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Oxidation with Hypervalent Iodine Reagents. Part II: Novel Cyclohexadienones as Precursors for the Synthesis of Anthraquinones

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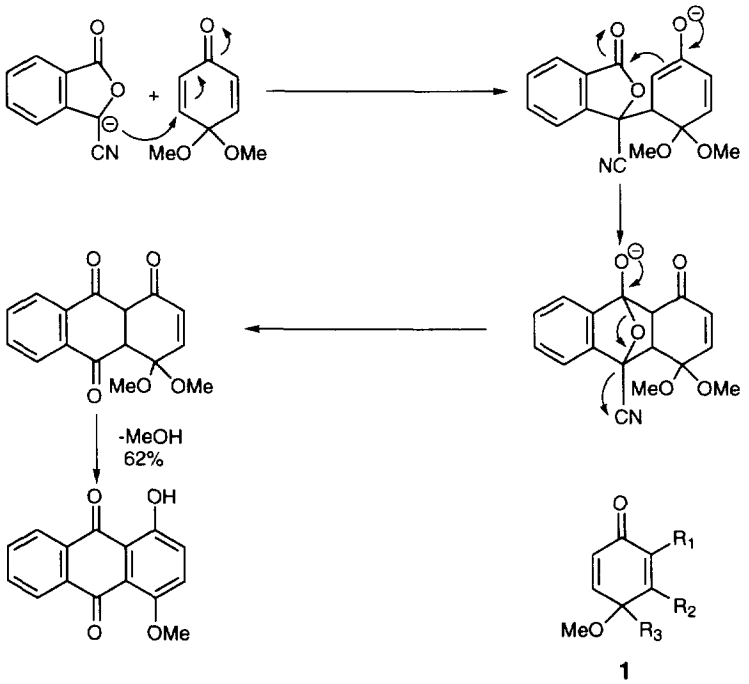
Abstract: The oxidation of substituted phenols with phenyliodonium diacetate in methanol was found to afford 2,4-cyclohexadienones, 2,5-cyclohexadienones or mixtures of isomers, depending on the substrate being oxidized. Annulation of these cyclohexadienones with the anion of 3-cyanophthalide afforded anthraquinones in high yields. © 1997 Elsevier Science Ltd.

The annulation of quinone monoketals (4,4-dimethoxycyclohexa-2,5-dienones) with the anions derived from stabilized phthalide anions has now become a standard method for the construction of anthraquinones and anthracyclines[1] (Scheme 1). Although anthraquinones may be easily prepared from 4-methoxyphenols using an oxidation/annulation sequence, this method is limited to the synthesis of 1,4-dioxygenated anthraquinones. We were interested to know under what conditions 4-alkyl-4-methoxycyclohexa-2,5-dienones (1) could be prepared, and if they would undergo annulation with stabilized phthalide anions to form anthraquinones[2]. Although 1-hydroxyanthraquinones without oxygenation in the 4-position have been prepared by annulation of



Scheme 1

appropriately substituted cyclohexenones[1], the ready accessibility of a wide range of 4-substituted phenols means that this proposed route offers much greater flexibility and convenience.

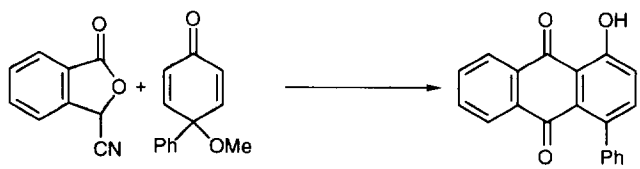
Oxidation of 4-Alkylphenols

Standard methods for the preparation of quinone monoketals involve either the selective monohydrolyis of electrochemically derived quinone bis(ketals)[3] or the chemical oxidation of 4-methoxyphenols. Although both of these methods have also been applied to 4-alkylphenols to form compounds related to (1), we decided to focus on chemical oxidations. Thallium trinitrate[4,5] or hypervalent iodine reagents[6-10] are both useful for the oxidation of 4-methoxyphenols to quinone monoketals. However, for the oxidation of 4-alkylphenols the use of hypervalent iodine reagents as oxidants is crucial, because McKillop[4], commenting on the reactivity of thallium trinitrate in methanol, reported that "*4-alkylphenols reacted markedly more slowly than the corresponding 4-methoxy compounds and, except in the cases where there was also substituent groups in the 2- and 6-positions, gave complex mixtures of products which proved impossible to separate.*"

Although recent applications of hypervalent iodine based reagents have focused mainly upon the oxidation of 4-methoxyphenols to quinone monoketals[6-10], isolated cases of 4-alkylphenols being oxidized have been reported[6,7,10-12]. However, with the exception of the study of Pelter[6,7], there has been little examination of the reactions between substituted phenols and hypervalent iodine reagents prior to this study.

Oxidation of 4-phenylphenol with phenyliodonium diacetate in methanol afforded 4-methoxy-4-phenylcyclohexa-2,5-dienone (2) in 73% yield. The ^{1}H n.m.r. spectrum of (2) showed a resonance attributable to the methoxy group (δ 3.43), two sets of doublets at δ 6.40 and 6.80, attributable to the α- and β-protons respectively, and a complex multiplet due to the phenyl ring. The mass spectrum was complex, but a molecular ion at *m/z* 200 was observed.

Annulation of dienone (2) with the anion of cyanophthalide (3) afforded 1-hydroxy-4-phenylanthraquinone (4) in 88% yield. Examination of the ^{1}H n.m.r. spectrum of the annulated product showed the hydroxyl resonance at δ 13.19. The large chemical shift of this proton can be attributed to the strong internal hydrogen bonding with the quinonoid carbonyl group; shifts as high as δ 14.3 have been reported for such protons[13-17]. This observation is consistent with the 1,4-addition of the cyanophthalide anion to the dienone (2). As the reaction proceeded the colour changed from the golden yellow of the cyanophthalide anion to the deep blue colour of the anthraquinone anion. This is also a useful indication that the annulation reaction has occured.



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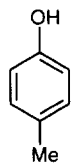
The oxidation of phenols with phenyliodonium diacetate could be conveniently followed by ^{1}H n.m.r. spectroscopy in deuterated methanol. Thus, oxidation of *para*-cresol (5) with one equivalent of phenyliodonium diacetate in deuteriomethanol resulted in the complete disappearance of the aromatic cresol resonances, with the quantitative formation of two sets of doublets at δ 6.6 and 6.9 with a 10 Hz coupling

constant. These resonances are typical of α,β-unsaturated carbonyl groups, and were assigned to the α- and β-protons of the cyclohexadienone unit respectively. The methyl group resonance shifted from δ 2.0, typical of benzylic methyl groups, to a singlet at δ 1.4, consistent with the formation of (6)[18].



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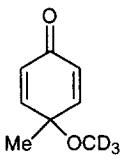

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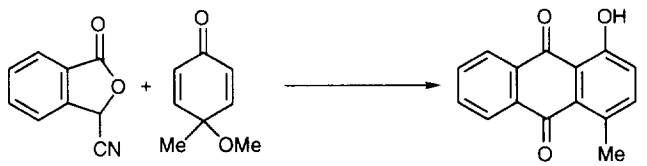
Oxidation of *para*-cresol with phenyliodonium diacetate in methanol afforded a mixture of (7) and iodobenzene. Although this mixture could be separated by flash chromatography, it was more convenient to perform the annulation on the unseparated mixture. The iodobenzene was inert to the annulation reaction conditions, and was readily separated from the resulting product by column chromatography. The isolated yield of the known[19] anthraquinone (8) was 88%.



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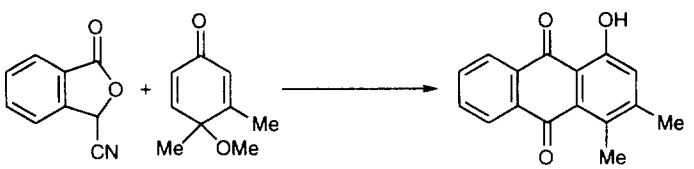
Similarly, 3,4-dimethylphenol was oxidized and annulated with the anion of cyanophthalide (3) to afford the known 1-hydroxy-3,4-dimethylanthraquinone[20] (10) in 96% yield.



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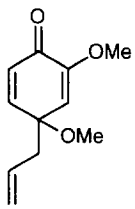
Preparation of *ortho*-Quinone Monoketals

Although the chemistry of *para*-quinone monoketals has been thoroughly documented, reactions of the corresponding *ortho*-quinone monoketals have received little attention[3]. Anodic oxidation of eugenol in methanol containing 2% lithium perchlorate afforded a mixture of the 2,5-dienone (11) in 3% yield, the 2,4-dienone (12) in 8% yield, the phenolic dimer (13) in 10% yield and the tricyclic species (14) in 21% yield[21].



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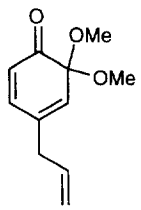

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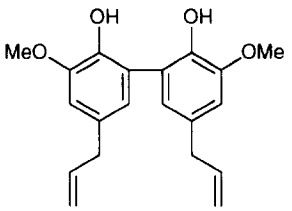

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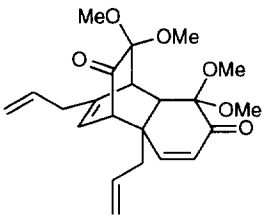

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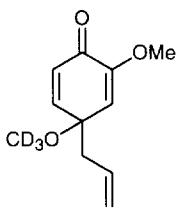
This unusual product is formally the Diels-Alder dimer of (12), and formed spontaneously when (12) was allowed to stand at room temperature for several hours[21].

In constrast to anodic oxidation, treatment of eugenol with phenyliodonium diacetate in deuterated methanol lead to the rapid formation of a single product, which was expected to be 2,5-cyclohexadienone (15) or the *ortho*-quinone ketal (16). However, as the chemical shift of the single methoxy group was expected to be similar for both isomers, it was not possible to assign unequivocally either structure (15) or (16) to the product by ^1H n.m.r. spectroscopy. Accordingly, a sample of eugenol was oxidized in non-deuterated methanol, and after aqueous work-up and extraction a mixture of dienone and iodobenzene was obtained. The ^1H n.m.r. spectrum of this mixture in deuteriochloroform showed a six proton methoxy resonance at δ 3.4, indicating that the two methoxy groups were equivalent. The oxidized product was assigned the *ortho*-quinone ketal structure (17).



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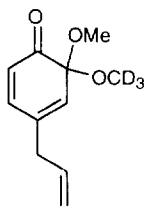

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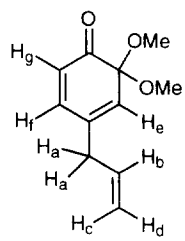

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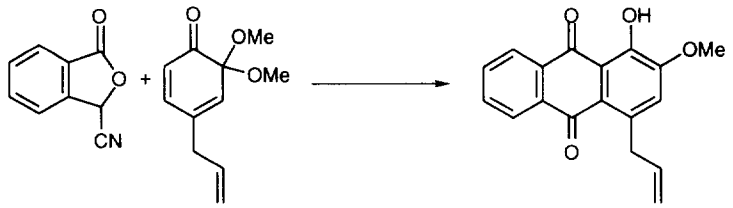
Further confirmation of the structure of (17) was afforded by selective decoupling experiments. Allylic coupling from H_a caused significant broadening of H_e and H_f; irradiation of H_a (δ 3.0) caused H_e and H_f to sharpen. Also, the complex multiplet at δ 5.83, assigned to H_b, collapsed into a doublet of doublets. Irradiation of H_b caused H_a to collapse into a very broad singlet, with the broadening being due to allylic coupling to four protons.

Although the mixture of *ortho*-quinoneketal (17) and iodobenzene was stable for at least several hours in the freezer, attempted chromatography on silica or storage at ambient temperature resulted in decomposition of the ketal with the formation of dimer (14). Consequently, the annulation reaction was performed on the mixture of (17) and iodobenzene. Carrying the iodobenzene through this reaction sequence caused no difficulties, and flash chromatography separated the iodobenzene from the substituted alizarin (18), which was isolated in 92% yield.



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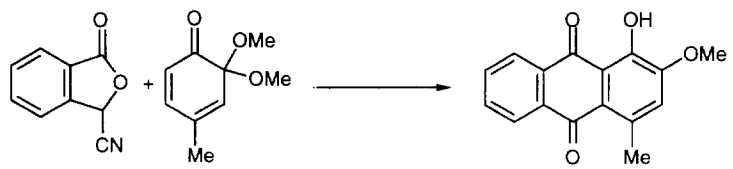
Oxidation of creosol[22] with phenyliodonium diacetate in methanol afforded the dienone (20); this was immediately annulated with the anion of cyanophthalide (3) to afford (19) in 78% yield. This two step preparation of (19) compares favourably in yield and is more convenient than an alternative Diels-Alder approach[23], which involved the five step preparation of an unstable diene.



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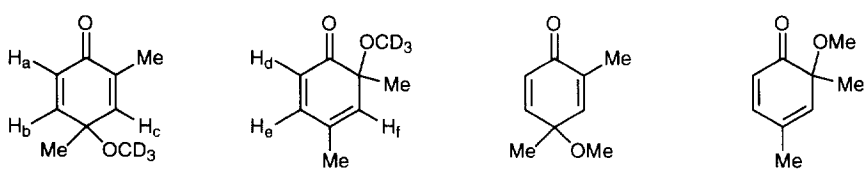
Oxidations Affording Mixed Products

Oxidation of 2,4-dimethylphenol with phenyliodonium diacetate in deuterated methanol afforded two products. The major product (21) was easily recognised by ^{1}H n.m.r spectroscopy: H_a appeared as a 10 Hz doublet at δ 6.27, H_b a doublet of doublets at δ 6.85 (J=10 Hz and 3.2 Hz) and H_c as a broad multiplet at δ 6.65 due to allylic coupling. The minor product was assigned the 2,4-cyclohexadienone structure (22); H_d was broadened by allylic coupling to the methyl group. Integration of the resonances of the protons on the quaternary methyl groups showed that the ratio of (21):(22) was about 7:2.



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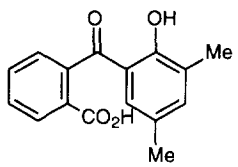
The mixture of dienones (23) and (24) were prepared by oxidation of 2,4-dimethylphenol in methanol and immediately annulated with the anion of cyanophthalide (3); both dienones afforded 1-hydroxy-2,4-dimethylanthraquinone (25) after workup.

The synthesis of 1-hydroxy-2,4-dimethylanthraquinone (25) by the cyclization of the benzoylbenzoic acid (26) with hot concentrated sulfuric acid has been reported[19] by Bentley *et al.*, however the reported melting point, 173-5° C, was significantly lower than the melting point of the product obtained from the annulation

reaction (180-181° C). Surprisingly, cyclization of (26) with aluminium chloride afforded 1-hydroxy-3,4-dimethylanthraquinone (10), in which the methyl group had migrated from the 2-position to the 3-position[20]. The rearranged benzoylbenzoic acid (27) was also be isolated from this reaction, indicating that rearrangement occurs (at least partially) before cyclization[20].



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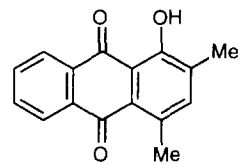

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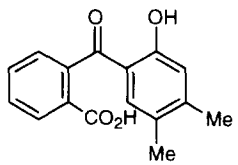

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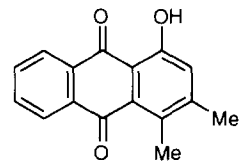

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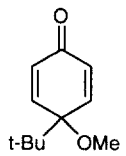
Modern spectroscopic and chromatographic techniques were not available to Bentley *et al.*, and the product obtained may possibly have been a mixture of (25) and the rearranged product (10), inseparable by crystallization. Due to the uncertain nature of the reported anthraquinones, the structures of both (25) and (10) were investigated using modern spectroscopic techniques.

The structure of (10) was not in doubt as the product prepared from the annulation reaction and the Friedel-Crafts reaction[20] had identical physical properties. The ^{1}H n.m.r. spectrum of (10) showed the typical pattern of an unsubstituted anthraquinone ring, a low field resonance at δ 13.20 due to the internally hydrogen bonded hydroxyl group, an aromatic singlet of the substituted ring (δ 7.14) and two benzylic methyl groups (δ 2.66 and 2.43). The ^{1}H n.m.r. spectrum of (25) was very similar; the hydroxyl group resonance had shifted downfield to δ 13.57 and the aromatic singlet appeared at δ 7.37. Substitution in the 2-position of 1-hydroxyanthraquinones tends to cause a downfield shift of the hydroxyl proton, an effect that may be a result of steric compression forcing the proton a little further into the deshielding region of the carbonyl group[24]. The unambiguous assignment of the ^{1}H n.m.r. spectra of (10) and (25) was made by using two-dimensional COSY spectroscopy. The COSY spectrum of (10) showed a long range benzylic coupling from the aromatic proton to only one methyl group, whereas the COSY spectrum of (25) showed long range correlations from the aromatic proton to both methyl groups. It was possible to assign the non-correlated methyl group (δ 1.66) of (135) to the 4-methyl group. The lower field methyl resonance of (25) was assigned to the 4-methyl group by analogy. This was expected as the quinone carbonyl would slightly deshield the methyl group in the 4-position, but the 2-methyl group would remain unaffected.

The oxidation of 4-*tert*-butylphenol was followed in deuterated methanol; complete oxidation required more than one equivalent of phenyliodonium diacetate. Two products were formed in nearly equal amounts, as determined by integration of their *tert*-butyl resonances. Oxidation of 4-*tert*-butylphenol with 1.5 equivalents of phenyliodonium diacetate in methanol on a preparative scale afforded (in addition to iodobenzene) a mixture of two compounds which were easily separable by radial or flash chromatography. The least polar product (28)

was isolated in 54% yield; it showed resonances attributable to the *tert*-butyl group (δ 1.00) and the methoxy group (δ 3.19), with a 10 Hz doublet at δ 6.40 and another doublet at δ 6.88. The more polar product, which was isolated in 43% yield, showed a *tert*-butyl resonance (δ 1.17) and a methoxy resonance (δ 3.37); however these integrated to a 6:9 ratio. The olefinic region also lacked symmetry; a 10 Hz doublet of δ 6.03 was



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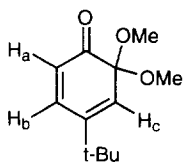

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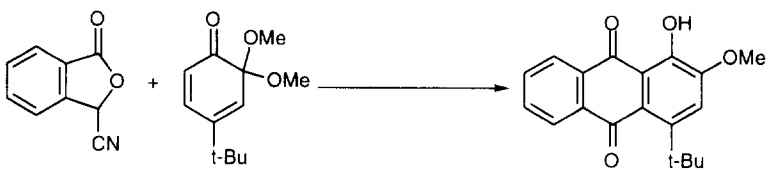
assigned to H_a, a 2 Hz doublet was assigned to H_c and the doublet of doublets at δ7.03 was assigned to H_b. This spectrum was entirely consistent with the 2,4-dienone structure (29). These dienones were partially unstable to silica and were not further characterized.

The formation of the *ortho*-quinoneketal (29) probably involves the intermediacy of 2-methoxy-4-*tert*-butylphenol, which would be expected to have a lower oxidation potential than 4-*tert*-butylphenol, and therefore would react preferentially with phenyliodonium diacetate. The oxidation of 4-*tert*-butylphenol to (29) requires two equivalents of oxidant, which also explains why more than one equivalent of phenyliodonium diacetate was required. Unlike the *ortho*-quinoneketals derived from eugenol and creosol, which underwent rapid self-dimerization, the *ortho*-quinoneketal (29) was indefinitely stable . This stability can probably be ascribed to the bulkiness of the *tert*-butyl group, which effectively prevents the dimerization reaction. It is known that large groups in the 5-position stabilize *ortho*-quinone monoketals[3].

The *ortho*-quinoneketal (29) was annulated efficiently with the anion of cyanophthalide (3) to afford anthraquinone (30) in 84% yield. However, attempted annulation of dienone (28) led to the formation of much polar material from which no trace of anthraquinone could be detected. The reason for this is unknown.



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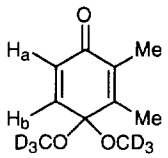
The oxidation of 2,3-dimethylphenol with excess phenyliodonium diacetate in deuterated methanol was studied. Analysis of the reaction mixture by ^1H n.m.r. showed that two products were formed. The major product of oxidation (31) showed only a single olefinic bond, with H_a at δ 6.38 and H_b at δ 6.83, and a 10 Hz coupling. The H_a doublet of the minor oxidation product (32) resonated at δ 6.00, and was significantly broadened by long range coupling to H_c and the methyl group. The methyl group region of the ^1H n.m.r. spectrum was complex and partially obscured by the large peak from the acetic acid liberated by the oxidation. Integration of the olefinic resonances showed that the dienones (31) and (32) were produced in a 2:1 ratio.



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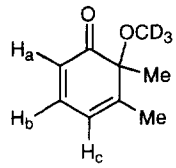

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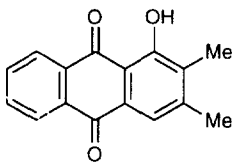
A sample of 2,3-dimethylphenol was oxidized with 1.5 equivalents of phenyliodonium diacetate on a preparative scale. The unseparated mixture of dienones was immediately annulated with the anion of cyanophthalide (3). The mixture of anthraquinones produced was readily separated by flash chromatography to afford (33) in 23% yield and (34) in 40% yield.



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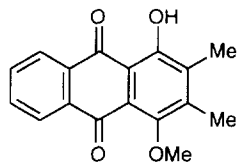

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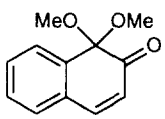
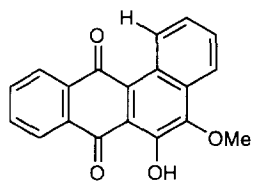
Miscellaneous Oxidations

Oxidation of β-naphthol with two equivalents of phenyliodonium diacetate in methanol afforded the crude naphthalenone (35), which was not isolated, but immediately annulated with the anion of cyanophthalide (3). The benzanthraquinone (36) was isolated in 62% yield after flash chromatography. The ^{1}H n.m.r. spectrum of (36) showed the H1 proton at δ 9.5 to be significantly deshielded by the quinone carbonyl group; the deshielding of annular protons in compounds of this type has been noted before[25,26].

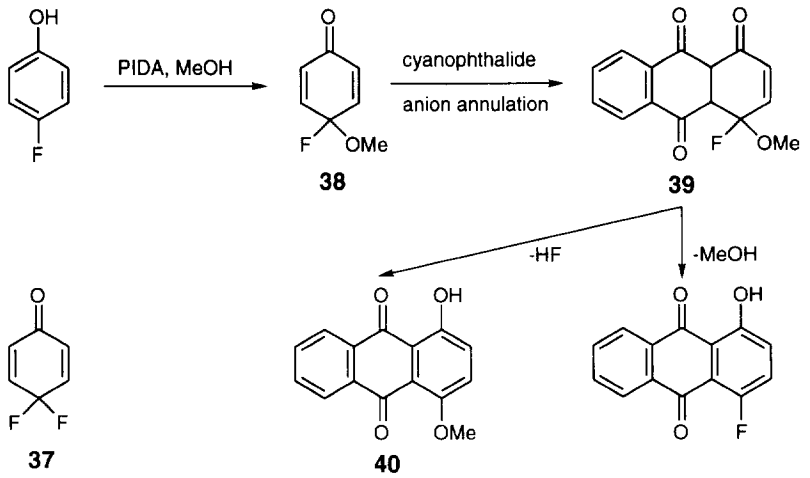


35



36

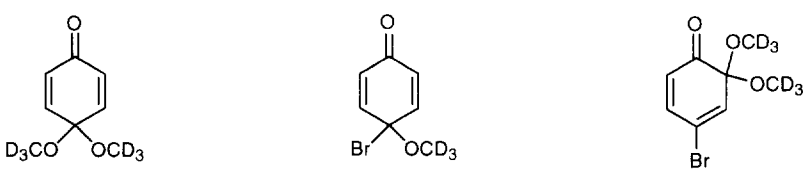
Rozhkov and Alyer[27] prepared 4,4-difluorocyclohexa-2,5-dienone (37) electrochemically and stated that "*the allylic fluorine atoms in [(37)] are quite stable towards replacement.*" In view of this statement, the possibility of preparing fluoroanthraquinones *via* phthalide anion annulation of the fluorodienone (38) was investigated. These reactions are outlined in Scheme 2.



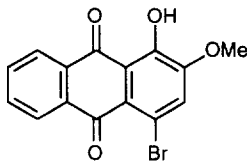
Scheme 2

The annulated intermediate (39) can aromatize by elimination of methanol or elimination of hydrogen fluoride. It was anticipated that due to the very high strength of the carbon-fluorine bond, elimination of methanol would predominate. The oxidation of 4-fluorophenol with phenyliodonium diacetate in methanol was slightly exothermic, and afforded a mixture of 2,5-dienone and iodobenzene. The dienone was annulated efficiently, producing a single anthraquinone in 95% yield. Suprisingly, ^{1}H n.m.r. analysis, mass spectrometry and comparison of the anthraquinone with authentic material showed the product to be 1-hydroxy-4-methoxyanthraquinone (40). Oxidation of 4-fluorophenol with phenyliodonium diacetate in deuterated methanol showed that a single product was formed. The ^{1}H n.m.r. spectra of this product and 4,4-dimethoxy-2,5-cyclohexadienone were identical. Obviously, methanolysis of the fluoride group of (38) was occurring, and the stability of the monofluorodienone (38) was far less than the reported stability of the difluorodienone (37).

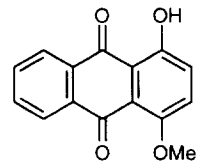
Treatment of 4-bromophenol in deuterated methanol with excess phenyliodonium diacetate resulted in the formation of three products in approximately equal amounts. One product was identified as the quinone monoketal (41) by comparison of the ^{1}H n.m.r. spectrum with an authentic sample. The ^{1}H n.m.r. spectrum of the second product showed a symmetrical olefinic region with slightly different chemical shifts to (41). This product was tentatively assigned the bromodienone structure (42). The remaining product had no axis of symmetry, and the ^{1}H n.m.r. spectrum showed a 10 Hz doublet at δ 6.0, a 3 Hz doublet at δ 6.8 and a doublet of doublets at δ 6.9, consistent with the formation of the 2,4-dienone (43). The formation of (43) from 4-bromophenol is analogous to the formation of 6,6-dimethoxycyclohexa-2,5-dienone from 4-*tert*-butylphenol.



A crude mixture containing the non-deuterated analogues of (41), (42) and (43) was prepared from 4-bromophenol and phenyliodonium diacetate in methanol, and was annulated with the anion of cyanophthalide (3). The major product isolated was the bromoalizarin (44), and a small amount of quinizarin monomethyl ether (40) was also formed. However, no 4-bromo-1-hydroxyanthraquinone was detected in the annulated mixture.



44



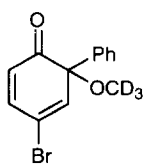
40

A General Observation of the Chemical Shifts of the α-Proton of 2,4- and 2,5-Cyclohexadienones

The chemical shifts of the proton α- to the carbonyl group of some selected cyclohexadienones are shown in Table 1. Several of these compounds were unstable, and the ^{1}H n.m.r. spectra of these compounds was determined by oxidizing the phenol with phenyliodonium diacetate in methanol, diluting the reaction mixture with water and extracting with chloroform. The organic extract was dried over magnesium sulfate and evaporated *in vacuo*. The spectrum was determined on the a deuteriochloroform solution of the residue, which contained an equimolar mixture of the desired product(s) and iodobenzene. It can be seen by inspection of Table 1, that the proton α- to the carbonyl group in 2,4-cyclohexadienones resonates 0.3-0.4 ppm further upfield than the corresponding proton in 2,5-cyclohexadienones.

Oxidation and Annulation of 4-Bromo-2-phenylphenol

The oxidation of 4-bromo-2-phenylphenol with phenyliodonium diacetate in deuterated methanol occurred cleanly with the formation of two products. Although the phenyl group partially obscured the olefinic resonances, the α-proton resonances of the α,β-unsaturated carbonyl group of both products were clearly visible. The chemical shift of the α-proton of the major product, a doublet at δ 6.0, was consistent with the formation of the 2,4-cyclohexadienone (45) (*vide infra*). The ^{1}H n.m.r. spectrum of the minor oxidation product showed a doublet at δ 6.3, and this product was tentatively assigned a 2,5-cyclohexadienone structure. It was not possible to distinguish between the two possible 2,5-cyclohexadienone structures (46) and (47) by ^{1}H n.m.r. spectroscopy. However, an authentic sample of (46) prepared by the oxidation of 2-phenylphenol with excess phenyliodonium diacetate in deuterated methanol had an identical ^{1}H n.m.r. spectrum to the minor product. It seems most likely that the initially formed (47) underwent rapid solvolysis to (46).



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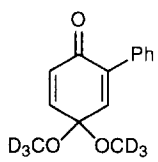

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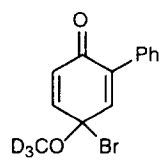
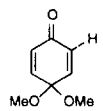
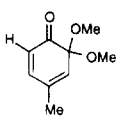
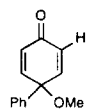
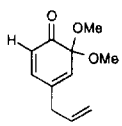
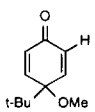
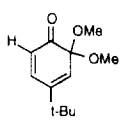
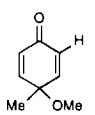
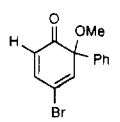
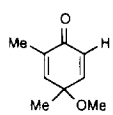
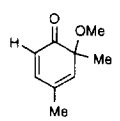
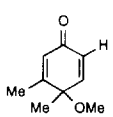
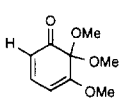
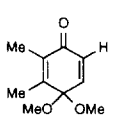
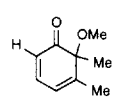
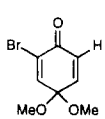
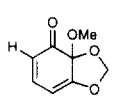


47

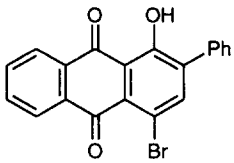
Table 1. Comparison of the 270 MHz ^1H n.m.r Chemical Shifts of the α-Protons of Selected 2,4- and 2,5-Cyclohexadienones in Deuteriochloroform.

2,5-cyclohexadienone	chemical shift (ppm)	2,4-cyclohexadienone	chemical shift (ppm)
	6.27		5.97[a]
	6.40		6.01[a]
	6.40		6.03
	6.32		6.02
	6.30[a]		6.09[a]
	6.29[a]		5.40[b]
	6.43[a]		6.05[a]
	6.39[b]		5.66[b]

a) contains iodobenzene.

b) data taken from ref. 28.

2-Phenyl-4-bromophenol was oxidized with phenyliodonium diacetate in methanol on a preparative scale, and annulation of the mixture of crude dienones afforded the anthraquinones (49) and (50) in 90% and 10% yields respectively.



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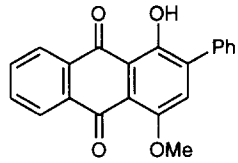
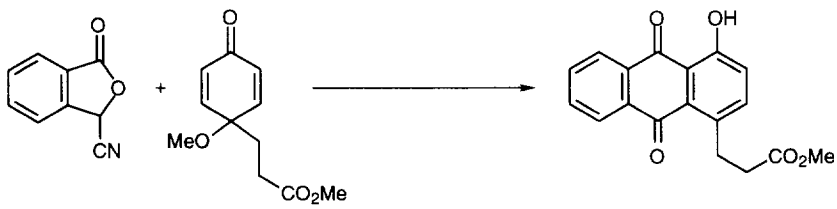


50

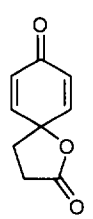
Anthraquinones with Functionalized Side-chains

Methyl 3-(4-hydroxyphenyl)propionate was oxidized with phenyliodonium diacetate in methanol to afford the crude dienone (51), which was immediately annulated with the anion of cyanophthalide (3). The resulting anthraquinone (52) was isolated in 56% yield.



3 **51** **52**

An alternative route to (52) was devised which involved the annulation of spirolactone (53). Although several early synthesis of (53) were reported[29-32], it was not until the advent of hypervalent iodine oxidations that the preparation of this molecule on a synthetically useful scale became practical[10,33]. Tamura *et al.* reported the oxidation of phloretic acid (54) to the spirolactone (53) using phenyliodonium bis(trifluoroacetate) in acetonitrile containing pyridine to neutralize the trifluoroacetic acid liberated by the reaction[10]. McKillop *et al.* found that slightly higher yields of spirolactone could be obtained when pyridine was omitted from the reaction mixture[33]. Although phloretic acid (54) could be oxidized to (53) with phenyliodonium bis(trifluoroacetate) in acetonitrile, this substrate was found to be inert towards phenyliodonium diacetate under the same conditions. However, a 50% yield of (53) could be obtained by oxidizing (54) with phenyliodonium diacetate in methanol. The spirolactone prepared in this manner was accompanied by an equal amount of an additional product, which was not fully characterized, but assigned the structure (55) on the basis of its ^{1}H n.m.r. spectrum and high polarity on chromatographic media.



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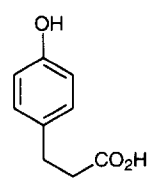

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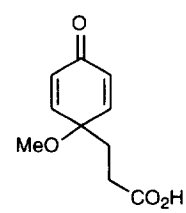
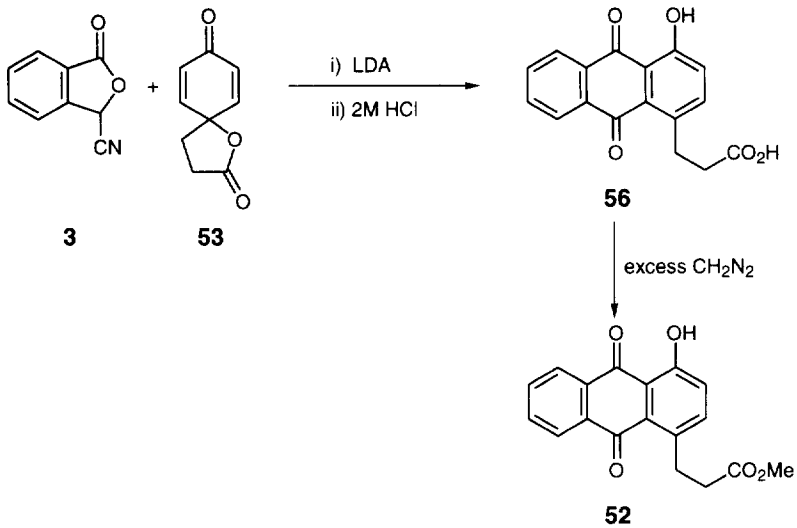


55

Annulation of the spirolactone (53) with the anion of cyanophthalide (3) afforded a quantitative yield of anthraquinone (56). This compound streaked severely on chromatography, and was therefore characterized as the methyl ester (52), which was readily prepared in 96% yield by treatment of the crude acid (56) with excess ethereal diazomethane (Scheme 3).

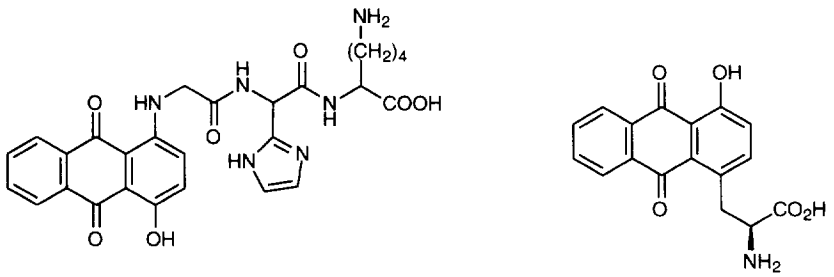


3 53 56 52

Scheme 3

An Anthraquinone Derived from Tyrosine

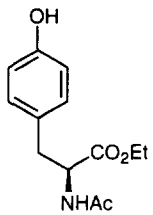
The anthraquinone (57) forms a biologically active copper complex which have been shown to possess anticancer activity[34,35]. The anthraquinone (58), with an α-amino acid side chain, might also be a useful molecule for further elaboration into compounds of biological significance. In view of the above reports, it would be interesting to compare the behaviour and reactivity of copper complexes of peptides incorporating (58).



57 58

N-Acetyl-L-tyrosine ethyl ester (59) was oxidized with phenyliodonium diacetate in deuterated methanol. The ^1H n.m.r. spectrum of the oxidized mixture was extremely complex and not amenable to first order analysis. However, three olefinic resonances at δ 5.98, 6.13, and 6.25, each with a coupling of 10 Hz, were believed to be due to the α-protons of three distinct compounds. Two of these compounds were tentatively

assigned the diastereomeric 2,5-cyclohexadienone structures (60) and (61). The third component was assigned the 2,4-cyclohexadienone structure (62) on the basis of the higher field chemical shift of the proton α- to the carbonyl group.



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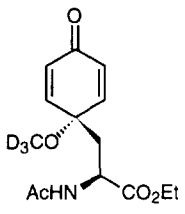

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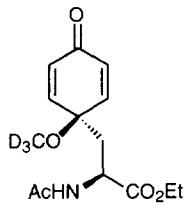

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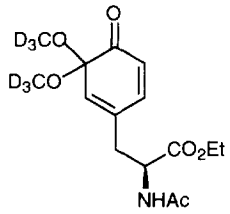
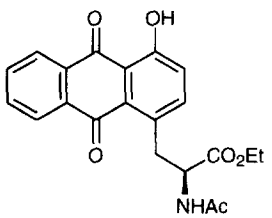
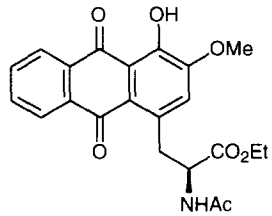


62

A sample of (59) was oxidized with phenyliodonium diacetate in methanol, and the mixture of dienones immediately annulated with the anion of cyanophthalide (3). The ^{1}H n.m.r. spectrum of the crude annulation product showed two low field hydroxyl resonances at δ 13.2 and δ 13.8, which were assigned to the anthraquinones (63) and (64) respectively. Chromatography of the mixture on silica afforded (63) in 63% yield. The oxidation-annulation reaction sequence was mild, and the anthraquinone (63) was found to be optically active, with $[\alpha]_D^{25}$ = 3.86. The isolation and characterization of the anthraquinone (64) was frustrated by its poor solubility, although with careful chromatography a small sample of (64) was obtained. The optical rotation of (64) was unable to be determined due to its poor solubility.



63



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Conclusion

A study of the oxidation of phenols with phenyliodonium diacetate in methanol was performed. Phenols are oxidized to 2,4-cyclohexadienones, 2,5-cyclohexadienones or mixtures of isomers depending on the substituents present on the phenol. These dienones (with one exception) undergo cyanophthalide anion annulation to form anthraquinones in high yields. The cyanophthalide anion annulation of 1-oxaspiro[4.5]deca-6,9-diene-2,8-dione proved an efficient route to the anthraquinone (52). The optically active anthraquinone (63) incorporating an α-amino acid functionality was prepared.

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We would like to thank Dr. Ernest Della at Flinders University for determining the high resolution mass spectra and Dr. Alan Arnold of the Australian Defence Force Academy for measuring the optical rotation of (63). The support of the Australian Research Grants Scheme is gratefully acknowledged.

Experimental

General Methods.

Infrared spectra were recorded as potassium bromide discs between 4000 and 400 cm^{-1} on a Biorad FTS-7 Fourier-transform spectrophotometer. ^{1}H n.m.r. and ^{13}C n.m.r. spectra were recorded as deuteriochloroform or deuteriomethanol solutions on a JEOL JNM-GX270 spectrometer. Chemical shifts are reported in parts per million downfield from tetramethylsilane reference on a δ scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants, integration and interpretation. Ultraviolet-visible spectra were recorded with a Hitachi U-3200 spectrophotometer. Electron impact mass spectra were recorded with a Hewlett Packard 5988A spectrometer. High resolution mass spectra were recorded on a Kratos M25RF spectrometer. Melting points were determined using a Reichert hot stage apparatus and are uncorrected. Microanalyses were performed by the Australian National University Microanalytical Service. Flash chromatography[36] was performed on Merck silica gel 60 (230-400 mesh). Thin layer chromatography was carried out on Merck silica gel 60 F_{254} precoated plates. Preparative radial chromatography was performed on Merck silica gel 60 GF_{254} rotors of 2 mm thickness, using a Harrison Research Model 7924T chromatotron. Tetrahydrofuran was purified by distillation under argon from the potassium ketyl of benzophenone.

Standardization of n-butyllithium.

A solution of 2,5-dimethoxybenzyl alcohol (80 mg, 476 μmol) and tetrahydrofuran (2 ml) in a flask equipped with a septum cap and magnetic stirrer bar under argon was cooled to 0° in an ice bath. This stirred solution was titrated with n-butyllithium added *via* a gas-tight syringe until a persistent yellow end point was achieved (*ca.* 300 μl). The concentration of n-butyllithium was calculated given that the yellow colour was due to the removal of the second proton from the benzyl alcohol.

General procedure for the preparation and annulation of dienones.

Phenyliodonium diacetate[37] (1 mmol) was added in small portions to a solution of the phenol (1 mmol) in methanol (10 ml). After 5 min. at ambient temperature, the solution was diluted with water (20 ml) and extracted with chloroform (3 x 15 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to afford the crude dienone, which was used directly in the subsequent step.

A solution of lithium diisopropylamide was prepared from diisopropylamine (1.1 mmol) and n-butyllithium (1.0 mmol) in tetrahydrofuran (10 ml) under argon at -78°. After 5 min., a solution of isobenzofuran-1(3**H**)-one-3-carbonitrile[38] (1 mmol) in tetrahydrofuran (5 ml) was added *via* syringe dropwise with stirring. After a further 5 min., the solution of crude dienone in tetrahydrofuran (5 ml) was added *via* syringe and allowed to stir at -78°. After 30 min., the cooling bath was removed and the reaction allowed to equilibrate to ambient temperature. The reaction was then diluted with hydrochloric acid (2 M, 30 ml) and extracted with chloroform (3 x 30 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The pure anthraquinone was recovered by flash chromatography of the residue on silica, using dichloromethane as the eluant.

4-Methoxy-4-phenylcyclohexa-2,5-dienone (2).

A solution of 4-phenylphenol (590 mg 3.47 mmol) in methanol (20 ml) was treated with phenyliodonium diacetate (1.23 g, 3.82 mmol). After 10 min. at ambient temperature, the solution was diluted with water (20 ml) and extracted with chloroform (2 x 20 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* (bath temp. < 20°). The residue was purified by flash chromatography on silica, using dichloromethane as the eluant, to afford the *title compound* (500 mg, 73%) as colourless plates, m.p. 90-92°. (Found M=200.0833. $C_{13}H_{12}O_2$ requires M=200.0837). I.r. ν_{max} 536, 693, 702, 757, 855, 947, 1061, 1076, 1094, 1172, 1388, 1448, 1489, 1601, 1624, 1672, 1690, 2825, 2932, 2941, 2997 cm^{-1}. ^1H n.m.r. δ 3.43, s, 3H, OCH_3; 6.40, d *J=10 Hz*, 2H, **H**2 and **H**6; 6.80, d, 10 Hz, **H**3 and **H**5. ^{13}C n.m.r. δ 52.8; 125.64; 128.28; 128.75; 130.04; 138.23; 150.4; 185.50. Mass spectrum *m/z* 200 (57) M, 185 (25), 172 (53), 157 (95), 115 (100).

1-Hydroxy-4-phenylanthracene-9,10-dione (4).

A solution of isobenzofuran-1(3**H**)-one-3-carbonitrile (160 mg, 1.0 mmol) in tetrahydrofuran (5 ml) was added dropwise *via* syringe to a solution of lithium diisopropylamide in tetrahydrofuran (6 ml) prepared from diisopropylamine (242 µl, 1.6 mmol) and n-butyllithium (735 µl of 1.36 M solution in hexanes, 1.0 mmol) at -78°. After 5 min., a solution of 4-methoxy-4-phenylcyclohexa-2,4-dienone (200 mg, 1.0 mmol) in tetrahydrofuran (6 ml) was added dropwise with vigorous stirring. After 30 min. at -78°, the reaction was slowly warmed to ambient temperature, diluted with hydrochloric acid (0.1 M, 30 ml) and extracted with chloroform (2 x 20 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was recrystallized from chloroform/ethanol to afford 145 mg of product. Concentration of the mother liquors afforded a further 55 mg of product, and a further 64 mg was obtained by flash chromatography of the mother liquors, eluting with dichloromethane, for a combined yield of 264 mg (88.0%). An analytical sample was purified by preparative radial chromatography to afford the *title compound* as orange yellow needles, m.p. 206-207°. (Found M = 299.0749. $C_{20}H_{12}O_3$ requires M = 299.0708). U.v. λ_{max} (log ε) (acetonitrile) 224 (4.373), 252 (4.515), 277 sh (4.123), 407 (3.714). I.r. ν_{max} 538, 590, 654, 700, 732, 762, 798, 883, 1087, 1154, 1223, 1238, 1281, 1298, 1351, 1356, 1410, 1361, 1591, 1639, 1675, 3050br, 3400br cm^{-1}. ^1H n.m.r. δ 7.22-7.28, 7.39-7.46, m, 5H, **H**2'-**H**6'; 7.31, d *J=9.6 Hz*, 1H, **H**2 or **H**3; 7.50, d *J=9.6 Hz*, 1H, **H**3 or **H**2; 7.72-7.82, m, 2H, **H**6 and **H**7; 8.08-8.14, m, 1H, **H**5 or **H**8; 8.28-8.34, m, 1H, **H**8 or **H**5; 13.21, s, 1H, Ar**OH**. ^{13}C n.m.r. δ 116.48; 123.63; 126.52; 127.08; 127.50; 128.05; 128.21; 130.12; 132.56; 133.75; 134.79; 136.84; 140.75; 141.94; 162.71; 189.25. Mass spectrum *m/z* 300 (51) M, 299 (100), 271 (10).

1-Hydroxy-4-methylanthracene-9,10-dione (8).

The crude dienone (7) was prepared from 4-methylphenol (108 mg, 1.0 mmol) and phenyliodonium diacetate (322 mg, 1.0 mmol). This was annulated with the anion generated from isobenzofuran-1(3**H**)-one-3-carbonitrile (160 mg, 1.0 mmol), diisopropylamine (242 µl, 1.1 mmol) and n-butyllithium (735 µl of 1.36 M solution in hexanes, 1.0 mmol) as described in the general procedure, to afford the *title compound* as golden-yellow needles (210 mg, 88.1%), m.p. 169-170° (lit.[39] 169-170°, lit.[19] 175°).

1-Hydroxy-3,4-dimethylanthracene-9,10-dione (10).

The crude dienone (9) was prepared from 3,4-dimethylphenol (156 mg, 1.28 mmol) and phenyliodonium diacetate 450 mg, 1.39 mmol) in methanol (5 ml). This was annulated with the anion generated from isobenzofuran-1(3**H**)-one-3-carbonitrile (203 mg, 1.28 mmol), diisopropylamine (234 µl, 1.55 mmol) and n-butyllithium (940 µl of 1.36 M solution in hexanes, 1.28 mmol), as described in the general procedure. Following workup, the crude residue was recrystallized from glacial acetic acid to afford the *title product* (162 mg) as yellow needles. Evaporation and flash chromatography of the mother liquors afforded further product (147 mg, overall yield, 96.0%). m.p. 168-169°, (lit.[20] 168-169°).

4-Allyl-1-hydroxy-2-methoxyanthracene-9,10-dione (18).

The crude dienone (12) was prepared from 4-allyl-2-methoxyphenol (155 mg, 944 µmol) and phenyliodonium diacetate (306 mg, 950 µmol) in methanol (10 ml). Iodobenzene was removed from the crude product *in vacuo* (22°/0.07 mmHg), and the crude product was annulated with the anion generated from isobenzofuran-1(3**H**)-one-3-carbonitrile (150 mg, 943 µmol), diisopropylamine (150 µl, 990 µmol) and n-butyllithium (695 µl of 1.36 M solution in hexanes, 945 µmol) as described in the general procedure. After workup, the crude residue was recrystallized from methanol to afford the *title compound* as orange-yellow needles (156 mg), m.p. 144-145°. Evaporation and flash chromatography of the mother liquors (silica, dichloromethane) afforded further product (100 mg, overall yield 92.1%). (Found: C, 73.22; H, 4.95. $C_{18}H_{14}O_4$ requires C, 73.46; H, 4.79%). U.v. λ_{max} (log ε) (acetonitrile) 234 sh (4.289), 250 (4.520), 280 sh (4.136), 329 sh (3.477) 426 (3.801). I.r. ν_{max} 797, 830, 990, 1057, 1094, 1119, 1262s, 1310, 1350, 1387, 1426, 1440, 1468, 1592, 1636, 1654, 1734, 1750, 3100br, 3400br cm^{-1}. ^1H n.m.r. δ 4.0, s, 3H, OCH_3; 5.03-5.15, m, 1H, -C**H**=CH_2; 6.03-6.18, m, 2H, -CH=C**H**$_2$; 6.98, s, 1H, **H**3; 7.73-7.84, m, 2H, **H**6 and **H**7; 8.25-8.32, m, 2H, **H**5 and **H**8; 13.77, s, 1H, ArO**H**. ^{13}C n.m.r. 29.72; 116.46; 123.63; 126.51; 127.06; 127.48; 128.05; 128.21; 132.53; 133.73; 134.54; 134.75; 136.80; 140.74; 141.94; 162.71; 182.78; 189.22. Mass spectrum *m/z* 294 (39) M, 279 (100), 277 (70), 263 (28).

1-Hydroxy-2-methoxy-4-methylanthracene-9,10-dione (19).

The crude dienone (20) was prepared from 2-methoxy-4-methylphenol[22] (135 mg, 1.0 mmol) and phenyliodonium diacetate (350 mg, 1.1 mmol) in methanol (5 ml). This was annulated with a solution of the anion generated from isobenzofuran-1(3**H**)-one-3-carbonitrile (160 mg, 1.0 mmol), diisopropylamine (242 ml, 1.6 mmol) and n-butyllithium (735 µl of 1.36 M solution in hexanes, 1.0 mmol). Flash chromatography of the residue afforded the *title compound* (212 mg, 79%) as orange-yellow needles. m.p. 212.5-213° (lit.[23] 212.5°).

1-Hydroxy-2,4-dimethylanthracene-9,10-dione (25).

A mixture of the crude dienones (23) and (24) was prepared from 2,4-dimethylphenol (122 mg, 1.0 mmol) and phenyliodonium diacetate (322 mg, 1.0 mmol) in methanol (5 ml). These were annulated with the anion generated from isobenzofuran-1(3**H**)-one-3-carbonitrile (160 mg, 1.0 mmol), diisopropylamine (242 µl, 1.6 mmol) and n-butyllithium (735 µl of 1.36 M solution in hexanes, 1.0 mmol), as described in the general procedure. Chromatography of the reaction mixture afforded the *title compound* as golden-yellow needles (206 mg, 81.7%). mp. 180-181° (lit.[39] 173.5°) ^1H n.m.r. δ 2.36, s, 3H, 3-CH_3; 2.73, s, 3H, 4-CH_3; 7.37, s, 1H, **H**3;

7.73-7.84, m, 2H, **H**6 and **H**7; 8.24-8.32, m, 2H, **H**5 and **H**8; 13.57, s, 1H, Ar**OH**. Mass spectrum *m/z* 252 (100) **M**, 237 (33), 223 (5), 209 (8).

4-tert-*Butyl-4-methoxy-2,5-cyclohexadienone (28) and 4*-tert-*Butyl-6,6-dimethoxy-2,4-cyclohexadienone (29).*

Addition of phenyliodonium diacetate (483 mg, 1.5 mmol) to a solution of 4-*tert*-butylphenol (150 mg, 1.0 mmol) in methanol (6 ml) caused a transient purple colouration which rapidly faded to give a yellow solution. The reaction was diluted with water (20 ml) and extracted with chloroform (3 x 15 ml). The organic extracts were dried ($MgSO_4$), evaporated *in vacuo* (bath temperature < 30°) and subjected to preparative radial chromatography on silica, using dichloromethane as the mobile phase. The least polar fraction contained iodobenzene, and was discarded. The second fraction afforded *4*-tert-*butyl-4-methoxy-2,5-cyclohexadienone (28)* as a golden oil, which solidified in the freezer (m.p. < 15°) (98 mg, 54.4%). ^{1}H n.m.r. δ 1.00, s, 9H, C(**CH**$_3$)$_3$; 3.19, s, 3H, O**CH**$_3$; 6.40, d, 10 Hz, 2H, **H**2 and **H**4; 6.80, d, 10 Hz, 2H, **H**1and **H**5.

Continued elution with dichloromethane/methanol (99:1) afforded an unstable yellow oil which was formulated as*6,6-dimethoxy-4-tert-butyl-2,4-cyclohexadienone (29)* (90 mg, 42.8%). ^{1}H n.m.r. δ 1.17, s, 9H, C(**CH**$_3$)$_3$; 3.37, s, 6H, O**CH**$_3$; 6.03, d *J=10.3 Hz*, 1H, **H**2; 6.09, d *J=2 Hz*, 1H, **H**5; 7.03, dd $J_{3,5}$*=2 Hz*, $J_{2,3}$*=10.3 Hz*, 1H, **H**3.

4-tert-*Butyl-1-hydroxy-4-methoxyanthracene-9,10-dione (30).*

A solution of isobenzofuran-1(3**H**)-one-3-carbonitrile (95 mg, 0.6 mmol) in tetrahydrofuran (3 ml) was added to solution of lithium diisopropylamide in tetrahydrofuran (5 ml) prepared from diisopropylamine (100 µl, 0.72 mmol) and n-butyllithium (441 µl of 1.36 M solution in hexanes, 600 µmol) under argon at -78°. After 5 min., a solution of 6,6-dimethoxy-4-tert-butyl-2,4-cyclohexadienone (125 mg, 600 µmol) in tetrahydrofuran (13 ml) was added. After stirring for 30 min. at -78°, the cooling bath was removed and the solution allowed to warm to ambient temperature. The reaction mixture was diluted with hydrochloric acid (2 M, 20 ml) and extracted with chloroform (3 x 30 ml). The dried ($MgSO_4$) organic extracts were evaporated *in vacuo*, and the residue subjected to flash chromatography (silica, dichloromethane) to afford the *title compound* (155 mg) as large irregular orange plates, m.p. 160-163°. (Found: C, 73.68; H, 6.00. $C_{19}H_{18}O_4$ requires C, 73.53; H 5.85%). (Found M=310.1244. $C_{19}H_{18}O_4$ requires M=310.1205). U.v. λ_{max} (log ε) (acetonitrile) 235 sh (4.202), 250 (4.487), 265 (4.296), 281 sh (4.111) 428 (3.749). I.r. ν_{max} 731, 801, 829, 899, 985, 1057, 1090, 1156, 1193, 1214, 1231, 1251, 1302, 1352, 1359, 1393, 1401, 1438, 1468, 1582, 1592, 1632, 1660, 2970 br, 3150 br cm^{-1}. ^{1}H n.m.r. δ 1.54, s, 9H, C(**CH**$_3$)$_3$; 4.01, s, 3H, O**CH**$_3$; 7.39, s, 1H, **H**3; 7.65 - 7.78, m, 2H, **H**6 and **H**7; 8.10-8.19, m, 2H, **H**5 and **H**8; 13.75, s, 1H, Ar**OH**. ^{13}C n.m.r. 29.66; 31.23; 37.38; 55.95; 116.93; 117.71; 125.99; 126.14; 127.02; 132.01; 132.81; 134.72; 136.76; 147.94; 152.01; 152.12; 185.85; 190.02. Mass spectrum *m/z* 310 (100) M, 295 (76), 293 (78), 28 (17), 268(35), 267 (90), 237 (20), 152 (28).

1-Hydroxy-2,3-dimethylanthracene-9,10-dione (33) and 1-hydroxy-4-methoxy-2,3-dimethylanthracene-9,10-dione (34).

A solution of 2,3-dimethylphenol (122 mg, 1.0 mmol) in methanol (10 ml) was oxidized with phenyliodonium diacetate (644 mg, 2.0 mmol). After 5 min. the reaction was diluted with water (20 ml) and

extracted with chloroform (3 x 15 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to afford a mixture of crude dienones.

A solution of isobenzofuran-1(3**H**)-one-3-carbonitrile (160 mg 1.0 mmol) in tetrahydrofuran (3 ml) was added *via* syringe to a solution of lithium diisopropylamide in tetrahydrofuran (5 ml) prepared from diisopropylamine (242 µl, 1.6 mmol) and n-butyllithium (735 µl of 1.36 M solution in hexanes, 1.0 mmol) at -78° under argon. After 5 min., a solution of the crude dienones in tetrahydrofuran (5 ml) was added dropwise *via* syringe to the vigorously stirred solution. After 30 min. at -78° the cooling bath was removed and the reaction allowed to warm to ambient temperature. The reaction was quenched with hydrochloric acid (2 M, 20 ml) and extracted with chloroform (3 x 20 ml). The chloroform extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue subjected to flash chromatography on silica using dichloromethane as the mobile phase. The initial fraction contained iodobenzene and was discarded. Continued elution with dichloromethane afforded *2,3-dimethyl-1-hydroxyanthracene-9,10-dione (33)* as orange yellow needles m.p. 220-221.5° (57 mg, 22.6%). (Found C, 76.17; H, 4.83. $C_{16}H_{12}O_3$ requires C, 76.18; H: 4.79%). U.v. λ_{max} (log ε) (acetonitrile) 230 sh (4.214), 241 sh (4.364), 246 (4.435), 264 (4.471) 288 sh (4.038), 329 (3.467), 411 (3.782). I.r. ν_{max} 716, 787, 798, 932, 992, 1012, 1102, 1279, 1324, 1360, 1400, 1481, 1591, 1633, 1671, 3000 br, 3350 br cm^{-1}. ^1H n.m.r. δ 2.31, s, 3H, C**H**$_3$; 2.44, s, 3H, C**H**$_3$; 7.67, s, 1H, **H**4; 7.75-7.83, m, 2H, **H**6 and **H**7; 8.25-8.35, m, 2H, **H**5 and **H**8; 13.05, s, 1H, ArO**H**. ^{13}C n.m.r. δ 11.68; 20.87; 113.44; 121.06; 126.69; 127.15; 130.11; 132.85; 133.32; 133.65; 133.84; 134.25; 146.48; 160.81; 182.51; 188.25. Mass spectrum *m/z* 252 (100) M, 237 (19), 223 (6), 200 (11), 152 (15).

Continued elution with dichloromethane afforded the more polar *1-hydroxy-4-methoxy-2,3-dimethylanthracene-9,10-dione (34)* (136mg, 48.2%) as orange-yellow needles m.p. 159-160°. (Found: C, 72.24; H, 5.07. $C_{17}H_{14}O_4$ requires C, 72.33; H, 5.00%). U.v. λ_{max} (log ε) (acetonitrile) 234sh (4.283), 250 (4.539), 280sh (4.134), 333sh (3.391), 427 (3.829). I.r. ν_{max} 541, 633, 668, 678, 739, 795, 821, 832, 890, 950, 1002, 1096, 1134, 1207, 1255s, 1360, 1400, 1437, 1458, 1593, 1630, 1670, 2946, 3200 br, 3450 br cm^{-1}. ^1H n.m.r. δ 2.33, s, 3H, C**H**$_3$; 2.36, s, 3H, C**H**$_3$; 3.86, s, 3H, OC**H**$_3$; 7.74-7.81, m, 2H, **H**6 and **H**7; 8.26-8.31, m, 2H, **H**5 and **H**8; 13.69, s, 1H, ArO**H**. ^{13}C n.m.r. 12.56; 13.35; 61.01; 96.12; 113.08; 126.34; 127.21; 132.63; 133.32; 134.39; 134.88; 135.47; 143.65; 152.87; 158.58; 181.76; 188.50. Mass spectrum *m/z* 282 (100) M, 253 (82), 239 (31).

6-Hydroxy-5-methoxybenz[a]anthracene-7,12-dione (36).

Following the general procedure, the crude naphthalenone (35) was prepared from 2-naphthol (144 mg, 1.0 mmol) and phenyliodonium diacetate (644 mg, 2.0 mmol) in methanol (10 ml). This was annulated with the anion prepared from isobenzofuran-1(3**H**)-one-3-carbonitrile (160 mg, 1.0 mmol), diisopropylamine (170 µl, 1.1 mmol) and n-butyllithium (735 µl of 1.36 M solution in hexanes, 1.0 mmol) in tetrahydrofuran (10 ml) at -78°. After work-up, the product was purified by flash chromatography to afford the *title product* (179 mg, 61.2%) as wine red microcrystals. An analytical sample was purified by preparative radial chromatography on silica, eluting with dichloromethane, m.p. 148-150°. (Found C, 75.15; H, 4.07. $C_{19}H_{12}O_4$ requires C, 74.99; H, 3.97%). U.v. λ_{max} (log ε) (acetonitrile) 258 (4.463), 296 (4.291), 308 sh (4.261), 392 (3.475), 501 (3.649). I.r. ν_{max} 612, 657, 755, 769, 949, 972, 1028, 1063, 1109, 1119, 1163, 1215, 1235, 1267, 1304, 1315, 1334, 1346, 1387, 1437, 1454, 1592, 1638, 1653, 2960, 3050 br cm^{-1}. ^1H n.m.r. δ 4.22, s, 1H, OC**H**$_3$; 7.50-7.53, m, 2H, **H**9 and **H**10; 7.6-7.72, m, 2H, **H**9 and **H**12; ^{13}C n.m.r. δ 61.16; 120.12; 121.31; 124.19; 126.16; 126.90;

127.13; 128.25; 128.39; 128.90; 131.77; 132.66; 133.13; 134.91; 148.23; 148.34; 184.17; 190.62. Mass spectrum *m/z* 304 (100) M, 289 (43), 275 (18), 261 (38), 233 (38), 176 (44).

1-Hydroxy-4-methoxyanthracene-9,10-dione (40) from 4-fluorophenol.

A solution of 4-fluorophenol (262 mg 2.34 mmol) in methanol (10 ml) was oxidized with phenyliodonium diacetate (850 mg, 2.64 mmol). The reaction was diluted with chloroform (20 ml) and water (20 ml). The organic phase was separated and the aqueous phase extracted with chloroform (20 ml). The combined organic extracts were dried rapidly ($MgSO_4$), filtered and evaporated *in vacuo* (bath temp. < 20°), to afford a yellow oil, which was stored at -20° until ready for use. Meanwhile, working rapidly as possible, a solution of isobenzofuran-1(3**H**)-one-3-carbonitrile (372 mg, 2.323 mmol) in tetrahydrofuran (5 ml) was added to a solution of lithium diisopropylamide in tetrahydrofuran (5 ml) prepared from diisopropylamine (390 µl, 2.58 mmol) and n-butyllithium (1.71 ml of 1.36 M solution in hexanes, 2.32 mmol) at -78° under argon. After 5 min., the solution of crude dienone in tetrahydrofuran (5 ml) was added slowly *via* syringe. The reaction was stirred at -78° for 30 min., allowed to warm to ambient temperature over 1 hr, diluted with hydrochloric acid (0.1 M, 30 ml) and extracted with chloroform (3 x 20 ml). The dried ($MgSO_4$) organic phase was evaporated and the residue purified by flash chromatography on silica, using ether as the eluant. This afforded the *title compound* (566 mg, 95.1%) as orange microcrystals, m.p. 169-170° (lit.[40] 170°).

1-Hydroxy-4-methoxyanthracene-9,10-dione (40) and 1-hydroxy-4-bromo-2-methoxyanthracene-9,10-dione (44) from 4-bromophenol.

Following the general procedure, the crude dienones were prepared from 4-bromophenol (173 mg, 1.00 mmol) and phenyliodonium diacetate (483 mg, 1.5 mmol) in methanol (5 ml). These were annulated with the anion generated from isobenzofuran-1(3**H**)-one-3-carbonitrile (160 mg, 1.0 mmol), diisopropylamine (242 µl, 1.6 mmol) and n-butyllithium (735 µl of 1.36 M solution in hexanes, 1.0 mmol) in tetrahydrofuran (10 ml) at -78°. After work-up, flash chromatography afforded *1-hydroxy-4-methoxyanthracene-9,10-dione (40)* (17 mg, 6.7%) as small orange needles, m.p. 169-170° (lit.[40] 170°). Further elution afforded *4-bromo-1-hydroxy-2-methoxyanthracene-9,10-dione (44)* (120 mg, 36.0%) as orange microcrystals, m.p. 246-247° (lit.[41] 234-235°).

4-Bromo-1-hydroxy-2-phenylanthracene-9,10-dione (49) and 1-hydroxy-4-methoxy-2-phenylanthracene-9,10-dione (50).

A mixture of crude dienones was prepared from 4-bromo-2-phenylphenol[42] (250 mg, 1.0 mmol) and phenyliodonium diacetate (322 mg, 1.0 mmol) in methanol (5 ml). These were annulated with the anion prepared from isobenzofuran-1(3**H**)-one-3-carbonitrile (160 mg, 1.0 mmol), diisopropylamine (242 µl, 1.6 mmol) and n-butyllithium (735 µl of 1.36 M solution in hexanes, 1.0 mmol) in tetrahydrofuran (15 ml), according to the general procedure. After acidic work-up, the residue was chromatographed to afford *4-bromo-1-hydroxy-2-phenylanthracene-9,10-dione (49)* as yellow needles (341 mg, 89.9%), m.p. 210-212°. (Found M = 377.9909. $C_{20}H_{11}{}^{79}BrO_3$ requires M = 377.9892) U.v. λ_{max} (log ε) (acetonitrile) 257 (4.583), 290sh (3.930), 330sh (3.466), 425 (3.876). I.r. ν_{max} 536, 689, 718, 770, 794, 891, 1018, 1119, 1161, 1205, 1249, 1268, 1293, 1350, 1385, 1401, 1430, 1591, 1634, 1675, 2976, 3150 br, 3400 br cm^{-1}. ^1H n.m.r. δ 7.42-7.54, m, 5H, **H**2'-**H**6'; 7.78-7.89, m, 2H, **H**6 and **H**7; 8.00, s, 1H, **H**3; 8.29-8.36, m, 2H, **H**5 and **H**8; 14.05, s, 1H,

ArO**H**. ^{13}C n.m.r. δ 113.31; 117.81; 126.68; 127.73; 128.32; 128.50; 128.70; 129.31; 132.22; 133.97; 134.01; 134.14; 134.47; 135.15; 137.95; 160.82; 181.04; 188.53. Mass spectrum *m/z* 380 (89) M+2, 378 (100) M, 349 (3), 299 (24); 270 (11), 242 (10), 213 (25).

Further elution afforded *1-hydroxy-4-methoxy-2-phenylanthracene-9,10-dione (50)* as orange needles (30 mg, 9.1%), m.p. 179-180° (from ethanol). ^{1}H n.m.r. δ 4.06, s, 3H, OC**H**$_3$; 7.43-7.56, m, 6H, **H**2'-**H**6' and **H**3; 7.73-7.87, m, 2H, **H**6 and **H**7; 8.25-8.34, m, 2H, **H**5 and **H**8; 13.73, s, 1H, ArO**H**. Mass spectrum *m/z* 330 (100) M, 301 (59), 283 (9), 255 (7), 202 (14).

Methyl 3-(4-hydroxyphenyl)propionate (51).

A mixture of 3-(4-hydroxyphenyl)propionic acid (2.5 g) and 48% methanolic boron trifluoride (25 ml) were heated under reflux for 2 min., cooled to room temperature, diluted with saturated aqueous sodium chloride (100 ml) and extracted with ether (3 x 50 ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (20 ml) and water (20 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by short path distillation (145°/0.1 mmHg, lit.[43] 186-7°/17 mmHg) to afford the *title compound* (2.09 g, 77%), which on standing crystallized as large colourless rhomboidal plates, m.p. 38-40° (lit.[43] 40-41°).

Methyl 3-(1'-hydroxyanthracene-9',10'-dion-4'-yl)propionate (52).

The crude dienone (51) was prepared from methyl 3-(4-hydroxyphenyl) propionate (180 mg, 1.0 mmol) and phenyliodonium diacetate (322 mg, 1.0 mmol) in methanol (10 ml) as described in the general procedure. This was annulated with the anion generated from isobenzofuran-1(3**H**)-one-3-carbonitrile (160 mg 1.0 mmol), diisopropylamine (166 μl, 1.1 mmol) and n-butyllithium (735 μl of 1.36 M solution in hexanes, 1.0 mmol) in tetrahydrofuran (10 ml) at -78°. After work-up, the residue was purified by chromatography to afford the *title compound* as yellow needles (166 mg, 53.5%). An analytical sample was purified by preparative radial chromatography (silica/dichloromethane), m.p. 156-157°. (Found C, 69.52; H, 4.49. $C_{18}H_{14}O_5$ requires C, 69.67; H, 4 .55%). U.v. λ_{max} (log ε) (acetonitrile) 219 (4.307), 252 (4.453), 276 sh (4.107), 315 (3.546), 410 (3.754). I.r. ν_{max} 591, 731, 788, 860, 1058, 1069, 1158, 1191, 1251, 1275, 1290, 1311, 1362, 1470, 1591, 1638, 1668, 1732, 2970, 3000 br, 3450 br cm^{-1}. ^{1}H n.m.r. δ 2.73, t *J=7.3 Hz*, 2H, **H**2; 3.43, t *J=7.3 Hz*, 2H, **H**3; 3.68, s, 3H, CO_2CH_3; 7.24, d *J=8.8 Hz*, 1H, **H**2' or **H**3'; 7.56, d *J=8.8 Hz*, 1H, **H**3' or **H**2'; 7.74-7.85, m, 2H, **H**6' and **H**7'; 7.22-7.32, m, 2H, **H**5' and **H**8'; 13.23, s, 1H, ArO**H**. ^{13}C n.m.r. δ 34.30; 51.57; 116.68; 124.47; 126.42; 127.39; 130.06; 130.55; 132.40; 133.71; 134.51; 134.65; 136.31; 141.38; 162.40; 173.56; 184.07; 188.93. Mass spectrum *m/z* 310 (43) M, 279 (13), 249 (100), 236 (43), 165 (12), 152 (19), 139 (6), 105 (3), 77 (7).

1-Oxaspiro[4.5]deca-6,9-diene-2,8-dione (53) and 3-(4'-methoxy-2',5'-cyclohexadienon-4'-yl)propionic acid (54).

Phenyliodonium diacetate (1.0 g, 3.1 mmol) was added in small portions to a solution of 3-(4-hydroxyphenyl)propionic acid (522 mg, 3.1 mmol) in methanol (10 ml). After 10 min. the solution was diluted with water (20 ml) and extracted with chloroform (4 x 20 ml). The combined chloroform extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by preparative radial chromatography on silica,

eluting with dichloromethane. The first fraction contained iodobenzene and was discarded. The second fraction contained *1-oxaspiro[4.5]deca-6,9-diene-2,8-dione (53)* (227 mg, 44.5%), m.p. 100-104° (lit.[32] 100-102°). Continued elution with 1:9 methanol/dichloromethane afforded a yellow oil which was not fully characterized, but formulated as *3-(4'-methoxy-2',5'-cyclohexadienon-4'-yl)propionic acid (54)* (230 mg, 37.8%). ^{1}H n.m.r. δ 2.07, t, 7 Hz, 2H, $\mathbf{CH_2CO_2H}$; 2.38, t, 7 Hz, 2H, $\mathbf{CH_2CH_2CO_2H}$; 3.21, s, 3H, $\mathbf{OCH_3}$; 6.39, d *J=10 Hz*, 2H, **H**2' and **H**6'; 6.74, d J=10 Hz, 2H, **H**3' and **H**5'.

(1'-Hydroxyanthracene-9',10'-dion-4'-yl)propionic acid (56)and methyl 3-(1'-hydroxyanthracene-9',10'-dion-4'-yl)propionate (52).

A solution of isobenzofuran-1(3**H**)-one-3-carbonitrile (220 mg, 1.38 mmol) in tetrahydrofuran (5 ml) was added to a solution of lithium diisopropylamide in tetrahydrofuran (10 ml), prepared from diisopropylamine (230 µl, 1.52 mmol) and n-butyllithium (1017 µl of 1.36 M solution in hexanes, 1.38 mmol) at -78°. After stirring for 2 min., a solution of 1-oxaspiro[4.5]deca-6,9-diene-2,8-dione (227 mg, 1.38 mmol) in tetrahydrofuran (5 ml) was added slowly *via* syringe. After 20 min. the cooling bath was removed. After the reaction mixture had warmed to ambient temperature, it was diluted with hydrochloric acid (2 M, 20 ml) and extracted with chloroform (2 x 20 ml). The combined organic layers were dried ($MgSO_4$) and evaporated to afford crude *3-(1'-hydroxyanthracene-9',10'-dion-4'-yl)propionic acid (56)*, m.p. 98-103°. ^{1}H n.m.r. δ 2.66, t *J=7.6 Hz*, 2H, **H**3; 3.94, t *J=7.6 Hz*, 2H, **H**2; 7.26, d *J=8.8 Hz*, 1H, **H**2' or **H**3'; 7.57, d *J=8.8 Hz*, 1H,.**H**3' or **H**2'; 7.72-7.86, m, 2H, **H**6' and **H**7'; 8.25-8.34, m, 2H, **H**5' and **H**8'; 13.24, s, 1H, Ar**OH**; Mass spectrum *m/z* 296 (46) M, 278 (2.5), 249 (100), 236 (33).

An ethereal solution of diazomethane, prepared from N-methyl-N-nitroso-*para*-toluenesulfonamide (4.28 g, 2.0 mmol), potassium hydroxide (850 mg, 15 mmol), ethanol (20 ml), water (2 ml) and ether (100 ml) according to Vogel[44] was distilled into a suspension of crude *3-(1'-hydroxyanthracene-9',10'-dion-4'-yl)propionic acid* in ether (100 ml). The excess diazomethane and ether were allowed to evaporate in the fume cupboard overnight. Flash chromatography of the residue afforded *methyl 3-(1'-hydroxyanthracene-9',10'-dion-4'-yl)propionate (52)* (413 mg, 96.3% from the spirolactone (53)), m.p. 155-157°, identical to that produced above.

Ethyl (+)-(2S)-2-acetamido-3-(1'-hydroxyanthracene-9',10'-dion-4'-yl)propionate (63).

A mixture of crude dienones were prepared from *ethyl (2S)-2-acetamido-3-(4-hydroxyphenyl)propionate* (260 mg, 1.03 mmol) and phenyliodonium diacetate (333 mg, 1.03 mmol) in methanol (6 ml) as described in the general procedure. The mixture of dienones was annulated with the anion prepared from isobenzofuran-1(3**H**)-one-3-carbonitrile (165 mg, 1.03 mmol), diisopropylamine (172 µl, 1.14 mmol) and n-butyllithium (757 µl of 1.36 M solution in hexanes, 1.03 mmol) in tetrahydrofuran (10 ml). After acidic work-up, the residue was purified by flash chromatography to afford the *title compound* (250 mg, 62.5%). Recrystallization from ethyl acetate afforded an analytical sample as fine felted bright yellow needles, m.p. 232.5-233° with sublimation from about 190°. (Found C, 66.12; H, 5.08; N, 3.55. $C_{21}H_{19}NO_6$ requires C, 66.13; H, 5.02; N, 3.67%). $[\alpha]_D^{25}$ = 3.86. λ_{max} (log ε) (acetonitrile) 218 (4.317), 253 (4.479), 277sh (4.110), 324 (3.488), 410 (3.773). I.r. ν_{max} 500, 586, 653, 731, 798, 832, 865, 987, 1026, 1073, 1137, 1162, 1205, 1257, 1283, 1351, 1424, 1468, 1549, 1591, 1634 C=O, 1650 amide C=O, 1665 C=O, 1738 ester C=O, 2970, 3306 cm^{-1}. ^{1}H n.m.r. δ 1.25, t *J=7.3*

Hz, 3H, OCH_2CH_3; 1.89, s, 3H, $NHCOCH_3$; 3.50-3.54, m, 2H, $H3_a$ and $H3_b$; 4.02-4.26, m, 2H, $OCH_aH_bCH_3$ 4.82-4.95, m, 1H, **H2**; 6.50, broad d, NHAc; 7.26, d *J=8.8 Hz*, 1H, **H2'** or **H3'**; 7.53, d *J=8.8 Hz*, 1H, **H3'** or **H2'**; 7.78-7.86, m, 2H, **H6'** and **H7'**; 8.23-8.32, m, 2H, **H5'** and **H8'**, 13.22, s, 1H, ArOH. ^{13}C n.m.r. δ 14.16; 23.03; 36.49; 53.58; 61.53; 116.65; 124.58; 126.63; 127.53; 131.36; 132.14; 132.58; 134.04; 134.65; 134.77; 141.40; 162.82; 169.77; 172.00; 185.29; 188.76. Mass spectrum *m/z* 381 (2) M, 322 (19), 265 (5), 249 (100), 238 (59), 209 (8), 181 (11), 152 (17), 102 (13), 74 (6).

Ethyl (2-acetamido-3-(1'-hydroxy-2'-methoxyanthracene-9',10'-dion-4'-yl)propionate (64).

Phenyliodonium diacetate (1.9 g, 6 mmol) was added to a solution of *ethyl (2S)-2-acetamido-3-(4-hydroxyphenyl)propionate* (1.0 g, 4 mmol) in methanol (20 ml). After 10 min. the solution was diluted with water (100 ml) and extracted with chloroform (2 x 100 ml). The organic extracts were dried and evaporated *in vacuo* to an orange oil. The mixture of crude dienones was dissolved in tetrahydrofuran (20 ml) and annulated with the anion prepared from isobenzofuran-1(3**H**)-one-3-carbonitrile (700 mg, 4.4 mmol), diisopropylamine (670 µl, 4.8 mmol) and n-butyllithium (3.7 ml of 1.29 M solution in hexanes, 4.4 mmol) in tetrahydrofuran (20 ml) at -78°. After 30 min. the cooling bath was removed and the reaction vessel allowed to warm to ambient temperature. The reaction was quenched with hydrochloric acid (2 M, 60 ml) and extracted with chloroform (3 x 80 ml). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography of the residue (silica, dichloromethane) afforded a dark red oil which was discarded. Continued elution with 9:1 (v/v) dichloromethane:methanol afforded a crude mixture of anthraquinones (1.32 g). A portion of the crude mixture (120 mg) was purified by preparative radial chromatography, eluting with 99:2 dichloromethane:methanol, to afford *ethyl (+)-(2S)-2-acetamido-3-(1'-hydroxyanthracene-9',10'-dion-4'-yl)propionate (63)* (33 mg, 33%), identical to the sample prepared previously, and the *title compound* (32 mg, 33%) as yellow needles, m.p. 289-292°(dec.). (Found C, 64.24; H, 5.26; N, 3.31. $C_{22}H_{21}NO_7$ requires C, 64.23; H, 5.14; N, 3.40%). Mass spectrum *m/z* 411 (3) M, 352 (35), 279 (100), 267 (30), 254 (8), 239 (6), 224 (6), 168 (4), 152 (5), 139 (7), 102 (6).

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