Pergamon

Tetrahedron 55 (1999) 12637–12646

TETRAHEDRON

Concise synthesis of tetrahydro derivatives of the pyrido[2,3-*b*]acridine and pyrido[3,2-*b*]acridine ring systems

M^{a} del Mar Blanco, Carmen Avendaño, and J. Carlos Menéndez

Departamento de Química Orgánica y Farmacéutica,
Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain.‡

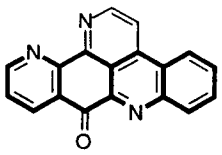
Received 6 July 1999; revised 2 August 1999; accepted 19 August 1999

Abstract. 5,6,7,8-Tetrahydro-1,4-acridinequinones were readily prepared by Friedländer reaction between cyclohexanone and 2-amino-3,6-dimethoxybenzaldehydes or 2-amino-3,6-dimethoxyacetophenones, followed by oxidative demethylation. Their Diels-Alder reactions with 1-dimethylamino-1-azadienes gave pyrido[3,2-*b*]acridines in a regioselective fashion. The regiochemistry of the cycloaddition could be inverted through the introduction of a bromine atom at the C-5 position, to give pyrido[2,3-*b*]acridines. The latter ring system is a structural fragment common to several polyciclic marine natural products with antitumour properties, including ascididemin, eilatin and biemnadin.

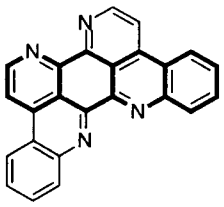
Key words: Marine metabolites, quinones, acridines, quinolines, Diels-Alder reactions.

INTRODUCTION

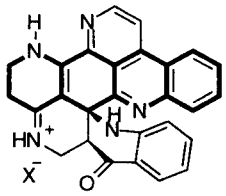
One of the most interesting groups of compounds of marine origin is the family of polycyclic aromatic alkaloids derived from the pyrido[*kl*]acridine skeleton.[1] They have been normally isolated from sponges or tunicates,[2] although they have been assumed to derive from associated microorganisms because of the wide diversity of their natural sources.[3] These compounds exhibit very interesting biological properties,[1e,4] including excellent antitumour activities,[1e,3,4bd,5] but they are normally isolated in minute amounts and their natural sources are not readily available. Since these factors have precluded their systematic study, there is a clear need for synthetic routes to the natural products themselves and to their analogues in order to define the structural requirements for their biological properties. A common feature found in several of these alkaloids, including ascididemin,[6] eilatin,[7] and biemnadin,[8] is a linear pyrido[2,3-*b*]acridine substructure.



Ascididemin



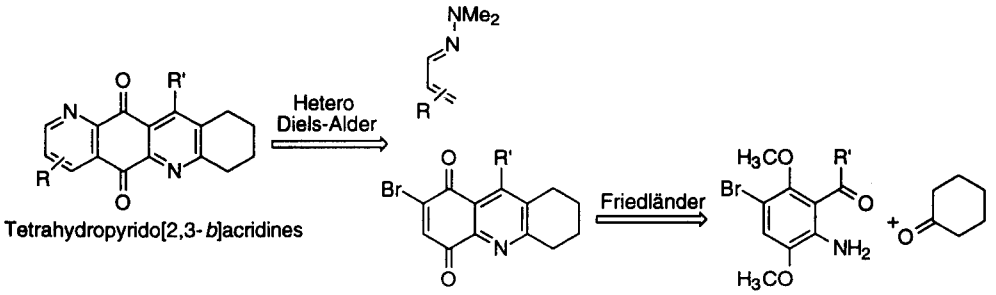
Eilatin



Biemnadin

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00738-3

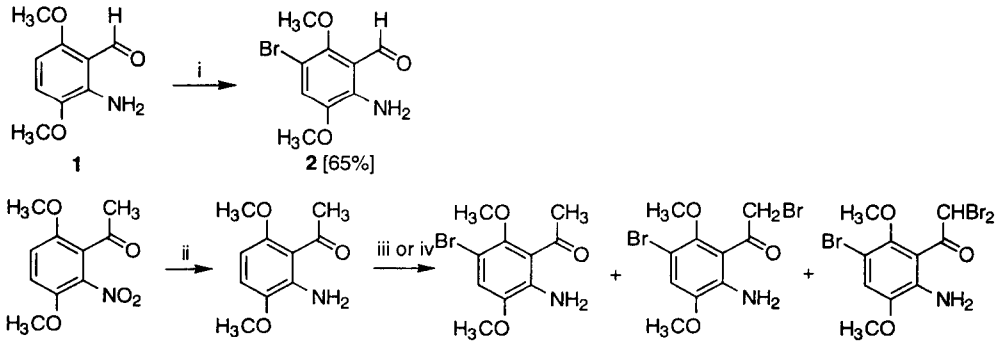
Bracher[9,10] and other authors[11,12] have studied an efficient route to this tetracyclic system, consisting of the conjugate addition of *o*-aminoacetophenones to quinolinequinone followed by acid-promoted cyclization. However, this method is suitable only for the preparation of the fully unsaturated system. We describe here our studies on a complementary method that allows the preparation of tetrahydro derivatives of the pyrido[2,3-*b*]acridine ring system by combined use of the Friedländer and hetero Diels-Alder reactions for the construction of the pyridine rings, and using a bromine atom to direct the regiochemistry of the latter reaction (Scheme 1).



Scheme 1

METHODS AND RESULTS

The brominated aminocarbonyl compounds used as starting materials for the Friedländer reactions were prepared as shown in Scheme 2. Treatment of 2-amino-3,6-dimethoxybenzaldehyde **1**[13] with bromine in acetic acid at room temperature afforded 65 % of compound **2** in a regioselective fashion. 2-Amino-3,6-dimethoxyacetophenone **4** was prepared in quantitative yield by reduction of the corresponding nitro derivative **3**, prepared by nitration of 2,5-dimethoxyacetophenone through a slight modification of a literature procedure.[14] Its



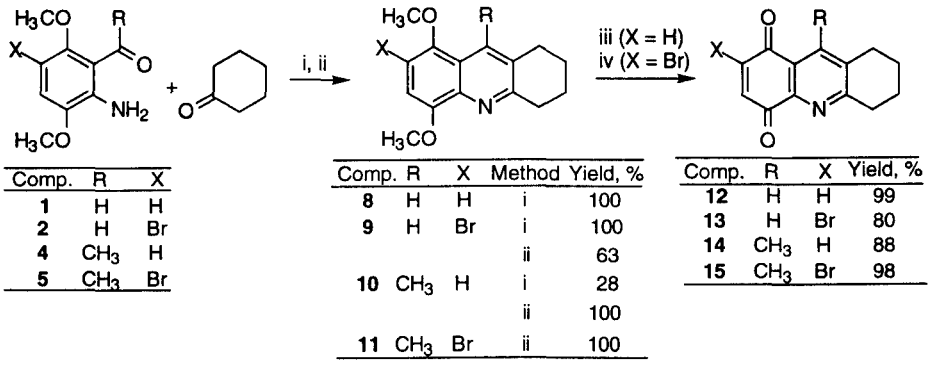
Conditions	% 5	% 6	% 7
i	25	21	4
iv	62	3	0

Reagents and conditions. i. Br_2, AcOH, r.t., 1 h. ii. Fe, AcOH-EtOH, HCl (cat.), reflux, 30 min. iii. Br_2 (1.03 eq.), Et_2O, $CHCl_3$, 1 h. iv. Br_2 (0.9 eq.), Et_2O, $CHCl_3$, 15 min.

Scheme 2

bromination to give **5** proved troublesome since, as expected, there was interference from the methyl group adjacent to the carbonyl, leading to mono- and dibromo derivatives at that position (compounds **6** and **7**). Fortunately, we found after some experimentation that use of a slight deficiency of bromine resulted in an almost chemoselective bromination of the C-5 position of compound **4**, affording **5** in 62 % yield.

The Friedländer reaction[15] between aldehydes **1** or **2** and cyclohexanone in the presence of potassium hydroxide in refluxing ethanol led to tetrahydroacridines **8** or **9** in quantitative yield. Although these conditions were not suitable for the acetophenone derivatives **4** and **5**, we found that the acidic conditions developed by Fehnel (*i.e.*, acetic acid containing a trace of sulfuric acid[16] gave quantitative yields of the tetrahydroacridines **10** and **11**, respectively. Oxidative demethylation of compounds **8-11** with cerium ammonium nitrate (CAN) led to the corresponding quinones **12-15** with excellent yields (Scheme 3).



Comp.	R	X
1	H	H
2	H	Br
4	CH_3	H
5	CH_3	Br

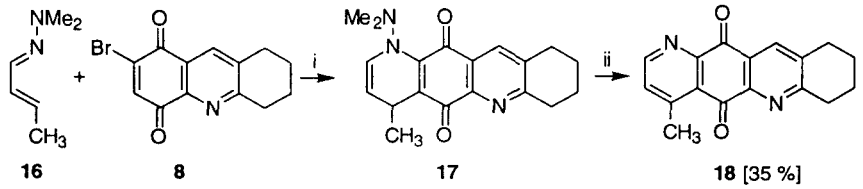
Comp.	R	X	Method	Yield, %
8	H	H	i	100
9	H	Br	i	100
			ii	63
10	CH_3	H	i	28
			ii	100
11	CH_3	Br	ii	100

Comp.	R	X	Yield, %
12	H	H	99
13	H	Br	80
14	CH_3	H	88
15	CH_3	Br	98

Reagents and conditions: i. KOH, EtOH, reflux, 18-22 h. ii. AcOH, H_2SO_4 (cat.), reflux, 2 h. iii. CAN, $CHCl_3$-H_2O,r.t., 30 min. iv. CAN, CH_3CN, H_2O, r.t., 1 h.

Scheme 3

The Diels-Alder reactions of 6,7,8,9-tetrahydro-1,4-acridinequinones must show a regioselectivity similar to those of 5,8-quinolinequinone. In agreement with literature precedent for the latter system,[17,18] the reactions between 6,7,8,9-tetrahydro-1,4-acridinequinones and 1-dimethylamino-1-azadienes ought to show a marked



16 **8** **17** **18** [35 %]

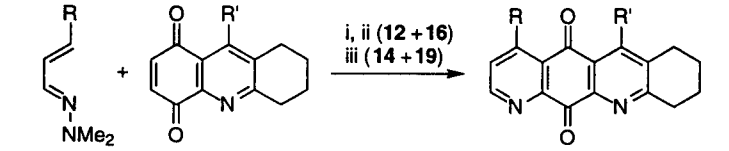
19 **11** **20** [79 %]

Reagents and conditions: i. r.t., 30 min. ii. 110 °C, 0.1 torr, 2 h. iii. 18 h, r.t.

Scheme 4

preference for the 1,8-diazaanthraquinone regioisomer because of the increased electron deficiency at the carbonyl neighbouring the nitrogen atom. Therefore, in order to obtain the desired pyrido[2,3-*b*]acridine derivatives, we required that the bromine atom at C-2 in compounds **8** and **11** caused a reversal of this selectivity. As shown in Scheme 4, and in agreement with this expectation, treatment of compound **8** with crotonaldehyde dimethylhydrazone **16**[19] led to a single reaction product which was identified by ^{1}H-NMR analysis as compound **17**, presumably arising from elimination of hydrobromic acid from the primary cycloadduct. Aromatization of the dihydropyridine ring of **17** under thermal conditions led to compound **18** in 35 % overall yield. The related reaction between bromoquinone **11** and acrolein dimethylhydrazone **19**[20] gave directly 79 % of the aromatic compound **20** after 18 h at room temperature. The preparation of **20** has been previously mentioned in a preliminary communication, in the context of a synthesis of 1,2,3,4-tetrahydroascididemin.[21]

In order to confirm the regiochemistry of the above cycloadditions, we studied the reaction of azadienes **16** and **19** with the non-brominated quinones **12** and **14**, which was expected to give the opposite regioselectivity. Indeed, compounds **21** and **22** thus obtained showed different physical and spectral data from **18** and **20**, respectively, confirming the structure of the latter compounds (Scheme 5). The pyrido[3,2-*b*]acridine structure thus obtained is not present in the natural products, but is of interest for studies of antitumour activity.



Comp.	R
16	CH_3
19	H

Comp.	R'
12	H
14	CH_3

Comp.	R	R'	Yield, %
21	CH_3	H	28
22	H	CH_3	26

Reagents and conditions: i. R.t., 30 min. ii. EtOH, reflux, 16 h. iii. R.t., 90 min

Scheme 5

EXPERIMENTAL

All reagents were of commercial quality (Aldrich, Fluka, SDS, Probus) and were used as received. Solvents (SDS, Scharlau) were dried and purified using standard techniques. "Petroleum ether" refers to the fraction boiling at 40-60 °C. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (Macherey-Nagel Alugram Sil G/UV$_{254}$). Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230-400 mesh). Melting points were measured with a Reichert 723 hot stage microsope, and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrophotometer, with all compounds examined in KBr pellets or as films on a NaCl disk. NMR spectra were obtained on Bruker AC-250 (250 MHz for ^{1}H, 63 MHz for ^{13}C) or Varian VXR-300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) spectrometers, with $CDCl_3$, as solvent (Servicio de Espectroscopía, Universidad Complutense). Elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense, on a Perkin-Elmer 2400 CHN microanalyzer.

2-Amino-5-bromo-3,6-dimethoxybenzaldehyde (2)

To a stirred solution of 2-amino-3,6-dimethoxybenzaldehyde **1**[13] (446 mg, 2.46 mmol) in acetic acid (10 mL) at 0 °C was added a solution of bromine (400 mg, 2.5 mmol) in acetic acid (5 mL). The solution was stirred at room temperature for 60 min, diluted with water (20 mL) and extracted with chloroform (3 x 50 mL). The organic layers were joined, dried over sodium sulphate and evaporated. The residue was purified by rapid chromatography on silica gel, eluting with 1:1 dichloromethane-petroleum ether, yielding 417 mg (65 %) of compound **2**, as a yellow oil, unstable to air, which was used for the next step within a few hours. δ_H (250 MHz, $CDCl_3$) 10.18 (1H, s, CHO); 6.85 (1H, s, H_4); 6.73-6.52 (2H, br. s, NH_2); 3.81 and 3.77 (6H, 2 s, OCH_3) ppm. δ_C (63 MHz, $CDCl_3$) 191.70 (CO); 153.69 (C_6); 143.67 (C_3); 142.01 (C_2); 117.91 (C_4); 112.04 (C_1); 98.82 (C_5); 63.08 (C_6-OCH_3); 56.12 (C_3-OCH_3) ppm.

2-Amino-5-bromo-3,6-dimethoxyacetophenone (4)

A mixture of 5-bromo-2-nitro-3,6-dimethoxyacetophenone[14] (2.734 g, 11.6 mmol) and iron powder (5 g) was added to a mixture of ethanol (40 mL), acetic acid (40 mL), water (20 mL) and 35 % hydrochloric acid (1 drop). The suspension was refluxed while vigorously strirred for 30 min, cooled and filtered through celite. The filtrate was diluted with water (300 mL) and extracted with chloroform (3 x 50 mL). The organic layers were joined, sequentially washed with 9 % aqueous sodium bicarbonate (200 mL) and water (2 x 200 mL), dried over sodium sulphate and evaporated. The residue (2.344 g, 99 %) was identified as analytically pure compound **4**, as a pale orange oil. [Found: C, 61.58; H, 6.60; N, 7.26. $C_{10}H_{13}NO_3$ requires C, 61.56; H, 6.66; N, 7.17]. ν_{max} (NaCl) 3485, 3352 (NH_2); 1615 (C=O); 1266 (OCH_3) cm^{-1}. δ_H (250 MHz, $CDCl_3$) 6.71 (1H, d, *J*=8.7 Hz, H_4); 6.31 (2H, br. s, NH_2); 6.03 (1H, d, *J*=8.7 Hz, H_5); 3.79 (6H, s, OCH_3); 2.56 (3H, s, CH_3) ppm. δ_C (63 MHz, $CDCl_3$) 201.16 (CO); 155.15 (C_6); 141.68 and 141.48 (C_3 and C_2); 112.76 (C_4); 111.61 (C_1); 95.69 (C_5); 56.11 and 55.32 (2 OCH_3); 33.76 (CH_3).

Bromination of compound (4)

Method A. To a solution of the aminoacetophenone **4** (1.342 mg, 6.88 mmol) in ethyl ether (30 mL) and chloroform (30 mL), at 0 °C, was added a solution of bromine (1.0 g, 6.25 mmol) in ethyl ether (30 mL). The solution was stirred at room temperature for 15 min, diluted with water (20 mL) and extracted with ethyl ether (3 x 50 mL). The combined ethereal phases were dried over sodium sulphate and evaporated. The residue was chromatographed on silica gel, eluting with 2:1 petrol-dichloromethane, yielding 175 mg (13%) of recovered **4**, 1.161 g (62%) of 2-amino-5-bromo-3,6-dimethoxyacetophenone (**5**), as a pale yellow oil, and 84 mg (3%) 2-amino-α,5-dibromo-3,6-dimethoxyacetophenone (**6**), as a pale yellow oil. Method B. Starting from 246 mg (1.26 mmol) of **4** and 208 mg (1.3 mmol) of bromine and stirring for 1 h, the yields obtained were: 17 mg (9 %) of recovered **4**, 107 mg (25 %) of **5**, 93 mg (21 %) of **6**, and 22 mg (4%) of 2-amino-α,α,5-tribromo-3,6-dimethoxyacetophenone (**7**), as an unstable yellow oil.

Data for **5**: [Found: C, 44.03; H, 4.19; N,4.89. $C_{10}H_{12}BrNO_3$ requires C, 43.79; H, 4.38; N, 5.11]. δ_H (250 MHz, $CDCl_3$) 6.95 (1H, s, H_4); 6.12 (2H, br. s, NH_2); 3.81 and 3.73 (6H, 2 s, OCH_3); 2.61 (3H, s, CH_3). δ_C (63 MHz, $CDCl_3$) 201.47 (CO); 151.08 (C_6); 144.07 (C_3); 140.26 (C_2); 115.93 (C_4); 115.17 (C_1); 100.47 (C_5); 61.94 (C_6-OCH_3); 55.93 (C_3-OCH_3); 32.07 (CH_3).

Data for **6**: [Found; C, 34.12; H, 2.98; N, 4.09. $C_{10}H_{11}Br_2NO_3$ requires C, 33.99; H, 3.12; N, 3.97]. δ_H (250 MHz, $CDCl_3$) 6.89 (1H, s, H_4); 6.18 (2H, br. s, NH_2); 4.61 (2H, s, CH_2Br); 3.82 and 3.77 (6H, 2.s,

OCH_3). δ_C (63 MHz, $CDCl_3$) 193.60 (CO); 150.47 (C_6); 144.27 (C_3); 141.36 (C_2); 116.70 (C_4); 112.43 (C_1); 100.36 (C_5); 62.48 (C_6-OCH_3); 56.13 (C_3-OCH_3); 37.67 (CH_2Br).

Data for 7: δ_H (250 MHz, $CDCl_3$) 7.15 (1H, s, CH_2Br); 6.90 (1H, s, H_4); 5.95 (2H, br. s, NH_2); 3.83 and 3.78 (6H, 2 s, OCH_3) ppm.

Friedländer reactions. General procedures.

Method A (basic conditions). To a solution of the suitable aldehyde and cyclohexanone (1.2 eq.) in absolute ethanol (10 mL per mmol of aldehyde) was added a 10 % solution of potassium hydroxide in absolute ethanol (1 eq.). The solution was refluxed under an argon atmosphere for 18-24 h, cooled and evaporated. The residue was chromatographed on silica gel under the conditions indicated for each case.

Method B (acid conditions). To a solution of the suitable aldehyde in acetic acid (2 mL per mmol of aldehyde) was added cyclohexanone (1 eq.) and 96 % sulfuric acid (0.1 mL). The solution was refluxed for 2 h, cooled and poured onto a mixture of 25 % aqueous ammonia (10 mL) and crushed ice (20 mL). This mixture was stirred for 15 min and extracted with chloroform (3 x 50 mL). The chloroform layers were dried over sodium sulphate and evaporated, and the residue was chromatographed on silica gel.

5,8-Dimethoxy-1,2,3,4-tetrahydroacridine (8)

Method A was used, starting from compound **1** (398 mg, 2.2 mmol), with 18 h reaction time followed by chromatography eluting with chloroform. Yield, 534 mg (100 %) of **8** as pale yellow crystals. [Found: C, 74.21; H, 6.83; N, 5.68. $C_{15}H_{17}NO_2$ requires C, 74.09; H, 6.99; N, 5.76]. Mp, 84 °C. ν_{max} (KBr) 1266 (OCH_3) cm^{-1}. δ_H (250 MHz, $CDCl_3$) 8.11 (1H, s, H_9); 6.73 (1H, d, J=8.4 Hz, H_6); 6.55 (1H, d, J=8.4 Hz, H_7); 3.93 and 3.84 (6H, 2 s, 2 OCH_3); 3.12 (2H, t, J=6.4 Hz, H_4); 2.89 (2H, t, J=6.4 Hz, H_1); 1.94-1.75 (4H, m, H_2 and H_3). δ_C (63 MHz, $CDCl_3$) 158.54 (C_{4a}); 148.75 (C_5); 148.11 (C_8); 138.70 (C_{10a}); 130.50 (C_{9a}); 129.69 (C_9); 120.34 (C_{8a}); 105.29 (C_7); 102.26 (C_6); 56.65 and 54.61 (2 OCH_3); 33.64 (C_4); 29.10 (C_1); 23.04 (C_3); 22.76 (C_2).

7-Bromo-5,8-dimethoxy-1,2,3,4-tetrahydroacridine (9)

Method A was used, starting from compound **2** (169 mg, 0.65 mmol), with 22 h reaction time, followed by chromatography eluting with chloroform. Yield, 209 mg (100 %) of **9** as pale yellow crystals. Starting from 260 mg (1.0 mmol) of **2** and using method B, a yield of 202 mg (63 %) of **9** was obtained. [Found: C, 56.01; H, 4.93; N, 4,48. $C_{15}H_{16}BrNO_2$ requires C, 55.94; H, 4.97; N, 4.35]. Mp, 118 °C. ν_{max} (KBr) 1208 (OCH_3) cm^{-1}. δ_H (250 MHz, $CDCl_3$) 7.94 (1H, s, H_9); 6.92 (1H, s, H_6); 3.92 and 3.85 (6H, 2 s, 2 OCH_3); 3.07 (2H, t, J=6.4 Hz, H_4); 2.92 (2H, t, J=6.0 Hz, H_1); 1.96-1.76 (4H, m, H_2 and H_3). δ_C (63 MHz, $CDCl_3$) 158.77 (C_{4a}); 151.62 (C_5); 145.33 (C_8); 138.08 (C_{10a}); 132.21 (C_{9a}); 129.42 (C_9); 123.21 (C_{8a}); 110.82 (C_7); 110.07 (C_6); 61.48 and 56.09 (2 OCH_3); 33.59 (C_4); 29.19 (C_1); 22.89 (C_3); 22.59 (C_2).

9-Methyl-5,8-dimethoxy-1,2,3,4-tetrahydroacridine (10)

Starting from compound **4** (273 mg, 1.4 mmol) and using method A, a yield of 101 mg (28 %) of **10** (pale yellow crystals) was obtained after a 24-h reflux and chromatography eluting with chloroform. Starting from 1.950 (10 mmol) of **4** and using method B, a yield of 2.562 g (100%) of **10** was obtained. [Found: C, 74.51; H, 7.54; N, 5.31. $C_{16}H_{19}NO_2$ requires C, 74.73; H, 7.39; N, 5.44]. Mp, 108 °C. ν_{max} (KBr) 1255 (OCH_3) cm^{-1}. δ_H (250 MHz, $CDCl_3$) 6.74 (d, 1H, J=8.5 Hz, H_6); 6.60 (d, 1H, J=8.5 Hz, H_7); 3.92 and 3.79 (2s, 6H, 2 OCH_3); 3.11 (m, 2H, H_4); 2.77 (m, 2H, H_1); 2.68 (s, 3H, CH_3); 1.86-1.81 (m, 4H, H_2 and H_3). δ_C (63 MHz, $CDCl_3$) 157.50 (C_{4a}); 150.83 (C_5); 149.07 (C_8); 142.99 (C_9); 139.24 (C_{10a}); 129.65 (C_{9a}); 120.54 (C_{8a});

105.00 (C_7); 104.00 (C_6); 55.87 and 55.68 (2 OCH_3); 34.75 (C_4); 27.17 (C_1); 23.39 (C_3); 22.56 (C_2); 17.71 (CH_3).

7-Bromo-9-methyl-5,8-dimethoxy-1,2,3,4-tetrahydroacridine (11)

Starting from compound **5** (600 mg, 2.19 mmol) and using method B, a yield of 734 mg (100%) of **11**, as off-white crystals, was obtained. [Found: C, 57.32; H, 5.11; N, 4.18. $C_{16}H_{18}BrNO_2$ requires C, 57.18; H, 5.35; N, 4.16]. Mp, 137 °C. ν_{max} (KBr) 1207 (OCH_3) cm^{-1}. δ_H (250 MHz, $CDCl_3$) 6.95 (1H, s, H_6); 3,.93 and 3.67 (6H, 2 s, 2 OCH_3); 3.05 (2H, m, H_4); 2.76 (2H, m, H_1); 2.68 (3H, s, CH_3); 1.85-1.80 (4H, m, H_2 and H_3). δ_C (63 MHz, $CDCl_3$) 157.52 (C_{4a}); 151.68 (C_5); 146.65 (C_8); 141.11 (C_9); 138.50 (C_{10a}); 131.20 (C_{9a}); 122.85 (C_{8a}); 113.11 (C_7); 110.00 (C_6); 61.01 and 56.05 (2 OCH_3); 34.49 (C_4); 27.03 (C_1); 22.99 (C_3); 22.56 (C_2); 15.73 (CH_3).

Oxidative demethylations. General procedures.

Method A. To a solution of the suitable 5,8-dimethoxyacridine derivative in chloroform (10 mL per mmol of substrate) was added a slolution of cerium ammonium nitrate (3 eq.) in water (2.5 mL per g of cerium ammonium nitrate). The biphasic system was vigorously stirred for 30 min and was then diluted with water (1.5 times the volume used to dissolve the oxidant) and extracted with chloroform (3 x 50 mL). The combined chloroform layers were dried over sodium sulphate and evaporated, giving the desired quinones as orange crystals.

Method B. To a solution of the suitable 5,8-dimethoxyacridine derivative in acetonitrile (20 mL per mmol of substrate) was added a solution of cerium ammonium nitrate (4 eq.) in water (5 mL per g of cerium ammonium nitrate). The homogeneous solution was stirred at room temperature for 40 min, diluted with water (1.5 times the volume used to dissolve the oxidant) and extracted with chloroform (3 x 50 mL). The combined chloroform layers were dried over sodium sulphate and evaporated, giving the desired quinones as orange crystals.

1,2,3,4-Tetrahydro-5,8-acridinequinone (12)

Starting from compound **8** (530 mg, 2.18 mmol), a yield of 459 mg (99 %) of **12** was obtained using method A. [Found: C, 73.16; H, 5.27; N, 6.32. $C_{13}H_{11}NO_2$ requires C: 73.26; H, 5.16; N, 6.57]. Mp, 142-144 °C. ν_{max} (KBr) 1688 and 1661 (CO) cm^{-1}. δ_H (250 MHz, $CDCl_3$) 7.93 (1H, s, H_9); 6.99 (1H, d, J=10.4 Hz, H_6); 6.89 (1H, d, J=10.4 Hz, H_7); 3.04 (2H, t, J=6.3 Hz, H_4); 2.86 (2H, t, J=6.1 Hz, H_1); 1.87-1.79 (4H, m, H_2 and H_3). δ_C (63 MHz, $CDCl_3$) 184.83 (C_5); 183.57 (C_8); 164.29 (C_{4a}); 144.80 (C_{10a}); 138.15 (C_9 and C_{9a}); 126.84 (C_6 and C_7); 33.15 (C_4); 29.63 (C_1); 22.81 and 22.04 (C_2 and C_3).

7-Bromo-1,2,3,4-tetrahydro-5,8-acridinequinone (13)

Starting from compound **9** (170 mg, 0.53 mmol), a yield of 123 mg (80 %) of **13** was obtained. [Found: C, 53.26; H, 3.27; N, 4.82. $C_{13}H_{10}BrNO_2$ requires C, 53.47; H, 3.42; N, 4.79]. Mp, 73-75 °C. ν_{max} (KBr) 1681 (CO) cm^{-1}. δ_H (250 MHz, $CDCl_3$) 8.09 (1H, s, H_9); 7.57 (1H, s, H_6); 3,11 (2H, t, J=6.2 Hz, H_4); 2.93 (2H, t, J=6.2 Hz, H_1); 1.92-1.88 (4H, m, H_2 and H_3).

9-Methyl-1,2,3,4-tetrahydro-5,8-acridinequinone (14)

Starting from compound **10** (632 mg, 2.46 mmol), a yield of 488 mg (88 %) of **14** was obtained using method A. [Found: C, 73.96; H, 5.90; N, 5.95. $C_{14}H_{13}NO_2$ requires C, 74.03; H, 5.72; N, 6.16]. Mp, 98-100 °C. ν_{max} (KBr) 1686 and 1654 (CO) cm^{-1}. δ_H (300 MHz, $CDCl_3$) 6.92 (d, 1H, J=10.3 Hz, H_6); 6.83 (d, 1H, J=10.3 Hz, H_7); 3.05 (m, 2H, H_4); 2.74 (m, 2H, H_1); 2.58 (s, 3H, CH_3); 1.82 (m, 4H, H_2 and H_3) ppm. δ_C

(75 MHz, $CDCl_3$) 187.32 and 183.85 (C_8 and C_5); 162.32 (C_{4a}); 148.73 (C_{10a}); 145.54 (C_9); 139.84 (C_7); 137.48 (C_{9a}); 136.54 (C_6); 125.32 (C_{8a}); 34.02 (C_4); 26.80 (C_1); 22.44 and 21.20 (C_2 and C_3); 15.76 (CH_3).

7-Bromo-9-methyl-1,2,3,4-tetrahydro-5,8-acridinequinone (15)

Starting from compound **11** (160 mg, 0.47 mmol), a yield of 143 mg (98 %) of **15** was obtained using method B. [Found: C, 55.13; H, 3.62; N, 4.31. $C_{14}H_{12}BrNO_2$ requires C, 54.94; H, 3.92; N, 4.57]. Mp, 58-60 °C (ethyl ether). ν_{max} (KBr) 1675 (CO) cm^{-1}. δ_H (300 MHz, $CDCl_3$) 7.48 (s, 1H, H_6); 3,05 (m, 2H, H_4); 2,77 (m, 2H, H_1); 2.60 (s, 3H, CH_3); 1.84 (m, 4H, H_2 and H_3). δ_C (75 MHz, $CDCl_3$) 181.37 (C_2); 179.46 (C_8); 163.04 (C_{4a}); 148.82 (C_{10a}); 145.35 (C_9); 141.34 (C_7); 138.56 (C_{9a}); 137.69 (C_6); 124.97 (C_{8a}); 34.05 (C_4); 26.99 (C_1); 22.31 and 21.81 (C_2 and C_3); 16.27 (CH_3).

Hetero Diels-Alder reactions with acrolein dimethylhydrazone. General procedure.

To a solution of the suitable acridinequinone in chloroform (7 mL per mmol of quinone) was added acrolein dimethylhydrazone **19**[20] (3 eq.). The deep purple solution was stirred at room temperature for the times indicated in each case, and the volatile compounds were evaporated *in vacuo*. The residue was chromatographed on silica gel, eluting with a gradient from neat chloroform to neat ethyl acetate.

11-Methyl-7,8,9,10-tetrahydropyrido[2,3-*b*]acridine-5,12-dione (20)

Starting from quinone **11** (230 mg, 0.75 mmol), a yield of 165 mg (79 %) of **20** (pale yellow crystals) was obtained after 18 h. [Found: C, 73.22; H, 4.88; N, 10.23. $C_{17}H_{14}N_2O_2$ requires C, 73.40; H, 5.06; N, 10.06]. Mp, 172-174 °C. ν_{max} (KBr) 1689 (CO) cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9.06 (1H, dd, *J*=4.6 and 1.7 Hz, H_2); 8.60 (1H, dd, *J*=7.9 and 1.7 Hz, H_4); 7.69 (1H, dd, *J*=7.9 and 4,6 Hz, H_3); 3.11 (2H, m, H_7); 2.81 (2H, m, H_{10}); 2.72 (3H, s, CH_3); 1.89-1.87 (4H, m, H_8 and H_9) ppm. δ_C (75 MHz, $CDCl_3$) 183.75 and 182.21 (C_5 and C_{12}); 163.17 (C_{6a}); 155.14 (C_2); 150.04 (C_{5a}); 149.13 (C_{12a}); 146.15 (C_{11}); 138.26 (C_{10a}); 135.27 (C_4); 129.13 (C_3); 127.59 (C_{11a}); 34.16 (C_7); 27.04 (C_{10}); 22.33 and 21.87 (C_8 and C_9); 16.58 (CH_3).

6-Methyl-7,8,9,10-tetrahydropyrido[2,3-*b*]acridine-5,12-dione (22)

Starting from quinone **14** (89 mg, 0.39 mmol), a yield of 28 mg (26 %) of **22** (pale yellow crystals) was obtained after 90 min. [Found: C, 73.19; H, 4.90; N, 10.24. $C_{17}H_{14}N_2O_2$ requires C, 73,40; H, 5,03; N, 10,06]. Mp, 178-180 °C. ν_{max} (KBr) 1696 and 1669 (CO) cm^{-1}. δ_H (300 MHz, $CDCl_3$) 9,09 (1H, dd, *J*=4,6 and 1,7 Hz, H_2); 8,57 (1H, dd, *J*=1,7 and 8,0 Hz, H_4); 7,72 (1H, dd, *J*=4,6 and 8,0 Hz, H_3); 3,18 (2H, m, H_{10}); 2,86 (2H, m, H_7); 2,75 (3H, s, CH_3); 1,94-1,88 (4H, m, H_8 and H_9). δ_C (75 MHz, $CDCl_3$) 185.65 and 181.50 (C_8 and C_{12}); 163.63 (C_{10a}); 155.14 (C_2); 149.88 (C_{11a}); 148.29 (C_{5a}); 147.37 (C_{12a}); 138.34 (C_6); 135.63 (C_4); 131.40 (C_{6a}); 128.20 (C_3); 126.82 (C_{4a}); 34.40 (C_{10}); 27.27 (C_7); 22.55 and 22.09 (C_8 and C_9); 16.77 (CH_3).

4-Methyl-7,8,9,10-tetrahydropyrido[2,3-*b*]acridine-5,12-dione (18)

To a solution of quinone **8** (100 mg, 0.34 mmol) in acetonitrile (7 mL) was added azadiene **16**[19] (120 mg, 1.07 mmol). The solution was stirred at room temperature for 10 min and evaporated *in vacuo*. The purple residue was identified as 1-dimethylamino-4-methyl-1,4,7,8,9,10-hexahydropyrido[2,3-*b*]acridine-5,12-dione (**17**). The crude compound **17** was heated neat at 110 °C for 2 h, and the reaction product was chromatographed on silica gel, eluting with ethyl acetate to yield 33 mg (35 %) of compound **18** as yellow crystals.

Data for 17: δ_H (250 MHz, $CDCl_3$) 7.88 (1H, s, H_{11}); 6.21 (1H, d, *J*=7.9 Hz, H_2); 5.18 (1H, dd, *J*=7.9 and 5.1 Hz, H_3); 3.72 (1H, m, H_4); 3.05 (2H, m, H_7); 2.83 (6H, s, $N(CH_3)_2$); 2.75 (2H, m, H_{10}); 1.81 (4H, m, H_8 and H_9); 1.12 (3H, d, *J*=6.5 Hz, CH_3).

Data for 18: [Found: C, 73.30; H, 5.49; N, 10.19. $C_{17}H_{14}N_2O_2$ requires C, 73.40; H, 5.06; N, 10.06]. Mp, 185-187 °C. ν_{max} (KBr) 1689 (CO) cm^{-1}. δ_H (300 MHz, $CDCl_3$) 8.90 (1H, d, *J*=4.8 Hz, H_2); 8.28 (1H, s, H_{11}); 7.50 (1H, d, *J*=4.8 Hz, H_3); 3.15 (2H, t, *J*=5.9 Hz, H_7); 2.96 (2H, t, *J*=5.9 Hz, H_{10}); 2.90 (3H, s, CH_3); 1.94-1.89 (4H, m, H_8 and H_9). δ_C (75 MHz, $CDCl_3$) 183.30 and 181.88 (C_5 and C_{12}); 165.52 (C_{6a}); 153.41 (C_2); 151.96 (C_{5a}); 149.40 (C_{12a}); 146.34 (C_4); 138.61 (C_{10a}); 135.25 (C_{11}); 131.39 (C_3); 129.23 (C_{4a}); 127.30 (C_{11a}); 33.39 (C_7); 29.08 (C_{10}); 22.58 and 21.96 (C_8 and C_9); 14.03 (CH_3).

4-Methyl-7,8,9,10-tetrahydropirido[3,2-*b*]acridine-5,12-dione (21)

To a solution of quinone **12** (358 mg, 1.68 mmol) in chloroform (10 mL) was added azadiene **16**[19] (191 mg, 1.70 mmol). The solution was stirred at room temperature for 30 min and evaporated *in vacuo*. The residue was dissolved in ethanol and the solution was refluxed for 24 h and evaporated. The residue was chromatographed on silica gel, eluting with ethyl acetate. Yield, 132 mg (28 %) of compound **22** as pale yellow crystals. [Found: C, 73.61; H, 5.23; N, 9.94. $C_{17}H_{14}N_2O_2$ requires C, 73.40; H, 5.03; N: 10.06]. Mp, 184-186 °C. Mixed mp with **18**, 180-181 °C. ν_{max} (KBr) 1661 (CO) cm^{-1}. δ_H (250 MHz, $CDCl_3$) 8.84 (d, 1H, *J*=4.9 Hz, H_2); 8.11 (s, 1H, H_6); 7.44 (d, 1H, *J*=4.9 Hz, H_3); 3.12 (t, 2H, *J*=6.3 Hz, H_{10}); 2.92 (t, 2H, *J*=6.1 Hz, H_7); 2.81 (s, 3H, CH_3); 1.90-1.86 (m, 4H, H_8 and H_9).

ACKNOWLEDGEMENTS

We thank Ms. M. V. Tuñón for the preparation of several grams of compound **3**. Financial support from CICYT (grant PTR-95-0230) is gratefully acknowledged.

REFERENCES

1 a) Álvarez, M.; Salas, M; Joule, J.A. *Heterocycles* **1991**, *32*, 759. b) Molinski, T.F. *Chem. Rev.* **1993**, *93*, 1825. c) Groundwater, P.W.; Munawar, M.A. *Adv. Heterocycl. Chem.* **1998**, *70*, 89. d) Ding, Q.; Chichak, K.; Lown, J.W. *Current Med. Chem.* **1999**, *6*, 1.

2 Davidson, B.S. *Chem. Rev.* **1993**, *93*, 1771.

3 Kobayashi, J.; Ishibashi, M. *Chem. Rev.* **1993**, *93*, 1753.

4 a) Schmitz F.J.; de Guzmán, F.S.; Choi, Y.H.; Hossain, M.B.; Rizui, S.K.; van der Helm, D. *Pure Appl. Chem.* **1990**, *62*, 1393. b) McCarthy, P.J.; Pitts, T.P.; Gunawardana, G.P.; Kelly-Borges, M.; Pomponi, S.A. *J. Nat. Prod.* **1992**, *55*, 1664. c) Tarapowerala, I.B.; Cessac, J.W.; Chanh, T.C.; Delgado, A.V.; Schinazi, R.F. *J. Med. Chem.* **1992**, *35*, 2744. d) McDonald, L.A.; Edredge, G.S.; Barrows, L.R.; Ireland, C.M. *J. Med. Chem.* **1994**, *37*, 3819. e) Lindsay, B.S., Barrows, L.R., Copp, B.R. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 739.

5 a) Burres, N.S.; Sazesh ,S.; Gunawardana, G.P.; Clement, J.J. *Cancer Res.* **1989**, *49*, 5267. b) Longley, R.E.; McConnell, OJ; Essich, E.; Harmody, D. *J. Nat. Prod.* **1993**, *56*, 915. c) Spector, I.; Shochet, N.R.;

Kashman, Y.; Amira, R.; Gellerman, G. U.S. US 5,432,172. (*Chem. Abstr.* **1995**, 123: 218394m). d) Spector, I.; Shochet, N.R.; Kashman, Y.; Amira, R.; Gellerman, G. PCT Int. Appl. WO 94 03,433. (*Chem. Abstr.* **1994**, 121:157945b). e) Michal, E.; Arnon, N.; Lishner, M.; Amiel, A.; Yarkoni, S.; Amira, R. *Clin. Cancer Res.* **1995**, *1*, 823. f) Bonnard, I.; Bontemps, N.; Lahmy, S.; Banaigs, B.; Combaut, G.; Francisco, C.; Colson, P.; Houssier, C.; Waring, M.J.; Bailly, C. *Anti-Cancer Drug Res.* **1995**, *10*, 333. g) Bracher, F. *Pharmazie* **1997**, *52*, 57.

6 Kobayashi, J.; Cheng, J.; Nakamura, H.; Ohizumi, Y.; Hirata, Y.; Sasaki, T.; Ohta, T.; Nozoe, S. *Tetrahedron Lett.* **1988**, *29*, 1177.

7 Rudi, A.; Kashman, Y. *J. Org. Chem.* **1989**, *54*, 5331.

8 Zeng, C.M.; Ishibashi, M.; Matsumota, K.; Nakaike, S.; Kobayashi, J. *Tetrahedron* **1993**, *49*, 8337.

9 Bracher, F. *Heterocycles* **1989**, *29*, 2093.

10 Bracher, F. *Liebigs Ann Chem.* **1990**, 205.

11 Peterson, J.R.; Zjawiony, J.K.; Liu, S.; Hufford, C.D.; Clark, A.M.; Rogers, R.D. *J Med Chem*, **1992**, *35*, 4069.

12 Kitahara, Y.; Nakahara, S.; Yonezawa, T.; Nagatsu, M.; Shibano, Y.; Kubo, A. *Tetrahedron*, **1997**, *53*, 17029.

13 Blanco, M.M.; Avendaño, C.; Cabezas, N.; Menéndez, J.C. *Heterocycles* **1993**, *36*, 1387.

14 Valderrama, J.A.; Valderrama, C. *Synth. Commun.* **1997**, *27*, 2143.

15 a) Caluwe, P. *Tetrahedron* **1980**, *36*, 2359. b) Cheng, C.C.; Yan, S.J. *Org. Reactions* **1982**, *28*, 37.

16 Fehnel, E.A.; Deymp, J.A., Davidson, M.B. *J. Org. Chem.* **1958**, *23*, 1996.

17 a) Potts, K. T.; Walsh, E. B.; Bhattacharjee, D., *J. Org. Chem.* **1987**, *52*, 2285. b) Villacampa, M.; Pérez, J. M.; Avendaño, C.; Menéndez, J. C., *Tetrahedron* **1994**, *50*, 10047.

18 a) Nebois, P.; Fillion, H.; Benameur, L., *Tetrahedron* **1993**, *49*, 9767. b) Tapia, A. R.; Quintanar, C.; Valderrama, J. A., *Heterocycles* **1996**, *43*, 447.

19 Waldner, A. *Helv. Chim. Acta* **1988**, *71*, 486.

20 Gómez-Bengoa, E.; Echavarren, A.M. *J. Org. Chem.* **1991**, *56*, 3497.

21 Blanco, M. M.; Avendaño, C.; Menéndez, J. C., *Tetrahedron Lett.* **1999**, *40*, 4097.