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The Synthesis of Ascididemin

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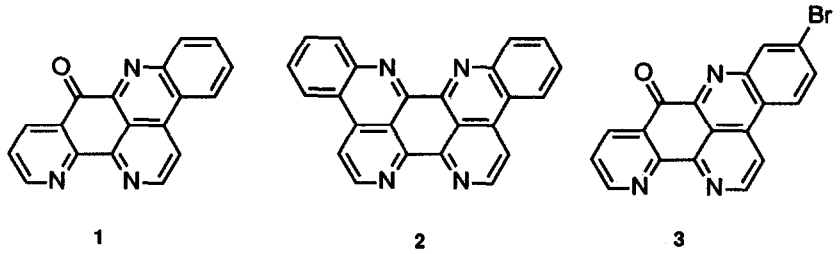
Abstract: A short synthesis of the pentacyclic marine alkaloid ascididemin **1** (four steps, 21% yield) from 1,10-phenanthroline **16** is described. The key step, photocyclisation of the quinoneimine **14** in sulphuric acid, is the first such aza stilbene photocyclisation of a quinoneimine. Intermediate **14** is prepared in a single, but low yielding, step from the quinone **4** in an aza Wadsworth-Emmons reaction, or in much better yield from the epoxide **17** by treatment with 2-iodoaniline and triethylaluminium, followed by oxidation with barium manganate.

Over the past decade the isolation and characterisation of marine alkaloids has been a steadily growing field, limited only by the high field NMR techniques available for their structure elucidation. To date the largest family of marine alkaloids characterised has been based on the pyrido[k,l]acridine skeleton. As a group, these natural products show a broad range of biological properties from antineoplastic activity and topoisomerase inactivation to antibacterial activity. Despite their structural similarities, these alkaloids are found in a number of different marine animals: tunicates and ascidians from *Phylum Chordata*; sponges from *Phylum Porifera*; and sea anemones from *Phylum Cnidaria*.

Our interest in the synthesis of natural heterocycles led us to propose a novel route[1] to the alkaloid ascididemin **1**.[2] In view of the 1,10-phenanthroline structure common to ascididemin **1**, eilatin 2[3] and 2-bromoleptoclinidinone 3[4] we decided that this tricyclic structure would serve as a suitable starting point for a synthesis of ascididemin which might also be extended to the other two. Thus, concentrating on ascididemin it may be seen that two disconnections rapidly yield the known 1,10-phenanthroline-5,6-quinone **4** (Scheme 1). Two possible routes are made available by this retrosynthesis, one involving a 4-arylphenanthroline **5**, and one an N-arylquinoneimine **6**. We chose the latter route since the imine derivative **6** appeared easier to synthesise, by an aza-Wittig reaction,



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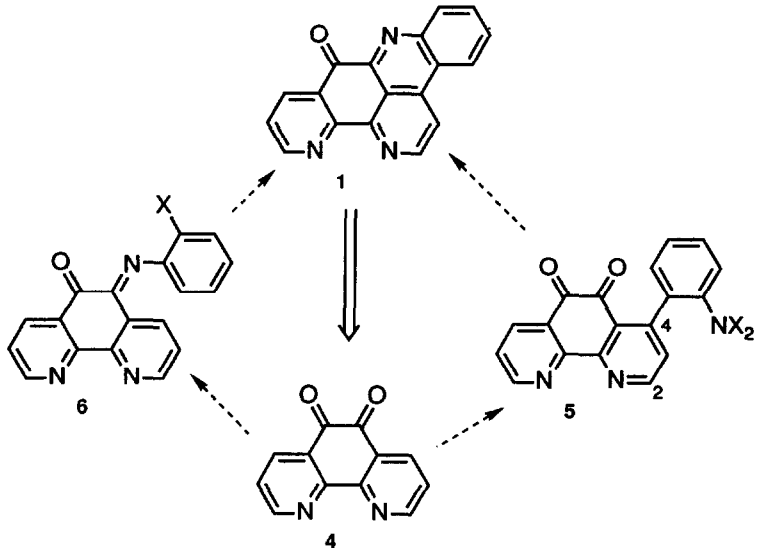


Scheme 1

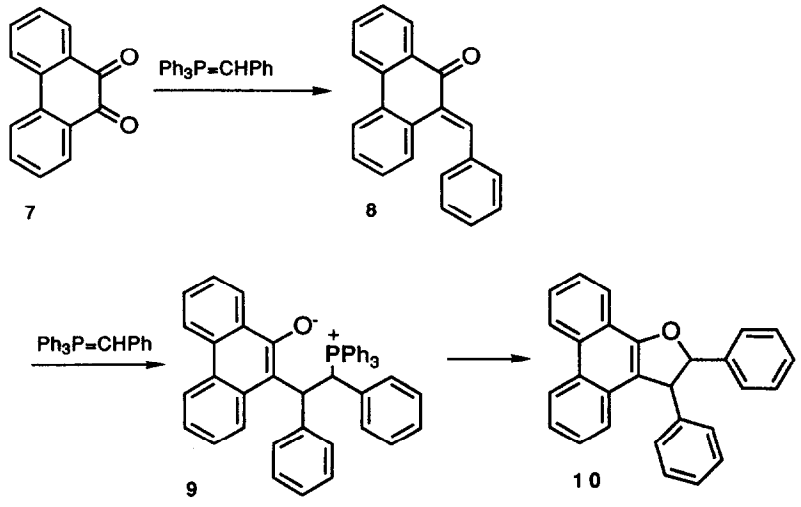
than the 4-aryl derivative **5** , and **6** incorporates an azastilbene (imine) sub-structure which could hopefully be induced to undergo photocyclisation. Considerable effort has been expended in the area of imine and iminium ion photochemistry and there are three excellent reviews on the subject,[5] the last being concerned only with stilbene-type cyclisations. The imine functionality, like the carbonyl group shows two major UV absorbances, at about 160 nm (π,π^*) and 255 nm (n,π^*). Photolysis at 254 nm causes isomerisation from the *trans* to *cis* isomer as with alkenes. However, with imines the higher energy *cis* isomer rapidly reverts to the *trans* so that the equilibrium concentration of the *cis* isomer is very low at ambient temperatures. Thus, whereas *N*-phenyl benzaldehyde imine is barely cyclised even at -10 °C, the benzophenone analogue - whose *cis* and *trans* isomers are identical - is converted into the phenanthridine in 30 % yield. This latter result reveals a second point: unlike

stilbenes, the cyclisation of these imines from the $^1(\pi,\pi^*)$ state must compete with rapid internal conversion to the lower energy $^1(n,\pi^*)$ state, thus lowering the quantum yield; stilbenes typically cyclise in very high yields.

Protonation of imines radically alters their photochemical properties. The iminium species show only one major transition in the UV spectrum, the (π,π^*). Typically there is a high ground state rotational barrier (since there is no possibility of nitrogen inversion), and photolysis parallels that of alkenes exactly. The high concentration of the *cis* isomer coupled with the lack of internal conversion [since the $^1(\pi,\pi^*)$ is the lowest energy state available] means that photolysis of such species efficiently yields phenanthridines. The reactions are normally carried out in concentrated sulphuric acid because of its acidic, non-hydrolysing and solubilising properties. A recent communication reported the successful replacement of this acid with boron trifluoride-etherate in dichloromethane.[6]

RESULTS AND DISCUSSION

The quinone 4 was synthesised from phenanthroline as reported by Gillard and Hill,[7] in low overall yield (20 %), and we then turned our attention to the aza-Wittig reaction. Inspection of the literature showed that phenanthrene-5,6-quinone 7 underwent the Wittig reaction but that the quinonemethide product 8 reacted further in a Michael fashion producing the dihydrofuran 10 (Scheme 2).[8] Despite the complication this result boded well for aza-Wittig reactions on our quinone, since the quinoneimine product would presumably not be susceptible to the same reaction as the methide.

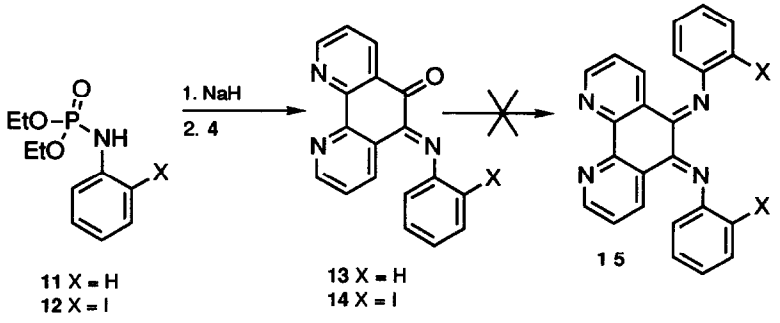


Scheme 2

Although intermolecular aza-Wittig reactions on quinones have been effected with triphenylarsine phenylimine,[9] the phosphorus analogues are less satisfactory. The difference in reactivity is quite marked; for example triphenylphosphine phenylimine reacts with benzophenone only when heated to 150 °C for 22 hours, whilst the analogous arsine reacts in excellent yield after a few minutes in boiling benzene.[9]

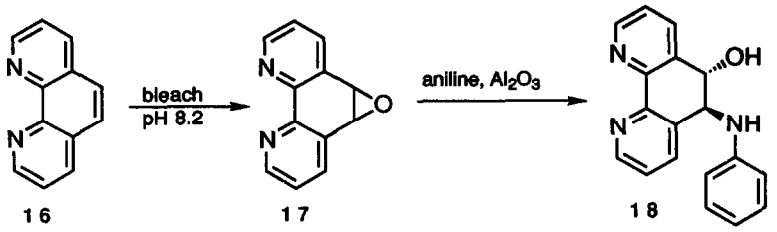
The hazard involved in applying this methodology to our case made us look a little further afield to the Wadsworth - Emmons reaction. As early as 1964 Wadsworth and Emmons [10] had examined the reaction of *N*-alkylphosphoramidate anions with a variety of carbonyl compounds, but this reaction has not been extended to the *N*-aryl analogues, which can usually be prepared by more straightforward means.

We synthesised the required phosphoramidate **11** and found that it did indeed react successfully (when deprotonated with sodium hydride) with quinone **4** to give the purple *N*-phenyl-1,10-phenanthroline-5,6-quinonemonoimine **13** in 50 % yield (Scheme 3). Attempted extension of this reaction to formation of the bisimine **15** produced a green tar which was found to be a complex mixture by NMR, and was not investigated further. A possible reason for the failure of this second reaction is the steric crowding about the remaining carbonyl group of **13**. Synthesis of the iodo analogue, *N*-(2-iodophenyl)-1,10-phenanthroline-5,6-quinone monoimine **14**, was rather less satisfactory than that of **13**, and the purple compound could be isolated in only 10 % yield.



Scheme 3

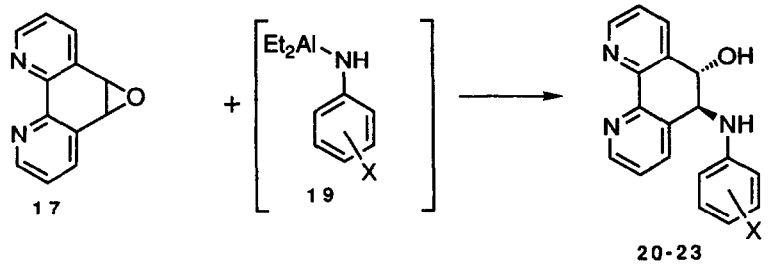
This route to the quinoneimines, though short, did not produce sufficient quantities for a full investigation of the photocyclisation and so an alternative, slightly longer route was devised. 1,10-Phenanthroline **16** was readily epoxidised in dilute bleach [11] to give **17** in excellent yield. This epoxide could be opened with aniline preadsorbed on basic alumina[12] to give 5,6-dihydro-5-anilino-6-hydroxy-1,10-phenanthroline **18** (98 %) (Scheme 4).



Scheme 4

This method did not extend to *ortho*-substituted anilines, presumably because of steric congestion on the alumina reaction surface. However, the use of Overman's aluminium amide approach[13] yielded products from a number of substituted anilines (Table 1).

Table 1 Conversion of epoxide 17 into aminoalcohols 20-23

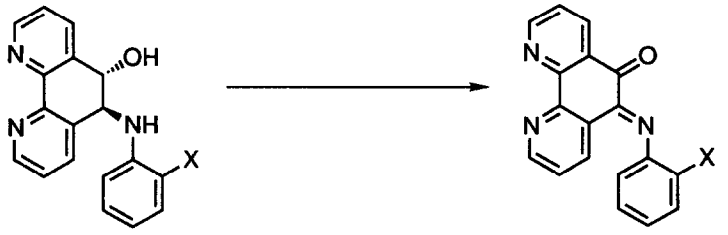


X in 19-23	Product	Yield (%)
2-I	20	79
2-Br	21	76
4-OMe	22	74
2-CN	23	74

Oxidation of these aminoalcohols to the quinoneimines was attempted using a number of oxidants (Table 2). Though most showed clean conversion of the starting materials into the purple imines, isolation of the products was difficult in a number of cases. Thus DDQ, though an excellent oxidant, was very difficult to remove from quinoneimine 13 because of their similar chromatographic properties. Heterogenous oxidants were examined to eliminate this problem; apart from nickel peroxide, which caused extensive destruction, the oxidations were very successful. Barium

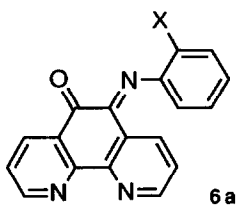
manganate[14] is the reagent of choice because it adsorbed less of the product than did activated manganese dioxide.[15]

Table 2 Oxidation of the aminoalcohols to quinoneimines

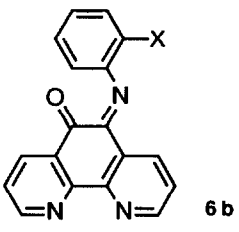


Aminoalcohol	X	Oxidant	Product	Yield (%)
18	H	MnO_2	**13**	70
18	H	NiOx	**13**	23
18	H	DDQ	**13**	32
20	I	MnO_2	**14**	65
20	I	$BaMnO_4$	**14**	83
21	Br	MnO_2	**24**	67

With gram quantities of a number of quinoneimines to hand we set about investigating their photolysis, but we first attempted to find out which geometrical isomer **6a** or **6b** we had made. If



6a



6b

this is **6a** then no photoisomerisation is required prior to cyclisation, implying that photolysis could be carried out on the neutral imine, without protonation. However if it is **6b** then photoisomerisation will be required before cyclisation can occur, and irradiation should be carried out in acidic solution. Unfortunately nOe experiments were inconclusive, though computerised energy minimisation of the two isomers **6a,b** (X=H) using the MM2 programme gave the heat of formation of **6b** as 21 kJ less than for **6a**, implying that photochemical isomerisation would be necessary

before cyclisation. This agreed with the experimental observation that the quinoneimines were unchanged upon irradiation in dichloromethane at room temperature or in methylcyclohexane at -34°C, but were changed upon irradiation in high dilution in concentrated sulphuric acid. The parent quinoneimine **13** gave complex mixtures of products with high or low pressure mercury lamps irradiating through quartz or pyrex filters. This was not a result of the high reactivity of **13**, but rather that long irradiation times were required to achieve a reasonable consumption of starting material, suggesting that there was no major, preferred reaction pathway.

With the related stilbene cyclisations this difficulty is often overcome by the inclusion of an *ortho* iodine atom to serve as an activator of the reaction and as a leaving group.[16] We therefore irradiated the iodo analogue **14** under a similar range of conditions, and the starting material was consumed more quickly, in a much cleaner (by TLC) reaction. Extensive chromatographic purification of the major yellow product of irradiation in sulphuric acid gave ascididemin **1** in 32% yield after optimisation.

In summary, this represents a short synthesis of the marine alkaloid ascididemin **1**in four steps (overall yield 21%) from phenanthroline. We believe that the key step, azastilbene photocyclisation of a quinoneimine, is the first example of such a reaction of a quinoneimine, and it offers the possibility of rapid synthesis of related polycylic natural products.

EXPERIMENTAL

Manganese dioxide was prepared [15] and stored at 75 °C and barium manganate was prepared [14] and powdered immediately before use. Preparative chromatography was carried out using the flash technique [17] when the stationary phase was silica [Merck Kieselgel 60H (70 - 230 mesh)], and standard gravity type when using alumina [acidic, neutral, or basic Brockmann I grade].

1,10-Phenanthroline-5,6-quinone **4**

To a stirred suspension of 5-nitrophenanthroline[18] (2.5 g, 11.1 mmol) in 5 % aqueous potassium hydroxide (22 ml) sodium borohydride (1.1 g, 29 mmol) was added cautiously in portions such as to keep the temperature below 80 °C. After the addition was complete the temperature was maintained at 80 °C for a further 2.5 h, before the slurry was cooled and filtered. The solids were washed with ice cold water (30 ml) and acetone (15 ml) and air dried at 60 °C. This solid was then powdered and added to cold concentrated sulphuric acid (11 ml) in small portions, and then fuming nitric acid (11 ml) was added. The resultant solution was heated to 120 - 130 °C for 2 h. After this time the reaction mixture was cooled as much as possible (while maintaining a reasonable rate of stirring) and ice cold water (20 ml) was added. The stirred cold suspension was neutralised with concentrated aqueous ammonia (**caution**), before being extracted with chloroform (3 x 150 ml) and ethyl acetate (3 x 150 ml). The combined organic extracts were dried over magnesium sulphate and the solvent removed *in*

vacuo. Recrystallisation from methanol gave the title compound (0.9 g, 40 %) as a yellow solid, m.p. 246 - 248 °C (lit.,[7] 245 - 248 °C) ; δ_H (270 MHz, $CDCl_3$) 9.09 (2H, dd 4.6, 1.7 Hz, phenH-2 & 9), 8.48 (2H, dd 7.8, 1.7 Hz, phenH-4 & 7), 7.57 (2H, dd 7.8, 4.6 Hz, phenH-3 &8).

Diethyl N-phenylphosphoramidate **11**

To a stirred solution of freshly distilled aniline (2.19 g, 10 mmol) and triethylamine (1.54 ml, 1.1 eq.) in dry benzene (25 ml) under argon at room temperature diethyl phosphorochloridate (1.45 ml, 10 mmol) was added dropwise. After 4 days the suspension was filtered and the filtrate washed with water (2 x 40 ml) and brine (40 ml) and dried over sodium sulphate. Removal of the solvents *in vacuo* yielded the title compound (3.30 g, 92 %) as a gum; δ_H (270 MHz, $CDCl_3$) 7.22 (2H, "t" 7.2 Hz, PhH), 7.15 (2H, d 7.2 Hz, PhH), 6.94 (1H, "t" 7.2 Hz, PhH), 6.45 (1H, brd, 10.1 Hz, NH), 4.00 - 4.24 (4H, m, CH_2), 1.26 (6H, dt 7.2, 1.1 Hz, CH_3).

Diethyl N-(2-iodophenyl)phosphoramidate **12**

This was prepared as above, and the title compound was isolated as an off white gum in a yield of 98 %; δ_H (270 MHz, $CDCl_3$) 7.67 (1H, dt 7.8, 1.5 Hz, PhH-6), 7.27 (1H, dd 8.0, 1.7 Hz, PhH-3), 7.20 (1H, ddd 8.0, 7.1, 1.5 Hz, PhH-4), 6.65 (1H, ddd, 7.8, 7.1, 1.7 Hz, PhH-5), 5.42 (1H brd 8.05 Hz, NH), 4.01 - 4.22 (4H, m, CH_2), 1.28 (6H, dt 7.1, 1.0 Hz, CH_3).

N-Phenyl-1,10-phenanthroline-5,6-quinone monoimine **13**

To a solution of the phosphoramidate **11** (248 mg, 0.7 mmol) in dry benzene (20 ml) under argon was added sodium hydride (37.3 mg, 1.1 eq., 45 % in hexanes) with stirring. After 30 min this solution was added to the quinone **4** (147 mg, 0.7 mmol) in dry benzene (120 ml) under argon, and stirred overnight. The solvent was removed *in vacuo* and the remaining oil triturated well with ether and then DCM. The solvents were removed *in vacuo* and the oil purified by chromatography on alumina (eluting with chloroform) to give the *title compound* (157 mg, 55 %) as a purple solid, m.p. 135 - 136 °C (Found: M^+ 285.0902. $C_{18}H_{11}N_3O$ requires M 285.0902); λ_{max} (CH_3OH) 203 (log ε 4.42), 206 (4.43), 232 (4.42), 554 (2.83); ν_{max} ($CHCl_3$) 1693, 1578, 1463, 1298; δ_H (250 MHz, $CDCl_3$) 9.08 (1H, dd 4.7, 1.8 Hz, phenH-2 or 9), 9.02 (1H, dd 4.7, 1.8 Hz, phenH-9 or 2), 8.64 (1H, dd 8.2, 1.8 Hz, phenH-7 or 4), 8.32 (1H, dd 8.2, 1.8 Hz, phenH-4 or 7), 7.53 (1H, dd 8.2, 4.7 Hz, phenH-8 or 3), 7.48 (1H, dd 8.2, 4.7 Hz, phenH-3 or 8), 7.39 (2H, brt 8.2 Hz, PhH), 7.17, (1H, brt 8.2 Hz, PhH), 6.82 (2H, brd 8.2 Hz, PhH); *m/z* (200 °C) 287 (M^+ + 2, 36 %), 285 (M^+, 52 %), 257 (100 %), 182 (19 %).

N-(2-Iodophenyl)-1,10-phenanthroline-5,6-quinone monoimine **14**

This was prepared in the same way as N-phenyl-1,10-phenanthroline-5,6-quinone monoimine, and the *title compound* was isolated as a purple solid (11 %), m.p. 124 °C dec. (Found: M^+

410.9869. $C_{18}H_{10}IN_3O$ requires M 410.9869); λ_{max} (CH_3OH) 212 (log ε 4.56), 248 (4.46), ca. 560 (2.88); ν_{max} ($CHCl_3$) 3060 (br), 2973, 1692, 1615, 1578, 1461; δ_H (250 MHz, $CDCl_3$) 9.00 (1H, dd 4.7, ca. 1.2 Hz, phen<u>H</u>-9 or 2), 8.97 (1H, dd 4.6, 1.6 Hz, phen<u>H</u>-9 or 2), 8.69 (1H, dd 8.0, 1.6 Hz, phen<u>H</u>-7 or 4), 8.26 (1H, dd 7.6, ca. 1.2 Hz, phen<u>H</u>-7 or 4), 7.83 (1H, brd ca. 8 Hz, Ph<u>H</u>), 7.50 (1H, dd 8.0, 4.6 Hz, phen<u>H</u>-8 or 3), 7.43 (1H, dd 7.6, 4.7 Hz, phen<u>H</u>-8 or 3), 7.30, (1H, brt ca. 8 Hz, Ph<u>H</u>), 6.82 (2H, brd ca. 8 Hz, Ph<u>H</u>), 6.67 (1H, brd ca. 8 Hz, Ph<u>H</u>); *m/z* (200 °C) 411 (M^+, 35 %), 285 (100 %), 256 (39 %). Despite numerous modifications to the experimental procedure, the yield of this reaction could not be significantly improved.

1,10-Phenanthroline-5,6-epoxide **17**

To a mechanically stirred mixture of industrial bleach (900 ml) and water (600 ml) adjusted to pH 8.2 - 8.3 with concentrated hydrochloric acid was added a mixture of tetrabutylammonium hydrogen sulphate (5 g) and phenanthroline monohydrate (6 g) dissolved in chloroform (500 ml). The reaction was followed by NMR. After completion the organic layer was separated and washed with water (3 x 500 ml) and brine (500 ml). Drying over sodium sulphate and removal of the solvents *in vacuo* yielded the title compound as a powder (6.4 g, 98 %), m.p. 164 - 165 °C (lit.,[11] 163 - 165 °C); δ_H (270 MHz, $CDCl_3$) 8.92 (2H, dd 4.6, 1.7 Hz, phen<u>H</u>-9 & 2), 8.02 (2H, dd 7.6, 1.7 Hz, phen<u>H</u>-4 & 7), 7.42 (2H, dd 7.6, 4.6 Hz, phen<u>H</u>-8 & 3), 4.64 (2H, s, phen<u>H</u>-5 & 6).

trans-*5-Anilino-6-hydroxy-5,6-dihydro-1,10-phenanthroline* **18**

To a slurry of basic alumina (22.5 g) with DCM was added aniline (0.9 g). After stirring for 10 min, phenanthroline epoxide (**17**) (588 mg, 3 mmol) in the minimum of DCM was added dropwise. After a further 5.5 h methanol (200 ml) was added and the suspension allowed to stand for 4 h. Filtration and removal of most of the solvent was followed by addition of hexane. The *title compound* was obtained (850 mg, 98 %) as a fine powder, m.p. 206 °C dec (Found: C, 74.8; H, 5.2; N, 14.3. $C_{18}H_{15}N_3O$ requires C, 74.7; H, 5.2; N, 14.5 %); ν_{max} ($CHCl_3$) 3071, 2961, 2931, 2874, 1728, 1603, 1582, 1270 (br); δ_H (270 MHz, d_6-DMSO) 8.67 (1H, dd 4.9, 1.5 Hz, phen<u>H</u>-2 or 9), 8.64 (1H, dd 4.6, 1.7 Hz, phen<u>H</u>-2 or 9), 7.90 (1H, dd 7.8, 1.7 Hz, phen<u>H</u>-4 or 7), 7.76 (1H, dd 7.6, 1.5 Hz, phen<u>H</u>-4 or 7), 7.44 (1H, dd 7.8, 4.6 Hz, phen<u>H</u>-3 or 8), 7.39 (1H, dd 7.6, 4.9 Hz, phen<u>H</u>-3 or 8), 7.19 (2H, brt 7.6 Hz, Ph<u>H</u>), 6.71 (2H, brd 7.6 Hz, Ph<u>H</u>), 6.56 (1H, dd 5.9, 5.9 Hz, Ph<u>H</u>), 5.95 (1H, d 7.1 Hz, N<u>H</u> or O<u>H</u>), 5.83 (1H, d 5.3 Hz, N<u>H</u> or O<u>H</u>), 4.83 (1H, dd 5.4, 10.4 Hz, PhC<u>H</u>), 4.68 (1H, dd 7.1, 10.4 Hz, PhC<u>H</u>); δ_C (67.5 MHz, d_6-DMSO) 150.5, 150.1, 149.1, 149.0, 148.3, 136.4, 135.7, 135.2, 135.15, 133.6, 129.0, 124.1, 124.0, 116.1, 112.4, 68.4, 68.3, 56.9; *m/z* (190 °C) 289 (M^+,8 %), 271 (16 %), 197 (100 %).

trans-*5-(2-Iodoanilino)-6-hydroxy-5,6-dihydro-1,10-phenanthroline* **20**

To a stirred solution of 2-iodoaniline (1.25 g, 5.7 mmol) in dry DCM (28 ml) at 5 °C under argon in the dark triethylaluminium (3 ml, 5.7 mmol, 1.9 M in toluene) was added in one portion. This solution was then allowed to warm to room temperature. After 30 min phenanthroline epoxide (17) (1.09 g, 5.58 mmol) in dry DCM (8 ml) was added dropwise. The resulting solution was stirred for a further 22 h, when an excess of sodium sulphate decahydrate - celite mixture (1:3) was added in portions. After 4 h the slurry was filtered, the solids washed with DCM and the solution concentrated *in vacuo*. Crystallisation by addition of hexane gave the *title compound* (1.83 g, 79 %) as a powder, m.p. 128 - 130 °C (Found: M^+ 415.0176. $C_{18}H_{14}IN_3O$ requires M 415.0182); λ_{max} (CH_3CN) 246 (log ε 3.24), 297 (3.05); ν_{max} ($CHCl_3$) 3575 (br), 3372 (br), 3062, 2970; δ_H (270 MHz, $CDCl_3$) 8.76 (1H, ddd 4.9, 1.7, 0.8 Hz, phen<u>H</u>-2 or 9), 8.74 (1H, ddd 4.9, 1.7, 0.8 Hz, phen<u>H</u>-2 or 9), 8.08 (1H, ddd 7.8, 1.7, 1.0 Hz, phen<u>H</u>-4 or 7), 7.72 (1H, dd 7.8, 1.7 Hz, phen<u>H</u>-4 or 7), 7.72 (1H, brdd 7.8, ca. 1.5 Hz, Ph<u>H</u>), 7.38 (1H, dd 7.8, 4.9 Hz, phen<u>H</u>-3 or 8), 7.28 (1H, dd 7.8, 4.9 Hz, phen<u>H</u>-3 or 8), 7.18 (1H, ddd 7.8, 7.8, ca. 1.5 Hz, Ph<u>H</u>), 6.96 (1H, dd 7.8, ca. 1.5 Hz, Ph<u>H</u>-3'), 6.55 (1H, ddd 7.8, 7.8, ca. 1.5 Hz, Ph<u>H</u>), 5.14 (1H, dd 10.7, 3.9 Hz, PhC<u>H</u>OH), 4.90 (1H, dd 10.7, 8.5 Hz, PhC<u>H</u>NH), 4.59 (1H, d 8.5 Hz, N<u>H</u>), 3.41 (1H, d 3.9 Hz, O<u>H</u>); δ_C (125 MHz, $CDCl_3$) 150.1, 149.1 (C_2 and C_9), 146.6 ($C_{1'}$), 139.0, 135.6, 134.7 (C_4 or C_7), 134.1 (C_4 or C_7), 133.1, 129.2, 124.2 (C_3 or C_8), 124.1 (C_3 or C_8), 119.5, 111.5 ($C_{3'}$), 85.8 ($C_{2'}$), 69.9 (C_5), 58.9 (C_6) ; *m/z* (220 °C) 415 (M^+, 0.3 %), 397 (100 %), 270 (73 %), 197 (13 %).

trans-*5-(2-Bromoanilino)-6-hydroxy-5,6-dihydro-1,10-phenanthroline* **21**

This was prepared by the same procedure as for the iodo analogue, and was isolated as *crystals* (76 %), m.p. 128 °C (from benzene) (Found: C, 64.6; H, 4.4; N, 9.35. $C_{18}H_{14}BrN_3O.C_6H_6$ requires C, 64.6; H, 4.5; N, 9.4 %) (Found: M^+ 367.0320. $C_{18}H_{14}BrN_3O$ requires M 367.0320); ν_{max} ($CHCl_3$) 3581 (br), 3398 (br), 3071, 3039, 2960; δ_H (270 MHz, $CDCl_3$) 8.80 (1H, ddd 4.9, 1.2, 0.5 Hz, phen<u>H</u>-2 or 9), 8.79 (1H, ddd 4.9, 1.2, 0.5 Hz, phen<u>H</u>-2 or 9), 8.08 (1H, ddd 7.8, 1.2, 1.5 Hz, phen<u>H</u>-4 or 7), 7.73 (1H, ddd 7.8, 1.5, 1.2 Hz, phen<u>H</u>-4 or 7), 7.53 (1H, dd 8.1, 1.5 Hz, Ph<u>H</u>), 7.42 (1H, dd 7.8, 4.9 Hz, phen<u>H</u>-3 or 8), 7.33 (1H, dd 7.8, 4.9 Hz, phen<u>H</u>-3 or 8), 7.16, (1H, ddd 8.3, 8.1, 0.5 Hz, Ph<u>H</u>), 6.80 (1H, dd 8.3, 1.2 Hz, Ph<u>H</u>), 6.71 (1H, ddd 8.1,8.1, 1.5 Hz, Ph<u>H</u>), 5.10 (1H, dd 10.3, 3.7 Hz, PhC<u>H</u>), 4.93 (1H, dd 10.3, 9.3 Hz, PhC<u>H</u>), 4.71 (1H, d 9.3 Hz, N<u>H</u> or O<u>H</u>), 2.96 (1H, d 3.7 Hz, N<u>H</u> or O<u>H</u>); *m/z* (170 °C) 369, 367 (M^+, 2 %), 349, 350 (13 %), 270 (16 %), 197 (68 %), 78 (100 %).

trans-*5-(4-Methoxyanilino)-6-hydroxy-5,6-dihydro-1,10-phenanthroline* **22**

This was prepared by the same procedure as for the iodo analogue, and was isolated as an *amorphous solid* (74 %), m.p. 233 - 235 °C (Found: M^+ 319.1321. $C_{19}H_{17}N_3O_2$ requires M

319.132); ν_{max} ($CHCl_3$) 3547 (br), 3384 (br), 3000, 2957; δ_H (270 MHz, $CDCl_3$) 8.775 (1H, ddd 4.6, 1.7, 0.7 Hz, phen<u>H</u>-2 or 9), 8.74 (1H, ddd 4.6, 1.5, 0.7 Hz, phen<u>H</u>-2 or 9), 8.05 (1H, ddd 7.8, 1.7, 0.7 Hz, phen<u>H</u>-4 or 7), 7.78 (1H, ddd 7.6, 1.5, 0.7 Hz, phen<u>H</u>-4 or 7), 7.38 (1H, dd 7.8, 4.6 Hz, phen<u>H</u>-3 or 8), 7.26 (1H, dd 7.6, 4.6 Hz, phen<u>H</u>-3 or 8), 6.83 (2H, d 9.0 Hz, Ph<u>H</u>), 6.71, (2H, d 9.0 Hz, Ph<u>H</u>), 5.00 (1H, brd 10.5 Hz, PhC<u>H</u>), 4.75 (1H, brd 10.5 Hz, PhC<u>H</u>), 3.92 (1H, brs, N<u>H</u> or O<u>H</u>), 3.77 (3H, s, C<u>H</u>3), 3.29 (1H, brs, N<u>H</u> or O<u>H</u>); *m/z* (170 °C) 319 (M^+, 3 %), 301 (100 %), 286 (67 %), 197 (40 %), 83 (48 %).

trans-*5-(2-Cyanoanilino)-6-hydroxy-5,6-dihydro-1,10-phenanthroline* **23**

This was prepared by the same procedure as for the iodo analogue, and was isolated as a *amorphous solid* (74 %), m.p. 130 - 131 °C (Found: M^+ 296.1062. $C_{19}H_{14}N_4O$ requires M 296.1062); ν_{max} ($CHCl_3$) 3693 (br), 3608 (br), 3407 (br), 3065, 3026, 2972 (br), 2216; δ_H (500 MHz, $CDCl_3$) 8.61 (1H, ddd 4.7, 1.5, 0.6 Hz, phen<u>H</u>-2 or 9), 8.60 (1H, ddd 4.8, 1.6, 0.6 Hz, phen<u>H</u>-2 or 9), 8.01 (1H, ddd 7.8, 1.6, 0.6 Hz, phen<u>H</u>-4 or 7), 7.61 (1H, ddd 7.8, 1.5, 0.6 Hz, phen<u>H</u>-4 or 7), 7.31 (1H, dd 8.1, 1.3 Hz, Ph<u>H</u>), 7.27 (1H, dd 7.8, 4.8 Hz, phen<u>H</u>-3 or 8), 7.23 (1H, ddd 8.1, 7.4, 1.7 Hz, Ph<u>H</u>), 7.17 (1H, dd 7.8, 4.7 Hz, phen<u>H</u>-3 or 8), 6.63 (2H, brt 7.8 Hz, Ph<u>H</u>), 5.28 (1H, brs, N<u>H</u> or O<u>H</u>), 5.22 (1H, brd 7.6 Hz, N<u>H</u> or O<u>H</u>), 5.11 (1H, brd 10.7 Hz, PhC<u>H</u>), 4.85 (1H, brdd 10.7, 7.6 Hz, PhC<u>H</u>); *m/z* (160 °C) 314 (M^+, 0.2 %), 396 (100 %), 270 (9 %), 197 (3 %).

N-Phenyl-1,10-phenanthroline-5,6-quinone monoimine **13**

(a) By oxidation with Attenburrow activated manganese dioxide. To a solution of the amino-alcohol **18** (289 mg, 1 mmol) in chloroform (50 ml) was added Attenburrow activated manganese dioxide (3 g), and the suspension was stirred overnight before being filtered though a pad of neutral alumina, and the solids were washed well with chloroform. The solvent was removed *in vacuo* to give the title compound (200 mg, 70 %) identical with that prepared from the quinone 4.

(b) By oxidation with DDQ. To a stirred solution of the aminoalcohol **18** (144.5 mg, 0.5 mmol) in chloroform (20 ml) under argon was added dichlorodicyanobenzoquinone (DDQ) (250 mg, 2.2 eq.) in one portion. After 3 h the solution was washed repeatedly with saturated aqueous sodium hydrogen carbonate until the aqueous washings were colourless. The organic solution was dried over potassium carbonate, and the solvent removed *in vacuo*. Repeated chromatography on silica (eluting with chloroform / methanol) gave the title compound (47.6 mg, 32 %) as a purple solid identical with that prepared above.

(c) *By oxidation with nickel peroxide.* To a solution of the aminoalcohol **18** (144.5 mg, 0.5 mmol) in benzene (100 ml) was added nickel peroxide (170 mg, ca. 1.2 eq. [O]) in one portion, and the suspension stirred for 3 h, before being filtered though a pad of neutral alumina, and the solids washed well with benzene. The solvent volume was reduced to a minimum *in vacuo*, and the residue

passed through a short pad of silica (eluting with chloroform) to give the title compound (33.2 mg, 23 %) identical with that prepared above.

N-(2-Iodophenyl)-1,10-phenanthroline-5,6-quinone monoimine **14**

(a) By oxidation with barium manganate. To a stirred solution of the aminoalcohol **20** (809 mg, 1.95 mmol) in DCM (80 ml) in the dark was added freshly powdered barium manganate (8 g) in portions over 20 min. The green suspension was stirred until all the starting material had been consumed (TLC), before being filtered though a pad of neutral alumina, and the solids washed well with chloroform. The solvent was removed *in vacuo* to give the title compound (665 mg, 83 %) identical with that described earlier.

(b) By oxidation with Attenburrow activated manganese dioxide. The same procedure as for N-phenyl-1,10-phenanthroline-5,6-quinone monoimine was used and gave the product (65%) identical with that prepared above.

N-(2-Bromophenyl)-1,10-phenanthroline-5,6-quinone monoimine **24**

By oxidation with Attenburrow activated manganese dioxide. The same procedure as for N-phenyl-1,10-phenanthroline-5,6-quinone monoimine, was used and gave the product as a *purple solid* (67 %), m.p. 178 - 179 °C (Found: M^+ 363.0007. $C_{18}H_{10}BrN_3O$ requires M 363.0007); ν_{max} ($CDCl_3$) 3060, 1693, 1618, 1579,643; δ_H (270 MHz, $CDCl_3$) 9.07 (1H, dd 4.6, 1.9 Hz, phen<u>H</u>-2 or 9), 9.03 (1H, dd 4.6, 1.9 Hz, phen<u>H</u>-2 or 9), 8.72 (1H, dd 8.1, 1.7 Hz, phen<u>H</u>-4 or 7), 8.31 (1H, dd 7.8, 1.4 Hz, phen<u>H</u>-4 or 7), 7.62 (1H, dd 8.1, 1.2 Hz, Ph<u>H</u>), 7.55 (1H, dd 8.1, 4.6 Hz, phen<u>H</u>-3 or 8), 7.48 (1H, dd 7.8, 4.6 Hz, phen<u>H</u>-3 or 8), 7.33, (1H, ddd 7.3, 7.8, 1.2 Hz, Ph<u>H</u>), 7.02 (1H, ddd 7.3, 8.1, 1.5 Hz, Ph<u>H</u>), 6.77 (1H, dd 7.8, 1.5 Hz, Ph<u>H</u>); *m/z* (220 °C) 365, 363 (M^+, 4 %), 337, 335 (7 %), 284 (100 %), 256 (35 %).

Photolysis of N-phenyl-1,10-phenanthroline-5,6-quinone monoimine **13**

(a) In methylcyclohexane. The quinoneimine **13** (192 mg, 0.7 mmol) was dissolved in freshly distilled methylcyclohexane (500 ml) in a Hanovia type photoreactor with an internal high pressure mercury lamp, quartz filter, cooling jacket and nitrogen sparge. The whole system was immersed in a dry ice - acetone cooling bath, from which the acetone was pumped through the internal cooling jacket. The solution was sparged for 30 min and then irradiated. The internal temperature stabilised at - 34 °C after a few min. Irradiation was continued for 4 h but no reaction had taken place. The experiment was discontinued.

(b) In dichloromethane. A solution of the quinoneimine **13** (14.8 mg, 0.05 mmol) and iodine (14.5 mg, 1.1 eq.) in DCM (50 ml) was degassed using the freeze - pump - thaw technique, then sparged for 30 min and finally irradiated at ambient temperature in a pyrex tube immersed in a 1000

W Rayonet photoreactor emitting predominantly at 254 nm. The irradiation was continued for 3 h but no reaction had occurred.

(c) In dichloromethane with boron trifluoride etherate. To a solution of quinoneimine **13** (23.3 mg, 0.08 mmol) in dry DCM (30 ml) was added a large excess of boron trifluoride etherate (4.1 ml) producing a yellow - brown suspension. This was divided into two portions. One was irradiated as in (b) above, and the other was washed with saturated sodium hydrogen carbonate (3 x 10 ml). After irradiating for 3 h the photolysed suspension was also washed with sodium hydrogen carbonate. TLC of the two separate aliquots showed that they were identical. The two were combined and the products partitioned between methanol (100 ml) and hexane (100 ml). The methanolic extracts were reduced to a volume of 10 ml *in vacuo*, and ether was added to precipitate a yellow solid (13.8 mg), m.p. 143 - 146 °C, whose NMR was identical with that of authentic 1,10-phenanthroline-5,6-quinone **4**.

(d) In sulphuric acid. The quinoneimine (**13**) (127 mg) was dissolved in cold concentrated sulphuric acid (300 ml) and the dark green solution transferred to a Hanovia type photoreactor with quartz filter, internal water cooling, and high pressure mercury lamp. After sparging with nitrogen for 30 min, the solution was irradiated. After 4 h a large number of products had begun to appear, as shown by TLC monitoring of a neutralised aliquot extracted into ethyl acetate. As the photolysis proceeded, more products appeared, but none could be isolated pure. The reaction was repeated several times, using pyrex instead of the quartz filter, air instead of nitrogen to sparge, and a low pressure mercury source instead of the high pressure one. In each case the photolysis began slowly but after 3 to 4 h large numbers of products started to appear (TLC). In all runs using the pyrex filter the starting material could be isolated at early stages in the photolysis by pouring the sulphuric acid solution onto ice, neutralising with concentrated aqueous ammonia, extracting with chloroform, and passing this solution through a neutral alumina pad.

Ascididemin **1**

The iodoquinoneimine **14** (131 mg, 0.319 mmol) was dissolved in cold sulphuric acid (300 ml) and the solution transferred to a Hanovia type photoreactor with nitrogen sparge and water jacketed internal pyrex filter. After sparging for 30 min the solution was irradiated with a Phillips HPK125 high pressure mercury lamp for 2 h. The solution was then poured onto ice (500 g) and concentrated aqueous ammonia added to neutralise the acid. The product was extracted with chloroform (3 x 150 ml) and ethyl acetate (3 x 150 ml), and the combined extracts dried over magnesium sulphate. The solvents were removed *in vacuo* and the residual oil purified by chromatography first on neutral alumina (eluting with chloroform) and then on silica (eluting with chloroform) to give some starting material (22.0 mg, 17 % recovery) and the title compound as a yellow solid with a characteristic fluorescence on TLC (28.9 mg, 32 %) m.p. > 320 °C (Found: M^+ 283.0746. $C_{18}H_9N_3O$ requires M 283.0746); ν_{max} ($CHCl_3$) 1683, 1604, 1582, 1415,1267, 740; δ_H (270 MHz, $CDCl_3$) 9.27

(1H, d 5.7 Hz, H-6), 9.17 (1H, dd 4.6, 1.7 Hz, H-9), 8.80 (1H, dd 7.8, 1.7 Hz, H-11), 8.68 (1H, dt 8.1, 1.5Hz, H-4), 8.65 (1H, dt 8.05, 1.5 Hz, H-1), 8.55 (1H, d 5.7 Hz, H-5), 8.02 (1H, ddd 8.05, 7.1, 1.5 Hz, H-2), 7.94, (1H, ddd 8.1, 7.1, 1.5 Hz, H-3), 7.68 (1H, dd 7.8, 4.6 Hz, H-10); *m/z* (C.I.) 284 $(M + H)^+$, (E.I.) 283 (M^+), 270, 255. All these data were in complete agreement with the literature values.[2]

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