Pergamon

Tetrahedron, Vol. 52, No. 34, pp. 11307-11320, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00657-6

A New Approach to the Synthesis of 4,5-Dioxoaporphine Alkaloids from Preformed Biaryl Bond Precursors.

Rafael Suau,[a,*] Juan Manuel López-Romero,[a] Rodrigo Rico,[a]
Francisco J. Alonso,[b] and Carolina Lobo[b]

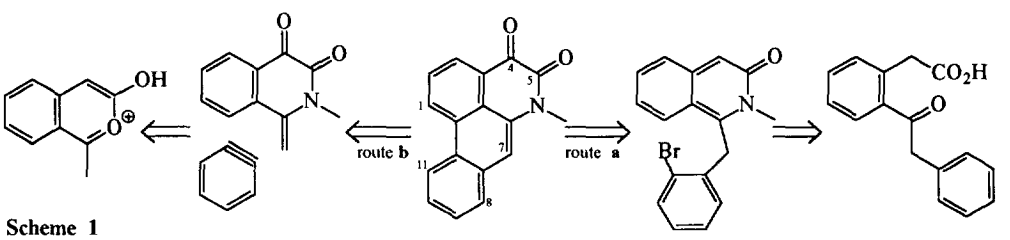
a) Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Málaga, E-29071 Málaga, Spain.

b) Departamento de Bioquímica y Biología Molecular, Facultad de Ciencias, Universidad de Málaga, E-29071 Málaga, Spain

Abstract: The synthesis of cepharadione-B and 2-demethoxy analogues is described. Starting from fluorenones, ring C was formed by cyclization of (biphenyl-2-yl)acetyl morpholines under Bischler-Napieralsky conditions. The photochemistry of chloroacetamides was used to form ring B. The cytotoxicity of these compounds on several tumor cell lines was evaluated.

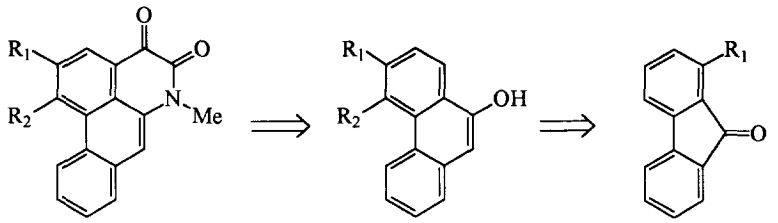
4,5-Dioxoaporphine alkaloids[1] constitute a class of highly oxidized aporphinoids that exhibit DNA-modifying bioactivity[2] and are chemically and biosynthetically related to aristolactams and aristolochic acids of recognized antitumoral activity.[3] Their functionality is also distinctive of 4,5-dioxo-1-azaaporphinoids (imbiline-type alkaloids)[1] and 3,4-dioxocularine alkaloids[4]. It has been suggested that these highly coloured alkaloids might act as post-infectional phytoalexins, with the reduced aporphines as the immediate precursors.[5] Their thermal and photochemical stability suggest that their antimicrobial activity might be related to their ability to act as singlet oxygen sensitizer.

The partial synthesis of dioxoaporphines has been accomplished by air oxidation[6] and direct[7] or sensitized photooxygenation[8] of dehydroaporphines (in yields below 15%), as well as by chemical oxidation (with iodine or DDQ) of 4-hydroxyaporphines.[9] The total synthesis of these alkaloids has been achieved by two different approaches (Scheme 1). One of them involves the biaryl bond formation in the last steps (route a) of the synthetic sequence. The photocyclization of 1-(2'-bromo-benzyl)isoquinoline-3-ones proceeds with moderate yield directly to the 4,5-dioxoaporphine.[10] Yields have been improved in the radical cyclization of these intermediates to give 5-oxodehydroaporphines that are readily oxidized to the 4,5-dioxoaporphines.[11] This approach is of interest when substituents at positions 1, 2, 9 and 10 of the aporphine nucleus are the same, since the key step in the preparation of the



Scheme 1

bromobenzylisoquinoline is the self condensation of the appropriately substituted phenylacetic acid. The second approach (route b) uses a more convergent synthetic scheme and is based on the formation of two strategic bonds in a single step. The intermolecular benzyne cycloaddition to *in situ* generated 1-methylene-3,4-dioxoisoquinolines gave acceptable yields for the dioxoaporphine.[12] Although the reaction exhibits good regioselectivity, it is specially useful for ring-D unsubstituted alkaloids; the overall yield depends on the accessibility of the isoquinoline component. An intramolecular aryne approach was recently developed, that failed in the cyclization of oxidized precursors, however.[13]



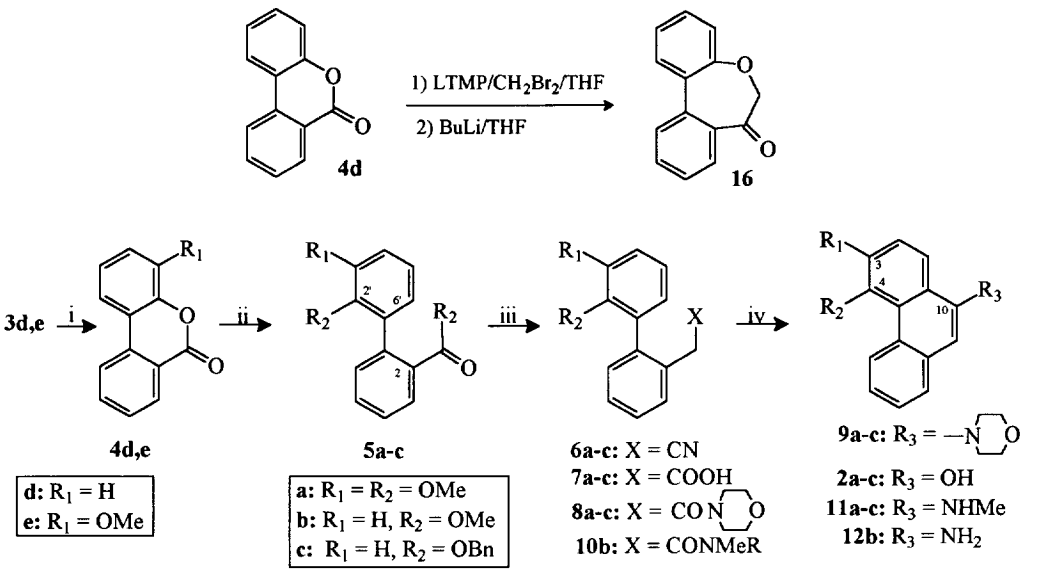
a: $R_1 = R_2 = OMe$
b: $R_1 = H$; $R_2 = OMe$
c: $R_1 = H$; $R_2 = OBn$
d: $R_1 = H$
e: $R_1 = OMe$

Scheme 2

We recently started a program aimed at testing the thermal, photochemical and biological properties of these alkaloids and their synthetic analogue. This paper reports on our exploratory work on the total synthesis of cepharadione-B (**1a**) and 2-demethoxy analogues (**1b,c**) by use of a new and simple approach based on fluorenones as the starting compounds (Scheme 2). The synthesis uses a cyclization related to the Bischler-Napieralsky reaction to assemble the phenanthrene ring system and the photocyclization of chloroacetamides to build up the isoquinolone fragment. Our preliminary results for the cytotoxic activity of these 4,5-dioxoaporphines against human and murine tumor cell lines are also reported.

Results and Discussion

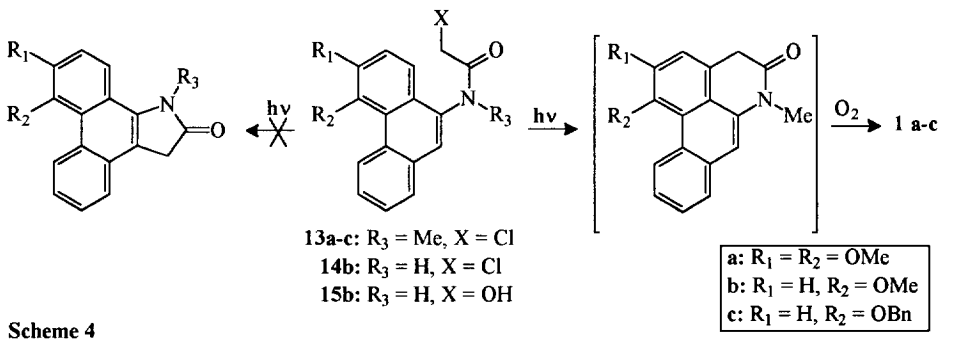
The synthesis of dioxoaporphines **1a-c** is depicted in Schemes 3 and 4; it started with the Baeyer-Villiger[14] oxidation of fluorenone **3d** and 1-methoxyfluorenone **3e**. The reaction was performed with sodium perborate in acetic acid,[15] and lactones **4d** and **4e** were obtained in excellent yield with the expected regioselectivity.[16] The heterocyclic oxygen introduced in this way became the oxygenated substituent at C-1 position of the target dioxoaporphines. Direct homologation of the lactone **4d** to the corresponding arylacetic acid via α-bromo α-keto dianion rearrangement[17] was attempted. However, the unrearranged 6,7-dihydro-dibenz[b,d]oxepin-6-one (**16**) was the only product isolated from the reaction mixture, as inferred from the carbonyl resonance (δ_C 203.7 ppm) and chemical shift for the methylene protons (δ_H 4.83 ppm) observed in the NMR spectra. Consequently, the conventional multistep homologation was selected. Opening of the lactone ring with potassium hydroxide in the presence of methyl iodide or benzyl bromide afforded the biphenyl carboxylates **5a-c**. In one pot reaction, the carboxylates were reduced to the benzyl alcohol, transformed to the benzyl chloride and substituted to the corresponding nitriles (**6a-c**).



Reagents: i) $NaBO_3.H_2O$/AcOH; ii) KOH/MeI or KOH/BnBr; iii) 1: $LiAlH_4$/THF 2: $SOCl_2$/TBME, 3: NaCN/ CH_3CN, 4: KOH/EtOH/H_2O, 5: C_6H_6/Py/$SOCl_2$ or $(COCl)_2$, 6: Et_3N/morpholine or 40% aq. $MeNH_2$; iv) 1: $POCl_3/C_6H_6/C_6H_5CH_3$, 2: 1M HCl/THF, 3: $NaHSO_3$/40% aq. $MeNH_2$ or conc. aq. NH_3.

Scheme 3

The cyclization to phenanthrenes proved more difficult than expected. Thus, the Hoesch condensation of **6b** was attempted, with both PPA and $ZnCl_2$/HCl; however, no cyclization to the phenanthrol **2b** was observed. Attempts at cyclizing the acids **7a-c**, as well as their acid chloride derivatives, under Friedel-Crafts conditions, also failed. However, the cyclization succeeded when the morpholine amides **8a-c** were treated with phosphoryl chloride (an analogue of the Bischler-Napieralsky reaction used by McLean[18] in the synthesis of dibenzoxepinones) and the 10-morpholinophenanthrenes **9a-c** were obtained in good yields. Unfortunately, the cyclization of the amide **10b** (R = H), which would allow direct access to the amine **11b**, did not occur. The morpholines **9a-c** were hydrolysed to the air sensitive phenanthrols **2a-c**. The Bucherer amination reaction[19] of the phenanthrols with methylamine or ammonia afforded the phenanthrylamines **11a-c** and **12b**, which were readily transformed to the



Scheme 4

corresponding chloroacetamides under Schotten-Baumann conditions.

Two products (Scheme 4) can be expected from the photochemistry of these chloroacetamides,[20] *viz.* that resulting from cyclization at C-1 to afford the desired aporphinoid lactam, or that involving the formation of a five member ring through C-10. In the former case, the photocyclization is known to occur via an electron transfer mechanism, so it exhibits a hight solvent sensitivity; in the latter case, an alternative mechanism is suspected to operate.[21] Since the formation of the new C-C bond at the *para* position of a methoxyl group is the preferred choice in aqueous solvents, **14b** was irradiated ($\lambda > 300$ nm) in acetonitrile-water. After 3 h, photosolvolysis to the hydroxyacetamide **15b** was the sole observed reaction. The absence of cyclization has occasionally been attributed to inefficient exciplex formation owing to geometrical restrictions.[21] However, the amide geometry can be changed on conversion from *N*-monosubstituted to tertiary amides. In fact, the irradiation of the N-methyl chloroacetamides **13a-c** proceeded as expected. The appearance of a strong yellow colour indicated the correct cyclization, followed by the air oxidation of the lactam intermediate to the 4,5-dioxo compounds **1a-c**, in 31, 60 and 57 % yields, respectively.

A thermal approach via the Bobbit modification of the Pomerantz-Fritz reaction as an alternative to the isoquinoline ring formation was also studied. However, no phenanthrene formation was observed when the amide **10b** [R = $CH_2CH(OMe)_2$] was treated with phosphoryl chloride.

The above results support this novel synthetic approach to 4,5-dioxoaporphinoids with the sequential formation of rings C and B. The synthesis of 4-alkoxy-10-phenanthrols from simple fluorenone precursors complements alternative choices.[22] Furthermore, the photochemical cyclization step requires a tertiary chloroacetamide, so it does not give access to the *N*-nor-4,5-dioxoaporphine alkaloids.

The results for the cytotoxicity of cepharadione-B (**1a**) and their 2-demethoxy analogues (**1b,c**) are shown in Table 1. The potency of these 4,5-dioxoaporphines as cytotoxic agents varied among the different cell lines tested. The compounds exhibited significant activity against both wild-type, and adriamycin-resistant P-388 cell lines, and were also active against H-29 human colon adenocarcinoma and the MDA-MB-231 human breast carcinoma cells.

Table 1. Cytotoxicity of 4,5-dioxoaporphines **1a-c**

Compound	IC_{50} (μg/ml) (48 h treatment)			
	Cell line			
	MDA	HT-29	P-388	SCHABEL
1a	6.1	6.1	2.1	2.9
1b	3.5	5.5	1.9	2.6
1c	3.3	10.0	2.0	2.5

The IC_{50} values obtained are consistent with those reported for artabotrine[2] and suggest that 4,5-dioxoaporphines may function as antineoplastic agents.

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 HP-MS 5988A and Kratos MS 50 spectrometers, respectively, both operating at 70 eV. NMR spectra were obtained on Bruker WP-200 SY instrument at 200 MHz for ^1H and 50 MHz for ^{13}C. ^1H Chemical shifts (δ_H) are given relative to either residual $CHCl_3$ (δ 7.24 ppm) in $CDCl_3$ or residual CHD_2SOCD_3 (δ 2.50 ppm) in DMSO-d_6. J values are in Hz. ^{13}C Chemical shifts (δ_C) are given relative to either $CDCl_3$ (δ 77.0 ppm) in $CDCl_3$ or CD_3SOCD_3 (δ 39.7 ppm) in DMSO-d_6. Irradiations were conducted with a 125 W medium-pressure mercury lamp (General Electric H125/27) in Pyrex tubes at RT. TLC analyses were performed on silica gel 60 F 256 plates, and column chromatography was carried out on silica gel 60 (70-230 mesh). 3'-Methoxy-biphenyl-2,2'-carbolactone (**4e**) and biphenyl-2,2'-carbolactone (**4d**) were prepared from 1-methoxy-9-fluorenone[23] (**3e**) and 9-fluorenone (**3d**), respectively, by oxidation with sodium perborate/acetic acid, following the procedure described by McKillop.[15]

Synthesis of biphenyl-2-carboxylates 5a-c:

To a mixture of powdered KOH (255 mmol) and methyl iodide (510 mmol) in acetonitrile (300 ml), the biphenyl carbolactone **4d,e** (51 mmol) was added. After stirring for 12 h at RT, the solvent was evaporated and H_2O added to the residue. Extraction with $CHCl_3$, drying the organic layer with $MgSO_4$ and evaporation, afforded compounds **5a,b**. Under identical conditions, the reaction of **4d** with benzyl bromide gave **5c.**

Methyl 2',3'-dimethoxy-biphenyl-2-carboxylate **5a**: Yield: 93%; yellowish syrup; ν (film) cm^{-1} 1730 (C=O); δ_H ($CDCl_3$) 7.89 (1H, dd, J=7.5 and 1.7, H-3), 7.52 (1H, ddd, J=7.5, 7.5 and 1.7, H-5), 7.37 (1H, ddd, J=7.5, 7.5 and 1.5, H-4), 7.34 (1H, dd, J=7.5 and 1.5, H-6), 7.08 (1H, t, J=7.7, H-5'), 6.92 (1H, dd, J=7.7 and 1.7, H-4'), 6.81 (1H, dd, J=7.7 and 1.7, H-6'), 3.88 (3H, s, 3'-OMe), 3.66 (3H, s, COOMe), 3.47 (3H, s, 2'-OMe); δ_C ($CDCl_3$) 168.2 (CO), 152.3 (C-3'), 145.9 (C-2'), 138.6, 135.8, 131.1 (C), 131.2, 131.2, 129.6, 127.2, 123.7, 121.9, 111.8 (CH), 60.2 (2'-OMe), 55.8 (3'-Ome), 51.8 (COO*Me*); *m/z* (%) 272 (M^+, 32), 241 (100); Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.56; H, 5.93%, found C, 70.09; H, 5.88.

Methyl 2'-methoxy-biphenyl-2-carboxylate **5b**: Yield: 95%; yellowish syrup; ν (film) cm^{-1} 1729 (C=O); δ_H ($CDCl_3$) 7.87 (1H, dd, J=7.6 and 1.4, H-3), 7.54 (1H, ddd, J=7.6, 7.6 and 1.4, H-5), 7.43-7.23 (4H, m, Ar-H), 7.04 (1H, ddd, J=7.4, 7.4 and 1.0, H-5'), 6.90 (1H, dd, J=7.4 and 1.0, H-3'), 3.71 (3H, s, OMe), 3.64 (3H, s, COOMe); δ_C ($CDCl_3$) 168.4 (CO), 155.9 (C-2'), 138.6, 131.5, 130.4 (C), 131.4, 131.2, 129.8, 129.2, 128.7, 126.9, 120.6, 110.0 (CH), 55.0 (OMe), 51.5 (COO*Me*); *m/z* (%) 242 (M^+, 74), 211 (100); Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.35; H, 5.83%, found C, 74.33; H, 5.85.

Benzyl 2'-benzyloxy-biphenyl-2-carboxylate **5c**: Yield: 83%, syrup that crystallized on standing; m.p. 74-76 °C; ν (KBr) cm^{-1} 1718 (C=O); δ_H ($CDCl_3$) 7.97 (1H, d, J=7.5, H-3), 7.6-6.8 (16H, m, Ar-H), 6.87 (1H,

d, J=8.2, H-3'), 5.05 (2H, s, OCH_2Bn), 4.88 (2H, s, CO_2CH_2Bn); δ_C ($CDCl_3$) 167.7 (CO), 155.3 (C-2'), 139.2, 137.1, 135.6, 131.6, 131.3 (C), 131.5, 131.5, 130.0, 129.7, 128.6, 128.2, 128.1, 127.8, 127.4, 127.1, 126.6, 121.1, 112.6 (CH), 70.1 (OCH_2Bn), 66.5 (CO_2CH_2Bn); *m/z* (%) 394 (M^+, 2), 303 (11), 91 (100); Anal. Calcd. for $C_{27}H_{22}O_3$: C, 82.21; H, 5.62%, found C, 82.30; H, 5.82.

Homologation reaction. Synthesis of 6a-c:

A N_2 purged solution of **5a-c** (45 mmol) in dry THF (120 ml), was supplied with $LiAlH_4$ (68 mmol) in small portions over a period of 30 min. After stirring the reaction medium for 1 h at RT, excess hydride was decomposed by the addition of 1M H_2SO_4, and the resulting suspension treated with more dilute acid and extracted with TBME. The extract was carefully dried ($MgSO_4$) and the volume reduced to 50 ml. This ether solution was ice cooled and thionyl chloride (68 mmol) was added dropwise. The mixture was stirred at RT for 30 min. TBME and excess thionyl chloride were removed in vacuo without heating. The crude products were dissolved in acetonitrile (400 ml), NaCN (450 mmol) was added and the mixture refluxed for 48 h. After evaporation of the solvent, the residue was dissolved in H_2O, extracted with $CHCl_3$ and dried over $MgSO_4$, and concentrated under reduced pressure to give the corresponding cyanides, **6a-c**.

***(2',3'-Dimethoxy)biphenyl-2-yl acetonitrile* 6a**: Yield: 82%; yellowish syrup; ν (film) cm^{-1} 2255 (CN); δ_H ($CDCl_3$) 7.6-7.2 (4H, m, Ar-H), 7.13 (1H, t, J=8.0, H-5'), 6.97 (1H, dd, J=8.0 and 1.4, H-4'), 6.78 (1H, dd, J=8.0 and 1.4, H-6'), 3.90 (3H, s, 3'-OMe), 3.79 (1H, d, J=18.5, *H*CH), 3.50 (1H, d, J=18.5, HC*H*), 3.46 (3H, s, 2'-OMe); δ_C ($CDCl_3$) 152.8 (C-3'), 145.9 (C-2'), 137.6, 134.0, 129.1 (C), 118.3 (CN), 130.3, 128.1, 127.9, 127.7, 124.5, 122.6, 112.1 (CH), 60.7 (2'-OMe), 55.8 (3'-OMe), 21.8 (CH_2); *m/z* (%) 253 (M^+, 100), 238 (57), 210 (37); Anal. Calcd. for $C_{16}H_{15}NO_2$: 75.86; H, 5.97; N, 5.53%, found C, 75.69; H, 6.09; N, 5.53.

***(2'-Methoxy)biphenyl-2-yl acetonitrile* 6b**: Yield: 95%; yellowish syrup; ν (film) cm^{-1} 2257 (CN); δ_H ($CDCl_3$) 7.6-6.9 (8H, m, Ar-H), 3.78 (3H, s, OMe), 3.63 (1H, d, J=18.7, *H*CH), 3.47 (1H, d, J=18.7, HC*H*); δ_C ($CDCl_3$) 156.1 (C-2'), 138.2, 129.2, 128.5 (C), 118.4 (CN), 131.1, 130.7, 129.6, 128.1, 128.0, 128.0, 120.9, 110.7 (CH), 55.3 (OMe), 21.6 (CH_2); *m/z* (%) 223 (M^+, 100), 208 (82), 190 (62); HRMS calcd. for $C_{15}H_{13}NO$ (M^+) *m/z* 223.0997, found 223.1000; Anal. Calcd. for $C_{15}H_{13}NO$: C, 80.68; H, 5.87; N, 6.28%, found C, 80.19; H, 5.91; N, 6.54.

***(2'-Benzyloxy)biphenyl-2-yl acetonitrile* 6c**: Yield: 88%; white syrup that crystallized on standing; m.p. 40-41 °C; ν (Kbr) cm^{-1} 2255 (CN); δ_H ($CDCl_3$) 7.6-7.0 (13H, m, Ar-H), 5.09 (1H, d, J=11, *H*CHBn), 5.00 (1H, d, J=11, HC*H*Bn), 3.67 (1H, d, J=18.6, *H*CHCN), 3.49 (1H, d, J=18.6, HC*H*CN); δ_C ($CDCl_3$) 155.3 (C-2'), 138.2, 136.7, 129.2 (C), 118.3 (CN), 131.1, 130.7, 129.5, 128.4, 128.0, 127.9, 127.7, 126.7, 121.5, 113.3 (CH), 70.4 (CH_2Bn), 21.8 (CH_2CN); *m/z* (%) 299 (M^+, 6), 91 (100); Anal. Calcd. for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N 4.68%, found C, 83.73; H, 5.77; N 4.76.

Synthesis of 4-(biphenyl-2-yl)acetyl morpholines 8a-c

To a solution of **6a-c** (36.3 mmol) in ethanol (400 ml), KOH (363 mmol) and water (170 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.

(2',3'-Dimethoxy)biphenyl-2-yl acetic acid **7a**: Yield: 93%; white solid; m.p. 89-91 °C ($CHCl_3$); ν (KBr) cm^{-1} 3600-2400 (OH), 1707 (C=O); δ_H ($CDCl_3$) 7.5-7.2 (4H, m, Ar-H), 7.09 (1H, t, J=7.8, H-5'), 6.94 (1H, dd, J=7.8 and 1.5, H-4'), 6.72 (1H, dd, J=7.8 and 1.5, H-6'), 3.88 (3H, s, 3'-OMe), 3.52 (3H, s, 2'-OMe), 3.37 (2H, s, CH_2); δ_C ($CDCl_3$) 174.9 (CO), 152.7 (C-3'), 145.7 (C-2'), 138.0, 135.3, 133.7 (C), 130.1, 129.4, 128.1, 126.8, 124.4, 122.7, 111.9 (CH), 60.7 (2'-OMe), 55.7 (3'-OMe), 40.7 (CH_2); *m/z* (%) 272 (M^+, 32), 271 (66), 228 (18), 196 (79), 195 (100); Anal. Calcd. for $C_{16}H_{16}O_4$ 1/2 H_2O: C, 68.30; H, 6.10%, found C, 68.65; H, 6.14.

(2'-Methoxy)biphenyl-2-yl acetic acid **7b**: Yield: 94%; colourless crystals; m.p. 140-141 °C (ether); ν (KBr) cm^{-1} 3400-2200 (OH), 1705 (C=O); δ_H ($CDCl_3$) 9.7 (1H, br s, COOH), 7.5-6.9 (8H, m, Ar-H), 3.73 (1H, d, J=16.8, *H*CH), 3.71 (3H, s, OMe), 3.49 (1H, d, J=16.8, HC*H*); δ_C ($CDCl_3$) 177.5 (CO), 156.2 (C-2'), 138.8, 132.4, 129.8 (C), 131.2, 130.3, 130.0, 128.9, 127.4, 127.1, 120.5, 110.4 (CH), 54.9 (OMe), 38.5 (CH_2); *m/z* (%) 242 (M^+, 73), 224 (35), 198 (31), 165 (100); HRMS calcd. for $C_{15}H_{14}O_3$ (M^+) *m/z* 242.0943, found 242.0940; Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.35; H, 5.83%, found C, 74.60; H, 5.87.

(2'-Benzyloxy)biphenyl-2-yl acetic acid **7c**: Yield: 85%; colourless prisms; m.p. 95-97 °C (MeOH); ν (film) cm^{-1} 3475-2400 (OH), 1707 (C=O); δ_H ($CDCl_3$) 7.4-6.9 (13H, m, Ar-H), 4.98 (2H, s, CH_2Bn), 3.50 (2H, s, CH_2COOH); δ_C ($CDCl_3$) 177.7 (CO), 155.4 (C-2'), 138.9, 137.0, 132.3, 130.4 (C), 131.4, 130.5, 129.8, 128.9, 128.3, 127.5, 127.4, 127.1, 126.5, 121.1, 113.1 (CH), 70.1 (CH_2Bn), 38.7 (CH_2COOH); *m/z* (%) 318 (M^+, 4), 300 (9), 91 (100); Anal. Calcd. for $C_{21}H_{18}O_3$ 1/6 H_2O: C, 78.48; H, 5.75%, found C, 78.28; H, 5.83.

Over an ice cooled solution of compound **7a-c** (12.4 mmol) and pyridine (1 ml) in benzene (200 ml), thionyl chloride (248 mmol) (oxalyl chloride for **7a**) was added dropwise. The ice-bath was removed and the mixture stirred at RT for 45 min. The solvent and excess reagent were distilled and the resulting acid chloride was dissolved in $CHCl_3$ (5 ml). This solution was added to a cooled mixture of morpholine (124 mmol), triethylamine (4.6 ml) and $CHCl_3$ (50 ml) with stirring. The reaction mixture was stirred at RT for 30 min and washed sequentially with 1M NaOH, 1M HCl, and water. The organic solution was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by crystallization.

4-(2',3'-Dimethoxybiphenyl-2-yl)acetyl morpholine **8a**: Yield: 85%; white solid; m.p. 78-80 °C (MeOH); ν (KBr) cm^{-1} 1643 (C=O); δ_H ($CDCl_3$) 7.4-7.2 (4H, m, Ar-H), 7.06 (1H, t, J=7.8, H-5'), 6.9-6.7 (2H, m, Ar-H), 3.86 (3H, s, OMe), 3.67-3.09 (10H, m, morpholine-H, CH_2CO), 3.45 (3H, s, OMe); δ_C ($CDCl_3$) 170.0 (CO), 152.5, 145.9 (C-2', C-3'), 137.6, 135.1, 133.7 (C), 129.9, 128.4, 127.6, 126.3, 124.0, 122.8, 111.4

(CH), 66.5, 66.2 (CH_2OCH_2), 60.5 (OMe), 55.6 (OMe), 46.0, 41.8 (CH_2NCH_2), 37.9 (CH_2); *m/z* (%) 341 (M^+, 49), 310 (23), 227 (78), 209 (75), 196 (75), 195 (96), 114 (100); Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.35; H, 6.79; N 4.10%, found C, 70.22; H, 6.83; N 4.00.

***4-(2'-Methoxybiphenyl-2-yl)acetyl morpholine* 8b**: Yield: 99%; white needles; m.p. 111-113 °C (EtOH); ν (KBr) cm^{-1} 1639 (C=O); δ_H ($CDCl_3$) 7.4-6.9 (8H, m, Ar-H), 3.73 (3H, s, OMe), 3.7-3.0 (8H, m, morpholine-H), 3.59 (1H, d, J=14.0, *H*CHCO), 3.43 (1H, d, J=14.0, HC*H*CO); δ_C ($CDCl_3$) 169.6 (CO), 155.9 (C-2'), 137.6, 133.4, 128.9 (C), 130.6, 130.0, 128.7, 127.8, 127.2, 126.2, 120.2, 110.3 (CH), 66.1, 65.8 (CH_2OCH_2), 54.8 (OMe), 45.5, 41.5 (CH_2NCH_2), 37.9 (*C*H_2CO); *m/z* (%) 311 (M^+, 17), 197 (18), 182 (18), 165 (30), 114 (100); HRMS calcd. for $C_{19}H_{21}NO_3$ (M^+) *m/z* 311.1521, found 311.1517.

***4-(2'-Benzyloxybiphenyl-2-yl)acetyl morpholine* 8c**: Yield: 82%; colourless solid; m.p. 96-98 °C (MeOH); ν (KBr) cm^{-1} 1643 (C=O); δ_H ($CDCl_3$) 7.4-7.0 (13H, m, Ar-H), 4.99 (2H, s, C*H*$_2$Bn), 3.6-3.4 (6H, m, CH_2CO, CH_2OCH_2), 3.1-2.9 (4H, m, CH_2NCH_2); δ_C ($CDCl_3$) 170.0 (CO), 155.3 (C-2'), 138.0, 136.6, 133.7, 129.2 (C), 129.0, 131.1, 130.3, 128.3, 127.8, 127.6, 126.6, 126.5, 121.2, 112.9 (CH), 70.2 (*C*H_2Bn), 66.4, 66.0 (CH_2OCH_2), 45.9, 41.7 (CH_2NCH_2), 38.5 (*C*H_2CO); *m/z* (%) 387 (M^+, 1), 181 (40), 91 (100); Anal. Calcd. for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.70; N 3.45%, found C, 74.35; H, 6.30; N 3.29.

Cyclization to 4-(10-phenanthryl)morpholines 9a-c

A mixture of the amides **8a-c** (11.7 mmol), dry toluene (34 ml), dry benzene (16 ml) and phosphoryl chloride (117 mmol) was refluxed for 1 h. The cold mixture was diluted with ether and a 1M NaOH aqueous solution was added. The organic layer was washed with water, dried over anhydrous $MgSO_4$ and concentrated in vacuo. Compound **9c** was purified by column chromatography (SiO_2, 20:2 hexane-EtOAc as eluent).

***4-[10-(3,4-Dimethoxy)phenanthryl]morpholine* 9a**: Yield: 74%; amorphous solid; λ ($CHCl_3$) nm (log ϵ): 366 (3.28), 348 (3.35), 318 (4.01), 262 (4.59); δ_H ($CDCl_3$) 9.58 (1H, m, H-5), 8.16 (1H, d, J=9.0, H-1), 7.34 (1H, d, J=9.0, H-2), 7.77 (1H, m, H-8), 7.54 (2H, m, H-6, -7), 7.16 (1H, s, H-9), 4.03 (3H, s, OMe), 3.95 (3H, s, OMe), 3.95-4.03 (4H, m, CH_2OCH_2), 3.13 (4H, br s, CH_2NCH_2); δ_C ($CDCl_3$) 151.5, 147.3, 147.1 (C-3, C-4, C-10), 133.4, 127.3, 126.1, 124.5 (C), 127.6, 127.5, 126.6, 125.3, 120.2, 113.2, 112.3 (CH), 67.3 (CH_2OCH_2), 59.7 (OMe), 56.3 (OMe), 53.3 (CH_2NCH_2); *m/z* (%) 323 (M^+, 100), 322 (26), 308 (26); HRMS calcd. for $C_{20}H_{21}NO_3$ (M^+) *m/z* 323.1521, found 323.1527.

***4-[10-(4-Methoxy)phenanthryl]morpholine* 9b**: Yield: 75%; colourless prisms; 139-140 °C ($CHCl_3$); λ (MeOH) nm (log ϵ): 358 (3.06), 342 (3.03), 308 (3.79), 244 (4.18); δ_H ($CDCl_3$) 9.56 (1H, m, H-5), 8.03 (1H, d, J=8.0, H-1), 7.78 (1H, m, H-8), 7.58-7.49 (3H, m, Ar-H), 7.31 (1H, s, H-9), 7.16 (1H, d, J=8.0, H-3), 4.11 (3H, s, OMe), 3.99 (4H, br t, CH_2OCH_2), 3.14 (4H, br s, CH_2NCH_2); δ_C ($CDCl_3$) 159.2 (C-4), 147.1 (C-10), 131.2, 127.9, 122.2 (C), 128.4, 127.5, 126.3, 126.1, 125.2, 116.5, 115.6, 108.5 (CH), 67.4 (CH_2OCH_2), 55.7 (OMe), 53.3 (CH_2NCH_2); *m/z* (%) 293 (M^+, 100), 235 (31), 204 (19), 165 (23), 114 (28); HRMS calcd. for $C_{19}H_{19}NO_2$ (M^+) *m/z* 293.1416, found 293.1416.

***4-[10-(4-Benzyloxy)phenanthryl]morpholine* 9c**: Yield: 66%; colourless crystals; m.p. 126-127 °C (hexane-EtOAc); λ ($CHCl_3$) nm (log ε): 360 (3.34), 342 (3.36), 312 (3.92), 272 (4.19); δ_H ($CDCl_3$) 9.70 (1H, d, J=8.3, H-5), 8.10 (1H, d, J=7.7, H-1), 7.82 (1H, d, J=8.3, H-8), 7.6-7.4 (8H, m, Ar-H), 7.36 (1H, s, H-9), 7.23 (1H, d, J=7.7, H-3), 5.38 (2H, s, CH_2Bn), 4.03 (4H, br t, CH_2OCH_2), 3.18 (4H, br s, CH_2NCH_2); δ_C ($CDCl_3$) 158.1 (C-4), 147.0 (C-10), 136.8, 132.8, 131.3, 127.9, 122.5 (C), 128.6, 128.5, 128.0, 127.6, 127.5, 126.2, 126.0, 125.2, 116.9, 115.6, 110.1 (CH), 71.2 (*C*H_2Bn), 67.4 (CH_2OCH_2), 53.3 (CH_2NCH_2); *m/z* (%) 369 (M^+, 59), 278 (100), 91 (37); HRMS calcd. for $C_{25}H_{23}NO_2$ (M^+) *m/z* 369.1729, found 369.1729.

Synthesis of 10-phenanthrols 2a-c

A solution of the amines **9a-c** (8.5 mmol) in THF (90 ml) and 1M HCl (70 ml) was heated at 60 °C for 12 h. After cooling, TBME was added and the organic layer washed with H_2O, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The phenanthrols obtained were manipulated under an N_2 atmosphere to prevent oxidation to the quinone.

***3,4-Dimethoxy-10-phenanthrol* 2a**: Yield: 87%; amorphous reddish solid; 160-163 °C ($CHCl_3$); ν (KBr) cm^{-1} 3379 (OH); δ_H ($CDCl_3$) 9.51 (1H, m, H-5), 8.11 (1H, d, J=9.0, H-1), 7.34 (1H, d, J=9.0, H-2), 7.63 (1H, m, H-8), 7.52-7.40 (2H, m, H-6, -7), 6.85 (1H, s, H-9), 4.03 (3H, s, OMe), 3.93 (3H, s, OMe); δ_C ($CDCl_3$) 151.9, 149.5, 146.8 (C-3, C-4, C-10), 133.9, 126.0, 125.8, 121.8 (C), 127.6, 126.7, 126.4, 124.0, 118.9, 112.3, 104.8 (CH), 59.7 (OMe), 56.3 (OMe); *m/z* 254 (M^+, 100), 239 (50); HRMS calcd. for $C_{16}H_{14}O_3$ (M^+) *m/z* 254.0943, found 254.0942.

***4-Methoxy-10-phenanthrol* 2b**: Yield: 74%; amorphous reddish solid; m.p. 153-155 °C ($CHCl_3$); ν (KBr) cm^{-1} 3361 (OH); δ_H ($CDCl_3$) 9.52 (1H, m, H-5), 8.01 (1H, dd, J=7.8 and 0.8, H-1), 7.63 (1H, m, H-8), 7.53 (1H, t, J=7.8, H-2), 7.46-7.40 (2H, m, H-6, -7), 7.23 (1H, s, OH), 7.16 (1H, dd, J=7.8 and 0.8, H-3), 7.05 (1H, s, H-9), 4.09 (3H, s, OMe); δ_C ($CDCl_3$+CD_3OD) 158.8, 148.9 (C-4, C-10), 132.9, 127.9, 126.7, 121.9 (C), 128.5, 126.5, 126.4, 126.2, 124.1, 114.7, 109.1, 107.3 (CH), 55.7 (OMe); *m/z* (%) 224 (M^+, 100), 209 (20), 181 (40); HRMS calcd. for $C_{15}H_{12}O_2$ (M^+) *m/z* 224.0837, found 224.0838.

***4-Benzyloxy-10-phenanthrol* 2c**: Yield: 67%; amorphous reddish solid; m.p. 124-127 °C ($CHCl_3$); ν (KBr) cm^{-1} 3375 (OH); δ_H ($CDCl_3$+CD_3OD) 9.59 (1H, d, J=8.4, H-5), 8.02 (1H, d, J=8.4, H-1), 7.65-7.19 (10H, m, Ar-H), 7.02 (1H, s, H-9), 5.33 (2H, s, CH_2Bn); δ_C ($CDCl_3$+CD_3OD) 157.6, 150.1 (C-4, C-10), 136.8, 133.5, 128.6, 122.0 (C), 128.5, 127.9, 127.6, 126.1, 126.1, 125.9, 123.4, 115.4, 110.5, 106.5 (CH), 71.1 (*C*H_2Bn); *m/z* (%) 300 (M^+, 34), 209 (9), 91 (100); HRMS calcd. for $C_{21}H_{16}O_2$ (M^+) *m/z* 300.1150, found 300.1156.

Synthesis of phenanthrylamines 11a-c and 12b

A stirred mixture of phenanthrols **2a-c** (3.6 mmol), 40% aq. sodium bisulfite (8.6 ml) and 40% aq. methylamine (36 mmol) was heated at 150 °C in a sealed tube for 18 h. The reaction mixture was cooled and extracted with ether, the organic layer being washed (1M NaOH and H_2O), dried over anhydrous $CaCl_2$ and evaporated in vacuo.

10-N-Methylamino-3,4-dimethoxy phenanthrene **11a**: Yield: 62%; amorphous yellow solid; ν (KBr) cm^{-1} 3445 (NH); δ_H ($CDCl_3$) 9.47 (1H, dd, J=7.8 and 1.5, H-5), 7.65 (1H, dd, J=7.8 and 1.5, H-8), 7.60-7.24 (4H, m, Ar-H), 6.64 (1H, s, H-9), 3.99 (3H, s, OMe), 3.91 (3H, s, OMe), 3.04 (3H, s, NMe); δ_C ($CDCl_3$) 151.5, 147.6, 141.9 (C-3, C-4, C-10), 134.8, 125.7, 124.7, 121.8 (C), 127.7, 126.8, 126.4, 122.9, 116.2, 112.0, 101.3 (CH), 59.7 (OMe), 56.3 (OMe), 31.1 (NMe); *m/z* (%) 267 (M^+, 100), 252 (37), 237 (17), 209 (34); HRMS calcd. for $C_{17}H_{17}NO_2$ (M^+) *m/z* 267.1259, found 267.1259.

10-N-Methylamino-4-methoxy phenanthrene **11b**: Yield: 88%; brownish syrup; ν (film) cm^{-1} 3447 (NH); δ_H ($CDCl_3$) 9.59 (1H, dd, J=8.4 and 1.3, H-5), 7.79 (1H, dd, J=8.4 and 1.7, H-8), 7.53 (4H, m, Ar-H), 7.15 (1H, dd, J=7.8 and 1.7, H-3), 6.85 (1H, s, H-9), 4.09 (3H, s, OMe), 3.04 (3H, s, NMe); δ_C ($CDCl_3$) 159.3 (C-4), 141.8 (C-10), 134.1, 128.0, 125.1, 121.4 (C), 128.3, 126.3, 126.2, 126.1, 122.7, 112.6, 108.5, 103.3 (CH), 55.5 (OMe), 31.0 (NMe); *m/z* (%) 237 (M^+, 100%), 222 (22), 207 (14); HRMS calcd. for $C_{16}H_{15}NO$ (M^+) *m/z* 237.1154, found 237.1152.

10-N-Methylamino-4-benzyloxy phenanthrene **11c**: Yield: 62%, brown syrup; ν (film) cm^{-1} 3420 (NH); δ_H ($CDCl_3$) 9.76 (1H, d, J=8.5, H-5), 7.89 (1H, d, J=8.5, H-8), 7.8-7.3 (10H, m, Ar-H), 7.00 (1H, s, H-9), 5.53 (2H, s, CH_2Bn), 3.24 (3H, s, NMe); δ_C ($CDCl_3$) 158.4 (C-4), 141.8 (C-10), 136.8, 134.1, 128.2, 125.1, 121.8 (C), 128.6, 128.5, 128.0, 127.6, 126.4, 126.2, 122.8, 113.0, 110.3, 103.5 (CH), 71.2 (CH_2Bn), 31.3 (NMe); *m/z* (%) 313 (M^+, 37), 222 (49), 91 (100); HRMS calcd. for $C_{22}H_{19}NO$ (M^+) *m/z* 313.1467, found 313.1466.

10-Amino-4-methoxy-phenanthrene **12b**: Yield: 96%; brown syrup; δ_H ($CDCl_3$) 9.59 (1H, m, H-5), 7.67 (1H, m, H-8), 7.55-7.47 (4H, m, Ar-H), 7.16 (1H, m, H-3), 6.97 (1H, s, H-9), 4.08 (3H, s, OMe), 4.05 (2H, br s, NH_2); δ_C ($CDCl_3$) 159.2 (C-4), 139.4 (C-10), 133.5, 127.9, 121.5 (C), 128.4, 126.2, 126.1, 126.0, 123.2, 113.7, 109.0, 108.6 (CH), 55.6 (OMe); *m/z* (%) 223 (M^+, 100), 208 (18), 180 (41); HRMS calcd. for $C_{15}H_{13}NO$ (M^+) *m/z* 223.0997, found 223.0998.

Synthesis of 10-phenanthryl chloroacetamides 13a-c and 14b

An ice cooled mixture of 10% aq. NaOH (1.6 ml) and a dichloromethane solution (6 ml) of the amines **11a-c** and **12b** (2.5 mmol) was stirred while chloroacetyl chloride (3 mmol) in dichloromethane (4 ml) was added dropwise. The mixture was stirred for a further hour at RT and diluted with CH_2Cl_2. The organic layer was washed with H_2O, dried over anhydrous $MgSO_4$ and concentrated in vacuo. Chloroacetamide **13a** was purified by TLC (SiO_2, 20:0.2 CH_2Cl_2-MeOH as eluent).

10-N-Methyl-chloroacetamido-3,4-dimethoxy phenanthrene **13a**: Yield: 59%; white solid; m.p. 128-130 °C (CH_2Cl_2); ν (KBr) cm^{-1} 1676 (C=O); λ ($CHCl_3$) nm (log ϵ) 362 (2.97), 344 (3.11), 306 (3.75), 280 (3.90), 260 (4.31); δ_H ($CDCl_3$) 9.64 (1H, dd, J=7.5 and 1.9, H-5), 7.82 (1H, dd, J=7.5 and 1.9, H-8), 7.74-7.55 (3H, m, Ar-H), 7.54 (1H, s, H-9), 7.38 (1H, d, 1H, J=9.0, H-1), 4.03 (3H, s, OMe), 3.92 (1H, d, J=13.4, *H*CH), 3.74 (1H, d, J=13.4, HC*H*), 3.97 (3H, s, OMe), 3.40 (3H, s, NMe); δ_C ($CDCl_3$) 167.1 (CO), 152.5, 147.6 (C-3, C-4), 136.8 (C-10), 132.0, 129.7 126.3, 124.0 (C), 128.7, 127.9, 127.3, 125.2, 118.9, 113.6 (CH), 59.8 (OMe), 56.4 (OMe), 41.7 (CH_2), 37.6 (NMe); *m/z* (%) 345 (M^+, 31), 343 (M^+, 90), 254 (100);

HRMS calcd. for $C_{19}H_{18}NO_3{}^{35}Cl$ (M^+) *m/z* 343.0975, found 343.0970.

10-N-Methyl-chloroacetamido-4-methoxy phenanthrene **13b**: Yield: 98%, brown solid; m.p. 216-218 °C (MeOH); ν (KBr) cm^{-1} 1677 (C=O); λ (EtOH) nm (log ϵ) 356 (3.08), 340 (3.13), 276 (4.21), 246 (4.28); δ_H ($CDCl_3$) 9.67 (1H, d, *J*=8.5, H-5), 7.87 (1H, dd, *J*=7.6 and 1.8, H-8), 7.8-7.6 (2H, m, H-6 ,-7), 7.73 (1H, s, H-9), 7.62 (1H, t, *J*=8.1, H-2), 7.44 (1H, d, *J*=8.1, H-1), 7.25 (1H, d, *J*=8.1, H-3), 4.16 (3H, s, OMe), 3.90 (1H, d, *J*=13.3, *H*CH), 3.74 (1H, d, *J*=13.3, HC*H*), 3.42 (3H, s, NMe); δ_C ($CDCl_3$) 167.2 (CO), 159.4 (C-4), 136.7 (C-10), 131.4, 130.8, 130.4, 122.2 (C), 128.7, 128.6, 128.0, 127.9, 127.8, 126.7, 115.0, 109.5 (CH), 55.9 (OMe), 41.8 (CH_2), 37.6 (NMe); *m/z* (%) 315 (M^+, 7), 313 (M^+, 36), 224 (88), 195 (29), 165 (22), 152 (37), 90 (100); HRMS calcd. for $C_{18}H_{16}NO_2{}^{35}Cl$ (M^+) *m/z* 313.0870, found 313.0871.

10-N-Methyl-chloroacetamido-4-benzyloxy phenanthrene **13c**: Yield: 90%; solid foam; m.p. 74-75 °C; ν (KBr) cm^{-1} 1674 (C=O); λ ($CHCl_3$) nm (log ϵ) 374 (3.03), 358 (3.11), 340 (3.18), 278 (3.91), 256 (4.05); δ_H ($CDCl_3$) 9.73 (1H, m, H-5), 7.86 (1H, m, H-8), 7.74 (1H, s, H-9), 7.7-7.4 (9H, m, Ar-H), 7.31 (1H, d, *J*=7.9, H-3), 5.42 (2H, s, CH_2Bn), 3.90 (1H, d, *J*=13.4, *H*CHCl), 3.73 (1H, d, *J*=13.4, HC*H*Cl), 3.42 (3H, s, NMe); δ_C ($CDCl_3$) 167.2 (CO), 158.4 (C-4), 136.7 (C-10), 136.3, 131.5, 130.9, 130.3, 122.4 (C), 128.9, 128.8, 128.8, 128.6, 128.3, 128.0, 127,9, 127.9, 127.7, 127.7, 126.7, 115.3, 111.0 (CH), 71.4 (*C*H_2Bn) 41.8 (CH_2Cl), 37.6 (NMe); *m/z* (%) 391 (M^+, 5), 389 (M^+, 15), 340 (1), 300 (17), 165 (13), 152 (7), 91 (100); HRMS calcd. for $C_{24}H_{20}NO_2{}^{35}Cl$ (M^+) *m/z* 389.1183, found 389.1172.

10-Chloroacetamido-4-methoxy phenanthrene **14b**: Yield: 98%; white solid; m.p. 232 °C ($CHCl_3$); ν (KBr) cm^{-1} 3260 (NH), 1668 (C=O); λ (EtOH) nm (log ϵ) 358 (3.17), 340 (3.21), 304 (3.93), 276 (4.23), 242 (4.27), 214 (4.17); δ_H ($CDCl_3$+CD_3OD) 9.50 (1H, m, H-5), 7.92 (1H, s, H-9), 7.72 (1H, m, H-8), 7.53-7.39 (4H, m, Ar-H), 7.12 (1H, m, H-3), 4.21 (2H, s, CH_2), 4.00 (3H, s, OMe); δ_C ($CDCl_3$+CD_3OD) 166.1 (CO), 158.9 (C-4), 131.4 (C-10), 129.8, 128.9, 128.9, 121.5 (C), 128.1, 128.0 126.7, 126.3, 126.0, 123.9, 113.9, 108.7 (CH), 55.4 (OMe), 42.6 (CH_2); *m/z* (%) 301 (M^+, 30) 299 (M^+, 100), 224 (26), 223 (24), 195 (43); HRMS calcd. for $C_{17}H_{14}NO_2{}^{35}Cl$ (M^+) *m/z* 299.0713, found 299.0708.

Irradiation of *N*-methyl-10-phenanthryl chloroacetamides 13a-c. Synthesis of 4,5-dioxoaporphines 1a-c

A non-degassed solution of the chloroacetamide **15a-c** (0.2 mmol) in 30% aqueous methanol or 30% aqueous acetonitrile (50 ml) was irradiated until a deep yellow colour developed (4h approximately). The solvent was evaporated and the residue purified by preparative TLC (SiO_2, 20:1 CH_2Cl_2-MeOH as eluent).

Cepharadione-B **1a**: Yield: 31%; orange crystals; m.p. 257-260 °C (EtOH) (lit.[24] 266-268).

2-Demethoxy-cepharadione-B **1b**: Yield: 60%; amorphous orange powder; m.p. 255-257 °C (EtOH); ν (KBr) cm^{-1} 1653 (C=O); λ (EtOH) nm (log ϵ) 398 (2.57), 308 (2.74), 276 (2.92), 240 (3.18), 214 (3.30); δ_H (DMSO-d_6) 9.40 (1H, m, H-11), 8.45 (1H, d, *J*=8.7, H-3), 8.08 (1H, m, H-8), 7.91 (1H, s, H-7), 7.75-7.60 (2H, m, H-9, -10), 7.60 (1H, d, *J*=8.7, H-2), 4.24 (3H, s, OMe), 3.68 (3H, s, NMe); δ_C (DMSO-d_6) 174.7 (C-4), 164.6, 156.0 (C-1, C-5), 131.9, 131.8 (C-6a, C-7a), 126.2, 124.2, 120.8, 118.5 (C), 130.9, 129.1,

127.6, 127.2, 127.1 (CH), 115.8 (C-7), 111.3 (C-2), 56.8 (OMe), 30.4 (NMe); *m/z* (%) 291 (M^+, 100), 263 (98), 248 (31), 220 (44); HRMS calcd. for $C_{18}H_{13}NO_3$ (M^+) *m/z* 291.0895, found 291.0895.

1-Benzyloxy-2-demethoxy-cepharadione-B **1c**: Yield: 57%; yellow needles; 279-280 °C ($CHCl_3$); ν (KBr) cm^{-1} 1655 (C=O); λ (EtOH) nm (log ϵ) 400 (2.70), 308 (2.90), 276 (3.10), 248 (3.32); δ_H ($CDCl_3$) 9.54 (1H, d, *J*=7.9, H-11), 8.66 (1H, d, *J*=8.6, H-3), 7.92 (1H, d, *J*=7.9, H-8), 7.66 (1H, s, H-7), 7.6-7.3 (8H, m, Ar-H), 5.54 (2H, s, CH_2), 3.86 (3H, s, NMe); δ_C ($CDCl_3$) 175.2 (C-4), 164.1, 156.7 (C-1, C-5), 135.0 (C-1'), 131.9, 131.8 (C-6a, C-7a), 127.1, 124.9, 121.2, 119.8 (C), 131.5, 129.0, 129.0, 128.8, 128.3, 128.0, 128.0, 127.4, 127.4 (CH), 115.8 (C-7), 111.7 (C-2), 71.9 (CH_2), 30.6 (NMe); *m/z* (%) 367 (M^+, 10), 339 (1), 91 (100); HRMS calcd. for $C_{24}H_{17}NO_3$ (M^+) *m/z* 367.1208, found 367.1209.

Irradiation of 14b

A solution of the chloroacetamide **14b** (0.055 g, 0.18 mmol) in acetonitrile (65 ml) and water (15ml) was irradiated for 3 h. After that time, the reaction acquired a pale brownish colour and the solution was concentrated to dryness to give **15b**.

10-Hydroxyacetamido-4-methoxy phenanthrene **15b**: Yield: 95%; amorphous brownish solid; ν (KBr) cm^{-1} 3329 (NH, OH), 1699 (C=O); λ ($CHCl_3$) nm (log ϵ) 360 (3.20), 344 (3.26), 306 (3.79), 278 (4.07), 256 (4.25); δ_H ($CDCl_3$+CD_3OD) 9.54 (1H, m, H-5), 8.21 (1H, s, H-9), 7.80 (1H, m, H-8), 7.58-7.47 (4H, m, Ar-H), 7.14 (1H, dd, *J*=6.9 and 2.2, H-3), 4.24 (2H, s, CH_2) 4.07 (3H, s, OMe); δ_C ($CDCl_3$+CD_3OD) 171.2 (CO), 159.2 (C-4), 132.0 (C-10), 129.3, 128.9, 127.7 (C), 128.3, 128.3, 126.9, 126.2, 126.2, 121.7, 113.4, 108.7 (CH), 62.5 (CH_2), 55.7 (OMe); *m/z* (%) 281 (M^+, 100), 223 (75), 152 (35); HRMS calcd. for $C_{17}H_{15}NO_3$ (M^+) *m/z* 281.1052, found 281.1051.

Reaction of 4d with dibromomethane

Under an N_2 atmosphere, a THF (6 ml) solution of lithium 2,2,6,6-tetramethyl piperidide (LTMP) was added dropwise to a stirred solution of dibromomethane (4.4 mmol) in THF (6 ml), at -94 °C (hexane/ liq. N_2). After 5 min, a solution of **4d** (2 mmol) in THF (5 ml) was added, followed by 1.6M *n*-butyllithium in hexane (10 mmol). The reaction mixture was allowed to warm up to RT, and after 15 min, poured into an ice-cooled solution of acetyl chloride (5 ml) in ethanol (25 ml). The mixture was diluted with ether and washed with 10% H_2SO_4, 5% aq. $NaHCO_3$, and saturated brine. The ether layer was dried over anhydrous $CaCl_2$ and evaporated to dryness. The residue was purified by column chromatography (SiO_2, 20:2 hexane-EtOAc) to afford **16**.

6,7-Dihydro-dibenz[b,d]oxepin-6-one **16**: Yield: 63%; colourless needles, m.p. 79-80 °C (MeOH); ν (KBr) cm^{-1} 1685 (C=O); λ ($CHCl_3$) nm (log ϵ) 310 (3.50), 248 (3.96); δ_H ($CDCl_3$) 7.90 (1H, dd, *J*=8.0, 1,5, Ar-H), 7.71-7.19 (7H, m, Ar-H), 4.83 (2H, s, CH_2); δ_C ($CDCl_3$) 203.7 (CO), 156.7 (C-2'), 136.9, 136.0, 133.2 (C), 133.5, 130.2, 130.2, 129.4, 129.3, 127.9, 125.9, 121.3 (CH), 82.7 (CH_2); *m/z* (%) 210 (M^+, 96), 181 (100), 165 (37), 152 (78); HRMS calcd. for $C_{14}H_{10}O_2$ (M^+) *m/z* 210.0681, found 210.0680.

Cytotoxicity testing

HT-29 and MDA-MB-231 cells were obtained from the American Type Culture Collection; P-388 and Schabel cells were kindly provided by Pharmamar (Madrid, Spain). The effects of the alkaloids on cellular proliferation were assayed by the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] colorimetric method.[25] Each cell line was initiated at an appropriate concentration in 96-well culture plates. After 12 h incubation, the medium culture was discarded and the test compounds were added in serial dilutions to the wells. After exposure to the alkaloids for 2 days, MTT was added and the culture allowed to stand at 37ºC for 3h. Formazan crystals were redissolved (0.04 M HCl in isopropanol) and plate absorbance measured spectrophotometrically (570 nm) on a Antos 2000 ELISA plate reader.

Acknowledgement: This work was financially supported from the DGICYT (Project 94/1498).

REFERENCES

1. Guinaudeau, H.; Leboeuf, M.; Cave, A. *Lloydia* **1975**, *38*, 275-338. Guinaudeau, H.; Leboeuf, M.; Cave, A. *J. Nat. Prod.* **1979**, *42*, 325-360. Guinaudeau, H.; Leboeuf, M.; Cave, A. *J. Nat. Prod.* **1983**, *46*, 761-835. Guinaudeau, H.; Leboeuf, M.; Cave, A. *J. Nat. Prod.* **1988**, *51*, 389-474. Guinaudeau, H.; Leboeuf, M.; Cave, A. *J. Nat. Prod.* **1994**, *57*, 1033-1135.
2. Wijeratne, E.M.K.; Gunatilaka, A.A.L.; Kingston, D.G.I.; Haltiwanger, R.C.; Eggleston, D.S. *Tetrahedron* **1995**, *51*, 7877-7882.
3. Chen, Z.-L.; Zhu, D.-Y. Aristolochia Alkaloids. In *The Alkaloids*; Brossi, A. Ed.; Academic Press, Inc.: New York, 1988; Vol. 31; Chap. 2; pp. 29-65.
4. Castedo, L.; Suau, R. Cularine Alkaloids. In *The Alkaloids*; Brossi, A. Ed.; Academic Press, Inc.: New York, 1986; Vol. 29; Chap. 6; pp. 287-324.
5. Chen, C.-L.; Chang, H.-M.; Cowling, E. B. *Phytochemistry* **1976**, *15*, 1161-1167.
6. Kunimoto, J.-I.; Murakami, Y.; Oshikata, M.; Shingu, T.; Akasu, M.; Lu, S.-T.; Chen, I.-S. *Phytochemistry* **1980**, *19*, 2735-2739.
7. Saá, J. M.; Mitchell, M. J.; Cava, M.P. *Tetrahedron Lett.* **1976**, *17*, 601-602.
8. Castedo, L.; Fumega, J.; Riguera, R.; Saá, J. M.; Suau, R. *An. Quím.* **1978**, *74*, 164-165.
9. Castedo, L.; Suau, R.; Mouriño, A. *Tetrahedron Lett.* **1976**,*17*, 501-504.
10. Castedo, L.; Estévez, J. R.; Saá, J. M.; Suau, R.; *J. Heterocyclic Chem.* **1982**, *19*, 1319-1323.
11. Estévez, J.C.; Villaverde, M. C.; Estévez, J. R.; Castedo, L. *Tetrahedron*, **1994**, *50*, 2107-2114.
12. Atanes, N; Castedo, L.; Guitian, E.; Saá, J. M.; Suau, R. *J. Org. Chem.* **1991**, *56*, 2984-2988.
13. Estévez, J. C.; Estévez, J. R.; Castedo, L. *Tetrahedron* **1995**, *51*, 10801-10810.
14. Krow, G.R. The Baeyer-Villiger Oxidation of Ketones and Aldehydes. In *Organic Reactions*; Paquette, L. et al. Eds.; Wiley: New York, 1993; Vol. 43; Chap. 3; pp. 251-798.

15. McKillop, A.; Tarbin, J.A. *Tetrahedron* **1987**, *43*, 1753-1758.
16. Horner, L.; Baston, D.W. *Liebigs Ann. Chem.* **1973**, 910-935.
17. Kowalski, C. J.; Haque, M. S.; Fields, K. W. *J. Am. Chem. Soc.* **1985**, *107*, 1429-1430.
18. Noguchi, I; MacLean, D. B. *Can. J. Chem.* **1975**, *53*, 125-130.
19. Fieser, L. F.; Jacobsen, R. P.; Price, C. C. *J. Am. Chem. Soc.* **1936**, *36*, 2163-2166. Drake, N. L. The Bucherer Reaction. In *Organic Reactions.* Adams, R. et al. Ed.; Wiley: New York, 1942; Vol. 1; Chap. 5; pp. 105-128.
20. Sunberg, R. J. Chloroacetamide Photocyclization and other Aromatic Alkylations Initiated by Photoinduced Electron Transfer. In *Organic Photochemistry*; Padwa, A. Ed.; Marcel Dekker, Inc.; 1983; Vol. 6; Chap. 2; pp. 121-176.
21. Hamada, T.; Okuno, Y.; Ohmori, M.; Nishi, T.; Yonemitsu, O. *Heterocycles* **1977**, *8*, 251-256.
22. Fu, J.-M.; Sharp, M. J.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5459-5462.
23. Horner, L.; Baston, D. W. *Liebigs Ann. Chem.* **1973**, 910-935.
24. Akasu, M.; Itokawa, H.; Fujita, M. *Tetrahedron Lett.* **1974**, *41*, 3609-3612.
25. Mosmann, T. *J. Immunol. Meth.* **1983**, *65*, 55-63.

(*Received in UK* 4 *June* 1996; *revised* 8 *July* 1996; *accepted* 11 *July* 1996)