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Note

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

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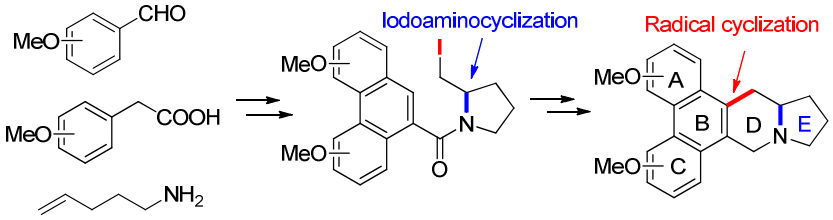
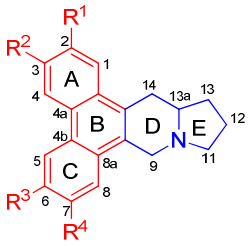
Abstract Graphics



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 as well as (±)-deoxypergularinine in six steps. Using commercially available L-prolinol 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 various biological activities such as anti-tumor,[1] anti-arthritis,[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, 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]



$R^1 = R^2 = R^3 = R^4 =$ 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.

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

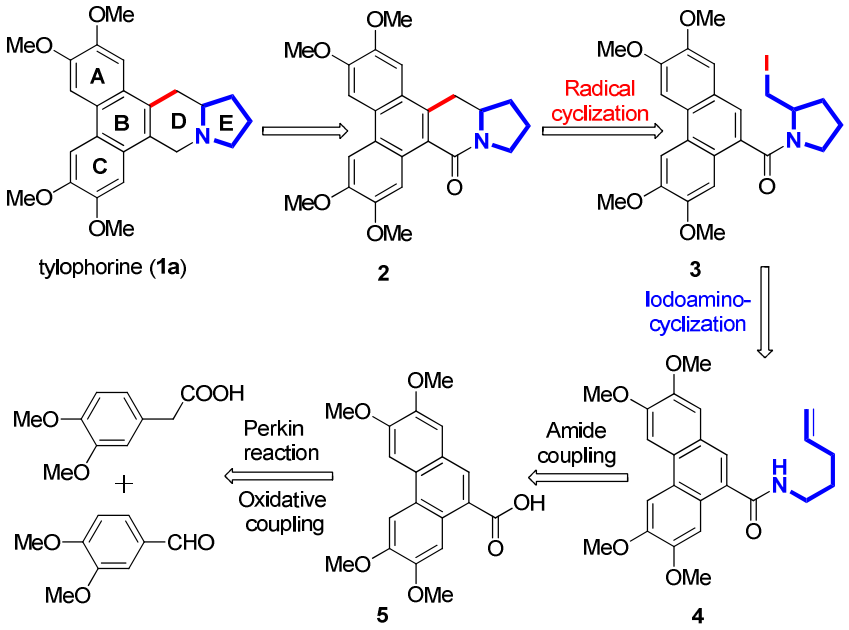
With respect to enantioselective approaches, several enantioselective synthetic strategies have been reported in the literature so far.[8b] One representative strategy, first reported by Rapoport and Buckley,[13] used the ex-chiral-pool-approach which was

also employed in later syntheses based on proline,[14] aminoadipate,[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. Since 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 free radical ring closure process.[22]

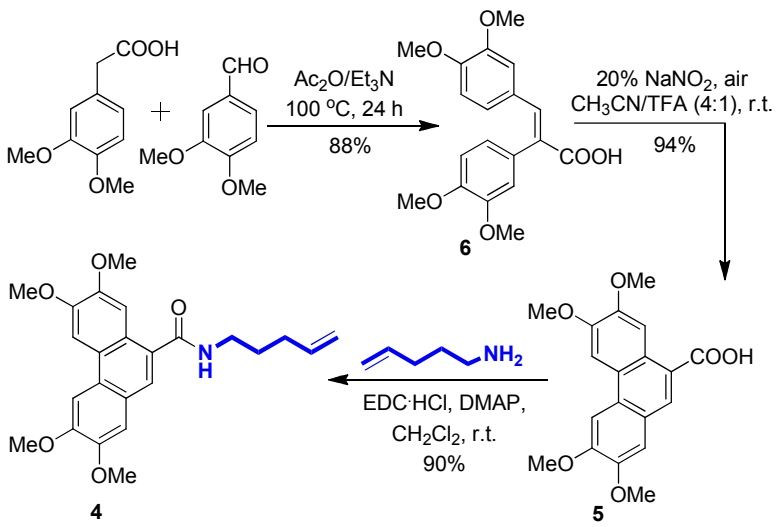
A retrosynthetic analysis for tylophorine is shown in Scheme 1. The target molecule **1a** could be accessible via reduction of amide **2** which was envisioned to be constructed from compound **4** through an iodoaminocyclization followed by a free radical ring closure. Compound **4** could be easily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

Scheme 1. Retrosynthetic analysis of tylophorine.



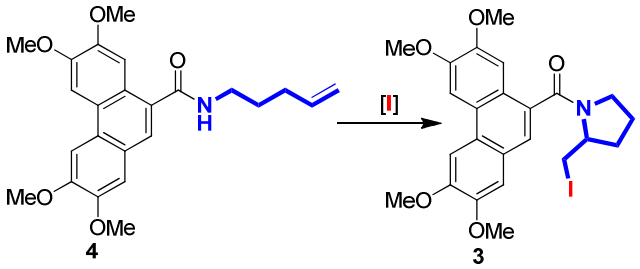
The synthesis began with preparation of 2,3-diphenylacrylic acid **6** by condensation of veratraldehyde and homoveratric acid in a mixture of triethylamine and acetic anhydride. This compound underwent oxidative cyclization upon treatment with sodium nitrite and air in acid medium to furnish the phenanthrene-9-carboxylic 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).

Scheme 2. Synthesis of olefinic amide **4**.



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 only in low yield (entry 2).[26] The substrate was also inert towards N-iodosuccinimide (NIS) (entry 3). However, formation of the desired compound **3** from olefinic amide **4** could be accomplished with molecular iodine and sodium hydrogen carbonate in acetonitrile in moderate yield (entry 4).[27] Prolonged reaction time and elevated reaction temperature 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.

Table 1. Optimization studies for iodoaminocyclization.[a]



4 3

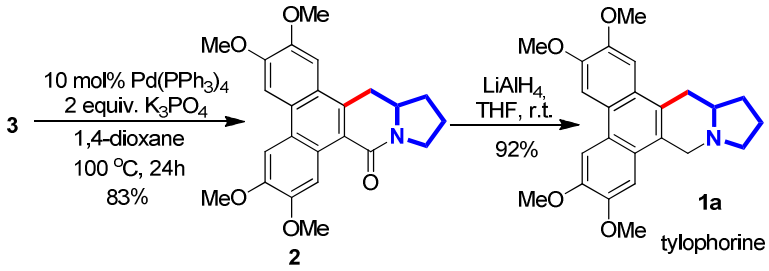
entry	reagent	temp.	isolated yield (%)
1	$PhI(OAc)_2$, KI	r.t.	<1
2	$PhI(OAc)_2$, TMSI	r.t.	27
3	NIS	r.t.	<1
4[b]	I_2, $NaHCO_3$	r.t.	51
5[b,c]	I_2, $NaHCO_3$	90 °C	72

[a] Reaction conditions: substrate (0.5 mmol), reagent (0.55 mmol), CH_2Cl_2 (10 mL), 24 h. [b] reagent (0.3 mmol), CH_3CN as solvent. [c] 36 h.

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 the 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 the 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**,

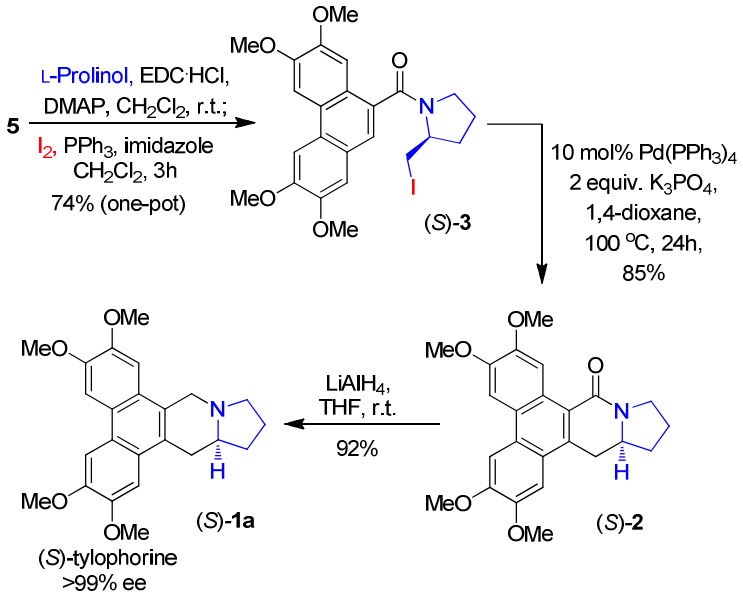
which was obtained in 41% overall yield over six steps.

Scheme 3. Synthesis of (±)-tylophorine.



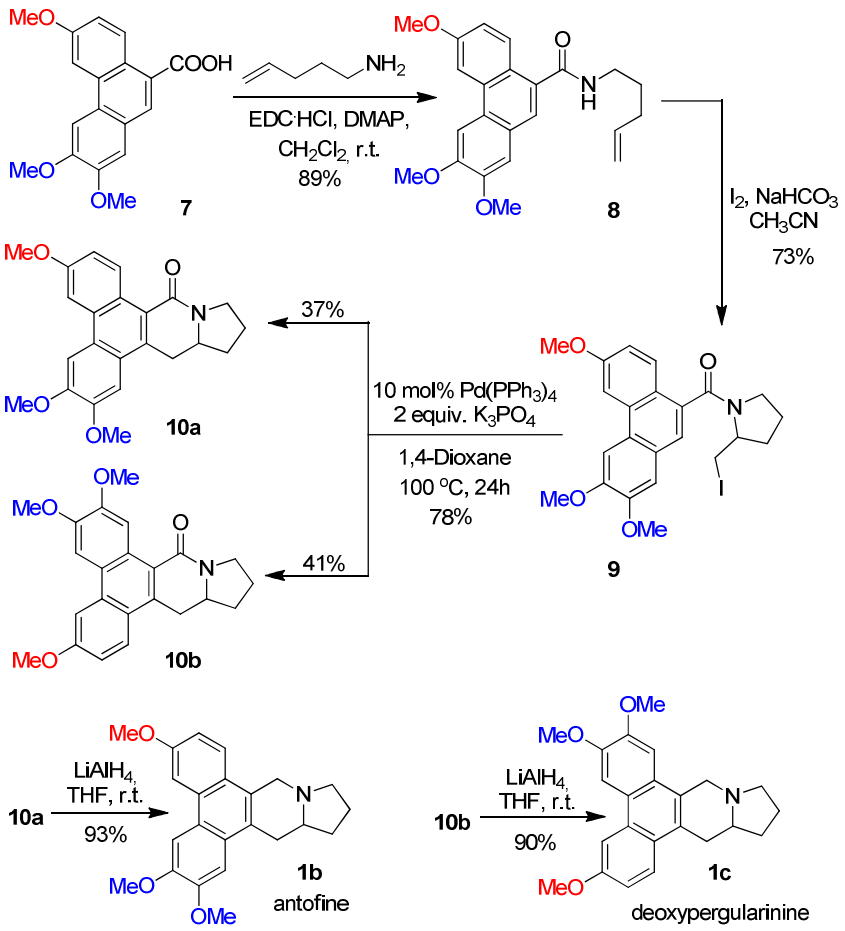
In previous work in the phenanthroquinolizidine series, we have successfully employed a Zard-type radical cyclization of a xanthate to close the D-ring at the same oxidation state. The preparation of the radical precursor was however more lengthy than the present route.[22e] To investigate whether the 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** in a one-pot procedure. Iodide (*S*)-**3** was subjected to the 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 acceptable isolated yield. To our surprise, two products in almost 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** could be separated by flash column chromatography and structure of the compounds were also established by 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.

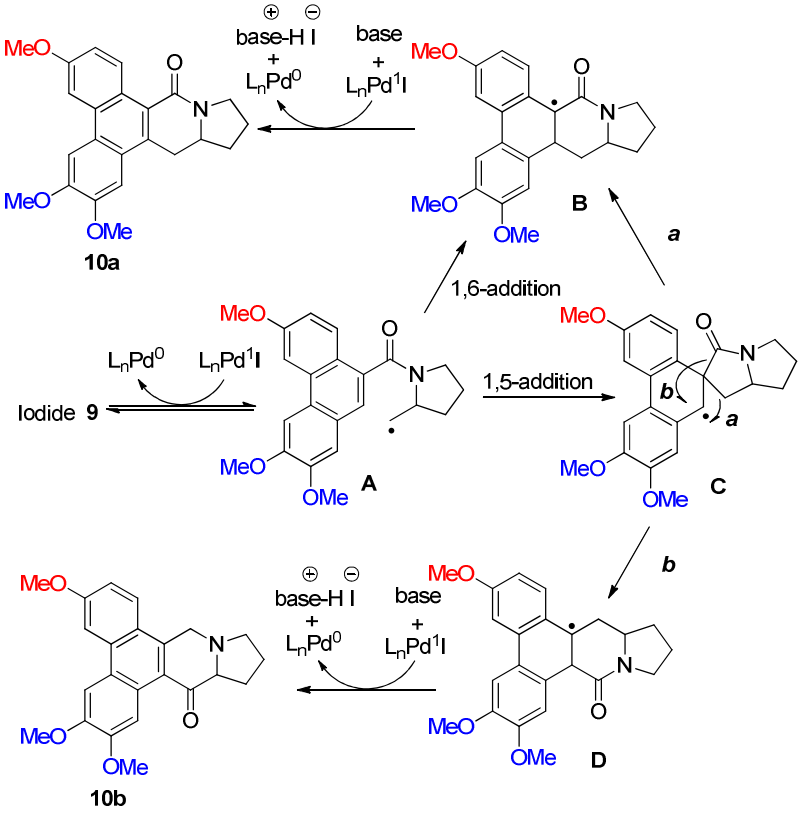
Scheme 5. Synthesis of (±)-antofine and (±)-deoxypergularinine.



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 radical **B** and **D** could occur *via* single-electron

oxidation followed by deprotonation to give the lactam **10a** and **10b**, respectively.

Scheme 6. Plausible mechanism for radical cyclization.



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 equimolar ratio had already been made by Alexanian and coworkers 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 a iodoaminocylization 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 were 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 of 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 ($CDCl_3$: ^1H, δ = 7.26 ppm;

^{13}C, δ = 77.16 ppm. DMSO-d_6: ^{1}H, δ = 2.50 ppm; ^{13}C, δ = 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 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, and 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-dimethylaminopropyl)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 1N 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 (cyclohexane/EtOAc = 2/1) 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=CH_2), 4.07 (s, 3H, C^3-OCH_3), 4.05 (s, 3H, C^6-OCH_3), 3.98 (s, 3H, C^2-OCH_3), 3.96 (s, 3H, C^7-OCH_3), 3.55 (dd, *J* = 13.2, 6.9 Hz, 2H, -NHCH_2-), 2.29–2.18 (m, 2H, -CH_2CH=CH_2), 1.87–1.75 (m, 2H, -CH_2C$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 (*C*10), 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 crude residue, which was purified by flash column chromatography (cyclohexane/EtOAc = 1/1) to give the 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, -CH_2I), 4.14 (s, 3H, C^3-OCH_3), 4.13 (s, 3H, C^6-OCH_3), 4.10–4.08 (m, 1H, H-2'), 4.03 (s, 3H, 3H, C^2-OCH_3), 4.03 (s, 3H, 3H,

C^7-OCH_3), 3.69 (dd, *J* = 9.7, 2.3 Hz, 1H, -CH_2I), 3.44–3.37 (m, 1H, 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 (*C*9), 125.2 (*C*10), 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 ($C^{3,7}$-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(11*H*)-one (**2**). A vial in a glove box under 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 glove box and heated in oil bath at 100 °C, stirring for 24 h. The reaction mixture was allowed to cool to ambient temperature, was quenched with 1N 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 crude residue, which was purified by flash column chromatography (cyclohexane/EtOAc = 1/2) to give lactam **2** as 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 (*C*O), 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*C*H$_3$), 55.9 (*C*13a), 55.2 (C^7-O*C*H$_3$), 45.4 (*C*11), 33.9 (*C*14), 32.5 (*C*12), 23.5 (*C*13). 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 x 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 (EtOAc/MeOH = 1/10) 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-*H1*), 4.52 (d, ^2J = 14.7 Hz, 1H, *H*-9), 4.02 (s, 6H, $C^{3,6}$-OC*H*$_3$), 4.00(s, 3H, C^2-OC*H*$_3$), 4.00 (s, 3H, C^7-OC*H*$_3$), 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 (*C*1), 103.4 (C8), 103.2 (C4), 103.1 (C5), 60.2 (*C*13a), 56.0 ($C^{3,6}$-OCH_3), 55.9 ($C^{2,7}$-OCH_3), 55.2 (*C*11), 54.1 (*C*9), 33.9 (*C*14), 31.3 (*C*12), 21.6 (*C*13). 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 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 1N HCl solution, dried with Na_2SO_4 and concentrated to give crude amide, which was purified by flash column chromatography (cyclohexane/EtOAc = 1/1) to give compound (*S*)-**3** as a yellow oil (395.9 mg, 74%). $[\alpha]_{22}^{D}$= –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(11*H*)-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 (cyclohexane/EtOAc = 1/2) as a

yellow solid (34.6 mg, 85%). Mp: 288–289 °C (ref,[38] Mp: 287–289 °C; ref,[22b] Mp: 286–287 °C). $[\alpha]_{22}^{D}$= +157.9 (c = 1.0, $CHCl_3$) (ref,[39] $[\alpha]_{25}^{D}$ = +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 (EtOAc/MeOH = 1/10) 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%. $[\alpha]_{22}^{D}$= +79.0 (c = 0.5, $CHCl_3$) (ref,[22c] $[\alpha]_{22}^{D}$= +78.9, c = 0.5, $CHCl_3$; ref,[39] $[\alpha]_{22}^{D}$= +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 (cyclohexane/EtOAc = 2/1) 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(*C*OOH),

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-O*C*H$_3$), 55.2 (C^2-O*C*H$_3$), 54.9 (C^6-O*C*H$_3$). 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 (cyclohexane/EtOAc = 2/1) 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, -C*H*=CH$_2$), 5.17–4.99 (m, 2H, -CH=C*H*$_2$), 4.04 (s, 3H, C^3-OC*H*$_3$), 3.99 (s, 3H, C^2-OC*H*$_3$), 3.97 (s, 3H, C^6-OC*H*$_3$), 3.54 (dd, *J* = 13.2, 6.9 Hz, 2H, -NHC*H*$_2$-), 2.26–2.18 (m, 2H, -C*H*$_2$CH=CH$_2$), 1.85–1.75 (m, 2H, -*C*H$_2$C*H*$_2$CH$_2$-). ^{13}C NMR, HSQC, HMBC (100 MHz, $CDCl_3$) δ=170.0 (*C*ONH), 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-O*C*H$_3$), 55.9 (C^2-O*C*H$_3$), 55.5 (C^6-O*C*H$_3$), 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 (cyclohexane/EtOAc = 2/1) 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-*H*1), 4.34 (d, *J* = 6.3 Hz, 1H, -CH_2I), 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, -CH_2I), 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 glove box, a vial was charged with iodide **9** (50.5 mg, 100 μmol) and 1,4-dioxane (1 mL) under 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 glove box and heated in oil bath to 100 °C under stirring for 24 h. The reaction mixture was allowed to cool to ambient temperature, quenched with 1N 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 crude residue, which was purified by flash column chromatography (cyclohexane/EtOAc = 1/2) to give lactam **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, cyclohexane/EtOAc = 1:2. 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-OCH_3), 4.08 (s, 3H, C^2-OCH_3), 4.04 (s, 3H, C^6-OCH_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, cyclohexane/EtOAc = 1:2. 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-OCH_3), 4.11 (s, 3H, C^6-OCH_3), 4.06 (s, 3H, C^3-OCH_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 (EtOAc/MeOH = 15/1) 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-O*C*H_3), 4.08 (s, 3H, C^2-O*C*H_3), 4.04 (s, 3H, C^6-O*C*H_3), 3.77 (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-OCH_3), 55.9 (C^2-OCH_3), 55.5 (C^6-OCH_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 (EtOAc /MeOH = 15/1) 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-OCH_3), 4.07 (s, 3H, C^6-OCH_3), 4.04 (s, 3H, C^3-OCH_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-OCH_3), 56.0 (C^6-OCH_3), 55.5 (C^3-OCH_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

NMR spectra for all compounds and HPLC data of (*S*)-tylophorine. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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