Regioselective Synthesis of Highly Substituted Naphthols

Philip Turnbull and Harold W. Moore*

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

Received August 29, 1994[⊗]

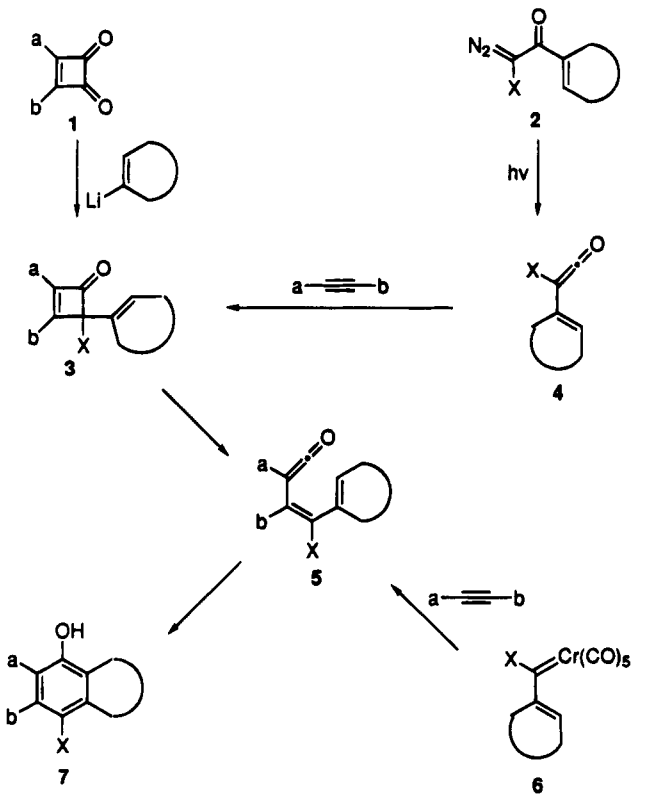
2,3,4-Trisubstituted 4-hydroxy-2-cyclobutenones, prepared by regiospecific synthesis of substituted cyclobutenediones, undergo Lewis acid facilitated ionization to cyclobutenyl cations, which are trapped by trialkylsilanes in a regioselective sense. Thermolysis of the resulting cyclobutenones affords phenols in high yields.

Investigations of new methods for the regioselective synthesis of highly substituted aromatic systems have received significant attention in recent years. Classical approaches to this problem generally rely on electrophilic and nucleophilic aromatic substitution reactions, the nature of which often dictates problems of regiocontrol. Important modern methods for the synthesis of highly substituted aromatic compounds that address the regiochemical problem involve annulation reactions. Such methods are usually convergent, and thus the substitution pattern of the aromatic ring is dictated by the functionality and structure of the starting materials.[1] Two representative annulation methods are the use of Fischer vinyl carbenes **6** and the ring expansion of cyclobutenones **3**.[2,3] These examples are related in that both involve dienylketenes **5**, intermediates having a propensity to undergo electrocyclic ring closure to quinones, phenols, hydroquinones, and various other aromatic compounds **7** (Scheme 1).

Of key importance to the cyclobutenone method is the construction of 4-R_{unsat}-2-cyclobutenones **3**. In the case of X = OH, the desired cyclobutenones are readily prepared by the addition of organolithium reagents to substituted cyclobutenediones **1**.[4–6] Thermolysis followed by oxidation of the resulting hydroquinone provides an excellent route to highly substituted quinones.

For the synthesis of cyclobutenones where X ≠ OH, alternative methods of construction must be considered. Noteworthy solutions to this problem take two different approaches: [2 + 2] cycloaddition of vinylketenes to electron rich alkynes (**4** → **3**) and palladium-catalyzed cross-coupling of 4-chloro-2-cyclobutenones with vinyl- and arylstannanes. Danheiser's [2 + 2] cycloaddition method relies on the generation of vinylketenes such as **4** *via* thermolysis of the appropriate cyclobutenone or from the photochemical Wolff rearrangement of α-diazo ketones such as **2**.[7,8] The palladium cross-coupling method developed by Liebeskind and co-workers uses methodology similar to that employed in the synthesis of quinones.[9] That is, regiospecifically constructed cyclobutenones bearing a proton and a hydroxyl at the 4-position are chlorinated using CCl_4 and PPh_3. The resulting 4-chlorocyclobutenones provide allyl cation synthons for palladium-mediated coupling. Regioselectivity in the coupling reaction stems from exclusive bond formation at the less substituted terminus of the π-allyl system.

Scheme 1



[⊗] Abstract published in *Advance ACS Abstracts,* January 15, 1995.

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(2) For a review on the synthetic utility of Fischer carbenes see: Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587.

(3) For reviews on the ring expansions of cyclobutenones see: (a) Moore, H. W.; Yerxa, B. R. *Chemtracts* **1992**, *5*, 273. (b) Moore, H. W.; Decker, O. H. W. *Chem. Rev.* **1986**, *86*, 821. (c) Liebeskind, L. S. *Tetrahedron* **1989**, *45*, 3053. (d) Bellus, D.; Ernst, B. *Angew Chem.* **1988**, *100*, 820.

(4) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067.

(5) Liebeskind, L. S.; Jewell, C. F.; Iyer, S. *J. Org. Chem.* **1986**, *51*, 3065.

(6) Perri, S. T.; Moore, H. W. *J. Am. Chem. Soc.* **1988**, *53*, 996.

(7) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672–1674.

(8) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093–3100.

(9) Krysan, D. J.; Gurski, A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 1412–1418.

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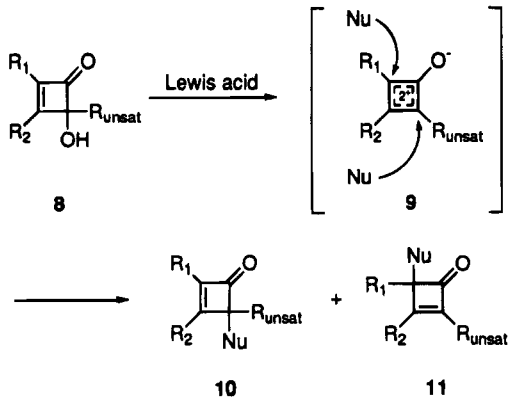
Scheme 2

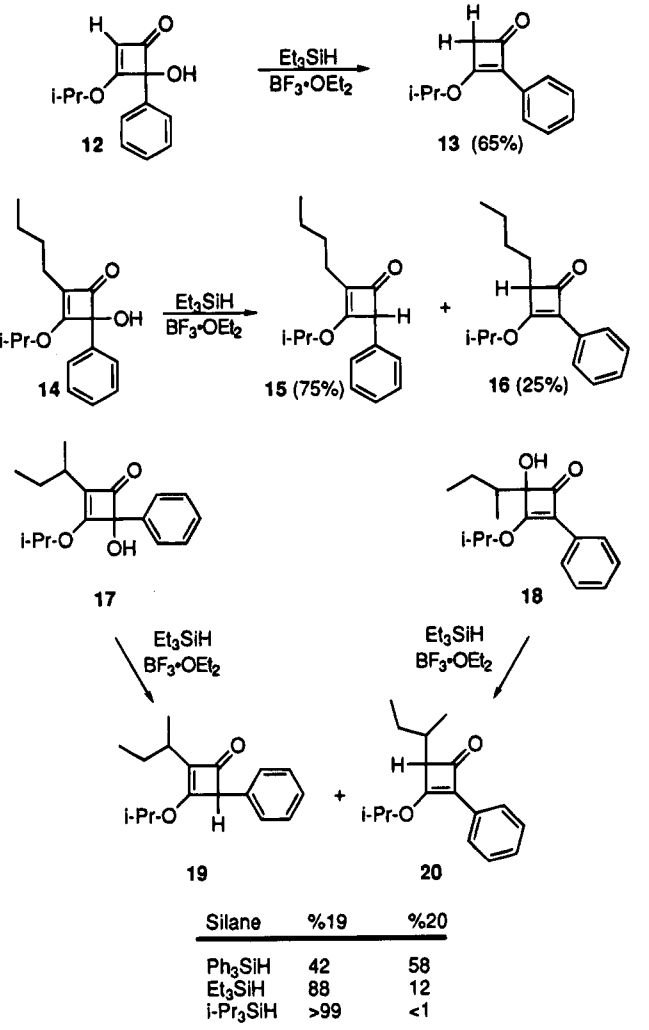


Reported herein is a complementary procedure resting on the reductive dehydroxylation of 4-hydroxycyclobutenones. The method provides a general and convenient route to highly substituted naphthols and stems from readily available 4-hydroxycyclobutenones, which are precursors to the aromatic dication **9**,[10] formed upon treatment with BF_3–etherate (Scheme 2).[3,11] When generated in the presence of a variety of trialkylsilanes the respective 4-protiocyclobutenones (ionic hydrogenation) were obtained, and these readily ring expanded to the corresponding naphthols.[12]

The regiospecificity of the ionic hydrogenation and thus the substitution pattern of the subsequent phenol is dependent upon the substituents of the starting 4-hydroxycyclobutenone. A combination of electronic and steric effects as well as the size of the silane reagent affect the course of the reaction. This study is compared to previous work involving chlorination of cations **9**, a reaction taking place predominately at that site bearing the substituent best able to stabilize a cationic charge.[11] Interestingly, cyclobutenone **13** was the sole product obtained from ionic hydrogenation of hydroxycyclobutenone **12**, despite the significant cation-stabilizing effect of a phenyl group compared to a proton (Scheme 3). Increasing the size of the substituent at position-2 dramatically changes the course of the reaction. For example, hydrogenation of **14** takes place predominantly at the benzylic position to give **15** as the major product (75%) with less reduction next to the butyl group to give **16** (25%). Increasing the steric demands even further as in **17** continued this trend, giving **19** (88%) and **20** (12%) as diastereomeric mixtures, respectively, de = 0 and de = 34%. Finally, it is noteworthy that **19** and **20** were obtained in the same regioisomeric and diastereomeric ratios when cyclobutenone **18** was subjected to the same conditions as its regioisomer **17**. Thus, the reaction proceeds through a common intermediate, most likely the carbocation **9**.

The fact that diastereomeric mixtures of both **19** and **20** were obtained in the reaction of **17** with triethylsilane made it an informative substrate to study changes in the regioisomeric ratios as a function of silane steric bulk. In this regard, the relatively unhindered triphenylsilane

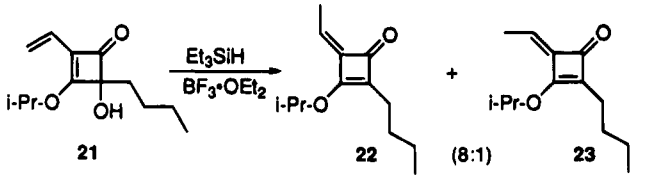
Scheme 3



Silane	%19	%20
Ph_3SiH	42	58
Et_3SiH	88	12
$i\text{-}Pr_3SiH$	>99	<1

gave a slight preference for hydrogenation adjacent to *sec*-butyl, i.e., **19** (42%) and **20** (58%). As noted above, regioisomeric ratios were significantly reversed using triethylsilane [**19** (88%) and **20** (12%)]. Employing the most bulky hydride source, triisopropylsilane, gave a near-quantitative conversion to **19** *via* ^1H NMR analysis of the crude. The diastereomeric ratios did not change significantly throughout this study.

An interesting example showing a marked steric effect in the trapping of the carbocation intermediates is exemplified by the reduction of **21**. Here, the extended allylic cation is trapped exclusively at the vinyl terminus, resulting in a *Z*/*E* mixture (8:1) of methylenecyclobutenones **22** and **23**.



In addition to the above steric effects, evidence of an important electronic component was also obtained. Specifically, reduction of **24** gave exclusively **25** (Scheme 4). Such an outcome would not be expected on the basis of steric arguments, but it is consistent with a significant electronic effect. Another example is the reduction of **26**. Here the aryl groups are of similar steric bulk but differ

(10) The cyclobutadiene dication should possess aromatic character because it is likely a planar, monocyclic system that contains two π-electrons. For evidence of the cyclobutadienyl dication see: Olah, G. A.; Staral, J. S. *J. Am. Chem. Soc.* **1976**, *98*, 6290.

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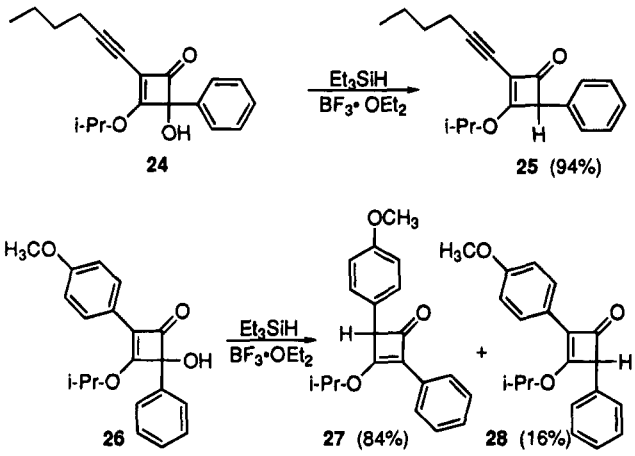
(12) For a review on ionic hydrogenation see: Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis*, **1974**, 633.

(13) Ezcurra, J. E.; Pham, C.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 4787.

Scheme 4



in electronic character. Deoxygenation of hydroxycyclobutenone **26** gave an inseparable mixture of **27** and **28** in respective yields of 84% and 16% as evidenced by ^{1}H NMR analysis. These results suggest the paradigm that the electronic effect favors carbocation capture at the site bearing the substituent better able to stabilize an adjacent positive charge, e.g., benzylic > propargylic.

Selected cyclobutenones resulting from ionic hydrogenation were thermolyzed (refluxing toluene) to afford the corresponding naphthols in excellent yield. Various examples illustrating the scope of this reaction are provided in Scheme 5. In all cases the structure of the naphthol is in complete accord with its spectral and analytical properties.

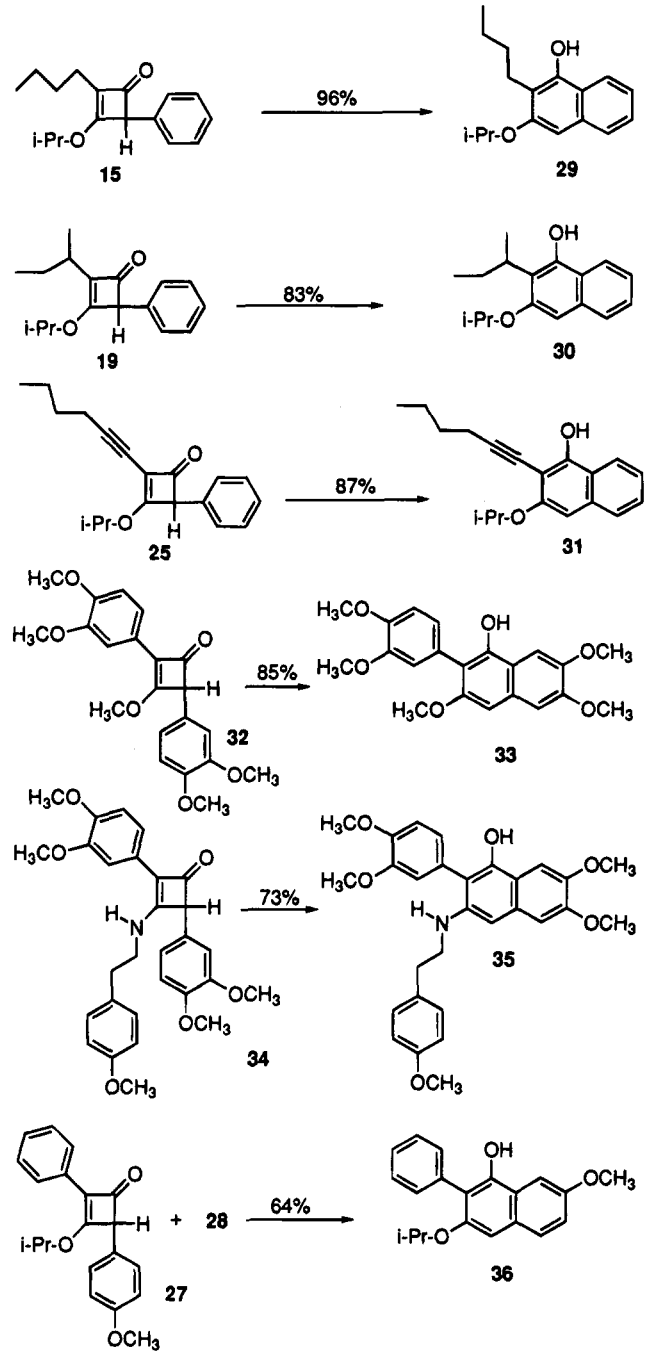
In addition to illustrating the utility of the naphthol synthesis, the ring expansions also aid in structural assignments of the starting cyclobutenones. This is particularly important for **25** and **27** where spectral data alone do not allow an unambiguous assignment. As a result, the conversion of **25** to **31** provides good evidence of the structure of **25** since only that particular regioisomer would be expected to ring expand to a naphthol. The conversion of **27** to **36** is equally instructive. Here, the 5.25:1 mixture of **27** and **28** was thermolyzed and naphthol **36**, arising from the major cyclobutenone regioisomer, was obtained in 64% yield. Most revealing is the ^{1}H NMR spectrum of the product which shows an AB pattern in the aromatic region (doublet at δ 7.61, J = 9.0 Hz and a doublet of doublets at δ 7.03, J = 9.0, 3.0 Hz) corresponding to structure **36**. Hence, the major isomer produced in the reduction of **26** must be **27** and the minor product is **28**.

In summary, a simple method for the regiocontrolled construction of highly substituted naphthols starting from readily synthesized 4-hydroxycyclobutenones is presented. This method is experimentally simple, and the yields are generally higher than those reported from the related methods. Finally, unlike the routes outlined in Scheme 1, the cyclobutenone precursors can be isolated, purified, and converted to modified derivatives, e.g., **32** → **34**, and thus to the naphthols **33** and **35**, respectively.

Experimental Section

General Methods and Materials. All reactions were performed in oven- or flame-dried glassware under a positive pressure of nitrogen. Reaction mixtures were agitated by magnetic stirring. Air- and moisture-sensitive liquids were

Scheme 5



transferred via syringe through rubber septa. Removal of volatiles was accomplished on a Büchi rotary evaporator at approximately 20 mmHg. Baker silica gel (230–400 mesh) was used for column chromatography. Solvents were distilled from CaH_2 prior to use. Reagents were used as received. ^{1}H NMR spectra were recorded on Bruker AC-300 (300 MHz) and Omega (500 MHz) spectrometers. ^{13}C NMR spectra were recorded on the same machines but at 74.8 and 124.7 MHz, respectively. All NMR recordings were referenced to $CHCl_3$ resonances (7.26 and 77.0 ppm) unless otherwise specified. IR spectra were recorded on a Perkin-Elmer 1600 ratio recording spectrometer.

Representative Procedure for the Preparation of 4-Hydroxycyclobutenones.[14] 3-Isopropoxy-4-phenyl-4-hydroxy-2-cyclobutenone (12). A THF solution (35 mL) of 3-isopropoxy-3-cyclobutene-1,2-dione (0.500 g, 3.57 mmol, 1 equiv), prepared according to published procedure,[14] was cooled

(14) Synthesized according to the methods described in refs 4–6.

to ca. −78 °C (dry ice/acetone) under a blanket of N_2 and treated with phenyllithium (1.8 M, 1.98 mL, 1 equiv). TLC indicated full consumption of starting material upon complete addition of the lithium reagent. The reaction mixture was quenched in a separatory funnel containing 10% NH_4Cl (5 mL) and EtOAc (10 mL). The aqueous layer was back-extracted with EtOAc (2 × 10 mL), and the combined organic portions were dried ($MgSO_4$) and concentrated to afford a yellow oil. Flash silica gel chromatography (60% hexanes/EtOAc) gave 0.408 g (52%) of **12** as a pale yellow semicrystalline solid: mp 94−95 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 7.5 Hz, 2H), 7.41−7.33 (m, 3H), 5.40 (s, 1H), 4.64 (quintet, J = 6.0 Hz, 1H), 3.20 (broad s, 1H), 1.45 (overlapping d, J = 6.0 Hz, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 189.0, 185.6, 136.2, 128.6, 128.5, 112.3, 92.6, 78.8, 21.51, 21.49; IR (thin film) 3342, 2973, 2930, 1745, 1561, 1449, 1312, 1214, 1154, 1098 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{14}O_3$ 218.0943, found 218.0949.

2-*n*-Butyl-3-isopropoxy-4-phenyl-4-hydroxy-2-cyclobutenone (14): 68% yield; white needles, mp 69−70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, J = 7.3 Hz, 2H), 7.30−7.19 (m, 3H), 4.63 (quintet, J = 6.1 Hz, 1H), 2.15−2.07 (m, 2H), 1.51 (quintet, J = 7.1 Hz, 2H), 1.39−1.25 (m, 5H), 1.00 (d, J = 6.2 Hz, 3H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.2, 181.8, 137.3, 128.9, 128.4, 127.8, 125.5, 92.4, 77.7, 29.2, 22.62, 22.57, 22.3, 13.7; IR (thin film) 3334, 3062, 2958, 2933, 2872, 1748, 1612, 1450, 1387, 1344, 1100, 1036 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{22}O_3$ 274.1569, found 274.1578.

2-*sec*-Butyl-3-isopropoxy-4-phenyl-4-hydroxy-2-cyclobutenone (17): 67% yield; a mixture of diastereomers as white needles, mp 98−99 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 8.0 Hz, 2H), 7.35 (t, J = 7 Hz, 2H), 7.28 (t, J = 7.5 Hz, 1H), 5.30 (broad s, 1H), 4.66 (quintet, J = 6.5 Hz, 1H), 2.38 (sextet, J = 7.0 Hz, 1H), 1.71−1.66 (m, 1H), 1.54−1.50 (m, 1H), 1.34 (overlapping d, J = 6.0 Hz, 3H), 1.20 (overlapping d, J = 7.0 Hz, 3H), 1.02 (overlapping d, J = 6.0 Hz, 3H), 0.95 (overlapping t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.7, 181.4, 137.6, 133.5, 133.4, 128.5, 127.8, 125.6, 92.6, 77.9, 30.8, 30.7, 27.7, 27.6, 22.78, 22.75, 22.38, 22.35, 18.0, 17.9, 12.1; IR (thin film) 3323, 3063, 3029, 2965, 2933, 2876, 1746, 1608, 1495, 1450, 1387, 1341, 1318, 1179, 1100 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{22}O_3$ 274.1569, found 274.1575.

2-Phenyl-3-isopropoxy-4-*sec*-butyl-4-hydroxy-2-cyclobutenone (18) was synthesized according to **12** using *s*-BuLi instead of PhLi: 65% yield; a mixture of diastereomers as a water white oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 7.0 Hz, 2H), 7.27−7.20 (m, 3H), 5.05−5.03 (m, 1H), 4.39 (overlapping s, 1H), 2.20−1.93 (m, 1H), 1.52 (overlapping d, J = 5.5 Hz, 3H), 1.45 (overlapping d, J = 6.0 Hz, 3H), 1.38−1.32 (m, 1H), 1.15−1.09 (m, 1H), 1.20 (d, J = 6.5 Hz, 3H), 0.95 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.9, 190.7, 182.5, 182.2, 128.74, 128.71, 128.3, 128.2, 128.0, 127.6, 126.9, 126.6, 124.0, 123.8, 96.3, 96.0, 78.5, 78.4, 39.9, 39.8, 25.9, 24.4, 23.20, 23.17, 22.8, 15.3, 14.0, 12.6, 12.0; IR (thin film) 3372, 3058, 2968, 2878, 1731, 1624, 1590, 1494, 1393, 1331, 1095 cm^{-1}; HRMS (CI) calcd for $C_{17}H_{22}O_3$ 274.1569, found 275.1640 (MH^+).

2-Ethenyl-3-isopropoxy-4-*n*-butyl-4-hydroxy-2-cyclobutenone (21) was synthesized according to **12** using *n*-BuLi instead of PhLi: 60% yield; white needles, mp 48−49 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.04 (d of d, J = 17.6, 10.9 Hz, 1H), 5.88 (d of d, J = 17.6, 2.1 Hz, 1H) 5.30 (d of d, J = 10.9, 2.1 Hz, 1H), 4.86 (quintet, J = 6.2 Hz, 1H), 3.63 (broad s, 1H), 1.92−1.76 (m, 2H), 1.42 (overlapping d, J = 6.2 Hz, 6H), 1.36−1.23 (m, 4H), 0.86 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0, 179.9, 122.2, 122.1, 121.0, 91.8, 32.7, 26.9, 22.7, 22.4, 22.3, 13.8; IR (thin film) 3374, 2959, 2934, 2873, 1740, 1637, 1572, 1421, 1322, 1101 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1404.

2-*n*-Hexynyl-3-isopropoxy-4-phenyl-4-hydroxy-2-cyclobutenone (24): 69% yield; pale yellow semicrystalline solid, mp 70−71 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 7.0 Hz, 2H), 7.36−7.28 (m, 3H), 5.20 (quintet, J = 6.0 Hz, 1H), 3.80 (broad s, 1H), 2.36 (t, J = 7.0 Hz, 2H), 1.55−1.37 (m, 10H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.1, 182.0, 135.9, 128.3, 125.6, 108.9, 95.7, 92.1, 78.8, 67.2, 30.2, 22.2, 21.9, 21.7, 19.0, 13.3; IR (thin film) 3374, 3062, 3030, 2958, 2934, 2872, 2230, 1755, 1599, 1450, 1387, 1325, 1199, 1178, 1097 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{22}O_3$ 298.1569, found 298.1577.

2-(4-Methoxyphenyl)-3-isopropoxy-4-hydroxy-4-phenyl-2-cyclobutenone (26): 77% yield; pale yellow foam; ^{1}H NMR (500 MHz, CD_3OD) δ 7.73 (d, J = 9.0 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.32 (t, J = 7.5 Hz, 1H), 6.96 (d, J = 9.5 Hz, 2H), 4.83 (quintet, J = 6.0 Hz, 1H), 3.80 (s, 3H), 1.44 (d, J = 6.5 Hz, 3H), 1.06 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 191.0, 181.0, 160.9, 138.8, 129.6, 129.3, 129.1, 126.8, 126.7, 122.8, 115.1, 94.7, 80.3, 55.7, 23.1, 22.8; IR (thin film) 3361, 2983, 2934, 2838, 1741, 1622, 1597, 1512, 1449, 1387, 1343, 1309, 1251, 1178, 1087 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{20}O_4$ 324.1361, found 324.1356.

2,4-(3,4-Dimethoxyphenyl)-3-methoxy-4-hydroxy-2-cyclobutenone. 4-Bromoveratrole (1.93 g, 8.87 mmol, 1.1 equiv) was dissolved in THF (80 mL) and cooled to ca. −78 °C prior to dropwise treatment with *n*-BuLi (1.6M, 6.05 mL, 9.67 mmol, 1.2 equiv). After 0.5 h the newly generated lithium reagent was transferred via cannula to a ca. −78 °C THF (350 mL) solution of 2-(3,4-dimethoxyphenyl)-3-methoxycyclobutenedione (2.00 g, 8.06 mmol, 1 equiv). TLC indicated full consumption of the starting material upon complete addition of the lithium reagent. The mixture was worked up according to **12**. The resulting bright yellow oil gave 2.29 g (74%) of pale yellow microneedles from Et_2O: mp 163−164 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d of d, J = 8.5 Hz, 2.0 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 7.13 (d, J = 2.0 Hz, 1H), 6.96 (d of d, J = 8.5, 2.0 Hz, 1H), 6.80 (overlapping d, J = 8.5 Hz, 2H), 4.80 (broad s, 1H), 4.02 (s, 3H), 3.87 (s, 3H), 3.85 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.7, 179.0, 149.2, 148.94, 148.90, 148.7, 129.3, 126.4, 121.4, 120.3, 117.9, 111.1, 110.9, 109.8, 108.9, 93.2, 60.2, 55.90, 55.89, 55.83; IR (thin film) 3439, 3001, 2956, 2943, 2832, 1747, 1629, 1596, 1511, 1461, 1360, 1258 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{22}O_7$ 386.1365, found 386.1329.

General Procedure for the Ionic Hydrogenation of 4-Hydroxycyclobutenones to 4-Protiocyclobutenones. 2-*n*-Hexynyl-3-isopropoxy-4-phenyl-2-cyclobutenone (25). 2-*n*-Hexynyl-3-isopropoxy-4-phenyl-4-hydroxy-2-cyclobutenone (**24**) (0.501 g, 1.68 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (25 mL) under N_2 in a 50 mL round bottom flask, equipped with an N_2 inlet tube, septum, and magnetic stirring. The solution was treated with triethylsilane (0.402 mL, 3.46 mmol, 1.5 equiv) (silanes of varying steric bulk can be substituted for triethylsilane without change in the general procedure, i.e., triphenylsilane or triisopropylsilane) and cooled to ca. 0 °C prior to dropwise addition of BF_3·OEt_2 (0.309 mL, 3.46 mmol, 1.5 equiv). The ice bath was removed after 20 min, and after an additional 10 min, the reaction mixture was quenched with saturated aqueous sodium bicarbonate (10 mL). Further dilution with CH_2Cl_2 (30 mL) was followed by extraction. The organic layer was washed with saturated aqueous sodium chloride (10 mL), and the combined aqueous layers were backwashed with CH_2Cl_2 (2 × 30 mL). The combined organic portions were dried ($MgSO_4$) and concentrated to give a yellow oil. Flash silica gel chromatography (80% hexanes/EtOAc) provided 0.445 g (94%) of **25** as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.22 (m, 5H), 5.26 (sep., J = 6.5 Hz, 1H), 4.52 (s, 1H), 2.35 (t, J = 7.0 Hz, 2H), 1.51 (overlapping quintets, J = 7.0 Hz, 2H), 1.46 (overlapping d, J = 6.0 Hz, 6H), 1.41 (overlapping hextets, J = 7.0 Hz, 2H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.2, 178.6, 134.3, 128.7, 127.7, 127.1, 104.9, 93.1, 78.4, 67.8, 64.9, 30.6, 22.35, 22.30, 22.0, 19.1, 13.6; IR (neat) 3022, 2949, 2917, 2864, 2222, 1763, 1605, 1489, 1453, 1389, 1326, 1100 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{22}O_2$ 282.1620, found 282.1619.

2-Phenyl-3-isopropyl-2-cyclobutenone (13). Prepared as described for **25**. A CH_2Cl_2 solution of 3-isopropoxy-4-phenyl-4-hydroxy-2-cyclobutenone (**12**) (0.300 g, 1.38 mmol, 1 equiv) was treated with triethylsilane (1.01mL, 6.88 mmol, 5 equiv) followed by BF_3·OEt_2 (0.846 mL, 6.88 mmol, 5 equiv) and stirred for 12 h at room temperature. Workup and purification by flash silica gel chromatography (60% hexanes/EtOAc) gave 0.181 g (65%) of **13** as a pale yellow crystalline solid: mp 69−71 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J

= 7.5 Hz, 2H), 7.33 (t, J = 8.0 Hz, 2H), 7.20 (t, J = 7.5 Hz, 1H), 4.61 (quintet, J = 6.5 Hz, 1H), 3.45 (s, 2H), 1.48 (d, J = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.7 174.3, 129.5, 128.3, 126.9, 126.1, 120.2, 79.0, 47.6, 23.1; IR (CH_2Cl_2) 3060, 2983, 2936, 1747, 1632, 1598, 1496, 1390, 1330, 1138, 1097 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{14}O_2$ 202.0994, found 202.0988.

2-*n*-Butyl-3-isopropoxy-4-phenyl-2-cyclobutenone (15). Prepared as described for **25** using triisopropylsilane instead of triethylsilane. A CH_2Cl_2 solution of 2-*n*-butyl-3-isopropoxy-4-phenyl-4-hydroxy-2-cyclobutenone (**14**) (0.100 g, 0.37 mmol, 1 equiv) was treated with triisopropylsilane (0.373 mL, 1.82 mmol, 5 equiv) and BF_3·OEt_2 (0.224 mL, 1.82 mmol, 5 equiv) and stirred at room temperature for 16.5 h. Workup was followed by flash silica gel chromatography giving 0.081 g (85%) of **15** as a pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 2H), 7.25 (m, 3H), 4.55 (s, 1H), 4.51 (quintet, J = 6.0 Hz, 1H), 2.14 (overlapping t, J = 7.5 Hz, 2H), 1.57 (overlapping quintet, J = 6.0 Hz, 2H), 1.38−1.28 (m, 5H), 1.23 (d, J = 6.5 Hz, 3H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.9, 175.8, 135.7, 128.8, 127.5, 127.0, 124.3, 64.8, 29.9, 29.7, 23.1, 22.6, 22.3, 22.1, 13.8; IR (neat) 3067, 3029, 2926, 2870, 1756, 1620, 1493, 1465, 1451, 1381, 1310, 1095, 917 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{22}O_2$ 258.1620, found 258.1621.

2-Phenyl-3-isopropoxy-4-*n*-butyl-2-cyclobutenone (16). Prepared as described for **25**. A CH_2Cl_2 (15 mL) solution of **14** (0.25 g, 0.91 mmol, 1 equiv) was treated with triethylsilane (0.73 mL, 4.56 mmol, 5 equiv) and BF_3·OEt_2 (0.56 mL, 4.56 mmol, 5 equiv). After 5 h the mixture was worked up and concentrated to a pale yellow oil. PMR showed a mixture of regioisomers as the sole products. The product with a proton adjacent to phenyl was manifested by a singlet at 4.55 ppm and integrated for 75% of the mixture. The other regioisomer, with a proton adjacent to *n*-butyl, was evidenced most readily by overlapping triplets centered at 3.74 ppm and accounted for the other 25% of the mixture. In order to most easily separate the minor regioisomer from the major, the crude mixture was heated to reflux in toluene (see experimental for **29**). The title compound was separated from the resulting naphthol *via* flash column chromatography (90% hexanes/EtOAc) as a pale yellow oil weighing 37 mg (25%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.0 Hz, 2H), 7.34 (t, J = 7.2 Hz, 2H), 7.22 (t, J = 7.4 Hz, 1H), 4.68 (quintet, J = 6.2 Hz, 1H), 3.74 (overlapping t, J = 7.0 Hz, 1H), 1.89−1.82 (m, 1H), 1.73−1.71 (m, 1H), 1.50−1.31 (m, 10H), 0.90 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.7, 177.9, 129.6, 128.3, 126.9, 126.5, 120.1, 77.5, 60.2, 28.7, 28.6, 23.6, 22.8, 22.7, 13.8; IR (Neat) 3049, 2931, 2861, 1743, 1625, 1490, 1384, 1143, 1096 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{22}O_2$ 258.1620, found 258.1625.

2-*sec*-Butyl-3-isopropoxy-4-phenyl-2-cyclobutenone (19). Prepared as described for **25**. A CH_2Cl_2 solution of 2-*sec*-butyl-3-isopropoxy-4-phenyl-4-hydroxy-2-cyclobutenone (**17**) (0.100 g, 0.37 mmol, 1 equiv) was treated with triisopropylsilane (0.373 mL, 1.82 mmol, 5 equiv) and BF_3·OEt_2 (0.224 mL, 1.82 mmol, 5 equiv) and stirred for 16 h. Workup was followed by flash silica gel chromatography (90% hexanes/EtOAc) giving 0.080 g (85%) of a diastereomeric mixture of **19** as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.23 (m, 5H), 4.55 (overlapping s, 1H), 4.56−4.39 (m, 1H), 2.35−2.33 (m, 1H), 1.68−1.66 (m, 1H), 1.51−1.49 (m, 1H), 1.34 (d, J = 6.0 Hz, 3H), 1.20 (d, J = 7.0 Hz, 3H), 1.15 (d, J = 6.0 Hz, 3H), 0.95 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.00, 184.97, 175.4, 175.3, 135.8, 129.3, 129.2, 128.9, 127.5, 126.9, 64.8, 64.7, 31.1, 31.0, 28.0, 27.98, 27.86, 23.28, 23.25, 22.3, 22.2, 18.5, 18.4, 12.2, 12.1; IR (neat) 3013, 2959, 2874, 1751, 1623, 1495, 1453, 1378, 1256, 1097 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{22}O_2$ 258.1620, found 258.1622.

2-Phenyl-3-isopropoxy-4-*sec*-butyl-2-cyclobutenone (20). Prepared as described for **16**. A CH_2Cl_2 solution of **17** (0.250 g, 0.91 mmol, 1 equiv) was treated with triethylsilane (0.729 mL, 4.56 mmol, 5 equiv) and BF_3·OEt_2 (0.561 mL, 4.56 mmol, 5 equiv) and stirred for 5 h at room temperature. Workup and removal of volatiles afforded a pale yellow oil. ^{1}H NMR analysis showed this to be a mixture of four diastereomers and that the major pair (88%), formed in equal amounts, bear a proton adjacent to the phenyl group as evidenced by overlapping singlets at 4.56 and 4.55 ppm. The minor diastereomeric pair (12%) showed characteristic doublets at 3.81 ppm and 3.72 ppm, respectively, and the higher field doublet was in 34% de. In order to most easily separate the minor regioisomer from the major, the crude mixture was heated to reflux in toluene (see the experimental details for **30**). The less polar diastereomer (higher field diastereomer) of **20** was isolated as a pale yellow semicrystalline solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 7.5 Hz, 2H), 7.31 (t, J = 7.9 Hz, 2H), 7.21 (t, J = 7.2 Hz, 1H), 4.69 (quintet, J = 6.1 Hz, 1H), 3.81 (d, J = 3.6 Hz, 1H), 1.70−1.63 (m, 1H), 1.59−1.42 (m, 8H), 1.01−0.96 (m, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 186.3, 177.4, 129.5, 128.3, 126.9, 126.5, 120.8, 77.3., 64.8, 34.8, 28.1, 23.6, 22.7, 15.3, 12.3; IR (neat) 3060, 2966, 2872, 1743, 1631, 1455, 1384 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{22}O_2$ 258.1620, found 258.1611.

(*Z*/*E*)-4-Ethylidene-3-isopropoxy-2-*n*-butyl-2-cyclobutenone (22 and 23). 2-Ethenyl-3-isopropoxy-4-*n*-butyl-4-hydroxy-2-cyclobutenone (**21**) (0.25 g, 1.12 mmol, 1 equiv) was dissolved in CH_2Cl_2 (15 mL) and treated with triethylsilane (0.90 mL, 5.61 mmol, 5 equiv) followed by BF_3·OEt_2 (0.69 mL, 5.61 mmol, 5 equiv). After 15 h at ambient temperature, the mixture was worked up in the standard way. Concentration of the crude gave an orange oil which was analyzed by ^{1}H NMR. The mixture of diastereomers **22** and **23** comprised >90% of the crude mixture (NMR data are in accord with previously published methylene cyclobutenones).[13] Differentiation between the *Z* and *E* isomers was made on the basis of the 1-position's deshielding effect upon the vinyl proton and the terminal methyl group. The *Z* isomer's vinyl proton is shielded (quartet centered at 5.06 ppm) compared to that of the *E* isomer (quartet centered at 5.27 ppm). A deshielding effect upon the *Z* isomer's terminal methyl group is evidenced by a doublet centered at 1.91 ppm. The *E* isomer's methyl group doublet is centered at 1.78 ppm. Attempts to purify/separate the mixture resulted in extensive decomposition.

2,4-(3,4-Dimethoxyphenyl)-3-methoxy-2-cyclobutenone (32). A CH_2Cl_2 solution of 2,4-(3,4-dimethoxyphenyl)-3-methoxy-4-hydroxy-2-cyclobutenone (1.50 g, 3.9 mmol, 1 equiv) was treated with triethylsilane (0.931 mL, 5.8 mmol, 1.5 equiv) and BF_3·OEt_2 (0.717 mL, 5.8 mmol, 1.5 equiv) and stirred for 0.5 h (until the initially brilliant blue color faded to yellow). Standard workup was followed by concentration to a bright yellow oil which was crystallized from Et_2O to afford **32** as pale yellow fine needles: mp 134−135 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.33 (m, 2H), 6.88−6.84 (m, 3H), 6.80 (d, J = 1.0 Hz, 1H), 4.78 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 3.858 (s, 3H), 3.853 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.7, 174.4, 149.6, 148.9, 148.5, 127.6, 122.2, 122.1, 119.60, 119.57, 111.7, 111.1, 110.1, 109.6, 77.25, 65.3, 60.3, 55.97, 55.94, 55.91, 55.88; IR (neat) 3004, 2955, 2836, 1750, 1636, 1600, 1513, 1464, 1364, 1263 cm^{-1}; HRMS (CI) calcd for $C_{21}H_{22}O_6$ 370.1416, found 371.1507 (MH^+).

2,4-(3,4-Dimethoxyphenyl)-3-[(4-methoxyphenethyl)-amino]-2-cyclobutenone (34). 2,4-(Dimethoxyphenyl)-3-methoxy-4-hydroxy-2-cyclobutenone (**32**) (0.400 g, 1.08 mmol, 1 equiv) was dissolved in acetonitrile (30 mL), treated with 4-methoxyphenethylamine (0.816 g, 5.41 mmol, 5 equiv), and stirred for 15 h at room temperature. Volatiles were removed to afford a pale yellow oil which was flash column chromatographed (70% EtOAc/hexanes). Concentration gave **34** as a light brown foam weighing 0.432 g (82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (s, 1H), 6.91−6.75 (m, 9H), 6.00−5.90 (m, 1H), 4.39 (s, 1H), 3.86 (s, 9H), 3.83 (s, 3H), 3.78 (s, 3H), 3.35−3.29 (m, 2H), 2.69−2.56 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.3, 164.0, 158.6, 149.4, 148.6, 147.2, 129.7, 129.4, 128.6, 124.4, 119.8, 117.2, 114.7, 114.2, 111.6, 111.4, 110.40, 110.35, 108.98, 108.95, 77.3, 64.1, 55.9, 55.3, 55.2, 47.4, 36.2; IR (thin film) 3288, 3067, 2993, 2940, 2835, 1728, 1606, 1585, 1512, 1464, 1348, 1248 cm^{-1}; HRMS (CI) calcd for $C_{29}H_{31}NO_6$ 489.2151, found 490.2234 (MH^+).

General Method for the Thermolysis of 4-Protiocyclobutenones To Form Naphthols. 2-*n*-Butyl-3-isopropoxynaphthol (29). A CH_2Cl_2 solution of **14** (0.250 g, 0.91 mmol, 1 equiv) was treated with triethylsilane (0.729 mL, 4.56 mmol, 5 equiv) and BF_3·OEt_2 (0.561 mL, 4.56 mmol, 5 equiv) and stirred for 5 h at room temperature. Workup and concentration was followed by ^{1}H NMR analysis which showed

75% of the hydrogenation had taken place adjacent to the phenyl group and 25% adjacent to the butyl substituent. The crude yellow oil (0.150 g, ca. 0.58 mmol) was dissolved in dry toluene (12 mL, 0.05 M) and heated to reflux under N_2 for 1 h. The resulting crude mixture was concentrated to a yellow oil and flash column chromatographed (90% hexanes/EtOAc) giving 0.108 g (72%, 96% with respect to starting ratio) of **29** as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.39 (t, J = 7.0 Hz, 1H), 7.31 (t, J = 7.0 Hz, 1H), 6.77 (s, 1H), 5.22 (s, 1H), 4.72 (sep., J = 6.5 Hz, 1H), 2.78 (t, J = 7.5 Hz, 2H), 1.60 (quintet, J = 7.0 Hz, 2H), 1.47–1.36 (m, 8H), 0.97 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 149.2, 133.3, 126.3, 125.9, 122.7, 121.0, 120.0, 115.4, 100.0, 69.6, 31.5, 23.3, 22.7, 22.0, 13.9; IR (neat) 3572, 3059, 2957, 2870, 2331, 1632, 1446 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{22}O_2$ 258.1620, found 258.1626.

2-*sec*-Butyl-3-isopropoxynaphthol (30). A CH_2Cl_2 solution of **17** (0.250 g, 0.91 mmol, 1 equiv) was treated with triethylsilane (0.729 mL, 4.56 mmol, 5 equiv) and BF_3·OEt_2 (0.561 mL, 4.56 mmol, 5 equiv) and stirred for 5 h at room temperature. Workup was followed by removal of volatiles to afford a pale yellow oil which was analyzed by ^{1}H NMR showing that 88% of the hydrogenation had taken place adjacent to phenyl and 12% proton adjacent to *sec*-butyl. The entire amount of crude hydrogenation product was dissolved in dry toluene (18 mL, 0.05 M) and heated to reflux for 2 h. The resulting crude mixture was concentrated to a yellow oil and flash column chromatographed (95% hexanes/EtOAc) giving 0.171 g (73%, 83% with respect to starting ratio) of **30** as an off-white semicrystalline solid: mp 71–72 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 9.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 7.0 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 6.78 (s, 1H), 5.33 (s, 1H), 4.73 (quintet, J = 6.5, 1H), 1.97 (m, 1H), 1.80 (m, 1H), 1.43 (m, 10H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 133.2, 126.2, 126.0, 122.7, 120.8, 120.2, 118.7, 100.3, 77.2, 69.4, 28.2, 22.0, 19.2, 13.0; IR (CH_2Cl_2) 3564, 3058, 2961, 2928, 2874, 1624, 1454 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{22}O_2$ 258.1620, found 258.1611.

2-*n*-Hexynyl-3-isopropoxynaphthol (31). A toluene solution of **25** (0.180 g, 6.38 mmol, 1 equiv) was refluxed for 1 h. Workup and purification by flash silica gel chromatography (95% hexanes/EtOAc) gave 0.157 g (87%) of naphthol **31** as an off-white crystalline solid: mp 34–35 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 8.5 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 6.73 (s, 1H), 6.45 (s, 1H) 4.70 (quintet, J = 6.5 Hz, 1H), 2.61 (t, J = 7.0 Hz, 2H), 1.70–1.65 (m, 2H), 1.61–1.56 (m, 2H), 1.44 (d, J = 6.5 Hz, 6H), 1.00 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 154.9, 134.1, 127.4, 126.4, 123.1, 122.2, 118.9, 101.8, 100.9, 98.9, 72.1, 71.1, 30.8, 22.0, 21.9, 19.7, 13.6; IR (neat) 3471, 3061, 2966, 2924, 2210, 1626, 1595, 1569, 1500, 1464 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{22}O_2$ 282.1620, found 282.1614.

2-(3,4-Dimethoxyphenyl)-3,6,7-trimethoxynaphthol (33). A solution of **32** (0.350 g, 0.95 mmol) in toluene (60 mL) was heated to reflux under a blanket of N_2 for 45 min. Removal of volatiles gave a pale pink solid which was triturated with Et_2O to give **33** as a light pink solid weighing 0.298 g (85%): mp 195–196 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.06 (s, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.98 (d of d, J = 8.0 Hz, 2.0 Hz, 1H), 6.92 (d, J = 2.0 Hz, 1H), 6.75 (s, 1H), 5.60 (s, 1H), 4.00 (overlapping s, 6H), 3.95 (s, 3H), 3.89 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 150.4, 149.6, 148.9, 148.3, 147.4, 129.9, 124.9, 123.0, 114.3, 114.0, 112.7, 111.8, 105.6, 101.6, 97.4, 77.3, 55.93, 55.89, 55.81, 55.67; IR (KBr) 3425, 2983, 2940, 2824, 1633, 1606, 1585, 1506, 1459, 1422, 1406, 1237, 1153 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{22}O_6$ 370.1416, found 370.1428.

6,7-Dimethoxy-2-(3,4-dimethoxyphenyl)-3-[(4-methoxyphenethyl)amino]naphthol (35) was prepared by the same method as **33**. The cyclobutenone **34** (0.300 g, 0.61 mmol) was dissolved in toluene (12 mL) and heated to reflux under a blanket of N_2 for 2h. Crystals of **35** from 1:1 hexanes/EtOAc weighed 0.219 g (73%): mp 165–167 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (s, 1H), 6.96–6.90 (m, 4H), 6.81 (d of d, J = 8.0 Hz, 1.5 Hz, 1H), 6.77–6.72 (m, 4H), 6.51 (broad s, 1H), 5.19 (s, 1H), 3.99 (s, 3H), 3.97 (s, 6H), 3.79 (s, 3H), 3.78 (s, 3H), 3.36 (t, J = 7.0 Hz, 2H), 2.84–2.79 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 150.34, 150.26, 149.3, 147.8, 131.1, 129.6, 123.5, 113.9, 113.7, 112.4, 111.4, 105.0, 101.6, 77.4, 77.1, 76.9, 55.93, 55.87, 55.73, 55.19, 33.9; IR (neat) 3478, 3447, 2984, 2930, 2825, 1633, 1621, 1580, 1512, 1454, 1417, 1323, 1296, 1243 cm^{-1}; HRMS (CI) calcd for $C_{29}H_{31}NO_6$ 489.2151, found 490.2134 (MH^+).

3-Isopropoxy-7-methoxy-2-phenylnaphthol (36). A CH_2Cl_2 solution of 2-(4-methoxyphenyl)-3-isopropoxy-4-phenyl-4-hydroxy-2-cyclobutenone[13] (**26**) (0.200 g, 0.65 mmol, 1 equiv) was treated with triethylsilane (0.516 mL, 3.23 mmol, 5 equiv) and BF_3·OEt_2 (0.397 mL, 3.23 mmol, 5 equiv) and stirred for 1.5 h at room temperature. Workup and concentration was followed by ^{1}H NMR analysis, which showed a mixture composed of **27** and **28** in respective yields of 84% and 16%. The crude yellow oil (0.175 g, 0.59 mmol) was dissolved in dry toluene (12 mL) and heated to reflux under N_2 for 1.5 h. The resulting crude mixture was concentrated to a yellow oil and flash silica gel chromatographed giving 0.165 g of a pale yellow oil. Fractional crystallization (90% hexanes/EtOAc) afforded **36** as white needles weighing 0.112 g (64%): mp 99–100 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 9.0 Hz, 1H), 7.55–7.42 (m, 6H), 7.14 (d of d, J = 9.0, 3.0 Hz, 1H), 6.85 (s, 1H), 5.56 (s, 1H), 4.50 (quintet, J = 6.1 Hz, 1H), 3.93 (s, 3H), 1.22 (d, J = 6.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 152.0, 148.1, 133.2, 131.0, 129.5, 129.1, 127.9, 127.8, 120.4, 119.6, 116.4, 101.9, 100.9, 70.8, 55.4, 21.9; IR (neat) 3526, 2966, 2934, 2827, 1601, 1504, 1396, 1284 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{20}O_3$ 308.1412, found 308.1407.

Acknowledgment. The authors thank the National Institutes of Health (GM-36312) for financial support of this work and SmithKline Beecham for a generous gift of squaric acid.

Supplementary Material Available: Copies of ^{13}CMR spectra of all compounds (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO941484I