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Total synthesis of two natural phenanthrenes: confusarin and a regioisomer

Sylvie Radix[a,b,*] and Roland Barret[a,b,*]

[a]*Université de Lyon, Lyon F-69003, France*
[b]*Université Claude Bernard Lyon 1, ISPB and INSERM U863, IFR62, 8 avenue Rockefeller, Lyon Cedex 08 F-69373, France*

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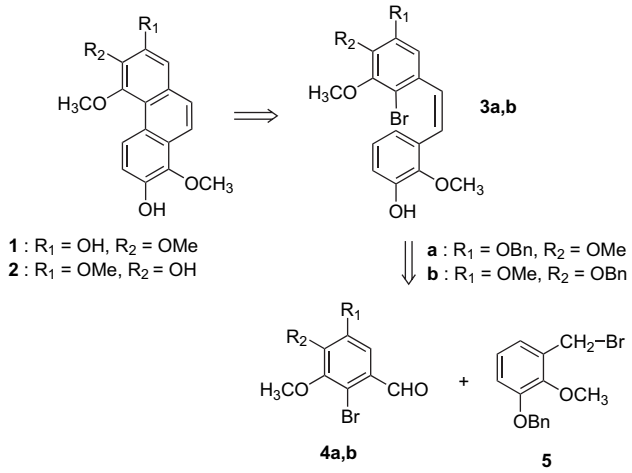
Abstract—The title compounds were synthesized by radical cyclization of the corresponding stilbenes intermediates. The latter ones arose from a Wittig reaction in a stereoselective manner (*Z* isomer is either the only one or the major one). Confusarin (**1**) was prepared in 13 steps from gallic acid. Its regioisomer (**2**) was obtained in five steps from syringaldehyde.

1. Introduction

Confusarin (**1**) and 2,4,8-trimethoxyphenanthrene-3,7-diol (**2**) have been isolated from a series of Indian orchids, *Eria Confusa*,[1a] *Bulbophyllum gymnopus*,[1b] *Catasetum barbatum Lindl.*,[1c] *Bulbophyllum reptans*,[1d] *Cymbidium pendulum*[1e] and *Thunia alba*.[1f] Very recently, compound (**1**) has been extracted for the first time from the fresh rhizomes of *Tamus communis*.[1g,h] Moreover, phenanthrene (**2**) has also been identified from *Dendrobium densiflorum* used in traditional Chinese folk medicine,[2] and from *Eulophia nuda Lindl.*, a terrestrial orchid found in the Central and Southeast Asian regions.[3] The structures of these phenanthrenes have been unequivocally established from both homonuclear {^{1}H; ^{1}H} and heteronuclear {^{1}H; ^{13}C} 2D NMR correlation studies.[4] Confusarin (**1**) has been evaluated for its cytotoxicity in the human leukaemia K562 cells (IC_{50}=46.5 μg mL^{-1}).[5] Moreover, it has been found that **1** had notable antitumour activity on the mouse HePA and ESC.[6] On the other hand, phenanthrene (**2**) induced a concentration-dependant inhibition of the spontaneous contractions of the rat ileum with potencies comparable or higher to that of papaverine.[7] Moreover, these compounds have shown stronger antioxidative activity than BHA.[8] Finally, both of them have been evaluated for their anti-inflammatory activity.[1h]

Among the considerable number of synthetic routes now available to prepare phenanthrene derivatives,[9–13] we decided to use the efficient radical cyclization methodology developed by Harrowven et al.,[14] to synthesize the target molecules as shown in the following retrosynthetic scheme (Scheme 1).



Scheme 1. Retrosynthetic scheme of **1** and **2**.

2. Results and discussion

The synthesis started with the preparation of the benzyl bromide (**5**), which was used during the Wittig process as a precursor of the phosphonium derivative for the synthesis of both stilbenes (**3a**) and (**3b**). Compound **5** was prepared in four steps from commercially available 2,3-dihydroxybenzaldehyde with an overall 65% yield via selective methylation of the more acidic C2-hydroxy group of the starting material,[15] O-benzylation, $NaBH_4$ reduction of the aldehyde and bromination of the resulting benzylic alcohol (**7**) (Scheme 2).

Keywords: Total synthesis; Wittig reaction; Radical cyclization; Stilbenes; Aromatics; Phenanthrenes; 2,4,8-Trimethoxyphenanthrene-3,7-diol; Confusarin.
* Corresponding authors. Tel.: +33 4 78777542; fax: +33 4 78777549 (R.B.); tel.: +33 4 78777253; fax: +33 4 78777549 (S.R.); e-mail addresses: sylvie.radix@univ-lyon1.fr; barret@rockefeller.univ-lyon1.fr

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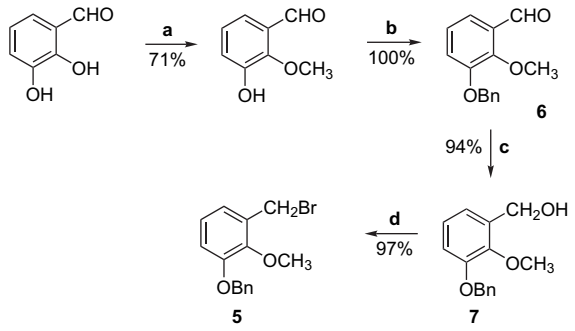
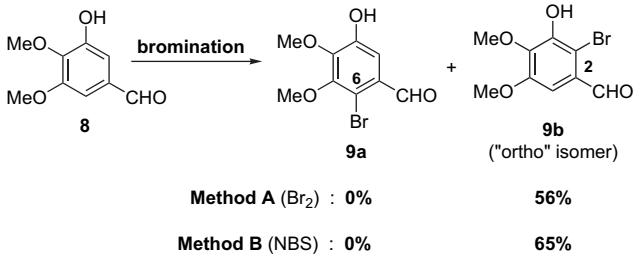


Scheme 2. Reagents and conditions: (a) K_2CO_3, CH_3I, DMF; (b) BnBr, K_2CO_3, DMF; (c) $NaBH_4$, *i*-PrOH; (d) PBr_3, CH_2Cl_2.

The next step was the synthesis of **4a** involving the regioselective aromatic bromination of the hydroxy benzaldehyde (**8**) as shown in Scheme 3.



Scheme 3. Bromination of **8**.

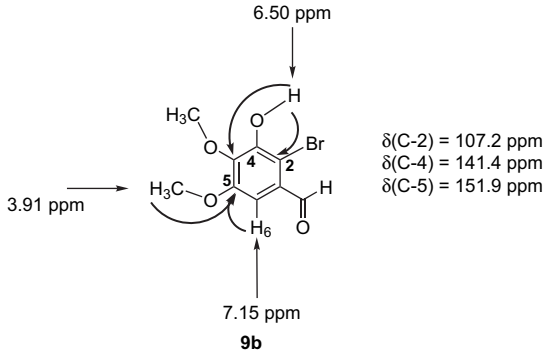
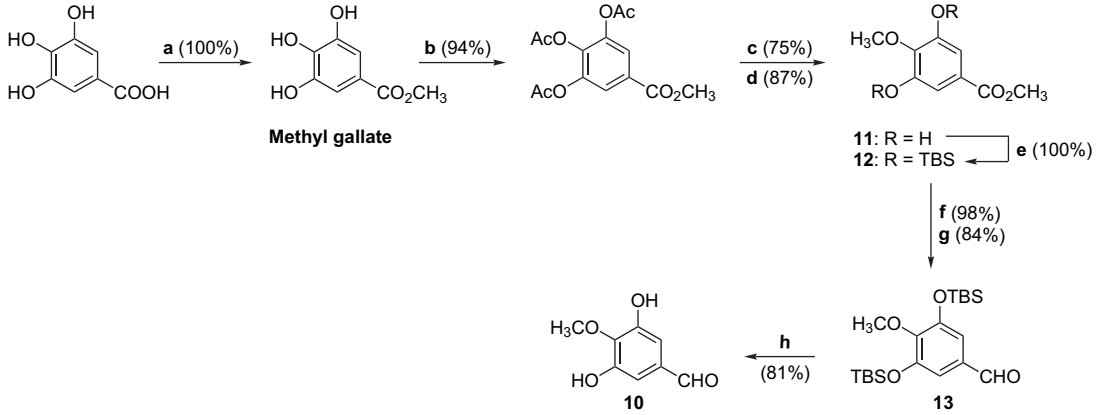


Figure 1. Establishment of the structure of **9b** by HMBC NMR sequence.

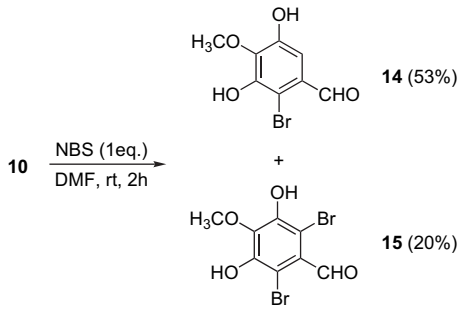
As described by Ellis and Lenger,[16] **8** was prepared in a two-step sequence from bromo vanillin[17] with an overall 52% yield. The crucial bromination at C-6 position was then attempted. But, whatever the brominating conditions we used to obtain the *para*-bromophenol (**9a**)[18] (either Br_2/CH_2Cl_2 (method A), or NBS/DMF (method B)), the reaction produced only '*ortho*' isomer (**9b**) with a moderate yield (Scheme 3). The structure of **9b** was determined by NMR analysis including {^{1}H; ^{13}C} HMBC correlation, as shown in Figure 1. Long-distance coupling constants ^3J were measured between the hydroxy proton (6.50 ppm), C-2 (107.2 ppm) and C-4 (141.4 ppm) on one hand, and H-6 (7.15 ppm) and C-5 (151.9 ppm) on the other hand.

At this point, we decided to develop an alternative route to **4a** using 3,5-dihydroxybenzaldehyde (**10**) as an important intermediate. This compound was prepared according to an efficient procedure based on the selective methylation of the 4-hydroxy group of methyl gallate.[19] This four-step sequence was reproduced from commercially available gallic acid and led to methyl 4-methoxy gallate (**11**) with an overall 61% yield. The final stages of this synthesis entailed silylation of both hydroxy groups followed by the reduction of the resulting ester (**12**) with lithium aluminium hydride in anhydrous ether.[20] In this last step, it should be noted that it was necessary to add silica gel during the hydrolysis of the metal alkoxide to avoid extensive cleavage of *tert*-butyldimethylsilyl (TBS) ethers. Oxidizing the resulting alcohol with pyridinium dichromate (PDC) in dichloromethane led to the corresponding aldehyde (**13**),[20,21] whose silicon protecting groups were removed under acidic conditions providing **10** with a satisfactory overall 41% yield from gallic acid (Scheme 4).

With compound (**10**) in hand, the synthesis of **4a** posed special challenges including monobromination of **10** and regioselective O-alkylation (O-benzylation or O-methylation) of the resulting 3,5-dihydroxybenzaldehyde (**14**). Unfortunately, despite the use of a single equivalent of *N*-bromosuccinimide (NBS) and a meticulous monitoring of the reaction by TLC, the bromination of **10** always led to a mixture of the monobromo derivative (**14**) and of the dibromo product (**15**) in a disappointing 7:3 ratio (Scheme 5). However, **14** and **15** were easily separated by column chromatography on silica gel. The regioselectivity of O-alkylation was then studied.



Scheme 4. Reagents and conditions: (a) AcCl, CH_3OH; (b) Ac_2O, NEt_3; (c) K_2CO_3, CH_3I, DMF; (d) K_2CO_3, CH_3OH, H_2O; (e) TBSCl, imidazole, DMF; (f) $LiAlH_4$, Et_2O then SiO_2; (g) PDC, CH_2Cl_2; (h) HCl 32%, THF.



Scheme 5. Bromination of **10**.

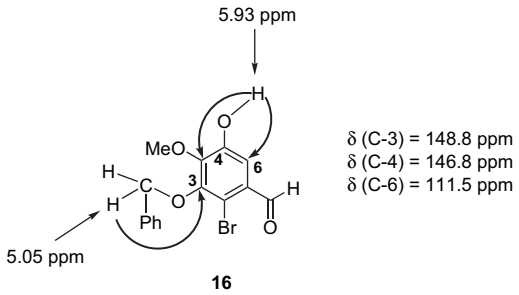
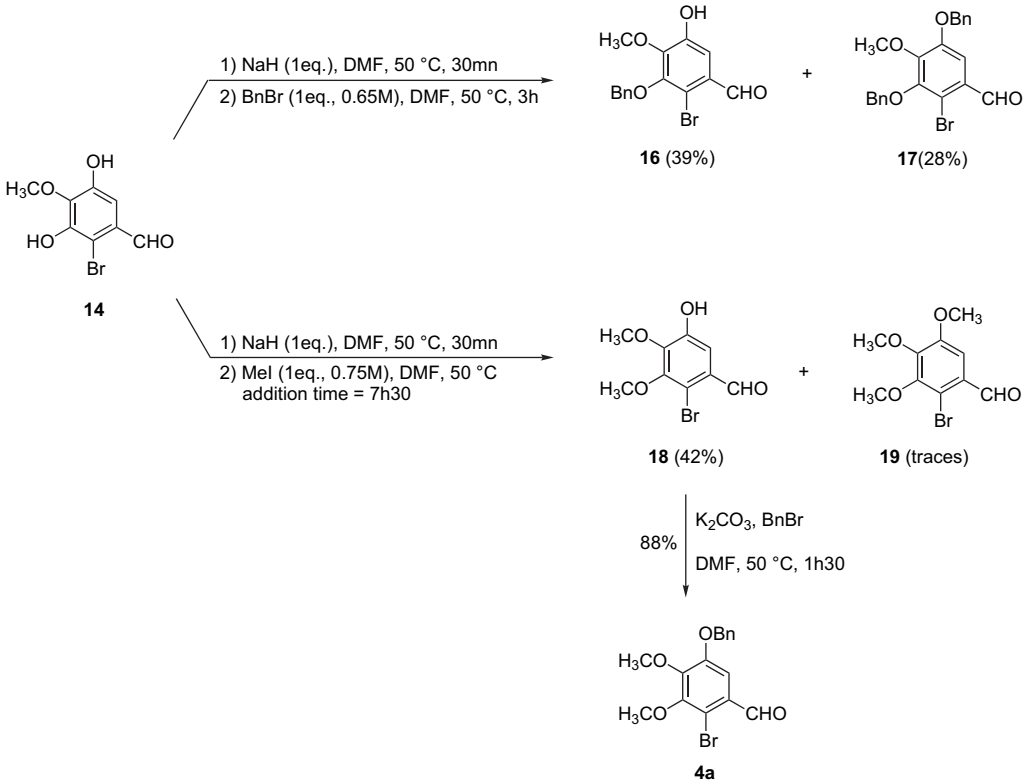


Figure 2. Establishment of the structure of **16** by HMBC NMR sequence.

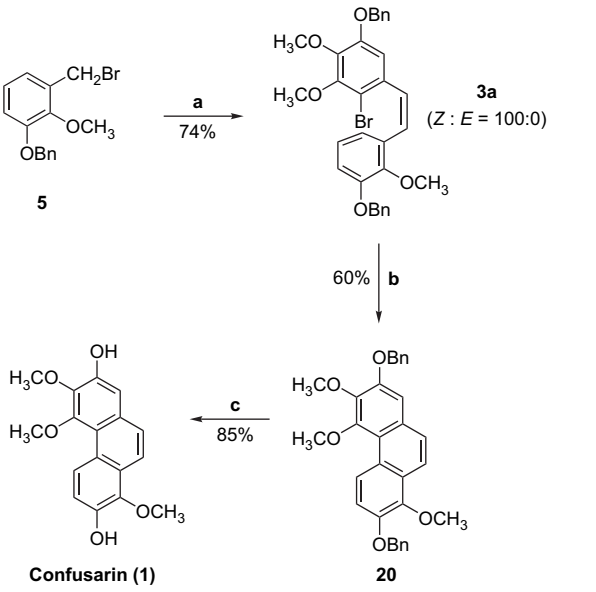
An O-benzylation reaction was then performed on **14** and led to a mixture of the 3-benzyloxy derivative (**16**) (39%) and dibenzyloxy product (**17**) (28%) (Scheme 6).

As mentioned in Figure 2, the HMBC NMR correlation allowed to assign all ^{1}H and ^{13}C chemical shifts of the regioisomer (**16**) and unambiguously established that O-alkylation took place at the C-3 hydroxy group. Since a methoxy group was necessary at C-3 position, **14** was then converted to derivative (**18**) by the action of (i) NaH (1 equiv) and (ii) MeI (1 equiv) (Scheme 8). Using a diluted solution of **14** in DMF (0.15 M) and adding iodomethane very slowly with a syringe pump for at least 7 h improved the yield in **18** (42%), whereas only traces of trimethoxy product (**19**) were obtained. Furthermore, the starting material (**14**), which did not react during O-methylation, was able to be recycled after purification by column chromatography. Finally, the last hydroxy group remaining on benzaldehyde (**18**) was benzylated to give **4a** (Scheme 6).

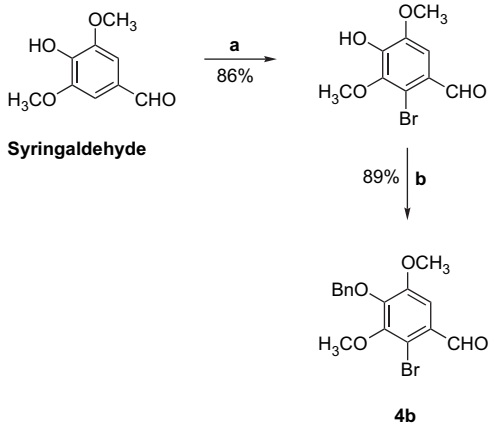
The completion of the confusarin synthesis is summarized in Scheme 7. First, immediately after its preparation, the benzyl bromide (**5**) was directly treated with triphenylphosphine without any further purification. The resulting phosphonium bromide was then allowed to react with benzaldehyde (**4a**) to provide stilbene (**3a**). The Wittig reaction[22] was totally stereoselective and gave a single stereoisomer. Harrowven et al. have demonstrated that *Z*-selectivities of Wittig reaction was notably enhanced by electron donating substituents in both the aldehyde and ylide components.[23] Literature has also shown that using lithium methoxide as a base in DMF mainly led to the desired (*Z*)-alkene.[24,25] Nevertheless, NMR analysis did not allow us to ensure the double bond configuration of **3a**. Thus, in order to confirm its (*Z*)-stereochemistry, we chose to subject **3a** to free-radical cyclization conditions to generate the phenanthrene ring system. The radical reaction was performed by slow dropwise addition of a degassed-toluene solution of tributyltin hydride and azobisisobutyronitrile (AIBN)



Scheme 6. O-alkylation of **14**.



Scheme 7. Reagents and conditions: (a) PPh_3, DMF, then **4a**, CH_3OLi, DMF; (b) AIBN, Bu_3SnH, toluene; (c) H_2 (20 bar), Pd/C, AcOEt.

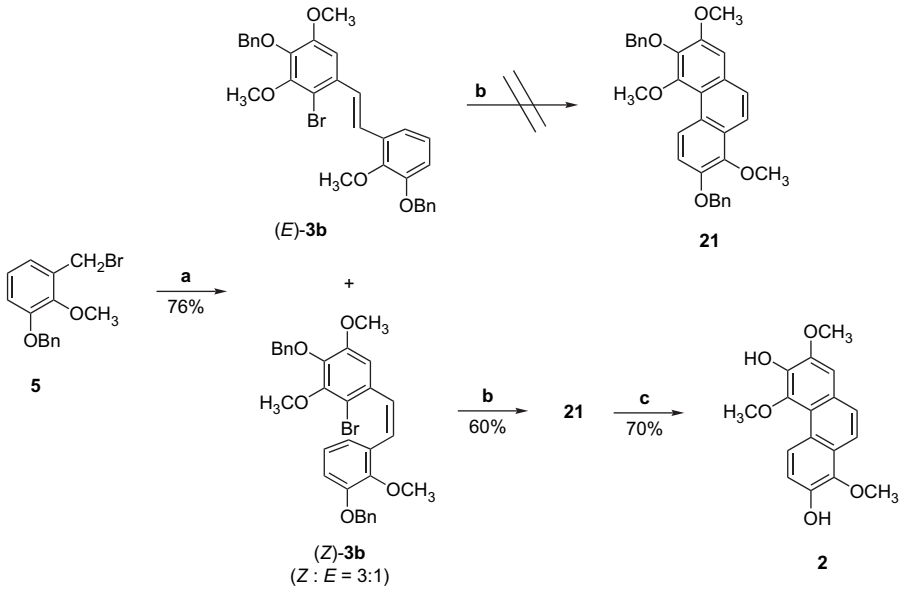


Scheme 8. Reagents and conditions: (a) Br_2, CH_2Cl_2; (b) K_2CO_3, BnBr, DMF.

to a degassed-toluene solution of stilbene. As anticipated, the desired phenanthrene (**20**) was obtained with 60% yield after a 6 h 30 min reflux. Interestingly, the free-radical cyclization was able to be carried out using a rather concentrated mixture (0.08 M). Finally, confusarin (**1**) was obtained by double phenolic hydroxy deprotection of **20**. Unexpectedly, this double hydrogenolysis needed a high H_2 pressure (20 bar). The improved conditions provided 85% yield of a white solid whose ^1H NMR and mass spectral characteristics were identical to those published for the natural product (**1**).[1a] In addition, the ^{13}C NMR spectral data were also consistent within a 2% margin of error, leading us to conclude that synthetic **1** was identical to natural confusarin.

Then, this efficient strategy was used to synthesize phenanthrene (**2**). The synthesis of bromo benzaldehyde (**4b**) has proved easier than preparation of its regioisomer (**4a**). Bromination of syringaldehyde[26] was followed by O-benzylation to provide **4b** with an overall 77% yield (Scheme 8). Benzyl bromide (**5**) and bromo benzaldehyde (**4b**) were eventually engaged into the Wittig procedure to give stilbene (**3b**) as a mixture of stereoisomers (3:1). The individual products were isolated but assessing ^1H NMR data did not allow the assignment of double bond configurations.

Each product was then subjected to free-radical cyclization conditions (AIBN, Bu_3SnH and toluene). It was correctly anticipated that the major isomer was the *Z* isomer and gave the desired dibenzyloxy phenanthrene (**21**) when the minor one (*E* isomer) did not react in these conditions (Scheme 9). Finally, the double benzyl deprotection of **21** using improved hydrogenolysis conditions led to a white solid with a 70% yield. Its ^1H NMR, mass and UV spectral characteristics were identical to those published for the natural product (**2**).[1e] In addition, the ^{13}C NMR spectral data were also in agreement within a 2% margin of error, leading us to conclude that synthetic **2** was identical to the natural 2,4,8-trimethoxyphenanthrene-3,7-diol.



Scheme 9. Reagents and conditions: (a) PPh_3, DMF, then **4b**, CH_3OLi, DMF; (b) AIBN, Bu_3SnH, toluene; (c) H_2 (20 bar), Pd/C, AcOEt.

3. Conclusion

A strategy for the total synthesis of two natural polymethoxylated phenanthrenes is described. This strategy was designed to use stilbenic intermediates, which were able to be entailed in free-radical cyclization to provide the phenanthrene skeleton. Confusarin (**1**) was obtained from gallic acid and benzyl bromide (**5**) with an overall 3% yield from gallic acid. Its regioisomer (**2**) was more rapidly synthesized, with an overall 24% yield from syringaldehyde and **5**. Finally, due to the interesting and various biological activities shown by **1** and **2**, we decided to prepare other phenanthrene analogues for a future structure–biological activity study.

4. Experimental

4.1. General procedures

All air- and moisture-sensitive reactions were carried out under a nitrogen atmosphere. For Wittig reaction, toluene was degassed by nitrogen flush before use. All melting points were measured on a Barnstead Electrothermal 9200 apparatus and were uncorrected. Ultraviolet spectra (UV) were recorded on a Shimadzu UV mini 1240 spectrometer. Infrared spectra (IR) were recorded using NaCl film or KBr pellets on a Perkin–Elmer FT-IR SPECTRUM ONE spectrometer. ^{1}H spectra were recorded with Bruker AC200, Bruker ALS300 and Bruker DRX300 Fourier transform spectrometers, using an internal deuterium lock, operating at 200 and 300 MHz, respectively. ^{13}C NMR spectra were recorded with Bruker AC200 and Bruker DRX300 Fourier transform spectrometers, using an internal deuterium lock, operating at 50 and 75 MHz, respectively. Chemical shifts are reported in part per million (ppm) relative to residual protons of deuterated solvents (δ=7.26 ppm for ^{1}H NMR and δ=77.16 ppm for ^{13}C NMR for $CDCl_3$). Carbon multiplicity was determined by DEPT experiments. Low- and high-resolution mass spectroscopy was recorded with a ThermoQuest FINNIGAN MAT 95 XL apparatus operating at 70 eV. Elemental analyses were performed by the Service Central d'Analyses du CNRS, Solaize, France. Product purification by flash column chromatography was performed using Merck Kieselgel 60 Å (40–63 μm). Analytical thin layer chromatography (TLC) was carried out using Merck commercial aluminium sheets coated (0.2 mm layer thickness) with Kieselgel 60 F_{254}, with visualization by ultraviolet. All commercially available chemicals were used as received. 3-Hydroxy-2-methoxybenzaldehyde,[15] bromo vanillin,[17] 2-bromosyringaldehyde,[25] compounds **8**,[16] methyl triacetoxygallate and **11**,[19] **12**[20] and **13**[20,21] were prepared according to the literature procedures.

4.2. 3-Benzyloxy-2-methoxybenzaldehyde (6)

Benzyl bromide (1 mL, 8.4 mmol) was added to a mixture of 3-hydroxy-2-methoxybenzaldehyde (1.02 g, 6.7 mmol) and potassium carbonate (1.39 g, 10.1 mmol) in DMF (50 mL). The mixture was heated at 50 °C for 1.5 h. After cooling, it was portioned between toluene and water. The aqueous phase was extracted with toluene. The combined organic layers were washed with water, dried over Na_2SO_4, filtered and evaporated. The crude residue was chromatographed on silica gel (petroleum ether (PE)/AcOEt: 92:8) to give the compound (**6**) (1.66 g, 100%) as a white solid. Mp 71–73 °C; IR (KBr) ν_{max} (cm^{-1}) 3066, 2981, 2937, 2747, 1683, 1583, 1482, 1455; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.04 (s, 3H, OMe), 5.17 (s, 2H, CH_2), 7.11 (t, 1H, *J* 8.1 Hz, H-5), 7.21 (dd, 1H, *J* 1.8, 8.1 Hz, H-4), 7.36–7.48 (m, 6H, H-6, H-arom), 10.46 (s, 1H, CHO).

4.3. [3-(Benzyloxy)-2-methoxyphenyl]methanol (7)

Benzaldehyde (**6**) (3.85 g, 16 mmol) was refluxed in *i*-PrOH (50 mL) in the presence of $NaBH_4$ (0.31 g, 8 mmol) for 1.5 h. The reaction was monitored by TLC until completion. The solution was cooled to room temperature and quenched with aqueous HCl (10%). The solution was extracted with AcOEt. The combined organic phases were washed with aqueous $NaHCO_3$ (2%) and water, dried (Na_2SO_4), filtered and evaporated. The crude residue was chromatographed on silica gel (PE/AcOEt: 80:20) to give the benzyl alcohol (**7**) (3.69 g, 94%) as a white solid. Mp 58–60 °C; IR (KBr) ν_{max} (cm^{-1}) 3450, 3060, 2930, 2860, 2820, 1580, 1560, 1475, 1450; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.44 (br s, 1H, OH), 3.95 (s, 3H, OMe), 4.72 (s, 2H, CH_2Ph), 5.14 (s, 2H, CH_2OH), 6.92–7.08 (m, 3H, H-4, H-5, H-6), 7.34–7.50 (m, 5H, H-arom); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 61.0 (CH_3), 61.6 (CH_2), 70.9 (CH_2), 114.2 (CH), 121.2 (CH), 124.1 (CH), 127.4 (2×CH-arom), 128.0 (CH-arom), 128.6 (2×CH-arom), 134.8 (C), 137.0 (C), 147.6 (C), 151.6 (C).

4.4. 1-(Benzyloxy)-3-(bromomethyl)-2-methoxybenzene (5)

Phosphorous tribromide (300 μL, 3.16 mmol) was added dropwise to a stirred solution of the benzyl alcohol (**7**) (1.54 g, 6.3 mmol) in CH_2Cl_2 (30 mL) and cooled at 0 °C. After 40 min of vigorous stirring the reaction mixture was slowly quenched with ice water. The dichloromethane layer was separated and the aqueous layer was further extracted with dichloromethane. The combined extracts were washed twice with water. The organic solution was dried over Na_2SO_4 and evaporated to give 1.87 g (yield 97%) of the benzyl bromide (**5**) as colourless oil.

4.5. General procedures for the bromination of (8)

4.5.1. Method A. To a solution of the hydroxy benzaldehyde (**8**) (0.183 g, 1 mmol) in CH_2Cl_2 (2 mL) was added dropwise a solution of Br_2 (55 μL, 1 mmol) in CH_2Cl_2 (0.8 mL) at 0 °C and under nitrogen. After 3 h of stirring at 0 °C, the reaction mixture was quenched with brine and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with brine and water, dried ($MgSO_4$) and evaporated. The crude residue was chromatographed on silica gel (PE/AcOEt: 75:25) to give the compound (**9b**) (0.146 g, 56%) as a pale yellow solid.

4.5.2. Method B. To a solution of the hydroxy benzaldehyde (**8**) (1.62 g, 8.9 mmol) in DMF (40 mL) was added dropwise a solution of NBS (1.74 g, 9.8 mmol) in DMF (40 mL) at 0 °C and under nitrogen. After 2.5 h of stirring at 0 °C, the reaction mixture was quenched with water and the aqueous phase was extracted with toluene. The combined organic

extracts were washed with water, dried (Na_2SO_4) and evaporated. The crude residue was chromatographed on silica gel (PE/AcOEt: 90:10) to give the compound (**9b**) (1.51 g, 65%) as a pale yellow solid.

4.5.3. 2-Bromo-3-hydroxy-4,5-dimethoxybenzaldehyde (9b). Mp 138–141 °C; IR (KBr) ν_{max} (cm^{-1}) 3379, 3104, 3068, 2954, 2944, 2770, 1675, 1579, 1575, 1489; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.91 (s, 3H, C_5-OCH_3), 4.01 (s, 3H, C_4-OCH_3), 6.50 (s, 1H, OH), 7.15 (s, 1H, H-6), 10.28 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 56.6 (C_5-O*C*H_3), 61.7 (C_4-O*C*H_3), 104.9 (CH, C-6), 107.2 (C, C-2), 129.0 (C, C-1), 141.4 (C, C-4), 147.4 (C, C-3), 151.9 (C, C-5), 191.5 (CH, CHO).

4.6. 3,5-Dihydroxy-4-methoxybenzaldehyde (10)

Aqueous HCl (32%, 13 mL, 114 mmol) was added to a solution of bis-silylanoxy benzaldehyde (**13**) (11.05 g, 28 mmol) in THF (80 mL). After 16 h of stirring at room temperature, brine was added and aqueous phase was extracted with AcOEt. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and evaporated. The crude residue was recrystallised from PE/Et_2O to give the dihydroxybenzaldehyde (**10**) (3.83 g, 81%) as a violet solid. Mp 147–148 °C; IR (KBr) ν_{max} (cm^{-1}) 3376, 3065, 2954, 2854, 1684, 1592, 1524, 1465; ^1H NMR ($CDCl_3$+1 drop of DMSO-d_6, 300 MHz) δ 3.87 (s, 3H, OMe), 6.88 (s, 2H, H-1, H-2), 8.26 (s, 2H, 2×OH), 9.65 (s, 1H, CHO).

4.7. General procedure for the bromination of 10

To a solution of benzaldehyde (**10**) (1.70 g, 10 mmol) in DMF (50 mL) was added dropwise a solution of NBS (2.7 g, 15 mmol) in DMF (30 mL) at room temperature and under nitrogen. After 2 h of stirring, the mixture was quenched with water and the aqueous phase was extracted with AcOEt. The combined organic extracts were washed with water, dried (Na_2SO_4) and evaporated. The crude residue was chromatographed on silica gel (PE/AcOEt: 70:30) to give the product (**14**) (1.31 g, 53%) as a pale brown solid and the dibromo derivative (**15**) (0.649 g, 20%) as a white solid.

4.7.1. 2-Bromo-3,5-dihydroxy-4-methoxybenzaldedyde (14). Mp 161–164 °C (decomp.); IR (KBr) ν_{max} (cm^{-1}) 3433, 3275, 3004, 2956, 1682, 1582, 1498, 1461, 1438; ^1H NMR ($CDCl_3$+1 drop of DMSO-d_6, 200 MHz) δ 3.96 (s, 3H, OMe), 7.11 (s, 1H, H-6), 8.52 (s, 1H, OH), 9.32 (s, 1H, OH), 10.23 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$+1 drop of DMSO-d_6, 50 MHz) δ 60.9 (CH_3), 105.6 (C), 108.9 (CH), 129.0 (C), 141.6 (C), 148.3 (C), 150.0 (C), 191.7 (CHO).

4.7.2. 2,6-Dibromo-3,5-dihydroxy-4-methoxybenzaldedyde (15). Mp 149–151 °C; IR (KBr) ν_{max} (cm^{-1}) 3439, 3272, 2944, 2904, 1682, 1560, 1481, 1437; ^1H NMR ($CDCl_3$+1 drop of DMSO-d_6, 200 MHz) δ 3.75 (s, 3H, OMe), 8.72 (br s, 2H, 2×OH), 10.03 (s, 1H, CHO).

4.8. General procedure for the O-benzylation of 14

NaH (50% dispersion in mineral oil, 0.058 g, 1 mmol) was added to a solution of benzaldehyde (**20**) (0.243 g, 14 mmol) in DMF (0.2 M, 5 mL) at room temperature under nitrogen. The reaction mixture was heated to 50 °C for 30 min and the colour of the solution changed to black. Then a solution of benzyl bromide (120 μL, 1 mmol) in DMF (0.65 M, 2 mL) was added at 50 °C with a syringe pump for 1 h 30 min. The solution was cooled to room temperature and acidified with aqueous HCl (10%) to pH 1. Water was added and the aqueous phase was extracted with AcOEt. The combined organic extracts were washed with brine to pH 4–5, dried (Na_2SO_4), filtered and evaporated. The crude residue was chromatographed on silica gel (PE/AcOEt: 90:10) to give the 3-benzyloxy compound (**16**) (0.131 g, 39%) as a pale brown solid and the 3,5-dibenzyloxy product (**17**) (0.120 g, 28%) as a white solid.

4.8.1. 3-Benzyloxy-2-bromo-5-hydroxy-4-methoxybenzaldehyde (16). Mp 138–141 °C; IR (KBr) ν_{max} (cm^{-1}) 3306, 3066, 3028, 2946, 2868, 1672, 1596, 1476, 1422, 1399, 1340, 1255, 1163, 1078; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.05 (s, 3H, OMe), 5.05 (s, 2H, CH_2), 5.93 (s, 1H, OH), 7.40–7.46 (m, 4H, H-6, H-arom *meta*, H-arom *para*), 7.53–7.58 (m, 2H, H-arom *ortho*), 10.30 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 61.5 (CH_3), 75.9 (CH_2), 111.5 (CH, C-6), 114.8 (C, C-2), 128.7 (4*CH, CH-arom *ortho*, *meta*), 128.7 (CH, CH-arom *para*), 130.0 (C, C-1), 136.4 (C, C-arom *ipso*), 146.8 (C, C-4), 148.8 (C, C-3), 149.6 (C, C-5), 191.4 (CH, CHO).

4.8.2. 3,5-Dibenzyloxy-2-bromo-4-methoxybenzaldehyde (17). Mp 74–76 °C; IR (KBr) ν_{max} (cm^{-1}) 3064, 3033, 2940, 2866, 1683, 1574, 1561, 1480, 1453, 1432, 1418, 1383, 1329, 1284, 1183, 1098; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.01 (s, 3H, OMe), 5.11 (s, 2H, CH_2Ph), 5.18 (s, 2H, CH_2Ph), 7.36–7.46 (m, 9H, H-6, H-arom), 7.50–7.61 (m, 2H, H-arom), 10.32 (s, 1H, CHO).

4.9. 2-Bromo-5-hydroxy-3,4-dimethoxybenzaldehyde (18)

NaH (50%, dispersion in mineral oil, 0.55 g, 11.5 mmol) was added to a solution of benzaldehyde (**14**) (2.83 g, 11.4 mmol) in DMF (0.1 M, 100 mL) at room temperature under nitrogen. The reaction mixture was heated to 50 °C for 30 min and the colour of the solution changed to black. Then a solution of methyl iodide (710 μL, 11.4 mmol) in DMF (0.76 M, 15 mL) was added at 50 °C with a syringe pump for 7 h 30 min. The solution was cooled to room temperature and acidified with aqueous HCl (10%) to pH 1. Water was added and the aqueous phase was extracted with AcOEt. The combined organic extracts were washed with brine to pH 4–5, dried (Na_2SO_4), filtered and evaporated. The crude residue was chromatographed on silica gel (PE/AcOEt: 90:10) to give the compound (**18**) (1.24 g, 42%) as a yellow oil. ^1H NMR (200 MHz) δ 3.88 (s, 3H, OMe), 4.03 (s, 3H, OMe), 6.53 (s, 1H, OH), 7.33 (s, 1H, H-6), 10.23 (s, 1H, CHO).

4.10. 5-Benzyloxy-2-bromo-3,4-dimethoxybenzaldehyde (4a)

Benzyl bromide (680 μL, 5.7 mmol) was added to a mixture of **18** (1.23 g, 4.7 mmol) and potassium carbonate (0.98 g, 7.1 mmol) in DMF (40 mL). The mixture was heated at 50 °C for 1.5 h. After cooling, it was portioned between

AcOEt and water. The aqueous phase was extracted with AcOEt. The combined organic layers were washed with brine and water, dried over $MgSO_4$, filtered and evaporated. The crude residue was chromatographed on silica gel (PE/AcOEt: 90:10) to give benzaldehyde (**4a**) (1.46 g, 88%) as a colourless oil. IR (NaCl) ν_{max} (cm^{-1}) 3066, 3033, 2939, 2868, 1683, 1575, 1497, 1478, 1454, 1426, 1403, 1378, 1329, 1284, 1242, 1214, 1184, 1164, 1098, 1044, 1005, 931, 911, 851, 815, 733, 698, 677, 605; ^{1}H NMR (300 MHz) δ 3.92 (s, 3H, OMe), 3.99 (s, 3H, OMe), 5.15 (s, 2H, CH_2), 7.32–7.48 (m, 6H, H-6, H-arom), 10.28 (s, 1H, CHO).

4.11. 1-Benzyloxy-4-bromo-5-[(*Z*)-2-(3-benzyloxy-2-methoxyphenyl)-vinyl]-2,3-dimethoxy-benzene (3a)

Under nitrogen atmosphere, benzyl bromide (**5**) (1.20 g, 3.45 mmol) was treated with triphenylphosphine (1.03 g, 3.92 mmol) in DMF (15 mL) at 110 °C for 1 h. After complete formation of the phosphonium salt, the solution was cooled to 90 °C and a solution of benzaldehyde (**4a**) (1.46 g, 4.1 mmol) in DMF (8 mL) was added, followed by dropwise addition of a solution of methyl lithium (1.6 M in Et_2O, 2.5 mL, 4.0 mmol) in methanol (7 mL). The colour of the solution changed to yellow. Heating and stirring were continued for 16 h. The cooled reaction mixture was poured into water and extracted with AcOEt. The combined organic extracts were washed with water, dried (Na_2SO_4), filtered and evaporated. The crude residue was chromatographed on silica gel (PE/AcOEt: 92:8) to give stilbene (**3a**) (1.44 g, 74%) as a white solid. Mp 88–89 °C. Found C, 66.11%; H, 5.41%. $C_{31}H_{29}BrO_5$ requires C, 66.31%; H, 5.21%; IR (KBr) ν_{max} (cm^{-1}) 3066, 3032, 2937, 2830, 1573, 1556, 1499, 1475, 1465, 1427, 1387, 1332, 1290, 1161, 1097, 1050, 1010, 858, 796, 749, 700; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.85 (s, 3H, OMe), 3.90 (s, 3H, OMe), 3.93 (s, 3H, OMe), 4.66 (s, 2H, CH_2), 5.14 (s, 2H, CH_2), 6.62–6.86 (m, 6H, H-6, H-vinyl, H-arom), 7.12–7.49 (m, 10H, H-arom); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 60.8 (CH_3), 61.1 (CH_3), 61.3 (CH_3), 70.9 (CH_2), 70.9 (CH_2), 111.0 (C), 111.6 (CH), 113.7 (CH), 122.7 (CH), 123.5 (CH), 126.4 (CH), 127.1 (2×CH), 127.3 (2×CH), 127.9 (CH), 128.0 (CH), 128.5 (2×CH), 128.6 (2×CH), 129.9 (CH), 131.2 (C), 132.8 (C), 136.7 (C), 137.1 (C), 142.9 (C), 147.9 (C), 151.0 (C), 151.3 (C), 152.0 (C); MS (EI) *m/z* 562 (M^+ [^{81}Br]), 560 (M^+ [^{79}Br]), 390, 299, 91; HRMS (EI) found (M^+) 560.1197, $C_{31}H_{29}{}^{79}BrO_5$ requires 560.1198.

4.12. 2,7-Dibenzyloxy-3,4,8-trimethoxy-phenanthrene (20)

Under nitrogen atmosphere, to a solution of stilbene (**3a**) (0.887 g, 1.6 mmol) in degassed toluene (20 mL) was added dropwise a solution of AIBN (0.134 g, 0.82 mmol) and Bu_3SnH (550 μL, 2 mmol) in degassed toluene (20 mL) at room temperature. After refluxing for 6.5 h, the cooled reaction mixture was poured into water. The aqueous phase was extracted with chloroform. The combined organic extracts were washed with a saturated aqueous solution of KF and water, dried (Na_2SO_4), filtered and evaporated. The crude residue was recrystallised from PE/AcOEt/Et_2O to give dibenzyloxy phenanthrene (**20**) (0.461 g, 60%) as a pale yellow solid. Mp 143–145 °C. Found C, 77.23%; H, 5.96%. $C_{31}H_{28}O_5$ requires C, 77.48%; H, 5.87%; IR (KBr) ν_{max} (cm^{-1}) 3058, 3029, 2931, 2870, 1605, 1564, 1473, 1462, 1433, 1393, 1375, 1352, 1281, 1228, 1152, 1112, 1070, 1054, 1008, 852, 786, 755, 722, 697; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.03 (s, 3H, OMe), 4.06 (s, 6H, 2×OMe), 5.29 (s, 2H, CH_2), 5.32 (s, 2H, CH_2), 7.17 (s, 1H, H-1), 7.35–7.61 (m, 12H, H-6, H-10, H-arom), 8.08 (d, 1H, *J* 9.5 Hz, H-9), 9.24 (d, 1H, *J* 9.5 Hz, H-5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 60.4 (CH_3), 61.4 (2×CH_3), 70.8 (CH_2), 71.5 (CH_2), 107.2 (CH, C-1), 115.5 (CH, C-6), 119.2 (C, C-4a), 120.3 (CH, C-9), 123.2 (CH, C-5), 125.4 (C, C-4b), 127.1 (CH, C-10), 127.4 (2×CH-arom), 127.42 (2×CH-arom), 127.7 (C, C-8a), 127.9 (CH-arom *para*), 128.0 (CH-arom *para*), 128.6 (2×CH-arom), 128.7 (2×CH-arom), 129.2 (C, C-10a), 136.9 (C, C-arom *ipso*), 137.5 (C, C-arom *ipso*), 143.3 (C, C-3), 144.1 (C, C-8), 148.0 (C, C-2), 151.2 (C, C-7), 152.2 (C, C-4); MS (EI) *m/z* 983 ($2M^+$+Na), 503 ($2M^+$+Na), 481 (MH^+), 449, 412, 390, 299, 271, 256.

4.13. Confusarin (1)

Dibenzyloxy phenanthrene (**20**) (0.521 g, 1.08 mmol) and Pd/C (45 wt %) were mixed in AcOEt (30 mL). The required pressure of hydrogen (20 bar) was then introduced. The reaction mixture was stirred at room temperature for 24 h. The excess pressure was vented and the reaction mixture was filtered on Celite® and evaporated. The crude residue was chromatographed on silica gel (PE/AcOEt: 80:20) to give confusarin (**1**) (0.275 g, 85%) as a white solid. Mp 185–187 °C (lit.[1a] 185 °C). Found C, 67.69%; H, 5.71%. $C_{17}H_{16}O_5$ requires C, 67.99%; H, 5.37%; IR (KBr) ν_{max} (cm^{-1}) 3286, 3005, 2983, 2932, 2832, 1623, 1605, 1575, 1542, 1486, 1450, 1174, 1159, 1099, 827, 815, 797, 782, 756, 715; ^{1}H NMR ($CDCl_3$+1 drop of DMSO-d_6, 200 MHz) δ 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.40 (br s, 2H, 2×OH), 7.06 (s, 1H, H-1), 7.18 (d, 1H, *J* 9.3 Hz, H-6), 7.44 (d, 1H, *J* 9.1 Hz, H-9), 7.81 (d, 1H, *J* 9.1 Hz, H-10), 9.04 (d, 1H, *J* 9.3 Hz, H-5); ^{13}C NMR ($CDCl_3$+1 drop of DMSO-d_6, 50 MHz) δ 59.8 (OCH_3), 61.2 (OCH_3), 61.5 (OCH_3), 108.6 (CH, C-1), 117.0 (CH, C-6), 118.7 (C, C-4a), 119.5 (CH, C-9), 123.5 (CH, C-5), 124.5 (C, C-4b), 126.7 (C, C-8a), 127.00 (CH, C-10), 129.2 (C, C-10a), 141.3 (C, C-3), 141.5 (C, C-8), 145.9 (C, C-7), 148.3 (C, C-2), 151.1 (C, C-4); MS (EI) *m/z* 300 (M^+), 285, 253, 242, 227, 199, 167.

4.14. 4-(Benzyloxy)-2-bromo-3,5-dimethoxybenzaldehyde (4b)

Benzyl bromide (1.85 mL, 15.5 mmol) was added to a mixture of 2-bromosyringaldehyde (3.36 g, 13 mmol) and potassium carbonate (2.67 g, 19 mmol) in DMF (55 mL). The mixture was heated at 50 °C for 1.5 h. After cooling, it was portioned between toluene and water. The aqueous phase was extracted with toluene. The combined organic layers were washed with water, dried over Na_2SO_4, filtered and evaporated. The crude residue was chromatographed on silica gel (PE/AcOEt: 95:5) to give benzaldehyde (**4b**) (4.05 g, 89%) as a white solid. Mp 58 °C; IR (KBr) ν_{max} (cm^{-1}) 3060, 3020, 2940, 2840, 1680, 1560, 1450, 1187, 1160, 1040, 980, 960, 920, 740; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.90 (s, 3H, OMe), 3.92 (s, 3H, OMe), 5.17

(s, 2H, CH_2), 7.32–7.51 (m, 6H, H-6, H-arom), 10.31 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 56.3 (CH_3), 61.3 (CH_3), 75.6 (CH_2), 107.6 (CH), 115.6 (C), 128.3 (CH), 128.4 (2×CH), 128.5 (2×CH), 129.1 (C), 136.8 (C), 147.7 (C), 151.3 (C), 153.4 (C), 191.1 (CHO); MS (EI) *m/z* 352 (M^+, [^{81}Br]), 350 (M^+, [^{79}Br]), 324, 322, 271, 91.

4.15. General procedure for the synthesis of (*Z*)-3b and (*E*)-3b

Under nitrogen atmosphere, benzyl bromide (**5**) (1.108 g, 3.51 mmol) was treated with triphenylphosphine (0.926 g, 3.53 mmol) in DMF (12 mL) at 110 °C for 1 h. After complete formation of the phosphonium salt, the solution was cooled to 90 °C and a solution of benzaldehyde (**4b**) (1.234 g, 3.51 mmol) in DMF (6 mL) was added, followed by dropwise addition of a solution of methyl lithium (1.6 M dans Et_2O, 2.2 mL, 3.52 mmol) in methanol (5 mL). The colour of the solution changed to yellow. Heating and stirring were continued for 15 h. The cooled reaction mixture was poured into water and extracted with AcOEt. The combined organic extracts were washed with water, dried (Na_2SO_4), filtered and evaporated. The crude residue was chromatographed on silica gel (PE/AcOEt: 96:4) to give stilbene (*Z*)-**3b** (1.146 g, 58%) as a white solid and stilbene (*E*)-**3b** (0.354 g, 18%) as a yellow oil.

4.15.1. 2-Benzyloxy-4-bromo-5-[(*Z*)-2-(3-benzyloxy-2-methoxyphenyl)-vinyl]-1,3-dimethoxy-benzene (*Z*)-3b. Mp 107–109 °C; IR (KBr) ν_{max} (cm^{-1}) 3061, 3027, 2934, 1573, 1475, 1463, 1429, 1167, 1102, 1050, 785, 744, 710; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.38 (s, 3H, OMe), 3.91 (s, 3H, OMe), 3.92 (s, 3H, OMe), 5.03 (s, 2H, CH_2), 5.13 (s, 2H, CH_2), 6.51 (s, 1H, H-6), 6.62–6.88 (m, 5H, H-vinyl, H-arom), 7.32–7.50 (m, 10H, H-arom); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 55.7 (CH_3), 60.8 (CH_3), 61.1 (CH_3), 70.8 (CH_2), 75.4 (CH_2), 109.8 (CH), 110.4 (C), 113.8 (CH), 122.7 (CH), 123.4 (CH), 126.5 (CH), 127.3 (2×CH), 127.98 (CH), 128.04 (CH), 128.3 (4×CH), 128.6 (2×CH), 130.15 (CH), 131.22 (C), 133.1 (C), 137.1 (C), 137.4 (C), 141.2 (C), 147.9 (C), 151.2 (C), 151.8 (C), 152.3 (C); MS (EI) *m/z* 562 (MH^+), 561 (M^+), 481, 451, 391, 361, 329, 301, 271, 255, 240, 207, 165, 137, 91, 85, 71, 67.

4.15.2. 2-Benzyloxy-4-bromo-5-[(*E*)-2-(3-benzyloxy-2-methoxyphenyl)vinyl]-1,3-dimethoxy-benzene (*E*)-3b. ^1H NMR (200 MHz) δ 3.93 (s, 9H, 3×OMe), 5.08 (s, 2H, CH_2), 5.17 (s, 2H, CH_2), 6.66–7.10 (m, 4H), 7.26–7.58 (m, 12H).

4.16. 3,7-Dibenzyloxy-2,4,8-trimethoxy-phenanthrene (21)

Under nitrogen atmosphere, to a solution of stilbene (*Z*)-**3b** (0.906 g, 1.6 mmol) in degassed toluene (12 mL) was added dropwise a solution of AIBN (0.134 g, 0.8 mmol) and Bu_3SnH (560 μL, 2.08 mmol) in degassed toluene (8 mL) at room temperature. After refluxing for 5 h, the cooled reaction mixture was poured into water. The aqueous phase was extracted with chloroform. The combined organic extracts were washed with a saturated aqueous solution of KF and water, dried (Na_2SO_4), filtered and evaporated. The crude residue was chromatographed on silica gel (PE/AcOEt: 96:4) to give dibenzyloxy phenanthrene (**21**) (0.547 g, 60%) as a white solid. Mp 116–118 °C. Found C, 77.24%; H, 5.80%. $C_{31}H_{28}O_5$ requires C, 77.48%; H, 5.87%; UV ($CHCl_3$; $c=5.6\times10^{-5}$ mol l^{-1}) 311 (log ε 4.10), 348 (3.38), 365 (3.41); IR (KBr) ν_{max} (cm^{-1}) 3095, 3060, 2960, 2940, 2840, 1620, 1565, 1500, 1480, 1455, 1195, 1160, 1120, 1070, 1015, 760, 730, 700; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.00 (s, 3H, OMe), 4.05 (s, 3H, OMe), 4.08 (s, 3H, OMe), 5.20 (s, 2H, CH_2), 5.34 (s, 2H, CH_2), 7.12 (s, 1H, H-1), 7.32–7.47 (m, 7H, H-arom), 7.54–7.67 (m, 5H, H-arom), 8.12 (d, 1H, *J* 9.3 Hz, H-9), 9.28 (d, 1H, *J* 9.3 Hz, H-5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 55.9 (CH_3), 60.4 (CH_3), 61.4 (CH_3), 71.5 (CH_2), 75.7 (CH_2), 105.5 (CH, C-1), 115.6 (CH, C-6), 119.00 (C, C-4a), 120.3 (CH, C-9), 123.2 (CH, C-5), 125.44 (C, C-4b), 127.1 (CH, C-10), 127.4 (2×CH-arom), 127.6 (C, C-8a), 127.96 (2×CH-arom), 127.99 (CH-arom), 128.4 (CH-arom), 128.42 (2×CH-arom), 128.6 (2×CH-arom), 129.5 (C, C-10a), 137.5 (C, C-arom *ipso*), 137.9 (C, C-arom *ipso*), 141.9 (C, C-3), 144.2 (C, C-8), 148.0 (C, C-4), 152.4 (C, C-7), 152.44 (C, C-2); MS (EI) *m/z* 503 (M^++Na), 481 (MH^+), 449, 412, 390, 359, 299.

4.17. 2,4,8-Trimethoxyphenanthrene-3,7-diol (2)

Dibenzyloxy phenanthrene (**21**) (0.422 g, 0.88 mmol) and Pd/C (45 wt %) were mixed in AcOEt (30 mL). The required pressure of hydrogen (20 bar) was then introduced. The reaction mixture was stirred at room temperature for 24 h. The excess pressure was vented and the reaction mixture was filtered on Celite® and evaporated. The crude residue was chromatographed on silica gel (PE/AcOEt: 80:20) to give phenanthrene (**2**) (0.228 g) as a yellow oil, which was triturated in petroleum ether to obtain a white solid (0.179 g, 70%). Mp 149–150 °C (lit.[1e] 152 °C). Found C, 67.66%; H, 5.54%. $C_{17}H_{16}O_5$ requires C, 67.99%; H, 5.37%; IR (KBr) ν_{max} (cm^{-1}) 3490, 3440, 3020, 2975, 2940, 1615, 1580, 1510, 1480, 1440, 1195, 1170, 1100, 1050, 805, 710; UV (EtOH; $c=9\times10^{-5}$ mol l^{-1}) 311 (log ε 3.95), 345 (3.39), 363 (3.45); ^1H NMR ($CDCl_3$, 200 MHz) δ 3.96 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 5.91 (br s, 1H, OH), 6.08 (br s, 1H, OH), 7.10 (s, 1H, H-1), 7.33 (d, 1H, *J* 9.3 Hz, H-6), 7.64 (d, 1H, *J* 9.0 Hz, H-9), 7.84 (d, 1H, *J* 9.0 Hz, H-10), 9.18 (d, 1H, *J* 9.3 Hz, H-5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 56.2 (OCH_3), 59.9 (OCH_3), 61.9 (OCH_3), 105.0 (CH, C-1), 116.1 (CH, C-6), 118.0 (CH, C-9), 119.2 (C, C-4a), 124.0 (CH, C-5), 124.3 (C, C-4b), 125.8 (C, C-8a), 126.6 (C, C-10a), 127.5 (CH, C-10), 139.4 (C, C-3), 140.8 (C, C-8), 144.1 (C, C-4), 145.6 (C, C-7), 146.9 (C, C-2); MS (EI) *m/z* 623 ($2M^+$+Na), 470, 416, 402, 345, 323 (M^++Na), 301 (MH^+), 269.

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