Intramolecular [2 + 2] Photocyclizations. 2. Total Synthesis of (±)-Hibiscone C (Gmelofuran)

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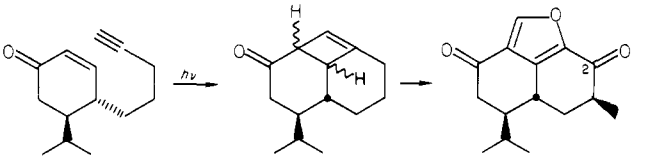
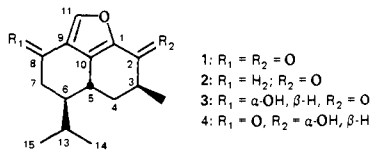
Abstract: We describe here a full account of the first total synthesis of (±)-hibiscone C (gmelofuran) (**1**), a structurally novel



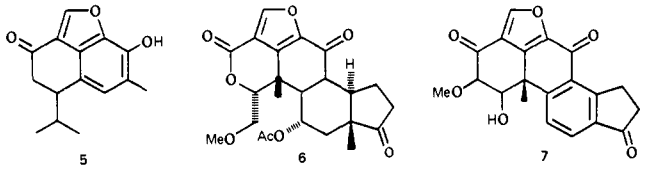
furanosesquiterpene isolated from the heartwood of *Hibiscus elatus* (Blue Mahoe), the national tree of Jamaica. The synthesis proceeds in 10 steps (2.5% overall yield) from 5-isopropyl-3-ethoxy-2-cyclohexenone. Central to the synthetic strategy was the first example of an intramolecular [2 + 2]-photochemical cycloaddition of an acetylenic moiety to an α,β-unsaturated ketone. The resultant cyclobutene was then exploited as a latent furan. Final installation of a carbonyl at C(2) and an axial methyl group at C(3) led to (±)-hibiscone C (**1**).

Introduction and Background[2]

Hibiscone C (**1**), member of a small group of tricyclic furanosesquiterpenes that now includes hibiscone A[4] (**2**), B[4] (**3**), D[4] (**5**), and agarol[5] (**4**), was independently isolated by Pelter[3] and

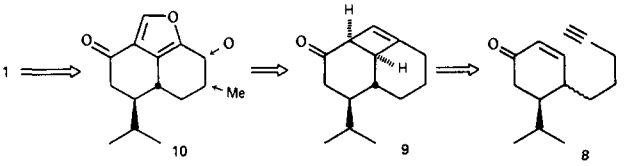


1: $R_1 = R_2 = O$
2: $R_1 = H_2$; $R_2 = O$
3: R_1 = α-OH, β-H, $R_2 = O$
4: $R_1 = O$, R_2 = α-OH, β-H

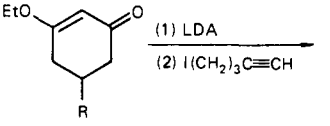


Thomson[4] in the late 1970's. The key architectural feature of this family, namely the tricyclofuran ring skeleton, also appears as a central structural unit in the more complex fungal antibiotics wortmannin (**6**)[6] and viridin (**7**).[7]

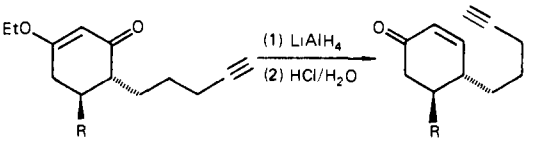
Scheme I



Scheme II



12a: R = H
12b: R = *i*-Pr



11a: R = H
11b: R = *i*-Pr

Our interest in hibiscone C as a synthetic target stemmed from the realization that the tricyclic nucleus of **1** might be rapidly assembled from intermediate **8** via an intramolecular [2 + 2] photocycloaddition of the acetylenic moiety to the α,β-enone functionality, (Scheme I).[8,9] The resultant cyclobutene ring in turn could serve as a latent furan. That is, oxidative cleavage of the olefinic linkage would produce a 1,4-dicarbonyl compound which could be anticipated[10] to yield **10** upon cyclization–dehy-

(1) Camille and Henry Dreyfus Teacher–Scholar, 1978–1983; National Institutes of Health (National Cancer Institute) Career Development Award, 1980–1985.

(2) A preliminary account of this work has been published: *J. Am. Chem. Soc.* **1982**, *104*, 5568 (Taken in part from Koft, E., Ph.D. Thesis, University of Pennsylvania, 1983).

(3) Gmelofuran (**1**), isolated from the roots of *Gmelina aborea* in 1978, was shown by Thomson[4] to be identical with hibiscone C, see: Joshi, K. C.; Singh, P.; Pardusani, R. T.; Pelter, A.; Ward, R. S.; Reinhardt, R. *Tetrahedron Lett.* **1978**, 4917.

(4) Hibiscone A–D were isolated in 1980 by Thomson's group from the heartwood of *Hibiscus elatus* and *Hibiscus tiliaceus*, see: Thomson, R. H.; Ali, S.; King, T. J.; Ferreira, M. A. *J. Chem. Soc., Perkin Trans.* **1980**, *1*, 249; also: Thomson, R. H.; Singh, P.; Ali, S. *Ibid.* **1980**, 257.

(5) Hibiscone C was also found to co-occur with agarol (**4**) in the stem wood of *Aquilaria agallocha*, see: Plant, P.; Rastogi, R. P. *Phytochem.* **1980**, *19*, 1869.

(6) MacMillan, J. M.; Simpson, T. J.; Yeboah, S. K. *J. Chem. Soc., Chem. Commun.* **1972**, 1063.

(7) Grove, J. F.; McCloskey, P.; Moffatt, J. S. *J. Chem. Soc.* **1966**, 743.

(8) For a review of the synthetic aspects of [2 + 2] photochemical cycloadditions of olefinic and enones, see: Baldwin, S. W. In "Organic Photochemistry"; Padwa, P., Ed.; Marcel Dekker: New York, 1981; Vol. 5, p 123.

(9) For a recent review of intramolecular olefin enone [2 + 2]-photocycloadditions in synthesis, see: Oppolzer, W. *Acc. Chem. Res.* **1982**, *15*, 135.

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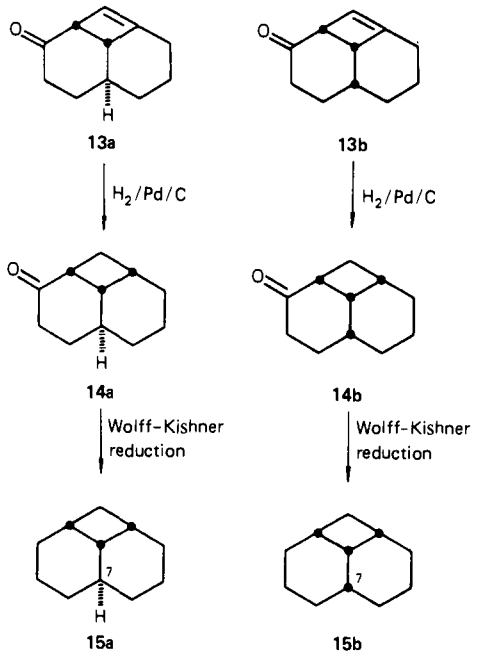
Scheme III



dration. Completion of the synthesis of hibiscone C (**1**) would then only require installation of a carbonyl at C(2)[11] and an axial methyl group at C(3).[11]

Although the *intermolecular* [2 + 2]-photocycloaddition of terminal acetylenes to cyclic α,β-unsaturated enones has been studied in some detail,[12,13] a careful search of the literature revealed no examples of the *intramolecular* version of this reaction. Interestingly, in the intermolecular case the behavior of terminal acetylenes differs in two important respects from their olefinic counterpart.[12] First, no trans fused products have been isolated. Second, the regioselectivity observed with terminal acetylenes is often opposite[12,13] that predicted by the so-called "Corey rule".[14]

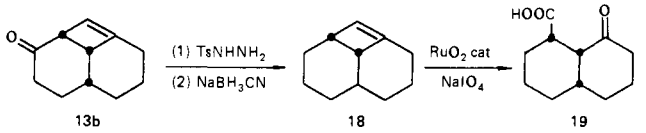
Results and Discussion

Since our synthetic strategy for hibiscone C depended critically on the proposed intramolecular [2 + 2]-cycloaddition process, we thought it prudent to undertake a model study. As substrate we selected enone **11a**. The latter was prepared via alkylation of the kinetic enolate[15] of **12a** with 5-iodo-1-pentyne, followed by reduction with LAH and acid hydrolysis (Scheme II). The overall yield was 60%.

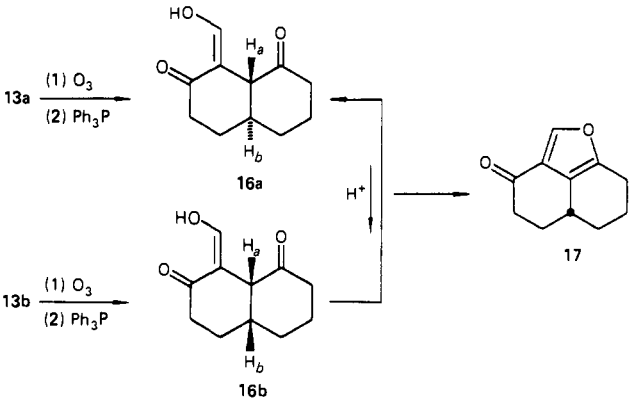
Irradiation of this ketone as a dilute hexane solution led to a 2:1 mixture of ketones **13a** and **13b**, which could be conveniently separated by MPLC; the combined yield was 55%. Central to the success of this photolysis was the use of a uranium glass filter to avoid secondary photochemical decomposition of the resultant β,γ-unsaturated ketones.

Initial definition of the carbon framework of **13a** and **13b** derived from the chemical transformations outlined in Scheme III. In particular, individual hydrogenation gave an isomeric pair of saturated ketones (**14a** and **14b**), which upon Wolff–Kishner reduction[16] produced hydrocarbons **15a** and **15b**, respectively. In each case the fully decoupled ^{13}C NMR spectra displayed seven lines with appropriate off-resonance multiplicities consistent with a highly symmetrical tricyclo[5.3.1.$0^{3,11}$]undecane skeleton. This information, in conjunction with the fact that intermolecular

Scheme IV



version of cyclohexenone–alkyne cycloaddition is known to produce only cis fused cyclobutenes, led logically to the supposition that **13a** and **13b** differ only in their relative stereochemistry at C(7). To establish conclusively this stereochemical question, **13a** and **13b** were individually subjected to ozonolysis followed by reduction with triphenylphosphine. Analysis of the 250-MHz ^1H NMR



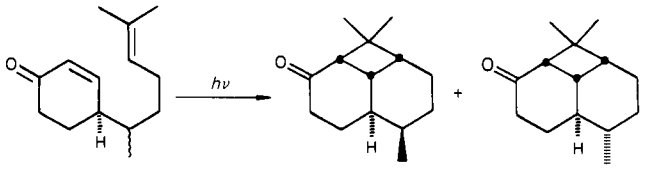
spectrum of the derived diketones (**16a** and **16b**) allowed assignment of the doublets respectively at δ 3.26 and 3.37 to H_a. The $J_{a,b}$ value in **16a** proved to be 9.4 Hz, while this value in **16b** was 5.6 Hz. Such coupling constants are consistent with the assigned trans and cis ring fusions.[17] Interestingly, brief acid treatment of either **16a** or **16b** (*p*-TsOH, benzene, 80 °C) afforded a mixture of **16a**, **16b** and a small amount of furan **17**. Prolonged acid treatment on the other hand with water removal (Dean–Stark trap) gave **17** in 64% yield at the expense of **16a** and **16b**. Needless to say, this observation was quite significant vis-â-vis the proposed hibiscone strategy.

Final confirmation of both structure and stereochemistry of **13a** and **13b** came via chemical correlation (see Scheme IV). In particular, removal of the carbonyl in **13b** via the Hutchins tosylhydrazone–$NaCNBH_3$ procedure[18] afforded a hydrocarbon (**18**), which upon oxidation with $RuO_4/NaIO_4$[19] gave a crystalline ketoacid (**19**). This material was shown by 250-MHz NMR as well as mixed melting point (undepressed) to be identical with that of a sample prepared by Wheeler in 1962.[20]

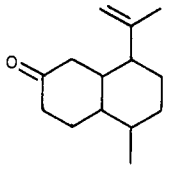
Several comments concerning the formation of both *cis*- and *trans*-decalones during irradiation of **11** are in order. First, in a closely analogous case White[21] observed that photolysis of **20** gave two adducts (**21a** and **21b**) along with **22**, the latter presumbly via a photoene process.

The stereochemistry of both **21a** and **21b** were rigorously established by X-ray crystallographic analysis. Unlike **11a**, however, tricyclic products containing the *cis*-decalone ring system were not observed. It is clear from this example (and **11a**) that an equatorial bond has been formed between the β-carbon of the enone and the side chain. A plausible explanation for this observation would be that the trans fused products arise from a twisted (π–π^*) state[22] wherein the C(4) appendage of the enone

(10) Newkome, G. R.; Paudler, W. W. "Contemporary Heterocyclic Chemistry"; Wiley: New York, **1982**; 17.
(11) The numbering system used here is that of Thomson (ref 4).
(12) Serebryakov, E. P.; Kulomzina-Pletneva, S. D.; Margaryan, A. K. *Tetrahedron* **1979**, *35*, 77.
(13) Serebryakov, E. P.; Burstein, K. Ya. *Tetrahedron* **1978**, *34*, 3233.
(14) Corey, E. J.; Bass, J. D.; Le Mahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570.
(15) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1175.
(16) Huang-Minlon *J. Am. Chem. Soc.* **1946**, *68*, 2487.
(17) Jackman, L. M.; Steinhell, S. "Applciations of Nuclear Magnetic Resonance Spectroscopy In Organic Chemistry", 2nd ed.; Pergamon Press; Oxford, 1969; Chapter 4 and references cited therein.
(18) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662.
(19) Sharpless, K. B.; Carlsen, Per H. J.; Katsuki, T.; Martin, V. S. *J. Org. Chem.* **1981**, *46*, 3936.
(20) Wheeler, D. M. S.; Wheeler, M. M. *J. Org. Chem.* **1962**, *27*, 3796. We thank these authors for their generous gift of this material.
(21) White, A. H.; Croft, K. D.; Ghisalberti, E. L.; Jefferies, P. R.; Stuart, A. D.; Raston, C. L. *J. Chem. Soc., Perkin Trans. 2*, 1473.
(22) Chan, C. D.; Schuster, D. I. *J. Am. Chem. Soc.* **1982**, *104*, 2928 and references cited therein.



20 21a 21b



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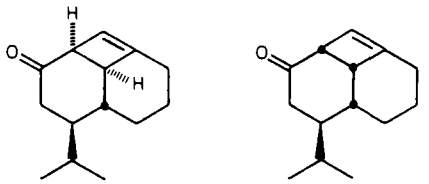
is equatorially disposed (Figure 1). The reason(s) for the difference in the stereoselectivity employing an acetylenic vs. an olefinic moiety is presumably due to the fewer degrees of freedom associated with the alkyne vis-á-vis the alkene.

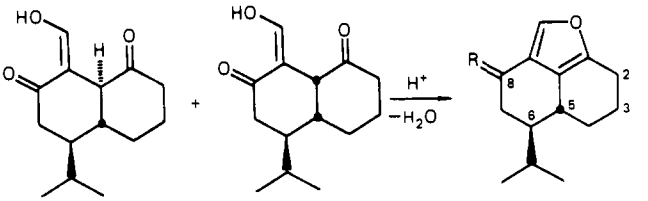
With the success of the key photochemical transformation assured, we turned to the synthesis of hibiscone C. The starting material for this endeavor was enone **12b**,[23] readily available in two steps from malonic ester and 5-methyl-3-hexen-2-one. Employing identical methodology used to prepare our model substrate, **12b** was converted to **11b**; the overall yield was 60%. As in the model study photolysis of **11b** gave two photoproducts (**23a** and **23b**; 1.5:1, respectively), in 60% combined yield. Operationally,



23a 23b

in this and in subsequent steps leading to **10**, separation of the individual isomers was necessary only for the purposes of characterization, the critical stereochemistry at C(5) and C(6) of hibiscone C having been set during the initial construction of **12b**.

Continuing with the synthetic venture, individual ozonolysis of **23a** and **23b** produced **24a** and **24b**, respectively; stereochemical



24a 24b

10: R = O
25: R = OCH_2CH_2O

assignments here were made via comparison of the 250-MHz ^1H NMR spectra to those of **16a** and **16b**. Acid-catalyzed dehydration then led to a single product (**10**) in 50% overall yield from **23a** and **23b**.

At this point, we faced the task of introducing oxygen at the secondary allylic position of **10**. Before doing so it seemed desirable to protect the C(8)-carbonyl of **10** in order to simplify the penultimate step, namely alkylation at C(3). Toward this end, it was observed that ketal **25** could be obtained from **24** in a single operation simply by adding ethylene glycol to the reaction mixture after the cyclization–dehydration was complete. Unfortunately exposure of **25** to *n*-bromosuccinimide (NBS) in THF/CCl_4 under incandescent illumination followed by an aqueous work-up (i.e., solvolysis of the benzylic bromide) led to a complex mixture of products from which keto alcohol **26** could be isolated in only 20%

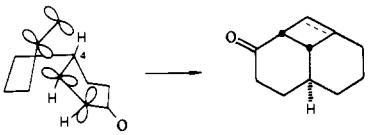
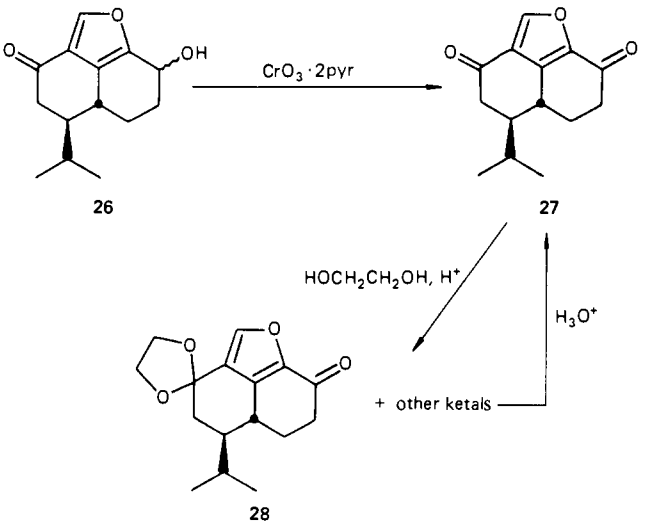


Figure 1.

yield. Examination of the remainder of the product mixture by NMR revealed the absence of resonances attributable to an aromatic (furan) hydrogen. Presumably under these conditions, electrophilic substitution competes significantly with allylic bromination. We reasoned that unwanted electrophilic attack of the furan ring might be suppressed by employing ketone **10** rather than its ketal (**25**). That is, the electron withdrawing effect of the carbonyl group in **10** would deactivate the furan ring toward electrophilic substitution. In practice, treatment of **10** with NBS followed as before by aqueous work-up produced alcohol **26** in as high as 40% yield; the efficiency of this transformation however proved to be sensitive to small variations in reaction conditions.

Having successfully introduced an oxygen at C(2) we next attempted ketalization of the C(8)-carbonyl of **26** prior to oxidation of the C(2)-hydroxyl and introduction of the axial methyl group.



26 27

28

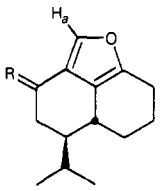
Unfortunately all attempts at such a process met with failure. Our only option at this point was to prepare diketone **27** and then attempt to introduce selectively the C(3)-methyl substituent. Toward this end Collins oxidation[24] proceeded smoothly to furnish dione **27** in 60% yield. Interestingly, although it appears that simple furans are quite stable to the Collins reagent,[25] direct allylic oxidation[26,27] of **10** or **25** resulted in extensive decomposition; the yield of **27** so obtained was in the 10–20% range. Furan **10** also suffered destruction when oxidation was attempted with selenium dioxide. Thus the two-step protocol NBS/H_2O–Collins oxidation proved most effective.

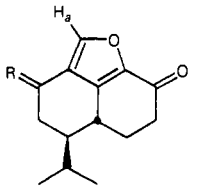
Our rationale for differentiation of the C(2)- and C(8)-carbonyl groups derived from the expectation that the C(2)-carbonyl would be less reactive due to its position relative to the furan ring. In practice, exposure of **27** to ethylene glycol under acidic conditions furnished a mixture in which the desired monoketal **28** predominated. Despite the modest yield (~40%), **28** was easily separated from the remainder of the reaction mixture (i.e., starting material and other ketalization products). The latter could be hydrolyzed to regenerate **27** and then recycled.

Structure assignment of **28** as the C(8)-monoketal followed directly from the chemical shift of the furan hydrogen (i.e., H_a).

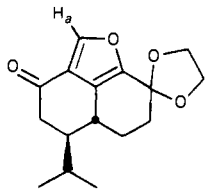
(23) Frank R. L.; Hall, H. K. *J. Am. Chem. Soc.* **1950**, *72*, 1645.

(24) Collins, J. C.; Hess; W. W.; Frank, F. J. *Tetrahedron Lett.* **196**,, 3363.
(25) Henderson, M. S.; McCrindle, R.; McMaster, D. *Can. J. Chem.* **1973**, *51*, 1346.
(26) For a discussion of allylic oxidations of furans, see: Dean, F. M. *Adv. Heterocycl. Chem.* **1982**, *30*, 167.
(27) Fullerton, D. S.; Chen, C.-M. *Synth. Commun.* **1976**, *6*, 217.





	δ H_a		δ H_a
10: R = O	7.82 ppm	**27**: R = O	8.10 ppm
25: R = OCH_2CH_2O	7.36	**28**: R = OCH_2CH_2O	7.56



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In particular, ketalization of **10** gave **25** wherein a 0.46 ppm upfield shift of H_a had occurred. A similar effect upon ketalization of **27** to afford **28** would lead to a predicted value of δ 7.64. This is in close agreement with the observed value of δ 7.56. In the case of the C(2)-monoketal **29**, the signal for H_a would be expected to occur between δ 7.82 and 8.1.

With **28** in hand, introduction of an axial methyl substituent at C(3) via alkylation of the derived enolate, followed by ketal hydrolysis would complete the synthesis of hibiscone C. From the outset our confidence that the axial configuration would in fact obtain derived from examination of molecular models of the enolate of **28**. That is, axial approach of methyl iodide to the α (undesired) face of the enolate of **28** (Scheme V) results in considerable tortional strain in the furan C(2)-π system during rehybridization at C(3). Approach to the β face on the other hand permits a high degree of orbital overlap during product development.

Experimentally the deprotonation of **28** was not without difficulty. Addition of **28** to a solution of LDA at −78 °C in THF employing bipyridyl as indicator resulted in rapid decoloration of the solution. Examination of the reaction mixture by TLC revealed a complex mixture, which we attribute to the known propensity of LDA to participate in radical-anion-induced reductions.[28] Fortunately, the desired deprotonation could be affected without complication when lithium hexamethyldisilazane was used as base. Under these conditions addition of excess methyl iodide followed by hydrolysis furnished (±)-hibiscone C (**1**) in 64% yield.[29] The latter was identical in all respects with an authentic sample of hibiscone C kindly provided by Professor Thomson.[29] Interestingly, the 250-MHz NMR spectra of the crude alkylation mixture revealed an additional small doublet at δ 1.20 (J = 7 Hz). We attribute this resonance to a small amount (ca. 7%) of the equatorial methyl epimer of hibiscone C; the latter however has not been fully characterized.

Summary

The first total synthesis of (±)-hibiscone C has been achieved. The approach proved to be both economic (10 steps) and efficient (2.5% overall yield). Central to the synthetic strategy was the first example of an intramolecular [2 + 2]-photochemical cycloaddition of an acetylenic moiety to an α,β-unsaturated ketone. The derived cyclobutene was then exploited as a latent furan. Studies to explore further the utility of such cycloadditions for natural product synthesis continue in our laboratory.

(28) Kowalski, C.; Creary, X.; Rollin, A. J.; Burke, M. C. *J. Org. Chem.* **1978**, *43*, 2601.

(29) We are grateful to Professor Thomson of the University of Aberdeen for his generous gift of **1**.

Experimental Section[30]

Preparation of 3-Ethoxy-6-(4-pentynyl)-2-cyclohexenone. To a solution of 9.1 mL (0.091 mol) of diisopropylamine in 50 mL of dry THF at 0 °C under argon was added 47 mL (0.078 mol) of 1.67 M *n*-butyllithium in hexane. After 15 min at 0 °C, the solution was cooled to −78 °C, and 3-ethoxy-2-cyclohexenone[32] (9.2 g, 0.065 mol) in 25 mL of THF was added dropwise over 30 min. When the addition was complete the solution was warmed to −40 °C and HMPA (0.09 mol, 16 g) in 20 mL of THF was added, followed by 1-iodo-4-pentyne[33] (neat, 0.1 mol, 19.6 g). The reaction mixture was allowed to warm to 25 °C over 1 h and then held at that temperature for an additional hour. Saturated ammonium chloride solution was then added. The organic phase was diluted with 200 mL of hexane, washed with water, dried ($MgSO_4$), and evaporated. The resulting oil was purified by flash chromatography[34] (silica gel, hexane/ethyl acetate; 10:1) to yield 9.05 g (66%) of 3-ethoxy-6-(4-pentynyl)-2-cyclohexenone: IR (CCl_4) 3320 (s), 2940 (s), 2100 (w), 1660 (s), 1610, 1380 (s), 1200 cm^{-1}; NMR ($CDCl_3$, 250 MHz) 1.34 (t, J = 6.8 Hz, 3 H), 1.4–2.24 (m, 10 H), 2.4 (t, J = 5.8 Hz, 2 H), 3.9 (q, J = 6.8 Hz, 2 H), 5.26 (s, 1 H); exact mass calcd for $C_{13}H_{18}O_2$: 206.1306; found: 206.1286.

Preparation of 4-(4-Pentynyl)-2-cyclohexenone (11a). 3-Ethoxy-6-(4-pentynyl)-2-cyclohexenone (9.05 g, 0.043 mol) in 25 mL of ether was added dropwise to a stirred suspension of lithium aluminum hydride (1.3 g, 0.033 mol.) in 100 mL of ether under argon. The reaction mixture was stirred at 25 °C for 30 min; the excess hydride was destroyed by addition of solid sodium sulfate decahydrate. Water (25 mL) was then added, followed by sufficient 2 N HCl to adjust the pH of the aqueous phase to 2. After stirring 30 min, the organic phase was removed and washed with saturated sodium bicarbonate and brine and dried. Evaporation followed by purification via flash chromatography[34] (silica gel, ethyl acetate/hexane, 1:10) gave 6.46 g (92%) of **11a**: IR (CCl_4) 3320, 3020 (w), 2940 (s), 1685 (s), 1250, 900 (s), 620 cm^{-1}; NMR ($CDCl_3$, 250 MHz) 1.98 (t, J = 2.5 Hz, 1 H), 1.5–2.56 (m, 11 H), 6.0 (dd, J = 10, 2.5 Hz, 1 H), 6.86 (d, J = 10 Hz, 1 H); exact mass calcd for $C_{11}H_{14}O$: 162.1045; found 162.1014.

Preparation of Tricyclo[5.3.1.0^{3,11}]undec-1-ene-4-ones (13a and 13b). Acetylenic enone **11a** (1.0 g, 6.2 mmol) in 250 mL of hexane contained in a Pyrex photolysis collar was purged was argon. This solution was irradiated (Hanovia 450-W medium pressure lamp with an uranium glass filter) for 16 h, after which time the solvent was removed in vacuo. The residue was purified by MPLC (60- × 1.4-cm silica gel column, ethyl acetate/hexane, 1:20) to afford 0.366 g of **13a** and 0.185 g of **13b** (combined yield 55%). **13a**: IR (CCl_4) 3050 (w), 2940 (s), 1710 (s), 900 cm^{-1}. NMR ($CDCl_3$, 250 MHz) 1.04–1.30 (m, 2 H), 1.48–1.7 (m, 2 H), 1.88–2.1 (m, 4 H), 2.16–2.46 (m, 3 H), 2.58–2.72 (m, 1 H), 3.52 (t, J = 3.4 Hz, 1 H), 5.58 (s, 1 H); exact mass calcd for $C_{11}H_{14}O$: 162.1045; found 162.1040.

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.33; H, 8.67. **13b**: IR (CCl_4) 3050 (w), 2940 (s), 1710 (s), 900 cm^{-1}; NMR ($CDCl_3$, 250 MHz) 1.4–1.8 (m, 4 H), 2.0–2.3 (m, 6 H), 2.6 (d, J = 14 Hz, 1 H), 3.0 (s, 1 H), 3.35 (m, 1 H), 5.54 (s, 1 H); exact mass calcd for $C_{11}H_{14}O$:162.1045; found: 162.1047.

(30) All melting points were obtained on a Thomas-Hoover apparatus and are corrected. Infrared spectra were recorded in solution in the solvent indicated on a Perkin-Elmer model 337 spectrophotometer. Proton NMR spectra were recorded on an IBM WP-200 SY (200 MHz) or a Bruker WM-250 (250 MHz) instrument; ^{13}C NMR (52.3 MHz) were obtained on an IBM WP-200 SY instrument. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane or chloroform. High-resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Sevice, Dr. T. Terwilliger, Director, employing a Hitachi–Perkin-Elmer RMH-2 instrument. All solvents were reagent grade unless otherwise noted. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone prior to use. Diisopropylamine was distilled from KOH and stored over KOH pellets. Butyllithium was purchased from Alfa Ventron and standardized by titration with diphenylacetic acid.[31] Precoated 0.25-mm thickness silica gel plates with fluorescent indicator (E. Merck) were used for analytical TLC. Preparative TLC was performed with 0.5-mm silica gel plates supplied by E. Merck. Column chromatography was performed with the solvents indicated on Merck silica gel (particle size 0.04–0.063 mm).

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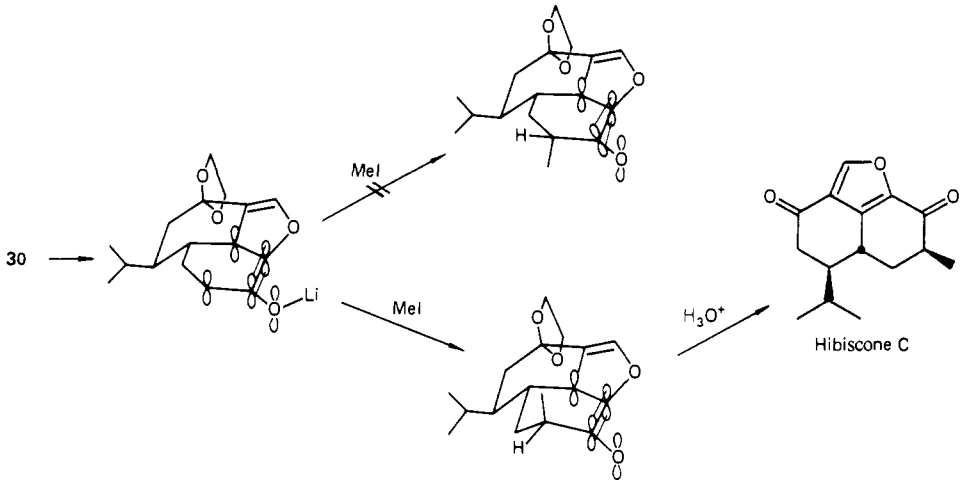
(35) Multiplicities were determined by using a spin–echo technique, see: Le Cocq, C.; Lallemand, J. *J. Chem. Soc., Chem. Commun.* **1981**, 150.

Scheme V



Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.37; H, 8.88.

Preparation of Tricyclo[5.3.1.0^{3,11}]undecan-4-ones (14a and 14b). Photoproduct **13a** (0.19 g, 1.2 mmol) in 10 mL of THF along with 10 mg of 5% Pd on carbon was stirred under 1.0 atm of hydrogen of 1 h. The reaction mixture was then filtered and evaporated to yield **14a** (0.19 g, ~100%): IR (CCl_4) 2940 (s), 1710 (s), 1450, 1250, 900 cm^{-1}; NMR ($CDCl_3$, 250 MHz) 1.1 (m, 1 H), 1.16–2.02 (m, 8 H), 2.08–2.65 (m, 6 H), 2.80 (dd, J = 8.2, 15 Hz, 1 H); exact mass calcd for $C_{11}H_{16}O$: 164.1202; found: 164.1194.

In a similar manner, **14b** was obtained from **13b**: IR (CCl_4) 2940 (s), 1710 (s), 1450, 1170 cm^{-1}; NMR ($CDCl_3$, 250 MHz) 1.2–1.6 (m, 6 H), 1.7–2.34 (m, 6 H), 2.4–2.77 (m, 3 H), 2.9 dd, J = 8.2, 16.4 Hz, 1 H); exact mass calcd for $C_{11}H_{16}O$: 164.1202; found: 164.1197.

Preparation of Tricyclo[5.3.1.0^{3,11}]undecanes (15a and 15b). Ketone **14b** (0.138 g, 0.84 mmol) was added to a solution of 1 g of potassium hydroxide in 2 mL of diethylene glycol and 1 mL of hydrazine hydrate and heated at 130 °C with stirring. The reaction temperature was then raised to 200 °C and held at that temperature for 4.5 h. The mixture was diluted with water and extracted with pentane. The organic phase was dried ($MgSO_4$), filtered through a plug of silica gel, and carefully evaporated to give 50 mg (40%) of **15b**: ^{13}C NMR[35] 50.32 MHz ($CDCl_3$) 19.8 (t), 26.9 (t), 28.9 (t), 29.2 (d), 31.2 (d), 33.2 (d), 35.4 (t); exact mass calcd for $C_{11}H_{18}$: 150.1409; found: 150.1407.

In an analogous manner, hydrocarbon **15a** was prepared from ketone **14a**: ^{13}C NMR[35] (50.32 MHz, $CDCl_3$) 22.1 (t), 25.5 (t), 27.3 (t), 29.5 (d), 31.6 (d), 35.3 (t), 38.6 (d); exact mass calcd for $C_{11}H_{18}$: 150.1409; found: 150.1393.

Preparation of Tricyclo[5.3.1.0^{3,11}]undec-1-ene (18). Photoproduct **13b** (0.32 g, 2 mmol) was dissolved in 10 mL of THF along with 0.43 g (2.4 mmol) of toluenesulfonyl hydrazine. The reaction mixture was heated at reflux for 2 h. The solvent was removed in vacuo, and the residue was chromatographed (silica gel, ethyl acetate/hexane, 1:5) to afford 0.37 g (55%) of the tosylhydrazone of **13b**, mp 120 °C (dec): NMR ($CDCl_3$, 250 MHz), 1.2–2.3 (m, 10 H), 2.4 (s, 3 H), 2.5 (m, 1 H), 2.8 (m, 1 H), 3.3 (m, 1 H), 5.45 (s, 1 H), 7.2–7.4 (m, 3 H), 7.82 (d, J = 7, 2 H).

This material (0.37 g, 1.12 mmol) was dissolved in 2.5 mL of dry dimethylformamide and 2.5 mL of sulfolane. *p*-Toluenesulfonic acid (50 mg) and 0.32 g (5 mmol) of sodium cyanoborohydride were added, and the reaction vessel was purged with argon. The reaction mixture was heated at 110 °C for 5 h and then cooled and diluted with water. The product was extracted into pentane, dried ($MgSO_4$), filtered through a plug of silica gel, and evaporated. The yield of **18** was 0.066 g (40%): NMR ($CDCl_3$, 250 MHz) 1.1–2.2 (m, 13 H), 2.6 (m, 1 H), 2.88 (m, 1 H), 5.58 (d, J = 2 Hz, 1 H); exact mass calcd for $C_{11}H_{16}$: 148.1252; found: 148.1245.

Preparation of (1β,4aβ,8aβ)-8-Oxodecahydronaphthalene-1-carboxylic Acid (19). Olefin **18** (0.048 g, 0.32 mmol) was dissolved in 1 mL of carbon tetrachloride and 1 mL of acetonitrile and added to 1.5 mL of an aqueous solution of 0.28 g (1.28 mmol) of sodium periodate and 5 mg of RuO_2. The resultant mixture was stirred vigorously for 2 h at 25 °C and then extracted into methylene chloride. The organic phase was dried ($MgSO_4$), concentrated in vacuo, filtered through Celite, and evaporated. The residue was purified by preparative TLC (silica gel, ethyl acetate/hexane, 1:1) and gave 20 mg of **19** (mp 146–148 °C). The melting point was not depressed upon admixture with authentic **19** kindly provided by Professor Wheeler:[20] IR ($CHCl_3$) 3500–2500 (s, br), 2950 (s), 1690 (br, s), 1410, 1380, 1290, 1225 (s) cm^{-1}; NMR ($CDCl_3$, 250 MHz) 1.06–1.44 (m, 3 H), 1.5–2.04 (m, 7 H), 2.12–2.4 (m, 4 H), 3.26 (t, J = 4.4 Hz, 1 H) (Carboxylic acid proton not observed).

Preparation of 8-Formyldecahydronaphthalene-1,7-diones (16a and 16b). Ozone was passed through a solution of 100 mg of **13b** in 20 mL of methylene chloride at −78 °C until the blue color of dissolved ozone persisted. Excess ozone was then removed in a stream of argon; 2 mL of dimethyl sulfide was added, and the reaction mixture was allowed to warm to room temperature with stirring for 3 h. The solvent was evaporated, and the residue purified by flash chromatography (silica gel, ethyl acetate/hexane, 1:5) to yield 96 mg (80%) of **16b**: IR ($CHCl_3$) 3100–2800, 1710 (s), 1625–1575 (s), 1300, 750 cm^{-1}; NMR ($CDCl_3$, 250 MHz) 1.1–2.56 (m, 11 H), 3.37 (d, J = 5.6 Hz, 1 H), 8.65 (d, J = 2.3 Hz, 1 H) (Enolic proton not observed.); exact mass calcd for $C_{11}H_{14}O_3$: 194.0943; found: 194.0942.

Similarly, compound **16a** (mp 77–78 °C) was obtained from photoproduct **13a**: IR ($CHCl_3$) 3100–2800, 1710 (s), 1625–1575 (s), 1300, 750 cm^{-1}; NMR ($CDCl_3$, 250 MHz) 1.52–2.6 (m, 11 H), 3.26 (d, J = 9.36 Hz, 1 H), 8.84 (d, J = 2.3 Hz, 1 H) (Enolic proton not observed.).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.05; H, 7.13.

Equilibration and Cyclization of 16b; Preparation of Furan 17. Compound **16b** (60 mg) was dissolved in 15 mL of benzene containing 15 mg of *p*-toluenesulfonic acid. The solution was heated at reflux in a flask equipped with a Dean–Stark trap and reflux condenser. After 30 min, examination of the reaction mixture of TLC revealed unchanged **16b** accompanied by two compounds of higher R_f. An aliquot was removed, and the components were separated by preparative TLC (ethyl acetate/hexane, 1:1). The material slightly less polar than **16b** was identified as **16a** by comparison (250-MHz NMR, TLC) with a sample obtained via ozonolysis of **13a**. After 3 h at reflux, TLC revealed that both **16a** and **16b** had been consumed with a concomitant increase in the least polar component. The reaction mixture was cooled, washed with saturated sodium bicarbonate, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue gave 35 mg (64%) of **17**: IR (CCl_4) 3150 (w), 2940 (s), 2850, 1690 (s), 1530, 1190, 1120 cm^{-1}; NMR ($CDCl_3$, 250 MHz) 1.18 (m, 1 H), 1.48 (m, 1 H), 1.9 (m, 1 H), 2.06–2.24 (m, 3 H), 2.44–2.8 (m, 5 H), 7.82 (s, 1 H); exact mass calcd for $C_{11}H_{12}O_2$: 176.0837; found: 176.0835.

Preparation of 6-(4-Pentynyl)-5-isopropyl-3-ethoxy-2-cyclohexenone. 5-Isopropyl-3-ethoxy-2-cyclohexenone **11b** (7.28 g, 0.04 mol) in 25 mL of THF was added dropwise to a solution of 0.048 mol LDA in 50 mL THF at −78 °C under argon. The reaction mixture was allowed to warm to −40 °C over 30 min and then 10.8 g (0.06 mol) of HMPA in 20 mL of THF was added. 1-Iodo-4-pentyne (12 g, 0.06 mol) was then added and the reaction was warmed to 25 °C and stirred for 1 h. Workup and chromatography, as in the preparation of 6-(4-pentynyl)-3-ethoxy-2-cyclohexenone, afforded 7.41 g (74%) of 6-(4-pentynyl)-5-isopropyl-3-ethoxy-2-cyclohexenone: IR (CCl_4) 3310 (s), 2950 (s), 2100 (w), 1660, 1620 (s), 1380, 1220 (s), 1040 cm^{-1}; NMR ($CDCl_3$, 250 MHz) 0.86 (d, J = 6.1 Hz, 3 H), 0.94 (d, J = 6.1 Hz, 3 H), 1.35 (t, J = 7 Hz, 3 H), 1.4–1.9 (m, 7 H), 2.05–2.4 (m, 5 H), 3.8 (q, J = 7 Hz, 2 H), 5.16 (s, 1 H); exact mass calcd for $C_{16}H_{24}O_2$: 248.1776; found: 248.1772.

Preparation of 5-Isopropyl-4-(4-pentynyl)-2-cyclohexenone (11b). 6-(4-Pentynyl)-5-isopropyl-3-ethoxy-2-cyclohexenone (7.41 g, 0.03 mol) was reduced with lithium aluminum hydride and hydrolyzed as in the preparation of **11a**. The yield of **11b** thus obtained was 5 g (82%) after

purification by flash chromatography (silica gel, ethyl acetate/hexane, 1:10): IR (CCl_4) 3125, 2950 (s), 1685 (s), 1250, 630 cm^{-1}; NMR ($CDCl_3$, 250 MHz) 0.84 (d, J = 7 Hz, 3 H), 0.92 (d, J = 7 Hz, 3 H), 1.22–2.0 (m, 8 H), 2.1–2.5 (m, 4 H), 5.9 (dd, J = 2.38 10 Hz, 1 H), 6.5 (dd, J = 3, 10 Hz, 1 H); exact mass calcd for $C_{14}H_{20}O$: 204.1514; found: 204.1478.

Preparation of 6-Isopropyltricyclo[5.3.1.$0^{3,11}$]undec-1-en-4-ones (23a and 23b). Acetylenic enone **11b** (0.75 g) in 200 mL of hexane was irradiated under an argon atmosphere (Hanovia 450-W medium-pressure lamp, uranium glass filter) for 24 h. After evaporation of the solvent, purification by MPLC (ethyl acetate/hexane, 1:20) gave **23a** (mp 63–64 °C, 270 mg) and **23b** (oil, 182 mg) in 60% combined yield.

23a: IR (CCl_4) 3050 (w), 2940 (s), 1710 (s), 1450, 1350, 1200, 1120 cm^{-1}; NMR ($CDCl_3$, 250 MHz) 0.75 (d, J = 7.1 Hz, 3 H), 0.85 (d, J = 7.1 Hz, 3 H), 1.08 (m, 1 H), 1.,53 (m, 1 H), 1.74–1.9 (m, 2 H), 1.95–2.3 (m, 6 H), 2.43 (dd, J = 4.3, 10.7 Hz, 1 H), 2.57 (dd, J = 10.7, 14 Hz, 1 H), 3.52 (t, J = 2.8 Hz, 1 H), 5.64 (s, 1 H); exact mass calcd for $C_{14}H_{20}O$: 204.1544; found: 204.1503.

23b: IR (CCl_4) 3050 (w), 2940 (s), 1710 (s), 1450, 1350, 1200, 1120 cm^{-1}; NMR ($CDCl_3$, 250 MHz) 0.76 (d, J = 7.1 Hz, 3 H), 0.90 (d, J = 7.1 Hz, 3 H), 1.32–1.67 (m, 3 H), 1.8–2.1 (m, 6 H), 2.20 (d, J = 14 Hz, 1 H), 2.40 (d, J = 14 Hz, 1 H), 2.93 (m, 1 H), 3.25 (t, J = 3.25 Hz, 1 H), 5.46 (s, 1 H); exact mass calcd for $C_{14}H_{20}O$: 204.1544; found: 240.1506.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.86. Found: (**23a**) C, 82.31; H, 9.89; (**23b**) C, 82.17; H, 9.90.

Preparation of 5-Isopropyl-8-formyldecahydronaphthalene-1,7-diones (24a and 24b). A mixture of **23a** and **23b** (1.2 g, 5.9 mmol) was ozonized in 50 mL of methylene chloride at −78 °C as in the preparation of compounds **16a** and **16b**. After reduction with triphenylphosphine (1.9 g, 7.3 mmol, −78–25 °C), the reaction mixture was evaporated and purified by flash chromatography (silica gel, ethyl acetate/hexane, 1:5) to give 1.05 g (75%) of **24a** and **24b** as a mixture.

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.09; H, 8.59.

A sample of the mixture (70 mg) was purified by preparative TLC (silica gel, ethyl acetate, hexane, 1:1) affording pure **24a** (mp 106–108 °C) and **24b** (mp 102–104 °C). **24a**: IR ($CHCl_3$) 3100–2800 (s), 1710 (s), 1640 (m), 1580 (m), 1375 (w), 1210 (w) cm^{-1}; NMR ($CDCl_3$, 250 MHz) 0.78 (d, J = 7 Hz, 3 H), 0.96 (d, J = 7 Hz, 3 H), 1.38–1.89 (m, 5 H), 1.92–2.58 (m, 6 H), 3.4 (d, J = 9.75 Hz, 1 H), 8.85 (s, 1 H), 14.8 (s, 1 H); exact mass calcd for $C_{14}H_{20}O_3$: 236.1412; found: 236.1407.

24b: IR ($CHCl_3$) 3100–2800 (s), 1710 (s), 1640 (m), 1580 (m), 1350 (m), 1190 (w) cm^{-1}; NMR ($CDCl_3$, 250 MHz) 0.75 (d, J = 7 Hz, 3 H), 0.9 (d, J = 7 Hz, 3 H), 1.6–2.55 (m, 11 H), 3.81 (d, J = 5.4 Hz, 1 H), 8.56 (s, 1 H), 14.38 (s, 1 H); exact mass calcd for $C_{14}H_{20}O_3$: 236.1412; found: 236.1402.

Preparation of 5β-Isopropyl-4,5,5aβ,6,7,8-hexahydro-3*H*-naphtho[1,8-*bc*]furan-3-one (10). Compounds **24a** and **24b** (0.69 g, 2.9 mmol) were dissolved in 50 mL of benzene along with 20 mg of *p*-toluenesulfonic acid in a flask equipped with a Dean–Stark trap and reflux condenser. The reaction mixture was heated at reflux for 3 h, cooled and washed with saturated sodium bicarbonate solution, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue (ethyl acetate/hexane, 1:10) afforded 0.42 g (67%) of **10** (mp 60–62 °C) after recrystallization from hexane: IR (CCl_4) 3140 (w), 2960 (s), 1690 (s), 1530 (m), 1280 (m), 1120 (m) cm^{-1}; NMR ($CDCl_3$, 250 MHz) 0.94 (d, J = 7 Hz, 3 H), 1.06 (d, J = 7 Hz, 3 H), 1.1 (m, 1 H),1.66–2.0 (m, 2 H), 2.06–2.36 (m, 4 H), 2.46–2.8 (m, 4 H), 7.82 (s, 1 H); exact mass calcd for $C_{14}H_{18}O_2$: 218.1317; found: 218.1292.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.27; H, 8.17.

Ketalization of 10; Preparation of 25. A mixture of **24a** and **24b** (110 mg, 0.47 mmol) was dissolved in 20 mL of benzene along with 10 mg of *p*-toluenesulfonic acid contained in a flask equipped with a Dean–Stark trap and reflux condenser. The mixture was heated at reflux for 3 h and then 0.5 mL of ethylene glycol was added and the heating continued for an additional 2 h. The mixture was cooled, washed with saturated sodium bicarbonate, dried ($MgSO_4$), and evaporated. The residue was quickly chromatographed (silica gel, methylene chloride) to yield 100 mg (81%) of **25**: NMR ($CDCl_3$, 250 MHz) 0.84 (d, J = 7 Hz, 3 H), 1.0 (d, J = 7 Hz, 3 H), 0.98 (m, 1 H), 1.42–2.15 (m, 7 H), 2.24–2.7 (m, 3 H), 4.02 (m, 4 H), 7.36 (s, 1 H).

Preparation of 8-Hydroxy-5β-isopropyl-4,5,5aβ,6,7,8-hexahydro-3*H*-naphtho[1,8-*bc*]furan-3-one (26). (A) **From Oxidation of 25.** Ketal **25** (29 mg, 0.11 mmol) was dissolved in 10 mL of carbon tetrachloride and 3 mL of THF; calcium carbonate (22 mg, 0.22 mmol) was added, followed by 19 mg (0.12 mmol) of *N*-bromosuccinamide (freshly recrystallized from benzene). The mixture was stirred at 25 °C while illuminated with a 40-W incandescent bulb. After 30 min, the mixture was poured into saturated sodium bicarbonate solution and extracted with methylene chloride. The organic phase was dried ($MgSO_4$) and evaporated; the residue was purified by preparative TLC (ethyl acetate/hexane, 1:1) to afford 5.3 mg (20%) of **26**: IR (CCl_4) 3650–3200 (s), 3150 ns), 2950 (s), 1680 (s), 1530 (m), 1060 (s), 920 (s) cm^{-1}; NMR ($CDCl_3$, 250 MHz) 0.90 (d, J = 7 Hz, 3 H), 1.0 (d, J = 7 Hz, 3 H), 1.08–1.4 (m, 2 H), 1.64–2.70 (m, 8 H), 4.90 (br s, 1 H), 7.90 (s, 1 H); exact mass calcd for $C_{14}H_{18}O_3$: 234.1256; found: 234.1251.

(B) **From Oxidation of (10).** Ketone **10** (0.355 g, 1.63 mmol) was dissolved in 60 mL of carbon tetrachloride and 20 mL of THF. Calcium carbonate (0.35 g, 3.2 mmol) and 0.35 g of *N*-bromosuccinamide (1.96 mmol) were added, and the reaction mixture was stirred at 25 °C for 1 h under illumination from a 100-W incandescent bulb. The reaction was worked up as in part A and purified by flash chromatography (silica gel, ethyl acetate/hexane, 1:10) to yield 0.17 g of **26** (43%).

Preparation of 5-β-Isopropyl-4,5,5aβ,6,7,8-hexahydro-3*H*-naphtho-[1,8-*bc*]furan-3,8-dione (27). (A) **From Oxidation of (26).** Keto alcohol **26** (30 mg, 0.13 mmol) was added to a solution of 80 mg (0.8 mmol) of CrO_3 and 250 mg (2 mmol) of pyridine in 5.0 mL of methylene chloride. After stirring 30 min at 25 °C, the reaction mixture was washed with 10% HCl followed by saturated sodium bicarbonate, dried ($MgSO_4$), and evaporated. The residue was purified by preparative TLC (ethyl acetate/hexane, 1:1) to afford 18 mg (60%) of **27**: IR (CCl_4) 3150 (w), 2960 (s), 2870 (m), 1730 (m), 1680 (s), 1180 (s) cm^{-1}; NMR ($CDCl_3$, 250 MHz) 0.90 (d, J = 7 Hz, 3 H), 0.98 (d, J = 7 Hz, 3 H), 1.80–2.64 (m, 8 H), 2.92 (dt, J = 4.7, 11.2 Hz, 1 H), 8.10 (s, 1 H); exact mass calcd for $C_{14}H_{16}O_3$: 232.1100 found: 232.1101.

(B) **From Allylic Oxidation of 10.** Ketone **10** (25.0 mg, 0.09 mmol) was added to 15 equiv of Collins' reagent (prepared from 0.15 g of CrO_3 and 0.24 g of pyridine) in 5 mL of methylene chloride. The reaction mixture was stirred at 25 °C for 36 h and then worked up and purified as in part A. The yield of **27** was 4.0 mg (20%).

Ketalization of 27: Preparation of 28. Dione **27** (30 mg, 1.3 mmol) was combined with 5 mg of *p*-toluenesulfonic acid and 20 mg of ethylene glycol in 10 mL of benzene. After 1 h at reflux, examination of the reaction mixture of TLC (ethyl acetate/hexane, 1:1) revealed starting material plus three additional product with higher R_f values. The reaction mixture was cooled, washed with saturated sodium bicarbonate, dried ($MgSO_4$), and evaporated. Preparative TLC (ethyl acetate/hexane) of the residue gave 6 mg of recovered **27** and 12 mg of the deisred monoketal **28**. The two least polar components were dissolved in 2 mL of THF with 1 drop of 10% HCl and stirred at 25 °C for 1 h. After the usual workup preparative TLC afforded 10 mg of dione **27**. Spectral data for **28**: NMR ($CDCl_3$, 250 MHz) 0.8 (d, J = 7 Hz, 3 H), 0.93 (d, J = 7 Hz, 3 H), 1.18–1.70 (m, 3 H), 1.80–1.92 (m, 2 H), 2.25 (m, 1 H), 2.44–2.7 (m, 3 H), 4.0 (m, 4 H), 7.56 (s, 1 H); exact mass calcd for $C_{16}H_{20}O_4$: 276.1356; found: 276.1348.

Preparation of (±)-Hibiscone C (1). A 0.1 M solution of lithium hexamethyldisilazane was prepared as follows. Hexamethyldisilazane (0.2 g, 1.2 mmol, freshly distilled from CaH_2) was placed in a 10-mL argon-purged volumetric flask equipped with a stirring bar. The flask was placed in an ice bath, and 5 mL of THF was added, followed by 0.7 mL (1 mmol, 1.44 M) of *n*-butyllithium in hexane. The volume of the solution was brought to 10 mL with dry THF, and the solution was stirred at 0 °C for 15 min. Ketal **28** (10 mg, 0.036 mmol) in 0.5 mL of THF was then added to 0.6 mL (0.06 mmol) of the above lithium hexamethyldisilazane solution at −78 °C under an atmosphere of argon. The reaction mixture was warmed to −50 °C and held at that temperature for 45 min. Freshly distilled methyl iodide (0.1 mL) was added; the reaction was allowed to warm to 0 °C and then quenched by the addition of saturated ammonium chloride solution. The product was extracted into ether and dried ($MgSO_4$), and the solvent was evaporated. The residue was taken up in 5 mL of THF to which 5 drops of 10% HCl had been added. After 1 h at 25 °C, the reaction mixture was partitioned between saturated sodium bicarbonate and ether. The crude product after drying and evaporation of the solvent was purified by preparative TLC (ethyl acetate/hexane, 1:1) to give 6.3 mg (64%) of (±)-hibiscone (**1**), mp 103–106 °C. (±)-Hibiscone was identical in all respects (IR, NMR, TLC, UV) with an authentic sample of **1** provided by Professor Thomson except of course for chiroptical properties: IR ($CHCl_3$) 3150 (w), 2960 (s), 1675 (s), 1600 (m), 1450 (m), 1380 (m), 1040 (m), 900 (m) cm^{-1}; NMR ($CDCl_3$, 250 MHz) 0.95 (d, J = 7 Hz, 3 H), 1.0 (d, J = 7 Hz, 3 H), 1.36 (d, J = 7 Hz, 3 H), 1.8–2.12 (m, 3 H), 2.2 (m, 1 H), 2.36 (dd, J = 13, 17 Hz, 1 H), 2.62 (dd, J = 3, 17 Hz, 1 H), 2.82 (m, 1 H), 3.06 (ddd, J = 5, 11, 11 Hz, 1 H), 8.1 (s, 1 H); exact mass calcd for $C_{15}H_{18}O_3$: 246.1256; found: 246.1251.

Attempted Epimerization of 1. Natural hibiscone (5 mg) was stirred with 3 drops of 10% HCl in 1 mL of THF for 75 min at 25 °C. After evaporation and purification by preparative TLC, the 250-MHz ^1H NMR was unchanged (i.e., showed no resonance at δ 1.20).

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Copper-Mediated Hydroxylation of an Arene: Model System for the Action of Copper Monooxygenases. Structures of a Binuclear Cu(I) Complex and Its Oxygenated Product

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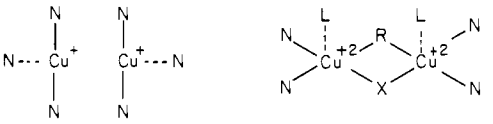
Abstract: A chemical system possessing features that mimic the structures and reactivity of the active sites of the copper oxygen carrier hemocyanin (Hc) and the monooxygenase tyrosinase (Tyr) is presented. When a dinuclear 3-coordinate Cu(I) complex, II, of a binucleating ligand, I, where the two tridentate nitrogen donor groups are separated by a *m*-xylyl bridge is reacted with dioxygen, the specific hydroxylation of the aromatic ring occurs in high yield (>90%). This produces a binuclear pentacoordinate phenolato and hydroxo doubly bridged Cu(II) complex, IIIB. Manometric and mass spectrometric measurements utilizing isotopically labeled $^{18}O_2$ show that the phenolate and hydroxy oxygen atoms in IIIB are derived from dioxygen, making this reaction an excellent biomimic for the action of the copper monooxygenases. Removal of the copper ions from IIIB gives a new phenol, IV, completing the sequence of the copper-mediated hydroxylation of an aromatic ring, I → IV. Crystallographic studies have been completed on both II and III. II crystallizes in the triclinic space group $P\bar{1}$ with $Z = 2$ and $a = 11.264$ (3) Å, $b = 11.448$ (3) Å, $c = 15.722$ (4) Å, $\alpha = 95.72$ (2)°, $\beta = 102.05°$, $\gamma = 94.77°$. IIIB crystallizes in the monoclinic space group $P2_1/c$, $Z = 4$, with $a = 18.221$ (3) Å, $b = 13.323$ (3) Å, $c = 18.643$ (4) Å, and $\beta = 102.39$ (2)°. The structural features of these complexes are compared to those of other related compounds and to the active sites of the copper proteins. The biological relevance of the monooxygenase model system is also discussed.

Copper compounds have been established to be some of the most versatile and most useful catalysts for oxidation reactions by molecular oxygen in both biological and nonbiological systems. There is considerable interest in the development of chemical model systems which mimic aspects of the biological oxygenases. Studies on nonenzymatic oxygenation reactions as biological mimics can and have contributed to the understanding of the oxygenase-catalyzed reactions.[1-4] Just as important is the use of the concepts derived from the highly efficient enzymes to develop synthetic systems capable of effecting mild selective oxidation or oxygenation by O_2 of organic substrates. The use of molecular oxygen is desirable, since this is the least energy-intensive functionalization agent.[4]

Our biomimetic investigations have focused on the metalloproteins hemocyanin and tyrosinase which contain electronically coupled binuclear copper active centers. Hemocyanins[1,5,6] function as oxygen carriers in the hemolymph of molluscs and arthropods, whereas tyrosinase[1,5,7] is a monooxygenase utilizing O_2 in the hydroxylation of monophenols (monophenol → *o*-diphenol) and further acts as a two-electron oxidase (*o*-diphenol → *o*-quinone). A variety of evidence suggests that in the deoxy form of hemocyanin two[8,10] or three[9,10] imidazole ligands from histidine coordinate to each cuprous ion. Upon oxygenation, substantial changes occur giving rise to tetragonally coordinated Cu(II) ions separated by 3.6 Å and bridged by an exogenous O_2^{2-} ligand (derived from



O_2) and an endogenous oxygen-containing group.[8-11] Strong parallels exist between the active sites of hemocyanin and tyrosinase; the latter binds O_2 forming oxy-Tyr which has spectral features nearly identical with oxy-Hc.[12]

In our studies with binuclear Cu(I) and Cu(II) moieties,[13] we have employed the new binucleating ligand *m*-XYLpy$_2$, (I, Figure 1), where two tridentate donor groups are separated by a *m*-xylyl bridge.[13-15] A principal focus of our work has been to isolate,

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