Tetrahedron 64 (2008) 7504–7510

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Iron(III) chloride-based mild synthesis of phenanthrene and its application to total synthesis of phenanthroindolizidine alkaloids

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ARTICLE INFO

Article history:
Received 20 March 2008
Received in revised form 28 May 2008
Accepted 3 June 2008
Available online 6 June 2008

Keywords:
Iron (III) chloride
Oxidative coupling
Phenanthrene ring system
Total synthesis

ABSTRACT

Iron(III) chloride has been used to prepare polymethoxy-substituted phenanthrene-9-carboxylic acid via intramolecular oxidative coupling at room temperature in excellent yields. Mild reaction conditions and the use of environmentally friendly $FeCl_3$ provide a novel practical route for the synthesis of the important phenanthrene ring. The further application of this protocol as the key step to total synthesis of tylophorine, deoxytylophorinine, and antofine was achieved starting from readily available pyrrole in 48%, 44%, and 46% overall yields, respectively. This new and efficient strategy enjoys a number of advantages. The experimental procedure is simple under mild conditions, atom economy is very high without any protecting-group, starting materials are cheap or easily prepared. Hence this short and practical method is applicable to large-scale production.

1. Introduction

Phenanthroindolizidine alkaloids isolated mainly from *Cynanchum*, *Pergularia*, *Tylophora*, and some genera of the *Asclepiadaceae* family exhibit interesting biological activities and pharmacological properties,[1] among which antitumor activity is most notable.[2] We have found that (−)-antofine (**3**) (Fig. 1) from *Cynanchum komarovii* possesses excellent antiviral activity against the tobacco mosaic virus (TMV).[3] As a consequence of their exceptional bioactivity and unusual pentacyclic architecture, together with very low natural abundance, many synthetic studies have been made on phenanthroindolizidine alkaloids and their derivatives.[1b,4] As part of our ongoing program aimed at screening plants for biologically active natural products as alternatives to conventional synthetic agrochemicals, we have recently focused on the synthesis of phenanthroindolizidine alkaloids and developed three different synthetic approaches to (+)-tylophorine (**1**), (+)-deoxytylophorinine (**2**), and 2,3,6,7-tetramethoxyphenanthro[9,10,3′,4′]-indolizidine (**4**) (Fig. 1).[5] But these reported approaches were not suitable for large-scale preparation due to low yield, harsh conditions or long steps.

The synthesis of polymethoxy-substituted phenanthrene unit is the key step in the preparation of these alkaloids.[1b,1c,4] Therefore, development of an effective protocol to access polymethoxy-substituted phenanthrenes is noteworthy. Pschorr proposed the first synthesis of phenanthrene core in 1896 via an arenediazonium salt to effect intramolecular coupling,[6] and the Pschorr reaction has been widely used and become a classical method to synthesize phenanthrene ring system.[7] But the long linear sequence and low overall yields restrict the practical application of this method. Subsequently, a number of alternative methods have been developed to synthesize the phenanthrene ring system.[1b,1c,4] Specially, intramolecular oxidative coupling to yield phenanthrene ring system using oxidative coupling reagents such as thallium(III) triflouroacetate (TTFA),[8] lead(IV) tetraacetate ($Pb(OAc)_4$),[9] phenyliodine(III) bis(trifluoroacetate) (PIFA) and phenyliodine(III) diacetate (PIDA).[10] Among them vanadium oxytrifluoride (VOF_3)[4g,11] has attracted more and more attention. However, extensive application of these reagents has been limited by high toxicity, severe conditions, and low yields. We have recently reported the use of vanadium oxytrichloride ($VOCl_3$) for the synthesis of polymethoxy-substituted phenanthrene derivatives by oxidative coupling of substituted methyl (*E*)-α-phenyl cinnamate.[12] Despite that we decrease the loading of the oxidant and increase the yield, broad scope of synthesis has been limited by severe conditions and side reactions. In addition, there was an example of using iron(III) complex and some iron(III) solvates for oxidative aryl–aryl coupling reactions,[13] but the preparation of the complex was usually troubled and the yield was moderate. Therefore, an improved method for the synthesis of the phenanthrene ring system needs to be explored.

Iron(III) chloride is extensively used in organic synthesis in recent years since it is an inexpensive, environmentally friendly, and strong oxidizing agent for several useful reactions such as

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doi:10.1016/j.tet.2008.06.003

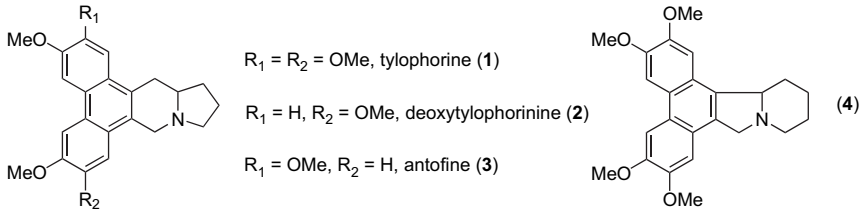


Figure 1. Structures of alkaloids (**1**), (**2**), (**3**), and their analogue (**4**).

polymerizations and oxidations.[14,15] For example, binaphthols and polycyclic arenes have been synthesized through $FeCl_3$-mediated oxidative couplings.[16] We found that construction of phenanthrene-9-carboxylate from 2,3-diphenylacrylate was achieved by intramolecular oxidative coupling using iron(III) chloride in excellent yield.[17]

Herein, we wish to report a facile synthesis of polymethoxy-substituted phenanthrene-9-carboxylic acid by using $FeCl_3$ at room temperature with excellent yield and its further application to the total synthesis of the representative phenanthroindolizidine alkaloids, tylophorine, deoxytylophorinine, and antofine.

2. Results and discussion

The *E*- and *Z*-2,3-diphenylacrylic acid **7** are easily available from Perkin condensation of the appropriate benzeneacetic acid **5** with the corresponding aromatic aldehyde **6** as shown in Scheme 1 (R_1, R_2=OMe, H).[11a,12,18] We found that such condensations invariably yield a mixture of *E*-isomer as the main product and *Z*-isomer as the minor product. For example, Perkin condensation of 3,4-dimethoxyphenylacetic acid with 3,4-dimethoxybenzadehyde provided (*E*)-methyl 2,3-bis(3,4-dimethoxyphenyl)acrylic acid *E*-**7a**, at the same time, (*Z*)-methyl 2,3-bis(3,4-dimethoxyphenyl)acrylic acid *Z*-**7a** as a minor product. Compounds *E*-**7a** and *Z*-**7a** can be obtained, respectively, by precipitation at different pH.[11a,18]

Construction of phenanthrene-9-carboxylic acid **8** from the mixture of *E*- and *Z*-2,3-diphenylacrylic acid **7** was achieved by an intramolecular oxidative coupling reaction using iron(III) chloride at room temperature in excellent yield for the first time. Hence, by using this facile and efficient protocol as the key step, we explored a practical synthetic route for the large-scale preparation of the phenanthroindolizidine alkaloids tylophorine **1** (R_1=R_2=OMe), deoxytylophorinine **2** (R_1=H, R_2=OMe), and antofine **3** (R_1=OMe, R_2=H) from pyrrole as shown in Scheme 2.

Tylophorine **1** was chosen as our initial target since its simplicity would allow us to test the feasibility of the approach (Scheme 3). The key intermediate for our synthesis was the known carboxylic acid **8a**, which was obtained from the commercially available homoveratric acid **5a** and veratraldehyde **6a**. Perkin condensation[11a,18] of acid **5a** with aldehyde **6a** gave mainly (*E*)-isomer **7a** and (*Z*)-isomer **7a** as a separable mixture (82%, 10:1 *E*/*Z*) by recrystallization from methanol. Interestingly, not only (*E*)-isomer **7a** but also (*Z*)-isomer **7a** gave the same oxidative coupling product **8a** in the presence of $FeCl_3$ at room temperature in 87% yield. In contrast to the Pschorr synthesis of phenanthrene, the reaction makes full use of the minor (*Z*)-isomer **7a**, which was a byproduct in the Pschorr reaction. This facile and efficient synthesis of the oxidative coupling product **8a** has been applicable to large-scale production.

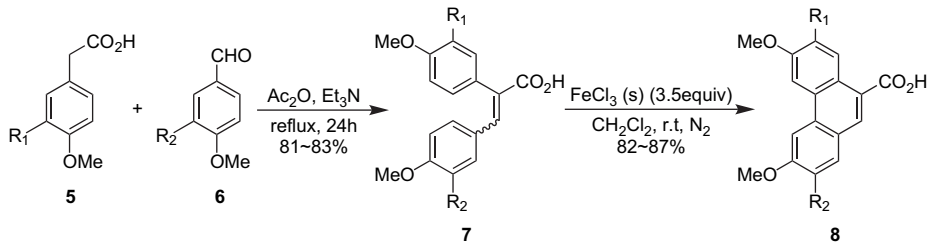
With a large amount of carboxylic acid **8a** in hand, we use intermolecular Friedel–Crafts acylation of the corresponding acylchloride (prepared by chlorination of acid **8a** with oxalyl chloride) and pyrrole catalyzed by tin tetrachloride ($SnCl_4$) to construct pyrrolidine ring system **9a** under mild conditions in 79% yield. As expected, pyrrole is an electron-rich aromatic heterocycle, which has stronger electrophilic substitution reaction ability than furan, thiophene, and free benzene ring. This synthesis is very straight forward but unspectacular during the total synthesis of phenanthroindolizidine alkaloids.

2-Acylpyrrole **9a** was transformed to the corresponding 2-alkylpyrrole **11a** by using sodium borohydride in boiling 2-propanol[19] with 94% yield. Subsequent catalytic hydrogenation[20] of **11a** in acetic acid gave a quantitative yield of pyrrolidine **10a**. Finally, the Pictet–Spengler cyclomethylenation of **10a** afforded the racemic tylophorine **1** in 95% yield.[4h] Thus, the shortest synthetic route to a large-scale preparation of tylophorine **1** was achieved starting from readily available pyrrole under mild conditions free of any protecting-group in 48% overall yield. We have used the route and synthesized 200 g of tylophorine for testing against TMV.

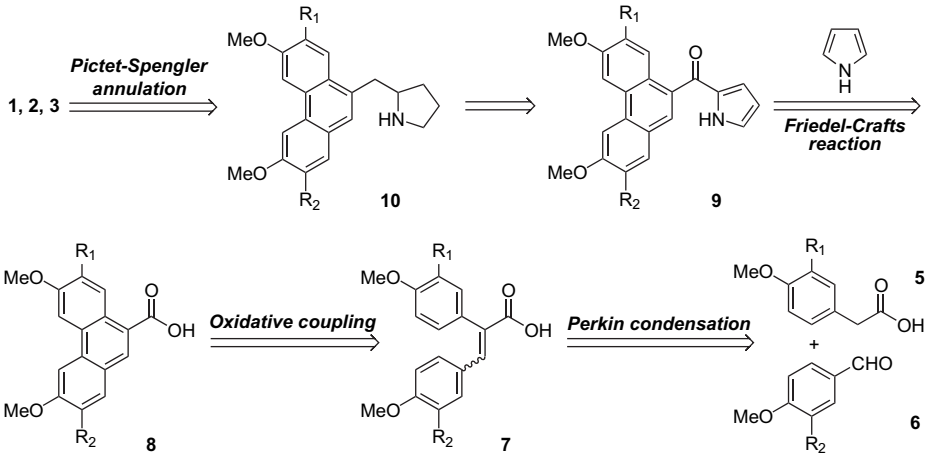
Having demonstrated the feasibility of the above synthetic pathway to tylophorine **1**, we then turned our attention to the preparation of deoxytylophorinine **2** and antofine **3** (Scheme 3). Deoxytylophorinine **2** and antofine **3** have been synthesized on a large scale in 44% and 46% overall yields, respectively, in six steps such as Perkin condensation of the appropriate benzeneacetic acids **5b**,**c** and the corresponding aromatic aldehydes **6b**,**c**, intramolecular oxidative coupling of acids **7b**,**c** in the presence of $FeCl_3$, chlorination of acids **8b**,**c**, and subsequent intermolecular Friedel–Crafts reactions with pyrrole in one pot, deketonization of 2-acylpyrroles **9b**,**c**, catalytic hydrogenation of 2-alkylpyrroles **11b**,**c**, and Pictet–Spengler cyclomethylenation of pyrrolidines **10b**,**c**.

3. Conclusion

In summary, iron(III) chloride has been applied to prepare polymethoxy-substituted phenanthrene-9-carboxylic acid via



Scheme 1. Synthesis of the compounds **7** and **8**.



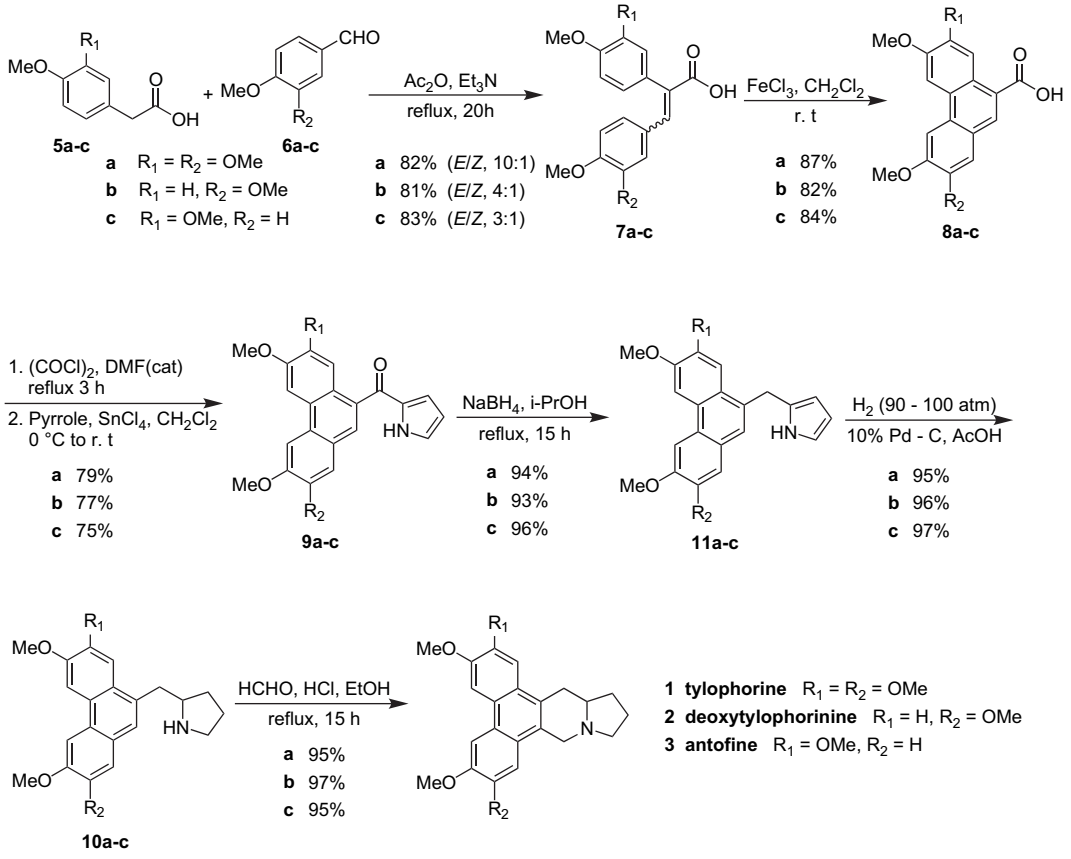
Scheme 2. Retrosynthetic analysis of phenanthroindolizidine alkaloids **1**, **2**, and **3**.

intramolecular oxidative coupling at room temperature in excellent yield. This reaction utilizes environmentally friendly oxidant $FeCl_3$ and can be carried out in one step under simple and mild conditions. And it is suitable for large-scale synthesis of phenanthrene derivatives. By using this facile and efficient protocol as the key step, we have developed the shortest, practical, green, and modular route to naturally occurring phenanthroindolizidine alkaloids. The versatility and flexibility of the method have been demonstrated by the large-scale preparations of three representative phenanthroindolizidine alkaloids, tylophorine, deoxytylophorinine, and antofine in 48%, 44% and 46% overall yields, respectively. This new and efficient strategy enjoys a number of advantages of which the experimental procedure is simple under mild conditions, atom economy is very high without any protecting-group, starting materials are cheap or easily prepared. Hence this shortest and practical method is applicable to large-scale production.

4. Experimental

4.1. General

The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and were uncorrected. ^1H NMR spectra were



Scheme 3. Synthesis of tylophorine (**1**), deoxytylophorinine (**2**), and antofine (**3**).

obtained using a Bruker AC-P 300 and a Varian Mercury Plus 400 MHz spectrometer. Chemical shift values (δ) are given in parts per million and were downfield from internal tetramethylsilane. ^{13}C NMR spectra were recorded using a Bruker AC-P 300 (75 MHz) and a Varian Mercury Plus 400 spectrometer (100 MHz) using $CDCl_3$ or DMSO-d_6 as a solvent. Chemical shift values (δ) are reported in parts per million from the solvent peak (77.0 ppm). IR spectra were recorded with an EQUINOX FTIR (Bruker Company) spectrometer. Mass spectra were obtained on a VG ZAB-HS instrument spectrometer using the EI method and LCQ Advantage instrument spectrometer using the ESI method. HRMS was obtained on FT-ICR MS (Ionspec, 7.0T). All anhydrous solvents were dried and purified by standard techniques just before use. $FeCl_3$ is commercially available from J&K Chemical Ltd. and it was used without further purification.

4.2. Preparation of 2,3-bis(3,4-dimethoxyphenyl)acrylic acid (7a)

A mixture of homoveratric acid **5a** (98.0 g, 0.5 mol), veratraldehyde **6a** (90.0 g, 0.54 mol), acetic anhydride (200 mL), and triethylamine (100 mL) was heated at reflux for 20 h with the exclusion of moisture. The solution was allowed to cool to room temperature, water (400 mL) was added, and the mixture was stirred for 1 h. The mixture was then poured into aqueous potassium carbonate (350.0 g in 800 mL water) and refluxed until nearly all the gummy material was dissolved. The solution obtained was cooled, extracted with ether (3×120 mL), and carefully acidified with concentrated hydrochloric acid (pH 4∼5) to produce a white precipitate. The solid was collected and washed with methanol (400 mL) to give 2,3-bis(3,4-dimethoxyphenyl)acrylic acid **7a** (141.0 g, 82%) as a mixture of *E*/*Z* isomer (10:1). The solid was collected and recrystallized from methanol to give *E*-2,3-bis(3,4-dimethoxyphenyl)acrylic acid **7a** as a white solid (118.7 g, 69%). Mp 214–216 °C (lit.[21] mp 216–217 °C); ^1H NMR (400 MHz, DMSO) δ 12.50 (br, 1H), 7.68 (s, 1H), 6.54–6.98 (m, 6H), 3.74 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.45 (s, 3H).

4.3. Preparation of 2-(4-methoxyphenyl)-3-(3,4-dimethoxyphenyl)acrylic acid (7b)

By following the same procedure as for **7a** gave **7b** as a mixture of *E*/*Z* isomer (4:1) in 81% yield. The solid was recrystallized from methanol to give *E*-2-(4-methoxyphenyl)-3-(3,4-dimethoxyphenyl)acrylic acid **7b** as a white solid in 67% yield. Mp 208–210 °C (lit.[22] mp 213–214 °C); ^1H NMR (400 MHz, DMSO) δ 12.55 (br, 1H), 7.69 (s, 1H), 6.54–7.12 (m, 7H), 3.78 (s, 3H), 3.72 (s, 3H), 3.37 (s, 3H).

4.4. Preparation of 2-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)acrylic acid (7c)

By following the same procedure as for **7a** gave **7c** as a mixture of *E*/*Z* isomer (3:1) in 83% yield. The mixture was recrystallized from methanol to give *E*-2-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)acrylic acid **7c** as a white solid in 66% yield. Mp 210–212 °C (lit.[23] mp 207–208 °C); ^1H NMR (400 MHz, DMSO) δ 12.48 (br, 1H), 7.71 (s, 1H), 6.70–7.09 (m, 7H), 3.80 (s, 3H), 3.72 (s, 3H), 3.68 (s, 3H).

4.5. Preparation of 2,3,6,7-tetramethoxyphenanthrene-9-carboxylic acid (8a)

To a solution of the mixture of *E*/*Z* isomer **7a** (24.1 g, 0.07 mol) in CH_2Cl_2 (600 mL) was added anhydrous $FeCl_3$ (39.8 g, 0.25 mol). The reaction solution was stirred at room temperature for 8 h, and then quenched with methanol (150 mL). The mixture was concentrated and the residue was washed with methanol (200 mL), filtered, washed with methanol (3×30 mL) again to give acid **8a** (20.8 g, 87%) as a light yellow solid. Mp 285–287 °C (lit.[24] mp 280–282 °C); ^1H NMR (300 MHz, DMSO) δ 8.58 (s, 1H), 8.43 (s, 1H), 8.03 (s, 1H), 7.99 (s, 1H), 7.54 (s, 1H), 4.08 (s, 3H), 4.07 (s, 3H), 3.94 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 169.0, 151.0, 148.8, 148.7, 129.6, 126.4, 124.9, 124.1, 123.4, 122.8, 109.5, 106.8, 103.9, 103.4, 55.9, 55.8, 55.5, 55.2.

4.6. Preparation of 2,3,6-trimethoxyphenanthrene-9-carboxylic acid (8b)

To a solution of the mixture of *E*/*Z* isomer **7b** (15.7 g, 0.05 mol) in CH_2Cl_2 (500 mL) was added anhydrous $FeCl_3$ (28.4 g, 0.17 mol). The reaction solution was stirred at room temperature for 8 h, the mixture was concentrated, and the residue was washed with ethyl ether (200 mL), filtered, washed with ethyl ether (3×30 mL) again to give acid **8b** (12.8 g, 82%) as a light yellow solid. Mp 221–223 °C (lit.[25] mp 220–221 °C); ^1H NMR (300 MHz, DMSO) δ 8.87 (dd, $^4J_{HH}$=1.2 Hz, $^3J_{HH}$=9.3 Hz, 1H), 8.35 (s, 1H), 8.13 (s, 1H), 7.10 (s, 1H), 7.60 (s, 1H), 7.30 (dd, $^4J_{HH}$=1.8 Hz, $^3J_{HH}$=9.3 Hz, 1H), 4.07 (s, 3H), 4.01 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 168.9, 157.8, 150.9, 149.6, 131.4, 128.9, 127.9, 126.0, 125.2, 124.0, 122.7, 116.1, 109.6, 104.5, 103.9, 56.0, 55.6, 55.4.

4.7. Preparation of 2,3,6-trimethoxyphenanthrene-10-carboxylic acid (8c)

By following the same procedure as for **8b** gave **8c** as a light yellow solid (84%). Mp 210–212 °C (lit.[26] mp 215 °C); ^1H NMR (300 MHz, DMSO) δ 13.0 (br, 1H), 8.58 (s, 1H), 8.45 (s, 1H), 8.14 (s, 1H), 8.10 (d, $^4J_{HH}$=2.1 Hz, 1H), 8.03 (d, $^3J_{HH}$=9.0 Hz, 1H), 7.28 (dd, $^4J_{HH}$=2.1 Hz, $^3J_{HH}$=8.7 Hz, 1H), 4.06 (s, 3H), 4.04 (s, 3H), 3.92 (s, 3H).

4.8. Preparation of (2,3,6,7-tetramethoxyphenanthren-9-yl)(1*H*-pyrrol-2-yl)methanone (9a)

To acid **8a** (6.84 g, 0.02 mol) was added dropwise freshly distilled oxalyl chloride (50 mL, 0.58 mol) and dimethylformamide (two drops) at 0 °C. The reaction mixture was then stirred at room temperature for 1 h and refluxed for 3 h. The excess of oxalyl chloride was removed under reduced pressure, the residue was dissolved in dry CH_2Cl_2 (150 mL) at 0 °C, and a solution of anhydrous $SnCl_4$ (2.8 mL, 0.024 mol) in CH_2Cl_2 (30 mL) was added slowly under N_2. The mixture was stirred at 0 °C for 0.5 h, and a solution of freshly distilled pyrrole (1.87 g, 0.028 mol) in CH_2Cl_2 (50 mL) was slowly added to the mixture and warmed to room temperature for 10 h, and quenched with 5% dilute hydrochloric acid (100 mL). The mixture was filtered on Celite and washed with CH_2Cl_2 (3×30 mL), the organic phase was washed successively with 10% aqueous Na_2CO_3 (30 mL), water, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 10:1 v/v) to obtain acylpyrrole **9a** (6.17 g, 79%) as a light yellow solid. Mp 258–260 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 9.83 (br, 1H), 7.97 (s, 1H), 7.81–7.84 (m, 3H), 7.25 (s, 1H), 7.20–7.21 (m, 1H), 6.83–6.84 (m, 1H), 6.34–6.36 (m, 1H), 4.16 (s, 3H), 4.14 (s, 3H), 4.03 (s, 3H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.7, 150.9, 149.6, 149.3, 133.1, 131.9, 127.7, 126.2, 125.7, 125.4, 124.8, 123.9, 120.1, 111.2, 109.3, 106.7, 103.0, 102.9, 56.3, 56.2, 56.1, 56.0; IR (KBr, cm^{-1}) 3313, 3296, 3093, 2294, 1619, 1508, 1468, 1427, 1375, 1319, 1254, 1157, 1105, 781, 750, 608, 531; MS (EI) *m*/*z* 391 (M^+, 42), 360 (2), 196 (5), 94 (10), 44 (18), 28 (100); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{22}NO_5$ $[M+H]^+$ 392.1493, found 392.1493.

4.9. Preparation of (2,3,6-trimethoxyphenanthren-9-yl)(1*H*-pyrrol-2-yl)methanone (9b)

By following the same procedure as for **9a** gave **9b** as a white solid (77%). Mp 244–246 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.25 (br, 1H), 8.08–8.19 (m, 3H), 7.94 (s, 1H), 7.60 (s, 1H), 7.25–7.30 (m, 2H), 6.68 (d, $^4J_{HH}$=1.2 Hz, 1H), 6.27 (d, $^4J_{HH}$=1.8 Hz, 1H), 4.10 (s, 3H), 4.03 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 185.3, 158.0, 150.3, 149.7, 132.9, 132.4, 131.3, 127.5, 126.7, 125.4, 125.3, 124.9, 122.6, 119.7, 115.9, 110.2, 109.5, 104.6, 104.0, 56.0, 55.5; IR (KBr, cm^{-1}) 3361, 3332, 3107, 2926, 2831, 1612, 1510, 1452, 1416, 1373, 1315, 1285, 1256, 1196, 1162, 1104, 1075, 1024, 981, 835, 763, 683; MS (ESI) *m*/*z* 761 [2M+K]$^+$; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{19}NO_4Na$ [M+Na]$^+$ 384.1206, found 384.1212.

4.10. Preparation of (2,3,6-trimethoxyphenanthren-10-yl)(1*H*-pyrrol-2-yl)methanone (9c)

By following the same procedure as for **9a** gave **9c** as a light yellow solid (75%). Mp 182–184 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.00 (br, 1H), 8.00 (s, 1H), 7.92 (s, 1H), 7.82–7.87 (m, 3H), 7.18–7.24 (m, 2H), 6.81–6.84 (m, 1H), 6.32–6.35 (m, 1H), 4.12 (s, 3H), 4.04 (s, 3H), 3.98 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 185.3, 159.4, 149.4, 149.2, 132.4, 131.8, 131.4, 131.2, 127.0, 126.7, 124.6, 124.2, 123.8, 119.6, 116.3, 110.2, 106.3, 104.5, 104.2, 55.9, 55.6, 55.2; IR (KBr, cm^{-1}) 3296, 3223, 3107, 2908, 2940, 2831, 1605, 1510, 1460, 1416, 1380, 1315, 1264, 1097, 1024, 886, 865, 748, 596; MS (ESI) *m*/*z* 362 [M+H]$^+$, 745 [2M+Na]$^+$; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{20}NO_4$ [M+H]$^+$ 362.1387, found 362.1389.

4.11. Preparation of 2-((2,3,6,7-tetramethoxyphenanthren-9-yl)methyl)-1*H*-pyrrole (11a)

A mixture of **9a** (5.87 g, 0.015 mol), sodium borohydride (3.42 g, 0.09 mol), and 2-propanol (500 mL) was refluxed under nitrogen for 15 h. The solution was concentrated under reduced pressure, diluted with methylene chloride (200 mL) and water (50 mL), acidified with 10% hydrochloric acid (pH ~ 6). The organic phase was washed with water (2×50 mL), brine (2×50 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel to obtain **11a** (5.32 g, 94%) as a white solid. Mp 220–222 °C (lit.[20a] mp 212 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (br, 1H), 7.70 (s, 1H), 7.66 (s, 1H), 7.35 (s, 1H), 7.34 (s, 1H), 7.09 (s, 1H), 6.62–6.63 (m, 1H), 6.16–6.18 (m, 2H), 4.36 (s, 2H), 4.05 (s, 6H), 3.96 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 148.9, 148.6, 130.9, 130.1, 126.2, 125.5, 125.0, 124.8, 124.0, 116.9, 108.4, 108.1, 106.3, 105.1, 103.2, 102.8, 56.0, 55.9, 55.8, 55.7, 32.7; IR (KBr, cm^{-1}) 3376, 3267, 3006, 2904, 2831, 1612, 1510, 1460, 1431, 1249, 1191, 1140, 1031, 981, 828, 763, 712, 647, 581, 509; MS (EI) *m*/*z* 377 (M$^+$, 100), 346 (6), 311 (8), 189 (10), 80 (7); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{24}NO_4$ [M+H]$^+$ 378.1700, found 378.1702.

4.12. Preparation of 2-((2,3,6-trimethoxyphenanthren-9-yl)methyl)-1*H*-pyrrole (11b)

By following the same procedure as for **11a** gave **11b** as a white solid (93%). Mp 218–220 °C (lit.[27] mp 203 °C); ^{1}H NMR (300 MHz, DMSO) δ 10.66 (s, 1H), 8.07–8.12 (m, 3H), 7.20–7.37 (m, 3H), 6.65 (s, 1H), 5.94–5.95 (m, 1H), 5.76–5.80 (m, 1H), 4.32 (s, 2H), 4.02 (s, 3H), 3.99 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 157.6, 149.4, 148.7, 132.5, 131.3, 129.8, 127.1, 126.2, 124.6, 123.5, 123.2, 116.4, 115.2, 108.2, 107.3, 105.9, 104.7, 104.3, 55.9, 55.4, 31.3; IR (KBr, cm^{-1}) 3376, 2933, 2831, 1612, 1503, 1460, 1431, 1285, 1249, 1184, 1148, 1119, 1017, 981, 879, 828, 785, 712, 589, 531; MS (ESI) *m*/*z* 346 [M−H]$^-$; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{22}NO_3$ [M+H]$^+$ 348.1594, found 348.1595.

4.13. Preparation of 2-((2,3,6-trimethoxyphenanthren-10-yl)methyl)-1*H*-pyrrole (11c)

By following the same procedure as for **11a** gave **11c** as a white solid (96%). Mp 184–185 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.80 (d, $^4J_{HH}$=2.4 Hz, 1H), 7.72 (d, $^3J_{HH}$=8.7 Hz, 1H), 7.45 (s, 1H), 7.38 (s, 1H), 7.18 (dd, $^4J_{HH}$=2.4 Hz, $^3J_{HH}$=8.7 Hz, 1H), 6.57–6.59 (m, 1H), 6.14–6.17 (m, 2H), 4.38 (s, 2H), 4.07 (s, 3H), 4.00 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 157.7, 149.0, 148.6, 131.4, 130.1, 129.8, 129.5, 126.2, 125.5, 124.4, 116.5, 115.7, 107.3, 105.9, 105.5, 104.7, 104.1, 55.9, 55.5, 55.4, 31.7; IR (KBr, cm^{-1}) 3396, 2998, 2824, 1605, 1503, 1452, 1423, 1235, 1208, 1148, 1119, 1017, 865, 785, 712, 523; MS (ESI) *m*/*z* 346 [M−H]$^-$; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{22}NO_3$ [M+H]$^+$ 348.1594, found 348.1593.

4.14. Preparation of 2-((2,3,6,7-tetramethoxyphenanthren-9-yl)methyl)pyrrolidine (10a)

The mixture of **11a** (4.9 g, 0.013 mol), acetic acid (350 mL), and 10% Pd–C (1.5 g) was shaken under hydrogen at a pressure of 90–100 atm for 12 h. The mixture was filtered, and the filtrate was evaporated to dryness in vacuo. The residue was dissolved in H_2SO_4 (2 N, 200 mL) at 0 °C and washed with ether (60 mL). The acid layer was cooled and made alkaline with aqueous NaOH to pH ~ 12, and then extracted with chloroform (2×150 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give amine **10a** (4.70 g, 95%) as a white solid. Mp 155–157 °C (lit.[28] mp 152 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.76 (s, 1H), 7.47 (s, 1H), 7.43 (s, 1H), 7.18 (s, 1H), 4.12 (s, 3H), 4.11 (s, 3H), 4.05 (s, 3H), 4.02 (s, 3H), 3.45–3.55 (m, 1H), 3.05–3.22 (m, 3H), 2.82–2.90 (m, 1H), 1.70–1.95 (m, 3H), 1.47–1.60 (m, 1H); ^{13}C NMR (75 MHz, DMSO) δ 149.1, 149.0, 148.75, 148.7, 128.7, 125.6, 124.8, 124.7, 124.4, 123.7, 108.2, 104.8, 104.6, 103.8, 59.0, 56.0, 55.4, 44.1, 34.8, 29.6, 22.7; IR (KBr, cm^{-1}) 3400, 2955, 2831, 1612, 1510, 1467, 1416, 1358, 1242, 1198, 1140, 1031, 981, 843, 763, 523; MS (ESI) *m*/*z* 382 [M+H]$^+$, 745 [2M+H]$^+$; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{28}NO_4$ [M+H]$^+$ 382.2013, found 382.2009.

4.15. Preparation of 2-((2,3,6-trimethoxyphenanthren-9-yl)methyl)pyrrolidine (10b)

By following the same procedure as for **10a** gave **10b** as a white solid (96%). Mp 143–145 °C (lit.[27] mp 140 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, $^3J_{HH}$=9.0 Hz, 1H), 7.87 (d, $^4J_{HH}$=2.4 Hz, 1H), 7.81 (s, 1H), 7.39 (s, 1H), 7.18–7.22 (m, 1H), 7.15 (s, 1H), 4.07 (s, 3H), 4.00 (s, 3H), 3.99 (s, 3H), 3.40–3.50 (m, 1H), 3.14–3.17 (m, 2H), 3.02–3.09 (m, 1H), 2.75–2.84 (m, 1H), 1.65–1.90 (m, 4H), 1.45–1.55 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 149.5, 148.7, 132.6, 131.6, 127.5, 126.2, 125.2, 124.1, 123.6, 114.8, 108.0, 104.6, 103.4, 59.1, 56.1, 55.8, 55.5, 46.2, 40.0, 31.7, 24.8; IR (KBr, cm^{-1}) 3296, 2955, 2926, 2853, 1721, 1605, 1510, 1460, 1431, 1293, 1249, 1206, 1155, 1119, 1082, 981, 821, 770, 690, 567, 523; MS (ESI) *m*/*z* 352 [M+H]$^+$; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{26}NO_3$ [M+H]$^+$ 352.1907, found 352.1912.

4.16. Preparation of 2-((2,3,6-trimethoxyphenanthren-10-yl)methyl)pyrrolidine (10c)

By following the same procedure as for **10a** gave **10c** as a white solid (97%). Mp 147–149 °C (lit.[4h] mp 144–145 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69–7.74 (m, 2H), 7.60 (d, $^4J_{HH}$=1.5 Hz, 1H), 7.42 (s, 1H), 7.28 (s, 1H), 7.12 (dd, $^4J_{HH}$=2.1 Hz, $^3J_{HH}$=8.7 Hz, 1H), 4.06 (s, 3H), 4.01 (s, 3H), 3.90 (s, 3H), 3.72–3.78 (m, 1H), 3.46–3.51 (m, 1H), 3.21–3.33 (m, 2H), 1.86–2.10 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 149.8, 148.9, 130.7, 129.9, 127.5, 126.0, 125.6, 125.4, 124.6, 115.4, 104.4, 103.9, 103.7, 59.8, 56.7, 55.9, 55.4, 44.6, 35.7, 30.4, 23.2; IR (KBr, cm^{-1}) 3412, 2962, 2752, 1605, 1518, 1460, 1380, 1271, 1206,

1148, 1111, 1066, 1024, 865, 828, 785, 573, 531; MS (ESI) *m*/*z* 352 $[M+H]^+$; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{26}NO_3$ $[M+H]^+$ 352.1907, found 352.1910.

4.17. Preparation of (±)-tylophorine (1)

To a solution of **10a** (4.95 g, 0.013 mol) in EtOH (150 mL) were added 37% formaldehyde (75 mL) and concentrated HCl (7.5 mL). The reaction mixture was refluxed for 15 h in the dark. The reaction mixture was concentrated to near dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 (300 mL) and washed with 1 N NaOH (100 mL), water (50 mL), and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford tylophorine (**1**) (4.85 g, 95%) as a white solid. Mp 275–282 °C dec (lit.[29] mp 287 °C dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 2H), 7.31 (s, 1H), 7.16 (s, 1H), 4.62 (d, $^2J_{HH}$=14.7 Hz, 1H), 4.11 (s, 6H), 4.05 (s, 6H), 3.66 (d, $^2J_{HH}$=14.7 Hz, 1H), 3.44–3.50 (m, 1H), 3.32–3.39 (m, 1H), 2.86–2.95 (m, 1H), 2.41–2.50 (m, 2H), 2.17–2.30 (m, 1H), 1.76–2.05 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 148.6, 148.5, 126.4, 126.1, 125.9, 124.4, 123.7, 123.5, 104.1, 103.6, 103.5, 103.3, 60.2, 56.1, 55.9, 55.8, 55.2, 54.1, 33.9, 31.3, 21.6; IR (KBr, cm^{-1}) 3400, 2966, 2919, 2788, 1612, 1510, 1460, 1423, 1249, 1191, 1140, 1039, 1010, 835, 763, 689, 516; MS (ESI) *m*/*z* 394 $[M+H]^+$; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{28}NO_4$ $[M+H]^+$ 394.2013, found 394.2015.

4.18. Preparation of (±)-deoxytylophorinine (2)

By following the same procedure as for tylophorine **1** gave **2** as a light yellow solid (97%). Mp 250 °C dec (lit.[27] mp 252–254 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.94 (m, 3H), 7.19–7.22 (m, 1H), 7.13 (s, 1H), 4.58 (d, $^2J_{HH}$=14.8 Hz, 1H), 4.09 (s, 3H), 4.05 (s, 3H), 4.00 (s, 3H), 3.61 (d, $^2J_{HH}$=14.8 Hz, 1H), 3.37–3.48 (m, 2H), 2.88–2.94 (m, 1H), 2.40–2.46 (m, 2H), 2.17–2.25 (m, 1H), 1.67–2.05 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 149.4, 148.3, 130.4, 127.0, 125.6, 125.5, 125.3, 125.1, 123.4, 114.8, 104.6, 104.1, 103.2, 60.1, 56.0, 55.9, 55.5, 55.1, 53.9, 33.6, 31.3, 21.6; IR (KBr, cm^{-1}) 3419, 2940, 2868, 2766, 1605, 1503, 1467, 1409, 1249, 1206, 1149, 1031, 821, 777, 589, 509; MS (ESI) *m*/*z* 364 $[M+H]^+$; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{26}NO_3$ $[M+H]^+$ 364.1907, found 364.1903.

4.19. Preparation of (±)-antofine (3)

By following the same procedure as for tylophorine **1** gave **3** as a light yellow solid (97%). Mp 210 °C dec (lit.[4c] mp 212–214 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.90 (d, $^4J_{HH}$=2.0 Hz, 1H), 7.82 (d, $^3J_{HH}$=8.8 Hz, 1H), 7.31 (s, 1H), 7.20 (dd, $^4J_{HH}$=2.4 Hz, $^3J_{HH}$=9.2 Hz, 1H), 4.69 (d, $^2J_{HH}$=14.8 Hz, 1H), 4.11 (s, 3H), 4.06 (s, 3H), 4.02 (s, 3H), 3.69 (d, $^2J_{HH}$=14.8 Hz, 1H), 3.44–3.49 (m, 1H), 3.32–3.37 (m, 1H), 2.86–2.93 (m, 1H), 2.42–2.50 (m, 2H), 2.20–2.27 (m, 1H), 1.86–2.05 (m, 2H), 1.74–1.80 (m, 1H); ^{13}C NMR δ 157.5, 149.4, 148.4, 130.2, 127.1, 126.7, 125.6, 124.2, 124.1, 123.5, 114.8, 104.7, 104.1, 104.0, 60.2, 56.0, 55.9, 55.5, 55.1, 53.9, 33.7, 31.3, 21.6; IR (KBr, cm^{-1}) 3419, 2955, 2911, 2617, 2788, 1612, 1510, 1467, 1416, 1255, 1213, 1169, 1133, 1039, 995, 828, 770, 596, 516; MS (ESI) *m*/*z* 364 $[M+H]^+$; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{26}NO_3$ $[M+H]^+$ 364.1907, found 364.1902.

Acknowledgements

We thank the National Key Project for Basic Research (2003CB114404) and the National Natural Science Foundation of China (20472039) and the Key Project of Chinese Ministry of Education (106046).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.06.003.

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