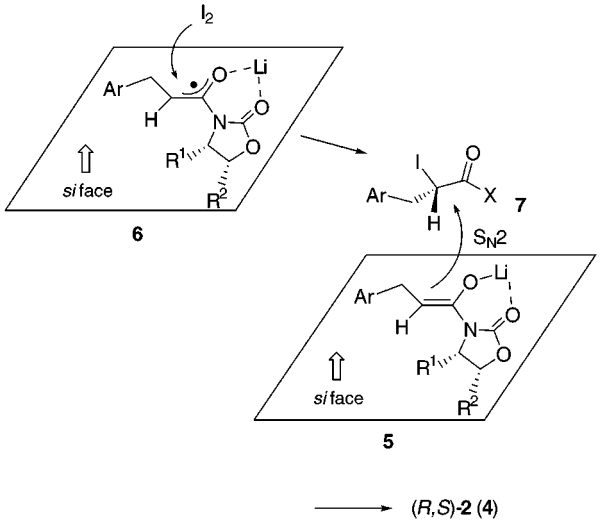
Scheme 4



	oxidant			
8a: R = Me	$TiCl_4$	**9a**	68%	*R,R*:*R,S* = >95:5
	I_2	**9a**	65%	*R,R*:*R,S* = >95:5
8b: R = Et	$TiCl_4$	**9b**	95%	*R,R*:*R,S* = 95:5

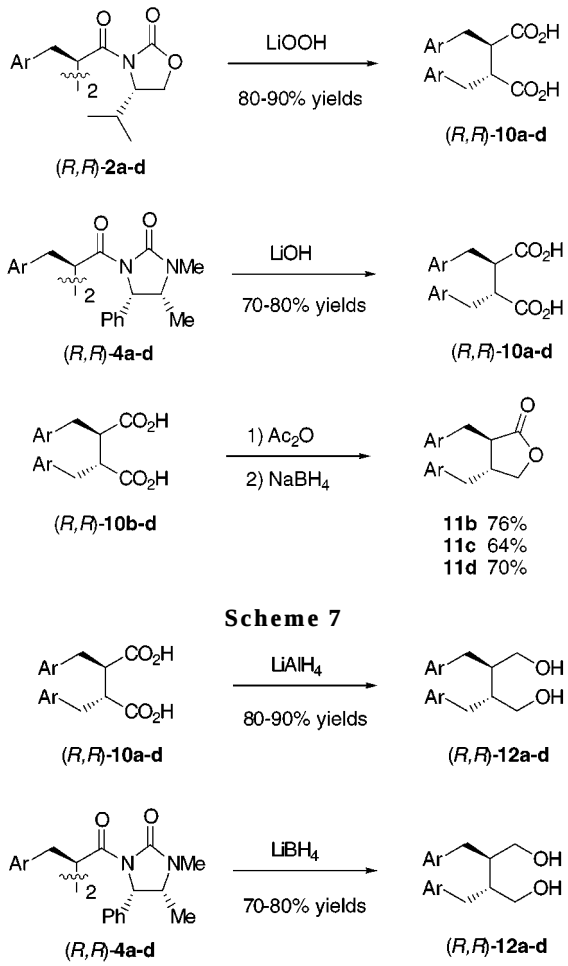
Scheme 5



formed to titanium enolate (**5**, M = $TiCl_3$).[11] The metal-chelated (*Z*)-enolate **5** is subsequently oxidized to radical intermediate **6** by a single electron-transfer (SET) process. The *syn*-*Z*-type radicals **6** couple each other at the less hindered β side (*si* face) to give the *R*,*R*-isomer of **2** or **4** stereoselectively. It seems that the aryl group in the radical intermediate **6** may inhibit the homocoupling at the *si* face and decrease the *R*,*R*-selectivity. In fact, the oxidative homocouplings of **8**, less bulky substrates than **1** (Ar → H, Me), with LDA−$TiCl_4$ gave the dimer **9** with >95% *R*,*R*-selectivity, higher than those in the reactions of **1** (85−87% *R*,*R*-selectivity) (Scheme 4).

On the other hand, there is an alternative mechanism[9] for the oxidative homocoupling with LDA−I_2 (Scheme 5). That is, iodide **7** is formed by the attack of iodine on the radical **6** from the less hindered β side (*si* face), and then the iodide **7** reacts with **5** at the *si* face to yield the *R*,*S*-isomer of **2** or **4**. The increase of *R*,*S*-selectivity in the oxidative homocouplings of **1** and **3** with I_2 can be explained by the S_N2 mechanism. The oxidative coupling of **8a** with LDA−I_2, however, gave the dimer **9** with >95% *R*,*R*-selectivity (Scheme 4). This result shows that the radical coupling mechanism is predominant in the reaction of **8a**, since **8a** is less bulky than **1** (Ar → H). Similar high stereoselectivities have been reported in the oxidative homocoupling of (4*S*,5*R*)-3,4-dimethyl-5-phenyl-1-propanoyl-2-imidazolidinone with LDA−I_2.[6b]

Scheme 6



Scheme 7

Synthesis of Dibenzylbutyrolactones. The *R*,*R*-isomers of **2** were hydrolyzed with LiOOH in THF/H_2O to give (2*R*,3*R*)-2,3-dibenzylsuccinic acids (*R*,*R*)-**10** (Scheme 6). The hydrolysis of the *R*,*R*-isomers of **4** with LiOH in refluxing THF/H_2O also afforded (*R*,*R*)-**10**. Naturally, hydrolysis of the *R*,*S*-isomers of **2** and **4** gave *meso*-2,3-dibenzylsuccinic acids *meso*-**10**. The treatment of (*R*,*R*)-**10b** with Ac_2O and the subsequent reduction of the resultant anhydride with $NaBH_4$ in THF gave (−)-hinokinin (**11b**)[12] in 76% yield. (−)-Dimethylmatairesinol (**11c**)[13] and **11d**[14] were prepared by the same method from (*R*,*R*)-**10c** and (*R*,*R*)-**10d**, respectively. It has been reported that the demethylation of **11d** with BBr_3 gave (−)-enterolactone (Ar in **11** = 3-C_6H_4OH).[14]

Synthesis of Dibenzylbutanediols. The *R*,*R*-isomers of **10** were transformed to (2*R*,3*R*)-2,3-dibenzylbutanediols (*R*,*R*)-**12** by reduction with $LiAlH_4$ in refluxing THF (Scheme 7). Alternatively, the treatment of the *R*,*R*-isomers of **4** with $LiBH_4$ in THF afforded (*R*,*R*)-**12**. (−)-Dihydrocubebin ((*R*,*R*)-**12b**)[15] and (−)-dimethylsecoisolariciresinol ((*R*,*R*)-**12c**)[13] were obtained by these methods. (−)-Dihydrocubebin ((*R*,*R*)-**12b**) can be transformed to

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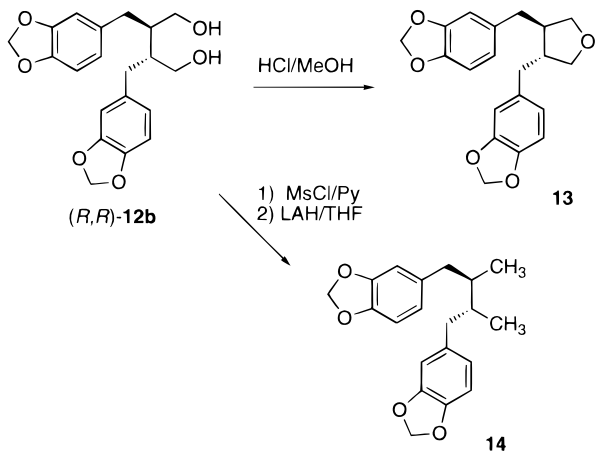
Scheme 8



(−)-dehydroxycubebin (**13**)[16] and australobailignan-5 (**14**)[17] by the usual procedures (Scheme 8). The reductions of the *R,S*-isomers of **4** and **10** yielded *meso*-2,3-dibenzylbutanediols *meso*-**12**.

Conclusion

The oxidative homocouplings of (4*S*)-3-(3-arylpropanoyl)-4-isopropyl-2-oxazolidinones **1** and (4*R*,5*S*)-1-(3-arylpropanoyl)-3,4-dimethyl-5-phenyl-2-imidazolidinones **3** with LDA−oxidant couples exhibited high *R,R*-stereoselectivities. The choice of oxidant is $TiCl_4$ or $PhI(OAc)_2$ for **1**, while it is $TiCl_4$ or $CuCl_2$ for **3**. In the oxidative homocoupling of **3**, the use of $PhI(OAc)_2$ as an oxidant increased the yields of the dimers, although the *R,R*-selectivities somewhat decreased. In addition, the *R,S*-dimers were formed preferentially from **3** using I_2 as an oxidant. Enantiomerically pure dibenzylbutyrolactone lignans, such as (−)-hinokinin and (−)-dimethylmatairesinol, and dibenzylbutanediol lignans, such as (−)-dihydrocubebin and (−)-dimethylsecoisolariciresinol, were synthesized from the major *R,R*-dimers.

Experimental Section

General Methods. Column chromatography was performed on silica gel 60 (Merck). Tetrahydrofuran was distilled from benzophenone ketyl.

Starting Materials. (4*S*)-3-(3-Arylpropanoyl)-4-isopropyl-2-oxazolidinones **1** were prepared from (4*S*)-4-isopropyl-2-oxazolidinones and 3-arylpropanoyl chlorides by the reported methods.[18] (4*R*,5*S*)-1-(3-Arylpropanoyl)-3,4-dimethyl-5-phenyl-2-imidazolidinones **3** were obtained similarly from commercially available (4*S*,5*R*)-1,5-dimethyl-4-phenyl-2-imidazolidinone. The products were purified by column chromatography on silica gel or recrystallization from hexanes−ethyl acetate.

Oxidative Homocoupling of 1 (3) with LDA−$TiCl_4$. To a solution of LDA (2.4 mmol) in hexane−THF (5 mL) was added a solution of **1** (**3**) (2 mmol) in THF (5 mL) dropwise at −78 °C. After the mixture was stirred for 15 min, $TiCl_4$ was added (0.26 mL, 2.4 mmol) at this temperature. The temperature was gradually raised to room temperature, and then the dark blue solution was stirred for 24 h. The mixture was quenched with 1 M HCl (40 mL) and extracted with ether (3 × 20 mL). The *R,R*- and *R,S*-dimers of **2a**, **2b**, and **4a**−**d** were isolated by column chromatography on silica gel. The *R,R*-dimer of **2c** could be isolated by recrystallization of the diastereomeric mixtures from hexanes−ethyl acetate. The *R,R*-dimer of **2d** was purified by the repetition of column chromatography on silica gel. The *R,S*-dimers of **2c** and **2d** could not be purified.

Oxidative homocoupling of 1 (3) with LDA−$PhI(OAc)_2$ was similarly performed using $PhI(OAc)_2$ (0.78 g, 2.4 mmol) in place of $TiCl_4$. After addition of $PhI(OAc)_2$, the mixture was stirred for 12 h at room temperature.

Oxidative Homocoupling of 1 (3) with LDA−$CuCl_2$. To a solution of LDA (2.4 mmol) in hexane−THF (5 mL) was added a solution of **1** (**3**) (2.0 mmol) in THF (5 mL) dropwise at −78 °C. After the solution was stirred for 15 min, $CuCl_2$ (0.32 g, 2.4 mmol) and DMPU (0.5 mL) were added to the mixture at this temperature successively. The mixture was allowed to warm to room temperature, stirred for 12 h, and then quenched with 1 M HCl (40 mL). The products were isolated as described above.

Oxidative Homocoupling of 1 (3) with LDA−I_2. To a solution of LDA (2.4 mmol) in hexane−THF (5 mL) was added a solution of **1** (**3**) (2.0 mmol) in THF (5 mL) dropwise at −78 °C. After the solution was stirred for 15 min, a solution of I_2 (307 mg, 1.2 mmol) and DMPU (0.5 mL) in THF (5 mL) was added to the mixture at this temperature. After being stirred for a further 30 min, the mixture was allowed to warm to room temperature, stirred for 6 h, and then quenched with 1 M HCl (40 mL). The products were isolated as described above.

Hydrolysis of 2. To an ice-cooled solution of **2** (1 mmol) in THF (5 mL) and H_2O (4 mL) was added $LiOH·H_2O$ (0.17 g, 4 mmol) and 30% H_2O_2 (1 mL) successively. The mixture was stirred at room temperature. After the hydrolysis was complete (12−24 h), the mixture was treated with 1.5 M Na_2SO_3 (4 mL) at 0 °C and extracted with CH_2Cl_2 (3 × 5 mL). The aqueous phase was acidified with 3 M HCl (pH < 2) and evaporated in vacuo. The residue was extracted with CH_2Cl_2 (30 mL). After evaporation of CH_2Cl_2, the diacid **10** was obtained as a white solid and recrystallized from hexanes−ethyl acetate (80−90% yield).

Hydrolysis of 4. To a solution of **4** (1 mmol) in THF (5 mL) and H_2O (5 mL) was added $LiOH·H_2O$ (0.21 g, 5 mmol). The mixture was refluxed for 24−48 h until almost all of **4** was consumed (checked by TLC). The diacid **10** was isolated as described above (70−80% yield).

(1*R*,2*R*)-1,2-Bis[(3,4-methylenedioxyphenyl)methyl]ethane-1,2-dicarboxylic acid (10b): mp 172−174 °C, lit.[12] mp 174−175 °C; $[\alpha]^{20}_D$ −12.0 (*c* 1.08, acetone), lit.[12] $[\alpha]^{20}_D$ −12.4 (*c* 1.032, acetone).

Synthesis of Dibenzylbutyrolactones 11. To (*R,R*)-**10b** (200 mg, 0.52 mmol) was added Ac_2O (4 mL) at 0 °C, and the resulting mixture was stirred at 0 °C for 15 min. The mixture was then cooled to − 70 °C and diluted with methanol (12 mL). The solution was stirred below 0 °C for 10 min. The solvents were then removed at reduced pressure to give a pale yellow solid of acid anhydride. To an ice-cooled suspension of $NaBH_4$ (20 mg, 0.53 mmol) in dry THF (2 mL) was slowly added the crude acid anhydride in dry THF (2 mL). The ice bath was removed, and stirring was continued for 1 h. The mixture was acidified carefully with 1 N HCl (1 mL) and then stirred at room temperature for 1 h. The solvents were removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes−ethyl acetate, 2:1) to yield 140 mg (0.40 mmol, 76%) of (−)-hinokinin **11b** as a pale yellow oil. (−)-Dimethylmatairesinol (**11c**) and **11d** were obtained by the same procedure in 64% and 70% yields, respectively.

(−)-Hinokinin (11b): $[\alpha]^{20}_D$ −33.0 (*c* 0.63, $CHCl_3$), lit.[12] $[\alpha]^{17}_D$ −34.0 (*c* 0.981, $CHCl_3$).

(−)-Dimethylmatairesinol (11c): mp 127−128 °C, lit.[13] mp 126−127 °C; $[\alpha]^{20}_D$ −33.6 (*c* 1.05, $CHCl_3$), lit.[13] $[\alpha]^{20}_D$ −37.5 (*c* 1.00, $CHCl_3$).

(3*R*,4*R*)-3,4-Bis[(3-methoxyphenyl)methyl]-3,4,5-trihydrofuran-2-one (11d): $[\alpha]^{20}_D$ −43.7 (*c* 1.50, $CHCl_3$), lit.[14] $[\alpha]^{23}_D$ −42.3 (*c* 0.98, $CHCl_3$).

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Reduction of 10. To an ice-cooled solution of **10** (1 mmol) in dry THF (10 mL) was added LAH (114 mg, 3 mmol), and the suspension was refluxed for 12 h. After the usual workup, the diol **12** was isolated by column chromatography on silica gel (80−90% yield). (−)-Dihydroxycubebin ((*R*,*R*)-**12b**) and (−)-dimethylsecoisolariciresinol ((*R*,*R*)-**12c**) were prepared by this method.

Reduction of 4. To a solution of **4** (1 mmol) in dry THF (10 mL) was added $LiBH_4$ (0.11 g, 5 mmol), and the mixture was stirred at room temperature for 24−48 h until **4** was completely consumed (checked by TLC). The mixture was quenched with 1 M HCl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). After evaporation of the solvent, the diol **12** was isolated by column chromatography on silica gel (70−80% yield). (−)-Dimethylsecoisolariciresinol ((*R*,*R*)-**12c**) was obtained as a mixture with (4*S*,5*R*)-1,5-dimethyl-4-phenyl-2-imidazolidinone. Therefore, (*R*,*R*)-**12c** was separated with the imidazolidinone as follows. After silylation of (*R*,*R*)-**12c** by the treatment with *tert*-butyldimethylsilane and imidazole in DMF, the disilylated (*R*,*R*)-**12c** was separated by silica gel column chromatography and then desilylated with Bu_4NF in THF.

(−)-Dihydroxycubebin ((*R*,*R*)-12b): mp 102−104 °C, lit.[15] mp 104 °C; $[\alpha]^{20}_D$ −35.1 (*c* 1.05, $CHCl_3$), lit.[15] $[\alpha]^{19.8}_D$ −32.4 (*c* 3.3, $CHCl_3$).

(−)-Dimethylsecoisolariciresinol ((*R*,*R*)-12c): $[\alpha]^{20}_D$ −31.7 (*c* 1.02, $CHCl_3$), lit.[13] $[\alpha]_D$ −32.9 ($CHCl_3$).

Supporting Information Available: Compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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