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Heck-mediated synthesis and photochemically induced cyclization of [2-(2-styrylphenyl)ethyl]carbamic acid ethyl esters and 2-styryl-benzoic acid methyl esters: total synthesis of naphtho[2,1*f*]isoquinolines (2-azachrysenes)☆

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Abstract—We describe two new closely related total syntheses of naphtho[2,1-*f*]isoquinolines. The first synthesis consists of a Heck coupling reaction between trifluoromethanesulfonic acid 2-(2-ethoxycarbonylaminoethyl)phenyl esters and styrenes to give [2-(2-styrylphenyl)ethyl]carbamic acid ethyl esters. These compounds cyclize to give (2-phenanthren-1-yl-ethyl)carbamic acid ethyl esters, from which 2-azachrysenes can be obtained in a three-step sequence. The second synthesis includes a new total synthesis of 2-styrylbenzoic acid methyl esters by Heck coupling of methyl *o*-iodobenzoates to styrenes, followed by the transformation of the resulting benzoic acid derivatives into phenanthrene-1-carboxylic acid methyl esters and then into the target compounds by a six-step sequence including a Bischler–Napieralski cyclization.

Polycyclic aromatic hydrocarbons (PAHs) have attracted considerable attention because they are ubiquitous environmental contaminants produced in the incomplete combustion of fossil fuels and organic matter, as well as being components of tobacco smoke.[2] Some PAHs are potent carcinogens and it is now generally accepted that carcinogenic PAHs are activated by cytochrome P-450 enzymes to form a reactive diol epoxide that binds covalently to DNA, resulting in mutations that may lead to tumorigenesis. Existing data indicate that PAHs such as pyrene and benzo[*e*]pyrene possess very little or no carcinogenicity, whereas other PAHs such as benz[*a*]anthracene, benzo[*a*]-pyrene and chrysene (Fig. 1) are potent carcinogens.[3] Studies on the relationship between the chemical structure of PAHs and carcinogenicity have related this property with the presence of a rigid planar embedded 2-phenylnaphthalene subunit within the condensed ring systems, which may facilitate the interaction of their diol epoxide derivatives with DNA.[4,5]

The benzo[*c*]phenanthridine ring system resembles the structure of the carcinogenic PAH chrysene and this led to concern as to whether the former compounds could also be carcinogenic. However, it was found that benzo[*c*]phenanthridines are not mutagenic.[6] This finding led to suggestions that structural modifications of PAHs may afford antineoplastic compounds. This idea is supported, for example, by the powerful anticancer activity of benzo[*c*]phenanthridines such as nitidine and fagaronine (Fig. 1). These properties indicate that the presence of a nitrogen atom in

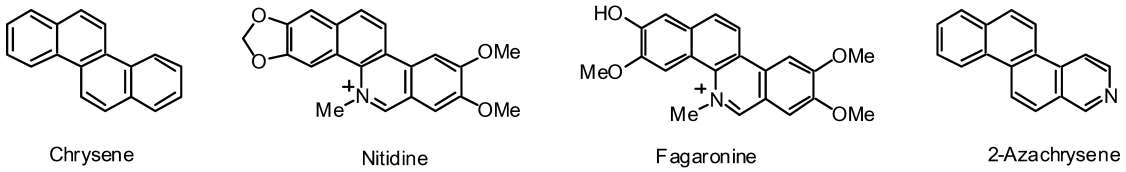

Figure 1.

☆ See Ref. 1.

Keywords: Heck reactions; isoquinolines; photochemistry; polycyclic heterocyclic compounds.
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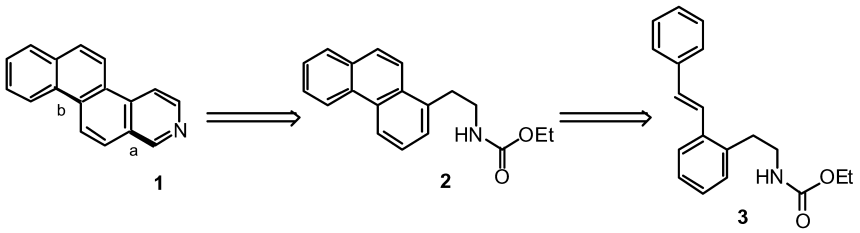


Scheme 1.

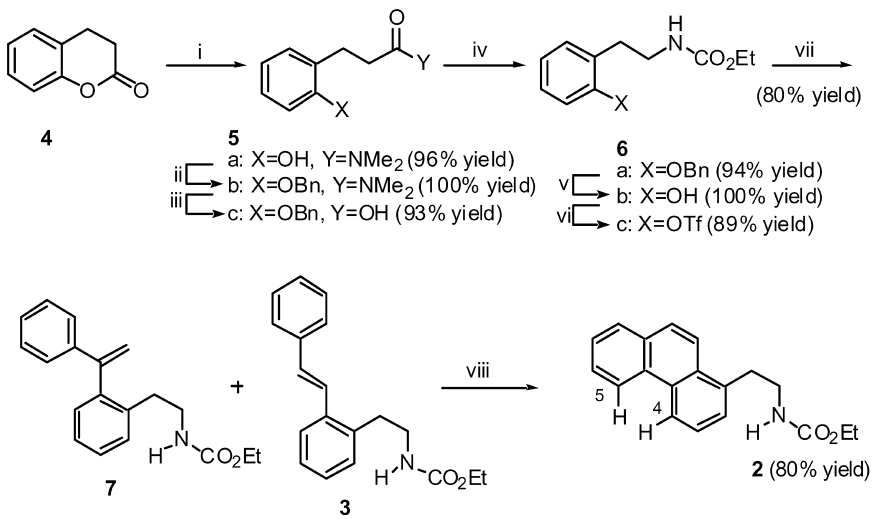
these alkaloids could modify the overall electronic distribution of the tetracyclic ring system and the presence of alkoxy groups at strategic positions may interfere with the in vivo epoxidation-hydroxylation processes necessary for mutagenic and oncogenic action.[7] These facts clearly imply that the antineoplastic action and mutagenicity (or carcinogenicity) of a compound can be separated by appropriate structural modifications. Such a possibility provides a sound reason for an extensive search for biologically, pharmacologically, and clinically antineoplastic active compounds of both natural and synthetic origin.

On the basis of the above considerations, benzo[*c*]phenanthridines may be regarded as azachrysenes because the tetracyclic ring system can be constructed by replacement of the CH group at position C(5) of chrysene by a nitrogen atom. 2-Azachrysenes are structurally related to chrysene in a similar way as benzo[*c*]phenanthridines and, therefore, like the latter, should show antineoplastic activity. However, the chemistry of 2-azachrysenes has received much less attention than benzo[*c*]phenanthridines. Indeed, the synthesis of 2-azachrysenes has been almost completely overlooked[8] and investigation of their properties[9] has been limited to studies concerning pollution by 2-azachrysene (Fig. 1).

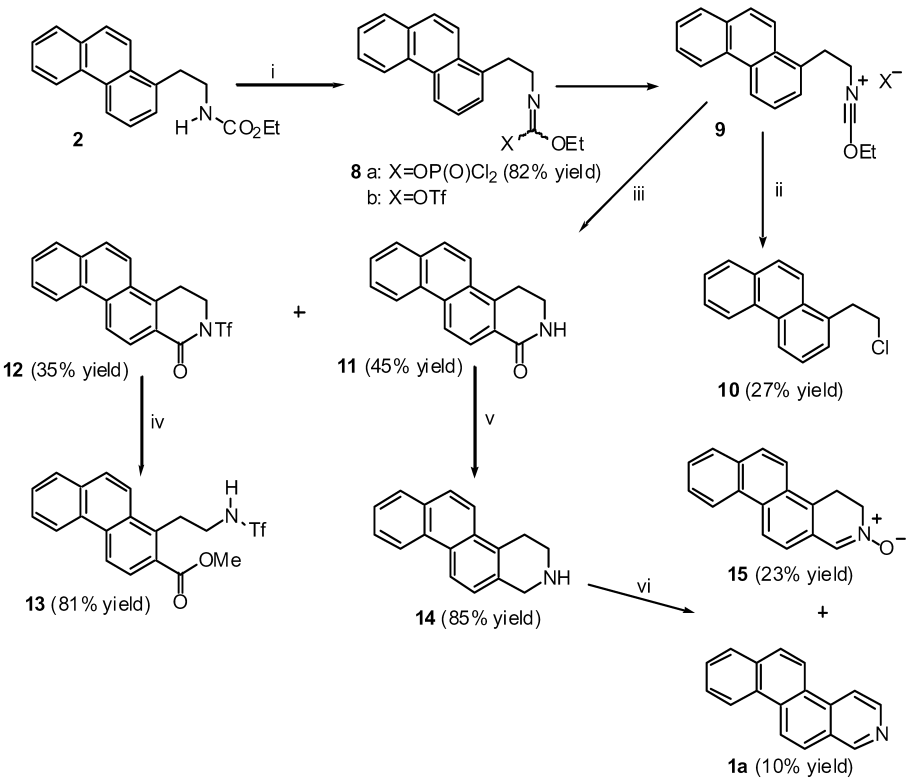
We describe here two new total syntheses of 2-azachrysenes. Retrosynthetic consideration of structures **1** suggested a strategy based on formation of bonds b and a, in that order, starting from styrylphenylethylurethanes **3**. These compounds contain an appropriate stilbene-like system for construction of phenanthrene ring system of the phenanthrenylethylurethanes **2** and a nitrogen substituent for final construction of the nitrogen ring by Bischler–Napieralski cyclization of compounds **2** (Scheme 1).

We first prepared the starting *o*-triflylphenylethylurethane **6c**, which was efficiently obtained as indicated in Scheme 2. Treatment of 2-chromanone (**4**)[10] with dimethylamine at room temperature provided 96% yield of hydroxyamide **5a**, which was quantitatively converted into benzyloxyacetamide **5b** by treatment with sodium hydride and benzyl bromide at room temperature for 1 h. Acetamide **5b** was then converted into its *o*-triflyl derivative **6c** in a four-step sequence, starting with basic hydrolysis of **5b** to give 93% yield of phenylpropionic acid **5c**. This compound was tranformed into carbamate **6a** through a Curtius sequence by heating a solution of **5c**, DPPA and Et_3N under reflux for 1 h, followed by addition of CuCl and EtOH, and further heating of this mixture under reflux for 1 h. Finally, when **6a** was subjected to catalytic hydrogenation, a quantitative yield of carbamate **6b** was obtained. Treatment of this compound with phenyltriflylamide and Et_3N for 6 days provided the desired triflate **6c** in 89% yield.

We proceeded to study the viability of this route by preparing 2-azachrysene (**1a**, Scheme 3) from *o*-styrylphenylethylurethane **3**, which was easily obtained by Heck[11] coupling of triflate **6c** to styrene (Scheme 2). A deoxygenated solution of **6c**, styrene, palladium acetate, Ph_3P and LiCl in dry, deoxygenated acetonitrile was heated



Scheme 2. (i) Et_3N, rt, 30 min. (ii) TBAF, NaH, BnBr, THF, argon, rt, 1 h. (iii) 11 M KOH, EtOH, rt, 22 h. (iv) (a) diphenylphophoryl azide, Et_3N, dry PhMe, reflux, 1 h; (b) $CuCl_2$, dry EtOH, reflux, 1 h. (v) H_2 (1 atm), Pd/C, AcOEt, rt, 2 h. (vi) *N*-triflimide, Et_3N, CH_2Cl_2, rt, 2 days. (vii) $Pd(OAc)_2$ (5% M), Ph_3P, LiCl, Et_3N, MeCN, argon, 100°C, 3 days. (viii) UV light, I_2, Et_2O/CH_2Cl_2, rt 2 h.



Scheme 3. (i) $POCl_3$, argon, reflux, 32 h. (ii) $TPOCl_3$, 155°C, 28 h. (iii) Tf_2O, DMPA, dry CH_2Cl_2, argon, 0°C→rt, 21 h. (iv) Et_3N, MeOH, Pd/C, rt, 24 h. (v) $LiAlH_4$, THF, argon, rt, 15 h. (vi) I_2, AcONa, dry EtOH, argon, reflux, 15 h.

at 100°C in a sealed tube for 3 days. This reaction gave the desired compound **3** in 77% yield together with a small amount (3% yield) of the corresponding α-coupled alkene **7**. Although it was impossible to separate these two compounds by chromatography because of their similar R_f values, the mass spectrum of the mixture confirmed the expected molecular weight (m/z=295) for both isomers. Furthermore, it was possible to assign the signals of the major component from the ^{1}H NMR spectrum of the mixture, and hence to establish the *E* configuration of the double bond of compound **3** on the basis of a doublet at 7.90 ppm (1H, J=16.0 Hz); the doublet due to the other alkene proton was masked by the signals corresponding to the aromatic protons.

We next studied the photochemically induced electrocyclic cyclization[12] of styrylphenylethylurethane **3**. Irradiation for 2 h of a solution of iodine and the above mixture of **3** and **7** in diethyl ether with a 450 W Hanovia medium-pressure lamp equipped with a Pyrex filter, led to a product mixture from which compound **7** was recovered and the cyclization product **2** was isolated in 80% yield. The structure of compound **2** was easily deduced from its spectroscopic and analytical data. The ^{1}H NMR spectrum of this product showed signals for a total of nine aromatic protons (two fewer than the starting material), including a multiplet at 8.65–8.75 ppm corresponding to the deshielded protons at C(4) and C(5).

Finally, construction of the nitrogen ring of 2-azachrysene (**1a**) was attempted by treatment of phenanthrene **2** with $POCl_3$ under classical Bischler–Napieralski conditions.[13] However, in this case compound **8a** was obtained instead of the desired naphthoisoquinolinone **11** (Scheme 3). In an attempt to promote the desired cyclization, the reaction was repeated in the presence of $SnCl_4$, but **8a** was once again the only reaction product.[14] In a third experiment, when the reaction temperature was increased to 160°C and the reaction time to 28 h, compound **8a** gave a new compound, which was identified as chloro-compound **10** on the basis of its spectroscopic data; the mass spectrum contained peaks at m/z 240 and 242 with relative intensities of 3:1 and the ^{1}H NMR spectrum contained signals for a total of nine aromatic protons and two multiplets at 3.55–3.61 and 3.82–3.87 ppm, corresponding to the two methylene groups. Formation of compound **10** may be regarded in terms of a von Braun reaction: nucleophilic attack of a chloride ion at the α carbon of the nitrilium salt **9**, with concomitant formation of ethyl cyanide.[15] This unexpected result seems to be a consequence of the lack of reactivity of the phenanthrene system of **2** to give the desired Bischler–Napieralski cyclization to **11**, probably due to the absence of electron-donating substituents on the phenenthrene ring system of intermediate **9**, a factor that would facilitate this cyclization.[16]

Taking into account the unsatisfactory results described above, we decided to assess the desired cyclization **2** to **11** under the harsher conditions described by Banwell.[17] Thus, treatment of a solution of compound **2** in dichloromethane with excess Tf_2O/DMAP (5:3) at room temperature for 21 h led to the expected isoquinolinone **11** via **8b** and **9**, together with a compound identified as *o*-triflyldihydroisoquinoline **12**. Formation of the latter compound under Banwell conditions is probably due to the use of excess Tf_2O, which can promote *N*-triflation of the initially formed

isoquinolinone **11**. This situation was confirmed when a smaller amount of Tf_2O was used, a change that gave only compound **11** in the reaction. The ^1H NMR spectrum of **11** showed signals for eight aromatic protons and two multiplets at 3.38–3.43 and 3.45–3.57 ppm, each corresponding to two protons, due to the two methylene groups. The IR spectrum includes a band at 3437 cm^{-1} due to the NH group and another at 1658 cm^{-1} due to the carbonyl group of the lactam. On the other hand, the mass spectrum of compound **12** confirmed its molecular mass (m/z=379, M^+) and the ^1H NMR spectrum also contained signals for eight aromatic protons together with two triplets at 3.69 ppm (2H, J=5.9 Hz) and 4.37 ppm (2H, J=5.9 Hz), corresponding to the two methylene groups.

Surprisingly, when we attempted to remove the triflate substituent of imidate **12** by catalytic hydrogenation, subjecting a solution of **12** in methanol containing a Pd/C catalyst to hydrogenation under a hydrogen pressure of 50 psi for 24 h, an unknown compound of molecular formula $C_{19}H_{16}F_3NO_4S$ was obtained. Identification of this compound proved impossible on the basis of its spectroscopic data, but the structure of **13** was established by X-ray[18] analysis. This is the first time that compounds like **13** have been described and they may result from the opening of the *N*-triflyl lactam ring of compound **12** by attack of MeOH on the highly reactive carbonyl (Fig. 2).

Finally, transformation of isoquinolinone **11** into 2-azachrysene (**1a**) was accomplished as follows: compound **11** was reacted with $LiAlH_4$ at room temperature for 15 h and the resulting tetrahydroisoquinoline **14** was subjected to conditions for aromatization[19] of its nitrogen ring (by refluxing a solution of compound **14**, I_2 and NaOAc in EtOH for 15 h) to give compound **1a** in 10% yield along with 23% of isoquinoline *N*-oxide **15**. Both of these compounds were easily identified from analytical and spectroscopic data. The mass spectrum confirmed the mass expected for compound **1a** (m/z=229) and elemental analysis supported the molecular formula $C_{17}H_{11}N$. Its ^1H NMR spectrum showed signals for a total of eleven aromatic protons, including a singlet at 9.37 ppm, corresponding to the deshielded proton at C(1).

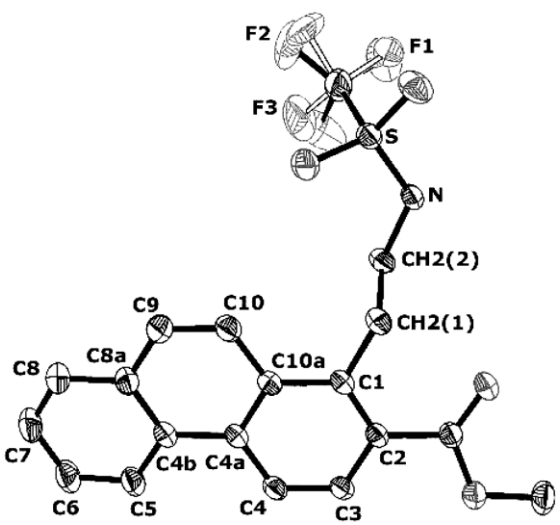


Figure 2. X-Ray structure of compound **13**.

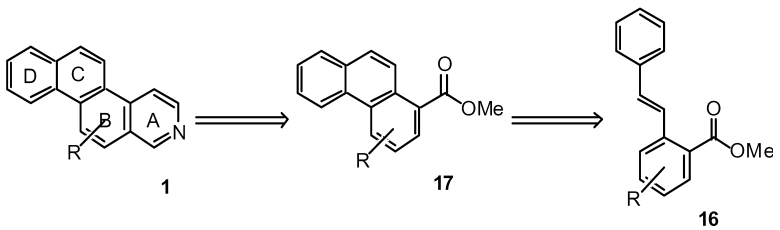
Taking into account this unsatisfactory result in terms of yield, we decided to introduce a slight modification to this low yielding route to 2-azachrysene (**1a**), a change that resulted in the development of a general and more efficient total synthesis of 2-azachrysenes. The new approach also involves a sequential construction of rings C and A of 2-azachrysenes, but in this case starting from *o*-styrylbenzoic acid esters **16**; these latter compounds contain a stilbene-like system that allows construction of the phenanthrene ring system of phenanthrenoic acid esters **17**, which were then efficiently transformed into the target compounds **1** (Scheme 4).

We first studied the preparation of starting methyl *o*-styrylbenzoates **16** by Heck coupling of methyl *o*-iodobenzoates **18** to styrene (Scheme 5).

A methanolic solution of commercial *o*-iodobenzoic acid containing a few drops of concentrated sulfuric acid was heated under reflux and readily gave methyl *o*-iodobenzoate **18a**. Coupling of this compound to styrene was carried out under the Heck[11] conditions described above for the preparation of stilbene **3**, by heating at 100°C for 24 h a mixture of **18a**, catalytic amounts of palladium acetate and triphenylphosphine and a stoichometric amount of triethylamine in acetonitrile. This reaction gave the desired *o*-styrylbenzoate **16a** (75% yield) together with 4% of alkene **19a** resulting from the α-coupling of iodobenzoate **18a** to styrene.[20] The structures of both compounds were easily established from analytical and spectroscopic data. In particular, the ^1H NMR spectrum of compound **16a** contained signals for a total of seven aromatic protons, together with a singlet at 3.78 ppm, corresponding to the methoxy group, and two doublets at 6.92 ppm (1H, J=16.3 Hz) and 8.02 ppm (1H, J=16.3 Hz), corresponding to the protons of a double bond having an *E* configuration. The initial total yield of this coupling reaction (79% yield) was improved when the reaction was carried out at 80°C. Under these conditions, compound **16a** was obtained in 84% yield and compound **19a** in 5% yield. This result is probably due to the fact that the competitive dehalogenation reaction of **18a** now occurs to a lesser extent. However, this hypothesis could not be proved because the volatility of the resulting methyl benzoate precluded its isolation.

In accordance with our plan, a solution of methyl *o*-styrylbenzoate **16a** and iodine in methanol was irradiated[21] for 30 h with a 450 W Hanovia medium-pressure lamp equipped with a Pyrex filter. This process gave 80% yield of the expected phenanthrylbenzoate **17a**, the structure of which was deduced from its spectroscopic and analytical data. The ^1H NMR spectrum of this compound showed signals for a total of nine aromatic protons, including two doublets at 8.78 ppm (J=9.4 Hz) and 8.92 ppm (J=8.4 Hz), corresponding to the deshielded protons at C(4) and C(5).

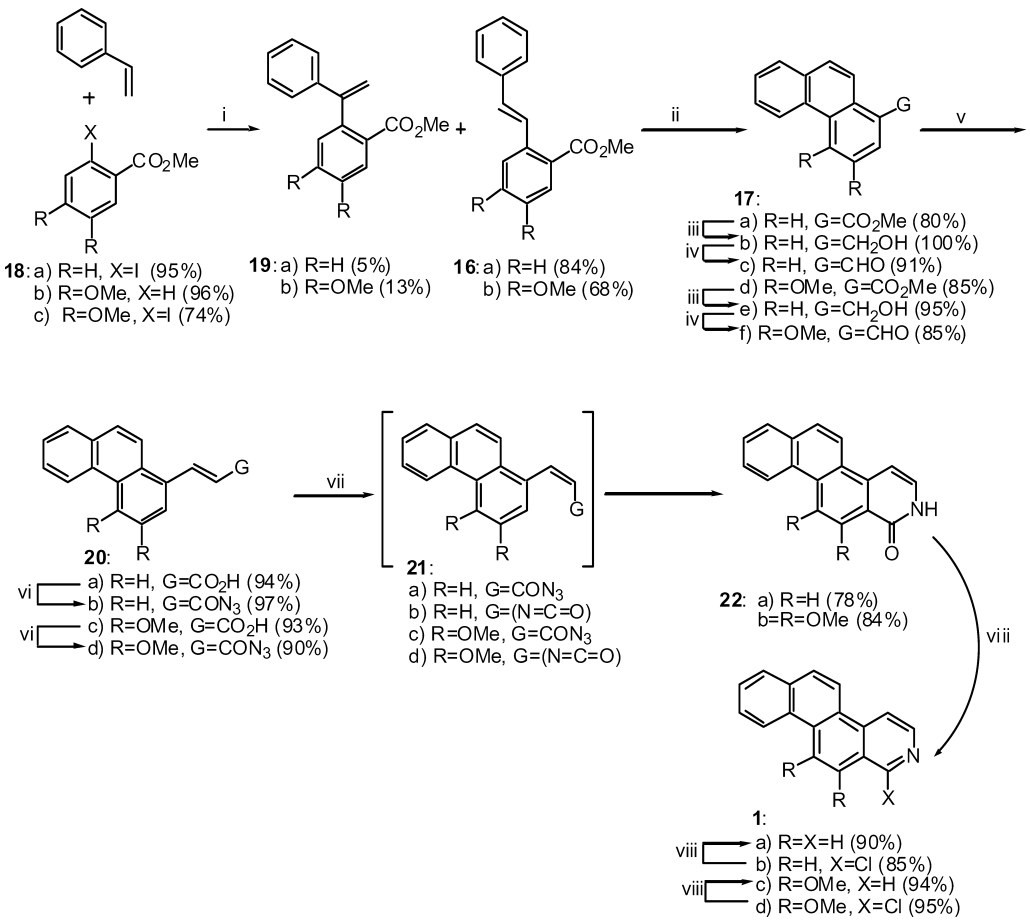
Finally, construction of the nitrogen ring of 2-azachrysene (**1a**) was efficiently accomplished through a six-step sequence,[22] which included initial transformation of the methoxycarbonyl group of phenanthrene **17a** into a formyl group. Treatment of a solution of **17a** in THF with $LiAlH_4$ at room temperature gave quantitatively the corresponding



Scheme 4.

alcohol **17b**, which was efficiently oxidized to aldehyde **17c** upon treatment with MnO_2 at 40°C for 24 h. Elongation of the lateral chain of this aldehyde was then carried out in order to achieve the necessary functionality for the construction of the nitrogen ring of 2-azachrysene (**1a**). Condensation of aldehyde **17c** with malonic acid provided a 94% yield of (*E*)-3-phenanthren-1-yl-acrylic acid (**20a**), which was identified from its analytical and spectroscopic data. The mass spectrum confirmed the molecular mass expected for the compound (*m*/*z*=248) and the *E* configuration of the double bond was easily established from the ^1H NMR spectrum, which showed two doublets at 6.64 ppm (1H, *J*=15.7 Hz) and 8.49 ppm (1H, *J*=15.7 Hz). A cooled solution of acid **20a**, $ClCO_2Et$ and Et_3N was stirred for 45 min and then NaN_3 and water were added. The resulting mixture was stirred for a further 30 min to furnish acyl azide **20b** in 97% yield. This compound was dissolved in Ph_2O and the solution was heated under reflux for 1 h in the presence of Bu_3N to give compound **22a** through a process involving isomerization of the double bond and transformation of the azyl azide group of **21a** into the isocyanate intermediate **21b**. This intermediate spontaneously cyclized to give lactam **22a**. The mass spectrum of this compound contained a peak at *m*/*z* 245 corresponding to its molecular ion and the IR spectrum showed a band at 1650 cm^{-1} corresponding to the amide carbonyl group. The ^1H NMR spectrum showed a complex group of signals due to the presence of 10 aromatic protons. Finally, a solution of compound **22a** was heated under reflux in $POCl_3$ for 3 h to provide 85% yield of 1-chloro-2-azachrysene (**1b**), which was immediately reacted with Zn and AcOH at room temperature for 2 h to remove the chloro substituent. 2-Azachrysene (**1a**) was thus obtained in 90% yield.

We proceeded to apply the same strategy to the preparation of dimethoxyazachrysene **1c**.



Scheme 5. (i) $Pd(OAc)_2$ (5% M), Ph_3P, Et_3N, MeCN, argon, 80°C, 24 h. (ii) UV light, I_2, Et_2O, rt, 3 h. (iii) $LiAlH_4$, THF, rt, 1.5 h. (iv) MnO_2, $CHCl_3$, 40°C, 24 h. (v) $CH_2(CO_2H)_2$, piperidine, pyr, 80°C, 2 h, then reflux, 1 h. (vi) (a) $ClCO_2Et$, Et_3N, acetone, 0°C, 45 min; (b) NaN_3, H_2O, 0°C, 30 min. (vii) Bu_3N, Ph_2O, reflux, 1 h. (viii) (a) $POCl_3$, reflux, 3 h; (b) Zn, AcOH, reflux, 2 h.

The required *o*-iodobenzoic acid ester **18c** was easily obtained in 74% yield by esterification of commercial 3,4-dimethoxybenzoic acid with methanol followed by reaction of the resulting ester **18b** with Ipy_2BF_4 and trifluoromethanesulfonic acid.[23] Heck coupling of the resulting *o*-iodobenzoate **18c** to styrene under the same conditions as for its analogue **18a** gave a slightly unsatisfactory result. The expected dimethoxylated *o*-styrylbenzoate **16b** was isolated in 68% yield, together with 13% yield of the α-coupled alkene **19b** and 19% yield of the reduced starting material **18b**.

Stilbenic compound **16b** was then converted into dimethoxylated 2-azachrysene **1c** in a similar manner to the transformation of stilbene **16a** into 2-azachrysene (**1a**). Photocyclization of **16b** under the same conditions as for **16a** gave a 85% yield of the expected phenanthrenecarboxilic acid ester **17d**, which was converted into the corresponding phenanthrene aldehyde **17f** by treatment with $LiAlH_4$ and oxidation of the resulting alcohol **17e** with MnO_2. Construction of the nitrogen ring of **1c** was carried out by treatment of **17f** with malonic acid followed by the transformation of the resulting derivative **20c** into isoquinolinone **22b** via acyl azide **20d**. Finally, treatment of **22b** with $POCl_3$ provided the desired 1-chloro isoquinoline **1d**, from which the target compound **1c** was readily obtained by removal of the chlorine atom by reduction of **1d** with zinc and acetic acid. This new 2-azachrysene **1c** was easily identified from analytical and spectroscopical data. The microanalysis and the mass spectrum confirmed the molecular formula $C_{19}H_{15}NO_2$ expected for the product. The ^{1}H NMR showed two singlets at 4.04 and 4.25 ppm, corresponding to the methoxy substituents, and signals for a total of nine aromatic protons (one more than its precursor **1d**), including two singlets at 9.77 and 9.69 ppm, corresponding to the protons at C(1) and C(10), respectively, both of which are deshieldied due to steric interaction with methoxy substituents at C(12) and C(11), respectively. 2-Azachrysene **1c** was obtained more efficiently than its analogue **1a**, mainly due to the fact that photocyclization of stilbene **16b** was more efficient than that of **16a** and the yield corresponding to the cyclization of acyl azide **20d** was higher than the similar cyclization of **20b**. This is probably due to a favorable electronic effect of substituents in both key steps.

In conclusion, we describe here the first two total syntheses of 2-azachrysenes. One route includes new general syntheses of 2-styrylbenzoic acids and phenanthrenylbenzoic acids that are simpler and more efficient than previously described routes.[24,25] Work is now in progress to obtain a range of 2-azachrysenes for a systematic study of their chemical and biological properties, including their antineoplastic activity.

1. Experimental

1.1. General

Melting points were determined on a Kofler Thermogerate apparatus and are uncorrected. Infrared spectra were recorded on a MIDAC FTIR spectrophotometer. Nuclear magnetic resonance spectra were recorded, unless otherwise specified, 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 eluant; 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.

1.1.1. *N,N*-Dimethyl-3-(2-hydroxyphenyl)propionamide (5a). 33% Aq. dimethylamine (6 mL) was added to a solution of chroman-2-one (**4**) (500 mg, 3.375 mmol) in THF (6 mL) and the mixture was stirred at rt for 30 min. The solvent was removed in vacuo, the residue was poured into aq. hydrochloric acid (25 mL) and the resulting suspension was extracted with dichloromethane (3×20 mL). The combined organic extracts were washed with water (50 mL), dried, filtered and concentrated to drynes to give *N,N*-dimethyl-3-(2-hydroxyphenyl)propionamide (**5a**) (625 mg, 96% yield) as a white solid. Mp 102–104°C (methanol). IR (ν, cm^{-1}, NaCl): 3306 (–OH), 1632 (CO). ^{1}H NMR (δ, ppm): 9.80 (s, 1H, –OH), 7.15–7.00 (m, 2H, 2×ArH), 6.90–6.78 (m, 2H, 2×ArH), 2.91–2.86 (m, 8H, $-CH_2-$ and 2×-NCH_3), 2.67–2.62 (m, 2H, $-CH_2-$). ^{13}C NMR (δ, ppm): 173.64 (CO), 155.15 (C), 130.42 (ArH), 128.15 (C), 127.59 (ArH), 119.81 (ArH), 117.43 (ArH), 36.81 ($-NCH_3$), 35.54 ($-NCH_3$), 34.95 ($-CH_2-$), 24.50 ($-CH_2-$). MS (*m/z*, %): 193 (M^+, 32), 149 (100).

1.1.2. 3-(2-Benzyloxyphenyl)-*N,N*-dimethylpropionamide (5b). Tetrabutylammonium bromide (67 mg, 0.207 mmol), 80% sodium hydride (75 mg, 2.484 mmol) and benzyl bromide (0.27 mL, 2.484 mmol) were added to a solution of hydroxyphenylpropionamide **5a** (400 mg, 2.069 mmol) in dry THF (10 mL) and the mixture was stirred at rt under argon for 1 h. The solvent was removed under vacuum using a rotary evaporator and the solid residue was suspended in water (30 mL) and acidified with 10% hydrochloric acid. The resulting suspension was extracted with dichloromethane (2×25 mL) and the combined organic extracts were washed with water (30 mL), dried, filtered and concentrated in vacuo to provide 3-(2-benzyloxyphenyl)-*N,N*-dimethylpropionamide (**5b**) (586 mg, 100%) as a white solid. Mp 97–99°C (methanol). IR (ν, cm^{-1}, NaCl): 1633 (CO). ^{1}H NMR (δ, ppm): 7.44–7.32 (m, 5H, 5×ArH), 7.25–7.15 (m, 2H, 2×ArH), 6.93–6.87 (m, 2H, 2×ArH), 5.07 (s, 2H, $-CH_2-$), 3.01–2.95 (m, 2H, $-CH_2-$), 2.98 (s, 3H, $-CH_3$), 2.77 (s, 3H, $-CH_3$), 2.62–2.56 (m, 2H, $-CH_2-$). ^{13}C NMR (δ, ppm): 173.64 (CO), 155.15 (C), 130.42 (ArH), 128.15 (C), 127.59 (ArH), 119.81 (ArH), 117.43 (ArH), 36.81 ($-NCH_3$), 35.54 ($-NCH_3$), 34.95 ($-CH_2-$), 24.50 ($-CH_2-$). MS (*m/z*, %): 283 (M^+, 1), 192 (22), 91 (100).

1.1.3. 3-(2-Benzyloxyphenyl)propionic acid (5c). 11 M Potassium hydroxide (20 mL) was added to a solution of propionamide **5b** (1.070 g, 3.776 mmol) in ethanol (25 mL) and the mixture was heated under reflux with the exclusion of moisture (calcium chloride tube) for 22 h. The solvent

was removed in vacuo, the aqueous residue was acidified with 20% hydrochloric acid and the suspension was extracted with dichloromethane (3×30 mL). The combined organic extracts were dried, filtered and concentrated in vacuo to give 3-(2-benzyloxyphenyl)propionic acid (**5c**) (968 mg, 93%) as a yellow oil. IR (ν, cm^{-1}, NaCl): 2916 (COOH), 1711 (CO). ^1H NMR (δ, ppm): 7.37–7.20 (m, 5H, 5×ArH), 7.15–7.06 (m, 2H, 2×ArH), 6.84–6.78 (m, 2H, 2×ArH), 5.01 (s, 2H, $-CH_2-$), 2.96–2.89 (m, 2H, $-CH_2-$), 2.64–2.58 (m, 2H, $-CH_2-$). ^{13}C NMR (δ, ppm): 179.62 (CO), 156.50 (C), 137.15 (C), 130.07 (ArH), 128.78 (C), 128.55 (2×ArH), 127.77 (ArH), 127.66 (ArH), 126.99 (2×ArH), 120.74 (ArH), 111.54 (ArH), 69.70 ($-CH_2-$), 33.95 ($-CH_2-$), 25.87 ($-CH_2-$). MS (*m*/*z*, %): 256 (M^+, 1), 91 (100).

1.1.4. [2-(2-Benzyloxyphenyl)ethyl]carbamic acid ethyl ester (6a). Diphenylphosphoryl azide (2.40 mL, 11.159 mmol) and triethylamine (1.55 mL, 11.159 mmol) were added to a solution of phenylpropionic acid **5c** (2.6 g, 10.114 mmol) in dry toluene (50 mL) and the mixture was heated under reflux for 1 h under argon. Copper(II) chloride (105 mg, 1.014 mmol) and anhydrous ethanol (25 mL) were added and the mixture was heated under reflux for a further 1 h. The reaction mixture was concentrated in vacuo, the solid residue was dissolved in diethyl ether and the solution was successively washed with saturated sodium bicarbonate (100 mL) and water. The organic extract was dried, filtered and concentrated in vacuo to give [2-(2-benzyloxyphenyl)-ethyl]carbamic acid ethyl ester (**6a**) (2.846 mg, 94% yield) as colourless oil. IR (ν, cm^{-1}, NaCl): 3336 (–NH), 1717 (CO). ^1H NMR (δ, ppm): 7.52–7.37 (m, 5H, 5×ArH), 7.31–7.21 (m, 2H, 2×ArH), 7.01–6.95 (m, 2H, 2×ArH), 5.14 (s, 2H, $-CH_2-$), 4.9 (bs, 1H, –NH), 4.39 (q, J=7.1 Hz, 1H, $-OCH_2CH_3$), 4.12 (q, J=7.1 Hz, 2H, $-OCH_2CH_3$), 3.54–3.46 (m, 2H, $-CH_2-$), 2.96–2.91 (m, 2H, $-CH_2$), 1.45 (t, J=7.1 Hz, 1.5H, $-OCH_2CH_3$), 1.26 (t, J=7.1 Hz, 3H, $-OCH_2CH_3$). ^{13}C NMR (δ, ppm): 156.60 (CO), 150.55 (C), 136.98 (C), 136.68 (C), 130.68 (ArH), 129.69 (ArH), 128.52 (2×ArH), 127.84 (ArH), 127.73 (ArH), 127.58 (C), 127.18 (2×ArH), 125.21 (ArH), 120.85 (ArH), 120.01 (ArH), 119.94 (ArH), 111.60 (ArH), 69.87 ($-CH_2-$), 65.47 ($-OCH_2CH_3$), 60.46 ($-OCH_2CH_3$), 41.02 ($-CH_2-$), 30.65 ($-CH_2-$), 29.65 ($-CH_2-$), 16.04 ($-OCH_2CH_3$), 14.58 ($-OCH_2CH_3$). MS (*m*/*z*, %): 299 (M^+, 1), 91 (100).

1.1.5. [2-(2-Hydroxyphenyl)ethyl]carbamic acid ethyl ester (6b). Pd/C (3 g) was added to a deoxygenated solution of carbamate **6a** (2.92 g, 9.754 mmol) in ethyl acetate (100 mL) and the suspension was stirred at rt under a hydrogen atmosphere for 2 h. This suspension was filtered through celite, which was washed with ethyl acetate, and the filtrate was concentrated in vacuo to give [2-(2-hydroxy-phenyl)ethyl]carbamic acid ethyl ester (**6b**) (2.041 g, 100% yield) as an oil. IR (ν, cm^{-1}, NaCl): 3334 (–NH, –OH), 1691 (CO). ^1H NMR (δ, ppm): 7.50 (bs, 1H, –OH), 7.16–6.95 (m, 2H, 2×ArH), 6.78–6.70 (m, 2H, 2×ArH), 5.13 (bs, 1H, –NH), 4.03 (q, J=7.0 Hz, 2H, $-OCH_2CH_3$), 3.35–3.28 (m, 2H, $-CH_2-$), 2.78–2.72 (m, 2H, $-CH_2-$), 1.14 (t, J=7.0 Hz, 3H, $-OCH_2CH_3$). ^{13}C NMR (δ, ppm): 157.48 (CO), 154.71 (ArOH), 130.61 (ArH), 127.83 (ArH), 124.93 (C), 120.16 (ArH), 115.58 (ArH), 61.07 ($-OCH_2CH_3$), 60.54 ($-OCH_2CH_3$), 41.20 ($-CH_2-$), 30.88 ($-CH_2-$), 14.50 ($-OCH_2CH_3$), 14.08 ($-OCH_2CH_3$). MS (*m*/*z*, %): 209 (M^+, 23), 120 (100).

1.1.6. Trifluoromethanesulfonic acid 2-(2-ethoxycarbonylamino-ethyl)phenyl ester (6c). To a stirred deoxygenated solution of carbamic acid ethyl ester **6b** (2.041 g, 9.754 mmol) in dry dichloromethane (30 mL) was added *N*-triflimide (3.48 g, 9.754 mmol) and triethyl amine (1.5 mL, 10.729 mmol). The reaction mixture was stirred at rt for 2 days, poured into 10% sodium hydroxide (30 mL) and the resulting suspension was extracted with dichloromethane (3×20 mL). The combined organic extracts were washed with saturated sodium carbonate, dried and concentrated in vacuo. The residue was purified by column chromatography (eluant: 1:3 ethyl acetate/hexane) to yield triflate **6c** (2.963 g, 89% yield) as a yellow oil. IR (ν, cm^{-1}, NaCl): 3332 (–NH), 1701 (CO). ^1H NMR (δ, ppm): 7.40–7.27 (m, 4H, 4×ArH), 4.89 (bs, 1H, –NH), 4.13 (q, J=7.1 Hz, 2H, $-OCH_2CH_3$), 3.53–3.45 (m, 2H, $-CH_2-$), 2.99–2.94 (m, 2H, $-CH_2-$), 1.25 (t, J=7.1 Hz, 3H, $-OCH_2CH_3$). MS (*m*/*z*, %, FAB): 342 ($[M+1]^+$, 100).

1.1.7. [2-(2-Styrylphenyl)ethyl]carbamic acid ethyl ester (3). A deoxygenated solution of triflate **6c** (1.5 g, 4.395 mmol), styrene (1.01 mL, 8.789 mmol), palladium acetate (97 mg, 0.439 mmol), triphenylphosphine (23 mg, 0.878 mmol), lithium chloride (560 mg, 13.185 mmol) and triethylamine (0.674 mL, 4.834 mmol) in dry acetonitrile was heated under argon in a sealed tube at 100°C for 3 days. The suspension was then filtered through celite, the filtrate was washed with water and the organic extracts were dried with anhydrous sodium sulfate and concentrated in vacuo. The oily residue, consisting of a 1:23 mixture of compounds **3** and **7** (718 mg, 80% global yield), was used directly in the next step without further purification. IR (ν, cm^{-1}, NaCl): 3335 (–NH), 1695 (CO). MS (*m*/*z*, %): 295 (M^+, 6), 206 (100).

Data for compound **3**. ^1H NMR (δ, ppm): 7.90 (d, J=16.0 Hz, 1H, $-CH$=CH–), 7.73–7.53 (m, 3H, 3×ArH), 7.47–7.21 (m, 7H, 7×ArH), 4.88 (bs, 1H, –NH), 4.12 (q, J=7.0 Hz, 2H, $-OCH_2CH_3$), 3.52–3.44 (m, 2H, $-CH_2-$), 3.08–3.03 (m, 2H, $-CH_2-$), 1.24 (t, J=7.0 Hz, 3H, $-OCH_2CH_3$). ^{13}C NMR (δ, ppm): 156.58 (CO), 137.38 (C), 136.59 (C), 136.47 (C), 130.73 (ArH), 130.12 (ArH), 128.63 (2×ArH), 127.71 (ArH), 127.65 (ArH), 126.96 (ArH), 126.58 (2×ArH), 125.87 (ArH), 125.66 (ArH), 60.66 ($-OCH_2CH_3$), 41.80 ($-CH_2-$), 33.53 ($-CH_2-$), 14.52 ($-OCH_2CH_3$).

1.1.8. (2-Phenanthren-1-yl-ethyl)carbamic acid ethyl ester (2). Air was bubbled for 10 min through a stirred solution of the mixture of compounds **3** and **7** (100 mg, 0.338 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 irradiated for 2 h in a photochemical reactor equipped with a Pyrex condenser and a Hanovia 450 W medium pressure Hg vapour lamp. Saturated sodium thiosulfate (100 mL) was added, the organic layer was dried, filtered and concentrated in vacuo. The residue was purified by column chromatography (eluant 3:7 ethyl acetate/hexane) to afford phenanthrene **2** (77 mg, 80% yield). Mp 86–89°C (ethyl

acetate). IR (ν, cm^{-1}, NaCl): 3342 (–NH), 1701 (CO). ^1H NMR (δ, ppm): 8.75–8.65 (m, 2H, 2×ArH), 8.10 (d, J=9.1 Hz, 1H, ArH), 7.96–7.93 (m, 1H, ArH), 7.84 (d, J=9.1 Hz, 1H, ArH), 7.73–7.59 (m, 3H, 3×ArH), 7.48 (d, J=7.0 Hz, 1H, ArH), 4.96 (bs, 1H, –NH), 4.21 (q, J=7.0 Hz, 2H, $-OCH_2CH_3$), 3.62–3.56 (m, 2H, $-CH_2-$), 3.41–3.35 (m, 2H, $-CH_2-$), 1.31 (t, J=7.0 Hz, 3H, $-OCH_2CH_3$). ^{13}C NMR (δ, ppm): 156.64 (CO), 135.94 (C), 131.41 (C), 130.54 (C), 130.49 (C), 130.16 (C), 128.31 (ArH), 127.68 (ArH), 127.03 (ArH), 126.51 (ArH), 126.44 (ArH), 126.00 (ArH), 122.72 (ArH), 122.08 (ArH), 121.53 (ArH), 60.60 ($-OCH_2CH_3$), 41.75 ($-CH_2-$), 33.62 ($-CH_2-$), 14.52 ($-OCH_2CH_3$). MS (*m/z*, %): 293 (M^+, 25), 204 (100). Anal. calcd for $C_{19}H_{19}NO_2$, C 77.79, H 6.53, N 4.77; found, C 78.02, H 6.31, N 4.95.

1.1.9. (2-Phenanthren-1-yl-ethyl)-carbamic acid ethyl ester derivative (8a). A solution of compound **2** (48 mg, 0.164 mmol) in $POCl_3$ (3 mL) was refluxed under argon for 2 h and then concentrated in vacuo. The residue was suspended in saturated sodium bicarbonate (5 mL), the suspension was extracted with dichloromethane (3×10 mL) and the combined organic extracts were washed with water (15 mL), dried and concentrated to dryness to give compound **8a** (55 mg, 82% yield) as a yellow solid. ^1H NMR (δ, ppm): 8.61–8.53 (m, 2H, 2×ArH), 8.04 (d, J=9.2 Hz, 1H, ArH), 7.82–7.72 (m, 2H, 2×Ar-H), 7.56–7.40 (m, 4H, 4×ArH), 4.23 (q, J=7.1 Hz, 2H, $-OCH_2-$), 4.11–4.00 (m, 2H, $-CH_2-$), 3.98–3.37 (m, 2H, $-CH_2-$), 1.24 (t, J=7.1 Hz, 3H, $-CH_3$). ^{13}C NMR (δ, ppm): 152.49 (d, J=6.3 Hz, C–P), 134.00 (C), 131.48 (C), 130.68 (C), 130.52 (C), 130.41 (C), 128.42 (ArH), 127.41 (ArH), 126.68 (ArH), 126.60 (ArH), 126.20 (ArH), 122.83 (ArH), 122.12 (ArH), 64.21 ($-OCH_2-$), 48.39 ($-CH_2-$), 34.13 ($-CH_2-$), 13.89 ($-CH_3$). MS (*m/z*, %): 411 [$(M+2)^+$, 0.03)]; 409 (M^+, 0.12), 204 (100).

1.1.10. 1-(2-Chloroethyl)phenanthrene (10). A dry, oxygen-free mixture of compound **2** (65 mg, 0.222 mmol) and $POCl_3$ (5 mL) was heated in a sealed tube at 155°C for 28 h and the mixture was concentrated to dryness. The residue was dissolved in dichloromethane (10 mL) and the solution was washed with saturated potassium carbonate, dried and concentrated in vacuo. The solid residue was subjected to preparative TLC (eluant: 5% ethyl acetate/hexane) and compound **10** (14 mg, 27% yield) was isolated as a white solid. ^1H NMR (δ, ppm): 8.70–8.63 (m, 2H, 2×ArH), 7.94–7.87 (m, 2H, 2×ArH), 7.79 (d, J=9.2 Hz, 1H, Ar-H), 7.66–7.47 (m, 4H, 4×ArH), 3.87–3.82 (m, 2H, $-CH_2-$), 3.61–3.55 (m, 2H, $-CH_2-$). ^{13}C NMR (δ, ppm): 134.61 (C), 131.52 (C), 130.84 (C), 130.63 (C), 130.00 (C), 128.51 (ArH), 128.11 (ArH), 127.43 (ArH), 126.82 (ArH), 126.70 (ArH), 126.24 (ArH), 122.92 (ArH), 122.23 (ArH), 121.69 (ArH), 44.29 ($-CH_2-$), 36.87 ($-CH_2-$). MS (*m/z*, %): 242 [$(M+2)^+$, 10]; 240 (M^+, 32), 191 (100).

1.1.11. 3,4-Dihydro-2*H*-naphtho[2.1-*f*]isoquinolin-1-one (11) and 2-trifluoromethanesulfonyl-3,4-dihydro-2*H*-naphtho[2.1-*f*]isoquinolin-1-one (12). Triflic anhydride (0.0930 mL, 5.529 mmol) was added dropwise over 5 min to a solution of compound **2** (325 mg, 1.1 mmol) and DMAP (406 mg, 3.320 mmol) in dry dichloromethane (12 mL) at 0°C and the mixture was stirred for 21 h under argon at room temperature. Dichloromethane (10 mL) was added and the solution was washed with water (20 mL), saturated potassium carbonate (20 mL) and water (25 mL). The organic layer was dried and concentrated in vacuo to give a residue that was purified by column chromatography (eluant: dichloromethane/hexane 4:1) to afford compound **11** (123 mg, 45% yield) and compound **12** (146 mg, 35%).

Data for compound **11**. Mp 233–235°C (methanol). IR (ν, cm^{-1}, NaCl): 3437 (–NH), 1658 (CO). ^1H NMR (δ, ppm): 8.90–8.82 (m, 2H, 2×ArH), 8.18–7.95 (m, 4H, 4×ArH), 7.76–7.67 (m, 2H, 2×ArH), 3.57–3.45 (m, 2H, $-CH_2-$), 3.43–3.38 (m, 2H, $-CH_2-$). ^{13}C NMR (δ, ppm): 165.28 (CO), 137.70 (C), 132.40 (C), 132.33 (C), 130.17 (C), 129.00 (ArH), 128.94 (C), 128.14 (ArH), 128.09 (ArH), 127.85 (C), 127.75 (ArH), 125.12 (ArH), 124.08 (ArH), 123.07 (ArH), 121.89 (ArH), 39.37 ($-CH_2-$), 24.59 ($-CH_2-$). MS (*m/z*, %): 247 (M^+, 100). Anal. calcd for $C_{17}H_{13}NO$, C 82.57, H 5.30, N 5.66; found, C 82.29, H 5.67, N 5.39.

Data for compound **12**. Mp 189–190°C (methanol). IR (ν, cm^{-1}, NaCl): 1703 (CO). ^1H NMR (δ, ppm, DMSO): 8.94–8.92 (m, 2H, 2×ArH), 8.21 (d, J=8.8 Hz, 1H, ArH), 8.10–8.06 (m, 3H, 3×ArH), 7.79–7.76 (m, 2H, 2×ArH), 4.37 (t, J=5.9 Hz, 2H, $-CH_2-$), 3.69 (t, J=5.9 Hz, 2H, $-CH_2-$). ^{13}C NMR (δ, ppm, DMSO): 163.24 (CO), 139.95 (C), 133.92 (C), 132.79 (C), 129.57 (C), 128.99 (ArH), 128.90 (ArH), 128.85 (ArH), 128.66 (C), 127.99 (ArH), 125.42 (ArH), 124.63 (C), 124.37 (ArH), 122.92 (ArH), 122.68 (ArH), 47.12 ($-CH_2-$), 25.49 ($-CH_2-$). MS (*m/z*, %): 379 (M^+, 100), 246 (M^+-Tf, 42).

1.1.12. 1-(2-Trifluoromethanesulfonylaminoethyl)phenanthrene-2-carboxylic acid methyl ester (13). A solution of compound **12** (100 mg, 0.243 mmol) and dry triethylamine (0.92 mL) in methanol (15 mL) and isopropanol (2 mL) was stirred in the presence of Pd/C (100 mg) at rt for 24 h and then concentrated in vacuo. The solid residue was purified by column chromatography (eluant: 15% ethyl acetate/hexane) and added to give 1-(2-trifluoromethanesulfonylaminoethyl)phenanthrene-2-carboxylic acid methyl ester (**13**) (85 mg, 81% yield) as a white solid. IR (ν, cm^{-1}, NaCl): 1634 (C=O). ^1H NMR (δ, ppm): 8.74–8.68 (m, 2H, 2×ArH), 8.06–7.87 (m, 4H, 4×ArH), 7.72–7.67 (m, 2H, 2×Ar-H), 7.03 (bs, 1H, ArH), 4.02 (s, 3H, $-CO_2CH_3$), 3.82–3.78 (m, 2H, $-CH_2-$), 3.73–3.67 (m, 2H, $-CH_2-$). ^{13}C NMR (δ, ppm): 170.29 (CO), 136.04 (C), 133.24 (C), 132.11 (C), 130.47 (C), 130.03 (C), 128.76 (ArH+C), 128.58 (ArH), 127.93 (ArH), 127.30 (ArH), 126.80 (ArH), 123.45 (ArH), 122.29 (ArH), 121.69 (ArH), 53.12 ($-CO_2CH_3$), 44.97 ($-CH_2-$), 28.87 ($-CH_2-$). MS (*m/z*, %): 411 (M^+, 29), 249 (100). High resolution MS calcd for $C_{19}H_{16}F_3NO_4S$, 411.0752; found, 411.0755.

1.1.13. 1,2,3,4-Tetrahydronaphtho[2,1-*f*]isoquinoline (14). A mixture of isoquinolinone **11** (70 mg, 0.283 mmol) and lithium aluminium hydride (54 mg, 0.849 mmol) in THF (10 mL) was stirred for 15 h at room temperature under argon. Water (0.054 mL), 10% aq. sodium hydroxide (0.054 mL) and water (0.016 mL) were successively added to the reaction mixture and the resulting mixture was filtered. The solid residue was washed with a mixture of

95:5 dichloromethane/methanol and the filtrate was concentrated in vacuo to give tetrahydroisoquinoline **14** (56 mg, 85% yield) as a yellow solid. Mp 164–165°C (methanol, sublimation). IR (ν, cm^{-1}, NaCl): 3429 (–NH). ^1H NMR (δ, ppm): 8.68 (d, J=8.0 Hz, 1H, ArH), 8.54 (d, J=8.5 Hz, 1H, ArH), 7.92–7.82 (m, 3H, 3×ArH), 7.66–7.59 (m, 2H, 2×ArH), 7.32 (d, J=8.5 Hz, 1H, ArH), 4.20 (s, 2H, $-CH_2-$), 3.36–3.31 (m, 2H, $-CH_2-$), 3.26–3.24 (m, 2H, $-CH_2-$). ^{13}C NMR (δ, ppm): 131.74 (C), 131.22 (C), 130.23 (C), 130.14 (C), 129.41 (C), 128.72 (C), 128.21 (ArH), 127.06 (ArH), 126.46 (ArH), 126.14 (ArH), 124.82 (ArH), 122.48 (ArH), 120.99 (ArH), 120.65 (ArH), 47.53 ($-CH_2-$), 42.93 ($-CH_2-$), 25.01 ($-CH_2-$). MS (*m*/*z*, %): 233 (M^+, 52), 204 (100). Anal. calcd for $C_{17}H_{15}N$, C 87.52, H 6.48, N 6.00; found, C 87.73, H 6.27, N 5.79.

1.1.14. Naphtho[2.1-*f*]isoquinoline (1a) and 3.4-dihydronaphtho[2,1-*f*]isoquinoline-2-oxide (15). A solution of tetrahydroisoquinoline **14** (61 mg, 0.261 mmol), iodine (134 mg, 0.523 mmol) and sodium acetate (28 mg, 0.339 mmol) in anhydrous ethanol (8 mL) was refluxed for 15 h under argon. Saturated sodium thiosulfate was added dropwise to the reaction mixture until the iodine colour had disappeared. The product was extracted with dichloromethane (3×20 mL) and the combined organic extracts were washed with saturated sodium chloride, dried, filtered and concentrated in vacuo. The oily residue was subjected to preparative TLC (eluant 98:2 dichloromethane/methanol) and naphthoisoquinoline **1a** (6 mg, 10% yield) and *N*-oxide **15** (15 mg, 23% yield) were isolated.

Data for compound **1a**. Mp 224–226°C (methanol). IR (ν, cm^{-1}, NaCl): 2925 (ArH), 1728 (–C=N–). ^1H NMR (δ, ppm): 9.37 (bs, 1H, ArH), 8.85–8.78 (m, 3H, 3×ArH), 8.65 (d, J=9.0 Hz, 1H, ArH), 8.50 (d, J=5.5 Hz, 1H, ArH), 8.11–8.01 (m, 3H, 3×ArH), 7.80–7.67 (m, 2H, 2×ArH). ^{13}C NMR (δ, ppm): 152.09 (ArH), 144.59 (ArH), 134.53 (C), 133.04 (C), 130.62 (C), 130.13 (C), 128.75 (ArH), 128.16 (ArH), 127.39 (ArH), 127.14 (ArH), 126.53 (C), 125.56 (ArH), 123.45 (ArH), 122.77 (ArH), 120.76 (ArH). MS (*m*/*z*, %): 229 (M^+, 100).

Data for compound **15**. Mp 268–270°C (methanol). IR (ν, cm^{-1}, NaCl): 1657 (–C=N–). ^1H NMR (δ, ppm): 8.71–8.63 (m, 2H, 2×ArH), 8.52 (bs, 1H, –C*H*=N–), 7.96 (d, J=9.2 Hz, 1H, ArH), 7.92–7.89 (m, 1H, ArH), 7.82 (d, J=9.2 Hz, 1H, ArH), 7.72–7.60 (m, 2H, 2×ArH), 7.57 (d, J=8.4 Hz, 1H, ArH), 3.95 (t, J=7.4 Hz, 2H, $-CH_2-$), 3.19 (t, J=7.4 Hz, 2H, $-CH_2-$). ^{13}C NMR (δ, ppm): 160.81 (–*CH*=N–), 133.69 (C), 132.32 (C), 132.21 (C), 130.38 (C), 128.93 (C), 128.64 (ArH), 127.75 (ArH), 127.31 (ArH), 127.01 (ArH), 125.20 (ArH), 123.18 (ArH), 121.57 (ArH), 121.54 (ArH), 47.44 ($-CH_2-$), 21.36 ($-CH_2-$). MS (*m*/*z*, %): 247 (M^+, 63), 189 (100).

1.1.15. 2-Styrylbenzoic acid methyl ester (16a). A deoxygenated mixture of methyl 2-iodobenzoate (**18a**) (1 g, 3.816 mmol), styrene (0.525 mL, 4.579 mmol), palladium acetate (65 mg, 0.286 mmol), triphenylphosphine (150 mg, 0.572) and triethylamine (0.640 mL, 4.579 mmol) in dry acetonitrile (20 mL) was heated in a sealed tube at 80°C for 21 h. The suspension was filtered through celite, the filtrate was washed with water (5 mL), dried and concentrated in vacuo. The resulting oil was purified by column chromatography (eluant: 3:7 dichloromethane/hexane) to give compound **16a** (762 mg, 84% yield) as a colourless oil, together with a small amount of compound **19a** (45 mg, 5% yield).

Data for compound **16a**. IR (ν, cm^{-1}, NaCl): 1719 (CO). ^1H NMR (δ, ppm): 8.02 (d, J=16.3 Hz, 1H, –C*H*=CH–), 7.86 (dd, J=7.8, 1.3 Hz, 1H, ArH), 7.58 (d, J=7.7 Hz, 1H, ArH), 7.51–7.47 (m, 2H, 2×ArH), 7.35–7.17 (m, 5H, 5×ArH), 6.92 (d, J=16.3 Hz, 1H, –CH=C*H*–), 3.78 (s, 3H, $-CO_2CH_3$). ^{13}C NMR (δ, ppm): 167.28 (CO), 138.86 (C), 137.05 (C), 131.79 (ArH), 130.99 (ArH), 130.35 (ArH), 128.32 (2×ArH), 128.02 (C), 127.49 (ArH), 127.04 (ArH), 126.73 (ArH), 126.54 (3×ArH), 51.62 ($-CO_2CH_3$). MS (*m*/*z*, %): 238 (M^+, 79), 178 (100). High resolution MS calcd for $C_{16}H_{14}O_2$, 238.0994; found, 238.0991.

1.1.16. Phenanthrene-1-carboxylic acid methyl ester (17a). Irradiation of stilbene **16a** (350 mg, 1.291 mmol) under the same conditions as for the cyclization of **2** afforded phenanthrene **17a** (242 mg, 80% yield) as a yellow oil. IR (ν, cm^{-1}, NaCl): 1714 (CO). ^1H NMR (δ, ppm): 8.92 (d, J=8.4 Hz, 1H, ArH), 8.78 (d, J=9.4 Hz, 1H, ArH), 8.70 (d, J=7.9 Hz, 1H, ArH), 8.22 (d, J=7.4 Hz, 1H, ArH), 7.93 (d, J=7.4 Hz, 1H, ArH), 7.87 (d, J=9.4 Hz, 1H, ArH), 7.70–7.64 (m, 3H, 3×ArH), 4.04 (s, 3H, $-CO_2CH_3$). ^{13}C NMR (δ, ppm): 168.25 (CO), 131.42 (C), 130.73 (C), 130.46 (C), 129.83 (C), 129.69 (ArH), 128.62 (ArH), 128.37 (ArH), 127.95 (C), 126.97 (ArH), 126.92 (ArH), 126.75 (ArH), 125.12 (ArH), 123.57 (ArH), 122.26 (ArH), 52.17 ($-CO_2CH_3$). MS (*m*/*z*, %): 236 (M^+, 100). High resolution MS calcd for $C_{16}H_{12}O_2$, 236.0837; found, 236.0832.

1.1.17. Phenanthren-1-yl-methanol (17b). Lithium aluminium hydride (273 mg, 7.195 mmol) was added over 3 h to a stirred solution of phenathrene **17a** (340 mg, 1.439 mmol) in dry THF (10 mL) at 0°C under argon. The reaction mixture was stirred for 1.5 h at rt. Water (273 μL), 15% sodium hydroxide (273 μL) and water (820 μL) were consecutively added to the cooled (0°C) reaction mixture to destroy the excess lithium aluminiun hydride. The resulting precipitate was filtered off and the filtrate was dried, filtered and concentrated in vacuo to give phenanthrenylmethanol **17b** (300 mg, 100% yield) as a white solid. Mp 162–163°C (methanol/diethyl ether). IR (ν, cm^{-1}, NaCl): 3296 (–OH). ^1H NMR (δ, ppm): 8.72–8.66 (m, 2H, 2×ArH), 8.05 (d, J=9.2 Hz, 1H, ArH), 7.92–7.88 (m, 1H, ArH), 7.80 (d, J=9.2 Hz, 1H, ArH), 7.69–7.59 (m, 4H, 4×ArH), 5.15 (s, 2H, $-CH_2OH$). ^{13}C NMR (δ, ppm): 136.77 (C), 131.33 (C), 130.20 (C), 129.48 (2×C), 128.14 (ArH), 126.81 (ArH), 126.31 (ArH), 126.23 (ArH), 125.77 (ArH), 125.74 (ArH), 122.49 (ArH), 122.24 (ArH), 121.86 (ArH), 63.07 ($-CH_2OH$). MS (*m*/*z*, %): 208 (M^+, 69), 179 (100). Anal. calcd for $C_{15}H_{12}O$, C 86.51, H 5.81; found, C 86.93, H 6.08.

1.1.18. Phenanthrene-1-carbaldehyde (17c). Manganese(IV) oxide (1.064 g, 12.140 mmol) was added to a solution of alcohol **17b** (255 mg, 12.240 mmol) in chloroform (30 mL) and the stirred mixture was heated at 35°C for 24 h. The suspension was filtered through celite, which was washed with chloroform, and the filtrate was washed with water (5 mL), dried and concentrated in vacuo to give

aldehyde **17c** (230 mg, 91% yield) as a white solid. Mp 97–99°C (methanol). IR (ν, cm^{-1}, NaCl): 1682 (CO). ^1H NMR (δ, ppm): 10.36 (s, –CHO), 8.99 (d, J=9.3 Hz, 1H, ArH), 8.72 (d, J=8.3 Hz, 1H, ArH), 8.50–8.46 (m, 1H, ArH), 7.88 (dd, J=7.2, 1.1 Hz, 1H, ArH), 7.82–7.77 (m, 2H, 2×ArH), 7.61–7.54 (m, 3H, 3×ArH). ^{13}C NMR (δ, ppm): 193.32 (–CHO), 134.87 (ArH), 131.52 (C), 131.30 (C), 130.54 (C), 130.08 (C), 129.96 (ArH), 129.49 (C), 128.71 (ArH), 128.42 (ArH), 127.07 (ArH), 126.96 (ArH), 125.39 (ArH), 122.60 (ArH), 121.94 (ArH). MS (*m/z*, %): 206 (M^+, 92), 178 (100). Anal. calcd for $C_{15}H_{10}O$, C 87.36, H 4.89; found, C 86.97, H 5.08.

1.1.19. 3-Phenanthren-1-yl-acrylic acid (20a). A solution of aldehyde **17c** (220 mg, 1.066 mmol), dry pyridine (7 mL), malonic acid (255 mg, 2.45 mmol) and two drops of piperidine was heated for 2 h at 80°C under argon. The reaction mixture was poured into a 1:1 mixture of 10% hydrochloric acid and ice. The resulting precipitate was filtered off and washed with water (3×25 mL) to give acid **20a** (1.007 mg, 94% yield) as a white solid. Mp 225–228°C (methanol). IR (ν, cm^{-1}, NaCl): 3430 (–COOH), 1723 (CO). ^1H NMR (δ, ppm): 12.65 (bs, –OH), 8.97–8.85 (m, 2H, 2×ArH), 8.49 (d, J=15.7 Hz, 1H, –C*H*=CH–), 8.16 (d, J=9.2 Hz, 1H, ArH), 8.06–8.02 (m, 2H, 2×ArH), 7.97 (d, J=9.2 Hz, 1H, ArH), 7.77–7.66 (m, 3H, 3×ArH), 6.64 (d, J=15.7 Hz, 1H, –CH=C*H*–). ^{13}C NMR (δ, ppm): 167.99 (CO), 141.20 (–*C*H=CH–), 132.24 (C), 131.73 (C), 130.74 (C), 130.32 (C), 129.95 (C), 129.04 (ArH), 128.58 (ArH), 127.87 (ArH), 127.77 (ArH), 127.17 (ArH), 126.39 (ArH), 125.62 (ArH), 123.78 (ArH), 122.87 (ArH), 122.04 (ArH). MS (*m/z*, %): 248 (M^+, 24), 203 (100). Anal. calcd for $C_{17}H_{12}O_2$, C 82.24, H 4.87; found, C 81.89, H 5.11.

1.1.20. 3-Phenanthren-1-yl-acrylic acid acyl azide (20b). Triethylamine (190 μL, 1.360 mmol) and a solution of ethyl chloroformate (62 μL, 0.679 mmol) in dry acetone (10 mL) were added to a suspension of acid **20a** (150 mg, 0.604 mmol) in dry acetone (10 mL) and the mixture was stirred for 45 min. A solution of sodium azide (74 mg, 1.133 mmol) in water (4 mL) was added dropwise and the mixture was stirred at 0°C for 30 min and then poured into ice/water. The resulting precipitate was filtered off to give acylazide **20b** (160 mg, 97% yield) as a yellow solid, which was used without purification. IR (ν, cm^{-1}, NaCl): 2138 (N_3), 1679 (CO). ^1H NMR (δ, ppm): 8.76–8.60 (m, 3H, 3×ArH), 8.04 (d, J=9.2 Hz, 1H, ArH), 7.90–7.57 (m, 6H, 6×ArH), 6.49 (d, J=15.6 Hz, 1H, –CH=C*H*–). ^{13}C NMR (δ, ppm): 171.93 (CO), 143.93 (–CH=*C*H–), 131.62 (C), 131.46 (C), 130.79 (C), 130.27 (C), 130.17 (C), 128.62 (ArH), 128.36 (ArH), 127.12 (ArH), 127.09 (ArH), 126.10 (ArH), 125.78 (ArH), 125.60 (ArH), 122.84 (ArH), 121.65 (ArH), 121.37 (ArH). MS (*m/z*, %): 273 (M^+, 20), 203 (100).

1.1.21. 2*H*-Naphtho[2,1-*f*]isoquinolin-1-one (22a). A solution of acylazide **20b** (155 mg, 0.567 mmol) in diphenyl ether (10 mL) was added slowly under argon to a solution of tributylamine (1.62 mL) in diphenyl ether (10 mL) and the mixture was heated under reflux for 1 h, allowed to cool and then diluted with hexane (20 mL). The resulting yellow precipitate was filtered off and washed with hexane (5 mL) to give isoquinolinone **22a** (108 mg, 78% yield) as a white solid. Mp 254–255°C (hexane). IR (ν, cm^{-1}, NaCl): 3014 (–NH), 1650 (CO). ^1H NMR (δ,ppm): 8.90–8.83 (m, 2H, 2×ArH), 8.53 (d, J=9.2 Hz, 1H, ArH), 8.36 (d, J=8.9 Hz, 1H, ArH), 8.06–7.99 (m, 2H, 2×ArH), 7.71–7.68 (m, 2H, 2×ArH), 7.46–7.41 (m, 2H, 2×ArH). ^{13}C NMR (δ, ppm): 162.35 (CO), 136.76 (C), 132.81 (C), 132.34 (C), 130.82 (ArH), 130.05 (C), 129.03 (ArH), 128.29 (ArH), 128.19 (ArH), 127.81 (ArH), 126.95 (C), 124.67 (ArH), 124.58 (C), 124.29 (ArH), 122.64 (ArH), 121.82 (ArH), 101.19 (ArH). MS (*m/z*, %): 245 (M^+, 100). Anal. calcd for $C_{17}H_{11}NO$, C 83.25, H 4.52, N 5.71; found, C 83.53, H 4.77.

1.1.22. 1-Chloronaphtho[2,1-*f*]isoquinoline (1b). A stirred solution of naphthoisoquinolinone **22a** (45 mg, 0.183 mmol) and $POCl_3$ (2 mL) was heated under reflux for 3 h, allowed to cool and poured into ice/water (10 mL). The mixture was neutralized with saturated potassium carbonate solution and the product was extracted with dichloromethane (3×10 mL). The combined organic extracts were washed with water, dried, filtered and concentrated in vacuo to give chloroisoquinoline **1b** (41 mg, 85% yield) as a yellow solid. Mp 165–167°C (MeOH, sublimation). IR (ν, cm^{-1}, NaCl): 1568 (–C=N–). ^1H NMR (δ, ppm): 8.83 (d, J=9.4 Hz, 1H, ArH), 8.75 (d, J=7.9 Hz, 1H, ArH), 8.53 (d, J=9.1 Hz, 1H, ArH), 8.47–8.38 (m, 3H, 3×ArH), 8.06–8.00 (m, 2H, 2×ArH), 7.77–7.72 (m, 2H, 2×ArH). ^{13}C NMR (δ, ppm): 151.66 (C-Cl), 142.55 (ArH), 136.69 (C), 132.93 (C), 130.71 (C), 129.69 (C), 128.61 (2×ArH), 127.72 (ArH), 127.28 (ArH), 126.32 (C), 125.15 (C), 123.92 (ArH), 123.52 (ArH), 123.35 (ArH), 120.64 (ArH), 116.43 (ArH). MS (*m/z*, %): 265 (M^++2, 35), 263 (M^+, 100). Anal. calcd for $C_{17}H_{10}ClN$, C 77.42, H 3.82, Cl 13.44, N 5.31; found, C 77.12, H 4.11, Cl 13.78, N 5.13.

1.1.23. Naphtho[2,1-*f*]isoquinoline (1a). A stirred suspension of 1-chloroisoquinoline **1b** (35 mg, 0.133 mmol) and zinc (113 mg, 1.725 mmol) in acetic acid (3 mL) was refluxed for 2 h under argon and then allowed to cool down. 10% Sodium hydroxide was added to neutralize the mixture and the product was extracted with chloroform (3×10 mL). The combined organic extracts were washed with water, dried, filtered and concentrated in vacuo to give naphthoisoquinoline **1a** (27 mg, 90% yield) as a yellow solid. Mp 224–226°C (methanol). IR (ν, cm^{-1}, NaCl): 2925 (ArH), 1728 (–C=N–). ^1H NMR (δ, ppm): 9.37 (bs, 1H, ArH), 8.85–8.78 (m, 3H, 3×ArH), 8.65 (d, J=9.0 Hz, 1H, ArH), 8.50 (d, J=5.5 Hz, 1H, ArH), 8.11–8.01 (m, 3H, 3×ArH), 7.80–7.67 (m, 2H, 2×ArH). ^{13}C NMR (δ, ppm): 152.09 (ArH), 144.59 (ArH), 134.53 (C), 133.04 (C), 130.62 (C), 130.13 (C), 128.75 (ArH), 128.16 (ArH), 127.39 (ArH), 127.14 (ArH), 126.53 (C), 125.56 (ArH), 123.45 (ArH), 122.77 (ArH), 120.76 (ArH). MS (*m/z*, %): 229 (M^+, 100). Anal. calcd for $C_{17}H_{11}N$, C 89.06, H 4.84, N 6.11; found, C 88.83, H 4.61, N 5.99.

1.1.24. 2-Iodo-4,5-dimethoxybenzoic acid methyl ester (18c). Trifluoromethanesulfonic acid (2.364 mL) was added over 5 min to a stirred solution of methyl benzoate **18b** (2.18 g, 11.131 mmol) and IPy_2BF_4 (4.97 g, 13.357 mmol) in dichloromethane (15 mL) and the stirring was continued for 30 min. The reaction mixture was then poured into saturated sodium thiosulfate (30 mL), the resulting suspension was extracted with dichloromethane (3×15 mL), the

combined organic extracts were washed with water (5 mL), dried, filtered and concentrated in vacuo. The solid residue was purified by column chromatogaphy (eluant: 3:2 dichloromethane/hexane) to give methyl iodobenzoate **18c** (2.653 g, 74% yield) as a white solid. Mp 105–107°C (methanol). IR (ν, cm^{-1}, NaCl): 1708 (CO). ^1H NMR (δ, ppm): 7.39 (s, 1H, ArH), 7.34 (s, 1H, ArH), 3.89 (s, 3H, $-OCH_3$), 3.88 (s, 3H, $-OCH_3$). ^{13}C NMR (δ, ppm): 165.05 (CO), 151.23 (ArOMe), 147.92 (ArOMe), 125.15 (C), 123.02 (ArH), 113.15 (ArH), 84.21 (C–I), 55.72 ($-OCH_3$), 55.44 ($-OCH_3$), 51.73 ($-CO_2CH_3$). MS (*m/z*, %): 322 (M^+, 100).

1.1.25. 4,5-Dimethoxy-2-styrylbenzoic acid methyl ester (16b). Compound **16b** was prepared in 68% yield from compound **18c** (1 g, 3.104 mmol) and styrene (0.392 mL, 3.415 mmol) following the same procedure as for compound **16a**. Mp 86–88°C (methanol). IR (ν, cm^{-1}, NaCl): 1708 (CO). ^1H NMR (δ, ppm): 8.07 (d, J=16.2 Hz, 1H, $-CH$=CH–), 7.54–7.51 (m, 2H, 2×ArH), 7.44 (s, 1H, ArH), 7.36–7.22 (m, 3H, 3×ArH), 7.10 (s, 1H, ArH), 6.89 (d, J=16.2 Hz, 1H, –CH=CH–), 3.94 (s, 3H, $-OCH_3$), 3.89 (s, 3H, $-OCH_3$), 3.87 (s, 3H, $-CO_2CH_3$). ^{13}C NMR (δ, ppm): 166.94 (CO), 151.76 (C), 147.63 (C), 137.27 (C), 133.69 (C), 129.69 (ArH), 128.39 (2×ArH), 127.41 (ArH), 127.38 (ArH), 126.45 (2×ArH), 120.14 (C), 112.75 (ArH), 108.67 (ArH), 55.71 ($-OCH_3$), 55.68 ($-OCH_3$), 51.69 ($-CO_2CH_3$). MS (*m/z*, %): 298 (M^+, 100). Anal. calcd for $C_{18}H_{18}O_4$, C 72.47, H 6.08; found, C 72.13, H 5.97.

1.1.26. 3,4-Dimethoxyphenanthrene-1-carboxylic acid methyl ester (17d). Irradiation of stilbene **16b** (320 mg, 0.993 mmol) under the same conditions as for the cyclization of **16a** afforded the corresponding phenanthrenecarboxylic acid **17d** in 80% yield. Mp 108–111°C (ethyl acetate). IR (ν, cm^{-1}, NaCl): 1712 (CO). ^1H NMR (δ, ppm): 9.66–9.62 (m, 1H, ArH), 8.65 (d, J=9.3 Hz, 1H, ArH), 7.92 (s, 1H, ArH), 7.88–7.84 (m, 1H, ArH), 7.69 (d, J=9.3 Hz, 1H, ArH), 7.65–7.60 (m, 2H, 2×ArH), 4.06 (s, 3H, $-OCH_3$), 4.02 (s, 3H, $-OCH_3$), 3.97 (s, 3H, $-CO_2CH_3$). ^{13}C NMR (δ, ppm): 168.10 (CO), 150.69 (C), 150.07 (C), 132.59 (C), 129.33 (C), 128.18 (ArH), 127.96 (ArH), 127.67 (C), 127.53 (ArH), 126.97 (ArH), 126.78 (ArH), 125.34 (C), 123.94 (C), 123.42 (ArH), 116.01 (ArH), 59.93 ($-OCH_3$), 56.54 ($-OCH_3$), 52.38 ($-CO_2CH_3$). MS (*m/z*, %): 296 (M^+, 100). Anal. calcd for $C_{18}H_{16}O_4$, C 72.96, H 5.44; found, C 73.24, H 5.29.

1.1.27. (3,4-Dimethoxyphenanthren-1-yl)methanol (17e). Reduction of phenanthrenecarboxylic acid ester **17d** (180 mg, 0.607 mmol) with lithium aluminiun hydride (115 mg, 3.037 mmol) under the same conditions as for **17a** provided the expected phenanthrenylmethanol **17e** as an oil in 95% yield. IR (ν, cm^{-1}, NaCl): 3392 (–OH). ^1H NMR (δ, ppm): 9.57 (d, J=8.5 Hz, 1H, ArH), 7.72–7.46 (m, 4H, 4×ArH), 7.39 (d, J=9.1 Hz, 1H, ArH), 7.14 (s, 1H, ArH), 4.87 (s, 2H, $-CH_2OH$), 3.78 (s, 3H, $-OCH_3$), 3.66 (s, 3H, $-OCH_3$). ^{13}C NMR (δ, ppm): 150.27 (C), 146.03 (C), 132.99 (C), 132.48 (C), 129.49 (C), 128.02 (ArH), 127.55 (ArH), 126.31 (2×ArH), 125.56 (ArH), 125.16 (C), 124.54 (C), 121.62 (ArH), 112.53 (ArH), 62.98 ($-CH_2-$), 59.46 ($-OCH_3$), 55.85 ($-OCH_3$). MS (*m/z*, %): 268 (M^+, 100). High resolution MS calcd for $C_{17}H_{16}O_3$, 268.1099; found, 268.1094.

1.1.28. 3,4-Dimethoxyphenanthrene-1-carbaldehyde (17f). Compound **17f** was prepared in 85% yield from phenanthrenylmethanol **17e** (186 mg, 0.559 mmol) and activated manganese dioxide (486 mg, 5.50 mmol) following the same procedure as for the oxidation of compound **17b**. Mp 85–87°C (ethyl acetate). IR (ν, cm^{-1}, NaCl): 1680 (CO). ^1H NMR (δ, ppm): 10.53 (s, 1H, –CHO), 9.60–9.56 (m, 1H, ArH), 8.80 (d, J=9.3 Hz, 1H, ArH), 7.84–7.81 (m, 1H, ArH), 7.75 (s, 1H, ArH), 7.69 (d, J=9.3 Hz, 1H, ArH), 7.65–7.56 (m, 2H, 2×ArH), 4.02 (s, 3H, $-OCH_3$), 3.98 (s, 3H, $-OCH_3$). ^{13}C NMR (δ, ppm): 191.05 (CO), 152.47 (C), 150.62 (C), 132.49 (C), 129.13 (C), 128.71 (ArH), 128.32 (C), 128.27 (ArH), 127.76 (ArH), 127.07 (ArH), 127.02 (ArH + C), 125.00 (C), 120.51 (ArH), 117.68 (ArH), 59.94 ($-OCH_3$), 56.34 ($-OCH_3$). MS (*m/z*, %): 266 (M^+, 100). Anal. calcd for $C_{17}H_{14}O_3$, C 76.68, H 5.30; found, C 76.39, H 5.53.

1.1.29. 3-(3,4-Dimethoxyphenanthren-1-yl)acrylic acid (20c). Compound **17f** (255 mg, 0.957 mmol) was reacted with malonic acid (460 mg, 4.404 mmol) following the same conditions as for compound **17c** to give compound **20c** in 93% yield. Mp 220–223°C (methanol). IR (ν, cm^{-1}, NaCl): 3436 (–COOH), 1693 (CO). ^1H NMR (δ, ppm): 9.62 (d, J=7.8 Hz, 1H, ArH), 8.58 (d, J=15.7 Hz, 1H, $-CH$=CH–), 7.99 (d, J=9.1 Hz, 1H, ArH), 7.87–7.83 (m, 1H, ArH), 7.68–7.60 (m, 3H, 3×ArH), 7.57 (s, 1H, ArH), 6.48 (d, J=15.7 Hz, 1H, –CH=CH–), 4.06 (s, 3H, $-OCH_3$), 3.96 (s, 3H, $-OCH_3$). ^{13}C NMR (δ, ppm): 168.93 (CO), 150.78 (C), 148.91 (C), 142.68 (ArH), 132.57 (C), 129.34 (C), 128.12 (ArH), 128.07 (C), 127.75 (ArH), 126.74 (2×ArH), 126.59 (ArH), 124.87 (C), 121.46 (ArH), 120.44 (ArH), 111.58 (ArH), 59.73 ($-OCH_3$), 56.27 ($-OCH_3$). MS (*m/z*, %): 308 (M^+, 100). Anal. calcd for $C_{19}H_{16}O_4$, C 74.01, H 5.23; found, C 73.76, H 5.47.

1.1.30. 3-(3,4-Dimethoxyphenanthren-1-yl)acrylic acid acyl azide (20d). Compound **20c** (150 mg, 0486 mmol) was transformed into acyl azide **20d** (145 mg, 90%), a yellow solid, following the procedure used to obtain **20b**. Mp 130–131°C (water). IR (ν, cm^{-1}, NaCl): 2251 (N_3), 1636 (CO). ^1H NMR (δ, ppm): 9.62 (d, J=7.8 Hz, 1H, ArH), 8.59 (d, J=15.5 Hz, 1H, $-CH$=CH–), 7.93 (d, J=9.2 Hz, 1H, ArH), 7.86–7.82 (m, 1H, ArH), 7.67–7.60 (m, 3H, 3×ArH), 7.49 (s, 1H, ArH), 6.43 (d, J=15.5 Hz, 1H, –CH=CH–), 4.03 (s, 3H, $-OCH_3$), 3.96 (s, 3H, $-OCH_3$). ^{13}C NMR (δ, ppm): 171.83 (CO), 150.97 (C), 150.06 (C), 143.85 (ArH), 132.66 (C), 129.51 (C), 128.32 (ArH), 128.00 (ArH), 127.16 (ArH+C), 127.02 (2×ArH), 125.20 (C), 121.23 (ArH), 120.77 (ArH), 111.71 (ArH), 59.96 ($-OCH_3$), 56.47 ($-OCH_3$). MS (*m/z*, %): 333 (M^+, 10), 305 (100).

1.1.31. 11,12-Dimethoxy-2*H*-naphtho[2,1-*f*]isoquinolin-1-one (22b). Compound **22b** was prepared in 84% yield from acyl azide **20d** (100 mg, 0.300 mmol) following the same procedure as for **22a**. Mp 263–265°C (methanol). IR (ν, cm^{-1}, NaCl): 3157 (–NH), 1645 (CO). ^1H NMR (δ, ppm): 11.37 (bs, 1H, –NH), 9.63–9.61 (m, 1H, ArH), 8.53 (d, J=9.3 Hz, 1H, ArH), 8.08–8.06 (m, 1H, ArH), 7.97 (d, J=9.3 Hz, 1H, ArH), 7.75–7.72 (m, 2H, 2×ArH), 7.41 (d, J=7.5 Hz, 1H, ArH), 7.34–7.33 (m, 1H, ArH), 3.95 (s, 3H, $-OCH_3$), 3.92 (s, 3H, $-OCH_3$). ^{13}C NMR (δ, ppm): 159.54

(CO), 151.11 (C), 149.56 (C), 134.59 (C), 133.15 (C), 129.49 (ArH), 128.45 (C), 128.34 (ArH), 127.69 (ArH), 127.59 (ArH), 127.25 (ArH), 127.04 (ArH), 126.93 (C), 124.76 (C), 122.15 (ArH), 119.58 (C), 100.02 (ArH), 61.53 (−OCH_3), 60.21 (−OCH_3). MS (*m/z*, %): 305 (M^+, 100). Anal. calcd for $C_{19}H_{15}NO_3$, C 74.74, H 4.95, N 4.59; found, C 75.01, H 5.14, N 4.32.

1.1.32. 1-Chloro-11,12-dimethoxynaphtho[2,1-*f*]isoquinoline (1d). Treatment of naphthoisoquinolinone **22b** (10 mg, 0.0327 mmol) with $POCl_3$ (2 mL) under the same conditions as for preparation of **1b** gave chloronaphthoisoquinoline **1d** (10 mg, 95% yield) as a yellow solid. Mp 177–179°C (methanol). IR (ν, cm^{-1}, NaCl): 1552 (−C═N−). ^1H NMR (δ, ppm): 9.75–9.72 (m, 1H, ArH), 8.59–8.45 (m, 3H, 3×ArH), 8.03–7.98 (m, 2H, 2×ArH), 7.75–7.72 (m, 2H, 2×ArH), 4.19 (s, 3H, −OCH_3), 4.03 (s, 3H, −OCH_3). ^{13}C NMR (δ, ppm): 151.94 (C), 147.54 (C), 146.75 (C), 142.14 (ArH), 135.30 (C), 133.78 (C), 129.14 (C), 128.44 (2×ArH), 128.22 (ArH), 127.69 (ArH), 127.54 (C), 127.26 (ArH), 125.69 (C), 121.68 (C), 120.81 (ArH), 116.14 (ArH), 61.78 (−OCH_3), 60.18 (−OCH_3). MS (*m/z*, %): 323 (M^+, 100). Anal. calcd for $C_{19}H_{14}ClNO_2$, C 70.48, H 4.36, Cl 10.95, N 4.33; found, C 72.81, H 4.09, Cl 11.17, N 4.28.

1.1.33. 11,12-Dimethoxynaphtho[2,1-*f*]isoquinoline (1c). Following the same procedure as for reduction of **1b**, reaction of chloronaphthoquinone **1d** (9 mg, 0.028 mmol) with zinc (24 mg, 0.361 mmol) provided naphthoisoquinoline **1c** (7.6 mg, 94%) as a yellow solid. Mp 152–154°C (methanol). IR (ν, cm^{-1}, NaCl): 2927 (ArH), 1446 (−C═N−). ^1H NMR (δ, ppm): 9.77 (d, J=8.3 Hz, 1H, ArH), 9.69 (bs, 1H, ArH), 8.77 (bs, 1H, ArH), 8.63 (d, J=9.0 Hz, 1H, ArH), 8.46–8.45 (m, 1H, ArH), 8.01–7.98 (m, 2H, 2×ArH), 7.74–7.68 (m, 2H, 2×ArH), 4.25 (s, 3H, −OCH_3), 4.04 (s, 3H, −OCH_3). ^{13}C NMR (δ, ppm): 149.19 (C), 147.02 (C), 146.87 (ArH), 144.04 (ArH), 133.89 (C), 132.12 (C), 129.85 (C), 128.57 (ArH), 128.17 (ArH), 127.91 (ArH), 127.52 (C), 127.29 (ArH), 127.03 (ArH), 125.78 (C), 120.61 (ArH), 116.17 (ArH), 61.80 (−OCH_3), 60.31 (−OCH_3). MS (*m/z*, %): 289 (M^+, 2), 58 (100). Anal. calcd for $C_{19}H_{15}NO_2$, C 78.87, H 5.23, N 4.84; found, C 78.53, H 5.41, N 4.96.

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References

1. A preliminary communication concerning the work described here has recently been published. See: Pampín, C.; Estévez, J. C.; Castedo, L.; Estévez, R. J. *Tetrahedron Lett.* **2001**, *42*, 2307.
2. (a) Harvey, R. G. *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenesis*; Cambridge University: Cambridge, 1991. (b) Harvey, R. G. In *The Handbook of Environmental Chemistry. Part I: PAHs and Related Compounds*; Hutzinger, O., Neilson, A., Eds.; Springer: Heidelberg, 1997; Vol. 3, pp 1–54 Chapter 1.
3. Wu Harvey, R. G. *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenesis*; Wiley-VCH: New York, 1997.
4. (a) Denisenko, M. F.; Pao, A.; Tang, M.; Pfeifer, G. P. *Science* **1996**, *274*, 430. (b) Pfeifer, G. P.; Denissenko, M. F. *Environ. Mol. Carcin.* **1998**, *31*, 197. (c) Denissenko, M. F.; Cheng, J. X.; Tang, M.; Pfeifer, G. P. *Proc. Natl Acad. Sci. USA* **1997**, *94*, 3893. (d) Cheng, J. X.; Zheng, Y.; West, M.; Tang, M. *Cancer Res.* **1998**, *58*, 2170.
5. Cheng, C. C. Structural Aspects of Antineoplastic Agents—A New Approach. *Progress in Medicinal Chemistry*; Ellis, G. P., West, G. B., Eds.; Elsevier (Biomedical Division): Amsterdam, 1988; Vol. 25, pp 35–83.
6. Cheng, C. C.; Engle, R. R.; Hudson, J. R.; Ing, R. B.; Wood, H. B.; Yan, S. J.; Zee-Cheng, R. K. Y. *J. Pharm. Sci.* **1977**, *66*, 1781.
7. (a) Zee-Cheng, K. Y.; Cheng, C. C. *J. Heterocycl. Chem.* **1973**, *10*, 867. (b) Zee-Cheng, K. Y.; Cheng, C. C. *J. Med. Chem.* **1975**, *18*, 66. (c) Stermitz, F. R.; Gillespie, L. G.; Amoros, L. G.; Romero, R.; Stermitz, T. A.; Larson, K. A.; Earl, S.; Ogg, J. E. *J. Med. Chem.* **1975**, *18*, 708. (d) Huang, A.-X.; Li, Z.-H. *Acta Chim. Sin.* **1980**, *38*, 535. (e) Fang, S.-D.; Wang, L.-K.; Hetch, S. M. *J. Org. Chem.* **1993**, *58*, 5025. (f) Taira, Z.; Matsumoto, M.; Ishida, S.; Icikawa, T.; Sakiya, Y. *Chem. Pharm. Bull.* **1994**, *42*, 1556.
8. (a) Whaley, W. M.; Meadow, M. *J. Org. Chem.* **1954**, *19*, 661. (b) Galiazzo, G.; Bortolus, P.; Masetti, F. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1712. (c) Masetti, F.; Bartocci, G.; Mazzucato, U. *Gazz. Chim. Ital.* **1982**, *112*, 255. (d) Tanga, M. J.; Almquist, R. G.; Smith, T. H. *J. Heterocycl. Chem.* **1985**, *22*, 1597.
9. Chen, H.-Y.; Preston, M. R. *Environ. Sci. Technol.* **1998**, *32*, 577.
10. Sthephan, E.; Aubouet, R.; Pourcelot, G.; Gresson, P. *Tetrahedron: Asymmetry* **1994**, *5*, 41.
11. (a) Ziegler, C. B.; Heck, R. F. *J. Org. Chem.* **1978**, *46*, 4416. (b) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.
12. (a) Floyd, A. J.; Dyke, S. F.; Ward, S. E. *Chem. Rev.* **1976**, *76*, 509. (b) Mallory, F. B.; Mallory, C. W. *Org. React.* **1984**, *30*, 1. (c) Liu, L.; Yang, B.; Katz, T. J.; Poindexter, M. K. *J. Org. Chem.* **1991**, *56*, 3769.
13. (a) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74. (b) Nagubandi, S.; Fodor, G. *Heterocycles* **1981**, *15*, 165.
14. Tsuda, Y.; Isobe, K.; Taba, J. *Heterocycles* **1976**, *5*, 157.
15. Nabugandi, S.; Fodor, G. *Tetrahedron* **1980**, *36*, 1279.
16. Nabugandi, S.; Fodor, G. *Heterocycles* **1981**, *15*, 165.
17. Banwell, M. G.; Bisset, 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**, *24*, 2551.
18. Crystal structure determination of **13**. A suitable crystal of compound **13** (prism, colourless, dimensions 0.45×0.30×0.20 mm^3) was used for the structure determination. X-Ray data were collected using a Bruker SMART CCD area detector single-crystal diffractometer with graphite monochromatized Mo Kα radiation (λ=0.71073 Å) by the phi−omega scan method at 298(2) K. A total of 1271 frames of intensity data were collected for each compound. The first 50 frames were recollected at the end of data collection to monitor for decay. The crystal used for the diffraction study showed slight decomposition during data collection (0.1%). The integration process yield a total of 10600 reflections, of

which 36756 [R(int)=0.0200] were independent. Absorption corrections were applied using the SADABS (a) program (maximum and minimum transmission coefficients, 0.9542 and 0.9009). The structure was solved using the Bruker SHELXTL-PC (b) software by direct methods and refined by full-matrix least-squares methods on F^2. Hydrogen atoms were located on residual density maps and refined in the riding mode. For **13** convergence was reached at a final $R1$=0.0370 [for $I>2\sigma(I)$], $wR2$=0.01066 [for all data], 337 parameters, with allowance for the thermal anisotropy for all non-hydrogen atoms. The weighting scheme employed was $w=[\sigma^2(F_o^2)+(0.0812P)^2+(0.4066P)]$ and $P=(|F_o|^2+2|F_c|^2)/3$ and the goodness-of-fit on F^2 was 1.031 for all observed reflections. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC- 196493. 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). Crystallographic data for **13**: $C_{19}H_{16}NO_4F_3S$, M=411.39. Monoclinic, space group $P2(1)/c$ with a=10.2567(6) Å, b=6.6768(4) Å, c=26.2812(16) Å, α=90°, β=93.3560(1)°, γ=90°, V=1797.75(19) Å^3, D_c (Z=4)=1.524 g cm^{-3}. F(000)=848. Absorption coefficient=0.0097(11) cm^{-1}(a) Sheldrick, G. M. *SADABS: Program for absorption corrections using Bruker CCD data*; University of Göttingen: Germany, 1996. (b) Sheldrick, G.M. *SHELXTL-PC: Program for Crystal Structure Solution*; University of Göttingen: Göttingen, Germany, 1997.

19. Sotomayor, N.; Domínguez, E.; Lete, E. *Tetrahedron* **1995**, *51*, 12721.
20. Preparation of an *o*-styrylbenzoic acid by Heck coupling of iodobenzene to *o*-vinylbenzoic acid has recently been carried out by Kim, B. M.; Park, J. K. *Bull. Kor. Chem. Soc.* **1999**, *20*, 744. As far as we know, other *o*-styrylbenzoic acids have not been obtained by similar procedures: see Refs. 23,24.
21. Karmakar, A. C.; Kar, G. K.; Ray, J. K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1997.
22. (a) Rubin, M. B.; Welner, S. *J. Org. Chem.* **1980**, *45*, 1847. (b) Koszyk, F. J.; Lenz, G. R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1273.
23. Ezquerra, J.; Pechegal, C.; Lamas, C.; Barluenga, J.; Pérez, M.; García-Martín, M. A.; González, J. M. *J. Org. Chem.* **1996**, *61*, 5804.
24. For previous syntheses of *o*-styrylbenzoic acids, see Ref. 1. See also: (a) Noda, M. *Chem. Pharm. Bull.* **1998**, *46*, 1157. (b) Zehnter, R.; Gerlach, H. *Tetrahedron: Asymmetry* **1995**, *6*, 2779. (c) Yoshikawa, M.; Harada, E.; Yagi, N.; Okuno, Y.; Muraoka, O.; Aoyama, H.; Murakami, N. *Chem. Pharm. Bull.* **1994**, *42*, 721. (d) Mal, D.; Majumdar, G.; Pal, R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1115. (e) Bowden, K.; Ghadir, K. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1333. (f) Lazer, E. S.; Wong, H. C.; Wegner, C. D.; Graham, A. G.; Farina, P. R. *J. Med. Chem.* **1990**, *33*, 1892. (g) Eicher, T.; Tiefensee, K.; Pick, R. *Synthesis* **1988**, 525. (h) Bellinger, G. C. A.; Campbell, W. E.; Giles, R. G. F.; Tobias, J. D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2819. (i) Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372.
25. (a) Citterio, A.; Pesce, L.; Sebastiano, R.; Santi, R. *Synthesis* **1990**, 142. (b) Caluwe, P.; Pepper, T. *J. Org. Chem.* **1988**, *53*, 1786. (c) Rubin, M. B.; Welner, S. *J. Org. Chem.* **1980**, *45*, 1847.
26. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon: New York, 1988.