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Short asymmetric synthesis of phenanthroindolizidines through chiral homoallylic sulfinamines†

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An efficient stereocontrolled preparation of chiral phenanthroindolizidines is detailed. The synthesis relies on the stereoselective indium-mediated allylation of 2-(phenanthren-9-yl)acetaldehyde derivatives with chiral *tert*-butylsulfinamide. Chemoselective transformations from the corresponding homoallylic sulfinamine allow the synthesis of the phenanthroindolizidines in only three synthetic operations, without any detectable racemization. Following this procedure, the synthesis of natural (–)-tylophorine was successfully accomplished.

Introduction

The use of plants of the Asclepiadaceae family, including Tylophora indica, Cryptocarya and Ficus species, in the traditional medicine led to the discovery of phenanthroindolizidine alkaloids.[1] It has been shown that compounds of this family, in which (–)-antofine, (–)-tylophorine and (–)-tylocrebine are representative members (Fig. 1), display a wide range of biological activities, such as antibacterial,[2] antiasthmatic,[3] antiviral[4] and anti-inflamamatory[5] activities. Moreover, their extremely high cytotoxicity (IC_{50} ~ 10 nM) against different cancer cell lines by a unique mode of action has especially attracted the attention of medicinal chemists.[6]

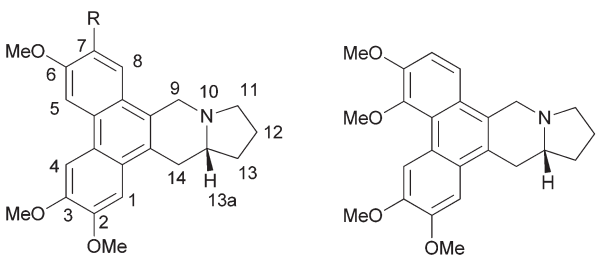

Fig. 1 Naturally occurring phenanthroindolizidines.

Due to the CNS toxicity of natural phenanthroindolizidines,[7] the search for potent non-toxic analogues with improved pharmacokinetic properties is a very active research area. Interestingly, the unnatural (*S*)-tylophorine was found to be even more potent in the inhibition of some specific cancer cell growth.[8] In this context, the development of robust methods that allows the rapid construction of the required enantioenriched phenanthroindolizidine scaffold is a need that has been addressed by a number of research groups. Some successful approaches reported in the last decade include the use of catalytic methods,[9] chiral building blocks[10] and chiral auxiliaries.[11] Importantly, access to both enantiomers, either *R*- or *S*-, phenanthroindolizidine alkaloids is highly desirable to explore their biological profiles and we anticipated that the corresponding chiral homoallylc sulfinamines should provide a very convenient entry.[12] Herein, we report the realization of this strategy.[13]

Results and discussion

In our retrosynthetic analysis of phenanthroindolizidines we propose the formation of ring D in a late stage by a reliable Pictet–Spengler annulation.[9a–c] Importantly, the chiral *tert*-butyl sulfinyl auxiliary[14] could be removed under the required acidic conditions for the cyclization, minimizing functional group manipulation (Scheme 1). The formation of the pyrrolidine intermediate **7** was anticipated by straightforward synthetic elaboration of homoallyl sulfinamine **5**, which could be prepared from aldehyde **4** using a one-pot protocol developed in our group.[15]

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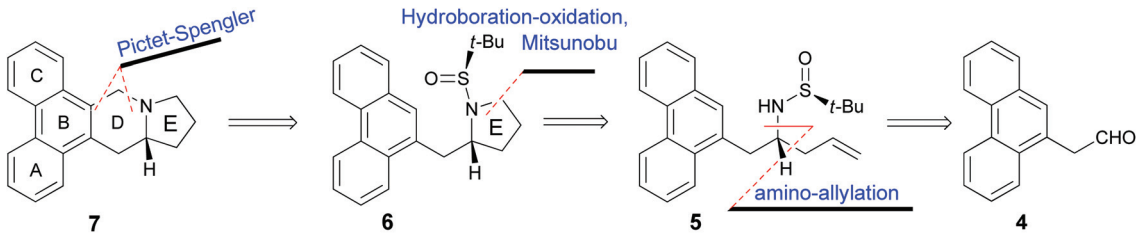
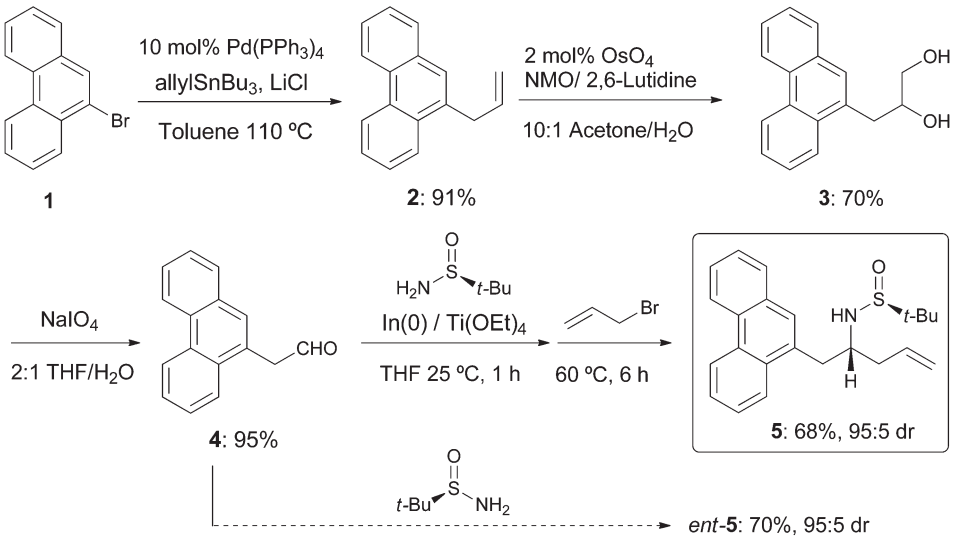
†Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **2–8**, **10–13**, diastereomeric mixtures of **5** and **12**, and (–)-tylophorine are provided. HPLC traces of compounds **5** and **12**, with the corresponding diastereomeric mixtures, and chiral analysis for compounds **8** and *ent*-**8** are included. See DOI: 10.1039/c4ob01133c



Scheme 1 Retrosynthetic analysis of phenanthroindolizidine.

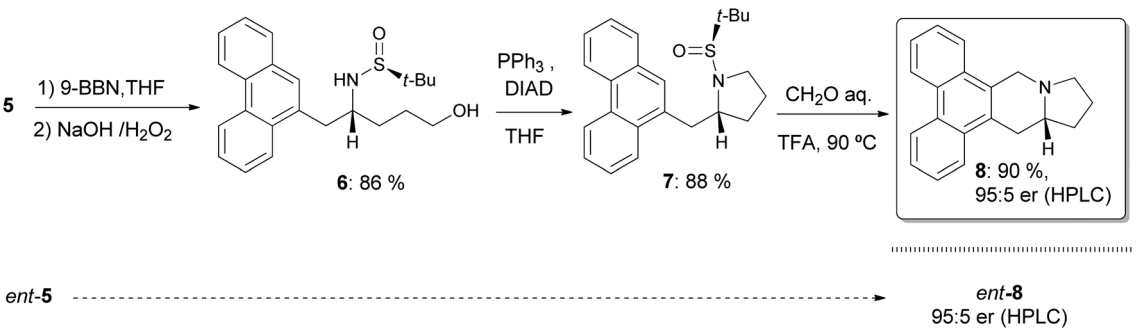


Scheme 2 Synthesis of homoallylsulfinamines **5** and *ent*-**5**.

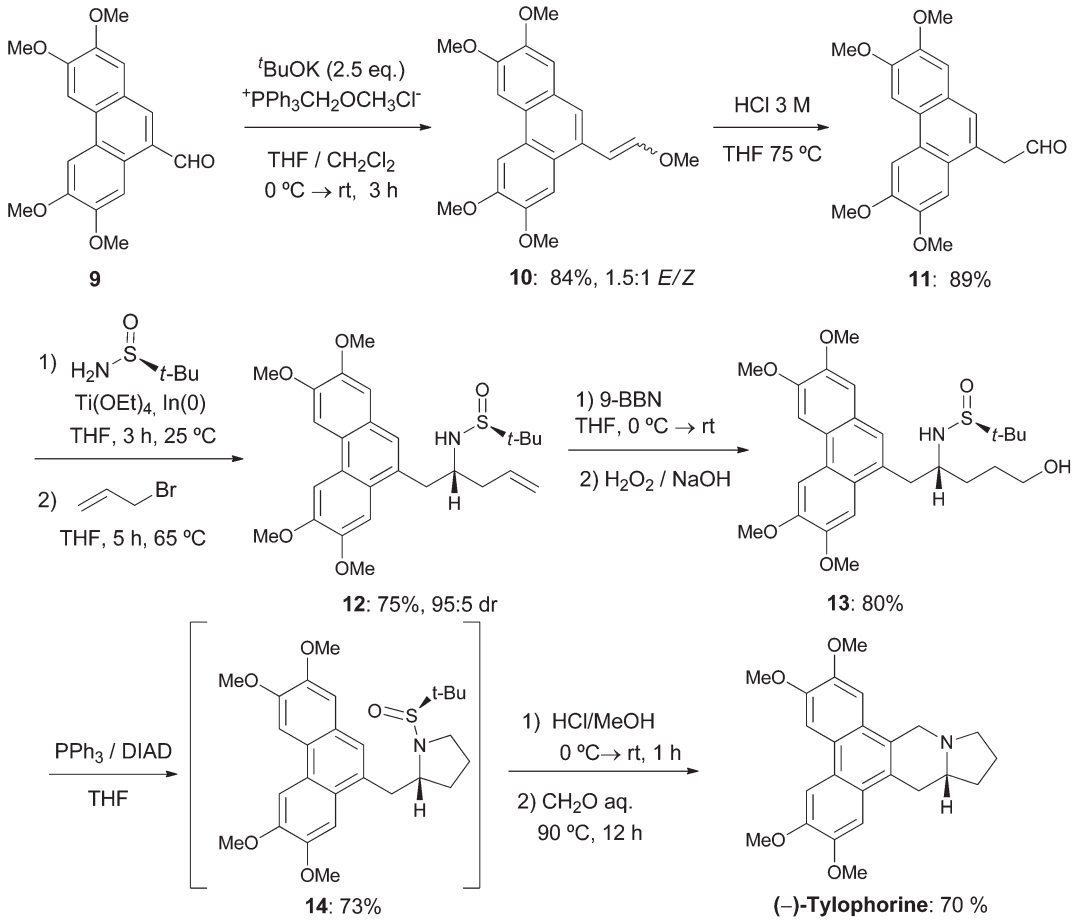
As outlined in Scheme 2, our synthesis began with the preparation of aldehyde **4**. Stille coupling of commercially available 9-bromophenanthrene with allyltri-*n*-butyltin afforded compound **2** in excellent yield. After having explored different conditions for the oxidative cleavage of the olefinic double bond, including ozonolysis and Johnson–Lemieux oxidation, aldehyde **4** was efficiently prepared in a two-step procedure. The very low solubility of the intermediate diol **3** allowed its purification by recrystallization from ethyl acetate, before being oxidatively cleaved by $NaIO_4$. This method afforded aldehyde **4** which was pure enough to be used directly in the next step. The indium-mediated aminoallylation took place with good yield and high diastereoselectivity,[16] either with (S_S)-*tert*-butylsulfinamide to obtain compound **5** or with (R_S)-*tert*-butylsulfinamide to prepare *ent*-**5**.[17]

Crucial to our synthetic plan was the use of chemoselective reactions to prepare pyrrolidine **7**, while using the *tert*-butylsulfinyl as the protecting group. We thus subjected intermediate **5** to a hydroboration-oxidation sequence, which took place without any detectable oxidation of the sulfur atom, and the obtained sulfinamine-alcohol **6** was cyclized under Mitsunobu conditions to furnish the desired compound **7** in very good overall yield.[18] Finally, a solution of this compound in TFA was treated with aqueous formalin at 90 °C for 12 h, and deprotection of the amino group was followed by the corresponding iminium formation and Pictet–Spengler annulations, affording compound **8** in excellent isolated yield. Physical and spectral data of compound **8** are in good agreement with those previously reported for a racemic sample.[19] Following the same route (Scheme 3), but from *ent*-**5** we also prepared compound *ent*-**8**. Chiral HPLC analysis of both final products clearly evidenced that racemization did not occur in the reaction sequence used from each chiral homoallylic sulfinamine (**5** or *ent*-**5**), obtaining identical enantiomeric ratios in the final products (95 : 5 er). Despite the high occurrence of the phenanthroindolizidine scaffold in prominent bioactive natural products, to the best of our knowledge this is the first report on the synthesis of the enantioenriched parent compounds.

Having developed a convenient procedure for the synthesis of phenanthroindolizidines, the stage was set to target naturally occurring family members and we illustrate the applicability of this protocol in the synthesis of (−)-tylophorine (Scheme 4). The synthesis commenced by a two-step homologation of the readily available phenanthryl aldehyde **9**.[20] A Wittig olefination with methoxymethyl phosphorous ylide allowed the preparation of a diastereomeric mixture of enol ethers **10** (*E*/*Z* 3 : 2, according to ^{1}H-NMR), which were hydrolyzed to furnish the required aldehyde **11** in very good overall yield. The indium-mediated amino allylation of this aldehyde took place with 75% yield to afford the homoallylic amine **12**



Scheme 3 Synthesis of phenanthroindolizidines **7** and *ent*-**7**.



Scheme 4 Synthesis of (–)-tylophorine.

with good diastereoselectivity [95 : 5 dr, determined by ^{1}H-NMR and HPLC, see the ESI†].[16] The hydroboration–oxidation sequence occurred with similar good efficiency to the one observed in the preparation of compound **6** and the obtained compound **13** was subjected to Mitsunobu cyclization conditions, which also took place with 73% isolated yield. Although the pyrrolidine **14** could not be efficiently separated from the triphenylphosphine oxide byproduct, it was used in the next step. Deprotection of the amino group with HCl was followed by *in situ* addition of aqueous formalin and after heating to 90 °C for 12 h, the desired (*R*)-(−)-tylophorine was obtained, which was isolated in good yield after chromatography purification. The spectroscopic data and the specific optical rotation value {$[\alpha]_D^{20}$ −85.0 (*c* 0.5, $CHCl_3$)} obtained for our synthetic tylophorine are in accordance with those reported for the natural compound.[9b,10b,11]

Conclusions

We have developed a practical procedure to build enantioenriched phenanthroindolizidines in which the indium-mediated aminoallylation of 2-(phenanthren-9-yl)acetaldehyde derivatives with chiral *tert*-butylsulfinamide is a key step. Importantly, in this synthetic approach the *tert*-butylsulfinyl group acted not only as a chiral director group, but also as a protecting group in the whole sequence, allowing the formation of target phenanthroindolizidines in only three synthetic operations from the corresponding homoallylic amine. From each enantiomer of *tert*-butylsulfinamide, the corresponding enantioenriched parent phenanthroindolizidine was prepared, the enantiomeric ratio of the final products being identical to the diastereomeric ratio of the corresponding chiral homoallylic sulfinamines. The usefulness of this protocol was illustrated by the synthesis of natural (−)-tylophorine and we hope it will find applications in the optimization of the biological profile of this family of bioactive compounds.

Experimental

General remarks

TLC was performed on silica gel 60 F_{254}, using aluminum plates and visualized by exposure to ultraviolet light or with phosphomolybdic acid (PMA) stain. Flash chromatography was carried out on handpacked columns of silica gel 60 (230–400 mesh). Melting points are uncorrected. Optical rotations were measured using a polarimeter with a thermally jacketed 5 cm cell at approximately 20 °C and concentrations (*c*) are given in g per 100 mL. Infrared analysis was performed with a spectrophotometer equipped with an ATR component; wavenumbers are given in cm^{-1}. Mass spectra (EI) were obtained at 70 eV; and fragment ions in *m*/*z* with relative intensities (%) are in parentheses. HRMS analyses were carried out using the Electron Impact (EI) mode at 70 eV or by Q-TOF using Electro Spray Ionization (ESI) mode. GC analyses were performed with an HP-5 column (30 m × 0.25 mm, ID × 0.25 μm) and an EI (70 EV) detector. The temperature program: hold at 60 °C for 3 min, ramp from 60 °C to 270 °C at 15 °C min^{-1}, hold at 270 °C for 10 min. ^{1}H NMR spectra were recorded at 300 or 400 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR, using $CDCl_3$ or DMSO-d_6 as the solvent and TMS as an internal standard (0.00 ppm). The data are reported as (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br s = broad signal, coupling constant (*s*) in Hz, integration). ^{13}C NMR spectra were recorded with ^{1}H-decoupling at 100 MHz and referenced to $CDCl_3$ at 77.16 ppm or to DMSO-d_6 at 39.52 ppm. DEPT-135 experiments were performed to assign CH, CH_2 and CH_3.

9-Allylphenanthrene (2)

To a solution of 9-bromophenanthrene (918 mg, 3.5 mmol) in dry toluene (50 mL), under an argon atmosphere, was added allyltributylstannane (2.17 mL, 7 mmol), palladium tetrakis (464 mg, 0.35 mmol) and lithium chloride (178 mg, 4.2 mmol). The resulting mixture was heated to 110 °C for 2 h, when full conversion was verified by TLC. After cooling to room temperature, the mixture was diluted with EtOAc (50 mL), washed with brine (20 mL), dried over $MgSO_4$ and concentrated to dryness. The obtained residue was purified by flash chromatography (hexane) to obtain the desired product as a white amorphous solid (693 mg, 91%): R_f 0.37 (100% hexane); GC t_R = 15.82 min. ^{1}H NMR, ^{13}C NMR, IR and MS were in agreement with previously reported data.[21]

3-(Phenanthren-9-yl)propane-1,2-diol (3)

To a solution of compound **2** (540 mg, 2.48 mmol) in acetone–water (35 mL/3.5 mL) were sequentially added 2,6-lutidine (0.90 mL, 7.80 mmol), NMO (704 mg, 5.8 mmol) and a solution of OsO_4 in *t*-BuOH (2.5% wt in *t*-BuOH, 0.90 mL). The mixture was stirred under an argon atmosphere for 3.5 h before being quenched with water (10 mL) and observing full consumption of the starting material by TLC. The mixture was extracted with EtOAc (3 × 15 mL) and the collected organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The solid obtained was recrystallized from EtOAc (~14 mL) to provide the pure diol **3** as a grey solid (300 mg). The filtrate was concentrated under reduced pressure to dryness and purified by column chromatography (1 : 1 hexane–EtOAc to 100% EtOAc) to afford another 133 mg of product (70% total yield): R_f 0.12 (1 : 1 hexane–EtOAc); IR ν 3377, 3290, 2884, 1385, 1305, 1112, 1033, 842, 722 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 8.90–8.83 (m, 1H), 8.81–8.75 (m, 1H), 8.24–8.17 (m, 1H), 7.94–7.88 (m, 1H), 7.74–7.58 (m, 5H), 4.76–4.69 (m, 2H), 3.92–3.82 (m, 1H), 3.53–3.37 (m, 3H), 2.95 (dd, *J* = 14.0, 7.9 Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ 133.9 (*C*), 131.3 (*C*), 131.1 (*C*), 130.1 (*C*), 129.1 (*C*), 127.9 (*C*H), 127.6 (*C*H), 126.8 (*C*H), 126.6 (*C*H), 126.3 (*C*H), 126.1 (*C*H), 124.7 (*C*H), 123.3 (*C*H), 122.6 (*C*H), 71.5 (*C*H), 65.8 (CH_2), 37.6 (CH_2) ppm; LRMS (EI) *m*/*z* (%) 252 (M+, 36), 207 (19), 191 (100), 178 (14), 165 (12), 151 (4); HRMS (EI) calcd for $C_{17}H_{16}O_2$ 252.1150, found 252.1156.

2-(Phenanthren-9-yl)acetaldehyde (4)

To a suspension of diol **3** (350 mg, 1.39 mmol) in THF–H_2O (14.25 mL/6.75 mL) was added $NaIO_4$ (356 mg, 1.68 mmol) and the reaction mixture was stirred under an argon atmosphere at 23 °C for 2.5 h (full consumption of starting material by TLC). The THF was removed under reduced pressure and the aqueous phase was extracted with EtOAc (3 × 15 mL). The collected organic layers were washed with brine, dried over $MgSO_4$ and concentrated to dryness to furnish pure aldehyde **4** as a brownish solid in almost excellent yield (290 mg, 95%): R_f 0.38 (9 : 1 hexane–EtOAc); GC t_R = 16.66 min; IR ν 3075, 2922, 2851, 2820, 1710, 739, 719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (t, *J* = 2.4 Hz, 1H), 8.79–8.74 (m, 1H), 8.69 (dd, *J* = 8.2, 0.5 Hz, 1H), 7.92 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.87 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.74–7.59 (m, 5H), 4.14 (dd, *J* = 2.4, 0.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0 (*C*HO), 131.6 (*C*), 131.2 (*C*), 130.9 (*C*), 130.4 (*C*), 129.5 (*C*), 128.5 (*C*), 127.3 (*C*H),

127.1 (2*C*H + *C*), 126.9 (*C*H), 124.4 (*C*H), 123.5 (*C*H), 122.7 (*C*H), 48.9 (*C*H_2); LRMS (EI) *m*/*z* (%) 220 (M^+, 44), 191 (100), 165 (22), 94 (4), 82 (3); HRMS (EI) calcd for $C_{16}H_{12}O$ 220.0888, found 220.0881.

(4*R*,*S*$_S$)-(*N*-*tert*-Butylsulfinyl)-5-[9-phenanthryl]-pent-1-en-4-amine (5)

To a dry flask were added (*S*$_S$)-*N*-*tert*-butylsulfinamide (161 mg, 1.33 mmol) followed by indium powder (191 mg, 1.66 mmol) under Ar. Then a solution of aldehyde **4** (306 mg, 1.39 mmol) in dry THF (2.7 mL) and Ti(OEt)$_4$ (0.6 mL, 2.66 mmol) were added successively and the reaction mixture was stirred under an argon atmosphere for 1 h at 23 °C. At this time allyl bromide (170 μL, 2.00 mmol) was added to the mixture and the reaction was allowed to reach 60 °C and stirred at that temperature for 6 h. The mixture was allowed to reach room temperature and was carefully added over a stirring mixture of 4 : 1 EtOAc–brine (10 mL). The resulting white suspension was filtered through a short pad of Celite, washed with EtOAc and concentrated under reduced pressure. The resulting suspension was diluted in 4 : 1 EtOAc–hexane (50 mL) and filtered again through Celite. Organics were concentrated to dryness and the residue was purified by flash chromatography (hexane–EtOAc 7 : 3 to 6 : 4) to obtain the desired product as a white amorphous solid (328 mg, 68%, 95 : 5 according to ^{1}H-NMR and HPLC, see ESI†): $[\alpha]_D^{20}$ 4.8 (*c* 0.68, MeOH); R_f 0.16 (7 : 3 hexane–EtOAc); HPLC analysis [Tracer Excel 120 column 15 cm × 0.46 cm, isocratic elution with 99 : 1 *n*-hexane–i-PrOH, 1.0 mL min^{-1}, UV detection at 254 nm, t_R (minor diastereoisomer) 45.05 min/t_R (major diastereoisomer) 49.23 min]; IR ν 3216, 3075, 2958, 2925, 1636, 1449, 1260, 1048,747, 726 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79–8.71 (m, 1H), 8.71–8.63 (m, 1H), 8.15–8.06 (m, 1H), 7.88–7.79 (m, 1H), 7.74–7.54 (m, 5H), 5.96–5.77 (m, 1H), 5.23 (d, *J* = 12,9, 2H), 3.90–3.76 (m, 1H), 3.57–3.40 (m, 2H), 3.20 (dd, *J* = 14.1, 7.3 Hz, 1H), 2.59–2.34 (m, 2H), 1.10 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.3 (*C*H), 132.7131.6 (*C*), 131.2 (*C*), 130.9 (*C*), 130.0 (*C*), 128.9 (*C*H), 128.2 (*C*H), 127.0 (*C*H), 126.9 (*C*H), 126.5 (*C*H), 126.4 (*C*H), 124.5 (CH), 123.4 (*C*H), 122.6 (*C*H), 119.6 (*C*H), 55.9 (*C*), 54.7 (*C*H), 40.3 (*C*H_2), 39.7 (*C*H_2), 22.6 (*C*H_3); LRMS (EI) *m*/*z* (%) 365 (M^+, 0.2), 309 (55), 191 (100), 165 (20), 118 (50), 70 (47), 57 (26), 41 (9); HRMS (ESI) calcd for $C_{23}H_{28}NOS$ 366.1892, found 366.1888.

(4*S*,*R*$_S$)-(*N*-*tert*-Butylsulfinyl)-5-[9-phenantryl]-pent-1-en-4-amine (*ent*-5)

It was prepared from aldehyde **4** (330 mg, 1.50 mmol) and (*R*$_S$)-*N*-*tert*-butylsulfinamide (173 mg, 1.43 mmol) following the same procedure described above for compound **5**. The expected compound was obtained as a white amorphous solid (365 mg, 70%) with identical spectroscopy and physical data than compound **5** except for $[\alpha]_D^{20}$ −6.7 (*c* 1.00, MeOH).

(4*R*,*S*$_S$)-(*N*-*tert*-Butylsulfinyl)-5-[9-phenantryl]-pent-1-ol-4-amine (6)

To a solution of compound **5** (803 mg, 2.20 mmol) in dry THF (3.3 mL), at 0 °C under an argon atmosphere, was added a solution of 9-BBN in THF (13.2 mL, 0.5 M). The cooling bath was removed and the reaction mixture was stirred for 15 h at 25 °C. The reaction mixture was cooled down to 0 °C and a solution of 6 M NaOH (5.9 mL) was carefully added, followed by H_2O_2 (5.1 mL, 33%). The reaction mixture was left stirring for 8 h, while the temperature increased to 25 °C. The mixture was extracted with EtOAc (3 × 20 mL), the collected organic layers were washed with water (10 × 5 mL), brine (1 × 5 mL), dried over $MgSO_4$ and concentrated to dryness. The crude product was purified by flash chromatography (EtOAc 100% to EtOAc–MeOH 98 : 2) to obtain the desired product as a white amorphous solid (725 mg, 86%): $[\alpha]_D^{20}$ −11.4 (*c* 0.7, MeOH); R_f 0.30 (98 : 2 EtOAc–MeOH); IR ν 3233, 3075, 2925, 2866, 1449, 1038, 747, 726 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78–8.71 (m, 1H), 8.70–8.62 (m, 1H), 8.11–8.03 (m, 1H), 7.86–7.78 (m, 1H), 7.71–7.54 (m, 5H), 3.84–3.56 (m, 4H), 3.35 (dd, *J* = 14.0, 7.1 Hz, 1H), 3.26 (dd, *J* = 14.1, 6.4 Hz, 1H), 2.02–1.86 (m, 1H), 1.86–1.63 (m, 4H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.9 (*C*), 131.6 (*C*), 131.3 (*C*), 130.9 (*C*), 129.9 (*C*), 128.8 (*C*H), 128.2 (*C*H), 126.9 (*C*H), 126.8 (*C*H), 126.5 (*C*H), 126.4 (*C*H), 124.4 (*C*H), 123.5 (*C*H), 122.6 (*C*H), 62.8 (*C*H_2), 57.5 (*C*H), 56.0 (*C*), 41.1 (*C*H_2), 32.8 (*C*H_2), 28.7 (*C*H_2), 22.7 (*C*H_3); LRMS (EI) *m*/*z* (%) 327 ($M^+ - C_4H_8$, 44), 245 (11), 191 (100), 165 (22), 118 (70), 88 (60), 71 (51), 57 (27), 41 (9); HRMS (ESI) calcd for $C_{23}H_{30}NO_2S$ 384.1997, found 384.1980.

(4*S*,*R*$_S$)-(*N*-*tert*-Butylsulfinyl)-5-[9-phenantryl]-pent-1-ol-4-amine (*ent*-6)

It was prepared following the same procedure described above for compound **6**, showing identical spectroscopy and physical data except for $[\alpha]_D^{20}$ +9.4 (*c* 0.9, MeOH).

(2*R*,*S*$_S$)-(*N*-*tert*-Butylsulfinyl)-2-(phenanthren-9-ylmethyl)-pyrrolidine (7)

To a solution of compound **6** (617 mg, 1.61 mmol) in dry THF (16 mL) under an argon atmosphere was added PPh_3 (512 mg, 1.95 mmol), followed by DIAD (400 μL, 2.03 mmol) at 25 °C. The reaction mixture turned yellow and was stirred for 16 h. The mixture was concentrated to dryness under reduced pressure and the residue was purified by flash chromatography (7 : 3 hexane–EtOAc). The desired product was obtained as a white amorphous solid (518 mg, 88%): $[\alpha]_D^{20}$ +29.6 (*c* 0.95, MeOH); R_f 0.24 (7 : 3 hexane–EtOAc); IR ν 3733, 3632, 2963, 1450, 1360, 1065, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77–8.71 (m, 1H), 8.70–8.63 (m, 1H), 8.19–8.11 (m, 1H), 7.86–7.79 (m, 1H), 7.73–7.65 (m, 2H), 7.63–7.55 (m, 3H), 4.18–4.06 (m, 1H), 3.87–3.76 (m, 1H) 3.68 (dd, *J* = 13.5, 4.5 Hz, 1H), 2.97–2.84 (m, 2H), 1.98–1.83 (m, 1H), 1.78–1.57 (m, 3H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.3 (*C*), 131.8 (*C*), 131.1 (*C*), 130.8 (*C*), 130.0 (*C*), 128.2 (*C*H), 127.8 (*C*H), 127.0 (*C*H), 126.8 (*C*H), 126.5 (*C*H), 126.4 (*C*H), 124.7 (*C*H), 123.4 (*C*H), 122.6 (*C*H), 65.5 (*C*H), 57.4 (*C*), 41.8 (*C*H_2), 41.5 (*C*H_2), 31.8 (*C*H_2), 26.0 (*C*H_2), 24.1 (*C*H_3); LRMS (EI) *m*/*z* (%) 365 (M+, 0.1), 309 ($M^+ - C_4H_8$, 25), 191 (46), 118 (100), 70 (14), 57 (6), 41 (4); HRMS (EI) calcd for $C_{19}H_{19}NOS$ 309.1187, found 309.1177.

(2*S*,R_S)-(*N*-*tert*-Butylsulfinyl)-2-(phenanthren-9-ylmethyl)-pyrrolidine (*ent*-7)

It was prepared following the same procedure described above for compound **7**, showing identical spectroscopy and physical data except for $[\alpha]_D^{20}$ −27.7 (*c* 0.95, MeOH).

(*R*)-9,11,12,13,13a,14-Hexahydrodibenzo[*f*,*h*]pyrrolo[1,2-*b*]-isoquinoline (8)

To a solution of compound **7** (244 mg, 0.67 mmol) in TFA (6 mL) under an argon atmosphere, was added 37% aqueous CH_2O (2.50 mL, 1.18 mL) and the reaction mixture was heated to 90 °C for 12 h. After cooling to room temperature, H_2O (15 mL) and 2 M NaOH (15 mL) were sequentially added to the mixture (pH > 12) and the product was extracted with EtOAc (3 × 40 mL). The collected organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The orange solid obtained was purified by flash chromatography (CH_2Cl_2–MeOH 98 : 2 to 90 : 10) to obtain a pale yellow solid (164 mg, 90%, 95 : 5 er according to chiral HPLC): $[\alpha]_D^{20}$ −146 (*c* 1.0, $CHCl_3$); mp 159–160 °C (MeOH) {lit.[19] mp 153–154 °C for racemic mixture}; R_f 0.20 (95 : 5 CH_2Cl_2–MeOH); HPLC analysis [AD-H column 25 cm × 0.46 cm, isocratic elution with 75 : 25 : 0.1 *n*-hexane–i-PrOH–Et_3N, 1.0 mL min^{-1}, UV detection at 254 nm], t_R (minor) 9.54 min, t_R (major) 19.77 min. ^1H NMR, ^{13}C NMR, IR and MS were in agreement with previously reported data.[19]

(*S*)-9,11,12,13,13a,14-Hexahydrodibenzo[*f*,*h*]pyrrolo[1,2-*b*]-isoquinoline (*ent*-8)

It was prepared following the same procedure described above for compound **8**, showing identical spectroscopy and physical data except for $[\alpha]_D^{20}$ +138 (*c* 0.5, $CHCl_3$). The analysis by chiral HPLC also showed a 95 : 5 er (see ESI† for HPLC traces).

2,3,6,7-Tetramethoxy-9-(2-methoxyvinyl)phenanthrene (10)

To a suspension of *t*-BuOK (469 mg, 4.2 mmol) in dry THF (25 mL) was added phosphonium salt (1.420 g, 4.1 mmol) at 0 °C and stirred for 30 min under an argon atmosphere. Then the suspension was stirred for 20 min at room temperature, cooled again to 0 °C and a solution of compound **9** (529 mg, 1.62 mmol) in CH_2Cl_2 (20 mL) was added. The reaction mixture was left stirring for 3 h while the temperature increased to 25 °C. At this point, the reaction was quenched by adding a saturated solution of NH_4Cl (25 mL). The mixture was extracted with EtOAc (3 × 25 mL) and the collected organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by recrystallization from 1-propanol to give compound **10** (481 mg, 84%) as a yellow solid (diastereomeric mixture, *E*/*Z* ratio ≈ 1.5/1): R_f 0.35 (6 : 4 hexane–EtOAc); IR ν 2999, 2951, 2926, 2852, 1706, 1509, 1252, 1148, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 0.43H, (*Z*)), 7.82 (s, 1H, (*E*)), 7.76 (s, 1H, (*Z*)), 7.48 (d, *J* = 12.9 Hz, 1H, (*Z*)), 7.43 (s, 0.56 H, (E)), 7.19 (d, *J* = 10.7 Hz, 1H, (*E*/*Z*)), 6.97 (d, *J* = 12.4 Hz, 0.57H, (*E*)), 6.41 (d, *J* = 7.1 Hz, 0.47H, (*Z*)), 6.38 (d, *J* = 7.9 Hz, 0.54H, (*E*)), 5.78 (d, *J* = 7.1 Hz, 0.42H, (*Z*)), 4.12 (2s, 3H), 4.11 (2s, 3H), 4.05 (2s, 3H), 4.03 (bs, 3H), 3.82 (2s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.0 (*C*H), 149.14 (*C*), 149.10 (*C*), 149.05 (*C*), 149.01 (*C*), 148.9 (*C*), 148.84 (*C*), 148.7 (*C*), 148.6 (*C*H), 148.6 (*C*), 129.7 (*C*), 127.5 (*C*), 126.7 (*C*), 126.6 (*C*), 125.6 (*C*), 125.2 (*C*H), 125.1 (*C*), 124.8 (*C*), 123.9 (*C*), 123.7 (*C*), 121.8 (*C*H), 108.5 (*C*H), 108.2 (*C*H), 105.4 (*C*H), 105.3 (*C*H), 103.4 (*C*H), 103.3 (*C*H), 103.0 (*C*H), 102.9 (*C*H), 102.4 (*C*H), 60.8 (*C*H), 57.3 (*C*H), 56.3 (*C*H_3), 56.2 (*C*H_3), 56.17 (*C*H_3), 56.0 (*C*H_3), 55.96 (*C*H_3); LRMS (EI) *m*/*z* (%) 354 (M+, 100), 339 (15), 324 (10), 308 (17), 177 (7); HRMS (EI) calcd for $C_{21}H_{22}O_5$ 354.1467, found 354.1466.

2-(2,3,6,7-Tetramethoxyphenanthren-9-yl)acetaldehyde (11)

To a suspension of compound **10** (531 mg, 1.5 mmol) in dry THF (1.85 mL) was added a solution of 3 M HCl (0.65 mL). The mixture was stirred and heated to 75 °C under an argon atmosphere for 2.5 h, before being quenched with aqueous solution of $NaHCO_3$ (6 mL, 10%). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the collected organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (hexane–EtOAc 65 : 35 to 55 : 45) to obtain a yellow amorphous solid (454 mg, 89%): R_f 0.32 (1 : 1 hexane–EtOAc); ^1H NMR, ^{13}C NMR and MS were in agreement with previously reported data.[13]

(4*R*,S_S)-(*N*-*tert*-Butylsulfinyl)-5-[2,3,6,7-tetramethoxyphenanthren-9-yl]-pent-1-en-4-amine (12)

To a mixture of aldehyde **11** (622 mg, 1.83 mmol), (S_S)-*N*-*tert*-butylsulfinamide (210 mg, 1.74 mmol), indium powder (252 mg, 2.20 mmol) in dry THF (3.5 mL), was added $Ti(OEt)_4$ (0.8 mL, 3.48 mmol) at 25 °C. After 3 h, allyl bromide (226 μL, 1.4 mmol) was added to the mixture and the reaction was allowed to reach 65 °C and stirred at that temperature for 6 h. The mixture was allowed to reach room temperature and was carefully added over a stirring mixture of 4 : 1 EtOAc–brine (25 mL). The resulting white suspension was filtered through a short pad of Celite, washed with EtOAc (5 × 20 mL) and concentrated under reduced pressure. The crude was purified by flash chromatography (hexane–EtOAc 3 : 7) to obtain the desired product as a pale yellow solid (672 mg, 75%, 95 : 5 according to ^1H-NMR and HPLC): $[\alpha]_D^{20}$ +34.8 (*c* 1.2, $CHCl_3$); {lit.[13] $[\alpha]_D^{25}$ +42.6 (*c* 1.0, $CHCl_3$)}; R_f 0.22 (3 : 7 hexane–EtOAc); HPLC analysis [Tracer Excel 120 column 15 cm × 0.46 cm, isocratic elution with 95 : 5 *n*-hexane–i-PrOH, 1.0 mL min^{-1}, UV detection at 254 nm], t_R (minor) 14.71 min/t_R (major) 17.16 min]; ^1H NMR, ^{13}C NMR, IR and MS were in agreement with previously reported data.[13]

(4*R*,S_S)-(*N*-*tert*-Butylsulfinyl)-5-[2,3,6,7-tetramethoxyphenanthren-9-yl]-pent-1-ol-4-amine (13)

To a solution of compound 12 (485 mg, 1 mmol) in dry THF (1 mL) was added a solution of 9-BBN in THF (6 mL, 0.5 M) at 0 °C, under an argon atmosphere. After being stirred for 15 h at room temperature, a solution of 6 M NaOH (2.7 mL) followed by H_2O_2 (3.3 mL, 33%) were added to the mixture with ice cooling. The reaction mixture was left stirring for 8 h, while

the temperature increased to 25 °C. The mixture was extracted with EtOAc (3 × 20 mL), the collected organic layers were washed with water (10 × 5 mL), brine (1 × 5 mL), dried over $MgSO_4$ and concentrated to dryness. The crude product was purified by flash chromatography (EtOAc–MeOH 98 : 2 to 95 : 5) to obtain the desired product as a white amorphous solid (403 mg, 80%): $[\alpha]_D^{20}$ −5.7 (*c* 1.03, MeOH); R_f 0.15 (98 : 2 EtOAc–MeOH); IR ν 3298, 3179, 3003, 2930, 2830, 1614, 1509, 1470, 1252, 1146, 1029, 836, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.76 (s, 1H), 7.40 (d, J = 11.3 Hz, 2H), 7.15 (s, 1H), 4.12 (s, 3H), 4.11 (s, 3H), 4.08 (s, 3H), 4.02 (s, 3H), 3.84 (d, J = 5.5 Hz, 1H), 3.81–3.71 (m, 1H), 3.71–3.63 (m, 1H), 3.63–3.53 (m, 1H), 3.36 (dd, J = 14.0, 6.2 Hz, 1H), 3.09 (dd, J = 14.0, 7.5 Hz, 1H), 2.51 (s, 1H), 1.98–1.81 (m, 1H), 1.81–1.64 (m, 3H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1 (*C*), 149.0 (2*C*), 148.9 (*C*), 130.2 (*C*), 126.3 (*C*H), 126.2 (*C*), 125.4 (*C*), 125.1 (*C*), 123.9 (*C*), 108.0 (*C*H), 104.8 (*C*H), 103.6 (*C*H), 102.9 (*C*H), 62.69 (CH_2), 56.8 (*C*H), 56.3 (CH_3), 56.2 (CH_3), 56.1 (CH_3), 56.0 (CH_3), 55.9 (*C*), 41.5 (CH_2), 32.3 (CH_2), 28.7 (CH_2), 22.7 (CH_3); LRMS (EI) *m*/*z* (%) 503 (M+, 8.3), 447 (5), 382 (7), 311 (100), 118 (25), 88 (26), 71(13), 57 (13), 46 (9); HRMS (ESI) calcd for $C_{27}H_{38}NO_6S$ $[M + H]^+$ 504.2420, found 504.2411.

(*R*)-Tylophorine

To a solution of compound **13** (312 mg, 0.62 mmol) in dry THF (6.2 mL) under an argon atmosphere was added PPh_3 (195 mg, 0.74 mmol), followed by DIAD (154 μL, 0.78 mmol) at 25 °C. The reaction mixture turned yellow and was stirred for 16 h. The mixture was concentrated to dryness under reduced pressure and the residue was purified by flash chromatography (hexane–EtOAc 4 : 6 to 75% EtOAc). The obtained intermediate **14** [R_f 0.16 (3 : 7 hexane–EtOAc)] was contaminated with triphenylphosphine oxide according to ^1H NMR, and used in the next step without further purification.

To a mixture of compound **14** (155.2 mg, 0.52 mmol) in MeOH (5.2 mL) was added a solution of 4 M HCl in dioxane (3.25 mL) at 0 °C, under an argon atmosphere. The mixture was stirred for 1 h at 25 °C, then was added 37% formaldehyde (10.4 mL) and the solution was heated to 90 °C and stirred for 12 h in the dark. The cooled mixture was diluted with water (20 mL) and solution of 2 M NaOH (20 mL). The organics phases were extracted with CH_2Cl_2 (3 × 25 mL) and washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by flash column (100% CH_2Cl_2 to 95 : 5 CH_2Cl_2–MeOH), to obtain the desired product as a yellow solid (171 mg, 70%): $[\alpha]_D^{20}$ −85.0 (*c* 0.5, $CHCl_3$). {lit[13] $[\alpha]_D^{20}$ −87 (*c* 1.0, $CHCl_3$)}; R_f 0.38 (95 : 5 CH_2Cl_2–MeOH); ^1H NMR, ^{13}C NMR, IR and MS were in agreement with previously reported data.[9b,10b,11]

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