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Synthesis of γ-Lactone Derivatives as a Key Intermediate for the Spiroketal Fragment in Calyculin A

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Abstract : A simple and safe route to the D-xylone-1,4-lactone derivative **3**, a key intermediate for the synthesis of the spiroketal fragment in calyculin A (**1**) has been explored without the use of hazardous diazomethane on a large scale.
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Calyculin A (**1**), isolated from the marine sponge *Discodermia calyx*, has the unique molecular structure and strong biological activities.[1] Many research groups have been investigating the total synthesis[2] of calyculins, because they are interested in the relationship between the structure and biological activities.[1,3] Our laboratories have already reported a formal total synthesis of calyculin A[4] and the synthesis of some building units for calyculins.[5] As for the spiroketal fragment in calyculins, the stereoselective synthesis of the γ-lactone derivatives[5,6] via the chiral versatile butenolide from D-mannitol or L-malate as a starting material have also been completed. The groups of Tomioka[7] and Hanessian[8] reported the synthesis of the key intermediate of the γ-lactone derivative **3** by the use of diazomethane. In this paper, we now wish to report a simple and safe route to the γ-lactone derivative **3** using the potassium glycerate derivative **4** as a starting material without the use of hazardous diazomethane on a large scale.

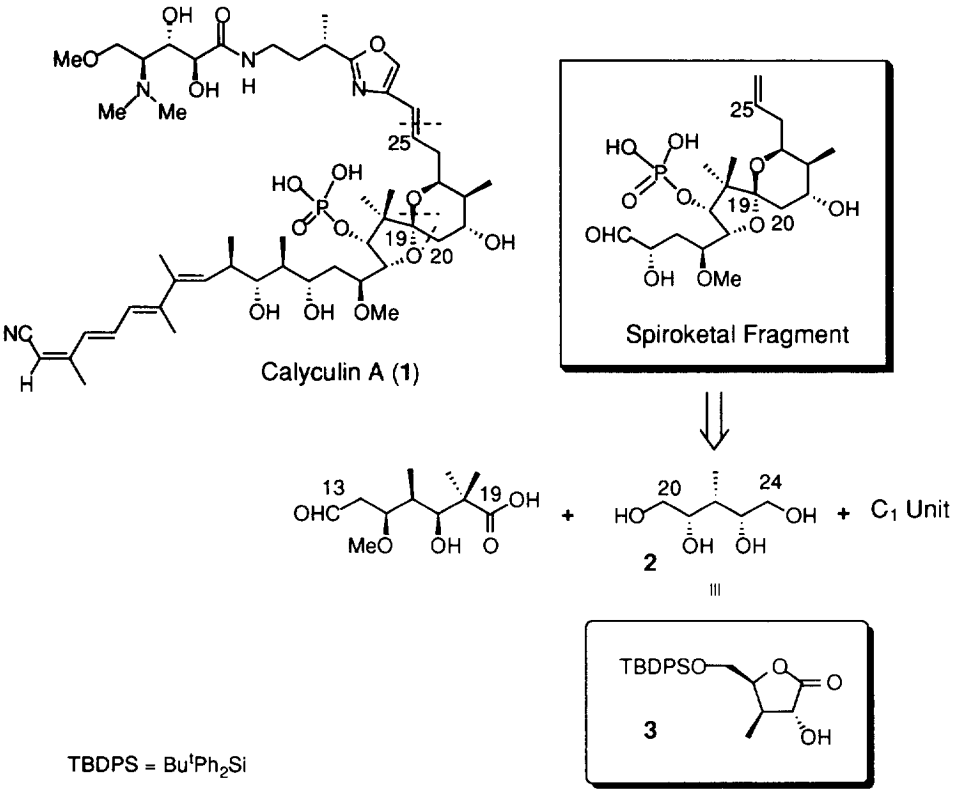
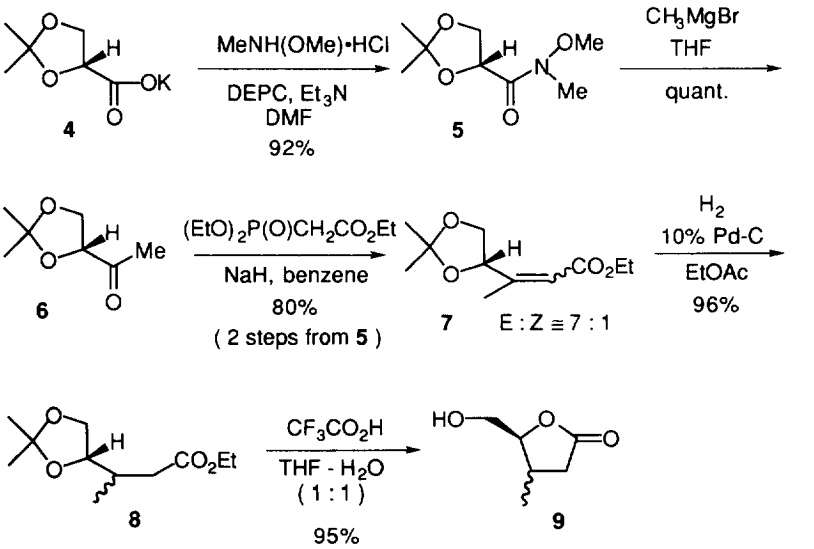


Figure 1 Calyculin A (**1**) and the chiral γ-lactone derivative **3**

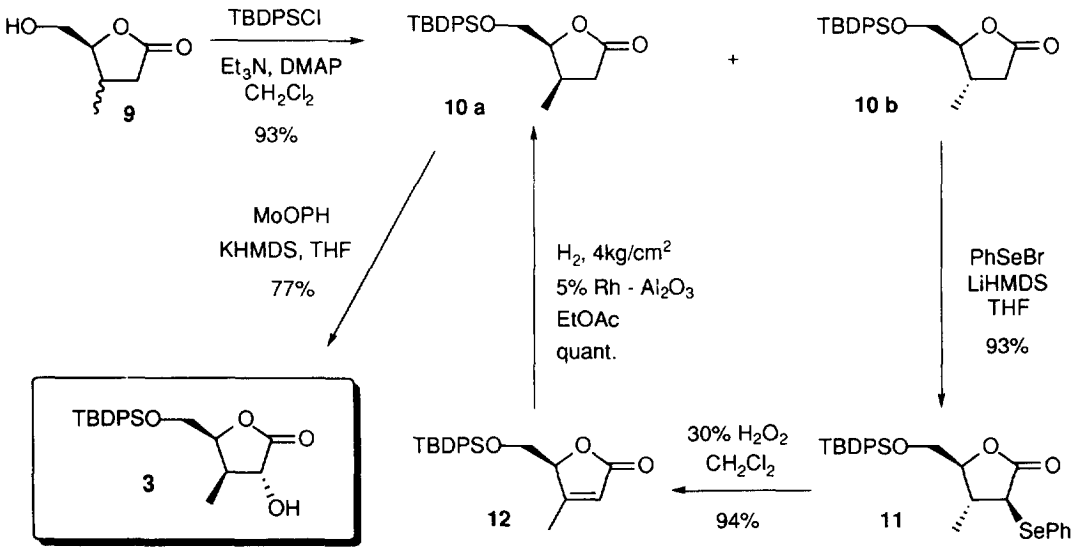


Scheme 1

Addition of a two carbon unit to the γ-lactone derivative was achieved as outlined in Scheme 1. Coupling of the potassium glycerate **4** with methoxymethylamine hydrochloride was achieved by use of diethyl phosphorocyanidate (DEPC, $(C_2H_5O)_2P(O)CN$)[9] in the presence of triethylamine. The Grignard reaction of the amide **5** with methylmagnesium bromide afforded the unstable methylketone derivative **6**. Without purification, treatment of **6** with sodium hydride followed by the Wadsworth-Emmons reaction with ethyl diethoxyphosphinylacetate in benzene gave the α,β-unsaturated ester **7** in 80% yield (*E* : *Z* = 7 : 1). Catalytic hydrogenation of the crude ester **7** over Pd-C afforded the ester **8** as a diastereomeric mixture. Because the separation of the diastereomeric mixture **8** was too difficult by silica gel column chromatography, the saturated esters **8** were transformed into the γ-lactone derivatives **9** by deacetalization and cyclization with trifluoroacetic acid in aqueous THF.

After protection of the hydroxy function with *tert*-butyldiphenylsilyl (TBDPS) chloride in the presence of triethylamine and 4-dimethylaminopyridine (DMAP), two diastereomeric isomers **10a** and **10b** could be separated by silica gel column chromatography, as shown in Scheme 2. The γ-lactone **10a** having the desired stereocenters was obtained as the major product in a ratio of 4 to 1. The undesired γ-lactone **10b** could be easily converted to the desired γ-lactone **10a**. Thus treatment of **10b** with phenylselenium bromide and lithium hexamethyldisilazide (LiHMDS), followed by oxidation with 30% H_2O_2 gave the butenolide derivative **12**.[8] Stereoselective reduction of the butenolide **12** over Rh-Al_2O_3,[8] which was developed and improved in our laboratories,[6,10] gave the desired γ-lactone **10a**. The stereoselective hydroxylation with the Vedejs reagent[11] (oxodiperoxymolybdenum-pyridine-HMPA complex: MoOPH) in the presence of potassium hexamethyldisilazide (KHMDS) at -78℃ gave the hydroxy lactone **3** having the three contiguous stereocenters as the key intermediate.[8,12]

In summary, we have accomplished a simple and safe route to the γ-lactone derivative **3** without the use of hazardous diazomethane. This synthesis is practical, easily manipulated, adequately suitable on a large scale, and applicable to a synthesis of starting materials of other compounds such as sugars *etc*.



Scheme 2

Experimental

(*R*)-2,2-Dimethyl-4-(N-methoxy-N-methylcarbamoyl)-1,3-dioxolane (5). To a solution of 5.53 g (30 mmol) of the potassium glycerate **4** in 100 ml of DMF was added 3.51 g (36 mmol) of N,O-dimethylhydroxyamine·HCl salt and 9.8 g (60 mmol) of DEPC at 0℃. After 15 min, 3.64 g (36 mmol) of Et_3N was added at this temperature. The resulting solution was stirred at room temperature for 15.5 h, and the mixture was diluted with 100 ml of water. The mixture was extracted with three 100 ml portions of EtOAc - benzene (2 : 1). The organic layer was washed with 100 ml of saturated aqueous $NaHCO_3$, brine and dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (140 g of silica gel BW-820 MH, hexane : EtOAc =2 : 1 and then EtOAc) afforded 5.24 g (92 %) of the Weinreb amide **5** as a colorless oil; b.p. 86-88℃ / 0.3-0.4 mmHg; $[\alpha]_D^{26}$ +29° (c 0.75, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3505, 1751, 1675, 1458, 1382, 1375, 1219, 844; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.43 (3H, s), 1.49 (3H, s), 3.71 (3H, s), 4.07 (1H, bs), 4.25 (1H, bt, J=7.3Hz), 4.80-4.92 (1H, bs); EIMS m/z (relative intensity) : 189 (M^+, 5), 174 (45), 131 (14), 101 (100); HRMS Calcd for $C_8H_{15}NO_4$ (M^+) : 189.1001, Found : 189.1005.

(*R*)-4-Acetyl-2,2-dimethyl-1,3-dioxolane (6). To a solution of 2.5 g (13.2 mmol) of **5** in 45 ml of THF was added dropwise 8.8 ml (26.4 mmol) of 3 M methylmagnesium bromide in ether at 0℃ under an argon atmosphere. The resulting solution was stirred for 1 h at 0℃ and then cautiously quenched by addition of 10 ml of citric acid. The mixture was extracted with three 100 ml portions of Et_2O - CH_2Cl_2 (2 : 1). The combined organic extracts were washed with 50 ml saturated aqueous $NaHCO_3$ and brine, dried (K_2CO_3 and $MgSO_4$), filtered and concentrated to give 2.02 g (quantitative) of **6** as a colorless oil, which was an unstable oil and used for the next step without further purification; $[\alpha]_D^{26}$ +68° (c 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3586, 1718, 1419, 1373, 1261, 1213, 1153, 1068; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.39 (3H, s), 1.49 (3H, s), 2.25 (3H, s), 3.99 (1H, dd, J=5.6, 8.5 Hz) 4.19 (1H, dd, J=7.9, 8.5 Hz), 4.41 (1H, dd, J=5.6, 7.5 Hz); EIMS m/z (relative intensity) : 144 (M^+, 15), 143 (100), 85 (28); HRMS Calcd for $C_7H_{11}O_3$ (M^+-H) : 143.0708, Found : 143.0707.

Ethyl 3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-(2*E*)- and (2*Z*)-butenoates (7). To a stirred suspension of 1.32 g (33 mmol) of NaH (60 % oil suspension) in 65 ml of benzene was added dropwise 7.94 ml (39.6 mmol) of ethyl diethoxyphosphinylacetate at 0℃ under an argon atmosphere. The resulting pale yellow solution was stirred at room temperature for 40 min. The ketone **6** (1.9 g, 13.2 mmol) in 6 ml of benzene (plus 3 ml of benzene rinse) was added at room temperature, and the mixture was stirred at reflux for 2 h. The brine was cautiously added to the resulting mixture and the mixture was extracted with three 100 ml portions of EtOAc. The combined organic extracts were washed with 50 ml of brine, dried (K_2CO_3 and $MgSO_4$), filtered, and concentrated. Column chromatography (40 g silica gel BW-820 MH, hexane : Et_2O = 5 : 1) of the residue afforded 2.26 g (80 % in 2 steps from **5**) of a mixture of the *E*- and *Z*-isomers **7** in a ratio of 7 : 1 as a colorless oil. The mixture of the isomers was directly used for the next step.
E-olefin **7**; $[\alpha]_D^{25}$ +37.1° (c 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1716, 1660, 1372, 1229, 1155, 1070, 852; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.27 (3H, t, J=7.2 Hz), 1.38 (3H, s), 1.48 (3H, s), 1.94 (3H, d, J=1.3 Hz), 3.57 (1H, dd, J=6.9, 8.2 Hz), 4.13 (2H, q, J=7.2 Hz), 4.39 (1H, dd, J=7.2, 8.2 Hz), 5.72 (1H, brt, J=6.9 Hz), 5.76 (1H, d, J=1.3 Hz); EIMS m/z (relative intensity) : 199 (M^+-CH_3, 70), 169 (20), 111 (100); HRMS Cacld for $C_{10}H_{15}O_4$ (M^+-CH_3) : 199.0970, Found : 199.0973.
Z-olefin **7**; $[\alpha]_D^{25}$ +89.3° (c 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1712, 1647, 1445, 1379, 1240, 1211, 1154,

1051; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.28 (3H, t, J=7.2 Hz), 1.41 (3H, s), 1.47 (3H, s), 2.10 (3H, d, J=1.3 Hz), 3.65 (1H, dd, J=7.5, 8.2 Hz), 4.12-4.23 (3H, m), 4.52 (1H, brt, J=6.9 Hz), 6.01 (1H, t, J=1.3 Hz); EIMS m/z (relative intensity) : 199 (M^+-CH_3, 20), 169 (15), 156 (50), 111 (100); HRMS Calcd for $C_{10}H_{15}O_4$ (M^+-CH_3) : 199.0970, Found : 199.0969.

Ethyl 3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-(3*R*)- and (3*S*)-butanoate (8). A mixture of 214 mg (1 mmol) of the *E*- and *Z*- isomers **7** and 20 mg of 10 % Pd-C in 10 ml EtOAc was stirred at room temperature for 2 h under a hydrogen atmosphere, and was then filtered using celite. The filtrate was evaporated to give 208 mg (96 %) of the two diastereomers **8** as a colorless oil, which was used for the next step without further purification; IR ν_{max}^{neat} cm^{-1} 2985, 1736, 1459, 1370, 1264, 1216, 1180, 1065, 860.

(4*R*,5*S*)- and (4*S*,5*S*)-5-Hydroxymethyl-4-methyl-1,4-butyrolactone (9). To a solution of 207 mg (0.95 mmol) of the ester **8** in 2 ml of THF - H_2O (1 : 1) was added 0.1 ml (1.3 mmol) of trifluoroacetic acid, and the reaction mixture was stirred at room temperature for 3 h. After addition of 50 ml (0.65 mmol) of trifluoroacetic acid, the mixture was stirred at room temperature for 2 h and then concentrated. Column chromatography (7 g of silica gel BW-820 MH, hexane : Et_2O = 1 : 1) of the residue afforded 117 mg (95 %) of the lactone diastereomers **9** as a colorless oil. These lactone diastereomers were unstable and unserviceable for separation.; IR ν_{max}^{neat} cm^{-1} 3420, 2968, 1767, 1218, 1172, 1092.

(4*R*,5*S*)- and (4*S*,5*S*)-5-*tert*-Butyldiphenylsiloxymethyl-4-methyl-1,4-butyrolactone (10). To a solution of 130 mg (1 mmol) of the lactone **9** in 3 ml of CH_2Cl_2 was added 202 mg (2 mmol) of triethylamine at 0℃. After the mixture was stirred for 10 min, 412 mg (1.5 mmol) of *tert*-butylchlorodiphenylsilane and 6 mg (0.04 mmol) of 4-dimethylaminopyridine (DMAP) were added at this temperature. The resulting solution was stirred at room temperature for 5 h. The mixture was extracted with three 50 ml portions of CH_2Cl_2. The combined organic extracts were washed with 100 ml portions of 1N HCl, water, 5% $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), filtered, and then concentrated. The residue, a mixture of the (4*R*)-methyl lactone **10a** and (4*S*)-isomer **10b**, was purified by column chromatography (250 g of silica gel BW-820 MH, hexane : EtOAc = 3 : 1) to give 285 mg (77 %) of the (4*R*)-methyl lactone **10a** as colorless crystals. The desired (4*R*)-methyl lactone **10a**; m.p. 87-88℃; $[\alpha]_D^{26}$ +50.7°(c 2.3, $CHCl_3$) (lit.[8]: m.p. 88-89℃, $[\alpha]_D^{26}$ +50.8° (c 2.2, $CHCl_3$)); IR ν_{max}^{neat} cm^{-1} 2943, 1779, 1428, 1169, 1105, 1039 1006, 872, 707; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.04 (9H, s), 1.22 (1H, dd, J=6.8 Hz), 2.50 (1H, dd, J=10.0, 16.8 Hz), 2.61 (1H, dd, J=8.5, 16.8 Hz), 2.68-2.88 (1H, m), 3.77 (1H, dd, J=2.9, 11.7 Hz), 3.87 (1H, dd, J=3.6, 11.7 Hz), 4.42-4.53 (1H, m), 7.35-7.50 (6H, m), 7.59-7.70 (4H, m); EIMS m/z (relative intensity) 311 (M^+-Bu^t, 58), 199 (100); HRMS Calcd for $C_{18}H_{19}O_3Si$ (M^+-Bu^t) : 311.1103, Found : 311.1105; Anal. Calcd for $C_{22}H_{28}O_3Si$: C 71.69, H 7.65; Found : C 71.55, H 7.70.

The undesired (4*S*)-methyl lactone **10b** was obtained as a colorless oil, 57 mg (15 %); $[\alpha]_D^{26}$ +33.2° (c 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1782, 1428, 1212, 1170, 1114, 1048, 934, 822; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.05 (9H, s), 1.12 (3H, d, J=7.0 Hz), 2.16 (1H, dd, J=6.8, 17.3 Hz), 2.54-2.65 (1H, m), 2.81 (1H, dd, J=8.7, 17.3 Hz), 3.72 (1H, dd, J=3.4, 11.4 Hz), 3.86 (1H, dd, J=3.4, 11.4 Hz), 4.05-4.13 (1H, m), 7.32-7.50 (6H, m), 7.60-7.70 (4H, m); EIMS m/z (relative intensity) 311 (M^+-^{t}Bu, 100), 199 (50); HRMS Calcd for $C_{18}H_{19}O_3Si$ (M^+-Bu^t) : 311.1103, Found : 311.1102.

(3*R*, 4*R*, 5*S*)-5-*tert*-Butyldiphenylsiloxymethyl-3-hydroxy-4-methyl-1,4-butyrolactone (3). To a stirred solution of 1.1 g (3 mmol) of the lactone **10a** in 20 ml of THF at -78℃ was added dropwise a solution of 12 ml (6 mmol) of potassium hexamethyldisilazide (0.5 M in toluene) under an argon atmosphere. After the reaction mixture was stirred for 30 min at -78℃, 1.95 g (4.5 mmol) of the solid oxodiperoxymolybdenum-pyridine-HMPA complex (MoOPH) was added quickly. The reaction mixture was warmed to -30℃ gradually during 1.5 h, and the resulting blue-green solution was quenched by the addition of 20 ml of freshly prepared saturated Na_2SO_3. The mixture was extracted with three 100 ml portions of Et_2O. The combined organic extracts were washed with 100 ml each portions of saturated aqueous Na_2SO_3, H_2O, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (100 g of silica gel BW-820 MH, hexane : EtOAc = 4 : 1 and then hexane : EtOAc = 3 : 1) of the residue afforded 886 mg (77 %) of the hydroxylactone **3** as a colorless prism : m.p. 139-140℃ (Et_2O-hexane); $[\alpha]_D^{25}$ +3.0° (c 4.5, $CHCl_3$); IR ν_{max}^{KBr} cm^{-1} 3464, 2966, 1763, 1427, 1333, 1176, 1113; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.03 (9H, s), 1.36 (3H, d, J=7.0 Hz), 2.61-2.72 (1H, m), 2.72-2.83 (1H, bs, disappeared with D_2O), 3.72 (1H, dd, J=1.4, 12.2 Hz), 3.89 (1H, dd, J=2.4, 12.2 Hz), 4.44(1H, m), 4.56 (1H, d, J=10.5 Hz), 7.38-7.46 (6H, m), 7.61-7.67 (4H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 177.68, 135.63, 135.50, 132.43, 131.69, 130.04, 130.00, 127.91, 80.16, 72.91, 62.18, 40.80, 26.70, 18.97, 12.26 (lit.[12] 177.90, 135.53, 133.40, 132.39, 131.69, 129.92, 129.88, 127.80, 80.09, 72.85, 62.13, 40.69, 26.63, 18.87, 12.13); EIMS m/z (relative intensity) 327 (M^+-Bu^t, 2), 309 (2.9), 199 (32), 181 (100), 163 (45); Anal. Calcd for $C_{22}H_{28}O_4Si$: C 68.71, H 7.33; Found : C 68.80, H 7.44.

(3*S*, 4*R*, 5*S*)-5-*tert*-Butyldiphenylsiloxymethyl-4-methyl-3-phenylselenyl-1,4-butyrolactone (11). To a stirred solution of 85 mg (0.23 mmol) of the lactone **10b** in 1 ml of THF at -78℃ was added dropwise a solution of 0.3 ml (0.3 mmol) of lithium hexamethyldisilazide (1 M solution in THF) under an argon atmosphere. After the reaction mixture was stirred for 30 min at -78℃, a solution of 57.3 mg (0.3 mmol) of phenylselenyl bromide in 1 ml of THF (plus 0.5 ml of THF rinse) was added quickly. After the reaction mixture was stirred for 2 h at -78℃ and then warmed to -40℃ gradually during 1 h, the resulting solution was quenched by the addition of 0.5 ml of 1N HCl. The mixture was extracted with three 10 ml portions of Et_2O. The combined organic extracts were washed with 10 ml each portions of saturated aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. Purification by column chromatography (10 g of silica gel BW-820 MH, hexane : Et_2O = 10 : 1 and then hexane : Et_2O = 2 : 1) afforded 112 mg (93 %) of the phenylselenide **11** as a colorless oil; $[\alpha]_D^{26}$ +10.7° (c 0.55, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2931, 1775, 1428, 1159, 1114, 1042, 823, 740; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.00 (9H, s), 1.10 (3H, d, J=6.8 Hz), 2.29-2.45 (1H, m), 3.49 (1H, d, J=10.5 Hz), 3.62 (1H, dd, J=4.6, 11.7 Hz), 3.72 (1H, dd, J=3.9, 11.7 Hz), 3.99-4.08 (1H, m), 7.20-7.30 (3H, m), 7.30-7.48 (6H, m), 7.58-7.70 (6H, m); EIMS m/z (relative intensity) 467 (M^+-^{t}Bu, 8), 241 (100), 223 (18), 199 (18); HRMS Calcd for $C_{24}H_{23}O_3SeSi$ (M^+-Bu^t) : 467.0581, Found : 467.0584.

(*S*)-5-*tert*-Butyldiphenylsiloxymethyl-4-methyl-3,4-dehydro-1,4-butyrolactone (12). To a stirred solution of 76 mg (0.14 mmol) of the phenylselenide **11** in 2 ml of CH_2Cl_2 at 0℃ was added dropwise a solution of 0.4 ml of ice-cold 30 % hydrogen peroxide. The reaction mixture was vigorously stirred at 0℃ for 30 min and then stirred at room temperature for 15 h . The mixture was diluted with 40 ml of EtOAc and washed with 10 ml each portions of water and brine. The organic layer was dried (Na_2SO_4),

filtered, and concentrated. Purification by column chromatography (15 g of silica gel BW-820 MH, hexane : EtOAc = 4 : 1 and then EtOAc) afforded 50 mg (94 %) of the butenolide **12** as a colorless oil; $[\alpha]_D^{25}$ -19° (c 2.2, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2931, 1759, 1651, 1428, 1132, 1065, 899, 822, 703; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.01 (9H, s), 2.06 (3H, m), 3.86 (1H, dd, J=3.4, 11.4 Hz), 4.01 (1H, dd, J=3.4, 11.4 Hz), 4.80-4.88 (1H, m), 5.88-5.97 (1H, m),7.35-7.58 (6H, m), 7.63-7.68 (4H, m); EIMS m/z (relative intensity) 309 (M^+-^{t}Bu, 100), 199 (82); HRMS Calcd for $C_{22}H_{26}O_3Si$ (M^+-^{t}Bu) : 309.0947, Found : 309.0959.

(4*R*,5*S*)-5-*tert*-Butyldiphenylsiloxymethyl-4-methyl-1,4-butyrolactone (10a). A mixture of 130 mg (0.35 mmol) of the enone **12** and 5 % Rh-Al_2O_3 in 10 ml of EtOAc and 0.2 ml of H_2O was shaken under hydrogen atmosphere (4 kg/cm^2) at room temperature for 1 h, and was then filtered using celite. The filtrate was evaporated, the residue was purified by column chromatography (10 g of silica gel BW-820 MH, hexane : EtOAc = 5 : 1) to give 138 mg (quantitative) of the lactone **10a** as white crystals : m.p. 105-107℃ (EtOAc-hexane); $[\alpha]_D^{25}$ +50.7° (c 2.3, $CHCl_3$); IR ν_{max}^{KBr} cm^{-1} 2963, 1780, 1429, 1257, 1170, 1041, 709; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05 (9H, s), 1.21 (3H, d, J=6.9 Hz), 2.52 (1H, dd, J=9.9, 17.0 Hz), 2.59 (1H, dd, J=8.6, 17.0 Hz), 2.78 (1H, q, J=6.9, 7.2, 8.6, 9.9 Hz), 3.77 (1H, dd, J=2.9, 11.5 Hz), 3.87 (1H, dd, J=3.6, 11.5 Hz), 4.44 (1H, ddd, J=2.9, 3.6, 7.2 Hz), 7.42-7.48 (6H, m), 7.64-7.69 (4H, m); EIMS m/z (relative intensity) : 311 (M^+-CH_3, 58), 199 (100); Anal. Calcd for $C_{22}H_{28}O_3Si$: C 71.69, H 7.65; Found : C 71.77, H 7.78.

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