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Synthesis and Antioxidant Activity of Olivil-Type Lignans

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Olivil-type lignans, an enantiomeric type of natural olivil, were synthesized for the first time to evaluate the relationship between the structure of olivil and its antioxidant activity. A comparison of the antioxidant activity with that of other synthesized tetrahydrofuran lignans indicated reduced activity with the tertiary hydroxy group. A different effect of the two phenolic groups of olivil on the antioxidant activity was also observed.

Key words: *Eucommia ulmoides*; Eucommiaceae; oliv; antioxidant activity; olivil

It is known that lignans play an important role in the antioxidant activity of foods and plants.[1)] In respect of the relationship between the antioxidant activity and structure, the effect of the phenolic part of natural compounds on the antioxidant activity is already known.[2)] However, the effect of the main body of natural compounds on the antioxidant activity has not previously been reported. It has recently been found that the antioxidant activity of furofuran lignan was affected by the tertiary hydroxy group on the furofuran ring.[3)] This discovery stimulated us to further study the effect of the tertiary hydroxy group on the antioxidant activity of olivil-type lignan, which is the best-known tetrahydrofuran lignan bearing a tertiary hydroxy group. It has been shown that the degree of oxidation of the main body of lignan was important for its biological activity.[4)] Our project to clarify the relationship between this oxidation degree and antioxidant activity in olivil will contribute to biological research into lignan.

In this experiment, two olivil-type lignans, **1** and **2** which were enantiomeric types of natural olivil, and two tetrahydrofuran lignans, **3** and **4**, were synthesized (Fig. 1); their antioxidant activity was then compared to clarify the effect of hydroxy groups. To examine the effect of each phenolic group of olivil, compounds **1** and **2** were valuable in having only one phenolic group at different positions. In respect of synthetic research into olivil, the synthesis of diastereomers of olivil-type lignan has been reported.[5,6)] This article describes the first enantioselective synthesis of olivil-type lignan having an absolute configuration opposite to that of natural olivil and the different effect of the three hydroxy groups of olivil on the antioxidant activity. This is the first reported study on the relationship between the main structure and antioxidant activity of olivil by employing the organic synthetic technique.

Results and Discussion

*Synthesis of **1–4***

The synthesis of olivil-type lignan **1** was started by the aldol condensation of lactone **5**[7)] with 4-benzyloxy-3-methoxybenzaldehyde to give aldol product **6** as a mixture of *erythro*/*threo* = 7/3 (Scheme 1). After conversion to olefin **7** as a mixture of $Z/E = 8/2$, stereoselective osmium oxidation was performed to give glycol **8**. The results of an NOE experiment confirmed the preferential production of the *Z* form of olefin **7**. Selective dehydroxylation of the benzylic position was accomplished by using Et_3SiH and CF_3CO_2H,[8)] leading to α-hydroxy lactone **9**. This lactone **9** was subjected to $LiAlH_4$ reduction, and then the crude tetraol was treated with 10-camphorsulfonic acid to give SN1 cyclization product **10**. The configuration of **10** was confirmed by a differential NOE experiment, NOE being observed between 7-H and 9-H_2, and between 7-H and 7′-H_2. Hydrogenolysis of **10** gave olivil-type lignan **1**.

To synthesize olivil-type lignan **2**, *cis*-lactone **17** was prepared from **11**[9)] (Scheme 2). The two chiral centers were constructed by employing Evans's *anti*-aldol condensation[10)] to give **12** (more than 99% d.e.). No production of the *syn*-aldol product was apparent. After protection of the hydroxy group as a triisopropylsilyl ether, the auxiliary was reductively removed to afford alcohol **14**. After protection of the primary hydroxy group as a pivaloyl ester, resulting olefin **15** was converted to aldehyde **16** by oxidative cleavage. Desilylation and subsequent oxidation of the resulting hemiacetal gave lactone **17**. Olivil-type lignan **2** was obtained from lactone **17** by the same synthetic method as that described for the synthesis of **1** (Scheme 3). The enantioselective syntheses of the (+)-olivil type lignans were thus successful.

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Abbreviation: AAPH, 2,2′-azobis(2-aminopropane)dihydrochloride

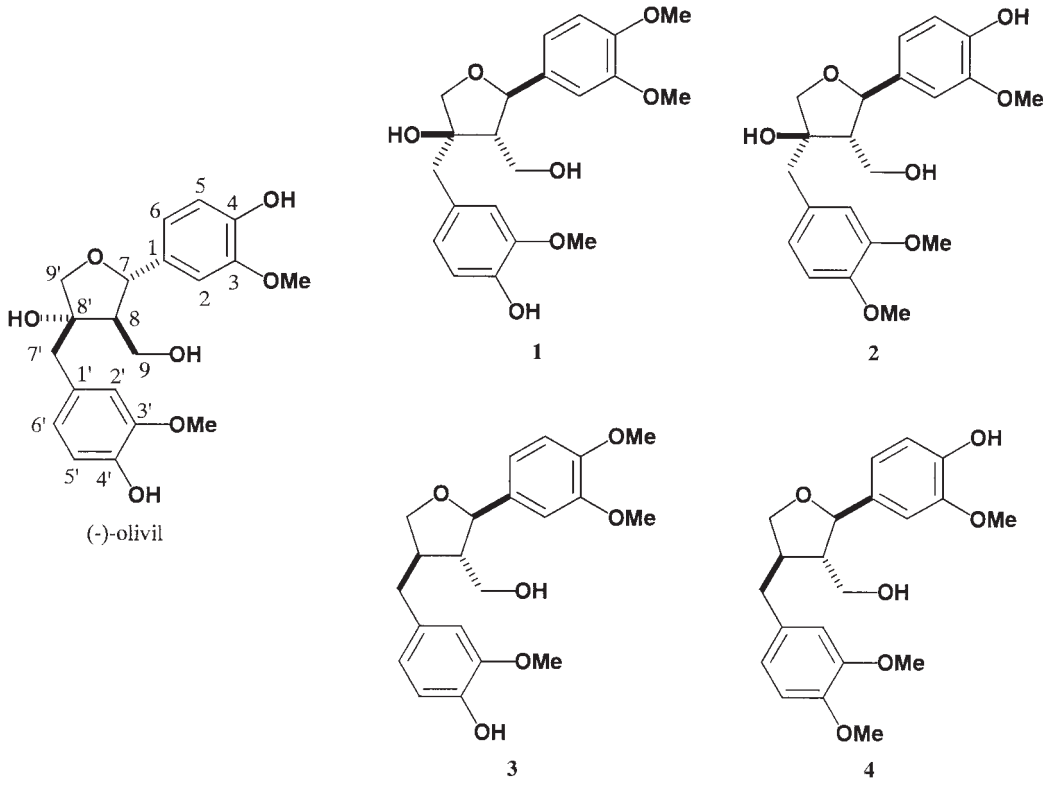
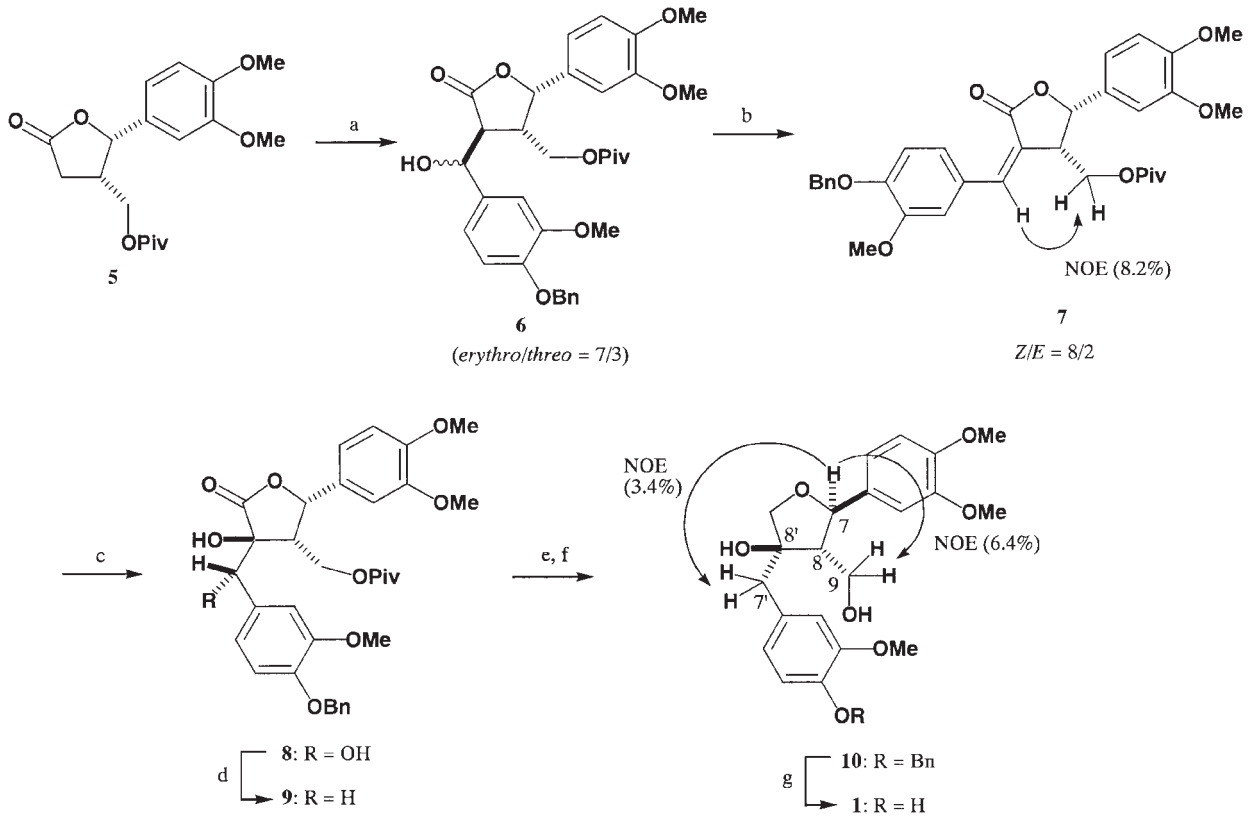
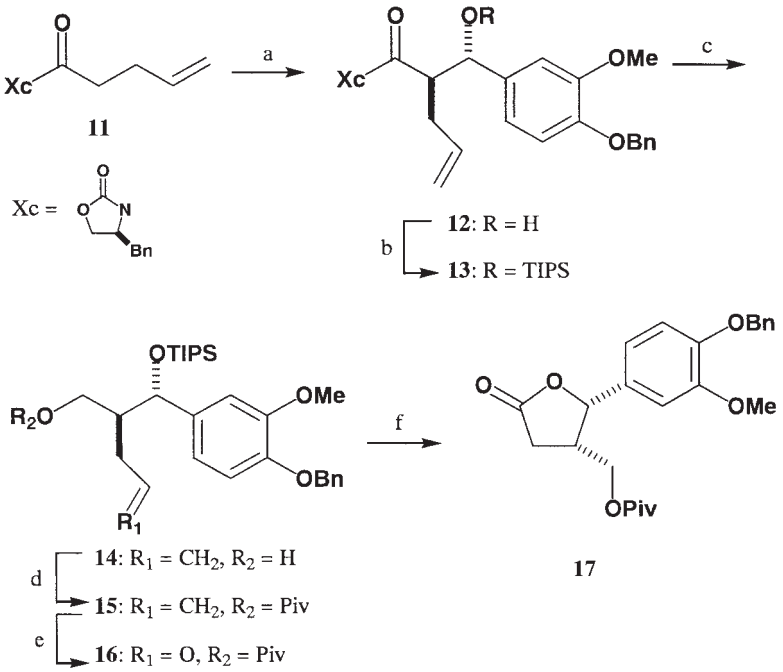


Fig. 1.



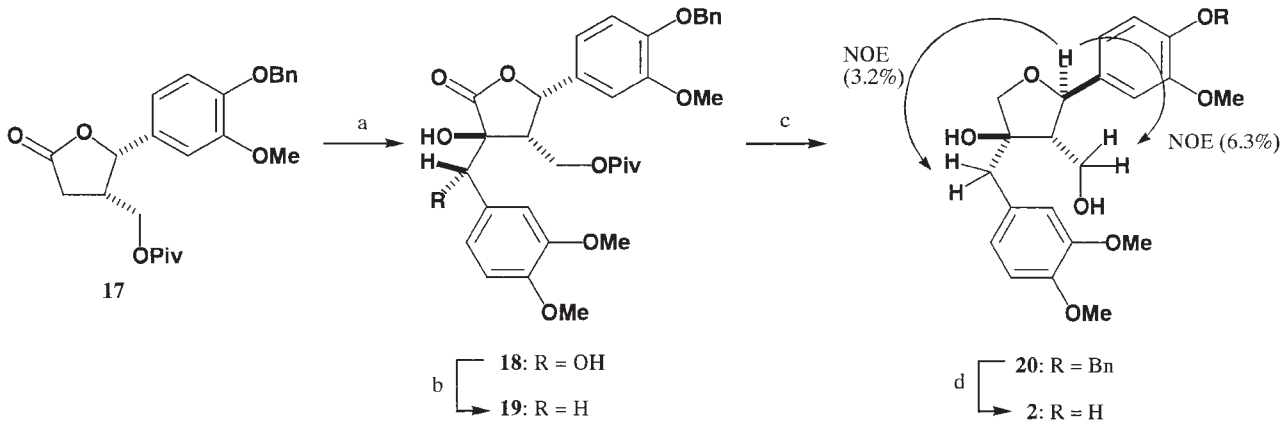
Scheme 1. Synthesis of Olivil-Type Lignan **1**.

(a) KHMDS, 4-benzyloxy-3-methoxybenzaldehyde, THF, −70 °C, 1 h (86%); (b) $KHSO_4$, toluene, reflux, 30 min (100%); (c) OsO_4, NMO, aq. acetone, *tert*-BuOH, r.t., 16 h (52%); (d) Et_3SiH, CF_3CO_2H, r.t., 16 h (50%); (e) $LiAlH_4$, THF, r.t., 30 min; (f) CSA, CH_2Cl_2, 2 °C, 16 h (56%, 2 steps); (g) H_2, 5% Pd/C, EtOAc, r.t., 7 h (73%).



Scheme 2. Preparation of γ-Butyrolactone **17**.

(a) i) 4-benzyloxy-3-methoxybenzaldehyde, $MgCl_2$, Et_3N, Me_3SiCl, EtOAc, r.t., 1 h; ii) CF_3CO_2H, MeOH, r.t., 1 h (99%, 2 steps); (b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1.5 h (78%); (c) $LiBH_4$, MeOH, THF, r.t., 16 h (61%); (d) PivCl, pyridine, CH_2Cl_2, r.t., 2 h (100%); (e) i) OsO_4, NMO, aq. acetone, *tert*-BuOH, r.t., 16 h; ii) $NaIO_4$, MeOH, r.t., 1 h (86%); (f) i) $(n\text{-Bu})_4NF$, THF, 0 °C, 1 h; ii) PCC, MS 4A, CH_2Cl_2, r.t., 16 h (77%, 2 steps).



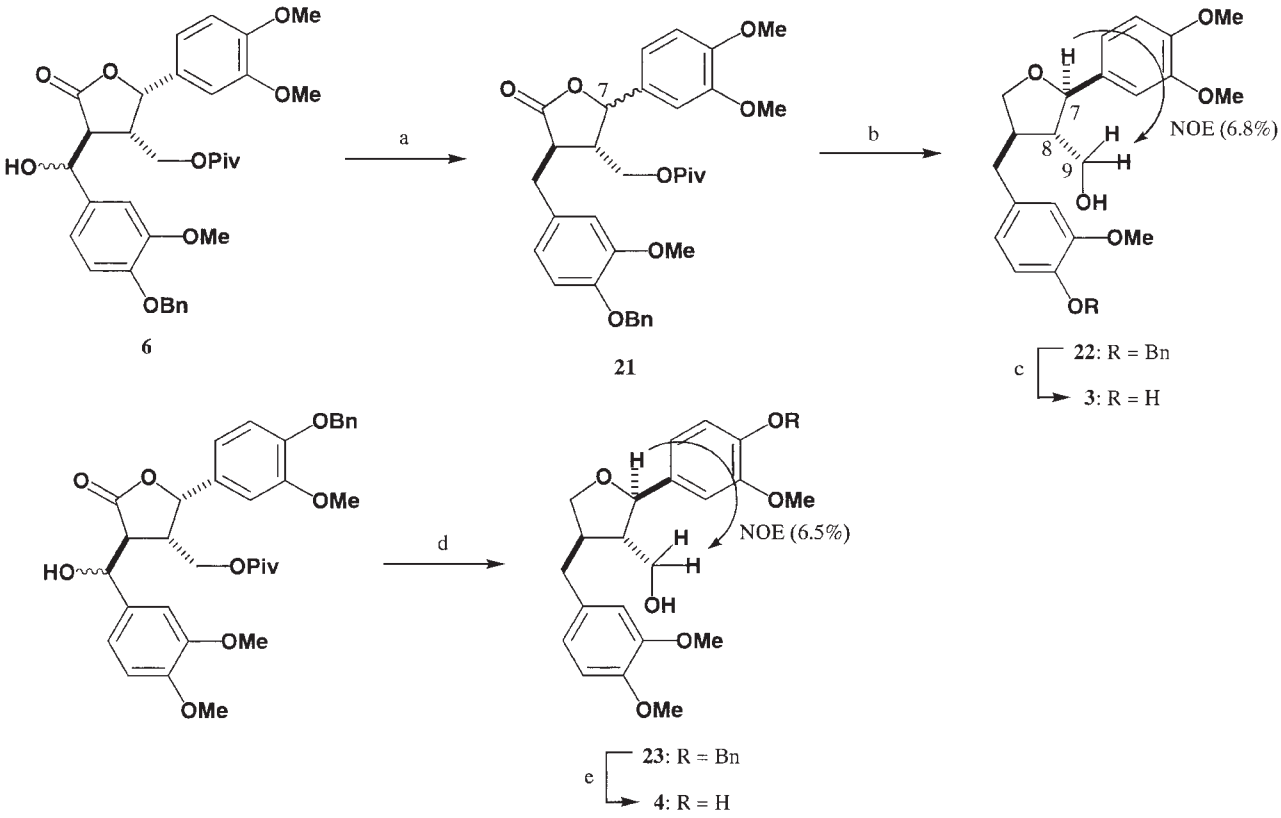
Scheme 3. Synthesis of Olivil-Type Lignan **2**.

(a) (i) KHMDS, 3,4-dimethoxybenzaldehyde, THF, −70 °C, 1 h (81%); (ii) $KHSO_4$, toluene, reflux, 30 min, recrystallization (62%); (iii) OsO_4, NMO, aq. acetone, *tert*-BuOH, r.t., 16 h (66%); (b) Et_3SiH, CF_3CO_2H, r.t., 16 h (51%); (c) (i) $LiAlH_4$, THF, r.t., 30 min; (ii) CSA, CH_2Cl_2, 2 °C, 16 h (56%, 2 steps); (d) H_2, 5% Pd/C, EtOAc, r.t., 7 h (61%).

Tetrahydrofuran lignan **3** lacking the tertiary hydroxy group of olivil-type lignan was synthesized from aldol product **6** (Scheme 4). Dehydroxylation of the benzylic hydroxy group was achieved by employing Et_3SiH in the presence of $BF_3 \cdot OEt_2$[11] to give **21** as a mixture of $7R/7S = 1/1$. Epimerization at the 4-position was observed in this stage. Since this 4-position would be stereoconvergently converted to the 2-position of **22**, this epimerization was no problem. After $LiAlH_4$ reduction of **21**, the resulting crude triol was stereoconvergently cyclized to tetrahydrofuran derivative **22** in the presence of 10-camphorsulfonic acid. The presence of NOE between 7-H and 9-H_2 in **22** suggested this configuration. Hydrogenolysis of **22** gave tetrahydrofuran lignan **3**. Tetrahydrofuran lignan **4** was also obtained by the same method as that described for the synthesis of **3** (Scheme 4).

Antioxidant activity

The antioxidant activity of compounds **1**–**4** was examined in a Tween 20 micelle system[12] (Fig. 2). The activity of all compounds was weaker than that of



Scheme 4. Synthesis of Tetrahydrofuran Lignans **3** and **4**.

(a) Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2, 2 °C, 1 h (55%); (b) (i) $LiAlH_4$, THF, r.t., 30 min; (ii) CSA, CH_2Cl_2, r.t., 40 h (50%, 2 steps); (c) H_2, 5% Pd/C, EtOAc, r.t., 7 h (96%); (d) (i) Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2, 2 °C, 1 h (52%); (ii) $LiAlH_4$, THF, r.t., 30 min; (iii) CSA, CH_2Cl_2, r.t., 40 h (53%, 2 steps); (e) H_2, 5% Pd/C, EtOAc, r.t., 7 h (99%).

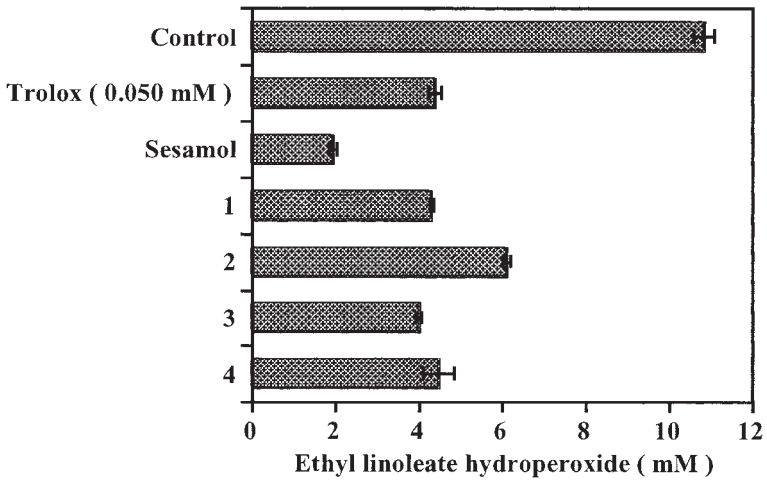


Fig. 2. Antioxidant Activity of Olivil-Type Lignans and Tetrahydrofuran Lignans **1–4** in a Tween 20 Micelle System [0.3 M Tween 20–0.05 M phosphate buffer (pH 7.4)].

Conditions: final concentration of a test sample and sesamol, 0.10 mM (0.05 mM for Trolox); AAPH, 10 mM; ethyl linoleate, 50 mM.

sesamol, although an effect of the tertiary hydroxy group of the tetrahydrofuran ring on the antioxidant activity was found. A comparison of **1** with **3** showed that the presence of the tertiary hydroxy group reduced the activity. This tendency was more clearly apparent between **2** and **4**, the obviously higher activity of **4** than that of compound **2** being shown. As well as in the furofuran lignans,[3] the tertiary hydroxy group on tetrahydrofuran ring reduced the antioxidant activity. The different effect of the phenolic groups of olivil on the antioxidant activity was also shown, the activity of **1** being higher than that of **2**. This fact suggested that the

phenolic group on the 4′-position of olivil played a more important role in the antioxidant activity than the phenolic group on 4-position. It could be assumed that the structure of the benzylic position connected to the phenolic group was related to the degree of antioxidant activity. In the case of olivil, the primary benzylic position (7′-position) was more important for higher antioxidant activity than the secondary benzylic position (7-position).

This is the first report on the relationship between the antioxidant activity and main structure of olivil. The different effect of three hydroxy groups of olivil on the antioxidant activity was demonstrated for the first time. This discovery is important to evaluate the antioxidant activity of other lignans and will contribute to the effective utilization of natural resources containing lignan.

Experimental

Melting point data (mp) are uncorrected. NMR data were measured by a JNM-EX400 spectrometer, IR spectra were determined with a Shimadzu FTIR-8100 spectrophotometer, FABMS data were measured with a JMS-MS700V spectrometer, and optical rotation values were evaluated with a HORIBA SEPA-200 instrument. The silica gel used was Wakogel C-300 (Wako, 200–300 mesh). The numbering of compounds was changed to follow IUPAC nomenclature rules.

*(2S,3S,4S)-2-[(S)-(4-Benzyloxy-3-methoxyphenyl)-(hydroxy)methyl]-4-(3,4-dimethoxyphenyl)-2-hydroxy-3-pivaloyloxymethyl-4-butanolide (**8**).* To a solution of KHMDS (30.8 ml, 0.5 M in toluene, 15.4 mmol) in THF (150 ml) was added a solution of lactone **5** (4.71 g, 14.0 mmol) in THF (50 ml) at −70 °C. After stirring at −70 °C for 15 min, a solution of 4-benzyloxy-3-methoxybenzaldehyde (3.73 g, 15.4 mmol) in THF (20 ml) was added, and then the reaction mixture was stirred at −70 °C for 1 h before addition of sat. aq. NH_4Cl solution. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (10% EtOAc/toluene) gave aldol product **6** (6.95 g, 12.0 mmol, 86%) as an *erythro*/*threo* mixture of 7/3. A reaction mixture of aldol product **6** (3.49 g, 6.03 mmol) and $KHSO_4$ (1.55 g, 11.4 mmol) in toluene (80 ml) was heated under refluxing for 30 min. After cooling to room temperature, H_2O was added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 2/3) gave benzylidene **7** (3.38 g, 6.03 mmol, 100%) as a *Z*/*E* mixture of 8/2. A reaction solution of benzylidene (3.38 g, 6.03 mmol), 4-methylmorpholine *N*-oxide (0.85 g, 7.26 mmol), and OsO_4 (2.5 ml, 2% aq. solution) in acetone (30 ml), *tert*-BuOH (10 ml), and H_2O (10 ml) was stirred at room temperature for 16 h before addition of $Na_2S_2O_3$ (5 g) in H_2O (5 ml). 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 followed by silica gel column chromatography (20% EtOAc/toluene) gave glycol **8** (1.87 g, 3.14 mmol, 52%) as a colorless oil, $[\alpha]^{20}_D = -7.9$ (*c* 1.1, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3590, 3029, 2967, 1781, 1727, 1518, 1466, 1266, 1240, 1144, 1026 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.18 (9H, s, *tert*-Bu), 2.73 (1H, br. s, OH), 2.95 (1H, m, 3-H), 3.09 (1H, s, OH), 3.84 (3H, s, OCH_3), 3.858 (3H, s, OCH_3), 3.863 (3H, s, OCH_3), 3.89 (1H, dd, $J = 12.0$, 2.1, C*H*HOPiv), 4.42 (1H, dd, $J = 12.0$, 4.2, CH*H*OPiv), 4.88 (1H, s, ArC*H*OH), 5.12 (2H, s, OCH_2Ar), 5.97 (1H, d, $J = 5.4$, 4-H), 6.81–6.89 (4H, m, ArH), 7.00 (1H, dd, $J = 8.3$, 2.0, ArH), 7.13 (1H, d, $J = 2.0$, ArH), 7.28–7.31 (1H, m, ArH), 7.34–7.38 (2H, m, ArH), 7.42–7.43 (2H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ 27.0, 38.6, 49.8, 55.9, 55.96, 56.00, 60.2, 70.9, 72.8, 79.0, 80.1, 108.6, 111.1, 112.3, 113.3, 117.6, 120.6, 127.2, 127.3, 127.9, 128.5, 130.5, 136.9, 148.4, 148.8, 149.1, 149.2, 173.6, 177.7. Anal. Calcd. for $C_{33}H_{38}O_{10}$: C, 66.65; H, 6.44. Found: C, 66.41; H, 6.48.

*(2R,3S,4S)-2-(4-Benzyloxy-3-methoxybenzyl)-4-(3,4-dimethoxyphenyl)-2-hydroxy-3-pivaloyloxymethyl-4-butanolide (**9**).* To an ice-cooled solution of glycol **8** (1.19 g, 2.00 mmol) and Et_3SiH (7.14 ml, 44.7 mmol) in CH_2Cl_2 (20 ml) was added CF_3CO_2H (0.97 ml, 12.6 mmol). The reaction solution was stirred at room temperature for 16 h before addition of sat. aq. $NaHCO_3$ solution. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (10% EtOAc/toluene) gave α-hydroxy lactone **9** (0.58 g, 1.00 mmol, 50%) as a colorless oil, $[\alpha]^{20}_D = +17$ (*c* 0.88, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3550, 3029, 2967, 1781, 1728, 1518, 1466, 1260, 1237, 1179, 1144, 1028, 909 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.21 (9H, s, *tert*-Bu), 2.78 (1H, m, 3-H), 2.83 (1H, s, OH), 2.85 (1H, d, $J = 5.1$, ArC*H*H), 3.23 (1H, d, $J = 5.1$, ArCH*H*), 3.72 (1H, dd, $J = 12.2$, 0.5, C*H*HOPiv), 3.85 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.17 (1H, dd, $J = 12.2$, 3.9, C*H*HOPiv), 5.13 (2H, s, OCH_2Ar), 5.99 (1H, d, $J = 5.9$, 4-H), 6.81–6.86 (5H, m, ArH), 6.99 (1H, s, ArH), 7.30–7.31 (1H, m, ArH), 7.34–7.38 (2H, m, ArH), 7.42–7.44 (2H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ 27.0, 37.9, 38.6, 49.5, 55.9, 56.0, 59.7, 70.9, 76.6, 80.2, 108.4, 111.2, 113.9, 114.5, 117.5, 122.7, 126.8, 127.2, 127.3, 127.8, 128.5, 137.0, 147.6, 148.9, 149.2, 149.5, 175.8, 177.7. Anal. Calcd. for $C_{33}H_{38}O_9$: C, 68.50; H, 6.62. Found: C, 68.25; H, 6.64.

*(2R,3S,4R)-4-(4-Benzyloxy-3-methoxybenzyl)-2-(3,4-dimethoxyphenyl)-4-hydroxy-3-hydroxymethyltetrahydrofuran (**10**).* To an ice-cooled suspension of $LiAlH_4$ (0.27 g, 7.11 mmol) in THF (10 ml) was added a solution of lactone **9** (0.26 g, 0.45 mmol) in THF (10 ml). The reaction mixture was stirred at room temperature for 1 h

before additions of sat. aq. $MgSO_4$ and K_2CO_3. After stirring at room temperature for 30 min, the mixture was filtered. The filtrate was concentrated to give crude tetraol. The crude tetraol was dissolved in CH_2Cl_2 (8 ml). To this solution was added 10-camphorsulfonic acid (5 mg). The reaction solution was stood at 2 °C for 16 h before addition of a few drops of Et_3N and concentration. The residue was applied to silica gel column chromatography (EtOAc/hexane = 6/1) to give tetrahydrofuran derivative **10** (0.12 g, 0.25 mmol, 56%) as colorless crystals, mp 144–145 °C, $[\alpha]^{20}_D = +32$ (*c* 1.1, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3631, 3011, 2900, 1514, 1466, 1264, 1237, 1161, 1142, 1028 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2.20 (1H, s, OH), 2.51 (1H, m, 3-H), 2.96 (1H, d, $J = 13.7$, ArC*H*H), 3.07 (1H, d, $J = 13.7$, ArCH*H*), 3.68 (1H, d, $J = 9.3$, 5-*H*H), 3.82–3.90 (1H, m, OC*H*HOH), 3.87 (3H, s, OCH_3), 3.89 (6H, s, OCH_3), 3.93 (1H, d, $J = 9.3$, 5-H*H*), 3.94–4.00 (1H, m, CH*H*OH), 4.73 (1H, d, $J = 7.8$, 2-H), 5.15 (2H, s, OCH_2Ar), 6.76 (1H, dd, $J = 8.3$, 2.0, ArH), 6.82–6.91 (3H, m, ArH), 6.93 (1H, d, $J = 8.3$, ArH), 7.03 (1H, d, $J = 2.0$, ArH), 7.30–7.32 (1H, m, ArH), 7.35–7.39 (2H, m, ArH), 7.43–7.45 (2H, m, ArH). ^{13}C-NMR (sp^3-C, C_5D_5N) δ 40.7, 55.7, 55.9, 56.0, 60.5, 62.2, 71.4, 78.1, 81.9, 84.7. ^{13}C-NMR (sp^2-C, $CDCl_3$) δ 109.4, 110.9, 114.0, 114.2, 118.7, 122.2, 127.3, 127.8, 128.5, 129.5, 134.5, 137.2, 147.3, 148.8, 149.3, 149.7. EIHRMS ($M^+ + 1$, *m/z*): 481.2223. Calcd. for $C_{28}H_{33}O_7$: 481.2224.

*(2R,3S,4R)-2-(3,4-Dimethoxyphenyl)-4-hydroxy-4-(4-hydroxy-3-methoxybenzyl)-3-hydroxymethyltetrahydrofuran (**1**).* A reaction mixture of benzyl ether **10** (55 mg, 0.12 mmol) and 5% Pd/C (30 mg) in EtOAc (10 ml) was stirred at ambient temperature for 7 h before filtration. After the filtrate was concentrated, the residue was applied to silica gel TLC (3% MeOH/$CHCl_3$) to give olivil-type lignan **1** (34 mg, 0.087 mmol, 73%) as colorless crystals, mp 137–138 °C, $[\alpha]^{20}_D = +29$ (*c* 0.31, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3548, 3011, 2938, 1514, 1466, 1269, 1240, 1161, 1140, 1038, 909 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.77 (1H, br. s, OH), 2.26 (1H, s, OH), 2.50 (1H, m, 3-H), 2.94 (1H, d, $J = 13.9$, ArC*H*H), 3.05 (1H, d, $J = 13.9$, ArCH*H*), 3.68 (1H, d, $J = 8.8$, 5-*H*H), 3.82 (1H, dd, $J = 10.3$, 5.4, C*H*HOH), 3.866 (3H, s, OCH_3), 3.877 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.93 (1H, d, $J = 8.8$, 5-H*H*), 3.96 (1H, dd, $J = 10.3$, 6.9, CH*H*OH), 4.73 (1H, d, $J = 7.8$, 2-H), 5.62 (1H, s, ArOH), 6.77 (1H, dd, $J = 7.8$, 2.0, ArH), 6.81–6.92 (4H, m, ArH), 7.02 (1H, d, $J = 1.5$, ArH). ^{13}C-NMR (sp^3-C, C_5D_5N) δ 40.7, 55.7, 55.8, 56.0, 60.5, 62.1, 78.2, 82.0, 84.8. ^{13}C-NMR (sp^2-C, $CDCl_3$) δ 109.4, 110.9, 112.8, 114.4, 118.6, 122.9, 128.2, 134.4, 144.7, 146.5, 148.8, 149.2. EIHRMS (M^+, *m/z*): 390.1680. Calcd. for $C_{21}H_{26}O_7$: 390.1678.

*(4S)-4-Benzyl-3-{(R)-2-[(S)-(4-benzyloxy-3-methoxyphenyl)(hydroxy)methyl]-4-pentenoyl}-2-oxazolidinone (**12**).* A reaction mixture of acylated oxazolidinone **11** (7.62 g, 29.4 mmol), 4-benzyloxy-3-methoxybenzaldehyde (8.54 g, 35.2 mmol), $MgCl_2$ (2.80 g, 29.4 mmol), Et_3N (8.20 ml, 58.8 mmol), and Me_3SiCl (5.60 ml, 44.1 mmol) in EtOAc (100 ml) was stirred at room temperature for 16 h before filtration through silica gel with ether. After the filtrate was concentrated, the residue was dissolved in MeOH (100 ml), and then a few drops of CF_3CO_2H was added. The reaction mixture was stirred at room temperature for 1 h. After addition of a few drops of Et_3N, the mixture was concentrated. The residue was recrystallized from EtOH to give *anti*-aldol product **12** (14.7 g, 29.3 mmol, 99%, more than 99% d.e.) as colorless crystals, mp 124 °C, $[\alpha]^{20}_D = -5.9$ (*c* 1.0, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3526, 3013, 1779, 1698, 1514, 1385, 1254, 1235, 1196, 1140, 1019, 909 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2.33 (1H, m, CH_2=CH–C*H*H), 2.45 (1H, m, CH_2=CH–CH*H*), 2.56 (1H, dd, $J = 13.7$, 9.3, ArC*H*H), 3.11 (1H, dd, $J = 13.7$, 3.4, ArCH*H*), 3.19 (1H, d, $J = 7.8$, OH), 3.90 (3H, s, OCH_3), 4.06–4.14 (2H, m, 5-H_2), 4.56 (1H, m, O=CCH), 4.63 (1H, m, 4-H), 4.81 (1H, dd, $J = 7.8$, 7.3, ArC*H*OH), 4.98–5.07 (2H, m, CH_2=CH), 5.12 (2H, s, $ArCH_2O$), 5.74 (1H, m, CH_2=C*H*), 6.85 (1H, d, $J = 8.3$, ArH), 6.90 (1H, d, $J = 8.3$, ArH), 7.02 (1H, s, ArH), 7.09–7.11 (2H, m, ArH), 7.25–7.34 (6H, m, ArH), 7.40–7.42 (2H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ 34.3, 37.5, 48.7, 55.3, 56.0, 65.8, 71.0, 75.5, 109.8, 113.7, 117.4, 118.6, 127.2, 127.3, 127.8, 128.5, 128.9, 129.4, 134.5, 135.1, 135.3, 137.0, 147.8, 149.8, 153.5, 175.5. Anal. Calcd. for $C_{30}H_{31}O_6N$: C, 71.84; H, 6.23. Found: C, 71.97; H, 6.20.

*(4S)-4-Benzyl-3-{(R)-2-[(S)-(4-benzyloxy-3-methoxyphenyl)(triisopropylsilyloxy)methyl]-4-pentenoyl}-2-oxazolidinone (**13**).* To an ice-cooled solution of alcohol **12** (5.47 g, 10.9 mmol) and 2,6-lutidine (2.54 ml, 21.8 mmol) in CH_2Cl_2 (60 ml) was added TIPSOTf (5.00 ml, 14.9 mmol). The resulting solution was stirred in an ice-bath for 1.5 h before addition of sat. aq. $NaHCO_3$ solution. The organic solution was separated, washed with sat. aq. $CuSO_4$ solution, and brine, and dried (Na_2SO_4). After concentration, the residue was recrystallized from MeOH to give silyl ether **13** (5.57 g, 8.47 mmol, 78%) as colorless crystals, mp 115 °C, $[\alpha]^{20}_D = -27.1$ (*c* 1.33, $CHCl_3$). IR ν_{max} ($CHCl_3$): 2946, 2869, 1781, 1698, 1510, 1466, 1455, 1385, 1350, 1254, 1235, 1196, 1098, 1065, 1017, 909 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 0.91–0.99 (21H, m, *iso*-pr), 1.90 (1H, m, CH_2=CH–C*H*H), 2.13 (1H, m, CH_2=CH–CH*H*), 2.61 (1H, dd, $J = 11.2$, 3.2, ArC*H*H), 3.53 (1H, dd, $J = 13.2$, 2.9, ArCH*H*), 3.92 (3H, s, OCH_3), 4.06 (1H, dd, $J = 8.8$, 8.8, 5-*H*H), 4.11 (1H, dd, $J = 8.8$, 2.4, 5-H*H*), 4.54 (1H, m, O=CCH), 4.60 (1H, m, 4-H), 4.87–4.94 (2H, m, CH_2=CH), 5.04 (1H, d, *J* 8.8, ArC*H*OH), 5.14 (2H, s, $ArCH_2O$), 5.57 (1H, m, CH_2=C*H*), 6.82 (2H, s, ArH), 7.08 (1H, s, ArH), 7.25–7.30 (5H, m, ArH), 7.33–7.37 (3H, m, ArH), 7.42–7.44 (2H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ 12.6, 17.9, 18.1, 34.3, 38.4, 51.4,

56.0, 65.9, 71.0, 111.0, 113.3, 116.8, 120.1, 127.2, 127.3, 127.8, 128.4, 128.9, 129.3, 134.9, 135.5, 135.9, 137.0, 147.9, 149.7, 153.4, 174.6. Anal. Calcd. for $C_{39}H_{31}O_6NSi$: C, 71.20; H, 7.81; N, 2.13. Found: C, 71.32; H, 8.10; N, 2.10.

*(2S)-2-[(S)-(4-Benzyloxy-3-methoxyphenyl)(triisopropylsilyloxy)methyl]-4-penten-1-ol (**14**).* To an ice-cooled solution of $LiBH_4$ (2.79 g, 0.13 mol) and MeOH (5.36 ml, 0.13 mol) in THF (150 ml) was added a solution of acyl oxazolidinone **13** (36.3 g, 55.2 mmol) in THF (200 ml). The reaction solution was stirred at room temperature for 16 h 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 and silica gel column chromatography (EtOAc/hexane = 1/9) gave alcohol **14** (16.2 g, 33.4 mmol, 61%) as a colorless oil, $[\alpha]^{20}_D = -45$ (*c* 1.4, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3500, 2946, 2869, 1512, 1466, 1260, 1140, 1084, 1036, 1015, 884 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 0.96–1.02 (21H, m, *iso*-Pr), 1.83–1.96 (2H, m, 2-H, OH), 2.18 (1H, m, CH_2=CH–C*H*H), 2.65 (1H, m, CH_2=CH–CH*H*), 3.58 (1H, m, 1-*H*H), 3.79 (1H, m, 1-H*H*), 3.88 (3H, s, OCH_3), 4.85 (1H, d, $J = 5.4$, ArCHOTIPS), 4.98–5.14 (2H, m, C*H*$_2$=CH), 5.14 (2H, s, $ArCH_2O$), 5.73 (1H, m, CH_2=C*H*), 6.57 (1H, dd, $J = 8.3$, 1.5, ArH), 6.82 (1H, d, $J = 8.3$, ArH), 6.95 (1H, d, $J = 1.5$, ArH), 7.28–7.31 (1H, m, ArH), 7.34–7.37 (2H, m, ArH), 7.42–7.44 (2H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ 12.5, 17.9, 18.0, 32.4, 48.4, 55.9, 63.1, 71.1, 78.3, 110.5, 113.4, 116.4, 119.2, 127.3, 127.8, 128.5, 136.5, 136.8, 137.1, 147.5, 149.5. Anal. Calcd. for $C_{29}H_{44}O_4Si$: C, 71.85; H, 9.15. Found: C, 72.03; H, 9.12.

*(4S,5S)-5-(4-Benzyloxy-3-methoxyphenyl)-4-pivaloyloxymethyl-5-(triisopropylsilyloxy)-1-pentene (**15**).* To an ice-cooled solution of alcohol **14** (16.2 g, 33.4 mmol) and pyridine (5.41 mmol, 66.9 mmol) in CH_2Cl_2 (20 ml) was added PivCl (5.41 ml, 43.9 mmol). After the reaction mixture was stirred at room temperature for 2 h, EtOAc and H_2O were added. The organic solution was separated, washed with 6 M aq. HCl solution and brine, and dried (Na_2SO_4). Concentration and silica gel column chromatography (5% EtOAc in hexane) gave pivaloyl ester **15** (19.1 g, 33.5 mmol, 100%) as a colorless oil, $[\alpha]^{20}_D = -8.9$ (*c* 1.5, $CHCl_3$). IR ν_{max} ($CHCl_3$): 2946, 2869, 1721, 1510, 1464, 1285, 1262, 1163, 1140, 1092 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 0.96–1.01 (21H, m, *iso*-Pr), 1.23 (9H, s, *tert*-Bu), 1.54 (1H, m, 4-H), 2.21 (1H, m, 3-*H*H), 2.36 (1H, m, 3-H*H*), 3.81 (1H, dd, $J = 11.2$, 8.3, PivOC*H*H), 3.86 (3H, s, OCH_3), 4.16 (1H, dd, $J = 11.2$, 4.4, PivOC*H*H), 4.91–4.98 (3H, m, 1-H_2, 5-H), 5.13 (2H, s, $ArCH_2O$), 5.72 (1H, m, 2-H), 6.69 (1H, dd, $J = 8.3$, 2.0, ArH), 6.81 (1H, d, $J = 8.3$, ArH), 6.89 (1H, d, $J = 2.0$, ArH), 7.26–7.38 (3H, m, ArH), 7.43–7.45 (2H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ 12.4, 18.0, 18.1, 27.3, 30.2, 38.8, 45.8, 55.9, 63.9, 71.1, 73.9, 110.8, 113.4, 116.4, 119.3, 127.4, 127.8, 128.5, 135.0, 136.6, 137.2, 147.4, 149.3, 178.2. Anal. Calcd. for $C_{34}H_{32}O_5$: C, 71.79; H, 9.21. Found: C, 71.89; H, 9.37.

*(3S,4S)-4-(4-Benzyloxy-3-methoxyphenyl)-3-pivaloyloxymethyl-4-(triisopropylsilyloxy)butanal (**16**).* A reaction mixture of olefin **15** (14.5 g, 25.5 mmol), NMO (3.69 g, 31.5 mmol), and OsO_4 (2 ml, 2% aq. solution) in acetone (150 ml), *tert*-BuOH (40 ml), and H_2O (40 ml) was stirred at room temperature for 16 h under N_2 gas in dark. After addition of $Na_2S_2O_3$, the mixture was filtered. The filtrate 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). After concentration, the residue was dissolved in MeOH (100 ml). To this solution was added $NaIO_4$ (6.25 g, 29.2 mmol), and then the reaction mixture was stirred at room temperature for 1 h before concentration. The residue was dissolved in H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After concentration, the residue was applied to silica gel column chromatography (EtOAc/hexane = 1/8) to give aldehyde **16** (13.6 g, 21.9 mmol, 86%) as a colorless oil, $[\alpha]^{20}_D = -9.5$ (*c* 1.1, $CHCl_3$). IR ν_{max} ($CHCl_3$): 2946, 2869, 1725, 1512, 1464, 1283, 1262, 1233, 1161, 1142, 1088, 909 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 0.95–1.01 (21H, m, *iso*-Pr), 1.22 (9H, s, *tert*-Bu), 2.05 (1H, ddd, $J = 16.6$, 6.1, 1.0, 2-*H*H), 2.50 (1H, ddd, $J = 16.6$, 6.6, 2.7, 2-H*H*), 2.89 (1H, m, 3-H), 3.88 (3H, s, OCH_3), 3.88 (1H, dd, $J = 11.2$, 8.3, PivOC*H*H), 3.98 (1H, dd, $J = 11.2$, 5.9, PivOCH*H*), 4.97 (1H, d, $J = 5.4$, ArCHOTIPS), 5.13 (2H, s, $ArCH_2O$), 6.66 (1H, dd, $J = 8.3$, 1.5, ArH), 6.82 (1H, d, $J = 8.3$, ArH), 6.87 (1H, d, $J = 1.5$, ArH), 7.26–7.38 (3H, m, ArH), 7.42–7.44 (2H, m, ArH), 9.73 (1H, dd, *J* 2.7, 1.0 Hz, CHO). ^{13}C-NMR ($CDCl_3$) δ 12.3, 17.9, 18.0, 27.2, 38.8, 41.1, 41.3, 55.9, 64.4, 71.1, 73.9, 110.7, 113.4, 119.2, 127.3, 127.8, 128.5, 133.6, 137.0, 147.7, 149.5, 178.0, 200.9. Anal. Calcd. for $C_{37}H_{30}O_6Si$: C, 69.43; H, 8.83. Found: C, 69.51; H, 8.65.

*(3S,4S)-4-(4-Benzyloxy-3-methoxyphenyl)-3-pivaloyloxymethyl-4-butanolide (**17**).* To an ice-cooled solution of silyl ether **16** (12.3 g, 19.9 mmol) in THF (80 ml) was added (n-Bu)$_4$NF (22.2 ml, 1 M in THF, 22.2 mmol). After the reaction solution was stirred in an ice-bath for 1 h, sat. aq. NH_4Cl solution was added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After concentration, the residue was applied to silica gel column chromatography (EtOAc/hexane = 1/2) to give hemiacetal (7.76 g, 18.8 mmol, 94%) as a colorless oil. A reaction mixture of this hemiacetal (7.76 g, 18.8 mmol), PCC (4.62 g, 21.4 mmol), and MS 4A (0.3 g) in CH_2Cl_2 (40 ml) was stirred at room temperature for 16 h before the addition of dry 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 lactone

17 (6.78 g, 16.4 mmol, 82%) as colorless crystals, mp 94 °C (*iso*-Pr_2O), $[\alpha]^{20}_D = -34$ (*c* 1.1, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3031, 2973, 1782, 1727, 1516, 1279, 1260, 1233, 1167, 1144, 1034, 1022 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.14 (9H, s, *tert*-Bu), 2.57 (1H, dd, $J = 17.3, 4.2$, 2-*H*H), 2.82 (1H, dd, $J = 17.3, 8.5$, 2-H*H*), 3.04 (1H, m, 3-H), 3.64 (1H, dd, $J = 11.5, 6.6$, PivOC*H*H), 3.86 (1H, dd, $J = 11.5, 5.4$, PivOCH*H*), 3.87 (3H, s, OCH_3), 5.13 (2H, s, $ArCH_2O$), 5.62 (1H, d, $J = 6.8$, 4-H), 6.75 (1H, dd, $J = 7.8, 2.0$, ArH), 6.81 (1H, d, $J = 2.0$, ArH), 6.88 (1H, d, $J = 7.8$, ArH), 7.27–7.38 (3H, m, ArH), 7.42–7.44 (2H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ 27.0, 32.5, 38.6, 39.3, 56.1, 62.7, 71.0, 82.0, 109.0, 114.0, 117.6, 127.2, 127.86, 127.89, 128.5, 136.8, 148.3, 149.9, 175.6, 177.9. Anal. Calcd. for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.94; H, 6.95.

*(2S,3S,4S)-4-(4-Benzyloxy-3-methoxyphenyl)-2-[(S)-(3,4-dimethoxyphenyl)(hydroxy)methyl]-2-hydroxy-3-pivaloyloxymethyl-4-butanolide (**18**).* Aldol condensation of lactone **17** with 3,4-dimethoxybenzaldehyde by the same method as that described above gave aldol product in 81% yield as an *erythro*/*threo* mixture of 1/1 as a colorless oil. *Z*-Benzylidene was obtained from the resulting aldol product by the same method as that described for dehydration of **6** and recrystallization from EtOH, mp 110 °C, in 62% yield, $[\alpha]^{20}_D = +11$ (*c* 0.35, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3013, 1744, 1728, 1516, 1275, 1146 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.11 (9H, s, *tert*-Bu), 3.59 (1H, m, 3-H), 3.83–3.94 (2H, m, CH_2OPiv), 3.88 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 5.15 (2H, s, OCH_2Ar), 5.67 (1H, d, $J = 6.8$, 4-H), 6.81 (1H, d, $J = 8.3$, ArH), 6.86–6.90 (3H, m, ArH), 6.93 (1H, s, ArH), 7.26–7.32 (2H, m, ArH), 7.35–7.38 (2H, m, ArH), 7.42–7.44 (2H, m, ArH), 8.21 (1H, d, $J = 1.5$, C=CHAr). ^{13}C-NMR ($CDCl_3$) δ 27.0, 38.7, 47.2, 55.8, 55.9, 56.1, 63.6, 71.1, 79.4, 109.3, 110.3, 113.7, 114.0, 118.1, 123.0, 126.1, 126.7, 127.2, 127.9, 128.1, 128.5, 136.9, 142.0, 148.2, 148.5, 149.9, 150.9, 168.6, 178.0. Anal. Calcd. for $C_{33}H_{36}O_8$: C, 70.70; H, 6.47. Found: C, 70.63; H, 6.59. Glycol **18** was obtained from *Z*-benzylidene by the same method as that described above in 66% yield as a colorless oil, $[\alpha]^{20}_D = -6.4$ (*c* 0.78, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3598, 3027, 2967, 1781, 1727, 1516, 1262, 1233, 1179, 1144, 1026 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.18 (9H, s, *tert*-Bu), 2.63 (1H, d, $J = 4.2$, ArCHO*H*), 2.95–2.97 (1H, m, 3-H), 2.96 (1H, s, OH), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.88 (1H, dd, $J = 12.0, 2.6$, C*H*HOPiv), 4.44 (1H, dd, $J = 12.0, 4.2$, CH*H*OPiv), 4.90 (1H, d, $J = 4.2$, ArC*H*OH), 5.13 (2H, s, OCH_2Ar), 5.97 (1H, d, $J = 5.4$, 4-H), 6.79 (1H, d, $J = 8.3$, ArH), 6.85–6.88 (2H, m, ArH), 7.07 (1H, d, $J = 8.3$, ArH), 7.10 (1H, s, ArH), 7.26–7.32 (2H, m, ArH), 7.34–7.38 (2H, m, ArH), 7.42–7.43 (2H, m, ArH); ^{13}C-NMR ($CDCl_3$) δ 27.1, 38.6, 49.8, 55.8, 55.9, 56.2, 60.2, 71.1, 72.9, 79.0, 80.0, 109.2, 110.8, 111.7, 114.0, 117.6, 120.6, 127.3, 127.9, 128.0, 128.5, 129.9, 136.8, 148.0, 148.7, 149.3, 149.9, 173.6, 177.7. Anal. Calcd. for $C_{33}H_{38}O_{10}$: C, 66.65; H, 6.44. Found: C, 66.35; H, 6.55.

*(2R,3S,4S)-4-(4-Benzyloxy-3-methoxyphenyl)-2-(3,4-dimethoxybenzyl)-2-hydroxy-3-pivaloyloxymethyl-4-butanolide (**19**).* α-Hydroxy lactone **19** was obtained from **18** by the same method as that described above in 51% yield as colorless crystals, mp 152 °C (MeOH), $[\alpha]^{20}_D = +35$ (*c* 1.2, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3548, 3029, 2965, 1781, 1728, 1516, 1466, 1264, 1238, 1181, 1146, 1028 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.21 (9H, s, *tert*-Bu), 2.53 (1H, s, OH), 2.80 (1H, m, 3-H), 2.88 (1H, d, $J = 5.1$, ArC*H*H), 3.22 (1H, d, $J = 5.1$, ArCH*H*), 3.74 (1H, dd, $J = 12.2, 2.9$, C*H*HOPiv), 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.17 (1H, dd, $J = 12.2, 4.1$, OCH*H*OPiv), 5.14 (2H, s, OCH_2Ar), 5.98 (1H, d, $J = 5.9$, 4-H), 6.79–6.90 (5H, m, ArH), 6.97 (1H, s, ArH), 7.30–7.32 (1H, m, ArH), 7.35–7.38 (2H, m, ArH), 7.42–7.44 (2H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ 27.0, 37.8, 38.6, 49.4, 55.79, 55.82, 56.1, 59.6, 71.0, 76.6, 80.2, 109.0, 111.2, 113.8, 114.0, 117.5, 122.7, 126.3, 127.2, 127.3, 127.85, 127.94, 128.4, 128.5, 136.7, 148.0, 148.4, 148.8, 149.8, 175.8, 177.6. Anal. Calcd. for $C_{33}H_{38}O_9$: C, 68.50; H, 6.62. Found: C, 68.22; H, 6.67.

*(2R,3S,4R)-2-(4-Benzyloxy-3-methoxyphenyl)-4-(3,4-dimethoxybenzyl)-4-hydroxy-3-hydroxymethyltetrahydrofuran (**20**).* Tetrahydrofuran derivative **20** was obtained from **19** by the same method as that described above in 56% yield as colorless crystals, mp 153–154 °C, $[\alpha]^{20}_D = +19$ (*c* 2.0, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3679, 3011, 2945, 1732, 1516, 1466, 1264, 1242, 1142, 1028 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.63 (1H, s, OH), 2.21 (1H, s, OH), 2.51 (1H, m, 3-H), 2.96 (1H, d, $J = 3.7$, ArC*H*H), 3.08 (1H, d, $J = 3.7$, ArCH*H*), 3.68 (1H, d, $J = 9.3$, 5-*H*H), 3.81–3.99 (2H, m, C*H*$_2$OH), 3.879 (3H, s, OCH_3), 3.882 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.93 (1H, d, $J = 9.3$, 5-H*H*), 4.72 (1H, d, $J = 8.3$, 2-H), 5.15 (2H, s, OCH_2Ar), 6.83–6.84 (5H, m, ArH), 7.04 (1H, s, ArH), 7.29–7.31 (1H, m, ArH), 7.34–7.37 (2H, m, ArH), 7.42–7.44 (2H, m, ArH); ^{13}C-NMR ($CDCl_3$) δ 39.1, 55.90, 55.92, 56.0, 58.9, 60.7, 71.1, 77.2, 81.3, 83.0, 109.9, 111.3, 113.5, 113.8, 118.6, 122.2, 127.2, 127.8, 128.5, 128.9, 135.0, 137.1, 147.9, 148.1, 148.9, 149.9. EIHRMS ($M^+ + 1$, *m*/*z*): 481.2226. Calcd. for $C_{28}H_{33}O_7$: 481.2224.

*(2R,3S,4R)-4-(3,4-Dimethoxybenzyl)-4-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyltetrahydrofuran (**2**).* Olivil-type lignan **2** was obtained from **20** by the same method as that described above in 61% yield as colorless crystals, mp 211–212 °C, $[\alpha]^{20}_D = +19$ (*c* 0.26, C_5H_5N); ^{1}H-NMR (DMSO-d_6) δ 2.14 (1H, m, 3-H), 2.80 (1H, d, $J = 13.7$, ArC*H*H), 2.88 (1H, d, $J = 13.7$, ArCH*H*), 3.43 (1H, d, $J = 8.8$, 5-*H*H), 3.56 (1H, dd, $J = 11.0, 6.1$, C*H*HOH), 3.62 (1H, d, $J = 8.8$, 5-H*H*), 3.67 (1H, dd, $J = 11.0, 4.9$, CH*H*OH), 3.72 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 4.60

(1H, d, $J = 7.3$ Hz, 2-H), 6.69 (1H, d, $J = 8.3$, ArH), 6.77–6.90 (4H, m, ArH), 7.03 (1H, d, $J = 1.5$, ArH), 8.79 (1H, br. s, ArOH); ^{13}C-NMR (sp^3-C, C_5H_5N) δ 40.6, 55.7, 55.8, 55.9, 60.4, 62.2, 78.0, 81.9, 84.8; ^{13}C-NMR (sp^2-C, DMSO-d_6) δ 110.9, 111.3, 114.3, 114.7, 119.2, 122.1, 130.9, 134.4, 145.6, 147.1, 147.2, 148.0. EIHRMS (M^+, m/z): 390.1687. Calcd. for $C_{21}H_{26}O_7$: 390.1678.

*(2R,3S,4R)-4-(4-Benzyloxy-3-methoxybenzyl)-2-(3,4-dimethoxyphenyl)-3-hydroxymethyltetrahydrofuran (**22**).* To a solution of aldol product **6** (2.02 g, 3.49 mmol) and Et_3SiH (0.84 ml, 5.26 mmol) in CH_2Cl_2 (20 ml) was added $BF_3 \cdot OEt_2$ (0.49 ml, 3.87 mmol) at 2 °C. After the reaction solution was stirred at 2 °C for 1 h, sat. aq. $NaHCO_3$ 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 = 1/2) gave lactone **21** (1.08 g, 1.92 mmol, 55%) as a mixture of benzylic epimers (1/1) as a colorless oil. To a suspension of $LiAlH_4$ (55 mg, 1.45 mmol) in THF (10 ml) was added a solution of lactone **22** (0.69 g, 1.23 mmol) in THF (10 ml). The reaction mixture was stirred at room temperature for 1 h, and then sat. aq. $MgSO_4$ and K_2CO_3 were added. After stirring for 30 min, the mixture was filtered. The filtrate was concentrated to give crude triol. A solution of this crude triol and 10-camphorsulfonic acid (5 mg) in CH_2Cl_2 (8 ml) was stirred at room temperature for 40 h before addition of a few drops of Et_3N. After concentration, the residue was applied to silica gel column chromatography (EtOAc/hexane = 1/1) to give tetrahydrofuran derivative **22** (0.29 g, 0.62 mmol, 50%) as a colorless oil, $[\alpha]^{20}_D = -9.9$ (c 0.50, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3283, 3017, 1516, 1466, 1456, 1264, 1237, 1192, 1140, 1028 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.64 (1H, br. s, OH), 1.99 (1H, m, 4-H), 2.50 (1H, m, 3-H), 2.69 (1H, dd, $J = 13.7$, 8.8, ArC*H*H), 2.79 (1H, dd, $J = 13.7$, 6.8, ArCH*H*), 3.62 (2H, d, $J = 5.4$, CH_2OH), 3.84 (1H, dd, $J = 8.8$, 5.4, 5-*H*H), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.91 (1H, dd, $J = 8.8$, 7.2, 5-H*H*), 4.63 (1H, d, $J = 7.8$, 2-H), 5.11 (2H, s, OCH_2Ar), 6.64 (1H, dd, $J = 7.8$, 2.0, ArH), 6.70 (1H, d, $J = 2.0$, ArH), 6.79–6.84 (2H, m, ArH), 6.90–6.95 (2H, m, ArH), 7.27–7.31 (1H, m, ArH), 7.34–7.37 (2H, m, ArH), 7.42–7.44 (2H, m, ArH); ^{13}C-NMR ($CDCl_3$) δ 39.3, 44.0, 55.4, 55.87, 55.90, 56.0, 62.8, 71.1, 73.0, 83.9, 109.3, 111.0, 112.5, 114.3, 118.5, 120.6, 127.3, 127.8, 128.5, 133.4, 134.6, 137.2, 146.7, 148.5, 149.1, 149.6. Anal. Calcd. for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 71.91; H, 6.93.

*(2R,3S,4R)-2-(3,4-Dimethoxyphenyl)-4-(4-hydroxy-3-methoxybenzyl)-3-hydroxymethyltetrahydrofuran (**3**).* Hydrogenolysis of **22** was performed by the same method as that described above to give tetrahydrofuran lignan **3** in 96% yield as a colorless oil, $[\alpha]^{20}_D = +8.3$ (c 0.60, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3528, 3011, 2938, 1516, 1466, 1267, 1238, 1159, 1140, 1028 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.30 (1H, br. s, CH_2O*H*), 2.01 (1H, m, 4-H), 2.50 (1H, m, 3-H), 2.69 (1H, dd, $J = 13.7$, 8.3, ArC*H*H), 2.79 (1H, dd, $J = 13.7$, 6.8, ArCH*H*), 3.64 (2H, d, $J = 5.4$, CH_2OH), 3.84–3.88 (1H, m, 5-*H*H), 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.96 (1H, dd, $J = 8.8$, 7.3, 5-H*H*), 4.63 (1H, d, $J = 7.8$, 2-H), 5.52 (1H, s, ArOH), 6.66–6.67 (2H, m, ArH), 6.82–6.85 (2H, m, ArH), 6.91–6.95 (2H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ 39.4, 44.2, 55.4, 55.89, 55.91, 62.9, 73.0, 84.0, 109.3, 111.0, 111.2, 114.4, 118.5, 121.3, 132.0, 134.6, 144.0, 146.5, 148.5, 149.1. EIHRMS ($M^+ + 1$, m/z): 375.1807. Calcd. for $C_{21}H_{27}O_6$: 375.1807.

*(2R,3S,4R)-2-(4-Benzyloxy-3-methoxyphenyl)-4-(3,4-dimethoxybenzyl)-3-hydroxymethyltetrahydrofuran (**23**).* Tetrahydrofuran derivative **23** was obtained from aldol product by the same method as that described above in 28% yield through 3 steps as a colorless oil, $[\alpha]^{20}_D = +4.0$ (c 0.50, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3500, 3013, 2938, 1516, 1466, 1262, 1238, 1140, 1028 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.50 (1H, br. s, OH), 1.99 (1H, m, 4-H), 2.49 (1H, m, 3-H), 2.68 (1H, dd, $J = 13.7$, 8.8, ArC*H*H), 2.79 (1H, dd, $J = 13.7$, 6.8, ArCH*H*), 3.61 (2H, d, $J = 5.9$, CH_2OH), 3.82–3.85 (1H, m, 5-*H*H), 3.84 (6H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.94 (1H, dd, $J = 8.8$, 7.3, 5-H*H*), 4.61 (1H, d, $J = 7.8$, 2-H), 5.13 (2H, s, OCH_2Ph), 6.67–6.70 (2H, d, $J = 2.0$, ArH), 6.77 (1H, d, $J = 8.3$, ArH), 6.84 (2H, s, ArH), 6.97 (1H, s, ArH), 7.27–7.30 (1H, m, ArH), 7.33–7.37 (2H, m, ArH), 7.42–7.43 (2H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ 39.2, 44.0, 47.1, 55.3, 55.8, 56.0, 62.7, 71.0, 72.9, 83.8, 109.9, 111.2, 111.9, 113.9, 118.4, 120.6, 127.2, 127.7, 128.4, 132.7, 135.2, 137.1, 147.4, 147.6, 148.8, 149.7. EIHRMS (M^+, m/z): 464.2199. Calcd. for $C_{28}H_{32}O_6$: 464.2199.

*(2R,3S,4R)-4-(3,4-Dimethoxybenzyl)-2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyltetrahydrofuran (**4**).* Hydrogenolysis of **23** was performed by the same method as that described above to give tetrahydrofuran lignan **4** in 99% yield as a colorless oil, $[\alpha]^{20}_D = -4.2$ (c 0.71, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3545, 3011, 2940, 1516, 1460, 1264, 1240, 1157, 1142, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.70 (1H, br. s. OH), 1.99 (1H, m, 4-H), 2.51 (1H, m, 3-H), 2.69 (1H, dd, $J = 13.7$, 8.3, ArC*H*H), 2.81 (1H, dd, $J = 13.7$, 6.8, ArCH*H*), 3.63 (2H, d, $J = 5.4$, CH_2OH), 3.83–3.87 (1H, m, 5-*H*H), 3.851 (3H, s, OCH_3), 3.855 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.96 (1H, dd, $J = 8.8$, 7.3, 5-H*H*), 4.60 (1H, d, $J = 7.8$, 2-H), 5.69 (1H, s, ArOH), 6.68–6.72 (2H, m, ArH), 6.78 (1H, d, $J = 8.3$, ArH), 6.85–6.89 (2H, m, ArH), 6.92 (1H, s, ArH). ^{13}C-NMR ($CDCl_3$) δ 39.2, 44.0, 55.5, 55.8, 55.9, 62.7, 72.9, 84.0, 108.7, 111.2, 111.9, 114.2, 119.2, 120.6, 132.7, 133.9, 145.1, 146.6, 147.5, 148.9. EIHRMS (M^+, m/z): 374.1728. Calcd. for $C_{21}H_{26}O_6$: 374.1729.

*Examination of the antioxidant activity of olivil derivatives **1** and **2** and related compounds **3** and **4**.* The method of Masuda *et al.*[10] was slightly modified. To 160 µl of the DMSO solution of a test sample (5.0 mM) were added freshly purified ethyl linoleate (139 µl) and 0.3 M Tween 20–0.05 M phosphate buffer (pH 7.4, 8 ml). The mixture was vigorously stirred by a vortex mixer for 2 min and then sonicated in a bath sonicator (Branson model 2210) for 3 min to give a clear micelle solution. Two milliliters of this micelle solution was put into a straight vial (35 mm dia.; 75 mm height), and 100 µl of 0.2 M AAPH aqueous solution was added to the solution. After stirring again with the vortex mixer, the vial was incubated at 37 °C in the dark while continuously shaking (82 shakes/min; Taitec P-11 water bath shaker). After 3 h of incubation, 20-µl aliquot was taken from the solution and poured into 380 µl of a methanolic solution of trolox (0.2 mM). Ten microliters of the diluted solution was injected into the HPLC instrument to analyze ethyl linoleate hydroperoxide under the following conditions: column, YMC-Pack ODS-A (4.6 × 150 mm); solvent, CH_3CN–H_2O=9:1; flow rate, 1.0 ml/min; detection, 234 nm. The concentration of the hydroperoxide was calculated from the peak area obtained by the following equation: $Y = 2.29X \times 10^{-6} - 4.38 \times 10^{-4}$, where Y is the concentration of ethyl linoleate hydroperoxide (mM) and X is the peak area of hydroperoxide.

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