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Total Synthesis of Phenanthroindolizidine Alkaloids by Combining Iodoaminocyclization with Free Radical Cyclization

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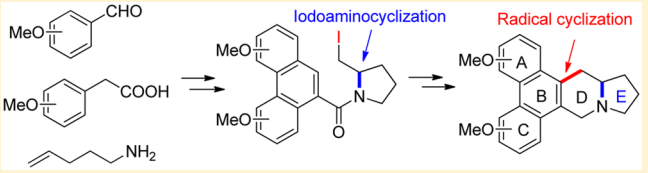
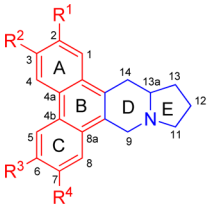
Supporting Information

ABSTRACT: A concise and modular synthesis of phenanthroindolizidine alkaloids was achieved by combining iodoaminocylization with a free radical cyclization approach. The route described allowed the preparation of (±)-tylophorine, (±)-antofine, and (±)-deoxypergularinine in six steps. When commercially available L-prolinol was used as a chiral building block, (*S*)-(+)-tylophorine was also synthesized in 49% yield and >99% ee over five linear steps.



The phenanthroindolizidine alkaloids represent a group of pentacyclic natural products (Figure 1) which exhibit



$R^1 = R^2 = R^3 = R^4$ = OMe, tylophorine (**1a**)
$R^1 = R^2 = R^3$ = OMe, R^4 = H, antofine (**1b**)
R^1 = H, $R^2 = R^3 = R^4$ = OMe, deoxypergularinine (**1c**)

Figure 1. Representative of phenanthroindolizidine alkaloids.

various biological activities such as antitumor,[1] antiarthritis,[2] anti-inflammatory,[3] and anti-lupus effects.[4] To date, close to 100 structurally related phenanthroindolizidines together with their *seco*-derivatives and N-oxides have been isolated and characterized from the genera *Cynanchum*, *Pergularia*, and *Tylophora*.[5] Due to their potent biological activities, they represent interesting targets for synthesis, structural modification, and structure−activity relationship (SAR) studies since their first isolation in 1935.[6]

Since the first total synthesis of (±)-tylophorine in 1961,[7] continuous efforts have been devoted to the preparation of phenanthroindolizidine alkaloids owing to their potent biological activity and their somewhat low natural abundance.[8] These strategies include intramolecular double Michael reactions,[9] Friedel−Crafts acylation,[10] intramolecular cycloaddition,[11] and biomimetic syntheses.[12]

With respect to enantioselective approaches, several synthetic strategies have been reported in the literature so far.[8b] One representative strategy, first reported by Rapoport and Buckley,[13] used the ex-chiral pool approach which was also employed in later syntheses based on proline,[14] glutamate,[15] and pyroglutamate.[16] Other strategies included a chiral auxiliary approach,[17] the use of a chiral allylic alcohol,[18] enantioselective carboamination,[19] and enantioselective phase-transfer alkylation.[20]

Nevertheless, low enantiomeric purity of the product is an issue in many of the reported syntheses, and there is still a need for high-yielding, straightforward, and generally applicable approaches to these natural products. Because the enantiomeric series of the phenanthro-alkaloids possess different bioactivity profiles, syntheses providing products of high optical purity are of particular value. Herein, we report a general, practical, and fully modular access to phenanthroindolizidine alkaloids through an iodoaminocyclization of unactivated olefins[21] and a free radical ring closure process.[22]

A retrosynthetic analysis for tylophorine is shown in Scheme 1. The target molecule **1a** could be accessible via reduction of amide **2**, which was envisioned to be constructed from compound **4** through an iodoaminocyclization followed by a free radical ring closure. Compound **4** could be easily prepared from commercially available veratric aldehyde and homoveratric acid by the Perkin reaction followed by amide coupling and intramolecular oxidative coupling.

The synthesis began with preparation of 2,3-diphenylacrylic acid **6** by condensation of veratraldehyde and homoveratric acid in a mixture of triethylamine and acetic anhydride. This compound underwent oxidative cyclization upon treatment with sodium nitrite and air in an acid medium to furnish the phenanthrene-9-carboxylic acid **5**.[23] EDC coupling of **5** with pent-4-en-1-amine[24] gave the aminoiodocyclization precursor **4** in 90% isolated yield (Scheme 2).

Initial attempts for the iodoaminocyclization of amide **4** were performed with (diacetoxyiodo)benzene and potassium iodide.[25] Under these reaction conditions, iodoaminocyclization of **4** did not occur (Table 1, entry 1). $PhI(OAc)_2$ in combination with TSMI promoted iodoamidation of **4** but gave the desired product in only low yields (entry 2).[26] The substrate was also inert toward *N*-iodosuccinimide (NIS) (entry 3). However, formation of the desired compound **3** from

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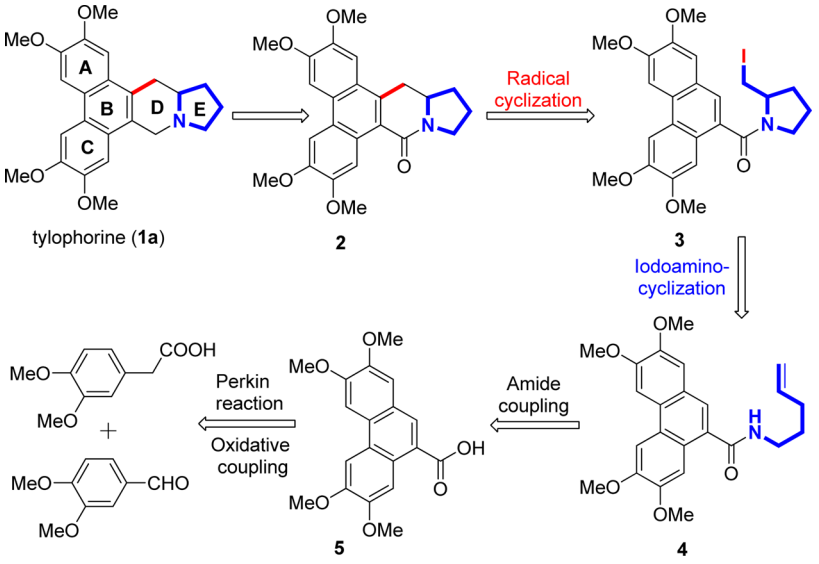
Scheme 1. Retrosynthetic Analysis of Tylophorine



Scheme 2. Synthesis of Olefinic Amide 4

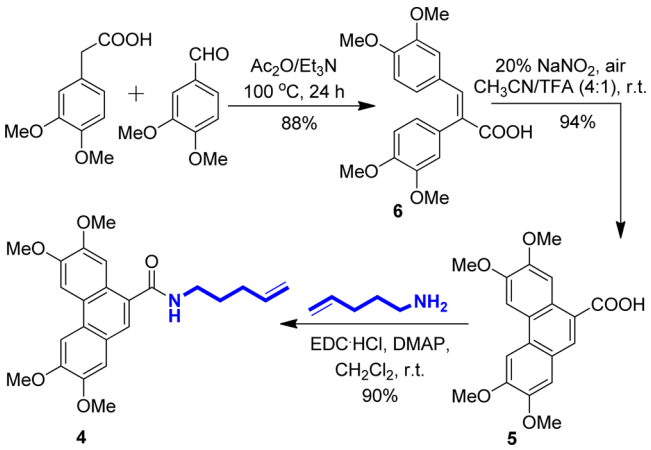
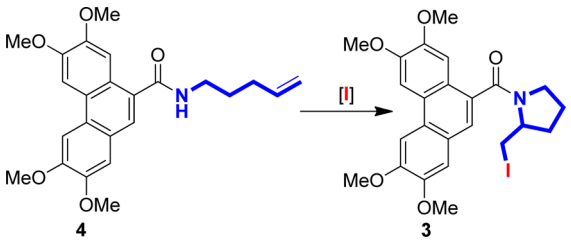


Table 1. Optimization Studies for Iodoaminocyclization[a]



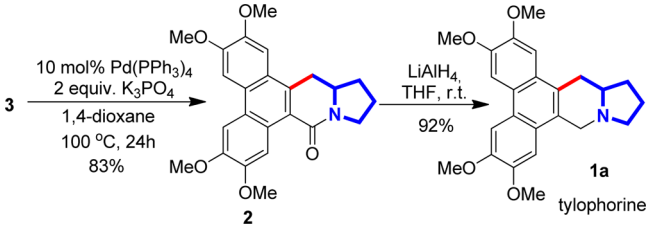
	reagent	temperature	isolated yield (%)
1	$PhI(OAc)_2$, KI	rt	<1
2	$PhI(OAc)_2$, TMSI	rt	27
3	NIS	rt	<1
4[b]	I_2, $NaHCO_3$	rt	51
5[b,c]	I_2, $NaHCO_3$	90 °C	72

[a]Reaction conditions: substrate (0.5 mmol), reagent (0.55 mmol), CH_2Cl_2 (10 mL), 24 h. [b]Reagent (1.5 mmol), CH_3CN as the solvent. [c]36 h.

olefinic amide **4** could be accomplished with molecular iodine and sodium hydrogen carbonate in acetonitrile in moderate yields (entry 4).[27] Prolonged reaction times and elevated reaction temperatures significantly increased the yield of iodoamidation product **3** (entry 5). There are surprisingly few literature reports on iodoaminocyclizations of this type, and they mostly utilize amides preactivated by O-silylation[28] or alkylation.[29] In addition, no iodination of the electron-rich phenanthrene core took place in our case.

With radical precursor **3** in hand, we turned to our attention to radical ring closure to construct the D-ring of tylophorine. Recently, Alexanian reported the palladium-catalyzed direct ring-forming C−H alkylation for the construction of indoline derivatives via a free radical process using simple alkyl halides.[30] We envisioned that cyclization of iodide **3** using the above-mentioned method would be perfectly suited to construct the D-ring of tylophorine. We were delighted to find that cyclization of iodide **3** proceeded readily using 10 mol % $Pd(PPh_3)_4$ as the catalyst, giving the desired pentacyclic lactam **2** in 83% yield (Scheme 3). Finally, reduction of lactam **2** with $LiAlH_4$ completed the synthesis of (±)-tylophorine **1a**, which was obtained in 41% overall yield over six steps.

Scheme 3. Synthesis of (±)-Tylophorine



In previous work on the phenanthroquinolizidine series, we successfully employed a Zard-type radical cyclization of a xanthate to close the D-ring at the same oxidation state. The preparation of the radical precursor was, however, more lengthy than that of the present route.[22e] To investigate whether the stereochemical integrity of the neighboring α-center is retained during radical generation and cyclization, we performed a synthesis of (*S*)-tylophorine using the same ring closure on a precursor synthesized from commercial L-prolinol. Thus, phenanthrene-9-carboxylic acid **5** and L-prolinol were coupled with EDC followed by subsequent conversion to iodide (*S*)-**3**

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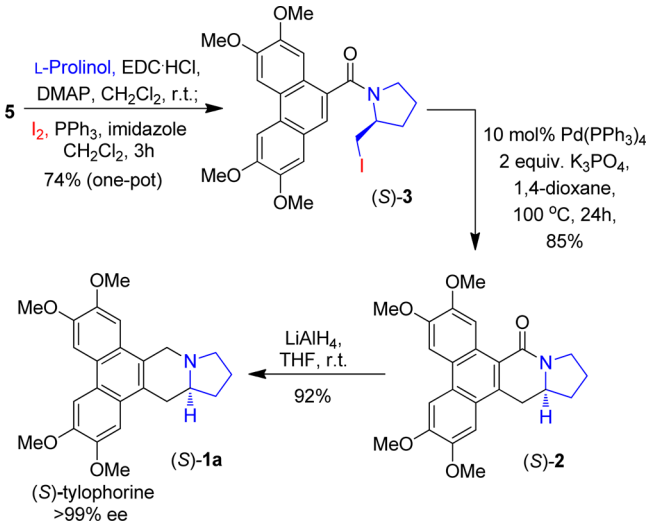
in a one-pot procedure. Iodide (*S*)-**3** was subjected to Pd-catalyzed radical cyclization, resulting in the pentacyclic lactam (*S*)-**2** in 85% yield. Reduction with $LiAlH_4$ produced (*S*)-(+)-tylophorine (*S*)-**1a** with excellent enantiomeric excess (>99% ee) and in high yield (Scheme 4).

Scheme 4. Synthesis of (*S*)-Tylophorine

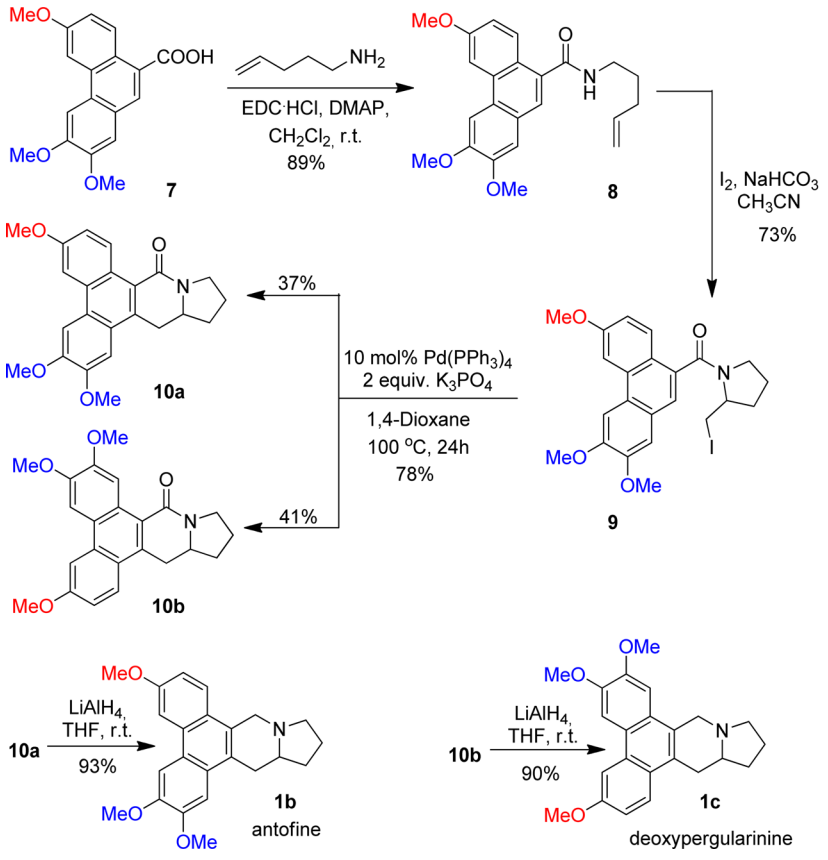


This approach allows for a variation at the oxygen-substituted aromatic rings A and C, so the strategy was also applied to the synthesis of antofine. The phenanthrene carboxylate **7** was prepared by condensation of 2-(4-methoxyphenyl)acetic acid and veratraldehyde followed by sodium nitrite-mediated ring closure. The olefinic amide **8** was readily obtained in 89% yield by EDC-coupling of **7** with pent-4-en-1-amine (Scheme 5). Iodocylization produced lactam **9** in an acceptable isolated yield. To our surprise, two products in almost an equimolar ratio were obtained simultaneously when a radical cyclization of **9** to **10** based on Alexanian's method was carried out in 1,4-dioxane. **10a** and **10b** were separated by flash column chromatography, and structures of the compounds were also established by two-dimensional (2D) NMR experiments, which were in agreement with results reported by Su and co-workers.[31] In a last step, antofine (**1b**) and deoxypergularinine (**1c**) were obtained from **10a** and **10b** through reduction with $LiAlH_4$ in high yield.

The formation of the regioisomers **10a** and **10b** can be rationalized on the basis of the mechanism shown in Scheme 6. The reaction is initiated by a reversible single electron oxidative addition of the iodide **9** and generates the carbon-centered radical A,[30] which can either add in a 1,6-fashion to give lactam **10a** after rearomatization of the radical intermediate **B**, or by 1,5-addition (*ipso* attack),[32] giving rise to spirocyclic intermediate **C**. Intermediate **C** can then undergo radical migration through path **a** to **B** or path **b** to **D**.[33] Rearomatization of radicals **B** and **D** could occur via single-electron oxidation followed by deprotonation to give the lactams **10a** and **10b**, respectively.

The observed formation of equal amounts of the two regioisomeric products **10a** and **10b** suggests that the 1,5-addition is the dominant cyclization process. A similar observation of two regioisomers being formed in an equimolar ratio had already been made by Alexanian and co-workers,

Scheme 5. Synthesis of (±)-Antofine and (±)-Deoxypergularinine



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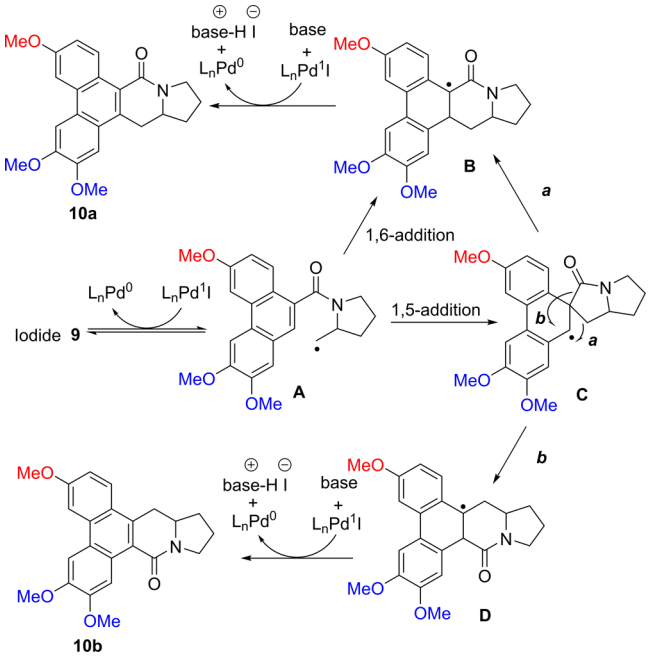
Scheme 6. Plausible Mechanism for Radical Cyclization



although the possibility of a 1,5-cyclization was not taken into consideration in favor of a 1,6-cyclization followed by a 1,2-alkyl shift, which is not an option in our case.[30]

In summary, a strategy for the synthesis of phenanthroindolizidine alkaloids is presented, comprising an iodoaminocyclization and a radical ring closure process as the key steps, furnishing this class of alkaloids in six steps from readily available starting materials. Using the same cyclization step, the highly stereoselective synthesis of (*S*)-tylophorine was achieved using readily available L-prolinol from the chiral pool. It requires only five steps, provides the target compound in an overall yield of 49% with an enantiomeric excess of more than 99%, and is devoid of any protecting group manipulations. To the best of our knowledge, this represents the shortest asymmetric synthesis of tylophorine known so far.

EXPERIMENTAL SECTION

General Experimental Information. All reactions requiring the exclusion of air and/or moisture were conducted in flame-dried glassware under an argon atmosphere. Solvents were dried and distilled prior to use. THF was distilled from potassium/benzophenone under an argon atmosphere. CH_2Cl_2 was dried over calcium hydride and distilled under an argon atmosphere. Ethyl acetate and cyclohexane were purchased in technical quality and purified by distillation. All other chemicals were purchased from commercial suppliers and used without prior purification unless otherwise stated. Flash chromatography was performed on silica with 25−40 μm particle size. NMR spectra were recorded on 300, 400, or 600 MHz spectrometers using standard pulse sequences. Chemical shifts are expressed in ppm relative to tetramethylsilane referenced to the residual solvent signals ($CDCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.16 ppm. DMSO-d_6: ^{1}H, 2.50 ppm; ^{13}C, 39.52 ppm). ESI-HRMS was performed on a Q-TOF instrument with a dual source and a suitable external calibrant. Thin-layer chromatography (TLC) was carried out on 0.25 mm silica gel plates with a fluorescence indicator. Melting points were measured on an electrothermal apparatus with a digital thermometer.

*(E)-2,3-Bis(3,4-dimethoxyphenyl)acrylic Acid (**6**).* A mixture of homoveratric acid (1.96 g, 10 mmol), veratraldehyde (1.83 g, 11 mmol), acetic anhydride (10 mL), and triethylamine (5 mL) was heated to reflux for 24 h with the exclusion of moisture. The solution was allowed to cool to room temperature; water (200 mL) was added, and the mixture was stirred for 1 h. The mixture was then poured into aqueous potassium carbonate (30.0 g in 80 mL of water) and refluxed until nearly all the gummy material was dissolved. The solution obtained was cooled and carefully acidified with concentrated hydrochloric acid (pH 4−5) to produce a white precipitate. The solid was collected and recrystallized from methanol to give compound **6** as a white solid (3.03 g, 88%). Mp 215−216 °C (ref 10b mp 214−216 °C). ^{1}H NMR (300 MHz, DMSO) δ 12.45 (s, 1H), 7.70 (s, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.84−6.78 (m, 3H), 6.75−6.64 (m, 1H), 6.56 (s, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 3.68 (s, 3H), 3.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 150.7, 149.6, 149.0, 148.5, 142.6, 129.0, 128.5, 127.4, 126.1, 122.6, 113.2, 112.9, 111.8, 110.8, 56.2, 56.1, 56.0, 55.5. Spectral data are in agreement with literature values.[10b]

*2,3,6,7-Tetramethoxyphenanthrene-9-carboxylic Acid (**5**).* To a solution of compound **6** (344 mg, 1.00 mmol) in TFA/CH_3CN (1/4) (10 mL) was added $NaNO_2$ (13.8 mg, 200 μmol) under an atmosphere of air. The mixture was stirred at room temperature for 1 h, and water (10 mL) was added to the mixture. The mixture was then filtered and washed with EtOAc to give compound **5** as a white solid (321.6 mg, 94%). Mp 285−286 °C (ref 23 mp 283−285 °C; ref 34 mp 285−286 °C). ^{1}H NMR (300 MHz, DMSO) δ 12.88 (brs, 1H), 8.56 (s, 1H), 8.43 (s, 1H), 8.06 (s, 1H), 8.02 (s, 1H), 7.57 (s, 1H), 4.07 (s, 3H), 4.06 (s, 3H), 3.92 (s, 3H), 3.90 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 169.5, 151.5, 149.3, 149.2, 130.2, 126.9, 125.3, 124.6, 123.9, 123.0, 109.9, 107.1, 104.2, 103.8, 56.4, 56.2, 56.0, 55.6. Spectral data are in agreement with literature values.[23]

*2,3,6,7-Tetramethoxy-N-(pent-4-en-1-yl)phenanthrene-9-carboxamide (**4**).* At 0 °C, acid **5** (342 mg, 1.00 mmol) was added to a solution of 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDC-HCl) (211 mg, 1.10 mmol) and DMAP (12.2 mg, 1.00 mmol) in CH_2Cl_2 (25 mL). Then, pent-4-en-1-amine[24] (85.1 mg, 1.00 mmol) was added to the mixture. The ice bath was removed and warmed to room temperature. After 24 h at room temperature, the solution was diluted with Et_2O (20 mL) and washed with 1 N HCl solution. The aqueous layer was then extracted twice with Et_2O (20 mL). The combined ether layers were dried with Na_2SO_4 and concentrated to give crude amide, which was purified by flash column chromatography (2/1 cyclohexane/EtOAc) to give compound **4** as a white solid (368.3 mg, 90%). Mp 175−176 °C. ^{1}H NMR, COSY (300 MHz, $CDCl_3$) δ 7.72 (s, 1H, Phen-*H*10), 7.57 (s, 1H, Phen-*H*4), 7.52 (s, 1H, Phen-*H*5), 7.51 (s, 1H, Phen-*H*1), 7.01 (s, 1H, Phen-*H*9), 6.52 (t, *J* = 5.5 Hz, 1H, -N*H*-), 5.89 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H, −C*H*=CH$_2$), 5.17−4.98 (m, 2H, −CH=C*H*$_2$), 4.07 (s, 3H, C^3 −OC*H*$_3$), 4.05 (s, 3H, C^6 −OC*H*$_3$), 3.98 (s, 3H, C^2 −OC*H*$_3$), 3.96 (s, 3H, C^7−OC*H*$_3$), 3.55 (dd, *J* = 13.2, 6.9 Hz, 2H, -NHC*H*$_2$-), 2.29−2.18 (m, 2H, −C*H*$_2$CH=CH$_2$), 1.87−1.75 (m, 2H, −CH$_2$C*H*$_2$CH$_2$−). ^{13}C NMR, HSQC, HMBC (75 MHz, $CDCl_3$) δ 170.3 (CONH), 149.5 (C^3-OMe), 148.7 (C^6-OMe), 148.4 (C^{2,7}-OMe), 137.7 (−*C*H=CH$_2$), 130.1 (C9), 124.9 (C10), 124.5 (C10a), 124.4 (C4b), 123.5 (C4a), 122.7 (C8a), 115.3 (−CH=*C*H$_2$), 108.2 (C8), 105.9 (C1), 102.2 (C4), 102.0 (C5), 55.7 (C^{2,3,6,7}-OMe), 39.4 (C1′), 31.2 (C3′), 28.9 (C2′). HRMS−ESI (*m*/*z*) [M + H]$^+$ calcd for $C_{24}H_{27}NO_5$, 410.1967; found 410.1976.

*(2-(Iodomethyl)pyrrolidin-1-yl)(2,3,6,7-tetramethoxyphenanthren-9-yl)methanone (**3**).* To a stirred solution of amide **4** (204 mg, 500 μmol) in CH_3CN (10 mL) containing solid $NaHCO_3$ (126 mg, 1.50 mmol) was added I_2 (381 mg, 1.50 mmol) in portions. The reaction mixture was stirred for 36 h at 90 °C. The reaction mixture was allowed to cool to ambient temperature. CH_2Cl_2 (10 mL) was then added, and the mixture was washed with aqueous $Na_2S_2O_3$. The combined organic layer was dried with Na_2SO_4 and concentrated to give a crude residue which was purified by flash column chromatography (1/1 cyclohexane/EtOAc) to give compound **3** as yellow oil (192.7 mg, 72%). ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ 7.80 (s, 1H, Phen-*H*10), 7.77 (s, 1H, Phen-*H*4), 7.60 (s, 1H, Phen-*H*5), 7.38 (s, 1H, Phen-*H*1), 7.20 (s, 1H, Phen-*H*9), 4.36−4.31 (m, 1H, −C*H*$_2$I), 4.14 (s, 3H, C^3−OC*H*$_3$), 4.13 (s, 3H, C^6−OC*H*$_3$), 4.10−4.08 (m, 1H, H-2′), 4.03 (s, 3H, 3H, C^2−OC*H*$_3$), 4.03 (s, 3H, 3H, C^7−OC*H*$_3$), 3.69 (dd, *J* = 9.7, 2.3 Hz, 1H, −C*H*$_2$I), 3.44−3.37 (m, 1H,

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H-5′), 3.29−3.24 (m, 1H, H-5′), 2.33−2.19 (m, 1H, H-3′), 2.02−1.89 (m, 2H, H-3′ and H-4′), 1.82−1.70 (m, 1H, H-4′). ^{13}C NMR, HSQC, HMBC (100 MHz, $CDCl_3$) δ 170.4 (CO), 150.0 (C^3-OMe), 149.4 (C^6-OMe), 149.2 (C^2-OMe), 149.1 (C^7-OMe), 131.3 (C9), 125.2 (C10), 124.9 (C10a), 124.8 (C4b), 123.1 (C4a), 122.3 (C8a), 108.5 (C8), 105.7 (C1), 103.0 (C4), 102.7 (C5), 57.1 (C^3−OCH_3), 56.4 (C^6−OCH_3), 56.1 ($C^{2,7}$-OCH_3), 56.0 (C1′), 50.3 (C5′), 31.6 (C2′), 24.6 (C4′), 12.5 (−CH_2I). HRMS−ESI (m/z) $[M + H]^+$ calcd for $C_{24}H_{26}INO_5$, 536.0934; found 536.0925.

*2,3,6,7-Tetramethoxy-12,13,13a,14-tetrahydrodibenzo[f,h]-pyrrolo[1,2-b]isoquinolin-9(11H)-one (**2**).* A vial in a glovebox under an argon atmosphere was charged with iodide **3** (53.5 mg, 100 μmol) and 1,4-dioxane (1 mL). $Pd(PPh_3)_4$ (11.6 mg, 10 μmol) and K_3PO_4 (42.4 mg, 200 μmol) were subsequently added. The reaction vial was removed from the glovebox and heated in an oil bath at 100 °C under stirring for 24 h. The reaction mixture was allowed to cool to ambient temperature and quenched with 1 N HCl, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried with Na_2SO_4 and concentrated to give a crude residue which was purified by flash column chromatography (1/2 cyclohexane/EtOAc) to give lactam **2** as a white solid (33.9 mg, 83%). Mp 282−283 °C (ref 35 mp 283−289; ref 36 mp 284−286 °C). ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ 9.03 (s, 1H, Phen-*H*4), 7.74 (s, 1H, Phen-*H*5), 7.72 (s, 1H, Phen-*H*8), 7.22 (s, 1H, Phen-*H*1), 4.13 (s, 3H, C^3−OCH_3), 4.11 (s, 3H, C^6−OCH_3), 4.09 (s, 3H, C^2−OCH_3), 4.02 (s, 3H, C^7−OCH_3), 3.91−3.76 (m, 3H, *H*-11, *H*-13), 3.50 (dd, J = 15.6, 4.1 Hz, 1H, *H*-14), 2.86 (dd, J = 15.6, 13.4 Hz, 1H, *H*-14), 2.44−2.37 (m, 1H, *H*-13a), 2.20−2.14 (m, 1H, *H*-12), 1.99−1.87 (m, 2H, *H*-12, *H*-13). ^{13}C NMR, HSQC, HMBC (100 MHz, $CDCl_3$) δ 164.7 (CO), 150.2 (C^3-OMe), 148.9 (C^6-OMe), 148.7 (C^2-OMe), 148.6 (C^7-OMe), 133.2(C14), 126.6 (C8a), 124.3 (C14a), 124.3 (C8b), 123.1 (C4a), 122.4 (C4b), 108.0 (C1), 104.8 (C8), 103.0 (C4), 102.3 (C5), 56.0 ($C^{3,6,2}$-O CH_3), 55.9 (C13a), 55.2 (C^7−OCH_3), 45.4 (C11), 33.9 (C14), 32.5 (C12), 23.5 (C13). Spectral data are in agreement with literature values.[35]

*rac-Tylophorine (**1a**).* Under a nitrogen atmosphere, to a stirred suspension of $LiAlH_4$ (17.0 mg, 500 μmol) in dry THF (50 mL) was added the solution of lactam **2** (40.7 mg, 100 μmol) in THF (50 mL) dropwise at 0 °C, and the mixture was stirred overnight. The resulting suspension was cooled to 0 °C and quenched by slow addition of 6 M NaOH (10 mL). The resulting mixture was extracted with ether (4 × 30 mL), and the combined ether extracts were dried with Na_2SO_4 and concentrated to give crude residue which was purified by flash column chromatography (1/10 EtOAc/MeOH) to give *rac*-tylophorine **1a** as a pale yellow solid (36.2 mg, 92%). Mp 279−280 °C (ref 37 mp 279−281 °C; ref 10b mp 275−282 °C). ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ 7.73 (s, 1H, Phen-*H*4), 7.72 (s, 1H, Phen-*H*5), 7.18 (s, 1H,, Phen-*H*8), 7.06 (s, 1H, Phen-*H*1), 4.52 (d, ^2J = 14.7 Hz, 1H, *H*-9), 4.02 (s, 6H, $C^{3,6}$-OCH_3), 4.00(s, 3H, C^2−OCH_3), 4.00 (s, 3H, C^7−OCH_3), 3.56 (d, ^2J = 14.7 Hz, 1H, *H*-9), 3.38 (td, J = 8.5, 2.0 Hz, 1H, *H*-11), 3.27 (dd, J = 15.8, 2.4 Hz, 1H, *H*-14), 2.81 (dd, J = 15.8, 10.5 Hz, 1H, *H*-14), 2.44−2.31 (m, 2H, H-13a, *H*-11), 2.17−2.12 (m, 1H, *H*-12), 2.02−1.89 (m, 1H, *H*-13), 1.88−1.77 (m, 1H, *H*-13), 1.74−1.61 (m, 1H, *H*-12). ^{13}C NMR, HMBC, HSQC (100 MHz, $CDCl_3$) δ 148.6 ($C^{3,6}$-OMe), 148.4 ($C^{2,7}$-OMe), 126.3 (C14), 126.0 (C8a), 125.8 (C14a), 124.3 (C8b), 123.6 (C4a), 123.6 (C4b), 103.9 (C1), 103.4 (C8), 103.2 (C4), 103.1 (C5), 60.2 (C13a), 56.0 ($C^{3,6}$-OCH_3), 55.9 ($C^{2,7}$-OCH_3), 55.2 (C11), 54.1 (C9), 33.9 (C14), 31.3 (C12), 21.6 (C13). Spectral data are in agreement with literature values.[37]

*(S)-(2-(Iodomethyl)pyrrolidin-1-yl)(2,3,6,7-tetramethoxyphenanthren-9-yl)methanone ((S)-**3**).* At 0 °C, acid **5** (342 mg, 1.00 mmol) was added to a solution of EDC-HCl (211 mg, 1.10 mmol) and DMAP (12.2 mg, 100 μmol) in CH_2Cl_2 (25 mL). Then, L-prolinol (101 mg, 1.00 mmol) was added to the mixture. The ice bath was removed and warmed to room temperature, and the reaction mixture was stirred 24 h at room temperature. Then, triphenylphosphine (288 mg, 1.10 mmol), imidazole (74.8 mg, 1.10 mmol), and iodine (279 mg, 1.10 mmol) were added to the reaction mixture. After 3 h, the reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate solution (50 mL), and the organic layer was washed with saturated aqueous sodium thiosulfate solution (100 mL) and a 1 N HCl solution, dried with Na_2SO_4, and concentrated to give a crude amide, which was purified by flash column chromatography (1/1 cyclohexane/EtOAc) to give compound (*S*)-**3** as a yellow oil (395.9 mg, 74%). $[\alpha]_D^{22}$ = −9.2 (c = 0.5, $CHCl_3$). The NMR data correspond to those of the racemic compound.

*(S)-2,3,6,7-Tetramethoxy-12,13,13a,14-tetrahydrodibenzo[f,h]-pyrrolo[1,2-b]isoquinolin-9(11H)-one ((S)-**2**).* Compound (*S*)-**2** was synthesized from compound (*S*)-**3** (53.5 mg) via the same procedure employed to synthesize compound **2**. Compound (*S*)-**2** was purified by flash column chromatography (1/2 cyclohexane/EtOAc) as a yellow solid (34.6 mg, 85%). Mp 288−289 °C (ref 38 mp 287−289 °C; ref 22b mp 286−287 °C). $[\alpha]_D^{22}$ = 157.9 (c = 1.0, $CHCl_3$) (ref 39 $[\alpha]_D^{25}$ = 165.4, c = 1.04, $CHCl_3$). The NMR data correspond to those of the racemic compound.

*(S)-Tylophorine ((S)-**1a**).* Compound (*S*)-**1a** was synthesized from compound (*S*)-**2** (40.7 mg) via the same procedure employed to synthesize compound **1a**. Compound (*S*)-**1a** was purified by flash column chromatography (1/10 EtOAc/MeOH) to yield a yellow solid (36.2 mg, 92%). Mp 282−283 °C (ref 22c mp 280−283 °C). Chiral HPLC analysis (CHIRALPAK AD-H, 20% 2-propanol/*n*-hexane → 35% 2-propanol/*n*-hexane in 15 min, 40 °C, 1.0 mL min^{-1}, 10.34 min (*S* isomer), 12.18 min (*R* isomer)) showed that the compound (*S*)-**1a** had an enantiomeric excess of >99%. $[\alpha]_D^{22}$ = 79.0 (c = 0.5, $CHCl_3$) (ref 22c $[\alpha]_D^{22}$ = 78.9, c = 0.5, $CHCl_3$; ref 39 $[\alpha]_D^{22}$ = 64.2, c = 0.57, $CHCl_3$). The NMR data correspond to those of the racemic compound.

*2,3,6-Trimethoxyphenanthrene-9-carboxylic acid (**7**).* Compound **7** was synthesized from (*E*)-3-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)acrylic acid (314.1 mg) via the same procedure ($NaNO_2$ 13.8 mg) employed to synthesize compound **4**. Compound **7** was purified by flash column chromatography (2/1 cyclohexane/EtOAc) as a yellow solid (287.1 mg, 92%). Mp 221−222 °C (ref 22e mp 222 °C; ref 40 mp 232−233 °C). ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 11.20 (brs, 1H, COO*H*), 9.06 (d, J = 9.3 Hz, 1H, Phen-*H*8), 8.47 (s, 1H, Phen-*H*10), 8.16 (s, 1H, Phen-*H*4), 8.14 (d, J = 2.6 Hz, 1H, Phen-*H*5), 7.56 (s, 1H, Phen-*H*1), 7.29 (dd, J = 9.3, 2.6 Hz, 1H, Phen-*H*7), 4.12 (s, 3H, C^3−OCH_3), 4.04 (s, 3H, C^2−OCH_3), 4.03 (s, 3H, C^6−OCH_3). ^{13}C NMR, HSQC, HMBC (100 MHz, Acetone) δ 168.3(COOH), 158.3 (C_q-OMe), 151.7 (C_q-OMe), 150.3 (C_q-OMe), 132.0 (C4b), 129.7 (C10), 128.3 (C8), 126.8 (C4a), 125.7 (C10a), 123.4 (C9), 123.3 (C8a), 116.1 (C7), 109.5 (C1), 104.1 (C5), 103.7 (C4), 55.5 (C^3−OCH_3), 55.2 (C^2−OCH_3), 54.9 (C^6−OCH_3). Spectral data are in agreement with literature values.[22e]

*2,3,6-Trimethoxy-N-(pent-4-en-1-yl)phenanthrene-9-carboxamide (**8**).* Compound **8** was synthesized from compound **7** (312.1 mg) via the same procedure employed to synthesize compound **4**. Compound **8** was purified by flash column chromatography (2/1 cyclohexane/EtOAc) as a yellow solid (337.5 mg, 89%). Mp 166−167 °C. ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ 8.20 (d, J = 9.1 Hz, 1H, Phen-*H*8), 7.70 (d, J = 2.5 Hz, 1H, Phen-*H*5), 7.63 (s, 1H, Phen-*H*4), 7.47 (s, 1H, Phen-*H*4), 7.17 (dd, J = 9.1, 2.5 Hz, 1H, Phen-*H*7), 7.01 (s, 1H, Phen-*H*1), 6.45 (brs, 1H, N*H*), 5.89 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H, −CH=CH_2), 5.17−4.99 (m, 2H, −CH=CH_2), 4.04 (s, 3H, C^3−OCH_3), 3.99 (s, 3H, C^2−OCH_3), 3.97 (s, 3H, C^6−OCH_3), 3.54 (dd, J = 13.2, 6.9 Hz, 2H, -NHCH_2-), 2.26−2.18 (m, 2H, −CH_2CH=CH_2), 1.85−1.75 (m, 2H, -$CH_2CH_2CH_2$−). ^{13}C NMR, HSQC, HMBC (100 MHz, $CDCl_3$) δ 170.0 (CONH), 158.2 (C8), 149.7 (C3), 149.4 (C2), 137.8 (C4b), 131.5 (C14b), 131.4 (C8b), 127.9 (C14a), 125.7 (C6), 124.9 (C8a), 122.9 (C4a), 122.5 (C7), 115.5 (C5), 115.4 (C1), 108.4 (C4), 55.9 (C^3−OCH_3), 55.9 (C^2−OCH_3), 55.5 (C^6−OCH_3), 39.5 (C1′), 31.2 (C3′), 28.9 (C2′). HRMS−ESI (m/z) $[M + H]^+$ calcd for $C_{23}H_{25}NO_4$, 380.1862; found 380.1850.

*(2-(Iodomethyl)pyrrolidin-1-yl)(2,3,6-trimethoxyphenanthren-9-yl)methanone (**9**).* Compound **9** was synthesized from compound **8** (189.6 mg) via the same procedure employed to synthesize compound **3**. Compound **9** was purified by flash column chromatography (2/1 cyclohexane/EtOAc) as a yellow oil (184.4 mg, 73%). ^{1}H NMR, COSY (600 MHz, $CDCl_3$) δ 7.99 (d, J = 8.9 Hz, 1H, Phen-*H*8), 7.87 (d, J = 2.4 Hz, 1H, Phen-*H*5), 7.84 (s, 1H, Phen-*H*10), 7.56 (s, 1H, Phen-*H*4), 7.22 (dd, J = 8.9, 2.4 Hz, 1H, Phen-*H*7), 7.21 (s, 1H, Phen-

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*H*1), 4.34 (d, *J* = 6.3 Hz, 1H, −C*H*$_2$I), 4.11 (s, 3H, C^3−OMe), 4.05−4.02 (m, 4H, C^2−OMe and H-2′), 4.01 (s, 3H, C^6−OMe), 3.71 (d, *J* = 9.3 Hz, 1H, −C*H*$_2$I), 3.39−3.30 (m, 1H, H-5′), 3.26−3.17 (m, 1H, H-5′), 2.31−2.18 (m, 1H, H-3′), 2.00−1.94 (m, 1H, H-4′), 1.93−1.87 (m, 1H, H-3′), 1.81−1.70 (m, 1H, H-4′). ^{13}C NMR, HSQC, HMBC (150 MHz, $CDCl_3$) δ 170.0 (CO), 158.4 (C8), 149.7 (C3), 149.7 (C2), 132.2 (C4b), 131.4 (C14b), 127.5 (C8b), 126.3 (C14a), 124.6 (C6), 122.2 (C8a), 121.9 (C4a), 115.9 (C7), 108.5 (C5), 104.4 (C1), 103.2 (C4), 56.1 (C^3−O*C*H$_3$), 57.1 (C^2−O*C*H$_3$), 56.0 (C^6−O*C*H$_3$), 55.6 (C1′), 50.2 (C5′), 31.6 (C2′), 24.5 (C4′), 12.3 (−*C*H$_2$I). HRMS−ESI (*m*/*z*) [M + H]$^+$ calcd for $C_{23}H_{24}INO_4$, 506.0828; found 506.0834.

*Synthesis of **10a** and **10b**.* In a glovebox, a vial was charged with iodide **9** (50.5 mg, 100 μmol) and 1,4-dioxane (1 mL) under an argon atmosphere. Pd(PPh$_3$)$_4$ (11.6 mg, 10 μmol) and K_3PO_4 (42.4 mg, 200 μmol) were subsequently added. The reaction vessel was removed from the glovebox and heated in an oil bath to 100 °C under stirring for 24 h. The reaction mixture was allowed to cool to ambient temperature and quenched with 1 N HCl, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo to give a crude residue which was purified by flash column chromatography (1/2 cyclohexane/EtOAc) to give lactams **10a** (13.9 mg, 37%, yellow solid) and **10b** (15.5 mg, 41%, yellow solid).

*2,3,6-Trimethoxy-12,13,13a,14-tetrahydrodibenzo[f,h]pyrrolo-[1,2-b]isoquinolin-9(11H)-one (**10a**).* R_f = 0.21, SiO_2, 1/2 cyclohexane/EtOAc. Mp 253−254 °C (ref 31 mp 252−253 °C; ref 33 mp 262−264 °C). ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ 9.32 (d, *J* = 9.3 Hz, 1H, Phen-*H*8), 7.93 (s, 1H, Phen-*H*4), 7.87 (d, *J* = 2.6 Hz, 1H, Phen-*H*5), 7.34 (s, 1H, Phen-*H*1), 7.27 (dd, *J* = 9.3, 2.6 Hz, 1H, Phen-*H*7), 4.15 (s, 3H, C^3−O*C*H$_3$), 4.08 (s, 3H, C^2−O*C*H$_3$), 4.04 (s, 3H, C^6−O*C*H$_3$), 3.97−3.77 (m, 3H, *H*-11, *H*-13), 3.56 (dd, *J* = 15.6, 4.0 Hz, 1H, *H*-14), 2.93 (dd, *J* = 15.5, 13.4 Hz, 1H, *H*-14), 2.55−2.37 (m, 1H, *H*-13a), 2.24−2.13 (m, 1H, *H*-12), 2.03−1.87 (m, 2H, *H*-13). ^{13}C NMR, HSQC, HMBC (100 MHz, $CDCl_3$) δ 164.3 (CO), 157.7 (C8), 150.1 (C3), 149.5 (C2), 132.5 (C4b), 131.0 (C14b), 129.6 (C8b), 126.4 (C14a), 124.4 (C6), 123.7 (C8a), 123.6 (C4a), 115.2 (C7), 104.9 (C5), 104.2 (C1), 103.8 (C4), 56.0 (C13a), 55.9 (C^3−O*C*H$_3$), 55.5 (C^2−O*C*H$_3$), 55.2 (C^6−O*C*H$_3$), 45.3 (C11), 33.9 (C14), 32.7 (C13), 23.6 (C12). Spectral data are in agreement with literature values.[31]

*3,6,7-Trimethoxy-12,13,13a,14-tetrahydrodibenzo[f,h]pyrrolo-[1,2-b]isoquinolin-9(11H)-one (**10b**).* R_f = 0.19, SiO_2, 1/2 cyclohexane/EtOAc. Mp 200−201 °C (ref 31 mp 200−201 °C; ref 22d mp 195−197 °C). ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ 9.05 (s, 1H, *H*-8), 8.01 (d, *J* = 9.2 Hz, 1H, *H*-1), 7.89 (d, *J* = 2.5 Hz, 1H, *H*-4), 7.87 (s, 1H, *H*-5), 7.24 (dd, *J* = 9.2, 2.5 Hz, 1H, *H*-1), 4.13 (s, 3H, C^7−O*C*H$_3$), 4.11 (s, 3H, C^6−O*C*H$_3$), 4.06 (s, 3H, C^3−O*C*H$_3$), 3.95−3.78 (m, 3H, *H*-11, *H*-13), 3.67 (dd, *J* = 15.7, 4.1 Hz, 1H, *H*-14), 3.00−2.89 (m, 1H, *H*-14), 2.53−2.36 (m, 1H, *H*-13), 2.23−2.16 (m, 1H, *H*-12), 2.02−1.87 (m, 2H, *H*-13). ^{13}C NMR, HSQC, HMBC (100 MHz, $CDCl_3$) δ 164.7 (CO), 159.3(C3), 149.5 (C7), 148.5 (C6), 134.2 (C4b), 133.1 (C8b), 126.7 (C14b), 125.3 (C14a), 124.3 (C1), 123.0 (C8a), 122.0 (C4a), 115.5 (C2), 108.1 (C4), 104.4 (C5), 102.9 (C8), 55.9 (C13a), 55.9 (C^7 −OCH$_3$), 55.5 (C^6−OCH$_3$), 55.3 (C^3−OCH$_3$), 45.4 (C11), 33.9 (C14), 32.3 (C13), 23.5 (C12). Spectral data are in agreement with literature values.[31]

*rac-Antofine (**1b**).* Compound **1b** was synthesized from compound **10a** (37.7 mg) via the same procedure employed to synthesize compound **1a**. Compound **1b** was purified by flash column chromatography (15/1 EtOAc/MeOH) as a yellow solid (33.8 mg, 93%). Mp 211−212 °C (ref 31 mp 211−212 °C; ref 22d mp 205−207 °C). ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ 7.93 (s, 1H, Phen-*H*4), 7.92 (d, *J* = 2.6 Hz, 1H, Phen-*H*5), 7.81 (d, *J* = 9.1 Hz, 1H, Phen-*H*8), 7.32 (s, 1H, Phen-*H*1), 7.22 (dd, *J* = 9.1, 2.6 Hz, 1H, Phen-*H*7), 4.73 (d, *J* = 14.9 Hz, 1H, *H*-9), 4.13 (s, 3H, C^3 −OC H_3), 4.08 (s, 3H, C^2 −OC H_3), 4.04 (s, 3H, C^6 −OC H_3), 3.77 (d, *J* = 14.9 Hz, 1H, *H*-9), 3.54−3.42 (m, 1H *H*-11), 3.37 (dd, *J* = 15.9, 2.6 Hz, 1H, *H*-14), 3.04−2.92 (m, 1H, *H*-14), 2.61−2.50 (m, 2H, *H*-13a, *H*11), 2.33−2.23 (m, 1H, *H*-13), 2.14−2.03 (m, 1H, *H*-12), 2.03−1.89 (m, 1H, *H*-12), 1.88−1.77 (m, 1H, *H*-13). ^{13}C NMR, HSQC, HMBC (100 MHz, $CDCl_3$) δ 157.5 (C8), 149.4 (C3), 148.4 (C2), 130.2 (C4b), 126.9 (C14b), 125.4 (C8b), 125.2 (C14a), 124.2 (C6), 124.0 (C8a), 123.6 (C4a), 114.9 (C7), 104.7 (C5), 104.0 (C1), 103.8 (C4), 60.3 (C13a), 56.0 (C^3−O*C*H$_3$), 55.9 (C^2−O*C*H$_3$), 55.5 (C^6−O*C*H$_3$), 54.9 (C11), 53.6 (C9), 33.4 (C14), 31.1 (C13), 21.6 (C12). Spectral data are in agreement with literature values.[31]

*rac-Deoxypergularinine (**1c**).* Compound **1c** was synthesized from compound **10b** (37.7 mg) via the same procedure employed to synthesize compound **1a**. Compound **1c** was purified by flash column chromatography (15/1 EtOAc/MeOH) as a yellow solid (32.7 mg, 90%). Mp 208−209 °C (ref 31 mp 209−210 °C; ref 22d mp 225−228 °C).^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 9.0 Hz, 1H, *H*-1), 7.93 (s, 1H, *H*-5), 7.91 (d, *J* = 2.5 Hz, 1H, *H*-4), 7.24 (dd, *J* = 9.0, 2.5 Hz, 1H, *H*-2), 7.15 (s, 1H, *H*-8), 4.66 (d, *J* = 14.7 Hz, 1H, *H*-9), 4.12 (s, 3H, C^7−O*C*H$_3$), 4.07 (s, 3H, C^6−O*C*H$_3$), 4.04 (s, 3H, C^3−O*C*H$_3$), 3.76 (d, *J* = 14.7 Hz, 1H, *H*-9), 3.60−3.49 (m, 1H, *H*-11), 3.45 (dd, *J* = 16.2, 2.8 Hz, 1H *H*-14), 3.00 (1H, dd, J = 16.2, 10.6 Hz, *H*-14), 2.63−2.51 (m, 2H, *H*-13a, *H*-11), 2.33−2.23 (m, 1H, *H*-13), 2.18−2.05 (m, 1H, *H*-12), 2.04−1.96 (m, 1H, *H*-12), 1.89−1.75 (m, 1H, *H*-13). ^{13}C NMR, HSQC, HMBC (100 MHz, $CDCl_3$) δ 157.7 (C3), 149.5 (C7), 148.3 (C6), 130.4 (C4b), 126.8 (C8b), 125.4 (C14b), 125.3 (C14a), 125.2 (C1), 123.4 (C8a, C4a), 114.9 (C2), 104.6 (C4), 103.9 (C5), 103.0 (C8), 60.2 (C13a), 56.0 (C^7−O*C*H$_3$), 56.0 (C^6−O*C*H$_3$), 55.5 (C^3−O*C*H$_3$), 55.0 (C11), 53.6 (C9), 33.1 (C14), 31.1 (C13), 21.6 (C12). Spectral data are in agreement with literature values.[31]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01161.

NMR spectra for all compounds and HPLC data of (*S*)-tylophorine (PDF)

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Notes

The authors declare no competing financial interest.

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