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# Improved Stereoselective Synthesis of Optically Active Methylene Lactone, Key Intermediate for the Synthesis of 1,2-Oxidized Furofuran Lignan, by Direct α-Methylenation to Butanolide

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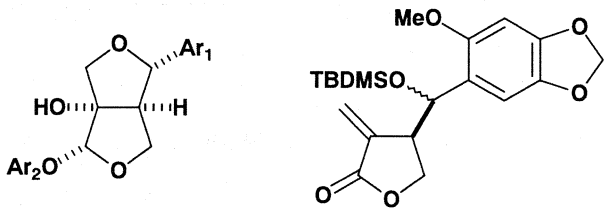
**(3*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilyl)oxy-1-(2-methoxy-4,5-methylenedioxyphenyl)methyl]-2-methylene-4-butanolide, which is a key intermediate for the synthesis of 1,2-oxidized furofuran lignan, was stereoselectively synthesized from L-glutamic acid by applying direct methylenation to butanolide.**

**Key words:** lignan; furofuran lignan; stereoselective synthesis

The furofuran lignans display a wide variety of biological activities.[1] Although 1,2-oxidized furofuran lignan **1** can be expected to have many interesting biological activities, research into this compound has not proceeded. To explore this research, the development of an efficient and stereoselective synthetic method for optically active 1,2-oxidized furofuran lignan is necessary. The synthesis of oxidized lignan involves the difficulty of stereoselective oxidation and selective protection of the hydroxy group. We have recently shown the stereoselective synthesis of methylene lactone **2** (Fig.), which is a synthetic intermediate to 1,2-oxidized furofuran lignan, from L-glutamic acid.[2] In this paper, a more efficient synthesis of methylene lactone **2** from L-glutamic acid in fewer steps is reported.

Our plan for the synthesis of **2**, involving direct methylenation to butanolide as the key reaction, is shown in scheme 1. Methylene lactone **2** would be obtained by methylenation to butanolide **3**. Aldol product **4**, which could be obtained by an aldol condensation of trityloxypentanolide **5** with 2-methoxy-4,5-methylenedioxybenzaldehyde, might be transformed to butanolide **3** through reduction, deprotection, and oxidation. Stereoselectivity at the 2 position of aldol product **4** would occur due to the existence of a trityloxymethyl group at the 4 position of **5**. This 2 position of aldol product **4** might be converted to the 3 position of **2**. Trityloxypentanolide **5** can be prepared from L-glutamic acid.[3,4]




**1** **2**

**Fig.**

## Results and Discussion

(*S*)-(+)-Hydroxypentanolide **6** was prepared from L-glutamic acid.[3] The enantiomeric excess was determined by Mosher's method[5] as 99%. After converting to trityloxypentanolide **5**,[4] aldol condensation with 2-methoxy-4,5-methylenedioxybenzaldehyde, using lithium diisopropylamide, was carried out to give *erythro* aldol product **7** in 42% yield and *threo* aldol product **7** in 41% yield. The coupling constant between the benzylic proton and 2-*H* of the *erythro* isomer was 2.9 Hz. On the other hand, that of the *threo* isomer was 9.3 Hz.[6] A NOE experiment showed the steric configuration at the 2 position as *S*, since no NOE was apparent between 2-*H* and 4-*H*.[7] The *erythro* or *threo* selectivity was not important, because one furofuran lignan having the desired steric configuration has been obtained from both isomers of **2**.[8] After separating the *erythro* and *threo* isomers, synthesis was started from both respective isomers.

The *erythro* benzylic hydroxy group was protected as a methoxymethyl ether by using *N*,*N*-diisopropylethylamine and chloromethyl methyl ether in 93% yield. Although the *tert*-butyldimethylsilyl ether is the best protective group for the benzylic hydroxy group of aldol product **7**,[8] selective detritylation in the subsequent process was difficult, so the methoxymethyl ether was adopted.

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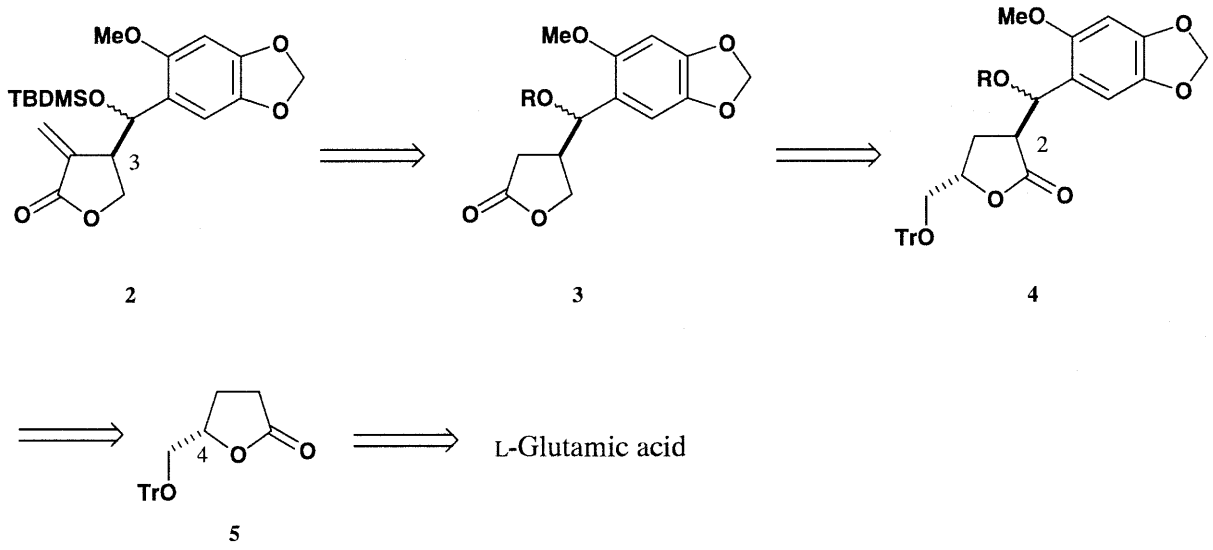
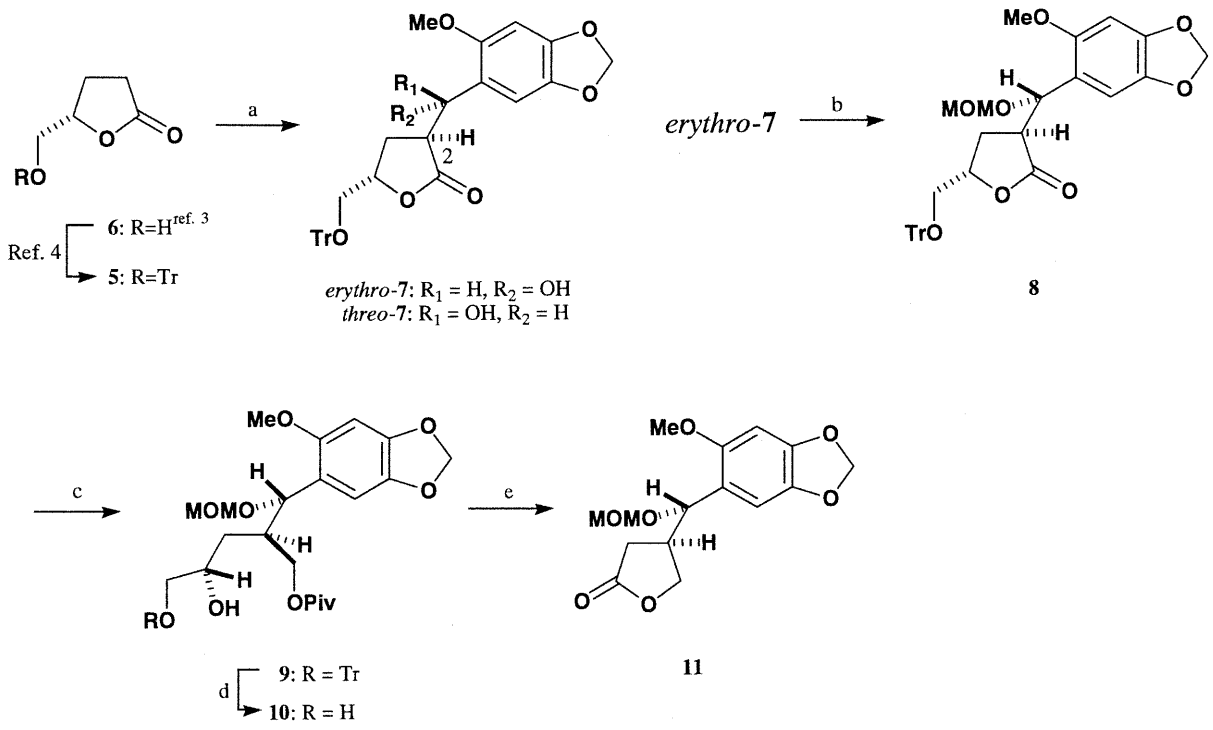



**Scheme 1.** Retrosynthetic Analysis of Methylene Lactone **2**.

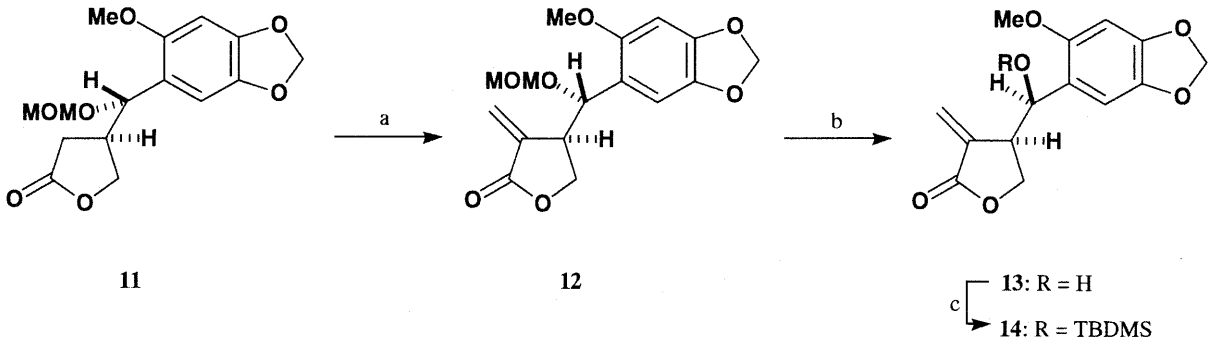


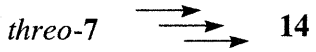

**Scheme 2.** Synthesis of Methylene Lactone (1).

(a) LDA, 2-methoxy-4,5-methylenedioxybenzaldehyde, THF, −75°C, 1 h (*erythro* **7**: 42% yield; *threo* **7**: 41% yield). (b) MOMCl, *iso*-$Pr_2NEt$, $CH_2Cl_2$, r.t., 16 h (93% yield). (c) (1) $LiAlH_4$, THF, 0°C, 30 min; (2) PivCl, pyridine, r.t., 17 h (88% yield, 2 steps). (d) $HCO_2H$, ether, −5°C, 1 h (91% yield). (e) (1) 1 N aq. NaOH, EtOH, r.t., 20 h; (2) $NaIO_4$, aq. *tert*-BuOH, r.t., 1.5 h; (3) $Ag_2CO_3$-Celite, toluene, reflux, 1 h (81% yield, 3 steps).

The lithium aluminum hydride reduction of **8** proceeded well to give the corresponding diol, although detritylation of the resulting diol with formic acid or pyridinium *p*-toluenesulfonate was accompanied by demethoxymethylation. Conversion of the diol to pivaloyl ester **9** using pivaloyl chloride and pyridine (88% yield from **8**) was necessary to avoid cleavage of the methoxymethyl ether during the detritylation process. The selective cleavage of trityl ether **9** was successful by using formic acid to give glycol **10** in 91% yield. Hydrolysis of **10** in an alkaline solution and subsequent oxidative cleavage of the resulting glycol by using sodium periodate and silver carbonate-Celite oxidation gave butanolide **11** in 81% yield (Scheme 2).

Methylenation to butanolide **11** was achieved by




**Scheme 3.** Synthesis of Methylene Lactone (2).
(a) (1) LDA, $CH_2=N^+(CH_3)_2I^-$, THF, from $-75°C$ to $0°C$, 3.5 h; (2) MeI, MeOH, r.t., 56 h (58% yield, 2 steps). (b) TMSBr, $CH_2Cl_2$, $-20°C$, 1 h (69% yield). (c) TBDMSOTf, 2,6-lutidine, $CH_2Cl_2$, $0°C$, 1 h (78% yield).

treating with Eschenmoser's salt and methyl iodide,[9] giving *erythro* methylene lactone **12** in 58% yield. The same procedure gave *threo* methylene lactone **12** from *threo* aldol product **7** in 31% overall yield. To exchange the protective group of the benzylic hydroxy group, the methoxymethyl ether was cleaved by employing bromotrimethylsilane.[10] At this stage, epimerization at the benzylic position of *erythro* methylene lactone **12** occurred to give *threo* hydroxylactone **13** as a single isomer in 69% yield. *Threo* methylene lactone **12** gave *threo* hydroxylactone **13** as a single isomer in 73% yield under the same reaction conditions. Finally, silyloxylactone **14**, which is a synthetic intermediate to 1,2-oxidized furofuran lignan, was obtained by silylation with *tert*-butyldimethylsilyl trifluoromethanesulfonate and 2,6-lutidine in 78% yield (Scheme 3). The NMR data for **14** agreed with the previous data.[2]

The synthetic intermediate to 1,2-oxidized furofuran lignan, (3*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsilyl) oxy - 1 - (2 - methoxy - 4,5 - methylenedioxyphenyl) methyl]-2-methylene-4-butanolide (**14**), was stereoselectively synthesized from L-glutamic acid by 15 steps in 5.8–6.2% overall yield. This new stereoselective synthetic method for optically active 1,2-oxidized furofuran lignan involves fewer steps than the previously described method from L-glutamic acid.

## Materials and Methods

All melting point (mp) data are uncorrected. NMR data were measured by a JNM-EX400 spectrometer. EIMS data were measured with a Hitachi M-80B instrument, 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 $60F_{254}$ (0.5 mm thickness, $20\times20$ cm).

*(2S, 4S)-2-[(1S)-1-Hydroxy-1-(2-methoxy-4,5-methylenedioxyphenyl)methyl]-5-trityloxy-4-pentanolide (erythro-7) and (2S, 4S)-2-[(1R)-1-hydroxy-1-(2-methoxy-4,5-methylenedioxyphenyl)methyl]-5-trityloxy-4-pentanolide (threo-7).* Lithium diisopropylamide was prepared from diisopropylamine (4.80 ml, 34.2 mmol) and *n*-butyllithium (21.0 ml, 1.6 M in hexane, 33.6 mmol) in tetrahydrofuran (150 ml) at $-10°C$. To the solution of lithium diisopropylamide was added 4-pentanolide **5** (10.1 g, 28.2 mmol) in tetrahydrofuran (80 ml) at $-75°C$. After the mixture was stirred at $-75°C$ for 30 min, a solution of 2-methoxy-4,5-methylenedioxybenzaldehyde (5.08 g, 28.2 mmol) in tetrahydrofuran (20 ml) was added. The reaction solution 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 (ethyl acetate/hexane = 1/4) gave *erythro* **7** (6.34 g, 11.8 mmol, 42%) as colorless crystals, mp 174–175°C (ethyl acetate/hexane = 3/1) and *threo* **7** (6.23 g, 11.6 mmol, 41%) as colorless crystals, mp 183–184°C (ethyl acetate/hexane = 3/1). *Erythro* **7**: $[\alpha]_D^{20} = +4.5$ (*c* 0.90, $CHCl_3$). NMR $\delta_H$ ($CDCl_3$): 1.67 (1H, ddd, $J$ = 13.2, 9.8, 3.4 Hz), 2.34 (1H, ddd, $J$ = 13.2, 9.8, 9.8 Hz), 2.47–2.62 (1H, br.), 3.04 (1H, dd, $J$ = 10.3, 3.9 Hz), 3.38 (1H, ddd, $J$ = 9.8, 9.8, 2.9 Hz), 3.42 (1H, dd, $J$ = 10.3, 3.4 Hz), 3.67 (3H, s), 4.59 (1H, m), 5.53 (1H, d, $J$ = 2.9 Hz), 5.90 (2H, s), 6.49 (1H, s), 6.97 (1H, s), 7.19–7.31 (10H, m), 7.37–7.44 (5H, m). NMR $\delta_C$

($CDCl_3$): 24.1, 45.5, 56.0, 65.4, 66.8, 77.7, 87.0, 94.0, 101.2, 106.6, 122.2, 127.1, 127.8, 127.9, 128.6, 141.1, 143.5, 143.9, 147.3, 150.7, 178.5. IR $\nu_{max}$ ($CHCl_3$): 3609, 3088–2840, 1763, 1505, 1485, 1464, 1451, 1428, 1192, 1179, 1152, 1094, 1076, 1042, 1009, 706 $cm^{-1}$. EIMS *m/z* (20 eV): 538 ($M^+$, 0.7), 358 (16), 281 (25), 258 (17), 243 (100), 180 (42). *Anal.* Found: C, 73.49; H, 5.79%. Calcd. for $C_{33}H_{30}O_7$: C, 73.59; H, 5.61%. *Threo* **7**: $[\alpha]_D^{20} = +48.8$ (*c* 1.00, $CHCl_3$). NMR $\delta_H$ ($CDCl_3$): 1.82 (1H, ddd, *J* = 13.2, 9.3, 2.9 Hz), 2.05 (1H, ddd, *J* = 13.2, 9.3, 9.3 Hz), 3.10 (1H, dd, *J* = 10.3, 3.9 Hz), 3.15 (1H, ddd, *J* = 9.3, 9.3, 9.3 Hz), 3.41 (1H, dd, *J* = 10.3, 3.4 Hz), 3.72 (3H, s), 4.17 (1H, br. s), 4.58 (1H, m), 5.17 (1H, d, *J* = 9.3 Hz), 5.92 (1H, d, *J* = 1.2 Hz), 5.94 (1H, d, *J* = 1.2 Hz), 6.50 (1H, s), 6.93 (1H, s), 7.22–7.32 (10H, m), 7.34–7.39 (5H, m). NMR $\delta_C$ ($CDCl_3$): 27.3, 46.2, 56.6, 65.1, 68.1, 77.6, 87.2, 94.6, 101.3, 107.1, 121.3, 127.3, 127.9, 128.6, 141.8, 143.3, 147.9, 151.8, 179.7. IR $\nu_{max}$ ($CHCl_3$): 3500, 3088–2842, 1752, 1505, 1487, 1466, 1451, 1431, 1192, 1154, 1096, 1082, 1042, 706 $cm^{-1}$. EIMS *m/z* (20 eV): 538 ($M^+$, 1), 358 (16), 281 (26), 258 (17), 243 (100), 180 (43). *Anal.* Found: C, 73.36; H, 5.57%. Calcd. for $C_{33}H_{30}O_7$: C, 73.59; H, 5.61%.

*(2S, 4S)-2-[(1S)-1-Methoxymethoxy-1-(2-methoxy-4,5-methylenedioxyphenyl) methyl]-5-trityloxy-4-pentanolide (8).* A reaction mixture of *erythro* aldol product **7** (3.96 g, 7.35 mmol), *N,N*-diisopropylethylamine (24.0 ml, 138 mmol), and chloromethyl methyl ether (3.60 ml, 47.4 mmol) in dichloromethane (50 ml) was stirred at room temperature for 16 h before addition of $H_2O$ and dichloromethane. The organic solution was separated, successively washed with a 1 N 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 = 2/7) gave *erythro* methoxymethyl ether **8** (3.96 g, 6.80 mmol, 93%) as colorless crystals, mp 152–154°C (diisopropyl ether), $[\alpha]_D^{20} = -60.0$ (*c* 1.00, $CHCl_3$). NMR $\delta_H$ ($CDCl_3$): 1.67 (1H, m), 2.37 (1H, ddd, *J* = 12.7, 8.8, 8.8 Hz), 3.05 (1H, dd, *J* = 10.5, 3.7 Hz), 3.24 (1H, dd, *J* = 8.8, 8.8 Hz), 3.38 (3H, s), 3.40 (1H, dd, *J* = 10.5, 2.8 Hz), 3.70 (3H, s), 4.58 (2H, s), 4.60–4.64 (1H, m), 5.53 (1H, s), 5.91 (2H, d, *J* = 1.5 Hz), 6.50 (1H, s), 6.84 (1H, s), 7.19–7.28 (10H, m), 7.37–7.39 (5H, m). NMR $\delta_C$ ($CDCl_3$): 24.5, 45.1, 56.0, 56.2, 65.5, 70.3, 77.6, 87.0, 94.3, 94.9, 101.1, 106.5, 119.8, 127.1, 127.9, 128.6, 141.0, 143.5, 147.4, 151.5, 177.6. IR $\nu_{max}$ ($CHCl_3$): 3088–2840, 1767, 1505, 1485, 1464, 1451, 1428, 1192, 1175, 1150, 1102, 1076, 1040, 1034, 706 $cm^{-1}$. EIMS *m/z* (20 eV): 582 ($M^+$, 27), 243 (80), 225 (100), 165 (86). *Anal.* Found: C, 72.09; H, 5.98%. Calcd. for $C_{35}H_{34}O_8$: C, 72.18; H, 5.88%.

*Threo*-**8**: Colorless oil, 100% yield, $[\alpha]_D^{20} = +77.6$ (*c* 0.99, $CHCl_3$). NMR $\delta_H$ ($CDCl_3$): 2.11 (2H, dd, *J* = 7.3, 7.3 Hz), 3.09–3.14 (2H, m), 3.29–3.34 (1H, m), 3.41 (3H, s), 3.71 (3H, s), 4.54–4.58 (1H, m), 4.54 (1H, d, *J* = 6.8 Hz), 4.58 (1H, d, *J* = 6.8 Hz), 5.21 (1H, d, *J* = 5.9 Hz), 5.92 (2H, d, *J* = 3.4 Hz), 6.49 (1H, s), 6.92 (1H, s), 7.21–7.32 (10H, m), 7.40–7.42 (5H, m). NMR $\delta_C$ ($CDCl_3$): 28.6, 45.2, 56.1, 65.3, 71.8, 77.3, 86.8, 94.1, 94.6, 101.2, 107.5, 119.2, 127.1, 127.8, 127.9, 128.6, 128.7, 141.3, 143.5, 143.7, 147.8, 152.0, 176.0. IR $\nu_{max}$ ($CHCl_3$): 3088–2828, 1771, 1505, 1485, 1466, 1451, 1428, 1192, 1173, 1152, 1098, 1078, 1034, 706 $cm^{-1}$. EIMS *m/z* (20 eV): 582 ($M^+$, 12), 243 (100), 225 (75), 165 (55). *Anal.* Found: C, 71.89; H, 6.05%. Calcd. for $C_{35}H_{34}O_8$: C, 72.18; H, 5.88%.

*(2S, 4R, 5S)-5-Methoxymethoxy-5-(2-methoxy-4,5-methylenedioxyphenyl)-4-pivaloyloxymethyl-1-trityloxy-2-pentanol (9).* To an ice-cooled suspension of lithium aluminum hydride (1.44 g, 37.9 mmol) in tetrahydrofuran (50 ml) was added a solution of *erythro* lactone **8** (7.38 g, 12.7 mmol) in tetrahydrofuran (80 ml). After stirring at 0°C for 30 min, sat. aq. $MgSO_4$ and $K_2CO_3$ were added. The mixture was stirred at room temperature for 30 min and filtered. The filtrate was concentrated to give a crude diol. To a solution of this crude diol in pyridine (50 ml) was added pivaloyl chloride (1.54 ml, 12.5 mmol), and then the reaction mixture was stirred at room temperature for 17 h. After additions of ethyl acetate and $H_2O$, the organic solution was separated, successively washed with a 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 and 1/1) gave (5*S*)-pivaloyl ester **9** (7.51 g, 11.2 mmol, 88%) as colorless crystals, mp 141–142°C (ethyl acetate/hexane = 1/4), $[\alpha]_D^{20} = -59.6$ (*c* 1.28, $CHCl_3$). NMR $\delta_H$ ($CDCl_3$): 1.20 (9H, s), 1.45 (1H, ddd, *J* = 14.6, 10.8, 3.8 Hz), 1.67 (1H, ddd, *J* = 14.6, 10.5, 3.4 Hz), 2.30 (1H, m), 2.47 (1H, d, *J* = 3.9 Hz), 3.01 (1H, dd, *J* = 9.3, 6.8 Hz), 3.08 (1H, dd, *J* = 9.3, 3.9 Hz), 3.32 (3H, s), 3.69 (3H, s), 3.83 (1H, m), 3.99–4.05 (2H, m), 4.45 (1H, d, *J* = 6.8 Hz), 4.48 (1H, d, *J* = 6.8 Hz), 5.13 (1H, d, *J* = 5.4 Hz), 5.86 (1H, d, *J* = 1.5 Hz), 5.89 (1H, d, *J* = 1.5 Hz), 6.47 (1H, s), 6.79 (1H, s), 7.20–7.31 (10H, m), 7.40–7.42 (5H, m). NMR $\delta_C$ ($CDCl_3$): 27.2, 30.3, 38.8, 39.4, 56.1, 56.2, 64.3, 68.2, 68.8, 71.7, 86.5, 94.4, 94.5, 101.0, 107.4, 120.5, 127.0, 127.8, 128.6, 141.2, 143.9, 147.3, 152.3, 178.4. IR $\nu_{max}$ ($CHCl_3$): 3588, 3088–2828, 1719, 1505, 1483, 1466, 1449, 1426, 1289, 1192, 1173, 1154, 1092, 1076, 1034, 708 $cm^{-1}$. EIMS *m/z* (20 eV): 670 ($M^+$, 5), 263 (33), 243 (45), 225 (100), 165 (50). *Anal.* Found: C, 71.49; H, 6.90%. Calcd. for $C_{40}H_{46}O_9$: C, 71.66; H, 6.92%.

(5*R*)-**9**: Colorless crystals, mp 157–159°C (ethyl

acetate/hexane = 1/3), 71% yield, $[\alpha]_D^{20} = +48.6$ (*c* 1.25, $CHCl_3$). NMR $\delta_H$ ($CDCl_3$): 1.17 (9H, s), 1.32–1.45 (2H, m), 2.20–2.29 (1H, m), 2.24 (1H, d, *J* = 4.4 Hz), 2.97 (1H, dd, *J* = 9.3, 6.8 Hz), 3.07 (1H, dd, *J* = 9.3, 3.4 Hz), 3.32 (3H, s), 3.64 (3H, s), 3.87 (1H, m), 4.24 (1H, dd, *J* = 11.2, 3.9 Hz), 4.28 (1H, dd, *J* = 11.2, 4.4 Hz), 4.44 (1H, d, *J* = 6.8 Hz), 4.47 (1H, d, *J* = 6.8 Hz), 5.06 (1H, d, *J* = 7.3 Hz), 5.89 (1H, d, *J* = 1.0 Hz), 5.91 (1H, d, *J* = 1.0 Hz), 6.47 (1H, s), 6.82 (1H, s), 7.20–7.29 (10H, m), 7.36–7.38 (5H, m). NMR $\delta_C$ ($CDCl_3$): 27.2, 31.2, 38.9, 40.2, 55.9, 56.6, 62.9, 67.9, 68.4, 71.5, 86.5, 94.4, 94.5, 101.1, 107.3, 120.8, 127.0, 127.8, 128.6, 141.6, 143.8, 147.4, 152.8, 178.4. IR $\nu_{max}$ ($CHCl_3$): 3600, 3088–2826, 1721, 1505, 1483, 1466, 1449, 1287, 1192, 1171, 1152, 1094, 1075, 1034, 708 $cm^{-1}$. EIMS *m/z* (20 eV): 670 ($M^+$, 5), 243 (41), 225 (100), 165 (49). *Anal.* Found: C, 71.61; H, 6.99%. Calcd. for $C_{40}H_{46}O_9$: C, 71.66; H, 6.92%.

*(2S, 4R, 5S)-5-Methoxymethoxy-5-(2-methoxy-4,5-methylenedioxyphenyl)-4-pivaloyloxymethyl-1,2-pentanediol (**10**).* To a solution of (5*S*)-trityl ether **9** (8.18 g, 12.2 mmol) in ether (1000 ml) was added formic acid (600 ml) at −5°C. After stirring at −5°C for 1 h, a sat. aq. $NaHCO_3$ soln. 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 = 1/4 and 1/1) gave (5*S*)-glycol **10** (4.76 g, 11.1 mmol, 91%) as colorless crystals, mp 83–85°C (diisopropyl ether), $[\alpha]_D^{20} = -106$ (*c* 1.03, $CHCl_3$). NMR $\delta_H$ ($CDCl_3$): 1.21 (9H, s), 1.49 (1H, ddd, *J* = 14.2, 8.1, 3.2 Hz), 1.66 (1H, ddd, *J* = 14.2, 10.2, 4.4 Hz), 2.20–2.26 (1H, m), 2.26–2.31 (1H, m), 3.00 (1H, m), 3.38 (3H, s), 3.56 (1H, m), 3.72 (3H, s), 4.00 (1H, dd, *J* = 10.7, 7.1 Hz), 4.05 (1H, dd, *J* = 10.7, 5.4 Hz), 4.50 (2H, d, *J* = 1.5 Hz), 5.10 (1H, d, *J* = 6.4 Hz), 5.91 (1H, d, *J* = 1.0 Hz), 5.92 (1H, d, *J* = 1.0 Hz), 6.50 (1H, s), 6.82 (1H, s). NMR $\delta_C$ ($CDCl_3$): 27.1, 30.5, 38.8, 40.0, 56.2, 56.3, 64.6, 67.2, 70.4, 71.9, 94.5, 101.2, 107.3, 120.1, 141.3, 147.5, 152.4, 178.6. IR $\nu_{max}$ ($CHCl_3$): 3577, 3025–2828, 1721, 1505, 1483, 1466, 1426, 1289, 1271, 1192, 1173, 1152, 1034 $cm^{-1}$. EIMS *m/z* (20 eV): 428 ($M^+$, 8), 225 (94), 165 (100). *Anal.* Found: C, 58.80; H, 7.44%. Calcd. for $C_{21}H_{32}O_9$: C, 58.87; H, 7.53%.

(5*R*)-**10**: Colorless oil, 82% yield, $[\alpha]_D^{20} = +75.2$ (*c* 1.13, $CHCl_3$). NMR $\delta_H$ ($CDCl_3$): 1.17 (9H, s), 1.41 (2H, dd, *J* = 6.6, 6.6 Hz), 2.26 (1H, m), 3.36 (3H, s), 3.39 (1H, dd, *J* = 10.7, 7.3 Hz), 3.57 (1H, dd, *J* = 10.7, 3.4 Hz), 3.74 (3H, s), 3.82 (1H, m), 4.20 (1H, dd, *J* = 11.2, 5.1 Hz), 4.25 (1H, dd, *J* = 11.2, 4.4 Hz), 4.48 (2H, s), 5.09 (1H, d, *J* = 6.3 Hz), 5.91 (1H, d, *J* = 1.0 Hz), 5.93 (1H, d, *J* = 1.0 Hz), 6.50 (1H, s), 6.85 (1H, s). NMR $\delta_C$ ($CDCl_3$): 27.1, 31.0, 38.9, 40.5, 56.0, 56.5, 63.2, 67.1, 70.0, 71.8, 94.5, 101.1, 107.3, 120.4, 141.5, 147.5, 152.6, 178.7. IR $\nu_{max}$ ($CHCl_3$): 3500, 3025–2828, 1721, 1505, 1483, 1466, 1426, 1289, 1269, 1215, 1192, 1171, 1150, 1096, 1073, 1036 $cm^{-1}$. EIMS *m/z* (20 eV): 428 ($M^+$, 8), 225 (97), 165 (100). *Anal.* Found: C, 58.69; H, 7.58%. Calcd. for $C_{21}H_{32}O_9$: C, 58.87; H, 7.53%.

*(3R)-3-[(1S)-1-Methoxymethoxy-1-(2-methoxy-4,5-methylenedioxyphenyl) methyl]-4-butanolide (erythro-**11**).* A reaction solution of (5*S*)-pivaloyl ester **10** (2.23 g, 5.20 mmol) in 1 N aq. NaOH soln. (50 ml) and ethanol (50 ml) was stirred at room temperature for 20 h before addition of ethyl acetate and NaCl. The organic solution was separated and dried ($Na_2SO_4$). Concentration gave a crude triol. A reaction mixture of this crude triol and $NaIO_4$ (2.08 g, 9.72 mmol) in *tert*-butyl alcohol (60 ml) and $H_2O$ (30 ml) was stirred at room temperature for 1.5 h. After its concentration, 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 = 1/1) gave a hemiacetal. A reaction mixture of this hemiacetal and $Ag_2CO_3$-Celite (5.57 g, containing *ca.* 5.57 mmol of the silver salt) in toluene (40 ml) was heated under refluxing for 1 h. After filtration, the filtrate was concentrated. The residue was applied to silica gel column chromatography (ethyl acetate/hexane = 1/2) to give *erythro* lactone **11** (1.31 g, 4.22 mmol, 81%) as colorless crystals, mp 90–91°C (diisopropyl ether), $[\alpha]_D^{20} = -164$ (*c* 1.32, $CHCl_3$). NMR $\delta_H$ ($CDCl_3$): 2.51 (1H, dd, *J* = 18.1, 9.1 Hz), 2.61 (1H, dd, *J* = 18.1, 6.8 Hz), 2.89 (1H, m), 3.40 (3H, s), 3.76 (3H, s), 4.17 (1H, dd, *J* = 9.3, 5.9 Hz), 4.26 (1H, dd, *J* = 9.3, 7.8 Hz), 4.48 (1H, d, *J* = 6.8 Hz), 4.51 (1H, d, *J* = 6.8 Hz), 5.02 (1H, d, *J* = 5.9 Hz), 5.93 (1H, d, *J* = 1.5 Hz), 5.94 (1H, d, *J* = 1.5 Hz), 6.51 (1H, s), 6.83 (1H, s). NMR $\delta_C$ ($CDCl_3$): 30.5, 40.9, 56.1, 56.3, 70.2, 72.1, 94.3, 94.4, 101.3, 106.7, 119.2, 141.6, 147.9, 152.2, 177.2. IR $\nu_{max}$ ($CHCl_3$): 3025–2828, 1771, 1505, 1485, 1466, 1426, 1269, 1192, 1173, 1150, 1096, 1076, 1036, 1021, 938 $cm^{-1}$. EIMS *m/z* (20 eV): 310 ($M^+$, 15), 225 (46), 165 (100). *Anal.* Found: C, 58.00; H, 5.88%. Calcd. for $C_{15}H_{18}O_7$: C, 58.06; H, 5.85%.

*Threo*-**11**: Colorless crystals, mp 93–94°C (diisopropyl ether), 85% yield, $[\alpha]_D^{20} = +159$ (*c* 1.11, $CHCl_3$). NMR $\delta_H$ ($CDCl_3$): 2.41 (2H, d, *J* = 8.3 Hz), 2.88 (1H, m), 3.39 (3H, s), 3.76 (3H, s), 4.32 (1H, d, *J* = 10.7 Hz), 4.36 (1H, dd, *J* = 10.7, 1.5 Hz), 4.47 (1H, d, *J* = 6.8 Hz), 4.50 (1H, d, *J* = 6.8 Hz), 5.03 (1H, d, *J* = 6.8 Hz), 5.93 (1H, d, *J* = 1.2 Hz), 5.94 (1H, d, *J* = 1.2 Hz), 6.52 (1H, s), 6.82 (1H, s). NMR $\delta_C$ ($CDCl_3$): 31.1, 41.1, 56.2, 56.3, 70.4, 72.2, 94.3, 94.4, 101.3, 106.5, 119.2, 141.6, 147.9, 152.3, 177.0. IR $\nu_{max}$ ($CHCl_3$): 3025–2828, 1775, 1505, 1485, 1466,

1426, 1260, 1223, 1192, 1171, 1150, 1098, 1073, 1034, 1021, 938 $cm^{-1}$. EIMS *m/z* (20 eV): 310 ($M^+$, 28), 225 (85), 165 (100). *Anal.* Found: C, 58.02; H, 5.93%. Calcd. for $C_{15}H_{18}O_7$: C, 58.06; H, 5.85%.

*(3R)-3-[(1S)-1-Methoxymethoxy-1-(2-methoxy-4,5-methylenedioxyphenyl)methyl]-2-methylene-4-butanolide (erythro-**12**).* A lithium diisopropylamide solution in tetrahydrofuran was prepared from diisopropylamine (0.90 ml, 6.42 mmol) and *n*-butyllithium (4.00 ml, 1.6 M in hexane, 6.40 mmol) in tetrahydrofuran (20 ml) at −10°C. To this solution was added *erythro* lactone **11** (1.31 g, 4.22 mmol) in tetrahydrofuran (10 ml) at −75°C. After 30 min at −75°C, *N,N*,-dimethylmethyleneammonium iodide (1.60 g, 8.65 mmol) was added, and the reaction mixture was warmed to 0°C. After stirring at 0°C for 3.5 h, the mixture was concentrated. The residue was dissolved in methanol (20 ml), and then methyl iodide (1.05 ml, 16.9 mmol) was added. After the reaction mixture was stirred at room temperature for 56 h, a sat. aq. $NaHCO_3$ soln. and ethyl acetate were added. The organic solution was separated, successively washed with a 6 N HCl soln., sat. aq. $NaHCO_3$ soln. and brine, and dried ($Na_2SO_4$). Concentration followed by silica gel column chromatography (benzene/ethyl acetate = 5/1) gave *erythro* methylene lactone **12** (0.79 g, 2.45 mmol, 58%) as colorless crystals, mp 91–92°C, $[\alpha]_D^{20} = -72.3$ (*c* 1.04, $CHCl_3$). NMR $\delta_H$ ($CDCl_3$): 3.34 (1H, m), 3.37 (3H, s), 3.77 (3H, s), 4.19 (1H, dd, *J* = 9.3, 3.7 Hz), 4.28 (1H, dd, *J* = 9.3, 7.8 Hz), 4.47 (1H, d, *J* = 7.1 Hz), 4.49 (1H, d, *J* = 7.1 Hz), 5.08 (1H, d, *J* = 6.3 Hz), 5.45 (1H, d, *J* = 1.5 Hz), 5.94 (2H, s), 6.30 (1H, d, *J* = 1.5 Hz), 6.53 (1H, s), 6.79 (1H, s). NMR $\delta_C$ ($CDCl_3$): 43.6, 56.2, 56.3, 68.4, 73.6, 94.3, 94.5, 101.3, 107.4, 118.6, 124.9, 134.6, 141.3, 147.9, 152.2, 171.1. IR $\nu_{max}$ ($CHCl_3$): 3027–2828, 1759, 1505, 1483, 1466, 1428, 1275, 1192, 1173, 1150, 1125, 1034, 1011, 939 $cm^{-1}$. EIMS *m/z* (20 eV): 322 ($M^+$, 2), 225 (62), 165 (100). HRMS (EI) *m/z*: calcd. for $C_{16}H_{18}O_7$, 322.1052; found, 322.1059.

*Threo*-**12**: 63% yield, colorless crystals, mp 54–56°C, $[\alpha]_D^{20} = +199$ (*c* 1.20, $CHCl_3$). NMR $\delta_H$ ($CDCl_3$): 3.29–3.40 (1H, m), 3.33 (3H, s), 3.73 (3H, s), 4.26 (1H, dd, *J* = 8.8, 8.8 Hz), 4.46–4.53 (3H, m), 5.11 (1H, d, *J* = 6.4 Hz), 5.33 (1H, s), 5.94 (2H, d, *J* = 4.4 Hz), 6.23 (1H, s), 6.51 (1H, s), 6.86 (1H, s). NMR $\delta_C$ ($CDCl_3$): 44.2, 56.2, 67.5, 73.4, 94.3, 94.4, 101.3, 106.7, 118.7, 123.1, 135.7, 141.4, 147.9, 152.5, 170.8. IR $\nu_{max}$ ($CHCl_3$): 3027–2828, 1759, 1505, 1483, 1466, 1428, 1267, 1229, 1192, 1173, 1150, 1123, 1032, 1013, 939 $cm^{-1}$. EIMS *m/z* (20 eV): 322 ($M^+$, 3), 225 (54), 165 (100). *Anal.* Found: C, 59.74; H, 5.60%. Calcd. for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63%.

*(3R)-3-[(1R)-1-Hydroxy-1-(2-methoxy-4,5-methylenedioxyphenyl)methyl]-2-methylene-4-butanolide (**13**).* To a solution of *erythro* methoxymethyl ether **12** (25 mg, 0.078 mmol) in dichloromethane (5 ml) was added trimethylsilyl bromide (16 μl, 0.12 mmol) at −20°C. After the reaction solution was stirred at −20°C for 1 h, a sat. aq. $NaHCO_3$ soln. was added. The organic solution was separated, washed with brine, and dried ($Na_2SO_4$). Concentration followed by silica gel column chromatography (benzene/ethyl acetate = 3/1) gave *threo* benzyl alcohol **13** (15 mg, 0.054 mmol, 69%) as a colorless oil. From *threo* methoxymethyl ether **12**, *threo* benzyl alcohol **13** was obtained in 73% yield. $[\alpha]_D^{20} = +62.3$ (*c* 0.53, $CHCl_3$). NMR $\delta_H$ ($CDCl_3$): 2.48 (1H, d, *J* = 5.9 Hz), 3.44 (1H, m), 3.78 (3H, s), 4.33 (1H, dd, *J* = 9.3, 7.8 Hz), 4.54 (1H, dd, *J* = 9.3, 3.9 Hz), 4.88 (1H, dd, *J* = 5.9, 5.9 Hz), 5.16 (1H, d, *J* = 2.2 Hz), 5.94 (1H, d, *J* = 1.0 Hz), 5.95 (1H, d, *J* = 1.0 Hz), 6.21 (1H, d, *J* = 2.2 Hz), 6.54 (1H, s), 6.82 (1H, s). NMR $\delta_C$ ($CDCl_3$): 44.8, 56.1, 67.9, 71.6, 94.4, 101.4, 107.7, 120.7, 123.7, 135.3, 141.3, 148.0, 151.7, 170.8. IR $\nu_{max}$ ($CHCl_3$): 3605, 3021–2919, 1759, 1505, 1485, 1466, 1428, 1271, 1192, 1125, 1042, 1021 $cm^{-1}$. EIMS *m/z* (20 eV): 278 ($M^+$, 3), 181 (100). HRMS (EI) *m/z*: calcd. for $C_{14}H_{14}O_6$, 278.0789; found, 278.0793.

*(3R)-3-[(1R)-1-(tert-Butyldimethylsilyl)oxy-1-(2-methoxy-4,5-methylenedioxyphenyl)methyl]-2-methylene-4-butanolide (**14**).* To a solution of benzyl alcohol **13** (50 mg, 0.18 mmol) and 2,6-lutidine (0.10 ml, 0.86 mmol) in dichloromethane (10 ml) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.10 ml, 0.44 mmol) at 0°C. After the reaction solution was stirred at 0°C for 1 h, a sat. aq. $NaHCO_3$ soln. was 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 silyl ether **14** (55 mg, 0.14 mmol, 78%) as a colorless oil, $[\alpha]_D^{20} = +113$ (*c* 0.30, $CHCl_3$) (lit.[2] $[\alpha]_D^{20} = +104$, *c* 0.63, $CHCl_3$).

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