Supporting Information

Total synthesis of crambescidin 359

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General

Melting points (mp) were recorded with a JASCO DIP-370 polarimeter. IR spectra were measured with a JASCO VALOR-III FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on JNM-EX-300 and DELTA-NMR-ECP500 instruments. Mass spectra were recorded on JEOL JMA-HX110 spectrometers. Flash chromatography was performed on silica gel 60 (230-400 mesh; E-Merck Darmstadt, Germany).

Synthesis of **(3*S*)-3-(*tert*-Butyl-dimethylsilyloxy)-4,8-nonadien (13)** (Scheme 2).

(2*S*)-1-Benzyloxy-2-butanol (11). To a CuCN (100 mg, 1.1 mmol) twice gently flame-dried under vacuum followed by flushing with N_2, dry ether (300 mL) was added with a syringe and the suspension was cooled to –15°C. MeMgBr (0.9M solution in THF, 43 mL) was added dropwise and the reaction mixture was stirred at –15°C for 15 min. Then *S*-(+)-benzylglycidyl ether **10** (5 g, 30 mmol) was added and the mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched with aqueous sat.NH_4Cl and 25% NH_3 solution and the resulting mixture was stirred at room temperature until the color turned blue. The organic layers were extracted with ether, washed with brine, dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography with hexanes:ether 8:2 to give **11** (8.82 g,

80%).

(2*S*)-2-(*tert*-Butyl-dimethylsilyloxy)butan-1-ol (12). The mixture of **11** (8.82 g, 50 mmol), imidazole (10.2 g, 150 mmol), TBDMSCl (9.8 g, 65 mmol) and a catalytic amount of DMAP in dichloromethane (200 mL) was stirred at room temperature for overnight. The reaction mixture was quenched with sat.$NaHCO_3$, and the mixture was extracted with ether. The organic extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography with hexanes to give silyl ether (11.2g, 78%). This silyl ether (11.2 g, 38 mmol) was dissolved in ethyl acetate and treated with H_2 over $Pd(OH)_2/C$ for 1.5 h at room temperature. The reaction mixture was filtered and concentrated *in vacuo* to give **12** (7.6 g, 97%).

(3*S*)-3-(*tert*-Butyl-dimethylsilyloxy)-4,8-nonadien (13). To an oxalyl chloride (4.23 mL, 48 mmol) in dichloromethane (350 mL) at –78°C, DMSO (9.1 mL) was slowly added and the mixture was stirred for 10 min. To the resulting mixture was added **12** (6.6 g, 32 mmol) in dichloromethane (30 mL). After stirring for 1 h, the resulting mixture was added triethylamine, and the whole mixture was stirred at room temperature for another 1 h. The reaction mixture was diluted with ether and washed with brine. The organic layer was dried ($MgSO_4$), filtered and evaporated *in vacuo* to give the aldehyde. This aldehyde in THF (30 mL) was reacted with phosphonium ylide prepared from 1-penten-5-triphenylphosphonium bromide and n-BuLi 1.5M in THF (500 mL) at 0°C for 20 min, then room temperature for 30 min. The reaction mixture was quenched with aqueous sat.NH_4Cl, and diluted with ether. The organic layer was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was purification by silica gel column chromatography with hexanes to give **13** (5.28 g, 62%, 2 steps). $[\alpha]_D$ = +21.1°(*c* 1.6, $CHCl_3$). IR (neat): 2900, 1650, 1470, 1260, 1080, 840, 790 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.79 (m, 1H), 5.32 (m, 2H), 4.99 (m, 2H), 4.29 (m, 1H), 2.11 (m, 5H), 1.41 (m, 4H), 0.85 (s, 9H), 0.027 (s, 3H), 0.008 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.15, 134.36, 128.07, 114.86, 70.17, 33.77, 31.36, 27.30, 25.87, 18.50, 9.83, -4.33, -4.77.

Total synthesis of crambescidin 359 (**4**) (Scheme 3) .

(2*S*, 3a*R*, 4*S*, 4'*R*)-2-[4'-(*tert*-Butyl-dimethylsilyloxy)-pentyl]-4-hydroxy-hexahydropyrrolo[1,2-b]isoxazole (16). A mixture of the nitrone **14** (600 mg, 5.9 mmol) and the olefin **15** (4 g, 17.5 mmol) in toluene (100 mL) was heated at 100°C for 24 h. After cooling, the reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with hexanes-ethyl acetate to give **16** (1.3 g, 67%). $[\alpha]_D$ = -18.9°(*c* 1.6, $CHCl_3$). IR (neat): 3300, 2950, 1470, 1380, 1260, 1080 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 4.10 (m, 1H), 3.90 (m, 1H), 3.73 (m, 1H), 3.57 (m, 1H), 3.38 (m, 1H), 3.16 (m, 1H), 2.11 (m, 3H), 1.93 (m, 1H), 1.66 (m, 6H), 1.07 (d, *J* = 6 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 78.01, 73.41, 72.31, 68.40, 55.32, 40.22, 39.63, 34.02, 33.87, 25.89, 23.73, 22.64, 18.13, -4.04, -4.72. HRMS (FAB, M+ Na): calculated for $C_{17}H_{35}NNaO_3Si$ 352.2284, found: 352.2278.

(2*S*, 3a*S*, 4'*R*)-2-[4'-(*tert*-Butyl-dimethylsilyloxy)-pentyl]-hexahydropyrrolo[1,2-b] isoxazole (17). To a stirred solution of **16** (700 mg, 2.1 mmol) in pyridine (10 mL) and dichloromethane (10 mL) at 0°C was added phenyl chlorothionoformate (0.9 mL, 6.5 mmol) and a catalytic amount of DMAP. The resulting mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography with hexanes, hexanes:ether 7:3 to give thiocarbonate (880 mg, 86%). To a solution of this thiocarbonate (880 mg, 1.8 mmol) in toluene (50 mL) was added n-Bu_3SnH (1.0 mL) and a catalytic mount of AIBN, and the resulting mixture was refluxed for 30 min. The reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography with hexanes, hexanes:ether 80:20 to give **17** (345 mg, 60%). $[\alpha]_D$ = -34.5 °(*c* 1.8, $CHCl_3$). IR (neat): 3300, 2900, 1735, 1470, 1380, 1260, 1080 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.98 (m, 1H), 3.74 (m, 2H), 3.10 (m, 2H), 2.00 (m, 2H), 1.86 (m, 2H), 1.65 (m, 1H), 1.39 (m, 6H), 1.09 (d, *J* = 6 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 76.45, 68.51, 64.89, 57.15, 42.51, 39.71, 34.06, 31.76, 25.90, 24.34, 23.72, 22.71, 18.14, -4.41, -4.72. HRMS (FAB, M+Na) calculated for $C_{17}H_{35}NaNO_2Si$ 336.2335, found: 336.2332.

(2*S*, 3a*S*, 6*S*, 6"*R*)-2-[5'-(*tert*-Butyl-dimethylsilyloxy)-3-hepten-yl]-6-[6"-(*tert*-butyl-dimethylsilyloxy)-pentyl]-hexahydropyrrolo[1,2-b] isoxazole (19). To a solution of **17** (200 mg, 0.63 mmol) in dichloromethane (10 mL) was added mCPBA (162 mg, 0.94 mmol) at 0°C and the reaction mixture was stirred for 20 min. To the reaction mixture was added large excess of $Ca(OH)_2$, and the resulting mixture was stirred at room temperature for another 20 min. The mixture was filtered through a pad of Celite and the filtrates were concentrated *in vacuo* to give **18** as a clear brown oil. A mixture of **18** and the olefin **13** (1 g, 4 mmol) in toluene (20 mL) was heated at 100°C for 2 days. After removal of the solvent *in vacuo*, the residue was purified by silica gel column chromatography with hexanes, hexanes:ether 1:1 to give **19** (240 mg, 65%, 2 steps). $[\alpha]_D$ = -29.8° (*c* 0.6, $CHCl_3$). IR (neat): 3350, 2925, 1720, 1460, 1380, 1260, 1050 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.34 (m, 2H), 4.28 (m, 1H), 4.02 (m, 1H), 3.92 (m, 1H), 3.77 (m, 2H), 3.29 (m, 1H), 2.07 (m, 2H), 1.94 (m, 2H), 1.70 (m, 2H), 1.46 (m, 19H), 1.09 (d, *J* = 6 Hz, 3H), 0.86 (s, 18H) 0.85, (t, overlaps, 3H), 0.02 (s, 6H), 0.002 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 134.76, 127.73, 74.64, 70.05, 69.04, 68.66, 64.72, 63.84, 41.78, 39.90, 39.12, 37.68, 32.77, 31.32, 31.04, 29.04, 25.90, 25.84, 24.72, 23.73, 22.04, 18.19, 18.13, 9.82, 23.69, 22.50, 21.87, 18.19, 18.13, -4.31, -4.36, -4.69, -4.74. HRMS (FAB, M+H-OH) calculated for $C_{33}H_{70}NO_3Si_2$ 584.4894, found: 584.4924.

(2*R*, 2'*S*, 2"*S*, 5*S*, 6'*S*, 7"*S*)-2-[6'-(*tert*-Butyl-dimethylsilyloxy)-2'-hydroxyheptyl]-5-[(7"-*tert*- butyl-dimethylsilyloxy)-2"hydroxy-5'-nonenyl]pyrrolidine (21). To a solution of **19** (200 mg, 0.33 mmol) in dichloromethane (10 mL) was added mCPBA (86 mg, 0.49 mmol) at 0°C and the mixture was stirred for 30 min. To the reaction mixture was added large excess of $Ca(OH)_2$, and the resulting mixture was stirred at room temperature for another 20 min. The reaction mixture was filtered through a pad of Celite and the filtrates were concentrated *in vacuo* to give **20** as a clear brown oil. This nitrone **20** was dissolved in ethanol (20 mL), and $NaBH_4$ (126 mg, 33 mmol) was added in 2 portions at 0°C. The reaction mixture was warmed to room temperature and stirred for 2 h. The solvent was concentrated *in vacuo* and the residue was taken up in aqueous K_2CO_3. The organic phase was extracted with dichloromethane, and the extracts were dried ($MgSO_4$),

filtered, and evaporated *in vacuo*. The residue was purified with hexanes, hexanes:ether 90:10, 1:1 to give hydroxylamines of desired *cis*–isomer (123 mg, 60%) and *trans*- isomer (18 mg, 9%). To an solution of the cis-hydroxylamine (50 mg, 0.08 mmol) in acetonitrile (10 mL) and water (2 mL) was added $Mo(CO)_6$ (25 mg, 0.09 mmol), and the mixture was refluxed for 3 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography with ethyl acetate and ethyl acetate:methanol 9:1 to give **21** (35 mg, 70%) as a clear brown oil. $[\alpha]_D$ = -5.1° (*c* 1.4, $CHCl_3$). IR (neat): 3355, 2925, 1720, 1680, 1260, 1050 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.30 (m, 2H), 4.29 (m, 1H), 3.91 (m, 3H), 3.76 (m, 2H), 2.07 (m, 6H), 1.82 (m, 2H), 1.66 (m, 2H), 1.44 (m, 14H), 1.08 (d, *J* = 6 Hz, 3H), 0.85 (s, 18H), 0.82 (t, overlaps, 3H), 0.02 (s, 6H), -0.05 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 134.73, 128.02, 78.11, 71.05, 70.09, 68.49, 67.54, 60.38, 57.10, 39.58, 36.79, 31.35, 30.63, 29.69, 28.48, 25.92, 25.87, 24.03, 23.69, 21.69, 21.04, 18.20, 18.14, -4.24, -4.39, -4.69. HRMS (FAB, M-OH) calculated for $C_{33}H_{70}NO_3Si_2$ 584.4894, found: 584.4900.

(-)-Crambescidin 359 (4). To a mixture of pyrrolidine **21** (161 mg, 0.27 mmol), bis-Boc-thiourea (88 mg, 0.32 mmol) and triethylamine (0.94 mmol, 0.13 mL) in DMF (2 mL) was added $HgCl_2$ (87 mg, 0.32 mmol) at 0°C, and the resulting mixture was stirred for 30 min. The reaction mixture was diluted with ethyl acetate, and filtered through a pad of Celite. The filtrates were concentrated *in vacuo*, and the residue was purified by silica gel column chromatography with hexanes, hexanes:ether 1:1, ether to give the bis-Boc protected guanidine **22**. (136 mg, 60%). To the solution of **22** (9.8 mg, 0.0116 mmol) in dichloromethane (1 mL) was added NMO (5 mg, 0.046 mmol) and a catalytic amount of tetrapropylammonium perrutenate, and the resulting mixture was stirred at 0°C for 30 min. The reaction mixture was loaded on a short silica gel column directly with hexanes:ether 1:1, ether to give the diketone **23** (9.8 mg, 100%). The solution of diketone **23** (9.8 mg, 0.0116 mmol) in toluene (2 mL) was added D-10-camphorsulfonic acid (2.7 mg, 0.0116 mmol), and the resulting mixture was heated at 110°C for 20 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography with chloroform, chloroform:methanol to give crambescidin 359 (**4**) as a camphorsulfonate (3 mg, 44%, 3 steps). The solution of camphorsulfonate of **4** (3 mg) in dichloromethane (3 mL) was added sat.$NaBF_4$ (3 mL),

and the mixture was vigorously stirred at room temperature for 2 h. The resulting mixture was extracted 5 times with chloroform, and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography with chloroform:methanol to give (-)-crambescidin 359 (**4**) as HBF_4 salt (2.3 mg). $[\alpha]_D$ = -8°(*c* 0.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.13 (brs, 1H), 8.04 (brs, 1H), 5.65 (brdd, *J* = 10.7, 6.9 Hz, 1H), 5.48 (brd, *J* = 11.2 Hz, 1H), 4.47 (m, 1H), 4.06 (m, 1H), 4.04 (m, 1H), 3.80 (m, 1H), 2.59 (dd, *J* = 12.7, 4.4 Hz, 1H), 2.54 (ddd, *J* = 15.1, 13.7, 2.0 Hz, 1H), 2.34 (m, 1H), 2.31 (m, 2H), 2.20 (m, 2H), 2.15 (m, 1H), 2.08 (m, 2H), 1.87 (dd, *J* = 15.1, 5.9 Hz, 1H), 1.77 (m, 1H), 1.73 (m, 1H), 1.71 (m, 1H), 1.70 (m, 1H), 1.60 (m, 1H), 1.55 (m, 1H), 1.48 (m, 1H), 1.44 (m, 1H), 1.34 (dd, *J* = 12.7, 12.7 Hz, 1H), 1.18 (m, 1H), 1.05 (d, *J* = 6.4 Hz, 3H), 0.82 (t, *J* = 7.1 Hz, 3H). To a solution of HBF_4 salt of **4** in chloroform (3 mL) was added sat. NH_4Cl (3 mL), and the mixture was stirred for overnight at room temperature. The resulting mixture was extracted 5 times with chloroform, and the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified again in the same way with chloroform:methanol to give (-)-crambescidin 359 (**4**) as a HCl salt (2 mg). $[\alpha]_D$ = -8°(*c* 0.2, CH_2Cl_2). IR (neat): 3450, 2850, 1660, 1630, 1470, 1180, 1100, 1030 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.93 (brs, 1H), 9.96 (brs, 1H), 5.65 (brdd, *J* = 10.3, 7.8 Hz, 1H), 5.48 (brd, *J* = 11.2 Hz, 1H), 4.51 (m, 1H), 3.99 (m, 1H), 3.98 (m, 1H), 3.86 (m, 1H), 2.55 (dd, *J* = 13.2, 4.9 Hz, 1H), 2.52 (m, 1H), 2.30 (m, 1H), 2.27 (m, 3H), 2.18 (m, 1H), 2.17 (m, 1H), 1.88 (m, 1H), 1.73 (m, 1H), 1.72 (m, 1H), 1.65 (m, 3H), 1.57 (m, 1H), 1.50 (m, 1H), 1.42 (m, 2H), 1.28 (dd, J = 12.7, 12.2 Hz, 1H), 1.16 (m, 1H), 1.05 (d, *J* = 5.9 Hz, 3H), 0.82 (t, *J* = 7.3 Hz, 3H). HRMS (FAB, M+H) calculated for $C_{21}H_{34}N_3O_2$ 360.2651, found: 360.2656.