Supporting Information for
Total Synthesis of (+)-Yatakemycin

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Experimental Section

General Remarks: All reactions were carried out in oven-dried glassware under a slight positive pressure of argon unless otherwise noted. ^1H -NMR (400 or 500 MHz) and ^{13}C -NMR (100 or 125 MHz) spectra were determined on a JEOL ECX400 or a JEOL ECX500. Chemical shifts for ^1H -NMR are reported in parts per million (ppm) downfield from tetramethylsilane as the internal standard and coupling constants are in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Chemical shifts for ^{13}C -NMR are reported in ppm, relative to the central line of a triplet at 77.0 ppm for deuteriochloroform. Infrared (IR) spectra were recorded on a JASCO FT/IR-410 Fourier Transform Infrared Spectrometer and are reported in wavenumbers (cm^{-1}). Where noted “neat”, the sample was loaded as a thin film on zinc-selenium plate. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter with a sodium lamp. Melting points (mp) were measured on a YANACO MP-500V. High-resolution mass spectra (HRMS) were obtained on a JEOL JMS-700 in positive FAB ionization method, using Kanto Chemical’s PEG 1000, 600, 400, or 200 matrix as the internal standard. Analytical thin layer chromatography (TLC) separations were performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F₂₅₄. Preparative TLC separations were performed on Merck analytical plates (0.25 or 0.50 mm thick) precoated with silica gel 60 F₂₅₄. Flash chromatography separations were performed on Kanto Chemical Silica Gel 60 (normal or neutral, 40 100 mesh).

Materials: Copper iodide (99.5% purity) and cesium acetate were purchased from Wako Pure Chemical Industries, Ltd. and were used as supplied. Cesium acetate was weighed under argon atmosphere to prevent absorption of moisture. Dry DMSO and dichloromethane were purchased from Aldrich Chemical Co. and Wako Pure Chemical Industries, Ltd., respectively. Other dry solvents were supplied from Kanto Chemical Co., Inc. (unless otherwise noted). Substrates were prepared according to the procedures outlined below. Spectroscopic data for all new compounds are also listed below.

(-)-(2S)-1-(4-(Benzyloxy)-2,6-dibromophenyl)-3-chloropropan-2-ol (7). A flame-dried 1-L three-necked round-bottomed flask equipped with a digital thermometer, a dropping funnel, and a mechanical stirrer was charged with 4-benzyloxy-2,6-dibromiodobenzene (**5**) (23.4 g, 50.0 mmol) and dry toluene (500 mL). The colorless solution was cooled to -78 °C. To the solution was added *n*-BuLi (1.51 M, 33.1 mL, 50.0 mmol) dropwise over 40 min at the rate that inner temperature was maintained under -75 °C. To the resulting viscous suspension was added (S)-epichlorohydrin (**6**) (3.91 mL, 50.0 mmol) dropwise over 5 min. After BF₃·OEt₂ (6.34 mL, 50.0 mmol) was added rapidly, the reaction mixture was stirred for 5 min, after which time TLC (hexane-dichloromethane = 3:2) indicated complete consumption of **5**. The reaction was quenched

with saturated aqueous sodium bicarbonate at $-78\text{ }^{\circ}\text{C}$ and let warm to room temperature. The resulting mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered through thin pad of silica gel. The resulting filtrate was concentrated under reduced pressure to afford analytically pure **7** (20.2 g, 46.5 mmol, 93%). The residue can be recrystallized from hexane-dichloromethane to give optically pure as fine colorless needles. The enantiomeric excess of **7** was determined by HPLC (DAICEL-CHIRALCEL-OJ, hexane-*i*-PrOH = 85:15, flow rate = 1.0 mL/min, t_{S} = 20.9 min, t_{R} = 24.9 min). Mp: $90.1\text{--}90.4\text{ }^{\circ}\text{C}$ (hexane-dichloromethane). R_{f} = 0.49 (CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3): δ 7.41–7.32 (m, 5H), 7.21 (s, 2H), 5.02 (s, 2H), 4.27–4.18 (m, 1H), 3.73–3.64 (m, 2H), 3.35 (dd, 1H, J = 12.8, 7.2 Hz), 3.15 (dd, 1H, J = 12.8, 5.6 Hz), 2.27 (d, 1H, J = 8.4 Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 157.9, 135.7, 128.7, 128.5, 128.4, 127.5, 125.7, 119.2, 70.9, 70.5, 50.1, 40.1. IR (neat, cm^{-1}): 3403, 2977, 1700, 1603, 1507, 1392, 1366, 1253, 1169, 750, 700. $[\alpha]_{\text{D}}^{27} = -18.1$ (c 1.02, CHCl_3). Anal. calcd. for $\text{C}_{16}\text{H}_{15}\text{Br}_2\text{ClO}_2$: C, 44.22; H, 3.48; Found: C, 44.06; H, 3.55.

(–)-(2S)-3-Azido-1-(4-(benzyloxy)-2,6-dibromophenyl)propan-2-ol (S1). A 500-mL round-bottomed flask equipped with a magnetic stirring bar was charged with chlorohydrin (**7**) (11.9 g, 27.4 mmol) and dry DMF (27.4 mL). To the solution was added NaN_3 (5.34 g, 82.2 mmol). The resulting mixture was heated to $90\text{ }^{\circ}\text{C}$ for 9 h, after which time TLC (dichloromethane) indicated complete consumption of **7**. After the flask was cooled to room temperature, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give analytically pure azide **S1** (12.8 g) as colorless plates, which was used to the next reaction without further purification. Mp: $99.2\text{--}100.4\text{ }^{\circ}\text{C}$ (hexane-ethyl acetate). R_{f} = 0.36 (hexane-ethyl acetate = 3:1). ^1H NMR (400 MHz, CDCl_3): δ 7.44–7.32 (m, 5H), 7.20 (s, 2H), 5.01 (s, 2H), 4.22–4.12 (m, 1H), 3.47 (dd, 1H, J = 12.4, 6.8 Hz), 3.41 (dd, 1H, J = 12.4, 4.0 Hz), 3.24 (dd, 1H, J = 14.0, 8.0 Hz), 3.11 (dd, 1H, J = 14.0, 6.0 Hz), 2.07 (d, 1H, J = 5.6 Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 157.9, 135.7, 128.7, 128.6, 128.4, 127.5, 125.7, 119.3, 70.6, 70.5, 56.4, 40.2. IR (neat, cm^{-1}): 3393, 2932, 2103, 1594, 1542, 1450, 1382, 1253, 1024, 923, 839, 738, 695. $[\alpha]_{\text{D}}^{25} = -9.1$ (c 1.18, CHCl_3). Anal. calcd. for $\text{C}_{16}\text{H}_{15}\text{Br}_2\text{N}_3\text{O}_2$: C, 43.56; H, 3.43; N, 9.53; Found: C, 43.26; H, 3.48; N, 9.34.

(+)-(2S)-3-Azido-1-(4-(benzyloxy)-2,6-dibromophenyl)propan-2-yl tert-butyldimethylsilyl ether (S2).

A 500-mL round-bottomed flask equipped with a magnetic stirring bar was charged with the crude **S1** (12.8 g), imidazole (2.80 g, 41.1 mmol), DMAP (167 mg, 1.37 mmol), and dry DMF (27.4 mL). To the solution was added TBSCl (4.54 g, 30.1 mmol). The resulting reaction mixture was heated to $50\text{ }^{\circ}\text{C}$ for 6 h, after which time TLC (hexane-ethyl acetate = 3:1) indicated complete consumption of the alcohol **S1**. The

reaction mixture was diluted with ethyl acetate. The organic layer was extracted with water, washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane-ethyl acetate = 9:1) to afford pure azide **S2** (15.0 g, 27.0 mmol, 99%) as viscous colorless liquid. R_f = 0.58 (hexane-ethyl acetate = 3:1). ^1H NMR (400 MHz, CDCl_3): δ 7.42-7.33 (m, 5H), 7.18 (s, 2H), 5.02 (s, 2H), 4.29-4.22 (m, 1H), 3.33-3.23 (m, 3H), 3.07 (dd, 1H, J = 14.0, 5.6 Hz), 0.86 (s, 9H), 0.03 (s, 3H), -0.17 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 157.7, 135.7, 129.2, 128.7, 128.3, 127.5, 126.0, 119.2, 70.6, 70.4, 56.6, 40.8, 25.8, 17.8, 14.1, -4.9. IR (neat, cm^{-1}): 2952, 2928, 2856, 2103, 1594, 1543, 1454, 1378, 1294, 1255, 1105, 1025, 962, 837, 808, 777, 737, 696. $[\alpha]_D^{27}$ = +5.1 (c 1.81, CHCl_3). Anal. calcd. for $\text{C}_{22}\text{H}_{29}\text{Br}_2\text{N}_3\text{O}_6\text{Si}$: C, 47.58; H, 5.26; N, 7.57; Found: C, 47.71; H, 5.29; N, 7.27.

(+)-((2*S*)-3-(*o*-Nitrobenzenesulfonylamino)-1-(4-(benzyloxy)-2,6-dibromophenyl)propan-2-yloxy)(*tert*-butyl)dimethylsilane (8**).** A 500-mL round-bottomed flask equipped with a magnetic stirring bar was charged with azide **S2** (14.3 g, 25.7 mmol) and dry THF (64 mL). To the clear solution was added tri-*n*-butylphosphine (6.98 mL, 28.3 mmol) at room temperature. Nitrogen gas started to evolve within 5 min. The reaction mixture was stirred at room temperature for 30 min, after which time TLC (hexane-ethyl acetate = 3:1) indicated complete consumption of **S2**. To the iminophosphorane generated *in situ* was added water (25 mL) and the resulting solution was stirred for 2 h at room temperature. To the pale yellow solution were added saturated aqueous sodium bicarbonate and NsCl (*o*-nitrobenzenesulfonyl chloride) (6.83 g, 30.8 mmol). The mixture was stirred for 18 h, after which time another portion of nosyl chloride (1.71 g, 7.72 mmol) was added and the resulting yellow suspension was stirred for another 24 h at room temperature. The reaction mixture was poured into 1 M hydrochloric acid and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane-ethyl acetate = 85:15 to 75:25, gradient) to afford nosyl amide **8** (16.4 g, 23.0 mmol, 89%) as colorless amorphous. R_f = 0.34 (hexane-ethyl acetate = 3:1). ^1H NMR (400 MHz, CDCl_3): δ 8.09-8.03 (m, 1H), 7.89-7.83 (m, 1H), 7.76-7.68 (m, 2H), 7.43-7.32 (m, 5H), 7.17 (s, 2H), 5.69 (t, 1H, J = 5.2 Hz), 5.02 (s, 2H), 4.33-4.26 (m, 1H), 3.28 (dd, 1H, J = 13.8, 8.2 Hz), 3.24 (dd, 1H, J = 13.4, 5.2 Hz), 3.15-3.07 (m, 1H), 3.05 (dd, 1H, J = 13.6, 5.8 Hz), 0.79 (s, 9H), -0.08 (s, 3H), -0.22 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 157.7, 148.1, 135.7, 133.5, 133.3, 132.7, 130.9, 128.8, 128.7, 128.3, 127.5, 126.0, 125.3, 119.2, 70.4, 69.5, 49.0, 40.5, 25.6, 17.7, -4.9, -5.0. IR (neat, cm^{-1}): 3353, 2929, 2856, 1594, 1542, 1452, 1406, 1362, 1256, 1172, 1104, 1040, 909, 837, 779, 737, 697, 668. $[\alpha]_D^{28}$ = +2.3 (c 1.27, CHCl_3). Anal. calcd. for $\text{C}_{28}\text{H}_{34}\text{Br}_2\text{N}_2\text{O}_6\text{SSi}$: C, 47.07; H, 4.80; N, 3.92; Found: C, 47.05; H, 4.75; N, 3.85.

(–)-(3*S*)-7-Benzoyloxy-5-bromo-1-(*o*-nitrobenzenesulfonyl)-1,2,3,4-tetrahydro-3-(*tert*-butyldimethylsilyloxy)quinoline (9). A flame-dried 100-mL round-bottomed flask equipped with a magnetic stirring bar was charged with nosyl amide **8** (3.13 g, 4.39 mmol), copper iodide (417.1 mg, 2.19 mmol), cesium acetate (4.21 g, 21.9 mmol), and dry DMSO (14.6 mL) under argon atmosphere. The resulting pale green solution was stirred at 60 °C for 24 h, after which time TLC (hexane-dichloromethane = 3:2) indicated complete consumption of **8**. After the flask was cooled to room temperature, the reaction mixture was poured into 5% aqueous sodium chloride in 10% aqueous ammonium hydroxide and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (dichloromethane-hexane = 1:1 to 3:1, gradient) to afford pure **9** (2.32 g, 3.66 mmol, 83%) as white solid, which can be recrystallized from hexane-dichloromethane to afford fine colorless needles. Mp: 106.3–106.9 °C (hexane-dichloromethane). R_f = 0.42 (hexane-ethyl acetate = 3:1). ^1H NMR (400 MHz, CDCl_3): δ 7.90 (d, 1H, J = 8.4 Hz), 7.74–7.68 (m, 2H), 7.64–7.59 (m, 1H), 7.40–7.30 (m, 5H), 7.07 (d, 1H, J = 2.4 Hz), 6.95 (d, 1H, J = 2.4 Hz), 4.94 (s, 2H), 4.17–4.09 (m, 1H), 4.02 (dd, 1H, J = 13.2, 4.0 Hz), 3.41 (dd, 1H, J = 14.0, 8.4 Hz), 2.91 (dd, 1H, J = 17.6, 6.4 Hz), 2.59 (dd, 1H, J = 17.6, 7.6 Hz), 0.88 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 157.0, 147.8, 137.7, 136.1, 134.0, 133.8, 132.1, 130.4, 128.6, 128.1, 127.5, 125.3, 124.6, 120.8, 116.8, 108.7, 70.2, 65.0, 52.0, 37.4, 25.7, 18.0, –4.81, –4.83. IR (neat, cm^{-1}): 2929, 2856, 1605, 1546, 1471, 1367, 1254, 1168, 1111, 1023, 839, 779, 738. $[\alpha]_D^{27}$ = –26.6 (c 1.17, CHCl_3). Anal. calcd. for $\text{C}_{28}\text{H}_{33}\text{BrN}_2\text{O}_6\text{SSi}$: C, 53.08; H, 5.25; N, 4.42; Found: C, 53.01; H, 5.26; N, 4.44.

*When **8** was treated with CuI (20 mol%) and CsOAc (2.7 equiv) at 50 °C for 36 h, the reaction didn't complete and the desired product was obtained in 63% yield. The reaction system became complex at 80 °C in the presence of CuI (20 mol%) and CsOAc (2.5 equiv).

(–)-(Z)-3-[(3*S*)-7-Benzoyloxy-1-(*o*-nitrobenzenesulfonyl)-1,2,3,4-tetrahydro-3-(*tert*-butyldimethylsilyloxy)-quinolin-5-yl]-benzyloxycarbonylamino-acrylic acid methyl ester (11). A flame-dried 80-mL Schlenk tube equipped with a magnetic stirring bar was charged with aryl bromide **9** (1.92 g, 3.02 mmol), dehydroamino acid derivative **10** (1.42 g, 6.04 mmol), $\text{Pd}_2(\text{dba})_3$ (138.3 mg, 0.151 mmol), 2-di(*tert*-butyl)phosphine-1,1'-biphenyl (180.2 mg, 0.604 mmol), lithium chloride (128.0 mg, 3.02 mmol), triethyl amine (1.69 mL, 12.1 mmol), and dry DMF (7.6 mL) under argon atmosphere. The reaction mixture was degassed by three freeze-pump-thaw cycles and heated to 90 °C for 1 h, after which time TLC (hexane-ethyl acetate = 3:1) indicated complete consumption of **9**. The reaction mixture was diluted with ethyl acetate and washed with water, brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane-ethyl acetate = 3:1 to 1:1, gradient) to afford pure **11** (2.12 g, 2.69 mmol, 89%) as off-white amorphous. R_f = 0.53 (hexane-ethyl acetate = 1:1). ^1H NMR (400 MHz, CDCl_3): δ 7.82 (d, 1H, J = 8.0 Hz), 7.69–7.55 (m, 3H), 7.42–7.21 (m, 10H), 7.10 (s, 1H), 6.99 (d, 1H, J = 2.2 Hz), 6.85 (d, 1H, J = 2.2 Hz), 6.30 (brs, 1H), 5.03 (dd, 2H, J = 18.4, 12.2 Hz), 4.88 (s, 2H), 4.13–4.03 (m, 1H), 3.83 (s, 3H), 3.35 (dd, 1H, J = 11.8, 7.4 Hz), 2.70 (dd, 1H, J =

16.4, 5.6 Hz), 2.44 (dd, 1H, $J = 16.4, 6.8$ Hz), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 165.0, 156.7, 153.2, 147.9, 137.2, 136.4, 135.7, 134.6, 133.8, 133.6, 132.0, 130.4, 128.52, 128.49, 128.3, 128.05, 128.00, 127.5, 126.9, 126.4, 124.4, 120.6, 112.2, 110.3, 70.1, 67.4, 65.1, 52.7, 52.0, 34.1, 31.5, 25.7, 17.9, -4.80, -4.84. IR (neat, cm^{-1}): 3403, 2977, 1700, 1603, 1507, 1392, 1366, 1253, 1169, 750, 700. $[\alpha]_{\text{D}}^{29} = -38.7$ (c 0.756, CHCl_3). Anal. calcd. for $\text{C}_{40}\text{H}_{45}\text{N}_3\text{O}_{10}\text{SSi}$: C, 60.97; H, 5.76; N, 5.33; Found: C, 60.99; H, 5.68; N, 5.31.

(+)-(Z)-3-[(3S)-7-Benzyloxy-1,2,3,4-tetrahydro-3-(*tert*-butyldimethylsilyloxy)-quinolin-5-yl]-benzyloxy carbonylamino-acrylic acid methyl ester (S3). A 100-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **11** (2.08 g, 2.64 mmol), cesium carbonate (1.29 g, 3.96 mmol), and dry acetonitrile (13.2 mL). To the stirred suspension was added thiophenol (0.339 mL, 3.17 mmol). The reaction mixture was stirred for 30 min at room temperature, after which time TLC (hexane-ethyl acetate = 3:1) indicated complete consumption of **11**. Cesium carbonate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (neutral silica gel, hexane-ethyl acetate = 3:1 to 1:1, gradient) to afford tetrahydroquinoline **S3** (1.57 g, 2.60 mmol, 99%) as yellow amorphous. $R_f = 0.60$ (hexane-ethyl acetate = 1:1). ^1H NMR (400 MHz, CDCl_3): δ 7.36-7.24 (m, 10H), 7.12 (s, 1H), 6.41 (d, 1H, $J = 2.6$ Hz), 6.27 (brs, 1H), 6.11 (d, 1H, $J = 2.82$ Hz), 5.09 (s, 2H), 4.88 (s, 2H), 4.13-4.02 (m, 1H), 3.82 (s, 3H), 3.30-3.23 (m, 1H), 3.01 (t, 1H, $J = 12.0$ Hz), 2.82-2.74 (m, 1H), 2.50 (dd, 1H, $J = 15.6, 9.2$ Hz), 0.89 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 165.3, 157.5, 153.7, 145.2, 136.8, 135.7, 133.7, 128.33, 128.31, 128.0, 127.9, 127.7, 127.5, 127.3, 126.2, 112.0, 103.6, 100.9, 69.6, 67.2, 65.3, 52.4, 48.2, 34.0, 25.7, 17.9, -4.7, -4.8. IR (neat, cm^{-1}): 3404, 2953, 2856, 1724, 1602, 1497, 1259, 1219, 1174, 1114, 1060, 868, 837, 776, 697. $[\alpha]_{\text{D}}^{29} = +19.0$ (c 1.68, CHCl_3). Anal. calcd. for $\text{C}_{34}\text{H}_{42}\text{N}_2\text{O}_6\text{Si}$: C, 67.75; H, 7.02; N, 4.65; Found: C, 67.65; H, 7.05; N, 4.55.

(+)-(Z)-3-[(3S)-7-Benzyloxy-6-bromo-1,2,3,4-tetrahydro-3-(*tert*-butyldimethylsilyloxy)-quinolin-5-yl]-benzyloxy carbonylamino-acrylic acid methyl ester (12). A 500-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **S3** (1.57 g, 2.60 mmol), dry dichloromethane (52.0 mL). The resulting solution was cooled to 0 °C. To the solution was added NBS (462.8 mg, 2.60 mmol) portionwise over 15 min. The reaction mixture was stirred at 0 °C for 5 min, after which time TLC (dichloromethane) indicated complete consumption of the **S3**. The reaction mixture was diluted with ethyl acetate and washed with aqueous sodium thiosulfite, brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (neutral silica gel, dichloromethane) to afford **12** (1.59 g, 2.34 mmol, 90%) as yellow amorphous. $R_f = 0.45$ (dichloromethane). ^1H NMR (400 MHz, CDCl_3): δ 7.45 (d, 2H, $J = 7.2$ Hz), 7.38 (t, 2H, $J = 7.8$ Hz), 7.34-

7.27 (m, 6H), 6.94 (s, 1H), 6.16 (brs, 1H), 6.09 (s, 1H), 5.08-5.04 (s, 4H, overlapped), 4.05, 3.98 (m, 1H), 3.82 (s, 3H), 3.27-3.18 (br, 1H), 3.04-2.94 (m, 1H), 2.75-2.60 (br, 1H), 2.43 (dd, 1H, $J = 15.6, 8.4$ Hz), 0.86 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 164.5, 153.7, 153.6, 153.2, 144.0, 136.4, 135.6, 134.6, 128.6, 128.37, 128.31, 128.05, 128.02, 127.7, 126.7, 111.6, 99.6, 99.4, 70.5, 67.2, 64.8, 52.5, 48.1, 34.5, 25.7, 17.9, -4.7, -4.9. IR (neat, cm^{-1}): 3405, 2952, 2856, 1727, 1579, 1453, 1260, 1219, 1118, 1061, 838, 779, 739, 696. $[\alpha]_{\text{D}}^{24} = +26.4$ (c 0.590, CHCl_3). Anal. calcd. for $\text{C}_{34}\text{H}_{42}\text{BrN}_2\text{O}_6\text{Si}$: C, 59.90; H, 6.06; N, 4.11; Found: C, 60.03; H, 6.01; N, 4.16.

(+)-(S)-3-Benzyl 2-methyl 4-(benzyloxy)-6,7,8,9-tetrahydro-8-(*tert*-butyldimethylsilyloxy) pyrrolo[3,2-*f*]quinoline-2,3-dicarboxylate (2). A flame-dried 100-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **12** (1.36 g, 1.99 mmol), copper iodide (378.2 mg, 1.99 mmol), and cesium acetate (955.0 mg, 4.98 mmol). The flask was evacuated then backfilled with argon. To the mixture was added dry DMSO (20 mL). The resulting pale green solution was stirred at room temperature under argon atmosphere for 12 h, after which time TLC (hexane-ethyl acetate = 1:1) indicated complete consumption of **12**. The reaction mixture was poured into 5% aqueous sodium chloride in 10% aqueous ammonium hydroxide and extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (neutral silica gel, dichloromethane) to afford the middle segment **2** (1.19 g, quant.) as light yellow amorphous. $R_f = 0.70$ (hexane-ethyl acetate = 1:1). ^1H NMR (400 MHz, CDCl_3): δ 7.46-7.18 (m, 10H), 7.09 (s, 1H), 6.19 (s, 1H), 5.06 (s, 2H), 5.02 (s, 2H), 4.24-4.14 (m, 1H), 3.82 (s, 3H), 3.34-3.26 (m, 1H), 3.08 (dd, 1H, $J = 10.0, 10.0$ Hz), 3.03 (dd, 1H, $J = 15.8, 5.2$ Hz), 2.75 (dd, 1H, $J = 15.8, 8.2$ Hz), 0.89 (s, 9H), 0.12 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3): 161.2, 152.9, 144.7, 138.7, 136.5, 134.5, 128.6, 128.5, 128.3, 128.1, 127.8, 127.3, 122.6, 109.2, 103.3, 99.3, 70.7, 70.2, 65.7, 52.0, 49.4, 33.3, 25.9, 25.8, 18.1, -4.59, -4.67. IR (neat, cm^{-1}): 3407, 2953, 2852, 1768, 1715, 1598, 1549, 1498, 1438, 1390, 1231, 1167, 1099, 837, 697. $[\alpha]_{\text{D}}^{22} = +40.3$ (c 0.890, CHCl_3). HRMS-FAB calcd. for $\text{C}_{34}\text{H}_{40}\text{N}_2\text{O}_6\text{Si}$ (M^+), 600.2656; found 600.2655.

*When **12** was treated with CuI (20 mol%) and CsOAc (2.5 equiv) at 50 °C for 12 h, the desired product **2** was obtained in only 10% yield and 12% of the starting material **12** was recovered. When the reaction was conducted using 50 mol% of CuI at 50 °C for 12 h, **2** was obtained in 42% yield.

1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinoline (S5). A 1-L round-bottomed flask equipped with a magnetic stirring bar was charged with homoveratrylamine (**S4**) (50.9 g, 281 mmol). To the flask was added formic acid (141 mL) slowly at 0 °C and the resulting orange solution was stirred at 0 °C for 5 min.

Paraformaldehyde (8.43 g, 281 mmol) was added to the flask and the resulting mixture was heated to 50 °C for 11 h, after which time TLC (methanol-dichloromethane = 3:7) indicated complete consumption of **S4**. Excess formic acid was removed under reduced pressure. The residual viscous oil was then poured into 1 M aqueous sodium hydroxide saturated with sodium chloride. The aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over anhydrous sodium sulfate and filtered. The filtrate was removed under reduced pressure to afford crude tetrahydroisoquinoline **S5** (56.5 g, quant) as pale yellow crystals which was used to the next step without further purification. The crude material can be purified by recrystallization from dichloromethane to give pale yellow needles. Mp: 77.7-78.8 °C (dichloromethane). R_f = 0.10 (methanol-dichloromethane = 1:9). ^1H NMR (400 MHz, CDCl_3): δ 6.58 (s, 1H), 6.50 (s, 1H), 3.94 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.12 (t, 2H, J = 6.0 Hz), 2.71 (t, 2H, J = 6.0 Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 147.3, 147.2, 127.4, 126.3, 111.8, 108.9, 55.8 (2C overlapped), 47.7, 43.8, 28.5. IR (neat, cm^{-1}): 3318, 2933, 2834, 1611, 1518, 1465, 1255, 1227, 1107, 1025, 853, 807. HRMS-FAB calcd. for $\text{C}_{11}\text{H}_{15}\text{NO}_2$ (M^+), 193.1103; found 193.1106.

2,2,2-Trifluoro-1-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-2(1H)-yl)ethanone (13). A 1-L round-bottomed flask equipped with a magnetic stirring bar was charged with crude **S5** (56.5 g), dry dichloromethane (280 mL), and pyridine (27.2 mL, 337 mmol). The yellow solution was cooled to 0 °C and TFAA (47.6 mL, 337 mmol) in dry dichloromethane (50 mL) was added to the solution dropwise over 30 min. After addition of TFAA was finished, the flask was let warm to room temperature and stirred for 2 h, after which time TLC (methanol-dichloromethane = 1:19) indicated complete consumption of **S5**. To the flask was added 1 M aqueous hydrochloric acid (300 mL). The mixture was extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by recrystallization from hexane-dichloromethane to afford **13** (73.1 g, 253 mmol, 90% from homoveratrylamine) as pale yellow needles. Mp: 101.5-102.7 °C (hexane-dichloromethane). R_f = 0.43 (hexane-ethyl acetate = 3:1). ^1H NMR (400 MHz, CDCl_3): δ 6.63 (s, 1H), 6.62 (s, 1H), 4.73 (s, 2H), 3.88 (t, 2H, J = 6.4 Hz), 3.873 (s, 3H), 3.867 (s, 3H), 2.89 (t, 2H, J = 6.4 Hz) (rotamer, major peaks). ^{13}C NMR (100 MHz, CDCl_3): δ 156.1, 148.1, 148.0, 125.0, 123.2, 118.0, 111.1, 109.0, 55.98, 55.96, 46.7, 45.2, 43.4, 28.8 (rotamer, major peaks). IR (neat, cm^{-1}): 1693, 1613, 1520, 1463, 1254, 1231, 1186, 1133, 1113, 1014, 925, 655. Anal. calcd. for $\text{C}_{13}\text{H}_{14}\text{F}_3\text{NO}_3$: C, 53.98; H, 4.88; N, 4.84; Found: C, 54.09; H, 4.94; N, 4.83.

1-(5,8-Dibromo-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-2(1H)-yl)-2,2,2-trifluoroethanone (S6). A

4-necked 300-mL round-bottomed flask was charged with FeCl_3 (3.80 g, 23.4 mmol), **13** (3.21 g, 11.1 mmol), and dry dichloromethane (22 mL). The resulting mixture was cooled to 0 °C. To the flask was added Br_2 (1.22 mL, 24.4 mmol) in dichloromethane (12 mL) dropwise over 15 min. The reaction mixture was stirred at 0 °C for 30 min, after which time TLC (hexane-ethyl acetate = 3:1) indicated complete consumption of **13**. To the flask was added dichloromethane followed by crushed ice. The mixture was stirred vigorously and extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous sodium bicarbonate, aqueous sodium thiosulfite, brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane-ethyl acetate = 9:1 to 4:1, gradient) to provide pure dibrominated compound **S6** (4.39 g, 9.82 mmol, 88%) as fine white powder. R_f = 0.48 (hexane-ethyl acetate = 3:1). ^1H NMR (400 MHz, CDCl_3): δ 4.74 (major, s, 1H), 3.97-3.74 (m, 8H), 2.95 (major, t, 2H, J = 6.4 Hz) (complexity due to rotamers). ^{13}C NMR (100 MHz, CDCl_3): 150.1, 150.0, 149.8, 131.5, 130.7, 128.7, 128.3, 120.0, 119.6, 117.7, 117.2, 116.7, 114.9, 60.93, 60.87, 60.85, 60.83, 47.98, 47.95, 46.59, 49.55, 42.84, 42.80, 40.93, 30.5, 30.4, 28.9 (complexity due to rotamers). IR (neat, cm^{-1}): 1698, 1462, 1407, 1307, 1194, 1142, 1030, 771. Anal. calcd. for $\text{C}_{26}\text{H}_{23}\text{NO}_6$: C, 34.93; H, 2.71; N, 3.13; Found: C, 35.22; H, 2.85; N, 3.24.

5,8-Dibromo-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (S7). A 500-mL round-bottomed flask equipped with a stirring bar was charged with trifluoroacetamide **S6** (25.86 g, 57.8 mmol), methanol (240 mL), and dichloromethane (60 mL). To the suspension was added powdered K_2CO_3 (23.99 g, 174 mmol). The mixture was stirred vigorously for 6 h at room temperature, at which time TLC (hexane-ethyl acetate = 3:1) indicated complete consumption of **S6**. K_2CO_3 was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in dichloromethane and the solution was washed with water, brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give the crude corresponding secondary amine **S7** (18.66 g) which was used for the next reaction without further purification. The crude material can be purified by recrystallization from dichloromethane to give colorless prisms. Mp: 94.2-95.0 °C (dichloromethane). R_f = 0.43 (methanol-dichloromethane = 1:9). ^1H NMR (400 MHz, CDCl_3): δ 3.94 (s, 2H), 3.887 (s, 3H), 3.885 (s, 3H), 3.10 (t, 2H, J = 6.0 Hz), 2.71 (t, 2H, J = 6.0 Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 149.3, 149.0, 133.2, 132.5, 120.2, 117.1, 60.84, 60.80, 49.5, 43.3, 30.2. IR (neat, cm^{-1}): 3325, 2939, 2872, 1457, 1400, 1292, 1223, 1104, 1016, 978, 934, 792, 743. HRMS-FAB calcd. for $\text{C}_{11}\text{H}_{14}\text{Br}_2\text{NO}_2$ ($\text{M}+\text{H}^+$), 349.9391; found 349.9396.

5,8-Dibromo-3,4-dihydro-6,7-dimethoxyisoquinoline (14). A 1-L round-bottomed flask equipped with a magnetic stirring bar was charged with the crude amine **S7** (18.66 g), dry dichloromethane (500 mL), and

manganese oxide (particle size: <5 μm , 100 g, 1.16 mol). The resulting mixture was stirred vigorously at room temperature for 18 h, after which time TLC (methanol-dichloromethane = 1:19) indicated complete consumption of **S7**. The reaction mixture was filtered through celite pad and the filtrate was concentrated under reduced pressure to afford analytically pure **14** (18.16 g, 52.0 mmol, 90% over 2 steps) as white plates. Mp: 67.9-69.0 $^{\circ}\text{C}$ (dichloromethane). R_f = 0.26 (hexane-ethyl acetate = 1:1). ^1H NMR (400 MHz, CDCl_3): δ 8.60 (brs, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.76 (t, 2H, J = 7.6 Hz), 2.78 (t, 2H, J = 7.6 Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 157.7, 153.1, 150.0, 135.1, 124.2, 118.8, 118.4, 60.91, 60.89, 46.7, 25.0. IR (neat, cm^{-1}): 2940, 1622, 1525, 1456, 1406, 1366, 1322, 1300, 1177, 1113, 1028, 988, 938, 897, 731. Anal. calcd. for $\text{C}_{11}\text{H}_{11}\text{Br}_2\text{NO}_2$: C, 37.85; H, 3.18; N, 4.01; Found: C, 38.00; H, 3.21; N, 3.71.

5,8-Dibromo-2-(*o*-nitrobenzenesulfonyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-hydroxyisoquinoline (15).

A 30-mL round-bottomed flask equipped with a stirring bar was charged with **14** (344.2 mg, 0.986 mmol) and dry THF (4.9 mL). To the solution was added nosyl chloride (262.2 mg, 1.18 mmol) in THF (1.0 mL) dropwise at 0 $^{\circ}\text{C}$ over 5 min and the resulting mixture was let warm to room temperature over 1 h. To the solution was added saturated aqueous sodium bicarbonate. The mixture was stirred vigorously for 30 min, after which time TLC (dichloromethane) indicated complete consumption of **14**. The aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was passed through silica pad to afford crude hemiaminal **15** (562.1 mg) as pale yellow amorphous. R_f = 0.18 (dichloromethane). ^1H NMR (400 MHz, CDCl_3): δ 8.15-8.10 (m, 1H), 7.77-7.72 (m, 2H), 7.71-7.66 (m, 1H), 6.51 (d, 1H, J = 4.4 Hz), 4.05-3.98 (m, 1H), 3.899 (s, 3H), 3.895 (s, 3H), 3.79 (d, 1H, J = 4.4 Hz), 3.64 (dt, 1H, J = 12.8, 5.2 Hz), 3.03-2.88 (m, 2H) (1 proton is obscured by MeO-3H). ^{13}C NMR (100 MHz, CDCl_3): 151.5, 150.0, 147.9, 134.0, 133.2, 132.2, 131.6, 131.0, 130.8, 124.6, 119.8, 118.9, 67.1, 60.9, 60.8, 37.8, 30.2. IR (neat, cm^{-1}): 3518, 2941, 1542, 1462, 1373, 1303, 1172, 1026, 964, 776, 731, 586. Anal. calcd. for $\text{C}_{17}\text{H}_{16}\text{Br}_2\text{N}_2\text{O}_7\text{S}$: C, 36.98; H, 2.92; N, 5.07; Found: C, 36.95; H, 3.08; N, 4.95.

(2-(2-(*o*-Nitrobenzenesulfonyl)aminoethyl)-3,6-dibromo-4,5-dimethoxyphenyl)methanol (16). A 50-mL round-bottomed flask equipped with a magnetic stirring bar was charged with the crude hemiaminal **15** (562.1 mg) and dry methanol (10 mL). The resulting solution was cooled to 0 $^{\circ}\text{C}$. To the solution was added sodium borohydride (112.0 mg, 2.96 mmol) portionwise over 10 min. The resulting mixture was let warm to room temperature over 1 h, after which time TLC (dichloromethane) indicated complete consumption of **15**. To the reaction mixture was added 1 M hydrochloric acid at 0 $^{\circ}\text{C}$ and the mixture was extracted with ethyl

acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (dichloromethane) to give pure **16** (425.5 mg, 0.768 mmol, 78% over 2 steps) as white solid which can be purified by recrystallization from hexane-dichloromethane to provide colorless fine prisms. Mp: 154.4-154.9 °C (hexane-dichloromethane). R_f = 0.28 (hexane-ethyl acetate = 1:1). ^1H NMR (400 MHz, CDCl_3): δ 8.17-8.11 (m, 1H), 7.85-7.77 (m, 1H), 7.74-7.67 (m, 2H), 6.06 (t, 1H, J = 6.4 Hz), 4.95 (d, 2H, J = 5.6 Hz), 3.874 (s, 3H), 3.865 (s, 3H), 3.41 (td, 2H, J = 7.2, 6.4 Hz), 3.26 (t, 2H, J = 7.2 Hz), 2.36 (t, 1H, 5.6 Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 151.2, 150.0, 147.8, 135.2, 134.5, 133.7, 133.4, 132.7, 131.1, 125.2, 121.1, 120.9, 62.6, 60.8, 42.6, 33.9, 30.9. IR (neat, cm^{-1}): 3523, 3341, 2935, 1541, 1459, 1405, 1364, 1344, 1303, 1164, 1099, 1011, 731, 590. Anal. calcd. for $\text{C}_{17}\text{H}_{18}\text{Br}_2\text{N}_2\text{O}_7\text{S}$: C, 36.84; H, 3.27; N, 5.05; Found: C, 36.74; H, 3.27; N, 5.05.

***N*-(*o*-Nitrobenzenesulfonyl)-4-hydroxymethyl-5-bromo-6,7-dimethoxyindoline (**17**)**. A flame-dried 250-mL Schlenk tube equipped with a magnetic stirring bar was charged with **16** (13.41 g, 24.2 mmol), copper iodide (460.9 mg, 2.42 mmol), and cesium acetate (11.62 g, 60.5 mmol). The flask was evacuated then backfilled with argon. To the mixture was added dry DMSO (96.8 mL). The resulting pale green solution was stirred at 80 °C under argon atmosphere for 24 h, after which time TLC (hexane-ethyl acetate = 1:1) indicated complete consumption of **16**. The reaction mixture was poured into 5% aqueous sodium chloride in 10% aqueous ammonium hydroxide and extracted with ethyl acetate. The combined organic extracts were washed with water, brine, and dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was passed through silica pad to provide crude indoline **17** (12.02 g) as off-white amorphous which decomposed gradually at room temperature. R_f = 0.18 (hexane-ethyl acetate = 1:1). ^1H NMR (400 MHz, CDCl_3): δ 8.24-8.18 (m, 1H), 7.78-7.69 (m, 3H), 4.69 (s, 2H), 4.36 (t, 2H, J = 8.0 Hz), 3.77 (s, 3H), 3.33 (s, 3H), 3.21 (t, 2H, J = 8.0 Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 149.8, 147.2, 143.4, 135.1, 134.7, 133.2, 131.9, 131.7, 130.9, 130.4, 124.1, 116.2, 62.5, 60.6, 59.7, 53.5, 28.9. IR (neat, cm^{-1}): 3545, 3400, 2943, 1541, 1470, 1407, 1354, 1165, 1085, 1002, 964, 913, 781, 732, 602, 570. HRMS-FAB calcd. for $\text{C}_{17}\text{H}_{17}\text{BrN}_2\text{O}_7\text{S}$ (M^+), 471.9940; found 471.9939.

***N*-(*o*-Nitrobenzenesulfonyl)-4-formyl-5-bromo-6,7-dimethoxyindoline (**S8**)**. A flame-dried 1-L round-bottomed flask equipped with a stirring bar was charged with the crude alcohol **17** (12.02 g), NMO (4.25 g, 36.3 mmol), and dry dichloromethane (100 mL). To the solution was added MS4Å (12.1 g, activated) and the mixture was stirred for 5 min. TPAP (165.4 mg, 0.484 mmol) was added to the mixture at one portion and the reaction mixture was stirred at room temperature, after which time TLC (hexane-ethyl acetate = 1:1)

indicated complete consumption of **17**. The reaction mixture was diluted with ether and passed through celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (dichloromethane) to afford benzaldehyde **S8** (9.75 g, 20.7 mmol, 85% over 2 steps) as white solid, which can be purified by recrystallization with hexane-dichloromethane to afford fine colorless needles. Mp: 160.2-161.0 °C (hexane-dichloromethane). R_f = 0.35 (hexane-ethyl acetate = 1:1). ^1H NMR (400 MHz, CDCl_3): δ 10.36 (s, 1H), 8.21-8.14 (m, 1H), 7.79-7.69 (m, 3H), 4.35 (t, 2H, J = 8.0 Hz), 3.80 (s, 3H), 3.46 (s, 3H), 3.44 (t, 2H, J = 8.0 Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 192.1, 149.6, 147.9, 147.2, 135.7, 135.3, 135.0, 133.3, 131.6, 130.2, 124.9, 124.2, 120.1, 60.8, 59.9, 53.9, 30.1. IR (neat, cm^{-1}): 2947, 1687, 1542, 1471, 1359, 1319, 1166, 1117, 1085, 964, 915, 783, 741, 606, 570. Anal. calcd. for $\text{C}_{17}\text{H}_{15}\text{BrN}_2\text{O}_7\text{S}$: C, 43.33; H, 3.21; N, 5.94; Found: C, 43.03; H, 3.43; N, 5.86.

(Z)-3-[N-(*o*-Nitrobenzenesulfonyl)-5-bromo-6,7-dimethoxy-indolin-4-yl]-benzyloxycarbonylamino

acrylic acid methyl ester (19). A 100-mL round-bottomed flask equipped with a magnetic stirring bar was charged with benzaldehyde **S8** (4.95 g, 10.5 mmol), phosphonate **18** (4.50 g, 11.0 mmol), and dry dichloromethane (21.0 mL). The flask was cooled to 0 °C and 1,1,3,3-tetramethylguanidine (1.38 mL, 11.0 mmol) was added to the solution. The reaction mixture was let warm to room temperature over 6 h, after which time TLC (hexane-ethyl acetate = 1:1) indicated complete consumption of **S8**. To the solution was added 1 M hydrochloric acid. The mixture was extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium bicarbonate, brine, dried over sodium sulfite, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane-ethyl acetate = 3:1) to afford dehydroamino acid derivative **19** (6.66 g, 8.45 mmol, 84%) as pale yellow amorphous. R_f = 0.29 (dichloromethane). ^1H NMR (400 MHz, CDCl_3): δ 8.22-8.18 (m, 1H), 7.76-7.66 (m, 3H), 7.44-7.21 (m, 10H), 7.06 (s, 1H), 6.34 (brs, 1H), 5.29 (s, 2H), 5.03 (s, 2H), 4.18 (t, 2H, J = 7.6 Hz), 3.76 (s, 3H), 3.36 (s, 3H), 2.80 (t, 2H, J = 8.0 Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 163.8, 152.9, 149.8, 147.1, 143.4, 135.4, 135.1, 134.8, 134.7, 133.2, 131.5, 130.9, 130.3, 128.4, 128.3, 128.12, 128.10, 127.7, 126.8, 125.5, 124.0, 115.5, 67.5, 67.4, 60.4, 59.6, 53.6, 29.7 (Two carbons are missing due to overlapping). IR (neat, cm^{-1}): 3331, 3029, 2946, 1723, 1542, 1469, 1360, 1244, 1166, 1065, 968, 852, 755, 699, 656. HRMS-FAB calcd. for $\text{C}_{34}\text{H}_{30}\text{BrN}_3\text{O}_{10}\text{S}$ (M^+), 751.0835; found 751.0845.

Benzyl 3-(*o*-nitrobenzenesulfonyl)-4,5-dimethoxy-6-benzyloxycarbonyl-1,2-dihydro-3H-pyrrolo[3,2-*e*]

indole-7-carboxylate (20). A flame-dried 500-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **19** (6.66 g, 8.45 mmol), copper iodide (1.61 g, 8.45 mmol), and cesium acetate (8.11 g,

42.3 mmol). The flask was evacuated then backfilled with argon. To the mixture was added dry DMSO (42.3 mL). The resulting pale green solution was stirred at room temperature under argon atmosphere for 12 h, after which time TLC (hexane-ethyl acetate = 1:1) indicated complete consumption of **19**. The reaction mixture was poured into 5% aqueous sodium chloride in 10% aqueous ammonium hydroxide and extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (neutral silica gel, hexane-ethyl acetate = 1:1) to afford dihydropyrroloindole **20** (4.35 g, 6.48 mmol, 77%) as yellow amorphous. R_f = 0.40 (hexane-ethyl acetate = 1:1). ^1H NMR (400 MHz, CDCl_3): δ 8.15-8.10 (m, 1H), 7.73-7.64 (m, 3H), 7.45-7.33 (m, 5H), 7.10 (s, 1H), 5.34 (s, 2H), 5.31 (s, 2H), 4.42 (t, 2H, J = 7.6 Hz), 3.68 (s, 3H), 3.38 (s, 3H), 3.12 (t, 2H, J = 7.6 Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 160.2, 152.5, 147.4, 142.9, 138.1, 135.3, 134.8, 134.2, 133.1, 131.8, 131.6, 131.4, 130.6, 130.4, 128.8, 128.7, 128.6, 128.52, 128.48, 128.42, 124.0, 123.3, 119.8, 110.3, 70.9, 67.1, 61.1, 59.8, 54.3, 28.9. IR (neat, cm^{-1}): 2947, 1770, 1715, 1541, 1491, 1351, 1253, 1165, 1029, 750, 698, 605. HRMS-FAB calcd. for $\text{C}_{34}\text{H}_{29}\text{N}_3\text{O}_{10}\text{S}$ (M^+), 671.1574; found 671.1572.

*When **19** was treated with CuI (10 mol%) and CsOAc (2.5 equiv) at 80 °C for 15 h, the pyrroindole was obtained in 91% yield. The product was not observed at all when we carried out the reaction at room temperature.

Benzyl 4,5-dimethoxy-1,2-dihydro-3H-pyrrolo[3,2-*e*]indole-7-carboxylate (S9). A 50-mL round-bottomed flask equipped with a magnetic stirring bar was charged **20** (2.10 g, 3.13 mmol), cesium carbonate (3.06 g, 9.38 mmol), and dry acetonitrile (6.26 mL). To the suspension was added PhSH (481.6 μL , 4.69 mmol). The reaction mixture was vigorously stirred at room temperature for 3 h, after which time TLC (hexane-ethyl acetate = 1:1) indicated complete consumption of **20**. The reaction mixture was diluted with ethyl acetate and filtered through celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (neutral silica gel, dichloromethane to hexane-ethyl acetate = 1:1) to afford **S9** (1.45 g, 2.98 mmol, 95%) as viscous yellow liquid. R_f = 0.29 (hexane-ethyl acetate = 1:1). ^1H NMR (400 MHz, CDCl_3): δ 7.44-7.31 (m, 10H), 7.06 (s, 1H), 5.34 (s, 2H), 5.30 (s, 2H), 3.90 (s, 3H), 3.76 (s, 3H), 3.65 (t, 2H, J = 8.4 Hz), 3.10 (t, 2H, J = 8.4 Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 160.6, 153.1, 141.7, 139.3, 137.8, 135.6, 134.4, 128.8, 128.59, 128.55, 128.47, 128.3, 128.1, 127.8, 127.0, 120.8, 115.5, 110.1, 70.6, 66.7, 61.2, 60.2, 48.3, 29.3. IR (neat, cm^{-1}): 3370, 2941, 1766, 1713, 1495, 1240, 1198, 1148, 1028, 750, 698. HRMS-FAB calcd. for $\text{C}_{28}\text{H}_{26}\text{N}_2\text{O}_6$ (M^+), 486.1791; found 486.1792.

Benzyl 3-((9H-fluoren-9-yl)methoxycarbonyl-4,5-dimethoxy-6-benzylloxycarbonyl-1,2-dihydro-pyrrolo[3,2-*e*]indole-7-carboxylate (S10). A 100-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **S9** (1.57 g, 3.23 mmol), NaHCO₃ (814.1 mg, 9.69 mmol), THF (15 mL), and H₂O (5 mL). To the suspension was added FmocCl (835.6 mg, 3.23 mmol) portionwise over 5 min at room temperature. The resulting mixture was stirred for 10 min, after which time TLC (hexane-ethyl acetate = 1:1) indicated complete consumption of **S9**. The reaction mixture was diluted with ethyl acetate and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane-ethyl acetate = 3:1 to 3:2, gradient) to afford *N*-Fmoc-dihydropyrroloindole **S10** (2.09 g, 2.95 mmol, 91%). *R*_f = 0.58 (hexane-ethyl acetate = 1:1). ¹H NMR (400 MHz, CDCl₃): δ 7.74 (d, 2H, *J* = 7.2 Hz), 7.56 (d, 2H, *J* = 8.4 Hz), 7.46-7.21 (m, 14H), 7.13 (s, 1H), 5.36 (s, 2H), 5.32 (s, 2H), 4.55 (d, 2H, *J* = 6.4 Hz), 4.29 (t, 1H, *J* = 6.4 Hz), 4.15 (t, 2H, *J* = 7.2 Hz), 3.85 (s, 3H), 3.76 (s, 3H), 3.05 (t, 2H, *J* = 7.2 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 160.3, 154.8, 152.8, 143.8, 143.6, 141.3, 138.4, 135.4, 134.2, 131.8, 130.0, 128.8, 128.65, 128.62, 128.51, 128.47, 128.44, 128.3, 127.6, 127.0, 125.0, 122.2, 119.9, 119.6, 110.3, 70.8, 67.6, 67.0, 61.1, 60.2, 51.6, 47.3, 28.4. IR (neat, cm⁻¹): 2947, 1769, 1714, 1452, 1414, 1391, 1325, 1250, 1214, 1163, 741, 568. HRMS-FAB calcd. for C₄₃H₃₆N₂O₈ (M⁺), 708.2472; found 708.2465.

3-((9H-Fluoren-9-yl)methoxycarbonyl-4,5-dimethoxy-1,2-dihydro-6H-pyrrolo[3,2-*e*]indole-7-carboxylic acid (S11). A 100-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **S10** (2.02 g, 2.85 mmol), 10% Pd/C (303.3 mg, 0.285 mmol), THF (14.3 mL), and EtOH (14.3 mL). To the flask was charged with hydrogen gas (1 atm) at room temperature. The resulting suspension was vigorously stirred for 3 h, after which time TLC (hexane-ethyl acetate = 1:1) indicated complete consumption of **S10**. The reaction mixture was filtered through celite pad and the filtrate was concentrated under reduced pressure. The residue was passed through silica pad to give carboxylic acid **S11** (1.40 g) as yellow viscous liquid, which was used for the next step without further purification. *R*_f = 0.20 (methanol-chloroform = 1:9). ¹H NMR (500 MHz, CDCl₃): δ 9.19 (brs, 1H), 7.75 (d, 2H, *J* = 7.5 Hz), 7.58 (d, 2H, *J* = 7.7 Hz), 7.39 (dd, 2H, *J* = 7.7, 7.5 Hz), 7.27 (dd, 2H, *J* = 7.7, 7.5 Hz), 7.16 (d, 1H, *J* = 2.0 Hz), 4.57 (d, 2H, *J* = 6.9 Hz), 4.31 (t, 1H, *J* = 6.9 Hz), 4.18 (t, 2H, *J* = 7.7 Hz), 4.03 (s, 3H), 3.90 (s, 3H), 3.10 (t, 2H, *J* = 7.7 Hz). ¹³C NMR (125 MHz, CDCl₃): δ 165.9, 161.3, 155.2, 143.9, 142.4, 141.3, 137.5, 130.9, 130.5, 127.7, 127.0, 125.0, 122.1, 120.6, 119.9, 108.6, 67.7, 61.2, 60.4, 51.8, 47.3, 28.7. IR (neat, cm⁻¹): 3453, 3286, 2941, 1698, 1537, 1449, 1416, 1329, 1248, 1190, 1036, 909, 759, 738. HRMS-FAB calcd. for C₂₈H₂₄N₂O₆ (M⁺), 484.1634; found 484.1631.

Methyl 3-(9H-fluoren-9-yl)methoxycarbonyl-4,5-dimethoxy-1,2-dihydro-6H-pyrrolo[3,2-*e*]indole-7-thiocarboxylate (21). A 100-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **S11** (1.40 g), DMAP (69.6 mg, 0.570 mmol), and WSCD•HCl (1.64 g, 8.55 mmol). The resulting mixture was cooled to 0 °C. To the mixture was added saturated MeSH in DMF (14.3 mL) and the resulting mixture was stirred at 0 °C for 3 h, after which time TLC (hexane-ethyl acetate = 1:1) indicated complete consumption of **11**. The reaction mixture was diluted with ethyl acetate and 1 M hydrochloric acid. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were washed with aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane-ethyl acetate = 3:1 to 3:2, gradient) to afford **21** (1.11 g, 2.16 mmol, 76% over 2 steps) as pale yellow amorphous. R_f = 0.56 (hexane-ethyl acetate = 1:1). ^1H NMR (400 MHz, CDCl_3): δ 9.00 (brs, 1H), 7.76 (d, 2H, J = 7.2 Hz), 7.58 (d, 2H, J = 7.6 Hz), 7.39 (dd, 2H, J = 7.6, 7.2 Hz), 7.27 (dd, 2H, J = 7.6, 7.2 Hz), 7.13 (d, 1H, J = 1.6 Hz), 4.56 (d, 2H, J = 7.2 Hz), 4.31 (t, 1H, J = 7.2 Hz), 4.18 (t, 2H, J = 7.6 Hz), 3.99 (s, 3H), 3.89 (s, 3H), 3.10 (t, 2H, J = 7.6 Hz), 2.52 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 183.8, 155.1, 143.9, 142.6, 141.3, 137.6, 134.5, 131.2, 130.0, 127.6, 127.0, 125.1, 122.1, 120.4, 119.9, 106.1, 67.6, 61.1, 60.3, 51.8, 47.3, 28.7, 22.6. IR (neat, cm^{-1}): 3318, 2941, 1712, 1640, 1502, 1449, 1415, 1327, 1281, 1244, 1186, 1147, 1121, 1021, 908, 871, 759, 734. HRMS-FAB calcd. for $\text{C}_{29}\text{H}_{26}\text{N}_2\text{O}_5\text{S}$ (M^+), 514.1562; found 514.1569.

Methyl 3-(9H-fluoren-9-yl)methoxycarbonyl -4-hydroxy-5-methoxy-1,2-dihydro-6H-pyrrolo[3,2-*e*]indole-7-thiocarboxylate (3). A flame-dried 300-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **21** (1.35 g, 2.62 mmol), dry dichloromethane (52 mL). BCl_3 (1 M dichloromethane solution, 2.62 mL, 2.62 mmol) was added to the solution dropwise at 0 °C over 5 min. The red reaction mixture was stirred vigorously for 15 min. Furthermore, another BCl_3 (1 M dichloromethane solution, 0.78 mL, 0.78 mmol) was added to the reaction mixture dropwise over 5 min, after which time TLC (hexane-ethyl acetate = 1:1) indicated complete consumption of **21**. The excess reagent was quenched by saturated aqueous ammonium chloride and the mixture was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (dichloromethane) to give the left fragment **3** (1.28 g, 2.55 mmol, 97%) as light yellow solid. R_f = 0.62 (hexane-ethyl acetate = 1:1). ^1H NMR (400 MHz, CDCl_3): δ 11.30 (s, 1H), 8.93 (brs, 1H), 7.80 (d, 2H, J = 7.2 Hz), 7.63 (d, 2H, J = 8.0 Hz), 7.44 (dd, 2H, J = 8.0, 7.2 Hz), 7.35 (dd, 2H, J = 8.0, 7.2 Hz), 7.08 (s, 1H), 4.61 (t, 2H, J = 6.4 Hz), 4.34 (t, 1H, J = 6.4 Hz), 4.11 (t, 2H, J = 7.6 Hz), 4.01 (s, 3H), 3.22 (t, 2H, J = 7.6 Hz), 2.50 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 183.4, 155.2, 143.4, 141.3, 138.6, 133.8, 132.7, 130.5, 127.9, 127.2, 126.0, 124.8, 120.1, 119.7, 117.5, 106.3, 68.8, 60.7, 49.3, 47.0, 26.7, 21.0. IR (neat, cm^{-1}): 3323, 2930, 1663, 1629, 1450, 1335, 1243, 1144, 1060, 1019, 908, 871, 736. HRMS-FAB calcd. for $\text{C}_{29}\text{H}_{26}\text{N}_2\text{O}_5\text{S}$ (M^+), 500.1406; found 500.1404.

3-Benzyloxy-4-methoxybenzaldehyde (S13). A 500-mL round-bottomed flask equipped with a magnetic stirring bar was charged with isovanillin (**S12**) (25.0 g, 164 mmol), powdered K_2CO_3 (25.0 g, 181 mmol), and dry acetonitrile (160 mL). To the resulting mixture was added BnBr (19.5 mL, 164 mmol). The reaction mixture was heated to reflux for 1 h, after which time TLC (hexane-ethyl acetate = 1:1) indicated complete consumption of **S12**. The reaction mixture was filtered through celite pad and the filtrate was concentrated under reduced pressure to provide analytically pure **S13** (41.3 g) as pale yellow liquid which was gradually solidified at room temperature. R_f = 0.52 (hexane-ethyl acetate = 1:1). ^1H NMR (400 MHz, CDCl_3): δ 9.81 (s, 1H), 7.48-7.42 (m, 3H), 7.38 (dd, 2H, J = 7.2, 7.2 Hz), 7.31 (t, 1H, J = 7.2 Hz), 7.00 (s, 1H), 6.98 (s, 1H), 5.18 (s, 2H), 3.95 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 190.8, 155.0, 148.6, 136.2, 129.9, 128.6, 128.1, 127.4, 126.8, 111.2, 110.7, 70.8, 56.1. IR (neat, cm^{-1}): 3318, 2933, 2834, 1518, 1465, 1256, 1227, 1107. HRMS-FAB calcd. for $\text{C}_{15}\text{H}_{14}\text{O}_3$ (M^+), 242.0943; found 242.0932.

5-Benzyloxy-2-bromo-4-methoxybenzaldehyde (S14). A 500-mL round-bottomed flask equipped with a magnetic stirring bar was charged with the crude benzaldehyde **S13** (41.3 g), dichloromethane (80 mL), and methanol (80 mL). The resulting colorless solution was cooled to 0 °C. To the solution was added bromine (9.24 mL, 180 mmol) in dichloromethane (20 mL) at 0 °C dropwise over 30 min. The reaction mixture was let warm to room temperature and stirred for 2 h, after which time TLC (hexane-ethyl acetate = 1:1) indicated complete consumption of **S13**. To the reaction mixture was added water and the mixture was extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous sodium bicarbonate, aqueous sodium sulfite, brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford pale yellow solid. Recrystallization from hexane-ethyl acetate provided **S14** as colorless needles (45.4 g, 141 mmol, 86% over 2 steps). Mp. 142.4-143.3 °C (hexane-ethyl acetate). R_f = 0.63 (hexane-ethyl acetate = 1:1). ^1H NMR (400 MHz, CDCl_3): δ 10.16 (s, 1H), 7.48 (s, 1H), 7.44 (d, 2H, J = 6.8 Hz), 7.41-7.31 (m, 3H), 7.07 (s, 1H), 5.16 (s, 2H), 3.95 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): 190.7, 155.0, 147.8, 135.8, 128.6, 128.2, 127.5, 126.3, 120.6, 115.6, 112.3, 70.8, 56.4. IR (neat, cm^{-1}): 1681, 1591, 1505, 1438, 1384, 1268, 1216, 1160, 1025, 739. Anal. calcd. for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_2$: C, 56.10; H, 4.08; Found: C, 55.86; H, 4.10.

Benzyl (Z)-1-(methoxycarbonyl)-2-(5-(benzyloxy)-2-bromo-4-methoxyphenyl)vinylcarbamate (S16). A 50-mL round-bottomed flask equipped with a magnetic stirring bar was charged with 5-benzyloxy-2-bromo-

4-methoxybenzaldehyde (**S14**) (3.21 g, 10.0 mmol), phosphonate **S15** (3.48 g, 10.5 mmol), and dry dichloromethane (20 mL). The reaction mixture was cooled to 0 °C. To the solution was added 1,1,3,3-tetramethylguanidine (1.51 mL, 12.0 mmol). The reaction mixture was let warm to room temperature over 2 h, after which time TLC (hexane-ethyl acetate = 1:1) indicated complete consumption of **S14**. To the solution was added 1 M hydrochloric acid, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. Recrystallization from hexane-ethyl acetate provided **S16** as fine colorless needles (5.03 g, 9.56 mmol, 96%). Mp. 159.1-159.7 °C (hexane-ethyl acetate). R_f = 0.41 (hexane-ethyl acetate = 1:1). ^1H NMR (400 MHz, CDCl_3): δ 7.41 (s, 1H), 7.36-7.24 (m, 10H), 7.18 (s, 1H), 7.05 (s, 1H), 6.29 (brs, 1H), 5.06 (s, 2H), 4.89 (s, 2H), 3.88 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 165.5, 153.4, 150.7, 147.1, 136.3, 135.6, 129.2, 128.58, 128.52, 128.36, 128.31, 128.1, 127.3, 126.0, 124.1, 116.8, 115.6, 113.7, 71.0, 67.6, 56.1, 52.8. IR (neat, cm^{-1}): 1724, 1696, 1598, 1523, 1497, 1435, 1262, 1206, 1171, 1069, 697. Anal. calcd. for $\text{C}_{26}\text{H}_{24}\text{BrNO}_6$: C, 59.33; H, 4.60; N, 2.66; Found: C, 59.08; H, 4.60; N, 2.80.

Methyl 5-(benzyloxy)-6-methoxy-1H-indole-2-carboxylate (S17). A flame-dried 30-mL round-bottomed flask equipped with a magnetic stirring bar was charged with benzyl (Z)-1-(methoxycarbonyl)-2-(5-benzyloxy-2-bromo-4-methoxyphenyl)vinylcarbamate (**S16**) (1.28 g, 2.43 mmol), copper iodide (462.8 mg, 2.43 mmol), and cesium acetate (2.33 g, 12.1 mmol). The flask was evacuated then backfilled with argon. To the mixture was added dry DMSO (12.2 mL). The resulting pale green solution was stirred at 90 °C under argon atmosphere for 24 h, after which time TLC (hexane-ethyl acetate = 1:1) indicated complete consumption of **S16**. The reaction mixture was poured into 5% aqueous sodium chloride in 10% aqueous ammonium hydroxide and extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford indolecarboxylic acid methyl ester **S17** (862.1 mg, 1.94 mmol, 80%) as white solid, which can be purified by recrystallization from hexane-ethyl acetate to provide colorless fine needles. Mp. 182.7-183.5 °C (hexane-ethyl acetate). R_f = 0.38 (hexane-ethyl acetate = 1:1). ^1H NMR (400 MHz, CDCl_3): δ 8.74 (brs, 1H), 7.48 (d, 2H, J = 7.2 Hz), 7.37 (dd, 2H, J = 7.2, 6.8 Hz), 7.31 (dd, 1H, J = 6.8, 6.8 Hz), 7.08 (s, 1H), 7.06 (dd, 1H, J = 2.0, 0.8 Hz), 6.86 (s, 1H), 5.17 (s, 2H), 3.94 (s, 3H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 162.2, 150.7, 145.1, 137.2, 132.4, 128.5, 127.8, 127.3, 125.6, 120.3, 108.9, 105.7, 93.9, 71.5, 56.1, 51.8. IR (neat, cm^{-1}): 1683, 1524, 1285, 1255, 1212, 1148. Anal. calcd. for $\text{C}_{18}\text{H}_{17}\text{NO}_4$: C, 69.44; H, 5.50; N, 4.50; Found: C, 69.17; H, 5.74; N, 4.42.

5-(Benzyloxy)-6-methoxy-1H-indole-2-carboxylic acid (S18). A 30-mL round-bottomed flask equipped with a magnetic stirring bar was charged with indole carboxylic acid methyl ester **S17** (175.2 mg, 0.563

mmol), 1,4-dioxane (6.0 mL), and water (3.0 mL). To the colorless solution was added LiOH·H₂O (210.0 mg, 5.00 mmol). The solution was stirred at 50 °C for 2 h, after which time TLC (hexane-ethyl acetate = 1:1) indicated complete consumption of **S17**. The reaction mixture was poured into 3 M hydrochloric acid and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give the corresponding indole carboxylic acid **S18** (168.1 mg, quant.) as off-white solid. Further purification can be performed by recrystallization from hexane-ethyl acetate to afford pale yellow prisms. Mp. 207.6-208.9 °C (hexane-ethyl acetate). *R*_f = 0.10 (hexane-ethyl acetate = 1:1). ¹H NMR (400 MHz, acetone-*d*₆): δ 10.98 (brs, 1H), 10.57 (brs, 1H), 7.52 (d, 2H, *J* = 7.6 Hz), 7.38 (dd, 2H, *J* = 7.6, 7.2 Hz), 7.31 (t, 2H, *J* = 7.2 Hz), 7.23 (s, 1H), 7.06 (s, 2H, overlapped), 5.11 (s, 2H), 3.86 (s, 3H). ¹³C NMR (100 MHz, acetone-*d*₆): δ 162.8, 151.6, 146.2, 138.8, 134.1, 129.1, 128.5, 128.4, 127.1, 121.4, 109.1, 106.4, 95.5, 71.9, 56.1. IR (neat, cm⁻¹): 3417, 2941, 1670, 1532, 1251, 1006. Anal. calcd. for C₁₇H₁₅NO₄: C, 68.68; H, 5.09; N, 4.71; Found: C, 68.57; H, 5.29; N, 4.61. (**S18** is also commercially available from Spectrum Chemical.)

5-(Benzyloxy)-6-methoxy-1H-indole-2-carbonyl chloride (4). A flame-dried 20-mL round-bottomed flask equipped with a magnetic stirring bar was charged with indole carboxylic acid **S18** (647.5 mg, 2.18 mmol) and dry dichloromethane (20 mL). To the white suspension was added thionyl chloride (5.0 mL) and the mixture was heated to reflux for 30 min, after which time TLC (hexane-ethyl acetate = 1:1) indicated complete consumption of **S18**. The reaction mixture was concentrated under reduced pressure to give crude left fragment **4** (689.2 mg) as light yellow powder, which was used for the next coupling reaction without further purification.

0.48 (hexane-ethyl acetate = 0.48). ^1H NMR (400 MHz, CDCl_3): δ 9.83 (brs, 1H), 7.47 (d, 2H, $J = 7.2$ Hz), 7.36 (dd, 2H, $J = 7.2, 7.2$ Hz), 7.32-7.18 (m, 12H), 6.99 (s, 1H), 6.92 (s, 1H), 6.88 (s, 1H), 6.37 (s, 1H), 5.14 (s, 2H), 5.07 (s, 2H), 4.80 (s, 2H), 4.43-4.32 (m, 1H), 4.28-4.15 (m, 1H), 4.11-3.97 (m, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.26 (dd, 1H, $J = 16.8, 5.6$ Hz), 2.92 (dd, 1H, $J = 16.8, 5.6$ Hz), 0.81 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 160.8, 152.4, 150.2, 144.8, 143.4, 137.4, 135.9, 134.1, 133.0, 131.9, 128.6, 128.51, 128.49, 128.41, 128.39, 128.3, 128.1, 127.9, 127.7, 127.62, 127.59, 127.3, 127.0, 125.6, 120.2, 113.8, 109.6, 108.2, 105.7, 94.17, 94.14, 71.5, 70.9, 70.6, 66.2, 55.88, 52.1, 33.6, 31.5, 25.6, 22.6, 17.9, 14.1, -4.8, -4.9. IR (neat, cm^{-1}): 3293, 2951, 1773, 1717, 1608, 1517, 1390, 1238, 838, 697. $[\alpha]_{\text{D}}^{23} = -16.5$ (c 1.48, CHCl_3). HRMS-FAB calcd. for $\text{C}_{51}\text{H}_{53}\text{N}_3\text{O}_9\text{Si}$ ($\text{M}^+ + \text{H}$), 879.3551; found 879.3554.

(-)-((8*S*)-4-Benzoyloxy-3-benzyloxycarbonyl-2-methoxycarbonyl-8,9-dihydro-8-(methanesulfonyloxy)pyrrolo[3,2-*f*]quinolin-6(7*H*)-yl)(5-(benzyloxy)-6-methoxy-1*H*-indol-2-yl)methanone (S19). A flame-dried 100-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **22** (1.76 g, 2.00 mmol) and dry THF (20 mL). TBAF (1 M in THF, 2.10 mL, 2.10 mmol) was added to the solution and the resulting mixture was stirred for 30 min, after which time TLC (hexane-ethyl acetate = 1:1) indicated complete consumption of **22**. THF was removed under reduced pressure. The residue was dissolved in dry dichloromethane (20 mL) and pyridine (3.24 mL, 40.0 mmol). The resulting mixture was cooled to 0 °C and MsCl (1.55 mL, 20.0 mmol) was added to the solution dropwise over 5 min. The reaction mixture was stirred at room temperature for 4 h, after which time TLC (hexane-ethyl acetate = 1:3) indicated complete consumption of the secondary alcohol. The mixture was diluted with ethyl acetate and washed with 1 M hydrochloric acid, aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane-ethyl acetate-dichloromethane = 2:1:2 to 1:1:2, gradient) to afford **S19** (1.64 g, 1.94 mmol, 97%) as beige solid, which was recrystallized from hexane-dichloromethane to give colorless prisms. Mp: 189.9-190.8 °C (hexane-dichloromethane). $R_f = 0.42$ (hexane-ethyl acetate = 1:3). ^1H NMR (400 MHz, CDCl_3): δ 9.90 (brs, 1H), 7.49-7.13 (m, 16H), 6.92 (s, 1H), 6.85 (s, 1H), 6.81 (s, 1H), 6.28 (s, 1H), 5.37 (s, 1H), 5.08 (s, 2H), 5.04 (m, 2H), 4.76 (s, 2H), 4.70-4.56 (m, 1H), 4.08-3.94 (m, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.36 (dd, 1H, $J = 17.2, 4.2$ Hz), 3.26 (dd, 1H, $J = 17.2, 3.2$ Hz), 2.78 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 163.7, 160.7, 152.3, 150.6, 145.0, 144.0, 137.3, 135.7, 134.0, 133.0, 132.2, 128.75, 128.72, 128.65, 128.5, 128.4, 128.3, 128.0, 127.9, 127.72, 127.70, 127.3, 126.7, 126.6, 125.8, 120.2, 111.7, 109.2, 108.6, 106.4, 105.6, 94.1, 71.4, 71.0, 70.8, 55.9, 52.3, 38.5, 31.5, 30.3, 22.6, 14.1. IR (neat, cm^{-1}): 3291, 3030, 2947, 1771, 1716, 1605, 1517, 1385, 1308, 1239, 1172, 1023, 966, 891, 754, 697. $[\alpha]_{\text{D}}^{23} = -30.3$ (c 1.94, CHCl_3). Anal. calcd. for $\text{C}_{46}\text{H}_{41}\text{N}_3\text{O}_{11}\text{S}$: C, 65.47; H, 4.90; N, 4.98; Found: C, 65.40; H, 4.95; N, 4.95.

(–)-(8*S*)-4-Benzoyloxy-6-(5-benzoyloxy-6-methoxy-1*H*-indol-2-yl)carbonyl-6,7,8,9-tetrahydro-8-methanesulfonyloxy-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylic acid (23**).** A 50-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **S19** (1.18 g, 1.40 mmol) and THF (21 mL). To the resulting suspension was added LiOH•H₂O (1.17 g, 28.0 mmol) in water (7.0 mL). The suspension was stirred for 18 h at room temperature, after which time TLC (methanol-chloroform = 1:9) indicated completion of the reaction. The reaction mixture was acidified with 1 M hydrochloric acid and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give the analytically pure **23** (897.3 mg, 1.29 mmol, 92%) as pale yellow solid. *R*_f = 0.18 (methanol-chloroform = 1:9). ¹H NMR (500 MHz, acetone-*d*₆): δ 11.11 (brs, 1H), 10.48 (brs, 1H), 7.41–7.18 (m, 9H), 7.06 (s, 2H), 6.79 (s, 1H), 6.32 (s, 1H), 5.48–5.41 (m, 1H), 5.05 (s, 2H), 4.94 (d, 1H, *J* = 12.3 Hz), 4.90 (d, 1H, *J* = 12.3 Hz), 4.59 (dd, 1H, *J* = 13.8, 4.0 Hz), 4.10 (dd, 1H, *J* = 13.8, 3.1 Hz), 3.84 (s, 3H), 3.56 (dd, 1H, *J* = 18.3, 6.1 Hz), 3.30 (dd, 1H, *J* = 18.3, 4.6 Hz), 3.09 (s, 3H). ¹³C NMR (125 MHz, DMSO-*d*₆): δ 163.3, 162.5, 161.5, 152.3, 149.1, 144.3, 143.3, 142.8, 137.4, 136.8, 136.2, 134.2, 131.8, 128.44, 128.37, 128.32, 127.8, 127.7, 127.5, 127.1, 126.6, 119.5, 111.6, 106.7, 104.6, 94.5, 79.2, 75.1, 70.2, 55.5, 49.3, 37.7, 29.5. IR (neat, cm^{–1}): 3288, 2935, 1770, 1600, 1519, 1311, 1241, 1197, 1171, 905, 751, 697. [α]_D²⁶ = –44 (*c* 0.10, CHCl₃). HRMS-FAB calcd. for C₃₇H₃₃N₃O₉S (M⁺), 695.1938; found 695.1938.

(–)-Methyl 3-((8*S*)-4-benzoyloxy-6-(5-benzoyloxy-6-methoxy-1*H*-indol-2-yl)carbonyl-6,7,8,9-tetrahydro-8-methanesulfonyloxy-3*H*-pyrrolo[3,2-*f*]quinoline-2-yl)carbonyl-4-hydroxy-5-methoxy-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-thiocarboxylate (24**).** A flame-dried 100-mL round-bottomed flask equipped with a magnetic stirring bar was charged with the left segment **3** (742.8 mg, 1.48 mmol) and dry THF (12.4 mL). To the resulting mixture was added TBAF (1 M THF solution, 1.61 mL, 1.61 mmol) dropwise over 5 min. The reaction mixture was stirred for 30 min, after which time TLC (hexane-ethyl acetate = 1:1) indicated complete removal of the Fmoc group. To the reaction mixture were added WSCD•HCl (1.19 g, 6.20 mmol), the middle-left segment **23** (860.4 mg, 1.24 mmol), and HOBt (379.8 mg, 2.48 mmol). The mixture was stirred vigorously at room temperature for 2 h, after which time TLC (methanol-chloroform = 1:9) indicated complete consumption of **27**. The reaction mixture was diluted with chloroform (25 mL) and passed through silica pad (THF-chloroform = 1:2) to afford the desired coupling product **24** (1.15 g, 1.19 mmol, 96%) as yellow powder. *R*_f = 0.61 (methanol-chloroform = 1:9). ¹H NMR (500 MHz, DMF-*d*₇): δ 12.07 (brs, 1H), 11.98 (brs, 1H), 11.38 (brs, 1H), 11.19 (s, 1H), 7.51 (d, 2H, *J* = 7.2 Hz), 7.48–7.42 (m, 2H), 7.41–7.35 (m, 2H), 7.34–7.25 (m, 6H), 7.16 (s, 1H), 7.11 (s, 1H), 6.88 (s, 1H), 6.48 (s, 1H), 5.47–5.40 (m, 1H), 5.08 (s, 2H), 5.02 (d, 1H, *J* = 12.3 Hz), 4.98 (d, 1H, *J* = 12.3 Hz), 4.90–4.83 (m, 2H), 4.70 (dd, 1H, *J* = 13.0, 3.3 Hz), 4.17 (d, 1H, *J* = 12.2 Hz), 3.95 (s, 3H), 3.87 (s, 3H), 3.64 (dd, 1H, *J* = 17.6, 6.2 Hz), 3.45 (t, 2H, *J* = 8.0 Hz), 3.36 (dd, 1H, *J* = 17.6, 3.4 Hz), 3.25 (s, 3H), 2.47 (s, 3H). ¹³C NMR (125 MHz, DMF-*d*₇): δ 183.1, 164.0, 161.8, 150.5, 145.6, 144.4, 140.4, 138.7, 137.7, 135.6, 134.3, 133.1, 133.0, 132.6, 131.2, 130.3, 129.1, 129.0, 128.9, 128.8, 128.4, 128.3, 128.23, 128.15, 127.1, 126.4, 122.8, 120.9, 118.5, 112.1, 107.5,

106.7, 105.9, 105.5, 95.6, 76.4, 71.6, 70.8, 64.2, 60.7, 56.1, 54.3, 49.9, 38.1, 28.3, 10.9. IR (neat, cm^{-1}): 3312, 2929, 1607, 1512, 1303, 1235, 900, 867, 797, 726, 694, 526. $[\alpha]_{\text{D}}^{24} = -120$ (c 0.38, DMF). HRMS-FAB calcd. for $\text{C}_{50}\text{H}_{46}\text{N}_5\text{O}_{11}\text{S}_2$ ($\text{M}+\text{H}^+$), 956.2635; found 956.2673.

(-)-Methyl 3-((8*S*)-4-hydroxy-6-(5-hydroxy-6-methoxy-1*H*-indol-2-yl)carbonyl-6,7,8,9-tetrahydro-8-methanesulfonyloxy-3*H*-pyrrolo[3,2-*f*]quinoline-2-yl)carbonyl-4-hydroxy-5-methoxy-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-thiocarboxylate (25**).** A flame-dried 100-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **24** (480.8 mg, 0.496 mmol), pentamethylbenzene (735.3 mg, 4.96 mmol), and dry dichloromethane (24.8 mL). The solution was cooled to $-78\text{ }^{\circ}\text{C}$. To the solution was added BCl_3 (1.0 M in dichloromethane, 1.98 mL, 1.98 mmol) dropwise over 5 min. The resulting mixture was stirred vigorously at $-78\text{ }^{\circ}\text{C}$ for 15 min, after which time TLC (methanol-chloroform = 1:9) indicated complete consumption of **24**. The excess BCl_3 was quenched with 10% MeOH/ CHCl_3 at $-78\text{ }^{\circ}\text{C}$. The reaction mixture was purified by silica gel chromatography (methanol-chloroform = 1:9) to give debenzylated product **25** as fine yellow powder (320.1 mg, 0.413 mmol, 83%). $R_f = 0.46$ (methanol-chloroform = 1:9). ^1H NMR (500 MHz, $\text{DMF}-d_7$): δ 12.04 (brs, 1H), 11.53 (brs, 1H), 11.31 (s, 1H), 11.25 (brs, 1H), 9.87 (s, 1H), 8.48 (s, 1H), 7.47 (d, 1H, $J = 2.3$ Hz), 7.34 (d, 1H, $J = 2.3$ Hz), 7.02 (s, 1H), 6.89 (s, 1H), 6.64 (s, 1H), 6.37 (s, 1H), 5.52-5.47 (m, 1H), 4.89-4.85 (m, 2H), 4.60 (d, 1H, $J = 14.2$ Hz), 4.13 (d, 1H, $J = 14.2$ Hz), 3.95 (s, 3H), 3.85 (s, 3H), 3.61 (dd, 1H, $J = 18.0, 6.2$ Hz), 3.5 (2H were obscured by water), 3.32 (dd, 1H, $J = 18.0, 4.2$ Hz), 3.24 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (125 MHz, $\text{DMF}-d_7$): δ 183.1, 149.0, 143.8, 142.5, 140.5, 135.6, 134.2, 133.2, 133.1, 132.2, 130.5, 130.0, 129.6, 128.9, 128.8, 128.7, 125.9, 122.9, 121.4, 118.5, 110.3, 107.7, 107.6, 107.00, 106.98, 105.6, 94.9, 79.8, 76.7, 60.7, 56.1, 54.1, 49.8, 38.1, 28.3, 10.9. IR (neat, cm^{-1}): 3334, 2929, 1634, 1523, 1505, 1437, 1315, 1232, 1197, 1172, 1119, 1019, 871, 755, 529. $[\alpha]_{\text{D}}^{24} = -100$ (c 0.18, DMF). HRMS-FAB calcd. for $\text{C}_{36}\text{H}_{33}\text{N}_5\text{O}_{11}\text{S}_2$ (M^+), 775.1618; found 775.1617.

(+)-Yatakemycin (1**).** A 500-mL round-bottomed flask equipped with a magnetic stirring bar was charged with sodium bicarbonate (1.79 g, 21.3 mmol) and water (11.8 mL). To the aqueous sodium bicarbonate was added **29** (550.8 mg, 0.710 mmol) in DMF (23.7 mL). The resulting mixture was stirred vigorously at room temperature for 2 h, after which time TLC (methanol-chloroform = 1:9) indicated complete consumption of **29**. The reaction mixture was acidified with AcOH (2.44 mL) and the mixture was dried under reduced pressure. The residue was purified by silica gel chromatography (methanol-chloroform = 10:90 to 15:85, gradient) to afford (+)-yatakemycin (**1**) (453.8 mg, 0.669 mmol, 94%) as fine pale yellow powder. $R_f = 0.45$ (methanol-chloroform = 1:9). ^1H NMR (500 MHz, pyridine- d_5): δ 14.65 (brs, 1H), 13.72 (s, 1H), 12.74 (s,

1H), 11.71 (s, 1H), 10.71 (brs, 1H), 7.73 (s, 1H), 7.64 (s, 1H), 7.52 (d, 1H, $J = 2.0$ Hz), 7.24 (s, 1H), 6.74 (s, 1H), 4.54-4.42 (m, 4H), 4.03 (s, 3H), 3.85 (s, 3H), 3.23 (t, 2H, $J = 8.1$ Hz), 2.98 (dd, 1H, $J = 7.6, 4.8$ Hz), 2.49 (s, 3H), 1.77 (dd, 1H, $J = 7.7, 3.8$ Hz), 1.45 (t, 1H, $J = 4.8$ Hz). ^{13}C NMR (125 MHz, pyridine- d_5): δ 183.5, 178.5, 161.92, 161.89, 161.3, 150.4, 144.8, 140.5, 136.0, 134.5, 133.4, 133.1, 132.7, 130.5, 130.3, 129.2, 128.9, 122.4, 122.0, 118.6, 112.9, 107.8, 107.66, 107.64, 106.6, 94.4, 60.5, 55.9, 55.6, 53.9, 31.5, 28.2, 26.1, 24.0, 11.2. IR (neat, cm^{-1}): 3312, 2925, 2852, 1633, 1505, 1386, 1290, 1256, 1017, 870, 750. $[\alpha]_{\text{D}}^{23} = +99$ (c 0.060, DMF). HRMS-FAB calcd. for $\text{C}_{35}\text{H}_{30}\text{N}_5\text{O}_8\text{S}$ ($\text{M}+\text{H}^+$), 680.1838; found 680.1815.

^1H NMR of Synthetic (+)-Yatakemycin (**1**) (500 MHz, pyridine- d_5)