Concerning the Mechanism of the Hooker Oxidation

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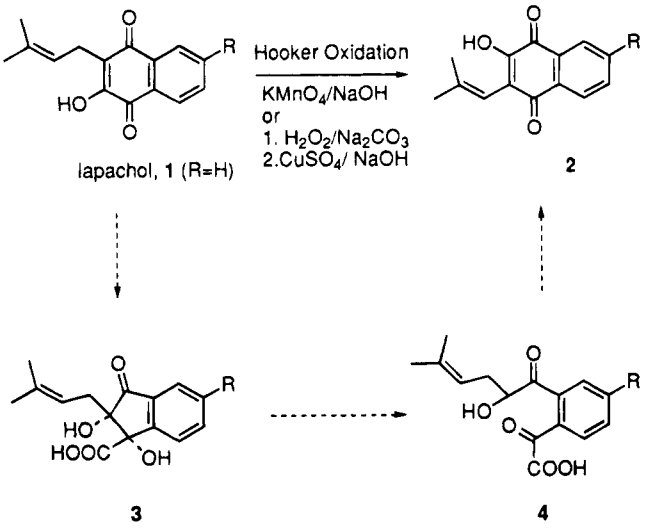
The Hooker oxidation is one of the more remarkable reactions in organic chemistry. A historic example is the conversion of lapachol (**1**, R = H, Scheme 1) to the lower homologue (**2**), a reaction discovered by Hooker and studied in detail by the Fiesers and their co-workers.[1,2] Two important observations are apparent from this example: (1) the prenyl substituent is shortened by one carbon unit and (2) the regiochemical arrangement of the 2-alkyl group and the 3-hydroxy substituent in the product are reversed from their positions in the starting quinone. This unusual reaction and its mechanistic consequences have dominated interest in the Hooker oxidation since the seminal work of Hooker and the Fiesers some 50 years ago. It is surprising that its synthetic potential has not been realized; only recently has work appeared pointing in this direction.[3]

Reported in this note are data supporting the mechanism for the rearrangement initially proposed by Fieser and Fieser in 1948.[2a] Most revealing is the observation that hydroxynaphthoquinone **9**, enriched with ^{13}C at the 1-position of the ethyl substituent, rearranged to **10** under Hooker conditions and that the isotope enrichment was observed to be at a quinone sp^2 carbon atom (Scheme 2).

The synthesis of **9** stems from di-*tert*-butyl squarate (**5**), a reagent previously shown to be a useful precursor to hydroxy quinones.[4] Treatment of **5** with [1-^{13}C]-ethylmagnesium iodide followed by hydrolysis (TFAA) gave **6** in 70% isolated yield.[5] Addition of 1-lithio-2,4-dimethoxybenzene (THF) to **6** at −78 °C afforded cyclobutenone **7** in 52% yield. Thermolysis of **7** in refluxing toluene gave the corresponding hydroquinone which was directly converted to quinone **8** (92%) upon Ag_2O oxidation.[6] De-*tert*-butylation (TFA) then gave the desired hydroxynaphthoquinone **9** in nearly quantitative yield.

Oxidation of **9** under Hooker conditions (1. H_2O_2/Na_2CO_3; 2. $CuSO_4$/NaOH) gave **10** in 72% isolated yield, the structure of which is in complete accord with the observed spectral properties (Experimental Section). In addition, **10** was independently synthesized from 3-*tert*-butoxy-4-methylcyclobutene-1,2-dione (**12**) as outlined in Scheme 2. Treatment of **12** with 1-lithio-3,5-dimethoxybenzene gave cyclobutenone **13** in 32% isolated yield which was then converted to **10** (78%) upon thermolysis in refluxing toluene followed by Ag_2O oxidation and de-*tert*-butylation. Comparison of the quinone obtained by this sequence with the product of the above Hooker oxidation using a sample of **9** that had not been enriched with ^{13}C showed them to be identical in all respects.

Scheme 1



Tracking the course of the ^{13}C label in the conversion of **9** to **10** provides critical information regarding the mechanism of the Hooker oxidation. The ^{13}C NMR spectra of these two hydroxynaphthoquinones clearly show that the label is maintained in both compounds and that an sp^3 C atom (16.4 ppm) is enriched in the former and an sp^2 C atom (122.0 ppm) in the latter. Verification of a direct bond connection between the methyl group (8.8 ppm) and the ^{13}C-enriched vinyl carbon (122.0 ppm) in **10** was accomplished by a carbon–carbon correlation (INADEQUATE) experiment. In addition, when a carbon–proton long-range coupling (INAPT) experiment was performed by irradiating the methyl proton absorption, three C-atom absorptions (122, 151, and 184 ppm) were affected. Thus, the vinyl C atom absorbing at 122 ppm is directly attached to the methyl group, the carbonyl C atom (184 ppm), and the vinyl C atom (151 ppm) bearing the hydroxyl group.

Further confirmation of the mechanism was obtained by a structural analysis of an intermediate formed in the rearrangement. In a series of elegant experiments, first reported by Fieser and Fieser and later by Fieser and Bader, an intermediate in the Hooker oxidation was isolated and characterized primarily on the basis of chemical data.[2a,c] For example, when lapachol (**1**) was treated with H_2O_2/Na_2CO_3, *cis*-2-alkyl-1-oxoindan-3-carboxylic acid (**3**) was isolated and subsequently shown to rearrange to quinone **2** upon treatment with $CuSO_4$/NaOH. Even though the data presented in the above studies are in accord with structure **3**, the rigor of modern NMR analysis is needed. In addition, some confusion arose in 1977 when Otten and Rosazza reported that fermentation of lapachol (**1**) with *Penicillium notatum* gave a polar metabolite they claimed to be **4**, a compound

(1) (a) Hooker, S. C. *J. Am. Chem. Soc.* **1936**, *58*, 1168. (b) Hooker, S. C. *J. Am. Chem. Soc.* **1936**, *58*, 1174. (c) Hooker, S. C.; Steyermark, A. *J. Am. Chem. Soc.* **1936**, *58*, 1179.

(2) (a) Fieser, L. F.; Fieser, M. *J. Am. Chem. Soc.* **1948**, *70*, 3215. (b) Fieser, L. F.; Hartwell, J. L.; Seligman, A. M. *J. Am. Chem. Soc.* **1936**, *58*, 1223. (c) Fieser, L. F.; Bader, A. R. *J. Am. Chem. Soc.* **1951**, *73*, 681.

(3) Lee, K. H.; Moore, H. W. *Tetrahedron Lett.* **1993**, *34*(2), 235.

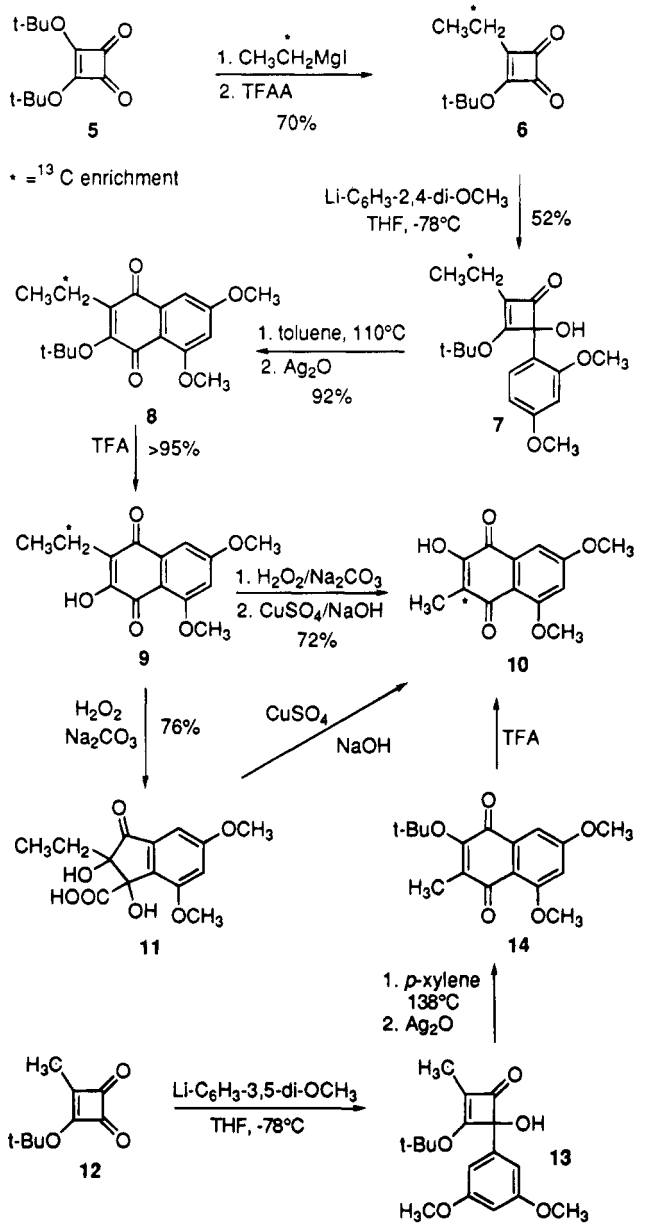
(4) Enhsen, A.; Karabelas, K.; Heerding, J. M.; Moore, H. W. *J. Org. Chem.* **1990**, *55*, 1177.

(5) For leading references concerning the synthesis of substituted cyclobutenones, see: (a) Liebeskind, L. S.; Wirtz, K. R. *J. Org. Chem.* **1990**, *55*, 5350. (b) Gayo, L. M.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 6896. (c) Reed, M. W.; Pollart, D.; Perri, S. T.; Foland, L.; Moore, H. W. *J. Org. Chem.* **1988**, *53*, 2477. (d) Liebeskind, L. S.; Fengal, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *53*, 2482.

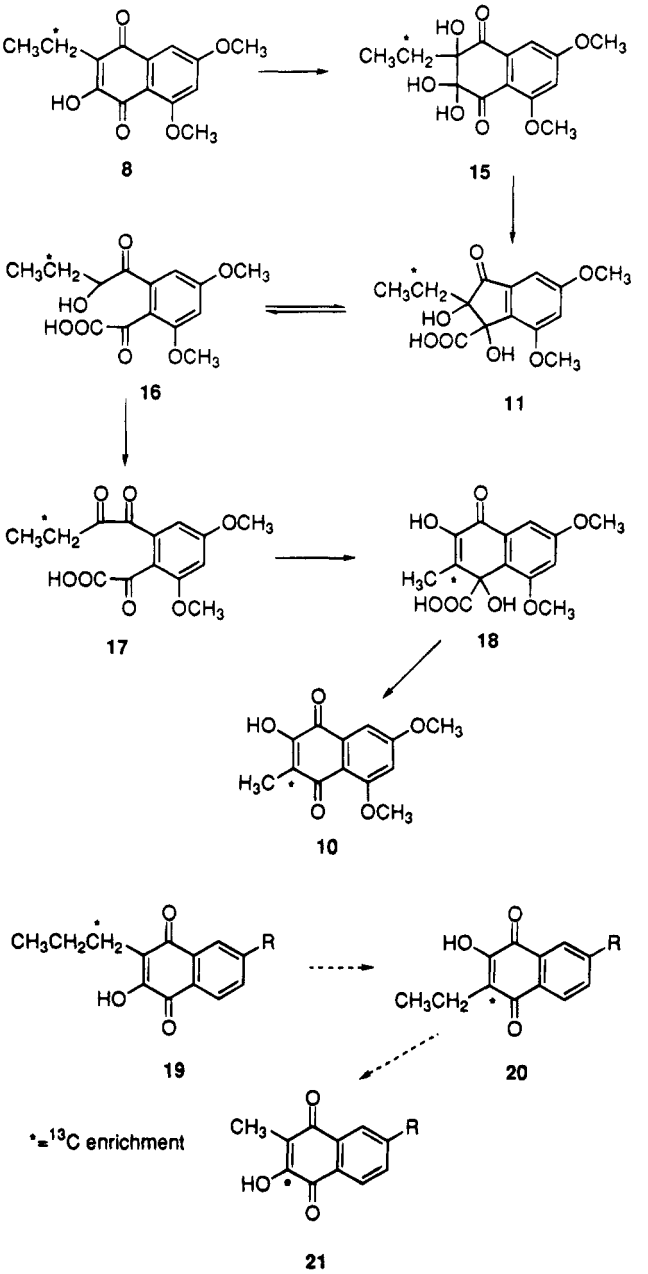
(6) For reviews concerning the ring expansion of 4-aryl, 4-alkenyl-, and 4-alkynylcyclobutenones, see: (a) Moore, H. W.; Yerxa, B. R. *Chemtracts* **1992**, *5*, 273. (b) Moore, H. W.; Decker, O. H. W. *Chem. Rev.*, **1986**, *86*, 821. (c) Liebeskind, L. S. *Tetrahedron* **1989**, *45*, 3053. (d) Moore, H. W.; Yerxa, B. R. *Advances in Strain in Organic Chemistry*; JAI Press LTD: Hampton Hill, U.K., 1994. For a review of the utility of cyclobutenones in natural product synthesis, see: Bellus, D.; Ernst, B. *Angew. Chem.* **1988**, *100*, 820.

0022-3263/95/1960-0461$09.00/0

Scheme 2



Scheme 3



that had previously been suggested as an undetected intermediate in the Hooker oxidation.[2a,7] This assignment, however, is questionable since the ^{1}H NMR data [δ 7.52 (m, 4H, ArH), 4.97 (t, J = 8.0 Hz, 1H, =CH—), 4.82 (s, 3H, OH), 2.87 to 2.13 (m, 2H, CH_2), 1.47 (s, 3H, CH_3), 1.33 (s, 3H, CH_3)] do not list an absorption for a CHOH group, and no ^{13}C NMR data were presented.

Support for an indanone structure for the intermediate in the Hooker oxidation is provided below. Treatment of 2-ethyl-3-hydroxy-5,7-dimethoxy-1,4-naphthoquinone (**9**) with H_2O_2/Na_2CO_3 gave a white crystalline solid in 76% isolated yield. ^{13}C and ^{1}H NMR spectra showed the appropriate chemical shifts and both proton and carbon counts to be in accord with structure **11** [^{1}H NMR (CD_3OD, 500 MHz) δ 6.78 (s, 2H), 4.90 (s, 2H, OH), 3.81 (s, 3H), 3.80 (s, 3H), 1.95 (q, J = 7.3 Hz, 1H), 1.54 (q, J = 7.3 Hz, 1H), 0.81 (t, J = 7.3 Hz, 3H); ^{13}C NMR (CD_3OD, 500 MHz) δ 204.9, 165.2, 160.4, 140.5, 140.1, 132.9, 108.0, 98.4, 88.8, 84.5, 57.2, 57.1, 30.6, 9.1]. In addition, a DEPT-90 experiment showed no absorptions in the 50–90 ppm region as would be expected for a compound lacking a -*CH*OH moiety. Furthermore, the IR spectrum shows an intense absorption at 1757 cm^{-1} which supports the existence of a carbonyl group as in an indanone moiety. Finally, the indanone intermediate gave quinone **10** in 66% when subjected to $CuSO_4$/NaOH oxidation.

In conclusion, the following points are noted: (1) synthesis of the ^{13}C-enriched hydroxynaphthoquinone **9** and its rearrangement to **10** provides data in agreement with the mechanism of the Hooker oxidation originally proposed by Fieser and Fieser, i.e. **8** → **15** → **11** → **16** → **17** → **18** (Scheme 3),[2a] (2) synthesis of **9** and its rearrangement to **10** presents a prototypical method for the regiocontrolled construction of specifically labeled quinones and related compounds, e.g., two successive oxidations starting with **19** would result in respectively **20** and then **21**.

Experimental Section

General Procedure. Commercial reagents were used without further purification. Tetrahydrofuran and diethyl ether were

(7) Otten, S.; Rosazza, J. P. *Appl. Environ. Microbiol.* **1978**, *35*, 554.

distilled from sodium/benzophenone ketyl immediately before use. Toluene was distilled from calcium hydride. All air- or water-sensitive reactions were carried out in flame-dried glassware under a positive pressure of argon or nitrogen. Air-sensitive solutions were transferred via cannula and were introduced into the reaction vessels through rubber septa. Lithium reagents were introduced via syringe. Reaction solutions were concentrated on a Buchi rotary evaporator at 15–30 mmHg. Column chromatography was performed with E. Merck silica gel (230–400 mesh) employing hexanes/ethyl acetate as eluent.

Instrumentation. Proton and carbon NMR were recorded on a General Electric Ω 500 NMR or a General Electric GN 500 NMR spectrometer. Infrared spectra were recorded on a Perkin-Elmer FT IR spectrophotometer (1600 series). Low-resolution mass spectra (MS) were recorded on a Finnigan 4000 spectrometer and high-resolution mass spectra (HRMS) were measured with a VG Analytic 7070E spectrometer.

3-*tert*-Butoxy-4-([1-^{13}C]ethylcyclobutene-1,2-dione (6). Magnesium ribbon (360 mg, 15 mmol) and a few crystals of iodide were placed in a flame-dried round bottom flask containing anhydrous Et_2O (30 mL). An ether solution (50 mL) of ^{13}C-labeled ethyl iodide (1 g, 6.4 mmol) was then added dropwise over 30 min, and the resulting reaction mixture was heated to reflux for 1 h. After cooling to 0 °C, the gray mixture was transferred via cannula to a solution of di-*tert*-butyl squarate (**5**) (1.8 g, 8.0 mmol, −78 °C) in dry THF (100 mL). Upon stirring for 30 min, a white solid formed and TFAA (1.5 mL, 10 mmol) was added via syringe. The reaction mixture was stirred for 10 min, and then the reaction was quenched with H_2O (10 mL). The crude mixture was then extracted with Et_2O (200 mL) and H_2O (30 mL) followed by back-extraction of the aqueous portion with Et_2O (2 × 100 mL). The combined organic portions were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash column chromatography (3:1 hexanes/EtOAc) gave 820 mg (70%) of **6** as a pale yellow oil: IR ($CDCl_3$, cm^{-1}) 2986, 2945, 1791, 1748, 1575, 1558, 1464, 1374, 1307, 1153, 1077, 985; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.75 (q, J = 7.5 Hz, 1H), 2.50 (q, J = 7.5 Hz, 1H) (C–H coupling = 29.7 Hz), 1.61 (s, 9H), 1.27 (dt, J = 7.5, 4.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.3, 197.3, 193.1, 187.5, 88.5, 29.3, 19.1 (largest), 10.6; MS (EI), m/z (rel intensity) 143 (2), 100 (29), 99 (100), 87 (16), 83 (3); MS (CI), m/z 184 (MH^+); HRMS, m/z calcd for $C_9{}^{13}CH_{14}O_3$ 183.0976, found 184.1062 (MH^+).

3-*tert*-Butoxy-2-ethyl-4-hydroxy-4-(2,4-dimethoxyphenyl)-cyclobuten-2-one (7). *n*-Butyllithium (1.6 M in hexanes, 1.5 mL, 2.4 mmol) was slowly added to a solution of 2,4-dimethoxybromobenzene (0.38 mL, 2.6 mmol, −78 °C) in dry THF (50 mL). After stirring for 30 min, the reaction mixture was transferred via cannula to a solution of **6** (386 mg, 2.1 mmol; 9:1 mixture of the ^{12}C isomer and **6**) in dry THF (40 mL). The resulting mixture was stirred for 30 min, and then the reaction was quenched with a 5% NH_4Cl solution (3 mL). The reaction solution was extracted with Et_2O (100 mL) and H_2O (20 mL). The aqueous portion was back-extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash column chromatography (3:1 hexanes/EtOAc) gave 352 mg (52%) of **7** as a thick yellow oil: IR (neat, cm^{-1}) 3372, 2977, 2398, 2839, 1748, 1614, 1504, 1463, 1371, 1309, 1209, 1159, 1032, 828; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.18 (d, J = 8.2 Hz, 1H), 6.45 (d, J = 8.2 Hz, 1H), 6.43 (s, 1H), 4.92 (s, 1H, OH), 3.83 (s, 3H), 3.76 (s, 3H), 2.1 (q, J = 7.4 Hz, 2H), 1.44 (s, 9H), 1.13 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 191.9, 177.4, 160.4, 158.2, 130.2, 128.2, 117.8, 104.6, 99.4, 93.4, 83.4, 55.8, 54.9, 28.9, 16.5 (largest), 11.0; MS (EI), m/z (rel intensity) 264 (17), 247 (32), 246 (100), 231 (10), 178 (47), 175 (16), 165 (97), 149 (24), 121 (17), 97 (17), 56 (78), 55 (34); MS(CI), m/z 321 (MH^+), 265, 247; HRMS, m/z calcd for $C_{17}{}^{13}CH_{24}O_5$ 321.1657, found 322.1815 (MH^+).

3-*tert*-Butoxy-2-ethyl-5,7-dimethoxy-1,4-naphthoquinone (8). A toluene solution (50 mL) of cyclobutenone **7** (180 mg, 0.56 mmol) was placed in a flame-dried round bottom flask and heated to reflux for 1 h. Upon cooling to ambient temperature, Ag_2O (200 mg) and K_2CO_3 (140 mg, 0.95 mmol) were added. After 2 h of stirring, the solvent was removed *in vacuo* . Flash column chromatography (3:1 hexanes/EtOAc) gave 164 mg (92%) of **8** as a yellow solid: mp 91–92 °C; IR ($CDCl_3$, cm^{-1}) 2977, 2940, 1664, 1592, 1570, 1460, 1368, 1352, 1211, 1151, 982; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.22 (s, 1H), 6.66 (s, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 2.56 (q, J = 7.4 Hz, 2H), 1.46 (s, 9H), 1.09 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.6, 180.9, 164.1, 161.3, 157.4, 138.1, 136.2, 113.7, 103.4, 102.5, 84.0, 56.2, 55.6, 29.3, 17.7, 12.8; MS(EI), m/z (rel intensity) 263 (33), 262 (100), 248 (15), 247 (49), 220 (14), 219 (45), 151 (14), 115 (3), 106 (6); MS (CI), m/z 321 (MH^+); HRMS, m/z calcd for $C_{17}{}^{13}CH_{24}O_5$ (reduced form) 321.1657, found 321.1629.

2-Ethyl-3-hydroxy-5,7-dimethoxy-1,4-naphthoquinone (9). 1,4-Naphthoquinone **8** (90 mg, 0.28 mmol) was added to TFA (30 mL) in a round bottom flask at 0 °C. After the solution was stirred for 15 min, toluene (30 mL) was added and the solvent was removed *in vacuo*. Flash column chromatography (1:1 hexanes/EtOAc) gave a quantitative yield of **9** as a yellow solid: mp 193–194 °C; IR ($CDCl_3$, cm^{-1}) 3348, 2974, 2941, 1648, 1596, 1566, 1460, 1385, 1357, 1260, 1219, 1160, 984; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.88 (s, 1H, OH), 7.37 (d, J = 2.4 Hz, 1H), 6.67 (d, J = 2.4 Hz, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 2.58 (q, J = 7.7 Hz, 2H), 1.15 (t, J = 7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 184.3, 178.5, 166.5, 162.5, 153.3, 137.5, 112.1, 106.1, 104.4, 102.2, 56.2, 55.8, 16.4 (largest), 12.4; MS (EI), m/z (rel intensity) 263 (31), 262 (100), 220 (20), 219 (73), 165 (13), 151 (23), 106 (13), 77 (8); HRMS, m/z calcd for $C_{13}{}^{13}C\ H_{14}O_5$ 263.0875, found 263.0829.

2-Hydroxy-5,7-dimethoxy-3-methyl-1,4-naphthoquinone (10). Hydroxyquinone **9** (131 mg, 0.5 mmol) was added to a 50 mL round bottom flask charged with dioxane (1.5 mL) and H_2O (1.5 mL) containing 64 mg (0.6 mmol) of Na_2CO_3. The resulting burgundy colored reaction mixture was heated with 30% H_2O_2 (0.20 mL) at 60 °C until the solution became colorless to pale yellow. Upon cooling (ice bath), the reaction mixture was treated with concd HCl (5 drops) and H_2O saturated with SO_2. A stream of nitrogen was then bubbled through the solution for 30 min. Next, the mixture was treated with a 25% NaOH solution (1 mL) and a solution containing $CuSO_4$ (0.5 g, 3 mmol) in H_2O (4 mL) and heated at 70 °C until the starting blue solution became red in color (ca. 1 h). The solid components were removed by vacuum filtration through a pad of Celite. The filtrate was then treated with concd HCl, resulting in a yellow solution (pH 1–2). Extraction with $CHCl_3$ (3 × 50 mL) was followed by a back-washing of the aqueous with $CHCl_3$ (2 × 25 mL). The combined organic portions were washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Flash column chromatography (3:1 hexanes/EtOAc) gave 89 mg (72%) of **10** as a yellow solid: mp 223–225 °C; IR ($CDCl_3$, cm^{-1}) 3433, 2942, 1645, 1596, 1566, 1465, 1389, 1320, 1289, 1208, 1159, 1067; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.25 (d, J = 1.7 Hz, 1H), 6.99 (s, 1H, OH), 6.75 (d, J = 1.7 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 183.8, 181.3, 177.1, 163.7, 161.5, 150.9, 133.0, 122.0, 114.2, 105.1, 103.0, 56.3, 55.8, 8.8; MS (EI), m/z (rel intensity) 249 (40), 248 (100), 220 (28), 219 (49), 205 (19), 191 (27), 190 (13), 177 (29), 147 (22), 135 (26), 106 (14), 91 (10), 83 (13), 63 (16); HRMS, m/z calcd for $C_{12}{}^{13}CH_{12}O_5$ 249.0718, found 249.0733.

2-Ethyl-4,6-dimethoxy-1-oxoindan-3-carboxylic acid (11). Hydroxyquinone **9** (262 mg, 1.0 mmol) was added to a 50 mL round bottom flask charged with dioxane (5 mL) and H_2O (5 mL) containing Na_2CO_3 (120 mg, 1.13 mmol). The resulting burgundy reaction mixture was next treated with 30% H_2O_2 (0.20 mL) and heated at 70 °C until the solution became a pale orange (1.5 h). The mixture was then cooled on an ice bath and treated with 36% HCl (5 drops) followed by H_2O saturated with SO_2. Remaining SO_2 was purged with a gentle stream of N_2 for 0.5 h. Extraction with EtOAc (3 × 30 mL) and combination of the organic portions was followed by a brine wash and drying ($MgSO_4$). Concentration afforded a yellow oil which gave 224 mg (76%) of **11** as white platelets from $CHCl_3$: mp 148–150 °C; IR (KBr, cm^{-1}) 3468, 3274, 2980, 1757, 1704, 1611, 1500, 1463, 1408, 1357, 1314; ^{1}H NMR (CD_3OD, 500 MHz) δ 6.78 (s, 2H), 4.90 (s, 2H, OH), 3.81 (s, 3H), 3.80 (s, 3H), 1.95 (q, J = 7.3 Hz, 1H), 1.54 (q, J = 7.3 Hz, 1H), 0.81 (t, J = 7.3 Hz, 3H); ^{13}C NMR (CD_3OD, 125 MHz) δ 204.9, 165.2, 160.4, 140.5, 140.1, 132.9, 108.0, 98.4, 88.8, 84.5, 57.2, 57.1, 30.6, 9.1; MS (CI), m/z (rel intensity) 297 (2), 279 (25), 235 (39), 210 (10), 209 (100); HRMS, m/z calcd for $C_{14}H_{16}O_7$ 296.0896, found 297.1011 (MH^+).

2-Hydroxy-3-methyl-5,7-dimethoxy-1,4-naphthoquinone (10) from Indanone 11. Indanone **11** (87 mg, 0.29 mmol) was suspended in H_2O (2 mL) and treated with a 25%

NaOH solution (0.80 mL) to afford an homogeneous pale yellow solution. Addition of an aqueous solution (1.5 mL of H_2O) of $CuSO_4$ (277 mg, 1.7 mmol) gave a blue reaction mixture which was heated (10 min) to 70 °C. The resulting burgundy/brown suspension was worked up as described above to give 48 mg (66%) of **10** as orange needles from MeOH: mp 225–226 °C; IR (thin film, cm^{-1}) 3411, 2968, 2921, 1659, 1641, 1629, 1587, 1557, 1455, 1377, 1312, 1198, 1156, 1054; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.263 (s, overlapping with $CHCl_3$, 1H), 6.96 (s, 1H, OH), 6.75 (s, 1H), 3.96(s, 3H), 3.94 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 184.0, 181.5, 163.8, 161.7, 151.1, 133.2, 122.1, 114.3, 105.4, 103.2, 56.5, 56.0, 8.9; HRMS (EI), m/z calcd for $C_{13}H_{12}O_5$ 248.0685, found 248.0686.

3-*tert*-Butoxy-2-methyl-4-hydroxy-4-(3,5-dimethoxyphenyl)cyclobuten-2-one (13). To a solution (−78 °C) of 3,5-dimethoxybromobenzene (427 mg, 1.97 mmol) in dry THF (15 mL) was slowly added *n*-BuLi (1.6 M in hexanes, 1.3 mL, 2.15 mmol) via syringe. After 30 min of stirring, the cold solution was transferred via cannula to a THF (15 mL) solution of 3-*tert*-butoxy-4-methylcyclobutene-1,2-dione (300 mg, 1.79 mmol), prepared according to the published procedure.[4] After being stirred for 30 min, the reaction mixture was worked up according to **7**. Flash column chromatography (7:3 hexanes/EtOAc) gave 175 mg (32%) of **13** as a thick yellow oil: IR (neat, cm^{-1}) 3363, 2980, 2933, 2837, 1748, 1593, 1455, 1425, 1389, 1342, 1198, 1150, 1060, 1030, 911; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.63 (dd, J = 1 Hz, 2H), 6.37 (d, J = 1 Hz, 1H), 3.758 (s, 3H), 3.756 (s, 3H), 1.81 (s, 3H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 191.5, 179.3, 160.8, 139.9, 124.4, 103.9, 100.1, 92.9, 84.3, 55.3, 28.3, 8.4; HRMS (EI), m/z calcd for $C_{17}H_{22}O_5$ 306.1467, found 306.1473.

2-*tert*-Butoxy-5,7-dimethoxy-3-methyl-1,4-naphthoquinone (14). Cyclobutenone **13** (148 mg, 0.48 mmol) was dissolved in *p*-xylene (9 mL) and heated to reflux under N_2 for 15 min. Upon cooling to ambient temperature, Ag_2O (224 mg, 0.97 mmol) and K_2CO_3 (134 mg, 0.97 mmol) were added and the reaction mixture was stirred for 20 min. Filtration through a pad of Celite afforded a bright yellow filtrate. Removal of the volatiles gave a dark yellow oil which crystallized from hexanes/EtOAc (3:2) as bright orange platelets weighing 115 mg (78%): mp 129–130 °C; IR (thin film, cm^{-1}) 2977, 2931, 2841, 1671, 1643, 1615, 1592, 1564, 1457, 1423, 1372, 1333, 1294, 1156, 1102, 965; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.21 (d, J = 2.5 Hz, 1H), 6.68 (d, J = 2.0 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 2.07 (s, 3H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 184.3, 182.8, 164.0, 161.2, 154.2, 139.0, 135.4, 114.3, 103.9, 102.9, 83.7, 56.2, 55.6, 29.2, 11.2; HRMS (CI), m/z calcd for $C_{17}H_{20}O_5$ 304.1311, found 307.1545 (MH^+, reduced form calcd for 306.1467).

2-Hydroxy-5,7-dimethoxy-3-methyl-1,4-naphthoquinone (10) from 14. 1,4-Naphthoquinone **14** (115 mg, 0.38mmol) was dissolved in CH_2Cl_2 (5 mL) and treated with TFA (1 mL). The resulting deep purple solution was stirred for 5 min prior to concentration to an orange solid, which gave 71 mg (75%) of bright orange needles from methanol. All data are in accord with the same hydroxyquinone synthesized by the alternate route.

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Supplementary Material Available: Copies of ^{13}C NMR spectra of **6** (and ^1H NMR), **7–11**, and **13** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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