A Potentially General Regiospecific Synthesis of Substituted Quinones from Dimethyl Squarate

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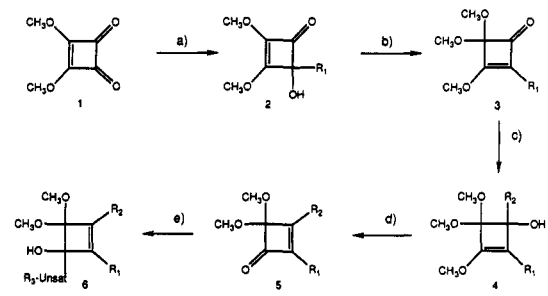
A potentially general regiospecific synthesis of benzo- and naphthoquinones is described. This method starts with dimethyl squarate (1), which is converted to the cyclobutenone ketal 3 upon sequential treatment with an organolithium reagent and then BF_3 etherate or TFAA in THF/methanol. Treatment of these with a second lithium reagent followed by hydrolysis gives the cyclobutenones 5. Addition of an alkynyl-, alkenyl- or aryllithium agent to 5 followed by hydrolysis of the ketal linkage gives the corresponding 4-alkynyl- 4-alkenyl- or 4-aryl-4-hydroxycyclobutenones 7–9, and these readily rearrange to the respective quinones or hydroquinones upon thermolysis in refluxing benzene. In a similar fashion, 15 was employed as a reagent to prepare mono- and disubstituted hydroquinones and quinones.

Reported here is a complimentary strategy to that described by Liebeskind, Granberg, and Zhang[1] for a potentially general and regiospecific synthesis of benzo- and naphthoquinones starting from readily available dimethyl squarate (1) (Scheme I and II).[2] The method starts with the addition of an organolithium reagent (R_1Li, R_1 = alkyl, aryl, alkenyl, alkynyl) to 1 to give the cyclobutenone 2 in good to excellent yields.[3-9] Methanolysis of the β-hydroxy enol ether moiety in 2 gives the cyclobutenedione monoketals 3.[10] As an illustration, dimethyl squarate (1) was converted to **2a** in 90% yield upon treatment with phenyllithium in THF at −78 °C. This adduct was then converted to **3a** in 85% yield when treated with BF_3 etherate and methanol. In a related manner, **3a** was obtained in the same overall yield (77%) from 1 in a "one pot" procedure. That is, the reaction solution resulting from phenyllithium addition to 1 was quenched with trifluoroacetic anhydride (TFAA) and after a few minutes methanol was added. Standard workup then gave **3a** directly.

The cyclobutenone monoketals 3 were next treated with a second organolithium reagent (R_2Li) to give the cyclobutenes 4 which were not isolated but converted directly to the corresponding cyclobutenedione monoketals 5 upon treatment with TFAA. Treatment of these with an unsaturated organolithium reagent gave 6, and hydrolysis of the ketal linkage (concentrated $HCl/CHCl_3$) provided the key synthetic intermediates 7, 8, and 9 (Scheme II).

Previously it was shown that 3-alkoxy-4-alkynyl-4-hydroxycyclobutenones, analogs which are structurally related to 7, undergo thermally induced ring expansion to 1,4-benzoquinones.[3-5] Similarly, 4-alkenyl- or 4-aryl-4-hydroxycyclobutenones were shown to ring expand to the corresponding hydroquinones which are easily converted to the quinones upon mild oxidation.[6-9] Thus, thermolysis of **7a–c** or the 4-alkenyl (**8**) or 4-aryl analog (**9**) gave the corresponding quinones in good yields. Specifically, according to the sequence of reactions generally outlined above, the appropriately substituted cyclobutenes **6** were prepared and converted to the corresponding key quinone precursors, **7a–c**, **8**, and **9**. These were then directly transformed to the respective quinones **10a–c**, **11**, and **12** in refluxing benzene in overall yields ranging from 61 to 90%. It is of interest to note that the rates of the ring expansions of these cyclobutenones are significantly faster than those observed for their 3-alkoxy or 2,3-dialkoxy analogs.[4,7,8,11] Indeed, the rearrangements reported herein usually accompany the isolation and purification of the cyclobutenone precursors while those for the alkoxy series require prolonged heating. As a result, the cyclobutenones

Scheme I[a]



	R_1	R_2	Unsat-R	Yield
3a	C_6H_5	–	–	85
3b	$C_6CH_2C_6H_5$	–	–	80
3c	C_2H_3	–	–	80
3d	n-C_4H_9	–	–	65
5a	C_6H_5	CH_3	–	94
5b	C_6H_5	n-C_4H_9	–	98
5c	C_2H_3	n-C_4H_9	–	90
5d	C_2H_3	C_2H_3	–	95
6a	C_6H_5	CH_3	C_2-n-C_4H_9	75
6b	C_2H_3	n-C_4H_9	C_2H_3	72
6c	C_6H_5	n-C_4H_9	C_2H_3	70
6d	C_6H_5	n-C_4H_9	C_2-n-C_4H_9	67
6e	C_6H_5	CH_3	C_6H_5	78

[a] (a) R_1Li, THF, −78 °C; (b) $BF_3/(C_2H_5)_2O$, THF/MeOH or TFAA followed by CH_3OH; (c) R_2Li, THF, −78 °C; (d) TFAA; (e) $R_3UnsatLi$/hexane, −5 °C.

† This work was taken primarily from the Ph.D. Dissertation of Leah Gayo.

(1) Liebeskind, L. S.; Granberg, K. L.; Zhang, J. *J. Org. Chem.*, **1992**, *57*, 4345.

(2) For the syntheses of related cyclobutenediones, see the following selected references: Reed, M. W.; Pollart, D. J.; Perri, S. T.; Foland, L. D.; Moore, H. W. *J. Org. Chem.* **1988**, *53*, 2477. Liebeskind, L. S.; Fengl, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *53*, 2482. Liebeskind, L. S.; Wang, J. *Tetrahedron Lett.* **1990**, *31*, 4293. Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359. Xu, S.; Yerxa, B. R.; Sullivan, R. W.; Moore, H. W. *Tetrahedron Lett.* **1991**, *32*, 1129.

(3) Karlsson, J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 3392.

(4) Foland, L. D.; Karlsson J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975.

(5) Perri, S. T.; Dyke, H. J.; Moore, H. W. *J. Org. Chem.* **1989**, *54*, 2032.

(6) Perri, S. T.; Moore H. W. *J. Am. Chem. Soc.* **1990**, *112*, 1897.

(7) Liebeskind, L. S.; Iyer, S.; Jewell, C. F. *J. Org. Chem.* **1986**, *51*, 3065.

(8) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067.

(9) Selwood, D. L.; Jandu, K. S. *Heterocycles* **1988**, *27*, 1191.

(10) For a related synthesis of cyclobutenedione monoketals, see: Liebeskind, L. S.; Wirtz, K. R. *J. Org. Chem.* **1990**, *55*, 5350.

(11) Sullivan, R. W.; Moore, H. W. Unpublished data. For example, the half-life ($t_{1/2}$) for the ring expansion of 4-hydroxy-2,3-dimethoxy-4-(3-phenylpropynyl)cyclobutenone is approximately 1250 min at 75 °C (acetonitrile) while that for 2-*n*-butyl-4-hydroxy-3-methoxy-4-(3-phenylpropynyl)cyclobutenone is 20 min. The rate of ring expansion of **10c** appears to be faster still.

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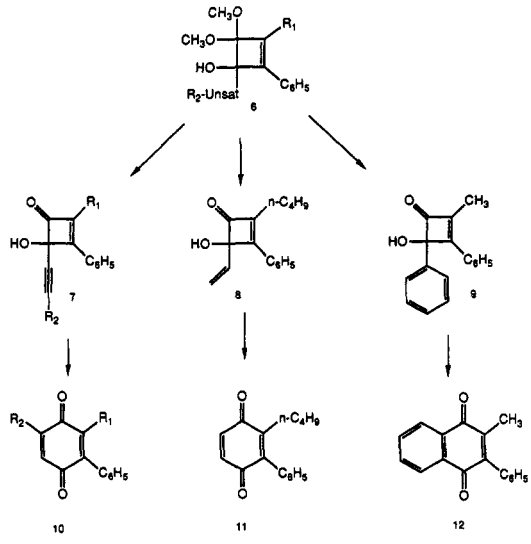
Scheme II



Compound	R_1	R_2	Yield (from 6)
10a	n-C_4H_9	n-C_4H_9	79
10b	n-C_4H_9	$CH_2C_6H_5$	61*
10c	CH_3	n-C_4H_9	80
11			75
12			90

* Overall yield from 5b

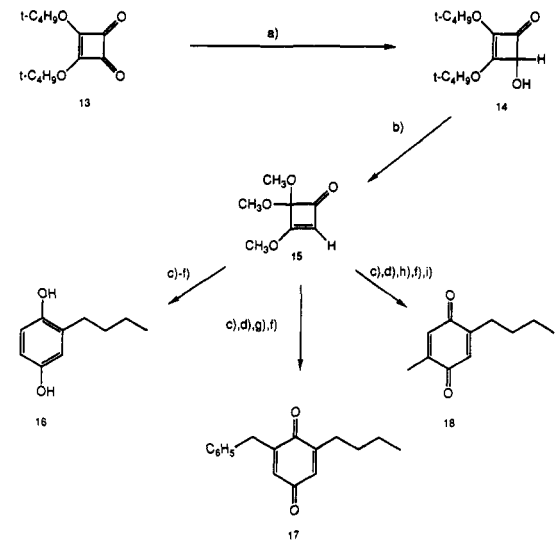
were not rigorously purified but used directly after their rapid filtration through a plug of Florisil.

This work was extended to include the synthesis of quinones and hydroquinones having simpler substitution patterns than those presented above. The availability of the required cyclobutenone ketal **15** made this possible (Scheme III). Reduction of di-*tert*-butyl squarate (**13**) ($LiAlH(O\text{-}t\text{-}C_4H_9)_3$) gave the cyclobutenone **14** which was converted directly to **15** (65% overall yield from **13**) upon treatment with boron trifluoride etherate in methanol. The cyclobutenone ketal **15** was then employed as generally outlined above as the starting material for the synthesis of a variety of quinones and hydroquinones. Selected examples are **16**, **17**, and **18**. Butyllithium was used as the first organolithium reagent for each of these compounds. The resulting 3-*n*-butyl-4,4-dimethoxycyclobutenone was then converted to **16** (46%), **17** (45%), and **18** (50%) by employing vinyllithium, 1-lithio-3-phenylpropyne, and 2-lithiopropene, respectively.

The examples described in this paper illustrate the utility of this method for the regiospecific synthesis of a variety of benzoquinones and naphthoquinones. 4-Alkynyl-4-hydroxycyclobutenones of structural type **7** can be employed for the synthesis of 2,3,5-trisubstituted quinones while the 4-alkenyl analogs **8** lead to 2,3-disubstituted and conceivably to 2,3,5-trisubstituted or 2,3,5,6-tetrasubstituted 1,4-benzoquinones. Mono-, 2,6-di-, and 2,5-disubstituted examples are also available from **15**. The 4-aryl analogs **9** provide a simple route to annulated derivatives. The fact that the substituents are introduced from organolithium reagents is particularly advantageous since such are generally readily available. It is also of interest to note that the method outlined here nicely compliments previous studies employing the ring expansion of analogous cyclobutenones formed from the regiospecific addition of the appropriate organolithium reagent to the 4-position of 2-alkyl-, 2-alkynyl-, 2-alkenyl-, and 2-aryl-3-alkoxycyclobutenediones.[5,12] Taken together, these rearrangements provide one of the most versatile controlled synthetic routes to highly substituted quinones and hydroquinones. They also add to the growing importance of the ring expansions of cyclobutenones to a variety of other ring systems including chlorophenols, quinone methides, benzofuranes, methylenebenzofuranes, bicyclo[3.2.0]heptenones, indolizines, indolizine-5,8-diones, [3.2.2]cyclazines, and 2-alkylidene-1,3-cyclopentenediones.[13]

(12) Heerding, J.; Moore, H. W. *J. Org. Chem.* **1991**, *56*, 4048.

Scheme III[a]



[a] (a) $LiAlH(O\text{-}t\text{-}Bu)_3$; (b) $BF_3/(C_2H_5)_2O$, CH_3OH; (c) butyllithium; (d) TFAA; (e) vinyllithium; (f) $HCl/H_2O/CHCl_3$; (g) 1-lithio-3-phenylpropyne; (h) 2-lithiopropene; (i) Ag_2O, K_2CO_3.

Experimental Section

All air- or water-sensitive reactins were run in flame-dried glassware under N_2 which was dried by passage through a column of NaOH and Drierite. THF was freshly distilled from CaH_2 and then sodium/benzophenone. Other anhydrous solvents such as benzene were freshly distilled from CaH_2. All higher boiling solvents were removed in vacuo in bath temperatures of 30–60 °C. Commercial reagents were used without any further purification unless otherwise noted. All reactions were followed by TLC using E. Merck precoated plates of silica gel 60 F_{254}. Silica gel used in flash column chromatography was E. Merck silica gel 60 (mesh 230–400). Florisil used was Fisher Scientific Florisil (mesh 100–200). ^1H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, in $CDCl_3$. *J* values are in hertz.

Representative Procedure for the Synthesis of Cyclobutenedione Monoketals 3. 2-Phenyl-3,4,4-trimethoxy-2-cyclobuten-1-one (3a). A solution of 2,3-dimethoxy-4-phenyl-4-hydroxy-2-cyclobuten-1-one (0.300 g, 1.36 mmol) and 50 mL of freshly distilled THF was stirred under N_2 at 0 °C. Freshly distilled MeOH (0.11 mL, 2.73 mmol) was added dropwise via a syringe followed by distilled $BF_3{\cdot}Et_2O$ (0.20 mL, 1.64 mmol) also introduced dropwise via syringe. The resulting solution was stirred for 3 h and then neutralized with 10% $NaHCO_3$ (20 mL) and diethyl ether (20 mL). The aqueous layer was separated and extracted with portions of diethyl ether (2 × 15 mL). The combined organic layers were washed with brine (2 × 20 mL) and dried

(13) See, for examples: Enhsen, A.; Karabelas, K.; Heerding, J. M.; Moore, H. W. *J. Org. Chem.* **1990**, *55*, 1177. Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 989. Iyer, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1987**, *109*, 2759. Liebeskind, L. S.; Baysdon, S. L.; South, M. S.; Iyer, S.; Leeds, J. P. *Tetrahedron Symposium in Print* **1985**, *41*, 5839. Xu, S. L.; Moore, H. W. *J. Org. Chem.* **1989**, *54*, 4024. Liebeskind, L. S. *Tetrahedron Symposium in Print* **1989**, *45*, 3053. Moore, H. W.; Perri, S. T. *J. Org. Chem.* **1988**, *53*, 996. Liebeskind, L. S.; Chidambaram, R. *J. Am. Chem. Soc.* **1987**, *109*, 7908. Liebeskind, L. S.; Mitchell, D.; Foster, B. *J. Am. Chem. Soc.* **1987**, *109*, 7908. Liebeskind, L. S.; Chidambaram, R.; Mitchell, D.; Foster, B. *Pure Appl. Chem.* **1988**, *60*, 27. Xu, S. L.; Moore, H. W. *J. Org. Chem.* **1989**, *54*, 6018. Xu, S.; Moore, H. W. *J. Org. Chem.* **1991**, *56*, 6104. Xu, S.; Xia, H.; Moore, H. W. *J. Org. Chem.* **1991**, *56*, 6094. Yerxa, B. R.; Moore, H. W. Unpublished data.

($MgSO_4$). Removal of the solvent in vacuo followed by column chromatography (4:1 hexanes/ethyl acetate) on Florisil provided the desired product, acquired as the first of the 2 bands. Concentration of the desired fractions yielded **3a** (0.270 g, 85% yield) as a clear oil: IR ($CHCl_3$) 1747, 1632 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78 (d, 2 H, J = 7.1), 7.35 (dd, 2 H, J = 7.4, 7.1), 7.28 (d, 1 H, J = 7.4), 4.22 (s, 3 H), 3.56 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 189.5, 180.7, 129.0, 128.5, 128.4, 127.9, 127.0, 115.1, 60.1, 53.7; MS (EI) m/e (rel int) 234 (43), 219 (100); HRMS calcd for $C_{13}H_{14}O_4$ (M^+) 234.0892, found 234.0889. Compound **3a** was also directly obtained from dimethyl squarate: A solution of dimethyl squarate (0.351 g, 2.47 mmol) and 50 mL of freshly distilled THF was stirred under N_2 at −78 °C. Phenyllithium (1.65 mL, 2.97 mmol) was then introduced dropwise via syringe. After the solution was stirred for 20 min, trifluoroacetic anhydride (0.37 mL, 2.6 mmol) was added via syringe, and the solution was allowed to stir an additional 15 min at −78 °C. Freshly distilled MeOH (10 mL) was then introduced, the cold bath was removed, and the reaction was stirred for 15 min. The reaction mixture was then neutralized, worked up, and purified as described above to provide **3a** (0.447 g, 77% yield).

2-(3-Phenyl-1-propynyl)-3,4,4-trimethoxy-2-cyclobuten-1-one (3b): 0.843 g, 80% yield; IR ($CHCl_3$) 2361, 2235, 1773, 1622 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 4.30 (s, 3 H), 3.77 (s, 2 H), 3.52 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 188.1, 184.6, 136.2, 129.3, 128.5, 127.6, 113.0, 95.8, 69.3, 61.7, 54.1, 26.6; MS (EI) m/e (rel int) 272 (2.5), 58 (100); HRMS calcd for $C_{16}H_{16}O_4$ (M^+) 272.1049, found 272.1049.

2-Ethenyl-3,4,4-trimethoxy-2-cyclobuten-1-one (3c): 0.294 g, 80% yield; IR ($CHCl_3$) 1788, 1748, 1621 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.06 (dd, 1 H, J = 11.2, 17.6), 5.84 (dd, 1 H, J = 2.0, 17.6), 5.27 (dd, 1 H, J = 2.0, 11.2), 4.03 (s, 3 H), 3.35 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 188.8, 179.4, 127.5, 122.1, 121.4, 112.8, 60.0, 53.0; MS (EI) m/e (rel int) 184 (12), 125 (68), 99 (91), 53 (100); MS (CI) 185, 153, 85; HRMS calcd for $C_9H_{12}O_4$ (M^+) 184.0736, found 184.0715.

2-*n*-Butyl-3,4,4-trimethoxy-2-cyclobuten-1-one (3d): 0.758 g, 65% yield; IR ($CHCl_3$) 1760, 1711, 1623 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.09 (s, 3 H), 3.49 (s, 6 H), 2.13 (t, 2 H, J = 7.6), 1.50 (m, 2 H), 1.31 (m, 2 H), 0.88 (t, 3 H, J = 7.3); ^{13}C NMR ($CDCl_3$) δ 191.8, 182.5, 132.9, 113.5, 59.5, 53.5, 29.4, 22.5, 21.6, 13.6; HRMS calcd for $C_{11}H_{18}O_4$ (M^+) 214.1205, found 214.1208.

Representative Procedure for the Synthesis of Cyclobutenedione Monoketals 5. 2-Phenyl-3-methyl-4,4-dimethoxy-2-cyclobuten-1-one (5a). A solution of 2-phenyl-3,4,4-trimethoxy-2-cyclobuten-1-one (0.437 g, 1.87 mmol) and 75 mL of freshly distilled THF was stirred under N_2 at −78 °C. MeLi (4.00 mL, 5.68 mmol) was then introduced dropwise via a syringe. The resulting solution was allowed to stir for 30 min. Trifluoroacetic anhydride (TFAA) (0.396 mL, 2.80 mmol) was then syringed in dropwise. After stirring an additional 15 min, the reaction mixture was neutralized, worked up, and purified as described for **3a** to provide **5a** (0.381, 94% yield) as a light yellow oil: IR ($CHCl_3$) 1748, 1638 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.71 (m, 2 H), 7.38 (m, 3 H), 3.51 (s, 6 H), 2.46 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 192.3, 174.9, 150.5, 129.6, 129.3, 128.7, 127.7, 115.7, 53.0, 12.8; MS (EI) m/e (rel int) 218 (12), 203 (28); HRMS calcd for $C_{13}H_{14}O_3$ (M^+) 218.0943, found 218.0932.

2-Phenyl-3-butyl-4,4-dimethoxy-2-cyclobuten-1-one (5b): 0.196 g, 98% yield; IR ($CHCl_3$) 1758, 1632 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73 (d, 2 H, J = 7.3), 7.40 (m, 3 H), 3.54 (s, 6 H), 2.84 (t, 2 H, J = 8), 1.76 (tt, 2 H, J = 8, 7.3), 1.48 (m, 2 H), 0.97 (t, 3 H, J = 7.34); ^{13}C NMR ($CDCl_3$) δ 193.3, 179.4, 150.3, 129.6, 128.9, 128.8, 127.8, 116.9, 53.4, 28.7, 27.9, 23.3, 13.7; MS (EI) m/e (rel int) 260 (5), 189 (26), 129 (83), 115 (100); MS (CI) 261, 229, 215; HRMS calcd for $C_{16}H_{20}O_3$ (M^+) 260.1412, found 260.1409.

2-Ethenyl-3-*n*-butyl-4,4-dimethoxy-2-cyclobuten-1-one (5c): 0.796 g, 90% yield; IR ($CHCl_3$) 1759, 1648 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.24 (dd, 1 H, J = 10.8, 17.6), 6.10 (dd, 1 H, J = 1.7, 17.6), 5.54 (dd, 1 H, J = 1.7, 10.8), 3.45 (s, 6 H), 2.57 (t, 2 H, J = 7.8), 1.65 (tt, 2 H, J = 7.4, 7.8), 1.38 (tt, 2 H, J = 7.4, 7.4), 0.92 (t, 3 H, J = 7.4); ^{13}C NMR ($CDCl_3$) δ 192.8, 178.8, 149.6, 125.1, 123.1, 116.4, 53.1, 28.8, 27.4, 22.9, 13.6; HRMS calcd for $C_{12}H_{18}O_3$ (M^+) 210.1256, found 210.1248.

2,3-Diethenyl-4,4-dimethoxy-2-cyclobuten-1-one (5d): 0.511 g, 95% yield; IR ($CHCl_3$) 1753, 1637 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.74 (dd, 1 H, J = 10.8, 17.6), 6.30 (dd, 1 H, J = 10.8, 17.6), 6.16 (dd, 1 H, J = 1.7, 17.6), 6.14 (dd, 1 H, J = 1.4, 17.6), 5.78 (dd, 1 H, J = 1.4, 10.8), 5.61 (dd, 1 H, J = 1.7, 10.8), 3.46 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 194.4, 169.2, 148.1, 128.8, 127.0, 125.9, 123.5, 117.8, 54.2; MS (EI) m/e (rel int) 180 (22), 165 (21), 149 (36), 121 (33), 91 (60), 77 (95), 59 (100); MS (CI) 181, 1149, 135; HRMS calcd for $C_{10}H_{12}O_3$ (M^+) 180.0786, found 180.0776.

3-*n*-Butyl-4,4-dimethoxy-2-cyclobuten-1-one. 3-*n*-Butyl-4,4-dimethoxy-2-cyclobuten-1-one was prepared in the same fashion as **5a** starting with **15**. Radial chromatography (3:1 hexanes/ethyl acetate) on silica gel afforded the title compound (0.177 g, 91% yield): IR (neat) 1770, 1641 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.37 (s, 1 H), 3.48, (s, 6 H), 2.57, (t, 2 H, J = 7.7), 1.64 (m, 2 H), 1.42 (m, 2 H), 0.94, (t, 3 H, J = 7.3); ^{13}C NMR ($CDCl_3$) δ 192.8, 189.9, 141.1, 116.2, 53.1, 28.1, 28.0, 22.5, 13.7; MS (EI) m/e (rel int) 184 (7), 81 (100); HRMS calcd for $C_{10}H_{16}O_3$ (M^+) 184.1099, found 184.1094.

Representative Procedure for the Synthesis of Cyclobutene Monoketals (6). 1-Hydroxy-1-(1-hexynyl)-2-phenyl-3-methyl-4,4-dimethoxy-2-cyclobutene (6a). A solution of 1-hexyne (0.32 mL, 2.75 mmol) and freshly distilled hexanes (30 mL) was cooled to −5 °C under N_2. *n*-BuLi (1.72 mL, 2.75 mmol) was then added dropwise via syringe, and the resulting solution was stirred for 30 min at −5 °C. A solution of 2-phenyl-3-methyl-4,4-dimethoxy-2-cyclobuten-1-one (0.060 g, 0.275 mmol) and 30 mL of freshly distilled hexanes was cooled to −5 °C under N_2 and then transferrred by cannulation to the hexynyllithium solution. The cloudy white mixture was allowed to stir 4 h at −5 °C. Acetic acid (0.19 mL, 3.3 mmol) was then introduced via syringe and stirring was continued for an additional 5 min. The reaction mixture was then neutralized, worked up, and purified as described for **3a** to provide **6a** (0.062 g, 75% yield) as an oil: IR ($CHCl_3$) 3530, 2240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68 (m, 2 H), 7.37 (m, 2 H), 7.30 (m, 1 H), 3.56 (s, 3 H), 3.53 (s, 3 H), 3.23 (s, 1 H), 2.25 (t, 2 H, J = 7.1), 1.50 (m, 2 H), 1.38 (m, 2 H) 0.86 (t, 3 H, J = 7.4); ^{13}C NMR ($CDCl_3$) δ 146.6, 139.6, 131.3, 128.4, 128.3, 127.8, 103.6, 87.9, 77.5, 76.5, 52.2, 51.7, 30.5, 21.9, 18.7, 13.5, 12.5; MS (EI) m/e (rel int) 300 (5), 115 (100); HRMS calcd for $C_{19}H_{24}O_3$ (M^+) 300.1725, found 300.1697.

1-Hydroxy-1,2-diethenyl-3-*n*-butyl-4,4-dimethoxy-2-cyclobutene (6b): 0.254 g, 72% yield; IR ($CHCl_3$) 3548 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.29 (dd, 1 H, J = 11, 6.4), 6.02 (dd, 1 H, J = 10.8, 6.4), 5.52 (m, 2 H), 5.24 (d, 2 H, J = 10.8), 3.44 (s, 3 H), 3.26 (s, 3 H), 3.04 (s, 1 H), 2.27 (m, 2 H), 1.56 (tt, 2 H, J = 7.8, 7.4), 1.34 (m, 2 H), 0.91 (t, 3 H, J = 7.4); ^{13}C NMR ($CDCl_3$) δ 146.1, 144.7, 137.3, 125.7, 120.1, 115.4, 105.5, 83.4, 51.4, 30.1, 26.9, 22.8, 13.8; MS (EI) m/e (rel int) 238 (0.8), 55 (100); HRMS calcd for $C_{14}H_{22}O_3$ (M^+) 238.1569, found 238.1552.

1-Hydroxy-1-ethenyl-2-phenyl-3-*n*-butyl-4,4-dimethoxy-2-cyclobutene (6c): 0.078 g, 70% yield; IR ($CHCl_3$) 3547 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52 (d, 2 H, J = 7.1), 7.25–7.33 (m, 3 H), 6.13 (dd, 1 H, J = 10.8, 17.6), 5.62 (dd, 1 H, J = 17.3, 2.0), 5.29 (dd, 1 H, J = 10.8, 2.0), 3.52 (s, 3 H), 3.32 (s, 3 H), 3.21 (s, 1 H), 2.60 (m, 2 H), 2.45 (m, 2 H), 1.65 (m, 2 H), 0.94 (t, 3 H, J = 7.4); ^{13}C NMR ($CDCl_3$) δ 146.2, 144.1, 137.7, 132.3, 116.0, 128.3, 128.1, 127.8, 105.3, 83.6, 51.8, 51.3, 29.7, 27.3, 23.1, 13.8; HRMS calcd for $C_{18}H_{25}O_3$ (MH^+) 289.1804, found 289.1797.

1-Hydroxy-1-(1-hexynyl)-2-phenyl-3-*n*-butyl-4,4-dimethoxy-2-cyclobutene (6d): 0.065 g, 67% yield; IR ($CHCl_3$) 3529, 2240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68 (m, 2 H), 7.34 (m, 3 H), 3.55 (s, 3 H), 3.54 (s, 3 H), 3.20 (s, 1 H), 2.38–2.59 (m, 2 H), 2.25 (t, 2 H, J = 7.0), 1.18–1.68 (m, 8 H), 0.92 (t, 3 H, J = 7.4), 0.86 (t, 3 H, J = 7.4); ^{13}C NMR ($CDCl_3$) δ 146.2, 144.6, 131.5, 128.4, 128.3, 127.9, 104.2, 87.8, 77.7, 76.6, 52.1, 51.7, 30.05, 29.4, 27.3, 23.1, 21.8, 18.8, 13.8, 13.6; MS (EI) m/e (rel int) 342 (2), 115 (100), 91 (80), 55 (77); HRMS calcd for $C_{22}H_{30}O_3$ (M^+) 342.2195, found 342.2171.

1-Hydroxy-1,2-diphenyl-3-methyl-4,4-dimethoxy-2-cyclobutene (6e): 0.105 g, 78% yield; IR ($CHCl_3$) 3542 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60 (m, 2 H), 7.19–7.38 (m, 8 H), 3.58 (s, 1 H), 3.55 (s, 3 H), 2.80 (s, 3 H), 2.26 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 146.2, 140.4, 139.0, 131.5, 128.4, 128.04, 128.01, 127.7, 127.0, 126.9, 104.8, 84.7, 52.1, 50.5, 12.3; HRMS calcd for $C_{19}H_{21}O_3$ (MH^+) 297.1491, found 297.1471.

Representative Procedure for the Synthesis Quinones 10, 11, and 12. 2-Phenyl-3-methyl-5-*n*-butyl-2,5-cyclohexadiene-1,4-dione (10c). 1-Hydroxy-1-(1-hexynyl)-2-

phenyl-3-methyl-4,4-dimethoxy-2-cyclobutene (0.054 g, 0.179 mmol) was dissolved in 15 mL of $CHCl_3$ and the solution was stirred at 0 °C. To this was added a solution of concentrated HCl in excess (3 drops) in $CHCl_3$ (3 mL). After 15 min of stirring, the reaction mixture was neutralized with 10% $NaHCO_3$ (15 mL) and $CHCl_3$ (15 mL). The aqueous layer was separated and extracted with portions of $CHCl_3$ (2 × 10 mL). The combined organic layers were washed with brine (2 × 15 mL) and dried ($MgSO_4$). After the solvent was removed in vacuo, the crude product was immediately flushed thru a Florisil plug (6:1 hexanes/ethyl acetate). The solvent was then removed in vacuo and immediately replaced with 20 mL of freshly distilled benzene. The solution was allowed to reflux under N_2 for 1 h and 45 min. The solvent was removed in vacuo and after column chromatography (6:1 hexanes/ethyl acetate) on silica gel afforded **10c** (0.037 g, 80% yield): IR ($CHCl_3$) 1651, 1611 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (m, 3 H), 7.15 (m, 2 H), 6.61 (m, 1 H), 2.49 (m, 2 H), 1.96 (s, 3 H), 1.53 (m, 2 H), 1.42 (m, 2 H), 0.96 (t, 3 H, J = 7.4); ^{13}C NMR ($CDCl_3$) δ 188.4, 187.0, 149.4, 143.4, 141.7, 132.9, 132.2, 129.5, 128.5, 128.1, 29.9, 28.8, 22.4, 14.1, 13.8; MS (EI) m/e (rel int) 254 (20), 212 (100), 197 (46), 115 (66); MS (CI) 255 (100); HRMS calcd for $C_{17}H_{18}O_2$ (M^+) 254.1307, found 254.1314.

2-Phenyl-3,5-di-*n*-butyl-2,5-cyclohexadiene-1,4-dione (10a): 0.028 g, 79% yield; IR ($CHCl_3$) 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (m, 3 H), 7.13 (m, 2 H), 6.59 (m, 1 H), 2.48 (m, 2 H), 2.34 (m, 2 H), 1.19–1.55 (m, 8 H), 0.96 (t, 3 H, J = 7.4), 0.77 (t, 3 H, J = 7.4); ^{13}C NMR ($CDCl_3$) δ 188.1, 187.4, 149.5, 146.0, 143.5, 133.0, 132.1, 129.0, 128.3, 128.1, 31.7, 29.9, 28.8, 27.5, 22.9, 22.5, 13.8, 13.6; MS (EI) m/e (rel int) 296 (42), 211 (100), 197 (84); MS (CI) 297, 279, 215; HRMS calcd for $C_{20}H_{24}O_2$ (M^+) 296.1776, found 296.1761.

2-Phenyl-3-*n*-butyl-5-benzyl-2,5-cyclohexadiene-1,4-dione (10b): 0.025 g, 61% overall yield from **5b**; IR ($CHCl_3$) 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32–7.44 (m, 6 H), 7.11 (m, 4 H), 6.39 (t, 1 H), 3.81 (d, 2 H, J = 2.0), 2.34 (m, 2 H) 1.35 (m, 2 H), 1.21 (m, 2 H), 0.77 (t, 3 H, J = 7.4); ^{13}C NMR ($CDCl_3$) δ 187.8, 187.3, 148.5, 145.9, 143.6, 136.7, 133.0, 132.9, 129.4, 129.0, 128.8, 128.4, 128.1, 126.9, 35.3, 31.7, 27.5, 22.9, 13.6; MS (EI) m/e (rel int) 330 (19), 91 (100); HRMS calcd for $C_{23}H_{22}O_2$ (M^+) 330.1620, found 330.1620.

2-Phenyl-3-*n*-butyl-2,5-cyclohexadiene-1,4-dione (11). At the completion of thermolysis, the benzene solution was cooled to room temperature. K_2CO_3 (10 equv) and Ag_2O (10 equiv) were added, and the suspension was stirred for 30 min. The mixture was filtered through Celite and purified as described for **10c**: 0.024 g, 75% yield; IR ($CHCl_3$) 1654 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41 (m, 3 H), 7.14 (d, 2 H, J = 7.1), 6.83 (d, 1 H, J = 10.1), 6.80 (d, 1 H, J = 9.9), 2.34 (t, 2 H, J = 7.8), 1.33 (m, 2 H), 1.20 (m, 2 H), 0.76 (t, 3 H, J = 7.4); ^{13}C NMR ($CDCl_3$) δ 193.0, 190.7, 145.9, 143.9, 136.6, 136.2, 132.8, 129.0, 128.5, 128.1, 31.7, 27.3, 22.8, 13.6; MS (EI) m/e (rel int) 240 (37), 197 (100); MS (CI) 241, 215; HRMS calcd for $C_{16}H_{16}O_2$ (M^+) 240.1150, found 240.1166.

2-Phenyl-3-methyl-1,4-napthoquinone (12): 0.075 g, 90% yield; IR ($CHCl_3$) 1662 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.13 (m, 2 H), 7.74 (m, 2 H), 7.45 (m, 3 H), 7.23 (s, 2 H), 2.09 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 185.8, 184.2, 146.2, 144.1, 133.7, 133.6, 133.5, 132.1, 129.3, 128.5, 128.1, 126.6, 14.6; HRMS calcd for $C_{17}H_{13}O_2$ (MH^+) 249.0915, found 249.0889.

2,2,3-Trimethoxy-3-cyclobuten-1-one (15). Distilled MeOH was the solvent for the methanolysis of 2,3-di-*tert*-butoxy-4-hydroxy-2-cyclobuten-1-one. **15**: 0.742 g, 71% yield; IR ($CHCl_3$) 1764, 1588 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.48 (s, 1 H), 4.02 (s, 3 H), 3.51 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 188.8, 188.3, 115.1, 111.7, 60.3, 53.1; HRMS calcd for $C_7H_{11}O_4$ (MH^+) 159.0657, found 159.0643.

2-*n*-Butyl-1,4-hydroquinone (16). 1-Hydroxy-1-ethenyl-3-*n*-butyl-4,4-dimethoxy-2-cyclobutene was prepared in the same fashion as **6a** (silica gel chromatography) and hydrolyzed as described for **10c**. The product of the hydrolysis was allowed to stand at ambient temperature under N_2 for 1–3 h to allow for complete rearrangement to the hydroquinone **16**. Column chromatography (6:1 hexanes/ethyl acetate) on silica gel afforded **16** as a white solid (0.026 g, 46% overall yield): mp 79–80.5 °C; IR ($CHCl_3$) 3604, 3360 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.66–6.52 (m, 3 H), 4.40 (s, 2 H), 2.55 (t, 2 H, J = 7.5), 1.58 (m, 2 H), 1.37 (m, 2 H), 0.94 (t, 3 H, J = 7.3); ^{13}C NMR ($CDCl_3$) δ 149.2, 147.3, 129.9, 116.8, 116.0, 113.2, 31.8, 29.7, 22.5, 14.0; HRMS calcd for $C_{10}H_{15}O_2$ (MH^+) 167.1072, found 167.1052.

2-*n*-Butyl-6-benzyl-2,5-cyclohexadiene-1,4-dione (17): 0.039 g, 45% overall yield; IR ($CHCl_3$) 1654, 1612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (m, 5H), 6.49 (m, 1 H), 6.30 (m, 1 H), 3.74 (s, 2 H), 2.42 (m, 2 H), 1.48 (m, 2 H), 1.37 (m, 2 H), 0.93 (t, 3 H, J = 7.3); ^{13}C NMR ($CDCl_3$) δ 188.0, 187.4, 149.7, 148.8, 136.6, 133.0, 132.2, 129.3, 128.8, 126.9, 35.4, 29.9, 28.9, 22.4, 13.8; HRMS calcd for $C_{17}H_{19}O_2$ (MH^+) 255.1385, found 255.1364.

2-*n*-Butyl-5-methyl-2,5-cyclohexadiene-1,4-dione (18). Freshly distilled THF (5 mL) was cooled to −78 °C under N_2. 2-Bromopropene (0.48 mL, 5.44 mmol) was then delivered via syringe, followed by *t*-BuLi (6.39 mL, 5.44 mmol) also via syringe. After the solution was stirred for 20 min, freshly distilled hexanes cooled to −78 °C was transferred by cannulation to the solution. After being stirred an additional 20 min, the solution was warmed to −5 °C for 10 min. A solution of 3-*n*-butyl-4,4-dimethoxy-2-cyclobuten-1-one (0.100 g, 0.543 mmol) and freshly distilled hexanes (20 mL) was cooled to −5 °C under N_2 and then transferred by cannulation to the organolithium solution. The resultant mixture was allowed to stir for 1 h at −5 °C and then quenched with 10% NH_4Cl (10 mL) and diethyl ether (10 mL). Following standard workup and hydrolysis, the product was allowed to ring expand as previously described for **16**. The resulting hydroquinone was then dissolved in freshly distilled toluene, oxidized, and purified as described for **11** to provide compound **18** (0.048 g, 50% overall yield): IR ($CHCl_3$) 1655, 1614 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.57 (s, 1 H), 6.53 (s, 1 H), 2.39 (t, 2 H, J = 7.3), 2.20 (s, 3 H), 1.46 (m, 2 H), 1.36 (m, 2 H), 0.92 (t, 3 H, J = 7.4); ^{13}C NMR ($CDCl_3$) δ 188.3, 187.8, 149.6, 145.5, 133.6, 132.4, 29.9, 28.4, 22.4, 15.4, 13.8; MS (EI) m/e (rel int) 178 (4), 108 (100); HRMS calcd for $C_{11}H_{14}O_2$, 178.0994 (M^+), found 178.0995.

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