Synthetic Utility of Alkenylcyclobutenedione Monoketals. Michael Additions and the Synthesis of a Natural Benzofuranosesquiterpenequinone

Hui Liu, Leah M. Gayo, Robert W. Sullivan, Angela Y. H. Choi, and Harold W. Moore*

Department of Chemistry, University of California, Irvine, California 92717

Received February 7, 1994•

A new synthetic route to highly substituted cyclobutenones is reported. This involves the 1,6-addition of both heteroatom- and carbon-based nucleophiles to 4,4-dimethoxy-3-ethenyl-2-methylcyclobuten-1-one (8) to give further functionalized cyclobutenedione monoketals. These ketals function as precursors to quinones as illustrated by the synthesis of the natural benzofuranosesquiterpene 23.

A useful strategy for the regiospecific synthesis of highly substituted quinones and related aromatic compounds is presented in this paper. The methodology rests on the following three previously reported observations: (1) cyclobutenones of structural type 1 (Scheme 1), bearing unsaturated substituents at position-4, thermally rearrange to quinones (R = alkynyl) or related aromatic compounds (R = alkenyl or aryl);[1] (2) readily available dialkyl squarates can be regiospecifically converted to cyclobutenedione monoketals 2 (precursors to 1) in which the groups a and b stem from a plethora of available organometallic reagents;[2] (3) 3-alkenyl-4-methoxycyclobutenedione 3 was shown to be a valuable synthetic intermediate since it can be readily modified by Michael additions to the 3-alkenyl group thus providing a variety of substituted cyclobutenedione precursors to quinones.[3]

Merger of the above three observations is now reported. Specifically, the cyclobutenedione monoketal 8, like 3, was also observed to undergo facile Michael additions thus demonstrating its utility as a valuable precursor for the regiospecific synthesis of the ring-expanded quinones. The scope of this methodology is illustrated by selected general examples as well as by the synthesis of the naturally occurring sesquiterpene furanoquinone 23.

The synthesis of 8 (72% overall yield) (Scheme 1) represents a potentially general route to cyclobutenedione monoketals bearing an activated (Michael acceptor) alkene moiety. Dimethyl squarate 4 was converted to the cyclobutenone 5 and then to 2-methyl-3,4,4-trimethoxycyclobuten-1-one (6) in 77% yield by sequential treatment with methyllithium followed by methanolysis (TFAA, CH_3OH). Subsequent treatment of 6 with vinyllithium followed by hydrolysis (TFAA, H_2O) of the β-hydroxy enol ether group in 7 gave 8 in 93% yield.

The cyclobutenedione monoketal 8 was observed to undergo facile Michael additions with heteroatom nucleophiles as well as carbon nucleophiles. For example, treatment of 8 with 9-mercaptoanthracene and triethylamine afforded the 1,6-adduct 9 in 77% yield (Scheme 2). Analogously, treatment with thiophenol gave 10 in 72% yield. When HBr (g) was bubbled through a CH_2Cl_2 solution of 8, the cyclobutenedione 11 was realized in 93% yield. In comparison, simple ketal hydrolysis was observed when 8 was treated with 48% HBr. Finally, addition of diethylamine to the alkenyl group in 8 to give 12 was realized in 87% yield.

Addition of carbon-based nucleophiles is of particular interest (Scheme 3). Facile 1,6-addition of organolithium reagents to the alkenyl group was observed with selected examples, e.g., 13 → 14 (48%). Unfortunately, competitive 1,2-additions to the carbonyl group preempted this as a generally useful reaction. Addition of organocuprates, however, is much more reliable and thus provides a potentially general and regiospecific route to cyclobutenedione monoketals and subsequently to quinones and related aromatic compounds. Selected examples are outlined in Scheme 3, e.g., additions of alkyl (15, 77%), aryl (17, 63%), and alkenyl (16, 85%; 18, 73%).

An example of the target-directed synthetic utility of this methodology in the natural products area is outlined in Scheme 4. Specifically, the naturally occurring benzofuranosesquiterpenequinone 23 was synthesized for the first time in 59% overall yield from 8.[4] That is, treatment of 8 with the cuprate obtained from (*E*)-1-bromopropene gave the 1,6-adduct 19 in 82% yield. In a related experiment the same compound was prepared in 85% yield from the cyclobutenedione monoketal 6 by the route generally outlined in Scheme 1 starting with 5-lithio-2(*E*)-pentene.[5]

A careful investigation of the reaction of 19 with 3-lithio-4-methylfuran[6] showed that complete conversion to the desired adduct 21 could not be accomplished even in the presence of excess lithium reagent. Specifically, the ratio of 21 to recovered 19 was approximately 2:1 throughout a series of experiments in which the lithiofuran concentration was varied between 4–11 equiv. This concentration independence was shown to be due to competitive reactions involving 1,2-addition to the carbonyl and proton abstraction from the homoenolic position of the pentenyl side chain. That is, when the reaction mixture was quenched

• Abstract published in *Advance ACS Abstracts*, April 15, 1994.

(1) For a detailed review of this subject see: Moore, H. W.; Yerxa, B. R. *ChemTracts* **1992**, *5*, 273.

(2) (a) Gayo, L. M.; Winters, M. P.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 6896. (b) Liebeskind, L. S.; Granberg, K. L.; Zhang, J. *J. Org. Chem.* **1992**, *57*, 4345.

(3) Xu, S.; Yerxa, B. R.; Sullivan, R. W.; Moore, H. W. *Tetrahedron Lett.* **1991**, *32*, 1129.

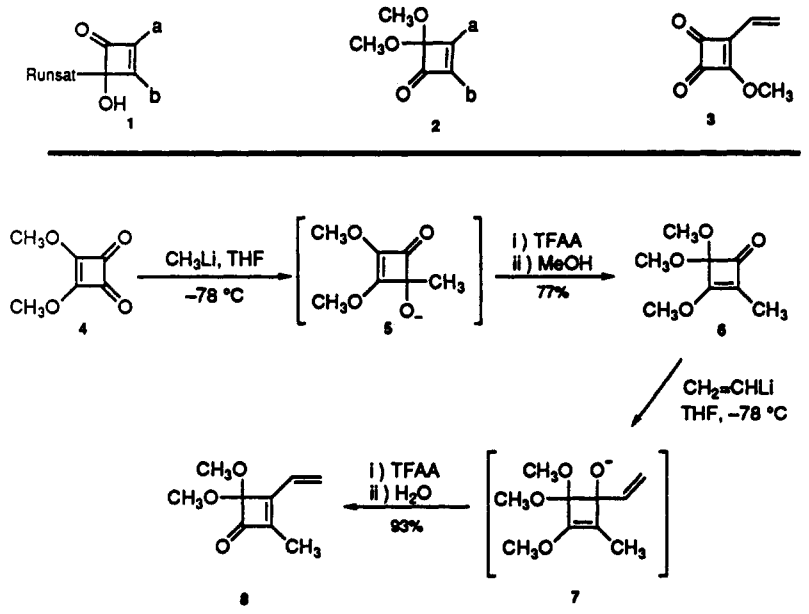
(4) This is one of three benzofuranosesquiterpenes recently isolated from *Ligularia virgaurea* Mattf., a traditional Chinese medicinal herb which has been used for the cure of coughs and inflammation. See: Jia, Z.-J.; Chen, H.-M. *Phytochemistry* **1991**, *30*, 3132. *A Dictionary of the Traditional Chinese Medicines*; Jiangsu College of New Medicine: Shanghai, 1986; p 2349.

(5) Blokhin, A. V.; Kurts, A. L.; Matveeva, E. D.; Grishin, Yu, K.; Bazhenov, D. V.; Bundel, Yu. G. *Vestn. Mosk. Univ., Ser. 2: Khim.* **1988**, *29*, 286. See: *Chem. Abstr.* **1989**, *110*, 114320z.

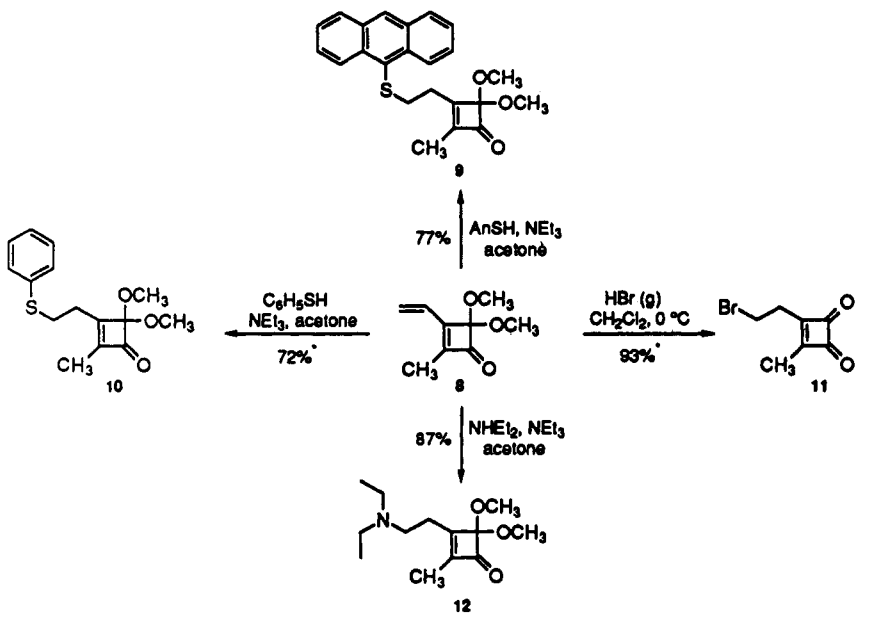
(6) Reich, H. J.; Olson, R. E. *J. Org. Chem.* **1987**, *52*, 2315.

0022-3263/94/1959-3284$04.50/0

Scheme 1



Scheme 2



[a] Compounds 10 and 11 readily eliminate thiophenol and HBr, respectively; yields are based on crude material. Compound purity >95% based on ^{1}H NMR.

with D_2O, deuterocyclobutenone **20** was realized along with the adduct **21** after selective hydrolysis with aqueous HCl in cold $CHCl_3$. This problem was circumvented when the cerium salt of the furan was employed.[7] Here the adduct **21** was realized in 93% yield and no starting cyclobutenone **19** was detected.

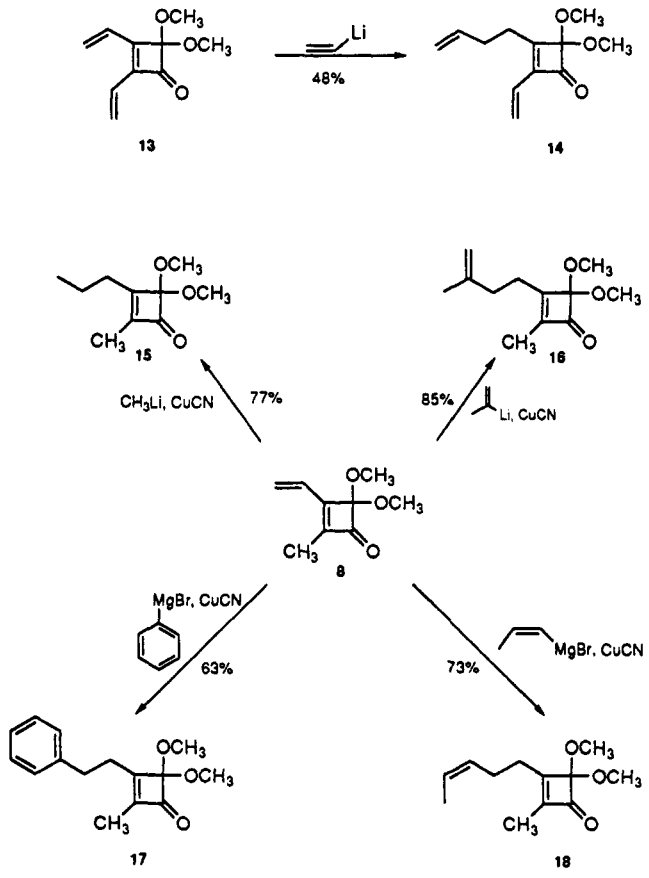
Thermolysis of **21** (refluxing toluene) gave the hydroquinone **22**. This was immediately treated with Ag_2O or air to give **23** in 77% yield.

Previously, the structure of **23** was based upon spectral data alone and this did not allow an unambiguous distinction to be made between the isomeric structures **23–26**.[4] Thus by routes analogous to the above using the appropriate cuprates and furans, quinones **24** (66%), **25** (29%), and **26** (27%) were prepared starting with the cyclobutenedione monoketal **8**. Comparison of the ^{13}C NMR chemical shifts for the quinones **23–26** with those reported for the natural product confirms structure **23** for the natural quinone. These data (Table 1) show only minor differences in chemical shifts (Δ = 0.2–0.6 ppm) between those of **23** and the reported data for the natural product. In contrast, significant differences are revealed for **24**, **25**, **26** and the natural quinone.

In conclusion, the significant points of this work are the following: (1) new methodology is presented which allows efficient modification of the alkenyl group of alkenylcyclobutenedione monoketals such as **8** *via* facile 1,6-addition reactions of a variety of nucleophiles; (2) this provides additional versatility to the quinone syntheses stemming from the ring expansion of cyclobutenones bearing an unsaturated group at the 4-position; (3) these points are combined in the regiospecific syntheses of a series of benzofuranosesquiterpenequinones which allowed the unambiguous assignment of one of these (**23**), and this further constitutes the first total synthesis of the natural product.

(7) Imamoto, T.; Sugiura, Y.; Takyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.

Scheme 3



Experimental Section

2-Methyl-3,4,4-trimethoxy-2-cyclobuten-1-one (6). Under an atmosphere of nitrogen MeLi·LiBr (1.5 M in ether, 14.7 mL, 22 mmol) was added dropwise over 15 min to a solution of dimethyl squarate (2.84 g, 20 mmol) in THF (150 mL) at −78 °C. After stirring for 20 min at −78 °C, trifluoroacetic anhydride (TFAA) (4.41 g, 21 mmol) was added dropwise over 10 min. After stirring for an additional 20 min at −78 °C, anhydrous methanol (mL) was added and the cooling bath was removed. After 20 min the reaction was quenched with ether–water (40 mL–40 mL) and separated. The aqueous layer was extracted with ether (40 mL × 2). The combined organic phase was washed with 10% $NaHCO_3$ (30 mL) and brine (30 mL) and dried over $MgSO_4$. Flash chromatography (silica gel, 4:1, 2:1 hexanes/ethyl acetate) afforded **6** as a pale yellow oil (2.66 g, 77%): IR (neat) 1766, 1627, 1459, 1388, 1350, 1257, 1086, 1037, 990, 917 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.10 (3 H, s), 3.47 (6 H, s), 1.72 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 182.9, 127.7, 113.0, 59.6, 53.4 (2 C), 6.4; LRMS *m/e* 172 (M^+, 47), 157 (100), 141 (12), 129 (21); HRMS calcd for $C_8H_{12}O_4$ 172.0736, found 172.0729.

4,4-Dimethoxy-3-ethenyl-2-methyl-2-cyclobuten-1-one (8). A solution of 2-methyl-3,4,4-trimethoxy-2-cyclobuten-1-one (**6**) (0.516 g, 3.00 mmol) and 30 mL of freshly distilled THF in a dry 100-mL round-bottom flask was stirred under an atmosphere of nitrogen at −78 °C. Vinyllithium (3.91 mL, 9.00 mmol) was then introduced dropwise *via* syringe. The resulting solution was allowed to stir 30 min; trifluoroacetic anhydride (TFAA) (0.636 mL, 4.50 mmol) was then added dropwise *via* syringe. After stirring an additional 15 min, the reaction mixture was 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 over $MgSO_4$. Removal of the solvent *in vacuo* followed by column chromatography (4:1 hexanes/ethyl acetate) on Florisil provided **8** (0.467 g, 93%) as a light yellow oil: IR ($CHCl_3$) 2943, 1755, 1635, 1413, 1255, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.67 (1 H, dd, J = 17.6, 10.9 Hz), 6.06 (1 H, dd, J = 17.6, 1.2 Hz), 5.74 (1 H, dd, J = 10.9, 1.2 Hz), 3.42 (6 H, s), 1.80 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.6, 172.9, 151.0, 127.3, 124.9, 116.9, 53.4, 7.7; MS (CI) *m/e* 169, 137; HRMS calcd for $C_9H_{13}O_3$ (MH^+) 169.0865, found 169.0858.

3-[2-(9-Anthracenylthio)ethyl]-4,4-dimethoxy-2-methyl-2-cyclobuten-1-one (9). See Representative Procedure for Sulfur Nucleophilic Addition (below): 77% yield; yellow oil; IR ($CHCl_3$) 2938, 1765, 1635, 1438, 1266, 1094 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.91 (2 H, d, J = 8.8 Hz), 8.50 (1 H, s), 8.03 (2 H, d, J = 8.3 Hz), 7.61 (2 HH, td, J = 7.7, 1.3 Hz), 7.51 (2 H, td, J = 7.5, 1.1 Hz), 3.31 (6 H, s), 3.19 (2 H, t, J = 7.6 Hz), 2.66 (2 H, t, J = 7.6 Hz), 1.63 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6, 179.1, 153.1, 134.7, 131.8, 129.4, 129.1, 128.0, 127.0, 126.8, 125.5, 116.4, 53.1, 33.3, 28.0, 7.8; HRMS for $C_{23}H_{22}O_3S$ 378.1290, found 378.1258.

Representative Procedure for Sulfur Nucleophilic Addition: 4,4-Dimethoxy-2-methyl-3-[2-(phenylthio)ethyl]-2-cyclobuten-1-one (10). To a flask containing 3-ethenyl-4,4-dimethoxy-2-methylcyclobuten-1-one (**8**) (0.0259 g, 0.1542 mmol) in acetone (5 mL) was added triethylamine in excess (1 drop). Thiophenol (0.024 mL, 0.232 mmol) was then introduced *via* syringe, and the resulting solution stirred at room temperature for 2 h. Removal of most of the solvent *in vacuo* followed by column chromatography (3:1 hexanes/ethyl acetate, 3 drops acetic acid/100 mL solvent) on Florisil provided **10** (0.310 g) as an oil in 72% yield: IR ($CHCl_3$) 2938, 1772, 1603, 1437, 1092 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (2 H, m), 7.31(2 H, m), 7.22 (1 H, m), 3.44 (6 H, s), 3.22 (2 H, t, J = 7.4 Hz), 2.86 (2 H, t, J = 7.4 Hz), 1.78 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.8, 178.7, 153.4, 138.2, 135.0, 129.9, 129.1, 126.6, 53.2, 30.6, 27.1, 7.8; HRMS calcd for $C_{15}H_{18}O_3S$ 278.0977, found 278.0959.

3-(2-Bromoethyl)-4-methyl-3-cyclobutene-1,2-dione (11). Hydrogen bromide gas was bubbled into a flask containing 4,4-dimethoxy-3-ethenyl-2-methylcyclobuten-1-one (**8**) (0.0300 g, 0.1786 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After stirring 5 min, the reaction was neutralized with 10% $NaHCO_3$ (10 mL) and diethyl ether (10 mL). The aqueous layer was then separated and extracted with portions of diethyl ether (2 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried over $MgSO_4$. Removal of the solvent *in vacuo* provided **11** (0.0338 g) in 93% yield (purity greater than 95% based on ^1H NMR) as an oil: IR ($CHCl_3$) 3027, 1773, 1711, 1420, 1364, 1229 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.73 (2 H, t, J = 7.0 Hz), 3.39 (2 H, t, J = 7.0 Hz), 2.41 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.7, 198.9, 198.7, 198.2, 29.8, 26.5, 11.7; HRMS calcd for $C_7H_8BrO_2$ (MH^+) 202.9708, found 202.9702.

3-[2-(Diethylamino)ethyl]-4,4-dimethoxy-2-methyl-2-cyclobuten-1-one (12). To a flask containing 4,4-dimethoxy-3-ethenyl-2-methylcyclobuten-1-one (**8**) (0.0202 g, 0.1190 mmol) in acetone (5 mL) was added triethylamine in excess (1 drop). Excess diethylamine (3 drops) was then introduced, and the resulting solution was stirred at room temperature for 1 h. Removal of the solvent *in vacuo* provided **12** (0.0250 g) in 87% yield (purity greater than 95% based on ^1H NMR) as a brown oil: IR (neat) 3386, 2929, 1764, 1635, 1462, 1256, 1097, 1068 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.42 (6 H, s), 2.77 (2 H, m), 2.67 (2 H, t, J = 8.4 Hz), 2.55 (4 H, q, J = 7.3 Hz), 1.75 (3 H, s), 1.01 (6 H, t, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.8, 180.4, 152.8, 116.3, 53.0, 49.2, 46.4, 24.7, 11.7, 7.7; HRMS calcd for $C_{13}H_{24}O_3N$ (MH^+) 242.1756, found 242.1731.

3-(3-Butenyl)-4,4-dimethoxy-2-ethenyl-2-cyclobuten-1-one (14). The representative procedure for organolithium additions was followed using vinyllithium and cyclobutenone monoketal **13**[2a] to give **14** in 48% yield as a light yellow oil: IR ($CHCl_3$) 2944, 1755, 1647, 1457, 1412, 1267, 1244, 1094 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.27 (1 H, dd, J = 17.6, 11.2 Hz), 6.13 (1 H, dd, J = 17.6, 2.0 Hz), 5.85 (1 H, m), 5.58 (1 H, dd, J = 11.2, 2.0 Hz), 5.10 (1 H, dq, J = 17.1, 1.5 Hz), 5.04 (1 H, dq, J = 10.3, 1.5 Hz), 3.48 (6 H, s), 2.70 (2 H, t, J = 7.4 Hz), 2.45 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 177.6, 149.9, 136.7, 125.4, 123.1, 116.5, 115.9, 53.3, 30.5, 27.0; LRMS (CI) 209, 177, 117, 99; HRMS calcd for $C_{12}H_{17}O_3$ (MH^+) 209.1178, found 209.1173.

4,4-Dimethoxy-2-methyl-3-propyl-2-cyclobuten-1-one (15). The procedure for preparation of **16** was followed except MeLi (1.4 M in ether) was substituted for 2-bromopropene and *t*-BuLi. Cyclobutenone **15** was obtained as a light yellow oil in 77% yield from **8**: IR ($CDCl_3$) 1763, 1635, 1461, 1382, 1252, 1094, 955 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.43 (6 H, s), 2.50 (2 H, t, J = 7.6 Hz), 1.75 (3 H, s), 1.69 (2 H, hex, J = 7.5 Hz), 0.98 (3 H, t, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1, 182.1, 152.4, 116.5, 53.1 (2 C), 29.3, 20.2, 14.4, 7.7; LRMS *m/e* 184 (M^+, 28), 169 (99),

Scheme 4

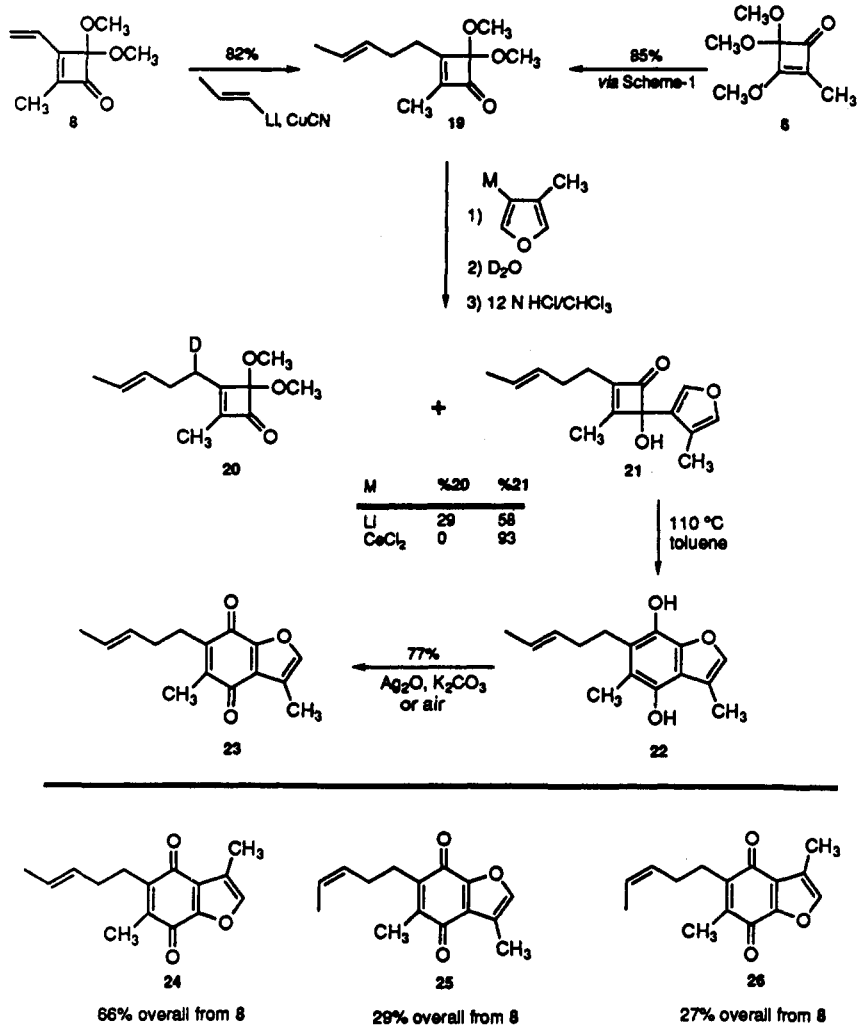


Table 1. Carbon NMR Comparisons of Furanylquinones (in ppm)

C-shift	nat 23	synth 23	24	25	26
a	184.2	184.6	184.0	184.5	184.0
b	175.3	175.7	176.2	175.7	176.2
c	151.2	151.4	151.4	151.3	151.3
d	144.5	144.7	144.8	144.7	144.7
e	143.1	143.3	144.6	143.2	144.6
f	141.1	141.4	140.1	141.3	140.1
g	129.6	129.8	129.9	128.7	128.8
h	126.3	126.6	126.6	126.5	126.6
i	125.9	126.3	126.2	125.3	125.3
j	120.6	120.9	121.0	120.8	120.9
k	31.4	31.7	31.8	26.1	26.5
l	26.3	26.5	26.9	25.9	26.1
m	17.6	17.9	17.9	12.7	12.7
n	11.7	12.3	11.9	12.2	11.9
o	8.3	8.7	8.6	8.6	8.5

153 (23), 141 (24), 113 (75), 69 (100); HRMS calcd for $C_{10}H_{16}O_3$ 184.1099, found 184.1098.

4,4-Dimethoxy-2-methyl-3-(3-methyl-3-butenyl)-2-cyclobuten-1-one (16). To freshly distilled THF (10 mL) was added dropwise *t*-BuLi (1.7 M in pentane, 1.8 mL, 3.0 mmol) at −78 °C under nitrogen. The solution immediately turned yellow. 2-Bromopropene (184 mg, 1.50 mmol) was added dropwise and the mixture was warmed up to −23 °C for about 5 min while the yellow color faded. The reaction mixture was recooled to −78 °C. CuCN (64 mg, 0.75 mmol) was added and the mixture was stirred at −78 °C for 2 h. A solution of freshly prepared cyclobutenone 8 (126 mg, 0.75 mmol) in THF (5 mL) was cooled to −78 °C and added over 10 min, *via* cannula, to the above cuprate. After stirring for an additional 10 min at −78 °C, the reaction mixture was quenched with 10% NH_4Cl (30 mL) and ether (30 mL), filtered, and separated. The aqueous layer was extracted with ether (20 mL × 2). The combined organic phase was washed with 10% $NaHCO_3$ (20 mL) and brine (20 mL), and dried over $MgSO_4$. Flash chromatography (silica gel, 2:1 pentane/ether) afforded **16** (134 mg, 85% yield) as a light yellow oil: IR (neat) 3077, 2941, 1763, 1636, 1448, 1259, 1094, 1066, 890 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (1 H, s), 4.73 (1 H, s), 3.46 (6 H, s), 2.70 (2 H, t, J = 7.9 Hz), 2.36, (2 H, t, J = 7.9 Hz), 1.77 (6 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0, 181.4, 152.5, 144.2, 116.5, 110.6, 53.3 (2 C), 33.9, 25.6, 22.6, 7.8; LRMS *m/e* 195 (10), 182 (54), 179 (10), 167 (94), 163 (37), 107 (100); HRMS calcd for $C_{11}H_{15}O_3$ (M − CH_3) 195.1021, found 195.1019.

Representative Procedure for Organolithium Additions: 4,4-Dimethoxy-2-methyl-3-(2-phenylethyl)-2-cyclobuten-1-one (17). THF (30 mL) was added to a flask containing 4,4-dimethoxy-3-ethenyl-2-methylcyclobuten-1-one (8) (0.0450 g, 0.2679 mmol) and cooled to −78 °C under an atmosphere of nitrogen. Phenyllithium (0.74 mL, 1.34 mmol) was then introduced dropwise *via* syringe. After stirring 2 h at −78 °C, the reaction mixture was quenched with 5% NH_4Cl (5 mL) and diethyl ether (10 mL). The aqueous layer was separated and extracted with portions of diethyl ether (2 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried over $MgSO_4$. Removal of the solvent *in vacuo* followed by radial chromatography (5:1 hexanes/ethyl acetate) provided the desired product **17** (0.0150 g) in 23% yield as a light yellow oil: IR ($CHCl_3$) 2944, 1762, 1634, 1454, 1262, 1093 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30, (2 H, m), 7.22 (3 H, m), 3.48 (6 H, s), 2.98 (2 H, t, J = 7.3 Hz), 2.86 (2 H, t, J = 7.3 Hz), 1.56 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.9, 180.5, 153.0, 140.5, 128.6, 128.3, 126.4, 116.5, 53.2, 32.7, 29.0, 7.4; LRMS (EI) m/e 246 (1.3), 231 (8), 203 (10), 91 (100); HRMS calcd for $C_{15}H_{19}O_3$ (MH^+) 247.1334, found 247.1327.

(*Z*)-4,4-Dimethoxy-2-methyl-3-(3-pentenyl)-2-cyclobuten-1-one (18). 1-Propenylmagnesium bromide (15 mmol) prepared

from 1-bromopropene (4:1 cis to trans, 1.27 mL, 15 mmol) and magnesium strips (0.457 g, 19 mmol) in distilled THF (75 mL) was cooled to −10 °C under an atmosphere nitrogen. A solution of CuCN (1.34 g, 15 mmol) and LiCl (1.25 g, 30 mmol) in THF was then introduced. The cloudy mixture was allowed to stir 10 min. A solution of cyclobutenone 8 (0.500 g, 2.976 mmol) and TMSCl (0.65 g, 6 mmol) in THF (25 mL) cooled to −10 °C was then added *via* cannula to the cuprate solution. The reaction was stirred for 1 h at −10 °C and then quenched with 10% NH_4Cl (50 mL) and diethyl ether (50 mL). The aqueous layer was then separated and extracted with portions of diethyl ether (2 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL) and dried over $MgSO_4$. Column chromatography (6:1 hexanes/ethyl acetate) on Florisil afforded 18 (0.457 g, 73% yield) as a light yellow oil: IR ($CDCl_3$) 2944, 1770, 1633, 1445, 1264, 1094, 960 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.52 (1 H, m), 5.38 (1 H, m) 3.47 (6 H, s), 2.59 (2 H, t, J = 7.6 Hz), 2.42 (2 H, q, J = 7.6 Hz), 1.77 (3 H, s), 1.62 (3 H, dd, J = 7.6, 0.7 Hz) (The vinylic proton signals at δ 5.52 and 5.38 each had J = 10.7 Hz, characteristic of cis coupling); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0, 181.5, 152.6, 128.6, 125.6, 116.4, 53.1, 27.1, 24.0, 12.8, 7.7; LRMS (EI) m/e 210 (0.5), 163 (12), 107 (56), 55 (100); HRMS calcd for $C_{12}H_{19}O_3$ (MH^+) 211.1334, found 211.1341.

(*E*)-4,4-Dimethoxy-2-methyl-3-(3-pentenyl)-2-cyclobuten-1-one (19). The procedure for preparation of 16 was followed except *trans*-1-bromopropene was substituted for 2-bromopropene. Cyclobutenone 19 was obtained as a pale yellow oil in 82% yield from 8: IR (neat) 1764, 1636, 1449, 1262, 1094, 1068, 968 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.46 (2 H, m), 3.46 (6 H, s), 2.60 (2 H, t, J = 7.7 Hz), 2.35 (2 H, m), 1.76 (3 H, s), 1.65 (3 H, dd, J = 5.8, 0.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.0, 181.4, 152.5, 129.5, 126.5, 116.5, 53.2 (2 C), 29.5, 27.4, 17.9, 7.8; LRMS m/e 210 (M^+, 5), 195 (25), 179 (31), 167 (100), 163 (48), 107 (88); HRMS calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1251.

(*E*)-4-Hydroxy-3-methyl-4-(4-methylfuran-3-yl)-2-(3-pentenyl)-2-cyclobuten-1-one (21). To a 10-mL round-bottom flask containing 1 mL of freshly distilled THF was added dropwise *t*-BuLi (1.65 M in pentane, 0.73 mL, 1.2 mmol) at −78 °C under an atmosphere of nitrogen. To this yellow solution was added dropwise 3-iodo-4-methylfuran[6] (125 mg, 0.60 mmol). The reaction mixture was warmed up to −23 °C for 5 min and recooled to −78 °C after the yellow color faded and white solids precipitated. Cyclobutenone 19 (21 mg, 0.1 mmol) was then added dropwise with a syringe. After stirring at −78 °C for 30 min, the reaction was quenched with D_2O (2 mL), diluted with water (10 mL), and extracted with ether (15 mL × 2). The ether phase was washed with brine (15 mL), and concentrated with a rotary evaporator. The residue was dissolved in $CHCl_3$ (10 mL) and the resulting solution was cooled to 0 °C. A solution of concentrated HCl (2 drops) in $CHCl_3$ (2 mL) was added. After stirring at 0 °C for 10 min, the reaction was quenched with 10% $NaHCO_3$ (10 mL). The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic phase was washed with brine (15 mL) and dried over $MgSO_4$. Chromatography (silica gel, 7:1, 2:1 hexane/ethyl acetate) afforded the deuterium-substituted cyclobutenone 20 (6.1 mg, 29%) and adduct 21 (14.3 mg, 58%) as a light yellow oil. 21: IR (neat) 3397, 2932, 1751, 1634, 1438, 1378, 1167, 1052, 967 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (1 H, d, J = 1.6 Hz), 7.15 (1 H, br d, J = 1.6 Hz), 5.41 (2 H, m), 3.20 (1 H, s), 2.22 (4 H, m), 2.15 (3 H, s), 1.98 (3 H, d, J = 0.9 Hz), 1.61 (3 H, d, J = 5.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.0, 178.5, 152.7, 140.9, 140.8, 129.6, 126.4, 123.0, 118.5, 91.0, 29.5, 23.4, 17.9, 11.4, 9.1; LRMS m/e 246 (M^+, 33), 231 (29), 217 (24), 191 (100), 163 (86), 135 (36), 109 (58), 91 (24); HRMS calcd for $C_{15}H_{18}O_3$ 246.1256, found 246.1254.

(*E*)-3,5-Dimethyl-6-(3-pentenyl)-4,7-benzofurandione (23). In a 10-mL round-bottom flask cerium(III) chloride (148 mg, 0.6 mmol) was heated with stirring at 150 °C for 2 h under oil pump vacuum (ca. 0.1 mmHg) and cooled to 0 °C.[7] Freshly distilled THF (3 mL) was added with stirring under nitrogen, and stirring was continued at room temperature for 8 h. To a separate 10-mL flask containing 2.5 mL of THF was added dropwise at −78 °C *t*-BuLi (1.7 M in pentane, 0.59 mL, 1 mmol) and then 3-iodo-4-methylfuran (104 mg, 0.5 mmol).[6] The reaction mixture was warmed up to −23 °C for 5 min and recooled to −78 °C. This lithium reagent was added *via* cannula to the above cerium chloride/THF mixture and the whole was stirred at −78 °C for 1 h. A solution of 19 (42 mg, 0.20 mmol) in THF (1 mL) was cooled to −78 °C and added rapidly *via* cannula to the cerium reagent. After stirring at −78 °C for 4 h, the reaction was quenched with 10% NH_4Cl (10 mL) and extracted with ether (10 mL × 3). The combined organic phase was washed with brine (10 mL × 2). After removal of solvent with a rotatory evaporator, the residue was dissolved in 10 mL of $CHCl_3$ and cooled to 0 °C. Chloroform (2 mL) containing 2 drops of 12 N HCl was added dropwise. Upon stirring at 0 °C for 10 min, the reaction was quenched with 10% $NaHCO_3$ (10 mL) and separated. The aqueous layer was extracted with CH_2Cl_2 (15 mL). The combined organic phase was wahsed with brine (15 mL) and dried over Na_2SO_4. After removal of solvent, the residue was subjected to column chromatography (silica gel, 4:1, 2:1 hexane/ethyl acetate) to give 46 mg of 21 (93% yield from 19). The solution of 21 (46 mg) in degased toluene (10 mL) was brought to reflux for 15 min with a preheated oil bath (130 °C) and cooled to room temperature. Air was bubbled in for 1 h. Removal of solvent followed by chromatography (silica gel, 9:1 hexane/ethyl acetate) afforded 23 (35 mg, 72% yield from 19) as a yellow solid: mp 89–90 °C (lit. 90–91 °C);[4] IR (neat) 3124, 2928, 1660, 1532, 1437, 1369, 1318, 1231, 1152, 1030, 969 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (1 H, q, J = 1.0 Hz), 5.45 (2 H, m), 2.61 (2 H, t, J = 7.8 Hz), 2.27 (3 H, d, J = 1.0 Hz), 2.12 (2 H, m), 2.07 (3 H, s), 1.63 (3 H, dd, J = 3.3, 1.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.6, 175.7, 151.4, 144.7, 143.3, 141.4, 129.8, 126.6, 126.3, 120.9, 31.7, 26.5, 17.9, 12.3, 8.7; LRMS m/e 244 (M^+, 100) 229 (47), 215 (26), 190 (36), 169 (16), 131 (10), 69 (52), 55 (32); HRMS calcd for $C_{15}H_{16}O_3$ 244.1099, found 244.1097.

(*E*)-3,6-Dimethyl-5-(3-pentenyl)-4,7-benzofurandione (24). The procedure for preparation of 23 was followed except 2-bromo-4-methylfuran[8] was substituted for 3-iodo-4-methylfuran. Quinone 24 was obtained as a yellow solid in 80% yield from 19: mp 96–97 °C; IR (neat) 3126, 2937, 1656, 1533, 1450, 1372, 1314, 1230, 962 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (1 H, q, J = 1.0 Hz), 5.44 (2 H, m), 2.56 (2 H, t, J = 7.8 Hz), 2.26 (3 H, d, J = 1.0 Hz), 2.11 (2 H, m), 2.07 (3 H, s), 1.61 (3 H, dd, J = 3.4, 1.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.0, 176.2, 151.4, 144.8, 144.6, 140.1, 129.9, 126.6, 126.2, 121.0, 31.8, 26.9, 17.9, 11.9, 8.6; LRMS m/e 244 (M^+, 68), 229 (30), 215 (24), 201 (15), 190 (63), 55 (100); HRMS calcd for $C_{15}H_{16}O_3$ 244.1099, found 244.1099.

(*Z*)-3,5-Dimethyl-6-(3-pentenyl)-4,7-benzofurandione (25). The procedure for the preparation of 23 was followed using 3-iodo-4-methylfuran and the cyclobutenedione monoketal 18 to give 25 in 40% overall yield as a dark orange solid: mp 89–90 °C; IR (KBr) 1661, 1534, 1306, 1232, 690; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (1 H, s), 5.45 (2 H, m), 2.61 (2 H, t, J = 7.7 Hz), 2.27 (3 H, s), 2.20 (2 H, dt, J = 7.7, 7.3 Hz), 2.09 (3 H, s), 1.59 (3 H, d, J = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.5, 175.7, 151.3, 144.7, 143.2, 141.3, 128.7, 126.5, 125.3, 120.8, 26.1, 25.9, 12.7, 12.2, 8.6; HRMS calcd for $C_{15}H_{16}O_3$ (M^+) 244.1099, found 244.1105.

(*Z*)-3,6-Dimethyl-5-(3-pentenyl)-4,7-benzofurandione (26). The procedure for the preparation of 23 was followed using 2-bromo-4-methylfuran and the cyclobutenedione monoketal 18 to give 26 in 37% overall yield as a dark orange solid: mp 93–94 °C; IR (KBr) 1665, 1535, 1306, 1215, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (1 H, d, J = 1.1 Hz), 5.45 (2 H, m), 2.60 (2 H, t, J = 7.7 Hz), 2.22 (3 H, d, J = 1.0 Hz), 2.20 (2 H, dt, J = 7.7, 7.3 Hz), 2.12 (3 H, s), 1.59 (3 H, dd, J = 7.6, 1.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.0, 176.2, 151.3, 144.7, 144.6, 140.1, 128.8, 126.6, 125.3, 120.9, 26.5, 26.1, 12.7, 11.9, 8.5; HRMS calcd for $C_{15}H_{17}O_3$ (MH^+) 245.1178, found 245.1199.

Acknowledgment. The authors thank the National Institutes of Health (GM-36312) for financial support of this work. We are also grateful to Catherine A. Moore for technical assistance and to Smith Kline Beecham for a generous gift of squaric acid.

Supplementary Material Available: Copies of ^{13}C NMR spectra of all compounds (17 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.

(8) Knight, D. W.; Rustidge, D. C. *J. Chem. Soc. Perkin Trans. 1* 1981, 679.