General Regiospecific Synthesis of Annulated Quinones

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A general regiospecific synthesis of annulated hydroquinones/quinones is presented. This specifically involves the thermal rearrangement of the 4-aryl-4-hydroxycyclobutenones **1a–k** to the corresponding annulated hydroquinones. The synthetic scope and mechanism of this rearrangement are discussed.

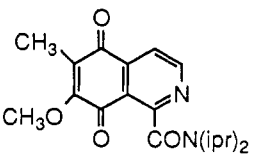
Reported here are the details of a general, convergent, regiospecific and high-yield synthesis of annulated hydroquinones and quinones.[1,2] It involves the thermal rearrangement of 4-aryl-4-hydroxycyclobutenones **1** to the corresopnding hydroquinones, which were generally not isolated as such but were directly converted to the corresponding quinones **2** or **3** via an oxidative workup. Scheme I provides an outline of this transformation and some specific examples (**2a–f** and **3g–k**, 73–94%).[3]

The starting cyclobutenones **1** were readily obtained (48–77% yields) from the corresponding cyclobutenediones upon treatment with the respective aryllithium reagents in THF at −78 °C.[4,5]

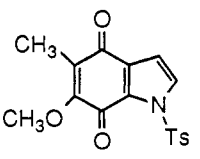
The examples given in Scheme I illustrate the selectivity of this reaction. Only quinone products were observed, and these were obtained as single regioisomers. They arise from the cyclobutenones bearing the respective 4-aryl groups, i.e., phenyl (**1a**), 4-methylphenyl (**1b**), 4-methoxyphenyl (**1c**), 2-methylphenyl (**1d**), 2-methoxyphenyl (**1e**), 2,5-dimethoxyphenyl (**1f**), 2-thienyl (**1g**), 2-furyl (**1h**), 3-furyl (**1i**), 2-furyl (**1j**), and 2-*N*-methylpyrrolyl (**1k**). Special note is made of the benzofuranquinones **3h** and **3i**, which particularly illustrate the regiocontrol provided by this method. Such quinones were readily obtained from their cyclobutenone precursors **1h** and **1i**, which were prepared as single regioisomers from the reaction of 3-butyl-4-methoxycyclobutenedione (**4**) with 2-lithiofuran and 3-lithiofuran, respectively.

The examples given here along with those reported by Liebeskind et al.,[1b] who independently discovered this quinone synthesis, speak to the general nature of the method. Three complementary examples from their work are **5–7**.

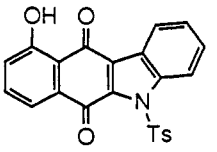
Upon close inspection, the cyclobutenone precursors to **2a–f** and **3g–k** would be expected to give only the indicated regioisomers. However, the 2-naphthyl derivative **1l** could conceivably give two different polyaromatic quinones via ring closure at either the 1- or the 3-position of the naphthalene group. The former mode would give an unsymmetrical phenanthraquinone and the latter a symmetrical anthraquinone isomer. Interestingly, only the unsymmetrical isomer **8** (90%) was observed (Scheme II).[6] Since the 1-position of naphthalene is the favored position for electrophilic attack, it is apparent that the rearrangement of **1l** to **8** requires some such electrophilic character in the transition state.[7] As expected, **8** (87%) was also obtained from the thermolysis of **1m**.



5 (67%)



6 (60%)



7 (86%)

Cyclobutenones **1n** and **1o** would also be amenable to the formation of two regioisomeric quinones, i.e., ring closure at the position either para or ortho to the R substituent (Scheme II). In fact, both isomers were observed to arise from these cyclobutenones upon thermolytic rearrangement. For **1o** the strong electron-donating methoxy group plays a major role and significantly favors ring closure at the position para to the substituent. Thus, the thermolysis of **1o** gave the quinones **2c** and **2e** in a respective ratio of 10:1 (80%). For **1n** no selectivity was observed. That is, quinones **2b** and **2d** were obtained in a 1:1 ratio (83%). The selectivity described here (**1l** > **1o** > **1n**) is clearly in the order expected for electrophilic aromatic substitution, and thus, some such character must be apparent in the mechanism of the cyclobutenone/hydroquinone rearrangement.

An initial attempt to obtain the linear polyaromatic 1,4-anthraquinone system also reveals some evidence of electrophilic character in the transition state as demonstrated in Scheme III. Electrocyclic ring opening of cyclobutenone **1p** to the corresponding conjugated ketene **9** followed by ring closure was expected to provide the

(1) Preliminary communications describing some aspects of this work have appeared. See: (a) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067. (b) Liebeskind, L. S.; Jewell, C. F.; Iyer, S. *J. Org. Chem.* **1986**, *51*, 3065.

(2) For a related contribution in this series, see: Karlsson, J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 3392.

(3) This is analogous to the ring expansion of other substituted cyclobutenones to naphthols or phenols. See: Smith, L. I.; Hoehn, H. H. *J. Am. Chem. Soc.* **1939**, *61*, 2619. Smith, L. I.; Hoehn, H. H. *J. Am. Chem. Soc.* **1941**, *63*, 1181. Nieuwenhuis, J.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1958**, *77*, 1153. Wittmann, H.; Illi, V.; Steck, H.; Ziegler, E. *Monatsh. Chem.* **1968**, *99*, 1982. Zubovics, Z.; Wittmann, H. *Justus Liebigs Ann. Chem.* **1972**, *765*, 15. Kipping, C.; Schiefer, H.; Schonfelder, K. *J. Prakt. Chem.* **1973**, *315*, 887. Neuse, E. W.; Green, B. R. *Justus Liebigs Ann. Chem.* **1974**, 1534. Mayr, H. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 500. Huisgen, R.; Mayr, H. *J. Chem. Soc., Chem. Commun.* **1976**, 55 and 57. Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672.

(4) For a discussion of the reactions of organolithium reagents with dimethyl squarate, see: Kraus, J. L. *Tetrahedron Lett.* **1985**, *26*, 1867. For a general review of the chemistry of squaric acids, see: Schmidt, A. M. *Synthesis* **1980**, 961.

(5) It is necessary to protonate the initially formed alkoxide at −78 °C. If not, other chemistry dominates. For analogies, see: Swenton, J. S.; Jackson, D. K.; Manning, M. J.; Raynolds, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 6182. Spangler, L. A.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 1800. Spangler, L. A.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1986**, 828.

(6) An analogous unsymmetrical product was observed when the metal chelated vinyl ketene was obtained upon treatment of an alkyne with a 2-naphthylcarbene complex. See: Dotz, K. H.; Dietz, R. *Chem. Ber.* **1978**, *111*, 2517. Dotz, K. H. *Pure Appl. Chem.* **1983**, *55*, 1689.

(7) A complex mixture was obtained upon thermolysis of 4-hydroxy-2,3-dimethoxy-4-(1-methoxy-2-naphthyl)cyclobutenone in an attempt to obtain the anthracene hydroquinone.

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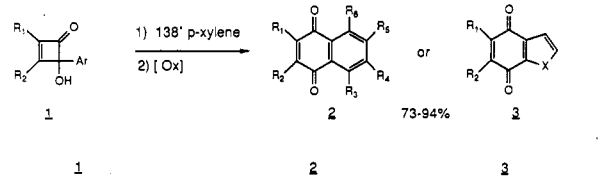
Scheme I



1 2 3

a $R_1,R_2=CH_3O$ $Ar=C_6H_5$- $R_1,R_2=CH_3O$ $R_3,R_4,R_5,R_6=H$

b $R_1,R_2=CH_3O$ $Ar=4$-$CH_3C_6H_4$- $R_1,R_2=CH_3O$ $R_3,R_4,R_6=H$ $R_5=CH_3$

c $R_1,R_2=CH_3O$ $Ar=4$-$CH_3OC_6H_4$- $R_1,R_2=CH_3O$ $R_3,R_4,R_6=H$ $R_5=OCH_3$

d $R_1,R_2=CH_3O$ $Ar=2$-$CH_3C_6H_4$- $R_1,R_2=CH_3O$ $R_4,R_5,R_6=H$ $R_3=CH_3$

e $R_1,R_2=CH_3O$ $Ar=2$-$CH_3OC_6H_4$- $R_1,R_2=CH_3O$ $R_4,R_5,R_6=H$ $R_3=OCH_3$

f $R_1,R_2=CH_3O$ $Ar=2,5$-$(CH_3O)_2C_6H_3$- $R_1,R_2=CH_3O$ $R_4,R_5=H$ $R_3,R_6=OCH_3$

g $R_1,R_2=CH_3O$ $Ar=2$-C_4H_3S-[a] $R_1,R_2=CH_3O$ $X=S$

h $R_1=C_4H_9$ $R_2=CH_3O$ $Ar=2$-C_4H_3O-[b] $R_1=C_4H_9$ $R_2=CH_3O$ $X=O$

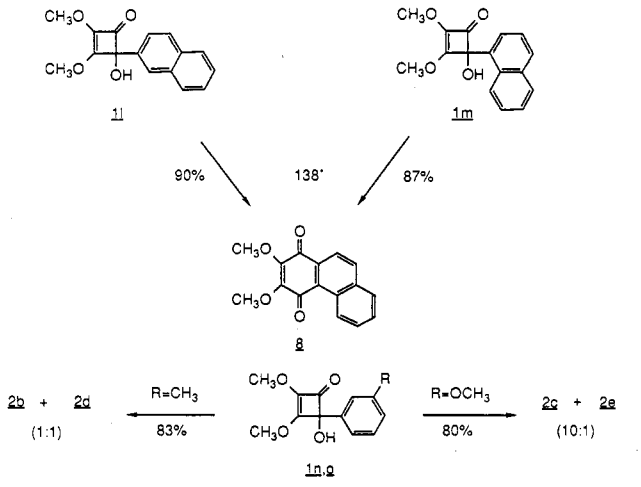
i $R_1=C_4H_9$ $R_2=CH_3O$ $Ar=3$-C_4H_3O-[b] $R_1=CH_3O$ $R_2=C_4H_9$ $X=O$

j $R_1,R_2=CH_3O$ $Ar=2$-C_4H_3O-[b] $R_1,R_2=CH_3O$ $X=O$

k $R_1=C_6H_5$ $R_2=CH_3O$ $Ar=2$-$CH_3NC_4H_3$-[c] $R_1=C_6H_5$ $R_2=CH_3O$ $X=NCH_3$

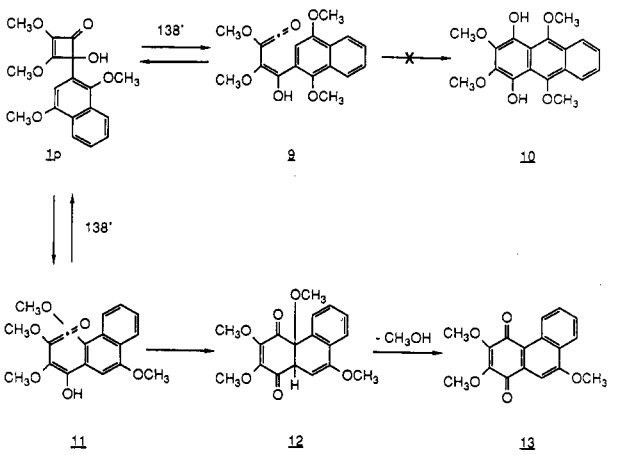
[a] C_4H_3S = thienyl. [b] C_4H_3O = furyl. [c] $CH_3NC_4H_3$ = *N*-methylpyrrolyl.

Scheme II



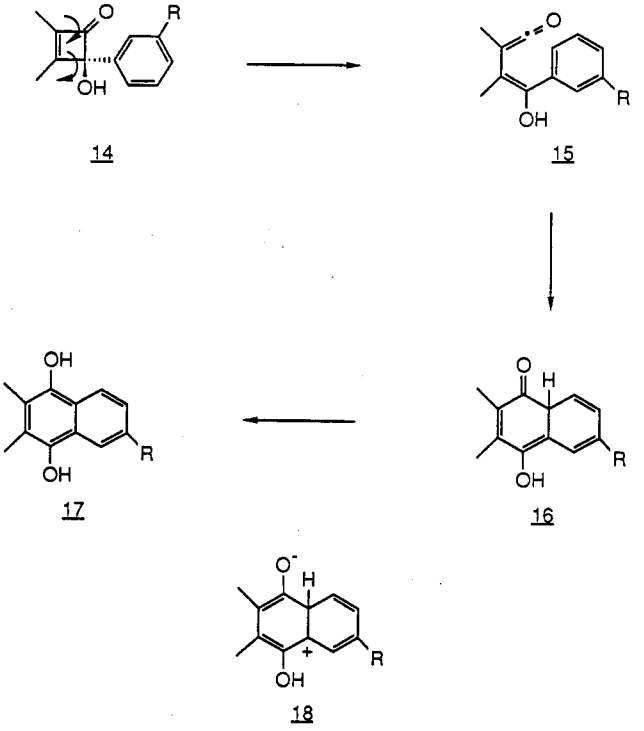
1l 1m 8 1n,o

Scheme III



1p 9 10 11 12 13

Scheme IV



14 15 16 17 18

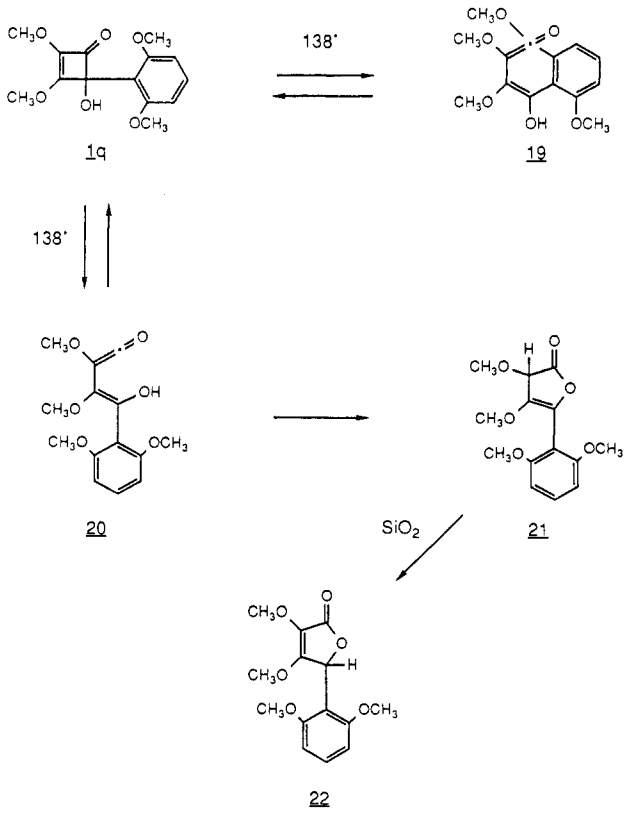
linear hydroquinone **10**. However, a mixture of products was obtained, which was determined to be the cyclohexenedione **12** and the 1,4-phenanthrenedione **13**. These products arise by a selective ring closure of the conjugated ketene **11** at the carbon bearing the methoxy group followed by tautomerization to the cyclohexenedione **12**. Loss of methanol then gives the 1,4-phenanthrenedione **13**. Verification of cyclohexenedione **12** as the quinone precursor was achieved by independently subjecting it to thermolysis in refluxing methanol and observing the formation of the corresponding 1,4-phenanthrenedione **13** in high yield.

A mechanism that is generally consistent with the data provided here is outlined in Scheme IV. Specifically, the cyclobutenone **14** is envisaged to undergo electrocyclic cleavage to the conjugated ketene **15**. Electrocyclic ring closure of **15** would give **16**, which upon aromatization would result in the hydroquinone **17**. In order to account for the electronic effects outlined above, some electrophilic character in the electrocyclic ring closure of **15** to **16** must be invoked. In a limiting representation this is illustrated by the zwitterion **18** which would arise via electrophilic attack of the ketene on the aryl group.[8] Thus, electron-donating substituents (R) would be expected to have an influence on the regiochemistry of the ring closure.

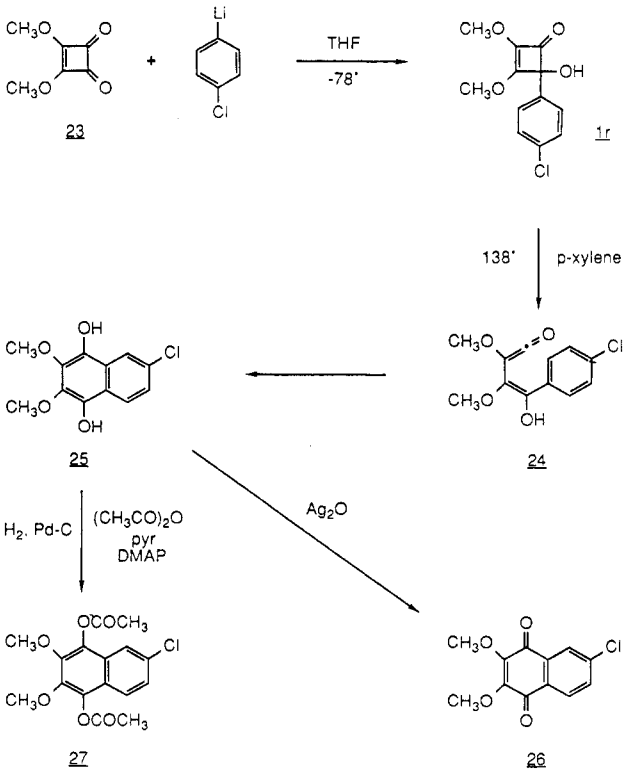
Perhaps the most unusual aspect of this rearrangement involves the stereoelectronic consequence of the electrocyclic cleavage of the cyclobutenone **14** to the ethenyl ketene **15**. This must be a highly selective process which proceeds by the conrotatory motion in which the OH substituent rotates outward. Thus, the resulting ketene **15** has the aryl group and the ketene moiety proximally located to allow their direct interaction. The opposite conrotatory opening would result in an inward rotation of the hydroxyl group. This generally does not happen since the resulting ketene should immediately collapse to a butenolide, and no such products could be detected for the examples thus far described. However, for one additional case the butenolide was obtained as the sole product (Scheme V). Specifically, thermolysis of **1q** at 138 °C (*p*-xylene) gives a mixture of the butenolides **21** and **22** in a respective ratio of 2:1 (89%). The butenolide **22** was

(8) For examples of electrophilic attack of ketene on aromatic nuclei, see: Hurd, C. D. W. *J. Am. Chem. Soc.* **1925**, *47*, 2777.

Scheme V



Scheme VI



obtained as the exclusive isomer upon treatment of the initially formed mixture with silica gel. Ring closure of the presumed kinetic isomeric ethenyl ketene **19** apparently does not compete with that of **20**. Thus, butenolide products result.

Although little has appeared regarding the ring opening of cyclobutenones with respect to the above suggested favored rotational mode, several relevant studies have been reported on the thermal ring opening of cyclobutenes.[9-12] These have recently been evaluated in a computational study, which concludes that the observed outward rotation of electron-donating groups can be rationalized on the basis of electronic effects.[13] It was demonstrated that electron donors at C_3 and C_4 of cyclobutenes preferentially rotate outward in order to minimize the repulsive four-electron interaction between the donor nonbonding electron pair on the substituent with the C_3C_4 σ-orbital and to maximize the stabilizing two-electron interaction between the same donor electrons and the C_3C_4 σ^*-orbital. Furthermore, it was noted that this tendency for outward rotation increases as the electron-donor ability of the substituent increases, and such selectivity can be exceptional. For example, the outward rotation of an OH group is estimated to be more favorable than inward rotation by 14 kcal/mol. A Cl group is favored by 9 kcal/mol and an NH_2 by as much as 26 kcal/mol. Thus, the suggested selective ring opening of **14** to **15** is analogous to the theoretical and experimental studies of cyclobutenes.

To illustrate the convergence and the relative ease of obtaining a variety of annelated hydroquinones by this route, we accomplished an efficient and practical synthesis of the antipsoriatic drug Lonapalene. Lonapalene (**27**) is a selective 5-lipoxygenase inhibitor which is currently in phase II clinical trials for the treatment of psoriasis.[14,15] The two syntheses of this compound that have been reported suffer some shortcomings. One of these starts with readily available precursors (chloroprene and 1,4-benzoquinone) but involves an overall lengthy procedure.[15] The other is more efficient but utilizes 2,3-dimethoxy-1,4-benzoquinone, a compound that is not easily obtained.[16]

The synthesis of Lonapalene initiating from dimethyl squarate (**23**) and 4-bromochlorobenzene, both of which are readily available,[17] is illustrated in Scheme VI. Specifically, 4-lithiochlorobenzene was generated from 4-bromochlorobenzene by treatment with *n*-butyllithium in THF at −78 °C. This was then added to a THF solution containing dimethyl squarate, which was quenched after 15 min with 5% NH_4Cl. After workup and chromatography, cyclobutenone **1r** was isolated as a white crystalline solid in 55% yield. A sample of **1r** was converted to the quinone **26** by thermolysis to generate the intermediate ketene **24**. Ring closure of **24** and subsequent oxidation of hydroquinone **25** afforded the quinone **26** in 85% yield after recrystallization.

The synthesis of Lonapalene itself was accomplished without isolation and purification of any of the intermediates. As described above, 4-lithiochlorobenzene was generated from 4-bromochlorobenzene and added to a solution of dimethyl squarate in THF at −78 °C. After

(9) Curry, M. J.; Stevens, I. D. R. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1391.
(10) Arnold, B. J.; Sammes, P. G.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 409 and 415.
(11) Dolbier, W. R.; Koroniak, H.; Burton, D. J.; Bailey, A. R.; Shaw, G. S.; Hansen, S. W. *J. Am. Chem. Soc.* **1984**, *106*, 1871.
(12) Kirmse, W.; Randan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989.
(13) Randan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099.
(14) Krishna Murthy, D. V.; Kruseman-Aretz, M.; Rouhafza-Fard, S.; Bedford, C. J.; Young, J. M.; Jones, G.; Venuti, M. *Neuropharmacology* **1985**, *44*, 886.
(15) Jones, G. H.; Venuti, M. C.; Young, J. M.; Krishna Murthy, D. V.; Loe, B. E.; Simpson, R. A.; Berks, A. H.; Spires, D. A.; Maloney, P. J.; Kruseman, M.; Rouhafza, S.; Kappas, K. C.; Unger, S. H.; Cheung, P. S. *J. Med. Chem.* **1986**, *29*, 1504.
(16) Flynn, D. L.; Nies, D. E. *Tetrahedron Lett.* **1986**, *27*, 5075.
(17) Dimethyl squarate **23** was prepared from commercially available squaric acid. See: Cohen, S.; Cohen, S. G. *J. Am. Chem. Soc.* **1966**, *88*, 1533. 4-Bromochlorobenzene is commercially available.

quenching of the reaction with 5% NH_4Cl, the resulting crude cyclobutenone **1r** was dissolved in *p*-xylene and the solution was refluxed for 3 h. After cooling to ambient temperature, the solution was placed under an atmosphere of hydrogen over a catalyst of Pd/C to assure a maximum concentration of the hydroquinone **25**. The *p*-xylene solution was then treated with acetic anhydride, pyridine, and DMAP to convert the hydroquinone to the diacetate. After workup, column chromatography, and recrystallization, Lonapalene was obtained in 52% overall yield from dimethyl squarate.

In conclusion, the significant points of this study include the following: (1) a general synthetic route to highly substituted annulated quinones is reported; (2) the proposed mechanism of this rearrangement must involve a very selective ring opening of the cyclobutenone precursors such that the 4-hydroxy group at C_4 rotates outward during the conrotatory process; (3) ring closure of the resulting conjugated ketene may not be strictly a concerted 6-π-electron process, i.e., it must at least be one showing significant charge character in the transition state to account for the observed substituent effects.

Experimental Section

Instrumentation. Proton NMR spectra were recorded on either a Varian FT80A, a Bruker WM-250, a General Electric QE 300 NMR, or a General Electric QE 500 NMR spectrometer. Chemical shifts were referenced to internal solvent resonances and are reported relative to TMS in $CDCl_3$ solvent. Infrared spectra were recorded on a Perkin-Elmer spectrophotometer (double beam) using CH_2Cl_2 as the solvent and the reference solvent in a set of matched solution cells (Perkin-Elmer). Low-resolution mass spectra (MS) were determined on a Finnigan 4000 spectrometer; high-resolution mass spectra (HRMS) were measured with a VG analytic 7070E spectrometer. Elemental analyses were performed by the Robertson Laboratory, Inc., of Florham Park, NJ. Melting points are uncorrected.

General Procedures. All reactions were performed in flame-dried glassware under a positive pressure of nitrogen. Reaction mixtures were stirred magnetically. Air-sensitive solutions were transferred via cannula and were introduced into the reaction vessels through rubber septa. Butyllithium was introduced to the reaction vessels via syringe. Reaction solutions were concentrated by using a Büchi rotary evaporator at 15–20 mmHg, and *p*-xylene was removed in the same manner with a bath temperature of 60 °C. Column chromatography was performed by using E. Merck silica gel (230–400 mesh), with hexane and ethyl acetate as the eluants.

Chemicals. Commercial grade reagents and solvents were used without further purification except as indicated below. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Benzene and *p*-xylene were also distilled from calcium hydride before being used.

4-Hydroxy-2,3-dimethoxy-4-phenylcyclobutenone (1a). A solution of 0.50 g (3.52 mmol) of 1,2-dimethoxycyclobutenedione (**23**) (dimethyl squarate) in 50 mL of dry THF in a 100-mL round-bottomed flask was cooled to −78 °C (dry ice/acetone bath) under a positive stream of N_2. To this flask was added dropwise via syringe 2.33 mL (3.50 mmol) of 1.50 M phenyllithium. The solution was stirred for 10 min and then quenched by pouring it into a separatory funnel containing 10 mL of 5% NH_4Cl and 20 mL of ether. The separatory funnel was shaken and warmed until phase separation was achieved with no ice present. The layers were separated, the aqueous layer was extracted with ether (2 × 20 mL), and the ether layers were combined. The ether layer was washed with brine (2 × 30 mL) and then dried over $MgSO_4$. Filtration followed by concentration under reduced pressure resulted in a yellow oil. Trituration with ether afforded a white solid, which was recrystallized from ether to give 0.59 g (77%) of **1a** as white needles: mp 96–98 °C; IR ($CHCl_3$) 3467, 3005, 2952, 1772, 1632, 1464, 1341, 1042, 992, and 841 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.28 (s, 1 H), 4.01 (s, 3 H), 4.06 (s, 3 H), 7.35 (m, 3 H), 7.53 (d, J = 9.1 Hz, 2 H); MS (EI) 220 (54), 205 (38), 145 (20), 105 (100), 89 (30); MS (CI) 221 (100), 203 (28), 189 (98); HRMS, m/e calcd for $C_{12}H_{12}O_4$ (M^+) 220.0735, found 220.0745.

General Procedure for the 1,2-Addition of Aryllithium Reagents to Cyclobutenediones by Halogen–Metal Exchange. As a typical example, the 1,2-addition of 4-lithiotoluene from 4-bromotoluene was accomplished in the following manner. **4-Hydroxy-2,3-dimethoxy-4-(4-methylphenyl)cyclobutenone (1b).** A solution of 1.01 g (5.39 mmol) of 4-bromotoluene in 50 mL of dry THF in a 100-mL round-bottomed flask was cooled to −78 °C under a positive pressure of N_2. To this flask was added dropwise via syringe 3.15 mL (7.30 mmol) of 2.30 M *n*-butyllithium. The resulting solution was stirred for 20 min to generate the aryl anion and then transferred by cannula to another flask (250 mL) containing 1.00 g (7.04 mmol) of **23** dissolved in 100 mL of dry THF also under N_2 pressure at −78 °C. The solution was stirred for 15 min and then quenched by pouring the reaction mixture into a separatory funnel containing 10 mL of 5% NH_4Cl and 20 mL of ether. The separatory funnel was shaken and warmed until phase separation was achieved with no ice present. The layers were separated, the aqueous layer was extracted with ether (2 × 20 mL), and the ether layers were combined. The ether layer was washed with brine (2 × 30 mL) and then dried over $MgSO_4$. Filtration followed by concentration under reduced pressure resulted in a white solid. Recrystallization from ether afforded 1.20 g (73%) of **1b** as white crystals: mp 126–128 °C; IR ($CHCl_3$) 3400, 2947, 1772, 1635, 1464, 1337, 1040, 992, and 848 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.35 (s, 3 H), 2.99 (s, 1 H), 4.01 (s, 3 H), 4.07 (s, 3 H), 7.19 (d, J = 8.0 Hz, 2 H), 7.41 (d, J = 8.1 Hz, 2 H); MS (EI) 234 (65), 219 (51), 119 (100), 103 (40), 91 (61); MS (CI) 235 (100), 217 (25), 203 (25). Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.64; H, 6.03. Found: C, 66.69; H, 6.01.

The other halogen–metal-exchange reactions were carried out in a similar manner as described for **1b** from the corresponding bromo-substituted aromatic compounds.

4-Hydroxy-2,3-dimethoxy-4-(4-methoxyphenyl)cyclobutenone (1c): 55% yield; colorless crystals (ether); mp 96–98 °C; IR ($CHCl_3$) 3400, 3001, 2958, 1780, 1638, 1511, 1469, 1433, 1348, 1253, 1173, 1050, 993, and 849 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.50 (s, 1 H), 3.81 (s, 3 H), 4.00 (s, 3 H), 4.06 (s, 3 H), 6.88 (d, J = 9.1 Hz, 2 H), 7.44 (d, J = 9.1 Hz, 2 H); MS (EI) 250 (22), 235 (30), 218 (43), 207 (7), 191 (10), 175 (13), 162 (84), 147 (100), 135 (64), 119 (98); MS (CI) 251 (54), 233 (16), 219 (100); HRMS, m/e calcd for $C_{13}H_{14}O_5$ (M^+) 250.0841; found 250.0828.

4-Hydroxy-2,3-dimethoxy-4-(2-methylphenyl)cyclobutenone (1d): 56% yield; colorless crystals (ether); mp 98–100 °C; IR ($CHCl_3$) 3400, 3040, 3005, 2960, 1770, 1642, 1637, 1470, 1340, 1038, 985, and 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.63 (s, 3 H), 2.79 (s, 1 H), 3.99 (s, 3 H), 4.20 (s, 3 H), 7.17 (m, 3 H), 7.42 (d, J = 7.6 Hz, 1 H); MS (EI) 234 (57), 219 (52), 191 (26), 131 (27), 119 (48), 103 (100), 91 (57); MS (CI) 235 (100), 217 (25), 203 (12). Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.64; H, 6.03. Found: C, 66.89; H, 6.12.

4-Hydroxy-2,3-dimethoxy-4-(2-methoxyphenyl)cyclobutenone (1e): 56% yield; colorless crystals (ether); mp 103.5–105 °C; IR ($CHCl_3$) 3500, 3001, 2953, 1779, 1639, 1491, 1453, 1432, 1340, 1241, 1110, 1034, 988, and 839 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.93 (s, 3 H), 4.00 (s, 3 H), 4.14 (s, 3 H), 5.01 (s, 1 H), 6.98 (t, J = 6.8 Hz, 2 H), 7.30 (m, 2 H); MS (EI) 250 (64), 235 (29), 218 (24), 207 (16), 191 (29), 175 (51), 164 (45), 149 (38), 135 (52), 119 (31), 104 (13), 91 (100), 77 (41); MS (CI) 251 (10), 233 (100), 219 (65); HRMS, m/e calcd for $C_{13}H_{14}O_5$ (M^+) 250.0841, found 250.0828.

4-Hydroxy-2,3-dimethoxy-4-(2,5-dimethoxyphenyl)cyclobutenone (1f): 59% yield; white crystalline solid (ether); mp 65–67 °C; IR ($CHCl_3$) 3500, 3028, 3010, 2957, 2840, 1780, 1644, 1497, 1468, 1345, 1040, and 885 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.77 (s, 3 H), 3.90 (s, 3 H), 3.99 (s, 3 H), 4.13 (s, 3 H), 5.15 (s, 1 H), 6.86 (m, 3 H); MS (EI) 280 (18), 249 (100), 221 (30), 205 (21), 192 (58), 179 (20), 121 (27); MS (CI) 281 (6), 263 (100), 249 (29); HRMS, m/e calcd for $C_{14}H_{16}O_6$ (M^+) 280.0947, found 280.0940.

4-Hydroxy-2,3-dimethoxy-4-(2-thienyl)cyclobutenone (1g): 63% yield; colorless crystals (ether); mp 68–69 °C; IR ($CHCl_3$) 3580 (overtone), 3400, 3008, 2956, 1781, 1644, 1635, 1470, 1432, 1348, 1040, and 984 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.51 (s, 1 H), 4.01 (s, 3 H), 4.11 (s, 3 H), 7.03 (dd, J = 1.4, 3.6 Hz, 1 H),

7.10 (dd, J = 1.2, 2.4 Hz, 1 H), 7.33 (dd, J = 1.2, 4.9 Hz, 1 H); MS (EI) 226 (35), 193 (14), 183 (15), 151 (16), 138 (15), 127 (51), 111 (100), 95 (21), 69 (18); MS (CI) 227 (100), 209 (18), 195 (20); HRMS, m/e calcd for $C_{10}H_{10}O_4S$ (M^+) 226.0300, found 226.0297.

2-*n*-Butyl-4-(3-furyl-)-4-hydroxy-3-methoxycyclobutenone (1i): 68% yield; brown solid. Comparison of the crude reaction product to the purified product revealed only one regioisomer: mp 44–46 °C; IR ($CHCl_3$) 3591 (overtone), 3350, 2979, 2938, 1757, 1619, 1460, 1361, 1012, and 870 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 9.0 Hz, 3 H), 1.35 (m, 2 H), 1.55 (m, 2 H), 1.69 (s, 1 H), 2.15 (t, J = 7.5 Hz, 2 H), 4.05 (s, 3 H), 6.32 (d, J = 3.0 Hz, 1 H), 7.41 (t, J = 3.0 Hz, 1 H), 7.52 (d, J = 3.0 Hz, 1 H); MS (EI) 236 (26), 221 (4), 207 (2), 193 (7), 179 (67), 165 (15), 151 (12), 137 (12), 123 (5), 109 (7), 95 (100), 77 (8); MS (CI) 237 (100), 219 (18); HRMS, m/e calcd for $C_{13}H_{16}O_4$ (M^+) 236.1048, found 236.1044.

4-Hydroxy-2,3-dimethoxy-4-(2-naphthyl)cyclobutenone (1l): 62% yield; white crystals (ether); mp 98–100 °C; IR ($CHCl_3$) 3589 (overtone), 3400, 3010, 2961, 1781, 1635, 1471, 1434, 1350, 1123, 1050, 984, 860, and 803 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.73 (s, 1 H), 4.01 (s, 3 H), 4.04 (s, 3 H), 7.50 (m, 2 H), 7.57 (dd, J = 2.3, 10.5 Hz, 1 H), 7.79 (m, 3 H), 8.02 (d, J = 1.2 Hz, 1 H); MS (EI) 270 (26), 255 (23), 238 (45), 195 (20), 182 (68), 167 (57), 155 (33), 139 (100), 127 (30), 69 (28); MS (CI) 271 (100), 253 (16), 239 (88); HRMS, m/e calcd for $C_{16}H_{14}O_4$ (M^+) 270.0892, found 270.0892.

4-Hydroxy-2,3-dimethoxy-4-(1-naphthyl)cyclobutenone (1m): 48% yield; colorless crystals (ether); mp 108–110 °C; IR ($CHCl_3$) 3589 (overtone), 3400, 3058, 3011, 2958, 1773, 1642, 1469, 1431, 1338, 1232, 1033, 982, 861, 828, and 793 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.09 (s, 1 H), 4.00 (s, 3 H), 4.24 (s, 3 H), 7.38 (t, J = 8.0 Hz, 1 H), 7.53 (m, 2 H), 7.67 (d, J = 8.0 Hz, 1 H), 7.82 (dd, J = 4.8, 8.0 Hz, 2 H), 8.69 (d, J = 8.0 Hz, 1 H); MS (EI) 270 (29), 255 (21), 238 (12), 212 (13), 195 (12), 181 (28), 167 (56), 155 (14), 139 (100), 127 (20), 70 (17); MS (CI) 271 (77), 253 (19), 239 (100); HRMS, m/e calcd for $C_{16}H_{14}O_4$ (M^+) 270.0892, found 270.0891.

4-Hydroxy-2,3-dimethoxy-4-(3-methylphenyl)cyclobutenone (1n): 67% yield; colorless crystals (ether); mp 96–98 °C; IR ($CHCl_3$) 3560 (overtone), 3400, 3038, 3014, 2958, 2932, 2863, 1778, 1640, 1471, 1350, 1050, and 990 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.37 (s, 3 H), 2.95 (s, 1 H), 4.02 (s, 3 H), 4.08 (s, 3 H), 7.15 (d, J = 7.0 Hz, 1 H), 7.32 (M, 3 H); MS (EI) 234 (31), 219 (23), 191 (19), 159 (18), 135 (20), 119 (100), 103 (35), 91 (79); MS (CI) 235 (100), 217 (20), 203 (16); HRMS, m/e calcd for $C_{13}H_{14}O_4$ (M^+) 234.0891, found 234.0889.

4-Hydroxy-2,3-dimethoxy-4-(3-methoxyphenyl)cyclobutenone (1o): white solid; mp 46–48 °C; IR ($CHCl_3$) 3589 (overtone), 3400, 3004, 2958, 1779, 1635, 1468, 1431, 1350, 1289, 1253, 1161, 1045, 1001, 987, and 880 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.52 (s, 1 H), 3.81 (s, 3 H), 4.00 (s, 3 H), 4.05 (s, 3 H), 6.87 (dd, J = 2.5, 6.8 Hz, 1 H), 7.09 (m, 2 H), 7.28 (t, J = 6.8 Hz, 1 H); MS (EI) 250 (31), 235 (25), 218 (52), 207 (10), 190 (18), 175 (71), 162 (55), 147 (29), 135 (32), 119 (100); MS (CI) 251 (68), 235 (15), 219 (100), 201 (15); HRMS, m/e calcd for $C_{13}H_{14}O_5$ (M^+) 250.0841, found 250.0831.

4-(4-Chlorophenyl)-4-hydroxy-2,3-dimethoxycyclobutenone (1r): 55% yield; white crystals (ether); mp 93–95 °C; IR (KBr) 3321, 2953, 1769, 1602, 1463, 1350, 1200, 1048, 980, 853, and 492 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.21 (s, 1 H), 4.01 (s, 3 H), 4.07 (s, 3 H), 7.33 (d, J = 8.7 Hz, 2 H), 7.44 (d, J = 8.6 Hz, 2 H); MS (EI) 254 (18), 239 (15), 219 (53), 191 (37), 176 (24), 166 (17), 151 (24), 139 (100), 123 (41), 111 (50), 75 (40); MS (CI) 255 (100); HRMS, m/e calcd for $C_{12}H_{11}ClO_4$ (M^+) 254.0346, found 254.0327.

General Procedure for the 1,2-Addition of 2-Lithiofuran to Cyclobutenediones by Deprotonation. As a typical example, the 1,2-addition of 2-lithiofuran from furan was accomplished in the following manner. **2-*n*-Butyl-4-(2-furyl)-4-hydroxy-3-methoxycyclobutenone (1h).** A solution of 0.93 g (13.7 mmol) of furan in 30 mL of dry THF was cooled to −20 °C (glycol/dry ice) under a positive pressure of N_2. To this solution was added dropwise via syringe 2.36 mL (5.55 mmol) of 2.35 M *n*-butyllithium. The solution was stirred for 1.5 h at −20 °C plus 1.5 h at 0 °C. The solution was then cooled to −78 °C, treated with **4**, and worked up in a similar manner as described for **1b**. Concentration under reduced pressure resulted in an oil. The oil was purified by column chromatography on silica gel (elution with hexane/ethyl acetate), which provided 0.81 g (62%) of a low-melting brown solid. Comparison of the crude reaction product to the purified product by ^1H NMR revealed the presence of only one regioisomer: mp 58–60 °C; IR ($CHCl_3$) 3580 (overtone), 3325, 2962, 2937, 2865, 1757, 1625, 1462, 1371, 1151, 1003, 912, and 875 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, J = 9.0 Hz, 3 H), 1.37 (m, 2 H), 1.55 (m, 2 H), 1.74 (s, 1 H), 2.17 (t, J = 7.5 Hz, 2 H), 4.05 (s, 3 H), 6.40 (dd, J = 1.5, 3.0 Hz, 1 H), 6.46 (d, J = 3.0 Hz, 1 H), 7.41 (d, J = 1.5 Hz, 1 H); MS (EI) 236 (32), 208 (20), 193 (31), 179 (32), 165 (51), 151 (27), 137 (13), 123 (10), 109 (10), 95 (100), 77 (16); MS (CI) 237 (100), 219 (7); HRMS, m/e calcd for $C_{13}H_{16}O_4$ (M^+) 236.1048, found 236.1047.

4-(2-Furyl)-4-hydroxy-2,3-dimethoxycyclobutenone (1j). In a similar manner as described for **1h**, **1j** was obtained from **23** in 59% yield as colorless crystals: mp 78–80 °C; IR ($CHCl_3$) 3400, 3042, 3012, 2960, 1782, 1643, 1632, 1470, 1350, 1152, 1053, 1014, and 982 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 3.68 (s, 1 H), 4.00 (s, 3 H), 4.08 (s, 3 H), 6.44 (m, 2 H), 7.39 (m, 1 H); MS (EI) 210 (77), 182 (65), 167 (37), 139 (44), 122 (33), 111 (100), 95 (66), 68 (54); MS (CI) 211 (100), 193 (13), 179 (11); HRMS, m/e calcd for $C_{10}H_{10}O_5$ (M^+) 210.0528, found 210.0522.

4-Hydroxy-3-methoxy-4-(*N*-methyl-2-pyrrolyl)-2-phenylcyclobutenone (1k). To a solution of 0.40 g (5.69 mmol) of 1-methylpyrrole and 0.79 g (6.82 mmol) of TMEDA in 12 mL of dry ether was added 3.67 mL (5.69 mmol) of 1.55 M *n*-butyllithium dropwise via syringe at room temperature with stirring under a positive stream of N_2. The mixture was heated at reflux for 1 h and then cooled to −78 °C. This solution was transferred via cannula to another solution containing 3-methoxy-4-phenyl-3-cyclobutene-1,2-dione in 125 mL of dry THF at −78 °C under N_2. After 20 min of stirring, the reaction was quenched in the same manner as described for **1b**, the aqueous layer was extracted with ether (2 × 20 mL), and the organic layers were combined. The organic phase was washed with cold 0.5 M HCl (20 mL each) followed by saturated $NaHCO_3$ and then finally with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a yellow residue. Recrystallization from CH_2Cl_2/hexanes afforded 0.70 g (49%) of **1k** as white fluffy crystals: mp 133–135 °C; IR ($CHCl_3$) 3360, 3005, 1757, 1633, 1601, 1493, 1461, 1450, 1368, and 1333 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.38 (s, 1 H), 3.89 (s, 3 H), 4.36 (s, 3 H), 6.06 (q, J = 0.9, 2.7 Hz, 1 H), 6.15 (q, J = 1.7, 1.9 Hz, 1 H), 6.64 (t, J = 2.3 Hz, 1 H), 7.32 (m, 3 H), 7.72 (d, J = 6.8 Hz, 2 H); MS (EI) 269 (100), 254 (40), 236 (47), 208 (18), 180 (8), 170 (8), 145 (13), 139 (9), 129 (15), 108 (58); MS (CI) 270 (100); HRMS calcd for $C_{16}H_{15}NO_3$ 269.1052, found 269.1039.

4-Hydroxy-2,3-dimethoxy-4-(1,4-dimethoxy-2-naphthyl)cyclobutenone (1p). Ortho metalation of 1,4-dimethoxynaphthalene was accomplished by treatment of a solution of 0.86 g (4.57 mmol) of 1,4-dimethoxynaphthalene in 15 mL of ether at 0 °C with 3.41 mL (4.67 mmol) of 1.37 M *n*-butyllithium followed by refluxing under Ar for 2 days. The flask was cooled to −78 °C, and the contents were transferred via cannulae to another flask containing 0.62 g (4.37 mmol) of **23** under Ar pressure at −78 °C. The reaction mixture was quenched and worked up in a similar manner as described for **1b** and then dried over solid K_2CO_3. Filtration and concentration of the solution under reduced pressure afforded an oil. Purification by column chromatography provided 0.73 g (48%) of **1p** as a yellow oil: IR (neat) 3422, 2958, 1783, 1645, 1601, 1467, 1350, and 1101 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.97 (s, 3 H), 4.06 (s, 3 H), 4.11 (s, 3 H), 4.13 (s, 3 H), 6.01 (s, 1 H), 6.57 (s, 1 H), 7.55 (m, 2 H), 8.02 (d, J = 8.4 Hz, 1 H), 8.24 (d, J = 8.4 Hz, 1 H); MS (EI) 330 (5), 299 (100), 267 (22), 256 (10), 227 (24), 213 (9), 199 (10), 184 (7), 171 (5), 128 (8); MS (CI) 331 (4), 313 (100), 299 (76); HRMS, m/e calcd for $C_{18}H_{18}O_6$ (M^+) 330.1103, found 330.1126.

4-Hydroxy-2,3-dimethoxy-4-(2,6-dimethoxyphenyl)cyclobutenone (1q). Metalation of resorcinol dimethyl ether was accomplished by a previously published method[18] using 1.02 g (7.38 mmol) of resorcinol dimethyl ether and 3.28 mL (7.04 mmol) of 2.15 M *n*-butyllithium. After completion of the reaction, the flask was cooled to −78 °C and the contents were transferred via

(18) Shirley, D. A.; Johnson, J. R.; Hendrik, J. P. *J. Organomet. Chem.* **1968**, *11*, 209.

cannula to another flask (250 mL) containing 0.98 g (6.98 mmol) of **23** under N_2 pressure at −78 °C. The resulting solution was stirred for 20 min. The reaction mixture was quenched and worked up in a similar manner as described for **1b**. Concentration of the solution under reduced pressure resulted in a white solid. Recrystallization from CH_2Cl_2/hexane afforded 1.15 g (60%) of **1q** as white crystals: mp 123–125 °C; IR ($CHCl_3$) 3500, 3004, 2952, 1781, 1644, 1637, 1600, 1593, 1480, 1470, 1435, 1339, 1251, 1110, 1038, and 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.88 (s, 6 H), 3.97 (s, 3 H), 4.08 (s, 3 H), 5.80 (s, 1 H), 6.64 (d, J = 8.4 Hz, 2 H), 7.25 (t, J = 8.4 Hz, 1 H); MS (EI) 280 (20), 249 (13), 237 (24), 221 (17), 205 (23), 194 (26), 179 (32), 165 (33), 149 (26), 121 (30), 107 (16), 91 (100), 76 (32); MS (CI) 281 (15), 263 (57), 249 (100); HRMS, m/e calcd for $C_{14}H_{16}O_6$ (M^+) 280.0947, found 280.0952.

Thermolysis and Oxidation of 4-Aryl-4-hydroxycyclobutenones. Method A. 2,3-Dimethoxy-1,4-naphthoquinone (2a). A 0.30-g (1.36 mmol) portion of **1a** was dissolved in 30 mL of freshly distilled *p*-xylene. The solution was heated at reflux for 2 h and then cooled to room temperature. TLC revealed two spots. One spot was quinone active (leucomethylene blue), and the other was hydroquinone active (Emmerie-Engel). The solution was concentrated under reduced pressure at a bath temperature of 65 °C to afford an oil. The oil was oxidized by dissolution in 50 mL of CH_2Cl_2, then treatment with 9.04 g of 20% Ce(IV)/SiO_2 reagent (3.32 g/mmol Ce(IV),[19] and then stirring for 5 min. The mixture was filtered through a fritted filter and the SiO_2 washed with CH_2Cl_2 (6 × 25 mL). The solution was then concentrated under reduced pressure to yield a yellow solid. Recrystallization from ether afforded 0.22 g (73%) of **2a** as yellow needles: mp 115–117 °C; IR (CH_2Cl_2) 3012, 3002, 1667, 1580, 1320, 1268, 1041, 1010, and 907 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.12 (s, 6 H), 7.70 (dd, J = 3.2, 4.1 Hz, 2 H), 8.08 (dd, J = 3.2, 4.1 Hz, 2 H); MS (EI) 218 (85), 203 (85), 173 (91), 147 (41), 104 (100), 89 (24), 76 (87); MS (CI) 219 (100); HRMS, m/e calcd for $C_{12}H_{10}O_4$ (M^+) 218.0579, found 218.0574.

Thermolysis and Oxidation of 4-Aryl-4-hydroxycyclobutenones. Method B. 2,3,6-Trimethoxy-1,4-naphthoquinone (2c). Similar thermolysis of 0.15 g (0.60 mmol) of **1c** and concentration of the solution under reduced pressure as described for **2a** resulted in a yellow solid. The yellow solid was oxidized to the corresponding quinone by dissolving it in 40 mL of freshly distilled benzene under a positive pressure of N_2 and adding 0.30 g (2.40 mmol) of K_2CO_3 followed by 0.56 g (2.40 mmol) of Ag_2O. After the mixture was stirred for 1 h, TLC revealed one spot that was quinone active (leucomethylene blue). The reaction mixture was vacuum filtered through a bed of Celite and rinsed with ether (40 mL). The filtrate was concentrated under reduced pressure, which resulted in a yellow solid. Recrystallization from CH_2Cl_2/hexanee afforded 0.12 g (80%) of **2c** as yellow crystals: mp 115–117 °C; IR ($CHCl_3$) 3001, 2951, 2850, 1669, 1593, 1493, 1462, 1453, 1353, 1323, 1305, 1278, 1103, 1035, 1018, 1005, 900, 880, 848, and 832 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 3 H), 4.08 (s, 3 H), 4.12 (s, 3 H), 7.15 (dd, J = 2.8, 7.2 Hz, 1 H), 7.52 (d, J = 2.8 Hz, 1 H), 8.00 (d, J = 7.2 Hz, 1 H); MS (EI) 248 (83), 233 (100), 219 (25), 203 (55), 187 (14), 177 (44), 134 (91), 119 (28), 106 (60), 75 (22), 63 (56); MS (CI) 249 (100), 219 (10); HRMS, m/e calcd for $C_{13}H_{12}O_5$ (M^+) 248.0685, found 248.0687.

2,3-Dimethoxy-6-methyl-1,4-naphthoquinone (2b): method A; 87% yield; yellow needles (MeOH/H_2O); mp 90–92 °C; IR ($CHCl_3$) 3005, 2952, 1670, 1612, 1602, 1307, 1273, 1230, and 1038 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.48 (s, 3 H), 4.10 (s, 3 H), 4.11 (s, 3 H), 7.49 (d, J = 8.1 Hz, 1 H), 7.86 (s, 1 H), 7.94 (d, J = 7.9 Hz, 1 H); MS (EI) 232 (100), 217 (94), 203 (18), 187 (80), 161 (38), 118 (88), 103 (17), 89 (67), 63 (30); MS (CI) 233 (100), 71 (46); HRMS, m/e calcd for $C_{13}H_{12}O_4$ 232.0735, found 232.0726.

2,3-Dimethoxy-5-methyl-1,4-naphthoquinone (2d): method A; 76% yield; yellow crystals (ether); mp 85–87 °C; IR ($CHCl_3$) 3020, 2950, 1660, 1620, 1591, 1315, 1245, 1096, and 1035 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.74 (s, 3 H), 4.08 (s, 3 H), 4.10 (s, 3 H), 7.51 (m, 2 H), 8.02 (d, J = 5.9 Hz, 1 H); MS (EI) 232 (100), 217 (69), 187 (66), 161 (35), 118 (68), 89 (61), 63 (61); MS (CI) 233 (100), 71 (29). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.22; H, 5.21. Found: C, 66.92; H, 5.11.

2,3,5-Trimethoxy-1,4-naphthoquinone (2e): method B; 80% yield; yellow crystals (CH_2Cl_2/hexane); mp 102.5–104 °C; IR ($CHCl_3$) 3011, 2951, 2944, 1662, 1622, 1589, 1450, 1324, 1275, 1242, 1135, 1097, 1055, 1016, 932, 889, and 822 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.00 (s, 3 H), 4.07 (s, 3 H), 4.10 (s, 3 H), 7.27 (d, J = 8.9 Hz, 1 H), 7.63 (t, J = 8.9 Hz, 1 H), 7.75 (d, J = 8.9 Hz, 1 H); MS (EI) 248 (17), 233 (36), 203 (40), 187 (9), 177 (21), 160 (7), 147 (8), 134 (43), 119 (17), 104 (45), 91 (19), 76 (100); MS (CI) 249 (100); HRMS, m/e calcd for $C_{13}H_{12}O_5$ (M^+) 248.0685, found 248.0676.

2,3,5,8-Tetramethoxy-1,4-naphthoquinone (2f): method B; 80% yield; orange needles (CH_2Cl_2/petroleum ether); mp 138–139.5 °C; IR ($CHCl_3$) 3040, 3015, 2952, 2851, 1661, 1630, 1478, 1270, 1186, 1060, and 1018 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.95 (s, 6 H), 4.05 (s, 6 H), 7.27 (s, 2 H); MS (EI) 278 (100), 263 (84), 248 (50), 233 (77), 217 (31), 207 (25), 189 (37), 175 (17), 163 (53), 134 (35), 106 (20), 76 (33); MS (CI) 281 (100); HRMS, m/e calcd for $C_{14}H_{14}O_6$ (M^+) 278.0790, found 278.0778.

5,6-Dimethoxy-4,7-thianaphthenequinone (3g): method B; 84% yield; orange needles (CH_2Cl_2/petroleum ether); mp 171.5–173 °C; IR ($CHCl_3$) 3038, 3011, 2952, 1667, 1603, 1397, 1292, 1027, and 857 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.08 (s, 6 H), 7.50 (d, J = 5.0 Hz, 1 H), 7.60 (d, J = 5.0 Hz, 1 H); MS (EI) 224 83), 209 (100), 195 (27), 179 (83), 163 (14), 153 (56), 138 (34), 110 (90), 95 (12), 84 (32); MS (CI) 225 (100); HRMS, m/e calcd for $C_{10}H_8O_4S$ (M^+) 224.0143, found 224.0128. Anal. Calcd for $C_{10}H_8O_4S$: C, 53.57; H, 3.61; S, 14.27. Found: C, 53.33; H, 3.61; S, 14.07.

5-*n*-Butyl-6-methoxy-4,7-benzofuranquinone (3h): method B; 91% yield; red oil; IR ($CHCl_3$) 2960, 2935, 1680, 1662, 1569, 1480, 1368, 1260, 1131, 1070, 1047, 1021, 994, 973, 952, 931, 900, and 883 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.93 (t, J = 7.1 Hz, 3 H), 1.40 (m, 4 H), 2.49 (t, J = 7.4 Hz, 2 H), 4.07 (s, 3 H), 6.81 (d, J = 1.8 Hz, 1 H), 7.66 (d, J = 1.8 Hz, 1 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 182.7, 171.9, 156.2, 150.1, 148.5, 134.3, 128.9, 108.5, 61.7, 31.6, 23.5, 23.1, 14.1; MS (EI) 234 (51), 219 (8), 192 (100), 177 (68), 163 (25), 149 (23), 133 (7), 123 (6), 107 (6), 95 (15), 92 (9), 77 (15), 66 (14); MS (CI) 235 (100); HRMS, m/e calcd for $C_{13}H_{14}O_4$ (M^+) 234.0892, found 234.0911.

6-*n*-Butyl-5-methoxy-4,7-benzofuranquinone (3i): method B; 94% yield; red oil; IR ($CHCl_3$) 2958, 2932, 1679, 1665, 1568, 1482, 1370, 1354, 1134, 1082, 1047, 1016, 1000, 975, 952, 934, and 877 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.93 (t, J = 7.3 Hz, 3 H), 1.40 (m, 4 H), 2.52 (t, J = 7.3 Hz, 2 H), 4.05 (s, 3 H), 6.78 (d, J = 2.6 Hz, 1 H), 7.65 (d, J = 2.6 Hz, 1 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 179.0, 176.5, 156.9, 151.6, 147.8, 132.9, 126.4, 108.0, 61.7, 31.5, 23.2, 23.0, 14.1; MS (EI) 234 (58), 219 (9), 192 (100), 177 (63), 163 (27), 149 (27), 133 (7), 95 (13), 77 (16), 66 (13); MS (CI) 235 (100); HRMS, m/e calcd for $C_{13}H_{14}O_4$ (M^+) 234.0892, found 234.0886.

5,6-Dimethoxy-4,7-benzofuranquinone (3j): method B; 93% yield; red crystals (CH_2Cl_2/petroleum ether); mp 136–138 °C; IR ($CHCl_3$) 3047, 3012, 2952, 1672, 1612, 1571, 1481, 1369, 1296, 1209, 1130, 1032, and 1017 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.06 (s, 6 H), 6.81 (d, J = 1.8 Hz, 1 H), 7.67 (d, J = 1.8 Hz, 1 H); MS (EI) 208 (100), 193 (90), 179 (30), 163 (90), 147 (14), 137 (56), 122 (42), 94 (67), 66 (59); MS (CI) 209 (100),; HRMS, m/e calcd for $C_{10}H_8O_5$ (M^+) 208.0372, found 208.0365.

6-Methoxy-1-methyl-5-phenyl-4,7-indoloquinone (3k). Similar thermolysis of 0.14 g (0.52 mmol) of **1k** as described for **2a**, followed by stirring open to air for 6 h at ambient temperature, resulted in the quinone **3k** as an orange solid after concentration under reduced pressure. Recrystallization from ether afforded 0.13 g (93%) of the indoloquinone as orange crystals: mp 137–138.5 °C; IR ($CHCl_3$) 3003, 1664, 1657, 1592, 1512, 1443, 1402, 1321, 1311, 1250, 1052 and 990 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.72 (s, 3 H), 4.02 (s, 3 H), 6.60 (d, J = 2.6 Hz, 1 H), 6.86 (d, J = 2.6 Hz, 1 H), 7.30 (m, 2 H), 7.39 (m, 3 H); MS (EI) 267 (100), 252 (38), 236 (15), 224 (25), 196 (16), 167 (9), 139 (7), 126 (8), 81 (25); MS (CI) 268 (100); HRMS, m/e calcd for $C_{16}H_{13}NO_3$ (M^+) 267.0890, found 267.0880.

6-Chloro-2,3-dimethoxy-1,4-naphthoquinone (2o): method B; 85% yield, yellow crystals (ether); mp 122–124 °C; IR ($CHCl_3$) 2950, 1667, 1610, 1590, 1571, 1300, 1251, 1092, 1029, and 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 4.10 (s, 3 H), 4.12 (s, 3 H), 7.65 (dd, J = 2.1, 9.3 Hz, 1 H), 8.02 (m, 2 H); MS (EI) 252 (26), 237 (54),

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207 (48), 138 (100), 123 (19), 110 (72), 75 (83); MS (CI) 253 (100); HRMS, m/e calcd for $C_{12}H_9ClO_4$ (M^+) 252.0189, found 252.0183.

3-*n*-Butyl-4-methoxycyclobutenedione (4). A solution of 4.00 g (28.2 mmol) of **23** in 400 mL of dry THF was cooled to −78 °C under a positive pressure of N_2. To this solution was added dropwise via syringe 12.6 mL (29.6 mmol) of 2.35 M *n*-butyllithium. The solution was stirred for 10 min and then quenched with 20 mL of 6 M HCl followed by 60 mL of ether. The solution was warmed to ambient temperature and stirred for 2 h. The reaction mixture was then poured into a separatory funnel containing 150 mL of H_2O and 150 mL of ether. The phases were separated, and the aqueous phase was extracted with ether after neutralization with 10% $NaHCO_3$. The ether layers were combined, washed with brine, and dried over $MgSO_4$. Filtration followed by concentration of the solution under reduced pressure resulted in an oil. The oil was purified by column chromatography on silica gel (elution with hexane/ethyl acetate) to afford 2.47 g (44%) of the dione as an oil; IR ($CHCl_3$) 2980, 2939, 1802, 1761, 1602, 1462, 1370, 1189, and 1030 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 0.91 (t, J = 8.0 Hz, 3 H), 1.35 (m, 2 H), 1.55 (m, 2 H), 2.55 (t, J = 8.0 Hz, 2 H), 4.41 (s, 3 H); MS (EI) 168 (12), 140 (30), 125 (52), 111 (18), 97 (17), 81 (21), 69 (29), 57 (100), 54 (42); MS (CI) 169 (100); HRMS, m/e calcd for $C_9H_{12}O_3$ (M^+) 168.0786, found 168.0791.

2,3-Dimethoxy-1,4-phenanthrenedione (8). Similar thermolysis and oxidation of **1m** by method B resulted in an 87% yield of **8** as orange crystals (CH_2Cl_2/hexane). Similar thermolysis and oxidation by method B of **11** also resulted in a 90% yield of **8**: mp 111–113 °C; IR ($CHCl_3$) 3028, 3011, 2954, 1661, 1630, 1593, 1461, 1432, 1288, 1231, 1173, 1113, 1063, 1033, 1017, and 841 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.06 (s, 3 H), 4.08 (s, 3 H), 7.63 (t, J = 7.2 Hz, 1 H), 7.72 (t, J = 8.0 Hz, 1 H), 7.88 (d, J = 8.8 Hz, 1 H), 8.15 (q, J = 7.2, 8.0 Hz, 2 H), 9.50 (d, J = 9.6 Hz, 1 H); MS (EI) 268 (100), 253 (69), 239 (10), 223 (26), 197 (38), 155 (60), 139 (13), 126 (97); MS (CI) 271 (100); HRMS, m/e calcd for $C_{16}H_{12}O_4$ (M^+) 268.0736, found 268.0720. Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.62; H, 4.51. Found: C, 71.61; H, 4.35.

Thermolysis of 4-Hydroxy-2,3-dimethoxy-4-(3-methylphenyl)cyclobutenone (1n). Similar thermolysis and oxidation of 0.30 g (1.28 mmol) of **1n** by method A resulted in 0.25 g (83%) of an oil after concentration of the solution under reduced pressure. ^1H NMR (250 MHz, $CDCl_3$) of the oil revealed a 1/1 mixture of **2b** and **2d**.

Thermolysis of 4-Hydroxy-2,3-dimethoxy-4-(3-methoxyphenyl)cyclobutenone (1o). Similar thermolysis and oxidation of 0.25 g (1.00 mmol) of **1o** by method B resulted in 0.21 g (84%) of a yellow crystalline solid after concentration of the solution under reduced pressure. ^1H NMR (300 MHz, $CDCl_3$) of the reaction product revealed a 10/1 mixture of **2c** and **2e**, respectively.

Thermolysis of 4-Hydroxy-2,3-dimethoxy-4-(1,4-dimethoxy-2-naphthyl)cyclobutenone (1p). Similar thermolysis of 188 mg (0.57 mmol) of **1p** for 3.5 h followed by oxidation by method B resulted in a solid after concentration under reduced pressure. Purification by column chromatography provided 43 mg of **13** and 42 mg of **12**. Characterization of **12**: IR ($CHCl_3$) 2949, 1712, 1701, 1590, 1517, 1467, 1266, 1110, 1093, and 840 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.20 (s, 3 H), 3.48 (s, 3 H), 3.51 (s, 3 H), 4.16 (s, 3 H), 4.35 (s, 1 H), 7.43 (s, 1 H), 7.65 (m, 2 H), 7.74 (m, 1 H), 8.38 (d, J = 7.8 Hz, 1 H); MS (EI) 330 (8), 299 (100), 283 (5), 256 (6), 240 (14), 213 (10), 156 (5); HRMS, m/e calcd for $C_{18}H_{18}O_6$ (M^+) 330.1103, found 330.1087.

Characterization of **13**: mp 121–123 °C; IR ($CHCl_3$) 2951, 1663, 1635, 1587, 1516, 1461, 1351, 1292, 1243, and 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.07 (s, 3 H), 4.13 (s, 3 H), 4.16 (s, 3 H), 7.44 (s, 1 H), 7.59 (m, 2 H), 7.70 (m, 1 H), 8.31 (dd, J = 1.0, 9.0 Hz, 1 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 183.6, 183.2, 160.4, 148.0, 144.2, 133.3, 131.8, 130.5, 128.1, 127.9, 127.8, 122.5, 119.5, 99.9, 61.6, 61.5, 56.4; MS (EI) 298 (100), 283 (73), 269 (14), 255 (31), 227 (54), 185 (65), 156 (50), 113 (41); MS (CI) 299 (100); HRMS, m/e calcd for $C_{17}H_{14}O_5$ (M^+) 298.0841, found 298.0830.

Conversion of 12 to 13. Conversion of **12** to **13** was accomplished by refluxing 30 mg of **12** in 20 mL of methanol for 18 h. After being cooled to ambient temperature, the solution was concentrated under reduced pressure, which afforded a red solid. ^1H NMR of the solid revealed the same spectral properties as **13**.

In a separate experiment, 356 mg (1.08 mmol) of **1p** was heated at reflux for 6 h in 40 mL of *p*-xylene under Ar. Concentration of the solution under reduced pressure afforded a red residue. The residue was dissolved in 40 mL of methanol and refluxed for 18 h. Concentration of the solution under reduced pressure afforded a red solid. Purification by column chromatography afforded 135 mg (42%) of **13**.

3,4-Dimethoxy-5-(2,6-dimethoxyphenyl)-2(3*H*)-furanone (21) and 3,4-Dimethoxy-5-(2,6-dimethoxyphenyl)-2(5*H*)-furanone (22). Thermolysis of 0.20 g (0.71 mmol) of **1q** as described for **2a** with extended refluxing for 14 h resulted in two products by TLC. Concentration of the solution under reduced pressure (bath temperature 65 °C) provided a yellow oil. ^1H NMR (250 MHz, $CDCl_3$) and IR analysis of the reaction product revealed a 2/1 mixture of **21** and **22**, respectively. Purification of the mixture by column chromatography on silica gel (elution with hexane/ethyl acetate) provided 20 mg (10%) of **21** as an oil and 120 mg (60%) of **22** as a white crystalline solid after recrystallization from CH_2Cl_2/hexane. Duplication of the above procedure to obtain the mixture of **21** and **22** followed by stirring in 60 mL of CH_2Cl_2 in the presence of 4.00 g of SiO_2 for 2 h resulted in exclusive formation of **22**. Recrystallization from CH_2Cl_2/hexane afforded a 70% yield of **22**. Characterization of **21**: IR (neat) 2939, 2842, 1802, 1708, 1597, 1475, 1432, 1358, 1256, 1115, 1041, and 1001 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.57 (s, 3 H), 3.59 (s, 3 H), 3.84 (s, 6 H), 4.84 (s, 1 H), 6.57 (d, J = 9.2 Hz, 2 H), 7.35 (t, J = 9.2 Hz, 1 H); MS (EI) 280 (45), 249 (10), 237 (13), 221 (18), 205 (10), 194 (7), 178 (16), 165 (100), 150 (14), 135 (5), 122 (7), 107 (25), 91 (13), 77 (20); MS (CI) 281 (100); HRMS, m/e calcd for $C_{14}H_{16}O_6$ (M^+) 280.0947, found, 280.0944. Characterization of **22**: mp 122–124 °C; IR ($CHCl_3$) 3001, 2939, 1761, 1680, 1597, 1478, 1340, 1252, 1128, 1109, and 1053 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.74 (s, 3 H), 3.84 (s, 3 H), 3.87 (s, 3 H), 4.05 (s, 3 H), 6.26 (s, 1 H), 6.55 (q br, J = 7.8, 7.8 Hz, 2 H), 7.29 (t, J = 9.0 Hz, 1 H); MS (EI) 280 (82), 249 (27), 237 (41), 221 (41), 206 (9), 194 (25), 178 (45), 165 (100), 151 (18), 135 (14), 119 (9), 107 (27), 91 (25), 77 (34); MS (CI) 281 (100); HRMS, m/e calcd for $C_{14}H_{16}O_6$ (M^+) 280.0947, found 280.0942. Anal. Calcd for $C_{14}H_{16}O_6$: C, 59.98; H, 5.77. Found: C, 59.69; H, 5.98.

6-Chloro-2,3-dimethoxy-1,4-naphthalenediol Diacetate (Lonapalene) (27). 4-Bromochlorobenzene (2.16 g, 11.3 mmol) and 7.95 mL (11.3 mmol) of 1.42 M *n*-butyllithium were treated with 1.50 g (10.6 mmol) of **23** as described for **1b**. The reaction was quenched as described previously with 40 mL of 5% NH_4Cl in 50 mL of ether. After an aqueous workup, the organic layers were combined, washed with brine, and then dried over solid K_2CO_3. The solution was filtered and concentrated to approximately 50 mL, then freshly distilled *p*-xylene (175 mL) was added, and the remainder of THF and ether was removed under pressure. The resulting solution was heated at reflux for 3 h under Ar and then cooled to ambient temperature. The *p*-xylene solution was then placed under a H_2 atmosphere over Pd/C (10%, 0.27 g) to keep the hydroquinone in its reduced form. While under a blanket of H_2, 10.78 g (105.6 mmol) of acetic anhydride, 8.35 g (105.6 mmol) of pyridine, and 0.13 g (1.06 mmol) of DMAP were added and stirred overnight. The mixture was filtered to remove the catalyst and concentrated to a thick oil. The residue was dissolved in ether (225 mL) and washed with 1 M HCl (3 × 50 mL) and then with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to a white solid. The product was purified by column chromatography on silica gel (hexane/ethyl acetate) and then recrystallized from ether/hexane to afford 1.84 g (52%) of Lonapalene as white crystals: mp 87.5–89 °C; IR ($CHCl_3$) 3032, 2943, 1771, 1768, 1601, 1417, 1389, 1369, 1239, 1182, and 1167 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.48 (s, 3 H), 2.49 (s, 3 H), 3.94 (s, 3 H), 3.95 (s, 3 H), 7.38 (dd, J = 2.0, 8.9 Hz, 1 H), 7.68 (d, 1 H), 7.72 (d, 1 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.8, 145.0, 144.2, 137.0, 136.1, 132.6, 127.2, 125.3, 123.0, 120.2, 61.2, 20.8; MS (EI) 338 (5), 296 (10), 254 (100), 239 (33), 207 (5), 196 (3), 138 (10), 110 (6); MS (CI) 339 (17), 297 (100), 237 (30); HRMS, m/e calcd for $C_{16}H_{15}ClO_6$ (M^+) 338.0555, found 338.0560.

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A Concise Total Synthesis of Defucogilvocarcin V by Application of the Meyers Biaryl Strategy: Ortho- and Para-Selective Functionalizations of the A Ring

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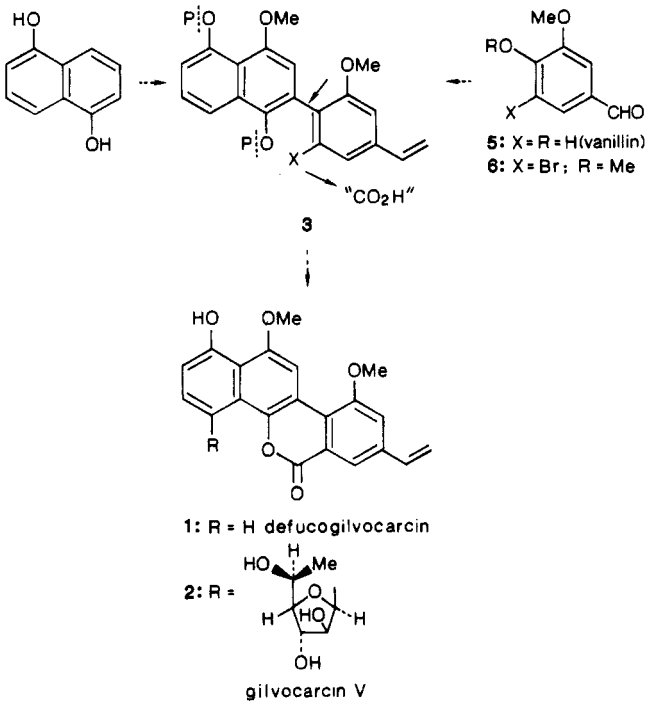
Coupling of the Grignard reagent derived from 1,5-bis(methoxymethoxy)-4-methoxy-2-bromonaphthalene with the oxazoline derived from 2,3-dimethoxy-5-ethenylbenzoic acid is the key step in a very concise synthesis of defucogilvocarcin V. Functionalization of the A ring in a fashion required for a synthesis of gilvocarcin has been achieved.

A variety of structures containing aromatic and carbohydrate segments are of considerable current and potential importance in cancer chemotherapy. The best known of these compounds are of the anthracycline type such as adriamycin and daunomycin. In these systems, the carbohydrate sector is attched through an *O*-glycosidic bond.[1] Apparently, neither the anthracycline nor the carbohydrate exhibit useful biological properties. There is a newer class of antibiotic–antitumor agents wherein the aromatic and carbohydrate domaines are joined through a carbon–carbon bond.[2] While none of these *C*-(aryl)glycosyl compounds has reached the stage of serious clinical application, the broad range of such compounds with promising activity has already begun to engender interest in their mode of action, as well as in their synthesis.[3] Since in such *C*-glycosyl compounds the cleavage of the aromatic system from the carbohydrate is not simply executed, there is a dearth of information on the activity of the individual "aglycon" and carbohydrate moieties.

A striking situation is found in the gilvocarcin family.[4] A variety of such compounds, of which gilvocarcin V (**2**) is typical, has been isolated from various *Streptomyces* species.[5] Compound **2** possesses antitumor properties as well as the capacity to induce bacteriophage λ in *Escherichia coli* upon activation by low doses of light.[6] On the basis of some structure activity work, the two properties appear to be related. Analogy with the psoralens has already been drawn.[6]

Interestingly, the compound defucogilvocarcin V (**1**), formally the "aglycon" of **2** has itself been isolated from *Streptomyces arenae* 2064.[7] Compound **1** is also active in promoting light-dependent prophage activity identical

Scheme I



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