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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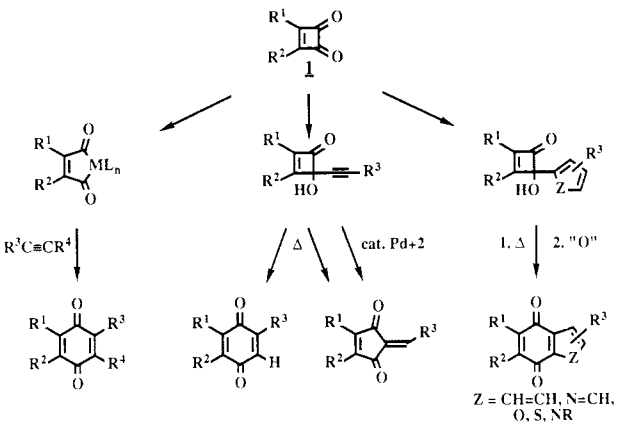
Practical and high yielding routes to substituted cyclobutenediones are described. 3,4-Bis(1-methylethoxy)cyclobut-3-ene-1,2-dione (diisopropyl squarate), a stable, crystalline derivative of squaric acid, was easily prepared by refluxing squaric acid in 2-propanol/benzene with azeotropic removal of H_2O. 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

(1) Fellow of the Alfred P. Sloan Foundation, 1983-1988. Camille and Henry Dreyfus Foundation Teacher-Scholar, 1985-1991.

(2) Liebeskind, L. S.; Baysdon, S. L.; South, M. S.; Blount, J. F. *J. Organomet. Chem.* **1980**, *202*, C73. (b) Liebeskind, L. S.; Baysdon, S. L.; South, M. S. *J. Am. Chem. Soc.* **1980**, *102*, 7397. (c) Baysdon, S. L.; Liebeskind, L. S. *Organometallics* **1982**, *1*, 771. (d) South, M. S.; Liebeskind, L. S. *J. Org. Chem.* **1982**, *47*, 3815. (e) South, M. S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1984**, *106*, 4181. (f) Liebeskind, L. S.; Leeds, J. P.; Baysdon, S. L.; Iyer, S. *J. Am. Chem. Soc.* **1984**, *106*, 6451. (g) Liebeskind, L. S.; Baysdon, S. L. *Tetrahedron Lett.* **1984**, *25*, 1747. (h) Liebeskind, L. S.; Jewell, C. F., Jr. *J. Organomet. Chem.* **1985**, *285*, 305. (i) Jewell, C. F., Jr.; Liebeskind, L. S.; Williamson, M. *J. Am. Chem. Soc.* **1985**, *107*, 6715. (j) Liebeskind, L. S.; Baysdon, S. L.; South, M. S.; Iyer, S.; Leeds, J. P. *Tetrahedron, Symp.* **1985**, *41*, 5839. (k) Liebeskind, L. S.; Baysdon, S. L.; Chidambaram, R.; Goedken, V. *Organometallics* **1985**, *5*, 1086. (l) Liebeskind, L. S.; Iyer, S.; Jewell, C. F., Jr. *J. Org. Chem.* **1986**, *51*, 3065. (m) Iyer, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1987**, *109*, 2759.

(3) (a) Karlsson, J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 3392. (b) Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1987**, *52*, 1174-1175.

(4) Liebeskind, L. S.; Mitchell, D.; Foster, B. S. *J. Am. Chem. Soc.*, in press.

(5) (a) Liebeskind, L. S.; Iyer, S.; Jewell, C. F., Jr. *J. Org. Chem.* **1986**, *51*, 3065-3067. (b) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *Ibid.* **1986**, *51*, 3067-3068. (c) Moore, H. W.; Reed, M. W. *J. Org. Chem.* **1987**, *52*, 3491-3492. (d) Perri, S. T.; Moore, H. W. *Tetrahedron Lett.* **1987**, *28*, 4507-4510.

(6) Cole, R. J.; Kirksey, J. W.; Cutler, H. G.; Doupnik, B. L.; Peckham, J. C. *Science (Washington, D.C.)* **1973**, *179*, 1324.

(7) Springer, J. P.; Clardy, J.; Cole, R. J.; Kirksey, J. W.; Hill, R. K.; Carlson, R. M.; Isidor, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 2267.

(8) Fischer, H.; Bellus, D. Offenlegungsschrift 26 16 756, Deutsches Patentamt from 28.10.76, Ciba-Geigy AG, Basel, 1976.

(9) Burka, L. T.; Doran, J.; Wilson, B. J. *Biochem. Pharmacol.* **1982**, *31*, 79.

0022-3263/88/1953-2482$01.50/0

interesting antitumor properties.[10,11]

Short and practical synthetic approaches to cyclobutenediones would significantly enhance the development of the aforementioned synthetic applications and perhaps even spur the introduction of new synthetic methods, while providing easy access to new cyclobutenediones for biological assay. In this manuscript we describe, in detail, the procedure that we have found most practical for the synthesis of multigram quantities of substituted cyclobutenediones.[12]

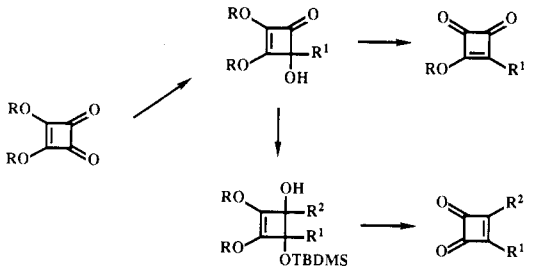
Background

The preparative chemistry of cyclobutenediones (and benzocyclobutenediones) up to 1978 has been reviewed in three comprehensive articles.[13] Of the numerous methods for the synthesis of cyclobutenediones described in these articles, no procedure stands out as sufficiently general to allow the preparation of diversely substituted compounds. The thermal [2 + 2] cycloaddition of perhaloethylenes to arylacetylenes, followed by hydrolysis, is particularly useful for the synthesis of aryl-substituted cyclobutenediones, but the procedure appears to be limited to arylacetylenes. A similar criticism holds for the thermal [2 + 2] cycloaddition of tetraalkoxyethylenes to electron-deficient alkenes. A method based on the cycloaddition of dichloroketene to alkynes provides an entry to some substituted cyclobutenediones, but yields are generally not high in this chemistry and the process is far from general. Starting with 3,4-diethoxy-3-cyclobutene-1,2-dione (diethyl squarate), a few simple alkyl derivatives of cyclobutenediones were prepared by reaction with Grignard reagents, but these reactions do not proceed in high yield.

Since the publication of the three review articles mentioned above, other newer methods of cyclobutenedione synthesis have appeared. Interest in the biological activity of semisquaric acid has spurred the development of improved processes for the synthesis of hydroxycyclobutenedione derivatives.[14] Two newer methods for synthesizing the parent 3-cyclobutene-1,2-dione have been described,[15] and we have communicated a simple approach to some cyclic and acyclic cyclobutenediones based on the cycloaddition of dichloroketene to vinyl sulfides.[16] As described in the next section, the 1,4-addition of Grignard reagents to various squaric acid esters has been probed, in detail, as a route to substituted cyclobutenediones,[17] but the specific systems studied have limitations. Our cumulative experiences in cyclobutenedione synthesis over the last 8 years led us to the conclusion that there were no truly satisfactory methods for the easy preparation of generally substituted cyclobutenediones. Our attempts to rectify this situation are described herein.

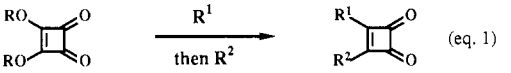
(10) Kraus, J.-L. *Tetrahedron Lett.* **1985**, *26*, 1867.
(11) Kraus, J.-L. *Tetrahedron Lett.* **1987**, *28*, 1765.
(12) A synthetic route to substituted cyclobutenediones very similar to that described in this manuscript was independently discovered by Moore and co-workers and is described in the preceding paper.
(13) (a) Schmidt, A. H.; Reid, W. *Synthesis* **1978**, 1. (b) Knorr, H.; Ried, W. *Synthesis* **1978**, 649. (c) Schmidt, A. H.; Ried, W. *Synthesis* **1978**, 869.
(14) (a) Bellus, D.; Fischer, H.; Greuter, H.; Martin, P. *Helv. Chim. Acta* **1978**, *61*, 1784. (b) Bellus, D. *J. Am. Chem. Soc.* **1978**, *100*, 8026. (c) Scharf, H.-D.; Frauenrath, H.; Pinske, W. *Chem. Ber.* **1978**, *111*, 168. (d) Bellus, D. *J. Org. Chem.* **1979**, *44*, 1208. (e) Brady, W. T.; Saidi, K. *J. Org. Chem.* **1980**, *45*, 727. (f) Bellus, D.; Martin, P.; Sauter, H.; Winkler, T. *Helv. Chim. Acta* **1980**, *63*, 1130. (g) Brady, W. T.; Watts, R. D. *J. Org. Chem.* **1980**, *45*, 3525.
(15) (a) Kasai, M.; Oda, M.; Kitahara, Y. *Chem. Lett.* **1978**, 217. (b) Martin, H.-D.; Oftring, A.; Iden, R. *Tetrahedron Lett.* **1982**, *23*, 841. (c) Hinshaw, J. C. *J. Chem. Soc. D* **1971**, 630.
(16) Liebeskind, L. S.; Baysdon, S. L. *Tetrahedron Lett.* **1984**, *25*, 1747.
(17) (a) Dehmlow, E. V.; Schell, H. G. *Chem. Ber.* **1980**, *113*, 1–8. (b) Kraus, J. L. *Tetrahedron Lett.* **1985**, *26*, 1867–1870.

Scheme II



Results and Discussion

After evaluating the various methods known for synthesizing substituted cyclobutenediones, including our procedure based on the cycloaddition of dichloroketene to vinyl sulfides, we concluded that the most practical way to prepare large quantities of material would be to rely on the elaboration of squaric acid. This decision was predicated on the fact that squaric acid can be prepared on a kilogram scale by reaction of hexachlorobutadiene with morpholine followed by hydrolysis.[18] If a method could be found to cleanly substitute the two alkoxy groups of a dialkyl squarate, *in a stepwise fashion and in high yield*, then substituted cyclobutenediones could be prepared easily in large quantities (eq 1).

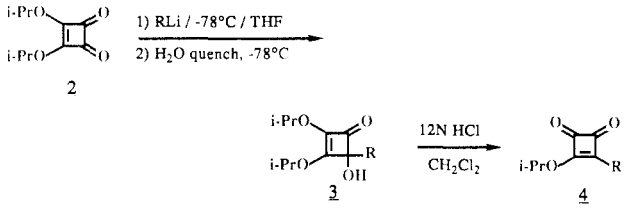


(eq. 1)

In an extention of the original Chickos procedure for preparing 3-hydroxy-3-methylcyclobut-3-ene-1,2-dione,[19] Dehmlow and Schell[17a] reacted a number of dialkyl squarate derivatives (diethyl, di-*n*-propyl, diisopropyl, di-*n*-butyl, di-*tert*-butyl, and dibenzyl) with Grignard reagents and, after hydrolysis, obtained the corresponding 3-alkoxy-4-alkyl-3-cyclobutene-1,2-diones in yields ranging from 2% to 65%. The chemistry is somewhat complicated by varying degrees of simultaneous 1,2- and 1,4-addition and by overaddition of the Grignard reagent to the dialkyl squarate. However, the authors demonstrated that the 1,2-adducts could be converted to 3-alkoxy-3-substituted-cyclobut-3-ene-1,2-diones on treatment with mild acid, thus establishing the utility of 1,2-adducts of squaric acid esters in the preparation of cyclobutenediones. Kraus very recently showed that dimethyl squarate reacted with organolithium reagents via a clean 1,2-addition pathway to give mixtures of mono-1,2-adduct and bis-1,2-adducts, while three Grignard reagents were shown to react via a 1,4-addition pathway to directly provide varying mixtures of monosubstituted and disubstituted cyclobutenediones in moderate to good yields.[17b] The Grignard reactions of the Kraus work, when compared to the Dehmlow and Schell results, suggested that the alkoxy group used to esterify squaric acid might play a role in controlling the amount of 1,2- versus 1,4-addition; the larger alkoxy groups used in the Dehmlow–Schell work somewhat disfavored the 1,4-addition of Grignard reagents. By combining the observations of Dehmlow–Schell and Kraus, we anticipated that a practical, high yield route to substituted cyclobutenediones could be established by using organolithium reagents to perform a selective 1,2-addition at low temperature (Scheme II). Then, the resulting 1,2-adducts could be rearranged under acid catalysis to 3-alkoxy-4-

(18) A description of this chemistry along with pertinent references is contained in Paine [Paine, A. J. *Tetrahedron Lett.* **1984**, *25*, 135]. Squaric acid can be purchased on a kilogram scale from Aldrich Chemical Company.
(19) Chickos, J. C. *J. Am. Chem. Soc.* **1970**, *92*, 5749–5750.

Table I. Addition of Organolithium Reagents to Diisopropyl Squarate

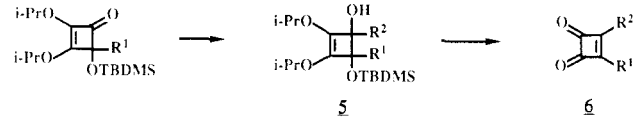


compd	R	yield of 3 (%)	yield of 4 (%)
a	H	89	65
b	Me	97	92
c	*n*-Bu	80	88
d	*t*-Bu	83	95
e	Ph	93	89
f	2-thienyl	98	96
g	C≡CPh	84	98
h	C≡CBu	82	88
i	C≡CTMS	70 (22% C≡CH)	93
j	C_6H_4C≡CTMS-4′	88	90

substituted-3-cyclobutene-1,2-diones. In addition, after protection of the free hydroxyl of the initial 1,2-adduct, addition of a second organolithium reagent and acid-catalyzed rearrangement might produce a differentially disubstituted cyclobutenedione. Although Kraus showed that organolithium reagents added in a clean 1,2-fashion to dimethyl squarate, monoaddition was complicated by some double addition in a number of cases. We thought that the use of a larger alkoxy group to esterify squaric acid would provide better selectivity for monoaddition over bisaddition because of the increased steric environment imparted by a larger alkoxy group. Also greater hydrolytic stability of the intermediates of the synthetic sequence was expected for alkoxy groups more hydrophobic than the methyl or ethyl esters.

Diisopropyl squarate (**2**), a free-flowing, stable, white solid was chosen as the substrate for our studies. In contrast to diisopropyl squarate, both dimethyl and diethyl squarate are oils at ambient conditions, both are powerful vesicants when brought in contact with the skin, and both squaric acid esters have induced an allergic skin irritation in certain individuals in our laboratory. The use of an easily handled solid derivative of squaric acid such as diisopropyl squarate would simplify handling and should minimize unexpected physical contact. Dehmlow and Schell previously reported that diisopropyl squarate could be prepared from isopropyl bromide and the bis (Ag salt) of squaric acid in 51% yield.[17a] We discovered that refluxing squaric acid in excess benzene/2-propanol over a period of 3 days with periodic removal of the azeotrope produced diisopropyl squarate in 86% yield. This material was previously shown to react with Grignard reagents followed by hydrolysis to give moderate yields of 3-(1-methylethoxy)-4-alkyl-3-cyclobutene-1,2-diones (RMgX/yield: EtMgX/43%; *i*-PrMgX/65%; *t*-BuMgX/14%).[17a] In our hands, this chemistry seldom proceeded cleanly and required careful chromatography. In contrast, diisopropyl squarate reacted with organolithium reagents to provide very high yields of isolable 4-hydroxy-4-substituted-2,3-bis(1-methylethoxy)-2-cyclobuten-1-ones **3**, Table I. Substrates **3**, in turn, were converted into 3-(1-methylethoxy)-4-substituted-cyclobut-3-ene-1,2-diones **4** simply by stirring in methylene chloride in the presence of a small amount of 12 N HCl in a two-phase system at room temperature. Presumably the allylic alcohol functionality of **3** undergoes acid-catalyzed allylic equilibration to an isomeric hemiketal which loses 2-propanol to give the observed product **4**. It was also possible to form cyclobutenediones **4** directly from **2** without isolation of **3**. In our experience the addition of organolithium reagents to diisopropyl squarate followed by treatment with catalytic acid is the best procedure available for the preparation of semisquaric acid derivatives. The isopropyl esters can be hydrolyzed to the free acids in good yields.

Table II. Synthesis of Differentially 3,4-Disubstituted-3-cyclobutene-1,2-diones



compd	R^1	R^2	yield of 5 (%)	yield of 6 (%)
a	H	Me	81	88
b	H	*n*-Bu	80	94
c	H	*t*-Bu	85	90
d	H	2-thienyl	96	90
e	Me	Me	91	96
f	Me	*n*-Bu		79
g	Me	*t*-Bu		96
h	Me	Ph		78

A few of the results shown in Table I are worth highlighting. The practicality of the sequence was confirmed by performing the synthesis of 2,3-bis(1-methylethoxy)-4-hydroxy-4-methylcyclobut-2-en-1-one (**3b**) on a multigram scale. A large-scale synthesis (21 g) of 3-hydroxy-4-methyl-3-cyclobutene-1,2-dione, a compound of use in the synthesis of naturally occurring antitumor quinones,[20] was also conducted by addition of methyllithium to diisopropyl squarate followed by hydrolysis of the crude reaction product (65% overall yield of crystalline product). Use of LiAl(O-*t*-Bu)$_3$H as a source of a hydridic nucleophile provided the simplest known route to semisquaric acid (as the isopropyl ester **4a**) in multigram quantities (entry 1).[14] Partial desilylation occurred during the preparation of the (trimethylsilyl)ethynyl adduct **3i**, allowing the isolation of 2,3-bis(1-methylethoxy)-4-ethynyl-4-hydroxycyclobut-2-en-1-one (**3i′**) in 22% yield. Acid treatment provided the corresponding semisquaric acid derivative, 4-ethynyl-3-(1-methylethoxy)cyclobut-3-ene-1,2-dione (**4i′**) in 63% yield.

The ease of isolating 4-hydroxy-4-substituted-2,3-bis-(1-methylethoxy)cyclobut-2-en-1-ones **3** in very high yields allowed us to test the feasibility of introducing two different substituents into diisopropyl squarate to give differentially disubstituted cyclobutenediones. This concept was probed with the monoadducts **3a**, R = H, and **3b**, R = Me. Protection of the free OH as the *tert*-butyldimethylsilyl (TBDMS) ether in **3a**, R = H, proceeded in 96% yield by using TBDMSCl in DMF with 4-(dimethylamino)pyridine (DMAP), while the more hindered tertiary alcohol in **3b**, R = Me, gave the corresponding TBDMS ether in 60% yield. The TBDMS ethers underwent reaction with organolithium reagents to give the adducts **5** in high isolated yields (Table II). Treatment with 12 N HCl in CH_2Cl_2 (two-phase) then led to excellent yields of the differentially disubstituted cyclobutenediones **6**.

Most of the compounds of Table II are stable, distillable materials. Attempts were made to purify compounds **5f–h** by Kuglrohr distillation, but led only to decomposition.

(20) Relevant chemistry is described in ref 2, 3, and 5.
(21) Treibs, A.; Jacob, K.; Tribollet, R. *Justus Liebigs. Ann. Chem.* 1970, *741*, 101.

Direct conversion of the crude products to **6f–h** gave the indicated isolated yields. The monosubstituted cyclobutenediones **6a–c**, R_1 = H (entries 1–3 of Table II), represent a new series of compounds, monoalkyl-substituted cyclobutenediones. Although the very reactive parent cyclobutenedione (**6**, R^1, R^2 = H) is known,[15] the only common monosubstituted compounds previously described are derivatives of semisquaric acid and 3-(aryl-substituted)cyclobut-3-ene-1,2-diones. The stepwise procedure described in this paper is a very practical method for the preparation of substituted cyclobutenediones.

Conclusions

Simple and practical procedures for the synthesis of substituted cylcobutenediones have been described. A two-step sequence, 1,2-addition of an organolithium reagent to diisopropyl squarate followed by acid-catalyzed rearrangement, has been demonstrated to provide substituted semisquaric acid derivatives in very good yields. Protection of the free alcohol of the intermediate 1,2-adduct as a *tert*-butyldimethylsilyl ether allows addition of a second organolithium reagent, and then acid hydrolysis generates differentially disubstituted cyclobutenediones in very good yields.

Experimental Section

General Methods. All melting points were performed in open capillary tubes and are uncorrected. Analytical thin-layer chromatography was done with E. Merck silica gel 60F-254 glass-backed plates of 0.25-mm thickness which were visualized with appropriate combinations of UV light, phosphomolybdic acid stain, $KMnO_4$ (5% in water), and vanillin stain. Preparative scale separations were effected with "Flash grade" silica gel available from Aldrich Chemical Company and by radial chromatography using a Model 7924T chromatotron purchased from Harrison Research on rotors coated with Merck PF254 silica gel. Methylene chloride was purified for use by distillation over CaH_2 under a N_2 atmosphere. Benzene, tetrahydrofuran, and ether were freshly distilled from sodium and benzophenone. All other solvents were reagent grade quality and used as received. Squaric acid was purchased on a kilogram scale from Aldrich Chemical Company.

Preparation of 3,4-Bis(1-methylethoxy)cyclobut-3-ene-1,2-dione (Diisopropyl Squarate, 2). Squaric acid (40 g) was slurried in 400 mL of 1:1 benzene/2-propanol in a 500-mL round-bottomed flask equipped with a Dean–Stark apparatus and a stir bar. The suspension was heated to reflux with stirring (dissolution occurs overnight) with continuous removal of the azeotrope over a 72-h period. As the azeotrope was removed, 1:1 benzene/2-propanol was replenished (total 1:1 benzene/2-propanol ≥ 1 L). The solution was cooled, the stir bar was removed, and the solvents were removed on a rotary evaporator equipped with a dry ice trap. The resulting oil was dissolved in 1.5 L of reagent grade diethyl ether, the organic layer was washed with 2 × 30 mL of saturated $NaHCO_3$ and once with saturated NaCl, and then the organic layer was dried over Na_2SO_4. Filtration and evaporation (rotary evaporator) left a golden oil that was concentrated under vacuum to a viscous oil. If no solid formed crystallization was usually initiated after standing under N_2 overnight. The residual solvent was removed as the crystals formed. The product was crushed and placed under a vacuum to complete removal of solvent to yield 59.8 g (86%) of **2**. TLC (1:1 hexane/ether) showed no baseline; single spot R_f 0.6. The product was stored under N_2 as a precaution; however, after 2 weeks under air no decomposition was detected: mp 43–44 °C (lit.[17a] mp 43–44 °C); IR (CH_2Cl_2, cm^{-1}) 1810, 1730, 1600; ^1H NMR (360 MHz, $CDCl_3$) δ 5.35 (hept, J = 7 Hz, 1 H), 1.46 (d, J = 7 Hz, 6 H).

Typical Experimental Procedure for the Preparation of Monoadducts of Diisopropyl Squarate (3). A solution of 5.15 g (25.9 mmol) of diisopropyl squarate (**2**) under N_2 in 50 mL of THF was cooled to −78 °C and 36.7 mL (1.01 equiv) of MeLi (1.40 M in Et_2O) was added dropwise. The reaction was kept at −78 °C and monitored by TLC (SiO_2; 30% Et_2O in hexanes) for disappearance of starting material. After 30 min, the reaction was quenched with 10 mL of H_2O at −78 °C. The mixture was diluted with 40 mL of Et_2O and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL); the combined organic layers were dried over Na_2SO_4 and the solvents were removed by rotary evaporator and vacuum pump. The product was dissolved in a small amount of Et_2O and passed through a small plug of SiO_2 with Et_2O. The solvent was removed on a rotary evaporator followed by a vacuum pump to give 5.54 g (99%) of pure **2,3-bis(1-methylethoxy)-4-hydroxy-4-methylcyclobut-2-en-1-one (3b)** as a clear liquid: IR (CH_2Cl_2, cm^{-1}) 3590, 3400, 2990, 1770, 1625, 1390, 1340; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.89, 4.87 (overlapping hept, J = 6 Hz each, 2 H total), 2.60 (s, 1 H), 1.50 (s, 3 H), 1.41 (d, J = 6 Hz, 3 H), 1.39 (d, J = 6 Hz, 3 H), 1.29 (d, J = 6 Hz, 3 H), 1.26 (d, J = 6 Hz, 3 H). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.67; H, 8.47. Found: C, 61.58; H, 8.49.

Large-Scale Preparation of 3-Hydroxy-4-methylcyclobut-3-ene-1,2-dione. Treatment of bis(1-methylethoxy) squarate (56.0 g, 0.283 mol) with MeLi according to the procedure described above gave 62 g of crude 2,3-bis(1-methylethoxy)-4-hydroxy-4-methylcyclobut-2-en-1-one (**3b**). The crude product was dissolved in 60 mL of hexanes (bp 68.3–69.5 °C) and 60 mL of 6 N aqueous HCl was added. The resulting two-phase system was refluxed with vigorous magnetic stirring for 36 h and cooled, and the solvents were removed on a rotary evaporator. The gummy, light brown solid was dissolved in 300 mL of water and extracted with methylene chloride (5 × 20 mL) to remove impurities (the product remains in the water layer). The aqueous phase was evaporated, dried on a vacuum pump, dissolved in reagent grade acetone (300 mL), and filtered through Celite to remove any residual squaric acid derived from the hydrolysis of unreacted diisopropyl squarate. The acetone filtrate was evaporated to a volume of approximately 150 mL and crystallization was induced by addition of 300 mL of pentane directed into the acetone solution. The off-white, crystalline material was collected on a glass frit and washed with pentane. The filtrate was evaporated and recrystallized from acetone/pentane to give a combined yield of 20.55 g (64.9%) of 3-hydroxy-4-methylcyclobut-3-ene-1,2-dione, mp 161–162.5 °C (lit.[19] mp 162–164 °C).

2,3-Bis(1-methylethoxy)-4-hydroxycyclobut-2-en-1-one (3a). Analogous reaction of **2** (10.0 g, 50.45 mmol) with lithium tri-*tert*-butoxyaluminum hydride (16.0 g, 62.93 mmol) in 50 mL of dry tetrahydrofuran was performed at −10 °C under N_2. The reaction was complete (TLC, SiO_2, 50% Et_2O/hexane) after 30 min and was quenched with a saturated solution of potassium sodium tartrate (100 mL—to aid removal of aluminum salts). The aqueous phase was extracted with Et_2O (3 × 200 mL) and dried with Na_2SO_4. Concentration of the organic phase, filtration through a small plug of SiO_2 with ether, and removal of residual solvent under vacuum yielded 7.26 g (72%) of spectroscopically pure **3a** as a colorless liquid: IR (CH_2Cl_2, cm^{-1}) 3580, 3350, 2980, 2940, 1770, 1620, 1390, 1325; ^1H NMR (300 MHz, $CDCl_3$) δ 4.90 (m, 3 H), 3.1 (br s, 1 H), 1.41 (d, J = 6.2 Hz, 3 H), 1.40 (d, J = 6.2 Hz, 3 H), 1.29 (d, J = 2.3 Hz, 3 H), 1.27 (d, J = 3.4 Hz, 3 H). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.99; H, 8.06. Found: C, 59.89; H, 8.07.

*The following monoadducts **3** were prepared according to the typical procedure described above for **3b**. The products were purified by chromatography on a chromatotron using a 2-mm SiO_2 rotor with 40% Et_2O in hexanes as the eluent.*

2,3-Bis(1-methylethoxy)-4-*n*-butyl-4-hydroxycyclobut-2-en-1-one (3c). Analogous reaction of **2** (0.201 g) with *n*-BuLi gave an 80% yield of **3c** (0.206 g) as a pale yellow oil: IR (CH_2Cl_2, cm^{-1}) 3580, 3300, 2980, 2930, 1765, 1620, 1315; ^1H NMR ($CDCl_3$, 360 MHz) δ 4.89 (hept, J = 6 Hz, 1 H), 4.88 (hept, J = 6 Hz, 1 H), 2.36 (s, 1 H), 1.82 (q, J = 7 Hz, 2 H), 1.40 (d, J = 6 Hz, 3 H), 1.39 (d, J = 6 Hz, 3 H), 1.35–1.18 (m, 4 H), 1.29 (d, J = 6 Hz, 3 H), 1.27 (d, J = 6 Hz, 3 H), 0.90 (t, J = 7 Hz, 3 H). Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.36; H, 9.50.

2,3-Bis(1-methylethoxy)-4-*tert*-butyl-4-hydroxycyclobut-2-en-1-one (3d). Analogous reaction of **2** (0.100 g) with *t*-BuLi gave an 83% yield of **3d** (0.108 g) as a colorless solid: mp 45–46 °C (CH_2Cl_2/hexanes); IR (CH_2Cl_2, cm^{-1}) 3580, 3400, 2960, 1760, 1615, 1380, 1310, 1080; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.90, 4.88 (overlapping hept, J = 6 Hz, 2 H total), 2.62 (s, 1 H), 1.40 (d, J = 6 Hz, 3 H), 1.38 (d, J = 6 Hz, 3 H), 1.28 (d, J = 6 Hz, 3 H), 1.26 (d, J = 6 Hz, 3 H), 1.07 (s, 9 H). Anal. Calcd for $C_{14}H_{24}O_4$:

C, 65.60; H, 9.44. Found: C, 65.33; H, 9.53.

2,3-Bis(1-methylethoxy)-4-hydroxy-4-phenylcyclobut-2-en-1-one (3e). Analogous reaction of **2** (0.201 g) with PhLi gave a 93% yield of **3e** (0.261 g) as a yellow oil: IR (CH_2Cl_2, cm^{-1}) 3570, 3380, 2980, 1768, 1620, 1318; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.56–7.51 (m, 2 H), 7.40–7.29 (m, 3 H), 4.96, 4.91 (overlapping hept, J = 6 Hz each, 2 H total), 2.81 (s, 1 H), 1.41 (d, J = 6 Hz, 3 H), 1.35 (d, J = 6 Hz, 3 H), 1.34 (d, J = 6 Hz, 3 H), 1.30 (d, J = 6 Hz, 3 H). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.29. Found: C, 69.31; H, 7.36.

2,3-Bis(1-methylethoxy)-4-hydroxy-4-(2-thienyl)cyclobut-2-en-1-one (3f). Analogous reaction of **2** (0.100 g) with 2-lithiothiophene (generated by addition of 1.05 equiv of n-BuLi to a THF solution of thiophene at −78 °C and stirring at −78 °C for 15 min and then at −23 °C for 30 min[22]) gave a 98% yield of **3f** (0.139 g) as a colorless oil: IR (CH_2Cl_2, cm^{-1}) 3570, 3380, 2990, 1770, 1630, 1320; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.30 (dd, J = 5 Hz, 1 Hz, 1 H), 7.10 (dd, J = 1 Hz, 4 Hz, 1 H), 7.00 (dd, J = 4 Hz, 5 Hz, 1 H), 4.93 (hept, J = 6 Hz, 2 H), 3.73 (s, 1 H), 1.41 (d, J = 6 Hz, 3 H), 1.34 (d, J = 6 Hz, 3 H), 1.33 (d, J = 6 Hz, 3 H), 1.30 (d, J = 6 Hz, 3 H). Anal. Calcd for $C_{14}H_{18}O_4S$: C, 59.56; H, 6.43. Found: C, 59.50; H, 9.51.

2,3-Bis(1-methylethoxy)-4-hydroxy-4-(phenylethynyl)cyclobut-2-en-1-one (3g). Analogous reaction of **2** (0.203 g) with lithium phenylacetylide (generated by addition of 1.0 equiv of n-BuLi to a THF solution of phenylacetylene at −15 °C and stirring at −15 °C for 30 min) gave an 86% yield of **3g** (0.259 g) as a yellow solid: mp 73–74 °C (CH_2Cl_2/hexanes); IR (CH_2Cl_2, cm^{-1}) 3560, 2980, 1775, 1627, 1320; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50–7.40 (m, 2 H), 7.38–7.28 (m, 3 H), 5.04 (hept, J = 6 Hz, 1 H), 4.91 (hept, J = 6 Hz, 1 H), 3.03 (s, 1 H), 1.48 (d, J = 6 Hz, 3 H), 1.46 (d, J = 6 Hz, 3 H), 1.33 (d, J = 6 Hz, 3 H), 1.31 (d, J = 6 Hz, 3 H). Anal. Calcd for $C_{18}H_{20}O_4$: C, 72.20; H, 5.59. Found: C, 72.10; H, 5.60.

2,3-Bis(1-methylethoxy)-4-(1-hexynyl)-4-hydroxycyclobut-2-en-1-one (3h). Analogous reaction of **2** (0.100 g) with 1-lithiohexyne (generated by addition of 1.05 equiv of n-BuLi to a THF solution of 1-hexyne at −78 °C and stirring for 1 h at −78 °C and 1 h at 0 °C) gave an 82% yield of **3h** (0.196 g) as a pale yellow oil: IR (CH_2Cl_2, cm^{-1}) 3570, 2940, 2230, 1778, 1630, 1390, 1323; ^1H NMR ($CDCl_3$, 360 MHz) δ 5.02 (hept, J = 6 Hz, 1 H), 4.87 (hept, J = 6 Hz, 1 H), 3.53 (s, 1 H), 2.26 (t, J = 7 Hz, 2 H), 1.55–1.35 (m, 4 H), 1.45 (d, J = 6 Hz, 3 H), 1.43 (d, J = 6 Hz, 3 H), 1.30 (d, J = 6 Hz, 3 H), 1.28 (d, J = 6 Hz, 3 H), 0.90 (t, J = 7 Hz, 3 H). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.39; H, 8.72.

2,3-Bis(1-methylethoxy)-4-hydroxy-4-[(trimethylsilyl)ethynyl]cyclobut-2-en-1-one (3i). Analogous reaction of **2** (0.200 g) with lithium (trimethylsilyl)acetylide (generated by addition of 1.05 equiv of n-BuLi to a THF solution of (trimethylsilyl)-acetylene at −78 °C and stirring for 1 h at −78 °C and 30 min at −5 °C) gave a 70% yield of **3i** (0.212 g) as a white solid, mp 107–108 °C (CH_2Cl_2/hexanes): IR (CH_2Cl_2, cm^{-1}) 3560, 2980, 2160, 1775, 1625, 1385, 1320, 1095; ^1H NMR ($CDCl_3$, 360 MHz) δ 5.00 (hept, J = 6 Hz, 1 H), 4.88 (hept, J = 6 Hz, 1 H), 2.80 (s, 1 H), 1.45 (d, J = 6 Hz, 3 H), 1.43 (d, J = 6, 3 H), 1.30 (d, J = 6 Hz, 3 H), 1.29 (d, J = 6 Hz, 3 H), 0.19 (s, 9 H). Anal. Calcd for $C_{15}H_{24}O_4Si$: C, 60.78; H, 8.16. Found: C, 60.68; H, 8.19. In addition, a 22% (0.050 g) yield of the desilylated addition product, 2,3-bis(1-methylethoxy)-4-hydroxy-4-ethynylcyclobut-2-en-1-one (**3i'**) was isolated as a white solid: mp 80–81 °C (CH_2Cl_2/hexanes): IR (CH_2Cl_2, cm^{-1}) 3570, 3300, 2990, 1790, 1635, 1390, 1325, 1100; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.98 (hept, J = 6 Hz, 1 H), 4.88 (hept, J = 6 Hz, 1 H), 3.09 (s, 1 H), 2.78 (s, 1 H), 1.45 (d, J = 6 Hz, 3 H), 1.44 (d, J = 6 Hz, 3 H), 1.30 (d, J = 6 Hz, 3 H), 1.29 (d, J = 6 Hz, 3 H). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.28; H, 7.19. Found: C, 64.35; H, 7.20.

2,3-Bis(1-methylethoxy)-4-hydroxy-4-[4-[(trimethylsilyl)ethynyl]phenyl]cyclobut-2-en-1-one (3j). Analogous reaction of **2** (0.286 g) with (4-lithiophenyl)(trimethylsilyl)acetylene (generated by addition of 1.05 equiv of n-BuLi to a THF solution of (4-bromophenyl)(trimethylsilyl)acetylene[23] at −100 °C and stirring at −100 °C for 45 min) gave an 88% yield of **3j** (0.473 g) as a colorless oil: IR (CH_2Cl_2, cm^{-1}) 3570, 2995, 2170, 1780, 1630, 1390, 1325; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.55–7.42 (m, 4 H), 4.92 (hept, J = 6 Hz, 1 H), 4.85 (hept, J = 6 Hz, 1 H),m 1.38 (d, J = 6 Hz, 3 H), 1.33 (d, J = 6 Hz, 3 H), 1.31 (d, J = 6 Hz, 3 H), 1.30 (d, J = 6 Hz, 3 H), 0.25 (s, 9 H). Anal. Calcd for $C_{21}H_{28}O_4Si$: C, 67.71; H, 7.58. Found: C, 68.05; H, 7.80.

General Procedure for Substituted Semisquarate Formation. 2,3-Bis(1-methylethoxy)-4-n-butyl-4-hydroxycyclobut-2-en-1-one (**3c**) (1.1239 g, 4.38 mmol) was dissolved in 30 mL of CH_2Cl_2 at room temperature and 4 drops of concentrated HCl were added. The reaction was monitored by TLC (SiO_2, 35% Et_2O in hexanes) for disappearance of starting material. After 30 min, the reaction mixture was diluted with 30 mL of CH_2Cl_2 and dried with K_2CO_3. Solvent was removed to yield a clear oil which was purified on a 4-mm rotor (SiO_2, 35% Et_2O in hexanes) to yield 0.7753 g (90% yield) of **4-n-butyl-3-(1-methylethoxy)cyclobut-3-ene-1,2-dione (4c)** as a clear oil: IR (CH_2Cl_2, cm^{-1}) 2960, 2930, 1790, 1750, 1590, 1390, 1095; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.41 (hept, J = 6 Hz, 1 H), 2.60 (t, J = 8 Hz, 2 H), 1.67 (m, 2 H), 1.46 (d, J = 6 Hz, 3 H), 1.37 (m, 2 H), 0.94 (t, J = 8 Hz, 3 H). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.33; H, 8.22. Found: C, 67.26; H, 8.27.

3-(1-Methylethoxy)cyclobut-3-ene-1,2-dione (4a) was synthesized analogously in 65% yield (0.272 g from 0.598 g of **3a**) as a pale yellow oil: IR (CH_2Cl_2, cm^{-1}) 3120, 2998, 1780, 1570; ^1H NMR ($CDCl_3$, 360 MHz) δ 8.57 (s, 1 H), 5.02 (hept, J = 6 Hz, 1 H), 1.51 (d, J = 6 Hz, 6 H). Anal. Calcd for $C_7H_8O_3$: C, 60.00; H, 5.76. Found: C, 60.08; H, 5.81.

3-(1-Methylethoxy)-4-methylcyclobut-3-ene-1,2-dione (4b) was synthesized analogously in 82% yield (0.150 g from 0.253 g of **3b**) as a colorless oil: IR (CH_2Cl_2, cm^{-1}) 2995, 1800, 1765, 1600, 1410, 1355; ^1H NMR ($CDCl_3$, 360 MHz) δ 5.40 (hept, J = 6 Hz, 1 H), 2.22 (s, 3 H), 1.48 (d, J = 6 Hz, 6 H). Anal. Calcd for $C_8H_{10}O_3$: C, 62.34; H, 6.54. Found: C, 62.45; H, 6.59.

4-*tert*-Butyl-3-(1-methylethoxy)cyclobut-3-ene-1,2-dione (4d) was synthesized analogously in 95% yield (0.177 g from 0.243 g of **3d**) as a colorless oil: IR (CH_2Cl_2, cm^{-1}) 2960, 1785, 1750, 1580, 1090; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.43 (hept, J = 6 Hz, 1 H), 1.45 (d, J = 6 Hz, 6 H), 1.33 (s, 9 H). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.33; H, 8.22. Found: C, 67.27; H, 8.25.

3-(1-Methylethoxy)-4-phenylcyclobut-3-ene-1,2-dione (4e) was synthesized analogously in 89% yield (0.126 g from 0.182 g of **3e**) as a yellow solid: mp 113–114 °C (CH_2Cl_2/hexanes); IR (CH_2Cl_2, cm^{-1}) 3060, 2980, 1780, 1747, 1605, 1585, 1390; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.10–8.00 (m, 2 H), 7.60–7.45 (m, 3 H), 5.63 (hept, J = 6 Hz, 1 H), 1.57 (d, J = 6 Hz, 6 H). Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.20; H, 5.59. Found: C, 72.10; H, 5.60.

3-(1-Methylethoxy)-4-(2-thienyl)cyclobut-3-ene-1,2-dione (4f) was synthesized analogously in 96% yield (0.526 g from 0.694 g of **3f**) as a yellow solid: mp 93–94.5 °C (CH_2Cl_2/hexanes); IR (CH_2Cl_2, cm^{-1}) 2990, 1790, 1738, 1600, 1505, 1420, 1395; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.90 (dd, J = 1 Hz, 4 Hz, 1 H), 7.80 (dd, J = 1 Hz, 5 Hz, 1 H), 7.30 (dd, J = 5 Hz, 4 Hz, 1 H), 5.60 (hept, J = 6 Hz, 1 H), 1.57 (d, J = 6 Hz, 6 H). Anal. Calcd for $C_{11}H_{10}O_3S$: C, 59.45; H, 4.54. Found: C, 59.52; H, 4.59.

3-(1-Methylethoxy)-4-(phenylethynyl)cyclobut-3-ene-1,2-dione (4g) was synthesized analogously in 99% yield (0.258 g from 0.323 g of **3g**) as a yellow solid: mp 85–86 °C (CH_2Cl_2/hexanes); IR (CH_2Cl_2, cm^{-1}) 2980, 2198, 1785, 1605, 1580, 1490, 1400; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.6–7.4 (m, 5 H), 5.49 (hept, J = 6 Hz, 1 H), 1.57 (d, J = 6 Hz, 6 H). Anal. Calcd for $C_{15}H_{12}O_3$: C, 75.00; H, 5.04. Found: C, 74.81; H, 5.10.

4-(1-Hexynyl)-3-(1-methylethoxy)cyclobut-3-ene-1,2-dione (4h) was synthesized analogously in 88% yield (0.091 g from 0.131 g of **3h**) as a pale yellow oil: IR (CH_2Cl_2, cm^{-1}) 2960, 2930, 2220, 1790, 1760, 1585, 1395; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.38 (hept, J = 6 Hz, 1 H), 2.62 (t, J = 7 Hz, 2 H), 1.63 (m, 2 H), 1.51 (d, J = 6 Hz, 6 H), 1.50–1.40 (m, 2 H), 0.95 (t, J = 7 Hz, 3 H). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.96; H, 7.37.

3-(1-Methylethoxy)-4-[(trimethylsilyl)ethynyl]cyclobut-3-ene-1,2-dione (4i) was synthesized analogously in 93% yield (0.428 g from 0.575 g of **3i**) as a yellow solid: mp 35–36 °C (CH_2Cl_2/hexanes); IR (CH_2Cl_2, cm^{-1}) 2960, 1785, 1760, 1580, 1378, 1323; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.40 (hept, J = 6 Hz, 1 H), 1.52 (d, J = 6 Hz, 6 H), 0.28 (s, 9 H). Anal. Calcd for $C_{12}H_{16}O_3Si$:

(22) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945–948.

(23) Eaborn, C.; Walton, D. R. M. *J. Organomet. Chem.* **1964**, *2*, 95.

C, 60.99; H, 6.82. Found: C, 61.04; H, 6.84.

4-Ethynyl-3-(1-methylethoxy)cyclobut-3-ene-1,2-dione (4i') was synthesized analogously in 63% yield (0.114 g from 0.250 g of **3i'**) as a yellow solid: mp 77–78 °C dec (CH_2Cl_2/hexanes); IR (CH_2Cl_2, cm^{-1}) 3290, 2980, 2100, 1785, 1580, 1370, 1320, 1085; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.39 (hept, J = 6 Hz, 1 H), 4.76 (s, 1 H), 1.53 (d, J = 6 Hz, 6 H). Anal. Calcd for $C_9H_8O_3$: C, 65.86; H, 4.91. Found: C, 65.93; H, 4.95.

3-(1-Methylethoxy)-4-[4-[(trimethylsilyl)ethynyl]phenyl]cyclobut-3-ene-1,2-dione (4j) was synthesized analogously in a 90% yield (0.312 g from 0.413 g of **3j**) as a yellow solid: mp 153–154 °C (CH_2Cl_2/hexanes); IR (CH_2Cl_2, cm^{-1}) 2995, 2990, 2160, 1788, 1755, 1610, 1595, 1510, 1400; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.98 (d, J = 8 Hz, 2 H), 7.56 (d, J = 8 Hz, 2 H), 5.62 (hept, J = 6 Hz, 1 H), 1.60 (d, J = 6 Hz, 6 H), 0.27 (s, 9 H). Anal. Calcd for $C_{18}H_{20}O_3Si$: C, 69.20; H, 6.45. Found: C, 69.34; H, 6.56.

Preparation of the *tert*-Butyldimethylsilyl Ethers of 3a and 3b. 4-(*tert*-Butyldimethylsiloxy)-2,3-bis(1-methylethoxy)-4-methylcyclobut-2-en-1-one. 2,3-Bis(1-methylethoxy)-4-hydroxy-4-methylcyclobut-2-en-1-one (5.00 g, 23.34 mmol) was added to a solution of 4-(dimethylamino)pyridine (3.71 g, 30.35 mmol) and *tert*-butyldimethylsilyl chloride (4.92 g, 32.27 mmol) in 50 mL of dry DMF at room temperature under N_2. The reaction was quenched after 12 h with 50 mL of water and extracted with hexanes (6 × 100 mL). The combined organics were washed once with 50 mL of water, dried with Na_2SO_4, and concentrated. The resulting oil was distilled (bp 87–89 °C, 0.40 mmHg) to give 4.91 g (64%) of pure product: IR (CH_2Cl_2, cm^{-1}) 2980, 2960, 2935, 2890, 2860, 1770, 1626, 1466, 1386, 1375, 1323, 1145, 1140, 11048, 1000, 940, 844, 780; ^1H NMR (360 MHz, $CDCl_3$) δ 4.862 (hept, J = 6.1 Hz, 1 H), 4.857 (hept, J = 6.1 Hz, 1 H), 1.430 (s, 3 H), 1.388 (d, J = 6.1 Hz, 3 H), 1.380 (d, J = 6.1 Hz, 3 H), 1.279 (d, J = 6.1 Hz, 3 H), 1.248 (d, J = 6.1 Hz, 3 H), 0.855 (s, 9 H), 0.120 (s, 3 H), 0.087 (s, 3 H); ^{13}C ($CDCl_3$) 187, 169, 130, 84, 76, 73, 25, 23, 22.5, 22.3, 22.2, 20.6, 18, –4. Anal. Calcd for $C_{17}H_{32}O_4Si$: C, 62.15; H, 9.82. Found: C, 62.11; H, 9.81.

4-(*tert*-Butyldimethylsiloxy)-2,3-bis(1-methylethoxy)-cyclobut-2-en-1-one. 4-(Dimethylamino)pyridine (4.36 g, 35.69 mmol) and *tert*-butyldimethylsilyl chloride (5.80 g, 38.52 mmol) were added consecutively to a solution of 2,3-bis(1-methylethoxy)-4-hydroxycyclobut-2-en-1-one (5.51 g, 27.51 mmol) in 25 mL of dry DMF at 25 °C. The reaction was complete in 3 h (TLC, SiO_2, 30% Et_2O/hexane) and after quenching with water was extracted with hexanes, dried (Na_2SO_4), and concentrated. Simple distillation gave 8.33 g (96.3%) of pure colorless liquid (bp 89–91 °C, 0.30 mmHg): IR (neat, cm^{-1}) 2980, 2960, 2930, 2890, 2860, 1778, 1636, 1475, 1388, 1325, 1260, 1196, 1172, 1149, 1105, 1066, 1018, 948, 920, 880, 848, 790; ^1H NMR (300 MHz, $CDCl_3$) δ 4.87 (hept, J = 6.2 Hz, 1 H), 4.86 (s, 1 H), 4.82 (hept, J = 6.2 Hz, 1 H), 1.39 (d, J = 6.2 Hz, 3 H), 1.38 (d, J = 6.2 Hz, 3 H), 1.28 (d, J = 6.2 Hz, 3 H), 1.258 (d, J = 6.2 Hz, 3 H), 0.90 (s, 9 H), 0.13 (s, 6 H). Anal. Calcd for $C_{16}H_{30}O_4Si$: C, 61.10; H, 9.62. Found: C, 61.26; H, 9.68.

Preparation of Substituted Cyclobutenediones by Sequential Addition of Organolithium Reagents. 4-(*tert*-Butyldimethylsiloxy)-2,3-bis(1-methylethoxy)-1-methylcyclobut-2-en-1-ol (5a). 4-(*tert*-Butyldimethylsiloxy)-2,3-bis(1-methylethoxy)cyclobut-2-en-1-one (3.820 g, 12.15 mmol) was dissolved in 10 mL of dry THF, cooled to –78 °C, and treated with methyllithium (9.7 mL, 1.5 M in Et_2O, 1.2 equiv). The reaction was complete within 1 h (TLC, SiO_2, 30% Et_2O/hexane). Aqueous quench at –78 °C followed by extraction (3 × 50 mL of Et_2O), drying (Na_2SO_4), and distillation (74–75 °C, 0.25 mmHg) afforded 3.273 g (82%) of a colorless liquid: IR (CH_2Cl_2, cm^{-1}): 3520, 2980, 2935, 1300, 1107, 1060, 2890, 2860, 1710, 1465, 1370, 1345, 1013, 946, 870, 840, 782; ^1H NMR (300 MHz, $CDCl_3$) δ 4.456 (hept, J = 6.0 Hz, 1 H), 4.317 (hept, J = 6.3 Hz, 1 H), 4.282 (s, 1 H), 2.633 (s, 1 H), 1.378 (s, 3 H), 1.27–1.20 (m, 12 H), 0.919 (s, 9 H), 0.122 (s, 6 H); ^{13}C ($CDCl_3$) 134, 128, 75, 74, 72, 71, 26, 22.6, 22.5, 22.4, 22.3, 21, 18, –4.6, –4.8. Anal. Calcd for $C_{17}H_{34}O_4Si$: C, 61.77; H, 10.37. Found: C, 61.71; H, 10.41.

3-Methylcyclobut-3-ene-1,2-dione (6a). 4-(*tert*-Butyldimethylsiloxy)-2,3-bis(1-methylethoxy)-1-methylcyclobut-2-en-1-ol (1.615 g, 4.87 mmol) was dissolved in 15 mL of CH_2Cl_2 and treated with 5 drops of 12 N HCl. After being stirred for 4 h the reaction was complete (TLC, SiO_2, 30% Et_2O/hexane). The reaction mixture was drawn through a fritted funnel containing Na_2SO_4 with CH_2Cl_2 and concentrated at 15 mmHg. Distillation at 3.6 mmHg, 68–70 °C, gave 0.412 g (88%) of a golden liquid: IR (CH_2Cl_2, cm^{-1}) 1783 (s, br, shoulders at 1795 and 1760), 1602, 1568, 1435, 1370, 1133, 1106, 1070, 1040, 995, 890; ^1H NMR (300 MHz, $CDCl_3$) δ 9.303 (q, J = 1.2 Hz, 1 H), 2.468 (d, J = 1.08 Hz, 3 H); exact mass calcd for $C_5H_4O_2$ 96.02113, found 96.02068.

1-*n*-Butyl-4-(*tert*-butyldimethylsiloxy)-2,3-bis(1-methylethoxy)cyclobut-2-en-1-ol (5b). 4-(*tert*-Butyldimethylsiloxy)-2,3-bis(1-methylethoxy)cyclobut-2-en-1-one (2.83 g, 9.0 mmol) was dissolved in 10 mL of dry THF, cooled to –78 °C, and treated dropwise with *n*-butyllithium (4.3 mL, 2.5 M in hexanes, 1.2 equiv). The reaction was complete in 2 h (TLC, SiO_2, 30% Et_3O/hexane) and was quenched at –78 °C. The reaction mixture was extracted with Et_2O (3 × 50 mL), the combined organic layers were dried (Na_2SO_4) and concentrated, and then simple distillation gave 2.67 g (80%) of colorless product as the only fraction (bp 96–97 °C, 0.30 mmHg): IR (CH_2Cl_2, cm^{-1}) 3000, 2960, 2935, 2860, 1708, 1468, 1370, 1300, 1108, 1048, 1005, 950, 870, 840, 780; ^1H NMR (360 MHz, $CDCl_3$) δ 4.445 (hept, J = 6.1 Hz, 1 H), 4.326 (hept, J = 6.1 Hz, 1 H), 4.315 (s, 1 H), 2.760 (s, 1 H), 1.77–1.60 (m, 2 H), 1.43–1.26 (m, 4 H), 1.257–1.205 (4 apparent peaks, 12 H), 0.916 (s, 9 H), 0.90 (br s, 3 H), 0.123 (s, 3 H), 0.116 (s, 3 H); ^{13}C NMR ($CDCl_3$) 134, 129, 77, 73, 72, 72, 35, 27, 26, 23, 22.6, 22.4, 18, 14, –4.6, –4.7. Anal. Calcd for $C_{20}H_{40}O_4Si$: C, 64.47; H, 10.82. Found: C, 64.43; H, 10.85.

3-*n*-Butylcyclobut-3-ene-1,2-dione (6b). 1-*n*-Butyl-4-(*tert*-butyldimethylsiloxy)-2,3-bis(1-methylethoxy)cyclobut-2-en-1-ol (1.64 g, 4.41 mmol) was dissolved in 10 mL of CH_2Cl_2 at room temperature and treated with 8 drops of concentrated HCl. The reaction was complete after 3 h (TLC, SiO_2, 30% Et_2O/hexane). The reaction mixture was drawn through a fritted funnel containing Na_2SO_4 with CH_2Cl_2 and concentrated. The resulting yellow oil was distilled to give 0.573 g (94%) of product (bp 53–56 °C, 2.5 mmHg): IR (CH_2Cl_2, cm^{-1}) 2955, 2925, 2862, 1779, 1551, 1460, 1065, 885; ^1H NMR (360 MHz, $CDCl_3$) δ 9.267 (br s, 1 H), 2.799 (t, J = 7.4 Hz, 2 H), 1.702 (pent, J = 7.6 Hz, 2 H), 1.419 (hext, J = 7.5 Hz, 2 H), 0.953 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 208, 200, 197, 185, 28, 27, 22, 13. Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.44; H, 7.36.

1-*tert*-Butyl-4-(*tert*-butyldimethylsiloxy)-2,3-bis(1-methylethoxy)cyclobut-2-en-1-ol (5c). 4-(*tert*-Butyldimethylsiloxy)-2,3-bis(1-methylethoxy)-2-cyclobuten-1-one (0.329 g, 1.05 mmol) in 5 mL THF at –78 °C was treated with *tert*-butyllithium (0.74 mL, 1.7 M in hexanes, 1.2 equiv) and was warmed to –10 °C after which the reaction was complete (TLC, SiO_2, 30% Et_2O/hexane) and was quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted with Et_2O and the solvent evaporated. The crude product was passed through a plug of SiO_2 (5 g) with Et,2*o*, the solvent removed, and the oil dried at 0.20 mmHg for an hour to give 0.331 g (85%) of pure product: IR (CH_2Cl_2, cm^{-1}) 3500, 2960, 2940, 2870, 1709, 1469, 1389, 1377, 1369, 1340, 1300, 1250, 1065, 1020, 1012, 980, 945, 890, 860, 840, 782; ^1H NMR (300 MHz, $CDCl_3$) δ 4.464 (hept, J = 6 Hz, 1 H), 4.424 (s, 1 H), 4.283 (hept, J = 6 Hz, 1 H), 2.88 (s, 1 H) 1.194–1.253 (overlapping doublets, 12 H), 0.958 (s, 9 H), 0.909 (s, 9 H), 0.138 (s, 3 H), 0.120 (s, 3 H). Anal. Calcd for $C_{20}H_{40}O_4Si$: C, 64.47; H, 10.82. Found: C, 64.54; H, 10.83.

3-*tert*-Butylcyclobut-3-ene-1,2-dione (6c). 1-*tert*-Butyl-4-(*tert*-butyldimethylsiloxy)-2,3-bis(1-methylethoxy)cyclobut-2-en-1-ol (1.19 g, 3.18 mmol) was dissolved in 10 mL of CH_2Cl_2 and treated with 4 drops of concentrated HCl. The reaction was complete after stirring for 3 h at room temperature (TLC, SiO_2, 30% Et_2O/hexane) and was filtered through a plug of Na_2SO_4 with CH_2Cl_2. Removal of solvent at 15 mmHg followed by sublimation of the product at 80 °C and 0.3 mmHg onto a coldfinger at –78 °C gave 0.391 g (90%) of pure product as a slightly yellow solid: mp 83–85 °C; IR (CH_2Cl_2, cm^{-1}) 2970, 2930, 2905, 2870, 1780, 1750w, 1550, 1460, 1368, 1230, 1180, 1100, 1055, 880; ^1H NMR (360 MHz, $CDCl_3$) δ 9.139 (s, 1 H), 1.341 (s, 9 H). Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.57; H, 7.34.

4-(*tert*-Butyldimethylsiloxy)-2,3-bis(1-methylethoxy)-1-(2-thienyl)cyclobut-2-en-1-ol (5d). 4-(*tert*-Butyldimethylsiloxy)-2,3-bis(1-methylethoxy)cyclobut-2-en-1-one (1.01 g, 3.22 mmol) was added to a solution of 2-lithiothiophene [1.2 equiv formed from thiophene (307 mg, 3.65 mmol) and *n*-butyllithium

(1.46 mL, 2.5 M in hexanes, 1.0 equiv) in dry THF at −20 °C] in 5 mL of THF at −78 °C. After 2 h the starting material had disappeared (TLC, SiO_2, 30% Et_2O/hexane) and the reaction was quenched at −78 °C with water. Et_2O (40 mL) was added, the layers were separated, and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The product was purified by radial chromatography (Chromatotron, 2 mm SiO_2 plate, 30% Et_2O/hexane). Removal of solvent at reduced pressure gave 1.23 g (96%) of a pure colorless liquid: IR (neat, cm^{-1}) 3480, 2970, 2950, 2925, 2955, 2855, 1706 (m, br), 1463, 1368, 1335, 1297, 1252, 1230, 1200, 1180, 1138, 1105, 1056, 939, 879, 836, 810, 780, 697, 670; ^1H NMR (360 MHz, $CDCl_3$) δ 7.234 (dt, J = 3.0, 0.65 Hz, 1 H), 6.976 (m, 2 H), 4.459 (hept, J = 5.9 Hz, 1 H), 4.395 (hept, J = 6 Hz, 1 H), 4.284 (br s, 1 H), 3.498 (s, 1 H), 1.304–1.266 (4 peaks, 9 H), 1.13 (d, J = 6.2 Hz, 3 H), 0.924 (s, 9 H), 0.107 (s, 3 H), 0.093 (s, 3 H); exact mass calcd 398.19472, found 398.19531.

3-(2-Thienyl)cyclobut-3-ene-1,2-dione (6d). 4-(*tert*-Butyldimethylsiloxy)-2,3-bis(1-methylethoxy)-1-(2-thienyl)cyclobut-2-en-1-ol (0.990 g, 2.48 mmol) was dissolved in 10 mL of CH_2Cl_2 and treated with 30 drops of concentrated HCl. The starting material had disappeared after stirring at room temperature for 22 h. The mixture was filtered through a plug of Na_2SO_4 with CH_2Cl_2 and then passed through a short plug (3 × 2 cm) of flash silica gel with CH_2Cl_2. The solvent was removed and the solid dissolved in a minimal amount of warm CH_2Cl_2 and then placed in the freezer to precipitate the product. Hexanes (80 mL) were added to complete precipitation and the product was collected via suction filtration. The remaining product was recovered by concentration of the filtrate and chromatography of the residual oil (SiO_2, 2 × 20 cm., 50% CH_2Cl_2/hexanes). Removal of solvent at reduced pressure gave additional product. The total combined weight was 0.365 g (90% yield) of red-orange product, mp 136–138 °C: IR (CH_2Cl_2, cm^{-1}) 1774, 1563, 1480, 1405, 1358, 1168, 1103, 1073, 1048, 877, 860; ^1H NMR (360 MHz, $CDCl_3$) δ 9.212 (s, 1 H), 8.081 (dd, J = 4.0 Hz, J < 1 Hz, 1 H), 7.964 (dd, J = 5.0, J < 1 Hz, 1 H), 7.325 (dd, J = 5 Hz, J = 4 Hz, 1 H); exact mass calcd for $C_8H_4O_2S$ 163.99320123, found 163.99233204.

4-(*tert*-Butyldimethylsiloxy)-2,3-bis(1-methylethoxy)-1,4-dimethylcyclobut-2-en-1-ol (5e). 4-(*tert*-Butyldimethylsiloxy)-2,3-bis(1-methylethoxy)-4-methylcyclobut-2-en-1-one (1.48 g, 4.50 mmol) in 5.0 mL of dry THF at −78 °C was treated dropwise with methyllithium (3.6 mL, 1.5 M in Et_2O, 1.2 equiv). Reaction was complete in 3 h (TLC, SiO_2, 30% Et_2O/hexane) and was quenched at −78 °C. The aqueous phase was extracted with ether (3 × 50 mL) and the combined extracts were dried (Na_2SO_4). The solvent was removed and simple distillation afforded 1.42 g (91.4%) of product as a colorless liquid (bp 71–72 °C, 0.25 mmHg): IR (CH_2Cl_2, cm^{-1}) 3480, 2970, 2930, 2890, 2855, 1710, 1615, 1465, 1375, 1300, 1220, 1103, 1070, 980, 950, 840; ^1H NMR (300 MHz, $CDCl_3$) δ 4.432 (m, 2 H), 3.360 (s, 1 H), 1.349 (s, 3 H), 1.306 (s, 3 H), 1.258 (d, J = 6 Hz, 3 H), 1.253 (d, J = 6 Hz, 3 H), 1.241 (d, J = 6 Hz, 3 H), 1.210 (d, J = 6 Hz, 3 H), 0.889 (s, 9 H), 0.174 (s, 3 H), 0.145 (s, 3 H); ^{13}C ($CDCl_3$) 133, 131, 78, 77, 76, 72, 71, 26, 23, 22.3, 22.2, 19.3, 19.0, 18, −3.62, −3.68. Anal. Calcd for $C_{18}H_{36}O_4Si$: C, 62.74; H, 10.53. Found: C, 62.55; H, 10.45.

3,4-Dimethylcyclobut-3-ene-1,2-dione (6e). 4-(*tert*-Butyldimethylsiloxy)-2,3-bis(1-methylethoxy)-1,4-dimethylcyclobut-2-en-1-ol (1.419 g, 4.118 mmol) was dissolved in 10 mL of CH_2Cl_2 at room temperature and treated with 4 drops of concentrated HCl. After 30 min, the reaction was complete (TLC, SiO_2, 30% Et_2O/hexane). The reaction mixture was drawn through a fritted funnel containing Na_2SO_4 with CH_2Cl_2 and concentrated at 15 mmHg. Simple distillation (0.3 mmHg) gave 0.436 g (96.1%) of pure product as the only fraction. Spectral properties of the product were identical with published data.[21]

3-*n*-Butyl-4-methylcyclobut-3-ene-1,2-dione (6f). 4-(*tert*-Butyldimethylsiloxy)-2,3-bis(1-methylethoxy)-4-methylcyclobut-2-en-1-one (324 mg, 0.9862 mmol) in 5 mL of THF at −78 °C was treated with *n*-butyllithium (0.5 mL, 2.5 M in hexanes, 1.3 equiv). After the starting material had dissappeared (TLC, SiO_2, 30% Et_2O/hexane), 20 drops of concentrated HCl was added. After warming to room temperature over 20 min, 50 mL of ether was added and the solution was dried briefly with Na_2SO_4. The solvent was removed and the product chromatographed (15 g of SiO_2, 30% Et_2O/hexane) to give 0.119 g (79%) of golden dione: IR (CH_2Cl_2, cm^{-1}) 2934, 2960, 2870, 1768, 1786, 1600, 1455, 1465, 1380, 1037; ^1H NMR (360 MHz, $CDCl_3$) δ 2.730 (t, J = 7.62 Hz, 2 H), 2.343 (s, 3 H), 1.701 (m, 2 H), 1.39 (apparent hexet, J = 7.4 Hz, 2 H), 0.949 (t, J = 7.36 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 203, 200, 199.3, 199.1, 28, 26, 22.70, 14, 11. Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.92; H, 7.96.

3-*tert*-Butyl-4-methylcyclobut-3-ene-1,2-dione (6g). 4-(*tert*-Butyldimethylsiloxy)-2,3-bis(1-methylethoxy)-4-methylcyclobut-2-en-1-one (1.00 g, 3.04 mmol) in 5 mL of dry THF at −78 °C was treated with *tert*-butyllithium (2.15 mL, 1.7 M in hexanes, 1.2 equiv) and stirred for 2 h after which the reaction was complete (TLC, SiO_2, 30% Et_2O/hexane). After quenching at −78 °C, Et_2O (20 mL) was added, the organic layer was separated, and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic layers were concentrated, and the residue was dissolved in 10 mL of CH_2Cl_2 and treated with 4 drops of concentrated HCl. The reaction was complete after 5 h and was filtered through a plug of Na_2SO_4 with CH_2Cl_2. Removal of the solvent at reduced pressure followed by radial chromatography (Chromatotron, 2 mm SiO_2 plate, 10% Et_2O/hexanes) gave 0.445 g (96%) of pure product. The product can be distilled if necessary, bp 50–52 °C, 0.2 mmHg: IR (CH_2Cl_2, cm^{-1}) 2975, 2935, 2908, 2875, 1790, 1770, 1588, 1480, 1460, 1400, 1370, 1323, 1210, 1120, 1060, 1024; ^1H NMR (360 MHz, $CDCl_3$) δ 2.412 (s, 3 H), 1.382 (s, 9 H). Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95; Found: C, 70.92; H, 7.97.

3-Methyl-4-phenylcyclobut-3-ene-1,2-dione (6h). 4-(*tert*-Butyldimethylsiloxy)-2,3-bis(1-methylethoxy)-4-methylcyclobut-2-en-1-one (465 mg, 1.41 mmol) in 5 mL of THF at −78 °C was treated with phenyllithium (1.29 mL, 1.32 M in Et_2O, 1.2 equiv). The reaction was complete after 2 h (TLC, SiO_2, 30% Et_2O/hexane), 20 drops of concentrated HCl were added, and the reaction was stirred for 6 h. Et_2O (20 mL) was added, and the mixture was dried (Na_2SO_4) and concentrated. The product was chromatographed (5 g of SiO_2) by using 30% Et_2O/hexane to remove the impurities and then with Et_2O to recover the product. After removal of solvent, 190 mg (78%) of golden product (mp 98–100 °C) was obtained: IR (CH_2Cl_2, cm^{-1}) 1780, 1765, 1603, 1590, 1088, 1068; ^1H NMR (300 MHz, $CDCl_3$) δ 8.016 (m, 2 H), 7.61–7.53 (m, 3 H), 2.653 (s, 3 H); ^{13}C: ($CDCl_3$) 198, 197, 194, 191, 133, 129, 128.6, 128.5, 12; exact mass calcd for $C_{11}H_8O_2$ 172.0524, found 172.052307.

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