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Synthesis of Optically Active Olivil Type of Lignan from L-Arabinose Using *threo*-Selective Aldol Condensation as a Key Reaction

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The *threo*-selective aldol condensation of (3*R*, 4*S*)-3-hydroxy-5-trityloxy-4-pentanolide, which was prepared from L-arabinose, with piperonal was applied to the stereoselective synthesis of the olivil type of lignan, (2*R*, 3*R*, 4*R*)-4-benzyl-4-hydroxy-3-hydroxymethyl-2-(3,4-methylenedioxyphenyl)tetrahydrofuran.

Key words: lignan; tetrahydrofuran lignan; olivil; *threo* selective aldol condensation

Olivil (**1**) (Fig.), which is a 4-oxidized 2-aryl-4-benzyl-3-hydroxymethyltetrahydrofuran type of lignan, was isolated from the bark of *Fraxinus mandschurica* Rupr. var *japonica* Maxim (oleaceae), which was used as a diuretic, an antipyretic, an analgesic, and an antirheumatic agent and expected to provide new classes of chemotherapeutic agents.[1] As for the stereoselective synthesis of optically active 4-oxidized 2-aryl-4-benzyl-3-hydroxymethyltetrahydrofuran, synthesis of 2,3-*trans*-olivil type of lignan from D-xylose was done recently.[2] As a next experiment, synthesis of the 2,3-*cis* olivil type of lignan **2** was tried.

The discovery of *erythro* or *threo* selective aldol condensation of γ-butyrolactone with methoxybenzaldehydes[3] has provided us the stimulus for search further *erythro* or *threo* selective aldol condensation. In our effort, it was found that the aldol condensation of 4-pentanolide **3**, which was prepared from L-arabinose, with piperonal gave predominantly *threo* aldol product **4** (*erythro*:*threo* = 1:9, Scheme 1). This result could be applied to synthesis of the 2,3-*cis* olivil type of lignan **2**.

The stereoselective synthetic plan, in which the configuration at the benzylic position of aldol product **4** could be kept through all the steps, is shown in Scheme 2. The benzylic position of aldol product **4** would be transformed to the C2 carbon of 2,3-*cis*-olivil type of lignan **5**. The 2,3-*cis*-olivil type of lignan **5** might be obtained from ketone **6** through stereoselective benzylation. This ketone **6** could be obtained from tetrahydrofuran derivative **7**. The hemiacetal **8** could be converted to tetrahydrofuran derivative **7** by halogenation followed by radical elimination while retaining intact the benzylic stereochemistry. This hemiacetal **8** would be obtained from *threo* aldol product **4**.

This report describes the stereoselective synthesis of (2*R*, 3*R*, 4*R*)-4-benzyl-4-hydroxy-3-hydroxymethyl-2-(3,4-methylenedioxyphenyl) tetrahydrofuran (**2**) using *threo* selective aldol condensation as a key reaction. This is a first report of a stereoselective synthesis of an optically active 2,3-*cis* olivil type of lignan.

Results and Discussion

The 4-pentanolide **3** was prepared from L-arabinose through 4 steps in 46% overall yield by a modification of Sharma and Marquez's method.[4]

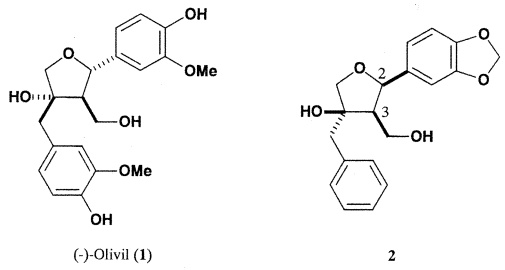
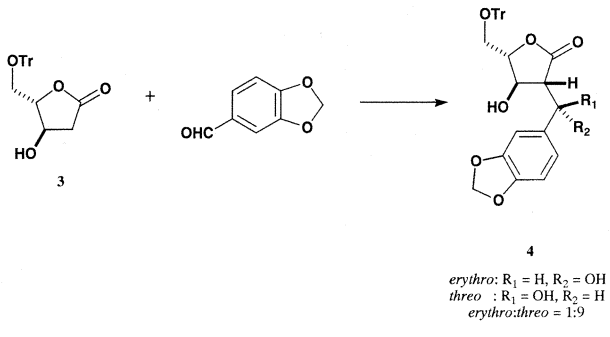


Fig.



Scheme 1. *Threo* Selective Aldol Condensation of 4-Pentanolide **3** with Piperonal.

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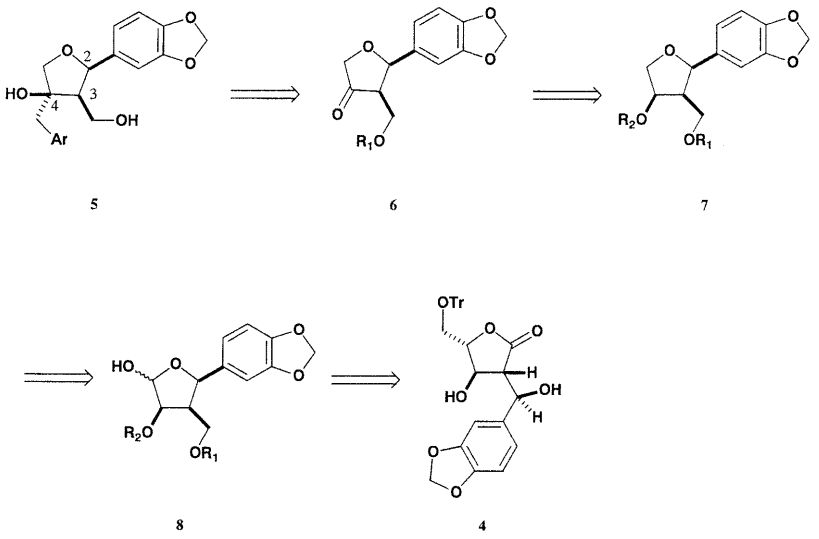
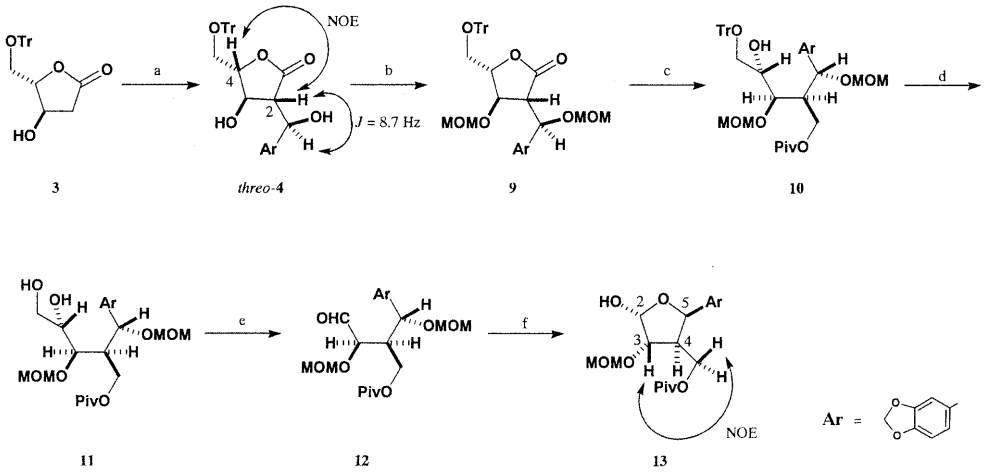


Scheme 2. Retrosynthetic Analysis of Olivil Type of Lignan **5**.



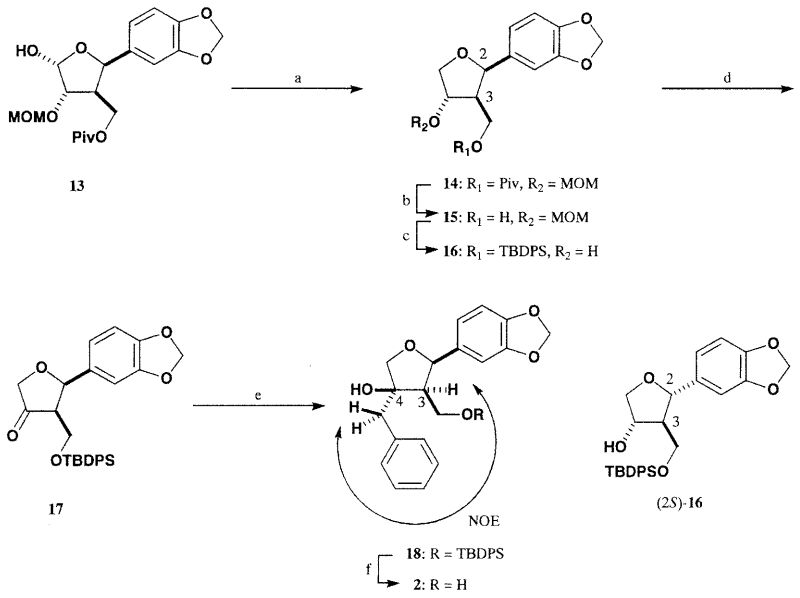
Scheme 3. Synthesis of Olivil Type of Lignan **2** (1).

(a) LDA, piperonal, THF, −75°C, 1 h (56% yield). (b) MOMCl, (*iso*-Pr)$_2$EtN, CH_2Cl_2, r.t., 3 h (84% yield). (c) (1) $LiAlH_4$, THF, r.t., 30 min; (2) PivCl, pyridine, r.t., 1 h (88% yield, 2 steps). (d) PPTS, MeOH, reflux, 3 h (76% yield). (e) $NaIO_4$, MeOH, r.t., 3 h (85% yield). (f) PPTS, *tert*-butyl alcohol, reflux, 2 h (82% yield).

The aldol condensation of this 4-pentanolide **3** with piperonal using lithium diisopropylamide gave selectively *threo* aldol product **4** in 56% yield. The *erythro* isomer was produced in only 6% yield. The coupling constant between benzylic proton and 2-*H* of *threo* isomer was 8.7 Hz. On the other hand, that of *erythro* isomer was 4.4 Hz.[5] The stereochemistry at the 2 position of aldol product **4** was identified by a differential NOE experiment. The fact that the NOE was observed between 2-*H* and 4-*H* confirmed that the configuration at 2 position was *R*.

Methoxymethyl ether was selected for the protection of two hydroxy groups of aldol product **4**. The bis(methoxymethyl) ether **9** was obtained by treatment of **4** with chloromethyl methyl ether and *N*-ethyldiisopropylamine in 84% yield. When the aldol product **4** was converted to bis(*tert*-butyldimethylsilyl) ether, the desilylation occurred in the next reduction process. After lithium aluminum hydride reduction of **9**, the primary hydroxy group of the resulting diol was protected as a pivaloyl ester by using pivaloyl chloride in pyridine in 88% yield. The detritylation of **10** was done by treatment with pyridinium *p*-toluenesulfonate in refluxing methanol to give glycol **11** in 76% yield. The sodium periodate oxidation of **11** (85%) followed by selective deprotection of methoxymethyl ether at the benzylic position using pyridinium *p*-toluenesulfonate in refluxing *tert*-butyl alcohol[6] afforded hemiacetal **13** as a single isomer in 82% yield. The existence of NOE between 3-*H* and two methylene protons of pivaloyloxymethyl group at 4 position clarified the epimerization at 3 position to *S*. Because of no NOE between 2-*H* and 4-*H*, the configuration of 2 position was assumed to be *R* (Scheme 3).

Next stage was reduction of hemiacetal **13** to



Scheme 4. Synthesis of Olivil Type of Lignan **2** (2).
(a) (1) $(COCl)_2$, DMF, CH_2Cl_2, 0°C, 30 min; (2) $(n\text{-}Bu)_3SnH$, AIBN, toluene, reflux, 1 h (71% yield, 2 steps). (b) DIBAL, CH_2Cl_2, −75°C, 30 min (86% yield). (c) (1) 1% conc. HCl, EtOH, reflux, 30 min; (2) TBDPSCl, imidazole, DMF, r.t., 2 h (67% yield, 2 steps). (d) $(COCl)_2$, DMSO, CH_2Cl_2, −75°C, 1 h, and then Et_3N, warmed to 0°C (86% yield). (e) BnMgCl, THF, 0°C, 30 min (58% yield). (f) $(n\text{-}Bu)_4NF$, THF, 0°C, 30 min (67% yield).

tetrahydrofuran derivative **14**. The conversion of hemiacetal **13** to phenylthioacetal was low yield (9% yield), however, the transformation to chloride using oxalyl chloride proceeded well. Without purification, the chloride was treated with tri-*n*-butyltin hydride and 2,2′-azobis(isobutyronitrile) to give 2,3-*cis*-tetrahydrofuran derivative **14** in 71% yield from hemiacetal **13**. After deprotection of pivaloyl ester **14** by diisobutylaluminum hydride reduction (86%), the resulting methoxymethyl ether was treated with HCl to give a crude diol. Without purification, the crude diol was converted to *tert*-butyldiphenylsilyl ether **16** by using *tert*-butyldiphenylsilyl chloride and imidazole in 67% yield. In the process of demethoxymethyl ether by HCl, partial epimerization at the benzylic 2 position occurred, giving (2*S*)-**16** in 6% yield. The chemical shift of 3-*H* of (2*S*)-**16** resonated at higher field (2.10 ppm) than that of (2*R*)-**16** (2.60–2.68 ppm), because of the shielding effect of the aromatic ring of 2 position.

After Swern oxidation of (2*R*)-**16** (86% yield), the resulting ketone **17** was stereoselectively benzylated using benzylmagnesium chloride to give benzyltetrahydrofuran **18** as a single isomer in 58% yield. The existence of NOE between two benzylic protons at 4 position and 3-*H* showed that the configuration at 4 position was *R*. Finally, desilylation of **18** by treatment with tetra-*n*-butylammonium fluoride gave the olivil type of lignan **2** in 67% yield (Scheme 4).

(2*R*, 3*R*, 4*R*)-4-Benzyl-4-hydroxy-3-hydroxymethyl-2-(3,4-methylenedioxyphenyl)tetrahydrofuran **2**, which was an olivil type of lignan, was stereoselectively synthesized from L-arabinose through 19 steps in 1.4% overall yield. This result showed a stereoselective model synthesis of optically active stereoisomer of olivil using *threo* selective aldol condensation as a key reaction.

Experimental

All melting point (mp) data are uncorrected. NMR data were measured by a JNM-EX400 spectrometer. EIMS and FABMS data were measured with Hitachi M-80B and JEOL HX-110 spectrometers, respectively, and optical rotation values were evaluated with a HORIBA SEPA-200. The silica gel used was Wakogel C-300 (Wako, 200–300 mesh), and preparative TLC was done with Merck silica gel 60 F_{254} (0.5 mm thickness, 20 × 20 cm).

(3R, 4S)-3-Hydroxy-5-trityloxy-4-pentanolide (3). After a reaction mixture of L-arabinose (40.0 g, 0.27 mol), 4-dimethylaminopyridine (0.20 g, 0.0016 mol), and trityl chloride (75.3 g, 0.27 mol) in pyridine (50 ml) was stirred at 60°C for 1 h, H_2O and ethyl acetate were added. The organic solution was separated, washed with sat. aq. $CuSO_4$ soln., sat. aq. $NaHCO_3$ soln., and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (ethyl acetate/hexane = 1/1) gave trityloxymethyl hemiacetal (70.6 g, 0.18 mol, 67%) as a colorless oil. To a mixture of the trityloxymethyl hemiacetal (57.2 g, 0.15 mol) and $NaHCO_3$ (480 g, 5.71 mol) in 10% H_2O/ethanol (500 ml) was added 2 M bromine solu-

tion in 10% H_2O/ethanol (550 ml). The resulting reaction mixture was stirred at room temperature for 16 h before addition of $Na_2S_2O_3$. After the mixture was filtered, the filtrate was concentrated, and then the residue was dissolved in ethyl acetate and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (ethyl acetate/hexane = 1/1) gave (2*R*, 3*R*, 4*S*)-2,3-dihydroxy-5-trityloxy-4-pentanolide (49.1 g, 0.13 mol, 87%) as a colorless oil. $[\alpha]_D^{20} = -20.0$ (*c* 0.95, $CHCl_3$). NMR δ_H ($CDCl_3$): 3.32 (1H, dd, J = 10.9, 4.4 Hz), 3.32–3.35 (1H, m), 3.49 (1H, dd, J = 10.9, 3.2 Hz), 4.05 (1H, br. s), 4.23 (1H, ddd, J = 8.3, 4.4, 3.2 Hz), 4.31 (1H, ddd, J = 8.3, 8.3, 3.4 Hz), 4.43 (1H, br. d, J = 8.3 Hz), 7.19–7.30 (11H, m), 7.40–7.42 (4H, m). To a solution of (2*R*, 3*R*, 4*S*)-2,3-dihydroxy-5-trityloxy-4-pentanolide (39.4 g, 0.10 mol), pyridine (12.5 ml, 0.15 mol), and 4-dimethylaminopyridine (2.50 g, 0.020 mol) in acetonitrile (200 ml) was added phenyl chlorothionoformate (19.9 ml, 0.14 mol) in acetonitrile (50 ml) at 0°C. After stirring at 0°C for 1 h, ethyl acetate and H_2O were added. The organic solution was separated, washed with sat. aq. $CuSO_4$ soln., sat. aq. $NaHCO_3$ soln. and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (ethyl acetate/hexane = 1/4) gave (2*R*, 3*S*, 4*S*)-3-hydroxy-2-(phenoxythiocarbonyl)oxy-5-trityloxy-4-pentanolide (45.2 g, 0.086 mol, 86%) as a colorless oil. $[\alpha]_D^{20} = -25.2$ (*c* 0.95, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.99 (1H, s), 3.35 (1H, d, J = 10.3 Hz), 3.62 (1H, d, J = 10.3 Hz), 4.43 (1H, m), 4.76 (1H, m), 6.08 (1H, d, J = 6.8 Hz), 7.15 (2H, d, J = 7.8 Hz), 7.25–7.34 (10H, m), 7.46–7.51 (8H, m). A reaction solution of (2*R*, 3*S*, 4*S*)-3-hydroxy-2-(phenoxythiocarbonyl)oxy-5-trityloxy-4-pentanolide (45.2 g, 0.086 mol), tri-*n*-butyltin hydride (28.5 ml, 0.11 mol), and 2,2′-azobis(isobutyronitrile) (1.76 g, 0.011 mol) in benzene (300 ml) was heated under refluxing for 1 h. Concentration of the solvent followed by silica gel column chromatography (ethyl acetate/hexane = 1/4) gave 4-pentanolide **3** (29.6 g, 0.079 mol, 92%) as colorless crystals, mp 132–133°C (diisopropyl ether/methanol = 9/1). $[\alpha]_D^{20} = -30.8$ (*c* 1.72, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.30 (1H, d, J = 4.4 Hz), 2.49 (1H, dd, J = 18.1, 2.4 Hz), 3.04 (1H, dd, J = 18.1, 6.8 Hz), 3.20 (1H, dd, J = 10.7, 2.9 Hz), 3.52 (1H, dd, J = 10.7, 3.9 Hz), 4.40–4.42 (2H, m), 7.22–7.32 (11H, m), 7.37–7.39 (4H, m). NMR δ_C ($CDCl_3$): 38.5, 63.2, 69.9, 86.4, 87.4, 127.3, 128.0, 128.5, 143.2, 175.7. IR ν_{max} ($CHCl_3$): 3609, 3088–2876, 1779, 1491, 1449, 1227, 1186, 1154, 1102, 1092 cm^{-1}. EIMS m/z (20 eV): 374 (M^+, 24), 243 (100), 183 (91), 105 (83). *Anal.* Found: C, 76.91; H, 6.02. Calcd. for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92%.

(2R, 3R, 4S)-3-Hydroxy-2-[(1R)-1-hydroxy-1-(3,4-methylenedioxyphenyl)methyl-5-trityloxy-4-pentanolide (threo-4). Lithium diisopropylamide was prepared from diisopropylamine (19.9 ml, 0.14 mol) and *n*-butyllithium (92.0 ml, 1.5 M in hexane, 0.14 mol) in tetrahydrofuran (300 ml) at −10°C. To this solution was added 4-pentanolide **3** (24.7 g, 0.066 mol) in tetrahydrofuran (100 ml) at −75°C. After 15 min at −75°C, piperonal (10.0 g, 0.067 mol) in tetrahydrofuran (50 ml) was added. The reaction mixture was stirred at −75°C for 1 h before addition of sat. aq. NH_4Cl soln. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (10% ethyl acetate/benzene) gave *erythro*-**4** (2.15 g, 0.0041 mol, 6%) as a colorless oil and *threo*-**4** (19.4 g, 0.037 mol, 56%) as a colorless oil. *Erythro*-**4**. $[\alpha]_D^{20} = -40.0$ (*c* 0.90, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.69 (1H, d, J = 3.4 Hz, O*H*), 2.61 (1H, d, J = 4.4 Hz, 2-*H*), 2.95 (1H, dd, J = 8.3, 3.9 Hz), 3.34 (1H, dd, J = 10.7, 4.9 Hz), 3.47 (1H, dd, J = 10.7, 3.9 Hz), 4.23 (1H, m), 4.59 (1H, m), 5.26 (1H, dd, J = 4.4, 3.4 Hz, ArC*H*OH), 5.94 (2H, s), 6.79 (1H, d, J = 7.8 Hz), 6.81–6.88 (2H, m), 7.22–7.38 (11H, m), 7.43–7.45 (4H, m). NMR δ_C ($CDCl_3$): 56.1, 62.3, 70.1, 82.2, 86.9, 101.2, 106.0, 106.1, 108.5, 118.7, 127.2, 127.4, 127.8, 127.9, 128.0, 128.3, 128.6, 128.7, 134.5, 143.0, 143.4, 147.3, 148.1, 174.0. IR ν_{max} ($CHCl_3$): 3611, 3092–3038, 2897, 1775, 1505, 1491, 1480, 1449, 1254, 1242, 1042 cm^{-1}. FABMS m/z: 547 ($(M+Na)^+$, 50), 243 (100), 173 (56), 165 (30). HRMS (FAB) m/z $(M+Na)^+$: Calcd. for $C_{32}H_{28}O_7Na$, 547.1733; found, 547.1730. *Threo*-**4**. $[\alpha]_D^{20} = -43.6$ (*c* 0.78, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.52 (1H, d, J = 3.4 Hz), 2.90 (1H, dd, J = 8.7, 8.7 Hz, 2-*H*), 3.22 (1H, dd, J = 10.7, 4.4 Hz), 3.48 (1H, dd, J = 10.7, 3.2 Hz), 3.98 (1H, s), 4.09 (1H, ddd, J = 4.4, 3.9, 3.2 Hz), 4.24 (1H, ddd, J = 8.7, 3.9, 3.4 Hz), 4.84 (1H, d, J = 8.7 Hz, ArC*H*OH), 5.92 (1H, d, J = 6.3 Hz), 5.93 (1H, d, J = 6.3 Hz), 6.77 (2H, s), 6.90 (1H, s), 7.22–7.41 (15H, m). NMR δ_C ($CDCl_3$): 55.1, 61.9, 69.9, 73.2, 82.6, 87.0, 101.3, 107.0, 108.4, 120.1, 127.2, 128.0, 128.3, 128.5, 128.6, 133.3, 143.1, 143.2, 147.9, 148.2, 175.5. IR ν_{max} ($CHCl_3$): 3598, 3090–3088, 2924, 1765, 1505, 1489, 1449, 1250, 1177, 1096, 1042 cm^{-1}. FABMS m/z: 547 ($(M+Na)^+$, 71), 243 (100), 173 (40), 165 (22). HRMS (FAB) m/z $(M+Na)^+$: Calcd. for $C_{32}H_{28}O_7Na$, 547.1733; found, 547.1729.

(2R, 3R, 4S)-3-Methoxymethoxy-2-[(1R)-1-methoxymethoxy-1-(3,4-methylenedioxyphenyl)methyl-5-trityloxy-4-pentanolide (9). A reaction mixture of *threo*-diol **4** (26.3 g, 0.050 mol), *N*-ethyldiisopropylamine (280 ml, 1.61 mol), and chloromethyl methyl ether (63.6 ml, 0.84 mol) in dichloromethane (50 ml) was stirred at room temperature for 3 h. After additions of dichloromethane and H_2O, the organic solution was separated, washed with 1 M aq. HCl soln., sat. aq. $NaHCO_3$ soln., and brine, and dried

(Na_2SO_4). Concentration followed by silica gel column chromatography (ethyl acetate/hexane = 1/3) gave bis(methoxymethyl) ether **9** (25.5 g, 0.042 mol, 84%) as a colorless oil. $[\alpha]_D^{20} = +14.5$ (*c* 3.04, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.91 (1H, dd, $J = 10.7$, 5.4 Hz), 3.10–3.15 (2H, m), 3.13 (3H, s), 3.34 (3H, s), 4.24 (1H, m), 4.29 (1H, m), 4.42 (2H, s), 4.57 (2H, s), 5.10 (1H, d, $J = 4.4$ Hz), 5.85 (2H, s), 6.64 (1H, d, $J = 8.1$ Hz), 6.74 (1H, d, $J = 8.1$ Hz), 6.85 (1H, s), 7.21–7.30 (11H, m), 7.36–7.38 (4H, m). NMR δ_C ($CDCl_3$): 54.2, 55.5, 56.0, 62.7, 74.6, 74.9, 82.7, 94.1, 95.7, 101.0, 107.9, 108.2, 121.1, 127.1, 127.3, 127.9, 128.0, 128.5, 128.6, 131.1, 143.2, 143.4, 147.5, 147.8, 173.4. IR ν_{max} ($CHCl_3$): 2934, 2896, 1775, 1505, 1489, 1449, 1254, 1242, 1221, 1154, 1103, 1042 cm^{-1}. EIMS *m/z* (20 eV): 612 (M^+, 2), 243 (100), 195 (47). *Anal.* Found: C, 70.15; H, 5.91. Calcd. for $C_{36}H_{36}O_9$: C, 70.57; H, 5.92%.

(2S, 3R, 4R,5R)-3,5-Bis(methoxymethoxy)-5-(3,4-methylenedioxyphenyl) - 4 - pivaloyloxymethyl - 1-trityloxy-2-pentanol (10). To an ice-cooled suspension of lithium aluminum hydride (1.05 g, 0.028 mol) in tetrahydrofuran (20 ml) was added a solution of lactone **9** (15.0 g, 0.024 mol) in tetrahydrofuran (50 ml). The reaction mixture was stirred at room temperature for 30 min, and then sat. aq. $MgSO_4$ soln. and K_2CO_3 were added. After this was stirred at room temperature for 1 h, the mixture was filtered. The filtrate was concentrated to give the crude diol. To a solution of the crude diol in pyridine (50 ml) was added pivaloyl chloride (3.66 ml, 0.030 mol). After this was stirred at room temperature for 1 h, ethyl acetate and H_2O were added. The organic solution was separated, washed with sat. aq. $CuSO_4$ soln., sat. aq. $NaHCO_3$ soln. and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (ethyl acetate/hexane = 1/4) gave pivaloyl ester **10** (14.7 g, 0.021 mol, 88%) as a colorless oil. $[\alpha]_D^{20} = +56.2$ (*c* 1.30, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.19 (9H, s), 2.47 (1H, m), 2.68 (1H, br. s), 3.13 (1H, dd, $J = 10.0$, 5.4 Hz), 3.15 (3H, s), 3.30 (3H, s), 3.33 (1H, dd, $J = 10.0$, 3.7 Hz), 3.61 (1H, dd, $J = 7.3$, 4.4 Hz), 3.74 (1H, m), 4.28 (1H, d, $J = 6.6$ Hz), 4.33 (1H, d, $J = 6.6$ Hz), 4.41–4.43 (2H, m), 4.45 (2H, s), 4.92 (1H, d, $J = 6.8$ Hz), 5.92 (1H, d, $J = 1.5$ Hz), 5.95 (1H, d, $J = 1.5$ Hz), 6.76 (1H, d, $J = 7.8$ Hz), 6.80 (1H, dd, $J = 7.8$, 1.5 Hz), 6.85 (1H, d, $J = 1.5$ Hz), 7.20–7.29 (11H, m), 7.35–7.37 (4H, m). NMR δ_C ($CDCl_3$): 27.2, 38.8, 46.8, 55.9, 56.1, 61.5, 64.4, 70.8, 76.1, 79.2, 86.7, 94.4, 98.0, 101.0, 107.9, 108.0, 121.3, 127.1, 127.8, 128.7, 134.6, 143.7, 147.0, 147.8, 178.3. IR ν_{max} ($CHCl_3$): 3715, 3088–2778, 1721, 1505, 1489, 1449, 1287, 1240, 1211, 1156, 1096, 1034 cm^{-1}. EIMS *m/z* (20 eV): 700 (M^+, 1), 243 (100), 195 (68). *Anal.* Found: C, 69.77; H, 6.97. Calcd. for $C_{41}H_{48}O_{10}$: C, 70.27; H, 6.90%.

(2S, 3R, 4R, 5R)-3,5-Bis(methoxymethoxy)-5-(3,4-methylenedioxyphenyl) - 4 - pivaloyloxymethyl - 1, 2-pentanediol (11). A reaction solution of trityl ether **10** (2.81 g, 4.01 mmol), pyridinium *p*-toluenesulfonate (10 mg, 0.040 mmol) in methanol (40 ml) was refluxed for 3 h, and then a few drops of triethylamine was added. After concentration, the residue was applied to silica gel column chromatography (ethyl acetate/hexane = 1/1) to give glycol **11** (1.40 g, 3.05 mmol, 76%) as a colorless oil. $[\alpha]_D^{20} = +46.0$ (*c* 0.50, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.19 (9H, s), 2.29 (1H, m), 3.35 (3H, s), 3.40 (3H, s), 3.60–3.69 (4H, m), 4.29 (1H, dd, $J = 11.7$, 6.8 Hz), 4.35 (1H, dd, $J = 11.7$, 3.4 Hz), 4.48 (2H, s), 4.58–4.65 (2H, m), 4.91 (1H, d, $J = 5.9$ Hz), 5.96 (2H, s), 6.76–6.84 (3H, m). NMR δ_C ($CDCl_3$): 27.1, 38.7, 47.2, 56.1, 56.3, 61.2, 63.3, 71.4, 76.2, 81.1, 94.7, 98.4, 101.1, 107.4, 108.1, 120.8, 134.1, 147.1, 147.9, 178.2. IR ν_{max} ($CHCl_3$): 3715, 2975–2778, 1723, 1505, 1489, 1445, 1285, 1242, 1156, 1096, 1073, 1040, 936 cm^{-1}. EIMS *m/z* (20 eV): 458 (M^+, 3), 195 (100). *Anal.* Found: C, 57.41; H, 7.47. Calcd. for $C_{22}H_{34}O_{10}$: C, 57.63; H, 7.47%.

(2R, 3R, 4R) - 2, 4 - Bis(methoxymethoxy) - 4 - (3, 4-methylenedioxyphenyl) - 3 - pivaloyloxymethylbutanal (12). A reaction mixture of glycol **11** (1.54 g, 3.36 mmol) and $NaIO_4$ (0.87 g, 4.07 mmol) in methanol (30 ml) was stirred at room temperature for 3 h. After the mixture was concentrated, the residue was dissolved in H_2O and ethyl acetate. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (ethyl acetate/hexane = 1/3) gave aldehyde **12** (1.22 g, 2.86 mmol, 85%) as a colorless oil. $[\alpha]_D^{20} = +100$ (*c* 0.22, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.21 (9H, s), 2.67 (1H, m), 3.32 (3H, s), 3.36 (3H, s), 3.88 (1H, m), 4.31 (1H, dd, $J = 11.2$, 7.8 Hz), 4.41 (1H, d, $J = 6.8$ Hz), 4.45 (1H, d, $J = 6.8$ Hz), 4.54 (1H, dd, $J = 11.2$, 3.4 Hz), 4.60 (1H, d, $J = 6.8$ Hz), 4.67 (1H, d, $J = 7.8$ Hz), 4.69 (1H, d, $J = 7.8$ Hz), 5.97 (2H, s), 6.76 (1H, d, $J = 9.3$ Hz), 6.85–6.87 (2H, m), 9.08 (1H, s). NMR δ_C ($CDCl_3$): 27.2, 38.8, 49.2, 56.1, 61.4, 74.2, 80.7, 93.9, 97.5, 101.2, 108.1, 108.2, 122.4, 132.5, 147.9, 148.1, 178.1, 201.7. IR ν_{max} ($CHCl_3$): 2975–2780, 1727, 1505, 1487, 1445, 1283, 1248, 1157, 1096, 1030, 939 cm^{-1}. EIMS *m/z* (20 eV): 426 (M^+, 14), 195 (100), 135 (32). *Anal.* Found: C, 59.06; H, 7.13. Calcd. for $C_{21}H_{30}O_9$: C, 59.15; H, 7.09%.

(2R, 3S, 4R, 5R)-2-Hydroxy-3-methoxymethoxy-5-(3,4-methylenedioxyphenyl)-4-pivaloyloxymethyl-tetrahydrofuran (13). A reaction solution of bis(methoxymethyl) ether **12** (1.53 g, 3.59 mmol) and pyridinium *p*-toluenesulfonate (10 mg, 0.040 mmol) in *tert*-butyl alcohol (40 ml) was heated under refluxing for 2 h before addition of a few drops of triethylamine. Concentration of the solvent followed

by silica gel column chromatography (20% ethyl acetate/benzene) gave hemiacetal **13** (1.13 g, 2.95 mmol, 82%) as a colorless oil. $[\alpha]_D^{20} = -28.0$ (*c* 0.82, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.14 (9H, s), 2.71 (1H, d, $J=2.4$ Hz), 3.13 (1H, m), 3.42 (3H, s), 3.79 (1H, dd, $J=11.2$, 6.4 Hz), 3.83 (1H, dd, $J=11.2$, 8.3 Hz), 4.15 (1H, d, $J=5.4$ Hz), 4.70 (1H, d, $J=6.8$ Hz), 4.75 (1H, d, $J=6.8$ Hz), 5.30 (1H, d, $J=9.8$ Hz), 5.64 (1H, d, $J=2.4$ Hz), 5.94 (2H, s), 6.72 (1H, d, $J=7.8$ Hz), 6.79 (1H, dd, $J=7.8$, 1.5 Hz), 6.97 (1H, d, $J=1.5$ Hz). NMR δ_C ($CDCl_3$): 27.1, 38.6, 42.8, 55.9, 60.5, 81.5, 81.9, 96.9, 100.7, 101.0, 107.6, 108.2, 121.2, 132.0, 147.2, 147.5, 178.1. IR ν_{max} ($CHCl_3$): 3602, 2975–2780, 1725, 1505, 1489, 1482, 1447, 1285, 1256, 1242, 1156, 1042, 939 cm^{-1}. EIMS *m/z* (20 eV): 382 (M^+, 53), 195 (57), 189 (65), 149 (100). *Anal.* Found: C, 59.76; H, 6.90. Calcd. for $C_{19}H_{26}O_8$: C, 59.68; H, 6.85%.

(2R, 3R, 4S)-4-Methoxymethoxy-2-(3,4-methylenedioxyphenyl)-4-pivaloyloxymethyltetrahydrofuran (14). To an ice-cooled solution of hemiacetal **13** (1.31 g, 3.43 mmol) in dichloromethane (20 ml) and *N,N*-dimethylformamide (0.82 ml) was added oxalyl chloride (1.05 ml, 12.0 mmol). The reaction mixture was stirred in an ice-bath for 30 min and poured into an ice-cooled sat. aq. $NaHCO_3$ soln. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After concentration, the residue was dissolved in toluene (40 ml). To the solution was added tri-*n*-butyltin hydride (1.10 ml, 4.09 mmol) and 2,2′-azobis(isobutyronitrile) (40 mg, 0.24 mmol). The reaction solution was heated under refluxing for 1 h under N_2 atmosphere. Concentration of the solvent followed by silica gel column chromatography (10% ethyl acetate/benzene) gave tetrahydrofuran derivative **14** (0.89 g, 2.43 mmol, 71%) as a colorless oil. $[\alpha]_D^{20} = -9.7$ (*c* 0.72, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.14 (9H, s), 2.80 (1H, m), 3.40 (3H, s), 3.82–3.86 (2H, m), 3.92 (1H, dd, $J=11.2$, 7.8 Hz), 4.23 (1H, dd, $J=10.3$, 1.0 Hz), 4.34 (1H, m), 4.67 (1H, d, $J=6.8$ Hz), 4.73 (1H, d, $J=6.8$ Hz), 5.03 (1H, d, $J=9.3$ Hz), 5.91 (1H, d, $J=1.5$ Hz), 5.92 (1H, d, $J=1.5$ Hz), 6.71 (1H, d, $J=7.8$ Hz), 6.79 (1H, dd, $J=7.8$, 1.5 Hz), 6.97 (1H, d, $J=1.5$ Hz). NMR δ_C ($CDCl_3$): 27.2, 38.6, 46.3, 55.7, 61.0, 73.1, 78.0, 81.6, 96.3, 100.9, 107.6, 108.2, 120.9, 133.1, 147.2, 147.6, 178.1. IR ν_{max} ($CHCl_3$): 3011–2780, 1723, 1505, 1489, 1482, 1445, 1285, 1250, 1244, 1161, 1154, 1042, 939 cm^{-1}. EIMS *m/z* (20 eV): 366 (M^+, 53), 219 (53), 202 (92), 189 (76), 176 (58), 149 (100). *Anal.* Found: C, 62.39; H, 6.90. Calcd. for $C_{19}H_{26}O_7$: C, 62.28; H, 7.21%.

(2R,3R,4S)-3-Hydroxymethyl-4-methoxymethoxy-2-(3,4-methylenedioxyphenyl)tetrahydrofuran (15). To a solution of pivaloyl ester **14** (0.89 g, 2.43 mmol) in dichloromethane (10 ml) was added diisobutylaluminum hydride (3.65 ml, 1 M in toluene, 3.65 mmol) at −75°C. The reaction solution was stirred at −75°C for 30 min, and then 1 M aq. HCl soln. was added. The organic solution was separated, washed with sat. aq. $NaHCO_3$ soln, and brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (ethyl acetate/hexane = 2/1) gave alcohol **15** (0.59 g, 2.09 mmol, 86%) as a colorless oil. $[\alpha]_D^{20} = +46.3$ (*c* 0.82, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.15 (1H, br. s), 2.74 (1H, m), 3.25–3.32 (1H, m), 3.41 (3H, s), 3.50 (1H, dd, $J=11.2$, 9.3 Hz), 3.92 (1H, dd, $J=9.8$, 4.4 Hz), 4.17 (1H, dd, $J=9.8$, 2.4 Hz), 4.46 (1H, m), 4.71 (1H, d, $J=6.6$ Hz), 4.73 (1H, d, $J=6.6$ Hz), 4.97 (1H, d, $J=8.8$ Hz), 5.94 (2H, s), 6.74 (1H, d, $J=8.3$ Hz), 6.77 (1H, d, $J=8.3$ Hz), 6.94 (1H, s). NMR δ_C ($CDCl_3$): 48.9, 55.8, 59.4, 72.7, 79.5, 81.3, 96.8, 100.9, 107.6, 107.7, 120.2, 133.0, 146.9, 147.5. IR ν_{max} ($CHCl_3$): 3605, 3081–2780, 1505, 1489, 1445, 1250, 1242, 1150, 1119, 1103, 1071, 1042, 939 cm^{-1}. EIMS *m/z* (20 eV): 282 (M^+, 47), 237 (28), 219 (25), 189 (100), 151 (37). *Anal.* Found: C, 59.12; H, 6.35. Calcd. for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43%.

(2R, 3S, 4S)-3-(tert-Butyldiphenylsilyl)oxymethyl-4-hydroxy-2-(3,4-methylenedioxyphenyl) tetrahydrofuran (16). A reaction solution of methoxymethyl ether **15** (0.55 g, 1.95 mmol) in ethanol containing 1% conc. HCl (15 ml) was heated under refluxing for 30 min. After cooling to room temperature, sat. aq. $NaHCO_3$ soln. and ethyl acetate were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration gave a crude diol. To a solution of the crude diol and imidazole (0.33 g, 4.85 mmol) in *N,N*-dimethylformamide (0.5 ml) was added *tert*-butyldiphenylsilyl chloride (0.56 ml, 2.15 mmol), and then the reaction solution was stirred at room temperature for 2 h before additions of H_2O and ethyl acetate. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (20% ethyl acetate/benzene) gave silyl ether (2*R*, 3*S*, 4*S*)-**16** (0.62 g, 1.30 mmol, 67%) as a colorless oil and (2*S*, 3*S*, 4*S*)-**16** (0.06 g, 0.12 mmol, 6%) as a colorless oil. (2*R*, 3*S*, 4*S*)-**16**. $[\alpha]_D^{20} = -14.3$ (*c* 0.70, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.10 (9H, s), 2.60–2.68 (2H, m, 3-*H* and O*H*), 3.41 (1H, dd, $J=10.7$, 5.4 Hz), 3.59 (1H, dd, $J=10.7$, 10.3 Hz), 3.94 (1H, dd, $J=9.8$, 3.9 Hz), 4.14 (1H, d, $J=9.8$ Hz), 4.62 (1H, m), 4.89 (1H, d, $J=8.3$ Hz), 5.89 (2H, s), 6.63 (2H, s), 6.82 (1H, s), 7.34–7.38 (4H, m), 7.41–7.43 (2H, m), 7.52–7.55 (4H, m). NMR δ_C ($CDCl_3$): 19.0, 26.8, 49.2, 61.3, 73.8, 75.0, 81.3, 100.8, 107.3, 107.7, 119.7, 127.8, 129.8, 129.9, 132.9, 133.2, 135.4, 135.5, 146.7, 147.4. IR ν_{max} ($CHCl_3$): 3569, 3075–2778, 1505, 1489, 1445, 1429, 1256, 1240, 1113, 1067, 1044, 939 cm^{-1}. EIMS *m/z* (70 eV): 477 ($(M+1)^+$, 1), 191 (57), 161

(100). *Anal.* Found: C, 71.04; H, 6.83. Calcd. for $C_{28}H_{32}O_5Si$: C, 70.56; H, 6.77%. (2*S*, 3*S*, 4*S*)-**16**. $[\alpha]_D^{20} = +36.4$ (*c* 0.88, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.07 (9H, s), 2.10 (1H, m, 3-*H*), 3.13 (1H, br. s), 3.83–3.94 (3H, m), 4.24 (1H, dd, *J* = 9.8, 3.9 Hz), 4.64 (1H, br. s), 4.73 (1H, d, *J* = 9.8 Hz), 5.91 (2H, s), 6.52 (1H, d, *J* = 6.8 Hz), 6.63–6.65 (2H, m), 7.35–7.45 (6H, m), 7.60–7.66 (4H, m). NMR δ_C ($CDCl_3$): 19.1, 26.9, 53.8, 60.6, 74.1, 75.7, 80.4, 100.9, 106.5, 108.0, 119.8, 127.9, 130.0, 130.1, 132.5, 135.0, 135.5, 135.6, 147.1, 147.8. IR ν_{max} ($CHCl_3$): 3500, 3075–2861, 1505, 1489, 1472, 1447, 1429, 1252, 1113, 1082, 1042, 938 cm^{-1}. FABMS *m/z*: 476 (M^+, 5), 191 (48), 161 (100), 135 (76). HRMS (FAB) *m/z* $(M+Na)^+$: Calcd. for $C_{28}H_{32}O_5SiNa$, 499.1916; found, 499.1914.

(4R, 5R)-4-(tert-Butyldiphenylsilyl)oxymethyl-5-(3,4-methylenedioxyphenyl)dihydro-3(2H)-furanone (17). To a solution of dimethylsulfoxide (0.051 ml, 0.72 mmol) in dichloromethane (10 ml) was added oxalyl chloride (0.031 ml, 0.36 mmol). After 10 min at −75°C, alcohol (2*R*)-**16** (0.14 g, 0.29 mmol) in dichloromethane (5 ml) was added. The reaction solution was stirred at −75°C for 1 h before addition of triethylamine (0.14 ml, 1.00 mmol). After the mixture was warmed to 0°C, sat. aq. NH_4Cl soln. and dichloromethane were added, and then the organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (ethyl acetate/hexane = 1/3) gave ketone **17** (0.12 g, 0.25 mmol, 86%) as a colorless oil. $[\alpha]_D^{20} = +31.3$ (*c* 0.51, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.04 (9H, s), 2.35 (1H, m), 3.66 (1H, dd, *J* = 10.3, 2.9 Hz), 3.99 (1H, d, *J* = 16.8 Hz), 4.16 (1H, dd, *J* = 10.3, 3.4 Hz), 4.34 (1H, d, *J* = 16.8 Hz), 5.27 (1H, d, *J* = 9.8 Hz), 5.95 (2H, s), 6.74 (2H, s), 6.84 (1H, s), 7.37–7.44 (6H, m), 7.63–7.65 (4H, m). NMR δ_C ($CDCl_3$): 19.3, 26.8, 57.2, 58.9, 72.4, 81.2, 101.1, 106.6, 108.2, 120.1, 127.7, 127.8, 129.9, 132.6, 132.9, 133.6, 135.6, 135.7, 147.7, 148.1, 213.9. IR ν_{max} ($CHCl_3$): 3013–2861, 1763, 1507, 1489, 1472, 1449, 1429, 1254, 1113, 1042, 974, 938 cm^{-1}. FABMS *m/z*: 497 ($(M+Na)^+$, 100), 267 (66), 173 (60), 135 (93). HRMS (FAB) *m/z* $(M+Na)^+$: Calcd. for $C_{28}H_{30}O_5SiNa$, 497.1760; found, 497.1759.

(2R, 3R, 4R)-4-Benzyl-3-(tert-butyldiphenylsilyl)oxymethyl-4-hydroxy-2-(3,4-methylenedioxyphenyl)tetrahydrofuran (18). To an ice-cooled solution of ketone **17** (88 mg, 0.19 mmol) in tetrahydrofuran (5 ml) was added benzylmagnesium chloride (0.57 mmol, 1 M in diethyl ether, 0.57 mmol). After the reaction solution was stirred in an ice-bath for 30 min, sat. aq. NH_4Cl soln. and ethyl acetate were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel TLC (ethyl acetate/hexane = 1/3) gave benzyltetrahydrofuran **18** (62 mg, 0.11 mmol, 58%) as a colorless oil. $[\alpha]_D^{20} = +23.4$ (*c* 0.56, $CHCl_3$). NMR δ_H ($CDCl_3$): 0.95 (9H, s), 2.46 (1H, ddd, *J* = 8.3, 7.8, 5.9 Hz), 2.92 (1H, d, *J* = 13.7 Hz), 3.09 (1H, d, *J* = 13.7 Hz), 3.25 (1H, s), 3.29 (1H, dd, *J* = 10.7, 5.9 Hz), 3.70 (1H, dd, *J* = 10.7, 7.8 Hz), 3.89 (2H, s), 5.04 (1H, d, *J* = 8.3 Hz), 5.86 (1H, d, *J* = 1.5 Hz), 5.87 (1H, d, *J* = 1.5 Hz), 6.61 (2H, s), 6.76 (1H, s), 7.23–7.25 (3H, m), 7.27–7.36 (7H, m), 7.39–7.45 (3H, m), 7.49–7.51 (2H, m). NMR δ_C ($CDCl_3$): 18.9, 26.8, 45.2, 51.4, 61.7, 78.4, 81.9, 82.3, 100.8, 107.2, 107.7, 119.6, 126.6, 127.6, 127.7, 128.4, 129.7, 129.8, 130.2, 132.6, 132.7, 133.0, 135.5, 137.1, 146.6, 147.4. IR ν_{max} ($CHCl_3$): 3380, 3056–2778, 1505, 1489, 1445, 1429, 1254, 1240, 1113, 1105, 1042, 939 cm^{-1}. FABMS *m/z*: 589 ($(M+Na)^+$, 86), 199 (65), 161 (94), 135 (100), 91 (55). HRMS (FAB) *m/z* $(M+Na)^+$: Calcd. for $C_{35}H_{38}O_5SiNa$, 589.2387; found, 589.2388.

(2R, 3R, 4R)-4-Benzyl-4-hydroxy-3-hydroxymethyl-2-(3,4-methylenedioxyphenyl)tetrahydrofuran (2). To an ice-cooled solution of silyl ether **18** (49 mg, 0.086 mmol) in tetrahydrofuran (5 ml) was added tetra-*n*-butylammonium fluoride (0.10 ml, 1 M in tetrahydrofuran, 0.10 mmol). After the reaction solution was stirred in an ice-bath for 30 min, sat. aq. NH_4Cl soln. and ethyl acetate were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel TLC (ethyl acetate/hexane = 1/1) gave olivil type lignan **2** (19 mg, 0.058 mmol, 67%) as colorless crystals, mp 123–125°C. $[\alpha]_D^{20} = +58.2$ (*c* 0.38, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.49 (1H, m), 3.01 (2H, d, *J* = 12.2 Hz), 3.09 (1H, s), 3.32–3.38 (1H, m), 3.61 (1H, br. dd, *J* = 10.7, 7.8 Hz), 3.87 (2H, s), 5.04 (1H, d, *J* = 8.3 Hz), 5.93 (2H, s), 6.76 (1H, d, *J* = 7.8 Hz), 6.80 (1H, dd, *J* = 7.8, 1.5 Hz), 6.92 (1H, d, *J* = 1.5 Hz), 7.26–7.37 (5H, m). NMR δ_C ($CDCl_3$): 45.2, 51.6, 60.5, 78.4, 82.2, 82.5, 101.0, 107.1, 108.0, 119.5, 127.0, 128.5, 130.2, 132.9, 136.7, 147.0, 147.8. IR ν_{max} ($CHCl_3$): 3577, 3087–2778, 1505, 1491, 1455, 1445, 1254, 1242, 1042, 939 cm^{-1}. EIMS *m/z* (20 eV): 328 (M^+, 51), 151 (100), 91 (65). HRMS (EI) *m/z* (M^+): Calcd. for $C_{19}H_{20}O_5$, 328.1309; found, 328.1307.

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