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Sequential Bicyclization of Biphenyl Acetamides Promoted by $(COCl)_2/SnCl_4$. Total Synthesis of 4,5-Dioxoaporphines

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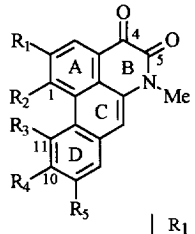
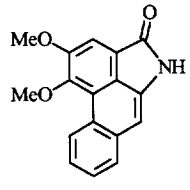
Abstract: The reaction of biphenyl acetamides with excess of oxalyl chloride/stannyl chloride offers a one pot, high-yield entry to 4,5-dioxoaporphine alkaloids. This strategy has been applied to the synthesis of 4,5-dioxodehydrocorydine starting from 1-iodo-2,3-dimethoxybenzene. The cytotoxicity of tetraoxygenated 4,5-dioxoaporphines has been evaluated. © 1997 Elsevier Science Ltd.

4,5-Dioxoaporphines (**1**) are a class of isoquinoline alkaloids,[1] structurally and chemically related to aristolactams (e.g. cepharanone-B, **2**) and aristolochic acids (e.g. aristolochic acid I, **3**), which have been postulated as their biogenetic precursors.[2] These naturally occurring nitrogenous substances are commonly found among the *Aristolochiaceae*; extracts of many of them have been used in folk medicine.[3] The aristolochic acids display a wide range of biological activities, including mutagenicity and carcinogenesis,[4] and are used currently as inhibitors of the phospholipase A(2).[5] The aristolactams can be regarded as the decarbonylation products of 4,5-dioxoaporphines. Chemically this implies a benzylic acid type of rearrangement followed by oxidative decarboxylation.[6] They are also of interest because they have been involved in the carcinogenesis induced by aristolochic acids.[7]



1

	R_1	R_2	R_3	R_4	R_5
1a	H	OMe	H	H	H
1b	OMe	OMe	H	H	H
1c	H	OBn	H	H	H
1d	OMe	OH	OMe	OMe	H
1e	OMe	OMe	H	OMe	OMe



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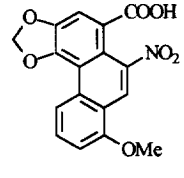
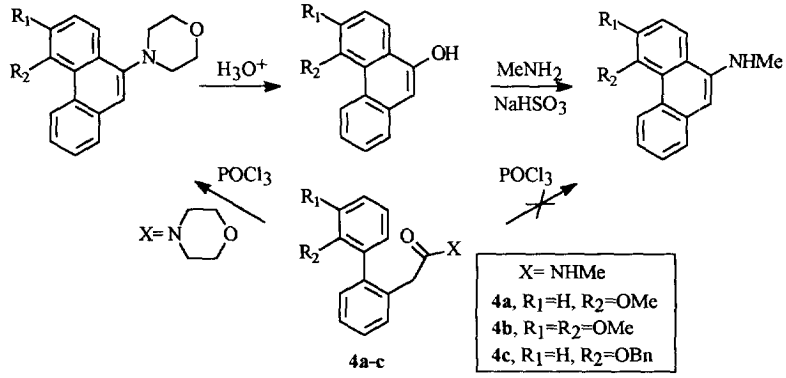


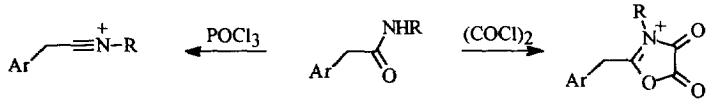
3

Recent findings concerning the cytotoxicity of 4,5-dioxoaporphines,[8] including the *N*-methoxylated artabotrine,[9] prompted us to explore new synthetic approaches to this type of alkaloid that could be extended to aristolactams and aristolochic acids. The strategy designed uses fluorenones, with a preformed biaryl bond, as precursors. The synthesis was developed in two stages: (1) formation of the aporphine ring C, which involves the transformation of fluorenones into phenanthrylamines, and (2) construction of the isoquinoline nucleus, by photocyclization of the corresponding α-chloroacetamides. To make ring C appropriately functionalized has required a sequence of reactions that includes: (1) a Bischler-Napieralsky type of cyclization of an *N*-morpholino-biphenylacetamide, (2) hydrolysis to the corresponding phenanthrol, and (3) Bucherer reaction with methylamine (Scheme 1).[8]



Scheme 1

This synthetic sequence could be shortened if cyclization of secondary amides were possible. This cyclization process, induced by $POCl_3$, must generate a nitrilium ion as the electrophilic reactive species.[10] We tried the reaction of *N*-methyl or *N*-cyclohexyl biphenylacetamides, but the desired phenanthrylamines were not obtained, instead biphenylacetonitriles were produced. The lack of cyclization cannot be attributed to deactivation of the aryl group. Quite likely, some geometrical restriction to the cyclization favours the observed retro-Ritter reaction.[10] Larsen[11] has recently reported a modified Bischler-Napieralsky procedure for the synthesis of 3-arylisoquinolines. The secondary amides are activated *via* an *N*-acyliminium with oxalyl chloride/$FeCl_3$, thus the intermediacy of nitrilium ion is avoided (Scheme 2).



Nitrilium ion *N*-Acyliminium ion

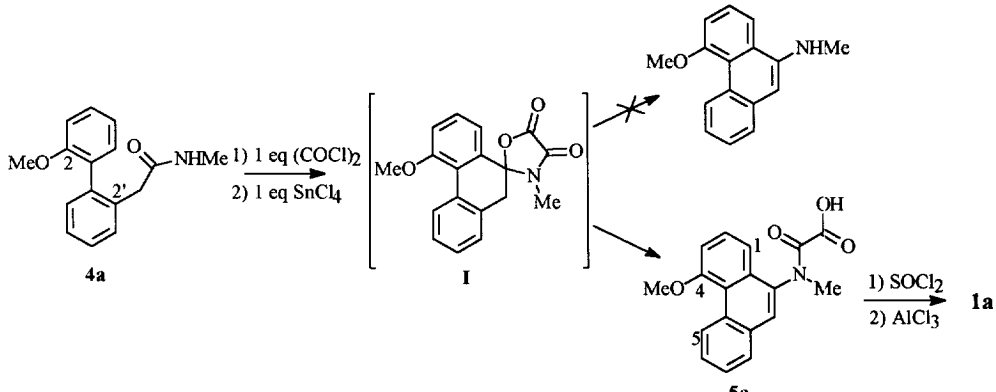
Scheme 2

Based on this strategy, in this paper we report in detail the reaction of *N*-methyl-biphenylacetamides **4a,b** with oxalyl chloride/$SnCl_4$ to promote a double cyclization to afford 4,5-dioxoaporphines in a single step by sequential formation of rings C and B.[12] In this cyclization, oxalyl chloride[13] plays a three fold role: (1) it generates the 2-chloro-oxazolidine-4,5-dione precursor of the electrophilic *N*-acyliminium ion, (2) it acts as an

α-dicarbonyl transfer agent, and (3) it produces the acid chloride needed in the last cyclization. We describe also a straightforward synthesis of the aporphinoid 4,5-dioxodehydrocorydine (**1d**) — which has a 1,2,10,11-oxygenation pattern difficult to achieve by other methodologies — from 1-iodo-2,3-dimethoxybenzene.

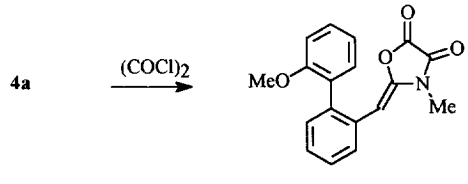
Results and Discussion

It is known[11,14] that in the reaction of (phenylethyl)amides with oxalyl chloride/Lewis acid, the oxalyl adduct of the isoquinoline can be isolated or readily hydrolysed to the 3,4-dehydroisoquinoline. Accordingly, it was expected that the reaction with *N*-methyl-biphenylacetamide (**4a**) would give the spiro-dihydrophenanthrene **I** that should hydrolyse to the desired phenanthrylamine[8] (Scheme 3).



Scheme 3

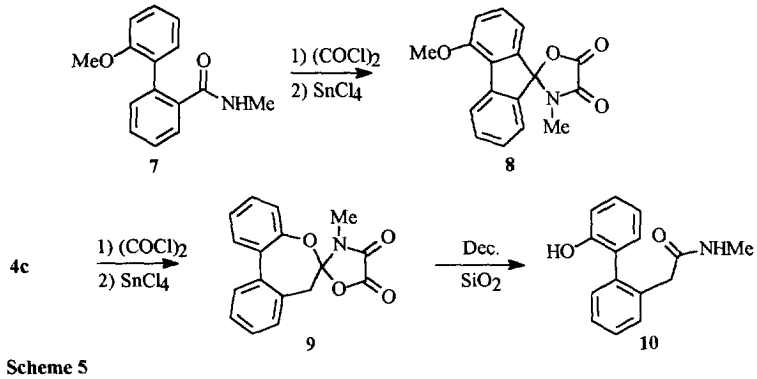
However, when the reaction of **4a** was carried out with stoichiometric amounts of $(COCl)_2$ and $SnCl_4$, followed by aqueous work-up, no phenanthrylamine was isolated, instead, the phenanthrylamide **5a** was obtained although in low yield (12%, Scheme 3). Since the Friedel-Crafts acylation reaction (with either $SOCl_2/AlCl_3$ or $(COCl)_2/SnCl_4$) of **5a** afforded the synthetic target 2-demethoxy-cepharadione-B (**1a**) in almost quantitative yield, a closer look to the formation of **5a** was undertaken. It was proved that in the absence of Lewis acid no cyclization of **4a** occurs, instead the 2-alkylidene-oxazolidine-4,5-dione **6** was obtained quantitatively (Scheme 4). This enamide could not be protonated, and was unreactive under Lewis acid conditions



Scheme 4

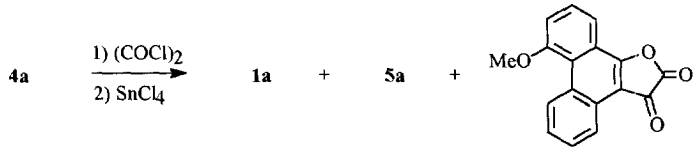
From these results we concluded that opening of the spiro intermediate **I** takes place in the course of the reaction and not during the work up, with aromatization to the phenanthrene being the required driving force. If this is so, the sequential C/B ring formation reaction from **4a** to the 4,5-dioxoaporphine (**1a**) ought to take place in a single step.

The evidence for the early ring opening of intermediate **I** points in this direction. First, it was proved that spiroxazolidin-4,5-diones without α-hydrogens were stable to the reaction conditions. In fact, the biphenylcarboxyamide **7** was cyclized and isolated in high yield (**8**), and even the spiro compound **9** can be isolated from the reaction of **4c** (Scheme 5). Second, when the reaction of **4a** was monitored by ^{1}H-NMR, a very low field multiplet (9.68 ppm) increased its intensity with the reaction progress, a signal that was assigned to the H-5 proton of the phenanthrene nucleus.



Scheme 5

As expected, when the amide **4a** was treated with an excess of reagents under several conditions the double cyclization product **1a** was obtained together with the amide **5a** (Scheme 6). In some experiments, the furanedione **11** was also isolated. Its formation might be the result of the opening of the spiroxazolidinedione intermediate (**I**) to the secondary amide this then activated again by the oxalyl chloride.



Scheme 6

11

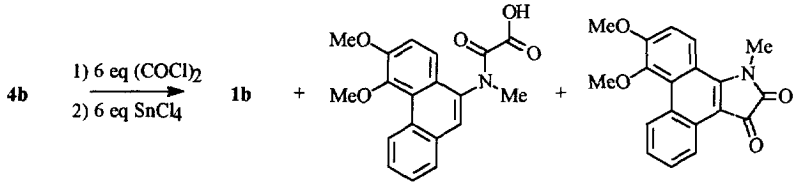
Table 1. Reaction of amide **4a** with oxalyl chloride/Lewis acid in CH_2Cl_2 as solvent.

Entry	$(COCl)_2$ (eq)	Lewis Acid (eq)	T (°C)	t	6 (%)	1a (%)	5a (%)	11 (%)
1	3	none	20	15 min	99	-	-	-
2	1	$SnCl_4$ (1)	5	3 d	-	-	12	-
3	3	$SnCl_4$ (3)	5	3 h	-	30	18	-
4	6	$SnCl_4$ (6)	5	3 d	-	80	6	2
5	6	$FeCl_3$ (6)	5	3 d	-	35	12	-
6	8	$SnCl_4$ (6)	65	5 h	-	20	33	14

The maximum yield of **1a** (Table 1, entry 4) was reached when 6 eq of oxalyl chloride were added to a CH_2Cl_2 solution of **4a**, and left at room temperature for 15 min, the mixture cooled to −10 °C, 6 eq of $SnCl_4$

added and maintained at 5 °C for 3 d. Much lower yields were obtained when $FeCl_3$ was used as Lewis acid (entry 5), or when to accelerate the reaction, a higher excess of oxalyl chloride was tried and the temperature was increased to 65°C (entry 6).

Under the optimised reaction conditions, the amide **4b** afforded cepharadione-B (**1b**) and oxalylamide (**5b**) in 45% and 49% yield respectively (Scheme 7), and a small amount of the indanedione **12** Since **5b** was almost quantitatively cyclized to **1b**, the 4,5-dioxoaporphine was obtained from the amide **4b** in an overall yield higher than 90%.



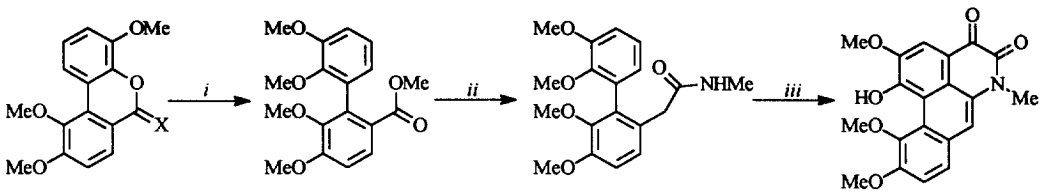
Scheme 7

Many synthetic approaches to the aporphine alkaloids have been developed.[15] Most of them, however, face severe limitations to achieve the 1,2,10,11- substitution pattern.[15,16] In fact, the synthesis of 4,5-dioxoaporphine oxygenated at positions 10,11 of ring D *via* morpholinoamide cyclization/Bucherer reaction[8] could not be achieved. In addition to a low yield at the cyclization step, the hydrolysis of the phenanthrylmorpholine **13** rapidly acquired a strong red colour, and the phenanthroquinone **14** was isolated as the main reaction product.

Scheme 8

These secondary processes were avoided using the oxalyl chloride approach, which was successfully applied to the synthesis of a 1,2,10,11-tetraoxygenated 4,5-dioxoaporphine. This synthetic achievement allowed us to compare its cytotoxicity with that of pontevedrine (**1e**), the 1,2,9,10-tetramethoxylated 4,5-dioxoaporphine of significant activity against several tumoral cell lines (*vide infra*).

The palladium-catalysed reaction of 1-iodo-2,3-dimethoxybenzene[17] is known to give not only the formation of the biaryl bond but also the oxidation of a methyl group to the dibenzopyran **15**. Oxidation to the dibenzopyranone **16** and lactone opening by hydroxyl ion in the presence of an excess of methyl iodide afforded the tetramethoxy biphenyl carboxylate **17**. Homologation *via* nitrile (see experimental) gave entry to the amide **20**. Reaction of **20** with oxalyl chloride/$SnCl_4$, under the conditions described above, brought about the double cyclization to give 4,5-dioxodehydrocorydine (**1d**) in 70% yield.



15, X=H,H
16, X=O

17 **20** **1d**

Reaction Conditions: i) 1: PCC, 2: MeI/KOH/CH_3CN; *ii*) 1: LAH, 2: $SOCl_2$, 3: NaCN, 4: HCl/H_2O, 5: $SOCl_2/MeNH_2$; *iii*) 1: $(COCl)_2/CH_2Cl_2$, 2: $SnCl_4/CH_2Cl_2$.

Scheme 9

The loss of the methyl group from the methoxy group at position 1 was not unexpected.[18] In fact, MM2 calculations for the 1,2,10,11-tetramethoxylated 4,5-dioxoaporphine showed that while both methyl groups at positions 1 and 11 are more accessible to nucleophiles, since they lie out of the plane of the molecule, the carbonyl group at C-4 provides a driving force for the observed regioselectivity. Experimentally, the structure of the demethylated product was proved from the observed C-1/H-3 correlation from the HMBC spectrum.

The cytotoxicity of the tetraoxygenated 4,5-dioxoaporphines **1d** and **1e** (pontevedrine) was tested with several tumoral cell lines (MDA, HT-29, P-388 and SCHABEL).[8] While **1d** displayed a significant activity against all cell lines (IC_{50} between 1.2 and 2.6 μg/mL), **1e** was more selective against the SCHABEL cell line (IC_{50} 0.5 μg/mL).[19]

In conclusion, a new and short synthesis of the oxidised aporphine alkaloids, based on the cyclization of biphenylacetamides to build up rings B and C in a single reaction, is described. The easy access to appropriate substituted biaryl derivatives from substituted fluorenones or by using organometallic chemistry[20] makes the reported methodology particularly convenient.

EXPERIMENTAL

General Methods

M.p.s. were determined on a Gallenkamp instrument and are given uncorrected. UV spectra were recorded on a Hewlett-Packard 8452A spectrophotometer, and IR spectra on a Perkin-Elmer 883 spectrophotometer. Low- and high-resolution mass spectra were recorded on a HP-MS 5988A and Kratos MS 50 spectrometers, respectively, both operating at 70 eV. NMR spectra were obtained on Bruker WP-200 SY or Bruker WM-500 instruments at 200 or 500 MHz for ^1H and 50.3 or 125.8 MHz for ^{13}C. ^1H Chemical shifts (δ_H) are given relative to residual $CHCl_3$ (δ_H 7.24 ppm) in deuteriochloroform. *J* values are in Hz. ^{13}C Chemical shifts (δ_C) are given relative to $CDCl_3$ (δ_C 77.0 ppm) in deuteriochloroform. TLC analyses were performed on silica gel 60 F 256 plates, and column chromatography was carried out on silica gel 60 (70-230 mesh).

Synthesis of amides 4a-c and 7.

General Procedure: To an ice cooled solution of the corresponding acid[8] (12.4 mmol) and pyridine (1mL) in benzene (200 mL), oxalyl chloride (21.6 mL, 248 mmol) was added dropwise. The mixture stirred at 20 °C for 30 min. Benzene and excess reagent were removed in vacuo and the resulting acid chloride was dissolved in acetone (5 mL). This solution was added to a cooled mixture of methylamine (40% in water, 9.6 mL, 124 mmol), TEA (4.6 mL) and water (5 mL). The reaction mixture was stirred at 20 °C for 1 h and washed sequentially with 1M NaOH, 1M HCl, and water. The organic solution was dried over anhydrous $MgSO_4$ and concentrated in vacuo.

(2-Methoxy)biphenyl-2'-yl N-methyl-acetamide (**4a**): Yield: 2.69 g, 85%; colourless needles; m.p. 125-126 °C (EtOH); ν (KBr) cm^{-1} 3287 (ν_{NH}), 1638 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε): 280 (3.53), 244 (3.72); δ_H ($CDCl_3$) 7.4-7.2 (5H, m, Ar-H), 7.1-6.9 (3H, m, Ar-H), 5.49 (1H, br s, N<u>H</u>CH_3), 3.72 (3H, s, OCH_3), 3.41 (2H, s, CH_2), 2.66 (3H, d, *J*=4.8, NHC<u>H</u>$_3$); δ_C ($CDCl_3$) 171.8 (CO), 156.1 (C-2), 139.0, 133.8, 129.4 (C), 131.0, 130.9, 130.1, 129.2, 128.0, 127.2, 120.8, 110.7 (CH), 55.3 (OCH_3), 41.3 (CH_2), 26.3 ($NHCH_3$); *m/z* (%) 255 (M^+, 34), 224 (M^+-OCH_3, 19), 197 (29), 166 (87), 165 ($C_{13}H_9$, 100); Anal. Calcd. for $C_{16}H_{17}NO_3$: C 75.26, H 6.72, N 5.49%, found C 75.29, H 6.68, N 5.47.

(2,3-Dimethoxy)biphenyl-2'-yl N-methyl-acetamide (**4b**): Yield: 3.18 g, 90%; white solid; m.p. 93-96 °C (MeOH); ν (KBr) cm^{-1} 3317 (ν_{NH}), 1654 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε): 274 (3.58), 244 (3.88); δ_H ($CDCl_3$) 7.50-7.15 (4H, m, Ar-H), 7.09 (1H, t, *J*=7.7, H-5), 6.91 (1H, dd, *J*=7.7, 1.4, H-4), 6.71 (1H, dd, *J*=7.7, 1.4, H-6), 5.82 (1H, br s, N<u>H</u>CH_3), 3.89 (3H, s, OCH_3), 3.55 (3H, s, OCH_3), 3.38 (2H, s, CH_2), 2.65 (3H, d, *J*=4.8, NHC<u>H</u>$_3$); δ_C ($CDCl_3$) 172.0 (CO), 152.8 (C-3), 145.8 (C-2), 138.2, 135.4, 134.1 (C), 130.3, 129.7, 128.1, 126.8, 124.3, 122.8, 112.0 (CH), 60.8 (OCH_3), 55.8 (OCH_3), 41.2 (CH_2), 26.4 (NH<u>C</u>H_3); *m/z* (%) 285 (M^+, 100), 254 (M^+-OCH_3, 20), 228 (M^+-$CONCH_3$, 48), 197 (42), 196 (89), 195 (71); Anal. Calcd. for $C_{17}H_{19}NO_3$: C 71.54, H 6.72, N 4.91%, found C 71.64, H 6.73, N 4.91.

(2-Benzyloxy)biphenyl-2'-yl N-methyl-acetamide (**4c**): Yield: 3.94 g, 96%; white solid; m.p. 85-86 °C (EtOH); ν (KBr) cm^{-1} 3322 (ν_{NH}), 1645 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε): 276 (3.44), 244 (3.63); δ_H ($CDCl_3$) 7.37-7.01 (13H, m, Ar-H), 5.41 (1H, br s, N<u>H</u>CH_3), 4.98 (2H, s, C<u>H</u>$_2$Bn), 3.41 (2H, s, CH_2CO), 2.29 (3H, d, *J*=4.8, NHC<u>H</u>$_3$); δ_C ($CDCl_3$) 171.8 (CO), 155.2 (C-2), 138.7, 136.6, 134.0, 130.6 (C), 131.0, 130.7, 129.8, 129.1, 128.5 (2), 128.0, 127.8, 127.0, 126.6 (2), 121.6, 113.5 (CH), 70.7 (<u>C</u>H_2Bn), 41.2 (<u>C</u>H_2CO), 25.9 ($NHCH_3$); *m/z* (%) 331 (M^+, 4), 300 (M^+-OCH_3, 4), 181 ($C_{13}H_9O$, 43), 165 (16), 91 (Bn, 100); Anal. Calcd. for $C_{22}H_{21}NO_2$: C 79.73, H 6.39, N 4.23%, found C 79.15, H 6.29, N 4.11.

(2-Methoxy)biphenyl-2'-N-methyl-carboxamide (7): Yield: 2.81 g, 94%; amorphous white solid; m.p. 108-110 °C (EtOH); ν (KBr) cm^{-1} 3323 (ν_{NH}), 1632 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε): 286 (3.51), 248 (3.71); δ_H ($CDCl_3$) 7.74 (1H, dd, *J*=7.2, 2.0, Ar-H), 7.49-7.21 (5H, m, Ar-H), 7.02 (1H, dt, *J*=7.2, 1.1, Ar-H), 6.93 (1H, d, *J*=8.5, Ar-H), 5.5 (1H, br s, N<u>H</u>CH_3), 3.74 (3H, s, OCH_3), 2.65 (3H, d, *J*=4.9, NHC<u>H</u>$_3$); δ_C ($CDCl_3$) 169.8 (CO), 156.3 (C-2), 136.2, 135.8, 129.3 (C), 130.9, 130.7, 130.0, 129.5, 128.4, 127.6, 121.0, 110.7 (CH), 55.4 (OCH_3), 26.4 ($NHCH_3$); *m/z* (%) 241 (M^+, 9), 210 (M^+-OCH_3, 100), 196 (24), 168 (17), 139 (17); Anal. Calcd. for $C_{15}H_{15}NO_2$: C 74.67, H 6.27, N 5.80%, found C 74.65, H 6.27, N 5.83.

Reaction of 4a,b with 1 eq of $(COCl)_2/SnCl_4$.

To a N_2 degassed solution of **4a,b** (0.8 mmol) in dichloromethane (8 mL), in a septum sealed round botton flask, oxalyl chloride (0.07 mL, 0.8 mmol) was added. The solution was stirred at 20 °C for 15 min, cooled at 5 °C, and stannyl chloride (0.09 mL, 0.8 mmol) added. The mixture was stirred at 5 °C for 72 h, diluted with dichloromethane (20 mL) and washed with 2M HCl (100 mL). The organic layer was extracted with 2M NaOH, and the extracts acidified with concentrated HCl and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$, and the solvent removed to give **5a,b**.

10-N-Methyl-oxalylamido-4-methoxy-phenanthrene (**5a**): Yield: 0.030 g, 12%; brown solid; m.p. 148-149 °C dec. (AcOEt); ν (KBr) cm^{-1} 3600-2400 (ν_{OH}), 1748 (ν_{CO}), 1655 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε): 356 (2.58), 340 (2.62), 278 (3.70), 252 (4.32); δ_H ($CDCl_3$+TFA) 9.68 (1H, br d, *J*=8.6, H-5), 7.86 (1H, m, Ar-H), 7.79-7.60 (4H, m, Ar-H), 7.45 (1H, m, Ar-H), 7.31 (1H, m, Ar-H), 4.18 (3H, s, OCH_3), 3.53 (3H, s, NCH_3); δ_C ($CDCl_3$+TFA) 165.1 (CO), 163.1 (CO), 159.5 (C-4), 134.5, 131.0, 129.9, 128.6, 122.5 (C), 129.1, 128.8 (2), 128.3, 128.2, 127.1, 115.5, 110.6 (CH), 56.0 (OCH_3), 37.5 (NCH_3); *m/z* (%) 309 (M^+, 15), 294 (M^+-CH_3, 30), 265 (M^+-CO_2, 92), 248 (37), 237 (M^+-CO_2, -CO, 100); Anal. Calcd. for $C_{18}H_{15}NO_4$: C 69.89, H 4.89, N 4.53%, found C 69.80, H 4.83, N 4.58.

10-N-Methyl-oxalylamido-3,4-dimethoxy-phenanthrene (**5b**): Yield: 0.081 g, 30%; amorphous solid; m.p. 171-175 °C dec. (H_2O); ν (KBr) cm^{-1} 3600-2400 (ν_{OH}), 1747 (ν_{CO}), 1654 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε): 360 (2.92), 344 (3.02), 306 (3.66), 256 (4.25); δ_H ($CDCl_3$) 9.56 (1H, d, *J*=8.3, H-5), 8.22 (1H, br s, COOH), 7.75-7.50 (4H, m, Ar-H), 7.43 (1H, s, H-9), 7.30 (1H, d, *J*=9.0, Ar-H), 3.96 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.31 (3H, s, NCH_3); δ_C ($CDCl_3$) 162.3 (CO), 161.6 (CO), 152.2, 147.4 (C-3, C-4), 136.1, 131.8, 129.8, 126.1, 123.9 (C), 128.7, 127.8 (2), 127.1, 124.9, 119.4, 113.5 (CH), 59.7 (OCH_3), 56.3 (OCH_3), 37.2 (NCH_3); *m/z* (%) 339 (M^+, 11), 295 (M^+-CO_2, 100), 278 (40), 267 (M^+-CO_2, -CO, 32); HRMS calcd. for $C_{19}H_{17}NO_5$ (M^+) *m/z* 339.1107, found 339.1107.

Cyclization of oxalylamides 5a,b under Friedel-Crafts conditions.

General Procedure: A solution of **5a,b** (0.32 mmol) and oxalyl chloride (0.2 mL, 2.3 mmol) in dry dichloromethane (4 mL) was stirred at 20 °C for 30 min. The mixture was treated with stannyl chloride (0.27 mL, 2.3 mmol) and stirred at 20 °C for 48 h. The organic layer was washed with 1M HCl and water, dried over anhydrous $MgSO_4$ and concentrated in vacuo to give **1a,b**.

2-Demethoxy-cepharadione-B (**1a**): Yield: 0.09 g, 96%; orange powder; m.p. 255-257 °C (EtOH).[8]

Cepharadione-B (**1b**): 0.09 g, Yield: 92%; orange crystals; m.p. 257-260 °C (EtOH) (lit.[21] 266-268).

Reaction of 4a with $(COCl)_2$.

A solution of **4a** (0.2 g, 0.8 mmol) and oxalyl chloride (0.4 mL, 4.6 mmol) in dry dichloromethane (8 mL) was stirred at 20 °C for 15 min. After that time, the reaction mixture was concentrated in vacuo to give **6**.

2-[2-Methoxy-biphenyl-2'-yl]methylene N-methyl-oxazolidine-4,5-dione (**6**): Yield: 0.25 g, 99%; amorphous solid; m.p. 134-138 °C (CH_2Cl_2); ν (KBr) cm^{-1} 1818 (ν_{CO}); 1749 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε): 348 (3.98),

248 (4.06); δ_H ($CDCl_3$) 7.88 (1H, d, *J*=7.2, Ar-H), 7.42-6.97 (7H, m, Ar-H), 5.27 (1H, s, C=CH), 3.74 (3H, s, OCH_3), 3.08 (3H, s, NCH_3); δ_C ($CDCl_3$) 154.9 (CO), 156.4 (CO), 149.5, 140.8, 138.5, 129.8, 129.2 (C), 131.6, 130.7, 129.4, 128.7, 127.7, 127.5, 120.7, 110.9 (CH), 90.8 (C=CH), 55.5 (OCH_3), 27.2 (NCH_3); *m/z* (%) 309 (M^+, 36), 224 ($C_{15}H_{12}O_2$, 100), 181 ($C_{13}H_9O$, 79), 165 (71), 152 (69); HRMS calcd. for $C_{18}H_{15}NO_4$ (M^+) *m/z* 309.1001, found 309.1003.

Reaction of 4a-c with excess of $(COCl)_2/SnCl_4$.

General Procedure: To a degassed (N_2) solution of **4a-c** (4 mmol) in dichloromethane (8 mL), in a septum sealed round botton flask, oxalyl chloride (1.0 mL, 12 mmol) was added. The solution was stirred at 20 °C for 15 min, cooled at -10 °C, and stannyl chloride (1.2 mL, 10 mmol) added. The mixture was stirred at 5 °C for 72 h and poured into 2M HCl (100 mL) and extracted with CH_2Cl_2. The organic layer was washed with water, dried over $MgSO_4$ and the solvent removed.

The crude reaction of **4a** was purified by column chromatography (SiO_2, CH_2Cl_2 and 10:2 CH_2Cl_2:CH_3OH) to give **1a**, **5a** and **11**.

2-Demethoxy-cepharadione-B (**1a**): Yield: 0.91 g, 80%.

10-N-Methyl-oxalylamido-4-methoxy-phenanthrene (**5a**): Yield: 0.072 g, 6%.

8-Methoxy-phenanthro[9,10-b]furane-4,5-dione **11**: Yield: 0.022 g, 2%; light orange; m.p. 197-198 °C dec. ($CHCl_3$); ν (KBr) cm^{-1} 1831, 1716 (ν_{CO}), 1621 ($\nu_{C=C}$); λ_{max} (EtOH) nm (log ε): 396 (3.72), 250 (4.52), 206 (4.34); δ_H ($CDCl_3$) 9.49 (1H, m, H-7), 8.62 (1H, m, H-4), 7.84 (1H, d, *J*=7.9, Ar-H), 7.69-7.56 (3H, m, Ar-H), 7.44 (1H, d, Ar-H), 4.15 (3H, s, OCH_3); δ_H (C_6D_6+TFA) 9.42 (1H, m, H-7), 8.36 (1H, m, H-4), 7.46-7.37 (3H, m, Ar-H), 7.14 (1H, t, H-10), 6.79 (1H, d, *J*=8.0, H-9), 3.43 (3H, s, OCH_3); δ_C ($CDCl_3$+TFA) 176.3 (CO), 168.1 (CO), 158.9, 156.8 (C-1a, C-8), 127.6, 126.9, 124.6, 120.8, 110.3 (C), 129.2, 129.0, 128.5, 127.6, 123.8, 116.4, 116.2 (CH), 56.0 (OCH_3); *m/z* (%) 278 (M^+, 4), 250 (M^+-CO, 100), 235 (9), 207 (17), 194 (22); HRMS calcd. for $C_{17}H_{10}O_4$ (M^+) *m/z* 278.0579, found 278.0588.

Column chromatography (SiO_2, 10:1 CH_2Cl_2:CH_3OH) of crude reaction of **4b** (1.14 g, 4 mmol) gave **1b**, **5b** and **12**.

Cepharadione-B (**1b**): Yield: 0.58 g, 45%; orange crystals.

10-N-Methyl-oxalylamido-3,4-dimethoxy-phenanthrene (**5b**): Yield: 0.66 g, 49%.

1-Methyl-8,9-dimethoxy-dibenzo[e,g]indano-2,3-dione (**12**): Yield: 0.051 g, 4%; orange solid; m.p. 179-182 °C ($CHCl_3$/MeOH); ν (KBr) cm^{-1} 1696 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε): 414 (3.02), 302 (3.50), 250 (3.87); δ_H ($CDCl_3$) 9.65 (1H, m, H-7), 9.07 (1H, m, Ar-H), 8.93 (1H, d, *J*=8.8, H-11), 7.76-7.68 (2H, m, Ar-H), 7.42 (1H, d, *J*=8.8, H-10), 4.06 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.18 (3H, s, NCH_3); δ_C ($CDCl_3$) 170.1 (CO), 169.9 (CO), 153.9, 151.9 (C-8, C-9), 132.5, 127.5, 127.4, 126.4, 125.2, 120.8 (C), 129.1, 128.2, 128.1, 125.6, 123.0, 114.3 (CH), 59.9 (OCH_3), 56.4 (OCH_3), 19.9 (NCH_3); *m/z* (%) 321 (M^+, 100), 306 (M^+-CH_3, 62); HRMS calcd. for $C_{19}H_{15}NO_4$ (M^+) *m/z* 321.1001, found 321.1001.

Reaction of **4c** (0.2 g, 0.6 mmol) gave **9**, which was isolated following the general procedure. Attempts to purify **9** by column chromatography (SiO_2, $CHCl_3$:CH_3OH) gave **10**.

Dibenzo[b,d]oxepine-11-spiro-2'-N-methyl-oxazolidine-4,5-dione (**9**): Yield: 0.19 g, 79%; solid foam; ν (KBr) cm^{-1} 1827 (ν_{CO}), 1753 (ν_{CO}); δ_H ($CDCl_3$) 7.7-7.2 (8H, m, Ar-H), 3.57 (1H, d, *J*=14.9, HCH), 3.19 (1H, d, *J*=14.9, HCH), 2.85 (3H, s, NCH_3); δ_C ($CDCl_3$) 156.8 (CO), 152.7 (CO), 149.7 (C-2'), 136.9, 132.2, 131.1, 116.5 (C), 129.7, 129.6, 129.4, 129.1, 128.6, 128.4, 126.8, 123.4 (CH), 41.9 (CH_2), 28.3 (NCH_3); *m/z* (%) 295 (M^+, 69), 223 (M^+-C_2O_3, 29), 210 (M^+-$C_3H_3NO_2$, 89), 181 ($C_{13}H_9O$, 100), 165 ($C_{13}H_9$, 39).

(2-Hydroxy)biphenyl-2'-yl N-methyl-acetamide (**10**): Syrup; ν (KBr) cm^{-1} 3305 (ν_{OH}, ν_{NH}), 1642 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε): 272 (3.69), 248 (3.76); δ_H ($CDCl_3$) 7.4-6.8 (8H, m, Ar-H), 6.01 (1H, br d, *J*=4.0, NH), 3.41 (2H, s, CH_2), 2.85 (3H, d, *J*=4.0, NCH_3); δ_C ($CDCl_3$) 173.0 (CO), 153.5 (C-2), 138.5, 133.8, 128.0 (C), 131.1, 130.6, 129.8, 129.2, 128.2, 127.5, 120.1, 116.7 (CH), 40.8 (CH_2), 26.4 (NCH_3); *m/z* (%)241 (M^+, 61), 210 (M^+-OCH_3, 88), 182 (56), 181 ($C_{13}H_9O$, 100), 166 (89), 165 ($C_{13}H_9$, 88); HRMS calcd. for $C_{15}H_{15}NO_2$ (M^+) *m/z* 241.1103, found 241.1103.

Reaction of 7 with excess of $(COCl)_2$/$SnCl_4$.

Following the general procedure with excess of reagents, amide **7** (0.19 g, 0.8 mmol) was converted to **8**. This product was purified by preparative TLC (1:2, AcOEt:hexane).

4-Methoxy-fluorene-9-spiro-2'-N-methyl-oxazolidine-4,5-dione (**8**): Yield: 0.20 g, 86%; white solid; m.p. 190-192 °C dec. (MeOH); ν (KBr) cm^{-1} 1817 (ν_{CO}), 1743 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε): 328 (3.60), 294 (3.98), 284 (3.96), 266 (3.92), 246 (4.27); δ_H ($CDCl_3$) 7.98 (1H, d, *J*=7.5, Ar-H), 7.50 (1H, dt, *J*=7.5, 1.4, Ar-H), 7.36-7.21 (3H, m, Ar-H), 7.03 (1H, d, *J*=8.3, Ar-H), 6.86 (1H, d, *J*=7.5, Ar-H), 4.00 (3H, s, OCH_3), 2.65 (3H, s, NCH_3); δ_C ($CDCl_3$) 158.8 (CO), 156.1 (CO), 152.4 (C-4), 140.0, 138.5, 135.9, 128.4 (C), 97.9 (C-9), 132.4, 130.5, 128.1, 124.9, 123.2, 115.5, 114.6 (CH), 55.7 (OCH_3), 26.5 (NCH_3); *m/z* (%) 295 (M^+, 46), 223 (M^+-C_2O_3, 41), 195 ($C_{14}H_{11}O$, 100); Anal. Calcd. for $C_{17}H_{13}NO_4$: C 69.15, H 4.44, N 4.74%, found C 68.94, H 4.44, N 4.64.

Synthesis of 4,5-dioxodehydrocorydine (1d).

2,3,3'-Trimethoxy-biphenyl-2',6-carbolactone (**16**): A solution of **15**, (2.16 g, 8.0 mmol) prepared from 1-iodo-2,3-dimethoxybenzene[22] according to the procedure described by Dyker,[17] in anhydrous dichloromethane (80 mL) was refluxed for 24 h, and over this period, PCC (6.88 g, 32.0 mmol) was added in four portions. The reaction mixture was diluted with ether and filtered through SiO_2. The filtrate was evaporated and the residue was crystallized with AcOEt to give **16**. Yield: 1.59 g, 70%; yellowish solid; m.p. 172-173 °C (AcOEt); ν cm^{-1} (KBr) 1728 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε): 314 (3.65), 272 (4.09); δ_H ($CDCl_3$) 8.51 (1H, dd, *J*=8.5, 1.2, H-6'), 8.25 (1H, d, *J*=8.8, H-5), 7.23 (1H, t, *J*=8.5, H-5'), 7.15 (1H, d, *J*=8.8, H-4), 7.03 (1H, dd, *J*=8.5, 1.2, H-4'), 4.00, 3.95, 3.89 (3 x 3H, 3 x s, 3 x OCH_3); δ_C ($CDCl_3$) 160.7, 158.6, 147.7, 145.9, 141.0 (CO, C-2, C-2', C-3, C-3'), 128.4, 118.2, 115.0 (C), 128.2, 124.1, 119.0, 112.7, 112.3 (CH), 60.0, 56.2, 56.2 (3 x OCH_3); *m/z* (%):

286 (M^+, 100), 271 (M^+-OCH_3, 46), 240 (30); Anal. Calcd. for $C_{16}H_{14}O_5$: C 67.13, H 4.93%, found C 66.83, H 4.95.

Methyl 2,2',3,3'-tetramethoxy-biphenyl-6-carboxylate (**17**): To a mixture of powdered KOH (26 mmol) and methyl iodide (3.3 mL, 52 mmol) in acetonitrile (50 mL), the biphenyl carbolactone **16** (1.50 g, 5.2 mmol) was added. After stirring for 12 h at 20 °C, the solvent was removed and H_2O was added to the residue. Extraction with $CHCl_3$, drying the organic layer with $MgSO_4$ and evaporation, afforded compound **17**. Yield: 1.69 g, 97%; colourless crystals; m.p. 110-112 °C ($CHCl_3$); ν (KBr) cm^{-1} 1726 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε): 280 (3.66), 252 (4.03); δ_H ($CDCl_3$) 7.75 (1H, d, *J*=8.8, H-5), 7.05 (1H, t, *J*=7.9, H-5), 6.93 (1H, d, *J*=8.8, H-4), 6.91 (1H, dd, *J*=7.9, 1.7, H-6), 6.69 (1H, dd, *J*=7.9, 1.7, H-4), 3.91, 3.87, 3.57 (3 x 3H, 3 x s, 3 x OCH_3), 3.60 (6H, s, 2 x OCH_3); δ_C ($CDCl_3$) 166.9 (CO), 155.8, 152.2, 146.8, 146.1 (C-2, C-2', C-3, C-3'), 134 4, 131.5, 123.4 (C), 126.7, 123.0, 122.1, 111.5, 110.5 (CH), 60.4, 60.0 (2,2'-OCH_3), 55.7, 55.6 (3,3'-OCH_3), 51.5 ($COO\underline{C}H_3$); *m/z* (%) 332 (M^+, 58), 301 (M^+-OCH_3, 100), 271 ($C_{16}H_{15}O_4$, 12), 209 (15); Anal. Calcd. for $C_{18}H_{20}O_6$: C 65.04, H 6.07%, found C 64.87, H 5.94.

(2,2',3,3'-Tetramethoxy)biphenyl-6-yl acetonitrile (**18**): To a N_2 purged solution of **17** (1.49 g, 4.5 mmol) in dry THF (100 mL), LAH (0.76 g, 20 mmol) was added in small portions over a period of 15 min. After stirring for 1 h at 20 °C, the excess of hydride was decomposed by the addition of 1M H_2SO_4, and the resulting suspension treated with more dilute acid and extracted with TBME (3x50 mL). The extract was carefully dried ($MgSO_4$) and the volume reduced to 50 mL. This ether solution was ice cooled and thionyl chloride (6 mL, 6.9 mmol) added dropwise with stirring. The temperature was rised to 20 °C and mantained for 30 min. TBME and excess thionyl chloride were removed in vacuo without heating. The crude residue was dissolved in acetonitrile (100 mL), NaCN (2.2 gr, 45 mmol) was added and the mixture refluxed for 48 h. After removal of the solvent, the residue was dissolved in H_2O, extracted with $CHCl_3$, dried over $MgSO_4$, and concentrated under reduced pressure to give **18**. Yield: 1.25 g, 89%; syrup that crystallized on standing; m.p. 97-99 °C; ν (KBr) cm^{-1} 2254 (ν_{CN}); λ_{max} ($CHCl_3$) nm (log ε): 280 (3.57), 244 (3.72); δ_H ($CDCl_3$) 7.23 (1H, d, *J*=8.5, H-5), 7.11 (1H, t, *J*=7.8, H-5'), 6.96 (1H, dd, *J*=7.8, 1.6, H-6'), 6.94 (1H, d, *J*=8.5, H-4), 6.72 (1H, dd, *J*=7.8, 1.6, H-4'), 3.88 (6H, s, 2 x OCH_3), 3.64 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 3.49 (1H, d, *J*=18.7, $\underline{H}CH$), 3.28 (1H, d, *J*=18.7, $HC\underline{H}$); δ_C ($CDCl_3$) 152.8, 152.3, 146.8, 146.2 (C-2, C-2', C-3, C-3'), 132.2, 129.6, 121.9 (C), 124.0, 123.3, 122.6, 112.1, 111.7 (CH), 118.3 (CN), 60.7, 60.5 (2,2'-OCH_3), 55.7, 55.6 (3,3'-OCH_3), 21.2 (CH_2); *m/z* (%) 313 (M^+, 100), 298 (M^+-OCH_3, 52), 267 (25), 255 ($C_{15}H_{11}O_4$, 25); Anal. Calcd. for $C_{18}H_{19}NO_4$: C 68.99, H 6.11, N 4.47%, found C 68.93, H 6.09, N 4.44.

(2,2',3,3'-Tetramethoxy)biphenyl-6-yl acetic acid (**19**): To a solution of **18** (0.91 g, 2.9 mmol) in ethanol (35 mL), KOH (1.9 g, 29 mmol) and water (15 mL) were added. After refluxing the mixture for 24 h, most of the ethanol was removed in vacuo. The resulting suspension was diluted with 1M NaOH and washed with $CHCl_3$. The aqueous layer was acidified with concentrated HCl and extracted with $CHCl_3$. The extracts were dried over anhydrous $MgSO_4$ and the solvent evaporated. Yield: 0.90 g, 94%; syrup that crystallized on standing; m.p. 115-116 °C; ν (KBr) cm^{-1} 3600-2400 (ν_{OH}), 1703 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε): 280 (3.56), 244 (3.76); δ_H ($CDCl_3$) 7.1-7.0 (3H, m, Ar-H), 6.90 (1H, d, *J*=8.4, Ar-H), 6.69 (1H, dd, *J*=7.5, 1.6, Ar-H), 3.86 (6H, s, 2 x

OCH_3), 3.62 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 3.31 (2H, s, CH_2); δ_C ($CDCl_3$) 176.6 (CO), 152.6, 151.7, 146.6, 146.3 (C-2, C-2', C-3, C-3'), 133.1, 130.7, 125.7 (C), 125.2, 123.7, 123.2, 111.9, 111.7 (CH), 60.6, 60.4 (2,2'-OCH_3), 55.7, 55.7 (3,3'-OCH_3), 38.2 (CH_2); *m/z* (%) 332 (M^+, 46), 331 (45), 288 (36), 257 (27), 256 (60), 255 ($C_{15}H_{11}O_4$, 100), 242 (32), 241 (58), 226 (24), 225 (38); HRMS calcd. for $C_{18}H_{20}O_6$ (M^+) *m/z* 332.1260, found 332.1260.

(2,2',3,3'-Tetramethoxy)biphenyl-6-yl N-methyl-acetamide (**20**): The acetamide **20** was prepared from **19** (0.23 g, 0.69 mmol) as above. Yield: 0.23 g, 95%; syrup; ν (film) cm^{-1} 3379 (ν_{NH}), 1654 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε): 244 (3.93), 276 (3.75); δ_H ($CDCl_3$) 7.15-6.85 (4H, m, Ar-H), 6.66 (1H, dd, *J*=7.5, 1.6, H-4'), 3.88 (6H, s, 2 x OCH_3), 3.67 (3H, s, OCH_3), 3.60 (3H, s, OCH_3), 3.21 (2H, s, CH_2), 2.62 (3H, d, *J*=4.7, $NHCH_3$); δ_C ($CDCl_3$) 171.9 (CO), 152.7, 151.5, 146.6, 146.1 (C-2, C-2', C-3, C-3'), 133.1, 130.6, 127.0 (C), 125.1, 123.7, 122.5, 112.0, 111.9 (CH), 60.5, 60.3 (2,2'-OCH_3), 55.6, 55.5 (3,3'-OCH_3), 40.5 (CH_2), 29.1 ($NHCH_3$); *m/z* (%) 345 (M^+, 90), 314 (M^+-OCH_3, 26), 272 ($C_{16}H_{16}O_4$, 38), 256 (99), 255 (100); Anal. Calcd. for $C_{19}H_{23}NO_5$: C 66.06, H 6.72, N 4.06%, found C 66.00, H 6.70, N 4.02.

4,5-Dioxodehydrocorydine (**1d**): Following the general procedure, **1d** was obtained from the reaction of amide **20** (0.16 g, 0.46 mmol), oxalyl chloride (0.2 mL, 2.3 mmol) and stannyl chloride (0.27 mL, 2.3 mmol) in dichloromethane (4.6 mL). Yield: 0.12 g, 70%; orange solid; m.p. 258-262 °C (EtOH); ν (KBr) cm^{-1} 3477 (ν_{OH}), 1652 (ν_{CO}), 1638 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε): 454 (3.56), 316 (3.54), 222 (4.17), 208 (4.32). (EtOH+OH^-) 474 (3.73), 316 (3.79), 234 (3.89), 216 (4.55); δ_H (500 MHz) ($CDCl_3$) 11.88 (1H, s, OH), 8.28 (1H, s, H-3), 7.74 (1H, s, *J*=8.7, H-8), 7.41 (1H, d, *J*=8.7, H-9), 7.39 (1H, s, H-7), 4.14 (3H, s, 2-OCH_3), 4.09 (3H, s, 10-OCH_3), 3.86 (3H, s, NCH_3), 3.85 (3H, s, 11-OCH_3); δ_C (125.8 MHz) ($CDCl_3$) 174.8 (C-4), 156.6 (C-5), 153 5 (C-1), 151.7 (C-10), 150.0 (C-2), 142.2 (C-11), 131.0 (C-6a), 127.3 (C-8), 121.5 (C-11c), 120.7 (C-11a), 120.2 (C-7a), 116.9 (C-3a, C-11b), 113.8 (C-9), 113.7 (C-7), 111.8 (C-3), 62.8 (11-OCH_3), 56.7 (2-OCH_3), 56.6 (10-OCH_3), 30.7 (NCH_3); *m/z* (%) 367 (M^+, 100), 339 (M^+-CO, 10), 324 (21), 296 (20), 281 (21); HRMS calcd. for $C_{20}H_{17}NO_6$ (M^+) *m/z* 367.1056, found 367.1054.

4-(2,2',3,3'-Tetramethoxybiphenyl-6-yl)acetyl morpholine (**21**): As described above, the amide **21** was prepared from **19** (0.69 mmol), oxalyl chloride (1.2 mL, 13.8 mmol), pyridine (0.1 mL), benzene (10 mL), morpholine (0.6 mL, 6.9 mmol), TEA (0.3 mL) and chloroform (1.5 mL). Yield: 0.27 g, 97%; syrup; λ_{max} ($CHCl_3$) nm (log ε): 280 (3.73), 242 (3.99); δ_H ($CDCl_3$) 7.15-6.85 (4H, m, Ar-H), 6.67 (1H, dd, *J*=7.6, 1.6, H-4'), 3.89, 3.88 (2 x 3H, 2 x s, 2 x OCH_3), 3.61, 3.60 (2 x 3H, 2 x s, 2 x OCH_3), 3.7-3.0 (10H, m, morpholine-H); δ_C ($CDCl_3$) 170.2 (CO), 152.7, 151.4, 146.5, 146.3 (C-2, C-2', C-3, C-3'), 132.5, 130.8, 126.9 (C), 124.0, 123.6, 123.0, 111.6, 111.5 (CH), 66.7, 66.4 (CH_2OCH_2), 60.6, 60.4 (2,2'-OCH_3), 55.6 (3,3'-OCH_3), 46.0, 41.9 (CH_2NCH_2), 37.4 (CH_2CO); *m/z* (%) 401 (M^+, 19), 287 (M^+-$C_5H_8NO_2$, 16), 272 (29), 256 (60), 255 ($C_{15}H_{11}O_4$, 100); HRMS calcd. for $C_{22}H_{27}NO_6$ (M^+) *m/z* 401.1838, found 401.1838.

4-[10-(3,4,5,6-Tetramethoxy)phenanthryl]morpholine (**13**): A N_2 purged mixture of **21** (0.2 g, 0.5 mmol), dry toluene (1.4 mL), dry benzene (0.6 mL), and phosphoryl chloride (0.56 mL) was refluxed for 1 h. The reaction mixture was diluted with benzene (12 mL) and 10% aq. $NaHCO_3$ (50 mL) added dropwise. The organic layer

was separated, washed with cool water (10 mL), dried over $MgSO_4$ and concentrated in vacuo without heating. The residue was purified by column chromatography (SiO_2, 20:0.4 CH_2Cl_2:MeOH). The obtained syrup (**13**) was manipulated under an N_2 atmosphere. Yield: 0.080 g, 42%; yellowish syrup; δ_H ($CDCl_3$) 7.89 (1H, d, *J*=9.0, Ar-H), 7.35 (1H, d, *J*=8.6, Ar-H), 7.29 (1H, d, *J*=9.0, Ar-H), 7.23 (1H, d, *J*=8.6, Ar-H), 6.88 (1H, s, H-9), 3.99, 3.97, 3.68, 3.61 (4 x 3H, 4 x s, 4 x OCH_3), 4.0-3.9 (4H, t, CH_2OCH_2), 3.08 (4H, br t, CH_2NCH_2); δ_C ($CDCl_3$) 151.2, 150.4, 148.2, 148.0, 145.3 (C-3, C-4, C-5, C-6, C-10), 129.3, 125.2, 124.5, 119.9 (C), 121.0, 118.5, 114.4, 113.3, 111.8 (CH), 67.4 (CH_2OCH_2), 60.7 (2 x OCH_3), 57.2 (OCH_3), 56.8 (OCH_3), 53.0 (CH_2NCH_2); *m/z* (%) 383 (M^+, 100), 368 (M^+-OCH_3, 51); HRMS calcd. for $C_{22}H_{25}NO_5$ (M^+) *m/z* 383.1733, found 383.1732.

Hydrolysis of 13.

A solution of **13** (0.060 g, 0.16 mmol) in THF (1 mL) and HCl 1M (1 mL) was heated at 60 °C for 12 h under N_2. After cooling, TBME was added and the organic layer washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by preparative TLC to afford **14**.

3,4,5,6-Tetramethoxy-9,10-phenanthraquinone (**14**): Yield: 0.028 g, 53%; yellow solid; m.p. 233-236 °C (CH_2Cl_2/MeOH); ν (KBr) cm^{-1} 1669 (ν_{CO}); λ_{max} ($CHCl_3$) nm (log ε): 376 (3.69), 246 (4.10); δ_H ($CDCl_3$) 7.83 (2H, d, *J*=8.6, Ar-H), 6.96 (2H, d, *J*=8.6, Ar-H), 3.97 (6H, s, 2 x OCH_3), 3.72 (6H, s, 2 x OCH_3); δ_C ($CDCl_3$) 182.2 (CO), 159.3, 148.1 (C-3, C-4, C-5, C-6), 128.0, 124.7 (C), 126.7, 111.9 (CH), 61.4, 56.2 (OCH_3); *m/z* (%) 328 (M^+, 51), 300 (M^+-CO, 100); HRMS calcd. for $C_{18}H_{16}O_6$ (M^+) *m/z* 328.0947, found 328.0946.

Cytotoxicity testing.

Cytotoxicity studies[8] were carried out following the colorimetric method described by Mosmann.[23]

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