Stereocontrolled Syntheses of Diequatorial and Axial–Equatorial Furofuran Lignans

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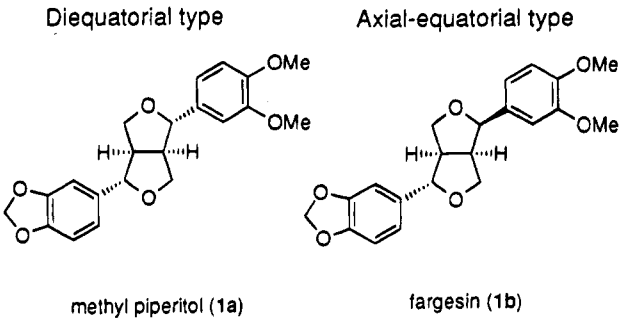
Methyl piperitol, a representative example of the diequatorial furofuran lignan, was synthesized in a good overall yield based on a highly stereocontrolled conjugate addition–aldol reaction. Fargesin, a representative example of the axial–equatorial furofuran lignans, was also synthesized in a good overall yield based on a new method for inversion of the stereochemistry at C-4 of **5a**.

Lignans of the furofuran series[1] are of considerable interest because of their wide range of intriguing biological activities, e.g., antihypertensive, phosphodiesterase inhibitory, and antioxidant activities.[2] Several synthetic methods have been developed for these lignans including those based on (i) the dimerization of cinnamic acids,[3] (ii) the reaction of succinamide dianion with aldehydes,[4] (iii) the aldol-type reaction of lactones,[5] (iv) the intramolecular Diels-Alder reaction,[6] and (v) the photocyclization reaction of 5-aryltetrahydrofuran-3-one.[7,8] Of these methods, however, only a few methods including Pelter's ingenious work[5b] and Takano's asymmetric synthesis[6] are applicable to the stereocontrolled synthesis of the stereoisomers of the furofuran lignans having two different aryl groups.

In connection with our synthetic studies in search of new compounds having intriguing biological activities from lignan derivatives,[9] we have been interested in the synthesis of lignans of the furofuran series. In this report, we present a full account of our efforts toward the efficient and stereocontrolled syntheses of lignans of the diequatorial and axial–equatorial furofuran series having two different aryl groups.[10] These synthetic methods involve new approaches based on the stereocontrolled conjugate addition–aldol reaction using a cyanohydrin, 2-butenolide, and an aldehyde, and the acid-catalyzed inversion of the stereochemistry of the benzylic position.



Results and Discussion

In our synthetic studies methyl piperitol (**1a**) and its stereoisomer fargesin (**1b**) were selected as representative examples of the diequatorial and axial–equatorial furofuran lignans having two different aryl groups, respectively.

Synthesis of Methyl Piperitol. In Scheme 1 is illustrated the strategy for the synthesis of methyl piperitol. We envisaged that **1a** would be synthesized *via* the key intermediate **3a**. The four contiguous carbon centers of **3a** would be stereochemically defined based on (i) the stereocontrolled conjugate addition–aldol reaction using the cyanohydrin (**2**), 2-butenolide and veratral, which defines the relative stereochemistry among C-2, C-3, and C-4; (ii) the stereoselective reduction of the carbonyl group at C-1, which defines the relative stereochemistry between C-1 and C-2 to be *syn*.

According to the strategy described above, we first examined the synthesis of **5a** (Scheme 2). Conjugate addition reaction of the anion generated by treatment of the cyanohydrin **2** with LDA to 2-butenolide in THF at −78 °C, followed by treatment of the resulting lithium enolate with veratral at the same temperature, afforded the condensation product **4**. Without isolation of the product, the reaction mixture was treated with tetra-

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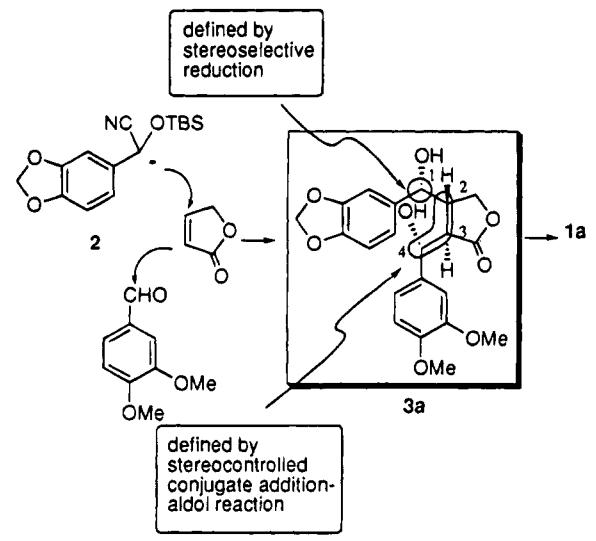
Scheme 1



Scheme 2

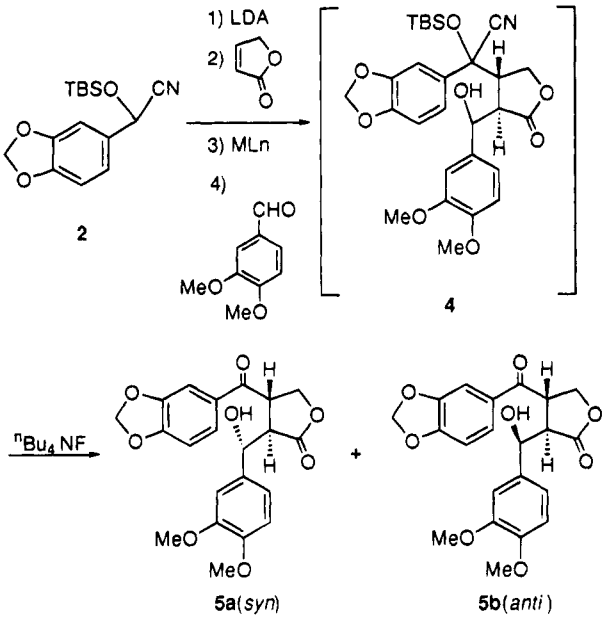
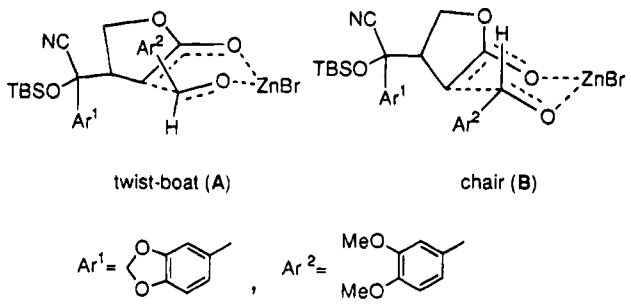


Table 1. Effect of Countercation of the Enolate on the Product Yield and Stereoselectivity

run	MLn	5a:5b[a]	yield (%)
1	none	46:54	91
2	$MgBr_2$	84:16	80
3	$Sn(OTf)_2$	91:9	61
4	$ZnBr_2$	98:2	82

[a] The ratio of **5a** to **5b** was determined by HPLC analysis. The stereochemistries at C-4 of **5a,b** were determined based on the House's empirical rule of aldol products.[11]

butylammonium fluoride in THF at room temperature to furnish a mixture of **5a** and its *anti*-isomer **5b** in 91% yield. The desired *syn*-isomer **5a** was not obtained stereoselectively; the ratio of **5a** to **5b** being 46:54 (Table 1, run 1). It is well-documented that the aldol reaction of an *E*-lithium enolate with an aldehyde generally gives the *anti*-isomer preferentially.[12] However, Evans, Mukaiyama, and Hoffmann have suggested that in the aldol reaction of an *E*-metal enolate with an aldehyde, the *syn*-selectivity in the use of a transition metal enolate inclines to be higher than that in the use of a lithium enolate.[13] On the basis of these information, we decided to examine the effect of the countercation of the enolate generated in the conjugate addition reaction on the stereochemistry of the product. Thus, we attempted to transform the lithium salt of the cyanohydrin **2** into the other metal salts. The lithium salt of **2** was treated with $MgBr_2{\cdot}OEt_2$, $CuI{\cdot}SMe_2$, and $ZnBr_2$ at −50 °C in THF. However, the expected conjugate addition did not take place because of the decomposition of the transmetalated salt of the cyanohyrins. We next examined the exchange of the countercation of the enolate anion produced by conjugate addition reaction by addition of a transition metal salt such as $MgBr_2{\cdot}OEt_2$, $Sn(OTf)_2$, and $ZnBr_2$ at −50 °C. In each case *syn*-selectivity was observed (Table 1, run 2−4). The best result was obtained in the use of $ZnBr_2$; the ratio of **5a** to **5b** was found to be 98:2 which was determined on the basis of the HPLC analysis of the reaction mixture after treatment of **4** with Bu_4NF. The pure *syn*-isomer (**5a**) was obtained in 82% yield by recrystallization from MeOH. The extremely high *syn*-selectivity observed in the use of the zinc enolate is probably elucidated by the fact that the twist-boat transition structure **A** leading to the *syn*-isomer is usually more predominant than the chair transition structure **B** leading to the *anti*-isomer in the aldol reaction of the transition metal enolate with an aldehyde.[14]



We next examined the stereoselective reduction of the carbonyl group of **5a** to **3a**. We anticipated that in the reduction of **5a** with a hydride reagent, the hydride would attack preferentially from the sterically less hindered side. Indeed, the reduction of **5a** by the use of $NaBH_4$, $Zn(BH_4)_2$, or lithium tri-*sec*-butylborohydride (L-Selectride) gave **3a** predominantly (Table 2). The best result was obtained in the case of L-Selectride; treatment of **5a** with L-Selectride (1.1 equiv) in THF at −78 °C resulted in formation of a mixture of **3a** and **6**, the ratio of **3a**:**6** being 97:3. The products were separated by silica gel column chromatography to give **3a** in 87% yield.

We finally examined the conversion of **3a** into methyl piperitol (**1a**) (Scheme 3). Treatment of **3a** with lithium aluminum hydride (LAH) in THF at room temperature

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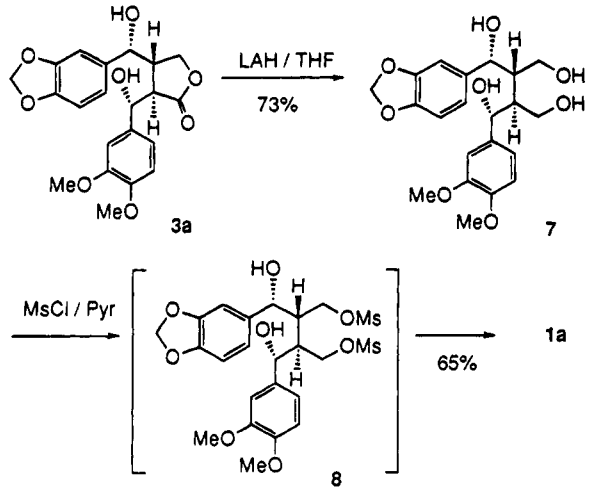
(14) This *syn*-selectivity would be elucidated by the following information. The *syn*-selectivity is frequently observed in the aldol reaction of an *E*-transition metal enolate with an aldehyde. On the other hand, the *anti*-selectivity is usually observed in the case of an *E*-lithium enolate; the results have been elucidated utilizing the Zimmerman's chair transition model;[12] Houk has recently suggested the possibility on the basis of the theoretical calculation that the twist-boat transition structure is more stable than the chair transition structure in the aldol reaction of an *E*-transition metal enolate with an aldehyde.[15]

Table 2. Effect of Reducing Agent on the Product Yield and Stereoselectivity

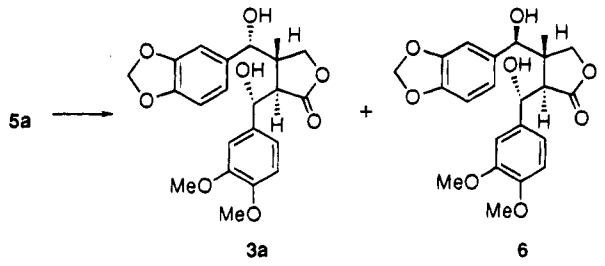
reagent (equiv)	solvent	reaction conditions	3a:6[a]	% yield of 3a[b]
$NaBH_4$ (2)	THF	0 °C, 30 min	76:24	52
$Zn(BH_4)_2$ (10)	benzene	0 °C, 30 min	92:8	78
L-Selectride (1.1)	THF	−78 °C, 10 min	97:3	87

[a] The ratio was determined by HPLC analysis of the crude product. [b] Isolated yield.

Scheme 3



for 14 h gave the tetraol **7** in 73% yield. Mesylation of the two primary hydroxyl groups of **7** using 3 equiv of methanesulfonyl chloride (MsCl) in the presence of pyridine at 0 °C provided the dimesylate **8** which



underwent the intramolecular cyclization spontaneously to afford the desired **1a** in 65% yield. The physical and spectroscopic properties of **1a** thus obtained were in accord with those reported.[16]

Stereocontrolled Synthesis of Fargesin. We initially tried to obtain the *anti*-aldol **5b**, the key intermediate for the synthesis of fargesin (**1b**), based on the strategy similar to that for the synthesis of methyl piperitol. In spite of intensive investigation, however, the C-4 *anti*-selectivity was not realized in the conjugate addition−aldol reaction; although a low *anti*-selectivity (*anti*/*syn* = 2/1) was observed by using Et_2O as a solvent, no remarkable change of selectivity was observed even by addition of the additives (Table 3).

Thus, we examined the inversion of the stereochemistry at C-4 of **5a** by an S_N2 type reaction, according to the alternative strategy described in Scheme 4. However, an attempt to inverse the stereochemistry at C-4 of **5a** using the Mitsunobu reaction was unsuccessful. Furthermore, the reaction of **5a** with MsCl in pyridine,

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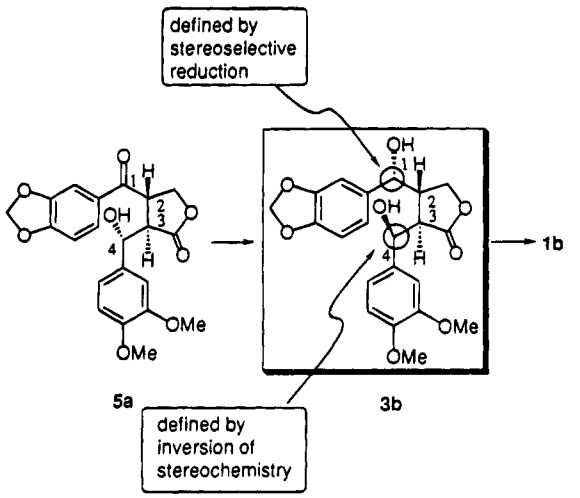
Table 3. Effect of Solvent and Additive on the Product Yield and Stereoselectivity

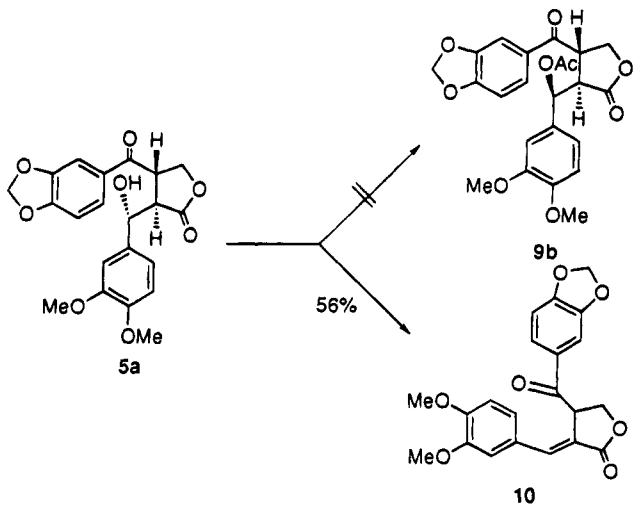
solvent	additive	yield (%)[a]	5a:5b[a]
THF	–	94	46:54
toluene	–	94	40:60
$^iPr_2O$	–	89	39:61
THF−hexane	–	96	43:57
Et_2O	–	92	34:66
Et_2O	HMPA	91	43:57
Et_2O	TMEDA	91	44:56

[a] Determined by HPLC analysis of the crude product.

Scheme 4



followed by treatment of the mesylate with NaOAc did not afford **9b**, but the benzylidene lactone **10** was obtained in 56% yield.

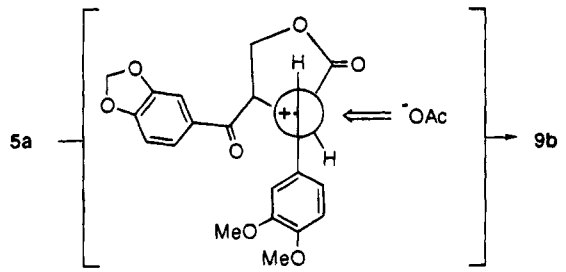


We anticipated that the inversion of the stereochemistry at C-4 of **5a** would proceed effectively *via* the carbonium ion **11**; the nucleophilic attack of an acetate anion on **11** would take place preferentially from the opposite side of the bulky 3,4-(methylenedioxy)benzoyl group in the Felkin-like model to afford the *anti*-acetate **9b**. On the basis of this working hypothesis, we examined the inversion of the stereochemistry at C-4 of **5a** *via* **11**. Treatment of **5a** with a mixture of AcOH, TFA, and CH_2Cl_2 at 0 °C gave a mixture of **9a**, **9b**, and **10** (Table 4). The yield of **9b** changed depending on both the reaction period and the ratio of the solvents used. The best result was obtained by treatment of **5a** with a mixture of TFA, AcOH, and CH_2Cl_2 (1:10:1) for 11 h, the

Table 4. Effect of Solvent Ratio on the Product Yield and Stereoselectivity

solvent ratio CH_2Cl_2–AcOH–TFA	yield of **9b** (%)	**9a**:**9b**[a]
1:1:1	16[b]	1:7.1
1:5:1	55	1:6.9
1:10:1	62	1:6.9
1:20:1	18[c]	1:7.0

[a] Determined by HPLC analysis of the crude reaction product. [b] **10** and **9a** were obtained in 36 and 51% yields, respectively. [c] **5a** was recovered in 55% yield.



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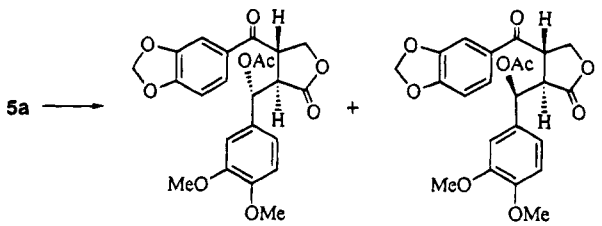
isolated yield of **9b** being 62%. The structure of **9b** was confirmed by comparison with the authentic sample prepared from **5b** by acetylation.



9a(*syn*) **9b**(*anti*)

We next examined the conversion of **9b** into fargesin (**1b**). Reduction of **9b** with L-Selectride in THF at −50 °C afforded **12** selectively in 87% yield, the ratio of **12** to the corresponding isomer being 98:2. Compound **12** was reduced with LAH in THF to afford **13** in 73% yield. Treatment of **13** with methanesulfonyl chloride in pyridine at room temperature furnished fargesin (**1b**) in 66% yield (Scheme 5). The structure of **1b** was confirmed on the basis of the spectral data. The spectroscopic and physical properties of **1b** thus obtained were in accord with those of natural fargesin.[17]

As described above, we have established the efficient and stereoselective methods for synthesis of methyl piperitol and fargesin. These methods should be applicable to the synthesis of the symmetrically and unsymmetrically substituted furofuran lignans of the diequatorial and the axial–equatorial series.

Experimental Section

2(*S)-[α(*R**)-Hydroxy-3,4-dimethoxybenzyl]-3(*S**)-[3,4-(methylenedioxy)benzoyl]butyrolactone (5a) and 2(*S**)-[α(*S**)-hydroxy-3,4-dimethoxybenzyl]-3(*S**)-[3,4-(methylenedioxy)benzoyl]butyrolactone (5b).** LDA (2.2 mmol) was prepared by addition of butyllithium (1.6 M in hexane, 1.5 mL, 2.2 mmol) to a solution of diisopropylamine (222 mg, 2.2 mmol) in THF (2 mL) at −78 °C under nitrogen atmosphere. The mixture was stirred for 10 min at −78 °C. To

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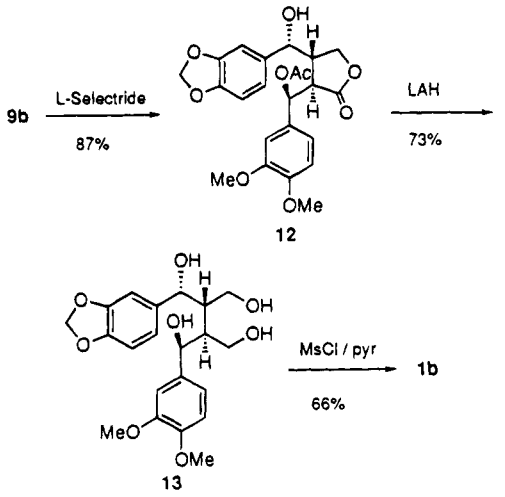
Scheme 5



the mixture were added dropwise successively cyanohydrin (**2** ; 582 mg, 2 mmol) in THF (2 mL), 2-butenolide (168 mg, 2 mmol) in THF (1 mL), and veratral (300 mg, 2 mmol) in THF (1 mL) at the same temperature. The mixture was quenched by addition of water (20 mL) containing AcOH (264 mg, 4.4 mmol). The organic layer was separated and the aqueous layer was extracted with EtOAc (50 mL). The combined organic layer was washed with brine (10 mL) and dried ($MgSO_4$). Evaporation of the solvent provided the crude product (**4**) as an oil. To the solution of the oil in CH_2Cl_2 (50 mL) was added 1 M Bu_4NF in THF (2.2 mmol) at room temperature. After 30 min, the solution was washed with water (10 mL), 10% citric acid (2 × 5 mL), and brine (10 mL) and dried ($MgSO_4$). Evaporation of the solvent afforded a mixture of **5a** and **5b** (730 mg, 91%), which was separated by silica gel column chromatography using hexane/AcOEt (1:2) as an eluent to afford **5a** (250 mg, 31%) and **5b** (276 mg, 35%).

5a: mp 143–144 °C (MeOH); IR (KBr) 1750 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 2.6 (brs, 1H), 3.61 (dd, 1H, J = 3.0, 7.6 Hz), 3.71 (s, H), 3.79 (s, 3H), 4.09 (t, 1H), 4.3–4.7 (m, 1H), 4.59 (dd, 1H, J = 6.2, 8.8 Hz), 5.44 (brs, 1H), 6.04 (s, 1H), 6.6–6.9 (m, 4H), 7.05 (d, 1H, J = 1.6 Hz), 7.51 (dd, 1H, J = 1.6, 11.4 Hz); MS *m/z* (rel inten) 400 (M^+, 5), 234 (30), 166 (88), 149 (100). Anal. Calcd for $C_{21}H_{20}O_8$: C, 63.00; H, 5.03. Found: C, 62.96; H, 5.33.

5b: mp 143–146 °C (MeOH); IR (KBr) 1752 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 2.8–3.1 (m, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 3.82 (d, 1H, J = 2.0 Hz), 4.0–4.2 (m, 2H), 4.3–4.5 (m, 1H), 6.05 (s, 2H), 6.61 (d, 1H, J = 8.8 Hz), 6.7–6.9 (m, 3H), 7.12 (d, 1H, J = 1.6 Hz), 7.19 (dd, 1H, J = 1.6, 11.4 Hz); MS *m/z* (rel inten) 400 (M^+, 7), 234 (31), 166 (88), 149 (100). Anal. Calcd for $C_{21}H_{20}O_8$: C, 63.00; H, 5.03. Found: C, 62.99; H, 5.17.

Stereoselective Preparation of 5a by Transmetalation. To a solution of LDA (22 mmol) prepared from a solution of diisopropylamine (2.22 g, 22 mmol) in THF (20 mL) and butyllithium (1.6 M in hexane, 15 mL, 22 mmol) were added dropwise successively cyanohydrin (**2**; 5.82 g, 20 mmol) in THF (20 mL), 2-butenolide (1.68 g, 20 mmol) in THF (10 mL), and $ZnBr_2$ (1 M in Et_2O, 22 mL) at −78 °C. The mixture was allowed to warm to −50 °C and stirred at the same temperature. After 15 min, veratral (3.0 g, 20 mmol) in THF (10 mL) was added to the mixture at the same temperature. The mixture was then quenched by addition of AcOH (2.64 g, 44 mmol) in water (200 mL) and warmed to room temperature. The mixture was filtered through a Celite pad. The organic layer was separated, and the aqueous layer was extracted with EtOAc (100 mL). The combined organic layer was washed with brine (100 mL) and dried ($MgSO_4$). Evaporation of the solvent provided the crude product (**4**) as an oil. To a stirred solution of the product in CH_2Cl_2 (50 mL) was added 1 M Bu_4NF in THF (2.2 mmol) at room temperature. After 30 min, the solution was washed with water (10 mL), 10% citric acid (2 × 5 mL), and brine (10 mL) and dried ($MgSO_4$). Everporation of the solvent afforded a mixture of **5a** and **5b** (6.87 g,

86%) as a solid, which was recrystallized from AcOEt to give pure **5a** (6.55 g, 82%).

Reduction of the Ketone 5a. Method A. To a solution of **5a** (0.5 g, 1.25 mmol) in THF (20 mL) was added portionwise $NaBH_4$ (23 mg, 0.62 mmol) at 0 °C under vigorous stirring. After 30 min, the mixture was quenched by addition of AcOH (37 mg). The solvent was removed under reduced pressure. The residue was diluted with AcOEt (50 mL). The solution was washed with brine (2 × 10 mL), dried ($MgSO_4$), and concentrated to give a mixture of **2(S*)-(α(R*)-hydroxy-3,4-(dimethoxybenzyl)-3(S*)-[α(R*)-hydroxy-3,4-(methylenedioxy)benzyl]butyrolactone (3a) and 2(S*)-[α(S*)-hydroxy-3,4-dimethoxybenzyl]-3(S*)-[α(R*)-hydroxy-3,4-(methylenedioxy)benzyl]butyrolactone (6).** The mixture was chromatographed on silica gel using hexane/AcOEt (1:2) as an eluent to afford **3a** (260 mg, 52%) and **6** (60 mg, 12%).

3a: mp 186–188 °C (MeOH); IR (KBr) 1755 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 2.5–2.9 (m, 2H), 3.73, (s, H), 3.83 (s, 3H), 4.2–4.6 (m, 3H), 4.9–5.3 (m, 3H), 5.90 (s, 2H), 6.26 (s, 1H), 6.46 (s, 1H), 6.68 (s, 2H); MS *m/z* (rel inten) 402 (M^+, 4), 384 (23), 166 (69), 151 (100). Anal. Calcd for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51. Found: C, 62.71; H, 5.43.

6: mp 174–178 °C (MeOH); IR (KBr) 1755 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 2.5–2.9 (m, 2H), 3.77, (s, H), 3.85 (s, 3H), 4.2–4.6 (m, 3H), 4.9–5.3 (m, 3H), 5.9–6.6 (m, 4H), 6.6–6.9 (m, 2H); MS *m/z* (rel inten) 402 (M^+, 4), 384 (25), 166 (72), 151 (100). Anal. Calcd for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51. Found: C, 62.69; H, 5.47.

Method B. To a suspension of anhydrous zinc chloride (400 mg, 3 mmol) in Et_2O (10 mL) was added portionwise $NaBH_4$ (230 mg, 6 mmol) at room temperature under vigorous stirring. The mixture was vigorously stirred for 3 h. To the mixture was added **5a** (0.5 g 1.25 mmol) in dry benzene (10 mL) at 0 °C. After 30 min, excess reagent was destroyed by dropwise addition of AcOH until the evolution of hydrogen ceased. The solution was washed with brine (2 × 10 mL), dried ($MgSO_4$), and concentrated. Crystallization of the residue from acetone afforded **3a** (390 mg, 78%).

Method C. To a solution of **5a** (0.5 g, 1.25 mmol) in THF (20 mL) was added dropwise L-Selectride (1 M in THF, 1.4 mL, 1.4 mmol) at −78 °C. After 10 min, the mixture was quenched by addition of AcOH (84 mg in 10 mL of THF). The mixture was allowed to warm to room temperature and diluted with AcOEt (50 mL). The organic layer was separated, washed with brine (2 × 10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue on silica gel chromatography using chloroform/MeOH (50:1) as an eluent afforded of **3a** (435 mg, 87%).

(1S*,2R*,3R*,4S*)-2,3-Bis(hydroxymethyl)-1-[3,4-(methylenedioxy)phenyl]-4-(3,4-dimethoxyphenyl)butane-1,4-diol (7). To a suspension of LAH (950mg, 25 mmol) in THF (10 mL) was added **3a** (1.0 g, 2.5 mmol) in THF (10 mL) at 0 °C under vigorous stirring. The mixture was stirred for 14 h at room temperature, quenched with 10% NaOH (2 mL), and filtered through a Celite pad. The solvent was removed under reduced pressure. The residue was purified on silica gel chromatography using chloroform/MeOH (20:1) as an eluent to afford **7** (732 mg, 73%) as a foam: IR (KBr) 3100 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 1.8–2.2 (m, 2H), 3.2–3.8 (m, 4H), 3.60 (s, 3H), 3.70 (s, 3H), 4.5–4.7 (m, 2H), 4.9–5.1 (m, 2H), 5.2–5.5 (m, 2H), 5.90 (s, 2H), 6.3–6.8 (m, 6H); MS *m/z* (rel inten) 406 (M^+, 1), 388 (41), 370 (54), 151 (100), 135 (69). Anal. Calcd for $C_{21}H_{26}O_8$: C, 62.06; H, 6.45. Found: C, 62.19; H, 6.47.

***Methyl* Piperitol (1a).** To a solution of **7** (1.0 g, 2.46 mmol) in CH_2Cl_2 (20 mL) were added pyridine (2 mL) and MsCl (845 mg, 7.38 mmol) at 0 °C. The mixture was stirred for 6 h at 0 °C and then for 10 h at room temperature. The mixure was washed with water (10 mL), 10% citric acid (2 × 5 mL), brine (10 mL), and dried ($MgSO_4$). The solvent was evaporated to dryness *in vacuo*. The residue was purified on silica gel chromatography using hexane/AcOEt (4:1) as an eluent to afford **1a** (574 mg, 65%): mp 74–76 °C [lit.[16] mp 76–78 °C]; ^1H NMR (δ in $CDCl_3$) 2.8–3.1 (m, 2H), 3.6–3.9 (m, 2H), 3.86, (s, 3H), 3.89 (s, 3H), 4.2–4.4 (m, 2H), 4.72 (d, 2H, *J* = 4 Hz), 5.95 (s, 2H), 6.7–7.0 (m 6H); ^{13}C NMR (δ in $CDCl_3$) 54.07, 54.26, 55.84, 71.61, 85.61, 86.66, 100.90, 106.33, 107.99, 109.10, 110.93, 118.07, 119.15, 134.94, 133.38 , 146.87, 147.75, 148.43, 148.99; MS *m/z* (rel inten) 370 (M^+, 100), 177 (42), 165 (48), 149 (67), 135 (53). Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 5.99. Found: C, 68.22; H, 5.96.

***(E)*-2-(3,4-Dimethoxybenzylidene)-3-[3,4-(methylenedioxy)benzoyl]butyrolactone (10).** To a solution of **5a** (100 mg, 0.25 mmol) in CH_2Cl_2 (2 mL) containing pyridine (0.2 mL) was added dropwise MsCl (42 mg, 0.37 mmol) at 0 °C. The mixture was stirred for 6 h at the same temperature and then for 10 h at room temperature. The mixure was diluted with CH_2Cl_2 (20 mL) and washed with water (10 mL), 10% citric acid (2 × 5 mL), and brine (10 mL). The organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was dissolved in THF (1 mL). To the solution was added NaOMe (14 mg, 0.25 mg) at 0 °C. After 2 h, the mixure was diluted with CH_2Cl_2 (20 mL), washed with brine (10 mL), dried ($MgSO_4$), and evaporated to dryness *in vacuo*. Crystallization of the residue from AcOEt afforded **10** (53 mg, 56%): mp 179–181 °C; ^1H NMR (δ in $CDCl_3$) 3.55, (s, H), 3.85 (s, 3H), 4.35 (dd, 1H, *J* = 4.5, 9.0 Hz), 4.70 (t, 1H, *J* = 9.0 Hz), 5.0–5.2 (m, 1H), 6.06 (s, 2H,), 6.26 (d, 1H, *J* = 3.4 Hz), 6.7–7.0 (m 4H), 7.30 (d, 1H, *J* = 1.6 Hz), 7.55 (dd, 1H, *J* = 1.6, 11.4 Hz), 7.71 (d, 1H, *J* = 2.2 Hz); MS *m/z* 382 (M^+, 49), 367 (11) 149 (100). Anal. Calcd for $C_{21}H_{18}O_7$: C, 65.97; H, 4.74. Found: C, 65.88; H, 4.77.

Preparation of Authentic Sample of 2(S*)-[α(R*)-acetoxy-3,4-dimethoxybenzyl)-3(S*)-[3,4-(methylenedioxy)benzoyl]butyrolactone (9a) and 2(S*)-[α(S*)-acetoxy-3,4-dimethoxybenzyl]-3(S*)-[3,4-(methylenedioxy)-benzoyl]butyrolactone (9b). To a solution of **5a** (100 mg, 0.25 mmol) in pyridine (3 mL) was added Ac_2O (44 mg, 0.38 mmol) at 0 °C. After 3 h, the solvent was evaporated to dryness *in vacuo* and the residue was dissolved in chloroform (10 mL). The solution was washed with water (10 mL), 10% citric acid (2 × 5 mL), aqueous saturated $NaHCO_3$ (3 × 5 mL), and brine (2 mL). The organic layer was dried over $MgSO_4$ and concentrated to dryness *in vacuo*. The residue was crystallized from AcOEt to provide **9a** (91 mg, 82%): mp 135–138 °C ; IR (KBr) 1780, 1745, 1741 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 2.08 (s, 3H), 3.78, (s, H), 3.83 (s, 3H), 3.7–3.9 (m, 2H), 4.0–4.4 (m, 2H), 6.00 (s, 2H), 6.26 (d, 1H, *J* = 5.4 Hz), 6.6–7.0 (m 4H), 7.2–7.4 (m, 2H); MS *m/z* (rel inten) 442 (M^+, 8), 382 (23), 234 (44) 165 (32), 149 (100). Anal. Calcd for $C_{23}H_{22}O_9$: C, 62.44; H, 5.01. Found: C, 62.55; H, 5.11.

9b was also prepared in 74% yield from **5b**: mp 138–140 °C ; IR (KBr) 1780, 1745, 1741 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 2.06 (s, 3H), 3.79, (s, H), 3.82 (s, 3H), 3.8–3.9 (m, 1H), 4.0–4.7 (m, 3H), 6.06 (s, 2H), 6.26 (d, 1H, *J* = 3.4 Hz), 6.6–6.9 (m 4H) 7.10 (d, 1H, *J* = 1.6 Hz), 7.25 (dd, 1H, *J* = 1.6, 11.4 Hz); MS *m/z* (rel inten) 442 (M^+, 6), 382 (21), 234 (44) 165 (28), 149 (100). Anal. Calcd for $C_{23}H_{22}O_9$: C, 62.44; H, 5.01. Found: C, 62.51; H, 5.21.

Stereoselective Preparation of 9b from 5a. To a solution of **5a** (800 mg, 2 mmol) in CH_2Cl_2–AcOH (1:10, 11 mL) was added TFA (1 mL) at 0 °C. The mixture was stirred at the same temperature for 11 h. The resulting mixure was diluted with CH_2Cl_2 (100 mL). The solution was washed with saturated aqueous $NaHCO_3$ (3 × 50 mL), and brine (20 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give a mixture of **9a** and **9b**, which was recrystallized from AcOEt to afford **9b** (542 mg, 62%).

2(S*)-[α(S*)-Acetoxy-3,4-dimethoxybenzyl]-3(S*)-[α(R*)-hydroxy-3,4-(methylenedioxy)benzyl]butyrolactone (12). To a solution of **9b** (0.5 g, 1.25 mmol) in THF (20 mL) was added L-Selectride (1 M in THF, 1.4 mL, 1.4 mmol) at −78 °C. After 10 min, the mixture was quenched by addition of AcOH (84 mg in 10 mL of THF). The solution was allowed to warm to room temperature. The mixture was diluted with AcOEt (50 mL). The solution was washed with brine (2 × 10 mL), dried ($MgSO_4$), and concentrated to dryness *in vacuo*. The residue was crystallized from acetone to afford **12** (435 mg, 87%): mp 156–158 °C; IR (KBr) 3300, 1755 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 2.04 (s, 3H), 2.5–2.9 (m, 2H), 3.76, (s, H), 3.88 (s, 3H), 4.2–4.6 (m, 3H), 4.9–5.3 (m, 3H), 5.97 (s, 2H), 6.2–

6.8 (m, 6H); MS *m/z* (rel inten) 444 (M^+, 7), 384 (21), 151 (100). Anal. Calcd for $C_{23}H_{24}O_9$: C, 62.15; H, 5.44. Found: C, 62.11; H, 5.45.

(1*S,2*R**,3*R**,4*R**)-2,3-Bis(hydroxymethyl)-1-[3,4-(methylenedioxy)phenyl]-4-(3,4-dimethoxyphenyl)butane-1,4-diol (13).** To a suspension of LAH (900 mg, 24 mmol) in THF (10 mL) was added **12** (1.0 g, 2.3 mmol) in THF (10 mL) at 0 °C under vigorous stirring. After stirring for 14 h at room temperature, the mixture was quenched by addition of 10% NaOH (2 mL). The insoluble materials were filtered off by a Celite pad. The filtrate was evaporated to dryness *in vacuo*. The residue was purified by silica gel chromatography using chloroform/MeOH (20:1) as an eluent to afford **13** (711 mg, 73%) as a colorless oil: IR (KBr) 3300 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 1.8–2.2 (m, 2H), 3.2–3.8 (m, 4H), 3.60 (s, 3H), 3.70 (s, 3H), 4.5–4.7 (m, 2H), 4.9–5.1 (m, 2H), 5.2–5.5 (m, 2H), 5.92 (s, 2H), 6.3–6.8 (m, 6H); MS *m/z* (rel inten) 406 (M^+, 2), 388 (44), 370 (53), 151 (100), 135 (69); MS *m/z* 406 (M^+). Anal. Calcd for $C_{21}H_{26}O_8$: C, 62.06; H, 6.45. Found: C, 62.00; H, 6.49.

Fargesin (1b). To a stirred solution of **13** (1.0 g, 2.46 mmol) in CH_2Cl_2 (20 mL) containing pyridine (2 mL) was added dropwise MsCl (845 mg, 7.38 mmol) at 0 °C. The mixture was stirred at 0 °C for 6 h and at room temperature for 10 h. The mixure was washed with water (10 mL), 10% citric acid (2 × 5 mL), and brine (10 mL) and dried ($MgSO_4$), and the solvent was evaporated *in vacuo*. The residue was purified on silica gel chromatography using hexane/AcOEt (4:1) as an eluent to afford **1b** (613 mg, 66%): mp 138–141 °C [lit.[17] mp 140–142 °C]. ^1H NMR (δ in $CDCl_3$) 2.8–3.1 (m, 1H), 3.2–3.4 (m, 2H), 3.6–3.7 (m, 2H), 3.85, (s, 3H), 3.89 (s, 3H), 4.15 (d, 1H, J = 10 Hz), 4.42 (d, 1H, J = 7.0 Hz), 4.85 (d, 1H, J = 5.0 Hz), 5.93 (s, 2H), 6.7–7.2 (m, 6H); ^{13}C NMR (δ in $CDCl_3$) 54.03, 54.52, 55.79, 69.58, 70.84 81.82, 87.48, 100.86, 106.33, 107.92, 108.95, 110.98, 117.57, 119.27, 130.84, 135.08, 146.94, 147.72, 147.83, 148.66; MS *m/z* (rel inten) 370 (M^+, 100), 177 (44), 165 (47), 149 (66), 135 (52). Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 5.99. Found: C, 68.32; H, 5.98.

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