Supporting information for:

Total Synthesis of (±)-Mitorubrinic Acid

Maurice A. Marsini, Kristoffer M. Gowin, and Thomas R.R. Pettus*

Department of Chemistry and Biochemistry,
University of California at Santa Barbara

Santa Barbara, CA 93106-9150

pettus@chem.ucsb.edu

Table of Contents

- I. General Techniques, page S1 - S2**
- II. Experimental Procedures for compounds 4, 10-22, pages S2 - S10**
- III. References**
- IV. ¹H NMR spectra, ¹³C NMR spectra, IR spectra, LRMS spectra for compounds 10-20, 22, and 4, pages S11 - S41**

I. General Techniques – In reactions, where water was *not* present as solvent, reagent, or by-product, vessels were flame-dried under a slow nitrogen flow. A slight positive pressure of dry nitrogen was maintained via rubber septa seal during the course of the reaction. The nitrogen stream originated from a regulated high pressure 55 L N₂(l) tank and was further dried by passage through a Drierite® tube. Reagents were purified according to the procedures describe in the *Perrin & Perrin* laboratory manual.

Reactions were monitored by analytical thin-layer chromatography on EM-Science hard layer silica gel-60^{F-250} plates cut into 1x2.5cm pieces. Visualization was effected by ultraviolet light (254 nm), followed by staining [Seebach or permanganate] the plate, followed by drying on a *Fisher*® micro-hot plate. The Seebach stain was made with 25 g of phosphomolybdic acid, 10 g of cerium sulfate, 60 mL H₂SO₄, and 940 mL of H₂O. The potassium permanganate stain was made with 200 mL H₂O, 1.33 g KMnO₄, 13.33 g of K₂CO₃, and 4 mL of 5% NaOH.

All reactions were stirred with Teflon®-coated magnetic stir bars by *Thomas*® Magna-Matic magnetic stirrers. Removal of solvents was typically accomplished using a *Buchi*® rotary evaporator (model #R-114) connected to a Fisher KNF®-vacuum pump (model #UN820-3). The condenser was cooled to 0 °C by a Fisher® chiller circulator bath (model #1013S). If the product was non-volatile, trace solvents were removed using a *Labconco*® freeze dryer system at a pressure of approximately 0.01 mmHg. Ethyl

acetate (anhydrous) and dimethylformamide (anhydrous) were utilized directly from the bottle. Deuterated chloroform was filtered through basic alumina prior to use. Deuterated dimethylformamide was employed directly from the ampoule. Solvents were distilled before use, under a slight positive pressure of nitrogen. Diethyl ether, tetrahydrofuran, dioxane, dimethoxyethane, benzene, and toluene were distilled from sodium and benzophenone. Dichloromethane, 1,2-dichloroethane, and nitromethane were distilled from CaH₂. Atmosphere (1 atm) hydrogenations were carried out using a balloon. A pressure Parr® shaker (1-100 psi) or a Parr® bomb (100-2000 psi) were used for high-pressure hydrogenations.

For distillation, a specific low pressure (760 – 1 mm Hg) was obtained and monitored with a Buchi®-vacuum controller (model #B-721) in combination with a Welch® direct drive pump (model #8915A). Lower pressures were achieved using a vacuum manifold connected to an oil-diffusion pump and backed by a Welch® direct drive vacuum pump, (model #8910A). Chromatography was performed following the method prescribed by W. C. Still.

¹H-NMR spectra were recorded at 400 MHz on a Varian® Unity Inova spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance of CDCl₃ (7.27 ppm) or DMF-d₇ (2.92 ppm). ¹³C NMR spectra were recorded at (100 MHz) with a solvent resonance of CDCl₃ (77.23 ppm). Infrared spectra were recorded on a Shimadzu® FTIR-8300 Fourier transform infrared spectrometer with 2 cm resolution in a solution cell (CH₂Cl₂). Infrared frequencies are reported in reciprocal centimeters (cm⁻¹). Specific rotations were measured using a JASCO DIP-1000 polarimeter with a 10 cm (1 mL) glass cell. UV-Vis spectra were recorded using a Beckman DU-640 UV-Vis spectrophotometer. Silica columns for HPLC, supplied by Jones Chromatography®, were 25 cm long in length and contained 5 μm spherisorb. In some instances, flash chromatography was performed using a Jones Flashmaster Solo model 605. Mass spectra were recorded on a VG-7035 mass spectrometer at an ionizing voltage of either 70 or 20 eV.

II. Experimental Procedures

4-O-(*t*-butoxycarbonyl)-2-hydroxy-3,5-dimethyl methylbenzoate (10a)

To a stirred solution of 2,4-dihydroxy-3,5-dimethyl methylbenzoate (10 g, 50.97 mmol) in CH₂Cl₂ (60 mL) was added di-*tert*-butyl dicarbonate (11.08 g, 59.5 mmol). To this solution was added 4-dimethylaminopyridine (1.04 g, 0.85 mmol) and N-ethyldiisopropylamine (3.95 mL, 2.27 mmol). The resulting solution was stirred for 4 hours, after which it was concentrated *in vacuo* and purified by flash chromatography on silica gel (10% EtOAc/Hexanes) providing 13.76 g of mono-Boc phenol **10a** as a white crystalline solid. Isolated yield: 93%. Mp: 67-69 °C.

¹H NMR [CDCl₃, 400 MHz] δ 11.89(s, 1 H), 6.53(s, 1 H), 3.95(s, 3 H), 2.5(s, 3 H), 2.09(s, 3 H), 1.56(s, 9 H); ¹³C NMR [CDCl₃, 100 MHz] δ 172.54, 162.92, 153.21, 151.26, 139.72, 116.88, 116.29, 109.81, 83.98, 52.39, 29.92, 24.26, 8.98; IR [CH₂Cl₂

solution, $\nu_{\max}$ cm^{-1}] 2984, 2937, 2361, 1757, 1661, 1250, 1151, 1115, 756, 698; UV-Vis ($\lambda_{\max}$ nm) 239, 339; HRMS (ESI) m/z calculated for $\text{C}_{15}\text{H}_{20}\text{O}_6$ 296.12599, found 319.1155 ($\text{M}+\text{Na}$)⁺.

4-O-(*t*-butoxycarbonyl)-3,5-dimethyl-2-(trimethylsilyl)ethoxy methylbenzoate (11)

To a stirred solution of **1** (7.68 g, 25.9 mmol) in THF (30 mL) was added triphenylphosphine (10.19 g, 38.9 mmol) and 2-(trimethylsilyl)ethanol (5.57 mL, 38.9 mmol). The solution was cooled to 0 °C, and diisopropyl diazodicarboxylate (DIAD) (7.65 mL, 38.9 mmol) was added dropwise. The solution was stirred for 1 hour, after which it was concentrated *in vacuo* and redissolved in 1:1 Et_2O /Hexanes, causing triphenylphosphine oxide to precipitate from the solution. The resulting solution was filtered through a pad of Celite, concentrated, and purified by flash chromatography on silica gel (10% Et_2O /Hexanes) providing 10.18 g of bis-protected methyl ester **11** as a clear, viscous oil. Isolated yield: 99%.

^1H NMR [CDCl_3 , 400 MHz] δ 6.75(s, 1H), 3.96-3.92(m, 2H), 3.90(s, 3H), 2.90(s, 3H), 2.26(s, 3H), 1.56(s, 9H), 1.15-1.11(m, 2H), 0.04(s, 9H); ^{13}C NMR [CDCl_3 , 100 MHz] δ 168.77, 155.89, 151.55, 150.93, 134.48, 126.85, 122.25, 119.07, 83.83, 72.83, 52.39, 27.84, 19.36, 19.19, 9.68, -1.25; IR [CH_2Cl_2 solution, $\nu_{\max}$ cm^{-1}] 2955, 1757, 1730, 1577, 1458, 1371, 1275, 1253, 1145, 1105, 1063, 860, 839; HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{32}\text{O}_6\text{Si}$ 396.19682, found 419.1882 ($\text{M}+\text{Na}$)⁺.

4-O-(*t*-butoxycarbonyl)-3-methyl-5-(2-oxopropyl)-2-(trimethylsilyl)ethoxy methylbenzoate (12)

To a stirred solution of diisopropylamine (3.72 mL, 26.5 mmol) in THF (12 mL) at -78 °C was added *n*BuLi (16 mL, 1.61 M in hexanes) dropwise. The cloudy white solution was warmed to 0 °C and allowed to stir for 15 minutes. The resulting clear solution was then cooled to -78 °C, and a solution of bis-protected methyl ester **11** (10 g, 25.2 mmol) in THF (126 mL) was added via cannula, resulting in a deep red solution. After 15 minutes, TMEDA (3.81 mL, 25.2 mmol) was added via syringe, followed immediately by *N*-methoxy-*N*-acetamide (5.36 mL, 50.4 mmol) by syringe, and the reaction was allowed to stir for 2 hours at -78 °C, slowly turning from a deep red to bright orange colored solution. The reaction was then quenched by the addition of 2N HCl (40 mL) and ethyl acetate (40 mL) and allowed to warm to room temperature with stirring over 2 hours. The solution was then extracted with ethyl acetate (3 x 150 mL), and the combined organic layers were washed with water, brine, dried over MgSO_4 , filtered, and concentrated. Purification by flash chromatography on silica gel (13% EtOAc /Hexanes) provided 8.98 g of ketone **12** as a clear, slightly yellow oil. Isolated yield: 81%.

^1H NMR [CDCl_3 , 400 MHz] δ 6.78(s, 1H), 3.96-3.92(m, 2H), 3.85(s, 3H), 3.66(s, 3H), 2.12(s, 3H), 1.54(s, 9H), 1.24-1.12(m, 2H), 0.02(s, 9H); ^{13}C NMR [CDCl_3 , 100 MHz] δ 205.34, 168.12, 156.82, 151.42, 151.29, 131.8, 126.29, 124.38, 119.87, 84.01, 72.92, 52.45, 48.48, 29.88, 29.56, 27.81, 19.16, 9.89, -1.26; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}] 2955, 1759, 1735, 1726, 1577, 1371, 1275, 1251, 1144, 1105, 1063, 860, 839; HRMS (ESI) m/z calculated for $\text{C}_{22}\text{H}_{34}\text{O}_7\text{Si}$ 438.20738, found 461.1964 ($\text{M}+\text{Na}$) $^+$.

8-(2-(trimethylsilyl)ethoxy)-3,7-dimethyl-1-oxo-1H-isochromen-6-yl *tert*-butyl carbonate (14)

To a stirred suspension of NaH (543 mg, 21.5 mmol) (95%, dispersion in mineral oil) in THF (287 mL) at $-20\text{ }^\circ\text{C}$ was added ketone **12** (8.98 g, 20.5 mmol) in THF (100 mL) dropwise via cannula. After complete addition of **12**, 2 drops of *t*BuOH were added and the solution was stirred for 1.5 hours with warming to $0\text{ }^\circ\text{C}$. The reaction was then quenched with a saturated aqueous solution of NH_4Cl (40 mL) and allowed to warm to room temperature. The solution was then concentrated *in vacuo*, redissolved in ethyl acetate, and extracted (3x 100 mL). The combined organic layers were washed with water and brine, dried over MgSO_4 , filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (10% EtOAc/Hexanes) to provide 8.12 g of isocoumarin **4** as a white amorphous solid. Isolated yield: 98%.

^1H NMR [CDCl_3 , 400 MHz] δ 6.87(s, 1H), 6.12(s, 1H), 4.06-4.01(m, 2H), 2.21(s, 3H), 2.20(s, 3H), 1.57(s, 9H), 1.36-1.31(m, 2H), 0.04(s, 9H); ^{13}C NMR [CDCl_3 , 100 MHz] δ 161.05, 159.32, 155.16, 154.8, 125.33, 113.28, 103.41, 99.86, 97.97, 84.49, 66.75, 27.81, 19.61, 9.99, -1.22; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}] 2957, 2359, 1760, 1732, 1273, 1255, 1122, 1099, 862, 837; HRMS (ESI) m/z calculated for $\text{C}_{21}\text{H}_{30}\text{O}_6\text{Si}$ 406.1812, found 429.1712 ($\text{M}+\text{Na}$) $^+$.

3-(2-(trimethylsilyl)ethoxy)-4-formyl-2-methyl-5-(2-oxopropyl)phenyl-*tert*-butyl carbonate (14a)

To a stirred solution of isocoumarin **14** (1.00 g, 2.594 mmol) in THF (13 mL) at $-78\text{ }^\circ\text{C}$ was added a solution of diisobutylaluminum hydride (3.113 mL, 1 M in hexanes) dropwise via syringe, causing the clear solution to become a light yellow-green color. The resulting solution was allowed to stir at $-78\text{ }^\circ\text{C}$ for 30 minutes, after which it was quenched by the addition of ethyl acetate (1 mL) and a 1M solution of Rochelle's salt (4 mL) and allowed to stir for 1 hour at room temperature. The solution was extracted with ethyl acetate (3 x 30 mL), and the organic layers were washed with water and brine, dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography to provide 875.8 mg of bis-protected keto-aldehyde **14a** as a white amorphous solid. Isolated yield: 83%.

^1H NMR [CDCl_3 , 400 MHz] δ 10.36(s, 1H), 6.77(s, 1H), 3.99-3.98(m, 2H), 3.96(s, 2H), 2.31(s, 3H), 2.17(s, 3H), 1.56(s, 9H), 1.25-1.21(m, 2H), 0.05(s, 9H); ^{13}C NMR [CDCl_3 , 100 MHz] δ 205.13, 191.94, 164.23, 154.31, 150.97, 135.73, 125.64, 124.64, 122.01, 84.37, 75.03, 48.90, 30.20, 27.81, 19.05, 9.66, -1.23; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}] 2984, 2957, 2870, 2559, 2341, 1759, 1722, 1684, 1574, 1371, 1275, 1251, 1155, 1109, 1080, 860, 839; HRMS (ESI) m/z calculated for $\text{C}_{21}\text{H}_{32}\text{O}_6\text{Si}$ 408.1968, found 431.1865 ($\text{M}+\text{Na}$) $^+$.

2,4-dihydroxy-3-methyl-6-(2-oxopropyl)benzaldehyde **15**¹

To a stirred solution of bis-protected keto-aldehyde (200 mg, 0.4895 mmol) in CH_3NO_3 (1.5 mL) was added ZnBr_2 (437 mg, 1.96 mmol) at room temperature. The solution was stirred for 5 hours, after which it was quenched by the addition of 2 N HCl and allowed to stir for an additional 2 hours. The solution was then extracted with ethyl acetate (3 x 30), and the combined organic layers were washed with water, brine, dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (40% EtOAc/Hex) to afford 84.9 mg of keto-aldehyde **15**. All spectral data match the data reported in the literature.¹ Isolated yield: 84%.

Azaphilone **17**

To a solution of **15** (20 mg, .09612 mmol) in AcOH (320 μL , 0.3M) was added anhydrous *p*TsOH (23.7 mg, .1246 mmol) and the reaction was stirred at room temperature for 2 hours. The mixture was concentrated *in vacuo*, redissolved in 1,2-dichloroethane (1.5 mL), and IBX (30.2 mg, .1057 mmol) and tetra-*n*-butyl ammonium iodide (3.6 mg, .009612) was added. The resulting solution was stirred for 6 hours, after which it was quenched by the addition of saturated aqueous $\text{Na}_2\text{S}_2\text{O}_4$ and ethyl acetate. The resulting mixture was extracted with ethyl acetate (3 x 30), and the combined organic layers were washed with pH 8.6 buffer ($\text{Na}_2\text{CO}_3/\text{NaHCO}_3$), water, brine, dried over Na_2SO_4 , filtered, and concentrated. The crude product was purified by flash chromatography (75% EtOAc/Hex) to afford 10 mg of azaphilone **17**. Isolated yield: 57%.

^1H NMR [CDCl_3 , 400 MHz] δ 7.88(s, 1H), 6.14(s, 1H), 5.52(s, 1H), 3.92(s, OH), 2.20(s, 3H), 1.56(s, 3H); ^{13}C NMR [CDCl_3 , 100 MHz] δ ; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}]; HRMS (ESI) m/z calculated for $\text{C}_{11}\text{H}_{10}\text{O}_4$ 206.0579, found 206.05766.

8-(2-(trimethylsilyl)ethoxy)-3-formyl-7-methyl-1-oxo-1*H*-isochromen-6-yl *tert*-butyl carbonate (**14b**)

To a stirred solution of isocoumarin **14** (2.38 g, 5.85 mmol) in anhydrous dioxane (117 mL) was added SeO_2 (974 mg, 8.79 mmol). The resulting solution was then heated to reflux and stirred for 12 hours, over which time Se metal

was deposited on the sides of the reaction vessel. The reaction was then allowed to cool to room temperature, and was filtered through a thick pad of Celite, concentrated *in vacuo*, and purified by flash chromatography on silica gel (15% EtOAc/Hexanes) to afford 1.8 g of aldehyde **14b** as a pink amorphous solid. Isolated yield: 73%.

¹H NMR [CDCl₃, 400 MHz] δ 9.56(s, 1H), 7.25(s, 1H), 7.15(s, 1H), 4.10-4.06(m, 2H), 2.29(s, 3H), 1.59(s, 9H), 1.37-1.33(m, 2H), 0.05(s, 9H); ¹³C NMR [CDCl₃, 100 MHz] δ 183.54, 156.58, 155.39, 150.67, 149.37, 134.91, 130.51, 116.82, 115.09, 114.39, 111.01, 85.09, 73.74, 27.81, 19.36, 10.56, -1.23; IR [CH₂Cl₂ solution, ν_{max} cm⁻¹] 2954, 1753, 1701, 1250, 1151, 1121, 1101, 862, 837; HRMS (ESI) *m/z* calculated for C₂₁H₂₈O₇Si 420.16043, found 443.1506 (M+Na)⁺.

8-(2-(trimethylsilyl)ethoxy)-3-*E*-(*tert*-butylacrylate)-7-methyl-1-oxo-1*H*-isochromen-6-yl *tert*-butyl carbonate (18**)**

To a stirred solution of aldehyde **14a** (2.26 g, 5.39 mmol) in CH₂Cl₂ (27 mL) was added (*tert*-butoxycarbonylmethylene)triphenylphosphorane (2.13 g, 5.65 mmol) as a solid. The reaction was stirred for 3 hours, after which it was concentrated *in vacuo* and redissolved in 1:1 Et₂O/Hexanes, causing precipitation of triphenylphosphine oxide from the solution. The resulting mixture was filtered through a pad of Celite, concentrated *in vacuo*, and purified by flash chromatography (8% EtOAc/Hexanes) to provide 2.1 g of *t*-butyl ester **18** a white amorphous solid. The *E/Z* ratio was found to be greater than 20:1. Isolated yield (*E* isomer): 75%.

¹H NMR [CDCl₃, 400 MHz] δ 7.07(d, *J*=15 Hz, 1H), 7.03(s, 1H), 6.60(d, *J*=15 Hz, 1H), 6.50(s, 1H), 4.08-4.03(m, 2H), 2.23(s, 3H), 1.57(s, 9H), 1.50(s, 9H), 1.36-1.31(m, 2H), 0.04(s, 9H); ¹³C NMR [CDCl₃, 100 MHz] δ 165.66, 161.46, 157.58, 155.24, 150.79, 150.48, 137.05, 133.51, 127.79, 124.36, 115.12, 113.12, 110.27, 84.74, 81.22, 73.32, 28.27, 27.8, 19.31, 10.26, -1.22; IR [CH₂Cl₂ solution, ν_{max} cm⁻¹] 2981, 2957, 1760, 1738, 1707, 1618, 1315, 1253, 1155, 1120, 1101, 860, 839; HRMS (ESI) *m/z* calculated for C₂₇H₃₈O₈Si 518.2336, found 541.2248 (M+Na)⁺.

Lactol 18a

To a stirred solution of *t*-butyl ester **18** (1.81 g, 3.52 mmol) in THF (18 mL) at -78 °C was added a solution of diisobutylaluminum hydride (5.23 mL, 1 M in hexanes) dropwise via syringe, causing the clear solution to become a light yellow-green color. The resulting solution was allowed to warm to room temperature over 4 hours, after which it had turned orange in color. The reaction was then cooled to 0 °C, quenched by the addition of ethyl acetate (15 mL) and a 1M aqueous solution of

Rochelle's salt (15 mL), and allowed to stir for 1 hour at room temperature. The solution was extracted with ethyl acetate (3 x 30 mL), and the combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to provide 1.83 g of the crude lactol **18a** as a yellow-green amorphous solid used directly in the next step. Isolated yield: 100%.

¹H NMR [CDCl₃, 400 MHz] δ 7.09(d, *J*=15 Hz, 1H), 6.80(s, 1H), 6.63(d, *J*=7 Hz, 1H), 6.38(d, *J*=15Hz, 1H), 6.22(s, 1H), 4.09-3.94(m, 2H), 3.05(d, *J*=7 Hz, 1H), 2.17(s, 3H), 1.57(s, 9H), 1.51(s, 9H), 1.26-1.19(m, 2H), 0.06(s, 9H); ¹³C NMR [CDCl₃, 100 MHz] δ 166.35, 155.29, 151.1, 147.36, 137.18, 128.32, 125.1, 121.78, 120.89, 114.36, 109.67, 99.86, 89.16, 84.03, 80.78, 72.83, 28.33, 27.84, 19.25, 10.22, -1.19; IR [CH₂Cl₂ solution, ν_{max} cm⁻¹] 3566, 2933, 2906, 1759, 1703, 1633, 1612, 1369, 1256, 1151, 1119, 1097, 1007, 974, 860, 839; HRMS (ESI) *m/z* calculated for C₂₇H₃₉O₈Si 520.2514, found 543.2386 (M+Na)⁺.

Ketal **18b**

To a stirred solution of lactol **18a** (1.83 g, 3.52 mmol) in anhydrous methanol (11.4 mL) was added anhydrous *p*-toluenesulfonic acid 130 mg, 0.71 mmol). The solution was stirred for 5 min, then diluted with Et₂O (25 mL) and pH 8.5 buffer (15 mL) and allowed to stir for 30 min. The solution was extracted with Et₂O (3 x 25 mL), washed with water and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to provide 1.78 g of crude ketal **18b** as an off white amorphous solid used directly in the next step. Isolated yield: 95%.

¹H NMR [CDCl₃, 400 MHz] δ 7.07(d, *J*=15 Hz, 1H), 6.77(s, 1H), 6.37(d, *J*=15 Hz, 1H), 6.23 (s, 2H), 4.03-3.91(m, 2H), 3.55(s, 3H), 2.15(s, 3H), 1.56(s, 9H), 1.53(s, 9H), 1.25-1.21(m, 2H), 0.07(s, 9H); ¹³C NMR [CDCl₃, 100 MHz] δ 166.39, 151.95, 151.2, 147.46, 137.32, 128.87, 124.98, 120.86, 120.05, 114.3, 110.8, 99.86, 95.74, 83.89, 80.79, 72.53, 55.22, 28.36, 27.84, 19.36, 10.18, -1.2; IR [CH₂Cl₂ solution, ν_{max} cm⁻¹] 2981, 2933, 2370, 1759, 1701, 1633, 1612, 1369, 1272, 1256, 1151, 1122, 1097, 974, 860, 839; HRMS (ESI) *m/z* calculated for C₂₈H₄₂O₈Si 534.2649, found 557.2554 (M+Na)⁺.

Phenol **19**

To a stirred solution of ketal **18b** (1.78 g, 3.33 mmol) in THF (3 mL) at 0 °C was added a solution of tetra-*n*-butylammonium fluoride (20 mL, 1M in THF) dropwise via syringe, resulting in a deep red solution and gradual evolution of gas. The resulting solution was allowed to warm to room temperature and stirred for 6 hours. The reaction was then quenched by the addition of water, followed by Et₂O, and allowed to stir for 10 minutes, resulting in a yellow solution. The resulting solution was

extracted with ethyl acetate (3 x 40 mL), and the combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was triturated (1:4 Et₂O/pentane) to provide 1.25 g of phenol **9** as a tan amorphous solid. Isolated yield: 86%.

¹H NMR [CDCl₃, 400 MHz] δ 7.03(d, *J*=15 Hz, 1H), 6.57(s, 1H), 6.33(d, *J*=15 Hz, 1H), 6.31 (s, 1H), 6.09(s, 1H), 3.60(s, 3H), 2.10(s, 3H), 1.56(s, 9H), 1.52(s, 9H); ¹³C NMR [CDCl₃, 100 MHz] δ 166.38, 152.08, 151.66, 150.89, 147.59, 136.88, 129.02, 121.02, 118.37, 111.87, 111.07, 110.25, 97.29, 83.97, 80.89, 55.09, 28.34, 27.84, 9.28; IR [CH₂Cl₂ solution, ν_{max} cm⁻¹] 3055, 2926, 2854, 1757, 1701, 1369, 1262, 1244, 1135, 1123, 731, 704; HRMS (ESI) *m/z* calculated for C₂₃H₃₀O₈ 434.1941, found 457.1835 (M+Na)⁺.

Azaphilone **21**

To a stirred solution of phenol **19** (150 mg, .3421 mmol) in 1,2-dichloroethane (3.3 mL) at 0 °C was added trifluoroacetic acid (171 μL) dropwise, resulting in a deep red solution. IBX (97.8 mg, .3421 mmol) and tetra-*n*-butylammonium iodide (1.7 mg, .0513 mmol) were then added, and reaction was stirred at 0 °C for 6 hours. Saturated aqueous sodium hydrosulfite (2 mL) was then added, and the reaction was allowed to stir for 1 hour, after which it was quenched with water and ethyl acetate and allowed to stir for 10 minutes. The resulting solution was extracted with ethyl acetate (3 x 30 mL), and the combined organic layers were washed with pH 8.5 buffer (2 x 20 mL), water (2 x 20 mL), and brine successively. The dried solution was filtered, concentrated *in vacuo*, and purified by flash chromatography on silica gel (40% EtOAc/hexanes) to provide 42 mg of azaphilone **21** as a yellow amorphous solid. Isolated yield: 40%.

¹H NMR [CDCl₃, 400 MHz] δ 7.90(s, 1H), 7.04(d, *J*=15.6 Hz, 1H), 6.50(d, *J*=15.7 Hz, 1H), 6.45 (s, 1H), 5.71(s, 1H), 3.88(s, 1H), 1.57(s, 3H), 1.53(s, 9H); ¹³C NMR [CDCl₃, 100 MHz] δ 196.5, 195.2, 164.6, 157.8, 152.4, 142.2, 138.7, 132.3, 127.3, 114.9, 108.6, 84.0, 82.2, 28.6, 28.2; IR [CH₂Cl₂ solution, ν_{max} cm⁻¹]; HRMS (ESI) *m/z* calculated for C₇H₁₈O₆ 318.1103, found 318.1092.

To a stirred solution of aldehyde **22a**² (250 mg, 1.62 mmol) in THF (2 mL) was added di-*tert*-butyl dicarbonate (665 mg, 3.57 mmol). To this solution was added 4-dimethylaminopyridine (59.5 mg, 0.487 mmol) and N-ethyldiisopropylamine (0.084 mL, 0.487 mmol). The resulting solution was stirred for 4 hours, after which it was

concentrated *in vacuo*. The residue was then dissolved in *t*BuOH/H₂O (5:1, 46 mL), and NaHPO₄ (232 mg, 2.1 mmol) was added, followed by NaClO₂ (509 mg, 5.62 mmol) and 2-methyl-2-butene (1.08 mL, 8.42 mmol). The resulting solution was allowed to stir for 24 hours, after which it was concentrated *in vacuo*. The crude residue was redissolved in ethyl acetate and extracted. The combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by flash chromatography (20% EtOAc/Hex, 1% AcOH) to afford 392 mg of bis-Boc acid **22** as an off-white amorphous solid. Isolated yield: 75%.

¹H NMR [CO(CD₃)₂, 400 MHz] δ ; 7.05(s, 1H), 7.01(s, 1H), 1.53(s, 9H), 1.50(s, 9H); ¹³C NMR [CO(CD₃)₂, 100 MHz] δ; 166.9, 152.9, 151.9, 150.4, 140.1, 122.2, 115.7, 115.3, 84.3, 84.05, 27.9, 27.5, 26.8; IR [CH₂Cl₂ solution, ν_{max} cm⁻¹] 3427, 2933, 1765, 1614, 1371, 1246, 1136; HRMS (ESI) *m/z* calculated for C₁₈H₂₄O₈ 368.1471, found 391.1371 (M+Na)⁺.

Bis-boc-Mitorubrinic acid *t*-butyl ester (**21a**)

To a stirred solution of **22** (6.5 mg, .01728 mmol) in CH₂Cl₂ (500 μL) is added 2,4,6-trichlorobenzoyl chloride (2.4 μL, .01728 mmol), and Et₃N (2.4 μL, .01728 mmol). After stirring for 3 hours, a solution of azaphilone **21** (5 mg, 0.01571 mmol) in toluene (500 μL) is added via cannula. To this mixture are added NEt₃ (2.4 μL, .01728 mmol) and DMAP (2.1 mg, .01728

mmol), and the solution is heated to 40 °C for 4 hours. The solution is then quenched with saturated aqueous NH₄Cl. The resulting mixture is extracted with CH₂Cl₂ (3 x 15 mL), and the combined organic layers are washed with water, brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product is purified by flash chromatography (20% EtOAc/Hexanes) isolated, and used directly in the next step.

Mitorubrinic Acid (**4**)

To a stirred solution of **21a** (~10 mg) in dioxane (400 μL) was added a solution of 3M HCl (200 μL). The resulting solution was heated to reflux over 4 hours. The solution was then allowed to cool to room temperature, and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered, and

concentrated *in vacuo*. The crude product was purified by flash chromatography (8% MeOH/CHCl₃) to provide 2 mg of mitorubrinic acid (**4**) as yellow solid. All spectroscopic data matched data from the literature for natural mitorubrinic acid. Isolated yield: 31% from **21**.

^1H NMR [$\text{CO}(\text{CD}_3)_2$, 400 MHz] δ 10.76(s, OH), 8.17(s, 1H), 7.34(d, $J=15.9$ Hz, 1H), 7.04(s, 1H), 6.54(d, $J=15.9$ Hz, 1H), 6.36 (s, 1H), 6.23(s, 1H), 5.76(s, 1H), 5.63(s, OH), 2.61(s, 3H), 1.68(s, 3H); ^{13}C NMR [$\text{CO}(\text{CD}_3)_2$, 100 MHz] δ ; IR [CH_2Cl_2 solution, ν_{max} cm^{-1}]; HRMS (EI) m/z calculated for $\text{C}_{21}\text{H}_{16}\text{O}_9$ 412.0794, found 412.0807.

III. References:

- 1) Suzuki, T.; Okada, C.; Arai, K.; Awaji, A.; Shimizu, T.; Tanemura, K.; Horaguchi, T.; *J. Heterocyclic Chem.* **2001**, 38, 1409.
- 2) Solladie, G.; Rubio, A.; Carreño, M. C.; Ruano, J. L. G.; *Tetrahedron: Asymmetry* **1990**, 3, 187

IV. Spectroscopic Data (¹H NMR, ¹³C NMR, FTIR, LRMS) for compound shown

INDEX	FREQUENCY	PPM	HEIGHT
1	4757.048	11.884	12.9
2	2610.254	6.525	19.2
3	1580.882	3.952	56.5
4	1001.319	2.504	33.7
5	836.830	2.090	36.3
6	625.086	1.583	151.9

INDEX	FREQUENCY	PPM	HEIGHT
1	17351.588	172.537	24.8
2	16590.128	164.886	9.4
3	16384.122	162.817	32.6
4	15407.500	153.208	28.5
5	15212.175	151.264	21.8
6	14050.811	138.717	39.8
7	11754.323	116.850	13.1
8	11684.810	116.288	151.4
9	11043.228	108.589	28.3
10	8446.815	83.884	46.4
11	7802.855	77.381	35.5
12	7788.484	77.247	41.9
13	7736.438	76.826	40.4
14	5268.941	52.392	134.2
15	3005.977	28.920	12.7
16	2891.477	26.752	13.2
17	2788.393	27.828	588.5
18	2783.782	26.855	12.2
19	2651.889	26.388	18.3
20	2439.789	24.268	133.0
21	903.135	8.888	101.9
22	-1314.102	-13.887	10.0

Sample Name: marsini.pettus,mw296,mm-1-pub
Acq. File: pet030206qe.wiff
Acq. Date: Thursday, March 02, 2006

*TOF MS: 7.962 to 8.219 min from Sample 2 (marsini.pettus,mw296,mm-1-pub) of pet030206qe.wiff
a=3.50672877764782420e-004, t0=3.46564556210371250e+001

Max: 738.6 counts.

Sample Name: marsini/pettus,mw396.9,mw-2-pub, esit/tof
Acq. File: pet022306qc.wiff
Acq. Date: Thursday, February 23, 2006

+TOF MS: 12.220 to 13.553 min from pet022306qc.wiff
a=3.50978900037769210e-004, t0=3.07250051995228010e+001

Max. 119.8 counts.

Sample Name: marsini/pettus,mw438,mm3-pub, esi+/tof
Acq. File: pet022306ga.wiff
Acq. Date: Thursday, February 23, 2006

+TOF MS: 22.856 to 28.524 min from pet022306ga.wiff
a=3.50978800037769210e-004, W=3.07250051985228010e+001

Max. 162.7 counts.

Sample Name: marsini/pettus,mw 420,mw-4-pub, esi+/tof
 Acq. File: pet022306qe.wiff
 Acq. Date: Thursday, February 23, 2006

+TOF MS: 7.719 to 8.119 min from pet022306qe.wiff
 a=3.50978800037769210e-004, t0=3.07250061995228010e+001

Max. 320.2 counts.

Sample Name: marsini/pettus,mw 518,mm-S-pub, esi+/tof
 Acq. File: pet022306gg.wiff
 Acq. Date: Thursday, February 23, 2006

+TOF MS: 4.385 to 5.135 min from pet022306gg.wiff
 a=3.50978800037769210e-004, t0=3.07250051995228010e+001

Max. 144.2 counts.

Sample Name: marsini.pettus,mw520,mm-6-pub, esi+/tof
 Acq. File: pet022806qc.wiff
 Acq. Date: Tuesday, February 28, 2006

+TOF MS: 15.671 to 15.887 min from pet022806qc.wiff
 a=3.50678800037769210e-004, t0=3.07250051995228010e+001

Max. 174.3 counts.

Sample Name: marsini,pettus,mv534,mm-7-pub

Acq. File: pet030206qa.wiff

Acq. Date: Thursday, March 02, 2006

+TOF MS: 9.019 to 9.536 min from pet030206qa.wiff
a=3.50972877764782420e-004, t0=3.46564556210371250e+001

Max. 107.9 counts.

Sample Name: marsini.pettus,mw434,m=8-pub

Acq. File: pet030206qc.wiff

Acq. Date: Thursday, March 02, 2006

+TOF MS: 16.271 to 16.721 min from pet030206qc.wiff
a=3.50972877764782420e-004, t0=3.46564556210371250e+001

Max. 118.9 counts.

+TOF MS: 3.134 to 7.419 min from pet042706ga.wiff
a=3.50850263210803380e-004, t0=3.34122002585298220e+001

Max. 127.5 counts.