Metalloporphyrin-Catalyzed Oxidation of 2-Cycloalkyl-3-hydroxynaphthoquinones

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Mild H_2O_2 oxidation of a small series of 2-cycloalkyl-3-hydroxynaphthoquinones catalyzed by 5,-10,15,20-tetrakis(pentafluorophenyl)-21*H*,23*H*-porphineiron(III) chloride in methanol−dichloromethane leads in each case to the isolation of a dehydro-dimer identified as a 3-cycloalkyl-3-(2-cycloalkylnaphthoquinon-3-yl)oxy-2-oxo-2,3-dihydronaphtho-1,4-quinone and in some cases to a 2-cycloalkyl-2,3-dihydroxy-1-oxoindan-3-carboxylate. The mechanism of formation of the former is rationalized in terms of nucleophilic attack of unreacted hydroxynaphthoquinone anion upon an epoxide primary oxidation product, while that of the latter is proposed to involve nucleophilic attack of solvent methanol on the same epoxide followed by rearrangement.

Introduction

2-Hydroxynaphthoquinone (**1a**) also known as lawsone, henna, or isojuglone, has been used as a dyestuff since antiquity.[1] The chemistry of hydroxynaphthoquinones, particularly 2-(3-methylbut-2-enyl)-3-hydroxynaphtho-1,4-quinone lapacol (**1**: R = 3-methylbut-2-enyl, R′ = H) which is isolated from the heartwood of various Bignoniacceae,[1] and which has been known since 1858,[2] was extensively studied by Paterno,[3] Hooker,[4] and Fieser[5] among others in the first half of this century. More generally, both natural and synthetic 2-alkyl-3-hydroxynaphtho-1,4-quinones have been proposed as anti-infectives for treatment of a range of diseases, including malaria in humans,[5,6] and more recently have been studied[7] and patented[8] as agents for both the prevention and treatment of theileria and other infections in cattle and sheep. In 1983, 2-cyclohexyl-3-hydroxynaphtho-1,4-quinone **1b**, also known as parvaquone (or Clexon) was marketed as an effective treatment for East Coast Fever in African cattle. More recently, the hydroxynaphthoquinone atovaquone (2-(*trans*-4-(4-chlorophenyl)cyclohexyl)-3-hydroxynaphtho-1,4-quinone), a broad spectrum antiparasitic agent, was licensed for use against pneumocystis carinii pneumonia as Mepron or Wellvone and in combination with proguanil as Malarone for malaria.[9] The mechanism of action is by inhibition of mitrochondial electron transport.[10]

The in vivo oxidation (human metabolism) of certain alkylhydroxynaphthoquinones was investigated by Fieser, who found products resulting from hydroxylation of the alkyl group along with other unidentified products.[6]

The *chemical* oxidation of a series of 2-alkyl-3-hydroxynaphtho-1,4-quinones, again in particular 2-(3-methylbut-2-enyl)-3-hydroxynaphtho-1,4-quinone lapacol (**1**, R = 3-methylbut-2-enyl, R′ = H), was investigated by Hooker and reported in 1936.[11] He used a rather vigorous oxidant, alkaline $KMnO_4$, and found a product in which the 2-alkyl group is shortened by one carbon (see Scheme 1). Fieser later modified the oxidation by using a two stage H_2O_2/Na_2CO_3 and $CuSO_4$/NaOH procedure and proposed a mechanism (vide infra).[12] The reaction was most recently revisited by Moore et al. in 1995[13] who used ^{13}C-labeling studies to further support the mechanism, initially proposed by Fieser,[12b] and slightly modified since,[14] summarized in Scheme 1; of the intermediate compounds shown, only the indanone **2** has been isolated.

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Scheme 1

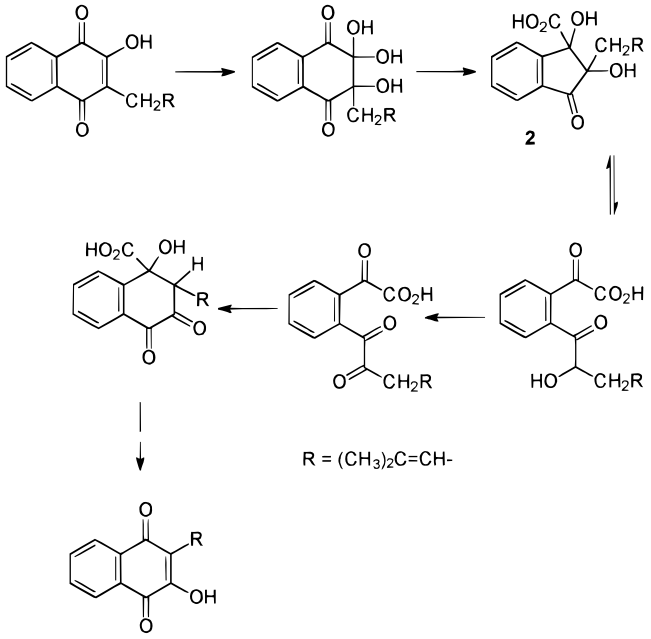
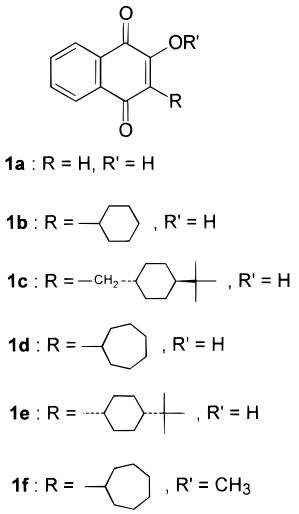


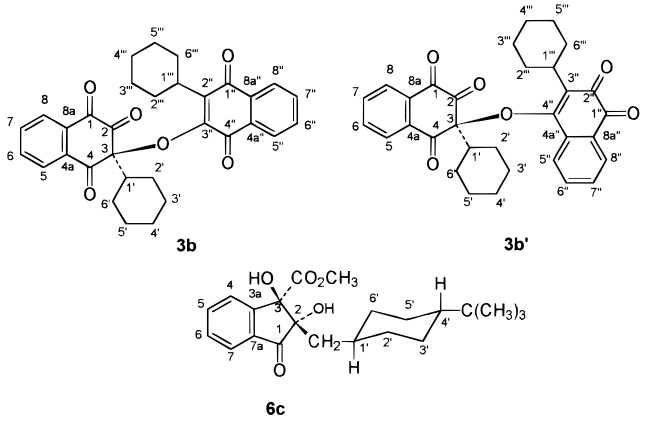
Chart 1



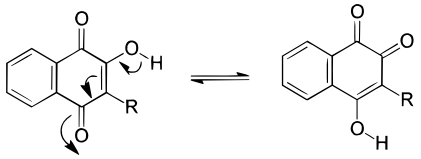
Interestingly the *nonbiomimetic* CrO_3 oxidant appears to yield hydroxylated alkyl products from 2-alkyl-3-hydroxynaphtho-1,4-quinones.[15]

In this work we have used a much milder oxidation system,[16] comprising 5,10,15,20-tetrakis(pentafluorophenyl)-21*H*,23*H*-porphineiron(III) chloride-catalyzed H_2O_2 oxidation in organic solvent at room temperature to investigate the oxidation of a small range of 2-cycloalkyl-3-hydroxynaphtho-1,4-quinones **1b**−**f** (Chart 1) and to isolate and identify products relevant to metabolism and the mechanism of the Hooker oxidation.

Chart 2



Scheme 2



Results

Oxidation of 2-cyclohexyl-3-hydroxynaphtho-1,4-quinone (**1b)** at ca. 0.07 mol dm^{-3} in dichloromethane/methanol in the presence of ca. 0.2% 5,10,15,20-tetrakis(pentafluorophenyl)-21*H*,23*H*-porphineiron(III) catalyst with slow addition (over 90 min) of a slight excess of hydrogen peroxide resulted in almost complete consumption of **1b** as judged by TLC. No reaction was observed in the absence of either the oxidant or the catalyst. Concentration of the solution to ca. 50% volume resulted in the formation of a yellow precipitate, which was collected and shown to be a single compound by TLC.

The precipitate shows a HRMS appropriate for a formula of $C_{32}H_{30}0_6$. The ^{13}C NMR/DEPT spectrum shows ten CH_2 and two aliphatic CH signals indicative of two cyclohexyl rings, one aliphatic quaternary C signal, eight aromatic CH signals, six quaternary aromatic/alkene signals, and five carbonyl signals, while inspection of the H,H COSY spectrum shows that there are two separate aromatic systems. From this information it is clearly a dehydro-dimer, either 3-cyclohexyl-3-(2-cyclohexylnaphtho-1,4-quinon-3-yl)oxy-2-oxo-2,3-dihydronaphtho-1,4-quinone **3b** or its 1,2-quinon-4-yl isomer **3b′** (see Chart 2 for numbering). The possibility of two isomers arises from tautomerization of the 2-alkyl-3-hydroxynaphtho-1,4-quinone to the 3-alkyl-4-hydroxynaphtho-1,2-quinone (Scheme 2). A structure analogous to **3b′** was proposed, based on UV evidence, for the long-known dehydro-dimer obtained from the PbO_2 oxidation of lapachol (**1**, R = 3-methylbut-2-enyl, R′ = H).[17] The IR spectrum of *our* precipitate shows carbonyl peaks typical of an aryl α-diketone (Ar−CO−CO) at 1743 cm^{-1} and an α-alkoxy-α′-aryl ketone (Ar−CO) at 1697 cm^{-1}, but additional peaks consistent with a 3-alkoxy-2-alkylnaphtho-1,4-quinone or a 4-alkoxy-3-alkylnaphtho-1,2-quinone at 1652, 1592, and 1569 cm^{-1}.[18] Ettlinger quotes a peak at ca. 1690 cm^{-1} as characteristic of a naphtho-1,2-quinone;[19] unfortunately, if present in our samples it would be obscured by the 1697 cm^{-1} Ar−CO peak.

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Table 1. ^{13}C NMR Assignments for 3-Cyclohexyl-3-(3-cyclohexylnaphtho-1,4-quinon-2-yl)oxy-2-oxo-2,3-dihydronaphtho-1,4-quinone (3b) in $CDCl_3$

carbon	δ_C
	Carbonyl
C1	180.65
C4	189.04
C4″	182.40
C2	184.69
C1″	184.63
	Aromatic
C5	128.06
C8	128.99
C6, C7	134.69, 136.03
C5″, C8″	126.17, 126.35
C7″	134.42
C6″	132.71
C4a	135.16
C8a	133.22
C8a″	132.09
C4a″	130.47
	Cyclohexyl
C1′	45.96
C1‴	36.72
C2′−C6′, C2‴−C6‴	25.80, 26.13, 26.19, 26.26, 27.06, 27.08, 27.43, 27.85, 29.24, 29.44
	Quaternary
C3	95.94
C3″	151.51
C2″	136.11

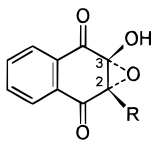
Table 2. ^{1}H NMR Assignments for 3-cyclohexyl-3-(3-cyclohexylnaphtho-1,4-quinon-2-yl)oxy-2-oxo-2,3-dihydronaphtho-1,4-quinone (3b) in $CDCl_3$

hydrogen	δ_H
	Cyclohexyl
H1′	2.12 (tt, J = 10.2[a] and 3.1[b] Hz)
H1‴	3.37 (tt, J = 12.5[c] and 3.9[d] Hz)
H2′, H6′	1.23−1.31 (2 H, m), 1.64−1.70 (1 H, m), 1.76−1.85 (1 H, m Hz)
H2‴$_{eq}$, H6‴$_{eq}$	2.20 (2 H, dq, J = 12.5[e] and 3.9[f] Hz)
H2‴$_{ax}$, H6‴$_{ax}$	1.76−1.85 (2 H, m)
H3′, H4′, H5′, H3‴, H4‴, H5‴	1.05−1.21 (4 H, m), 1.34−1.43 (3 H, m), 1.64−1.70 (1 H, m), 1.76−1.85 (2 H, m), 1.90−1.94 (2 H, m)
	Aromatic
H5	8.19 (dd, J = 6.9 and 1.7 Hz)
H6	7.93 (td, J = 7.2 and 1.7 Hz)
H7	7.91 (td, J = 7.3 and 1.8 Hz)
H8	8.42 (dd, J = 6.9 and 1.7 Hz)
H8″	7.99 (dd, J = 8.0 and 1.2 Hz)
H7″	7.63 (td, J = 7.9 and 1.2 Hz)
H6″	7.47 (td, J = 7.2 and 1.2 Hz)
H5″	7.61 (dd, J = 7.6 and 1.2 Hz)

[a] $J_{ax,ax}$ coupling of axial H1′ to H2′$_{ax}$ and H6′$_{ax}$. [b] $J_{ax,eq}$ coupling of axial H1′ to H2′$_{eq}$ and H6′$_{eq}$. [c] $J_{ax,ax}$ coupling of axial H1‴ to H2‴$_{ax}$ and H6‴$_{ax}$. [d] $J_{ax,eq}$ coupling of axial H1‴ to H2‴$_{eq}$ and H6‴$_{eq}$. [e] H2‴$_{eq}$, geminal coupling to H2‴$_{ax}$; H6‴$_{eq}$, geminal coupling to H6‴$_{ax}$. [f] H2‴$_{eq}$, coupling to H1‴, H3‴$_{eq}$, H3‴$_{ax}$; H6‴$_{eq}$, coupling to H1‴, H5‴$_{eq}$, H5‴$_{ax}$.

In view of the uncertainty, we have used a detailed NMR study based on H,C and H,H COSY experiments to determine the structure of the dehydro-dimer and to assign peaks (Tables 1 and 2). A full analysis is given in the Supporting Information, but key assignments are outlined below. For either **3b** or **3b′** the "entry point" is the characteristic low-field methine signal at 3.37 ppm in the ^{1}H NMR which can be assigned to H1‴ which is "allylic" to the naphthoquinone C═C. H,C COSY experiments assign Cl‴, Cl′ (remaining aliphatic methine) and the H1′ signal at 2.12 ppm. A H,C COSY experiment set to detect two- and three-bond couplings (^{2}J and ^{3}J, typically 8 Hz) was used to assign the quaternary carbon signals. The H1′ at 2.12 ppm is coupled to the C2/C4 carbonyl signals at 189.04 and 184.69 ppm, and since only the former is also coupled to an ArH signal (at 8.19 ppm), C4, C2, and H5 can be assigned. Normal H,C COSY and H,H COSY experiments allow assignment of the H6−H8. and C5−C8 signals, while the ^{2}J and ^{3}J H,C COSY assigns Cl. The long-range coupling of the 182.40 ppm carbonyl to an ArH (7.61 ppm), along with the *lack* of long-range coupling to H1″, assigns C4″ in **3b** or C1″ in **3b′**. H,C and H,H COSY experiments allow assignment of the H5″−H8″ and C5″−C8″ signals. The long-range coupling between the H1″ signal at 3.27 ppm and the remaining carbonyl carbon at 184.63 identifies it as C1″ in **3b** or C2″ in **3b′**. Importantly, the clearly identifiable (the "furthest round" from the already identified C4″ in **3b** or C1″ in **3b′**) H8″ (in **3b**, but H5″ in **3b′**) signal shows clear long-range coupling to this 184.63 ppm carbon. This shows it to be C1″ in **3b**; C2″ in **3b′** would be five bonds distant from H5″ and indeed four bonds distant from any ArH. The ^{2}J and ^{3}J H,C COSY experiment was used to assign the C4a, C8a, C4a″, C8a″, C2″, C3″, and C3 (the only remaining) signals. In summary, the NMR supports the dehydro-dimer structure as **3b** rather than 3-cyclohexyl-3-(3-cyclohexylnaphtho-1,2-quinon-4-yl)oxy-2-oxo-2,3-dihydronaphtho-1,4-quinone (**3b′**). As expected the occurrence of coupling constants of 12.5 and 10.2 Hz in the splitting of the Hl″ and H1′ signals, respectively, shows that these protons are axial. The product **3b** was isolated in up to 8% yield.

The residue, after removal of **3b** by filtration and of solvent by evaporation, gave a ^{1}H NMR spectrum suggestive of a single main component. Despite repeated attempts (including silica gel chromatography, preparative silica gel TLC, HPLC, sublimation, and attempted trapping via acetylation) this material could not be isolated. TLC showed extensive streaking, and SiO_2 chromatography resulted in the formation of mostly resinous material which remained at the origin. The crude ^{1}H NMR of this compound (see Experimental Section) shows peaks which can be attributed to a cyclohexyl group, to the protons of the aromatic ring and to one hydroxyl group (br s at 3.90 ppm). The signal due to the methine proton of the cyclohexyl group, typically appearing ca. 3 ppm in the starting material **1b**, has shifted to 1.95 ppm indicating loss of the naphthoquinone C═C. We believe this material to be an initially formed epoxide (**4b**), the formation and reactivity of which will be discussed below.

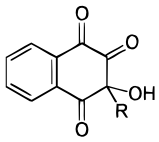


4b : R = 

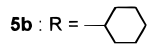
Repeated silica gel chromatography of the epoxide **4b** followed by HPLC led to the isolation of a trace of a

(18) Ettlinger, (Ettlinger, M. G. *J. Am. Chem. Soc.* **1950**, *72*, 3666) quotes peaks for 2-methoxy-3-alkylnaphtho-1,4-quinones in the 1672−1644 and 1605−1587 cm^{-1} regions. The former is noted as being resolvable into two peaks, although it is not apparent in our dehyro-dimer samples. In spectra illustrated in the Ettlinger paper, a shoulder is apparent on the 1605−1587 cm^{-1} peak which probably corresponds to our 1569 cm^{-1} peak.

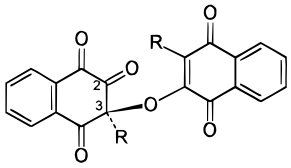
further product (from a large amount of intractable residue); its ^{1}H NMR spectrum shows signals due to aryl protons, a cyclohexyl group (CH signal as a tt at 2.55 ppm), and a hydroxyl proton (5.11 ppm). On the basis of this ^{1}H NMR spectrum and the molecular ion peak at 272 in the LRMS, structure **5b** is assigned to this compound; TLC showed that it was not present in the original reaction mixture, and we believe that it is formed from **4b** on silica.



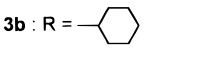
5b : R =



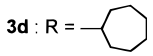
Under similar conditions compounds **1c**, **1d**, and **1e** gave precipitates **3c**, **3d**, and **3e**, respectively. All are identified by their HRMS molecular ion, and by comparison of their characteristic ^{13}C NMR, ^{1}H NMR, and IR spectra with those of **3b** (cf. Tables 1 and 2, and Experimental Section). In particular, all ^{13}C NMR spectra



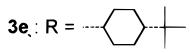
3b : R =



3c : R =



3d : R =



3e : R =

show the pattern of five carbonyl, eight aryl methine, six aryl or alkenyl quaternary, and one alkyl quaternary signals, as well as signals for two alkyl substituents. The ^{1}H NMR spectra show the characteristic aryl pattern seen for **3b** and the low-field allylic H1‴ in the region 3.2−3.5 ppm (2.75 ppm for the CH_2 of **3c**). The H1‴ signal at 3.52 ppm for **3e** (derived from the (*cis*-4-*tert*-butylcyclohexyl)naphthoquinone) shows only couplings of the order of 5.4 Hz, indicating that it is equatorial and that the naphthoquinonyl is in an axial position relative to the cyclohexyl ring with the *tert*-butyl group equatorial. Yields of compounds **3b**−**e**, were each <10% although further traces were seen (TLC, ^{1}H NMR) in the crude residues after collection of the precipitates.

Examination, in each case, of the crude residues after filtration and concentration, showed a ^{1}H NMR spectrum analogous to that obtained for the cyclohexyl compound **1b**, and again we propose an epoxide analogous to **4b** as primary oxidation product in all cases. As with the cyclohexyl compound, repeated attempts to isolate the epoxide were unsuccessful.

Oxidation of **1c** with more rapid addition of hydrogen peroxide, followed by silica gel chromatography allowed

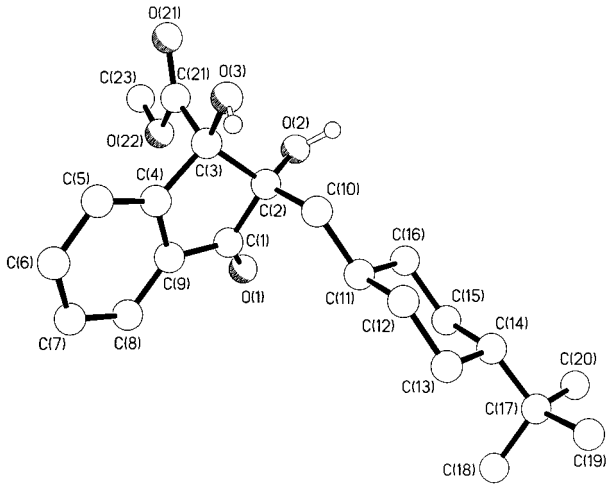
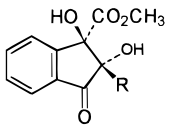


Figure 1. ORTEP diagram of methyl *trans*-2-(*trans*-4-*tert*-butylcyclohexyl)methyl-2,3-dihydroxy-1-oxoindan-3-carboxylate (**6c**) (arbitrary numbering).

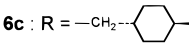
Table 3. ^{13}C NMR Assignments for Methyl *trans*-2-(*trans*-4-*tert*-Butylcyclohexyl)methyl-2,3-dihydroxy-1-oxoindonyl-3-carboxylate (6c) in $CDCl_3$ (shift values are in ppm and are relative to TMS)

carbon	δ_C
Carbonyl	
C1	202.66
$-CO_2-$	172.71
Aromatic	
C4, C7	123.53, 124.24
C5, C6	130.11, 135.42
C3a, C7a	134.99, 148.36
Cyclohexyl	
C2′, C3′, C5′, C6′	27.19, 27.23, 35.06, 35.21
C1′, C4′	32.80, 47.59
Substituent	
$(CH_3)_3$	27.49
C of *t*-Bu	32.30
CH_2	42.67
CH_3O	53.74
Quaternary	
C2, C3	83.98, 88.46

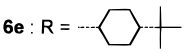
the isolation of a further product, clearly stable on silica, namely, methyl *trans*-2-(*trans*-4-*tert*-butylcyclohexyl)-methyl-2,3-dihydroxy-1-oxoindan-3-carboxylate (**6c**), in 23% yield (see Chart 2 for numbering). The structure is confirmed by X-ray crystallography, in particular the trans arrangement of the 2,3-dihydroxy groups (Figure 1). The IR shows two carbonyl groups, one at 1752 cm^{-1}



6c : R =



6e : R =



typical of the indanone system and the other at 1719 cm^{-1} due to the α-hydroxy ester. The NMR assignments shown in Tables3 and 4 are based on shifts, coupling patterns, and COSY experiments and are explained in the Sup-

Table 4. ^{1}H NMR Assignments for Methyl *trans*-2-(*trans*-4-*tert*-Butylcyclohexyl)methyl-2,3-dihydroxy-1-oxoindonyl-3-carboxylate 6c in $CDCl_3$. Shift Values Are in ppm and Are Relative to TMS. Coupling Constants Are in Hz

hydrogen	δ_H
	Cyclohexyl
H1′, H4′	0.72−0.97 (1 H, m), 1.21−1.34 (1 H, m)
H2′, H3′, H5′, H6′	0.72−0.97 (4 H, m), 1.49−1.55 (1 H, m), 1.60−1.67 (2 H, m), 1.84−1.92 (1 H, m)
CH_2	1.21−1.34 (1 H, m), 1.84−1.92 (1 H, m)
	Substituent
$(CH_3)_3$	0.79 (s)
CH_3O	3.63 (s)
2-OH, 3-OH	3.25 (1 H, br s), 4.43 (1 H, br s)
	Aromatic
H4, H7	7.64 (d, J = 7.5 Hz), 7.82 (d, J = 7.6 Hz)
H5, H6	7.56 (t, J = 7.3 Hz), 7.72 (t, J = 7.4 Hz)

porting Information. The ester carbonyl (172.71 ppm) and the C1 (202.66 ppm) signal are distinguished since the former shows long range (^3J) coupling to the ester CH_3 at 3.63 ppm. Compound **6c** is a trans analogue of the *cis*-dihydroxyoxoindane carboxylic acid intermediate **2** isolated from Hooker oxidation in aqueous solution.[13]

From the oxidation of compound **1e** an analogue **6e** was isolated in crude form and identified by comparison of its ^{1}H NMR with that of **6c**.

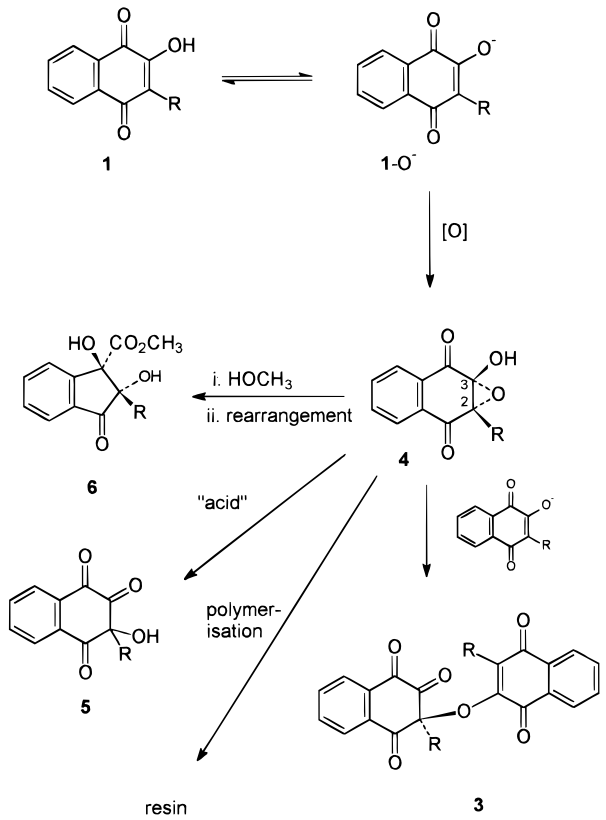
The unsubstituted 2-hydroxynaphtho-1,4-quinone **1a** gave a product identified as 2,3-dihydroxynaphtho-1,4-quinone **7**; this product was also isolated by Fieser following the Hooker oxidation.[19]

Discussion

It can be seen that in all cases 5,10,15,20-tetrakis-(pentafluorophenyl)-21*H*,23*H*-porphineiron(III) chloride-catalyzed oxidation in the presence of a relatively small excess of oxidant leads to complete consumption of the starting hydroxynaphthoquinone **1**. We propose that the C2−C3 double bond is epoxidized to give the reactive epoxide **4**, a process common to this type of metalloporphyrin catalyst. It is clear that the conjugate base (**1**-O$^-$) is the reactive species,[20] since the methylated **1f** is not oxidized by the H_2O_2−metalloporphyrin system, showing that a highly electron-rich double bond is required for such complete oxidation as observed here. The isolated products **3**, **5**, and **6** are byproducts derived from the initially formed epoxide **4** as shown in Scheme 3 (vide infra).[21]

The dehydro-dimer **3** is a 1,4 analogue of the 1,2-dehydro-dimers (which have the general structure corresponding to **3b′**), the most well-known of which is "lapachol peroxide" which results from the PbO_2/acetic acid oxidation of lapachol.[1,11a,17] This was proposed to arise from coupling of radicals derived from the 2-hydroxynaphtho-1,4-quinone and the 4-hydroxynaphtho-1,2-quinone tautomers. The 1,2 (**3b′**) structure for the dehydro-dimer in our case has already been dismissed in favor of the naphtho-1,4-quinon-2-yl isomer **3b** (vide supra), and a radical coupling mechanism is unlikely in this case. We propose that **3b** arises from nucleophilic attack of unoxidized **1**-O$^-$, derived from the 2-hydroxynaphtho-1,4-quinone tautomer, but this time at C2 of the epoxide **4** (Scheme 3).

Scheme 3



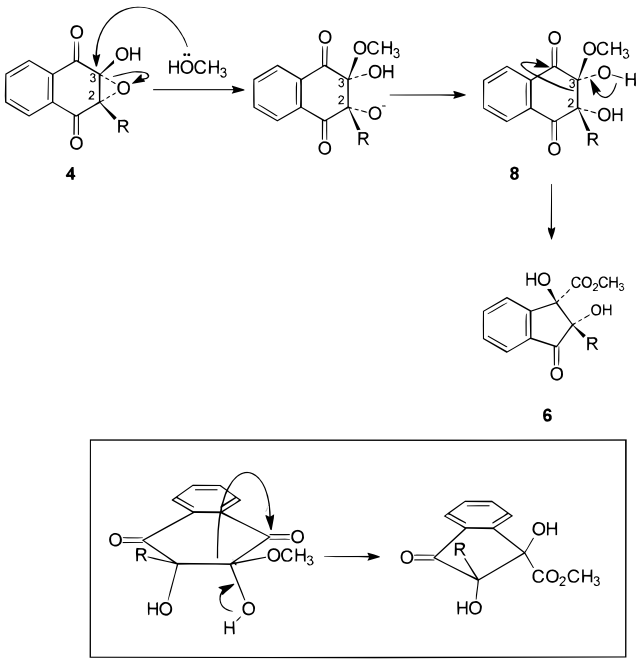
The oxoindane ester **6** is probably formed by rearrangement of a hemiacetal **8** via the mechanism of Scheme 4 (a *gem*-diol precursor has been proposed as an intermediate leading to the carboxylic acid **2** via the Hooker oxidation) (Scheme 1). This hemiacetal **8** would result from nucleophilic attack of solvent methanol at C3 of the epoxide **4**. It is possible that the electron-deficient catalyst 5,10,15,20-tetrakis(pentafluorophenyl)-21*H*,23*H*-porphineiron(III) chloride (which persists largely undegraded throughout the oxidation) acts as a Lewis acid coordinating to the epoxide oxygen facilitating ring opening. The detection of the trans 2,3-dihydroxy compound **6** *only* (no cis) supports the mechanism of Scheme 4. First, the lack of cis product suggests a *concerted* rearrangement of **8** to **6** as shown in Scheme 4 (various ring-opening and benzylic acid-type rearrangements have been postulated for reactions under Hooker conditions).

(19) Fieser, L. F. *J. Am. Chem. Soc.* **1941**, *63*, 2948.

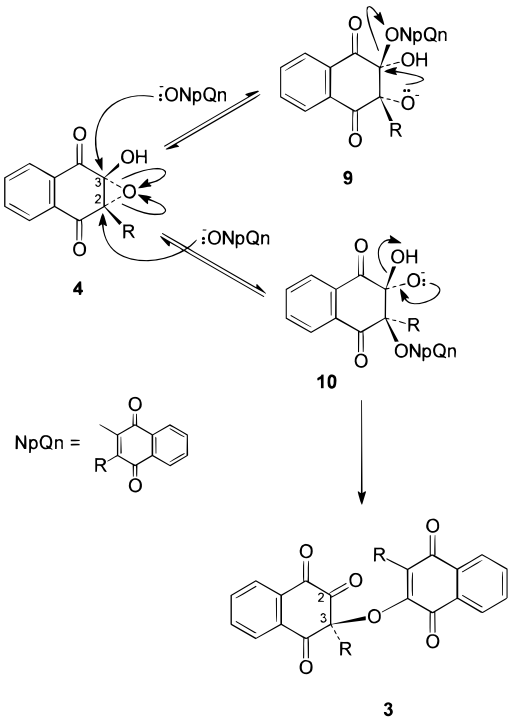
(20) The 2-hydroxynaphtho-1,4-quinones are relatively strong acids with pK_a values typically 4−5 in water (pK_a value for **1a** of 3.98 at 25 °C) rising to >6 in more organic solvents (e.g., 50% acetone:water). See: Fieser, L. F.; Fieser, M. *J. Am. Chem. Soc.* **1934**, *56*, 1565. Ball, E. G. *J. Biol. Chem.* **1934**, *106*, 515.

(21) The evidence for a high-valent oxo-perferryl species (por)Fe^V=O or (por$^{\cdot+}$)Fe^{IV}=O, capable of electrophilic oxygenation of an alkene, for this catalyst and H_2O_2 is strong. Traylor, T. G.; Kim, C.; Richards, J. L.; Xu, F.; Perrin, C. L. *J. Am. Chem. Soc.* **1995**, *117*, 3468. Traylor, T. G.; Tsuchiya, S.; Byun, Y.-S.; Kim, C. *J. Am. Chem. Soc.* **1993**, *115*, 2775. Artaud, I.; Ben-Aziza, K.; Mansuy, D. *J. Org. Chem.* **1993**, *58*, 3373. A "nucleophilic oxygenation" mechanism involving a (por)Fe^{III}−O−O$^-$ species has been proposed for epoxidation of naphthoquinones: Sisemore, M. F.; Burstyn, J. N.; Valentine, J. S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 206−208. A similar mechanism has been proposed for the metallophthalocyanine-catalyzed epoxidation of chloroquinones: Meunier, B.; Sorokin, A. *Acc. Chem. Res.* **1997**, *30*, 470. However, in our case a nucleophilic oxygenation is unlikely. First, oxygenated forms of our perfluorinated catalyst are likely to be much less nucleophilic; second, it is unlikely that a nucleophilic oxygenation would prefer the more electron-rich (−O:$^-$) to the less electron-rich (−OMe) C=C.; third, the bulk of the 2-cycloalkyl substituents would favor the "electrophilic approach" from above the C=C.

Scheme 4



Scheme 5

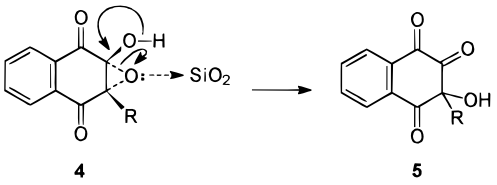


Second, given a concerted rearrangement, the trans **6** must derive from a cis dihydroxy **8**; a cis dihydroxy **8** is strong evidence for an epoxide **4** precursor. Interestingly, Hooker oxidation of similar compounds (e.g., lapacol (**1**, R = 3-methylbut-2-enyl, R′ = H)) yields only *cis*-2,3-dihydroxyoxoindane carboxylic acid **2** presumably from a *gem*-diol analogue of **8** (see Scheme 1).[13,14a] Presumably, when the CH_3O group of **8** is replaced by a hydroxy (as in Scheme 1), this hydroxy is the more reactive of the two.

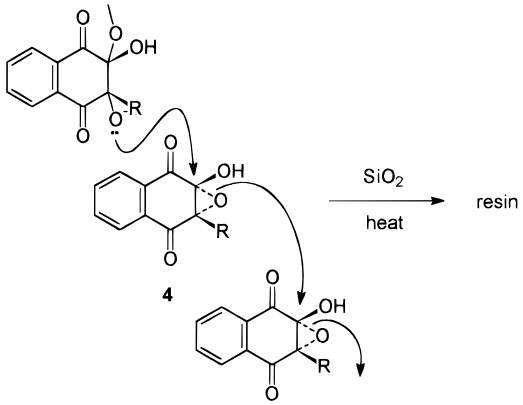
The reason for attack of methanol at C3 rather than C2 of **4** (to yield the hemiacetal **8**) in the reaction leading to the ester **6** can be explained as the commonly observed preference for an epoxide to undergo nucleophilic ring-opening via an A2 mechanism (i.e., S_N2-like attack of the nucleophile on the epoxide carbon) at the less hindered site, C3 in this case (Scheme 4). Furthermore, if as seems likely here, the ring-opening proceeds via a Lewis acid-catalyzed A2 mechanism (borderline A2/A1), the site with the greater $\delta+$ would be C3 with the adjacent electron-donating OH and preference for attack at C3 would be enhanced.[22]

The fact that **3** is derived from nucleophilic attack at the apparently less favored C2 of **4** we explain as follows (Scheme 5). As above, the more electrophilic site is C3, assuming an A2 opening of a Lewis acid-complexed epoxide. However, since the nucleophile $^{-}$:ONpQn is a much better leaving group than $^{-}$:OCH_3, the reverse reaction of the "kinetic" product **9** (or its protonated form) becomes important. The slower attack at C2 yields the product **10**, and while this would likewise be susceptible to reverse to **4**, there is now a facile *irreversible* collapse of the mono-deprotonated gem-diol **10** (or its protonated form) to the keto form **3**, the irreversibility enhanced by the ready precipitation of **3**. We found no evidence for the presence of the ONpQn analogue of **6**; compound **5**, which we isolated in trace amount and which might ostensibly result from breakdown of a ONpQn hemiacetal, appeared to form only after SiO_2 chromatography of the crude product and is probably derived directly from the epoxide **4** (Scheme 6). Acid- or heat-induced polymerization via nucleophilic ring opening might account for the conversion of the crude epoxide **4** to resinous material on subjection to SiO_2 chromatography or attempted distillation/sublimation (Scheme 7).

Scheme 6



Scheme 7

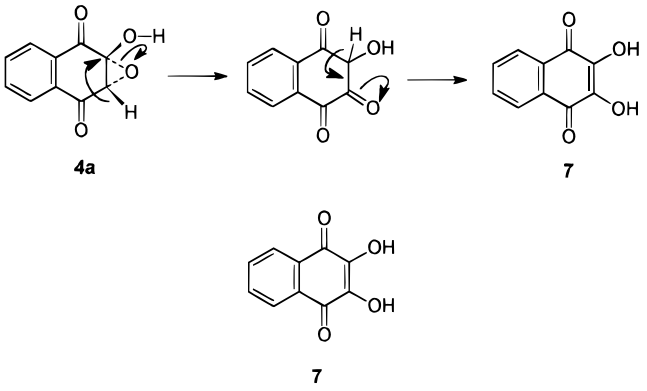


The putative epoxide 1° oxidation product **4a** from **1a** (2-hydroxynaphtho-1,4-quinone) has a rearrangement mode, analogous to the 'NIH' shift in aryl hydroxylation,[23] shown in Scheme 8, yielding the 2,3-dihydroxynaphtho-1,4-quinone **7**.

(22) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley-Interscience: New York, 1991; p 369.

(23) Ortiz de Montellano, P. R. *Cytochrome P450, Structure, Mechanism and Biochemistry*, 2nd ed.; Plenum: New York, 1995; p 264.

Scheme 8



The products and intermediates identified in this work are different in nature to those isolated from metabolic studies; these arising mainly from to hydroxylation of the alkyl groups.[6] However, the possibility that metabolism produces an epoxide 1° product such as **4** cannot be dismissed. The high electrophilicity of **4** is evident throughout this work, but whether such a species is active in the mechanism of therapeutic activity shown by the hydroxnaphthoquinones can, at this stage, only be speculative.

Experimental Section

General. Melting points were determined using a Kofler or Reichert hot stage apparatus and are uncorrected. Yields refer to material homogeneous by TLC and ^{1}H NMR unless indicated otherwise. New compounds were considered to be "fully characterized" when accompanied by HRMS and by ^{1}H NMR evidence of >95% purity along with no obvious indication of impurity as judged by ^{13}C NMR and melting point (see Supporting Information for detailed assessment of purity for all compounds, both fully and partially characterized, mentioned in the Experimental Section). ^{1}H and ^{13}C NMR spectra were recorded using a 300 or a 600 MHz spectrometer; the reference was TMS.

Materials. The 5,10,15,20-tetrakis(pentafluorophenyl)-21*H*,23*H*-porphineiron(III) chloride was supplied by Aldrich and was used as received while 2-hydroxynaphtho-1,4-quinone (**1a**) was supplied by Lancaster Synthesis. The 2-alkyl-3-hydroxynaphtho-1,4-quinones are all known compounds; they were supplied by Glaxo Wellcome; literature methods were used to prepare and characterize **1b**,[24] **1c**,[8c,d] **1d**,[8b] and **1e**.[25]

Typical Procedure. Oxidation of 2-Cyclohexyl-3-hydroxynaphtho-1,4-quinone 1b To Yield 3b. 2-Cyclohexyl-3-hydroxynaphtho-1,4-quinone (516 mg, 2.0 mmol) was dissolved in a 3:1 mixture of methanol and dichloromethane (20 cm^3) and a portion of 5,10,15,20-tetrakis(pentafluorophenyl)-21*H*,23*H*-porphineiron(III) chloride (4.3 mg, 4.0 μmol) was washed into the solution with 3 × 1 cm^3 of dichloromethane. Hydrogen peroxide, 30% w/v, (275 μL, ca. 2.4 mmol) was added to the reaction mixture at room temperature in 25 μL aliquots over a period of 90 min via a 25 μL syringe. The reaction mixture was reduced to ca. 5 cm^3 by evaporation of the solvent under reduced pressure. This resulted in precipitation of a small quantity of yellow solid which was collected by filtration and washed with cold methanol to yield 3-cyclohexyl-3-(2-cyclohexylnaphtho-1,4-quinon-3-yl)oxy-2-oxo-2,3-dihydronaphtho-1,4-quinone (**3b**) (43 mg, 8%): mp 221−223 °C (from methanol); IR ν_{max} (KBr)/cm^{-1} 1743 (Ar−CO−CO), 1697 (Ar−CO), 1652, 1592, 1569 (3-alkoxynaphtho-1,4-quinone); ^{13}C NMR δ_C (150 MHz, $CDCl_3$) see Table 1; ^{1}H NMR δ_H (600 MHz, $CDCl_3$) see Table 2; MS *m*/*z* (FAB) 511 (M + 1$^+$, 100%), 417 (7), 401 (8), 273 (3) (HRMS found 510.20093, $C_{32}H_{30}O_6$ requires 510.20424).

Repetition of the reaction with precipitation of the yellow solid **3b** followed by concentration in vacuo yielded a crude oily product which showed streaking on silica gel TLC and a crude ^{1}H NMR spectrum indicating the 2,3-epoxide **4b**: δ_H (300 MHz, $CDCl_3$) 0.90−1.80 (10 H, m), 1.95 (1 H, m), 3.90 (1 H, br s, OH), 7.90 (2 H, m), 8.25 (1 H, d), 8.30 (1 H, d). This material was not further characterized.

Attempts to isolate or purify the crude epoxide by silica gel column chromatography and/or repeated silica gel HPLC yielded <5 mg of 3-cyclohexyl-3-hydroxy-2-oxo-2,3-dihydronaphtho-l,4-quinone (**5b**) as an oil: δ_H (300 MHz, $CDCl_3$) 1.26−1.35 (3 H, m), 1.44−1.64 (3 H, m), 1.74−1.80 (2 H, m), 1.95−2.01 (2 H, m), 2.55 (1 H, tt, J = 11.0 and 2.9 Hz), 5.11 (1 H, s, OH), 7.87−7.90 (2 H, m), 7.99−8.01 (2 H, m); MS *m*/*z* (EI) 272 (M$^+$, 3%), 162 (46), 134 (20), 133 (21), 111(79), 105 (40), 104 (23), 99 (21), 84 (27), 83 (100).

Oxidation of 2-(*trans*-4-*tert*-Butylcyclohexyl)methyl-3-hydroxynaphtho-1,4-quinone (1c) To Yield 3c and 6c. 2-(*trans*-4-*tert*-Butylcyclohexyl)methyl-3-hydroxynaphtho-1,4-quinone (614 mg, 1.88 mmol) was dissolved in a 1:1 mixture of methanol and dichloromethane (30 cm^3), and a portion of 5,10,15,20-tetrakis(pentafluorophenyl)-21*H*,23*H*-porphineiron-(III) chloride (7.9 mg, 7.4 μmol) was washed into the solution with 3 × 1 cm^3 of dichloromethane. A dropping funnel was charged with a solution of 60% w/v hydrogen peroxide (200 μL, ca. 3.5 mmol) in methanol (5 cm^3). This solution was gradually added to the stirred reaction mixture at room temperature over a period of 2 h. TLC of the reaction solution after this time indicated complete consumption of the starting material. The volume of the reaction solution was reduced to ca. 5 cm^3 by evaporation of the solvent in vacuo resulting in precipitation of a yellow solid. The solid was collected by filtration and washed with cold methanol to yield 3-(*trans*-4-*tert*-butylcyclohexyl)methyl-3-(2-(*trans*-4-*tert*-butylcyclohexyl)-methylnaphtho-1,4-quinon-3-yl)oxy-2-oxo-2,3-dihydronaphtho-1,4-quinone (**3c**) (73.5 mg, 6%): mp 193−201 °C; IR ν_{max}(KBr)/cm^{-1} 1748 (Ar−CO−CO), 1701 (Ar−CO), 1654, 1592, 1570 (3-alkoxynaphtho-1,4-quinone); ^{13}C NMR δ_C (90 MHz, $CDCl_3$) 29.43, 33.72, 36.36, 36.40, 37.18, 37.23, 29.58, 29.65, 34.40, 34.46, 35.04, 40.19, 49.69, 50.30, 46.81, 96.02, 128.30, 128.63, 130.67, 131.03, 134.91, 136.38, 136.69, 138.08, 132.99, 133.84, 134.63, 135.12, 136.43, 153.63, 183.22, 184.17, 186.68, 190.93; ^{1}H NMR δ_H (360 MHz, $CDCl_3$) 0.84 (9 H, s), 0.86 (9 H, s), 0.78−1.26 (10 H, m), 1.69−1.85 (9 H, m), 1.90−1.96 (3H, m), 2.75 (2 H, d, J = 7.1 Hz), 7.48 (1 H, t, J = 6.9 Hz), 7.63 (2 H, m), 7.89 (2H, m), 8.03 (1 H, d, J = 7.4 Hz), 8.22 (1 H, d, J = 8.7 Hz), 8.41 (1 H, d, J = 8.5 Hz); MS *m*/*z* (EI) 650 (M$^+$, 2%), 326 (100), 188 (100) (HRMS found 650.36349, $C_{42}H_{50}O_6$ requires 650.36074).

In a repeat oxidation of **1c** (518 mg, 1.59 mmol), the hydrogen peroxide was added over ca. 1 min and the reaction mixture was allowed to stir for 16 h at room temperature. Water was then added, and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. Silica gel column chromatography (petroleum ether:diethyl ether) of the residue yielded a yellow solid which was recrystallized from petroleum ether as methyl *trans*-2-(*trans*-4-*tert*-butylcyclohexyl)methyl-2,3-dihydroxy-1-oxoindan-3-carboxylate (**6c**) (136 mg, 23%); mp 139−140 °C; IR ν_{max} (KBr)/cm^{-1} 3488 (OH), 3414 (OH), 1752 (indanone CO), 1719 (α-HO ester CO); ^{13}C NMR δ_C (75 MHz, $CDCl_3$) see Table 3; ^{1}H NMR δ_H (300 MHz, $CDCl_3$) see Table 4; MS *m*/*z* (EI) 374 (M$^+$, 41%), 315 (82), 297 (24), 218 (56), 43 (100) (HRMS found 374.20915, $C_{22}H_{30}O_5$ requires 374.20932). Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. found: C, 70.00; H, 8.22. X-ray crystallographic data for **6c** is given as Supporting Information.

Oxidation of 2-Cycloheptyl-3-hydroxynaphtho-1,4-quinone (1d) To Yield 3d. 2-Cycloheptyl-3-hydroxynaphtho-1,4-quinone (534 mg, 1.98 mmol) gave a yellow precipitate of 3-cycloheptyl-3-(2-cycloheptylnaphtho-1,4-quinon-3-yl)oxy-2-

(24) Fieser, L. F. *J. Am. Chem. Soc.* **1948**, *70*, 3165.
(25) Lindner, W.; Becker, B.; Steffans, R.; Wachendorf-Neumann, U.; Brandes, W.; Dutzmann, S.; Stendel, W. German Patent *Offenlegungsschrift* 3801 743, 19 January 1989; *Chem. Abstr.* **1989**, *111*, P7086b.

oxo-2,3-dihydronaphtho-1,4-quinone (**3d**) (50 mg, 9%): mp 212−215 °C (dec) (from methanol); IR ν_{max} (KBr)/cm^{-1} 1739 (Ar−CO−CO), 1706 (Ar−CO), 1652, 1596, 1571 (3-alkoxynaphtho-l,4-quinone); ^{13}C NMR δ_C (75 MHz, $CDCl_3$) 26.91, 27.03, 27.32, 27.87, 28.11, 28.17, 28.84, 28.93, 29.12, 29.69, 32.00, 32.17, 37.48, 48.11, 96.04, 126.12, 126.39, 128.00, 128.95, 132.73, 134.40, 134.63, 135.97, 130.49, 131.99, 133.25, 135.37, 138.11, 150.51, 180.92, 182.53, 184.44, 185.08, 189.28; ^{1}H NMR δ_H (300 MHz, $CDCl_3$) 1.26−1.53 (9 H, m), 1.53−1.80 (9 H, m), 1.80−2.05 (4 H, m), 2.11−2.25 (3 H, m), 3.47 (1 H, m), 7.47 (1 H, t, J = 7.3 Hz), 7.61(1 H, d, J = 8.7 Hz), 7.62 (1 H, t, J = 7.8 Hz), 7.90 (2 H, t, J = 6.4 Hz), 7.99 (1 H, d, J = 7.7 Hz), 8.15−8.18 (1 H, m), 8.40−8.43 (1 H, m); MS *m*/*z* (EI) 538 (M^+, 7%), 494 (9), 414 (17), 270 (90), 131 (100) (HRMS found 538.23599, $C_{34}H_{34}O_6$ requires 538.23554).

Oxidation of 2-(*cis*-4-*tert*-Butylcyclohexyl)-3-hydroxynaphtho-1,4-quinone (1e) To Yield 3e. 2-(*cis*-4-*tert*-Butylcyclohexyl)-3-hydroxynaphtho-l,4-quinone (510 mg, 1.63 mmol) gave a yellow precipitate of 3-(*cis*-4-*tert*-butylcyclohexyl)-3-(2-(*cis*-4-*tert*-buty1cyclohexyl)naphtho-l,4-quinon-3-yl)oxy-2-oxo-2,3-dihydronaphtho-1,4-quinone (**3e**) (13 mg, 3%): mp > 222 °C (dec) (from methanol); IR ν_{max} (KBr)/cm^{-1} 1747 (Ar−CO−CO), 1695 (Ar−CO), 1647, 1591, 1568 (3-alkoxynaphtho-1,4-quinone); ^{13}C NMR δ_C (75 MHz, $CDCl_3$) 22.77, 22.94, 23.06, 23.29, 23.37, 23.48, 25.56, 25.67, 27.48, 27.68, 30.74, 32.83, 33.13, 41.87, 41.93, 42.60, 95.59, 126.15, 126.39, 128.22, 128.99, 130.49, 132.13, 132.71, 133.22, 134.39, 134.66, 135.19, 135.96, 137.03, 151.42, 180.89, 182.33, 184.59, 184.69, 189.23; ^{1}H NMR δ_H (300 MHz, $CDCl_3$) 0.75 (9 H, s), 0.92 (9 H, s), 1.06−1.85 (16 H, m), 2.20−2.31 (3 H, m), 3.52 (1 H, septet, J = 5.4 Hz Hz), 7.47 (1 H, t, J = 8.0 Hz), 7.61 (1 H, d, J = 7.6 Hz), 7.62 (1 H, t, J = 7.6 Hz), 7.90−7.93 (2 H, m), 7.99 (1 H, d, J = 7.7 Hz), 8.17−8.20 (1 H, m), 8.40−8.43 (1 H, m); MS *m*/*z* (EI) 622 (2%), 312 (100), 255 (48) (HRMS found 622.32825, $C_{40}H_{46}O_6$ requires 622.32944).

The experiment was repeated, and silica gel column chromatography of the concentrated solution (after removal of the precipitate) gave methyl 2-(*cis*-4-*tert*-butylcyclohexyl)-2,3-dihydroxy-1-oxoindan-3-carboxylate (**6e**) as a white solid (8 mg, 1%): mp 116−117 °C (from hexane); ^{13}C NMR δ_C (75 MHz, $CDCl_3$) 22.99, 24.64, 26.67, 27.52, 30.92, 32.66, 44.92, 53.74, 84.45, 90.37, 123.04, 123.65, 130.04, 135.56, 136.20, 149.20, 173.20; ^{1}H NMR δ_H (300 MHz, $CDCl_3$) 0.79 (9 H, s), 0.79−1.68 (7 H, m), 2.07−2.17 (1 H, m), 2.19−2.24 (2 H, m), 3.13 (1 H, br s), 3.62 (3 H, s), 4.37 (1 H, br s), 7.55 (t, J = 7.5 Hz), 7.59 (d, J = 7.5 Hz), 7.71 (t, J = 7.5 Hz), 7.79 (d, J = 7.5 Hz). This material was not characterized further.

Oxidation of 2-Hydroxynaphtho-1,4-quinone (1a). 2-Hydroxynaphtho-1,4-quinone (1.03 g, 5.92 mmol) gave after oxidation, and silica gel chromatography an impure sample of the known 2,3-dihydroxynaphtho-l,4-quinone,[19] (300 mg, 27%); ^{1}H NMR δ_H (300 MHz, $CDCl_3$) 4.65 (br s, HO and water), 7.81−7.90 (2 H, m), 8.02−8.13 (2 H, m); MS *m*/*z* (EI) 190 (M^+, 79%), 162 (96), 144 (13), 132 (33), 104 (100).

Methylation of 2-Cycloheptyl-3-hydoxynaphtho-1,4-quinone. To a solution of 2-cycloheptyl-3-hydroxynaphtho-l,4-quinone (503 mg, 1.86 mmol) and benzyltributylammonium chloride (665 mg, 2.12 mmol) in dichloromethane (10 cm^3) and water (15 cm^3) was added solid sodium hydroxide (177 mg, 4.44 mmol). Vigorous stirring resulted in a mauve reaction mixture to which was added methyl iodide (0.35 cm^3, 5.60 mmol). After overnight stirring at room-temperature, the mixture was extracted with dichloromethane and concentrated in vacuo to leave a wet oily residue. This was taken up in diethyl ether, washed with 2 mol dm^{-3} aqueous ammonium hydroxide, 2 mol dm^{-3} aqueous sodium hydroxide and saturated brine before being dried ($MgSO_4$), filtered, and concentrated in vacuo to give 2-cycloheptyl-3-methoxynaphtho-1,4-quinone (**1f**) as a orange oil (84.2 mg, 16%): ^{1}H NMR δ_H (300 MHz, $CDCl_3$) 1.47−1.71 (8 H, m), 1.79−1.87 (2 H, m), 1.89−2.02 (2 H, m), 3.23 (1 H, tt, J = 10.6 and 3.5 Hz), 4.07 (3 H, s), 7.64−7.72 (2 H, m), 8.01−8.07 (2 H, m).

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Supporting Information Available: Explanation of NMR assignments (see Tables 1−4) for compounds **3b** and **6c**; ^{13}C and ^{1}H NMR assignments for compounds **3c**−**e**, **4b**, **5b**, **6e** and **1f**; assessment of purity for compounds **3b**, **4b**, **5b**, **3c**, **6c**, **3d**, **3e**, **6e**, and **1f** with relevant ^{1}H (and for **3b** and **3d** ^{13}C) NMR spectra; and X-ray crystallographic data for **6c**. This material is available free of charge via the Internet at http//pubs.acs.org.

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