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TOTAL SYNTHESIS OF PHENANTHROQUINOLIZIDINE ALKALOID CRYPTOPLEURINE AND PHENANTHROINDOLIZIDINE ALKALOID TYLOPHORINE[‡]

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Abstract – Total synthesis of phenanthroquinolizidine alkaloid cryptopleurine was achieved in 11 steps from commercially available 6-bromoveratraldehyde. The crucial step of phenanthrene construction is a formal [2 + 2] cycloaddition of 2-acyl-2'-vinyl-1,1'-biaryl, followed by an acid promoted ring-contraction/ring-opening sequence. The key point to complete the total synthesis of cryptopleurine is use of nosyl amide as a nucleophile for cyclization of piperidine ring. The synthesis of tylophorine was also achieved in the similar manner.

INTRODUCTION

Phenanthroindolizidine and phenanthroquinolizidine alkaloids,¹⁻³ such as tylophorine (**1**) and cryptopleurine (**2**), respectively, have been paid considerable attention not only by organic chemists but

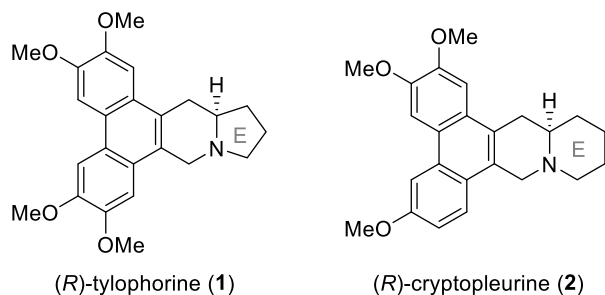


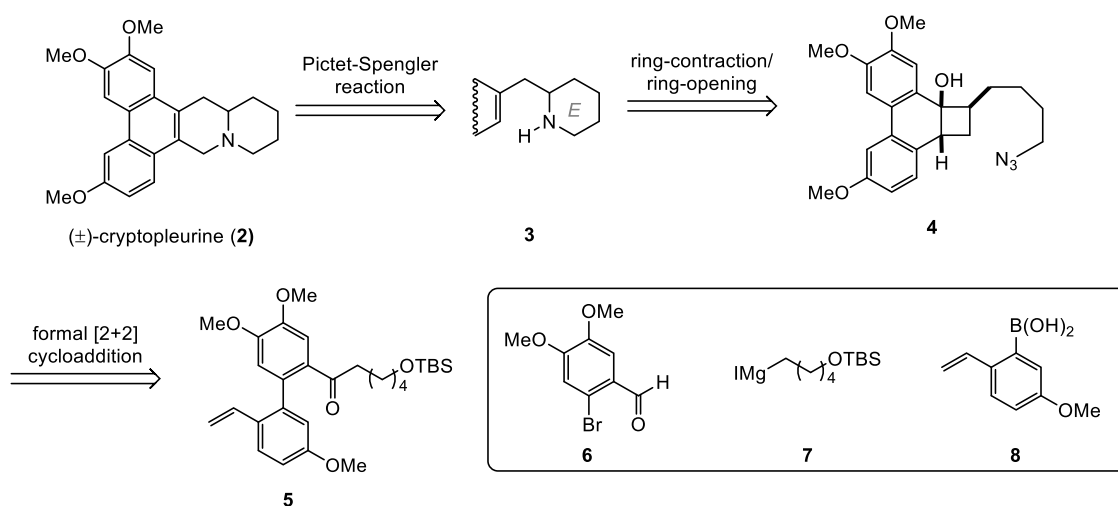
Figure 1. Structures of phenanthroindolizidine and phenanthroquinolizidine alkaloids

[‡]Dedicated to Prof. Kiyoshi Tomioka on the occasion of his 70th birthday

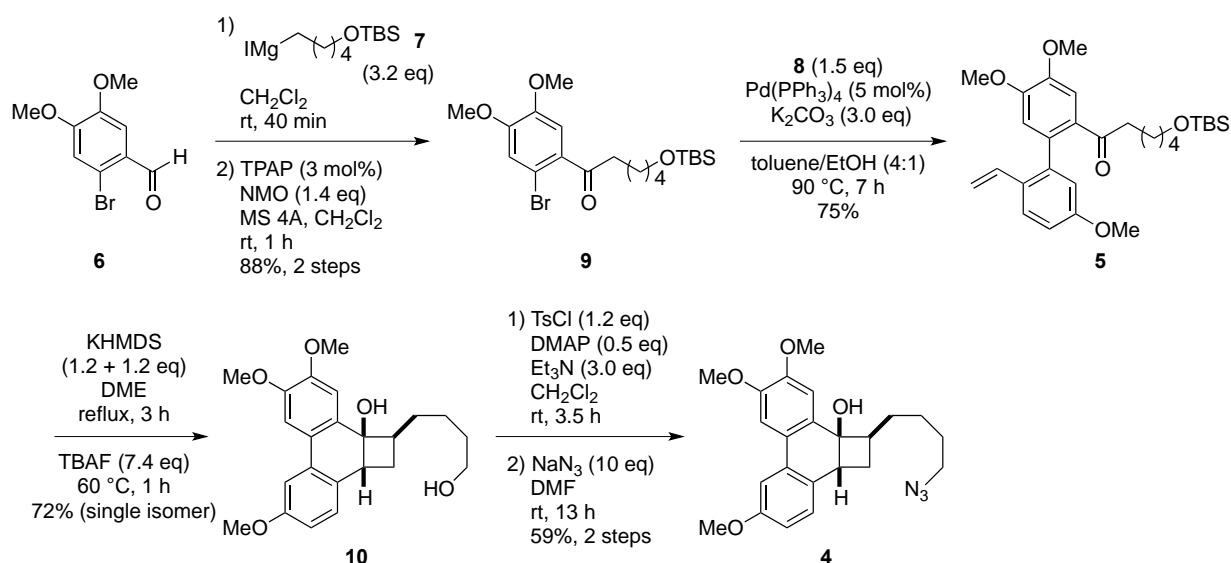
also medicinal chemists, because these alkaloids exhibit several interesting biological activities, such as antitumor⁴ and anti-inflammatory⁵ (Figure 1). We have recently reported the asymmetric total synthesis of tylophorine (**1**) through a formal [2 + 2] cycloaddition followed by migrative ring opening of a cyclobutane⁶ and late stage catalytic enantioselective hydrogenation.⁷ To extend our research on phenanthroindolizidines, we attempted to synthesize phenanthroquinolizidine alkaloid cryptopleurine (**2**).

RESULTS AND DISCUSSION

We envisioned the total synthesis of cryptopleurine (**2**) by using the previous method already reported for the synthesis of tylophorine. The retrosynthetic analysis of **2** is shown in Scheme 1. Cryptopleurine (**2**) could be synthesized from **3** by a Pictet-Spengler reaction. Piperidine **3** could be built by an



Scheme 1. Retrosynthetic analysis of cryptopleurine (**2**)

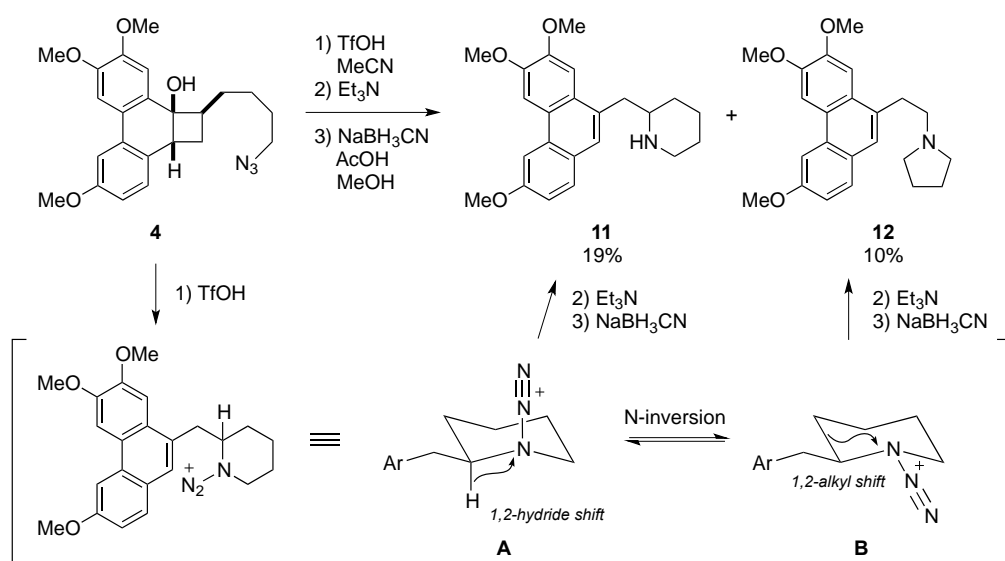


Scheme 2. Preparation of phenanthreno-cyclobutanol **4** having an azide group

acid-promoted ring-contraction/ring-opening sequence of azide **4**, followed by reduction of the in situ generated imine. Azide **4** could be formed through a base-promoted intramolecular [2 + 2] cycloaddition of biaryl **5**.⁶ The compound **5** could be prepared from three fragments **6**, **7** and **8**, all of which are readily prepared from commercially available materials.

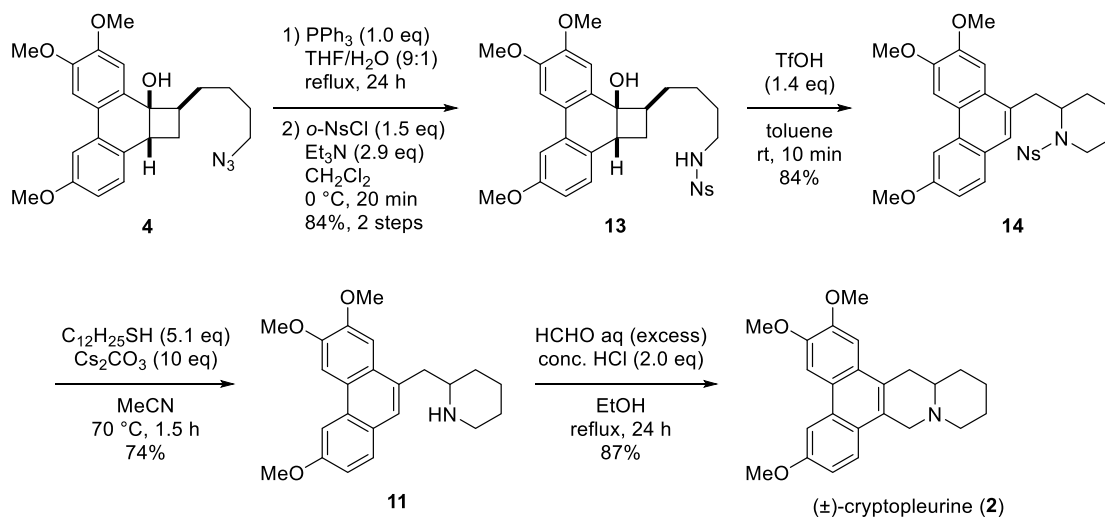
Azide **4** was prepared starting from aldehyde **6** in six steps by using the similar route to our previous report (Scheme 2).⁷ Aryl ketone **9** was synthesized by a Grignard reaction of **6** with **7**, followed by TPAP oxidation, in high yield. Suzuki-Miyaura coupling of ketone **9** and arylboronic acid **8** provided biaryl compound **5** bearing acyl and vinyl groups at the 2 and 2' positions, respectively, in 75% yield. KHMDS-promoted [2 + 2] cycloaddition of **5**, followed by TBS deprotection, afforded phenanthrol-cyclobutanol **10** as a single diastereomer. Finally, selective azidation of **10** delivered the desired azide **4** in good yield.

Then, we attempted the transformation of **4** into piperidine **11** by an acid promoted domino ring-contraction/ring-opening reaction,⁸⁻¹⁰ followed by NaBH₃CN reduction of in situ generated imine (Scheme 3). Unexpectedly, the desired piperidine **11** was obtained in only 19% yield along with pyrrolidine **12** in 10% yield and unidentified byproducts. Several acids and solvents were screened to improve the yield of **11**, none of which proved to be effective at all. The desired **11** was obtained by 1,2-hydride shift through the conformation **A**, in which the leaving N₂ group is occupied at the axial orientation. On the other hand, 1,2-alkyl shift from the N₂ equatorial conformer **B** proceeded to give the undesired product **12**. In case of the total synthesis of tylophorine (**1**),⁷ the 1,2-alkyl shift was completely suppressed presumably due to the formation of the strained 4-membered ring. In this case, however, it turned out that the formation of the undesired 5-membered ring was hard to be avoided, leading to the low yield of desired piperidine **11**.



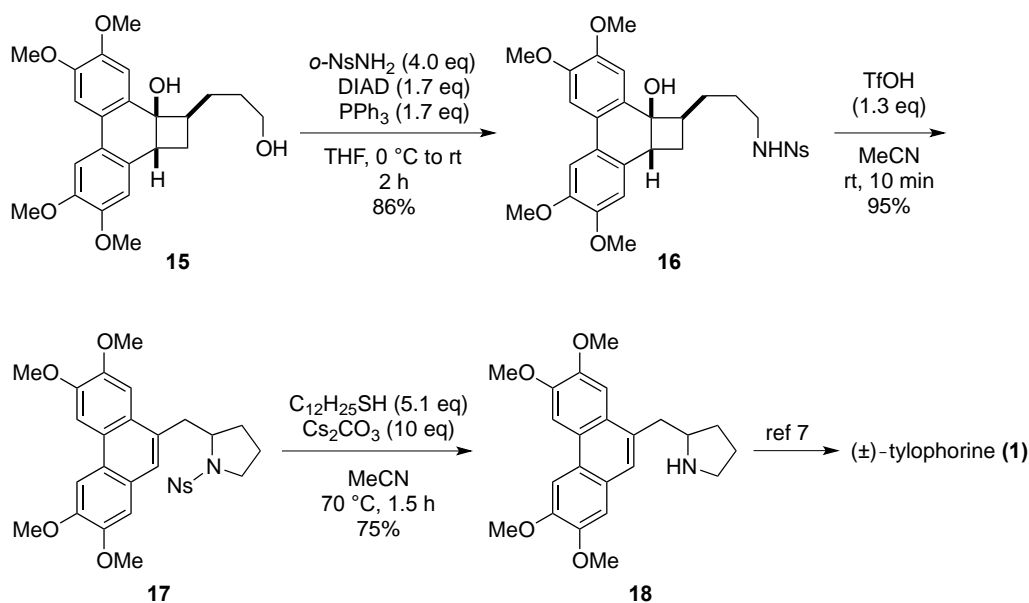
Scheme 3. Formation of **11** and **12** from azide **4**

To overcome this problem, we investigated an alternative method for the formation of the 6-membered ring, which utilizes cyclization of nosyl (2-nitrobenzenesulfonyl) amide¹¹ (Scheme 4). Nosyl amide **13** was prepared from reduction of azide **4**, followed by treatment with nosyl chloride. As expected, nosyl amide **13** was subjected to TfOH promoted cyclization conditions to afford the desired piperidine **14** in high yield. Subsequently, removal of the nosyl group by odorless thiol¹² and a Pictet-Spengler reaction were conducted to lead to (±)-cryptopleurine (**2**) in high yield.



Scheme 4. Completion of the synthesis of cryptopleurine (**2**)

Finally, we also applied the method through nosyl amide to the synthesis of tylophorine (**1**), which was previously synthesized through the 1,2-hydride shift of azide (Scheme 5).



Scheme 5. Synthesis of phenanthroindolizidine alkaloid tylophorine (**1**)

Diol **15**⁷ was converted into the corresponding nosyl amide **16** by a Mitsunobu reaction in 86% yield. The TfOH-promoted domino ring-contraction/ring-opening reaction of **16** afforded pyrrolidine **17** without any problem. Subsequently, removal of the nosyl group and the Pictet-Spengler reaction gave tylophorine (**1**). Thus, it was proved that this nosyl amide strategy could be applied to synthesis of natural product which bear a different size of the E ring. Although this synthesis is racemic and the number of steps was not reduced compared to our previous synthesis, the total chemical yield was improved.

In summary, we achieved the racemic total synthesis of cryptopleurine (**2**) and tylophorine (**1**). We have succeeded in total syntheses of natural alkaloids with a different size of the E ring by the cyclization of nosyl amide. We will contribute to the further development of structure-activity relationship (SAR) studies in the future by synthesis of other alkaloids.

EXPERIMENTAL

General Procedure: 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 employing pre-coated silica gel plate (Merck Silica Gel 60 F254) with visualization by ultraviolet (UV) irradiation at 254 nm and/ or indicated stains. IR spectra were measured on Shimadzu IRAffinity-1. The ¹H and ¹³C NMR spectra were recorded on JEOL ECS-400 (¹H, 400 MHz; ¹³C, 100 MHz) or JEOL ECS-500 (¹H, 500 MHz; ¹³C, 125 MHz). Chemical shifts are presented in ppm relative to tetramethylsilane (¹H, 0.00) or solvents as follows: CDCl₃ (¹³C, 77.0); acetone-*d*₆ (¹H, 2.04; ¹³C, 30.0). Abbreviations are as follows: s, singlet; d, doublet; dd, double of doublets; t, triplet; td, triplet of doublets; q, quartet; m, multiplet; br, broad. Low-resolution mass spectra were recorded on JEOL JMS-700 (FAB), JEOL JMS-HX211A (FAB) with 3-nitrobenzyl alcohol (NBA) as a matrix, or Shimadzu GCMS-QP2010 SE (EI) mass spectrometer. High-resolution mass spectra were recorded on Shimadzu LCMS-IT-TOF (ESI) mass spectrometer using MeOH as a mobile phase.

1-(2-Bromo-4,5-dimethoxyphenyl)-6-[(*tert*-butyldimethylsilyl)oxy]hexan-1-one (**9**).

Preparation of the Grignard reagent (7**):** To a suspension of Mg turnings (1.17 g, 47.7 mmol) in anhydrous Et₂O (4 mL), 1,2-dibromoethane (1 drop) was added at room temperature under argon atmosphere. After being stirred for 5 min, *tert*-butyl-[(5-iodopentyl)oxy]dimethylsilane¹³ (8.64 g, 26.3 mmol) in Et₂O (20 mL) was dropwise added over 10 min, and the resulting mixture was stirred for 30 min. The supernatant was used for the following step.

Grignard reaction: To a stirred solution of 2-bromo-4,5-dimethoxybenzaldehyde (**6**) (1.96 g, 8.0 mmol) in anhydrous CH₂Cl₂ (50 mL) under argon atmosphere, the prepared Grignard reagent was added at room

temperature. After being stirred for 40 min, the resulting mixture was quenched with sat. aq NH_4Cl and the organic layer was separated. The aqueous layer was extracted twice with CHCl_3 . The combined organic layers were washed with brine, dried over MgSO_4 , filtered, concentrated *in vacuo*. The residue was purified by silica gel chromatography (Hexane/EtOAc = 5/1 to 2/1) to afford 1-(2-bromo-4,5-dimethoxyphenyl)-6-[(*tert*-butyldimethylsilyl)oxy]hexan-1-ol (3.13 g, 88%) as a colorless oil; R_f = 0.35 (Hexane/EtOAc = 3/1, UV); ^1H NMR (CDCl_3 , 500 MHz): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.34–1.43 (m, 3H), 1.47–1.57 (m, 3H), 1.63–1.73 (m, 2H), 2.14 (br m, 1H), 3.60 (t, J = 6.6 Hz, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 4.99 (dd, J = 8.0, 4.9 Hz, 1H), 6.95 (s, 1H), 7.05 (s, 1H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz): δ –5.3, 18.3, 25.5, 25.6, 25.9, 32.7, 37.9, 55.9, 56.1, 63.1, 72.6, 109.6, 111.5, 115.0, 136.0, 148.4, 148.6 ppm; IR (neat) ν_{max} : 3526, 3414, 2932, 2855, 1604, 1501, 1462, 1439, 1381, 1254, 1211, 1157, 1099, 1034, 833, 775 cm^{-1} ; EIMS m/z : 389 $[\text{M}-\text{C}_4\text{H}_9]^+$; HRMS–ESI m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{35}^{79}\text{BrNaO}_4\text{Si}$, 469.1386; found, 469.1379.

To a stirred mixture of 1-(2-bromo-4,5-dimethoxyphenyl)-6-[(*tert*-butyldimethylsilyl)oxy]hexan-1-ol (3.13 g, 7.0 mmol), NMO (1.17 g, 10 mmol) and MS4A powder (1.8 g) in anhydrous CH_2Cl_2 (30 mL) under argon atmosphere, TPAP (69.8 mg, 0.20 mmol) was added at room temperature. After being stirred for 1 h, the resulting mixture was filtered through Celite[®] pad (CHCl_3 eluent) and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (Hexane/EtOAc = 5/1 to 3/1) to afford **9** (3.13 g, quant.) as a pale yellow oil; R_f = 0.46 (Hexane/EtOAc = 3/1, UV); ^1H NMR (CDCl_3 , 500 MHz): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.38–1.44 (m, 2H), 1.53–1.59 (m, 2H), 1.70–1.76 (m, 2H), 2.98 (t, J = 7.4 Hz, 2H), 3.62 (t, J = 6.4 Hz, 2H), 3.89 (s, 3H), 3.91 (s, 3H), 7.01 (s, 1H), 7.04 (s, 1H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz): δ –5.3, 18.3, 24.3, 25.5, 25.9, 32.6, 42.4, 56.1, 56.2, 62.9, 110.7, 111.9, 116.2, 133.2, 148.1, 151.1, 202.9 ppm; IR (neat) ν_{max} : 2932, 2855, 1694, 1593, 1508, 1462, 1377, 1258, 1215, 1169, 1099, 1026, 837, 771 cm^{-1} ; EIMS m/z : 387 $[\text{M}-\text{C}_4\text{H}_9]^+$; HRMS–ESI m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{33}^{79}\text{BrNaO}_4\text{Si}$, 467.1229; found, 467.1238.

(5-Methoxy-2-vinylphenyl)boronic acid (**8**).

To a stirred solution of 2-bromo-4-methoxy-1-vinylbenzene¹⁴ (7.93 g, 37.2 mmol) in THF (160 mL) under argon atmosphere, 1.6 M hexane solution of *n*-BuLi (28 mL, 44.8 mmol) was added dropwise at –78 °C. The reaction mixture was stirred at the same temperature for 15 min, then trimethyl borate (12.5 mL, 112 mmol) was added. The resulting mixture was stirred for further 1 h and then allowed to warm to room temperature. After being stirred for 1 h, the reaction mixture was acidified with 10% aq HCl. The organic layer was separated, and the aqueous layer was extracted three times with Et_2O . The combined organic layers were washed with water twice, followed by brine, dried over Na_2SO_4 , filtered, and

concentrated *in vacuo*. The residue was triturated with hexane/EtOAc to afford **8** (1.18 g, 18%) as white solids; mp 137–138 °C; $R_f = 0.36$ (Hexane/EtOAc = 1/1, UV); $^1\text{H NMR}$ (acetone- d_6 /D $_2$ O, 500 MHz): δ 3.77 (s, 3H), 5.03 (dd, $J = 10.9, 1.4$ Hz, 1H), 5.52 (dd, $J = 17.5, 1.2$ Hz, 1H), 6.88 (dd, $J = 8.6, 2.9$ Hz, 1H), 7.10 (d, $J = 2.9$ Hz, 1H), 7.23 (dd, $J = 17.6, 11.0$ Hz, 1H), 7.53 (d, $J = 8.6$ Hz, 1H) ppm; $^{13}\text{C NMR}$ (acetone- d_6 /D $_2$ O, 125 MHz): δ 55.3, 111.9, 115.9, 118.9, 126.5, 135.0, 138.5, 159.4 ppm (the aromatic C connected to B atom was not observed); IR (neat) ν_{max} : 3418, 2947, 1597, 1489, 1412, 1335, 1273, 1234, 1045, 1026, 907, 837, 772, 714 cm^{-1} ; EIMS m/z : 480 [boroxine, M] $^+$; HRMS–ESI m/z : [dimethyl ester+H] $^+$ calcd for C $_{11}$ H $_{16}$ BO $_3$, 207.1192; found, 207.1187.

6-[(*tert*-Butyldimethylsilyloxy)-1-[4,5,5'-trimethoxy-2'-vinyl-(1,1'-biphenyl)-2-yl]hexan-1-one (5).

To a stirred mixture of **9** (1.56 g, 3.5 mmol), (5-methoxy-2-vinylphenyl)boronic acid (**8**) (939 mg, 5.25 mmol), K $_2$ CO $_3$ (1.46 g, 11 mmol) in toluene/EtOH (4/1, v/v, 35 mL) under argon atmosphere, Pd(PPh $_3$) $_4$ (210 mg, 0.18 mmol) was added. After being heated at 90 °C for 7 h, the resulting mixture was cooled to room temperature and then the organic solvent was removed *in vacuo*. The residue was suspended in Et $_2$ O and filtered through Celite $^{\text{®}}$ pad (Et $_2$ O eluent) and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (Hexane/EtOAc = 6.5/1 to 5/1) to afford **5** (1.30 g, 75%) as a pale yellow viscous oil; $R_f = 0.45$ (Hexane/EtOAc = 3/1, UV); $^1\text{H NMR}$ (CDCl $_3$, 500 MHz): δ 0.01 (s, 6H), 0.87 (s, 9H), 1.03–1.09 (m, 2H), 1.30–1.45 (m, 4H), 2.15–2.19 (m, 2H), 3.49 (t, $J = 6.6$ Hz, 2H), 3.80 (s, 3H), 3.89 (s, 3H), 3.96 (s, 3H), 5.06 (d, $J = 11.2$ Hz, 1H), 5.55 (d, $J = 17.5$ Hz, 1H), 6.45 (dd, $J = 17.5, 11.2$ Hz, 1H), 6.69 (s, 2H), 6.93 (dd, $J = 8.7, 2.4$ Hz, 1H), 7.24 (s, 1H), 7.58 (d, $J = 8.9$ Hz, 1H), ppm; $^{13}\text{C NMR}$ (CDCl $_3$, 125 MHz): δ –5.3, 18.3, 24.5, 25.3, 25.9, 32.5, 41.8, 55.4, 56.0, 56.1, 63.0, 111.2, 113.4, 113.5, 114.3, 115.0, 126.6, 129.1, 132.9, 133.2, 134.1, 141.1, 148.1, 150.5, 158.9, 204.4 ppm; IR (neat) ν_{max} : 2936, 2859, 1674, 1601, 1562, 1516, 1462, 1350, 1288, 1250, 1215, 1150, 1099, 1026, 837, 764 cm^{-1} ; EIMS m/z : 441 [M–C $_4$ H $_9$] $^+$; HRMS–ESI m/z : [M+Na] $^+$ calcd for C $_{29}$ H $_{42}$ NaO $_5$ Si, 521.2699; found, 521.2700.

(2*S,2*aS**,10*bR**)-2-(4-Hydroxybutyl)-4,5,8-trimethoxy-1,2,2*a*,10*b*-tetrahydrocyclobuta[*l*]phenanthren-2*a*-ol (10).**

To a stirred refluxing solution of **5** (203 mg, 0.41 mmol) in DME (3.6 mL) under argon atmosphere, KHMDS (1 M in THF, 0.49 mL, 0.49 mmol) was added. After being stirred for 2 h, the resulting mixture was added another portion of KHMDS (1 M in THF, 0.49 mL, 0.49 mmol). After being stirred for 1 h, the resulting mixture was cooled to 60 °C and TBAF (1.0 M in THF, 3.0 mL, 3.0 mmol) was added. After being stirred for 1 h, the resulting mixture was cooled to room temperature, and quenched with sat. aq

NH₄Cl and then extracted three times with EtOAc. The combined organic layers were washed with water twice, followed by brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Hexane/EtOAc = 1/3 to 1/5) to afford **10** (112 mg, 72%) as a white amorphous without significant impurities detectable by ¹H NMR. An analytically pure sample was prepared via recrystallization from Hexane/CHCl₃ to afford white crystals; mp 152–153 °C; R_f = 0.25 (Hexane/EtOAc = 1/5, UV); ¹H NMR (CDCl₃, 400 MHz): δ 1.47–1.56 (m, 4H), 1.61–1.70 (m, 3H), 1.82–1.88 (m, 1H), 2.04–2.11 (m, 1H), 2.23 (br s, 1H), 2.47–2.53 (m, 1H), 3.64 (t, *J* = 9.6 Hz, 1H), 3.67–3.73 (m, 2H), 3.86 (s, 3H), 3.93 (s, 3H), 3.98 (s, 3H), 6.77 (dd, *J* = 8.2, 2.8 Hz, 1H), 7.01 (s, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 7.30 (s, 1H), 7.32 (d, *J* = 2.3 Hz, 1H) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 23.7, 28.1, 29.8, 32.7, 44.6, 48.4, 55.4, 56.0, 62.7, 71.5, 105.3, 109.4, 110.2, 111.6, 124.9, 128.2, 129.4, 132.3, 132.9, 149.1, 149.9, 158.8 ppm (one peak was missing due to incidental equivalence); IR (neat) ν_{max}: 3372, 3275, 2936, 1605, 1566, 1504, 1462, 1423, 1346, 1269, 1234, 1204, 1177, 1150, 1084, 1042, 910, 864, 783, 733 cm⁻¹; EIMS *m/z*: 366 [M–H₂O]; HRMS–ESI *m/z*: [M+K]⁺ calcd for C₂₃H₂₈KO₅, 423.1574; found, 423.1587.

(2S*,2aS*,10bR*)-2-(4-Azidobutyl)-4,5,8-trimethoxy-1,2,2a,10b-tetrahydrocyclobuta[*l*]phenanthren-2a-ol (4).

To a stirred mixture of **10** (247 mg, 0.64 mmol), DMAP (37.3 mg, 0.31 mmol), and Et₃N (0.27 mL, 1.9 mmol) in CH₂Cl₂ (10 mL) under argon atmosphere, TsCl (148 mg, 0.776 mmol) was added at room temperature. After being stirred for 3.5 h, the resulting mixture was quenched with sat. aq NH₄Cl and extracted three times with CHCl₃. The combined organic layers were washed with water, followed by sat. aq NaHCO₃ and brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. To a stirred solution of the residue in DMF (1.3 mL) under argon atmosphere, NaN₃ (421 mg, 6.48 mmol) was added at room temperature. After being stirred for 13 h, the resulting mixture was quenched with water and then extracted three times with EtOAc. The combined organic layers were washed with water, followed by brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Hexane/EtOAc = 2/1) to afford white amorphous solid, which was triturated with Hexane/EtOAc to afford **4** (155 mg, 59%) as a white powder; mp 117–118 °C; R_f = 0.39 (Hexane/EtOAc = 2/1, UV); ¹H NMR (CDCl₃, 500 MHz): δ 1.45–1.57 (m, 3H), 1.64–1.75 (m, 3H), 1.83–1.88 (m, 1H), 2.02–2.09 (m, 1H), 2.17 (s, 1H), 2.45–2.52 (m, 1H), 3.33 (t, *J* = 6.7 Hz, 2H), 3.63 (t, *J* = 9.3 Hz, 1H), 3.84 (s, 3H), 3.93 (s, 3H), 3.96 (s, 3H), 6.76 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.99 (s, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 7.28 (s, 1H), 7.30 (d, *J* = 2.3 Hz, 1H) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 24.7, 28.1, 29.1, 29.6, 44.5, 48.2, 51.4, 55.4, 56.0, 71.4, 105.3, 109.3, 110.0, 111.6, 124.8, 128.1, 129.4, 132.2, 132.8, 149.1,

149.9, 158.8 ppm (one peak was missing due to incidental equivalence); IR (neat) ν_{\max} : 3468, 2936, 2859, 2095, 1605, 1566, 1516, 1462, 1346, 1265, 1238, 1204, 1153, 1088, 1042, 972, 910, 864, 733 cm^{-1} ; FABMS m/z : 432 $[\text{M}+\text{Na}]^+$; HRMS–ESI m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{NaO}_4$, 432.1899; found, 432.1891; Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_4$: C, 67.46; H, 6.65; N, 10.26. Found: C, 67.26; H, 6.83; N, 10.00.

***N*-{4-[(1*S**,2*aR**,10*bS**)-10*b*-Hydroxy-5,8,9-trimethoxy-1,2,2*a*,10*b*-tetrahydrocyclobuta[*l*]phenanthren-1-yl]butyl}-2-nitrobenzenesulfonamide (13).**

To a stirred mixture of **4** (100 mg, 0.24 mmol) in THF (2.3 mL) and H_2O (0.25 mL), was added PPh_3 (66.0 mg, 0.25 mmol) at room temperature. After being refluxed for 24 h, the resulting mixture was cooled to room temperature and diluted with CHCl_3 , and the organic layer was washed with brine, dried over Na_2SO_4 , filtered, concentrated *in vacuo* to afford the crude amine. To a stirred solution of the crude amine and Et_3N (0.10 mL, 0.72 mmol) in CH_2Cl_2 (2.5 mL) under argon atmosphere, 2-nitrobenzenesulfonyl chloride (81.1 mg, 0.37 mmol) was added at 0 °C. After being stirred for 20 min, the resulting mixture was quenched with sat. aq NaHCO_3 and extracted twice with CHCl_3 . The combined organic layers were washed with water, brine, dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Hexane/EtOAc = 1/1 to 1/2) to afford **13** (116 mg, 84%, 2 steps) as pale yellow amorphous; R_f = 0.43 (Hexane/EtOAc = 1/2, UV); ^1H NMR (CDCl_3 , 500 MHz): δ 1.43–1.52 (m, 3H), 1.55–1.65 (m, 3H), 1.76–1.81 (m, 1H), 1.96–2.03 (m, 1H), 2.20 (s, 1H), 2.40–2.45 (m, 1H), 3.16 (q, J = 6.9 Hz, 2H), 3.60 (t, J = 9.5 Hz, 1H), 3.85 (s, 3H), 3.93 (s, 3H), 3.97 (s, 3H), 5.42 (t, J = 6.0 Hz, 1H), 6.76 (dd, J = 8.3, 2.3 Hz, 1H), 6.98 (s, 1H), 7.04 (d, J = 8.3 Hz, 1H), 7.29 (s, 1H), 7.31 (d, J = 2.6 Hz, 1H), 7.69–7.75 (m, 2H), 7.83–7.85 (m, 1H), 8.12–8.14 (m, 1H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz): δ 24.4, 28.0, 29.4, 29.7, 43.5, 44.7, 48.1, 55.4, 55.96, 55.99, 71.4, 105.3, 109.3, 110.1, 111.6, 124.8, 125.3, 128.0, 129.4, 131.0, 132.2, 132.7, 133.5, 133.7, 148.0, 149.1, 149.9, 158.8 ppm (one peak was missing due to incidental equivalence); IR (neat) ν_{\max} : 3545, 3337, 2936, 1605, 1539, 1516, 1466, 1420, 1342, 1265, 1234, 1204, 1161, 1088, 1042, 926, 853, 760 cm^{-1} ; FABMS m/z : 591 $[\text{M}+\text{Na}]^+$; HRMS–ESI m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{29}\text{H}_{32}\text{N}_2\text{NaO}_8\text{S}$, 591.1777; found, 591.1777.

1-[(2-Nitrophenyl)sulfonyl]-2-[(3,6,7-trimethoxyphenanthren-9-yl)methyl]piperidine (14).

To a stirred solution of **13** (30.4 mg, 54 μmol) in toluene (0.32 mL) under argon atmosphere, TfOH (0.10 M in toluene, 0.75 mL, 75 μmol) was added. After being stirred at room temperature for 10 min, the resulting mixture was quenched with 15% aq NaOH and then extracted three times with CHCl_3 . The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Hexane/EtOAc = 2/3 to 0/1) to afford **14** (24.8

mg, 84%) as pale yellow crystals; mp 208–210 °C; R_f = 0.60 (Hexane/EtOAc = 1/2, UV); ^1H NMR (CDCl_3 , 500 MHz): δ 1.46–1.70 (m, 4H), 1.77 (d, J = 13.5 Hz, 1H), 1.83–1.91 (m, 1H), 3.38 (dd, J = 13.9, 9.3 Hz, 1H), 3.46–3.55 (m, 2H), 3.82 (dd, J = 13.8, 3.2 Hz, 1H), 4.02 (s, 3H), 4.126 (s, 3H), 4.134 (s, 3H), 4.55–4.59 (m, 1H), 7.15 (dd, J = 8.9, 2.3 Hz, 1H), 7.25–7.28 (m, 1H), 7.32–7.39 (m, 3H), 7.61 (s, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 2.3 Hz, 1H), 7.86 (s, 1H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz): δ 18.2, 25.4, 26.8, 34.7, 41.5, 53.3, 55.6, 56.1, 56.4, 103.8, 105.1, 115.2, 123.8, 124.7, 125.6, 126.3, 126.5, 129.1, 129.7, 130.2, 130.6, 131.3, 132.5, 133.9, 147.1, 148.8, 149.9, 158.1 ppm (one peak was missing due to incidental equivalence); IR (neat) ν_{max} : 3021, 2940, 1609, 1543, 1524, 1512, 1470, 1439, 1369, 1339, 1269, 1215, 1157, 1034, 756 cm^{-1} ; FABMS m/z : 573 $[\text{M}+\text{Na}]^+$; HRMS–ESI m/z : $[\text{M}+\text{K}]^+$ calcd for $\text{C}_{29}\text{H}_{30}\text{KN}_2\text{O}_7\text{S}$, 589.1411; found, 589.1417.

2-[(3,6,7-Trimethoxyphenanthren-9-yl)methyl]piperidine (**11**).

To a stirred solution of **14** (49.7 mg, 90 μmol) in MeCN (0.90 mL) under argon atmosphere, 1-dodecanethiol (0.11 mL, 0.46 mmol) and Cs_2CO_3 (303 mg, 0.93 mmol) were added at room temperature. After being stirred at 70 °C for 1.5 h, the resulting mixture was cooled to room temperature, diluted with Et_2O and then washed with water. The organic layer was extracted with 10% aq HCl and the acidic aqueous layer was washed twice with Et_2O . The resulting aqueous layer was basified with NaOH pellets (*ca.* pH 11) and then extracted three times with CHCl_3 . The combined organic layers were washed with water, followed by brine, dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to afford **11** (24.3 mg, 74%) as pale yellow crystals; mp 140–141 °C; R_f = 0.44 (MeOH/28% NH_3 aq = 30/1, UV, ninhydrin); ^1H NMR (CDCl_3 , 500 MHz): δ 1.23–1.42 (m, 2H), 1.44–1.53 (m, 1H), 1.56–1.67 (m, 1H), 1.79–1.89 (m, 3H), 2.48 (td, J = 11.9, 2.9 Hz, 1H), 2.90–3.01 (m, 3H), 3.23 (dd, J = 13.5, 4.0 Hz, 1H), 4.02 (s, 3H), 4.07 (s, 3H), 4.12 (s, 3H), 7.19 (dd, J = 8.7, 2.4 Hz, 1H), 7.42 (s, 1H), 7.51 (s, 1H), 7.74 (d, J = 8.9 Hz, 1H), 7.85 (d, J = 2.3 Hz, 1H), 7.93 (s, 1H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz): δ 24.9, 26.1, 33.4, 41.6, 47.1, 55.6, 55.96, 56.02, 56.4, 103.90, 103.94, 105.1, 115.4, 125.0, 125.85, 125.89, 126.7, 129.72, 129.76, 130.4, 148.7, 149.2, 157.9 ppm; IR (neat) ν_{max} : 3310, 2932, 1609, 1508, 1474, 1439, 1269, 1234, 1207, 1161, 1111, 1034, 910, 733 cm^{-1} ; FABMS m/z : 388 $[\text{M}+\text{Na}]^+$; HRMS–ESI m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{28}\text{NO}_3$, 366.2069; found, 366.2062. Spectroscopic data were consistent with those previously reported in the literature.¹⁵

(±)-Cryptopleurine (**2**).

To a stirred solution of **11** (24.3 mg, 67 μmol) in EtOH (2.0 mL) were added 37% HCHO aq (2.0 mL, 26.9 mmol) and conc. HCl (11 μL , 0.13 mmol) at room temperature. After being refluxed in the dark for

24 h, the resulting mixture was cooled to room temperature, basified with 15% aq NaOH (*ca.* pH 11) and then extracted three times with CHCl₃. The combined organic layers were washed with water, followed by brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by PTLC (CHCl₃/MeOH = 30/1) to afford (±)-cryptopleurine (**2**) (21.8 mg, 87%) as pale yellow crystals; mp 192–193 °C; *R_f* = 0.48 (CHCl₃/MeOH = 10/1, UV, ninhydrin); ¹H NMR (CDCl₃, 500 MHz): δ 1.39–1.49 (m, 1H), 1.49–1.57 (m, 1H), 1.72–1.83 (m, 2H), 1.88 (d, *J* = 12.6 Hz, 1H), 2.01–2.03 (m, 1H), 2.29 (td, *J* = 11.2, 4.0 Hz, 1H), 2.34–2.39 (m, 1H), 2.87 (dd, *J* = 16.3, 10.6 Hz, 1H), 3.06 (dd, *J* = 16.6, 2.9 Hz, 1H), 3.26 (d, *J* = 10.9 Hz, 1H), 3.61 (d, *J* = 15.5 Hz, 1H), 4.00 (s, 3H), 4.05 (s, 3H), 4.09 (s, 3H), 4.42 (d, *J* = 15.5 Hz, 1H), 7.18 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.23 (s, 1H), 7.78 (d, *J* = 9.2 Hz, 1H), 7.88 (d, *J* = 2.9 Hz, 1H), 7.89 (s, 1H) ppm; ¹³C NMR (CDCl₃, 125 MHz): δ 24.3, 25.9, 33.7, 34.7, 55.5, 55.9, 55.96, 56.04, 56.2, 57.5, 103.8, 104.7, 114.8, 123.4, 123.6, 124.1, 124.4, 125.5, 126.5, 130.1, 148.2, 149.3, 157.4 ppm (one peak was missing due to incidental equivalence); IR (neat) *v*_{max}: 2928, 1612, 1528, 1512, 1470, 1420, 1258, 1231, 1204, 1169, 1123, 1042, 910, 845, 783, 733 cm⁻¹; FABMS *m/z*: 378 [M+H]⁺; HRMS–ESI *m/z*: [M+H]⁺ calcd for C₂₄H₂₈NO₃, 378.2069; found, 378.2068. Spectroscopic data were consistent with those previously reported in the literature.¹⁵

***N*-{3-[(1*S**,2*aR**,10*bS**)-10*b*-Hydroxy-4,5,8,9-tetramethoxy-1,2,2*a*,10*b*-tetrahydrocyclobuta[*l*]phenanthren-1-yl]propyl}-2-nitrobenzenesulfonamide (**16**).**

To a solution of **15** (160 mg, 0.40 mmol), PPh₃ (179 mg, 0.68 mmol), 2-nitrobenzenesulfonamide (324 mg, 1.6 mmol) in THF (4.0 mL) was added diisopropyl azodicarboxylate (134 μL, 0.68 mmol) at 0 °C. After being stirred for 2 h at room temperature, the reaction was quenched with water. The biphasic mixture was then extracted with EtOAc (20 mL x 2). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc/Hexane = 2/1) to afford **16** (200 mg, 86%) as pale yellow amorphous; *R_f* = 0.37 (EtOAc/Hexane = 3/1, UV), ¹H NMR (CDCl₃, 500 MHz): δ 1.50–1.59 (m, 1H), 1.62–1.76 (m, 3H), 1.77–1.88 (m, 1H), 2.04–2.14 (m, 1H), 2.17 (br s, 1H), 2.43–2.52 (m, 1H), 3.20 (q, *J* = 6.3 Hz, 2H), 3.60 (t, *J* = 9.3 Hz, 1H), 3.89 (s, 3H), 3.91 (s, 3H), 3.96 (s, 3H), 3.99 (s, 3H), 5.52 (t, *J* = 5.6 Hz, 1H), 6.64 (s, 1H), 6.97 (s, 1H), 7.21 (s, 1H), 7.24 (s, 1H), 7.69–7.79 (m, 2H), 7.83–7.92 (m, 1H), 8.10–8.18 (m, 1H) ppm; ¹³C NMR (CDCl₃, 125 MHz): δ 27.0, 27.7, 28.0, 43.8, 44.9, 47.6, 55.8, 56.0, 56.1, 56.4, 71.3, 105.1, 106.7, 110.2, 111.3, 123.6, 125.2, 125.3, 128.5, 131.0, 131.6, 132.7, 133.5, 133.7, 148.0, 148.1, 148.6, 149.1, 149.2 ppm; IR (neat) *v*_{max}: 3499, 3309, 3016, 2935, 2854, 1604, 1539, 1508, 1462, 1408, 1338, 1246, 1165, 1138, 1041 cm⁻¹; HRMS–ESI *m/z*: [M+Na]⁺ calcd for C₂₉H₃₂N₂NaO₉S: 607.1721, found: 607.1721.

1-[(2-Nitrophenyl)sulfonyl]-2-[(2,3,6,7-tetramethoxyphenanthren-9-yl)methyl]pyrrolidine (17).

To a stirred solution of **16** (62.0 mg, 0.11 mmol) in MeCN (2.0 mL) under argon atmosphere, TfOH (12.2 μ L, 0.14 mmol) was added at room temperature. After being stirred for 5 min, the resulting mixture was quenched with Et₃N (28 μ L, 0.20 mmol) and stirred for 10 min. The mixture was directly purified by silica gel chromatography (Hexane/EtOAc = 1/1 to 1/2) to afford **17** (57.3 mg, 95%) as pale yellow amorphous. R_f = 0.25 (EtOAc/Hexane = 1/1, UV); ¹H NMR (CDCl₃, 500 MHz): δ 1.59–1.72 (m, 1H), 1.82–1.99 (m, 2H), 2.09–2.24 (m, 1H), 2.89 (dd, J = 13.5, 11.2 Hz, 1H), 3.28–3.39 (m, 1H), 3.54–3.64 (m, 1H), 3.84 (dd, J = 13.5, 3.4 Hz, 1H), 4.03 (s, 3H), 4.12 (s, 3H), 4.13 (s, 3H), 4.14 (s, 3H), 4.49–4.62 (m, 1H), 7.15 (s, 1H), 7.35 (s, 1H), 7.55–7.59 (m, 1H), 7.59–7.68 (m, 2H), 7.76 (s, 2H), 7.82 (s, 1H), 8.01 (dd, J = 7.7, 1.7 Hz, 1H) ppm; ¹³C NMR (CDCl₃, 125 MHz): δ 23.7, 29.4, 40.5, 48.1, 55.7, 55.8, 55.9, 56.2, 60.7, 102.5, 102.9, 105.1, 107.7, 123.80, 123.82, 124.5, 125.3, 125.7, 125.8, 130.0, 130.3, 131.3, 131.9, 133.4, 148.1, 148.6, 148.80, 148.83, 149.0 ppm; IR (neat) ν_{\max} : 3016, 2937, 1543, 1508, 1473, 1431, 1369, 1346, 1253, 1199, 1149 cm⁻¹; HRMS–ESI m/z : [M+Na]⁺ calcd for C₂₉H₃₀N₂NaO₈S: 589.1615, found: 589.1612.

2-[(3,6,7-Trimethoxyphenanthren-9-yl)methyl]piperidine (18).

To a stirred solution of **17** (170 mg, 0.30 mmol) in MeCN (3.0 mL) under argon atmosphere, 1-dodecanethiol (0.36 mL, 1.5 mmol) and Cs₂CO₃ (977 mg, 3.0 mmol) were added at room temperature. After being stirred at 70 °C for 1.5 h, the resulting mixture was cooled to room temperature, diluted with Et₂O and then washed with water. The organic layer was extracted with 10% aq HCl and the acidic aqueous layer was washed twice with Et₂O. The resulting aqueous layer was basified to pH 11 with NaOH pellets and then extracted three times with CHCl₃. The combined CHCl₃ layers were washed with water, followed by brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford **18** (86.3 mg, 75%) as pale yellow solids. Spectroscopic properties were consistent with those reported in the literature.⁷

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