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Total Synthesis of Phenanthropiperidine Alkaloids by Sequential Alkylation of *N,N*-Dibenzylaminoacetonitrile

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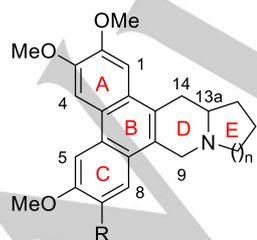
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Abstract: Two representative members of the phenanthropiperidine alkaloid family, tylophorine (**1**) and cryptopleurine (**2**), were synthesized by a bidirectional alkylation strategy employing dibenzylaminoacetonitrile as a substrate. This approach relies on the unprecedented condensation of metallated α -aminonitriles with bromomethylphenanthrenes to provide fully substituted α -aminonitriles that are submitted to a NaBH₄-mediated reductive decyanation process to form homobenzyl amines. From these intermediates, a terminal leaving group was introduced by simple chemical manipulation, and its displacement by a free primary amine under two favourable cyclization processes led to the formation of the future E-ring of both alkaloids in high yields. Finally, a late Pictet–Spengler cyclization ensured the formation of a D-ring for the alkaloids **1** and **2**.

Introduction

Phenanthropiperidine alkaloids represent a small group of pentacyclic natural products (Figure 1) that have been used in folk medicine for untold centuries. These compounds have been isolated from plants found throughout India, Africa and Australia. Tylophorine (**1**) was first isolated in 1935 by Rathnagiriswaran and Venkatachalam from the roots and leaves of *Tylophora asthmatica*,^[1] whereas cryptopleurine (**2**) was isolated in 1947 by de la Lande from the bark of *Cryptocarya pleurosperma*, an evergreen tree indigenous to Australia.^[2]



R = OMe, n = 1, tylophorine (**1**)
R = H, n = 2, cryptopleurine (**2**)

Figure 1. Representative members of phenanthropiperidine alkaloids (tylophorine numbering).

Phenanthropiperidines present marked biological properties^[3] such as antiproliferative effects against various cell lines^[4] or have been shown to selectively inhibit hypoxia-inducible factor-1 (HIF-1) in several human cancer lines.^[5] Phenanthrene-based derivatives also interact with the nuclear factor-kappa B (NF- κ B) signaling pathway^[6] or present anti-inflammatory activity by reducing the production of tumor necrosis factor-alpha (TNF α).^[7] Many derivatives are also potent inhibitors of hepatitis C and tobacco mosaic virus replication.^[8] In addition, cryptopleurine together with various small molecules inhibits protein synthesis in eukaryotic cells by targeting mRNA and tRNA binding sites of the ribosome.^[9]

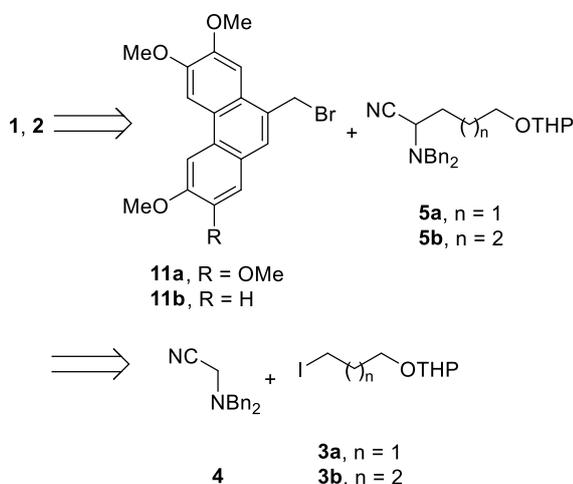
These significant biological properties have incited chemists to propose numerous syntheses. The most recent racemic approaches to alkaloids **1** and **2** rely on various methodologies, including iterative Suzuki–Miyaura reaction of boronic acids,^[10] intramolecular aza-Diels–Alder condensation,^[11] free radical cyclizations,^[12] Cp*Co^{III} or Rh^{III}-catalysed annulation of terminal alkynes,^[13] Pd-catalysed aryne annulation by *o*-halostyrenes,^[14] Stevens rearrangement of a nitrile stabilized ylide,^[15] or Negishi cross-coupling reaction.^[16] Several well-designed approaches utilizing chiral catalysts have also led to the synthesis of title alkaloids with high enantiomeric ratios.^[17] Similarly, successful asymmetric syntheses have been carried out through chiral auxiliary-based approaches,^[18] or via chemical manipulation of enantiopure amino acids.^[19]

Despite their apparent similarities, phenanthropiperidine alkaloids exhibit several distinguishable features. First, these compounds display phenanthrene rings that differed in their number and position of methoxy groups. Second, compounds **1** and **2** possess saturated nitrogen-containing heterocycles of indolizidine and quinolizidine, respectively. Thus, for the present work, it was necessary to develop a general and modular access to phenanthropiperidine alkaloids, which is delineated retrosynthetically in Scheme 1.

For the synthesis of tylophorine, the central feature of our approach is based on the condensation of α -aminonitrile **5a** (n = 1) with known bromide **11a** to form the future C13a–C14 bond of the target molecule.^[20] Accordingly, the synthesis of cryptopleurine can be carried out by a proper selection of the alkyl chain length (n = 2) of **5** and the substitution pattern of the phenanthrene moiety. Then, the construction of the future pyrrolidine ring (E ring) of **1** should be performed through a favoured 5-*exo-tet* cyclization process between N-10 and a terminal cyclizing group, while a 6-*exo-tet* annulation process

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should form the piperidine ring of **2**. It is worth noting that in both alkaloids, we planned that the future C8b-C9 bond should be realised by late Pictet–Spengler cyclomethylation.



Scheme 1. Retrosynthetic Analysis of Phenanthropiperidines **1**, and **2** from α -Amino-Nitriles **5a**, and **b**.

Results and Discussion

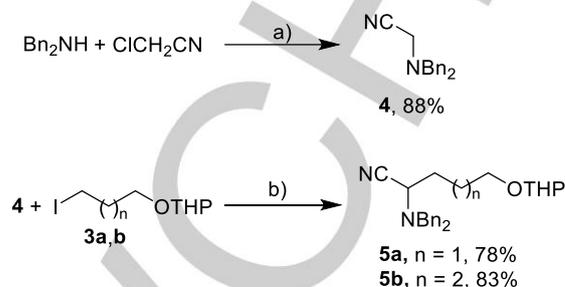
Synthesis of α -aminonitriles **4**, **5**.

Our synthesis began with the condensation of chloroacetonitrile and dibenzylamine, which was carried out in acetonitrile in the presence of a catalytic amount (up to 5% in mass) of *n*-tetrabutylammonium iodide (Bu_4NI) and diisopropylethylamine (DIPEA, Hünigs base) as the proton scavenger (Scheme 2). After treatment and removal of the DIPEA hydrochloride salt by filtration, α -aminonitrile **4** was obtained in 88% yield after slow crystallization in a mixture of diethyl ether and petroleum ether.

With the required derivative in hand, we turned to the deprotonation of **4** in the presence of a strong base. Scrutinizing the literature data revealed that studies devoted to the reactivity of lithiated α -aminonitrile **4** are scarce. Nevertheless, in the continuation of the seminal work of Stork in 1978,^[21] Husson reported the double deprotonation of **4** to synthesize cyclohexylaminonitriles,^[22] whereas Rychnovsky described a sequential process aimed at the preparation of fully substituted α -aminonitriles.^[23] In these studies, primary alkyl bromides and iodides were used as electrophiles, while Mangeney condensed several aldehydes to synthesize a set of β -aminoalcohols with a high level of diastereoselectivity.^[24] α -Aminonitrile **5** was synthesized in two steps: deprotonation of **4** and condensation of the resulting α -aminocarbanion on the requisite electrophile. Based on our previous experience in α -aminonitrile chemistry, we believe that LDA should be the base of choice and THF the preferred solvent.^[25]

Thus, treatment of a 0.4 M THF solution of α -aminonitrile **4** cooled to -80°C by 1.20 equivalents of LDA provided the rapid formation of a deep red anion solution that was warmed to -30°C over a 1.5 h period. The solution was next cooled to -80°C , and 1.10 equivalents of bifunctional iodide **3a** were added at this temperature. After aqueous work-up, α -aminonitrile **5a** was obtained in 78% yield after chromatographic purification (Scheme

2). It is important to mention that common additives such as TMEDA or DMPU were ineffective or had a detrimental effect. When similar experiments were carried out with iodide **3b**, the expected α -aminonitrile **5b** was obtained in 83% yield, indicating that the length of the carbon chain and the presence of a tethered OTHP group did not affect the anion alkylation.

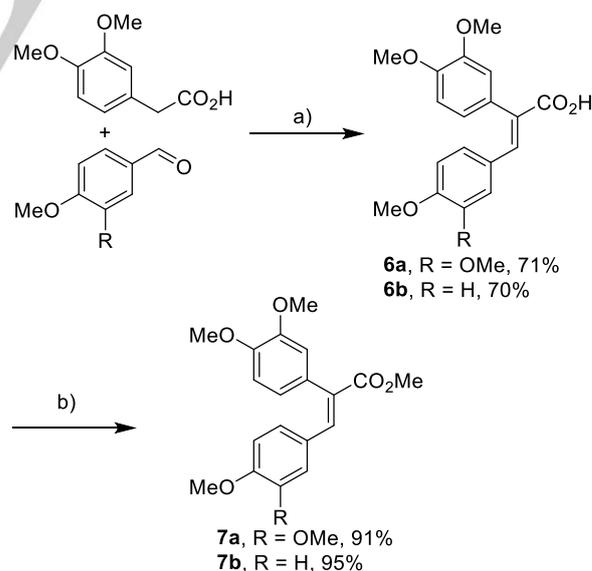


Scheme 2. Syntheses for α -aminonitriles **4**, and **5**. Reagents and conditions: a) DIPEA, Bu_4NI (5% in mass), CH_3CN , rt, 72 h; b) LDA, THF, -80 to -30°C , 1.5 h, then **3**, -80°C to rt.

Synthesis of bromides **11**.

With an efficient route to α -aminonitriles **5**, we turned to the synthesis of bromides **11**, which was carried out according to a known reaction sequence.^[26] However, problems associated with the oxidative coupling of acrylic esters **7**, prompted us to report our own results.

The synthesis began with the preparation of acrylic acid **6a** by condensing homoveratric acid and veratraldehyde in the presence of 3.6 equivalents of freshly distilled triethylamine and 5.5 equivalents of acetic anhydride (Scheme 3).

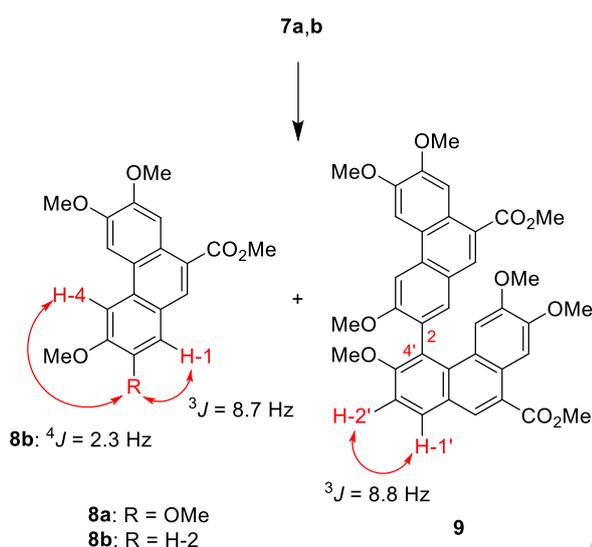


Scheme 3. Synthesis of acrylic esters **7**. Reagents and conditions: a) $\text{Et}_3\text{N}/\text{Ac}_2\text{O}$, 80°C , 24 h (**6a**) or 5 h (**6b**); b) MeOH, H_2SO_4 (ca. 1 equiv.), reflux for 24 h.

The reaction mixture was refluxed under an argon atmosphere at 80°C for 24 h, and a simplified treatment (see the experimental section for details) afforded the expected 2,3-

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diphenylacrylic acid **6a** in 71% yield. Similarly, compound **6b** was obtained in 70% yield, but the synthesis required a much shorter reaction time for the reaction to be complete. The ^1H and ^{13}C spectra were consistent with the proposed structures and indicated that acids **6** were isolated as single isomers.^[27] Then, Fisher esterification produced acrylic esters **7** in nearly quantitative yields. Efforts were next directed to the synthesis of phenanthrenes **8**, which were thought to be readily available through a dehydrogenative cross-coupling reaction (Scheme 4).



Scheme 4. Synthesis of phenanthrenes **8a,b** and bis-phenanthrene **9**.

Our initial attempts to cyclize acrylic ester **7a** were carried out according to existing methods (Table 1, entries 1–2) and failed to produce the expected phenanthrene **8a**.^[28] Only the starting material was recovered from the reaction mixture, and this lack of reactivity under these specified reaction conditions was puzzling

and prompted us to investigate alternate procedures. We continued our study with inspiration from the work of Rathore, who reported the oxidative coupling of polymethoxy biaryl units in the presence of dichloro-dicyano-benzoquinone (DDQ) as the preferred oxidant.^[29] Notably, quinones are redox-active organic molecules that are involved in many oxidative processes that are found *in vivo* and in the laboratory.^[30] As recently highlighted by Hammes-Schiffer, the E^0 values of quinones can be increased by the presence of electron-withdrawing substituents.^[31] For example, 1,4-benzoquinone (BQ) displayed an E^0 redox potential of + 0.65 V vs NHE, whereas tetrachloro-1,4-benzoquinone (chloranil) and DDQ were shown to have a more elevated E^0 values of 0.70 V and 0.99 V vs NHE, respectively.^[32] Our first experiment (entry 3) was carried out in a dichloromethane (DCM) solution of ester **7a** under conditions defined by Rathore (DCM/MeSO₃H) but with chloranil (entry 3) as the selected quinone and, once again, only the starting material was recovered. In sharp contrast, the addition of a stoichiometric amount of DDQ (entry 4), led to an immediate colouration of the reaction mixture, which turned dark green after a few minutes. A basic aqueous treatment with sodium carbonate allowed the selective removal of DDQH₂ and afforded the expected phenanthrene **8a** in a 95% isolated yield. Upon comparing entries 4 and 5, one can see that the concentration of acid had an influence on the kinetics of the reaction. Indeed, when the experiment was carried out in a 99:1 mixture of dichloromethane and methane sulfonic acid, the reaction was half-completed after 1 h of stirring at 0 °C. Complementing the synthetic efforts mentioned above, we turned to the synthesis of phenanthrene **8b**. Thus, when a 120 mmol solution of ester **7b** (entry 7) in a mixture of dichloromethane and methane sulfonic acid (9:1) was treated with 1.1 equivalent of DDQ, the solution immediately turned dark green, providing evidence that a redox reaction also took place. Stirring was continued for 30 minutes, and standard aqueous work-up afforded a complex reaction mixture from which no detectable amount of phenanthrene **8b** could be detected.

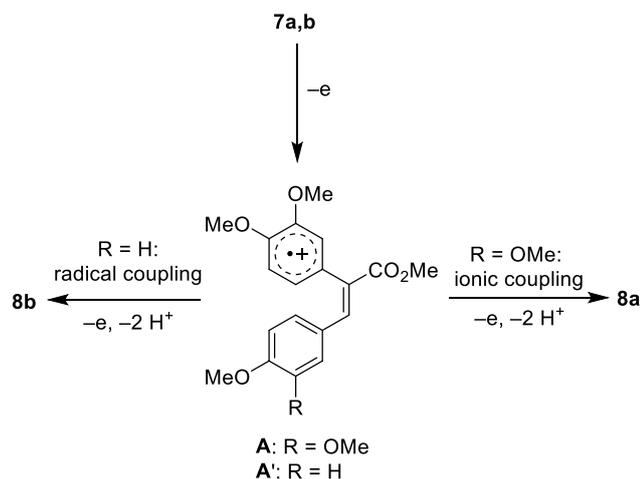
Table 1. Optimization study for the oxidative coupling of esters **7**.

Entry	N°, concentration (mmol)	Conditions	Product distribution	Yield [a]
1	7a , 75	FeCl ₃ (5 equiv.), DCM, rt, 12 h	7a/8a (90:10)	8
2	7a , 30	NaNO ₂ (20 mol%)/O ₂ (air)/ACN/TFA (95:5), rt, 10 h	7a/8a (>95:5)	5
3	7a , 65	Chloranil (1.1 equiv.)/DCM/MeSO ₃ H (9:1), 0 °C, 1 h.	7a/8a (>99:1)	<1
4	7a , 140	DDQ (1.1 equiv.)/DCM/MeSO ₃ H (9:1), 0 °C, 30 min, then rt, 1 h.	7a/8a (>1:99)	>95
5	7a , 140	DDQ (1.1 equiv.)/DCM/MeSO ₃ H (99:1), 0 °C, 1 h, then rt, 1 h.	7a/8a (50:50)	50
6	7a , 65	VOF ₃ (2.5 equiv.)/DCM/TFA (97:3), 0 °C, 1 h, then rt, 1 h.	7a/8a (>1:99)	>95
7	7b , 120	DDQ (1.1 equiv.)/DCM/MeSO ₃ H (9:1), 0 °C, 30 min, then rt, 1 h.	n.d.	n.d.
8	7b , 15	DDQ (1.1 equiv.)/DCM/MeSO ₃ H (50:1), 0 °C, 2 h, then rt, 1 h.	8b/9 (90:10)	66
9	7b , 65	VOF ₃ (1.1 equiv.)/DCM/TFA (97:3), 0 °C, 1 h.	7b/8b/9 (20:35:45)	80 [b]
10	7b , 65	VOF ₃ (2.5 equiv.)/DCM/TFA (97:3), 0 °C, 1 h.	8b/9 (5:95)	85 [b]

[a] Yields are given for the isolated product unless stated otherwise. [b] The product ratio was determined by ^1H NMR spectroscopy.

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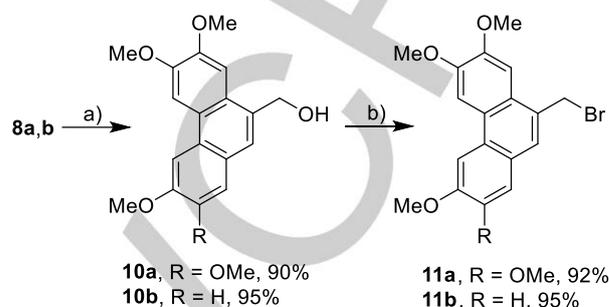
This surprising result prompted us to examine several protocols that would hopefully form ester **8b**. We also reasoned (Scheme 5) that in the case of **7a**, the formation of a new carbon to carbon bond should be carried out according to the ionic properties of cation radical **A** (R = OMe), whereas in the case of ester **7b**, the radical properties of cation radical **A'** (R = H) ought to dominate.^[33, 34] With these considerations in mind, a new experiment was undertaken under more diluted conditions.



Scheme 5. Possible options for the oxidative coupling of esters **7**.

Hence, the addition of 1.1 equivalent of DDQ to a 15 mmol solution of ester **7b** (entry 8) in a mixture of dichloromethane and methane sulfonic acid (50:1) resulted in the isolation of **8b** in 66% yield after chromatographic purification. Structural determination of **8b** was straightforward. In the ¹H NMR spectrum recorded in CDCl₃, H-2 exhibits a characteristic doublet of doublets (³J = 8.7, ⁴J = 2.3 Hz) at δ = 7.22 ppm, and in the ¹³C NMR spectrum, 19 independent resonance lines were found between δ = 52.0 ppm and 168.2 ppm. Moreover, upon close examination of the reaction mixture, we detected the presence of the more polar bisphenanthrene **9**, which was easily isolated (10% yield) by column chromatography. As shown in the supplementary material, the ¹H NMR spectrum of compound **9**, well resolved, displayed 8 singlets (δ = 2.79–4.19 ppm), which were attributed to nonequivalent methoxymethyl groups, providing the first evidence that **9** is unsymmetrical. In addition, examination of the coupling patterns revealed that the ⁴J coupling constant formerly observed in **8b** could not be detected in the spectrum for **9**, indicating that the 2 and 4' positions (Scheme 4) were mutually occupied by a phenanthrene ring.^[35] To gain further insight into the formation of **9**, several experiments were undertaken. First, stirring ester **8b** in the presence of DDQ afforded **9** in a poor 20% yield. Entries 9 and 10, however, clearly show the effect of the stoichiometry of the coupling promoter. When a 10 mmol solution of ester **8b** in a mixture of dichloromethane and trifluoroacetic acid (9:1) was treated with 1.1 equivalents of VOF₃, basic treatment yielded a mixture of compounds **7b/8b/9** in a 20:35:45 ratio, whereas the addition of an excess of VOF₃ (entry 10) provided dimer **9** in a satisfactory 85% yield. Taken together, these results show that the chemical outcome of the oxidation process, can be controlled by the proper selection of the concentration, stoichiometry and chemical structure of the coupling agent.

Next, the synthesis of the expected bromides **11** proceeded by the hydride reduction of esters **8** followed by bromination of the intermediary alcohols **10** in the presence of PBr₃ (Scheme 6). Bromide **11a** was purified by slow crystallization in a dichloromethane/diethyl ether biphasic system, while its homologue **11b** should be used rapidly due to a marked tendency to polymerize.^[36]



Scheme 6. Synthesis of bromides **11**. Reagents and conditions: a) LiAlH₄, THF, 0 °C, then rt, 12 h; b) PBr₃, DCM, 0 °C, then rt, 3 h.

Synthesis of alcohols **16**.

With bromides **11** available in good yields, we turned to the synthesis of α-aminonitriles **12** (Scheme 7). Thus, treatment of α-aminonitriles **5** with LDA generated the corresponding nitrile anions, which readily displaced the primary bromide. The reaction was monitored by proton NMR spectroscopy, which clearly showed the disappearance of the diagnostic singlet signal at δ = 4.99 ppm, which is easily attributed to the benzylic protons of bromides **11**. After an independent aqueous treatment, the reaction mixtures were stirred in diethyl ether for approximately 1 h to afford quaternary α-aminonitriles **12** in yields ranging between 70% and 80%.

The reductive decyanation of α-aminonitriles consists of the neat replacement of the nitrile group by a hydrogen atom.^[37] In light of our previous experiences, this process can be efficiently performed by stirring a mixture of α-aminonitrile **12a** and NaBH₄ in ethanol at ambient temperature for 12 h. After treatment, the expected tertiary amine **13a** was recovered in a poor 30% yield, and these findings suggest that the cleavage of the C–CN bond does not provide the intermediary iminium ion. However, rapid procedural optimization provided more consistent yields. Indeed, prolonged stirring of α-aminonitrile **12a** in ethanol with a subsequent reflux period led to better results due to the presence of adventitious borane salts formed *in situ*. In this way, the hydride reduction of intermediary iminium salts bond was efficiently achieved, and compounds **13a** and **13b** were recovered in 83% and 75% yields, respectively.

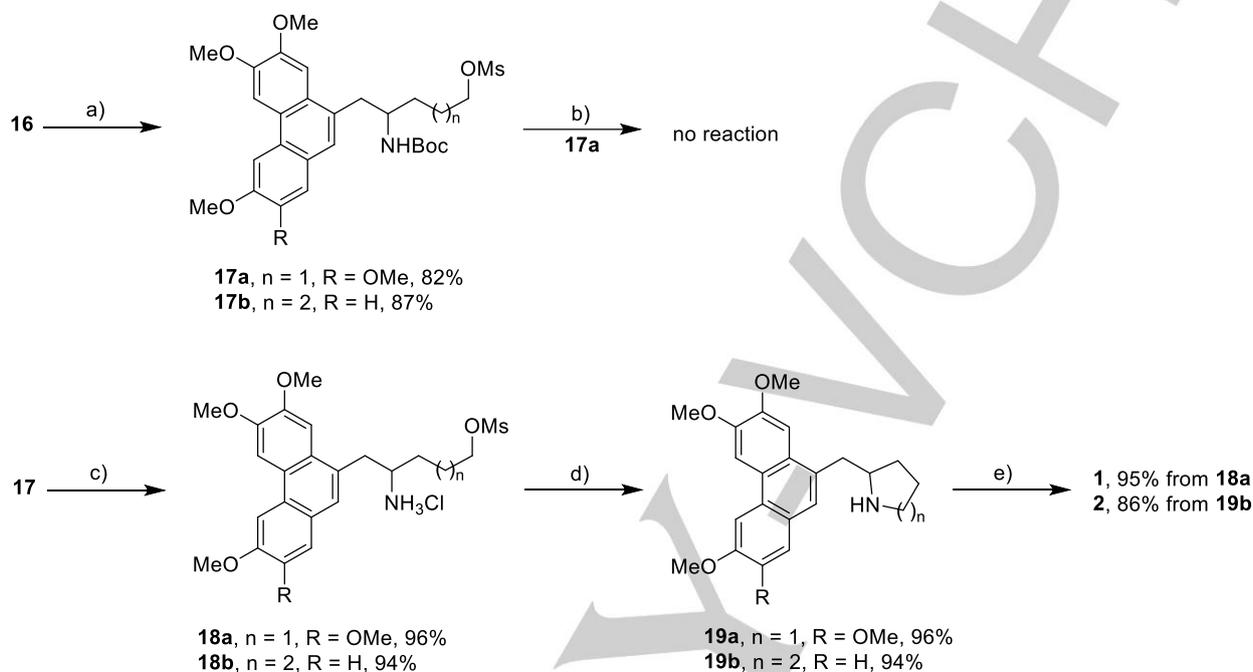
The hydrogenolysis of simple benzylamines is a common process that is generally carried out at ambient temperature in the presence of various Pd/C or 20% Pd/(OH)₂ (Pearlman's catalyst) catalysts. The first experiment was carried out with Pearlman's catalyst (10% in mass) under a hydrogen pressure of 5 bars, with **13a** as the substrate, which was dissolved in a 70:30 mixture of methanol and ethanol. The resulting suspension was stirred for 48 h, and after treatment, only the starting material was recovered. Prolonged stirring (up to 120 h) did not significantly modify the conversion. This result prompted us to examine alternate procedures and revealed that the best yields and reaction rates

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treatment of the crude reaction mixtures and removal of DIPEA in excess, afforded secondary amines **19** in high yield.

Finally, the Pictet–Spengler annulation of both amines **19** was carried out according to a formerly reported procedure in which the amines were refluxed in formic acid in the presence of an excess of paraformaldehyde (up to 9 equivalents).^[38] Under

these reaction conditions, the title alkaloids **1** and **2** were obtained in 95% and 86% yields, respectively, and the proton and carbon spectroscopy data were found to be consistent with that reported in the literature.^[10a, 18c]



Scheme 8. Synthesis of phenanthropiperidine alkaloids **1** and **2**. Reagents and conditions: a) MsCl, Et₃N/DMAP, CH₂Cl₂, rt, 5 h; b) NaH, DMF, 0 °C, 30 min., then rt, 12 h; c) HCl 2 M, dioxane, rt, 48 h; d) DIPEA, DCM, rt, 12 h; e) HCO₂H, (CH₂O)_n, 55 °C, 18 h.

Conclusion

In summary, new and efficient syntheses for tylophorine and cryptopleurine, adaptable to the elaboration of a set of phenanthropiperidine alkaloids, were developed. The key steps involved a) a new utilization of the readily available dibenzylaminoacetonitrile in alkaloid synthesis, b) the unprecedented condensation of bromomethyl-phenanthrenes with metallated α -aminonitriles, c) the efficacy of a 5- or 6-*exo-tet* to form pyrrolidine or piperidine rings, and d) the general high yields of the reported processes. Further developments are in progress and will be reported in due course.

Experimental Section

General Techniques.

Purification by column chromatography was performed with 70–230 mesh silica gel. TLC analyses were carried out on alumina sheets precoated with silica gel 60 F254; R_f values are given for guidance. The ¹H NMR spectra were recorded with a 500 MHz, a 400 MHz or a 300 MHz spectrometer. The ¹³C NMR spectra were recorded with a 125 MHz, a 100 MHz or a 75 MHz spectrometer. Positive-ion mass spectra were recorded

on an orthogonal acceleration quadrupole time-of-flight mass spectrometer equipped with a standard electrospray probe. Melting points were measured on a Kofler apparatus, the values reported in °C, and were uncorrected. For air-sensitive reactions, the glassware was oven-dried (90 °C) for 24 h and cooled under a stream of argon before use. All commercially available reagents were used as supplied and THF was distilled over sodium benzophenone ketyl. Diisopropylamine was distilled from solid potassium hydroxide.

2-(3-Iodopropoxy)tetrahydro-2H-pyran (3a). *Step 1. Synthesis of 3-iodopropan-1-ol.* From an adapted procedure reported in the literature.^[39] A 250 mL round-bottom flask, equipped with a reflux condenser and a magnetic bar, was flushed with argon and successively charged with 150 mL of acetone, 10.60 mL (12.00 g, 126.81 mmol, 1.0 equiv.) of 3-chloropropan-1-ol and 28.50 g (190.14 mmol, 1.5 equiv.) of NaI. The resulting mixture was refluxed under argon for 72 h under a vigorous stirring. The resulting suspension was cooled to room temperature and sodium chloride (ca. 7.5 g) was removed by filtration over a fritted glassware. The filtrate was concentrated under reduced pressure and the resulting paste was taken-up with 150 mL of diethyl ether. The excess of NaI (ca. 8.5 g) was removed by a filtration on a fritted glassware and the ethereal solution was concentrated *in vacuo* to afford an oily brown residue (23.3 g) which was stirred for 30 minutes in a biphasic mixture of dichloromethane (150 mL) and water (100 mL) containing 3.0 g of sodium sulfite. The organic phase was dried over MgSO₄, and concentrated to afford a slightly yellow oily residue which was distilled under reduced pressure (50 °C, 10⁻² mbar, 75.10⁻⁴ Torr) to afford 21.90 g (93%) of 3-iodopropan-1-ol as a colorless oil. $R_f = 0.50$ (petroleum ether/diethyl ether, 50:50). ¹H NMR (CDCl₃, 300 MHz) $\delta = 1.71$ (s, broad, 1 H), 2.04 (quint, J

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= 5.90 Hz, 2 H), 3.31 (t, $J = 6.70$ Hz, 2 H), 3.74 (t, $J = 6.70$ Hz, 2 H). ^{13}C NMR (CDCl_3 , 75 MHz) $\delta = 3.07$ (s), 35.5 (s), 62.3 (s). *Step 2. Synthesis of derivative 3a.* From an adapted procedure reported in the literature.^[40] A 200-mL, one necked Schlenk tube, fitted with a magnetic stirring bar, and connected to an argon inlet tube was successively charged with 50 mL of dichloromethane, 28.60 g (153.8 mmol, 1.0 equiv.) of 3-iodopropan-1-ol, 16.80 mL (15.57 g, 185.14 mmol, 1.2 equiv.) of 3,4-dihydro-2H-pyran and 2.85 g (11.34 mmol, 10% in mass, 7% in mole) of pyridinium *p*-toluenesulfonate (PPTS) and reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the material was taken-up in 100 mL of diethyl ether and stirred vigorously with an aqueous solution (0.1 M) of sodium sulfite for 30 minutes. The solvent was removed under reduced pressure and the crude reaction mixture was distilled under reduced pressure (65 °C, 10^{-2} mbar, 75.10^{-4} Torr) to afford 36.50 g (88%) of iodide **3a** as a slightly yellow oil. $R_f = 0.50$ (petroleum ether/diethyl ether, 70:30). ^1H NMR (CDCl_3 , 300 MHz) $\delta = 1.50$ –1.74 (m, 6 H), 2.09 (quint, $J = 6.1$ Hz, 2 H), 3.30 (t, $J = 6.8$ Hz, 2 H), 3.40–3.53 (m, 2 H), 3.77–3.90 (m, 2 H), 4.60 (t, $J = 2.9$ Hz, 1 H). ^{13}C NMR (CDCl_3 , 75 MHz) $\delta = 3.4$ (s), 19.4 (s), 25.4 (s), 30.6 (s), 33.6 (s), 62.2 (s), 66.8 (s), 98.9 (t). The analytical data were in agreement with those reported in the literature.^[41]

2-(4-Iodobutoxy)tetrahydro-2H-pyran (3b). *Protocol 1 (from 4-chlorobutan-1-ol, 78% overall yield).* From an adapted procedure reported in the literature.^[42] A 250 mL round-bottom flask, was successively charged with 120 mL of dichloromethane, 4.60 mL (5.00 g, 46.10 mmol, 1.0 equiv.) of 4-chlorobutan-1-ol, 5.03 mL (4.66 g, 55.43 mmol, 1.2 equiv.) of 3,4-dihydro-2H-pyran, 0.92 g (3.66 mmol, 8% in mole) of pyridinium *p*-toluenesulfonate (PPTS) and the resulting mixture was stirred at ambient temperature for 24 h. The organic phase was stirred with 100 mL of water for 15 minutes and the organic phase was dried over MgSO_4 , and concentrated to afford 8.45 g (95%) of 2-(4-chlorobutoxy)tetrahydro-2H-pyran as a slightly yellow oil which was used in the next step without purification. ^1H NMR (CDCl_3 , 300 MHz) $\delta = 1.50$ –1.95 (m, 10 H), 3.59–3.54 (m, 2 H), 3.58 (t, $J = 6.50$ Hz, 2 H), 3.74–3.89 (m, 2 H), 4.58 (t, $J = 3.0$ Hz, 1 H). ^{13}C NMR (CDCl_3 , 75 MHz) $\delta = 19.6$ (s), 25.5 (s), 27.1 (s), 29.7 (s), 30.7 (s), 45.0 (s), 62.3 (s), 66.6 (s), 98.8 (t). A 250 mL round-bottom flask, equipped with a reflux condenser and a magnetic bar, was flushed with argon and successively charged with 190 mL of acetone, 8.00 g (41.52 mmol) of 2-(4-chlorobutoxy)tetrahydro-2H-pyran, 9.31 g (62.11 mmol, 1.5 equiv.) of NaI and 0.43 g (4.05 mmol, 0.10 equiv.) of sodium carbonate. The resulting mixture was refluxed under argon for 72 h under a vigorous stirring. The resulting suspension was cooled to room temperature and sodium chloride (ca. 3.4 g) was removed by filtration over a fritted glassware. The filtrate was concentrated under reduced pressure and the resulting paste was taken-up with 150 mL of diethyl ether. The excess of NaI (ca. 3.0 g) was removed by a filtration on a fritted glassware and the ethereal solution was stirred with 100 mL of water containing 5.0 g of sodium sulfite. The organic phase was dried over MgSO_4 , and concentrated to afford a slightly yellow oily residue which was poured into a chromatographic column prepared with 120 g of silica and 90:10 petroleum ether/ethyl acetate. The combined fractions were collected and concentrated to afford 9.60 g (81%) of iodide **3b** as a slightly yellow oil. $R_f = 0.75$ (petroleum ether/ethyl acetate, 90:10). ^1H NMR (CDCl_3 , 400 MHz) $\delta = 1.50$ –1.60 (m, 4 H), 1.67–1.75 (m, 3 H), 1.77–1.85 (m, 1 H), 1.90–2.00 (m, 2 H), 3.23 (t, $J = 7.0$ Hz, 2 H), 3.40–3.43 (m, 1 H), 3.48–3.53 (m, 1 H), 3.82–3.87 (m, 2 H), 4.56–4.58 (m, 1 H). ^{13}C NMR (CDCl_3 , 100 MHz) $\delta = 6.8$ (s), 19.6 (s), 25.4 (s), 30.5 (s), 30.6 (s), 30.7 (s), 62.3 (s), 66.2 (s), 99.8 (t). IR (film, cm^{-1}): 868, 1029, 2938. HRMS (ESI⁺, CH_3OH , $\text{C}_9\text{H}_{17}\text{O}_2\text{Na}$ [$\text{M} + \text{Na}^+$]) calcd for 307.01655, found, 307.0165. *Protocol 2 (from tetrahydrofuran, overall 30% yield).* From an adapted procedure reported in the literature.^[43] A 200-mL, one necked Schlenk tube, fitted with a magnetic stirring bar, and connected to an argon inlet tube was successively charged with 115 mL of dry tetrahydrofuran and 1.79 g (47.31 mmol) of NaBH_4 . The flask was cooled to 0 °C, and 24.00 g (94.56 mmol) of iodine dissolved in 40 mL of tetrahydrofuran were added dropwise over a 1 h period. Stirring was continued for 24 h and the solution was poured in a mixture of dichloromethane (150 mL) and water (100 mL) containing 5.0 g of sodium sulfite. The resulting biphasic system was stirred for 30

minutes and the organic phase was dried over MgSO_4 and concentrated to afford a crude residue which was distilled under reduced pressure (60 °C, 10^{-1} mbar, 75.10^{-3} Torr) to afford 14.0 g (37%) of 4-iodobutan-1-ol as a yellow oil. $R_f = 0.50$ (petroleum ether/diethyl ether, 30:70). ^1H NMR (CDCl_3 , 300 MHz) $\delta = 1.67$ (quint, $J = 5.90$ Hz, 2 H), 1.92 (quint, $J = 5.90$ Hz, 2 H), 2.56 (s, 1 H), 3.24 (t, $J = 6.70$ Hz, 2 H), 3.67 (t, $J = 6.70$ Hz, 2 H). Iodide **3b**. The synthesis was as reported for the synthesis of 2-(4-chlorobutoxy)tetrahydro-2H-pyran by stirring a mixture of 19.0 g (95.00 mmol, 1.0 equiv.) of 4-iodobutan-1-ol, 0.50 g (1.99 mmol, 2% in mole) of pyridinium *p*-toluenesulfonate (PPTS), 10.50 mL (9.73 g, 115.71 mmol, 1.2 equiv.) of 3,4-dihydro-2H-pyran, in 200 mL of dichloromethane for 24 h. Aqueous work-up followed by a chromatographic purification afforded 21.5 g (80%) of iodide **3b** as a slightly colored viscous oil. *Protocol 3 (from 1,4-butanediol, overall 30% yield).* A 250 mL round-bottom flask, was successively charged with 250 mL of dichloromethane, 9.83 mL (10.00 g, 111.26 mmol, 1.0 equiv.) of 1,4-butanediol, 2.79 g (11.10 mmol, 10% in mole) of pyridinium *p*-toluenesulfonate (PPTS) and 10.5 mL (9.73 g, 115.71 mmol, 1.0 equiv.) of 3,4-dihydro-2H-pyran. The resulting mixture was stirred at ambient temperature for 72 h. The solvent was evaporated and the crude reaction mixture was poured onto into a chromatographic column prepared with 100 g of silica and 50:50 petroleum ether/diethyl ether. The less polar 1,4-bis((tetrahydro-2H-pyran-2-yl)oxy)butane ($R_f = 0.7$) eluted first, followed by 4-((tetrahydro-2H-pyran-2-yl)oxy)butan-1-ol which was obtained as a colorless oil (7.00 g, 35%). $R_f = 0.2$ (petroleum ether/diethyl ether, 50:50). ^1H NMR (CDCl_3 , 400 MHz) $\delta = 1.45$ –1.85 (m, 10 H), 2.55–2.65 (s, 1 H, br.), 3.37–3.43 (m, 1 H), 3.46–3.51 (m, 1 H), 3.60–3.67 (m, 2 H, br.), 3.74–3.79 (m, 1 H), 3.81–3.86 (m, 1 H), 4.56–4.58 (m, 1 H). ^{13}C NMR (CDCl_3 , 100 MHz) $\delta = 19.5$ (s), 25.4 (s), 26.5 (s), 30.0 (s), 30.6 (s), 62.3 (s), 62.5 (s), 67.5 (s), 98.8 (t). IR (film, cm^{-1}): 905, 1020, 2939, 3407. HRMS (ESI⁺, CH_3OH , $\text{C}_9\text{H}_{18}\text{O}_3\text{Na}$ [$\text{M} + \text{Na}^+$]) calcd for 197.11481, found, 197.1148. The analytical data were in agreement with those reported in the literature.^[44] *Synthesis of iodide 3b.* A 200-mL, one necked Schlenk tube, fitted with a magnetic stirring bar, and connected to an argon inlet tube was successively charged with 150 mL of dichloromethane, 6.50 g (37.30 mmol) of 4-((tetrahydro-2H-pyran-2-yl)oxy)butan-1-ol, 5.00 g (73.44 mmol, 2.0 equiv.) of imidazole, 12.70 g (48.42 mmol, 1.3 equiv.) of triphenylphosphine. The resulting solution was cooled to 0 °C, then, molecular iodine (13.25 g, 52.20 mmol, 1.4 equiv.) were added portion wise over a 20 minutes period. The resulting orange solution was warmed up to ambient temperature and stirring was continued for 2 hours before the addition of 100 mL of water containing 3.5 g of sodium sulfite. The biphasic system was vigorously stirred for 30 minutes and the organic phase was washed with 50 mL of water (x 3), dried over MgSO_4 and concentrated to yield a colorless solid which was taken-up in a mixture (100 mL) of petroleum ether and diethyl ether (75:25) until the precipitation of triphenylphosphine oxide which was removed by filtration over a sintered glass filter. The filtrate was concentrated to yield (10.7 g) a colorless paste which was poured into a chromatographic column (30 x 2.5 cm, petroleum ether/diethyl ether 90:10) filled with 100 g of silica. The combined fractions were evaporated *in vacuo* at a temperature of 40 °C to afford 9.2 g (87%) of iodide **3b** as a yellowish oil.

2-(Dibenzylamino)acetonitrile, 4. From an adapted procedure reported in the literature.^[22] An oven dried, 250-mL Schlenk tube, fitted with a magnetic stirring bar, was flushed with argon and was successively charged with 100 mL of acetonitrile, 39.0 mL (40.00 g, 202.83 mmol, 1.0 equiv.) of dibenzylamine, 15.30 mL (18.25 g, 241.77 mmol, 1.2 equiv.) of chloroacetonitrile, 42.40 mL (31.67 g, 245.05 mmol, 1.2 equiv.) of diisopropylethylamine (Hünig's base) and 2.00 g (5% in mass) of Bu_4NI . The resulting homogeneous solution was stirred in the dark under an argon atmosphere for 72 h at room temperature. The solvent and the excess of diisopropylethylamine were removed under reduced pressure to afford an orange paste which was taken-up with 300 mL of diethyl ether until the complete precipitation of the diisopropylethylamine hydrochloride which was removed by filtration over a fritted glassware. The ethereal solution was stirred with 100 mL of a 0.2 M aqueous solution of sodium sulfite for 30 minutes, and dried over MgSO_4 . The solvent was evaporated under reduced pressure to afford a yellow paste (44.0 g) which was immediately dissolved in 200 mL of a mixture of petroleum ether/diethyl ether (9:1). The

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resulting solution was kept at 5 °C for 24 hours until the complete crystallization of α -aminonitrile **4** (38.0 g, 79%) which was obtained as beige flakes. The remaining solution was concentrated and the brown residue (ca. 5.0 g) was poured into a chromatography column (30 x 5.0 cm, petroleum ether/diethyl ether, 80:20). The combined fractions were evaporated to afford 4.2 g of α -aminonitrile **4** in an overall 88% yield. Mp = 53 °C. R_f = 0.70 (petroleum ether/diethyl ether, 90:10). $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ = 3.41 (s, 2 H), 3.81 (s, 4 H), 7.36–7.48 (m, 10 H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ = 40.8 (s), 58.3 (s), 114.7 (q), 127.9 (t), 128.7 (t), 129.0 (t), 137.23 (t). IR (film, cm^{-1}): 699, 1419, 2224, 2821, 3030. HRMS (ESI^+ , CH_3OH , $\text{C}_{16}\text{H}_{16}\text{N}_2\text{Na}$ [$\text{M} + \text{Na}$] $^+$) calcd for 259.12057, found, 259.1205.

2-(Dibenzylamino)-5-((tetrahydro-2H-pyran-2-yl)oxy)pentanenitrile, 5a.

New compound. An oven-dried, one necked 200-mL Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube was flushed with argon and was successively charged with 20 mL of dry THF and 3.80 mL (2.73 g, 26.90 mmol, 1.35 equiv.) of diisopropylamine. The flask was then cooled to –80 °C (ethanol/liquid nitrogen bath) and 15.0 mL (24.00 mmol, 1.2 equiv.) of *n*-butyllithium (1.6 M in hexane) were slowly added to the previous solution. Stirring was continued for 30 min and the solution was stirred at 0 °C (ice bath) for an additional 30 minutes period at that temperature. The LDA solution was rapidly transferred (via a cannula) into a 200-mL Schlenk tube cooled to –80 °C containing 4.72 g (19.97 mmol, 1.0 equiv.) of α -aminonitrile **4** dissolved in 30 mL of dry THF. The solution turned rapidly deep red and was allowed to warm to –30 °C for 1.5 hours and cooled to –80 °C. Then, 5.90 g (21.84 mmol, 1.1 equiv.) of iodide **3a** were added to the anion solution and the reaction mixture was warmed to 0 °C over a 1.5 hours period. The reaction was quenched by the addition of 10 mL of ethanol and the solvents were evaporated under reduced pressure to afford a yellow paste which was poured into a mixture of diethyl ether (100 mL) and water (50 mL). The ethereal layer was separated, dried over MgSO_4 and concentrated to afford a yellow viscous oil (6.95 g) which was dissolved in 10 mL of a 50:50 mixture of petroleum ether and diethyl ether and poured on a chromatography column (30 x 5.0 cm, petroleum ether/diethyl ether, 80:20) filled with 50 g of silica. The combined fractions were evaporated to afford 5.90 g (78%) of α -aminonitrile **5a** as a highly yellowish viscous oil. R_f = 0.5 (petroleum ether/diethyl ether, 7:3). $^1\text{H NMR}$ [CDCl_3 , 400 MHz, 2 diastereoisomers, splitting signals are indicated with an asterisk (*)] δ = 1.40–2.00 (m, 10 H), 3.25–3.35 (m, 1 H), 3.36 (d, J_{AB} = 13.60 Hz, 2 H), 3.42–3.45 (m, 1 H), 3.62–3.82 (m, 3 H), 3.36 (d, J_{AB} = 13.60 Hz, 2 H), [4.42 (t, J = 2.05 Hz, 0.5 H), 4.43 (t, J = 2.05 Hz, 0.5 H)]*, 7.26–7.41 (m, 10 H). $^{13}\text{C NMR}$ [CDCl_3 , 100 MHz, 2 diastereoisomers, splitting signals are indicated with and asterisk (*)] δ = [19.52 (s), 19.60 (s)]*, [25.40 (s), 25.42 (s)]*, 25.9 (s), [28.2 (s), 28.3 (s)]*, [30.58 (s), 30.61 (s)]*, [52.60 (t), 52.64 (t)]*, [55.36 (s), 55.39 (s)]*, [62.25 (s), 62.35 (s)]*, [66.1 (s), 66.2 (s)]*, [98.8 (t), 98.9 (t)]*, 117.5 (q), 127.5 (t), 128.6 (t), 128.8 (t), 137.9 (q). IR (film, cm^{-1}) 697, 1028, 1453, 2222, 2940. HRMS (ESI^+ , $\text{CH}_3\text{CN}/\text{CH}_3\text{OH}$ (90:10), $\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_2\text{Na}$ [$\text{M} + \text{Na}$] $^+$) calcd for 401.21995, found, 401.2197.

2-(Dibenzylamino)-6-((tetrahydro-2H-pyran-2-yl)oxy)hexanenitrile, 5b.

New compound. The synthesis was as reported for **5a** but with 4.68 g (19.80 mmol, 1.0 equiv.) of α -aminonitrile **4** and 6.20 g (21.82 mmol, 1.1 equiv.) of iodide **3b** as the alkylating agent. The crude oily residue (8.30 g) was diluted in 10 mL of a mixture of petroleum ether and diethyl ether (50:50) and poured into a chromatographic (30 x 5.0 cm, petroleum ether/diethyl ether, 70:30) filled with 50 g of silica. The combined fractions were evaporated to afford 6.21 g (83%) of α -aminonitrile **5b** as a yellowish highly viscous oil. R_f = 0.50 (petroleum ether/diethyl ether, 70:30). $^1\text{H NMR}$ (CDCl_3 , 400 MHz, 2 diastereoisomers) δ = 1.40–1.75 (m, 9 H), 1.77–2.00 (m, 3 H), 3.30–3.36 (m, 1 H), 3.39 (d, J_{AB} = 13.60 Hz, 2 H), 3.45–3.55 (m, 1 H), 3.60 (t, 3J = 7.35 Hz, 1 H), 3.66–3.75 (m, 1 H), 3.80–3.90 (m, 1 H), 3.97 (d, J_{AB} = 13.60 Hz, 2 H), 4.56–4.58 (m, 1 H), 7.26–7.41 (m, 10 H). $^{13}\text{C NMR}$ [CDCl_3 , 100 MHz, 2 diastereoisomers, splitting signals are indicated with an asterisk (*)] δ = 19.6 (s), [22.7 (s), 22.73 (s)]*, 25.5 (s), 28.8 (s), 30.7 (s), 31.1 (s), [52.66 (t), 52.70 (t)]*, 55.3 (s), 62.2 (s), 66.9 (s), [98.75 (t), 98.79 (t)]*, 117.6 (q), 127.5 (t), 128.5 (t), 128.8 (t), 137.9 (q). IR (film, cm^{-1}) 697, 1028, 1453, 2223, 2939. HRMS (ESI^+ , CH_3OH , $\text{C}_{25}\text{H}_{32}\text{N}_2\text{O}_2\text{Na}$ [$\text{M} + \text{Na}$] $^+$) calcd for 415.2356, found, 415.2351.

(E)-2,3-bis(3,4-dimethoxyphenyl)acrylic acid, 6a. From an adapted procedure reported in the literature.^[19c] An oven-dried two-necked 250-mL round bottom flask, equipped with a reflux condenser and connected to an argon inlet tube, was successively charged with 9.80 g (49.95 mmol, 1.0 equiv.) of veratric acid, 9.13 g (54.94 mmol, 1.1 equiv.) of veratraldehyde, 26.0 mL (28.08 g, 275.05 mmol, 5.5 equiv.) of acetic anhydride and 25.0 mL (18.15 g, 179.36 mmol, 3.6 equiv.) of *freshly distilled* triethylamine. The resulting solution was refluxed under argon at 80 °C for 24 h. Then, 40 mL of ethanol were added and the reaction mixture was refluxed for an additional 1 h period. The solvents were evaporated under reduced pressure to afford an viscous residue was stirred with 150 mL of water until the precipitation of an orange powder which was poured onto 100 mL of ethanol and stirred for 30 min to yield 12.2 g (71%) of acrylic acid **6a** as a slightly yellow powder. Mp = 216 °C (ethanol). $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ = 3.50 (s, 3 H), 3.82 (s, 3 H), 3.87 (s, 3 H), 3.90 (s, 3 H), 6.56 (d, J = 1.9 Hz, 1 H), 6.74 (d, J = 8.5 Hz, 1 H), 6.81 (d, J = 1.9 Hz, 1 H), 6.84–6.86 (m, 2 H), 6.93 (d, J = 8.5 Hz, 1 H), 7.86 (s, 1 H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ = 55.3 (p), 55.8 (p), 55.9 (p), 110.5 (t), 111.6 (t), 112.6 (t), 113.0 (t), 122.3 (t), 125.7 (t), 127.3 (q), 128.5 (q), 129.2 (q), 141.9 (t), 148.3 (q), 148.7 (q), 149.4 (q), 150.3 (q), 173.1 (q). IR (powder, cm^{-1}) 1016, 1133, 1252, 1506, 1666. HRMS (ESI^+ , $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$, 9:1), $\text{C}_{19}\text{H}_{20}\text{O}_6\text{Na}$ [$\text{M} + \text{Na}$] $^+$) calcd 367.11521, found 367.1151.

(E)-2-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)acrylic acid, 6b.

The synthesis of acrylic acid **6b** has been carried out according to the similar procedure used for its homologue **6a** but with 10.00 g (50.96 mmol, 1.0 equiv.) of 3,4-dimethoxybenzoic acid, 7.63 g (56.04 mmol, 1.1 equiv.) of 4-methoxybenzaldehyde, 12.0 mL (12.96 g, 126.94 mmol, 2.5 equiv.) of acetic anhydride, and 12.0 mL (8.71 g, 86.09 mmol, 1.7 equiv.) of triethylamine. The reaction mixture was heated at 80 °C for 5 hours. Then, 50 mL of ethanol were added and the resulting mixture was refluxed for 1 h. The solvents were distilled under reduced pressure and the remaining acetic acid was removed by a series of distillations with dioxane (50 mL), methanol (100 mL) and dichloromethane (100 mL x 2) to afford a yellow paste which was stirred overnight in 80 mL of diethyl ether to afford 11.1 g (70%) of acrylic acid **6b**. $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ = 3.79 (s, 3 H), 3.83 (s, 3 H), 3.94 (s, 6 H), 6.73 (d, J = 8.9 Hz, 2 H), 6.79 (d, J = 1.5 Hz, 1 H), 6.83 (dd, J = 8.1, 1.5 Hz, 1 H), 6.93 (d, J = 8.1 Hz, 1 H), 7.08 (d, J = 8.9 Hz, 2 H), 7.90 (s, 1 H). $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ = 55.3 (p), 55.8 (p), 55.9 (p), 111.5 (t), 112.9 (t), 113.8 (t), 122.2 (t), 127.0 (q), 128.1 (q), 128.8 (q), 132.7 (t), 142.5 (t), 148.7 (q), 149.2 (q), 160.7 (q), 173.4 (q). IR (powder, cm^{-1}) 833, 1025, 1251, 1508, 1665, 2958. HRMS (ESI^+ , $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$, 90:10), $\text{C}_{18}\text{H}_{18}\text{O}_5\text{Na}$ [$\text{M} + \text{Na}$] $^+$) calcd 337.10464, found 337.1044. The analytical data were in agreement with those reported in the literature.^[45]

Methyl (E)-2,3-bis(3,4-dimethoxyphenyl)acrylate, 7a.

From an adapted procedure reported in the literature.^[29a] A one-necked one bottom 500 mL flask, equipped with a reflux condenser was charged with 16.0 g (46.46 mmol, 1.0 equiv.) of acid **6a**, 400 mL of methanol and 2.50 mL (4.57 g, 46.64 mmol, 1.0 equiv.) of concentrated sulfuric acid. The resulting suspension was vigorously stirred and refluxed for 15 hours. Then, approximately 300 mL of methanol were distilled under reduced pressure and the resulting solution was standing overnight at 5 °C to afford 15.1 g (91%) of ester **7a** which were filtered over a fritted glassware. Slightly yellow powder. M.p. = 128 °C. $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ = 3.50 (s, 3 H), 3.81 (s, 3 H), 3.83 (s, 3 H), 3.86 (s, 3 H), 3.91 (s, 3 H), 6.54 (d, J = 1.9 Hz, 1 H), 6.73 (d, J = 8.4 Hz, 1 H), 6.79 (d, J = 1.9 Hz, 1 H), 6.84 (dd, J = 8.2, 1.9 Hz, 2 H), 6.93 (d, J = 8.2 Hz, 1 H), 7.78 (s, 1 H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ = 52.3 (p), 55.2 (p), 55.8 (p), 55.9 (p), 55.96 (p), 110.5 (t), 111.6 (t), 112.5 (t), 113.0 (t), 122.3 (t), 125.3 (t), 127.5 (q), 128.8 (q), 129.7 (q), 140.3 (t), 148.2 (q), 148.6 (q), 149.3 (q), 150.0 (q), 168.6 (q). IR (powder, cm^{-1}) 1019, 1130, 1162, 1222, 1249, 1410, 1469, 1510, 1594, 1698. HRMS (ESI^+ , $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$, 95:5), $\text{C}_{20}\text{H}_{22}\text{O}_6\text{Na}$ [$\text{M} + \text{Na}$] $^+$) calcd for 381.13086; found 381.1307.

Methyl (E)-2-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)acrylate, 7b.

A one-necked one bottom 500 mL flask, equipped with a reflux condenser was charged with 8.26 g (26.28 mmol, 1.0 equiv.) of acrylic acid **6b**, 200

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mL of methanol and 0.70 mL (1.28 g, 13.07 mmol, 0.5 equiv.) of concentrated sulfuric acid and the resulting solution was refluxed for 24 hours. Then, 200 mL of methanol were distilled under reduced pressure and the resulting solution was standing at 5 °C for 3 days until the complete crystallization of 8.2 g (95%) of ester **7b** which was collected on a fritted glassware. Mp = 124 °C. R_f = 0.6 (dichloromethane/diethyl ether, 1:1). ^1H NMR (CDCl_3 , 400 MHz) δ = 3.78 (s, 3 H), 3.81 (s, 3 H), 3.82 (s, 3 H), 3.94 (s, 3 H), 6.72 (d, J = 8.9 Hz, 2 H), 6.76 (d, J = 1.5 Hz, 1 H), 6.79 (dd, J = 8.2, 1.5 Hz, 1 H), 6.92 (d, J = 8.2 Hz, 1 H), 7.04 (d, J = 8.9 Hz, 2 H), 7.79 (s, 1 H). ^{13}C NMR (CDCl_3 , 100 MHz) δ = 52.3 (p), 55.2 (p), 55.8 (p), 55.9 (p), 111.4 (t), 112.8 (t), 113.7 (t), 122.1 (t), 127.3 (q), 128.6 (q), 129.6 (q), 132.4 (t), 140.2 (t), 148.6 (q), 149.1 (q), 160.3 (q), 168.7 (q). HRMS (ESI⁺, $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$, 90:10, $\text{C}_{19}\text{H}_{20}\text{O}_5\text{Na}$ [M + Na]⁺) calcd 351.12029, found 351.1205. The analytical data were in agreement with those reported in the literature.^[28a]

Methyl 2,3,6,7-tetramethoxyphenanthrene-9-carboxylate, 8a. From an adapted procedure reported in the literature.^[29c] An oven dried, 250-mL Schlenk tube, fitted with a magnetic stirring bar, was flushed with argon and was successively charged with 45 mL of dichloromethane, 2.0 g (5.58 mmol, 1.0 equiv.) of ester **7a**, and 5 mL (7.40 g, 77.0 mmol, 13.8 equiv.) of methanesulfonic acid. The solution was cooled to 0 °C and 1.33 g (5.86 mmol, 1.05 equiv.) of DDQ were added portion wise over a 10 minutes period upon which a characteristic green color evolved. The solution was stirred for 30 minutes at 0 °C and at room temperature for 1 h. The organic phase (plus 80 mL of dichloromethane) was treated by 3 x 50 mL of a 20% NaHCO_3 solution. The aqueous phases were discarded and the organic phase was dried over MgSO_4 and concentrated to afford a beige powder which was taken-up in 100 mL of diethyl ether. The resulting suspension was collected over on a fritted glassware to afford 1.80 g (90%) of phenanthrene **8a** as a beige powder which could be used in the next step without purification. R_f = 0.6 (petroleum ether/acetone, 6:4). Mp = 196 °C. ^1H NMR (CDCl_3 , 400 MHz) δ = 4.04 (s, 3 H), 4.06 (s, 3 H), 4.10 (s, 3 H), 4.15 (s, 3 H), 4.16 (s, 3 H), 7.28 (s, 1 H), 7.79 (s, 1 H), 7.83 (s, 1 H), 8.44 (s, 1 H), 8.67 (s, 1 H). ^{13}C NMR (CDCl_3 , 100 MHz) δ = 52.0 (p), 55.9 (p), 56.0 (p, 2 C), 56.1 (p), 102.5 (t), 102.8 (t), 106.9 (t), 109.3 (t), 122.2 (q), 124.2 (q), 124.6 (q), 125.2 (q), 127.2 (q), 130.4 (t), 149.1 (q), 149.4 (q), 151.3 (q), 168.3 (q). IR (powder, cm^{-1}) 779, 1129, 1509, 1712, 2900. HRMS (ESI⁺, $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$, 90:10, $\text{C}_{20}\text{H}_{20}\text{O}_6\text{Na}$ [M + Na]⁺) calcd for 379.11521, found, 379.1155. The analytical data were in agreement with those reported in the literature.^[46]

Methyl 3,6,7-trimethoxyphenanthrene-9-carboxylate, 8b. An oven dried, 1 L round-bottom flask, fitted with a magnetic stirring bar, was flushed with argon and was successively charged with 400 mL of dichloromethane, 2.0 g (6.09 mmol, 1.0 equiv.) of ester **7b**, and 7.91 mL (11.71 g, 121.90 mmol, 20.0 equiv.) of methanesulfonic acid. The solution was cooled to 0 °C and 1.52 g (6.70 mmol, 1.1 equiv.) of DDQ were added portion-wise over a 10 minutes period. The solution was stirred for 2 hours at 0 °C and at room temperature for 1 h. The organic phase was treated by 250 mL of a 50% aqueous K_2CO_3 solution. The aqueous phases were discarded, and the organic phase was washed with 100 mL of water (x 2) and dried over MgSO_4 and concentrated to afford a beige powder which was dissolved in dichloromethane and poured on a chromatographic column (30 x 10 cm) prepared with 80 g of silica, and 40:40:20 petroleum ether/dichloromethane/diethyl ether. The phenanthrene **8b** eluted first followed by the more polar biphenanthrene **9**. The combined fractions were evaporated to yield 1.31 g (66%) of phenanthrene **8b** as a colorless powder. Mp = 156 °C, R_f = 0.5 (petroleum ether/dichloromethane/diethyl ether, 40:40:20). ^1H NMR (CDCl_3 , 400 MHz) δ = 4.03 (s, 3 H), 4.04 (s, 3 H), 4.10 (s, 3 H), 4.12 (s, 3 H), 7.22 (dd, J = 8.7, 2.4 Hz, 1 H), 7.80 (d, J = 1.5 Hz, 1 H), 7.85 (d, J = 8.7, Hz, 1 H), 7.86 (s, 1 H), 8.44 (s, 1 H), 8.66 (s, 1 H). ^{13}C NMR (CDCl_3 , 100 MHz) δ = 52.0 (p), 55.5 (p), 55.85 (p), 55.88 (p), 103.2 (t), 103.7 (t), 106.9 (t), 116.0 (t), 121.6 (q), 124.2 (q), 124.9 (q), 125.1 (q), 131.3 (t), 131.8 (t), 133.4 (q), 148.8 (q), 149.9 (q), 160.1 (q), 168.2 (q). IR (powder, cm^{-1}) 831, 1026, 1106, 1220, 1613, 1713, 2944. HRMS (ESI⁺, $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$, 90:10, $\text{C}_{19}\text{H}_{18}\text{O}_5\text{Na}$ [M + Na]⁺) calcd 349.10464, found 349.1043. The analytical data were in agreement with those reported in the literature.^[46]

Dimethyl 3,3',6,6',7,7'-hexamethoxy-[2,4'-biphenanthrene]-9,9'-dicarboxylate, 9. An oven dried, 250 mL Schlenk tube, fitted with a magnetic stirring bar, was flushed with argon and was successively charged with 20 mL of dichloromethane, 0.30 g (0.92 mmol, 1.0 equiv.) of ester **8b**, and 1.19 mL (1.76 g, 18.33 mmol, 20.0 equiv.) of methanesulfonic acid. The solution was cooled to 0 °C and 0.21 g (0.92 mmol, 1.0 equiv.) of DDQ were added portion-wise over a 10 minutes period. The solution was stirred for 2 hours at 0 °C and at room temperature for 1 h and the organic phase was treated with 50 mL of a 50% aqueous K_2CO_3 solution. The aqueous phases were discarded and the organic phase was washed with 100 mL of water (x 2) and dried over MgSO_4 and concentrated to afford a beige powder which was dissolved in dichloromethane and poured on a chromatographic column (30 x 3.0 cm) prepared with 20 g of silica, and 40:40:20 petroleum ether/dichloromethane/diethyl ether. Trace amount of unreacted ester **8b** eluted first, followed by the more polar dimer **9** (0.06 g, 20%) which was obtained as a white powder. Mp = 257 °C. R_f = 0.30 (petroleum ether/dichloromethane/diethyl ether, 40:40:20). ^1H NMR (CDCl_3 , 400 MHz) δ = 2.79 (s, 3 H), 3.84 (s, 3 H), 3.93 (s, 3 H), 4.00 (s, 6 H), 4.06 (s, 3 H), 4.14 (s, 3 H), 4.19 (s, 3 H), 7.43 (d, J = 8.8 Hz, 1 H), 7.47 (s, 1 H), 7.83 (s, 1 H), 7.97 (s, 1 H), 8.06 (s, 1 H), 8.04 (d, J = 8.8 Hz, 1 H), 8.45 (s, 1 H), 8.51 (s, 1 H), 8.57 (s, 1 H), 8.73 (s, 1 H). ^{13}C NMR (CDCl_3 , 100 MHz) δ = 52.06 (p), 52.09 (p), 54.3 (p), 55.6 (p), 55.9 (p), 56.0 (p, 2 C), 56.6 (p), 102.1 (t), 103.1 (t), 106.3 (t), 107.1 (t), 108.6 (t), 111.8 (t), 121.4 (q), 122.0 (q), 122.2 (q), 124.8 (q), 124.9 (q), 125.3 (q), 125.5 (q), 125.8 (q), 126.1 (q), 130.3 (q), 131.1 (t), 132.2 (t, 2 C), 132.3 (q), 133.0 (q), 133.1 (t), 147.0 (q), 148.7 (q), 149.1 (q), 150.1 (q), 158.2 (q), 159.0 (q), 168.18 (q), 168.23 (q). HRMS (ESI⁺, $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$, 90:10, $\text{C}_{38}\text{H}_{34}\text{O}_{10}\text{Na}$ [M + Na]⁺) calcd 673.20442, found 673.2045. The analytical data were in agreement with those reported in the literature.^[35]

(2,3,6,7-Tetramethoxyphenanthren-9-yl)methanol, 10a. From an adapted procedure reported in the literature.^[26a] An oven dried, 250-mL round-bottom flask, fitted with a magnetic stirring bar, was flushed with argon and was successively charged with 120 mL of dry THF and 6.06 g (17.00 mmol, 1.0 equiv.) of ester **8a**. The resulting suspension was cooled to 0 °C and 21.2 mL (50.88 mmol, 3.0 equiv.) of a 2.4 M solution of LiAlH_4 in THF were slowly added by syringe. The resulting clear solution was stirred for 12 h at room temperature and was slowly poured on a cold 1 M solution (135 mL) of HCl. **Caution: the utilization of a 2 M HCl aqueous solution caused the formation (up to 20%) of the unwanted 9-(chloromethyl)-2,3,6,7-tetramethoxyphenanthrene.** The aqueous layer was extracted with 70 mL of dichloromethane (x 3) and the combined organic layers were washed with 100 mL of water, dried over MgSO_4 and concentrated under reduced pressure to afford a grey powder which was stirred for 12 h in 75 mL of diethyl ether. The resulting suspension was filtered over a fritted glassware to afford 5.0 g (90%) of alcohol **10a** as a white powder. Mp = 182 °C. R_f = 0.3 ($\text{CH}_2\text{Cl}_2/\text{EtOH}$, 97:3). ^1H NMR (CDCl_3 , 400 MHz) δ = 2.25 (s, 1 H, br.), 3.92 (s, 3 H), 3.99 (s, 3 H), 4.05 (s, 3 H), 4.07 (s, 3 H), 4.99 (s, 2 H), 7.02 (s, 1 H), 7.41 (s, 2 H), 7.59 (s, 1 H), 7.66 (s, 1 H). ^{13}C NMR (CDCl_3 , 100 MHz) δ = 55.77 (p), 55.85 (p), 55.95 (p), 55.98 (p), 64.5 (s), 102.7 (t), 103.1 (t), 104.7 (t), 108.3 (t), 123.7 (t), 124.4 (q), 124.5 (q), 124.9 (q), 125.8 (q), 132.0 (q), 148.6 (q), 148.7 (q), 148.9 (q), 149.2 (q). IR (powder, cm^{-1}) 828, 1148, 1509, 1509, 1615, 2833, 3507. HRMS (ESI⁺, $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$, 90:10, $\text{C}_{19}\text{H}_{20}\text{O}_5\text{Na}$ [M + Na]⁺) calcd for 351.12029, found, 351.1205. The analytical data were in agreement with those reported in the literature.^[19b]

(3,6,7-Trimethoxyphenanthren-9-yl)methanol, 10b. The synthesis of alcohol **10b** has been carried out according to the similar procedure used for its homologue **10a** but with 1.37 g (4.20 mmol, 1.0 equiv.) of ester **8b**, and 5.25 mL (12.60 mmol, 3.0 equiv.) of a 2.4 M solution of LiAlH_4 in THF. After aqueous work-up, the organic phase was concentrated to afford a colorless powder which was stirred in diethyl ether overnight to afford 1.19 g (95%) of alcohol **10b**. Colorless solid. Mp = 162 °C. R_f = 0.70 (petroleum ether/acetone, 70:30). ^1H NMR (CDCl_3 , 500 MHz) δ = 2.00 (s, 1 H, br.), 4.01 (s, 3 H), 4.04 (s, 3 H), 4.09 (s, 3 H), 5.04 (s, 2 H), 7.17 (dd, J = 8.8, 2.4 Hz, 1 H), 7.48 (s, 1 H), 7.54 (s, 1 H), 7.72 (d, J = 8.8 Hz, 1 H), 7.77 (d, J = 2.4 Hz, 1 H), 7.90 (s, 1 H). ^{13}C NMR (CDCl_3 , 125 MHz) δ = 55.5 (p),

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55.9 (p), 56.0 (p), 64.6 (s), 103.7 (t), 103.9 (t), 104.8 (t), 115.4 (t), 124.5 (t), 124.8 (q), 125.5 (q), 125.8 (q), 130.2 (t), 131.2 (q), 131.4 (q), 148.8 (q), 149.4 (q), 158.3 (q). IR (powder, cm^{-1}) 827, 1030, 1202, 1528, 1609, 3490. HRMS (ESI⁺, $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$, 90:10, $\text{C}_{18}\text{H}_{18}\text{O}_4\text{Na}$ [M + Na]⁺) calcd 321.10973, found 321.1097. The analytical data were in agreement with those reported in the literature.^[45]

9-(Bromomethyl)-2,3,6,7-tetramethoxyphenanthrene, 11a. *Step 1: Synthesis of crude bromide 11a.* From an adapted procedure reported in the literature.^[26a] An oven dried, 250-mL round-bottom flask, fitted with a magnetic stirring bar, was flushed with argon and was successively charged with 70 mL of dichloromethane and 2.28 g (6.94 mmol, 1.0 equiv.) of alcohol **10a** and the solution was cooled to 0 °C. Then, 10.5 mL (10.50 mmol, 1.5 equiv.) of a 1.0 M solution of PBr_3 in dichloromethane were slowly added to the previous solution. The reaction mixture was warmed to room temperature, stirred for 3 h and poured on a biphasic mixture of water (80 mL) and dichloromethane (50 mL). The organic layer was washed (3 x 80 mL) with water until neutral pH, dried over MgSO_4 , and concentrated to afford a crude reaction mixture which was stirred for 1 hour in 50 mL of diethyl ether to afford 2.50 g (92%) of bromide **11a** as a white powder. *Step 2: Recrystallization of bromide 11a.* A Schlenk tube was successively charged with 2.38 g of bromide **11a** and 25 mL of chloroform. The solution was gently heated to 60 °C until the complete dissolution of **11a**. Then, 120 mL of diethyl ether were slowly added to the previous solution and the biphasic system was allowed to stand for 3 days at room temperature. The solvents were removed *via* a cannula, and the resulting powder was stirred in 30 mL of diethyl ether. The resulting suspension was filtered over a fritted glassware to afford 2.10 g (88%) of bromide **11a**. White powder. Mp = 220 °C, dec. ¹H NMR (CDCl_3 , 500 MHz) δ = 4.03 (s, 3 H), 4.11 (s, 3 H), 4.13 (s, 3 H), 4.14 (s, 3 H), 4.99 (s, 2 H), 7.18 (s, 1 H), 7.53 (s, 1 H), 7.66 (s, 1 H), 7.75 (s, 1 H), 7.82 (s, 1 H). ¹³C NMR (CDCl_3 , 125 MHz) δ = 33.7 (s), 55.93 (p), 55.99 (p), 56.1 (p, 2 C), 102.8 (t), 103.4 (t), 105.0 (t), 108.4 (t), 124.1 (q), 125.26 (q), 125.7 (q), 128.8 (q), 148.8 (q), 149.0 (q), 149.3 (q), 149.9 (q). IR (powder, cm^{-1}) 770, 1256, 1508, 1621, 2998. HRMS (ESI⁺, CH_3CN , $\text{C}_{19}\text{H}_{19}\text{BrO}_4\text{Na}$ [M + Na]⁺) calcd for 413.03589, found, 413.0364.

10-(Bromomethyl)-2,3,6-trimethoxyphenanthrene, 11b. The synthesis of bromide **11b** was carried out according to the same procedure than that followed for the synthesis of bromide **11a** but with 1.28 g (4.29 mmol, 1.0 equiv.) of alcohol **10b** and 6.45 mL (6.45 mmol, 1.5 equiv.) of a 1.0 M solution of PBr_3 in dichloromethane. The organic layer was dried over MgSO_4 , and concentrated to afford a crude reaction mixture which was stirred in 50 mL of diethyl ether to afford 1.47 g (95%) of bromide **11b** as a white powder which was used without further purification in the next step. Colorless solid. Mp = 166 °C. R_f = 0.45 (petroleum ether/acetone, 70:30). ¹H NMR (CDCl_3 , 300 MHz) δ = 4.01 (s, 3 H), 4.10 (s, 3 H), 4.11 (s, 3 H), 4.97 (s, 2 H), 7.18 (dd, J = 8.8, 2.4 Hz, 1 H), 7.52 (s, 1 H), 7.68 (s, 1 H), 7.75 (d, J = 8.8 Hz, 1 H), 7.82 (d, J = 2.4 Hz, 1 H), 7.91 (s, 1 H). ¹³C NMR (CDCl_3 , 75 MHz) δ = 33.8 (s), 55.5 (p), 56.00 (p), 56.05 (p), 103.9 (t), 104.0 (t), 105.0 (t), 115.7 (t), 125.1 (q), 125.2 (q), 125.3 (q), 127.0 (t), 128.1 (q), 130.4 (t), 131.8 (q), 149.1 (q), 149.4 (q), 158.9 (q). IR (powder, cm^{-1}) 789, 1028, 1508, 1618, 2827. HRMS (ESI⁺, CH_3CN , $\text{C}_{18}\text{H}_{17}\text{O}_3\text{BrNa}$ [M + Na]⁺) calcd 383.02533, found 383.0250. The analytical data were in agreement with those reported in the literature.^[26a]

2-(Dibenzylamino)-5-((tetrahydro-2H-pyran-2-yl)oxy)-2-((2,3,6,7-tetramethoxyphenanthren-9-yl)methyl)pentanenitrile, 12a. *Step 1: Metalation of α -aminonitrile 5a.* *New compound.* An oven-dried one necked 200-mL Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube was flushed with argon and was successively charged with 15 mL of dry THF and 1.60 mL (1.15 g, 11.34 mmol, 1.8 equiv.) of diisopropylamine. The flask was then cooled to -80 °C (ethanol/liquid nitrogen bath) and 6.40 mL (10.24 mmol, 1.6 equiv.) of *n*-butyllithium (1.6 M in hexane) were slowly added to the previous solution. Stirring was continued for 30 min and the solution was stirred at 0 °C for an additional 30 minutes period at that temperature. The LDA solution was rapidly transferred (*via* a cannula) into a 250-mL round-bottom flask,

flushed with argon, fitted with a magnetic stirring bar and cooled to -80 °C containing 3.58 g (9.46 mmol, 1.5 equiv.) of α -aminonitrile **5a** dissolved in 15 mL of dry THF. The solution turned rapidly yellow and was allowed to warm to -30 °C for 2 hours and then cooled to -100 °C. *Step 2: Synthesis of α -aminonitrile 12a.* A one-necked 250-mL Schlenk tube was successively charged with 2.46 g (6.29 mmol, 1.0 equiv.) of crystallized bromide **11a** and 120 mL of dry THF. The suspension was heated until the obtention of a clear solution (at ca 40 °C) which was added portion wise by a syringe onto the vigorously stirred solution of metalated α -aminonitrile **5a** cooled to -100 °C. The solution was warmed to -50 °C over a 1 h period and the reaction mixture was quenched by the addition of 10 mL of ethanol. The solvents were distilled under reduced pressure to yield an orange paste which was stirred in a mixture of dichloromethane (100 mL) and water (20 mL) containing 0.2 g of sodium cyanide. The organic phase was dried over MgSO_4 and concentrated to yield an orange oily residue which was taken-up in 30 mL of diethyl ether and stirred for 1 hour at 0 °C to yield 3.45 g (80%) of α -aminonitrile **12a** as a yellow powder. Mp = 172-174 °C (diethyl ether). ¹H NMR (CDCl_3 , 500 MHz, 2 diastereoisomers) δ = 1.39-1.64 (m, 6 H), 1.94-2.19 (m, 4 H), 3.15-3.40 (m, 3 H), 3.50-3.66 (m, 3 H), 4.04 (d, J_{AB} = 14.5 Hz, 2 H), 4.07 (s, 6 H), 4.14 (s, 6 H), 4.22 (d, J_{AB} = 14.5 Hz, 2 H), 4.42 (s, 1 H), 7.20-7.22 (m, 3 H), 7.27-7.30 (m, 4 H), 7.35 (s, 1 H), 7.40-7.42 (m, 4 H), 7.77-7.79 (m, 2 H), 7.84 (s, 1 H). ¹³C NMR (CDCl_3 , 125 MHz, 2 diastereoisomers) δ = 19.4 (s), [24.07 (s), 24.16 (s)]*, 25.4 (s), 30.5 (s), 31.8 (s), [36.6 (s), 36.7 (s)]*, 54.9 (s), [55.90 (p), 55.91 (p)]*, 55.95 (p), 56.0 (p), 56.1 (p), 62.1 (s), [66.4 (s), 66.5 (s)]*, [67.1 (q), 67.2 (q)]*, [98.63 (t), 98.68 (t)]*, 102.8 (t), 103.4 (t), [105.1 (t), 105.2 (t)]*, 108.18 (t), [120.92 (q), 120.96 (q)]*, 124.1 (q), [125.68 (q), 125.70 (q)]*, [125.89, 125.90 (q)]*, [126.91 (t), 126.98 (t)]*, 127.01 (q), 127.03 (q), 127.1 (t), 128.4 (t), 128.5 (t), 139.6 (t), 148.4 (q), [148.93 (q), 149.95 (q)]*, 149.0 (q), 149.5 (q). IR (powder, cm^{-1}) 699, 1254, 1509, 1621, 2473, 2954. HRMS (ESI⁺, Acetone, $\text{C}_{43}\text{H}_{48}\text{N}_2\text{O}_6\text{Na}$ [M + Na]⁺) calcd for 711.34046, found, 711.3409.

2-(Dibenzylamino)-6-((tetrahydro-2H-pyran-2-yl)oxy)-2-((3,6,7-trimethoxyphenanthren-9-yl)methyl)hexanenitrile, 12b. *New compound.* The synthesis of α -aminonitrile **12b** was carried out according to the same procedure than that followed for derivative **12a** but with 1.0 g (2.77 mmol, 1.0 equiv.) of crude bromide **11b** and 1.73 g (4.41 mmol, 1.6 equiv.) of α -aminonitrile **5b**. After aqueous work-up, the crude reaction mixture was stirred in 50 mL of diethyl ether at 0 °C overnight to afford 1.30 g (70%) of α -aminonitrile **12b** as a colorless powder. M.p. = 140 °C. ¹H NMR (CDCl_3 , 300 MHz, 2 diastereoisomers) δ = 1.28-2.04 (m, 12 H), 3.20-3.87 (m, 6 H), 3.91 (d, J_{AB} = 14.5 Hz, 2 H), 4.01 (s, 3 H), 4.07 (s, 3 H), 4.11 (s, 3 H), 4.15 (d, J_{AB} = 14.5 Hz, 2 H), 4.42-4.51 (m, 1 H), 7.11-7.45 (m, 12 H), 7.81-7.87 (m, 3 H), 7.91 (s, 1 H). ¹³C NMR (CDCl_3 , 75 MHz, 2 diastereoisomers) δ = [19.51 (s), 19.57 (s)]*, 20.4 (s), 22.2 (s), 25.4 (s), 25.9 (s), [29.2 (s), 29.3 (s)]*, 30.6 (s), 31.7 (s), 34.7 (s), 36.6 (s), 55.2 (s), 55.6 (p), 55.9 (p), 56.0 (p), [62.2 (s), 62.3 (s)]*, 66.8 (s), 67.1 (q), [98.7 (t), 98.8 (t)]*, [103.8 (t), 103.9 (t)]*, 105.2 (t), 115.7 (t), 120.9 (q), 124.9 (q), 125.5 (q), 126.3 (q), 126.8 (q), 127.1 (t), 127.5 (t), 128.3 (t), 128.4 (t), 130.0 (t), 130.6 (q), 139.6 (q), 148.7 (q), 149.0 (q), 158.3 (q). HRMS (ESI⁺, Acetone, $\text{C}_{43}\text{H}_{48}\text{N}_2\text{O}_5\text{Na}$ [M + Na]⁺) calcd for 695.34564, found, 695.3460.

***N,N*-dibenzyl-5-((tetrahydro-2H-pyran-2-yl)oxy)-1-(2,3,6,7-tetramethoxyphenanthren-9-yl)pentan-2-amine, 13a.** *New compound.* α -Aminonitrile **12a** (3.0 g, 4.35 mmol, 1.0 equiv.) was poured in a one-necked flask containing 100 mL of ethanol and 0.72 g (19.03 mmol, 4.4 equiv.) of NaBH_4 was added in portions. The solution was stirred for 5 hours at ambient temperature and heated at 50 °C overnight. The solution was cooled to 20 °C and 0.35 g (9.25 mmol, 2.1 equiv.) of NaBH_4 were added to the previous solution which was refluxed for an additional 3 h period. The solvents were evaporated under reduced pressure, and the crude material was taken-up with 20 mL of a 15% ammonia solution and the aqueous layer was extracted with 50 mL (x 2) of dichloromethane. The combined organic layers were washed with 40 mL of water, dried over MgSO_4 , filtered, and concentrated. The crude oily residue was diluted in 5 mL of dichloromethane and poured into a chromatographic column (50 x 2.5 cm), prepared with 70 g of silica and 8:2 diethyl ether/petroleum ether. The combined fractions were evaporated, to afford 2.41 g (83%) of amine

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13a. Slightly yellow powder. Mp = 95 °C. R_f = 0.5 (diethyl ether/petroleum ether, 8:2). $^1\text{H NMR}$ (CDCl_3 , 500 MHz, 2 diastereoisomers) δ = 1.38–1.95 (m, 10 H), 3.12–3.17 (m, 1 H), 3.25–3.58 (m, 4 H), 3.60–3.82 (m, 9 H), 4.06 (s, 3 H), 4.16 (s, 3 H), 4.17 (s, 3 H), 4.43–4.45 (m, 0.5 H), 4.49–4.50 (m, 0.5 H), 7.11–7.18 (m, 12 H), 7.38 (s, 1 H), 7.84 (s, 1 H), 7.87 (s, 1 H). $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz, 2 diastereoisomers) δ = [19.6 (s), 19.7 (s)]*, 25.5 (s), [26.7 (s), 26.8 (s)]*, [27.5 (s), 27.7 (s)]*, [30.7 (s), 30.8 (s)]*, [34.4 (s), 34.6 (s)]*, 53.4 (p), [55.70 (p), 55.73 (p)]*, 55.9 (p), [56.11 (p), 56.15 (p)]*, [57.3 (t), 57.4 (t)]*, [62.3 (s), 62.4 (s)]*, [67.4 (s), 67.5 (s)]*, 98.8 (t), 102.9 (t), 103.5 (t), 105.1 (t), 107.9 (t), 123.6 (q), 124.87 (q), 125.95 (q), 126.06 (t), 126.10 (t), 126.4 (q), 126.6 (t), [127.97 (t), 127.99 (t)]*, [128.53 (t), 128.54 (t)]*, [132.09 (q), 132.13 (q)]*, [140.09 (q), 140.10 (q)]*, 148.4 (q), 148.77 (q), 148.81 (q), 148.84 (q). IR (powder, cm^{-1}): 697, 1250, 1509, 1620, 2934, 2998. HRMS (ESI⁺, Acetone, $\text{C}_{42}\text{H}_{50}\text{NO}_6$ [M + H]⁺) calcd for 664.36326, found, 664.3638.

N,N-dibenzyl-6-((tetrahydro-2H-pyran-2-yl)oxy)-1-(3,6,7-trimethoxyphenanthren-9-yl)hexan-2-amine, 13b. *New compound.* The synthesis of amine **13b** was carried out according to the same procedure than that followed for derivative **13a** but with 2.46 g (3.65 mmol, 1.0 equiv.) of α -aminonitrile **12b**. After work-up, the crude reaction mixture was dissolved in dichloromethane and poured on a chromatographic column (30 × 3.0 cm) prepared with 20 g of silica, and 80:20 diethyl ether/petroleum ether. The fractions were collected and concentrated to afford 1.77 g (75%) of amine **13b**. White powder. Mp = 126 °C. R_f = 0.65 (petroleum ether/ether, 20:80). $^1\text{H NMR}$ (CDCl_3 , 500 MHz, 2 diastereoisomers) δ = 1.31–1.85 (m, 12 H), 3.14–3.18 (m, 1 H), 3.25–3.40 (m, 3 H), 3.49–3.48 (m, 1 H), 3.60–3.95 (m, 6 H), 3.71 (s, 3 H), 4.08 (s, 3 H), 4.16 (s, 3 H), 4.54–4.58 (m, 1 H), 7.00–7.20 (m, 11 H), 7.25 (d, J = 8.5 Hz, 1 H), 7.44 (s, 1 H), 7.73 (d, J = 8.5 Hz, 1 H), 7.93 (s, 1 H), 7.98 (s, 1 H). $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz, 2 diastereoisomers) δ = [19.64 (s), 19.66 (s)]*, [24.21 (s), 24.26 (s)]*, 25.5 (s), [29.87 (s), 29.92 (s), 29.96 (s)]*, 30.8 (s), [34.66 (s), 34.70 (s)]*, 53.3 (s), 55.6 (p), 55.7 (p), 56.1 (p), 57.2 (t), [62.2 (s), 62.3 (s)]*, [67.3 (s), 67.4 (s)]*, [98.7 (t), 98.8 (t)]*, [103.90 (t), 103.95 (t)]*, 105.1 (t), 115.4 (t), 124.7 (q), 126.1 (q), 126.58 (q), 127.2 (q), 127.9 (t), 128.5 (t), 129.6 (t), 130.3 (q), 131.5 (q), 140.1 (q), 148.6 (q), 149.0 (q), 157.8 (q). IR (powder, cm^{-1}): 735, 983, 1268, 1475, 1607, 2935. HRMS (ESI⁺, $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$, 90:10, $\text{C}_{42}\text{H}_{49}\text{O}_5\text{Na}$ [M + Na]⁺) calcd 670.35029, found 670.3504.

5-((Tetrahydro-2H-pyran-2-yl)oxy)-1-(2,3,6,7-tetramethoxyphenanthren-9-yl)pentan-2-amine, 14a. *New compound.* A 300-mL high-pressure hydrogenator was charged with 45 mL of ethanol, 20 mL of methanol, 0.20 g (10% in mass) of 20% Pd(OH)₂/C and 2.19 g (3.30 mmol) of amine **13a**. Air was removed from the reactor by alternatively filling it with hydrogen and venting it three times. The hydrogen pressure (3.75 × 10³ Torr, 5 bars) was applied, and the suspension was stirred for 48 h at 70 °C. The resulting clear solution was filtered over a small pad of Celite® and the vessel was washed with ethanol. The filtrate was concentrated under reduced pressure, to afford 1.50 g (94%) of amine **14a** which was utilized in the next step without purification. Colorless solid. Mp = 220 °C. R_f = 0.5 (dichloromethane/methanol, 9:1). $^1\text{H NMR}$ (CDCl_3 , 500 MHz, 2 diastereoisomers) δ = 1.47–2.00 (m, 10 H), 1.90 (s, 2 H, br.), 2.86–2.90 (m, 1 H), 3.30–3.37 (m, 2 H), 3.43–3.50 (m, 2 H), 3.78–3.86 (m, 2 H), 4.03 (s, 3 H), 4.06 (s, 3 H), 4.12 (s, 3 H), 4.13 (s, 3 H), 4.57–4.58 (m, 1 H), 7.18 (s, 1 H), 7.40 (s, 1 H), 7.46 (s, 1 H), 7.77 (s, 1 H), 7.84 (s, 1 H). $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz, 2 diastereoisomers) δ = [19.67 (s), 19.71 (s)]*, 25.4 (s), [26.66 (s), 26.74 (s)]*, [30.73 (s), 30.76 (s)]*, 34.8 (s), 42.3 (s), [51.07 (t), 51.11 (t)]*, 55.88 (p), 55.95 (p), 55.96 (p), 56.06 (p), 56.14 (p), [62.44 (s), 62.48 (s)]*, 67.6 (s), 99.0 (t), 102.9 (t), 103.5 (t), 105.0 (t), 108.0 (t), 123.8 (q), 125.1 (q), 125.4 (t), 125.5 (q), 126.2 (q), 131.0 (q), 148.6 (q), 148.90 (q), 148.93 (q), 149.0 (q). IR (powder, cm^{-1}): 842, 1028, 1249, 1506, 1618, 2934. HRMS (ESI⁺, $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$, 90:10, $\text{C}_{28}\text{H}_{38}\text{NO}_6$ [M + H]⁺) calcd for 484.26936, found, 484.2696.

6-((Tetrahydro-2H-pyran-2-yl)oxy)-1-(3,6,7-trimethoxyphenanthren-9-yl)hexan-2-amine, 14b. *New compound.* The synthesis of amine **14b** was carried out according to the same procedure than that followed for

derivative **14a** but with 1.50 g (2.31 mmol) of amine **13b**. The evaporation of ethanol afforded amine **14b** (1.03 g, 95%) which slowly solidified upon cooling. White foam. Mp = <50 °C. R_f = 0.2 (dichloromethane/methanol, 90:10). $^1\text{H NMR}$ (CDCl_3 , 500 MHz, 2 diastereoisomers) δ = 1.43–1.83 (m, 12 H), 3.02–3.09 (m, 1 H), 3.28–3.48 (m, 4 H), 3.55–3.80 (s, 2 H, br.), 3.71–3.75 (m, 1 H), 3.79–3.88 (m, 1 H), 4.00 (s, 3 H), 4.05 (s, 3 H), 4.09 (s, 3 H), 4.49–4.51 (m, 1 H), 7.17 (dd, J = 8.7, 2.3 Hz, 1 H), 7.37 (s, 1 H), 7.49 (s, 1 H), 7.75 (d, J = 8.7 Hz, 1 H), 7.80 (d, J = 2.3 Hz, 1 H), 7.89 (s, 1 H). $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz, 2 diastereoisomers) δ = 19.7 (s), [22.97 (s), 22.99 (s)]*, 25.4 (s), 29.7 (s), 30.7 (s), 36.4 (s), 40.8 (s), 51.3 (p), 55.5 (p), [55.99 (p), 56.13 (p)]*, [62.43 (s), 62.46 (s)]*, [67.26 (s), 67.30 (s)]*, [98.95 (t), 98.98 (t)]*, [103.87 (t), 103.99 (t)]*, 104.8 (t), 115.4 (t), 124.9 (q), 125.8 (q), 126.1 (t), 126.5 (q), 129.3 (q), 129.8 (t), 130.5 (q), 148.7 (q), 149.4 (q), 158.0 (q). IR (powder, cm^{-1}): 787, 853, 1029, 1120, 1160, 1353, 1384, 1508, 1608, 2862, 2934. HRMS (ESI⁺, $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$, 90:10, $\text{C}_{28}\text{H}_{37}\text{NO}_5\text{Na}$ [M + Na]⁺) calcd for 490.25639, found 490.2566.

tert-Butyl 5-((tetrahydro-2H-pyran-2-yl)oxy)-1-(2,3,6,7-tetramethoxyphenanthren-9-yl)pentan-2-yl)carbamate, 15a. *New compound.* An oven dried, 50-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube was successively charged with 10 mL of dichloromethane, 1.50 g (3.10 mmol, 1.0 equiv.) of amine **14a**, and 0.75 g (3.44 mmol, 1.1 equiv.) of di-*tert*-butyl dicarbonate (Boc₂O). The reaction mixture was stirred at room temperature for 24 h and the solvent was evaporated. The crude reaction mixture was poured into a chromatographic column (20 × 2.0 cm) prepared with 15 g of silica and diethyl ether. The combined fractions were evaporated to yield 1.70 g (94%) of carbamate **15a**. Colorless powder. Mp = 84 °C. R_f = 0.6 (diethyl ether). $^1\text{H NMR}$ (CDCl_3 , 400 MHz, 2 diastereoisomers) δ = 1.32–1.82 (m, 10 H), 1.32 (s, 9 H), 2.79–2.90 (m, 1 H), 3.25–3.47 (m, 2 H), 3.63–3.79 (m, 3 H), 4.00–4.10 (m, 1 H), 4.04 (s, 3 H), 4.13 (s, 3 H), 4.15 (s, 3 H), 4.19 (s, 3 H), 4.41 (m, 0.5 H), 4.52 (m, 0.5 H), 4.82–4.85 (m, 1 H), 7.18 (s, 1 H), 7.40 (s, 1 H), 7.80 (s, 1 H), 7.85 (s, 1 H), 7.98 (s, 1 H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz, diastereoisomers) δ = [19.5 (s), 19.7 (s)]*, 25.4 (s), [25.99 (s), 26.05 (s)]*, 28.4 (p), 30.4 (s), 30.60 (s), [40.83 (s), 40.87 (s)]*, 50.7 (t), 55.9 (p), 56.0 (p), 56.1 (p), 56.4 (p), [62.2 (s), 62.5 (s)]*, [67.03 (s), 67.23 (s)]*, 79.01 (q), [98.7 (t), 99.1 (t)]*, 102.8 (t), 103.12 (t), 105.9 (t), 108.0 (t), 123.9 (q), 124.8 (q), 125.6 (t), 125.9 (q), 126.2 (q), 130.6 (q), 148.7 (q), 148.9 (q, 2 C), 155.72 (q). IR (powder, cm^{-1}): 1031, 1117, 1148, 1199, 1249, 1428, 1438, 1473, 1507, 1701, 2934. HRMS (ESI⁺, $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$, 90:10, $\text{C}_{33}\text{H}_{45}\text{NO}_8\text{Na}$ [M + Na]⁺) calcd for 606.30374, found 606.3035.

tert-Butyl 6-((tetrahydro-2H-pyran-2-yl)oxy)-1-(3,6,7-trimethoxyphenanthren-9-yl)hexan-2-yl)carbamate, 15b. *New compound.* The synthesis of carbamate **15b** was carried out according to the same procedure than that followed for derivative **15a** but with 1.0 g (2.13 mmol, 1.0 equiv.) of amine **14b** and 0.51 g (2.35 mmol, 1.1 equiv.) of di-*tert*-butyl dicarbonate (Boc₂O). After work-up, the crude reaction mixture was dissolved in dichloromethane and poured on a chromatographic column (30 × 3.0 cm) prepared with 30 g of silica, and 60:20:20 diethyl ether/dichloromethane/petroleum ether. The fractions were collected and concentrated to afford 0.97 g (80%) of carbamate **15b**. White powder. Mp = 134 °C. R_f = 0.7 (diethyl ether/dichloromethane/petroleum ether, 60:20:20). $^1\text{H NMR}$ (CDCl_3 , 500 MHz, 2 diastereoisomers) δ = 1.24–1.80 (m, 13 H), 1.46 (s, 9 H), 2.79–2.90 (m, 1 H), 3.27–3.35 (m, 1 H), 3.48–3.83 (m, 1 H), 3.51–3.60 (m, 1 H), 3.62–3.72 (m, 1 H), 3.75–3.84 (m, 1 H), 4.00–4.02 (m, 1 H), 4.03 (s, 3 H), 4.14 (s, 3 H), 4.19 (s, 3 H), 4.45–4.51 (m, 1 H), 4.53–4.65 (m, 1 H), 7.19 (dd, J = 8.7, 2.3 Hz, 1 H), 7.41 (s, 1 H), 7.73 (d, J = 8.7 Hz, 1 H), 7.86 (d, J = 2.3 Hz, 1 H), 7.94 (s, 1 H). $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz, 2 diastereoisomers) δ = [19.7 (s), 19.8 (s)]*, [22.8 (s), 23.0 (s)]*, 25.4 (s), 28.4 (p), [29.4 (s), 29.5 (s)]*, 30.7 (s), [33.4 (s), 33.5 (s)]*, [40.9 (s), 40.9 (s)]*, 50.9 (t), 55.6 (p), 56.0 (p), 56.4 (p), [62.3 (s), 62.5 (s)]*, [67.2 (s), 67.3 (s)]*, 79.0 (q), [98.8 (t), 99.0 (t)]*, [103.7 (t), 103.9 (t)]*, 105.8 (t), 115.3 (t), 124.6 (q), 125.9 (q), 126.1 (t), 127.1 (q), 129.6 (q), 129.8 (q), 130.6 (q), 148.7 (q), 149.7 (q), 155.7 (q), 157.9 (q). IR (powder, cm^{-1}): 650, 830, 1032, 1158, 1268, 1386, 1462, 1523, 1609, 1690, 2937, 3372. HRMS (ESI⁺, $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$, 90:10, $\text{C}_{33}\text{H}_{45}\text{NO}_7\text{Na}$ [M + Na]⁺) calcd for 590.30882, found 590.3089.

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tert-Butyl (5-hydroxy-1-(2,3,6,7-tetramethoxyphenanthren-9-yl)pentan-2-yl)carbamate, 16a. *New compound.* A 200-mL, one necked Schlenk tube, fitted with a magnetic stirring bar, and connected to an argon inlet tube was successively charged with 25 mL of methanol, 1.70 g (2.91 mmol) of carbamate **15a**, and 0.11 g (0.44 mmol, 15% in mole) of pyridinium *p*-toluenesulfonate (PPTS). The reaction mixture was heated at 50 °C for 12 h. The solvent was removed under reduced pressure, and the crude material was stirred for 15 minutes in a biphasic mixture of dichloromethane (100 mL) and water (20 mL). The organic layer was dried over MgSO₄ and concentrated to yield a crude reaction mixture which was taken-up in 100 mL of diethyl ether for 12 h to yield 1.26 g (87%) of carbamate **16a** as a white powder. M.p. = 181 °C. *R*_f = 0.4 (diethyl ether/methanol 99:1). ¹H NMR (CDCl₃, 400 MHz) δ = 1.39–1.81 (m, 5 H), 1.46 (s, 9 H), 2.91–2.93 (m, 1 H), 3.50–3.60 (m, 4 H), 4.05 (s, 3 H), 4.14 (s, 3 H), 4.15 (s, 3 H), 4.17 (s, 3 H), 4.64 (m, 1 H), 7.19 (s, 1 H), 7.41 (s, 1 H), 7.80 (s, 1 H), 7.86 (s, 2 H). ¹³C NMR (CDCl₃, 100 MHz) δ = 28.4 (p), 29.1 (s), 30.4 (s), 40.9 (s), 50.7 (t), 55.9 (p), 56.07 (p), 56.15 (p), 56.3 (p), 62.6 (s), 79.26 (q), 102.9 (t), 103.3 (t), 105.6 (t), 108.0 (t), 123.9 (q), 124.8 (q), 125.6 (t), 125.8 (q), 126.1 (q), 130.3 (t), 148.8 (q), 148.9 (q), 149.0 (q), 155.8 (q). IR (powder, cm⁻¹): 882, 1145, 1249, 1510, 1619, 1698, 2938, 3353, 3530. HRMS (ESI⁺, CH₃OH/CH₂Cl₂ (90:10), C₂₈H₃₇NO₇Na [M + Na]⁺) calcd for 522.24622, found, 522.2463.

tert-Butyl (6-hydroxy-1-(3,6,7-trimethoxyphenanthren-9-yl)hexan-2-yl)carbamate, 16b. *New compound.* The synthesis of carbamate **16b** was carried out according to the same procedure than that followed for derivative **16a** but with 0.40 g (0.70 mmol) of carbamate **16b**. After work-up, the crude reaction mixture was stirred in diethyl ether overnight to afford 0.32 g (94%) of alcohol **16b** as a colorless powder. White powder. M.p. = 166 °C. *R*_f = 0.4 (diethyl ether). ¹H NMR (CDCl₃, 500 MHz) δ = 1.11–1.73 (m, 6 H), 1.46 (s, 9 H), 2.87 (t, *J* = 6.8 Hz, 1 H), 3.63–3.49 (m, 3 H), 4.04 (s, 3 H), 3.98–4.09 (m, 1 H), 4.14 (s, 3 H), 4.18 (s, 3 H), 4.60–4.51 (m, 1 H), 7.20 (d, *J* = 8.2 Hz, 1 H), 7.41 (s, 1 H), 7.74 (d, *J* = 8.2 Hz, 1 H), 7.87 (s, 1 H), 7.88 (s, 1 H), 9.94 (s, 1 H). ¹³C NMR (CDCl₃, 125 MHz) δ = 22.3 (s), 28.4 (p), 32.4 (s), 33.6 (s), 40.9 (s), 50.7 (p), 55.6 (p), 56.0 (p), 56.4 (p), 62.6 (s), 79.2 (q), 103.7 (t), 103.9 (t), 105.7 (t), 115.3 (t), 124.7 (q), 125.9 (q), 126.1 (t), 127.0 (q), 129.6 (t), 129.7 (t), 130.6 (q), 148.8 (q), 149.7 (q), 155.7 (q), 157.9 (q). IR (powder, cm⁻¹) 611, 788, 829, 1030, 1065, 1157, 1220, 1365, 1462, 1522, 1610, 1689, 2936, 3381. HRMS (ESI⁺, CH₃OH/CH₂Cl₂, 90:10, C₂₈H₃₇NO₆Na [M + Na]⁺) calcd for 506.25131, found 506.2514.

4-((tert-Butoxycarbonyl)amino)-5-(2,3,6,7-tetramethoxyphenanthren-9-yl)pentyl methanesulfonate, 17a. *New compound.* From an adapted procedure reported in the literature.^[18c] An oven dried, 50-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube and cooled to 0 °C, was successively charged with 30 mL of dichloromethane, 0.40 g (0.80 mmol) of carbamate **16a**, 0.17 mL (0.12 g, 1.22 mmol, 1.5 equiv.) of triethylamine, 0.10 mL (0.15 g, 1.29 mmol, 1.6 equiv.) of mesyl chloride and 0.023 g (0.19 mmol, 0.23 equiv.) of *N,N*-dimethylaminopyridine (DMAP) and the reaction mixture was stirred for 5 hours at room temperature. Then, 30 mL of saturated NaHCO₃ were poured on the previous mixture and the resulting biphasic system was stirred for one hour to hydrolyze the excess of mesyl chloride. The organic phase was dried over MgSO₄ and concentrated to afford a crude reaction mixture which was dissolved in 5 mL of dichloromethane and poured on a chromatographic column (20 × 3.0 cm) prepared with 20 g of silica and 80:20 of diethyl ether/dichloromethane. The combined fractions were evaporated to yield 0.38 g (82%) of mesylate **17a**. White solid. M.p. = 166 °C. *R*_f = 0.44 (diethyl ether). ¹H NMR (DMSO-d₆, 300 MHz) δ = 1.36 (s, 9 H), 1.40–1.92 (m, 4 H), 2.81–2.95 (m, 1 H), 3.04 (s, 3 H), 3.23–3.37 (m, 1 H), 3.77–4.25 (m, 3 H), 3.89 (s, 3 H), 4.00 (s, 3 H), 4.02 (s, 3 H), 4.03 (s, 3 H), 7.02 (d, *J* = 8.7 Hz, 1 H), 7.29 (s, 1 H), 7.44 (s, 1 H), 7.70 (s, 1 H), 7.97 (s, 1 H), 8.02 (s, 1 H). ¹³C NMR (DMSO-d₆, 75 MHz) δ = 25.6 (s), 28.5 (p), 29.3 (s), 36.4 (p), 40.1 (s), 50.1 (t), 55.3 (p), 55.4 (p), 55.89 (p), 55.93 (p), 70.4 (s), 77.7 (q), 103.7 (t), 104.3 (t), 105.2 (t), 108.1 (t), 123.4 (q), 124.5 (q), 125.1 (t), 125.7 (q), 130.3 (q), 148.5 (q), 148.6 (q), 148.7 (q), 148.8 (q), 155.7 (q). IR (powder, cm⁻¹) 528, 828, 968, 1041, 1146, 1167,

1252, 1464, 1507, 1530, 1683, 3346. HRMS (ESI⁺, CH₃OH/CH₂Cl₂, 90:10, C₂₉H₃₉NO₈NaS [M + Na]⁺) calcd 600.22377; found 600.2242.

5-((tert-Butoxycarbonyl)amino)-6-(3,6,7-trimethoxyphenanthren-9-yl)hexyl methanesulfonate, 17b. *New compound.* The synthesis of mesylate **17b** was carried out according to the same procedure than that followed for derivative **17a** but with 0.30 g (0.62 mmol, 1.0 equiv.) of carbamate **16b**, 0.13 mL (0.094 g, 0.93 mmol, 1.5 equiv.) of triethylamine, 0.019 g (0.15 mmol, 0.25 equiv.) of DMAP, and 0.07 mL (0.10 g, 0.90 mmol, 1.45 equiv.) of mesyl chloride in 20 mL of dichloromethane. After work-up, the crude reaction mixture was dissolved in 3 mL of dichloromethane and poured on a chromatographic column (30 × 2.0 cm) prepared with 15 g of silica, and 80:20 diethyl ether/dichloromethane. The fractions were collected and concentrated to afford 0.33 g (95%) of mesylate **17b**. White powder. M.p. = 116 °C. *R*_f = 0.6 (diethyl ether/dichloromethane, 80:20). ¹H NMR (CDCl₃, 500 MHz) δ = 1.41–1.43 (m, 2 H), 1.37 (s, 9 H), 1.43–1.61 (m, 4 H), 2.72–2.80 (m, 1 H), 2.78 (s, 3 H), 3.46–3.48 (m, 1 H), 3.93 (s, 3 H), 4.00–4.05 (m, 3 H), 4.04 (s, 3 H), 4.08 (s, 3 H), 4.45 (d, *J* = 8.0 Hz, 1 H), 7.10 (dd, *J* = 8.7, 2.3 Hz, 1 H), 7.30 (s, 1 H), 7.64 (d, *J* = 8.7 Hz, 1 H), 7.70 (d, *J* = 2.3 Hz, 1 H), 7.77 (s, 1 H), 7.84 (s, 1 H). ¹³C NMR (CDCl₃, 125 MHz) δ = 21.1 (s), 27.4 (p), 27.7 (s), 32.0 (s), 36.2 (p), 40.0 (s), 49.5 (t), 54.6 (p), 55.0 (p), 55.3 (p), 68.6 (s), 78.3 (q), 102.7 (t), 102.8 (t), 104.6 (t), 114.4 (t), 123.6 (q), 124.8 (q), 125.1 (t), 125.9 (q), 128.5 (q), 128.6 (t), 129.6 (t), 147.8 (q), 148.7 (q), 154.7 (q), 157.0 (q). IR (powder, cm⁻¹) 788, 829, 1031, 1160, 1508, 1608, 1700, 2936, 3376. HRMS (ESI⁺, CH₃OH/CH₂Cl₂, 90:10, C₂₉H₃₉NO₈NaS [M + Na]⁺) calcd for 584.22886, found 584.2293.

5-((Methylsulfonyl)oxy)-1-(2,3,6,7-tetramethoxyphenanthren-9-yl)pentan-2-aminium chloride, 18a. *New compound.* An oven dried, 50-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar, connected to an argon inlet tube, was successively charged with a solution of mesylate **17a** (0.45 g, 0.78 mmol) in 10 mL of dioxane and 10 mL of a 4 M HCl solution in dioxane. The resulting solution was stirred for 48 h and the solvent was evaporated in vacuo. The resulting suspension was taken-up with diethyl ether (10 mL × 3) and was filtered over a fritted glassware to afford 0.36 g (96%) of hydrochloride **18a** as a slightly brown powder. M.p. >220 °C (dec.). ¹H NMR (DMSO-d₆, 400 MHz) δ = 1.60–1.75 (m, 2 H), 1.80–1.96 (m, 2 H), 3.06 (s, 3 H), 3.14–3.25 (m, 1 H), 3.50–3.70 (m, 2 H), 3.91 (s, 3 H), 4.00 (s, 3 H), 4.03 (s, 3 H), 4.04 (s, 3 H), 4.10–4.30 (m, 2 H), 7.34 (s, 1 H), 7.45 (s, 1 H), 7.55 (s, 1 H), 8.00 (s, 1 H), 8.06 (s, 1 H), 8.33 (s, 3 H). ¹³C NMR (DMSO-d₆, 100 MHz) δ = 24.8 (s), 28.5 (s), 36.9 (p), 50.6 (t), 55.9 (p), 56.5 (p), 70.5 (s), 104.2 (t), 105.0 (t), 105.5 (t), 108.7 (t), 124.2 (q), 125.0 (q), 125.2 (q), 126.0 (q), 126.4 (t), 128.3 (q), 149.2 (q), 149.4 (q), 149.6 (q). HRMS (ESI⁺, H₂O, C₂₄H₃₂NO₇S [M]⁺) calcd 478.1894; found 478.1894.

6-((Methylsulfonyl)oxy)-1-(3,6,7-trimethoxyphenanthren-9-yl)hexan-2-aminium chloride, 18b. *New compound.* The synthesis of hydrochloride **18b** was carried out according to the same procedure than that followed for derivative **18a** but with 0.36 g (0.64 mmol) of carbamate **17b** dissolved in dioxane (15 mL) and 15 mL of a 4 M HCl solution in dioxane. The resulting solution was stirred for 48 h and the solvent was evaporated in vacuo. The resulting suspension was taken-up with diethyl ether (10 mL × 3) and was filtered over a fritted glassware to afford 0.30 g (94%) of hydrochloride **18b**. White powder. M.p. = 200 °C. ¹H NMR (DMSO-d₆, 500 MHz) δ = 1.37–1.70 (m, 6 H), 3.11 (s, 3 H), 3.20–3.25 (m, 1 H), 3.51–3.60 (m, 2 H), 4.02 (s, 3 H), 4.00 (s, 3 H), 4.05 (s, 3 H), 4.08–4.16 (m, 2 H), 7.22 (dd, *J* = 8.7, 2.3 Hz, 1 H), 7.48 (s, 1 H), 7.59 (s, 1 H), 7.82 (d, *J* = 8.7 Hz, 1 H), 8.07 (s, 1 H), 8.14 (s, 1 H), 7.35 (s, 3 H). ¹³C NMR (DMSO-d₆, 125 MHz) δ = 20.6 (s), 28.3 (s), 31.4 (s), 36.3 (s), 36.5 (p), 50.3 (t), 55.6 (p), 55.9 (p), 56.1 (s), 70.1 (s), 104.1 (t), 104.95 (t), 104.99 (t), 115.9 (t), 124.5 (q), 125.2 (q), 125.8 (q), 126.3 (t), 127.5 (q), 129.7 (t), 130.4 (q), 148.8 (q), 149.5 (q), 158.0 (q). IR (powder, cm⁻¹) 837, 948, 1265, 1468, 1609, 2836, 3225. HRMS (ESI⁺, H₂O, C₂₄H₃₂NO₆S [M]⁺) calcd 462.19448; found 462.1945.

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2,3,6,7-Tetramethoxy-9,11,12,13,13a,14-

hexahydrodibenzof[h]pyrrolo[1,2-b]isoquinoline, tylophorine, 1. *Step 1: Cyclization to pyrrolidine 19a.* An oven dried, 50-mL, one-necked Schlenk tube, fitted with a magnetic stirring bar was successively charged with 1.06 g (2.21 mmol, 1.0 equiv.) of hydrochloride **18a**, 10 mL of dichloromethane, and 1.80 mL (1.34 g, 10.40 mmol, 4.7 equiv.) of diisopropylethylamine. The resulting suspension was stirred overnight to yield a yellow solution which was stirred for 15 minutes in the presence of 10 mL of water. The organic layer was dried over MgSO₄ and concentrated *in vacuo* to afford 0.79 g of pyrrolidine **19a** which proved to be sensitive to aerial carbonation and was used in the next step without purification. ¹H NMR (CDCl₃, 300 MHz) δ = 1.43–1.96 (m, 5 H), 2.80–2.89 (m, 1 H), 3.04–3.12 (m, 1 H), 3.17 (d, *J* = 6.7 Hz, 1 H), 3.52 (q, *J* = 6.8 Hz, 1 H), 4.02 (s, 3 H), 4.05 (s, 3 H), 4.11 (s, 3 H), 4.12 (s, 3 H), 7.18 (s, 1 H), 7.43 (s, 1 H), 7.47 (d, *J* = 8.7 Hz, 1 H), 7.76 (s, 1 H), 7.83 (s, 1 H). ¹³C NMR (CDCl₃, 75 MHz) δ = 24.9 (s), 31.7 (s), 40.0 (s), 46.2 (s), 55.8 (p), 55.9 (p), 55.96 (p), 56.13 (p), 58.6 (t), 102.7 (t), 103.3 (t), 104.8 (t), 107.9 (t), 123.6 (q), 124.6 (t), 124.9 (q), 125.5 (q), 126.3 (q), 131.6 (q), 129.6 (t), 148.4 (q), 148.5 (q), 148.7 (q), 148.8 (q). *Step 2: Pictet-Spengler cyclization.* From an adapted procedure reported in the literature.^[38] Then, 3.0 mL of formic acid, 0.50 g (16.66 mmol, 7.5 equiv.) of paraformaldehyde were added to yield a homogeneous solution which was heated at 55 °C for 18 h. The resulting mixture was poured in 10 mL of water and the clear solution was basified by the addition of solid NaOH. The aqueous suspension of tylophorine was extracted (50 mL x 2) with dichloromethane, and the combined organic layers were dried over MgSO₄ and concentrated to afford 0.83 g (95% from **18a**) of tylophorine (**1**). Yellow powder. Mp >280 °C (dec.). *R*_f = 0.4 (CH₂Cl₂/MeOH, 95:5). ¹H NMR (CDCl₃, 400 MHz) δ = 1.65–2.10 (m, 4 H), 2.23–2.31 (m, 1 H), 2.45–2.55 (m, 2 H), 2.93 (dd, *J* = 10.6, 10.0 Hz, 1 H), 3.38 (dd, *J* = 15.9, 2.7 Hz, 1 H), 3.49 (t, *J* = 6.60 Hz, 1 H), 3.68 (d, *J* = 14.7 Hz, 1 H), 4.05 (s, 3 H), 4.06 (s, 3 H), 4.13 (s, 6 H), 4.63 (d, *J* = 14.7 Hz, 1 H), 7.17 (s, 1 H), 7.33 (s, 1 H), 7.84 (s, 2 H). ¹³C NMR (CDCl₃, 100 MHz) δ = 21.6 (s), 31.3 (s), 33.8 (s), 54.0 (s), 55.2 (s), 55.88 (p), 55.92 (p), 56.0 (p, 2 C), 60.2 (t), 103.1 (t), 103.3 (t), 103.4 (t), 104.0 (t), 123.4 (q), 123.6 (q), 124.3 (q), 125.8 (q), 126.0 (q), 126.3 (q), 148.4 (q), 148.5 (q), 148.7 (q). IR (powder, cm⁻¹) 842, 1018, 1148, 1196, 1207, 1245, 1425, 1443, 1467, 1512, 1617, 2918. HRMS (ESI⁺, CH₃OH/CH₂Cl₂, C₂₄H₂₈NO₄ [M + H]⁺) calcd 394.20128, found 394.2010. The analytical data were in agreement with those reported in the literature.^[10a]

2-(3,6,7-Trimethoxyphenanthren-9-yl)methyl)piperidine, 19b. The synthesis of piperidine **19b** was carried out according to the same procedure than that followed for pyrrolidine **19a** but with 0.20 g (0.40 mmol) of hydrochloride **18b**, 15 mL of dichloromethane, and 0.35 mL (0.26 g, 2.02 mmol, 5.0 equiv.) of diisopropylethylamine. The organic layer was concentrated *in vacuo* to afford 0.14 g (95%) of piperidine **19b** which was used in the next step without purification. White powder. Mp = 148 °C. *R*_f = 0.2 (diethyl ether/dichloromethane/methanol, 20:20:3). ¹H NMR (CDCl₃, 400 MHz) δ = 1.13–1.52 (m, 4 H), 1.70–1.75 (m, 2 H), 2.20–2.30 (s, 1 H, br.), 2.42 (td, *J* = 10.5, 3.5 Hz, 1 H), 2.79–2.97 (m, 3 H), 3.14–3.60 (dd, *J* = 10.5, 3.5 Hz, 1 H), 3.92 (s, 3 H), 3.98 (s, 3 H), 4.03 (s, 3 H), 7.10 (dd, *J* = 8.7, 2.2 Hz, 1 H), 7.34 (s, 1 H), 7.41 (s, 1 H), 7.65 (d, *J* = 8.7 Hz, 1 H), 7.65 (d, *J* = 2.2 Hz, 1 H) 7.84 (s, 1 H). ¹³C NMR (CDCl₃, 100 MHz) δ = 23.8 (s), 25.0 (s), 32.3 (s), 36.3 (s), 40.5 (s), 46.1 (s), 54.6 (p), 54.98 (p), 55.0 (p), 55.5 (t), 102.9 (t), 103.0 (t), 104.1 (t), 114.4 (t), 123.9 (q), 124.9 (t), 125.7 (q), 128.66 (q), 128.72 (q), 129.4 (t), 147.7 (q), 148.2 (q), 157.0 (q). IR (powder, cm⁻¹) 787, 1031, 1386, 1608, 2852, 3317. HRMS (ESI⁺, CH₃OH/CH₂Cl₂, 90:10, C₂₃H₂₈NO₃ [M + H]⁺) calcd for 366.20637, found 366.2066. The analytical data were in agreement with those reported in the literature.^[47]

2,3,6-Trimethoxy-11,12,13,14,14a,15-hexahydro-9H-dibenzof[h]pyrrolo[1,2-b]isoquinoline, cryptopleurine, 2. The synthesis of cryptopleurine was carried out according to the same procedure than that followed for tylophorine but with 0.15 g (0.41 mmol) of piperidine **19b**, 2.5 mL of formic acid, and 0.12 g (4.00 mmol, 9.7 equiv.) of paraformaldehyde. After work-up, the crude reaction mixture was dissolved in 3 mL of dichloromethane and poured on a chromatographic column (30 x 2.0 cm) prepared with 10 g of silica, and 40:40:6 diethyl

ether/dichloromethane/methanol. The fractions were collected and concentrated to afford 0.13 g (86%) of cryptopleurine. Beige powder. Mp = 190 °C (dec.). *R*_f = 0.5 (diethyl ether/dichloromethane/methanol, 45:45:7). ¹H NMR (CDCl₃, 400 MHz) δ = 1.42–1.57 (m, 2 H), 1.76–1.90 (m, 3 H), 2.00–2.03 (m, 1 H), 2.25–2.37 (m, 2 H), 2.82–2.89 (m, 1 H), 3.02–3.06 (m, 1 H), 3.25–3.26 (m, 1 H), 3.58 (d, *J* = 14.5 Hz, 1 H), 4.02 (s, 3 H), 4.06 (s, 3 H), 4.10 (s, 3 H), 4.40 (d, *J* = 14.5 Hz, 1 H), 7.18 (dd, *J* = 8.7, 2.2 Hz, 1 H), 7.23 (s, 1 H), 7.77 (d, *J* = 8.7 Hz, 1 H), 7.84 (s, 2 H). ¹³C NMR (CDCl₃, 100 MHz) δ = 24.4 (s), 25.9 (s), 33.8 (s), 34.7 (s), 55.5 (p), 55.9 (p), 55.0 (p), 56.1 (s), 56.2 (s), 57.5 (t), 103.85 (t), 103.87 (t), 104.7 (t), 114.8 (t), 123.4 (q), 123.7 (q), 124.1 (t), 124.4 (q), 125.6 (q), 126.5 (t), 130.1 (q), 148.3 (q), 149.4 (q), 157.4 (q). IR (powder, cm⁻¹) 635, 845, 1039, 1208, 1510, 2914. HRMS (ESI⁺, CH₃OH/CH₂Cl₂, 90:10, C₂₄H₂₈NO₃ [M + H]⁺) calcd for 378.20637, found 378.2067. The analytical data were in agreement with those reported in the literature.^[47]

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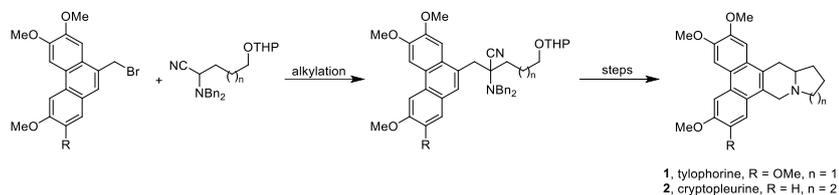
Keywords: Alkaloids • Fused Ring System • Lithiation • Phenanthroquinolizidine • Radical ion

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Tylophorine (**1**) and cryptopleurine (**2**) were synthesized by the condensation of metallated α -aminonitriles with bromomethylphenanthrenes to provide fully substituted α -aminonitriles that are submitted to a reductive decyanation to form homobenzylic amines. From these intermediates, the E- and D-rings of alkaloids **1** and **2** were formed through the displacement of a terminal leaving group and by a late Pictet-Spengler condensation, respectively.