Biosci. Biotechnol. Biochem., **63** (8), 1453–1462, 1999

Stereoselective Syntheses of (−)-Podorhizol Lignan and its Derivatives: *erythro* and *threo* Preferential Aldol Condensation of Potassium Enolate from γ-Butyrolactone with Alkoxybenzaldehyde

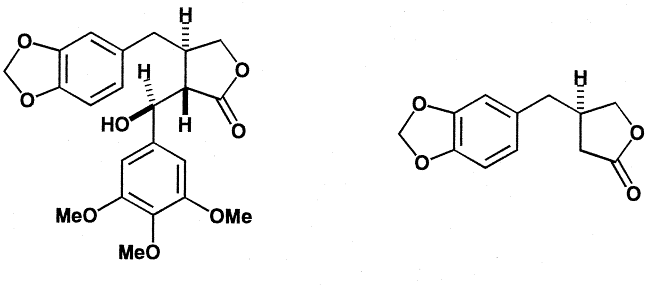
Satoshi YAMAUCHI,† Mitsuo MACHI, and Yoshiro KINOSHITA

College of Agriculture, Ehime University, Tarumi 3-5-7, Matsuyama, Ehime 790-8566, Japan

Received April 7, 1999; Accepted May 7, 1999

(−)-Podorhizol (1) was stereoselectively synthesized by *erythro* preferential aldol condensation of 3,4,5-trimethoxybenzaldehyde with potassium enolate from (+)-(*R*)-3-(3,4-methylenedioxybenzyl)-4-butanolide (2) (*erythro*: *threo* = 85:15). *Erythro* selectivity was observed in the aldol condensation of many alkoxybenzaldehydes with potassium enolate from (+)-γ-butyrolactone 2. However, benzaldehydes having methoxy groups at both the 2 and 6 positions gave *threo* selectivity in the aldol condensation with potassium enolate from (+)-γ-butyrolactone 2.

Key words: lignan; γ-butyrolactone; dibenzyl-γ-butyrolactone; podorhizol; aldol condensation



1

(+)-2

Fig.

Our interest in (−)-podorhizol (1),[1] which has the *erythro* relationship between the β-benzylic position (*S*) and α-position of γ-butyrolactone (*S*), led us to explore the *erythro* selective aldol condensation between (+)-(*R*)-3-(3,4-methylenedioxybenzyl)-4-butanolide (2)[2] and 3,4,5-trimethoxybenzaldehyde (Fig.). It is known that the α,β-dibenzyl-γ-butyrolactone type of lignan could offer interesting biological activity,[3] so stereoselective synthesis of this type of lignan is important.

(±)-Podorhizol has been synthesized by an aldol condensation between (±)-γ-butyrolactone 2 and 3,4,5-trimethoxybenzaldehyde by using lithium bis(trimethylsilyl)amide, giving both *erythro* and *threo* products in the ratio of 1:1.[4] It has been shown that the preference for stereoselectivity in an aldol condensation depended on metal enolates.[5] In our experiment, the *erythro* and *threo* preference in the aldol condensation was examined by using lithium enolate and potassium enolate from (+)-γ-butyrolactone 2. This report describes the *erythro* and *threo* selective aldol condensation of potassium enolate from (+)-γ-butyrolactone 2 with many alkoxybenzaldehydes, including 3,4,5-trimethoxybenzaldehyde.

Materials and Methods

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 was evaluated with HORIBA SEPA-200 equipment. The silica gel used was Wakogel C-300 (Wako, 200–300 mesh).

Aldol condensation with lithium diisopropylamide (LDA). To a solution of diisopropylamine (0.17 ml, 1.20 mmol) in the solvent (4 ml) was added *n*-butyllithium (0.78 ml, 1.54 M in hexane, 1.20 mmol) at −10°C. After 15 min at −10°C, the solution was cooled to −75°C, and then a solution of (+)-γ-butyrolactone 2 (0.21 g, 1.00 mmol) in the solvent (3 ml) was added. After 30 min at −75°C, a solution of each benzaldehyde (1.00 mmol) in the solvent (6 ml) was added. The reaction solution was stirred at −75°C for 1 h before adding a saturated aqueous NH_4Cl solution and ethyl acetate. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography gave the aldol product.

Aldol condensation with potassium diisopropylamide (KDA). To a suspension of diisopropylamine (0.17 ml, 1.20 mmol) and potassium *tert*-butoxide (0.13 g, 1.20 mmol) in the solvent (4 ml) was added *n*-butyllithium (0.78 ml, 1.54 M in hexane, 1.20 mmol) at −10°C. After 15 min at −10°C, the solution was cooled to −75°C, and then a solution of (+)-γ-butyrolactone 2 (0.22 g, 1.00 mmol) in the solvent (3 ml) was added. After 30 min at −75°C, a solution of each benzaldehyde (1.00 mmol) in the solvent (6 ml) was added. The reaction solution was stirred at −75°C for 1 h before adding a saturated NH_4Cl solution and ethyl acetate. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography gave the aldol product.

---

† To whom correspondence should be addressed. Fax: +81-89-977-4364; E-mail: syamauch@agr.ehime-u.ac.jp

Aldol condensation with lithium bis(trimethylsilyl) amide (LHMDS) or potassium bis(trimethylsilyl)amide (KHMDS). To a solvent (4 ml) containing lithium bis(trimethylsilyl)amide (0.12 ml, 1 M in hexane, 0.12 mmol) or potassium bis(trimethylsilyl)amide (0.24 ml, 0.5 M in toluene, 0.12 mmol) was added a solution of (+)-γ-butyrolactone **2** (0.22 g, 1.00 mmol) in the solvent (3 ml) at −75°C. After 30 min at −75°C, a solution of each benzaldehyde (1.00 mmol) in the solvent (6 ml) was added. The reaction solution was stirred at −75°C for 1 h before adding a saturated aqueous NH_4Cl solution and ethyl acetate. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography gave the aldol product.

(−)-Podorhizol (**1**). The *erythro* ((−)-podorhizol (**1**)) and *threo* isomers were separated by silica gel column chromatography ($CH_3OH/CHCl_3=1/99$). *Erythro* **1**, mp 123–125°C (diisopropyl ether), ref. 1, 125–126°C; $[\alpha]_D^{20}=-56.00$ (*c* 0.50, $CHCl_3$), ref. 1, $[\alpha]_D^{20}=-51.80$ (*c* 1.04, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.27 (1H, dd, *J*=13.8, 8.1 Hz), 2.47 (1H, dd, *J*=13.8, 7.8 Hz), 2.63 (1H, dd, *J*=5.9, 2.9 Hz, 3-*H*), 2.75 (1H, d, *J*=4.9 Hz, O*H*), 2.81 (1H, m), 3.83 (9H, s), 3.97 (1H, dd, *J*=8.8, 5.9 Hz), 4.38 (1H, dd, *J*=8.8, 8.8 Hz), 5.27 (1H, dd, *J*=4.9, 2.9 Hz, ArC*H*OH), 5.90 (1H, d, *J*=1.5 Hz), 5.94 (1H, d, *J*=1.5 Hz), 6.23 (1H, d, *J*=1.5 Hz), 6.31 (1H, dd, *J*=7.8, 1.5 Hz), 6.48 (2H, s), 6.59 (1H, d, *J*=7.8 Hz). *threo*-**1**, mp 110–111°C (diisopropyl ether), ref. 4, 113–115°C; $[\alpha]_D^{20}=-21.33$ (*c* 1.13, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.16 (1H, dd, *J*=13.7, 4.9 Hz), 2.23 (1H, dd, *J*=13.7, 9.3 Hz), 2.46 (1H, m), 2.61 (1H, dd, *J*=7.8, 7.8 Hz, 3-*H*), 3.84 (3H, s), 3.88 (6H, s), 3.90 (1H, dd, *J*=8.8, 8.8 Hz), 4.06 (1H, s), 4.16 (1H, dd, *J*=8.8, 8.8 Hz), 4.80 (1H, d, *J*=7.8 Hz, ArC*H*OH), 5.91 (2H, s), 6.33–6.37 (2H, m), 6.65 (2H, s), 6.65–6.69 (1H, m).

(3S, 4R)-3-[(1S and 1R)-1-Hydroxy-1-(2,3,4-trimethoxyphenyl)methyl]-4-(3,4-methylenedioxybenzyl) dihydro-2(3H)-furanone (**3**). The *erythro* and *threo* isomers were separated by silica gel column chromatography ($CH_3OH/CHCl_3=1/99$). 1*S-erythro*-**3**, colorless oil, $[\alpha]_D^{20}=-82.08$ (*c* 0.13, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.24 (1H, dd, *J*=13.9, 6.4 Hz), 2.29 (1H, dd, *J*=13.9, 8.3 Hz), 2.75–2.85 (3H, m), 3.83 (3H, s), 3.84–3.89 (1H, m), 3.87 (3H, s), 3.90 (3H, s), 4.21 (1H, dd, *J*=8.8, 7.8 Hz), 5.51 (1H, br. s, d by D_2O exchange, *J*=2.0 Hz, ArC*H*OH), 5.89 (2H, s), 6.34 (1H, d, *J*=1.5 Hz), 6.37 (1H, dd, *J*=7.8, 1.5 Hz), 6.62 (1H, d, *J*=7.8 Hz), 6.71 (1H, d, *J*=8.5 Hz), 7.21 (1H, d, *J*=8.5 Hz). NMR δ_C ($CDCl_3$): 36.62, 38.91, 50.78, 55.95, 60.72, 67.22, 67.30, 72.13, 100.89, 106.91, 108.10, 108.65, 120.57, 121.44, 126.34, 131.88, 141.72, 146.13, 147.69, 150.01, 153.50, 178.30. IR ν_{max} ($CHCl_3$): 1763 cm^{-1}. HRMS (FAB) *m*/*z* ($M+Na^+$): calcd. for $C_{22}H_{24}O_8Na$, 439.1368; found, 439.1368. 1*R-threo*-**3**, colorless oil, $[\alpha]_D^{20}=-46.87$ (*c* 0.06, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.13–2.17 (2H, m), 2.59–2.66 (2H, m), 3.84 (1H, dd, *J*=9.0, 9.0 Hz), 3.86 (6H, s), 3.95 (3H, s), 4.19 (1H, dd, *J*=9.0, 7.6 Hz), 4.31 (1H, s), 5.12 (1H, d, *J*=8.3 Hz, ArC*H*OH), 5.90 (2H, s), 6.38 (1H, dd, *J*=7.8, 2.0 Hz), 6.39 (1H, d, *J*=2.0 Hz), 6.64 (1H, d, *J*=7.8 Hz), 6.73 (1H, d, *J*=8.8 Hz), 7.16 (1H, d, *J*=8.8 Hz). NMR δ_C ($CDCl_3$): 38.21, 39.68, 51.20, 55.97, 60.81, 68.64, 68.74, 72.07, 100.93, 107.90, 108.26, 108.61, 121.28, 122.17, 126.13, 131.63, 141.95, 146.27, 147.82, 151.22, 153.67, 179.62. IR ν_{max} ($CHCl_3$): 1754 cm^{-1}. HRMS (FAB) *m*/*z* ($M+Na^+$): calcd. for $C_{22}H_{24}O_8Na$, 439.1368; found, 439.1367.

(3S, 4R)-3-[(1S and 1R)-1-Hydroxy-1-(2,4,5-trimethoxyphenyl)methyl]-4-(3,4-methylenedioxybenzyl)-dihydro-2(3H)-furanone (**4**). The *erythro* and *threo* isomers were separated by silica gel column chromatography ($CH_3OH/CHCl_3=1/99$). 1*S-erythro*-**4**, colorless oil, $[\alpha]_D^{20}=-55.55$ (*c* 0.05, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.22 (1H, dd, *J*=13.8, 6.8 Hz), 2.33 (1H, dd, *J*=13.8, 8.5 Hz), 2.80 (1H, m), 2.88 (1H, dd, *J*=7.1, 2.9 Hz, 3-*H*), 3.76 (3H, s), 3.85 (1H, dd, *J*=8.3, 3.4 Hz), 3.89 (6H, s), 4.28 (1H, dd, *J*=8.3, 8.3 Hz), 5.53 (1H, d, *J*=2.9 Hz, ArC*H*OH), 5.89 (2H, s), 6.28 (1H, s), 6.29 (1H, d, *J*=7.3 Hz), 6.41 (1H, s), 6.58 (1H, d, *J*=7.3 Hz), 7.10 (1H, s). NMR δ_C ($CDCl_3$): 36.55, 39.17, 49.97, 55.69, 56.10, 56.76, 67.29, 72.31, 96.71, 100.85, 108.01, 108.73, 110.54, 120.25, 121.40, 131.78, 143.08, 146.00, 147.56, 149.00, 149.58, 178.61. IR ν_{max} ($CHCl_3$): 1759 cm^{-1}. HRMS (FAB) *m*/*z* (M^+): calcd. for $C_{22}H_{24}O_8$, 416.1471; found, 416.1473. 1*R-threo*-**4**, colorless oil, $[\alpha]_D^{20}=-32.25$ (*c* 0.06, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.18–2.20 (2H, m), 2.56 (1H, dd, *J*=8.3, 8.3 Hz, 3-*H*), 2.66 (1H, m), 3.84 (3H, s), 3.84–3.89 (1H, m), 3.85 (3H, s), 3.89 (3H, s), 4.22 (1H, dd, *J*=9.3, 7.8 Hz), 5.27 (1H, d, *J*=8.3 Hz, ArC*H*OH), 5.92 (2H, s), 6.30 (1H, s), 6.34 (1H, d, *J*=7.8 Hz), 6.54 (1H, s), 6.64 (1H, d, *J*=7.8 Hz), 7.00 (1H, s). NMR δ_C ($CDCl_3$): 38.33, 39.44, 51.39, 56.10, 56.37, 56.59, 67.50, 72.12, 97.19, 100.99, 108.12, 108.49, 110.66, 120.12, 121.34, 131.63, 143.82, 146.23, 147.80, 149.49, 150.60, 179.46. IR ν_{max} ($CHCl_3$): 1752 cm^{-1}. HRMS (FAB) *m*/*z* (M^+): calcd. for $C_{22}H_{24}O_8$, 416.1471; found, 416.1472.

(3S, 4R)-3-[(1S and 1R)-1-Hydroxy-1-(2,4,6-trimethoxyphenyl)methyl]-4-(3,4-methylenedioxybenzyl)-dihydro-2(3H)-furanone (**5**). The *erythro* and *threo* isomers were separated by silica gel column chromatography (20% ethyl acetate/benzene). 1*S-erythro*-**5**, colorless oil, $[\alpha]_D^{20}=-39.47$ (*c* 0.23, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.56 (2H, d, *J*=7.8 Hz), 2.72 (1H, dd, *J*=5.7, 5.4 Hz, 3-*H*), 2.92 (1H, m), 3.79 (6H, s), 3.80 (3H, s), 3.94 (1H, dd, *J*=8.8, 4.6 Hz), 4.26 (1H, dd, *J*=8.8, 7.3 Hz), 4.55 (1H, d, *J*=10.7, O*H*), 5.44 (1H, dd, *J*=10.7, 5.4 Hz, ArC*H*OH), 5.91 (2H, s), 6.10 (2H, s), 6.44 (1H, s), 6.45 (1H, d, *J*=7.3 Hz), 6.70 (1H, d, *J*=7.3 Hz). NMR δ_C ($CDCl_3$): 38.38, 39.38, 51.14, 55.24, 55.65, 67.57, 67.68, 71.45, 90.95, 100.88, 107.98, 108.35, 108.79, 121.74, 132.03, 146.07, 147.65, 158.24, 160.81, 177.21. IR ν_{max} ($CHCl_3$): 1765 cm^{-1}. HRMS (FAB) *m*/*z* ($M+Na^+$): calcd. for $C_{22}H_{24}O_8Na$, 439.1368; found, 439.1366. 1*R-threo*-**5**, colorless oil, $[\alpha]_D^{20}=-62.50$ (*c* 0.03, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.35–2.48 (3H, m), 2.95 (1H, dd, *J*=9.3, 4.6 Hz, 3-*H*), 3.77 (6H, s), 3.81

(3H, s), 3.95 (1H, dd, J=9.0, 4.2 Hz), 4.15 (1H, br. s), 4.34 (1H, dd, J=9.0, 6.6 Hz), 5.27 (1H, d, J=9.3 Hz, ArC*H*OH), 5.90 (2H, d, J=1.0 Hz), 6.10 (2H, s), 6.27 (1H, d, J=1.5 Hz), 6.35 (1H, dd, J=7.8, 1.5 Hz), 6.62 (1H, d, J=7.8 Hz). NMR δ_C ($CDCl_3$): 38.66, 40.48, 49.61, 55.28, 55.72, 66.52, 71.69, 90.97, 100.84, 107.99, 108.60, 121.58, 132.01, 146.02, 147.61, 158.76, 161.12, 178.13. IR ν_{max} ($CHCl_3$): 1763 cm^{-1}. HRMS (FAB) m/z ($M+Na^+$): calcd. for $C_{22}H_{24}O_8Na$, 439.1368; found, 439.1366.

(3S, 4R)-3-[(1S and 1R)-1-Hydroxy-1-(2,3-dimethoxyphenyl)methyl]-4-(3,4-methylenedioxybenzyl)dihydro-2(3H)-furanone (**6**). The *erythro* and *threo* isomers were separated by silica gel column chromatography ($CH_3OH/CHCl_3$=1/99). 1*S-erythro*-**6**, colorless oil, $[\alpha]_D^{20}$= −108.57 (c 0.70, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.10 (1H, dd, J=13.6, 5.4 Hz), 2.21 (1H, dd, J=13.6, 9.5 Hz), 2.83 (1H, m), 2.90 (1H, dd, J=8.1, 1.4 Hz, 3-*H*), 3.84 (1H, dd, J=8.5, 8.5 Hz), 3.86 (6H, s), 4.18 (1H, dd, J=8.5, 8.5 Hz), 5.60 (1H, d, J=1.4 Hz, ArC*H*OH), 5.89 (2H, s), 6.33 (1H, d, J=7.8 Hz), 6.34 (1H, s), 6.61 (1H, d, J=7.8 Hz), 6.88 (1H, d, J=7.8 Hz), 7.12 (1H, dd, J=7.8, 7.8 Hz), 7.18 (1H, d, J=7.8 Hz). NMR δ_C ($CDCl_3$): 36.55, 38.99, 50.68, 55.66, 60.50, 67.18, 72.06, 100.81, 108.14, 108.70, 111.99, 118.03, 121.35, 124.06, 132.00, 134.26, 145.21, 146.07, 147.62, 152.28, 178.25. IR ν_{max} ($CHCl_3$): 1761 cm^{-1}. HRMS (EI) m/z (M^+): calcd. for $C_{21}H_{22}O_7$, 386.1364; found, 386.1360. 1*R-threo*-**6**, colorless oil, $[\alpha]_D^{20}$= −31.70 (c 0.41, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.00 (1H, dd, J=13.8, 4.6 Hz), 2.08 (1H, dd, J=13.8, 9.3 Hz), 2.60–2.70 (1H, m), 2.61 (1H, dd, J=8.3, 8.3 Hz, 3-*H*), 3.84 (1H, dd, J=8.8, 8.8 Hz), 3.88 (6H, s), 4.18 (1H, dd, J=8.8, 7.8 Hz), 4.27–4.45 (1H, br.), 5.23 (1H, d, J=8.3 Hz, ArC*H*OH), 5.90 (2H, s), 6.33 (1H, d, J=7.8 Hz), 6.34 (1H, s), 6.64 (1H, dd, J=6.6, 1.7 Hz), 6.90 (1H, dd, J=7.3, 2.4 Hz), 7.07–7.14 (2H, m). NMR δ_C ($CDCl_3$): 38.14, 39.52, 51.05, 55.76, 61.04, 68.61, 72.16, 100.86, 108.22, 108.76, 112.17, 119.19, 121.36, 124.66, 131.68, 133.80, 146.18, 146.40, 147.73, 152.57, 179.71. IR ν_{max} ($CHCl_3$): 1761 cm^{-1}. HRMS (EI) m/z (M^+): calcd. for $C_{21}H_{22}O_7$, 386.1364; found, 386.1361.

(3S, 4R)-3-[(1S and 1R)-1-Hydroxy-1-(2,4-dimethoxyphenyl)methyl]-4-(3,4-methylenedioxybenzyl)dihydro-2(3H)-furanone (**7**). The *erythro* and *threo* isomers were separated by silica gel column chromatography ($CH_3OH/CHCl_3$=1/99). 1*S-erythro*-**7**, colorless crystals, mp 119–120°C (MeOH), $[\alpha]_D^{20}$= −98.93 (c 0.37, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.21 (1H, dd, J=13.7, 7.3 Hz), 2.35 (1H, dd, J=13.7, 7.8 Hz), 2.77 (1H, m), 2.86 (1H, dd, J=6.8, 2.9 Hz, 3-*H*), 3.72 (3H, s), 3.81 (3H, s), 3.91 (1H, dd, J=8.8, 5.9 Hz), 4.31 (1H, dd, J=8.8, 8.8 Hz), 5.50 (1H, d, J=2.9 Hz, ArC*H*OH), 5.89 (2H, d, J=2.4 Hz), 6.22 (1H, d, J=2.0 Hz), 6.30 (1H, dd, J=7.8, 2.4 Hz), 6.32 (1H, d, J=2.4 Hz), 6.51 (1H, dd, J=8.3, 2.0 Hz), 6.58 (1H, d, J=7.8 Hz), 7.40 (1H, d, J=8.3 Hz). NMR δ_C ($CDCl_3$): 36.45, 39.31, 49.66, 55.03, 55.26, 67.57, 72.47, 98.18, 100.86, 103.70, 107.78, 108.59, 121.49, 121.54, 126.68, 131.75, 145.97, 147.55, 156.33, 160.44, 178.69. IR ν_{max} ($CHCl_3$): 1761 cm^{-1}. Anal. Found: C, 65.09; H, 5.63%. Calcd. for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74%. 1*R-threo*-**7**, colorless oil, $[\alpha]_D^{20}$= −14.28 (c 0.07, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.15–2.26 (2H, m), 2.55–2.70 (2H, m), 3.81 (3H, s), 3.83 (3H, s), 3.85 (1H, dd, J=9.0, 8.3 Hz), 4.07 (1H, br. s), 4.19 (1H, dd, J=9.0, 7.8 Hz), 5.20 (1H, d, J=7.3 Hz, ArC*H*OH), 5.91 (2H, s), 6.33 (1H, s), 6.33 (1H, d, J=7.8 Hz), 6.47 (1H, d, J=2.4 Hz), 6.54 (1H, dd, J=8.3, 2.4 Hz), 6.65 (1H, d, J=7.8 Hz), 7.37 (1H, d, J=8.3 Hz). NMR δ_C ($CDCl_3$): 38.29, 39.79, 51.13, 55.36, 68.27, 71.93, 98.45, 100.93, 104.91, 108.24, 108.58, 121.16, 121.32, 128.61, 131.79, 146.21, 147.78, 157.45, 160.74, 179.25. IR ν_{max} ($CHCl_3$): 1757 cm^{-1}. HRMS (EI) m/z (M^+): calcd. for $C_{21}H_{22}O_7$, 386.1364; found, 386.1353.

(3S, 4R)-3-[(1S and 1R)-1-Hydroxy-1-(2,5-dimethoxyphenyl)methyl]-4-(3,4-methylenedioxybenzyl)dihydro-2(3H)-furanone (**8**). The *erythro* and *threo* isomers were separated by silica gel column chromatography (CH_3OH/CH_2Cl_2=1/99). 1*S-erythro*-**8**, colorless oil, $[\alpha]_D^{20}$= −67.39 (c 1.83, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.15 (1H, dd, J=13.8, 6.6 Hz), 2.29 (1H, dd, J=13.8, 8.3 Hz), 2.66 (1H, br. s), 2.81 (1H, m), 2.92 (1H, dd, J=7.3, 2.9 Hz, 3-*H*), 3.73 (3H, s), 3.81 (3H, s), 3.90 (1H, dd, J=8.7, 6.6 Hz), 4.29 (1H, dd, J=8.7, 8.7 Hz), 5.56 (1H, d, J=2.9 Hz, ArC*H*OH), 5.89 (2H, d, J=1.0 Hz), 6.25 (1H, s), 6.28 (1H, d, J=7.8 Hz), 6.58 (1H, d, J=7.8 Hz), 6.70 (1H, d, J=6.8 Hz), 6.77 (1H, dd, J=8.8, 2.9 Hz), 7.15 (1H, d, J=2.9 Hz). NMR δ_C ($CDCl_3$): 36.36, 39.10, 49.47, 55.46, 55.81, 67.40, 72.29, 100.81, 107.98, 108.71, 110.80, 112.66, 112.84, 121.46, 130.07, 131.79, 146.01, 147.55, 149.57, 153.77, 178.53. IR ν_{max} ($CHCl_3$): 1759 cm^{-1}. HRMS (EI) m/z (M^+): calcd. for $C_{21}H_{22}O_7$, 386.1364; found, 386.1360. 1*R-threo*-**8**, colorless oil, $[\alpha]_D^{20}$= −34.83 (c 0.89, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.13–2.20 (2H, m), 2.59 (1H, dd, J=7.8, 7.8 Hz, 3-*H*), 2.67 (1H, m), 3.78 (3H, s), 3.82 (3H, s), 3.86 (1H, dd, J=8.8, 8.3 Hz), 4.18 (1H, dd, J=8.8, 7.8 Hz), 5.29 (1H, d, J=7.8 Hz, ArC*H*OH), 5.91 (2H, s), 6.31 (1H, s), 6.33 (1H, d, J=7.8 Hz), 6.65 (1H, d, J=7.8 Hz), 6.82 (1H, dd, J=9.3, 2.9 Hz), 6.86 (1H, d, J=9.3 Hz), 7.06 (1H, d, J=2.9 Hz). NMR δ_C ($CDCl_3$): 38.28, 39.48, 51.30, 55.69, 56.14, 67.87, 72.08, 100.93, 108.20, 108.55, 111.93, 112.99, 114.34, 121.31, 129.69, 131.71, 146.21, 147.76, 150.45, 154.17, 179.21. IR ν_{max} ($CHCl_3$): 1752 cm^{-1}. HRMS (EI) m/z (M^+): calcd. for $C_{21}H_{22}O_7$, 386.1364; found, 386.1359.

(3S, 4R)-3-[(1S and 1R)-1-Hydroxy-1-(2,6-dimethoxyphenyl)methyl]-4-(3,4-methylenedioxybenzyl)dihydro-2(3H)-furanone (**9**). The *erythro* and *threo* isomers were separated by silica gel column chromatography (10% ethyl acetate/benzene). 1*S-erythro*-**9**, colorless oil, $[\alpha]_D^{20}$= −31.74 (c 0.06, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.54 (2H, d, J=7.8 Hz), 2.75 (1H, dd, J=5.9, 5.9 Hz, 3-*H*), 2.97 (1H, m), 3.83 (6H, s), 3.94 (1H, dd, J=9.0, 5.1 Hz), 4.26 (1H, dd, J=9.0, 7.6 Hz), 4.60–4.80 (1H, br.), 5.54 (1H, d, J=5.9 Hz, ArC*H*OH), 5.92 (2H, s), 6.43–6.44 (2H, m), 6.56 (2H, d, J=8.3 Hz),

6.60 (1H, d, J=8.3 Hz), 7.21 (1H, dd, J=8.3, 8.3 Hz). NMR δ_C ($CDCl_3$): 38.28, 39.23, 50.95, 55.72, 67.66, 71.32, 100.86, 104.30, 108.07, 108.84, 115.73, 121.71, 129.22, 131.99, 146.09, 147.66, 157.57, 177.04. IR ν_{max} ($CHCl_3$): 1767 cm^{-1}. HRMS (EI) m/z (M^+): calcd. for $C_{21}H_{22}O_7$, 386.1364; found, 386.1372. 1*R-threo*-**9**, colorless oil, $[\alpha]_D^{20}=-70.17$ (c 0.11, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.37 (1H, dd, J=11.2, 5.9 Hz), 2.44 (1H, m), 2.49 (1H, dd, J=11.2, 7.3 Hz), 2.94 (1H, dd, J=8.8, 4.6 Hz, 3-*H*), 3.79 (6H, s), 3.95 (1H, dd, J=9.0, 4.2 Hz), 4.36 (1H, dd, J=9.0, 6.6 Hz), 5.37 (1H, d, J=8.8 Hz, ArC*H*OH), 5.90 (2H, s), 6.27 (1H, d, J=1.5 Hz), 6.33 (1H, dd, J=7.8, 1.5 Hz), 6.56 (2H, d, J=8.8 Hz), 6.62 (1H, d, J=7.8 Hz), 7.23 (1H, dd, J=8.8, 8.8 Hz). NMR δ_C ($CDCl_3$): 38.65, 40.45, 49.67, 55.80, 66.89, 66.94, 71.71, 100.83, 104.38, 108.09, 108.67, 115.87, 121.58, 128.30, 129.57, 131.98, 146.05, 147.61, 157.99, 177.82. IR ν_{max} ($CHCl_3$): 1767 cm^{-1}. HRMS (EI) m/z (M^+): calcd. for $C_{21}H_{22}O_7$, 386.1364; found, 386.1370.

(3S, 4R)-3-[(1S and 1R)-1-Hydroxy-1-(3,4-dimethoxyphenyl)methyl]-4-(3,4-methylenedioxybenzyl)dihydro-2(3H)-furanone (**10**). The *erythro* and *threo* isomers were separated by silica gel column chromatography ($CH_3OH/CHCl_3=1/99$). 1*S-erythro*-**10**, colorless oil, $[\alpha]_D^{20}=-58.56$ (c 1.14, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.26 (1H, dd, J=13.7, 7.8 Hz), 2.43 (1H, dd, J=13.7, 7.8 Hz), 2.61 (1H, dd, J=6.4, 2.9 Hz, 3-*H*), 2.71 (1H, d, J=4.4 Hz, O*H*), 2.80 (1H, m), 3.81 (3H, s), 3.88 (3H, s), 3.94 (1H, dd, J=8.6, 5.4 Hz), 4.33 (1H, dd, J=8.3, 8.3 Hz), 5.28 (1H, dd, J=4.4, 2.9 Hz, ArC*H*OH), 5.89 (1H, d, J=1.5 Hz), 5.92 (1H, d, J=1.5 Hz), 6.22 (1H, s), 6.32 (1H, d, J=7.8 Hz), 6.59 (1H, d, J=7.8 Hz), 6.67 (1H, s), 6.83 (1H, d, J=8.3 Hz), 6.89 (1H, d, J=8.3 Hz). NMR δ_C ($CDCl_3$): 36.32, 39.31, 52.69, 55.69, 55.80, 71.95, 72.72, 101.04, 107.87, 108.20, 108.51, 110.84, 117.20, 121.53, 131.42, 133.38, 146.18, 147.74, 148.47, 149.03, 178.36. IR ν_{max} ($CHCl_3$): 1759 cm^{-1}. HRMS (EI) m/z (M^+): calcd. for $C_{21}H_{22}O_7$, 386.1364; found, 386.1359. 1*R-threo*-**10**, colorless oil, $[\alpha]_D^{20}=-41.15$ (c 0.49, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.10 (1H, dd, J=13.7, 5.4 Hz), 2.17 (1H, dd, J=13.7, 9.8 Hz), 2.46 (1H, m), 2.60 (1H, dd, J=8.3, 8.3 Hz, 3-*H*), 3.88 (1H, dd, J=9.0, 9.0 Hz), 3.89 (3H, s), 3.90 (3H, s), 4.13 (1H, dd, J=9.0, 8.1 Hz), 4.81 (1H, d, J=8.3 Hz, ArC*H*OH), 5.91 (1H, d, J=1.5 Hz), 5.92 (1H, d, J=1.5 Hz), 6.32 (1H, s), 6.34 (1H, dd, J=7.8, 2.0 Hz), 6.65 (1H, d, J=7.8 Hz), 6.88 (1H, d, J=8.3 Hz), 6.93–6.97 (2H, m). NMR δ_C ($CDCl_3$): 38.14, 39.80, 51.44, 55.90, 55.91, 71.90, 74.41, 101.00, 108.23, 108.56, 109.26, 110.81, 119.12, 121.35, 131.41, 132.58, 146.33, 147.84, 149.33, 149.50, 179.00. IR ν_{max} ($CHCl_3$): 1754 cm^{-1}. HRMS (EI) m/z (M^+): calcd. for $C_{21}H_{22}O_7$, 386.1364; found, 386.1360.

(3S, 4R)-3-[(1S and 1R)-1-Hydroxy-1-(3,5-dimethoxyphenyl)methyl]-4-(3,4-methylenedioxybenzyl)dihydro-2(3H)-furanone (**11**). The *erythro* and *threo* isomers were separated by silica gel column chromatography (10% ethyl acetate/benzene). 1*S-erythro*-**11**, colorless oil, $[\alpha]_D^{20}=-77.73$ (c 1.42, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.24 (1H, dd, J=13.7, 7.8 Hz), 2.40 (1H, dd, J=13.7, 8.3 Hz), 2.61 (1H, dd, J=6.3, 2.9 Hz, 3-*H*), 2.68 (1H, d, J=4.4 Hz, O*H*), 2.83 (1H, m), 3.76 (6H, s), 3.93 (1H, dd, J=8.9, 5.9 Hz), 4.33 (1H, dd, J=8.9, 8.9 Hz), 5.29 (1H, dd, J=4.4, 2.9 Hz, ArC*H*OH), 5.90 (1H, d, J=1.5 Hz), 5.91 (1H, d, J=1.5 Hz), 6.27 (1H, d, J=2.0 Hz), 6.31–6.34 (2H, m), 6.46 (2H, d, J=2.5 Hz), 6.59 (1H, d, J=7.8 Hz). NMR δ_C ($CDCl_3$): 36.21, 39.30, 52.51, 55.28, 71.90, 72.69, 99.61, 100.93, 103.13, 107.96, 108.64, 121.52, 131.56, 143.44, 146.17, 147.67, 160.97, 178.22. IR ν_{max} ($CHCl_3$): 1761 cm^{-1}. HRMS (EI) m/z (M^+): calcd. for $C_{21}H_{22}O_7$, 386.1364; found, 386.1368. 1*R-threo*-**11**, colorless oil, $[\alpha]_D^{20}=-43.47$ (c 1.50, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.12 (1H, dd, J=13.9, 5.1 Hz), 2.17 (1H, dd, J=13.9, 9.3 Hz), 2.47 (1H, m), 2.58 (1H, dd, J=8.3, 8.3 Hz, 3-*H*), 3.80 (6H, s), 3.88 (1H, dd, J=8.3, 8.3 Hz), 4.10 (1H, br. s), 4.13 (1H, dd, J=8.3, 8.3 Hz), 4.79 (1H, d, J=8.3 Hz, ArC*H*OH), 5.91 (2H, s), 6.35–6.36 (2H, m), 6.43 (1H, d, J=2.0 Hz), 6.58 (2H, d, J=2.0 Hz), 6.66 (1H, d, J=8.3 Hz). NMR δ_C ($CDCl_3$): 38.10, 39.77, 51.24, 55.38, 71.95, 74.60, 100.45, 100.98, 104.59, 108.26, 108.68, 121.37, 131.54, 142.33, 146.32, 147.83, 161.15, 178.93. IR ν_{max} ($CHCl_3$): 1754 cm^{-1}. HRMS (EI) m/z (M^+): calcd. for $C_{21}H_{22}O_7$, 386.1364; found, 386.1369.

3,4,5-Tribenzyloxybenzaldehyde (**12**). After a reaction mixture of methyl gallate (10.0 g, 0.054 mol) and K_2CO_3 (44.7 g, 0.32 mol) in acetone was stirred at room temperature for 20 min, benzyl bromide (20.2 ml, 0.17 mol) was added, and then the resulting reaction mixture was stirred at 70°C for 16 h before filtration. The filtrate was concentrated, and the residue was dissolved in dichloromethane and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by recrystallization from diisopropyl ether gave methyl 3,4,5-tribenzyloxybenzoate (21.8 g, 0.048 mol, 89%) as colorless crystals, mp 96–98°C. NMR δ_H ($CDCl_3$): 3.88 (3H, s), 5.11 (2H, s), 5.12 (2H, s), 5.13 (2H, s), 7.24–7.25 (4H, m), 7.37–7.42 (13H, m). To an ice-cooled suspension of lithium aluminum hydride (1.36 g, 0.036 mmol) in tetrahydrofuran (20 ml) was added a solution of methyl 3,4,5-tribenzyloxybenzoate (21.8 g, 0.048 mol) in tetrahydrofuran (200 ml). After the reaction mixture was stirred at 0°C for 1.5 h, a saturated aqueous $MgSO_4$ solution and K_2CO_3 were added, and then the mixture was stirred at room temperature for 1 h. Filtration, concentration of the filtrate, and recrystallization from ethyl acetate gave 3,4,5-tribenzyloxybenzyl alcohol (8.04 g, 0.019 mmol, 40%) as colorless crystals, mp 112–114°C. NMR δ_H ($CDCl_3$): 4.56 (2H, br. s), 5.04 (2H, s), 5.10 (4H, s), 6.66 (2H, s), 7.25–7.26 (4H, m), 7.31–7.38 (6H, m), 7.41–7.43 (5H, m). A reaction mixture of 3,4,5-tribenzyloxybenzyl alcohol (2.00 g, 4.69 mmol), pyridinium chlorochromate (1.11 g, 5.15 mmol), and 4A molecular sieves (0.3 g) in dichloromethane (20 ml) was stirred at room temperature for 15 h before adding of ether. After filtration, the filtrate was concentrated. Silica gel column chromatography (ethyl acetate/hexane=1/3) followed by recrystallization from diisopropyl ether gave **12** (1.36 g, 3.20 mmol, 68%) as colorless crystals, mp 105–107°C. NMR δ_H ($CDCl_3$): 5.16 (6H, s), 7.18 (2H, s), 7.25–7.27 (4H, m), 7.33–7.43 (11H, m), 9.80 (1H, s). IR ν_{max} ($CHCl_3$): 1692 cm^{-1}. Anal. Found: C, 79.08; H, 5.84%. Calcd. for $C_{28}H_{24}O_4$: C, 79.23; H, 5.70%.

(3S, 4R)-3-[(1S and 1R)-1-(3,4,5-Tribenzyloxyphenyl)-1-hydroxymethyl]-4-(3,4-methylenedioxybenzyl)dihydro-2(3H)-furanone (**13**). 1*S-erythro*-**13**. $[\alpha]_D^{20} = -41.90$ (*c* 0.53, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.07 (1H, dd, J=13.8, 7.8 Hz), 2.24 (1H, dd, J=13.8, 7.6 Hz), 2.49 (1H, dd, J=6.1, 2.7 Hz, 3-*H*), 2.57–2.61 (2H, m), 3.87 (1H, dd, J=8.8, 5.9 Hz), 4.26 (1H, dd, J=8.8, 8.8 Hz), 5.05 (6H, s), 5.20 (1H, d, J=2.7 Hz, ArC*H*OH), 5.81 (1H, d, J=1.5 Hz), 5.86 (1H, d, J=1.5 Hz), 6.11 (1H, d, J=1.5 Hz), 6.23 (1H, dd, J=7.8, 1.5 Hz), 6.51 (2H, s), 6.58 (1H, d, J=7.8 Hz), 7.20–7.25 (4H, m), 7.30–7.44 (11H, m). NMR δ_C ($CDCl_3$): 36.07, 39.14, 52.54, 70.95, 71.08, 71.83, 72.74, 75.02, 101.08, 104.51, 107.80, 108.54, 121.49, 127.39, 127.46, 127.78, 127.90, 128.10, 128.50, 131.32, 136.33, 136.96, 137.74, 146.21, 152.74, 178.22. IR ν_{max} ($CHCl_3$): 1759 cm^{-1}. HRMS (FAB) m/z (M^+): calcd. for $C_{40}H_{36}O_8$, 644.2410; found, 644.2404. 1*R-threo*-**13**. $[\alpha]_D^{20} = -22.05$ (*c* 0.14, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.83–1.90 (2H, m), 2.24 (1H, m), 2.42 (1H, dd, J=8.3, 8.3 Hz, 3-*H*), 3.77 (1H, dd, J=9.3, 9.3 Hz), 3.98 (1H, dd, J=9.3, 9.3 Hz), 4.06 (1H, s), 4.67 (1H, d, J=8.3 Hz, ArC*H*OH), 5.07 (2H, d, J=2.0 Hz), 5.11 (2H, s), 5.13 (2H, s), 5.88 (1H, d, J=1.0 Hz), 5.89 (1H, d, J=1.0 Hz), 6.24 (1H, s), 6.26 (1H, d, J=1.5 Hz), 6.62–6.65 (3H, m), 7.16–7.21 (3H, m), 7.29–7.47 (12H, m). NMR δ_C ($CDCl_3$): 37.89, 39.39, 51.35, 71.09, 71.88, 74.50, 75.04, 101.01, 106.16, 108.21, 108.64, 121.38, 127.39, 127.84, 127.90, 128.53, 128.66, 131.31, 135.32, 136.93, 137.52, 138.24, 146.31, 147.83, 152.97, 178.95. IR ν_{max} ($CHCl_3$): 1752 cm^{-1}. HRMS (FAB) m/z (M^+): calcd. for $C_{40}H_{36}O_8$, 644.2410; found, 644.2415.

3-Benzyloxy-4,5-diphenylmethylenedioxybenzaldehyde (**14**). To an ice-cooled suspension of lithium aluminum hydride (0.17 g, 4.48 mmol) in tetrahydrofuran (10 ml) was added a solution of methyl 3-benzyloxy-4,5-diphenylmethylenedioxybenzoate[6] (2.00 g, 4.56 mmol) in tetrahydrofuran (20 ml). The reaction mixture was stirred in an ice bath for 1 h before adding a saturated aqueous $MgSO_4$ solution and K_2CO_3. After stirring at room temperature for 1 h, the mixture was filtered, and then the filtrate was concentrated. The residue was applied to silica gel column chromatography (ethyl acetate/hexane=1/3) to give 3-benzyloxy-4,5-diphenylmethylenedioxybenzyl alcohol (1.51 g, 3.68 mmol, 81%) as a colorless oil. NMR δ_H ($CDCl_3$): 4.50 (2H, d, J=5.4 Hz), 5.23 (2H, s), 6.56 (1H, s), 6.60 (1H, s), 7.30–7.42 (11H, m), 7.56–7.58 (4H, m). A reaction mixture of 3-benzyloxy-4,5-diphenylmethylenedioxybenzyl alcohol (1.21 g, 2.95 mmol), pyridinium chlorochromate (3.18 g, 14.8 mmol), and 4A molecular sieves (0.5 g) in dichloromethane (150 ml) was stirred at room temperature for 1.5 h before adding ether. After filtration, the filtrate was concentrated. The residue was applied to silica gel column chromatography (10% ethyl acetate/hexane) to give **14** (1.08 g, 2.64 mmol, 89%) as colorless crystals, mp 115–117°C (diisopropyl ether). NMR δ_H ($CDCl_3$): 5.26 (2H, s), 7.11 (1H, d, J=1.5 Hz), 7.14 (1H, d, J=1.5 Hz), 7.32–7.43 (11H, m), 7.55–7.57 (4H, m), 9.72 (1H, s). IR ν_{max} ($CHCl_3$): 1690 cm^{-1}. Anal. Found: C, 79.12; H, 5.03%. Calcd. for $C_{27}H_{20}O_4$: C, 79.40; H, 4.94%.

(3S, 4R)-3-[(1S and 1R)-1-(3-Benzyloxy-4,5-diphenylmethylenedioxyphenyl)-1-hydroxymethyl]-4-(3,4-methylenedioxybenzyl)dihydro-2(3H)-furanone (**15**). 1*S-erythro*-**15**. $[\alpha]_D^{20} = -43.14$ (*c* 0.39, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.15 (1H, dd, J=13.7, 7.3 Hz), 2.27 (1H, dd, J=13.7, 8.5 Hz), 2.50 (1H, dd, J=6.4, 2.9 Hz, 3-*H*), 2.56 (1H, d, J=4.9 Hz, O*H*), 2.72 (1H, m), 3.87 (1H, dd, J=8.8, 5.9 Hz), 4.24 (1H, dd, J=8.8, 8.8 Hz), 5.16 (1H, dd, J=4.9, 2.9 Hz, ArC*H*OH), 5.17 (2H, s), 5.79 (2H, s), 6.24 (1H, d, J=7.8 Hz), 6.27 (1H, s), 6.40 (1H, s), 6.49 (1H, d, J=8.3 Hz), 6.61 (1H, s), 7.25–7.40 (11H, m), 7.40–7.58 (4H, m). NMR δ_C ($CDCl_3$): 36.25, 39.15, 52.64, 71.58, 71.75, 72.48, 99.90, 100.88, 107.52, 108.05, 108.72, 117.56, 121.47, 126.35, 127.57, 128.01, 128.20, 128.23, 128.51, 129.10, 129.12, 131.53, 134.87, 135.43, 136.80, 139.92, 140.06, 142.33, 146.17, 147.69, 148.95, 178.06. IR ν_{max} ($CHCl_3$): 1761 cm^{-1}. HRMS (FAB) m/z (M^+): calcd. for $C_{39}H_{32}O_8$, 628.2097; found, 628.2098. 1*R-threo*-**15**. $[\alpha]_D^{20} = -63.32$ (*c* 0.76, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.76 (1H, dd, J=14.2, 4.3 Hz), 2.00 (1H, dd, J=14.2, 4.9 Hz), 2.34 (1H, m), 2.45 (1H, dd, J=8.3, 8.3 Hz, 3-*H*), 3.80 (1H, dd, J=8.3, 8.3 Hz), 4.04 (1H, s, O*H*), 4.05 (1H, dd, J=8.3, 8.3 Hz), 4.68 (1H, d, J=8.3 Hz, ArC*H*OH), 5.23 (1H, d, J=12.2 Hz), 5.27 (1H, d, J=12.2 Hz), 5.89 (2H, s), 6.24 (1H, d, J=7.8 Hz), 6.30 (1H, s), 6.59 (1H, d, J=8.3 Hz), 6.64 (2H, d, J=10.3 Hz), 7.25–7.40 (11H, m), 7.54–7.56 (4H, m). NMR δ_C ($CDCl_3$): 38.01, 39.73, 51.49, 71.73, 71.88, 74.48, 100.94, 101.28, 108.28, 108.68, 109.14, 117.77, 121.35, 126.35, 126.37, 127.57, 128.01, 128.19, 128.22, 128.52, 129.12, 129.16, 131.48, 134.38, 135.71, 136.83, 139.74, 139.84, 142.49, 146.27, 147.78, 148.99, 178.92. IR ν_{max} ($CHCl_3$): 1755 cm^{-1}. HRMS (FAB) m/z (M^+): calcd. for $C_{39}H_{32}O_8$, 628.2097; found, 628.2097.

2,4,5-Tribenzyloxybenzaldehyde (**16**). After a mixture of protocatechualdehyde (25.0 g, 0.18 mol) and K_2CO_3 (100 g, 0.72 mol) in acetone (400 ml) was stirred at room temperature for 1 h, benzyl bromide (47.4 ml, 0.40 mol) was added. The reaction mixture was stirred at room temperature for 16 h and filtered. After the filtrate was concentrated, the residue was dissolved in dichloromethane and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by recrystallization from benzene/hexane=1/1 gave 3,4-dibenzyloxybenzaldehyde (45.3 g, 0.14 mol, 78%) as colorless crystals, mp 90–92°C. NMR δ_H ($CDCl_3$): 5.27 (2H, s), 5.28 (2H, s), 7.20–7.52 (13H, m), 9.85 (1H, s). After a mixture of *m*-chloroperbenzoic acid (4.83 g, 0.028 mol) and KF[7] (2.73 g, 0.047 mol) in dichloromethane (200 ml) was stirred at room temperature for 1 h, 3,4-dibenzyloxybenzaldehyde (5.94 g, 0.018 mol) was added at 0°C. The reaction mixture was stirred at room temperature for 2 h before filtration. After the filtrate was concentrated, a 1 N aqueous NaOH solution was added to the residue. The reaction mixture was stirred at room temperature for 1 h before adding a 1 N aqueous HCl solution and dichloromethane. The organic solution was separated, successively washed with a saturated aqueous $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Concentration followed by recrystallization from diisopropyl ether gave 3,4-dibenzyloxyphenol (2.24 g, 0.0073 mol, 41%) as colorless crystals, mp 102–104°C. NMR δ_H ($CDCl_3$): 4.73 (1H, br. s), 5.05 (2H, s), 5.09 (2H, s), 6.28 (1H, dd, J=8.3, 2.4 Hz), 6.48 (1H, d, J=2.4 Hz), 6.78 (1H, d, J=8.3 Hz), 7.25–7.37 (7H, m), 7.40–7.43 (3H, m). To an ice-cooled suspension of sodium hydride (0.17 g, 60% in oil, 4.25 mmol) in *N*,*N*-dimethylformamide (2 ml) was added a solution of 3,4-dibenzyloxyphenol (1.0 g, 3.26 mmol) in *N*,*N*-dimethylformamide (10 ml). After the reaction mixture was stirred at room temperature for 1 h, H_2O and ethyl acetate were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (ethyl acetate/hexane=1/9) gave 1,3,4-tribenzyloxybenzene (1.08 g, 2.72 mmol, 83%) as a colorless oil. NMR δ_H ($CDCl_3$): 4.95 (2H, s), 5.07 (2H, s), 5.11 (2H, s), 6.45 (1H, dd, J=8.8, 2.9), 6.64 (1H, d, J=2.9 Hz), 6.85 (1H, d, J=8.8 Hz), 7.28–7.41 (15H, m). To a mixture of *N*,*N*-dimethylformamide (0.33 ml, 4.26 mmol) and phosphorus oxichloride (0.40 ml, 4.29 mmol) was added 1,3,4-tribenzyloxybenzene (1.05 g, 2.65 mmol). The reaction mixture was stirred at 70°C for 16 h and then poured into an ice-cooled solution of sodium acetate (32 g) in H_2O (100 ml). After the mixture was extracted with ethyl acetate, the ethyl acetate solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by recrystallization from ethanol gave **16** (0.80 g, 1.88 mmol, 71%) as colorless crystals, mp 130–132°C. NMR δ_H ($CDCl_3$): 5.05 (2H, s), 5.11 (2H, s), 5.17 (2H, s), 6.57 (1H, s), 7.25–7.44 (16H, m), 10.33 (1H, s). IR ν_{max} ($CHCl_3$): 1667 cm^{-1}. Anal. Found: C, 79.45; H, 5.85%. Calcd. for $C_{28}H_{24}O_4$: C, 79.22; H, 5.69%.

(3S, 4R)-3-[(1S and 1R)-1-(2,4,5-Tribenzyloxyphenyl)-1-hydroxymethyl]-4-(3,4-methylenedioxybenzyl) dihydro-2(3H)-furanone (**17**). 1*S*-*erythro*-**17**. $[\alpha]_D^{20}$= −40.00 (*c* 0.20, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.14 (1H, dd, J=13.7, 7.3 Hz), 2.21 (1H, dd, J=13.7, 8.3 Hz), 2.64 (1H, m), 2.84 (1H, dd, J=6.8, 2.9 Hz, 3-*H*), 3.84 (1H, dd, J=8.3, 6.1 Hz), 4.22 (1H, dd, J=8.3, 8.3 Hz), 4.87 (2H, s), 5.10 (2H, d, J=3.9 Hz), 5.13 (2H, d, J=4.9 Hz), 5.55 (1H, d, J=2.9 Hz, ArC*H*OH), 5.85 (1H, d, J=1.5 Hz), 5.86 (1H, d, J=1.5 Hz), 6.16 (1H, s), 6.17 (1H, d, J=7.8 Hz), 6.49 (1H, s), 6.51 (1H, d, J=7.8 Hz), 7.18 (1H, s), 7.26–7.40 (14H, m), 7.47 (1H, d, J=7.3 Hz). NMR δ_C ($CDCl_3$): 36.25, 39.01, 49.82, 67.39, 70.43, 71.82, 72.29, 72.39, 100.82, 101.90, 107.96, 108.80, 114.77, 121.47, 122.11, 126.92, 127.43, 127.68, 127.80, 127.91, 127.98, 128.43, 128.50, 128.65, 131.69, 136.60, 137.00, 137.51, 143.15, 145.96, 147.51, 148.93, 149.10, 178.34. IR ν_{max} ($CHCl_3$): 1763 cm^{-1}. HRMS (FAB) *m*/*z* (M^+): calcd. for $C_{40}H_{36}O_8$, 644.2410; found, 644.2407. 1*R*-*threo*-**17**. $[\alpha]_D^{20}$= −17.64 (*c* 0.51, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.94 (2H, d, J=7.8 Hz), 2.41 (1H, dd, J=8.8, 8.8 Hz, 3-*H*), 2.51 (1H, m), 3.76 (1H, dd, J=8.8, 8.8 Hz), 4.07 (1H, dd, J=8.8, 7.8 Hz), 4.15 (1H, d, J=2.0 Hz, O*H*), 4.92 (1H, d, J=11.7 Hz), 4.97 (1H, d, J=11.7 Hz), 5.09 (1H, d, J=11.7 Hz), 5.12 (2H, s), 5.14 (1H, d, J=11.7 Hz), 5.24 (1H, dd, J=8.8, 2.0 Hz, ArC*H*OH), 5.88 (1H, d, J=1.5 Hz), 5.90 (1H, d, J=1.5 Hz), 6.21 (1H, s), 6.23 (1H, d, J=7.8 Hz), 6.60 (1H, d, J=6.4 Hz), 6.61 (1H, s), 7.08 (1H, s), 7.26–7.39 (13H, m), 7.43 (2H, d, J=7.3 Hz). NMR δ_C ($CDCl_3$): 38.23, 39.33, 51.49, 67.26, 71.71, 71.73, 71.85, 72.08, 100.97, 102.48, 108.10, 108.47, 114.89, 121.26, 127.37, 127.54, 127.59, 127.78, 127.91, 128.24, 128.43, 128.48, 128.72, 131.68, 136.59, 136.87, 137.32, 143.82, 146.20, 147.78, 149.27, 150.22, 179.44. IR ν_{max} ($CHCl_3$): 1754 cm^{-1}. HRMS (FAB) *m*/*z* (M^+): calcd. for $C_{40}H_{36}O_8$, 644.2410; found, 644.2415.

4,5-Dibenzyloxy-2-methoxybenzaldehyde (**18**). A mixture of 3,4-dibenzyloxyphenol (5.60 g, 0.018 mol) and K_2CO_3 (5.05 g, 0.037 mol) in acetone (150 ml) was stirred at room temperature for 1 h before adding dimethyl sulfate (1.90 ml, 0.020 mol). The reaction mixture was stirred at room temperature for 17 h, and then filtered. After the filtrate was concentrated, 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 (1% ethyl acetate/benzene) gave 1,2-dibenzyloxy-4-methoxybenzene (5.88 g, 0.018 mol, 100%) as a colorless oil. NMR δ_H ($CDCl_3$): 3.70 (3H, s), 5.07 (2H, s), 5.11 (2H, s), 6.37 (1H, dd, J=8.3, 2.9 Hz), 6.56 (1H, d, J=2.9 Hz), 6.85 (1H, d, J=8.3 Hz), 7.22–7.37 (7H, m), 7.40–7.44 (3H, m). To a mixture of *N*,*N*-dimethylformamide (2.40 ml, 0.031 mol) and phosphorus oxichloride (2.89 ml, 0.031 mol) was added 1,2-dibenzyloxy-4-methoxybenzene (5.80 g, 0.018 mol). The reaction mixture was stirred at 70°C for 16 h and then poured into an ice-cooled solution of sodium acetate (32 g) in H_2O (100 ml). After the mixture was extracted with ethyl acetate, the ethyl acetate solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by recrystallization from ethanol gave **18** (3.67 g, 0.011 mol, 61%) as colorless crystals, mp 88–89°C. NMR δ_H ($CDCl_3$): 3.81 (3H, s), 5.11 (2H, s), 5.24 (2H, s), 6.52 (1H, s), 7.25–7.39 (8H, m), 7.43–7.44 (3H, m), 10.27 (1H, s). IR ν_{max} ($CHCl_3$): 1667 cm^{-1}. Anal. Found: C, 75.84; H, 5.87%. Calcd. for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79%.

(3S, 4R)-3-[(1S and 1R)-1-(4,5-Dibenzyloxy-2-methoxyphenyl)-1-hydroxymethyl]-4-(3,4-methylenedioxybenzyl)dihydro-2(3H)-furanone (**19**). 1*S*-*erythro*-**19**. $[\alpha]_D^{20}$= −32.08 (*c* 0.37, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.16

(1H, dd, $J=13.7$, 7.3 Hz), 2.26 (1H, dd, $J=13.7$, 7.8 Hz), 2.47–2.60 (1H, br.), 2.61 (1H, m), 2.81 (1H, dd, $J=6.4$, 2.4 Hz, 3-*H*), 3.62 (3H, s), 3.87 (1H, dd, $J=8.8$, 6.3 Hz), 4.26 (1H, dd, $J=8.8$, 8.8 Hz), 5.09–5.18 (4H, m), 5.46 (1H, d, $J=2.4$ Hz, ArC*H*OH), 5.86 (1H, d, $J=1.2$ Hz), 5.87 (1H, d, $J=1.2$ Hz), 6.16 (1H, d, $J=2.0$ Hz), 6.19 (1H, dd, $J=8.0$, 2.0 Hz), 6.41 (1H, s), 6.54 (1H, d, $J=8.0$ Hz), 7.17 (1H, s), 7.25–7.36 (7H, m), 7.42–7.47 (3H, m). NMR δ_C ($CDCl_3$): 36.28, 39.05, 49.60, 55.43, 67.42, 71.93, 72.38, 72.56, 100.30, 100.82, 107.93, 108.83, 115.09, 121.54, 127.48, 127.71, 127.79, 127.93, 128.30, 128.41, 128.49, 131.64, 137.08, 137.56, 142.76, 145.96, 147.50, 149.16, 150.15, 178.57. IR ν_{max} ($CHCl_3$): 1759 cm^{-1}. HRMS (FAB) m/z (M^+): calcd. for $C_{34}H_{32}O_8$, 568.2097; found, 568.2093. 1*R*-*threo*-**19**. $[\alpha]_D^{20}=-9.36$ (*c* 4.91, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.93–2.02 (2H, m), 2.43 (1H, dd, $J=8.8$, 8.8 Hz, 3-*H*), 2.52 (1H, m), 3.73 (3H, s), 3.79 (1H, dd, $J=8.8$, 8.8 Hz), 4.13 (1H, dd, $J=8.8$, 7.8 Hz), 5.07 (1H, d, $J=12.5$ Hz), 5.14 (1H, d, $J=12.5$ Hz), 5.16 (2H, s), 5.20 (1H, d, $J=8.8$ Hz, ArC*H*OH), 5.90 (2H, d, $J=1.5$ Hz), 6.24 (1H, d, $J=2.0$ Hz), 6.27 (1H, dd, $J=7.8$, 2.0 Hz), 6.55 (1H, s), 6.63 (1H, d, $J=7.8$ Hz), 7.08 (1H, s), 7.25–7.36 (7H, m), 7.39–7.44 (3H, m). NMR δ_C ($CDCl_3$): 38.26, 39.37, 51.36, 56.26, 67.41, 71.83, 72.01, 72.09, 100.94, 108.15, 108.46, 115.32, 121.22, 121.26, 127.44, 127.62, 127.76, 127.91, 128.41, 128.46, 131.75, 136.90, 137.35, 143.43, 146.19, 147.76, 149.45, 151.12, 179.45. IR ν_{max} ($CHCl_3$): 1754 cm^{-1}. HRMS (FAB) m/z (M^+): calcd. for $C_{34}H_{32}O_8$, 568.2097; found, 568.2091.

4,5-Dibenzyloxy-2-methoxymethoxybenzaldehyde (**20**). After a reaction mixture of 3,4-dibenzyloxyphenol (5.30 g, 0.017 mol), pulverized KOH (1.91 g, 0.034 mol), and 18-crown-6 (0.90 g, 3.43 mol) in acetonitrile (150 ml) was stirred at room temperature for 1 h, chloromethyl methyl ether (1.42 ml, 0.019 mol) was added. The reaction mixture was stirred at room temperature for 17 h before adding 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 (10% ethyl acetate/hexane) gave 1,2-dibenzyloxy-4-methoxymethoxybenzene (5.88 g, 0.017 mol, 100%) as a colorless oil. NMR δ_H ($CDCl_3$): 3.44 (3H, s), 5.06 (2H, s), 5.08 (2H, s), 5.13 (2H, s), 6.54 (1H, dd, $J=8.8$, 2.4 Hz), 6.70 (1H, d, $J=2.4$ Hz), 6.85 (1H, d, $J=8.8$ Hz), 7.24–7.37 (6H, m), 7.41–7.45 (4H, m). To a mixture of *N*,*N*-dimethylformamide (1.90 ml, 0.025 mol) and phosphorus oxichloride (2.40 ml, 0.026 mol) was added 1,2-dibenzyloxy-4-methoxymethoxybenzene (5.37 g, 0.015 mol). The reaction mixture was stirred at 70°C for 16 h and then poured into an ice-cooled solution of sodium acetate (16 g) in H_2O (50 ml). After the mixture was extracted with ethyl acetate, the ethyl acetate solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (10% ethyl acetate/hexane) gave **20** (5.37 g, 0.014 mol, 93%) as a colorless oil. NMR δ_H ($CDCl_3$): 3.48 (3H, s), 5.12 (2H, s), 5.16 (2H, s), 5.22 (2H, s), 6.84 (1H, s), 7.30–7.37 (7H, m), 7.41–7.45 (4H, m), 10.29 (1H, s). IR ν_{max} ($CHCl_3$): 1669 cm^{-1}. Anal. Found: C, 72.87; H, 5.90%. Calcd. for $C_{23}H_{22}O_5$: C, 73.00; H, 5.86%.

(3S, 4R)-3-[(1S and 1R)-1-(4,5-Dibenzyloxy-2-methoxymethoxy-phenyl)-1-hydroxymethyl]-4-(3,4-methylenedioxybenzyl)dihydro-2(3H)-furanone (**21**). 1*S*-*erythro*-**21**. $[\alpha]_D^{20}=-48.29$ (*c* 0.35, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.15 (1H, dd, $J=13.8$, 7.6 Hz), 2.27 (1H, dd, $J=13.8$, 7.8 Hz), 2.49 (1H, d, $J=3.5$ Hz, O*H*), 2.63 (1H, m), 2.77 (1H, dd, $J=6.6$, 2.7 Hz, 3-*H*), 3.39 (3H, s), 3.87 (1H, dd, $J=8.8$, 5.9 Hz), 4.27 (1H, dd, $J=8.8$, 8.8 Hz), 4.96 (1H, d, $J=6.8$ Hz), 4.98 (1H, d, $J=6.8$ Hz), 5.09–5.18 (4H, m), 5.50 (1H, dd, $J=3.5$, 2.7 Hz, ArC*H*OH), 5.86 (2H, d, $J=1.0$ Hz), 6.14 (1H, s), 6.17 (1H, d, $J=7.8$ Hz), 6.52 (1H, d, $J=7.8$ Hz), 6.73 (1H, s), 7.16 (1H, s), 7.25–7.36 (6H, m), 7.43–7.48 (4H, m). NMR δ_C ($CDCl_3$): 36.08, 39.09, 49.95, 56.04, 67.30, 71.47, 72.29, 72.45, 95.05, 100.84, 103.30, 108.02, 108.78, 114.33, 121.48, 122.03, 127.49, 127.54, 127.58, 127.66, 127.80, 127.90, 128.44, 131.54, 136.91, 137.53, 143.67, 146.01, 147.99, 149.08, 178.47. IR ν_{max} ($CHCl_3$): 1760 cm^{-1}. Anal. Found: C, 69.79; H, 5.70%. Calcd. for $C_{35}H_{34}O_9$: C, 70.22; H, 5.72%. 1*R*-*threo*-**21**. $[\alpha]_D^{20}=-12.98$ (*c* 0.31, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.87 (1H, dd, $J=13.7$, 5.4 Hz), 1.93 (1H, dd, $J=13.7$, 9.3 Hz), 2.40 (1H, dd, $J=8.8$, 8.8 Hz, 3-*H*), 2.50 (1H, m), 3.44 (3H, s), 3.80 (1H, dd, $J=8.8$, 8.8 Hz), 4.13 (1H, dd, $J=8.8$, 8.3 Hz), 4.16 (1H, s), 5.05 (2H, s), 5.06 (2H, s), 5.15 (2H, s), 5.22 (1H, d, $J=8.8$ Hz, ArC*H*OH), 5.89 (1H, d, $J=1.5$ Hz), 5.90 (1H, d, $J=1.5$ Hz), 6.25 (1H, s), 6.26 (1H, d, $J=7.8$ Hz), 6.62 (1H, d, $J=8.3$ Hz), 6.84 (1H, s), 7.05 (1H, s), 7.24–7.36 (6H, m), 7.41–7.69 (4H, m). NMR δ_C ($CDCl_3$): 38.31, 39.41, 51.47, 56.31, 67.27, 71.37, 71.72, 72.17, 96.11, 100.96, 103.89, 108.14, 108.51, 114.45, 121.25, 121.71, 127.49, 127.54, 127.77, 127.87, 128.44, 131.70, 136.75, 137.30, 144.34, 146.22, 147.78, 149.06, 149.38, 179.56. IR ν_{max} ($CHCl_3$): 1752 cm^{-1}. Anal. Found: C, 69.56; H, 5.71%. Calcd. for $C_{35}H_{34}O_9$: C, 70.22; H, 5.72%.

Results and Discussion

(+)-γ-Butyrolactone **2**[2] was prepared from L-glutamic acid *via* (*S*)-4-hydroxymethyl-4-butanolide[8] (99%ee by Mosher's method[9]). To examine the *erythro* or *threo* preference, the aldol condensation of (+)-γ-butyrolactone **2** with alkoxybenzaldehydes, using a lithium or potassium base, was tried.

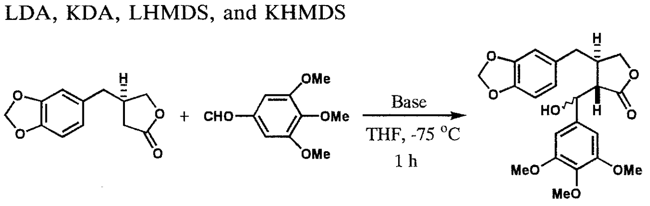
The *erythro* and *threo* isomers of the aldol products were determined by the coupling constant between the β-benzylic proton (Hb) and α-proton (Ha) of γ-butyrolactone.[10] The typical coupling constant between Ha and Hb of *erythro* isomer is 2–4 Hz and that of the *threo* isomer is 6–9 Hz, because the Ha-Hb relationship of the *erythro* isomer is axial-equatorial and that of the *threo* isomer is diaxial due to the formation of a hydrogen bond between hydrogen of the benzylic hydroxy group and oxygen of the carbonyl group. The ratio of the *erythro* and *threo* isomer was determined by 400 MHz ^{1}H-NMR.

Table 1 shows the *erythro* and *threo* ratio of the aldol product in the reaction of (+)-γ-butyrolactone **2** with

3,4,5-trimethoxybenzaldehyde. The lithium enolate did not show *erythro* and *threo* selectivity (entries a and c), whereas employing the potassium enolate led to the preferential production of the *erythro* isomer (entries b and d) which has the same stereochemistry as that of natural (−)-podorhizol. As can be seen from a comparison of potassium diisopropylamide with potassium bis(trimethylsilyl)amide, the bulky potassium base is available to preferentially produce the *erythro* isomer. The *erythro* and *threo* isomers were separated by silica gel column chromatography to afford pure (−)-podorhizol (**1**). The ^{1}H-NMR spectral data agree with these of the literature.[4]

Table 2 shows the effect of the solvent on *erythro* and *threo* selectivity. In the reaction with potassium bis(trimethylsilyl)amide in the presence of hexamethylphosphoramide (HMPA), the stereoselectivity remained in favor of the *erythro* product (entries a and b). The *erythro* preference also remained by the change of solvent to ethylene glycol dimethyl ether (DME), toluene, or hexane from tetrahydrofuran (entries c, d, and e). It seems that the stereoselectivity was decreased a little by adding HMPA or hexane. The stereoselectivity in the aldol condensation with the lithium enolate was not increased by changing the solvent or adding HMPA (entries f, g, and h).

Table 1. *Erythro* and *Threo* Selectivity in the Aldol Condensation of (+)-γ-Butyrolactone **2** with 3,4,5-Trimethoxybenzaldehyde, Using LDA, KDA, LHMDS, and KHMDS



(+)-2

1

Entry	Base	*Erythro* (podorhizol):*threo*	Yield (%)
a	LDA	45:55	55
b	KDA	63:37	76
c	LHMDS	53:47	80
d	KHMDS	85:15	80

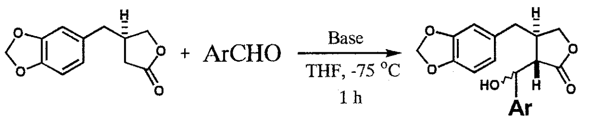
Table 3 shows the *erythro* and *threo* selectivity of the aldol condensation between (+)-lactone **2** and 2,3,4-trimethoxybenzaldehyde, 2,4,5-trimethoxybenzaldehyde or 2,4,6-trimethoxybenzaldehyde when using lithium bis(trimethylsilyl)amide or potassium bis(trimethylsilyl)-amide. The stereoselectivity was reduced by employing the lithium base. Although the aldol condensation of 3,4,5-trimethoxybenzaldehyde (Table 2), 2,3,4-trimethoxybenzaldehyde, and 2,4,5-trimethoxybenzaldehyde gave *erythro* selectivity, *threo* selectivity was observed in the aldol condensation of 2,4,6-trimethoxybenzaldehyde when using potassium bis(trimethylsilyl)amide.

To clarify the relationship between the stereoselectivity of this aldol condensation and the positions of the methoxy groups in benzaldehyde, six dimethoxybenzaldehydes were tested in the aldol condensation with (+)-γ-butyrolactone **2** (Table 4). The aldol condensation of 2,6-dimethoxybenzaldehyde with potassium bis(trimethylsilyl)amide preferentially gave the *threo* product. On the other hand, the stereoselectivity of the other alde-

Table 2. Effect of Solvent on the *Erythro* and *Threo* Selectivity in the Aldol Condensation of (+)-γ-Butyrolactone **2** with 3,4,5-Trimethoxybenzaldehyde

Entry	Base	Solvent	Additive	*Erythro* (podorhizol):*threo*	Yield (%)
a	KHMDS	THF	HMPA (2.0 eq.)	68:32	43
b	KHMDS	THF	HMPA (5.0 eq.)	69:31	39
c	KHMDS	toluene		76:24	93
d	KHMDS	DME		80:20	92
e	KHMDS	THF:hexane=2:1		70:30	65
f	LDA	THF	HMPA (2.0 eq.)	50:50	60
g	LDA	DME		56:44	51
h	LHMDS	toluene		50:50	67

Table 3. *Erythro* and *Threo* Selectivity in the Aldol Condensation of (+)-γ-Butyrolactone **2** with 2,3,4- 2,4,5-, and 2,4,6-Trimethoxybenzaldehyde, Using LHMDS and KHMDS

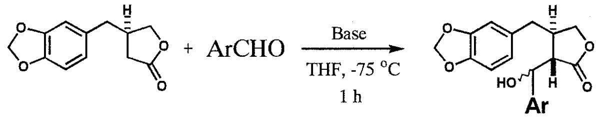


3: Ar = 2,3,4-trimethoxyphenyl
4: Ar = 2,4,5-trimethoxyphenyl
5: Ar = 2,4,6-trimethoxyphenyl

(+)-2

Base	**3**		**4**		**5**	
	Erythro:*threo*	Yield (%)	*Erythro*:*threo*	Yield (%)	*Erythro*:*threo*	Yield (%)
LHMDS	60:40	94	75:25	82	47:53	93
KHMDS	78:22	94	82:18	77	13:87	77

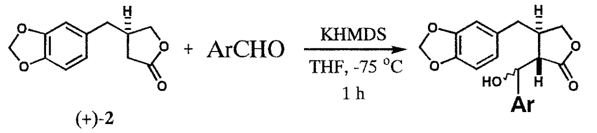
Table 4. *Erythro* and *Threo* Selectivity in the Aldol Condensation of (+)-γ-Butyrolactone **2** with Dimethoxybenzaldehydes, Using LHMDS and KHMDS

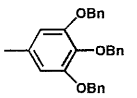
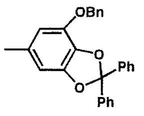
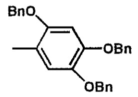
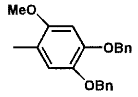
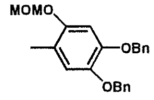


6: Ar = 2,3-dimethoxyphenyl
7: Ar = 2,4-dimethoxyphenyl
8: Ar = 2,5-dimethoxyphenyl
9: Ar = 2,6-dimethoxyphenyl
10: Ar = 3,4-dimethoxyphenyl
11: Ar = 3,5-dimethoxyphenyl

Base	**6**		**7**		**8**		**9**		**10**		**11**	
	Erythro:*threo*	Yield (%)	*Erythro*:*threo*	Yield (%)	*Erythro*:*threo*	Yield (%)	*Erythro*:*threo*	Yield (%)	*Erythro*:*threo*	Yield (%)	*Erythro*:*threo*	Yield (%)
LHMDS	64:36	97	72:28	95	59:41	96	37:63	76	54:46	97	49:51	84
KHMDS	74:26	73	96:4	86	78:22	79	22:78	73	82:18	91	66:34	92

Table 5. Stereoselectivity in the Aldol Condensation of (+)-γ-Butyrolactone **2** with Miscellaneous Benzaldehydes **12**, **14**, **16**, **18**, and **20**, Using KHMDS



Ar	ArCHO	Aldol product	*Erythro*:*threo*	Yield (%)
	**12**	**13**	75:25	44
	**14**	**15**	67:33	68
	**16**	**17**	88:12	68
	**18**	**19**	83:17	67
	**20**	**21**	86:14	63

hydes with potassium bis(trimethylsilyl)amide was in favor of *erythro* products. It was found that the presence of methoxy groups at both the 2 and 6 positions of benzaldehyde caused *threo* selectivity. Higher stereoselectivity was shown by the potassium enolate than the lithium enolate. The highest *erythro* selectivity was achieved in the aldol condensation of 2,4-dimethoxybenzaldehyde (*erythro*:*threo*=96:4).

Finally, miscellaneous protected benzaldehydes **12**, **14**, **16**, **18**, and **20** was subjected to aldol condensation with the potassium enolate of (+)-γ-butyrolactone **2** prepared by potassium bis(trimethylsilyl)amide (Table 5). In all cases, *erythro* selectivity was observed.

It was found that the stereoselectivity of the aldol condensation of alkoxybenzaldehydes with the potassium enolate prepared from (+)-γ-butyrolactone **2** and potassium bis(trimethylsilyl)amide favored *erythro* products (*erythro*:*threo*=66:34–96:4), except for the aldol condensation with 2,4,6-trimethoxybenzaldehyde and 2,6-dimethoxybenzaldehyde, which preferencially gave the *threo* product (*erythro*:*threo*=22:78–13:87). In this experiment, (−)-podorhizol (**1**) was *erythro*-selectively obtained (*erythro*:*threo*=85:15).

Acknowledgments

We measured the 400 MHz NMR data in Advanced Instrumentation Center For Chemical Analysis Ehime University. We thank the staff of Advanced Instrumentation Center For Chemical Analysis Ehime University for EIMS measurements, and the staff of NMR and MS Operation Center in Faculty of Pharmaceutical Science at Fukuoka University for FABMS measurements.

References

1) Kuhn, K. and Wartburg, A. V., Podophyllum-Lignane: Struktur und Absolutkonfiguration von Podorhizol-β-D-glucosid. *Helv. Chem. Acta*, **50**, 1546–1565 (1967).
2) Tomioka, K., Mizuguchi, H., and Koga, K., Stereoselective Reactions V. Design of the Asymmetric Synthesis of Lignan Lactones. Synthesis of Optically Active Podorhizon and Deoxypodorhizon by 1,3-Asymmetric Induction. *Chem. Pharm. Bull.*, **30**, 4303–4313 (1982).
3) Ayres, D. C. and Loike, J. D., Lignans. Cambridge University Press, Cambridge (1990).
4) Robin, J.-P., Dhal, R., and Brown, E., Syntheses Totales et

Etudes de Lignanes Biologiquement Actifs-II. *Tetrahedron*, **38**, 3667–3671 (1982).

5) Denmark, S. E. and Henke, B. R., Investigations on Transition-State Geometry in the Aldol Condensation. *J. Am. Chem. Soc.*, **113**, 2177–2194 (1991).

6) Jurd, L., Plant Polyphenols. VI. Experiments on the Synthesis of 3,3′- and 4,4′-Di-O-Methylellagic Acid. *J. Am. Chem. Soc.*, **81**, 4606–4610 (1959).

7) Camps, F., Coll, J., Messeguer, A., and Pericas, M. A., Improved Oxidation Procedure with Aromatic Peroxyacids. *Tetrahedron Lett.*, **22**, 3895–3896 (1981).

8) a) Taniguchi, M., Koga, K., and Yamada, S., Stereochemical Studies XXX. Stereoselective Synthesis of D-Ribose from L-glutamic Acid. *Tetrahedron*, **30**, 3547–3552 (1974). b) Ravid, U., Silverstein, R. M., and Smith, L., R., Synthesis of the Enantiomers of 4-Substituted γ-Lactones with Known Absolute Configuration. *Tetrahedron*, **34**, 1449–1452 (1978).

9) Dale, J. A., Dull, D. L., and Mosher, H. S., α-Methoxy-α-trifluoromethylphenylacetic Acid, a Versatile Reagent for the Determination of Enantiomeric Composition of Alcohols and Amines. *J. Org. Chem.*, **34**, 2543–2549 (1969).

10) a) House, H. O., Crumrine, D. S., Teranishi, A. Y., and Olmstead, H. D., Chemistry of Carbanions. XXIII. Use of Metal Complexes to Control the Aldol Condensation. *J. Am. Chem. Soc.*, **95**, 3310–3324 (1973). b) Ziegler, F. E. and Schwartz, J. A., Synthetic Studies on Lignan Lactones: Aryl Dithiane Route to (±)-Podorhizol and (±)-Isopodophyllotoxone and Approaches to the Stegane Skeleton. *J. Org. Chem.*, **43**, 985–991 (1978). (c) Almeida, W. P. and Coelho, F., Piperonal as Electrophile in the Baylis-Hillman Reaction. A Synthesis of Hydroxy-β-Piperonyl-γ-Butyrolactone Derivative. *Tetrahedron Lett.*, **39**, 8609–8612 (1998).