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Syntheses and Antimicrobial Activity of Tetrasubstituted Tetrahydrofuran Lignan Stereoisomers

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The syntheses of all stereoisomers of tetrasubstituted tetrahydrofuran lignan were accomplished, and the antimicrobial activity was examined. The 9,9′-diol compound bearing (7*R*,7′*R*,8*R*,8′*R*) and (7*R*,7′*S*,8*R*,8′*R*) stereochemistry showed the strongest antibacterial activity against *Listeria denitrificans* and *Bacillus subtilis*, respectively. It was also found that (−)-virgatusin bearing (7*S*,7′*R*,8*S*,8′*S*) stereochemistry had strongest antifungal activity.

Key words: lignan; tetrahydrofuran lignan; antimicrobial activity

The tetrahydrofuran lignan, (−)-virgatusin, is expected to have anti-virus activity.[1)] In our previous study on tetrasubstituted tetrahydrofuran lignan, the antifungal activity[2)] of (−)-virgatusin and antibacterial activity[3)] of (7*R*,7′*S*,8*R*,8′*R*)-9-*O*,9′-*O*-demethyl virgatusin have been reported (Fig. 1). Some stereoisomers of their compounds have been synthesized, and their antimicrobial activities have been evaluated.[4)] In this study, the other stereoisomers ((−)-, (+)-**1**–(−)-, (+)-**10**) (Schemes 1–3) were synthesized, and their antimicrobial activities were examined to show the effect of the stereochemistry of tetrasubstituted tetrahydrofuran lignan. The antimicrobial activities of all 16 stereoisomers of tetrasubstituted tetrahydrofuran lignan were elucidated. The activity of some tetrasubstituted tetrahydrofuran lignans had been reported,[5)] however, the effect of stereochemistry on the antimicrobial activity has not been described. This is the first report describing the relationship between the stereochemistry and antimicrobial activity of tetrasubstituted tetrahydrofuran lignan. There are a few reports about the effect of stereochemistry on the biological activity of many known biologically active lignans.[6–9)]

Stereoisomers **1** and **2** were synthesized by the method described in the literature (Scheme 1).[10)] For the syntheses of **3**–**6** (Schemes 1 and 2), SN1 cyclization using methanesulfonyl chloride or a catalytic amount of acid was employed. To obtain **7**–**10**, stereoselective hydroboration to a diene was attempted (Scheme 3).

Results and Discussion

Preparation of the stereoisomers of tetrasubstituted tetrahydrofuran lignans

Stereoisomers (−)-, (+)-**1** and (−)- and (+)-**2** were synthesized by the same procedure as that described in the literature (Scheme 1).[10)]

SN1 cyclization was planned to obtain the stereochemistry of **3** and **4**. Starting material **17** was obtained by Evans's *anti* aldol reaction.[11)] The hydroxy group of *anti*-Evans aldol product **17** was protected as a triethylsilyl ether to give **18**. The treatment of **18** with $LiBH_4$ followed by protection of the resulting primary hydroxy group as a *tert*-butyldiphenylsilyl ether gave **19**. Selective deprotection of the secondary hydroxy group under acidic conditions, followed by OsO_4 oxidation, $NaIO_4$ oxidation, and pyridinium chlorochromate oxidation gave lactone **21**. After aldol condensation using lithium diisopropylamide, the hydroxy group of the resulting aldol mixture (*erythro*/*threo* = 1/4; coupling constant of the new benzylic proton: *erythro*, $J = 4.4$ Hz; *threo*, $J = 7.2$ Hz)[12)] was protected as a triethylsily ether, giving pure *threo* product **22**. $LiBH_4$ reduction followed by *tert*-butyldiphenylsilyl protection of the primary hydroxy group gave benzyl alcohol **23**. After selective cleavage of the triethylsilyl ether under acidic conditions, resulting diol **24** was subjected to SN1 cyclization. The reaction with a catalytic amount of 10-camphorsulfonic acid gave many products; however, treatment with methanesulfonyl chloride, followed by desilylation with *n*-Bu_4NF gave desired (+)-**3** (41%) and undesired **25** (56%).[4)] Methylation of diol **3** by using NaH and CH_3I gave (+)-**4**. In the differential NOE experiment irradiated at 7′-H (5.44 ppm, d, $J = 5.0$ Hz) of (+)-**4**, the effects were observed at both 8-H (2.66 ppm) and 8′-H (2.71 ppm), and the signals of both 9-H_2 and 9′-H_2 were disappeared. The enantiomeric excess was determined as more than 99% by employing chiral column chromatography. Enantiomers (−)-**3** and (−)-**4** were synthesized from the enantiomer of **17**.

To construct the stereochemistry of (−)-**5** and (−)-**6**, triethylsilyloxy benzyl alcohols **30** and **31** or dibenzyl alcohols **32** and **33** were selected as substrates for the SN1 cyclization reaction. To prepare these substrates,

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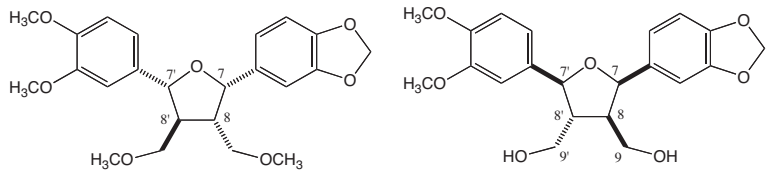
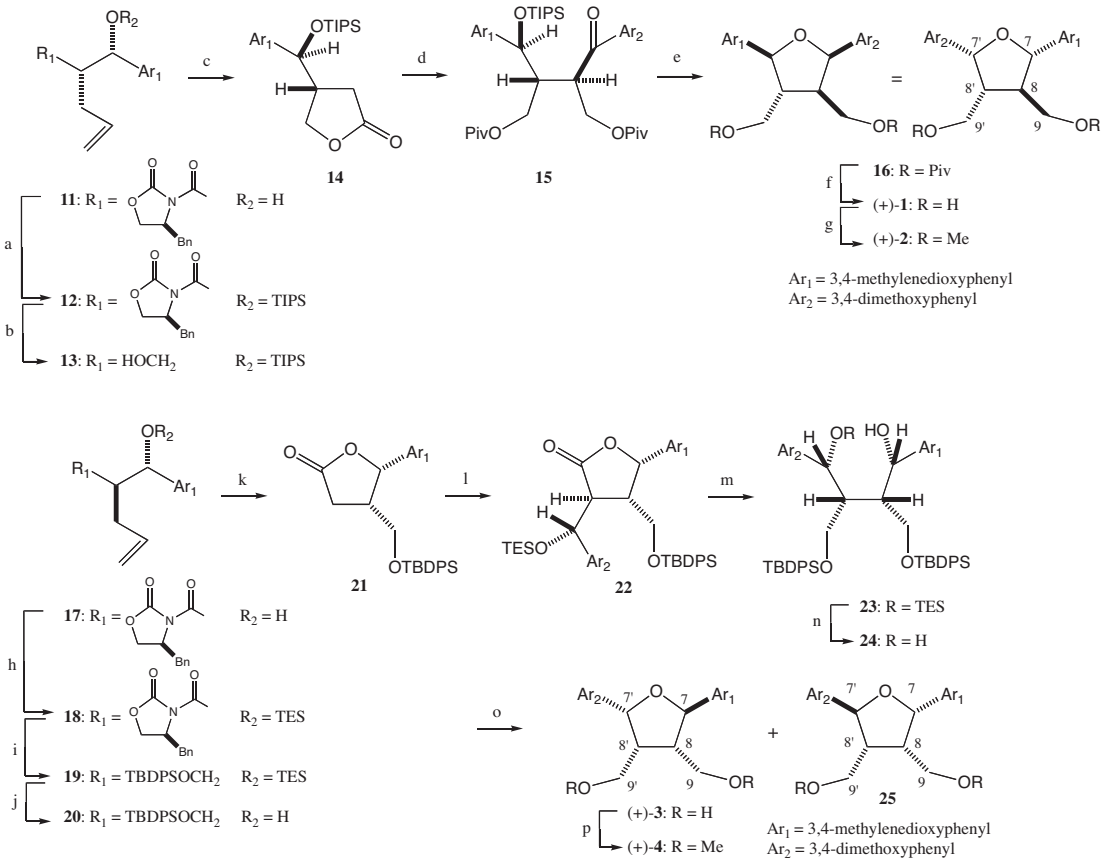


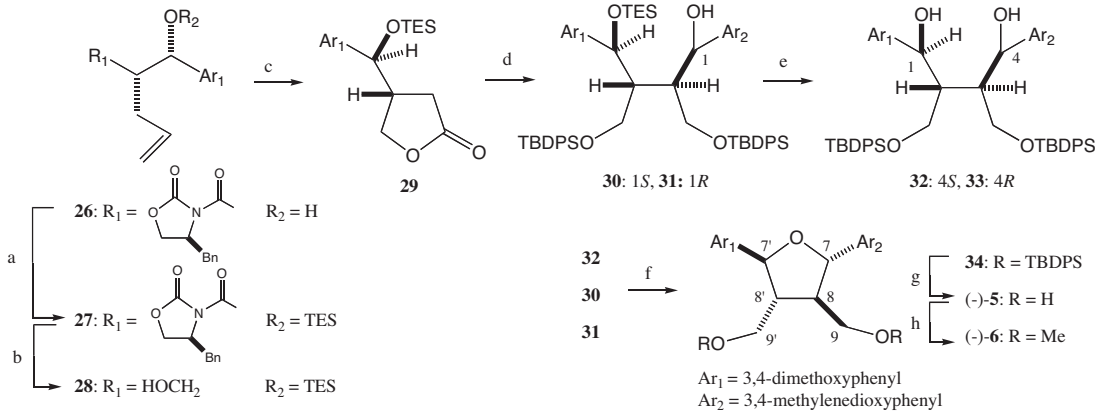
Fig. 1. Antimicrobial Tetrasubstituted Tetrahydrofuran Lignans.



Scheme 1. Synthesis of (+)-**1**–(+)-**4**.

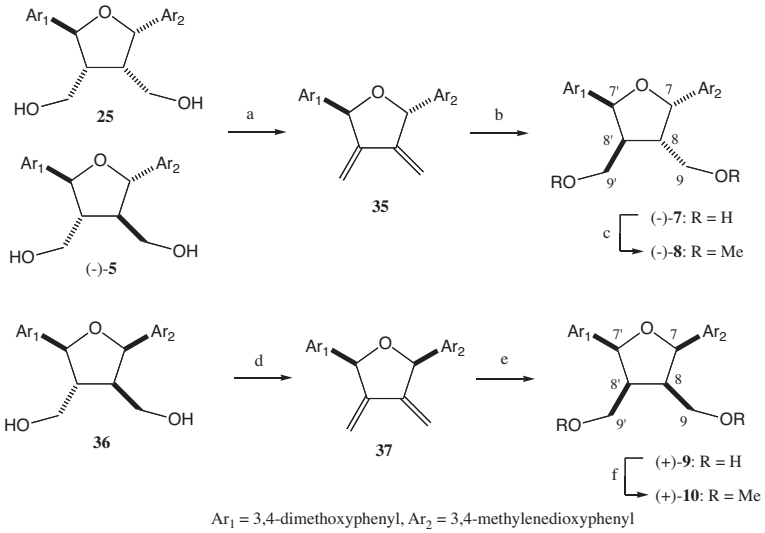
(a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, r.t., 2 h (100% yield); (b) $LiBH_4$, MeOH, THF, r.t., 4 h (52% yield); (c) (1) OsO_4, NMO, aq. acetone, *tert*-BuOH, r.t., 16 h; (2) $NaIO_4$, MeOH, r.t., 1 h; (3) PCC, MS 4A, CH_2Cl_2, r.t., 16 h (44%, 3 steps); (d) (1) KHMDS, 3,4-dimethoxybenzaldehyde, THF, −70 °C, 30 min (81% yield); (2) $LiBH_4$, THF, 0 °C, 16 h; (3) PivCl, pyr., r.t., 1 h; (4) PCC, MS 4A, CH_2Cl_2, 16 h (43% yield, 3 steps); (e) (1) *n*-Bu_4NF, AcOH, THF, r.t., 30 min; (2) H_2, 10% $Pd(OH)_2/C$, EtOAc, r.t., 10 min (58% yield, 2 steps); (f) aq. NaOH, EtOH, r.t., 16 h (63% yield); (g) NaH, CH_3I, THF, r.t., 16 h (100% yield); (h) TESOTf, 2,6-lutidine, CH_2Cl_2, r.t., 30 min (100% yield); (i) (1) $LiBH_4$, THF, r.t., 2.5 h; (2) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, r.t., 2 h (41% yield, 2 steps); (j) 6 M aq. HCl, THF, 0 °C, 30 min (100% yield); (k) (1) OsO_4, NMO, aq. acetone, *tert*-BuOH, r.t., 16 h; (2) $NaIO_4$, MeOH, r.t., 1 h; (3) PCC, MS 4A, CH_2Cl_2, r.t., 16 h (67% yield, 3 steps); (l) (1) LDA, 3,4-dimethoxybenzaldehyde, THF, −70 °C, 1 h (*erythro*/*threo* = 1/4, 98% yield); (2) TESOTf, 2,6-lutidine, CH_2Cl_2, r.t., 30 min (62% yield); (m) (1) $LiBH_4$, THF, 65 °C, 3 h; (2) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, r.t., 2 h (62% yield, 2 steps); (n) 6 M aq. HCl, THF, 0 °C, 1 h (92%); (o) (1) MsCl, Et_3N, CH_2Cl_2, r.t., 1 h (mixture of (7*R*,7′*R*) and (7*S*,7′*S*), 64% yield); (2) TBAF, THF, r.t., 1 h (**3**: 41% yield, **25**: 56% yield); (p) NaH, CH_3I, THF, r.t., 16 h (93% yield).

syn-Evans aldol product **26**[10] was used as a starting material (Scheme 2). This compound **26** was converted to primary alcohol **28** by protection as a triethylsilyl ether and $LiBH_4$ reduction. OsO_4 oxidation, $NaIO_4$ oxidation, and pyridinium chlorochromate oxidation gave lactone **29**. The aldol condensation of this lactone **29** with piperonal, using potassium bis(trimethylsilyl)amide, gave the corresponding aldol product as a 5/1 mixture of *erythro* and *threo* (coupling constant of the new benzylic proton: *erythro*, $J = 2.9$ Hz; *threo*, $J = 6.8$ Hz).[12] The $LiBH_4$ reduction of the aldol mixture, followed by protection of the resulting primary hydroxy group as a *tert*-butyldiphenylsilyl ether gave separable benzyl alcohol derivatives 1*S*-**30** and 1*R*-**31**. The partially separated major *erythro* aldol product could be converted to 1*S*-**30**. Selective cleavage of the triethylsilyl group of **30** and **31** under acidic conditions gave **32** and **33**, respectively. Treatment of **30** and **31** with methanesulfonyl chloride and then tetra-*n*-butyl ammonium fluoride at −10 °C stereoconvergently gave **34** as a single isomer. However, the yield was very low, and many unknown compounds were obtained. It could be assumed that benzylic SN1 cyclization of 4*S*-diol **32** might give the desired stereochemistry, so attaching a 4-benzylic hydroxy group to the 1-benzylic cation of 4*S*-**32** and attaching a 1-benzylic hydroxy group to the 4-



Scheme 2. Synthesis of (−)-**5** and (−)-**6**.

(a) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min (97% yield); (b) $LiBH_4$, MeOH, THF, r.t., 30 min (41% yield); (c) (1) OsO_4, NMO, aq. acetone, *tert*-BuOH, r.t., 16 h; (2) $NaIO_4$, MeOH, r.t., 1 h; (3) PCC, MS 4A, CH_2Cl_2, r.t., 16 h (71% yield, 3 steps); (d) (1) KHMDS, piperonal, −70 °C, 1 h (mixture of *erythro*/*threo* = 5/1, 91% yield); (2) $LiBH_4$, THF, 0 °C, 16 h; (3) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, r.t., 3 h (**30**: 67% yield, 2 steps; **31**: 15% yield, 2 steps); (e) 6 M aq. HCl, THF, r.t., 10 min (**32**: 73% yield; **33**: 78% yield); (f) method A: CSA, CH_2Cl_2, 18 h (from (1*S*)-**32**, 96% yield); method B: (1) MsCl, Et_3N, benzene, 0 °C, 1 h; (2) *n*-Bu_4NF, THF, −10 °C, 1 h (from **30**, 19% yield, from **31**, 15% yield); (g) *n*-Bu_4NF, THF, r.t., 2 h (86% yield); (h) NaH, CH_3I, THF, r.t., 16 h (91% yield).



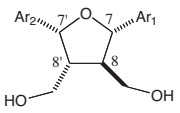
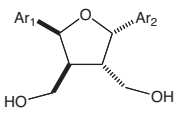
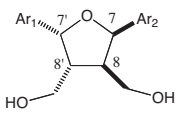
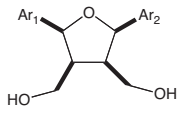
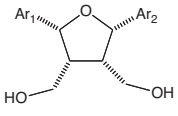
Scheme 3. Synthesis of (−)-**7**–(+)-**10**.

(a) (1) MsCl, Et_3N, CH_2Cl_2, r.t., 30 min; (2) NaI, DBU, DMF, 80 °C, 3 h (58% from **25**, 52% from (−)-**5**, 2 steps); (b) (1) $BH_3 \cdot SMe_2$, THF, r.t., 1 h; (2) H_2O_2, sat. aq. $NaHCO_3$, r.t., 2 h (47% yield); (c) NaH, CH_3I, THF, r.t., 16 h (100% yield); (d) (1) TsCl, Pyr., r.t., 1 h; (2) NaI, DBU, DMF, 80 °C, 3 h (34%, 2 steps); (e) (1) $BH_3 \cdot SMe_2$, THF, r.t., 30 min; (2) H_2O_2, sat. aq. $NaHCO_3$, r.t., 2 h (49% yield); (f) NaH, CH_3I, THF, r.t., 16 h (81% yield).

benzylic cation of 4*S*-**32** would give the desired stable symmetrical stereochemistry of **34**. The reaction of 4*S*-dibenzyl alcohol **32** with a catalytic amount of 10-camphorsulfonic acid gave **34** as a single isomer in 96% yield, however, the reaction of 4*R*-dibenzyl alcohol **33** gave a mixture of many products containing the desired compound under the same conditions. The ^{1}H-NMR spectrum of **34** suggested a symmetrical structure, and NOE between two benzylic protons and methylene protons of the 9 and 9′ positions was observed. Disilyl compound **34** was converted to (−)-**5** and (−)-**6**. The enantiomeric excess was determined as more than 99% by employing chiral column chromatography. Enantiomers (+)-**5** and (+)-**6** were synthesized from the enantiomer of **26**.

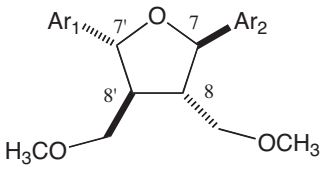
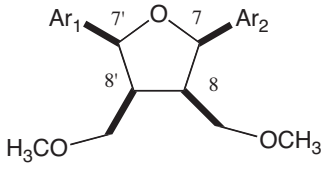
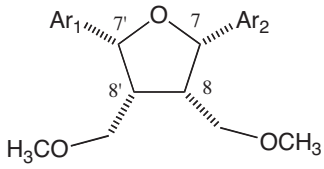
To prepare (−)-**7**, (−)-**8**, (+)-**9**, and (+)-**10**, stereoselective hydroboration to dienes **35** and **37** was attempted (Scheme 3). Diene **35** was obtained from **25** or (−)-**5** by conversion to a dimesylate followed by treatment with NaI and 1,8-diazabicyclo[5.4.0]undec-7-ene. Diol **36** was transformed to diene **37** by the same method. Although the yields were low, desired diols (−)-**7** and (+)-**9** were obtained from dienes **35** and **37** as single isomers, respectively. The NMR spectra of (−)-**7** and (+)-**9** showed a symmetrical structure. Diols (−)-**7** and (+)-**9** were respectively converted to (−)-**8** and (+)-**10**, which were determined as being more than 99% ee by using a chiral column. Enantiomers (+)-**7** and (+)-**8** were synthesized from the enantiomer of **25** or (+)-**5**. Enantiomers (−)-**9** and (−)-**10** were synthesized from the enantiomer of **36**. The syntheses of all 16 stereoisomers of tetrasubstituted tetrahydrofuran lignan were achieved.

Table 1. Antibacterial Activity of Stereoisomers (MIC, mM)

	 (+)-**1**	 (-)-**7**	 (+)-**7**	 (+)-**9**	 (-)-**9**
B. subtilis	>50	>50	>50	>50	>50
S. aureus	>50	>50	>50	>50	>50
L. denitrificans	25	25	6.25	50.0	50.0

Ar_1 = 3,4-dimethoxyphenyl, Ar_2 = 3,4-methylenedioxyphenyl

Table 2. Growth Rate (% ± σ, n = 3) of *Colletotrichum lagenarium* at 0.25 mM of the Stereoisomers

 (+)-**6**	 (+)-**10**	 (-)-**10**
86.6 ± 3.71	92.6 ± 5.12	83.4 ± 4.15

Ar_1 = 3,4-dimethoxyphenyl, Ar_2 = 3,4-methylenedioxyphenyl

Growth (%), (colony diameter of sample/colony diameter of control) × 100.

Antimicrobial activity

In the antibacterial activity test, the (7*R*,7′*R*,8*R*,8′*R*) form ((+)-**7**) showed the strongest activity (MIC of 6.25 mM) against *Listeria denitrificans* (Table 1). This activity was stronger than that of the (7*S*,7′*R*,8*R*,8′*S*) stereoisomer (MIC of 12.5 mM).[4] The other stereoisomers showed weaker activity. The (7'*R*,8*R*) stereochemistry was found in those compounds having the highest antibacterial activity against *Listeria denitrificans*, and the (7*R*,7′*R*,8*R*,8′*R*) form ((+)-**7**)) was the best stereochemistry. Against *Bacillus subtilis*, the (7*R*,7′*S*,8*R*,8′*R*) form (Fig. 1) was the best stereochemistry (MIC of 12.5 mM),[3] because the other stereoisomers did not show activity against *Bacillus subtilis* in this and previous studies.[3,4] The 8*R* form is common stereochemistry for high antibacterial activity against *Listeria denitrificans* and *Bacillus subtilis*. In the antifungal activity test against *Colletotrichum lagenarium* (Table 2), (+)-**6**, (+)-**10**, and (−)-**10** showed weaker activity at 0.25 mM than that of natural (−)-virgatusin bearing (7*S*,7′*R*,8*S*,8′*S*) stereochemistry (50% growth inhibition).[2] Since the compounds having other stereochemistry did not show stronger activity,[2,4] the natural (7*S*,7′*R*,8*S*,8′*S*) stereochemistry was best for antifungal activity. The weaker activity of the (7*R*,7′*S*,8*R*,8′*R*), (7*S*,7′*R*,8*R*,8′*S*), (7*R*,7′*S*,8*R*,8′*S*), (7*S*,7′*R*,8*S*,8′*R*), and (7*R*,7′*R*,8*S*,8′*S*) stereoisomers was observed in this and previous studies. In the case of epimers with natural stereochemistry, only 7′ the epimer did not show any activity, white the activity of the other epimers was weak. With stereochemistries bearing the (7*S*,7′*R*) form, only (8*R*,8′*R*) stereochemistry did not show any activity. The effect of the stereochemistry of tetrasubstituted tetrahydrofuran lignan on antimicrobial activity was demonstrated for the first time.

Material and Methods

Melting point (mp) data are uncorrected. NMR data were measured by a JNM-EX400 spectrometer, using TMS as a standard (0 ppm), MS data were measured with a JMS-MS700V spectrometer, and optical rotation values were evaluated with a Horiba SEPA-200 instrument. Elemental analysis was carried out with Yanako MT-5 CHN coder. The silica gel used was Wakogel C-300 (Wako, 200–300 mesh).

*(*S*)-4-Benzyl-3-{(*S*)-2-[(S)-(3,4-methylenedioxyphenyl)(triisopropylsilyloxy)methyl]-4-pentenoyl}-2-oxazolidinone (**12**).* To an ice-cooled solution of **11** (17.3 g, 0.042 mol) and 2,6-lutidine (8.43 ml, 0.072 mol) in CH_2Cl_2 (200 ml) was added TIPSOTf (14.4 ml, 0.054 mol). The resulting reaction solution was stirred at room temperature for 2 h before addition of sat. aq. $NaHCO_3$ solution. The organic solution was separated, washed with sat. aq. $CuSO_4$ solution and sat. aq. $NaHCO_3$ solution, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/4) gave **12** (23.8 g, 0.042 mol, 100%) as a colorless oil, $[\alpha]^{20}_D$ +45 (*c* 1.1, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.96–1.06 (19H, m), 1.13–1.16 (2H, m), 2.60 (1H, dd, *J* = 13.2, 9.8 Hz), 2.65 (1H, m), 2.77 (1H, m), 3.14 (1H, dd, *J* = 13.2, 2.9 Hz), 3.65 (1H, dd, *J* = 8.3, 8.3 Hz), 3.95 (1H, dd, *J* = 8.3, 2.0 Hz), 4.25 (1H, m), 4.43 (1H, m), 4.87 (1H, d, *J* = 7.8 Hz), 5.02 (1H, d, *J* = 9.8 Hz), 5.11 (1H, d, *J* = 17.1 Hz), 5.81–5.93 (1H, m), 5.90 (1H, d, *J* = 6.8 Hz), 5.91 (1H, d, *J* = 6.8 Hz), 6.69 (1H, d, *J* = 7.8 Hz), 6.78 (1H, dd, *J* = 7.8, 2.0 Hz), 6.90 (1H, d, *J* = 2.0 Hz), 7.16 (2H, d, *J* = 6.4 Hz), 7.22–7.31 (3H, m). NMR δ_C ($CDCl_3$): 12.4, 12.5, 17.9, 18.1, 34.0, 37.9, 51.9, 55.7, 65.6, 76.9, 100.9, 107.4, 107.6, 116.8, 120.4, 127.2, 128.8, 129.4, 135.4, 136.8, 146.9, 147.2, 152.7, 173.6. Found: C, 68.05; H, 7.77; N 2.49. Calcd. for $C_{32}H_{43}O_6NSi$: C, 67.93; H, 7.66; N, 2.47%. *(R)-{(R)-[(R)]}-(**12**)*, $[\alpha]^{20}_D$ −44 (*c* 0.8, $CHCl_3$).

*(*R*)-2-[(S)-(3,4-Methylenedioxyphenyl)(triisopropylsilyloxy)methyl]-4-penten-1-ol (**13**).* To an ice-cooled solution of $LiBH_4$ (1.00 g, 0.046 mol) and MeOH (1.86 ml) in THF (50 ml) was added a solution of **12** (27.3 g, 0.048 mol) in THF (100 ml). After the reaction solution was stirred at room temperature for 4 h, sat. aq. NH_4Cl solution was added. The mixture was concentrated, and then the residue was dissolved in H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by

silica gel column chromatography (EtOAc/hexane = 1/4) gave **13** (10.0 g, 0.025 mol, 52%) as a colorless oil, $[\alpha]^{20}_D$ −22 (*c* 0.6, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.96–1.07 (19H, m), 1.13–1.16 (2H, m), 1.75 (1H, m), 1.94 (1H, m), 2.23 (1H, m), 3.19 (1H, dd, *J* = 5.4, 2.0 Hz), 3.47 (1H, m), 3.61 (1H, ddd, *J* = 8.8, 8.8, 2.0 Hz), 4.93 (1H, d, *J* = 4.4 Hz), 5.02–5.07 (2H, m), 5.79 (1H, m), 5.96 (2H, s), 6.77 (2H, s), 6.89 (1H, s). NMR δ_C ($CDCl_3$): 12.1, 17.8, 17.9, 18.0, 32.6, 46.8, 63.2, 77.8, 100.9, 107.6, 107.7, 120.5, 134.7, 146.8, 147.4. Found: C, 67.24; H, 9.20. Calcd. for $C_{22}H_{36}O_4Si$: C, 67.30; H, 9.24%. *(S)-2-[(R)]-(**13**)*, $[\alpha]^{20}_D$ +21 (*c* 0.4, $CHCl_3$).

*(*R*)-3-[(*S*)-(3,4-Methylenedioxyphenyl)(triisopropylsilyloxy)methyl]-4-butanolide (**14**).* A reaction solution of **13** (10.0 g, 0.025 mol), NMO (3.76 g, 0.032 mol), and OsO_4 (3.5 ml, 2% in H_2O) in acetone (250 ml), *tert*-BuOH (50 ml), and H_2O (50 ml) was stirred under N_2 gas at room temperature for 16 h before addition of sat. aq. $Na_2S_2O_3$ solution. After the mixture was concentrated, the residue was dissolved in H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration gave a crude glycol. A reaction mixture of this crude glycol and $NaIO_4$ (7.52 g, 0.035 mol) in MeOH (150 ml) was stirred at room temperature for 1 h before concentration. The residue was dissolved in CH_2Cl_2 and H_2O. The organic solution was separated and dried (Na_2SO_4). Concentration gave crude hemiacetal. A reaction mixture of this crude hemiacetal, PCC (6.50 g, 0.030 mol), and MS 4A (0.5 g) in CH_2Cl_2 (200 ml) was stirred at room temperature for 16 h before addition of ether. After the mixture was filtered, the filtrate was concentrated. The residue was applied to silica gel column chromatography (EtOAc/hexane = 1/4) to give **14** (4.38 g, 0.011 mol, 44%, 3 steps) as a colorless oil, $[\alpha]^{20}_D$ −63 (*c* 0.5, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.95–1.05 (21H, m), 2.54 (1H, dd, *J* = 17.6, 9.0 Hz), 2.62 (1H, dd, *J* = 17.6, 7.8 Hz), 2.84 (1H, m), 4.09 (1H, dd, *J* = 9.3, 6.8 Hz), 4.15 (1H, dd, *J* = 9.3, 7.8 Hz), 4.68 (1H, d, *J* = 6.4 Hz), 5.97 (2H, s), 6.71 (1H, d, *J* = 8.1 Hz), 6.75 (1H, d, *J* = 8.1 Hz), 6.80 (1H, s). NMR δ_C ($CDCl_3$): 12.5, 18.0, 18.1, 31.0, 44.5, 69.5, 75.5, 101.1, 106.6, 108.0, 119.8, 135.9, 147.4, 147.9, 176.8. Found: C, 64.55; H, 8.38. Calcd. for $C_{21}H_{32}O_5Si$: C, 64.25; H, 8.22%. *(S)-3-[(R)]-(**14**)*, $[\alpha]^{20}_D$ +63 (*c* 0.3, $CHCl_3$).

*(2*R*,3*R*)-2-(3,4-Dimethoxybenzoyl)-3-[(*S*)-(methylenedioxyphenyl)-(triisopropylsilyloxy)methyl]tetramethylene dipivaloate (**15**).* To a solution of KHMDS (24 ml, 0.5 M in toluene, 12.0 mmol) in THF (80 ml) was added a solution of **14** (4.06 g, 10.3 mmol) in THF (20 ml) at −70 °C, and then a solution of 3,4-dimethoxybenzaldehyde (1.66 g, 0.010 mol) in THF (10 ml) was added. After the resulting solution was stirred at −70 °C for 30 min, sat. aq. NH_4Cl solution was added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave an aldol product (4.69 g, 8.39 mmol, 81%) as a mixture of *erythro*/*threo* = 9/1. To a solution of $LiBH_4$ (1.50 g, 68.9 mmol) in THF (10 ml) was added a solution of the aldol mixture (4.69 g, 8.39 mmol) in THF (20 ml) at −10 °C. The resulting solution was stirred at 0 °C for 16 h before addition of sat. aq. NH_4Cl solution. After concentration, the residue was dissolved in H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration gave a crude triol. To an ice-cooled solution of this crude triol in pyridine (10 ml) was added PivCl (2.07 ml, 16.8 mmol). The resulting reaction mixture was stirred at room temperature for 1 h before additions of EtOAc and H_2O. The organic solution was separated, washed with 6 M aq. HCl solution, sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). Concentration gave a crude dipivaloate. A reaction mixture of this crude dipivaloate, PCC (1.07 g, 4.96 mmol), and MS 4A (0.2 g) in CH_2Cl_2 (80 ml) was stirred at room temperature for 16 h, and then ether was added. After filtration, the filtrate was concentrated. The resulting residue was applied to silica gel column chromatography (5% EtOAc in toluene) to give **15** (2.65 g, 3.64 mmol, 43%, 3 steps) as a colorless oil, $[\alpha]^{20}_D$ −4 (*c* 1.0, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.99–1.15 (21H, m), 1.04 (9H, s), 1.21 (9H, s), 2.57 (1H, m), 3.84 (1H, dd, *J* = 9.8, 3.9 Hz), 3.93 (3H, s), 3.98 (3H, s), 4.11 (1H, dd, *J* = 9.8, 3.9 Hz), 4.28 (1H, m), 4.42 (1H, dd, *J* = 9.8, 3.9 Hz), 4.49 (1H, dd, *J* = 9.8, 9.8 Hz), 4.89 (1H, d, *J* = 7.0 Hz), 5.92 (1H, d, *J* = 12.5 Hz), 5.93 (1H, d, *J* = 12.5 Hz), 6.59 (1H, d, *J* = 7.9 Hz), 6.66 (1H, d, *J* = 7.9 Hz), 6.74 (1H, s), 6.88 (1H, d, *J* = 8.3 Hz), 7.54 (1H, s), 7.61 (1H, d, *J* = 8.3 Hz). NMR δ_C ($CDCl_3$): 12.5, 18.0, 18.1, 27.0, 27.1, 38.5, 38.7, 43.6, 46.7, 55.9, 56.1, 61.4, 62.9, 73.7, 101.0, 107.1, 107.7, 109.9, 110.8, 120.4, 123.3, 129.6, 136.1, 147.2, 147.7, 149.2, 153.5, 177.8, 178.0, 198.2. Found: C, 65.79; H, 8.24. Calcd. for $C_{40}H_{60}O_{10}Si$: C, 65.90; H 8.30%. *(2S,3S)-[(R)]-(**15**)*, $[\alpha]^{20}_D$ +5 (*c* 0.4, $CHCl_3$).

*(7*S*,7′*R*,8*R*,8′*R*)-3′,4′-Dimethoxy-3,4-methylenedioxy-7,7′-epoxylignane-9,9′-diyl dipivaloate (**16**).* To an ice-cooled solution of **15** (2.65 g, 3.64 mmol) in THF (15 ml) were added AcOH (0.25 ml) and *n*-Bu_4NF (4.00 ml, 1 M in THF, 4.00 mmol). After the reaction solution was stirred at room temperature for 30 min, sat. aq. $NaHCO_3$ solution was added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration gave a crude hemiacetal. A reaction mixture of this crude hemiacetal and 10% $Pd(OH)_2/C$ (0.7 g) in EtOAc (15 ml) was stirred at ambient temperature for 10 min under H_2 gas before filtration. The resulting filtrate was concentrated, and then the residue was applied to silica gel column chromatography (EtOAc/hexane = 1/3) to give **16** (1.18 g, 2.12. mmol, 58%, 2 steps) as a colorless oil, $[\alpha]^{20}_D$ +13 (*c* 0.9, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.08 (9H, s), 1.20 (9H, s), 2.33 (1H, m), 2.73 (1H, m), 3.76 (1H, dd, *J* = 11.2, 8.7 Hz), 3.85 (1H, dd, *J* = 11.2, 6.2 Hz), 3.87 (3H, s), 3.90 (3H, s), 4.21 (1H, dd, *J* = 11.5, 5.5 Hz), 4.28 (1H, dd, *J* = 11.5, 5.5 Hz), 4.67 (1H, d, *J* = 8.5 Hz), 5.13 (1H, d, *J* = 7.5 Hz), 5.98 (2H, s), 6.81–6.86 (2H, m), 6.91–6.96 (3H, m), 7.01 (1H, d, *J* = 1.5 Hz). NMR δ_C ($CDCl_3$): 27.0, 27.1, 38.6, 38.9, 45.3, 50.8, 55.9, 63.8, 64.9, 81.1, 82.8, 101.1, 106.8, 108.2, 109.5, 111.1, 118.6, 120.3, 130.2, 133.9, 147.5, 148.0, 148.5, 148.9, 178.2, 178.3. Found: C, 67.02; H, 7.33. Calcd. for $C_{31}H_{40}O_9$: C, 66.89; H, 7.24%. *(7R,7′S,8S,8′S)-(**16**)*, $[\alpha]^{20}_D$ −13 (*c* 0.4, $CHCl_3$).

*(7*S*,7′*R*,8*R*,8′*R*)-3′,4′-Dimethoxy-3,4-methylenedioxy-7,7′-epoxylignane-9,9′-diol ((+)-**1**).* A reaction solution of **16** (1.14 g, 2.05 mmol) in EtOH (20 ml) and 1 M aq. NaOH solution (10 ml) was stirred at room temperature for 16 h before additions of $CHCl_3$ and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/6) gave (+)-**1** (0.50 g, 1.29 mmol, 63%) as a colorless oil, $[\alpha]^{20}_D$ +30 (*c* 0.5, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.17 (1H, m), 2.54 (1H, m), 3.07 (1H, dd, *J* = 10.6, 10.6 Hz), 3.29 (1H, dd, *J* = 10.6, 4.5 Hz), 3.53 (1H, dd, *J* = 9.5, 9.5 Hz), 3.69 (1H, dd, *J* = 9.5, 3.7 Hz), 3.865 (3H, s), 3.869 (3H, s), 4.44 (1H, d, *J* = 9.4 Hz), 5.09 (1H, d, *J* = 8.5 Hz), 5.97 (2H, s), 6.80 (1H, d, *J* = 7.9 Hz), 6.82 (1H, d, *J* = 7.8 Hz), 6.85–6.91 (3H, m), 7.01 (1H, s). NMR δ_C ($CDCl_3$): 50.8, 55.2, 55.8, 62.7, 63.6, 81.2, 82.5, 101.1, 106.9, 108.1, 109.6, 110.9, 118.7, 120.4, 131.3, 133.9, 147.5, 147.9, 148.4, 148.7. EIMS *m*/*z*: 388 (M^+, 100), 191 (64), 174 (65). HRMS (EI) *m*/*z* (M^+): calcd. for $C_{21}H_{24}O_7$, 388.1522; found, 388.1522. *(7R,7′S,8S,8′S)-((−)-**1**)*, $[\alpha]^{20}_D$ −30 (*c* 0.6, $CHCl_3$).

*(7*S*,7′*R*,8*R*,8′*R*)-3′,4′,9,9′-Tetramethoxy-3,4-methylenedioxy-7,7′-epoxylignane ((+)-**2**).* To an ice-cooled suspension of NaH (0.12 g, 60% oil suspension, 3.00 mmol) in THF (5 ml) was added a solution of (+)-**1** (0.50 g, 1.29 mmol) in THF (10 ml). After the resulting mixture was stirred at room temperature for 30 min, CH_3I (0.40 ml, 6.43 mmol) was added. The reaction solution was stirred at room temperature for 16 h before additions of sat. aq. NH_4Cl solution and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/1) gave (+)-**2** (0.54 g, 1.29 mmol, 100%) as a colorless oil, $[\alpha]^{20}_D$ +20 (*c* 0.8, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.30 (1H, m), 2.62 (1H, m), 2.94 (1H, dd, *J* = 9.2, 5.7 Hz), 3.05 (1H, dd, *J* = 9.2, 9.2 Hz), 3.08 (3H, s), 3.37 (3H, s), 3.50 (1H, dd, *J* = 9.4, 4.9 Hz), 3.54 (1H, dd, *J* = 9.4, 5.3 Hz), 3.89 (3H, s), 3.90 (3H, s), 4.71 (1H, d, *J* = 8.1 Hz), 5.09 (1H, d, *J* = 7.3 Hz), 5.97 (2H, s), 6.81 (1H, d, *J* = 8.1 Hz), 6.85 (1H, d, *J* = 8.1 Hz), 6.94–6.96 (3H, m), 7.05 (1H, d, *J* = 1.6 Hz). NMR δ_C ($CDCl_3$): 46.5, 51.1, 55.8, 55.9, 58.6, 59.0, 72.9, 81.5, 82.5, 100.9, 107.0, 106.9, 108.0, 109.7, 110.7, 118.5, 120.0, 131.3, 135.6, 147.0, 147.7, 148.5. EIMS *m*/*z*: 416 (M^+, 99), 208 (58), 173 (100). HRMS (EI) *m*/*z* (M^+): calcd. for $C_{23}H_{28}O_7$, 416.1835; found, 416.1834. >99% ee (HPLC, DAICEL OD-H chiral column, detected at 280 nm, 1 ml min^{-1}, 10% *iso*-PrOH in hexane, t_R 37 min). *(7R,7′S,8S,8′S)-((−)-**2**)*, $[\alpha]^{20}_D$ −21 (*c* 0.4, $CHCl_3$), >99% ee, t_R 15 min.

*(S)-4-Benzyl-3-{(R)-2-[(S)-(hydroxy)(3,4-methylenedioxyphenyl)-methyl]-4-pentenoyl}-2-oxazolidinone (**17**).* A reaction mixture of (*S*)-4-benzyl-3-(4-pentenoyl)-2-oxazolidinone (22.0 g, 84.8 mmol), piperonal (12.8 g, 85.3 mmol), Et_3N (23.9 ml, 0.17 mol), TMSCl (16.2 ml, 0.13 mol), and $MgCl_2$ (0.85 g, 8.92 mmol) in EtOAc (200 ml) was stirred at room temperature for 16 h before filtration with silica gel and ether. After the filtrate was concentrated, the residue was dissolved in MeOH. To the resulting solution was added CF_3CO_2H (5 ml) at 0 °C, and then the reaction solution was stirred at 0 °C for 30 min before addition of Et_3N. After concentration of the resulting mixture, the residue was applied to silica gel column chromatography (EtOAc/hexane = 1/3), giving **17** (25.0 g, 61.1 mmol, 72%) as a colorless oil, $[\alpha]^{20}_D$ +8 (*c* 2.2, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.16 (1H, m), 2.40 (1H, m), 2.67 (1H, dd, *J* = 13.6, 9.3 Hz), 3.15 (1H, d, *J* = 7.3 Hz), 3.20 (1H, dd, *J* = 13.6, 3.4 Hz), 4.10–4.13 (2H, m), 4.48 (1H, m), 4.66 (1H, m), 4.78 (1H, dd, *J* = 7.5, 7.3 Hz), 4.98 (1H, d, *J* = 10.3 Hz), 5.03 (1H, d, *J* = 7.0 Hz), 5.72 (1H, m), 5.92 (1H, d, *J* = 9.2 Hz), 5.93 (1H, d, *J* = 9.2 Hz), 6.78 (1H, d, *J* = 8.0 Hz), 6.87 (1H, dd, *J* = 8.0, 1.5 Hz), 6.97 (1H, d, *J* = 1.5 Hz), 7.15 (2H, d, *J* = 6.8 Hz), 7.23–7.33 (3H, m). NMR δ_C ($CDCl_3$): 34.2, 37.5, 49.1, 55.4, 65.8, 75.8, 101.1, 106.9, 108.1, 117.4, 120.1, 127.2, 128.9, 129.4, 134.4, 135.2, 136.1, 147.3, 148.0, 153.5, 175.3. EIMS *m/z*: 409 (M^+, 8), 259 (100), 151 (62). HRMS (EI) *m/z* (M^+): calcd. for $C_{23}H_{23}O_6N$, 409.1525; found, 409.1525. *(R)-{(S)-[(R)]}-**17***, $[\alpha]^{20}_D$ −8 (*c* 2.3, $CHCl_3$).

*(S)-4-Benzyl-3-{(R)-2-[(S)-(3,4-methylenedioxyphenyl)(triethylsilyloxy)methyl]-4-pentenoyl}-2-oxazolidinone (**18**).* To an ice-cooled solution of **17** (2.30 g, 5.62 mmol) and 2,6-lutidine (1.33 ml, 11.4 mmol) in CH_2Cl_2 (50 ml) was added TESOTf (1.91 ml, 8.45 mmol). The resulting reaction solution was stirred at room temperature for 30 min before addition of sat. aq. $NaHCO_3$ solution. The organic solution was separated, washed with sat. aq. $CuSO_4$ solution, sat. aq. $NaHCO_3$, and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave **18** (2.94 g, 5.62 mmol, 100%) as a colorless oil, $[\alpha]^{20}_D$ −30 (*c* 1.1, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.34–0.47 (6H, m), 0.83 (9H, t, *J* = 8.0 Hz), 1.91 (1H, m), 2.15 (1H, m), 2.69 (1H, dd, *J* = 13.2, 3.2 Hz), 3.46 (1H, dd, *J* = 13.2, 3.2 Hz), 4.07–4.14 (2H, m), 4.50 (1H, m), 4.67 (1H, m), 4.84 (1H, d, *J* = 9.4 Hz), 4.89 (1H, d, *J* = 10.7 Hz), 4.93 (1H, d, *J* = 17.5 Hz), 5.63 (1H, m), 5.97 (1H, d, *J* = 4.8 Hz), 5.98 (1H, d, *J* = 4.8 Hz), 6.75 (1H, d, *J* = 8.0 Hz), 6.82 (1H, dd, *J* = 8.0, 1.6 Hz), 6.98 (1H, d, *J* = 1.6 Hz), 7.24–7.30 (3H, m), 7.34–7.37 (2H, m). NMR δ_C ($CDCl_3$): 4.7, 6.7, 34.1, 38.1, 50.9, 55.6, 65.7, 77.1, 101.0, 107.66, 107.70, 116.9, 121.1, 127.2, 128.9, 129.4, 134.7, 135.8, 136.4, 147.3, 147.7, 153.2, 174.7. Found: C, 66.19; H, 7.20; N, 2.62. Calcd. for $C_{29}H_{37}O_6NSi$: C, 66.49; H, 7.13; N, 2.68%. *(R)-{(S)-[(R)]}-(**18**)*, $[\alpha]^{20}_D$ +31 (*c* 0.6, $CHCl_3$).

*(4S,5S)-4-(*tert*-Butyldiphenylsilyloxy)methyl-5-(3,4-methylenedioxyphenyl)-5-(triethylsilyloxy)-1-pentene (**19**).* To an ice-cooled solution of $LiBH_4$ (1.62 g, 74.4 mmol) and MeOH (1.54 ml) in THF (50 ml) was added a solution of **18** (10.4 g, 19.9 mmol) in THF (50 ml). The resulting reaction solution was stirred at room temperature for 2.5 h before addition of sat. aq. NH_4Cl solution. The mixture was concentrated, and then the residue was dissolved in EtOAc and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration gave crude alcohol. A reaction mixture of this crude alcohol, Et_3N (2.86 ml, 20.5 mmol), DMAP (50 mg, 0.41 mmol), and TBDPSCl (4.20 ml, 16.2 mmol) in CH_2Cl_2 (50 ml) was stirred at room temperature for 2 h before addition of H_2O and CH_2Cl_2. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (5%EtOAc in hexane) gave **19** (4.77 g, 8.10 mmol, 41%, 2 steps) as a colorless oil, $[\alpha]^{20}_D$ −35 (*c* 1.3, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.46 (6H, q, *J* = 7.9 Hz), 0.84 (9H, t, *J* = 7.9 Hz), 1.08 (9H, s), 1.65 (1H, m), 1.94 (1H, m), 2.21 (1H, m), 3.51 (1H, dd, *J* = 10.4, 7.1 Hz), 3.70 (1H, dd, *J* = 10.4, 5.8 Hz), 4.82 (1H, d, *J* = 17.1 Hz), 4.83 (1H, d, *J* = 10.3 Hz), 4.89 (1H, d, *J* = 5.6 Hz), 5.57 (1H, m), 5.92 (1H, d, *J* = 7.3 Hz), 5.93 (1H, d, *J* = 7.3 Hz), 6.67 (1H, d, *J* = 7.9 Hz), 6.71 (1H, dd, *J* = 7.9, 1.4 Hz), 6.82 (1H, d, *J* = 1.4 Hz), 7.33–7.43 (6H, m), 7.62–7.67 (4H, m). NMR δ_C ($CDCl_3$): 4.8, 6.8, 19.3, 27.0, 30.4, 49.0, 63.0, 73.5, 100.7, 107.3, 107.4, 115.6, 120.2, 127.6, 129.5, 133.9, 135.6, 136.9, 137.3, 146.4, 147.2. Found: C, 71.60; H, 8.43. Calcd. for $C_{35}H_{48}O_4Si_2$: C, 71.36; H, 8.22%. *(4R,5R)-(**19**)*, $[\alpha]^{20}_D$ = +36 (*c* 1.3, $CHCl_3$).

*(1S,2S)-2-(*tert*-Butyldiphenylsilyloxy)methyl-1-(3,4-methylenedioxyphenyl)-4-penten-1-ol (**20**).* To an ice-cooled solution of **19** (4.77 g, 8.10 mmol) in THF (5 ml) was added 6 M aq. HCl solution (5 ml). After the resulting reaction mixture was stirred at 0 °C for 30 min, EtOAc and H_2O were added. The organic solution was separated, washed with sat. aq. $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/9) gave **20** (3.83 g, 8.07 mmol, 100%) as a colorless oil, $[\alpha]^{20}_D$ +24 (*c* 1.2, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.09 (9H, s), 1.84 (1H, m), 2.00 (1H, m), 2.12 (1H, m), 3.66 (1H, dd, *J* = 10.5, 5.8 Hz), 3.86 (1H, dd, *J* = 10.5, 3.2 Hz), 4.01 (1H, d, *J* = 4.5 Hz), 4.71 (1H, dd, *J* = 6.6, 4.5 Hz), 4.88 (1H, d, *J* = 10.1 Hz), 4.90 (1H, d, *J* = 17.2 Hz), 5.57 (1H, m), 5.94 (2H, s), 6.75 (1H, d, *J* = 7.9 Hz), 6.79 (1H, dd, *J* = 7.9, 1.6 Hz), 6.88 (1H, d, *J* = 1.6 Hz), 7.35–7.46 (6H, m), 7.63–7.68 (4H, m). NMR δ_C ($CDCl_3$): 19.1, 26.9, 32.7, 46.4, 65.1, 77.1, 100.9, 106.8, 107.8, 116.6, 119.8, 127.8, 129.9, 132.58, 132.62, 135.60, 135.64, 136.1, 137.6, 146.7, 147.7. Found: C, 73.09; H, 7.47. Calcd. for $C_{29}H_{34}O_4Si$: C, 73.37; H, 7.22%. *(1R,2R)-**20***, $[\alpha]^{20}_D$ −23 (*c* 1.1, $CHCl_3$).

*(3S,4S)-3-(*tert*-Butyldiphenylsilyloxy)methyl-4-(3,4-methylenedioxyphenyl)-4-butanolide (**21**).* A reaction solution of **20** (3.40 g, 7.16 mmol), NMO (0.86 g, 7.34 mmol), and OsO_4 (1.00 ml, 2% aq. solution) in acetone (64 ml), *tert*-BuOH (16 ml), and H_2O (16 ml) was stirred at room temperature for 16 h before addition of sat. aq. $Na_2S_2O_3$ solution. After the mixture was concentrated, the residue was dissolved in H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration gave a crude glycol. A reaction mixture of this glycol and $NaIO_4$ (2.04 g, 9.54 mmol) in MeOH (50 ml) was stirred at room temperature for 1 h before concentration. The resulting residue was dissolved in H_2O and CH_2Cl_2. The organic solution was separated and dried (Na_2SO_4). Concentration gave a crude hemiacetal. A reaction mixture of this hemiacetal, PCC (1.89 g, 8.77 mmol), and MS 4A (0.3 g) in CH_2Cl_2 (100 ml) was stirred at room temperature for 16 h before addition of ether. After filtration, the filtrate was concentrated. The residue was applied to silica gel column chromatography to give **21** (2.29 g, 4.82 mmol, 67%, 3 steps) as colorless crystals, mp 116–117 °C (EtOAc), $[\alpha]^{20}_D$ +20 (*c* 0.6, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.01 (9H, s), 2.60 (1H, dd, *J* = 17.2, 4.6 Hz), 2.72 (1H, dd, *J* = 17.2, 8.3 Hz), 2.80 (1H, m), 3.29 (1H, dd, *J* = 10.7, 5.2 Hz), 3.39 (1H, dd, *J* = 10.7, 5.2 Hz), 5.57 (1H, d, *J* = 6.8 Hz), 5.96 (2H, s), 6.70 (1H, d, *J* = 7.9, 1.2 Hz), 6.75 (1H, d, *J* = 7.9 Hz), 6.78 (1H, d, *J* = 1.2 Hz), 7.30–7.36 (4H, m), 7.38–7.43 (4H, m), 7.51–7.53 (2H, m). NMR δ_C ($CDCl_3$): 19.0, 26.7, 32.3, 42.1, 62.1, 82.6, 101.2, 106.3, 106.4, 108.2, 119.0, 127.7, 129.5, 129.8, 132.7, 135.5, 147.3, 147.8, 176.2. Found: C, 70.85; H, 6.33. Calcd. for $C_{28}H_{30}O_5Si$: C, 70.84; H, 6.37%. *(3R,4R)-(**21**)*, $[\alpha]^{20}_D$ −20 (*c* 1.0, $CHCl_3$).

*(2S,3S,4S)-3-(*tert*-Butyldiphenylsilyloxy)methyl-2-[(R)-(3,4-dimethoxyphenyl)(triethylsilyloxy)methyl]-4-(3,4-methylenedioxyphenyl)-4-butanolide (**22**).* To a solution of LDA (5.80 mmol) in THF (10 ml) was added a solution of **21** (2.29 g, 4.82 mmol) in THF (10 ml) at −70 °C, and then a solution of 3,4-dimethoxybenzaldehyde (0.88 g, 5.30 mmol) in THF (5 ml) was added. The reaction solution was stirred at −70 °C for 1 h before additions of sat. aq. NH_4Cl solution and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave an aldol product (3.04 g, 4.71 mmol, 98%) as a mixture of *erythro*/*threo* = 1/4. To an ice-cooled solution of this aldol product (3.04 g, 4.71 mmol) and 2,6-lutidine (1.10 ml, 9.44 mmol) in CH_2Cl_2 (20 ml) was added TESOTf (1.21 ml, 5.35 mmol). The resulting solution was stirred at room temperature for 30 min before addition of sat. aq. $NaHCO_3$ solution. The organic solution was separated, washed with sat. aq. $CuSO_4$ and sat. aq. $NaHCO_3$ solution, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (1% EtOAc in toluene) gave *threo*-**22** (2.20 g, 2.91 mmol, 62%) as a colorless oil, $[\alpha]^{20}_D$ +63 (*c* 0.8, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.47 (6H, q, *J* = 7.9 Hz), 0.81 (9H, t, *J* = 7.9 Hz), 1.00 (9H, s), 2.79 (1H, m), 3.04 (1H, dd, *J* = 5.1, 4.0 Hz),

3.24 (1H, dd, $J = 10.6$, 6.2 Hz), 3.67 (1H, dd, $J = 10.6$, 4.0 Hz), 3.84 (3H, s), 3.88 (3H, s), 4.82 (1H, d, $J = 7.5$ Hz), 5.29 (1H, d, $J = 4.0$ Hz), 5.93 (1H, d, $J = 3.9$ Hz), 5.94 (1H, d, $J = 3.9$ Hz), 6.60 (1H, d, $J = 9.5$ Hz), 6.70 (1H, s), 6.71 (1H, d, $J = 8.3$ Hz), 6.80 (1H, d, $J = 8.3$ Hz), 6.88 (1H, dd, $J = 8.3$, 1.8 Hz), 6.91 (1H, d, $J = 1.8$ Hz), 7.28–7.33 (6H, m), 7.35–7.43 (2H, m), 7.47 (2H, d, $J = 7.9$ Hz). NMR δ_C ($CDCl_3$): 4.6, 6.7, 19.0, 26.8, 43.5, 52.7, 55.77, 55.84, 62.9, 72.8, 81.8, 101.1, 106.8, 108.0, 109.3, 110.7, 118.3, 119.3, 127.5, 127.6, 129.6, 129.7, 129.9, 132.8, 132.9, 133.1, 135.5, 135.6, 147.1, 147.6, 148.6, 148.7, 176.0. Found: C, 68.62; H, 7.28. Calcd. for $C_{43}H_{54}O_8Si_2$: C, 68.38; H, 7.21%. *(2R,3R,4R)-[(S)]-(***22***).* $[\alpha]^{20}_D$ −63 (*c* 0.8, $CHCl_3$). Determination of the stereochemistry as *threo* form. To an ice-cooled solution of **22** (50 mg, 0.066 mmol) in THF (0.5 ml) was added 6 M aq. HCl solution (0.5 ml). After the reaction solution was stirred at 0 °C for 30 min, EtOAc was added. The organic solution was separated, washed with sat. aq. $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave a *threo* aldol product (37 mg, 0.058 mmol, 88%) as a colorless oil, $[\alpha]^{20}_D$ −44 (*c* 0.7, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.97 (9H, s), 2.72 (1H, m), 2.94 (1H, dd, $J = 7.3$, 7.3 Hz), 3.01 (2H, d, $J = 6.2$ Hz), 3.76 (3H, s), 3.77 (3H, s), 3.79 (1H, d, $J = 2.7$ Hz, OH), 4.96 (1H, dd, $J = 7.3$, 2.7 Hz, ArC*H*OH), 5.42 (1H, d, $J = 7.8$ Hz), 5.94 (2H, s), 6.54 (1H, d, $J = 8.2$ Hz), 6.64 (1H, dd, $J = 8.2$, 1.5 Hz), 6.69–6.73 (3H, m), 6.82 (1H, d, $J = 1.5$ Hz), 7.27–7.35 (6H, m), 7.37–7.44 (4H, m). NMR δ_C ($CDCl_3$): 19.0, 26.8, 44.6, 49.6, 55.7, 55.8, 62.5, 73.7, 81.9, 101.2, 106.8, 108.1, 109.1, 110.8, 119.0, 127.6, 127.7, 129.1, 129.75, 129.82, 132.4, 132.5, 132.7, 135.5, 147.5, 147.7, 149.0, 149.2, 177.7. Found: C, 69.24; H, 6.33. Calcd. for $C_{37}H_{40}O_8Si$: C, 69.35; H, 6.29%.

*(1*S*,2*S*,3*R*,4*R*)-2,3-Bis[(*tert*-butyldiphenylsilyloxy)methyl]-4-(3,4-dimethoxyphenyl)-4-(triethylsilyloxy)-1-(3,4-methylenedioxyphenyl)-1-butanol (***23***).* To an ice-cooled solution of $LiBH_4$ (2.65 g, 0.12 mol) in THF (40 ml) was added a solution of **22** (2.20 g, 2.91 mmol) in THF (10 ml), and then the resulting solution was stirred at 65 °C for 3 h before addition of sat. aq. NH_4Cl solution. After concentration of the mixture, the residue was dissolved in EtOAc and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration gave a crude diol. A reaction solution of crude diol, Et_3N (0.44 ml, 3.16 mmol), DMAP (29 mg, 0.24 mmol), and TBDPSCl (0.72 ml, 2.77 mmol) in CH_2Cl_2 (20 ml) was stirred at room temperature for 2 h before additions of H_2O and CH_2Cl_2. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/7) gave **23** (1.79 g, 1.79 mmol, 62%, 2 steps) as a colorless oil, $[\alpha]^{20}_D$ +43 (*c* 0.9, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.18–0.24 (6H, m), 0.63 (9H, t, $J = 7.9$ Hz), 1.00 (9H, s), 1.03 (9H, s), 2.09 (1H, m), 2.43 (1H, m), 3.62 (3H, s), 3.83 (3H, s), 3.83–3.88 (2H, m), 4.00 (2H, d, $J = 6.3$ Hz), 4.65 (1H, d, $J = 5.4$ Hz), 4.92 (1H, dd, $J = 4.0$, 1.3 Hz), 5.10 (1H, d, $J = 1.3$ Hz), 5.90 (1H, d, $J = 6.3$ Hz), 5.91 (1H, d, $J = 6.3$ Hz), 6.45 (1H, s), 6.55 (1H, d, $J = 8.2$ Hz), 6.59 (1H, d, $J = 8.2$ Hz), 6.65–6.70 (2H, m), 6.80 (1H, s), 7.21–7.42 (12H, m), 7.46 (2H, d, $J = 6.8$ Hz), 7.54–7.61 (6H, m). NMR δ_C ($CDCl_3$): 4.7, 6.7, 19.0, 19.1, 26.7, 26.9, 46.5, 48.2, 55.4, 55.7, 62.0, 64.6, 73.8, 77.2, 100.7, 107.3, 107.6, 109.4, 110.3, 118.8, 120.0, 127.4, 127.6, 129.5, 129.6, 132.7, 132.9, 133.0, 133.2, 135.4, 135.5, 135.6, 135.9, 137.5, 146.4, 147.5, 147.9, 148.3. Found: C, 70.95; H, 7.75. Calcd. for $C_{59}H_{76}O_8Si_3$: C, 71.03; H, 7.68%. *(1R,2R,3S,4S)-(***23***),* $[\alpha]^{20}_D$ −43 (*c* 1.3, $CHCl_3$).

*(1*R*,2*R*,3*S*,4*S*)-2,3-Bis[(*tert*-butyldiphenylsilyloxy)methyl]-1-(3,4-dimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)-1,4-butanediol (***24***).* To an ice-cooled solution of **23** (0.63 g, 0.63 mmol) in THF (2 ml) was added 6 M aq. HCl solution (2 ml). The resulting solution was stirred at 0 °C for 1 h before additions of sat. aq. $NaHCO_3$ solution and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave **24** (0.51 g, 0.58 mmol, 92%) as a colorless oil, $[\alpha]^{20}_D$ +9 (*c* 1.7, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.06 (9H, s), 1.07 (9H, s), 2.40 (2H, m), 3.75 (3H, s), 3.82–3.91 (4H, m), 3.90 (3H, s), 3.95 (2H, br. s), 4.77 (1H, br. d, $J = 5.3$ Hz), 4.84 (1H, br. d, $J = 6.5$ Hz), 5.95 (2H, s), 6.67 (1H, d, $J = 7.9$ Hz), 6.71 (2H, d, $J = 8.0$ Hz), 6.77 (1H, s), 6.80 (2H, s), 7.24–7.42 (8H, m), 7.33–7.42 (4H, m), 7.48–7.56 (8H, m). NMR δ_C ($CDCl_3$): 19.05, 19.10, 26.96, 26.99, 43.6, 55.6, 55.9, 61.55, 61.59, 72.7, 73.1, 100.9, 106.4, 107.8, 108.6, 110.9, 117.6, 118.8, 127.7, 127.75, 127.79, 129.9, 129.98, 130.03, 132.08, 132.11, 132.2, 132.3, 135.55, 135.61, 136.3, 137.7, 146.3, 147.6, 147.7, 148.8. EIMS *m/z*: 882 (M^+, 4), 448 (63), 432 (58), 199 (98), 135 (100). HRMS (EI) *m/z* (M^+): calcd. for $C_{53}H_{62}O_8Si_2$, 882.3983; found, 882.3982. *(1S,2S,3R,4R)-(***24***),* $[\alpha]^{20}_D$ −9 (*c* 1.2, $CHCl_3$).

*(7*R*,7′*R*,8*S*,8′*R*)-3′,4′-Dimethoxy-3,4-methylenedioxy-7,7′-epoxylignane-9,9′-diol ((+)-***3***).* To an ice-cooled solution of **24** (0.54 g, 0.61 mmol) and Et_3N (0.17 ml, 1.22 mmol) in CH_2Cl_2 (10 ml) was added MsCl (0.66 ml, 0.83 mmol). The reaction mixture was stirred at room temperature for 1 h before additions of sat. aq. $NaHCO_3$ solution and CH_2Cl_2. The organic solution was separated and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/6) gave tetrahydrofuran compound as a mixture of (7*R*,7′*R*) and (7*S*,7′*S*) (0.34 g, 0.39 mmol, 64%). To a solution of this mixture (0.34 g, 0.39 mmol) in THF (20 ml) was added TBAF (0.86 ml, 1 M in THF, 0.86 mmol). After the reaction solution was stirred at room temperature for 1 h, sat aq. NH_4Cl solution was added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) and chiral column (OD-H, 1 ml/min, 280 nm, 20% EtOH/hexane) gave desired (7*R*,7′*R*,8*S*,8′*R*)-(+)-**3**, (t_R 28 min, 62 mg, 0.16 mmol, 41%) and undesired (7*S*,7′*S*,8*S*,8′*R*)-**25** (t_R 13 min, 85 mg, 0.22 mmol, 56%). (7*R*,7′*R*,8*S*,8′*R*)-(+)-**3**, $[\alpha]^{20}_D$ +76 (*c* 0.2, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.04 (1H, br. s), 2.75 (2H, m), 3.07 (1H, br. s), 3.36 (1H, dd, $J = 10.0$, 2.0 Hz), 3.68 (1H, dd, $J = 10.0$, 9.6 Hz), 3.79–3.91 (2H, m), 3.88 (6H, s), 4.95 (1H, d, $J = 9.2$ Hz), 5.48 (1H, d, $J = 5.0$ Hz), 5.96 (2H, s), 6.78 (1H, d, $J = 7.9$ Hz), 6.83–7.00 (4H, m), 7.26 (1H, s). NMR δ_C ($CDCl_3$): 48.4, 54.4, 55.90. 55.94, 59.8, 81.1, 82.9, 101.0, 106.2, 108.2, 108.8, 111.1, 117.8, 119.4, 131.5, 136.6, 147.2, 148.0, 148.2, 149.0. EIMS *m/z*: 388 (M^+, 100), 191 (73), 174 (75). HRMS (EI) *m/z* (M^+): calcd. for $C_{21}H_{24}O_7$, 388.1522; found, 388.1521. *(7S,7′S,8R,8′S)-(−)-(***3***),* t_R 16 min, $[\alpha]^{20}_D$ −76 (*c* 0.2, $CHCl_3$).

*(7*R*,7′*R*,8*S*,8′*R*)-3′,4′,9,9′-Tetramethoxy-3,4-methylenedioxy-7,7′-epoxylignane ((+)-***4***).* To an ice-cooled suspension of NaH (13 mg, 60% oil suspension, 0.34 mmol) in THF (3 ml) was added (+)-**3** (60 mg, 0.15 mmol) in THF (2 ml). After the mixture was stirred at room temperature for 30 min, CH_3I (0.47 ml, 7.55 mmol) was added. The resulting reaction solution was stirred at room temperature for 16 h before additions of sat. aq. NH_4Cl solution and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave (+)-**4** (58 mg, 0.14 mmol, 93%) as a colorless oil, $[\alpha]^{20}_D$ +45 (*c* 0.4, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.66 (1H, m), 2.71 (1H, m), 3.08 (1H, dd, $J = 9.8$, 3.3 Hz), 3.11 (3H, s), 3.20 (1H, dd, $J = 9.8$, 3.9 Hz), 3.30 (3H, s), 3.45 (1H, dd, $J = 9.1$, 5.7 Hz), 3.62 (1H, dd, $J = 9.1$, 8.4 Hz), 3.89 (6H, s), 4.97 (1H, d, $J = 8.2$ Hz), 5.44 (1H, d, $J = 5.7$ Hz), 5.94 (2H, s), 6.77 (1H, d, $J = 8.1$ Hz), 6.83–6.89 (3H, m), 6.93 (1H, s), 7.03 (1H, s). NMR δ_C ($CDCl_3$): 46.3, 51.7, 55.8, 55.9, 58.5, 58.8, 69.2, 70.4, 82.7, 83.5, 100.9, 106.5, 108.0, 109.6, 110.6, 118.5, 119.4, 132.2, 137.6, 146.9, 147.8, 148.0, 148.6. EIMS *m/z*: 416 (M^+, 72), 208 (86), 173 (100). HRMS (EI) *m/z* (M^+): calcd. for $C_{23}H_{28}O_7$, 416.1835; found, 416.1837. >99% ee (HPLC, DAICEL OD-H chiral column, detected at 280 nm, 1 ml min^{-1}, 10% EtOH in hexane, t_R 26 min). *(7S,7′S,8R,8′S)-(−)-***4**, $[\alpha]^{20}_D$ −45 (*c* 0.1, $CHCl_3$), >99% ee, t_R 11 min.

*(*S*)-4-Benzyl-3-{(*S*)-2-[(*S*)-(3,4-dimethoxyphenyl)(triethylsilyloxy)-methyl]-4-pentenoyl}-2-oxazolidinone (***27***).* To an ice-cooled solution of **26** (8.33 g, 20.0 mmol) and 2,6-lutidine (4.51 ml, 38.7 mmol) in CH_2Cl_2 (70 ml) was added TESOTf (6.53 ml, 28.9 mmol). After the reaction solution was stirred at 0 °C for 30 min, sat. aq. $NaHCO_3$ solution was added. The organic solution was separated, washed with sat. aq. $CuSO_4$ solution and sat. aq. $NaHCO_3$ solution, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/5) gave **27** (10.4 g, 19.3 mmol, 97%) as a colorless oil, $[\alpha]^{20}_D$ −79 (*c* 1.1, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.41–0.56 (6H, m), 0.87 (9H, t, $J = 7.8$ Hz), 2.60 (1H, dd, $J = 13.3$, 9.8 Hz), 2.66 (1H, m), 2.74 (1H, m), 3.11 (1H, dd, $J = 13.3$, 3.2 Hz), 3.52 (1H, dd,

J = 8.7, 8.3 Hz), 3.83 (3H, s), 3.87 (3H, s), 3.89 (1H, dd, J = 8.7, 1.7 Hz), 4.15 (1H, m), 4.49 (1H, m), 4.70 (1H, d, J = 8.3 Hz), 5.02 (1H, d, J = 10.3 Hz), 5.12 (1H, d, J = 17.1 Hz), 5.87 (1H, m), 6.12 (1H, d, J = 7.8 Hz), 6.78 (1H, d, J = 8.3 Hz), 6.98 (1H, s), 7.13–7.15 (2H, m), 7.21–7.31 (3H, m). NMR δ_C ($CDCl_3$): 4.7, 6.7, 33.9, 37.9, 51.4, 55.7, 55.78, 55.81, 65.6, 76.5, 109.7, 110.0, 116.7, 119.0, 127.2, 128.8, 129.4, 135.2, 135.3, 135.6, 148.4, 148.6, 152.8, 173.7. Found: C, 66.98; H, 7.70; N 2.63. Calcd. for $C_{30}H_{41}O_6NSi$: C, 66.76; H, 7.66; N, 2.60%. *(R)-[(R)-[(R)]]-(**27**)*, $[\alpha]^{20}_D$ +81 (*c* 1.8, $CHCl_3$).

*(*R*)-2-[(*S*)-(3,4-Dimethoxyphenyl)(triethylsilyloxy)methyl]-4-penten-1-ol (**28**).* To an ice-cooled solution of $LiBH_4$ (1.68 g, 77.1 mmol) and MeOH (1.59 ml) in THF (50 ml) was added **27** (10.4 g, 19.3 mmol) in THF (50 ml), and then the reaction solution was stirred at room temperature for 30 min before addition of sat. aq. NH_4Cl solution. After concentration, the residue was dissolved in EtOAc and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/4) gave **28** (2.90 g, 7.91 mmol, 41%) as a colorless oil, $[\alpha]^{20}_D$ −39 (*c* 1.3, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.45–0.60 (6H, m), 0.89 (9H, t, J = 8.1 Hz), 1.86 (1H, m), 2.00–2.13 (2H, m), 2.76 (1H, br. s), 3.47 (1H, dd, J = 11.0, 3.7 Hz), 3.59 (1H, dd, J = 11.0, 7.6 Hz), 3.88 (3H, s), 3.89 (3H, s), 4.84 (1H, d, J = 4.9 Hz), 5.02–5.06 (2H, m), 5.78 (1H, m), 6.80–6.85 (2H, m), 6.92 (1H, d, J = 1.5 Hz). NMR δ_C ($CDCl_3$): 4.6, 6.7, 31.8, 47.4, 55.7, 55.8, 63.0, 76.7, 109.9, 110.4, 116.3, 119.0, 134.5, 137.0, 148.2, 148.6. Found: C, 65.81; H, 9.46. Calcd. for $C_{20}H_{34}O_4Si$: C, 65.53; H, 9.35%. *(S)-[(R)]-**28***, $[\alpha]^{20}_D$ +40 (*c* 1.5, $CHCl_3$).

*(*R*)-3-[(*S*)-(3,4-Dimethoxyphenyl)(triethylsilyloxy)methyl]-4-butanolide (**29**).* A reaction solution of **28** (2.70 g, 7.37 mmol), NMO (1.15 g, 9.82 mmol), and OsO_4 (1.5 ml, 2% aq. solution) in acetone (60 ml), *tert*-BuOH (15 ml), and H_2O (15 ml) was stirred at room temperature for 16 h before addition of sat. aq. $Na_2S_2O_3$ solution. After concentration, the residue was dissolved in H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration gave a crude glycol. A reaction mixture of this crude glycol and $NaIO_4$ (2.05 g, 9.58 mmol) in MeOH (150 ml) was stirred at room temperature for 1 h before concentration. The residue was dissolved in EtOAc and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration gave a crude hemiacetal. A reaction mixture of this hemiacetal, PCC (2.06 g, 9.56 mmol), and MS 4A (0.5 g) in CH_2Cl_2 (150 ml) was stirred at room temperature for 16 h before addition of ether. After filtration, the filtrate was concentrated, and then the residue was applied to silica gel column chromatography (EtOAc/hexane = 1/4) to give **29** (1.91 g, 5.21 mmol, 71%, 3 steps) as a colorless oil, $[\alpha]^{20}_D$ −67 (*c* 1.0, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.46–0.56 (6H, m), 0.87 (9H, t, J = 8.1 Hz), 2.48 (1H, dd, J = 17.8, 8.8 Hz), 2.65 (1H, dd, J = 17.8, 6.8 Hz), 2.79 (1H, m), 3.88 (6H, s), 4.07 (1H, dd, J = 9.3, 6.1 Hz), 4.18 (1H, dd, J = 9.3, 6.8 Hz), 4.58 (1H, d, J = 5.9 Hz), 6.78 (1H, dd, J = 8.3, 2.0 Hz), 6.82 (1H, d, J = 8.3 Hz), 6.84 (1H, d, J = 1.5 Hz). NMR δ_C ($CDCl_3$): 4.7, 6.7, 30.4, 44.2, 55.8, 70.1, 75.1, 108.9, 110.8, 118.3, 134.8, 148.7, 149.1, 177.0. Found: C, 62.17; H, 8.11. Calcd. for $C_{19}H_{30}O_5Si$: C, 62.26; H, 8.25%. *(S)-[(R)]-(**29**)*, $[\alpha]^{20}_D$ +68 (*c* 1.0, $CHCl_3$).

*(1*S*,2*R*,3*R*,4*S*)-2,3-Bis[(*tert*-butyldiphenylsilyloxy)methyl]-4-(3,4-dimethoxyphenyl)-1-(3,4-methylenedioxyphenyl)-4-(triethylsilyloxy)-1-butanol (**30**) and (1*R*,2*R*,3*R*,4*S*)-2,3-bis[(*tert*-butyldiphenylsilyloxy)-methyl]-4-(3,4-dimethoxyphenyl)-1-(3,4-methylenedioxyphenyl)-4-(triethylsilyloxy)-1-butanol (**31**).* To a solution of KHMDS (12.2 ml, 0.5 M in toluene, 6.10 mmol) in THF (10 ml) was added a solution of **29** (1.91 g, 5.21 mmol) in THF (5 ml) and a solution of piperonal (0.87 g, 5.79 mmol) in THF (5 ml) at −70 °C. The resulting reaction solution was stirred at −70 °C for 1 h before additions of sat. aq. NH_4Cl solution and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave a 5/1 mixture of an *erythro*/*threo*-aldol product (2.45 g, 4.74 mmol, 91%). To a solution of $LiBH_4$ (0.80 g, 36.7 mmol) in THF (20 ml) was added a solution of this aldol mixture (2.45 g, 4.74 mmol) in THF (40 ml) at 0 °C. After the reaction mixture was stirred at 0 °C for 16 h, sat. aq. NH_4Cl solution was added. After concentration of the mixture, the residue was dissolved in H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration gave a crude triol. A reaction solution of this crude triol, Et_3N (1.57 ml, 11.3 mmol), DMAP (49 mg, 0.40 mmol), and TBDPSCl (2.42 ml, 9.31 mmol) in CH_2Cl_2 (5 ml) was stirred at room temperature for 3 h before additions of H_2O and CH_2Cl_2. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/9 and 1/4) gave (1*S*,2*R*,3*R*,4*S*)-isomer **30** (3.21 g, 3.21 mmol, 67%, 2 steps) as a colorless oil and (1*R*,2*R*,3*R*,4*S*)-isomer **31** (0.69 g, 0.69 mmol, 15%, 2 steps) as a colorless oil. *(1S,2R,3R,4S)* isomer **30**, $[\alpha]^{20}_D$ −40 (*c* 1.2, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.21–0.27 (6H, m), 0.65 (9H, t, J = 8.1 Hz), 1.02 (9H, s), 1.07 (9H, s), 2.01 (1H, m), 2.36 (1H, m), 3.59 (1H, dd, J = 10.3, 6.3 Hz), 3.62–3.66 (1H, overlapped), 3.64 (3H, s), 3.84 (3H, s), 3.88 (1H, dd, J = 9.3, 4.4 Hz), 4.04 (1H, dd, J = 9.3, 8.8 Hz), 4.31 (1H, d, J = 5.9 Hz), 4.62 (1H, d, J = 3.9 Hz), 5.18 (1H, br. s), 5.93 (1H, d, J = 15.9 Hz), 5.94 (1H, d, J = 15.9 Hz), 6.21 (1H, s), 6.35 (1H, s), 6.49 (1H, d, J = 8.3 Hz), 6.58–6.61 (3H, m), 7.25–7.30 (2H, m), 7.34–7.44 (10H, m), 7.56–7.65 (6H, m), 7.69–7.72 (2H, m). NMR δ_C ($CDCl_3$): 4.5, 6.7, 19.0, 19.2, 26.8, 26.9, 44.5, 44.9, 55.2, 55.5, 63.5, 63.8, 72.3, 74.7, 100.8, 106.1, 107.1, 108.4, 109.9, 118.0, 118.4, 127.6, 127.69, 127.72, 129.5, 129.6, 129.7, 129.8, 132.5, 132.8, 133.3, 133.7, 135.5, 135.55, 135.64, 135.7, 138.2, 145.6, 147.1, 147.6, 148.2. Found: C, 69.79; H, 7.55. Calcd. for $C_{59}H_{76}O_8Si_3$: C, 71.04; H, 7.68%. (1*R*,2*S*,3*S*,4*R*)-**30**, $[\alpha]^{20}_D$ +39 (*c* 1.8, $CHCl_3$). *(1R,2R,3R,4S)* isomer **31**, $[\alpha]^{20}_D$ −67 (*c* 1.1, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.21 (6H, q, J = 7.8 Hz), 0.60 (9H, t, J = 7.8 Hz), 0.91 (9H, s), 0.94 (9H, s), 1.56 (1H, m), 2.26 (1H, m), 3.48 (1H, dd, J = 10.3, 8.3 Hz), 3.54–3.58 (1H, overlapped), 3.55 (3H, s), 3.77 (3H, s), 3.92 (1H, dd, J = 9.8, 7.6 Hz), 4.08 (1H, dd, J = 9.8, 4.4 Hz), 4.39 (1H, s), 4.50 (1H, d, J = 8.8 Hz), 4.80 (1H, d, J = 3.4 Hz), 5.81 (1H, d, J = 20.0 Hz), 5.82 (1H, d, J = 20.0 Hz), 6.17–6.20 (3H, m), 6.42 (1H, d, J = 7.8 Hz), 6.51 (1H, d, J = 7.8 Hz), 6.57 (1H, d, J = 8.3 Hz), 7.23–7.30 (8H, m), 7.31–7.37 (4H, m), 7.45–7.49 (4H, m), 7.51–7.56 (4H, m). NMR δ_C ($CDCl_3$): 4.7, 6.8, 19.0, 19.1, 26.86, 26.93, 43.1, 48.8, 55.2, 55.7, 62.1, 65.3, 73.4, 77.8, 100.9, 106.8, 107.0, 108.5, 110.2, 113.6, 118.1, 120.9, 127.6, 127.70, 127.72, 129.6, 129.8, 132.76, 132.81, 133.2, 133.4, 135.57, 135.65, 135.70, 136.2, 137.0, 146.5, 147.5, 147.7, 148.4. Found: C, 71.51; H, 7.74. Calcd. for $C_{59}H_{76}O_8Si_3$: C, 71.04; H, 7.68%. *(1S,2S,3S,4R)-isomer**31***, $[\alpha]^{20}_D$ +65 (*c* 1.7, $CHCl_3$).

*(1*S*,2*R*,3*R*,4*S*)-2,3-Bis[(*tert*-butyldiphenylsilyloxy)methyl]-1-(3,4-dimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)-1,4-butanediol (**32**) and (1*S*,2*R*,3*R*,4*R*)-2,3-bis[(*tert*-butyldiphenylsilyloxy)methyl]-1-(3,4-dimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)-1,4-butanediol (**33**).* To an ice-cooled solution of (1*S*,2*R*,3*R*,4*S*)-**30** (0.12 g, 0.12 mmol) in THF (2 ml) was added 6 M aq. HCl solution (1 ml). After the reaction solution was stirred at room temperature for 10 min, sat. aq. $NaHCO_3$ solution and EtOAc were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/4) gave (1*S*,2*R*,3*R*,4*S*)-**32** (77 mg, 0.087 mmol, 73%) as colorless crystals, mp 166–168 °C (20% EtOAc in hexane), $[\alpha]^{20}_D$ +28 (*c* 1, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.06 (9H, s), 1.08 (9H, s), 2.31 (1H, m), 2.36 (1H, m), 3.67 (3H, s), 3.84 (1H, dd, J = 10.9, 4.9 Hz), 3.87 (3H, s), 4.00 (1H, dd, J = 10.9, 2.9 Hz), 4.05 (2H, d, J = 6.7 Hz), 4.60–4.68 (2H, m), 5.93 (1H, d, J = 20.5 Hz), 5.94 (1H, d, J = 20.5 Hz), 6.20 (1H, s), 6.34 (1H, s), 6.46 (1H, d, J = 8.0 Hz), 6.54–6.55 (2H, m), 6.67 (1H, d, J = 8.3 Hz), 7.35–7.41 (8H, m), 7.43–7.47 (4H, m), 7.65–7.67 (8H, m). NMR δ_C ($CDCl_3$): 19.0, 19.1, 26.8, 44.95, 45.03, 55.2, 55.7, 64.6, 64.8, 73.7, 73.8, 101.0, 106.0, 107.3, 108.4, 110.4, 117.7, 118.6, 127.8, 127.9, 129.95, 130.01, 132.35, 132.38, 132.5, 135.50, 135.54, 135.59, 135.63, 135.8, 137.3, 146.1, 147.3, 147.6, 148.5. EIMS m/z: 882 (M^+, 4), 551 (50), 199 (100). HRMS (EI) m/z (M^+): calcd. for $C_{53}H_{62}O_8Si_2$, 882.3983; found, 882.3985. (1*R*,2*S*,3*S*,4*R*)-**32**, $[\alpha]^{20}_D$ −28 (*c* 0.6, $CHCl_3$). (1*S*,2*R*,3*R*,4*R*)-isomer **33**. Diol **33** was obtained from **31** in 78% yield as a colorless oil, $[\alpha]^{20}_D$ −18 (*c* 1.1, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.02 (9H, s), 1.03 (9H, s), 2.21 (1H, m), 2.31 (1H, m), 3.71 (3H, s), 3.82–3.92 (4H, m), 3.90 (3H, s), 3.94 (1H, br. s), 4.05 (1H, br. s), 4.49 (1H, d, J = 5.4 Hz), 4.83 (1H, br. s), 5.89 (2H, s), 6.33–6.35 (2H, m), 6.54 (1H, d, J = 8.3 Hz), 6.67 (1H, s), 6.72 (1H, d, J = 8.1 Hz), 6.80 (1H, d, J = 8.2 Hz), 7.25–7.49 (14H, m), 7.59–7.64 (6H, m). NMR δ_C ($CDCl_3$): 18.96, 19.0, 26.7, 26.8, 45.3, 49.8, 55.5,

56.0, 62.2, 63.8, 73.2, 77.2, 100.8, 106.5, 107.4, 108.8, 110.9, 117.8, 119.5, 127.7, 127.8, 129.8, 129.91, 129.93, 132.16, 132.22, 132.6, 132.7, 135.32, 135.53, 135.6, 136.3, 136.8, 146.4, 147.4, 147.8, 148.8. EIMS *m/z*: 882 (M^+, 1), 551 (50), 199 (100), 135 (71). HRMS (EI) *m/z* (M^+): calcd. for $C_{53}H_{62}O_8Si_2$, 882.3983; found, 882.3980.

*(7S,7′S,8R,8′R)-9,9′-Bis[(*tert*-butyldiphenylsilyloxy)methyl]-3′,4′-dimethoxy-3,4-methylenedioxy-7,7′-epoxylignane (**34**).* Method A. A reaction solution of (1*S*,2*R*,3*R*,4*S*)-**32** (49 mg, 0.055 mmol) and CSA (5 mg, 0.022 mmol) in CH_2Cl_2 (10 ml) was stirred at room temperature for 18 h before addition of a few drops of Et_3N. After concentration of the mixture, the residue was applied to silica gel column chromatography (EtOAc/hexane = 1/6) to give **34** (46 mg, 0.053 mmol, 96%) as a colorless oil. Method B. To an ice-cooled solution of (1*S*,2*R*,3*R*,4*S*)-**30** (1.06 g, 1.06 mmol) and Et_3N (0.16 ml, 1.15 mmol) in benzene (10 ml) was added MsCl (0.089 ml, 1.15 mmol). After the reaction mixture was stirred at 0 °C for 1 h, ether and H_2O were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After concentration, the residue was dissolved in THF (10 ml). To this solution was added *n*-Bu_4NF (1.17 ml, 1 M in THF, 1.17 mmol) at −10 °C. After the reaction solution was stirred at −10 °C for 1 h, sat. aq. NH_4Cl solution and EtOAc were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/9) gave **34** (0.17 g, 0.20 mmol, 19%). From (1*R*,2*R*,3*R*,4*S*)-**31**, **34** was obtained in 15% yield. $[\alpha]^{20}_D$ −25 (*c* 1.0, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.011 (9H, s), 1.014 (9H, s), 2.44 (2H, m), 3.60–3.67 (4H, m), 3.80 (3H, s), 3.87 (3H, s), 5.15 (1H, d, *J* = 7.8 Hz), 5.18 (1H, d, *J* = 7.8 Hz), 5.93 (2H, s), 6.71 (2H, s), 6.77 (1H, d, *J* = 8.3Hz), 6.83 (1H, dd, *J* = 8.3, 1.5 Hz), 6.88 (1H, s), 6.94 (1H, d, *J* = 1.5 Hz), 7.25–7.41 (16H, m), 7.52–7.60 (4H, m). NMR δ_C ($CDCl_3$): 19.27, 19.31, 26.9, 51.8, 52.1, 55.7, 55.9, 61.3, 61.5, 82.3, 82.4, 100.9, 106.7, 107.9, 109.2, 110.9, 118.7, 119.7, 127.67, 127.69, 127.7, 129.68, 129.71, 129.8, 133.2, 133.4, 135.2, 135.5, 135.58, 135.61, 136.9, 146.8, 147.8, 148.4, 149.1. EIMS *m/z*: 864 (M^+, 29), 551 (56), 253 (68), 197 (56), 135 (100). HRMS (EI) *m/z* (M^+): calcd. for $C_{53}H_{60}O_7Si_2$, 864.3877; found, 864.3878. *(7R,7′R,8S,8′S)*-**34**, $[\alpha]^{20}_D$ +25 (*c* 0.8, $CHCl_3$).

*(7S,7′S,8R,8′R)-3′,4′-Dimethoxy-3,4-methylenedioxy-7,7′-epoxylignane-9,9′-diol ((−)-**5**).* A reaction solution of **34** (99 mg, 0.11 mmol) and TBAF (0.25 ml, 1 M in THF, 0.25 mmol) in THF (5 ml) was stirred at room temperature for 2 h before additions of sat. aq. NH_4Cl solution and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 2/1) gave (−)-**5** (37 mg, 0.095 mmol, 86%) as a colorless oil, $[\alpha]^{20}_D$ −54 (*c* 0.7, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.25 (2H, m), 3.55 (2H, br. dd, *J* = 10.1, 7.9 Hz), 3.73 (2H, br. d, *J* = 10.1 Hz), 3.77–3.89 (2H, br.), 3.86 (3H, s), 3.89 (3H, s), 4.70 (1H, d, *J* = 8.3 Hz), 4.72 (1H, d, *J* = 7.1 Hz), 5.95 (2H, s), 6.78 (2H, s), 6.85 (2H, d, *J* = 7.9 Hz), 6.91 (2H, d, *J* = 6.2 Hz). NMR δ_C ($CDCl_3$): 55.92, 56.86, 57.2, 62.7, 62.8, 83.1, 83.2, 101.1, 106.6, 108.1, 109.4, 111.0, 118.8, 119.8, 133.8, 135.6, 147.3, 148.0, 148.8, 149.2. EIMS *m/z*: 388 (M^+, 100), 194 (61), 174 (55). HRMS (EI) *m/z* (M^+): calcd. for $C_{21}H_{24}O_7$, 388.1522; found, 388.1521. *(7R,7′R,8S,8′S)*-(+)-**5**, $[\alpha]^{20}_D$ +54 (*c* 1.1, $CHCl_3$).

*(7S,7′S,8R,8′R)-3′,4′,9,9′-Tetramethoxy-3,4-methylenedioxy-7,7′-epoxylignane ((−)-**6**).* To an ice-cooled suspension of NaH (9 mg, 60% in oil, 0.23 mmol) in THF (5 ml) was added a solution of (−)-**5** (40 mg, 0.10 mmol) in THF (2 ml). After the mixture was stirred at room temperature for 30 min, CH_3I (0.32 ml, 5.14 mmol) was added, and then the reaction solution was stirred at room temperature for 16 h before additions of sat. aq. NH_4Cl solution and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave (−)-**6** (38 mg, 0.091 mmol, 91%) as a colorless oil, $[\alpha]^{20}_D$ −27 (*c* 0.9, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.36 (2H, m), 3.33 (6H, s), 3.42–3.46 (2H, m), 3.48 (2H, dd, *J* = 9.5, 5.1 Hz), 3.87 (3H, s), 3.90 (3H, s), 4.95 (1H, d, *J* = 7.8 Hz), 4.97 (1H, d, *J* = 9.0 Hz), 5.94 (2H, s), 6.77 (1H, d, *J* = 7.9 Hz), 6.84 (1H, d, *J* = 8.3 Hz), 6.88 (1H, dd, *J* = 8.3, 1.6 Hz), 6.94 (1H, dd, *J* = 8.3, 1.9 Hz), 6.97 (1H, d, *J* = 1.6 Hz), 7.00 (1H, d, *J* = 1.9 Hz). NMR δ_C ($CDCl_3$): 51.0, 51.3, 55.86, 55.89, 59.00, 72.26, 72.33, 82.76, 82.82, 100.89, 106.7, 108.0, 109.4, 110.9, 118.5, 119.6, 134.9, 136.6, 146.8, 147.8, 148.4, 149.0. EIMS *m/z*: 416 (M^+, 100), 208 (93). HRMS (EI) *m/z* (M^+): calcd. for $C_{23}H_{28}O_7$, 416.1835; found, 416.1835. >99% ee (HPLC, DAICEL OD-H chiral column, detected at 280 nm, 1 ml min^{-1}, 5% EtOH in hexane, t_R 13 min). *(7R,7′R,8S,8′S)*-(+)-**6**, $[\alpha]^{20}_D$ +27 (*c* 0.8, $CHCl_3$), >99% ee (HPLC, DAICEL OD-H chiral column, detected at 280 nm, 1 ml min^{-1}, 5% EtOH in hexane, t_R 15 min).

*(2S,5S)-2-(3,4-Dimethoxyphenyl)-5-(3,4-methylenedioxyphenyl) tetrahydrofuran-3,4-diylidene (**35**).* To an ice-cooled solution of (7*S*,7′*S*,8*S*,8′*R*)-**25** (0.25 g, 0.64 mmol) and Et_3N (0.36 ml, 2.58 mmol) in CH_2Cl_2 (10 ml) was added MsCl (0.19 ml, 2.45 mmol). After the resulting reaction mixture was stirred at room temperature for 30 min, H_2O and CH_2Cl_2 were added. The organic solution was separated and dried (Na_2SO_4). After concentration, a reaction mixture of the residue, NaI (0.29 g, 1.93 mmol), and DBU (0.19 ml, 1.27 mmol) in DMF (8 ml) was stirred at 80 °C for 3 h before additions of H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave unstable **35** (0.13 g, 0.37 mmol, 58%) as a colorless oil. NMR δ_H ($CDCl_3$): 3.88 (3H, s), 3.89 (3H, s), 4.89 (2H, s), 5.53 (1H, s), 5.57 (1H, s), 5.62 (2H, s), 5.95 (2H, s), 6.78 (1H, d, *J* = 7.8 Hz), 7.83–6.89 (3H, m), 6.92–6.94 (2H, m). NMR δ_C ($CDCl_3$): 55.9, 82.7, 82.8, 101.0, 106.0, 106.1, 106.2, 107.6, 108.0, 110.3, 110.8, 119.7, 120.9, 133.5, 135.2, 147.3, 147.7, 147.8, 148.9, 149.1. EIMS *m/z*: 352 (M^+, 47), 219 (100). HRMS (EI) *m/z* (M^+): calcd. for $C_{21}H_{20}O_5$, 352.1311; found, 352.1310. From diol (−)-**5**, **35** was obtained in 52% yield.

*(7S,7′S,8S,8′S)-3′,4′-Dimethoxy-3,4-methylenedioxylignane-9,9′-diol ((−)-**7**).* To an ice-cooled solution of **35** (0.15 g, 0.43 mmol) in THF (10 ml) was added $BH_3{\cdot}SMe_2$ (0.20 ml, 2.11 mmol). The reaction solution was stirred at room temperature for 1 h, and then H_2O_2 and sat. aq. $NaHCO_3$ solution were added. After the mixture was stirred at room temperature for 2 h, $CHCl_3$ was added. The organic solution was separated and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 3/2) gave (−)-**7** (78 mg, 0.20 mmol, 47%) as a colorless oil, $[\alpha]^{20}_D$ −22 (*c* 0.2, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.02 (1H, br. s), 2.29 (1H, br. s), 2.73 (2H, m), 3.13–3.20 (2H, m), 3.56 (2H, dd, *J* = 11.3, 2.3 Hz), 3.89 (3H, s), 3.91 (3H, s), 5.52 (1H, d, *J* = 6.2 Hz), 5.54 (1H, d, *J* = 6.9 Hz), 5.97 (2H, s), 6.79 (2H, s), 6.84–6.87 (4H, m). NMR δ_C ($CDCl_3$): 49.0, 49.1, 56.0, 62.71, 62.74, 82.55, 82.62, 101.1, 106.7, 108.1, 109.4, 111.0, 118.3, 119.3, 132.9, 134.4, 147.0, 147.8, 148.9. EIMS *m/z*: 388 (M^+, 55), 194 (100). HRMS (EI) *m/z* (M^+): calcd. for $C_{21}H_{24}O_7$, 388.1522; found, 388.1524. *(7R,7′R,8R,8′R)*-(+)-**7**, $[\alpha]^{20}_D$ +22 (*c* 0.1, $CHCl_3$)

*(7S,7′S,8S,8′S)-3′,4′,9,9′-Tetramethoxy-3,4-methylenedioxy-7,7′-epoxylignane ((−)-**8**).* To an ice-cooled suspension of NaH (30 mg, 60% in oil, 0.75 mmol) in THF (5 ml) was added a solution of (+)-**7** (30 mg, 0.077 mmol) in THF (10 ml). After the mixture was stirred at room temperature for 30 min, CH_3I (0.20 ml, 3.21 mmol) was added. The reaction solution was stirred at room temperature for 16 h, and then sat. aq. NH_4Cl solution and EtOAc were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/2) gave (−)-**8** (32 mg, 0.077 mmol, 100%) as a colorless oil, $[\alpha]^{20}_D$ −23 (*c* 0.3, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.74 (2H, m), 2.81–2.87 (2H, m), 3.14–3.18 (2H, overlapped), 3.16 (3H, s), 3.18 (3H, s), 3.89 (3H, s), 3.90 (3H, s), 5.53 (1H, d, *J* = 4.8 Hz), 5.54 (1H, d, *J* = 6.2 Hz), 5.96 (2H, s), 6.78–6.81 (2H, m), 6.84–6.90 (4H, m). NMR δ_C ($CDCl_3$): 45.3, 45.4, 55.85, 55.89, 58.7, 71.8, 82.29, 82.31, 100.9, 107.0, 107.9, 109.6, 110.7, 118.5, 119.5, 132.8, 134.3, 145.6, 147.5, 148.1, 148.6. EIMS *m/z*: 416 (M^+, 15), 208 (100). HRMS (EI) *m/z* (M^+): calcd. for $C_{23}H_{28}O_7$, 416.1835; found, 416.1836. >99% ee (HPLC, DAICEL OD-H chiral column, detected at 280 nm, 1 ml min^{-1}, 5% EtOH in hexane, t_R 14 min). *(7R,7′R,8R,8′R)*-(+)-**8**, $[\alpha]^{20}_D$ +23 (*c* 0.2, $CHCl_3$), >99% ee, t_R 22 min.

*(2S,5R)-2-(3,4-Dimethoxyphenyl)-5-(3,4-methylenedioxyphenyl)-tetrahydrofuran-3,4-diylidene (**37**).* A reaction solution of **36** (0.19 g, 0.49 mmol) and TsCl (0.47 g, 2.47 mmol) in pyridine (3 ml) was stirred

at room temperature for 1 h before additions of H_2O and EtOAc. The organic solution was separated, washed with 1 M aq. HCl solution, sat. aq. $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). After concentration, a reaction solution of the residue, NaI (0.22 g, 1.47 mmol), and DBU (0.15 ml, 1.00 mmol) in DMF (10 ml) was stirred at 80 °C for 3 h before additions of H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/4) gave **37** (60 mg, 0.17 mmol, 34%, 2 steps) as a colorless oil, $[\alpha]^{20}_D$ +4 (*c* 0.7, $CHCl_3$). NMR δ_H ($CDCl_3$): 3.887 (3H, s), 3.889 (3H, s), 4.68 (2H, m), 5.35 (2H, m), 5.52 (1H, d, J = 3.9 Hz), 5.53 (1H, d, J = 2.9 Hz), 5.96 (2H, s), 6.80 (1H, d, J = 8.3 Hz), 6.86–6.93 (4H, m), 6.98 (1H, dd, J = 8.3, 1.9 Hz). NMR δ_C ($CDCl_3$): 55.85, 55.91, 83.39, 83.52, 101.1, 105.8, 107.9, 108.1, 110.89, 110.92, 113.7, 120.6, 121.9, 133.0, 134.6, 147.6, 147.9, 148.9, 149.0, 149.05, 149.09. EIMS *m/z*: 352 (M^+, 2), 154 (100), 136 (62). HRMS (EI) *m/z* (M^+): calcd. for $C_{21}H_{20}O_5$, 352.1311; found, 352.1309. *(2R,3S)-**37***, $[\alpha]^{20}_D$ −4 (*c* 1.1, $CHCl_3$).

*(7R,7′S,8R,8′S)-3′,4′-Dimethoxy-3,4-methylenedioxy-7,7′-epoxylignane-9,9′-diol ((+)-**9**).* To an ice-cooled solution of **37** (60 mg, 0.17 mmol) in THF (2 ml) was added $BH_3 \cdot SMe_2$ (0.08 ml, 0.84 mmol). The reaction solution was stirred at room temperature for 30 min. After additions of sat. aq. $NaHCO_3$ solution (4 ml) and 30% aq. H_2O_2 solution (4 ml), the resulting mixture was stirred at room temperature for 2 h, and then EtOAc was added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave (+)-**9** (32 mg, 0.083 mmol, 49%) as a colorless oil, $[\alpha]^{20}_D$ +3 (*c* 0.6, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.66 (1H, br. s), 2.66 (1H, br. s), 2.93 (2H, m), 3.39 (2H, dd, J = 11.3, 3.7 Hz), 3.49 (2H, dd, J = 11.3, 11.3 Hz), 3.89 (3H, s), 3.90 (3H, s), 5.12 (1H, d, J = 5.1 Hz), 5.13 (1H, d, J = 6.5 Hz), 5.98 (2H, s), 6.81 (1H, d, J = 8.1 Hz), 6.86–6.89 (3H, m), 6.93 (1H, s), 6.97 (1H, d, J = 8.1 Hz). NMR δ_C ($CDCl_3$): 48.0, 48.1, 55.92, 55.94, 60.88, 60.91, 80.95, 80.98, 101.1, 106.6, 108.2, 109.4, 111.2, 118.2, 119.3, 131.3, 132.8, 146.9, 147.8, 148.4, 148.9. EIMS *m/z*: 388 (M^+, 100), 222 (65), 191 (77), 174 (76). HRMS (EI) *m/z* (M^+): calcd. for $C_{21}H_{24}O_7$, 388.1522; found, 388.1524. *(7S,7′R,8S,8′R)-(−)-**9***, $[\alpha]^{20}_D$ −3 (*c* 0.7, $CHCl_3$).

*(7R,7′S,8R,8′S)-3′,4′,9,9′-Tetramethoxy-3,4-methylenedioxy-7,7′-epoxylignane ((+)-**10**).* To an ice-cooled suspension of NaH (16 mg, 60% in oil, 0.39 mmol) was added (+)-**9** (14 mg, 0.036 mmol) in THF (1 ml), and then the mixture was stirred at room temperature for 30 min. After addition of CH_3I (0.11 ml, 1.77 mmol), the resulting reaction solution was stirred at room temperature for 10 h, and then H_2O and EtOAc were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave (+)-**10** (12 mg, 0.029 mmol, 81%) as a colorless oil, $[\alpha]^{20}_D$ +6 (*c* 0.4, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.85 (2H, m), 3.01 (2H, dd, J = 9.6, 6.1 Hz), 3.045 (3H, s), 3.051 (3H, s), 3.25 (2H, dd, J = 9.6, 6.1 Hz), 3.90 (3H, s), 3.91 (3H, s), 5.15 (1H, d, J = 6.8 Hz), 5.17 (1H, d, J = 7.0 Hz), 5.97 (2H, s), 6.81 (1H, d, J = 8.1 Hz), 6.88 (1H, d, J = 8.2 Hz), 6.93 (1H, d, J = 8.1 Hz), 7.02 (1H, d, J = 8.2 Hz), 7.03 (1H, s), 7.06 (1H, s). NMR δ_C ($CDCl_3$): 46.46, 46.50, 55.8, 55.9, 58.4, 70.08, 70.11, 81.4, 81.5, 100.9, 107.3, 107.8, 110.2, 110.7, 118.8, 119.9, 131.8, 133.2, 146.5, 147.4, 148.0, 148.5. EIMS *m/z*: 416 (M^+, 89), 189 (91), 173 (100). HRMS (EI) *m/z* (M^+): calcd. for $C_{23}H_{28}O_7$, 416.1835; found, 416.1835. >99% ee (HPLC, DAICEL OD-H chiral column, detected at 280 nm, 1 ml min^{-1}, 10% *iso*-PrOH in hexane, t_R 15 min). *(7S,7′R,8S,8′R)-(−)-**10***, $[\alpha]^{20}_D$ −6 (*c* 0.4, $CHCl_3$), >99% ee, t_R 26 min.

Organisms. Bacillus subtilis subsp. *subtiis* NBRC 13719^T, *Pseudomonas fluorescens* NBRC 14160^T, and *Staphylococcus aureus* subsp. *aureus* NBRC 14462 were purchased from the National Institute of Technology and Evaluation (NITE), Biological Resource Center, Japan. *Escherichia coli* JCM 1649, *Listeria denitrificans* JCM 11481, *Salmonella choleraesuis* subsp. *choleraesuis* JCM 6977 and *Yersinia intermedia* JCM 7579 were obtained from RIKEN, Japan. The phytopathogenic fungi, *Colletotrichum lagenarium*, had been isolated from a farm at Ehime University and was kindly presented by Dr. Ohguchi. Each fungus was cultured on potato dextrose agar (PDA, Sigma-Aldrich, Canada).

Antibiotic spectra. The ability of each compound to inhibit the growth of a variety of Gram-positive and Gram-negative bacterial strains was assessed by the paper disc method (Advantec Toyo, Japan, 6-mm thin paper disc), and the minimum inhibitory concentration (MIC) was determined for those strains that showed sensitivity to the tested compounds. The paper disc test used agar plates containing "Nissui" nutrient broth (Nissui Pharmaceutical Co.) A hundred microliter of an exponential culture of each respective strain was made into molten agar containing the nutrient broth. After the agar had solidified, a paper disc containing 15 µl of 50 mM of the tested compound was put on to the agar plate. The plate was incubated for 24 h at 30 °C (*L. denitrificans* and *P. fluorescens*) or at 37 °C (*B. subtilis*, *S. aureus*, *E. coli*, *S. choleraesuis* and *Y. intermedia*), and the diameter of any halo of inhibition around the paper disc was measured. The MIC value was determined from a two-fold dilution series for any strain that showed a halo of inhibition. The test was done three times.

Antifungal assay. The paper disc method was adopted for the first screening. Briefly, fungal mycelia were spotted on the center of the PDA plate (φ100 mm dishes) and incubated at 28 °C until the colony diameter became 4–5 cm. A disc paper soaked in dimethyl sulfoxide containing a test chemical was placed at the edge of the colony. Growth inhibition was observed after culturing at 28 °C for 7–10 d. A further inhibition test was performed with the active compounds. Each compound was added to three aliquots each containing 3 ml of PDA at 50 °C, mixed rapidly and poured on to the PDA plates (φ50 mm dishes). Dimethyl sulfoxide without any test compound served as the control. After incubating at 28 °C for 7–10 d, the area of the mycelial colony was measured by a caliper, the assays being triplicated.

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