Total Synthesis of Strobilurin B using a Hetero-bis-metallated Linchpin

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Supplementary Information

General. Proton (400 MHz) and $^{13}$C (100 MHz) NMR spectra were recorded on a Bruker DRX-400 spectrometer in CDCl$_3$ using CHCl$_3$ ($^1$H $\delta$ 7.27) and CDCl$_3$ 77.0 ($^{13}$C $\delta$ 77.0) as internal standards. High resolution mass spectra were recorded on a Micromass Q-TOF2 instrument at The Ohio State University Chemistry Mass Spectrometry Facility. All reactions were conducted in either oven-dried (120 °C) glassware or flame-dried glassware, under an argon atmosphere when necessary. Tetrahydrofuran (THF) was distilled from benzophenone ketyl. Triethylamine and dichloromethane were distilled from calcium hydride prior to use. Cesium fluoride was ground to a fine powder using a mortar and pestle and then dried under high vacuum at 100 °C for 4 h. All other chemicals were used as received.

Methyl (Z)-2-Iodo-3-methoxypropenoate (3). A mixture of methyl (E)-3-methoxypropenoate (1.16 g, 10.0 mmol), N-iodosuccinimide (2.70 g, 12.0 mmol), glacial acetic acid (1.5 mL, 20 mmol), and dichloromethane (20 mL) was stirred at room temperature for 24 h. Triethylamine (4.2 mL, 30 mmol) was added, and the reaction mixture was stirred at room temperature for 12 h before water (30 mL) was added. The organic layer was separated, and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium thiosulfate (2...
x 20 mL), saturated aqueous sodium bicarbonate (2 x 20 mL), and water (2 x 20 mL), and were dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (silica, 1:5 ether/hexane) to afford 3 (1.87 g, 77%) as a white solid: mp 51.0-51.5 °C (hexane) (lit:⁷ 47-48 °C; lit:⁶ 66-67 °C); IR (thin film) ν max/cm⁻¹ 3001, 1699, 1620, 1136, 752; ¹H NMR (CDCl₃, 400 MHz) δ 7.69 (1 H, s), 4.01 (3 H, s), 3.80 (3 H, s); ¹³C NMR (CDCl₃, 100 MHz) δ 164.4, 164.3, 64.9, 62.0, 52.9; HRMS (ESI), m/z 264.9333 (C₅H₇I₂O₃Na requires 264.9338).

![2-Chloro-5-iodoanisole (4)](image)

2-Chloro-5-iodoanisole (4). A solution of sodium nitrite (0.380 g, 5.50 mmol) in water (3 mL) was added over 30 min to a mixture of 4-chloro-3-methoxyaniline (0.788 g, 5.00 mmol), concentrated aqueous hydrochloric acid (10 mL), and water (10 mL) at 0 °C. The reaction mixture was stirred for 30 min at this temperature, and was added over 30 min via cannula to a solution of potassium iodide (8.35 g, 50.0 mmol) in water (15 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 d and was warmed at reflux for 1 h before it was allowed to cool to room temperature and was diluted with ether (100 mL). The organic layer was separated, and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic extracts were washed with 1 M aqueous sodium hydroxide (2 x 20 mL), saturated aqueous NaCl (2 x 20 mL), and were dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (silica, 100:2 hexane/ethyl acetate) to afford 4 (1.12 g, 84%) as a white solid: mp 39-40 °C; IR (thin film) ν max/cm⁻¹ 3001, 2926, 1573, 835, 799; ¹H NMR (CDCl₃, 400 MHz) δ 7.23-7.18 (2 H, m), 7.06 (1 H, d, J = 8.1 Hz), 3.88 (3 H, s); ¹³C NMR (CDCl₃,100 MHz)
δ 155.5, 131.4, 130.3, 122.7, 121.3, 91.4, 56.3; HRMS (ESI), m/z 290.9039 (C₇H₆ClIONa requires 290.9050).

\[\text{(Z)-4-Tri-} n\text{-butylstannyl-3-penten-1-yne (12).} \]

A mixture of (Z)-1-trimethylsilyl-4-tri-\textit{n}-butylstannyl-3-penten-1-yne (11) (1.19 g, 2.79 mmol), potassium fluoride (1.62 g, 27.9 mmol), and methanol (10 mL) was warmed at 50 °C for 24 h. After cooling to room temperature, water (10 mL) and ether (10 mL) were added. The aqueous layer was separated and was extracted with ether (2 x 10 mL). The combined organic extracts were washed with water (2 x 15 mL), and were dried (Na₂SO₄) and concentrated to afford 12 (0.98, 99%) as a colorless liquid, which was used without further purification: IR (thin film) ν_max/cm⁻¹ 3311, 2955, 2097, 1461, 835; ^1H NMR (CDCl₃, 400 MHz) δ 6.10 (1 H, quintet, J = 1.6 Hz, ^3J_{Sn-H} = 112 Hz), 2.78 (1 H, d, J = 2.0 Hz), 2.02 (3 H, d, J = 1.6 Hz, ^3J_{Sn-H} = 40.0 Hz), 1.58-1.48(6 H, m), 1.33 (6 H, sextet, J = 7.2 Hz), 1.04 (6 H, t, J = 8.0 Hz), 0.91 (9 H, t, J = 7.2 Hz); ^13C NMR (CDCl₃, 100 MHz) δ 162.0, 118.5, 80.6, 75.6, 29.1 (^3J_{Sn-C} = 20.1 Hz), 27.4 (^2J_{Sn-C} = 57.3 Hz), 27.3 (^2J_{Sn-C} = 29.1 Hz), 13.7, 9.87 (^1J_{Sn-C} = 340.1/324.0 Hz); MS (EI), m/z 298.6 (M⁺ – C₄H₈), 242.9, 184.5, 144.5.

\[\text{2-((1E,3Z)-4-((Tri-} n\text{-butylstannyl)penta-1,3-dienyl)-4,4,5,5-}
\text{tetramethyl-1,3,2-dioxaborolane (2).} \]

A flame-dried flask was charged with sodium borohydride (0.157 g, 4.14 mmol), 2,5-dimethyl-2,4-hexadiene (1.20 mL, 8.28 mmol),
and 2 mL of anhydrous diglyme. The mixture was cooled to 0 °C and dimethyl sulfate (0.4 mL, 4.14 mmol) was added over 30 min. The reaction mixture was stirred at 0 °C for 3 h, when enyne 12 (0.980 g, 2.76 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h and was allowed to warm to room temperature. Water (0.4 mL) was added and the reaction mixture was stirred for 30 min, and was treated with an aqueous solution of formaldehyde (0.4 mL, 37 wt%, 4.14 mmol). After stirring for 1 h, pinacol (0.359 g, 3.04 mmol) was added. The reaction mixture was stirred at room temperature for 24 h before water (10 mL) and ether (10 mL) were added. The aqueous layer was separated and was extracted with ether (3 x 10 mL). The combined organic extracts were washed with water (2 x 15 mL), and were dried (Na₂SO₄) and concentrated. Purification of the residue by flash chromatography (silica, 100:6 hexane/ether) afforded 2 (1.01 g, 75%) as a pale yellow liquid: IR (thin film) ν max/cm⁻¹ 2925, 2853, 1614, 1145, 850; ¹H NMR (CDCl₃, 400 MHz) δ 6.98 (1 H, dd, J = 17.1, 10.6 Hz), 6.75 (1 H, dd, J = 10.8, 1.2 Hz), 5.43 (1 H, d, J = 17.2 Hz), 2.04 (3 H, s, 3 J Sn-H = 41.4 Hz), 1.55-1.48 (6 H, m), 1.34 (6 H, sextet, J = 7.3 Hz), 1.26 (12 H, s), 1.00 (6 H, t, J = 8.2 Hz), 0.91 (9 H, t, J = 7.3 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 153.8, 151.7, 142.8, 82.9, 29.7 (3 J Sn-C = 20.0 Hz), 27.5, 27.3 (2 J Sn-C = 55.0 Hz), 24.8, 13.6, 10.2 (1 J Sn-C = 331.0/316.0 Hz) [Note: the carbon attached to boron was not observed due to quadrupole broadening caused by the boron nucleus]; HRMS (ESI), m/z 507.2444 (C₂₃H₄₅BO₂SnNa requires 507.2432).

[Vinylstannane 14. A flame-dried flask was charged with (t-Bu₅P)₂Pd (19.1 mg, 0.0373 mmol) in a dry box. Anhydrous THF (4 mL) was added to]
the flask. Under an argon atmosphere, solid 2-chloro-5-iodoanisole (4) (0.100 g, 0.373 mmol) was added to the flask. After 5 min, a solution of 2-((1E,3Z)-4-((tri-n-butylstannyl)penta-1,3-dienyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2) (0.200 g, 0.414 mmol) in 8 mL of THF was added via cannula. Solid sodium hydroxide (44.8 mg, 1.12 mmol) and water (20 µL, 1.12 mmol) were added in sequence under the protection of an argon atmosphere. The reaction mixture was warmed at 60 °C for 5 h before it was allowed to cool to room temperature, when water (10 mL) and ether (10 mL) were added. The aqueous layer was separated and extracted with ether (3 x 10 mL). The combined organic extracts were washed with water (2 x 10 mL), and were dried (Na₂SO₄) and concentrated. Purification of the residue by flash chromatography (silica, 100:3 hexane/ether) provided 14 (0.137 g, 74%) as a pale yellow liquid: IR (thin film) ν max/cm⁻¹ 3001, 2956, 1590, 1067, 801; ¹H NMR (CDCl₃, 400 MHz) δ 7.29 (1 H, d, J = 8.0 Hz), 6.91 (1 H, d, J = 1.6 Hz), 6.88 (1 H, dd, J = 8.0 and 1.6 Hz), 6.83 (1 H, dd, J = 10.8 and 1.6 Hz), 6.68 (1 H, dd, J = 15.2 and 10.4 Hz), 6.40 (1 H, d, J = 15.2 Hz), 3.93 (3 H, s), 2.09 (3 H, s, JSn-H = 42.8 Hz), 1.61–1.50 (6 H, m), 1.34 (6 H, sextet, J = 7.4 Hz), 1.05 (6 H, t, J = 8.0 Hz), 0.90 (9 H, t, J = 7.4 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 155.0, 149.8, 140.4, 137.9, 131.4, 130.2, 129.8, 121.0, 119.2, 109.2, 55.9, 29.2 (JSn-C = 29.2 Hz), 27.6, 27.4 (JSn-C = 55.9 Hz), 13.6, 10.4; HRMS (ESI), m/z 521.1615 (C₂₄H₃₉ClOSnNa requires 521.1609).
**Strobilurin B (1).** A flame-dried flask was charged with \((\text{t-Bu}_3\text{P})_2\text{Pd} \ (5.2 \ mg, \ 0.0102 \ mmol)\), cuprous iodide \((3.9 \ mg, \ 0.0204 \ mmol)\), and cesium fluoride \((34.1 \ mg, \ 0.224 \ mmol)\) in a dry box. Anhydrous DMF \((2 \ mL)\) was added to the flask. Under the protection of an argon atmosphere, solid \((Z)-2\text{-iodo-3-methoxypropenoate (3)} \ (24.8 \ mg, \ 0.102 \ mmol)\) was added. After 5 min, a solution of compound 14 \((60 \ mg, \ 0.120 \ mmol)\) in DMF \((2 \ mL)\) was added via cannula. The reaction mixture was warmed at 90 °C for 2 hr. After cooling to room temperature, water \((10 \ mL)\) and ether \((10 \ mL)\) were added. The aqueous layer was separated and extracted with ether \((3 \times 10 \ mL)\). The combined organic extracts were washed with water \((2 \times 10 \ mL)\), and were dried \((\text{Na}_2\text{SO}_4)\) and concentrated. Purification of the residue by flash chromatography \((\text{silica, 2:1 hexane/ether})\) provided strobilurin B \((1)\) as a cream white solid \((15 \ mg, \ 45\%): \) mp 92-93 °C \((\text{lit.} \ 95 °C)\); IR \((\text{thin film})\) \(\nu_{\text{max}}/\text{cm}^{-1} \ 2920, \ 1705, \ 1627, \ 1460, \ 1237, \ 1119, \ 804;^1\text{H NMR (CDCl}_3, \ 400 \ MHz) \ \delta \ 7.45 \ (1 \ H, \ s), \ 7.27 \ (1 \ H, \ d, \ J = 8.4 \ Hz), \ 6.92 \ (1 \ H, \ d, \ J = 8.4 \ Hz), \ 6.86 \ (1 \ H, \ s), \ 6.59 \ (1 \ H, \ dd, \ J = 15.6, \ 10.8 \ Hz), \ 6.45 \ (1 \ H, \ d, \ J = 15.6 \ Hz), \ 6.26 \ (1 \ H, \ d, \ J = 10.4), \ 3.92 \ (3 \ H, \ s), \ 3.87 \ (3 \ H, \ s), \ 3.76 \ (3 \ H, \ s), \ 2.00 \ (3 \ H, \ s);^13\text{C NMR (CDCl}_3, \ 100 \ MHz) \ \delta \ 167.7, \ 158.9, \ 154.9, \ 137.9, \ 132.1, \ 130.2, \ 130.1, \ 129.5, \ 127.2, \ 121.1, \ 119.1, \ 110.7, \ 110.0, \ 61.9, \ 56.1, \ 51.6, \ 23.7; \) HRMS \((\text{ESI}), \ m/z \ 345.0857 \ (\text{C}_{17}\text{H}_{19}\text{ClO}_4\text{Na requires 345.0870})\).