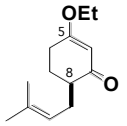
Supporting Information

Total Synthesis of (±)-Garsubellin A

Akiyoshi Kuramochi, Hiroyuki Usuda, Kenzo Yamatsugu, Motomu Kanai,* and Masakatsu Shibasaki*

General: Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-LA500, ECX500 or ECA500 spectrometer, operating at 500 MHz for ^{1}H NMR and 125.65 MHz for ^{13}C NMR. Chemical shifts were reported in ppm on the δ scale relative to residual $CHCl_3$ (δ = 7.24 for ^{1}H NMR and δ = 77.0 for ^{13}C NMR) or C_6H_6 (δ = 7.15 for ^{1}H NMR and δ = 128.0 for ^{13}C NMR) as an internal reference, respectively. ESI mass spectra were measured on Waters-ZQ4000. FAB mass spectra were measured on a JEOL JMS-BU20 GCmate or a JEOL JMS-700V. Optical rotations were measured on a JASCO P-1010 polarimeter. Column chromatography was performed with silica gel Merck 60 (230-400 mesh ASTM). The enantiomeric excess was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the flowing: pump, 880-PU or PU-980; detector, 875-UV or UV-970, measured at 254 nm; Reaction were carried out in dry solvents under an argon atmosphere, unless otherwise stated. Dry solvents of diethyl ether (Et_2O), tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were purchased from Kanto Chemical. Co., Inc. TMSCl, Et_3N, 2,6-lutidine, *N*, *N*-diisopropylethyl amine, HMPA, DMF, TMEDA, pyridine and chlorobenzene were distilled from CaH_2 or $CaSO_4$. Other reagents were used as received from commercial sources, unless otherwise stated. Numbers in compound nomenclatures are garsubellin numbering.

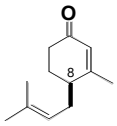
5-Ethoxy-8-(14-methyl-13-butenyl)-6-cyclohexen-9-one (20):



To a solution of LDA (328 mmol) in THF (760 ml) was added 3-ethoxy-2-cyclohexen-1-one (**8**: 41.6 ml, 285 mmol, purchased from Lancaster) in THF (170 ml) from a dropping funnel at -78 °C for 20 min, and the mixture was stirred for 45 min at the same temperature and additionally for 45 min at -20 °C. After cooling to -78 °C, tetrabutylammonium iodide (52.8 g, 142 mmol) was added in one portion, then prenyl bromide (36.4 ml, 314 mmol) was added from a dropping funnel for 15 min. The mixture was stirred for 2 hours at the same temperature and additionally for 2 hours at -40 °C. The reaction was quenched with saturated NH_4Cl solution (100 ml). The organic layer was separated, and the aqueous layer was extracted twice with Et_2O (1.2 L). The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated to give crude **20** (65.7 g) as a pale yellow oil, which was used for the next reaction without further purification. A small amount of crude **20** was purified by thin layer chromatography. ; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.25 (s, 1H), 5.04 (t, *J* = 6.7 Hz, 1H), 3.82 (dq, *J* = 4.0, 7.0 Hz, 2H), 2.45 (m, 1H), 2.34 (m, 2H), 2.12 (m, 1H), 2.03 (dd, *J* = 8.6, 14.4 Hz, 1H), 1.97 (dq, *J* = 4.6, 13.1 Hz, 1H), 1.62 (s, 3H), 1.61 (m, 1H), 1.54 (s, 3H), 1.29 (t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.0, 176.8, 133.2, 121.9, 102.2, 64.0, 45.5, 28.1, 28.0, 25.8, 25.7, 17.7, 14.0.; IR (neat, cm^{-1}) 2932, 1655, 1608; ESI-MS *m/z* 231 $[M+Na]^+$; FAB-HRMS Calcd for $C_{13}H_{21}O_2$ $[M+H]^+$: 209.1536, Found:

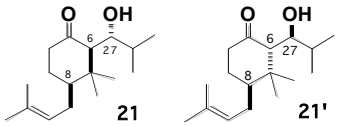
209.1538.

9-Methyl-8-(14-methyl-13-butenyl)-6-cyclohexen-9-one (7):



To a solution of crude **20** (65.7 g; 285 mmol) in THF (380 ml) was added MeLi-LiBr (252 ml, 378 mmol; 1.5 M in Et_2O) from a dropping funnel for 1 hour at -78 °C, and the mixture was stirred for 1 hour at the same temperature. The mixture was gradually warmed up to 4 °C, then aqueous HCl solution (316 ml, 633 mmol; 2.0 M) was added from a dropping funnel for 1 hour. After stirring for 6 hours at the same temperature, aqueous NaOH solution (70 ml, 3.0 M) was added. The organic layer was separated, and the aqueous layer was extracted twice with Et_2O (750 ml). The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated to give crude **7** as a pale yellow oil, which was used for the next reaction without further purification. A small amount of crude **7** (53 mg) was purified by silica gel column chromatography (SiO_2 5 g, EtOAc/hexane = 1/8) to give pure **7** (49 mg, 0.275 mmol; 100% yield in 3 steps) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) 5.62 (s, 1H), 4.92 (m, 1H), 2.21 (ddd, *J* = 4.9, 10.7, 17.1 Hz, 1H), 2.08 (m, 2H), 2.04 (dd, *J* = 5.2, 6.4 Hz, 1H), 1.97 (m, 1H), 1.82 (m, 1H), 1.78 (s, 3H), 1.67 (m, 1H), 1.52 (s, 3H), 1.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 198.6, 165.0, 133.3, 126.4, 121.5, 39.5, 33.6, 29.3, 26.1, 25.3, 22.5, 17.4; IR (neat, cm^{-1}) 2918, 1672, 1626.; ESI-MS *m/z* 201 $[M + Na]^+$; FAB-HRMS Calcd for $C_{12}H_{18}OCs$ $[M+Cs]^+$: 311.0406, Found: 311.0406.

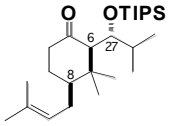
(6*R,8*R**,27*R**)-6-(27-Hydroxy-28-methylpropyl)-9,9-dimethyl-8-(14-methyl-13-butenyl)-cyclohexan-5-one (21):**



To a solution of crude **7** (39.5 g, 200 mmol) and CuI (8.4 g, 44.0 mmol) in THF (1.39 L) and Me_2S (139 ml) was added MeMgBr (473 ml, 440 mmol; 0.93 M in THF) from a dropping funnel for 1 hour at 4 °C. The mixture was stirred for 1 hour at the same temperature. To the mixture was added freshly distilled isobutyraldehyde (72.7 ml, 800 mmol) from a dropping funnel for 2 min at 4 °C. After stirring for 25 min at the same temperature, the reaction was quenched with saturated NH_4Cl solution (200 ml). The organic layer was separated, and the aqueous layer was extracted twice with Et_2O (1.5 L). The combined organic layer was washed with saturated NH_4Cl solution, saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated to give a brown oil, which was purified by silica gel column chromatography (SiO_2 730 g, CH_2Cl_2/hexane = 1/1 to 2/1) to give **21** (32.4 g, 122 mmol; 61% yield) and **21'** (8.0 g, 30.4 mmol; 16% yield) as a white crystal. The relative configuration between C6 and C8 was assigned based on NOESY observation. The relative configuration between C6 and C27 was assigned based on the analogy to the model substrate.[1] ^{1}H NMR (C_6D_6, 500 MHz) 5.04 (m, 1H), 4.38 (d, *J* = 11.3 Hz, 1H), 3.48 (dd, *J* = 8.2, 10.7 Hz, 1H), 2.08 (m, 2H), 2.07 (s, 1H), 1.84 (m, 2H), 1.72 (m, 1H), 1.69 (s, 3H), 1.51 (m, 1H), 1.48 (s, 3H), 1.19 (m, 2H), 1.09 (d, *J* = 6.7 Hz, 3H), 1.00 (s, 3H), 0.94 (s, 3H), 0.76 (d, *J* = 6.7

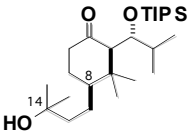
Hz, 1H); ^{13}C NMR (C_6D_6, 125 MHz) δ 216.3, 132.1, 124.3, 75.8, 59.8, 48.4, 44.0, 43.3, 35.0, 29.2, 28.7, 26.7, 25.9, 20.4, 20.0, 17.8, 17.1; IR (neat, cm^{-1}) 3501, 2962, 1695; ESI-MS *m/z* 289 $[M + Na]^+$; FAB-HRMS Calcd for $C_{17}H_{31}O_2$ $[M+H]^+$: 267.2319, Found: 267.2316.

(6*R,8*R**,27*R**)-9,9-Dimethyl-8-(14-methyl-13-butenyl)-6-{(28-methyl-27-triisopropylsilanyloxy)-propyl)-cyclohexan-5-one (9):**



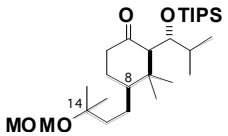
To a solution of **21** (19.0 g, 71.9 mmol) and 2,6-lutidine (16.7 ml, 144 mmol) in CH_2Cl_2 (600 ml) was added TIPSOTf (29.0 ml, 108 mmol) from a dropping funnel for 30 min at -40 °C. The mixture was stirred for 2.5 hours at the same temperature. The reaction was quenched with H_2O (20 ml). The organic layer was separated, and the aqueous layer was extracted twice with Et_2O (600 ml). The combined organic layer was washed with H_2O, saturated $CuSO_4$ solution, and brine, and dried over Na_2SO_4. Evaporation of the solvent gave **9** (39.1 g) as a pale yellow oil, which was used for the next reaction without further purification. A small amount of crude **9** (38.3 mg) was purified by thin layer column chromatography to give pure **9** (29.8 mg, 70.5 μmol; 92% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.08 (m, 1H), 4.21 (dd, *J* = 1.9, 4.0 Hz, 1H), 2.38 (ddd, *J* = 4.0, 6.7, 13.8 Hz, 1H), 2.32 (s, 1H), 2.22 (m, 1H), 2.01 (m, 1H), 1.95 (m, 1H), 1.70 (m, 1H), 1.68 (s, 3H), 1.57 (s, 3H), 1.45 (m, 2H), 1.13 (s, 3H), 1.05 (m, 21H), 0.94 (s, 3H), 0.92 (d, *J* = 6.7 Hz, 1H), 0.88 (d, *J* = 6.7 Hz, 1H);^{13}C NMR ($CDCl_3$, 125 MHz) δ 211.5, 132.4, 123.6, 76.2, 62.7, 48.4, 41.8, 41.7, 33.8, 28.1, 27.9, 27.5, 25.8, 20.1, 19.9, 18.5, 18.4, 18.0, 17.8, 13.5; IR (neat, cm^{-1}) 2964, 1711, 1629.; ESI-MS *m/z* 445 $[M + Na]^+$; FAB-HRMS Calcd for $C_{26}H_{51}O_2Si$ $[M+H]^+$: 423.3653, Found: 423.3662.

(6*R,8*S**,27*R**)-8-{(14-Hydroxy-14-methyl)butyl}-9,9-dimethyl-6-{(28-methyl-27-triisopropylsilanyl-oxy)propyl}cyclohexan-5-one (22):**



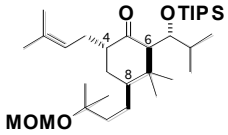
To a solution of crude **9** (5.70 g, 10.5 mmol) in THF (67 ml) were added freshly distilled $PhSiH_3$ (3.33 ml, 27.0 mmol) and $Co(acac)_2$ (694 mg, 2.7 mmol) at room temperature. The atmosphere in the flask was replaced by O_2 in a balloon and the mixture was vigorously stirred at 25 °C, which was kept with a water bath. After 6 hours, THF was evaporated to give a green oil, which was purified by silica gel column chromatography (SiO_2 110 g, EtOAc/hexane = 1/4) to give **22** (3.38 g, 7.67 mmol; 73% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.20 (dd, *J* = 1.9, 4.0 Hz, 1H), 2.42 (ddd, *J* = 4.0, 7.1, 13.8 Hz, 1H), 2.30 (s, 1H), 2.23 (m, 1H), 2.00 (m, 2H), 1.69 (ddt, *J* = 2.5, 4.0, 12.5 Hz, 1H), 1.57 (dt, *J* = 4.6, 13.1 Hz, 1H), 1.50 (m, 1H), 1.30 (m, 3H), 1.20 (s, 3H), 1.19 (s, 3H), 1.10 (s, 3H), 1.05 (m, 21H), 0.94 (s, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H);^{13}C NMR ($CDCl_3$, 125 MHz) δ 211.4, 76.2, 71.0, 62.6, 47.9, 42.7, 41.8, 41.6, 33.9, 29.5, 29.1, 27.9, 27.7, 24.1, 20.1, 19.8, 18.5, 18.4, 17.9, 13.5; IR (neat, cm^{-1}) 2963, 2867, 1709, 1630; ESI-MS *m/z* 463 $[M + Na]^+$; FAB-HRMS Calcd for $C_{26}H_{53}O_3Si$ $[M+H]^+$: 441.3758, Found: 441.3763.

(6*R,8*S**,27*R**)-8-{(14-Methoxymethoxy-14-methyl)butyl}-9,9-dimethyl-6-{(28-methyl-27-triisopropylsilanyloxy)propyl}cyclohexan-5-one (23):**



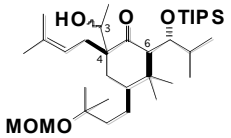
To a solution of **22** (3.25 g, 7.69 mmol) and *N*, *N*-diisopropylethylamine (4.02 ml, 23.1 mmol) in CH_2Cl_2 (38 ml) were added MOMCl (1.17 ml, 15.4 mmol) and tetrabutylammonium iodide (1.42 g, 3.84 mol) at 4 °C. The mixture was stirred for 24 hours at room temperature, and the reaction was quenched with H_2O (10 ml). The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2 (40 ml). The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated to give a pale yellow oil, which was purified by silica gel column chromatography (neutral silica gel 100 g, EtOAc/hexane = 1/15) to give **23** (3.58 g, 7.38 mmol; 96% yield) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) 4.66 (s, 2H), 4.20 (d, *J* = 4.3 Hz, 1H), 3.33 (s, 3H), 2.41 (ddd, *J* = 4.0, 6.7, 13.4 Hz, 1H), 2.30 (s, 1H), 2.24 (m, 1H), 2.00 (m, 2H), 1.68 (m, 1H), 1.58 (dt, *J* = 4.3, 13.4 Hz, 1H), 1.49 (m, 1H), 1.34 (dt, *J* = 3.7, 12.5 Hz, 1H), 1.28 (m, 1H), 1.19 (s, 3H), 1.18 (s, 3H), 1.10 (s, 3H), 1.05 (m, 22H), 0.93 (s, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H);^{13}C NMR ($CDCl_3$, 125 MHz) 211.4, 91.0, 76.2, 76.2, 62.7, 55.1, 48.0, 41.9, 41.6, 40.7, 33.9, 27.8, 27.7, 26.5, 26.2, 23.7, 20.1, 19.8, 18.5, 18.4, 17.9, 13.5; IR (neat, cm^{-1}) 3438, 2944, 1711, 1637.; ESI-MS *m/z* 507 $[M + Na]^+$; FAB-HRMS Calcd for $C_{28}H_{57}O_4Si$ $[M+H]^+$: 485.4021, Found: 485.4027.

(4*S,6*R**,8*S**,27*R**)-8-{(14-Methoxymethoxy-14-methyl)butyl}-9,9-dimethyl-4-(19-methyl-18-butenyl)-6-{(28-methyl-27-triisopropylsilanyloxy)propyl}cyclohexan-5-one (6):**



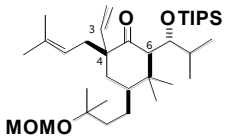
To a solution of azeotropically dried **23** (2.23 g, 4.60 mmol) in THF (46 ml) and HMPA (4.0 ml) was added KHMDS (46.0 ml, 23.0 mmol; 0.5 M in toluene) at -78 °C. The mixture was stirred for 1 hour at the same temperature. To the mixture was added prenyl bromide (3.73 ml, 32.2 mmol) and tetrabutylammonium iodide (850 mg, 2.30 mmol) at -78 °C, and the mixture was stirred for 1 hour. The reaction was quenched with saturated NH_4Cl solution (10 ml). The organic layer was separated, and the aqueous layer was extracted twice with Et_2O (80 ml). The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated to give a pale yellow oil, which was purified by silica gel column chromatography (SiO_2 120 g, EtOAc/hexane = 1/40 to 1/20) to give **6** (2.49 g, 4.51 mmol; 98% yield) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) 5.03 (m, 1H), 4.66 (s, 2H), 4.11 (d, *J* = 2.8 Hz, 1H), 3.32 (s, 3H), 2.73 (m, 1H), 2.25 (m, 1H), 2.09 (s, 1H), 1.96 (m, 1H), 1.69 (m, 2H), 1.64 (s, 3H), 1.56 (s, 3H), 1.53 (m, 2H), 1.26 (dt, *J* = 3.7, 15.9 Hz, 1H), 1.18 (s, 3H), 1.17 (s, 3H), 1.11 (s, 3H), 1.03 (m, 23H), 0.99 (d, *J* = 6.8, 3H), 0.90 (s, 3H), 0.84 (d, *J* = 6.8 Hz, 3H);^{13}C NMR ($CDCl_3$, 125 MHz) 214.2, 132.4, 122.0, 91.0, 76.4, 76.2, 60.3, 55.1, 46.9, 43.9, 40.0, 39.6, 35.5, 33.3, 29.5, 29.3, 26.5, 26.2, 25.8, 24.0, 20.5, 18.5, 18.4, 18.1, 17.8, 17.8, 13.6; IR (neat, cm^{-1}) 2965, 2868, 1637; ESI-MS *m/z* 575 $[M + Na]^+$; FAB-HRMS Calcd for $C_{33}H_{65}O_4Si$ $[M+H]^+$: 553.4647, Found: 553.4648.

(3*R/*S**,4*R**,6*R**,8*S**,27*R**)-4-(3-Hydroxyethyl)-8-{(14-methoxymethoxy-14-methyl)butyl}-9,9-dimethyl-4-(19-methyl-18-butenyl)-6-{(28-methyl-27-triisopropylsilanyloxy)propyl}cyclohexan-5-one (24):**



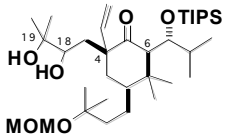
To a solution of LDA (2.80 mmol) and TMEDA (1.69 ml, 11.2 mmol) in THF (4.0 ml) was added **6** (500 mg, 0.904 mmol) in THF (6.0 ml) at -78 °C. The mixture was stirred for 1 hour at the same temperature, and additionally for 1 hour at -20 °C. After the mixture was cooled to -78 °C, freshly distilled acetaldehyde (1.02 ml, 18.1 mmol) added drop by drop. After stirring for 30 min, the reaction was quenched with saturated NH_4Cl solution (5 ml). The organic layer was separated, and the aqueous layer was extracted twice with EtOAc (30 ml). The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated to give a pale yellow oil, which was purified by silica gel column chromatography (SiO_2 15 g, EtOAc/hexane = 1/6) to give a 1:1 diastereomeric mixture **24** (509 mg, 0.850 mmol; 94% yield) as a colorless oil, which was used for the next reaction without further purification.

(4*R,6*R**,8*S**,27*R**)-8-{(14-Methoxymethoxy-14-methyl)butyl}-9,9-dimethyl-4-(19-methyl-18-butenyl)-6-{(28-methyl-27-triisopropylsilanyloxy)propyl}-4-vinylcyclohexan-5-one (10):**



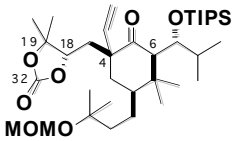
To a solution of diastereomeric mixture of **24** (466 mg, 0.781 mmol) in benzene (3.9 ml) was added Martin sulfurane (578 mg, 0.859 mmol), which was freshly prepared[2] and used without recrystallization, in benzene (3.9 ml) at room temperature. The mixture was stirred for 1 hour at the same temperature. The reaction was quenched with saturated $NaHCO_3$ solution (5 ml). The organic layer was separated, and the aqueous layer was extracted twice with EtOAc (30 ml). The combined organic layer was washed with saturated NH_4Cl solution and brine, dried over Na_2SO_4, and concentrated to give a pale yellow oil, which was purified by silica gel column chromatography (SiO_2 100 g; EtOAc/hexane = 1/50) to give **10** (442 mg, 0.765 mmol; 98% yield) as a colorless oil. ^{1}H NMR (C_6D_6, 500 MHz) 5.76 (dd, *J* = 10.7, 17.4 Hz, 1H), 5.32 (m, 1H), 5.17 (d, *J* = 17.4 Hz, 1H), 5.09 (d, *J* = 10.7 Hz, 1H), 4.60 (s, 1H), 4.45 (dd, *J* = 1,9, 4.6 Hz, 1H), 3.21 (s, 3H), 2.82 (d, *J* = 1.8 Hz, 1H), 2.55 (dd, *J* = 6.8, 14.6 Hz, 1H), 2.42 (dd, *J* = 7.9, 14.6 Hz, 1H), 2.22 (m, 1H), 2.09 (dd, *J* = 3.4, 14.1 Hz, 1H), 1.79 (m, 1H), 1.65 (m, 3H), 1.63 (s, 3H), 1.54 (s, 3H), 1.42 (dt, *J* = 4.6, 11.9 Hz, 1H), 1.31 (s, 3H), 1.26 (m, 1H), 1.15 (m, 25H), 1.12 (d, *J* = 4.6 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.94 (s, 3H);^{13}C NMR (C_6D_6, 125 MHz) 210.5, 142.7, 133.6, 121.0, 115.8, 91.1, 77.4, 76.2, 62.3, 55.9, 54.9, 46.5, 43.4, 41.5, 37.3, 36.9, 33.2, 27.0, 26.6, 26.2, 26.1, 23.9, 22.0, 20.2, 18.8, 18.3, 18.1, 13.8; IR (neat, cm^{-1}) 2943, 1703; ESI-MS *m/z* 601 $[M + Na]^+$; FAB-HRMS Calcd for $C_{35}H_{67}O_4Si$ $[M+H]^+$: 579.4803, Found: 579.4802.

(4*S,6*R**,8*S**,18*R**/*S**,27*R**)-4-{(18,19-Dihydroxy-19-methyl)butyl}-8-{(14-methoxymethoxy-14-methyl)butyl}-9,9-dimethyl-6-{(28-methyl-27-triisopropylsilanyloxy)propyl}-4-vinylcyclohexan-5-one (11):**



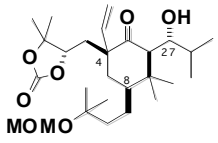
To a solution of **10** (379 mg, 0.656 mmol) in water (20 ml) and *tert*-butyl alcohol (20 ml) were added AD-mix-β (0.92 g, 0.4 mol % $K_2Os(OH)_4$ to **10**) and $CH_3SO_2NH_2$ (311 mg, 3.28 mmol) at room temperature. The mixture was stirred for 12 hours at the same temperature. The reaction was quenched with saturated $NaHSO_3$ solution (5 ml), and the mixture was stirred for 1 hour. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc (30 ml). The combined organic layer was washed with saturated $NaHCO_3$ solution, saturated NH_4Cl solution and brine, and dried over Na_2SO_4, and concentrated to give a while amorphous **11** (580 mg), which was used for the next reaction without further purification.

(4*S,6*R**,8*S**,18*S**,27*R**)-18-([8-{(14-Methoxymethoxy-14-methyl)butyl}-9,9-dimethyl-6-{(28-methyl-27-triisopropylsilanyloxy)propyl}-5-oxo-4-vinylcyclohexyl]methyl)-19,19-dimethyl-[31,33]-dioxolan-32-one (25):**



To a solution of crude diastereomeric mixture of **11** (580 mg, 0.656 mmol) and pyridine (0.42 ml, 5.25 mmol) in CH_2Cl_2 (6.6 ml) was added triphosgene (0.656 ml, 0.656 mmol; 1.0 M solution in CH_2Cl_2) at -78 °C. The mixture was stirred for 1 hour at the same temperature. The reaction was quenched with saturated NH_4Cl solution (5 ml). The organic layer was separated, and the aqueous layer was extracted twice with EtOAc (30 ml). The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated to give a colorless oil. The residue was purified by silica gel column chromatography (SiO_2 10 g, CH_2Cl_2/EtOAc/$^iPr_2O$ = 100/1/1) to give diastereomeric pure **25** (129 mg, 0.394 mmol; 30% in 2 steps) as a colorless oil. ^1H NMR (C_6D_6, 500 MHz) δ 5.69 (dd, *J* = 10.7, 17.4 Hz, 1H), 5.04 (m, 2H), 4.67 (d, *J* = 7.6 Hz, 1H), 4.66 (d, *J* = 7.6 Hz, 1H), 4.34 (dd, *J* = 1.3, 4.3 Hz, 1H), 4.17 (d, *J* = 8.2 Hz, 1H), 3.31 (s, 3H), 2.65 (s, 3H), 2.14 (m, 1H), 2.06 (dd, *J* = 3.7, 14.4 Hz, 1H), 1.99 (d, *J* = 15.0 Hz, 1H), 1.92 (t, *J* = 12.6 Hz, 1H), 1.82 (m, 1H), 1.67 (m, 1H), 1.44 (m, 1H), 1.37 (dd, *J* = 5.2, 9.2 Hz, 1H), 1.21 (s, 3H), 1.19 (s, 3H), 1.18 (s, 3H), 1.16 (m, 22H), 1.13 (s, 3H), 1.07 (d, *J* = 7.1 Hz, 1H), 0.95 (d, *J* = 6.7 Hz, 1H), 0.91 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (C_6D_6, 125 MHz) δ 209.8, 153.6, 142.9, 116.2, 91.3, 84.0, 82.6, 76.8, 75.9, 60.3, 55.1, 54.7, 45.8, 43.8, 41.6, 37.4, 36.6, 34.0, 27.0, 26.8, 26.2, 24.7, 23.9, 20.8, 20.6, 20.4, 18.7, 18.7, 18.4, 13.8; IR (neat, cm^{-1}) 2964, 1801, 1701, 1633; ESI-MS *m/z* 661 $[M + Na]^+$; FAB-HRMS Calcd for $C_{36}H_{67}O_7Si$ $[M+H]^+$: 639.4651, Found: 639.4650.

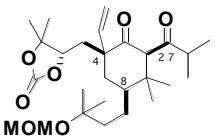
(4*S,6*R**,8*S**,18*S**,27*R**)-18-([6-{(27-Hydroxy-28-methyl)propyl}-8-{(14-methoxymethoxy-14-methyl)butyl}-9,9-dimethyl-5-oxo-4-vinylcyclohexyl]methyl)-19,19-dimethyl-[31,33]dioxolan-32-one (26):**



To a solution of **25** (257 mg, 0.394 mmol) and pyridine (3.58 ml) in THF (29 ml) was added HF-Pyridine complex

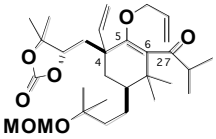
(7.16 ml, purchased from Aldrich) at 4 °C. The mixture was stirred for 48 hours at room temperature. The reaction was cooled to 4 °C, and quenched with aqueous 5 N NaOH solution drop by drop until the mixture was neutral. The organic layer was separated, and the aqueous layer was extracted twice with EtOAc (50 ml). The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated to give **26** (230 mg) as a colorless oil, which was used for the next reaction without further purification.

(4*S,6*R**,8*S**,18*S**)-18-([6-Isobutyryl-8-{(14-methoxymethoxy-14-methyl)butyl}-9,9-dimethyl-5-oxo-4-vinylcyclohexyl]methyl)-19,19-dimethyl-[31,33]dioxolan-32-one (12):**



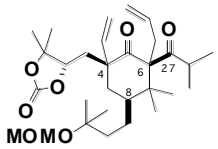
To a solution of crude **26** (230 mg, 0.394 mmol) in 1,2-dichloroethane (3.9 ml) were added PDC (2.97 g, 7.88 mmol) and celite (1.48 g) at room temperature. The mixture was stirred for 6 hours at 45 °C. The reaction was cooled to room temperature, filtered through a pad of florisil and celite, and washed three times with EtOAc (15 ml). The filtrate was concentrated to give the residue, which was purified with flash column chromatography (SiO_2 10 g, EtOAc/hexane = 1/3) to give **12** (134 mg, 0.276 mmol; 70% yield in 2 steps) as a colorless oil. ^{1}H NMR (C_6D_6, 500 MHz) □ 5.67 (dd, *J* = 10.3, 17.8 Hz, 1H), 5.01 (d, *J* = 10.3 Hz, 1H), 4.93 (d, *J* = 17.8 Hz, 1H), 4.67 (d, *J* = 7.5 Hz, 1H), 4.65 (d, *J* = 7.5 Hz, 1H), 4.10 (d, *J* = 9.8 Hz, 1H), 3.77 (s, 1H), 3.29 (s, 3H), 2.27 (sep, *J* = 6.9 Hz, 1H), 2.01 (dd, *J* = 3.4, 14.3 Hz, 1H), 1.83 (m, 2H), 1.67 (m, 2H), 1.50-1.25 (m, 4H), 1.18 (s, 3H), 1.18 (s, 3H), 1.15 (s, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.04 (m, 1H), 0.97 (s, 3H), 0.94 (s, 3H), 0.88 (m, 1H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.82 (s, 3H); ^{13}C NMR (C_6D_6, 125 MHz) □ 209.3, 208.9, 153.4, 143.1, 116.9, 91.3, 83.8, 81.9, 75.9, 67.4, 55.2, 54.5, 44.8, 43.6, 43.1, 41.5, 37., 37.1, 31.9, 26.8, 26.4, 26.1, 24.6, 22.9, 20.6, 18.0, 17.4.; IR (neat, cm^{-1}) 2973, 1798, 1726, 1698, 1636.; ESI-MS *m/z* 503 $[M + Na]^+$.; FAB-HRMS Calcd for $C_{27}H_{44}O_7Cs$ $[M+Cs]^+$: 613.2136, Found: 613.2127.

(4*S,8*S**,18*S**)-18-([5-Allyloxy-6-isobutyryl-8-{(14-methoxymethoxy-14-methyl)butyl}-9,9-dimethyl-4-vinylcyclohex-2-enyl]methyl)-19,19-dimethyl-[31,33]dioxolan-32-one (5):**



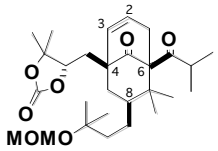
To a solution of **5** (1.06 g, 2.21 mmol), ethylene carbonate (0.33 ml, 4.96 mmol) and MS 4A (1.11 g) in THF (22 ml) and HMPA (5.1 ml) was added NaHMDS (6.63 ml, 6.63 mmol; 1.0 M in THF) at 4 °C. After stirring for 1 hour at the same temperature, allyl iodide (4.04 ml, 44.2 mmol) was added at 4 °C. The mixture was stirred for 2 hours at the same temperature. The reaction was quenched with pH 7 buffer solution to keep the mixture pH 6-8, and the mixture was vigorously stirred for 1 hour at room temperature. The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated to give a colorless oil. The residue was quickly purified to exclude HMPA by short pad silica gel column chromatography (neutral silica gel 10 g, hexane only to EtOAc/hexane = 1/4) to give **5** (944 mg, 1.81 mmol, 82% yield) as a colorless oil, which was used for the next reaction without further purification.

(4*S,6*R**,8*S**,18*S**)-18-([6-Allyl-6-isobutyryl-8-{(14-methoxymethoxy-14-methyl)butyl}-9,9-dimethyl-5-oxo-1-vinylcyclohexyl]methyl)-19,19-dimethyl-[31,33]dioxolan-32-one (4):**



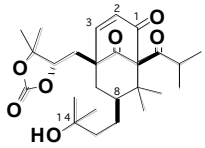
A solution of **5** (31 mg, 59.4 μmol) and sodium acetate (98 mg, 118 μmol) in toluene (1.0 ml) in sealed tube was heated at 200 °C for 4 hours. The reaction was cooled to room temperature, and concentrated to give a colorless oil, which was purified by thin layer chromatography (SiO_2 3 g, EtOAc/hexane = 1/2) to give **4** (30 mg, 57.1 μmol; 96% yield) as a colorless oil. ^{1}H NMR (C_6D_6, 500 MHz) δ 5.45 (dd, *J* = 10.7, 17.4 Hz, 1H), 5.42 (m, 1H), 5.09 (d, *J* = 17.4 Hz, 1H), 4.93 (d, *J* = 10.7 Hz, 1H), 4.91 (m, 2H), 4.66 (d, *J* = 7.3 Hz, 1H), 4.63 (d, *J* = 7.3 Hz, 1H), 4.11 (d, *J* = 8.3 Hz, 1H), 3.28 (s, 3H), 3.15 (dd, *J* = 5.2, 14.0 Hz, 1H), 2.55 (sep, *J* = 6.4 Hz, 1H), 2.15-2.02 (m, 4H), 1.79 (m, 1H), 1.75-1.62 (m, 2H), 1.42 (d, *J* = 6.4 Hz, 3H), 1.40 (m, 1H), 1.30 (dd, *J* = 9.5, 15.3 Hz, 1H), 1.18 (s, 3H), 1.17 (m, 1H), 1.16 (s, 3H), 1.14 (d, *J* = 6.4, 3H), 1.11 (s, 3H), 0.91 (s, 3H), 0.89 (s, 3H), 0.84 (s, 3H);^{13}C NMR (C_6D_6, 125 MHz) δ 213.7, 211.7, 153.5, 140.7, 134.9, 117.4, 115.1, 91.3, 84.0, 83.0, 76.6, 75.9, 55.1, 54.1, 42.2, 41.7, 41.4, 38.8, 38.7, 37.1, 32.2, 26.8, 26.2, 24.4, 23.6, 22.3, 22.2, 21.8, 20.5, 20.3; IR (neat, cm^{-1}) 2979, 2280, 1801, 1692, 1636; ESI-MS *m/z* 543 $[M + Na]^+$; FAB-HRMS Calcd for $C_{30}H_{49}O_7$ $[M+H]^+$: 521.3473, Found: 521.3477.

(4*S,6*R**,8*S**,18*R**)-18-([6-Isobutyryl-8-{(14-methoxymethoxy-14-methyl)butyl}-9,9-dimethyl-5-oxo-bicyclo[3.3.1]non-2-en-4-yl]methyl)-19,19-dimethyl-[31,33]dioxolan-32-one (14):**



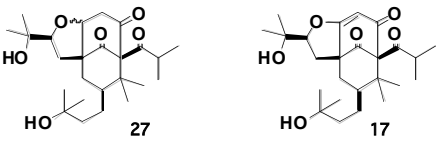
To a solution of **4** (524 mg, 1.01 mmol) in toluene (2 L) was added Hoveyda-Grubbs 2nd generation catalyst **14** (127 mg, 0.202 mmol) at room temperature. The mixture was refluxed for 48 hours. The reaction was cooled to room temperature and concentrated to give the green residue, which was purified by flash column chromatography (SiO_2 20 g, EtOAc/hexane = 1/4) to give **15** (458 mg, 929 μmol; 92% yield) as a colorless oil. ^{1}H NMR (C_6D_6, 500 MHz) δ 5.62 (dt, *J* = 3.4, 9.5 Hz, 1H), 5.40 (d, *J* = 9.5 Hz, 1H), 4.63 (d, *J* = 7.3 Hz, 1H), 4.61 (d, *J* = 7.3 Hz, 1H), 4.21 (d, *J* = 10.1 Hz, 1H), 3.25 (s, 3H), 2.63 (sep, *J* = 6.4 Hz, 1H), 2.59 (m, 2H), 1.82 (dd, *J* = 4.3, 13.4 Hz, 1H), 1.76-1.44 (m, 5H), 1.33 (d, *J* = 6.4 Hz, 3H), 1.19 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H), 1.13 (s, 3H), 1.04 (s, 3H), 1.04 (s, 3H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 3H);^{13}C NMR (C_6D_6, 125 MHz) δ 213.5, 213.3, 153.5, 131.9, 128.5, 91.2, 83.9, 81.7, 75.8, 69.5, 55.1, 48.6, 46.3, 41.5, 41.3, 40.4, 40.0, 34.0, 33.9, 26.7, 26.2, 24.8, 22.9, 22.6, 22.2, 20.7, 20.4, 17.6; IR (neat, cm^{-1}) 2974, 1798, 1715; ESI-MS *m/z* 515 $[M + Na]^+$; FAB-HRMS Calcd for $C_{28}H_{45}O_7$ $[M+H]^+$: 493.3160, Found: 493.3161.

(4*S,6*R**,8*S**,18*S**)-4-{(19,19-Dimethyl-32-oxo-[31,33]dioxolan-18-yl)methyl}-8-{(14-hydroxy-14-methyl)butyl}-6-isobutyryl-9,9-dimethylbicyclo[3.3.1]non-2-ene-1,5-dione (16):**



To a solution of **15** (146 mg, 0.296 mmol), pyridine (2.39 ml, 29.6 mmol), MS 4A (148 mg), and $PhIO_2$[3] (699 mg, 2.96 mmol) in chlorobenzene (0.5 ml) in a sealed tube was added diphenyldiselenide (2.97 ml, 0.593 mmol; 0.2 M in chlorobenzene) at room temperature. The mixture was stirred for 15 min at the same temperature, and for 4 hours at 150 °C. The reaction was cooled to room temperature and quenched with water (5 ml). The organic layer was separated, and the aqueous layer was extracted twice with EtOAc (20 ml). The combined organic layer was washed with saturated $Na_2S_2O_3$ solution, water and brine, dried over Na_2SO_4, and concentrated to give **15** and MOM protected (at C-14 OH) **16** as a yellow oil, which was used for the next reaction without further purification. To a solution of crude MOM protected **16** in MeOH (5.8 ml) was added (+/-)-camphor sulfonic acid (687 mg, 2.96 mmol) at room temperature. The mixture was stirred for 30 min at the same time. The reaction was quenched with saturated $NaHCO_3$ (5 ml). The organic layer was separated, and the aqueous layer was extracted twice with EtOAc (10 ml). The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated to give a pale yellow oil, which was purified with flash column chromatography (SiO_2 5 g, EtOAc/hexane = 1/1) to give **16** (96 mg, 207 mmol, 70% in 2 steps) as a colorless oil. ^1H NMR (C_6D_6, 500 MHz) 6.61 (d, *J* = 9.9 Hz, 1H), 6.30 (d, *J* = 9.9 Hz, 1H), 4.23 (dd, *J* = 2.8, 9.2 Hz, 1H), 2.15 (sep, *J* = 6.4 Hz, 1H), 1.81 (dd, *J* = 3.4, 12.9 Hz, 2H), 1.68-1.55 (m, 3H), 1.49-1.41 (m, 2H), 1.42 (s, 3H), 1.34 (d, *J* = 6.4 Hz, 3H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.15 (s, 3H), 1.12 (m, 1H), 1.09 (s, 3H), 1.08 (s, 3H), 1.05 (s, 3H), 1.02 (m, 1H), 0.93 (s, 3H); ^{13}C NMR (C_6D_6, 125 MHz) 207.9, 207.6, 196.0, 153.5, 150.4, 132.2, 85.3, 84.1, 811, 70.1, 51.1, 48.4, 43.4, 42.4, 41.8, 37.2, 32.5, 29.6, 29.3, 24.8, 22.8, 22.6, 21.6, 20.8, 16.3; IR (neat, cm^{-1}) 3444, 2974, 1793, 1731, 1662; ESI-MS *m/z* 486 $[M + Na]^+$; FAB-HRMS Calcd for $C_{26}H_{38}O_7Cs$ $[M+Cs]^+$: 595.1666, Found: 595.1669.

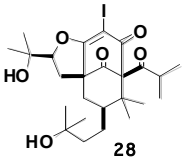
(4*S,6*R**,8*S**,18*S**)-8-(14-Hydroxy-14-methylbutyl)-18-(19-hydroxy-19-methylethyl)-6-isobutyryl-7,7-dimethyl-31-oxatricyclo[6.3.1.0^{4,3}]dodec-3-ene-1,27-dione (17)**



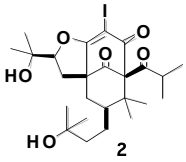
To a solution of **16** (109 mg, 0.236 mmol) in THF (1.65 ml) was added aqueous LiOH solution (1.65 ml, 0.825 mmol, 0.5 M solution) at room temperature. The mixture was stirred for 30 min at the same temperature, and quenched with saturated NH_4Cl solution (3.0 ml). The organic layer was separated, and the aqueous layer was extracted twice with EtOAc (20 ml). The combined organic layer was washed with saturated NH_4Cl solution, saturated $NaHCO_3$ solution, and brine, dried over Na_2SO_4, and concentrated to give crude **27** (diastereomeric mixture) as a colorless oil, which was used for the next reaction without further purification. To a solution of crude **26** and NaOAc[3] (189 mg, 2.31 mmol) in AcOH (2.4 ml), *t*BuOH (2.4 ml)[3] and H_2O (2.4 ml) was added TBHP (0.63 ml, 4.62 mmol; 70% solution in water) and Na_2PdCl_4 (341 mg, 1.16 mmol) at room temperature. The stirred mixture was heated at 75 °C (KEEP BELOW 80 °C) for 3 hours. The mixture was cooled to room temperature, and quenched with saturated $Na_2S_2O_3$ solution (8 ml) and 3 N aqueous NaOH solution (5 ml). The

mixture was extracted twice with EtOAc (20 ml), washed with saturated $NaHCO_3$ solution, saturated NH_4Cl solution, and brine, dried over Na_2SO_4 and concentrated to give a colorless oil, which was purified with flash column chromatography (SiO_2 5 g, EtOAc/hexane = 1/1) to give **17** (72 mg, 0.168 mmol; 71% yield in 2 steps) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) 5.90 (s, 1H), 4.57 (dd, *J* = 5.2, 10.9 Hz, 1H), 2.66 (dd, *J* = 13.7, 16.0 Hz, 1H), 2.08 (m, 1H), 2.06 (sep, *J* = 6.9 Hz, 1H), 1.78 (dd, *J* = 5.7, 13.7 Hz, 2H), 1.62-1.41 (m, 5H), 1.36 (s, 3H), 1.24 (s, 3H), 1.20 (s, 3H) 1.17 (s, 6H), 1.07 (d, *J* = 6.9, 3H), 1.02 (s, 3H), 0.96 (s, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 208.8, 204.4, 193.8, 178.3, 104.5, 91.0, 82.5, 77.3, 70.8, 70.6, 59.7, 47.0, 42.2, 42.0, 38.4, 29.7, 29.4, 29.2, 26.9, 24.3, 22.7, 22.5, 21.5, 20.5, 16.1; IR (neat, cm^{-1}) 2973, 1732, 1625; ESI-MS *m/z* 458 [M + Na]$^+$; FAB-HRMS Calcd for $C_{25}H_{38}O_6Cs$ [M+Cs]$^+$: 567.1717, Found: 567.1721.

(4*S,6*R**,8*S**,18*S**)-18-(19-Hydroxy-19-methylethyl)-2-iodo-6-isobutyryl-7,7-dimethyl-8-(24-methyl-23-butenyl)-31-oxatricyclo[6.3.1.0^{4,3}]dodec-2-ene-1,27-dione (2)**



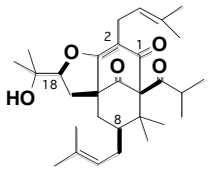
28



2

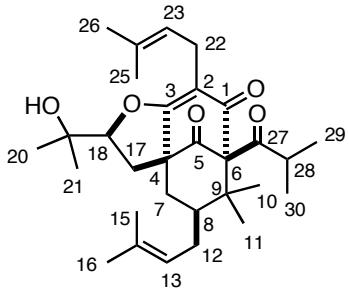
To a solution of **17** (47 mg, 0.113 mmol) in CH_3CN (1.13 ml) were added CAN (923 mg, 1.69 mmol) and I_2 (430 mg, 1.69 mmol) at 4 °C. The mixture was stirred for 15 min at the same temperature and additionally 2 hours at room temperature, and quenched with saturated $Na_2S_2O_3$ solution (5 ml). The organic layer was separated, and the aqueous layer was extracted twice with EtOAc (20 ml). The combined organic layer was washed with saturated NH_4Cl solution, saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated to give crude **28** as a yellow solid, which was used for the next reaction without further purification. To a solution of crude **28** in toluene (2.2 ml) was added *p*TsOH hydrate (215 mg, 1.13 mmol) at room temperature. The mixture was stirred for 6 hours at 50 °C (KEEP BELOW 60 °C). The mixture was cooled to room temperature, and quenched with saturated $NaHCO_3$ solution (5 ml). The mixture was extracted twice with EtOAc (20 ml), washed with saturated $NaHCO_3$ solution, saturated NH_4Cl solution, and brine, dried over Na_2SO_4, and concentrated to give a yellow solid, which was purified with flash column chromatography (neutral silica gel 5 g, EtOAc/hexane = 1/4) to give **2** (49 mg, 90.4 mol; 80% yield in 2 steps) as a white amorphous. ^{1}H NMR (C_6D_6, 500 MHz) 4.75 (m, 1H), 3.94 (dd, *J* = 5.8, 10.6 Hz, 1H), 2.82 (dd, *J* = 10.6, 13.5 Hz, 1H), 2.10 (sep, *J* = 6.9 Hz, 1H) 1.97 (m, 1H), 1.89 (dd, *J* = 4.6, 13.5 Hz, 1H), 1.65 (m, 1H), 1.53 (s, 3H), 1.50 (s, 3H), 1.40 (s, 3H), 1.31 (m, 2H), 1.25 (d, *J* = 6.9 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 1H), 1.18 (s, 3H), 1.12-1.02 (m, 1H), 0.94 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (C_6D_6, 125 MHz) 207.3, 204.0, 188.3, 178.6, 133.3, 128.3, 122.8, 91.3, 82.0, 72.4, 69.9, 61.6, 47.3, 42.9, 39.1, 30.8, 27.0, 26.4, 25.9, 24.6, 23.1, 21.9, 20.8, 17.9, 16.4; IR (neat, cm^{-1}) 3445, 2975, 2927, 1734, 1654, 1605; ESI-MS *m/z* 566 [M + Na]$^+$; FAB-HRMS Calcd for $C_{25}H_{36}O_5I$ [M+H]$^+$: 543.1601, Found: 543.1604.

Garsubellin A (1)



To a solution of **2** (26 mg, 53.5 μmol) in DMF (0.54 ml) were added $PdCl_2$(dppf) (78 mg, 107 μmol) and $^{n}Bu_3$(prenyl)Sn[5] (181 μl, 535 μmol) at room temperature. The mixture was degassed through 3 cycles of freeze-pump-thaw. The mixture was heated for 2 hours at 80 °C (KEEP BELOW 90 °C). The mixture was cooled to room temperature, added TBAF (1.07 ml, 1.07 mmol, 1.0 M in THF), and vigorously stirred for 1 hour at the same temperature. The mixture was filtered through a pad of celite, which was washed three times with Et_2O (30 ml). The filtrate was washed with saturated $NaHCO_3$ solution, saturated NH_4Cl solution and brine, dried over Na_2SO_4, and concentrated to give a dark brown oil, which was purified with flash column chromatography (neutral silica gel 20 g, EtOAc/hexane = 1/7 to 1/4) to give **1** (5.1 mg, 10.7 μmol; 20% yield). FAB-HRMS Calcd for $C_{30}H_{45}O_5$ $[M+H]^+$: 485.3262, Found: 485.3267.

Comparison of ^{1}H NMR and IR between Synthetic and Natural Garsubellin A



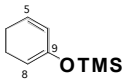
Position	Synthetic Garsubellin A	Natural Garsubellin A
	1H	1H
7	-	1.30 (dd, *J* = 11.3, 13.6 Hz, 1H)
	-	1.32 (dd, *J* = 5.9, 12.9 Hz, 1H)
8	1.74 (m, 1H)	1.74 (dddd, *J* = 3.6, 4.5, 7.1, 11.3 Hz, 1H)
10	1.24 (s, 3H)	1.24 (s, 3H)
11	1.60 (s, 3H)	1.60 (s, 3H)
12	1.58 (m, 1H)	1.58 (m, 1H)
	2.08 (m, 1H)	2.09 (ddd, *J* = 3.6, 7.1, 13.4 Hz, 1H)
13	4.95 (dd, *J* = 7.1, 7.1 Hz, 1H)	4.96 (dd, *J* = 7.1, 7.1 Hz, 1H)
15	1.44 (s, 3H)	1.45 (s, 3H)
16	1.57 (s, 3H)	1.58 (s, 3H)
17	1.92 (dd, *J* = 4.6, 13.7 Hz, 1H)	1.93 (dd, *J* = 4.5, 13.6 Hz, 1H)
	2.72 (dd, *J* = 10.8, 13.1 Hz, 1H)	2.73 (dd, *J* = 10.7, 12.9 Hz, 1H)
18	3.91 (dd, *J* = 6.3, 10.8 Hz, 1H)	3.92 (dd, *J* = 5.9, 10.7 Hz, 1H)
20	0.93 (s, 3H)	0.94 (s, 3H)
21	0.76 (s, 3H)	0.77 (s, 3H)

22	3.20 (dd, *J* = 7.4, 14.3 Hz, 1H)	3.21 (dd, *J* = 7.3, 14.2 Hz, 1H)
	3.38 (dd, *J* = 7.4, 14.3 Hz, 1H)	3.39 (dd, *J* = 7.1, 14.2 Hz, 1H)
23	5.39 (dd, *J* = 7.4, 7.4 Hz, 1H)	5.40 (dd, *J* = 7.1, 7.3 Hz, 1H)
25	1.69 (s, 3H)	1.70 (s, 3H)
26	1.60 (s, 3H)	1.61 (s, 3H)
28	2.25 (dq, *J* = 6.8, 6.8 Hz, 1H)	2.26 (dq, *J* = 6.6, 6.6 Hz, 1H)
29	1.30 (d, *J* = 6.8 Hz, 3H)	1.30 (d, *J* = 6.6 Hz, 3H)
30	1.36 (d, *J* = 6.8 Hz, 3H)	1.37 (d, *J* = 6.6 Hz, 3H)

IR

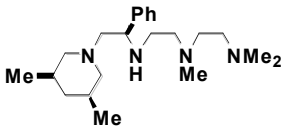
Functional groups	Synthetic Garsubellin A	Natural Garsubellin A
OH	3448	3499
C=O	1731	1730
conjugate C=O	1627	1626

(5,8-Cyclohexadienyloxy)trimethylsilane (29):



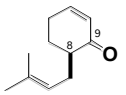
To a solution of LiHMDS (62.0 ml, 62.0 mmol; 1.0 M in THF) in THF (120 ml) was added 2-cyclohexen-1-one (5.0 ml, 51.6 mmol) at 4 °C. After stirring for 30 min at the same temperature, TMSCl (13.1 ml, 103 mmol) was added at 4 °C. The mixture was stirred for 45 min at the same temperature, and the reaction was quenched with Et_3N (1.0 ml) and saturated $NaHCO_3$ solution (30 ml). The organic layer was separated, and the aqueous layer was extracted twice with hexane (150 ml). The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated to give a colorless oil, which was distilled (60 °C / 9 mmHg) to give **29** (8.08 g; 93% yield) as a colorless oil. This product was used for the next reaction immediately.

{2-[(2-Dimethylaminoethyl)methylamino]ethyl}-[2-(3,5-dimethylpiperidin-1-yl)-1-phenylethyl]amine (18):



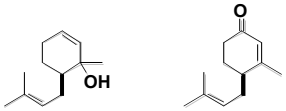
Generous gift from the late Professor Koga and Dr. Manabe in RIKEN Institute. ^{1}H NMR (C_6D_6, 500 MHz) □ 7.55 (d, *J* = 7.2 Hz, 2H), 7.27 (d, *J* = 7.2 Hz, 2H), 7.15 (m, 1H), 3.82 (dd, *J* = 3.4, 10.7 Hz, 1H), 3.00 (m, 2H), 2.65-2.24 (m, 9H), 2.11 (s, 9H), 1.69 (m, 2H), 1.55 (m, 1H), 1.46 (t, *J* = 11.0 Hz, 1H), 1.29 (t, *J* = 11.0 Hz, 1H), 0.84 (d, *J* = 6.7 Hz, 3H), 0.71 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (C_6D_6, 125 MHz) □ 144.5, 128.6, 128.5, 127.9, 127.2, 66.9, 63.7, 61.2, 60.2, 58.3, 58.2, 56.5, 46.0, 42.6, 42.4, 31.6, 31.5, 19.9, 19.6; IR (neat, cm^{-1}) 3304, 2949, 2804; $[\square]^{28}_D$ –45.8 (c = 1.09, CH_2Cl_2); ESI-MS *m/z* 384 $[M + Na]^+$.

8-(14-Methyl-13-butenyl)-6-cyclohexen-9-one (19):



To **29** (3.84 ml, 20.1 mmol) was added MeLi-LiBr (13.2 ml, 20.1 mmol; 1.53 M in Et_2O, purchased from Aldrich) drop by drop, followed by Et_2O (166 ml) at room temperature. The mixture was stirred for 10 min at the same temperature. After cooling to -20 °C, to the mixture was added freshly distilled ligand **18** (362 mg, 1.00 mmol) in Et_2O (22 ml) drop by drop at the same temperature. After stirring for 2 hours at the same temperature, freshly distilled *N*, *N*, *N'*, *N'*-tetramethyl-1,3-propanediamine (6.7 ml, 40.2 mmol) was added drop by drop. After stirring for 20 min, the mixture was cooled to -78 °C, and freshly distilled prenyl bromide (23.3 ml, 201 mmol) was added drop by drop. The mixture was stirred for 1 hour at the same temperature, and 14 hours at -50 °C. The reaction was quenched with citric acid (10 ml). The organic layer was separated, and the aqueous layer was extracted twice with EtOAc (150 ml). The combined organic layer was washed with saturated $CuSO_4$ solution, 2 N aqueous HCl solution, saturated NH_4Cl solution and brine, dried over Na_2SO_4, and concentrated to give a yellow oil. The residue was purified by silica gel column chromatography (SiO_2 220 g, EtOAc/hexane = 1/15) to give **19** (2.15 g, 13.1 mmol; 65% yield) as a pale yellow oil. The enantiomeric excess was determined to be 95% using chiral HPLC analysis. [DAICEL CHIRALPAK AS-H, hexane/2-propanol = 98/2, 0.7 ml/min, t_R 14.0 min (major), 15.9 min (minor).]; ^{1}H NMR ($CDCl_3$, 500 MHz) □ 6.90 (dt, *J* = 10.1, 3.4 Hz, 1H), 5.97 (d, *J* = 10.1 Hz, 1H), 5.09 (t, *J* = 8.0 Hz, 1H), 2.50 (m, 1H), 2.35 (m, 2H), 2.28 (m, 1H), 2.07 (m, 2H), 1.70 (m, 1H), 1.68 (s, 3H), 1.59 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) □201.5, 149.6, 133.5, 130.0, 121.7, 47.0, 27.7, 27.4, 25.8, 25.3, 17.8; IR (neat, cm^{-1}) 2922, 1677; [□]$^{27}_D$ –67.4 (c = 1.10, CH_2Cl_2); ESI-MS *m/z* 187 $[M + Na]^+$; FAB-HRMS Calcd for $C_{22}H_{41}N_4$ $[M+H]^+$: 361.3326, Found: 361.3321.

9-Methyl-8-(14-methyl-13-butenyl)-6-cyclohexen-9-one (7):



30 **7**

To a solution of **19** (1.78 g, 10.8 mmol) in Et_2O (144 ml) was added MeLi-LiBr (11.5 ml, 17.2 mmol; 1.5 M in Et_2O) drop by drop at 4 °C. The mixture was stirred for 1 hour at the same temperature. The reaction was quenched with saturated NH_4Cl solution (10 ml). The organic layer was separated, and the aqueous layer was extracted twice with EtOAc (100 ml). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated to give crude **30** (2.06 g) as a pale yellow oil, which was used for the next reaction without further purification. To a solution of crude **30** (1.95 g, 10.8 mmol) in CH_2Cl_2 (220 ml) was added PCC (5.6 g, 13.2 mmol) at room temperature. The mixture was stirred for 2 hours at the same temperature, and diluted with Et_2O (150 ml). After the addition of celite (5.6 g) and stirring for 10 min, the mixture was filtered through a pad of florisil and celite, which was washed three times with EtOAc (70 ml). The filtrate was concentrated to give a colorless oil, which was purified by silica gel column chromatography (SiO_2 80 g, CH_2Cl_2/hexane = 3/1) to give **7** (1.79 g, 10.0 mmol; 93% in 2 steps) as a colorless oil. Spectrum data is shown above.

References

[1] (a) Usuda, H.; Kanai, M.; Shibasaki, M. *Org. Lett*. **2002**, *4*, 859. (b) Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett*. **2002**, *43*, 3621.

[2] Martin, J. C.; Arhart, R. J.; Franz, J. A.; Perozzi, E. F.; Kaplan, L. J. *Org. Synth.* **1977**, *57*, 22.

[3] Kazmierczak, P.; Skulski, L.; Kraszkiewicz, L. *Molecules* **2001**, *6*, 881.

[4] Modification of the Wacker conditions by adding *t*BuOH and NaOAc was recently reported by Cook et al.: Liao, X.; Zhou, H.; Wearing X. Z.; Ma, J.; Cook, J. M. *Org. Lett.* **2005**, *7*, 3501.

[5] Engler, T. A.; Reddy, J. P.; Combrink, K. D.; Vander, V. D. *J. Org. Chem.* **1990**, *55*, 1248.