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The Intramolecular Aryne Cycloaddition Approach to Aporphinoids. A New Total Synthesis of Aristolactams and Phenanthrene Alkaloids

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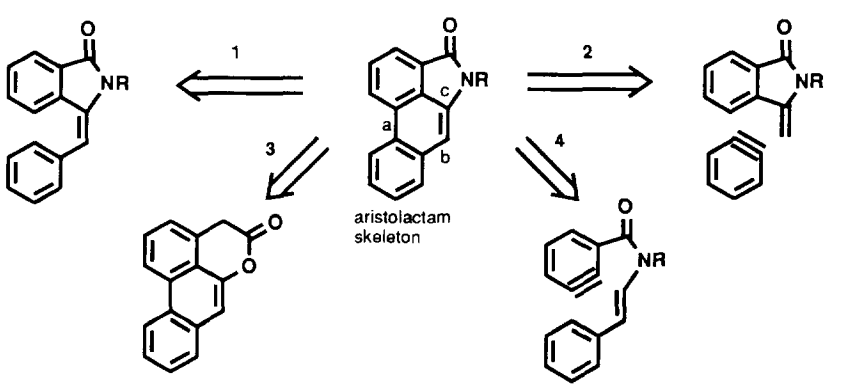
Abstract. A new procedure for the total synthesis of aristolactams and phenanthrene alkaloids, based on the intramolecular Diels-Alder reaction between styrenes and arynes, is described.

The aporphinoids are a large group of alkaloids biogenetically derived from isoquinolines that includes compounds such as aporphines, aristolactams and phenanthrene alkaloids. Despite receiving considerable chemical attention owing to their pharmacological properties, satisfactory syntheses of these alkaloids are few and often afford moderate to poor yields.[1] The search for new synthetic strategies for the preparation of aporphinoids therefore continues to be necessary.

Our work on new approaches to the syntheses of aporphinoids began some time ago and as a part of this work we have developed three alternative routes to the synthesis of aristolactams (Scheme 1). The key step in our first approach was formation of the bi-arylic bond **a** of the phenanthrene ring system by photocyclization (route 1);[2] our second approach involved the simultaneous formation of bonds **a** and **b** by an intermolecular benzyne cycloaddition (route 2);[3] and our third approach involved contraction of the lactone ring of

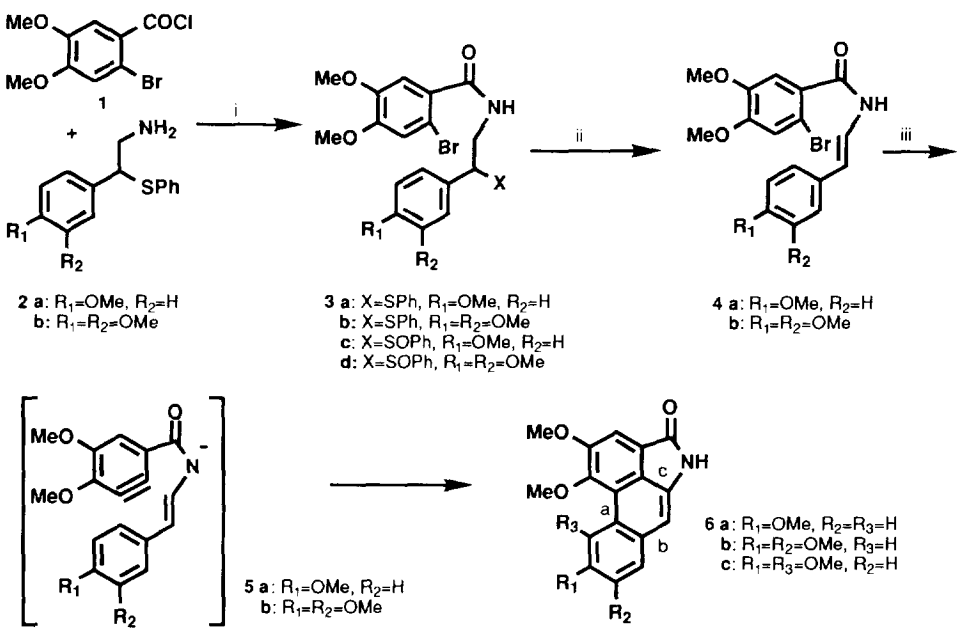


Scheme 1: *Retrosynthetic scheme for the synthesis of aristolactams*

dehydrodibenzochromanones, and subsequent lactamization of the resulting five membered lactone (route 3); the bi-arylic bond of the chromanones was formed by means of a highly efficient tributyltin-mediated radical cyclization of 2′-bromophenylactetylphenylacetic acids.[4] A further approach to aristolactams would be the simultaneous formation of bonds **a** and **c** of the tetracyclic ring system by intramolecular cycloaddition of arynes generated from *N*-styrylamides having an appropriate carbon skeleton and functionality (route 4).

As predicted, *N*-styrylamides **4** undergo a dehydrohalogenation typical of aryl halides upon treatment with LDA, and the resulting aryne intermediates **5** can be cyclized intramolecularly to afford the desired phenanthrenic ring system **6** (Scheme 2).[5] Herein we give a full account of application of this strategy to the synthesis of aristolactams, and report its extension to synthesis of aporphinoid derivatives (Schemes 3 and 4).

N-Styrylbromobenzamide **4a** (Scheme 2) was obtained, following our general procedure,[6] by oxidizing *N*-phenylethylbromobenzamide **3a** (prepared by reaction of bromobenzoyl chloride **1** with phenylethylamine **2a**) to sulfoxide **3c**, and then heating this with sodium carbonate in toluene. In the subsequent key cycloaddition step, **4a** was added to a cooled (0°C) solution of LDA in THF (prepared *in situ* from *n*-BuLi and diisopropylamine), from which, following work-up, the aristolactam **6a** was isolated in 35% yield. The spectroscopic data of **6a** agree with those reported for the naturally occurring compound.[7]



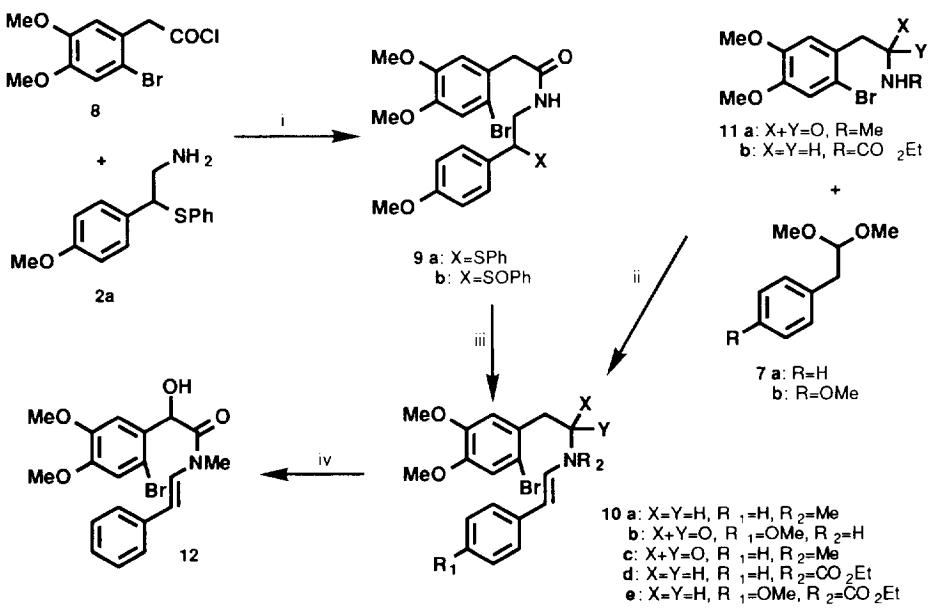
Scheme 2. *Reagents:* i) NaOH, diethyl ether/water, rt, 1h. ii) Na_2CO_3, toluene, reflux, 6h. iii) LDA, THF, rt, 1h.

Confirmation of the utility of this synthetic strategy was obtained by the analogous transformation of *N*-styrylbromobenzamide **4b** (prepared similarly to **4a**, from benzoyl chloride **1** and phenylethylamine **2b**)[6] into a mixture of aristolactams **6b** and **6c** (both isolated in approximately 15% yield each), also by treating it with LDA in cool THF (0 °C). This result indicates that the cyclization of the aryne intermediate **5b** shows no

preference for either of the two possible cyclization products. It should be noted that aristolactam **6c** is the first example of a 1,2,10,11-tetrasubstituted aristolactam.[1g, 8]

Next we applied the IAC (Intramolecular Aryne Cycloaddition) approach to the synthesis of aporphines. Previously, attempts to obtain aporphines from enamines such as **10a** using this approach have produced isoindole compounds.[9] It occurred to us that this might be due to the availability of the unshared electron pair of the nitrogen, and that protection of this atom and/or formation of the amide might facilitate aporphine synthesis. Accordingly, our first approach was to use the *N*-styrylamides **10b** and **10c** (Scheme 3), which are similar to the precursors used in the preparation of aristolactams.

N-styrylamide **10b** was prepared by condensation of bromophenylacetyl chloride **8** with phenylethylamine **2a**, oxidation of the sulfide product **9a** to a sulfoxide **9b**, and elimination of the sulfoxide.[6] *N*-methyl-*N*-styrylamide **10c** was easily prepared by condensation of *N*-methylphenylacetamide **11a** and acetal **7a**.[10] However, neither **10b** nor **10c** proved appropriate starting materials for the preparation of aporphines: **10b** was stable in LDA under the conditions described for aristolactam preparation, while treatment of **10c** with LDA in dry THF at 0°C gave compound **12**, probably by metalation and subsequent oxidation at the benzylic position (Scheme 3).



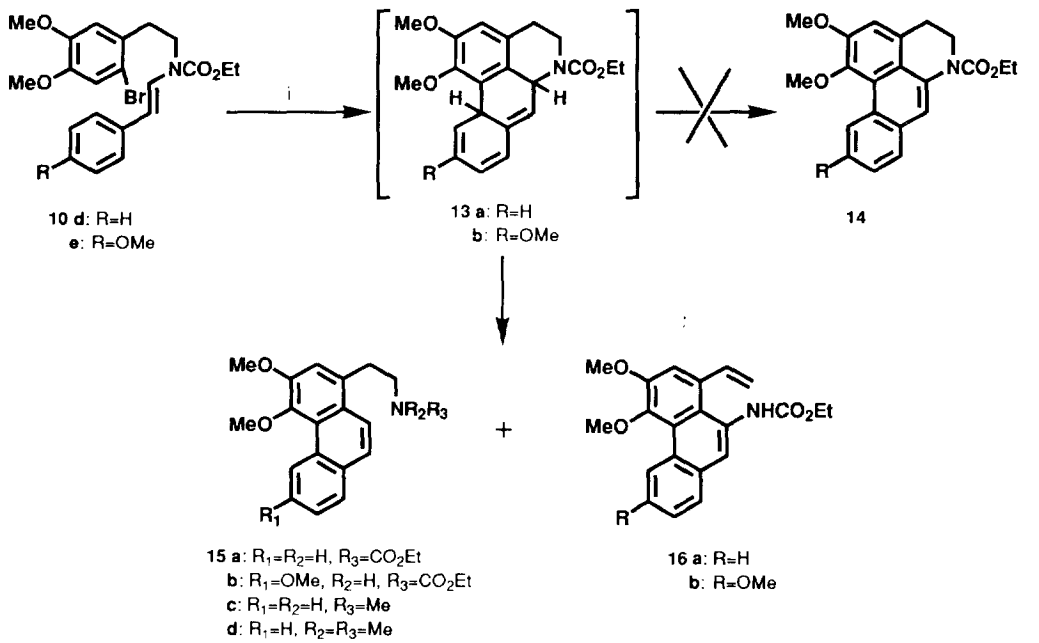
Scheme 3 *Reagents:* i) NaOH, diethyl ether/water, rt, 1h. ii) CF_3CO_2H, molecular sieve, benzene, reflux, 12h. iii) Na_2CO_3, toluene, reflux, 6h. iv) LDA, THF, rt, 1h.

These unsatisfactory results led us to try protecting the nitrogen atom of the required styryl-compounds by formation of the corresponding urethane. *N*-Styrylurethane **10d** was obtained easily and in very good yield by condensation of the commercially available acetal **7a** with *N*-carbethoxybromophenylethylamine **11b**.[10] When **10d** was treated with LDA in dry THF at 0°C, the expected *N*-carbethoxyaporphine **14** was not obtained

(Scheme 4). Rather, the major reaction product was the phenanthrene **15a**[11] (60% yield), which gave *N*-noratherosperminine **15c**[12] upon reduction with LAH, and can also be easily transformed into atherosperminine (**15d**)[11]. A minor reaction product identified as the phenanthrene **16a** (15% yield), was also isolated.

N-Styrylurethane **10e**, which was easily prepared by condensation of *N*-carbethoxy-bromophenylethylamine **11b** with acetal **7b**[10] (prepared[13] from 4-methoxybenzaldehyde), gave similar results upon treatment with LDA, as above: a mixture of phenanthrene **15b** (56% yield) and a small amount of phenanthrene **16b** (11% yield) was obtained.

These results showed that, while the desired IAC reaction was more efficient for phenylethylamines than for benzamides, the initial adducts **13** underwent further transformations under the basic reaction conditions, giving phenanthrenes **15** and **16**.



Scheme 4. *Reagents:* i) LDA, THF, rt, 1h.

In summary, the application of intramolecular Diels-Alder methodology allowed easy preparation of aristolactams and phenanthrene alkaloids, constituting a new application of enamides in natural product synthesis.[14]

EXPERIMENTAL SECTION

Melting points were determined on a Kofler Thermogerate apparatus and are uncorrected. Infrared spectra were recorded in a Perkin Elmer 1420 spectrophotometer; nuclear magnetic resonance spectra of samples in deuterochloroform solution containing tetramethylsilane as internal standard were recorded in a Bruker WM-250 apparatus; and mass spectra were obtained in a Kratos MS 50 TC mass spectrometer. Thin layer chromatography (tlc) was performed on Merck GF-254 type 60 silica gel plates using dichloromethane-methanol mixtures as eluant and ultraviolet light or iodine vapour to visualize the tlc spots. Column chromatography was carried out using Merck type 9385 silica gel. Solvents were purified as per ref. 15 and dried with anhydrous sodium sulphate. Compounds **2a** and **2b** were prepared as per ref. 16; compound **11a** as per ref. 17; compound **11b** as per ref. 10; and compound **7b** as per ref. 13.

***N*-[2-(4'-Methoxyphenyl)-2-phenylthioethyl]-2-bromo-4,5-dimethoxybenzamide (3a).**

A mixture of 2-bromo-4,5-dimethoxybenzoic acid[18] (0.8 g, 3.1 mmol) and thionyl chloride (5 ml) was refluxed under a dry atmosphere (calcium chloride tube) for 1 h. Excess solvent was removed in a rotary evaporator and the residue was dissolved in dry diethyl ether (10 ml). This solution was added dropwise over 5 min to a cooled (0 °C) stirred mixture of 2-(4'-methoxyphenyl)-2-phenylthioethylamine (**2a**)[16] (0.79 g, 3.1 mmol), diethyl ether (10 ml) and 10% aqueous sodium hydroxide solution (7 ml), which was then left at room temperature for 1 hour. The diethyl ether was evaporated and the mixture was diluted in water (100 ml) and extracted with methylene chloride (3x25 ml). The combined organic layers were washed with 10% hydrochloric acid (50 ml) and with water (50 ml) and then dried, and the solvent was evaporated *in vacuo* to afford *N*-phenylethylbromobenzamide **3a** (1.4 g, 91% yield) as an amorphous solid. IR (film; ν/cm^{-1}): 3290 (-NH), 1640 (C=O). ^1H NMR, δ/ppm: 3.78-3.98 (m, 11H, 3x-OCH_3 and -CH_2-), 4.47 (t, J=7.8 Hz, 1H, -CH-), 6.50 (bs, 1H, -NH), 6.84 (d, J=8.6 Hz, 2H, 2xAr-H), 6.92 (s, 1H, Ar-H), 7.10 (s, 1H, Ar-H), 7.22-7.26 (m, 5H, 5xAr-H), 7.34-7.38 (m, 2H, 2xAr-H). EI/MS, m/z (%): 394 (29), 392 (28), 245 (97), 243 (100), 229 (56), 134 (91). Anal.: required for $C_{24}H_{24}BrNO_4S$, C 57.37, H 4.81, N 2.79; found, C 57.08, H 4.66, N 2.51.

***N*-[2-(4'-Methoxyphenyl)-2-phenylsulfinylethyl]-2-bromo-4,5-dimethoxybenzamide (3c).**

To a solution of *N*-phenylethylbromobenzamide **3a** (0.75 g, 1.5 mmol) in methanol (150 ml), cooled in an ice-water bath, a solution of sodium periodate (0.5 g) in a minimal amount of water was added dropwise over 5 min. The mixture was stirred at room temperature for 48 hours and the white solid formed was filtered out and washed with ethyl acetate. The filtrate was concentrated *in vacuo* and the solid residue was redissolved in methylene chloride (75 ml). This solution was washed with water (2x30 ml) and dried, and then the solvent was evaporated to afford a quantitative yield of sulfoxide **3c** (0.77 g), which was used directly for preparation of **4a**.

***(E)*-*N*-(4'-Methoxystyryl)-2-bromo-4,5-dimethoxybenzamide (4a).**

Anhydrous sodium carbonate (0.19 g) was added to a stirred solution of sulfoxide **3c** (0.77 g, 1.5 mmol) in dry toluene (30 ml), and the mixture was refluxed under argon for 6 h. The solvent was removed *in vacuo* and the solid residue was suspended in water (100 ml) and extracted with methylene chloride (3x25 ml). The combined

organic layers were dried and the solvent was evaporated *in vacuo*, to afford a quantitative yield of *N*-styrylbromobenzamide **4a** (0.58 g). M.p. 149-150 °C (methanol). IR (KBr; ν/cm^{-1}): 3240 (-NH), 1640 (C=O). ^1H NMR, δ/ppm: 3.80 (s, 3H, -OCH_3), 3.88 (s, 6H, 2x-OCH_3), 6.22 (d, J=14.6 Hz, 1H, -CH=C-), 6.85 (d, J=8.3 Hz, 2H, 2xAr-H), 6.99 (s, 1H, Ar-H), 7.26-7.31 (m, 3H, 3xAr-H), 7.55 (dd, J=14.6 and 10.5 Hz, 1H, -C=CH-), 8.22 (d, J=10.5 Hz, 1H, -NH). EI/MS, m/z (%): 393 (M^+, 26), 391 (M^+, 26), 245 (98), 243 (100). Anal.: required for $C_{18}H_{18}BrNO_4$, C 55.12, H 4.62, N 3.57; found, C 55.26 H 4.43, N 3.29

3,4,6-Trimethoxyaristolactam (6a).

n-Butyl lithium 1.55 M (0.78 ml, 1.20 mmol) was added dropwise to a cooled (0 °C) solution of diisopropylamine (0.17 ml, 1.2 mmol) in dry THF (5 ml), stirring under argon, stirred at room temperature for 20 minutes. After recooling the reaction mixture to 0°C, a cooled (0°C), stirred solution of *N*-styrylbromobenzamide **4a** (0.1 g, 0.25 mmol) in dry THF (3 ml) was added dropwise to it (still under argon) over 10 min, whereupon the mixture was stirred for 1 h. Water (1 ml) was added dropwise, and then the quenched reaction mixture was concentrated *in vacuo* to a solid residue, which was suspended in water (25 ml) and extracted with methylene chloride (3x10 ml). The combined organic layers were dried and, after removal of the solvent in a rotary evaporator, the solid residue was purified by preparative tlc (chloroform/methanol, 99:1) to give **6a** (27 mg, 35% yield) as yellow solid. M.p. 200-201 °C (methanol). UV (ethanol; λ_{max}/nm): 236, 295, 305, 390. IR (KBr; ν/cm^{-1}): 3150 (-NH), 1680 (C=O). ^1H NMR, δ/ppm: 3.99 (s, 3H, -OCH_3), 4.07 (s, 3H, -OCH_3), 4.13 (s, 3H, -OCH_3), 7.04 (s, 1H, Ar-H), 7.22 (dd, J=8.8 and 2.7 Hz, 1H, Ar-H), 7.72 (d, J= 8.8 Hz, 1H, Ar-H), 7.83 (s, 1H, Ar-H), 7.86 (bs, 1H, -NH), 8.81 (d, J= 2.7 Hz, 1H, Ar-H). EI/MS, m/z (%): 310 [$(M+1)^+$, 21], 309 (M^+, 100), 294 (20), 279 (50), 264 (24), 192 (23). Anal.: required for $C_{18}H_{15}NO_4$, C 69.89, H 4.89, N 4.53; found, C 69.76, H 5.03, N 4.79.

***N*-[2-(3',4'-Dimethoxyphenyl)-2-phenylthioethyl]-2-bromo-4,5-dimethoxybenzamide (3b).**

2-Bromo-4,5-dimethoxybenzoic acid[18] (0.98 g, 3.8 mmol) was converted into the corresponding bromobenzoyl chloride **1**. Subsequently, treatment of 2-(3',4'-dimethoxyphenyl)-2-phenylthioethylamine (**2b**) (1.1 g, 3.8 mmol) with this bromobenzoyl chloride **1** under the conditions described for the preparation of **3a** afforded *N*-phenylethylbromobenzamide **3b** (1.7 g, 84% yield) as an amorphous solid. IR (KBr; ν/cm^{-1}): 3320 (-NH), 1630 (C=O). ^1H NMR, δ/ppm: 3.75-4.01 (m, 14H, 4x-OCH_3 and -CH_2-), 4.45 (t, J=7.5 Hz, 1H, -CH-), 6.45 (bs, 1H, -NH), 6.89 (s, 1H, Ar-H), 7.06 (s, 1H, Ar-H), 7.22-7.26 (m, 8H, 8xAr-H). EI/MS, m/z (%): 533 (M^+, 5), 531 (M^+, 5), 245 (85), 243 (87), 134 (100) . Anal.: required for $C_{25}H_{26}BrNO_5S$, C 56.39, H 4.92, N 2.63; found, C 56.31, H 5.01, N 2.49.

***N*-[2-(3',4'-Dimethoxyphenyl)-2-phenylsulfinylethyl]-2-bromo-4,5-dimethoxybenzamide (3d).**

Using the oxidation procedure described for preparation of **3c**, *N*-phenylethylbromobenzamide **3b** (1 g, 1.9 mmol) was quantitatively converted into sulfoxide **3d** (1 g), which was used directly for preparation of **4b**.

***(E)*-*N*-(3',4'-Dimethoxystyryl)-2-bromo-4,5-dimethoxybenzamide (4b).**

Treatment of sulfoxide **3d** (1g, 1.8 mmol) with sodium carbonate (0.23 g) in toluene (36 ml), as described for **4a**, gave a quantitative yield of *N*-styrylbromobenzamide **4b** (0.77 g). M.p. 168-169 °C (methanol). IR (KBr; ν/cm^{-1}): 3240 (-NH), 1640 (C=O), 1600, 1520. ^1H NMR, δ/ppm: 3.86 (s, 6H, 2x-OCH_3), 3.88 (s, 6H,

2x-OCH_3), 6.23 (d, J=14.6 Hz, 1H, -CH=C-), 6.67-6.91 (m, 3H, 3xAr-H), 6.92 (s, 1H, Ar-H), 6.97 (s, 1H, Ar-H), 7.55 (dd, J=14.6 and 10.6 Hz, 1H, -C=CH-), 8.36 (d, J=10.6 Hz, 1H, -NH). EI/MS, m/z (%): 423 (M^+, 12), 421 (M^+, 12), 372 (16), 253 (100), 225 (85), 223 (84), 165 (90), 151 (55). Anal.: required for $C_{19}H_{20}BrNO_5$ C 54.04, H 4.77, N 3.32; found, C 53.86, H 4.89, N 3.15.

3,4,6,7-Tetramethoxyaristolactam (6b) and 3,4,5,6-tetramethoxyaristolactam (6c).

Reaction of *N*-styrylbromobenzamide **4b** (0.1 g, 0.24 mmol) with LDA, as described for **6a**, gave a solid residue which was subjected to HPLC (PARTISIL M9 10/50 ODS-3 reverse phase column), using 80:20 methanol-water (3 ml/min) as eluent. After 18 and 24 min respectively, the known 3,4,6,7-tetramethoxyaristolactam (**6b**)[2] (14 mg, 18% yield) and 3,4,5,6-tetramethoxyaristolactam (**6c**) (12 mg, 15% yield) were obtained and in both cases isolated as yellow solids. **6c.** M.p. 215-216 °C (methanol). UV (ethanol, λ_{max}/nm): 220, 270, 297, 380. IR (KBr; ν/cm^{-1}) 3200 (-NH), 1680 (C=O). ^1H NMR, δ/ppm: 3.77 (s, 3H, -OCH_3), 3.85 (s, 3H, -OCH_3), 4.03 (s, 3H, -OCH_3), 4.08 (s, 3H, -OCH_3), 7.03 (s, 1H, Ar-H), 7.30 (d, J=8.6 Hz, 1H, Ar-H), 7.53 (d, J=8.6 Hz, 1H, Ar-H), 7.85 (s, 1H, Ar-H), 8.50 (bs, 1H, -NH). EI/MS, m/z (%): 340 [$(M+1)^+$, 25], 339 (M^+, 100), 324 (19), 311(12), 296 (17). Anal.: required for $C_{19}H_{17}NO_5$, C 67.25, H 5.05, N 4.13; found, C 67.49, H 5.10, N 4.28.

***N*-[2-(4'-Methoxyphenyl)-2-phenylthioethyl]-2-bromo-4,5-dimethoxyphenylacetamide (9a).**

Starting from phenylethylamine **2a** (1.1 g, 4.2 mmol) and 2-bromo-4,5-dimethoxyphenylacetic acid[17] (1.17 g, 4.2 mmol), applying the procedure described for **3a**, *N*-phenylethylbromophenylacetamide **9a** (1.8 g, 82% yield) was obtained as an amorphous solid. IR (KBr; ν/cm^{-1}): 3300 (-NH), 1660 (C=O). ^1H NMR, δ/ppm: 3.53-3.93 (m, 2H, -CH_2-), 3.55 (s, 2H, -CH_2-), 3.78 (s, 3H, -OCH_3), 3.80 (s, 3H, -OCH_3), 3.86 (s, 3H, -OCH_3), 4.26 (t, J=7.3 Hz, 1H, -CH-), 5.64 (bs, 1H, -NH), 6.71 (s, 1H, Ar-H), 6.76 (d, J=8.7 Hz, 2H, 2xAr-H), 6.96 (s, 1H, Ar-H), 7.08 (d, J=8.7 Hz, 2H, 2xAr-H), 7.11-7.30 (m, 5H, 5xAr-H). EI/MS, m/z (%): 408 (36), 406 (36), 231 (39), 229 (84), 150 (100). Anal.: required for $C_{25}H_{26}BrNO_4S$ C 58.14, H 5.07, N 2.71; found, C 58.39, H 5.29, N 2.79.

***N*-[2-(4'-Methoxyphenyl)-2-phenylsulfinylethyl]-2-bromo-4,5-dimethoxyphenylacetamide (9b).**

Using the procedure described for **3c**, *N*-phenylethylbromophenylacetamide **9a** (1 g, 1.9 mmol) was oxidized in quantitative yield to sulfoxide **9b** (1 g), which was isolated as an unstable gum. This was used directly for preparation of **10b**.

***(E)*-*N*-(4'-Methoxystyryl)-2-bromo-4,5-dimethoxyphenylacetamide (10b).**

Treatment of sulfoxide **9b** (0.9 g, 1.7 mmol) with anhydrous sodium carbonate (0.21 g) and toluene (34 ml), as described for **4a**, gave *N*-styrylbromophenylacetamide **10b** in quantitative yield (0.68 g) . M.p. 161-162 °C (methanol). IR (KBr; ν/cm^{-1}): 3290 (-NH), 1640 (C=O). ^1H NMR, δ/ppm: 3.74 (s, 2H, -CH_2-), 3.79 (s, 3H, -OCH_3), 3.88 (s, 3H, -OCH_3), 3.89 (s, 3H, -OCH_3), 5.98 (d, J=14.5 Hz, 1H, -CH=C-), 6.82 (d, J=8.6 Hz, 2H, 2xAr-H), 6.86 (s, 1H, Ar-H), 7.07 (s, 1H, Ar-H), 7.20-7.26 (m, 3H, 2xAr-H and -NH), 7.36 (dd, J=14.5 and 10.7 Hz, 1H, -C=CH-). EI/MS, m/z (%): 407 (M^+, 23), 405 (M^+, 23), 326 (18), 231 (28), 229 (29), 149 (100). Anal.: required for $C_{19}H_{20}BrNO_4$, C 56.17, H 4.96, N 3.45; found, C 56.39, H 4.65, N 3.70.

***(E)-N-* Methyl-*N*-styryl-2-bromo-4,5-dimethoxyphenylacetamide (10c).**

A solution of *N*-methyl-2-bromo-4,5-dimethoxyphenylacetamide (**11a**)[17] (1.5 g, 5.21 mmol), phenylacetaldehydedimethylacetal (1.39 g, 8.37 mmol) and trifluoroacetic acid (2.76 g, 24.21 mmol) in dry benzene (100 ml) was refluxed over molecular sieve (10 g) and under argon for 12 h. The solids were filtered out, and the filtrate was concentrated *in vacuo* to afford a solid residue, which was suspended in water (100 ml) and extracted with methylene chloride (3x25 ml). The combined organic layers were dried and the solvent was removed in a rotary evaporator. Flash chromatography (eluent: 99:1 methylene chloride:methanol) of the solid residue afforded *N*-methyl-*N*-styrylbromophenylacetamide **10c** (1.4 g, 69%) as a white solid. M.p. 82-83 °C (methanol). IR (KBr; ν/cm^{-1}): 1670 (C=O) and 1640 (C=O). ^1H NMR, δ/ppm: 3.26 (s, 3H, N-CH_3), 3.83 (s, 3H, -OCH_3), 3.86 (s, 3H, -OCH_3), 3.93 and 4.01 (2xs, 2H, -CH_2-), 5.96 and 6.02 (2d, J=15.0 and J=14.1 Hz, 1H, -CH=C-), 6.80 (s, 1H, Ar-H), 7.04 (s, 1H, Ar-H), 7.17-7.34 (m, 5H, 5xAr-H), 7.42 and 8.12 (2d, J=15.0 and 14.1 Hz, 1H, -C=CH-). EI/MS, m/z (%): 391 (M^+, 6), 389 (M^+, 6), 310 (74), 231 (53), 229 (55), 151 (46), 133 (100), 91 (54). Anal.: required for $C_{19}H_{20}BrNO_3$, C 58.47, H 5.16, N 3.59; found, C 58.35, H 5.35, N 3.86.

***N*-Methyl-*N*-styryl-2-(2'-bromo-4',5'-dimethoxyphenyl)-2-hydroxyacetamide (12).**

Treatment of *N*-methyl-*N*-styrylbromophenylacetamide **10c** (50 mg, 0.13 mmol) with LDA as described for **6a** gave, in quantitative yield (52 mg), *N*-methyl-*N*-styrylbromophenylhydroxyacetamide **12** as a white solid. M.p. 148-149 °C (methanol). IR (KBr; ν/cm^{-1}): 1640 (C=O). ^1H NMR, δ/ppm: 3.25 (s, 3H, -N-CH_3), 3.90 (s, 6H, 2x-OCH_3), 5.57 (s, 1H, -CH-), 5.74 (d, J=14.3 Hz, 1H, -C=CH-), 6.85 (s, 1H, Ar-H), 6.98 (s, 1H, Ar-H), 7.09-7.14 (m, 1H, Ar-H), 7.25-7.34 (m, 4H, 4xAr-H), 7.51 (d, J=14.3 Hz, 1H, -CH=C-). EI/MS, m/z (%): 407 (M^+, 8), 405 (M^+, 8), 284 (31), 91 (100) Anal.: required for $C_{19}H_{20}BrNO_4$, C 56.17, H 4.96, N 3.45; found, C 56.34, H 4.92, N 3.36.

***(E)-N*-Carbethoxy-*N*-styryl-2-(2'-bromo-4',5'-dimethoxyphenyl)ethylamine (10d).**

Reaction of *N*-carbethoxy-2-bromo-4,5-dimethoxyphenylethylamine (**11b**)[10] (0.6 g, 1.8 mmol) and phenylacetaldehydedimethylacetal (0.48 g, 2.88 mmol) under the conditions described for **10c**, afforded *N*-carbethoxy-*N*-styrylbromophenylethylamine **10d** (0.63 g, 80% yield) as a white solid. M.p. 49-50 °C (methanol). IR (KBr; ν/cm^{-1}): 1660 (C=O). ^1H NMR, δ/ppm: 1.05-1.19 (m, 3H, -CH_3), 2.87-3.01 (m, 2H, -CH_2-), 3.71-3.94 (m, 8H, 2x-OCH_3 and -CH_2-), 4.01-4.16 (m, 2H, -CH_2-), 5.84-6.17 (m, 1H, -CH=C-), 6.57-6.79 (m, 1H, Ar-H), 6.93 (s, 1H, Ar-H), 7.06-7.64 (m, 6H, 5xAr-H and -C=CH-). EI/MS, m/z (%): 435 (M^+, 60]) 433 (M^+, 58), 354 (100), 204 (35), 100 (55). Anal.: required for $C_{21}H_{24}BrNO_4$ C 58.07, H 5.57, N 3.22; found, C 58.31, H 5.61, N 3.18.

***N*-Carbethoxy-3,4-dimethoxy-1-phenanthrenylethylamine (15a) and 10-*N*-carbethoxy-3,4-dimethoxy-1-phenanthrenylethene (16a).**

Treatment of *N*-carbethoxy-*N*-styrylbromophenylethylamine **10d** (0.5 g, 1.1 mmol) with LDA as described for compound **6a** gave, after flash chromatography (eluent: methylene chloride) of the resulting mixture, the known *N*-carbethoxyphenanthrenylethylamine **15a**[11] (245 mg, 60% yield) and *N*-carbethoxyphenanthrenylethene (**16a**) (60 mg, 15% yield). M.p. 86-87 °C (methanol). UV (ethanol, λ_{max}/nm): 221, 262, 253, 318, 381. IR (KBr; ν/cm^{-1}): 3320 (-NH), 1730 (C=O). ^1H NMR, δ/ppm: 1.34 (t,

J=7.1 Hz, 3H, -CH_3), 3.88 (s, 3H, -OCH_3), 4.05 (s, 3H, -OCH_3), 4.27 (q, J=7.1 Hz, 2H, -CH_2-), 5.47 (d, J=10.8 Hz, 1H, -CH=C-), 5.61 (d, J=17.1 Hz, 1H, -C=CH-), 7.05-7.95 (m, 7H, 5xAr-H, -CH=C- and -NH), 9.56 (d, J=9.4 Hz, 1H, Ar-H). EI/MS, m/z (%): 351 (M^+, 2), 262 (6), 44 (100). Anal.: required for $C_{21}H_{21}NO_4$, C 71.78, H 6.02, N 3.99; found, C 71.93, H 6.23, N 4.09.

***(E)*-*N*- Carbethoxy-*N*-(4'-methoxystyryl)-2-(2'-bromo-4',5'-dimethoxyphenyl)ethylamine (10e).**
Condensation of *N*-carbethoxybromophenylethylamine **11b** (1.0 g, 3.0 mmol) with 4-methoxyphenylacetaldehydedimethylacetal (**7b**)[13] (0.95 g, 4.8 mmol) under the conditions described for **10c** gave *N*- carbethoxy-*N*-styrylbromophenylethylamine **10e** (1.15 g, 82% yield) as a white solid. M.p. 57-58 °C (methanol). IR (KBr; ν/cm^{-1}): 1660 (C=O). ^1H NMR, δ/ppm: 1.15-1.41 (m, 3H, -CH_3), 2.89-3.08 (m, 2H, -CH_2-), 3.70-3.91 (m, 11H, 3x-OCH_3 and -CH_2-), 4.03-4.38 (m, 2H, -CH_2-), 5.91-6.18 (m, 1H, -CH=C-), 6.60-6.90 (m, 3H, 3xAr-H), 6.99 (s, 1H, Ar-H), 7.11-7.62 (m, 3H, 2xAr-H and -C=CH-). EI/MS, m/z (%): 465 (M^+, 3), 463 (M^+, 3) 244 (11), 229 (9), 135 (100). Anal.: required for $C_{22}H_{26}BrNO_5$, C 56.90, H 5.64, N 3.02; found, C 56.73, H 5.49, N 2.98.

***N*-Carbethoxy-(3,4,6-trimethoxy)-1-phenanthrenylethylamine (15b) and 10-*N*-carbethoxy-3,4,6-trimethoxy-1-phenanthrenylethene (16b).**
Proceeding as for the obtention of **15a** and **16a**, reaction of *N*- carbethoxy-*N*-styrylbromophenylethylamine **10e** (0.5 g, 1.1 mmol) with LDA afforded *N*-carbethoxyphenanthrenylethylamine **15b** (231 mg, 56% yield) and *N*-carbethoxyphenanthrenylethene **16b** (45 mg, 11%). Compound **15b**. M.p. 73-74 °C (methanol). UV (ethanol, λ_{max}/nm): 218, 260, 306, 318, 352, 372. IR (KBr; ν/cm^{-1}): 3360 (-NH), 1720 and 1615 (C=O). ^1H NMR, δ/ppm: 1.21-1.38 (m, 3H, -CH_3), 3.29-3.38 (m, 2H, -CH_2-), 3.50-3.63 (m, 2H, -CH_2-), 3.94 (s, 3H, -OCH_3), 4.00 (s, 3H, -OCH_3), 4.08 (s, 3H, -OCH_3), 4.18 (q, J=7.1 Hz, 2H, -CH_2-), 4.84 (m, 1H, -NH), 7.21-7.32 (m, 2H, 2xAr-H), 7.61 (d, J=9.0 Hz, 1H, Ar-H), 7.74-7.78 (m, 2H, 2xAr-H), 9.27 (d, J=2.3 Hz, 1H, Ar-H). EI/MS, m/z (%): 383 (M^+, 46), 337 (9), 291 (100), 267 (11). Anal.: required for $C_{22}H_{25}NO_5$, C 68.91, H 6.57, N 3.65; found, C 69.11, H 6.62, N 3.65. Compound **16b**. M.p. 97-98 °C (methanol). UV (ethanol, λ_{max}/nm): 224, 256, 262, 322, 376. IR (KBr; ν/cm^{-1}): 3340 (-NH), 1730 (C=O). ^1H NMR, δ/ppm: 1.33 (t, J=7.0 Hz, 3H, -CH_3), 3.89 (s, 3H, -OCH_3), 3.96 (s, 3H, -OCH_3), 4.04 (s, 3H, -OCH_3), 4.26 (q, J=7.0 Hz, 2H, -CH_2-), 5.43 (d, J=10.8 Hz, 1H, -CH=C-), 5.56 (d, J=17.1 Hz, 1H, -C=CH-), 7.00 (bs, 1H, Ar-H), 7.19-7.26 (m, 2H, 2xAr-H), 7.47 (dd, J=17.1 and 10.8 Hz, 1H, -C=CH-), 7.69 (d, J=8.7 Hz, 1H, Ar-H), 7.79 (bs, 1H, -NH), 9.17 (d, J=2.2 Hz, 1H, Ar-H). EI/MS, m/z (%): 381 (M^+, 100), 292 (41), 262 (19). Anal.: required for $C_{22}H_{23}NO_5$, C 69.28, H 6.08, N 3.67; found, C 69.07, H 6.17, N 3.89.

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