Supporting Information

Total Synthesis of Garsubellin A.

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Experimental

General Procedures. All reactions were performed in flame-dried round bottomed or modified Schlenk (Kjeldahl shape) flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary solutions were deoxygenated by alternative freeze (liquid nitrogen)/evacuation/ thaw cycles ($\geq$ three iterations). Organic solutions were concentrated by rotary evaporation at $\sim$ 25 Torr. Flash column chromatography was performed as described by Still et al. (Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923-2925.) Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or exposure to ceric ammonium molybdate, phosphomolybdic acid, or an acidic solution of *p*-anisaldehyde followed by heating on a hot plate.

Materials. Commercial reagents and solvents were used as received with the following exceptions. Chlorotrimethylsilane, triethylamine, and diisopropylamine were distilled from calcium hydride at 760 Torr under dinitrogen atmosphere. Benzene, dichloromethane, ethyl ether, toluene, and tetrahydrofuran were purified using Solv-Tek, Inc. solvent purification systems. The molarity of *n*-butyllithium was determined by titration against diphenylacetic acid.

Instrumentation. Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) were recorded with Bruker AMX-400 spectrometer. Chemical shifts for protons are reported in parts per million scale (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvents (CHCl_3 : δ 7.26, $\text{C}_6\text{D}_5\text{H}$: δ 7.15). Chemical shifts for carbon are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl_3 : δ 77.0, C_6D_6 : δ 128.0). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, coupling constant in Hz, and assignment. Infrared (IR) spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrophotometer referenced to a polystyrene standard. Data are represented as follows: frequency of the absorption (cm^{-1}), intensity of absorption (s = strong, sb = strong broad, m = medium, w = weak, br = broad), and assignment (where appropriate).

Alkene 3:

A solution of *n*-butyllithium (64 ml, 0.159 mol, 1.1 eq, 2.49 M in hexanes) was added over 5 min to **2** (prepared from 3,5-dimethoxyphenol in one step, Landi, J. J. Jr.; Ramig, K. *Synth. Commun.* **1991**, *21*, 167.)(45.1g, 0.145 mol, 1.0 eq) in THF at 0 °C with a mild exotherm. The cooling bath was removed and the yellow solution was stirred at 23 °C for 1h then placed back in an ice bath for 30 min. Prenyl bromide was added over a 10 min period then the cooling bath was removed and the solution was stirred for an additional 15 min. Concentrated aqueous ammonium chloride solution (100ml) was added followed by water (1L) and the biphasic mixture was extracted with 1:1 EtOAc:hexanes (500 ml). The organic extract was dried over Na₂SO₄, filtered, and concentrated to provide **3** as a light yellow oil (55.4 g, 98%).

R_f 0.71 (20% EtOAc-hexanes); ¹H NMR (400 MHz, CDCl₃) δ 6.08 (s, 2H), 5.14 (t, 1H, *J* = 5.8 Hz), 3.74 (s, 6H), 3.23 (d, 2H, *J* = 7.0 Hz), 1.73 (s, 3H), 1.64 (s, 3H), (m, 3H), 1.2 (d, 18H, *J* = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 158.6, 155.5, 130.7, 123.9, 111.3, 96.6, 55.9, 26.0, 22.1, 18.2, 17.9, 12.9; FTIR (neat film), cm⁻¹ 2944 (s), 1602 (s), 1591 (s), 1494 (m), 1456 (s); LRMS *m/z* 401.3 (M + Na⁺).

Diol 4:

Solid potassium carbonate (98.3 g, 0.711 mol, 3.0 eq), potassium ferricyanide (234 g, 0.711 mol, 3.0 eq), potassium osmate dihydrate (175 mg, 0.47 mmol, 0.002 eq), DABCO (265 mg, 2.37 mmol, 0.01 eq), and methanesulfonamide (23 g, 0.237 mol, 1 eq) were added sequentially to a solution of alkene **3** (90 g, 0.237 mol, 1.0 eq) in a 1:1 solution of *t*-BuOH-H₂O (1.2 L) at 23 °C. The biphasic redish-brown solution was stirred rapidly at 23 °C for 48 h then excess oxidant was quenched by the addition of concentrated sodium thiosulfate solution (300 ml). After stirring at 23 °C for 20 min the organic phase was collected and the aqueous phase was extracted with EtOAc (250 ml), the combined organic extracts were dried over Na₂SO₄, filtered, and concentrated to provide **4** as a brown oil (88 g, 90%).

R_f 0.25 (33% EtOAc-hexanes); ¹H NMR (400 MHz, CDCl₃) δ 5.98 (s, 2H), 3.63 (s, 6H), 3.37 (dd, 1H, *J* = 10.0, 2.3 Hz), 2.79 (dd, 1H, *J* = 13.9, 2.2 Hz), 2.52 (dd, 1H, *J* = 9.9, 13.9 Hz), 1.19-1.11 (m, 9H), 1.00 (d, 18H, *J* = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 158.7, 156.2, 108.3, 98.8, 79.3, 73.0, 55.8, 26.0, 25.5, 23.9, 18.1, 12.8; FTIR (neat film), cm⁻¹ 3445 (bs), 2943 (s), 1606 (bs), 1495 (m), 1019 (m); LRMS *m/z* 435.0 (M + Na⁺).

Phenol 5:

Solid *p*-toluenesulfonic acid monohydrate (2.2 g, 0.012 mol, 0.05 eq) was added in one portion to a solution of diol **4** (88 g, 0.213 mol, 1.0 eq) in 5:1 acetone-2,2-dimethoxypropane (800 ml) at 23 °C. The solution was stirred at 23 °C for 1 h then concentrated to 300 ml and diluted with 1:1 EtOAc-hexanes (1 L) and the solution was washed with concentrated aqueous sodium bicarbonate solution (100 ml), brine (300 ml), and water (500 ml) then dried over Na₂SO₄, filtered, and concentrated to provide the corresponding acetone as a brown oil (91g, 94%).

R_f 0.67 (33% EtOAc-hexanes); ¹H NMR (400 MHz, CDCl₃) δ 6.06 (s, 2H), 4.00 (dd, 1H, *J* = 7.7, 5.6 Hz), 3.72 (s, 6H), 2.83 (m, 2H), 1.62 (s, 3H), 1.29 (s, 3H), 1.22-1.17 (m, 6H), 1.11 (d, 18H, *J* = 7 Hz), 0.95 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 159.1, 156.2, 107.6, 105.8, 96.8, 82.1, 80.8, 55.7, 28.8, 27.2, 26.0, 22.9, 22.8, 18.1, 12.9; FTIR (neat film), cm⁻¹ 2944 (s), 1605 (s), 1495 (m), 1463 (m), 1368 (m); LRMS *m/z* 453.3, (M + H⁺), 475.1 (M + Na⁺).

A solution of TBAF (210 ml, 0.21 mol, 1.05 eq, 1.0 M in THF) was added to acetone (91g, 0.20 mol, 1.0 eq) (formed in the previous reaction) in THF (650 ml) at 23 °C. The grey solution was stirred at 23 °C for 10 min then excess TBAF was quenched by the addition of concentrated aqueous NH₄Cl solution (300 ml). The mixture was extracted with hexanes (300 ml) and the aqueous layer was extracted again with EtOAc (600 ml) the combined organic extracts were dried over Na₂SO₄, filtered, and concentrated to provide a brown oil. The oil was loaded on a short plug of silica gel and eluted with 1:2 EtOAc-hexanes (2.1 L), the filtrate was concentrated to provide a light brown oil.

Recrystallization from toluene (100 ml) provided a first crop of colorless crystals of **5** (44g, 74%) and a second crop after concentration (4g, 7%). mp 144 °C

R_f 0.42 (33% EtOAc-hexanes); ^1H NMR (400 MHz, CDCl_3) δ 6.01 (s, 2H), 4.04 (t, 1H, J = 6.4 Hz), 3.71 (s, 6H), 2.91 (dd, 1H, J = 13.7, 6.6 Hz), 2.72 (dd, 1H, J = 13.7, 6.3 Hz), 1.43 (s, 3H), 1.31 (s, 3H), 1.22 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.2, 156.4, 106.5, 92.4, 82.7, 81.1, 55.7, 28.8, 27.3, 26.1, 22.9; FTIR (neat film), cm^{-1} 3353 (bs), 2981 (m), 2936 (m), 1615 (s), 1472 (s), 1372 (m); LRMS m/z 297.1 ($\text{M} + \text{H}^+$), 319.0 ($\text{M} + \text{Na}^+$), 330.7 ($\text{M} + \text{Cl}^-$).

Ketone 6:

Solid Pd(OAc)₂ (200mg, 0.892 mmol, 0.02 eq) and PPh₃ (936 mg, 3.57 mmol, 0.08 eq) were added to a suspension of phenol **5** (12.0g, 0.045 mol, 1.0 eq) in benzene (250 ml) at 23 °C. With stirring allyl methyl carbonate (12.7 ml, 0.112 mol, 2.5 eq) was added followed by Ti(O-*i*Pr)₄ (2.6 ml, 8.9 mmol, 0.2 eq) whereupon the solution turned a deep red. The mixture was placed in a 50 °C oil bath and after stirring for 5 min the solids had dissolved. After stirring for 40 min extensive gas evolution occurred and continued for 10 min. The solution was removed from the heating bath and concentrated aqueous ammonium chloride solution (50 ml) was added and the solution was stirred at 23 °C for 5 min. A solution of 1N HCl (100 ml) was added and the organic phase was collected. The aqueous phase was extracted with EtOAc (2 × 250 ml) and the combined organic extracts were dried over Na₂SO₄, filtered, and concentrated to provide a red sludge. The crude ketone was purified by flash column chromatography (33-100% EtOAc-hexanes) to provide ketone **6** as an off white solid (9.4 g, 62%). mp 107 °C

R_f 0.27 (EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 5.46 (s, 1H), 5.37 (s, 1H), 5.28 (m, 1H), 4.84-4.76 (m, 2H), 3.61 (s, 3H), 3.56 (s, 3H), 3.16 (d, 1H, *J* = 8.6 Hz), 2.48 (dd, 1H, *J* = 7.1, 13.3 Hz), 2.41 (dd, 1H, *J* = 7.6, 13.3 Hz), 1.91 (dd, 1H, *J* = 9.3, 14.0 Hz), 1.75 (d, 1H, *J* = 13.8 Hz), 1.17 (s, 3H), 1.00 (s, 1H), 0.95 (s, 1H), 0.90 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 188.2, 173.8, 172.2, 131.9, 117.9, 106.4, 103.8, 102.7, 79.8, 79.3, 55.7, 55.5, 50.0, 41.1, 36.1, 28.3, 26.3, 24.8, 22.4; FTIR (neat film), cm⁻¹ 2980 (m), 2938 (m), 1654 (s), 1625 (m), 1954 (m), 1207 (s); LRMS *m/z* 337.2 (M + H⁺), 359.2 (M + Na⁺).

Diketone **11**:

Perchloric acid in water (9.8 ml, 0.09 mol, 3.0 eq, 60% w/w solution) was added to a solution of **6** (10.2 g, 0.03 mol, 1.0 eq) in dioxane-water (5:1, 200ml). The light yellow reaction was placed in a 50 °C oil bath and stirred for 12 h then allowed to cool to 23 °C and diluted with brine (100ml). The solution was extracted with EtOAc (4 × 100 ml) and the combined extracts were dried over Na₂SO₄, filtered, and concentrated to provide a yellow semisolid. The crude diketone was purified by flash column chromatography (0-3% MeOH-CH₂Cl₂) to provide diketone **11** as a thick light yellow oil (5.4 g, 72%).

R_f 0.42 (EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 5.66-5.54 (m, 2H), 5.20-5.14 (m, 2H), 4.52 (dd, 1H, *J* = 5.6, 10.7 Hz), 3.47 (d, 1H, *J* = 19.6 Hz), 3.15 (d, 1H, *J* = 19.6 Hz), 2.57 (m, 2H), 2.31 (dd, 1H, *J* = 10.7, 12.9 Hz), 2.03 (dd, 1H, *J* = 5.6, 13.2), 1.30 (s, 3H), 1.16 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 201.8, 192.9, 181.4, 130.7, 121.2, 101.9, 90.9, 70.9, 61.4, 49.5, 42.5, 28.2, 26.8, 24.5; FTIR (neat film), cm⁻¹ 3418 (bs), 2978 (m), 1732 (m), 1646 (s), 1615 (s), 1362 (s), 1212 (m), 1177 (m); LRMS *m/z* 251.0 (M + H⁺), 273.0 (M + Na⁺), 289.0 (M + K⁺), 284.9 (M + Cl⁻).

Diketone 12:

Grubb's 2nd generation catalyst (1.43 g, 1.68 mmol, 0.08 eq) was added in one portion to a solution of diketone **11** (5.6 g, 22.4 mmol, 1.0 eq) in CH₂Cl₂-2-methyl-2-butene (3:2, 150 ml). The solution was placed in a 40 °C oil bath and stirred for 16 h then an additional portion of Grubb's 2nd generation catalyst (0.56 g, 0.56 mmol, 0.03 eq) was added and the solution was stirred at 40 °C for an additional 8 h. The dark brown solution was concentrated to 20 ml and loaded directly on a silica gel column. The crude diketone was purified by flash column chromatography (2-5% MeOH-CH₂Cl₂) to provide diketone **12** as a thick light brown oil (4.23 g, 68%).

R_f 0.46 (EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 5.60 (s, 1H), 4.92 (t, 1H, *J* = 7.9 Hz), 4.49 (dd, 1H, *J* = 5.5, 10.7 Hz), 3.43 (d, 1H, *J* = 19.5), 3.11 (d, 1H, *J* = 19.5 Hz), 2.60 (dd, 1H, *J* = 8.3, 15 Hz), 2.45 (dd, 1H, *J* = 6.5 Hz, 15 Hz), 1.64 (s, 3H), 1.57 (s, 3H), 1.29 (s, 3H), 1.13 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 202.4, 193.0, 181.7, 138.3, 116.5, 101.8, 91.0, 70.9, 61.9, 49.5, 36.9, 28.5, 26.8, 26.0, 24.4, 18.2; FTIR (neat film), cm⁻¹ 3434 (bs), 2978 (s), 2932 (s), 1738 (m), 1666 (s), 1614 (s), 1453 (m), 1360 (s); LRMS *m/z* 279.1 (M + H⁺), 301.0 (M + Na⁺), 316.9 (M + K⁺), 313.0 (M + Cl⁻).

Diiodide **13**:

Solid iodine (14.0 g, 0.055mol, 3.0 eq), potassium iodide (9.1 g, 0.055 mol, 3.0 eq), and potassium hydrogen carbonate (5.5 g, 0.055 mol, 3.0 eq) were added sequentially to a solution of alkene **12** (5.1 g, 0.018 mol, 1.0 eq) in THF-water (4:1, 180 ml) at 23 °C. The deep red solution was stirred at 23 °C for 50 min then concentrated aqueous Na₂S₂O₃ solution (100 ml) was added to quench excess iodine and the solution was stirred at 23 °C for 1 h then extracted with EtOAc (500 ml). The organic extract was washed with brine (100 ml) then dried over Na₂SO₄, filtered, and concentrated to provide a yellow solid. The crude diiodide was purified by flash column chromatography (25-50% EtOAc-hexanes) to provide diiodide **13** as white solid (8.1 g, 85%) that discolored upon prolonged exposure to air. mp 175 °C (decomp.)

R_f 0.66 (EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 5.78 (s, 1H), 4.57 (dd, 1H, *J* = 5.4, 11 Hz), 4.46 (dd, 1H, *J* = 4.8, 12.8 Hz), 2.77 (dd, 1H, *J* = 12, 13 Hz), 2.63 (dd, 1H, *J* = 4.9, 13.8 Hz), 2.44 (m, 1H), 1.99 (bs, 1H), 1.90 (dd, 1H, 5.4, 13.4 Hz), 1.40 (s, 3H), 1.33 (s, 3H), 1.20 (s, 3H), 1.16 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 195.3, 190.2, 101.4, 91.8, 77.0, 70.6, 61.5, 55.3, 48.9, 43.8, 31.9, 30.3, 28.6, 26.7, 24.7, 23.9; FTIR (neat film), cm⁻¹ 3466 (bs), 2979 (s), 1741 (s), 1632 (s), 1464 (m), 1373 (m); LRMS *m/z* 530.8 (M + H⁺), 552.9 (M + Na⁺), 568.8 (M + K⁺), 564.9 (M + Cl⁻).

Triiodide **14**:

Solid iodine (2.13 g, 8.4 mmol, 1.0 eq) and CAN (4.6 g, 8.4 mmol, 1.0 eq) were added to a solution of diiodide **13** (4.48g, 8.4 mmol, 1.0 eq) in acetonitrile (80 ml). The solution was placed in a 50 °C oil bath and stirred for 2 h. The solution was cooled to 23 °C and excess oxidant was quenched by addition of concentrated aqueous Na₂S₂O₃ solution (100 ml) and concentrated aqueous NaHCO₃ solution (20 ml). The solution was stirred at 23 °C for 40 min then extracted with EtOAc (2 × 200 ml) and the extracts were dried over Na₂SO₄, filtered, and concentrated to provide a yellow solid. The crude triiodide was purified by flash column chromatography (5-9% EtOAc-CH₂Cl₂) to provide triiodide **14** as white solid (4.24 g, 77%) that discolored upon prolonged exposure to air. mp 202 °C (decomp.)

R_f 0.5 (50% EtOAc-hexanes); ¹H NMR (400 MHz, CDCl₃) δ 4.70 (dd, 1H, *J* = 5.5, 10.9 Hz), 4.32 (dd, 1H, *J* = 4.7, 12.8 Hz), 2.93 (m, 1 H), 2.66 (dd, 1H, *J* = 4.8, 13.9 Hz), 2.42 (t, 1H, *J* = 13 Hz), 2.11 (dd, 1H, *J* = 5.5, 13.4 Hz), 1.44 (s, 3H), 1.36 (s, 3H), 1.20 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 194.4, 185.1, 176.6, 92.1, 73.6, 70.6, 68.2, 62.5, 49.6, 44.0, 32.0, 31.6, 28.0, 27.0, 24.7, 23.9; FTIR (neat film), cm⁻¹ 3521 (bs), 2979 (m), 1742 (s), 1666 (m), 1600 (s), 1464 (m), 1228 (s); LRMS *m/z* 678.8 (M + Na⁺), 690.7 (M + Cl⁻).

Cyclopropane **15**:

A solution of *i*PrMgCl (3.3 ml, 6.66 mmol, 3.5 eq, 2.0 M in THF) was added to a solution of **14** (1.25 g, 1.90 mmol, 1.0 eq) in THF-Et₂O (1:1, 60 ml) at -78 °C and the dry ice cooling bath was removed and the solution was stirred at 23 °C for 75 min. A solution of Li₂CuCl₄ (1 ml, 7.6 mmol, 0.05 eq, 0.1 M in THF) was added followed by addition of allyl bromide (0.643 ml, 7.6 mmol, 4.0 eq) and the solution was stirred at 23 °C for 4 h. Aqueous concentrated NH₄Cl solution (10 ml) and aqueous concentrated NaHCO₃ solution (10 ml) were added and the organic phase was collected. The aqueous phase was extracted with EtOAc (100 ml) and the combined organic extracts were dried over Na₂SO₄, filtered, and concentrated to provide a clear oil. The crude cyclopropane was purified by flash column chromatography (20% EtOAc-hexanes) to provide **15** as a white foam (403 mg, 67%).

R_f 0.41 (50% EtOAc-hexanes); ¹H NMR (400 MHz, CDCl₃) δ 5.72 (m, 1H), 4.91-4.86 (m, 2H), 4.58 (dd, 1H, *J* = 5.7, 10.9 Hz), 3.00 (dd, 1H, *J* = 5.7, 14.9 Hz), 2.90 (dd, 1H, *J* = 6.7, 14.9 Hz), 2.52 (dd, 1H, *J* = 11.1, 13.1 Hz), 2.36 (dd, 1H, *J* = 8.2, 13.6 Hz), 1.94 (bs, 1H), 1.87 (dd, 1H, *J* = 5.7, 13.2 Hz), 1.77 (dd, 1H, *J* = 5.3, 13.7 Hz), 1.47 (s, 3H), 1.33 (s, 3H), 1.16 (s, 3H), 1.13-1.05 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 195.9, 191.1, 175.4, 135.6, 114.8, 114.7, 92.0, 75.4, 70.9, 54.3, 43.5, 37.8, 27.7, 27.5, 26.6, 26.1, 24.3, 23.2, 19.5; FTIR (neat film), cm⁻¹ 3550 (bs), 2976 (m), 1765 (s), 1651 (s), 1599 (s), 1378 (m), 1221 (s); LRMS *m/z* 316.9 (M + H⁺), 323.3 (M + Li⁺), 339.1 (M + Na⁺), 355.2 (M + K⁺), 351.0 (M + Cl⁻).

Iodide 16:

Iodotrimethylsilane (0.469 ml, 3.3 mmol, 1.2 eq) was added to a solution of **15** (870 mg, 2.75 mmol, 1.0eq) in CH₂Cl₂ (25 ml) at 0 °C. The solution was stirred for 5 min then 1 N HCl (5 ml) was added and the solution was stirred for 5 min at 0 °C then concentrated aqueous NaHCO₃ solution (10 ml) and concentrated aqueous Na₂S₂O₄ solution (10 ml) and the biphasic mixture was extracted with EtOAc (200 ml). The organic extract was washed with brine (2 × 50 ml) and dried over Na₂SO₄, filtered, and concentrated to provide **16** as a clear, colorless oil (1.17 g, 98%).

R_f 0.45 (50% EtOAc-hexanes); ¹H NMR (400 MHz, CDCl₃) δ 5.70 (m, 1H), 4.97-4.91 (m, 2H), 4.54 (dd, 1H, *J* = 5.6, 10.8 Hz), 4.27 (dd, 1H, *J* = 5.0, 12.7 Hz), 3.19 (s, 1H), 3.08 (dd, 1H, *J* = 5.9, 14.6 Hz), 2.96 (dd, 1H, *J* = 7.1, 14.6 Hz), 2.65-2.54 (m, 2H), 2.40 (t, 1H, *J* = 13.2 Hz), 1.78-1.73 (m, 2H), 1.29 (s, 3H), 1.14 (s, 3H), 1.13 (s, 3H), 1.06 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 200.7, 191.9, 173.3, 135.3, 115.3, 114.7, 90.7, 70.8, 69.8, 62.1, 44.0, 34.5, 29.8, 29.1, 27.4, 26.9, 24.3, 24.1, 23.9; FTIR (neat film), cm⁻¹ 3459 (bs), 2974 (m), 1738 (s), 1620 (s), 1449 (m), 1366 (m), 1224 (m); LRMS *m/z* 445.0 (M + H⁺), 467.1 (M + Na⁺), 479.1 (M + Cl⁻).

Alkene 17:

Solid AIBN (31 mg, 0.190 mmol, 0.15 eq) was added to a solution of **16** (562 mg, 1.26 mmol, 1.0 eq) in benzene-allyltributyltin (1:2, 8 ml) and the solution was degassed by argon blown through the reaction for 2×5 min. The reaction flask was placed in a 80 °C oil bath and stirred for 2h then cooled to 23 °C and diluted with CH₃CN (30 ml) and the acetonitrile layer was collected and washed with hexanes (3×10 ml) then concentrated to provide pure diallyl **17** as a light yellow foam (370 mg, 82%).

R_f 0.46 (50% EtOAc-hexanes); ¹H NMR (400 MHz, CDCl₃) δ 5.78-5.60 (m, 2H), 5.02-4.91 (m, 4H), 4.53 (dd, 1H, J = 5.7, 10.8 Hz), 3.11 (ddt, 1H, J = 1.6, 5.7, 14.8 Hz), 3.00 (dd, 1H, J = 7.3, 14.8 Hz), 2.86 (s, 1H), 2.62 (dd, 1H, J = 10.9, 13.0 Hz) 2.31 (m, 1H), 2.08 (dd, 1H, J = 4.2, 13.5 Hz), 1.78-1.69 (m, 3H), 1.46 (dd, 1H, J = 12.1, 13.6 Hz), 1.31 (s, 3H), 1.14 (s, 3H), 0.86 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 204.0, 193.0, 174.6, 136.8, 135.8, 117.2, 115.0, 114.5, 90.5, 73.4, 71.1, 60.1, 42.6, 39.7, 37.9, 33.7, 29.8, 27.3, 27.0, 26.9, 24.2, 20.7; FTIR (neat film), cm⁻¹ 3460 (bm), 2974 (m), 1733 (s), 1623 (vs), 1373 (m), 1227 (m); LRMS m/z 359.3 (M + H⁺), 381.2 (M + Na⁺), 397.3 (M + K⁺), 393.1 (M + Cl⁻).

Deisobutrylgarsubellin A(18):

Grubb's 2nd generation catalyst (0.189 g, 0.22 mmol, 0.15 eq) was added in one portion to a solution of **17** (528 mg, 1.47 mmol, 1.0 eq) in CH₂Cl₂-2-methyl-2-butene (1:1, 14 ml). The solution was placed in a 40 °C oil bath and stirred for 24 h. The solution was removed from the oil bath and concentrated to provide a dark brown oil. The crude deisobutryl-garsubellin (**18**) was purified by flash column chromatography (4% EtOAc-CH₂Cl₂) to provide **18** as a light brown foam (443 mg, 73%).

R_f 0.53 (50% EtOAc-hexanes); ¹H NMR (400 MHz, CDCl₃) δ 5.01 (tt, 1H, *J* = 1.3, 6.6 Hz), 4.96 (m, 1H), 4.52 (dd, 1H, *J* = 5.7, 10.7 Hz), 2.99 (dd, 1H, *J* = 5.7, 14.4 Hz), 2.92 (dd, 1H, *J* = 6.3, 14.1 Hz), 2.81 (s, 1H), 2.56 (dd, 1H, *J* = 10.8, 12.9 Hz) 2.11 (m, 1H), 2.02 (dd, 1H, *J* = 4.2, 13.6 Hz), 1.72-1.62 (m, 3H), 1.67 (s, 3H), 1.65 (s, 3H), 1.59 (s, 3H), 1.51 (s, 2H), 1.46 (dd, 1H, *J* = 12.1, 13.3 Hz), 1.29 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H), 0.85 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 204.3, 193.3, 173.8, 133.6, 132.2, 122.4, 121.9, 116.3, 90.3, 73.5, 71.1, 60.0, 42.7, 40.7, 38.1, 29.9, 27.5, 26.9, 26.8, 26.1, 25.8, 24.1, 22.1, 20.7, 18.1, 18.0; FTIR (neat film), cm⁻¹ 3460 (bs), 2970 (s), 2929 (s), 1732 (s), 1622 (s), 1455 (m), 1373 (m), 1210 (m); LRMS *m/z* 415.3 (M + H⁺), 437.2 (M + Na⁺), 449.1 (M + Cl⁻).

Iodide **19**:

Chlorotrimethylsilane was added to a solution of **18** (32 mg, 0.077 mmol, 1.0 eq) in THF (7 ml) at $-78\text{ }^{\circ}\text{C}$ followed by the addition of a solution of freshly prepared LDA (0.620 ml, 0.308 mmol, 4.0 eq, 0.5 M in THF). The yellow solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 2 min then transferred to an ice water bath and stirred for 12 min then iodine (176 mg, 0.693 mmol, 9.0 eq) dissolved in THF (1 ml) was added in one portion. The red solution was stirred at $0\text{ }^{\circ}\text{C}$ for 20 min. The solution was diluted with EtOAc-hexane (1:2, 50 ml) and the solution was washed with concentrated aqueous $\text{Na}_2\text{S}_2\text{O}_4$ solution (10 ml) and brine (20 ml) then dried over Na_2SO_4 , filtered, and concentrated to provide a yellow oil. Crude iodide was purified by flash column chromatography (1-3% EtOAc-hexanes) to generate **19** as a clear, colorless oil (11.7 mg, 25%).

R_f 0.38 (10% EtOAc-hexanes); ^1H NMR (400 MHz, CDCl_3) δ 5.04 (t, 1H, $J = 6.6$ Hz), 4.94 (m, 1H), 4.45 (dd, 1H, $J = 6.0, 10.2$ Hz), 2.99 (m, 2H), 2.75 (dd, 1H, $J = 10.3, 13.2$ Hz), 2.22 (m, 1H), 2.03 (dd, 1H, $J = 3.8, 13.8$ Hz), 1.79 (dd, 1H, $J = 6.0, 13.3$ Hz), 1.76-1.72 (m, 2H), 1.67 (s, 3H), 1.66 (s, 3H), 1.62 (s, 3H), 1.53 (s, 3H), 1.48 (dd, 1H, $J = 11.9, 13.3$ Hz), 1.28 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H), 0.90 (s, 3H), 0.08 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 198.2, 190.2, 173.3, 134.0, 132.4, 122.4, 121.4, 113.6, 91.3, 87.3, 74.1, 59.9, 48.1, 40.3, 38.5, 31.6, 29.8, 28.2, 26.7, 26.1, 25.9, 25.6, 23.4, 21.0, 18.1, 18.1, 2.6 ; FTIR (neat film), cm^{-1} 2974 (m), 2926 (m), 1741 (m), 1631 (s), 1370 (m), 1250 (m); LRMS m/z 613.3 ($\text{M} + \text{H}^+$), 635.2 ($\text{M} + \text{Na}^+$), 647.2 ($\text{M} + \text{Cl}^-$).

Garsubellin-TMS Ether:

A solution of *i*PrMgCl (34 μ l, 0.069 mmol, 7.0 eq, 2.0 M solution in THF) was added to solution iodide **19** (6 mg, 0.010 mmol, 1.0 eq) in Et₂O (1 ml) at -78 °C. The bright yellow solution was stirred at -78 °C for 2 min then the isobutyraldehyde (9.1 μ l, 0.10 mmol, 10 eq) was added after 1 min the yellow color dissipated. After 10 min at -78 °C the cooling bath was removed and the solution was stirred for 5 min then saturated aqueous ammonium chloride solution (1 ml) was added. The solution was diluted with EtOAc (15 ml) and washed with brine (2 $\times$ 10 ml), dried over Na₂SO₄, filtered, and concentrated to provide **20** as a mixture of isomers. The crude **20** (>85% pure by ¹H NMR) was dissolved in CH₂Cl₂ (1 ml) and solid Dess-Martin periodinane (10 mg, 0.024, 2.4 eq based on **19**) and the heterogeneous mixture was stirred at 23 °C for 4 h. Excess oxidant was quenched by the addition of concentrated aqueous Na₂S₂O₃ solution (5 ml) and the biphasic reaction was stirred rapidly at 23 °C for 30 min then extracted with EtOAc-hexanes (1:1, 20 ml) and the organic phase was washed with brine (15 ml), dried over Na₂SO₄, filtered, and concentrated to provide a clear oil. Crude material was purified by flash column chromatography (1-3% EtOAc-hexanes) to generate garsubellin-TMS ether a clear, colorless oil (3.6 mg, 68% 2-steps).

*R*_f 0.50 (10% EtOAc-hexanes); ¹H NMR (400 MHz, CDCl₃) δ 5.05 (t, 1H, *J* = 6.3 Hz), 4.92 (m, 1H), 4.45 (dd, 1H, *J* = 6.2, 9.9 Hz), 3.12 (dd, 1H, *J* = 7.7, 14.0 Hz), 2.98 (dd, 1H, *J* = 6.5, 14.3 Hz), 2.75 (dd, 1H, *J* = 10.1, 13.1 Hz), 2.12 (m, 1H), 1.99 (m, 1H), 1.95 (qq, 1H, *J* = 6.5, 6.5 Hz), 1.72-1.65 (m, 3H), 1.69 (s, 3H), 1.67 (s, 3H), 1.61 (s, 3H), 1.53 (s, 3H), 1.48 (m, 1H), 1.37 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H), 1.08 (d, 3H, *J* = 6.5 Hz), 1.02 (s, 3H), 0.96 (d, 2H, *J* = 6.6 Hz), 0.07 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 209.4,

205.0, 193.1, 173.8, 133.6, 132.4, 122.6, 121.4, 116.2, 91.1, 82.2, 74.2, 59.9, 46.4, 42.7, 42.2, 39.6, 30.2, 26.8, 26.7, 26.3, 26.1, 25.9, 23.0, 22.5, 21.6, 20.6, 18.1, 18.1, 16.4, 2.5;
FTIR (neat film), cm^{-1} 2966 (s), 2926 (s), 1732 (s), 1626 (s), 1451 (bw), 1371 (m);
LRMS m/z 557.4 ($\text{M} + \text{H}^+$), 579.3 ($\text{M} + \text{Na}^+$), 591.3 ($\text{M} + \text{Cl}^-$).

Garsubellin A (1):

Triethylamine trihydrofluoride (23 μ l, 0.14 mmol, 20 eq) was added to a solution of garsubellin TMS ether (4 mg, 0.007mmol, 1.0 eq) in THF (700 μ l) at 23 °C. The solution was stirred at 23 °C for 7 h then saturated aqueous NaHCO₃ solution (5 ml) was added to quench the excess hydrogenfluoride. The solution was stirred for 10 min then extracted with EtOAc (3 $\times$ 10 ml), the combined organic extracts were dried over Na₂SO₄, filtered, and concentrated to provide a clear oil. Purification of the crude material by flash column chromatography (5-15% EtOAc-hexanes) provided garsubellin A (**1**) as a clear, colorless oil (2.7 mg, 80%).

R_f 0.68 (50% EtOAc-hexanes); ¹H NMR (400 MHz, C₆D₆) δ 5.40 (dd, 1H, J = 7.3, 7.3Hz), 4.97 (dd, 1H, J = 6.9, 7.0 Hz), 3.92 (dd, 1H, J = 5.8, 10.6 Hz), 3.39 (dd, 1H, J = 7.1, 14.1 Hz), 3.21 (dd, 1H, J = 7.6, 14.3 Hz), 2.73 (dd, 1H, J = 10.8, 13.1 Hz), 2.26 (qq, 1H, J = 6.6, 6.6 Hz), 2.09 (m, 1H), 1.93 (dd, 1H, J = 4.5, 13.6 Hz), 1.74 (m, 1H), 1.70 (s, 3H), 1.61 (s, 6H), 1.58 (m, 1H), 1.58 (s, 3H), 1.45 (s, 3H), 1.37 (d, 3H, J = 6.5 Hz), 1.32-1.30 (m, 2H), 1.30 (d, 3H, J = 6.5 Hz), 1.24 (s, 3H), 0.94 (s, 3H), 0.77 (s, 3H); ¹³C NMR (100 MHz, C₆D₆) δ 208.9, 205.0, 193.3, 173.6, 133.5, 132.8, 123.6, 122.4, 117.1, 90.5, 83.0, 70.6, 60.2, 47.0, 43.3, 43.1, 39.4, 30.6, 27.4, 26.7, 26.3, 26.1, 24.8, 23.5, 23.0, 22.3, 21.3, 18.3, 18.2, 16.9; FTIR (neat film), cm⁻¹ 3444 (m), 2956 (s), 1732 (s), 1626 (s), 1372 (m); LRMS m/z 485.4 (M + H⁺), 507.4 (M + Na⁺), 519.2 (M + Cl⁻).

synthetic garsubellin A

natural garsubellin A

4

S24

6

II

17

14

15

TMS-Garsubellin A