(10 mL), and extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with water (3 × 10 mL) and brine (2 × 10 mL), dried over anhydrous magnesium sulfate, and filtered and the solvent removed in vacuo. The crude product was purified by silica gel chromatography (20% ethyl acetate/hexane) and recrystallization (ether/pentane) to yield an orange solid (12.8 mg, 33%): mp 271–273 °C; TLC (97:3 $CHCl_3/CH_3OH$) R_f 0.20; IR ($CHCl_3$) 1705, 1600 (s), 1330, 970 cm^{-1}; UV λ_{max} 268 (ϵ 20 100), 278 (20 700), 282 (22 100), 449 nm (7800); ^1H NMR δ 2.14 (3 H, s, H-6′), 2.91 (2 H, t, J = 7.1 Hz, H-3′ or H-4′), 2.99 (2 H, t, J = 7.1 Hz, H-4′ or H-3′), 6.62 (1 H, d, J = 2.5 Hz, H-7), 7.18 (1 H, s, H-4), 7.85 (1 H, d, J = 2.5 Hz, H-5), 8.02 (1 H, s, H-1′), 11.40 (1 H, s), 12.15 (1 H, s), 13.21 (1 H, s); DCI (no ionizing gas), m/z (relative intensity) 367 (9), 366 (37), 324 (26), 323 (98), 310 (10), 309 (9), 73 (18), 69 (10), 61 (11), 57 (10), 55 (10), 45 (13), 43 (100), 41 (8); HRMS obsd m/z 366.0749, $C_{20}H_{14}O_7$ requires 366.0740.

Synthetic Versicolorone. To a 500-mL flask equipped with a dropping funnel and reflux condenser were added hydroxyversicolorone (216 mg, 0.56 mmol) and enough tetrahydrofuran (100 mL) to dissolve the material. Water (200 mL) was added, and the mixture was cooled to 0 °C. An aqueous solution of sodium borohydride (21.7 mg/50 mL, 0.57 mmol) was added dropwise, giving a red solution upon addition. After 0.5 h, more sodium borohydride (12 mg, 0.31 mmol) was added, and the reaction mixture was stirred for an additional 1.5 h. The reaction was quenched with 10% aqueous hydrochloric acid and partitioned between ethyl acetate and water. The aqueous layer was reextracted with ethyl acetate, the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed under reduced pressure.

After purification by preparative TLC (40% acetone/hexane) and Chromatotron (50% ethyl acetate/hexane), the product was recrystallized (five times from acetone/water) and dried under vacuum: mp 208–210 °C; UV (EtOH) λ_{max} 222 (ϵ 26 700), 252 (13 300), 264 (16 500), 298 (17 700), 318 (26 400), 468 (6000), 483 nm (6400); IR ($CHCl_3$) 3020, 1700, 1600, 1185, 800, 670 cm^{-1}; ^1H NMR δ 1.94 (2 H, m, H-3′), 2.06 (3 H, s, H-6′), 2.20 (1 H, dt, J = 7.4, 17.6 Hz, H-4′), 2.34 (1 H, dt, J = 7.8, 17.6 Hz, H-4′), 3.38 (1 H, m, H-2′), 3.68 (1 H, dd, J = 6.6, 10.0 Hz, H-1′), 3.75 (1 H, dd, J = 7.6, 10.0 Hz, H-1′), 6.57 (1 H, d, J = 2.6 Hz, H-7), 7.09 (1 H, d, J = 2.6 Hz, H-5), 7.19 (1 H, s, H-4), 11.21 (1 H, br s, 6-OH), 12.18 (1 H, s, 8-OH), 12.82 (1 H, s, 1-OH); MS, m/z (relative intensity) 368 (28), 325 (6), 310 (100), 297 (19), 285 (6); HRMS obsd m/z 368.0905, $C_{20}H_{17}O_7$ requires 368.0896.

Natural Versicolorone (10). A large growth (16 L of medium) of mutant WE-47 was grown as standing cultures for 1 week. The mycelia were filtered, washed well with water, and pulverized in a blender with acetone. The residual cells were extracted with acetone until colorless. The solvent was removed, and the material was extracted with pentane. The residue was preadsorbed and chromatographed on silica gel eluted with 97:3 chloroform/methanol. The fraction containing mainly hydroxyversicolorone was recrystallized several times from ethyl acetate/hexane to afford pure hydroxyversicolorone and a supernatant that was enriched with component A. This material was purified further by using a Chromatotron and was eluted with 50:50 ethyl acetate/hexane. The component A fraction was recrystallized from acetone/water several times to afford an orange powder, which was dried under vacuum for 12 h. Mobility on TLC, MS fragmentation pattern, and the ^1H NMR data were indistinguishable from those of the synthetic material above: mp 209–211 °C (lit.[19] mp 210 °C); $[\alpha]^{25}_D$ 0°.

Alcohol 11. Alcohol **11** was obtained from sodium borohydride reduction of **2** in water (0 °C, 5 min) and isolated by Chromatotron (70:30 ethyl acetate/hexane), dried under vacuum at refluxing toluene temperature for 2 h: mp 245–248 °C; UV λ_{max} (ethanol) 222 (ϵ 24 100), 266 (17 100), 297 (18 300), 316 (21 400), 479 (5500), 545 nm (3000); ^1H NMR (acetone-d_6) δ 1.10 (3 H, d, J = 6.7 Hz, H-6′), 1.4 (2 H, m, H-4′), 1.85 (2 H, m, H-3′), 3.70 (2 H, m, H-2′, H-5′), 3.93 (1 H, dd, J = 11.0, 4.0 Hz, H-1′), 4.14 (1 H, dd, J = 11.0, 5.3 Hz, H-1′), 6.60 (1 H, d, J = 2.3 Hz, H-7), 7.18 (1 H, d, J = 2.3 Hz, H-5), 7.20 (1 H, s, H-4); MS m/z (relative intensity) 370 (8), 368 (11), 358 (13), 339 (20), 310 (43), 297 (23), 285 (21); HRMS calcd 370.1053, obsd 370.1057.

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Registry No. **1**, 14016-29-6; **2a**, 111975-78-1; **2b**, 113794-77-7; **4**, 6807-96-1; **5**, 1162-65-8; **10**, 84062-31-7.

Synthesis of 4-Substituted-3-alkoxy-3-cyclobutene-1,2-diones

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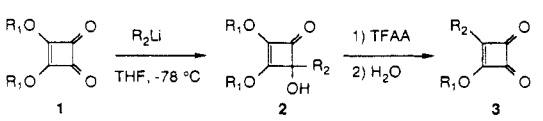
4-Substituted-3-alkoxycyclobutenediones **3** were obtained from dialkoxycyclobutenediones (dialkyl squarates) **1** by the addition of organolithium reagents followed by hydrolysis of the resulting hydroxycyclobutenone **2**. A particularly useful one-pot procedure is described which involves treatment of **1** with the organolithium reagent at −78 °C in THF followed by addition of trifluoroacetic anhydride (TFAA) and an aqueous workup.

Reported here is a general and useful method for the synthesis of a variety of 4-substituted-3-alkoxycyclobutenediones **3** starting from 3,4-dialkoxycyclobutenediones **1**.[1,2] Such compounds are of interest since they can function as starting materials for highly substituted annulated hydroquinones and benzoquinones from the thermolysis of respectively 4-aryl-4-hydroxy- and 4-alkynyl-4-hydroxy(or trialkylsiloxy or allyloxy)cyclobutenones.[3-5] In addition, they are of further interest since

Scheme I

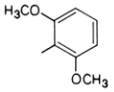
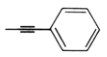
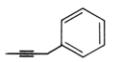
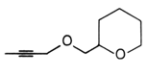
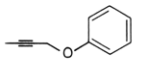
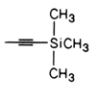


(1) For an independent report of this synthetic methodology, see: Liebeskind, L. S.; Fengl, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.*, following article in this issue.

(2) Diethoxycyclobutenedione (diethyl squarate) is now commercially available from Aldrich Chemical Co.

0022-3263/88/1953-2477$01.50/0

Table I. Synthesis of Cyclobutenols 2 and Cyclobutenediones 3

compd 2	R_1	R_2	% yield[a]	compd 3	method[b]	% yield[a]
2a	Et	n-C_4H_9	68	**3a**	A (1.2)	81
2b	Me	t-C_4H_9	92	**3b**	A (1.2)	63
2c	Me		61	**3c**	A (1.2)	74
2d	Me		77	**3d**	B (2.0)	79
2e	Me		60	**3e**	A (1.7)	50
2f	Me		80	**3f**	A (1.2)	78
2g	Me		59	**3g**	A (1.2)	66
2h	Me		79	**3h**	B (2.0)	72
2i	Me		82	**3i**	*d*	80
2j	Me		95	**3j**	A (1.2)	81
2k	Me		95	**3k**	A (1.2)	58
2l	Me		80	**3l**	B (5.0)	88[c]
2m	Et		88	**3m**	A (1.2)	91
2n	Et		85	**3n**	A (1.2)	82

[a] Yield of products after recrystallization or chromatography. [b] Equivalents of TFAA in parentheses. [c] Crude yield (compd was unstable to silica gel), ^1H NMR showed purity >90%. [d] Thionyl chloride/pyridine was used.

they are reasonable precursors to semisquaric acid analogues **3** (R_1 = H) which are related to the biologically important natural mycotoxin moniliformin, **3** (R_1 = R_2 = H).[6,7]

Our preparation of cyclobutenediones **3** involves 1,2-addition of an organolithium reagent to a dialkoxycyclobutenedione, followed by hydrolysis of the β-hydroxy enol ether moiety in the initially formed 4-substituted-4-hydroxy-2,3-dialkoxycyclobutenones.[8] The addition of a wide variety of organolithium reagents to dialkyl squarates **1** occurs rapidly (5–30 min) at −78 °C in dilute THF. Generally, after quenching the reaction with 10% NH_4Cl at −78 °C, the mixture was extracted with ether, dried ($MgSO_4$), and concentrated in vacuo. The product **2** was isolated in good to excellent yield after flash chromatography. Table I lists some of the 4-substituted-4-hydroxycyclobutenones **2** which were prepared by this method.

Conversion of the alcohol **2** to the desired dione **3** was readily accomplished under mild hydrolytic conditions. Addition of a slight excess of trifluoroacetic anhydride (TFAA) to an ethereal solution of the alcohol **2** and pyridine (method A) gave clean reactions at 0 °C. Only the highly hindered alcohol **2e** required additional TFAA to effect complete reaction. Aqueous workup removed the pyridine and pyridinium salts and generated the dione **3**.

In the absence of pyridine (method B) the disappearance of starting material was slow and excess TFAA or H_2SO_4 were frequently required. In some cases additional reactions occurred. For example, under these conditions the dithiane alcohol **2n** underwent an unusual rearrangement to give compound **4** (single-crystal X-ray structure determination) in 48% yield (Figure 1). However, the de-

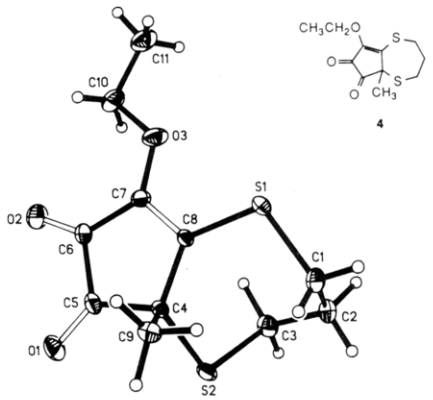


Figure 1. ORTEP plot of **4**.

(3) Liebeskind, L. S.; Jewell, C. F.; Iyer, S. *J. Org. Chem.* **1986**, *51*, 3065. Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067.

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

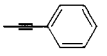
(5) Moore, H. W.; Decker, O. H. W. *Chem. Rev.* **1986**, *86*, 821.

(6) For a review of the synthesis of alkyl-, alkenyl-, and arylcyclobutenediones, see: Schmidt, A. H.; Ried, W. *Synthesis* **1978**, 1.

(7) For a review of moniliformin and related substances, see: West, R. "Oxocarbons"; Academic Press: New York, 1980; pp 101–117.

(8) For other examples of additions of organometallic reagents to cyclobutenediones, see: Dehmlow, E. V.; Schell, H. G. *Chem. Ber.* **1980**, *113*(1), 1. Kraus, J. L. *Tetrahedron Lett.* **1985**, *26*, 1867.

Table II. One-Pot Synthesis of Cyclobutenediones 3

compd 3	R_1	R_2	% yield
3o	Me	CH_3	68
3p	Et	CH_3	90
3a	Et	n-C_4H_9	63
3d	Me		80
3g	Me		84
3h	Me		86
3q	Me		97

sired dione **3n** was isolated in high yield under the conditions of method A. On the other hand, method B was clearly the procedure of choice for the synthesis of **31** since the sensitive ketal group in this compound does not survive the mildly acidic conditions needed to remove residual pyridine.

Recently we have discovered that the cyclobutenediones **3** can be obtained in a one-pot synthesis as follows. After addition of the organolithium reagent to the dialkyl squarate as described previously, the intermediate alkoxide was treated with TFAA at −78 °C. Aqueous workup then gave the desired diones **3** directly and in yields generally better than those realized by the other hydrolytic conditions (Table II). The lower yields for diones **3a** and **3o** reflect the difficulty in obtaining monoaddition of the more nucleophilic saturated organolithium reagents. Addition of methyllithium at −100 °C (isooctane/N_2(l) bath) minimized the amount of dialkylation and allowed isolation of dione **3o** in good yield.

It is noted that all of the transformations reported here can initiate from commercially available diethyl squarate. We have found this compound to undergo rapid transesterification when heated in alcohols. For example, the dimethoxy analogue (dimethyl squarate) can be obtained in 80% yield by refluxing a methanolic solution of diethyl squarate for several hours. This is a significant improvement on the earlier preparation for dimethyl squarate which involved treatment of the disilver salt of squaric acid with methyl iodide.[9]

In conclusion, 4-substituted-3-alkoxy-3-cyclobutene-1,2-diones **3** are readily obtained in good yield from the 1,2-addition products **2** of organolithium compounds with dialkoxycyclobutenediones **1**. The availability of such compounds significantly expands the utility of general quinone and hydroquinone syntheses previously reported.[3-5] As an illustration, we have recently converted dione **3m** to be versatile furochromone precursor khellinone in high yield via thermal ring expansion.[10] The utility of other functionalized diones of the general structure **3** as precursors to natural products is presently being investigated in our laboratory.

Experimental Section

General. All air- or water-sensitive reactions were carried out in flame-dried glassware under a slight positive pressure of argon or nitrogen which was purified by its passage through a column of Drierite. Ethereal solvents were distilled from sodium (benzophenone indicator). Unless specified as "dry", the solvents were of unpurified reagent grade. Removal of solvents at 15–30 Torr was accomplished on a rotary evaporator. Flash column chromatography was performed by using E. Merck silica gel (230–400 mesh). The purity of all products was determined to be >90–95% on the basis of ^{1}H NMR spectra. Elemental analysis of the hydroscopic and thermally unstable products was not deemed feasible.

Dimethoxycyclobutenedione (1). In the best of several runs, 2.00 g (11.75 mmol) of diethoxycyclobutenedione was taken up in 100 mL of freshly distilled methanol and refluxed under argon for 71 h. The solvent was then removed in vacuo and the residual solid was taken up in excess ether and filtered through a small bed of silica gel. The mother liquor was concentrated and cooled to afford 1.34 g (80%) of dimethoxycyclobutenedione, mp 52–53 °C (lit.[9] mp 55 °C).

Representative Procedure for the Preparation of Cyclobutenols 2. 2,3-Dimethoxy-4-hydroxy-4-(2-thienyl)-2-cyclobuten-1-one (2f). All alkylations were carried out by using the same general procedure. The organolithium reagent used was either commercially obtained or prepared by using standard procedures. It should be noted that the cyclobutenols **2**, especially the unsaturated compounds, are thermally unstable and should be stored under refrigeration. Purification of **2** and **3** by flash chromatography is recommended since decomposition may occur upon extended exposure to silica gel.

A solution of 0.60 g (3.70 mmol) of 2-bromothiophene in 50 mL of dry THF at −78 °C under argon was treated with 2.70 mL (3.70 mmol) of 1.37 M n-butyllithium, stirred for 20 min, and then transferred via cannula to a solution of 0.50 g (3.52 mmol) of dimethyl squarate in 125 mL of dry THF at −78 °C. The solution was stirred for 15 min and then quenched by pouring it into a separatory funnel containing 10 mL of 5% NH_4Cl and 20 mL of ether. The aqueous layer was extracted with 2 × 20 mL of ether and the combined organic layers were washed with brine, dried (K_2CO_3), and concentrated in vacuo. Flash chromatography (hexane/ethyl acetate) gave 0.64 g (80% yield) of **2f** as a white solid. Recrystallization from ether gave white crystals: mp 68–69 °C; IR ($CHCl_3$) 3400, 3008, 2956, 1781, 1644, 1635, 1470, 1432, 1348, 1040, and 984 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.51 (s, 1 H), 4.01 (s, 3 H), 4.11 (s, 3 H), 7.03 (dd, J = 1.4, 3.6 Hz, 1 H), 7.10 (dd, J = 1.2, 2.4 Hz, 1 H), 7.33 (dd, J = 1.2, 4.9 Hz, 1 H); MS(EI), m/e (relative intensity) 226 (35), 193 (14), 183 (15), 151 (16), 138 (15), 127 (51), 111 (100), 95 (21), 69 (18); CI 227 (100), 209 (18), 195 (20); HRMS, m/e calcd for $C_{10}H_{10}O_4S$ (M^+) 226.0300, found 226.0297.

Representative Procedure for the Preparation of Cyclobutenediones 3. Method A. 3-Methoxy-4-(2-thienyl)-3-cyclobutene-1,2-dione (3f). A solution of 180 mg (0.796 mmol) of the alcohol **2f** in 12 mL of diethyl ether and 78 μL (0.94 mmol) of pyridine was cooled to 0 °C under argon and treated with 134 μL (0.94 mmol) of trifluoroacetic anhydride. After 15 min, 5 mL of H_2O and 10 mL of ethyl acetate were added. The organic layer was washed with 5-mL portions of H_2O, 10% $NaHCO_3$ (aqueous) and brine, dried ($MgSO_4$), and stripped of solvent. The residue was recrystallized from methylene chloride/hexanes to yield 120 mg (78%) of **3f** as yellow crystals: mp 162–164 °C; IR (KBr) 3100, 1790, 1750, 1600, 1445, and 1370 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.57 (s, 3 H), 7.25 (dd, J = 4.9, 3.8 Hz, 1 H), 7.80 (dd, J = 4.9, 1.1 Hz, 1 H), 7.88 (dd, J = 3.8, 1.1 Hz, 1 H); MS(EI), m/e (relative intensity) 194 (67), 166 (20), 150 (15), 138 (70), 122 (100), 94 (61); HRMS, m/e calcd for $C_9H_6O_3S$ (M^+) 194.0038, found 194.0042.

Representative Procedure for the Preparation of Cyclobutenediones 3. Method B. 3-Methoxy-4-phenyl-3-cyclobutene-1,2-dione (3d). A solution of 2.65 g (12.05 mmol) of alcohol **2d** in 200 mL of diethyl ether at 0 °C under argon was treated with 5.06 g (24.0 mmol) of trifluoroacetic anhydride for 20 min. Three drops of concentrated H_2SO_4 were then added, and after 2 h the reaction was worked up by washing with 100-mL portions of H_2O, 5% $NaHCO_3$ (aqueous), and brine. After drying ($MgSO_4$) the solvent was removed in vacuo and the residue was recrystallized (methylene chloride/hexanes) to give 1.78 g (79%) of **3d** as a yellow solid: mp 149–151 °C (lit.[11] mp 151–152.2 °C) IR ($CHCl_3$) 3021, 1793, 1722, 1605, 1500, 1457, and 1377 cm^{-1}; ^{1}H

(9) Cohen, S.; Cohen, S. G. *J. Am. Chem. Soc.* **1966**, *88*, 1533.
(10) Reed, M. W.; Moore, H. W. *J. Org. Chem.* **1987**, *52*, 3491.
(11) Smutny, E. J.; Caserio, M. C.; Roberts, J. D. *J. Am. Chem. Soc.* **1960**, *82*, 1793.

NMR (300 MHz, $CDCl_3$) δ 4.60 (s, 3 H), 7.52 (m, 3 H), 8.03 (dd, J = 1.2, 6.0 Hz, 2 H); ME(EI), m/e (relative intensity) 188 (11), 160 (8), 145 (32), 117 (22), 89 (100), 63 (28); CI 189 (100); HRMS, m/e calcd for $C_{11}H_8O_3$ (M^+) 188.0473, found 188.0475.

Representative Procedure for the Preparation of Cyclobutenediones 3. One-Pot Synthesis. 3-Ethoxy-4-methyl-3-cyclobutene-1,2-dione (3p). To a solution of 510 mg (3.00 mmol) of diethyl squarate in 15 mL of THF at −78 °C under argon was added 2.0 mL of 1.5 M CH_3Li (3.00 mmol) in Et_2O over a period of 30 s. After 10 min, the solution was quenched with 0.51 mL (3.60 mmol) of trifluoroacetic anhydride, followed by 2.5 mL of 10% NH_4Cl (aqueous). The resulting colorless solution was warmed to room temperature and poured into 30 mL of Et_2O/30 mL of 5% $NaHCO_3$ (aqueous). The aqueous layer was washed with 20 mL of fresh Et_2O, and the combined organic layers were dried with brine and over $MgSO_4$. Removal of the solvent gave a light brown oil which was eluted through silica gel with 1:1 EtOAc/hexanes to give 380 mg of **3p** (90% yield) as a light yellow oil: IR (neat) 1810, 1765, 1605, 1345, 1070, 1020, and 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (t, J = 7 Hz, 3 H), 2.22 (s, 3 H), 4.78 (q, J = 7 Hz, 2 H); MS(EI), m/e (relative intensity) 140 (2), 112 (12), 83 (64); HRMS, m/e calcd for $C_7H_8O_3$ (M^+) 140.0473, found 140.0461.

3-Methoxy-4-(3-phenyl-1-propynyl)-3-cyclobutene-1,2-dione (3i). To a stirred solution of 0.10 g (0.39 mmol) of **2i** in 10 mL of THF was added 0.031 g (0.039 mmol) of pyridine followed by 0.028 mL (46.0 mg, 0.39 mmol) of thionyl chloride. A white precipitate formed upon addition of the thionyl chloride. The yellow suspension was stirred for 5 min at −78 °C, diluted with 15 mL of ether, and then quenched with 10 mL of water. The aqueous layer was extracted with 2 × 10 mL of ether and the combined organic layers were dried over $MgSO_4$. Solvent removal at reduced pressure yielded a light yellow oil that was purified by column chromtography (4:1 hexane/ethyl acetate) to give 70 mg (80% yield) of **3i**: mp 74–75 °C; IR (KBr) 2230, 1796, 1770, 1590, and 1132 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.33 (m, 5 H), 4.45 (s, 3 H), 4.01 (s, 2 H); MS(EI), m/e (relative intensity) 226 (6), 183 (35), 155 (38), 127 (100), 77 (64); MS(CI), 227 (100); HRMS, m/e calcd, for $C_{14}H_{10}O_3$ (M^+) 226.0630, found 226.0629.

6,7-Dioxo-8-ethoxy-5a-methyl-8-cyclopenteno[*b*][1,4]dithiepane (4). A solution of 180 mg (0.49 mmol) of alcohol **2n** in 6 mL of dry THF was stirred under argon while 0.30 mL (2.1 mmol) of trifluoroacetic acid was added dropwise. After 30 min, 1 drop of concentrated H_2SO_4 was added. The resulting red solution was stirred for 15 min, diluted with 20 mL of diethyl ether, and washed with 10% aqueous sodium bicarbonate and brine. The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo. The residue was recrystallized (diethyl ether/hexanes) to yield 75 mg (48%) of 4 as orange crystals: mp 125–126 °C; IR (KBr) 3000, 1760, 1675, 1525, 1380, and 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, J = 7.0 Hz, 3 H), 1.85 (s, 3 H), 2.20 (m, 2 H), 2.95 (m, 3 H), 3.75 (m, 1 H), 4.65 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 15.99, 24.67, 29.97, 30.12, 31.74, 53.36, 67.17, 156.28, 160.34, 174.56, 193.83; MS(EI), m/e (relative intensity) 258 (19), 230 (34), 173, (100), 145 (57), 99 (24), 71 (42), 67 (72), 59 (52); MS(CI), m/e (relative intensity) 259 (100); HRMS, m/e calcd for $C_{11}H_{14}O_3S_2$ (M^+) 258.0384, found 258.0377.

4-*n*-Butyl-2,3-diethoxy-4-hydroxy-2-cyclobuten-1-one (2a): pale yellow oil; IR (neat) 3420, 2960, 1780, 1630, 1335, and 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.0 Hz, 3 H), 1.29 (t, J = 7.0 Hz, 3 H), 1.32 (m, 4 H), 1.41 (t, J = 7.1 Hz, 3 H), 1.80 (m, 2 H), 2.60 (s, 1 H), 4.28 (q, J = 7.1 Hz, 2 H), 4.45 (m, 2 H); MS(EI), m/e 228, 210, 154, 125, 111, 97; HRMS, m/e calcd for $C_{12}H_{20}O_4$ (M^+) 228.1361, found 228.1355.

4-*tert*-Butyl-2,3-dimethoxy-4-hydroxy-2-cyclobuten-1-one (2b): white solid, mp 79–80 °C; IR ($CHCl_3$) 2950, 1767, 1634, 1465, 1340, 1059, and 976 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9 H), 2.26 (s, 1 H), 3.96 (s, 3 H), 4.14 (s, 3 H); MS(EI), m/e (relative intensity) 200 (26), 172 (7), 157 (11), 143 (100), 125 (16), 97 (16), 87 (27); MS(CI), m/e (relative intensity) 201 (100); HRMS calcd for $C_{10}H_{16}O_4$ (M^+) 200.1048, found 200.1032.

2,3-Dimethoxy-4-hydroxy-4-(2-propen-2-yl)-2-cyclobuten-1-one (2c): pale yellow oil; IR (neat) 3422, 2961, 1781, 1633, 1471, 1345, 1075, and 1031 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.82 (t, J = 1.1 Hz, 3 H), 3.05 (s, 1 H), 3.96 (s, 3 H), 4.09 (s, 3 H), 5.11 (s, 1 H), 5.28 (s, 1 H); MS(EI), m/e (relative intensity) 184 (9), 169 (9), 156 (7), 141 (25), 124 (18), 113 (55), 109 (20), 98 (25), 81 (51), 69 (75), 59 (37), 53 (100); MS(CI), m/e (relative intensity) 185 (100), 167 (47); HRMS m/e calcd for $C_9H_{12}O_4$ (M^+) 184.0735, found 184.0731.

2,3-Dimethoxy-4-hydroxy-4-phenyl-2-cyclobuten-1-one (2d): white solid, mp 96–98 °C; IR ($CHCl_3$) 3467, 3005, 2952, 1772, 1632, 1464, 1341, 1042, 992, and 841 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.28 (s, 1 H), 4.01 (s, 3 H), 4.06 (s, 3 H), 7.35 (m, 3 H), 7.53 (d, J = 9.1 Hz, 2 H); MS(EI), m/e (relative intensity) 220 (54), 205 (38), 145 (20), 105 (100), 89 (30); MS(CI), m/e (relative intensity) 221 (100), 203 (28), 189 (98); HRMS, m/e calcd for $C_{12}H_{12}O_4$ (M^+) 220.0735, found 220.0745.

2,3-Dimethoxy-4-(2,6-dimethoxyphenyl)-4-hydroxy-2-cyclobuten-1-one (2e): white solid, mp 123–125 °C; IR ($CHCl_3$) 3500, 3004, 2952, 1781, 1644, 1637, 1600, 1593, 1480, 1470, 1435, 1339, 1251, 1110, 1038, and 840 cm^{-1}; ^1H NMR δ (250 MHz, $CDCl_3$) δ 3.88 (s, 6 H), 3.97 (s, 3 H), 4.08 (s, 3 H), 5.80 (s, 1 H), 6.64 (d, J = 8.4 Hz, 2 H), 7.25 (t, J = 8.4 Hz, 1 H); MS(EI), m/e (relative intensity) 280 (20), 249 (13), 237 (24), 221 (17), 205 (23), 194 (26), 179 (32), 165 (33), 149 (26), 121 (30), 107 (16), 91 (100), 76 (32); MS(CI), m/e (relative intensity) 281 (15), 263 (57), 249 (100); HRMS, m/e calcd for $C_{14}H_{16}O_6$ (M^+) 280.0947, found 280.0952.

2,3-Dimethoxy-4-(2-furyl)-4-hydroxy-2-cyclobuten-1-one (2g): white solid, mp 78–80 °C; IR ($CHCl_3$) 3400, 3042, 3012, 2960, 1782, 1643, 1632, 1470, 1350, 1152, 1053, 1014, and 982 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 1 H), 4.00 (s, 3 H), 4.08 (s, 3 H), 6.44 (m, 2 H), 7.39 (m, 1 H); MS(EI), m/e (relative intensity) 210 (77), 182 (65), 167 (37), 139 (44), 122 (33), 111 (100), 95 (66), 68 (54); MS(CI), m/e (relative intensity) 211 (100), 193 (13), 179 (11); HRMS, m/e calcd for $C_{10}H_{10}O_5$ (M^+) 210.0528, found 210.0522.

2,3-Dimethoxy-4-hydroxy-(2-phenyl-1-ethynyl)-2-cyclobuten-1-one (2h): pale yellow oil; IR ($CHCl_3$) 3580, 3380, 3030, 2960, 2238, 1785, 1635, and 1445 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.38 (s, 1 H), 3.95 (s, 3 H), 4.20 (s, 3 H), 7.33 (m, 5 H); MS(EI), m/e (relative intensity) 244 (3), 243 (5), 229 (21), 158 (13), 145 (27), 129 (100); MS(CI), m/e (relative intensity) 245 (100), 227 (45), 143 (14); HRMS m/e, calcd for $C_{14}H_{12}O_4$ (M^+) 244.0735, found 244.0735.

2,3-Dimethoxy-4-hydroxy-4-(3-phenyl-1-propynyl)-2-cyclobuten-1-one (2i): white solid, mp 86–87 °C; UV (CH_3OH) 253 nm, ϵ 10500; IR ($CHCl_3$) 3575, 3439, 2997, 2950, 2230, 1780, 1640, 1420, 1035, and 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.07 (s, 1 H), 3.63 (s, 2 H), 3.95 (s, 3 H), 4.15 (s, 3 H), 7.25 (m, 5 H); MS(EI), m/e (relative intensity) 258 (0.1), 198 (2), 127 (22), 77 (7); MS(CI), m/e (relative intensity) 259 (10), 243 (10), 228 (15), 227 (100); HRMS, m/e calcd for $C_{15}H_{14}O_4$ (M^+) 258.0892, found 258.0876.

4-[3-(Benzyloxy)-1-propynyl]-2,3-dimethoxy-4-hydroxy-2-cyclobuten-1-one (2k): pale yellow oil; IR ($CHCl_3$) 3360, 1795, 1650, 1475, 1355, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.72 (s, 1 H), 3.95 (s, 3 H), 4.18 (s, 3 H), 4.24 (s, 2 H), 4.58 (s, 2 H), 7.33 (m, 5 H); MS(EI), m/e (relative intensity) 91 (100), 81 (22), 79 (27), 77 (29), 67 (39), 66 (26), 65 (35), 53 (21), 51 (32); MS(CI), m/e (relative intensity) 289 (100), 271 (30), 257 (20), 183 (72), 181 (90), 107 (61), 91 (36); HRMS, m/e (M^+) calcd for $C_{16}H_{16}O_5$ 288.0998, found 288.1017.

2,3-Dimethoxy-4-hydroxy-4-[3-[(tetrahydropyran-2-yl)-oxy]-1-propynyl]-2-cyclobuten-1-one (2j): pale yellow oil; IR ($CHCl_3$) 3580, 3500–3200, 3030, 2950, 1785, 1640, 1355, and 1025 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.65 (m, 6 H), 3.52 (m, 1 H), 3.82 (m, 1 H), 3.98 (s, 3 H), 4.20 (s, 3 H), 4.35 (d, 2 H, J = 2.0 Hz), 4.83 (m, 1 H); MS(EI), m/e (relative intensity) 166 (35), 138 (44), 123 (100); MS(CI), m/e (relative intensity) 167 (100), 121 (20); HRMS, m/e calcd for $C_{14}H_{18}O_6$ (M^+) 282.1103, found 282.1080.

2,3-Dimethoxy-4-[2-(2-methyl-1,3-dioxolan-2-yl)-1-ethynyl]-4-hydroxy-2-cyclobuten-1-one (2l): white solid, mp 96–98 °C; IR ($CHCl_3$) 3400, 1790, 1650, 1475, 1350, 1035, and 865 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69 (s, 3 H), 3.90 (s, 1 H), 3.95 (s, 3 H), 4.05 (m, 4 H), 4.17 (s, 3 H); MS(EI), m/e (relative intensity) 254 (3), 211 (35), 183 (98), 87 (60), 53 (27), 43 (100); MS(CI), m/e (relative intensity) 255 (82), 237 (20), 223 (34), 212 (24), 211 (100); HRMS, m/e calcd for $C_{12}H_{14}O_6$ (M^+) 254.0790, found 254.0782.

2,3-Diethoxy-4-hydroxy-4-[2-(trimethylsilyl)-1-ethynyl]-2-cyclobuten-1-one (2m): white solid, mp 90.5–91.5

°C; IR (KBr) 3500–3100, 2975, 2160, 1780, 1625, 1385, 1340, 1035, and 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.16 (s, 9 H), 1.30 (t, J = 7.1 Hz, 3 H), 1.44 (t, J = 7.1 Hz, 3 H), 3.13 (s, 1 H), 4.30 (q, J = 7.1 Hz, 2 H), 4.52 (q, J = 7.1 Hz, 2 H); MS(EI), m/e (relative intensity) 268 (6), 253 (19), 239 (16), 225 (39), 211 (100), 197 (49), 165 (35), 127 (74), 123 (26), 111 (46), 109 (32), 99 (90), 75 (99), 73 (86); HRMS, m/e calcd for $C_{13}H_{20}O_4Si$ (M^+) 268.1131, found 268.1121.

2,3-Diethoxy-4-hydroxy-4-(2-methyl-1,3-dithian-2-yl)-2-cyclobuten-1-one (2n): pale yellow oil; IR ($CHCl_3$) 3470, 3000, 1760, 1635, 1430, 1390, 1335, 1050, 930, and 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, 3 H, J = 7.1 Hz), 1.44 (t, 3 H, J = 7.1 Hz), 1.37 (s, 3 H), 1.82 (m, 1 H), 2.10 (m, 1 H), 2.55 (dd, 1 H, J = 5.0, 3.4 Hz), 2.60 (dd, 1 H, J = 4.8, 3.5 Hz), 3.00 (ddd, 1 H, J = 12.8, 11.2, 3.1 Hz), 3.40 (ddd, 1 H, J = 12.8, 11.2, 3.1 Hz), 3.82 (s, 1 H), 4.37 (q, J = 7.1 Hz, 2 H), 4.51 (m, 2 H); MS(EI), m/e (relative intensity) 304 (2), 134 (69), 133 (100), 115 (27), 59 (55); MS(CI), m/e (relative intensity) 305 (27), 289 (30), 288 (21), 287 (100), 259 (68), 199 (51), 107 (32); HRMS, m/e calcd for $C_{13}H_{20}O_4S_2$ (M^+) 304.0828, found 304.0798.

3-Ethoxy-4-*n*-butyl-3-cyclobutene-1,2-dione (3a): pale yellow oil; IR (neat) 2960, 1810, 1765, 1605, 1390, 1355, and 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3 H), 1.37 (m, 2 H), 1.46 (t, J = 7.1 Hz, 3 H), 1.64 (m, 2 H), 2.58 (t, J = 7.6 Hz, 2 H), 4.76 (q, J = 7.1 Hz, 2 H); MS(EI), m/e (relative intensity) 182 (4), 154 (27), 125 (100), 111 (53); HRMS, m/e calcd for $C_{10}H_{14}O_3$ (M^+) 182.0943, found 182.0946.

4-*tert*-Butyl-3-methoxy-3-cyclobutene-1,2-dione (3b): pale yellow oil; IR ($CHCl_3$) 2980, 1800, 1770, 1600, 1480, 1370, 1055, and 955 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 9 H), 4.36 (s, 3 H); MS(EI), m/e (relative intensity) 168 (17), 140 (67), 97 (38), 67 (24), 57 (100); HRMS, m/e calcd for $C_9H_{12}O_3$ (M^+) 168.0786, found 168.0787.

3-Methoxy-4-(1-propen-2-yl)-3-cyclobutene-1,2-dione (3c): yellow solid, mp 58–59 °C; IR ($CHCl_3$) 3040, 2970, 1795, 1760, 1590, 1470, 1395, 1055, and 930 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.07 (d, J = 1.0 Hz, 3 H), 4.49 (s, 3 H), 5.52 (t, J = 1.5 Hz, 1 H), 6.23 (m, 1 H); MS(EI), m/e (relative intensity) 152 (1), 110 (37), 82 (100), 67 (57), 54 (30), 53 (43); MS(CI), m/e (relative intensity) 153 (100), 139 (73); HRMS, m/e calcd for $C_8H_8O_3$ (M^+) 152.0473, found 152.0459.

4-(2,6-Dimethoxyphenyl)-3-methoxy-3-cyclobutene-1,2-dione (3e): yellow solid, mp 142.5–144 °C; IR (KBr) 2950, 1785, 1750, 1575, 1435, 1350, 1100, and 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 6 H), 4.40 (s, 3 H), 6.58 (d, J = 8.4 Hz, 2 H), 7.38 (t, J = 8.4 Hz, 1 H); MS(EI), m/e (relative intensity) 248 (2), 149 (25), 121 (38), 91 (100), 78 (26), 77 (22); HRMS, m/e calcd for $C_{13}H_{12}O_5$ (M^+) 248.0684, found 248.0658.

4-(2-Furyl)-3-methoxy-3-cyclobutene-1,2-dione (3g): yellow solid, mp 144–146 °C; IR (KBr) 3130, 1780, 1750, 1600, and 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.56 (s, 3 H), 6.66 (dd, J = 3.6, 1.6 Hz, 1 H), 7.34 (d, J = 3.6 Hz, 1 H), 7.76 (d, J = 1.6 Hz, 1 H); MS(EI), m/e (relative intensity) 178 (48), 122 (50), 107 (100), 51 (47); HRMS, m/e calcd for $C_9H_6O_4$ (M^+) 178.0266, found 178.0267.

3-Methoxy-4-(phenylethynyl)-3-cyclobutene-1,2-dione (3h): yellow solid, mp 140–141 °C; IR ($CHCl_3$) 3030, 2185, 1790, 1755, 1605, 1578, and 1370 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.40 (m, 5 H), 4.53 (s, 3 H); MS(EI), m/e (relative intensity) 212 (28), 156 (61), 141 (73), 100 (13); MS(CI), m/e (relative intensity) 213 (100), 156 (43). Anal. Calcd for $C_{13}H_8O_3$: C, 73.59; H, 3.80. Found: C, 73.68; H, 3.76.

4-[3-(Benzyloxy)-1-propynyl]-3-methoxy-3-cyclobutene-1,2-dione (3k): yellow solid, mp 63–65 °C; IR ($CHCl_3$) 1805, 1780, 1610, 1370, and 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.43 (s, 3 H), 4.52 (s, 2 H), 4.63 (s, 2 H), 7.35 (m, 5 H); MS(EI), m/e (relative intensity) 155 (24), 107 (25), 91 (80), 79 (100), 66 (21), 65 (42); MS(CI), m/e (relative intensity) 257 (70), 229 (39), 183 (100), 107 (31), 91 (41); HRMS, m/e calcd for $C_{15}H_{12}O_4$ (M^+) 256.0735, found 256.0711.

3-Methoxy-4-[3-[(tetrahydropyran-2-yl)oxy]-1-propynyl]-3-cyclobutene-1,2-dione (3j): yellow oil; IR ($CHCl_3$) 2960, 2230, 1805, 1760, 1610, 1375, 1035, and 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.58 (m, 6 H), 3.56 (m, 1 H), 3.82 (m, 1 H), 4.45 (s, 3 H), 4.52 (s, 2 H), 4.75 (m, 1 H); MS(EI), m/e (relative intensity) 166 (9), 123 (51), 95 (34), 93 (47), 85 (58), 79 (36), 78 (91), 77 (53), 67 (35), 66 (25), 57 (39), 55 (100); MS(CI), m/e (relative intensity) 251 (3), 167 (100), 85 (100); HRMS, m/e calcd for $C_{18}H_{14}O_5$ (M^+) 250.0841, found 166.0269 (M^+ – dihydropyran, calcd 166.0266).

3-Methoxy-4-[2-(2-methyl-1,3-dioxolan-2-yl)-1-ethynyl]-3-cyclobutene-1,2-dione (3l): yellow oil; IR ($CHCl_3$) 1800, 1775, 1610, 1370, and 1035; ^1H NMR (300 MHz, $CDCl_3$) δ 1.78 (s, 3 H), 4.07 (s, 4 H), 4.48 (s, 3 H); MS(EI), m/e (relative intensity) 222 (14), 194 (34), 151 (100), 93 (64), 91 (35), 87 (42); HRMS, m/e calcd for $C_{11}H_{10}O_5$ (M^+) 222.0526, found 222.0514.

3-Ethoxy-4-[2-(trimethylsilyl)-1-ethynyl]-3-cyclobutene-1,2-dione (3m): yellow oil; IR ($CHCl_3$) 2970, 2150, 1810–1760, 1590, 1405, 1375, 1340, 1255, 1090, 1030, 995, and 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, 9 H), 1.52 (t, J = 7.1 Hz, 3 H), 4.82 (q, J = 7.1 Hz, 2 H); MS(EI), m/e (relative intensity) 222 (15), 194 (10), 179 (12), 166 (13), 165 (100), 123 (42), 109 (40); HRMS, m/e calcd for $C_{11}H_{14}O_3Si$ (M^+) 222.0712, found 222.0712.

3-Ethoxy-4-(2-methyl-1,3-dithian-2-yl)-3-cyclobutene-1,2-dione (3n): yellow oil; IR ($CHCl_3$) 2950, 1800, 1770, 1590, 1390, 1350, and 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (t, J = 7.1 Hz, 3 H), 1.80 (s, 3 H), 1.85 (m, 1 H), 2.15 (m, 1 H), 2.72 (ddd, J = 14.8, 4.3, 3.3 Hz, 2 H), 3.20 (ddd, J = 13.7, 12.6, 2.5 Hz, 2 H), 4.85 (q, J = 7.1 Hz, 2 H); MS(EI), m/e (relative intensity) 258, 230, 173, 145, 133 (100), 106, 73, 67, 59; MS(CI), m/e (relative intensity) 259 (100), 155, 107; HRMS, m/e calcd for $C_{20}H_{16}O_4$ (M^+) 258.0380, found 258.0372.

3-Methoxy-4-methyl-3-cyclobutene-1,2-dione (3o). A solution of 2.34 mmol (1.61 mL of a 1.45 M solution in Et_2O) of CH_3Li in 20 mL of THF at −100 °C (isooctane, N_2(l)) was cannulated under positive argon pressure into a solution of 302 mg (2.12 mmol) of dimethyl squarate in 30 mL of THF at −100 °C. The solution was stirred for 30 min, treated with 450 μL (3.19 mmol) of trifluoroacetic anhydride, stirred for an additional 20 min, quenched with 6 mL of 10% NH_4Cl (aqueous), and poured into 50 mL of 5% $NaHCO_3$ (aqueous)/100 mL of Et_2O. The aqueous layer was extracted with 50 mL of Et_2O and the combined organic layers were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a yellow oil which was eluted thru silica gel with 1:1 EtOAc/hexanes to give 183 mg of **3o** (68% yield, greater than 95% pure by NMR) as a white solid, mp 39.5–44.5 °C. Recrystallization from Et_2O/hexanes gave 128 mg of pure **3o** (48% yield), mp 47–48 °C (lit.[12] mp 49–50 °C).

3-Methoxy-4-[2-(trimethylsilyl)-1-ethynyl]-3-cyclobutene-1,2-dione (3q): yellow solid, mp 37–37.5 °C; IR ($CHCl_3$) 2980, 1795, 1600, 1360, and 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.25 (s, 9 H), 4.47 (s, 3 H); MS(EI), m/e (relative intensity) 208 (16), 180 (21), 165 (78), 152 (26), 137 (100), 122 (44), 109 (48), 75 (22); HRMS, m/e calcd for $C_{10}H_{12}O_3Si$ (M^+) 208.0555, found 208.0544.

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Registry No. 1 (R_1 = Et), 5231-87-8; 1 (R_1 = Me), 5222-73-1; **2a**, 113976-67-3; **2b**, 113976-68-4; **2c**, 113976-69-5; **2d**, 98122-97-5; **2e**, 112597-42-9; **2f**, 112597-32-7; **2g**, 112597-35-0; **2h**, 113976-70-8; **2i**, 113976-71-9; **2j**, 113976-72-0; **2k**, 113976-73-1; **2l**, 113976-74-2; **2m**, 109364-34-3; **2n**, 113976-75-3; **3a**, 113976-76-4; **3b**, 113976-77-5; **3c**, 113976-78-6; **3d**, 711-78-4; **3e**, 113976-79-7; **3f**, 113976-80-0; **3g**, 113976-81-1; **3h**, 113976-82-2; **3i**, 113976-83-3; **3j**, 113976-84-4; **3k**, 113976-85-5; 3l, 113976-86-6; **3m**, 109364-35-4; **3n**, 113976-87-7; **3o**, 29769-77-5; **3p**, 75966-09-5; **3q**, 113976-89-9; **4**, 113976-88-8; *t*-C_4H_9Li, 594-19-4; CH_2=$C(CH_3)Li$, 6386-71-6; C_6H_5Li, 591-51-5; 2,6-di(OCH_3)C_6H_3Li, 2785-97-9; *n*-C_4H_9Li, 109-72-8; C_4H_3OLi, 2786-02-9; C_6H_5C≡CLi, 4440-01-1; $C_6H_5CH_2C$≡CLi, 102683-42-1; $C_6H_5CH_2OCH_2C$≡CLi, 64080-63-3; $(CH_3)_3SiC$≡CLi, 54655-07-1;

(12) Iyer, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1987**, *109*, 2759.

CH_3Li, 917-54-4; [3-(tetrahydropyran-2-yloxy)-1-propynyl]lithium, 37566-51-1; 2-bromothiophene, 1003-09-4; [2-(2-methyl-1,3-dioxol-2-yl)ethynyl]lithium, 113976-66-2; 2-lithio-2-methyl-1,3-dithiane, 27969-97-7.

Supplementary Material Available: Details of the X-ray crystal analysis of 4 including tables of thermal parameters, interatomic distances, and interatomic angles (6 pages). Ordering information is given on any current masthead page.

An Improved Method for the Synthesis of Substituted Cyclobutenediones

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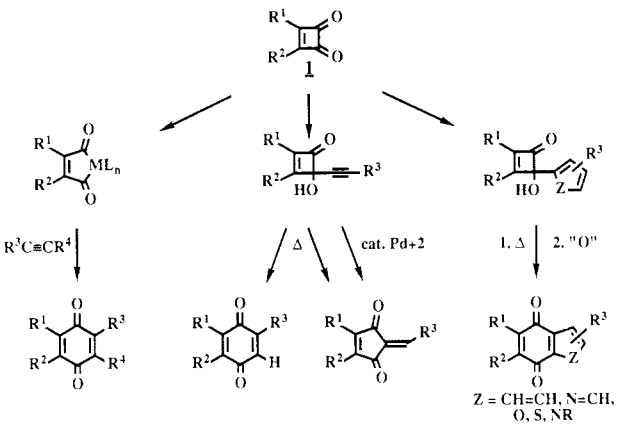
Practical and high yielding routes to substituted cyclobutenediones are described. 3,4-Bis(1-methylethoxy)cyclobut-3-ene-1,2-dione (diisopropyl squarate), a stable, crystalline derivative of squaric acid, was easily prepared by refluxing squaric acid in 2-propanol/benzene with azeotropic removal of H_2O. Reaction with organolithium reagents proceeded in very high yield to give stable, isolable 1,2-adducts. Treatment in a two-phase system (CH_2Cl_2/12 N HCl at room temperature) led to excellent yields of 3-(1-methylethoxy)-4-substituted-cyclobut-3-ene-1,2-diones. Alternatively, the free alcohol of the intermediate 1,2-adducts was protected as the *tert*-butyldimethylsilyl ether, and a 1,2-addition of a second and different organolithium reagent was achieved. Hydrolysis of these compounds led to very good yields of differentially disubstituted cyclobutenediones.

Introduction

Cyclobutenediones 1 are proving to be useful starting materials for the synthesis of highly functionalized, biologically relevant molecules (see Scheme I). Cyclobutenediones were shown to react with low-valent transition-metal complexes to form metallacycles, which in turn reacted with alkynes to give benzoquinones in a highly convergent fashion.[2] Moore and his co-workers showed that 4-alkynyl-4-hydroxycyclobutenones, prepared in good yield by addition of acetylides to cyclobutenediones, could be converted directly into benzoquinones or 5-alkylidene-2-cyclopentene-1,3-diones upon thermolysis.[3] The outcome of the thermolysis depended on the alkyne substitutent. A more general formation of 5-alkylidene-2-cyclopentene-1,3-diones was observed when the same alkynylated products were subjected to a catalytic amount of Pd^{2+}.[4] In this case, the rearrangement proceeded with high stereoselectivity for formation of the exocyclic double bond and provided potential precursors to the biologically important 4-oxygenated 5-alkylidenecyclopentenones. An even more general route to quinones was reported when it was discovered that aryl- and heteroaryllithium reagents added regioselectively to unsymmetrically substituted cyclobutenediones to give 4-(aryl or heteroaryl)-4-hydroxycyclobutenones. These compounds could be thermally rearranged in high yield to hydroquinone derivatives which upon oxidation produced highly substituted benzoquinones.[5] Analogous transformations using benzocyclobutenediones were established for each type of reaction shown in Scheme I.

Scheme I



Cyclobutenediones also exhibit biological activity. A strain of the mold *Fusarium moniliforme* was found to produce moniliformin,[6] identified as the sodium salt of 3-hydroxy-3-cyclobutene-1,2-dione (semisquaric acid).[7] Moniliformin and related compounds possess growth-regulating and phytotoxic effects on plants[1,8] and are toxic to mammals through selective inhibition of mitochondrial pyruvate and α-ketoglutarate oxidation.[9] It was recently suggested that cyclobutenedione derivatives might show

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