Synthesis Y. Yamaoka et al. Special Topic

Asymmetric Total Synthesis of Tylophorine through a Formal [2+2] Cycloaddition Followed by Migrative Ring Opening of a Cyclobutane

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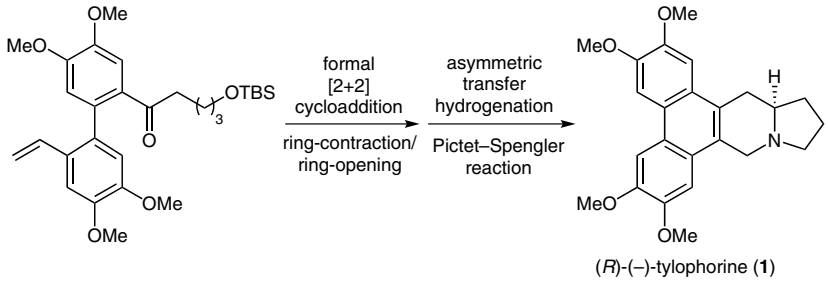

(*R*)-(–)-tylophorine (**1**)

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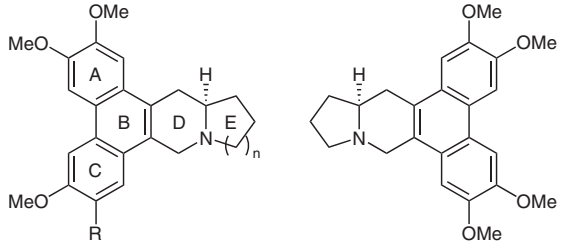
Abstract The asymmetric total synthesis of phenanthroindolizidine alkaloid (–)-tylophorine was achieved by asymmetric transfer hydrogenation of a cyclic imine. The cyclic imine with a pendant phenanthrene core was synthesized by a TfOH-promoted domino ring-contraction/ring-opening sequence of a cyclobutanol bearing an azide group, which was constructed by a formal [2+2] cycloaddition of a 2′-vinyl-1,1′-biaryl-2-yl ketone enolate. Catalytic asymmetric hydrogenation of the cyclic imine intermediate allowed the late-stage construction of the asymmetric center.

Key words heterocycles, natural products, cycloaddition, asymmetric synthesis, anticancer agents



R = OMe, n = 1: (*R*)-(–)-tylophorine (**1**) (*S*)-(+)-tylophorine (*ent*-**1**)
R = H, n = 1: (*R*)-(–)-antofine (**2**)
R = H, n = 2: (*R*)-(–)-cryptopleurine (**3**)

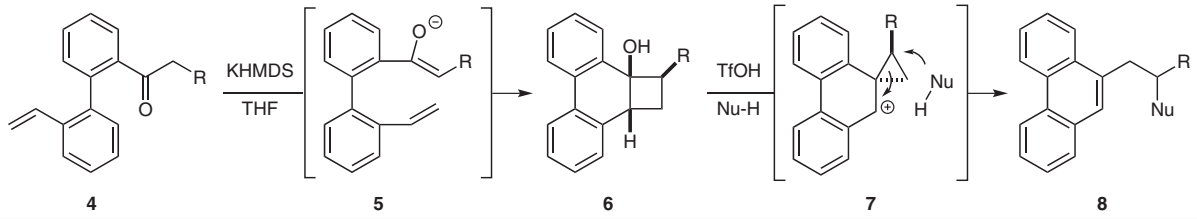
Figure 1 Structures of representative phenanthroindolizidine and phenanthroquinolizidine alkaloids

Phenanthroindolizidine and phenanthroquinolizidine alkaloids including tylophorine (**1**), antofine (**2**), and cryptopleurine (**3**), have received increasing attention over recent years because of their attractive biological activities (Figure 1).[1] Tylophorine (**1**), a phenanthroindolizidine alkaloid, was first isolated from *Tylophora indica*[2] and has been shown to have a wide range of biological activities such as anti-inflammatory[3] and antiviral activities.[4] It has also been shown to be a potent inhibitor of eukaryotic protein biosynthesis[5] and RNA transcription, as well as an inhibitor of several cyclins that regulate the cell cycle.[6]

Naturally occurring tylophorine is found as an almost racemic mixture, with a slight excess of the *R*-enantiomer (**1**).[7] Interestingly, the minor enantiomer, (*S*)-tylophorine (*ent*-**1**), has been found to be even more potent in the growth inhibition of some specific cancer cells.[8] This clearly demonstrates the importance of facile and selective access to both enantiomers of the alkaloids to enable investigation of their biological activities. To date, optically active phenanthroindolizidines have been synthesized by using chiral building blocks[9] and chiral auxiliaries.[10] The catalytic enantioselective synthesis of these alkaloids has also been reported.[11]

Recently, we reported a new method of preparing polycyclic aromatic hydrocarbons (PAHs, **8**).[12a] Deprotonation of 2′-vinylbiaryl-2-yl ketones **4** induced a formal [2+2] cycloaddition of enolates **5** to produce ring-fused cyclobutanols **6**. Subsequent treatment with acid promoted a domino ring-contraction/ring-opening sequence of **6** via cationic intermediate **7** in the presence of a nucleophile to give **8** (Scheme 1).[12b–d] Herein, we report a distinct enantioselective total synthesis of (*R*)-(–)-tylophorine by using our existing methodology for phenanthrene synthesis, followed by catalytic late-stage hydrogenation of a cyclic imine.

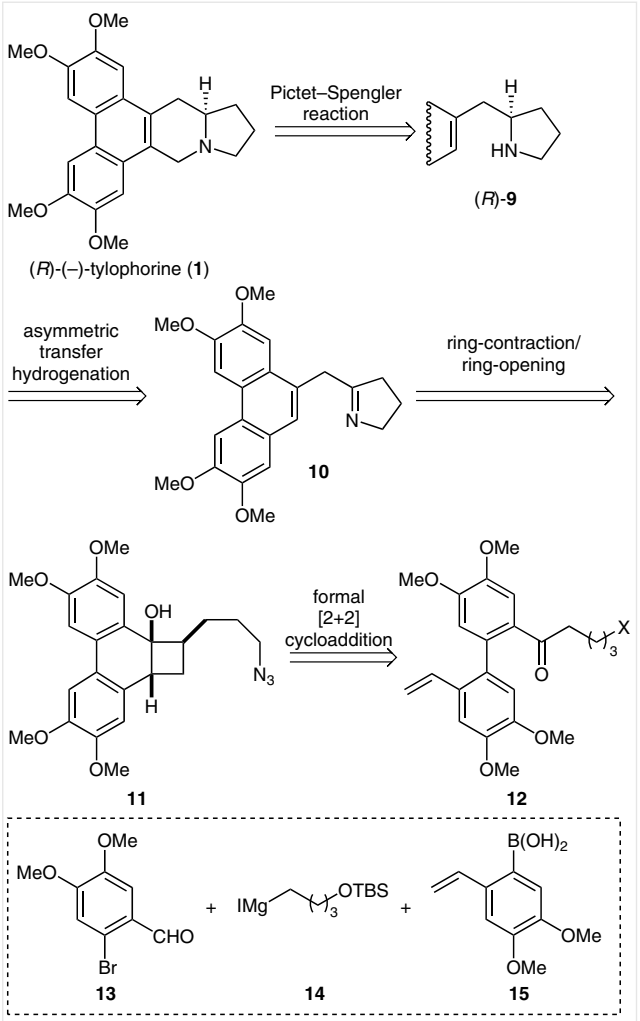
Our synthetic plan is shown in Scheme 2. (*R*)-(–)-Tylophorine (**1**) can be synthesized from (*R*)-**9** by using a well-established Pictet–Spengler method.[13] The asymmetric center of (*R*)-**9** would be generated by ruthenium-catalyzed asymmetric transfer hydrogenation[14] of cyclic imine **10**. We



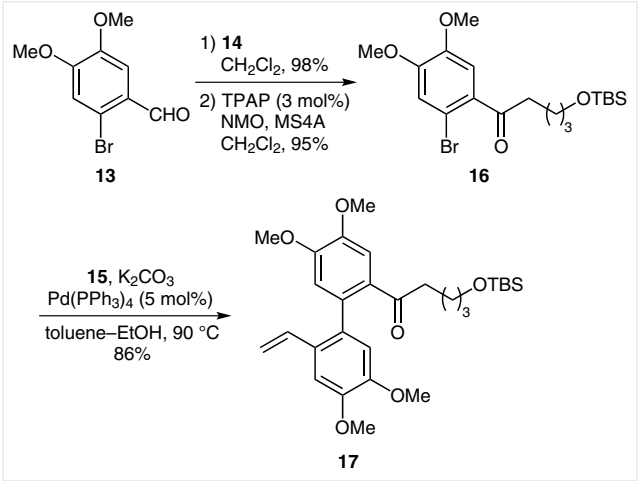
Scheme 1 Our synthetic methodology for the synthesis of PAHs

planned to synthesize cyclic imine **10** through a base-promoted formal [2+2] cycloaddition of biaryl **12**, followed by an acid-promoted domino ring-contraction/ring-opening sequence. Biaryl **12** could be prepared from readily available fragments **13**, **14**, and **15**.

Our synthesis began with preparation of biaryl **17**, the precursor to the key formal [2+2] cycloaddition (Scheme 3). Commercially available 6-bromoveratraldehyde (**13**) was converted into ketone **16** by a Grignard reaction followed by tetra-*n*-propylammonium perruthenate (TPAP) mediated oxidation of the resulting alcohol. The Suzuki–Miyaura cross-coupling reaction between ketone **16** and boronic acid **15** provided biaryl **17** in 86% yield.



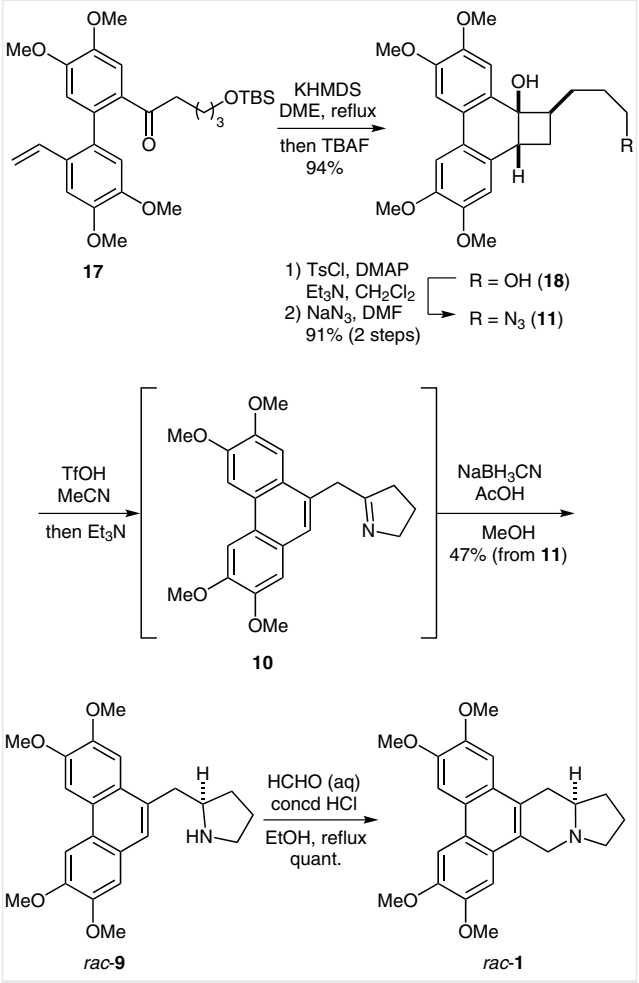
Scheme 2 Retrosynthetic analysis of tylophorine (**1**)



Scheme 3 Preparation of biaryl **17**

We then attempted the key formal [2+2] cycloaddition of **17** (Scheme 4). After brief experimentation, we found the optimal conditions to form the desired cyclobutanol as a single diastereomer in excellent yield was to treat biaryl **17** with potassium hexamethyldisilazide (KHMDS) in 1,2-dimethoxyethane (DME) at reflux. The cycloaddition reaction was followed by tetrabutylammonium fluoride (TBAF) mediated cleavage of the TBS group in situ, providing cyclobutanediol **18** in 94% yield. A two-step chemoselective azidation of cyclobutanediol **18** delivered the cyclobutanol **11**, bearing an azide group.

With cyclobutanol **11** in hand, we turned to our attention to the domino ring-contraction/ring-opening sequence to construct the E-ring of tylophorine. While it is known that an azide group reacts with carbocations under highly acidic conditions,[15] it has also been reported that some azide groups decompose to form aldehydes on reaction with TfOH.[16] Fortunately, simple TfOH treatment of **11** formed the cyclic imine ring system concomitantly with the phenanthrene skeleton in approximately 50% yield. To our

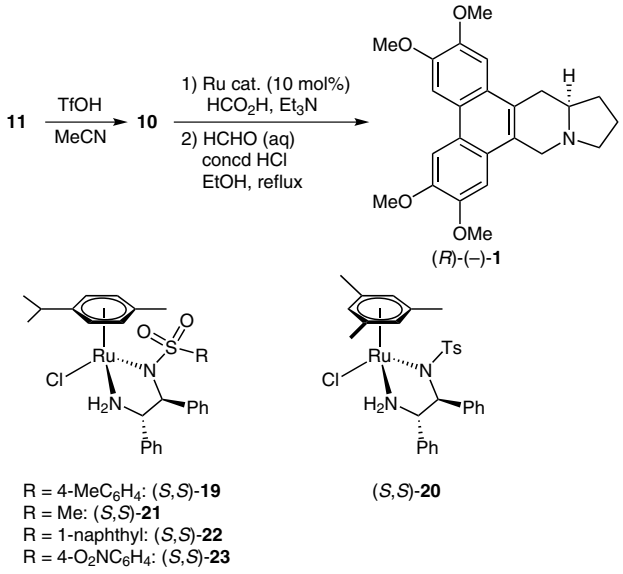


Scheme 4 Synthesis of racemic tylophorine (**1**)

knowledge, this is the first report of a cyclopropane ring being cleaved by nucleophilic attack of an organic azide. The TfOH-mediated construction of cyclic imine **10** was followed by neutralization with Et_3N, then reduction of the imine in situ gave amine *rac*-**9** in 47% yield from **11**. The amine *rac*-**9** was converted into (±)-tylophorine (**1**) with a Pictet–Spengler reaction according the reported procedure.[13]

Finally, asymmetric reduction by using Noyori–Ikariya asymmetric transfer hydrogenation[14] of cyclic imine **10** was investigated (Table 1). Asymmetric transfer hydrogenation of cyclic *N*-alkyl imines with chiral ruthenium catalysts can give racemic products.[17] Fortunately, the reduction of cyclic imine **10** with (*S*,*S*)-**19** as catalyst in *N*,*N*-dimethylformamide (DMF) gave the product **9** with good enantioselectivity (60% ee). After several experiments, the use of readily accessible ruthenium complex (*S*,*S*)-**23**[18] in a mixed solvent of dimethyl sulfoxide (DMSO) and CH_2Cl_2 at low temperature gave the desired product **9** with high enantioselectivity (84% ee). Subsequent Pictet–Spengler reaction provided (*R*)-(–)-tylophorine (**1**).

Table 1 Exploration of Asymmetric Transfer Hydrogenation Conditions[a]



Entry	Ru cat.	Solvent	Temp (°C)	Yield (%)[b]	ee (%)[c]
1[d]	(*S*,*S*)-**19**	DMF	r.t.	28	60
2	(*S*,*S*)-**19**	DMF	–40 to 0	42	72
3	(*S*,*S*)-**20**	DMF	–10	35	65
4	(*S*,*S*)-**21**	DMF	–10	27	45
5	(*S*,*S*)-**22**[e]	DMF	–10	25	73
6	(*S*,*S*)-**23**[e]	DMF	–10	30	76
7[f]	(*S*,*S*)-**23**[e]	DMSO/CH_2Cl_2	–20 to 0	37	84

[a] Unless otherwise noted, the reaction was carried out with freshly prepared crude imine **10** (1 equiv), Ru cat. (10 mol%), and a formic acid/triethylamine mixture in solvent (0.1 M) at the indicated temperature for 2 days.
[b] Isolated yield (from **11**) after chromatography on silica gel.
[c] Chiral HPLC analysis using a Daicel Chiralpak AD-H column.
[d] Reaction time: 18 hours.
[e] The catalyst was prepared in situ.
[f] Reaction time: 3 days.

In summary, we have achieved the asymmetric total synthesis of (*R*)-(–)-tylophorine (**1**) in 23% overall yield and 84% ee over nine operations. The key features of our synthesis are: (i) a formal [2+2] cycloaddition to provide a ring-fused cyclobutanol, (ii) an acid-promoted domino ring-contraction/ring-opening sequence of a cyclobutanol to form a cyclic imine ring concomitantly with a phenanthrene skeleton, and (iii) a catalytic late-stage installation of an asymmetric center by the asymmetric transfer hydrogenation of a cyclic imine. The syntheses of several other phenan-

throindolizidine and phenanthroquinolizidine alkaloids, and their unnatural derivatives, are in progress and will be reported in due course.

All solvents and materials were obtained from commercial suppliers and used without further purification unless otherwise noted. Column chromatography was performed on Fuji Silysia BW-200 silica gel. Reactions and chromatography fractions were analyzed with precoated silica gel plates (Merck Silica Gel 60 F254) and visualized by UV irradiation at 254 nm and/or with the indicated stains. IR spectra were measured with Shimadzu IRAffinity-1. ^{1}H and ^{13}C NMR spectra were recorded with JEOL ECS-400 (^{1}H, 400 MHz; ^{13}C, 100 MHz) or JEOL ECA-500 (^{1}H, 500 MHz; ^{13}C, 125 MHz) spectrometers. Chemical shifts are presented in ppm relative to tetramethylsilane (^{1}H, δ = 0.00 ppm) or solvents as follows: $CDCl_3$ (^{13}C, δ = 77.0 ppm); acetone-d_6 (^{1}H, δ = 2.04 ppm; ^{13}C, δ = 30.0 ppm). Abbreviations are as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; td, triplet of doublets; q, quartet; m, multiplet; br, broad. Low-resolution mass spectra were recorded with JEOL JMS-700 (FAB) or JEOL JMS-HX211A (FAB) spectrometers with 3-nitrobenzylalcohol (NBA) as matrix, or with a Shimadzu GCMS-QP2010 SE (EI) mass spectrometer. High-resolution mass spectra were recorded with a Shimadzu LCMS-IT-TOF (ESI) mass spectrometer using MeOH as mobile phase. Optical rotations were recorded with a JASCO P-1030 polarimeter. Chiral HPLC analyses were performed with a Shimadzu Prominence HPLC system.

1-(2-Bromo-4,5-dimethoxyphenyl)-5-[(*tert*-butyldimethylsilyl)oxy]pentan-1-one (16)

To a stirred solution of 2-bromo-4,5-dimethoxybenzaldehyde (6.13 g, 25.0 mmol) in anhydrous CH_2Cl_2 (175 mL) under an argon atmosphere, a freshly prepared 1.0 M Et_2O solution of {4-[(*tert*-butyldimethylsilyl)oxy]butyl}magnesium iodide (75 mL, 75.0 mmol) was added at r.t. over 10 min. After stirring for 1 h, the reaction was quenched with sat. aq NH_4Cl (50 mL), and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (2 × 100 mL) and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane–EtOAc, 3:1 → 2:1) to afford 1-(2-bromo-4,5-dimethoxyphenyl)-5-[(*tert*-butyldimethylsilyl)oxy]pentan-1-ol.

Yield: 10.6 g (98%); pale-yellow oil; R_f = 0.28 (hexane–EtOAc, 3:1, UV).

IR (neat): 3426, 2931, 2855, 1501, 1254, 1096, 833 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.88 (s, 9 H), 1.39–1.47 (m, 1 H), 1.50–1.64 (m, 3 H), 1.67–1.78 (m, 2 H), 2.04 (d, *J* = 2.9 Hz, 1 H), 3.63 (t, *J* = 5.4 Hz, 1 H), 3.86 (s, 3 H), 3.89 (s, 3 H), 5.02 (m, 1 H), 6.96 (s, 1 H), 7.07 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 5.3, 18.3, 22.1, 25.9, 32.4, 37.6, 56.0, 56.1, 63.1, 72.7, 109.7, 111.6, 115.1, 136.0, 148.6, 148.7.

MS (FAB): *m*/*z* = 432/434 [M]$^+$.

Anal. Calcd for $C_{19}H_{33}BrO_4Si$: C, 52.65; H, 7.67. Found: C, 52.44; H, 7.66.

To a stirred mixture of 1-(2-bromo-4,5-dimethoxyphenyl)-5-[(*tert*-butyldimethylsilyl)oxy]pentan-1-ol (10.6 g, 24.4 mmol), NMO (4.3 g, 36.6 mmol) and 4Å MS powder (4.8 g) in anhydrous CH_2Cl_2 (50 mL) under argon atmosphere, TPAP (284 mg, 0.808 mmol) was added at r.t. After stirring for 15 min, the resulting mixture was filtered through a Celite pad ($CHCl_3$ eluent) and the solvent was removed in vacuo. The residue was purified by silica gel chromatography (hexane–EtOAc, 5:1) to afford **16**.

Yield: 10.1 g (95%); colorless oil; R_f = 0.48 (hexane–EtOAc, 3:1, UV).

IR (neat): 2932, 2855, 1694, 1258, 1096, 837 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.88 (s, 9 H), 1.54–1.63 (m, 2 H), 1.73–1.81 (m, 2 H), 3.00 (t, *J* = 7.3 Hz, 2 H), 3.64 (t, *J* = 6.4 Hz, 2 H), 3.89 (s, 3 H), 3.91 (s, 3 H), 7.01 (s, 1 H), 7.04 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 5.4, 18.3, 21.0, 25.9, 32.2, 42.1, 56.1, 56.2, 62.8, 110.8, 112.0, 116.3, 133.2, 148.1, 151.2, 202.7.

MS (FAB): *m*/*z* = 431/433 [M + H]$^+$.

Anal. Calcd for $C_{19}H_{31}BrO_4Si$: C, 52.89; H, 7.24. Found: C, 52.71; H, 7.15.

(4,5-Dimethoxy-2-vinylphenyl)boronic Acid (15)

To a stirred solution of 1-bromo-4,5-dimethoxy-2-vinylbenzene[19] (8.18 g, 33.6 mmol) in anhydrous THF (170 mL) under an argon atmosphere, a solution of *n*-BuLi (1.6 M in hexane, 25.0 mL, 40.0 mmol) was added carefully at –78 °C. The reaction mixture was stirred at the same temperature for 20 min, then trimethyl borate (11.5 mL, 103 mmol) was added. The resulting mixture was stirred for a further 20 min and then warmed to r.t. The reaction mixture was acidified with 10% aq HCl, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with H_2O (2 × 100 mL), brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by trituration with EtOAc–hexane to afford **15**.

Yield: 4.78 g (68%); pale-yellow powder; mp 130–138 °C.

IR (neat): 3402, 3194, 1400, 1331, 1204, 795 cm^{-1}.

^{1}H NMR (500 MHz, acetone-d_6–D_2O): δ = 3.79 (s, 3 H), 3.84 (s, 3 H), 5.05 (dd, *J* = 1.4, 10.9 Hz, 1 H), 5.58 (dd, *J* = 1.3, 17.6 Hz, 1 H), 7.18 (s, 1 H), 7.19 (s, 1 H), 7.40 (dd, *J* = 11.0, 17.6 Hz, 1 H).

^{13}C NMR (100 MHz, acetone-d_6): δ = 55.8, 55.9, 108.7, 112.1, 117.9, 136.8, 138.8, 149.3, 151.4.

MS (FAB): *m*/*z* = 570 [boroxine, M]$^+$.

HRMS (ESI): *m*/*z* [dimethyl ester + H]$^+$ calcd for $C_{12}H_{18}BO_4$: 237.1298; found: 237.1291.

5-[(*tert*-Butyldimethylsilyl)oxy]-1-(4,4′,5,5′-tetramethoxy-2′-vinyl-[1,1′-biphenyl]-2-yl)pentan-1-one (17)

To a stirred mixture of **16** (6.34 g, 14.7 mmol), **15** (4.58 g, 22.0 mmol), and K_2CO_3 (6.10 g, 44.1 mmol) in anhydrous toluene–EtOH (4:1 v/v, 150 mL) under an argon atmosphere, $Pd(PPh_3)_4$ (849 mg, 0.74 mmol) was added. After heating at 90 °C for 3 h, the resulting mixture was cooled to r.t. and H_2O was added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane–EtOAc, 3:1 → 2:1) to afford **17**.

Yield: 6.49 g (86%); pale-yellow solid; mp 61–63 °C; R_f = 0.46 (hexane–EtOAc, 2:1, UV).

IR (neat): 2932, 2855, 1670, 1504, 1254 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.01 (s, 6 H), 0.85 (s, 9 H), 1.24–1.29 (m, 2 H), 1.37–1.50 (m, 2 H), 2.12–2.23 (m, 2 H), 3.44 (t, *J* = 6.4 Hz, 2 H), 3.85 (s, 3 H), 3.90 (s, 3 H), 3.96 (s, 3 H), 3.98 (s, 3 H), 5.10 (d, *J* = 11.2 Hz, 1 H), 5.57 (d, *J* = 17.5 Hz, 1 H), 6.49 (dd, *J* = 11.0, 17.3 Hz, 1 H), 6.64 (s, 1 H), 6.69 (s, 1 H), 7.14 (s, 1 H), 7.21 (s, 1 H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 5.4, 18.3, 21.0, 25.9, 32.2, 41.5, 55.9, 55.99, 56.01, 56.1, 62.7, 107.5, 111.0, 112.8, 113.4, 113.9, 128.7, 132.4, 132.9, 133.3, 134.4, 148.0, 148.6, 148.9, 150.4, 204.7

MS (FAB): *m*/*z* = 515 $[M + H]^+$.

Anal. Calcd for $C_{29}H_{42}O_6Si$: C, 67.67; H, 8.22. Found: C, 67.66; H, 8.30.

(2*S,2a*S**,10b*R**)-2-(3-Hydroxypropyl)-4,5,8,9-tetramethoxy-1,10b-dihydrocyclobuta[*l*]phenanthren-2a(2*H*)-ol (18)**

To a stirred solution of **17** (257 mg, 0.500 mmol) in anhydrous DME (4.4 mL) heated to reflux under an argon atmosphere, a solution of KHMDS (1.0 M in THF, 0.60 mL, 0.60 mmol) was added. After stirring for 30 min, the resulting mixture was cooled to r.t., then a solution of TBAF (1.0 M in THF, 2.50 mL, 2.50 mmol) was added. After stirring for 1 h, the reaction was quenched with sat. aq NH_4Cl, then the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O (2 × 5 mL), followed by brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane–EtOAc, 1:2 → 0:1) to afford **18**.

Yield: 188 mg (94%); white solid; mp 175–177 °C; R_f = 0.22 (EtOAc, UV).

IR (neat): 3480, 3364, 2936, 1508, 1246, 752 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.57–1.63 (m, 2 H), 1.70–1.79 (m, 3 H), 1.90 (ddd, *J* = 11.0, 9.9, 2.6 Hz, 1 H), 2.09 (br s, 1 H), 2.12–2.19 (m, 1 H), 2.54–2.58 (m, 1 H), 3.65 (t, *J* = 9.5 Hz, 1 H), 3.74–3.81 (m, 2 H), 3.90 (s, 3 H), 3.94 (s, 3 H), 3.98 (s, 3 H), 4.01 (s, 3 H), 6.66 (s, 1 H), 7.03 (s, 1 H), 7.24 (s, 1 H), 7.27 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.5, 28.3, 30.8, 45.0, 48.2, 55.8, 55.9, 56.1, 56.3, 62.9, 71.3, 105.1, 106.7, 110.3, 111.3, 123.7, 125.2, 128.7, 131.8, 148.0, 148.6, 149.0, 149.1.

MS (FAB): *m*/*z* = 383 [M – OH].

HRMS (ESI): *m*/*z* $[M + K]^+$ calcd for $C_{23}H_{28}KO_6$: 439.1523; found: 439.1529.

(2*S,2a*S**,10b*R**)-2-(3-Azidopropyl)-4,5,8,9-tetramethoxy-1,10b-dihydrocyclobuta[*l*]phenanthren-2a(2*H*)-ol (11)**

To a stirred solution of **18** (422 mg, 1.05 mmol), DMAP (130 mg, 1.06 mmol), and Et_3N (0.73 mL, 5.24 mmol) in anhydrous CH_2Cl_2 (10 mL) under an argon atmosphere, tosyl chloride (231 mg, 1.21 mmol) was added at r.t. After stirring for 8 h, additional tosyl chloride (171 mg, 0.90 mmol) was added to the resulting mixture. After stirring for 1.5 h, the reaction was quenched with sat. aq NH_4Cl and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (2 × 10 mL). The combined organic layers were washed with H_2O (2 × 10 mL), sat. aq $NaHCO_3$ (2 × 10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. To a stirred solution of the crude material in anhydrous DMF (5.3 mL) under an argon atmosphere, NaN_3 (683 mg, 10.5 mmol) was added at r.t. After stirring for 12 h, the reaction was quenched with H_2O (5 mL), then the mixture was extracted with Et_2O (5 × 10 mL). The combined organic layers were washed with H_2O (2 × 10 mL), followed by brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane–EtOAc, 1.5:1 → 1:1.5) to afford **11**.

Yield: 408 mg (91%); white solid; mp 100–102 °C; R_f = 0.48 (hexane–EtOAc, 2:1, UV).

IR (neat): 3487, 2936, 2095, 1508, 1246, 752 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.60 (ddd, *J* = 11.1, 8.5, 8.5 Hz, 1 H), 1.70–1.79 (m, 3 H), 1.91 (ddd, *J* = 11.0, 9.9, 3.2 Hz, 1 H), 2.07 (br s, 1 H), 2.08–2.17 (m, 1 H), 2.53–2.57 (m, 1 H), 3.34–3.42 (m, 2 H), 3.64 (t, *J* = 9.3 Hz, 1 H), 3.90 (s, 3 H), 3.94 (s, 3 H), 3.97 (s, 3 H), 4.00 (s, 3 H), 6.65 (s, 1 H), 7.00 (s, 1 H), 7.23 (s, 1 H), 7.27 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.0, 27.4, 28.2, 45.0, 47.7, 51.6, 55.9, 56.0, 56.1, 56.4, 71.4, 105.1, 106.7, 110.1, 111.3, 123.6, 125.2, 128.6, 131.7, 148.1, 148.7, 149.1, 149.2.

MS (FAB): *m*/*z* = 380 $[M - HN_2O]^+$.

Anal. Calcd for $C_{23}H_{27}N_3O_5$: C, 64.93; H, 6.40; N, 9.88. Found: C, 65.01; H, 6.45; N, 9.85.

(±)-2-[(2,3,6,7-Tetramethoxyphenanthren-9-yl)methyl]pyrrolidine (*rac*-9)

To a stirred solution of **11** (22.3 mg, 0.0524 mmol) in anhydrous MeCN (0.3 mL) under an argon atmosphere, TfOH (0.1 M in MeCN, 0.70 mL, 0.070 mmol) was added at r.t. After stirring for 5 min, the reaction was quenched with Et_3N (14 µL, 0.100 mmol) and the mixture was stirred for 10 min. To the resulting mixture, MeOH (0.50 mL), AcOH (0.01 mL, 0.175 mmol), and $NaBH_3CN$ (31.4 mg, 0.500 mmol) were added. After stirring for 24 h, the resulting mixture was acidified to pH 1 with 10% aq HCl. The acidic aqueous layer was washed with Et_2O (2 × 5 mL). The resulting aqueous layer was basified to pH 11 with NaOH pellets and then extracted with $CHCl_3$ (3 × 10 mL). The combined $CHCl_3$ layers were washed with H_2O (2 × 10 mL), followed by brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography [MeOH–NH_3 (28% aq), 30:1] to afford *rac*-**9**.

Yield: 9.4 mg (47%); pale-yellow solid; mp >150 °C; R_f = 0.34 [MeOH–NH_3 (28% aq), 30:1, UV].

IR (neat): 3368, 2955, 2936, 1620, 1508, 1474, 1427, 1254, 1200, 1150, 1042, 910, 841, 772, 729 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.50–1.58 (m, 1 H), 1.71–1.80 (m, 1 H), 1.83–1.94 (m, 3 H), 2.86 (ddd, *J* = 9.6, 7.7, 7.6 Hz, 1 H), 3.10 (ddd, *J* = 10.2, 7.6, 5.2 Hz, 1 H), 3.19 (d, *J* = 6.6 Hz, 2 H), 3.53 (ddd, *J* = 13.7, 6.8, 6.8 Hz, 1 H), 4.03 (s, 3 H), 4.05 (s, 3 H), 4.11 (s, 3 H), 4.12 (s, 3 H), 7.18 (s, 1 H), 7.44 (s, 1 H), 7.47 (s, 1 H), 7.77 (s, 1 H), 7.78 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7, 31.6, 39.6, 46.0, 55.8, 55.97, 56.03, 58.7, 102.7, 103.3, 104.8, 108.0, 123.6, 124.6, 124.9, 125.4, 126.2, 131.4, 148.5, 148.79, 148.84.

MS (FAB): *m*/*z* = 382 $[M + H]^+$.

(±)-Tylophorine (*rac*-1)

This reaction was performed by a modification of the reported method.[13] To a stirred solution of *rac*-**9** (39.1 mg, 0.103 mmol) in EtOH (2 mL), 37% aq HCHO (2 mL, 26.9 mmol) and conc. HCl (17 µL, 0.204 mmol) were successively added at r.t. After heating to reflux in the dark for 26 h, the resulting mixture was cooled to r.t., basified to pH 11 with 15% NaOH and then extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with H_2O (2 × 10 mL), followed by brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography ($CHCl_3$–MeOH, 20:1) to afford *rac*-**1**.

Yield: 40.7 mg (quant.); pale-yellow solid; mp >270 °C; R_f = 0.33 ($CHCl_3$–MeOH, 10:1, UV).

IR (neat): 2936, 1620, 1516, 1474, 1427, 1250, 1196, 1150, 1038, 1015, 910, 841, 756 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.73–1.81 (m, 1 H), 1.88–1.96 (m, 1 H), 2.00–2.09 (m, 1 H), 2.21–2.27 (m, 1 H), 2.43–2.51 (m, 2 H), 2.90 (dd, *J* = 10.7, 15.6 Hz, 1 H), 3.36 (dd, *J* = 2.7, 15.6 Hz, 1 H), 3.46–3.49 (m, 1 H), 3.65 (d, *J* = 14.6 Hz, 1 H), 4.05 (s, 3 H), 4.06 (s, 3 H), 4.11 (s, 6 H), 4.62 (d, *J* = 14.6 Hz, 1 H), 7.15 (s, 1 H), 7.30 (s, 1 H), 7.81 (s, 1 H), 7.82 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 31.3, 33.8, 54.0, 55.1, 55.8, 55.9, 56.0, 60.2, 103.1, 103.3, 103.4, 103.9, 123.4, 123.6, 124.3, 125.8, 126.0, 126.3, 148.4, 148.5, 148.7.

MS (FAB): *m*/*z* = 394 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{28}NO_4$: 394.2018; found: 394.2029.

Spectroscopic properties were consistent with those reported in the literature.

Asymmetric Synthesis of (*R*)-(−)-Tylophorine

To a stirred solution of **11** (132 mg, 0.310 mmol) in anhydrous MeCN (1.8 mL) under an argon atmosphere, TfOH (0.1 M in MeCN, 4.4 mL, 0.440 mmol) was added at r.t. After stirring for 10 min, the reaction was quenched with 15% NaOH and then extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford crude **10** (154 mg) as a brown amorphous solid, which was dissolved in anhydrous CH_2Cl_2 (1.55 mL). The resulting crude solution of **10** (0.2 M in CH_2Cl_2) was used for the following asymmetric transfer hydrogenation.

Asymmetric Transfer Hydrogenation of 10

To a stirred mixture of **10** (0.2 M in CH_2Cl_2, 0.50 mL, 0.100 mmol) and (*S*,*S*)-**23** (0.02 M in DMSO, 0.5 mL, 10.0 μmol) under an argon atmosphere, HCO_2H/Et_3N (5:2 v/v, 0.07 mL) was added at –20 °C. After stirring for 46 h, the resulting mixture was warmed to –10 °C. After stirring for 24 h, the mixture was acidified to pH 1 with 10% aq HCl. The acidic aqueous layer was washed with Et_2O (2 × 5 mL) and the resulting aqueous layer was basified to pH 11 with NaOH pellets and then extracted with $CHCl_3$ (3 × 5 mL). The combined $CHCl_3$ layers were washed with H_2O (2 × 5 mL), followed by brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography [$CHCl_3$–MeOH, 1:0 → 10:1, then MeOH–NH_3 (28% aq), 30:1] to afford (*R*)-**9** (15.0 mg, 39% from **11**) as a pale-yellow solid, which was used for the following reaction without further purification or characterization.

Pictet–Spengler Reaction

To a stirred solution of (*R*)-**9** (15.0 mg, 0.039 mmol) in EtOH (2 mL), 37% aq HCHO (2 mL, 26.9 mmol) and conc. HCl (10 μL, 0.120 mmol) were added at r.t. After heating to reflux in the dark for 14 h, the resulting mixture was cooled to r.t., basified to pH 11 with 15% NaOH and then extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were washed with H_2O (2 × 5 mL), followed by brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (EtOAc then $CHCl_3$–MeOH, 10:1) to afford (*R*)-(−)-**1**.

Yield: 14.7 mg (95%); white solid; $[\alpha]_D^{20}$ –73.1 (*c* 1.3, $CHCl_3$) {Lit.[10e] $[\alpha]_D^{30}$ –76.0 (*c* 0.10, $CHCl_3$)}.

The enantiopurity of **1** was determined to be 84% ee by chiral HPLC analysis (DAICEL CHIRALPAK AD-H; 0.46 cm × 25 cm; 25% *i*-PrOH–hexanes 0.1% Et_3N; 1.0 mL/min, λ = 254 nm): t_R = 12.6 (minor), 16.8 (major) min.

Spectroscopic properties were consistent with those reported in the literature.[10e]

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380430.

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