Total Synthesis of Piericidin A1 and B1

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(6)

NH₂OH·HCl (2.58 g, 35 mmol) was added to a stirred solution of **4** (3.4 g, 24 mmol) in EtOH (50 mL) at 25 °C. The solution was allowed to stir for 18 h, after which time 100 mL of saturated aqueous NH₄Cl was added. The solution was extracted with CH₂Cl₂ (2 × 100 mL) and the organic layer was dried (MgSO₄) and concentrated to give the oxime as a light tan oil (3.62 g, 3.76 g theoretical, 96%) sufficiently pure to use without further purification: ¹H NMR (CDCl₃, 400 MHz) δ 8.82 (bs, 1H), 5.42 (s, 1H), 5.18 (s, 1H), 4.37 (q, 1H, *J* = 7.2 Hz), 1.35 (t, 1H, *J* = 7.1 Hz), 1.96 (s, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 163.8, 154.1, 136.0, 120.9, 61.8, 18.0, 14.1; IR (film) ν_{max} 3407, 2985, 1739, 1626, 1371, 1247, 1095, 1012, 975 cm⁻¹; ESI-TOF HRMS *m/z* 180.0631 ([M + Na]⁺, C₇H₁₁NO₃ requires 180.0637)

(8)

A solution of **6** (980 mg, 6.2 mmol) in CCl₄ (20 mL) was treated sequentially with Et₃N (885 μL, 6.2 mmol) and methylsulfinyl chloride (766 μL, 6.2 mmol) at 0 °C and the mixture was stirred for 10 min during which time the formation of a white precipitate was observed. The mixture was added to a separatory funnel containing 100 mL of cold H₂O and was extracted with additional CCl₄ (2 × 30 mL). The organic phase was dried (Na₂SO₄) and concentrated to yield **7** as a yellow oil: ¹H NMR (CDCl₃, 400 MHz) δ 6.11 (s, 1H), 5.91 (s, 1H), 4.42 (q, 2H, *J* = 7.2 Hz), 3.14 (s, 3H), 2.00 (s, 3H), 1.39 (t, 3H, *J* = 7.2 Hz); IR (film) ν_{max} 2936, 1738, 1593, 1454, 1371, 1247, 1158, 1073 cm⁻¹; ESI-TOF HRMS *m/z* 242.0454 ([M + Na]⁺, C₈H₁₃NO₄S requires 242.0457). The crude diene **7** was dissolved in toluene (5 mL) and **5** (1.38 g, 9.3 mmol) was added and the mixture was stirred at 50 °C for 18 h. The mixture was concentrated under reduced pressure and purified by chromatography (SiO₂, 4 × 10 cm, 5% EtOAc–hexane) to afford **8** (1.45 g, 2.28 g theoretical, 64% for two steps) as a white solid: mp 116–118 °C; ¹H NMR (acetone-*d*₆, 600 MHz) δ 4.20 (q, 2H, *J* = 7.0 Hz), 3.52 (s, 6H), 3.36 (s, 6H), 3.24 (s, 3H), 2.42 (s, 2H), 1.29 (t, 3H, *J* = 7.1 Hz); ¹³C NMR (acetone-*d*₆, 150 MHz) δ 164.8, 125.2, 100.9, 129.2, 108.7, 105.9, 61.1, 44.4, 42.6, 18.9, 14.4; IR (neat) ν_{max} 2941, 2864,

1588, 1469, 1415, 1253, 1129, 981 cm^{-1} ; ESI-TOF HRMS m/z 390.1193 ($[\text{M} + \text{Na}]^+$, $\text{C}_{14}\text{H}_{25}\text{NO}_8\text{S}$ requires 390.1190).

(9)

A stirred solution of **8** (1.45 g, 3.9 mmol) in CH_2Cl_2 (10 mL) was treated with $\text{BF}_3\cdot\text{OEt}_2$ (874 μL , 9.7 mmol) and the mixture was stirred for 1 h at 23 $^\circ\text{C}$. Saturated aqueous NaHCO_3 (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3×10 mL), dried (MgSO_4), and concentrated. Chromatography (SiO_2 , 1.5×6 cm, 5% EtOAc–hexane) afforded **9** (770 mg, 875 mg theoretical, 88%) as a white solid: mp 34–36 $^\circ\text{C}$; ^1H NMR (CDCl_3 , 400 MHz) δ 6.87 (s, 1H), 4.38 (q, 2H, $J = 7.5$ Hz), 4.05 (s, 3H), 3.91 (s, 3H), 2.54 (s, 3H), 1.41 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (CDCl_3 , 150 MHz) δ 166.0, 146.0, 133.8, 130.7, 122.6, 120.2, 60.9, 55.8, 53.7, 19.7, 14.3; IR (neat) ν_{max} 2980, 1712, 1600, 1489, 1421, 1378, 1267, 1218, 1161, 1082, 1034 cm^{-1} ; ESI-TOF HRMS m/z 226.1074 ($[\text{M} + \text{H}]^+$, $\text{C}_{11}\text{H}_{15}\text{NO}_4$ requires 226.1074)

(10)

A stirred solution of **9** (895 mg, 3.97 mmol) in toluene (40 mL) at -78 $^\circ\text{C}$ was treated with diisobutylaluminium hydride (DIBAL) in toluene (1 M, 12 mL, 12 mmol) and the resulting mixture was warmed to 0 $^\circ\text{C}$ and stirred for 1 h. The solution was treated with H_2O (1 mL) and 1 N aqueous KOH (2 mL) and warmed to 25 $^\circ\text{C}$ and filtered. Extraction with saturated NaHCO_3 (30 mL) and Et_2O (2×30 mL), drying of the organic layer (Na_2SO_4), and concentration under reduced pressure yielded **10** (670 mg, 730 mg theoretical, 92%) as a clear oil: ^1H NMR (CDCl_3 , 400 MHz) δ 6.99 (s, 1H), 4.67 (s, 2H), 4.17 (s, 1H), 4.11 (s, 3H), 3.95 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 151.7, 142.7, 142.4, 121.3, 120.9, 61.0, 56.0, 53.6, 15.8; IR (neat) ν_{max} 3425, 2949, 1599, 1488, 1411, 1262, 1112, 994 cm^{-1} ; ESI-TOF HRMS m/z 184.0963 ($[\text{M} + \text{H}]^+$, $\text{C}_9\text{H}_{13}\text{NO}_3$ requires 184.0968).

(11)

A solution of **10** (300 mg, 1.63 mmol) and imidazole (221 mg, 3.26 mmol) in DMF (6 mL) at 25 $^\circ\text{C}$ was treated with TIPSCl (596 μL , 41.9 mmol) and the mixture was stirred for 18 h. Saturated aqueous NaHCO_3 (30 mL) was added and the solution was extracted with 5:1 EtOAc–hexanes (2×50 mL) and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (SiO_2 , 1.5×6 cm, 5–10%

EtOAc–hexane) yielded **11** (523 mg, 552 mg theoretical, 95%) as a clear oil: ^1H NMR (CDCl_3 , 400 MHz) δ 6.84 (s, 1H), 4.73 (s, 2H), 3.96 (s, 3H), 3.84 (s, 3H), 2.34 (s, 3H), 1.06 (m, 3H), 1.05 (d, 18H, $J = 7.1$ Hz); ^{13}C NMR (150 MHz) δ 151.9, 143.6, 145.7, 125.9, 121.2, 66.5, 56.5, 54.3, 18.9, 18.6, 13.0; IR (neat) ν_{max} 3320, 2914, 1636, 1522, 1437, 1201, 874 cm^{-1} ; ESI–TOF HRMS m/z 340.2301 ($[\text{M} + \text{H}]^+$, $\text{C}_{18}\text{H}_{33}\text{NO}_3\text{Si}$ requires 340.2302).

(12)

$n\text{BuLi}$ (1.4 mL of a 2 M solution in hexanes, 2.8 mmol) was slowly added to **11** (200 mg, 0.6 mmol) at -78 $^{\circ}\text{C}$ in THF (15 mL). The mixture was warmed to 0 $^{\circ}\text{C}$ and stirred for 1 h before being re-cooled to -78 $^{\circ}\text{C}$. Trimethyl borate (412 μL , 3.6 mmol) was added and the mixture was stirred for 30 min. A solution of peracetic acid (32 wt % in dilute acetic acid, 5 mL) was added and the mixture was warmed slowly to room temperature. The mixture was cooled to 0 $^{\circ}\text{C}$ and saturated aqueous sodium hydrogensulfite (5 mL) was added. The pH of the solution was adjusted to 10 with 1 N aqueous NaOH and the solution was extracted with Et_2O (3×30 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield pure **12** (188 mg, 213 mg theoretical, 88%) as a white solid: mp 143 – 145 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 600 MHz) δ 6.30 (s, 1H), 4.87 (s, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 2.06 (s, 3H), 1.21 (m, 3H), 1.04 (m, 18H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 154.4, 152.8, 101.0, 127.5, 64.4, 60.8, 53.3, 18.8, 18.6, 11.1, 10.7; IR (neat) ν_{max} 2943, 1734, 1600, 1507, 1458, 1419, 1252, 1128, 1051, 1021 cm^{-1} ; ESI–TOF HRMS m/z 356.2252 ($[\text{M} + \text{H}]^+$, $\text{C}_{18}\text{H}_{33}\text{NO}_4\text{Si}$ requires 356.2251).

(S1)

A stirred solution of **12** (5 mg, 0.014 mmol) in THF (0.1 mL) was treated with 1 M Bu_4NF in THF (21 μL , 0.021 mmol) and the mixture was stirred for 30 min. Saturated aqueous NaHCO_3 (1 mL) was added and the solution was extracted with Et_2O (3×2 mL), dried (MgSO_4), and concentrated. Flash chromatography (SiO_2 , 0.5×3 cm, 5% EtOAc–hexane) yielded **S1** (4 mg, 5 mg theoretical, 80%) as a white solid: ^1H NMR (CDCl_3 , 500 MHz) δ 6.24 (s, 1H), 4.79 (s, 2H), 4.02 (s, 3H), 3.96 (s, 3H), 2.29 (s, 3H), 1.23 (m, 3H), 1.15 (d, 18H, $J = 6.9$ Hz); ^{13}C NMR (CDCl_3 , 150 MHz) δ 155.0, 154.1, 150.3, 129.7, 114.7, 67.0, 61.4, 54.0, 18.8, 12.9, 10.9; IR (neat) ν_{max} 2942, 2866, 1589, 1419, 1388, 1258, 1192, 1127, 1062, 998, 882 cm^{-1} ; ESI–TOF HRMS m/z 356.2252 ($[\text{M} + \text{H}]^+$, $\text{C}_{18}\text{H}_{33}\text{NO}_4\text{Si}$ requires 356.2251).

(13)

A stirred solution **12** (160 mg, 0.45 mmol) in degassed THF (10 mL) was treated with 1 M Bu₄NF in THF (1.35 mL, 1.35 mmol) and the mixture was stirred for 36 h at 25 °C. Saturated aqueous NH₄Cl (20 mL) was added and the solution was extracted with Et₂O (3 × 20 mL), dried (Na₂SO₄) and concentrated under reduced pressure to yield **13** (85 mg, 89 mg theoretical, 96%) as a pure white solid: mp 145–147 °C; ¹H NMR (CDCl₃, 600 MHz) δ 6.33 (s, 1H), 4.56 (s, 2H), 4.55 (s, 1H), 4.35 (s, 1H), 4.00 (s, 3H), 3.88 (s, 3H), 2.00 (s, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 155.3, 154.6, 148.2, 129.3, 110.9, 62.0, 61.6, 54.2, 9.3; IR (neat) ν_{max} 3131, 2953, 1595, 1558, 1456, 1394, 1286, 1259, 1126, 1024, 977 cm⁻¹; ESI-TOF HRMS *m/z* 200.0918 ([M + H]⁺, C₉H₁₃NO₄ requires 200.0917).

(14)

A solution of **13** (100 mg, 0.50 mmol) in CH₂Cl₂ (5 mL) was treated with CBr₄ (165 mg, 0.50 mmol) and Ph₃P (132 mg, 0.50 mmol) at 25 °C. The reaction mixture was allowed to stir for 30 min at 25 °C before being concentrated under reduced pressure. Flash chromatography (SiO₂, 3 × 7 cm, 10–20% EtOAc–hexanes) afforded **14** (107 mg, 128 mg theoretical, 84%) as a white solid: mp 120–123 °C; ¹H NMR (CDCl₃, 600 MHz) δ 6.24 (s, 1H), 4.46 (s, 2H), 3.96 (s, 2H), 3.90 (s, 3H), 2.19 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 154.1, 153.8, 145.6, 114.4, 129.6, 60.6, 53.3, 33.1, 10.5; IR (neat) ν_{max} 3688, 3389, 2984, 1607, 1472, 1361, 1124 cm⁻¹; ESI-TOF HRMS *m/z* 262.0071 ([M + H]⁺, C₉H₁₂NO₃Br requires 260.0073).

(16)

A solution of **15** (2.80 g, 13.2 mmol), Ph₃P (3.8 g, 14.6 mmol), and 1-phenyl-1H-tetrazol-5-thiol (2.3 g, 13.2 mmol) at 0 °C in THF (100 mL) was treated with DEAD (2.5 mL, 15.8 mmol). The mixture was stirred for 30 min at 0 °C and treated with saturated aqueous NaHCO₃ (50 mL) and diluted with Et₂O (100 mL). The phases were separated and the aqueous phase was extracted with Et₂O (2 × 100 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL), dried (MgSO₄) and concentrated. This mixture was dissolved in CH₂Cl₂ and run through a short silica gel

column (5 × 5 cm) with 10% EtOAc–hexanes. Concentration of this solution and recrystallization with 1:1 hexanes–CH₂Cl₂ (25 mL) yielded **16** (3.5 g, 4.9 g theoretical, 71%) as a white solid: mp 74–76 °C; ¹H NMR (CDCl₃, 500 MHz) δ 7.56 (m, 5H), 6.06 (s, 1H), 3.49 (t, 3H, *J* = 7 Hz), 2.74 (t, 3H, *J* = 7 Hz), 1.90 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 153.8, 144.7, 133.6, 130.2, 129.8, 123.8, 77.9, 38.6, 31.1, 23.5; IR (neat) $\nu_{\max}$ 2927, 1596, 1559, 1499, 1412, 1386, 1288, 1262, 1242, 1141, 1080 cm⁻¹; ESI–TOF HRMS *m/z* 372.9964 ([M + H]⁺, C₁₂H₁₃IN₄S requires 372.9978).

(17)

A solution of **16** (1.50 g, 4.0 mmol) in EtOH (35 mL), THF (8 mL) and H₂O₂ (15 mL of a 30% aqueous solution) was treated with ammonium molybdate (988 mg, 0.8 mmol) at 25 °C. This mixture was stirred for 7 h at 25 °C and diluted with CH₂Cl₂ (50 mL) and saturated aqueous NH₄Cl (30 mL). The organic phase was separated and after further extraction of the aqueous phase with CH₂Cl₂ (2 × 30 mL) followed by drying (Na₂SO₄), the solution was concentrated under reduced pressure. Chromatography (SiO₂, 5 × 15 cm, 5% EtOAc–hexanes) yielded **17** (1.45 g, 1.63 g theoretical, 89%) as a white solid: mp 57–60 °C; ¹H NMR (CDCl₃, 600 MHz) δ 7.69 (m, 2H), 7.63 (m, 3H), 6.19 (s, 1H), 3.86 (m, 2H), 2.86 (m, 2H), 1.92 (s, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 153.2, 142.1, 132.9, 131.5, 129.8, 125.0, 78.9, 54.0, 31.7, 23.6; IR (neat) $\nu_{\max}$ 3069, 2917, 1594, 1497, 1347, 1157, 1142, 1015, 763 cm⁻¹; ESI–TOF HRMS *m/z* 426.9692 ([M + Na]⁺, C₁₂H₁₃IN₄O₂S requires 426.9698).

(S2)

A stirred solution of (*R*)-(–)-4-isopropyl-3-propionyl-2-oxazolidinone (818 mg, 4.41 mmol) in CH₂Cl₂ (15 mL) at 0 °C was treated with *i*-Pr₂NEt (923 μL, 5.30 mmol) and 1.0 M Bu₂BOTf in CH₂Cl₂ (8.83 mL, 8.83 mmol). After 30 min, the solution was cooled to –78 °C and *trans*-2-methyl-2-butenal (554 μL, 5.73 mmol) was added dropwise. After 2 h, the reaction mixture was treated with pH 7 aqueous phosphate buffer (16 mL) and a 1:1 solution of 35% aqueous H₂O₂–MeOH (16 mL) and the solution was allowed to warm slowly to 25 °C. The solvent was removed under reduced pressure and the resulting aqueous solution was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with 5% aqueous NaHCO₃ (50 mL) and saturated aqueous NaCl (50 mL), dried (MgSO₄), and concentrated under reduced pressure. Chromatography (SiO₂, 4 × 13 cm, 5–10% EtOAc–hexanes) yielded **S2** (0.78 g, 1.18 g theoretical, 67%; lit.^{S1} 81%) as a clear oil. For full characterization: see reference S1.

(S3)

A stirred solution *N,O*-dimethylhydroxylamine hydrochloride (546 mg, 5.55 mmol) in THF (5 mL) at 0 °C was treated slowly with 1.0 M Me₃Al in toluene (5.42 mL, 5.42 mmol) and the mixture was allowed to warm to 25 °C. The solution was stirred for 30 min before being recooled to 0 °C and treated slowly with a solution of **S2** (300 mg, 1.11 mmol) in THF (2 mL). The solution was allowed to warm to 25 °C and stirred for 18 h. The solution was treated with 0.5 M aqueous HCl (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. The residue was dissolved in DMF (3 mL) and treated with TBSCl (509 mg, 3.33 mmol) and imidazole (458 mg, 6.66 mmol) and stirred for 18 h at 25 °C. The resulting mixture was treated with H₂O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Mg₂SO₄) and concentrated under reduced pressure. Chromatography (SiO₂, 2 × 7 cm, 5–10% EtOAc–hexanes) yielded **S3** (119 mg, 180 mg theoretical, 66%; lit.^{S1} 65%) as a clear oil. For full characterization: see reference S1.

(18)

A solution of **S3** (75 mg, 0.23 mmol) in THF (2 mL) was treated slowly with 1 M DIBAL in toluene (0.69 mL, 0.69 mmol) at –78 °C. The solution was allowed to warm to 0 °C and stirred for 1.5 h before being treated with saturated aqueous NH₄Cl (5 mL). The mixture was allowed to warm to 25 °C, filtered through a pad of Celite, and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. Chromatography (SiO₂, 2 × 5 cm, 0.5–2% EtOAc–hexanes) yielded **18** (50 mg, 58 mg theoretical, 86%; lit.^{S1} 90%) as a clear oil. For full characterization: see reference S1.

(20)

A stirred solution of triethyl 2-phosphonopropionate (975 μL, 4.51 mmol) in THF (40 mL) was treated with NaH (60% in mineral oil, 236 mg, 5.90 mmol) at 0 °C and the mixture was allowed to stir for 10 min. This solution was treated slowly with **18** (1.05 g, 4.10 mmol) in THF (10 mL) and the mixture was allowed to warm to 25 °C and stirred for 18 h. This mixture was treated with H₂O (50 mL) and extracted with Et₂O (2 × 60 mL). The combined organic layers were dried (MgSO₄) and concentrated to yield **19** as mixture of *E:Z* isomers (7:3) that was carried forward without further purification. For characterization: see reference S2. A stirred solution of **19** in CH₂Cl₂ (80 mL) at –78 °C was treated with 1 M DIBAL in hexanes (16.4 mL, 16.4 mmol) and the mixture was

allowed to warm to 0 °C and stirred for 1 h. This solution was treated with MeOH (10 mL) and saturated aqueous NH₄Cl (20 mL) and was allowed to warm to 25 °C. This solution was filtered and extracted with CH₂Cl₂ (2 × 100 mL). The combined organic layers were dried (Mg₂SO₄) and concentrated under reduced pressure. Chromatography (SiO₂, 6 × 25 cm, 1.5% EtOAc–hexanes) yielded the desired *E*-isomer **20** (0.91 g, 1.27 g theoretical, 72% for 2 steps) as a pale yellow oil and the *Z*-isomer (0.25 g, 19%) as a pale yellow oil. For the *Z*-isomer: ¹H NMR (CDCl₃, 400 MHz) δ 5.33 (q, 1H, *J* = 6.4 Hz), 5.02 (m, 1H), 4.26 (dd, 1H, *J* = 2.0, 12.1 Hz), 3.81 (dd, 1H, *J* = 7.4, 12.1 Hz), 3.56 (d, 1H, *J* = 9.2 Hz), 2.88 (m, 1H), 2.77 (m, 1H), 1.78 (d, 3H, *J* = 1.6 Hz), 1.59 (d, 3H, *J* = 6.4 Hz), 1.57 (s, 3H), 0.84 (s, 9H), 0.73 (d, 3H, *J* = 6.8 Hz), −0.00 (s, 3H), −0.02 (s, 3H). For the *E*-isomer **20**: ¹H NMR (CDCl₃, 400 MHz) δ 5.32 (q, 1H, *J* = 6.4 Hz), 5.21 (d, 1H, *J* = 8.8 Hz), 3.99 (d, 2H, *J* = 6.0 Hz), 3.63 (d, 1H, *J* = 8 Hz), 2.56 (m, 1H), 1.67 (d, 3H, *J* = 1.0 Hz), 1.58 (d, 3H, *J* = 6.4 Hz), 1.55 (s, 3H), 0.83 (s, 9H), 0.74 (d, 3H, *J* = 6.8 Hz), −0.04 (s, 3H), −0.08 (s, 3H). For further characterization: see reference S2.

(21)

A solution of (COCl)₂ (40 μL, 0.44 mmol) in CH₂Cl₂ at −78 °C was treated with DMSO (63 μL, 0.88 mmol) and stirred for 10 min. This solution was treated with **20** (67 mg, 0.22 mmol) in CH₂Cl₂ (2 mL). After 10 min, Et₃N (628 μL, 4.4 mmol) was added and after 5 min the mixture was allowed to warm to 25 °C. This solution was extracted with saturated aqueous NaHCO₃ (10 mL) and CH₂Cl₂ (2 × 20 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. Redissolution of the residue in 1:1 hexanes–C₆H₆, filtration, and evaporation yielded **21** as a clear oil (66 mg, 67 mg theoretical, 99%): [α]_D²⁵ +3.5 (*c* 0.5, CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz) δ 9.40 (s, 1H), 6.36 (d, 1H, *J* = 10.6 Hz), 5.40 (q, 1H, *J* = 6.3 Hz), 3.81 (d, 1H, *J* = 7.6 Hz), 2.84 (m, 1H), 1.75 (s, 3H), 1.60 (d, 3H, *J* = 6.7 Hz), 1.56 (s, 3H), 0.89 (d, 3H, *J* = 6.8 Hz), 0.81 (s, 9H), −0.04 (s, 3H), −0.05 (s, 3H); IR (neat) ν_{max} 2927, 2858, 1734, 1559, 1507, 1458, 1259, 1253, 1053, 836 cm^{−1}; ESI-TOF HRMS *m/z* 319.2064 ([M + Na]⁺, C₁₇H₃₂O₂Si requires 319.2067).

(22)

A solution of **17** (166 mg, 0.41 mmol) at −60 °C in DME (30 mL) was treated slowly with a 0.5 M solution of KHMDS in toluene (0.86 mL, 0.44 mmol). The solution was allowed to stir for 20 min after which time **21** (93 mg, 0.34 mmol) in DME (3 mL) was added slowly. After 7 h at this temperature, the mixture was allowed to slowly warm to 25 °C during which time a white solid precipitated from the yellow solution. The mixture was diluted with Et₂O (20 mL) and extracted with saturated aqueous NaHCO₃.

(10 mL). The aqueous layer was extracted with Et₂O (20 mL) and the combined organic layers were dried (MgSO₄) and evaporated under reduced pressure. Chromatography (SiO₂, 2 × 6 cm, hexanes followed by 10% EtOAc–hexanes) yielded **22** (95 mg, 161 mg theoretical, 60%, 76% based on recovered starting material) as a clear oil and recovered aldehyde **21** (22 mg, 23%). For **22**: $[\alpha]_D^{25}$ –9.0 (*c* 0.2, CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz) δ 6.07 (d, 1H, *J* = 15.6 Hz), 5.92 (s, 1H), 5.42 (td, 1H, *J* = 7.1, 15.1 Hz), 5.32 (q, 1H, *J* = 6.4 Hz), 5.22 (d, 1H, *J* = 9.7 Hz), 3.63 (d, 1H, *J* = 8.0 Hz), 2.95 (m, 2H), 2.61 (m, 1H), 1.82 (s, 3H), 1.72 (s, 3H), 1.58 (d, 3H, *J* = 6.8 Hz), 1.55 (s, 3H), 0.81 (s, 9H), 0.76 (d, 3H, *J* = 6.8 Hz), –0.06 (s, 3H), –0.07 (s, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 147.1, 137.9, 137.1, 136.5, 132.6, 125.5, 122.5, 121.3, 83.5, 75.5, 42.7, 37.2, 30.3, 25.7, 23.9, 17.5, 13.0, 12.9, 10.8, –0.8, –5.1; IR (neat) $\nu_{\max}$ 2926, 2855, 1718, 1540, 1457, 1375, 1256, 1056, 964, 860, 836 cm^{–1}; ESI–TOF HRMS *m/z* 497.1715 ([M + Na]⁺, C₂₂H₃₉IOSi requires 497.1707).

(23)

A solution of **22** (90 mg, 0.19 mmol) in Et₂O (2 mL) at –78 °C was treated with 2.1 M *n*BuLi in hexanes (135 μL, 0.28 mmol) and the mixture was stirred for 20 min. After 20 min, tributyltin chloride (77 μL, 0.29 mmol) was added and after an additional 20 min the mixture was allowed to warm to 25 °C. Saturated aqueous NaHCO₃ (5 mL) was added and the mixture was extracted with Et₂O (2 × 10 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to yield essentially pure **23** that was used without further purification: ¹H NMR (CDCl₃, 500 MHz) δ 6.05 (d, 1H, *J* = 15.5 Hz), 5.54 (td, 1H, *J* = 7.5, 15.5 Hz), 5.51 (s, 1H), 5.32 (q, 1H, *J* = 6.5 Hz), 5.18 (d, 1H, *J* = 9.5 Hz), 3.6 (d, 1H, *J* = 8.0 Hz), 2.90 (d, 2H, *J* = 7 Hz), 2.62 (m, 1H), 1.75 (s, 3H), 1.74 (s, 3H), 1.59 (d, 3H, *J* = 7.0 Hz), 1.56 (s, 3H), 1.51–1.46 (m, 6H), 1.35–1.28 (m, 6H), 0.92–0.88 (m, 15H), 0.81 (s, 9H), 0.77 (d, 3H, *J* = 6.5 Hz), –0.06 (s, 3H), –0.07 (s, 3H); IR (neat) $\nu_{\max}$ 2325, 2854, 1457, 1375, 1256, 1056, 962, 851, 835 cm^{–1}.

(24)

A solution of **23** (57 mg, 0.09 mmol) and **14** (23 mg, 0.09) in dioxane (800 μL) was treated sequentially with LiCl (16 mg, 0.34 mmol), Pd₂(dba)₃ (20 mg, 0.023 mmol) and a 10% solution of P(*t*Bu)₃ in hexanes (40 μL, 0.046 mmol). The solution was warmed at 70 °C and stirred for 18 h. The solution was diluted with Et₂O (5 mL) and filtered and this solution was concentrated. Chromatography (SiO₂, 2 × 10 cm, 50% C₆H₆–CH₂Cl₂ followed by 5% EtOAc–hexanes) afforded **24** (35 mg, 47 mg theoretical, 74%) as a clear oil: $[\alpha]_D^{25}$ +9.6 (*c* 0.5, CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz) δ 6.04 (d, 1H, *J* = 15.6

Hz), 5.47 (dt, 1H, $J = 7.3, 15.6$ Hz), 5.40 (t, 1H, $J = 6.6$ Hz), 5.31 (m, 1H), 5.17 (d, 1H, $J = 9.6$ Hz), 3.95 (s, 3H), 3.86 (s, 3H), 3.62 (d, 1H, $J = 8$ Hz), 3.37 (d, 2H, $J = 6.8$ Hz), 2.77 (d, 2H, $J = 6.8$ Hz), 2.60 (m, 1H), 2.09 (s, 3H), 1.73 (s, 3H), 1.71 (s, 3H), 1.58 (d, 3H, $J = 6.4$ Hz), 1.55 (s, 3H), 0.80 (s, 9H), 0.75 (d, 3H, $J = 6.8$ Hz), -0.07 (s, 3H), -0.08 (s, 3H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 153.9, 153.5, 151.0, 137.2, 136.6, 135.4, 135.2, 133.0, 127.7, 125.0, 121.8, 121.1, 111.9, 83.6, 60.6, 53.0, 43.2, 37.2, 34.5, 29.7, 25.7, 17.5, 16.4, 13.1, 12.9, 10.8, 10.4, -4.95; IR (neat) ν_{max} 3362, 2962, 2359, 1587, 1469, 1260, 1085, 1018 cm^{-1} ; ESI-TOF HRMS m/z 530.3662 ($[\text{M} + \text{H}]^+$, $\text{C}_{31}\text{H}_{51}\text{NO}_4\text{S}$ requires 530.3662).

Piericidin A1 (**1**)

A solution of **24** (25 mg, 0.06 mmol) in THF (1 mL) over 4Å mol sieves was treated with 1 M Bu_4NF in THF (180 μL , 0.18 mmol) and the reaction mixture was warmed at 50 °C and stirred for 18 h. The reaction mixture was treated with saturated aqueous NH_4Cl (5 mL) and extracted with Et_2O (3×5 mL). The organic layer was dried (Na_2SO_4) and concentrated. Chromatography (SiO_2 , 2×6 cm, 10–20% EtOAc –hexanes) afforded **1** (25 mg, 27 mg theoretical, 93%) as a pale yellow oil: $[\alpha]_{\text{D}}^{25} +1.8$ (c 0.1, MeOH), +9.6 (c 0.5, CH_2Cl_2); ^1H NMR (CDCl_3 , 600 MHz) δ 6.09 (d, 1H, $J = 15.5$ Hz), 5.60 (dt, 1H, $J = 7.2, 15.5$ Hz), 5.49 (m, 1H), 5.42 (t, 1H, $J = 7$ Hz), 5.21 (d, 1H, $J = 9.5$ Hz), 3.95 (s, 3H), 3.86 (s, 3H), 3.62 (d, 1H, $J = 9$ Hz), 3.37 (d, 2H, $J = 7$ Hz), 2.79 (d, 2H, $J = 7$ Hz), 2.68 (m, 1H), 2.09 (s, 3H), 1.81 (s, 3H), 1.75 (s, 3H), 1.64 (s, 3H), 1.63 (s, 3H), 0.81 (d, 3H, $J = 7$ Hz); ^{13}C NMR (CDCl_3 , 150 MHz) δ 153.9, 153.5, 150.8, 136.1, 135.7, 135.5, 134.8, 133.1, 127.8, 126.8, 123.6, 122.2, 111.9, 82.8, 60.6, 53.0, 43.1, 36.9, 34.4, 17.4, 16.6, 13.2, 13.1, 10.5, 10.4; IR (neat) ν_{max} 2927, 2852, 1469, 1408, 1252, 1195, 1129, 1048, 968, 835 cm^{-1} ; ESI-TOF HRMS m/z 416.2799 ($[\text{M} + \text{H}]^+$, $\text{C}_{25}\text{H}_{37}\text{NO}_4$ requires 416.2795).

Piericidin A1 Pivolate (**25**)

A solution of **1** (5 mg, 0.012 mmol) in aqueous 5 N NaOH (100 μL) and CH_2Cl_2 (100 μL) was treated with HSO_4NBu_4 (0.5 mg) and trimethylacetyl chloride (3 mg, 0.024 mmol). The mixture was allowed to stir at 25 °C for 30 min. The reaction mixture was treated with saturated aqueous NH_4Cl (5 mL) and extracted with Et_2O (3×5 mL). The organic layer was dried with (Na_2SO_4) and concentrated to yield pure **25** (5.5 mg, 6 mg theoretical, 92%) as a white solid: ^1H NMR (CDCl_3 , 600 MHz) δ 6.09 (d, 1H, $J = 15.5$ Hz), 5.60 (dt, 1H, $J = 7.2, 15.5$ Hz), 5.49 (m, 1H), 5.42 (t, 1H, $J = 7$ Hz), 5.21 (d, 1H, $J = 9.5$ Hz), 3.95 (s, 3H), 3.86 (s, 3H), 3.62 (d, 1H, $J = 9$ Hz), 3.39 (d, 2H, $J = 7$ Hz), 2.79 (d, 2H, $J = 7$ Hz), 2.68 (m, 1H), 1.99 (s, 3H), 1.81 (s, 3H), 1.74 (s, 3H), 1.64 (s, 3H), 1.63 (s,

3H), 1.39 (s, 9H), 0.81 (d, 3H, $J = 7$ Hz); ESI-TOF HRMS m/z 500.3366 ($[M + H]^+$, $C_{30}H_{45}NO_5$ requires 500.3366).

Piericidin B1 Pivolate (**26**)

A solution of **25** (4 mg, 0.01 mmol) in DMF (100 μ L) was treated with NaH (0.8 mg in 60% mineral oil, 0.02 mmol) and MeI (4 μ L, 0.03 mmol) and the mixture was allowed to stir at 25 °C for 1 h. The solution was treated with saturated aqueous NH_4Cl (5 mL) and extracted with Et_2O (2×5 mL). The organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (SiO_2 , 1×4 cm, 5% EtOAc–hexanes) provided **26** (4 mg, 5.1 mg theoretical, 78%) as a clear oil: 1H NMR ($CDCl_3$, 600 MHz) δ 6.08 (d, 1H, $J = 15.5$ Hz), 5.51 (dt, 1H, $J = 7.2, 15.5$ Hz), 5.40 (m, 2H), 5.29 (d, 1H, $J = 8.5$ Hz), 3.96 (s, 3H), 3.75 (s, 3H), 3.65 (d, 1H, $J = 6.5$ Hz), 3.39 (d, 2H, $J = 9$ Hz), 3.12 (s, 3H), 2.79 (d, 2H, $J = 6$ Hz), 2.64 (m, 1H), 1.99 (s, 3H), 1.74 (s, 3H), 1.73 (s, 3H), 1.64 (s, 3H), 1.61 (s, 3H), 1.39 (s, 9H), 0.78 (d, 3H, $J = 7$ Hz); ESI-TOF HRMS m/z 520.3024 ($[M + H]^+$, $C_{31}H_{47}NO_5$ requires 520.3033).

Piericidin B1 (**2**)

A solution of **26** (4 mg, 0.007 mmol) in MeOH (200 μ L) was treated with *t*-BuONa (2.6 mg, 0.028 mmol) at 25 °C and the mixture was allowed to stir for 3 h. The solution was treated with Et_2O (5 mL) and saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with Et_2O (5 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (SiO_2 , 1×4 cm, 10% EtOAc–hexanes) provided **2** (2.8 mg, 3.2 mg theoretical, 88%) as a yellow oil: $[\alpha]_D^{25} +2.1$ (c 0.25, CH_2Cl_2), -7.3 (c 0.42, MeOH); 1H NMR ($CDCl_3$, 500 MHz) δ 6.14 (s, 1H), 6.08 (d, 1H, $J = 15.5$ Hz), 5.51 (dt, 1H, $J = 7.5, 15.5$ Hz), 5.41 (m, 2H), 5.29 (d, 1H, $J = 9$ Hz), 3.95 (s, 3H), 3.86 (s, 3H), 3.36 (d, 1H, $J = 7$ Hz), 3.16 (d, 2H, $J = 8.5$ Hz), 3.12 (s, 3H), 2.78 (d, 2H, $J = 6.5$ Hz), 2.64 (m, 1H), 2.09 (s, 3H), 1.74 (s, 3H), 1.64 (d, 3H, $J = 6.5$ Hz), 1.55 (s, 3H), 1.53 (s, 3H), 0.77 (d, 3H, $J = 6.5$ Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 153.9, 153.5, 150.9, 136.4, 135.1, 135.0, 133.9, 133.3, 127.7, 125.1, 124.2, 121.8, 111.9, 92.7, 60.6, 56.2, 53.0, 43.1, 35.4, 34.4, 17.7, 16.6, 13.0, 12.9, 10.44, 10.38; IR (neat) ν_{max} 2906, 1417, 1562, 1400, 1252, 1185, 1125 cm^{-1} ; ESI-TOF HRMS m/z 430.2955 ($[M + H]^+$, $C_{26}H_{39}NO_4$ requires 430.2952).

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