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Total Syntheses of (±)-Cryptopleurine, (±)-Antofine and (±)-Deoxypergularinine

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Abstract: The alkaloids (±)-cryptopleurine **1**, (±)-antofine **2**, and (±)-deoxypergularinine **3** were synthesized by Pictet-Spengler cyclization of the 2-arylmethylpiperidine and -pyrrolidines **4, 5** and **6** obtained by sequential *N*-deprotection-reduction of the parent enecarbamates **7, 8** and **9**. These latter were made by the Horner reaction of phosphorylated carbamates **12** and **13** with the appropriate aldehydes **10** and **11**.

Keywords: Enecarbamates; Amines; Cyclization; Alkaloids.

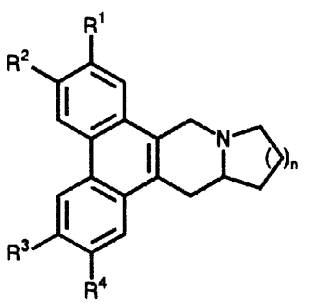
Introduction

Phenanthroizidine alkaloids are a small group of alkaloids belonging to the *Asclepiadaceae* family.[1-3] These natural products exhibit interesting biological properties, ranging from anti-tumour activity,[4,5] seemingly through inhibition of protein synthesis, to nerve growth stimulation and unusual cardiovascular and immunological effects, and even to probable anti-inflammatory action.[6] Most members of this small group of natural products display a phenanthroindolizidine framework as exemplified by antofine **2** and deoxypergularinine **3** (or deoxytylophorinine) although more rare phenanthroquinolizidines such as

1 $R^1 = H, R^2 = R^3 = R^4 = OMe;\ n = 2$

2 $R^1 = H, R^2 = R^3 = R^4 = OMe;\ n = 1$

3 $R^1 = R^2 = R^3 = OMe, R^4 = H;\ n = 1$



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cryptopleurine **1** are also known . As a result of their interesting biosynthesis,[1] these alkaloids have elicited lively synthetic efforts.[7] Numerous comprehensive reviews[1,2,8,9] are available which summarize efforts to determine chemical structure and stereochemistry and, most interesting of all, to synthesize these interesting heterocyclic compounds. The most commonly reported synthetic sequence towards the highly condensed compounds (±)-cryptopleurine,[10-18] (±)-antofine,[7,19-22] (±)-deoxypergularinine[23] involves, in the final step, the formation of the biaryl bond of the phenanthrene ring system after coupling the aromatic residues with the appropriate heterocycle. Ring closure of the pyrrolidine or piperidine-stilbene may be achieved by photochemical cyclization but oxidative annulation of the seco precursors with thallium (III) trifluoroacetate or vanadium (V) oxytrifluoride and radical-mediated cyclization of halogeno stilbene intermediates[24] to full-fledged phenanthroizidines have been also successfully accomplished. The other common sequence to these alkaloids involves differentially substituted phenanthrene starting materials which are coupled with the appropriate heterocycle through a halomethyl moiety. Completion of the alkaloid skeleton then proceeds invariably by Friedel-Crafts cyclization into the 9 or 10 positions of the phenanthrene nucleus and the construction of the central piperidine ring terminates the assemblage of the phenanthroizidine framework. More recently, sophisticated optically active syntheses of cryptopleurine **1**[24-26] and of the antipodal isomer of antofine **2**[27] with various levels of asymmetric induction have also appeared in the literature but several discrepancies with prior assignments have led to subjects of controversy.[25,26]

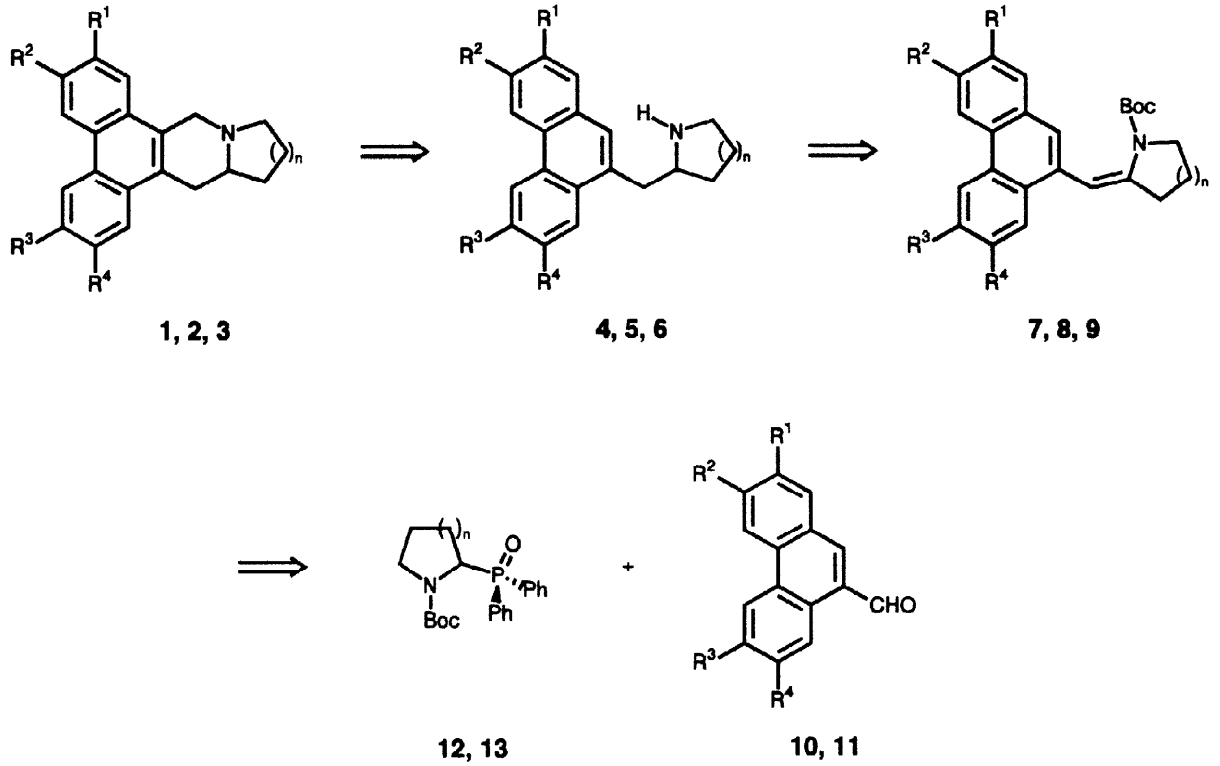
Although the total synthesis of phenanthroizidine alkaloids has been achieved by various groups, some of them based on biogenetic considerations,[10-12] we considered that for the convenient synthesis of an approachable range of phenanthroindo- and -quinolizidine natural products, a versatile procedure would be necessary and we thus set out to prepare the representative phenanthroindo- and -quinolizidine alkaloids cryptopleurine **1**, antofine **2** and deoxypergularinine **3** . Cryptopleurine **1** has been isolated from *Cryptocarya pleurosperma*[28,29] and *Boehmeria platyphilla*[30] and is the only known phenanthroquinolizidine alkaloid. Antofine **2** has been extracted from the bark of *Cynanchum vincetoxicum*[31] and deoxypergularinine **3** has been isolated from *Pergularia pallida*.[32] To the best of our knowledge only one synthesis of the latter alkaloid has been published.[23]

Results and discussion

Our strategy, which is depicted in the retrosynthetic Scheme 1, hinges upon the construction of the key intermediates enecarbamates **7-9** which possess the required structural features for the elaboration of the target natural products **1-3** . The synthesis of these protected enamines offers, if feasible, a double advantage. Indeed, the *N-tert*-butoxycarbonyl group of the dehydro precursors **7-9** can be easily removed under mild acidic conditions and the transient deprotected iminium ions can be easily reduced to deliver the 2-arylmethylpiperidine and -pyrrolidine derivatives **4**, **5** and **6** respectively. Final ring closure by Pictet-Spengler annulation should complete the synthesis of the highly condensed natural products **1-3** .

For the elaboration of the required parent enecarbamates we decided to apply a synthetic methodology which has been successfully developed for the synthesis of a wide range of *N*-acyl enamine derivatives.[33-36] The

procedure relies on the Horner reaction of the *N*-Boc-protected phosphorylated piperidine **12** and the pyrrolidine **13** with the differentially trialkoxy-substituted phenanthroic carboxaldehydes **10** and **11** .



1, 2, 3 **4, 5, 6** **7, 8, 9**

12, 13 **10, 11**

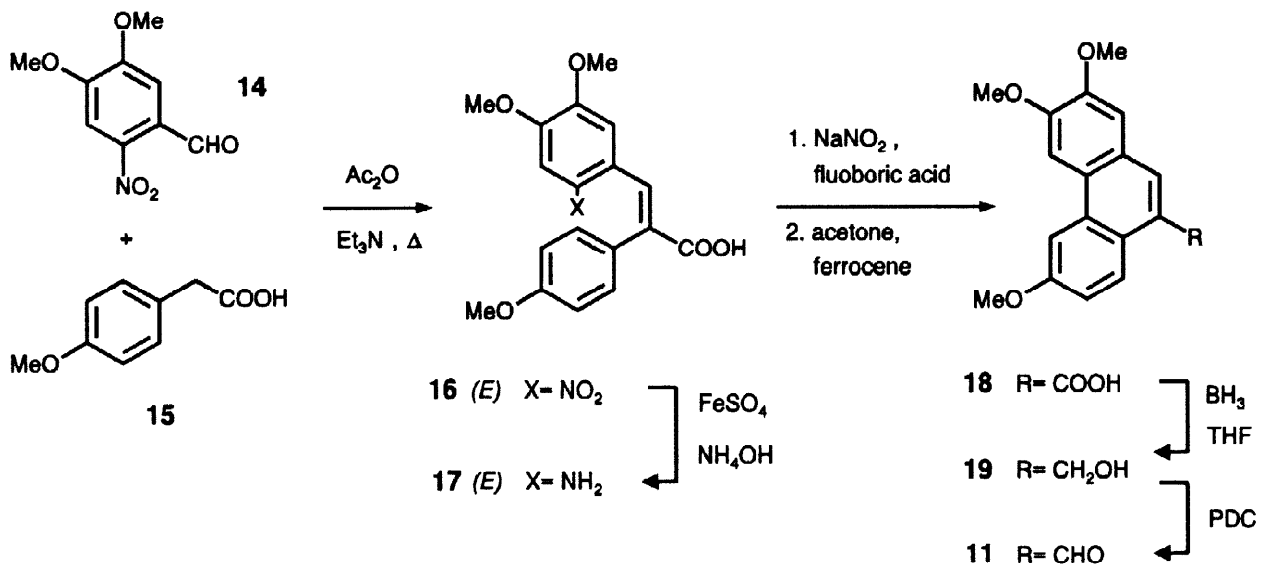
Compound	n	R^1	R^2	R^3	R^4
1, 4, 7	2	H	OMe	OMe	OMe
2, 5, 8	1	H	OMe	OMe	OMe
3, 6, 9	1	OMe	OMe	OMe	H
10	-	H	OMe	OMe	OMe
11	-	OMe	OMe	OMe	H

Scheme 1.

Initially the phosphorylated cyclic carbamates **12** (n = 2) and **13** (n = 1) were readily prepared by treatment of the corresponding phosphorylated cyclic amines with di-*tert*-butyl dicarbonate.[34,37]

Two different synthetic approaches were adopted for the elaboration of the second partners in the Horner reaction, namely the phenanthroic carboxaldehydes **10** and **11**, which differ by the construction of the phenanthrene unit. Thus, the former was readily accessible by applying a reported procedure in which the phenanthrene nucleus results from the vanadium oxytrifluoride mediated cyclization of a stilbenic precursor.[16] On the other hand, the phenanthroic carboxaldehyde **11** was prepared by adapting a recently reported procedure involving as the key step the formation of the phenanthrene unit by an improved free-radical Pschorr cyclization of an appropriately substituted stilbenic acid[38] (Scheme 2).

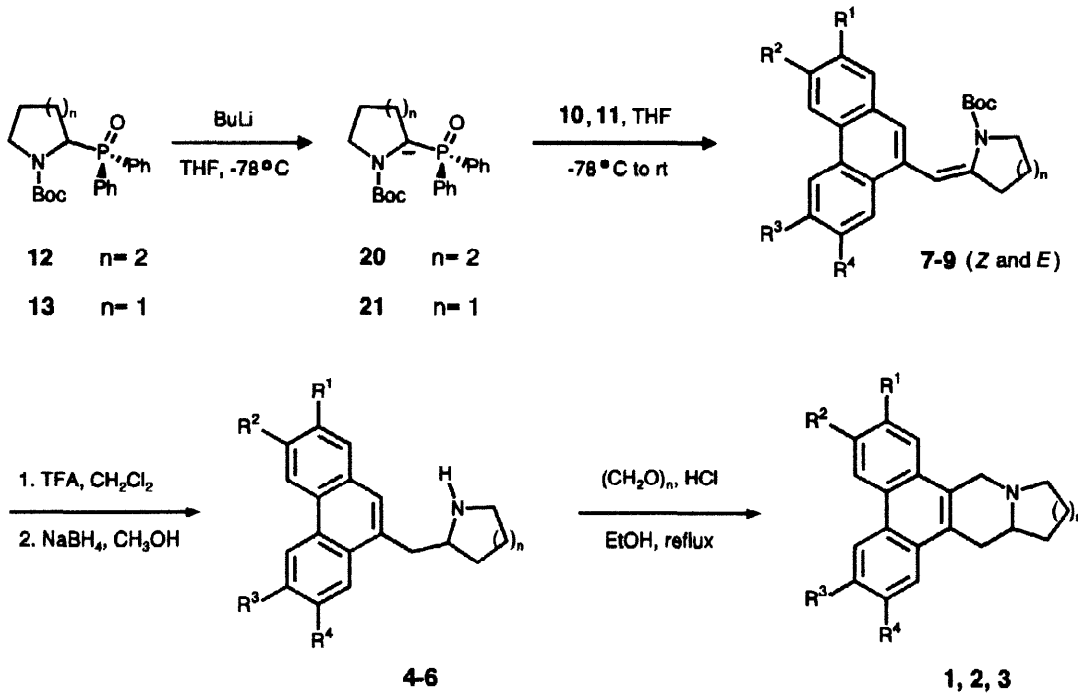
Initially the Perkin condensation involving the *o*-nitrobenzaldehyde derivative **14** and the phenylacetic acid **15** followed by reduction with ammoniacal ferrous sulfate of the intermediate nitrostilbenic derivative **16***(E)* provided the stilbenic acid **17***(E)* in a satisfactory yield (71%). This acid was easily converted by treatment with sodium nitrite in 48% fluoroboric acid into the diazonium tetrafluoroborate which was efficiently cyclized in anhydrous acetone with 20 mol % of catalytic ferrocene. This protocol delivered the phenanthroic acid **18** with a consistently high yield (90%). Conversion of the aromatic acid **18** into the alcohol **19** was performed by adapting the method of Buckley and Rapoport[26] and final oxidation with pyridinium dichromate terminated the synthesis of the required phenanthroic carboxaldehyde **11** in a very satisfactory overall yield (53% over five steps).



Scheme 2.

Exposure of the phosphorylated cyclic carbamates **12** and **13** to *n*-butyllithium at -78 °C in THF induced the formation of the phosphorylated α-aminocarbanions **20** and **21** (Scheme 3). The suitably substituted phenanthroic aldehydes **10** or **11** were then added and the reaction mixture was warmed to room temperature to ensure completion of the reaction; the *N*-tert-butoxycarbonyl-2-arylmethyl piperidine **7** and pyrrolidines **8**, **9** were quantitatively formed and isolated in high yields by this protocol (Scheme 3, Table). The phenanthroic enecarbamates were invariably obtained as mixtures of *Z*- and *E*-isomers (Table) but stereochemical consideration of the central double bond was not crucial for the outcome of the total synthesis with which we were concerned. Indeed, all attempts to perform asymmetric hydrogenation on the required *Z*-configured systems, even with Ru^{II} dicarboxylato-BINAP complexes which have been successfully used with enamides,[39,40] were unrewarding since reduction occurred preferentially at the sensitive 9,10 carbon-carbon double bond of the phenanthrene nucleus[41] under the hydrogenation conditions employed.

The structures and the stereochemical assignments of the enecarbamates **7-9** were unambiguously established from their ^1H NMR spectra with the help of NOE experiments whereby the irradiation of the vinylic proton (δ 6.20 ppm for **8**) showed a NO effect on the allylic proton (δ 2.32 ppm for **8**) which attests a *Z*-geometric configuration. Enecarbamates **7**, **8** and **9** appeared to be ideal substrates for the elaboration of the 2-arylmethylpiperidine **4** and -pyrrolidines **5**, **6**. Indeed *N*-deprotection of the enecarbamates **7-9** with



Scheme 3.

Table. Compounds **1-9** Prepared

					Enecarbamates			2-Arylmethyl cyclic amines		Target natural products	
R^1	R^2	R^3	R^4	n		*Z/E* ratio	Yield (%)		Yield (%)		Yield (%)
H	OMe	OMe	OMe	2	**7**	- :100	75	**4**	85	**1**	69
H	OMe	OMe	OMe	1	**8**	30:70	68	**5**	80	**2**	65
OMe	OMe	OMe	H	1	**9**	35:65	70	**6**	83	**3**	75

trifluoroacetic acid and subsequent reduction of the transient iminium ions were performed as a single, one-pot reaction and this procedure afforded straightforwardly the 2-arylmethyl piperidine **4** and pyrrolidines **5, 6** in fairly good yields (Scheme 3, Table). Pictet-Spengler cyclomethylenation of amines **4-6** by reaction with formaldehyde in boiling acidic aqueous ethanol generated the central piperidine template and consequently completed the synthesis of the target natural products **1-3** (Scheme 3, Table). The constitutions of the final compounds **1-3** were secured by matching their ^1H and ^{13}C NMR, IR, UV and mass spectra with those published for the natural and synthetic compounds by previous investigators.[10-23]

Conclusion

In summary, the total syntheses of (±)-cryptopleurine, (±)-antofine and (±)-deoxypergularinine which emphasize the synthetic potential of enecarbamates[42] have been accomplished. We also believe that this work

demonstrates general new methodology widely adaptable for the preparation of other naturally occurring phenanthroquinolizidine and -indolizidine alkaloids as well as their biogenetically related congeners.

Experimental

General.

Methanol and ethanol were distilled from magnesium turnings. Tetrahydrofuran (THF) and ether (Et_2O) were pre-dried with anhydrous Na_2SO_4 and distilled over sodium benzophenone ketyl under Ar before use. CH_2Cl_2, NEt_3, toluene were distilled from CaH_2. Dry glassware was obtained by oven-drying and assembly under dry Ar. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. For flash chromatography, Merck silica gel 60 (230-400 mesh ASTM) was used. The melting points were taken on a Reichert-Thermopan apparatus and are not corrected. Unless otherwise stated, proton, carbon and phosphorus NMR spectra were taken with $CDCl_3$ as solvent at 300, 75 and 121 MHz respectively on a Bruker AM 300 spectrometer. Microanalyses were performed by the CNRS microanalysis centre.

Phosphorylated carbamates 12 *and* 13.

1-*tert*-butoxycarboxy-2-diphenylphosphinylpiperidine **12** and -pyrrolidine **13** were prepared in the following manner. A solution of di-*tert*-butyl dicarbonate (24 g, 110 mmol) in dry THF (10 mL) was added dropwise under Ar to a solution of the corresponding phosphorylated amines[34,37] (100 mmol) in THF (50 mL) and the mixture was refluxed under Ar for 3 h. Then the solvent was removed under vacuum. Recrystallization of the residue from hexane-toluene afforded the phosphorylated carbamates **12, 13**.

1-tert-*butoxycarboxy-2-diphenylphosphinylpiperidine* **12** : (78 %) mp 147-148°C; IR (KBr, υ cm^{-1}): 1674 (CO), 1157 (PO); ^1H NMR δ (mixture of two rotational isomers A and B, 75:25) 1.10 (s, 9H, $C(CH_3)_3$, B), 1.13 (s, 9H, $C(CH_3)_3$), A), 1.21-1.38 (m, 1H, CH_2, A+B), 1.75-1.88 (m, 4H, $2CH_2$, A+B), 2.14-2.35 (m, 1H, CH_2, A+B), 3.29 (t, J = 12.5 Hz, 1H, NCH_2, A), 3.29 (t, J = 12.2 Hz, 1H, NCH_2, B), 3.77 (d, J = 13.3 Hz, 1H, NCH_2, A), 4.07 (d, J = 12.5 Hz, 1H, NCH_2, B), 4.77 (d, J = 3.9 Hz, 1H, CH-P, B), 5.10 (d, J = 3.9 Hz, 1H, CH-P, A), 7.17-7.48 (m, 6H, H_{arom}, A+B), 7.55-7.88 (m, 4H, H_{arom}, A+B); ^{13}C NMR δ (mixture of two rotational isomers A and B, 75:25) **C** 154.4 (CO, A), 153.6 (CO, B), 132.4 (d, J = 78.5 Hz), 79.8, **CH** 131.5 (d, J = 18 Hz), 130.8 (d, J = 8 Hz), 128.6 (d, J = 10.5 Hz), 127.9 (d, J = 13 Hz), 51.5 (d, J = 75.5 Hz, B), 49.6 (d, J = 77.5 Hz, A), **CH_2** 42.7 (A), 41.4 (B), 25.4 (A), 25.2 (B), 25.1 (B), 24.3 (A), 20.6 (B), 20.5 (A), **CH_3** 28.1 (A), 28.0 (B); ^{31}P NMR δ (mixture of two rotational isomers A and B, 75:25) 35.2 (A), 33.5 (B). Anal. Calcd for $C_{22}H_{28}NO_3P$: C, 68.57; H, 7.27; N, 3.63. Found: C, 68.41; H, 7.12; N, 3.71.

1-tert-*butoxycarboxy-2-diphenylphosphinylpyrrolidine* **13** : (72 %) mp 114-115°C; IR (KBr, υ cm^{-1}): 1675 (CO), 1166 (PO); ^1H NMR δ (mixture of two rotational isomers A and B, 60:40) 0.98 (s, 9H, $C(CH_3)_3$, B), 1.14 (s, 9H, $C(CH_3)_3$), A), 1.89-2.45 (m, 4H, $2CH_2$, A+B), 3.33-3.62 (m, 2H, NCH_2, A+B), 4.72 (brs, 1H, CH-P, B), 4.79 (brs, 1H, CH-P, A), 7.17-7.52 (m, 6H, H_{arom}, A+B), 7.60-7.92 (m, 4H, H_{arom}, A+B); ^{13}C NMR δ (mixture

of two rotational isomers A and B, 60:40) **C** : 154.2 (CO, A), 154.0 (CO, B), 130.9 (d, J = 81 Hz), 79.4, **CH** 131.5 (d, J = 8 Hz), 131.4 (d, J = 9 Hz), 128.6 (d, J = 11 Hz), 57.9 (d, J = 81 Hz, B), 57.4 (d, J = 74 Hz, A), **CH_2** 47.0 (A+B), 27.0 (B), 26.2 (A), 25.1 (A), 23.9 (B), **CH_3** 28.0 (A+B); ^{31}P NMR δ (mixture of two rotational isomers A and B, 60:40) 33.6 (A), 32.7 (B). Anal. Calcd for $C_{21}H_{26}NO_3P$: C, 67.92; H, 7.01; N, 3.77. Found: C, 67.99; H, 7.11; N, 3.83.

***Phenanthroic aldehydes* 10, 11.**

9-Formyl-3,6,7-trimethoxyphenanthrene **10** was synthesized following an already reported procedure[43] : (29 % over 5 steps); mp 139-140°C (Lit.[43] 136-144°); ^{1}H NMR δ 3.98 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 7.15 (d, J = 8.9 Hz, 1H, H_{arom}), 7.61 (d, J = 2.0 Hz, 1H, H_{arom}), 7.64 (s, 1H, H_{arom}), 7.77 (d, J = 8.9 Hz, 1H, H_{arom}), 7.86 (s, 1H, H_{arom}), 10.09 (s, 1H, CHO); ^{13}C NMR δ **C** 161.1, 150.5, 149.1, 134.0, 127.4, 124.7, 124.2, 123.8, **CH** 193.7, 140.2, 132.0, 116.0, 106.2, 103.8, 102.9, **CH_3** 55.9, 55.7, 55.5.

9-Formyl-2,3,6-trimethoxyphenanthrene **11**.

A solution of 6-nitroveratraldehyde **14**[44] (2.5 g, 12 mmol), NEt_3 (1.2 g, 12 mmol), 4-methoxyphenylacetic acid (2.82 g, 17 mmol) was refluxed with stirring under Ar for 20 min. Water (40 mL) was added to the reaction mixture and during the addition the temperature was maintained between 90°C and 100°C. The reaction mixture was cooled to rt then to 0°C and the solid was collected by filtration and recrystallized from EtOH to afford the acid **16***(E)* (3.3 g, 78 %); mp 183-184°C (lit.[45] 185-186°C).

To a solution of the acid **16***(E)* (2.5 g, 7mmol) in 10% aqueous NH_4OH (100 mL) was added ferrous sulfate heptahydrate (15 g) dissolved in distilled water (100 mL) and concentrated aqueous NH_4OH (100 mL). The reaction mixture was refluxed for 1 h, cooled to rt, filtered on Celite® and acidified with acetic acid (100 mL). The solid was collected by filtration and recrystallization from EtOH yielded the aminostilbenic acid **17***(E)* (2.1 g, 91%); mp 207-208°C (lit.[45] 206-207°C).

A solution composed of **17***(E)* (1 g, 3 mmol), NaOH (0.13 g, 3.3 mmol) and $NaNO_2$ (0.22 g, 3 mmol) in water (10 mL) was added dropwise over 30 min with stirring to 48% fluoboric acid (7.6 g, 43 mmol) at 0-5°C. The mixture was stirred for 1 h after which sulfamic acid was added until the mixture tested negative to starch-iodide paper. The crude solid was collected by filtration, dissolved in anhydrous acetone (10 mL) and then added dropwise with stirring over a 5 min period to ferrocene (0.056 g, 0.3 mmol) in acetone (5 mL) at rt. After an additional 15 min of stirring the green reaction mixture was added to water (100 mL). A light-yellow precipitate was collected and trace amounts of ferrocene were removed under vacuum to afford the acid **18** (430 mg, 90%) which was finally recrystallized from EtOH; mp 219-220°C (lit.[45] 222°C).

To a stirred solution of acid **18** (5 g, 16 mmol) in THF (100 mL) was added BH_3.THF (1M, 29 mL) over 1 h at 0°C. Upon completion of addition, the reaction mixture was stirred at rt for another 1 h, quenched with AcOH (10 mL). After evaporation the residue was partitioned between 100 mL portions of CH_2Cl_2 and 1N NaOH. The

organic layer was dried, filtered and evaporated, affording alcohol **19** (4.5 g, 94%); mp 187-188°C (EtOH, lit.[46] 186°C).

To a solution of alcohol **19** (2 g, 6.7 mmol) in CH_2Cl_2 (50 mL) was added pyridinium dichromate (3g, 8 mmol) and the reaction mixture was stirred under Ar for 4 h. Anhydrous Et_2O (50 mL) was added, the mixture was filtered on Celite®, the filtrate washed with saturated aqueous $NaHCO_3$ (20 mL). The organic layer was dried (Na_2SO_4) and the residue obtained after removal of the solvent was purified by flash column chromatography using AcOEt-hexanes (2:3) as eluent to afford 9-formyl-2,3,6-trimethoxyphenanthrene **11** (1.75 g, 88%) which was recrystallized from hexane-CH_2Cl_2; mp 160-161°C (lit.[47] 161°C); ^{1}H NMR δ 4.01 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 4.09 (s, 3H, OCH_3), 7.29 (s, 1H, H_{arom}), 7.30 (dd, J = 9.2, 2.5 Hz, 1H, H_{arom}), 7.80 (s, 1H, H_{arom}), 7.83 (d, J = 2.5 Hz, 1H, H_{arom}), 7.97 (s, 1H, H_{arom}), 9.30 (d, J = 9.2 Hz, 1H, H_{arom}), 10.23 (s, 1H, CHO); ^{13}C NMR δ **C** 162.8, 158.7, 152.2, 149.9, 138.4, 128.6, 125.3, 122.0, **CH** 193.5, 131.7, 127.7, 116.1, 109.5, 104.6, 103.4, **CH_3** 56.1, 56.0, 55.5.

***General procedure for the preparation of the enecarbamates* 7 *and* 8, 9.**

A commercial solution of *n*-BuLi (1.6M in hexanes, 1.8 mL, 2.86 mmol) was added dropwise to a solution of the phosphorylated carbamate **12, 13** (2.6 mmol) in THF (30 mL) at -78°C under Ar. After completion of the addition the mixture was stirred at -78°C for 15 min. A solution of the appropriate aldehyde **10, 11** (2.6 mmol) in THF (5 mL) was then added. After being stirred at -78°C for 15 min the reaction mixture was allowed to come to room temperature over 2 h. Saturated aqueous NH_4Cl (20 mL) was added and the organic layer separated. The aqueous layer was extracted with Et_2O (2 x 50 mL) and the combined organic layers were washed successively with water and brine and finally dried over $MgSO_4$. Evaporation of the solvent furnished an oily product which was purified by flash column chromatography using AcOEt-hexanes (2:3) as eluent. The products were finally purified by recrystallization from hexane-toluene.

Enecarbamate **7** : *(E)*-isomer, mp 135-136°C; IR (KBr, υ cm^{-1}): 1684 (CO); ^{1}H NMR (C_6D_6) δ 1.30-1.34 (m, 4H, CH_2), 1.51 (s, 9H, $C(CH_3)_3$), 2.19 (t, J = 5.5 Hz, 2H, $=CCH_2$), 3.54 (s, 6H, $2OCH_3$), 3.58 (s, 3H, OCH_3), 3.67 (t, J = 4.2 Hz, 2H, NCH_2), 7.04 (s, 1H, H_{vinyl}), 7.20 (dd, J = 8.7, 2.4 Hz, 1H, H_{arom}), 7.62 (s, 1H, H_{arom}), 7.69 (d, J = 8.7 Hz, 1H, H_{arom}), 7.95 (s, 1H, H_{arom}), 7.96 (s, 1H, H_{arom}), 8.02 (d, J = 2.4 Hz, 1H, H_{arom}); ^{13}C NMR (C_6D_6) δ: **C** 158.9 (CO), 154.4, 150.9, 150.4, 141.0, 131.5, 130.3, 126.7, 125.4, 79.6; **CH,** 130.5, 125.3, 123.2, 116.0, 108.2, 104.9, 104.6; **CH_2** 47.4, 28.5, 26.1, 25.8; **CH_3** 55.9, 55.7, 55.1, 28.6; Anal. Calcd for $C_{28}H_{33}NO_5$: C, 72.57; H, 7.13; N, 3.02. Found: C, 72.66; H, 7.09; N, 3.09.

Enecarbamate **8** : *(E)*- and *(Z)*-isomers (ratio 70:30 from ^{1}H NMR spectrum). *(E)*-isomer, IR (KBr, υ cm^{-1}): 1691 (CO); ^{1}H NMR (C_6D_6) δ 1.36-1.51 (m, 2H, CH_2), 1.53 (s, 9H, $C(CH_3)_3$), 2.43 (td, J = 7.2, 1.7 Hz, 2H, $=CCH_2$), 3.49 (t, J = 6.9 Hz, 2H, NCH_2), 3.57 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 7.16 (dd, J = 8.9, 2.1 Hz, 1H, H_{arom}), 7.20 (s, 1H, H_{vinyl}), 7.43 (s, 1H, H_{arom}), 7.49 (s, 1H, H_{arom}), 7.71 (d, J = 8.9 Hz, 1H, H_{arom}), 7.83 (d, J = 2.1 Hz, 1H, H_{arom}), 7.90 (s, 1H, H_{arom}); ^{13}C NMR (C_6D_6) δ: **C** 158.6 (CO), 153.0, 150.7, 150.1, 142.0, 131.5, 130.0, 127.3, 126.1, 124.3, 80.1, **CH** 129.7, 124.5, 115.3, 106.1, 105.5, 103.9, 103.6, **CH_2**

49.6, 31.0, 22.2, **CH_3** 55.6, 55.3, 55.1, 28.6; *(Z)*-isomer, ^{1}H NMR (C_6D_6, partial) δ 2.32 (t, *J* = 6.9 Hz, 2H, =CCH_2), 3.35 (t, *J* = 6.6 Hz, 2H, NCH_2), 3.54 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 6.20 (s, 1H, H_{vinyl}), 7.13 (d, *J* = 8.7, 2.0 Hz, 1H, H_{arom}), 7.45 (s, 1H, H_{arom}), 7.53 (s, 1H, H_{arom}), 7.73 (d, *J* = 8.7 Hz, 1H, H_{arom}), 7.80 (d, *J* = 2.0 Hz, 1H, H_{arom}), 7.93 (s, 1H, H_{arom}). Anal. Calcd for $C_{27}H_{31}NO_5$: C, 72.16; H, 6.90; N, 3.12. Found: C, 72.20; H, 6.93; N, 3.05.

Enecarbamate **9** : *(E)*- and *(Z)*-isomers (ratio 65:35 from ^{1}H NMR spectrum). *(E)*-isomer, IR (KBr, υ cm^{-1}): 1691 (CO); ^{1}H NMR (C_6D_6) δ 1.22-1.35 (m, 2H, CH_2), 1.54 (s, 9H, $C(CH_3)_3$), 2.46 (t, *J* = 6.8 Hz, 2H, =CCH_2), 3.41 (t, *J* = 6.7 Hz, 2H, NCH_2), 3.62 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 7.09-7.18 (m, 3H, $2H_{arom}$ + H_{vinyl}), 7.47 (s, 1H, H_{arom}), 7.91 (s, 1H, H_{arom}), 8.08 (d, *J* = 2.0 Hz, 1H, H_{arom}), 8.45 (d, *J* = 8.9 Hz, 1H, H_{arom}); ^{13}C NMR (C_6D_6) δ: **C** 158.8 (CO), 153.0, 150.8, 149.9, 141.9, 133.6, 126.7, 126.5, 124.2, 80.2, **CH** 132.2, 123.9, 115.2, 109.0, 106.4, 105.2, 104.8, **CH_2** 49.6, 30.9, 22.2, **CH_3** 55.7, 55.4, 55.0, 28.6; *(Z)*-isomer ^{1}H NMR (C_6D_6, partial) δ 2.30 (t, *J* = 7.0 Hz, 2H, =CCH_2), 3.61 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.75 (t, *J* = 6.9 Hz, 2H, NCH_2), 6.24 (s, 1H, H_{vinyl}), 7.32 (dd, *J* = 9.0, 2.3 Hz, 1H, H_{arom}), 7.87 (s, 1H, H_{arom}), 8.20 (d, *J* = 9.0 Hz, 1H, H_{arom}). Anal. Calcd for $C_{27}H_{31}NO_5$: C, 72.16; H, 6.90; N, 3.12. Found: C, 72.20; H, 6.93; N, 3.05.

***General procedure for the synthesis of the 2-arylmethylpiperidine* 4 *and -pyrrolidine* 5, 6.**
Trifluoroacetic acid (1.1 mL, 11 mmol) was added under Ar with stirring to a solution of the enecarbamates **7** and **8, 9** (1.1 mmol) in anhydrous CH_2Cl_2 (2 mL) and stirring was maintained overnight. Evaporation of the solvent and excess reagent under vacuum left a residue which was dissolved in anhydrous MeOH (30 mL). Sodium borohydride (430 mg, 11.1 mmol) was then added portionwise at 0°C and the reaction mixture was stirred at this temperature for an additional 1 h. EtOAc (50 mL) was then added and the organic solution was washed twice with aqueous NH_4OH (2 x 40 mL) then with water and brine and finally dried over Na_2SO_4. The solvent was removed under vacuum to leave an oily residue which was recrystallized from hexane-toluene.

Piperidine **4** : mp 122-123°C; ^{1}H NMR δ 1.27-1.63 (m, 3H, CH_2), 1.72-2.11 (m, 4H), 2.46 (td, *J* = 11.5, 2.7 Hz, 1H), 2.84-3.06 (m, 3H), 3.20 (brd, *J* = 10.3 Hz, 1H), 3.99 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 4.09 (s, 3H, OCH_3), 7.17 (dd, *J* = 8.7, 2.3 Hz, 1H, H_{arom}), 7.39 (s, 1H, H_{arom}), 7.48 (s, 1H, H_{arom}), 7.72 (d, *J* =8.7 Hz, 1H, H_{arom}), 7.82 (d, *J* = 2.3 Hz, 1H, H_{arom}), 7.82 (s, 1H, H_{arom}); ^{13}C NMR δ **C** 157.9, 149.2, 148.7, 130.4, 129.7, 126.7, 125.9, 124.9, **CH** 129.8, 126.0, 115.4, 105.1, 104.0, 103.9, 56.5, **CH_2** 47.1, 41.5, 33.3, 26.0, 24.9, **CH_3** 56.4, 56.0, 55.6. Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.62; H, 7.40; N, 3.83. Found: C, 75.69; H, 7.35; N, 3.86.

Pyrrolidine **5** : mp 145-146°C; ^{1}H NMR δ 1.36-1.90 (m, 4H, CH_2), 2.31-2.80 (m, 2H), 2.91-3.25 (m, 3H), 3.42-3.55 (m, 1H), 3.97 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 7.14 (dd, *J* = 8.0, 2.0 Hz, 1H, H_{arom}), 7.41 (s, 1H, H_{arom}), 7.46 (s, 1H, H_{arom}), 7.70 (d, *J* =8.6 Hz, 1H, H_{arom}), 7.78 (d, *J* = 2.0 Hz, 1H, H_{arom}), 7.86 (s, 1H, H_{arom}); ^{13}C NMR δ **C** 157.9, 149.3, 148.7, 130.6, 130.4, 126.7, 126.0, 124.8, **CH** 129.7, 125.2, 115.4, 104.8, 103.9, 103.8, 58.6, **CH_2** 45.9, 39.5, 31.6, 24.7, **CH_3** 56.0, 55.9, 55.5. Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.21; H, 7.12; N, 3.99. Found: C, 75.26; H, 7.18; N, 3.90.

Pyrrolidine **6** : mp 140-141°C; ^{1}H NMR ($CDCl_3$) δ 1.38-1.92 (m, 4H, CH_2), 2.23-2.56 (brs, 1H, NH), 2.72-2.84 (m, 1H), 2.93-3.18 (m, 3H), 3.33-3.52 (m, 1H), 3.97 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 7.14 (s, 1H, H_{arom}), 7.18 (dd, J = 9.0, 2.3 Hz, 1H, H_{arom}), 7.37 (s, 1H, H_{arom}), 7.79 (s, 1H, H_{arom}), 7.85 (d, J = 2.3 Hz, 1H, H_{arom}), 8.00 (d, J = 9.0 Hz, 1H, H_{arom}); ^{13}C NMR δ **C** 157.8, 149.5, 148.7, 132.4, 131.6, 127.4, 125.1, 123.5, **CH** 126.1, 124.1, 114.8, 108.0, 104.6, 103.3, 59.1, **CH_2** 46.1, 39.8, 31.6, 24.8, **CH_3** 56.0, 55.8, 55.5. Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.21; H, 7.12; N, 3.99. Found: C, 75.17; H, 7.19; N, 4.06.

***General procedure for the synthesis of (±)-cryptopleurine* 1, *(±)-antofine* 2 *and (±)-deoxypergularinine* 3.**
A solution of amine **4-6** (0.5 mmol), EtOH (5 mL) and formaldehyde (37%, 1.4 mL) was acidified with 0.5 ml of concentrated aqueous HCl and boiled under reflux for 12 h in the dark. The volatiles were removed by rotary evaporation, and the residue was dissolved in CH_2Cl_2 (15 mL) and treated with 10 mL of HCl (10%). The aqueous layer was washed with CH_2Cl_2 (10 mL) and the combined organic extracts were washed with water, brine and dried over Na_2SO_4. The dried solution was subjected to rotary evaporation and the residual solid was recrystallized from $CHCl_3$-MeOH. The analytical and spectral data of synthetic **1-3** matched those reported for the natural products.

(±)-Deoxypergularinine **3** : ^{13}C NMR δ **C** 157.3, 149.2, 148.4, 130.1, 127.2, 126.8, 125.5, 124.1, 123.4, **CH** 124.3, 114.7, 104.8, 103.9, 103.6, 60.2, **CH_2** 55.4, 53.9, 33.8, 31.4, 21.6, **CH_3** 56.0, 55.8, 55.6.

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