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Enantioselective Approach to 13a-Methylphenanthroindolizidine Alkaloids

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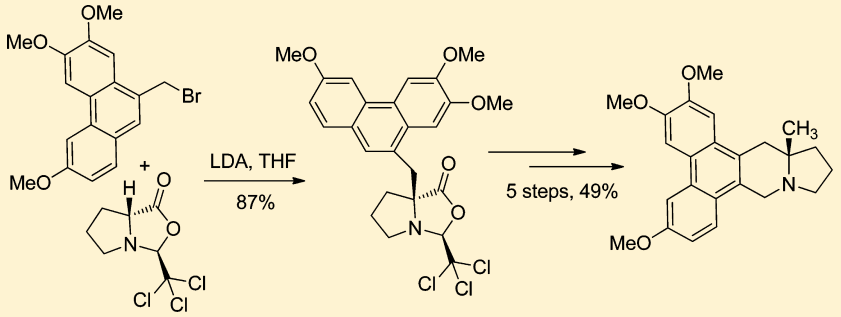
Supporting Information



ABSTRACT: The first enantioselective approach to 13a-methylphenanthroindolizidine alkaloids is reported, featuring an efficient stereoselective Seebach's alkylation and Pictet–Spengler cyclization. The proposed and other three most probable structures were ruled out, indicating hypoestestatin 1 needs further assignment.

INTRODUCTION

Phenanthroindolizidine alkaloids, mainly isolated from *Cynanchum, Pergularia, Tylophora,* and some genera of the *Asclepiadaceas* family, have attracted great and long-lasting attention in the past decades for their profound biological activities, among which the excellent cytotoxic activity against various cancer cell lines is most intriguing.[1] Among the more than 60 alkaloids of this class isolated until now, (*R*)-tylophorine (**1a**) and (*R*)-antofine (**1b**) are well-known representative 13a-H members (Figure 1).[2] In 1984, two novel phenanthroindolizidine alkaloids bearing a methyl group at the 13a-position were isolated from *Tylophora hirsuta* and named as 13a-methyltylohirsutine (**3a**) and 13a-methyltylohirsutinidine (**3b**) by Bhutani.[3] In the same year, Pettit et al reported another two 13a-methyl members, hypoestestatin 1 (**2a**) and hypoestestatin 2 (**2b**) and their very profound cytotoxic activity ($ED_{50} = 10^{-5}$ μg/mL against the murine P-388 cell line).[4] Some other 13a-methyl analogues (**3c** and **4**) and seco-analogues were subsequently reported in later years.[5]

Although a great many of synthetic strategies have been developed for the 13a-H members of phenanthroindolizidine alkaloids,[6] both syntheses and bioactivities of the 13a-methylphenanthroindolizidines were widely unexplored. The major challenge is the installation (especially from enantioselective) of the quaternary carbon center adjacent to the nitrogen. In 2007, Ishibashi and colleagues reported the first total synthesis of the proposed structure of hypoestestatin 1 ((±)-**2a**) in 12 steps and 7% overall yield, featuring a radical cascade cyclization as key step in which 39% yield was obtained.[7] Meanwhile, they gave a conclusion that the originally reported structure of hypoestestatin 1 (**2a**) was wrong because the spectroscopic data of the synthetic racemic sample could

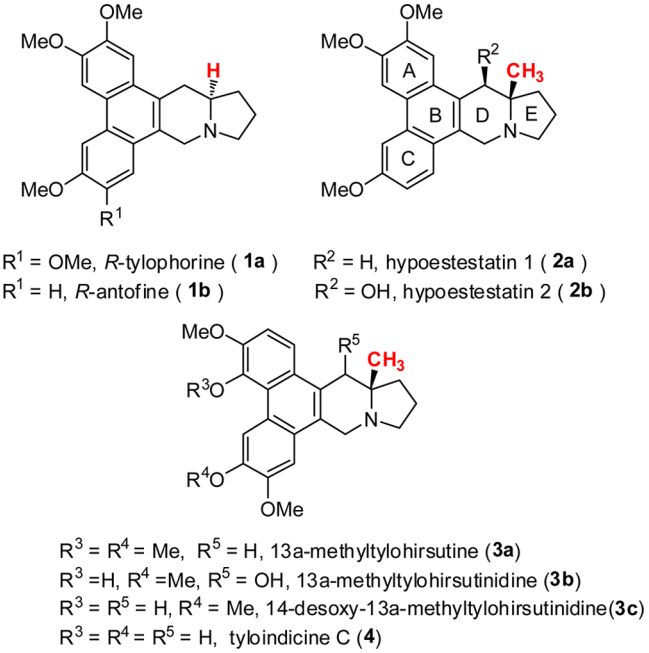


Figure 1. Representative structures of phenanthroindolizidines.

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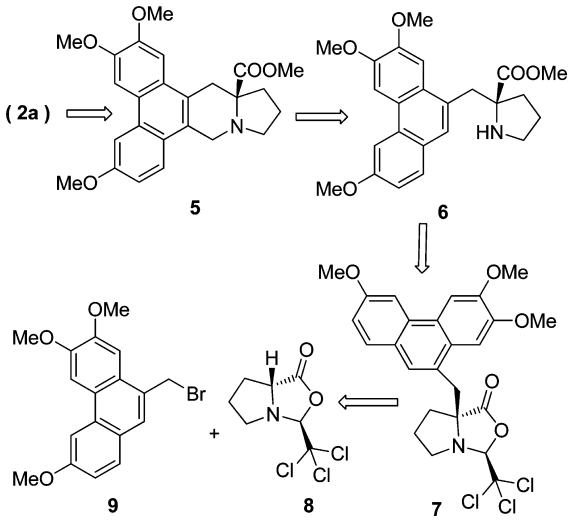
not match with the literature. Further investigation on the spectroscopic data of the proposed structure of hypoestestatin 1 was needed, since many factors, such as concentration, acid in the solvent, the identity of the counteranion, impurity in the sample, the degree of $CDCl_3$ decomposition (i.e., DCl content), and so on, could lead to variance (especially from alkaloids) in spectroscopic data.[8] As part of our ongoing research into the synthesis and biological evaluation of phenanthroindolizidine alkaloids,[1d,6a,e,9] we herein report the first enantioselective and general approach to the widely unexplored 13a-methylphenanthroindolizidine alkaloids.

RESULTS AND DISCUSSION

Our synthetic program provided another opportunity to showcase Seebach's concept of "self-regeneration of stereochemistry (SRS)",[10] a method for the asymmetric α alkylation of amino acids that has been widely applied in the synthesis of novel amino acids and peptidomimetics and in the total synthesis of several natural products.[11]

Retrosynthetically, to guarantee the success and efficiency of the installation of the angular methyl group in **2a**, our strategy relied on the transformation of the ester **5** (Scheme 1). The

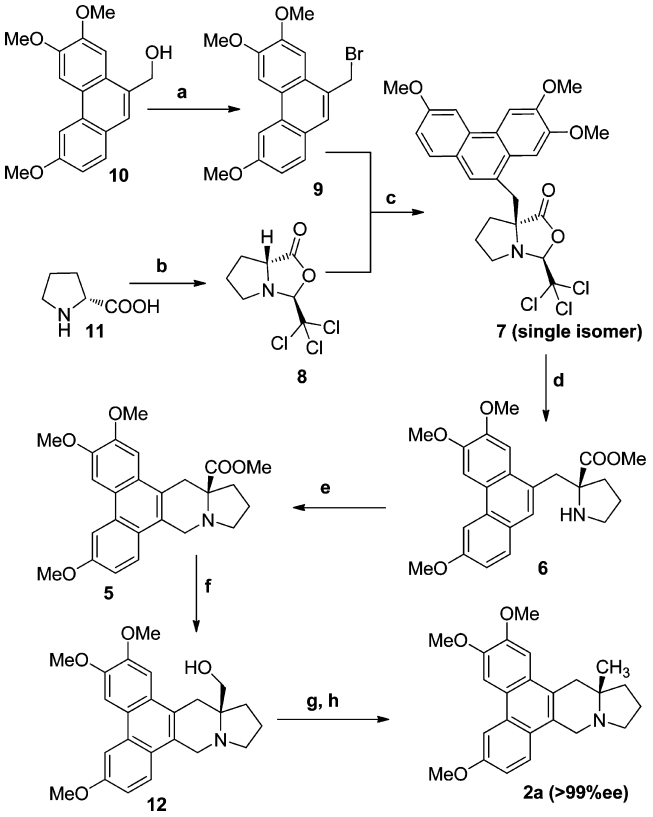
Scheme 1. Retrosynthetic Analysis of Hypoestestatin 1 (2a)



ester can be converted to alcohol or aldehyde, both of which can produce methyl group through deoxygenation. The D ring of the ester **5** was envisioned to arise from intermediate **6** via a Pictet–Spengler cyclization. We reasoned that the cyclization precursor **6** could be derived from phenanthryl bromide **9** and (*R*)-proline derivative **8** via sequential Seebach's stereoselective alkylation and hydrolysis.

The readily prepared known phenanthryl alcohol **10** served as the starting material in the total synthesis of **2a** (Scheme 2).[12] Treatment of alcohol **10** with PBr_3 provided bromide **9** in quantitative yield which was used without further purification due to its liability to decompose. As expected, the high stereoselectively alkylated compound **7** was obtained as the only diastereomer (confirmed by NMR and HPLC) and in excellent yield from bromide **9** and (*R*)-proline derivative **8**. Oxazolidinone **8** was prepared by a modified Seebach's procedure from (*R*)-proline.[13] It is worth noting that the modified Seebach's oxazolidinone **8** was obtained as a white

Scheme 2. Concise Total Synthesis of 2a[a]



[a]Reagents and conditions: (a) PBr_3, CH_2Cl_2; 0 °C to rt; (b) $Cl_3CCH(OH)_2$, $CHCl_3$, reflux for 6 h, 83%; (c) LDA, THF, −78 °C, 84% from **10**; (d) Na, CH_3OH, reflux for 30 min; then AcCl at 0 °C; then reflux for 12 h; (e) HCHO, HCl, EtOH, reflux for 8 h (75% over two steps); (f) $LiAlH_4$, THF, rt 30 min, 98%; (g) MsCl, NEt_3, CH_2Cl_2, 1 h; (h) $LiBHEt_3$, THF, −5 °C to rt (73% over two steps, >99% ee).

crystalline solid and was much more convenient for operation and storage.

With the key intermediate **7** in hand, we then subjected it to hydrolysis. Although the alkylation precursor **8** was sensitive to acid, **7** could not be hydrolyzed under acidic conditions. The amine ester **6** was obtained via a one-pot transesterification ring-opening without further purification. It was then converted to the phenanthroindolizidine ester **5** through a Pictet–Spengler cyclization. As we initially envisioned the angular methyl group in the target molecule, **2** was successfully and efficiently installed from ester **5** via a sequential $LiAlH_4$ reduction, methanesulfonylation, and superhydride reduction. It is also noteworthy that other deoxygenation methods, such as Barton–McCombie radical deoxygenation, transforming **12** to bromide then reduction, and transforming **12** to aldehyde then reduced under Wolff–Kishner conditions did not work well.

Our synthetic **2a** showed ^1H NMR and ^{13}C NMR spectra identical with those of racemic **2a** reported by Ishibashi and was unambiguously derived, thus supporting Ishibashi's conclusion that hypoestestatin 1 was misassigned.[7] We also found that the synthetic **2a** ($[\alpha]_D^{20}$ = +31.7 (*c* = 0.75, CH_2Cl_2) has opposite optical rotation with the isolated sample hypoestestatin 1 ($[\alpha]_D^{31}$ = −36.6 (*c* = 0.55, CH_2Cl_2),[4] suggesting that the absolute configuration of hypoestestatin 1 previously assigned by Pettit may also be wrong. Using the same strategy, we then synthesized its enantiomer ***R*-2a** from (*S*)-proline derivative

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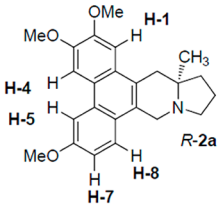
ent-8 and the specific rotation of ***R*-2a** ($[\alpha]_D^{20} = -34.4$ ($c = 0.5$, CH_2Cl_2) matched well with hypoestestatin 1.

Although the NMR spectra of **2a** and ***R*-2a** also could not match with those of hypoestestatin 1, some very interesting phenomena were noted. First, as Pettit had noted, **2a** was extremely sensitive to air and acid, especially in solution,[4] so great caution should be taken in its handling. Second, the ^{1}H NMR signal of 13a-methyl (varies from 1.02 to 1.6) could be affected by trace amounts of acid in the $CDCl_3$ and impurities residual in the sample; third, with incremental amounts of acid added to the sample, all of the chemical shift values of the aromatic protons increased, but just a little, with the same trend (Figure 2) (the titration experiment was done, see the



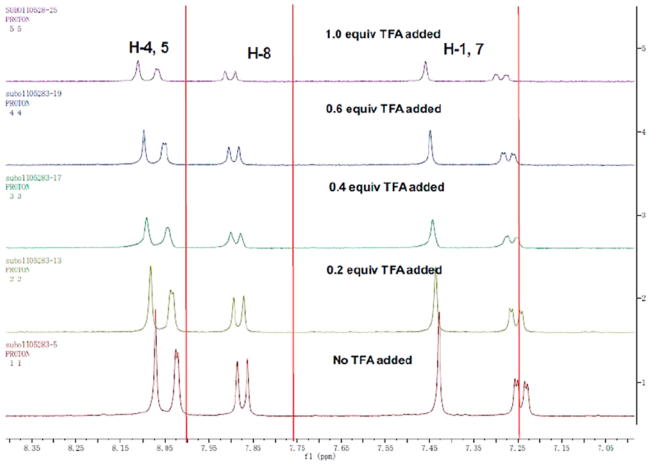
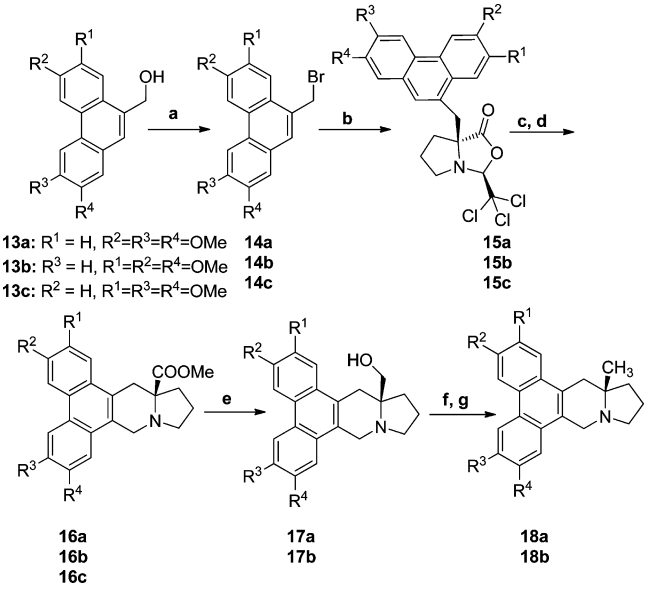


Figure 2. Variance of ^{1}H NMR of aromatic protons with incremental amounts of acid added (red lines indicate literature values for **2a**).

Supporting Information). From the interesting phenomena mentioned above, we can only assume that acidic impurities (at least not the only factor) in the NMR solvent or in the isolated product were not responsible for the difference observed in chemical shifts between the synthetic and natural materials.

In order to further demonstrate the true structure of hypoestestatin 1, we speculated that the placement of the three methoxyl groups on the aromatic nucleus assigned by Pettit was probably wrong. On the basis of the methoxyl groups distribution of the over 60 phenanthroindolizidine alkaloids isolated, three most probable placement of methoxyl groups were (a) 3,6,7-, (b) 2,3,7-, and (c) 2,6,7-. Although great synthetic efforts were made (Scheme 3),[14] unfortunately and disappointingly, none of the three arrangements (a–c) proved to be that in hypoestestatin 1, as revealed by NMR chemical shift data for the aromatic protons. These siginals differed significantly from those of hypoestestatin 1 (Figure 3). We also found that the widely differing 13a-substituents, such as

Scheme 3. Synthesis of the Three Most Probable Structures of 2a[a]



[a]Reagents and conditions: (a) PBr_3, CH_2Cl_2; 0 °C to rt; (b) LDA, THF, **8**, −78 °C; (c) Na, CH_3OH, reflux for 30 min; then AcCl at 0 °C; then reflux for 12 h; (d) HCHO, HCl, EtOH, reflux for 8 h; (e) $LiAlH_4$, THF, rt 30 min; (f) MsCl, NEt_3, CH_2Cl_2, 1 h; (g) $LiBHEt_3$, THF, −5 °C to rt.

methoxycarbonyl versus methyl, have little impact on the NMR chemical shifts of the aromatic signals.

■ CONCLUSION

In conclusion, we have developed an eight-step enantioselective strategy to both enantiomers of 13a-methylphenanthroindolizidine alkaloids (37% overall yield and >99% ee) from commercially available proline and readily prepared phenanthryl alcohols. The overall procedure is simple (chromatographic purification needed in only three steps), versatile, and preparative and thus provides sufficient sample for biological and SAR evaluation. In addition, besides the proposed structure, another three possible structures of hypoestestatin **1** were ruled out. Synthesis of other 13a-methylphenanthroindolizides and biological evaluation were in progress and will be reported in due course.

■ EXPERIMENTAL SECTION

The melting points were determined with an X-4 binocular microscope melting-point apparatus and were uncorrected. ^{1}H NMR spectra were obtained by using spectrometer (400 MHz). Chemical shifts (δ) were given in parts per million (ppm) and were measured downfield from internal tetramethylsilane. ^{13}C NMR spectra were recorded by using spectrometer (100 MHz) and $CDCl_3$ or CD_3OD as solvent. Chemical shifts (δ) are reported in parts per million. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, b = broad, td = triple doublet, dt = double triplet, dq = double quartet, m = multiplet. High-resolution mass spectra were obtained with an FT-ICR MS spectrometer. Optical rotations were measured. The enantiomeric excesses were determined by HPLC with a Chiralcel AD-H or AS-H column.

(3*S*,7a*R*)-3-(Trichloromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3H)-one (8).[13] To a suspension of (*R*)-proline **11** (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

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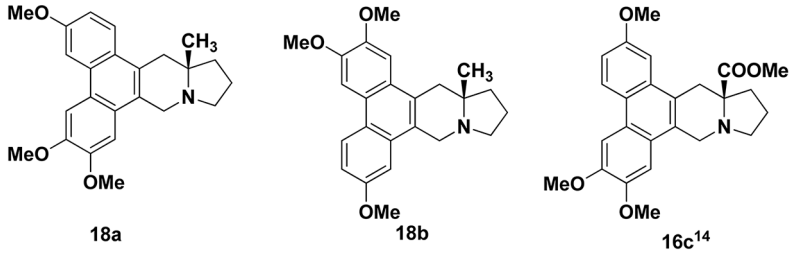

Figure 3. Aromatic ^{1}H NMR of isolated product and other most probable methoxyl groups distributions.

topped with a reflux condenser was attached to the reaction vessel, and the reaction mixture was heated at reflux until (*R*)-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 **8** (18.6 g, 83%) as a colorless to light brown crystals: mp 110−111 °C (lit.[13] mp 107−109 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (s, 1H) 4.12 (dd, J = 8.8, 4.6 Hz, 1H), 3.48−3.38 (m, 1H), 3.18−3.08 (m, 1H), 2.29−2.17 (m, 1H), 2.16−2.08 (m, 1H), 2.00−1.88 (m, 1H), 1.82−1.68 (m, 1H); HRMS (ESI) calcd for $C_7H_8Cl_3NO_2Na$ $(M + Na)^+$ 265.9518, found 265.9512; $[\alpha]_D^{25}$ = −32.8 (c = 2, C_6H_6).

(3*S*,7a*S*)-3-(Trichloromethyl)-7a-((3,6,7-trimethoxyphenanthren-9-yl)methyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one (7). To a solution of compound **10**[12] (1.79 g, 6 mmol) in CH_2Cl_2 (120 mL) was slowly added PBr_3 (3.25 g, 12 mmol) in CH_2Cl_2 (10 mL) over about 10 min at 0 °C. The mixture was stirred at room temperature for 3 h and then poured into ice−water (100 mL). The CH_2Cl_2 layer was separated, washed with ice−water (2 × 50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a pale white solid. The crude phenanthrenyl methane bromide **9** was used in the next step without further purification due to its liability to decompose. To a solution of (*i*-Pr)$_2$NH (0.90 g, 9 mmol) in THF (10 mL) was slowly added *n*-BuLi (4.3 mL, 2.2 M in hexane, 9.5 mmol) via syringe at −78 °C under an atmosphere of nitrogen. Ten minutes later, compound **8** (2.21 g, 9 mmol) in THF (30 mL) was added to the reaction mixture via syringe over 20 min. The reaction mixture was warmed to −35 °C and stirred for an additional 30 min, and then the above crude phenanthrenyl methane bromide **9** in THF (100 mL) was added via syringe over about 30 min. The reaction mixture was warmed to room temperature, stirred for an additional 3 h, and then quenched with a solution of saturated aqueous ammonium chloride (100 mL). After separation, the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layer was concentrated under reduced pressure to give a yellow oil which was purified by chromatography on silica gel (2:1 petroleum ether (60−90 °C)/EtOAc) to give compound **7** (2.7 g, 5.2 mmol, 86%) as a white solid: mp 217−220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.73 (s, 1H), 7.64 (s, 1H), 7.21 (dd, J = 8.8, 2.0 Hz, 1H), 5.05 (s, 1H), 4.13 (s, 3H), 4.09 (s, 3H), 4.03 (s, 3H), 3.73 (d, J = 14.6 Hz, 1H), 3.68 (d, J = 14.6 Hz, 1H), 3.07−2.98 (m, 1H), 2.80−2.70 (m, 1H), 2.05 (d, 6.0 Hz, 1H), 2.03 (d, 6.0 Hz, 1H), 1.53−1.41 (m, 1H), 1.30−1.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 158.3, 149.6, 148.8, 130.6, 130.1, 128.69, 127.62, 127.3, 125.8, 124.7, 115.7, 105.7, 103.7, 102.8, 100.6, 73.5, 58.2, 56.5, 56.0, 55.6, 38.84, 34.83, 25.0; HRMS (ESI) calcd for $C_{25}H_{24}Cl_3NO_5Na$ $(M + Na)^+$ 546.0612, found 546.0610; $[\alpha]_D^{20}$ = +1.65 (c = 0.31, $CHCl_3$).

(*S*)-Methyl 2,3,6-trimethoxy-9,11,12,13,13a,14-hexahydrodibenzo[*f*,*h*]pyrrolo[1,2-*b*]isoquinoline-13a-carboxylate (5). To a suspension of **7** (1.01 g, 2 mmol) in CH_3OH (100 mL) at 0 °C was added sodium metal (46 mg, 2 mmol) in small portions under an atmosphere of nitrogen. The reaction mixture was warmed to 50 °C and kept at this temperature until the substrates completely dissolved. The reaction mixture was then transferred to 0 °C, and AcCl (3.14 g, 40 mmol) was added through a pressure-equalizing addition funnel over about 30 min. The reaction mixture was stirred for an additional 1 h and then heated at reflux for 12 h. The reaction mixture was evaporation in vacuo, and then aqueous saturated sodium dicarbonate (30 mL) and CH_2Cl_2 (30 mL) were added. After separation, the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude amine **6**, without further purification, was dissolved in ethanol (100 mL) to which aqueous HCHO (3 mL, 30% w/w) and HCl (12 mol/L, 3 mL) were added. The resulting mixture was refluxed in the dark for 20 h under an atmosphere of nitrogen. The solvents were evaporated, and the residue was taken up in NaOH (3 mol/L, 30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (50:1 CH_2Cl_2/MeOH) to give **5** (0.84 g, 1.5 mmol, 75% over two steps) as a gray-white solid: mp 187−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.89 (s, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.35 (s, 1H), 7.21 (d, J = 8.8 Hz, 1H), 4.52 (d, J = 16.0 Hz, 1H), 4.46 (d, J = 16.0 Hz, 1H), 4.10 (s, 3H), 4.09 (s, 3H), 4.01 (s, 3H), 3.87 (d, J = 15.8 Hz, 1H), 3.56 (s, 3H), 3.39−3.31 (m, 1H), 3.29−3.21 (m, 1H), 2.98 (d, J = 15.8 Hz, 1H), 2.34−2.32 (m, 1H), 2.18−2.00 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 156.6, 148.4, 147.4, 129.2, 125.8, 124.8, 123.4, 123.0, 122.9, 122.6, 113.8, 103.6, 102.9, 65.1, 55.0, 54.9, 54.5, 50.7, 50.3, 46.7, 36.5, 32.5, 20.0; HRMS (ESI) calcd for $C_{25}H_{28}NO_5$ $(M + H)^+$ 422.1962, found 422.1966; $[\alpha]_D^{20}$ = +122.9 (c = 0.34, $CHCl_3$).

(*S*)-(2,3,6-Trimethoxy-9,11,12,13,13a,14-hexahydrodibenzo-[*f*,*h*]pyrrolo[1,2-*b*]isoquinolin-13a-yl)methanol (12). To a solution of **5** (1.26 g, 3 mmol) in THF (150 mL) was added $LiAlH_4$ (0.12 g, 3 mmol) in portions under an atmosphere of nitrogen. Two hours later, the reaction was quenched with aqueous saturated ammonium chloride (20 mL). After separation, the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was concentrated in vacuo, and the residue was dissolved in CH_2Cl_2 (100 mL), washed with water (3 × 30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give compound **12** (1.15 g, 2.9 mmol, 98%, >99%ee) as a light yellow solid: mp 163−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.91 (d, J = 2.2 Hz, 1H), 7.82 (d, J = 9.0 Hz, 1H), 7.31 (s, 1H), 7.21 (dd, J = 9.0, 2.2 Hz, 1H), 4.40 (d, J = 17.3 Hz, 1H), 4.29 (d, J = 17.3 Hz, 1H), 4.10 (s, 3H), 4.07 (s, 3H), 4.01 (s, 3H), 3.56 (d, J = 10.4 Hz, 1H), 3.47 (d, J = 10.4 Hz, 1H), 3.27−3.20 (m, 1H), 3.00 (d, J = 17.0 Hz, 1H), 2.87 (dd, J = 17.0, 8.5 Hz, 1H), 2.72 (d, J = 16.9 Hz, 1H), 2.30−2.20 (m, 1H), 1.96−1.84 (m, 2H), 1.83−1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 149.6, 148.5, 130.2, 126.7, 124.2, 124.2, 123.7, 123.3, 115.0, 104.9, 104.1, 103.6, 63.5, 61.4, 56.1, 56.0, 55.6, 52.1, 45.4, 34.3,

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28.1, 20.4; HRMS (ESI) calcd for $C_{24}H_{28}NO_4$ $(M + H)^+$ 394.2010, found 394.2009; $[\alpha]_D^{20}$ = +32.6 (c = 0.74, $CHCl_3$).

Proposed Structure of Hypoestestatin 1 (2a). To a solution of alcohol **12** (600 mg, 1.5 mmol) and CH_3SO_2Cl (204 mg, 1.8 mmol) in CH_2Cl_2 (50 mL) cooled with an ice−water bath was added triethylamine (198 mg, 1.95 mmol) in CH_2Cl_2 (8 mL). The reaction mixture was stirred for 2 h at room temperature and then quenched with saturated aqueous ammonium chloride (50 mL). After separation, the organic layer was washed with aqueous ammonium chloride (3 × 50 mL), water (3 × 50 mL), and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The methanesulfonate decomposed when purified by chromatography. To the crude methanesulfonate without further purification in freshly distilled THF (80 mL) at −5 °C under N_2 was added $LiHBEt_3$ (6 mL, 6 mmol, 1 M in THF). The mixture was transferred to room temperature, stirred for another 3 h, and quenched with saturated aqueous ammonium chloride (50 mL). After separation, the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was concentrated under reduced pressure and the residue was purified by chromatography on silica gel (20:1 CH_2Cl_2/MeOH) to give **2a** (0.42 g, 1.11 mmol, 73%, >99% ee) as a light-yellow solid: mp 195−199 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (s, 1H), 7.99 (d, J = 2.4 Hz, 1H), 7.84 (d, J = 9.0 Hz, 1H), 7.39 (s, 1H), 7.21 (dd, J = 9.0, 2.4 Hz, 1H), 4.44 (d, J = 16.4 Hz, 1H), 4.06 (d, J = 16.4 Hz, 1H), 4.05 (s, 3H), 4.00 (s, 3H), 3.99 (s, 3H), 3.14 (d, J = 16.4 Hz, 1H), 3.12−3.08 (m, 1H), 3.03 (d, J = 16.4 Hz, 1H), 2.96−2.87 (m, 1H), 2.06−1.94 (s, 4H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.3, 151.0, 150.1, 131.7, 128.2, 125.5, 125.36, 125.3, 125.2, 124.8, 124.5, 116.7, 105.4, 105.2, 60.4, 56.5, 56.3, 56.0, 51.7, 47.8, 39.7, 36.8, 20.9, 18.0; HRMS (ESI) calcd for $C_{24}H_{28}NO_3$ $(M + H)^+$ 378.2064, found 378.2068; $[\alpha]_D^{20}$ = +31.7 (c = 0.75, CH_2Cl_2).

(3*R*,7a*S*)-3-(Trichloromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one (ent-8). The synthesis procedure was similar to that of compound **8** using (*S*)-proline **ent-11** as starting material to give **ent-8** (82%) as a colorless to light brown crystals: mp 109−110 °C (lit.[13] mp 107−109 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (s, 1H) 4.13 (dd, J = 8.8, 4.6 Hz, 1H), 3.47−3.38 (m, 1H), 3.18−3.06 (m, 1H), 2.29−2.17 (m, 1H), 2.16−2.08 (m, 1H), 2.00−1.88 (m, 1H), 1.82−1.68 (m, 1H); 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).

(3*R*,7a*R*)-3-(Trichloromethyl)-7a-((3,6,7-trimethoxyphenanthren-9-yl)methyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one (ent-7). The synthesis procedure was similar to that of compound **7** to give compound **ent-7** (85% over two steps) as a white solid: mp 218−221 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.84 (d, J = 2.4 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.72 (s, 1H), 7.64 (s, 1H), 7.21 (dd, J = 8.8, 2.4 Hz, 1H), 5.04 (s, 1H), 4.12 (s, 3H), 4.09 (s, 3H), 4.02 (s, 3H), 3.72 (d, J = 14.6 Hz, 1H), 3.68 (d, J = 14.6 Hz, 1H), 3.06−2.98 (m, 1H), 2.81−2.71 (m, 1H), 2.05 (d, 6.0 Hz, 1H), 2.03 (d, 6.0 Hz, 1H), 1.53−1.40 (m, 1H), 1.30−1.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 158.3, 149.6, 148.8, 130.6, 130.1, 128.7, 127.6, 127.2, 125.8, 124.7, 115.7, 105.7, 103.8, 103.8, 102.8, 100.6, 73.5, 58.2, 56.5, 56.0, 55.6, 38.8, 34.8, 25.0; HRMS (ESI) calcd for $C_{25}H_{24}Cl_3NO_5Na$ $(M + Na)^+$ 546.0612, found 546.0615; $[\alpha]_D^{20}$ = +0.91 (c = 0.66, $CHCl_3$).

(*R*)-2,3,6-Trimethoxy-13a-((methylperoxy)methyl)-9,11,12,13,13a,14-hexahydrodibenzo[*f*,*h*]pyrrolo[1,2-*b*]isoquinoline (ent-5). The synthesis procedure was similar to that of compound **5** to give compound **ent-5** (80% over 2 steps, >99%ee) as a gray-white solid: mp 158−164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.82 (d, J = 9.0 Hz, 1H), 7.35 (s, 1H), 7.21 (dd, J = 9.0, 2.4 Hz, 1H), 4.53 (d, J = 16.0 Hz, 1H), 4.46 (d, J = 16.0 Hz, 1H), 4.11 (s, 3H), 4.09 (s, 3H), 4.01 (s, 3H), 3.88 (d, J = 15.9 Hz, 1H), 3.56 (s, 3H), 3.35 (dd, J = 14.8, 7.6 Hz, 1H), 3.25 (dd, J = 14.8, 7.6 Hz, 1H), 2.99 (d, J = 15.9 Hz, 1H), 2.42−2.34 (m, 1H), 2.19−2.11 (m, 1H), 2.10−2.03(m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 157.6, 149.4, 148.4, 130.2, 126.8, 125.8, 124.4, 124.1, 123.9, 123.6, 114.9, 104.7, 103.9, 100.0, 77.4, 77.1, 76.75, 66.2, 56.1, 56.0, 55.6, 51.8, 51.3, 47.8, 37.6, 33.6, 21.0; HRMS (ESI) calcd for $C_{25}H_{28}NO_5$ $(M + H)^+$ 422.1962, found 422.1969; $[\alpha]_D^{20}$ = −110.1 (c = 0.37, $CHCl_3$).

(*S*)-(2,3,6-Trimethoxy-9,11,12,13,13a,14-hexahydrodibenzo-[*f*,*h*]pyrrolo[1,2-*b*]isoquinolin-13a-yl)methanol (ent-12). The synthesis procedure was similar to that for compound **12** to give **ent-12** (99% ee) as a light yellow solid: mp 148−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.92 (d, J = 2.2 Hz, 1H), 7.83 (d, J = 9.0 Hz, 1H), 7.31 (s, 1H), 7.23 (dd, J = 9.0, 2.2 Hz, 1H), 4.41 (d, J = 17.4 Hz, 1H), 4.31 (d, J = 17.4 Hz, 1H), 4.12 (s, 3H), 4.08 (s, 3H), 4.02 (s, 3H), 3.57 (d, J = 10.4 Hz, 1H), 3.48 (d, J = 10.4 Hz, 1H), 3.28−3.20 (m, 1H), 3.00 (d, J = 17.0 Hz, 1H), 2.93−2.83 (dd, J = 17.1, 8.5 Hz, 1H), 2.71 (d, J = 17.0 Hz, 1H), 2.31−2.21 (m, 1H), 1.99−1.76 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 149.6, 148.5, 130.1, 126.7, 124.2, 124.1, 123.7, 123.3, 115.0, 104.9, 104.0, 103.5, 63.4, 56.1, 56.0, 55.6, 52.1, 45.4, 34.2, 30.3, 28.0, 20.4; HRMS (ESI) calcd for $C_{24}H_{28}NO_4$ $(M + H)^+$ 394.2010, found 394.2012; $[\alpha]_D^{20}$ = −25.3 (c = 0.74, $CHCl_3$).

Compound *R*-2a. The synthesis procedure was similar to that of **2a** to give ***R*-2a** (74% over two steps, >99%ee) as a yellow solid: mp 189−193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.92 (d, J = 2.2 Hz, 1H), 7.85 (d, J = 9.0 Hz, 1H), 7.33 (s, 1H), 7.22 (dd, J = 9.0, 2.2 Hz, 1H), 4.46 (d, J = 16.4 Hz, 1H), 4.13 (d, J = 16.4 Hz, 1H), 4.11 (s, 3H), 4.08 (s, 3H), 4.02 (s, 3H), 3.17−3.08 (m, 1H), 3.01 (s, 2H), 2.95−2.88 (m, 1H), 2.03−1.92 (s, 4H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 149.4, 148.3, 130.1, 127.4, 124.8, 124.6, 124.3, 124.2, 123.6, 114.9, 104.7, 103.9, 103.8, 57.6, 56.1, 55.9, 55.6, 50.8, 47.1, 39.4, 35.9, 20.2, 17.7. ^{1}H NMR (400 MHz, CD_3OD) δ 8.07 (s, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.88 (d, J = 9.0 Hz, 1H), 7.43 (s, 1H), 7.24 (dd, J = 9.0, 2.0 Hz, 1H), 4.47 (d, J = 16.3 Hz, 1H), 4.09 (s, J = 16.3 Hz, 1H), 4.10 (s, 3H), 4.04 (s, 3H), 4.03 (s, 3H), 3.17 (d, J = 16.4 Hz, 1H), 3.17−3.10 (m, 1H), 3.06 (d, J = 16.4 Hz, 1H), 2.99−2.90 (m, 1H), 2.09−1.95 (m, 4H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.4, 151.0, 150.1, 131.7, 128.5, 125.6, 125.4, 125.2, 125.2, 125.1, 116.7, 105.7, 105.5, 105.4, 59.4, 56.6, 56.4, 56.0, 51.5, 48.0, 39.9, 37.1, 20.8, 17.5; HRMS (ESI) calcd for $C_{24}H_{28}NO_3$ $(M + H)^+$ 378.2064, found 378.2059; $[\alpha]_D^{20}$ = −34.4 (c = 0.5, CH_2Cl_2).

Synthesis of 15a. The synthesis procedure was similar to that of **7** from the starting material **13a**.[12] The crude product was purified by chromatography on silica gel (2:1 petroleum ether (60−90 °C)/EtOAc) to give **15a** (86%) as a white solid: mp 122−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 2.0 Hz, 1H), 7.84 (s, 1H), 7.53 (s, 1H), 7.19 (dd, J = 9.0, 2.0 Hz, 1H), 7.15 (s, 1H), 5.03 (s, 1H), 4.10 (s, 3H), 4.04 (s, 3H), 4.02 (s, 3H), 3.78 (d, J = 14.4 Hz, 1H), 3.55 (d, J = 14.4 Hz, 1H), 2.96−2.87 (m, 1H), 2.63−2.53 (m, 1H), 2.16−2.09 (m, 1H), 2.04−1.95(m, 1H), 1.50−1.35(m, 1H), 1.19−1.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 157.6, 149.6, 149.2, 131.5, 129.0, 128.0, 127.4, 127.1, 126.0, 123.9, 114.8, 108.0, 104.2, 103.2, 102.8, 100.8, 73.1, 58.1, 56.1, 56.0, 55.5, 39.1, 34.5, 24.9; HRMS (ESI) calcd for $C_{25}H_{24}Cl_3NO_5Na$ $(M + Na)^+$ 546.0612, found 546.0614; $[\alpha]_D^{20}$ = +20.0 (c = 0.3, $CHCl_3$).

Synthesis of 13b. The synthesis procedure of **13b** was similar to that of **10**.[12] Compound **13b** was obtained as a white solid: mp 181−182 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, J = 9.1 Hz, 1H), 7.86 (s, 1H), 7.54 (s, 1H), 7.42 (s, 1H), 7.22 (d, J = 9.1 Hz, 1H), 7.16 (s, 1H), 5.06 (s, 2H), 4.08 (s, 3H), 4.01 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 149.3, 148.6, 134.4, 132.1, 125.8, 124.4, 124.1, 124.1, 123.7, 117.2, 108.4, 104.7, 103.2, 77.4, 77.1, 76.7, 64.6, 55.94, 55.91, 55.4; HRMS (ESI) calcd for $C_{18}H_{19}O_4$ $(M + H)^+$ 299.1278, found 299.1283.

Synthesis of 15b. Using the synthesis procedure similar to that of **7**, compound **15b** (66% from **13b**) was obtained as white crystalline solid: mp 203−204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 9.0 Hz, 1H), 7.94 (s, 1H), 7.70 (s, 1H), 7.63 (s, 1H), 7.24 (dd, J = 9.0, 2.6 Hz, 1H), 7.19 (d, J = 2.6 Hz, 1H), 5.05 (d, J = 5.6 Hz, 1H), 4.11 (s, 3H), 4.08 (s, 3H), 3.97 (s, 3H), 3.75 (d, J = 14.5 Hz, 1H), 3.70 (d, J = 14.5 Hz, 1H), 3.07−2.99 (m, 1H), 2.82−2.75(m, 1H), 2.08−2.02 (m, 2H), 1.54−1.42 (m, 1H), 1.32−1.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 157.8, 149.3, 148.8, 132.2, 130.5, 128.5, 126.0, 125.7, 123.7, 117.2, 108.1, 105.8, 103.2, 102.8, 100.6, 73.5, 58.2, 56.49, 55.9,

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55.5, 39.1, 34.9, 25.0; HRMS (ESI) calcd for $C_{25}H_{24}Cl_3NO_5Na$ (M + Na)$^+$ 546.0612, found 546.0621; $[\alpha]_D^{20}$ = +120.7 (c = 0.43, $CHCl_3$).

Synthesis of 13c. The synthesis procedure of **13c** was similar to that of **10**.[12] Compound **13c** was obtained as a white solid: mp 172−173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 9.1 Hz, 1H), 7.77 (s, 1H), 7.54 (s, 1H), 7.46 (s, 1H), 7.24 (d, J = 10.0 Hz, 1H), 7.05 (s, 1H), 5.04 (s, 2H), 4.05 (s, 3H), 3.94 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 149.4, 148.6, 132.1, 130.7, 125.9, 125.2, 125.1, 124.6, 124.2, 116.5, 108.3, 105.0, 102.6, 64.3, 55.9, 55.8, 55.4; HRMS (ESI) calcd for $C_{18}H_{19}O_4$ (M + H)$^+$ 299.1278, found 299.1274.

Synthesis of 15c. Using the similar synthesis procedure with that of **7**, conpound **15c** (60% from **13c**) was obtained as white crystalline solid: mp 186−188 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, J = 9.0 Hz, 1H), 7.89 (s, 1H), 7.77 (s, 1H), 7.66 (d, J = 2.4 Hz, 1H), 7.28 (dd, J = 9.0, 2.4 Hz, 1H), 7.17 (s, 1H), 5.05 (s, 1H), 4.11 (s, 3H), 4.04 (s, 3H), 4.00 (s, 3H), 3.71 (s, 2H), 3.09−2.98 (m, 1H), 2.82−2.72 (m, 1H), 2.10−2.04 (m, 2H), 1.55−1.41 (m, 1H), 1.35−1.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 157.9, 149.7, 148.9, 132.8, 130.3, 128.2, 125.4, 124.8, 124.2, 116.3, 108.1, 106.2, 102.8, 102.6, 100.6, 73.5, 58.2, 56.02, 55.99, 55.8, 38.6, 34.9, 25.0; HRMS (ESI) calcd for $C_{25}H_{24}Cl_3NO_5Na$ (M + Na)$^+$ 546.0612, found 546.0618; $[\alpha]_D^{20}$ = +47.9 (c = 0.52, $CHCl_3$).

Synthesis of 16a. The synthesis procedure was similar to that of compound **5**. The crude product was purified by chromatography on silicon gel (50:1 CH_2Cl_2/MeOH) to give compound **16a** (62%, over two steps) as a pale white solid: mp 203−204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 9.0 Hz, 1H), 7.90 (s, 2H), 7.23 (dd, J = 9.0, 2 Hz, 1H), 7.17 (s, 1H), 4.49 (d, J = 15.8 Hz, 1H), 4.38 (d, J = 15.8 Hz, 1H), 4.10 (s, 3H), 4.06 (s, 3H), 4.02 (s, 3H), 3.99 (d, J = 16.0 Hz, 1H), 3.53 (s, 3H), 3.42−3.33 (m, 1H), 3.32−3.26 (m, 1H), 3.01 (d, J = 16.0 Hz, 1H), 2.39−2.34 (m, 1H), 2.16−2.02 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 157.6, 149.4, 148.4, 130.5, 125.53, 125.4, 125.3, 125.1, 124.6, 123.3, 114.7, 104.7, 103.8, 103.2, 66.1, 56.0, 55.9, 55.6, 51.7, 51.4, 48.0, 37.5, 33.9, 21.0; HRMS (ESI) calcd for $C_{25}H_{28}NO_5$ (M + H)$^+$ 422.1962, found 422.1968; $[\alpha]_D^{20}$ = +117.5 (c = 0.57, $CHCl_3$).

Synthesis of 16b. The synthesis procedure was similar to that of compound **5** to give compound **16b** (71% over two steps) as a light yellow solid: mp 207−209 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 9.0 Hz, 1H), 7.93 (s, 1H), 7.35 (s, 1H), 7.23 (d, J = 9.0 Hz, 1H), 7.20 (s, 1H), 4.51 (d, J = 16.0 Hz, 1H), 4.42 (d, J = 16.0 Hz, 1H), 4.10 (s, 3H), 4.08 (s, 3H), 3.97 (s, 3H), 3.92 (d, J = 15.6 Hz, 1H), 3.56 (s, 3H), 3.44−3.34 (m, 1H), 3.34−3.24 (m, 1H), 3.03 (d, J = 15.6 Hz, 1H), 2.44−2.34 (m, 1H), 2.21−2.11 (m, 1H), 2.11−1.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 148.8, 148.7, 130.6, 126.5, 124.9, 124.4, 124.2, 123.6, 123.0, 115.5, 103.6, 103.3, 63.4, 61.4, 55.95, 55.9, 55.4, 52.1, 45.5, 34.2, 28.3, 20.4; HRMS (ESI) calcd for $C_{25}H_{28}NO_5$ (M + H)$^+$ 422.1962, found 422.1973; $[\alpha]_D^{20}$ = +121.9 (c = 0.72, $CHCl_3$).

Synthesis of 16c. The synthesis procedure was similar to that of compound **5** to give compound **16c** (67% over two steps) as a light yellow solid: mp 297−199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 9.0 Hz, 1H), 7.87 (s, 1H), 7.34 (s, 1H), 7.30 (d, J = 9.0 Hz, 1H), 7.13 (s, 1H), 4.94 (d, J = 17.2 Hz, 1H), 4.71 (d, J = 17.2 Hz, 1H), 4.12 (d, J = 14.6 Hz, 1H), 4.10 (s, 3H), 4.03 (s, 3H), 3.94 (s, 3H), 3.78 (s, 3H), 3.10 (d, J = 14.6 Hz, 1H), 2.96−2.81 (m, 1H), 2.45−2.25 (m, 2H), 2.08−1.98 (m, 1H), 1.86−1.74 (m, 1H), 1.56−1.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 156.3, 149.4, 149.0, 132.0, 131.6, 129.7, 125.5, 125.5, 124.8, 124.7, 122.6, 112.3, 107.6, 103.1, 70.4, 56.9, 56.0, 55.9, 52.4, 51.4, 43.8, 43.5, 33.3, 23.7; HRMS (ESI) calcd for $C_{25}H_{28}NO_5$ (M + H)$^+$ 422.1962, found 422.1957; $[\alpha]_D^{20}$ = +147.9 (c = 0.68, $CHCl_3$).

Synthesis of 17a. The synthesis procedure was similar to that of compound **12** to give compound **17a** (95%) as a light yellow solid: mp 178−182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 9.2 Hz, 1H), 7.94 (s, 1H), 7.92 (d, J = 1.8 Hz, 1H), 7.24 (dd, J = 9.2, 1.8 Hz, 1H), 7.18 (s, 1H), 4.45 (d, J = 16.4 Hz, 1H), 4.32 (d, J = 16.4 Hz, 1H), 4.12 (s, 3H), 4.06 (s, 3H), 4.03 (s, 3H), 3.70−3.58 (s, 2H), 3.45−3.36 (m, 1H), 3.16 (d, J = 17.0 Hz, 1H), 2.91 (d, J = 17.0 Hz, 1H), 2.85−2.74 (m, 1H), 2.26−2.15 (m, 1H), 2.01−1.91 (m, 1H), 1.88−1.77 (m, 1H), 1.76−1.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 149.7, 148.6, 130.7, 125.5, 125.2, 124.9, 124.7, 123.3, 122.1, 115.1, 104.8, 104.0, 102.9, 63.7, 56.1, 56.0, 55.6, 52.6, 45.8, 34.1, 28.2, 20.8; HRMS (ESI) calcd for $C_{24}H_{28}NO_4$ (M + H)$^+$ 394.2013, found 394.2009; $[\alpha]_D^{20}$ = +117.5 (c = 0.57, $CHCl_3$).

Synthesis of 17b. The synthesis procedure was similar to that of compound **12** to give compound **17b** (94%) as a light yellow solid: mp 168−172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 9.0 Hz, 1H), 7.95 (s, 1H), 7.31 (s, 1H), 7.23 (dd, J = 9.0, 2.4 Hz, 2H), 7.23 (d, J = 2.4 Hz, 1H), 4.37 (d, J = 17.2 Hz, 1H), 4.29 (d, J = 17.2 Hz, 1H), 4.11 (s, 3H), 4.07 (s, 3H), 3.97 (s, 3H), 3.56 (d, J = 10.4 Hz, 1H), 3.48 (d, J = 10.4 Hz, 1H), 3.30−3.21 (m, 1H), 3.03 (d, J = 17.2 Hz, 1H), 2.95−2.80 (m, 1H), 2.75 (d, J = 17.2 Hz, 1H), 2.32−2.21 (m, 1H), 2.00−1.76 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 148.8, 148.7, 130.6, 126.5, 124.9, 124.4, 124.2, 123.6, 123.0, 115.5, 103.6, 103.3, 63.4, 61.4, 56.0, 55.4, 52.1, 45.5, 34.2, 28.3, 20.4; HRMS (ESI) calcd for $C_{24}H_{28}NO_4$ (M + H)$^+$ 394.2013, found 394.2018; $[\alpha]_D^{20}$ = +29.6 (c = 0.67, $CHCl_3$).

Synthesis of 18a. The synthesis procedure was similar to that of compound **2a**. The crude product was purified by chromatography on silica gel (20:1 CH_2Cl_2/MeOH) to give compound **18a** (75%, over two steps) as a yellow solid: mp 189−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.8 Hz, 1H), 7.93 (s, 1H), 7.92 (d, J = 2.4 Hz, 1H), 7.24 (dd, J = 8.8, 2.4 Hz, 1H), 7.15 (s, 1H), 4.49 (d, J = 16.2 Hz, 1H), 4.32−4.20 (m, 1H), 4.12 (s, 3H), 4.07 (s, 3H), 4.03 (s, 3H), 3.30−3.05 (s, 4H), 2.18−1.95 (m, 4H), 1.22 (s, 3H); ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (s, 1H), 7.93 (s, H), 7.18 (s, 2H), 4.68 (d, J = 16.0 Hz, 1H), 4.42 (d, J = 16.0 Hz, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 3.92 (s, 3H), 3.34 (d, J = 16.4 Hz, 1H), 3.40−3.22 (m, 2H), 3.19 (d, J = 16.4 Hz,1H), 2.15−1.98 (m, 1H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 149.7, 148.6, 130.8, 125.3, 125.2, 125.1, 125.1, 124.9, 123.4, 115.01, 104.8, 104.0, 103.0, 56.1, 56.08, 56.03, 55.6, 51.0, 46.6, 38.7, 35.1, 20.0, 18.4; HRMS (ESI) calcd for $C_{24}H_{28}NO_3$ (M + H)$^+$ 378.2064, found 378.2063; $[\alpha]_D^{20}$ = +90.9 (c = 0.46, $CHCl_3$).

Synthesis of 18b. The synthesis procedure was similar to that of compound **2a**. The crude product was purified by chromatography on silicon gel (20:1 CH_2Cl_2/MeOH) to give compound **18b** (60%, over 2 steps) as a yellow solid: 132 °C dec. This compound was extremely unstable, so great caution should be taken when using it. ^{1}H NMR (300 MHz, MeOD) δ 8.48 (d, J = 9.0 Hz, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.21 (s, 1H), 7.19 (d, J = 9.0 Hz, 1H), 4.38 (d, J = 16.0 Hz, 1H), 4.01 (d, J = 16.0 Hz, 1H), 3.99 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H), 3.17−2.99 (m, 2H), 2.96−2.88 (s, 1H), 2.83 (brs, 1H), 1.97 (brs, 4H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, MeOD) δ 159.4, 150.4, 150.1, 131.7, 128.8, 126.6, 126.1, 125.5, 124.7, 124.6, 116.7, 105.4, 104.9, 104.5, 59.4, 56.4, 56.4, 55.8, 51.6, 39.9, 37.2, 20.9, 17.6; HRMS (ESI) calcd for $C_{24}H_{28}NO_3$ (M + H)$^+$ 378.2064, found 378.2067; $[\alpha]_D^{20}$ = +47.2 (c = 0.46, $CHCl_3$).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}NMR spectra for all of the new compounds, variation of ^{1}H NMR resonances of (*R*)-**2a** with added trifluoroacetic acid, and HPLC for **2a**, **5**, **7**, and their enantiomers. 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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(14) Although great effort was made to convert the ester group of **16c** to a methyl group, the transformation could not be achieved.