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The First Enantioselective Approach to 13a-Methyl-14-hydroxyphenanthroindolizidine Alkaloids – Synthetic Studies towards Hypoestestatin 2

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The first enantioselective approach to 13a-methyl-14-hydroxyphenanthroindolizidine alkaloids was achieved in six linear steps from phenanthryl alcohol and features a highly substrate-dependent Parham cycloacylation and Seebach's enantioselective alkylation as the key steps. The route is concise, protecting-group free, provides access to all stereoisomers, and works on a gram scale. In addition to the putative structure of hypoestestatin 2, the other three stereoisomers and two structurally related analogues were synthesized, none of which shows identical NMR spectra to those reported for natural hypoestestatin 2, which indicates that further structure revision is required.

Introduction

Phenanthroindolizidine alkaloids represent a group of pentacyclic natural products isolated mainly from *Cynanchum, Pergularia*, *Tylophora*, and some genera of the *Asclepiadaceas* family. Owing to their low natural abundance and potent biological activity, including antitumor, antiviral, antibacterial, anti-inflammatory, and antifungal activities, they have attracted great interest from synthetic and pharmaceutical chemists.[1] More than 60 members of this class have been isolated and characterized, among which 13a-H members represented by antofine (**1a**) and 14-hydroxyantofine (**1b**) have been widely investigated both in synthetic strategies and in their biological activities (Figure 1). In 1984, two structurally unique 13a-methylphenanthroindolizidine alkaloids hypoestestatin 1 (**2a**) and hypoestestatin 2 (**2b**) were reported by Pettit et al.[2] Meanwhile, they reported that both hypoestestatins exhibited very impressive cytotoxicity against murine P-388 cell line [ED_{50} (50% effective dose) values were as low as 10^{-5} μg/mL;]. Bhutani et al. reported another two 13a-methylphenanthroindolizidines, namely, 13a-methyltylohirsutine (**3a**) and 13a-methyltylohirsutinidine (**3b**), in the same year.[3] Some other analogues (**3c** and **4**) and seco-analogues were also subsequently isolated.[4]

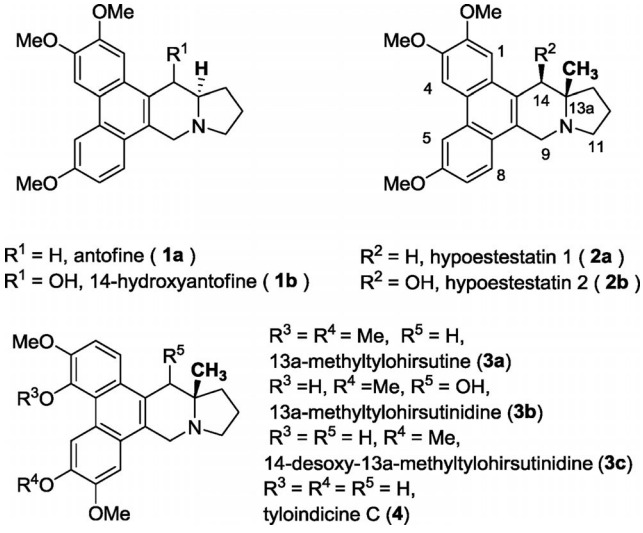

Figure 1. Representative structures of phenanthroindolizidine alkaloids.

Although a number of synthetic routes to phenanthroindolizidine alkaloids have been published in recent years,[5] the synthesis of 13a-methyl members has rarely been reported and, thus, their bioactivities are widely unexamined. One of the major challenges is the installation (especially in an enantioselective manner) of the angular methyl group. In 2007, the first total synthesis of racemic 13a-methylphenanthroindolizidine was reported by Ishibashi et al., in which cascade radical cyclization was used as the key step.[6] Recently, we reported an enantioselective total synthesis of 13a-methyl phenanthroindolizidine, which uses Seebach's self-regeneration of stereochemistry (SRS) approach as the key step, and reached the conclusion that the structure of hypoestestatin 1 (**2a**) had been misassigned.[7] As a part of

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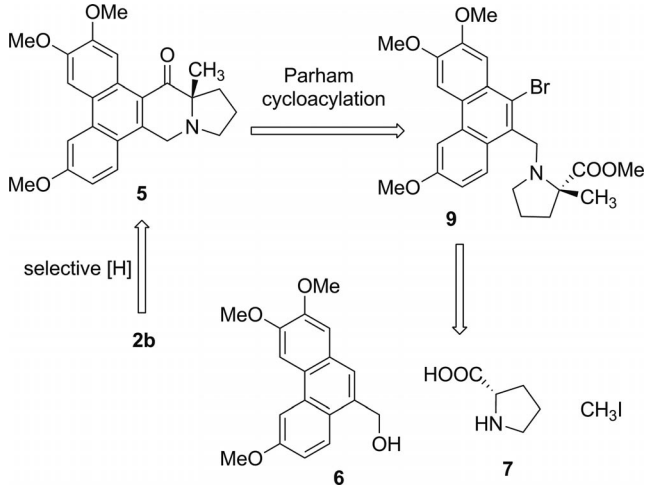
our ongoing research into the synthesis and biological evaluation of phenanthroindolizidine alkaloids,[1d,5a,5e,8] we herein report the first enantioselective and general approach to the widely unexplored 14-hydroxy-13a-methylphenanthroindolizidine alkaloids.

Results and Discussion

Seebach's concept of "self-regeneration of stereochemistry (SRS)",[9] a strategy for the stereoselective alkylation of amino acids was employed in our synthetic program, which provided another opportunity to showcase its powerful application in the total synthesis of natural products.[10] In addition, a very substrate-dependent Parham-type cycloacylation with an ester group as internal electrophile was also performed highly efficiently in our synthesis.

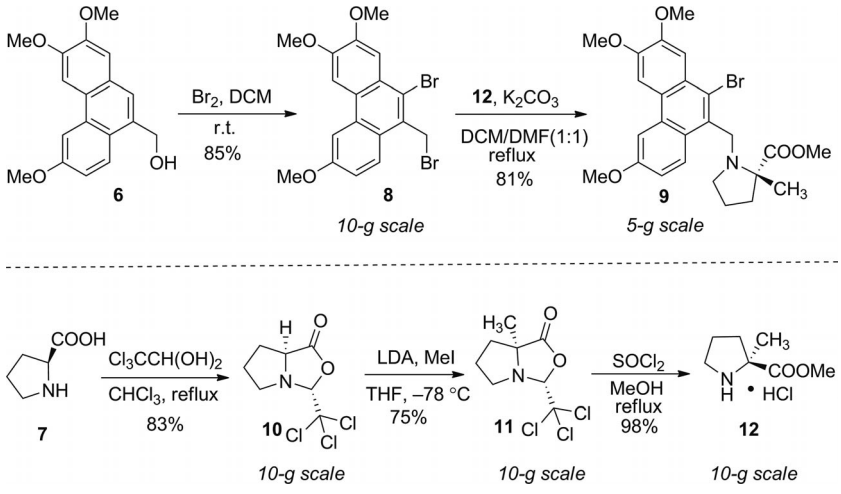
Retrosynthetically, hypoestestatin 2 (**2b**) could be derived from ketone **5** by stereoselective reduction, thus both 14-hydroxy isomers could be obtained from the same intermediate (Scheme 1). It seems to be that ketone **5** could be readily prepared by an intramolecular Friedel–Crafts reaction; however, owing to the presence of the nitrogen atom, such an apparently easy transformation proved to be very inefficient.[11] Thus, the construction of ketone **5** was planned by a Parham-type cycloacylation and the methyl group in ketone **5** was envisioned to be introduced enantioselectively by Seebach's SRS strategy from optical proline. The Parham cycloacylation precursor **9** could be derived from readily prepared phenanthryl alcohol **6** and commercially available L-proline **7** and methyl iodide.



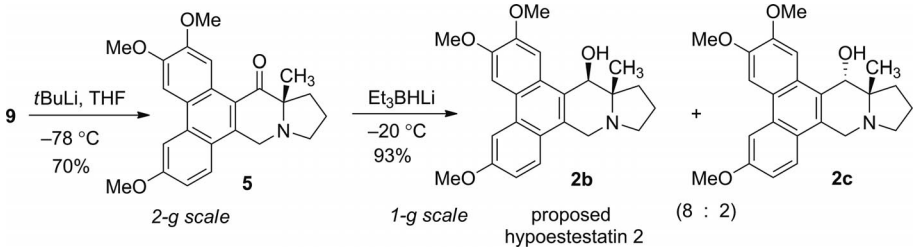
Scheme 1. Retrosynthetic analysis of the proposed structure of hypoestestatin 2 (**2b**).

The synthesis of the key intermediate **9** commenced with the known phenanthryl alcohol **6** (Scheme 2).[12] After treatment of **6** with bromine in dichloromethane (DCM), dibromide **8** was obtained in excellent yield.[13] The enantiopure proline derivative **12** was prepared from L-proline in three steps by Seebach's SRS strategy.[14] The modified oxazolidinone **10** was obtained through condensation of L-proline and chloral hydrate as a white crystalline solid, which makes its manipulation and storage very convenient. After consequent stereoselective methylation and methanolysis, enantiopure **12** could be obtained in 10 gram scale. It is worth mentioning that the seemingly easy coupling of compound **12** and dibromide **8** proved to be a weighty problem, because compound **12** is very hygroscopic and the dibromide **8** is sensitive to moisture. After extensive screening of bases [such as Et_3N, iPr_2NEt, diazabicycloundecene (DBU), K_2CO_3, Na_2CO_3, AcONa, Na_2SO_3, LiOH, and basic Al_2O_3], solvents [dichloromethane, tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF) and mixtures of them], and reaction temperature, the coupling reaction proceeded smoothly under the optimal reaction conditions [K_2CO_3 (5 equiv.), dichloromethane/DMF (1:1), reflux].

With the key intermediate **9** in hand, we were set for the Parham-type cycloacylation (Scheme 3). Notably, although a great many Parham cycloacylation reactions have been documented, most of the internal electrophiles were acids,[15] amides,[16] Weinreb amides,[17] carboxamides, and carbamates,[18] presumably as a consequence of the com-



Scheme 2. Synthesis of the key intermediate **9**.

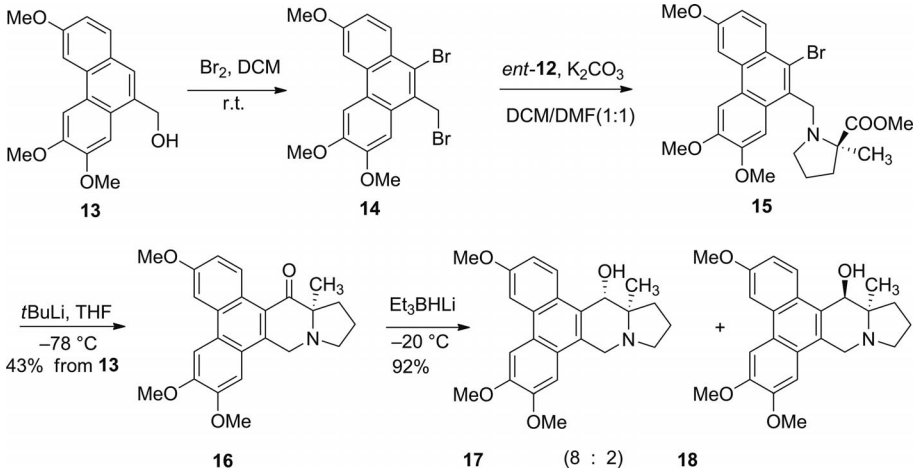


Scheme 3. Completion of the synthesis of the proposed hypoestestatin 2.

plex-induced proximity effect (CIPE).[19] The use of an internal ester group as the electrophile for a Parham cycloacylation has rarely been reported and is less efficient,[20] mainly because of the instability of the intermediate generated from acylation of the aryllithium and the possibility of competitive deprotonation with metal–halogen exchange. Fortunately, such a Parham cycloacylation in substrate **9** worked very well even in gram scale after simple optimization of the reaction conditions. The stereoselective reduction of ketone **5** was examined with a variety of hydride reagents. It was found that superhydride ($LiEt_3BH$) as the reducing agent gave the best selectivity (**2b**/**2c** 8:2), $LiAlH_4$ gave roughly the opposite selectivity, and $NaBH_4$ and bulky hydride agents such as DIBAL-H and L-selectride gave no reaction. As the diastereomers could be easily separated by column chromatography, the selective reduction was not further optimized.

Unfortunately, the ^1H NMR spectra (in CD_3OD and $CDCl_3$) of the synthetic **2b** {$[a]_D^{20}$ = +65.5 (*c* = 0.58, CH_2Cl_2)} and **2c** {$[a]_D^{20}$ = +82.1 (*c* = 0.56, CH_2Cl_2)} differ significantly from that of natural hypoestestatin 2 {$[a]_D^{31}$ = –80.0 (*c* = 0.53, CH_2Cl_2)}, and they have optical rotations opposite in sign.[2] In the ^1H NMR spectrum (in CD_3OD) of a synthetic sample of **2b**, the signal of the angular methyl group appeared as singlet at δ = 1.09 ppm, whereas the corresponding signal reported for hypoestestatin 2 appeared at δ = 1.25 ppm. We speculated that the lower-field shift of the isolated product is a result of the formation of the ammonium salt (e.g., formed with trace amounts of hydrochloric acid during the isolation process). With incremental amounts of trifluoroacetic acid added to the synthetic sample of **2b**, the signal of the angular methyl group shifted from δ = 1.09 to 1.88 ppm; however, the chemical shifts of the aromatic protons also do not match the reported data. By using a similar strategy, *ent*-**2b** {$[a]_D^{20}$ = –60.4 (*c* = 0.55, CH_2Cl_2)} and *ent*-**2c** {$[a]_D^{20}$ = –82.0 (*c* = 0.56, CH_2Cl_2)} were also synthesized from D-proline and phenanthryl alcohol **6** and its optical rotation had the same sign, which indicated that the sign of the specific rotation was determined by the absolute configuration of C-13a. Therefore, the absolute configuration of the proposed hypoestestatin 2 might also be wrong if the original proposed skeleton of hypoestestatin 2 was correct.

Based on the distributions of the methoxy groups of the over 60 known phenanthroindolizidine alkaloids and Pettit's original elucidation,[2] we speculated that the 3,6,7-trimethoxy arrangement is correct. By using alcohol **13** as starting material, another two analogues **17** and **18** were synthesized through the same strategy (Scheme 4). Notably, in addition to dibromide **14**, about 30% tribromide was also produced and they were inseparable. Without separation, the mixture was coupled with proline derivative *ent*-**12** and then treated with 3 equiv. *t*BuLi; ketone **16** was obtained as a single product in 43% yield from alcohol **13**. Disappointingly, although great synthetic effort was taken, the NMR spectra of both **17** and **18** also did not match with those of hypoestestatin 2 (Table 1, ^{1}NMR spectroscopic data of isolated product and synthetic samples).



Scheme 4. Synthesis of 3,6,7-trimethoxy analogues.

Table 1. ^{1}H NMR spectroscopic data (in CD_3OD) of hypoestestatin 2 and synthetic structures.

Hypoestestatin 2	^{1}H NMR: δ = 7.95 (2 H), 7.58 (1 H), 7.11 (1 H, d, J = 7.5 Hz), 7.09 (1 H, d, J = 7.5 Hz), 4.06 (3 H, s, OMe), 4.01 (6 H, s, 2× OMe), 1.25 (3 H, s, 13a-Me) ppm. ^{13}C NMR data was not given.
2b	^{1}H NMR: δ = 8.10 (s, 1 H), 8.03 (s, 1 H), 8.00 (d, J = 2.4 Hz, 1 H), 7.87 (d, J = 9.1 Hz, 1 H), 7.23 (dd, J = 9.0, 2.4 Hz, 1 H), 4.07 (s, 3 H), 4.03 (s, 3 H), 4.02 (s, 3 H), 1.09 (s, 3 H) ppm.
2c	^{1}H NMR: δ = 8.05 (s, 1 H), 7.95 (d, J = 2. 1 Hz, 1 H), 7.79 (s, 1 H), 7.40 (d, J = 9.0 Hz, 1 H), 7.02 (dd, J = 9.0, 2.1 Hz, 1 H), 4.86 (s, 1 H), 4.11 (s, 3 H), 4.07 (s, 3 H), 4.04 (s, 3 H), 0.82 (s, 3 H) ppm.
17	^{1}H NMR: δ = 8.50 (d, J = 9.2 Hz, 1 H), 8.03 (s, 1 H), 7.97 (d, J = 2.3 Hz, 1 H), 7.26 (s, 1 H), 7.20 (dd, J = 9.2, 2.4 Hz, 1 H), 4.06 (s, 3 H), 4.01 (s, 6 H), 1.10 (s, 3 H) ppm.
18	^{1}H NMR: δ = 8.10 (d, J = 9.2 Hz, 1 H), 7.73 (d, J = 2.4 Hz, 1 H), 7.60 (s, 1 H), 7.08 (dd, J = 9.1, 2.4 Hz, 1 H), 6.06 (s, 1 H), 4.55 (s, 1 H), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.59 (s, 3 H), 0.46 (s, 3 H) ppm.

Conclusions

In conclusion, the first enantioselective approach to 14-hydroxy-13a-methylphenanthroindolizidine alkaloids was achieved in six linear steps in 30% overall yield. The route is protecting-group free, practical, and adaptable to all of the stereoisomers, which is of importance for biological and pharmaceutical studies. In addition, a detailed study of the possible structure of hypoestestatin **2** was also conducted.

Experimental Section

General: Melting points were determined with an X-4 binocular microscope melting-point apparatus (Beijing Tech Instruments Co, Beijing, China). Chemical shifts (δ) are given in parts per million (ppm) and were measured downfield from internal tetramethylsilane. High-resolution mass spectra were obtained with an FT-ICR MS spectrometer (Ionspec, 7.0 T). Optical rotations were measured with an Autopol IV auto digital polarimeter (Rudolph Research Analytical). All anhydrous solvents were dried and purified by standard techniques before use. All reagents were purchased from commercial suppliers without further purification. Reactions were monitored by TLC on plates (GF254) supplied by Yantai Chemicals (China) with UV light as visualizing agent. If not specially mentioned, flash column chromatography was performed with silica gel (200–300 mesh) supplied by Tsingtao Haiyang Chemicals (China).

(3*R*,7a*S*)-3-(Trichloromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one (10):[14] To a suspension of L-proline **7** (11.5 g, 100 mmol) in chloroform (500 mL) was added 2,2,2-trichloroethane-1,1-diol (chloral hydrate, 26.5 g, 120 mmol). A 25-mL Dean–Stark trap topped with a reflux condenser was attached to the reaction vessel, and the reaction mixture was heated at reflux until L-proline was no longer visibly suspended. The reaction mixture was evaporated under reduced pressure, and the resulting brown crystalline solid was recrystallized from ethanol to give **10** (18.6 g, 83%) as colorless to light brown crystals, m.p. 110–111 °C (ref.[14] 107–109 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.17 (s, 1 H, 7a-H) 4.12 (dd, J = 8.8, 4.6 Hz, 1 H, 3-H), 3.48–3.38 (m, 1 H, 4-H), 3.18–3.08 (m, 1 H, 4-H), 2.29–2.17 (m, 1 H, 6-H), 2.16–2.08 (m, 1 H, 6-H), 2.00–1.88 (m, 1 H, 5-H), 1.82–1.68 (m, 1 H, 5-H) ppm. HRMS (ESI) calcd. for $C_7H_8Cl_3NO_2Na$ $[M + Na]^+$ 265.9518, found 265.9518; $[\alpha]_D^{25}$ = +33.4 (c = 2, C_6H_6; ref.[14] +34.2, c = 2, C_6H_6; ref.[21] +33, c = 2, C_6H_6).

(3*R*,7a*S*)-7a-Methyl-3-(trichloromethyl)tetrahydropyrrolo[1,2-*c*]-oxazol-1(3*H*)-one (11): To a solution of diisopropylamine (13.5 mL, 96 mmol) in THF (100 mL) was added *n*BuLi (42 mL, 2.4 M, 100.8 mmol) dropwise at –78 °C under an atmosphere of nitrogen. Ten minutes later, the freshly prepared lithium diisopropylamide (LDA) was transferred to a solution of oxazolidinone **10** (18 g, 80 mmol) in THF (300 mL) over 30 min at –78 °C, and the solution slowly turned brown. After 90 min, MeI (5.9 mL, 115.2 mmol) was added dropwise, and the reaction mixture was stirred at the same temperature for one hour and then slowly warmed to room temperature over 3 h. The reaction was quenched with aqueous saturated ammonium chloride (100 mL). After separation, the aqueous phase was extracted with ethyl acetate (3× 50 mL), and the combined extracts were evaporated under reduced pressure to give a yellow oily liquid, which was dissolved in dichloromethane (200 mL). The solution was washed with water (2× 50 mL), dilute hydrochloric acid (2× 50 mL), and brine (2× 50 mL), dried with magnesium sulfate, filtered, and then evaporated in vacuo. The residue was purified by flash column chromatography to give compound **11** (14.3 g, 75%) as a colorless to light yellow solid, m.p. 58–59 °C (ref.[14] 55–57 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.99 (s, 1 H, 7a-H), 3.44–3.34 (m, 1 H, 4-H), 3.28–3.15 (m, 1 H, 4-H), 2.27–2.18 (m, 1 H, 6-H), 2.03–1.92 (m, 1 H, 6-H), 1.92–1.73 (m, 2 H, 5-H), 1.53 (s, 3 H, Me) ppm.

Methyl (*S*)-2-Methylpyrrolidine-2-carboxylate Hydrochloride (12): To a solution of **11** (11.9 g, 50 mmol) in anhydrous methanol (150 mL) at 0 °C under an atmosphere of nitrogen was added thionyl chloride (8.7 mL, 120 mmol) dropwise. The reaction mixture was stirred at the same temperature for 30 min, at room temperature for an additional 30 min, and then heated at reflux for 4 h. The volatiles were removed under reduced pressure, and the residue was suspended in anhydrous toluene (40 mL) and then concentrated to remove traces of thionyl chloride. Trituration with anhydrous diethyl ether yielded a brown solid. The yellow diethyl ether was decanted, and the solid was washed with anhydrous diethyl ether (3× 30 mL). Trace amounts of diethyl ether were removed in vacuo to give compound **12** (8.8 g, 98%) as a pale brown solid, which was used without further purification, m.p. 142–144 °C (ref.[22] 133–135 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.48 (br. s, 1 H, NH_2), 9.53 (br. s, 1 H, NH_2), 3.86 (s, 3 H, OMe), 3.62 (br. s, 2 H, 5-H), 2.54–2.31 (m, 1 H, 3-H), 2.22–1.98 (m, 3 H, 3-H, 4-H), 1.86 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 68.8, 53.7, 45.3, 35.9, 22.6, 21.3 ppm.

10-Bromo-9-(bromomethyl)-2,3,6-trimethoxyphenanthrene (8): To a suspension of compound **6** (7.4 g, 24.8 mmol) in dichloromethane (500 mL) was added bromine [1.42 mL, 27.3 mmol, in dichloromethane (50 mL)] dropwise at room temperature. Three hours later, the reaction mixture was evaporated at reduced pressure, and the residue was purified by column chromatography [petroleum ether (PE)/DCM, 1:3] to give compound **8** (9.3 g, 85%) as a pale solid, m.p. 184–186 °C (ref.[13c] 180–186 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, J = 9.1 Hz, 1 H, Ar-H), 7.80 (d, J = 2.4 Hz, 1 H, Ar-H), 7.78 (s, 2 H, Ar-H), 7.27 (dd, J = 9.1, 2.3 Hz, 1 H, Ar-H), 5.33 (s, 2 H, 9-H), 4.10 (s, 3 H, OMe), 4.08 (s, 3 H, OMe), 4.01 (s, 3 H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 150.1, 150.1, 130.9, 129.4, 126.5, 125.8, 125.6, 124.1, 123.0, 116.0, 109.6, 104.9, 103.2, 56.1, 56.0, 55.6, 45.0 ppm.

Methyl (*S*)-[(10-Bromo-2,3,6-trimethoxyphenanthren-9-yl)methyl]-2-methylpyrrolidine-2-carboxylate (9): To a suspension of **8** (5.3 g,

12 mmol) and potassium carbonate (8.3 g, 60 mmol) in a mixture of dichloromethane and dimethylformamide (1:1, 200 mL) was added **12** (2.58 g, 14.4 mmol). The reaction mixture was heated at reflux for 10 h. The mixture was cooled to room temperature, the volatiles were evaporated at reduced pressure, and the residue was dissolved in dichloromethane (200 mL) and then washed with water (3× 100 mL) and brine (100 mL). The organic phase was dried with magnesium sulfate, filtered, and then evaporated in vacuo. After concentration, the crude product was purified by column chromatography (PE/DCM, 2:1, PE/DCM, 1:3) to give compound **9** (4.87 g, 81%) as a white solid, m.p. 150–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, J = 9.2 Hz, 1 H, Ar-H), 7.89 (s, 1 H, Ar-H), 7.87 (s, 1 H, Ar-H), 7.83 (s, 1 H, Ar-H), 7.21 (d, J = 9.2 Hz, 1 H, Ar-H), 4.50 (t, J = 14.0 Hz, 2 H, benzyl-CH_2), 4.12 (s, 3 H, OMe), 4.09 (s, 3 H, OMe), 4.02 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 3.01–2.92 (m, 1 H, 5-H), 2.72–2.66 (m, 1 H, 5-H), 2.34–2.22 (m, 1 H, 3-H), 1.82–1.53 (m, 3 H, 3-H, 4-H), 1.61 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.9, 158.1, 149.8, 149.4, 131.4, 130.7, 128.2, 126.2, 126.1, 125.1, 122.6, 115.1, 109.9, 104.2, 103.3, 67.6, 56.1, 56.0, 55.5, 51.5, 50.6, 49.8, 38.0, 21.5, 21.0 ppm. HRMS (ESI) calcd. for $C_{25}H_{29}BrNO_5$ [M + H]$^+$ 502.1229, found 502.1223; $[a]_D^{20}$ = +42.7 (c = 1.03, $CHCl_3$).

(*S*)-2,3,6-Trimethoxy-13a-methyl-11,12,13,13a-tetrahydrodibenzo-[*f*,*h*]pyrrolo[1,2-*b*]isoquinolin-14(9*H*)-one (5): To a solution of **9** (1.83 g, 3.6 mmol) in anhydrous THF (150 mL) was added *t*BuLi (5.0 mL, 1.6 M, 7.9 mmol) dropwise at –78 °C under an atmosphere of nitrogen. The reaction mixture was stirred at the same temperature for 1.5 h and then quenched with aqueous ammonium chloride (50 mL). After separation, the aqueous phase was extracted with ethyl acetate (3× 100 mL). The organic extracts were evaporated under reduced pressure, and the residue was dissolved in dichloromethane (100 mL). The solution was then washed with water (3× 100 mL) and brine (100 mL), dried with magnesium sulfate, and filtered. After concentration, the crude product was purified by column chromatography [PE/ethyl acetate(EA), 1:1, DCM/methanol, 30:1] to give compound **5** (0.99 g, 70%) as a yellow solid, m.p. 150–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.10 (s, 1 H, Ar-H), 7.99 (d, J = 9.2 Hz, 1 H, Ar-H), 7.87 (d, J = 2.4 Hz, 1 H, Ar-H), 7.87 (s, 1 H, Ar-H), 7.25 (dd, J = 9.2, 2.4 Hz, 1 H, Ar-H), 4.71 (s, 2 H, 9-H), 4.11 (s, 3 H, OMe), 4.10 (s, 3 H, OMe), 4.05 (s, 3 H, OMe), 3.23–3.16 (m, 1 H, 11-H), 3.09–3.01 (m, 1 H, 11-H), 2.72–2.65 (m, 1 H, 13-H), 1.95–1.76 (m, 3 H, 12-H, 13-H), 1.41 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.7, 160.4, 150.3, 148.7, 137.9, 134.4, 126.8, 124.6, 124.5, 122.4, 120.7, 115.8, 108.1, 104.6, 103.1, 68.2, 55.9, 55.9, 55.6, 51.8, 45.6, 35.2, 20.7, 19.5 ppm. HRMS (ESI) calcd. for $C_{24}H_{26}NO_4$ [M + H]$^+$ 392.1862, found 392.1863; $[a]_D^{20}$ = +42.1 (c = 0.56, $CHCl_3$).

Proposed Structure of Hypoestestatin 2 (2b): To a solution of **5** (1.02 g, 2.6 mmol) in THF (100 mL) was slowly added lithium triethylboronhydride (13 mL, 1 M, 13 mmol) at 0 °C under an atmosphere of nitrogen. Two hours later, the reaction mixture was quenched with aqueous saturated ammonium chloride (20 mL). After separation, the aqueous phase was extracted with ethyl acetate (3× 60 mL), and the organic extracts were evaporated under reduced pressure. The residue was purified by column chromatography (DCM/MeOH, 30:1, DCM/MeOH, 10:1) to give **2b** (0.76 g) and **2c** (0.19 g) in a combined yield of 93%. Compound **2b** was obtained as a light yellow solid, m.p. 120–124 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 8.10 (s, 1 H, Ar-H), 8.03 (s, 1 H, Ar-H), 8.00 (d, J = 2.4 Hz, 1 H, Ar-H), 7.87 (d, J = 9.1 Hz, 1 H, Ar-H), 7.23 (dd, J = 9.0, 2.4 Hz, 1 H, Ar-H), 5.21 (s, 1 H, 14-H), 4.29 (d, J = 16.0 Hz, 1 H, 9-H), 4.10 (d, J = 16.0 Hz, 1 H, 9-H), 4.07 (s, 3 H, OMe), 4.03 (s, 3 H, OMe), 4.02 (s, 3 H, OMe), 3.19–3.09 (m, 1 H, 11-H), 2.99–2.90 (m, 1 H, 11-H), 2.17–1.90 (m, 4 H, 12-H, 13-H), 1.09 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 159.8, 150.1, 149.8, 132.3, 129.2, 128.9, 128.0, 126.2, 125.9, 124.7, 116.8, 109.0, 105.3, 105.2, 75.2, 64.7, 56.5, 56.3, 56.0, 51.9, 48.8, 39.5, 21.5, 12.3 ppm. HRMS (MALDI) calcd. for $C_{24}H_{28}NO_4$ [M + H]$^+$ 394.2018, found 394.2015; $[a]_D^{20}$ = +65.5 (c = 0.58, CH_2Cl_2). Compound **2c** was obtained as a light yellow solid, m.p. 130–133 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 8.05 (s, 1 H, Ar-H), 7.95 (d, J = 2. 1 Hz, 1 H, Ar-H), 7.79 (s, 1 H, Ar-H), 7.40 (d, J = 9.0 Hz, 1 H, Ar-H), 7.02 (dd, J = 9.0, 2.1 Hz, 1 H, Ar-H), 4.86 (s, 1 H, 14-H), 4.11 (s, 3 H, OMe), 4.07 (s, 3 H, OMe), 4.04 (s, 3 H, OMe), 3.83 (d, J = 16.0 Hz, 1 H, 9-H), 3.60 (d, J = 16.0 Hz, 1 H, 9-H), 3.22–3.14 (m, 1 H, 11-H), 2.69 (dd, J = 17.2, 8.8 Hz, 1 H, 11-H), 2.61 (dd, J = 17.2, 8.8 Hz, 1 H, 13-H), 2.07–1.95 (m, 2 H, 12-H, 13-H), 1.73–1.64 (m, 1 H, 12-H), 0.82 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 159.8, 151.0, 150.1, 132.3, 128.6, 127.9, 127.6, 125.9, 125.6, 124.2, 116.7, 106.7, 105.4, 105.2, 70.4, 64.1, 56.6, 56.4, 55.9, 51.9, 48.9, 32.8, 21.1, 13.8 ppm. HRMS (MALDI) calcd. for $C_{24}H_{28}NO_4$ [M + H]$^+$ 394.2018, found 394.2019; $[a]_D^{20}$ = +82.1 (c = 0.56, CH_2Cl_2).

Methyl (*R*)-1-[(10-Bromo-2,3,6-trimethoxyphenanthren-9-yl)methyl]-2-methylpyrrolidine-2-carboxylate (*ent*-9): By using a similar synthetic procedure as that for **9**, *ent*-**9** (80%) was obtained as a pale white solid, m.p. 137–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (d, J = 9.2 Hz, 1 H, Ar-H), 7.87 (s, 1 H, Ar-H), 7.84 (s, 1 H, Ar-H), 7.81 (d, J = 2.5 Hz, 1 H, Ar-H), 7.20 (dd, J = 9.2, 2.5 Hz, 1 H, Ar-H), 4.49 (d, J = 12.4 Hz, 1 H, benzyl-CH_2), 4.46 (d, J = 12.4 Hz, 1 H, benzyl-CH_2), 4.11 (s, 3 H, OMe), 4.08 (s, 3 H, OMe), 4.01 (s, 3 H, OMe), 3.84 (s, 3 H, COOMe), 3.01–2.90 (m, 1 H, 5-H), 2.72–2.66 (m, 1 H, 5-H), 2.34–2.22 (m, 1 H, 3-H), 1.82–1.53 (m, 3 H, 3-H, 4-H), 1.62 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.9, 158.0, 149.8, 149.3, 131.3, 130.7, 128.2, 126.2, 126.0, 125.1, 122.5, 115.1, 109.9, 104.2, 103.2, 67.5, 56.1, 56.0, 55.5, 51.5, 50.6, 49.8, 38.0, 21.5, 21.0 ppm. HRMS (ESI) calcd. for $C_{25}H_{29}BrNO_5$ [M + H]$^+$ 502.1229, found 502.1224; $[a]_D^{20}$ = –37.5 (c = 0.64, $CHCl_3$).

(9a*S*)-3,6,7-Trimethoxy-9a-methyl-9a,10,11,12,12a,13-hexahydro-9*H*-cyclopenta[*b*]triphenylen-9-one (*ent*-5): By using a similar synthetic procedure as that for **5**, *ent*-**5** (65%) was obtained as a light yellow solid, m.p. 147–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.10 (s, 1 H, Ar-H), 8.0 (d, J = 9.2 Hz, 1 H, Ar-H), 7.88 (d, J = 2.4 Hz, 1 H, Ar-H), 7.87 (s, 1 H, Ar-H), 7.25 (dd, J = 9.2, 2.4 Hz, 1 H, Ar-H), 4.71 (s, 2 H, 9-H), 4.11 (s, 3 H, OMe), 4.10 (s, 3 H, OMe), 4.05 (s, 3 H, OMe), 3.23–3.16 (m, 1 H, 11-H), 3.09–3.01 (m, 1 H, 11-H), 2.72–2.65 (m, 1 H, 13-H), 1.95–1.76 (m, 3 H, 12-H, 13-H), 1.41 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.7, 160.4, 150.3, 148.6, 138.0, 134.3, 126.8, 124.6, 124.5, 122.4, 120.7, 115.8, 108.1, 104.6, 103.1, 68.1, 55.9, 55.9, 55.6, 51.8, 45.6, 35.2, 20.7, 19.5 ppm. HRMS (ESI) calcd. for $C_{24}H_{26}NO_4$ [M + H]$^+$ 392.1862, found 392.1863; $[a]_D^{20}$ = –103.8 (c = 0.48, $CHCl_3$).

ent-**2b** and *ent*-**2c** were obtained (combined yield: 96%) by using a similar synthetic procedure as that for **2b** and **2c**. *ent*-**2b**: M.p. 132–137 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 8.09 (s, 1 H, Ar-H), 8.03 (s, 1 H, Ar-H), 8.00 (d, J = 2.4 Hz, 1 H, Ar-H), 7.87 (d, J = 9.0 Hz, 1 H, Ar-H), 7.23 (dd, J = 9.0, 2.4 Hz, 1 H, Ar-H), 5.21 (s, 1 H, 14-H), 4.30 (d, J = 16.0 Hz, 1 H, 9-H), 4.10 (d, J = 16.0 Hz, 1 H, 9-H), 4.07 (s, 3 H, OMe), 4.02 (s, 6 H, 2× OMe), 3.19–3.09 (m, 1 H, 11-H), 2.99–2.90 (m, 1 H, 11-H), 2.17–1.90 (m, 4 H, 12-H, 13-H), 1.09 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 159.8, 150.1, 149.8, 132.4, 129.1, 128.8, 128.0, 126.2, 125.9, 124.7, 116.9, 109.0, 105.2, 105.2, 75.2, 64.7, 56.5, 56.3, 56.0, 51.9,

48.8, 39.5, 21.5, 12.2 ppm. HRMS (MALDI) calcd. for $C_{24}H_{28}NO_4$ $[M + H]^+$ 394.2018, found 394.2014; $[a]_D^{20}$ = –60.36 (*c* = 0.55, CH_2Cl_2). *ent*-**2c**: M.p. 127–131 °C. ^1H NMR (400 MHz, CD_3OD): δ = 8.05 (s, 1 H, Ar-H), 7.95 (d, *J* = 2.1 Hz, 1 H, Ar-H), 7.80 (s, 1 H, Ar-H), 7.39 (d, *J* = 9.0 Hz, 1 H, Ar-H), 7.02 (dd, *J* = 9.0, 2.1 Hz, 1 H, Ar-H), 4.86 (s, 1 H, 14-H), 4.12 (s, 3 H, OMe), 4.08 (s, 3 H, OMe), 4.05 (s, 3 H, OMe), 3.80 (d, *J* = 16.0 Hz, 1 H, 9-H), 3.59 (d, *J* = 16.0 Hz, 1 H, 9-H), 3.22–3.14 (m, 1 H, 11-H), 2.69 (dd, *J* = 17.2, 8.8 Hz, 1 H, 11-H), 2.62 (dd, *J* = 17.2, 8.8 Hz, 1 H, 13-H), 2.08–1.96 (m, 2 H, 12-H, 13-H), 1.73–1.65 (m, 1 H, 12-H), 0.82 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 159.7, 151.0, 150.1, 132.2, 128.6, 127.8, 127.5, 125.8, 125.5, 124.2, 116.6, 106.6, 105.3, 105.1, 70.4, 64.1, 56.6, 56.4, 55.9, 51.9, 48.8, 32.8, 21.0, 13.7 ppm. HRMS (MALDI) calcd. for $C_{24}H_{28}NO_4$ $[M + H]^+$ 394.2018, found 394.2018; $[a]_D^{20}$ = –82.0 (*c* = 0.56, CH_2Cl_2).

(*S*)-3,6,7-Trimethoxy-13a-methyl-11,12,13,13a-tetrahydrodibenzo-[*f*,*h*]pyrrolo[1,2-*b*]isoquinolin-14(9*H*)-one (16): Compound **15** was prepared by a similar procedure as that for compound **9** from the known compound **13**.[13c] A solution of **15** (1.02 g, 2 mmol) was treated with excess *t*BuLi (3 equiv.), and ketone **16** was obtained as a single isolated product in good yield (43% based on **13**) after column chromatographic purification. Yellow solid; m.p. 141–147 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.35 (d, *J* = 9.4 Hz, 1 H, Ar-H), 7.93 (s, 1 H, Ar-H), 7.90 (d, *J* = 2.3 Hz, 1 H, Ar-H), 7.32 (s, 1 H, Ar-H), 7.29 (s, 1 H, Ar-H), 4.69 (d, *J* = 17.8 Hz, 1 H, 9-H), 4.61 (d, *J* = 17.8 Hz, 1 H, 9-H), 4.16 (s, 3 H, OMe), 4.10 (s, 3 H, OMe), 4.04 (s, 3 H, OMe), 3.25–3.18 (m, 1 H, 11-H), 3.10–3.02 (m, 1 H, 11-H), 2.76–2.64 (m, 1 H, 13-H), 2.01–1.77 (m, 3 H, 12-H, 13-H), 1.42 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.1, 157.9, 151.2, 149.7, 136.1, 131.2, 129.4, 127.7, 123.8, 122.8, 122.5, 115.6, 104.7, 104.6, 103.9, 68.0, 56.1, 56.0, 55.5, 52.0, 45.8, 35.2, 20.8, 19.4 ppm. HRMS (ESI) calcd. for $C_{24}H_{26}NO_4$ $[M + H]^+$ 392.1862, found 392.1862; $[a]_D^{27}$ = –100.3 (*c* = 0.76, $CHCl_3$).

Compounds 17 and **18** were obtained (combined yield: 92%) by using a similar procedure as that for compounds **2b** and **2c**.

Compound 17: Light yellow solid; m.p. 113–117 °C. ^1H NMR (400 MHz, CD_3OD): δ = 8.50 (d, *J* = 9.2 Hz, 1 H, Ar-H), 8.03 (s, 1 H, Ar-H), 7.97 (d, *J* = 2.3 Hz, 1 H, Ar-H), 7.26 (s, 1 H, Ar-H), 7.20 (dd, *J* = 9.2, 2.4 Hz, 1 H, Ar-H), 5.24 (s, 1 H, 14-H), 4.24 (d, *J* = 16.0 Hz, 1 H, 9-H), 4.09 (d, *J* = 16.0 Hz, 1 H, 9-H), 4.06 (s, 3 H, OMe), 4.01 (s, 6 H, 2× OMe), 3.18–3.07 (m, 1 H, 11-H), 3.02–2.92 (m, 1 H, 11-H), 2.14–1.91 (m, 4 H, 12-H, 13-H), 1.10 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 159.2, 151.1, 150.5, 132.9, 130.7, 129.3, 127.5, 126.3, 126.3, 125.7, 116.0, 105.5, 105.1, 105.0, 74.8, 64.7, 56.6, 56.4, 55.9, 52.0, 48.8, 39.5, 21.6, 12.6 ppm. HRMS (MALDI) calcd. for $C_{24}H_{28}NO_4$ $[M + H]^+$ 394.2018, found 394.2018; $[a]_D^{27}$ = –102.7 (*c* = 0.67, CH_3Cl).

Compound 18: Yellow solid; m.p. 123–126 °C. ^1H NMR (400 MHz, CD_3OD): δ = 8.10 (d, *J* = 9.2 Hz, 1 H, Ar-H), 7.73 (d, *J* = 2.4 Hz, 1 H, Ar-H), 7.60 (s, 1 H, Ar-H), 7.08 (dd, *J* = 9.1, 2.4 Hz, 1 H, Ar-H), 6.06 (s, 1 H, Ar-H), 4.55 (s, 1 H, 14-H), 3.87 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 3.59 (s, 3 H, OMe), 3.01 (d, *J* = 16.0 Hz, 1 H, 9-H), 2.92–2.79 (m, 1 H, 11-H), 2.83 (d, *J* = 16.0 Hz, 1 H, 9-H), 2.40 (dd, *J* = 16.8, 9.4 Hz, 1 H, 11-H), 2.29 (dd, *J* = 16.8, 9.4 Hz, 1 H, 13-H), 1.87–1.66 (m, 2 H, 12-H, 13-H), 1.45–1.34 (m, 1 H, 12-H), 0.46 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 159.4, 150.3, 150.2, 132.4, 128.2, 127.5, 127.0, 126.8, 125.5, 125.2, 116.5, 105.1, 104.5, 104.1, 70.4, 64.0, 56.3, 56.0, 55.9, 51.9, 48.6, 32.6, 20.8, 13.4 ppm. HRMS (MALDI) calcd. for $C_{24}H_{28}NO_4$ $[M + H]^+$ 394.2018, found 394.2036; $[a]_D^{27}$ = –100.3 (*c* = 0.76, CH_3Cl).

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectroscopic data for **2b**, **2c**, *ent*-**2b**, *ent*-**2c**, **8**–**11** and **16**–**18**, DEPT 135 spectroscopic data for **2c**, *ent*-**2b**, *ent*-**2c**, **17** and **18**, and NOE data for **2c**.

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