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Synthesis of 13a-methylphenanthroindolizidines using radical cascade cyclization: synthetic studies towards (±)-hypoestestatin 1

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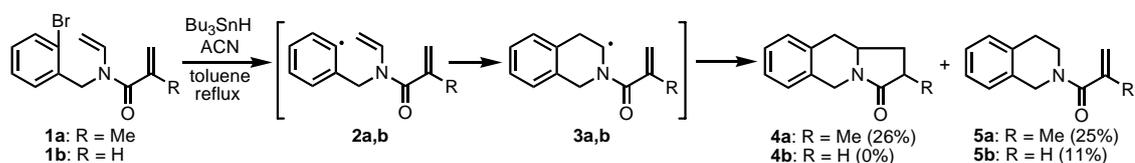
Abstract—A radical cascade involving 6-*endo* cyclization of aryl radicals generated from *N*-acryloyl-*N*-(1-methylethenyl)-9-bromophenanthren-10-ylmethyamines, followed by 5-*endo-trig* cyclization of the resulting α -amidoyl radicals afforded phenanthroindolizidines bearing a methyl substituent at the angular C13a position. 2,3,6-Trimethoxy derivative was synthesized by using this method, but its spectral data were not in accord with those of literature values reported for hypoestestatin 1. Further synthetic study towards hypoestestatin 1 is demonstrated.

Keywords: Enamide; Hypoestestatin 1; Ortho-lithiation; Phenanthroindolizidine; Radical cascade.

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1. Introduction

Radical cascade cyclization is recognized as a powerful tool for the construction of polycyclic compounds, including natural products.¹ We recently reported that Bu₃SnH-mediated radical cyclization of *N*-methacryloyl bromoenamine **1a** gave the tricyclic compound **4a** together with tetrahydroisoquiloline **5a**.² Formation of **4a** from **1a** can be explained in terms of a radical cascade that involves 6-*endo* cyclization of aryl radical **2a** and successive 5-*endo* cyclization of the resulting α -amidoyl radical **3a**. Compound **5a** might be a so-called reduction product derived from **3a**. We also reported that *N*-acryloyl enamine **1b** gave no corresponding radical cascade product **4b** but afforded only compound **5b**. These results indicated that the methyl substituent at the α -position of α,β -unsaturated amide acted as an effective radical-stabilizing group for the cyclization of α -amidoyl radical **3a**. We have now found that the introduction of a methyl substituent onto the alkenic bond of enamide (such as **6**) also gives the radical cascade product. In this paper, we describe the results in this area together with an application of this method to the synthesis of a phenanthroindolizidine skeleton bearing a methyl substituent at the angular position.



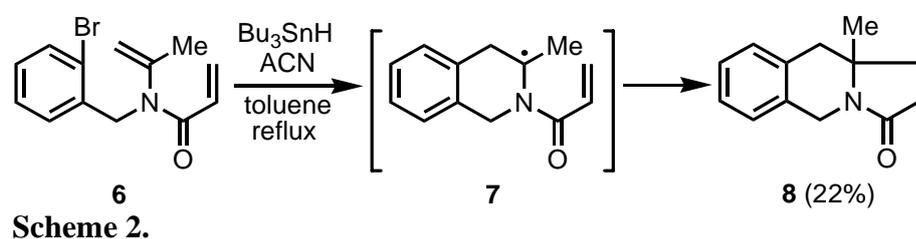
Scheme 1.

2. Results and discussion

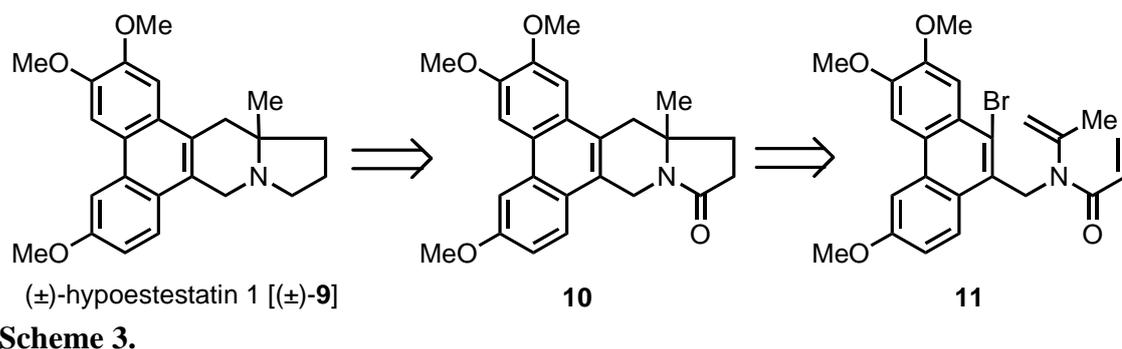
2.1. Attempt to synthesize hypoestestatin 1

The compound **6** having a methyl substituent on the alkenic bond of enamide was treated with

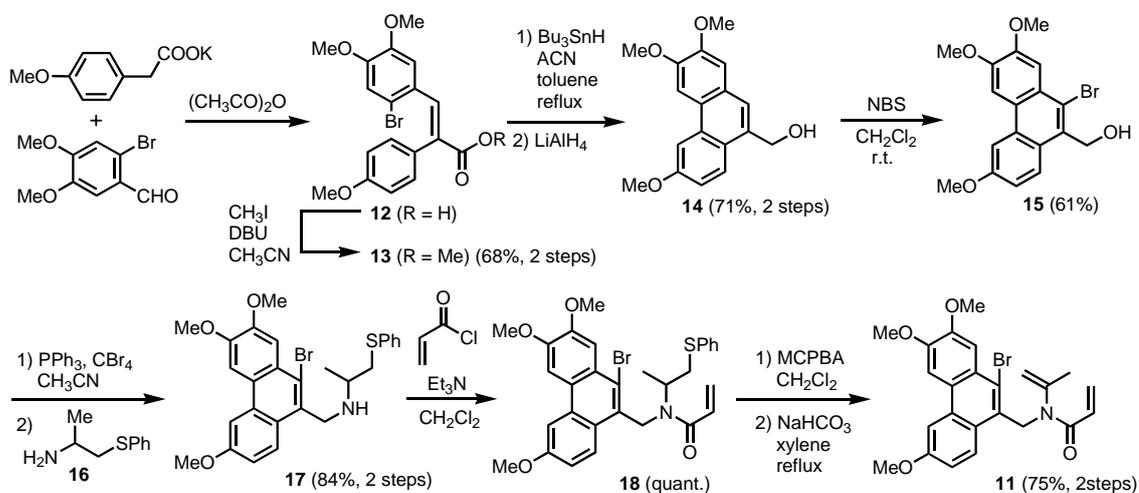
Bu₃SnH in the presence of azobis(cyclohexanecarbonitrile) (ACN) in boiling toluene to give the radical cascade product **8** in 22% yield (Scheme 2). As mentioned above, the compound **1b** having no methyl substituent on the alkenic bond of enamide gave no radical cascade product **4b** by the cyclization of **3b**.² The successful formation of **8** from **6** was probably because the presence of a methyl substituent on the radical center of α -amidoyl radical **7** retarded the intermolecular reduction with Bu₃SnH more effectively than the radical **3b**.



We then applied this method to the synthesis of phenanthroindolizidines³ bearing a methyl substituent at angular position. Hypoestestatin 1 (**9**) is one such compound that was isolated from the extract of the East African shrub *Hypoestes verticillaris* by Pettit's group⁴ and was found to markedly inhibit the growth of the murine P-388 cell line. There has been no report in the literature on the synthesis of hypoestestatin 1. Our retrosynthetic analysis of hypoestestatin 1 involved 6-*endo*/5-*endo* radical cascade cyclization of enamide **11** followed by reduction of the resulting lactam **10** (Scheme 3).



A radical precursor **11** was prepared as shown in Scheme 4. The Perkin reaction⁵ of potassium *p*-methoxyphenylacetate and 2-bromo-4,5-dimethoxybenzaldehyde gave carboxylic acid **12**, whose esterification gave the corresponding methyl ester **13**. Radical cyclization of **13**⁶ followed by reduction of the ester group with LiAlH₄ gave known phenanthrenyl methanol **14**.⁷ Treatment of **14** with NBS in CH₂Cl₂ afforded bromo alcohol **15**, which was converted to the secondary amine **17** by treatment with Ph₃P and CBr₄ and successive condensation of the resulting allyl bromide with amine **16**.⁸ Treatment of **17** with acryloyl chloride gave α,β-unsaturated amide **18**, whose oxidation with MCPBA and thermal elimination of the resulting sulfoxide in the presence of sodium hydrogen carbonate in boiling xylene gave **11**.



Scheme 4.

The radical cyclization of **11** with Bu₃SnH in the presence of ACN gave lactam **10** in 39% yield (Scheme 5). Lactam **10** was reduced with LiAlH₄ to give the target molecule **9**.



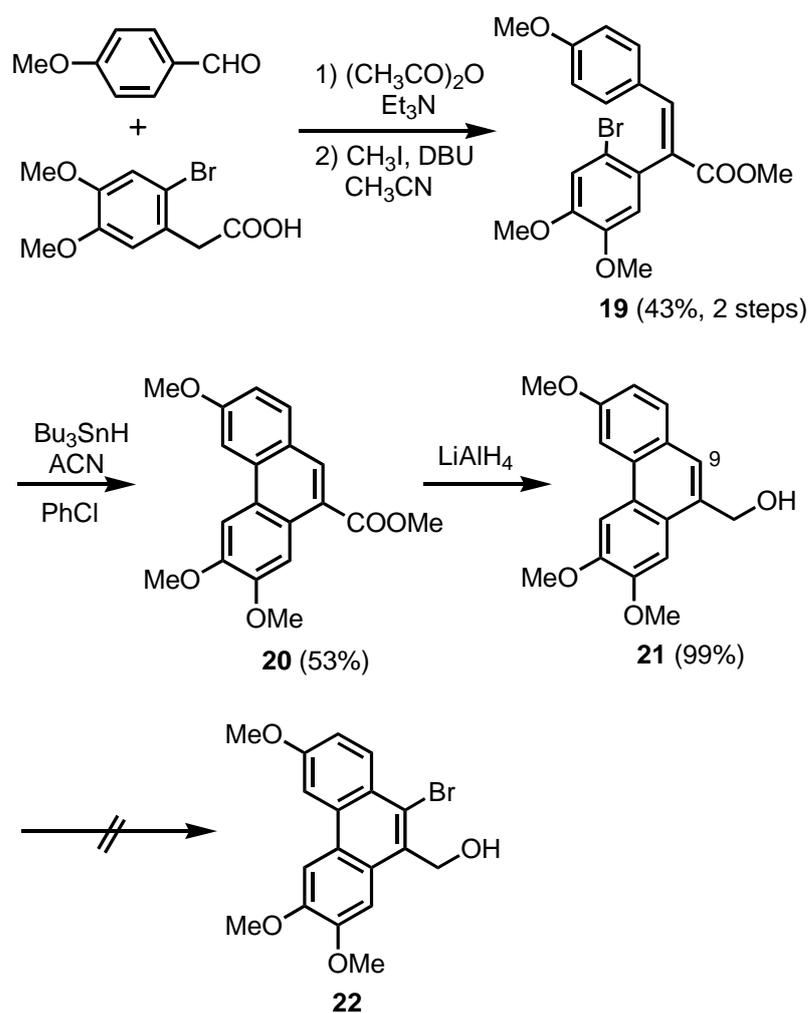
Scheme 5.

¹H and ¹³C NMR spectra of **9**, however, were not in accord with those of hypoestestatin 1 reported by Pettit et al. In the ¹H NMR spectrum of compound **9** in CD₃OD, the signal due to the angular methyl group appeared as a singlet at δ 1.07, whereas the corresponding signal reported for hypoestestatin 1 was shifted to a lower field at δ 1.30. Its lower field shift was presumed to be a result of the formation of the quaternary ammonium salt. Hence, we turned our attention to the ¹H NMR spectra of carbonate salt derived from compound **9**. In the event, the signal due to the methyl protons of carbonate salt of **9** was shifted to a lower field at δ 1.27, but the other signals were not in accord with those reported for hypoestestatin 1. Therefore, it was thought that compound **9** was not hypoestestatin 1.

2.2. Attempt to synthesize another possible structure of hypoestestatin 1

We speculated the correct structure of hypoestestatin 1 to be **32** in which three methoxy groups occupied 3, 6 and 7 positions on the phenanthroindolizidine ring. Our attention was then turned to the synthesis of **32** by radical cascade cyclization of compound **30** (Scheme 8). The synthesis of compound **30** was begun by Perkin reaction of 2-bromo-4,5-dimethoxyphenylacetic acid⁹ and *p*-anisaldehyde followed by esterification to

give **19** (Scheme 6). A subsequent radical cyclization of **19** in toluene gave the known phenanthrene ester **20**¹⁰ in 43% yield. The low yield of **20** might be ascribed to the formation of dehydro congener of **20** as a result that toluene acted as a hydrogen source. So, we then turned our attention to the use of chlorobenzene as a solvent for the radical cyclization of **19** to afford **20** in 53% yield.

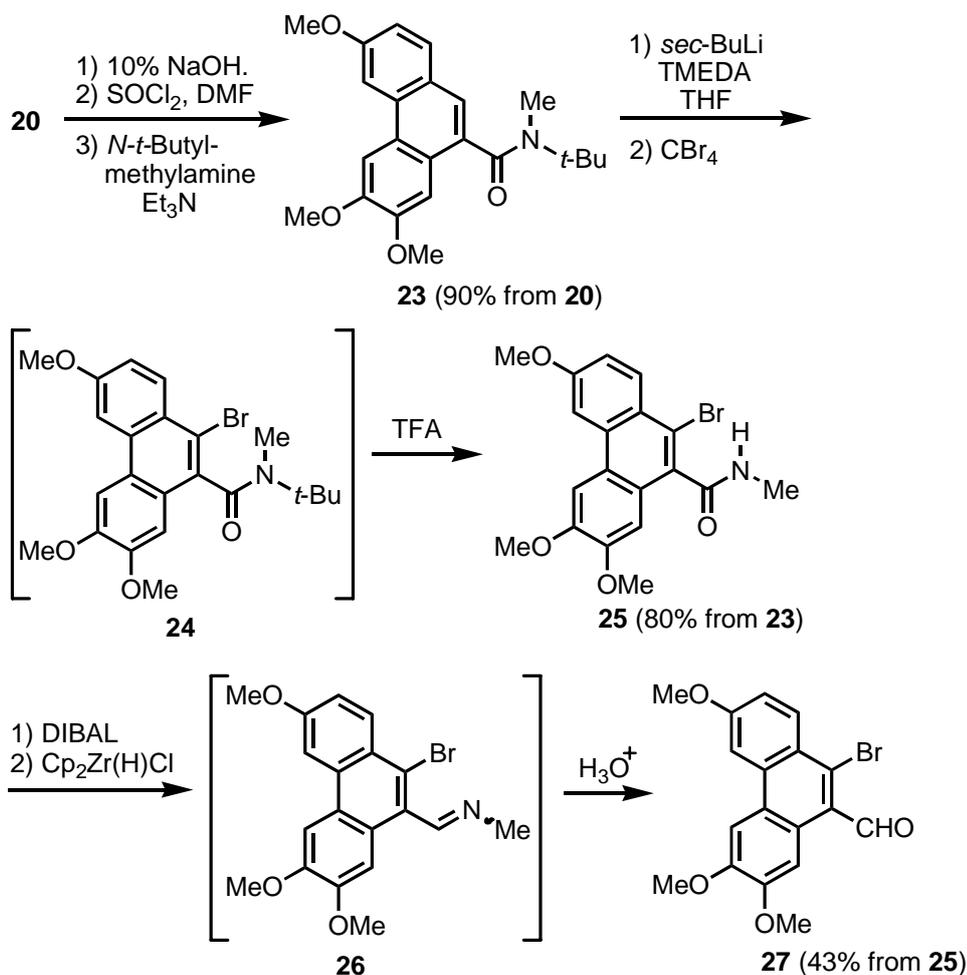


Scheme 6.

Reduction of **20** with LiAlH_4 gave alcohol **21**. However, treatment of **21** with NBS or Br_2 under various conditions afforded no brominated compound **22**. A substitution pattern of the

methoxy groups on the phenanthrene ring probably caused a reduction of relative electron density at the C-9 position of **21** as compared to compound **14**.

We therefore tried to introduce a bromine atom at the desired position through an *ortho*-lithiation of amide.¹¹ *N-tert*-Butylmethyl amide **23** was chosen as a substrate for the *ortho*-lithiation reaction, since the *tert*-butylmethyl amide group has higher direction ability for *ortho*-lithiation and is known to be hydrolyzed more easily than other tertiary amides such as diethylamide.¹² Lithiation of compound **23** with *sec*-BuLi in the presence of tetramethylethylenediamine (TMEDA) at -94 °C to -78 °C followed by bromination with CBr₄ gave the desired bromide **24**. Deprotection of the *tert*-butyl group of **24** with trifluoroacetic acid afforded secondary amide **25**. Subsequent hydrolysis of **25**, however, did not proceed under several conventional conditions, probably because of steric hindrance of a neighboring bromine. Therefore, we explored another functional group transformation of **25**: that is, hydride was used for the nucleophile instead of sterically more demanding hydroxide ion. It was found that a combination of DIBAL and Schwartz reagent¹³ reduced secondary amide **25** to the corresponding imine **26**, and aqueous treatment of **26** gave aldehyde **27** in a moderate yield.

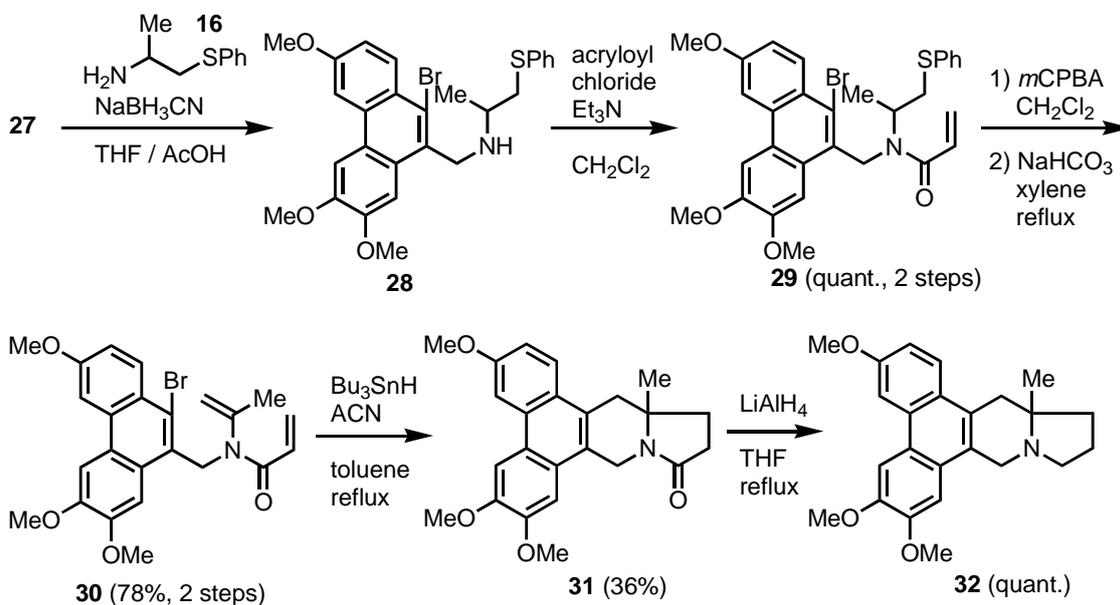


Scheme 7.

The method for the synthesis of the target compound **32** from aldehyde **27** is shown in Scheme 8.

8. Reductive amination of aldehyde **27** with primary amine **16** afforded the secondary amine **28**, which was converted to the radical precursor **30** via compound **29** by a similar sequence of reactions of **17** giving **11** (see Scheme 4). The radical cascade of **30** involving 6-*endo*/5-*endo* cyclizations proceeded successfully to give lactam **31**. The subsequent reduction of **31** with LiAlH_4 gave the target compound **32**. However, unfortunately, the ^1H NMR spectral data of **32** were again not in accord with those of hypoestestatin 1 reported by Pettit et al. In the ^1H NMR spectrum, the signal due to the angular methyl group of **32** appeared as a singlet at δ 1.07 in CD_3OD , whereas the corresponding signal of carbonate salt of **32** was shifted to a lower

field at δ 1.22 ppm. However, the other signals of carbonate salt of **32** were not in accord with those reported for hypoestestatin 1.



Scheme 8.

3. Conclusion

We accomplished the synthesis of 2,3,6-trimethoxy phenanthroindolizidine **9** and 3,6,7-trimethoxy isomer **32** by 6-*endo*/5-*endo* radical cascade cyclization of the corresponding bromo enamide **11** and **30**, respectively. Although ^1H NMR spectral data of the resulting **9** and **32** were not in accord with those of reported hypoestestatin 1, the present study revealed that a phenanthroindolizidine skeleton bearing a methyl substituent at the angular C13a position can be easily constructed by this method.

4. Experimental

4.1. General

Melting points are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100 spectrophotometer for solutions in CHCl₃. ¹H NMR and ¹³C NMR spectra were measured on a JEOL JNM-EX 270 or a JEOL JNM-GSX 500 spectrometer for solutions in CDCl₃. δ Values quoted are relative to tetramethylsilane. High resolution mass spectra (HRMS) were obtained with a JEOL JMS-SX-102A mass spectrometer. Column chromatography was performed on Silica gel 60 N (Kanto Kagaku Co., Ltd., spherical, neutral, 63-210 μ m) under pressure. Thin layer chromatography was carried out on silica gel Wakogel B-5F.

4.1.1. (\pm)-*N*-Acryloyl-*N*-(1-methylethenyl)-2-bromobenzylamine (6). To a solution of *N*-acryloyl-*N*-[1-methyl-2-(phenylsulfonyl)ethyl]-2-bromobenzylamine, prepared in a manner similar to that described for **18** (see Supplementary data), (1.09 g, 2.80 mmol) in CH₂Cl₂ (25 mL) was added dropwise a solution of MCPBA (80%) (604 mg, 2.80 mmol) in CH₂Cl₂ (25 mL) at 0 °C. After stirring at the same temperature for 30 min, an aqueous 10% Na₂S₂O₃ solution was added to the reaction mixture and the mixture was extracted with CHCl₃. The organic layer was washed with a saturated aqueous NaHCO₃ solution and brine, dried (MgSO₄), and concentrated under a reduced pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 3:1) to afford *N*-acryloyl-*N*-[1-methyl-2-(phenylsulfonyl)ethyl]-2-bromobenzylamine as a colorless oil.

The above sulfoxide (882 mg, 2.17 mmol) was heated in boiling xylene (40 mL) in the presence of NaHCO₃ (365 mg) for 12 h. A saturated aqueous NH₄Cl solution was added to the reaction mixture and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried (MgSO₄), and concentrated under a reduced pressure.

The residue was purified by column chromatography on silica gel (hexane/AcOEt, 10:1 →6:1) to afford **6** (490 mg, 62%, 2 steps) as a colorless oil. IR (CHCl₃) ν 1645, 1615 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 1.90 (3H, s), 4.77 (1H, s), 4.89 (2H, s), 5.03 (1H, d, J = 1.3 Hz), 5.69 (1H, dd, J = 10.1, 2.1 Hz), 6.45 (1H, dd, J = 16.8, 2.3 Hz), 6.65 (1H, dd, J = 16.8, 9.9 Hz), 7.10 (1H, td, J = 7.7, 1.9 Hz), 7.22-7.35 (2H, m), 7.52 (1H, dd, J = 7.9, 1.0 Hz); ¹³C NMR (68 MHz, CDCl₃) δ 21.2, 48.7, 115.6, 123.2, 127.3, 127.8, 128.0, 128.5, 129.4, 132.4, 136.2, 143.2, 165.0. Anal. Calcd for C₁₂H₁₂BrNO: C, 55.73; H, 5.04; N, 5.00. Found: C, 55.61; H, 5.04; N, 5.02.

4.1.2. (\pm)-1,2,3,5,10,10a-Hexahydro-10a-methylpyrrolo[1,2-b]isoquinolin-3-one (**8**).

To a boiling solution of **6** (264.0 mg, 0.94 mmol) in toluene (30 mL) was added dropwise a solution of Bu₃SnH (0.38 ml, 1.41 mmol) and ACN (46.7 mg, 0.19 mmol) in toluene (30 mL) over 2.5 h by employing a syringe-pump technique and the mixture was further heated for 10 min. After removal of solvent, the residue was purified by column chromatography on silica gel containing 10% KF (hexane/AcOEt, 3:1 →2:1 →1:1 →2:3) to afford **8** (41.1 mg, 22%) as a colorless oil. IR (CHCl₃) ν 1670 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 1.23 (3H, s), 1.95-2.15 (2H, m), 2.35-2.65 (2H, m), 2.76 (1 H, d, J = 15.6 Hz), 2.92 (1 H, d, J = 15.6 Hz), 4.16 (1 H, d, J = 17.6 Hz), 5.02 (1 H, d, J = 17.6 Hz), 7.06-7.36 (5 H, m); ¹³C NMR (68 MHz, CDCl₃) δ 23.8, 29.7, 33.1, 40.1, 41.5, 58.0, 126.4, 126.5, 126.6, 129.6, 131.0, 133.7, 173.4; HRMS calcd for C₁₃H₁₅NO: 201.1154, found: 201.1154.

4.1.3. 10-Bromo-9-hydroxymethyl-2,3,6-trimethoxyphenanthrene (**15**).

To a solution of **14** (119.0 mg, 0.399 mmol) in CH₂Cl₂ (5 mL) was added NBS (78.1 mg, 0.439 mmol) at room temperature in the dark and the mixture was stirred at the same

temperature for 3 h. An aqueous 10% Na₂S₂O₃ solution was added to the reaction mixture and the mixture was extracted with CH₂Cl₂. The organic layer was washed with a saturated aqueous NaHCO₃ solution and brine, dried (MgSO₄), and concentrated under a reduced pressure. The residue was purified by column chromatography on silica gel (CHCl₃) to afford **15** (92.0 mg, 61%) as a colorless crystal. Mp 176-177°C (hexane/AcOEt); IR (CHCl₃) ν 3020 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.96 (1H, t, J = 6.5 Hz), 4.02 (3H, s), 4.07 (3H, s), 4.11 (3H, s), 5.41 (2H, d, J = 6.5 Hz), 7.26 (1H, dd, J = 9.0, 2.5 Hz), 7.80 (1H, s), 7.83 (1H, s), 7.84 (1H, d, J = 2.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 55.5, 55.8, 56.0, 63.5, 103.1, 104.6, 109.3, 115.7, 121.9, 125.0, 125.2, 125.6, 127.1, 130.8, 132.1, 149.5, 149.7, 158.1. Anal. Calcd for C₁₉H₁₇BrO₄: C, 57.31; H, 4.54. Found : C, 57.23; H, 4.57.

4.1.4. (±)-
10-Bromo-2,3,6-trimethoxy-N-[1-methyl-2-(phenylsulfanyl)ethyl]phenanthren-9-yl methylamine (17). To a solution of **15** (151.2 mg, 0.401 mmol) in CH₃CN (40 mL) were added PPh₃ (485.6 mg, 1.84 mmol) and CBr₄ (597.0 mg, 1.80 mmol) at room temperature and the mixture was stirred at the same temperature for 2 h. After removal of solvent, the residue was purified by column chromatography on silica gel (CHCl₃) to afford 10-bromo-9-bromomethyl-2,3,6-trimethoxyphenanthrene quantitatively. ¹H NMR (270 MHz, CDCl₃) δ 4.02 (3H, s), 4.08 (3H, s), (3H, s), 5.24 (2H, s), 7.29 (1H, dd, J = 8.2, 2.3 Hz), 7.79 (1H, s), 7.80 (1H, s), 7.83 (1H, d J = 2.6 Hz), 8.08 (1 H, d, J = 8.2 Hz). Due to its lability, it was used in the next step immediately.

To a mixture of 1-methyl-2-(phenylsulfanyl)ethylamine (**16**) (149.6 mg, 0.89 mmol),

Na₂CO₃ (37.2 mg, 0.35 mmol), NaI (37.2 mg, 0.25 mmol) and Et₄NI (12.4 mg, 0.05 mmol) in THF (10 mL)/1,4-dioxane (5 mL) was added dropwise a solution of the above bromide (0.401 mmol) in THF (5 mL) at room temperature over 1.5 h and the mixture was stirred at the same temperature for 27 h. The reaction mixture was diluted with H₂O and the mixture was extracted with AcOEt. The organic layer was dried (MgSO₄) and concentrated under a reduced pressure. The residue was purified by column chromatography on silica gel (CHCl₃/MeOH, 50:1) to afford **17** (178.2 mg, 84%) as a yellow oil. ¹H NMR (270 MHz, CDCl₃) δ 1.33 (3H, d, *J* = 5.6 Hz), 1.87 (1H, brs), 2.98-3.13 (3H, m), 4.02 (3H, s), 4.09 (3H, s), 4.12 (3H, s), 4.40 (1H, d, *J* = 12.2 Hz), 4.51 (1H, d, *J* = 12.2 Hz), 7.13-7.33 (6H, m), 7.82 (1H, s), 7.84 (1H, s), 7.85 (1H, s), 8.14 (1H, d, *J* = 8.9 Hz); ¹³C NMR (68 MHz, CDCl₃) δ 20.9, 41.7, 49.8, 52.5, 55.9, 56.4, 56.5, 103.6, 105.0, 110.0, 116.2, 122.4, 125.3, 125.8, 126.5, 127.5, 129.2, 130.2, 131.3, 132.8, 136.5, 149.8, 150.3, 158.5. Anal. Calcd for C₂₇H₂₈BrNO₃S: C, 61.59; H, 5.36; N, 2.66. Found: C, 61.54; H, 5.49 N, 2.64.

4.1.5.

***N*-Acryloyl-10-bromo-*N*-(1-methylethenyl)-2,3,6-trimethoxyphenanthren-9-ylmeth
ylamine (11).** To a solution of **18** (753 mg, 1.30 mmol) in CH₂Cl₂ (30 mL) was added dropwise a solution of MCPBA (80%) (280 mg, 1.30 mmol) in CH₂Cl₂ (30 mL) at 0 °C and the mixture was stirred at the same temperature for 10 min. An aqueous 10% Na₂S₂O₃ solution was added to the reaction mixture and the mixture was extracted with CHCl₃. The organic layer was washed with a saturated aqueous NaHCO₃ solution and brine, dried (MgSO₄), and concentrated under a reduced pressure to give *N*-acryloyl-*N*-[1-methyl-2-(phenylsulfinyl)ethyl]-10-bromo-2,3,6-trimethoxyphenanthren-9-ylmethylamine. The residue was used in the next step without further

purification.

The above sulfoxide was heated in boiling xylene (30 mL) in the presence of NaHCO₃ (218 mg, 2.59 mmol) for 12 h. To the reaction mixture was added a saturated aqueous NH₄Cl solution and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried (MgSO₄), and concentrated under a reduced pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 2:1) to afford **11** (459 mg, 75%, 2 steps) as a colorless crystal. Mp 203 °C (hexane/AcOEt); IR (CHCl₃) ν 1615 cm⁻¹, 1645 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.76 (3H, s), 4.00 (3H, s), 4.10 (3H, s), 4.12 (3H, s), 4.30 (1H, s), 4.80 (1H, s), 5.68-5.72 (3H, m), 6.51-6.58 (2H, m), 7.24 (1H, dd, *J* = 9.0, 2.5 Hz), 7.86 (1H, d, *J* = 2.5 Hz), 7.86 (1H, s), 7.88 (1H, s), 8.18 (1H, d, *J* = 9.5 Hz); ¹³C NMR (68 MHz, CDCl₃) δ 22.6, 47.2, 55.8, 56.3, 56.4, 103.6, 105.0, 110.1, 116.1, 117.9, 124.7, 125.5, 126.1, 128.0, 128.5, 128.6, 129.7, 130.8, 142.2, 150.0, 150.2, 158.5, 164.7. Anal. Calcd for C₂₄H₂₄BrNO₄: C, 61.28; H, 5.14; N, 2.98. Found: C, 61.08; H, 5.33 N, 2.90.

**4.1.6. (±)-
9,11,12,13,13a,14-Hexahydro-2,3,6-trimethoxy-13a-methyldibenzo[f,h]pyrrolo[1,2-
b]isoquinolin-11-one (10)**

To a boiling solution of **11** (80 mg, 0.17 mmol) in toluene (15 mL) was added dropwise a solution of Bu₃SnH (0.07 ml, 0.26 mmol) and ACN (8 mg, 0.03 mmol) in toluene (15 mL) over 2 h by employing a syringe-pump technique. After removal of solvent, AcOEt (20 mL) and an aqueous 8% KF solution (20 mL) were added to the residue and the mixture was vigorously stirred at room temperature over night. The precipitate was filtered off and the filtrate was extracted with AcOEt. The organic layer was

washed with brine, dried (MgSO_4), and concentrated under a reduced pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 1:1 \rightarrow 1:3 \rightarrow AcOEt) to afford **10** (26 mg, 39%) as a colorless crystal. Mp 222-223 °C (dec) (hexane/AcOEt); IR (CHCl_3) ν 1675 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.35 (3H, s), 2.20-2.30 (2H, m), 2.52-2.69 (2H, m), 3.06 (1H, d, $J = 16.5$ Hz), 3.24 (1H, d, $J = 16.0$ Hz), 4.03 (3H, s), 4.07 (3H, s), 4.11 (3H, s), 4.49 (1H, d, $J = 16.5$ Hz), 5.47 (1H, dd, $J = 17.5, 2.5$ Hz), 7.25-7.28 (2H, m), 7.91 (1H, d, $J = 6.5$ Hz), 7.92 (1H, s), 7.94 (1H, s); ^{13}C NMR (68 MHz, CDCl_3) δ 24.3, 29.9, 33.4, 38.2, 38.6, 55.5, 55.9, 56.1, 57.5, 103.8, 104.1, 105.0, 115.1, 123.0, 123.3, 123.4, 124.0, 124.4, 126.7, 130.3, 148.7, 149.6, 157.9, 173.3; HRMS calcd for $\text{C}_{24}\text{H}_{27}\text{NO}_4$: 391.1784, found: 391.1782. Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{NO}_4$: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.36; H, 6.44 N, 3.56.

4.1.7. (±)-
9,11,12,13,13a,14-Hexahydro-2,3,6-Trimethoxy-13a-methyldibenzo[f,h]pyrrolo[1,2-b]isoquinoline (9). To a suspension of LiAlH_4 (6 mg, 0.13 mmol) in THF (5 mL) was added a solution of **10** (26 mg, 0.07 mmol) in THF (5 mL) at room temperature and the mixture was heated at reflux for 2 h. H_2O (0.1 mL) was added to the reaction mixture and the precipitate was filtered off through a Celite pad. The filtrate was concentrated in a reduced pressure and the residue was purified by column chromatography on silica gel ($\text{CHCl}_3/\text{MeOH}$, 15:1) to afford **9** (24 mg, 96%) as a yellow crystal. Mp was not determined due to its lability. ^1H NMR (500 MHz, CDCl_3) δ 1.05 (3H, s), 1.90-2.00 (4H, m), 2.88-2.94 (1H, m), 3.00 (2H, s), 3.08-3.14 (1H, m), 4.01 (3H, s), 4.07 (3H, s), 4.10 (3H, s), 4.11 (1H, d, $J = 16.5$ Hz), 4.45 (1H, d, $J = 16.5$ Hz), 7.21 (1H, dd, $J = 9.2, 2.4$ Hz), 7.33 (1H, s), 7.85 (1H, d, $J = 9.2$ Hz), 7.91 (1H, d, $J = 2.4$ Hz), 7.93 (1H, s); ^{13}C NMR (68 MHz, CDCl_3) δ 17.8, 20.1, 35.7, 39.3,

47.0, 50.8, 55.5, 55.9, 56.0, 58.9, 103.9, 104.0, 104.8, 114.9, 123.7, 124.1, 124.2, 124.4, 124.6, 127.3, 130.0, 148.4, 149.4, 157.5; HRMS calcd for C₂₄H₂₇NO₃: 377.1991, found: 377.1990.

4.1.8. 9-Bromo-2,3,6-trimethoxy-*N*-methylphenanthrene-10-carboxamide (25). To a solution of **23** (738 mg, 1.94 mmol) and TMEDA (0.35 ml, 2.32 mmol) in THF (20 mL) was added *sec*-BuLi (1.00 M in cyclohexane/hexane, 2.37 mL, 2.37 mmol) at -94 °C and the mixture was slowly warmed to -78 °C. After the mixture was stirred for 1 h, a solution of CBr₄ (3.27 g, 9.86 mmol) in THF (5 mL) was added and the mixture was slowly warmed to room temperature. H₂O was added to the reaction mixture and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried (Na₂SO₄), and concentrated under a reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/AcOEt, 3:1→1:1) to afford 9-bromo-*N*-*tert*-butyl-2,3,6-trimethoxy-*N*-methylphenanthrene-10-carboxamide (**24**) along with a little amount of **23**.

The mixture containing **24** was heated at reflux in TFA (5 mL) for 42 h. After evaporation of TFA, the residue was purified by column chromatography on silica gel (hexane/AcOEt, 1:1→1:3→AcOEt) to afford **25** (515 mg, ca. 80%) along with a little amount of inseparable by-product. HRMS calcd for C₁₉H₁₈O₄N⁸¹Br: 405.0399, found: 405.0411. This mixture was used in the next step without further purification:

4.1.9. 9-Bromo-2,3,6-trimethoxyphenanthrene-10-carbaldehyde (27). To a suspension of **25** containing a little amount of unidentified product (206 mg, 0.51 mmol) (purity of **25** = ca. 80%) in THF (18 mL) was added DIBAL (0.94 M in hexane,

0.66 mL, 0.62 mmol) at -20 °C, and the mixture was slowly warmed to room temperature. Cp₂Zr(H)Cl (191 mg, 0.74 mmol) was added at -20 °C and the mixture was stirred at room temperature for 4 h. The mixture was filtered off through short column on silica gel (AcOEt) and the filtrate was concentrated under a reduced pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 3:1 → 2:1 → 1:1 → 1:3). The first eluate gave **27** (101 mg, 43%, 3 steps) as a yellow crystal. Mp 185.5-186.0 °C (hexane/AcOEt); IR (CHCl₃) ν 1680cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.06 (H, s), 4.07 (3 H, s), 4.10 (3H, s), 7.28 (1H, dd, *J* = 9.3, 2.4 Hz), 7.78 (1H, s), 7.78 (1H, d, *J* = 2.4 Hz), 8.56 (1H, d, *J* = 9.3 Hz), 8.72 (1H, s), 10.9 (1H, s); ¹³C NMR (125 MHz, CDCl₃) δ 55.5, 55.7, 55.8, 102.6, 103.7, 105.3, 116.3, 123.3, 123.7, 124.3, 124.6, 130.8, 133.0, 134.0, 149.0, 150.4, 160.9, 196.0. Anal. Calcd for C₁₈H₁₅BrO₄: C, 57.62; H, 4.03. Found: C, 57.25; H, 3.99.

The second eluate gave the recovered **25** (68 mg) (purity of **25** = ca. 80%).

4.1.10.

9,11,12,13,13a,14-Hexahydro-3,6,7-trimethoxy-13a-methyldibenzo[f,h]pyrrolo[1,2-b]isoquinolin-11-one (31). To a boiling solution of **30** (39.1 mg, 0.083 mmol) in toluene (8 mL) was added dropwise a solution of Bu₃SnH (0.04 ml, 0.15 mmol) and ACN (4.6 mg, 0.02 mmol) in toluene (8 ml) over 2 h by employing a syringe-pump technique and the mixture was further heated for 1 h. After removal of solvent, the residue was purified by column chromatography on silica gel containing 10% KF (hexane/AcOEt, 1:1 → 1:3 → AcOEt) to give **31** (11.6 mg, 36%) as a pale yellow crystal. Mp 198.0-202.5 °C (dec) (Hexane/AcOEt); IR (CHCl₃) ν 1675 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.25 (3H, s, Me), 2.16 (2H, t, *J* = 8.0 Hz), 2.52-2.67 (2H, m), 2.86 (1H,

d, $J = 15.6$ Hz), 3.23 (1H, d, $J = 15.6$ Hz), 4.01 (3H, s), 4.02 (3H, s), 4.11 (3H, s), 4.34 (1H, d, $J = 17.1$ Hz), 5.24 (1H, d, $J = 17.1$ Hz), 7.18 (1H, dd, $J = 9.2, 2.4$ Hz), 7.80 (1H, d, $J = 9.2$ Hz), 7.88 (2H, like s); ^{13}C NMR (68 MHz, CDCl_3) δ 24.0, 29.8, 33.2, 37.9, 38.6, 55.4, 55.9, 55.9, 57.3, 102.7, 103.8, 104.6, 114.9, 121.1, 123.2, 124.6, 124.6, 124.7, 124.9, 130.6, 148.4, 149.5, 157.7, 173.3; HRMS calcd for $\text{C}_{24}\text{H}_{27}\text{NO}_4$: 391.1784, found: 391.1776.

4.1.11.

9,11,12,13,13a,14-Hexahydro-3,6,7-trimethoxy-13a-methyldibenzo[f,h]pyrrolo[1,2-b]isoquinoline (32). To a solution of **31** (12.2 mg, 0.03 mmol) in THF (2 mL) was added LiAlH_4 (10.5 mg, 0.28 mmol) at 0 °C and the mixture was heated at reflux for 30 min. H_2O was added to the reaction mixture at 0 °C and the precipitates were filtered off through a Celite pad. The filtrate was concentrated under a reduced pressure and the residue was purified by column chromatography on silica gel (MeOH/AcOEt, 1:4) to afford **32** (13.4 mg, quant.) as a pale yellow solid. Mp was not determined due to its lability. ^1H NMR (270 MHz, CDCl_3) δ 1.02 (3H, s), 1.80-2.05 (4H, m), 2.85-3.20 (4H, m), 4.02 (3H, s), 4.06 (3H, s), 4.06-4.10 (1H, m), 4.11 (3H, s), 4.38 (1H, d, $J = 16.2$ Hz), 7.20 (1H, s), 7.19-7.25 (2H, m), 7.91 (1H, d, $J = 2.5$ Hz), 7.93 (1H, s), 7.96 (1H, d, $J = 9.1$ Hz); ^{13}C NMR (68 MHz, CDCl_3) δ 17.3, 20.2, 36.1, 39.4, 47.4, 50.9, 55.5, 55.9, 56.0, 57.6, 103.1, 103.9, 104.7, 114.7, 123.2, 123.6, 125.0, 125.7, 125.8, 126.1, 130.5, 148.2, 149.4, 157.5; HRMS calcd for $\text{C}_{24}\text{H}_{27}\text{NO}_3$: 377.1991, found: 377.1987.

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Supplementary data

Experimental procedure for the preparation of **12**, **13**, **14**, **18**, **19**, **20**, **21**, **23**, **28**, **29** and **30**.

Supplementary data associated with this article can be found in the online version, at doi:

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