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Efficient and Chirally Specific Synthesis of Phenanthro-Indolizidine Alkaloids by Parham-Type Cycloacylation

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A concise, efficient and modular route involving Parham-type cycloacylation as the key step has been used to synthesize six enantiopure phenanthro-indolizidine alkaloids **1a**–**c**. The preparation of enantiomerically pure tylophora alkaloids and their *seco* analogues on a large-scale is now feasible. The alcohol intermediates **8a**–**c**, which are difficult to prepare by other synthetic methodologies, have been synthesized by a metallation–cyclization–reduction sequence in excellent yields.

Introduction

Since the first isolation of (–)-tylophorine [**1a-(*R*)**, see Scheme 2] in 1935,[1] many phenanthro-indolizidine alkaloids have been found to exhibit interesting pharmacological properties,[2] especially antitumour activity.[3] We have previously reported that (–)-antofine, isolated from *Cynanchum komarovii*, possesses excellent antiviral activity against the tobacco mosaic virus (TMV).[4] To extend our research on phenanthro-indolizidine alkaloids as antiviral agents, we developed an efficient approach to the preparation of racemic alkaloids on a large-scale.[5] Now to further explore the effect of α-C chirality on antiviral activity, a series of enantiopure phenanthro-indolizidine alkaloids need to be tested.

So far, many of the enantiopure alkaloids have been synthesized selectively using the chiron approach starting with either proline, glutamic acid or pyroglutamate, as well as the chiral auxiliary approach manifested in diastereoselective Grignard additions and double Michael additions, respectively.[6] However, these reported approaches are not suitable for large-scale preparation due to low yields, harsh conditions or the many steps required.

The construction of the phenanthrene and indolizidine nuclei always plays a key role in the synthesis of phenanthro-indolizidine alkaloids. In our previous work, $FeCl_3$ was used as the oxidative coupling reagent to construct the phenanthrene nucleus efficiently.[5,7] We then directed our attention towards the construction of the indolizidine nucleus. In the last three decades, the most commonly reported synthetic methodology for the construction of this structure was the acid-catalysed cyclization of an amino acid.[8] However, in each case, racemic products and low yields resulted due to the harsh conditions employed for ring closure.

On the other hand, the intramolecular cyclization reactions that employ aryllithiums generated by lithium–halogen exchange, known as Parham cyclization reactions, have become a valuable protocol for the regiospecific construction of carbocyclic and heterocyclic systems.[9] Inspired by the methodology of Lete and co-workers,[9g,9i] this aromatic metallation–cyclization procedure has been successfully used to prepare the indolizidine nucleus of phenanthro-indolizidine alkaloids. In these cases, the unstable ketone intermediates (analogues of **6**) were directly reduced to the corresponding alcohols **8a**–**c** to avoid decomposition. In this paper, we report full details of this synthetic approach to enantiopure phenanthro-indolizidine alkaloids **1a**–**c** in high overall yields.

Results and Discussion

To test the feasibility of this new approach the synthetic plan depicted in Scheme 1 was initially designed. Ester **2a** was treated with lithium aluminium hydride to give alcohol **3a** in 96% yield.

It has been reported that polymethoxylated benzyl alcohols can be converted into the corresponding dibromides in excellent yields in one step.[10] By using this procedure, **3a** was successfully converted into dibromide **4a** in 92% yield, thus improving the results previously reported by Ishibashi and co-workers.[11] *N*,*N*-Diethyl-1*H*-pyrrole-2-carboxamide was alkylated with the dibromide **4a** to produce the amide **5** in 95% yield. When **5** was treated with

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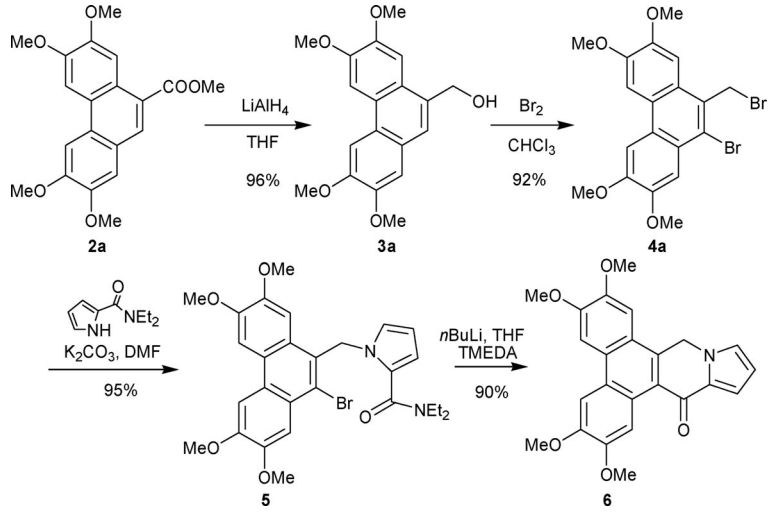
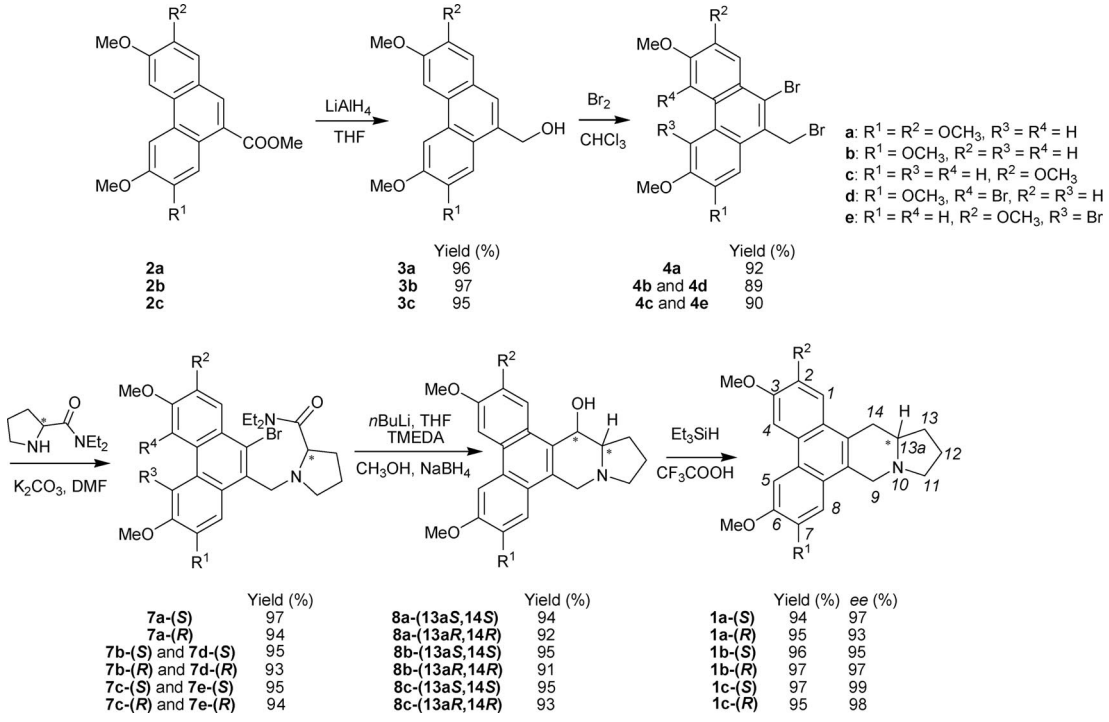


Scheme 1. Synthesis of the new structural *seco* analogue **6**.

*n*BuLi (2.2 equiv.) and TMEDA (2.3 equiv.) at –78 °C for 4 h, lithium–bromine exchange and the subsequent cyclization efficiently afforded the ketone **6** in 90% yield. However, if the reaction mixture was allowed to reach room temperature before quenching, the yield of ketone **6** was reduced to 82%. Similar results were also reported by Lete and co-workers.[9g,9i]

The synthetic route to enantiopure phenanthro-indolizidine alkaloids **1a**–**c** is illustrated in Scheme 2. Amide **7a-(*S*)** was prepared by alkylation of (*S*)-*N*,*N*-diethylpyrrolidine-2-carboxamide with dibromide **4a** under the above conditions. Amide **7a-(*S*)** was subsequently treated with *n*BuLi (2.2 equiv.) and TMEDA (2.3 equiv.) and then sodium borohydride (5 equiv.) to give **8a-(13a*S*,14*S*)** stereoselectively in 94% yield. The absolute configuration of **8a-(13a*S*,14*S*)** was determined by comparison with authentic samples (**DCB-3501** and **DCB-3503**) prepared according to a reported procedure.[6c] The alcohol **8a-(13a*S*,14*S*)** was reduced using triethylsilane and trifluoroacetic acid to give (+)-tylophorine [**1a-(*S*)**] in 94% yield and 97% *ee*. When using (*R*)-*N*,*N*-diethylpyrrolidine-2-carboxamide instead of (*S*)-*N*,*N*-diethylpyrrolidine-2-carboxamide, (–)-tylophorine [**1a-(*R*)**] was obtained by the same procedure in 73% overall yield and 93% *ee*.



Scheme 2. Synthesis of a series of phenanthro-indolizidine alkaloids **1a**–**c**.

Although a similar approach seemed directly applicable to the preparation of **1b**,**c**, differences were immediately noted. When **3b** was treated with bromine in chloroform at 0 °C, dibromide **4b** was obtained accompanied by a small percentage of tribromide **4d**. The two compounds could be separated by silica gel chromatography with chloroform/hexane (5:1) as eluent, and the mass ratio of **4b** and **4d** was about 19:1. The ^{1}H NMR spectrum of **4d** indicated that the additional bromine was located at the 5-position. As the bromides appeared to be sensitive to silica gel, **4b** and **4d** were directly converted into amides **7b-(*S*)** and **7d-(*S*)** in a combined yield of 95%. Because the bromine at the 5-position of **7d-(*S*)** could be reduced under metallation–cyclization–reduction conditions, **7d-(*S*)** could afford same product **8b-(13a*S*,14*S*)** as **7b-(*S*)**, but a little excess of *n*BuLi (3.2 equiv.), TMEDA (3.3 equiv.) and sodium borohydride (5 equiv.) was required. Without separation, **7b-(*S*)** and **7d-(*S*)** were directly converted into **8b-(13a*S*,14*S*)** in 95% yield. Alcohol **8b-(13a*S*,14*S*)** was reduced using triethylsilane and trifluoroacetic acid to give (+)-deoxytylophorinine [**1b-(*S*)**] in 96% yield and 95% *ee*. By using the same procedure, (–)-deoxytylophorinine [**1b-(*R*)**], (+)-antofine [**1c-(*S*)**] and (–)-antofine [**1c-(*R*)**] were obtained in overall yields of 71, 75 and 71% and enantiomeric excess of 97, 99 and 98%, respectively.

Conclusions

A short, simple and efficient route to enantiopure phenanthro-indolizidine alkaloids has been accomplished with Parham-type cycloacylation as the key step. This new procedure has distinct advantages over previous ones: It is simple and practical, allowing a series of phenanthro-indolizidine alkaloids to be prepared on a large scale, it involves few steps and high overall yields (>70%) and *ee* values (up to 99%) were obtained. The versatility and flexibility of the method was demonstrated by the preparation of six representative phenanthro-indolizidine alkaloids. As a result of the robust nature of this approach, a systematic exploration of the pharmacological profile of this promising class of bioactive natural products may be possible.

Experimental Section

General: The melting points were determined with an X-4 binocular microscope melting-point apparatus (Beijing Tech Instruments Co., Beijing, China) and are uncorrected. ^{1}H NMR spectra were obtained by using Bruker AC-P 300, Bruker AC-P 400 and Varian Mercury Plus 400 spectrometers. Chemical shifts (δ) are given in parts per million and were measured downfield from internal tetramethylsilane. ^{13}C NMR spectra were recorded by using Bruker AC-P 300 (75 MHz), Bruker AC-P 400 (100 MHz) and Varian Mercury Plus 400 spectrometers (100 MHz) and $CDCl_3$ as solvent. Chemical shifts (δ) are reported in parts per million using the solvent peak (δ =77.0 ppm) as reference. IR spectra were recorded with a MAGNA-560 FTIR (Nicolet Company) spectrometer. Mass spectra were obtained with VG ZAB-HS and LCQ Advantage spectrometers using the EI or FAB and ESI methods, respectively. High-resolution mass spectra were obtained with an FT-ICR MS spectrometer (Ionspec, 7.0 T). The enantiomeric excesses of **1a**–**c** were determined by HPLC with a Chiralcel AD-H column using Agilent 1100 instrument. Optical rotations were recorded with a Perkin–Elmer 341 MC polarimeter. Chromatographic separations were carried out under pressure on silica gel using flash column techniques. All anhydrous solvents were dried and purified by standard techniques just before use. The corresponding esters **2a**–**c**[7] and α-amino acid derivatives (*S*)-*N*,*N*-diethylpyrrolidine-2-carboxamide, (*R*)-*N*,*N*-diethylpyrrolidine-2-carboxamide[12] and *N*,*N*-diethyl-1*H*-pyrrole-2-carboxamide[13] were prepared by the reported procedures, and the ^{1}H NMR spectra of these compounds are in accord with the literature.

2,3,6,7-Tetramethoxy-9-(hydroxymethyl)phenanthrene (3a): A suspension of ester **2a** (15 g, 42 mmol) in dry tetrahydrofuran (200 mL) was added in small portions to a suspension of lithium aluminium hydride (4.8 g, 0.13 mol) in dry tetrahydrofuran (150 mL) at ice-bath temperature. After the reaction mixture had been stirred at room temperature under dry nitrogen for 3 h, the mixture was cooled and water (7 mL) was carefully added dropwise, followed by 20% HCl (10 mL) and water (25 mL). The precipitated inorganic salts were removed by filtration through Celite and washed with chloroform (100 mL). The organic layer was dried with anhydrous magnesium sulfate and the solvent was evaporated. The crude product was recrystallized from ethyl acetate to afford **3a** (13.27 g, 96%) as a white solid; m.p. 183–184 °C (ref.[8c] m.p. 183–184 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (s, 1 H, Ar-H), 7.53 (s, 1 H, Ar-H), 7.35 (s, 2 H, Ar-H), 6.95 (s, 1 H, Ar-H), 4.94 (s, 2 H, $ArCH_2$), 4.04 (s, 3 H, OMe), 4.02 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 2.37 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.8, 148.6, 148.4, 148.3, 131.9, 125.6, 124.7, 124.3, 124.1, 123.3, 108.1, 104.5, 102.9, 102.4, 64.1, 55.8, 55.8, 55.7, 55.6 ppm.

10-(Hydroxymethyl)-2,3,6-trimethoxyphenanthrene (3b): A procedure analogous to the preparation of alcohol **3a** was used. Ester **2b** (15 g, 46 mmol) gave **3b** (13.3 g, 97%) as a white solid; m.p. 161–162 °C (ref.[14] m.p. 155–156 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (s, 1 H, Ar-H), 7.79 (s, 1 H, Ar-H), 7.74 (d, J = 8.7 Hz, 1 H, Ar-H), 7.56 (s, 1 H, Ar-H), 7.50 (s, 1 H, Ar-H), 7.17 (d, J = 8.7 Hz, 1 H, Ar-H), 5.06 (s, 2 H, $ArCH_2$), 4.09 (s, 3 H, OMe), 4.04 (s, 3 H, OMe), 4.00 (s, 3 H, OMe), 1.78 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 149.4, 148.8, 131.4, 131.2, 130.2, 125.8, 125.5, 124.8, 124.6, 115.4, 104.8, 103.9, 103.7, 64.7, 56.0, 55.9, 55.5 ppm.

2,3,6-Trimethoxy-9-(hydroxymethyl)phenanthrene (3c): A procedure analogous to the preparation of alcohol **3a** was used. The ester **2c** (15 g, 46 mmol) gave **3c** (13 g, 95%) as a white solid; m.p. 183–184 °C (ref.[6c] m.p. 187 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, J = 9.0 Hz, 1 H, Ar-H), 7.83 (s, 1 H, Ar-H), 7.77 (s, 1 H, Ar-H), 7.45 (s, 1 H, Ar-H), 7.21 (d, J = 9.0 Hz, 1 H, Ar-H), 7.09 (s, 1 H, Ar-H), 5.07 (s, 2 H, $ArCH_2$), 4.06 (s, 3 H, OMe), 4.00 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 2.02 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 149.4, 149.1, 132.8, 131.7, 127.0, 126.1, 124.3, 124.1, 123.1, 115.1, 108.3, 104.6, 103.3, 64.2, 56.0, 55.8, 55.5 ppm.

9-Bromo-10-(bromomethyl)-2,3,6,7-tetramethoxyphenanthrene (4a): A solution of bromine (5.12 g, 32 mmol) in chloroform (50 mL) was added to a solution of alcohol **3a** (10 g, 30.5 mmol) in chloroform (250 mL) at 0 °C. The mixture was stirred at room temperature for 10 h and cooled to 0 °C for 1 h. Then the mixture was filtered to afford **4a** (13.18 g, 92%) as a grey solid; m.p. 245–246 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (s, 1 H, Ar-H), 7.73

(s, 1 H, Ar-H), 7.69 (s, 1 H, Ar-H), 7.44 (s, 1 H, Ar-H), 5.25 (s, 2 H, $ArCH_2$), 4.12 (s, 6 H, OMe), 4.10 (s, 3 H, OMe), 4.08 (s, 3 H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.1, 149.4, 149.1, 128.3, 125.6, 124.7, 124.4, 124.1, 123.1, 109.3, 105.0, 103.0, 102.5, 56.1, 56.0, 56.0, 33.4 ppm. IR (KBr): $\tilde{\nu}$ = 3018, 2832, 1617, 1507, 1410, 1253, 1196, 1150, 1058, 1040, 833, 759, 743, 657, 547 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 470 (20) $[M]^+$, 391 (100), 347 (8), 326 (8), 268 (7), 169 (13), 150 (9), 80 (8), 43 (7). HRMS (ESI): calcd. for $C_{19}H_{18}BrO_4$ $[M - Br]^+$ 389.0383; found 389.0377.

9-Bromo-10-(bromomethyl)-2,3,6-trimethoxyphenanthrene (4b) and 5,9-Dibromo-10-(bromomethyl)-2,3,6-trimethoxyphenanthrene (4d): A solution of bromine (5.9 g, 36.9 mmol) in chloroform (50 mL) was added to a solution of alcohol **3b** (10 g, 33.6 mmol) in chloroform (250 mL) at 0 °C and the mixture was stirred at room temperature for 10 h. The solvent was evaporated in vacuo and the residue was purified by column chromatography over silica gel eluting with chloroform to give a 19:1 (mass ratio) mixture of dibromide **4b** and tribromide **4d** (13.2 g, 89% combined yield). The mixture was purified by chromatography again with chloroform/hexane (5:1) to give **4b** and a little of **4d** for spectral and mass analysis. **4b**: m.p. 207–209 °C (dec.). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 9.2 Hz, 1 H, 8-H), 7.82 (s, 1 H, Ar-H), 7.78 (d, *J* = 2.4 Hz, 1 H, Ar-H), 7.45 (s, 1 H, 5-H), 7.24 (dd, *J* = 9.2, 2.4 Hz 1 H, 7-H), 5.23 (s, 2 H, $ArCH_2$), 4.10 (s, 3 H, OMe), 4.10 (s, 3 H, OMe), 4.02 (s, 3 H, OMe) ppm. ^{13}C NMR (100 MHz,$CDCl_3$): δ = 159.2, 149.9, 149.3, 132.3, 131.3, 127.9, 125.6, 124.4, 124.1, 124.1, 116.1, 105.3, 104.2, 103.8, 56.1, 56.0, 55.6, 33.3 ppm. IR (KBr): $\tilde{\nu}$ = 2925, 1615, 1527, 1506, 1457, 1434, 1261, 1205, 1118, 1060, 1036, 842 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{16}Br_2O_3Na$ $[M + Na]^+$ 460.9358; found 460.9360. **4d**: m.p. 224–226 °C (dec.). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.30 (s, 1 H, Ar-H), 8.49 (d, *J* = 9.1 Hz, 1 H, Ar-H), 7.50 (s, 1 H, Ar-H), 7.29 (d, *J* = 9.2 Hz, 1 H, Ar-H), 5.20 (s, 2 H, $ArCH_2$), 4.11 (s, 3 H, OMe), 4.10 (s, 3 H, OMe), 4.07 (s, 3 H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4, 149.5, 147.1, 131.2, 130.7, 130.4, 129.3, 126.9, 126.2, 124.0, 123.5, 111.7, 110.1, 104.8, 57.1, 56.3, 56.0, 33.0 ppm. IR (KBr): $\tilde{\nu}$ = 3437, 2954, 2922, 2850, 2380, 2310, 1598, 1531, 1502, 1469, 1378, 1279, 1266, 1206, 1150, 1127, 1068, 1055, 765, 750 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{15}Br_3NaO_3$ $[M + Na]^+$ 538.8464; found 538.8480.

10-Bromo-9-(bromomethyl)-2,3,6-trimethoxyphenanthrene (4c) and 5,10-Dibromo-9-(bromomethyl)-2,3,6-trimethoxyphenanthrene (4e): A procedure analogous to the preparation of **4b** and **4d** was used. The alcohol **3c** (10 g, 33.6 mmol) gave a 15:1 (mass ratio) mixture of dibromide **4c** and tribromide **4e** (13.4 g, 90% combined yield). **4c**: m.p. 180–182 °C (dec.). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 9.2 Hz, 1 H, 8-H), 7.74 (d, *J* = 2.4 Hz, 1 H, 5-H), 7.72 (s, 1 H, Ar-H), 7.71 (s, 1 H, Ar-H), 7.26 (dd, *J* = 9.2, 2.32 Hz, 1 H, 7-H), 5.19 (s, 2 H, $ArCH_2$), 4.08 (s, 3 H, OMe), 4.06 (s, 3 H, OMe), 4.00 (s, 3 H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.3, 150.0, 150.0, 130.8, 129.4, 126.4, 125.8, 125.4, 123.8, 122.8, 115.8, 109.4, 104.8, 103.1, 56.1, 56.0, 55.5, 32.8 ppm. IR (KBr): $\tilde{\nu}$ = 3007, 2958, 2931, 2849, 2833, 1616, 1511, 1469, 1420, 1261, 1235, 1205, 1165, 1061, 846, 754 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{16}Br_2O_3Na$ $[M + Na]^+$ 460.9358; found 460.9366. **4e**: m.p. 241–243 °C (dec.). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.30 (s, 1 H, Ar-H), 8.14 (d, *J* = 9.2 Hz, 1 H, Ar-H), 7.85 (s, 1 H, Ar-H), 7.34 (d, *J* = 9.2 Hz, 1 H, Ar-H), 5.24 (s, 2 H, $ArCH_2$), 4.10 (s, 3 H, OMe), 4.10 (s, 3 H, OMe), 4.08 (s, 3 H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 149.8, 147.9, 130.0, 128.9, 127.3, 126.0, 125.5, 125.3, 124.2, 111.8, 109.7, 109.0, 107.4, 57.1, 56.4, 56.0, 33.1 ppm. IR (KBr): $\tilde{\nu}$ = 3446, 2993, 2957, 2929, 2849, 2380, 2310, 1599, 1524, 1510, 1462, 1423, 1379, 1285, 1262, 1206, 1138, 1093, 1050, 850, 806, 765, 750 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{15}Br_3NaO_3$ $[M + Na]^+$ 538.8464; found 538.8466.

(*S*)-1-[(9-Bromo-2,3,6,7-tetramethoxyphenanthren-10-yl)methyl]-*N*,*N*-diethylpyrrolidine-2-carboxamide [7a-(*S*)]: A solution of bromide **4a** (5 g, 10.6 mmol), (*S*)-*N*,*N*-diethylpyrrolidine-2-carboxamide (1.99 g, 11.7 mmol) and potassium carbonate (6.46 g, 46.8 mmol) in *N*,*N*-dimethylformamide (150 mL) was heated at reflux for 8 h. After cooling, the reaction mixture was filtered and concentrated in vacuo and the residue was purified by flash column chromatography on silica gel to give amide **7a-(*S*)** (5.7 g, 97%) as a light-yellow solid; m.p. 150–151 °C. $[\alpha]_D^{20}$ = –75 (*c* = 2.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.52 (s, 1 H, Ar-H), 7.86 (s, 1 H, Ar-H), 7.78 (s, 1 H, Ar-H), 7.73 (s, 1 H, Ar-H), 4.54 (d, *J* = 12.2 Hz, 1 H, $ArCH_2$), 4.37 (d, *J* = 12.3 Hz, 1 H, $ArCH_2$), 4.21 (s, 3 H, OMe), 4.12 (s, 3 H, OMe), 4.11 (s, 3 H, OMe), 4.08 (s, 3 H, OMe), 3.33–3.50 (m, 5 H, N-CH_2, 2-H), 2.88–2.94 (m, 1 H, 5-H), 2.65–2.71 (m, 1 H, 5-H), 2.08–2.16 (m, 1 H, 3-H), 1.71–1.91 (m, 3 H, 3-H, 4-H), 1.10–1.09 (m, 6 H, NCH_2-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 149.5, 149.4, 149.3, 149.1, 131.0, 127.1, 125.4, 125.0, 123.9, 122.5, 109.9, 108.5, 102.9, 102.4, 64.0, 56.9, 56.1, 56.0, 56.0, 51.7, 41.4, 40.3, 29.8, 22.9, 14.8, 13.2 ppm. IR (KBr): $\tilde{\nu}$ = 2966, 2934, 1649, 1619, 1510, 1469, 1420, 1251, 1198, 1147, 1070, 846, 752 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{36}BrN_2O_5$ $[M + H]^+$ 559.1802; found 559.1810.

(*R*)-1-[(9-Bromo-2,3,6,7-tetramethoxyphenanthren-10-yl)methyl]-*N*,*N*-diethylpyrrolidine-2-carboxamide [7a-(*R*)]: A procedure analogous to the preparation of **7a-(*S*)** was used. Bromide **4a** (5 g, 10.6 mmol) and (*R*)-*N*,*N*-diethylpyrrolidine-2-carboxamide (1.99 g, 11.7 mmol) gave **7a-(*R*)** (5.6 g, 94%) as a light-yellow solid; m.p. 142–143 °C. $[\alpha]_D^{20}$ = +67.5 (*c* = 2.0, $CHCl_3$); other data are the same as those of **7a-(*S*)**.

(*S*)-1-[(9-Bromo-2,3,6-trimethoxyphenanthren-10-yl)methyl]-*N*,*N*-diethylpyrrolidine-2-carboxamide [7b-(*S*)] and (*S*)-1-[(4,10-Dibromo-3,6,7-trimethoxyphenanthren-9-yl)methyl]-*N*,*N*-diethylpyrrolidine-2-carboxamide [7d-(*S*)]: A procedure analogous to the preparation of **7a-(*S*)** was used. A mixture (19:1, mass ratio) of bromides **4b** and **4d** (5 g, 11.3 mmol) and (*S*)-*N*,*N*-diethylpyrrolidine-2-carboxamide (2.12 g, 12.5 mmol) gave a mixture of **7b-(*S*)** and **7d-(*S*)** (5.7 g, 95% combined yield). **7b-(*S*)**: m.p. 69–70 °C. $[\alpha]_D^{20}$ = –74 (*c* = 2.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.51 (s, 1 H, Ar-H), 8.36 (d, *J* = 9.2 Hz, 1 H, Ar-H), 7.78 (s, 1 H, Ar-H), 7.76 (s, 1 H, Ar-H), 7.18 (d, *J* = 9.0 Hz, 1 H, Ar-H), 4.48 (d, *J* = 12.1 Hz, 1 H, $ArCH_2$), 4.33 (d, *J* = 12.2 Hz, 1 H, $ArCH_2$), 4.22 (s, 3 H, OMe), 4.08 (s, 3 H, OMe), 3.98 (s, 3 H, OMe), 3.30–3.47 (m, 5 H, N-CH_2, 2-H), 2.89–2.92 (m, 1 H, 5-H), 2.61–2.72 (m, 1 H, 5-H), 2.06–2.14 (m, 1 H, 3-H), 1.69–1.88 (m, 3 H, 3-H, 4-H), 1.09–1.16 (m, 6 H, NCH_2-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 158.4, 149.8, 149.0, 132.0, 131.1, 131.2, 128.0, 124.5, 123.6, 123.1, 115.4, 108.5, 103.9, 102.6, 64.0, 56.9, 56.0, 55.9, 55.5, 51.7, 41.3, 40.3, 29.7, 22.8, 14.8, 13.2 ppm. IR (KBr): $\tilde{\nu}$ = 3445, 3080, 2968, 2934, 2871, 2851, 2380, 2310, 1648, 1615, 1526, 1504, 1468, 1414, 1379, 1260, 1236, 1206, 1168, 1121, 1070, 1035, 895, 751 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{34}BrN_2O_4$ $[M + H]^+$ 529.1696; found 529.1695. **7d-(*S*)**: m.p. 190–192 °C. $[\alpha]_D^{20}$ = –82.5 (*c* = 2.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.18 (s, 1 H, Ar-H), 8.55 (s, 1 H, Ar-H), 8.49 (d, *J* = 9.2 Hz, 1 H, Ar-H), 7.24 (d, *J* = 9.2 Hz, 1 H, Ar-H), 4.52 (d, *J* = 12.4 Hz, 1 H, $ArCH_2$), 4.36 (d, *J* = 12.4 Hz, 1 H, $ArCH_2$), 4.22 (s, 3 H, OMe), 4.08 (s, 3 H, OMe), 4.05 (s, 3 H, OMe), 3.26–3.47 (m, 5 H, N-CH_2, 2-H), 2.90–2.94 (m, 1 H, 5-H), 2.60–2.66 (m, 1 H, 5-H), 2.07–2.15 (m, 1 H, 3-H), 1.70–1.87 (m, 3 H, 3-H, 4-H), 1.08–1.15 (m, 6 H, NCH_2-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 155.6, 149.5, 146.7, 131.7, 131.1,

130.2, 129.3, 126.4, 123.5, 122.3, 111.2, 109.0, 107.7, 106.4, 63.8, 57.0, 56.9, 56.1, 56.0, 51.7, 41.3, 40.3, 29.8, 22.8, 14.8, 13.2 ppm. IR (KBr): $\tilde{\nu}$ = 3077, 2970, 2935, 2871, 2845, 1648, 1615, 1594, 1525, 1499, 1464, 1429, 1382, 1282, 1263, 1210, 1121, 1093, 1061, 862, 791, 753 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{33}Br_2N_2O_4$ $[M + H]^+$ 607.0802; found 607.0811.

(*R*)-1-[(9-Bromo-2,3,6-trimethoxyphenanthren-10-yl)methyl]-*N*,*N*-diethylpyrrolidine-2-carboxamide [7b-(*R*)] and (*R*)-1-[(4,10-Dibromo-3,6,7-trimethoxyphenanthren-9-yl)methyl]-*N*,*N*-diethylpyrrolidine-2-carboxamide [7d-(*R*)]: A procedure analogous to the preparation of **7a-(*S*)** was used. A mixture (19:1, mass ratio) of bromides **4b** and **4d** (5 g, 11.3 mmol) and (*R*)-*N*,*N*-diethylpyrrolidine-2-carboxamide (2.12 g, 12.5 mmol) gave a mixture of **7b-(*R*)** and **7d-(*R*)** (5.6 g, 93% combined yield). **7b-(*R*)**: m.p. 67–69 °C. $[\alpha]_D^{20}$ = +76 (*c* = 2.0, $CHCl_3$); other data are the same as those for **7b-(*S*)**. **7d-(*R*)**: m.p. 187–189 °C. $[\alpha]_D^{20}$ = +80 (*c* = 2.0, $CHCl_3$); other data are the same as those for **7d-(*S*)**.

(*S*)-1-[(10-Bromo-2,3,6-trimethoxyphenanthren-9-yl)methyl]-*N*,*N*-diethylpyrrolidine-2-carboxamide [7c-(*S*)] and (*S*)-1-[(5,10-Dibromo-2,3,6-trimethoxyphenanthren-9-yl)methyl]-*N*,*N*-diethylpyrrolidine-2-carboxamide [7e-(*S*)]: A procedure analogous to the preparation of **7a-(*S*)** was used. A mixture (15:1, mass ratio) of bromides **4c** and **4e** (5 g, 11.3 mmol) and (*S*)-*N*,*N*-diethylpyrrolidine-2-carboxamide (2.12 g, 12.5 mmol) gave a mixture of **7c-(*S*)** and **7e-(*S*)** (5.7 g, 95% combined yield). **7c-(*S*)**: m.p. 74–76 °C. $[\alpha]_D^{20}$ = –60 (*c* = 2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.93 (d, *J* = 9.2 Hz, 1 H, Ar-H), 7.85 (s, 2 H, Ar-H), 7.80 (d, *J* = 2.1 Hz, 1 H, Ar-H), 7.34 (dd, *J* = 9.2, 2.21 Hz, 1 H, Ar-H), 4.57 (d, *J* = 12.2 Hz, 1 H, $ArCH_2$), 4.32 (d, *J* = 12.3 Hz, 1 H, $ArCH_2$), 4.10 (s, 3 H, OMe), 4.07 (s, 3 H, OMe), 4.00 (s, 3 H, OMe), 3.26–3.54 (m, 5 H, N-CH_2, 2-H), 2.92–2.96 (m, 1 H, 5-H), 2.63–2.70 (m, 1 H, 5-H), 2.09–2.18 (m, 1 H, 3-H), 1.71–1.93 (m, 3 H, 3-H, 4-H), 1.10–1.17 (m, 6 H, NCH_2-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 158.1, 149.7, 149.2, 131.7,130.5, 129.5, 126.2, 126.0, 125.2, 122.0, 115.3, 109.8, 104.2, 103.2, 64.3, 56.1, 55.9, 55.8, 55.5, 51.9, 41.3, 40.3, 29.5, 22.9, 14.7, 13.1 ppm. IR (KBr): $\tilde{\nu}$ = 3445, 3084, 2961, 2931, 2871, 2853, 1729, 1643, 1617, 1510, 1466, 1435, 1366, 1302, 1261, 1233, 1204, 1164, 1129, 1069, 848, 830, 751 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{34}BrN_2O_4$ $[M + H]^+$ 529.1696; found 529.1701. **7e-(*S*)**: m.p. 174–176 °C. $[\alpha]_D^{20}$ = –62.5 (*c* = 2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.32 (s, 1 H, Ar-H), 9.22 (d, *J* = 9.3 Hz, 1 H, Ar-H), 7.90 (s, 1 H, Ar-H), 7.43 (d, *J* = 9.3 Hz, 1 H, Ar-H), 4.52 (d, *J* = 12.2 Hz, 1 H, $ArCH_2$), 4.31 (d, *J* = 12.2 Hz, 1 H, $ArCH_2$), 4.10 (s, 3 H, OMe), 4.09 (s, 3 H, OMe), 4.05 (s, 3 H, OMe), 3.28–3.57 (m, 5 H, N-CH_2, 2-H), 2.85–2.89 (m, 1 H, 5-H), 2.59–2.66 (m, 1 H, 5-H), 2.10–2.19 (m, 1 H, 3-H), 1.69–1.91 (m, 3 H, 3-H, 4-H), 1.10–1.20 (m, 6 H, NCH_2-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 155.5, 149.3, 147.1, 131.0, 129.5, 128.9, 128.3, 127.3, 125.0, 123.2, 112.1, 109.7, 109.3, 105.9, 64.4, 56.9, 56.3, 55.9, 51.8, 41.3, 40.4, 29.7, 22.9, 14.7, 13.0 ppm. IR (KBr): $\tilde{\nu}$ = 3446, 2963, 2933, 2870, 2854, 1643, 1598, 1509, 1463, 1426, 1385, 1283, 1261, 1213, 1142, 1107, 1051, 860, 751 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{33}Br_2N_2O_4$ $[M + H]^+$ 607.0802; found 607.0800.

(*R*)-1-[(10-Bromo-2,3,6-trimethoxyphenanthren-9-yl)methyl]-*N*,*N*-diethylpyrrolidine-2-carboxamide [7c-(*R*)] and (*R*)-1-[(5,10-Dibromo-2,3,6-trimethoxyphenanthren-9-yl)methyl]-*N*,*N*-diethylpyrrolidine-2-carboxamide [7e-(*R*)]: A procedure analogous to the preparation of **7a-(*S*)** was used. A mixture (15:1, mass ratio) of bromides **4c** and **4e** (5 g, 11.3 mmol) and (*R*)-*N*,*N*-diethylpyrrolidine-2-carboxamide (2.12 g, 12.5 mmol) gave a mixture of **7c-(*R*)** and **7e-(*R*)** (5.6 g, 94% combined yield). **7c-(*R*)**: m.p. 174–176 °C. $[\alpha]_D^{20}$ = +64 (*c* = 2.0, $CHCl_3$); other data are the same as those for **7c-(*S*)**. **7e-(*R*)**: m.p. 174–176 °C. $[\alpha]_D^{20}$ = +56.5 (*c* = 2.0, $CHCl_3$); other data are the same as those for **7e-(*S*)**.

1-[(9-Bromo-2,3,6,7-tetramethoxyphenanthren-10-yl)methyl]-*N*,*N*-diethyl-1*H*-pyrrole-2-carboxamide (5): A procedure analogous to the preparation of **7a-(*S*)** was used. The bromide **4a** (5 g, 10.6 mmol) and *N*,*N*-diethyl-1*H*-pyrrole-2-carboxamide (1.94 g, 11.7 mmol) gave **5** (5.6 g, 95%) as a light-yellow solid; m.p. 192–194 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (s, 1 H, Ar-H), 7.86 (s, 1 H, Ar-H), 7.80 (s, 1 H, Ar-H), 7.75 (s, 1 H, Ar-H), 6.43 (s, 1 H, 5-H), 6.39 (s, 1 H, 3-H), 6.14 (s, 2 H, $ArCH_2$), 5.94 (s, 1 H, 4-H), 4.15 (s, 3 H, OMe), 4.14 (s, 3 H, OMe), 4.10 (s, 3 H, OMe), 3.92 (s, 3 H, OMe), 3.62–3.64 (m, 4 H, N-CH_2), 1.29 (t, 6 H, NCH_2-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.2, 150.1, 149.7, 149.5, 149.4, 128.4, 126.1, 125.8, 125.6, 124.7, 124.3, 124.2, 123.4, 111.4, 109.7, 106.9, 106.7, 102.8, 102.8, 56.6, 56.2, 56.1, 56.0, 50.0, 41.6, 41.5, 13.8, 13.6 ppm. IR (KBr): $\tilde{\nu}$ = 3105, 3000, 2967, 2934, 2835, 1615, 1530, 1512, 1470, 1422, 1253, 1212, 1151, 1070, 752 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{32}BrN_2O_5$ $[M + H]^+$ 555.1489; found 555.1490.

Ketone 6: A solution of *n*BuLi in hexane (2.64 mL, 3.92 mmol) was added to a solution of amide **5** (1 g, 1.8 mmol) and TMEDA (0.48 g, 4.14 mmol) in dry tetrahydrofuran (80 mL) at –78 °C and the resulting mixture was stirred at this temperature for 4 h under nitrogen and then quenched by the addition of saturated ammonium chloride (30 mL) at –78 °C. The product was extracted with methylene dichloride (3 × 30 mL). The combined organic extracts were dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give **6** (0.65 g, 90%) as a yellow solid; m.p. 253–255 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.54 (s, 1 H, Ar-H), 7.56 (s, 2 H, Ar-H), 7.13 (s, 1 H, Ar-H), 7.09 (s, 1 H, 11-H), 6.88 (s, 1 H, 13-H), 6.48 (s, 1 H, 12-H), 5.41 (s, 2 H, 9-H), 4.08 (s, 9 H, OMe), 4.02 (s, 3 H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4, 151.3, 148.9, 148.9, 148.7, 129.7, 126.8, 125.0, 124.4, 123.0, 121.1, 120.5, 111.3, 111.1, 107.9, 104.7, 103.7, 103.5, 103.4, 55.9, 55.6, 55.6, 55.1, 45.5 ppm. IR (KBr): $\tilde{\nu}$ = 2992, 2956, 2925, 2851, 1622, 1527, 1513, 1473, 1423, 1403, 1338, 1260, 1197, 1149, 1097, 1043, 831, 764, 750 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{21}NNaO_5$ $[M + Na]^+$ 426.1312; found 426.1306.

(13a*S*,14*S*)-14-Hydroxytylophorine (DCB-3503) and (13a*S*,14*R*)-14-Hydroxytylophorine (DCB-3501): Following the reported synthetic sequences,[6c] **DCB-3503** and **DCB-3501** were prepared. **DCB-3503**: m.p. 271–272 °C (dec.) (ref.[6c] m.p. 270 °C). $[\alpha]_D^{20}$ = +81.0 (*c* = 2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (s, 1 H, Ar-H), 7.61 (s, 1 H, Ar-H), 7.38 (s, 1 H, Ar-H), 5.98 (s, 1 H, Ar-H), 4.83 (s, 1 H, 14-H), 4.15 (s, 3 H, OMe), 4.11 (s, 3 H, OMe), 4.10 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 3.28–3.35 (m, 1 H, 13a-H), 3.19 (d, *J* = 14.8 Hz, 1 H, 9-H), 2.89 (d, *J* = 14.8 Hz, 1 H, 9-H), 2.39–2.46 (m, 1 H, 11-H), 2.24–2.29 (m, 1 H, 11-H), 2.13–2.21 (m, 1 H, 13-H), 2.03–2.09 (m, 1 H, 13-H), 1.84–1.93 (m, 2 H, 12-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.7, 148.6, 148.4, 147.8, 127.7, 126.5, 125.9, 123.9, 123.8, 122.6, 105.5, 102.8, 102.7, 102.3, 65.5, 64.7, 56.1, 55.9, 55.6, 55.6, 53.2, 23.9, 21.6 ppm. **DCB-3501**: m.p. 243–245 °C (dec.) (ref.[6c] m.p. 245 °C). $[\alpha]_D^{20}$ = +74.9 (*c* = 2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (s, 1 H, Ar-H), 7.50 (s, 1 H, Ar-H), 7.47 (s, 1 H, Ar-H), 6.58 (s, 1 H, Ar-H), 4.41 (d, *J* = 7.5 Hz, 1 H, 14-H), 4.08 (s, 3 H, OMe), 4.05 (s, 3 H, OMe), 3.93 (d, *J* = 11.5 Hz, 1 H, 9-H), 3.91 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 2.96–3.01 (m, 1 H, 13a-H), 2.87 (d, *J* = 13.8 Hz, 1 H, 9-H), 1.95–2.00 (m, 1 H, 11-H), 1.85–1.90 (m, 1 H, 11-H), 1.73–1.79 (m, 1 H,

13-H), 1.55–1.62 (m, 1 H, 13-H), 1.43–1.50 (m, 1 H, 12-H), 1.23–1.33 (m, 1 H, 12-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.8, 148.6, 148.3, 148.1, 129.1, 127.4, 124.8, 124.3, 124.1, 123.3, 107.2, 103.4, 103.2, 102.9, 72.9, 68.7, 55.9, 55.9, 55.8, 54.8, 53.8, 29.7, 21.5 ppm.

(13a*S*,14*S*)-14-Hydroxytylophorine [8a-(13a*S*,14*S*)]: A solution of *n*BuLi in hexane (13.1 mL, 19.7 mmol) was added to a solution of amide **7a-(*S*)** (5 g, 8.9 mmol) and TMEDA (2.4 g, 20.6 mmol) in dry tetrahydrofuran (200 mL) at –78 °C and the resulting mixture was stirred at this temperature for 4 h under nitrogen. Then methanol (50 mL) and sodium borohydride (1.7 g, 44.7 mmol) were added to the mixture. After stirring at –40 °C for 1 h at room temperature for 8 h, the reaction mixture were quenched with water (100 mL) and the products were extracted with methylene dichloride (3 × 80 mL). The combined organic extracts were dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give **8a-(13a*S*,14*S*)** (3.4 g, 94%) as a light-yellow solid; m.p. 267–269 °C (dec.) (ref.[6c] m.p. 270 °C). $[\alpha]_D^{20}$ = +148.5 (*c* = 2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (s, 1 H, Ar-H), 7.62 (s, 1 H, Ar-H), 7.39 (s, 1 H, Ar-H), 6.00 (s, 1 H, Ar-H), 4.84 (s, 1 H, 14-H), 4.15 (s, 3 H, OMe), 4.12 (s, 3 H, OMe), 4.10 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 3.28–3.35 (m, 1 H, 13a-H), 3.19 (d, *J* = 13.9 Hz, 1 H, 9-H), 2.90 (d, *J* = 14.8 Hz, 1 H, 9-H), 2.39–2.46 (m, 1 H, 11-H), 2.24–2.29 (m, 1 H, 11-H), 2.13–2.21 (m, 1 H, 13-H), 2.03–2.09 (m, 1 H, 13-H), 1.84–1.93 (m, 2 H, 12-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.5, 148.3, 148.2, 147.5, 127.6, 126.7, 126.0, 123.6, 122.5, 105.4, 102.5, 102.4, 101.9, 65.4, 64.7, 56.1, 55.9, 55.7, 55.6, 53.1, 23.9, 21.6 ppm. IR (KBr): $\tilde{\nu}$ = 3445, 3167, 3103, 2956, 2830, 2379, 2310, 1620, 1512, 1472, 1424, 1249, 1211, 1197, 1149, 1115, 1047, 1020, 855, 836, 750 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{28}NO_5$ $[M + H]^+$ 410.1962; found 410.1970.

(13a*R*,14*R*)-14-Hydroxytylophorine [8a-(13a*R*,14*R*)]: A procedure analogous to the preparation of **8a-(13a*S*,14*S*)** was used. The amide **7a-(*R*)** (5 g, 8.9 mmol) gave **8a-(13a*R*,14*R*)** (3.36 g, 92%) as a light-yellow solid; m.p. 240–241 °C (dec.). $[\alpha]_D^{20}$ = –136 (*c* = 2.0, $CHCl_3$); other data are the same as those for **8a-(13a*S*,14*S*)**.

(13a*S*,14*S*)-Tylophorinine [8b-(13a*S*,14*S*)]: A procedure analogous to the preparation of **8a-(13a*S*,14*S*)** was used. A mixture of **7b-(*S*)** and **7d-(*S*)** (2 g, 3.8 mmol), TMEDA (1.45 g, 12.5 mmol) and *n*BuLi in hexane (8.1 mL, 12.1 mmol) gave **8b-(13a*S*,14*S*)** (1.35 g, 95%) as a light-yellow solid; m.p. 227–229 °C (dec.). $[\alpha]_D^{20}$ = +153 (*c* = 2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 9.1 Hz, 1 H, Ar-H), 7.64 (s, 1 H, Ar-H), 7.42 (s, 1 H, Ar-H), 7.22 (d, *J* = 9.0 Hz, 1 H, Ar-H), 6.09 (br., 1 H, OH), 5.81 (s, 1 H, Ar-H), 4.74 (s, 1 H, 14-H), 4.09 (s, 3 H, OMe), 4.03 (s, 3 H, OMe), 3.71 (s, 3 H, OMe), 3.15–3.22 (m, 1 H, 13a-H), 2.93 (d, *J* = 14.8 Hz, 1 H, 9-H), 2.69 (d, *J* = 14.7 Hz, 1 H, 9-H), 2.34–2.40 (m, 1 H, 11-H), 2.06–2.11 (m, 1 H, 11-H), 1.94–2.06 (m, 2 H, 13-H), 1.74–1.83 (m, 2 H, 12-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3, 148.3, 148.2, 130.4, 128.4, 126.9, 126.0, 125.4, 123.8, 123.4, 114.7, 103.9, 102.6, 102.5, 65.3, 64.3, 55.7, 55.6, 55.4, 55.3, 53.0, 23.7, 21.7 ppm. IR (KBr): $\tilde{\nu}$ = 3181, 3104, 2957, 2877, 2830, 2379, 2354, 2319, 2277, 2050, 1725, 1618, 1529, 1512, 1470, 1417, 1372, 1303, 1259, 1232, 1204, 1165, 1111, 1042, 1007, 974, 838, 751 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{26}NO_4$ $[M + H]^+$ 380.1856; found 380.1861.

(13a*R*,14*R*)-Tylophorinine [8b-(13a*R*,14*R*)]: A procedure analogous to the preparation of **8b-(13a*S*,14*S*)** was used. A mixture of **7b-(*R*)** and **7d-(*R*)** (2 g, 3.8 mmol) gave **8b-(13a*R*,14*R*)** (1.3 g, 91%) as a light-yellow solid; m.p. 229–231 °C (dec.). $[\alpha]_D^{20}$ = –156.5 (*c* = 2.0, $CHCl_3$); other data are the same as those for **8b-(13a*S*,14*S*)**.

(13a*S*,14*S*)-14-Hydroxyantofine [8c-(13a*S*,14*S*)]: A procedure analogous to the preparation of **8b-(13a*S*,14*S*)** was used. A mixture of **7c-(*S*)** and **7e-(*S*)** (2 g, 3.8 mmol) gave **8c-(13a*S*,14*S*)** (1.35 g, 95%) as a light-yellow solid; m.p. 229–231 °C (dec.). $[\alpha]_D^{20}$ = +209.5 (*c* = 2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (s, 1 H, Ar-H), 7.76 (s, 1 H, Ar-H), 7.59 (s, 1 H, Ar-H), 6.67 (d, *J* = 8.4 Hz, 1 H, Ar-H), 6.59 (d, *J* = 9.0 Hz, 1 H, Ar-H), 5.73 (br., 1 H, OH), 4.75 (s, 1 H, 14-H), 4.15 (s, 3 H, OMe), 4.08 (s, 3 H, OMe), 4.00 (s, 3 H, OMe), 2.96–3.02 (m, 1 H, 13a-H), 2.96 (d, *J* = 15.8 Hz, 1 H, 9-H), 2.81 (d, *J* = 15.1 Hz, 1 H, 9-H), 2.32–2.40 (m, 1 H, 11-H), 2.10–2.14 (m, 1 H, 11-H), 1.93–2.02 (m, 2 H, 13-H), 1.77–1.84 (m, 2 H, 12-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.6, 149.4, 148.3, 130.4, 127.7, 127.4, 127.0, 124.0, 123.7, 122.9, 114.5, 105.4, 103.9, 103.5, 65.4, 64.8, 56.1, 56.0, 55.4, 55.2, 53.3, 24.0, 21.5 ppm. IR (KBr): $\tilde{\nu}$ = 3177, 3105, 2956, 2936, 2877, 2830, 2379, 2310, 1618, 1512, 1469, 1416, 1305, 1257, 1234, 1203, 1142, 1112, 1036, 751 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{26}NO_4$ $[M + H]^+$ 380.1856; found 380.1861.

(13a*R*,14*R*)-14-Hydroxyantofine [8c-(13a*R*,14*R*)]: A procedure analogous to the preparation of **8b-(13a*S*,14*S*)** was used. A mixture of **7c-(*R*)** and **7e-(*R*)** (2 g, 3.8 mmol) gave **8c-(13a*R*,14*R*)** (1.32 g, 93% combined yield) as a light-yellow solid; m.p. 243–245 °C (dec.). $[\alpha]_D^{20}$ = –231 (*c* = 2.0, $CHCl_3$); other data are the same as those for **8c-(13a*S*,14*S*)**.

(+)-Tylophorine [1a-(*S*)]: Triethylsilane (0.64 g, 5.5 mmol) was added to a solution of **8a-(13a*S*,14*S*)** (1 g, 2.44 mmol) in trifluoroacetic acid (30 mL) and the resulting mixture was stirred at room temperature for 10 h in the dark. The solvent was evaporated in vacuo and the residue was made basic with a 10% aqueous solution of sodium carbonate. The product was extracted with methylene dichloride (3 × 50 mL). The combined organic extracts were dried with anhydrous magnesium sulfate and concentrated in vacuo to give **1a-(*S*)** (0.9 g, 94%) as a light-yellow solid; m.p. 282–284 °C (dec.). $[\alpha]_D^{20}$ = +102 (*c* = 1.0, $CHCl_3$) {ref.[6d] m.p. 284–286 °C, $[\alpha]_D^{21}$ = +73 (*c* = 0.7, $CHCl_3$)}; 97% *ee* [flow rate 1.0 mL/min *n*-hexane/2-propanol 75:25 and 0.1% triethylamine, 41 bar, 254 nm, t_R (major) = 10.38 min, t_R (minor) = 13.32 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (s, 2 H, Ar-H), 7.32 (s, 1 H, Ar-H), 7.16 (s, 1 H, Ar-H), 4.63 (d, *J* = 14.8 Hz, 1 H, 9-H), 4.12 (s, 6 H, OMe), 4.06 (s, 6 H, OMe), 3.69 (d, *J* = 14.9 Hz, 1 H, OMe), 3.46–3.50 (m, 1 H, 13a-H), 3.34–3.40 (m, 1 H, 14-H), 2.87–2.96 (m, 1 H, 14-H), 2.43–2.50 (m, 2 H, 11-H), 2.21–2.29 (m, 1 H, 13-H), 2.02–2.07 (m, 1 H, 13-H), 1.93–1.95 (m, 1 H, 12-H), 1.72–1.82 (m, 1 H, 12-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.7, 148.5, 148.4, 126.3, 126.0, 125.9, 124.4, 123.6, 123.4, 104.0, 103.5, 103.4, 103.2, 60.2, 56.0, 55.9, 55.9, 55.2, 54.0, 33.8, 31.3, 21.6 ppm. IR (KBr): $\tilde{\nu}$ = 3014, 2954, 2932, 2917, 2873, 2831, 2790, 2379, 2310, 1688, 1619, 1532, 1514, 1471, 1441, 1426, 1248, 1211, 1197, 1150, 1047, 1017, 841, 751 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{28}NO_4$ $[M + H]^+$ 394.2013; found 394.2009.

(–)-Tylophorine [1a-(*R*)]: A procedure analogous to the preparation of **1a-(*S*)** was used. **8a-(13a*R*,14*R*)** (1 g, 2.44 mmol) gave **1a-(*R*)** (0.91 g, 95%) as a light-yellow solid; m.p. 277–279 °C (dec.). $[\alpha]_D^{20}$ = –103 (*c* = 1.0, $CHCl_3$); 93% *ee* [flow rate 1.0 mL/min *n*-hexane/2-propanol 75:25 and 0.1% triethylamine, 46 bar, 254 nm, t_R (minor) = 11.31 min, t_R (major) = 14.98 min]; other data are the same as those for **1a-(*S*)**.

(+)-Deoxytylophorinine [1b-(*S*)]: A procedure analogous to the preparation of **1a-(*S*)** was used. **8b-(13a*S*,14*S*)** (1 g, 2.64 mmol) gave **1b-(*S*)** (0.92 g, 96%) as a light-yellow solid; m.p. 220–221 °C

(dec.). $[\alpha]_D^{20}$ = +90 (*c* = 2.0, $CHCl_3$) [ref.[15] m.p. 202 °C, $[\alpha]_D^{25}$ = +3.6 (*c* = 0.86, $CHCl_3$)]; 95% *ee* [flow rate 1.0 mL/min *n*-hexane/2-propanol 75:25 and 0.1% triethylamine, 48 bar, 254 nm, t_R (major) = 17.46 min, t_R (minor) = 24.82 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 9.1 Hz, 1 H, Ar-H), 7.91 (s, 1 H, Ar-H), 7.89 (d, *J* = 2.4 Hz, 1 H, Ar-H), 7.21 (dd, *J* = 2.4, 9.02 Hz, 1 H, Ar-H), 7.15 (s, 1 H, Ar-H), 4.60 (d, *J* = 14.7 Hz, 1 H, 9-H), 4.10 (s, 3 H, OMe), 4.06 (s, 3 H, OMe), 4.01 (s, 3 H, OMe), 3.65 (d, *J* = 14.5 Hz, 1 H, 9-H), 3.39–3.49 (m, 2 H, 13a-H, 14-H), 2.91–2.97 (m, 1 H, 14-H), 2.44–2.50 (m, 2 H, 11-H), 2.19–2.27 (m, 1 H, 13-H), 1.99–2.06 (m, 1 H, 13-H), 1.87–1.96 (m, 1 H, 12-H), 1.73–1.81 (m, 1 H, 12-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 149.4, 148.3, 130.4, 127.0, 125.6, 125.6, 125.2, 125.2, 123.3, 114.8, 104.6, 103.9, 103.1, 60.2, 56.0, 55.9, 55.5, 55.2, 53.9, 33.6, 31.2, 21.6 ppm. IR (KBr): $\tilde{\nu}$ = 3012, 2962, 2930, 2878, 2831, 2794, 1687, 1616, 1530, 1512, 1470, 1442, 1416, 1258, 1235, 1204, 1165, 1151, 1128, 1032, 1005, 918, 842, 822, 753 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{26}NO_3$ $[M + H]^+$ 364.1907; found 364.1914.

(–)-Deoxytylophorinine [1b-(*R*)]: A procedure analogous to the preparation of **1a-(*S*)** was used. **8b-(13a*R*,14*R*)** (1 g, 2.44 mmol) gave **1b-(*R*)** (0.93 g, 97%) as a light-yellow solid; m.p. 217–219 °C (dec.). $[\alpha]_D^{20}$ = –101 (*c* = 2.0, $CHCl_3$); 97% *ee* [flow rate 1.0 mL/min *n*-hexane/2-propanol 75:25 and 0.1% triethylamine, 41 bar, 254 nm, t_R (minor) = 16.52 min, t_R (major) = 23.18 min]; other data are the same as those for **1b-(*S*)**.

(+)-Antofine [1c-(*S*)]: A procedure analogous to the preparation of **1a-(*S*)** was used. **8c-(13a*S*,14*S*)** (1 g, 2.64 mmol) gave **1c-(*S*)** (0.93 g, 97%) as a light-yellow solid; m.p. 209–211 °C (dec.). $[\alpha]_D^{20}$ = +85 (*c* = 2.0, $CHCl_3$); 99% *ee* [flow rate 1.0 mL/min *n*-hexane/2-propanol 75:25 and 0.1% triethylamine, 48 bar, 254 nm, t_R (major) = 15.10 min, t_R (minor) = 17.80 min]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (s, 1 H, Ar-H), 7.88 (s, 1 H, Ar-H), 7.79 (d, *J* = 9.0 Hz, 1 H, Ar-H), 7.28 (s, 1 H, Ar-H), 7.19 (dd, *J* = 2.2, 9.00 Hz, 1 H, Ar-H), 4.68 (d, *J* = 14.9 Hz, 1 H, 9-H), 4.10 (s, 3 H, OMe), 4.05 (s, 3 H, OMe), 4.01 (s, 3 H, OMe), 3.68 (d, *J* = 14.9 Hz, 1 H, 9-H), 3.44–3.50 (m, 1 H, 13a-H), 3.29–3.34 (m, 1 H, 14-H), 2.85–2.96 (m, 1 H, 14-H), 2.42–2.50 (m, 2 H, 11-H), 2.19–2.26 (m, 1 H, 13-H), 2.00–2.06 (m, 1 H, 13-H), 1.89–1.94 (m, 1 H, 12-H), 1.75–1.79 (m, 1 H, 12-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.5, 149.4, 148.3, 130.1, 127.0, 126.5, 125.5, 124.2, 124.1, 123.5, 114.9, 104.6, 103.9, 103.8, 60.2, 56.0, 55.9, 55.5, 55.0, 54.4, 53.7, 48.8, 33.6, 31.2, 21.6 ppm. IR (KBr): $\tilde{\nu}$ = 3019, 2961, 2930, 2914, 2877, 2830, 2793, 1616, 1604, 1529, 1512, 1469, 1440, 1400, 1276, 1258, 1234, 1205, 1169, 1127, 1034, 843, 813, 751 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{26}NO_3$ $[M + H]^+$ 364.1907; found 364.1908.

(–)-Antofine [1c-(*R*)]: A procedure analogous to the preparation of **1a-(*S*)** was used. **8c-(13a*R*,14*R*)** (1 g, 2.64 mmol) gave **1c-(*R*)** (0.91 g, 95%) as a light-yellow solid; m.p. 210–212 °C (dec.). $[\alpha]_D^{20}$ = –124 (*c* = 2.0, $CHCl_3$) {ref.[16] m.p. 212–214 °C, $[\alpha]_D^{19}$ = –125.2 (*c* = 1.27, $CHCl_3$)}; 98% *ee* [flow rate 1.0 mL/min *n*-hexane/2-propanol 75:25 and 0.1% triethylamine, 43 bar, 254 nm, t_R (minor) = 14.55 min, t_R (major) = 19.99 min]; other data are the same as those for **1c-(*S*)**.

Supporting Information (see also the footnote on the first page of this article): Spectroscopic data for **3a–c**, **4a–e**, **7a-(*S*)**, **7b-(*S*)**, **7c-(*S*)**, **7d-(*S*)**, **7e-(*S*)**, **5**, **6**, **8a-(13a*S*,14*S*)**, **8b-(13a*S*,14*S*)**, **8c-(13a*S*,14*S*)**, **DCB-3503**, **DCB-3501**, **1a-(*S*)**, **1b-(*S*)** and **1c-(*S*)**. [To avoid repetition, the NMR, IR and HRMS spectra for **7a-(*R*)**, **7b-(*R*)**, **7c-(*R*)**, **7d-(*R*)**, **7e-(*R*)**, **8a-(13a*R*,14*R*)**, **8b-(13a*R*,14*R*)**, **8c-(13a*R*,14*R*)**, **1a-(*R*)**, **1b-(*R*)** and **1c-(*R*)** are not given.]

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