Supporting Information

A concise palladium-catalyzed carboamination route
to (+/-)-tylophorine

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General Experimental. All non-aqueous reactions were performed under an atmosphere of dry nitrogen unless otherwise specified. Commercial grade reagents and anhydrous solvents were used as received from vendors and no attempts were made to purify or dry these components further. Melting points were obtained using a hot stage melting point apparatus and are uncorrected. Infrared (IR) data were recorded with a FT-IR spectrometer and are reported as cm\(^{-1}\). NMR spectra were recorded on a 300 MHz or 500 MHz NMR spectrometer and are reported in ppm \(\delta\) values, using tetramethylsilane as an internal reference. Low-resolution mass spectroscopic analyses were performed on a single quadrupole mass spectrometer utilizing electrospray ionization (ESI). High-resolution mass spectroscopic analyses were performed on a Q-ToF mass spectrometer utilizing electrospray ionization (ESI).

\((+/-)-\text{tert-Butyl 2-(phenanthren-9-ylmethyl)pyrrolidine-1-carboxylate [(+/-)-8].}\) A degassed mixture of 9-bromophenanthrene (6a, 833 mg, 3.24 mmol), \(\text{tert-butyl pent-4-enylcarbamate (7, 500 mg, 2.70 mmol)}, \) palladium(II) acetate (72 mg, 0.32 mmol), 2,2'-bis(diphenylphosphino)diphenyl ether (DPE-phos, 247 mg, 0.46 mmol) and cesium carbonate (1.20 g, 6.21 mmol) in anhydrous 1,4-dioxane (20 mL) was heated at 100 ºC under nitrogen for 12 h. The cooled mixture was diluted with saturated NH\(_4\)Cl solution (250 mL) and extracted with ethyl acetate (3 x 75 mL). The combined organic extracts were dried over sodium sulfate, filtered and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/heptanes (gradient of 1:19 to 1:1), to provide racemic \(\text{tert-butyl 2-(phenanthren-9-ylmethyl)pyrrolidine-1-carboxylate [(+/-)-8]}\) as a yellow solid (531 mg, 57%): mp 187-188 ºC; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.73 (t, \(J = 2.5\) Hz, 1H), 8.66 (d, \(J = 8.0\) Hz, 1H), 8.46 (s, 1H), 7.83 (d, \(J = 7.5\) Hz, 1H), 7.69 (t, \(J = 5.0\) Hz, 1H), 7.65-7.54 (m, 3H), 7.54 (s, 1H), 4.37-4.31 (m, 1H), 3.84 (d, \(J = 11.5\) Hz, 1H), 3.53-3.38 (m, 2H), 2.80 (t, \(J = 11.5\) Hz, 1H), 2.04-1.94 (m, 1H), 1.87-1.77 (m, 2H), 1.71-1.62 (m, 1H), 1.54 (s, 9H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 154.7, 133.8, 131.8, 131.5, 130.6, 129.9, 128.1, 128.0, 126.6, 126.3, 126.2, 125.3, 123.1, 122.5 (2), 79.5, 57.0, 46.6, 38.2, 29.4, 28.7 (3), 22.9; IR (KBr) 1683, 1449, 1396, 1364, 1333 cm\(^{-1}\); MS (ESI) \(m/z\) 306 [M+H-Boc]\(^+\); HRMS (ESI) \(m/z\) 362.2107 [M+H]\(^+\) (362.2120 calculated for C\(_{24}\)H\(_{27}\)NO\(_2\)+H).
Trifluoroacetic acid (5 mL) was added to a mixture of racemic tert-butyl 2-(phenanthren-9-ylmethyl)pyrrolidine-1-carboxylate [(+/-)-8, 202 mg, 0.56 mmol] in formalin (2 mL, 37% solution of formaldehyde in water) at room temperature under nitrogen and the mixture was heated at 90 ºC for 12 h. The solvents were removed under reduced pressure after which the residue was diluted with water (10 mL) and the pH was adjusted to 9 with 2 N NaOH. The crude product was extracted with ethyl acetate (2 x 50 mL) and the combined organic extracts were washed with brine (50 mL), dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel, eluting with methanol/methylene chloride (gradient of 100% methylene chloride to 1:9), to provide the crude product, which was then recrystallized from methanol to provide racemic 9,11,12,13,13a,14-hexahydrodibenzo[f,h]pyrrolo[1,2-b]isoquinoline [(+/-)-12] as a white solid (96.3 mg, 63%): mp 153-154 ºC; 1H NMR (300 MHz, CDCl₃) δ 8.73-8.68 (m, 2H), 8.04 (d, J = 3.5 Hz, 1H), 7.91 (d, J = 4.5 Hz, 1H), 7.58-7.64 (m, 4H), 4.74 (d, J = 15.0 Hz, 1H), 3.74 (d, J = 15.0 Hz, 1H), 3.49-3.43 (m, 2H), 3.02-2.96 (m, 1H), 2.54-2.43 (m, 2H), 2.29-2.02 (m, 1H), 2.10-1.98 (m, 1H), 1.98-1.88 (m, 1H), 1.82-1.73 (m, 1H); 13C NMR (75 MHz, CDCl₃) δ 131.4, 130.0, 129.5, 129.3, 128.7, 128.2, 126.7 (2), 125.9, 125.8, 123.4, 122.9, 122.8, 122.5, 60.1, 55.0, 53.8, 33.5, 31.2, 21.6; IR (KBr) 2915, 2869, 2789, 1708, 1605, 1493, 1443, 1343, 1366 cm⁻¹; MS (ESI) m/z 274 [M+H]⁺; HRMS (ESI) m/z 274.1589 [M+H]+ (274.1596 calculated for C₂₀H₁₉N+H).

1,2-Bis(3,4-dimethoxyphenyl)ethyne (15).² Diisopropylamine (21.7 mL, 155 mmol) was added to a mixture of 4-ethynyl-1,2-dimethoxy benzene (13, 1.0 g, 6.17 mmol), 4-iodo-1,2-dimethoxybenzene (14, 1.46 g, 6.23 mmol), copper(I) iodide (351 mg, 1.85 mmol) and tetrakis(triphenylphosphine)palladium(0) (163 mg, 0.15 mmol) in anhydrous THF (100 mL) at room temperature under nitrogen and the mixture was heated to 60 ºC to stir for 12 h. The cooled mixture was filtered through a plug of silica gel under reduced pressure, eluting with ethyl acetate/methylene chloride (1:1), and the filtrate solvents were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/methylene chloride (gradient of 1:19 to 1:1), to provide 1,2-bis(3,4-dimethoxyphenyl)ethyne (15) as a yellow...
solid (1.61 g, 88%); mp 163-164 ºC; ¹H NMR (500 MHz, CDCl₃) δ 7.12 (d, J = 8.3 Hz, 2H), 7.03 (d, J = 1.9 Hz, 2H), 6.83 (d, J = 8.3 Hz, 2H), 3.90 (s, 12H); ¹³C (125 MHz, CDCl₃) δ 149.4 (2), 148.7 (2), 124.7 (2), 115.7 (2), 114.2 (2), 111.1 (2), 88.0 (2), 55.9 (4); IR (KBr) 1598, 1575, 1514, 1463, 1449, 1441, 1410, 1329 cm⁻¹; MS (ESI) m/z 299 [M+H]⁺; HRMS (ESI) m/z 299.1270 [M+H]⁺ (299.1270 calculated for C₁₈H₁₈O₄+H).

1,2-Bis(3,4-dimethoxyphenyl)ethane (16).³ Method A: A suspension of 1,2-bis(3,4-dimethoxyphenyl)ethyne (15, 3.31 g, 11.1 mmol) and 10% palladium on charcoal (500 mg) in 2N HCl (15 mL), methanol (75 mL) and THF (75 mL) was shaken under 40 psi of hydrogen on a Parr shaker apparatus for 24 h. The solids were removed by vacuum filtration and the filtrate solvents were removed under reduced pressure. The residue was purified by filtration through a plug of Celite, eluting with THF, to provide 1,2-bis(3,4-dimethoxyphenyl)ethane (16) as a tan solid (2.66 g, 79%): mp 114-115 ºC; ¹H NMR (500 MHz, CDCl₃) δ 6.78 (d, J = 8.1 Hz, 2H), 6.70 (d, J = 8.1, 2H), 6.66 (d, J = 1.9 Hz, 2H), 3.86 (s, 6H), 3.84 (s, 6H), 2.84 (s, 4H); ¹³C (125 MHz, CDCl₃) δ 148.7 (2), 147.3 (2), 134.4 (2), 120.4 (2), 111.9 (2), 111.2 (2), 55.9 (2), 55.8 (2), 37.7 (2); IR (KBr) 1605, 1590, 1511, 1464, 1449, 1418, 1332 cm⁻¹; MS (ESI) m/z 303 [M+H]⁺; HRMS (ESI) m/z 303.1608 [M+H]⁺ (303.1608 calculated for C₁₈H₂₂O₄+H).

Method B: A suspension of 1,2-bis(3,4-dimethoxyphenyl)ethyne (15, 1.1 g, 3.69 mmol) and 20% palladium on charcoal (220 mg) in trifluoroacetic acid (0.25 mL) and ethyl acetate (100 mL) was stirred under one atmosphere of hydrogen at room temperature for 72 h. The solids were removed by vacuum filtration and the filtrate solvents were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (gradient of 1:19 to 1:1), to provide 1,2-bis(3,4-dimethoxyphenyl)ethane (16) as an off-white solid (636 mg, 57%).

2,3,6,7-Tetramethoxyphenanthrene (17).³⁴ A solution of [bis(trifluoroacetoxy)iodo]benzene (PIFA, 430 mg, 1.00 mmol) and boron trifluoride diethyl etherate (0.25 mL, 2.02 mmol) in anhydrous methylene chloride (20 mL) was added slowly to a solution of 1,2-bis(3,4-dimethoxyphenyl)ethane (16, 265 mg, 0.88 mmol) in anhydrous methylene chloride (10 mL) at -20 ºC under nitrogen and the resulting mixture was stirred at -20 ºC for 2 h. The solvents were removed under reduced
pressure and the solvents were triturated with methylene chloride (20 mL) and the solids were collected by vacuum filtration, washing with methylene chloride (5 mL), to provide 2,3,6,7-tetramethoxyphenanthrene (17) as a white solid (204 mg, 78%): mp 185-186 ºC; $^1$H NMR (500 MHz, CD$_3$OD) δ 7.94 (s, 2H), 7.56 (s, 2H), 7.31 (s, 2H), 4.07 (s, 6H), 3.97 (s, 6H); $^{13}$C (125 MHz, CDCl$_3$) δ 149.3 (2), 148.8 (2), 126.4 (2), 124.4 (2), 124.3 (2), 108.4 (2), 102.9 (2), 56.1 (2), 55.9 (2); IR (KBr) 1621, 1609, 1509, 1471, 1436, 1406, 1373 cm$^{-1}$; MS (ESI) m/z 299 [M+H]$^+$; HRMS (ESI) m/z 299.1277 [M+H]$^+$ (299.1277 calculated for C$_{18}$H$_{18}$O$_4$+H).

**9-Bromo-2,3,6,7-tetramethoxyphenanthrene (18).** $N$-Bromosuccinimide (NBS, 98 mg, 0.55 mmol) was added to a solution of 2,3,6,7-tetramethoxyphenanthrene (17, 172 mg, 0.58 mmol) in anhydrous methylene chloride (5 mL) at 0 ºC under nitrogen, after which the mixture was stirred for 1 h and then slowly warmed to room temperature, stirring for a total of 7 h. The mixture was diluted with 5% Na$_2$S$_2$O$_3$ solution (50 mL) and extracted with methylene chloride (2 x 15 mL). The combined organic extracts were washed with sat. NaHCO$_3$ and brine solutions (20 mL each), dried over sodium sulfate, filtered and the solvent was removed under reduced pressure to provide 9-bromo-2,3,6,7-tetramethoxyphenanthrene (18) as a brown solid (204 mg, 98%): mp 219-220 ºC; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.87 (s, 1H), 7.75 (s, 1H), 7.70 (s, 1H), 7.65 (s, 1H), 7.09 (s, 1H), 4.13 (s, 3H), 4.11 (s, 3H), 4.08 (s, 3H), 4.02 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 149.2, 149.0, 148.8, 148.7, 127.1, 126.3, 124.8, 124.2, 123.4, 118.0, 107.7, 106.9, 102.4, 102.3, 55.7, 55.6, 55.5, 55.4; IR (KBr) 1618, 1508, 1474, 1429, 1349, 1344 cm$^{-1}$; MS (ESI) m/z 377 [M+H]$^+$; HRMS (ESI) m/z 377.0387 [M+H]$^+$ (377.0388 calculated for C$_{18}$H$_{17}$BrO$_4$+H).

**(+-)-**tert-**Butyl 2-((2,3,6,7-tetramethoxyphenanthren-9-yl)methyl)pyrrolidine-1-carboxylate [(+-)-19].** A degassed mixture of 9-bromo-2,3,6,7-tetramethoxyphenanthrene (18, 101.9 mg, 0.27 mmol), tert-butyl pent-4-enylcarbamate (7, 65.1 mg, 0.35 mmol), tris(dibenzylideneacetone)dipalladium(0) (51.2 mg, 0.06 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 62.0 mg, 0.11 mmol) and sodium tert-butoxide (68.4 mg, 0.71 mmol) in anhydrous 1,4-dioxane (5.0 mL) was heated at 100 ºC under nitrogen for 12 h. The cooled mixture was diluted with ethyl acetate (25 mL) and partially purified by filtration through a plug of Celite, eluting
with ethyl acetate, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/methylene chloride (gradient of 1:99 to 15:85), to provide racemic tert-butyl 2-\(((2,3,6,7\text{-}\text{tetramethoxyphenanthren-9-yl})\text{methyl})\text{pyrrolidine-1-carboxylate}\ [(+/-)-19]\ as an off-white solid (89.9 mg, 65%): mp 194-196 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.31 (s, 1H), 7.82 (s, 1H), 7.78 (s, 1H), 7.36 (s, 1H), 7.17 (s, 1H), 4.26-4.23 (m, 1H), 4.21 (s, 3H), 4.12 (s, 3H), 4.11 (s, 3H), 4.02 (s, 3H); 3.92 (d, $J = 5.4$ Hz, 1H), 3.50–3.47 (m, 1H), 3.32–3.30 (m, 1H), 2.59 (t, $J = 11.9$ Hz, 1H), 2.04–2.02 (m, 1H), 1.86–1.81 (m, 2H), 1.69–1.67 (m, 1H), 1.51 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 154.7, 149.0, 148.9, 148.8 (2), 131.7, 126.2, 126.1, 125.3, 124.7, 123.9, 107.9 (2), 106.7, 102.9, 79.0, 57.4, 56.6, 56.1, 55.9, 46.8, 38.5, 29.2, 28.6 (3), 23.4; IR (KBr) 1682, 1620, 1506, 1476, 1397, 1362 cm$^{-1}$; MS (ESI) $m/z$ 482 [M+H]$^+$; HRMS (ESI) $m/z$ 482.2546 [M+H]$^+$ (482.2543 calculated for C$_{28}$H$_{35}$NO$_6$+H).

(+/-)-Tylophorine [(+/-)-1].\(^{1,3a,5,6}\) A mixture of racemic tert-butyl 2-\(((2,3,6,7\text{-}\text{tetramethoxyphenanthren-9-yl})\text{methyl})\text{pyrrolidine-1-carboxylate}\ [(+/-)-19], 100.4 mg, 0.21 mmol) in a solution of HCl in methanol (5.0 ml, 1.25 M in methanol) was stirred at room temperature under nitrogen for 4 h, after which a solution of formalin (4.0 mL, 37% aqueous formaldehyde) was added and the mixture was heated to reflux to stir for 12 h. The cooled mixture was diluted with water (10 mL) and 2 N sodium hydroxide solution (20 mL) and extracted with methylene chloride (3 x 25 mL). The combined organic extracts were washed with brine (50 mL), dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with methanol/methylene chloride (gradient of 1:99 to 1:9), to provide racemic tylophorine [(+/-)-1] as an off-white solid (81.7 mg, 99%): mp 230 °C (dec); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.84 (s, 2H), 7.32 (s, 1H), 7.17 (s, 1H), 4.63 (d, $J = 14.5$ Hz, 1H), 4.09 (s, 6H), 4.06 (s, 6H), 3.68 (d, $J = 14.6$ Hz, 1H), 3.50–3.47 (m, 1H), 3.40–3.36 (m, 1H), 2.94–2.89 (m, 1H), 2.51–2.44 (m, 2H), 2.27–2.22 (m, 1H), 2.07–2.02 (m, 1H), 1.95–1.91 (m, 1H), 1.82–1.76 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$ + CD$_3$OD) $\delta$ 148.8, 148.7, 148.6, 126.2, 125.8, 125.5, 124.3, 123.8, 123.6, 104.1, 103.6, 103.5, 103.2, 60.4, 56.1, 56.0, 55.9, 55.0, 53.9, 33.4, 31.0, 21.5; IR (KBr) 1618, 1512,
1467, 1444, 1425 cm⁻¹; MS (ESI) m/z 394 [M+H]⁺; HRMS (ESI) m/z 394.1999 [M+H]⁺ (394.2018 calculated for C₂₄H₂₇NO₄+H).

References


