Regioselectivity in the Diels-Alder reaction of 8,8-dimethylnaphthalene-1,4,5(8*H*)-trione with 2,4-hexadien-1-ol

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Abstract: The Diels-Alder reactions of 8,8-dimethylnaphtalene-1,4,5(8*H*)-trione with 2,4-hexadien-1-ol and its *O*-acetyl derivative were investigated in different solvents. The regiochemistry of the cycloaddition of the hexadienol was determined through chemical correlation of one of the products. The solvent effect on the regioselectivity and *endo/exo* selectivity of this reaction is attributed to intermolecular hydrogen bonding between the hydroxyl group of the diene and the carbonyl oxygen atoms at C-4 and C-5 of the quinone in the transition state. The possible transition states have been modelled by AM1 calculations in order to better interpret these experimental results.

Keywords: *Diels-Alder reactions; quinones; regiocontrol; hydrogen bonding*

INTRODUCTION

Functionalized quinones are of interest as potential or actual chemotherapeutic agents, believed to act by DNA intercalation, free-radical-induced damage to DNA, and/or inhibition of topoisomerase II,[1] although different hypothetical mechanisms of action such as interference with mitochondrial electron transport or inhibition of other redox enzymes cannot be ruled out at this time. In fact, unlike the antitumor drugs mitoxantrone and ametantrone, some natural and synthetic quinones showing activity against the protozoon *Trypanosoma cruzi*, the causative agent of Chagas' disease, may exert their action primarily by upsetting the parasite's antioxidative defense mechanisms through interaction with trypanothione reductase.[2]

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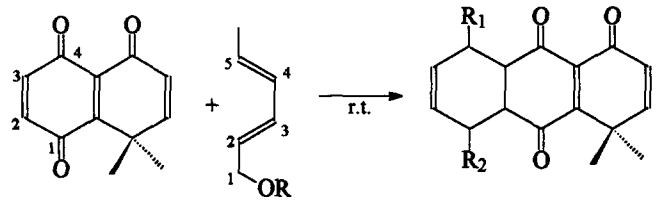
The recently synthesized and structurally simple 1,4-dihydro-4,4-dimethyl-(1*H*)-anthracene-1,5,8-trione (**1**)[3] exhibits potent lytic activity *in vitro* against *T. cruzi* and several *Leishmania* species.[4] Following this lead, and assuming that trypanothione reductase might be implicated in this compound's antiprotozoal actions, computational models were built for the *T. cruzi* enzyme (on the basis of its X-ray structure) and a series of variously substituted analogues of **1**, estimating their interaction energies using a docking protocol.[5] It was thus concluded that functionalization at C-5 or C-8 might provide more active substances. Consequently, and on the basis of previous experience, the Diels-Alder reactions of quinone **2**,[3] were explored with dienes bearing functionalized substituents not directly attached to the diene system.



2 **3**: R = H, **4**: R = Ac

5: R_1 = CH_2OH, R_2 = Me
6: R_1 = Me, R_2 = CH_2OH
7: R_1 = CH_2OAc, R_2 = Me
8: R_1 = Me, R_2 = CH_2OAc

Scheme 1

The role of intermolecular hydrogen bonding in the regio- and stereochemical outcome of Diels-Alder reactions has been well recognized, although only a moderate number of examples are known.[6,7] Diene-dienophile coordination through hydrogen bonding plays an important role in the course of asymmetric Diels-Alder cycloadditions, and it has been stated that this promotes chirality transfer. In particular, allylic hydroxyls in the diene moiety exert significant directing effects on diastereofacial selectivity. In the case of dienols, the preference in adduct formation has been explained by assuming a transition state which involves intermolecular hydrogen bonding between the diene OH group and the dienophile carbonyl group, and the observed solvent effects provide good support for this assumption.[6,7] Nevertheless, regioselectivity due to an intermolecular hydrogen bond between hydroxylated dienes and dienophiles with hydrogen bonding acceptor groups on both sides of the double bond requires that these groups possess different basicities. This requirement is specially difficult to satisfy when both groups in the dienophile are similar, as in the case of quinones, cyclic anhydrides or imides. As far as we know, this problem has not been addressed before.

RESULTS AND DISCUSSION

When naphthalenetrione **2** was allowed to react with (*E,E*)-2,4-hexadien-1-ol (**3**) at room temperature overnight in ethanol, an amphiprotic solvent,[8] a mixture of adducts was obtained in 99% yield, with the *endo* products **5** and **6** in a 67:33 ratio and about 35% of *exo* adducts. As has been shown previously, quinone **2** exhibits site specificity: only the C-2/C-3 double bond reacts despite the expected higher reactivity of the internal double bond, with the presence of the geminal methyl groups at C-8 preventing reaction at the internal site.[3] The composition of the crude reaction mixture was assessed by using the integrals of the ^{1}H NMR methyl doublets at δ 1.28 and 1.44 ppm (and 1.79 ppm for the *exo* adducts) or, alternatively, the singlets due to the geminal methyl groups at δ 1.35 and 1.55 (major isomer) and 1.47 and 1.51 (minor isomer). No additional methyl signals were observed in the spectrum. A study of the effect of changing the solvent for this cycloaddition showed that its regioselectivity and *endo/exo* selectivity could be improved by the use of less polar solvents. Thus, when anhydrous benzene, an inert solvent, was used as the reaction milieu under otherwise identical conditions, the reaction was also quantitative (98%), but the *endo* adduct ratio was 88:12 with a small and variable percentage of *exo* products. With acetone, a hydrogen bond acceptor, a mixture of adducts in 92% yield and an 80:20 ratio for the *endo* isomers was obtained, with about 20% *exo* adducts. In all cases, the same major regioisomer predominated. Finally, using formamide, a hydrogen bond donor as solvent, a 50:50 mixture of adducts was obtained. In the latter case the quantification was performed on the enolized products formed while eliminating the solvent under high vacuum. When the hydroxyl group of the diene was blocked by acetylation (compound **4**), the reaction also proceeded in high yield (97%) but was not regioselective, giving mixtures of adducts **7** and **8** in a 55:45 ratio in ethanol (with about 15% *exo* products), or 50:50 in benzene (with, surprisingly, no detectable *exo* products), as determined by ^{1}H NMR. These results contrast with the high regioselectivity observed in the Diels-Alder reaction of 1-acetoxy-(*E,E*)-2,4-hexadiene (**4**) with carbomethoxybenzoquinone.[9] In the latter case, the authors do not discuss the formation of *exo* isomers, although they mention the corresponding products for the cycloaddition of **4** and ethyl acrylate.

These observations strongly suggest that intermolecular hydrogen bonding between the hydroxyl group of the diene and the oxygen atom(s) of at least one of the carbonyl groups in the quinone controls the regiochemistry of this cycloaddition. Also, the decreasing proportion of *exo* products on going from ethanol to acetone to benzene, as assessed by ^{1}H NMR, may be rationalized on the basis of the same hydrogen bonding interaction, which would be expected to favor *endo* cycloaddition. The slight difference in the regiochemical outcome in ethanol and benzene when using the acetylated diene **4** may be attributable to the modification of the properties of quinone **2** by hydrogen bonding interactions with ethanol, which may also be responsible for the differences in the product ratios observed between acetone and ethanol in the cycloaddition of quinone **2** and

hexadienol **3**, as these solvents may be assumed to largely prevent hydrogen bonding between the diene and the dienophile by competing for the appropriate sites on the reagent molecules.

The presence of the two regioisomers in each reaction mixture was also indirectly established through NMR analysis of their enolization products, which were generated by treatment of the crude adduct mixtures with silica gel in benzene solution (Scheme 2). The enolization product ratio, however, proved to be less than the ratio of the *endo* cycloadducts. Thus, a crude cycloaddition mixture of **2** and **3** in benzene, containing **5** (85 mole %) and **6** (11 mole %), about 3 mole % of the *exo* cycloadducts and a trace of the hydroquinone reduction product of **2**, was stirred overnight in benzene with silica gel. The ^{1}H NMR spectrum of the product mixture, obtained in 98% yield, showed the signals due to two chelated protons at δ 13.50 (**9**, 67 mole %) and 13.16 ppm (**10**, 18 mole %), and an additional signal at δ 12.70 (15 mole %) corresponding to the aforementioned hydroquinone.[3] This result indicates that the Diels-Alder adducts must revert to the starting materials **2** and **3** and then re-form **5** and **6** in a less than 85:11 ratio. This is reasonable if it is thought that silica gel may form hydrogen bonds with both **2** and **3**, thus diminishing the regioselectivity of the cycloaddition as is the case with hydrogen bonding solvents. The idea that the Diels-Alder reaction is reversible in the presence of silica gel is supported by the appearance of 15 mole % of the dihydroxynaphthalenone which must be formed from **2** by reduction in the reaction milieu.

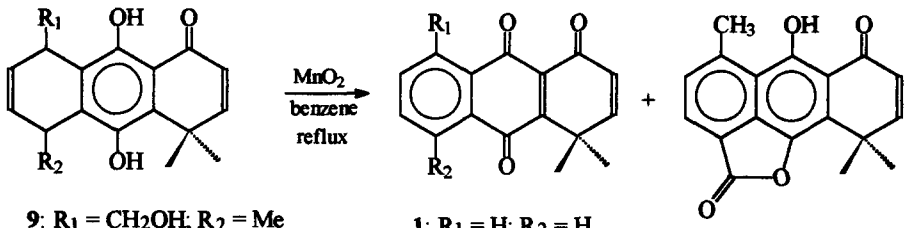
5: R_1= CH_2OH, R_2 = Me
6: R_1= Me, R_2 = CH_2OH
7: R_1= CH_2OAc, R_2 = Me
8: R_1= Me, R_2 = CH_2OAc

9: R_1= CH_2OH, R_2 = Me
10: R_1= Me, R_2 = CH_2OH
11: R_1= CH_2OAc, R_2 = Me
12: R_1= Me, R_2 = CH_2OAc

Scheme 2

Chromatographic separation of the mixture of dihydroxyanthracenones allowed both components to be isolated. Under the same conditions, the acetylated cycloadducts were transformed into the mixture of dihydroxyanthracenones **11** and **12**. With the purpose of assigning the regiochemistry of the corresponding products, the major dihydroxyanthracenone **9** generated in benzene solution was easily transformed to anthracenetrione **15** by oxidation with active manganese dioxide,[10] or DDQ in benzene solution at reflux. It is noteworthy that the oxidation of the major product with manganese dioxide gave trione **15** in good yield, while the minor regioisomer **10**, under similar conditions, afforded a mixture consisting of quinone **16**, alcohol **17**,

aldehyde **18** and lactone **19** (Scheme 3).



9: $R_1 = CH_2OH$; $R_2 = Me$
10: $R_1 = Me$; $R_2 = CH_2OH$
11: $R_1 = CH_2OAc$; $R_2 = Me$
12: $R_1 = Me$; $R_2 = CH_2OAc$
13: $R_1 = H$; $R_2 = Me$
14: $R_1 = Me$; $R_2 = H$

1: $R_1 = H$; $R_2 = H$
15: $R_1 = H$; $R_2 = Me$
16: $R_1 = Me$; $R_2 = H$
17: $R_1 = Me$; $R_2 = CH_2OH$
18: $R_1 = Me$; $R_2 = CHO$
20: $R_1 = CH_2OAc$; $R_2 = Me$
21: $R_1 = Me$; $R_2 = CH_2OAc$

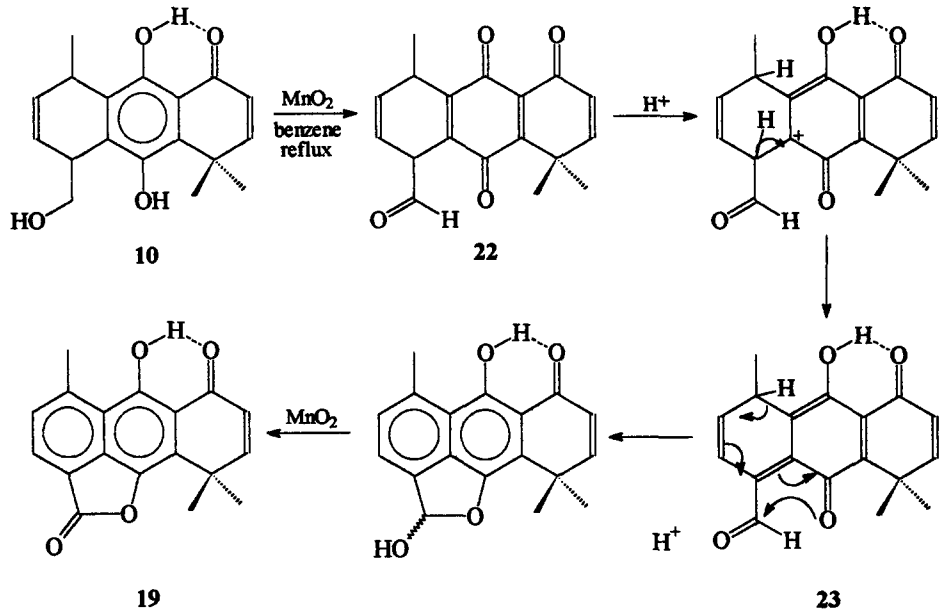
19

Scheme 3

By comparison of anthracenetriones **15** and **16** prepared here with the same compounds obtained by oxidation of the previously described dihydroxyanthracenones **13** and **14**,[3] it was possible to assess the regiochemistry of the cycloaddition. Thus, the major adduct obtained in the cycloaddition with 2,4-hexadienol (**3**) is 8-hydroxymethyl-4,4,8-trimethyl-5,8,8a,10a-tetrahydroanthracene-1,9,10(4*H*)-trione (**5**). The structure of compound **12** was clarified by the concerted use of HMQC and HMBC heteronuclear two-dimensional NMR experiments. This also allowed the structures of anthracenones **20** and **21** to be demonstrated unambiguously. Similar experiments confirmed the regiochemistry of the oxidation of dihydroxyanthracenone **9** and made the complete ^{13}C NMR signal assignments of products **17** and **18** possible.[11]

A mechanism which may explain the formation of product **19** (Scheme 4) involves, in a first step, the oxidation of both the hydroquinone and the hydroxymethyl moieties to afford the quinone intermediate **22**. Protonation of the carbonyl oxygen at C-9, favored by hydrogen bonding in the product, is followed by the elimination of one of the methine protons in the adjacent ring generating intermediate **23**, which through elimination of the other methine proton and concomitant attack of the oxygen atom upon the carbonyl group yields an aromatic lactol which is subsequently oxidized to lactone **19**.

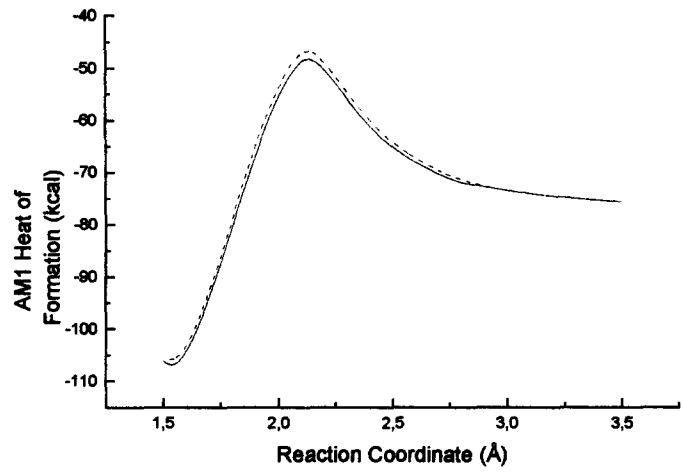
To evaluate the hypothesis that hydrogen bond interactions in the transition state are responsible for the regioselectivity of this Diels-Alder reaction, a series of AM1 molecular orbital calculations,[12] including full geometry optimization, were performed along the two reaction coordinates that produce both regioisomers.



Scheme 4

The transition states are located at a distance of 2.13 Å for both reaction coordinates,[13,14] and their natures were tested by performing a calculation of normal vibration modes. These results are in agreement with previous modeling of Diels-Alder reaction coordinate calculations.[13,14] We found one negative frequency in each case, which corroborates the structures corresponding to this distance as those of the activated complexes. The energies of the two activated complexes show a difference of 1.4 Kcal/mol, possibly due to differences in hydrogen bonding. The activated complex for the more stable regioisomer presents a hydrogen bond with the two carbonyl oxygens located at C-4 and C-5, with a distance of 2.34 Å to each oxygen nucleus, whereas in the other activated complex this bond can only involve the carbonyl oxygen located at C-1. Neglecting entropy differences between both activated complexes, a Boltzmann distribution calculation predicts a 91:9 percentage ratio for these two products, in excellent agreement with the experimental result (88:12) obtained for the **5**:**6** ratio when the cycloaddition was carried out in benzene.

Finally, we have calculated the energy profile for the rotation of the hydroxyl group of the diene through the dihedral angle defined by C-C-O-H, at the transition state structure for path I. We found a local minimum with barriers of rotation of 9 and 12 Kcal/mol, depending upon the sense of rotation.



This work is a new example of a regioselective Diels-Alder reaction governed by intermolecular hydrogen bonding to the more basic of two carbonyl groups. The difference between the basicities of both carbonyl groups in the quinonic dienophile may be explained on the basis of the delocalization of the double bond of the carbonyl group at C-1 to the other two carbonyl groups located at C-4 and C-5. The carbonyl groups at C-4 and C-5 can only delocalize to the C-1 carbonyl, which explains the lower basicity of the oxygen atom linked to C-1 and therefore the preference for hydrogen bond formation between the hydroxyl group of the hydroxymethyl diene and the carbonyl oxygen atoms at C-4 and/or C-5.

EXPERIMENTAL SECTION

General Procedures.

Melting points are uncorrected. All NMR spectra were acquired using a Bruker AVANCE DRX 300 spectrometer operating at 300.13 MHz (^{1}H) or 75.47 MHz (^{13}C). Measurements were carried out at a probe temperature of 300 K, using $CDCl_3$ containing tetramethylsilane (TMS) as an internal standard. Mass spectra were determined using electron impact ionization at 70 eV. Quinone **2** was synthesized as described previously.[3] Active MnO_2 was prepared by mixing warm aqueous solutions of $MnSO_4$ and $KMnO_4$.[7] All other reagents and solvents were purchased from commercial sources and were used without further purification.

Computational Details.

All the calculations were performed on a PC microcomputer using MOPAC version 6.0. The reaction

coordinates were defined as the distances between C-2 and C-5 of the diene and C-3 and C-2 of the dienophile, respectively (path I, affording the major product), and C-2 and C-5 of the diene and C-2 and C-3 of the dienophile, respectively (path II, to give the minor product). In these models we assumed a concerted reaction mechanism. The energy of the reacting system was calculated from full geometry optimizations, from a distance of 3.5 Å, at which the reactants did not show any interaction, up to a distance of 1.54 Å, which is a result of the full geometry optimization of the products.

Cycloaddition of quinone **2** *with* (E,E)-*2,4-hexadien-1-ol* (**3**). A solution of quinone **2** (157 mg, 0.78 mmole) and diene **3** (76 mg, 0.78 mmole) in C_6H_6 (10 mL) was left at room temperature for seven days. Removal of the solvent gave an 88:12 mixture of 8-hydroxymethyl-4,4,5-trimethyl-5,8,8a,10a-tetrahydroanthracene-1,9,10(4*H*)-trione (**5**), and 5-hydroxymethyl-4,4,8-trimethyl-5,8,8a,10a-tetrahydroanthracene-1,9,10(4*H*)-trione (**6**), as an oily liquid (233 mg, 100%) estimated to contain about 2% of *exo* adducts with a trace of the hydroquinone reduction product of **2**. ^{1}H NMR δ ($CDCl_3$) 1.28 (d, 3.1 H, J = 7.4 Hz, 5-CH_3), 1.35 (s, 2.7 H, 4-Me), 1.44 (d, 0.4 H, J = 7.8 Hz, 8-Me), 1.47 (s, 0.4 H, 4-Me), 1.51 (s, 0.4 H, 4-Me), 1.55 (s, 3 H, 4-Me), 1.79 (d, 0.64 H, J = 6.6 Hz, 5 and 8-Me), 2.22-2.70 (m, 1.3 H), 2.85-2.95 (m, 1.0 H), 2.95-3.20 (m, 2.7 H), 3.53 (dd, 0.13 H, J_1 = 11.0 Hz, J_2 = 3.7 Hz, C<u>H</u>$_2$-OH), 3.66 (d, 0.13 H J = 11 Hz, C<u>H</u>$_2$-OH), 4.14-4.27 (m, 0.95 H, C<u>H</u>$_2$-OH), 5.54 (m, 0.88 H, 6- or 7-H), 5.65-5.85 (m, 0.25H, 6- and 7-H), 5.87 (d, 0.87 H, 6- or 7-H), 6.1 (d, 1.0 H, J = 10.0 Hz, 2-H), 6.86 (d, 1.1 H, J = 10.0 Hz, 3-H). Using different solvents and the same procedure, the following mixtures of products **5** and **6** were obtained: absolute EtOH, **5**:**6** = 67:33 (99% yield, of which 35% was estimated to be *exo*); acetone, **5**:**6** = 80:20 (97% yield, of which 20% was estimated to be *exo*); when formamide was used, after concentrating an analytical sample to dryness, it was found to be a 50:50 mixture of hydroquinones **9** and **10**.

Cycloaddition of quinone **2** *with 1-acetoxy-*(E,E)-*2,4-hexadiene* (**4**). A solution of quinone **2** (516 mg, 2.55 mmole) and diene **4** (357 mg, 2.55 mmol) in C_6H_6 (35 mL) was kept at room temperature for a week. Removal of the solvent gave a 1:1 mixture of 8-acetoxymethyl-4,4,5-trimethyl-5,8,8a,10a-tetrahydroanthracene-1,9,10(4*H*)-trione (**7**), and 5-acetoxymethyl-4,4,8-trimethyl-5,8,8a,10a-tetrahydroanthracene-1,9,10(4*H*)-trione (**8**), as an oily liquid (840 mg, 97%). ^{1}H NMR δ ($CDCl_3$) 0.87 (d, 3 H, J = 7.4 Hz, 5- or 8-Me), 0.93 (d, 3 H, J = 7.3 Hz, 8- or 5-Me), 1.43 (s, 3 H, 4-Me), 1.54 (s, 6 H, 4-Me_2), 1.60 (s, 3 H, 4-Me), 2.01 (s, 3 H, Ac), 2.03 (s, 3 H, Ac), 2.60-2.80 (m, 4 H), 3.35-3.45 (m, 2 H), 3.55-3.70 (m, 2 H), 4.30-4.55 (m, 4 H, 5- and 8-H), 5.6-5.8 (m, 4H), 6.28 (d, 1 H, J = 10.0 Hz, 2-H), 6.31 (d, 1 H, J = 10.0 Hz, 2-H), 6.83 (d, 1 H, J = 10.0 Hz, 3-H), 6.88 (d, 1 H, J = 10.0 Hz, 3-H). The use of ethanol as solvent gave a 55:45 mixture of cycloadducts **7** and **8** (containing about 15% *exo* products giving a 5- and 8-Me doublet at 1.76 with J = 6.5 Hz) in 93% yield.

*9,10-Dihydroxy-8-hydroxymethyl-4,4,5-trimethyl-5,8-dihydroanthracene-1(4*H*)-one* (**9**) *and 9,10-dihydroxy-5-hydroxymethyl-4,4,8-trimethyl-5,8-dihydroanthracene-1(4*H*)-one* (**10**). The 88:12 mixture of adducts **5** and **6**,

containing traces of *exo* cycloadducts and the reduction product of **2** (183 mg), and silica gel (2 g) in C_6H_6 (10 mL) was stirred overnight at room temperature. The solution was filtered and the solid was washed repeatedly with MeOH. Removal of the solvent afforded a yellow solid (180 mg, 98 %) which was shown by ^{1}H NMR to contain anthracenones **9** (67 mole%) and **10** (18 mole%), plus the hydroquinone reduction product of **2** (15 mole%). Column chromatography on silica gel with an 80:20 light petrol:EtOAc mixture allowed both anthracenones to be separated. **9**: ^{1}H NMR δ ($CDCl_3$) 1.39 (d, 3 H, J = 7.1 Hz, 5-Me), 1.60 (s, 3 H, 4-Me), 1.65 (s, 3 H, 4-Me), 2.50 (s broad, OH), 3.42-3.55 (m, 1 H, C$\underline{H}_2$OH), 3.67-3.77 (m, 1 H, 5- or 8-H), 3.88-4.03 (m, 2 H, C$\underline{H}_2$-OH and 8- or 5-H), 4.50 (s, 1 H, OH), 6.00 (dd, 1 H, J_1 = 9.8 Hz, J_2 = 4.6 Hz, 6- or 7-H), 6.08 (dd, 1 H, J_1 = 9.8 Hz, J_2 = 4.8 Hz, 6 or 7-H), 6.25 (d, 1 H, J = 10.1 Hz, 2-H), 6.84 (d, 1 H, J = 10.1 Hz, 3-H), 13.50 (s, 1H, OH); ^{13}C NMR δ ($CDCl_3$) 23.0, 25.2, 25.4, 30.4, 38.1, 38.3, 66.3, 122.7, 123.6, 127.3, 131.3, 134.6, 140.3, 143.8, 154.3, 161.6, 191.3. M.p. 211-213 °C. IR (KBr) 3431, 1653 and 1592 cm.$^{-1}$ Anal. found: C, 72.09; H, 6.78; calc. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. **10**: ^{1}H NMR δ ($CDCl_3$) 1.29 (d, 3 H, J = 7.0 Hz, 8-Me), 1.58 (s, 3 H, 4-Me), 1.66 (s, 3 H, 4-Me), 2.6 (s, 1 H, OH), 3.56 (dd, broad, 1 H, J = 9.5 Hz, C$\underline{H}_2$OH), 3.74 (m, 1H, 5- or 8-H), 3.97 (m, 1 H, 8- or 5-H), 4.11 (dd, broad, 1 H, J_1 = 3.1 Hz, J_2 = 9.5 Hz, C$\underline{H}_2$OH), 5.76 (dd, 1 H, J_1 = 5.1 Hz, J_2 = 9.7 Hz, 6- or 7-H), 6.13 (dd, 1 H, J = 5.2 and 9.7 Hz, 7- or 6-H), 6.21 (d, 1 H, J = 10 Hz, 2-H), 6.83 (d, 1 H, J = 10 Hz, 3-H), 7.97 (s, 1 H, OH), 13.16 (s, 1H, OH); ^{13}C NMR δ ($CDCl_3$) 23.0, 25.0, 25.4, 29.6, 38.4, 70.0, 122.5, 124.0, 124.2, 134.9, 135.1, 144.4, 144.8, 154.3, 161.5, 191.6. M.p. 243-245 °C. IR (KBr) 3193, 1667, 1599 cm^{-1}. HRMS found M$^+$ 300.135620; $C_{18}H_{20}O_4$ requires M$^+$ 300.136159.

9,10-Dihydroxy-8-acetoxymethyl-4,4,5-trimethyl-5,8-dihydroanthracene-1(4H)-one (**11**) *and 9,10-Dihydroxy-5-acetoxymethyl-4,4,8-trimethyl-5,8-dihydroanthracene-1(4H)-one* (**12**). A mixture of **7** and **8** (840 mg, 2.45 mmole) and silica gel (6 g) in C_6H_6 (30 mL) was stirred for 3 h at room temperature. The solution was filtered and washed with EtOAc. Evaporation of the solvent gave a mixture of anthracenones **11** and **12** (795 mg, 95%) in a 55:45 ratio. **11**: ^{1}H NMR δ ($CDCl_3$) 1.39 (d, 3 H, J = 7.1 Hz, 5-Me), 1.60 (s, 3 H, 4-Me), 1.65 (s, 3 H, 4-Me), 2.03 (s, 3 H, Ac), 3.42-3.52 (m, 1 H, 5- or 8-H), 3.99-4.07 (m, 1 H, 8- or 5-H), 4.22 (dd, 1 H, J_1 = 6.8 Hz, J_2 = 10.3 Hz, C$\underline{H}_2$-OAc), 4.47 (dd, 1 H, J_1 = 4.1 Hz, J_2 = 10.3 Hz, C$\underline{H}_2$-OAc), 5.97-6.07 (m, 2 H, 6- and 7-H), 6.24 (d, 1 H, J = 10.1 Hz, 2-H), 6.82 (d, J = 10.1 Hz, 3-H), 7.36 (s, 1 H, OH), 13.26 (s, 1 H, OH); ^{13}C NMR δ ($CDCl_3$) 21.0, 22.3, 25.1, 25.3, 30.1, 34.5, 38.1, 67.0, 113.0, 121.5, 124.0, 126.2, 131.1, 133.2, 136.6, 142.0, 154.0, 160.9, 171.0, 191.2. M.p. 150-151 °C. IR (KBr) 3535, 1736, 1667, 1614, 1276 cm^{-1}. Anal. found: C, 69.98; H, 6.60; calcd. for $C_{20}H_{22}O_5$: C, 70.16, H, 6.48. **12**: ^{1}H NMR δ ($CDCl_3$) 1.33 (d, 3 H, J = 7.0 Hz, 5-Me), 1.60 (s, 3 H, 4-Me), 1.67 (s, 3 H, 4-Me), 2.17 (s, 3 H, Ac), 3.7-3.8 (m, 1 H, 5- or 8-H), 3.8-3.9 (m, 1 H, 5- or 8-H), 3.98 (dd, 1 H, J_1 = 7.3 Hz, J_2 = 10.8 Hz, C$\underline{H}_2$-OAc), 4.32 (dd, 1 H, J_1 = 5.8 Hz, J_2 = 10.8 Hz, C$\underline{H}_2$-OAc), 5.95 (dd, 1 H, J_1 = 9.7 Hz, J_2 = 4.9 Hz, 6- or 7-H), 6.19 (dd, 1 H, J_1 = 9.7 Hz, J_2 = 5.1 Hz, 6- or 7-H), 6.26 (d, 1 H, J = 10.1 Hz, 2-H), 6.81 (s, 1 H, OH), 6.84 (d, 1 H, J = 10.1 Hz, 3-H), 13.17 (s, 1 H, OH);

^{13}C NMR δ ($CDCl_3$) 20.9, 22.4, 24.9, 25.2, 29.6, 35.2, 38.3, 71.1, 113.7, 123.1, 123.9, 127.9, 130.3, 132.8, 134.8, 143.9, 154.0, 161.4, 171.8, 191.4. M.p. 140-143 °C. IR (KBr) 3369, 1726, 1667, 1613, 1257 cm^{-1}. HRMS found M^+ 342.147310; $C_{20}H_{22}O_5$ requires M^+ 342.146724.

4,4,5-Trimethylanthracene-1,9,10(4H)-trione (**15**). A mixture of anthracenone **9** (54 mg, 0.18 mmole) and MnO_2 (160 mg) in C_6H_6 (15 mL) was refluxed for 3 h. The solution was filtered, the solids washed with EtOAc, and the filtrate was concentrated under reduced pressure to afford compound **15** (44 mg, 91%): ^1H NMR δ ($CDCl_3$) 1.64 (s, 6 H, 4-Me_2); 2.73 (s, 3 H, 5-Me), 6.36 (d, 1 H, J = 10.1 Hz, 2-H), 6.81 (d, 1 H, J = 10.1 Hz, 3-H), 7.53 (d, 1 H, J = 7.5 Hz), 7.62 (t, 1 H, J = 7.6 Hz, 6-H), 7.97 (d, 1H, J = 7.5 Hz); ^{13}C NMR δ ($CDCl_3$) 22.7, 26.4, 39.1, 125.0, 127.3, 130.6, 132.6, 133.5, 133.7, 137.5, 140.8, 157.0, 158.0, 183.3, 183.3, 187.5. M.p. 161-163 °C. Anal. found C, 76.36; H 5.18; calc. for $C_{17}H_{14}O_3$: C, 76.71; H, 5.26. Reaction of the dihydroxy-anthracenone **9** with DDQ in C_6H_6 at reflux gave compound **15** as a single product in 90% yield.

Oxidation of compound **10**.

A mixture of anthracenone **10** (100 mg, 0.14 mmole) and MnO_2 (87 mg) in C_6H_6 (10 mL) was refluxed for 3 h. The solution was filtered, the solids washed with EtOAc, and the filtrate was concentrated under reduced pressure to afford 80 mg of a mixture assayed through ^1H NMR. Analytical samples were obtained after column chromatography on silica gel with light petrol:EtOAc 80:20 as eluent.

4,4,8-Trimethylanthracene-1,9,10(4H)-trione (**16**, 18 mole % of the mixture): ^1H NMR δ ($CDCl_3$) 1.61 (s, 6 H, 4-Me_2), 2.74 (s, 3 H, 8-CH_3), 6.38 (d, 1 H, J = 10.1 Hz, 2-H), 6.79 (d, 1 H, J = 10.1 Hz, 3-H), 7.54 (d, 1 H, J = 7.3 Hz, 6-H), 7.58 (t, 1 H, J = 7.7 Hz, 7-H), 7.95 (d, 1 H, J = 7.1 Hz, 5-H); ^{13}C NMR δ ($CDCl_3$) 21.7, 26.2, 38.5, 125.1, 127.5, 130.6, 132.7, 133.8, 135.5, 138.0, 140.3, 154.9, 157.7, 183.3, 184.9, 186.0. M.p. 166-170 °C (dec.). IR (KBr) 1779, 1691, 1648 and 1584 cm^{-1}. HRMS found M^+ 266.09470; $C_{17}H_{14}O_3$ requires M^+ 266.09429.

9-Hydroxy-5-oxo-4,8,8-trimethyl-1,9(8H)-anthracenecarbolactone (**19**, 10 mole % of the mixture): ^1H NMR δ ($CDCl_3$) 1.69 (s, 6 H, 8-Me_2), 3.06 (s, 3 H, 4-CH_3), 6.34 (d, 1 H, J = 10.2 Hz, 6-H), 6.84 (d, 1 H, J = 10.2 Hz, 7-H), 7.53 (dd, 1 H, J_1 = 0.7 Hz, J_2 = 7.3 Hz, 3-H), 8.1 (d, 1 H, J = 7.3 Hz, 2-H), 15.6 (s, 1 H, OH); ^{13}C NMR δ ($CDCl_3$) 23.3, 28.1, 30.1, 37.7, 110.4, 118.3, 120.5, 125.5, 126.7, 130.6, 131.0, 133.8, 138.0, 148.0, 158.3, 164.5, 167.1, 191.4. IR (KBr) 3432, 1773, 1644 and 1584 cm^{-1}. M.p. 220-224 °C (dec.). HRMS found M^+ 294.088715; $C_{18}H_{16}O_4$ requires M^+ 294.089209.

5-Hydroxymethyl-4,4,8-trimethylanthracene-1,9,10(4H)-trione (**17**, 6 mole % of the mixture): ^1H NMR δ ($CDCl_3$) 1.64 (s, 6 H, 4-Me), 2.79 (s, 3 H, 8-CH_3), 4.82 (s, 2 H, $C\underline{H_2}OH$), 6.36 (d, 1 H, J = 10.2 Hz, 2-H), 6.80 (d, 1 H, J = 10.2 Hz, 3-H), 7.54 (d, 1 H, J = 8.0 Hz, 7-H), 7.68 (d, 1 H, J = 8.0 Hz, 6-H); ^{13}C NMR δ ($CDCl_3$) 22.1, 26.6, 39.0, 64.8, 127.7, 132.3, 132.7, 134.5, 134.7, 135.4, 138.5, 140.3, 141.0, 155.8, 156.0, 158.2, 183.0, 185.3, 190.2. IR (KBr) 3532, 1687 and 1651 cm^{-1}. M.p. 135-140 °C (dec.). HRMS found M^+ 296.104859;

$C_{18}H_{16}O_4$ requires M^+ 296.104859.

5-Formyl-4,4,8-trimethylanthracene-1,9,10(4H)-trione (**18**, 66 mole % of the mixture): ^{1}H NMR δ ($CDCl_3$) 1.52 (s, 6 H, 4-Me_2), 2.66 (s, 3 H, 8-CH_3), 6.27 (d, 1 H, J = 10.2 Hz, 2-H), 6.69 (d, 1 H, J = 10.2 Hz, 3-H), 7.53 (d, 1 H, J = 8.1 Hz, 7-H), 7.78 (d, 1 H, J = 8.1 Hz, 6-H), 10.26 (s, 1 H, CHO); ^{13}C NMR δ ($CDCl_3$) 22.6, 26.5, 39.0, 127.9, 131.5, 132.4, 134.9, 135.6, 136.6, 138.3, 145.5, 155.5, 158.0, 182.8, 184.04, 188.1, 191.5. IR (KBr) 1776, 1692, 1648 and 1593 cm^{-1}. M.p. 148-150 °C. HRMS found M^+ 294.089209; $C_{18}H_{14}O_4$ requires M^+ 294.089209.

8-Acetoxymethyl-4,4,5-trimethyl-5,8-dihydroanthracene-1,9,10(4H)-trione (**20**). A mixture of anthracenone **11** (100 mg, 0.29 mmole) and MnO_2 (300 mg) in C_6H_6 (15 mL) was refluxed for 3 h. The solution was filtered, the solids washed with EtOAc, and the filtrate was concentrated under reduced pressure to afford compound **20** (79 mg, 80%): ^{1}H NMR δ ($CDCl_3$) 1.61 (s, 6 H, 4-Me_2), 2.17 (s, 3 H, MeCO), 2.70 (s, 3 H, 5-Me), 5.54 (s, 2 H, CH_2), 6.35 (d, 1 H, J = 10.2 Hz, 2-H), 6.80 (d, 1 H, J = 10.2 Hz, 3-H), 7.53 (d, 1 H, J = 8.1 Hz, 6-H), 7.65 (d, 1 H, J = 8.1 Hz, 7-H); ^{13}C NMR δ ($CDCl_3$) 21.0, 21.7, 26.2, 38.6, 64.5, 127.3, 131.3, 131.6, 132.1, 134.4, 136.2, 137.5, 139.6, 155.6, 157.8, 170.5, 182.7, 184.9, 188.1. IR (KBr) 1747, 1688 and 1649 cm^{-1}. M.p. 185-187 °C. Anal. found C, 71.02; H, 5.32; calc. for $C_{20}H_{18}O_5$: C, 71.00; H, 5.36.

5-Acetoxymethyl-4,4,8-trimethyl-5,8-dihydroanthracene-1,9,10(4H)-trione (**21**). A mixture of anthracenone **12** (100 mg, 0.29 mmole) and MnO_2 (300 mg) in C_6H_6 (15 mL) was refluxed for 3 h. The solution was filtered, the solids washed with EtOAc, and the filtrate was concentrated under reduced pressure to afford compound **21** (94 mg, 95%): ^{1}H NMR δ ($CDCl_3$) 1.61 (s, 6 H, 4-Me_2), 2.16 (s, 3 H, MeCO), 2.68 (s, 3 H, 5-Me), 5.55 (s, 2 H, CH_2), 6.35 (d, 1 H, J = 10.2 Hz, 2-H), 6.80 (d, 1 H, J = 10.2 Hz, 3-H), 7.49 (d, 1 H, J = 8.1 Hz, 6-H), 7.63 (d, 1 H, J = 8.1 Hz, 7-H); ^{13}C NMR δ ($CDCl_3$) 20.8, 22.4, 26.0, 38.5, 63.9, 127.0, 131.2, 131.8, 132.0, 134.0, 135.8, 136.8, 140.0, 156.4, 157.7, 170.3, 182.3, 184.8, 187.8. IR (KBr) 1742, 1700 and 1662 cm^{-1}. M.p. 154-156 °C. Anal. found C, 70.702; H, 5.344; calcd. for $C_{20}H_{18}O_5$: C, 71.00; H, 5.36.

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