Supporting Information

Total Synthesis, Structure Revision, and Absolute Configuration of (+)-Yatakemycin

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yatakemycin (1, correct structure). Compound **39** (0.6 mg, 0.84 μmol) was dissolved in 1:2 H_2O –DMF (1.0 mL), treated with NaHCO_3 (5.0 mg, 0.06 mmol), and the mixture was stirred vigorously for 2 h at 25 $^\circ\text{C}$. Acetic acid (50 μL) was added and the solvent was removed by a N_2 stream. H_2O (2.0 mL) was added and **1** (0.5 mg, 83%, typically 83–100%) was collected by filtration as a yellow solid: ^1H NMR (pyridine- d_5 , 500 MHz) δ 13.74 (1H, br s), 12.76 (1H, br s), 11.71 (1H, br s), 10.73 (1H, br s), 7.73 (1H, s), 7.64 (1H, s), 7.52 (1H, s), 7.24 (1H, s), 6.74 (1H, s), 4.42–4.54 (4H, m), 4.03 (3H, s), 3.85 (3H, s), 3.22 (2H, t, $J = 7.8$ Hz), 2.98 (1H, dd, $J = 4.8, 8.0$ Hz), 2.49 (3H, s), 1.77 (1H, dd, $J = 4.4, 7.5$ Hz), 1.44 (1H, t, $J = 4.8$ Hz); ^1H NMR (DMF- d_6 , 500 MHz) δ 12.35 (1H, br s), 12.04 (1H, s), 11.39 (1H, s), 11.11 (1H, s), 8.65 (1H, s), 7.33 (1H, d, $J = 2.0$ Hz), 7.10 (1H, s, $J = 2.0$ Hz), 7.09 (2H, s), 7.03 (1H, s), 6.91 (1H, s), 4.68–4.74 (2H, m), 4.66 (1H, dd, $J = 5.0, 10.7$ Hz), 4.52 (1H, d, $J = 10.7$ Hz), 3.95 (3H, s), 3.90 (3H, s), 3.43 (2H, t, $J = 8.0$ Hz), 3.15 (1H, dd, $J = 7.4, 5.0$ Hz), 1.94 (1H, dd, $J = 4.0, 8.0$ Hz), 1.70 (1H, t, $J = 4.0$ Hz); IR (film) ν_{max} 1623, 1498, 1381, 1251 cm^{-1} ; ESITOF–HRMS m/z 680.1812 ($\text{M} + \text{H}^+$, $\text{C}_{35}\text{H}_{29}\text{N}_5\text{O}_8\text{S}$ requires 680.1810). TLC (SiO_2) coelution with natural yatakemycin: 6% MeOH– CHCl_3 , $R_f = 0.4$; 40% THF– C_6H_6 , $R_f = 0.45$; 15% DMF–toluene, $R_f = 0.15$ and 25% DMF–toluene, $R_f = 0.45$. HPLC coelution with a sample of natural yatakemycin (Waters Nova-Pak[®] C_{18} , 3.9×300 mm, 0.7 mL/min flow rate, 50% CH_3CN – H_2O), $t_R = 9.9$ min).

1: $[\alpha]_{\text{D}}^{23} +100$ (c 0.1, DMF). Lit¹ $[\alpha]_{\text{D}}^{24} +99.9$ (c 0.39, DMF).

ent-1: $[\alpha]_{\text{D}}^{23} -94$ (c 0.1, DMF).

yatakemycin (2, published structure). Compound **27** (1.0 mg, 1.4 μmol) was dissolved in 1:1:1 CH_3CN – H_2O –THF (2.0 mL), treated with NaHCO_3 (5.0 mg, 60 μmol), and the mixture was stirred vigorously for 1 h at 25 $^\circ\text{C}$. The reaction mixture was diluted with C_6H_6 (3 mL), washed with H_2O (3 mL), dried (MgSO_4), and the solvent was removed in vacuo. The crude residue was purified by flash chromatography (SiO_2 , 40% THF– C_6H_6) to afford **2** (0.4 mg, 40%) as a sensitive yellow solid: ^1H NMR (pyridine- d_5 , 500 MHz) δ 7.70 (1H, s), 7.52 (1H, s), 7.48 (1H, s), 7.33 (1H, s), 7.25 (1H, s), 6.85 (1H, s),

6.70 (1H, s), 4.44–4.56 (4H, m), 4.05 (3H, s), 3.87 (3H, s), 3.22 (2H, t, $J = 7.8$ Hz), 2.92–2.97 (1H, m), 2.33 (3H, s), 1.74–1.79 (1H, m), 1.44–1.48 (1H, m); IR (film) $\nu_{\max}$ 3329, 2930, 1610, 1502, 1415, 1305 cm^{-1} ; MALDI-TOF-MS (DHB) m/z 680.1786 ($M + H^+$, $C_{35}H_{29}N_5O_8S$ requires 680.1810).

yatakemycin (3, second proposed structure). Compound **34** (0.8 mg, 1.1 μmol) was dissolved in 1:1:1 $\text{CH}_3\text{CN}-\text{H}_2\text{O}-\text{THF}$ (1.5 mL), treated with NaHCO_3 (5.0 mg, 60 μmol), and the mixture was stirred for 2 h at 25 $^\circ\text{C}$. Acetic Acid (50 μL) was added, the solvent was removed under a N_2 stream, and the precipitate was collected by filtration. Flash chromatography (SiO_2 , 2–5% $\text{MeOH}-\text{CHCl}_3$) afforded **3** (0.6 mg 75%) as a yellow solid: ^1H NMR (pyridine- d_5 , 500 MHz) δ 13.75 (1H, br s), 12.88 (1H, br s), 11.72 (1H, br s), 11.35 (1H, br s), 7.71 (1H, s), 7.51 (1H, s), 7.48 (1H, s), 7.34 (1H, s), 7.25 (1H, s), 6.74 (1H, s), 4.44–4.56 (4H, m), 4.03 (3H, s), 3.87 (3H, s), 3.22 (2H, t, $J = 7.7$ Hz), 2.97 (1H, m), 2.49 (3H, s), 1.78 (1H, dd, $J = 3.7, 7.3$ Hz), 1.47 (1H, t, $J = 4.4$ Hz); IR (film) $\nu_{\max}$ 3336, 2924, 1631, 1500, 1383, 1233 cm^{-1} ; ESITOF-MS m/z 678.1653 ($M - H^-$, $C_{35}H_{29}N_5O_8S$ requires 678.1664).

3: $[\alpha]_D^{23} +76$ (c 0.1, DMF).

ent-3: $[\alpha]_D^{23} -84$ (c 0.1, DMF).

2-benzyloxy-3-methoxy-4-nitrobenzaldehyde (5). Compound **4**¹⁵ (22.0 g, 111 mmol) was dissolved in DMF (300 mL), treated with BnBr (20.0 mL, 167 mmol), K_2CO_3 (30.8 g, 223 mmol), and the mixture was stirred for 14 h at 25 $^\circ\text{C}$. The solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 (500 mL), washed with H_2O (500 mL), 5% aqueous HCl (500 mL), saturated aqueous NaHCO_3 (250 mL), and dried (MgSO_4). The solvent was removed in vacuo and the residue was purified by flash chromatography (SiO_2 , 20% $\text{EtOAc}-\text{hexanes}$) to afford **5** (23.8 g, 74%) as a yellow solid: mp 69.6–70.3 $^\circ\text{C}$ (white needles, $\text{Et}_2\text{O}-\text{hexanes}$); ^1H NMR (CDCl_3 , 400 MHz) δ 10.12 (1H, s), 7.60 (1H, d, $J = 8.5$ Hz), 7.53 (1H, d, $J = 8.9$ Hz), 7.32–7.40 (5H, m), 5.25 (2H, s), 4.09 (3H, s); ^{13}C NMR (CDCl_3 , 100 MHz) δ 187.9, 155.6, 147.3, 134.7, 133.2, 129.1, 128.85, 128.84 (2C), 128.78 (2C), 122.5, 119.4, 77.1, 62.5; IR (film) $\nu_{\max}$ 2882, 1696, 1539, 1354 cm^{-1} . Anal. Calcd for $\text{C}_{15}\text{H}_{13}\text{NO}_5$: C, 62.72; H, 4.56; N, 4.88. Found: C, 62.53; H, 4.92; N, 5.05.

2-benzyloxy-3-methoxy-4-nitrobenzoic acid (6). A solution of 80% NaClO_2 (5.40 g, 47.8 mmol) in 1 N NaH_2PO_4 (45 mL) was added dropwise to a solution of **5** (11.5 g, 39.9 mmol) and 2-methyl-2-butene (45 mL) in $t\text{-BuOH}$ (300 mL). The reaction mixture was stirred for 2 h at 25 $^\circ\text{C}$. The solvent was removed in vacuo and the crude material was dissolved in EtOAc (500 mL). The organic layer was washed with 1 N aqueous HCl (500 mL), saturated aqueous NaCl (250 mL), dried (MgSO_4), and concentrated in vacuo to afford **6** (11.8 g, 97%) as a yellow solid: mp 130.5–131 $^\circ\text{C}$ (white prisms, C_6H_6); ^1H NMR (CDCl_3 , 400 MHz) δ 7.86 (1H, d, $J = 8.8$ Hz), 7.59 (1H, d, $J = 8.8$ Hz), 7.47–7.44 (2H, s), 7.32–7.29 (2H, s), 5.25 (2H, s), 4.09 (3H, s).

m), 7.42–7.36 (3H, m), 5.27 (2H, s), 4.07 (3H, s); ^{13}C NMR (CDCl_3 , 100 MHz) δ 166.1, 153.0, 147.9, 147.3, 134.5, 129.4, 129.2 (2C), 128.9 (2C), 128.0, 126.9, 119.6, 77.6, 62.7; IR (film) ν_{max} 2948, 1694, 1527, 1355 cm^{-1} ; MALDIFT–HRMS (DHB) m/z 326.0635 ($\text{M} + \text{Na}^+$, $\text{C}_{15}\text{H}_{13}\text{NO}_6$ requires 326.0635).

2-benzyloxy-3-methoxy-4-nitroaniline (7). Compound **6** (27.9 g, 91.8 mmol) was dissolved in THF (400 mL) and treated with Et_3N (30 mL). Diphenylphosphoryl azide (26.5 g, 96.4 mmol) was added dropwise and the reaction mixture was stirred for 3 h at 25 °C. H_2O (150 mL) was added and the reaction mixture was warmed at reflux for 2 h. The solvent was removed in vacuo and the residue was treated with saturated aqueous K_2CO_3 (100 mL), diluted with H_2O (500 mL), and extracted with EtOAc (2×500 mL). The combined organic extracts were washed with saturated aqueous NaCl (500 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by flash chromatography (SiO_2 , 25% EtOAc–hexanes) to afford **7** (19.5 g, 78%) as a yellow solid: mp 87.5–87.9 °C (yellow prisms, Et_2O –hexanes); ^1H NMR (CDCl_3 , 500 MHz) δ 7.69 (1H, d, $J = 8.8$ Hz), 7.44 (2H, d, $J = 7.5$ Hz), 7.42–7.36 (3H, m), 6.42 (1H, d, $J = 8.8$ Hz), 5.06 (2H, s), 4.34 (2H, br s), 4.03 (3H, s); ^{13}C NMR (CDCl_3 , 125 MHz) δ 149.5, 147.1, 138.4, 136.8, 134.2, 128.7 (2C), 128.6, 128.5 (2C), 123.0, 108.6, 75.0, 61.8; IR (film) ν_{max} 3356, 1606, 1505, 1300, 1211 cm^{-1} ; ESITOF–HRMS m/z 297.0844 ($\text{M} + \text{Na}^+$, $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_4$ requires 297.0846).

2-benzyloxy-3-methoxy-4-nitro-*N*-(*p*-toluenesulfonyl)aniline (8). Compound **7** (1.02 g, 3.73 mmol) was dissolved in pyridine (8 mL) and treated with *p*-toluenesulfonyl chloride (1.07 g, 5.60 mmol) and the mixture was stirred for 2 h at 25 °C. The solvent was removed in vacuo, the residue was dissolved in EtOAc (200 mL) and washed with 1 N aqueous HCl (200 mL), saturated aqueous NaHCO_3 (100 mL), and saturated aqueous NaCl (100 mL). The solvent was removed in vacuo and the residue was purified by flash chromatography (SiO_2 , 16% EtOAc–hexanes) to afford **8** (1.27 g, 79%) as a white solid: mp 128.8–129.6 °C (white plates, benzene); ^1H NMR (CD_3CN , 500 MHz) δ 7.95 (1H, br s), 7.67 (2H, d, $J = 8.1$ Hz), 7.55 (1H, d, $J = 9.2$ Hz), 7.40–7.35 (5H, m), 7.32 (2H, d, $J = 8.4$ Hz), 7.30 (1H, d, $J = 9.2$ Hz), 4.92 (2H, s), 3.86 (3H, s), 2.37 (3H, s); ^{13}C NMR (CD_3CN , 125 MHz) δ 148.7, 146.1, 142.8, 141.0, 137.8, 137.2, 137.1, 131.0 (2C), 129.8 (2C), 129.7, 129.6 (2C), 128.2 (2C), 121.7, 114.1, 76.2, 62.7, 21.6; IR (film) ν_{max} 3266, 2946, 1598, 1523, 1334 cm^{-1} ; MALDIFT–HRMS (DHB) m/z 451.0945 ($\text{M} + \text{Na}^+$, $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_6\text{S}$ requires 451.0934).

2-benzyloxy-3-methoxy-*N*¹-(*p*-toluenesulfonyl)benzene-1,4-diamine (9). Compound **8** (9.70 g, 22.6 mmol) was dissolved in 1:1 dioxane–EtOH (200 mL), treated with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (25.5 g, 113.2 mmol) and the mixture was warmed at reflux for 0.5 h. Saturated aqueous NaHCO_3 (200 mL) was added and the precipitate was removed by filtration. The solvent was removed in vacuo to afford **9** (8.27 g, 92%) as an orange solid: mp 167.9–168.4 °C (beige prisms, Et_2O –hexanes); ^1H NMR (CDCl_3 , 500 MHz) δ

7.52 (2H, d, $J = 7.7$ Hz), 7.34–7.43 (3H, m), 7.23 (2H, d, partially obscured), 7.11–7.18 (3H, m), 6.47 (1H, d, partially obscured), 6.46 (1H, br s), 4.54 (2H, s), 3.76 (2H, br s), 3.69 (3H, s), 2.35 (3H, s); ^{13}C NMR (CDCl_3 , 125 MHz) δ 143.8, 143.4, 139.7, 138.7, 136.8, 136.2, 129.3 (2C), 128.7 (2C), 128.3, 127.6 (2C), 127.2 (2C), 121.0, 118.9, 110.8, 74.6, 59.8, 21.5; IR (film) ν_{max} 3369, 2965, 2926, 1615, 1497, 1162 cm^{-1} ; MALDIFT–HRMS (DHB) m/z 398.1298 (M^+ , $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_4\text{S}$ requires 398.1295).

***N*⁴-(*tert*-butyloxycarbonyl)-2-benzyloxy-3-methoxy-*N*¹-(*p*-toluenesulfonyl)benzene-1,4-diamine (10).** Compound **9** (7.95 g, 20.0 mmol) was dissolved in THF (100 mL), treated with Boc_2O (5.23 g, 24.0 mmol) and the mixture was warmed at reflux for 14 h. The solvent was removed in vacuo and the residue was purified by flash chromatography (SiO_2 , 30% EtOAc–hexanes) to afford **10** (8.85 g, 89%) as a white solid: mp 146.5–146.9 °C (white needles, benzene); ^1H NMR (CD_3CN , 500 MHz) δ 7.68 (1H, d, $J = 9.2$ Hz), 7.53 (2H, dt, $J = 8.4, 1.8$ Hz), 7.36–7.41 (3H, m), 7.31–7.34 (2H, m), 7.24 (2H, d, $J = 8.4$ Hz), 7.22 (1H, br s), 7.21 (1H, br s), 7.13 (1H, d, $J = 8.8$ Hz), 4.67 (2H, s), 3.67 (3H, s), 2.34 (3H, s), 1.49 (9H, s); ^{13}C NMR (CD_3CN , 125 MHz) δ 153.9, 145.3, 144.3, 143.1, 138.1, 137.5, 131.7, 130.6 (2C), 129.5 (2C), 129.3, 129.2 (2C), 128.1 (2C), 126.3, 119.1, 115.1, 81.1, 75.5, 61.5, 28.6 (3C), 21.6; IR (film) ν_{max} 3340, 2977, 1726, 1520, 1154 cm^{-1} ; MALDIFT–HRMS (DHB) m/z 521.1735 ($\text{M} + \text{Na}^+$, $\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_6\text{S}$ requires 521.1717).

***tert*-butyl 3-benzyloxy-2-methoxy-4-(*p*-toluenesulfonyl)iminocyclohexa-2,5-dienylidenecarbamate (11).** Compound **10** (3.60 g, 7.22 mmol) was dissolved in CHCl_3 (50 mL) and cooled to 0 °C. $\text{Pb}(\text{OAc})_4$ (3.56 g, 7.63 mmol) was added slowly as a solution in CHCl_3 (15 mL) and the combined solution was stirred for 2 h at 25 °C. The solvent was removed in vacuo and the residue was purified by flash chromatography (SiO_2 , CH_2Cl_2) to afford **11** (3.45 g, 96%) as an orange solid: mp 100.7–101.5 °C (orange needles, C_6H_6 –hexanes); ^1H NMR ($\text{DMF-}d_6$, 600 MHz, 70 °C) δ 7.95 (2H, d, $J = 8.3$ Hz), 7.90 (1H, d, $J = 7.9$ Hz), 7.52 (2H, d, $J = 8.3$ Hz), 7.30–7.36 (5H, m), 7.00 (1H, d, $J = 10.1$ Hz), 5.09 (2H, s), 3.99 (3H, s), 2.49 (3H, s), 1.59 (9H, s); IR (film) ν_{max} 2979, 1716, 1606, 1248, 1151 cm^{-1} ; ESITOF–HRMS m/z 497.1739 ($\text{M} + \text{H}^+$, $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_6\text{S}$ requires 497.1741). Anal. Calcd for $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_6\text{S}$: C, 62.89; H, 5.68; N, 5.64; S, 6.46. Found: C, 62.72; H, 5.93; N, 5.48; S, 6.77.

4-((*tert*-butyloxycarbonyl)amino)-2-benzyloxy-3,6-dimethoxy-1-((*p*-toluenesulfonyl)amino)-5,8-dihydronaphthalene (12). Compound **11** (0.868 g, 1.75 mmol) was dissolved in THF (6 mL), treated with 2-methoxybutadiene (1.0 mL), and the mixture was stirred for 48 h at 40 °C. The solvent was removed by a N_2 stream and the residue was dissolved in 10% Et_3N – CH_2Cl_2 . The solution was stirred for 4 h at 25 °C, and the solvent was removed by a N_2 stream. The crude residue was purified by flash chromatography (SiO_2 , 30% EtOAc–hexanes) to afford **12** (0.564 g, 57%) as a white solid: mp 156.5–157 °C (white needles, benzene); ^1H NMR (acetone- d_6 , 600 MHz) δ 7.79 (1H, br s), 7.53 (2H, d,

$J = 8.3$ Hz), 7.46 (1H, br s), 7.31–7.38 (3H, m), 7.21 (2H, d, $J = 6.1$ Hz), 7.13 (2H, d, $J = 7.9$ Hz), 4.83 (2H, m), 4.77 (2H, s), 3.64 (2H, partially obscured), 3.63 (3H, s), 3.58 (3H, s), 3.33 (2H, t, $J = 4.8$ Hz), 2.32 (3H, s), 1.48 (9H, s); ^{13}C NMR (acetone- d_6 , 100 MHz) δ 155.0, 153.6, 148.7, 148.2, 143.7, 139.5, 138.6, 132.1, 130.5, 130.4, 130.0 (2C), 129.8, 129.0 (2C), 128.9 (2C), 128.5, 128.2 (2C), 127.4, 90.9, 79.8, 75.1, 61.0, 54.5, 28.6 (3C), 27.7, 21.5; IR (film) ν_{max} 3111, 2976, 2933, 1694, 1161 cm^{-1} ; MALDIFT–HRMS (DHB) m/z 603.2124 (M + Na $^{+}$, C $_{31}$ H $_{36}$ N $_2$ O $_7$ S requires 603.2135).

methyl 2-(7-benzyloxy-5-((*tert*-butyloxy)carbonyl)amino-2-hydroxy-6-methoxy-1-(*p*-toluenesulfonyl)indolin-4-yl)acetate (13). A solution of **12** (1.038 g, 1.79 mmol) and Sudan III dye (1.0 mg) in CH₂Cl₂–MeOH (1:1) was cooled to –78 °C and treated with a stream of O₃ gas until the red solution became colorless. The mixture was treated with Me₂S (1.0 mL) at –78 °C, stirred at –78 °C for 0.5 h, at –10 °C for 1 h, at 0 °C for 1 h, and at 25 °C for 1 h. The solvent was removed in vacuo and the residue was purified by flash chromatography (SiO₂, 50% EtOAc–hexanes) to afford **13** (0.777 g, 71%) as a tan oil: ¹H NMR (CD₃CN, 400 MHz) δ 7.59 (2H, d, *J* = 8.4 Hz), 7.35–7.65 (5H, m), 7.28 (2H, d, *J* = 8.0 Hz), 6.08 (1H, t, *J* = 5.7 Hz), 6.03 (1H, br s), 5.08 (1H, d, *J* = 11.2 Hz), 4.91 (1H, d, *J* = 11.2 Hz), 4.70 (1H, d, *J* = 5.7 Hz), 3.70 (3H, s), 3.58 (3H, s), 3.37–3.48 (2H, m), 2.90 (1H, dd, *J* = 7.9, 16.2 Hz), 2.63 (1H, d, *J* = 16 Hz), 2.33 (3H, s), 1.44 (9H, s); ¹³C NMR (CD₃CN, 100 MHz) δ 172.2, 156.0, 151.0, 145.5, 143.8, 139.2, 138.3, 133.2, 131.4, 131.0 (2C), 129.8, 129.7 (2C), 129.3 (2C), 129.2, 128.4 (2C), 126.7, 89.5, 81.0, 75.1, 62.4, 53.1, 38.3, 35.7, 29.0 (3C), 22.1; IR (film) ν_{max} 3353, 2978, 1716, 1738, 1162 cm^{–1}; MALDIFT–HRMS (DHB) *m/z* 635.2032 (M + Na⁺, C₃₀H₃₂N₂O₈S requires 635.2034).

methyl 2-(5-amino-7-benzyloxy-6-methoxy-1-(*p*-toluenesulfonyl)indol-4-yl)acetate (14). Compound **13** (0.727 g, 1.187 mmol) was treated with anhydrous 4 N HCl–EtOAc (10 mL) and the mixture was stirred for 0.5 h at 25 °C. The solvent was removed by a N₂ stream to afford **14** (0.566 g, 96%) as a tan oil: ¹H NMR (CDCl₃, 500 MHz) δ 7.71 (1H, d, *J* = 3.7 Hz), 7.57 (2H, d, *J* = 7.0 Hz), 7.52 (2H, d, *J* = 8.4 Hz), 7.43 (2H, t, *J* = 7.2 Hz), 7.38 (1H, t, *J* = 7.3 Hz), 7.01 (2H, d, *J* = 8.1 Hz), 6.61 (1H, d, *J* = 3.7 Hz), 5.12 (2H, s), 4.23 (2H, s), 3.74 (3H, s), 3.72 (2H, s), 3.70 (3H, s), 2.30 (3H, s); ¹³C NMR (CDCl₃, 125 MHz) δ 171.9, 143.9, 140.1, 139.1, 137.9, 137.1, 136.0, 129.4, 129.1 (2C), 128.7, 128.5 (2C), 128.2 (2C), 127.73 (2C), 127.71, 121.3, 105.8, 105.2, 75.3, 60.7, 52.2, 34.2, 21.5; IR (film) ν_{max} 2939, 1726, 1360, 1171 cm⁻¹; MALDIFT–HRMS (DHB) *m/z* 495.1580 (M + H⁺, C₂₆H₂₆N₂O₆S requires 495.1584).

4-benzyloxy-5-methoxy-7-oxo-3-(*p*-toluenesulfonyl)-7,8-dihydro-6*H*-pyrrolo[3,2-*e*]indole (15). A solution of **14** (534 mg, 1.08 mmol) in acetic acid (15 mL) was stirred at 25 °C for 24 h. The solvent was removed by a N₂ stream. The residue was purified by flash chromatography (SiO₂, 50%

EtOAc–hexanes) to afford **15** (454 mg, 91%) as a white solid: mp 200.0–201.0 °C (white prisms, CH₂Cl₂–hexanes); ¹H NMR (CDCl₃, 500 MHz) δ 8.44 (1H, s), 7.80 (1H, d, *J* = 3.7 Hz), 7.55 (2H, d, *J* = 7.0 Hz), 7.50, (2H, d, *J* = 8.4 Hz), 7.43 (2H, d, *J* = 7.0 Hz), 7.38 (1H, t, *J* = 7.0 Hz), 7.02 (2H, d, *J* = 8.1 Hz), 6.47 (1H, d, *J* = 4.0 Hz), 5.13 (2H, s), 3.76 (3H, s), 3.63 (2H, s), 2.30 (3H, s); ¹³C NMR (CDCl₃, 125 MHz) δ 176.9, 144.1, 139.4, 137.5, 135.9, 135.8, 133.2, 130.6, 129.2 (2C), 128.6 (2C), 128.2 (2C), 127.9, 127.6 (2C), 126.0, 124.7, 110.9, 104.5, 75.8, 61.6, 35.7, 21.5; IR (film) ν_{max} 3148, 1732, 1703, 1616, 1167, 1038 cm⁻¹; MALDIFT–HRMS (DHB) *m/z* 463.1322 (M + H⁺, C₂₅H₂₂N₂O₅S requires 463.1322).

4-benzyloxy-5-methoxy-7-oxo-7,8-dihydro-6H-pyrrolo[3,2-*e*]indole (16). Compound **15** (203 mg, 0.439 mmol) in MeOH (12 mL) was treated with Mg granules (50 mesh, 200 mg, 8.23 mmol) and the mixture was sonicated for 1.5 h. The reaction mixture was diluted with CH₂Cl₂ (100 mL), washed with 1 N aqueous HCl (100 mL), saturated aqueous NaHCO₃ (50 mL), and dried (MgSO₄). The crude residue was purified by flash chromatography (SiO₂, 70% EtOAc–hexanes) to afford **16** (130 mg, 96%) as a tan solid: mp 201.0–201.5 °C (white prisms, CH₂Cl₂–hexanes); ¹H NMR (CD₃CN, 500 MHz) δ 10.20 (1H, s), 9.20 (1H, s), 7.56 (2H, d, *J* = 7.3 Hz), 7.39 (2H, t, *J* = 7.0 Hz), 7.33 (1H, m), 7.26 (1H, t, *J* = 2.8 Hz), 6.30 (1H, dd, *J* = 2.9, 1.8 Hz), 5.22 (2H, s), 3.91 (3H, s), 3.53 (2H, s); ¹³C NMR (CD₃CN, 125 MHz) δ 177.1, 139.0, 137.5, 134.4, 131.6, 129.2 (2C), 129.1 (2C), 128.8, 127.8, 126.8, 123.6, 110.7, 100.1, 75.8, 61.9, 36.4; IR (film) ν_{max} 3262, 2939, 1694, 1247 cm⁻¹; MALDIFT–HRMS (DHB) *m/z* 308.1171 (M⁺, C₁₈H₁₆N₂O₃ requires 308.1161).

4-benzyloxy-5-methoxy-7-oxo-1,2,7,8-tetrahydro-3H,6H-pyrrolo[3,2-*e*]indole (17). Compound **16** (141 mg, 0.459 mmol) was dissolved in glacial acetic acid (12 mL), treated with NaCNBH₃ (58.0 mg, 0.923 mmol), and stirred for 2 h at 25 °C. The solvent was removed by a N₂ stream and the residue was dissolved in EtOAc (200 mL), washed with saturated aqueous NaHCO₃ (2 × 200 mL), saturated aqueous NaCl (100 mL), and dried (Na₂SO₄). The solvent was removed in vacuo and the residue was purified by flash chromatography (SiO₂, 80% EtOAc–hexanes) to afford **17** (130 mg, 96%) as a beige solid: mp 160 °C (dec.), (beige prisms, Et₂O–hexanes); ¹H NMR (CDCl₃, 500 MHz) δ 7.96 (1H, s), 7.43 (2H, d, *J* = 7.0 Hz), 7.32–7.41 (3H, m), 5.00 (2H, s), 3.89 (3H, s), 3.47 (2H, t, *J* = 8.1 Hz), 3.39 (2H, s), 2.88 (2H, t, *J* = 8.1 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 176.3, 141.1, 137.5, 136.1, 135.8, 128.5 (2C), 128.3 (2C), 128.2, 127.3, 122.4, 117.0, 74.6, 61.2, 48.2, 35.4, 28.7; IR (film) ν_{max} 3204, 2934, 1732, 1108 cm⁻¹; MALDIFT–HRMS (DHB) *m/z* 310.1310 (M⁺, C₁₈H₁₈N₂O₃ requires 310.1317).

4-benzyloxy-3-(*tert*-butyloxy)carbonyl-5-methoxy-7-oxo-1,2,7,8-tetrahydro-3H,6H-pyrrolo[3,2-*e*]indole (18). Compound **17** (119 mg, 0.384 mmol) was dissolved in THF (7 mL), treated with Boc₂O (168 mg, 0.768 mmol), and warmed at reflux for 1.5 h. The solvent was removed by a N₂ stream and the residue was purified by flash chromatography (SiO₂, 60% EtOAc–hexanes) to afford **18** (146 mg, 93%) as a beige solid: mp 160.5–161.0 °C (white prisms, CH₂Cl₂–hexanes); ¹H NMR (CDCl₃, 600 MHz) δ

7.40 (2H, d, $J = 7.5$ Hz), 7.32 (2H, t, $J = 7.5$ Hz), 7.28 (1H, d, $J = 7.0$ Hz), 5.01 (2H, s), 4.02 (2H, t, $J = 7.5$ Hz), 3.91 (3H, s), 3.38 (2H, s), 2.80 (2H, t, $J = 7.6$ Hz), 1.47 (9H, s); ^{13}C NMR (CDCl_3 , 150 MHz) δ 176.1, 153.8, 142.2, 137.4, 136.4, 132.2, 130.9, 128.3 (2C), 128.2 (2C), 127.9, 126.9, 115.7, 80.8, 73.7, 61.4, 51.0, 35.3, 28.1 (3C), 27.9; IR (film) ν_{max} 3203, 2923, 1699, 1339, 1161 cm^{-1} ; MALDIFT–HRMS (DHB) m/z 433.1737 ($\text{M} + \text{Na}^+$, $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_5$ requires 433.1734).

3-(tert-butyloxy)carbonyl-4-hydroxy-5-methoxy-7-oxo-1,2,7,8-tetrahydro-3H,6H-pyrrolo[3,2-*e*]indole (19).

Compound **18** (98.7 mg, 0.24 mmol) was dissolved in 1:1 THF–MeOH (4 mL), treated with 10% Pd/C (20 mg) and placed under H_2 (1 atm) for 2 h. The mixture was filtered through Celite and the solvent was removed in vacuo to afford **19** (74.8 mg, 97%) as a white solid: mp 205.5–206.5 °C (white prisms, CH_2Cl_2 –hexanes); ^1H NMR (CDCl_3 , 600 MHz) δ 7.40 (1H, s), 4.00 (2H, t, $J = 8.3$ Hz), 3.90 (3H, s), 3.35 (2H, s), 2.89 (2H, t, $J = 8.3$ Hz), 1.55 (9H, s); ^{13}C NMR (CDCl_3 , 150 MHz) δ 176.1, 154.7, 139.1, 132.5, 132.4, 124.4, 124.1, 111.1, 83.0, 60.7, 49.3, 34.9, 28.3 (3C), 26.3; IR (film) ν_{max} 2916, 1689, 1633, 1421, 1370 cm^{-1} ; MALDIFT–HRMS (DHB) m/z 343.1268 ($\text{M} + \text{Na}^+$, $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_5$ requires 343.1264).

3-(tert-butyloxy)carbonyl-4-hydroxy-5-methoxy-7-thio-1,2,7,8-tetrahydro-3H,6H-pyrrolo[3,2-*e*]indole (20).

A slurry of **19** (27.7 mg, 86.5 μmol) in DME (6 mL) was treated with Lawesson's reagent (36.0 mg, 89.0 μmol) and the mixture was stirred vigorously for 1.5 h at 25 °C. The solvent was removed by a N_2 stream and the residue was purified by flash chromatography (SiO_2 , 4% Et_2O – CH_2Cl_2) to afford **20** (28.0 mg, 96%) as a yellow solid: mp 168 °C (dec.), (yellow prisms, CH_2Cl_2 –hexanes); ^1H NMR ($\text{THF}-d_8$, 500 MHz) δ 9.31 (1H, s), 4.00 (2H, t, $J = 8.4$ Hz), 3.93 (3H, s), 3.87 (2H, s), 2.90 (2H, t, $J = 8.4$ Hz), 1.55 (9H, s); ^{13}C NMR ($\text{THF}-d_8$, 125 MHz) δ 204.3, 155.9, 140.5, 137.2, 133.4, 125.9, 124.8, 117.7, 83.5, 60.8, 50.6, 48.8, 28.6 (3C), 26.8; IR (film) ν_{max} 2993, 1661, 1455, 1146 cm^{-1} ; MALDIFT–HRMS (DHB) m/z 337.1223 ($\text{M} + \text{H}^+$, $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$ requires 337.1216).

7-acetylthio-3-((tert-butyloxy)carbonyl)-4-hydroxy-5-methoxy-1,2-dihydro-3H-pyrrolo[3,2-*e*]indole (21).

Compound **20** (10.3 mg, 31.5 μmol) was dissolved in CH_2Cl_2 (3 mL), treated with Ac_2O (100 μL , 90.1 mmol), pyridine (150 μL , 195 mmol), and stirred for 7 h at 25 °C. The reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with 1 N aqueous HCl (2×10 mL), saturated aqueous NaHCO_3 (5 mL), and dried (MgSO_4). Flash chromatography (SiO_2 , 4% Et_2O – CH_2Cl_2) afforded **21** (9.2 mg, 77%) as a yellow solid: mp 170–171 °C (white prisms, Et_2O –hexanes); ^1H NMR (CDCl_3 , 500 MHz) δ 8.33 (1H, s), 6.48 (1H, d, $J = 2.2$ Hz), 4.08 (2H, t, $J = 8.4$ Hz), 4.02 (3H, s), 3.15 (2H, t, $J = 8.4$ Hz), 2.41 (3H, s), 1.56 (9H, s); ^{13}C NMR (CDCl_3 , 125 MHz) δ 195.0, 155.0, 136.6, 132.6, 130.9, 125.5, 119.7, 118.1, 118.0, 109.0, 82.6, 60.2, 49.7, 29.8, 28.4 (3C), 26.7; IR (film) ν_{max} 3307, 2925, 1699, 1652, 1428, 1152 cm^{-1} ; MALDIFT–HRMS (DHB) m/z 378.1234 (M^+ , $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_5\text{S}$ requires 378.1244).

methyl 5-(benzyloxy)-3,6-bis(*tert*-butoxycarbonyl)-1-(chloromethyl)-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylate (22). Compound **22** was prepared according to literature methods¹³ and resolved by semi-preparative chiral HPLC (Daicel CHIRALCEL[®] OD column, 2 × 25 cm, 2% *i*-PrOH–hexanes, 7 mL/min, t_R : 33.9 min (*S*)-**22**, 41.3 min (*R*)-**22**). For (*S*)-**22**: $[\alpha]_D^{23}$ –14 (*c* 1.3, CHCl₃); for (*R*)-**22**: $[\alpha]_D^{23}$ +13 (*c* 1.5, CHCl₃).

methyl 3-[(6-hydroxy-5-methoxyindol-2-yl)carbonyl]-1-(chloromethyl)-5-benzyloxy-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylate (24). Compound **22** (15.5 mg, 0.0272 mmol) was dissolved in 4 N HCl–EtOAc (1 mL) and warmed at 70 °C for 1 h. The solution was cooled to 25 °C, the solvent was removed by a N₂ stream, and the sample was dried under high vacuum for 3 h. The crude residue was dissolved in DMF (0.15 mL), treated with EDCI (20.8 mg, 0.109 mmol), 6-hydroxy-5-methoxyindole-2-carboxylic acid¹⁴ (**23**, 6.7 mg, 0.033 mmol), and NaHCO₃ (2.3 mg, 0.027 mmol). The reaction mixture was stirred for 12 h at 25 °C, poured over saturated aqueous NaCl (5 mL), filtered, and washed with H₂O. The crude residue was taken on to the next step but could be purified by flash chromatography (SiO₂, 66% EtOAc–hexanes) to afford **24** (13.9 mg, 78%) as an off-white solid: mp 153–154 °C (dec.); ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.05 (1H, s), 8.07 (1H, s), 7.64 (2H, d, *J* = 7.1 Hz), 7.41 (2H, t, *J* = 7.3 Hz), 7.33–7.36 (3H, m), 7.09 (1H, s), 6.97 (1H, s), 6.88 (1H, s), 5.28 (2H, s), 4.73 (1H, t, *J* = 10.6 Hz), 4.42 (1H, dd, *J* = 6.8, 4.1 Hz), 4.11 (2H, m), 3.99 (1H, dd, *J* = 7.8, 3.3 Hz), 3.87 (3H, s), 3.79 (3H, s); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ 161.4, 159.6, 146.5, 145.0, 144.9, 138.5, 136.9, 131.8, 128.7, 128.4, 128.3 (2C), 127.7, 127.4 (2C), 126.3, 123.6, 119.9, 114.1, 106.6, 105.6, 102.6, 98.3, 97.2, 69.4, 55.8, 54.5, 51.8, 47.5, 42.0; IR (film) ν_{max} 3321, 2950, 1316, 1211 cm^{–1}; MALDIFT–HRMS (DHB) *m/z* 559.1507 (M⁺, C₃₀H₂₆ClN₃O₆ requires 559.1505).

(*S*)-**24**: $[\alpha]_D^{23}$ –4.0 (*c* 0.20, acetone).

(*R*)-**24**: $[\alpha]_D^{23}$ +3.4 (*c* 0.35, acetone).

3-[(6-hydroxy-5-methoxyindol-2-yl)carbonyl]-1-(chloromethyl)-5-benzyloxy-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylic acid (25). Compound **24** (30.2 mg, 0.0541 mmol) was dissolved in 3:2:1 THF–MeOH–H₂O (1.0 mL), treated with LiOH·H₂O (6.9 mg, 0.168 mmol), and the mixture was stirred for 14 h at 25 °C. 1 N aqueous HCl was added until the pH was less than 6, and the solution was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with saturated aqueous NaCl (5 mL), dried (Na₂SO₄), and concentrated in vacuo. The crude residue was purified by flash

chromatography (SiO₂, 50% EtOAc–hexanes containing 1% HOAc), and azeotropically dried with toluene to afford **25** (23.0 mg, 78%) as an off-white solid: mp 155–156 °C (dec.); ¹H NMR (acetone-*d*₆, 400 MHz) δ 11.00 (1H, br s), 10.50 (1H, br s), 8.22 (1H, s), 7.60 (2H, d, *J* = 7.2 Hz), 7.41 (2H, t, *J* = 7.0 Hz), 7.34 (1H, t, *J* = 7.3 Hz), 7.31 (1H, s), 7.18 (1H, s), 7.00 (1H, s), 7.03 (1H, s), 5.30 (2H, s), 4.80 (1H, t, *J* = 9.4 Hz), 4.64 (1H, dd, *J* = 6.8, 3.8 Hz), 4.18–4.21 (2H, m), 3.98 (1H, dd, *J* = 7.8, 2.9 Hz), 3.90 (3H, s); ¹³C NMR (acetone-*d*₆, 100 MHz) δ 162.6, 160.7, 147.6, 146.5, 145.5, 140.1, 138.1, 133.0, 130.4, 130.1, 129.3 (2C), 128.84 (2C), 128.79, 127.4, 125.1, 121.9, 115.2, 107.1, 106.8, 103.2, 99.4, 97.6, 70.9, 56.6, 55.8, 48.0, 43.9; IR (film) ν_{max} 3385, 1692, 1308, 1195 cm⁻¹; MALDIFT–HRMS (DHB) *m/z* 545.1340 (M⁺, C₂₉H₂₄ClN₃O₆ requires 545.1353).

(*S*)-**25**: [α]_D²³ +8 (*c* 0.20, acetone).

(*R*)-**25**: [α]_D²³ –8 (*c* 0.20, acetone).

3-[(6-hydroxy-5-methoxyindol-2-yl)carbonyl]-1-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylic acid (26**).** Compound **25** (23.0 mg, 0.0421 mmol) was dissolved in THF (2.0 mL), treated with 10% Pd/C (5 mg), and placed under H₂ (1 atm) at 25 °C for 2 h. The mixture was filtered through Celite, concentrated in vacuo, and then precipitated by the addition of CH₂Cl₂ to afford **26** (16.2 mg, 85%) as a beige solid: mp 220–221 °C (dec.); ¹H NMR (acetone-*d*₆, 500 MHz) δ 10.46 (1H, br s), 8.01 (1H, s), 7.29 (1H, s), 7.18 (1H, s), 7.05 (1H, d, *J* = 1.8 Hz), 7.02 (1H, s), 4.79 (1H, t, *J* = 10.3 Hz), 4.62 (1H, dd, *J* = 6.6, 4.0 Hz), 4.19 (2H, m), 3.90 (3H, s), 3.88 (1H, m); ¹³C NMR (acetone-*d*₆, 125 MHz) δ 162.7, 160.6, 147.6, 145.5, 144.5, 140.1, 132.9, 130.5, 128.8, 126.8, 125.5, 121.9, 114.1, 106.9, 106.7, 103.2, 102.1, 97.7, 56.6, 55.8, 48.1, 44.0; IR (film) ν_{max} 3353, 1599, 1310 cm⁻¹; MALDIFT–HRMS (DHB) *m/z* 456.0949 (M + H⁺, C₂₂H₁₈ClN₃O₆ requires 456.0957).

(*S*)-**26**: [α]_D²³ –3.5 (*c* 0.29, THF).

(*R*)-**26**: [α]_D²³ +3.4 (*c* 0.32, THF).

seco-yatakemycin (27**, for published structure).** Compound **21** (5.0 mg, 13.2 mmol) was dissolved in 10% TFA–CH₂Cl₂ (0.5 mL) and stirred for 0.5 h. The reaction was diluted with benzene (1.0 mL), the combined solvent was removed by a N₂ stream, and the residue was dried under high vacuum for 3 h. The counterion was exchanged by dissolving the crude residue in a solution of 3:2:1 THF–MeOH–H₂O saturated with NaCl (1 mL). The solvent was removed by a N₂ stream, and the amine hydrochloride salt was isolated by trituration with THF. The solvent was removed in vacuo and the residue was dissolved in DMF (0.15 mL), treated with EDCI (6.5 mg, 33.9 μmol) and **26** (4.0 mg, 8.8 μmol) and stirred for 24 h at 25 °C. The solvent was removed by a N₂ stream and the residue was purified by flash chromatography (SiO₂, 40% THF–C₆H₆). The residue was trituated with Et₂O (2 × 1.0 mL) to afford **27** (2.0 mg, 32%, typically 30–40%, unoptimized) as a tan solid: ¹H NMR (acetone-*d*₆, 500 MHz) δ

10.77 (1H, s), 10.64 (1H, s), 10.53 (1H, s), 10.48 (1H, s), 8.91 (1H, s), 8.04 (1H, s), 7.55 (1H, s), 7.48 (1H, d, $J = 1.5$ Hz), 7.18 (1H, s), 7.06 (1H, s), 7.03 (1H, s), 6.64 (2H, d, $J = 2.2$ Hz), 4.83–4.94 (2H, m), 4.81 (1H, t, $J = 9.5$ Hz), 4.65 (1H, dd, $J = 4.0, 11.0$ Hz), 4.18–4.27 (2H, m), 3.95 (2H, s), 3.91 (3H, s), 3.87–3.92 (1H, m), 3.40 (2H, t, $J = 7.89$ Hz), 2.39 (3H, s); IR (film) $\nu_{\max}$ 3371, 1697, 1607, 1456 cm^{-1} ; MALDI-TOF-MS (DHB) m/z 715.1483 (M^+ , $\text{C}_{35}\text{H}_{30}\text{ClN}_5\text{O}_8\text{S}$ requires 715.1498).

(*S*)-**27**: $[\alpha]_{\text{D}}^{23} -6.0$ (c 0.33, THF).

(*R*)-**27**: $[\alpha]_{\text{D}}^{23} +4.8$ (c 0.33, THF).

methyl 4-benzyloxy-5-methoxy-1,2-dihydro-3H-pyrrolo[3,2-*e*]indole-7-carboxylate (29).

Compound **28** (83.0 mg, 0.237 mmol) was dissolved in glacial acetic acid (4 mL), treated with NaCNBH_3 (74.4 mg, 1.18 mmol), and stirred for 2 h at 25 °C. The solvent was removed by a N_2 stream and the residue was dissolved in EtOAc (100 mL), washed with saturated aqueous NaHCO_3 (2×100 mL), saturated aqueous NaCl (50 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was purified by flash chromatography (SiO_2 , 40% EtOAc–hexanes) to afford **29** (69.0 mg, 83%) as tan oil: ^1H NMR (CDCl_3 , 500 MHz) δ 8.82 (1H, br s), 7.32–7.49 (5H, m), 6.99 (1H, d, $J = 2.2$ Hz), 5.10 (2H, s), 4.01 (3H, s), 3.93 (3H, s), 3.58 (2H, t, $J = 8.4$ Hz), 3.16 (2H, t, $J = 8.4$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 162.2, 141.0, 137.6, 137.2, 137.0, 128.5 (2C), 128.2 (2C), 128.1, 127.2, 127.1, 121.9, 114.9, 106.3, 74.8, 61.3, 51.8, 48.3, 29.5; IR (film) $\nu_{\max}$ 3333, 2945, 1704, 1531, 1511, 1279, 1258 cm^{-1} ; ESITOF-MS m/z 353.1496 ($M + \text{H}^+$, $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_4$ requires 353.1488).

methyl 3-(tert-butyloxy)carbonyl-4-benzyloxy-5-methoxy-1,2-dihydro-3H-pyrrolo[3,2-*e*]indole-7-carboxylate (30).

Compound **29** (69.0 mg, 0.196 mmol) was dissolved in THF (6 mL), treated with Boc_2O (85.6 mg, 0.392 mmol), and the mixture was warmed at reflux for 1.5 h. The solvent was removed by a N_2 stream and the residue was purified by flash chromatography (SiO_2 , 25% EtOAc–hexanes) to afford **30** (83.6 mg, 94%) as a tan oil: ^1H NMR (CDCl_3 , 500 MHz) δ 8.92 (1H, br s), 7.25–7.44 (5H, m), 7.04 (1H, d, $J = 2.2$ Hz), 5.05 (2H, s), 4.14 (2H, t, $J = 7.7$ Hz), 4.05 (3H, s), 3.94 (3H, s), 3.09 (2H, t, $J = 7.7$ Hz), 1.47 (9H, s); ^{13}C NMR (CDCl_3 , 125 MHz) δ 162.0, 154.5, 141.1, 137.8, 137.6, 131.9, 129.7, 128.3 (2C), 128.1 (2C), 127.8, 127.5, 121.6, 120.7, 107.0, 80.5, 74.3, 61.4, 51.9, 51.6, 28.6, 28.1 (3C); IR (film) $\nu_{\max}$ 3320, 2975, 1703, 1367, 1288, 1161 cm^{-1} ; ESITOF-MS m/z 453.2020 ($M + \text{H}^+$, $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_6$ requires 453.2020).

methyl 3-(tert-butyloxy)carbonyl-4-hydroxy-5-methoxy-1,2-dihydro-3H-pyrrolo[3,2-*e*]indole-7-carboxylate (31). Compound **30** (83.0 mg, 0.183 mmol) was dissolved in 1:1 THF–MeOH (3 mL),

treated with 10% Pd/C (10 mg), and the mixture was stirred for 4 h under 1 atm of H₂. The mixture was filtered through Celite, and concentrated in vacuo to afford **31** (61.0 mg, 92%) as a white solid, which was identical in all respects to authentic compound.^{19b}

3-((*tert*-butyloxy)carbonyl)-4-hydroxy-5-methoxy-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylic acid (32**).** Compound **31** (28.4 mg, 0.0784 mmol) was dissolved in 3:2:1 THF–MeOH–H₂O (2 mL), treated with LiOH·H₂O (12.9 mg, 0.314 mmol), and warmed at 65 °C for 2 h. The mixture was cooled to 25 °C, treated with 1 N aqueous HCl until the pH was less than 6, and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with saturated aqueous NaCl (5 mL), dried (Na₂SO₄), and concentrated in vacuo to afford **32** (25.9 mg, 95%) as a white solid, which was identical in all respects to authentic compound.^{19c}

methyl 3-((*tert*-butyloxy)carbonyl)-4-hydroxy-5-methoxy-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-thiocarboxylate (33**).** Compound **32** (15.3 mg, 44.0 μmol) was dissolved in DMF (2 mL), treated with EDCI (52.0 mg, 0.271 mmol), and HOAt (6.0 mg, 44 μmol). The solution was stirred for 0.5 h at 0 °C then cooled to –15 °C. MeSH was bubbled through the reaction vessel and the mixture was capped and stirred for 2 h at 0 °C. The crude mixture was poured onto EtOAc (50 mL) and washed with 1 N aqueous HCl (50 mL), saturated aqueous NaHCO₃ (50 mL), saturated aqueous NaCl (50 mL) and dried (Na₂SO₄). The solvent was removed in vacuo and the residue was purified by flash chromatography (SiO₂, 20% EtOAc–hexanes) to afford **33** (13.0 mg, 82%) as a light yellow solid: mp 180 °C (dec.), (white plates, CH₂Cl₂–hexanes); ¹H NMR (CDCl₃, 400 MHz) δ 8.87 (1H, s), 7.07 (1H, d, *J* = 2.6 Hz), 4.11 (2H, t, *J* = 8.6 Hz), 4.01 (3H, s), 3.19 (2H, t, *J* = 8.6 Hz), 2.49 (3H, s), 1.57 (9H, s); ¹³C NMR (CDCl₃, 100 MHz) δ 183.3, 155.0, 138.9, 133.6, 132.7, 130.4, 126.8, 119.6, 117.5, 106.3, 82.9, 60.7, 49.7, 28.4 (3C), 26.7, 11.1; IR (film) ν_{max} 3336, 2932, 1651, 1622, 1428, 1145 cm^{–1}; ESITOF–HRMS *m/z* 401.1137 (M + Na⁺, C₁₈H₂₂N₂O₅S requires 401.1142).

seco-yatakemycin (34**, for second proposed structure).** Compound **33** (3.64 mg, 9.6 μmol) was dissolved in 4 N HCl–EtOAc (0.5 mL), stirred for 0.5 h at 25 °C, and the solvent was removed by a N₂ stream. The crude residue was dissolved in DMF (0.15 mL), treated with EDCI (7.4 mg, 38 μmol), carboxylic acid **26** (4.38 mg, 9.6 μmol) and the mixture was stirred for 16 h at 25 °C. The solvent was removed by a N₂ stream and the residue was purified by flash chromatography (SiO₂, 40% THF–C₆H₆) to afford **34** (2.43 mg, 35%, unoptimized) as a tan solid: ¹H NMR (acetone-*d*₆, 500 MHz) δ 10.82 (1H,

s), 10.71 (1H, br s), 10.50 (1H, s), 8.95 (1H, br s), 8.04 (1H, s), 7.56 (1H, s), 7.50 (1H, s), 7.27 (1H, s), 7.18 (1H, s), 7.06 (1H, s), 7.04 (1H, s), 4.86–4.94 (2H, m), 4.81 (1H, t, $J = 10.1$ Hz), 4.64 (1H, dd, $J = 11.0, 4.0$ Hz), 4.17–4.27 (2H, m), 3.95 (3H, s), 3.91 (3H, s), 3.87–3.91 (1H, m), 3.47 (2H, t, $J = 8.1$ Hz), 2.46 (3H, s); IR (film) $\nu_{\max}$ 3345, 2925, 1634, 1504, 1311 cm^{-1} ; ESITOF–HRMS m/z 716.1589 ($M + H^+$, $\text{C}_{35}\text{H}_{30}\text{ClN}_5\text{O}_8\text{S}$ requires 716.1576).

(*S*)-**34**: $[\alpha]_D^{23} -3.3$ (c 0.24, THF).

(*R*)-**34**: $[\alpha]_D^{23} +4.1$ (c 0.24, THF).

3-[(5-hydroxy-6-methoxyindol-2-yl)carbonyl]-1-(chloromethyl)-5-benzyloxy-1,2-dihydro-3H-pyrrolo[3,2-*e*]indole-7-carboxylate (36**)**. Compound **22** (40.5 mg, 0.0710 mmol) was dissolved in 4 N HCl–EtOAc (1 mL) and warmed at 70 °C for 1 h. The solution was cooled to 25 °C, the solvent was removed by a N_2 stream, and the sample was dried in vacuo for 3 h. The crude residue was dissolved in DMF (0.30 mL), treated with EDCI (54.3 mg, 0.294 mmol), 5-hydroxy-6-methoxyindole-2-carboxylic acid²⁰ (**35**, 17.6 mg, 0.0852 mmol), NaHCO_3 (6.0 mg, 0.071 mmol), and the mixture was stirred for 12 h at 25 °C. The solvent was removed by a N_2 stream and the residue was purified by flash chromatography (SiO_2 , 66% EtOAc–hexanes) to afford **36** (28.0 mg, 71%) as a white solid: mp 250–251 °C; ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 8.56 (1H, br s), 8.08 (1H, s), 7.64 (2H, d, $J = 8.3$ Hz), 7.41 (2H, t, $J = 7.0$ Hz), 7.34 (2H, m), 6.99 (1H, s), 6.93 (1H, d, $J = 1.8$ Hz), 6.92 (1H, s), 5.28 (2H, s), 4.73 (1H, t, $J = 11.6$ Hz), 4.42 (1H, dd, $J = 7.0, 3.8$ Hz), 4.15 (1H, m), 4.10 (1H, m), 4.02 (1H, m), 3.88 (3H, s), 3.81 (3H, s); ^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz) δ 172.1, 161.5, 159.5, 148.3, 145.0, 142.5, 138.5, 136.9, 131.0, 129.1, 128.4, 128.3 (2C), 127.7, 127.4 (2C), 126.3, 123.6, 120.8, 114.3, 105.1, 105.0, 98.3, 94.1, 69.4, 55.5, 54.4, 51.8, 47.6, 42.0; IR (film) $\nu_{\max}$ 1682, 1505 cm^{-1} ; ESITOF–HRMS m/z 560.1573 ($M + H^+$, $\text{C}_{30}\text{H}_{26}\text{ClN}_3\text{O}_6$ requires 560.1583).

(*S*)-**36**: $[\alpha]_D^{23} -8$ (c 0.2, THF).

(*R*)-**36**: $[\alpha]_D^{23} +7$ (c 0.2, THF).

3-[(5-hydroxy-6-methoxyindol-2-yl)carbonyl]-1-(chloromethyl)-5-benzyloxy-1,2-dihydro-3H-pyrrolo[3,2-*e*]indole-7-carboxylic acid (37**)**. Compound **36** (14.4 mg, 0.0258 mmol) was dissolved in 3:2:1 THF–MeOH– H_2O (1.0 mL), treated with $\text{LiOH}\cdot\text{H}_2\text{O}$ (4.2 mg, 0.10 mmol), and the mixture was stirred for 12 h at 25 °C. 1 N aqueous HCl was added until the pH was less than 6, and the solution was extracted with EtOAc (3×5 mL). The combined organic extracts were washed with saturated aqueous NaCl (5 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by flash chromatography (SiO_2 , 50% EtOAc–hexanes containing 1% HOAc), and azeotropically dried with toluene to afford **37** (10.4 mg, 74%) as an off-white solid: mp 235–236 °C; ^1H NMR (acetone- d_6 , 400 MHz) δ 10.99 (1H, s), 10.49 (1H, s), 8.23 (1H, s), 7.61 (2H, d, $J = 7.5$ Hz), 7.41 (2H, t, $J = 7.1$ Hz), 7.34 (1H, t, $J = 7.2$ Hz), 7.32 (1H, s), 7.10 (1H, s), 7.09 (1H, s), 7.03 (1H, s), 5.30 (2H, s), 4.82 (1H, t, $J = 9.5$ Hz), 4.63 (1H, dd, $J = 6.9, 4.0$ Hz), 4.24 (1H, m), 4.19 (1H, dd, $J = 7.4, 3.5$ Hz), 3.97 (1H, m), 3.90 (3H,

s); ^{13}C NMR (acetone- d_6 , 100 MHz) δ 162.7, 153.0, 149.0, 146.5, 143.7, 140.1, 138.1, 132.1, 130.7, 130.2, 129.3 (2C), 128.8 (2C), 128.7, 127.4, 125.1, 122.7, 115.3, 107.0, 106.2, 105.8, 99.4, 94.6, 70.9, 60.6, 56.3, 48.1, 43.8; IR (film) ν_{max} 3255, 1700, 1308 cm^{-1} ; ESITOF-HRMS m/z 546.1418 ($\text{M} + \text{H}^+$, $\text{C}_{29}\text{H}_{24}\text{ClN}_3\text{O}_6$ requires 546.1426).

(*S*)-**37**: $[\alpha]_D^{23} +14$ (c 0.04, THF).

(*R*)-**37**: $[\alpha]_D^{23} -15$ (c 0.04, THF).

3-[(5-hydroxy-6-methoxyindol-2-yl)carbonyl]-1-(chloromethyl)-5-hydroxy-1,2-dihydro-3H-pyrrolo[3,2-*e*]indole-7-carboxylic acid (38**)**. Compound **37** (10.2 mg, 0.0187 mmol) was dissolved in THF (1.0 mL), treated with 10% Pd/C (1 mg), and placed under H_2 (1 atm) at 25 °C for 2 h. The mixture was filtered through Celite, concentrated in vacuo, and precipitated by the addition of CH_2Cl_2 to afford **38** (6.7 mg, 79%) as a white solid: mp 260 °C (dec.); ^1H NMR (acetone- d_6 , 400 MHz) δ 10.60 (1H, s), 10.50 (1H, s), 8.06 (1H, s), 7.303 (1H, s), 7.297 (1H, s), 7.16 (1H, s), 7.09 (1H, s), 7.08 (1H, s), 7.02 (1H, s), 4.80 (1H, t, $J = 9.8$ Hz), 4.62 (1H, dd, $J = 6.6, 3.7$ Hz), 4.22 (1H, m), 4.17 (1H, m), 3.93 (1H, m), 3.89 (3H, s); ^{13}C NMR (acetone- d_6 , 400 MHz) δ 162.7, 160.5, 149.0, 144.4, 143.7, 140.1, 132.1, 130.8, 129.9, 129.7, 126.8, 125.5, 122.7, 114.2, 107.0, 106.1, 105.8, 94.6, 56.3, 55.7, 48.1, 43.9; IR (film) ν_{max} 3285, 1694, 1312 cm^{-1} ; ESITOF-HRMS m/z 454.0815 ($[\text{M} - \text{H}]^-$, $\text{C}_{22}\text{H}_{18}\text{ClN}_3\text{O}_6$ requires 454.0811).

(*S*)-**38**: $[\alpha]_D^{23} -8$ (c 0.2, THF).

(*R*)-**38**: $[\alpha]_D^{23} +7$ (c 0.2, THF).

seco-yatakemycin (39**, correct structure)**. Compound **33** (4.41 mg, 11.7 μmol) was dissolved in 4 N HCl-EtOAc (0.5 mL) and stirred for 0.5 h at 25 °C. The solvent was removed by a N_2 stream and dried for 3 h under high vacuum. The crude residue was dissolved in DMF (0.15 mL), treated with EDCI (6 mg, 48 μmol), carboxylic acid **38** (3.54 mg, 7.78 μmol) and the mixture was stirred for 16 h at 25 °C. The solvent was removed by a N_2 stream, and the residue was purified by flash chromatography (SiO_2 , THF) then trituration (EtOAc) to afford **39** (2.6 mg, 47%) as a yellow solid; ^1H NMR (DMF- d_6 , 500 MHz) δ 12.01 (1H, s), 11.44 (1H, s), 11.28 (1H, s), 11.21 (1H, s), 10.04 (1H, s), 8.51 (1H, s), 8.01 (1H, s), 7.58 (1H, d, $J = 2.0$ Hz), 7.35 (1H, d, $J = 2.0$ Hz), 7.12 (2H, s), 7.05 (1H, s), 4.88–4.96 (2H, m), 4.83 (1H, t, $J = 10.0$ Hz), 4.62 (1H, dd, $J = 10.7, 3.4$ Hz), 4.33 (1H, dd, $J = 10.7, 3.4$ Hz), 4.22–4.29 (1H, m), 4.06 (1H, dd, $J = 8.7, 11.4$ Hz), 3.97 (3H, s), 3.90 (3H, s), 3.49 (2H, t, partially obscured), 2.50 (3H, s); IR (film) ν_{max} 3319, 2929, 1633, 1503, 1417, 1310 cm^{-1} ; ESITOF-HRMS m/z 716.1565 ($\text{M} + \text{H}^+$, $\text{C}_{35}\text{H}_{30}\text{ClN}_5\text{O}_8\text{S}$ requires 716.1576).

(*S*)-**39**: $[\alpha]_D^{23} -24$ (c 0.2, DMF).

(*R*)-**39**: $[\alpha]_D^{23} +25$ (c 0.2, DMF).

methyl 2-azido-3-(3-benzyloxy-4-methoxyphenyl)acrylate (S1). Na (0.377 g, 16.4 mmol) was dissolved in anhydrous MeOH (15 mL), treated with 3-benzyloxy-4-methoxybenzaldehyde (1.00 g, 4.11 mmol), and the mixture was cooled to -15°C . $\text{N}_3\text{CH}_2\text{CO}_2\text{Me}$ (1.89 g, 16.4 mmol) in MeOH (2 mL) was added dropwise to the reaction mixture. The mixture was stirred for 3 h at -15°C , for 24 h at 0°C , and then warmed to room temperature and treated with saturated aqueous NH_4Cl (10 mL). The beige solid that formed was collected by filtration and washed with water to afford the title compound **S1** (1.14 g, 82%): mp $93\text{--}94^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 600 MHz) δ 7.62 (1H, d, $J = 1.8$ Hz), 7.48 (2H, d, $J = 7.5$ Hz), 7.40 (2H, t, $J = 7.4$ Hz), 7.33 (1H, t, $J = 7.5$ Hz), 7.26 (1H, d, $J = 8.3$ Hz), 6.88 (1H, d, $J = 8.3$ Hz), 6.82 (1H, s), 5.22 (2H, s), 3.93 (3H, s), 3.89 (3H, s); ^{13}C NMR (CDCl_3 , 125 MHz) 164.4, 151.0, 147.8, 137.1, 128.8 (2C), 128.1, 127.4 (2C), 126.2, 126.0, 125.6, 123.2, 115.6, 111.2, 71.3, 56.1, 52.9; IR (film) ν_{max} 2123, 1712, 1515, 1252 cm^{-1} ; ESITOF-HRMS m/z 362.1106 ($\text{M} + \text{Na}^+$, $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_4$ requires 362.1111).

methyl 5-benzyloxy-6-methoxyindole-2-carboxylate (S2). Compound **S1** (0.582 g, 1.71 mmol) was dissolved in xylenes (5 mL) and the solution was warmed at 130°C for 12 h. The solution was cooled to room temperature and hexanes (5 mL) was added. The beige solid was collected by filtration. The filtrate was concentrated in vacuo and purified by flash chromatography (SiO_2 , 25% EtOAc–hexanes). The precipitate was determined to be pure product by ^1H NMR and was combined with the product isolated by chromatography to afford **S2** (0.349 g, 66%): mp $177\text{--}178^{\circ}\text{C}$ (white needles, CHCl_3 –hexanes); ^1H NMR (CDCl_3 , 600 MHz) δ 9.09 (1H, s), 7.48 (2H, d, $J = 7.5$ Hz), 7.38 (2H, t, $J = 7.5$ Hz), 7.32 (1H, t, $J = 7.5$ Hz), 7.10 (1H, s), 7.08 (1H, d, $J = 1.3$ Hz), 6.87 (1H, s), 5.18 (2H, s), 3.93 (3H, s), 3.92 (3H, s); ^{13}C NMR (CDCl_3 , 125 MHz) δ 162.6, 150.9, 145.3, 137.4, 132.8, 128.7 (2C), 128.0, 127.6 (2C), 125.8, 120.5, 109.1, 105.9, 94.3, 71.7, 56.2, 51.9; IR (film) ν_{max} 3318, 1682, 1257 cm^{-1} ; ESITOF-HRMS m/z 334.1046 ($\text{M} + \text{Na}^+$, $\text{C}_{18}\text{H}_{17}\text{NO}_4$ requires 334.1050).

5-benzyloxy-6-methoxyindole-2-carboxylic acid (S3). Compound **S2** (0.309 g, 0.993 mmol) was dissolved in 3:2:1 THF–MeOH– H_2O (5 mL), treated with LiOH– H_2O (0.163 g, 3.97 mmol), and the mixture was stirred for 4 h at 25°C . 1 N aqueous HCl was added until the pH was less than 6, and the solution was extracted with EtOAc (3×10 mL). The combined organic extracts were washed with saturated aqueous NaCl (5 mL), dried (Na_2SO_4), and concentrated in vacuo to afford **S3** (0.296 g, 99%) as a white solid: mp $208\text{--}209^{\circ}\text{C}$ (white needles, C_6H_6); ^1H NMR (acetone- d_6 , 600 MHz) δ 10.58 (1H, s), 7.52 (2H, d, $J = 7.0$ Hz), 7.39 (2H, t, $J = 7.5$ Hz), 7.32 (1H, t, $J = 7.5$ Hz), 7.24 (1H, s), 7.09 (1H, d, $J = 2.2$ Hz), 7.07 (1H, s), 5.11 (2H, s), 3.87 (3H, s); ^{13}C NMR (acetone- d_6 , 125 MHz) δ 163.0, 151.7, 146.3, 138.9, 134.3, 129.2 (2C), 128.6 (2C), 128.5, 127.2, 121.5, 109.2, 106.6, 95.7, 72.0, 56.2; IR (film) ν_{max} 2937, 1667, 1530, 1239 cm^{-1} ; ESITOF-HRMS m/z 298.1074 ($\text{M} + \text{H}^+$, $\text{C}_{17}\text{H}_{15}\text{NO}_4$ requires 298.1074).

5-hydroxy-6-methoxyindole-2-carboxylic acid (35). Compound **S3** (0.198 g, 0.665 mmol) was dissolved in MeOH (5.0 mL), treated with 10% Pd/C (20 mg), and placed under H₂ (1 atm) at 25 °C for 2 h. The mixture was filtered through Celite and concentrated in vacuo to afford **35** (0.114 g, 83%) as a tan solid: mp 206–207 °C (tan prisms, MeOH); ¹H NMR (acetone-*d*₆, 600 MHz) δ 10.52 (1H, br s), 7.07 (2H, br s), 7.03 (1H, s), 3.88 (3H, s); ¹³C NMR (acetone-*d*₆, 125 MHz) δ 163.5, 149.5, 143.8, 133.6, 127.1, 122.1, 109.0, 105.8, 94.7, 56.3; IR (film) ν_{max} 3328, 1684, 1252 cm⁻¹; ESITOF–HRMS *m/z* 206.0458 ([M – H][–], C₁₀H₉NO₄ requires 206.0459).

6-hydroxy-5-methoxyindole-2-carboxylic acid (23). 6-benzyloxy-5-methoxyindole-2-carboxylic acid (0.050 g, 0.168 mmol) (Spectrum Chemical) was dissolved in MeOH (2.0 mL), treated with 10% Pd/C (5 mg), and placed under H₂ (1 atm) at 25 °C for 2 h. The mixture was filtered through Celite and concentrated in vacuo to afford **23** (0.034 g, 99%) as a white solid: mp 241–242 °C (tan needles, MeOH); ¹H NMR (acetone-*d*₆, 600 MHz) δ 10.48 (1H, br s), 7.60 (1H, br s), 7.13 (1H, s), 7.07 (1H, s), 6.96 (1H, s), 3.88 (3H, s); ¹³C NMR (acetone-*d*₆, 125 MHz) δ 163.0, 148.0, 145.7, 134.4, 126.9, 121.3, 109.3, 103.1, 97.8, 56.5; IR (film) ν_{max} 3402, 1659, 1542, 1280 cm⁻¹; ESITOF–HRMS *m/z* 208.0605 (M + H⁺, C₁₀H₉NO₄ requires 208.0604).

authentic yatakemycin
pyridine-d5
500 MHz

Synthetic yatakemycin, 1
pyridine-d5
500 MHz