Articles

A Strategy for Generalization of the Regiospecific Synthesis of Substituted Quinones from Cyclobutenediones

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Documented within is a straightforward protocol for the synthesis of generally substituted benzoquinones and ring-fused quinones. Previously, the crucial issue of quinone substituent regiochemistry was resolved at the stage of addition of an unsaturated carbon nucleophile to a cyclobutenedione by using either symmetrically substituted cyclobutenediones or 3-alkoxy (or amino)-4-substituted-3-cyclobutenediones. In the former case there are no regioisomeric quinones formed, while in the latter, through resonance delocalization, the alkoxy (or amino) substituent renders one of the two carbonyl groups less reactive and directs the incoming nucleophile to the other. The placement of a wide variety of substituents about the quinone ring periphery has now been solved by the less restrictive strategy of sequential introduction of substituents onto a cyclobutenedione core. The chemistry commences with 3-isopropoxy-4-substituted-3-cyclobutene-1,2-diones. Addition of an aromatic, heteroaromatic, or alkenyl nucleophile to the more reactive carbonyl group provides 4-hydroxy-4-R_{unsat}-2-cyclobutenones, which are protected as the methyl ethers by treatment with $MeI/Ag_2O/K_2CO_3$ in MeCN. A second nucleophile is added, again in a 1,2-sense, providing highly substituted 3-isopropoxy-2-cyclobutenols that are arranged to cyclobutenones under acidic conditions. The resulting cyclobutenones are converted into substituted quinones by thermolysis at 140 °C in *o*-xylene followed by oxidative workup with ceric ammonium nitrate. The substitution pattern about the quinone core is rigorously controlled by the sequence of introduction of the substituents.

Introduction

Addition of alkynyl and C_{sp2}-based nucleophiles to cyclobutenediones **1** provides 1,2-adducts (**2** and **3**) that transform to quinones on thermolysis, directly in the former case,[2-5] and after oxidation in the latter (Scheme I).[6-13] The recent development of simple procedures for the synthesis of substituted cyclobutenediones[14-19] has furthered the establishment of this chemistry as a seminal method for construction of a wide variety of substituted and ring-fused quinones, important naturally occurring compounds widely distributed in both plants and animals.[20] To date, the crucial issue of quinone substituent regiochemistry has been resolved at the stage of addition of the unsaturated carbon nucleophile to the cyclobutenedione by using either symmetrically substituted cyclobutenediones (Scheme I, $R^1 = R^2$) or 3-alkoxy-4-substituted cyclobutenediones (Scheme I, $R^2 = OR$). In the former case there are no regioisomeric quinones formed, while in the latter, through resonance delocalization, the alkoxy substituent renders one of the two carbonyl groups less reactive and directs the incoming nucleophile to the other. The placement of a wider variety of substituents about the quinone ring periphery will require an alternate and less restrictive strategy for elaboration of 4-R_{unsat}-cyclobutenones **2** and **3**, the key precursors to quinones. We have described a method for the regiospecific synthesis of cyclobutenedione monoketals,[18] molecules that could be used to access the quinone precursors **2** or **3**.[21] However, in the course of considering a general construction of substituted quinones, a more direct route to 4-hydroxy-4-R_{unsat}-2-cyclobutenones **2** and **3** revealed itself. Documented herein is a straightforward protocol for the synthesis of generally substituted benzoquinones and ring-fused quinones via sequential introduction of substituents onto a cyclobutenedione core.

Results and Discussion

Scheme II shows the key synthetic strategy that allows the construction of substituted quinones in a general fashion. The chemistry commences with 3-isopropoxy-4-substituted-3-cyclobutene-1,2-diones **4**, which are readily available in high yield by nucleophilic substitution of diisopropylsquarates,[14,15] by palladium-catalyzed cross-coupling of organic halides and trifluoromethylsulfonates with

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(2) Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1987**, *52*, 1174.
(3) Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975.
(4) Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 989.
(5) Liebeskind, L. S.; Foster, B. F. *J. Am. Chem. Soc.* **1990**, *112*, 8612.
(6) Reed, M. W.; Moore, H. W. *J. Org. Chem.* **1988**, *53*, 4166.
(7) Moore, H. W.; Perri, S. T. *J. Org. Chem.* **1988**, *53*, 996.
(8) Perri, S. T.; Moore, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 1897.
(9) Liebeskind, L. S.; Iyer, S.; Jewell, C. F., Jr. *J. Org. Chem.* **1986**, *51*, 3065.
(10) Liebeskind, L. S. *Tetrahedron Symposium in Pring* **1989**, *45*, 3053.
(11) Liebeskind, L. S.; Zhang, J. *J. Org. Chem.* **1991**, *56*, 6379.
(12) Selwood, D. L.; Jandu, K. S. *Heterocycles* **1988**, *27*, 1191.
(13) Heerding, J. M.; Moore, H. W. *J. Org. Chem.* **1991**, *56*, 4048.
(14) Reed, M. W.; Pollart, D. J.; Perri, S. T.; Foland, L. D.; Moore, H. W. *J. Org. Chem.* **1988**, *53*, 2477.
(15) Liebeskind, L. S.; Fengl, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *53*, 2482.
(16) Liebeskind, L. S.; Wang, J. *Tetrahedron Lett.* **1990**, *31*, 4293.
(17) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359.
(18) Liebeskind, L. S.; Wirtz, K. R. *J. Org. Chem.* **1990**, *55*, 5350.
(19) Xu, S.; Yerxa, B. R.; Sullivan, R. W.; Moore, H. W. *Tetrahedron Lett.* **1991**, *32*, 1129.
(20) Thomson, R. H. *Naturally Occurring Quinones III*; Chapman and Hall: London, 1987; Vol. III.

(21) Through a personal communication, we are aware that Moore and co-workers are developing a general approach to substituted quinones using cyclobutenedione monoketals.

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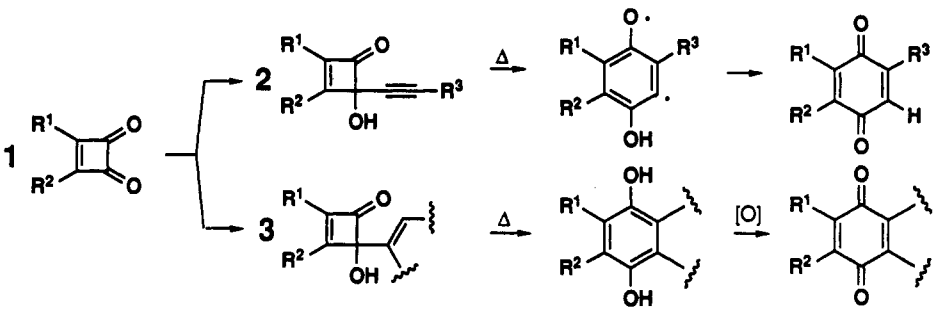
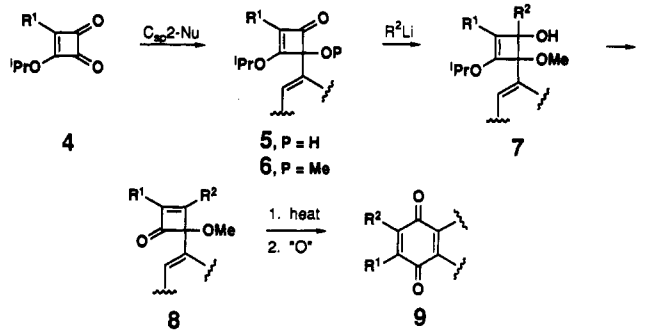
Scheme I



Scheme II

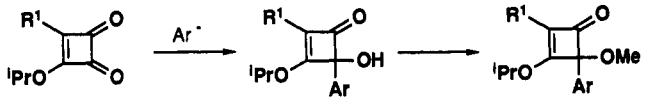


3-isopropoxy-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione,[17] or by cross-coupling of organostannanes with 3-chloro-4-isopropoxy-3-cyclobutene-1,2-dione.[16] Addition of an aromatic or heteroaromatic nucleophile to the more reactive carbonyl group of **4** provides the 4-hydroxy-4-R_{unsat}-2-cyclobutenones **5** which are easily protected as the methyl ethers **6** by treatment with $MeI/Ag_2O/K_2CO_3$ in MeCN.[22] A second nucleophile is added, again in a 1,2-sense, providing the highly substituted cyclobutenols **7**.[23] The crucial step in this strategy, the rearrangement of the 3-isopropoxy-2-cyclobutenol moiety of **7** to the enone **8**, *without disruption of the allylic/benzylic methyl ether moiety*, can be achieved by treatment of **7** under acidic conditions appropriate to each system (see below). The resulting cyclobutenones **8** are converted into substituted quinones by thermolysis at 140 °C in *o*-xylene followed by oxidative workup with ceric ammonium nitrate. The substitution pattern about the quinone core is rigorously controlled by the sequence of introduction of the substituents.

The results of conversion of cyclobutenediones **4a–c** into 4-methoxy-4-R_{unsat}-2-cyclobutenones **6** are listed in Table I. The addition of aromatic and heteroaromatic nucleophiles to the more reactive carbonyl group of **4a–c** follows established procedures.[3,7,9] For small-scale reactions, the methyl ethers **6** could be prepared by low-temperature quench of the alkoxide intermediate with $MeOSO_2CF_3$; however, on larger scale more reproducible results were obtained by quenching the alkoxide intermediate at low temperature with 10% NH_4Cl and then methylating the resulting alcohol with $MeI/Ag_2O/K_2CO_3$ in MeCN.

With a series of 4-methoxy-4-R_{unsat}-2-cyclobutenones **6** in hand, addition of the nucleophile R^2 and conversion into highly substituted quinones **9**, as proposed in Scheme II, was investigated. The results are shown in Table II.

Table I. Synthesis of 2-Substituted-3-isopropoxy-4-aryl (or heteroaryl)-4-methoxycyclobutenones



4a, R^1 = Me
4b, R^1 = *n*Bu
4c, R^1 = Ph

entry	dione	R^1	Ar	compd no.	yld (%)	compd no.	yld (%)
1	4a	Me	Ph	5a	61	6a	100
2	4a	Me	2-$MeOC_6H_4$	5b	60	6b	100
3	4a	Me	4-MeC_6H_4	5c	72	6c	100
4	4a	Me	2-furyl	5d	85	6d	92
5	4d	*n*-Bu	2-$MeOC_6H_4$	5e	79	6e	96
6	4b	*n*-Bu	4-MeC_6H_4	5f	64	6f	99
7	4b	*n*-Bu	2-furyl	5g	74	6g	94
8	4c	Ph	Ph	5h	56	6h	95
9	4c	Ph	4-MeC_6H_4	5i	76	6i	90

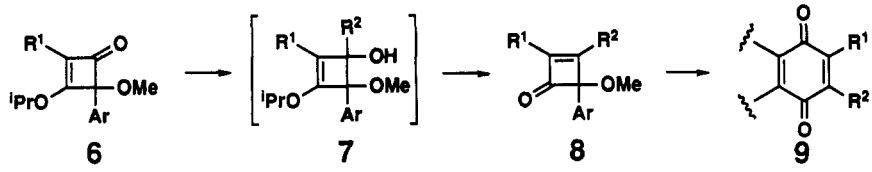
Addition of nucleophiles R^2 to cyclobutenones **6** generated 1,2-adducts **7** that were converted into the cyclobutenones **8** under conditions that were empirically derived in each case. During the early stages of the study, the reaction mixtures from addition of R^2Li to cyclobutenone **6** were quenched with aqueous NH_4Cl to give the highly substituted cyclobutenols **7**. Without purification these were treated with catalytic concentrated HCl to form the cyclobutenones **8**. To convert the 1,2-adducts **7**, where R^2 = H, to the corresponding cyclobutenones, trifluoroacetic anhydride/pyridine was required.[14] It was subsequently found that quenching the reaction mixtures from addition of R^2Li to cyclobutenone **6** with trifluoroacetic anhydride followed by addition of aqueous NH_4Cl led directly to cyclobutenones **8** in most cases. For the series of compounds where R^2 = Ph, the trifluoroacetic anhydride–NH_4Cl system led to ring-opened products but following the trifluoroacetic anhydride quench with aqueous $NaHCO_3$ allowed isolation of the desired cyclobutenones **8**. Attempts to add MeLi to cyclobutenones **6** to prepare compounds **8**, where R^2 = Me, were unsuccessful, perhaps due to the hindered nature of compounds **6** and the lower reactivity of MeLi compared to other alkyllithiums. However, the desired transformation could be achieved using $MeCeCl_2$.[24] Not all cyclobutenones **8** were amenable to purification by chromatography; in those cases the transformation from **6** to quinones **9** was carried out without purification of intermediates. The general instability of compounds **8** compromised attempts to obtain adequate elemental analyses.

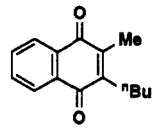
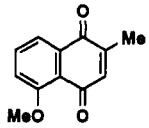
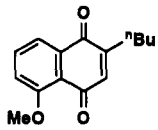
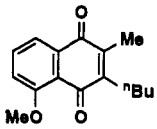
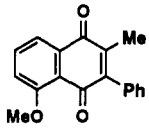
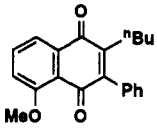
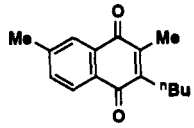
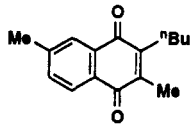
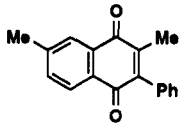
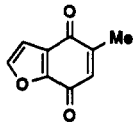
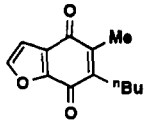
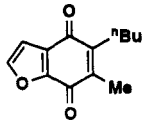
Not all quinone substitution patterns were accessible via the chemistry described. Cyclobutenone **6h**, where R^1 =

(22) Xu, S. L.; Moore, H. W. *J. Org. Chem.* **1989**, *54*, 6018.
(23) Though usually not isolated, it appears that cyclobutenes **7** are probably formed as single diastereomers in the cases that were studied. ^1H NMR and IR spectra of **7'** at varying concentrations show indications of strong intramolecular hydrogen bonding suggesting that the methoxy and hydroxy groups are cis in each case.

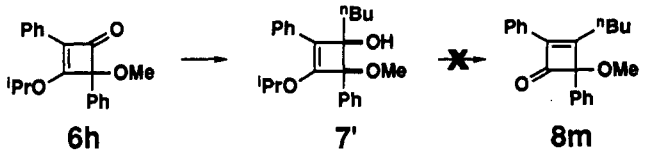
(24) Imamoto, T.; Kusumoto, T.; Tawarayam, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904.

Table II. Synthesis of Highly Substituted Quinones



entry	R^1	Ar	R^{2-}	Cond[a] 7 → 8	compd	yld (%)	quinone	compd no.	yld (%)
1	Me	Ph	*n*-BuLi	A	**8a**	60		**9a**	95
2	Me	2-$MeOC_6H_4$	$LiAlH_4$	B	**8b**	54		**9b**	80
3	*n*-Bu	2-$MeOC_6H_4$	$LiAlH_4$	B	**8c**			**9c**	40
4	Me	2-$MeOC_6H_4$	*n*-BuLi	C	**8d**	54		**9d**	88
5	Me	2-$MeOC_6H_4$	PhLi	D	**8e**	75		**9e**	85
6	*n*-Bu	2-$MeOC_6H_4$	PhLi	D	**8f**	70		**9f**	88
7	Me	4-MeC_6H_4	*n*-BuLi	A	**8g**	55		**9g**	90
8	*n*-Bu	4-MeC_6H_4	MeCeCl	E	**8h**			**9h**	66
9	Me	4-MeC_6H_4	PhLi	D	**8i**			**9i**	31
10	Me	2-furyl	$LiAlH_4$	A	**8j**			**9j**	36
11	Me	2-furyl	*n*-BuLi	A	**8k**	51		**9k**	82
12	*n*-Bu	2-furyl	$MeCeCl_2$	E	**8l**	56		**9l**	89

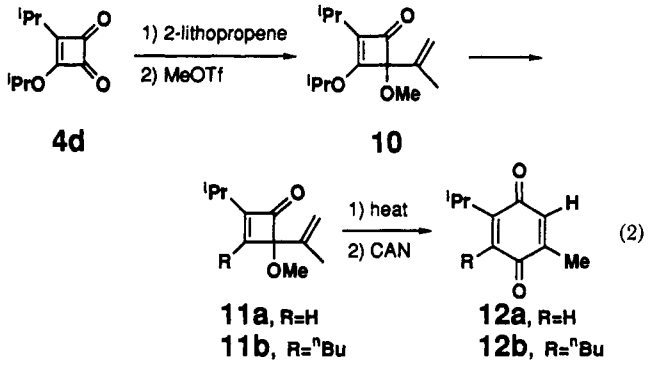
[a] Conditions: A, trifluoroacetic anhydride then 10% aqueous NH_4Cl; B, 10% aqueous NH_4Cl then trifluoroacetic anhydride/pyridine in ether at 0 °C; C, 10% aqueous NH_4Cl then catalytic concd HCl in CH_2Cl_2; D, trifluoroacetic anhydride then saturated aqueous $NaHCO_3$; E, 2 N HCl.



(1)

Ar = phenyl, represented a special case (eq 1). *n*-BuLi was added (as R^2) to cyclobutenone **6h** and the cyclobutenol 7′ was obtained in 46% yield as a stable white solid. However, attempts to convert 7′ into the corresponding cyclobutenone **8m** were unsuccessful. Note that the related substitution patterns present in compounds **8e**, **8f**, and **8i**, where R^1 = alkyl and R^2 = Ph, presented no synthetic difficulties (entries 5, 6, and 9 in Table II).

Variously substituted benzoquinones should also be preparable via the strategy outlined here. Two simple systems were synthesized to validate this assumption (eq 2). Because of instability of the intermediates in the



(2)

reaction sequences leading to the substituted benzoquinones, no purification of intermediates was performed. Methyl triflate quench (−78 °C) of the reaction of 2-lithiopropene with 3-isopropoxy-4-isopropyl-3-cyclobutene-1,2-dione (**4d**) provided an unstable adduct (**10**) that was directly reduced with $LiAlH_4$. Treatment of crude **10** with trifluoroacetic anhydride/pyridine gave a product (**11a**) that was thermolyzed in *o*-xylene at 100 °C for 20 min. The material from thermolysis was oxidized with ceric ammonium nitrate to provide 2-isopropyl-5-methyl-1,4-benzoquinone (**12a**, thymoquinone) in 17% overall yield from **4d**. In a similar fashion, 2-isopropyl-3-*n*-butyl-5-methyl-1,4-benzoquinone (**12b**) was prepared in 22% overall yield from **4d**. Although not yet optimized, it can be anticipated that a variety of substituted quinones will be accessible via this chemistry.

Conclusions

A general synthesis of substituted quinones has been developed. The method relies on the sequential addition of carbon nucleophiles to a cyclobutenedione core, beginning with 3-isopropoxy-4-substituted-3-cyclobutenediones. After a regiospecific 1,2-addition of a C_{sp^2}-nucleophile to the more reactive (nonvinylogous ester) carbonyl group, the resulting alcohol is protected as a methyl ether. Then, a second 1,2-addition reaction of a carbon nucleophile is effected at the vinylogous ester carbonyl group that remains, and the 3-isopropoxy-2-cyclobutenol moiety of the product undergoes loss of 2-propanol under acidic conditions to provide a 2,3-disubstituted-4-methoxy-4-R_{unsat}-2-cyclobutenone. Thermolysis and oxidation with ceric ammonium nitrate then provides a quinone product wherein the orientation of substituents about the quinone core has been rigorously controlled by the sequence of their introduction.

Experimental Section

Materials and Methods. Separations were accomplished by standard flash chromatography techniques using Baker SiO_2 (40 μm) or via radial chromatography using a 7924T Chromatotron from Harrison Research. The rotor was coated with Merck PF 254 silica gel. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium benzophenone ketyl solutions. All other solvents were reagent-grade quality and used without purification. Squaric acid was purchased from Aldrich Chemical Co.

Synthesis of Cyclobutenediones 4. 3-Methyl-4-isopropoxy-3-cyclobutene-1,2-dione (**4a**), 3-*n*-butyl-4-isopropoxy-3-cyclobutene-1,2-dione (**4b**), and 3-phenyl-4-isopropoxyl-3-cyclobutene-1,2-dione (**4c**) were prepared according to literature procedures.[15]

3-Isopropoxy-4-isopropyl-3-cyclobutene-1,2-dione (4d). To diisopropyl squarate (10.0 g, 50.0 mmol) in 100 mL of THF was added 1.03 equiv of isopropylmagnesium chloride (2 M in ether) at −78 °C with stirring for 1 h at −45 °C. The reaction was quenched with 40 mL of 10% NH_4Cl and extracted with ether (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), solvent was evaporated, and the residue was dissolved in 200 mL of CH_2Cl_2 and treated with 13 drops of concentrated HCl. After stirring at rt for 0.5 h, the dark red solution was neutralized with K_2CO_3 and purified by chromatography on SiO_2 to give 8.42 g (92%) of **4d** as a yellow oil: R_f = 0.67 (SiO_2, 1:4 ethyl acetate–hexanes, UV); ^1H NMR (300 MHz, $CDCl_3$) δ 5.42 (hept, J = 6.3 Hz, 1 H), 3.02 (hept, J = 6.9 Hz, 1 H), 1.46 (d, J = 6.0 Hz, 6 H), 1.30 (d, J = 6.9 Hz, 6 H); IR (CCl_4, cm^{-1}) 2970, 1790, 1750, 1600, 1585, 1390, 1378, 1345, 1099. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.95; H, 7.74. Found: C, 65.74; H, 7.78.

Synthesis of Cyclobutenones 5. General Experimental Procedure. A solution of 3-isopropoxy-4-substituted-3-cyclobutene-1,2-dione 4 in THF was cooled to −78 °C under N_2 and treated dropwise with the aryllithium reagent. The mixture was stirred until compound 4 was consumed (0.5–1 h) as detected by TLC. When completed, the reaction was quenched with 10% aqueous NH_4Cl and extracted once with ether and twice with methylene chloride. The combined organic layers were dried ($MgSO_4$), the solvent was removed, and the residue was chromatographed on SiO_2 (ethyl acetate–hexanes mixtures) to give compound **5**. Characterization was limited to ^1H NMR and IR analysis since these compounds were directly taken into the next step. 2-Lithioanisole was generated by addition of 1.0 equiv of PhLi to an ether solution of 2-bromoanisole at 25 °C and stirring at rt for 2 h. 4-Lithiotoluene was generated by addition of 1.0 equiv of *n*-BuLi to an ether solution of 4-iodotoluene at −78 °C and stirring at rt for 0.5 h. 2-Lithiofuran was generated by addition of 1.0 equiv of *n*-BuLi to an ether solution of furan and 1.0 equiv of tetramethylethylenediamine at −78 °C and stirring at rt for 4 h.

4-Hydroxy-3-isopropoxy-2-methyl-4-phenyl-2-cyclobutenone (5a). Reaction of **4a** (0.861 g, 5.59 mmol) with 1.07 equiv of PhLi for 1 h gave 61% of **5a** (796 mg) as a pale-yellow oil: R_f = 0.24 (SiO_2, 1:2 ethyl acetate–hexanes, UV); ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (m, 2 H), 734 (m, 3 H0, 4.74 (hept, J = 6.3 Hz, 1 H), 3.15 (s br, 1 H), 1.78 (s, 1 H), 1.40 (d, J = 6.0 Hz, 3 H), 1.24 (d, J = 6.0 hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 3566, 3061, 2983, 1758, 1396, 1310, 1097.

4-Hydroxy-3-isopropoxy-4-(2-methoxyphenyl)-2-methyl-2-cyclobutenone (5b). Reaction of **4a** (9.24 g, 60 mmol) with 1 equiv of 2-lithioanisole for 1 h gave 60% of **5b** (9.47 g) as a white solid: R_f = 0.26 (SiO_2, 1:1 ethyl acetate–hexanes, UV); mp 79–81 °C; ^1H NMR (300 MHz, $CDCl_3$) 7.32 (d, J = 7.5 Hz, 1 H), 7.24 (t, J = 7.8 Hz, 1 H), 6.91 (m, 2 H), 5.38 (s br, 1 H), 4.77 (hept, J = 6.0 Hz, 1 H), 3.82 (s, 3 H), 1.71 (s, 3 H), 1.39 (d, J = 6.0 Hz, 3 H), 1.28 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 190.5, 180.1, 156.8, 129.1, 127.1, 124.7, 122.2, 120.7, 111.5, 92.2, 76.5, 55.7, 22.2, 21.9, 6.4; IR ($CDCl_3$, cm^{-1}) 3506, 2980, 2936, 1761, 1621, 1315, 1105.

4-Hydroxy-3-isopropoxy-2-methyl-4-(4-methylphenyl)-2-cyclobutenone (5c). Reaction of **4a** (1.00 g, 6.49 mmol) with 1.05 equiv of 4-lithiotoluene for 1 h gave 72% of **5c** (1.15 g) as a pale-yellow oil: R_f = 0.1 (SiO_2, 1:4 ethyl acetate–hexanes, UV); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 8.1 Hz, 1 H), 7.16 (d,

J = 8.1 Hz, 1 H), 4.73 (hept, J = 6.2 Hz, 1 H), 3.51 (s br, 1 H), 2.33 (s, 3 H), 1.75 (s, 3 H), 1.39 (d, J = 6.3 Hz, 3 H), 1.22 (d, J = 6.3 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 3350, 3025, 2990, 2928, 2870, 1754, 1617, 1400, 1344, 1184.

4-(2-Furyl)-4-hydroxy-3-isopropoxy-2-methyl-2-cyclobutenone (5d). Reaction of **4a** (1.54 g, 10 mmol) with 1 equiv of 2-lithiofuran for 1 h gave 85% of **5d** (1.88 g) as a pale-yellow oil: R_f = 0.07 (SiO_2, 1:4 ethyl acetate–hexanes, UV); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 1 H), 6.43 (d, J = 3.6 Hz, 1 H), 6.36 (m, 1 H), 4.82 (hept, J = 6.2 Hz, 1 H), 4.40 (s br, 1 H), 1.72 (s, 3 H), 1.39 (d, J = 6.0 Hz, 3 H), 1.19 (d, J = 5.7 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 3338, 3053, 2983, 2926, 1759, 1617, 1396, 1311, 1268, 1097.

2-*n*-Butyl-4-hydroxy-3-isopropoxy-4-(2-methoxyphenyl)-2-cyclobutenone (5e). Reaction of **4b** (6.87 g, 35 mmol) with 1.1 equiv of 2-lithioanisole for 1 h gave 79% of **5e** (8.42 g) as an oil: R_f = 0.30 (SiO_2, 1:1 ethyl acetate–hexanes, UV); ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 2 H), 6.96 (t, J = 8.7 Hz, 2 H), 5.11 (s br, 1 H), 4.77 (hept, J = 6.0 Hz, 1 H), 3.89 (s, 3 H), 2.15 (m, 2 H0, 1.56 (q, J = 7.8 Hz, 2 H), 1.42 (d, J = 6.3 Hz, 3 H), 1.35 (m, 2 H0, 1.29 (d, J = 6.0 Hz, 3 H), 0.91 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 190.3, 179.4, 152.1, 129.4, 127.8, 127.2, 125.2, 121.1, 111.9, 93.1, 77.1, 56.1, 29.2, 2.6, 22.5, 22.2, 21.9, 13.6; IR ($CDCl_3$, cm^{-1}) 3502, 2900, 2961, 2933, 2876, 1552, 1617, 1489, 1460, 1389, 1311, 1097, 1019.

2-*n*-Butyl-4-hydroxy-3-isopropoxy-4-(4-methylphenyl)-2-cyclobutenone (5f). Reaction of **4b** (1.85 g, 9.4 mmol) with 1.06 equiv of 4-lithiotoluene for 0.5 h gave 64% of **5f** (1.75 g) as a pale-yellow oil: R_f = 0.18 (SiO_2, 1:4 ethyl acetate–hexanes, UV); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 8.1 Hz, 2 H), 7.15 (d, J = 7.8 Hz, 2 H), 4.68 (hept, J = 6.2 Hz, 1 H), 4.11 (s br, 1 H), 2.33 (s, 3 H), 2.15 (t, J = 7.2, 1 H), 2.14 (t, J = 7.2, 1 H), 1.56 (hept, J = 7.7 Hz, 2 H), 1.37 (m, 2 H), 1.36 (d, J = 6.3 Hz, 3 H), 1.12 (d, J = 6.3 Hz, 3 H), 0.91 (t, J = 7.4 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 3566, 2983, 2961, 2933, 2876, 1752, 1610, 1382, 1339, 1311, 1097.

2-*n*-Butyl-4-(2-furyl)-4-hydroxy-3-isopropoxy-2-cyclobutenone (5g). Reaction of **4b** (3.10 g, 15.8 mmol) with 1.26 equiv of 2-lithiofuran for 0.5 h gave 74% of **5g** (3.07 g) as a white solid: R_f = 0.19 (SiO_2, 1:4 ethyl acetate–hexanes, UV); mp 68–70 °C (ether/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (s, 1 H), 6.43 (d, J = 3.0 Hz, 1 H), 6.38 (dd, J = 3.3, 1.5 Hz, 1 H), 4.79 (hept, J = 6.3 Hz, 1 H), 3.45 (s, br, 1 H), 2.14 (t, J = 7.5 Hz, 2 H), 1.56 (m, 2 H), 1.39 (d, J = 6 Hz, 3 H), 1.33 (m, 2 H), 1.23 (m, 2 H), 1.16 (d, J = 6.3 Hz, 3 H), 0.91 (t, J = 7.4 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 3566, 2983, 2961, 2933, 1759, 1609, 1389, 1339, 1097.

3-Isopropoxy-2-phenyl-4-hydroxy-4-phenyl-2-cyclobutenone (5h). Reaction of **4c** (1.93 g, 8.93 mmol) with 1.03 equiv of phenyllithium for 1 h gave 56% of **5h** (1.10 g) as a white solid: mp 135–137 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, J = 1.2, 7.8 Hz, 2 H), 7.53 (dd, J = 1.5, 8.0 Hz, 2 H), 7.34 (m, 6 H), 4.82 (hept, J = 6.1 Hz, 1 H), 4.6 (s br, 1 H0, 1.46 (d, J = 6.0 Hz, 3 H), 1.08 (d, J = 6.0 Hz, 1 H); IR (CH_2Cl_2, cm^{-1}) 3559, 3054, 2983, 1752, 1624, 1595, 1417, 1396, 890.

3-Isopropoxy-2-phenyl-4-hydroxy-4-(4-methylphenyl)-2-cyclobutenone (5i). Reaction of **4c** (2.00 g, 9.26 mmol) with 1.08 equiv of 4-lithiotoluene for 1 h gave 76% of **5i** (2.16 g) as a pale-yellow solid: mp 89–90 °C (ethyl acetate/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (dd, J = 1.3, 7.1 Hz, 2 H), 7.30 (m, 5 H), 7.49 (d, J = 8.1 Hz, 2 H0, 4.83 (hept, J = 6.2 Hz, 1 H), 4.20 (s br, 1 H), 2.34 (s, 3 H), 1.45 (d, J = 6.3 Hz, 3 H), 1.10 (d, J = 6.3 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 3566, 3054, 2983, 1752, 1624, 1417, 1389, 1353, 890.

Synthesis of Cyclobutenones 6. General Experimental Procedure. A flame-dried flask wrapped with aluminum foil was charged with a solution of compound **5**, Ag_2O (2 equiv), and K_2CO_3 (5 equiv) in CH_3CN (0.3 M in **5**) at 0 °C. MeI (4 equiv) was added, and the mixture was stirred at rt overnight. The reaction mixture was filtered through a layer of Celite 545 with ether, the solvent was removed, and the residue was chromatographed on SiO_2 (ethyl acetate and hexanes mixture) to give compound **6**. If TLC and ^1H NMR showed the compound to be pure, it was used directly without further purification (**6a** and **6c**). In parentheses following each of the compounds shown below is an indication of the scale of the reaction and the yield of the product.

3-Isoproproxy-2-methyl-4-methoxy-4-phenyl-2-cyclobutenone (6a) (3.43 mmol, 100%): oil; R_f = 0.34 (SiO_2, 1:4 ethyl acetate–hexanes, UV); ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (m, 2 H), 7.31 (m, 3 H), 4.74 (hept, J = 6.3 Hz, 1 H), 3.48 (s, 3 H), 1.80 (s, 3 H), 1.39 (d, J = 6.0 Hz, 3 H), 1.29 (d, J = 6.0 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 2983, 1759, 1609, 1382, 1311, 1097. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.17; H, 7.39.

3-Isopropoxy-4-methoxy-4-(2-methoxyphenyl)-2-methyl-2-cyclobutenone (6b) (5.00 mmol, 100%): pale-yellow oil; R_f = 0.40 (SiO_2, 1:1 ethyl acetate–hexanes, UV); ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, J = 7.8, 1.5 Hz, 1 H), 7.27 (dt, J = 7.7, 1.5 Hz, 1 H), 6.97 (t, J = 7.5 Hz, 1 H), 6.87 (d, J = 8.1 Hz, 1 H), 4.70 (hept, J = 6.0 Hz, 1 H), 3.76 (s, 3 H), 3.46 (s, 3 H), 1.78 (s, 3 H), 1.37 (d, J = 6.0 Hz, 3 H), 1.26 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 1190.2, 180.6, 156.8, 129.2, 128.5, 123.7, 120.5, 111.3, 95.3, 76.2, 55.5, 52.5, 22.4, 22.2, 6.5; IR ($CDCl_3$, cm^{-1}) 2985, 1755, 1615, 1385, 1100. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.49; H, 7.34.

3-Isopropoxy-4-methoxy-2-methyl-4-(4-methylphenyl)-2-cyclobutenone (6c) (4.23 mmol, 100%): oil; R_f = 0.24 (SiO_2, 1:4 ethyl acetate–hexanes, UV); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8.1 Hz, 1 H), 7.14 (d, J = 8.1 Hz, 1 H), 4.73 (hept, J = 6.1 Hz, 1 H), 3.46 (s, 3 H), 1.79 (s, 3 H), 1.38 (d, J = 6.3 Hz, 3 H), 1.25 (d, J = 6.3 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 3054, 2983, 2926, 1752, 1610, 1382, 1318, 1090, 891. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.73; H, 7.75.

4-(2-Furyl)-3-isopropoxy-4-methoxy-2-methyl-2-cyclobutenone (6d) (8.47 mmol, 92%): oil; R_f = 0.30 (SiO_2, 1:4 ethyl acetate–hexanes, UV); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 1 H), 6.45 (d, J = 3.3 Hz, 1 H), 6.37 (d, J = 2.7 Hz, 1 H), 4.82 (hept, J = 6.2 Hz, 1 H), 3.46 (s, 3 H), 1.76 (s, 3 H), 1.39 (d, J = 6.0 Hz, 3 H), 1.23 (d, J = 6.3 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 3053, 2983, 2926, 1759, 1617, 1396, 1311, 1090. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.07; H, 6.85.

2-*n*-Butyl-3-isopropoxy-4-methoxy-4-(2-methoxyphenyl)-2-cyclobutenone (6e) (19.7 mmol, 96%): yellow oil; R_f = 0.61 (SiO_2, 5:8 ethyl acetate–hexanes, UV); ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, J = 7.5, 1.2 Hz, 1 H), 7.26 (dt, J = 7.5, 1.2 Hz, 1 H), 6.98 (t, J = 7.5 Hz, 1 H), 6.86 (d, J = 8.4 Hz, 1 H), 4.63 (hept, J = 6.0 Hz, 1 H), 3.76 (s, 3 H), 3.49 (s, 3 H), 2.18 (m, 2 H), 1.58 (m, 2 H), 1.38 (m, 2 H), 1.34 (d, J = 6.0 Hz, 3 H), 1.16 (d, J = 6.0 Hz, 3 H), 0.90 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 189.9, 180.5, 156.7, 129.4, 129.2, 128.9, 124.0, 120.7, 111.2, 95.7, 76.5, 55.3, 52.4, 29.4, 22.6, 22.6, 22.4, 22.0; IR (CCl_4, cm^{-1}) 2940, 1761, 1630, 1388, 1345, 1253, 1107. Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.67; H, 8.23. Found: C, 71.42; H, 8.16.

2-*n*-Butyl-3-isopropoxy-4-methoxy-4-(4-methylphenyl)-2-cyclobutenone (6f) (3.45 mmol, 99%): pale-yellow oil; R_f = 0.45 (SiO_2, 1:4 ethyl acetate–hexanes, UV); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 8.1 Hz, 2 H), 7.15 (d, J = 8.1 Hz, 2 H), 4.65 (hept, J = 6.2 Hz, 1 H), 3.49 (s, 3 H), 2.32 (s, 3 H), 2.20 (t, J = 7.4 Hz, 1 H), 2.19 (t, J = 7.6 Hz, 1 H), 1.59 (hept, J = 7.6 Hz, 2 H), 1.38 (m, 2 H), 1.35 (d, J = 6.3 Hz, 3 H), 1.14 (d, J = 6.3 Hz, 3 H), 0.92 (t, J = 7.4 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 2983, 2954, 2933, 1752, 1610, 1382, 1097. Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.48; H, 8.72.

2-*n*-Butyl-4-(2-furyl)-3-isopropoxy-4-methoxy-2-cyclobutenone (6g) (5.04 mmol, 94%): pale-yellow oil; R_f = 0.41 (SiO_2, 1:4 ethyl acetate–hexanes, UV); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (s, 1 H), 6.44 (d, J = 3.0 Hz, 1 H), 6.38 (d, J = 1.8 Hz, 1 H), 4.77 (hept, J = 6.2 Hz, 1 H), 3.47 (s, 3 H), 2.16 (t, J = 7.5 Hz, 2 H), 1.54 (m, 2 H), 1.37 (d, J = 6.3 Hz, 3 H), 1.33 (m, 2 H), 1.15 (d, J = 6.0 Hz, 3 H), 0.90 (t, J = 7.2 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 3047, 2954, 2933, 2869, 1759, 1610, 1382, 1339, 1154, 1097. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.10; H, 7.97.

3-Isopropoxy-2-phenyl-4-methoxy-4-phenyl-2-cyclobutenone (6d) (3.74 mmol, 95%): white solid; R_f = 0.54 (SiO_2, 1:4 ethyl acetate–hexanes, UV); mp 84–85 °C (ether–hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, J = 1.5, 8.3 Hz, 2 H), 7.54–7.29 (m, 8 H), 4.76 (hept, J = 6.22 Hz, 1 H), 3.64 (s, 3 H), 1.42 (d, J = 6.3 Hz, 3 H), 1.05 (d, J = 6.0 Hz); IR (CH_2Cl_2, cm^{-1}) 3060, 2983, 1751, 1626, 1591, 1389, 1347, 1089. Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 78.08; H, 6.55.

3-Isopropoxy-2-phenyl-4-methoxy-4-(4-methylphenyl)-2-cyclobutenone (6i) (7.01 mmol, 90%): white solid; mp 74–75 °C (ethyl acetate–hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 7.2 Hz, 2 H), 7.42–7.30 (m, 5 H), 7.16 (d, J = 8.1 Hz, 2 H), 4.76 (hept, J = 6.2 Hz, 1 H), 3.62 (s, 3 H), 2.33 (s, 3 H), 1.42

(d, J = 6.3 Hz, 3 H), 1.07 (d, J = 6.3 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 3054, 2990, 1752, 1624, 1595, 1389, 1346, 1090. Anal. Calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.30; H, 6.94.

Synthesis of Cyclobutenones 8. General Experimental Procedure. A solution of 3-isopropoxy-2-substituted-4-methoxy-4-aryl-2-cyclobutenone **6** 0.3–0.5 M in THF was cooled to −78 °C under N_2, and R^2Li was added. The mixture was stirred until compound **6** was consumed (15 min–0.5 h) as detected by TLC. When the reaction was complete, the reaction mixture was processed by different methods to fulfill the rearrangement of the 3-isopropoxy-2-cyclobutenol moiety to the cyclobutenone **8**.

Method A (for 8a, 8g, 8j, 8k). Quench with trifluoroacetic anhydride at −78 °C, then add 10% aqueous NH_4Cl, extract once with ether and twice with methylene chloride, and dry the combined organic layers ($MgSO_4$). **Method B (for 8b, 8c).** Quench with aqueous NH_4Cl, extract once with ether and twice with CH_2Cl_2, dry the combined organic layers ($MgSO_4$), and evaporate the solvent. The residue was redissolved in ether and cooled to 0 °C (ice bath). Pyridine (1 equiv) was added and then trifluoroacetic anhydride (1 equiv). The mixture was stirred for 15 min, and water was added. The aqueous phase was extracted with ethyl acetate, and the organic layer was dried over $MgSO_4$. **Method C (for 8d).** Quench with aqueous NH_4Cl, extract once with ether and twice with CH_2Cl_2, dry the combined organic layers ($MgSO_4$), evaporate solvent, dissolve in CH_2Cl_2, and treat with two drops of concentrated HCl followed by treatment with anhydrous K_2CO_3 after TLC indicates complete reaction. **Method D (for 8e, 8f, 8i).** Same as method A, except the trifluoroacetic anhydride quench is followed by treatment with saturated aqueous $NaHCO_3$, not NH_4Cl. **Method E (8h, 8l).** The $MeCeCl_2$ reaction was quenched with 2 N HCl, the reaction mixture was extracted once with ether and twice with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$).

The organic layer obtained from the above methods was evaporated, and when **8** was stable to SiO_2, the residue was chromatographed (SiO_2, ethyl acetate and hexanes) and spectroscopic data was obtained. Because of the instability of the products **8**, elemental analyses were not obtained. In some cases (**8c, 8h, 8i, 8j**), the cyclobutenone **8** was not stable to SiO_2. These compounds were heated directly and oxidized to give the quinone products **9**, shown below.

3-*n*-Butyl-2-methyl-4-methoxy-4-phenyl-2-cyclobutenone (8a, Method A). Reaction of 3-isopropoxy-4-methoxy-2-methyl-4-phenyl-2-cyclobutenone (**6a**) (0.235 g, 0.955 mmol) with 1.05 equiv of *n*-BuLi for 15 min gave 60% of **8a** (139 mg) as a pale-yellow oil: R_f = 0.73 (SiO_2, 1:4 ethyl acetate–hexanes, UV); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5 H), 3.40 (s, 3 H), 2.48 (t, J = 7.7 Hz, 2 H), 1.86 (s, 3 H), 1.55 (m, 2 H), 1.34 (m, 2 H), 0.87 (t, J = 7.4 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 3054, 2961, 2933, 2869, 1759, 1624, 1446, 1190, 1069.

4-Methoxy-4-(2-methoxyphenyl)-2-methyl-2-cyclobutenone (8b, Method B). Reaction of 3-isopropoxy-4-methoxy-4-(2-methoxyphenyl)-2-methyl-2-cyclobutenone (**6b**) (0.30 g, 1.08 mmol) with 2.01 equiv of $LiAlH_4$ in ether for 0.5 h gave 54% of **8b** (0.127 g) as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, J = 1.2 Hz, 1 H), 7.62 (dd, J = 7.2, 1.2 Hz, 1 H), 7.32 (dt, J = 7.2, 1.2 Hz, 1 H), 6.96 (t, J = 7.5 Hz, 1 H), 6.91 (d, J = 8.4 Hz, 1 H), 3.86 (s, 3 H), 3.34 (s, 3 H), 1.83 (d, J = 1.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 193.9, 164.6, 157.0, 154.5, 129.8, 128.8, 124.8, 120.4, 111.12, 96.7, 55.4, 53.4, 9.4; IR (CCl_4, cm^{-1}) 2922, 1760, 1486, 1243, 1088.

3-*n*-Butyl-4-methoxy-4-(2-methoxyphenyl)-2-methyl-2-cyclobutenone (8d, Method C). Reaction of 3-isopropoxy-4-methoxy-4-(2-methoxyphenyl)-2-methyl-2-cyclobutenone (**6b**) (0.553 g, 2.0 mmol) with 1.08 equiv of *n*-BuLi for 10 min gave 54% of **8d** (0.296 g) as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, J = 7.5, 1.2 Hz, 1 H), 7.27 (dt, J = 7.5, 1.2 Hz, 1 H), 6.98 (t, J = 7.8 Hz, 1 H), 6.87 (d, J = 8.1 Hz, 1 H), 3.74 (s, 3 H), 3.40 (s, 3 H), 2.41 (t, J = 7.8 Hz, 2 H), 1.81 (s, 3 H), 1.47 (q, J = 7.5 Hz, 2 H), 1.28 (m, 2 H), 0.84 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 193.1, 178.5, 157.0, 149.5, 129.2, 128.4, 125.0, 120.7, 111.5, 97.8, 55.6, 53.5, 28.5, 27.1, 22.8, 13.6, 7.9; IR (CCl_4, cm^{-1}) 2937, 2910, 1748, 1630, 1475, 1450, 1239, 1088, 1017.

4-Methoxy-4-(2-methoxyphenyl)-2-methyl-3-phenyl-2-cyclobutenone (8e, Method D). Reaction of 3-isopropoxy-4-methoxy-4-(2-methoxyphenyl)-2-methyl-2-cyclobutenone (**6b**) (0.555 g, 2.0 mmol) with 1.05 equiv of PhLi for 30 min gave 76% of **8e** (0.447 g) as a pale yellow solid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, J = 7.5, 1.5 Hz, 1 H), 7.67–7.61 (m, 2 H), 7.36 (m, 2 H), 7.22 (t, J = 8.3 Hz, 1 H), 7.00 (t, J = 7.2 Hz, 1 H), 6.78 (d, J = 8.1 Hz, 1 H), 3.60 (s, 3 H), 3.46 (s, 3 H), 2.17 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 193.7, 169.3, 156.9, 147.8, 131.6, 130.5, 129.1, 128.7, 128.2, 125.2, 120.7, 111.7, 98.0, 55.7, 52.6, 9; IR (CCl_4, cm^{-1}) 2925, 1759, 1618, 1482, 1245.

2-*n*-Butyl-3-phenyl-4-methoxy-4-(2-methoxyphenyl)-2-cyclobutenone (8f, Method D). Reaction of 2-*n*-butyl-3-isopropoxy-4-methoxy-4-(2-methoxyphenyl)-2-cyclobutenone (**6e**) (0.955 g, 3.0 mmol) with 1.05 equiv of PhLi for 30 min gave 70% of **8f** (0.711 g) as a pale yellow solid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, J = 7.5, 1.8 Hz, 1 H), 7.62 (m, 2 H), 7.37 (m, 3 H), 7.22 (dd, J = 7.2, 1.2 Hz, 1 H), 7.01 (t, J = 7.5 Hz, 1 H), 6.81 (d, J = 7.8 Hz, 1 H), 3.63 (s, 3 H), 3.46 (s, 3 H), 2.60 (m, 2 H), 1.74 (m, 2 H), 1.48 (hept, J = 7.5 Hz, 2 H), 0.98 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 193.7, 168.8, 157.0, 152.6, 131.7, 130.5, 129.1, 128.9, 128.8, 128.2, 125.2, 120.7, 111.7, 98.1, 55.5, 52.6, 28.9, 24.6, 23.0, 13.8; IR (CCl_4, cm^{-1}) 2960, 2934, 1758, 1486, 1461, 1250, 1029.

3-*n*-Butyl-4-methoxy-2-methyl-4-(4-methylphenyl)-2-cyclobutenone (8g, Method A). Reaction of 3-isopropyl-4-methoxy-2-methyl-4-(4-methylphenyl)-2-cyclobutenone (**6c**) (0.201 g, 0.773 mmol) with 1.03 equiv of *n*-BuLi for 0.5 h gave 55% of **8g** (110 mg) as a yellow oil: R_f = 0.39 (SiO_2, 1:10 ethyl acetate–hexanes, phosphomolybdic acid); ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 8.1 Hz, 2 H), 7.14 (d, J = 8.1 Hz, 2 H), 3.39 (s, 3 H), 2.47 (t, J = 7.7 Hz, 2 H), 2.32 (s, 3 H), 1.85 (s, 3 H), 1.56 (m, 2 H), 1.34 (m, 2 H), 0.87 (t, J = 7.4 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 3054, 2954, 2933, 2869, 1752, 1624, 1410, 1097, 884.

3-*n*-Butyl-4-(2-furyl)-4-methoxy-2-methyl-2-cyclobutenone (8k, Method A). Reaction of 4-(2-furyl)-3-isopropoxy-4-methoxy-2-methyl-2-cyclobutenone (**6d**) (0.241 g, 1.02 mmol) with 1.1 equiv of *n*-BuLi for 0.5 h gave 51% of **8k** (122 mg) as a brown oil: R_f = 0.50 (SiO_2, 1:4 ethyl acetate–hexanes, phosphomolybdic acid); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (s, 1 H), 6.40 (d, J = 3.0 Hz, 1 H), 6.36 (t, J = 1.2 Hz, 1 H), 3.38 (s, 3 H), 2.56 (t, J = 7.8 Hz, 2 H), 1.82 (s, 3 H), 1.57 (m, 2 H), 1.34 (m, 2 H), 0.89 (t, J = 7.4 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 2961, 2933, 1759, 1624, 1147.

2-*n*-Butyl-4-(2-furyl)-4-methoxy-3-methyl-2-cyclobutenone (8l, Method E). A THF solution of 2-*n*-butyl-4-(2-furyl)-3-isopropoxy-4-methoxy-2-cyclobutenone (**6g**) (0.628 g, 2.26 mmol) was added to 3.1 equiv of $MeCeCl_2$[24] (generated by addition of 1.0 equiv of MeLi to a THF solution of $CeCl_3$ at −78 °C and stirring at −78 °C for 1 h) at −78 °C and stirred for 15 min. The reaction was quenched with 2 N HCl and gave 56% of **8l** (295 mg) as a pale-yellow oil: R_f = 0.62 (SiO_2, 1:4 ethyl acetate–hexanes, phosphomolybdic acid); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 1 H), 6.40 (d, J = 2.7 Hz, 1 H), 6.37 (d, J = 2.4 Hz, 1 H), 3.37 (s, 3 H), 2.21 (t, J = 7.5 Hz, 2 H), 2.18 (s, 3 H), 1.55 (m, 2 H), 1.32 (m, 2 H), 0.91 (t, J = 7.4 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 3054, 2961, 2933, 2869, 1759, 1631, 1154.

Synthesis of Quinones 9. General Experimental Procedure. A solution of cyclobutenone **8** obtained above was heated at 140 °C for 15 min–1 h in *o*-xylene. The mixture was stirred until **8** was consumed as detected by TLC. The reaction mixture was then cooled to 0 °C, and 2–3 equivalents of 1:1 CH_3CN/0.5 N aqueous ceric ammonium nitrate solution was added. The mixture was stirred at rt until TLC showed completion of the reaction. The reaction mixture was extracted once with ether and twice with methylene chloride, the combined organic layers were dried ($MgSO_4$), the solvent was removed, and the residue was chromatographed on SiO_2 (1:4–1:15 ethyl acetate–hexanes mixture) to give compound quinone **9**. In parentheses following each of the compounds shown below is an indication of the scale of the reaction, the reaction time, and the yield of the product.

2-Methyl-3-*n*-butyl-1,4-naphthalenedione (9a) (0.51 mmol, 0.5 h, 95%): R_f = 0.36 (SiO_2, 1:10 ethyl acetate–hexanes, UV); yellow crystals: R_f = 0.36 (SiO_2 1:10 ethyl acetate–hexanes, UV); mp 68–69 °C (ether–hexanes) (lit.[25] mp 68–69 °C); ^1H NMR (300 MHz, $CDCl_3$) 8.05 (dd, J = 3.5, 5.6 Hz, 2 H), 7.66 (dd, J = 3.5, 5.9 Hz, 2 H), 2.61 (t, J = 7.4 Hz, 2 H), 2.17 (s, 3 H), 1.43 (m, 4

(25) Threadgill, M. D. *Synth. Commun.* **1989**, *19*, 167.

H), 0.93 (t, J = 6.9 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 2961, 2926, 2869, 1659, 1595, 1325, 1296. Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.81; H, 7.07.

2-Methyl-5-methoxy-1,4-naphthalenedione (plumbagin methyl ether, 9b) (0.46 mmol, 3.5 h, 80%): purification (SiO_2 1:5 ethyl acetate–hexanes, UV); yellow crystals; mp 92–94 °C (lit.[20] mp 92–94 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 6.9 Hz, 1 H), 7.65 (t, J = 7.8 Hz, 1 H), 7.29 (d, J = 8.1 Hz, 1 H), 6.73 (d, J = 1.5 Hz, 1 H), 4.00 (s, 3 H), 2.13 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 185.7, 184.4, 159.3, 145.3, 137.8, 134.5, 134.3, 119.8, 119.3, 117.6, 56.4, 15.7; IR (CCl_4, cm^{-1}) 2950, 1663, 1583, 1282, 1256. Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.98. Found: C, 71.01: H, 5.05.

2-Methyl-3-butyl-5-methoxy-1,4-naphthalenedione (9d) (0.68 mmol, 3 h, 88%): purification (SiO_2 1:10 ethyl acetate–hexanes, UV); brown crystals; mp 46–47 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 7.5 Hz, 1 H), 7.61 (t, J = 7.8 Hz, 1 H), 7.25 (d, J = 7.5 Hz, 1 H), 4.00 (s, 3 H), 2.60 (t, J = 7.2 Hz, 2 H), 1.44 (m, 4 H), 0.90 (dd, J = 6.6, 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 185.4, 184.0, 159.2, 149.1, 140.5, 134.3, 134.2, 119.9, 118.8, 117.1, 56.3, 30.8, 27.0, 23.1, 13.8, 12.2; IR (CCl_4, cm^{-1}) 2930, 1640, 1572, 1260. Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.13; H, 6.97.

2-Methyl-3-phenyl-5-methoxy-1,4-naphthalenedione (9e) (0.47 mmol, 5 h, 85%): purification (SiO_2 1:5 ethyl acetate–hexanes, UV); yellow crystals; mp 187–188 °C (CH_2Cl_2–hexanes); ^1H NMR (300 MHz, $CDCl_3$) 7.80 (d, J = 7.8 Hz, 1 H), 7.67 (t, J = 8.2 Hz, 1 H), 7.42 (m, 3 H), 7.29 (d, J = 8.4 Hz, 1 H), 7.20 (m, 2 H), 3.96 (s, 3 H), 2.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 186.1, 183.5, 159.6, 147.8, 141.7, 134.5, 134.3, 134.0, 129.3, 128.2, 127.9, 120.0, 118.9, 117.7, 56.4, 14.2; IR (CCl_4, cm^{-1}) 1658, 1585, 1467, 1340, 1321, 1578, 1557, 1520, 1050, 977. Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.58; H, 5.06.

2-*n*-Butyl-3-phenyl-5-methoxy-1,4-naphthalenedione (9f) (0.53 mmol, 5 h, 83%): purification (SiO_2 1:10 ethyl acetate–hexanes, UV); yellow crystals; mp 104–105 °C (ether–hexanes); ^1H NMR (300 MHz, $CDCl_3$) 7.77 (d, J = 7.5 Hz, 1 H), 7.64 (t, J = 7.8 Hz, 1 H), 7.41 (m, 3 H), 7.27 (d, J = 8.9 Hz, 1 H), 7.20 (m, 2 H), 3.93 (s, 3 H), 2.40 (t, J = 7.5 Hz, 2 H), 1.40 (m, 2 H), 1.24 (m, 2 H), 0.77 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 185.5, 183.7, 159.3, 147.6, 145.6, 134.3, 133.9, 128.9, 127.9, 127.8, 127.7, 119.8, 118.7, 117.5, 56.2, 31.4, 27.5, 22.7, 13.5; IR (CCl_4, cm^{-1}) 2960, 2930, 1662, 1585, 1468, 1448, 1280, 1212, 901. Anal. Calcd for $C_{21}H_{20}O_3$: C, 78.73; H, 6.29. Found: C, 78.80; H, 6.33.

2-Methyl-3-*n*-butyl-7-methyl-1,4-naphthalenedione (9g) (0.83 mmol, 1 h, 90%): yellow crystals; R_f = 0.43 (SiO_2 1:10 ethyl acetate–hexanes, UV); mp 69–70 °C (ether–hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 7.8 Hz, 1 H), 7.85 (s, 1 H), 7.46 (d, J = 8.1 Hz, 1 H), 2.61 (t, J = 7.4 Hz, 2 H), 2.46 (s, 3 H), 2.16 (s, 3 H), 1.42 (m, 4 H), 0.93 (t, J = 6.9 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 3054, 2990, 2954, 2926, 1659, 1595, 1417, 1304, 891. Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.25; H, 7.52.

5-Methyl-6-*n*-butyl-4,7-benzo[*b*]furandione (9k) (0.303 mmol, 15 min, 82%): yellow crystals; R_f = 0.54 (SiO_2 1:4 ethyl acetate–hexanes, UV); mp 73–74 °C (ether–hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 1.8 Hz, 1 H), 6.79 (d, J = 1.5 Hz, 1 H), 2.54 (t, J = 7.1 Hz, 2 H), 2.08 (s, 3 H), 1.41 (m, 4 H), 0.92 (t, J = 6.8 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 3054, 2954, 2862, 1659, 1574, 1481, 1360, 1168. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.47; H, 6.47.

5-*n*-Butyl-6-methyl-4,7-benzo[*b*]furandione (9l) (1.18 mmol, 1 h, 89%): yellow crystals; R_f = 0.30 (SiO_2 1:10 ethyl acetate–hexanes, UV); mp 74–75 °C (ether/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 1.2 Hz, 1 H), 6.79 (s, 1 H), 2.52 (t, J = 7.1 Hz, 2 H), 2.10 (s, 3 H), 1.39 (m, 4 H), 0.92 (t, J = 6.3 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 2961, 2869, 1659, 1581, 1481, 1360. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.40; H, 6.42.

Synthesis of Quinone 9 without Purification of Cyclobutenone 8. The same experimental procedure as described above for the synthesis of quinones **9** was applied, except compound **8** was used directly in the thermolysis and oxidation without purification.

2-*n*-Butyl-5-methoxy-1,4-naphthalenedione (9c). Reaction of 2-*n*-butyl-3-isopropoxy-4-methoxy-4-(2-methoxyphenyl)-2-cyclobutenone (**6e**) (638 mg, 2.0 mmol) with $LiAlH_4$ (1.2 mmol) took place at −40 °C for 0.5 h. The reaction was worked up by method B. The *o*-xylene solution was heated for 2 h and after ceric ammonium nitrate oxidation gave a 40% yield of **9c** (197 mg) as orange crystals: mp 80.5–81 °C (ether–hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 8.4 Hz, 1 H), 7.65 (t, J = 7.8 Hz, 1 H), 7.28 (d, J = 9.0 Hz, 1 H), 6.6 (s, 1 H), 4.00 (s, 3 H), 2.51 (t, J = 7.8 Hz, 2 H), 1.55 (m, 2 H), 1.42 (m, 2 H), 0.94 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 185.3, 184.5, 159.2, 149.0, 137.8, 134.5, 134.4, 119.7, 119.3, 117.5, 56.3, 29.8, 28.6, 22.4, 13.7; IR (CH_2Cl_2, cm^{-1}) 2960, 2930, 1660, 1585, 1465, 1283, 1266. Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.68; H, 6.64.

2-*n*-Butyl-3-methyl-7-methyl-1,4-naphthalenedione (9h). Reaction of 2-*n*-butyl-3-isopropoxy-4-methoxy-4-(4-methylphenyl)-2-cyclobutenone (**6f**) (328 mg, 1.09 mmol) with 6.3 equiv of $MeCeCl_2$ (generated by addition of 1.0 equiv of MeLi to a THF solution of $CeCl_3$ at −78 °C and stirring at −78 °C for 1 h) at −78 °C for 15 min. The reaction was worked up by method E. The *o*-xylene solution was heated for 0.5 h to give, after ceric ammonium nitrate oxidation, a 66% yield of **9h** (175 mg) as yellow crystals: R_f = 0.40 (SiO_2, 1:10 ethyl acetate–hexanes, UV); mp 50–51 °C (ether/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 7.8 Hz, 1 H), 7.85 (s, 1 H), 7.46 (d, J = 8.1 Hz, 1 H), 2.61 (t, J = 7.2 Hz, 2 H), 2.46 (s, 3 H), 2.16 (s, 3 H), 1.44 (m, 4 H), 0.93 (t, J = 6.8 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 3054, 2954, 2928, 2870, 1656, 1600, 1300. Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.11; H, 7.43.

2-Methyl-3-phenyl-7-methyl-1,4-naphthalenedione (9i). Reaction of 3-isopropoxy-4-methoxy-2-methyl-4-(4-methylphenyl)-2-cyclobutenone (**6c**) (206 mg, 0.79 mmol) with 1.1 equiv of PhLi for 0.5 h. The reaction was worked up by method D. The *o*-xylene solution was heated for 0.5 h to give, after ceric ammonium nitrate oxidation, a 31% yield of **9i** (65 mg) as yellow needles: R_f = 0.29 (SiO_2, 1:10 ethyl acetate–hexanes, UV); mp 102–103 °C (ether–hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 8.1 Hz, 1 H), 7.93 (s, 1 H), 7.52 (d, J = 7.5 Hz, 1 H), 7.43 (m, 3 H0, 7.22 (m, 2 H), 2.50 (s, 3 H), 2.06 (s, 3 H); IR (CH_2Cl_2, cm^{-1}) 3054, 2983, 1659, 1602, 1296. Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.33; H, 5.33.

5-Methyl-4,7-benzo[*b*]furandione (9j). Reaction of 3-(2-furyl)-3-isopropoxy-4-methoxy-2-methyl-2-cyclobutenone (**6d**) (320 mg, 1.44 mmol) with $LiAlH_4$ (0.8 mmol) at −20 °C for 15 min. The reaction was worked up by Method A. The *o*-xylene solution was heated for 0.5 h and after ceric ammonium nitrate oxidation gave a 36% yield of **9j** (84 mg) as yellow crystals: R_f = 0.45 (SiO_2, 1:4 ethyl acetate–hexanes, UV); mp 100–101 °C (ether–hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 2.1 Hz, 1 H), 6.83 (d, J = 1.5 Hz, 1 H), 6.53 (d, J = 1.5 Hz, 1 H), 2.12 (d, J = 1.2 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 3132, 3054, 1666, 1574, 1481, 1368, 1161, 884. Anal. Calcd for $C_9H_6O_3$: C, 66.67; H, 3.73. Found: C, 66.46; H, 3.77.

Synthesis of 1-*n*-Butyl-1-hydroxy-3-isopropoxy-2-phenyl-4-methoxy-4-phenyl-2-cyclobutene (7'). Into a 5 mL of 3-isopropoxy-2-phenyl-4-methoxy-4-phenyl-2-cyclobutenone (**6h**) (194 mg, 0.63 mmol) was added 0.26 mL of *n*-BuLi (2.5 M in hexanes) at −78 °C. After being stirred for 1 h, the reaction was quenched with 5 mL of saturated $NaHCO_3$ at −78 °C after TLC showed the reaction stopped and one major new spot at R_f = 0.56 (SiO_2, 1:4 ethyl acetate–hexanes, UV). The mixture was extracted with 10 mL of ether three times, and the combined organic layer was dried over $MgSO_4$. Solvents were evaporated on a rotary evaporator, and the residue was purified on SiO_2 by chromatotron elution with 1:8 ether acetate/hexanes to give a white solid that was recrystallized from CH_2Cl_2 and hexanes to give white needles, 107 mg (46%): mp 127–128 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, J = 1.8, 7.2 Hz, 2 H), 7.35 (m, 8 H), 3.59 (hept, J = 6.0 Hz, 1 H), 3.53 (s, 3 H), 3.32 (s, 1 H), 1.60 (m, 2 H), 1.43 (m, 2 H), 1.14 (m, 2 H), 0.77 (t, J = 7.2 Hz, 3 H), 0.69 (d, J = 6.3 hz, 3 H), 0.29 (d, J = 6.0 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 3573, 3054, 2983, 2869, 1652, 1417, 1360, 1097, 891; HRMS calcd for $C_{24}H_{30}O_3$ 366.21948, found 366.21949. Satisfactory elemental analysis was not obtained.

Synthesis of 2-Isopropyl-5-methyl-1,4-benzoquinone (Thymoquinone, 12a). To a solution of 2-bromopropene (0.234 mg, 2 mmol) in 10 mL of THF was added 2 equiv of *t*-BuLi at −78 °C followed by stirring for 0.5 h. The 2-lithiopropene formed was added via cannula to a solution of 3-isopropoxy-4-isopropylcyclobutene-1,2-dione (351 mg, 1.93 mmol) in 5 mL of THF

at -78 °C, and the mixture was stirred for 0.5 h. TLC showed the disappearance of starting material and the formation of a new spot at R_f = 0.25 (SiO_2, 1:4 ethyl acetate–hexanes, UV). The reaction was quenched at -78 °C with 2 equiv of methyl triflate (methylation product: R_f = 0.54, SiO_2, 1:4 ethyl acetate–hexanes, UV). To this mixture at -23 °C was added a solution of lithium aluminum hydride (1 M in ether, 2 mL) followed by stirring for 0.5 h. Once major spot was detected by TLC (R_f = 0.57, SiO_2 1:4 ethyl acetate–hexanes, phosphomolybdium acid). The reaction was quenched with 15 mL of 10% NH_4Cl and filtered with ether through a layer of Celite 545. The organic layer was separated, and the aqueous layer was extracted three times with 20 mL of ether. The combined organic layers were dried over $MgSO_4$, and the solvent was removed. The residue was quickly chromatographed on SiO_2 (1:10 ethyl acetate–hexanes). Decomposition on SiO_2 limited the yield to 28% (130 mg). This was then dissolved in 5 mL of ether with pyridine (79 mg, 1 mmol) at 0 °C. To this solution was added trifluoroacetic anhydride (210 mg, 1 mmol) followed by stirring for 0.5 h. The milky solution was added to 10 mL of water and extracted with ether (3 × 20 mL). The ether solution was dried over $MgSO_4$ and the solvent removed. The residue was heated in 5 mL of *o*-xylene at 100 °C for 20 min. The reaction solution was added to a mixture of 5 mL of CH_3CN and 5 mL of water at 0 °C. This was oxidized with 2 mL of 0.49 M ammonium cerium nitrate for 0.5 h and extracted with 10 mL of ether and twice with 15 mL of methylene chloride. The combined organic layers were dried over $MgSO_4$ and chromatographed on SiO_2 (1:10 ethyl acetate–hexanes) to give 60% (49 mg) of **12a** as a yellow solid: R_f = 062 (SiO_2, 1:10 ethyl acetate–hexanes, UV); mp 43–44 °C (sublimation) (lit.[26] 45.5 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 6.57 (q, J = 1.5 Hz, 1 H), 6.50 (d, J = 0.9 Hz, 1 H), 3.00 (d hept, J = 0.9, 6.8 Hz, 1 H), 2.01 (d, J = 1.5 Hz, 3 H), 1.10 (d, J = 6.9 Hz, 6 H); IR (CCl_4, cm^{-1}) 2969, 2936, 2877, 1660, 1613, 1241, 914.

Synthesis of 2-Isopropyl-3-*n*-butyl-5-methyl-1,4-benzoquinone (12b). Reaction of 3-isopropyl-4-isopropoxy-3-cyclobutene-1,2-dione (**2c**) with 1.07 equiv of 2-lithiopropene (generated by addition of 2 equiv of *t*-BuLi to a THF solution of 2-bromopropene at -78 °C and stirring for 0.5 h) took place for 0.5 h and then followed the same experimental procedure as the synthesis of thymoquinone, except the reaction was quenched with TFAA after the addition of *n*-BuLi and the product was directly heated and oxidized without purification to give 114 mg (22%) of product **12b** as a yellow oil: R_f = 0.59 (SiO_2, 1:10 ethyl acetate–hexanes, UV); ^1H NMR (300 MHz, $CDCl_3$) δ 6.42 (q, J = 1.2 Hz, 1 H), 2.98 (hept, J = 7.1 Hz, 1 H), 2.47 (t, J = 7.2 Hz, 2 H), 1.98 (d, J = 0.9 Hz, 3 H), 1.37 (m, 3 H), 1.26 (d, J = 6.9 Hz, 6 H), 0.92 (t, J = 6.9 Hz, 3 H); IR (CH_2Cl_2, cm^{-1}) 3687, 3054, 2961, 2933, 2869, 1645, 1602. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.29; H, 9.20. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.29; H, 9.20.

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Registry No. **2c**, 73279-65-9; **4a**, 114094-69-8; **4b**, 114094-70-1; **4c**, 114094-71-2; **5a**, 141462-19-3; **5b**, 141462-20-6; **5c**, 141462-21-7; **5d**, 141462-22-8; **5e**, 141462-23-9; **5f**, 141462-24-0; **5g**, 141462-25-1; **5h**, 141462-26-2; **5i**, 141462-27-3; **6a**, 141462-28-4; **6b**, 141462-29-5; **6c**, 141462-30-8; **6d**, 141462-31-9; **6e**, 141462-32-0; **6f**, 141462-33-1; **6g**, 141462-34-2; **6h**, 141462-35-3; **6i**, 141462-36-4; **7'**, 141462-37-5; **8a**, 141462-38-6; **8b**, 141462-39-7; **8d**, 141462-40-0; **8e**, 141462-41-1; **8f**, 141462-42-2; **8g**, 141462-43-3; **8k**, 141462-44-4; **8l**, 141462-45-5; **9a**, 2397-62-8; **9b**, 22266-99-5; **9c**, 92920-84-8; **9d**, 141462-46-6; **9e**, 80213-82-7; **9f**, 141462-47-7; **9g**, 141462-48-8; **9h**, 141462-49-9; **9i**, 141462-50-2; **9j**, 141462-51-3; **9k**, 141462-52-4; **9l**, 141462-53-5; **12a**, 490-91-5; **12b**, 141462-54-6; diisopropyl squarate, 61699-62-5; isopropylmagnesium chloride, 1068-55-9; PhLi, 591-51-5; 2-lithioanisole, 31600-86-9; 4-lithiotoluene, 2417-95-0; 2-lithiofuran, 2786-02-9; n-BuLi, 109-72-8; 2-bromopropene, 557-93-7.

(26) Zavarin, E.; Anderson, A. B. *J. Org. Chem.* **1955**, *20*, 82.

2-Thioalkyl Penems: An Efficient Synthesis of Sulopenem, a (5*R*,6*S*)-6-(1(*R*)-Hydroxyethyl)-2-[(*cis*-1-oxo-3-thiolanyl)thio]-2-penem Antibacterial

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A practical synthesis of potent penem antibacterials, CP-70,429 (**1**) (sulopenem) and CP-81,054 (**2**), is described. (L)-Aspartic acid was utilized to generate *both* the (3*S*)- and (3*R*)-thiolanylthio side chains of (5*R*,6*S*)-6-(1-(*R*)-hydroxyethyl)-2-[(*cis*-1-oxo-3-thiolanyl)thio]-2-penem-3-carboxylic acids **1** and **2**. This synthetic pathway provided in high yield enantiopure thioacetate intermediates **15** and **19**. To accommodate the fragile side chain sulfoxide moiety of the targeted β-lactams, standard penem synthetic methodology was modified to facilitate the conversion of **15** and **19** to **1** and **2**. The reactive chloroazetidinone **4b** was utilized to generate key azetidinone trithiocarbonate intermediate **22** which contains the requisite penem side chain. A chemoselective oxalofluoride-based azetidinone N-acylation procedure, which avoids sulfoxide O-acylation, was required for the conversion of **22** to the penem framework.

Introduction

The pioneering synthesis of penems by the Woodward/Ciba group[1] in 1976 along with the Merck discovery[2] of the broad-spectrum carbapenem, thienamycin, from fermentation sources have fueled an intense search, in recent years, for novel therapeutics from the penem and carbapenem families. While a number of candidates

(1) Woodward, R. B. In *Recent Advances in the Chemistry of Beta-Lactam Antibiotics*; Elks, J., Ed.; Special Publication No. 28; Chemical Society: London, 1977; p 167. Ernest, I.; Gosteli, J.; Greengrass, C. W.; Holick, W.; Jackman, D. E.; Pfaendler, H. R.; Woodward, R. B. *J. Am. Chem. Soc.* **1978**, *100*, 8214.

(2) Albers-Schonberg, G.; Arison, B. H.; Hensons, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E. A.; Rhodes, R. E.; Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, L. J.; Morin, R. B.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 6491.

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