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Efficient Synthesis of a New Structural Phenanthro[9,10,3′,4′]indolizidine Starting from Pyrrole

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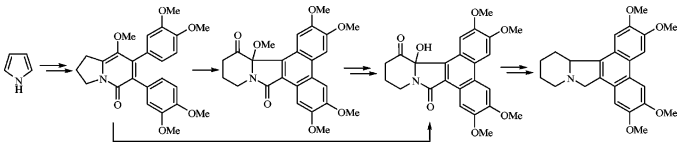

A new structural phenanthroindolizidine, 2,3,6,7-tetramethoxyphenanthro[9,10,3′,4′]indolizidine, has been synthesized efficiently from pyrrole. An important feature of this synthesis is that intramolecular oxidative coupling and rearrangement of 6,7-bis(3,4-dimethoxyphenyl)-8-methoxy-1,2,3-trihydroindolizin-5-one by using VOF_3 and TFA have been achieved in one pot.

Introduction

The phenanthroindolizidine and phenanthroquinolizidine alkaloids are structurally related groups of pentacyclic natural products, for example, (−)-antofine (**1**, Figure 1) and (−)-cryptopleurine (**2**, Figure 1).[1] Since the first isolation of (−)-tylophorine (**3**, Figure 1) in 1935,[2] more than 60 alkaloids and their seco analogues have been reported.[3,4] These alkaloids exhibit interesting pharmacological properties.[1,4,5] Among these interesting biological activities, antitumor activity is most notable,[4,6] and thus, it is responsible for considerable synthetic attention.[3,4,7] We have found that (−)-antofine from *Cynanchum komarovii* possesses excellent antiviral activity against the tobacoo mosaic virus (TMV).[8] Recently, we have developed two different approaches to (+)-tylophorine and (+)-deoxytylophorinine and found that the two phenanthroindolizidine alkaloids possess good antiviral activity against TMV.[9]

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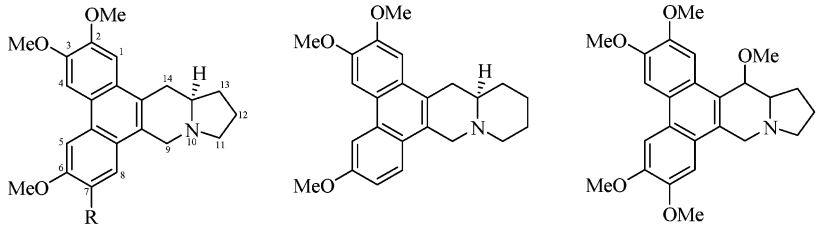
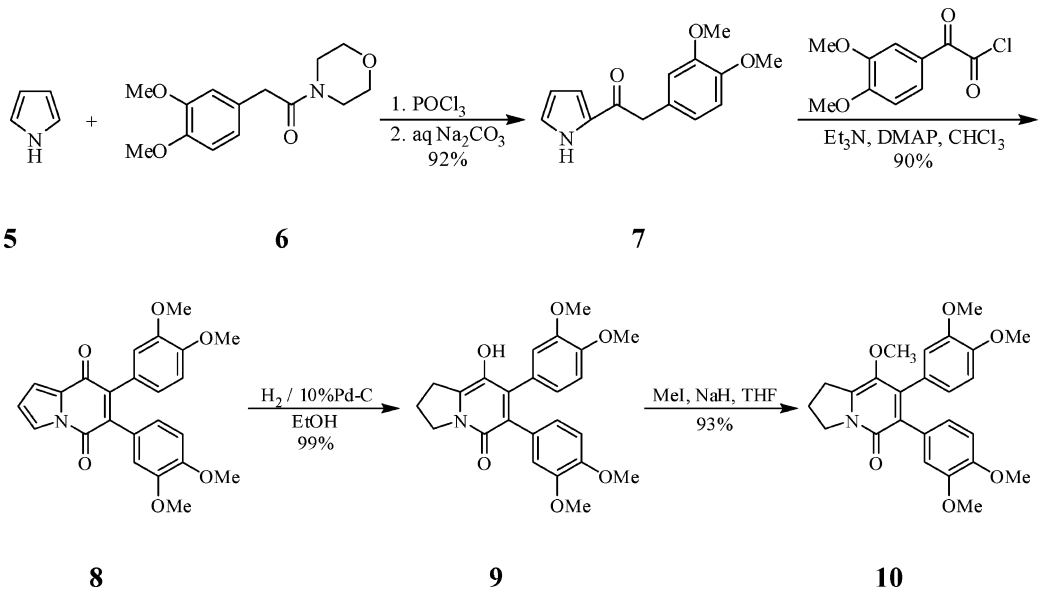
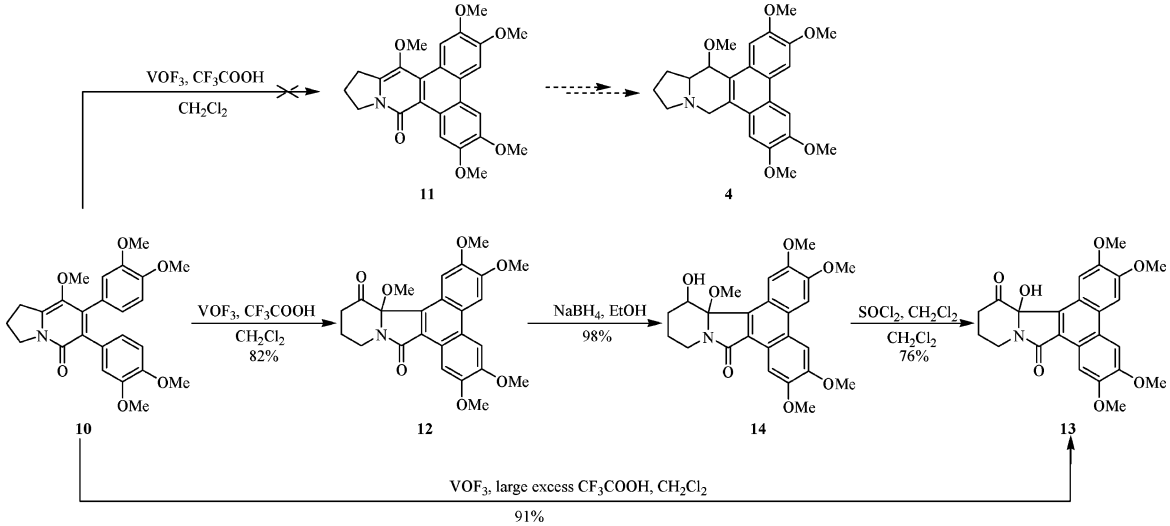


FIGURE 1. Chemical structures of compounds **1**−**4**.

SCHEME 1



SCHEME 2. Synthesis of a New Skeleton Intermediate 13



In order to extend our research work of phenanthroindolizidine alkaloids as antiviral agents and explore further the effect of the 14-methoxy substituent upon antiviral activity, we planned to synthesize 14-methoxytylophorine **4** (Figure 1) from pyrrole (Schemes 1 and 2). However, we were unable to obtain the desired oxidative coupling product **11** (Scheme 2), so we failed to gain the desired compound **4**. Fortunately, we obtained a new skeleton structural product **12** (Scheme 2), which is determined by ^{1}H, ^{13}C NMR, IR, MS, and X-ray diffraction. The compound **12** was used as a key intermediate to synthesize a new structural phenanthroindolizidine alkaloid, 2,3,6,7-tetramethoxyphenanthro-[9,10,3′,4′]indolizidine (**19**), which is different from tylophorine formulated as 2,3,6,7-tetramethoxyphenanthro[9,10,6′,7′]indolizidine. In this paper, we describe full details of our synthetic route to the new skeleton structural phenanthroindolizidine alkaloid **19**.

Results and Discussion

Starting with readily available pyrrole, compound **10** was rapidly assembled through the sequence of reactions as shown in Scheme 1 with good yields. Herz and Tocker have reported the synthesis of 2-acylpyrrole **7** by use of pyrrole, ethyl magnesium iodide, and 2-(3,4-dimethoxyphenyl)acetyl chloride, but only in 7.2% yield.[10] Friedel−Crafts acylation of pyrrole with 2-(3,4-dimethoxyphenyl)acetyl chloride afforded 2-acylpyrrole **7** in poor yield, although it is a convenient reaction for the acylation of substituted pyrroles.[11] We found that the Vilsmeier−Haack condensation of pyrrole with **6** in the presence of phosphorus oxychloride provided the expected 2-acylpyrrole **7** in 92% yield.

It has been reported that indolizinedione **8** was synthesized by a five-step sequence from dimethyl squarate and 4-bromoveratrole with 59% overall yield.[12] Herein, a different reaction sequence was employed for the preparation of the indolizinedione **8** easily. We found that N-acylation and aldol-type condensation reaction of the 2-acylpyrrole **7** with 2-(3,4-dimethoxyphenyl)-2-oxoacetyl chloride in the presence of Et_3N and DMAP have been proceeded in one pot to give the desired indolizinedione **8** at room temperature in 90% yield. This new and efficient synthesis of indolizinedione **8** enjoys a number of advantages in that the reaction is carried out under mild conditions, starting materials are cheap or easily prepared, the experimental procedure is very simple, the yield is high, and this method may be applicable to large-scale production.

Catalytic hydrogenation of **8** gave an essentially quantitative yield of **9**.[12] Compound **9** reacted with MeI in the presence of NaH to afford methyl ether **10** in 93% yield.

Indeed, vanadium(V) oxytrifluoride has proven to be a highly efficient reagent for intramolecular biaryl oxidative coupling of the substituted stilbenes.[13] Surprisingly, treatment of **10** with VOF_3 in the presence of trifluoroacetic acid provided **12**, not the desired product **11** (Scheme 2). This transformation involves oxidative coupling of bis(3,4-dimethoxyphenyl) and rearrangement of 8-methoxy-2,3-dihydroindolizin-5(1*H*)-one. The important intermediate **12** was a new skeleton structural phenanthroindolizidine derivative, which was determined by X-ray diffraction (Figure 2). The structure of the compound **12** shows a conjunction of phenanthrene and indolizidine moieties. The aromatic rings lie almost in the same plane. The observed bond lengths and angles are normal in their alternate single- and double-bond display. The pyrrolidine ring is almost coplanar with the phenanthrene ring. The pyrrolidine ring adopts an envelope conformation. Crystal **12** provides the first crystallographic evidence of the new structural phenanthro[9,10,3′,4′]-indolizidine alkaloid.

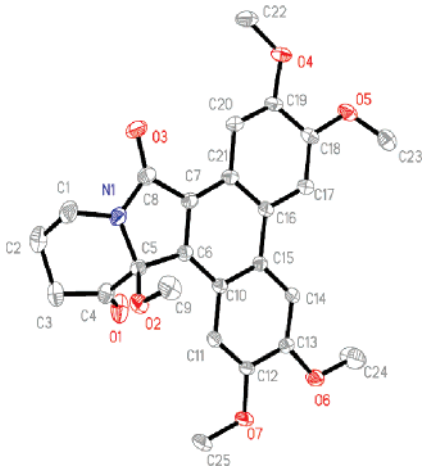


FIGURE 2. Molecular structure of **12** in the crystal.

Borohydride reduction of carbonyl function of **12** gave alcohol **14** in 98% yield, which was oxidized and demethylated in one pot by using $SOCl_2$ to obtain **13** with 76% yield.

Interestingly, while increasing the quantities of trifluoroacetic acid, the reaction of the compound **10** with VOF_3 gave the compound **13** in one step in 91% yield. Thus, an attractive approach to the synthesis of the new skeleton intermediate **13** involves the rearrangement reaction and oxidative coupling and demethylation outlined in Scheme 2.

Vanadium-induced organic synthesis has gained significant importance in recent years.[14] Oxovanadium-catalyzed epoxidation is an especially important reaction in organic synthesis.[15] Oxovanadium compounds participate in oxo-transfer reactions and cause either oxygenation or epoxidation. Hence, we propose that the new skeleton structural product **12** is formed by rearrangement of an epoxide intermediate **11a** in acidic media (TFA) as outlined in Scheme 3. Epoxidation of the oxidative coupling product **11** affords an epoxide **11a** which rearranges in acidic media to give **11c**. Deprotonation of **11c** yields the isolated product **12**, which has a new structural skeleton.

The compound **13** was easily converted to **19** as shown in Scheme 4. First, treatment of the compound **13** with Et_3SiH/CF_3COOH[16] gave **15** in 92% yield. Then reduction of **15** by using sodium borohydride afforded hydroxylactam **16** in 96% yield, which was treated with carbon tetrabromide and triphenylphosphine at 50 °C in THF to provide the bromolactam **17** in 96% yield. Upon hydrogenolysis with 10% palladium on carbon, the compound **17** was converted to **18** in 95% yield. Finally, the lactam **18** was reduced with a mixture of hydride reagent from lithium aluminum hydride and aluminum chloride

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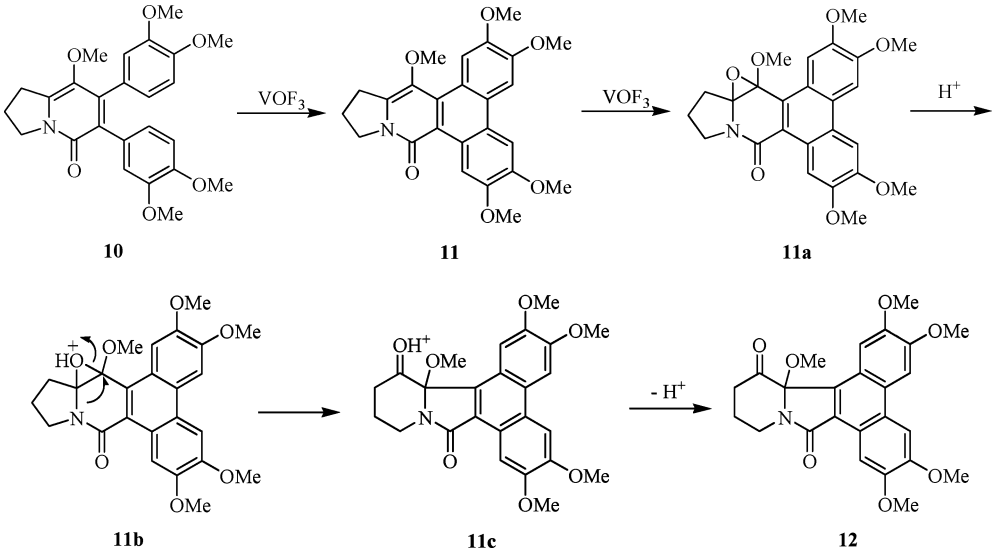
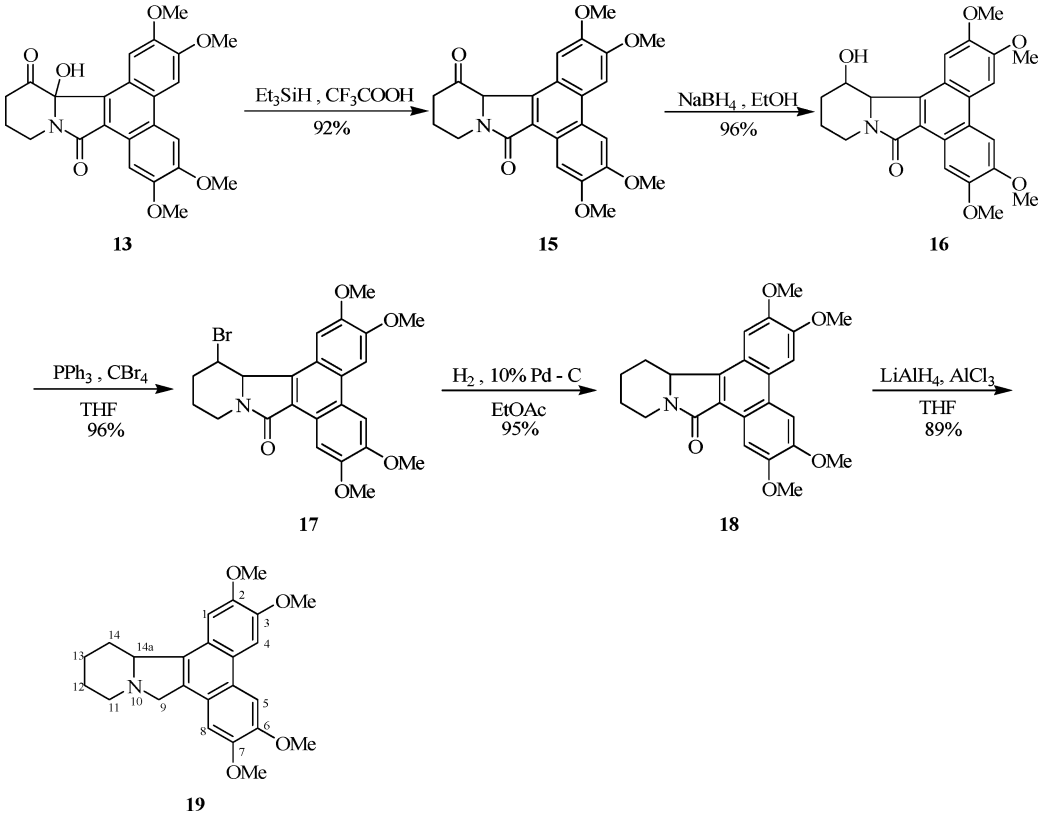
SCHEME 3



SCHEME 4



(3:1)[17] to afford 2,3,6,7-tetramethoxyphenanthro[9,10,3′,4′]-indolizidine (**19**) in 89% yield (Scheme 4).

In summary, the first synthesis of 2,3,6,7-tetramethoxyphenanthro-[9,10,3′,4′]indolizidine (**19**) was accomplished from commercially available chemicals in high overall yield. Intramolecular oxidative coupling and rearrangement of 6,7-bis(3,4-dimethoxyphenyl)-8-methoxy-1,2,3-trihydroindolizin-5-one (**10**) was successfully achieved in one pot by using VOF_3 and TFA.The chemistry described here provides a practical synthetic method of the new skeleton structural phenanthro[9,10,3′,4′]indolizidine alkaloids for biochemical and pharmaceutical studies.

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Experimental Section

2-(3,4-Dimethoxyphenylacetyl)pyrrole (7). To a magnetically stirred and cold (0 °C) solution of **6** (13.25 g, 0.05 mol) in anhydrous 1,2-dichloroethane (40 mL) was added dropwise freshly distilled phosphorus oxychloride (10 mL). The reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 4 h. A solution of freshly distilled pyrrole (3.35 g, 0.05 mol) in anhydrous 1,2-dichloroethane (60 mL) was added at 0 °C. Then the reaction mixture was refluxed for 5 h and cooled. A 10%

aqueous solution of sodium carbonate (250 mL) was added, and the resulting mixture was stirred slowly at first and then as rapidly as possible with vigorous stirring. The resulting mixture was refluxed for 15 min, and then the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic solution was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The dark solid was purified by flash column chromatography on silica gel and recrystallized from ethanol to give **7** (11.27 g, 92%) as a white solid: mp 101−102 °C (lit.[10] mp 99 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (br, 1H), 7.03 (m, 2H), 6.81−6.85 (m, 3H), 6.29−6.32 (m, 1H), 4.02 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H).

6,7-Bis(3,4-dimethoxyphenyl)indolizin-5,8-dione (8). To a solution of 1,2-dimethoxybenzene (6.58 g, 0.05 mol), ethyl oxalyl chloride (6.82 g, 0.05 mol), and 1,2-dichloroethane (50 mL) was added anhydrous aluminum chloride (6.04 g, 0.045 mol) portionwise at 0 °C. Then the reaction mixture was refluxed for 8 h and poured into ice-cold 5% dilute hydrochloric acid (100 mL). To the mixture was added CH_2Cl_2 (200 mL) with shaking. The organic layer was washed with a 10% aqueous solution of sodium carbonate (100 mL). The aqueous layer was separated, filtered, and made acidic with concentrated hydrochloric acid, and the product was extracted with CH_2Cl_2 (150 mL) and crystallized from ethyl acetate to yield 2-(3,4-dimethoxyphenyl)-2-oxoacetic acid (8.11 g, 81%) as a light yellow solid: mp 136−138 °C (lit.[18] mp 136−138 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, $^3J_{HH}$ = 8.4 Hz, 1H), 7.81 (d, $^4J_{HH}$ = 1.6 Hz, 1H), 6.94 (q, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.6 Hz, 1H), 3.99 (s, 3H), 3.95 (s, 3H).

The mixture of 2-(3,4-dimethoxyphenyl)-2-oxoacetic acid (8 g, 38 mmol), CH_2Cl_2 (30 mL), dimethylformamide (one drop), and oxalyl chloride (10.2 g, 80 mmol) was refluxed for 2 h, and then the solvent and excess oxalyl chloride were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL) and added dropwise to a solution of the ketone **7** (4.65 g, 19 mmol), triethylamine (3.8 g, 38 mmol), and DMAP (0.46 g, 3.8 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was warmed to room temperature, and stirring was continued for 10 h. The organic phase was washed successively with 10% aqueous hydrochloric acid, water, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel and recrystallized from CH_2Cl_2/Et_2O to give **8** (7.15 g, 90%) as a red prism: mp 200−202 °C (lit.[12] mp 196−198 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, $^3J_{HH}$ = 3.0 Hz, $^4J_{HH}$ = 1.5 Hz, 1H), 7.24 (dd, $^3J_{HH}$ = 3.6 Hz, $^4J_{HH}$ = 1.5 Hz, 1H), 6.75−6.79 (m, 3H), 6.73 (d, $^4J_{HH}$ = 1.8 Hz, 1H), 6.61−6.62 (m, 1H), 6.57 (d, $^4J_{HH}$ = 1.8 Hz, 1H), 6.47 (t, $^3J_{HH}$ = 3.3 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.64 (s, 3H), 3.63 (s, 3H). Anal. Calcd for $C_{24}H_{21}NO_6$: C, 68.73; H, 5.05; N, 3.34. Found: C, 68.51; H, 5.08; N, 3.53.

6,7-Bis(3,4-dimethoxyphenyl)-8-hydroxy-1,2,3-trihydroindolizin-5-one (9). 6,7-Bis(3,4-dimethoxyphenyl)indolizine-5,8-dione (**8**) (300 mg, 0.71 mmol) was dissolved in ethanol (200 mL), and palladium on carbon (200 mg, 10% Pd−C) was added. H_2 was bubbled through the solution, which was then stirred for 3 h. The catalyst was filtered off, and the filtrate was concentrated in vacuo to obtain a light yellow solid (0.3 g, 99%): mp 186−188 °C (lit.[12] mp 184−185 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, $^3J_{HH}$ = 8.4 Hz, 1H), 6.72 (dd, $^3J_{HH}$ = 6.6 Hz, $^4J_{HH}$ = 1.8 Hz, 1H), 6.62−6.67 (m, 3H), 6.51 (d, $^4J_{HH}$ = 1.8 Hz, 1H), 4.65 (br, 1H), 4.19−4.24 (m, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 3.64 (s, 3H), 3.63 (s, 3H), 3.12−3.18 (m, 2H), 2.19−2.29 (m, 2H).

6,7-Bis(3,4-dimethoxyphenyl)-8-methoxy-1,2,3-trihydroindolizin-5-one (10). To the solution of **9** (2.0 g, 4.7 mmol) in THF (150 mL) was added NaH (0.56 g , 60%, 14.1 mmol). The mixture was refluxed at 66 °C for 1 h, and then a solution of MeI (1.68 g, 11.83 mmol) in THF (30 mL) was added dropwise at 66 °C. After being stirred at 66 °C for 3 h, the mixture was cooled to 0 °C and quenched with H_2O carefully. The aqueous phase was extracted with CH_2Cl_2. The extracts were washed with brine, dried over $MgSO_4$, and evaporated in vacuo to yield a light yellow solid. Recrystallization from methanol gave the desired product **10** (1.92 g, 93%) as a colorless solid: mp 180−182 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62−6.74 (m, 6H), 4.22−4.27 (m, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.64 (s, 6H), 3.27 (s, 3H), 3.20−3.25 (m, 2H), 2.21−2.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 148.3, 148.1, 147.7, 147.0, 140.1, 136.7, 128.5, 128.1, 127.5, 123.9, 122.8, 114.8, 113.7, 110.6, 110.5, 60.7, 55.9, 55.81, 55.77, 55.71, 49.7, 29.1, 21.51; IR (KBr, cm^{-1}) 3070, 3021, 2986, 2934, 2904, 2877, 2831, 1648, 1604, 1463, 1261; EI-MS *m*/*z* 437 (M^+, 100), 422 (30), 394 (8), 391 (5), 363 (4), 348 (3), 211 (4), 68 (3), 41 (3); HRMS (EI) calcd for $C_{25}H_{27}NO_6$ (M^+) 437.1838, found 437.1831.

2,3,6,7,14a-Pentamethoxyphenanthro[9,10,3′,4′]-9,14-indolizidinedione (12). To the solution of **10** (1.0 g, 2.29 mmol) in 8 mL of dry CH_2Cl_2 containing two drops of trifluoroacetic anhydride was added vanadium oxytrifluoride (0.62 g, 5.04 mmol) at −18 °C under N_2, and then to the reaction mixture were added trifluoroacetic acid (1 mL) and two drops of trifluoroacetic anhydride in CH_2Cl_2 (8 mL) dropwise slowly. The dark brown mixture was stirred for an additional 10 h in an ice−salt bath, and CH_2Cl_2 (20 mL) was added. The mixture was quenched with cold 1 M aqueous citric acid, and the organic phase was washed successively with 1 M aqueous citric acid (2 × 20 mL), 3 M NH_4OH (3 × 30 mL), H_2O (2 × 20 mL), and brine (2 × 20 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel to recover the material **10** (0.37 g) and obtain the product **12** (0.53 g, 82%, based on the reacted materials), which was recrystallized from CH_2Cl_2/Et_2O to give a light yellow solid: mp 265 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.85 (s, 1H), 7.83 (s, 1H), 7.59 (s, 1H), 4.40−4.45 (m, 1H), 4.16 (s, 3H), 4.14 (s, 3H), 4.11 (s, 3H), 4.03 (s, 3H), 3.33−3.51 (m, 1H), 3.10−3.20 (m, 1H), 3.00 (s, 3H), 2.52−2.59 (m, 1H), 2.25−2.37 (m, 1H), 2.06−2.21 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 168.2, 151.0, 150.2, 149.9, 149.4, 135.2, 127.3, 126.4, 123.9, 121.8, 121.6, 106.7, 104.8, 103.0, 102.9, 94.2, 56.1, 50.0, 37.3, 35.4, 27.4; IR (KBr, cm^{-1}) 3091, 2995, 2935, 2883, 1731, 1698, 1622, 1444, 1257; EI-MS *m*/*z* 451 (M^+, 30), 423 (8), 392 (84), 380 (16), 190 (7), 31 (100); HRMS (EI) calcd for $C_{25}H_{25}NO_7$ (M^+) 451.1631, found 451.1637.

14a-Hydroxy-2,3,6,7-tetramethoxyphenanthro[9,10,3′,4′]-9,-14-indolizidinedione (13) from 10. To the solution of **10** (1.5 g, 3.43 mmol) in 15 mL of dry CH_2Cl_2 containing two drops of trifluoroacetic anhydride was added vanadium oxytrifluoride (0.94 g, 7.55 mmol) at −18 °C under N_2, and then to the reaction mixture were added trifluoroacetic acid (10 mL) and two drops of trifluoroacetic anhydride in CH_2Cl_2 (5 mL) dropwise slowly. The mixture was stirred for 10 h in an ice−salt bath, and CH_2Cl_2 (20 mL) was added. The mixture was quenched with colded 1 M aqueous citric acid, and the organic phase was washed successively with 1 M aqueous citric acid (2 × 20 mL), 3 M NH_4OH (3 × 30 mL), H_2O (2 × 20 mL), and brine (2 × 20 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel to recover the material **10** (0.4 g) and obtain the product **13** (1.0 g, 91%, based on the reacted materials) as a light yellow solid: mp >300 °C;[1] H NMR (300 MHz, DMSO) δ 8.68 (s, 1H), 8.11 (s, 1H), 8.10 (s, 1H), 7.75 (s, 1H), 7.59 (s, 1H), 4.14−4.23 (m, 1H), 4.10 (s, 3H), 4.07 (s, 3H), 3.92 (s, 3H), 3.85 (s, 3H), 3.40−3.52 (m, 1H), 3.13−3.23 (m, 1H), 2.37−2.45 (m, 1H), 2.22−2.34 (m, 1H), 1.88−2.00 (m, 1H); ^{13}C NMR (75 MHz, DMSO) δ 203.0, 166.3, 150.6, 149.7, 149.4, 148.3, 139.3, 126.8, 125.5, 121.4, 121.1, 120.8, 107.6, 104.2, 104.0, 103.9, 89.3, 56.0, 55.9, 55.4, 55.3, 36.7, 34.7, 27.5; IR (KBr, cm^{-1}) 3448, 3005, 2923, 2832, 1727, 1687, 1622, 1522, 1484, 1216; MS (EI) *m*/*z* 437 (M^+, 42), 409 (100), 380 (34), 296 (13), 148 (16); HRMS (MALDI) calcd for $C_{24}H_{24}NO_7$ $(M + H)^+$ 438.1547, found 438.1543.

(18) Palasz, P. D.; Utley, J. H. P.; Hardstone, J. D. *Acta Chem. Scand. B* **1984**, *38*, 281−292.

14-Hydroxy-2,3,6,7,14a-pentamethoxyphenanthro[9,10,3′,4′]-9-indolizidinone (14). To the solution of **12** (0.45 g, 1 mmol) in ethanol (50 mL) was added sodium borohydride (0.08 g, 2.1 mmol) in three portions at 0 °C. The mixture was warmed to room temperature over a period of 6 h. Ice−water (10 mL) was added, followed by a saturated aqueous solution of ammounium chloride (15 mL). The mixture was extracted with dichloromethane. The extracts were dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel to give **14** (0.44 g, 98%) as a white solid: mp 216 °C dec;[1] H NMR (300 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.10 (s, 1H), 7.69 (s, 1H), 7.65 (s, 1H), 4.21−4.34 (m, 1H), 4.05 (s, 3H), 4.02 (s, 3H), 3.95 (s, 6H), 3.28−3.41 (m, 1H), 2.90 (s, 3H), 2.72−2.83 (m, 1H), 2.58 (d, $^3J_{HH}$ = 8.4 Hz, 1H), 1.73−2.10 (m, 3H), 1.40−1.56 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 150.6, 150.0, 149.8, 149.0, 139.9, 127.2, 125.9, 123.8, 122.1, 121.4, 107.4, 105.0, 103.0, 102.8, 93.1, 76.1, 56.1, 56.0, 50.2, 35.3, 30.1, 24.5; IR (KBr, cm^{-1}) 3440, 3093, 2937, 2850, 1676, 1624, 1521, 1480, 1430, 1264, 1157, 1046; MS (EI) *m*/*z* 453 (M^+, 75), 438 (100), 421 (45), 393 (34), 378 (7), 362 (22), 350 (16), 325 (66); HRMS (EI) calcd for $C_{25}H_{27}NO_7$ (M^+) 453.1788, found 453.1791.

14a-Hydroxy-2,3,6,7-tetramethoxyphenanthro[9,10,3′,4′]-9,-14-indolizidinedione (13) from 14. $SOCl_2$ (0.3 g, 2.52 mmol) in CH_2Cl_2 (4 mL) was added to the solution of **14** (0.3 g, 0.66 mmol) in CH_2Cl_2 (5 mL) at room temperature. The mixture was stirred for 20 min at room temperature and then quenched with water. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed successively with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to afford the desired product **13** (0.22 g, 76%) as a light yellow solid.

2,3,6,7-Tetramethoxyphenanthro[9,10,3′,4′]-9,14-indolizidinedione (15). To the solution of **13** (1.31 g, 3 mmol) in CH_2Cl_2 (5 mL) were added trifluoroacetic acid (15 mL) and triethylsilane (1.74 g, 15 mmol). The mixture was stirred at room temperature for 10 min, diluted with 15 mL of distilled water, and extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel gave **15** (1.16 g, 92%) as a white solid: mp 230−240 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.73 (s, 1H), 7.72 (s, 1H), 7.44 (s, 1H), 5.28 (s, 1H), 4.52−4.58 (m, 1H), 4.13 (s, 3H), 4.12 (s, 3H), 4.10 (s, 3H), 4.04 (s, 3H), 3.47−3.55 (m, 1H), 2.64−2.72 (m, 1H), 2.53−2.60 (m, 1H), 2.23−2.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6, 169.8, 150.8, 149.8, 149.1, 135.8, 127.3, 125.4, 122.6, 122.0, 121.5, 107.2, 104.6, 103.3, 102.9, 66.8, 56.3, 56.2, 38.9, 38.1, 24.2; IR (KBr, cm^{-1}) 3095, 2934, 2835, 1715, 1675, 1622, 1522, 1481, 1449, 1256, 1217, 1199, 1169, 1047; MS (FAB) *m*/*z* 421 (M^+, 13), 307 (12), 154 (100), 136 (76), 88 (33); HRMS (MALDI) calcd for $C_{24}H_{24}NO_6$ $(M + H)^+$ 422.1598, found 422.1598.

14-Hydroxy-2,3,6,7-tetramethoxyphenanthro[9,10,3′,4′]-9-indolizidinone (16) was prepared from **15** by the same method as **14** in 96% yield: mp 238−240 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.81 (s, 1H), 8.24 (s, 1H), 8.05 (s, 2H), 5.82 (d, $^3J_{HH}$ = 5.7 Hz, 1H), 4.58 (d, $^4J_{HH}$ = 8.7 Hz, 1H), 4.24−4.38 (m, 1H), 4.07 (s, 3H), 4.05 (s, 3H), 3.92 (s, 3H), 3.91 (s, 3H), 2.83−3.12 (m, 2H), 1.94−2.11 (m, 1H), 1.67−1.87 (m, 2H), 1.28−1.46 (m, 1H); ^{13}C NMR (75 MHz, DMSO) δ 167.0, 150.2, 149.1, 149.0, 148.1, 143.2, 126.1, 124.6, 121.7, 121.6, 121.5, 108.9, 104.1, 103.9, 73.8, 63.9, 55.9, 55.8, 55.3, 55.2, 38.2, 34.4, 24.1; IR (KBr, cm^{-1} 3332.43, 3100, 2936, 2835, 1647, 1623, 1520, 1481, 1428, 1262, 1198, 1159, 1045; MS (EI) *m*/*z* 423 (M^+, 56), 366(18), 205 (36), 149 (74), 69 (88), 57 (100); HRMS (ESI) *m*/*z* calcd for $C_{24}H_{26}NO_6$ $(M + H)^+$ 424.1755, found 424.1746.

14-Bromo-2,3,6,7-tetramethoxyphenanthro[9,10,3′,4′]-9-indolizidinone (17). To the solution of the alcohol **16** (1.06 g, 2.5 mmol) in dry THF (50 mL) were added PPh_3 (1.31 g, 5 mmol) and CBr_4 (1.66 g, 5 mmol) at room temperature, and the mixture was warmed to 50 °C, stirred for 3 h, and then quenched with saturated aqueous $NaHCO_3$. After extraction with CH_2Cl_2, the extracts were washed with brine and dried ($MgSO_4$). After filtration and removal of solvent, the resulting mixture was purified by flash column chromatography on silica gel to afford **17** (1.17 g, 96%) as a light yellow solid: mp 172 °C dec;[1] H NMR (400 Hz, $CDCl_3$) δ 8.83 (s, 1H), 7.88 (s, 1H), 7.75 (s, 1H), 7.74 (s, 1H), 4.93 (d, $^3J_{HH}$ = 6.6 Hz, 1H), 4.55−4.63 (m, 1H), 4.14 (s, 3H), 4.12 (s, 3H), 4.10 (s, 3H), 4.08 (s, 3H), 3.64−3.70 (m, 1H), 3.07−3.16 (m, 1H), 2.42−2.50 (m, 1H), 2.22−2.35 (m, 1H), 1.86−1.98 (m, 1H), 1.66−1.78 (m, 1H); ^{13}C NMR (100 Hz, $CDCl_3$) δ 168.6, 150.6, 149.9, 149.8, 148.1, 141.8, 127.1, 125.4, 122.7, 122.3, 121.1, 108.5, 104.6, 103.2, 102.9, 64.4, 56.3, 56.2, 55.0, 38.9, 36.9, 26.2; IR (KBr, cm^{-1}) 3092, 2937, 2834, 1679, 1621, 1520, 1480, 1429, 1405, 1260, 1217, 1201, 1160, 1043; *m*/*z* (ESI+) 486 $[M + H]^+$; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{25}NO_5Br$ $(M + H)^+$ 486.0911, found 486.0903.

2,3,6,7-Tetramethoxyphenanthro[9,10,3′,4′]-9-indolizidinone (18). To the solution of **17** (0.2 g, 0.4 mmol) in EtOAc (100 mL) was added 10% palladium on carbon (0.2 g). H_2 was bubbled through the solution and stirred for 15 h at 40 °C. The catalyst was filtered off to obtain a clear solution, and the filtrate was concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel afforded the desired product **18** (0.16 g, 95%) as a white solid: mp 221−223 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.62 (s, 1H), 7.59 (s, 1H), 6.94 (s, 1H), 4.49−4.55 (m, 1H), 4.32−4.37 (m, 1H), 4.03 (s, 9H), 3.93 (s, 3H), 2.92−3.04 (m, 1H), 2.44−2.54 (m, 1H), 1.87−1.96 (m, 1H), 1.57−1.85 (m, 2H), 1.31−1.47 (m, 1H), 0.99−1.11 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 150.1, 149.5, 149.2, 148.8, 142.2, 126.6, 124.5, 122.5, 122.2, 120.5, 104.5, 104.0, 103.8, 102.8, 58.1, 56.0, 39.6, 33.2, 26.1, 24.1; IR (KBr, cm^{-1}) δ 3093, 2937, 2831, 1676, 1624, 1521, 1480, 1430, 1264, 1256, 1209, 1157, 1046, 761; MS (EI) *m*/*z* 407 (M^+, 18), 201 (50), 183 (30), 84 (82), 51 (46); HRMS (ESI) *m*/*z* calcd for $C_{24}H_{26}NO_5$ $(M + H)^+$ 408.1806, found 408.1807.

2,3,6,7-Tetramethoxyphenanthro[9,10,3′,4′]indolizidine (19). To a stirred suspension of $LiAlH_4$ (0.11 g, 3 mmol) and $AlCl_3$ (1.2 g, 9 mmol) in dry THF (30 mL) was added the solution of **18** (0.41 g, 1 mmol) in THF (20 mL) at −15 °C, and the mixture was stirred at −15 °C for 1 h and then at room temperature for 6 h under nitrogen. The reaction mixture was poured over ice, and the solid was filtered. The filtrate was washed with water and dried over $MgSO_4$. After filtration and removal of solvent, the resulting mixture was purified by flash column chromatography on silica gel to afford **19** (0.35 g, 89%) as a white solid: mp 210−219 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.81 (s, 1H), 7.18 (s, 1H), 7.00 (s, 1H), 4.45−4.57 (m, 2H), 4.30−4.34 (m, 1H), 4.11 (s, 6H), 4.02 (s, 3H), 4.01 (s, 3H), 3.32−3.37 (m, 1H), 3.04−3.19 (m, 1H), 2.24−2.39 (m, 1H), 1.88−2.00 (m, 1H), 1.40−1.85 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 148.8, 148.7, 148.5, 136.6, 131.2, 124.6, 124.1, 122.7, 122.3, 104.7, 104.6, 104.0, 103.8, 65.2, 56.1, 55.9, 55.1, 49.2, 29.6, 23.7, 22.3; IR (KBr, cm^{-1}) 3101, 2941, 2924, 2833, 1620, 1519, 1476, 1431, 1255, 1211, 1158, 1036, 841, 771; *m*/*z* (ESI+) 394 $[M + H]^+$; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{28}NO_4$$(M + H)^+$ 394.2013, found 394.2008.

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Supporting Information Available: General experimental methods, synthesisof *N*-(3,4-dimethoxyphenylacetyl)morpholine (**6**), spectroscopic data for **6**−**10** and **12**−**19**, and crystallographic data for **12** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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