H), 4.49 (d, J = 15.0 Hz, 1 H), 4.67 (d, J = 15.0 Hz, 1 H), 7.26–7.40 (m, 5 H).

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Registry No. 1·2HCl, 72351-21-4; **6**, 91259-93-7; **7**, 91280-46-5; **9**, 124287-83-8; **10**, 111535-89-8; **11**, 111515-79-8; **12**, 111515-76-5; (1*S*,5*R*)-**12**, 124375-96-8; **13**, 124287-84-9; (1*S*)-**13**, 124375-93-5; **14**, 124287-85-0; (1*S*,4*R*,5*R*)-**14**, 124375-94-6; **15**, 111515-77-6; (1*S*,5*R*)-**15**, 124375-95-7; **16**, 111515-78-7; **19**, 124287-86-1; **20**, 111515-87-8; **21**, 111515-88-9; **22**, 111515-89-0; **23**, 111515-90-3; **24**, 111515-80-1; **25**, 111515-81-2; **25** amine, 124287-89-4; **26**, 111515-82-3; **28**, 124287-87-2; **29**, 111515-83-4; **30**, 111515-84-5; **31**, 124287-88-3; **33**, 111515-85-6; **34**, 111515-86-7; **35**, 72351-18-9; **36**, 74615-83-1; **37**, 74615-84-2; **38**, 124375-92-4; fortimicin A disulfate, 72275-67-3.

Supplementary Material Available: ^{1}H NMR spectra of compounds **11**, **12**, **16**, **19**, **20**, **21**, **24**, **26**, **28**, **30**, **31**, **33**, **34**, **36**, and **38** (15 pages). Ordering information is given on any current masthead page.

Synthesis of Hydroxyquinones and Related Compounds: Semisquaric Acids, (±)-Terreic Acid, (±)-Perezone, and (±)-Isoperezone

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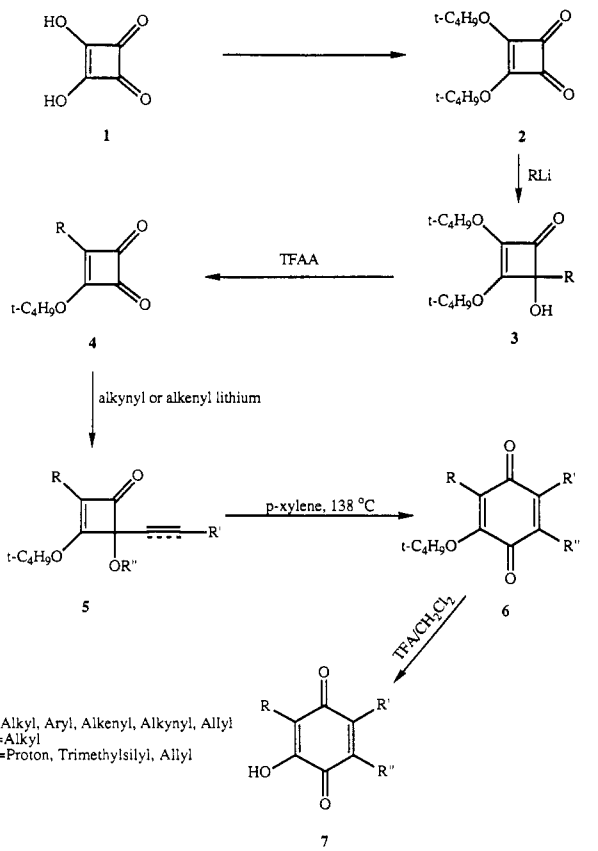
tert-Butoxyquinones were prepared from the thermal ring expansion of 4-alkynyl-, 4-alkenyl-, and 4-aryl-*tert*-butoxycyclobutenones and shown to be readily converted to hydroxyquinones upon treatment with trifluoroacetic acid at low temperature. This is a useful transformation since no reliable general route to hydroxyquinones has previously been available. The synthetic scope of this methodology as well as its specific utilization in the synthesis of a semisquaric acid, and the natural products, (±)-terreic acid, (±)-perezone, and (±)-isoperezone, are described.

Introduction

Although hydroxyquinones are among the most abundant of the naturally occurring quinones, no methodology has previously been confirmed to be generally applicable for their synthesis.[1] Indeed, in view of the ubiquity of these compounds, it is surprising that so few examples have been synthesized in the laboratory. A viable solution to this problem is now presented. Specifically, 2,3-di-*tert*-butoxycyclobutenedione **2**,[2] in conjunction with the recently reported ring expansions of 4-alkynyl-, 4-alkenyl-, and 4-arylcyclobutenones to quinones and related compounds, is reported here to be a useful synthon for hydroxyquinones. In this regard, cyclobutenedione **2**, readily available from squaric acid **1**, was converted to a variety of hydroxyquinones **7** as outlined in Scheme I. This was accomplished by its initial treatment with an organolithium reagent (alkyl, aryl, alkenyl, or alkynyl) to give the cyclobutenones **3**, which are readily hydrolyzed to the cyclobutenediones **4** upon treatment with trifluoroacetic anhydride (TFAA).[3] These were then converted to the cyclobutenones **5** by the regiospecific addition of an alkynyl-, alkenyl-, or aryllithium reagent to the more electrophilic (nonvinylogous ester) carbonyl group. Thermolysis of **5** gave the *tert*-butoxyquinones **6**, members of a rare class of quinones.[4-6] These were then converted to the hydroxyquinones **7** upon treatment with trifluoroacetic acid at 0 °C.[7]

Scheme I



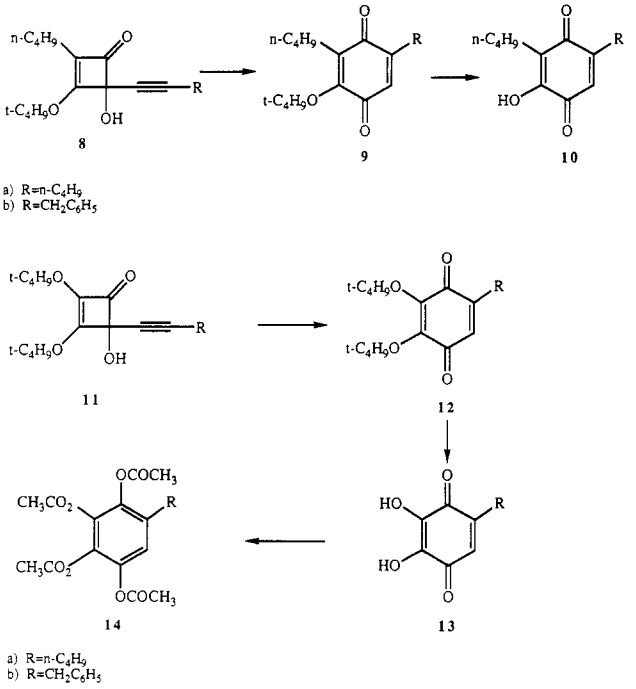
(1) An outstanding source listing for the structures of naturally occurring quinones is Thompson, R. H. *Naturally Occurring Quinones*; Chapman and Hall: London, 1987; Vols. I, II, III.

(2) (a) Pericas, M. A.; Serratosa, F. *Tetrahedron Lett.* **1977**, *50*, 4437. (b) Dehmlov, E. V.; Schell, H. G. *Chem. Ber.* **1980**, *113*, 1.

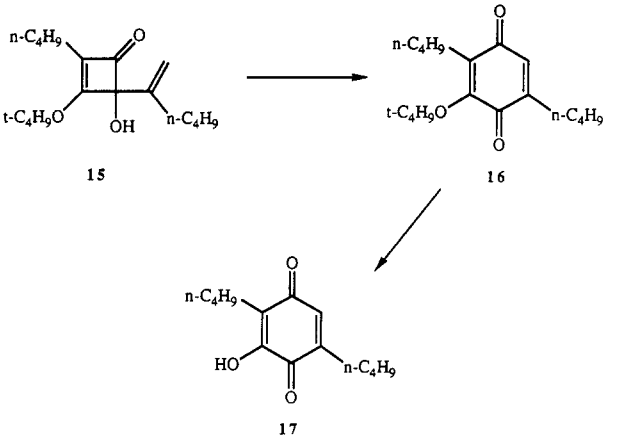
(3) For the conversion of squaric acid to substituted cyclobutenediones, see: (a) Reed, M. W.; Perri, S. T.; Pollart, D. J.; Foland, L. D.; Moore, H. W. *J. Org. Chem.* **1988**, *53*, 2477. (b) Liebeskind, L. S.; Fengl, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *53*, 2482.

0022-3263/90/1955-1177$02.50/0

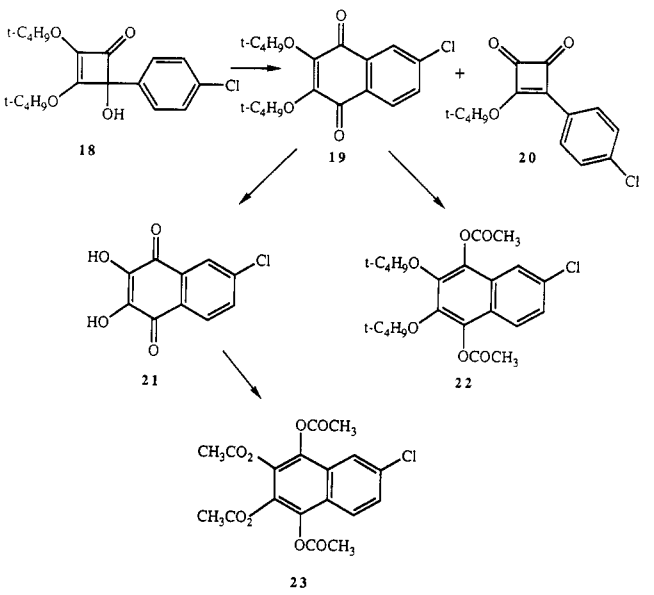
Scheme II



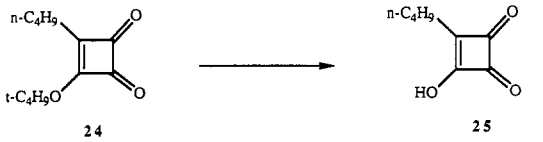
Scheme III



Scheme IV



Scheme V



The debutylation of *tert*-butoxyquinones is of particular note since it represents a mild, general route to the hydroxyquinone moiety. This transformation is analogous to the hydrolysis of *tert*-butyl esters, and thus mild hydrolytic conditions would be expected. In this regard, the lower homologues of the alkoxyquinones (also vinylogous esters) are, in general, unreliable precursors to hydroxyquinones since their hydrolysis usually requires prolonged treatment with strong acid or base and quinones (particularly benzoquinones) are often unstable to these reaction conditions.[8] *As a result, the utilization of tert-butoxycyclobutenediones as precursors to hydroxyquinones as outlined here is the method of choice for the construction of highly functionalized examples.*

General Synthetic Scope. Specific examples of hydroxyquinone syntheses employing the ring expansion of 4-alkynylcyclobutenones are given in Scheme II.[4] Conversions of the 4-alkynyl-3-*tert*-butoxy-2-butyl-4-hydroxycyclobut-2-enones **8a,b** to the hydroxyquinones **10a,b** were accomplished in 79% and 70% overall yields, respectively, by the sequence of reactions given above. Analogously, **11a,b** were converted to the 2,3-dihydroxyquinones **13a,b**, which were found to be generally unstable and were thus characterized as the tetraacetates **14a,b**.

An example of the ring expansion and removal of the *tert*-butyl protecting group of a 4-alkenylcyclobutenone is given in Scheme III.[5,6] Specifically, 3-*tert*-butoxy-2-butyl-4-(1-butylethenyl)-4-hydroxycyclobut-2-enone (**15**) was prepared as generally outlined in Scheme I and converted to 2,5-di-*n*-butyl-3-hydroxy-1,4-benzoquinone, **17**, in excellent overall yield (89%). This example, in comparison to the conversion of **8a** to **10a** is noteworthy since it illustrates the control of regiochemistry associated with this methodology, i.e., **17** results in the 2,5-dialkylated quinone and **10a** provides the 3,5-dialkylated regioisomer.

Finally, with regard to the general synthetic scope of this methodology, an example of the ring expansion of a 4-arylcyclobutenone to a hydroxynaphthoquinone is given in Scheme IV.[5] Here, the cyclobutenone **18** was prepared by treatment of **2** with 1-chloro-4-lithiobenzene. Thermolysis of **18** in refluxing *p*-xylene gave both **19** and **20**.

(4) For the conversion of 4-alkynylcyclobutenones to quinones, see: (a) Karlsson, J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 3392. (b) Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1987**, *52*, 1174. (c) Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975.

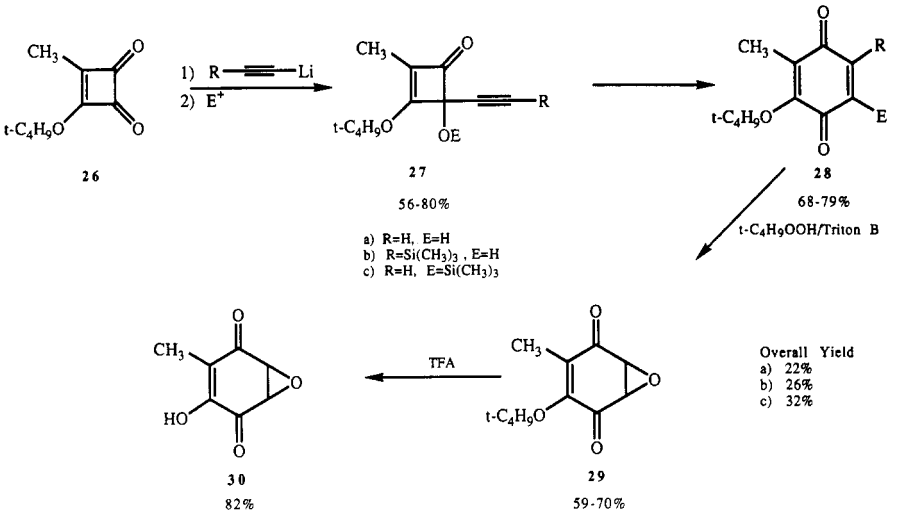
(5) For selected references to the conversion of 4-arylcyclobutenones to quinones, see: (a) Perri, S. T.; Foland, L. D.; Decker, O. H.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067. (b) Liebeskind, L. S.; Iyer, S.; Jewell, C. F. *J. Org. Chem.* **1986**, *51*, 3065. (c) Perri, S. T.; Moore, H. W. *Tetrahedron Lett.* **1987**, 4507. (d) Reed, M. W.; Moore, H. W. *J. Org. Chem.* **1988**, *53*, 4166. (e) Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 989.

(6) For the conversion of 4-alkenylcyclobutenones to quinones, see: (a) Perri, S. T.; Dyke, H. J.; Moore, H. W. *J. Org. Chem.* **1989**, *54*, 2032. (b) Perri, S. T.; Moore, H. W. *J. Am. Chem. Soc.*, in press.

(7) (a) Beyerman, H. C.; Bontekoe, J. S. *Proc. Chem. Soc.* **1961**, 249. (b) In some cases the use of 4 N HCl in refluxing 1,4-dioxane was found to be preferable, for example compounds **35** and **38**.

(8) For an example illustrating the difficulty of the conversion of methoxyquinones to hydroxyquinones, see: Garst, M. E.; Frazier, J. D. *J. Org. Chem.* **1987**, *52*, 446.

Scheme VI



It is important to make note that this ring expansion must be accomplished in the presence of a "Proton Sponge", which greatly reduces the amount of the hydrolysis product, **20**. Compound **19** was converted to the dihydroxyquinone **21** upon treatment with TFA as described above, and this was converted to the tetraacetate **23** for characterization. Additionally, reductive acylation (Zn/acetic anhydride) of **19** provided **22**, which is the *tert*-butoxy homologue of lonapalene, a drug used for the treatment of psoriasis.[9]

Synthetic Utility: A Semiquaric Acid, Terreic Acid, Perezone, and Isoperezone. Four examples of the specific synthetic utility of this methodology are given below. The first simply illustrates the application of the removal of the *tert*-butyl protecting group in the cyclobutenedione series, i.e., for the synthesis of a semisquaric acid, examples of which have been shown to exhibit significant antifungal activity.[10] The second example is the total synthesis of the natural antibiotic terreic acid, **30**, and the third is the total synthesis of the natural hydroxyquinone (±)-perezone, **35**, and finally its naturally occurring regioisomer (±)-isoperezone, **38**.

Semisquaric acids are of interest as potential antifungal drugs, and their synthesis has received a great deal of attention.[10] The reaction given in Scheme V for the preparation of **25** from **24** illustrates a potentially general route to such compounds since good methodology now exists for the synthesis of substituted cyclobutenediones from squaric acid, **1**.[3] Compound **24** was prepared from **2** upon treatment of the dione with butyllithium followed by hydrolysis with trifruoroacetic anhydride. Treatment of **24** with trifluoroacetic acid then gave the semisquaric acid **25** in 88% yield. In passing it is of interest to note that **24** survives trifluoroacetic anhydride but is readily deprotected with trifluoroacetic acid.

A more complex example of the synthetic utility of this methodology is given in Scheme VI, which outlines three total syntheses of (±)-terreic acid, **30**, a naturally occurring antibiotic.[11,12] All of these related syntheses are efficient and start with 3-*tert*-butoxy-4-methylcyclobutenedione, **26**, which gives the cyclobutenones **27a–c** in 56%, 67%, and 80% yields when treated with respectively lithium acetylide followed by ammonium chloride, lithium (trimethylsilyl)acetylide followed by ammonium chloride, or lithium acetylide followed by trimethylsilyl chloride. These transformations were carried out at −78 °C in THF, and the reported yields are for isolated and purified products. Thermolysis of these cyclobutenones in refluxing acetonitrile or benzene gave the benzoquinones **28a–c** in respective yields of 79%, 69%, and 68%. These quinones were then each directly converted to the epoxide **29** in respective yields of 59%, 68%, and 70% upon treatment with *tert*-butyl hydroperoxide/Triton B.[13] De-*tert*-butylation of **29** at 0 °C upon treatment with trifluoroacetic acid then gave (±)-terreic acid, **30**, in 84% yield. The syntheses given here correspond to respective overall yields of 22%, 26%, and 32%, starting with the cyclobutenedione **26**. These syntheses are superior to the other two routes to (±)-terreic acid, which have been reported.[12]

These syntheses were designed to compare the possible differences in selectivity of the ring expansion and epoxidation as a function of the presence and position of the trimethylsilyl group. In general, it appears that the epoxidation proceeds more efficiently with the silylquinones, but the regiochemistry is not important. Most interesting is the fact that alkynylation of **26** proceeds in the highest yield to give **27c**. It was noted that **27a** and **27b** are always accompanied by unreacted **26**, thus suggesting the alkynylation step to be reversible. Apparently, the reversibility is circumvented when the reaction is quenched with trimethylsilyl chloride.

The two most significant aspects of this synthesis are: (1) (±)-terreic acid survives the debutylation reaction conditions and this points to the possible general use of this methodology for the synthesis of related compounds in the highly oxygenated cyclohexane series, and (2) de-

(9) (a) 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.; Beard, C. C.; Unger, S. H.; Cheung, P. S. *J. Med. Chem.* **1986**, *29*, 1504. (b) Venuti, M. C.; Loe, B. E.; Jones, G. H.; Young, J. M. *J. Med. Chem.* **1988**, *31*, 2132. (c) Compound **23** shows inhibitory properties similar to that of lonapalene toward 5-hydroxylipogenase. We are grateful to Dr. John Edwards at Syntex Corporation for providing us with these data.

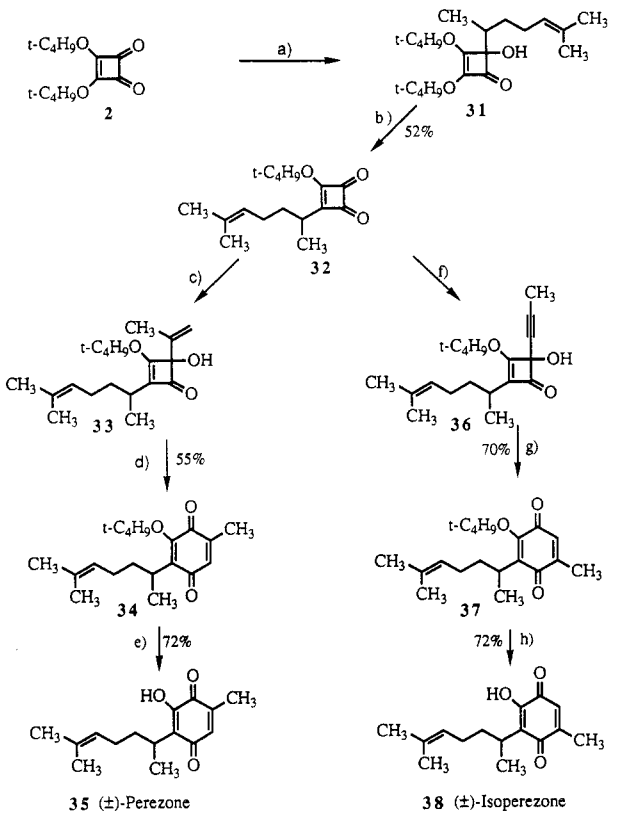
(10) For an excellent review, see: Bellus, D. In *Oxocarbons*; West, R., Ed.; Academic Press: New York, 1980.

(11) Read, G.; Westlake, D. W. S.; Vining, L. C. *Can. J. Biochem.* **1969**, *47*, 1071. Yamamoto, H.; Moriyama, K.; Jinnouchi, H.; Yagishita, K. *J Antibiot.* **1980**, *33*, 320. Yamamoto, H.; Takahashi, S.; Moriyama, K.; Jinnouchi, H.; Takahashi, N.; Yagishita, K. *Nihon Daigaku No-Juigakube Gakujutsu Kenkyu Hokaku* **1980**, *37*, 9.

(12) For previous syntheses of (±)-terreic acid, see: (a) Rashid, A.; Read, G. *J. Chem. Soc. C* **1967**, 1323. (b) Sheehan, J. C.; Lo, Y. S. *J. Med. Chem.* **1974**, *17*, 371. This paper also reports the interesting observation that the natural (−)-isomer and the unnatural (+)-isomer have similar antibiotic properties, and that the racemic mixture is, in fact, the most biologically active!

(13) Moore, H. W. *J. Org. Chem.* **1967**, *32*, 1996.

Scheme VII[a]



[a] Reagents: (a) (±)-2-lithio-6-methyl-hept-5-ene,[9] THF; (b) (i) pyridine, (ii) trifluoroacetic anhydride; (c) 2-lithiopropene, THF; (d) (i) benzene reflux, (ii) Ag_2O, K_2CO_3, benzene; (e) 4 N HCl, dioxane; (f) 1-lithiopropyne, THF; (g) benzene reflux; (h) 4 HCl, dioxane.

silylation of **28b** and **28c** directly accompanies the epoxidation step, a transformation which was established to take place at the silyl epoxide stage. That is, the silyl epoxide resulting from epoxidation of **28b** was isolated and shown to give **29** when treated with Triton B. This desilylation was surprising but it is not completely without precedent. For example, desilylation of trimethylsilyl epoxides was recently reported to take place upon treatment with tetrabutylammonium fluoride, a transformation presumably proceeding via the corresponding oxaranyl carbanion.[14]

As final illustrations of the synthetic utility of the hydroxyquinone synthetic methodology, efficient syntheses of the naturally occurring sesquiterpene hydroxyquinone (±)-perezone, **35**, and its naturally occurring regioisomer (±)-isoperezone, **38**, are described herein (Scheme VII).[15,16]

Treatment of di-*tert*-butyl squarate **2** with 6-lithio-2-methyl-2-heptene furnished cyclobutenone **31**.[17] Hydrolysis of this upon treatment with pyridine/trifluoroacetic anhydride gave the cyclobutenedione **32** in 52% yield, based on recovered starting material. Addition of 2-lithiopropene to **32** then provided cyclobutenone **33**, which was directly thermolyzed to give the quinone **34** in 55% yield after oxidation. Subsequent deprotection then provided (±)-perezone **35** in 72% yield. The spectral properties (^{13}C NMR and ^1H NMR) of this product were identical with those reported for the natural product. Overall, this synthesis provides a shorter route to (±)-perezone than that previously reported and gives a slightly higher overall yield (21% as compared to 18%).[18]

As a further example of the utility of the cyclobutenone/quinone rearrangement and the hydroxyquinone synthesis, (±)-isoperezone, **38** was prepared as follows. Treatment of the cyclobutenedione **32** with 1-lithiopropyne furnished the cyclobutenone **36**, which was thermolyzed directly to give quinone **37** in 70% yield. Deprotection with 4 N HCl in refluxing dioxane provided (±)-isoperezone **38** in 72% yield (26% overall).[19] To our knowledge, the only previous synthesis of (±)-isoperezone, reported in 1987, proceeded in 38% overall yield from parvifolene, a natural product isolated from *Pereziae* spp.[20]

Conclusion

The most significant points of this study include the following: (1) *tert*-butoxyquinones are readily prepared from *tert*-butoxycyclobutenones and easily converted to hydroxyquinones under mild acidic conditions; (2) *tert*-butoxycyclobutenones are readily available from squaric acid and function as viable precursors to the corresponding *tert*-butoxyquinones by the use of recently discovered ring expansions of 4-alkynyl-, 4-alkenyl-, and 4-arylcyclobutenones; (3) *together the ring expansions and deprotection of tert-butoxyquinones constitute the best known method for the synthesis of hydroxyquinones, an abundant class of natural products.*

Experimental Section

General. All air- or water-sensitive reactions were carried out under a slight positive pressure of argon, which was purified by passing through Drierite. THF was distilled from sodium (benzophenone indicator). Xylene, benzene, acetonitrile, and hexane were distilled from calcium hydride. Unless specified as dry, the solvents were of unpurified reagent grade. Removal of solvents was accomplished on a rotary evaporator at 10–20 Torr. All reactions were followed by TLC using E. Merck precoated sheets silica gel 60 F_{254}. Flash column chromatography was performed by using E. Merck silica gel 60 (230–400 mesh). Melting points were measured on a Büchi 510 melting point apparatus and are not corrected. NMR spectra were recorded on WM-250 Bruker, a General Electric QE 300 NMR, or a General Electric QE 500 NMR spectrometer. IR data were obtained from a Perkin-Elmer 281 spectrophotometer (double beam). Low-resolution mass spectra were determined on a Finnigan 4000 spectrometer, high-resolution mass spectra on a VG Analytic 7070E spectrometer. Elemental analysis were performed by Robertson Laboratories, Inc., Madison, NJ.

General Procedure for the Addition of Nucleophiles to Cyclobutenones. 3-*tert*-Butoxy-2-*n*-butyl-4-hex-1-ynyl-4-hydroxycyclobut-2-en-1-one (8a). *n*-Butyllithium (1.1 mL of a 1.6 M solution in hexane, 1.76 mmol) was added to a solution of 1-hexyne (0.20 mL, 1.73 mmol) in dry THF (35 mL) at −78 °C. After 10 min a solution of **24** (330 mg, 1.57 mmol) in dry THF (25 mL), precooled to −78 °C, was added via cannula over a 3-min period. After additional stirring for 10 min the reaction was quenched with 10% NH_4Cl (20 mL), allowed to warm to room

(14) Dubuffet, T.; Sauvetre, R.; Normant, J. F. *Tetrahedron Lett.* **1988**, 5923.

(15) Bohlmann, F.; Ahmed, M.; Grenz, M.; King, R. M.; Robinson, H. *Phytochemistry* **1983**, *22*, 2858.

(16) For recent syntheses of (±)-*O*-methylperezone, see: ref 6a and Saa, J. M.; Llobera, A. *Tetrahedron Lett.* **1987**, 5045.

(17) Oppolzer, W.; Zutterman, F.; Battig, K. *Helv. Chim. Acta* **1983**, *66*, 522.

(18) Sanchez, I. H.; Mendoza, S.; Calderon, M.; Larraza, M. I.; Flores, H. J. *J. Org. Chem.* **1985**, *50*, 5077.

(19) This synthesis also illustrates a potentially general route to a variety of analogues which will be of interest in a forthcoming study of the scope of intramolecular cycloadditions of hydroxyquinones related to the perezone/pipitzol rearrangement. For studies on this rearrangement, see: (a) Walls, F.; Padilla, J.; Joseph-Nathan, P.; Giral, F.; Escobar, M.; Romo, J. *Tetrahedron* **1966**, *22*, 2387. (b) Sanchez, I. H.; Basurto, F.; Joseph-Nathan, P. *J. Nat. Prod.* **1984**, *47*, 382. (c) Joseph-Nathan, P.; Mendoza, V.; Garcia, E. *Tetrahedron* **1977**, *33*, 1573.

(20) E. Garcia, G.; Mendoza, V.; A. Guzman B. *J. Nat. Prod.* **1987**, *50*, 1055.

temperature, and extracted with ether (2 × 30 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated, and the residue was purified by flash column chromatography (hexanes/ethyl acetate, 8:2) to give **8a** as colorless crystals (420 mg, 92%): mp 50–51 °C; TLC (hexanes/ethyl acetate, 8:2) R_f 0.38; IR ($CHCl_3$, cm^{-1}) 3350, 2930, 2230, 1755, 1600, 1370, 1160, 840; ^1H NMR ($CDCl_3$) δ 3.11 (s, 1 H), 2.25 (t, J = 6.9 Hz, 2 H), 2.07 (t, J = 7.1 Hz, 2 H), 1.59 (s, 9 H), 1.27–1.55 (m, 8 H), 0.89 (t, J = 7.1 Hz, 3 H), 0.88 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 189.2, 180.8, 132.4, 91.5, 85.5, 84.3, 76.0, 30.2, 28.9, 28.5, 22.4, 21.8, 21.7, 18.6, 13.6, 13.5; LRMS m/e (rel int) EI 292 (1), 236 (16), 207 (9), 193 (12), 151 (37), 57 (100); CI 293 (2), 237 (100); HRMS (EI) m/e calcd for $C_{18}H_{28}O_3$ (M^+) 292.2038, found 292.2026.

3-*tert*-Butoxy-2-*n*-butyl-4-hydroxy-4-(3-phenylprop-1-ynyl)cyclobut-2-en-1-one (8b). The genral procedure described for **8a** was followed by using 1-lithio-3-phenylprop-1-yne as the nucleophile, which, upon purification by flash column chromatography (hexanes/ethyl acetate, 7:3), gave **8b** as colorless crystals (330 mg, 64%): mp 79–80 °C; TLC (hexanes/ethyl acetate, 7:3) R_f 0.44; IR ($CHCl_3$, cm^{-1}) 3580, 2960, 1760, 1610, 1375, 1160, 850; ^1H NMR ($CDCl_3$) δ 7.24–7.31 (m, 5 H), 3.68 (s, 2 H), 3.12 (br s, 1 H), 2.09 (t, J = 7 Hz, 2 H), 1.28–1.63 (m, 4 H), 1.57 (s, 9 H), 0.90 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 188.2, 173.5, 135.7, 132.9, 128.5, 127.9, 126.6, 88.4, 85.7, 84.5, 48.8, 28.9, 28.5, 25.3, 22.4, 22.0, 13.7; LRMS m/e (rel int) EI 270 (9), 227 (8), 91 (15), 57 (100); CI 327 (2), 271 (100), 253 (13); HRMS (EI) m/e calcd for $C_{21}H_{26}O_3$ (M^+) 326.1882, found 326.1900.

General Procedure for the Thermolysis of Substituted Cyclobutenones. 2-*tert*-Butoxy-3,5-di-*n*-butylcyclohexa-2,5-diene-1,4-dione (9a). A solution of **8a** (81.1 mg, 0.28 mmol) in dry xylene (70 mL) was heated at reflux for 5 min and then allowed to cool to room temperature. After evaporation of the solvent the crude product was purified by flash column chromatography (hexanes/ethyl acetate, 8:2) to give **9a** as a yellow oil (72.4 mg, 89%): TLC (hexanes/ethyl acetate, 8:2) R_f 0.76; IR (neat, cm^{-1}) 2940, 1660, 1595, 1370, 1140, 890, 840; ^1H NMR ($CDCl_3$) δ 6.40 (s, 1 H), 2.37–2.50 (m, 4 H), 1.36–1.58 (m, 8 H), 1.41 (s, 9 H), 0.89–0.96 (m, 6 H); LRMS m/e (rel int) EI 292 (1), 236 (31), 193 (54), 151 (28), 57 (100); CI 279 (1), 237 (100), 195 (1); HRMS (EI) m/e calcd for $C_{14}H_{20}O_3$ (M^+ – t-Bu) 236.1412, found 236.1404.

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 74.06; H, 9.79.

2-*tert*-Butoxy-3-*n*-butyl-5-(phenylmethyl)cyclohexa-2,5-diene-1,4-dione (9b). Thermolysis in refluxing xylene gave **9b** as yellow crystals (40.5 mg, 82%): mp 54–55 °C; TLC (hexanes/ethyl acetate, 7:3) R_f 0.75; IR ($CHCl_3$, cm^{-1}) 2960, 1650, 1600, 1370, 1140; ^1H NMR ($CDCl_3$) δ 7.06–7.35 (m, 5 H), 6.17 (t, J = 1.5 Hz, 1 H), 3.73 (d, J = 1.5 Hz, 2 H), 2.48 (t, J = 7 Hz, 2 H), 1.30–1.60 (m, 2 H), 1.40 (s, 9 H), 0.92 (t, J = 7 Hz, 3 H); LRMS m/e (rel int) EI 270 (13), 227 (17), 91 (15), 57 (100); CI 311 (1), 271 (100), 195 (7); HRMS (EI) m/e calcd for $C_{21}H_{26}O_3$ (M^+) 326.1882, found 326.1895.

Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.23; H, 7.82.

General Procedure for the Cleavage of *tert*-Butyl Ethers. 3,5-Di-*n*-butyl-2-hydroxycyclohexa-2,5-diene-1,4-dione (10a). The protected quinone **9a** (24.4 mg, 0.084 mmol) was stirred in TFA (4 mL) for 10 min at 0 °C. The resulting orange mixture was evaporated with toluene (2 × 10 mL). Purification by flash column chromatography (hexanes/ethyl acetate, 8:2) gave **10a** as yellow crystals (17.6 mg, 89%): mp 33–34 °C; TLC (hexanes/ethyl acetate, 8:2) R_f 0.59; IR (neat, cm^{-1}) 3380, 2980, 1640, 1385, 1220, 960, 880; ^1H NMR ($CDCl_3$) δ 6.84 (s, 1 H), 6.49 (t, J = 1.5 Hz, 1 H), 2.41–2.48 (m, 4 H), 1.30–1.51 (m, 8 H), 0.93 (t, J = 7.0 Hz, 3 H) 0.91 (t, J = 7.0 Hz, 3 H); LRMS m/e (rel int) EI 236 (20), 193 (53), 151 (62), 123 (21), 55 (100); CI 293 (1), 279 (1), 237 (100), 195 (1); HRMS (EI) m/e calcd for $C_{14}H_{20}O_3$ (M^+) 236.1412, found 236.1411.

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.95; H, 8.54.

3-*n*-Butyl-2-hydroxy-5-(phenylmethyl)cyclohexa-2,5-diene-1,4-dione (10b). Deprotection of **9b** with TFA gave **10b** as yellow crystals (5.5 mg, 85%): mp 83.5–84.5 °C; TLC (hexanes/ethyl acetate, 8:2) R_f 0.56; IR ($CHCl_3$, cm^{-1}) 3400, 2940, 1645, 1390; ^1H NMR ($CDCl_3$) δ 7.22–7.36 (m, 5 H), 6.82 (br s, 1 H), 6.27 (t, J = 1.1 Hz, 2 H), 3.78 (s, 2 H), 2.44 (t, J = 7 Hz, 2 H), 1.30–1.48 (m, 4 H), 0.92 (t, J = 7 Hz, 3 H); LRMS m/e (rel int) EI 270 (47), 227 (96), 150 (29), 91 (100); HRMS (EI) m/e calcd for $C_{17}H_{18}O_3$ (M^+) 270.1256, found 270.1276.

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.49; H, 6.66.

2,3-Di-*tert*-butoxy-4-(1-hexynyl)-4-hydroxycyclobut-2-en-1-one (11a). The general procedure for **8a** was followed using 1-lithiohexyne, which, upon purification, gave **11a** as colorless crystals (110 mg, 24%, 54% based on recovered starting material): mp 97–98 °C; TLC (hexanes/ethyl acetate, 8:2) R_f 0.39; IR ($CHCl_3$, cm^{-1}) 3580, 2940, 2240, 1770, 1610, 1360, 1150, 1010, 960; ^1H NMR ($CDCl_3$) δ 2.56 (s, 1 H), 2.25 (t, J = 7.1 Hz, 2 H), 1.33–1.55 (m, 4 H), 1.55 (s, 9 H), 1.48 (s, 9 H), 0.90 (t, J = 7.1 Hz, 3 H); LRMS m/e (rel int) EI 196 (20), 155 (19), 126 (20), 57 (100); CI 197 (100); HRMS (CI) m/e calcd for $C_{14}H_{21}O_4$ (M^+ – t-Bu + 1) 253.1440, found 253.1442.

Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.55; H, 9.16.

2,3-Di-*tert*-butoxy-4-hydroxy-4-(3-phenyl-1-propynyl)-cyclobut-2-en-1-one (11b). The general procedure described for **8a** was followed using 1-lithio-3-phenylprop-1-yne as the nucleophile, which, upon purification, gave **11b** as colorless crystals (233 mg, 43%, 70% based on recovered starting material): mp 101–102 °C; TLC (hexanes/ethyl acetate, 8:2) R_f 0.29; IR ($CHCl_3$, cm^{-1}) 3580, 2985, 2240, 1770, 1610, 1375, 1155, 1010, 920; ^1H NMR ($CDCl_3$) δ 7.22–7.33 (m, 5 H), 3.69 (s, 2 H), 2.66 (s, 1 H), 1.49 (s, 9 H), 1.56 (s, 9 H); LRMS m/e (rel int) EI 230 (16), 149 (19), 91 (3), 57 (100); CI 287 (17), 269 (3), 231 (2), 213 (100), 157 (9); HRMS (CI) m/e calcd for $C_{17}H_{19}O_4$ (M^+ – t-Bu + 1) 287.1283, found 287.1259.

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.61; H, 7.95.

5-*n*-Butyl-2,3-di-*tert*-butoxycyclohexa-2,5-diene-1,4-dione (12a). Thermolysis of **11a** in refluxing xylene for 1.5 h gave, after purification by flash column chromatography (hexanes/ethyl acetate, 9:1), **12a** as a yellow oil (174.1 mg, 80%): TLC (hexanes/ethyl acetate, 9:1) R_f 0.50; IR (neat, cm^{-1}) 3540, 2970, 1770, 1660, 1590, 1460, 1370, 1140, 840; ^1H NMR ($CDCl_3$) δ 6.42 (s, 1 H), 2.41 (t, J = 7.1 Hz, 2 H), 1.25–1.55 (m, 4 H), 1.35 (s, 18 H), 0.91 (t, J = 7.2 Hz, 3 H); LRMS m/e (rel int) 196 (2), 57 (100); CI 253 (8), 197 (1), 179 (100); HRMS (CI) m/e calcd for $C_{18}H_{29}O_4$ (M^+ + 1) 309.2066, found 309.2058.

Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.35; H, 9.33.

2,3-Di-*tert*-butoxy-5-(phenylmethyl)cyclohexa-2,5-diene-1,4-dione (12b). Thermolysis of **11b** in refluxing xylene for 3 h gave, after purification by flash column chromatography (hexanes/ethyl acetate 8:2), **12b** as a yellow oil (79.8 mg, 77%): TLC (hexanes/ethyl acetate, 8:2) R_f 0.66; IR (neat, cm^{-1}) 2980, 1665, 1590, 1395, 1370, 1320, 1150, 950, 850; ^1H NMR ($CDCl_3$) δ 7.17–7.35 (m, 5 H), 6.23 (t, J = 1.6 Hz, 1 H), 3.74 (d, J = 1.5 Hz, 2 H), 1.35 (s, 9 H), 1.36 (s, 9 H); LRMS m/e (rel int) 230 (42), 57 (100); CI 233 (29), 231 (100); HRMS (EI) m/e calcd for $C_{13}H_{10}O_4$ (M^+ – 2t-Bu) 230.0579, found 230.0580.

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.54; H, 7.93.

5-*n*-Butyl-2,3-dihydroxycyclohexa-2,5-diene-1,4-dione (13a). Deprotection of **12a** gave **13a** as a crude product: brown semisolid (36.8 mg, 92%); TLC (chloroform/methanol, 9:1) R_f 0–0.50; IR ($CHCl_3$, cm^{-1}) 3580, 2985, 2240, 1770, 1610, 1375, 1155, 1010, 920; ^1H NMR (DMSO-d_6) δ 6.35 (s, 1 H), 2.35 (m, 2 H), 1.15–1.55 (m, 4 H), 0.78–0.97 (m, 3 H); LRMS m/e (rel int) EI 196 (11), 168 (18), 155 (23), 126 (100); CI 197 (100), 183 (3), 155 (4); HRMS (EI) m/e calcd for $C_{10}H_{12}O_4$ (M^+) 196.0735, found 196.0733.

2,3-Dihydroxy-5-(phenylmethyl)cyclohexa-2,5-diene-1,4-dione (13b). Deprotection of **12b** gave **13b** as a crude product: red-brown solid (32.6 mg, 88%); mp 138–139 °C; TLC (chloroform/methanol, 9:1) R_f 0–0.50; ^1H NMR (DMSO-d_6) δ 7.12–7.38 (m, 5 H), 6.23 (s, 1 H), 3.85 (br s, 1 H), 3.71 (s, 2 H); LRMS m/e (rel int) EI 230 (3), 115 (100), 91 (68); CI 233 (100), 231 (85), 155 (49), 149 (24); HRMS (EI) m/e calcd for $C_{13}H_{10}O_4$ (M^+) 230.0579, found 230.0578.

General Procedure for the Reductive Acetylation of Hydroxyquinones. 5-*n*-Butyl-1,2,3,4-tetraacetoxybenzene (14a).

Quinone **13a** (16.8 mg, 0.046 mmol) was dissolved in acetic anhydride (10 mL), and then zinc dust (0.5 g, 7.7 mmol) was added. After being stirred for 45 min the mixture was filtered, and the residue was washed with toluene. The filtrate was evaporated three times with toluene. The resulting residue was purified by flash column chromatography (hexane/ethyl acetate, 1:1) to give **14a** as colorless crystals (12.6 mg, 40%): mp 124–125 °C; TLC (hexanes/ethyl acetate, 1:1) R_f 0.56; IR ($CHCl_3$, cm^{-1}) 3020, 2980, 1790, 1490, 1450, 1375, 1180, 1100, 1040, 1020, 910; ^1H NMR ($CDCl_3$) δ 7.02 (s, 1 H), 2.49 (t, J = 7.5 Hz, 2 H), 2.29 (s, 3 H), 2.26 (s, 6 H), 2.25 (s, 3 H), 1.21–1.60 (m, 4 H), 0.91 (t, J = 7.2 Hz, 3 H); LRMS m/e (rel int) EI 366 (1), 282 (17), 240 (39), 198 (100), 155 (36); CI 367 (15), 325 (35), 307 (100), 283 (8); HRMS (CI) m/e calcd for $C_{18}H_{23}O_8$ (M^+ + 1) 367.1392, found 367.1364.

Anal. Calcd for $C_{18}H_{22}O_8$: C, 59.01; H, 6.05. Found: C, 59.20; H, 5.92.

5-(Phenylmethyl)-1,2,3,4-tetraacetoxybenzene (14b). Quinone **13b** was reduced and acetylated as above to give **14b** as colorless crystals (23.1 mg, 62%): mp 149–150 °C; TLC (hexanes/ethyl acetate, 1:1) R_f 0.47; IR ($CHCl_3$, cm^{-1}) 3020, 1790, 1490, 1450, 1375, 1190, 1050, 960, 700; ^1H NMR ($CDCl_3$) δ 7.15–7.30 (m, 5 H), 6.85 (s, 1 H), 3.87 (s, 2 H), 2.20 (s, 3 H), 2.22 (s, 3 H), 2.25 (s, 3 H), 2.26 (s, 3 H); LRMS m/e (rel int) EI 316 (13), 274 (31), 232 (100), 154 (24), 91 (19); CI 401 (37), 359 (51), 341 (100); HRMS (CI) m/e calcd for $C_{21}H_{21}O_8$ (M^+ + 1) 401.1236, found 401.1227.

Anal. Calcd for $C_{21}H_{20}O_8$: C, 63.00; H, 5.04. Found: C, 62.99; H, 5.17.

3-*tert*-Butoxy-2-*n*-butyl-4-(1-*n*-butylethenyl)-4-hydroxycyclobut-2-en-1-one (15). The addition of 2-lithio-1-hexene to **24** gave **15** as a colorless oil (320 mg, 53%, 91% based on recovered starting material): TLC (hexanes/ethyl acetate, 8:2) R_f 0.41; IR (neat, cm^{-1}) 3350, 2960, 1745, 1600, 1370, 1160, 910; ^1H NMR ($CDCl_3$) δ 5.35 (br s, 1 H), 5.07 (br s, 1 H), 2.83 s, 1 H), 2.13–2.20 (m, 2 H), 1.95–2.01 (m, 2 H), 1.27–1.59 (m, 8 H), 1.50 (s, 9 H), 0.81–0.94 (m, 6 H); LRMS m/e (rel int) EI 238 (3), 195 (8), 139 (15), 111 (5), 57 (100); CI 239 (100), 221 (49); HRMS (CI) m/e calcd for $C_{18}H_{31}O_3$ (M^+ + 1) 295.2273, found 295.2254.

Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.38; H, 10.34.

3-*tert*-Butoxy-2,5-di-*n*-butylcyclohexa-2,5-diene-1,4-dione (16). After thermolysis of **15** in refluxing xylene for 15 min the crude product was dissolved in dry benzene (30 mL) and oxidized with Ag_2O (940 mg, 4.05 mmol) in the presence of K_2CO_3 (560 mg, 3.64 mmol) under argon at room temperature. After 2 h the mixture was filtered through Celite and evaporated, and the crude product was purified by flash column chromatography (hexanes/ethyl acetate, 9:1) to give **16** as a yellow oil (96.2 mg, 96%): TLC (hexanes/ethyl acetate, 9:1) R_f 0.50; IR (neat, cm^{-1}) 2960, 1660, 1470, 1370, 1160, 1140, 940, 820, 730; ^1H NMR ($CDCl_3$) δ 6.45 (t, J = 1.4 Hz, 1 H), 2.36–2.48 (m, 4 H), 1.33–1.46 (m, 8 H), 1.30 (s, 9 H), 0.87–0.94 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 188.8, 185.6, 154.6, 147.8, 137.6, 132.3, 83.7, 30.7, 29.9, 29.4, 28.6, 24.1, 23.0, 22.3, 13.8; LRMS m/e (rel int) EI 292 (1), 236 (2), 194 (5), 152 (8), 123 (4), 57 (100); CI 293 (1), 237 (100); HRMS (CI) m/e calcd for $C_{18}H_{29}O_3$ (M^+ + 1) 293.2116, found 293.2090.

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 74.13; H, 9.72.

2,5-Di-*n*-butyl-2-hydroxycyclohexa-2,5-diene-1,4-dione (17). Deprotection of **16** and purification by flash column chromatography (hexanes/ethyl acetate, 8:2) gave **17** as orange crystals (45.1 mg, 93%): mp 89–90 °C; TLC (hexanes/ethyl acetate, 8:2) R_f 0.60; IR ($CHCl_3$, cm^{-1}) 3420, 2960, 1660, 1640, 1350, 1200, 1140, 1020; ^1H NMR ($CDCl_3$) δ 6.88 (s, 1 H), 6.45 (t, J = 1.3 Hz, 1 H), 2.40–2.46 (m, 4 H), 1.29–1.53 (m, 8 H), 0.88–0.96 (m, 6 H); LRMS m/e (rel int) EI 236 (31), 194 (48), 152 (100), 123 (23), 95 (9); CI 237 (100); HRMS (EI) m/e calcd for $C_{14}H_{20}O_3$ (M^+ + 1) 236.1412, found 236.1409.

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.44; H, 8.80.

4-(4-Chlorophenyl)-2,3-di-*tert*-butoxy-4-hydroxycyclobut-2-en-1-one (18). The addition of 4-lithiochlorobenzene to **2** using the general procedure described for **8a** gave **18** as colorless crystals (480 mg, 92%): mp 116–117 °C; TLC (hexanes/ethyl acetate, 8:2) R_f 0.38; IR ($CHCl_3$, cm^{-1}) 3350, 2980, 1765, 1605, 1370, 1360, 1155, 935, and 840; ^1H NMR ($CDCl_3$) δ 7.42 (d, J = 7.5 Hz, 2 H), 7.31 (d, J = 7.5 Hz, 2 H), 2.92 (br s, 1 H), 1.52 (s, 9 H), 1.56 (s, 9 H); LRMS m/e (rel int) EI 282 (1), 226 (6), 208 (1), 191 (37), 57 (100); CI 283 (14), 265 (9), 209 (100); HRMS (CI) m/e calcd for $C_{18}H_{24}ClO_4$ (M^+ + 1) 339.1353, found 339.1363.

Anal. Calcd for $C_{18}H_{23}ClO_4$: C, 63.81; H, 6.84. Found: C, 63.66; H, 6.87.

6-Chloro-2,3-di-*tert*-butoxy-1,4-naphthoquinone (19) and 3-*tert*-Butoxy-4-(4-chlorophenyl)cyclobut-3-ene-1,2-dione (20). (a) Compound **18** (140 mg, 0.41 mmol) was heated at reflux in xylene (100 mL) under argon for 1 h. After being allowed to cool to room temperature the solvent was evaporated, and the residue was purified by flash column chromatography (hexanes/ethyl acetate, 9:1) to give two fractions. (1) **19** as a yellow oil (11.3 mg, 8%): TLC (hexanes/ethyl acetate, 8:2) R_f 0.63; IR (neat, cm^{-1}) 2990, 1670, 1590, 1520, 1370, 1310, 1195, 1160, 1140, 995, 905, 830; ^1H NMR ($CDCl_3$) δ 8.04 (d, J = 1.9 Hz, 1 H), 8.01 (d, J = 8.1 Hz, 1 H), 7.65 (dd, J = 1.9 Hz, J = 8.1 Hz, 1 H), 1.43 (s, 18 H); LRMS m/e (rel int) EI 280 (1), 265 (1), 224 (24), 196 (11), 57 (100); CI 227 (33), 225 (100); HRMS (CI) m/e calcd for $C_{10}H_6ClO_4$ (M^+ – 2t-Bu + 1) 224.9939, found 224.9954. (2) **20** as colorless crystals (81.8 mg, 75%); mp 238–240 °C dec; TLC (hexanes/ethyl acetate, 8:2) R_f 0.47; IR ($CHCl_3$, cm^{-1}) 2990, 1780, 1755, 1600, 1580, 1390, 1155, 1095, 845; ^1H NMR ($CDCl_3$) δ 8.04 (d, J = 9 Hz, 2 H), 7.47 (d, J = 9 Hz, 2 H), 1.72 (s, 9 H); LRMS m/e (rel int) EI 264 (1), 208 (1), 152 (4), 123 (6), 57 (100); CI 265 (13), 209 (100); HRMS (EI) m/e calcd for $C_{14}H_{14}ClO_3$ (M^+ + 1) 265.0618, found 265.0631.

Anal. Calcd for $C_{14}H_{13}ClO_3$: C, 63.52; H, 4.95. Found: C, 63.34; H, 4.93.

(b) Compound **18** (301.5 mg, 0.89 mmol) and "Proton Sponge" [1,8-bis(dimethylamino)naphthalene, 210 mg, 0.98 mmol] were dissolved in xylene (130 mL) and heated at reflux for 9.5 h. After evaporation of the solvent the crude mixture was dissolved in dry benzene (30 mL) and oxidized with Ag_2O (940 mg, 4.05 mmol) in the presence of K_2CO_3 (560 mg, 3.64 mmol) under argon at room temperature. After 2 h the solution was filtered through Celite, and evaporation of the filtrate gave a crude product, which was purified as above to give three fractions: (1) **19** (190.2 mg, 57%, 88% based on recovered starting material, (2) **20** (less than 5%), (3) **18** (108 mg, 36%).

6-Chloro-2,3-dihydroxy-1,4-naphthoquinone (21). Trifluoroacetic acid (5 mL) was slowly added to **19** (92.5 mg, 0.27 mmol) at 0 °C and stirred for 15 min at room temperature. The reaction mixture was evaporated with toluene (2 × 10 mL) to give crude **21** as a red solid (61 mg, quant): TLC (chloroform/methanol, 9:1) R_f 0.10–0.38; IR (neat, cm^{-1}) 3350, 1640, 1580, 1430, 1330, 1310, 1260, 900, 850, 740; ^1H NMR (acetone-d_6) δ 9.00 (br s, 2 H), 8.13 (d, J = 8.2 Hz, 1 H), 8.04 (d, J = 2.1 Hz, 1 H), 7.93 (dd, J = 8.2 Hz, J = 2.1 Hz, 1 H); LRMS m/e (rel int) EI 224 (13), 196 (24), 149 (16), 105 (39), 57 (100); CI 227 (33), 225 (100), 197 (4); HRMS (EI) m/e calcd for $C_{10}H_5ClO_4$ (M^+) 223.9876, found 223.9873.

1,4-Diacetoxy-2,3-di-*tert*-butoxy-6-chloronaphthalene (22). Quinone **19** (47.5 mg, 0.14 mmol) was reduced in dry benzene (20 mL) with hydrogen in the presence of 5% Pd/C (20 mg). After 10 min the yellow color disappeared and pyridine (5 mL), acetic anhydride (5 mL), and DMAP (5 mg, 0.04 mmol) were added. The mixture was stirred for 1 h under H_2 atmosphere. After filtering the solvents were evaporated and the crude product purified by flash column chromatography (hexanes/ethyl acetate, 9:1) to give **22** as a colorless solid (43.9 mg, 74%): mp 159–160 °C; TLC (hexanes/ethyl acetate, 9:1) R_f 0.40; IR ($CHCl_3$, cm^{-1}) 2980, 1770, 1595, 1430, 1395, 1370, 1190, 1155, 1045, 990, 915, 870, 845; ^1H NMR ($CDCl_3$) δ 7.72 (d, J = 9 Hz, 1 H), 7.69 (d, J = 9 Hz, 1 H), 7.36 (dd, J = 9 Hz, J = 2 Hz, 1 H), 2.44 (s, 3 H), 2.43 (s, 3 H), 1.36 (s, 18 H); LRMS m/e (rel int) EI 366 (1), 310 (8), 268 (34), 226 (77), 57 (100); CI 311 (17), 269 (100), 251 (11), 209 (27); HRMS (CI) m/e calcd for $C_{14}H_{11}ClO_6$ (M^+ – 2t-Bu + 1) 311.0322, found 311.0317.

Anal. Calcd for $C_{22}H_{27}ClO_6$: C, 62.48; H, 6.44. Found: C, 62.77; H, 6.59.

6-Chloro-1,2,3,4-tetraacetoxynaphthalene (23). For proper characterization **21** was reduced and acetylated. The general procedure gave very poor yields of **23**. By using the procedure described for **22** compound **23** was obtained in good yield as colorless crystals (72.4 mg, 70%): mp 185–186 °C (lit. mp 184–185

°C); TLC (hexanes/ethyl acetate, 6:4) R_f 0.35; IR ($CHCl_3$, cm^{-1}) 3010, 1780, 1600, 1430, 1400, 1370, 1350, 1180, 1110, 1040, 870, 720; ^1H NMR ($CDCl_3$) δ 7.79 (d, J = 1.9 Hz, 1 H), 7.77 (d, J = 8.9 Hz, 1 H), 7.48 (dd, J = 8.9 Hz, 1.9 Hz, 1 H), 2.32 (s, 3 H), 2.43 (s, 3 H), 2.45 (s, 3 H); LRMS m/e (rel intensity) CI 395 (47), 353 (21), 335 (100), 293 (27), 251 (42); HRMS (EI) m/e calcd for $C_{18}H_{15}ClO_8$ (M^+) 394.0455, found 394.0452.

Anal. Calcd for $C_{18}H_{15}ClO_8$: C, 54.77; H, 3.83. Found: C, 54.47; H, 3.74.

3-*tert*-Butoxy-4-*n*-butylcyclobut-3-ene-1,2-dione (24). *n*-Butyllithium (3.5 mL of a 1.6 M solution in hexane, 5.6 mmol) was added to a solution of **2** (1.00 g, 4.42 mmol) in THF (50 mL) at −78 °C over a 3-min period. After 10 min trifluoroacetic anhydride (0.8 mL, 4.7 mmol) was added slowly. After stirring for an additional 10 min the reaction was quenched with saturated aqueous $NaHCO_3$ and allowed to warm to room temperature. The mixture was extracted with ether (2 × 40 mL), and the organic layers were combined and dried over $MgSO_4$. Removal of the solvents gave a light yellow oil, which was purified by flash column chromatography (hexanes/ethyl acetate, 8:2) to give **24** as a colorless oil (670 mg, 72%): TLC (hexanes/ethyl acetate, 8:2) R_f 0.54; IR (neat, cm^{-1}) 2960, 1795, 1755, 1585, 1380, 1155, 1000, 845; ^1H NMR ($CDCl_3$) δ 2.58 (t, J = 7.4 Hz, 2 H), 1.30–1.48 (m, 2 H), 1.60 (s, 9 H), 1.62–1.72 (t, J = 7.3 Hz, 2 H); LRMS m/e (rel intensity) CI 211 (27), 155 (100); HRMS (EI) m/e calcd for $C_{12}H_{18}O_3$ (M^+) 210.1256, found 210.1262.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.80; H, 8.68.

4-*n*-Butyl-3-hydroxycyclobut-3-ene-1,2-dione (25). A solution of **24** (141 mg, 0.67 mmol) in trifluoroacetic acid (8 mL) was stirred at 0 °C for 10 min and then for 10 min at room temperature. The mixture was evaporated with toluene (2 × 10 mL), and the residue was purified by flash column chromatography (toluene/acetone, 1:3) to give **25** as a light brown oil (91.3 mg, 88%): TLC (toluene/acetone, 1:3) R_f 0.10–0.27; IR (neat, cm^{-1}) 2930, 2150–2750 (broad), 1800, 1735, 1450, 1080, 900, 725; ^1H NMR ($CDCl_3$) δ 9.62 (br s, 1 H), 2.63 (t, J = 7.3 Hz, 2 H), 1.32–1.75 (m, 4 H), 0.93 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 201.0 (2), 194.6, 183.3, 27.7, 24.7, 22.7, 13.6; LRMS m/e (rel int) EI 154 (4), 126 (21), 97 (18), 70 (29), 55 (100); CI 155 (100); HRMS (CI) m/e calcd for $C_8H_{11}O_3$ (M^+ + 1) 155.0708, found 155.0724.

3-*tert*-Butoxy-4-methylcyclobut-3-ene-1,2-dione (26). A solution of MeLi (9.3 mL of a 1.5 M solution in ether, 14.0 mmol) in 50 mL of THF, precooled to −78 °C, was added via cannula to a solution of 3.00 g (13.3 mmol) of **2** in 200 mL of THF, precooled to −78 °C, over a period of 15 min. The mixture was stirred at −78 °C for 15 min, and 2.0 mL of TFAA was introduced via a syringe. The resulting solution was treated according to the general procedure. The crude product was subjected to flash column chromatography (hexanes/ethyl acetate, 3:1), yielding 1.84 g (82%) of the title compound as a white solid: mp 72–73 °C; TLC (hexanes/ethyl acetate, 3:1) R_f 0.23; IR ($CDCl_3$, cm^{-1}) 2995, 2960, 1805, 1750, 1585, 1405, 1355, 1155; ^1H NMR ($CDCl_3$) δ 2.18 (s, 3 H), 1.60 (s, 9 H); LRMS m/e (rel int) CI MS m/e (rel int) CI 169 (M^+ + 1, 74), 113 (100).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.58; H, 6.89.

3-*tert*-Butoxy-4-ethynyl-4-hydroxy-2-methylcyclobut-2-en-1-one (27a). Acetylene was condensed for 30 s into 50 mL of THF at −78 °C. *n*-BuLi (1.7 mL of a 1.5 M solution in hexanes, 2.6 mmol) was added over a period of 2 min, and the resulting solution was stirred at −78 °C for 10 min. A solution of 350 mg (2.08 mmol) of **26** in 30 mL of THF, precooled to −78 °C, was transferred via cannula to the lithium acetylide over a period of 10 min. The resulting solution was stirred at −78 °C for 10 min, and the alkoxide was quenched with 20 mL of 5% NH_4Cl (aq). Workup according to the general procedure followed by flash column chromatography (hexanes/ethyl acetate, 3:1) gave 226 mg (56%) of the title compound as a white solid. Also, 71 mg (20%) of the starting dione, **26**, was recovered. Compound **27a**: mp 86–87 °C dec; TLC (hexane/ethyl acetate, 3:1) R_f 0.09; IR ($CDCl_3$, cm^{-1}) 3580, 3320, 2295, 2250, 1770, 1605, 1400, 1355, 1160; ^1H NMR ($CDCl_3$) δ 3.70 (s, 1 H), 2.80 (s, 1 H), 1.71 (s, 3 H), 1.59 (s, 9 H); LRMS m/e (rel int) EI 138 (M^+ − *t*-Bu, 16), 57 (100). CI 195 (M^+ + 1, 1), 139 (100).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.02; H, 7.15.

3-*tert*-Butoxy-4-hydroxy-2-methyl-4-[(trimethylsilyl)ethynyl]cyclobut-2-en-1-one (27b). Via the general procedure, the lithium salt of (trimethylsilyl)ethyne was added to a solution of **26** in THF. The crude product was purified by flash column chromatography (hexanes/ethyl acetate, 3:1) to furnish 560 mg (67%) of **27b** as a white solid: mp 77–78 °C; TLC (hexanes/ethyl acetate, 3:1) R_f 0.14; IR ($CDCl_3$, cm^{-1}) 3580, 2980, 2260, 1770, 1615, 1400, 1350, 1260, 1160, 850; ^1H NMR ($CDCl_3$) δ 3.17 (s, 1 H), 1.69 (s, 3 H), 1.59 (s, 9 H), 0.16 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 187.90, 179.53, 127.41, 100.01, 95.16, 85.70, 84.58, 28.91 (3 C), 7.24, −0.44 (3 C); LRMS m/e (rel int) EI 210 (M^+ − *t*-Bu, 29), 195 (19), 136 (22), 121 (30), 75 (100), 57 (100); CI 267 (M^+ + 1, 2), 229 (25), 211 (100).

Anal. Calcd for $C_{14}H_{22}O_3Si$: C, 63.12; H, 8.32. Found: C, 63.10; H, 8.42.

3-*tert*-Butoxy-4-ethynyl-2-methyl-4-((trimethylsilyl)oxy)cyclobut-2-en-1-one (27c). The procedure for compound **27a** was followed, but the generated alkoxide was quenched with 0.8 mL of trimethylsilyl chloride. The mixture was allowed to reach room temperature, and the solvent was evaporated. Flash chromatography through a short column of silica gel (hexanes/ethyl acetate, 5:1) gave 440 mg (80%) of **27c** as a light yellow oil: TLC (hexanes/ethyl acetate, 5:1) R_f 0.26; IR ($CDCl_3$, cm^{-1}) 3315, 2990, 1770, 1605, 1390, 1350, 1255, 1155, 1120, 935, 850. ^1H NMR ($CDCl_3$) δ 2.77 (s, 1 H), 1.71 (s, 3 H), 1.56 (s, 9 H), 0.23 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 187.14, 179.10, 125.31, 85.06, 84.92, 80.12, 77.62, 28.84 (3 C), 7.90, 1.23 (3 C); LRMS m/e (rel int) CI 267 (M^+ + 1) (1), 211 (100), 121 (24); HRMS (CI) m/e calcd for $C_{10}H_{15}O_3Si$ (M^+ − tBu + 1) 211.0790, found 211.0760.

2-*tert*-Butoxy-3-methylcyclohexa-2,5-diene-1,4-dione (28a). This compound was prepared as described in the general procedure, using compound **27a** as starting material, acetonitrile as solvent, and a reaction time of 2 h. Purification by flash column chromatography (hexanes/ethyl acetate, 5:1) gave 220 mg (79%) of **28a** as an orange oil: TLC (hexane/ethyl acetate, 5:1) R_f 0.26; IR ($CDCl_3$, cm^{-1}) 2990, 1660, 1595, 1395–75, 1315, 1150, 1085; ^1H NMR ($CDCl_3$) δ 6.71 (d, J = 9.9 Hz, 1 H), 6.64 (d, J = 9.9 Hz, 1 H), 1.99 (s, 3 H), 1.40 (s, 9 H); LRMS m/e (rel int) CI 139 (M^+ + 1 − *t*-Bu, 100), 117 (83).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.05; H, 7.35.

2-*tert*-Butoxy-3-methyl-5-(trimethylsilyl)cyclohexa-2,5-diene-1,4-dione (28b). Via the general procedure, compound **27b** was heated in refluxing acetonitrile for 2 h. The crude product was purified by flash column chromatography, giving 380 mg (69%) of **28b** as a yellow oil, which solidified upon cooling: mp 36–38 °C; TLC (hexane/ethyl acetate, 9:1) R_f 0.36; IR ($CDCl_3$, cm^{-1}) 2995, 1665, 1635, 1585, 1155, 1110, 850; ^1H NMR ($CDCl_3$) δ 6.75 (s, 1 H), 1.97 (s, 3 H), 1.39 (s, 9 H), 0.24 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 192.32, 184.33, 154.45, 151.94, 142.22, 135.92, 84.21, 29.45 (3 C), 10.67, −1.63 (3 C); LRMS m/e (rel int) EI 266 (M^+, 2), 195 (67), 57 (100).

Anal. Calcd for $C_{14}H_{22}O_3Si$: C, 63.12; H, 8.32. Found: C, 63.10; H, 8.35.

3-*tert*-Butoxy-2-methyl-5-(trimethylsilyl)cyclohexa-2,5-diene-1,4-dione (28c). Compound **27c** was thermolyzed according to the general procedure in benzene for 2 h. Flash column chromatography (hexanes/ethyl acetate, 9:1) gave 305 mg (68%) of **28c** as an orange oil: TLC (hexane/ethyl acetate, 9:1) R_f 0.39; IR ($CDCl_3$, cm^{-1}) 2995, 1645, 1580, 1395–1370, 1255, 1150, 1115, 850; ^1H NMR ($CDCl_3$) δ 6.82 (s, 1 H), 1.96 (s, 3 H), 1.38 (s, 9 H), 0.23 (s, 9 H); LRMS m/e (rel int) CI 267 (M^+ + 1, 1) 211 (100).

Anal. Calcd for $C_{14}H_{22}O_3Si$: C, 63.12; H, 8.32. Found: C, 63.15; H, 8.32.

2-*tert*-Butoxy-5,6-epoxy-3-methylcyclohex-2-ene-1,4-dione (29). A mixture consisting of **28c** (137 mg, 0.52 mmol), *tert*-butyl hydroperoxide (0.19 mL of a 3 M solution in 2,2,4-trimethylpentane, 0.57 mmol), and a 1:1 solution of absolute ethanol/1,4-dioxane (4 mL) was cooled to 0–5 °C. Triton B (40 wt % solution of benzyltrimethylammonium hydroxide in methanol) (45 μL, 0.13 mmol) was added, and the mixture was stirred at room temperature for 1 h. The reaction mixture was filtered with suction through a pad of florisil (elution with ethyl acetate). Evaporation and subsequent flash column chromatography

(hexanes/ethyl acetate, 5:1) gave 76.0 mg (70%) of **29** as a light yellow oil: TLC (hexane/ethyl acetate, 5:1) R_f 0.23; IR ($CDCl_3$, cm^{-1}) 2990, 1710, 1685, 1600, 1380, 1350, 1300, 1150, 1135, 985, 875; ^1H NMR ($CDCl_3$) δ 3.86 (d, J = 4.0 Hz, 1 H), 3.81 (d, J = 4.0 Hz, 1 H), 1.91 (s, 3 H), 1.36 (s, 9 H); LRMS m/e (rel int) CI 155 ($M^+ + 1 - t$-Bu, 25), 57 (100).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 63.07; H, 6.68.

Epoxidation of compound **28b** using the same conditions as above yielded **29** in 68%. When compound **28a** was used as starting material, the epoxidation gave **29** in 43% yield. In this particular case, it was found that a reaction time of only 10 min improved the isolated yield of **29** to 59%.

Isolation of the Silyl Epoxide from the Epoxidation of 28b and Desilylation with Triton B. The same procedure as for compound **29** was used, but the reaction mixture was filtered after 10 min. Flash column chromatography (hexanes/ethyl acetate, 9:1) gave 47% of **2-*tert*-butoxy-5,6-epoxy-3-methyl-5-(trimethylsilyl)cyclohex-2-ene-1,4-dione** as a light yellow oil: TLC (hexane/ethyl acetate, 9:1) R_f 0.34; IR ($CDCl_3$, cm^{-1}) 2995, 1700, 1670, 1605, 1375, 1330, 1255, 1140, 1050, 845, 830; ^1H NMR ($CDCl_3$) δ 3.62 (s, 1 H), 1.88 (s, 3 H), 1.37 (s, 9 H), 0.19 (s, 9 H); LRMS m/e (rel int) CI 227 ($M^+ - t$-Bu + 1, 100), 211 (21). Anal. Calcd for $C_{14}H_{22}O_4Si$: C, 59.54; H, 7.85. Found: C, 59.77; H, 8.07.

Further elution gave also 32% of compound **29**. The desilylation was performed as follows: the silyl epoxide (55.0 mg, 0.195 mmol) was dissolved in 1.6 mL of absolute ethanol/1,4-dioxane (1:1), and the mixture cooled to 0–5 °C. Triton B (40 wt % solution of benzyltrimethylammonium hydroxide in methanol) (19 μL, 0.055 mmol) was added, and the mixture was stirred at room temperature for 15 min. Filtration with suction through a pad of florisil (elution with ethyl acetate), followed by flash column chromatography (hexanes/ethyl acetate, 5:1), gave 29.5 mg (72%) of a light yellow oil, with spectral properties that were identical with those for compound **29**.

(±)-Terreic Acid (30). Compound **29** (67.0 mg, 0.32 mmol) was deprotected according to the general procedure. Purification by flash column chromatography (chloroform/methanol, 9:1) gave 41.2 mg (84%) of the title compound as white solid: mp 131–132 °C, (lit.[12] mp 131.5–132 °C). The ^1H NMR and IR spectra of **30** matched those previously reported.[12]

(±)-2,3-Di-*tert*-butoxy-4-(1,5-dimethylhex-4-enyl)-4-hydroxycyclobut-2-en-1-one (31). To a mixture of Li/Na dispersion (98:2, 30% in mineral oil, 170 mg, 7.30 mmol) in dry hexane (15 mL) under argon was added 2-chloro-6-methylhept-5-ene (200 mg, 1.37 mmol) in dry hexane (8 mL), and the mixture was sonicated for 4 h.[17] After the salts settled the supernatant liquid was added via syringe pump (0.76 mL/min) to a −78 °C solution of **2** (206 mg, 0.913 mmol) in dry THF (75 mL) under argon and stirred for 35 min. The reaction was poured into a separatory funnel containing NH_4Cl (5%, 30 mL) and ethyl acetate (30 mL) and shaken until the ice melted. The aqueous layer was extracted with ethyl acetate (2 × 20 mL), and the organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give **31** as a yellow oil, which was used without purification.

(±)-3-*tert*-Butoxy-4-(1,5-dimethylhex-4-enyl)cyclobut-3-ene-1,2-dione (32). The crude alcohol **31** was placed in dry ether (100 mL) under argon and cooled to 0 °C. Pyridine (0.11 mL, 1.37 mmol) was added, and the mixture was stirred for 15 min, followed by TFAA (0.19 mL, 1.37 mmol). After 15 min more the reaction was poured into a separatory funnel containing 5% NH_4Cl (20 mL) and ethyl acetate (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL), and the organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give a bright yellow oil. The oil was purified by flash column chromatography on silica gel (10:1 hexane/ethyl acetate) to give **32** as a bright yellow oil (78 mg, 52% based on recovered starting material): IR (neat, cm^{-1}) 2985, 2945, 1795, 1755, 1580, 1390, 1160; ^1H NMR ($CDCl_3$) δ 5.03 (t, J = 7.1 Hz, 1 H), 2.88 (d × t, J = 7.5, 2.9 Hz, 1 H), 1.94 (m, 2 H), 1.77 (m, 2 H), 1.63 (s, 3 H), 1.58 (s, 9 H), 1.54 (s, 3 H), 1.25 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 198.55, 195.27, 193.13, 190.46, 132.33, 123.22, 87.25, 33.54, 31.36, 28.58, 25.91, 25.58, 17.58, 17.02; LRMS m/e (rel int) EI 208 (3), 193 (3), 69 (42), 57 (100); CI 209 (31), 193 (4), 151 (100), 89 (13), 71 (17); HRMS m/e calcd for $C_{16}H_{24}O_3$ (M^+) 264.1725, found 264.1733.

(±)-3-*tert*-Butoxy-2-(1,5-dimethylhex-4-enyl)-4-hydroxy-4-(1-methylethenyl)cyclobut-2-en-1-one (33). 2-Bromopropene (45 μL, 0.509 mmol) was placed in dry ether (20 mL) under argon and cooled to −78 °C. To the stirred solution was added *tert*-butyllithium (0.64 mL of a 1.6 M solution in hexane, 1.02 mmol). After 45 min the anion was added via cannula under positive argon pressure to a mixture of dione **32** (112 mg, 0.424 mmol) in dry THF (50 mL) at −78 °C. After 30 min the orange reaction mixture was poured into a separatory funnel containing NH_4Cl (5%, 20 mL) and ethyl acetate (20 mL) and shaken until the ice melted. The aqueous layer was extracted with ethyl acetate (2 × 10 mL), and the organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give alcohol **33** as a yellow oil, which was used without purification.

(±)-3-*tert*-Butoxy-2-(1,5-dimethylhex-4-enyl)-5-methylcyclohexa-2,5-diene-1,4-dione (34). The crude alcohol **33** was immediately dissolved in dry benzene (60 mL) and heated under argon at reflux for 1.5 h. Upon cooling to ambient temperature, K_2CO_3 (0.234 g, 1.70 mmol) and Ag_2O (0.393 g, 1.70 mmol) were added and stirred for 1.5 h. The golden solution was filtered through Celite and concentrated in vacuo. The golden oil was then purified by flash column chromatography on silica gel (9:1 hexane/ethyl acetate) to give **34** (68 mg, 53% from **32**) as a bright yellow oil: IR (neat, cm^{-1}) 2985, 2940, 1710, 1585, 1160, 1140, 835; ^1H NMR ($CDCl_3$) δ 6.41 (m, 1 H), 5.02 (m, 1 H), 3.10 (d × t, J = 7.2, 2.8 Hz, 1 H), 2.06 (m, 3 H), 1.85 (m, 2 H), 1.67 (m, 2 H), 1.62 (s, 3 H), 1.52 (s, 3 H), 1.35 (s, 9 H), 1.20 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 188.64, 185.74, 154.33, 143.16, 140.69, 134.21, 124.36, 131.49, 83.63, 34.76, 30.98, 29.38, 26.56, 25.68, 18.63, 17.59, 15.41; LRMS m/e (rel int) EI 248 (5), 166 (36), 69 (15), 57 (100), CI 305 (0.2), 249 (100), 167 (15), 70 (22); HRMS m/e calcd for $C_{19}H_{28}O_3$ (M^+) 304.2038, found 304.2023.

(±)-Perezone (35). To a solution of quinone **34** (39 mg, 0.157 mmol) in 1,4-dioxane (10 mL) was added 4 N HCl (0.27 mL, 1.21 mmol), and the system was heated at reflux for 4.5 h. After allowing to cool to ambient temperature the reaction mixture was poured into a separatory funnel containing $NaHCO_3$ (10%, 5 mL) and ethyl acetate (5 mL). The aqueous layer was extracted with ethyl acetate (2 × 10 mL), and the organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to a bright yellow oil. The oil was purified by flash column chromatography on silica gel (12:1 hexane/ethyl acetate) to give (±)-perezone as a bright yellow/orange solid (23 mg, 72%) (mp 71–72 °C, lit. mp 72–73 °C) which was identical with natural perezone by ^1H NMR and ^{13}C NMR analyses.[5]

(±)-3-*tert*-Butoxy-2-(1,5-dimethyl-4-hexenyl)-4-hydroxy-4-(prop-1-ynyl)cyclobut-2-en-1-one (36). The procedure for compound **38** was followed using 1-lithiopropyne as the nucleophile to give alcohol **36** as a light yellow oil, which was used without further purification.

(±)-2-*tert*-Butoxy-3-(1,5-dimethylhex-4-enyl)-5-methylcyclohexa-2,5-diene-1,4-dione (37). The crude alcohol **36** (0.38 mmol from above) was immediately dissolved in dry benzene (50 mL), heated at reflux under argon for 1.5 h, and then allowed to cool to ambient temperature and evaporated in vacuo to give a bright yellow oil, which was used without purification.

(±)-Isoperezone (38). The deprotection procedure for compound **35** was followed using the crude quinone **37** (0.38 mmol) to give a yellow oil, which was purified by flash column chromatography on silica gel (12:1 hexane/ethyl acetate) to give (±)-isoperezone as a bright yellow oil (43 mg, 46% from **36**): IR ($CHCl_3$, cm^{-1}) 3410, 2970, 2935, 1660, 1640, 1395, 1360; ^1H NMR ($CDCl_3$) δ 7.00 (s, 1 H), 6.55 (q, J = 1.6 Hz, 1 H), 5.08 (m, 1 H), 3.06 (sext, J = 6.7 Hz, 1 H), 2.10 (d, J = 1.6 Hz, 3 H), 1.85 (m, 4 H), 1.65 (s, 3 H), 1.52 (s, 3 H), 1.20 (d, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 187.37, 183.34, 150.75, 149.47, 131.36, 128.02, 124.82, 124.48, 34.03, 29.52, 26.66, 25.66, 18.20, 17.58, 16.73; LRMS m/e (rel int) EI 248 (11), 191 (7), 166 (100), 69 (34), 55 (58); CI 249 (100), 231 (67), 221 (19), 167 (12), 153 (10); HRMS m/e calcd for $C_{15}H_{20}O_3$ (M^+) 249.1490, found 249.1478.

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Registry No. **2**, 66478-66-8; (±)-**8a**, 124175-46-8; (±)-**8b**, 124175-74-2; **9a**, 124175-47-9; **9b**, 124175-75-3; **10a**, 124175-48-0; **10b**, 124175-76-4; (±)-**11a**, 124175-49-1; (±)-**11b**, 124175-77-5; **12a**, 124175-50-4; **12b**, 124175-78-6; **13a**, 124175-51-5; **13b**, 124175-79-7; **14a**, 124175-52-6; **14b**, 124175-80-0; (±)-**15**, 124175-53-7; **16**, 124175-54-8; **17**, 124175-55-9; (±)-**18**, 124175-56-0; **19**, 124175-57-1; **20**, 124175-58-2; **21**, 74237-20-0; **22**, 124175-59-3; **23**, 102631-99-2; **24**, 124175-60-6; **25**, 124175-61-7; **26**, 124175-62-8; (±)-**27a**, 124175-63-9; (±)-**27b**, 124175-81-1; (±)-**27c**, 124175-82-2; **28a**, 124175-64-0; **28b**, 124175-83-3; (±)-**28b** epoxide, 124175-73-1; **28c**, 124175-84-4; (±)-**29**, 124175-65-1; (±)-**30**, 15255-24-0; **31**, 124175-66-2; (±)-**32**, 124175-67-3; **33**, 124175-68-4; (±)-**34**, 124175-69-5; (±)-**35**, 98719-19-8; **36**, 124175-70-8; (±)-**37**, 124175-71-9; (±)-**38**, 124175-72-0; HC≡CBu-*n*, 693-02-7; HC≡CCH$_2$C$_6$H$_5$, 10147-11-2; CH$_2$=C(Li)Bu-*n*, 124156-74-7; 4-ClC$_6$H$_4$Li, 14774-78-8; HC≡CH, 74-86-2; HC≡CSi(CH$_3$)$_3$, 1066-54-2; (U)-CH$_3$CHCl(CH$_2$)$_2$CH=C(CH$_3$)$_2$, 72055-86-8; CH$_2$=C(Br)CH$_3$, 557-93-7; HC≡CCH$_3$, 74-99-7.

Synthesis of α-(Halomethyl)cycloalkanones†

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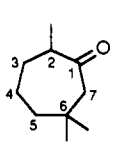
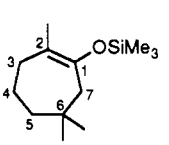
Cyclopropane unravelling of cyclopropanes and halocyclopropanes, prepared by cyclopropanation of 2,6,6-trimethyl-1-((trimethylsilyl)oxy)cycloheptene and 2-methyl-5-isopropyl-1-((trimethylsilyl)oxy)cyclohexene, is described. Solvolysis, halogenolysis, and protolysis of the cyclopropanes are discussed, and methods of facile synthesis of α-(halomethyl)cycloalkanones are introduced.

α-Alkyl-α-(halomethyl)cyclohexanones have served as useful intermediates in diterpene,[1] alkaloid[2], and sesquiterpene[3] syntheses. The preparation of the ketones has depended heretofore largely on the formation of cyclohexadienones in Reimer–Tiemann reactions as, for example, the construction of dienone products of the reactions of carvacrol (1) with chloroform[4] and bromoform en route to bicyclic ketones depicted in Scheme I (see the Experimental Section). Unfortunately several factors work against the frequent use of the Reimer–Tiemann reaction in this connection: (a) low yield of cyclohexadienone product, (b) the dienone being constrained to a six-membered ring, and (c) the halomethyl substituent being always a dichloromethyl or dibromomethyl group. Hence an alternate, more flexible route of synthesis of α-(halomethyl)cycloalkanones was in demand and a study of its development was initiated.

In principle, halogenolysis of cyclopropanol derivatives or protolysis of halocyclopropanol derivatives could be envisaged to yield ready access to α-(halomethyl)cycloalkanones.[5] Whereas especially the latter reaction has been assumed to take an alternate path (i.e. an electrocyclic process induced by halide solvolysis furnishing a conjugated enone product),[6] there were some indications that even in this case the desired ring opening could be accomplished.[7] Hence various ring cleavages of cyclopropanol derivatives were undertaken, all starting compounds being based on tetrahydroeucarvone (8).[8]



8



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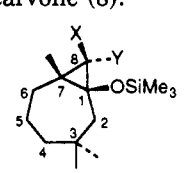
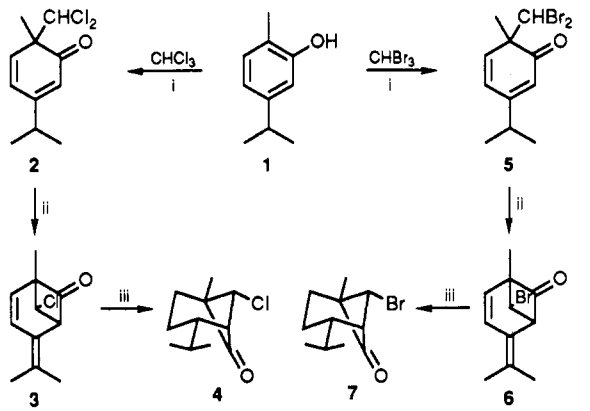


10a: X = Y = H
b: X = Y = Cl
c: X = Y = Br
d: X = Cl; Y = Br
e: X = Br; Y = Cl
f: X = Cl; Y = H

Bicyclo[5.1.0]octan-1-ol derivatives **10**, needed for the present study, were prepared in the following manner.

Scheme I[a]



[a] (i) 50% NaOH–H_2O, C_6H_6, 80 °C; (ii) Na_2CO_3, DMSO, 80 °C; (iii) H_2, 10% Pd/C, EtOAc.

Exposure of ketone **8** to trimethylsilyl chloride, sodium iodide, and triethylamine in acetonitrile afforded silyl enol ether **9** (91% yield),[9] whose cyclopropanation with methylene iodide and zinc–copper couple in ether gave bicycle

† Dedicated to the memory of Professor Edgar Lederer.

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