Supporting Information

First Asymmetric Total Synthesis of (-)-Antofine Using an Enantioselective Catalytic Phase Transfer Alkylation

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Full experimental procedures and analytical data of compounds; copies of ^1H NMR and ^{13}C NMR spectra of compounds **1**, **3**, **12**, and **15**; HPLC data of compound **12**.

General. All chemicals were reagent grade and used as purchased. All reactions were performed under an inert atmosphere of dry argon or nitrogen using distilled dry solvents. Reactions were monitored by TLC analysis using Merck silica gel 60 F-254 thin layer plates. Flash column chromatography was carried out on Merck silica gel 60 (230-400 mesh). Melting points are uncorrected. Optical rotations were measured using sodium light (D line 589.3 nm).

10-Bromomethyl-2,3,6-trimethoxy-phenanthrene (7).

A solution of phenanthryl alcohol **10** (1.28 g, 4.29 mmol), triphenylphosphine (1.9 g, 6.41 mmol) and carbon tetrabromide (2.13 g, 6.42 mmol) in dry acetonitrile (20 mL) was stirred for 1 h at 0 °C. After evaporation to dryness, the residue was purified by short flash column chromatography on silica gel (hexane/EtOAc, 2 : 1) to give phenanthryl bromide **7** (1.55 g, 98%) as a white solid; mp = 171-174 °C; IR (KBr, cm⁻¹); 2998, 2944, 2828, 1622, 1524, 1478, 1273, 1217, 1036, 847, 789; ¹H NMR (300 MHz, CDCl₃) δ 4.02 (s, 3H), 4.11 (s, 3H), 4.12 (s, 3H), 4.98 (s, 2H), 7.19 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.53 (s, 1H), 7.69 (s, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.82 (d, *J* = 2.4 Hz, 1H), 7.91 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 33.78, 55.52, 55.97, 56.04, 103.93, 103.99, 105.04, 115.69, 125.08, 125.16, 125.32, 126.98, 128.08, 130.40, 131.79, 149.13, 149.42, 158.88; HRMS (EI) calcd for C₁₈H₁₇BrO₃ (M⁺) 360.0361, found 360.0364.

2-(Benzhydrylidene-amino)-3-(3,6,7-trimethoxy-phenanthren-9-yl)-propionic acid *tert*-butyl ester (12).

To a mixture of phenanthryl bromide **7** (450 mg, 1.25 mmol), *N*-(diphenylmethylene)glycine *tert*-butyl ester **6** (442 mg, 1.50 mmol) and chiral catalyst **11** (24.6 mg, 0.025 mmol) was added PhCH₃/CHCl₃ (7 : 3, 9.34 mL). The reaction mixture was then cooled to 0 °C. To it was added aqueous NaOH (50%, 3.12 mL) was added slowly. The resulting mixture was stirred at 0 °C for 3 days. The suspension was diluted with diethyl ether (80 mL), washed with water (2 x 15 mL), dried over MgSO₄,

filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 4 : 1) afforded the desired product **12** (698 mg, 97%) as a waxy solid. $[\alpha]_D^{20} = -162.4$ (*c* 2.5, CHCl₃); The enantioselectivity was determined by chiral HPLC analysis. (CHIRALCEL OD-H, hexane/ 2-propanol (9:1, v/v), flow rate: 0.5 mL / min, λ 254 nm, retention time: *S* (major) 25.52 min, *R* (minor) 30.33 min, 96% ee); IR (film, cm⁻¹); 2972, 2827, 1732, 1610, 1523, 1473, 1269, 1207, 1159, 1035; ¹H NMR (300 MHz, CDCl₃) δ 1.49 (s, 9H), 3.55 (dd, *J* = 13.8, 9.9 Hz, 1H), 3.74 (dd, *J* = 13.8, 3.3 Hz, 1H), 3.81 (s, 3H), 3.99 (s, 3H), 4.10 (s, 3H), 4.46 (dd, *J* = 9.9, 3.3 Hz, 1H), 6.23 (br d, *J* = 5.4 Hz, 2H), 6.90 (t, *J* = 7.8 Hz, 2H), 7.09-7.31 (m, 6H), 7.43-7.48 (m, 3H), 7.66 (d, *J* = 8.7 Hz, 1H), 7.81 (d, *J* = 2.1 Hz, 1H), 7.87 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 28.09, 37.62, 55.47, 55.64, 56.02, 66.05, 81.15, 103.71, 103.74, 104.85, 115.26, 124.51, 125.90, 126.68, 126.83, 127.29, 127.53, 127.76, 128.61, 128.97, 129.76, 129.96, 130.37, 135.82, 139.41, 148.52, 149, 157.84, 170.48, 171.30; HRMS (CI) calcd for C₃₇H₃₈NO₅ [*M* + *H*]⁺ 576.2750, found 576.2747.

2-(Benzhydryl-amino)-3-(3,6,7-trimethoxy-phenanthren-9-yl)-propan-1-ol (**13**).

To a solution of chiral α -amino ester **12** (30 mg, 0.05 mmol) in dry THF (3 mL) was added LiAlH₄ (150 μ L, 1.0 M in THF, 0.15 mmol) at 0 °C. After 20 min, the solution was warmed to rt over 1 h. The reaction was quenched with 10% NaOH solution at 0 °C. The suspension was then filtered over a Celite pad, and the filtrate was concentrated in

vacuo. The residue was dissolved in EtOAc (40 mL), and washed with brine (10 mL), dried over MgSO₄, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 1 : 2) afforded the desired product **13** (21.5 mg, 81%) as a waxy solid. $[\alpha]_D^{19} = -27.8$ (*c* 2.10, CHCl₃); IR (film, cm⁻¹); 3524, 3022, 2935, 2833, 1608, 1510, 1471, 1236, 1161, 966; ¹H NMR (300 MHz, CDCl₃) δ 3.16-3.35 (m, 3H), 3.43 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.66 (dd, *J* = 10.8, 3.3 Hz, 1H), 3.76 (s, 3H), 4.03 (s, 3H), 4.12 (s, 3H), 4.90 (s, 1H), 6.99-7.11 (m, 5H), 7.17-7.26 (m, 7H), 7.43 (s, 1H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.85 (d, *J* = 2.4 Hz, 1H), 7.92 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 36.47, 55.52, 55.63, 55.74, 55.99, 62.74, 63.99, 103.82, 103.89, 104.86, 115.46, 124.79, 125.84, 126.15, 126.67, 127.09, 127.17, 127.24, 128.36, 128.42, 129.31, 129.69, 130.49, 143.02, 148.75, 149.24, 158.01; HRMS (CI) calcd for C₃₃H₃₄NO₄ [M + H]⁺ 508.2488, found 508.2480.

Benzhydryl-[1-(3,6,7-trimethoxy-phenanthren-9-ylmethyl)-allyl]-amine (14).

A solution of DMSO (0.13 mL, 1.86 mmol) in CH₂Cl₂ (1 mL) was added dropwise at –78 °C to a solution of oxalyl chloride (0.37 mL, 2.0 M in solution CH₂Cl₂, 0.74 mmol) in CH₂Cl₂ (3 mL). After 10 min, a solution of chiral α -amino alcohol **13** (314 mg, 0.62 mmol) in CH₂Cl₂ (2 mL) was added dropwise at –78 °C. After a further 15 min, Et₃N (0.43 mL, 3.10 mmol) was added. Then, the reaction was allowed to warm slowly to rt. After 30 min, water (10 mL) was added to the reaction mixture. It was extracted with

EtOAc (2 x 20 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and evaporated under reduced pressure to give the crude corresponding aldehyde, which was used in the following step without purification.

To a solution of methyl triphenylphosphonium iodide (1.0 g, 2.48 mmol) in dry THF (20 mL) was added *n*-BuLi (1.55 mL, 1.6 M in hexane, 2.48 mmol) at ice bath. After 20 min, the crude aldehyde in THF (3 mL) was added dropwise. After 30 min stirring at ice bath, water (2 mL) was added to the reaction mixture. The resulting mixture was diluted with EtOAc (50 mL), washed with brine (2 x 10 mL), dried over MgSO₄, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 4 : 1) afforded the desired product **14** (212.3 mg, 68% from **13**) as a waxy solid. $[\alpha]_D^{19} = -19.3$ (*c* 1.10, CHCl₃); IR (film, cm⁻¹); 2934, 2850, 1608, 1508, 1471, 1269, 1161, 1034, 850; ¹H NMR (300 MHz, CDCl₃) δ 1.76 (br s, 1H), 3.17 (dd, *J* = 13.8, 6.6 Hz, 1H), 3.32 (dd, *J* = 13.8, 7.8 Hz, 1H), 3.54 (m, 1H), 3.88 (s, 3H), 4.03 (s, 3H), 4.14 (s, 3H), 4.91 (s, 1H), 4.99 (d, *J* = 17.1 Hz, 1H), 5.15 (dd, *J* = 10.2, 1.5 Hz, 1H), 5.81 (m, 1H), 7.04-7.26 (m, 12H), 7.44 (s, 1H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.87 (d, *J* = 2.4 Hz, 1H), 7.94 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 40.68, 55.46, 55.62, 55.93, 58.14, 63.48, 103.71, 103.76, 105.01, 115.31, 116.04, 124.66, 125.81, 126.20, 126.70, 126.80, 127.12, 127.29, 128.17, 128.25, 129.30, 129.70, 130.40, 140.70, 143.27, 144.38, 148.52, 148.99, 157.86; HRMS (CI) calcd for C₃₄H₃₄NO₃ [M + H]⁺ 504.2538, found 504.2536.

Allyl-benzhydryl-[1-(3,6,7-trimethoxy-phenanthren-9-ylmethyl)-allyl]-amine (15).

A mixture of secondary amine **14** (100 mg, 0.2 mmol), allyl bromide (86.5 μ L, 1.0 mmol), and K_2CO_3 (82.8 mg, 0.6 mmol) in dry DMF (2 mL) was heated at 60 $^\circ\text{C}$ for 2 days. After being cooled to rt, water (10 mL) was added. The resulting mixture was extracted with EtOAc twice (2 x 50 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 4 : 1) provided the desired product **15** (93.5 mg, 86%) as a colorless oil. $[\alpha]_D^{19} = -32.2$ (c 0.67, CHCl_3); IR (film, cm^{-1}): 2936, 2851, 1611, 1524, 1474, 1269, 1206, 1161, 920, 851, 748; ^1H NMR (300 MHz, CDCl_3) δ 3.16 (dd, $J = 14.1, 6.9$ Hz, 1H), 3.33-3.54 (m, 3H), 3.85 (s, 3H), 3.89 (m, 1H), 4.04 (s, 3H), 4.14 (s, 3H), 4.79 (ddd, $J = 17.1, 1.8, 0.6$ Hz, 1H), 4.90-4.96 (m, 3H), 5.08 (dd, $J = 10.2, 1.5$ Hz, 1H), 5.83-6.02 (m, 2H), 6.95-7.25 (m, 12H), 7.39 (s, 1H), 7.75 (d, $J = 8.7$ Hz, 1H), 7.88 (d, $J = 2.4$ Hz, 1H), 7.95 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 37.10, 50.23, 55.52, 55.67, 55.95, 61.71, 70.13, 103.79, 103.81, 105.05, 115.26, 115.29, 116.92, 124.58, 126.00, 126.24, 126.56, 126.63, 127.05, 127.99, 128.36, 128.54, 129.63, 130.21, 130.64, 137.47, 138.84, 142.95, 143.37, 148.43, 149.02, 157.72; HRMS (CI) calcd for $\text{C}_{37}\text{H}_{38}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 544.2852, found 544.2855.

1-Benzhydryl-2-(3,6,7-trimethoxy-phenanthren-9-ylmethyl)-2,5-dihydro-1H-pyrrole (16).

A solution of bis-allylamine **15** (53 mg, 0.098 mmol) and Grubbs's catalyst (1.7 mg, 2 mole%) in dry CH_2Cl_2 (2 mL) was stirred at rt for 1 day. The reaction mixture was concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 4 : 1) to give **16** (46.5 mg, 92%) as a waxy solid. $[\alpha]_D^{22} = +25.7$ (c 1.64, CHCl_3); IR (film, cm^{-1}): 3022, 2936, 2831, 1608, 1524, 1510, 1269, 1206, 1159, 1034, 885; ^1H NMR (300 MHz, CDCl_3) δ 2.97 (dd, $J = 13.2, 9.6$ Hz, 1H), 3.21 (dd, $J = 13.2, 5.4$ Hz, 1H), 3.47 (ddd, $J = 9.6, 5.4, 2.1$ Hz, 1H), 3.73 (s, 3H), 3.80 (m, 1H), 4.01 (s, 1H), 4.09 (s, 1H), 4.33 (m, 1H), 4.96 (s, 1H), 5.46 (m, 1H), 5.74 (m, 1H), 7.06-7.34 (m, 9H), 7.47-7.52 (m, 4H), 7.67 (d, $J = 8.7$ Hz, 1H), 7.82 (d, $J = 2.1$ Hz, 1H), 7.89 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 39.50, 55.53, 55.89, 55.95, 58.87, 68.90, 72.59, 103.72, 105.39, 115.33, 124.57, 126.06, 126.56, 126.78, 126.99, 127.03, 127.82, 127.32, 128.36, 128.47, 128.60, 129.55, 130.10, 130.77, 131.84, 143.76, 143.86, 148.49, 148.99, 157.72; HRMS (FAB) calcd for $\text{C}_{35}\text{H}_{34}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 516.2539, found 516.2534.

2-(3,6,7-Trimethoxy-phenanthren-9-ylmethyl)-pyrrolidine (**3**).

A suspension of 2,5-dihydropyrrole **16** (28.2 mg, 0.055 mmol) and 10% Pd/C (28 mg) in EtOH (5 mL) was stirred under 1 atm of hydrogen for 16 h. The suspension was filtered over a Celite pad, and the solution was evaporated to dryness. The residue was purified by flash column chromatography on silica gel (CH₂Cl₂/MeOH, 9 : 1, 1% NH₄OH) to give **3** (15.8 mg, 82%) as a colorless gum. $[\alpha]^{17}_D = -4.6$ (*c* 0.44, CHCl₃); mp = 144–148 °C (lit.^{4a} mp = 145–146 °C); IR (KBr, cm⁻¹); 2934, 2831, 1611, 1516, 1275, 1161, 1113, 1034; ¹H NMR (300 MHz, CDCl₃) δ 1.64–1.94 (m, 4H), 3.02 (m, 1H), 3.15 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.25 (m, 1H), 3.41 (dd, *J* = 14.1, 6.3 Hz, 1H), 3.69 (m, 1H), 3.93 (s, 3H), 4.03 (s, 3H), 4.04 (s, 3H), 5.88 (br s, 1H), 7.12 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.34 (s, 1H), 7.42 (s, 1H), 7.69–7.16 (m, 2H), 7.77 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 23.89, 30.92, 37.44, 45.19, 55.42, 55.89, 56.37, 59.24, 103.69, 103.78, 104.50, 115.35, 124.64, 125.21, 125.72, 126.20, 128.85, 129.83, 130.47, 148.69, 149.48, 157.95; HRMS (FAB) calcd for C₂₂H₂₆NO₃ [M + H]⁺ 352.1913, found 352.1905.

2,3,6-Trimethoxy-9,10,11,12,12a,13-hexahydro-9a-aza-cyclopenta[b]triphenylene

(1).

A solution of amine **3** (21 mg, 0.06 mmol) and formaldehyde (37 %, 400 μL) in EtOH (2 mL) was acidified with concentrated HCl (50 μL). The mixture was stirred at reflux temperature for 21 h in the dark. The reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in CH₂Cl₂ (10 mL) and treated with

10% HCl (5 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL) and the combined organic extracts were washed with water, brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (CH₂Cl₂/MeOH, 10 : 1) afforded the desired product (-)-antofine (**1**) (14 mg, 64%) as a colorless gum. $[\alpha]_D^{22} = -108.2$ (*c* 0.71, CHCl₃); mp = 212–214 °C (lit.⁷ mp = 206–211 °C); IR (KBr, cm⁻¹); 1622, 1512, 1256, 1208, 1130, 1038; ¹H NMR (600 MHz, CDCl₃) δ 1.71–1.78 (m, 1H), 1.86–1.92 (m, 1H), 1.98–2.04 (m, 1H), 2.18–2.23 (m, 1H), 2.39–2.46 (m, 2H), 2.83–2.88 (m, 1H), 3.28 (dd, *J* = 15.6, 2.4 Hz, 1H), 3.44 (dt, *J* = 1.8, 8.5 Hz, 1H), 3.64 (d, *J* = 14.7 Hz, 1H), 3.99 (s, 3H), 4.04 (s, 3H), 4.08 (s, 3H), 4.66 (d, *J* = 14.7 Hz, 1H), 7.18 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.27 (s, 1H), 7.78 (d, *J* = 9.0 Hz, 1H), 7.86 (d, *J* = 2.5 Hz, 1H), 7.87 (s, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 21.53, 31.23, 33.61, 53.76, 55.01, 55.44, 55.80, 55.93, 60.12, 103.75, 103.91, 104.58, 114.79, 123.45, 124.05, 124.18, 125.47, 126.56, 127.00, 130.09, 148.26, 149.31, 157.39; HRMS (CI) calcd for C₂₃H₂₆NO₃ [M + H]⁺ 364.1912, found 364.1913.

15

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EXPNO 1
PROCNO 1

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1D NMR plot parameters
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2 JK_PTC_Chiral[02-12-16]

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 Run Time (min): 60.00

Injection Volume: 10.0
 Channel: UV_VIS_3
 Wavelength: 254
 Bandwidth: 1
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 Sample Amount: 1.0000

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2	30.33	n.a.	2.937	4.029	2.14	n.a.	BMB
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