Carbocyclization of Unsaturated Thioesters Under Palladium Catalysis

Supplementary Information
(26 pages)

Arun P. Thottumkara, Toshiki Kurokawa, J. Du Bois*

Department of Chemistry
Stanford University
Stanford, CA 94305-5080
General. All reagents were obtained commercially unless otherwise noted. Copper(I)-thiophene-2-carboxylate (CuTC) was prepared according to the procedure described by Liebeskind.1 Thioesters were prepared from the corresponding carboxylic acids under standard conditions.2 Reactions were performed using glassware that was flame-dried under vacuum (~1 Torr). Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated under reduced pressure (~15 Torr) by rotary evaporation. Solvents were purified by passage under 12 psi N2 through activated alumina columns. Chromatography was performed on Silicycle Silia-P Silica Gel (40-63 μm). Compounds purified by chromatography were typically applied to the adsorbent bed using the indicated solvent conditions with a minimum amount of additional benzene as needed for solubility. Thin layer chromatography was performed on Whatman Partisil K6F Silica Gel 60 Å plates (250 μm). Visualization of the developed chromatogram was accomplished by fluorescent quenching and by staining with aqueous potassium permanganate.

Nuclear magnetic resonance (NMR) spectra were acquired on a Varian Inova-300 operating at 300 and 75 MHz, a Varian Mercury-400 operating at 400 and 100 MHz, or a Varian Inova-500 operating at 500 and 125 MHz for 1H and 13C, respectively, and are referenced internally according to residual solvent signals. Data for 1H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet), integration, coupling constant (Hz). Data for 13C NMR are reported in terms of chemical shift (δ, ppm). Infrared spectra were recorded on a ThermoNicolet IR300 spectrometer as thin films using NaCl plates and are reported in frequency of absorption. High-resolution mass spectra were obtained from the Vincent Coates Foundation Mass Spectrometry Laboratory at Stanford University.

General procedure for substrate preparation. Ethanethiol (0.45 mL, 6.20 mmol, 5.0 equiv) was added to a solution of carboxylic acid (1.24 mmol), N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (284 mg, 1.49 mmol, 1.2 equiv), 4-(dimethylamino)pyridine (15 mg, 0.12 mmol, 10 mol%) in 12.4 mL of CH2Cl2. The mixture was stirred until the carboxylic acid was completely consumed, as determined by TLC (1–2 h). The reaction was then quenched with 15 mL of saturated aqueous NaHCO3. The mixture was transferred to a separatory funnel and the aqueous layer was extracted 3 x 20 mL CH2Cl2. The combined organic layers were washed with 25 mL of saturated aqueous sodium chloride, dried over MgSO4, filtered, and concentrated under reduced pressure. The desired product was isolated following purification by chromatography on silica gel (conditions given below).

Purified by chromatography on silica gel (9:1 hexanes/EtOAc); yellow oil (80%); TLC Rf = 0.81 (3:1 hexanes/EtOAc); 1H NMR (CDCl3, 500 MHz) δ 7.73 (dd, 1H, J = 8.5, 1.5 Hz), 7.42 (dt, 1H, J = 7.5, 1.5 Hz), 7.29-7.25 (m, 2H), 5.97 (ddt, 1H, J = 17.0, 10.0, 6.5 Hz), 5.06-4.99 (m, 2H), 3.60 (d, 2H, J = 6.5 Hz), 3.03 (q, 2H, J = 7.5 Hz), 1.35 (t, 3H, J = 7.5 Hz) ppm; 13C NMR (CDCl3, 100 MHz) δ 194.8, 138.3, 137.9, 137.0, 131.7, 130.8, 128.5, 126.3, 116.0, 37.6, 24.2, 14.8 ppm; IR (thin film) ν 2973, 2930, 1668, 1638, 1447, 1210, 914 cm⁻¹; HRMS (ES+) calcd for C13H16O4S 207.0836 found 207.0838 (M+H⁺).

Purified by chromatography on silica gel (9:1 hexanes/EtOAc); yellow oil (91%); TLC Rf = 0.58 (9:1 hexanes/EtOAc); 1H NMR (CDCl3, 400 MHz) δ 7.71 (dd, 1H, J = 8.0, 1.2 Hz), 7.40 (dt, 1H, J = 7.6, 1.2 Hz), 7.28-7.22 (m, 2H), 5.85 (ddt, 1H, J = 16.8, 10.0, 6.8 Hz), 5.07-4.94 (m, 2H), 3.04 (q, 2H, J = 7.2 Hz), 2.90 (t, 2H, J= 8.0 Hz), 2.39-2.32 (m, 2H), 1.36 (t, 3H, J = 7.2 Hz) ppm; 13C NMR (CDCl3, 100 MHz) δ 194.9, 140.3, 138.1, 138.0, 131.4, 130.8, 128.5, 126.0, 115.0, 35.6, 33.0, 24.2, 14.8 ppm; IR (thin film) ν 2970, 2930, 1668, 1641, 1453, 1265, 1207, 909 cm⁻¹; HRMS (ES+) calcd for C13H16O4S 221.0992 found 221.0995 (M+H⁺).

Purified by chromatography on silica gel (9:1 hexanes/EtOAc); yellow oil (87%); TLC R<sub>t</sub> = 0.67 (3:1 hexanes/EtOAc); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.31-7.26 (m, 2H), 7.23-7.15 (m, 3H), 5.64 (ddt, 1H, J = 17.6, 10.4, 7.2 Hz), 5.04-4.94 (m, 2H), 3.28 (tt, 1H, J = 14.8, 7.2 Hz), 2.90 (dd, 1H, J = 14.8, 6.8 Hz), 2.84-2.76 (m, 3H), 2.43-2.37 (m, 2H), 1.16 (t, 3H, J = 7.2 Hz) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 198.4, 143.2, 135.9, 128.5, 127.6, 126.7, 117.1, 49.5, 42.3, 40.4, 23.4, 14.8 ppm; IR (thin film) v 2973, 2930, 1688, 1641, 1453, 1265, 1054 cm<sup>-1</sup>; HRMS (ES<sup>+</sup>) calcd for C<sub>10</sub>H<sub>8</sub>OS 235.1150 found 235.1151 (M+H<sup>+</sup>).

Purified by chromatography on silica gel (99:1 hexanes/EtOAc); yellow oil (94%); TLC R<sub>t</sub> = 0.26 (19:1 hexanes/EtOAc); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.33-7.31 (m, 4H), 7.23-7.16 (m, 1H), 5.56-5.45 (m, 1H), 5.05-4.96 (m, 2H), 2.95 (d, 1H, J = 14.4 Hz), 2.82 (d, 1H, J = 14.4 Hz), 2.74 (q, 2H, J = 7.6 Hz), 2.60 (dd, 1H, J = 14.0, 6.8 Hz), 2.46 (dd, 1H, J = 14.0, 8.0 Hz), 1.47 (s, 3H), 1.13 (t, 3H, J = 7.6 Hz) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 197.4, 146.0, 134.4, 128.2, 126.20, 126.16, 118.2, 55.4, 46.9, 41.1, 24.6, 23.5, 14.8 ppm; IR (thin film) v 2970, 2930, 1688, 1639, 1604, 1446, 1374, 1012 cm<sup>-1</sup>; HRMS (ES<sup>+</sup>) calcd for C<sub>13</sub>H<sub>16</sub>OS 249.1307 found 249.1308 (M+H<sup>+</sup>).

Purified by chromatography on silica gel (49:1 hexanes/EtOAc); yellow oil (90%); TLC R<sub>t</sub> = 0.15 (49:1 hexanes/EtOAc); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.16 (dt, 1H, J = 7.6, 1.6 Hz), 7.09 (dd, 1H, J = 7.2, 1.6 Hz), 0.87 (dt, 1H, J = 7.4, 1.2 Hz), 6.83 (dd, 1H, J = 8.0, 0.8 Hz), 5.66 (ddt, 1H, J = 17.4, 10.0, 6.4 Hz), 5.03-4.91 (m, 2H), 4.04 (q, 2H, J = 6.8 Hz), 3.64 (dt, 1H, J = 14.4, 7.2 Hz), 2.96 (dd, 1H, J = 15.2, 7.2 Hz), 2.89 (dd, 1H, J = 15.2, 7.6 Hz), 2.80 (q, 2H, J = 7.2 Hz), 2.52-2.39 (m, 2H), 1.49 (t, 3H, J = 6.8 Hz), 1.16 (t, 3H, J = 7.6 Hz) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 198.8, 156.7, 136.6, 131.0, 128.5, 127.5, 120.3, 116.4, 111.6, 63.6, 48.3, 38.4, 37.0, 23.3, 15.0, 14.8 ppm; IR (thin film) v 2978, 2930, 1689, 1494, 146, 1290, 1241, 1125, 1049, 997, 916, 752 cm<sup>-1</sup>; HRMS (ES<sup>+</sup>) calcd for C<sub>16</sub>H<sub>20</sub>OS<sub>2</sub> 279.1412 found 279.1413 (M+H<sup>+</sup>).

Purified by chromatography on silica gel (19:1 hexanes/EtOAc); yellow oil (21%); TLC R<sub>t</sub> = 0.42 (9:1 hexanes/EtOAc); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 5.72-5.59 (m, 1H), 5.16-5.08 (m, 2H), 4.20 (q, 4H, J = 6.8 Hz), 3.20 (s, 2H), 2.86 (q, 2H, J = 7.2 Hz), 2.74 (d, 2H, 7.6 Hz), 1.28-1.20 (m, 9H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 196.3, 169.9, 132.2, 120.1, 61.9, 55.9, 45.8, 37.4, 23.6, 14.8, 14.1 ppm; IR (thin film) v 2982, 1737, 1690, 1287, 1214, 1192 cm<sup>-1</sup>; HRMS (ES<sup>+</sup>) calcd for C<sub>10</sub>H<sub>14</sub>NSNa<sup>+</sup> 325.1079 found 325.1080 (MNa<sup>+</sup>).

Purified by chromatography on silica gel (19:1 hexanes/EtOAc); yellow oil (17%); TLC R<sub>t</sub> = 0.27 (9:1 hexanes/EtOAc); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.47-7.29 (m, 5H), 5.73-5.60 (m, 1H), 5.23-5.16 (m, 2H), 3.23 (d, 1H, J = 15.6 Hz), 3.17 (d, 1H, J = 15.6 Hz), 2.86-2.71 (m, 4H), 1.15 (t, 3H, J = 7.6 Hz) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 194.2, 136.9, 131.1, 129.0, 128.3, 126.1, 121.1, 94.5, 51.4, 44.9, 44.6, 23.4, 14.6 ppm; IR (thin film) v 2929, 2359, 1688, 1495, 1449, 1265, 993 cm<sup>-1</sup>; HRMS (ES<sup>+</sup>) calcd for C<sub>14</sub>H<sub>18</sub>ONS 260.1109 found 260.1104 (M+H<sup>+</sup>).

Purified by chromatography on silica gel (19:1 hexanes/EtOAc); yellow oil (12%); TLC R<sub>t</sub> = 0.46 (9:1 hexanes/EtOAc); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.68 (d, 1H, J = 8.0 Hz), 7.45-7.32 (m, 3H), 7.16 (t, 1H, J = 7.4 Hz...
Purified by chromatography on silica gel (9:1 hexanes/EtOAc); yellow oil (86%); TLC \( R_f = 0.86 \) (3:1 hexanes/EtOAc); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.30-7.12 (m, 5H), 5.73 (ddt, 1H, \( J = 16.8, 10.4, 6.4 \) Hz), 5.05-4.94 (m, 2H), 2.98 (dd, 1H, \( J = 13.2, 7.6 \) Hz), 2.90-2.77 (m, 3H), 2.72 (dd, 1H, \( J = 13.2, 6.8 \) Hz), 2.17-1.97 (m, 2H), 1.87-1.75 (m, 1H), 1.61-1.50 (m, 1H), 1.18 (t, 3H, \( J = 7.2 \) Hz) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 202.8, 138.9, 137.7, 129.1, 128.4, 126.4, 115.4, 55.5, 39.0, 31.4, 31.3, 23.2, 14.8 ppm; IR (thin film) v 3028, 2929, 2856, 1683, 1641, 1453, 1265, 946, 915 cm\(^{-1}\); HRMS (ES\(^+\)) calcld for C\(_{10}\)H\(_9\)ONS 260.1109 found 260.1104 (M+H\(^+\)).

Purified by chromatography on silica gel (9:1 hexanes/EtOAc); yellow oil (53%); TLC \( R_f = 0.49 \) (9:1 hexanes/EtOAc); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.29-7.20 (m, 3H), 7.15-7.11 (m, 2H), 5.80 (ddt, 1H, \( J = 17.2, 10.0, 6.4 \) Hz), 5.07-4.94 (m, 2H), 3.08 (d, 1H, \( J = 13.2 \) Hz), 2.88 (q, 2H, \( J = 7.2 \) Hz), 2.76 (d, 1H, \( J = 13.6 \) Hz) 2.13-1.98 (m, 2H), 1.91 (ddd, 1H, \( J = 13.6, 11.2, 6.8 \) Hz), 1.53 (ddd, 1H, \( J = 13.6, 10.8, 6.0 \) Hz), 1.26 (t, 3H, \( J = 7.2 \) Hz), 1.20 (s, 3H) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 205.8, 128.3, 137.1, 130.5, 128.0, 126.5, 114.7, 53.8, 45.8, 38.9, 28.8, 23.2, 20.6, 14.7 ppm; IR (thin film) v 2973, 2930, 1671, 1641, 1454, 954, 913, 704 cm\(^{-1}\); HRMS (ES\(^+\)) calcld for C\(_{10}\)H\(_9\)OS 263.1469 found 263.1464 (M+H\(^+\)).

Purified by chromatography on silica gel (3:1 hexanes/EtOAc); clear oil (59%); TLC \( R_f = 0.74 \) (3:1 hexanes/EtOAc); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.31-7.19 (m, 5H), 5.72 (ddt, 1H, \( J = 16.8, 10.4, 6.4 \) Hz), 4.99-4.92 (m, 2H), 3.70 (t, 1H, \( J = 7.2 \) Hz), 2.86-2.70 (m, 2H), 2.24-2.14 (m, 1H), 1.96 (m, 2H), 1.91-1.81 (m, 1H), 1.15 (t, 3H, \( J = 7.2 \) Hz) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 200.5, 138.4, 137.5, 128.7, 128.3, 127.5, 115.6, 59.5, 32.3, 31.4, 23.6, 14.6 ppm; IR (thin film) v 2930, 1686, 1642, 1453, 1265, 996 cm\(^{-1}\); HRMS (ES\(^+\)) calcld for C\(_{13}\)H\(_{16}\)OS 235.1156 found 235.1151 (M+H\(^+\)).

Purified by chromatography on silica gel (19:1 hexanes/EtOAc); yellow oil (25%); TLC \( R_f = 0.56 \) (3:1 hexanes/EtOAc); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 5.82 (ddt, 1H, \( J = 16.8, 10.0, 6.8 \) Hz), 5.07-5.00 (m, 1H), 4.97-4.92 (m, 1H), 3.35 (s, 1H), 2.91 (q, 2H, \( J = 7.6 \) Hz), 2.72 (q, 2H, \( J = 12.4 \) Hz), 2.19-2.11 (m, 2H), 1.63-1.56 (m, 2H), 1.27 (t, 3H, \( J = 7.6 \) Hz), 1.24 (s, 3H) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 200.5, 138.5, 114.6, 72.2, 53.8, 41.0, 28.3, 26.6, 23.6, 14.7 ppm; IR (thin film) v 3519, 2972, 2931, 1671, 1642, 1454, 1377, 1126, 1013, 912 cm\(^{-1}\).

Purified by chromatography on silica gel (9:1 hexanes/EtOAc); yellow oil (83%); TLC \( R_f = 0.81 \) (3:1 hexanes/EtOAc); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 5.84-5.71 (m, 1H), 5.06-4.97 (m, 1H), 4.97-4.91 (m, 1H), 3.2 (d, 1H, \( J = 14.0 \) Hz), 3.06 (d, 1H, \( J = 14.4 \) Hz), 2.84 (q, 2H, \( J = 7.6 \) Hz), 2.13-2.04 (m, 3H), 1.99 (s, 3H), 1.85-1.75 (m, 1H), 1.49 (s, 3H), 1.22 (t, 3H, \( J = 7.6 \) Hz) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 195.9, 170.6, 137.9, 114.9, 81.6, 50.9, 38.0, 27.9, 24.1, 23.6, 22.4, 14.7 ppm; IR (thin film) v 3078, 2977, 2933, 1737, 1689, 1642, 1452, 1368, 1245, 1131, 1016, 913 cm\(^{-1}\).

S4
Purified by chromatography on silica gel (gradient elution: 99:1→19:1 hexanes/EtOAc); yellow oil (47%); TLC R$_f$ = 0.24 (19:1 hexanes/EtOAc); $^1$H NMR (CDCl$_3$, 400 MHz) δ 5.81 (ddt, 1H, $J = 16.8, 10.4, 6.8$ Hz), 5.01 (dq, 1H, $J = 16.8, 1.6$ Hz), 4.93 (dq, 1H, $J = 10.0, 1.2$ Hz), 2.84 (q, 2H, $J = 7.6$ Hz), 2.70 (s, 2H), 2.24-2.06 (m, 2H), 1.69-1.61 (m, 2H), 1.36 (s, 3H), 1.23 (t, 3H, $J = 7.6$ Hz), 0.86 (s, 9H), 0.09 (s, 6H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 197.0, 138.8, 114.3, 74.9, 55.5, 42.0, 28.6, 28.2, 25.9, 23.6, 18.3, 14.7, −1.9 ppm; IR (thin film) ν 2931, 2956, 2857, 1691, 1642, 1461, 1377, 1254, 1082, 836 cm$^{-1}$.

Purified by chromatography on silica gel (9:1 hexanes/EtOAc); yellow oil (82%); TLC R$_f$ = 0.81 (3:1 hexanes/EtOAc); $^1$H NMR (CDCl$_3$, 400 MHz) δ 5.95-5.97 (m, 1H), 5.27 (dq, 1H, $J = 17.2, 1.6$ Hz), 5.11 (dq, 1H, $J = 10.4, 1.6$ Hz), 3.94 (t, 1H, $J = 1.4$ Hz), 3.92 (t, 1H, $J = 1.4$ Hz), 2.90-2.83 (m, 4H), 1.96-1.55 (m, 8H), 1.24 (t, 3H, $J = 7.6$ Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 200.8, 138.0, 115.9, 73.5, 53.2, 44.5, 36.9, 34.0, 26.8, 25.0, 23.6, 21.7, 14.7 ppm; IR (thin film) ν 3524, 2932, 2860, 1668, 1446, 1391, 1302, 1078, 1014, 910 cm$^{-1}$.

Purified by chromatography on silica gel (9:1 hexanes/EtOAc); yellow oil (74%); TLC R$_f$ = 0.79 (7:3 hexanes/CH$_2$Cl$_2$); $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.33-7.27 (m, 2H), 7.24-7.19 (m, 3H), 3.38 (tt, 1H, $J = 14.0, 6.4$ Hz), 3.14 (dd, 1H, $J = 15.2, 6.4$ Hz), 2.89 (dd, 1H, $J = 15.2, 8.4$ Hz), 2.80 (q, 2H, $J = 7.2$ Hz), 2.54-2.37 (m, 2H), 1.76 (t, 3H, $J = 2.6$ Hz), 1.16 (t, 3H, $J = 7.2$ Hz) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 198.2, 142.7, 128.5, 127.4, 126.9, 126.5, 117.8, 116.9, 78.1, 76.5, 48.9, 41.6, 26.1, 23.4, 14.8, 3.6 ppm; IR (thin film) ν 2968, 2930, 1688, 1454, 1430, 1265, 1063 cm$^{-1}$; HRMS (ES$^+$) calcd for C$_{19}$H$_{19}$OS 247.1156 found 247.1151 (M+H$^+$).
**General procedure for carbocyclization of thioesters.** Thioester (0.20 mmol), Pd(OAc)$_2$ (2.2 mg, 0.01 mmol, 5 mol%), Cu(thiophene-2-carboxylate) (61.0 mg, 0.32 mmol, 1.6 equiv), and Zn(O$_2$CH)$_2$ (31.1 mg, 0.20 mmol, 1.0 equiv) were added sequentially to a flame-dried 10 mL round bottom flask. The flask was placed under vacuum and back-filled with N$_2$. THF (1.7 mL), which had been degassed by a freeze-pump-thaw cycle (3x), was added, followed immediately by P(OMe)$_3$ (24 µL, 0.20 mmol, 1.0 equiv). The brown suspension was stirred at 60 °C for 18 h, after which time the reaction was quenched with 6 mL of saturated aqueous NaHCO$_3$. The mixture was transferred to a separatory funnel and extracted with 3 x 15 mL of EtOAc. The combined organic layers were washed with 1 x 20 mL of saturated aqueous sodium chloride, dried over MgSO$_4$, filtered through a pad of Celite, and concentrated under reduced pressure to a brown residue. The desired product was isolated following purification by chromatography on silica gel (conditions given below).

Characterization data matched that reported in literature.\(^3\)

Characterization data matches that reported in literature.\(^4\)

Characterization data matches that reported in literature.\(^5\)

Purified by chromatography on silica gel (19:1 hexanes/EtOAc); yellow oil (83%); TLC $R_f = 0.34$ (9:1 hexanes/EtOAc); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.39-7.21 (m, 5H), 6.12-6.08 (m, 1H), 5.44-5.39 (m, 1H), 3.05-2.92 (m, 2H), 2.76 (d, 1H, $J = 17.0$ Hz), 2.64 (dd, 1H, $J = 17.2$, 1.6 Hz), 1.34 (d, 3H, $J = 1.3$ Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 205.4, 148.2, 144.2, 128.7, 126.5, 125.5, 118.4, 52.2, 43.7, 41.1, 30.1 ppm; IR (thin film) $\nu$ 2956, 2923, 1729, 1645, 14967, 1445, 1408 cm$^{-1}$; HRMS (ES$^+$) calcd for C$_{15}$H$_{17}$O 187.1123 found 187.1117 (M+H$^+$).

Purified by chromatography on silica gel (99:1 hexanes/EtOAc); yellow oil (80%); TLC $R_f = 0.16$ (19:1 hexanes/EtOAc); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.25-7.13 (m, 2H), 6.96-6.84 (m, 2H), 6.09-6.02 (m, 1H), 5.39-5.33 (m, 1H), 4.05 (q, 2H, $J = 6.8$ Hz), 3.74-3.62 (m, 1H), 3.07 (dd, 1H, $J = 16.2$, 7.6 Hz), 2.86-2.79 (m, 1H), 2.76 (dd, 1H, $J = 18.0$, 8.0 Hz), 2.59 (dd, 1H, $J = 18.0$, 9.6 Hz), 1.41 (t, 3H, $J = 7.2$ Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 206.7, 156.8, 145.2, 131.4, 127.8, 127.0, 120.4, 117.0, 111.4, 63.4, 44.6, 36.1, 34.0, 14.9 ppm; IR (thin film) $\nu$ 2979, 2917, 1642, 1494, 1242, 1118, 1046, 752 cm$^{-1}$; HRMS (ES$^+$) calcd for C$_{14}$H$_{17}$O$_2$ 217.1228 found 217.1223 (M+H$^+$).

---


Purified by chromatography on silica gel (9:1 hexanes/EtOAc); yellow oil (89%); TLC R_f = 0.29 (3:1 hexanes/EtOAc); ^1H NMR (CDCl_3, 400 MHz) δ 6.06 (s, 1H), 5.41 (s, 1H), 4.22 (q, 4H, J = 7.2 Hz), 3.23 (s, 2H), 2.91 (s, 2H), 1.25 (t, 6H, J = 7.2 Hz) ppm; ^13C NMR (CDCl_3, 100 MHz) δ 201.5, 170.7, 141.6, 119.0, 62.2, 54.2, 45.2, 37.0, 14.0 ppm; IR (thin film) ν 2939, 1733, 1645, 1284, 1246, 1189 cm^{-1}; HRMS (ESI) calcd for C_{15}H_{16}O_{5} 241.1076 found 241.1071 (M+H^+).

Purified by chromatography on silica gel (9:1 hexanes/EtOAc); yellow oil (94%); TLC R_f = 0.13 (9:1 hexanes/EtOAc); ^1H NMR (CDCl_3, 400 MHz) δ 7.53-7.30 (m, 5H), 6.24 (t, 1H, J = 2.4 Hz), 5.57 (t, 1H, J = 2.8 Hz), 3.53 (dt, 1H, J = 16.0, 2.8 Hz), 3.26-3.15 (m, 2H), 2.98 (d, 1H, J = 17.6 Hz) ppm; ^13C NMR (CDCl_3, 100 MHz) δ 200.0, 140.4, 137.9, 129.5, 129.2, 129.0, 125.7, 125.2, 121.1, 50.1 43.4 ppm; IR (thin film) ν 2924, 2854, 2238, 1734, 1645, 1496, 1449, 1404, 1266, 1125 cm^{-1}; HRMS (ESI) calcd for C_{15}H_{17}ON 217.1228 found 198.0919 (M+H^+).

Purified by chromatography on silica gel (9:1 hexanes/EtOAc); off-white foam (30%); TLC R_f = 0.11 (9:1 hexanes/EtOAc); ^1H NMR (CDCl_3, 400 MHz) δ 7.74 (td, 1H, J = 8.0, 1.2 Hz), 7.42-7.37 (m, 3H), 7.19-7.15 (qd, 1H, J = 6.0, 2.0 Hz), 6.36-6.35 (m, 1H), 5.58-5.59 (m, 1H), 4.31 (t, 2H, J = 6.0 Hz), 3.13 (td, 1H, J = 6.4, 1.2 Hz), 3.11 (td, 1H, J = 6.4, 1.2 Hz) ppm; ^13C NMR (CDCl_3, 100 MHz) δ 180.3, 140.4, 137.6, 134.5, 127.3, 125.9, 123.5, 123.3, 121.3, 110.4, 107.3, 41.3, 31.5 ppm; IR (thin film) ν 2922, 1671, 1621, 1524, 1477, 1326, 1162 cm^{-1}; HRMS (ESI) calcd for C_{16}H_{18}ON 198.0919 found 198.0913 (M+H^+).

Purified by chromatography on silica gel (49:1 hexanes/EtOAc); yellow oil (50%); TLC R_f = 0.43 (9:1 hexanes/EtOAc); ^1H NMR (CDCl_3, 400 MHz) δ 7.31-7.25 (m, 3H), 7.23-7.16 (m, 2H), 6.05-6.02 (m, 1H), 5.35-5.32 (m, 1H), 3.30-3.21 (m, 1H), 2.62-2.42 (m, 4H), 2.11-2.01 (m, 1H), 1.58-1.47 (m, 1H) ppm; ^13C NMR (100 MHz, CDCl_3) δ 207.2, 147.8, 140.0, 129.0, 128.5, 126.3, 117.7, 51.0, 35.9, 27.8, 26.4 ppm; IR (thin film) ν 2925, 2854, 1725, 1540, 1604, 1495, 1454, 1261, 1065, 941 cm^{-1}; HRMS (ESI) calcd for C_{16}H_{18}O 187.1123 found 187.1117 (M+H^+).

Purified by chromatography on silica gel (99:1 hexanes/EtOAc); yellow oil (33%); TLC R_f = 0.43 (9:1 hexanes/EtOAc); ^1H NMR (CDCl_3, 400 MHz) δ 7.33-7.18 (m, 3H), 7.16-7.07 (m, 2H), 6.08-6.03 (m, 1H), 5.37-5.31 (m, 1H), 2.85 (d, 1H, J = 13.6 Hz), 2.69 (d, 1H, J = 13.2 Hz), 2.60-2.39 (m, 2H), 1.64-1.53 (m, 2H), 1.06 (s, 3H) ppm; ^13C NMR (CDCl_3, 100 MHz) δ 210.3, 144.5, 137.9, 130.4, 128.2, 126.5, 118.5, 50.1, 42.6, 31.9, 25.8, 22.8 ppm; IR (thin film) ν 2927, 1723, 1672, 1638, 1454, 1262, 1024 cm^{-1}; HRMS (ESI) calcd for C_{18}H_{19}O 201.1279 found 201.1274 (M+H^+).
Purified by chromatography on silica gel (9:1 hexanes/EtOAc); yellow oil (73%); TLC Rf = 0.05 (9:1 hexanes/EtOAc); 1H NMR (CDCl3, 400 MHz) δ 5.94-5.91 (m, 1H), 5.37 (d, 1H, J = 6.0 Hz), 4.92 (d, 1H, J = 6.0 Hz), 3.96 (dd, 1H, J = 11.6, 1.3 Hz), 3.90 (d, 1H, J = 11.6 Hz), 2.67 (ddd, 1H, J = 13.6, 4.8, 2.6 Hz), 2.62-2.50 (m, 1H), 2.42 (ddd, 1H, J = 19.6, 5.2, 2.4 Hz), 2.25-2.14 (m, 1H), 2.04 (s, 3H) ppm. 13C NMR (CDCl3, 100 MHz) δ 200.5, 166.7, 125.9, 87.4, 65.9, 60.5, 28.0, 24.6 ppm; IR (thin film) ν 3179, 2925, 1734, 1646, 1604, 1499, 1383, 1310, 1228, 1162, 1113, 1042 cm⁻¹.

Purified by chromatography on silica gel (9:1 hexanes/EtOAc); yellow oil (37%); TLC Rf = 0.1 (9:1 hexanes/EtOAc); 1H NMR (CDCl3, 400 MHz) δ 5.42 (d, 1H, J = 6.2 Hz), 4.94 (d, 1H, J = 6.2 Hz), 3.98 (dd, 1H, J = 11.6, 1.3 Hz), 3.92 (d, 1H, J = 11.6 Hz), 2.71 (ddd, 1H, J = 13.6, 4.8, 2.6 Hz), 2.71 (s, 3H) 2.62-2.52 (m, 1H), 2.58 (ddd, 1H, J = 19.6, 5.2, 2.4 Hz), 2.27-2.16 (m, 1H), 2.09 (s, 3H) ppm. 13C NMR (CDCl3, 100 MHz) δ 200.6, 166.9, 126.1, 87.4, 65.9, 60.4, 31.1, 28.0, 25.2, 24.7 ppm; IR (thin film) ν 2972, 2928, 1739, 1733, 1638, 1444, 1380, 1312, 1228, 1170, 1040 cm⁻¹.

Purified by chromatography on silica gel (19:1 hexanes/EtOAc); yellow oil (81%); TLC Rf = 0.14 (9:1 hexanes/EtOAc); 1H NMR (CDCl3, 400 MHz) δ 5.89-5.86 (m, 1H), 5.22-5.19 (m, 1H), 3.84-3.76 (m, 2H), 2.81 (dd, 1H, J = 13.2, 4.0 Hz), 2.52-2.46 (m, 1H), 2.02-2.12 (m, 9H) ppm. 13C NMR (CDCl3, 100 MHz) δ 200.4, 168.1, 126.1, 82.4, 60.1, 36.9, 35.6, 33.9, 30.0, 27.2, 25.6 ppm; IR (thin film) ν 3520, 2928, 2855, 1725, 1640, 1388, 1345, 1289, 1100, 1010, 899 cm⁻¹.

Purified by chromatography on silica gel (9:1 hexanes/EtOAc); yellow oil (61%); TLC Rf = 0.19 (9:1 hexanes/EtOAc); 1H NMR (CDCl3, 400 MHz) δ 6.06-6.05 (m, 1H), 5.25-5.23 (m, 1H), 4.73 (t, 2H, J = 1.6 Hz), 2.59 (s, 2H), 1.97-1.44 (m, 8H) ppm. 13C NMR (CDCl3, 100 MHz) δ 198.9, 151.3, 126.3, 79.1, 68.9, 60.1, 43.1, 24.7 ppm; IR (thin film) ν 2901, 1734, 1646, 1604, 1499, 1309, 1159, 1034 cm⁻¹.

**General procedure for carbocyclization of alkyne-derived thioesters.** Thioester (0.44 mmol), Pd(OAc)₂ (9.9 mg, 0.04 mmol, 10 mol%), Cu(thiophene-2-carboxylate) (269.0 mg, 1.41 mmol, 3.2 equiv), tri(2-furyl)phosphine (20.5 mg, 0.09 mmol, 20 mol%), and phenylboronic acid (86.0 mg, 0.71 mmol, 1.6 equiv) were added sequentially to a flame-dried 10 mL round bottom flask. The flask was placed under vacuum and back-filled with N₂. THF (3.7 mL), which had been degassed by a freeze-pump-thaw cycle (3x), was added. The brown suspension was stirred at 60 °C for 18 h, after which time the reaction was quenched with 10 mL of saturated aqueous NaHCO₃. The mixture was transferred to a separatory funnel and extracted with 3 x 15 mL of EtOAc. The combined organic layers were washed with 1 x 20 mL of saturated aqueous sodium chloride, dried over MgSO₄, filtered through a pad of Celite, and concentrated under reduced pressure to a brown residue. The desired product was isolated following purification by chromatography on silica gel (conditions given below).
Purified by chromatography on silica gel (9:1 hexanes/EtOAc); yellow oil (56%); TLC $R_f = 0.20$ (9:1 hexanes/EtOAc); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.37-7.29 (m, 3H), 7.18-7.14 (m, 2H), 2.77 (tq, 2H, $J = 7.2$, 1.2 Hz), 2.32 (t, 2H, $J = 8.0$ Hz), 2.12 (t, 3H, $J = 1.6$ Hz), 1.97 (tt, 2H, $J = 7.6$, 7.2 Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 205.0, 146.5, 141.7, 132.2, 127.9, 127.5, 127.3, 40.3, 30.0, 24.9, 19.3 ppm; IR (thin film) $\nu$ 2962, 1772, 1712, 1624, 1440, 1411, 1191, 1125 cm$^{-1}$. HRMS (ES$^+$) calcd for C$_{13}$H$_{15}$O 187.1123 found 187.1117 (M+H$^+$).

Purified by chromatography on silica gel (gradient elution: 7:3 hexanes/CH$_2$Cl$_2$–8:1 hexanes/EtOAc); white solid (67%); TLC $R_f = 0.11$ (7:3 hexanes/CH$_2$Cl$_2$); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.41-7.17 (m, 10H), 3.52-3.40 (m, 1H), 3.26 (dd, 1H, $J = 16.2$, 7.8 Hz), 2.86-2.78 (m, 1H), 2.74 (dd, 1H, $J = 17.6$, 7.8 Hz), 2.54 (dd, 1H, $J = 17.6$, 10.8 Hz), 2.14 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 203.2, 147.2, 144.0, 141.5, 132.2, 128.8, 128.0, 127.7, 127.4, 126.8, 126.8, 47.6, 38.53, 38.46, 24.9 ppm; IR (thin film) $\nu$ 3206, 2891, 1706, 1621, 1596, 1491, 1440, 1193 cm$^{-1}$; HRMS (ES$^+$) calcd for C$_{19}$H$_{19}$O 263.1436 found 263.1430 (M+H$^+$).
Pulse Sequence: spul
Solvent: CDCl3

Relax. delay 3.000 sec
Pulse 90.1 degrees
Ampl. time 4.002 sec
Width 4997.5 Hz
16 repetitions

OBSERVED 81.10915551 Hz
DATA PROCESSING
FT size 65536
Total time 1 min

Sample directory:

Pulse Sequence: spul
Solvent: cdc13
Temp. 25.0 C / 298.1 K

Relax. delay 3.000 sec
Pulse 90.0 degrees
Ampl. time 6.002 sec
Width 5995.4 Hz
16 repetitions

OBSERVED 81.10971555 Hz
DATA PROCESSING
FT size 65536
Total time 1 min
Pulse Sequence: 2pul
Solvent: CDCl3

Relax. delay 1.000 sec
Pulse 52.1 degrees
Arg. time 6.002 sec
Width 6997.5 Hz
16 repetitions
OBSERVE 81, 400.1115375 MHz
DATA PROCESSING
FT size 65536
Total time 1 min

\[ \text{Ph} \quad \text{Me} \]

- ppm

Pulse Sequence: 2pul

sec
Pulse 52.1 degrees
Arg. time 6.002 sec
Width 6997.5 Hz
16 repetitions
OBSERVE 81, 400.1115368 MHz
DATA PROCESSING
FT size 65536
Total time 1 min

\[ \text{EtO} \quad \text{Ph} \]

- ppm
Electronic Supplementary Material (ESI) for Chemical Science
This journal is © The Royal Society of Chemistry 2013