First Total Synthesis of Antimitotic Compound, (+)-Phomopsidin

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General Information. ¹H and ¹³C NMR spectra were recorded on a JEOL AL-400 spectrometer. ¹H and ¹³C chemical shifts are reported in ppm downfield from tetramethylsilane (TMS, δ scale) with the solvent resonances as internal standards. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; b, broad. IR spectra were recorded on a JASCO FT/IR-8300. Melting points (mp) are uncorrected, recorded on a Yamato capillary melting point apparatus. Optical rotations were measured using a 2 ml cell with a 1 dm path length on a JASCO DIP-1000. Mass spectra and elemental analyses were provided at the Materials Characterization Central Laboratory, Waseda University. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and phosphomolybdic acid and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on self-made 0.3 mm E. Merck silica gel plates (60F-254).

Materials. THF was distilled from sodium/benzophenone ketyl, and methylene chloride (CH₂Cl₂), benzene, and toluene from calcium hydride. Toluene was distilled from sodium. DMF was distilled from CaH₂ under reduced pressure.

(-)-(5S)-5-Methyl-tetrahydro-pyran-2-one (6).

R_f=0.49 (hexane/ethyl acetate=2/1); ¹H NMR (400 MHz, CDCl₃) δ 4.24 (1H, ddd, J =11.0, 4.4, 2.0 Hz), 3.84 (1H, dd, J =11.0, 11.0 Hz), 2.57 (1H, ddd, J =17.7, 6.8, 4.2 Hz), 2.44 (1H, ddd, J =17.7, 10.0, 7.3 Hz), 2.08-1.86 (2H, m), 1.47 (1H, ddd, J =13.3, 10.0, 6.8 Hz), 0.94 (3H, d, J =6.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 171.0, 74.9, 29.1, 27.9, 27.5, 16.6; IR (neat) $\nu_{\max}$ 3452, 2968, 1734, 1508, 1464, 1398, 1346, 1254, 1214, 1182, 1096, 1050, 908, 888 cm⁻¹; FAB-MS [M+H]⁺ calculated for C₆H₁₁O₂: 115.0759, found: 115.0735; [α]_D¹⁹ -17.6 (c 0.3, CHCl₃).

(-)-(6*S*)-7-(1-Ethoxy-ethoxy)-6-methyl-1-trimethylsilanyl-hept-1-yn-3-one (8).

R_f =0.54 (hexane/ethyl acetate=4/1); ^1H NMR (400 MHz, CDCl_3) δ 4.65-4.60 (2/2H, m), 3.64-3.56 (2/2H, m), 3.47-3.34 (4/2H, m), 3.25-3.17 (2/2H, m), 2.64-2.49 (2H, m), 1.83-1.64 (2H, m), 1.53-1.44 (1H, m), 1.26 (3H, d, J =5.4 Hz), 1.16 (3H, t, J =7.1Hz), 0.89 (3H, d, J = 6.6Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 188.4, 100.3, 100.2, 70.8, 70.7, 61.4, 43.7, 33.7, 28.4, 20.5, 17.7, 16.1, 0.0; IR (neat) ν_{max} 2968, 1680, 1382, 1254, 1136, 1086, 1062, 848 cm^{-1} ; FAB-MS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{15}\text{H}_{29}\text{O}_3\text{Si}$: 285.1886, found : 285.1923; $[\alpha]_D^{29}$ -2.5 (c 0.5, CHCl_3).

(-)-(3*S*,6*S*)-7-(1-Ethoxy-ethoxy)-6-methyl-3-triisopropylsilanyloxy-hept-1-yne (10).

R_f =0.66 (hexane/ethyl acetate=4/1); ^1H NMR (400 MHz, CDCl_3) δ 4.67 (1H, q, J =5.4 Hz), 4.46 (1H, dt, J =6.0, 2.0 Hz), 3.70-3.62 (2/2H, m), 3.51-3.43 (3/2H, m), 3.36 (1/2H, dd, J =9.0, 6.6Hz), 3.29 (1/2H, dd, J =9.3, 5.9 Hz), 3.20 (1/2H, dd, J =9.0, 6.6 Hz), 2.37 (1H, d, J =2.2 Hz), 1.81-1.58 (5H, m), 1.30 (3H, d, J =5.4 Hz), 1.20 (3H, t, J =7.1 Hz), 1.12-1.05 (21H, m), 0.94 (3H, d, J =6.8 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 99.6, 85.6, 72.0, 70.5, 63.1, 60.7, 36.3, 33.4, 28.8, 19.9, 19.8, 18.1, 17.3, 15.4, 12.3; IR (neat) ν_{max} 2948, 2872, 1464, 1382, 1340, 1136, 1098, 1062, 882 cm^{-1} ; FAB-MS $[\text{M}-\text{H}]^+$ calculated for $\text{C}_{21}\text{H}_{41}\text{O}_3\text{Si}$: 369.2825, found : 369.2780; $[\alpha]_D^{20}$ -5.2 (c 0.9, CHCl_3).

(+)-(2*Z*,4*E*)-(6*S*,9*S*)-10-(1-Ethoxy-ethoxy)-3,9-dimethyl-6-triisopropylsilanyloxy-deca-2,4-dien-1-ol (11).

R_f =0.30 (hexane/ethyl acetate=4/1); ^1H NMR (400 MHz, CDCl_3) δ 6.51 (1H, d, J =15.6 Hz), 5.74 (1H, dd, J =15.6, 6.4 Hz), 5.54 (1H, t, J =6.9 Hz), 4.66 (1H, q, J =5.4 Hz), 4.34-4.23 (3H, m), 3.69-3.60 (2/2H, m), 3.51-3.39 (3/2H, m), 3.33 (1/2H, dd, J =9.3, 6.8 Hz), 3.27 (1/2H, dd, J =9.3, 5.7 Hz), 3.17 (1/2H, dd, J =9.3, 6.8 Hz), 1.85 (3H, s), 1.73-1.39 (5H, m), 1.29 (3H, d, J =5.4 Hz), 1.19 (3H, t, J =7.1 Hz), 1.07-1.03 (21H, m), 0.91 (3H, d, J =6.6 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 135.3, 134.8, 127.7, 125.2, 99.6, 99.6, 73.9, 70.6, 60.7, 60.7, 58.5, 36.1, 33.7, 33.7, 28.7, 28.7, 20.6, 19.9, 19.8, 18.3, 18.2, 18.1, 17.3, 15.4, 15.3, 12.5; IR (neat) ν_{max} 3448, 2944, 2872, 1464, 1382, 1342, 1136, 1086, 1060, 1014, 966, 884 cm^{-1} ; FAB-MS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{25}\text{H}_{50}\text{O}_4\text{Si}$: 442.3478, found : 442.3447; $[\alpha]_D^{19}$ +2.7 (c 0.9, CHCl_3).

(-)-(3E,9E,11Z)-(5S,8S)-5,11-Dimethyl-8-triisopropylsilyloxy-oxacyclotrideca-3,9,11-trien-2-one (4).

$R_f=0.34$ (hexane/ethyl acetate=10/1); ^1H NMR (400 MHz, CDCl_3) δ 7.06 (1H, dd, $J=15.9, 7.1$ Hz), 6.29 (1H, d, $J=16.1$ Hz), 5.70-5.58 (3H, m), 5.04 (1H, ddd, $J=13.9, 4.6, 1.5$ Hz), 4.47 (1H, dd, $J=13.9, 6.1$), 4.24 (1H, dd, $J=10.3, 4.6$), 1.86 (3H, s), 1.84-1.40 (5H, m), 1.70-0.94 (24H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 167.2, 157.3, 137.9, 133.5, 129.7, 122.7, 119.8, 71.3, 60.5, 35.5, 33.0, 31.6, 20.4, 18.1, 17.3, 12.3; IR (neat) ν_{max} 2944, 2868, 1724, 1460, 1368, 1244, 1162, 1084, 1062, 994, 882 cm^{-1} ; FAB-MS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{23}\text{H}_{41}\text{O}_3\text{Si}$: 393.2825, found : 393.2845; $[\alpha]_D^{19}$ -6.4 (c 0.08, CHCl_3).

4,9-Dimethyl-6-triisopropylsilyloxy-3a,5a,6,7,8,9,9a,9b-octahydro-3H-naphtho-[1,2-c]furan-1-one (3).

$R_f=0.33$ (hexane/ethyl acetate=4/1); ^1H NMR (400 MHz, CDCl_3) δ 5.81 (major-1H, s), 5.50 (minor-1H, s), 4.40-4.16 (major-2H, minor-2H, m), 3.97-3.89 (minor-1H, m), 3.79 (major-1H, ddd, $J=11.7, 9.5, 4.4$ Hz), 3.10-2.95 (major-1H, minor-1H, m), 2.88-2.77 (major-1H, m), 2.75-2.66 (minor-2H, m), 2.58-2.43 (major-1H, m), 2.24-1.89 (minor-3H, m), 1.83-1.54 (major-6H, minor-4H, m), 1.50-1.20 (major-3H, minor-2H, m), 1.09-1.00 (major-21H, minor-21H, m), 0.93-0.85 (major-3H, minor-3H, m) ^{13}C NMR (100 MHz, CDCl_3) δ 180.0, 178.8, 132.1, 130.3, 128.0, 125.2, 72.3, 71.9, 70.3, 70.3, 42.3, 41.8, 40.2, 39.9, 39.7, 38.8, 38.4, 33.5, 33.2, 32.3, 31.5, 28.8, 26.8, 26.6, 21.2, 21.1, 19.3, 18.2, 18.1, 17.1, 12.4.

(+)-4-Bromo-benzoic acid (3aS,5aS,6S,9S,9aR,9bS)-4,9-dimethyl-1-oxo-1,3,3a,5a,6,7,8,9,9a,9b-decahydro-naphtho[1,2-c]furan-6-yl ester (12).

$R_f=0.49$ (hexane/ethyl acetate=2/1); mp=78-80°C; ^1H NMR (400 MHz, CDCl_3) δ 7.88 (2H, d, $J=8.5$ Hz), 7.58 (2H, d, $J=8.5$ Hz), 5.77 (1H, s), 5.08 (1H, ddd, $J=11.8, 4.6, 4.6$ Hz), 4.36-4.30 (2H, m), 3.05 (1H, dd, $J=7.8, 2.9$ Hz), 2.87 (1H, s), 2.76 (1H, s), 1.99-1.87 (2H, m), 1.81-1.74 (4H, m), 1.60-1.39 (2H, m), 1.30-1.18 (1H, m), 0.98 (3H, d, $J=6.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 178.3, 164.7, 132.2, 131.6, 131.0, 129.5, 127.9, 124.0, 74.9, 70.2, 41.5, 39.5, 38.3, 35.8, 32.6, 28.8, 27.3, 21.2, 19.2; IR (KBr) ν_{max} 2932, 1768, 1714, 1592, 1486, 1398, 1378, 1270, 1214, 1174, 1150, 1102, 1070, 1034, 1012, 982, 848, 758 cm^{-1} ; FAB-MS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{21}\text{H}_{24}\text{BrO}_4$: 419.0858, found :

419.0842; $[\alpha]_D^{22} +40.7$ (c 0.1, CHCl₃).

(+)-(1*S*,4*S*,4*aS*,5*S*,6*R*,8*aS*)-5-(*tert*-Butyl-diphenyl-silanyloxymethyl)-6-ethynyl-4,7-dimethyl-1-triisopropyl-silanyloxy-1,2,3,4,4*a*,5,6,8*a*-octahydro-naphthalene (2).

$R_f=0.41$ (hexane/ethyl acetate=40/1); ^1H NMR (400 MHz, CDCl₃) δ 7.68-7.64 (4H, m), 7.43-7.34 (6H, m), 5.70 (1H, s), 4.13 (1H, dd, $J=10.5, 5.4$ Hz), 3.87 (1H, ddd, $J=11.2, 4.6, 4.6$ Hz), 3.70 (1H, dd, $J=10.5, 10.5$ Hz), 3.16-3.10 (1H, m), 2.77-2.70 (1H, m), 2.40-2.32 (1H, m), 1.90 (1H, d, $J=2.7$ Hz), 1.86-1.81 (1H, m), 1.69-1.52 (3H, m), 1.41-1.21 (2H, m), 1.10-1.01 (30H, m), 0.88 (3H, d, $J=6.6$ Hz); ^{13}C NMR (100 MHz, CDCl₃) δ 135.4, 134.1, 130.1, 129.4, 127.5, 122.5, 83.4, 73.3, 71.3, 62.1, 39.8, 38.5, 37.7, 31.8, 31.5, 28.4, 26.9, 22.4, 22.2, 19.5, 19.1, 18.3, 12.5; IR (neat) ν_{max} 3312, 3076, 2936, 2868, 1464, 1428, 1382, 1246, 1218, 1112, 1092, 1046, 1014, 1000, 882, 816, 762, 740, 702 cm⁻¹; FAB-MS $[\text{M}-\text{H}]^+$ calculated for C₄₀H₅₉O₂Si₂ : 627.4054, found : 627.4084; $[\alpha]_D^{22} +84.0$ (c 0.1, CHCl₃).

(-)-Benzoic acid (1*S*,4*S*,4*aS*,5*S*,6*R*,8*aS*)-5-hydroxymethyl-4,7-dimethyl-6-((*E*)-1-methyl-propenyl)-1,2,3,4,4*a*,5,6,8*a*-octahydro-naphthalen-1-yl ester (20).

$R_f=0.24$ (hexane/ethyl acetate=4/1); mp=47-48°C; ^1H NMR (400 MHz, CDCl₃) δ 8.09-8.05 (2H, m), 7.60-7.42 (3H, m), 5.69 (1H, s), 5.25 (1H, q, $J=5.1$ Hz), 5.03 (1H, ddd, $J=11.7, 4.6, 4.6$ Hz), 3.62 (1H, dd, $J=11.0, 6.6$ Hz), 3.42 (1H, dd, $J=11.0, 7.1$ Hz), 2.79-2.70 (2H, m), 2.30-2.23 (1H, m), 1.87-1.81 (1H, m), 1.77-1.59 (12H, m), 1.52-1.41 (1H, m), 1.23-1.11 (1H, m), 0.95 (3H, d, $J=6.6$ Hz); ^{13}C NMR (100 MHz, CDCl₃) δ 165.8, 135.6, 135.4, 132.7, 130.7, 129.5, 128.2, 122.6, 122.2, 75.7, 63.6, 48.2, 47.9, 39.0, 35.0, 32.8, 28.2, 27.4, 22.1, 19.0, 17.0, 13.7; IR (KBr) ν_{max} 3488, 2932, 1722, 1452, 1380, 1276, 1176, 1116, 1070, 1026, 982, 712 cm⁻¹; FAB-MS $[\text{M}+\text{H}]^+$ calculated for C₂₄H₃₃O₃ : 369.2430, found : 369.2422; $[\alpha]_D^{22} -37.9$ (c 0.1, CHCl₃).

(+)-phomopsidin (synthetic)

$R_f=0.20$ (hexane/ethyl acetate=1/1); mp=66°C; ^1H NMR (600 MHz, CD_3OD) δ 7.18 (1H, dd, $J=15.4, 10.8$ Hz), 6.29-6.24 (1H, m), 6.15 (1H, d, $J=15.1, 10.8$ Hz), 5.77 (1H, d, $J=15.4$ Hz), 5.73 (1H, s), 5.22 (1H, q, $J=6.7$ Hz), 3.57 (1H, ddd, $J=11.3, 4.6, 4.6$ Hz), 2.80-2.73 (2H, m), 2.67-2.62 (1H, m), 1.66-1.62 (2H, m), 1.60 (3H, s), 1.55 (3H, d, $J=6.7$ Hz), 1.48 (3H, s), 1.45-1.23 (3H, m), 1.04-0.96 (1H, m), 0.94 (3H, d, $J=6.7$ Hz); ^{13}C NMR (120 MHz, CDCl_3) δ 170.8, 148.8, 146.9, 136.4, 136.0, 129.0, 124.3, 123.5, 120.5, 73.3, 51.3, 45.3, 39.1, 34.1, 31.1, 29.9, 22.3, 19.4, 16.8, 13.5; $[\alpha]_D^{19} +22.6$ (c 0.1, CH_3OH).