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Total syntheses of 1-methyl-1,2,3,4-tetrahydronaphtho[2,1-*f*]-isoquinolines involving free radical cyclizations induced by tributyltin(IV) hydride

Elena Martínez, Juan C. Estévez, Ramón J. Estévez* and Luis Castedo

Departamento de Química Orgánica and Unidad Asociada al Instituto de Investigaciones Químicas (CSIC), University of Santiago, 15706 Santiago de Compostela, Spain

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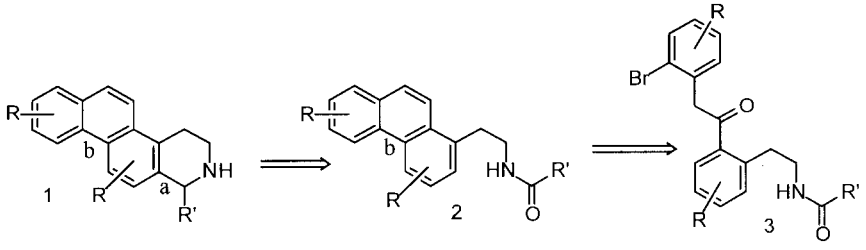
Abstract—We describe two total syntheses of 1-methyl-1,2,3,4-tetrahydronaphtho[1,2-*f*]isoquinolines based on free radical cyclization. One of them includes the cyclization of *N*-{2-[2-(2-bromophenyl)-1-methoxyethyl]phenylethyl}acetamides and subsequent transformation of the resulting *N*-[2-(10-methoxy-9,10-dihydro-1-phenanthryl)ethyl]acetamides. The second is based on the known cyclization of 1-(2-bromobenzyl)isochroman-3-ones to 4,5,6a,7-tetrahydrodibenzo[*de*,*g*]chroman-3-ones followed by transformation of the resulting 2-(1-phenanthryl)acetamides.

It is thought that naphthoisoquinolines may have antineoplastic properties: their tetracyclic ring system is similar to that of the carcinogenic hydrocarbon chrysene, but like the ring system of antibacterial and antitumoral benzophenanthridine alkaloids, includes a nitrogen atom.[1] Naphtho[1,2-*f*]-isoquinolines nevertheless received very little chemical attention[2] prior to the recent isolation of two members of this family, litebamine[3] and annoretine[4]. Subsequent partial synthesis of litebamine from the aporphine boldine led to the hypothesis of biogenetic degradation of aporphines to naphthoisoquinolines.[5,6] With a view to eventual corroboration of the structures proposed for litebamine and annoretine, and to the synthesis of other naphthoisoquinolines of possible chemical and biological interest, we have developed the first total synthesis of naphtho[1,2-*f*]isoquinolines **1** (Scheme 1).

Retrosynthetic considerations of structures **1** suggested a strategy based on formation of bonds **b** and **a**, in that order, starting from bromophenylacetylphenylethylacetamides **3**, which contain both a halogen atom conveniently placed for generation of the phenanthrene ring system by radical cyclization,[7] and a nitrogen substituent for final construction of the nitrogen ring by Bichler–Napieralski cyclization of compounds **2** (Scheme 1). We first studied the viability of this plan by applying it to **3a**, which was easily prepared by Friedel–Crafts acylation of *N*-acetylphenylethylamine **5a** with *o*-bromophenylacetyl chloride (**4b**).[8] Stirring a suspension of recently prepared **4b**, **5a** and $AlCl_3$ in nitromethane under argon for 3 h at room temperature, afforded **3a** in 65% yield (see Scheme 2); compound **3a** was reduced with $NaBH_4$ in methanol at room temperature to obtain methoxyphenylethylacetamide



Scheme 1.

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* Corresponding author. Tel.: +34-981-563100, ext. 14242; fax: +34-981-591014; e-mail: qorjec@usc.es

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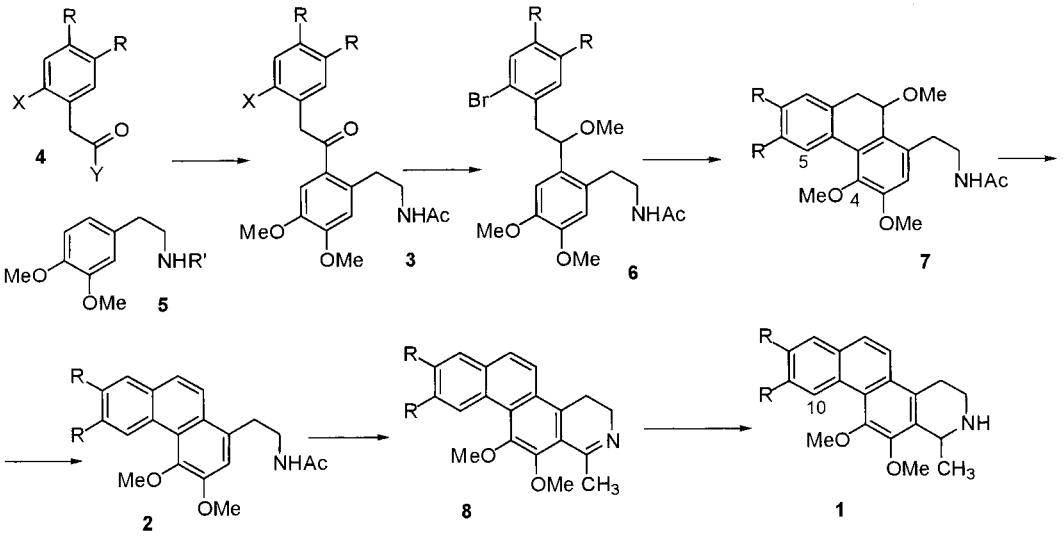
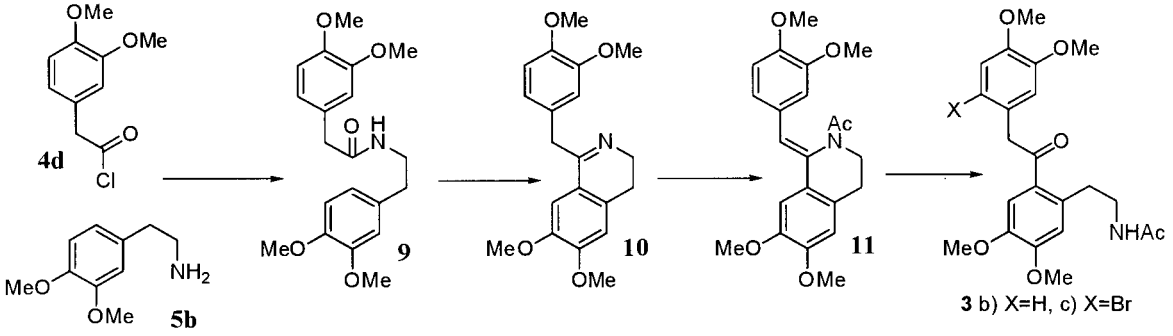


Scheme 2. 1, **2**, **6**, **7**, **8**: (a) R=H, (b) R=OMe, **3**: (a) R=H, X=Br; (b) R=OMe, X=H; (c) R=OMe, X=Br. **4**: (a) R=H, Y=OH, X=Br; (b) R=H, Y=Cl, X=Br; (c) R=OMe, Y=OH, X=H, (d) R=OMe, Y=Cl, X=H, **5**: (a) R′=Ac, (b) R′=H.

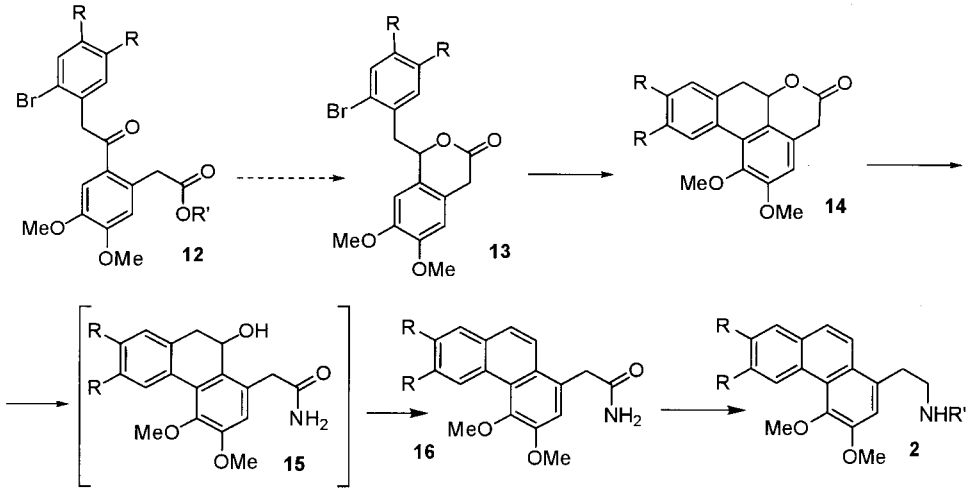
6a, which when refluxed with *n*-Bu_3SnH and AIBN in benzene for 9 h under argon[7d,9] afforded a 63% yield of the expected phenanthreneacetamide **7a**. Compound **7a** was easily identified from spectroscopic and analytical data: its ^1H NMR spectrum shows singlets at 3.28, 3.67 and 3.90 ppm corresponding to the three methoxy substituents (the 3.28 ppm signal belonging to the shielded methoxy at position C(4)), and signals for five aromatic protons (one less than the starting material), including a multiplet at 8.44 ppm for H(5), which is deshielded due to interaction with the methoxy substituent at C(4).

Treatment of methoxydihydrophenanthrene **7a** with 10% aq. HCl in dioxan at room temperature easily eliminated methanol to give phenanthrylethylacetamide **2a**, which was cyclized[10] to dihydronaphthoisoquinoline **8a** by refluxing with phosphoryl chloride in dry acetonitrile. Finally, compound **8a** was quantitatively reduced to naphthoisoquinoline **1a** when treated with $NaBH_4$ in methanol at room temperature. The structure of **1a** was deduced from microanalytic and spectroscopic data. Its tetrahydroisoquinoline character was established by the presence in its ^1H NMR spectrum of a doublet at 1.62 (3H) due to the methyl substituent and multiplets at 2.79–3.08 (2H), 3.22–3.39 (2H) and 4.61 (1H) ppm corresponding to the aliphatic protons on carbons on the nitrogen ring, while its phenanthrene character was confirmed by a multiplet at 9.63 ppm assigned to the deshielded proton at C(10).

We next applied the same strategy to the preparation of tetramethoxynaphthoisoquinoline **1b**. Attempts to prepare the required 2-bromophenyl-1-methoxyethylphenylethylacetamide **3c** in the same way as for **3a** (but introducing the bromine on **3b** to obtain **3c**) were unsuccessful; reacting dimethoxyphenylacetyl chloride **4d** with homoveratrylacetamide (**5a**) under the above Friedel–Crafts conditions afforded a complex reaction mixture, as in previous acylations with homoveratroyl chloride (**4d**)[11]. However, **3c** was successfully prepared by opening the nitrogen ring of *N*-acetyl-1-benzylideneisoquinoline **11** (Scheme 3).[12] To obtain **11**, phenylacetylphenylethylamide **9** was easily prepared from homoveratrylamine (**5b**) and phenylacetyl chloride (**4d**) and was then subjected to standard Bichler–Napieralski conditions to give benzyldihydroisoquinoline **10**,[10] which upon treatment with Ac_2O gave **11**. Refluxing **11** with 10% aq. HCl in methanol for 5 h then gave a 96% yield of the tetramethoxyphenylacetylphenylethylacetamide **3b** which was easily brominated in 86% yield by treatment with bromine in a mixture of glacial acetic acid and water at room temperature for 1 h. The presence of bromine at the required position of **3c** was easily established from its ^1H NMR spectrum, which exhibits singlets corresponding to



Scheme 3.



Scheme 4. 2: (a) R=H, R′=Ac; (b) R=OMe, R′=Ac; (c) R=R′=H; (d) R=Ome, R′=H, **12**, **13**, **14**, **15**, **16**: (a) R=H, (b) R=OMe.

four aromatic protons at 6.76, 6.77, 7.05 and 7.31 ppm. Note that preparation of **3b** involves the regiospecific intramolecular transfer of a phenylacetyl group from the nitrogen atom of phenylethylamide **9** to the desired *ortho* position in **3b** by a three-step sequence that includes a Bichler–Napieralski cyclization; this constitutes a way for acylating aromatic rings that is less dependent on the electronic properties of substituents than is Friedel–Crafts acylation.

Reduction of **3c** with $NaBH_4$ gave methoxyphenylethylphenylacetamide **6b** (Scheme 2), which was cyclized in 59% yield to phenanthreneacetamide **7b** when reacted with *n*-Bu_3SnH and AIBN as for **7a**. Subsequent treatment of **7b** with HCl led to phenanthrylethylacetamide **2b**, which was treated with $POCl_3$ to obtain dihydronaphthoisoquinoline **8b**, which was easily converted to tetramethoxynaphthoisoquinoline **1b** by reduction with $NaBH_4$. The spectra of **1b** are very similar to those of **1a**.

The moderate yields achieved in the radical cyclizations steps of the above syntheses led us to consider the alternative route of naphthoisoquinolines **1** starting from dibenzochromanones **14**, which we had previously obtained by *n*-Bu_3SnH-mediated radical cyclizations of benzylisochromanones **13** to dibenzochromanones **14**.[7c] In this work, the yields of cyclization of **13** to **14** are improved. Refluxing a solution of dimethoxybromobenzylisochromanone **13a**, *n*-Bu_3SnH and AIBN in benzene under argon for 9 h afforded **14a** in 76% yield (previous yield 45%). Subsequent opening of the lactone ring of **14a** by treatment with aq. ammonia furnished phenanthrylacetamide **16a** presumably by spontaneous dehydration of initially formed hydroxyphenanthrylacetamide **15a**, a process probably favoured by the gain in aromaticity. Compound **16a** was then reduced to the corresponding amine **2c**, which upon reaction with acetyl chloride gave **2a**. A similar sequence was used to cyclize tetramethoxybromobenzylisochromanone **13b** to the corresponding dibenzochromanone **14b** in 83% yield (previous yield 55%) and to transform this latter compound into phenanthrylacetamide **16b**, phenanthrylethylamine **2d** and phenanthrylethylacetamide **2b** (Scheme 4).

The above two syntheses constitute the first total syntheses of members of the new compounds **1a** and **1b** of the naphthoisoquinolines family. They confirm the usefulness of free radical cyclization for efficient construction of the bi-arylic bonds of phenanthrene systems.[7] It is envisaged that they may be used for preparation of the alkaloids litebamine and anoretine, and of other naphthoisoquinolines of potential pharmacological interest.

1. Experimental

Melting points were determined in a Kofler Thermogerate apparatus and are uncorrected. Infrared spectra were recorded on a MIDAC FTIR spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Bruker WM-250 apparatus, using deuteriochloroform solutions containing tetramethylsilane as internal standard. Mass spectra were obtained on a Kratos MS 50 TC mass spectrometer. Thin layer chromatography (TLC) was performed using Merck GF-254 type 60 silica gel and dichloromethane/methanol mixtures as eluant; the TLC spots were visualized with ultraviolet light or iodine vapor. Column chromatography was carried out using Merck type 9385 silica gel. Compounds **9** and **10** were prepared as per Ref. 9. Solvents were purified as per Ref. 13. Solutions of extracts in organic solvents were dried with anhydrous sodium sulphate.

1.1. General

1.1.1. *N*-{2-[2-(2-Bromophenyl)acetyl]-4,5-dimethoxyphenylethyl}acetamide (3a). A mixture of commercial *o*-bromophenylacetic acid (4.45 g, 20.7 mmol) and thionyl chloride (15 mL) was refluxed for 1 h under a dry atmosphere (calcium chloride tube). The excess thionyl chloride was evaporated in vacuo and the residue was dissolved in dry nitrobenzene (5 mL). This solution was added dropwise to a stirred suspension of aluminium trichloride (1.84 g, 13.8 mmol) in dry nitrobenzene (8 mL) cooled at 0°C in an ice/water bath, and to this mixture, maintained at 0°C, a solution of *N*-acetyl-3,4-dimethoxyphenylethylamine

(1.74 g, 7.8 mmol) in dry nitrobenzene (10 mL) was added dropwise over 15 min. The resulting mixture was stirred for 2.5 h at 35°C and then added to an ice/water mixture (100 mL). The nitrobenzene was evaporated by steam distillation and the mixture left was extracted with dichloromethane (3×50 mL). The pooled organic layers were washed with saturated sodium bicarbonate solution followed by water, dried and concentrated in vacuo to give an oil which when washed with a small volume of ethyl ether/ethyl acetate gave **3a** as a white solid that was separated by filtration (2.72 g, 83% yield). Mp 139–140°C (ethyl acetate). IR (ν, cm^{-1}, KBr): 3322 (–NH), 1666 (C═O), 1640 (C═O). ^1H NMR (δ, ppm): 1.87 (s, 3H, $-CH_3$), 2.95–3.02 (m, 2H, $-CH_2-$), 2.42–3.48 (m, 2H, $-CH_2-$), 3.92 (s, 3H, $-OCH_3$), 3.93 (s, 3H, $-OCH_3$), 4.39 (s, 2H, $-CH_2-$), 6.56 (bs, 1H, –NH), 6.78 (s, 1H, Ar–H), 7.12–7.38 (m, 4H, 4×Ar–H), 7.60 (m, 1H, Ar–H). MS (*m*/*z*, %): 421 (M^+, 1), 419 (M^+, 1), 361 (6), 208 (100), 191 847), 179 (20). Anal. calcd for $C_{20}H_{22}BrNO_4$, C 57.15, H 5.27, N 3.33; found, C 56.83, H 4.94, N 3.41.

1.1.2. *N*-{2-[2-(2-Bromophenyl)-1-methoxyethyl]-4,5-dimethoxyphenylethyl}acetamide (6a). Small portions of sodium borohydride (500 mg) were added over a period of 3 h to a stirred solution of phenylethylacetamide **3a** (2 g, 4.75 mmol) in methanol (40 mL), and the stirring was continued for 30 min at room temperature. The reaction mixture was then added to water (30 mL) and acidified to pH 3 with 20% aqueous hydrochloric acid solution. The methanol was removed in vacuo, and the residue was extracted with dichloromethane (4×40 mL). The pooled organic layers were washed with water (60 mL), dried and concentrated in vacuo to give compound **6a** (2.03 g, 98% yield) as a white solid. Mp 140–142°C (ethyl acetate/ethyl ether). IR (ν, cm^{-1}, KBr): 3284 (NH), 1647 (C═O). 1H NMR (δ, ppm): 1.92 (s, 3H, $-CH_3$), 2.54 (m, 1H, $-CH_2-$), 2.72 (m, 1H, $-CH_2-$), 2.99 (dd, J=13.4 and J=6.7 Hz, 1H, $-CH_2-$), 3.21 (s, 3H, $-OCH_3$), 3.24–3.33 (m, 2H, $-CH_2-$), 3.32 (dd, J=13.4 and J=6.7 Hz, 1H, $-CH_2-$), 3.86 (s, 3H, $-OCH_3$), 3.89 (s, 3H, $-OCH_3$), 4.69 (t, J=6.7 Hz, 1H, –CH–), 5.35 (bs, 1H, –NH), 6.57 (s, 1H, Ar–H), 6.95 (s, 1H, Ar–H), 6.97–7.16 (s, 3H, 3×Ar–H), 7.52 (s, 1H, Ar–H). MS (*m*/*z*, %): 267 (13), 266 (77), 192 (100), 191 (9), 177 (13), 170 (9), 161 (16). Anal. calcd for $C_{21}H_{22}BrNO_4$, C 57.81, H 6.00, N 3.21; found, C 57.97, H 6.11, N 3.33.

1.1.3. *N*-[2-(3,4,10-Trimethoxy-9,10-dihydro-1-phenanthryl)ethyl]acetamide (7a). A solution of tributyltin hydride (1.5 mmol) and AIBN (0.1 mmol) in deoxygenated dry benzene (10 mL) was added under argon over 6 h by means of a syringe pump to a refluxing solution of acetamide **6a** (300 mg, 0.69 mmol) in the same solvent (100 mL). Following completion of the addition, the reaction mixture was heated for an additional 3 h, the benzene was evaporated in vacuo and the residue was dissolved in acetonitrile (250 mL). This solution was washed with hexane (3×50 mL), dried and concentrated in vacuo, and the solid residue was subjected to flash column chromatography (eluant: 7:1 ethyl acetate/hexane), giving phenanthrylethylacetamide **7a** (124 mg, 63% yield). Mp 196–198°C (methanol). IR (ν, cm^{-1}, KBr): 1665 (C═O). ^1H NMR (δ, ppm): 1.84 (s, 3H, $-CH_3$), 2.86–3.23 (m, 2H, $-CH_2-$), 3.28 (s, 3H, $-OCH_3$), 3.33–3.52 (m, 4H, 2×$-CH_2-$), 3.67 (s, 3H, $-OCH_3$), 3.90 (s, 3H, $-OCH_3$), 4.63 (t, J=2.6 Hz, 1H, –CH–), 6.73 (bs, 1H, –NH), 7.13–7.34 (m, 4H, 4×–Ar–H), 8.44 (m, 1H, Ar–H). MS (*m*/*z*, %): 355 (M^+, 3), 323 (23), 264 (18), 207 (27), 164 (100), 151 (51). Anal. calcd for $C_{21}H_{25}NO_4$, C 70.96, H 7.09, N 3.94; found, C 70.72, H 6.95, N 3.82.

1.1.4. *N*[2-(3,4-Dimethoxy-1-phenanthryl)ethyl]acetamide (2a). *Procedure a*. A solution of phenanthrylacetamide **7a** (100 mg, 0.28 mmol), THF (3 mL) and 10% aqueous hydrochloric acid solution (2 mL) was stirred at room temperature for 5 min. After evaporation of the THF in vacuo, the residue was suspended in water (40 mL) and the suspension was extracted with dichloromethane (3×20 mL). The pooled organic layers were dried, filtered and concentrated in vacuo, giving a residue which when subjected to preparative thin layer chromatography (eluant: 7:1 ethyl acetate/hexane) gave compound **2a** (90 mg, 98% yield). Mp 110–112°C (ethyl acetate/diethyl ether). IR (ν, cm^{-1}, NaCl): 3284 (–NH), 1650 (C═O). ^1H NMR (δ, ppm): 1.95 (s, 3H, $-CH_3$), 3.24–3.38 (m, 2H, $-CH_2-$), 3.56–3.62 (m, 2H, $-CH_2-$), 3.93 (s, 3H, $-OCH_3$), 4.03 (s, 3H–OCH_3), 5.60 (s, 1H, –NH), 7.20 (s, 1H, Ar–H), 7.57–7.72 (m, 3H, 3×Ar–H), 7.82–7.98 (m, 2H, 2×Ar–H), 9.66 (m, 1H, Ar–H). MS (*m*/*z*, %): 324 [$(M+1)^+$, 13], 323 (M^+, 58), 264 (79), 251 (100), 249 (16), 217 (24), 165 (34). Anal. calcd for $C_{20}H_{21}NO_3$, C 74.28, H 6.54, N 4.33; found, C 74.41, H 6.69, N 4.29.

Procedure b. Acetyl chloride (1 mL) was added dropwise to a solution of phenanthrylethylamine **2c** (200 mg, 1.5 mmol) and triethylamine (1 mL) in dry dichloromethane (10 mL) at 0°C, and the mixture was then stirred at room temperature for 3 h. Water (15 mL) was added and the organic layer was isolated and washed with water (2×20 mL), dried, filtered and concentrated in vacuo, giving a residue which upon purification by flash column chromatography (eluant: 99:1 dichloromethane/methanol) gave acetamide **2a** (181 mg, 90% yield).

1.1.5. 11,12-Dimethoxy-1-methyl-3,4-dihydronaphtho-[2,1-*f*]isoquinoline (8a). $POCl_3$ (0.36 mL, 2.4 mmol) was added dropwise over 5 min to a solution of compound **6a** (180 mg, 0.48 mmol) in dry acetonitrile (15 mL) and the mixture was refluxed for 6 h under a calcium chloride tube. The reaction mixture was then concentrated in vacuo, the solid residue was dissolved in dichloromethane (20 mL), and this solution was washed with 10% aqueous sodium hydroxide solution 2×15 mL) and water (15 mL), dried, filtered and concentrated in vacuo giving a yellow oil identified as dihydronaphthoisoquinoline **8a** (120 mg, 70% yield). IR (ν, cm^{-1}, NaCl): 1665 (C═O). ^1H NMR (δ, ppm): 2.60 (s, 3H, $-CH_3$), 3.03–3.10 (m, 2H, $-CH_2-$), 3.65–3.70 (m, 2H, $-CH_2-$), 3.96 (s, 3H, $-OCH_3$), 4.08 (s, 3H, $-OCH_3$), 7.62–7.69 (m, 3H, 3×Ar–H), 7.73–7.95 (m, 2H, 2×Ar–H), 9.65 (m, 1H, Ar–H). MS (*m*/*z*, %): 306 [$(M+1)^+$, 22], 305 (M^+, 100), 304 (25). High resolution MS calcd for $C_{20}H_{19}NO_2$, 305.1416; found, 305.1414.

1.1.6. 11,12-Dimethoxy-1-methyl-1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinoline (1a). $NaBH_4$ (50 mg) was

added over 3 h, in small portions, to a solution of dihydroisoquinoline **8a** (100 mg, 0.33 mmol) in methanol (10 mL), after which stirring was continued for 30 min. The reaction mixture was then poured into water (20 mL) and acidified with 20% aqueous hydrochloric acid solution, the methanol was evaporated in vacuo, and the resulting mixture was extracted with chloroform (3×10 mL). The pooled organic layers were dried, filtered and concentrated in vacuo, giving a residue that when subjected to flash column chromatography (eluant: 7:1 eluant ethyl acetate/hexane) gave naphthoisoquinoline **1a** (95 mg, 94% yield). Mp 197–198°C (methanol). IR (ν, cm^{-1}, NaCl): 3223 (–NH). ^1H NMR (δ, ppm): 1.62 (d, J=6.2 Hz, 3H, $-CH_3$), 2.79–3.08 (m, 2H, $-CH_2-$), 3.22–3.39 (m, 2H, $-CH_2-$), 3.95 (s, 3H, $-OCH_3$), 3.98 (s, 3H, $-OCH_3$), 4.61 (m, 1H, –CH–), 7.58–7.78 (m, 3H, 3×Ar–H), 7.82–7.98 (m, 2H, 2×Ar–H), 9.63 (m, 1H, Ar–H). MS (*m/z*, %): 307 (M^+, 15), 293 (22), 292 (100). Anal. calcd. for $C_{20}H_{21}NO_2$, C 78.15, H 6.89, N 4.56; found, C 78.03, H 7.11, N 4.39.

1.1.7. *N*-Acetyl-1-(3,4-dimethoxybenzylidene)-3,4-dihydro-6,7-dimethoxyisoquinoline (11). A solution of isoquinoline **10** (2 g, 5.8 mmol) in 1:1 pyridine/acetic anhydride (16 mL) was heated at 90°C for 30 min and then stirred at room temperature for 18 h. The liquids were coevaporated in vacuo with ethyl acetate, giving benzylideneisoquinoline **11** (2.16 g, 97% yield) as a brown solid. Mp 194–195°C (ethyl acetate/ethyl ether). IR (ν, cm^{-1}, NaCl): 1638 (C═O). ^1H NMR (δ, ppm): 1.79 (s, 3H, $-CH_3$), 2.63–2.76 (m, 1H, $-CH_2-$), 3.11–3.21 (m, 2H, $-CH_2-$), 3.87 (s, 6H, 2×$-OCH_3$), 3.88 (s, 3H,$-OCH_3$), 3.96 (s, 3H,$-OCH_3$), 4.98–5.09 (m, 1H, $-CH_2-$), 6.61 (s, 1H, Ar–H), 6.70 (s, 1H, Ar–H), 6.84 (m, 1H, Ar–H), 7.01–7.04 (m, 2H, 2×Ar–H), 7.11 (s, 1H, Ar–H). MS (*m/z*, %): 384 [$(M+1)^+$, 25], 383 (M^+, 100), 369 (5), 368 (22), 326 (98). Anal. calcd for $C_{22}H_{25}NO_5$, C 68.91, H 6.57, N 3.65; found, C 68.83, H 6.41, N 3.84.

1.1.8. *N*-{2-[2-(3,4-Dimethoxyphenyl)acetyl]-4,5-dimethoxyphenylethyl}acetamide (3b). 10% Aqueous hydrochloric acid solution (5 mL) was added to a solution of benzylideneisoquinoline **11** (1.0 g, 2.60 mmol) in methanol (12.5 mL), and the mixture was refluxed for 5 h. The methanol was evaporated in vacuo and the resulting suspension was basified with saturated aqueous potassium carbonate solution and extracted with chloroform (3×75 mL). The pooled organic layers were dried, filtered and concentrated in vacuo, giving phenylethylacetamide **3b** (1.0 g, 96% yield) as a white solid. Mp 198–200°C (methanol). IR (ν, cm^{-1}, NaCl): 1657 (C═O). ^1H NMR (d, ppm): 1.87 (s, 3H, $-CH_3$), 2.81–2.98 (m, 2H, $-CH_2-$), 3.41–3.52 (m, 2H, $-CH_2-$), 3.85 (s, 3H, $-OCH_3$), 3.86 (s, 3H, $-OCH_3$), 3.90 (s, 3H, $-OCH_3$), 3.92 (s, 3H, $-OCH_3$), 4.15 (s, 2H, $-CH_2-$), 6,56 (bs, 1H, –NH), 6.72–6.96 (m, 4H, 4×Ar–H), 7.25 (s, 1H, Ar–H). MS (*m/z*, %): 402 [$(M+1)^+$, 1], 401 (M^+, 5), 209 (13), 208 (100). Anal. calcd for $C_{22}H_{27}NO_6$, C 65.82, H 6.78, N 3.49; found, C 65.97, H 6.92, N 3.61.

1.1.9. *N*-{2-[2-(2-Bromo-4,5-dimethoxyphenyl)acetyl]-4,5-dimethoxyphenylethyl}acetamide (3c). A solution of bromine (2.2 mL, 138 mmol) in glacial acetic acid (20 mL) was added dropwise over 30 min to a solution of styrylphenylethylacetamide **3b** (0.5 g, 1.25 mmol) in a 1:1 mixture of acetic acid/water (20 mL) cooled at 10°C with an ice/water bath. The mixture was then stirred at room temperature for 1 h, and the resulting precipitate was filtered out and washed with water, giving bromophenylacetylphenylethylacetamide **3c** (0.52 g, 86%) as a white solid. Mp 212–214°C (acetone). IR (ν, cm^{-1}, NaCl): 1659 (C═O). ^1H NMR (δ, ppm): 1.87 (s, 3H, $-CH_3$), 2.92–3.03 (m, 2H, $-CH_2-$), 3.41–3.58 (m, 2H, $-CH_2-$), 3.85 (s, 3H, $-OCH_3$), 3.86 (s, 3H, $-OCH_3$), 3.92 (s, 3H, $-OCH_3$), 3.93 (s, 3H, $-OCH_3$), 4.31 (s, 2H, $-CH_2-$), 6.57 (bs, 1H, –NH), 6.76 (s, 1H, Ar–H), 6.77 (s, 1H, Ar–H), 7.05 (s, 1H, Ar–H), 7.31 (s, 1H, Ar–H). MS (*m/z*, %): 481 (M^+, 2) 479 (M^+, 2), 209 (14), 208 (100). Anal. calcd for $C_{22}H_{26}BrNO_6$, C 55.01, H 5.46, N 2.92; found, C 55.19, H 5.44, N 32.83

1.1.10. *N*-{2-[2-(2-Bromo-4,5-dimethoxyphenyl)-1-methoxyethyl]-4,5-dimethoxyphenylethyl}-acetamide (6b). Compound **6b** was obtained in 72% yield from compound **3c** (0.46 g, 0.96 mmol) following the same procedure as for compound **6a**. Mp 198–200°C (ethyl acetate/ethyl ether). IR (ν, cm^{-1}, NaCl): 1653 (C═O). ^1H NMR (δ, ppm), 1.86 (s, 3H, $-CH_3$), 2.38–2.84 (m, 4H, 2×$-CH_2-$), 3.15 (s, 3H, $-OCH_3$), 3.16–3.26 (m, 2H, $-CH_2-$), 3.60 (s, 3H, $-OCH_3$), 3.75 (s, 3H, $-OCH_3$), 3.77 (s, 3H, $-OCH_3$), 3.81 (s, 3H, $-OCH_3$), 4.57 (t, J=6.7 Hz, 1H, –CH–), 5.72 (bs, 1H, –NH), 6.37 (s, 1H, Ar–H), 6.50 (s, 1H, Ar–H), 6.88 (s, 1H, Ar–H), 6.90 (s, 1H, Ar–H). MS (*m/z*, %): 267 (15), 266 (86), 234 (14), 193 (14), 192 (100), 191 (7). Anal. calcd for $C_{23}H_{30}BrNO_6$, C 55.65, H 6.09, N 2.82; found, C 55.51, H 5.95, N 3.02.

1.1.11. *N*-[2-(3,4,6,7,10-Pentamethoxy-9,10-dihydro-1-phenanthryl)ethyl]acetamide (7b). Compound **7b** was obtained in 59% yield from compound **6b** (283 mg, 0.57 mmol) by the same procedure as for compound **7a**. Mp 191–193°C (methanol). IR (ν, cm^{-1}, KBr): 1655 (C═O). ^1H NMR (δ, ppm): 1.85 (s, 3H, $-CH_3$), 2.77–296 (m, 2H, $-CH_2-$), 3.30 (s, 3H, $-OCH_3$), 3.39–3.57 (m, 4H, 2×$-CH_2-$), 3.65 (s, 3H, $-OCH_3$), 3.89 (s, 6H, 2×$-OCH_3$), 3.92 (s, 3H, $-OCH_3$), 4.61 (m, 1H, –CH–), 6.35 (bs, 1H, –NH), 6.68 (s, 1H, Ar–H), 6.78 (s, 1H, Ar–H), 8.17 (s, 1H, Ar–H). MS (*m/z*, %): 417 [$(M+2)^+$, 2], 416 [$(M+1)^+$, 12], 415 (M^+, 45), 384 (18), 383 (58), 326 (11), 325 (39), 324 (89), 311 (100). Anal. calcd for $C_{23}H_{29}NO_6$, C 66.49, H 7.03, N 3.37; found, C 66.71, H 6.95, N 3.39.

1.1.12. *N*-[2-(3,4,6,7-Tetramethoxy-1-phenanthryl)ethyl]-acetamide (2b). *Procedure a*. When compound **7b** (100 mg, 0.24 mmol) was subjected to the conditions for the transformation of **7a** (Procedure a), compound **2b** was obtained in 98% yield. Mp 135–138°C (ethyl acetate/ethyl ether). IR (ν, cm^{-1}, NaCl): 1649 (C═O). ^1H NMR (δ, ppm): 1.93 (s, 3H, $-CH_3$), 3.21–3.34 (m, 2H, $-CH_2-$), 3.57–3.63 (m, 2H, $-CH_2-$), 3.90 (s, 3H, $-OCH_3$), 3.99 (s, 3H, $-OCH_3$), 4.01 (s, 3H, $-OCH_3$), 4.05 (s, 3H, $-OCH_3$), 5.84 (s, 1H, –NH), 7.13 (s, 1H, Ar–H),), 7.17 (s, 1H, Ar–H), 7.51 (d, J=9.1 Hz, 1H, Ar–H), 7.78 (d, J=9.1 Hz, 1H, Ar–H). 9.24 (s, 1H, Ar–H). MS (*m/z*, %): 383 (M+, 100) 325 (20), 324 (83), 312 821), 311 (97), 309 (24), 297 (13), 293 (26). Anal. calcd for $C_{22}H_{25}NO_5$, C 68.91, H 6.57, N 3.65; found, C 68.94, H 6.78, N 3.56.

Procedure b. Alternatively, compound **2b** was prepared in 90% yield from compound **2d** (180 mg 0.53 mmol) following the same procedure as for preparation of compound **2a** (Procedure b).

1.1.13. 8,9,11,12-Tetramethoxy-1-methyl-3,4-dihydronaphtho [2,1-*f*]isoquinoline (8b). Compound **8b** was prepared as a yellow oil in 70% yield from compound **2b** (135 mg, 0.36 mmol) using the same procedure as for compound **8a**. ^{1}H NMR (δ, ppm): 2.60 (s, 3H, $-CH_3$), 3.02–3.13 (m, 2H, $-CH_2-$), 3.62–3.79 (m, 2H, $-CH_2-$), 3.96 (s, 3H, $-OCH_3$), 4.07 (s, 3H, $-OCH_3$), 4.08 (s, 3H, $-OCH_3$), 4.11 (s, 3H, $-OCH_3$), 7.28 (s, 1H, Ar–H), 7.64 (d, J=9.0 Hz, 1H, Ar–H), 7.86 (d, J=9.0 Hz, 1H, Ar–H), 9.22 (s, 1H, Ar–H). MS (*m*/*z*, %): 365 (M^+, 100), 364 (7), 351 (13), 350 (39), 311 (8), 310 (33). High resolution MS calcd for $C_{22}H_{23}NO_4$, 365.1627; found, 365.1628.

1.1.14. 8,9,11,12-Tetramethoxy-1-methyl-1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinoline (1b). Compound **1b** was prepared in 84% yield from compound **8b** (50 mg, 0.14 mmol) following the same procedure as for compound **1a**. Mp 231–233°C (methanol). IR (ν, cm^{-1}, KBr): 3200 (–NH). ^{1}H NMR (δ, ppm): 1.75 (d, J=6.1 Hz, 3H, $-CH_3$), 2.98–3.71 (m, 4H, 2×$-CH_2-$), 3.97 (s, 9H, 3×$-OCH_3$), 4.03 (s, 3H, $-OCH_3$), 4.88 (m, 1H, –CH–), 7.25 (s, 1H, Ar–H), 7.29 (s, 1H, Ar–H) 7.80 (d, J=9.1 Hz, 1H, Ar–H), 8.09 (d, J=9.1 Hz, 1H, Ar–H), 9.65 (s, 1H, Ar–H), 995 (bs, 1H, –NH). MS (*m*/*z*, %): 367 (M^+, 1), 352 (24), 351 (100). Anal. calcd for $C_{22}N_{25}NO_4$, C 71.91, H 6.86, N 3.81; found, C 71.69, H 6.75, N 4.02.

1.1.15. 1,2-Dimethoxy-4,5,6a,7-tetrahydrodibenzo[*de*,*g*]-chroman-5-one (14a). A solution of tributylin hydride (1.5 mmol) and AIBN (0.1 mmol) in deoxygenated dry benzene (15 mL) was added under argon over 6 h by means of a syringe pump to a refluxing solution of acetamide **6a** (800 mg, 2.12 mmol) in the same solvent (100 mL). Following completion of the addition, the reaction mixture was heated for an additional 3 h. The benzene was evaporated in vacuo, the residue was dissolved in acetonitrile (400 mL) and the resulting solution was washed with hexane (3×50 mL), dried and concentrated in vacuo. After thin layer chromatography of the solid residue (eluant: 95:5 dichloromethane/methanol), compound **14a** was isolated as a white solid (483 mg, 76% yield) and compared with an authentic sample.

1.1.16. 2-(3,4-Dimethoxy-1-phenanthryl)acetamide (16a). A mixture of lactone **14a** (250 mg, 0.84 mmol), methanol (5 mL) and concentrated aqueous ammonia solution (2 mL) was stirred at room temperature for 18 h, and then added to water (25 mL) acidified with 10% aqueous hydrochloric acid solution and extracted with chloroform (3×25 mL). The pooled organic layers were dried, filtered and concentrated in vacuo, giving a residue which after purification by thin layer chromatography (95:5 dichloromethane/methanol) gave **16a** (200 mg, 80% yield) as a white solid. Mp 147–148°C (methanol). IR (ν, cm^{-1}, KBr): 3360 (–NH), 1660 (C=O). ^{1}H NMR (δ, ppm): 3.95 (s, 3H, $-OCH_3$), 4.04 (s, 5H, $-CH_2-$ and $-OCH_3$), 5.34 (bs, 1H, $-NH_2$), 5.56 (bs, 1H, $-NH_2$), 7.25 (s, 1H, Ar–H), 7.57–7.68 (m, 2H, 2×Ar–H), 7.64 (d, J=9.1 Hz, 1H, Ar–H), 7.74 (d, J=9.1 Hz, 1H, Ar–H), 7.85 (s, 1H, Ar–H), 9.65 (s, 1H, Ar–H). MS (*m*/*z*, %): 295 (M^+, 74), 252 (19), 251 (100), 237 (19), 165 (20). Anal. calcd for $C_{19}H_{17}NO_3$, C 73.20, H 5.80, N 4.74; found, C 73.02, H 5.83, N 4.32.

1.1.17. 2-(3,4-Dimethoxy-1-phenanthryl)-1-ethylamine (2c). A solution of amide **16a** (200 mg, 0.68 mmol) in dry THF (10 mL) was added dropwise over 12 min to a vigorously stirred suspension of LAH (70 mg) in dry THF (20 mL). The mixture was refluxed for 5 h under a calcium chloride tube and was then stirred at room temperature overnight. After addition of a saturated solution of sodium sulphate (4 drops), the suspension was filtered and the filtrate was concentrated in vacuo, giving an oil identified as the phenanthrylethylamine **2c** (133 mg, 70% yield), which was used without further purification. ^{1}H NMR (δ, ppm): 3.15 (t, J=6.3 Hz, 2H, $-CH_2-$), 3.30 (t, J=6.3 Hz, 2H, $-CH_2-$), 3.92 (s, 3H, $-OCH_3$), 4.03 (s, 3H, $-OCH_3$), 7.24 (s, 1H, Ar–H), 7.50–7.70 (m, 3H, 3×Ar–H), 7.82 (m, 1H, Ar–H), 7.86 (d, J=9.2 Hz, 1H, Ar–H), 9.65 (d, J=8.3 Hz, 1H, Ar–H). MS (*m*/*z*, %): 281 (M^+, 36), 252 (90), 251 (100), 237 (23).

1.1.18. 1,2,9,10-Tetramethoxy-4,5,6a,7-tetrahydrodibenzo-[*de*,*g*]chroman-5-one (14b). Compound **14b** was prepared in 83% yield from compound **13b** (200 mg, 0.46 mmol) following the same procedure as for compound **14a** and was identified by comparison with an authentic sample.

1.1.19. 2-(3,4,6,7-Tetramethoxy-1-phenanthryl)acetamide (16b). Compound **16b** was prepared in 70% yield from compound **14b** (250 mg, 0.7 mmol) following the same procedure as for compound **16a**. Mp 162–163°C (methanol). IR (ν, cm^{-1}, KBr): 3430 (–NH), 1670 (C=O). ^{1}H NMR (δ, ppm): 3.96 (s, 3H, $-OCH_3$), 4.05 (s, 8H, $-CH_2-$ and 2×$-OCH_3$), 4.08 (s, 3H, $-OCH_3$), 5.34 (bs, 1H, $-NH_2$), 7.23 (s, 1H, Ar–H), 7.25 (s, 1H, Ar–H), 7.59 (d, J=9.1 Hz, 1H, Ar–H). 7.67 (d, J=9.1 Hz, 1H, Ar–H), 9.27 (s, 1H, Ar–H). MS (*m*/*z*, %): 370 (M^+, 100), 355 (42), 311 (39). Anal. calcd for $C_{20}H_{21}NO_5$, C 67.61, H 5.92, N 3.94; found, C 67.21, H 6.09, N 3.61. Anal. calcd for $C_{20}H_{21}NO_5$, C 67.59, H 5.96, N 3.94; found, C 67.86, H 5.61, N 3.69.

1.1.20. 2-(3,4,6,7-Tetramethoxy-1-phenanthryl)-1-ethylamine (2d). Compound **2d** was prepared in 75% yield from compound **16b** (0.5 g, 1.4 mmol) following the same procedure as for compound **2c**. ^{1}H NMR (δ, ppm): 1.89 (bs, 2H, $-NH_2$), 3.12 (t, J=6.0 Hz, 2H, $-CH_2-$), 3.24 (t, J=6.0 Hz, 2H, $-CH_2-$), 3.92 (s, 3H, $-OCH_3$), 4.03 (s, 3H, $-OCH_3$), 4.04 (s, 3H, $-OCH_3$), 4.07 (s, 3H, $-OCH_3$), 7.19 (s, 1H, Ar–H), 7.20 (s, 1H, Ar–H), 7.53 (d, J=9.1 Hz, 1H, Ar–H), 7.77 (d, J=9.1 Hz, 1H, Ar–H), 9.28 (s, 1H, Ar–H). MS (*m*/*z*, %): 343 [$(M+2)^+$, 23], 342 [$(M+1)^+$, 100], 311 (54), 265 (12).

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