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www.publish.csiro.au/journals/ajc *Aust. J. Chem.* **2003**, *56*, 691–702

The Synthesis of 5-Hydroxy-3-methylnaphtho[2,3-*c*]furan-4,9-dione and 5,8-Dihydroxy-1-methylnaphtho[2,3-*c*]furan-4,9-dione

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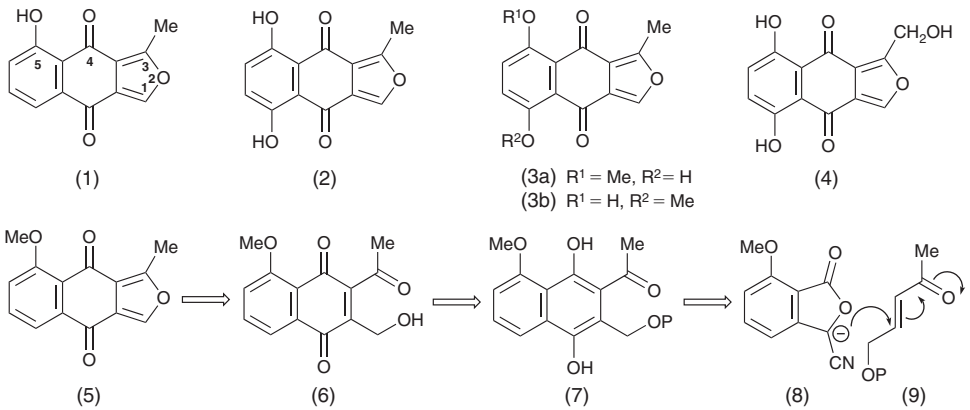
5-Hydroxy-3-methylnaphtho[2,3-*c*]furan-4,9-dione (1), a metabolite isolated from *Aloe ferox* and *Bulbine capitata*, has been synthesized by a sequence involving an annulation reaction between the anion of 4-methoxy-3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile (8) and (*E*)-pent-3-en-2-one, followed by subsequent construction of the furan ring through allylic bromination, hydrolysis, and dehydration as the key steps. The formation of several unusual products observed in annulation reactions between (8) and *O*-protected derivatives of (*E*)-5-hydroxypent-3-en-2-one (9) can be rationalized by invoking the intermediacy of a reactive *o*-quinone methide. 5,8-Dihydroxy-1-methylnaphtho[2,3-*c*]furan-4,9-dione (2), another naturally occurring naphtho[2,3-*c*]furan-4,9-dione, has been prepared by a Friedel–Crafts acylation of 1,4-dimethoxybenzene with 2-methylfuran-3,4-dicarbonyl dichloride. Arguments are presented that 5,8-dihydroxynaphtho[2,3-*c*]furan-4,9-dione is a better structural representation than the alternative 4,9-dihydroxynaphtho[2,3-*c*]furan-5,8-dione tautomer in such systems, as the latter would contain a reactive isobenzofuran moiety.

Manuscript received: 4 December 2002.
Final version: 6 March 2003.

Introduction

In recent years, several naturally occurring compounds incorporating the naphtho[2,3-*c*]furan-4,9-dione ring system have been characterized. In addition to nectriafurone[1] and the ventilones,[2–4] metabolites of this class of have been found in plant families which have been used traditionally for therapeutic purposes.[5,6] Thus 5-hydroxy-3-methylnaphtho [2,3-*c*]furan-4,9-dione (1) was isolated from *Aloe ferox* (Cape aloe)[5] and again from *Bulbine capitata* along with three related compounds (2), (3a) or (3b), and (4)[6,7] (Scheme 1; see also Scheme 8). The healing properties of the plants of the *Aloe* genus are well known,[8] and the milk decoction of the roots of *B. capitata* is used for the treatment of body rash and sexually transmitted diseases in Botswana.[6] Some of these and related 'isofuranonaphthoquinones' have been shown to possess antioxidant and weak antiplasmodial activity.[8] More recently, two other substituted naphtho[2,3-*c*]furan-4,9-diones have been isolated from cultures of the lichen *Arthonia cinnabarina* (DC.) Wallr.[9]

We have previously described the synthesis of ventilone A (5,8-dihydroxy-1-methyl-6,7-methylenedioxynaphtho[2,3-*c*]furan-4,9-dione) by a cycloaddition approach,[10] and in



Scheme 1.

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the present paper we detail the regioselective synthesis of 5-hydroxy-3-methylnaphtho[2,3-*c*]furan-4,9-dione (1) using a phthalide annulation reaction to construct a suitably substituted naphthoquinone, and then generating the furan ring of (1) at a later stage of the sequence. We also describe the synthesis of 5,8-dihydroxy-1-methylnaphtho[2,3-*c*]furan-4,9-dione (2) by a simple Friedel–Crafts acylation reaction.

Results and Discussion

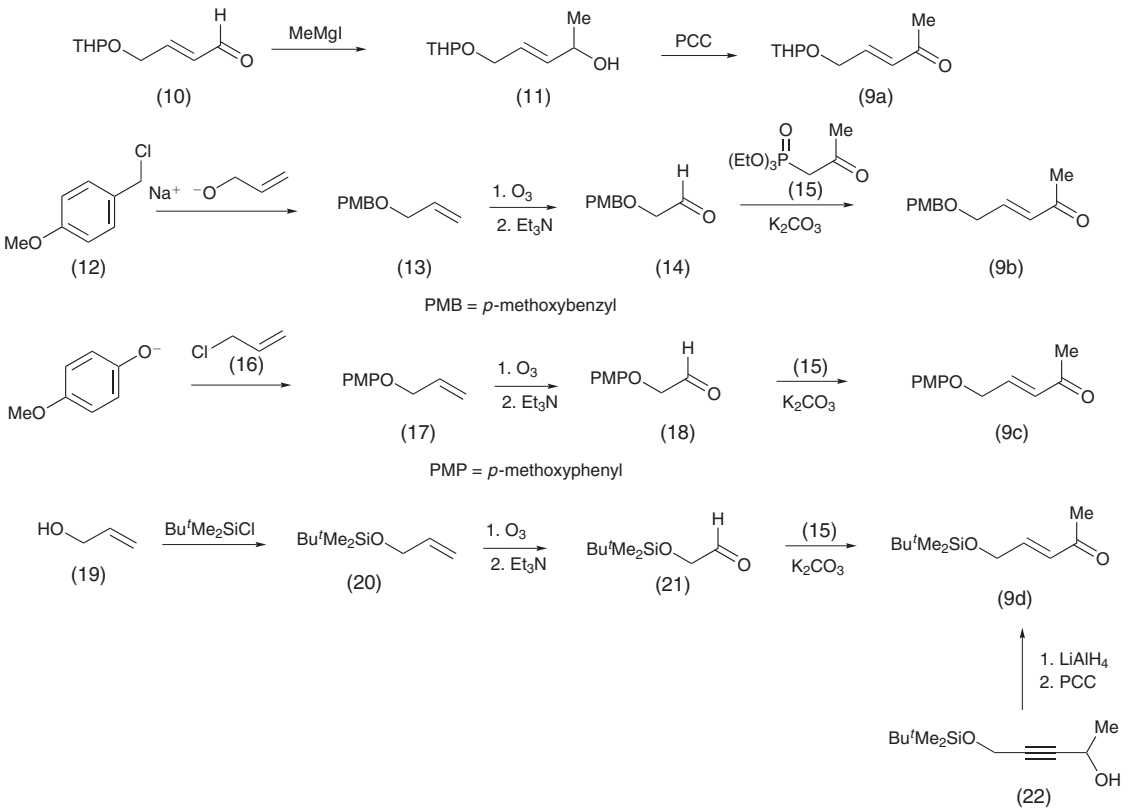
Synthesis of 5-Hydroxy-3-methylnaphtho[2,3-c]furan-4,9-dione (1) Using a Phthalide Annulation Reaction

Since the pioneering studies of Sammes,[11] Hauser,[12] and Kraus[13] and their coworkers, the phthalide annulation procedure has been used extensively for the regioselective construction of substituted 1,4-naphthoquinones of varying degrees of complexity. (For a review see ref. [14].) For the synthesis of (1) we envisaged that (5), the methyl ether of (1), would arise by dehydration of (6), which in turn should be accessible via (7) from the annulation between the cyanophthalide anion (8) and a suitably protected derivative (9) of 5-hydroxypent-3-en-2-one (Scheme 1).

In the event, it proved necessary to test several protecting groups, and the preparation of derivatives (9a)–(9d) is summarized in Scheme 2. The tetrahydropyranyl (THP) derivative (9a) was prepared from the known aldehyde (10)[15] by addition of methylmagnesium iodide followed by oxidation (Scheme 2). The *p*-methoxybenzyl (PMB) and *p*-methoxyphenyl (PMP) derivatives (9b) and (9c) were chosen also in view of their stability towards organometallic reagents and the fact that they are removed by mild oxidation.[16] It was thought that the latter property should allow their removal at the oxidative stage of the sequence involving the conversion of the hydroquinone (7) into the quinone (6) (Scheme 1). These derivatives were prepared by ozonolysis of the alkenes (13) and (17) followed by Wadsworth–Emmonds–Horner reaction of the respective aldehydes (14) and (18) with phosphonate (15). The silyl ether (9d) was obtained by a similar sequence starting with allyl alcohol (19), and also by partial reduction of the triple bond of the acetylenic alcohol (22) followed by oxidation of the hydroxyl group (Scheme 2).

Initial reactions between the phthalide anion (8) and the tetrahydropyranyl derivative (9a) followed by conventional work-up gave complex mixtures. When the crude product was treated with 20% ceric ammonium nitrate (CAN) adsorbed on silica, a mild reagent for the oxidation of 1,4- and 1,2-aromatic diols to the corresponding quinones,[17] the desired product (5) was obtained in 9% yield. Whilst the yield was disappointing, the result validated this approach to the naphtho[2,3-*c*]furan-4,9-dione ring system and it was decided to try and improve the efficiency of the sequence by using a Michael acceptor (9) possessing a different protecting group.

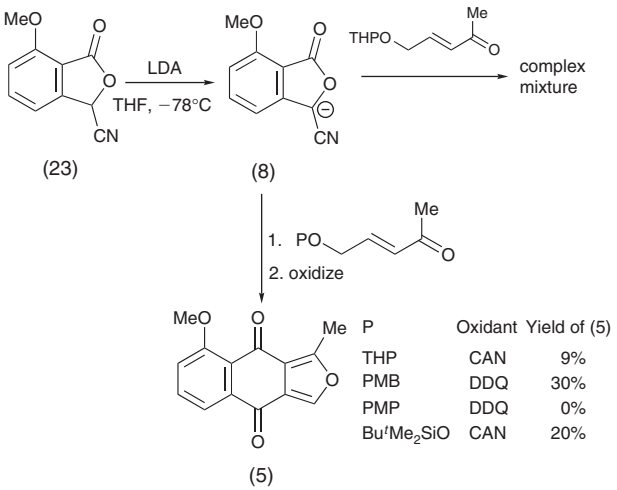
The cyanophthalide annulation reaction was repeated with the *p*-methoxybenzyl-protected Michael acceptor (9b) and the crude product was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and water in dichloromethane, a standard reagent for the deprotection of *p*-methoxybenzyl ethers.[16] This gave the desired naphtho[2,3-*c*]furan-4,9-dione (5) in 30% yield (Scheme 3). While this was a



Scheme 2.

significant improvement upon the result achieved with the tetrahydropyranyl derivative (9a), the yield was still unsatisfactory. Use of the *p*-methoxyphenyl-protected derivative (9c) followed by treatment of the crude product with CAN failed to give any recognizable product. Finally, reaction of the phthalide anion (8) with the *t*-butyldimethylsilyl derivative (9d), followed by treatment of the crude product with CAN in methanol,[18] gave (5) again in a disappointing yield (20%).

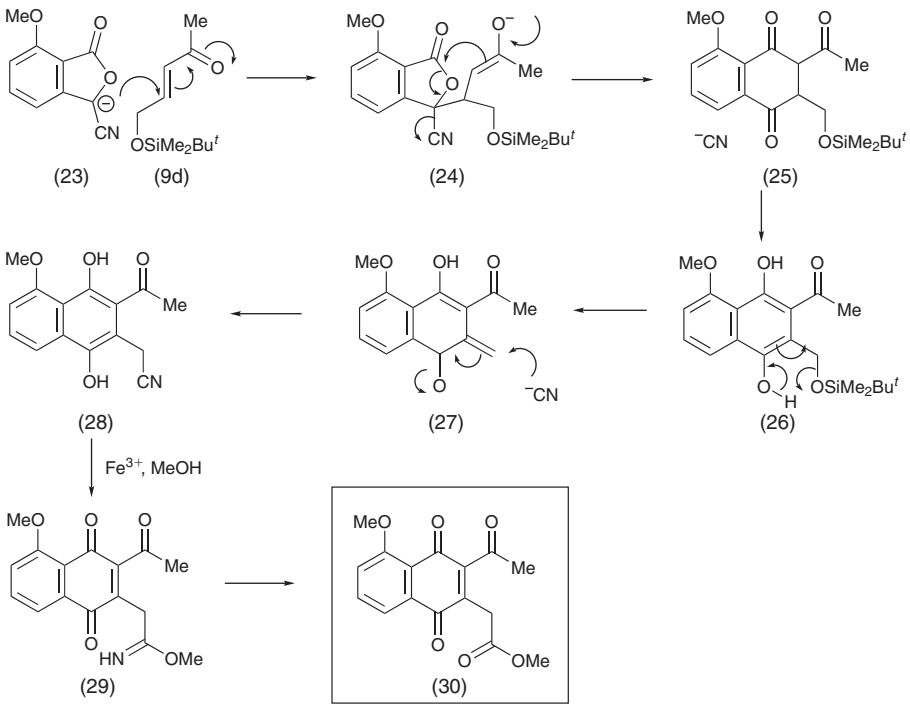
The reaction was repeated with a milder oxidation step in an attempt to isolate the expected intermediate quinone (6). Hydrated ferric chloride in methanol is known to oxidize aromatic 1,4-diols to the corresponding quinones,[19] but no sign of (6) or (5) could be found upon treatment of the crude product with this reagent. Unexpectedly, the ester (30) was isolated as a yellow, crystalline solid in 30% yield from this reaction (Scheme 4). The NMR spectroscopic data of this product revealed that the TBDMS group had been lost and that a methyl ester had been generated as shown by a resonance at δ 3.65 integrating for three protons, and carbon resonances at δ 169.4 and 52.3; structure (30) was confirmed by two-dimensional NMR spectroscopy.



Scheme 3.

The formation of (30) can be rationalized by beginning with the usual pathway of phthalide annulation (Scheme 4).[14] Intermediate (26) is suitably disposed to generate the reactive *o*-quinone methide (27) by a concerted elimination of *t*-butyldimethylsilanol; alternatively (27) can arise by expulsion of *t*-butyldimethylsilanoxide ion from the corresponding phenoxide ion at a stage when the reaction mixture is still alkaline. Addition of cyanide ion, which is generated earlier, to the *o*-quinone methide gives the hydroquinone (28) containing the benzylic nitrile functionality, which can undergo methanolysis to the imidate ester (29) and then hydrolysis followed by oxidation to give the observed product (30). As nitriles are relatively unreactive towards solvolysis or hydrolysis, it is possible that catalysis by ferric ions, coordinated to the proximate hydroxyl group, is involved in the conversion of (28) into (30) under these relatively mild reaction conditions.

The conclusion that the reactive *o*-quinone methide (27) is formed readily in this system explains the poor yields of the naphtho[2,3-*c*]furan-4,9-dione (5) observed with the other Michael acceptors (9), since expulsion of an alkoxide ion, or phenoxide ion in the case of (9c), can occur in each case. Because of the better leaving ability of phenoxide, *o*-quinone methide formation may well be particularly efficient in the system derived from (9c) and could explain our failure to isolate any of the dione (5) after oxidative treatment.



Scheme 4.

In each system, quinone methide (27) can be captured by a variety of nucleophiles other than cyanide ion, which may explain the observed complex reaction mixtures. The generation of *o*-quinone methides from hydroquinones possessing a suitably disposed leaving group as in (26) is a well-known phenomenon and is a key step in the action of anthracycline antitumour agents.[20]

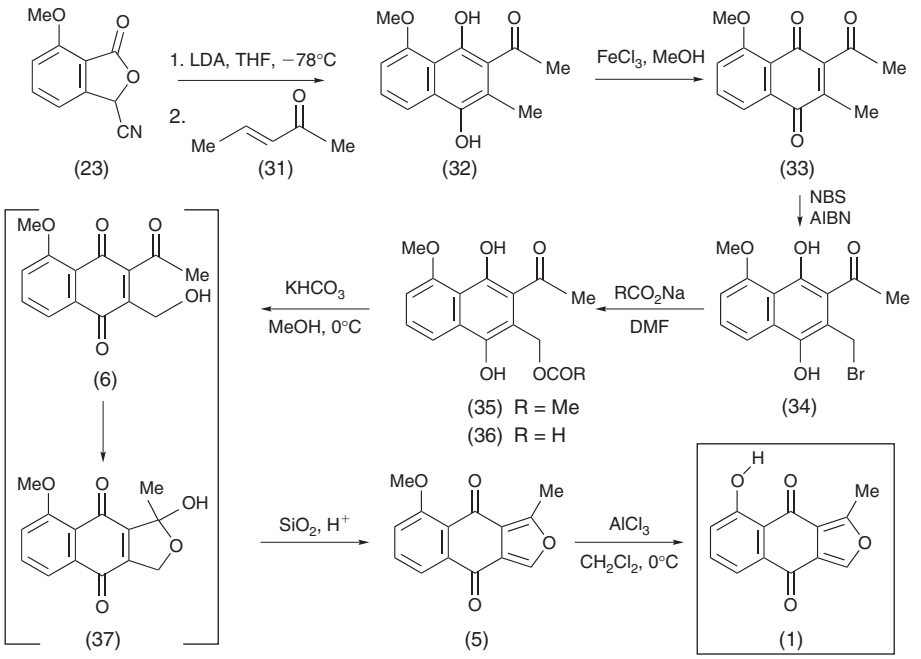
To confirm that these disappointing results were due to the unsuitability of the 5-alkoxy substituted Michael acceptors (9), the annulation reaction was repeated with (*E*)-pent-3-en-2-one (31). The expected methyl-substituted naphthalene-1,4-diol (32) was indeed isolated in 79% yield (Scheme 5) and the quinone (33) was obtained in quantitative yield by subsequent treatment of (32) with methanolic ferric chloride.

Since (33) was obtained in satisfactory overall yield, we investigated its elaboration into the target natural product. Irradiation of the quinone (33) and *N*-bromosuccinimide (NBS) in carbon tetrachloride in the presence of catalytic azobisisobutyronitrile (AIBN) produced the desired bromide (34) in 90% yield. The position of bromination was confirmed by two-dimensional NMR spectroscopy. Specifically, a two-bond correlation between the methyl protons and the exocyclic carbonyl carbon in the heteronuclear multiple bond correlation (HMBC) spectrum indicated that bromination had occurred as shown and not α to the carbonyl group. A similar outcome has been observed in a related system.[21]

In order to generate the hydroxy ketone (6) as a precursor to the furan ring, hydrolysis of the bromide functionality was required. Bromide (34) was resistant to hydrolysis under neutral conditions and decomposed upon addition of sodium hydroxide, presumably because of its propensity to undergo conjugate addition as shown later for (33) (Scheme 6). Treatment of (34) with sodium acetate in dimethylformamide (DMF) at 0°C gave acetate (35), but its hydrolysis under mild basic or acidic conditions also proved problematic. However, hydrolysis of the more labile formate ester (36) could be effected with aqueous potassium bicarbonate and methanol at 0°C,[22] but the expected alcohol (6) was not detected. On the basis of ^{1}H NMR spectroscopy, the crude product was a mixture of the furan (5) and the hemiacetal (37). Addition of this mixture to a suspension of acidified silica in dichloromethane completed the dehydration, affording (5) in 98% overall yield from the formate ester (36).

Thus, starting with the known 3-cyano-7-methoxyphthalide (23) and commercially available pent-3-en-2-one (31), 5-methoxy-3-methylnaphtho[2,3-*c*]furan-4,9-dione (5) was assembled in an overall yield of 70%. This is a marked improvement over the use of the 5-alkoxypent-3-en-2-ones (9) in which the best yield achieved was only 30%. Furthermore, the mild conditions required to carry out the necessary transformations would be tolerated by many functional groups and therefore should make this route amenable to the synthesis of many of the other natural products in this class.

Finally, it was necessary to cleave the methyl ether and liberate the phenol (1). Boron trichloride is the reagent of choice for the mild cleavage of methyl aryl ethers *peri* to a carbonyl group,[16] but even at −78°C this reagent caused considerable degradation to give what appeared, by ^{1}H NMR spectroscopy, to be products derived from opening of the furan ring. However, treatment of (5) with 10 molar equivalents of aluminium trichloride in dichloromethane gave the natural product 5-hydroxy-3-methylnaphtho[2,3-*c*]furan-4,9-dione (1) in 82% yield (Scheme 5). The ^{1}H NMR spectrum and mass spectrum of the synthetic product were virtually identical to those published for the natural material.[5,6] An authentic sample or ^{13}C NMR spectrum of (1) was not available (B. M. Abegaz, personal communication).

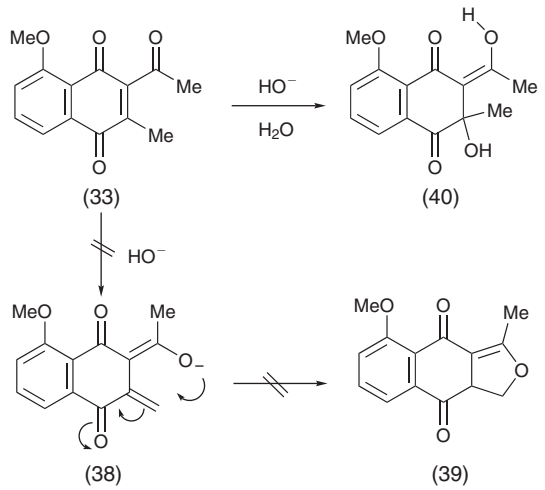


Scheme 5.

Further Conjugate Additions in the 2-Acetyl-1,4-naphthoquinone System

In addition to the problems caused by the facile formation of the *o*-quinone methide intermediate (27) in these studies (Scheme 4), we also observed that the 2-acetyl-1,4-naphthoquinone moiety of (33) is highly susceptible to conjugate addition. Thus in an experiment designed to test whether quinone (33) could be induced to enolize and cyclize by the action of sodium hydroxide in the manner indicated on structure (38) (and hence deliver (39) as indicated in Scheme 6), the addition product (40) was isolated as the only product. In another approach to the naphtho[2,3-*c*]furan-4,9-dione ring system (Scheme 7), the push–pull isobenzofuran (42) was intercepted with the acetylenic dienophile (43). The desired naphthoquinone (45) was not obtained, and only the product (46), derived by conjugate addition of cyanide ion to (45), was isolated in 17% yield.

The structure of (46) was evident from the ^{1}H NMR spectrum which showed a resonance at δ 18.07 suggesting the presence of a strongly hydrogen-bonded enolic or phenolic hydroxyl group. An AX system at δ 4.27 and 4.08 with $J_{gem} = 9.0$ Hz indicated the presence of two diastereotopic methylene protons, and signals at δ 52.4 and 117.3 in the ^{13}C NMR spectrum suggested the presence of a new quaternary carbon and a nitrile carbon respectively. The endocyclic nature of the enol double bond was established in the HMBC spectrum by a strong two-bond correlation between the methyl protons resonating at δ 2.61 and the carbonyl carbon resonating at δ 196.7, and a three-bond correlation between the aromatic proton appearing as a ddd centred at δ 8.25 and the enol carbon resonating at δ 175.5.

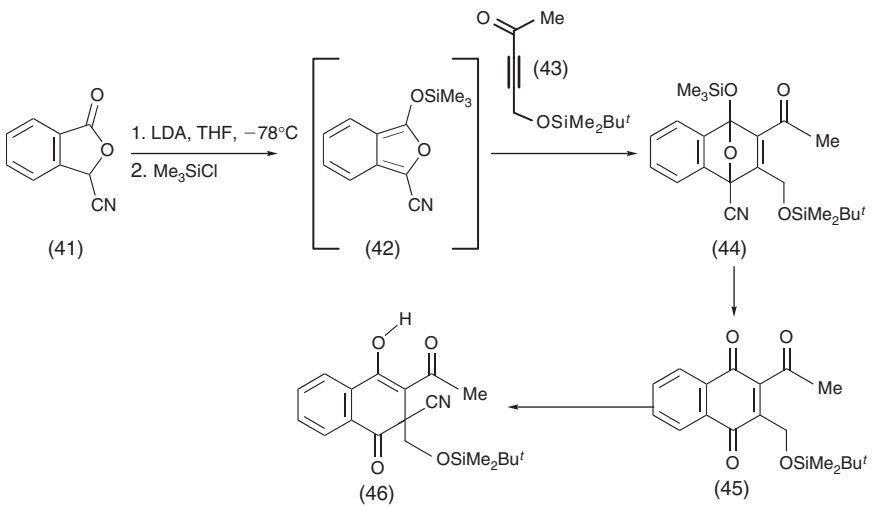


Scheme 6.

Synthesis of 5,8-Dihydroxy-1-methylnaphtho[2,3-c]-furan-4,9-dione (2) by Friedel–Crafts Acylation

The Lewis acid-catalyzed diacylation of aromatic nuclei with 3,4-furandicarbonyl dichlorides has been the most common route to naphtho[2,3-*c*]furan-4,9-diones,[23–28] and nectriafurone is the only natural product of this class that has been synthesized by this procedure.[29] The metabolite 5,8-dihydroxy-1-methylnaphtho[2,3-*c*]furan-4,9-dione (2) is also an obvious target for construction using a Friedel–Crafts reaction. The requisite precursor 2-methyl-3,4-furandicarboxylic acid was prepared by the standard Alder–Rickert route.[30] Friedel–Crafts acylation of 1,4-dimethoxybenzene (46) with the diacid dichloride (47) was carried out using a variation of the mild procedure of Harper and coworkers[31] using anhydrous aluminium chloride in 1,2-dichloroethane at room temperature. These conditions usually result in the demethylation of methoxy groups *peri* to carbonyl groups, and thus the bright orange natural product (2) was isolated directly in 32% yield. The ^{1}H NMR spectrum of the synthetic material was virtually identical to that reported for the natural product[5,6] and HMBC and heteronuclear multiple quantum coherence (HMQC) experiments enabled the resonances in the ^{13}C NMR spectrum of (2) to be fully assigned.

In addition to (2), an inseparable 9 : 1 mixture of the isomeric monomethyl ethers (3a) and (3b) was obtained in 18% yield (Scheme 8). The HMBC spectrum of the major



Scheme 7.

component of this mixture showed a weak four-bond coupling from the methyl protons at δ 2.68 to the carbonyl carbon at δ 179.4. A second four-bond coupling was observed between the phenolic proton and the other carbonyl carbon at δ 185.8. The major isomer was thus formulated as the 5-hydroxy-8-methoxy derivative (3a).

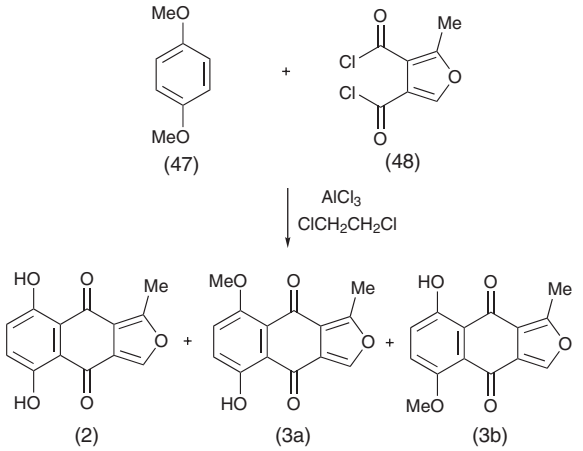
Unfortunately it is not clear from the ^{1}H NMR spectroscopic data which isomer corresponds to the natural product (3), and ^{13}C NMR data were not reported.[6] The melting point of the synthetic material (174–179°C) was significantly lower than that reported for the natural product (194–196°C),[6] but this could be a consequence of the fact that the former is a mixture. A decision regarding the site of *O*-methylation in the metabolite must await acquisition of the ^{13}C NMR spectrum of the natural product.

On the Question of Tautomerism in 5,8-Dihydroxynaphtho[2,3-c]furan-4,9-diones

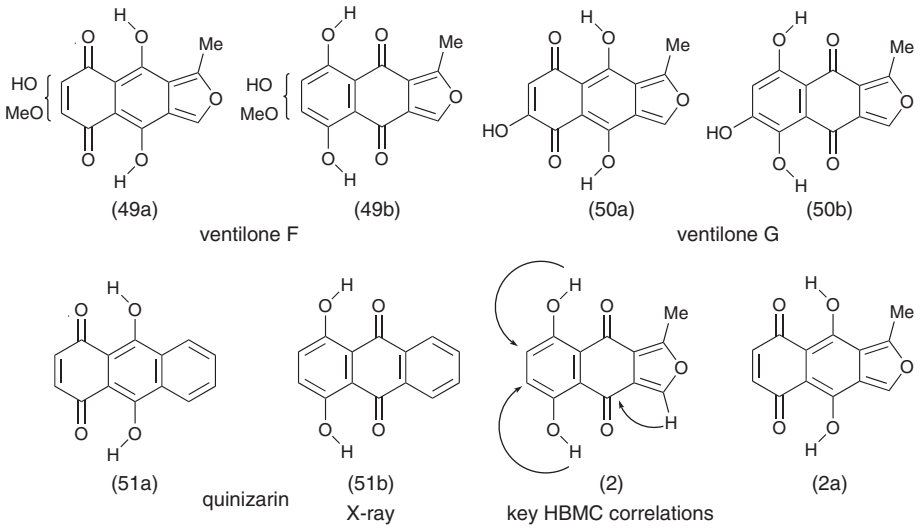
The natural products ventilone F and ventilone G were assigned the dihydroxyisobenzofuran structures (49a) and (50a) respectively,[3,4] but in view of the high reactivity expected for the isobenzofuran moiety,[32] the naphtho[2,3-*c*]furan-4,9-dione tautomers (49b) and (50b) seem more plausible structural representations (Scheme 9). Furthermore, the reasoning provided for the preference of the isobenzofuranoid tautomers is not conclusive. Thus Thomson and coworkers favoured structure (49a) for ventilone F because of the solubility of the compound in aqueous sodium bicarbonate, supposedly a result of the 1,3-relationship of the non-hydrogen-bonded hydroxyl group with the quinone carbonyl group.[3] This relationship permits delocalization of the phenoxide negative charge onto the carbonyl group, but it should be noted that analogous resonance stabilization also is possible in the anion derived from tautomer (49b).

In the case of ventilone G, the appearance of separate *peri*-hydroxyl signals in the ^{1}H NMR spectrum was said to favour structure (50a).[4] However, this provides no distinguishing evidence as the environment of the respective hydroxyl protons is different in both tautomers. A signal at δ 6.40 was said to indicate a proton attached to a quinonoid ring as in (50a) rather than to an aromatic ring, but the upfield chemical shift of this proton can be accounted for in tautomer (50b) by the shielding effect of the three hydroxy substituents in the aromatic ring. For example, H3 in benzene-1,2,4-triol resonates at δ 6.25.[33] Once again, the tautomer (50b) cannot be excluded on the basis of this spectroscopic evidence.

It is important to note that X-ray crystallography has established the structure of quinizarin (1,4-dihydroxyanthracene-9,10-dione) as tautomer (51b) and not (51a).[34] This finding represents a manifestation of Clar's rule for polycyclic aromatic systems which states that 'the preferred resonance structures are those which maximize the number of isolated aromatic sextets',[35] and this simple rule has been confirmed in more modern theoretical studies.[36] On this basis, the structures of ventilone F and ventilone G also should be represented by (49b) and (50b) respectively, since these structures each contain two isolated aromatic sextets (benzenoid and furanoid), whereas the alternative tautomers possess a single reactive 10 π-electron isobenzofuran system.



Scheme 8.



Scheme 9.

In the present study, the HMBC spectrum of the parent 5,8-dihydroxynaphtho[2,3-*c*]furan-4,9-dione (2) showed strong three-bond correlations of the phenolic protons resonating at δ 12.79 and 12.94 with the aromatic methine carbons resonating at δ 128.7 and 129.2 respectively (Scheme 9). This evidence favours structure (2) as the phenolic protons in (2a) would not be expected to correlate through five bonds with the quinonoid methine carbons. Weak three- and four-bond correlations were also observed between the furyl proton resonating at δ 8.06 and both carbonyl carbons and between the methyl protons resonating at δ 2.77 and the carbonyl carbon resonating at δ 185.2. Once again this supports tautomer structure (2) as the carbonyl groups in (2a) are too far removed from the furan moiety.

Thus the empirical evidence clearly shows that in solution (2) best represents the structure of the natural product. By analogy, ventilone G and ventilone F also should be depicted as the naphtho[2,3-*c*]furan-4,9-dione tautomers (49b) and (50b) respectively, as are the other members of this family. Accurate X-ray crystal structures of these dihydroxy derivatives would also be of interest, but at this stage are unavailable.

Conclusion

The above study has shown that the stabilized phthalide anion annulation protocol can be adapted for the synthesis of unsymmetrically substituted naphtho[2,3-*c*]furan-4,9-diones, provided that the Michael acceptor does not contain a leaving group capable of giving rise to a reactive quinone methide species, as is the case in general structure (9) in Scheme 1. The generation of the furan moiety by functionalization of the methyl group of (33) through the sequence depicted in Scheme 5 is an efficient process.

Experimental

Melting points were measured on a Kofler hot stage and are uncorrected. Kugelrohr distillation temperatures refer to the oven temperature. Organic extracts were dried over anhydrous $MgSO_4$. Rapid silica filtration refers to chromatography on SiO_2 (40–63 μm) packed in a short sintered glass funnel in which the eluent was drawn through under a gentle water-aspirator vacuum. Elution was carried out with increasing percentages of ethyl acetate in light petroleum, and fractions were monitored by thin-layer chromatography (TLC) on Whatman flexible plates (250 μm layer, Al Sil G/UV_{254}). Spots were visualized under UV light and by spraying with a 6% (w/w) solution of ceric sulfate in 2 M sulfuric acid, followed by heating. Radial chromatography was carried out using a Chromatotron model 7924T instrument. Microanalyses were performed by MHW Laboratories (Phoenix, AZ). Low- and high-resolution mass spectra were recorded on a VG Autospec instrument using a direct insertion probe and electron impact ionization unless other wise indicated. NMR spectra were acquired on Gemini 200 (200 MHz, ^{1}H), Bruker AM300 (300 Mz, ^{1}H; 75.5 MHz, ^{13}C), Bruker 500 (500 Mz, ^{1}H; 125 MHz, ^{13}C) spectrometers in $CDCl_3$ unless otherwise stated. Routine assignments of carbon spectra were made with the assistance of distortionless enhancement by polarization transfer (DEPT) 135 and DEPT 90 experiments. Homonuclear decoupling, HMQC, HMBC, and nuclear Overhauser enhancement spectroscopy (NOESY) experiments were carried out on the Bruker 500 instrument.

(E)-5-[(Tetrahydro-2H-pyran-2-yl)oxy]pent-3-en-2-ol (11)

A solution of methyl iodide (6.50 mL, 104 mmol) in anhydrous ether was added dropwise to a stirred suspension of magnesium turnings (2.79 g, 115 mmol) in anhydrous ether (30 mL) under argon. Upon completion of the reaction the Grignard reagent was allowed to cool to room temperature before being treated dropwise with a solution of (*E*)-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2-butenal (10)[15] (5.545 g, 32.6 mmol) in anhydrous ether (150 mL) over 1 h. The resultant white slurry was stirred at room temperature for 2 h and then diluted with cold, saturated aqueous ammonium chloride (200 mL) and brine (100 mL). The ether layer was separated and the aqueous phase was extracted with dichloromethane (3 × 150 mL). The combined organic solution was washed with brine (2 × 200 mL), dried and evaporated to give the title *alcohol* (11) as a pale yellow liquid (5.63 g, 93%). δ_H (300 MHz) 5.82–5.68 (m, 2 H, H3/H4), 4.61–4.60 (m, 1 H, H2′), 4.33–4.23 (m, 1 H, H2), 4.22–4.18 (m, 1 H, H5a), 3.97–3.91 (m, 1 H, H5b), 3.87–3.80 (m, 1 H, H6′a), 3.52–3.45 (m, 1 H, H6′b), 2.10 (br s, 1 H, OH), 1.85–1.46 (m, 8 H, H3′/H4′/H5′), 1.24 (d, $J_{1,2}$ 6.4, 3 H, CH_3). δ_C (75.5 MHz) 136.8 (vinyl CH), 126.0 (vinyl CH), 97.9 (C2′), 68.1 (C2), 67.0 (C5), 62.1 (C6′), 30.5 (CH_2), 25.3 (CH_2), 23.1 (CH_3), 19.3 (CH_2).

(E)-5-[(Tetrahydro-2H-pyran-2-yl)oxy]pent-3-en-2-one (9a)

A stirred suspension of anhydrous sodium acetate (7.30 g, 89 mmol) and powdered molecular sieves (4 Å, 10.4 g) in a solution of (*E*)-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]pent-3-en-2-ol (11) (5.54 g, 29.8 mmol) in anhydrous dichloromethane (100 mL) at 0°C, was treated with PCC (9.56 g, 44 mmol). After stirring for 30 min at 0°C and 2 h at room temperature, the reaction mixture was diluted with ether (150 mL) and filtered through a pad of Celite. The filter cake was washed several times with ether. The filtrate was evaporated to give a brown liquid which was dissolved in ether (500 mL) and washed with water (2 × 200 mL), ice-cold 1 M hydrochloric acid (2 × 200 mL), saturated aqueous sodium bicarbonate (2 × 200 mL), and brine (200 mL). The ether solution was dried and evaporated to give the title *enone* (9a) as a yellow liquid (2.66 g, 49%), which distilled (Kugelrohr, 125°C at 1 mm Hg) to give the analytical sample as a pale yellow liquid (Found C, 65.1; H, 8.7. $C_{10}H_{16}O_3$ requires C, 65.2; H, 8.7%). Mass spectrum *m*/*z* 184 (M, <1%), 147 (15), 101 (68), 100 (100), 95 (18). δ_H (300 MHz) 6.75 (ddd (apparent dt), $J_{4,3}$ 16.1, $J_{4,5a} = J_{4,5b}$ 4.3, 1 H, H4), 6.25 (ddd (apparent dt), $J_{3,4}$ 16.0, $J_{3,5a} = J_{3,5b}$ 2.0, 1 H, H3), 4.58 (dd (apparent br t), $J_{2',3a'} = J_{2',3b'}$ 3.3, 1 H, H2′), 4.36 (ddd, J_{gem} 16.4, $J_{5a,4}$ 4.1, $J_{5a,3}$ 2.1 Hz, 1 H, H5a), 4.08 (ddd, J_{gem} 16.4, $J_{5b,4}$ 4.6, $J_{5b,3}$ 1.9, 1 H, H5b), 3.79–3.72 (m, 1 H, H6a′), 3.48–3.41 (m, 1 H, H6b′), 2.20 (s, 3 H, CH_3), 1.85–1.40 (m, 6 H, H3′/H4′/H5′). δ_C (75.5 MHz) 198.1 (CO), 143.2 (C4), 129.9 (C3), 98.1 (C2′), 65.4 (C5), 61.9 (C6′), 30.2 (CH_2), 26.9 (CH_3), 25.1 (CH_2), 19.0 (CH_2). ν_{max}/cm^{-1} 1691.

1-Allyloxymethyl-4-methoxybenzene (13)

A solution of allyl alcohol (19) (3.00 g, 52 mmol) in anhydrous DMF (22.5 mL) was added to a stirred suspension of 55–65% sodium hydride dispersion in oil (4.32 g, 103 mmol) in anhydrous DMF (45 mL) under argon. A cold water bath was used to dissipate the heat generated. When the evolution of hydrogen had ceased, *p*-methoxybenzyl chloride (6.6 mL, 49 mmol) was added and stirring was continued overnight. The reaction mixture was diluted with water (300 mL) and extracted with petroleum (3 × 100 mL). The extract was evaporated and the residue was subjected to rapid silica filtration. Elution with petroleum removed the contaminating mineral oil and further elution with ether/petroleum (1 : 19) gave the title ether (13) as a colourless oil (7.7 g, 89%). δ_H (200 MHz) 7.29 (m, AA′ part of AA′XX′, 2 H, H2/H6), 6.90 (m, XX′ part of AA′XX′, 2 H, H3/H5), 5.97 (ddt, $J_{2',3'trans}$ 17.2, $J_{2',3'cis}$ 10.4, $J_{2',1'}$ 5.6, 1 H, H2′), 5.32 (m (apparent dq), 1 H, H3′*trans*), 5.21 (m, 1 H, H3′*cis*), 4.47 (s, 2 H, benzyl), 4.02 (ddd (apparent dt), $J_{1',2'}$ 5.6, $J_{1',3'trans} = J_{1',3'cis}$ 1.4, 2 H, allyl), 3.81 (s, 3H, CH_3).

(4-Methoxybenzyloxy)acetaldehyde (14)

Ozone was bubbled through a stirred solution of 1-(allyloxymethyl)-4-methoxybenzene (13) (5.00 g, 28.1 mmol) in dichloromethane (35 mL) at –78°C. TLC showed that the starting material was consumed in 1 h, but the solution did not turn blue. After flushing with oxygen to remove excess ozone, triethylamine (8 mL) was added portionwise to the solution, whereupon it immediately turned yellow. The solution was allowed

to warm to room temperature and was stirred for 4 h before being diluted with water (100 mL) and extracted with dichloromethane (3 × 50 mL). The extract was washed with water (50 mL), 1 M hydrochloric acid (50 mL), and brine (50 mL), dried and evaporated to give the title aldehyde (14) as a yellow oil (3.43 g, 68%), pure enough for the next step. δ_H (200 MHz) 9.69 (s, 1 H, CHO), 7.78 (AA′ part of AA′XX′, 2 H, H2′/H6′), 6.88 (XX′ part of AA′XX′, 2 H, H3′/5′), 4.56 (s, 2 H, benzyl), 4.07 (s, 2 H, CH_2), 3.80 (s, 3 H, CH_3O). This is a known compound.[37]

(4-Methoxyphenoxy)acetaldehyde (18)

A 55–65% sodium hydride dispersion in oil (8.16 g, 187 mmol) was added portionwise to a stirred solution of 4-methoxyphenol (20.00 g, 161 mmol) in anhydrous DMF (100 mL) at 0°C under argon. When the vigorous evolution of hydrogen had subsided, the ice bath was removed and stirring was continued for 1.75 h. The suspension was returned to 0°C before being treated with allyl chloride (16) (26.5 mL, 325 mmol). The ice bath was removed and stirring was continued overnight. The reaction mixture was diluted with brine (500 mL) and extracted with petroleum (3 × 150 mL). The extract was washed with 1 M aqueous sodium hydroxide (200 mL) and brine (200 mL), dried and evaporated to give a yellow oil. Vacuum distillation gave 1-allyloxy-4-methoxybenzene (17) as a very pale yellow oil (24.8 g, 94%), bp 88–90°C at 1.5 mm Hg. δ_H (200 MHz) 6.86 (AA′BB′, 4 H, aryl), 6.06 (ddt, $J_{2',3'trans}$ 17.3, $J_{2',3'cis}$ 10.5, $J_{2',1'}$ 5.3, 1 H, H2′), 5.41 (m (apparent dq), 1 H, H3′*trans*), 5.28 (m (apparent dq), 1 H, H3′*cis*), 4.50 (ddd (apparent dt), $J_{1',2'}$ 5.3, $J_{1',3'trans} = J_{1',3'cis}$ 1.5, 2 H, allyl), 3.78 (s, 3H, CH_3).

Ozonized oxygen was bubbled through a stirred solution of 1-allyloxy-4-methoxybenzene (17) (10.00 g, 61 mmol) in dichloromethane (70 mL) at −78°. TLC showed that the starting material was consumed within 1.5 h, but the solution did not turn blue. After flushing with oxygen to remove excess ozone, triethylamine (8 mL) was added portionwise to the solution. An exothermic reaction ensued and the solution turned pink and then orange. The solution was allowed to warm to room temperature before being diluted with water (200 mL) and extracted with dichloromethane (3 × 70 mL). The extract was washed with 1 M hydrochloric acid (70 mL), water (70 mL), and brine (70 mL), dried and evaporated to give a brown oil. Distillation (Kugelrohr, 150°C at 1.5 mm Hg) gave the title aldehyde (18) as a yellow oil (4.12 g, 41%). δ_H (200 MHz) 9.84 (s, 1 H, CHO), 6.85 (s, 4 H, aryl), 4.52 (s, 2 H, CH_2), 3.77 (s, 3 H, CH_3O).

(E)-5-(4-Methoxybenzyloxy)pent-3-en-2-one (9b)

A solution of potassium carbonate (0.30 g, 2.2 mmol) in water (0.37 mL) was added to a vigorously stirred mixture of (4-methoxybenzyloxy)acetaldehyde (14) (196 mg, 1.1 mmol) and diethyl (2-oxopropyl)phosphonate (15)[38] (0.26 g, 1.3 mmol). After 3 h the reaction mixture was diluted with water (20 mL) and extracted with petroleum (3 × 10 mL). The extract was washed with brine (2 × 10 mL), dried and evaporated to give the title *enone* (9b) as a yellow oil (190 mg, 79%), pure enough for the next step. Distillation under vacuum gave the analytical sample as a pale yellow oil (Found C, 70.8; H, 7.4. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%). Mass spectrum *m/z* 220 (M, 4%), 137 (44), 121 (100), 84 (15). δ_H (300 MHz) 7.27, m, AA′ part of AA′XX′, 2 H, H2′/H6′), 6.88 (m, XX′ part of AA′XX′, 2 H, H3′/H5′), 6.79 (dt, $J_{4,3}$ 16.1, $J_{4,5}$ 4.5, 1 H, H 4), 6.32, dt, $J_{3,4}$ 16.1, $J_{3,5}$ 1.9, 1 H, H3), 4.49, s, 2 H, benzyl), 4.16, dd, 2 H, $J_{5,4}$ 4.5, $J_{5,3}$ 1.9, CH_2), 3.79 (s, 3 H, CH_3O), 2.25 (s, 3 H, CH_3). δ_C (75.5 MHz) 198.1 (CO), 159.4 (C4′), 143.1 (C4), 130.3 (C3), 129.6 (C1′), 129.3 (C2′/C6′), 113.8 (C3′/C5′), 72.6 (benzyl), 68.5 (C5), 55.2 (CH_3O), 27.2 (C1). ν_{max}/cm^{-1} 1677.

(E)-5-(4-Methoxyphenoxy)pent-3-en-2-one (9c)

A solution of potassium carbonate (3.06 g, 22.1 mmol) in water (3.8 mL) at 0°C was added dropwise to a vigorously stirred mixture of (4-methoxyphenoxy)acetaldehyde (18) (2.00 g, 12.0 mmol) and diethyl (2-oxopropyl)phosphonate (15) (2.65 g, 13.6 mmol) at 0°C. After stirring for 30 min at 0°C and 30 min at room temperature the reaction mixture had solidified. The solid was dissolved in ether (5 mL), and diluted with water (50 mL), and the aqueous phase was extracted with ether (3 × 30 mL). The ether solution was washed with water (30 mL) and brine (30 mL), dried and evaporated to give the title *enone* (9c) as an off-white solid (2.48 g, 100%), which crystallized from dichloromethane/petroleum as colourless needles, mp 54–55°C (Found C, 69.9; H, 6.9. $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.8%). Mass spectrum *m/z* 206 (M, 22%), 124 (11), 123 (100), 95 (18). δ_H (300 MHz) 6.85 (dt, $J_{4,3}$ 16.1, $J_{4,5}$ 4.2, 1 H, H4), 6.81, s, 4 H, aryl), 6.38 (dt, $J_{3,4}$ 16.1, $J_{3,5}$ 2.0, 1 H, H3), 4.61 (dd, $J_{5,4}$ 4.2, $J_{5,3}$ 2.0, 2 H, CH_2), 3.72 (s, 3 H, CH_3O), 2.25 (s, 3 H, CH_3). δ_C (75.5 MHz) 197.7 (CO), 154.1 (C), 152.0 (C), 141.4 (C4), 130.4 (C3), 115.5 (aryl CH), 114.5 (aryl CH), 67.1 (C5), 55.5 (CH_3O), 27.2 (C1). ν_{max}/cm^{-1} 1681.

(E)-5-(t-Butyldimethylsilyloxy)pent-3-en-2-one (9d)

An ice-cold solution of potassium carbonate (0.78 g, 5.6 mmol) in water (0.96 mL) was added dropwise to a vigorously stirred mixture of (*t*-butyldimethylsilyloxy)acetaldehyde (21)[39] (0.505 g, 2.9 mmol) and diethyl (2-oxopropyl)phosphonate (15) (0.565 g, 2.9 mmol) in an ice/brine bath. After 1 h the ice bath was removed and stirring was continued for 30 min before the reaction mixture was partitioned between ether (40 mL) and water (40 mL). The ether layer was collected and the aqueous layer was extracted with ether (2 × 20 mL). The combined ether solution was washed with water (2 × 20 mL) and brine (2 × 20 mL), dried and evaporated at room temperature to give a pale yellow oil which was subjected to radial chromatography. Elution with petroleum, and then ether gave the title enone (9d) as a colourless oil (218 mg, 35%), identical with the material described below.

A stirred solution of 1-(*t*-butyldimethylsilyloxy)prop-2-yne[40] (2.538 g, 14.9 mmol) in anhydrous tetrahydrofuran (THF) (40 mL) at −78°C under argon, was treated with a 1.2 M hexane solution of Bu^nLi (18.6 mL, 22.3 mmol). The solution was stirred for 30 min then treated with acetaldehyde (2 mL, 34 mmol), and allowed to slowly warm to room temperature over 2 h. After a further 1 h at room temperature the orange solution was diluted with iced water (50 mL). The organic solvent was evaporated and the aqueous residue was extracted with ether (3 × 50 mL). The yellow extract was washed with cold 1 M hydrochloric acid (50 mL) and brine (2 × 50 mL), dried and evaporated to give a yellow liquid which was subjected to rapid silica filtration. Elution with ethyl acetate/petroleum (1 : 19) gave 5-(*t*-butyldimethylsilyloxy)pent-3-yn-2-ol (22) as a yellow liquid (1.75 g, 55%) pure enough for the following step. δ_H (200 MHz) 4.52 (qt, $J_{2,1}$ 6.6, $J_{2,5}$ 2.2, 1 H, H2), 4.30 (d, $J_{5,2}$ 2.2, 2 H, CH_2), 2.53 (br s, 1 H, OH), 1.41 (d, $J_{1,2}$ 6.6, 3 H, CH_3), 0.88 (s, 9 H, $C(CH_3)_3$), 0.10 (s, 6 H, $Si(CH_3)_2$).

A solution of 5-(*t*-butyldimethylsilyloxy)pent-3-yn-2-ol (22) (1.00 g, 4.7 mmol) in anhydrous THF (7 mL) was added to stirred suspension of LAH (141 mg) and sodium methoxide (0.37 g, 7.0 mmol) in anhydrous THF (25 mL) at 0°C under argon. The reaction mixture was allowed to warm to room temperature and was stirred for 2 h, before being quenched with saturated ammonium chloride solution (50 mL). The THF was evaporated and the aqueous residue was extracted with ether (3 × 25 mL). The extract was washed with brine (2 × 30 mL), dried and evaporated to give a pale yellow liquid. ^1H NMR spectroscopy of the crude product showed it to contain starting material so the crude mixture was dissolved in anhydrous THF (7 mL) and added to a stirred suspension of LAH (0.1 g, 2.6 mmol) and sodium methoxide (0.28 g, 5.2 mmol) in anhydrous THF (25 mL) at 0°C under argon. Once again the reaction mixture was allowed to warm to room temperature and stirred for 2 h. TLC [ethyl acetate/petroleum (1 : 4)] showed the presence of starting material so a fresh portion of LAH (spatula tip) was added. After 1 h, the starting material had been consumed and the reaction was worked up as before to give (*E*)-5-(*t*-butyldimethylsilyloxy)pent-3-en-2-ol as a pale yellow oil (536 mg, 53%), pure enough for the next step. δ_H (200 MHz) 5.75 (m, 2 H, H3/H4), 4.34 (m, 1 H, H2), 4.17 (m, 2 H, CH_2), 1.62 (br s, 1 H, OH), 1.27 (d, $J_{1,2}$ 6.7, 3 H, CH_3), 0.91 (s, 9 H, $C(CH_3)_3$), 0.08 (s, 6 H, $Si(CH_3)_2$).

A stirred suspension of sodium acetate (0.26 g, 3.17 mmol) and powdered molecular sieves (4 Å, 0.37 g) in a solution of (*E*)-5-(*t*-butyldimethylsilyloxy)pent-3-en-2-ol (229 mg, 1.06 mmol) in anhydrous dichloromethane (5 mL) at 0°C, was treated with PCC (0.34 g,

1.58 mmol). After stirring for 30 min at 0°C and 1 h at room temperature, the reaction mixture was diluted with ether (40 mL) and filtered through a pad of Celite. The filter cake was washed several times with ether and the filtrate was evaporated to give a brown oil which was adsorbed onto silica and filtered through a plug of silica to remove baseline material. The filtrate was evaporated to give the title enone (9d) as a colourless oil (185 mg, 82%) (Found C, 61.4; H, 10.1. $C_{11}H_{22}O_2Si$ requires C, 61.6; H, 10.3%). Mass spectrum m/z 214 (M, <1%), 157 (30), 117 (51), 83 (48), 75 (100), 73 (62), 71 (34), 69 (42). δ_H (300 MHz) 6.78 (dt, $J_{4,3}$ 15.8, $J_{4,5}$ 3.6, 1 H, H4), 6.28 (dt, $J_{3,4}$ 15.8, $J_{3,5}$ 2.2, 1 H, H3), 4.31 (dd, $J_{5,4}$ 3.6, $J_{5,3}$ 2.2, 2 H, CH_2), 2.21 (s, 3 H, CH_3), 0.87 (s, 9H, $C(CH_3)_3$), 0.03 (s, 6 H, $SiCH_3$). δ_C (75.5 MHz) 198.3 (CO), 146.2 (C4), 128.6 (C3), 62.0 (C5), 27.1 (C1), 25.7 ($C(CH_3)_3$), 18.2 (SiC), −5.6 ($(SiCH_3)_2$). ν_{max}/cm^{-1} 1682.

4-Methoxy-3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile (23)

3-Hydroxy-7-methoxyisobenzofuran-1(3*H*)-one[41] (5.00 g, 27.8 mmol) was added to a stirred solution of potassium cyanide (13.7 g, 210 mmol) in water (67 mL). After 10 min the yellow solution was cooled to 0°C before being treated dropwise with concentrated hydrochloric acid (47 mL). The reaction mixture was allowed to warm to room temperature and stirring was continued overnight. The precipitate that formed was collected by vacuum filtration and washed thoroughly with water. The aqueous washes were extracted with ethyl acetate (3 × 200 mL) and the organic extract was washed with water (3 × 100 mL), and brine (2 × 100 mL), and combined with the precipitate. The resulting solution was dried and evaporated to give the pure title cyanophthalide (23) as a pale yellow solid (5.17 g, 98%), which crystallized from ethyl acetate as yellow needles, mp 155°C (sweating), 164–167°C (melted) (lit.[42] 154–156°C). δ_H (200 MHz) 7.75 (dd (apparent t), $J_{6,5} = J_{6,7}$ 8.4, 1 H, H6), 7.22 (d, $J_{7,6}$ 8.4, 1 H, H7), 7.09 (d, $J_{5,6}$ 8.4, 1 H, H5), 6.01 (s, 1 H, H1), 4.03 (s, 3 H, CH_3O) (δ_H lit.[42] (80 MHz) 7.78 (t, J 10, 1 H), 7.21 (overlapping d, 2 H), 6.05 (s, 1 H), 4.05 (s, 3 H).)

Cyanophthalide Annulation of (23) with (9a): 5-Methoxy-3-methylnaphtho[2,3-c]furan-1,4-dione (5)

A stirred solution of diisopropylamine (168 μL, 1.2 mmol) in anhydrous THF (10 mL) at 0°C under argon, was treated dropwise with a 1.3 M hexane solution of Bu^nLi (0.85 mL, 1.1 mmol). After 15 min the lithium diisopropyl amide (LDA) solution was cooled to −78°C and a solution of 4-methoxy-3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile (23) (200 mg, 1.06 mmol) in anhydrous THF (7 mL) was added dropwise, whereupon the bright yellow cyanophthalide anion formed immediately. Stirring was continued for 20 min before the solution was treated dropwise with a solution of (*E*)-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]pent-3-en-2-one (9a) (195 mg, 1.06 mmol) in anhydrous THF (7 mL). The reaction mixture was stirred for 30 min and was then allowed to slowly warm to room temperature. The dark green solution was diluted with ice-cold 1 M hydrochloric acid (200 mL) and extracted with ethyl acetate (3 × 100 mL). The bright orange extract was washed with brine (3 × 100 mL), dried and evaporated to give an orange gum. The crude product was dissolved in dichloromethane (50 mL) and stirred with 20% CAN adsorbed on silica (7 g). After 2 h the solvent was evaporated and the residue was subjected to rapid silica filtration. Elution with ethyl acetate/petroleum (4 : 1) gave the title *compound* (5) (23 mg, 9%) as a pale yellow solid, identical with the material described later.

Cyanophthalide Annulation of (23) with (9b): 5-Methoxy-3-methylnaphtho[2,3-c]furan-1,4-dione (5)

A stirred solution of diisopropylamine (397 μL, 2.83 mmol) in anhydrous THF (3 mL) at −78°C under argon, was treated dropwise with a 1.2 M hexane solution of Bu^nLi (2.3 mL, 2.76 mmol). After 15 min a solution of 4-methoxy-3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile (23) (500 mg, 2.64 mmol) in anhydrous THF (10 mL) was added dropwise, whereupon the bright orange cyanophthalide anion formed immediately. Stirring was continued for 25 min during which time the orange lithium salt precipitated from solution. The slurry was treated dropwise with a solution of (*E*)-5-(4-methoxybenzyloxy)pent-3-en-2-one (9b) (581 mg, 2.27 mmol) in anhydrous THF (6 mL) and the reaction mixture was allowed to slowly warm to room temperature over 3 h. The dark red solution which formed was diluted with ice-cold 1 M hydrochloric acid (150 mL) and extracted with ethyl acetate (4 × 70 mL). The orange extract was washed with brine (3 × 100 mL), dried and evaporated to give a red oil. The crude product was dissolved in dichloromethane (25 mL), and water (1.5 mL) was added followed by DDQ (1.44 g, 6.34 mmol), whereupon the solution immediately turned dark brown. After 30 min of stirring, silica (5 g) was added, the solvent was evaporated and the residue was subjected to rapid silica filtration. Elution with ethyl acetate/petroleum (4 : 1) gave fractions containing the desired product and $DDQH_2$. The combined fractions in dichloromethane were washed with ice-cold 1 M sodium hydroxide solution (2 × 30 mL) and brine (3 × 50 mL), dried and evaporated to give an orange solid which crystallized from dichloromethane/petroleum to give the title dione (5) as yellow needles. The mother liquor was subjected to radial chromatography. Elution with dichloromethane gave more of (5) as a yellow solid (total yield 109 mg, 30%), identical with the material described later.

Cyanophthalide Annulation of (23) with (9d)

(*A*). A stirred solution of diisopropylamine (0.35 mL, 2.5 mmol) in anhydrous THF (4 mL) at −78°C under argon, was treated dropwise with a 1.2 M hexane solution of Bu^nLi (2.0 mL, 2.4 mmol). After 10 min a solution of 4-methoxy-3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile (23) (0.44 g, 2.3 mmol) in anhydrous THF (10 mL) was added dropwise, whereupon the bright orange cyanophthalide anion formed immediately. Stirring was continued for 15 min during which time the orange lithium salt precipitated from solution. The slurry was treated dropwise with a solution of (*E*)-5-(*t*-butyldimethylsilyloxy)pent-3-en-2-one (9d) (0.50 g, 2.3 mmol) in anhydrous THF (6 mL). Stirring was continued at −78°C for 1 h during which time the solid dissolved and a dark green solution formed. The reaction mixture was allowed to warm to 0°C over 1 h, and stirring was continued for a further 1 h at this temperature. Ice-cold saturated aqueous ammonium chloride (100 mL) was added, whereupon the organic phase turned orange. Extraction with ethyl acetate (4 × 70 mL) gave an orange solution, which was washed with brine (3 × 50 mL), dried and evaporated to give a red oil. The crude product was dissolved in methanol (50 mL) and cooled to 0°C before being treated with CAN (3.07 g, 5.6 mmol). After 20 min the reaction mixture was allowed to warm to room temperature and stirring was continued for 14 h. TLC of the reaction mixture showed the rapid oxidation of the hydroquinone to the quinone (24) and the slow appearance of the deprotected–cyclized product. The methanol was evaporated and the residue was dissolved in ethyl acetate (100 mL) and washed with saturated aqueous sodium bicarbonate (100 mL), water (100 mL), and brine (100 mL). The solution was dried and evaporated to give a brown tar, which was subjected to rapid silica filtration. Elution with ethyl acetate/petroleum (4 : 1) gave *5-methoxy-3-methylnaphtho[2,3-c]furan-1, 4-dione* (5) as a yellow solid (113 mg, 20%), identical with the material described later.

(*B*). A stirred solution of diisopropylamine (0.35 mL, 2.5 mmol) in anhydrous THF (4 mL) at −78°C under argon, was treated dropwise with a 1.2 M hexane solution of Bu^nLi (2.0 mL, 2.4 mmol). After 15 min a solution of 4-methoxy-3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile (23) (441 mg, 2.3 mmol) in anhydrous THF (10 mL) was added dropwise, whereupon the bright orange cyanophthalide anion formed immediately. Stirring was continued for 30 min during which time the orange lithium salt precipitated from solution. The slurry was treated dropwise with a solution of (*E*)-5-(*t*-butyldimethylsilyloxy)-3-penten-2-one (9d) (0.50 g, 2.3 mmol) in anhydrous THF (6 mL). The yellow-brown solution was allowed to warm to room temperature and stirring was continued overnight. The resulting muddy orange suspension was diluted with ice-cold saturated 1 M hydrochloric acid (100 mL) and extracted with ethyl acetate (3 × 50 mL). The deep red extract was washed with brine (3 × 50 mL), dried and evaporated to give a red solid. The crude product was dissolved in methanol (35 mL) then treated with iron(III) chloride (0.83 g, 5.1 mmol) and stirred for 2 h. TLC indicated that the reaction had not gone to completion so a fresh portion of iron(III) chloride (0.4 g, 2.5 mmol) was added and

stirring was continued for 3 h. The methanol was evaporated and the residue was subjected to rapid silica filtration. Elution with ethyl acetate/petroleum (4 : 1) gave *methyl (3-acetyl-5-methoxynaphthalen-1,4-dion-2-yl)acetate* (30) as a yellow solid (119 mg, 30%), which crystallized from dichloromethane/petroleum as yellow needles, mp 130–138°C (Found C, 63.7; H, 5.0. $C_{16}H_{14}O_6$ requires C, 63.6; H, 4.7%). Mass spectrum *m*/*z* 302 (M, 23%), 272 (42), 271 (32), 270 (74), 255 (33), 244 (47), 243 (100), 242 (70), 229 (48), 115 (29). δ_H (500 MHz) 7.67 (dd (overlapping), $J_{8',7'}$ 7.6, $J_{8',6'}$ 1.9, 1 H, H8′), 7.65 (dd (apparent t overlapping), $J_{7',8'} = J_{7',6'}$ 7.6, 1 H, H7′), 7.29 (dd, $J_{6',7'}$ 7.6, $J_{6',8'}$ 1.9, 1 H, H6′), 3.96 (s, 3 H, CH_3O), 3.65 (s, 3 H, CO_2CH_3), 3.53 (s, 2 H, CH_2), 2.45 (s, 3 H, CH_3). δ_C (125.8 MHz) 201.6 (*C*OCH$_3$), 184.2 (C1′), 182.5 (C4′), 169.4 (C1), 159.6 (C5′), 148.0 (C3′), 136.3 (C2′), 135.4 (C8′), 133.2 (C8a′), 119.4 (C7′), 118.8 (C4a′), 118.2 (C6′), 56.4 (CH_3O), 52.3 (CO_2CH_3), 31.5 (CO*C*H$_3$), 31.3 (C2). ν_{max}/cm^{-1} 1748, 1709, 1658, 1644.

2-Acetyl-8-methoxy-3-methylnaphthalene-1,4-diol (32)

A stirred solution of diisopropylamine (2.36 mL, 16.8 mmol) in anhydrous THF (20 mL) at −78°C under argon, was treated with a 1.3 M hexane solution of Bu^{n}Li (13.0 mL, 16.9 mmol). After 30 min a solution of 4-methoxy-3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile (23) (2.90 g, 15.3 mmol) in anhydrous THF (60 mL) was added dropwise over 25 min, whereupon the bright orange cyanophthalide anion formed. Stirring was continued for 45 min during which time the orange lithium salt precipitated from solution. The slurry was treated dropwise with a solution of (*E*)-pent-3-en-2-one (31) (1.32 g, 15.7 mmol) in anhydrous THF (30 mL) and the reaction mixture was allowed to slowly warm to room temperature overnight. The dark red solution was diluted with ice-cold 1 M hydrochloric acid (500 mL) whereupon it turned yellow. Extraction with ethyl acetate (4 × 200 mL) gave a yellow solution which was washed with water (200 mL) and brine (2 × 200 mL), dried and evaporated to give a brown tar which was subjected to rapid silica filtration. Elution with ethyl acetate/petroleum (4 : 1) gave the title *compound* (32) as a brown solid (2.98 g, 79%), containing a trace of the oxidized *2-acetyl-8-methoxy-3-methylnaphthalene-1,4- dione* (33). As the quinone (33) was required, the mixture was used in the next step. The pure *hydroquinone* (32) crystallized from dichloromethane/petroleum as large translucent yellow needles, mp 132–133°C (Found C, 68.3; H, 5.5. $C_{14}H_{14}O_4$ requires C, 68.3; H, 5.7%). Mass spectrum *m*/*z* 246 (M, 78%), 232 (14), 231 (100), 215 (15). δ_H (300 MHz) 9.16 (s, 1 H, OH), 7.64 (dd, $J_{5,6}$ 8.6, $J_{5,7}$ 0.9, 1 H, H5), 7.30 (dd, $J_{6,5}$ 8.6, $J_{6,7}$ 7.8, 1 H, H6), 6.72 (br d, $J_{7,6}$ 7.8, H7), 5.23 (br s, OH), 4.00 (s, 3 H, CH_3O), 2.60 (s, 3 H, $COCH_3$), 2.20 (s, 3 H, CH_3). δ_C (75.5 MHz) 206.6 (CO), 156.3 (C), 145.5 (C), 141.3 (C), 127.8 (C), 126.3 (CH), 124.4 (C), 116.4 (C), 115.3 (CH), 113.3 (C), 104.3 (CH), 56.1 (CH_3O), 32.4 (CO*C*H$_3$), 12.6 (CH_3). ν_{max}/cm^{-1} 3400, 1676, 1653.

2-Acetyl-8-methoxy-3-methylnaphthalene-1,4-dione (33)

A stirred solution of 2-acetyl-8-methoxy-3-methylnaphthalene-1,4-diol (32) (50 mg, 0.20 mmol) in methanol (5 mL) was treated with a solution of iron(III) chloride (0.07 g, 0.43 mmol) in methanol (5 mL). The reaction mixture was stirred at room temperature for 1 h during which time a white precipitate formed. The methanol was evaporated and the residue was washed through a plug of silica with dichloromethane. The filtrate was evaporated to give the title *quinone* (33) as a bright yellow crystalline solid (50 mg, 100%), which crystallized from dichloromethane/petroleum as yellow-brown rectangular plates, mp 170–172°C (Found C, 68.7; H, 4.9. $C_{14}H_{12}O_4$ requires C, 68.8; H, 4.9%). Mass spectrum *m*/*z* 244 (M, 100%), 231 (17), 229 (68), 202 (19), 201 (56), 115 (17). δ_H (300 MHz) 7.75 (dd, $J_{5,6}$ 7.7, $J_{5,7}$ 1.3, 1 H, H5), 7.68 (dd (apparent t), $J_{6,5} = J_{6,7}$ 8, 1 H, H6), 7.31 (dd, $J_{7,6}$ 8.3, $J_{7,5}$ 1.2, 1 H, H7), 4.00 (s, 3 H, CH_3O), 2.47 (s, 3 H, $COCH_3$), 2.04 (s, 3 H, CH_3). δ_C (75.5 MHz) 201.9 (*C*OCH$_3$), 185.3 (CO), 182.7 (CO), 159.7 (C), 147.2 (C), 139.9 (C), 135.3 (C5), 133.8 (C), 119.4 (CH), 119.0 (C), 118.0 (CH), 56.5 (CH_3O), 31.6 (CO*C*H$_3$), 12.6 (CH_3). ν_{max}/cm^{-1} 1713, 1653, 1642.

2-Acetyl-3-bromomethyl-8-methoxynaphthalene-1,4-dione (34)

A mixture of 2-acetyl-8-methoxy-3-methylnaphthalene-1,4-dione (33) (514 mg, 2.1 mmol), NBS (410 mg, 2.3 mmol), and a catalytic amount of AIBN in carbon tetrachloride (50 mL) under argon, was heated under reflux whilst being irradiated with a 150 W tungsten lamp. After 3 h, TLC (dichloromethane) indicated that starting material was still present so another equivalent of NBS (0.41 g, 2.3 mmol) and a fresh portion of AIBN was added to the reaction mixture. After 13 h the carbon tetrachloride was evaporated and the residue was subjected to rapid silica filtration. Elution with ethyl acetate/petroleum (4 : 1) gave fractions containing the desired product and a by-product. The crude material was dissolved in dichloromethane (50 mL) and washed with water (3 × 100 mL). The aqueous washes were back extracted with ether (2 × 20 mL) and the combined organic solution was washed with water (50 mL) and brine (2 × 50 mL), dried and evaporated to give the title *bromide* (34) as a yellow solid (609 mg, 90%), which crystallized from dichloromethane/petroleum as yellow needles, mp 108°C (dec.) (Found C, 52.0; H, 3.3. $C_{14}H_{11}BrO_4$ requires C, 52.0; H, 3.4%). Mass spectrum: *m*/*z* 324 ([M + 2], 1.6%), 322 (M, 1.6), 244 (40), 243 (100), 229 (23), 201 (27). δ_H (500 MHz) 7.79 (dd, $J_{5,6}$ 7.7, $J_{5,7}$ 1.1, 1 H, H5), 7.73 (dd, $J_{6,7}$ 8.4, $J_{6,5}$ 7.7, 1 H, H6), 7.35 (dd, $J_{7,6}$ 8.4, $J_{7,5}$ 1.1, 1 H, H7), 4.28 (s, 2 H, CH_2), 4.01 (s, 3 H, CH_3O), 2.55 (s, 3 H, $COCH_3$). δ_C (125.8 MHz)† 201.0 (*C*OCH$_3$), 182.7 (C4), 182.5 (C1), 159.8 (C8), 147.4 (C2), 138.4 (C3), 135.8 (C6), 133.3 (C4a), 119.7 (C5), 118.9 (C8a), 118.4 (C7), 56.5 (CH_3O), 31.6 (CO*C*H$_3$), 20.1 (CH_2). ν_{max}/cm^{-1} 1701, 1669, 1647.

2-Acetoxymethyl-3-acetyl-5-methoxynaphthalene-1,4-dione (35)

A stirred solution of 2-acetyl-3-bromomethyl-8-methoxynaphthalene-1,4-dione (34) (200 mg, 0.62 mmol) in anhydrous DMF (20 mL) under argon, was cooled in an ice/brine bath before being treated with anhydrous sodium acetate (5.1 g, 62 mmol). After 4 h, the reaction mixture was diluted with ether (20 mL), vacuum filtered through a short column of silica and washed through with ether (150 mL). The filtrate was evaporated and the residue was dissolved in ethyl acetate (50 mL) and washed with water (3 × 40 mL). The aqueous washes were back extracted with ethyl acetate (2 × 50 mL). The combined ethyl acetate solution was washed with brine (2 × 50 mL), dried and evaporated to give the title *acetate* (35) as an orange oil (171 mg, 91%), which crystallized from ether as orange crystals, mp 115–117°C (Found C, 63.6; H, 4.7. $C_{16}H_{14}O_6$ requires C, 63.6; H, 4.7%). Mass spectrum *m*/*z* 302 (M, < 2%), 260 (100), 242 (35), 232 (37), 218 (19), 217 (91). δ_H (300 MHz) 7.72 (m, AB part of ABX, 2 H, H7/H8), 7.33 (dd, $J_{6,7}$ 7.4, $J_{6,8}$ 2.3, 1 H, H6), 5.07 (s, 2 H, CH_2), 4.00 (s, 3 H, CH_3O), 2.51 (s, 3 H, $COCH_3$), 2.05 (s, 3 H, CH_3). δ_C (75.5 MHz) 200.7 (*C*OCH$_3$), 183.9 (CO), 182.6 (CO), 169.7 (CO_2), 159.8 (C5), 147.5 (C), 136.3 (C), 135.7 (C2), 133.4 (C), 119.4 (CH), 118.8 (C), 118.3 (CH), 57.9 (CH_2), 56.5 (CH_3O), 31.8 (CO*C*H$_3$), 20.4 (CH_3). ν_{max}/cm^{-1} 1735, 1740, 1653.

2-Acetyl-3-formyloxymethyl-8-methoxynaphthalene-1,4-dione (36)

A stirred solution of 2-acetyl-3-bromomethyl-8-methoxynaphthalene-1,4-dione (34) (53 mg, 0.16 mmol) in anhydrous DMF (5 mL), in an ice/brine bath under argon, was treated with anhydrous sodium formate (1.10 g, 16.2 mmol). Stirring was continued for 4 h after which time TLC showed the reaction to be complete. The reaction mixture was diluted with ether (20 mL) and filtered through a small plug of silica with ether (50 mL) and ethyl acetate (50 mL) washes. The filtrate was concentrated and diluted with ethyl acetate (60 mL), then washed with water (3 × 20 mL) and brine (3 × 40 mL), dried and evaporated to give the title *formate* (36) as an orange gum, which precipitated from dichloromethane/petroleum as an orange solid (48 mg, 100%) and crystallized from ether as red-brown crystals, mp 150–155°C (Found C, 62.4; H, 4.4. $C_{15}H_{12}O_6$ requires C, 62.5; H, 4.2%). Mass spectrum *m*/*z* 288 (M, 4%), 260 (71), 244 (69), 242 (80), 232 (58), 229 (51), 217 (100), 199 (75), 171 (67), 127 (53). δ_H (300 MHz) 8.02 (t, *J* 0.9, 1 H, CHO), 7.75 (m, AB part of ABX, 2 H, H5/H6), 7.35 (dd, $J_{5,6}$ 7.3, $J_{5,7}$ 2.4, 1 H, H7), 5.14 (d, *J* 0.9, 1 H, CH_2), 4.01 (s, 3 H, CH_3O), 2.52 (s,

3 H, $COCH_3$). δ_C (75.5 MHz) 200.8 ($COCH_3$), 183.7 (CO), 182.5 (CO), 159.9 (C8), 159.7 (CHO), 148.3 (C), 135.8 (CH), 135.6 (C), 133.3 (C), 119.5 (CH), 118.8 (C), 118.4 (CH), 57.0 (CH_2), 56.5 (CH_3O), 31.7 ($COCH_3$). ν_{max}/cm^{-1} 1716, 1698, 1668, 1648.

5-Methoxy-3-methylnaphtho[2,3-c]furan-4,9-dione (5)

A stirred solution of 2-acetyl-3-formyloxymethyl-8-methoxynaphthalene-1,4-dione (36) (72 mg, 0.25 mmol) in methanol/THF (3 : 2) (25 mL) under argon, was cooled in an ice/brine bath and then treated dropwise with an ice-cold solution of potassium bicarbonate (0.20 g, 2.0 mmol) in water (4 mL). After 1.5 h, TLC showed the reaction to be complete, and the reaction mixture was diluted with ether (75 mL) and vacuum filtered through a short column of silica. The column was washed with ether and the filtrate was dried and evaporated to give an orange solid (62 mg). ^1H NMR spectroscopy of the crude product showed it to be a mixture of the title *dione* (5) and the intermediate hemiacetal (37). The crude product was dissolved in dichloromethane (5 mL) and the solution was added to a stirred suspension of acidified silica (prepared by adding 1 drop of concentrated hydrochloric acid to silica (0.36 g) suspended in dichloromethane and stirring for 5 min) under argon. After 20 min the silica was filtered off and washed with dichloromethane. The filtrate was evaporated to give the title compound as a yellow solid (59 mg, 98%), which crystallized from dichloromethane/petroleum as yellow needles, mp 188–192°C (Found C, 69.3; H, 4.3. $C_{15}H_{12}O_6$ requires C, 69.4; H, 4.2%). Mass spectrum *m*/*z* 242 (M, 100%), 213 (33), 196 (28), 86 (22), 84 (32). δ_H (300 MHz) 7.96 (s, 1 H, H 1), 7.90 (dd, $J_{8,7}$ 7.8, $J_{8,6}$ 1.1, 1 H, H8), 7.65 (dd, $J_{7,6}$ 8.4, $J_{7,8}$ 7.8, 1 H, H7), 7.30 (dd, $J_{6,7}$ 8.4, $J_{6,8}$ 1.1, 1 H, H6), 4.00 (s, 3 H, CH_3O), 2.71 (s, 3 H, CH_3). δ_C (75.5 MHz) 180.4 (CO), 180.0 (CO), 161.0 (C), 159.6 (C), 142.4 (C1), 137.9 (C), 134.6 (C7), 123.4 (C), 122.8 (C), 119.9 (CH), 118.0 (CH), 117.7 (C), 56.4, CH_3O), 13.6 (CH_3). ν_{max}/cm^{-1} 1676, 1661.

5-Hydroxy-3-methylnaphtho[2,3-c]furan-4,9-dione (1)

A stirred solution of 5-methoxy-3-methylnaphtho[2,3-*c*]furan-4,9-dione (5) (26 mg, 0.11 mmol) in anhydrous dichloromethane (5 mL) under argon in an ice/brine bath, was treated with anhydrous aluminium chloride (0.14 g, 1.05 mmol), whereupon the yellow solution immediately turned red-black. After 30 min the reaction mixture was allowed to warm to room temperature and stirring was continued overnight. The reaction mixture was diluted with ice-cold 1 M hydrochloric acid (100 mL) and the aqueous phase was saturated with oxalic acid, and then extracted with ethyl acetate (4 × 15 mL). The orange extract was washed with water (2 × 30 mL) and brine (30 mL), dried and evaporated to give a brown solid. The crude product was dissolved in ether and the solution was filtered through a plug of silica. The filtrate was evaporated to give the title natural product (1) as a yellow crystalline solid (20 mg, 82%), which crystallized from dichloromethane/petroleum as long yellow needles, mp 193–195°C (lit.[5] 180–183°C, lit.[6] 188–90°C) (Found C, 68.2; H, 3.7. $C_{13}H_8O_4$ requires C, 68.4; H, 3.5%). Mass spectrum *m*/*z* 229 (15), 228 (M, 100%), 199 (37), 144 (11), 115 (21). δ_H (300 MHz) 12.85 (d, $J_{OH,7}$ 0.4, 1 H, OH), 8.04 (s, 1 H, H1), 7.79 (dd, $J_{8,7}$ 7.6, $J_{8,6}$ 1.2, 1 H, H8), 7.63 (ddd, $J_{7,6}$ 8.3, $J_{7,8}$ 7.6, $J_{7,OH}$ 0.4, 1 H, H7), 7.26 (dd, $J_{6,7}$ 8.3, $J_{6,8}$ 1.2, 1 H, H6), 2.78 (s, 3 H, CH_3). δ_C (75.5 MHz) 186.6 (CO), 179.0 (CO), 163.2 (C), 160.4 (C), 143.6 (C1), 136.2 (CH), 135.8 (C), 124.4 (CH), 123.2 (C), 119.4 (C6), 117.9 (C), 116.7 (C), 14.0 (CH_3). ν_{max}/cm^{-1} 1682, 1648.

2-Hydroxy-3-(2-hydroxyethylidene)-8-methoxy-2-methyl-2,3-dihydronaphthalene-1,4-dione (40)

A 1 M sodium hydroxide solution (10 mL, 10 mmol) was added to a vigorously stirred solution of 2-acetyl-8-methoxy-3-methylnaphthalene-1,4-dione (33) (50 mg, 0.20 mmol) and benzyltriethylammonium chloride (5 mg) in dichloromethane (30 mL) under argon. After 3 h the aqueous layer was separated and was diluted with ice-cold 1 M hydrochloric acid (20 mL). Extraction with ethyl acetate (3 × 30 mL) gave a pale yellow solution, which was washed with brine (2 × 40 mL), dried and evaporated to give a pale yellow solid. A 1 M sodium hydroxide solution (10 mL, 10 mmol) was added to the dichloromethane solution and stirring was continued overnight. The aqueous layer was worked up as before and combined with the first batch of product to give the title *compound* (40) as a pale yellow solid (45 mg, 84%), which crystallized from dichloromethane/petroleum as orange-brown plates, mp 129–134°C (Found C, 63.9; H, 5.5. $C_{14}H_{14}O_5$ requires C, 64.1; H, 5.4%). Mass spectrum *m*/*z* 262 (M, <1%), 244 (30), 229 (18), 219 (100), 201 (92), 177 (18). δ_H (500 MHz) 13.94 (br s, 1 H, enol OH), 7.58, dd, $J_{7,6}$ 8.2, $J_{7,8}$ 7.6, 1 H, H7), 6.98 (d, $J_{6,7}$ 8.2, 1 H, H6), 6.87 (d, $J_{8,7}$ 7.6, 1 H, H8), 4.92 (br s, 1 H, OH), 4.00 (s, 3 H, CH_3O), 1.96 (s, 3 H, vinyl CH_3), 1.91 (s, 3 H, CH_3). δ_C (125.8 MHz) 206.7 (C1), 193.9 (C4), 175.4 (enol COH), 158.1 (C5), 151.7 (C8a), 136.8 (C7), 124.6 (C4a), 115.4 (C8), 112.6 (C3), 112.2 (C6), 82.5 (C2), 56.1 (CH_3O), 22.8 (CH_3), 18.8 (vinyl CH_3). Assignments were made with the aid of NOESY, HMQC, and HMBC experiments. ν_{max}/cm^{-1} 3463 br, 1715, 1592.

5-(t-Butyldimethylsilyloxy)pent-3-yn-2-one (43)

A stirred solution of 1-(*t*-butyldimethylsilyloxy)-2-propyne (4.00 g, 23.5 mmol) in anhydrous THF (80 mL) at −78°C under argon, was treated with a 1.2 M solution of Bu^nLi in hexane (19.6 mL, 23.5 mmol). After 30 min acetic anhydride (4.5 mL, 48 mmol) was added in one portion. The reaction mixture was allowed to warm to room temperature over 2.5 h and then diluted with saturated ammonium chloride solution (250 mL). The organic solvents were evaporated and the aqueous phase was extracted with ether (3 × 70 mL). The organic phase was washed with saturated aqueous sodium bicarbonate (100 mL), water (100 mL), and brine (100 mL), dried and evaporated to give a yellow liquid. The crude product was distilled (Kugelrohr) to give fractions containing the desired product plus impurities and a pure middle fraction of the title ketone (42) as a colourless oil (2.92 g, 59%). δ_H (200 MHz) 4.46 (s, 2 H, CH_2), 2.35 (s, 3 H, CH_3), 0.92 (s, 9H, $C(CH_3)_3$), 0.15 (s, 6H, $Si(CH_3)_2$). This spectrum was similar to that acquired in CCl_4.[40]

3-Acetyl-2-[(t-butyldimethylsilyloxy)methyl]-4-hydroxy-1-oxo-1,2-dihydronaphthalene-2-carbonitrile (46)

A stirred solution of diisopropylamine (154 μL, 1.1 mmol) in anhydrous THF (5 mL) at −78°C under argon, was treated dropwise with a 0.95 M hexane solution of Bu^nLi (1.06 mL, 1.0 mmol). After 15 min a solution of 3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile (41) (159 mg, 1.0 mmol) in anhydrous THF (4 mL) was added dropwise, whereupon the dark orange-red cyanophthalide anion formed immediately. Stirring was continued for 15 min before trimethylsilyl chloride (152 μL, 1.2 mmol) was added. The reaction mixture was allowed to warm to room temperature for 5 min before being returned to −78°C and transferred using a cannula to a stirred solution of 5-(*t*-butyldimethylsilyloxy)pent-3-yn-2-one (43) (213 mg, 1.0 mmol) in refluxing anhydrous THF (6 mL). After 10 min, the reaction mixture was cooled and quenched with saturated ammonium chloride solution (50 mL) then extracted with ethyl acetate (3 × 25 mL). The extract was washed with water (2 × 25 mL) and brine (2 × 25 mL), dried and evaporated to give a dark red oil. The complex mixture of compounds was subjected to rapid silica filtration. Elution with ethyl acetate/petroleum (1 : 50) gave the *nitrile* (46) as a dark yellow gum (54 mg, 17%), which crystallized from petroleum as large yellow plates, mp 97–104°C. Mass spectrum: *m*/*z* 285 (24), 284 (100), 242 (52), 89 (26), 84 (31), 75 (51), 73 (58), 57 (21)), $[M+H]^{+\bullet}$ HR-MS (FAB) Found: 372.1626. $C_{20}H_{26}NO_4Si$ requires 372.1631. δ_H (500 MHz) 18.07 (s, 1 H, OH), 8.25 (ddd, $J_{5,6}$ 7.9, $J_{5,7}$ 1.2, $J_{5,8}$ 0.5, 1 H, H5), 8.09 (ddd, $J_{8,7}$ 7.8, $J_{8,6}$ 1.3, $J_{8,5}$ 0.5,1 H, H8), 7.81 (ddd, $J_{6,5}$ 7.8, $J_{6,7}$ 7.4, $J_{6,8}$ 1.3, 1 H, H6), 7.70 (ddd (apparent td), $J_{7,6} = J_{7,8}$ 7.6, $J_{7,5}$ 1.2, 1 H, H7), 4.27 (d, J_{gem} 9.0, 1 H, 1 of CH_2), 4.08 (d, J_{gem} 9.0, 1 H, 1 of CH_2), 2.61 (s, 3 H, $COCH_3$), 0.57 (s, 9H, $C(CH_3)_3$), −0.15 (s, 3 H, $SiCH_3$), −0.14 (s, 3 H, $SiCH_3$). δ_C (125.8 MHz) 196.7 ($COCH_3$), 189.2 (C1), 175.5 (C4), 135.5 (C6), 133.6 (C4a), 133.3 (C7), 131.3 (C8a), 127.0 (C8), 126.7 (C5), 117.3 (CN), 70.4 (CH_2), 52.4 (C2), 26.1 ($COCH_3$), 25.3 ($C(CH_3)_3$), 17.7 (SiC), −6.01 ($SiCH_3$), −5.95 ($SiCH_3$). Assignments were made with the aid of HMQC and HMBC experiments.

Acylation of 1,4-dimethoxybenzene (47) with 2-methylfuran-3,4-dicarbonyl dichloride (48)

A stirred solution of 1,4-dimethoxybenzene (47) (1.81 g, 13.1 mmol) and 2-methylfuran-3,4-dicarbonyl dichloride (48) (2.705 g, 13.1 mmol) in anhydrous 1,2-dichloroethane (140 mL) at 0°C under argon, was treated with anhydrous aluminium chloride (3.48 g, 26.1 mmol). The flask was stoppered and the reaction mixture was stirred for 5 days in the dark. TLC showed the presence of the desired product and the mono-demethylated product and thus the reaction mixture was cooled to 0°C and another molar equivalent of anhydrous aluminium chloride (1.75 g, 13.1 mmol) was added. The ice bath was removed and, after 4 h, the deep purple reaction mixture was diluted with 2 M hydrochloric acid (500 mL) and then saturated with oxalic acid. Extraction with ethyl acetate (until the extract was colourless) gave a red solution, which was washed with water (2×) and brine (2×), dried and evaporated to give a deep red solid. The crude product was subjected to rapid silica filtration. Elution with ethyl acetate/petroleum (1 : 19 then 1 : 9) gave 5,*8-dihydroxy-1-methylnaphtho[2,3-*c*]furan-4,9-dione* (2) as an orange solid (1.018 g, 32%), which crystallized from ethyl acetate/petroleum as bright orange needles, mp 181–185°C [lit.[6] 176–177°C] (Found C, 63.8; H, 3.5. $C_{13}H_8O_5$ requires C, 63.9; H, 3.5%). Mass spectrum *m*/*z* 244 (M, 100%), 215 (18), 205 (28). δ_H (500 MHz) 12.94 (s, 1 H, C8–OH), 12.79 (s, 1 H, C5–OH), 8.06 (s, 1 H, H3), 7.24 (d, $J_{6,7}$ 9.3, 1 H, aryl), 7.22 (d, $J_{6,7}$ 9.3, 1 H, aryl), 2.77 (s, 3 H, CH_3). δ_C (125.8 MHz) 185.2 (CO), 184.4 (CO), 160.4 (C1), 157.9 (C5 or C8), 157.8 (C5 or C8), 143.6 (C3), 129.2 (C7), 128.7 (C6), 123.0 (C3a), 116.5 (C9a), 114.76 (C4a or C8a), 114.75 (C4a or C8a), 14.0 (CH_3). ν_{max}/cm^{-1} 1638 br.

Further elution with ethyl acetate/petroleum (1 : 4) gave *5-hydroxy-8-methoxy-1-methylnaphtho[2,3-*c*]furan-4,9-dione* (3a) as an orange solid (616 mg, 18%) containing about 10% of the isomer *5-hydroxy-8-methoxy-3-methylnaphtho[2,3-*c*]furan-4,9-dione* (3b) by ^{1}H NMR spectroscopy. The isomers co-crystallized from ethyl acetate as red-brown rectangular plates in a ratio of 9 : 1 by ^{1}H NMR spectroscopy, mp 160°C (sweating), 177–179°C (melted) [lit.[6] (natural product) 194–196°C] (Found C, 64.9; H, 4.2. $C_{14}H_{10}O_5$ requires C, 65.1; H, 3.9%). Mass spectrum *m*/*z* 258 (M, 100%), 243 (32), 229 (69), 215 (19). ν_{max}/cm^{-1} 3449 br, 1659, 1631.

*5-Hydroxy-8-methoxy-1-methylnaphtho[2,3-*c*]furan-4,9-dione (3a)*. δ_H (500 MHz) 12.94 (s, 1 H, OH), 7.96 (s, 1 H, H3), 7.31 (d, $J_{7,6}$ 9.4, 1 H, H7), 7.19 (d, $J_{6,7}$ 9.4, 1 H, H6), 3.93 (s, 3 H, CH_3O), 2.68 (s, 3 H, CH_3). δ_C (125.8 MHz) 185.8 (C4), 179.4 (C9), 159.7 (C1), 157.9 (C5), 154.4 (C8), 142.8 (C3), 125.9 (C6), 123.7 (C7), 122.5 (C3a), 121.4 (C8a), 117.8 (C4a), 117.3 (C9a), 56.89 (CH_3O), 13.5 (CH_3).

*5-Hydroxy-8-methoxy-3-methylnaphtho[2,3-*c*]furan-4,9-dione (3b)*. δ_H (500 MHz) 13.08 (s, 1 H, OH), 7.90 (s, 1 H, H3), 7.29 (d, $J_{6,7}$ 9.4, 1 H, aryl), 7.19 (d, $J_{6,7}$ 9.4, 1 H, aryl), 3.92 (s, 3 H, CH_3O), 2.69 (s, 3 H, CH_3). δ_C (125.8 MHz) 186.4 (C4), 178.5 (C9), 159.7 (C), 157.8 (C), 154.5 (C), 143.1 (C1), 126.2 (CH, C), 124.2 (C), 123.3 (CH, C), 121.3 (C), 117.8 (C), 116.2 (C), 56.94 (CH_3O), 13.9 (CH_3).

Acknowledgments

We thank Dr Lindsay Byrne for the two-dimensional NMR spectra, and Dr Anthony Reeder for the mass spectra.

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