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Stereoselective Synthesis of (2*R*, 3*S*)-2-Benzyl-2-hydroxy-3-(3,4-methylenedioxybenzyl)-γ-butyrolactone from L-(+)-Arabinose

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As a model experiment for the stereoselective synthesis of optically active *cis*-α,β-dibenzyl-α-hydroxy-γ-butyrolactone, (2*R*, 3*S*)-2-benzyl-2-hydroxy-3-(3,4-methylenedioxybenzyl)-γ-butyrolactone (3) was stereoselectively synthesized from L-(+)-arabinose.

Key words: lignan; γ-butyrolactone; α,β-dibenzyl-γ-butyrolactone; stereoselective synthesis

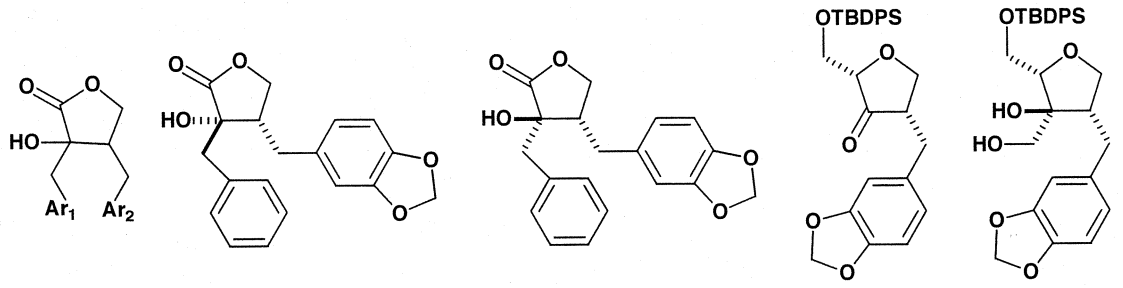
Introduction

Many of the α,β-dibenzyl-γ-butyrolactone type of lignans are known,[1] some of them having a tertiary hydroxy group at the α-position of γ-butyrolactone. It has been shown that α,β-dibenzyl-α-hydroxy-γ-butyrolactones (**1**) had interesting biological activities as antitumor[2] and Ca^{2+} antagonist compounds.[3] Further biological research into the difference in activity between *trans*-**1** and *cis*-**1** is also interesting. On the other hand, a number of precedents from lignan synthesis[4] could be applied to draw up the conversion of α,β-dibenzyl-α-hydroxy-γ-butyrolactones to other types of lignans having a tertiary hydroxy group. The intriguing biological activity and possibility as key intermediates for other lignans have made them challenging targets for synthesis. Moritani and co-workers have applied stereoselective direct α-hydroxylation to *trans*- and *cis*-α,β-dibenzyl-γ-butyrolactones in the stereoselective synthesis of *trans*- and *cis*- α,β-dibenzyl-α-hydroxy-γ-butyrolactones (**1**).[5] We have previously stereoselectively synthesized *trans*-(2*S*, 3*S*)-2-benzyl-2-hydroxy-3-(3,4-methylenedioxybenzyl)-γ-butyrolactone (**2**) from L-(+)-arabinose.[6] In this paper, we report the stereoselective synthesis of the optically active *cis*-α,β-dibenzyl-α-hydroxy-γ-butyrolactone, *cis*-(2*R*, 3*S*)-2-benzyl-2-hydroxy-3-(3,4-methylenedioxybenzyl)-γ-butyrolactone (**3**), as a model compound from L-(+)-arabinose.

In planning the synthesis of **3**, we wanted to extend our earlier work on the stereoselective synthesis of lignans having a tertiary hydroxy group.[6,7] The most important factor in the synthetic strategy for *cis*-**3** is the stereoselective introduction of a tertiary hydroxy group. In our previous research into the synthesis of *trans*-**2**, coupling of ketone (+)-**4** and benzylmagnesium chloride gave *trans*-dibenzyltetrahydrofuran having a tertiary hydroxy group.[6] To get the *cis*-form with a tertiary hydroxy group of opposite configuration, glycol (+)-**5** was adopted as the starting compound. This glycol had been prepared from ketone (+)-**4** *via* olefination and stereoselective osmium oxidation.[7] It was anticipated that transformation of the silyloxymethyltetrahydrofuran to γ-butyrolactone and the introduction of a phenyl group would lead to **3** (Fig.).

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), and preparative TLC was conducted with Merck silica gel 60 F_{254} (0.5 mm thickness, 20 × 20 cm).



1 (-)-2 3 4 (+)-5

Fig.

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(2'S, 3'S, 4'S)-2,2-Dimethyl-1,3-dioxolane-4-spiro-3'-[2'-[(tert-butyldiphenylsilyl)oxy]methyl-4'-(3,4-methylenedioxybenzyl)tetrahydrofuran] (**6**). A reaction solution of (+)-glycol **5** (1.64 g, 3.15 mmol), 2,2-dimethoxypropane (1.00 ml, 8.13 mmol), and a catalytic amount of *p*-toluenesulfonic acid in acetone (50 ml) was stirred at room temperature for 1 h before addition of a few drops of triethylamine. After concentration, the residue was applied to silica gel column chromatography (ethyl acetate/hexane=1/9) to give acetonide **6** (1.68 g, 3.00 mmol, 95%) as a colorless oil. $[\alpha]_D^{20}$-12.49° (*c* 0.40, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.07 (9H, s, $(CH_3)_3CSi$), 1.31 (3H, s, $(CH_3)_2C$), 1.44 (3H, s, $(CH_3)_2C$), 2.46–2.50 (2H, m, 4'-*H*, $ArCH_2$), 2.80 (1H, d, *J*=9.2 Hz, $ArCH_2$), 3.65 (1H, dd, *J*=8.9, 3.7 Hz, 5'-*H*), 3.77 (1H, dd, *J*=11.5, 4.1 Hz, $CH_2OTBDPS$), 3.79–3.83 (1H, m, 5'-*H*), 3.88 (1H, dd, *J*=11.5, 4.0 Hz, $CH_2OTBDPS$), 3.98 (1H, dd, *J*=4.0, 4.0 Hz, 2'-*H*), 4.19 (2H, s, 5-*H*), 5.92 (2H, s, OCH_2O), 6.55 (1H, dd, *J*=7.6, 1.5 Hz, Ar*H*), 6.61 (1H, d, *J*=1.5 Hz, Ar*H*), 6.71 (1H, d, *J*=7.6 Hz, Ar*H*), 7.37–7.47 (6H, m, Ar*H*), 7.69–7.76 (4H, m, Ar*H*). NMR δ_C ($CDCl_3$): 19.16, 26.59, 26.66, 26.87, 33.30, 50.21, 63.19, 65.27, 70.19, 86.20, 89.70, 100.84, 108.24, 108.43, 109.06, 121.62, 127.73, 127.77, 129.72, 129.78, 133.06, 133.08, 133.69, 135.66, 135.69, 145.91, 147.73. EIMS *m/z* (70 eV): 560 (M^+, 0.6), 503 (48), 425 (77), 217 (82), 173 (53), 135 (100). Found: C, 70.47; H, 7.20. Calcd. for $C_{33}H_{40}O_6Si$: C, 70.68; H, 7.19.

(2'S, 3'S, 4'S)-2,2-Dimethyl-1,3-dioxolane-4-spiro-3'-[2'-hydroxymethyl-4'-(3,4-methylenedioxybenzyl)-tetrahydrofuran] (**7**). To an ice-cooled solution of silyl ether **6** (2.22 g, 3.96 mmol) in tetrahydrofuran (10 ml) was added tetra-*n*-butylammonium fluoride (4.87 ml, 1 M in tetrahydrofuran, 4.87 mmol). The reaction solution was stirred at room temperature for 16 h before addition of 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 (ethyl acetate/hexane=1/3 and 2/1) gave alcohol **7** (1.23 g, 3.82 mmol, 96%) as a colorless oil. $[\alpha]_D^{20}$+17.50° (*c* 0.40, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.42 (3H, s, $(CH_3)_2C$), 1.44 (3H, s, $(CH_3)_2C$), 2.07 (1H, m, O*H*), 2.37 (1H, dd, *J*=13.7, 13.7 Hz, $ArCH_2$), 2.57 (1H, m, 4'-*H*), 2.87 (1H, dd, *J*=13.7, 3.9 Hz, $ArCH_2$), 3.61 (1H, dd, *J*=8.8, 5.9 Hz, 5'-*H*), 3.75–3.76 (1H, m, CH_2OH), 3.83–3.90 (1H, m, CH_2OH), 3.85 (1H, dd, *J*=8.8, 6.6 Hz, 5'-*H*), 3.95 (1H, dd, *J*=3.7, 3.7 Hz, 2'-*H*), 4.06 (1H, d, *J*=9.8 Hz, 5-*H*), 4.12 (1H, d, *J*=9.8 Hz, 5-*H*), 5.93 (2H, s, OCH_2O), 6.59 (1H, dd, *J*=7.8, 1.5 Hz, Ar*H*), 6.64 (1H, d, *J*=1.5 Hz, Ar*H*), 6.73 (1H, d, *J*=7.8 Hz, Ar*H*). NMR δ_C ($CDCl_3$): 26.64, 26.74, 33.20, 49.55, 61.05, 65.00, 70.49, 85.37, 88.70, 100.89, 108.29, 108.55, 108.90, 121.49, 133.37, 146.03, 147.79. FABMS (*m/z*): 345 ($M+Na^+$, 69), 135 (100). HRMS (FAB) *m/z* ($M+Na^+$): calcd. for $C_{17}H_{22}O_6Na$, 345.1314; found, 345.1312.

(2'R, 3'S, 4'S)-2,2-Dimethyl-1,3-dioxolane-4-spiro-3'-[2'-iodomethyl-4'-(3,4-methylenedioxybenzyl)tetrahydrofuran] (**8**). A reaction mixture of alcohol **7** (1.21 g, 3.75 mmol), triphenylphosphine (2.92 g, 11.1 mmol), imidazole (0.78 g, 11.5 mmol), and iodine (1.92 g, 7.56 mmol) in toluene (80 ml) was heated under refluxing for 1 h. After cooling the mixture to room temperature, water was added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (5% ethyl acetate/hexane and 25% ethyl acetate/hexane) gave iodide **8** (1.62 g, 3.75 mmol, 100%) as a colorless oil. $[\alpha]_D^{20}$+5.95° (*c* 0.84, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.42 (3H, s, $(CH_3)_2C$), 1.45 (3H, s, $(CH_3)_2C$), 2.37 (1H, dd, *J*=13.4, 13.4 Hz, $ArCH_2$), 2.70 (1H, m, 4'-*H*), 2.87 (1H, dd, *J*=13.4, 3.7 Hz, $ArCH_2$), 3.15 (1H, dd, *J*=10.3, 10.3 Hz, ICH_2), 3.50 (1H, dd, *J*=10.3, 2.4 Hz, ICH_2), 3.59 (1H, dd, *J*=8.8, 7.1 Hz, 5'-*H*), 3.88 (1H, dd, *J*=8.8, 7.3 Hz, 5'-*H*), 3.98 (1H, d, *J*=9.8 Hz, 5-*H*), 4.03 (1H, d, *J*=9.8 Hz, 5-*H*), 4.05 (1H, dd, *J*=10.3, 2.4 Hz, 2'-*H*), 5.93 (2H, s, OCH_2O), 6.59 (1H, dd, *J*=7.8, 2.0 Hz, Ar*H*), 6.63 (1H, d, *J*=2.0 Hz, Ar*H*), 6.72 (1H, d, *J*=7.8 Hz, Ar*H*). NMR δ_C ($CDCl_3$): 3.18, 26.40, 27.03, 33.73, 48.70, 63.94, 70.17, 85.32, 88.42, 100.95, 108.36, 108.76, 109.09, 109.95, 121.37, 129.76, 132.88, 146.16, 147.87. EIMS *m/z* (20 eV): 432 (M^+, 5), 264 (22), 229 (45), 175 (38), 135 (100). Found: C, 47.24; H, 4.86. Calcd. for $C_{17}H_{21}O_5I$: C, 47.24; H, 4.90.

(2S, 3S)-2-(3,4-Methylenedioxybenzyl)-3,4-dimethylmethylenedioxy-3-vinylbutan-1-ol (**9**). A reaction mixture of iodide **8** (1.09 g, 2.52 mmol) and zinc dust (0.68 g, 10.4 mmol) in ethanol (40 ml) was heated under refluxing for 30 min. After cooling to room temperature, the mixture was filtered. The filtrate was concentrated, and the resulting residue was applied to silica gel column chromatography (ethyl acetate/hexane=1/3) to give olefin **9** (0.77 g, 2.51 mmol, 100%) as a colorless oil. $[\alpha]_D^{20}$-10.60° (*c* 0.66, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.43 (3H, s, $(CH_3)_2C$), 1.46 (3H, s, $(CH_3)_2C$), 2.10 (1H, m, 2-*H*), 2.27 (1H, dd, *J*=13.9, 10.5 Hz, $ArCH_2$), 2.49 (1H, dd, *J*=13.9, 4.2 Hz, $ArCH_2$), 2.98 (1H, br. s, O*H*), 3.53 (1H, br. d, *J*=11.5 Hz, 1-*H*), 3.65 (1H, dd, *J*=11.5, 8.1 Hz, 1-*H*), 3.95 (1H, d, *J*=8.8 Hz, 4-*H*), 3.99 (1H, d, *J*=8.8 Hz, 4-*H*), 5.33 (1H, dd, *J*=10.7, 1.5 Hz, $CH=CH_2$), 5.49 (1H, dd, *J*=17.1, 1.5 Hz, $CH=CH_2$), 5.92 (1H, d, *J*=1.5 Hz, OCH_2O), 5.93 (1H, d, *J*=1.5 Hz, OCH_2O), 5.95 (1H, dd, *J*=17.1, 10.7 Hz, $CH=CH_2$), 6.60 (1H, dd, *J*=8.3, 1.5 Hz, Ar*H*), 6.66 (1H, d, *J*=1.5 Hz, Ar*H*), 6.72 (1H, d, *J*=8.3 Hz, Ar*H*). NMR δ_C ($CDCl_3$): 26.44, 26.66, 33.92, 50.97, 62.50, 73.22, 86.83, 100.89, 108.21, 109.25, 110.27, 116.29, 121.79, 121.84, 133.14, 137.42, 147.78. EIMS *m/z* (20 eV): 306 (M^+, 18), 200 (24), 178 (28), 135 (100), 127 (92), 69 (90). Found, C: 66.31; H, 7.17. Calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24.

(2'R/S, 3'S, 4'S)-2,2-Dimethyl-1,3-dioxolane-4-spiro-3'-[2'-hydroxy-4'-(3,4-methylenedioxybenzyl)tetrahydrofuran] (**10**). A reaction solution of olefin **9** (0.92 g, 3.00 mmol), 4-methylmorpholine *N*-oxide (0.48 g, 4.10

mmol), and 2% aqueous osmium tetroxide solution (1 ml) in acetone (12 ml), *tert*-butyl alcohol (3 ml), and water (3 ml) was stirred at room temperature for 48 h under N_2 gas in the dark. After addition of $NaHSO_3$ (2 g) in water, the mixture was filtered, and the resulting filtrate was concentrated. The residue was dissolved in water and ethyl acetate (100 ml), and the ethyl acetate solution was separated.

To the ethyl acetate solution was added sodium periodate (1.7 g, 7.95 mmol) in water (30 ml). After the reaction mixture had been stirred at room temperature for 30 min, the organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (ethyl acetate/hexane=1/2) gave hemiacetal **10** (0.80 g, 2.59 mmol, 86%) as a 3/7 mixture of isomers as colorless crystals, mp 68–72°C. $[\alpha]_D^{20}$+27.50° (*c* 0.40, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.43–1.46 (6H, s×3, $(CH_3)_2C$), 2.38 (0.7H, dd, *J*=13.4, 11.5 Hz, ArCH_2), 2.52 (0.3H, m, 4′-*H*), 2.63 (0.3H, dd, *J*=13.4, 13.4 Hz, ArCH_2), 2.69 (0.7H, m, 4′-*H*), 2.88 (1H, dd, *J*=13.4, 4.2 Hz, ArCH_2), 3.42 (0.7H, d, *J*=6.4 Hz, O*H*), 3.51 (0.7H, dd, *J*=8.8, 6.8 Hz, 5′-*H*), 3.81 (0.3H, dd, *J*=8.8, 4.9 Hz, 5′-*H*), 3.90 (0.7H, d, *J*=9.3 Hz, 5-*H*), 4.00 (0.7H, dd, *J*=8.8, 7.3 Hz, 5′-*H*), 4.03 (0.3H, dd, *J*=8.8, 7.7 Hz, 5′-*H*), 4.10 (0.3H, d, *J*=9.3 Hz, 5-*H*), 4.17 (0.7H, d, *J*=9.3 Hz, 5-*H*), 4.29 (0.3H, d, *J*=9.3 Hz, 5-*H*), 5.06 (0.7H, d, *J*=6.4 Hz, 2′-*H*), 5.28 (0.3H, s, 2′-*H*), 5.93 (2H, s, OCH_2O), 6.60 (1H, dd, *J*=7.8, 2.0 Hz, Ar*H*), 6.65 (1H, d, *J*=2.0 Hz, Ar*H*), 6.73 (1H, d, *J*=7.8 Hz, Ar*H*). NMR δ_C ($CDCl_3$): 26.30, 26.55, 33.47, 35.15, 44.45, 47.21, 64.87, 66.64, 69.89, 71.55, 87.91, 90.47, 99.06, 100.91, 102.29, 108.32, 108.79, 108.90, 109.62, 109.95, 121.37, 121.52, 132.93, 146.16, 147.84. EIMS *m/z* (20 eV): 308 (M^+, 17), 250 (8), 161 (14), 135 (100), 127 (33). Found: C, 62.01; H, 6.54. Calcd. for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54.

(2′S, 3′S)-2,2-Dimethyl-1,3-dioxolane-4-spiro-2′-[3′-(3,4-methylenedioxybenzyl)-γ-butyrolactone] (***11***). A reaction mixture of hemiacetal **10** (0.66 g, 2.14 mmol) and Ag_2CO_3-Celite (3.13 g, containing ca. 3.13 mmol of the silver salt) in toluene (40 ml) was heated under refluxing for 30 min. After cooling to room temperature, the mixture was filtered, and the resulting filtrate was concentrated. The residue was applied to silica gel column chromatography (ethyl acetate/hexane=1/3) to give lactone **11** (0.63 g, 2.06 mmol, 96%) as a colorless oil. $[\alpha]_D^{20}$+5.55° (*c* 0.54, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.51 (3H, s, $(CH_3)_2C$), 1.55 (3H, s, $(CH_3)_2C$), 2.43 (1H, dd, *J*=13.9, 11.5 Hz, ArCH_2), 2.76 (1H, m, 3′-*H*), 2.97 (1H, dd, *J*=13.9, 4.1 Hz, ArCH_2), 3.85 (1H, dd, *J*=9.3, 9.3 Hz, 4′-*H*), 4.08 (1H, d, *J*=9.3 Hz, 5-*H*), 4.25 (1H, dd, *J*=9.3, 7.3 Hz, 4′-*H*), 4.29 (1H, d, *J*=9.3 Hz, 5-*H*), 5.94 (2H, s, OCH_2O), 6.60 (1H, dd, *J*=8.3, 1.5 Hz, Ar*H*), 6.64 (1H, d, *J*=1.5 Hz, Ar*H*), 6.74 (1H, d, *J*=8.3 Hz, Ar*H*). NMR δ_C ($CDCl_3$): 25.34, 26.66, 32.20, 45.65, 65.87, 69.35, 82.54, 101.07, 108.52, 108.70, 111.80, 121.42, 131.12, 146.53, 148.08, 175.87. EIMS *m/z* (20 eV): 306 (M^+, 54), 162 (25), 135 (100), 127 (54), 69 (44). Found: C, 62.64; H, 5.96. Calcd. for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92.

(2S, 3S)-2-Hydroxy-2-hydroxymethyl-3-(3,4-methylenedioxybenzyl)-γ-butyrolactone (***12***). A reaction mixture of acetonide **11** (0.62 g, 2.02 mmol) in 1 N HCl (6 ml) and tetrahydrofuran (6 ml) was heated at 65°C for 20 h. After cooling to room temperature, saturated aqueous $NaHCO_3$ solution 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 (hexane/ethyl acetate=1/1) gave glycol **12** (0.53 g, 1.99 mmol, 99%) as a colorless oil. $[\alpha]_D^{20}$+18.76° (*c* 0.53, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.40 (1H, br. s, O*H*), 2.55 (1H, dd, *J*=13.7, 11.2 Hz, ArCH_2), 2.86 (1H, m, 3-*H*), 3.01 (1H, dd, *J*=13.7, 4.4 Hz, ArCH_2), 3.40 (1H, br. s, O*H*), 3.83 (1H, br. d, *J*=11.7 Hz, CH_2OH), 3.94 (1H, d, *J*=11.7 Hz, CH_2OH), 4.02 (1H, dd, *J*=8.8, 8.8 Hz, 4-*H*), 4.26 (1H, dd, *J*=8.8, 8.8 Hz, 4-*H*), 5.94 (2H, s, OCH_2O), 6.62 (1H, dd, *J*=7.8, 1.5 Hz, Ar*H*), 6.67 (1H, d, *J*=1.5 Hz, Ar*H*), 6.74 (1H, d, *J*=7.8 Hz, Ar*H*). NMR δ_C ($CDCl_3$): 31.97, 46.43, 63.25, 70.28, 75.78, 101.05, 108.51, 108.70, 121.39, 131.46, 146.48, 148.03, 178.73. EIMS *m/z* (20 eV): 266 (M^+, 51), 161 (49), 135 (100), 131 (39). HRMS (EI) *m/z* (M^+): calcd. for $C_{13}H_{14}O_6$, 266.0788; found, 266.0778.

(2R, 3S)-2-Hydroxy-2-iodomethyl-3-(3,4-methylenedioxybenzyl)-γ-butyrolactone (***13***). A reaction mixture of glycol **12** (0.12 g, 0.45 mmol), triphenylphosphine (0.39 g, 1.49 mmol), imidazole (0.10 g, 1.47 mmol), and iodine (0.26 g, 1.02 mmol) in toluene (250 ml) was heated under refluxing for 30 min, and then cooled to room temperature. After addition of water, the organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (ethyl acetate/benzene=1/9 and ethyl acetate/hexane=1/1) gave iodohydrin **13** (0.16 g, 0.43 mmol, 96%) as a colorless oil. $[\alpha]_D^{20}$+16.66° (*c* 1.32, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.48 (1H, dd, *J*=13.4, 13.4 Hz, ArCH_2), 2.84 (1H, m, 3-*H*), 3.03 (1H, dd, *J*=13.4, 4.2 Hz, ArCH_2), 3.20 (1H, s, O*H*), 3.37 (1H, d, *J*=11.2 Hz, ICH_2), 3.49 (1H, d, *J*=11.2 Hz, ICH_2), 4.05 (1H, dd, *J*=9.3, 6.8 Hz, 4-*H*), 4.28 (1H, dd, *J*=9.3, 6.8 Hz, 4-*H*), 5.95 (2H, s, OCH_2O), 6.63 (1H, d, *J*=7.8 Hz, Ar*H*), 6.68 (1H, s, Ar*H*), 6.76 (1H, d, *J*=7.8 Hz). NMR δ_C ($CDCl_3$): 5.81, 32.10, 47.59, 69.45, 74.63, 101.09, 108.55, 108.78, 121.59, 130.78, 146.61, 148.08, 174.77. EIMS *m/z* (20 eV): 376 (M^+, 32), 248 (12), 135 (100). HRMS (EI) *m/z* (M^+): calcd. for $C_{13}H_{13}O_5I$, 375.9807; found, 375.9798.

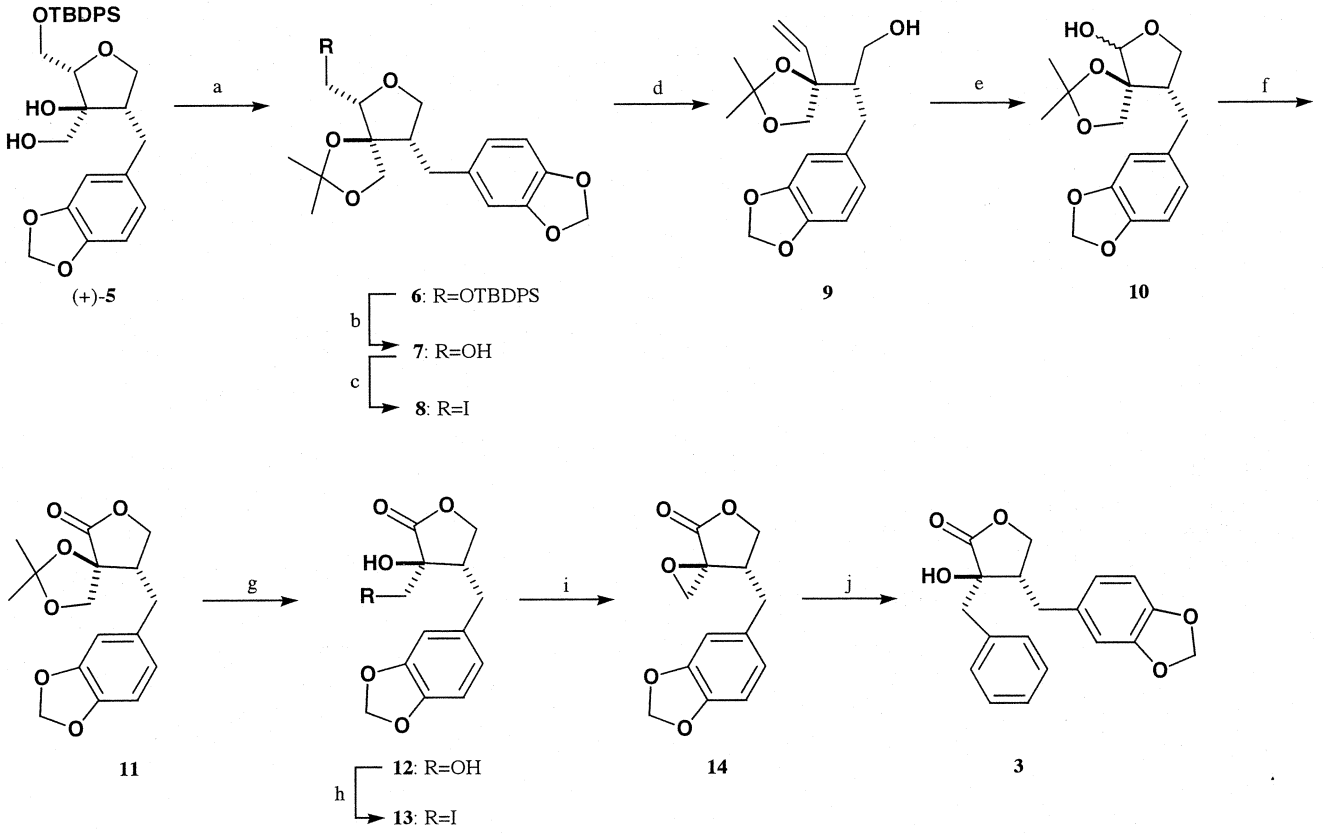
(2S, 3S)-3-(3,4-Methylenedioxybenzyl)-γ-butyrolactone-2-spirooxirane (***14***). A reaction mixture of iodohydrin **13** (0.16 g, 0.43 mmol) and K_2CO_3 (59 mg, 0.43 mmol) in acetone (10 ml) was stirred at room temperature for 16 h. After concentration, the residue was applied to silica gel column chromatography (ethyl acetate/hexane=1/2) to give epoxide **14** (0.09 g, 0.36 mmol, 84%) as colorless crystals, mp 99–101°C. $[\alpha]_D^{20}$+27.41° (*c* 0.62, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.52

(1H, dd, J=14.2, 10.7 Hz, ArCH_2), 2.80 (1H, dd, J=14.2, 5.1 Hz, ArCH_2), 3.00 (1H, m, 3-H), 3.14 (1H, d, J=5.9 Hz, 3′-H), 3.17 (1H, d, J=5.9 Hz, 3′-H), 4.13 (1H, dd, J=8.8, 8.8 Hz, 4-H), 4.46 (1H, dd, J=8.8, 8.8 Hz, 4-H), 5.95 (2H, s, OCH_2O), 6.59 (1H, dd, J=7.8, 1.4 Hz, ArH), 6.62 (1H, d, J=1.4 Hz, ArH), 6.75 (1H, d, J=7.8 Hz, ArH). NMR δ_C ($CDCl_3$): 35.10, 37.90, 49.68, 58.49, 70.06, 101.14, 108.49, 108.61, 121.28, 130.29, 146.71, 148.15, 173.45. EIMS m/z (20 eV): 248 (M^+, 26), 135 (100). HRMS (EI) m/z (M^+): calcd. for $C_{13}H_{12}O_5$, 248.0683; found, 248.0670.

(2R, 3S)-2-Benzyl-2-hydroxy-3-(3,4-methylenedioxybenzyl)-γ-butyrolactone (**3**). To a suspension of copper (I) cyanide (10 mg, 0.11 mmol) in tetrahydrofuran (1 ml) was added phenyl lithium (0.5 ml, 1.8 M cyclohexane-ether solution, 0.22 mmol) at −75°C, and then the mixture was warmed to 0°C. After 15 min, the mixture was cooled to −75°C, and then a solution of epoxide **14** (10 mg, 0.041 mmol) in tetrahydrofuran (1 ml) was added. The resulting reaction mixture was stirred at −75°C for 1 h before addition of 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 TLC (ethyl acetate/benzene=1/9) gave **3** (3 mg, 0.0092 mmol, 22%) as a colorless oil. $[\alpha]_D^{20}$+24.39° (*c* 0.12, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.65 (1H, dd, J=13.7, 11.2 Hz, 3-ArCH_2), 2.68 (1H, s, OH), 2.90 (1H, m, 3-H), 2.99 (1H, d, J=13.7 Hz, 2-ArCH_2), 3.04 (1H, d, J=13.7 Hz, 2-ArCH_2), 3.12 (1H, dd, J=13.7, 4.2 Hz, 3-ArCH_2), 3.88 (1H, dd, J=9.0, 9.0 Hz, 4-H), 4.20 (1H, dd, J=9.0, 7.6 Hz, 4-H), 5.95 (2H, s, OCH_2O), 6.63 (1H, dd, J=7.8, 1.5 Hz, ArH), 6.67 (1H, d, J=1.5 Hz, ArH), 6.76 (1H, d, J=7.8 Hz, ArH), 7.22–7.37 (5H, m, ArH). NMR δ_C ($CDCl_3$): 30.92, 38.54, 48.19, 69.29, 75.83, 101.07, 108.54, 108.71, 121.34, 127.67, 128.61, 130.39, 133.22, 174.42. EIMS m/z (20 eV): 326 (M^+, 38), 135 (100), 91 (51). HRMS (EI) m/z (M^+): calcd. for $C_{19}H_{18}O_5$, 326.1153; found, 326.1150.

Results and Discussion

The sequence leading to **3** is shown in the scheme. Glycol (+)-**5** has previously been obtained from L-(+)-arabinose through 12 steps in 4% overall yield.[7] After protection of glycol (+)-**5** as an acetonide by treatment with 2,2-dimethoxypropane and *p*-toluenesulfonic acid in acetone[8] (95%), desilylation of resulting **6** was performed by exposure to tetra-*n*-butylammonium fluoride[9] in tetrahydrofuran to give alcohol **7** in 96% yield. Transformation of the tetrahydrofuran ring to γ-butyrolactone was achieved *via* reductive ring opening



Scheme. Synthesis of *cis*-α,β-Dibenzyl-α-hydroxy-γ-butyrolactone **3**.

(a) 2,2-dimethoxypropane, *p*-TsOH, acetone, r.t., 1 h (95% yield). (b) *n*-Bu_4NF, THF, r.t., 16 h (96% yield). (c) I_2, Ph_3P, imidazole, toluene, reflux, 1 h (100% yield). (d) Zn, EtOH, reflux, 30 min (100% yield). (e) (1) OsO_4, NMO, acetone-*tert*-BuOH-H_2O, r.t., 48 h; (2) $NaIO_4$, EtOAc-H_2O, r.t., 30 min (86% yield, 2 steps). (f) Ag_2CO_3-Celite, toluene, reflux, 30 min (96% yield). (g) THF-1 N HCl, 65°C, 20 h (99% yield). (h) I_2, Ph_3P, imidazole, toluene, reflux, 30 min (96% yield). (i) K_2CO_3, acetone, r.t., 16 h (84% yield). (j) $Ph_2Cu(CN)Li_2$, THF, −75°C, 1 h (22% yield).

as the key reaction. This transformation began with the iodination of alcohol **7** with iodine, triphenylphosphine, and imidazole[10] in refluxing toluene in a quantitative yield. Reductive ring opening of resulting iodide **8** by using zinc[11] in refluxing ethanol gave olefin **9** in a quantitative yield. The oxidative cleavage of this olefin **9** by osmium tetroxide-*N*-methylmorpholine *N*-oxide[12] and sodium periodate oxidation led to hemiacetal **10** in 86% yield. Lactone **11** was then obtained by silver carbonate-Celite oxidation[13] of hemiacetal **10** in refluxing toluene in 96% yield.

The next stage was the introduction of a phenyl group, giving a benzyl group at the α-position of the γ-butyrolactone. We planned to convert **11** to epoxide **14**, which was expected as a substrate for the introduction of a phenyl group while maintaining the *cis* form. The protecting group of acetonide **11** was removed in 1 N hydrochloric acid and tetrahydrofuran at 65°C to give glycol **12** in 99% yield. Since one-step conversion of this glycol **12** to epoxide **14** by using 1-(*p*-toluenesulfonyl)imidazole and sodium hydride[14] in tetrahydrofuran failed, epoxidation of this glycol was performed in two steps. After treatment of the glycol **12** with iodine, triphenylphosphine, and imidazole[10] in refluxing toluene (96% yield), resulting iodohydrin **13** was exposed to potassium carbonate in acetone to afford epoxide **14** in 84% yield. Finally, the reaction of this epoxide **14** with a higher order, mixed organocuprate ($Ph_2Cu(CN)Li_2$)[15] in tetrahydrofuran at −75°C led to opening of the three-membered ring and formation of tertiary alcohol, giving *cis*-α,β-dibenzyl-α-hydroxy-γ-butyrolactone **3** in 22% yield. Epoxide **14** was recovered at 41%, and the yield was not improved by warming to 0°C.

This resulting *cis*-α,β-dibenzyl-α-hydroxy-γ-butyrolactone **3** gave a different ^{1}H-NMR spectrum from that of *trans*-α,β-dibenzyl-α-hydroxy-γ-butyrolactone **2**.[6] The main significant difference in the ^{1}H-NMR spectra between **2** and **3** was provided by the benzylic protons at the α position, which gave a singlet at 3.56 ppm for **2** and two doublets at 2.99 ppm and 3.04 ppm (J=13.7 Hz) for **3**.

We stereoselectively synthesized the optically active *cis*-α,β-dibenzyl-α-hydroxy-γ-butyrolactone lignan, *cis*-(2*R*, 3*S*)-2-benzyl-2-hydroxy-3-(3,4-methylenedioxybenzyl)-γ-butyrolactone (**3**), from L-(+)-arabinose in 23 steps and 0.6% overall yield. The stereoselective synthetic methods for optically active *trans* and *cis*-α,β-dibenzyl-γ-butyrolactone from L-(+)-arabinose were thus established.

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