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Synthesis of Phenanthridones, Quinolinequinones and 7-Azasteroids

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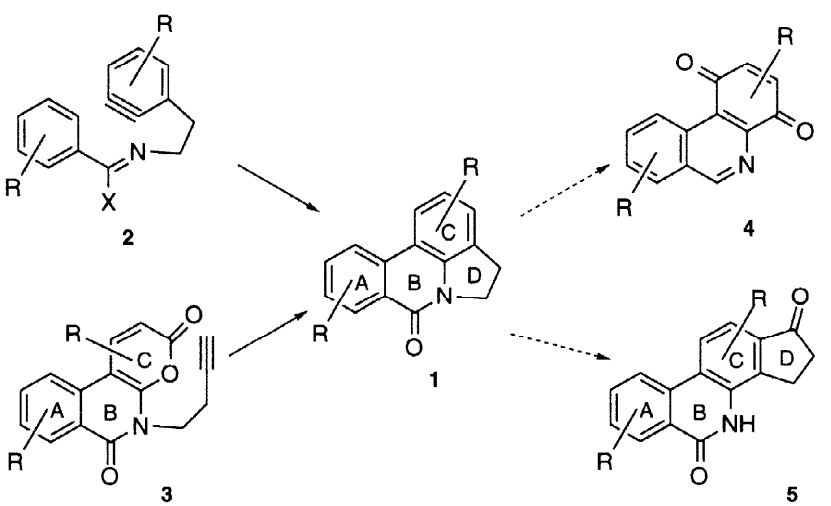
Abstract. Cleavage of ring D of lycorines, obtained by an intramolecular cycloaddition of an aryne to an azadiene, led to phenanthridines, which were either oxidized to quinolinequinones or cyclized to 7-azasteroids, both of which families are of potential pharmacological interest.

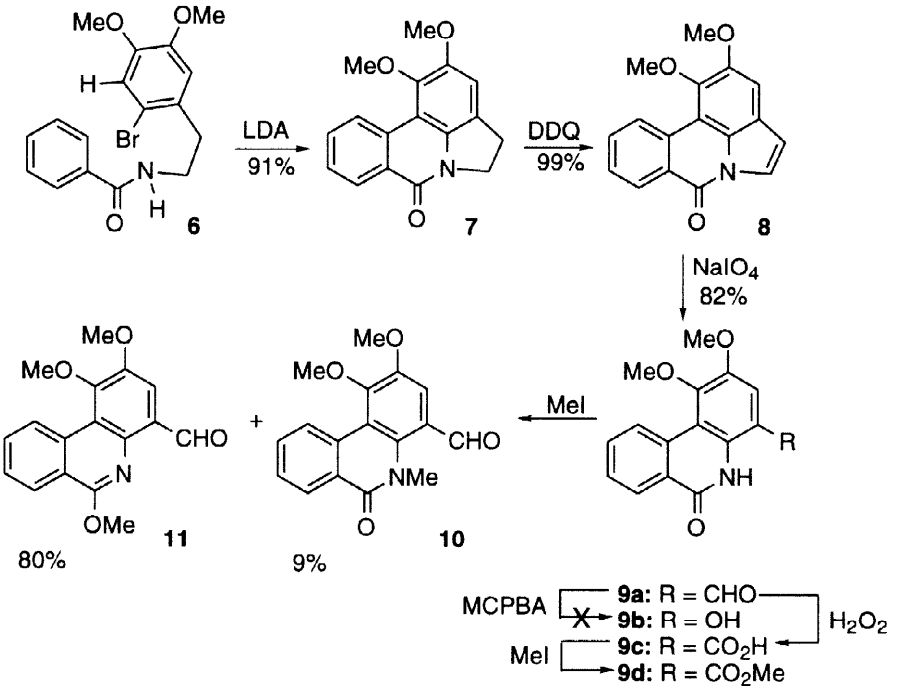
In recent years we have developed new strategies for the synthesis of lycorines with general structure **1**, which include antitumour agents such as anhydrolycorinium and hippadine, by intramolecular aryne cycloaddition of intermediates **2** or **3**.[1-3] We now report the use of lycorines **1** for the preparation of other compounds of potential pharmacological value, such as quinolinequinones **4** and, in particular, 7-azasteroids **5**. Some quinolinequinones have antitumour and antibiotic properties and inhibit AMV reverse transcriptase,[4-11] while several *n*-azasteroids have antifungal, antibacterial, anti-inflammatory or contraceptive properties,[12] or can be used for treatment of benign prostatic hyperplasia (the most common neoplastic disease of mankind).[13-19]



Scheme 1

PII: S0040-4020(99)00166-0

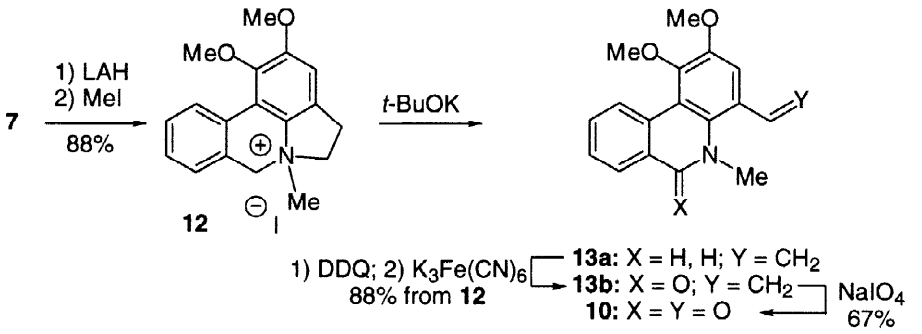
Treatment of amide **6** with LDA in THF achieved aryne formation and intramolecular cyclization to afford the tetracyclic amide **7** in good yield.[1] Mild oxidation of **7** with DDQ led to aromatization of the five-membered ring. The transformation of **6** into **8** can also be accomplished in one pot.[1]



Scheme 2

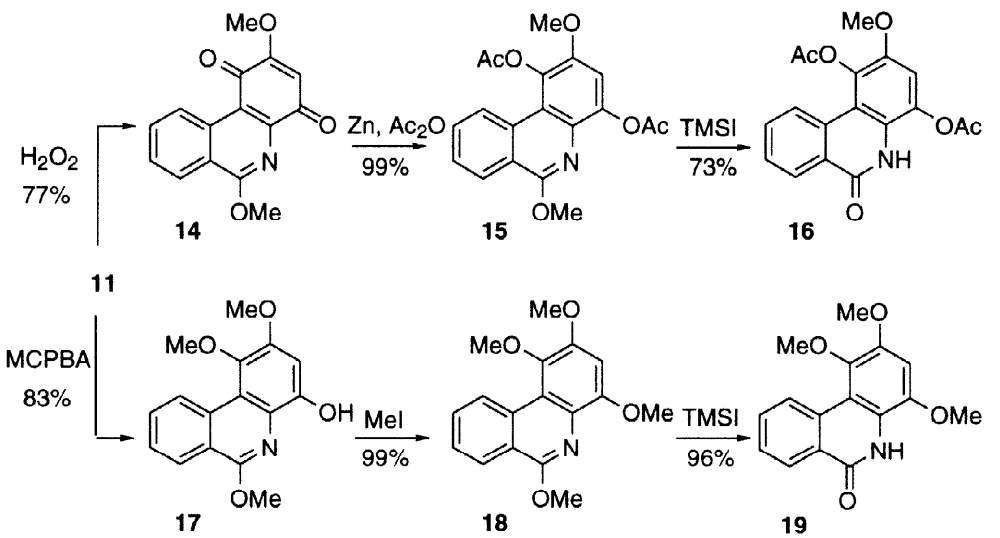
Compound **8** was transformed into phenanthridone **9a** by cleavage of the pyrrole ring with $NaIO_4$.[20] We then attempted to transform the formyl group of **9a** into an acetoxy or hydroxy group by Baeyer-Villiger oxidation: this transformation would allow the preparation of phenanthridones with alkoxy groups at this position (all other positions can be functionalized in the starting material) and would also facilitate transformation into the corresponding quinone. However, **9a** was unaffected by treatment with MCPBA, while Dakin oxidation with H_2O_2 afforded the carboxylic acid **9c**. This very unsoluble compound was characterized as the methyl ester **9d**, which was obtained by methylation with MeI. We attribute the resistance of **9a** to Baeyer-Villiger oxidation to the formation of a hydrogen bond between the amide hydrogen and the formyl oxygen, with conjugation between these groups.

To circumvent these problems we treated amide **9a** with MeI/K_2CO_3, which afforded a mixture of what appered to be **10** and **11** in 9 and 80% yield, respectively; since the two products exhibited very similar spectroscopic behaviour, we decided to confirm their structures by synthesis of **10**, as follows. Amide **7** was reduced with LAH to the corresponding amine, which was alkylated with MeI to the ammonium salt **12**. Hofmann elimination to **13a** was carried out with *t*-BuOK in good yield, and **13a** was transformed into the corresponding amide **13b** by dehydrogenation with DDQ followed by oxidation with $K_3Fe(CN)_6$.[21] Final oxidation to amide **10** by treatment with $NaIO_4$ confirmed the structure shown in Scheme 3.



Scheme 3

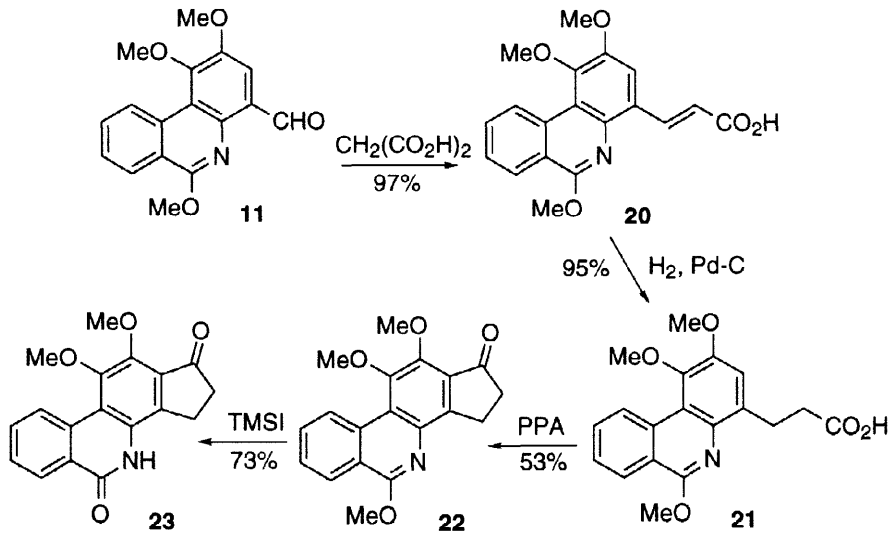
Treatment of lactimether **11** with H_2O_2 afforded quinone **14** in 77% yield, presumably through CHO→OH rearrangement followed by oxidation of the phenol to quinone, and reaction of **14** with Zn/Ac_2O[22] afforded a 99% yield of the corresponding diacetate **15**, which was transformed into the lactam **16** by treatment with trimethylsilyl iodide (TMSI) generated from NaI and TMSCl.[23] Oxidative rearrangement of lactim ether **11** with MCPBA instead of H_2O_2, followed by reduction, gave phenol **17** in 83% yield, and treatment of **17** with MeI/K_2CO_3 yielded **18**, which was demethylated to lactam **19** with TMSI.[23]



Scheme 4

Thus, phenanthridones functionalized at position 4 with CHO, OAc or OMe were obtained from lycorine **7** and quinolinequinones were obtained en route from the 4-CHO to the 4-OAc derivatives. Furthermore, the formyl group of **11** would also allow the introduction of chains to obtain bis-intercalating agents with pharmacological potential.

To obtain 7-azasteroids, we treated compound **11** with malonic acid in pyridine and reduced the resulting cinnamic acid **20** to **21** with H_2/Pd. Cyclization of **21** with PPA then afforded a 53% yield of the azasteroid **22**, which was transformed into the corresponding amide **23** by treatment with TMSI.



Scheme 5

In summary, lycorines **1** can be used as the starting point for synthesis of phenanthridones functionalized at position 4 (with easy control of the oxidation level), and for efficient preparation of quinolinequinones and 7-azasteroids of potential pharmacological value.

Experimental

General Procedures

All organic solvents were purified and freshly distilled prior to use following the methods of Armarego *et al.*[24] Analytical thin layer chromatography was carried out on commercial Kieselgel 60 aluminium plates using either UV absorption, iodine staining or ethanolic cerium-molybdenum spray for visualization. Flash chromatography was carried out using silica gel 60 (230-400 mesh). Melting points were determined on a Büchi 510 melting points apparatus and are uncorrected. Slow additions were carried out using a Harvard Apparatus syringe pump. IR spectra were recorded in KBr on a 1600 Fourier Transform spectrometer. Mass spectra were recorded on a Kratos MS-50 and a Hewlett Packard 5988A quadripolar spectrometer using electron impact ionization, unless otherwise indicated. UV spectra were recorded on a Hewlett Packard 8452A spectrophotometer at 25 °C, using ethanol as solvent and 1 cm path quartz cells. NMR spectra were recorded on a Bruker WM-250 spectrometer (^{1}H, 250 MHz; ^{13}C, 62.5 MHz) in deuterated solvents; where indicated, the number of protons attached to the peak corresponding to each carbon in the ^{13}C NMR spectrum was determined using DEPT (distortionless enhancement by polarization transfer) *J*-modulated spin-echo pulse sequence.

1,2-Dimethoxy-4,5-dihydro-7*H*-pyrrolo[3,2,1-*de*]phenanthridin-7-one (7).[1] A 0.28 M solution of LDA (11 mL, 2.8 eq., 0.28 M) in dry THF was slowly added (3 mL/h), by using a syringe pump to a solution of amide **6** (400 mg, 1.10 mol) in dry THF (300 mL) at -60 °C under argon. The mixture was stirred at -60 °C until the conversion of the starting material was complete (tlc monitoring on alumina plates). MeOH was added at -40 °C to destroy the excess LDA and O_2 was bubbled through the reaction mixture for 10 min. The cooling bath was removed and the mixture was stirred for 4 h. H_2O was added, THF was evaporated *in*

vacuo and the aqueous phase was extracted with dichloromethane. The extracts were dried over Na_2SO_4, filtered through Celite and concentrated to afford lactam **7** (280 mg, 91%) as a pale yellow solid.

1,2-Dimethoxy-7*H*-pyrrolo[3,2,1-*de*]phenanthridin-7-one (8).[1] DDQ (120 mg, 0.53 mmol) was added to a stirred solution of **7** (135 mg, 0.4 mmol) in dichloromethane (10 mL). The resulting solution was stirred for 1 h. The residue was purified by flash chromatography, eluting with 50:50 ethyl acetate-dichloromethane, to afford the lycorine **8** (133 mg, 99%) as yellow powder. Mp 178-179°C (EtOH). ^{1}H NMR ($CDCl_3$) δ 9.01 (1 H, dd, *J* = 8.2 and 1.0 Hz), 8.82 (1 H, dd, *J* = 8.2 and 2.0 Hz), 7.95 (1 H, d, *J* = 3.6 Hz), 7.79 (2 H, dt, *J* = 1.0 and 7.2 Hz), 7.59 (1 H, dt, *J* = 1.0 and 7.2 Hz), 7.28 (1 H, s), 6.77 (1 H, d, *J* = 3.6 Hz), 4.03 (3 H, s) and 3.98 (3 H, s). ^{13}C NMR ($CDCl_3$) δ 158.5, 151.3, 146.6, 133.8, 133.5, 129.4, 127.9, 127.1, 127.0, 126.2, 123.3, 122.7, 110.6, 110.1, 106.9, 60.5 and 56.8. IR υ_{max} 1685 cm^{-1}. UV λ_{max} 336 and 228 nm. LRMS *m/z* (%) 279 (M^+, 100), 264 (M^+ - Me, 80) and 51 (40). Anal. calcd. for $C_{17}H_{13}NO_3$: C 73.11, H 4.69, N 5.01; found: C 72.81, H 4.62, N 4.88.

Oxidation of 1,2-dimethoxy-7*H*-pyrrolo[3,2,1-*de*]phenanthridin-7-one (8). A 0.5 M aqueous solution of sodium periodate (8 mL, 3.94 mmol) was added to a stirred solution of lycorine **8** (110 mg, 0.39 mmol) in dioxane (5 mL). The resulting suspension was heated under reflux for 32 h. The solvent was removed under reduced pressure and the crude was partioned between diclorometane and 10% HCl. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting 40:60 ethyl acetate-hexane, to give recovered starting material (5 mg, 5%) and the amide **9a** (87 mg, 78%) as yellow needles. Mp 204-205 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ 12.07 (1 H, br s), 9.95 (1 H, s), 9.16 (1 H, dd, *J* = 1.2 and 8.6 Hz), 8.56 (1 H, dd, *J* = 1.7 and 7.9), 7.80 (1 H, dt, *J* = 8.6 and 7.8 Hz), 7.63 (1 H, dt, *J* = 1.2 and 7.5 Hz), 7.39 (1 H, s), 4.07 (3 H, s) and 4.01 (3 H, s). ^{13}C NMR (DEPT; $CDCl_3$) δ 192.9 (CH), 161.2 (C), 154.6 (C), 148.1 (C), 134.0 (C), 133.2 (CH), 133.1 (C), 128.6 (CH), 128.3 (CH), 127.3 (CH), 126.4 (C), 120.2 (CH), 114.9 (C), 113.7 (C), 60.5 (CH_3) and 56.8 (CH_3). IR υ_{max} 3226, 1649 and 1590 cm^{-1}. UV λ_{max} 376, 266 and 224 nm. LRMS *m/z* (%) 283 (M^+, 100) and 268 (M^+ - Me, 16). HRMS calcd. for $C_{16}H_{13}NO_4$: 283.0845; found: 283.0844. Anal. calcd. for $C_{16}H_{13}NO_4.1/4H_2O$: C 66.78, H 4.72, N 4.87; found: C 66.84, H 4.56, N 4.96.

Methyl 1,2-dimethoxy-5,6-dihydrophenanthridin-6-one-4-carboxylate (9d). Hydrogen peroxide (30%, 10 μL, 0.1 mmol) was added dropwise to a solution of aldehyde **9a** (22 mg, 0.08 mmol) and NaOH (2 M, 40 μL, 0.08 mmol) in dioxane (1 mL) at 40 °C. The resulting mixture was heated at 40 °C for 1 h, the dioxane was evaporated and the residue was partioned between ethyl acetate and HCl (5%). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was dissolved in acetone (10 mL) with anhydrous potassium carbonate (54 mg, 0.39 mmol), and methyl iodide (15 μl, 0.1 mmol) was added . The resulting suspension was heated under reflux for 1 h. The solvent was removed and the crude residue was partioned between dichloromethane and HCl (5%). The organic layer was separated and the aqueous phase was extracted with dichloromethane (2 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography, eluting with 30:70 ethyl acetate-hexane, to yield the amide **9d** (12 mg, 49%) as an amorphous pale yellow solid. Mp 167-168 °C. ^{1}H NMR ($CDCl_3$) δ 12.02 (1 H, br s), 9.20 (1 H, d, *J* = 8.4 Hz), 8.57 (1 H, dd, *J* = 7.9 and 1.5 Hz), 7.80-7.74 (2 H, m), 7.62 (1 H, t, *J* = 7.5 Hz),

4.01 (3 H, s), 3.98 (3 H, s) and 3.96 (3 H, s). ^{13}C NMR ($CDCl_3$; DEPT) δ 167.4 (C), 161.0 (C), 153.3 (C), 147.4 (C), 134.8 (C), 133.6 (C), 133.0 (CH), 128.3 (CH), 128.2 (CH), 127.3 (CH), 126.4 (C), 116.4 (CH), 114.0 (C), 107.9 (C), 60.3 (CH_3), 56.8 (CH_3) and 52.4 (CH_3). IR υ_{max} 3238, 1664 and 1598 cm^{-1}. UV λ_{max} 356, 248 and 224 nm. LRMS *m/z* (%) 313 (M^+, 100), 298 (M^+ - Me, 44), 266 (29) and 238 (40). HRMS calcd for $C_{17}H_{15}NO_5$: 313.0950; found: 313.0950.

Reaction of 9a with methyl iodide. A stirred suspension of amide **9a** (62 mg, 0.22 mmol), anhydrous potassium carbonate (151 mg, 1.09 mmol) and methyl iodide (30 μL, 0.44 mmol) in dry DMF (3 mL) was heated at 80 °C for 1 h. The solvent was evaporated and the residue was partioned between dichloromethane and water. The aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography, eluting with an ethyl acetate-hexane gradient (20:80, then 40:60) to afford 1,2,6-trimethoxyphenanthridine-4-carbaldehyde **10** (52 mg, 80%) and 4-formyl-5-methyl-1,2-dimethoxy-5,6-dihydrophenanthridin-6-one **11** (6 mg, 9%).

Data for **10**: white needles; mp 140-141 °C (AcOEt). ^1H NMR ($CDCl_3$) δ 11.36 (1 H, s), 9.40 (1 H, dd, *J* = 1.3 and 8.7 Hz), 8.40 (1 H, dd, *J* = 1.6 and 8.1 Hz), 7.89 (1 H, s), 7.84 (1 H, dt, *J* = 1.6 and 7.8 Hz), 7.68 (1 H, dt, *J* = 1.3 and 7.6 Hz), 4.22 (3 H, s) and 4.05 (6 H, s). ^{13}C NMR (DEPT; $CDCl_3$) δ 192.5 (CH), 158.5 (C), 152.4 (C), 149.7 (C), 141.0 (C), 133.7 (C), 131.5 (CH), 127.8 (CH), 127.1 (CH), 126.7 (C), 124.8 (CH), 120.5 (C), 117.2 (C), 111.9 (CH), 60.1 (CH_3), 56.4 (CH_3) and 53.8 (CH_3). IR υ_{max} 1686, 1620 and 1593 cm^{-1}. UV λ_{max} 376, 258 and 224 nm. LRMS *m/z* (%) 297 (M^+, 25), 270 (19) and 269 (100). HRMS calcd. for $C_{17}H_{15}NO_4$: 297.1001; found: 297.1003. Anal. calcd for $C_{17}H_{15}NO_4.1/6\ H_2O$: C 67.99, H 5.15, N, 4.66; found: C 67.96, H 5.04, N 4.88.

Data for **11**: yellow needles; mp 203-204 °C. ^1H NMR ($CDCl_3$) δ 10.32 (1 H, s), 9.18 (1 H, dd, *J* = 1.1 and 8.6 Hz), 8.57 (1 H, dd, *J* = 1.7 and 7.9 Hz), 7.78 (1 H, dt, *J* = 7.9 and 1.7 Hz), 7.63 (1 H, dt, *J* = 1.1 and 7.6 Hz), 7.59 (1 H, s), 4.01 (3 H, s), 4.00 (3 H, s) and 3.80 (3 H, s). ^{13}C NMR (DEPT; $CDCl_3$) δ 188.2 (CH), 163.0 (C), 152.4 (C), 148.8 (C), 137.3 (C), 133.1 (CH), 132.4 (C), 128.6 (2 x CH), 126.9 (CH), 125.8 (C), 121.2 (C), 116.5 (C), 114.0 (CH), 60.4 (CH_3), 56.4 (CH_3) and 41.6 (CH_3). IR υ_{max} 1665 and 1588 cm^{-1}. UV λ_{max} 368, 268 and 224 nm. LRMS *m/z* (%) 297 (M^+, 51) and 282 (M^+ - Me, 29). HRMS calcd. for $C_{17}H_{15}NO_4$: 297.1001; found: 297.1001.

6-Methyl-1,2-dimethoxy-4,5-dihydro-7*H*-pyrrolo[3,2,1-*de*]phenanthridinium iodide (12). Lithium aluminium hydride (117 mg, 3.02 mmol) was added at room temperature and under argon to a stirred solution of the lactame **5** (771 mg, 2.74 mmol) in dry THF (80 mL). The resulting suspension was heated under reflux for 2 h and then poured into a mixture of diethylether and ice. The organic layer was separated and the aqueous layer was extracted with diethylether (3 x 40 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was redissolved in dry acetone (20 mL) and methyl iodide was added (1 mL, 16.44 mmol). This mixture was heated under reflux for 2 h. The yellow precipitate formed was filtered out and washed with more acetone to afford pure amine **12** (988 mg, 88%). Mp 204-205 °C. ^1H NMR (DMSO-*d6*) δ 8.43 (1 H, d, *J* = 7.8 Hz), 7.65-7.57 (1 H, m), 7.52 (2 H, d, *J* = 4.1 Hz), 7.31 (1 H, s), 5.01 (2 H, dd, *J* = 13.9 and 19.8 Hz), 4.42 (1 H, m), 4.25 (1 H, m), 3.91 (3 H, s), 3.79 (3 H, s), 3.61 (1 H, m), 3.31 (1 H, m) and 3.08 (3 H, s). ^{13}C NMR (DMSO-*d6*) δ 155.7, 145.5, 130.2, 129.9, 128.9, 128.5, 127.9, 127.5, 126.7, 133.6, 117.9, 109.8, 68.0, 64.1, 60.0, 56.6, 48.1 and 27.0. UV

λ_{max} 272 nm. MS (FAB) *m/z* (%) 282 (MH^+ - I, 100), 266 (14) and 252 (12). HRMS calcd. for $C_{18}H_{22}NO_2$: 282.1494; found: 282.1480. Anal. calcd. for $C_{18}H_{21}INO_2$: C 52.83, H 4.92, N 3.42; found: C 52.63, H 4.90, N 3.57.

5-Methyl-1,2-dimethoxy-4-vinyl-5,6-dihydrophenanthridin-6-one (13b). A solution of potassium *t*-butoxide in *t*-butanol (0.8 mL, 10%) was added at room temperature and under argon to a stirred suspension of the amine **10** (94 mg, 0.23 mmol) in dry *t*-butanol (8 mL) The mixture was heated at 80 °C for 2 h. Water was added and the *t*-butanol was evaporated under reduced pressure. The aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford the amine **13a** as an oil that was redissolved in benzene (6 mL) and aqueous NaOH (1.9 mL, 5%) and treated dropwise with a solution of DDQ (137 mg, 0.60 mmol) in benzene (6 mL). The resulting mixture was stirred at room temperature for 1 h. Ethyl acetate was added (10 mL), the organic layer was separated, and the aqueous layer was reextracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting residue was dissolved in acetone and a saturated solution of HCl (g) in diethyl ether was added. The yellow precipitate formed was filtered out, washed with diethyl ether (5 mL) and dissolved in aqueous ethanol (10 mL, 50%), and a solution of KOH (0.1 g) and $K_3Fe(CN)_6$ (0.2 g) in water (2 mL) was added dropwise over 1 h. The aqueous layer was extracted with diethyl ether (3 x 10 mL), the combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography, eluting with 5:95 tetrahydrofuran-dichloromethane, to yield the amide **13b** (60 mg, 88%) as yellow needles. Mp 109-110 °C.

Data for 5-methyl-1,2-dimethoxy-4-vinyl-5,6-dihydrophenanthridine, **13a**: ^1H NMR ($CDCl_3$) δ 8.44 (1 H, d, *J* = 8.8 Hz), 7.40-7.23 (4 H, m), 7.09 (1 H, s), 5.68 (1 H, dd, *J* = 1.0 and 17.8 Hz), 5.29 (1 H, dd, *J* = 1.0 and 11.0 Hz), 4.04 (2 H, s), 3.95 (3 H, s), 3.75 (3 H, s) and 2.39 (3 H, s). ^{13}C NMR ($CDCl_3$; DEPT) δ 150.0 (C), 147.3 (C), 141.0 (C), 133.5 (CH), 130.0 (C), 128.8 (C), 127.4 (2 x CH), 127.3 (CH), 126.6 (CH), 123.0 (C), 113.3 (CH_2), 109.0 (CH), 60.5 (CH_3), 56.2 (CH_3), 55.5 (CH_2) and 41.3 (CH_3). LRMS *m/z* (%) 281 (M^+, 84), 266 (M^+ - Me, 100), 235 (61) and 222 (63).

Data for **13b**: ^1H NMR ($CDCl_3$) δ 9.18 (1 H, d, *J* = 8.4 Hz), 8.53 (1 H, dd, *J* = 7.9 and 1.4 Hz), 7.72 (1 H, dt, *J* = 7.9 and 1.6 Hz), 7.56 (1 H, t, *J* = 7.5 Hz), 7.12 (1 H, s), 6.98 (1 H, dd, *J* = 10.8 and 17.3 Hz), 5.61 (1 H, d, *J* = 17.3 Hz), 5.36 (1 H, d, *J* = 10.8 Hz), 3.96 (3 H, s), 3.90 (3 H, s) and 3.70 (3 H, s). ^{13}C NMR ($CDCl_3$; DEPT) δ 163.8 (C), 148.8 (C), 147.2 (C), 137.4 (CH), 133.2 (C), 133.0 (C), 132.6 (CH), 128.3 (CH), 127.9 (CH), 126.8 (CH), 126.0 (C), 123.7 (2 x C), 116.3 (C), 114.2 (CH), 114.0 (CH_2), 60.1 (CH_3), 56.4 (CH_3) and 40.2 (CH_3). IR υ_{max} 1654 cm^{-1}. UV λ_{max} 352, 310 and 248 nm. LRMS *m/z* (%) 295 (M^+, 83), 280 (M^+ - Me, 100) and 265 (15). HRMS calcd. for $C_{18}H_{17}NO_3$: 295.1208; found: 295.1205. Anal. calcd. for $C_{18}H_{17}NO_3.1/4\ H_2O$: C 72.10, H 5.88, N 4.67; found: C 72.15, H 5.69, N 4.88.

Oxidation of 13b. A stirred solution of the phenanthridone **13b** (18 mg, 0.06 mmol) in dioxane (1 mL) and an aqueous solution of sodium periodate (1.2 mL, 0.62 mmol, 0.5 M) was heated under reflux for 8 h. The solvents were evaporated and the crude mixture was partioned between dichloromethane and HCl (5%). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 10:90 tetrahydrofuran-dichloromethane, to yield the aldehyde **10** (12 mg, 67%).

2,6-Dimethoxyphenanthridine-1,4-dione (14). Five drops of a solution of hydrogen peroxide in formic acid (10 M), prepared 1 h in advance by mixing 30% hydrogen peroxide (3.1 mL, 0.1 mol) with 98% formic acid (10 mL), was added to a stirred solution of aldehyde **11** (30 mg, 0.10 mmol) in 98% formic acid (0.7 mL) at 0 °C. The resulting mixture was stirred for 30 min, formic acid was removed under reduced pressure and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography, eluting with 50:50 ethyl acetate-hexane, to yield the quinone **14** (21 mg, 77%) as an amorphous orange solid. Mp 212-213 °C. ^{1}H NMR ($CDCl_3$) δ 9.38 (1 H, d, J = 8.6 Hz), 8.30 (1 H, d, J = 8.0 Hz), 7.86 (1 H, t, J = 7.3 Hz), 7.67 (1 H, t, J = 7.6 Hz), 6.14 (1 H, s), 4.31 (3 H, s) and 3.92 (3 H, s). ^{13}C NMR ($CDCl_3$; DEPT) δ 183.9 (C), 181.9 (C), 164.4 (C), 160.2 (C), 144.4 (C), 134.7 (C), 133.6 (CH), 129.1 (CH), 127.1 (CH), 124.7 (CH), 121.3 (C), 117.9 (C), 107.1 (CH), 56.4 (CH_3) and 54.9 (CH_3). IR υ_{max} 1670 and 1625 cm^{-1}. UV λ_{max} 408, 276 and 226 nm. LRMS *m/z* (%) 269 (M^+, 100), 254 (M^+ - Me, 32) and 240 (21). HRMS calcd. for $C_{15}H_{11}NO_4$: 269.0688; found: 269.0686.

1,4-Diacetoxy-2,6-dimethoxyphenanthridine (15). Zinc powder (6 mg, 0.1 mmol) was added to a stirred orange suspension of quinone **14** (13 mg, 0.05 mmol) and anhydrous sodium acetate (98 mg, 1.20 mmol) in acetic anhydride (2 mL) at room temperature and under argon . The resulting mixture was heated at 80 °C for 2 h. Water was added and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 2:3 ethyl acetate-hexane, to yield the diacetoxy derivative **15** (17 mg, 99%) as white needles. Mp 212-213 °C. ^{1}H NMR ($CDCl_3$) δ 8.91 (1 H, d, J = 8.5 Hz), 8.37 (1 H, d, J = 8.1 Hz), 7.73 (1 H, t, J = 7.7 Hz), 7.65 (1 H, t, J = 7.5 Hz), 7.18 (1 H, s), 4.14 (3 H, s), 3.94 (3 H, s), 2.52 (3 H, s) and 2.48 (3 H, s). ^{13}C NMR ($CDCl_3$; DEPT) δ 169.4 (C), 168.5 (C), 158.0 (C), 147.7 (C), 144.4 (C), 134.3 (C), 133.2 (C), 131.1 (CH), 130.5 (C), 127.9 (CH), 125.8 (CH), 125.1 (CH), 121.2 (C), 117.7 (C), 107.5 (CH), 56.7 (CH_3), 53.4 (CH_3), 21.0 (CH_3) and 20.8 (CH_3). IR υ_{max} 1764 and 1753 cm^{-1}. UV λ_{max} 288, 260 and 238 nm. LRMS *m/z* (%) 355 (M^+, 9), 313 (M^+ -Ac, 16), 271 (100) and 256 (50). HRMS calcd. for $C_{19}H_{17}NO_6$: 355.1056; found: 355.1059.

1,4-Diacetoxy-2-methoxy-5,6-dihydrophenanthridin-6-one (16). 0.5 mL of a solution of trimethylsilylchloride (50 μL, 0.39 mmol) in dry acetonitrile (5 mL) was added to a stirred suspension of phenanthridine **15** (10 mg, 0.03 mmol) and anhydrous sodium iodide (5 mg, 0.03 mmol) in dry acetonitrile (2 mL). The resulting mixture was heated under reflux for 30 min. Water was added (5 mL) and the acetonitrile was evaporated under reduced pressure. The aqueous layer was extracted with dichloromethane (3 x 10 mL), and the combined organic layers were washed with an aqueous solution of sodium thiosulphate (5%, 2 x 10 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography, eluting with 3:1 ethyl acetate-hexane, to yield the amide **16** (7 mg, 73%) as white needles. Mp 245-246 °C. ^{1}H NMR (DMSO-d_6) δ 11.39 (1 H, br s), 8.68 (1 H, d, J = 8.3 Hz), 8.41 (1 H, d, J = 7.8 Hz), 7.88 (1 H, t, J = 8.1 Hz), 7.70 (1 H, t, J = 7.6 Hz), 7.33 (1 H, s), 3.77, 2.49 (3 H, s) and 2.39 (3 H, s). ^{13}C NMR (DMSO-d_6; DEPT)δ 169.7 (C), 168.5 (C), 160.1 (C), 145.9 (C), 134.9 (C), 134.6 (CH), 133.4 (CH), 132.1 (C), 128.7 (CH), 128.0 (CH), 126.7 (C), 125.8 (CH), 124.0 (C), 112.6 (C), 109.5 (CH), 56.8 (CH_3), 21.4 (CH_3) and 20.7 (CH_3). LRMS (FAB+ve) *m/z* (%) 342 (MH^+, 89). HRMS calcd. for $C_{18}H_{16}NO_6$: 342.0978; found: 342.0980.

4-Hydroxy-1,2,6-trimethoxyphenanthridine (17). A solution of aldehyde **11** (10 mg, 0.03 mmol) and *m*-chloroperoxybenzoic acid (9 mg, 0.05 mmol) in dry chloroform (1 mL) was stirred for 3 h at room temperature and under argon. Chloroform (10 mL) was added and the organic layer was washed with a saturated solution of sodium bicarbonate (5 mL) and then with brine (5 mL). The organic layer was dried (Na_2SO_4) concentrated under reduced pressure. The residue was dissolved in dry tetrahydrofuran (2 mL) at -78 °C and under argon. Then lithium aluminium hydride was added (5 mg, 0.1 mmol). The resulting suspension was stirred for 1 h at -78 °C and poured into a mixture of dichloromethane and ice. The organic layer was separated, washed with diluted HCl (5%, 2 x 5 mL) and then water, dried (Na_2SO_4) and concentrated under reduced pressure to give a residue which was purified by flash chromatography, eluting with 1:4 ethyl acetate-hexane, to yield the phenol **17** (8 mg, 83%) as white needles. Mp 108-109 °C. ^{1}H NMR ($CDCl_3$) δ 9.40 (1 H, d, J = 8.5 Hz), 8.38 (1 H, dd, J = 8.0 and 1.3 Hz), 7.85-7.79 (2 H, m), 7.66 (1 H, t, J = 7.5 Hz), 6.98 (1 H, s), 4.19 (3 H, s), 3.98 (3 H, s) and 3.91 (3 H, s). ^{13}C NMR ($CDCl_3$; DEPT) δ 157.4 (C), 150.3 (C), 147.9 (C), 139.1 (C), 134.6 (C), 131.4 (CH), 127.4 (CH), 127.2 (CH), 125.4 (C), 124.8 (CH), 121.2 (C), 116.6 (C), 98.7 (CH), 60.0 (CH_3), 56.6 (CH_3) and 53.7 (CH_3). IR υ_{max} 3368, 1630 and 1595 cm^{-1}. UV λ_{max} 296, 270 and 236 nm. LRMS *m/z* (%) 285 (M^+, 44), 270 (M^+ - Me, 100) and 227 (26). HRMS calcd. for $C_{16}H_{15}NO_4$: 285.1001; found: 285.1001.

1,2,4,6-Tetramethoxyphenanthridine (18). A stirred suspension of phenol **17** (22 mg, 0.08 mmol) and anhydrous potassium carbonate (53 mg, 0.38 mmol) in dry acetone (3 mL) and methyl iodide (0.1 mL, 1.54 mmol) was heated under reflux for 24 h. The solvents were concentrated and the residue was partioned between dichloromethane and water. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with ethyl 2:3 acetate-hexane, to yield the ether **18** (23 mg, 99%) as white needles. Mp 91-92 °C. ^{1}H NMR ($CDCl_3$) δ 9.46 (1 H, d, J = 8.6 Hz), 8.39 (1 H, d, J = 8.1 Hz), 7.80 (1 H, t, J = 7.7 Hz), 7.65 (1 H, t, J = 7.7 Hz), 6.92 (1 H, s), 4.25 (3 H, s), 4.09 (3 H, s), 4.02 (3 H, s) and 3.91 (3 H, s). ^{13}C NMR ($CDCl_3$; DEPT) δ 157.4 (C), 151.2 (C), 149.4 (C), 140.7 (C), 134.3 (C), 130.9 (CH), 129.3 (C), 127.4 (CH), 127.2 (CH), 124.6 (CH), 120.8 (C), 117.7 (C), 99.5 (CH), 59.9 (CH_3), 57.3 (CH_3), 56.9 (CH_3) and 53.4 (CH_3). IR υ_{max} 1621 and 1596 cm^1. UV λ_{max} 324, 294, 268 and 240 nm. LRMS *m/z* (%) 299 (M^+, 89), 284 (M^+ - Me, 100), 256 (29) and 241 (29). HRMS calcd. for $C_{17}H_{17}NO_4$: 299.1157; found: 299.1150.

1,2,4-Trimethoxy-5,6-dihydrophenanthridin-6-one (19). 0.5 mL of a solution of trimethylsilylchloride (50 µL, 0.39 mmol) in dry acetonitrile (5 mL) was added to a stirred suspension of phenanthridine **18** (10 mg, 0.03 mmol) and anhydrous sodium iodide (5 mg, 0.03 mmol) in dry acetonitrile (2 mL). The resulting mixture was heated under reflux for 30 min. Water was added (5 mL), the acetonitrile was evaporated under reduced pressure, and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with an aqueous solution of sodium thiosulphate (5%, 3 x 10 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography, eluting with 3:1 ethyl acetate-hexane , to yield the amide **19** (9 mg, 96%) as pale yellow needles. Mp 177-178 °C. ^{1}H NMR ($CDCl_3$) δ 9.21 (1 H, d, J = 8.4 Hz), 9.02 (1 H, br s), 8.57 (1 H, d, J = 7.9 Hz), 7.79 (1 H, t, J = 7.6 Hz), 7.61 (1 H, t, J = 7.5 Hz), 6.75 (1 H, s), 3.98 (3 H, s), 3.96 (3 H, s) and 3.88 (3 H, s). ^{13}C NMR ($CDCl_3$; DEPT) δ 160.7 (C), 148.2 (C), 141.9 (C), 141.6 (C), 134.3 (C), 133.0 (CH), 128.2 (CH), 128.0 (CH), 127.2 (CH), 126.7 (C),

120.6 (C), 113.3 (C), 98.7 (CH), 60.1 (CH_3), 56.3 (CH_3) and 56.3 (CH_3). IR υ_{max} 3189 and 1654 cm^{-1}. UV λ_{max} 306, 274 and 236 nm. LRMS *m/z* (%) 285 (M^+, 100), 270 (M^+ - Me, 94), 242 (25) and 227 (40). HRMS calcd. for $C_{16}H_{15}NO_4$: 285.1001; found: 285.1004.

3-[4-(1,2,6-Trimethoxyphenanthridine)]acrylic acid (20). A stirred solution of aldehyde **11** (20 mg, 0.07 mmol), piperidine (10 μL, 0.09 mmol) and malonic acid (9 mg, 0.09 mmol) in pyridine (1.5 mL) was heated at 80 °C for 1 h. Dichloromethane was added (10 mL) and the organic layer was washed with HCl (10%, 2 x 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 9:1 dichloromethane-methanol, to yield the acid **20** (22 mg, 97%) as an amorphous pale yellow solid. Mp (from dichloromethane) 197-198 °C. ^1H NMR (DMSO-d_6) δ 12.03 (1 H, br s), 9.37 (1 H, d, *J* = 8.1 Hz), 8.85 (1 H, d, *J* = 16.4 Hz), 8.33 (1 H, t, *J* = 7.0 Hz), 7.93 (2 H, br s), 7.76 (1 H, t, *J* = 7.0 Hz), 6.81 (1 H, d, *J* = 16.4 Hz), 4.18 (3 H, s), 4.03 (3 H, s) and 3.94 (3 H, s). ^{13}C NMR (DMSO-d_6) δ 169.6, 158.3, 151.0, 142.9, 137.7, 134.9, 134.0, 130.0, 129.6, 127.9, 127.2, 126.8, 121.1, 119.7, 117.8, 114.8, 60.9, 58.0 and 55.4. IR υ_{max} 2946, 1675, 1612 and 1593 cm^{-1}. UV λ_{max} 372, 322, 264 and 226 nm. LRMS *m/z* (%) 339 (M^+, 29), 294 (M^+ - CO_2H, 100), 264 (44) and 236 (20). HRMS calcd. for $C_{19}H_{17}NO_5$: 339.1107; found: 339.1106. Anal. calcd. for $C_{19}H_{17}NO_5$.1/3 H_2O: C 66.08, H 5.16, N 4.06; found: C 65.84, H 4.97,N 4.28.

3-[4-(1,2,6-Trimethoxyphenanthridine)]propionic acid (21). A suspension of acid **20** (342 mg, 1.01 mmol) and 5% palladium-on-carbon (170 mg) in absolute ethanol (40 mL) was shaken at room temperature under hydrogen for 24 h at 40 atmospheres. The mixture was filtered through Celite and the residue was washed with 1:1 tetrahydrofuran-methanol. The filtrate and washings were evaporated under reduced pressure and the residue was purified by flash chromatography, eluting with dichloromethane-methanol (90:10), to yield the *acid* **21** (325 mg, 95%) as an amorphous pale yellow solid. Mp 177-178 °C. ^1H NMR (DMSO-d_6) δ 12.09 (1 H, br s), 9.36 (1 H, d, *J* = 8.6 Hz), 8.31 (1 H, d, *J* = 7.7 Hz), 7.89 (1 H, t, *J* = 7.7 Hz), 7.73 (1 H, t, *J* = 7.5 Hz), 7.45 (1 H, s), 4.12 (3 H, s), 3.93 (3 H, s), 3.85 (3 H, s), 3.35 (2 H, t, *J* = 7.8 Hz) and 2.69 (2 H, t, *J* = 7.8 Hz). ^{13}C NMR (acetone-d_6) δ 174.8, 157.8, 150.5, 146.4, 137.3, 135.9, 135.1, 132.2, 128.5, 128.4, 125.5, 121.5, 117.8, 117.4, 60.3, 57.4, 54.1, 35.8 and 29.4. IR υ_{max} 2945, 1717, 1621 and 1597 cm^{-1}. LRMS *m/z* (%) 341 (M^+, 100), 326 (22), 296 (61), 282 (87), 280 (39) and 266 (37). HRMS calcd. for $C_{19}H_{19}NO_5$: 341.1263; found: 341.1267.

1,2,7-Trimethoxy-4,5-dihydro-3*H*-cyclopenta[c]phenanthridin-3-one (22). PPA (6 g) was mechanically stirred at 100 °C and acid **21** (30 mg, 87.98 μmol) was added in portions over 1 h. The mixture was stirred for a further 24 h, cooled, and poured onto crushed ice. The aqueous layer was basified with saturated $NaHCO_3$ and extracted with dichloromethane (5 x 10 ml), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 1:4 ethyl acetate-hexane, to yield the azasteroid **22** (15 mg, 53%) as an amorphous pale yellow solid. Mp 174-175 °C. ^1H NMR ($CDCl_3$) δ 9.47 (1 H, d, *J* = 8.7 Hz), 8.42 (1 H, dd, *J* = 8.0 and 1.2 Hz), 7.84 (1 H, dt, *J* = 7.9 and 1.6 Hz), 7.71 (1 H, dt, *J* = 7.6 and 1.2 Hz), 4.21 (3 H, s), 4.10 (3 H, s), 4.03 (3 H, s), 3.45 (2 H, t, *J* = 5.7 Hz) and 2.81 (2 H, t, *J* = 5.7 Hz). ^{13}C NMR ($CDCl_3$; DEPT) δ 205.5 (C), 159.2 (C), 151.1 (C), 150.6 (C), 147.1 (C), 137.8 (C), 134.5 (C), 131.7 (CH), 130.2 (CH), 128.7 (CH), 127.9 (CH), 125.2 (CH), 121.8 (C), 121.7 (C), 62.5 (CH_3), 61.0 (CH_3), 54.0 (CH_3), 37.6 (CH_2) and 24.2 (CH_2). IR υ_{max} 1703 cm^{-1}. LRMS (FAB+ve) *m/z* (%) 324 (MH^+, 100) and 307 (MH^+ - Me, 41). HRMS calcd. for $C_{19}H_{18}NO_4$: 324.1236;

found: 324.1220.

1,2-Dimethoxy-4,5,6,7-tetrahydro-3*H*-cyclopenta[c]phenanthridine-3,7-dione (23). 1 mL of a solution of trimethylsilylchloride (50 μL, 0.39 mmol) in dry acetonitrile (5 mL) was added to a stirred suspension of azasteroid **22** (20 mg, 58.65 μmol) and anhydrous sodium iodide (10 mg, 58.65 μmol) in dry acetonitrile (2 mL). The resulting mixture was heated under reflux for 30 min. Water was added (5 mL) and the acetonitrile was evaporated under reduced pressure. The aqueous layer was extracted with diethyl ether (3 x 10 mL), and the combined organic layers were washed with an aqueous solution of sodium thiosulphate (5%, 3 x 10 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography, eluting with ethyl acetate, to yield the amide **23** (13 mg, 73%) as pale yellow needles. Mp 248-249 °C. ^{1}H NMR (DMSO-d_6) δ 11.30 (1 H, br s), 9.18 (1 H, d, J = 8.4 Hz), 8.42 (1 H, dd, J = 7.9 and 1.4 Hz), 7.88 (1 H, dt, J = 7.8 and 1.4 Hz), 7.71 (1 H, dt, J = 7.5 and 0.9 Hz), 3.87 (3 H, s), 3.86 (3 H, s), 3.14 (2 H, m) and 2.69 (2 H, m). ^{13}C NMR (DMSO-d_6) δ 204.9, 162.2, 151.8, 146.6, 139.8, 134.9, 134.6, 131.9, 131.3, 130.9, 129.2, 128.9, 127.0, 117.6, 63.3, 62.2, 38.2 and 24.6. IR υ_{max} 3446, 1703 and 1663 cm^{-1}. LRMS (FAB+ve) *m/z* (%) 310 (MH^+, 100). HRMS calcd. for $C_{18}H_{16}NO_4$: 310.1079; found: 310.1077.

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