Total synthesis of 8,9,11,12-tetramethoxy-2-methyl-1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinoline and 8,9,11-trimethoxy-2-methyl-1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinolin-12-ol

M. Carme Pampín, Juan C. Estévez, Ramón J. Estévez,* and Luis Castedo

[a] *Departamento de Química Orgánica, Universidade de Santiago, 15782 Santiago de Compostela, Spain*
E-mail: qorjec@usc.es

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Abstract

We describe here the first total synthesis of two tetrasubstituted 1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinolines (8,9,11,12-tetramethoxy-2-methyl-1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinoline and 8,9,11-trimethoxy-2-methyl-1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinolin-12-ol). The key steps were the Bischler-Napieralski cyclization of ethyl (2-{2-[2-(3,4-dimethoxyphenyl)vinyl]-4,5-dimethoxyphenyl}ethyl)methylcarbamates to form the isoquinoline units and photocyclization of the resulting 5-[2-(3,4-dimethoxyphenyl)vinyl]-7,8-dimethoxy-2-methyl-3,4-dihydroisoquinolin-1(2*H*)-ones to 8,9,11,12-tetramethoxy-2-methyl-3,4-dihydronaphtho[2,1-*f*]isoquinolin-1(2*H*)-ones.

Keywords: Cyclization, isoquinolines, Heck reaction, photochemistry, stilbenes

Introduction

The isoquinoline ring system is found in many alkaloids and for this and other reasons the synthesis of isoquinoline derivatives has received considerable attention.[1] Nevertheless, naphtho[2,1-*f*]isoquinolines have received very little chemical attention prior to the recent isolation of two members of the only two natural members of this family - litebamine (**9a**)[2] and annoretine (**9b**)[3] Litebamine was the first phenanthrenic alkaloid isolated from *Litsea cubeba* and its activities as a platelet antiaggregant[4] and as an inhibitor of acetylcholinesterase[5] have been described. Subsequent partial syntheses of litebamine from the aporphine boldine led to the hypothesis of biogenetic degradation of aporphines to 1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinolines.[5,6] Annoretine was isolated from the leaves of *Annona montana* and it possesses significant cytotoxic activity against different human cell cultures such as KB, P-388, A-549 and HT-29.[3]

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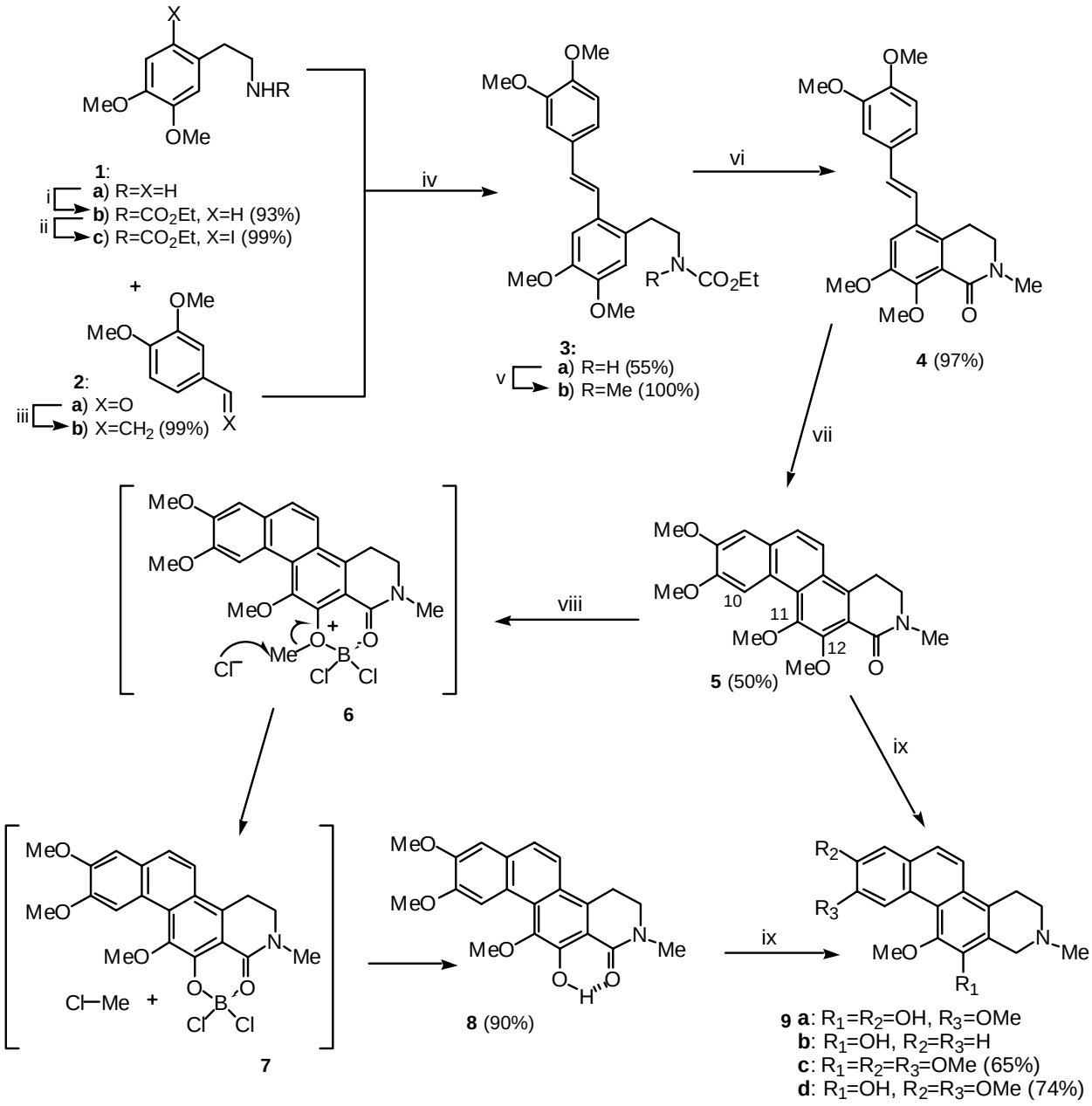
We have previously reported some exploratory work on the synthesis of 1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinolines[7] which was recently applied to the first total synthesis of the disubstituted 1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinoline annoretine.[8] This exercise allowed us to corroborate the structure proposed for this natural compound and provided a promising strategy for the synthesis of other members of this family of isoquinoline alkaloids. Here we describe the first total synthesis of the tetrasubstituted 1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinolines *O*,*O*-dimethyllitebamine (**9c**) and *O*-methyllitebamine **9d**, which constitutes a novel contribution to the synthesis of this new family of alkaloids.

Results and Discussion

We first studied the preparation of *O*,*O*-dimethyllitebamine (**9c**), starting from *o*-styrylphenylethylurethane **3a**, which was prepared by Heck[9] coupling of the appropriate halobenzene **1c** to styrene **2b**. A solution of homoveratrylamine (**1a**), ethyl chloroformate and Et_3N was stirred at room temperature for 16 hours to afford the *N*-ethoxycarbonyl derivative **1b**[10] in 93% yield. This compound was subsequently transformed quantitatively into iodobenzene derivative **1c** after treatment with IPy_2BF_4[11] and CF_3SO_3H. On the other hand, treatment[12] of 3,4-dimethoxybenzaldehyde (**2a**) with Ph_3PCH_3Br and *n*-BuLi in THF at room temperature for 4 hours gave the desired styrene **2b**[13] in 99% yield. Next, when a deoxygenated solution of **1c**, **2b**, triethylamine, triphenylphosphine and palladium acetate was heated at 100 °C in a sealed tube for 24 hours, the desired tetrasubstituted *o*-styrylphenylethylurethane **3a** was obtained in 55% yield. The mass spectrum of **3a** confirmed the expected molecular weight (*m*/*z* = 415) and the *E* configuration of the stilbene double bond was easily established from its ^{1}H NMR spectrum, which showed two doublets at 6.84 ppm (1 H, *J* = 16.0 Hz) and 7.25 ppm (1 H, *J* = 16.0 Hz), due to the protons on the double bond.

Next, compound **3a** was converted into its *N*-methyl derivative **3b**[14] and this was subjected to Bischler-Napieralski cyclization conditions with Tf_2O[15]. This reaction readily furnished the expected 5-styrylisoquinolinone **4** in 97% yield.

We next studied the photochemically induced electrocyclic cyclization[12] of styrylisoquinoline **4**. Irradiation of **4** with a 450 W Hanovia medium-pressure lamp equipped with a Pyrex filter gave the expected naphthoisoquinolinone **5**, which was identified from its analytical and spectroscopic data. The mass spectrum of this compound confirmed the molecular mass (M^+, *m*/*z* = 381), two units less than the starting material. In addition, the ^{1}H NMR spectrum showed signals for a total of four aromatic protons, including a singlet for a proton at 9.27 ppm due to the hydrogen at C(10), which is highly deshielded due to steric interaction with the methoxy substituent at position C(11).



Scheme 1. Conditions: (i) Et_3N, $ClCO_2Et$, dry CH_2Cl_2, argon 0°C->rt, 16 hours. (ii) CF_3CO_2H, Ipy_2BF_4, dry CH_2Cl_2, argon 0°C, 30 min. (iii) n-BuLi, $CH_2PPh_3^+Br^-$, THF, argon 0°C->rt, 4 hours (iv) $Pd(OAc)_2$ Ph_3P, Et_3N,dry MeCN, argon 100°C, 24 hours. (v) a) NaH, dry THF, argon, rt, 30 min.; b) MeI, argon, rt, 3 hours. (vi) Tf_2O, DMPA, dry CH_2Cl_2, 0°C->rt, 21 hours. (vii) UV light, I_2, Et_2O, rt, 3 hours. (viii) BDl_3, CH_2Cl_2, rt, 30 min. (ix) $LiAlH_4$, THF, 0°C->rt, 5 hours.

O,*O*-Dimethyllitebamine (**9c**) was next obtained by reduction of isoquinoline **5** with $LiAlH_4$ and its structure was easily established from analytical and spectroscopic data. The ^1H NMR spectrum showed at 3.77 ppm a singlet corresponding to the methylene group resulting from the

carbonyl group reduction and the ^{13}C NMR spectrum includes at 53.46 ppm a signal corresponding to this methylene group.

On the other hand, transformation of naphthoisoquinolinone **5** into *O*-methyllitebamine **9d** was accomplished in a two-step sequence starting with treatment of **5** with BCl_3 at room temperature during 15 minutes,[16] which led to compound **8** as a result of regiospecific demethylation of the methoxy substituent at C(12). Clear evidence for this process was provided by spectroscopic data, particularly the ^1H NMR spectrum, which showed a highly deshielded singlet for one proton at 12.98 ppm. This signal was assigned to the proton of the hydroxy substituent. The marked downfield chemical shift for this proton, due to its interaction with the carbonyl group, allowed us to establish that demethylation had occurred at the desired position. This conclusion was further supported by HMQC and HMBC experiments, which show a correlation between the OH proton and carbon atoms C(12a) and C(11), together with a correlation between the methoxy substituent at C(11) and the carbon at C(12a) (Figure 1). These correlations clearly indicate that the hydroxy substituent is located between the carbonyl group and the methoxy substituent.

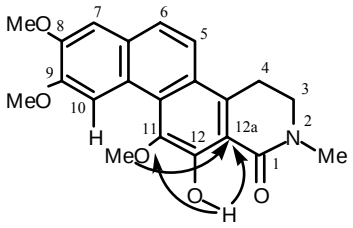


Figure 1. Important ^1H-^{13}C coupling observed in the HMQC and HMBC experiments of compound **8**.

Selective demethylation of the methoxy substituent at C(12) can be explained as being the result of the initial interaction between naphthoisoquinolinone **5** and BCl_3, which leads to a coordination complex **6** in which the boron atom is coordinated with oxygen atoms of the carbonyl and methoxy groups. Attack on such a complex by a chloride ion gives a second boron complex **7**, hydrolysis of which furnished the resulting phenolic naphthoisoquinoline **8**.[17]

Finally, reduction of compound **8** with $LiAlH_4$ provided *O*-methyllitebamine **9d** in 74% yield. Its mass spectrum confirmed the molecular weight expected for the compound (*m/z* = 353, M^+) and the ^1H NMR spectrum showed at 3.78 ppm a singlet of two protons, corresponding to the methylene arising from reduction of the carbonyl group.

Work is now in progress to synthesize litebamine and to prepare a range of non-natural 1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinolines other than *O*,*O*-dimethyllitebamine (**9c**) and *O*-methyl-litebamine **9d** for chemical and biological studies.

Experimental Section

General Procedures. Melting points were determined on a Kofler Thermograte apparatus and are uncorrected. Infrared spectra were recorded on a MIDAC FTIR spectrophotometer. Nuclear magnetic resonance spectra, unless otherwise specified, were recorded on a Bruker WM-250 apparatus using deuterochloroform 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 eluent; the tlc spots were visualized with ultraviolet light or iodine vapour. Column chromatography was carried out using Merck type 9385 silica gel. Solvents were purified as per ref. 18. Solutions of extracts in organic solvents were dried with anhydrous sodium sulfate. Compounds **1b**,[10] **2b**[13] and **3b**[14] have been previously prepared.

Ethyl [2-(3,4-dimethoxyphenyl)ethyl]carbamate (1b). Triethylamine (15.4 mL, 110 mmol) and then ethyl chloroformate (7.2 mL, 75.04 mmol) were added dropwise under argon to a solution of homoveratrylamine (**1a**) (4 g, 22.07 mmol) in dry dichloromethane (25 mL) at 0 ºC. The mixture was stirred for 16 h under argon at rt. The reaction mixture was concentrated *in vacuo*, the residue was suspended in water (25 mL) and the suspension was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with water, dried, filtered and concentrated *in vacuo*. The resulting oily residue was purified by column chromatography (eluent: 1:1 ethyl acetate/hexane) to give compound **1b** (5.20 g, 93% yield) as a white solid. Mp 53-55 °C (methanol). IR (ν , cm^{-1}, NaCl): 3304 (-NH), 1683 (CO). ^{1}H NMR (δ, ppm): 6.80-6.69 (m, 3H, 3 x ArH), 5.27 (bs, 1 H, -NH), 4.08 (q, *J* = 7.0 Hz, 2H, -O*CH*$_2$CH$_3$), 3.84 (s, 3H, -OCH$_3$), 3.82 (s, 3H, -OCH$_3$), 3.42-3.34 (m, 2H, -CH$_2$-), 2.77-2.71 (m, 2H, -CH$_2$-), 1.20 (t, *J* = 7.0 Hz, 3 H, -OCH$_2$*CH*$_3$). ^{13}C NMR (δ, ppm): 156.19 (CO); 148.38 (ArOCH$_3$); 147.03 (ArOCH$_3$); 130.98 (C); 120.13 (ArH); 111.45 (ArH); 110.83 (ArH); 59.98 (-O*CH*$_2$CH$_3$); 55.26 (-OCH$_3$); 55.17 (-OCH$_3$); 41.76 (-CH$_2$-); 35.16 (-CH$_2$-); 14.09 (-OCH$_2$*CH*$_3$). Ms (*m/z*, %): 253 (M^+, 14), 151 (100). Anal. calcd. for $C_{13}H_{19}NO_4$, C 61.64, H 7.56, N 5.53; found, C 61.78, H 5.81, N 4.59.

Ethyl [2-(2-iodo-4,5-dimethoxyphenyl)ethyl]carbamate (1c). Trifluoromethanesulfonic acid (1.15 mL, 12.90 mmol) was added dropwise under argon to a stirred solution of *N*-ethoxycarbonyl derivative **1b** (1.48 g, 5.86 mmol) and IPy_2BF_4 (2.4 g, 6.45 mmol) in dry dichloromethane (15 mL) at 0 ºC. Stirring was continued for a further 30 min under argon. The reaction mixture was poured into saturated sodium thiosulfate (40 mL), the resulting suspension was extracted with dichloromethane (3 x 25 mL), and the combined organic extracts were washed with water, dried, filtered and concentrated *in vacuo*. The resulting solid residue was purified by column chromatography (eluent 99:1 dichloromethane/methanol) to give iodo derivative **1c** (2.20 g, 99% yield) as a white solid. Mp 76-78 °C (methanol). IR (ν , cm^{-1}, NaCl): 3345 (-NH); 1683 (CO). ^{1}H NMR (δ, ppm): 7.19 (s, 1 H, ArH); 6.74 (s, 1 H, ArH); 5.12 (bs, 1 H, -NH); 4.11 (q, *J* = 7.1 Hz, 2 H, -O*CH*$_2$CH$_3$); 3.83 (s, 3 H, -OCH$_3$); 3.82 (s, 3 H, -OCH$_3$);

3.42-3.34 (m, 2 H, -CH_2-); 2.90-2.84 (m, 2 H, -CH_2-); 1.22 (t, *J* = 7.1 Hz, 3 H, -OCH_2CH_3). ^{13}C NMR (δ, ppm): 156.35 (CO); 148.97 ($ArOCH_3$); 147.78 ($ArOCH_3$); 133.57 (C); 121.29 (ArH); 112.34 (ArH); 87.77 (C); 60.34 (-OCH_2CH_3); 55.78 (-OCH_3); 55.55 (-OCH_3); 40.66 (-CH_2-); 39.96 (-CH_2-); 14.39 (-OCH_2CH_3). Ms (*m*/*z*, %): 379 (M^+, 44); 277 (100). Anal. calcd. for $C_{13}H_{18}NIO_4$, C 41.18, H 4.78, I, 33.47, N 5.53; found, C 40.97, H 4.91, N 5.71.

1,2-Dimethoxy-4-vinylbenzene (2b). A 1.5 M solution of *n*-BuLi in hexane (17 mL) was added under argon to a stirred suspension of methyltriphenylphosphonium bromide (8.6 g, 24.07 mmol) in dry THF (50 mL) at -78 °C (dry ice/acetone bath). The mixture was allowed to warm up to rt, stirred for 20 min, cooled again to -78 °C, and a solution of 3,4-dimethoxybenzaldehyde **2a** (2 g, 12.04 mmol) in dry THF (20 mL) was added dropwise. The resulting mixture was stirred for 4 h at rt. The solvent was removed *in vacuo*, the residue was suspended in water (100 mL) and the suspension was extracted with dichloromethane (3 x 70 mL). The combined organic extracts were washed with a 1:2 methanol/water mixture (100 mL), dried, filtered and concentrated *in vacuo*. The resulting solid residue was purified by column chromatography (eluent: 15:85 ethyl acetate/hexane) to give styrene **2b** (1.96 g, 99% yield) as a yellow oil, which was used without further purification. IR (ν, cm^{-1}, NaCl): 2944 (ArH); 1254 (C-O). ^{1}H NMR (δ, ppm): 6.97-6.91 (m, 2H, 2xArH); 6.81 (d, *J* = 8.1 Hz, 1 H, ArH); 6.65 (dd, *J* = 17.5 and 10.8 Hz, 1H, -C*H*=CH_2); 5.61 (dd, *J* = 17.5 and 0.8 Hz, 1 H, -CH=*CH*H); 5.14 (dd, *J* = 10.8 and 0.8 Hz, 1 H, -CH=*CH*H); 3.89 (s, 3H, -OCH_3); 3.87 (s, 3H, -OCH_3). ^{13}C NMR (δ, ppm): 148.81 (2xC); 136.35 (ArH); 130.55 (C); 119.32 (ArH); 111.66 (-CH_2-); 110.85 (ArH); 108.31 (ArH); 55.75 (-OCH_3); 55.65 (-OCH_3). Ms (*m*/*z*, %): 164 (M^+, 100). HRMS: $C_{10}H_{12}NO_2$ (M^+) calcd. 164.0837; found 164.0829.

Ethyl (2-{2-[2-(3,4-dimethoxyphenyl)vinyl]-4,5-dimethoxyphenyl}ethyl)carbamate (3a). A deoxygenated mixture of iodophenylethylamine derivative **1c** (1.5 g, 3.96 mmol), styrene **2b** (0.78 g, 0.40 mmol), palladium acetate (59 mg, 0.26 mmol, 10% molar), triphenylphosphine (0.14 g, 0.57 mmol, 20% molar) and triethylamine (0.44 mL, 3.16 mmol) in dry acetonitrile (14 mL) was heated in a sealed tube at 100 °C for 24 h under argon. The suspension was filtered through celite, the filtrate was washed with water (50 mL), dried and concentrated *in vacuo*. The resulting oily residue was purified by column chromatography (eluent: 1:1 ethyl acetate/hexane) to give compound **3a** (1.09 g, 55% yield) as a white solid. Mp 115-116 ºC (AcOEt). IR (ν , cm^{-1}, NaCl): 3381 (-NH); 1712 (CO). ^{1}H NMR (δ, ppm): 7.25 (d, *J* = 16.0 Hz, 1 H, -C*H*=CH-); 7.17 (d, *J* = 1.9 Hz, 1 H, ArH); 7.12 (s, 1 H, ArH); 7.03 (dd, *J* = 8.3 and 1.9 Hz, 1 H, ArH); 6.84 (d, *J* = 16.0 Hz, 1 H, -CH=C*H*-); 6.84 (d, *J* = 8.3 Hz, 1 H, ArH); 6.66 (s, 1 H, ArH); 4.77 (bs, 1 H, -NH); 4.05 (q, *J* = 7.1 Hz, 2 H, -OCH_2CH_3); 3.95 (s, 3 H, -OCH_3); 3.91 (s, 3 H, -OCH_3); 3.87 (s, 3 H, -OCH_3); 3.86 (s, 3 H, -OCH_3); 3.36 (bs, 2 H, -CH_2-); 2.95-2.89 (m, 2 H, -CH_2-); 1.17 (t, *J* = 7.1 Hz, 3 H, -OCH_2CH_3). ^{13}C NMR (δ, ppm): 156.58 (CO); 149.54 ($ArOCH_3$); 149.12 ($ArOCH_3$); 148.93 ($ArOCH_3$); 148.22 ($ArOCH_3$); 131.15 (C); 129.32 (2xC); 128.63 (ArH); 123.86 (ArH); 119.81 (ArH); 113.60 (ArH); 111.83 (ArH); 109.62 (ArH); 109.31 (ArH); 60.53 (-OCH_2CH_3); 56.09 (2x-OCH_3); 56.00 (2x-OCH_3); 42.22 (-CH_2-); 33.37 (-CH_2-); 14.44

(-OCH_2CH_3). Ms (*m*/z, %): 415 (M^+, 85); 326 (43); 151 (100). Anal. calcd. for $C_{23}H_{29}NO_6$, C 66.49, H 7.04, N 3.37; found, C 66.71, H 6.87, N 3.18.

Ethyl (2-{2-[2-(3,4-dimethoxyphenyl)vinyl]-4,5-dimethoxyphenyl}ethyl)methylcarbamate (3b). A solution of stilbene **3a** (865 mg, 2.08 mmol) in dry THF (6 mL) was added dropwise under argon to a stirred suspension of sodium hydride (290 mg, 12 mmol) in dry THF (6 mL). The stirring was continued at rt for 30 min and methyl iodide (2.92 mL, 46.9 mmol) was added. The resulting mixture was stirred for a further 3 h and diluted with water (20 mL). The THF was removed *in vacuo* and the remaining aqueous suspension was extracted with dichloromethane (3 x 20 mL), the combined organic extracts were washed with water (40 mL), dried, filtered and concentrated *in vacuo* to give *N*-methylcarbamate derivative **3b** (892 mg, 100% yield) as a yellow solid. Mp 158-160 °C (MeOH). IR (ν , cm^{-1}, NaCl): 1685 (CO). ^{1}H NMR (δ, ppm): 7.32-7.14 (m, 2 H, ArH and -C*H*=CH-); 7.12 (s, 1 H, ArH); 7.04 (dd, *J* = 8.3 and 1.9 Hz, 1 H, ArH); 6.85 (d, *J* = 8.3 Hz, 1 H, ArH); 6.84 (d, *J* = 16.0 Hz, 1 H, -CH=C*H*-)**;** 6.67 (s, 1 H, ArH); 4.08 (q, *J* = 7.1 Hz, 2 H, -O*CH*$_2$CH$_3$); 3.95 (s, 3 H, -OCH_3); 3.91 (s, 3 H, -OCH_3); 3.88 (s, 3 H, -OCH_3); 3.87 (s, 3 H, -OCH_3); 3.46-3.39 (m, 2 H, -CH_2-); 2.96-2.90 (m, 2 H, -CH_2-); 2.84 (s, 3 H, -NCH_3); 1.19 (t, *J* = 7.1 Hz, 3 H, -OCH_2CH_3). ^{13}C NMR (δ, ppm): 156.37 (CO); 149.64 ($ArOCH_3$); 149.19 ($ArOCH_3$); 149.04 ($ArOCH_3$); 148.28 ($ArOCH_3$); 131.31 (C); 129.66 (C); 129.35 (C); 128.61 (ArH); 124.03 (ArH); 119.81 (ArH); 113.76 (ArH); 111.92 (ArH); 109.73 (ArH); 109.33 (ArH); 61.04 (-O*CH*$_2$CH$_3$); 56.18 (2x-OCH_3); 56.09 (2x-OCH_3); 50.75 (-CH_2-); 34.89 (-NCH_3); 31.53 (-CH_2-); 14.63 (-OCH_2CH_3). Ms (*m*/z, %): 429 (M^+, 100). Anal. calcd. for $C_{24}H_{31}NO_6$, C 67.11, H 7.27, N 3.26; found, C 66.94, H 7.46, N 3.11.

5-[2-(3,4-Dimethoxyphenyl)vinyl]-7,8-dimethoxy-2-methyl-3,4-dihydro-2*H*-isoquinolin-1-one (4). Triflic anhydride (1.22 g, 4.31 mmol) was added dropwise over 5 min to a solution of compound **3b** (370 mg, 0.86 mmol) and DMAP (316 mg, 2.58 mmol) in dry dichloromethane (10 mL) at 0 °C. The mixture was stirred for 1.5 h under argon at rt. The reaction mixture was then diluted with dichloromethane (10 mL) and the resulting solution was successively washed with saturated potassium carbonate (20 mL), 10% aq. hydrochloric acid (30 mL) and water (50 mL). The solution was dried, filtered and concentrated *in vacuo* to give a yellow oil, which was purified by column chromatography (eluent: 98:2 dichloromethane/methanol) to give isoquinolinone **4** (320 mg, 97% yield) as a yellow oil. IR (ν , cm^{-1}, NaCl): 1643 (CO). ^{1}H NMR (δ, ppm): 7.19 (s, 1 H, ArH); 7.09-7.03 (m, 3 H, 3xArH); 6.87 (d, *J* = 7.8 Hz, 1 H, ArH); 6.84 (d, *J* = 16.0 Hz, 1 H, -CH=C*H*-); 3.99 (s, 3 H, -OCH_3); 3.94 (s, 3 H, -OCH_3); 3.93 (s, 3 H, -OCH_3); 3.91 (s, 3 H, -OCH_3); 3.50-3.45 (m, 2 H, -CH_2-); 3.17 (s, 3 H, -NCH_3); 2.99-2.94 (m, 2 H, -CH_2-). ^{13}C NMR (δ, ppm): 163.05 (CO); 152.53 ($ArOCH_3$); 149.48 ($ArOCH_3$); 149.08 (2x$ArOCH_3$); 130.79 (ArH); 130.25 (C); 130.17 (C); 129.40 (C); 124.39 (C); 123.20 (ArH); 119.68 (ArH); 112.28 (ArH); 111.22 (ArH); 108.97 (ArH); 61.49 (-OCH_3); 56.09 (-OCH_3); 55.85 (2x-OCH_3); 47.66 (-CH_2-); 34.77 (-NCH_3); 25.58 (-CH_2-). Ms (*m*/z, %): 383 (M^+, 53); 354 (100). HRMS: $C_{22}H_{25}NO_5$ (M^+) calcd. 383.1733; found 383.1737.

8,9,11,12-Tetramethoxy-2-methyl-3,4-dihydronaphtho[2,1-*f*]isoquinolin-1(2*H*)-one (5). Air was bubbled for 10 min through a stirred solution of stilbene derivative **4** (107 mg, 0.28 mmol) in diethyl ether (180 mL) and dichloromethane (5 mL). A catalytic amount of iodine (12 mg, 0.03 mmol) was added and the mixture was then irradiated for 3 h in a photochemical reactor equipped with a Pyrex condenser and a Hanovia 450 W medium-pressure Hg vapour lamp. Saturated sodium thiosulfate aqueous solution (100 mL) was added and the organic layer was dried, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (eluent 99:1 dichloromethane/methanol) to afford phenanthrene **5** (48 mg, 45% yield), as a yellow solid. Mp 146-149 °C (methanol). IR (ν , cm^{-1}, NaCl): 1632 (CO). ^{1}H NMR (δ, ppm): 9.27 (s, 1 H, ArH); 7.74 (d, *J* = 9.1 Hz, 1 H, ArH); 7.63 (d, *J* = 9.1 Hz, 1 H, ArH); 7.22 (s, 1 H, ArH); 4.16 (s, 3 H, $-OCH_3$); 4.12 (s, 3 H, $-OCH_3$); 4.06 (s, 3 H, $-OCH_3$); 3.99 (s, 3 H, $-OCH_3$); 3.65-3.60 (m, 2 H, $-CH_2-$); 3.36-3.31 (m, 2 H, $-CH_2-$); 3.24 (s, 3 H, $-NCH_3$). ^{13}C NMR (δ, ppm)): 163.14 (CO); 151.22 ($ArOCH_3$); 150.94 ($ArOCH_3$); 149.34 ($ArOCH_3$); 148.86 ($ArOCH_3$); 133.19 (C); 128.68 (C); 126.46 (C); 126.42 (ArH); 125.82 (C); 124.00 (C); 122.63 (C); 120.14 (ArH); 108.88 (ArH); 107.74 (ArH); 61.93($-OCH_3$); 60.02 ($-OCH_3$); 55.83 ($-OCH_3$); 55.73 ($-OCH_3$); 47.54 ($-CH_2-$); 34.78 ($-NCH_3$); 25.65 ($-CH_2-$). Ms (*m*/z, %): 381 (M^+, 100). Anal. calcd. for $C_{22}H_{23}NO_5$, C 69.28, H 6.08, N 3.67; found, C 68.99, H 6.19, N 3.48.

8,9,11,12-Tetramethoxy-2-methyl-1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinoline (9c). Lithium aluminium hydride (10 mg, 0.26 mmol) was added to a stirred solution of naphthoisoquinolinone **5** (20 mg, 0.05 mmol) in THF (3 mL) at 0 °C. The reaction mixture was stirred at rt for 3 h and the excess lithium aluminium hydride was destroyed by consecutive addition of water (0.013 mL), 15% aq sodium hydroxide (0.13 mL) and water (0.039 mL). The resulting suspension was filtered under vacuum, the solid residue was washed with a 95:5 dichloromethane/methanol mixture, the filtrate was concentrated in vacuo and the solid residue was purified by preparative tlc (eluent: 95:5 dichloromethane/methanol) to give the title compound (12 mg, 65% yield) as a yellow solid. Mp 64-68 °C (methanol). IR (ν , cm^{-1}, NaCl): 1517 (-CN-).^{1}H NMR (δ, ppm): 9.21 (s, 1 H, ArH); 7.75 (d, *J* = 9.1 Hz, 1 H, ArH); 7.62 (d, *J* = 9.1 Hz, 1 H, ArH); 7.23 (s, 1 H, ArH); 4.11 (s, 3 H, $-OCH_3$); 4.05 (s, 3 H, $-OCH_3$); 4.03 (s, 3 H, $-OCH_3$); 3.95 (s, 3 H, $-OCH_3$); 3.77 (s, 2 H, $-CH_2-$); 3.29-3.25 (m, 2 H, $-CH_2-$); 2.88-2.83 (m, 2 H, $-CH_2-$); 2.58 (s, 3 H, $-NCH_3$). ^{13}C NMR (δ, ppm): 148.63 ($ArOCH_3$); 148.50 ($2xArOCH_3$); 148.38 ($ArOCH_3$); 127.79 (2xC); 127.69 (C); 126.48 (C); 125.62 (C); 124.51 (ArH); 122.94 (C); 119.97 (ArH); 108.41 (ArH); 107.76 (ArH); 60.71 ($-OCH_3$); 59.90 ($-OCH_3$); 55.81 ($-OCH_3$); 55.72 ($-OCH_3$); 53.46 ($-CH_2-$); 52.60 ($-CH_2-$); 46.06 ($-NCH_3$); 26.93 ($-CH_2-$). Ms (*m*/z, %): 367 (M^+, 100). Anal. calcd. for $C_{22}H_{25}NO_4$, C 71.91, H 6.86, N 3.81; found, C 72.15, H 6.59, N 4.02.

12-Hydroxy-8,9,11-trimethoxy-2-methyl-3,4-dihydro-2*H*-naphtho[2,1-*f*]isoquinolin-1-one (8). A 1 M solution of boron trichloride in dichloromethane (1.05 mL) was added dropwise under argon to a stirred solution of isoquinolinone **5** (40 mg, 0.11 mmol) in dichloromethane (5 mL) and the mixture was stirred for 15 min. Water (5 mL) was added to the reaction mixture and this was stirred for a further 15 min. The product was extracted with dichloromethane (3 x 10 mL)

and the combined organic extracts were washed with water (15 mL), dried, filtered and concentrated in vacuo. The resulting solid residue was purified by preparative tlc (eluent: 98:2 dichloromethane/methanol) to give phenolic naphthoisoquinolinone **8** (34 mg, 90%) as a yellow solid. Mp 240-242 °C (methanol). IR (ν , cm^{-1}, NaCl): 3440 (-OH), 1641 (CO). ^{1}H NMR (δ, ppm): 12.98 (s, 1 H, -OH); 9.30 (s, 1 H, ArH); 7.62 (d, *J* = 9.2 Hz, 1 H, ArH); 7.47 (d, *J* = 9.2 Hz, 1 H, ArH); 7.15 (s, 1 H, ArH); 4.08 (s, 3 H, $-OCH_3$); 4.04 (s, 3 H, $-OCH_3$); 3.98 (s, 3 H, $-OCH_3$); 3.70-3.64 (m, 2 H, $-CH_2-$); 3.41-3.35 (m, 2 H, $-CH_2-$); 3.19 (s, 3 H, $-NCH_3$). ^{13}C NMR (δ, ppm): 168.73 (CO); 151.70 (ArOH); 149.52 ($ArOCH_3$); 148.55 ($ArOCH_3$); 143.41 ($ArOCH_3$); 131.05 (C); 129.06 (C); 127.61 (C); 124.56 (ArH); 123.59 (C); 121.70 (C); 120.13 (ArH); 112.09 (C); 109.41 (ArH); 107.77 (ArH); 59.55 ($-OCH_3$); 59.82 ($-OCH_3$); 55.74 ($-OCH_3$); 47.81 ($-CH_2-$); 34.60 ($-NCH_3$); 24.09 ($-CH_2-$). Ms (*m*/*z*, %): 367 (M^+, 97); 352 (100). Anal. calcd. for $C_{21}H_{21}NO_5$, C 68.65, H 5.76, N 3.81; found, C 68.51, H 5.93, N 3.63.

8,9,11-Trimethoxy-2-methyl-1,2,3,4-tetrahydro-naphtho[2,1-*f*]isoquinolin-12-ol (9d). Reduction of naphthoisoquinolinone **8** (14 mg, 0.038 mmol) with lithium aluminium hydride (7 mg, 0.19 mmol) under the same conditions as for **9c** provided 10 mg (74% yield) of the title compound as a white solid. Mp 189-190 °C ($CHCl_3$). IR (ν , cm^{-1}, NaCl): 3403 (-OH). ^{1}H NMR (δ, ppm): 8.88 (s, 1 H, ArH); 7.71 (d, *J* = 9.0 Hz, 1 H, ArH); 7.63 (d, *J* = 9.0 Hz, 1 H, ArH); 7.21 (s, 1 H, ArH); 4.07 (s, 3 H, $-OCH_3$); 4.04 (s, 3 H, $-OCH_3$); 3.81 (s, 3 H, $-OCH_3$); 3.78 (s, 2 H, $-CH_2-$); 3.27-3.25 (m, 2 H, $-CH_2-$); 2.90-2.85 (m, 2 H, $-CH_2-$); 2.59 (s, 3 H, $-NCH_3$). ^{13}C NMR (δ, ppm): 148.64 (C); 148.58 (C); 144.29 (C); 140.59 (C); 127.89 (C); 127.07 (C); 124.88 (C); 124.01 (ArH); 123.24 (C); 122.12 (C); 121.45 (C); 120.21 (ArH); 107.70 (ArH); 107.59 (ArH); 60.33 ($-OCH_3$); 55.78 ($-OCH_3$); 55.74 ($-OCH_3$); 52.96 ($-CH_2-$); 52.46 ($-CH_2-$); 45.87 ($-NCH_3$); 26.64 ($-CH_2-$). Ms (*m*/*z*, %): 353 (M^+, 86); 310 (100). Anal. calcd. for $C_{21}H_{23}NO_4$, C 71.37, H 6.56, N 3.96; found, C 71.62, H 6.47, N 4.13.

Acknowledgments

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