Pergamon

Tetrahedron 57 (2001) 309–317

TETRAHEDRON

Isobenzofurans and *ortho*-benzoquinone monoketals in syntheses of xestoquinone and its 9- and 10-methoxy derivatives

Hamish S. Sutherland, Kerianne C. Higgs, Nicholas J. Taylor and Russell Rodrigo*

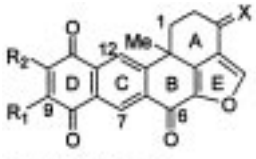
Department of Chemistry, Guelph-Waterloo Centre for Graduate Work in Chemistry and Biochemistry, University of Waterloo, Waterloo, Ontario, Canada, N2L 3G1

Received 7 April 2000; revised 30 May 2000; accepted 10 July 2000

Abstract—Syntheses of (±)-xestoquinone, (±)-9-methoxyxestoquinone and (±)-10-methoxyxestoquinone are described. A convergent CD plus ABE plan using the appropriate isobenzofuran (CD) and naphthofuranone (ABE) has been implemented to provide these marine metabolites in overall yields of 18.3, 9.5 and 8.5%, respectively. The latter pair of compounds, previously evaluated as inhibitors of Topoisomerase II as an inseparable mixture, are now available separate and pure for the first time.

Halenaquinone **1** was the first member[1] of a group of pentacyclic marine quinones isolated from tropical sponges of the genus *Xestospongia*. In succeeding years, this genus[2] and the related *Adocia*[3,4] have yielded many more compounds of the group including xestoquinone **2**, methoxyhalenaquinone **3** and adociaquinones **4**, **5** and **6**. More recently, an investigation[5] of sponges collected from the seas off the northern coast of the Philippine Islands resulted in the isolation of two inseparable isomeric methoxyxestoquinones **7** and **8**, chloro-hydroxy quinones **9** and **10**, adociaquinones **4** and **5** and their corresponding *seco* derivatives. Partially reduced derivatives, quinols and various hydrogenated quinones have also been found in these investigations on some occasions[2,4] and all these marine metabolites are now recognised as a structurally discrete group based on the parent pentacyclic ring system[6] 1H-benzo[6,7]phenanthro[10,1-bc]-furan. It has been conjectured[4] that the quinone ring D is triketide in origin and the rest of the molecule (14 carbons) comes from a sesquiterpene that has suffered demethylation to form the furan ring (E).

The quinones of the group have significant and potentially valuable pharmacological properties; **1** and **3** have proven[4] to be powerful irreversible inhibitors of some cytoplasmic and receptor protein tyrosine kinases (PTK) but not all PTK's are affected. It was suggested that Michael addition of the PTK to electrophilic sites at the A, E and D rings was responsible. These findings are relevant to the development of PTK antagonists as anti-proliferative agents in the treatment of cancer and psoriasis. Xestoquinone **2** was not a PTK antagonist, but a subsequent study[5] established that quinones **2**, **7**–**10** were inhibitors of Topoisomerase II, an enzyme found at elevated levels in cancer cells. A separate study determined[7] that both **1** and **2** bound to Topoisomerase I and prevented the unwinding of DNA during cell division though neither compound intercalated with the DNA helix. Xestoquinone was also found to be a useful modifier of myosin. It was suggested[8] that the quinone ring (D) interacted with specific SH groups of the protein and altered its conformation. In support of this hypothesis a xestoquinone-mercaptoethanol adduct **11** was prepared in vitro. In addition, xestoquinone activated actomyosin ATP-ase by enhancement of the interaction between actin and myosin. It had been previously shown to be a potential cardiotonic agent because of its positive inotropic effect on cardiac muscle.



1 X=O; R_1=R_2=H

2 X=H, H; R_1=R_2=H

3 X=O, R_1=OMe, R_2=H

7 X=H, H; R_1=OMe, R_2=H

8 X=H, H; R_1=H, R_2=OMe

9 X=H, H; R_1=Cl, R_2=OH

10 X=H, H; R_1=OH, R_2=Cl

11 X=H, H; R_1=R_2=SCH_2CH_2OH

Keywords: antitumour compounds; cycloadditions; quinones; sponges.

* Corresponding author. Fax: +1-519-746-0435; e-mail: rrodrigo@wlu.ca

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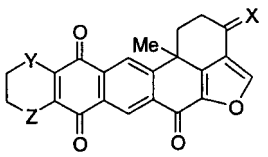
PII: S0040-4020(00)00938-8



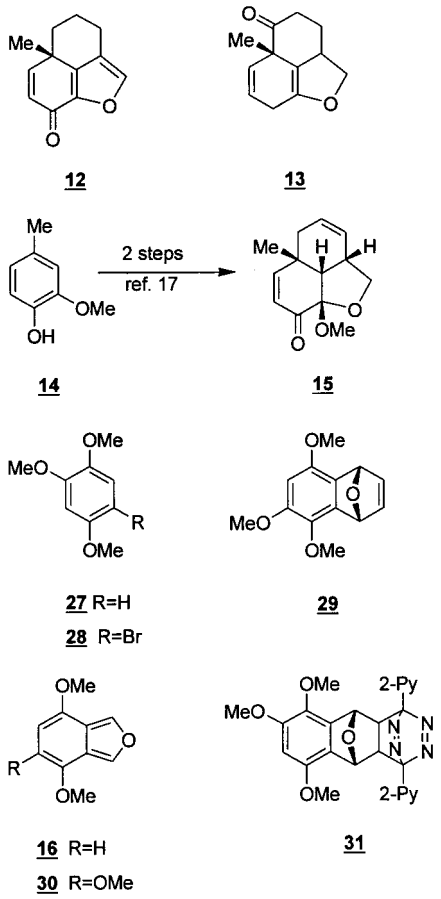
4 X=H, H; Y=NH, Z=SO_2

5 X=H, H; Y=SO_2, Z=NH

6 X=O; Y=NH, Z=SO_2

These marine metabolites have also attracted much attention from synthetic chemists. Beginning with optically pure Wieland–Mischler ketone (as rings A and B) Harada and co-workers completed syntheses of halenaquinone,[9] xestoquinone[10] and adociaquinones A and B[11] in 14–16 steps and yields of 4–6%. Rings C and D were affixed by a Diels–Alder reaction with dimethoxybenzocyclobutene, while ring E was built up from the tetracyclic adduct. After oxidative generation of the ring D quinone to produce (+)-xestoquinone,[10] reaction with 2-aminoethanesulfinic acid (hypotaurine) gave the adociaquinones[11] which were separated by HPLC. Two different syntheses published contemporaneously,[12,13] employed methoxynaphthalene precursors as the CD-ring synthons. In the first of these, the starting materials 2-bromo-3-carbethoxy-5,8-dimethoxynaphthalene and 2-*t*-butyldimethylsilyl-3-hydroxymethylfuran (ring E) were converted to (+)-xestoquinone (68% e.e.) in eleven steps and 11.3% overall yield. The key step which fabricated rings A and B of the homochiral pentacyclic precursor in 'one pot' was an intramolecular asymmetric Heck reaction–polyene cyclisation sequence catalysed by a Pd(0) species complexed with (*S*)-BINAP. A subsequent retracing of essentially the same reaction scheme with silver salts as additives in the polyene cyclisation step also resulted[14] in the preparation of (+) **2** in comparable yield. In the second asymmetric synthesis from a naphthalene starting material (+)-halenaquinone (85% e.e.) was obtained in 21 steps and low yield (ca. 2%). The key step this time was an intermolecular tandem Suzuki coupling Heck reaction (catalysed by palladium acetate-(*S*)-BINAP) between the naphthalene 2,3-ditriflate and an alkylborane to provide the BCD tricycle in 85% e.e. and 20% yield. Subsequent elaboration of this product incorporated the requisite 3-keto group and rings A and E of (+)-halenaquinone. In a completely different approach (±)-xestoquinone was synthesised by a convergent ABE+CD, Diels–Alder reaction.[15] The CD segment was a dimethoxy *o*-quinomethide again, but the novelty and attraction of this work lay in the first synthesis of a complete ABE tricyclic naphthofuranone used as the dienophile in the assembly of the pentacycle. This fragment was prepared by means of a novel protocol called 'furan ring transfer' by the authors, and although the chemistry of those particular steps was ingeniously conceived, the synthesis of the tricycle (**12**) took 11 steps to complete in moderate (6.3%) yield from α-furylmethanol.

Our laboratory has had a long-standing interest in such a convergent plan and had devoted considerable effort to elaborating a similar tricyclic system for use as a dienophile in the syntheses of xestoquinone and related naturally occurring pentacycles. Although a tricycle **13** was obtained[16] in good yield from guaiacol it could not be converted into a suitable dienophile for further progress towards (±) **2**. A completely new route to such a tricyclic target was therefore devised and successfully implemented. It involved oxidative functionalisation of 4-methylguaiacol **14** through an *o*-quinone monoketal, led to **15** in two steps and subsequently to (±)-xestoquinone.[17] This general intramolecular Diels–Alder, Cope rearrangement sequence was profitably applied to more complex systems by us[18,19] and others.[20] In this report we provide full details of the synthesis of (±) **2** modified slightly to provide a better overall yield, and adapt our synthetic route to afford 9-methoxy and 10-methoxyxestoquinones (**7** and **8**) separately for the first time. Furthermore, an X-ray crystallographic structure of a pure synthetic intermediate has been obtained in order to conclusively assign structures to this pair of isomers which had been isolated in small quantities (15 mg) and characterised previously only as an inseparable 70:30 mixture.



The synthesis of (±)-xestoquinone began with the preparation[17] of **15** in two steps from 4-methylguaiacol and 2,4-pentadienol in 56% yield. This tricycle, representing rings AB and E of the quinones reacted with the known[21] 4,7-dimethoxyisobenzofuran **16** to provide the adduct **17** in 78% yield.[22] The isobenzofuran **16** was prepared this time as a stable solid[23] by the dipyridyl-*s*-tetrazine route.[24] The ^{1}H NMR spectrum of **17** in $CDCl_3$ at ambient temperature showed very broad signals for all protons associated with the ABE segment. A spectrum in benzene-d_6 at 67°C was satisfactory but it still provided little information about the relative stereochemistry of the Diels–Alder adduct. An X-ray structure of **17** established that it was formed by

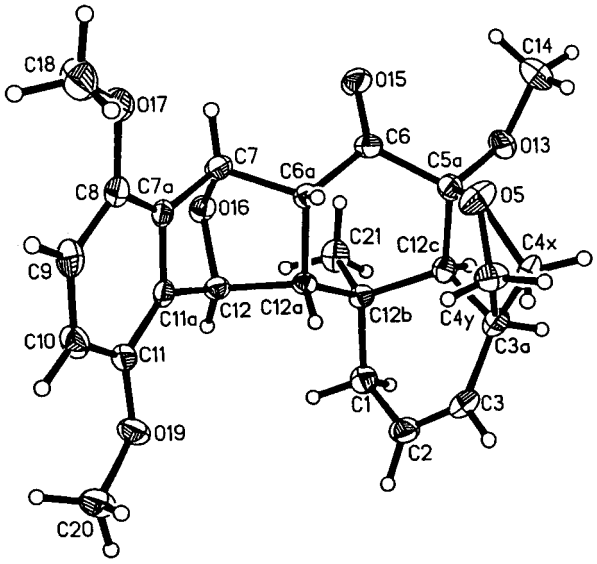
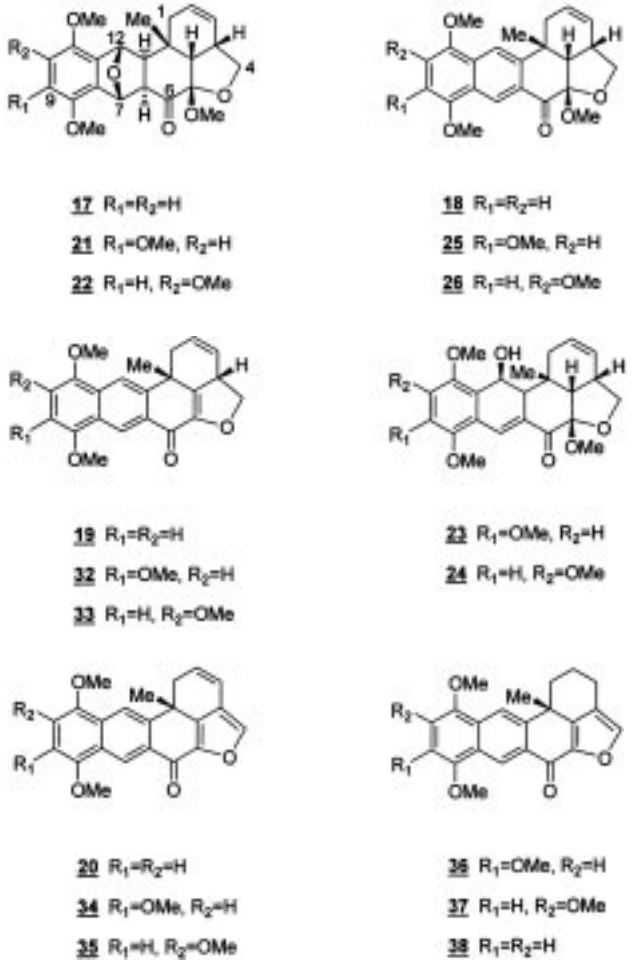


Figure 1. X-Ray structure of **17**.

face-selective *exo*-addition of the two reactants and the site of conformational disorder was identified as the methylene group at C-4 (Fig. 1).

Aromatisation via a 5-*endo-trig* cleavage[25] of the oxygen bridge and subsequent dehydration of the resulting 12-hydroxy derivative was accomplished in 'one pot' to provide an 85% yield of **18** by refluxing with methanolic sodium methoxide. The 5a-methoxyl group was eliminated by brief treatment with trifluoroacetic acid in methylene chloride at room temperature (**19**, 90%), and the furan **20** (ring E) was generated in 87% yield by dehydrogenation with chloranil in refluxing *p*-xylene. Catalytic hydrogenation of the 2,3-alkene was virtually quantitative and the final oxidation at ring D with ceric ammonium nitrate released (±)-xestoquinone **2** in 63% yield. This synthesis of (±) **2** is complete in eight steps and 18.3% overall yield from 4-methylguaiacol and is easily the most efficient route to this pentacyclic natural product to date.

The presence of a methoxyl group at C-9 (as in **7**) or C-10 (as in **8**) complicates the syntheses of these sponge metabolites[5] by any existing route because it introduces dissymmetry into the CD synthons hitherto employed. In embarking on a synthesis of these quinones it was our belief that the route described above for (±) **2** could be adapted at the 5-*endo-trig* oxygen bridge cleavage step to differentiate isomers **21** and **22**. Our experience with this reaction in natural product synthesis[26,27] had persuaded us that the alcohol intermediates **23** and **24** would dehydrate to the aromatics **25** and **26**, respectively, at different rates. The dehydration of the *para* methoxylated benzyl alcohol **23** would be assisted by the C-9 methoxyl group, in contrast to **24** where the C-10 methoxyl group was *meta* to the alcoholic function at C-12 but conjugated with the enone function C_6–C_{6a}–C_7. These effects would be expected to stabilise alcohol **24** but de-stabilise **23** with respect to the dehydration/aromatisation step. Such differences could not be observed of course, in the reaction of **17** and these postulates could only be verified by preparing bridged adducts **21** and **22** and subjecting them to the base-catalysed



5-*endo-trig* oxygen bridge cleavage.

Trimethoxybenzene **27** was brominated in 97% yield to the known[28] bromide **28** which reacted with redistilled furan in the presence of sodamide to provide the benzynefuran adduct **29** in 76% yield. The trimethoxyisobenzofuran **30** was generated from **29** by the dipyridyl-*s*-tetrazine route via the intermediate adduct **31**. In this instance however, the isobenzofuran was of marginal stability and the procedure had to be conducted in the presence of tricyclic dienophile **15**. A 61% yield of a 1:1 mixture of adducts was produced and the similarity of the ^{1}H NMR spectrum of this mixture with that of **17** enabled structures **21** and **22** to be assigned with confidence, to the individual components. Treatment of these mixed adducts with methoxide in refluxing methanol resulted in an approximately 1:1 mixture of alcohol **24** and naphthalene **25** as expected. They were easily separated by simple column chromatography on silica. Occasionally a small amount of naphthalene **26** was also detected in the product but it was removed from **25** by crystallisation. Conversion of **24** to the naphthalene **33** and **25** to **32** were then effected in almost quantitative yields by treatment of these substrates with trifluoroacetic acid. In this manner the two isomeric pentacycles **32** and **33** were obtained separate, pure and crystalline. The structural assignments were unequivocally settled by an X-ray crystallographic determination on intermediate **25**, the naphthalene formed directly by methoxide treatment

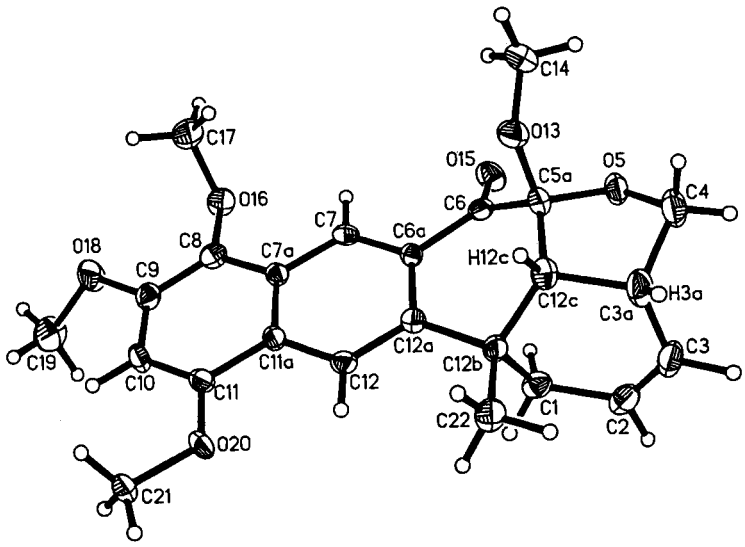


Figure 2. X-Ray structure of **25**.

of the bridged adduct mixture. Fig. 2 shows the methoxyl group in this compound at C-9, thus validating our original hypothesis and eventually permitting a secure structural correlation with one of the natural methoxyxestoquinones in the inseparable mixture isolated[5] from the Philippine sponge.

Subsequent processing of each of these naphthalenes separately (**32**→**34** and **33**→**35**) proceeded as before in comparable yields. Hydrogenation of **34** produced **36** and oxidation with ceric ammonium nitrate converted it to 9-methoxyxestoquinone **7** in an overall yield of 9.5% from trimethoxybenzene in 8 steps while **35** was hydrogenated to **37** and oxidised to 10-methoxyxestoquinone **8** for an overall yield of 8.5%. Thus the combined yield of **7** and **8** from trimethoxybenzene is 18%.

The final correlation with the natural quinones was made by comparison of the ^{1}H and ^{13}C NMR spectra of our synthetic samples with published data.[5] Since that data was obtained from a 70:30 mixture we prepared a similar mixture of our synthetic materials for a ^{1}H NMR spectrum (Fig. 3). We can now confirm that 9-methoxyxestoquinone whose structure is secured by X-ray analysis of **25**, is identical with the major constituent of the natural mixture (previously named 14-methoxyxestoquinone[5]). The minor isomer of that mixture is identical with 10-methoxyxestoquinone

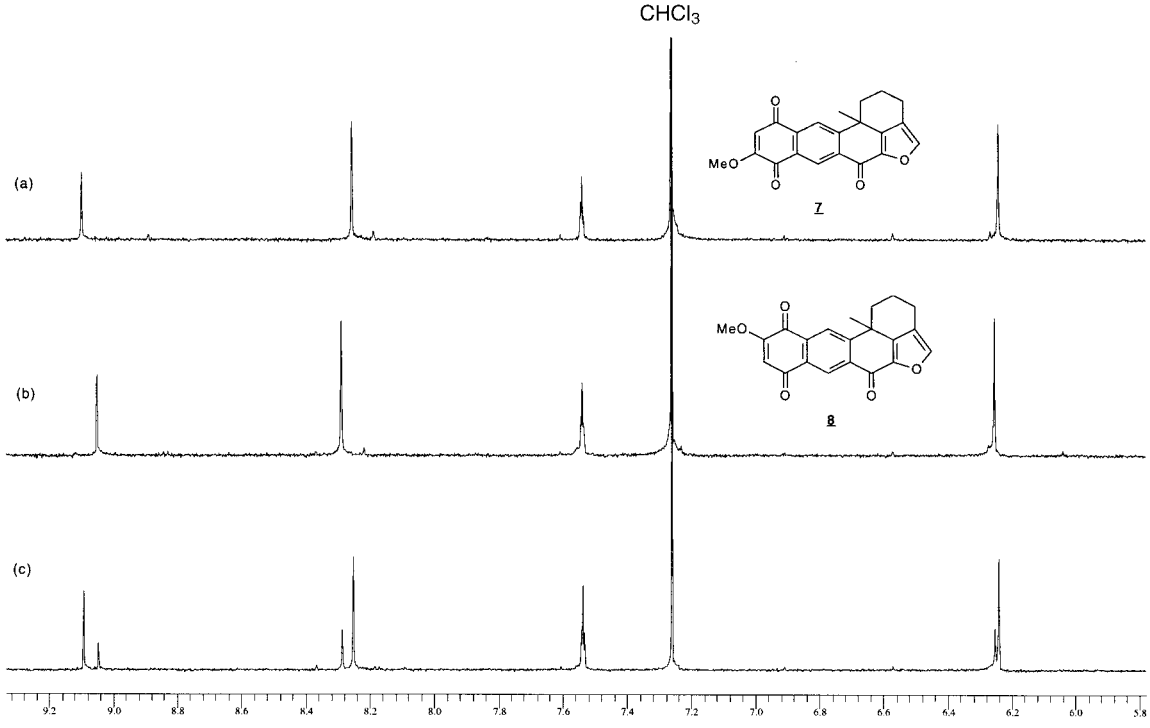


Figure 3. The aromatic regions of the ^{1}H NMR spectra; (a) 9-methoxyxestoquinone (**7**); (b) 10-methoxyxestoquinone (**8**); (c) a ca. 70:30 mixture of **7** and **8**.

(previously 15-methoxyxestoquinone). These assignments also validate the original structural postulates made on the basis of heteronuclear HMBC relationships detected in spectra of the natural mixture. Our synthetic route to the individual methoxyxestoquinones now makes it possible to evaluate these compounds separately as inhibitors of Topoisomerase II.

1. Experimental

1.1. General

All glassware and syringes were dried in an oven, and then cooled in a dry box before use. All temperatures are in °C. Tetrahydrofuran (THF) was distilled from potassium benzophenone ketyl, all other solvents were used as received. All reagents were purchased from Aldrich Chemical Company. Thin layer chromatography was carried out on Merck 5554 pre-coated silica gel 60 F_{254} aluminium sheets. After development, the sheets were viewed under UV light or with an oxidising stain consisting of ceric ammonium sulfate and hexammonium heptamolybdate in 1.8 M H_2SO_4. Flash chromatography was performed using Merck 9385 silica gel 60 (230–400 mesh). Fourier transform infrared spectra (FT-IR) were recorded on a Bomem MB-100 spectrometer or a Perkin–Elmer Spectrum RX spectrometer as neat films between NaCl plates, or KBr discs. ^{1}H and ^{13}C NMR spectra were obtained on Bruker AM-300 and AMX-500 instruments. Chemical shifts for NMR were determined relative to the internal standard tetramethylsilane (δ 0.00), C_6H_6 (δ 7.15) or $CHCl_3$ (δ 7.26) for ^{1}H spectra, and $CDCl_3$ (δ 77.0) for ^{13}C spectra. All ^{1}H NMR data listed have the following order: chemical shift (ppm), (number of protons, multiplicity, coupling constants, assignment). The ^{13}C NMR data listed have the following order: chemical shift (ppm), (assignment). Mass spectra were run at the McMaster Regional Centre for Mass Spectrometry, McMaster University, Hamilton, Ontario. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona.

1.1.1. 7,12-Epoxy-3a,4,5a,6a,7,12,12a-heptahydro-12b-methyl-5a,8,11-trimethoxy-1H-benzo[6,7]phenanthro[10,1-*bc*]furan-6-(12bH)-one (17). A solution of the naphthofuran[17] (**15**) (2.48 g, 11.3 mMol) and 4,7-dimethoxyisobenzofuran[21] (**16**) (2.50 g, 14.0 mMol) in toluene (100 mL) was refluxed for 42 h. Removal of solvent followed by column chroma-tography (30% ethyl acetate/hexanes) gave the bridged compound (**17**) (3.50 g, 78%) as a white solid. Mp 182–184°C (Found: C, 69.5; H, 6.5. $C_{23}H_{26}O_6$ requires C, 69.3; H, 6.6%) ν_{max} 2939, 1731, 1479, 1262 cm^{-1}; δ_H (500 MHz, 340 K, C_6D_6) 1.07 (s, C12b-CH_3), 1.52 (1H, dd, *J*=17.4, 2.4 Hz, H-1), 1.97 (1H, dd, *J*=17.4, 5.3 Hz, H-1), 2.42 (1H, d, *J*=9.4 Hz, H-12c), 2.51 (1H, d, *J*=9.5 Hz, H-12a), 2.68 (1H, bd, *J*=7.5 Hz, H-3a), 2.95 (1H, d, *J*=9.5 Hz, H-6a), 3.20 (1H, t, *J*=7.7 Hz, H-4), 3.37, 3.43 and 3.45 (s, C5a-OCH_3, C8-OCH_3 and C11-OCH_3), 3.82 (1H, t, *J*=8.3 Hz, H-4), 5.25 and 5.46 (2H, m, H-2 and H-3), 5.51 (1H, s, H-12), 6.31 (1H, s, H-7), 6.42 (2H, s, H-9 and H-10). *m/z* 398 (M^+, 1), 209 (17), 178 (100), 163 (29).

1.1.2. 3a,4,5a,12c-Tetrahydro-5a,8,11-trimethoxy-1H-benzo[6,7]phenanthro[10,1-*bc*]furan-6-(12bH)-one (18). Sodium (102 mg, 4.44 mMol) was added to a solution of the bridged compound (**17**) (354 mg, 0.89 mMol) in methanol (10 mL) at room temperature. The resulting mixture was heated under reflux for 4.5 h then concentrated in vacuo. The yellow residue was treated with 3N HCl (2 mL) and the aqueous layer extracted with ethyl acetate. Column chromatography gave the aromatic compound (**18**) (305 mg, 90%) as a yellow crystalline solid from ether/hexanes. mp 228–229°C (Found: C, 72.4; H, 6.3. $C_{23}H_{24}O_5$ requires C, 72.6; H, 6.3%) ν_{max} (KBr) 2928, 1704, 1454, 1268 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.64 (3H, s, C12b-CH_3), 1.87 (1H, dd, *J*=17.9, 5.8 Hz, H-1), 2.04 (1H, dd, *J*=17.9, 2.2 Hz, H-1), 2.74 (1H, dd, *J*=8.2, 1.8 Hz, H-12c), 3.12 (1H, m, H-3a), 3.21 (3H, s, C5a-OCH_3), 3.91 (1H, d, *J*=8.3 Hz, H-4), 3.95 and 3.97 (s, C8-OCH_3 and C11–OCH_3), 4.15 (1H, dd, *J*=8.3, 5.9 Hz, H-4), 5.69 (1H, dt, *J*=10.1 Hz, 3.0 Hz, H-3), 5.78 (1H, bd, *J*=10.1 Hz, H-2), 6.70 and 6.81 (1H each, d, *J*=8.4 Hz, H-9 and H-10), 8.21 (1H, s, H-12), 8.72 (1H, s, H-7). δ_C (125 MHz, $CDCl_3$) 24.5 (C12b–CH_3), 35.6 (C-12b), 37.9 (C-3a), 39.8 (C-1), 50.0 (5a-OCH_3), 54.3 (C-12c), 55.8 and 55.9 (OCH_3), 72.5 (C-4), 103.8 and 106.3 (C-9 and C-10), 105.5 (C-5a), 117.3 (C-12), 123.3 (C-7), 124.8, 128.5 and 131.8 (C-6a, C-7a and C-11a), 126.3 and 126.8 (C-2 and C-3), 146.2, 149.3 and 150.8 (C-12a, C-8, C-11), 193.2 (C-6). *m/z* 380 (M^+, 100), 365 (8), 349 (5), 281 (22), 253 (22).

1.1.3. 3,4-Dihydro-12b-methyl-8,11-dimethoxy-1H-benzo[6,7]phenanthro[10,1-bc]furan-6-(12bH)-one (19) and 12b-methyl-8,11-dimethoxy-1H-benzo[6,7]phenanthro[10,1-*bc*]furan-6-(12bH)-one (20). Trifluoroacetic acid (0.5 mL) was added to a solution of the ketone (**18**) (112 mg, 0.29 mMol) in dichloromethane (3 mL) and the mixture was stirred at room temperature for 15 min. $NaHCO_3$ was added in small portions followed by water (10 mL). The dienone (**19**) was extracted into ethyl acetate and isolated as a yellow oil. (Found: M^+, 348.1355. $C_{22}H_{20}O_4$ requires M, 348.1361), ν_{max} 2947, 2835, 1666, 1624, 1242 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.65 (3H, s, C12b–CH_3), 2.30 (1H, d, *J*=17.1 Hz, H-1), 2.98 (1H, dd, *J*=17.1, 4.1 Hz, H-1), 3.97 and 3.99 (s, C8–OCH_3 and C11-OCH_3), 4.05 (2H, m, H-3a and H-4), 4.94 (1H, dd, *J*=8.5, 6.8 Hz, H-4), 5.80 (2H, m, H-2 and H-3), 6.68 (1H, d, *J*=8.3 Hz, H-9 or H-10), 6.80 (1H, d, *J*=8.3 Hz, H-9 or H-10), 8.35 (1H, s, H-12), 9.22 (1H, s, H-7). δ_C (62 MHz, $CDCl_3$) 25.2 ((12b-CH_3), 37.6 (C-12b), 41.3 (C-3a), 43.4 (C-1), 55.7 (2×OCH_3), 76.0 (C-4), 103.1 and 105.6 (C-9 and C-10), 119.1 (C-12), 122.9 (C-7), 124.8, 127.7 and 129.9 (C-6a, C-12a and C-11a), 125.9 and 127.1 (C-2 and C-3), 140.4 (C-12c), 146.0, 146.8, 148.6 and 150.8 (C-5a, C-8, C-11 and C-7a), 176.4 (C-6). *m/z* 348 (M^+, 100), 333 (33), 318 (14), 303 (22). This oil was refluxed in xylenes (10 mL) with *p*-chloranil (145 mg, 0.59 mMol) for 48 h. Column chromatography of the concentrated reaction mixture gave the aromatic furan (**20**) as a yellow crystalline solid (88 mg, 86%). The ^{1}H NMR spectrum was identical with the literature spectrum.[12]

1.1.4. 12b-Methyl-8,11-dimethoxy-1H-benzo[6,7]phenanthro[10,1-*bc*]furan-6-(12bH)-one (38). Palladium on carbon (10%, 4.3 mg) and $NaHCO_3$ (50 mg) was added to a solution of the furan (**20**) (33.0 mg, 0.095 mMol) in ethyl acetate (15 mL), then treated with hydrogen (1 atmosphere)

for 4 h. The reaction mixture was filtered and concentrated to give an oil which on column chromatography (silica gel, ethyl acetate/hexanes) gave xestoquinol dimethyl ether (**38**) as yellow crystals (32.3 mg, 97%). The ^{1}H NMR spectrum was identical with the literature spectrum.[10]

1.1.5. Xestoquinone (2). The hydrogenated furan (**38**) (33 mg, 0.09 mMol) was dissolved in acetonitrile (2 mL) and ceric ammonium nitrate (153 mg, 0.28 mMol) in water (3 mL) was added dropwise at 0°C. The solution was stirred for 5 min at 0°C, then water (10 mL) was added. Extraction with ethyl acetate gave the crude product which was purified by column chromatography on silica gel using ethyl acetate/hexanes to give xestoquinone (**2**) (19 mg, 63%) as flaky orange crystals. The ^{1}H NMR spectrum was identical with the literature spectrum.[12]

1.1.6. Bromo-2,4,5-trimethoxybenzene (28). Bromine (1.59 mL, 30.9 mMol) in dichloromethane (50 mL) was added dropwise to a solution of 1,2,4-trimethoxybenzene (**27**) (4.945 g, 29.4 mMol) in dichloromethane (200 mL) at 0°C. The resulting mixture was washed with aqueous sodium bisulfite, aqueous sodium bicarbonate and water. Removal of the solvent gave bromo-2,4,5-trimethoxybenzene (**28**) (7.057 g, 97%) as a white solid, mp 53–54°C (lit.[28] mp 54–55.5°C).

1.1.7. 1,4-Dihydro-5,6,8-trimethoxy-1,4-epoxynapthalene (29). Bromo-2,4,5-trimethoxybenzene (**28**) (13.924 g, 56.4 mMol) in THF (100 mL) was added dropwise to a mixture of furan (70 mL, 0.96 mol) and sodium amide (9.20 g, 0.24 mol) in THF (140 mL) at 50°C under argon. The mixture was stirred at 55°C for 11 h, filtered and partitioned between water and ethyl acetate. The organic layer was dried, evaporated and the residue was chromatographed on silica gel (9:1 hexanes:ethyl acetate) to give 1,4-dihydro-5,6,8-trimethoxy-1,4-epoxynapthalene (**29**) (10.006 g, 76%). Recrystallisation from hexanes gave colourless prisms, mp 84–85°C. (Found: C, 67.21; H, 5.90. $C_{13}H_{14}O_4$ requires C, 66.66; H, 6.50%) ν_{max} (NaCl) 2940, 2839, 1631, 1614, 1491, 1464 cm^{-1}. δ_H 3.81(5), 3.82 and 3.85 (s, OCH_3), 5.92 (1H, d, J=1.3 Hz, H-1 or H-4), 5.96 (d, J=1.3 Hz, H-1 or H-4), 6.12 (1H, s, H-7), 7.00 (1H, dd, J=5.5, 1.7 Hz, H-2 or H-3), 7.05 (1H, dd, J=5.5, 1.7 Hz, H-2 or H-3). δ_C 56.3, 56.7 and 61.2 (OCH_3), 80.1, 80.6 (C-1 and C-4), 95.9 (C-7), 125.9, 138.6, 140.0, 148.2, 151.2 (C-4a, C-5, C-6, C-8, C-8a), 141.5, 143.0 (C-2 and C-3). m/z 234 (M^+, 73), 206 (34), 193 (77), 191 (100), 165 (21).

1.1.8. 7,12-Epoxy-3a,4,5a,6a,7,12,12a-heptahydro-12b-methyl-5a,8,9,11-tetramethoxy-1H-benzo[6,7]phenanthro[10,1-*bc*]furan-6-(12bH)-one (21) and 7,12-Epoxy-3a,4,5a,6a,7, 12,12a-heptahydro-12b-methyl-5a,8,10,11-tetramethoxy-1H-benzo[6,7]phenanthro[10,1-*bc*]furan-6-(12bH)-one (22). 3,6-(Dipyridin-2′-yl)tetrazine[24] (3.724 g, 15.8 mMol) was added to a solution of the bridged ether (**29**) (3.680 g, 15.7 mMol) in chloroform (180 mL). The reaction mixture was stirred for 1 h at room temperature. A solution of the naphthofuran[17] (**15**) (2.875 g, 1.31 mMol) in toluene (300 mL) was added and the resulting solution was refluxed for 25 h. The solution was concentrated in vacuo and the residue was chromatographed on silica (1:1 hexanes:ethyl acetate) to give an inseparable mixture (1:1) of the coupled products (**21**) and (**22**) (4.093 g, 61%). (Found: M^+, 428.1804. $C_{24}H_{28}O_7$ requires M, 428.1835) ν_{max} (NaCl) 2941, 2840, 1738, 1498 cm^{-1}. δ_H (300 MHz, C_6D_6, 340K) 1.06 (s, C12b-CH_3), 1.07 (s, C12b-CH_3), 1.56 (1H, dd, J=17.4, 2.6 Hz, H-1), 1.57 (1H, dd, J=17.4, 2.6 Hz, H-1), 1.97 (1H, dd, J=17.4, 5.3 Hz, H-1), 1.98 (1H, dd, J=17.4 Hz, 5.3 Hz, H-1), 2.44-2.52 (2H, m, H-12c and H-12a), 2.65-2.75 (1H, m, H-3a), 2.98 (1H, d, J=9.6 Hz, H-6a), 3.21-3.28 (1H, m, H-4), 3.35, 3.40, 3.41 and 3.47 (s, C5a-OCH_3, C8-OCH_3 and C11–OCH_3), 3.61 (s, C9-OCH_3 or C10–OCH_3), 3.68 (s, C9-OCH_3 or C10-OCH_3), 3.83 (1H, dd, J=8.4 Hz, H-4), 5.22-5.32 (1H, m, H-2), 5.40–5.50 (1H, m, H-3), 5.45 and 5.46 (1H, s, H-12), 6.13 and 6.15 (1H, s, H-7), 6.28 (1H, bs, H-9 or H-10). m/z 428 (M^+, 7), 400 (38), 385 (18), 293 (29), 245 (47), 165 (100).

1.2. Aromatisation of the B ring

Sodium methoxide (0.354 g, 6.55 mMol) was added to a solution of a 1:1 mixture of (**21**) and (**22**) (0.704 g, 1.64 mMol) in methanol (100 mL), then the solution was heated under reflux for 4 h. The mixture was concentrated, then acidified with 3N HCl. The aqueous solution was extracted with ethyl acetate to provide a yellow oil. Column chromatography on silica gel using ethyl acetate/hexanes followed by ethyl acetate as eluents gave in order of elution the aromatic compound (**25**) (0.289 g, 43%) and the alcohol (**24**) (0.275 g, 39%). **12b-Methyl-3a,4,5a,12c-tetrahydro-5a,8,9,11-tetramethoxy-1H-benzo[6,7]phenanthro[10,1-*bc*]furan-(12bH)-one (25).** Mp 202–203°C. (Found: C, 70.45; H, 6.49. $C_{24}H_{26}O_6$ requires C 70.23; H, 6.38%) ν_{max} 2938, 1703, 1599, 1463, 1359 cm^{-1}. δ_H (250 MHz, $CDCl_3$) 1.62 (3H, s, C12b-CH_3), 1.87 (1H, dd, J=17.7, 5.4 Hz, H-1), 2.05 (dd, 1H, dd, J=18.0, 2.0 Hz, H-1), 2.73 (1H, dd, J=8.2, 1.7 Hz, H-12c), 3.12 (1H, m, H-3a), 3.21 (3H, s, C5–OCH_3), 3.93 (1H, d, J=8.6 Hz, H-4), 3.95, 4.01 and 4.02 (s, C(8)–OCH_3, C(9)–OCH_3 and C(11)–OCH_3), 4.16 (1H, dd, J=8.4, 5.9 Hz, H-4), 5.69 (1H, ddd, J=10.1, 2.9, 2.9 Hz, H-3), 5.78 (1H, dddd, J=10.1, 5.5, 1.8, 1.8 Hz, H-2), 6.74 (1H, s, H-10), 8.16 (1H, s, H-12), 8.54 (1H, s, H-7). δ_C 24.4 (12b-CH_3), 35.2 (C-12b), 37.8 (C-3a), 39.6 (C-1), 49.8 (5a-OCH_3), 54.2 (C-12c), 54.2, 55.8 and 61.5 (OCH_3), 72.4 (C-4), 97.9 (C-10), 104.9 (C-5a), 117.5 (C-12), 122.1 (C-7), 123.1 (C-11a), 126.1 and 126.6 (C-2 and C-3), 127.8 and 132.9 (C-6a and C-7a), 138.0, 143.4, 148.6 and 152.2 (C-8, C-9, C-11 and C-12a), 193.3 (C-6). m/z 410 (100), 395 (63), 367 (25), 311 (31), 99 (40); and **12-hydroxy-12b-methyl-3a,4,5a,12,12c-pentahydro-5a,8,10,11-tetramethoxy-1H-benzo[6,7]phenanthro[10,1-*bc*]furan-6-(12bH)-one (24)** as a yellow foam. (Found: M^+, 428.1846. $C_{24}H_{28}O_7$ requires M 428.1835), ν_{max} 3479, 2932, 1699, 1593, 1468, 1328, 1224 cm^{-1}. δ_H (250 MHz, $CDCl_3$) 1.36 (3H, s, C12b-CH_3), 1.64 (1H, dd, J=18.0, 4.1 Hz, H-1), 2.05 (1H, d, J=18.0 Hz, H-1), 2.45 (1H, dd, J=2.8, 2.8 Hz, H-12a), 2.90 (1H, m, H-3a), 2.96 (1H, d, J=7.6 Hz, H-12c), 3.07 (3H, s, C5a-OCH_3), 3.85 (1H, concealed, H-4), 3.80, 3.82 and 3.88 (s, C8-OCH_3, C10-OCH_3 and C11-OCH_3), 3.95 (1H, dd, J=8.4, 5.4 Hz, H-4), 5.20 (1H, dd, J=10.2, 3.0 Hz, H-12), 5.54 (1H, d, J=10.1 Hz, H-3), 5.68 (1H, m, H-2), 6.41 (1H, s, H-9), 7.54 (1H, d, J=2.7 Hz, H-7). δ_C (50 MHz, $CDCl_3$) 24.1 (C12b–CH_3), 31.9 (C-12b), 35.0 (C-1), 37.9 (C-3a), 49.4,

50.5 and 61.8 (OCH_3), 55.2 and 55.8 (C-12a and C-12c), 61.8 (OCH_3), 62.5 (C-12), 72.0 (C-4), 96.1 (C-9), 104.7 (C-5a), 112.4 (C-10), 125.8, 126.4 and 127.0 (C-2, C-3 and C-7), 130.4, 133.5 and 139.7 (C-6a, C-7a and C-11a), 154.5 and 155.3 (C-8 and C-11), 195.0 (C-6). *m/z* 428 (M^+, 2), 209 (46), 208 (100), 193 (54).

1.2.1. 3,4-Dihydro-12b-methyl-8,9,11-trimethoxy-1H-benzo[6,7]phenanthro[10,1-*bc*]furan-6-(12bH)-one (32). Trifluoroacetic acid (2.5 mL) was added to a solution of the ketone (**25**) (450 mg, 1.10 mMol) in dichloromethane (40 mL) and the mixture was stirred at room temperature for 15 min. $NaHCO_3$ was added in small portions followed by water (40 mL), the product was extracted with ethyl acetate, removal of solvent gave the dienone (**32**) (409 mg, 99%) as a yellow oil. (Found: M^+, 378.1436. $C_{23}H_{22}O_5$ requires M 378.1467), ν_{max} (NaCl) 2966, 2936, 1662, 1624, 1596 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.64 (3H, s, C12b–CH_3), 2.29 (1H, bd, *J*=17.5 Hz, H-1), 2.91 (1H, dd, *J*=17.5, 3.6 Hz, H-1), 3.97, 4.02 and 4.03 (9H, s, 8-OCH_3, 9-OCH_3, 11-OCH_3), 4.03 (1H, concealed, H-3a), 4.12 (1H, dd, *J*=6.7, 2.0 Hz, H-4), 4.94 (1H, dd, *J*=8.5, 6.7 Hz, H-4), 5.80 (2H, m, H-2 and H-3), 6.75 (1H, s, H-10), 8.32 (1H, s, H-12), 9.05 (1H, s, H-7). δ_C (75 MHz, $CDCl_3$) 25.3 (12b-CH_3), 36.9 (C-12b), 41.3 (C-3a), 43.5 (C-1), 55.8, 57.5 and 61.6 (OCH_3), 75.9 (C-4), 97.9 (C-10), 119.5 (C-12), 121.8 (C-7), 122.8 (C-11a), 125.8, 127.1 (C-2 and C-3), 127.9 and 130.9 (C-7a and C-12a), 137.9, 140.7, 143.4, 146.8, 148.3 and 151.8 (C-5a, C-6a, C-8, C-9, C-11 and C-12c), 176.4 (C-6). *m/z* 378 (M^+, 25), 363 (16), 152 (27), 120 (49), 49 (100).

1.2.2. 12b-methyl-8,9,11-trimethoxy-1H-benzo[6,7]phenanthro-[10,1-*bc*]furan-6-(12bH)-one (34). A solution of the dienone (**32**) (260 mg, 0.69 mMol) and *p*-chloranil (345 mg, 1.40 mMol) in xylenes (30 mL) was refluxed for 52 h. Column chromatography of the concentrated reaction mixture gave the aromatic furan (**34**) (227 mg, 88%) as orange crystals from ethyl acetate/hexanes. mp 167–168°C (Found: C, 73.52; H, 5.32. $C_{23}H_{20}O_5$ requires C, 73.39; H, 5.36%) ν_{max} (NaCl) 2973, 2941, 1675, 1624, 1596 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.56 (3H, s, 12b-CH_3), 2.56 (1H, ddd, *J*=16.8, 3.0, 3.0 Hz, H-1), 3.13 (1H, dd, *J*=16.8, 6.1 Hz, H-1), 3.99, 4.02 and 4.03 (s, C8-OCH_3, C9–OCH_3 and C11-OCH_3), 6.11 (1H, ddd, *J*=9.7, 6.2, 1.8 Hz, H-2), 6.62 (1H, dd, *J*=9.7, 3.1 Hz, H-3), 6.76 (1H, s, H-10), 7.57 (1H, s, H-4), 8.22 (1H, s, H-12), 9.13 (1H, s, H-7). δ_C (75 MHz, $CDCl_3$) 32.2 (12b-CH_3), 35.2 (C-12b), 35.4 (C-1), 55.8, 57.4 and 61.6 (OCH_3), 98.0 (C-10), 117.5 (C-2), 118.6 (C-12), 121.0 and 122.4 (C-3a and C-11a), 123.2 (C-7), 127.7 (C-7a), 128.8 (C-3), 132.4 (C-12a), 138.0 (C-8), 141.5 (C-4), 143.1 and 144.2 (C-5a and C-12c), 144.4, 148.5 and 151.8 (C-6a, C-9 and C-11), 172.7 (C-6). *m/z* 376 (M^+, 87), 361 (100), 331 (21), 303 (14), 145 (24).

1.2.3. 12b-Methyl-8,9,11-trimethoxy-1H-benzo[6,7]phenanthro-[10,1-*bc*]furan-6-(12bH)-one (36). Palladium on carbon (10%, 20 mg) and $NaHCO_3$ (1.0 g) was added to a solution of the furan (**34**) (121 mg, 0.32 mMol) in ethyl acetate (50 mL), then treated with hydrogen (1 atm) for 4 h. The reaction mixture was filtered and concentrated to give an oil which on column chromatography (silica gel, ethyl acetate/hexanes) gave the xestoquinol dimethyl ether (**36**) (114 mg, 93%) as a yellow solid. mp 193–195°C (Found: C, 72.82; H, 5.78. $C_{23}H_{22}O_5$ requires C, 73.00; H, 5.86%) ν_{max} 2940, 1670, 1626, 1595 $cm^{-1.}$ δ_H (300 MHz, $CDCl_3$) 1.53 (3H, s, C12b-CH_3), 1.80 (1H, ddd, *J*=13.2, 4.4, 4.4 Hz, H-1), 2.11-2.15 (2H, m, H-2), 2.54-2.68 (2H, m, H-1 and H-3), 2.87 (1H, dd, *J*=17.1, 7.5 Hz, H-3), 3.96 (3H, s, OCH_3), 4.00 (6H, s, OCH_3), 6.75 (1H, s, H-10), 7.47 (1H, t, *J*=1.3 Hz, H-4), 8.23 (1H, s, H-12), 9.10 (1H, s, H-7); δ_C (75 MHz, $CDCl_3$) 17.2 (C-3), 18.7 (C-2), 32.1 (C-1), 33.8 (C12b–CH_3), 36.1 (C-12b), 55.8, 57.5 and 61.6 (OCH_3), 98.0 (C-10), 117.8 (C-12), 121.2 and 122.3 (C-3a and C-11a), 123.2 (C-7), 127.7 and 132.5 (C-7a and C-12a), 138.2 (C-8), 143.8, 144.2 and 144.7 (C-4, C-5a and C-12c), 146.8, 148.4 and 151.8 (C-6a, C-9 and C-11), 172.9 (C-6). *m/z* 378 (M^+, 86), 363 (100), 333 (19), 319 (20), 189 (19), 174 (37).

1.2.4. 9-Methoxyxestoquinone (7). The dimethyl ether (**36**) (100 mg, 0.26 mMol) was dissolved in acetonitrile (30 mL) and ceric ammonium nitrate (435 mg, 0.79 mMol) in water (20 mL) was added dropwise at 0°C. The solution was stirred for 5 min at 0°C, then water (30 mL) was added. Extraction with ethyl acetate gave the crude product which was purified by column chromatography on silica gel using ethyl acetate/hexanes (4:1) to give 9-methoxyxestoquinone (**7**) (55 mg, 60%) as fine yellow needles from acetonitrile. mp 307–310°C (Found: $M^{+\cdot}$, 348.0966. $C_{21}H_{16}O_5$ requires M, 348.0998) ν_{max} (NaCl) 2948, 1693, 1665, 1648, 1605 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.54 (3H, s, 12b-CH_3), 1.76 (1H, ddd, *J*=13.0, 4.5, 4.5 Hz, H-1), 2.11-2.37 (2H, m, H-2), 2.52-2.62 (1H, m, H-1), 2.66 (1H, dd, *J*=17.0, 9.0 Hz, H-3), 2.89 (1H, dd, *J*=17.0, 7.6 Hz, H-3), 3.94 (3H, s, OCH_3), 6.24 (1H, s, H-10), 7.54 (1H, dd, *J*=1.3, 1.3 Hz, H-4), 8.25 (1H, s, H-12), 9.10 (1H, s, H-7). δ_C (75 MHz, $CDCl_3$) 16.9 (C-3), 18.4 (C-2), 31.2 (C-1), 32.5 (12b-CH_3), 37.4 (C-12b), 56.6 (OCH_3), 110.1 (C-10), 121.5 (C-3a), 123.0 (C-12), 127.3 (C-7), 129.5 (C-7a), 133.5 (C-11a), 137.6 (C-6a), 144.0 (C-5a), 144.9 (C-4), 147.2 (C-12c), 156.7 (C-12a), 161.0 (C-9), 170.3 (C-6), 178.9 (C-8), 184.4 (C-11). *m/z* 348 (M^+, 40), 333 (100), 249 (11), 221 (10), 193 (10).

1.2.5. 3,4-Dihydro-12b-methyl-8,10,11-trimethoxy-1H-benzo-[6,7]phenanthro[10,1-*bc*]furan-6-(12bH)-one (33). Trifluoroacetic acid (5.0 mL) was added to a solution of the alcohol (**24**) (0.902 g, 2.11 mMol) in dichloromethane (60 mL) and the mixture was stirred at room temperature for 15 min. $NaHCO_3$ was added in small portions followed by water (50 mL). The product was extracted into ethyl acetate and removal of the solvent gave the dienone (**33**) as an orange crystalline solid (0.770 g, 97%). mp 178–179°C (Found: C, 72.88; H, 5.79. $C_{23}H_{22}O_5$ requires C, 73.00; H, 5.86%) ν_{max} (NaCl) 2968, 2940, 1676, 1656, 1618 cm^{-1}; δ_H 1.65 (3H, s, 12b-CH_3), 2.32 (1H, bd, *J*=17.1 Hz, H-1), 2.92 (1H, dd, *J*=17.1, 4.4 Hz, H-1), 3.95, 4.02 and 4.05 (s, C8-OCH_3, C10-OCH_3, C11-OCH_3), 4.03 (concealed, H-3a), 4.14 (1H, d, *J*=7.5 Hz, H-4), 4.95 (1H, dd, *J*=8.8, 7.5 Hz, H-4), 5.80 (2H, m, H-2 and H-3), 6.63 (1H, s, H-9), 8.14 (1H, s, H-12), 9.19 (1H, s, H-7). δ_C (75 MHz, $CDCl_3$) 25.2 (12b-CH_3), 36.9 (C-12b), 41.2 (C-3a), 43.3 (C-1), 55.6, 56.8 and 61.0 (OCH_3), 75.9 (C-4), 94.6 (C-9), 117.7 (C-12), 119.6 (C-11a), 123.5 (C-7), 125.9 (C-3), 126.9 (C-2), 127.7, 130.6 (C-7a and

C-12a), 135.5 and 139.8 (C-11 and C-12c), 146.6, 146.9, 150.6 and 154.2 (C-5a, C-6a, C-8 and C-10), 176.2 (C-6). *m/z* 378 (M^+, 100), 363 (82), 335 (28), 305 (15).

1.2.6. 12b-methyl-8,10,11-trimethoxy-1H-benzo[6,7]phenanthro-[10,1-*bc*]furan-6-(12bH)-one (35). A solution of the dienone (**33**) (757 mg, 2.00 mMol) and *p*-chloranil (995 mg, 4.05 mMol) in xylenes (50 mL) was refluxed for 48 h. Column chromatography of the concentrated reaction mixture gave the aromatic furan (**35**) (708 mg, 94%) as orange crystals from ethyl acetate/hexanes. mp 170–171°C (Found: C, 73.13; H, 5.54. $C_{23}H_{20}O_5$ requires C, 73.39; H, 5.36%) ν_{max} (NaCl) 2966, 2937, 1671, 1618 cm^{-1}; δ_H 1.56 (3H, s, 12b-CH_3), 2.65 (1H, ddd, *J*=16.7, 2.6, 2.6 Hz, H-1), 3.14 (1H, dd, *J*=16.7, 6.1 Hz, H-1), 3.95, 4.03 and 4.05 (s, C8–OCH_3, C10-OCH_3 and C11-OCH_3), 6.11 (1H, ddd, *J*=9.7, 6.2, 1.8 Hz, H-2), 6.62 (1H, dd, *J*=9.7, 3.1 Hz, H-3), 6.65 (1H, s, H-9), 7.56 (1H, s, H-4), 8.05 (1H, s, H-12), 9.26 (1H, s, H-7). δ_C 32.2 (12b-CH_3), 35.2 (C-12b and C-1), 55.7, 56.8 and 61.1 (OCH_3), 94.7 (C-9), 116.8 (C-2), 117.5 (C-12), 119.4 (C-11a), 120.9 (C-3a), 124.8 (C-7), 128.6 (C-3), 129.0 (C-7a), 130.5 (C-12a), 135.7 (C-11), 141.2 (C-4), 143.7 (C-5a), 144.2 (C-12c), 146.7 (C-6a), 151.0 (C-10), 154.3 (C-8), 172.6 (C-6). *m/z* 376 (M^+, 93), 361 (100), 346 (23), 331 (16), 303 (16).

1.2.7. 12b-Methyl-8,10,11-trimethoxy-1H-benzo[6,7]-phenanthro-[10,1-*bc*]furan-6-(12bH)-one (37). Palladium on carbon (10%, 30 mg) and $NaHCO_3$ (1.5 g) were added to a solution of the furan (**35**) (339 mg, 9.01 mMol) in ethyl acetate (50 mL), then treated with hydrogen (1 atmosphere) for 4 h. The reaction mixture was filtered and concentrated to give an oil which on column chromatography (silica gel, ethyl acetate/hexanes) gave the xestoquinol dimethyl ether (**37**) (297 mg, 87%) as a yellow solid. Mp 210–212°C (Found C, 73.00; H, 6.03. $C_{23}H_{22}O_5$ requires C, 73.00; H, 5.86%) ν_{max} 2967, 1670, 1656, 1609 cm^{-1}. δ_H 1.54 (3H, s, 12b-CH_3), 1.85 (1H, ddd, *J*=13.2, 4.2, 4.2 Hz, H-1), 2.10–2.30 (2H, m, H-2), 2.57–2.68 (2H, m, H-1 and H-3), 2.87 (1H, dd, *J*=17.1, 7.5 Hz, H-3), 3.94, 4.02 and 4.04 (s, 8-OCH_3, 10-OCH_3 and 11-OCH_3), 6.63 (1H, s, H-9), 7.46 (1H, t, *J*=1.3 Hz, H-4), 8.07 (1H, s, H-12), 9.23 (1H, s, H-7). δ_C 17.2 (C-3), 18.7 (C-2), 31.9 (C-1), 33.8 (12b-CH_3), 36.2 (C-12b), 55.7, 56.9 and 61.1 (OCH_3), 94.6 (C-9), 116.1 (C-12), 119.4 and 121.1 (C-3a and C-11a), 124.8 (C-7), 129.2 and 130.4 (C-7a and C-12a), 135.9 (C-11), 143.5 (C-4), 144.7, 146.2, 147.8, 150.9 and 154.3 (C-5a, C-6a, C-8, C-10 and C-12c), 172.8 (C-6). *m/z* 378 (M^+, 77), 363 (100), 348 (35), 333 (19), 305 (16), 174 (42).

1.2.8. 10-Methoxyxestoquinone (8). The dimethyl ether (**37**) (284 mg, 0.75 mMol) was dissolved in acetonitrile (60 mL) and ceric ammonium nitrate (1.23 g, 2.24 mMol) in water (40 mL) was added dropwise at 0°C. The solution was stirred for 5 min at 0°C, then water (60 mL) was added. Extraction with ethyl acetate gave the crude product was purified by column chromatography on silica gel using ethyl acetate/hexanes (4:1) to give 10-methoxyxestoquinone (**8**) (157 mg, 60%) as fine yellow needles from acetonitrile. mp 268–270°C (Found: C, 72.38; H, 4.90. $C_{21}H_{16}O_5$ requires C, 72.41; H, 4.63%) ν_{max} (NaCl) 2946, 1676, 1605 cm^{-1}. δ_H 1.54 (3H, s, 12b-CH_3), 1.76 (1H, ddd, *J*=13.2, 4.4, 4.4 Hz, H-1), 2.11–2.35 (2H, m, H-2), 2.58–2.70 (2H, m, H-1 and H-3), 2.88 (dd, *J*=17.1, 7.5 Hz, H-3), 3.93 (s, OCH_3), 6.26 (1H, s, H-9), 7.54 (1H, dd, *J*=1.3, 1.3 Hz, H-4), 8.29 (1H, s, H-12), 9.05 (1H, s, H-7). δ_C 16.9 (C-3), 18.4 (C-2), 31.2 (C-1), 32.5 (C12b-CH_3), 42.3 (C-12b), 56.6 (OCH_3), 110.6 (C-9), 121.5 (C-3a), 123.5 (C-12), 126.7 (C-7), 130.5 (C-7a), 132.4 (C-11a), 138.3 (C-6a), 144.0 (C-5a), 144.9 (C-4), 147.2 (C-12c), 155.7 (C-12a), 160.5 (C-10), 170.3 (C-6), 179.9 (C-11), 183.6 (C-8). *m/z* 348 (M^+, 39), 333 (100), 305 (6), 249 (11).

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada for support of this work.

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