Studies toward the total synthesis of popolohuanone E: enantioselective synthesis of 8-*O*-methylpopolohuanone E

– Supporting Information –

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Genaral Procedure.

All reactions were carried out using oven dried glassware and standard syringe, cannula, and septa techniques. Routine monitorings of reaction were carried out using glass-supported Merck Silica gel 60 F_{254} TLC plates. Flash column chromatography was performed on Merck silica gel F_{254} (230-400 mesh) with indicated solvents.

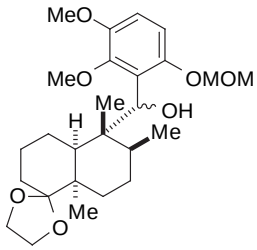
Materials.

All solvents and reagents were used as supplied with following exceptions. Tetrahydrofuran and ether were freshly distilled from sodium/benzophenone under argon. Toluene was distilled from sodium under argon. Dichloromethane, *N*,*N*-dimethylformamide (DMF), and hexamethylphosphoramide (HMPA) were distilled from calcium hydride under argon.

Instrumentation.

Measurements of optical rotations were performed with a JASCO P-1020 automatic digital polarimeter. Melting points were taken on a Yanaco MP-3 micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured with a Bruker AC-200 (200 MHz), a Bruker AM-400 (400 MHz), or a Bruker DRX-500 (500 MHz) spectrometer. Chemical shifts were expressed in ppm using tetramethylsilane (δ=0) as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). Infrared (IR) spectral measurements were carried out with a JASCO FT/IR-5300 spectrometer. Low resolution mass (MS) spectra and high resolution mass (HRMS) spectra were measured on a Hitachi M-80B spectrometer.

Coupling product 11.



11

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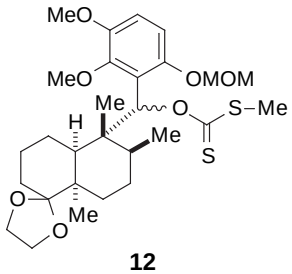
n-Butyllithium in hexane (1.52 M solution, 4.90 ml, 7.5 mmol) was added dropwise to a stirred solution of 1-bromo-2,3-dimethoxy-6-(methoxymethoxy)benzene[1] (**8**) (2.10 g, 7.6 mmol) in dry tetrahydrofuran (80 ml) at -40°C under argon. After 1 h, a solution of the *cis*-decaline **7**[2] (672 mg, 2.5 mmol) in dry tetrahydrofuran (10 ml) was added slowly at -40°C. The mixture was gradually warmed up to -20°C over 2 h. The reaction was quenched with water (20 ml), and the mixture was extracted with ethyl acetate (3 x 60 ml). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1→5:1) to give **11** (1.14 g, 97%) as a mixture of two diastereomers (3:1) as a colorless caramel: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.32 (2.25H, d, J=6.8 Hz), 0.42 (0.75H, d, J=6.7 Hz), 0.88 (3H, s), 1.15-1.75 (2.5H, m), 1.35 (0.75H, s), 1.39 (2.25H, s), 1.15-1.75 (7.5H, m), 2.16-2.23 (0.75H, m), 2.23 (0.75H, dd, J=12.1, 4.5 Hz), 2.08-2.15 (0.25H, m), 2.35-2.40 (0.25H, m), 3.45 (0.75H, s), 3.49 (2.25H, s), 3.79 (2.25H, s), 3.82 (0.75H, s), 3.83 (2.25H, s), 3.39-3.98 (3H, m), 3.93 (0.75H, s), 3.93-3.98 (1H, m), 4.27 (0.25H, d, J=11.5 Hz), 4.36 (0.75H, d, J=11.4 Hz), 5.08 (0.25H, d, J=6.9 Hz), 5.10 (0.25H, d, J=6.9 Hz), 5.14 (0.75H, d, J=6.9 Hz), 5.18 (0.75H, d, J=6.9 Hz), 5.26 (0.75H, d, J=11.4 Hz), 5.39 (0.25H, d, J=11.5 Hz), 6.75 (0.75H, d, J=9.0 Hz), 6.77 (0.25H, d, J=9.1 Hz), 6.82 (0.25H, d, J=9.1 Hz), 6.88 (0.75H, d, J=9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8, 15.1, 18.3, 18.6, 22.8, 22.9, 23.7, 23.8, 27.4, 27.5, 27.5, 27.6, 28.1, 28.1, 29.8, 30.1, 30.2, 30.2, 43.0, 43.0, 43.4, 43.7, 46.9, 47.0, 56.1, 56.1, 56.3, 56.5, 60.3, 61.2, 64.8, 64.8, 64.8, 64.8, 74.6, 75.1, 95.4, 95.4, 109.0, 109.6, 111.0, 112.0, 114.4, 114.4, 125.2, 125.6, 147.4, 147.8, 148.0, 149.1, 149.8, 150.9; IR (neat) 949, 1013, 1047, 1086, 1152, 1256, 1483, 1589, 1738, 2940, 3547 cm^{-1}; HREIMS m/z calcd for $C_{26}H_{40}O_7$ (M^+), 464.2745, found 464.2774.

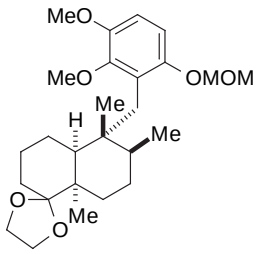
Methyl xanthate 12.



12

Sodium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M solution, 7.40 ml, 7.4 mmol) was added dropwise to a stirred solution of **11** (1.13 g, 2.4 mmol) in dry tetrahydrofuran (80 ml) at -78°C under argon. After 30 min, carbon disulfide (3.00 ml, 49 mmol) was added slowly. The mixture was gradually warmed up to -55°C over 1 h, and then iodomethane (1.50 ml, 25 mmol) was added slowly at -78°C. After 1 h, the mixture was gradually warmed up to -55°C over 1 h. The reaction was quenched with 20% aqueous sodium thiosulfate (10 ml), and the mixture was extracted with ethyl acetate (3 x 60 ml). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1) to give **12** (1.28 g, 94%) as a mixture of two diastereomers (3:2) as a pale yellow caramel: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.47 (1.8H, br d, J=4.3 Hz), 0.63 (1.2H, br s), 1.09 (1.8H, s), 1.13 (1.2H, s), 1.23 (1.2H, s), 1.33 (1.8H, s), 1.25-2.30 (12H, m), 2.56 (1.8H, s), 2.58 (1.2H, s), 3.47 (1.8H, s), 3.51 (1.2H, s), 3.76 (1.2H, s), 3.81 (1.2H, s), 3.82 (1.8H, s), 3.87-3.95 (4H, m), 3.99 (1.8H, s), 4.99 (0.6H, d, J=6.9 Hz), 5.09 (0.6H, d, J=6.9 Hz), 5.13 (0.4H, d, J=6.8 Hz), 5.16 (0.4H, d, J=6.8 Hz), 6.78 (0.6H, d, J=9.1 Hz), 6.79 (0.4H, d, J=9.0 Hz), 6.86 (0.6H, d, J=9.1 Hz), 6.87 (0.4H, d, J=9.0 Hz), 6.99 (0.4H, s), 7.06 (0.6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.3, 15.6, 18.5, 18.5, 18.8, 19.1, 22.7, 22.7, 25.2, 26.3, 26.8, 26.9, 27.6, 28.0, 29.1, 29.6, 30.2, 30.3, 30.8, 31.9, 42.0, 42.4, 44.7, 44.8, 47.0, 47.2, 55.9, 56.0, 56.0, 56.1, 60.2, 60.5, 64.6, 64.7, 64.7, 64.8, 86.5, 86.7, 95.8, 95.9, 109.1, 110.1, 112.4, 112.4, 114.1, 114.1, 120.8, 121.2, 147.4, 148.4, 148.8, 149.0, 150.9, 151.1, 213.4, 214.3; IR (neat) 922, 956, 1051, 1088, 1150, 1252, 1485, 1589, 2938 cm^{-1}; HREIMS m/z calcd for $C_{28}H_{42}O_7S_2$ (M^+), 554.2372, found 554.2390.

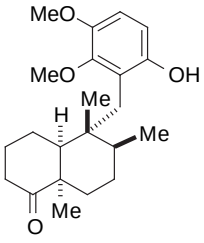
Deoxygenated product 13.



13

Tributyltin hydride (2.50 ml, 9.2 mmol) and 2,2'-azobisisobutyronitrile (38.0 mg, 0.23 mmol) were added successively to a stirred solution of **12** (1.28 g, 2.3 mmol) in dry toluene (80 ml) at room temperature. The mixture was frozen using liquid nitrogen and then evacuated *in vacuo* followed by filled with dry argon. The mixture was heated at reflux for 2 h. After cooling, the mixture was concentrated *in vacuo* to afford a residue, which was purified by column chromatography (hexane-ethyl acetate, 20:1) to give **13** (789 mg, 77%) as a colorless caramel: $[\alpha]_D^{20}$ +4.1 (*c* 1.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (3H, d, J=6.7 Hz), 0.92 (3H, s), 1.01-1.11 (1H, m), 1.18 (3H, s), 1.38-1.62 (6H, m), 1.62-1.81 (4H, m), 1.86 (1H, dt, J=5.0, 14.0 Hz), 2.63 (1H, d, J=13.0 Hz), 2.95 (1H, d, J=12.9 Hz), 3.48 (3H, s), 3.75 (3H, s), 3.82 (3H, s), 3.88-3.96 (4H, m), 5.10 (2H, s), 6.70 (1H, d, J=9.0 Hz), 6.82 (1H, d, J=9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.8, 18.8, 22.7, 25.0, 27.1, 28.3, 30.3, 30.6, 36.0, 37.1, 42.1, 42.9, 49.1, 56.0, 56.1, 59.9, 64.5, 64.6, 95.3, 108.7, 110.2, 114.4, 125.0, 147.7, 149.3, 151.4; IR (neat) 721, 756, 799, 922, 953, 1013, 1049, 1088, 1148, 1252, 1283, 1377, 1404, 1422, 1483, 1589, 2936 cm^{-1}; HREIMS m/z calcd for $C_{26}H_{40}O_6$ (M^+), 448.2825, found 448.2827.

Ketone 14.

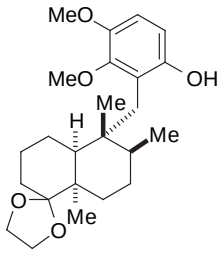


14

12 M Hydrochloric acid (2.80 ml, 34 mmol) was added to a stirred solution of **13** (768 mg, 1.7 mmol) in methanol (60 ml) at room temperature, and the mixture was heated at 40°C for 2.5 h. After cooling, the mixture was diluted with ethyl acetate (200 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine,

then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1) to give **14** (605 mg, 98%) as a colorless caramel: $[\alpha]_D^{20}$ +25.2 (*c* 0.89, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78 (1H, dt, J=4.3, 12.9 Hz), 0.85 (3H, s), 0.90 (3H, d, J=6.4 Hz), 1.20 (3H, s), 1.23-1.36 (2H, m), 1.39-1.48 (1H, m), 1.90-1.98 (2H, m), 1.98-2.21 (5H, m), 2.58-2.65 (1H, m), 2.64 (1H, d, J=13.8 Hz), 2.72 (1H, d, J=13.8 Hz), 3.76 (3H, s), 3.82 (3H, s), 4.49 (1H, s), 6.46 (1H, d, J=8.7 Hz), 6.68 (1H, d, J=8.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.5, 18.6, 21.3, 24.4, 28.4, 30.7, 54.6, 35.5, 36.4, 39.3, 44.2, 48.5, 52.1, 56.2, 60.0, 109.7, 111.0, 121.4, 146.8, 149.5, 149.7, 218.0; IR (neat) 972, 1046, 1082, 1258, 1290, 1383, 1424, 1464, 1495, 1599, 1686, 2936 cm^{-1}; HREIMS m/z calcd for $C_{22}H_{32}O_4$ (M^+), 360.2301, found 360.2315.

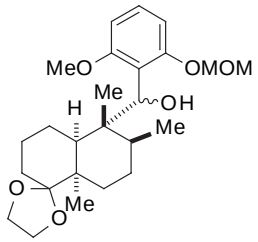
Phenolic segment 5.



5

Ethylene glycol (1.30 ml, 23 mmol) and *p*-toluenesulfonic acid monohydrate (32.0 mg, 0.17 mmol) were added to a solution of **14** (554 mg, 1.5 mmol) in benzene (50 ml) at room temperature. The mixture was placed in a Dean-Stark apparatus and then heated at reflux for 8 h. After cooling, the reaction was quenched with saturated aqueous sodium hydrogen carbonate (10 ml), and the mixture was extracted with ethyl acetate (3 x 60 ml). The combined extracts were washed with brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1 →5:1) to give **5** (584 mg, 94%) as a white amorphous solid: $[\alpha]_D^{20}$ +2.4 (*c* 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (3H, d, J=6.6 Hz), 0.98 (3H, s), 0.99-1.09 (1H, m), 1.17 (3H, s), 1.36-1.82 (10H, m), 1.86 (1H, dt, J=4.8, 14.1 Hz), 2.55 (1H, d, J=13.7 Hz), 2.92 (1H, d, J=13.7 Hz), 3.75 (3H, s), 3.81 (3H, s), 3.88-3.97 (4H, m), 4.45 (1H, s), 6.49 (1H, d, J=8.7 Hz), 6.67 (1H, d, J=8.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.6, 18.7, 22.6, 24.7, 27.8, 28.5, 30.5, 30.7, 36.4, 37.4, 42.0, 43.1, 49.3, 56.4, 59.9, 64.4, 64.5, 109.8, 111.3, 114.3, 122.0, 146.9, 149.4, 149.8; IR (KBr) 737, 795, 951, 1047, 1086, 1258, 1134, 1258, 1337, 1377, 1424, 1464, 1493, 1599, 2957, 3410 cm^{-1}; HRCIMS m/z calcd for $C_{24}H_{36}O_5$ (M^+), 404.2563, found 404.2590.

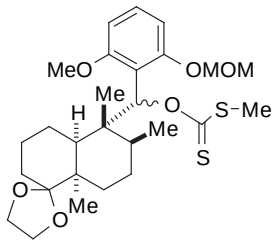
Coupling product 15.



15

n-Butyllithium in hexane (1.52 M solution, 1.50 ml, 2.3 mmol) was added dropwise to a stirred solution of 1-bromo-2-methoxy-6-(methoxymethoxy)benzene[3] (**9**) (562mg, 2.3 mmol) in dry tetrahydrofuran (25 ml) at -40°C under argon. After 30 min, a solution of the *cis*-decaline **7**[2] (202 mg, 0.76 mmol) in dry tetrahydrofuran (5 ml) was added slowly at -40°C. The mixture was gradually warmed up to -20°C over 30 min. The reaction was quenched with water (10 ml), and the mixture was extracted with ethyl acetate (3 x 30 ml). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1) to give **15** (296 mg, 97%) as a mixture of two diastereomers (1.8:1) as a colorless caramel: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.48 (1.07H, d, J=6.7 Hz), 0.57 (1.93H, d, J=6.7 Hz), 0.88 (1.93H, s), 0.90 (1.07H, s), 1.33 (1.07H, s), 1.34 (1.93H, s), 1.22-1.70 (9H, m), 1.82-1.92 (1H, m), 2.02-2.09 (0.36H, m), 2.09-2.16 (0.64H, m), 2.33-2.40 (1H, m), 3.46 (1.93H, s), 3.50 (1.07H, s), 3.79 (1.07H, s), 3.84 (1.93H, s), 3.39-3.97 (4H, m), 4.40 (0.36H, d, J=11.3 Hz), 4.48 (0.64H, d, J=11.8 Hz), 5.14 (0.64H, d, J=7.2 Hz), 5.16 (0.64H, d, J=7.2 Hz), 5.18 (0.36H, d, J=6.8 Hz), 5.24 (0.36H, d, J=6.8 Hz), 5.39 (0.64H, d, J=11.3 Hz), 5.45 (0.36H, d, J=11.3 Hz), 6.59 (1H, d, J=8.3 Hz), 6.78 (0.36H, d, J=8.3 Hz), 6.79 (0.64H, d, J=8.2 Hz), 7.15 (1H, dd, J=8.2, 8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8, 15.2, 18.5, 18.5, 22.7, 22.8, 24.2, 24.7, 26.7, 27.1, 27.6, 27.7, 28.0, 28.4, 30.1, 30.1, 30.6, 30.9, 42.7, 42.8, 43.3, 43.3, 47.2, 47.2, 55.3, 55.6, 56.2, 56.6, 64.3, 64.6, 64.7, 64.7, 73.8, 73.8, 94.9, 95.0, 105.1, 105.3, 107.3, 107.6, 114.4, 114.4, 119.8, 120.0, 128.2, 128.2, 156.1, 157.2, 158.3, 159.1; IR (neat) 756, 1071, 1086, 1154, 1231, 1441, 1470, 1593, 2951, 3547 cm^{-1}; HREIMS m/z calcd for $C_{25}H_{38}O_6$ (M^+), 434.2668, found 434.2651.

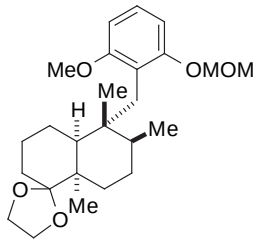
Methyl xanthate 16.



16

Carbon disulfide (1.70 ml, 28 mmol) was added dropwise to a stirred solution of **15** (568 mg, 1.4 mmol) in dry tetrahydrofuran (20 ml) at -78°C under argon. After 10 min, sodium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M solution, 2.80 ml, 2.8 mmol) was added slowly. The mixture was gradually warmed up to -70°C over 1 h, and then iodomethane (0.90 ml, 14 mmol) was added dropwise at -78°C. After 1 h, the mixture was gradually warmed up to -60°C over 30 min. The reaction was quenched with 20% aqueous sodium thiosulfate (5 ml), and the mixture was extracted with ethyl acetate (3 x 30 ml). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1) to give **16** (666 mg, 90%) as a mixture of two diastereomers (1.3:1) as a pale yellow caramel: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.67 (1.3H, br d, J=5.4 Hz), 0.71 (1.7H, br d, J=5.6 Hz), 1.10 (1.7H, s), 1.11 (1.3H, s), 1.24 (1.3H, s), 1.25 (1.7H, s), 1.14-1.78 (9H, m), 1.83-1.93 (1H, m), 2.00-2.08 (1H, m), 2.10-2.15 (1H, m), 2.54 (1.3H, s), 2.55 (1.7H, s), 3.48 (1.3H, s), 3.52 (1.7H, s), 3.74 (1.7H, s), 3.85 (1.3H, s), 3.90-3.95 (4H, m), 5.05 (0.43H, d, J=6.9 Hz), 5.13 (0.43H, d, J=6.9 Hz), 5.17 (0.57H, d, J=6.7 Hz), 5.19 (0.57H, d, J=6.7 Hz), 6.53 (0.57H, d, J=8.3 Hz), 6.57 (0.43H, d, J=8.1 Hz), 6.76 (0.57H, d, J=7.9 Hz), 6.78 (0.43H, d, J=8.0 Hz), 7.00 (1H, s), 7.16 (0.57H, dd, J=7.9, 8.3 Hz), 7.16 (0.43H, dd, J=8.0, 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.1, 15.5, 18.2, 18.6, 18.7, 18.9, 22.5, 22.6, 25.5, 25.7, 26.1, 26.6, 28.0, 28.0, 29.5, 29.7, 30.2, 30.3, 32.0, 32.3, 42.1, 42.1, 44.5, 44.5, 47.0, 47.1, 55.4, 56.1, 56.2, 56.3, 64.6, 64.6, 64.6, 64.6, 85.4, 85.7, 95.3, 95.4, 105.0, 105.6, 106.8, 108.1, 114.1, 114.1, 114.9, 115.3, 129.4, 129.4, 157.4, 157.7, 159.2, 159.6, 212.7, 212.9; IR (neat) 758, 924, 1011, 1067, 1152, 1250, 1383, 1439, 1470, 1593, 1640, 2936 cm^{-1}; HREIMS m/z calcd for $C_{26}H_{37}O_6S_2$ [$(M-Me)^+$], 509.2032, found 509.2060.

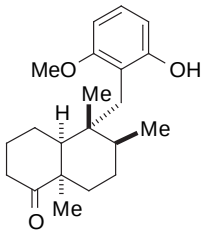
Deoxygenated product 17.



17

Tributyltin hydride (0.30 ml, 1.5 mmol) and 2,2'-azobisisobutyronitrile (6.0 mg, 40 μmol) were added successively to a stirred solution of **16** (191 mg, 0.36 mmol) in dry toluene (10 ml) at room temperature. The mixture was frozen using liquid nitrogen and then evacuated *in vacuo* followed by filled with dry argon. The mixture was heated at reflux for 2 h. After cooling, the mixture was concentrated *in vacuo* to afford a residue, which was purified by column chromatography (hexane-ethyl acetate, 40:1) to give **17** (123 mg, 81%) as a colorless oil: $[\alpha]_D^{20}$ +12.9 (*c* 0.62, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, d, J=6.5 Hz), 0.94 (3H, s), 0.94-1.04 (1H, m), 1.14 (3H, s), 1.33-1.41 (1H, m), 1.41-1.48 (1H, m), 1.48-1.62 (4H, m), 1.62-1.73 (4H, m), 1.87 (1H, dt, J=4.6, 14.0 Hz), 2.67 (1H, d, J=13.3 Hz), 2.93 (1H, d, J=13.3 Hz), 3.47 (3H, s), 3.76 (3H, s), 3.87-3.96 (4H, m), 5.14 (1H, d, J=7.0 Hz), 5.15 (1H, d, J=7.0 Hz), 6.53 (1H, d, J=8.2 Hz), 6.76 (1H, d, J=8.2 Hz), 7.09 (1H, dd, J=8.3, 8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 18.9, 22.7, 24.6, 27.9, 28.7, 30.7, 31.1, 35.7, 36.6, 41.8, 43.0, 48.6, 55.1, 56.0, 64.4, 64.6, 94.8, 104.1, 106.7, 114.4, 118.6, 126.9, 157.6, 159.5; IR (neat) 735, 754, 755, 924, 1020, 1071, 1092, 1146, 1238, 1271, 1337, 1441, 1470, 1593, 2955 cm^{-1}; HREIMS m/z calcd for $C_{25}H_{38}O_5$ (M^+), 418.2719, found 418.2764.

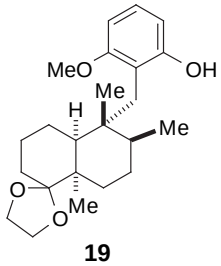
Ketone 18.



18

12 M Hydrochloric acid (1.60 ml, 19 mmol) was added to a stirred solution of **17** (473 mg, 1.1 mmol) in methanol (30 ml) at room temperature, and the mixture was heated at 40°C for 1 h. After cooling, the mixture was diluted with ethyl acetate (100 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1) to give **18** (354 mg, 95%) as a white amorphous solid: $[\alpha]_D^{20}$ +37.2 (*c* 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.76 (1H, dt, J=4.1, 12.9 Hz), 0.84 (3H, s), 0.90 (3H, d, J=6.3 Hz), 1.20 (3H, s), 1.22-1.34 (2H, m), 1.34-1.44 (1H, m), 1.90-1.94 (1H, m), 1.93-2.01 (1H, m), 2.05-2.21 (5H, m), 2.59-2.68 (1H, m), 2.66 (1H, d, J=14.1 Hz), 2.74 (1H, d, J=14.1 Hz), 3.77 (3H, s), 4.70 (1H, s), 6.39 (1H, d, J=8.1 Hz), 6.45 (1H, d, J=8.2 Hz), 7.04 (1H, dd, J=8.1, 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.5, 18.6, 21.2, 24.4, 28.4, 30.6, 34.2, 34.6, 36.3, 39.1, 44.0, 48.4, 52.1, 55.0, 102.7, 108.3, 114.9, 127.1, 155.9, 159.8, 218.1; IR (KBr) 744, 779, 1076, 1121, 1136, 1244, 1281, 1346, 1464, 1591, 1605, 1672, 2946, 2971, 3345 cm^{-1}; *Anal* calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15, found C, 76.27; H, 9.40.

Phenol 19.

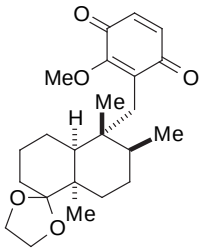


19

Ethylene glycol (0.56 ml, 10 mmol) and *p*-toluenesulfonic acid monohydrate (1.90 mg, 10 μmol) were added to a solution of **18** (166 mg, 0.50 mmol) in benzene (30 ml) at room temperature. The mixture was placed in a Dean-Stark apparatus and then heated at reflux for 8 h. After cooling, the reaction was quenched with saturated aqueous sodium hydrogen

carbonate (5 ml), and the mixture was extracted with ethyl acetate (3 x 40 ml). The combined extracts were washed with brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 6:1) to give **19** (169 mg, 90%) as a white amorphous solid: $[\alpha]_D^{20}$ +17.6 (*c* 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, d, J=6.3 Hz), 0.92-1.01 (1H, m), 0.99 (3H, s), 1.13 (3H, s), 1.28-1.40 (1H, m), 1.43-1.55 (2H, m), 1.55-1.66 (4H, m), 1.66-1.77 (3H, m), 1.89 (1H, dt, J=4.3, 14.1 Hz), 2.60 (1H, d, J=14.1 Hz), 2.87 (1H, d, J=14.2 Hz), 3.76 (3H, s), 3.86-3.95 (4H, m), 4.72 (1H, s), 6.42 (1H, d, J=8.1 Hz), 6.44 (1H, d, J=8.1 Hz), 7.03 (1H, dd, J=8.2, 8.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.1, 18.8, 22.6, 24.2, 28.5, 28.8, 30.6, 31.4, 35.8, 36.8, 41.6, 43.1, 48.6, 55.0, 64.4, 64.5, 102.7, 108.3, 114.2, 115.4, 127.0, 155.8, 159.8; IR (KBr) 734, 909, 1080, 1128, 1146, 1244, 1287, 1337, 1437, 1466, 1593, 1674, 2888, 2932, 2961, 3297 cm^{-1}; *Anal* calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15, found C, 73.44; H, 9.44.

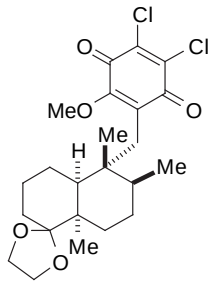
Quinone 20.



20

N,*N*-Bis(salicylidene)ethylenediiminocobalt(II) (130 mg, 0.40 mmol) was added to a stirred solution of **19** (99.6 mg, 0.27 mmol) in dry DMF (4 ml) at 0°C. The suspension was stirred under an oxygen atmosphere for 5 h at room temperature. The mixture was concentrated *in vacuo* to afford a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1) to give **20** (87.7 mg, 85%) as a yellow solid: $[\alpha]_D^{20}$ +8.0 (*c* 0.22, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, d, J=6.4 Hz), 0.90-0.95 (1H, m), 0.96 (3H, s), 1.10 (3H, s), 1.23-1.38 (3H, m), 1.46-1.77 (7H, m), 1.89 (1H, dt, J=4.1, 14.3 Hz), 2.49 (1H, d, J=12.8 Hz), 2.70 (1H, d, J=12.8 Hz), 3.85-3.96 (4H, m), 4.01 (3H, s), 6.60 (1H, d, J=10.0 Hz), 6.68 (1H, d, J=10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 18.4, 22.4, 23.5, 28.7, 29.1, 30.6, 31.9, 34.6, 37.4, 41.3, 44.2, 48.7, 60.5, 64.3, 64.5, 113.9, 132.3, 134.4, 136.9, 156.8, 183.5, 188.3; IR (KBr) 845, 1049, 1095, 1134, 1211, 1306, 1321, 1447, 1572, 1647, 1665, 2863, 2922, 2959 cm^{-1}; HREIMS m/z calcd for $C_{23}H_{32}O_2$ (M^+), 388.2250, found 388.2549.

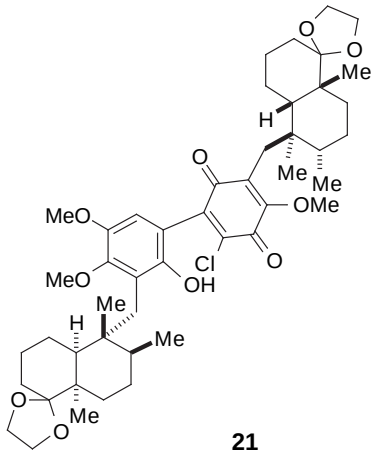
Quinone segment 6.



6

Thionyl choride (146 μl, 2.0 mmol) and pyridine (289 μl, 3.6 mmol) were added successively to a stirred solution of **20** (27.8 mg, 70 μmol) in dry benzene (3 ml), and the mixture was refluxed for 2 h. After cooling, the mixture was diluted with ethyl acetate (10 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1) to give **6** (25.6 mg, 78%) as a yellow oil: $[\alpha]_D^{20}$ +23.2 (*c* 0.34, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, d, J=6.4 Hz), 0.93-1.02 (1H, m), 0.96 (3H, s), 1.11 (3H, s), 1.26-1.37 (3H, m), 1.47-1.53 (2H, m), 1.54-1.62 (2H, m), 1.62-1.75 (3H, m), 1.93 (1H, dt, J=4.1, 14.2 Hz), 2.55 (1H, d, J=12.9 Hz), 2.77 (1H, d, J=12.8 Hz), 3.86-3.94 (4H, m), 4.05 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 18.4, 22.4, 23.7, 28.7, 29.1, 30.5, 31.9, 35.7, 37.6, 41.4, 44.6, 49.0, 61.1, 64.4, 64.5, 113.8, 132.5, 137.9, 141.2, 156.7, 174.4, 178.7; IR (neat) 756, 826, 914, 1028, 1090, 1136, 1165, 1208, 1304, 1379, 1447, 1578, 1615, 1678, 2878, 2957 cm^{-1}; HREIMS m/z calcd for $C_{23}H_{30}O_5Cl_2$ (M^+), 456.1470, found 456.1475.

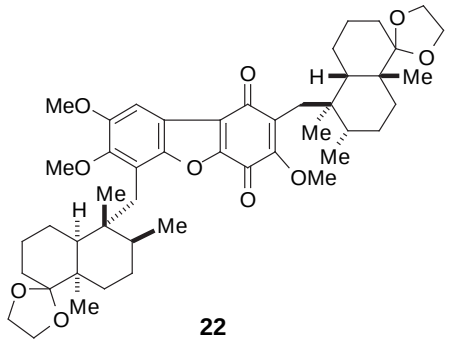
Coupling product 21.



21

Phenolic segment **5** (47.4 mg, 0.12 mmol) in dry tetrahydrofuran (1 ml) was added dropwise to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 9.4 mg, 0.23 mmol) in dry tetrahydrofuran (1 ml) at room temperature. After 30 min, a solution of quinone segment **6** (53.6 mg, 0.12 mmol) in dry tetrahydrofuran (1 ml) was then added slowly to the above mixture at -78°C. After 1 h, the reaction was quenched with saturated aqueous ammonium chloride (2 ml), and the resulting mixture was extracted with ethyl acetate (3 x 10 ml). The combined extracts were washed with brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1→5:1) to give **21** (91.3 mg, 94%) as a dark purple amorphous solid: solutions of this compound were deeply colored, therefore, an accurate measurement of optical rotation could not be carried out; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (3H, d, J=6.5 Hz), 0.89 (3H, d, J=6.3 Hz), 0.95-1.08 (2H, m), 0.98 (3H, s), 1.00 (3H, s), 1.13 (3H, s), 1.16 (3H, s), 1.22-1.35 (8H, m), 1.45-1.64 (8H, m), 1.64-1.84 (4H, m), 1.84-1.97 (2H, m), 2.53-2.65 (2H, m), 2.77 (1H, d, J=13.0 Hz), 2.88 (1H, d, J=13.0 Hz), 3.79 (3H, s), 3.82 (3H, s), 3.85-3.96 (8H, m), 4.06 (3H, s), 4.53-5.30 (1H, br s), 6.53 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 18.3, 18.5, 18.7, 20.9, 22.3, 22.5, 23.6, 24.5, 28.1, 28.5, 28.9, 30.4, 30.6, 31.0, 32.0, 34.7, 36.4, 37.2, 37.4, 41.4, 41.7, 43.2, 44.2, 48.3, 48.9, 56.1, 60.0, 60.3, 60.8, 64.3, 64.5, 64.5, 111.9, 113.9, 114.0, 115.2, 123.2, 133.2, 138.1, 143.2, 146.6, 146.7, 150.5, 156.3, 171.1, 176.4;IR (neat) 756, 1049, 1088, 1213, 1464, 1588, 1672, 2876, 2957, 3482 cm^{-1}; HREIMS m/z calcd for $C_{47}H_{65}O_{10}Cl$ (M^+), 824.4266, found 824.4261.

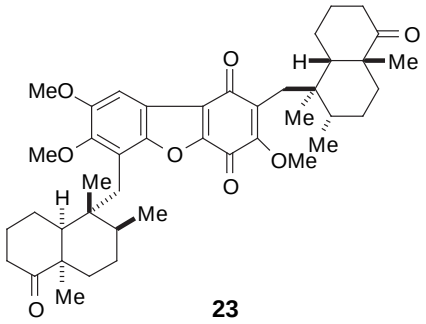
Cyclized product 22.



22

Amberlite®IRA-900 (319 mg) in dry tetrahydrofuran (3 ml) was stirred at room temperature for 4 h. A solution of **21** (32.9 mg, 40 μmol) in dry tetrahydrofuran (2 ml) was added to the above mixture. After 3 h, the reaction mixture was diluted with ethyl acetate (5 ml) and then filtrated. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1→5:1) to give **22** (25.2 mg, 80%) as a dark red amorphous solid: solutions of this compound were deeply colored, therefore, an accurate measurement of optical rotation could not be carried out; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78-0.91 (2H, m), 0.92 (3H, d, J=6.1 Hz), 0.98 (3H, d, J=6.3 Hz), 1.00 (3H, s), 1.05 (3H, s), 1.09 (3H, s), 1.15 (3H, s), 1.20-1.40 (6H, m), 1.43-1.65 (8H, m), 1.66-1.96 (8H, m), 2.55 (1H, d, J=12.8 Hz), 2.80 (1H, d, J=12.8 Hz), 2.89 (1H, d, J=13.6 Hz), 3.14 (1H, d, J=13.6 Hz), 3.82 (3H, s), 3.85-3.96 (8H, m), 3.97 (3H, s), 4.09 (3H, s), 7.45 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 18.5, 18.7, 18.7, 21.0, 22.4, 22.6, 23.7, 24.2, 28.6, 28.8, 29.1, 30.5, 30.7, 31.5, 31.9, 35.6, 36.2, 36.3, 37.5, 41.2, 41.7, 43.5, 44.3, 47.9, 49.4, 56.2, 60.6, 61.0, 64.3, 64.4, 64.5, 64.5, 101.7, 114.0, 114.1, 117.4, 120.0, 122.7, 132.6, 150.0, 151.1, 152.6, 152.7, 157.1, 172.5, 184.4; IR (neat) 756, 1049, 1073, 1090, 1134, 1279, 1460, 1559, 1655, 1672, 2874, 2934, 3435 cm^{-1}; HREIMS m/z calcd for $C_{47}H_{64}O_{10}$ (M^+), 788.4499, found 788.4476.

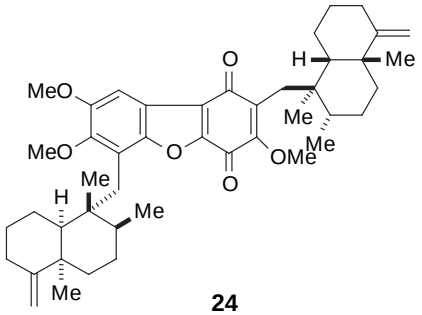
Diketone 23.



23

1.0 M Hydrochloric acid (1.0 ml, 1.00 mmol) was added to a stirred solution of **22** (25.2 mg, 30 μmol) in methanol (10 ml) at room temperature. After 15 min, the reaction was quenched with saturated aqueous sodium hydrogen carbonate (5 ml), and the mixture was extracted with ethyl acetate (3 x 20 ml). The combined extracts were washed with brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1 →5:1) to give **23** (22.4 mg, 100%) as a red amorphous solid: solutions of this compound were deeply colored, therefore, an accurate measurement of optical rotation could not be carried out; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.56-0.66 (1H, m), 0.76-0.91 (1H, m), 0.84 (3H, s), 0.93 (6H, s), 1.06 (3H, d, J=5.9 Hz), 1.13 (3H, s), 1.17-1.40 (8H, m), 1.23 (3H, s), 1.75-1.82 (2H, m), 1.97-2.39 (10H, m), 2.58-2.72 (2H, m), 2.61 (1H, d, J=13.1 Hz), 2.67 (1H, d, J=13.1 Hz), 2.96 (1H, d, J=13.9 Hz), 3.02 (1H, d, J=13.9 Hz), 3.84 (3H, s), 4.01 (3H, s), 4.11 (3H, s), 7.49 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.7, 18.2, 18.4, 18.5, 21.0, 21.2, 24.2, 24.6, 28.1, 28.2, 30.6, 30.7, 33.8, 34.4, 34.5, 34.7, 36.2, 36.3, 37.9, 39.6, 44.3, 45.4, 48.1, 48.3, 50.9, 52.4, 56.3, 60.8, 61.1, 102.0, 117.6, 119.0, 122.8, 131.7, 150.0, 151.3, 152.5, 152.8, 157.4, 172.3, 184.2, 216.8, 217.2; IR (neat) 756, 982, 1071, 1277, 1421, 1458, 1559, 1655, 1672, 1701, 2932, 3385 cm^{-1}; HREIMS m/z calcd for $C_{43}H_{56}O_8$ (M^+), 700.3975, found 700.3947.

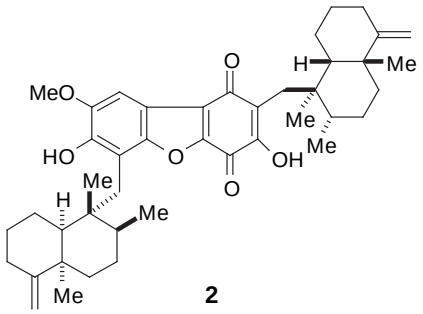
Popolohuanone E trimethyl ether 24.



24

Titanium tetrachloride in dichloromethane (1.0 M solution, 0.36 ml, 0.36 mmol) was added dropwise to a suspension of zinc dust (95.7 mg, 1.5 mmol) and dibromomethane (34 ml, 0.49 mmol) in dry tetrahydrofuran (2 ml) at 0°C, and the mixture was stirred at room temperature for 30 min. A solution of diketone **23** (22.8 mg, 33 μmol) in a dry tetrahydrofuran (2 ml) was added dropwise to the above mixture at room temperature. After 17 h, the reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate (5 ml), and the resulting mixture was diluted with ethyl acetate (20 ml). The organic layer was washed brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1) to give **24** (6.0 mg, 26%) as a redish orange amorphous solid: solutions of this compound were deeply colored, therefore, an accurate measurement of optical rotation could not be carried out; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85-0.97 (1H, m), 0.91 (3H, s), 0.92 (3H, d, J=6.1 Hz), 0.99 (3H, s), 1.00 (3H, s), 1.05 (3H, d, J=6.3 Hz), 1.09 (3H, s), 1.16 (1H, ddd, J=3.3, 13.8, 13.8 Hz), 1.18-1.23 (2H, m), 1.27-1.35 (1H, m), 1.34 (1H, br d, J=6.8 Hz), 1.36 (1H, br d, J=6.8 Hz), 1.38-1.45 (1H, m), 1.47-1.54 (2H, m), 1.63-1.70 (1H, m), 1.71-1.97 (5H, m), 1.97-2.07 (3H, m), 2.07-2.16 (2H, m), 2.19-2.27 (1H, m), 2.40-2.50 (2H, m), 2.57 (1H, d, J=13.0 Hz), 2.64 (1H, d, J=13.0 Hz), 2.89 (1H, d, J=13.7 Hz), 3.00 (1H, d, J=13.7 Hz), 3.82 (3H, s), 3.99 (3H, s), 4.08 (3H, s), 4.66 (1H, s), 4.68 (1H, s), 4.71 (1H, s), 4.71 (1H, s), 7.47 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.4, 18.7, 18.8, 19.0, 22.8, 22.9, 25.0, 25.2, 27.8, 28.0, 32.0, 32.1, 33.1, 33.2, 34.2, 34.7, 37.6, 37.8, 38.7, 39.5, 39.7, 40.4, 44.7, 45.9, 47.7, 49.5, 56.3, 60.7, 61.0, 101.8, 105.7, 105.9, 117.6, 119.6, 122.8, 132.4, 149.9, 151.3, 152.7, 152.8, 153.4, 153.7, 157.2, 172.5, 184.3; IR (neat) 758, 891, 982, 1046, 1073, 1103, 1233, 1273, 1383, 1420, 1458, 1557, 1603, 1655, 1672, 1782, 2866, 2932 cm^{-1}; HREIMS m/z calcd for $C_{45}H_{60}O_6$ (M^+), 696.4390, found 696.4392.

8-*O*-Methylpopolohuanone E (2).

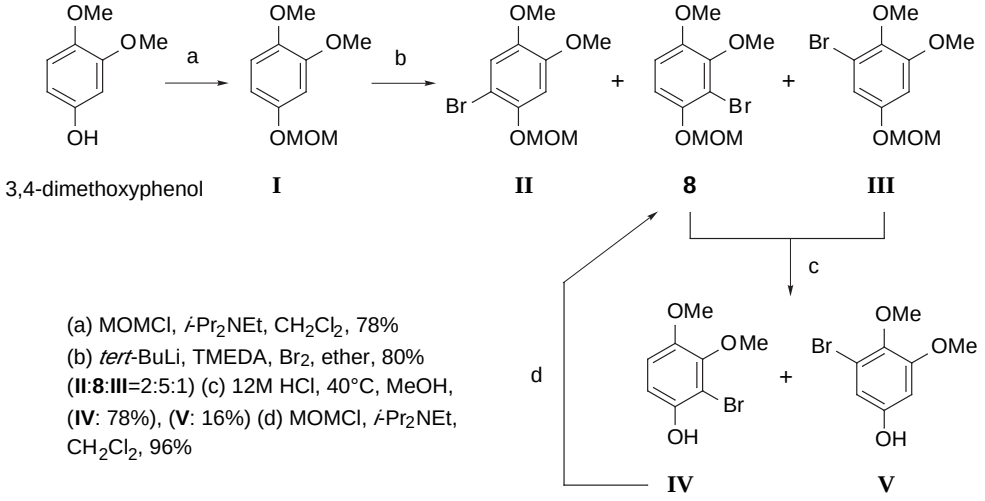


2

Lithium *n*-butylthiolate in HMPA solution (0.5 M, 0.30 ml, 0.16 mmol) was added to a stirred solution of **24** (3.7 mg, 5.3 μmol) in HMPA (1 ml) at room temperature, and the mixture was heated at 110°C for 2 h. After cooling, the reaction was quenched with saturated aqueous ammonium chloride (2 ml), and the mixture was extracted with ethyl acetate (3 x 5 ml). The combined extracts were washed with brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 4:1) to give **2** (1.2 mg, 34%) as a dark purple amorphous solid: solutions of this compound were deeply colored, therefore, an accurate measurement of optical rotation could not be carried out; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 0.92 (3H, s), 0.94-0.97 (1H, m), 0.97 (3H, d, J=6.5 Hz), 0.99 (3H, s), 1.00 (3H, s), 1.06 (3H, d, J=6.4 Hz), 1.07 (3H, s), 1.13 (1H, ddd, J=3.4, 13.8, 13.8 Hz), 1.16-1.25 (2H, m), 1.31-1.38 (2H, m), 1.38 (1H, br d, J=6.5 Hz), 1.40 (1H, br d, J=6.5 Hz), 1.47-1.59 (2H, m), 1.63-1.75 (3H, m), 1.76-1.92 (3H, m), 1.92-1.97 (1H, m), 1.98-2.04 (1H, m), 2.08-2.16 (2H, m), 2.14-2.21 (1H, m), 2.31-2.36 (1H, m), 2.42-2.51 (2H, m), 2.55 (1H, d, J=13.6 Hz), 2.63 (1H, d, J=13.6 Hz), 2.93 (1H, d, J=14.1 Hz), 3.05 (1H, d, J=14.1 Hz), 4.03 (3H, s), 4.68 (2H, dd, J=1.8, 1.8 Hz), 4.70 (2H, dd, J=1.6, 2.2 Hz), 6.50 (1H, s), 7.33 (1H, s), 7.43 (1H, s); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 18.7, 18.7, 18.9, 18.9, 23.1, 23.1, 25.4, 25.6, 28.3, 28.4, 32.3, 32.4, 33.2, 33.3, 33.5, 34.5, 38.1, 38.2, 39.2, 39.8, 40.0, 40.2, 44.9, 45.6, 48.2, 49.2, 57.1, 100.5, 105.9, 105.9, 111.1, 114.9, 119.1, 126.1, 147.4, 147.5, 149.2, 154.0, 154.1, 154.1, 155.0, 170.8, 185.0; IR (neat) 891, 1032, 1070, 1103, 1265, 1338, 1383, 1460, 1566, 1664, 2286, 2617, 2928, 3368, 3520 cm^{-1}; HREIMS m/z calcd for $C_{43}H_{56}O_6$ (M^+), 668.4077, found 668.4085.

References

1. The starting material **8** was prepared from commercially available 3,4-dimethoxyphenol, as shown in the following Scheme. Experimental procedures and characterization data for all new compounds depicted in this Scheme are as follows.



Preparation of 2-bromo-3,4-dimethoxyphenol (IV).

Chloromethyl methyl ether (9.60 ml, 0.13 mol) was added dropwise to a stirred solution of 3,4-dimethoxyphenol (13.0 g, 84 mmol) and *N*,*N*-diisopropylethylamine (29.4 ml, 0.17 mol) in dry dichloromethane (150 ml) at 0°C under argon at room temperature. After 17 h, the reaction was quenched with 1% aqueous hydrochloric acid (20 ml), and the organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1) to give **I** (13.0 g, 78%) as a white solid.

tert-BuLi in *n*-pentane (1.51 M solution, 57.2 ml, 83 mmol) was added dropwise to a stirred solution of **I** (13.0 g, 65 mmol) and *N*,*N*,*N*',*N*'-tetramethylethylenediamine (13.0 ml, 83 mmol) in dry diethyl ether (130 ml) at -78°C under argon. After 1 h, bromine (4.94 ml, 94 mmol) was added slowly at -78°C, and the mixture was gradually warmed up to 0°C over 3 h. The reaction was quenched with 20% aqueous sodium thiosulfate (25 ml), and the mixture was extracted with ethyl acetate (3 x 150 ml). The combined extracts were washed successively with 1% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 30:1) to give **II** (3.59 g, 20%) and a mixture of **8** and **III** (10.9 g, 60%) as an inseparable mixture of two regioisomer (5:1) as a white

solid. The regioisomeric mixture was separated by the operation described below.

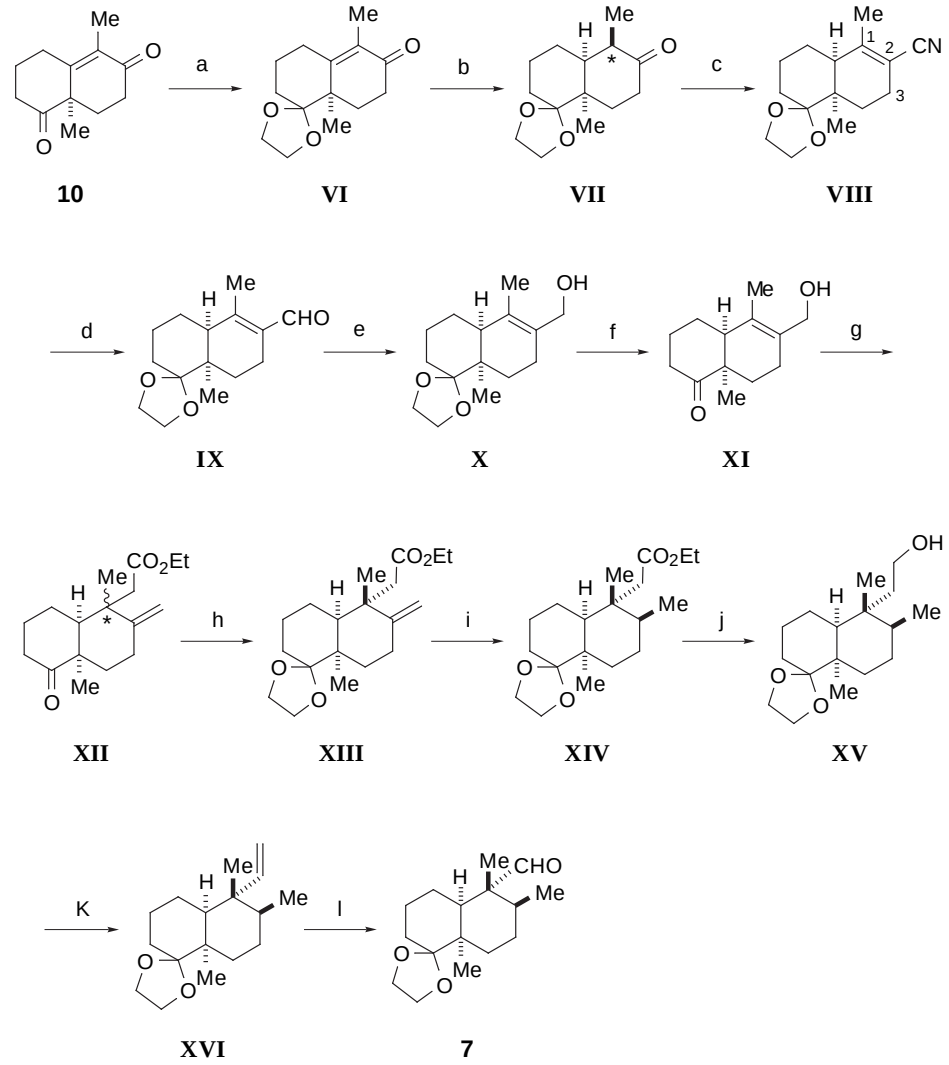
12 M Hydrochloric acid (39.0 ml, 0.16 mol) was added to a stirred solution of the mixture (**8** and **III**) (10.9 g, 39 mmol) in methanol (100 ml) at room temperature, and the mixture was then heated at 40°C for 5 h. After cooling, the mixture was diluted with ethyl acetate (150 ml) and extracted with ethyl acetate (2 x 80 ml). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1) to give **IV** (7.15 g, 78%) as a less polar product and **V** (1.48 g, 16%) as a more polor product.

IV: a white solid; mp 103-104°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (3H, s), 3.88 (3H, s), 5.20 (1H, s), 6.76 (1H, d, J=9.0 Hz), 6.83 (1H, d J=9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.8, 60.7, 106.7, 110.0, 113.1, 146.7, 147.1, 147.3; IR (KBr) 797, 822, 947, 1034, 1269, 1426, 1458, 1495, 3322 cm^{-1}; *Anal* calcd for $C_8H_9BrO_3$: C, 41.23; H, 3.89; Br, 34.28 found C, 41.30; H, 3.86; Br, 34.24.

Preparation of 1-bromo-2,3-dimethoxy-6-(methoxymethoxy)benzene (8).

Chloromethyl methyl ether (1.30 ml, 18 mmol) was added dropwise to a stirred solution of **IV** (2.75 g, 12 mmol) and *N*,*N*-diisopropylethylamine (4.10 ml, 24 mmol) in dry dichloromethane (20 ml) at 0°C under argon. The solution was stirred at room temperature for 3 h. The reaction was quenched with 1% aqueous hydrochloric acid, and the organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 6:1) to give **8** (3.13 g, 96%) as a white solid: mp 42-43°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.53 (3H, s), 3.84 (3H, s), 3.87 (3H, s), 5.17 (2H, s), 6.81 (1H, d, J=9.1 Hz), 6.88 (1H, d J=9.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.4, 56.5, 60.5, 95.9, 109.9, 116.6, 116.6, 147.6, 148.6, 149.0; IR (KBr) 798, 918, 999, 1036, 1144, 1163, 1175, 1256, 1298, 1403, 1439, 1487, 1593, 2905, 2948, 2971 cm^{-1}; *Anal* calcd for $C_{10}H_{13}BrO_4$: C, 43.34; H, 4.73; Br, 28.83 found C, 43.15; H, 4.62; Br, 28.79.

2. The starting material **7** has been previously prepared from the known (–)-Wieland-Miescher ketone analogue **10**, as shown in the following Scheme, in our preliminary communication (see Kawano, H.; Itoh, M.; Katoh, T.; Terashima, S. *Tetarahedron Lett.* **1997**, *38*, 7769-7772). Experimental procedures and characterization data for all new compound depicted in this Scheme are as follows.



(a) $(CH_2OH)_2$, *p*-TsOH, benzene, reflux, 89% (b) H_2 (10 atm), 10% Pd-C, piperidine, rt, 88% (β–Me : α–Me = 13 : 1) (c) i) KCN, AcOH, EtOH, 15°C ii) $SOCl_2$, pyridine, 30°C, 77% ($\Delta^{1,2}$: $\Delta^{2,3}$ = 20 : 1) (2 steps) (d) i) DIBAL, toluene, -78°C, 96% ii) separation (e) $NaBH_4$, THF-H_2O, 0°C, 99% (f) 4M HCl, MeOH, rt, 100% (g) $CH_3C(OEt)_3$, hydroquinone, 1,2-dichlorobenzene, 120°C→170°C, 86% (β–Me : α–Me=3 : 4) (h) $(CH_2OH)_2$, *p*-TsOH, benzene, reflux, 96% (i) H_2 (1 atm), $[Ir(cod)(Pcy_3)(py)]^+PF_6^-$, CH_2Cl_2, rt, 92% (j) $LiAlH_4$, THF, 0°C, 100% (k) *o*-nitrophenyl selenocyanate, *n*-Bu_3P, THF, rt ; 30% H_2O_2, rt, 95% (l) O_3, CH_2Cl_2-MeOH, -78°C ; PPh_3, rt, 92%

Preparation of ketal VI.

Ethylene glycol (29.3 ml, 0.53 mol) and *p*-toluenesulfonic acid monohydrate (99.8 mg, 0.50 mmol) were added to a solution of (–)-Wieland-Miescher ketone analogue **10** (10.1 g, 53 mmol) in benzene (200 ml) at room temperature. The mixture was placed in a Dean-Stark apparatus and then heated at reflux for 2 h. After cooling, the reaction was quenched with saturated aqueous sodium hydrogen carbonate (50 ml), and the mixture was extracted with ethyl acetate (3 x 100 ml). The combined extracts were washed with brine then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 4:1) to give **VI** (11.0 g, 89%) as a colorless oil: $[\alpha]_D^{20}$ -109 (*c* 0.53, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (3H, s), 1.58-1.72 (3H, m), 1.79 (3H, d, J=1.4 Hz), 1.79-1.84 (1H, m), 1.90 (1H, dt, J=4.7, 13.5 Hz), 2.11-2.19 (1H, m), 2.24 (1H, dt, J=5.3, 13.5 Hz), 2.40 (1H, dt, J=5.1, 16.6 Hz), 2.46 (1H, ddt, J=3.8, 5.3, 16.6 Hz), 2.74 (1H, dq, J=2.0, 15.4 Hz), 3.91-4.01 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.3, 20.7, 21.3, 26.3, 26.4, 29.6, 33.6, 45.2, 64.9, 65.2, 112.6, 130.0, 160.0, 198.5; IR (neat) 496, 671, 760, 920, 951, 1024, 1059, 1094, 1125, 1163, 1181, 1281, 1310, 1337, 1360, 1456, 1611, 1667, 2881, 2953, 3526 cm^{-1}; HREIMS m/z calcd for $C_{14}H_{20}O_3$ (M^+), 236.1412, found 236.1424.

Preparation of ketone VII.

10% Pd-C (50% wet, 50.0 g) was added to a solution of **VI** (25.3 g, 0.11 mol) in piperidine (500ml) at room temperature. The mixture was stirred 6 h under hydrogen (10 atm). The reaction mixture was diluted with ethyl acetate (300ml), and the catalyst was filtered off through a small pad of Celite. Concentration of the filtrate *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1) to give **VII** (22.5 g, 88%) as a mixture of two diastereomers (13:1) as a white solid. Recrystallization from hexane afforded a white solid, mp 84-85°C; $[\alpha]_D^{20}$ –72.0 (*c* 1.08, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (1H, dq, J=3.9, 13.5 Hz), 0.96 (3H, d, J=6.7 Hz), 1.27 (3H, s), 1.41-1.50 (1H, m), 1.54-1.71 (4H, m), 1.80 (1H, ddt, J=1.8, 7.3, 13.7 Hz), 1.98 (1H, ddt, J=1.9, 4.6, 13.3 Hz), 2.15 (1H, dt, J=5.4, 13.6 Hz), 2.28 (1H, ddd, J=1.8, 5.4, 14.7 Hz), 2.45 (1H, ddt, J=1.8, 5.4, 14.7 Hz), 2.86 (1H, q, J=6.0 Hz), 3.98 (4H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 16.9, 22.1, 22.3, 29.3, 29.4, 37.7, 42.6, 43.6, 49.3, 64.8, 65.0, 112.3, 213.3; IR (KBr) 471, 505, 538, 571, 700, 739, 766, 839, 876, 897, 947, 1022, 1088, 1115, 1154, 1186, 1229, 1285, 1350, 1379, 1456, 1707, 2884, 2944, 3397 cm^{-1}; *Anal* calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30, found C, 70.27; H, 9.49.

Preparation of nitrile VIII.

Acetic acid (36.0 ml, 0.63 mol) was added dropwise to a stirred solution of **VII** (5.00 g, 21 mmol) and potassium cyanide (41.0 g, 0.63 mol) in ethanol (250 ml) at 15°C. After 1.5 h, the reaction was quenched with water (60 ml), and the mixture was extracted with ethyl acetate (3 x 300 ml). The combined extracts were washed with water and brine, then dried over Na_2SO_4. The solvent was concentrated *in vacuo* to afford a crude product (5.53 g). This operation was repeated three times, and the combined crude products were used for the next dehydration reaction without further purification.

The combined crude products (16.6 g) in dichloromethane (225 ml) were added dropwise to a stirred solution of thionyl chloride (23.0 ml, 0.31 mol) and pyridine (61.0 ml, 0.76 mol) in dichloromethane (450 ml) at 30°C. After 1.5 h, the reaction was quenched with water (450 ml), and the mixture was extracted with dichloromethane (2 x 150 ml). The combined extracts were washed with brine and then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue which was purified by column chromatography (hexane-ethyl acetate, 16:1) to give a mixture of two possible regioisomers ($\Delta^{1,2}$:$\Delta^{2,3}$=20:1) **VIII** (12.0 g, 77%, 2 steps) as a colorless viscous oil. Recrystallization from hexane afforded a single isomer ($\Delta^{1,2}$) as colorless prisms, mp 85-87°C: $[\alpha]_D^{20}$ –81.5 (*c* 0.96, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (3H, s), 1.09-1.18 (1H, m), 1.51-1.69 (5H, m), 1.76-1.84 (2H, m), 1.99-2.03 (1H, m), 2.01 (3H, t, J=2.1 Hz), 2.21-2.29 (2H, m), 3.92-4.00 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9, 22.2, 22.2, 22.4, 24.5, 28.2, 29.6, 40.4, 46.7, 64.8, 64.8, 104.2, 111.5, 119.0, 156.2; IR (KBr) 471, 486, 525, 588, 611, 652, 702, 745, 820, 874, 907, 947, 966, 1032, 1092, 1111, 1144, 1167, 1190, 1224, 1275, 1331, 1348, 1374, 1385, 1443, 1636, 2207, 2872, 2955 cm^{-1}; *Anal* calcd for $C_{15}H_{21}NO_2$: C, 72.84; N, 5.66; H, 8.56, found C, 72.59; N, 5.61; H, 8.80.

Preparation of aldehyde IX.

Diisobutylaluminum hydride in toluene (1.01 M solution, 54.4 ml, 55 mmol) was added dropwise to a stirred solution of **VIII** (6.80 g, 27 mmol) in dry toluene (500 ml) at -78°C under argon. After 2 h, the reaction was quenched with 10% aqueous sodium hydroxide (30 ml), and the mixture was extracted with diethyl ether (3 x 100 ml). The combined extracts were washed with brine then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1→8:1) to give **IX** (6.68 g, 96%) as a white solid. Recrystallization from hexane furnished white prisms, mp 89-91°C: $[\alpha]_D^{20}$ –100.6 (*c* 1.02, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.83 (3H, s), 1.17-1.26 (1H, m), 1.56-1.72 (5H, m), 1.77-1.83 (1H, m), 1.84-1.90 (1H, m), 2.01 (1H, dd, J=4.1, 12.3 Hz), 2.07-2.15 (1H, m), 2.18 (3H, t, J=1.9 Hz), 2.35-2.41 (1H, m), 3.93-4.00 (4H, m), 10.14 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.2, 17.9, 19.6, 22.6, 22.6, 28.2, 29.7, 40.4, 49.5,

64.8, 64.8, 112.0, 131.1, 158.4, 191.3; IR (KBr) 428, 478, 598, 646, 737, 874, 905, 920, 949, 1019, 1036, 1059, 1096, 1136, 1163, 1196, 1244, 1281, 1358, 1377, 1443, 1632, 1667, 2888, 2942, 2986, 3300 cm^{-1}; *Anal* calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86, found C, 71.67; H, 9.10.

Preparation of alcohol X.

Sodium borohydride (2.10 g, 54 mmol) in water (24 ml) was added dropwise to a stirred solution of **IX** (6.80 g, 27 mmol) in dry tetrahydrofuran (240 ml) at 0°C. After 30 min, the reaction was quenched with saturated ammonium chloride (20 ml), and the mixture was extracted with ethyl acetate (3 x 150 ml). The combined extracts were washed with brine then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 6:1 →4:1) to give **X** (6.50 g, 99%) as a colorless oil: $[\alpha]_D^{20}$ –41.8 (*c* 1.13, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (3H, s), 1.08-1.18 (2H, m), 1.50-1.69 (5H, m), 1.72 (3H, t, J=2.0 Hz), 1.76-1.87 (3H, m), 2.10-2.22 (2H, m), 3.93-4.01 (4H, m), 4.04 (1H, d, J=11.5 Hz), 4.14 (1H, d, J=11.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.1, 18.3, 22.7, 23.9, 25.1, 28.7, 30.1, 40.9, 47.4, 63.1, 64.9, 64.9, 112.8, 127.3, 134.1; IR (neat) 474, 621, 756, 820, 872, 905, 951, 1005, 1096, 1113, 1167, 1188, 1223, 1279, 1348, 1373, 1445, 2878, 2940, 3399 cm^{-1}; HRCIMS m/z calcd for $C_{15}H_{24}O_3$ (M^+), 252.1725, found 252.1706.

Preparation of ketone XI.

4 M Hydrochloric acid (40.0 ml, 0.16 mol) was added to a stirred solution of **X** (4.00 g, 16 mmol) in methanol (80 ml) at room temperature. After 1 h, the mixture was diluted with ethyl acetate (100 ml) and then extracted with ethyl acetate (6 x 50 ml). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 4:1 →2:1) to give **XI** (3.30 g, 100%) as a colorless oil: $[\alpha]_D^{20}$ –129.0 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.07 (3H, s), 1.24-1.32 (2H, m), 1.58-1.69 (2H, m), 1.76 (3H, t, J=1.8 Hz), 1.90-1.96 (2H, m), 2.01-2.08 (2H, m), 2.10-2.17 (1H, m), 2.21-2.27 (1H, m), 2.31-2.36 (1H, m), 2.46-2.52 (1H, m), 4.10 (1H, d, J=11.7 Hz), 4.15 (1H, d, J=11.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.8, 20.3, 24.3, 24.4, 27.6, 28.0, 38.3, 47.8, 50.0, 63.0, 129.0, 132.1, 216.2; IR (neat) 683, 837, 1001, 1103, 1260, 1318, 1377, 1451, 1701, 2865, 2936, 3430 cm^{-1}; HREIMS m/z calcd for $C_{13}H_{20}O_2$ (M^+), 208.1463, found 206.1311.

Preparation of ester XII.

Triethyl orthoacetate (35.2 ml, 0.19 mol) and hydroquinone (0.53 g, 4.8 mmol) were added successively to a stirred solution of **XI** (2.00 g, 9.6 mmol) in dry *o*-dichlorobenzene (35 ml) at room temperature. The mixture was heated at 120°C for 4 h, 140°C for 3 h, and then 170°C for 23 h. After cooling, the reaction was quenched with water (50 ml), and the mixture was extracted with ethyl acetate (3 x 100 ml). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 20:1) to give desire β-Me product of **XII** (1.00 g, 37%) (less polar) and undesired α-Me product of **XII** (1.30 g, 49%) (more polar).

β-Me product of **XII :** a pale yellow oil; $[\alpha]_D^{20}$ –15.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (3H, s), 1.24 (3H, t, J=7.1 Hz), 1.24-1.32 (1H, m), 1.36 (3H, s), 1.59-1.72 (1H, m), 1.74-1.88 (1H, m), 1.93-2.06 (2H, m), 2.10-2.20 (1H, m), 2.28-2.42 (4H, m), 1.46-2.53 (1H, m), 2.58 (1H, d, J=15.3 Hz), 2.70 (1H, d, J=15.3 Hz), 4.10 (2H, q, J=7.1 Hz), 4.73 (1H, s), 4.79 (1H, d, J=1.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 22.7, 23.8, 25.8, 26.3, 29.4, 33.0, 36.8, 42.7, 44.9, 49.2, 49.9, 60.0, 108.0, 152.9, 171.7, 216.1; IR (neat) 675, 835, 897, 970, 992, 1034, 1098, 1159, 1184, 1252, 1319, 1343, 1372, 1458, 1640, 1703, 1734, 2940, 3086, 3385 cm^{-1}; HREIMS m/z calcd for $C_{17}H_{26}O_3$ (M^+), 278.1882, found 278.1901.

α-Me product of **XII :** colorless prisms (recrystallization from hexane); mp 64-65°C; $[\alpha]_D^{20}$ +14.2 (*c* 1.04, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (1H, ddd, J=4.6, 11.6, 13.1 Hz), 1.18 (3H, t, J=7.1 Hz), 1.31 (3H, s), 1.36 (3H, s), 1.84-1.91 (2H, m), 1.94-2.00 (2H, m), 2.10-2.16 (1H, m), 2.18 (1H, ddd, J=4.9, 4.9, 13.7 Hz), 2.32 (1H, ddd, J=5.3, 5.3, 15.3 Hz), 2.35 (1H, d, J=12.5 Hz), 2.37 (1H, ddd, J=4.8, 4.8, 13.2 Hz), 2.44 (1H, d, J=12.5 Hz), 2.45-2.51 (1H, m), 2.65 (1H, ddd, J=9.4, 9.4, 15.4 Hz), 3.96-4.06 (2H, m), 4.64 (1H, d, J=1.2 Hz), 4.75 (1H, d, J=0.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 21.3, 23.9, 25.4, 28.7, 30.1, 35.3, 36.3, 42.4, 43.4, 48.7, 55.7, 60.0, 107.9, 153.2, 171.3, 215.9; IR (KBr) 679, 839, 899, 1028, 1096, 1175, 1200, 1325, 1366, 1462, 1698, 1732, 2965, 2992, 3102, 3374, 3441 cm^{-1}; *Anal* calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41, found C, 73.09; H, 9.58.

Preparation of ketal XIII.

Ethylene glycol (1.60 ml, 29 mmol) and *p*-toluenesulfonic acid monohydrate (5.40 mg, 28 μmol) were added to a solution of the β-Me product of **XII** (793 mg, 2.9 mmol) in benzene (15 ml) at room temperature. The mixture was placed in a Dean-Stark apparatus and then heated at reflux for 4 h. After cooling, the reaction was quenched with saturated aqueous sodium hydrogen carbonate (7 ml), and the mixture was extracted with ethyl acetate (3 x 40 ml). The combined extracts were washed with

saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1) to give **XIII** (884 mg, 96%) as a colorless oil: $[\alpha]_D^{20}$ –15.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (1H, dd, J=3.5, 13.1 Hz), 1.19 (3H, s), 1.20 (3H, s), 1.23 (3H, t, J=7.1 Hz), 1.43-1.67 (6H, m), 1.81 (1H, dt, J=4.8, 13.3 Hz), 1.91 (1H, dd, J=4.1, 12.7 Hz), 2.21 (1H, ddd, J=2.8, 4.8, 14.4 Hz), 2.47-2.55 (1H, m), 2.68 (1H, d, J=14.4 Hz), 2.72 (1H, d, J=14.4 Hz), 3.92-3.97 (4H, m), 4.09 (2H, dq, J=2.0, 7.1 Hz), 4.65 (1H, s), 4.85 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 20.9, 22.3, 24.0, 25.8, 29.0, 29.6, 29.7, 42.8, 43.7, 46.3, 48.4, 59.8, 64.6, 64.8, 109.3, 113.6, 152.0, 172.1; IR (neat) 895, 949, 1024, 1088, 1123, 1169, 1256, 1283, 1302, 1343, 1371, 1642, 1638, 1734, 2872, 2951, 3086 cm^{-1}; HREIMS m/z calcd for $C_{19}H_{30}O_4$ (M^+), 322.2129, found 322.2144.

Preparation of hydrogenation product XIV.

$[Ir(cod)Pcy_3(py)]^+PF_6^-$ (22.0 mg, 27 μmol) was added to a stirred solution of **XIII** (884 mg, 2.7 mmol) in dry dichloromethane (20 ml) at room temperature. The mixture was frozen using liquid nitrogen and then evacuated *in vacuo* followed by filled with dry argon. The mixture was brought to room temperature. The mixture was frozen using liquid nitrogen and then evacuated *in vacuo* followed by filled with dry hydrogen. The mixture was stirred at –20°C for 48 h. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 15:1 →10:1) to give **XIV** (789 mg, 77%) as a colorless caramel: $[\alpha]_D^{20}$ +10.0 (*c* 0.98, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, d, J=6.2 Hz), 0.92-1.04 (1H, m), 1.03 (3H, s), 1.13 (3H, s), 1.18-1.30 (1H, m), 1.24 (3H, t, J=7.1 Hz), 1.48-1.84 (9H, m), 1.99 (1H, dt, J=14.2, 3.4 Hz), 2.32 (1H, d, J=13.7 Hz), 2.41 (1H, d, J=13.7 Hz), 3.85-3.97 (4H, m), 4.07 (1H, dq, J=10.8, 7.1 Hz), 4.13 (1H, dq, J=10.8, 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 16.9, 17.7, 21.6, 22.1, 28.8, 30.4, 30.8, 33.4, 37.8, 40.9, 42.1, 44.4, 47.6, 59.7, 64.2, 64.6, 113.6, 172.5; IR (neat) 856, 922, 951, 1007, 1036, 1051, 1094, 1113, 1136, 1194, 1283, 1304, 1368, 1445, 1464, 1728, 2874, 2957 cm^{-1}; HREIMS m/z calcd for $C_{19}H_{32}O_4$ (M^+), 324.2283, found 324.2301.

Preparation of alcohol XV.

A solution of **XIV** (1.70 g, 5.2 mmol) in dry tetrahydrofuran (10 ml) was added to a stirred suspension of lithium aluminum hydride (398 mg, 0.48 mmol) in dry tetrahydrofuran (50 ml) at 0°C. The mixture was gradually warmed up to room temperature over 2 h. The reaction was quenched with 10% aqueous sodium hydroxide (20 ml), and the mixture was extracted with ethyl acetate (3 x 40 ml). The combined extracts were washed with brine, and then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography

(hexane-ethyl acetate, 4:1) to give **XV** (1.49 g, 100%) as a white solid, mp 70-72°C: $[\alpha]_D^{20}$ +7.4 (*c* 1.00,$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, d, J=6.8 Hz), 0.92-1.08 (2H, m), 0.98 (3H, s), 1.13 (3H, s), 1.18-1.27 (1H, m), 1.28-1.40 (1H, m), 1.47-1.81 (10H, m), 1.91 (1H, dt, J=4.0, 14.2 Hz), 3.56-3.71 (2H, m), 3.84-3.98 (4H,m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.8, 18.5, 21.7, 22.2, 28.6, 30.1, 30.7, 33.1, 37.7, 39.8, 41.0, 42.4, 47.4, 59.3, 64.2, 64.6, 113.6; IR (neat) 920, 1032, 1096, 1179, 1341, 1383, 1466, 2881, 2957, 3360 cm^{-1}; HREIMS m/z calcd for $C_{17}H_{30}O_3$ (M^+), 282.2196, found 282.2195.

Preparation of olefin XVI.

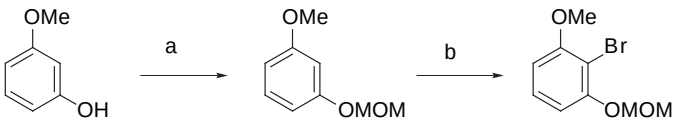
o-Nitrophenyl selenocyanate (3.30 g, 15 mol) and tri-*n*-butylphosphine (3.60 ml, 15 mmol) were added successively to a stirred solution of **XV** (1.36 g, 4.8 mmol) in dry tetrahydrofuran (100 ml) at room temperature. After 1 h, 31% aqueous hydrogen peroxide (9.60 ml, 97 mmol) was added slowly to the above mixture at 0°C. After stirring at room temperature for 2 h, the mixture was diluted with ethyl acetate (50 ml). The reaction was quenched with 3% aqueous hydrochloric acid (30 ml), and the mixture was extracted with ethyl acetate (2 x 50 ml). The combined extracts were washed with brine, and then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 20:1) to give **XVI** (1.21 g, 95%) as a colorless oil: $[\alpha]_D^{20}$ –9.09 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.74 (3H, d, J=6.8 Hz), 1.01 (1H, dt, J=13.9, 4.6 Hz), 1.08 (3H, s), 1.14 (3H, s), 1.18-1.32 (2H, m), 1.40 (1H, dd, J=2.7, 6.4 Hz), 1.43-1.80 (7H, m), 2.04 (1H, dt, J=14.2, 3.6 Hz), 3.86-4.00 (4H, m), 4.98 (1H, dd, J=1.4, 17.4 Hz), 5.02 (1H, dd, J=1.4, 10.7 Hz), 5.44 (1H, dd, J=10.7, 17.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 17.0, 21.6, 22.1, 28.3, 30.6, 30.9, 33.7, 40.1, 40.1, 45.2, 50.5, 64.2, 64.6, 112.0, 113.6, 152.0; IR (neat) 910, 952, 1005, 1026, 1051, 1096, 1138, 1177, 1213, 1248, 1283, 1306, 1343, 1375, 1453, 1634, 1707, 2874, 2936 cm^{-1}; HREIMS m/z calcd for $C_{17}H_{28}O_2$ (M^+), 264.2073, found 264.2089.

Preparation of aldehyde 7.

An ozone stream was bubbled through a solution of **XVI** (737 mg, 2.8 mmol) in a mixture of dry dichloromethane (45 ml) and dry methanol (15 ml) at –78°C until the solution was changed to blue color. The mixture was then purged with argon, and triphenylphosphine (2.20 g, 8.4 mmol) was added at –78°C. After warming to room temperature over 30 min, the reaction mixture was diluted with ethyl acetate (30 ml). The organic layer was washed with 5% aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 50:1 →15:1) to give **7** (679 mg, 92%) as a white solid: mp 57-58°C; $[\alpha]_D^{20}$ +7.4 (*c* 1.01, $CHCl_3$); ^{1}H NMR (500

MHz, $CDCl_3$) δ 0.92 (3H, d, J=7.3 Hz), 0.98 (3H, s), 0.99 (3H, s), 1.12-1.21 (1H, m), 1.30-1.64 (6H, m), 1.64-1.77 (2H, m), 1.83-1.94 (2H, m), 1.95-2.10 (1H, m), 3.86-4.00 (4H, m), 9.31 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.0, 17.5, 22.1, 23.4, 23.4, 26.3, 27.2, 30.1, 31.5, 41.6, 45.7, 52.8, 64.5, 64.7, 112.9, 207.0; IR (neat) 756, 957, 1030, 1051, 1090, 1138, 1179, 1215, 1244, 1283, 1345, 1383, 1454, 1721, 2685, 2872, 2955 cm^{-1}; HREIMS m/z calcd for $C_{16}H_{26}O_3$ (M^+), 266.1882, found 266.1862.

3. The starting material **9** was prepared from commercially available 3-methoxyphenol as shown in the following Scheme. Experimental procedures and characterization data for compounds depicted in this Scheme are as follows.



3-methoxyphenol **XVII** **9**

(a) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 91% (b) *tert*-BuLi, TMEDA, Br_2, ether, 73%

Preparation of 1-bromo-2-methoxy-6-(methoxymethoxy)benzene (9).

Chloromethyl methyl ether (18.4 ml, 0.24 mol) was added dropwise to a stirred solution of 3-methoxyphenol (20.0 g, 0.16 mol) and *N*,*N*-diisopropylethylamine (56.1 ml, 0.32 mol) in dry dichloromethane (200 ml) at 0°C under argon. The solution was stirred at room temperature for 3 h. The reaction was quenched with 1% aqueous hydrochloric acid, and the organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 15:1) to give **XVII** (24.7 g, 91%) as a colorless oil.

tert-BuLi in *n*-pentane (1.51 M solution, 129 ml, 0.20 mol) was added dropwise to a stirred solution of **XVII** (24.7 g, 0.15 mol) and *N*,*N*,*N*',*N*'-tetramethylethylenediamine (28.3 ml, 0.22 mol) in dry diethyl ether (360 ml) at -78°C under argon. After 1h, bromine (10.1 ml, 0.20 mol) was added slowly. The mixture was gradually warmed up to 0°C over 3 h. The reaction was quenched with 20% aqueous sodium thiosulfate (80 ml) and extracted with ethyl acetate (3 x 400 ml). The combined extracts were washed successively with 1% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 30:1) to give **9** (26.6 g, 73%) as a colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 3.52 (3H, s), 3.90 (3H, s), 5.25 (2H, s), 6.61 (1H, dd, J=1.0, 8.3 Hz), 6.80 (1H, dd J=1.0,

8.3 Hz), 7.20 (1H, dd J=8.3, 8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.4, 56.4, 95.1, 102.4, 105.6, 108.5, 128.2, 155.0, 157.2; IR (neat) 798, 918, 999, 1036, 1144, 1163, 1175, 1256, 1298, 1403, 1439, 1487, 1593, 2905, 2948, 2971 cm^{-1}; HREIMS m/z calcd for $C_9H_{11}BrO_3$ (M^+), 247.9872, found 247.9879.