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# (*Z*)-Ethyl 2-phenyl-1-(2-vinylphenyl)vinylcarbamates. Part 1: Synthesis and preliminary studies on their divergent transformation into benzo[*c*]phenanthridines and 2-phenyl-1,4-naphthoquinones

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ABSTRACT

Treatment of *N*-carbethoxy-1-benzylideneisoquinolines with LDA gives *N*-ethoxycarbonyl-1-amino-1-(2-vinylphenyl)-2-phenylethylenes, which can easily be transformed into *N*-carbethoxy-1-amino-2-phenylnaphthalenes. Bischler–Napieralski reaction of these latter compounds affords the corresponding benzo[*c*]phenanthridines, while their hydrolysis and subsequent oxidation constitutes a novel route to 2-phenyl-1,4-naphthoquinones.



## 1. Introduction

1-Benzylisoquinolines have received considerable attention both as synthetic and biogenetic precursors of a wide variety of natural compounds of pharmacological interest, including morphines, aporphines, protoberberines and benzo[*c*]phenanthridines (**1**).[1] These four families of isoquinoline alkaloids have a widespread occurrence in nature and a broad range of biological activities,[2,3] but only protoberberines and benzo[*c*]phenanthridines exhibit antineoplastic activity. In fact, nitidine (**1a**) and benzo[*c*]phenanthridine analogues, such as fagaronine (**1b**), exhibit potent antitumour activity by inhibition of DNA topoisomerase I,[3a,4] a property that has been related to their structural similarity with carcinogenic polycyclic aromatic hydrocarbons, such as chrysene and dimethylbenzanthracene. This behaviour has been attributed to the presence in their structures of a conformationally rigid embedded 2-phenylnaphthalene subunit, because other polycyclic aromatic hydrocarbons where this subunit is not present, such as triphenylene, do not show carcinogenic properties.[5] The antineoplastic properties of benzo[*c*]phenanthridines have been attributed to the fact that their tetracyclic framework includes the 2-phenylnaphthalene structural pattern present in chrysene, although in this case it is formed not only by carbon atoms. The presence of a nitrogen atom in these alkaloids modifies the electronic distribution of the annular system and, furthermore, the presence of alkoxy substituents at strategic positions of this annular system interferes with the epoxidation–hydroxylation processes involved in the carcinogenesis mechanism.

The range of 2-phenylnaphthalene-based compounds that show antineoplastic activity also includes several types of antibiotics with antitumour activity, such as 5*H*-benzo[*b*]carbazole-6,11-diones **2**[6] and ellipticine quinones **4**,[7] which retain a close structural relationship with ellipticine **3**,[8] a naturally occurring 6*H*-pyrido[4,3-*b*]carbazole alkaloid with powerful antitumour activity. The embedded 2-phenylnaphthalene subunits present in **2** and **4** are a 2-phenyl-1,4-naphthoquinone and a 6-phenylisoquinoline-5,8-dione, respectively (Fig. 1).

As a result of these important pharmacological properties, a variety of methods have been used for the synthesis of targets **1**,[9,10] **2**[11] and **4**,[12] and particularly attractive are those in which the key step is the annelation of an appropriate 2-phenylnaphthalene

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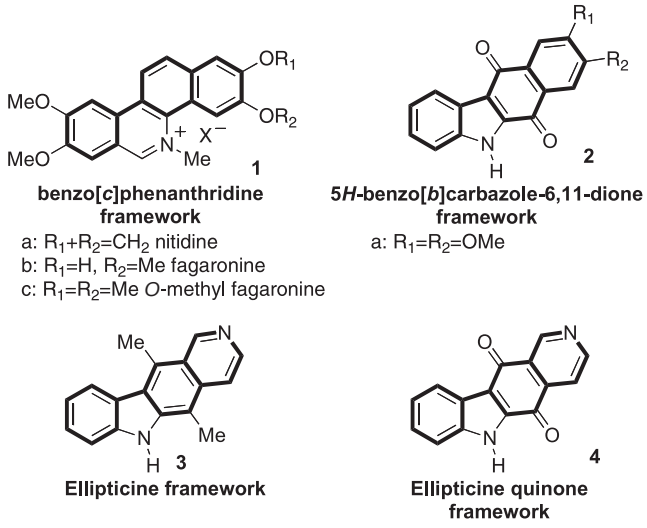



**Fig. 1.** Frameworks for benzo[*c*]phenanthridines, 5*H*-benzo[*b*]carbazole-6,11-diones, ellipticines and ellipticine quinones.

precursor. Accordingly, different approaches for the synthesis of 2-phenylnaphthalenes have been developed. These include recent approaches based on a key step consisting of the construction of their biarylic bond, a process, that is, usually very sensitive to steric hindrance.[13] The search for new and efficient approaches to 2-phenylnaphthalenes is therefore of current interest.

## 2. Results and discussion

In a previous communication[14] we reported preliminary results on a novel access to 2-phenylnaphthalenes **7** (Scheme 1) from 1-benzylideneisoquinolines **9** via the novel (*Z*)-alkyl 2-phenyl-1-(2-vinylphenyl)vinylcarbamates **8**, and their divergent transformation into benzo[*c*]phenanthridin-1-ones **5** and 2-phenyl-1,4-naphthoquinones **6**. The present article includes a full description of this chemistry, together with the following unpublished related results: (a) the novel photochemically induced transformation of compound **8b** into the complex compound **12** (Scheme 2); (b) a novel formal synthesis of *O*-methyl fagaronine (**1e**) (Scheme 2) and (c) the novel rearrangement of *N*-carbethoxy 1-(2-nitrobenzylide-ne) isoquinoline **9c** to 5-nitroisoquinolin-1(2*H*)-one **19**, which, in turn, rearranges to the novel 2-(2-methylamino-carbonyl)isoquinolin-1(2*H*)-one **21** via its derivative **20** (Scheme 5).

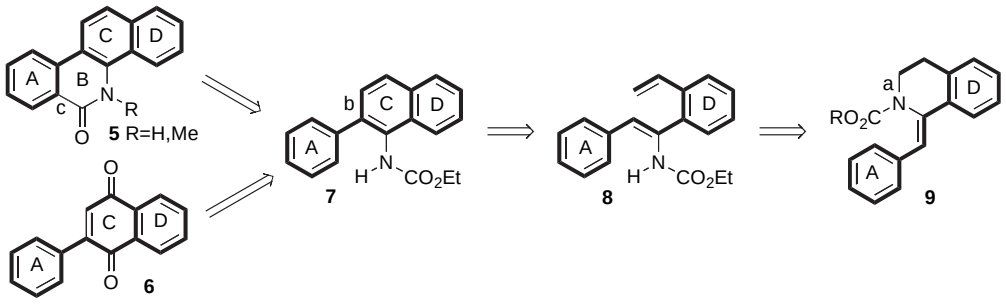
Our synthetic plan for benzo[*c*]phenanthridines **5** is based on the three key steps depicted in Scheme 1. We reasoned that disconnection of the strategic bond **a** in isoquinolines **9** should allow access to the novel stilbene-like compounds **8**, which have the required carbon skeleton and a suitable functionality for the sequential construction of the central C and B rings of our targets **5**. Ring C should result from an electrocyclic cyclization, allowing the transformation of stilbene compounds **8** into the corresponding 2-phenylnaphthalenes **7**. In addition, ring B should result from a previously described Bischler–Napieralski cyclization of 2-phenylnaphthalenes **7**.

According to our synthetic plan, treatment of the known 1-benzylideneisoquinoline **9a**[15] with LDA at 0 °C provided the styrylurethane **8a** resulting from the expected cleavage of its $C_3$–N bond (Scheme 2).[14]

The structure of compound **8a** was unambiguously established from its analytical data and by 1D and 2D NMR studies, including heteronuclear multiple-bond correlations (HMBC). A $^1$H NMR NOE experiment on **8a** established a Z configuration for its stilbenic double bond. This conclusion was based on the observation that irradiation of its $H_2$, $H_{6'}$ and N–H protons results in a large increase in the peak intensities of the protons indicated in Fig. 2.

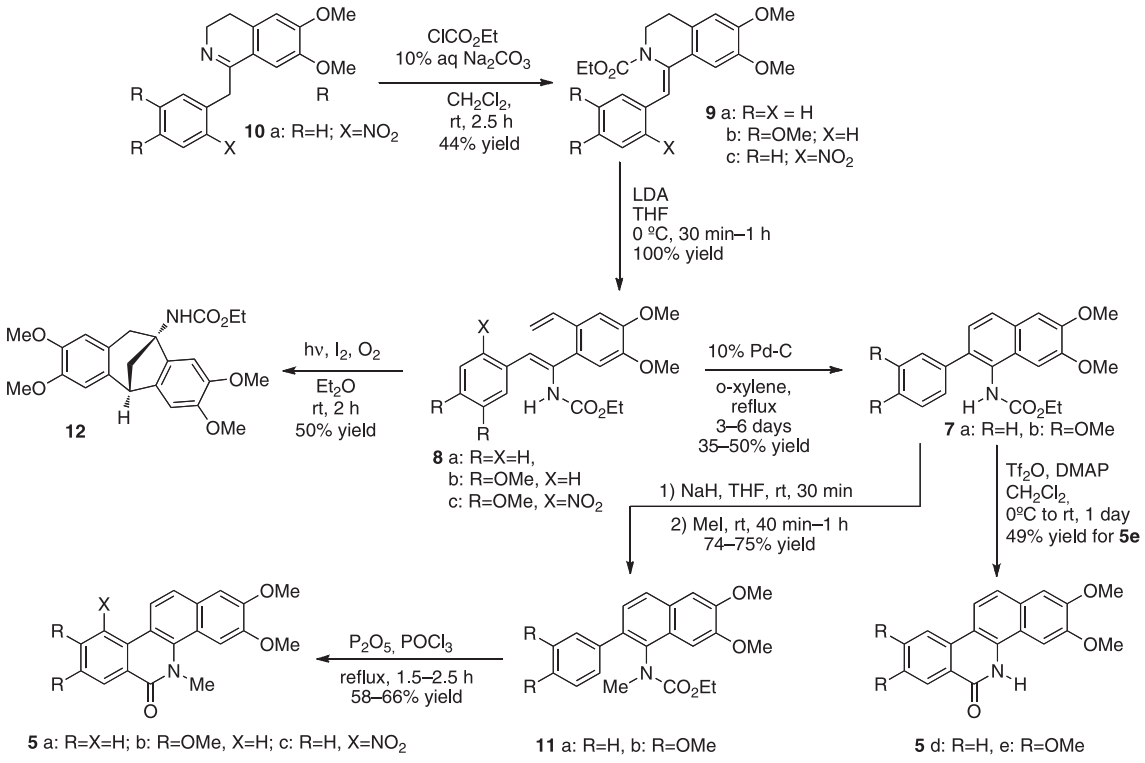
Continuing with our plan, when a solution of compound **8a** in *o*-xylene containing 10% Pd/C was refluxed for 3 days, the desired 2-phenylnaphthalene derivative **7a** was obtained in only a 35% yield,[16] as a result of the generation of its C ring by a thermically induced electrocyclic cyclization, as it was easily established from analytical and spectroscopic data. In fact, its mass spectrum showed the molecular weight expected for this compound (*m*/*z*=351, $M^+$, 100) and its $^1$H NMR spectrum includes signals for nine aromatic protons (two less than **8a**). After, compound **7a** was easily converted into its *N*-methyl derivative **11a** by treatment with MeI in a basic medium. Finally, following the designed plan for the sequential construction of rings B and C of our targets **5**, the formation of the B ring of benzo[*c*]phenanthridine target **5a** was easily achieved in a 57% yield by subjecting its precursor **11a** to the well known Bischler–Napieralski protocol for the synthesis of isoquinolines,[17] by refluxing a solution of **11a** and $P_2O_5$ in $POCl_3$ during 1.5 h. The successful outcome of these reaction was easily stated from analytic and spectroscopical data of **5a**. Thus, its mass spectrum allowed to establish its molecular weight of 319 (46 mass units fewer than those of **11a**). In addition, its $^1$H NMR spectrum includes signals for eight aromatic protons (a proton less than its precursor **11a**). A similar sequence led to the tetrasubstituted benzo[*c*]phenanthridine **5b** from the known 1-benzylideneisoquinoline **9b**,[15] via compounds **8b**, **7b** and **11b**.

Attempts to transform 2-phenylnaphthalene derivatives **7a** and **7b** into their respective *N*-unsubstituted benzo[*c*]phenanthridine-1-ones **5d** and **5e** were partially satisfactory (Scheme 2). Thus




**Scheme 1.**

2-phenylnaphthalene **7b** remained unaltered when subjected to the same Bischler–Napieralski cyclization conditions as for **11a**, but satisfactory results were achieved when harsher reaction conditions (triflic anhydride and DMAP) were used.[18] Under these




**Scheme 2.**

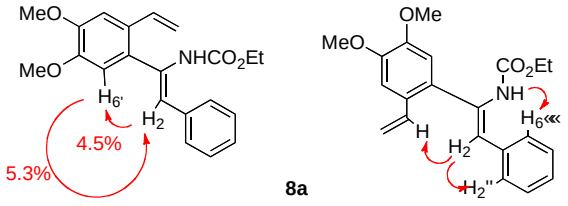



**Fig. 2.** Retrosynthetic plan for the divergent access to benzo[*c*]phenanthridines and 2-phenyl-1,4-napthoquinones.

conditions the expected compound **5e** was obtained in 49% yield. But the similar transformation of **7a** into **5d** did not occur under these conditions, probably due to the absence of electron-donating substituents on the A ring of **7a**.

In an attempt to improve the yield obtained in the transformation of compounds **8** into compounds **7**, we decided to explore the photoinduced electrocyclic cyclization of compound **8b**. Unexpectedly, irradiation of a solution of this compound in diethyl ether with a medium pressure lamp (Hanovia, 450 W) for an hour, using iodine and oxygen as oxidants,[19] led to a reaction mixture from which the desired phenylnaphthalene **7b** was isolated in only 4% yield. The main reaction product was the complex bicyclic compound **12**, as established from its analytical and spectroscopical data, including 1D and 2D NMR studies (COSY, HMQC, HMBC and NOESY). The signals at 2.42 ppm (d, $J$=9.5 Hz) and 2.72 ppm (dd, $J$=9.5 Hz and $J$=4.5 Hz), corresponding to one of the methylene groups, together with doublets at 2.98 ppm ($J$=15.6 Hz) and 3.47 ppm ($J$=15.6 Hz), both due to the second methylene group, are consistent with its central bicyclic moiety.

In addition, the COSY spectrum contains a signal at 3.85 ppm ($J$=4.5 Hz, H-5) coupled with a proton of the neighbouring methylene group at 2.72 ppm (Ha). Selected 2D, $^{1}$H-, $^{13}$C HMBC and NOE correlations shown in Fig. 3 provide additional evidence supporting the structure proposed for compound **12**.

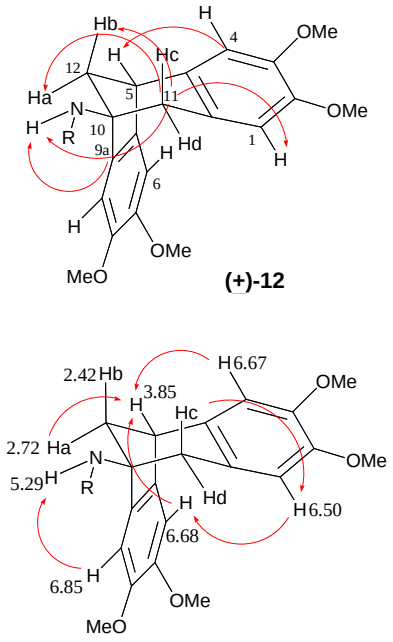
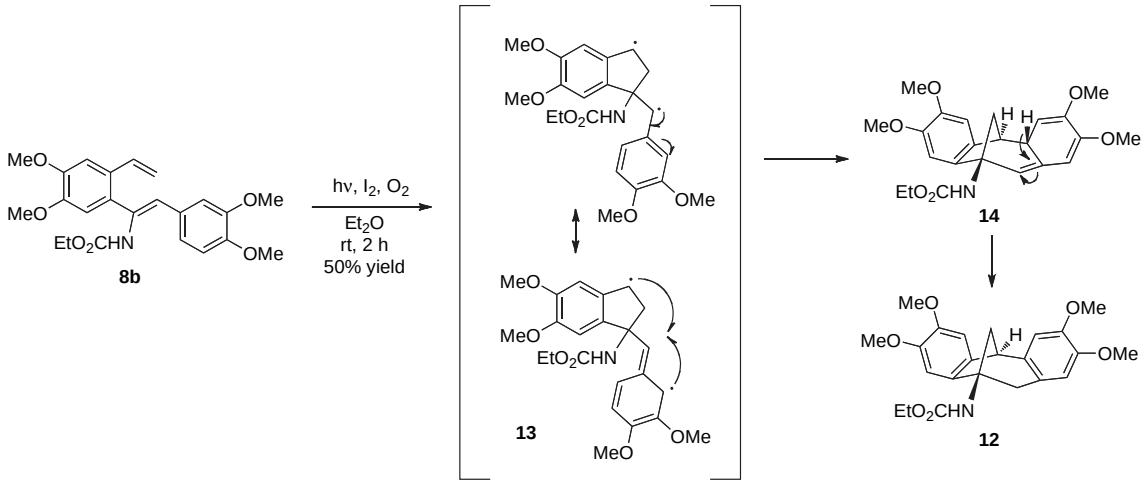



**Fig. 3.** Selected $^{13}$C HMBC and NOE correlations for compound **12**.

A tentative mechanism was proposed to explain the formation of this complex compound **12** (Scheme 3).[20] It was envisaged that the process begins with the formation of biradical **13** arising from an *endo* cyclization involving the styrene and the stilbene moieties of the starting material. Subsequent intramolecular biradical coupling affords the bicyclic intermediate **14**. Finally, an aromatization process by a [1,3] hydrogen sigmatropic rearrangement yields the bicycle **12**.

The present strategy for the synthesis of benzo[*c*]phenanthridin-1-ones **5** was successfully applied to the efficient

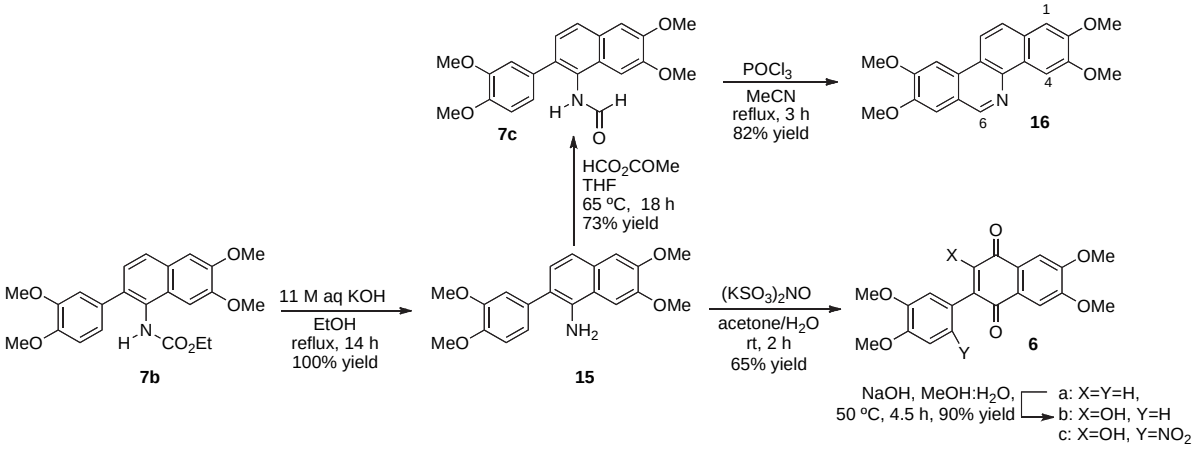



**Scheme 3.**

preparation of benzo[*c*]phenanthridine **16** (Scheme 4),[21] a synthetic precursor of the known *N*-methyl fagaronine iodide (**1c**, X=I).[21] When a solution of *N*-carbethoxy-1-amino-2-phenylnaphthalene **7b** and aq KOH in ethanol was refluxed for 14 h, the expected naphthylamine **15** was obtained quantitatively, as a result of a basic hydrolysis of its *N*-carbethoxy subunit. Compound **15** was directly solved in THF, formic-acetic anhydride was added and the resulting solution was next heated at 65 °C for 18 h. This provided a 73% yield of formamide **7c**, easily identified from analytical and spectroscopic data. Its mass spectrum confirmed the molecular weight expected for this compound (*m*/*z*=367, $M^+$, 100) and its IR spectrum showed at 3297 and at 1684 $cm^{-1}$ two band dues to its *N*–H and carbonyl groups, respectively. On the other hand, although its $^1H$ NMR and $^{13}C$ NMR spectra denoted the presence of a mixture of rotamers, a signal showed by its $^1H$ NMR spectrum at 8.47 ppm, was unambiguously attributed to its formyl proton.

As an additional synthetic application of the novel *N*-styrylurethanes **8**, we report here the first example of the transformation of these promising scaffolds into 2-phenyl-1,4-naphthoquinones. This process was carried out as depicted in Scheme 4. Thus, 1-amino-2-phenylnaphthalene **15** was easily converted into 2-phenyl-1,4-naphthoquinone **6a** by oxidation with Fremy's salt.[22] Finally, when a solution of this quinone in aqueous/methanolic NaOH was heated at 50 °C, the known 2-hydroxy-1,4-naphthoquinone **6b** was efficiently obtained.[14]

This novel access to 2-phenyl-1,4-naphthoquinone **6b**, combined with the previous transformation of the known quinone **6c** into 5*H*-benzo[*b*]carbazole-6,11-dione **2a**,[23] prompted us to explore the preparation of these targets by the novel synthetic approach to quinones described herein. The preparation of the model compound **2a** should start from 1-(*o*-nitrobenzylidene)isoquinoline **9c**, with a nitro substituent conveniently placed for further trans-




**Scheme 4.**

Finally, when a solution of this amide **7c** and $POCl_3$ in acetonitrile was refluxed for 3 h, a 82% yield of the expected benzo[*c*]phenanthridine **16** was obtained, as a result of the programmed Bischler–Napieralski cyclization. Its mass spectrum and microanalysis confirmed its molecular formula $C_{21}H_{19}NO_4$ and its $^1H$ NMR showed signals for a total of seven aromatic protons, including a signal at 9.26 ppm, corresponding to the highlight deshielded proton at C-6. As compound **7c** was previously converted into *O*-methyl fagaronine iodide (**1c**),[21] the present approach to **7c** formally constitutes a new, more efficient synthesis of **1c**.

formations. This isoquinoline was efficiently prepared according to a protocol described for the preparation of its analogues **9a** and **9b** (Scheme 2). Thus, treatment of the known dihydroisoquinoline **10a** with ethyl chloroformiate in a basic medium provided this key compound **9c**, as it was easily established from its analytical and spectroscopical data. Its IR spectrum includes at 1695 $cm^{-1}$ a band due to the carbamate carbonyl group, together with two bands at 1515 and 1340 $cm^{-1}$, dues to the nitro group. Its $^1H$ NMR and $^{13}C$ NMR spectra are similar to those of **9a** and **9b**, and the former spectrum includes signals for a total of six aromatic protons (one less than **9a**).

Proceeding as for **9a** and **9b**, reaction of compound **9c** with LDA in THF at 0 °C for 1.5 h surprisingly gave a complex reaction mixture that did not contain the desired stilbene **8c** (Scheme 2). However, new unexpected results were obtained when a solution of compound **9c** and NaH in DMF was heated at 130 °C for 3 h. The main reaction product was not the expected stilbene **8c** but the isoquinoline **18** (Scheme 5), as deduced from its analytical and spectroscopic data. The $^1$H NMR spectrum includes at 5.27, 5.66 and 7.03–7.15 ppm signals dues to the vinyl substituent, and a broad signal at 11.30 ppm was assigned to the amide proton. The IR spectrum shows at 1664 cm$^{-1}$ a strong band due to the amide carbonyl group and at 1515 and 1340 cm$^{-1}$ the typical bands of nitro groups.

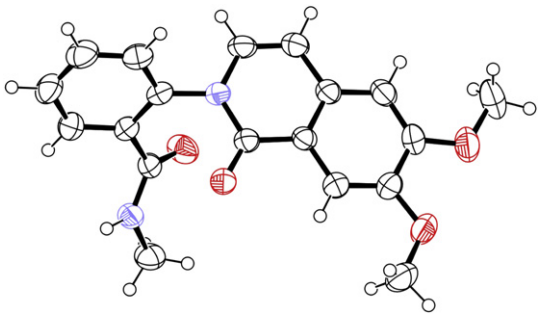
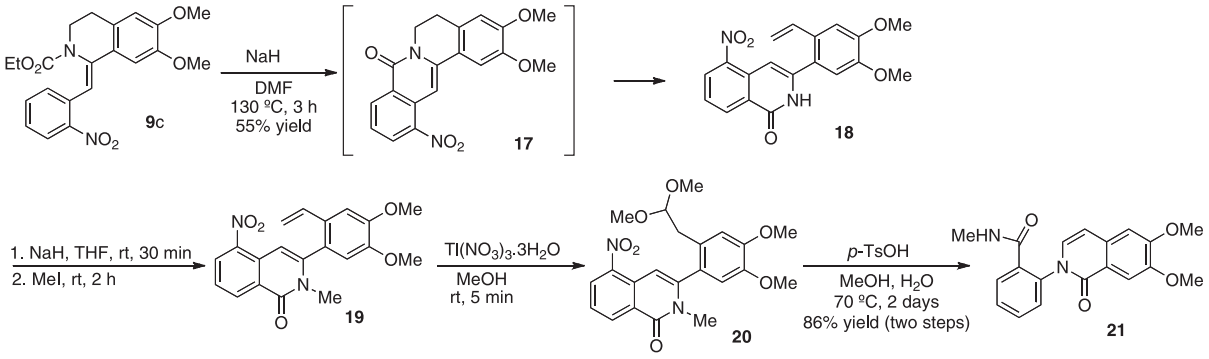


**Fig. 4.** ORTEP diagram of compound **21**.




**Scheme 5.**

Formation of isoquinoline **18** may be regarded as being the result of a nitro facilitated thermally promoted electrocyclic cyclization of **9c** involving its *N*-ethoxycarbonyl substituent, which should lead to protoberberine derivative **17**. Eventually, this compound could spontaneously be converted into compound **18** by a Hofmann-like elimination by the action of hydride (Scheme 5).

This route constitutes a novel access to 3-(2-vinylphenyl)-isoquinolin-1(2*H*)-ones (**18**), which have previously been converted into the corresponding benzo[*c*]phenanthridin-1-ones (**5**) by a protocol,[24] that when applied to isoquinolinone **18** produced unexpected results. Thus, once compound **18** was converted into its *N*-methyl derivative **19** by reaction with NaH and MeI, treatment of **19** with thallium trinitrate allowed us to obtain the slightly unstable acetal derivative **20**, as deduced from its $^1$H NMR spectrum, which showed at 2.70 ppm and at 3.10 ppm signals dues to its methylene protons and at 4.50 ppm the signal corresponding to the proton at the acetalic carbon.

This compound **20** was directly solved in a MeOH/$H_2O$ mixture, *p*-toluensulfonic acid was added and the solution was heated at 70 °C for two days. But, unfortunately, the expected benzo[*c*]phenanthridin-1-one **5c** was not obtained. Surprisingly, the resulting compound was the isoquinolin-1-one **21**, as it was established from its analytical and spectroscopical data. Its mass spectrum confirmed its molecular formula $C_{19}H_{19}N_2O_4$ and its IR spectrum includes bands at 3331 and 1651 cm$^{-1}$, due to its amide moiety, and no typical bands of nitro groups were present. Its $^1$H NMR includes a key signal at 2.71 ppm (d, $J$=5.2 Hz), corresponding to its NH–$CH_3$ moiety. In addition, structure of compound **21** was firmly established by means of an X-ray experiment (Fig. 4).[25]

We assumed that the nitro group prevents the cyclization required for the transformation of compound **19** into the corresponding benzo[*c*]phenanthridine **5c** in favour of the novel, complex rearrangement leading isoquinolinone **21**.

To sum up, we report here the novel base-promoted Hoffman-like opening of *N*-carbethoxy-1-benzylisoquinolines **9** to the novel (*Z*)-ethyl 2-phenyl-1-(2-vinylphenyl)vinylcarbamates **8**, which allowed the development of the first divergent synthesis of benzo[*c*]phenanthridines **5** and 3-phenyl-1,4-naphthoquinone **6a**. This new approach to benzo[*c*]phenanthridines involves the sequential construction of their central rings. Firstly, ring B results from a novel thermally induced electrocyclic cyclization of the key stilbene-like derivatives **8** and this is followed by a spontaneous oxidation. This provided a novel access to 2-phenylnaphthalenes **7**, from which the C ring of benzo[*c*]phenanthridines is formed by the known Bischler–Napieralski cyclization. Unfortunately, however, this first route for the preparation of (*Z*)-ethyl 2-phenyl-1-(2-vinylphenyl)vinylcarbamates **8** showed to be limited to benzylisoquinolines **9** without nitro substituents at their A ring. In fact, the 2-hydroxy-3-(*o*-nitrophenyl)-1,4-naphthoquinone **6c** could not be obtained from compound **9c** via compound **8c**, due to the unstability of **9c** under the standard basic reaction conditions involved in the transformation of compounds **9a** and **9b** into compounds **8a** and **8b**, respectively.

Ongoing work in this field includes the search for experimental conditions for the transformation of nitrobenzylydeneisoquinoline **9c** into the corresponding stilbene **8c** and for the transformation of isoquinolinone **19** into the corresponding benzo[*c*]phenanthridinone **5c**. Additional work is in progress, which is aimed at an alternative transformation of *N*-styrylurethanes **8** into benzo[*c*]phenanthridines **5**, involving the sequential construction of their B and C central rings in an opposite order to that here reported.

## 3. Experimental section

### 3.1. General

Melting points were determined on a Kofler Thermogerate apparatus and are uncorrected. Infrared spectra were recorded on a JASCO FT/IR-400 spectrophotometer. Nuclear magnetic resonance spectra were recorded, unless otherwise specified, on a Bruker WM-250 apparatus using deuterochloroform solutions containing tetramethylsilane as an internal standard. $^1$H NMR splitting

patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q) or quintuplet (p). All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Mass spectra were obtained on an HP 5988A mass spectrometer, using the electron impact (EI) or the chemical ionization (CI) techniques. Elemental analyses were performed on EA 1108 CHNS Fisons. Thin layer chromatography (TLC) was performed using Merck GF-254 type 60 silica gel and dichloromethane/methanol or ethyl acetate/hexane mixtures as eluents; 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. 26. Solutions of extracts in organic solvents were dried with anhydrous sodium sulfate.

### 3.2. (*Z*)-Ethyl 1-(2-vinylphenyl)-2-phenylvinylcarbamates 8: general procedure

A solution of diisopropylamine (9.29 mmol, 4.8 equiv) in dry THF (38 mL) was cooled to 0 °C and *n*-BuLi (1.20 M, 9.29 mmol) was added. The mixture was stirred at rt for 20 min and then cooled again to 0 °C. The freshly prepared LDA was added dropwise to a solution of **9** (1.93 mmol) in THF (23 mL) under an argon atmosphere. The mixture was stirred at 0 °C for 30 min for **9a** and 1 h for **9b**. Water (7 mL) was added dropwise, the mixture was concentrated to dryness in vacuo and water (30 mL) was added. The resulting suspension was extracted with $CH_2Cl_2$ (3×25 mL). The organic layer was dried and concentrated to dryness, to provide a chromatographically pure white solid of **8a** (100% yield) or **8b** (100 yield).

*3.2.1. (Z)-Ethyl 1-(4,5-dimethoxy-2-vinylphenyl)-2-phenylvinylcarbamate (**8a**).* White solid (100% yield); $R_f$=0.51 (40% AcOEt/hexane); mp 106–109 °C ($Et_2O$).[27]

*3.2.2. (Z)-Ethyl 1-(4,5-dimethoxy-2-vinylphenyl)-2-(3,4-dimethoxyphenyl)vinylcarbamate (**8b**).* White solid (100% yield); $R_f$=0.67 (10% MeOH/$CH_2Cl_2$); mp 137–139 °C (MeOH).[27]

### 3.3. Ethyl 2-phenylnaphthalen-1-ylcarbamates 7: general procedure

Pd/C (560 mg, 10% in weight Pd) was added to a degassed solution of carbamates **8** (1.59 mmol) in dry *o*-xylene (40 mL) and the resulting suspension was heated under reflux under argon for 4 days. The solids were filtered off through a Celite pad, which was washed with *o*-xylene, and the solvent was removed in vacuo. Compounds **7a** and **7b** were isolated by flash column chromatography (AcOEt/hexane 6:4).

*3.3.1. Ethyl 6,7-dimethoxy-2-phenylnaphthalen-1-ylcarbamate (**7a**).* White solid (26% yield); $R_f$=0.64 (50% AcOEt/hexane); mp 157–160 °C ($Et_2O$); IR ($\bar{\nu}$, $cm^{-1}$, NaCl): 1707 (C=O); $^1H$ NMR ($\delta$, ppm, $CDCl_3$): 0.99–1.30 (m, 3H, $CH_3$), 3.98–4.13 (m, 8H, 2×$OCH_3$+$CH_2$), 6.24 (s, 1H, NH), 7.15 (s, 1H, Ar–H), 7.22–7.63 (m, 7H, 7×Ar–H), 7.69 (d, 1H, *J*=8.4 Hz, Ar–H); $^{13}C$ NMR ($\delta$, ppm, $CDCl_3$): 14.6 ($CH_3$), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 61.3 ($OCH_2$), 102.3 (CH), 106.4 (CH), 126.0 (CH), 126.2 (CH), 126.9 (C), 127.1 (CH), 128.1 (C), 128.3 (2×CH), 129.1 (2×CH), 129.5 (C), 135.3 (C), 139.9 (C), 149.7 (C–OMe), 150.2 (C–OMe), 155.6 (C=O); MS (*m*/*z*, %): 351 ($M^+$, 100). Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 72.01; H, 5.97; N, 3.91.

*3.3.2. Ethyl 6,7-dimethoxy-2-phenylnaphthalen-1-ylcarbamate (**7b**).* White solid (26% yield); $R_f$=0.52 (60% AcOEt/hexane); mp 164–167 °C (AcOEt); IR ($\bar{\nu}$, $cm^{-1}$, NaCl): 1721 (C=O); $^1H$ NMR ($\delta$, ppm, $CDCl_3$): 1.24 (t, 3H, *J*=7.1 Hz, $CH_3$), 3.84 (s, 3H, $OCH_3$), 3.90 (s, 3H, $OCH_3$), 3.95 (s, 3H, $OCH_3$), 3.98 (s, 3H, $OCH_3$), 4.10 (q, 2H, *J*=7.1 Hz, $OCH_2$), 6.37 (s, 1H, NH), 6.92–6.96 (m, 3H, 3×Ar–H), 7.13 (s, 1H, Ar–H), 7.24 (s, 1H, Ar–H), 7.33 (d, 1H, *J*=8.4 Hz, Ar–H), 7.70 (d, 1H, *J*=8.4 Hz, Ar–H); $^{13}C$ NMR ($\delta$, ppm, $CDCl_3$): 14.6 ($CH_3$), 55.7 (2×$OCH_3$), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 61.3 ($OCH_2$), 102.4 (CH), 106.4 (CH), 111.1 (CH), 112.5 (CH), 121.4 (CH), 125.9 (CH), 126.2 (CH), 126.9 (C), 128.1 (C), 129.4 (C), 132.5 (C), 134.9 (C), 148.3 (C–OMe), 148.7 (C–OMe), 149.6 (C–OMe), 150.2 (C–OMe), 155.7 (C=O); MS (*m*/*z*, %): 411 ($M^+$, 100). Anal. Calcd for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.13; N, 3.40. Found: C, 67.25; H, 6.27; N, 3.23.

### 3.4. Ethyl 2-phenylnaphthalen-1-ylcarbamates 11: general procedure

A suspension of NaH (4.64 mmol, 8.7 equiv) in dry THF (5 mL) was stirred at 0 °C for 30 min under an argon atmosphere. A solution of **7** (0.53 mmol) in dry THF (5 mL) was added dropwise and the mixture was stirred at rt for 30 min $CH_3I$ (1.11 mL, 33.5 equiv) was added dropwise and stirring was continued at rt for 45 min. The excess NaH was destroyed by adding water (10 mL) and the THF was evaporated off. The aqueous layer was extracted with $CH_2Cl_2$ (3×20 mL), the combined extracts were dried, filtered and evaporated to dryness in vacuo to give a residue that was purified by column chromatography (AcOEt/hexane 3:7 for **11a** and AcOEt/hexane 1:1 for **11b**).

*3.4.1. Ethyl 6,7-dimethoxy-2-phenylnaphthalen-1-yl(methyl)carbamate (**11a**).* White solid (74% yield); $R_f$=0.53 (40% AcOEt/hexane); mp 245 °C (MeOH); IR ($\bar{\nu}$, $cm^{-1}$, NaCl): 1695 (C=O); $^1H$ NMR ($\delta$, ppm, $CDCl_3$): as a mixture 4.5:1 of rotamers, 1.05 (t, 3H, *J*=7.1 Hz, $CH_3$), 1.29 (t, 3H, *J*=7.1 Hz, $CH_3$), 2.91 (s, 3H, $NCH_3$), 3.00 (s, 3H, $NCH_3$), 3.94–4.26 (m, 8H, 2×$OCH_3$+$OCH_2$), 7.02 (s, 1H, Ar–H), 7.05 (s, 1H, Ar–H), 7.17 (s, 1H, Ar–H), 7.19 (s, 1H, Ar–H), 7.26–7.47 (m, 6H, Ar–H), 7.69 (d, 1H, *J*=8.4 Hz, Ar–H); $^{13}C$ NMR ($\delta$, ppm, $CDCl_3$) as a mixture 4.5:1 of rotamers, 14.8 ($CH_3$), 15.0 ($CH_3$), 36.9 ($NCH_3$), 37.0 ($NCH_3$), 55.8 ($OCH_3$), 55.9 ($OCH_3$), 56.0 ($OCH_3$), 61.5 ($OCH_2$), 61.6 ($OCH_2$), 101.5 (CH), 101.6 (CH), 106.7 (CH), 106.8 (CH), 126.2 (CH), 126.3 (CH+C), 126.4 (C), 126.7 (2×CH+C), 127.1 (CH), 127.3 (CH), 128.2 (2×CH), 128.4 (2×CH), 128.6 (2×CH), 128.8 (2×CH), 130.0 (C), 130.7 (C), 134.9 (C), 135.5 (C), 136.1 (C), 140.0 (C), 140.1 (C), 149.7 (C–OMe), 150.6 (C–OMe), 156.3 (C=O), 156.6 (C=O); MS (*m*/*z*, %): 365 ($M^+$, 100).

*3.4.2. Ethyl 2-(3,4-dimethoxyphenyl)-6,7-dimethoxynaphthalen-1-yl (methyl)carbamate (**11b**).* White solid (75% yield); $R_f$=0.61 (40% AcOEt/hexane); mp 152–155 °C (MeOH); IR ($\bar{\nu}$, $cm^{-1}$, NaCl): 1693 (C=O); $^1H$ NMR ($\delta$, ppm, $CDCl_3$): as a mixture 4.5:1 of rotamers,1.08 (t, 3H, *J*=7.1 Hz, $CH_3$), 1.33 (t, 3H, *J*=7.1 Hz, $CH_3$), 2.92 (s, 3H, $NCH_3$), 2.98 (s, 3H, $NCH_3$), 3.88–4.03 (m, 12H, 4×$OCH_3$), 4.06–4.34 (m, 2H, $OCH_2$), 6.92–6.98 (m, 3H, Ar–H), 7.02–7.06 (m, 1H, Ar–H), 7.17–7.19 (m,1H, Ar–H), 7.34 (d, 1H, *J*=8.4 Hz, Ar–H), 7.37 (d, 1H, *J*=8.4 Hz, Ar–H), 7.68 (d, 1H, *J*=8.4 Hz, Ar–H), 7.70 (d, 1H, *J*=8.4 Hz, Ar–H); $^{13}C$ NMR ($\delta$, ppm, $CDCl_3$): as a mixture of rotamers, 15.0 (2×$CH_3$), 36.7 ($NCH_3$), 36.8 ($NCH_3$), 55.8 (3×$OCH_3$), 55.9 (3×$OCH_3$), 56.0 ($OCH_3$), 56.1 ($OCH_3$), 61.6 ($OCH_2$), 61.7 ($OCH_2$), 101.5 (CH), 101.6 (CH), 106.7 (CH), 106.8 (CH), 110.9 (CH), 111.1 (CH), 111.8 (CH), 112.1 (CH), 120.9 (CH), 121.0 (CH), 126.2 (CH), 126.4 (CH), 126.5 (C+CH), 126.7 (CH), 129.5 (C), 129.8 (C), 132.5 (C), 132.8 (C), 134.8 (C), 135.0 (C), 135.4 (C), 135.7 (C), 147.7 (C–OMe), 148.2 (C–OMe), 148.5 (C–OMe), 148.7 (C–OMe), 149.6 (C–OMe), 150.6 (C–OMe), 156.3 (C=O), 156.6 (C=O); MS (*m*/*z*, %): 425 ($M^+$, 100).

### 3.5. 5-Methylbenzo[*c*]phenanthridin-6-(5*H*)-ones 5a and 5b: general procedure

$P_2O_5$ (374 mg, 2.63 mmol, 13.5 equiv) was added to a solution of **11a** or **11b** (0.195 mmol) in $POCl_3$ (8 mL, 8.9 mmol) under an argon atmosphere and the suspension was stirred and heated for 1.5 h for **11a** and 1 h for **11b**. The reaction mixture was evaporated to

dryness and the residue was taken up in water/ice (5 mL). The suspension was neutralized with saturated aqueous $NaHCO_3$ and extracted with $CH_2Cl_2$ (3×20 mL). The organic layer was dried and evaporated in vacuo to dryness to afford compounds **5a** or **5b**, which were purified by column chromatography (AcOEt/hexane 1:1 for **5a** and AcOEt/hexane 9:1 for **5b**).

*3.5.1. 2,3-Dimethoxy-5-methylbenzo[c]phenan-thridin-6-(5H)-one (**5a**).* White solid (57% yield); $R_f$=0.46 (5% MeOH/$CH_2Cl_2$); mp 193–195 °C (MeOH); IR ($\bar{\nu}$, $cm^{-1}$, NaCl): 1641 (C=O); $^1H$ NMR ($\delta$, ppm, $CDCl_3$): 4.00 (s, 3H, $CH_3$), 4.01 (s, 3H, $CH_3$), 4.02 (s, 3H, $CH_3$), 7.13 (s, 1H, Ar–H), 7.51–7.57 (m, 3H, 3×Ar–H), 7.69–7.76 (m, 1H, Ar–H), 8.04 (d, 1H, $J$=8.8 Hz, Ar–H), 8.20 (d, 1H, $J$=8.2 Hz, Ar–H), 8.52 (dd, 1H, $J$=7.9 Hz, $J$=1.4 Hz, Ar–H); $^{13}C$ NMR ($\delta$, ppm, $CDCl_3$): 41.0 ($NCH_3$), 56.0 (2×$OCH_3$), 105.3 (CH), 107.1 (CH), 116.4 (C), 118.4 (CH), 119.6 (C), 121.8 (CH), 122.8 (CH), 125.0 (C), 127.5 (CH), 128.5 (CH), 131.1 (C), 132.6 (CH), 134.2 (C), 135.7 (C), 148.1 (C–OMe), 149.6 (C–OMe), 164.9 (C=O); MS ($m/z$, %): 319 ($M^+$, 100). HRMS calcd for $C_{20}H_{17}NO_3$ $[M]^+$ 319.1203; found 319.1204.

*3.5.2. 2,3,8,9-Tetramethoxy-5-methylbenzo[c]phe-nanthridin-6(5H)-one (**5b**).* White solid (66% yield); $R_f$=0.42 (5% MeOH/$CH_2Cl_2$); mp 220–250 °C decomp. (MeCN); IR ($\bar{\nu}$, $cm^{-1}$, NaCl): 1616 (C=O); $^1H$ NMR ($\delta$, ppm, $CDCl_3$): 4.04 (s, 9H, 3×$CH_3$), 4.05 (s, 3H, $CH_3$), 4.10 (s, 3H, $CH_3$), 7.17 (s, 1H, Ar–H), 7.56–7.59 (m, 3H, 3×Ar–H), 7.90 (s, 1H, Ar–H), 7.98 (d, 1H, $J$=9 Hz, Ar–H); $^{13}C$ NMR ($\delta$, ppm, $CDCl_3$): 41.0 ($NCH_3$), 55.9 (2×$OCH_3$), 56.1 ($OCH_3$), 56.2 ($OCH_3$), 102.7 (CH), 105.4 (CH), 107.1 (CH), 108.5 (CH), 116.2 (C), 118.2 (CH), 119.0 (C), 119.7 (C), 122.6 (CH), 129.1 (C), 130.6 (C), 135.1 (C), 148.1 (C–OMe), 149.3 (C–OMe), 149.5 (C–OMe), 153.4 (C–OMe), 164.4 (C=O); MS ($m/z$, %): 379 ($M^+$, 100); HRMS calcd for $C_{22}H_{21}NO_5$ $[M]^+$ 379.1414; found 379.1417.

### 3.6. (±)-*N*-Ethoxycarbonyl-2,3,7,8-tetramethoxy-5,10-methylene-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl-amine (12)

In a photochemical reactor was dissolved **8b** (150 mg, 0.368 mmol) and $I_2$ (101 mg, 0.399 mmol, 1.1 equiv) in $Et_2O$ (200 mL). Oxygen was bubbled through this solution for 15 min and the mixture was then irradiated with a medium pressure lamp (Hanovia 450 W) for 2 h. The reaction mixture was washed with saturated aqueous $Na_2S_2O_3$ (2×200 mL) and the organic layer was dried and evaporated in vacuo to dryness. The residue was purified by column chromatography (AcOEt/cyclohexane 4:6) to afford compounds **12** (75 mg, 0.182 mmol, 50%) and **7b** (6 mg, 0.146 mmol, 4%), which were purified by column chromatography (AcOEt/hexane 4:6). Compound **12**, white solid (amorphous). $R_f$=0.51 (50% AcOEt/hexane); IR ($\bar{\nu}$, $cm^{-1}$, NaCl): 1708 (C=O); $^1H$ NMR ($\delta$, ppm, $CDCl_3$): 1.27 (t, 3H, $J$=7.6 Hz, $CH_3$), 2.42 (d, 1H, $J$=9.5 Hz, CH*H*), 2.72 (dd, 1H, $J$=9.5, 4.5 Hz, CH*H*), 2.98 (d, 1H, $J$=15.6 Hz, CH*H*), 3.47 (d, 1H, $J$=15.6 Hz, CH*H*), 3.75 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 3.82 (s, 3H, $OCH_3$), 3.85 (d, 1H, $J$=4.5 Hz, $H_5$), 3.87 (s, 3H, $OCH_3$), 4.15 (c, 2H, $J$=7.6 Hz, $OCH_2$), 5.29 (s, 1H, NH), 6.50 (s, 1H, Ar–H), 6.67 (s, 1H, Ar–H), 6.68 (s, 1H, Ar–H), 6.85 (s, 1H, Ar–H); $^{13}C$ NMR ($\delta$, ppm, $CDCl_3$): 14.6 ($CH_3$), 38.8 ($CH_2$), 45.6 (CH), 47.5 ($CH_2$), 55.8 ($OCH_3$), 56.0 ($OCH_3$), 56.1 ($OCH_3$), 56.2 ($OCH_3$), 60.7 ($OCH_2$), 62.6 (C), 105.2 (CH), 105.6 (CH), 109.2 (CH), 113.3 (CH), 125.6 (C), 134.5 (C), 135.6 (C), 140.7 (C), 146.9 (C–OMe), 147.6 (C–OMe), 148.5 (C–OMe), 148.6 (C–OMe), 155.6 (C=O); MS ($m/z$, %): 413 ($M^+$, 100); HRMS calcd for $C_{23}H_{27}NO_6$ $[M]^+$ 413.1833; found 413.1842.

### 3.7. 2,3,8,9-Tetramethoxybenzo[*c*]phenanthridin-6(5*H*)-one (5e)

A 1.10 M solution of triflic anhydride in dry $CH_2Cl_2$ (0.972 mmol) was added dropwise to a solution of **7b** (80 mg, 0.194 mmol) and DMAP (71.3 mg, 0.583 mmol) in $CH_2Cl_2$ (5 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred at rt for 24 h and diluted with $CH_2Cl_2$ (5 mL). The solution was washed with 20% aqueous acetic acid (10 mL) and saturated aqueous $Na_2CO_3$ (10 mL), dried ($Na_2SO_4$) and concentrated to dryness in vacuo. Purification by column chromatography (MeOH/$CH_2Cl_2$ 2:98) provided benzo[*c*]phenanthridine **5e** (35 mg, 49% yield) as a white solid. $R_f$=0.23 (50% AcOEt/hexane); mp 208–210 °C (acetone/$Et_2O$); IR ($\bar{\nu}$, $cm^{-1}$, NaCl): 1641 (C=O); $^1H$ NMR ($\delta$, ppm, DMSO-$d_6$): 3.92 (s, 3H, $CH_3$), 3.93 (s, 3H, $CH_3$), 4.00 (s, 3H, $CH_3$), 4.04 (s, 3H, $CH_3$), 7.41 (s, 1H, Ar–H), 7.62 (d, 1H, $J$=9 Hz, Ar–H), 7.76 (s, 1H, Ar–H), 7.90 (s, 1H, Ar–H), 8.20 (s, 1H, Ar–H), 8.29 (d, 1H, $J$=9 Hz, Ar–H), 11.76 (s, 1H, NH); $^{13}C$ NMR ($\delta$, ppm, DMSO-$d_6$): 55.7 ($OCH_3$), 55.8 ($OCH_3$), 56.4 ($OCH_3$), 56.5 ($OCH_3$), 102.5 (CH), 104.3 (CH), 107.8 (CH), 107.9 (CH), 112.5 (C), 117.4 (C), 118.9 (C), 119.3 (CH), 121.4 (CH), 129.3 (C), 130.4 (C), 131.1 (C), 149.3 (C–OMe), 149.9 (2×C–OMe), 153.8 (C–OMe), 161.5 (C=O); MS ($m/z$, %): 365 ($M^+$, 100); HRMS calcd for $C_{21}H_{19}NO_5$ $[M]^+$ 365.1258; found 365.1261.

### 3.8. 2-(3,4-Dimethoxyphenyl)-6,7-dimethoxynaphthalen-1-amine (15)

To a solution of carbamate **7b** (390 mg, 1.11 mmol, 1.00 equiv) in ethanol (2.5 mL) was added 11 M KOH (2 mL, 21.93 mmol, 30.58 equiv) and the resulting mixture was heated under reflux for 14 h. The solution was neutralized with HCl (20%) and the aqueous layer was extracted with $CH_2Cl_2$ (3×15 mL). The combined organic layers were washed with $H_2O$ and brine, dried ($Na_2SO_4$) and concentrated to dryness in vacuo. The residue was purified by recrystallization and brown crystals corresponding to the amine **15** (290 mg, 100% yield) were isolated. $R_f$=0.73 (50% AcOEt/hexane); mp 149–151 °C (EtOH); IR ($\bar{\nu}$, $cm^{-1}$, NaCl): 3377 (NH); $^1H$ NMR ($\delta$, ppm, $CDCl_3$): 3.83 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$), 3.94 (s, 3H, $OCH_3$), 3.95 (s, 3H, $OCH_3$), 6.89–7.19 (m, 7H, 7×Ar–H); $^{13}C$ NMR ($\delta$, ppm, $CDCl_3$): 55.8 (2×$OCH_3$), 55.9 (2×$OCH_3$), 100.4 (CH), 107.0 (CH), 111.4 (CH), 112.7 (CH), 117.4 (CH), 119.0 (C), 121.6 (C), 121.7 (CH), 126.8 (CH), 129.3 (C), 132.7 (C), 137.3 (C), 148.0 (C–OMe), 149.0 (C–OMe), 149.1 (C–OMe), 149.2 (C–OMe); MS ($m/z$, %): 339 ($M^+$, 100).

### 3.9. *N*-Formyl-2-(3,4-dimethoxyphenyl)-6,7-dimethoxynaphthalen-1-amine (7c)

86 μL (2.28 mmol, 3.2 equiv) of formic acid were added dropwise under argon over 175 μL (1.85 mmol, 2.6 equiv) of acetic anhydride externally cooled at 0 °C. The mixture was heated at 50–60 °C for 2 h, diluted with dry THF (0.3 mL) and added dropwise to a solution of phenylnaphthylamine **15** (242 mg, 0.713 mmol) in dry THF (2 mL). This solution was heated at 65 °C for 18 h and then concentrated in vacuo to dryness. The solid residue was submitted to flash column chromatography (eluent: AcOEt/hexane, 7:3→MeOH/$CH_2Cl_2$ 1:9) and compound **7c** was isolated (191 mg, 73% yield) as a light brown solid. $R_f$=0.16 (60% AcOEt/hexane); mp 222–223 °C (EtOH); IR ($\bar{\nu}$, $cm^{-1}$, NaCl): 3297 (NH), 1684 (C=O); $^1H$ NMR ($\delta$, ppm, $CDCl_3$): as a mixture 4.5:1 of rotamers, 3.86–3.92 (m, 15H, 2×$OCH_3$), 3.99–4.04 (m, 15H, 2×$OCH_3$), 6.92–6.95 (m, 7.5H, Ar–H), 7.12–7.19 (m, 4.5H, Ar–H), 7.31–7.48 (m, 4.25H, Ar–H+NH), 7.70–7.73 (m, 2.75H, Ar–H), 8.07–8.12 (m, 1.75H), 8.47 (s, 1H, CHO); $^{13}C$ NMR ($\delta$, ppm, $CDCl_3$): as a mixture 4.5:1 of rotamers, 55.8 (2×$OCH_3$), 55.9 (2×$OCH_3$), 101.4 (CH), 102.6 (CH), 106.5 (2×CH), 111.0 (CH), 111.3 (CH), 112.4 (CH), 113.0 (CH), 121.2 (CH), 122.1 (CH), 125.9 (CH), 126.0 (CH), 126.1 (C), 126.4 (CH), 126.6 (CH), 126.9 (C), 127.2 (C), 129.3 (2×C), 131.5 (C), 132.2 (C), 133.8 (C), 135.1 (C), 148.3 (C), 148.5 (C), 149.0 (C), 149.6 (C), 149.8 (C), 150.3 (C), 150.6 (C), 160.8 (CHO), 165.7 (CHO); MS ($m/z$, %):

367 ($M^+$, 100). Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 72.01; H, 5.97; N, 3.91.

### 3.10. 2,3,8,9-Tetramethoxybenzo[*c*]phenanthridine (16)

To a solution of amide **7c** (150 mg, 0.408 mmol) in dry MeCN (7 mL) $POCl_3$ (79.9 μL, 0.856 mmol, 2.1 equiv) was added dropwise and the reaction mixture was refluxed for 3 h. The excess of $POCl_3$ was removed under vacuum and the remaining suspension was filtered. The solid was washed with 10% NaOH (10 mL) and later with water (15 mL). The filtered solution was extracted with $CH_2Cl_2$ (3×20 mL), the pooled organic extracts were washed with water (30 mL), dried ($Na_2SO_4$) and concentrated in vacuo to dryness. The combined solid residues were crystallized from $CHCl_3$ to give compound **16** (117 mg, 82% yield) as white crystals. $R_f$=0.70 (5% MeOH/$CH_2Cl_2$); mp 80–90 °C (decomp.); IR ($\bar{\nu}$, $cm^{-1}$, NaCl): 1615 (C=N), 1268 (Ar–O–R), 1202 (Ar–O–R), 1153 (Ar–O–R); $^1$H NMR ($\delta$, ppm, $CDCl_3$): 4.08 (s, 3H, $OCH_3$), 4.10 (s, 3H, $OCH_3$), 4.16 (s, 3H, $OCH_3$), 4.20 (s, 3H, $OCH_3$), 7.30 (s, 1H, Ar–H), 7.40 (s, 1H, Ar–H), 7.87 (d, 1H, *J*=8.9 Hz, Ar–H), 7.90 (s, 1H, Ar–H), 8.30 (d, 1H, *J*=8.9 Hz, Ar–H), 8.74 (s, 1H, Ar–H), 9.26 (s, 1H, Ar–H); $^{13}$C NMR ($\delta$, ppm, $CDCl_3$): 56.0 ($OCH_3$), 56.1 (2×$OCH_3$), 56.2 ($OCH_3$), 101.6 (CH), 104.1 (CH), 107.0 (CH), 107.3 (CH), 118.0 (CH), 119.8 (C), 122.1 (C), 126.1 (CH), 127.5 (C), 128.2 (C), 129.0 (C), 140.2 (C), 149.6 (CH), 149.7 (C–OMe), 150.0 (2×C–OMe), 153.0 (C–OMe); MS (*m*/*z*, %): 349 ($M^+$, 100). Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.20; H, 5.48; N, 4.01. Found: C, 72.05; H, 5.41; N, 3.83.

### 3.11. 2-(3,4-Dimethoxyphenyl)-6,7-dimethoxynaphthalene-1,4-dione (6a)

A solution of Fremy's salt (961 mg, 3.65 mmol, 5 equiv) and potassium biphosphate (107 mg, 0.79 mmol, 1.1 equiv) in water (23 mL) were added to a solution of naphthylamine **15** (243 mg, 0.72 mmol) in acetone (13 mL). The suspension was stirred at rt for 1 h and the acetone was evaporated in vacuo. The residue was extracted with dichloromethane (3×15 mL) and the combined organic layers were washed with water (25 mL), dried and concentrated to dryness in vacuo. The solid residue was submitted to flash column chromatography (eluent: AcOEt/hexane, 4:6) and compound **6a** was isolated (164 mg, 65% yield) as a red solid. $R_f$=0.61 (50% AcOEt/hexane); mp 192–194 °C (MeOH); IR ($\bar{\nu}$, $cm^{-1}$, NaCl): 1649 (C=O); $^1$H NMR ($\delta$, ppm, $CDCl_3$): 3.87 (s, 6H, 2×$OCH_3$), 3.97 (s, 6H, 2×$OCH_3$), 6.87–6.90 (m, 2H, 2×Ar–H), 7.07–7.19 (m, 2H, 2×Ar–H), 7.44 (s, 1H, Ar–H), 7.51 (s, 1H, Ar–H); $^{13}$C NMR ($\delta$, ppm, $CDCl_3$): 55.9 (2×$OCH_3$), 56.3 ($OCH_3$), 56.4 ($OCH_3$), 107.1 (CH), 108.3 (CH), 110.8 (CH), 112.3 (CH), 122.7 (CH), 126.0 (C), 126.7 (C), 127.1 (C), 133.4 (CH), 146.8 (C), 148.6 (C), 150.7 (C), 153.2 (C), 153.3 (C), 184.0 (C=O), 184.5 (C=O); MS (*m*/*z*, %): 354 ($M^+$, 21), 58 (100); HRMS calcd for $C_{20}H_{18}O_6$ $[M]^+$ 354.1103; found 354.1099.

### 3.12. 2-(3,4-Dimethoxyphenyl)-3-hydroxy-6,7-dimethoxy-naphthalene-1,4-dione (6b)

A suspension of quinone **6a** (40 mg, 0.113 mmol), NaOH (23 mg, 0.619 mmol, 5.5 equiv) and a MeOH/$H_2O$ mixture (20 mL) was stirred under a dry atmosphere at 50 °C for 4.5 h. The mixture was acidified with 10% HCl. The resulting red solid was filtered off and washed with water. The aqueous layer was extracted with $CH_2Cl_2$ (3×10 mL). The combined organic layers were washed with $H_2O$, brine and dried ($Na_2SO_4$) and concentrated to dryness, to yield the same red solid. These solids were combined and purified by recrystallization to give quinone **6b** (37 mg, 90% yield). $R_f$=0.53 (50% AcOEt/hexane); mp 234–236 °C (MeOH); IR ($\bar{\nu}$, $cm^{-1}$, NaCl): 1645 (C=O), 3327 (OH); $^1$H NMR ($\delta$, ppm, $CDCl_3$): 3.98 (s, 3H, $OCH_3$), 3.99 (s, 3H, $OCH_3$), 4.01 (s, 3H, $OCH_3$), 4.02 (s, 3H, $OCH_3$), 7.00 (d, 1H, *J*=8 Hz, Ar–H), 7.08 (s, 1H, OH), 7.18 (d, 1H, *J*=8 Hz, Ar–H), 7.51 (s, 1H, Ar–H), 7.60 (s, 2H, 2×Ar–H); $^{13}$C NMR ($\delta$, ppm, $CDCl_3$): 55.8 ($OCH_3$), 55.9 ($OCH_3$), 56.5 ($OCH_3$), 56.6 ($OCH_3$), 107.5 (CH), 109.0 (CH), 110.6 (CH), 114.1 (CH), 120.8 (C), 122.6 (C), 123.4 (C), 123.9 (CH), 128.1 (C), 148.3 (C–O), 149.3 (C–O), 151.8 (C–O), 152.8 (C–O), 154.6 (C–O), 180.9 (C=O), 183.7 (C=O); MS (*m*/*z*, %): 370 ($M^+$, 100).

### 3.13. (*Z*)-6,7-Dimethoxy-2-carbethoxy-1-(2-nitrobenzylidene)-1,2,3,4-tetrahydroisoquinoline (9c)

A solution of ethyl chloroformiate (1.609 mL, 16.83 mmol) in $CH_2Cl_2$ (10 mL) was added to a cooled (ice-water bath) solution of dihydroisoquinoline **10a** (1.34 g, 4.11 mmol) in $CH_2Cl_2$ (40 mL) and 10% aqueous sodium carbonate (40 mL). The reaction mixture was then stirred at rt for 2.5 h and the two layers were separated. The organic layer was washed with water (2×50 mL) and 5% aqueous hydrochloric acid (2×50 mL), dried and concentrated to dryness. The resulting residue was purified by column chromatography (AcOEt/hexane 1:1), and compound **9c** (722 mg, 44% yield) was isolated as a yellow solid. $R_f$=0.68 (50% AcOEt/hexane); mp 153–155 °C ($CH_2Cl_2$/MeOH); IR ($\bar{\nu}$, $cm^{-1}$, NaCl): 1695 (C=O), 1516 ($NO_2$), 1258 ($NO_2$); $^1$H NMR ($\delta$, ppm, $CDCl_3$): 0.64–0.88 (m, 3H, $CH_3$), 2.85–2.97 (m, 2H, $CH_2$), 3.61–3.80 (m, 2H, $CH_2$), 3.88–3.99 (m, 8H, 2×$OCH_3$+$CH_2$), 6.62 (s, 1H, Ar–H), 7.25–7.27 (m, 2H, 2×Ar–H), 7.34–7.39 (m, 1H, Ar–H), 7.48–7.58 (m, 2H, 2×Ar–H), 8.06 (d, 1H, *J*=7.9 Hz, Ar–H); $^{13}$C NMR ($\delta$, ppm, $CDCl_3$): 13.8 ($CH_3$), 28.3 ($CH_2$), 43.7 ($CH_2$), 56.0 ($OCH_3$), 56.1 ($OCH_3$), 61.7 ($OCH_2$), 106.7 (CH), 111.4 (CH), 113.6 (CH), 124.1 (C), 124.6 (CH), 127.3 (CH), 128.1 (C), 130.1 (CH), 133.0 (CH), 133.1 (C), 135.8 (C), 147.6 (C), 147.9 (2×C), 149.9 (C); MS (*m*/*z*, %): 398 ($M^+$, 15), 164 (100).

### 3.14. 3-(4,5-Dimethoxy-2-vinylphenyl)-5-nitro-2*H*-isoquinolin-1-one (18)

A mixture of compound **9c** (100 mg, 0.251 mmol) and sodium hydride (42 mg, 1.757 mmol) in dry DMF (4 mL) was heated at 130 °C under argon for 3 h. The mixture was cooled and the excess sodium hydride was destroyed by adding a few drops of MeOH. The DMF was removed in vacuo. The resulting residue was neutralized with 20% aqueous acetic acid solution and extracted with $CH_2Cl_2$ (3×15 mL). The organic extracts were washed with water (30 mL), dried and evaporated to dryness. The resulting solid was purified by column chromatography (1:1 AcOEt/hexane) to afford compound **18** (43 mg, 55% yield) as an amorphous pale yellow solid. $R_f$=0.28 (50% AcOEt/hexane); IR ($\bar{\nu}$, $cm^{-1}$, NaCl): 1664 (C=O), 1600 (C=C), 1515 ($NO_2$), 1340 ($NO_2$); $^1$H NMR ($\delta$, ppm, $CDCl_3$): 3.98 (s, 3H, $OCH_3$), 4.00 (s, 3H, $OCH_3$), 5.27 (m, 1H, HC=CH*H*), 5.66 (m, 1H, HC=CH*H*), 7.03–7.15 (m, 2H, Ar–H+*H*C=$CH_2$), 7.25 (s, 1H, Ar–H), 7.47–7.56 (m, 1H, Ar–H), 7.79–7.82 (m, 2H, 2×Ar–H), 8.25 (d, 1H, *J*=7.7 Hz, Ar–H), 11.30 (s, broad 1H, NH); $^{13}$C NMR ($\delta$, ppm, $CDCl_3$): 56.0 ($OCH_3$), 56.1 ($OCH_3$), 109.0 (CH), 111.9 (CH), 115.4 ($CH_2$), 120.4 (C), 124.6 (C), 126.2 (CH), 126.9 (CH), 127.8 (CH), 130.4 (2×C), 134.1 (CH), 134.9 (CH), 148.7 (C), 149.1 (C), 150.8 (C), 152.7 (C), 163.6 (C=O); MS (*m*/*z*, %): 353 [$(M+H)^+$, 2.5], 309 (100); HRMS calcd for $C_{19}H_{17}N_2O_5$ $[M+H]^+$ 353.1132; found 353.1134.

### 3.15. 3-(4,5-Dimethoxy-2-vinylphenyl)-2-methyl-5-nitroiso-quinolin-1(2*H*)-one (19)

To a suspension of NaH (52 mg, 1.73 mmol) in dry THF (2 mL) at 0 °C compound **18** (70 mg, 0.199 mmol) in dry THF (2 mL) was slowly added under argon and the resulting mixture was stirred at rt for 30 min. MeI (0.414 mL, 6.66 mmol) was then added dropwise, and the reaction mixture was stirred at rt for 2 h. The NaH was destroyed adding water (1 mL) and the THF was evaporated off. The aqueous layer was extracted with $CH_2Cl_2$ (3×5 mL). The combined

extracts were dried, filtered and evaporated to dryness in vacuo, to give a residue that was purified by column chromatography (2:3 AcOEt/hexane) to afford compound **19** (50 mg, 69% yield) as a white solid. $R_f$=0.45 (60% AcOEt/hexane); IR ($\bar{\nu}$, $cm^{-1}$, NaCl): 1677 (C=O), 1513 ($NO_2$), 1268 ($NO_2$); $^1H$ NMR ($\delta$, ppm, $CDCl_3$): 3.33 (s, 3H, $NCH_3$), 3.90 (s, 3H, $OCH_3$), 3.97 (s, 3H, $OCH_3$), 5.18 (d, 1H, HC=CH*H*), 5.61 (d, 1H, HC=CH*H*), 6.45 (dd, 1H, $J_{cis}$=11 Hz, $J_{trans}$=17.3 Hz, *H*C=$CH_2$), 6.86 (s, 1H, Ar–H), 7.13 (s, 1H, Ar–H), 7.48–7.55 (m, 1H, Ar–H), 7.72–7.77 (m, 2H, 2×Ar–H), 8.33 (d, 1H, *J*=7.9 Hz, Ar–H); $^{13}C$ NMR ($\delta$, ppm, $CDCl_3$): 33.2 ($NCH_3$), 56.5 (2×$OCH_3$), 108.4 (CH), 110.9 (CH), 116.0 ($CH_2$), 121.1 (C), 126.9 (C), 127.1 (CH), 127.5 (CH), 127.9 (CH), 129.1 (2×C), 133.1 (CH), 134.8 (CH), 147.6 (C), 149.7 (C), 150.7 (C), 155.8 (C), 162.8 (C=O); MS (*m*/*z*, %): 321 ($M^+$–44, 58), 58 (100). Anal. Calcd for $C_{20}H_{19}N_2O_5$: C, 65.57; H, 4.95; N, 7.65. Found: C, 67.74; H, 5.22; N, 7.39.

### 3.16. 3-(2-(2,2-Dimethoxyethyl)-4,5-dimethoxyphenyl)-5-nitroisoquinolin-1(2*H*)-one (20)

A solution of thallium trinitrate trihydrate (68 mg, 0.154 mmol) in dry MeOH (2 mL) was added to a solution of compound **19** (50 mg, 0.137 mmol) in dry MeOH (2 mL) and the reaction mixture was stirred at rt for 5 min. It was then filtered and the MeOH of the filtrate was evaporated off. The residue was taken up in $CH_2Cl_2$ and the solution was washed with saturated aqueous $NaHCO_3$ solution (2×5 mL) and water (5 mL), dried and evaporated to dryness. The resulting unstable derivative **20** was used as a crude for the next step without further purification. $R_f$=0.27 (60% AcOEt/hexane); $^1H$ NMR ($\delta$, ppm, $CDCl_3$): 2.70 (dd, 1H, *J*=14, 4.5 Hz, ArCH*H*), 3.10 (dd, 1H, *J*=14, 6 Hz, ArCH*H*), 3.18 (s, 3H, $CH_3$), 3.25 (s, 3H, $CH_3$), 3.40 (s, 3H, $CH_3$), 3.88 (s, 3H, $CH_3$), 3.95 (s, 3H, $CH_3$), 4.50 [dd, 1H, *J*=6, 4.5 Hz, CH$(OMe)_2$], 6.79 (s, 1H, Ar–H), 6.96 (s, 1H, Ar–H), 7.53 (t, 1H, *J*=6.6 Hz, Ar–H), 7.74–7.77 (m, 2H, 2×Ar–H), 8.35 (d, 1H, *J*=8.1 Hz, Ar–H).

### 3.17. 6,7-Dimethoxy-2-(2-methylaminocarbonyl)isoquinolin-1(2*H*)-one (21)

To a solution of recently obtained **20** in a 1:1 mixture of MeOH/$H_2O$ (4 mL) *p*-toluensulfonic acid (52 mg, 0.273 mmol) was added and the resulting solution was heated at 70 °C for 2 days. The MeOH was removed in vacuo and more water was added (2 mL). The resulting suspension was extracted with $CH_2Cl_2$ (3×5 mL). The organic extracts were washed with 10% aqueous sodium hydroxide solution (5 mL) and water (5 mL), dried and evaporated to dryness. Column chromatography ($CH_2Cl_2$/MeOH 95:5) of the resulting solid residue provided compound **21** (43 mg, 86% yield), as a yellow solid. $R_f$=0.15 (80% AcOEt/hexane); IR ($\bar{\nu}$, $cm^{-1}$, NaCl): 3313 (NH), 1651 (C=O); $^1H$ NMR ($\delta$, ppm, $CDCl_3$): 2.71 (d, 3H, *J*=5.2 Hz, $NCH_3$), 4.02 (s, 3H, $OCH_3$), 4.03 (s, 3H, $OCH_3$), 6.53 (d, 1H, *J*=7.3 Hz, Ar–H), 6.95–7.00 (m, 3H, NH+2×Ar–H), 7.25–7.28 (m, 1H, Ar–H), 7.51–7.56 (m, 2H, 2×Ar–H), 7.67–7.71 (m, 1H, Ar–H), 7.80 (s, 1H, Ar–H); $^{13}C$ NMR ($\delta$, ppm, $CDCl_3$): 26.4 ($CH_3$), 56.1 (2×$OCH_3$), 106.2 (2×CH), 107.5 (CH), 119.5 (C), 128.2 (CH), 129.1 (2×CH), 130.9 (2×CH), 132.9 (C), 135.9 (C), 138.0 (C), 149.5 (C), 153.9 (C), 162.5 (C=O), 167.7 (C=O); MS (*m*/*z*, %): 339 [$(M+H)^+$, 56], 308 (100). Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.19; H, 5.53; N, 7.97.

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## Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.10.035. These data include MOL files and InChiKeys of the most important compounds described in this article.

## References and notes

1. (a) Shamma, M. *The Isoquinoline Alkaloids: Chemistry and Pharmacology*, In. Blomquist, A. T., Wasserman, H., Eds.; Academic Press: New York, London, Verlag Chemie, Weinheim, 1972; (b) Shamma, M.; Moniot, J. L. *Isoquinoline Alkaloids Research 1972-1977*, Plenum Press: New York, London, 1978; (c) Guinaudeau, H.; Leboeuf, M.; Cavé, A. *J. Nat. Prod.* **1990**, *53*, 235.
2. (a) Simánek, V. Benzophenanthridine Alkaloids In. *The Alkaloids. Chemistry and Pharmaology*; Brossi, A., Ed.; Academic.: Orlando, 1985; Vol. 26; p 229; (b) Bhakuni, D. S.; Jain, S. Protoberberine Alkaloids In. *The Alkaloids. Chemistry and Pharmacology*; Brossi, A., Ed.; Academic.: Orlando, 1986; Vol. 28; p 169.
3. (a) Fang, S.-D.; Wang, L.-K.; Hetch, S. M. *J. Org. Chem.* **1993**, *58*, 5025; (b) Rashid, M. A.; Gustafson, K. R.; Kashman, Y.; Cardellina, J. H., II; McMahon, J. B.; Boyd, M. R. *Nat. Prod. Lett.* **1995**, *6*, 153; (c) Huang, F.-C.; Kutchan, T. M. *Phytochemistry* **2000**, *53*, 555; (d) Ishikawa, T. *Med. Res. Rev.* **2001**, *21*, 61; (e) Chang, Y.-C.; Hsieh, P.-W.; Chang, F.-R.; Wu, R.-R.; Liaw, C.-C.; Lee, K.-H.; Wu, Y.-C. *Planta Med.* **2003**, *69*, 148.
4. (a) Cheng, C. C. Structural Aspects of Antineoplastic Agents-A New Approach In. *Progress in Medicinal Chemistry*; Ellis, G. P., West, G. B., Eds.; Elsevier Science, B. V. (Biomedical Division): Amsterdam, 1988; Vol. 25, pp 35–83; Vavreckova, C.; Gawlik, I.; Muller, K. *Planta Med.* **1996**, *62*, 397; (b) Nakanishi, T.; Suzuki, M. *J. Nat. Prod.* **1998**, *61*, 1263; (c) Fleury, F.; Sukhanova, A.; Ianoul, A.; Devy, J.; Kudelina, I.; Duval, O.; Alix, A. J. P.; Jardillier, J. C.; Nabiev, I. *J. Biol. Chem.* **2000**, *275*, 3501; (d) Gonzaga, W. A.; Weber, A. D.; Giacomelli, S. R.; Dalcol, I. I.; Hoelzel, S. C. S.; Morel, A. F. *Planta Med.* **2003**, *69*, 371.
5. (a) Harvey, R. G. *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenesis*; Cambridge University: Cambridge, 1991; (b) Harvey, R. G. The Handbook of Environmental Chemistry In. *Part I: PAHs and Related Compounds*; Hutzinger, O., Neilson, A., Eds.; Springer: Heidelberg, 1997; Vol. 3, pp 1–54 Chapter 1; (c) Wu Harvey, R. G. *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenesis*; Wiley-VCH: New York, NY, 1997.
6. (a) Bernardo, P. H.; Chai, C. L. L.; Le Guen, M.; Smith, G. D.; Waring, P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 82; (b) Marco-Contelles, J.; Molina, M. *Curr. Org. Chem.* **2003**, *7*, 1433; (c) Gould, S. J. *Chem. Rev.* **1997**, *97*, 2499; (d) Luo, Y.-L.; Chou, T.-C.; Cheng, C. C. *J. Heterocycl. Chem.* **1996**, *33*, 113; (e) Mocellin, S. *Microarray Technology and Cancer Gene Profiling*; Springer: Heidelberg, 2007, Chapter 8, p 98.
7. (a) Bennasar, M.-L. l.; Roca, T.; Ferrando, F. *J. Org. Chem.* **2005**, *70*, 9077; (b) Bernardo, P. H.; Chai, C. L. L.; Heath, G. A.; Mahon, P. J.; Smith, G. D.; Waring, P.; Wilkes, B. A. *J. Med. Chem.* **2004**, *47*, 4958; (c) Mal, D.; Senapati, B. K.; Pahari, P. *Tetrahedron* **2007**, *63*, 3768; (d) Ashcroft, W. R.; Dalton, L.; Beal, M. G.; Humphrey, G. L.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2409.
8. (a) Gribble, G. W. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, NY, 1990; Vol. 39; p 239; (b) Suffness, M.; Cordell, G. A. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, NY, 1985; Vol. 25, p 89; p 304; (c) Kansal, V. K.; Potier, P. *Tetrahedron* **1986**, *42*, 2389; (d) Gribble, G. W.; Saulnier, M. G.; Obaza-Nutaitis, J. A.; Ketcha, D. M. *J. Org. Chem.* **1992**, *57*, 5891; (e) Ishikura, M.; Yaginuma, T.; Agata, I.; Miwa, Y.; Yanada, R.; Taga, T. *Synlett* **1997**, 214; (f) Díaz, M. T.; Cobas, A.; Guitián, E.; Castedo, L. *Synlett* **1998**, 157; (g) Ergün, Y.; Patir, S.; Okay, G. *J. Heterocycl. Chem.* **1998**, *35*, 1445; (h) Ishikura, M.; Hino, A.; Yaginuma, T.; Agata, I.; Katagiri, N. *Tetrahedron* **2000**, *56*, 193; (i) Anderson, W. K.; Gopalsamy, A.; Reddy, P. S. *J. Med. Chem.* **1994**, *37*, 1955.
9. Mackay, S. P.; Meth-Cohn, O.; Waich, R. D. *Advances in Heterocyclic Chemistry*; Academic: New York, NY, 1997; Vol. 67,pp 345–389.
10. For a review covering benzo[c]phenanthridine synthesis until 1998, see: Ishikawa, T.; Ishii, H. *Heterocycles* **1999**, *50*, 627 For more recent articles on this topic, see: (a) Nakanishi, T.; Suzuki, M. *Org. Lett.* **1999**, *1*, 985; (b) Geen, G. R.; Mann, I. S.; Mullane, M. V.; McKillop, A. *Tetrahedron* **1998**, *54*, 9875; (c) Harayama, T.; Akamatsu, H.; Okamura, K.; Miyagoe, T.; Akiyama, T.; Abe, H.; Takeuchi, Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 523; (d) Treus, M.; Estevez, J. C.; Castedo, L.; Estevez, R. J. *Tetrahedron Lett.* **2002**, *43*, 5323; (e) Le, T. N.; Gang, S. G.; Cho, W.-J. *J. Org. Chem.* **2004**, *69*, 2768; (f) Harayama, T. *Heterocycles* **2005**, *65*, 697; (g) Styskala, J.; Cankar, P.; Soural, M.; Hlavac, J.; Hradil, P.; Vicar, J.; Simanek, V. *Heterocycles* **2007**, *73*, 769; (h) Kohno, K.; Azuma, S.; Choshi, T.; Nobuhiro, J.; Hibino, S. *Tetrahedron Lett.* **2009**, *50*, 590; (i) Mandadapu, A. K.; Saifuddin, M.; Agarwal, P. K.; Kundu, B. *Org. Biomol. Chem.* **2009**, *7*, 2796.
11. See: Salas, C. O.; Reboredo, F. J.; Estevez, J. C.; Tapia, R.; Estevez, R. J. *Synlett* **2009**, 3107 and references therein.
12. See: Mal, D.; Senapati, B. K.; Pahari, P. *Tetrahedron* **2007**, *63*, 3768 and references therein.
13. (a) Du, C.; Chen, J.; Guo, Y.; Lu, K.; Ye, S.; Zheng, J.; Liu, Y.; Shuai, Z.; Yu, G. *J. Org. Chem.* **2009**, *74*, 7322; (b) Brath, H.; Meskova, M.; Putala, M. *Eur. J. Org. Chem.* **2009**, 3315; (c) Zhou, W.-J.; Wang, K.-H.; Wang, J.-X. *J. Org. Chem.* **2009**, *74*, 5599.
14. Treus, M.; Estévez, J. C.; Castedo, L.; Estévez, R. J. *Tetrahedron Lett.* **2000**, *41*, 6351.

15. Cava, M. P.; Mitchell, M. J.; Havlicek, S. C.; Lindert, A.; Spangler, R. J. *J. Org. Chem.* **1970**, *35*, 175.
16. Mohanakrishnan, A. K.; Srinivasan, P. C. *J. Org. Chem.* **1995**, *60*, 1939.
17. Whaley, W. M.; Hartung, W. H. *J. Org. Chem.* **1949**, *14*, 650.
18. (a) Banwell, M. G.; Bissett, B. D.; Busato, S.; Cowden, C. J.; Hockless, D. C. R.; Holman, J. W.; Read, R. W.; Wu, A. W. *J. Chem. Soc., Chem. Commun.* **1995**, 2551; (b) Banwell, M. G.; Cowden, C. J.; Gable, R. W. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3515.
19. Pampin, M. C.; Estevez, J. C.; Estevez, R. J.; Maestro, M.; Castedo, L. *Tetrehedron* **2003**, *59*, 7231.
20. Šindler-Kulyk, M.; Škoric, I.; Tomšic, S.; Marinić, Ž; Mrvoš-Sermek, D. *Heterocycles* **1999**, *51*, 1355.
21. (a) Michael Quante, J.; Stermitz, F. R.; Miller, L. L. *J. Org. Chem.* **1979**, *44*, 293; (b) Beugelmans, R.; Chastanet, J.; Ginsburg, H.; Quintero-Cortes, L.; Roussi, G. *J. Org. Chem.* **1985**, *50*, 4933.
22. Teuber, H.-J.; Hasselbach, M. *Chem. Ber.* **1959**, 674.
23. (a) Estévez, J. C.; Estévez, R. J.; Castedo, L. *Tetrahedron Lett.* **1993**, *34*, 6479; (b) Cruces, J.; Martínez, E.; Treus, M.; Martínez, L. A.; Estévez, J. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **2002**, *58*, 3015.
24. (a) Hanaoka, M.; Motonishi, T.; Mukai, C. *J. Chem. Soc., Chem. Commun.* **1984**, 718; (b) Hanaoka, M.; Motonishi, T.; Mukai, C. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2253.
25. Crystallographic data for the structure of compound **21** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-800247. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail deposit@ccdc.cam.ac.uk/).
26. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon: New York, NY, 1988.
27. For spectroscopic properties of compounds **8a** and **8b**, see Ref. 14.