Ingenane Synthetic Studies. An Expedient Approach to Highly Oxygenated ABC Subunits of Ingenol via Reductive Dialkylative Annulation and α,β-Epoxy Ketone Photoisomerization

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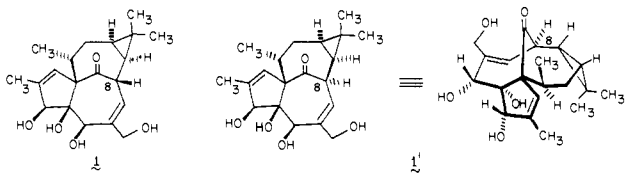
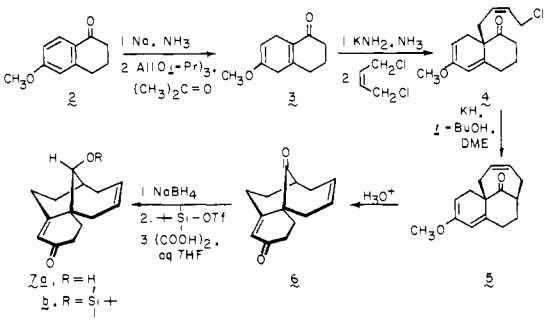
Abstract: The feasibility of using a hydronaphthalenone precursor for the synthesis of isoingenol (**1'**) has been examined. Following Birch reduction of 6-methoxy-1-tetralone, its twofold alkylation with (*Z*)-1,4-dichloro-2-butene was studied as a means of arriving at the tricyclic **6**. Following the successful implementation of this scheme, a detailed investigation of C-ring functionalization reactions was undertaken. Conformational factors and the possible role of neighboring group effects were given particular consideration. Recourse to X-ray analysis was made where necessary to confirm stereochemistry. The most promising process proved to be the singlet oxygenation of **7b**, which afforded **27** and **29** predominantly. Subsequently, application of a mild photochemical reaction to ring A epoxy ketones of this general structure resulted in efficient conversion to isomeric 1,3-diketones having the perhydroazulenoid A/B ring system characteristic of ingenol. The key elements of this work show promise in being serviceable as a means of ultimately gaining access to isoingenol by total synthesis.

The ingenanes comprise a structurally novel group of highly oxygenated tetracyclic diterpene esters that share in common the ingenol nucleus (**1**). The intense interest in these biologically



highly active natural products stems principally from the carcinogen or tumor-promoting property of certain derivatives that is evident upon continued application to mice following a subthreshold dose of a carcinogen[3] and from the powerful antileukemic activity of others.[4] The isolation and pharmacology of these substances have been thoroughly reviewed.[5] Structural and absolute configurational assignments for the series follow from X-ray crystal structure analysis of the triacetate of **1**.[6] Ongoing studies have revealed the ingenanes to be the single most widely distributed diterpene nucleus within the large genus *Euphorbia* (Spurge).[7] [Because our attempts to acquire the original X-ray data for ingenol triacetate in order to independently evaluate the unusual β configurational assignment at C-8 were unsuccessful,

Scheme I



one of us (J.P.S) has repeated the structure analysis on a sample kindly provided by Prof. A. D. Kinghorn (College of Pharmacy, University of Illinois at Chicago). On the basis of this study and detailed ^{1}H NMR analysis at 500 MHz carried out at the OSU Campus Instrument Center, the original assignment can be certified as correct. The relatively large coupling of H-8 with the neighboring cyclopropyl proton (J = 11.5 Hz) is especially diagnostic of the sizable dihedral angle existent in **1** but not **1'**. Copies of ORTEP diagrams and the 500-MHz spectrum can be obtained upon request from L.A.P. or J.P.S.] Chemical modifications of natural ingenol are currently being pursued by Hecker and his co-workers in Heidelberg.[8]

Central to the novel structure of ingenol is a highly strained trans-locked bicyclo[4.4.1]undecan-11-one to which cyclopentene and dimethylcyclopropane rings are fused. Eight chiral centers are present, the 1,2,3-*cis*-triol segment in the "southwest corner" of the molecule being particularly unique. Intrigued by the combination of structural features embodied in **1**, we have initiated studies aimed at a stereocontrolled total synthesis of the less strained isoingenol epimer (**1'**).

Our conceptual approach for gaining access to **1'** is based upon the premise that proper construction of the C/D segment might be most efficiently achieved by annulation of a partially reduced naphthalenic substrate (e.g., A → B). While this protocol is designed to take advantage of commercially available starting materials and to avoid from the outset the stereochemical vagueries of perhydroazulenoid systems, it does demand that a preparatively

(1) National Science Foundation Graduate Fellow, 1982-1985.
(2) Author to whom inquiries regarding the X-ray analyses should be directed at the Merck address.
(3) (a) Berenblum, I.; Shubik, P. *Br. J. Cancer* **1947**, *1*, 379. (b) Hecker, E. *Cancer Res.* **1968**, *28*, 2338. (c) Adolf, A.; Opferkuch, H.; Hecker, E. *Fette Seifen Anstrichm.* **1968**, *70*, 850. (d) Furstenberger, G.; Hecker, E. *Planta Med.* **1972**, *22*, 241. (e) Hecker, E.; Friesel, H.; Schmidt, R.; Siebert, D.; Marquardt, H. "Advances in Medical Oncology, Research and Education, Vol. 1, Carcinogenesis"; Margison, G. P., Ed., Pergamon Press: New York, 1969; p 207. (f) Fujiki, H.; Mori, M.; Sugimura, T.; Ohigashi, H.; Hirota, M.; Koshimizu, K. In "Cocarcinogenesis and Biological Effects of Tumor Promoters"; Hecker, E., et al., Eds.; Raven Press: New York, 1982, p 65. (g) Keller, R.; Keist, R.; Adolf, W.; Opferkuch, H. J.; Schmidt, R.; Hecker, E. *Exp. Cell Biol.* **1982**, *50*, 121.
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(6) Zechmeister, K.; Brandl, F.; Hoppe, W.; Hecker, E.; Opferkuch, H. J.; Adolph, W. *Tetrahedron Lett.* **1970**, 4075.
(7) See, for example: (a) Abo, K. A.; Evans, F. J. *Phytochemistry* **1982**, *21*, 725. (b) Falsone, G.; Crea, A. E. G.; Noack, E. A. *Arch. Pharm.* (*Weinheim, Ger.*) **1982**, *315*, 1026.
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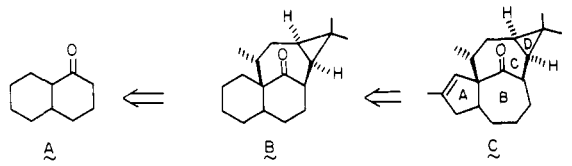


useful ring transposition strategy (i.e., B → C) be implemented at a later stage. Superimposed upon all of this is the need to maintain a suitable level of oxygenation in the various intermediates in order that the lone keto and four hydroxyl groups ultimately be introduced with proper stereochemical control.

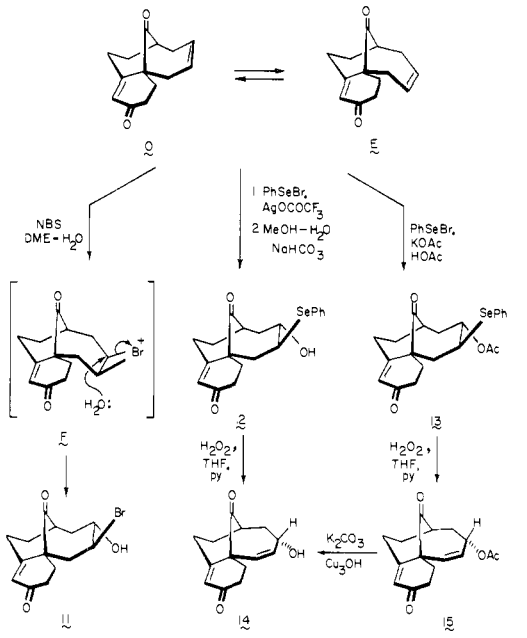
With this basic plan in mind, we have proceeded to elaborate highly oxygenated ABC subunits of ingenol and have uncovered information relevant to the stereospecific attachment of ring D. This successful endeavor, the details of which are recorded below, may well set the stage for the development of a viable route to **1**′. To our knowledge, no synthetic efforts directed toward ingenol have been previously reported.[9]

The Annulation Step. Aromatic ketones are recognized to respond well to metal–ammonia reduction.[10] Because carbanion character develops adjacent to the carbonyl center, reductive alkylations become feasible[11a,b] and have been applied in various synthetic contexts.[11c,d] For our purposes, 6-methoxy-1-tetralone (**2**) was converted to **3** (Scheme I) by modification of the original literature procedure.[10a] Treatment of **3** with 1 equiv of potassium amide followed by (*Z*)-1,4-dichloro-2-butene afforded **4**, which, without isolation, was cyclized to **5** with a suspension of potassium hydride in dimethoxyethane containing a catalytic quantity of *tert*-butyl alcohol. This two-stage procedure proved more efficient than the direct dialkylative option.[12] Strikingly, the use of lithium enolates proved entirely disadvantageous and had to be avoided.[13]

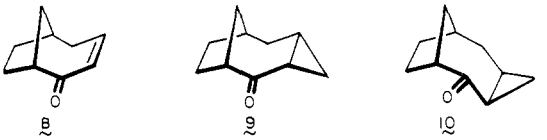
Although tricyclic enol ether **5** can be isolated by careful chromatography on silica gel, it is quite prone to hydrolysis. Accordingly, our standard laboratory practice was to transform **3** to the desired **6** prior to purification. This scheme provides a ready means for the preparation of **6** in 32% overall yield.

In a manner reminiscent of the behavior of the Wieland–Miescher ketone, **6** is reduced stereospecifically to **7a** with purified sodium borohydride.[14] Successful protection of the hydroxyl group in **7a** as the *tert*-butyldimethylsilyl ether proved highly dependent upon conditions. Thus, treatment of **7a** with the silyl chloride and imidazole in dimethylformamide[15] or with lithium sulfide in acetonitrile[16] failed to provide reasonable amounts of **7b** after 48 h, presumably for steric reasons. Reaction with the silyl triflate[17] proved quite satisfactory, particularly so if the reagent was introduced in the absence of solvent to a solution of **7a** in dry tetrahydrofuran at 0 °C. In order to engage all of **7a** in reaction, excess silyl triflate was needed, a requirement that afforded bissilylated product alongside **7b**. However, the silyl enol ether moiety is subject to controlled hydrolysis, thereby permitting the routine isolation of protected enone **7b** in 95% yield.

Scheme II



C-Ring Functionalization of 6. While little attention has been paid to the conformational analysis of bicyclo[4.4.1]undecane and bicyclo[4.3.1]decane derivatives,[18] most representations of the lower homologous bicyclo[4.2.1]nonane ring system presume a chair conformation for the seven-membered ring,[19] and this conclusion is supported by molecular mechanics calculations.[20] In contrast, NMR data for bicyclo[4.2.1]non-3-en-2-one (**8**) are



best accommodated in terms of a predominance of the boat form.[21] On this basis, the product of cyclopropanation of **8** with the dimethylsulfoxonium ylide reagent was *assumed* to be **9** and not **10**.[22]

For our purposes, tentative assignments of stereochemistry would not suffice. We fully anticipated both **6** and **7** to be in dynamic conformational equilibrium (D ⇄ E) near room temperature. Consequently, it was not at all clear which conformer would prove more reactive toward a given electrophilic reagent.

To gain information on this point, **6** was treated with *N*-bromosuccinimide in aqueous dimethoxyethane (Scheme II). The stereochemical features of the lone bromohydrin, which was

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(12) See, for example: (a) Froborg, J.; Magnusson, G.; Thorén, S. *J. Org. Chem.* **1974**, *39*, 848. (b) Still, W. C. *Synthesis* **1976**, 453. (c) Christie, J. J.; Varkey, T. E.; Whittle, J. A. *J. Org. Chem.* **1981**, *46*, 3590. (d) Garratt, P. J.; Hollowood, F. *Ibid.* **1982**, *47*, 68.

(13) See, for example: (a) Smith, A. B.; Richmond, R. E. *J. Am. Chem. Soc.* **1983**, *105*, 575. (b) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041.

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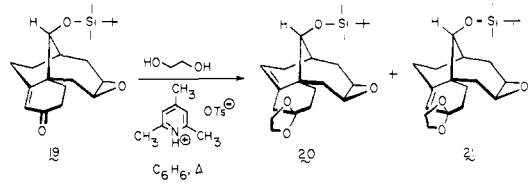
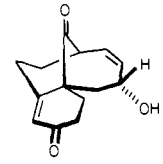
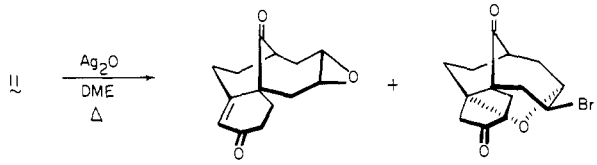
Scheme III



isolated in 80% yield, proved not to be convincingly decipherable by ^{1}H NMR methods. Consequently, recourse was made to X-ray crystallography in order to establish the molecule to be **11**. These results reveal bromonium ion F to be central to product formation, with rearside nucleophilic attack by water occurring at the carbon center more remote from the cyclohexenone ring. Comparable results were achieved upon reaction of **6** with phenylselenenyl bromide and silver trifluoroacetate followed by mild basic hydrolysis[23] and with phenylselenenyl bromide in acetic acid buffered with potassium acetate.[24] Spectral correlations involving **11**–**13** denote a common structural thread in the series. Furthermore, selenoxide elimination within **12** and **13** produced **14** and **15**, respectively. Chemical intercorrelation of these dienediones was achieved by mild hydrolysis of **15** to **14** whose structural features follow convincingly from its ^{1}H NMR spectrum. In particular, the absence of the required regioisomer **16** was clearly indicated.



The synthetic task of properly introducing an allylic hydroxyl group in **6** appeared to warrant initial utilization of an oxygen-centered electrophilic species. However, because direct peracid epoxidation of **6** led to a myriad of products, the response of **11** to the action of silver oxide was examined. Not unexpectedly, these alkaline conditions promoted competitive formation of epoxide **17** and the intramolecular Michael addition product **18**.

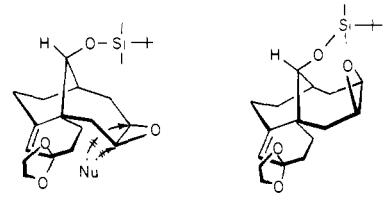


Although **17** was dominant in the reaction mixture, the relatively low yields of the two pure compounds (25 and 15%, respectively) realized following chromatography discouraged further pursuit of this synthetic pathway and led us to examine the chemical reactivity of **7b**.

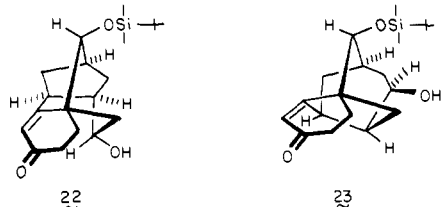
C-Ring Functionalization of 7b. In contrast to the above, exposure of **7b** to the action of buffered trifluoroperacetic acid at −78 °C efficiently delivered an epoxide that was shown by X-ray analysis to be **19**. With the stereochemistry of **19** secure, protection of the enone system was next addressed. Ketalization with ethylene glycol and pyridinium *p*-toluenesulfonate provided a 1:3.3 mixture of **20** and **21** (Scheme III). However, their combined yield was only 40%, the major portion of the reaction mixture resulting from transannular bond formation as determined subsequently. The use of *p*-toluenesulfonic acid, oxalic acid, and trimethylsilyl triflate[25] caused this unwanted pathway to be followed exclusively. When the exchange reagents 2-methyl-2-ethyl-1,3-dioxolane[26] and 2-methoxy-1,3-dioxolane[27] were found to be equally unsuited to our goals, attention was directed to the utilization of new, sterically hindered catalytic agents. To our delight, the *p*-toluenesulfonate salts of 2,6-lutidine and 2,4,6-collidine were found to be particularly effective in furnishing **20** and **21**, and the application of either reagent in circumstances of this type is strongly recommended. The isomeric ketals, which proved readily distinguishable by ^{1}H NMR spectroscopy, were found to be exceptionally prone to rearrangement in mildly acidic environments.

Our original intention was to effect base-promoted ring opening[28] within **20** and **21**. However, molecular models revealed that the orientation of the oxirane ring in these molecules did not permit proper stereoelectronic alignment with either set of neighboring C–H bonds. Therefore, it came as no surprise to find that **20**/**21** were recalcitrant toward a host of amide bases. At the extreme, no reaction was observed upon heating **20**/**21** with 6 equiv of lithium diethylamide in refluxing benzene–HMPA (5:1) for extended periods of time. Diethylaluminum 2,2,6,6-tetramethylpiperidide[29] likewise did not promote fission of the oxirane ring.

A comparable level of inertness was noted when **20** and **21** were treated with several powerful nucleophilic agents. All attempts to effect C–O bond cleavage with sodium phenylselenolate ($NaBH_4$ and PhSeSePh[30]) in ethanol, potassium phenylselenolate in THF–HMPA (2:1) at the reflux temperatures,[31] lithium mercaptide,[32] and potassium methylselenolate (MeSeSeMe[33] and K) in comparable solvent systems resulted in the return of unreacted starting material. The point should also be made that these substrates are inert to lithium triethylborohydride at ambient temperature over a period of 7 days. Evidently the desired reaction pathway is thwarted by high levels of steric hindrance in conformation G and an inability to flex into the more crowded folded arrangement H.



Confronted by these facts and recalling the rather more obligatory nucleophilic involvement in the chemistry of bromonium ion F and its phenylselenonium counterpart, we next examined the possibility of activating the oxirane oxygen as a prelude to ring fission. Two reagent systems were selected for study, the first being that produced upon admixture of chlorotrimethylsilane, sodium iodide, and DBU in acetonitrile[34] and the second resulting from admixture of triphenylphosphine with iodine in dichloromethane solvent.[35] Either set of conditions induced the rapid disappearance of **20**/**21** and the formation of two products identified as **22** and the more strained **23** in the approximate ratio of 3:2. The singularly successful involvement of the remote double



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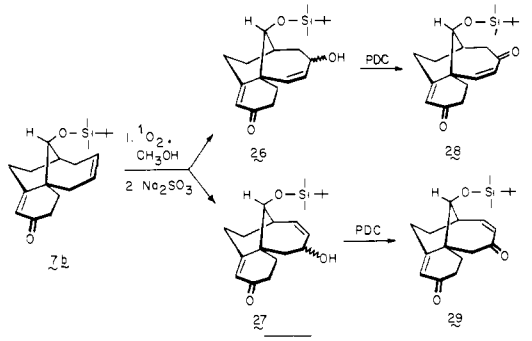
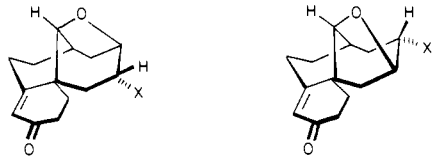
Scheme IV



bond was not exploitable for our purposes and was given no further attention.

A different neighboring group phenomenon was noted upon reaction of **7b** with *N*-bromosuccinimide or phenylselenenyl bromide and silver trifluoroacetate. Both of these reagents add to the double bond with a stereoselectivity opposite to that previously demonstrated for peracids, presumably in order to benefit from ultimate intramolecular capture of the apical oxygen atom. From the observed distributions of **24** and **25**, it is deduced that

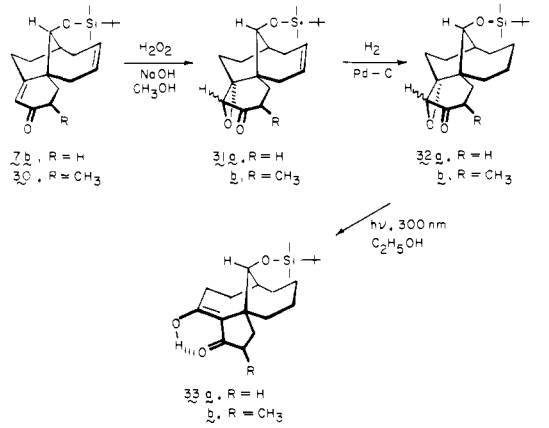


negligible regiochemical preferences are operative during formtion of the tetrahydrofuran rings.

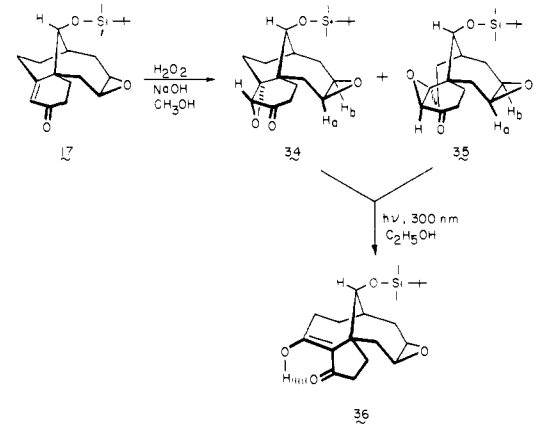
In order to bypass these complications and successfully complete this phase of our study, the possible utilitarian role of singlet oxygen was considered (Scheme IV). The results obtained from photooxygenation of **7b** in methanol with rose bengal as sensitizer and subsequent treatment with sodium sulfite proved highly interesting. Silica gel chromatography of the reaction mixture provided four distinct fractions. The first two in order of elution proved to be the diene diones **28** (6%) and **29** (18%). The direct generation of enones under these conditions, although not common, has been observed previously.[36] Allylic alcohols **26** and **27** (35%) comprised the third fraction. Analogy would suggest that the hydroxyl orientation in these isomers is endo, but this point was not delved into. Rather, the composite was converted via pyridinium dichromate oxidation into **28** and **29** (1:3). The last fraction (5%) consisted of an overoxidized mixture of compounds whose structural features were not investigated. The dominance of **27** and **29** produced upon singlet oxygenation of **7b** is especially suited to our purposes and sets the stage for continued elaboration of ring C and introduction of the cyclopropyl D ring.

Implementation of the Ring Transposition Scheme. The foregoing successful developments now required that a suitable ring transposition process be developed. To this end, we were attracted to the possible deployment of α,β-epoxy ketone substrates, since such substances are recognized to be capable of three distinctive photochemically induced reactions: (a) initial C_α–O bond cleavage followed by β-alkyl or β-hydrogen migration to form a 1,3-diketone,[37] (b) Norrish type I cleavage to form carbonyl and epoxy radicals, which react subsequently along separate pathways,[38] and

Scheme V



Scheme VI



(c) initial C_α–C_β cleavage with formation of ground-state ylide species.[39] The specific operation of one or the other of these reaction channels depends greatly on the nature and degree of substitution at C_β and on the electronic characteristics of the carbonyl group. Without doubt, the most synthetically useful systems studied to date have been 3-oxo-4,5-oxido steroids devoid of aryl substitution that photoisomerize according to (a).[40,41] One of the important open questions was whether conformational rigidity contributes in an important way to the evolution of the 3,5-dioxo-10(5→4)*abeo* derivatives. If this is the case, then adequate precedent was considered available to suggest that the tricyclic enones prepared in this work might well behave analogously.

Treatment of **7b** with alkaline hydrogen peroxide furnished a mixture of epimeric epoxy ketones **31a** (Scheme V). One isomer of **31a** was formed preferentially and could be isolated in a pure state. However, because our intent was to establish whether both isomers would undergo photoisomerization, the mixture was catalytically hydrogenated and subjected to irradiation with 300-nm light in ethanol solution. When the progress of this reaction was monitored by thin-layer chromatography, the two epimers of **32a** were observed to be consumed at approximately equal rates and to give rise to a single product, which was routinely

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isolated in 80% yield. This substance was identified as **33a** on the basis of its ^1H and ^{13}C NMR (18-line) NMR spectra and the appearance of enone-like infrared absorptions at 1650 and 1600 cm^{-1} (KBr). The enolic double bond is placed in the seven-membered ring in line with established precedent for such systems.[41d,42,43]

The presence of a methyl group in ring A of ingenol was taken into consideration by prior alkylation of **7b** with lithium diisopropylamide and methyl iodide. Following the isolation of **30**, its conversion to **33b** (Scheme V) proved equally efficient and independent of epoxide stereochemistry.

Although both isomers of epoxy ketones **31a** and **31b** were available, it was not possible to distinguish them by spectral means. For this reason, we were led to examine the epoxidation of **17**, a molecule that already contains oxiranyl protons of unique chemical shift which were expected to serve as internal probes of oxygen geometry in ring A. Substrates **34** and **35** were also attractive from a different vantage point. Since no specific information about the stability of remote three-membered rings to the excited-state ring transposition procedure could be found, these molecules represented important test cases.

Following conventional alkaline epoxidation of **17** (Scheme VI), the approximately equal mixture of **34** and **35** was separated into pure components by medium-pressure liquid chromatography on silica gel. The ^1H NMR spectrum of the more rapidly eluted isomer features a singlet at δ 3.02 due to the oxiranyl proton in ring A and multiplets of area 1 at δ 3.14 and 3.10 arising from H_a and H_b.[44] Comparison with the chemical shifts of H_a and H_b in **17** (δ 2.75 and 3.06) shows that a sizeable long-range deshielding effect has become operative at H_a in the diepoxide. Magnetic anisotropy influences of this magnitude are reasonable for the stereochemical arrangement found in **34**.[45] The second diepoxide, whose ring A oxiranyl proton appears at δ 3.16, exhibits additional signals due to H_a and H_b at δ 2.89 and 3.06 which are little changed in position relative to those in **17**. These findings are fully anticipated from the reversed spatial relationship of the oxiranyl oxygen to H_a found in **35**.

Where pure samples of **34** and **35** or mixtures thereof were irradiated in the manner described above, smooth rearrangement to **36** was observed as before.

Summary. A suitable means for annulating ketone **3** has been developed and shown to be useful for the preparation of tricyclic molecules such as **6** and **7**. Certain limits to the stereocontrolled introduction of select functional groups into ring C have been uncovered. Singlet oxygenation, in particular, provides direct entry to suitably substituted precursor molecules. By means of a mild photochemical rearrangement pathway, ring A epoxy ketones of this general structure undergo efficient conversion to their A/B hydroazulenoid isomers. Because the photoproducts are enolic 1,3-diketones, adequate oxygen functionality is considered present for ultimate conversion to isoingenol (**1'**). The present study has established that this brief synthetic scheme might well serve as an expedient route to **1'** and related natural products. The various ramifications of a total synthesis based upon this working premise are currently under active investigation.

Experimental Section

1,2,3,4,5,8-Hexahydro-1-oxo-6-methoxynaphthalene (3). To a suspension of 6-methoxy-1-tetralone (52.0 g, 0.300 mol) in 1250 mL of liquid ammonia, 240 mL of dry ether, and 425 mL of absolute ethanol was added 51.4 g (2.24 mol) of sodium metal over 3 h. After more than one-third of the sodium had been added, a deep green color was seen. The remainder of the metal was added at a rate so as to maintain a deep blue color. The ammonia was allowed to evaporate and the residue was partitioned between water (1 L) and ether (200 mL). The organic layer was separated and the aqueous phase was extracted with ether (2 × 250 mL). The combined organic extracts were washed with brine (4 × 200 mL), dried, and concentrated. The resulting brown oil was triturated with cold (−78 °C) ether (50 mL) to effect solidification. The solids were filtered, washed with cold ether until the filtrate was colorless, and dried in vacuo to provide 36.2 g (67%) of alcohol as a light beige powder, mp 74.5–75.5 °C (lit.[10a] mp 74 °C).

A solution of the above compound (36.1 g, 200 mmol) in dry toluene (160 mL) containing acetone (90 mL) and aluminum isopropoxide (6.1 g, 30 mmol) was heated at reflux with stirring for 4 h. The cooled reaction mixture was poured into 200 mL of brine and filtered through Celite. The filter cake was washed with ether (2 × 100 mL) and the aqueous phase was similarly extracted. The combined organic phases were washed with brine (2 × 100 mL), dried, and concentrated to leave a dark oil which was dissolved in ether (50 mL) and chilled to −78 °C. The solid that crystallized was filtered and dried in vacuo to provide 28.1 g of **3** as fine white needles, mp 49–51 °C (lit.[10a] mp 46–48 °C). An additional 2.3 g of **3** (mp 48–50 °C) was obtained from the mother liquors for a total yield of 88%.

(4a*R,9*R**)-3,4,8,9,10,11-Hexahydro-4a,9-methano-4a*H*-benzocyclononene-2,12(5*H*)-dione (6).** A cold (−78 °C) suspension of potassium amide [from potassium metal (4.7 g, 120 mmol) and ferric nitrate nonahydrate (0.1 g)] in 800 mL of purified dry ammonia was treated dropwise with a solution of **3** (17.8 g, 100 mmol) in tetrahydrofuran (100 mL) during 1 h. After 15 min, a solution of (*Z*)-1,4-dichloro-2-butene (15.8 mL, 150 mmol) in the same solvent (100 mL) was added rapidly (5 min). The cooling bath was removed and the ammonia was allowed to evaporate overnight. The reaction mixture was poured into water (1 L) and extracted with ether–petroleum ether (1:1) (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried, and concentrated to provide 32.4 g of a red oil; *m/e* (M^+ for $C_{15}H_{17}O_2{}^{35}Cl$) calcd 264.0917, obsd 264.0927.

This oil was dissolved in 1,2-dimethoxyethane (300 mL) and added dropwise over 2 h to a cold (−78 °C) suspension of potassium hydride (4.41 g, 110 mmol, washed free of mineral oil with dry petroleum ether) in 1,2-dimethoxyethane (400 mL) and *tert*-butyl alcohol (1.0 mL). The mixture was stirred for 2 h at −78 °C and overnight at room temperature. After being quenched with water (5 mL), the reaction mixture was poured into water (1 L) and extracted with ether–petroleum ether (1:1) (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried, and concentrated to leave a red oil (23.5 g), which was coated onto 50 g of Florisil and applied to the top of a 150-g column of Florisil (3.5 × 55 cm). Elution with ether–petroleum ether (1:5) provided 10.3 g of **5** as a bright yellow oil. A sample was further purified by rotary disk chromatography (ether/petroleum ether, 1:10): ^1H NMR ($CDCl_3$) δ 5.96 (m, 1 H), 5.75 (m, 1 H), 5.29 (m, 1 H), 5.12 (s, 1 H), 3.53 (s, 3 H), 2.83 (m, 1 H), 2.64–1.97 (m, 8 H), 1.79–1.62 (m, 2 H); ^{13}C NMR (ppm, $CDCl_3$) 216.04 (s), 134.42 (s), 130.35 (d), 129.50 (d), 119.61 (d), 97.58 (d), 54.44 (q), 48.73 (s), 46.00 (d), 32.89 (t), 32.41 (t), 32.16 (t), 27.37 (t), 24.70 (t) (one signal not observed); *m/e* (M^+) calcd 230.1307, obsd 230.1316.

The yellow oil was dissolved in tetrahydrofuran (100 mL) and 10 mL of 1.5 N hydrochloric acid was added. The solution was allowed to stand overnight at room temperature and then partitioned between water (1 L) and ether (200 mL). The aqueous phase was extracted with ether (2 × 100 mL) and the combined organic phases were washed with brine (2 × 100 mL), dried, and concentrated to provide 9.1 g of a pale yellow solid. Preparative HPLC purification of this material (Waters Prep 500, elution with 8% ethyl acetate in petroleum ether) afforded 6.8 g (32%) of **6**, as white plates, mp 102.5–103.5 °C (from ethanol); IR (cm^{-1}, KBr) 2900, 1690, 1655, 1610, 1420, 1230; ^1H NMR ($CDCl_3$) δ 6.02 (m, 1 H), 5.84 (d, J = 2.0 Hz, 1 H), 5.80 (m, 1 H), 3.28 (m, 1 H), 2.91 (m, 1 H), 2.76 (dd, J = 15.9 and 7.6 Hz, 1 H), 2.48 (m, 5 H), 2.36 (m, 1 H), 2.32 (m, 1 H), 2.23 (m, 1 H), 1.98 (m, 2 H); ^{13}C NMR (ppm, $CDCl_3$) 212.28 (s), 198.02 (s), 166.40 (s), 131.51 (d), 127.14 (d), 125.98 (d), 54.56 (s), 46.79 (d), 37.02 (t), 33.56 (t), 32.04 (t), 31.80 (t), 30.28 (t), 29.68 (t); *m/e* (M^+) calcd 216.1150, obsd 216.1156.

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.62; H, 7.42.

(4a*R,9*R**,12*S**)-3,4,8,9,10,11-Hexahydro-12-hydroxy-4a,9-methano-4a*H*-benzocyclononene-2(5*H*)-dione (7a).** To a chilled (0 °C) suspension of **6** (10.9 g, 50.0 mmol) in absolute ethanol (150 mL) was added dropwise a solution of sodium borohydride (567 mg, 15.0 mmol) in the same solvent (225 mL). After an additional 15 min of stirring, the reaction mixture was treated with a few drops of acetic acid and concentrated in vacuo. The resulting residue was partitioned between brine (50 mL) and ether (150 mL), and the aqueous phase was extracted with ether (2 × 100 mL). The combined organic layers were washed

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with brine, dried, and concentrated to give 9.84 g (90%) of **7a** as colorless prisms, mp 120–121.5 °C (from ether); IR (cm^{-1}, KBr) 3400, 2900, 1645, 1420, 1340, 1250, 1170, 790; ^1H NMR ($CDCl_3$) δ 5.86 (m, 1 H), 5.81 (d, J = 2 Hz, 1 H), 5.58 (m, 1 H), 3.81 (t, J = 5 Hz, 1 H), 3.08 (m, 1 H), 2.54 (m, 2 H), 2.54–2.10 (m, 7 H), 1.86 (m, 4 H); ^{13}C NMR (ppm, $CDCl_3$) 199.57 (s), 170.44 (s), 132.08 (d), 127.29 (d), 125.47 (d), 79.83 (d), 43.60 (s), 36.81 (d), 35.78 (t), 33.59 (t), 32.98 (t), 31.83 (t), 30.19 (t), 38.98 (t); m/e (M^+) calcd 218.1307, obsd 218.1313.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.99; H, 8.34.

(4a*R,9*R**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-3,4,8,9,10,11-hexahydro-4a,9-methano-4a*H*-benzocyclononen-2(5*H*)-one (7b).** To a chilled (0 °C) solution of **7a** (8.73 g, 40.0 mmol) in tetrahydrofuran (160 mL) containing 2,6-lutidine (11.6 mL, 100 mmol) was added rapidly in two equal portions a total of 18.4 mL of *tert*-butyldimethylsilyl triflate (80.0 mmol). After 20 min, the reaction mixture was treated with methanol (5 mL) and evaporated to dryness. The residues was partitioned between ether (150 mL) and water (50 mL), and the aqueous phase was extracted with ether (2 × 50 mL). The combined organic phases were washed with 5% sodium bicarbonate solution (3 × 50 mL), 10% potassium bisulfate solution (3 × 50 mL), and brine (2 × 50 mL) prior to drying and solvent evaporation. At this point, the bissilylated product can be isolated, if desired, by rotary disk chromatography (silica gel; elution with petroleum ether); mp 79.5–81.5 °C; IR (cm^{-1}, KBr) 3010, 2920, 2850, 1650, 1620, 1450, 1365, 1245, 1210, 1070, 875, 815, 760; ^1H NMR ($CDCl_3$) δ 5.72 (m, 1 H), 5.44 (m, 1 H), 5.26 (s, 1 H), 5.18 (m, 1 H), 3.76 (d, J = 5.0 Hz, 1 H), 2.77 (m, 1 H), 2.54–1.78 (m, 8 H), 1.27 (m, 2 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.13 (s, 3 H), 0.12 (s, 3 H), 0.041 (s, 6 H); ^{13}C NMR (ppm, $CDCl_3$) 150.65 (s), 35.47 (d), 33.04 (t), 31.35 (t), 27.76 (t), 27.46 (t), 27.16 (t), 26.07 (q), 25.76 (q), 18.36 (s), 18.12 (s), −3.90 (q), −4.15 (q), −4.39 (q), −4.81 (q); m/e (M^+) calcd 446.3036, obsd 446.3050.

The unpurified reaction mixture from above was dissolved in tetrahydrofuran (100 mL), treated with 15 mL of 0.5 N oxalic acid, and stirred for 72 h prior to solvent evaporation. The residue was partitioned between water (50 mL) and ether (150 mL) and the aqueous phase was extracted with ether (2 × 100 mL). The combined organic phases were washed with 5% sodium bicarbonate solution (3 × 50 mL) and brine (2 × 50 mL) before drying. The solid obtained after solvent evaporation was coated onto 50 g of Florisil and applied to a 150-g column of Florisil. Initial elution with 2% ethyl acetate in petroleum ether followed by an increase in polarity to 5% ethyl acetate furnished 12.6 g (95%) of pure **7b** as white needles, mp 132–133 °C (from ether); IR (cm^{-1}, KBr) 2900, 1660, 1610, 1250, 1080, 1000, 880, 830, 770; ^1H NMR ($CDCl_3$) δ 5.82 (m, 2 H), 5.55 (m, 1 H), 3.73 (d, J = 5.2 Hz, 1 H), 3.15 (m, 1 H), 2.80 (m, 2 H), 2.55–2.00 (m, 7 H), 1.94–1.59 (m, 3 H), 0.95 (s, 9 H), 0.063 (s, 6 H); ^{13}C NMR (ppm, $CDCl_3$) 199.14 (s), 169.65 (s), 132.39 (d), 127.84 (d), 125.96 (d), 81.17 (d), 44.09 (s), 37.35 (d), 36.38 (t), 33.89 (t), 33.17 (t), 31.71 (t), 29.89 (t), 29.04 (t), 25.94 (q), 18.24 (s), −3.84 (q), −4.93 (q); m/e ($M^+ - C_4H_9$) calcd 291.1416, obsd 291.1424.

Anal. Calcd for $C_{20}H_{32}O_2Si$: C, 72.20; H, 9.68. Found: C, 72.23; H, 9.70.

(4a*R,6*S**,7*S**,9*R**)-6-Bromo-3,4,6,7,8,9,10,11-octahydro-7-hydroxy-4a,9-methano-4a*H*-benzocyclononene-2,12(5*H*)-dione (11).** To a solution of **6** (1.08 g, 5.00 mmol) in 10 mL of 1,2-dimethoxyethane–water (9:1) was added a total of 1.07 g (6.00 mmol) of *N*-bromosuccinimide over 1 h. After 4 h, the reaction mixture was treated with a few drops of saturated sodium sulfite solution and partitioned between water (50 mL) and ethyl acetate (25 mL). The aqueous phase was extracted with ethyl acetate (2 × 25 mL) and the organic layers were washed with brine (2 × 25 mL), dried, and concentrated. Trituration of the solid residue with ether provided 0.89 g (57%) of **11** as white needles, mp 146.5–147 °C dec (from chloroform); IR (cm^{-1}, KBr) 3450, 2940, 2870, 1710, 1665, 1615, 1450, 1440, 1430, 1360, 1335, 1230, 1045, 685; ^1H NMR ($CDCl_3$) δ 5.92 (s, 1 H), 4.41 (m, 1 H), 3.65 (m, 1 H), 3.13–1.58 (m, 14 H); ^{13}C NMR (ppm, $CDCl_3$) 210.16 (s), 197.26 (s), 163.08 (s), 127.37 (d), 72.69 (d), 60.81 (d), 53.53 (s), 46.82 (t), 42.41 (d), 33.47 (t), 33.34 (t), 31.55 (t), 29.44 (t), 29.00 (t); m/e (M^+) calcd 312.0362, obsd 312.0370.

Anal. Calcd for $C_{14}H_{17}BrO_3$: C, 53.69; H, 5.47. Found: C, 53.53; H, 5.43.

(4a*R,6*S**,7*S**,9*R**)-3,4,6,7,8,9,10,11-Octahydro-7-hydroxy-6-(phenylseleno)-4a,9-methano-4*H*-benzocyclononene-1,12(5*H*)-dione (12).** Phenylselenenyl bromide was prepared in an addition funnel by adding bromine (0.20 mL, 4.0 mmol) to diphenyl diselenide (1.25 g, 4.00 mmol) dissolved in tetrahydrofuran (15 mL). After 5 min, this solution was added dropwise over 30 min to a cold (−78 °C) solution of **6** (1.08 g, 5.00 mmol) and silver trifluoroacetate (1.55 g, 7.00 mmol) in the same solvent (25 mL). After 30 min at −78 °C, 15 mL of a saturated sodium bicarbonate solution in water–methanol (3:2) was introduced, the ice bath was removed, and the reaction mixture was stirred overnight at room temperature. Following solvent removal, the residue was partitioned between water (50 mL) and ethyl acetate (25 mL). The aqueous phase was extracted with ethyl acetate (2 × 25 mL), and the combined organic layers were washed with brine (2 × 25 mL), dried, and concentrated in vacuo. Trituration of the resulting yellow solid with ether provided 1.23 g (63%) of **12** as a pale yellow powder. Recrystallization from methanol afforded a product, mp 146–147 °C; IR (cm^{-1}, KBr) 3320, 3050, 2940, 1705, 1665, 1605, 1475, 1435, 1420, 1365, 1270, 1250, 1240, 1185, 1110, 1070, 1040, 910, 880, 865, 835, 765, 740, 690; ^1H NMR ($CDCl_3$) δ 7.53 (m, 2 H), 7.30 (m, 3 H), 5.89 (d, J = 2.3 Hz, 1 H), 3.41 (m, 2 H), 3.17 (s, 1 H), 3.04–2.56 (m, 4 H), 2.52–2.29 (m, 3 H), 2.25–1.51 (m, 6 H); ^{13}C NMR (ppm, $CDCl_3$) 210.74 (s), 197.46 (s), 164.24 (s), 135.49 (d), 129.55 (d), 128.79 (s), 126.80 (d), 71.10 (d), 53.92 (s), 52.64 (d), 44.97 (t), 42.48 (d), 34.24 (t), 33.48 (t), 31.62 (t), 29.71 (t), 29.07 (t) (one signal not observed); m/e (M^+) calcd 390.0374, obsd 390.0801.

(4a*R,6*S**,7*S**,9*R**)-3,4,6,7,8,9,10,11-Octahydro-7-hydroxy-6-(phenylseleno)-4a,9-methano-4a*H*-benzocyclononene-2,12(5*H*)-dione Acetate (13).** A mixture of diphenyl diselenide (1.22 g, 3.9 mmol), bromine (0.19 mL, 3.8 mmol), tetrahydrofuran (10 mL), and acetic acid (10 mL) was stirred for 15 min and chilled to 0 °C. Potassium acetate (1.96 g, 20.0 mmol) and **6** (1.08 g, 5.00 mmol) were introduced, and the mixture was stirred overnight at room temperature, poured into 100 mL of water, and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with 5% sodium bicarbonate solution (3 × 25 mL) and brine (2 × 25 mL) prior to drying and solvent evaporation. The red oil (2.7 g) was chromatographed on silica gel (100 g, elution with 20% ethyl acetate in petroleum ether) to give 1.20 g of a yellow solid. Trituration with ether afforded 1.08 g (50%) of **13**, mp 126.5–127.5 °C (from methanol); IR (cm^{-1}, KBr) 2940, 1735, 1700, 1680, 1615, 1425, 1380, 1230, 1025, 885, 740, 690; ^1H NMR ($CDCl_3$) δ 7.51 (m, 2 H), 7.28 (m, 3 H), 5.83 (s, 1 H), 4.97 (dt, J = 8.5 and 4.1 Hz, 1 H), 3.73 (dt, J = 8.9 and 3.5 Hz, 1 H), 3.05–2.92 (m, 2 H), 2.58–1.85 (m, 11 H), 2.02 (s, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 210.43 (s), 197.40 (s), 169.29 (s), 164.44 (s), 134.50 (d), 129.36 (d), 128.79 (s), 128.28 (d), 126.49 (d), 74.81 (d), 53.73 (s), 44.92 (d), 44.34 (d), 39.23 (t), 33.16 (t), 32.39 (t), 30.22 (t), 29.33 (t), 27.60 (t), 20.96 (t).

Anal. Calcd for $C_{22}H_{24}O_4Se$: C, 61.25; H, 5.61. Found: C, 61.12; H, 5.68.

(4a*R,7*S**,9*R**)-3,4,8,9,10,11-Hexahydro-7-hydroxy-4a,9-methano-4a*H*-benzocyclononene-2,12(7*H*)-dione Acetate (15).** Unpurified **13** (2.7 g) was redissolved in tetrahydrofuran (20 mL). Pyridine (0.65 mL, 8.0 mmol) was added and the reaction mixture was cooled to −78 °C. Hydrogen peroxide (2.55 mL of 30%, 25.0 mmol) was added and the solution was stirred overnight at room temperature, poured into 100 mL of water, and extracted with ether (3 × 25 mL). The combined organic layers were washed with 10% potassium bisulfate solution (3 × 25 mL) and brine (2 × 25 mL) before drying and concentrated in vacuo. The residual yellow solid was filtered through a short column of Florisil (elution with 25% ethyl acetate in petroleum ether) to give 0.70 g (54% from **6**) of **15** as pale yellow needles, mp 143.5–144 °C (from methanol); IR (cm^{-1}, KBr) 2940, 1740, 1710, 1665, 1620, 1445, 1375, 1240, 1030, 730; ^1H NMR ($CDCl_3$) δ 5.92 (d, J = 1.5 Hz, 1 H), 5.76 (d, J = 11.7 Hz, 1 H), 5.58 (dd, J = 11.7 and 2.4 Hz, 1 H), 5.32 (m, 1 H), 3.14 (m, 1 H), 2.91 (m, 1 H), 2.46 (m, 2 H), 2.35 (m, 3 H), 2.08 (m, 1 H), 2.07 (s, 3 H), 1.89 (m, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 208.32 (s), 197.33 (s), 169.61 (s), 162.58 (s), 134.03 (d), 128.22 (d), 126.49 (d), 69.25 (d), 58.78 (s), 44.02 (d), 33.35 (2t), 29.39 (t), 28.24 (t), 27.48 (t), 20.96 (q).

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.96; H, 6.61.

(4a*R,7*S**,9*R**)-3,4,8,9,10,11-Hexahydro-7-hydroxy-4a,9-methano-4a*H*-benzocyclononene-2,12(7*H*)-dione (14). A. Selenoxide Elimination of 12.** Hydrogen peroxide (0.50 mL of 30%, 5.00 mmol) was added to a cold (−78 °C) solution of **12** (389 mg, 1.00 mmol) in tetrahydrofuran (4.0 mL) and pyridine (0.40 mL, 5.00 mmol). The reaction mixture was stirred overnight at room temperature, treated with a few drops of 10% sodium sulfite solution, poured into water (50 mL), and extracted with ethyl acetate (3 × 25 mL). The combined organic phases were washed with 10% potassium bisulfate solution (3 × 25 mL) and brine (2 × 25 mL) before drying and concentration in vacuo. Chromatography of the residue on silica gel (elution with 50% ethyl acetate in petroleum ether) furnished 204 mg (88%) of **14** as a colorless solid, mp 155–156 °C (from methanol); IR (cm^{-1}, KBr) 3400, 2940, 1710, 1650, 1615, 1350, 1220, 1050, 850, 755; ^1H NMR ($CDCl_3$) δ 5.89–5.86 (m, 2 H), 5.51 (dd, J = 11.6 and 2.4 Hz, 1 H), 4.35 (m, 1 H), 3.07 (m, 1 H), 2.92 (m, 1 H), 2.52 (br s, 1 H), 2.46 (m, 2 H), 2.30 (m, 3 H), 2.04 (dt, J = 13.6 and 4.4 Hz, 1 H), 1.85 (m, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 209.42 (s), 197.85 (s), 163.46 (s), 138.17 nd), 127.05 (d), 126.14 (d), 66.78 (d), 58.78 (s), 44.22 (d), 36.88 (t), 33.30 (t), 29.27 (t), 28.16 (t), 27.45 (t).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.12; H, 7.04.

B. Hydrolysis of 15. Finally divided potassium carbonate (0.69 g, 5.0 mmol) was added to a solution of **15** (274 mg, 1.00 mmol) in methanol (10 mL). After 5 min, the reaction mixture was poured into water (100 mL) and extracted with dichloromethane (3 × 25 mL). The combined organic phases were washed with brine (2 × 25 mL), dried, and concentrated in vacuo to provide 219 mg (94%) of **14**, spectroscopically identical with the material isolated by the previously described method.

(4a*R,6*R**,7*S**,9*R**)-6,7-Epoxy-3,4,6,7,8,9,10,11-octahydro-4a,9-methano-4a*H*-benzocyclononene-2,12(5*H*)-dione (17) and (4a*R**,7*S**,9*R**,10*R**,11a*S**)-10-Bromooctahydro-4a,9-epoxy-7,11a-methano-5*H*-benzocyclononene-3,12(4*H*)-dione (18).** A mixture of **11** (313 mg, 1.00 mmol) and silver oxide (0.93 g, 4.0 mmol) in 1,2-dimethoxyethane (20 mL) was heated at reflux for 72 h, filtered through Celite, and concentrated in vacuo. The residue was partitioned between water (25 mL), and ethyl acetate (25 mL). The aqueous phase was extracted with ethyl acetate (2 × 25 mL), and the combined organic extracts were washed with brine (2 × 25 mL), dried, and concentrated to dryness. Purification by MPLC (silica gel, elution with 45% ethyl acetate in petroleum ether) of the resulting yellow oil (0.27 g) provided 33.3 mg (10.6%) of **18** and 64.1 mg (27.6%) of **17**.

For **17**: mp 130.5–131.5 °C (from ether); IR (cm^{-1}, KBr) 2940, 1715, 1665, 1615, 1475, 1345, 1320, 1300, 1250, 1070, 1055, 1035, 870, 860, 830, 800, 770; ^1H NMR ($CDCl_3$) δ 5.79 (d, J = 1.8 Hz, 1 H), 3.38 (m, 1 H), 3.04 (m, 2 H), 2.39 (m, 7 H), 1.92 (m, 3 H), 1.75 (m, 2 H); ^{13}C NMR (ppm, $CDCl_3$) 210.11 (s), 197.33 (s), 163.67 (s), 126.49 (d), 53.79 (s), 53.45 (d), 51.62 (d), 46.32 (d), 32.91 (t), 32.08 (t), 28.05 (t), 27.73 (t), 27.41 (t), 26.58 (t); m/e (M^+) calcd 232.1099, obsd 232.1117.

For **18**: mp 159.5–160.5 °C (from ether); IR (cm^{-1}, KBr) 2950, 1705, 1455, 1410, 1240, 1205, 1040, 975, 900, 805, 770, 665; ^1H NMR ($CDCl_3$) δ 4.81 (d, J = 7.1 Hz, 1 H), 4.47 (dd, J = 7.2 and 5.5 Hz, 1 H), 2.76 (m, 1 H), 2.68–2.16 (m, 8 H), 1.97 (m, 4 H), 1.80 (m, 1 H), 1.34 (m, 1 H); ^{13}C NMR (ppm, $CDCl_3$) 213.05 (s), 209.74 (s), 88.61 (s), 81.84 (d), 56.54 (s), 51.75 (t), 50.09 (d), 44.72 (d), 35.91 (t), 35.59 (t), 34.82 (t), 32.01 (t), 25.24 (2t), 20.90 (t); m/e (M^+) calcd 312.0361, obsd 312.0337.

(4a*R,6*S**,7*R**,9*R**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-6,7-epoxy-3,4,6,7,8,9,10,11-octahydro-4a,9-methano-4a*H*-benzocyclononen-2-(5*H*)-one (19).** To a chilled (0 °C) mixture of 90% hydrogen peroxide (0.39 mL, 15 mmol) and dichloromethane (3.0 mL) was added trifluoroacetic anhydride (2.12 mL), 15.0 mmol). After the hydrogen peroxide had dissolved (5–10 min), the solution was diluted with an additional 30 mL of dichloromethane and added dropwise over 5 min to a mechanically stirred suspension of **7b** (3.32 g, 10.0 mmol) and sodium carbonate (10.6 g, 100 mmol) in dichloromethane (75 mL) maintained at −78 °C. The reaction mixture was stirred at this temperature for 3.5 h, warmed to room temperature, quenched with a few drops of saturated sodium sulfite solution, and poured into water (150 mL). The aqueous phase was extracted with dichloromethane (2 × 50 mL) and the combined organic layers were washed with brine (2 × 50 mL), dried, and concentrated. Purification on a Waters Prep 500 (silica gel, elution with 15% ethyl acetate in petroleum ether) provided 2.82 g (81%) of **19** as colorless needles, mp 160.5–161 °C (from ether); IR (cm^{-1}, KBr) 2950, 2850, 1660, 1610, 1240, 1100, 890, 825, 770; ^1H NMR ($CDCl_3$) δ 5.91 (d, J = 2.2 Hz, 1 H), 3.49 (d, J = 5.5 Hz, 1 H), 3.06 (m, 1 H), 2.74 (m, 2 H), 2.55–2.40 (m, 3 H), 2.39–2.34 (m, 1 H), 2.26–1.84 (m, 8 H), 1.62–1.51 (m, 1 H), 0.89 (s, 9 H), 0.018 (s, 6 H); ^{13}C NMR (ppm, $CDCl_3$) 198.90 (s), 165.64 (s), 127.90 (d), 80.62 (d), 54.89 (d), 53.44 (d), 43.79 (s), 36.79 (d), 34.87 (t), 33.65 (t), 31.95 (t), 29.16 (t), 27.64 (t), 26.43 (t), 25.88 (q), 18.18 (s), −4.09 (q), −4.93 (q); m/e (M^+-C_4H_9) calcd 291.1416, obsd 291.1424.

Anal. Calcd for $C_{20}H_{32}O_3Si$: C, 68.92; H, 9.25. Found: C, 68.64; H, 9.27.

Prior to elution of **19**, 0.32 g (8.9%) of the Baeyer–Villiger product of **19** was also obtained: mp 132–134.5 °C dec (from ether); IR (cm^{-1}, KBr) 2950, 2930, 2850, 1750, 1660, 1255, 1140, 1100, 1080, 880, 865, 830, 770; ^1H NMR ($CDCl_3$) δ 6.32 (s, 1 H), 3.78 (d, J = 4.2 Hz, 1 H), 3.00 (m, 1 H), 2.89 (m, 1 H), 2.74 (m, 1 H), 2.41 (dt, J = 13.1 and 4.3 Hz, 1 H), 2.25 (m, 2 H), 2.16–1.73 (m, 9 H), 0.86 (s, 9 H), 0.024 (s, 3 H), 0.022 (s, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 172.36 (s), 134.54 (d), 128.73 (s), 76.73 (d), 54.05 (d), 53.16 (d), 43.89 (s), 37.44 (t), 34.57 (d), 31.82 (t), 30.16 (t), 27.16 (t), 25.82 (q), 25.18 (t), 24.86 (t), 18.15 (s), −4.08 (q), −5.10 (q); m/e (M^+ − t-Bu) calcd 307.1366, obsd 307.1346.

(4a*R,6*S**,7*R**,9*R**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-6,7-epoxy-3,4,5,6,7,8,9,10-octahydro-4a,9-methano-4a*H*-benzocyclononen-2-(1*H*)-one Cyclic Ethylene Acetal (20) and (4a*R**,6*S**,7*R**,9*R**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-6,7-epoxy-3,4,6,7,8,9,10,11-octahydro-4a,9-methano-4a*H*-benzocyclononen-2-(5*H*)-one Cyclic Ethylene Acetal (21).** A mixture of **19** (785 mg, 2.25 mmol), collidinium *p*-toluenesulfonate (293 mg, 1.00 mmol), ethylene glycol (1.86 g, 30.0 mmol), and benzene (30 mL) was heated at reflux for 72 h with azeotropic removal of water. The reaction mixture was partitioned between water (25 mL) and ether (25 mL), the aqueous phase was extracted with ether (2 × 25 mL), and the combined organic layers were washed with brine (2 × 25 mL), dried, concentrated, and placed in vacuo at 0.10 torr for several hours to provide 880 mg (99.7%) of the **20**/**21** mixture as a colorless glass: IR (cm^{-1}, film) 2940, 2860, 1465, 1360, 1260, 1095, 1035, 950, 910, 870, 835, 770; ^1H NMR ($CDCl_3$) δ 5.27 and 5.24 (two s, 1 H), 3.96 (m, 2 H), 3.87 (m, 1 H), 3.75 (m, 1 H), 3.39 (d, J = 2.2 Hz, 1 H), 2.64 (m, 1 H), 2.33 (m, 1 H), 2.12 (m, 3 H), 1.55 (m, 10 H), 0.91 (s, 9 H), 0.066 (s, 3 H), 0.045 (s, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 149.17 (s), 119.08 (d), 113.91 (d), 106.18 (s), 81.39 (d), 74.17, 68.68 (d), 67.46, 64.65 (t), 64.34 (t), 48.24, 44.92, 43.38, 43.13, 42.62, 40.32, 40.19, 38.21 (t), 37.31, 35.65, 32.97, 32.46, 30.54, 29.46, 28.11, 27.03, 25.94 (t), 25.30 (t), 18.21 (s), −3.95 (q), −4.66 (q); m/e (M^+) calcd 392.2383; obsd 392.2417.

(2*R,3a*R**,4*S**,5a*R**,9b*S**,10*S**)-10-(*tert*-Butyldimethylsiloxy)-2,3,3a,4,5,6,7,9b-octahydro-4-hydroxy-2,5a-methano-5a*H*-benz[*e*]inden-8(1*H*)-one (22) and (1*R**,3*R**,4a*S**,8a*R**,9a*R**,10*S**)-10-(*tert*-Butyldimethylsiloxy)-2,3,4,4a,7,8,9,9a-octahydro-1-hydroxy-3,8a-methano-8a*H*-fluoren-6(1*H*)-one (23). Method A.** A mixture of trimethylsilyl chloride (0.38 mL), 3.0 mmol), acetonitrile (3.0 mL), and sodium iodide (450 mg, 3.0 mmol) was stirred at 0 °C for 15 min. To this mixture was added diazabicycloundecene (0.37 mL, 3.0 mmol) and **19** (196 mg, 0.500 mmol). The ice bath was removed and the mixture stirred for 36 h, quenched with saturated ammonium chloride solution, and partitioned between water (50 mL) and ether (25 mL). The aqueous phase was extracted with ether (2 × 25 mL) and the combined organic layers were washed with 5% sodium bicarbonate (3 × 25 mL), 10% potassium bisulfate (3 × 25 mL), and saturated sodium chloride solutions (2 × 25 mL) prior to drying and solvent removal. There was obtained 0.17 g of a white solid which was coated onto 0.5 g of silica gel and applied to a 10 g (0.5 × 30 cm) column of silica gel. Elution with 20% ethyl acetate in petroleum ether gave 125 mg (72%) of pure **22** as a colorless crystalline solid, mp 147–148 °C (from ether); IR (cm^{-1}, KBr) 3420, 2940, 2880, 1660, 1620, 1470, 1460, 1360, 1250, 1220, 1100, 1025, 945, 860, 830, 765; ^1H NMR ($CDCl_3$) δ 5.75 (s, 1 H), 3.79 (m, 1 H), 3.45 (d, J = 2.1 Hz, 1 H), 2.82 (t, J = 6.5 Hz, 1 H), 2.48 (m, 1 H), 2.38–2.17 (m, 5 H), 1.95 (m, 1 H), 1.84 (m, 2 H), 1.69–1.43 (m, 4 H), 0.93 (s, 9 H), 0.10 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 199.20 (s), 169.26 (s), 122.18 (d), 81.85 (d), 67.96 (d), 44.89 (t), 44.08 (d), 43.48 (s), 42.94 (d), 37.27 (t), 33.29 (2C, t), 31.88 (t), 25.87 (q), 25.07 (t), 18.12 (s), −3.92 (q), −4.73 (q) (one signal not observed).

Anal. Calcd for $C_{20}H_{32}O_3Si$: C, 68.92; H, 9.25. Found: C, 68.83; H, 9.19.

Method B. To a solution of iodine (83.8 mg, 0.330 mmol) in dichloromethane was added triphenylphosphine (86.6 mg, 0.330 mmol). After 5 min, **19** (118 mg, 0.300 mmol) was added. The reaction mixture was stirred for 12 h and partitioned between water (25 mL) and ether (25 mL). The aqueous layer was extracted with ether (2 × 25 mL) and the combined organic phases were washed with 10% sodium sulfite solution (3 × 25 mL) and brine (2 × 25 mL), dried, and concentrated to provide 0.20 g of a white solid. Purification as described above afforded 83.8 g (80%) of **22**, spectroscopically identical with the substance obtained in part A.

(2*R,3*R**,4a*S**,5*R**,11a*R**)-2-Bromo-2,3,4a,5,6,7,10,11-octahydro-3,5-methano-1*H*,9*H*-naphtho[1,8a-*b*]pyran-9-one (24a) and (2*R**,3*R**,4a*S**,10a*S**,10b*R**)-3-Bromo-3,4,4a,5,6,9,10,10b-octahydro-8*H*-2,10a-methano-2*H*-naphtho[1,2-*b*]pyran-8-one (25a).** A solution of *N*-bromosuccinimide (97.9 mg, 0.550 mmol) in 1,2-dimethoxyethane (2.5 mL) was added dropwise to a solution of **7b** (166 mg, 0.500 mmol) in 5 mL of 1,2-dimethoxyethane:water (7:1). After 2 h, a few drops of 10% sodium bisulfite solution was added and the mixture was concentrated in vacuo. The residue was partitioned between water (5 mL) and ether (15 mL). The aqueous phase was extracted with ether (2 × 10 mL), and the combined organic layers were washed with saturated sodium bicarbonate solution (3 × 5 mL) and brine (2 × 5 mL) prior to drying and solvent evaporation. Purification by rotary disk chromatography provided 100 mg (67%) of a 2:3 mixture of **24a** and **25a**. Recrystallization from ether gave an approximate 1:7 mixture of these isomers as a colorless solid, mp 125–132 °C dec; IR (cm^{-1}, KBr) 2440, 1660, 1610, 1450, 1350, 1325, 1255, 1230, 1020, 835, 795, 755; ^1H NMR ($CDCl_3$) δ 5.87–5.84 (m, 1 H), 4.46 (m, 1 H), 4.38 (m, 1 H), 3.85 and 3.74 (two d's, J = 6.5 and 5.5 Hz, 1 H), 2.73–1.80 (m, 12 H), 1.58 (m, 1 H); m/e (M^+) calcd 296.0408, obsd 296.0406.

(2*R,3*R**,4a*S**,5*R**,11a*R**)-2,3,4a,5,6,7,10,11-Octahydro-2-(phenylseleno)-3,5-methano-1*H*,9*H*-naphtho[1,8a-*b*]pyran-9-one (24b) and (2*R**,3*R**,4a*S**,10b*R**)-3,4,4a,5,6,9,10,10b-Octahydro-3-(phenylseleno)-8*H*-2,10a-methano-2*H*-naphtho[1,2-*b*]pyran-8-one (25b).** In an addition funnel, a solution of phenylselenenyl bromide was prepared by adding bromine (20.5 μL, 0.400 mmol) to a solution of diphenyl di-

selenide (125 mg, 0.400 mmol) in tetrahydrofuran (1.25 mL). After 5 min, this solution was added dropwise to a chilled (−10 °C) solution of **7b** (166 mg, 0.500 mmol) in tetrahydrofuran (1 mL) containing silver trifluoroacetate (155 mg, 0.700 mmol). After 30 min, 2 mL of a saturated sodium bicarbonate solution in methanol–water (1:2) was introduced, and the reaction mixture was stirred at room temperature for 6 h, poured into 25 mL of water, and extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with brine (2 × 15 mL), dried, and concentrated in vacuo. Recrystallization of the residue from ethyl acetate–ether:petroleum ether (1:1:6) provided 145 mg (73%) of a mixture of **24a** and **24b**, mp 139–148 °C; IR (cm^{-1}, KBr) 2940, 2890, 1675, 1615, 1565, 1470, 1330, 1260, 1250, 1030, 1010, 955, 865, 755, 735, 685; ^1H NMR ($CDCl_3$) δ 7.45 (m, 2 H), 7.26 (m, 3 H), 5.84 (m, 1 H), 4.34 (m, 1 H), 3.71 (m, 2 H), 2.70–1.61 (m, 13 H); *m/e* (M^+) calcd 374.0779, obsd 374.0694.

Singlet Oxygenation of 7b. A solution of **7b** (332 mg, 1.00 mmol) in methanol (250 mL) containing rose bengal (40 mg) was irradiated with a 500-W tungsten lamp while oxygen was continuously bubbled through the solution. After 18 h, 10 mL of 10% sodium sulfite solution was added and the reaction mixture was stirred overnight, filtered, and evaporated. The residue was partitioned between 10% brine (50 mL) and ethyl acetate (25 mL). The aqueous phase was extracted with ethyl acetate (2 × 25 mL), and the combined organic layers were washed with brine (2 × 25 mL) and dried. Following solvent removal, the red solid was filtered through a short column of Florisil (elution with 20% ethyl acetate in petroleum ether) and purified further by MPLC on silica gel. There was isolated in order of elution 83 mg (25%) of **7b**, 14.2 mg (5.5%) of **28**, 46.5 mg (17.4%) of **29**, 90.6 mg (34.7%) of a mixture of **26** and **27**, and 16.9 mg of an unidentified material.

For **28**: mp 154–154.5 °C (from ether); IR (cm^{-1}, KBr) 2950, 2850, 1670, 1650, 1255, 1220, 1090, 1000, 890, 825, 770, 670; ^1H NMR ($CDCl_3$) δ 6.09 (s, 2 H), 5.87 (d, J = 1.7 Hz, 1 H), 3.72 (d, J = 5.5 Hz, 1 H), 3.3 (dd, J = 15.7 and 6.1 Hz, 1 H), 2.53 (m, 3 H), 2.37–2.19 (m, 3 H), 1.97–1.64 (m, 4 H), 0.89 (s, 9 H), 0.096 (s, 3 H), 0.088 (s, 3 H); *m/e* (M^+) calcd 346.1964, obsd 346.1910.

For **29**: mp 158.5–159 °C (from ether); IR (cm^{-1}, KBr) 2960, 2860, 1675, 1650, 1255, 1100, 1085, 900, 860, 830, 770, 675; ^1H NMR ($CDCl_3$) δ 6.21 (d, J = 3.4 Hz, 2 H), 5.85 (d, J = 1.7 Hz, 1 H), 3.71 (d, J = 5.0 Hz, 1 H), 3.09 (d, J = 15.0 Hz, 1 H), 3.00 (m, 1 H), 2.65 (d, J = 15.0 Hz, 1 H), 2.44 (m, 2 H), 2.20 (m, 3 H), 1.78 (m, 3 H), 0.89 (s, 9 H), 0.11 (s, 3 H), 0.096 (s, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 206.17 (s), 198.23 (s), 164.18 (s), 140.86 (d), 134.16 (d), 127.06 (d), 79.22 (d), 47.02 (t), 43.32 (d), 43.06 (s), 36.29 (t), 33.67 (t), 28.18 (t), 26.71 (t), 25.75 (q), 18.15 (s), −4.14 (q), −4.84 (q).

Anal. Calcd for $C_{20}H_{30}O_3Si$: C, 69.32; H, 8.72. Found: C, 69.75; H, 8.77.

For **26/27**: IR (cm^{-1}, KBr) 3400, 2920, 2850, 1660, 1610, 1245, 1095, 1025, 880, 860, 830, 765; ^1H NMR ($CDCl_3$) δ 5.93–5.77 (m, 2 H), 5.56–5.36 (m, 1 H), 4.69 and 4.34 (two m, 1 H), 3.57 (d, J = 4.3 Hz, 1 H), 2.69 (m, 1 H), 2.61–2.18 (m, 7 H), 1.97–1.61 (m, 4 H), 0.91 (s, 9 H), 0.090 (s, 3 H), 0.078 (s, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 198.99 (s), 166.54 (s), 136.58 (d), 127.83 (d), 127.00 (d), 126.36 (d), 125.21 (d), 80.24 (d), 70.08 (d), 69.06 (d), 43.32 (s), 42.04 (d), 36.87, 36.55, 36.36, 35.08, 34.31, 33.67, 33.35, 30.67, 29.46, 27.86, 25.82 (q), 18.21 (s), −3.95 (q), −4.27 (q), −4.91 (q); *m/e* (M^+) calcd 348.2121, obsd 348.2077.

Oxidation of 26/27. A mixture of **26/27** (52.3 mg, 0.150 mmol), dichloromethane (2 mL), dry Celite (254 mg), and pyridinium dichromate (84.6 mg, 0.225 mmol) was magnetically stirred for 5 h, filtered through Celite, and passed through a short column of silica gel (elution with 20% ethyl acetate in petroleum ether). Separation of the two isomers was achieved by MPLC on silica gel (elution with 20% ethyl acetate in petroleum ether). There was obtained 10.0 mg (19.2%) of **28** and 31.1 mg (59.8%) of **29**.

(1*R,4a*R**,9*R**,11a*R**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-1,11a-epoxy-3,4,5,8,9,10,11,11a-octahydro-4a,9-methano-4a*H*-benzocyclononen-2(1*H*)-one (31a).** A solution of **7b** (3.0 g, 9.03 mmol) in methanol (300 mL) was cooled to 0 °C and treated with hydrogen peroxide (30 mL, 30%) followed by 4 N sodium hydroxide solution (15 mL). After 2 h at 0 °C, the mixture was allowed to warm up to room temperature, stirred for an additional 5 h, diluted with water (500 mL), and extracted with ether (3 × 250 mL). The combined organic layers were washed with saturated sodium sulfite solution (1 mL) and brine (2 × 200 mL) prior to drying and solvent evaporation. The residue was chromatographed on Florisil (elution with ether–petroleum ether, 1:9) to furnish 2.10 g (66%) of an isomer of **31a** as a white solid, mp 137.5–138 °C (from methanol); IR (cm^{-1}, $CDCl_3$) 3005, 2940, 2935, 2900, 2860, 1705, 1470, 1460, 1450, 1405, 1250, 1100, 1085, 835; ^1H NMR ($CDCl_3$) δ 5.81 (m, 1 H), 5.50 (m, 1 H), 4.00 (d, J = 8.0 Hz, 1 H), 3.05 (s, 1 H), 2.9–1.6 (series of m, 13 H), 0.890 (s, 9 H), 0.059 (s, 6 H); ^{13}C NMR (ppm, $CDCl_3$) 207.43 (s), 131.73 (d), 127.45 (d), 79.35 (d), 70.08 (s), 61.84 (d), 42.87 (s), 37.70 (d), 33.35 (t), 31.88 (t), 30.35 (t), 29.97 (t), 28.94 (t), 25.94 (q), 18.28 (s), −3.83 (q), −4.91 (q) (one signal not observed); *m/e* ($M^+ - C_4H_9$) calcd 291.1417, obsd 291.1466.

Anal. Calcd for $C_{20}H_{32}O_3Si$: C, 68.92; H, 9.25. Found: C, 69.07; H, 9.36.

(1*R,4a*R**,9*S**,11a*R**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-1,11a-epoxydecahydro-4a,9-methano-4a*H*-benzocyclononen-2(1*H*)-one (32a).** A solution of **31a** (2.0 g, 5.7 mmol) in ethyl acetate (60 mL) containing 10% palladium on carbon (100 mg) was stirred under a hydrogen atmosphere (1 atm) until hydrogen uptake ceased (3 h). The mixture was filtered through Celite and the solvent was removed under reduced pressure to yield 2.1 g (100%) of an opaque oil, which was crystallized from methanol to give an isomer of **32a** as a colorless solid, mp 62–62.5 °C; IR (cm^{-1}, $CDCl_3$) 2960, 2930, 2860, 1705, 1470, 1460, 1450, 1252, 1085, 835; UV λ_{max} (C_2H_5OH) 296 nm (ϵ 32.7); ^1H NMR ($CDCl_3$) δ 3.91 (d, J = 5.4 Hz, 1 H), 3.08 (s, 1 H), 2.57–2.24 (m, 4 H), 2.24–1.31 (m, 13 H), 0.93 (s, 9 H), 0.11 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 207.38 (s), 81.03 (d), 70.59 (s), 61.79 (d), 43.15 (s), 37.79 (d), 33.52 (t), 33.36 (t), 31.45 (t), 30.95 (t), 28.88 (t), 26.92 (t), 26.48 (t), 25.98 (q), 18.16 (s), −4.03 (q), −5.01 (q) (one signal not observed).

Anal. Calcd for $C_{20}H_{34}O_3Si$: C, 68.52; H, 9.78. Found: C, 68.40; H, 9.72.

(3a*R,8*R**,12*R**)-12-(*tert*-Butyldimethylsiloxy)-2,3,5,6,7,8,9,10-octahydro-11-hydroxy-3a,8-methano-3a*H*-cyclopentacyclodecen-1-(4*H*)-one (33a).** A solution of **32a** (2.34 g, 6.68 mmol) in absolute ethanol (200 mL) was deoxygenated with a stream of nitrogen and exposed to 3000-Å light through quartz for 18 h. At this point, TLC analysis (silica gel, elution with 10% ether–petroleum ether) showed only a trace of residual starting material. Solvent was removed under reduced pressure and the residue was recrystallized from acetone to give 1.87 g (80%) of **33a** as a white solid, mp 99.5–100 °C; IR (cm^{-1}, KBr) 2960, 2860, 1650, 1610, 1470, 1440, 1420, 1390, 1315, 1260, 1215, 1185, 1080, 962, 900, 880, 845, 835, 775; UV λ_{max} (C_2H_5OH) 287 nm (ϵ 8950); ^1H NMR ($CDCl_3$) δ 3.84 (d, J = 6.0 Hz, 1 H), 2.63–2.44 (m, 3 H), 2.24–2.14 (m, 2 H), 2.07–1.35 (m, 13 H), 0.94 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (ppm, $CDCl_3$) 209.27 (s), 176.63 (s), 119.20 (s), 81.58 (d), 50.66 (s), 42.36 (d), 39.10 (t), 35.90 (t), 34.75 (t), 32.01 (t), 27.09 (t), 26.00 (q), 24.60 (t), 23.57 (t), 18.27 (s), −3.82 (q), −5.10 (q) (one signal not observed); *m/e* (M^+) calcd 350.2277, obsd 350.2293.

Anal. Calcd for $C_{20}H_{34}O_3Si$: C, 68.52; H, 9.78. Found: C, 68.43; H, 9.87.

(4a*R,9*S**,12*R**)-12-(*tert*-Butyldimethylsiloxy)-3,4,8,9,10,11-hexahydro-3-methyl-4a,9-methano-4a*H*-benzocyclononen-2(5*H*)-one (30).** A solution of **7b** (7.0 g, 21 mmol) in anhydrous tetrahydrofuran (60 mL) was added dropwise during 1 h to a solution of lithium diisopropylamide (27 mmol, from 3.0 g of diisopropylamine and 16.8 mL of 1.60 M *n*-butyllithium) in the same solvent (50 mL) at 0 °C. Stirring was continued for an additional 15 min, methyl iodide (7.5 g, 54 mmol) was added rapidly, and the mixture was allowed to come to room temperature where stirring was maintained for 3 h. Water (100 mL) was added and the mixture was extracted with ether (3 × 100 mL). The combined organic phases were washed with 10% potassium bisulfate solution (2 × 75 mL) and brine (2 × 75 mL) before drying and solvent evaporation. The residue was chromatographed on silica gel (elution with 10% ether in petroleum ether) to furnish 5.6 g (77%) of **30** as a white solid, mp 88.5–90.5 °C (from methanol); IR (cm^{-1}, $CDCl_3$) 3010, 2960, 2935, 2900, 2860, 1665, 1615, 1470, 1450, 1370, 1360, 1260, 1220, 1110, 1100, 1085, 1002, 825; ^1H NMR ($CDCl_3$) δ 5.85–5.77 (m, 1 H), 5.75 (d, J = 2 Hz, 1 H), 5.54–5.48 (m, 1 H), 3.69 (d, J = 5.3 Hz, 1 H), 3.18–3.05 (dt, J = 6.6 and 6.2 Hz, 1 H), 2.82 (br s, 1 H), 2.77 (br s, 1 H), 2.51–2.43 (m, 1 H), 2.34–2.26 (m, 1 H), 2.16–1.97 (m, 4 H), 1.90–1.73 (m, 3 H), 1.10 (d, J = 6.6 Hz, 3 H), 0.92 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (ppm, $CDCl_3$) 201.59 (s), 168.57 (s), 132.43 (d), 128.00 (d), 125.65 (d), 81.58 (d), 45.94 (t), 44.85 (s), 37.30 (d), 37.03 (d), 32.82 (t), 32.05 (t), 29.97 (t), 29.10 (t), 25.94 (q), 18.33 (s), 15.21 (q), −3.87 (q), −4.85 (q).

Anal. Calcd for $C_{21}H_{34}O_2Si$: C, 72.77; H, 9.88. Found: C, 72.39; H, 9.80.

(1*R,3*R**,4a*S**,9*R**,11a*R**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-1,11a-epoxy-3,4,5,8,9,10,11,11a-octahydro-3-methyl-4a,9-methano-4a*H*-benzocyclononen-2(1*H*)-one (31b).** A solution of **30** (1.0 g, 3 mmol) in methanol (100 mL) was cooled to 0 °C and treated with hydrogen peroxide (10 mL, 30%) followed by 4 N sodium hydroxide solution (5 mL). The mixture was stirred at 0 °C for 3 h and at room temperature for 8 h. Saturated sodium sulfite solution (2 drops) was added and the mixture was diluted with water (150 mL) and extracted with ether (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried, and evaporated to give 610 mg (57%) of **31b** as a white solid, mp 74.5–75.5 °C (from methanol); IR (cm^{-1}, $CDCl_3$) 3020, 2960, 2940,

2900, 2860, 1703, 1470, 1460, 1450, 1255, 1212, 1100, 1080, 830; ^{1}H NMR ($CDCl_3$) δ 5.80–5.73 (m, 1 H), 5.51–5.41 (m, 1 H), 4.01–3.96 (overlapping d, 1 H), 3.17 and 3.06 (two s, 1 H total), 2.95–2.55 (m, 4 H), 2.40–1.50 (m, 10 H), 1.17–1.11 (overlapping d, $J \approx 6.5$ Hz, 3 H), 0.92 (s, 9 H), 0.10–0.08 (four s, 6 H total); ^{13}C NMR (ppm, $CDCl_3$) 209.79 (s), 131.54 (d), 127.45 (d), 79.21 (d), 70.31 (s), 61.59 (d), 48.40 (s), 39.29, 38.21, 37.63, 32.52, 30.10, 29.01, 25.94 (q), 18.28 (s), 17.96 (q), −3.89 (q), −4.85 (q) (one signal not observed).

Anal. Calcd for $C_{21}H_{34}O_3Si$: C, 69.56; H, 9.45. Found: C, 69.62; H, 9.53.

(1*R,3*R**,4a*R**,9*S**,11a*R**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-1,11a-epoxydecahydro-3-methyl-4a,9-methano-4a*H*-benzocyclononen-2-(1*H*)-one (32b).** A solution of **31b** (300 mg, 0.82 mmol) in ethyl acetate (10 mL) containing 10% palladium on carbon (30 mg) was stirred under a hydrogen atmosphere (1 atm) until no further hydrogen uptake was seen. The mixture was filtered through Celite and the solvent was removed to give an oil (300 mg, 100%) which was crystallized from methanol to give **32b** as a white solid, mp 74.5–75.5 °C; IR (cm^{-1}, KBr) 2960, 2930, 2860, 1705, 1460, 1450, 1440, 1250, 1085, 908, 870, 835, 770; UV λ_{max} (C_2H_5OH) 296.5 nm (ϵ 40.1); ^{1}H NMR ($CDCl_3$) δ 3.88 (d, J = 5.6 Hz, 0.8 H), 3.70 (d, J = 5.6 Hz, 0.2 H), 3.21 (s, 0.2 H), 3.06 (s, 0.8 H), 2.5–1.2 (series of m, 16 H), 1.15–1.10 (overlapping d, 3 H), 0.92 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 209.72 (s), 80.85 (d), 70.64 (s), 61.48 (d), 43.08 (s), 40.67, 38.33, 37.74, 33.97 (t), 31.05 (t), 28.77 (t), 28.58 (t), 26.95 (t), 26.56 (t), 25.98 (q), 18.17 (s), 17.52 (q), −4.12 (q), −5.03 (q).

Anal. Calcd for $C_{21}H_{36}O_3Si$: C, 69.18; H, 9.95. Found: C, 69.28; H, 10.02.

(2*R,3a*S**,8*S**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-2,3,5,6,7,8,9,10-octahydro-11-hydroxy-2-methyl-3a,8-methano-3a*H*-cyclopentacyclodecen-1(4*H*)-one (33b).** A solution of **32b** (100 mg 0.3 mmol) in ethanol (10 mL) was deoxygenated with a stream of nitrogen and exposed to 3000-Å light through quartz for 22 h. Solvent was evaporated and the residue was purified by preparative TLC (silica gel, elution with 5% ether in petroleum ether). Diketone **33b** was isolated as a white solid (85 mg, 85%), mp 124–125 °C (from methanol); IR (cm^{-1}, KBr) 2950, 2915, 2850, 1650, 1608, 1470, 1460, 1450, 1380, 1260, 1185, 1075, 915, 885, 845, 765; UV λ_{max} (C_2H_5OH) 287 nm (ϵ 13,106); ^{1}H NMR ($CDCl_3$) δ 3.81 (d, J = 6.4 Hz, 0.8 H), 3.75 (d, J = 6.4 Hz, 0.2 H), 2.70–2.40 (m, 2 H), 2.35–1.20 (series of m, 15 H), 1.12–1.10 (overlapping d, 3 H), 0.95 (s, 9 H), 0.054 (s, 3 H), 0.0051 (s, 3 H); ^{13}C NMR (ppm, $CDCl_3$) (major isomer) 211.00 (s), 176.32 (s), 119.02 (s), 81.90 (d), 48.75 (s), 45.68 (t), 42.55 (d), 39.55 (d and t), 32.08 (t), 27.16 (two t), 26.07 (q), 24.60 (t), 23.71 (t), 18.34 (s), 14.32 (q), −3.82 (q), −4.98 (q); minor isomer peaks are seen at 82.80, 51.37, 43.51, 41.91, 32.97, 27.92, 26.71, 25.43, 23.32.

Anal. Calcd for $C_{21}H_{36}O_3Si$: C, 69.18; H, 9.95. Found: C, 69.20; H, 9.91.

(1*R,4a*S**,6*S**,7*R**,9*R**,11a*R**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-1,11a:6,7-diepoxydecahydro-4a,9-methano-4a*H*-benzocyclononen-2(1*H*)-one (34) and (1*R**,4a*R**,6*R**,7*S**,9*S**,11a*R**,12*R**)-12-(*tert*-Butyldimethylsiloxy)-1,11a:6,7-diepoxydecahydro-4a,9-methano-4a*H*-benzocyclononen-2(1*H*)-one (35).** A solution of **17** (1.05 g, 3.00 mmol) and hydrogen peroxide (12.3 mL of 30%, 120 mmol) in methanol (115 mL) was stirred magnetically at 0 °C while 3.6 mL of 4 N sodium hydroxide solution was added dropwise. After 5.5 h at 0 °C, the reaction mixture was treated with 10% sodium bisulfite solution and concentrated in vacuo. The residue was partitioned between water (50 mL) and ethyl acetate (25 mL). The aqueous phase was extracted with ethyl acetate (2 × 25 mL) and the combined organic extracts were washed with brine (2 × 25 mL), dried, and concentrated in vacuo to leave a white solid (0.67 g). Filtration through a short column of silica gel (elution with 20% ethyl acetate in petroleum ether) provided 0.62 g (57%) of **34/35**. Isomer separation was achieved by MPLC on silica gel (elution with 12% ethyl acetate in petroleum ether).

For **34**: mp 164.5–165.5 °C (from methanol); IR (cm^{-1}, KBr) 2935, 2900, 2860, 1705, 1250, 1105, 1080, 1060, 995, 920, 900, 880, 830, 770, 675; ^{1}H NMR ($CDCl_3$) δ 3.70 (d, J = 4.6 Hz, 1 H), 3.09 (m, 2 H), 3.02 (s, 1 H), 2.64 (m, 1 H), 2.43 (dt, J = 14.7 and 6.5 Hz, 1 H), 2.14–1.58 (m, 10 H), 1.33 (ddd, J = 7.6, 6.3, and 1.5 Hz, 1 H), 0.89 (s, 9 H), 0.034 (s, 3 H), 0.010 (s, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 207.24 (s), 78.07 (d), 69.00 (s), 64.72 (d), 55.14 (d), 53.73 (d), 42.42 (s), 36.42 (d), 34.63 (t), 32.97 (t), 32.01 (t), 30.99 (t), 27.80 (t), 25.88 (q), 25.11 (t), 18.21 (s), −3.89 (q), −5.04 (q).

Anal. Calcd for $C_{20}H_{32}O_4Si$: C, 65.89; H, 8.85. Found: C, 65.85; H, 8.88.

For **35**: mp 112–113 °C (from methanol); IR (cm^{-1}, KBr) 2935, 2870, 1715, 1245, 1100, 1085, 1005, 935, 900, 880, 860, 830, 775, 680; ^{1}H NMR ($CDCl_3$) δ 3.85 (d, J = 3.3 Hz, 1 H), 3.16 (s, 1 H), 3.06 (m, 1 H), 2.89 (dt, J = 6.0 and 4.5 Hz, 1 H), 2.50–2.32 (m, 3 H), 2.14–1.78 (m, 7 H), 1.57 (m, 1 H), 1.22 (dd, J = 8.3 and 5.9 Hz, 1 H), 0.89 (s, 9 H), 0.048 (s, 6 H); ^{13}C NMR (ppm, $CDCl_3$) 207.79 (s), 78.84 (d), 67.59 (s), 61.27 (d), 55.20 (d), 53.67 (d), 43.06 (s), 37.25 (d), 33.29 (t), 30.29 (t), 28.62 (t), 27.67 (t), 25.94 (q), 25.30 (t), 18.21 (s), −4.08 (q), −4.85 (q) (one signal not observed).

Anal. Calcd for $C_{20}H_{32}O_4Si$: C, 65.89; H, 8.85. Found: C, 65.81; H, 8.91.

(3a*R,5*S**,6*R**,8*R**,12*S**)-12-(*tert*-Butyldimethylsiloxy)-5,6-epoxy-2,3,5,6,7,8,9,10-octahydro-11-hydroxy-3a,8-methano-3a*H*-cyclopentacyclodecen-1(4*H*)-one (36).** A deoxygenated ethanol (80 mL) solution of **34/35** (570 mg, 1.56 mmol) was irradiated with 3000-Å light for 18 h. Following solvent removal, the white residue was purified by MPLC on silica gel (elution with 7.5% ethyl acetate in petroleum ether) to furnish in order of elution 231 mg (40.5%) of **36**, 125 mg (21.9%) of **34**, and 112 mg (19.7%) of **35**.

For **36**: mp 133–134 °C (from methanol); IR (cm^{-1}, KBr) 2930, 2860, 1640, 1605, 1395, 1310, 1255, 1220, 1200, 1180, 1065, 985, 930, 880, 860, 830, 810, 790, 770, 680; ^{1}H NMR ($CDCl_3$) δ 3.63 (br s, 1 H), 3.10 (m, 1 H), 2.85 (m, 1 H), 2.73 (m, 1 H), 2.54–2.32 (m, 3 H), 2.17–2.00 (m, 5 H), 1.99–1.83 (m, 3 H), 1.60–1.50 (m, 2 H), 0.89 (s, 9 H), 0.045 (s, 3 H), 0.032 (s, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 209.15 (s), 179.19 (s), 113.08 (s), 81.96 (d), 55.65 (d), 53.28 (d), 50.41 (s), 42.17 (d), 36.99 (t), 34.57 (t), 34.38 (t), 32.71 (t), 28.56 (t), 27.54 (t), 25.88 (q), 18.15 (s), −4.14 (q), −4.72 (q).

Anal. Calcd for $C_{20}H_{32}O_4Si$: C, 65.89; H, 8.85. Found: C, 66.02; H, 8.93.

X-ray Analyses. Crystals of **11** formed as thick rods with symmetry $Pna2_1$ with a = 11.907 (3), b = 16.990 (2), and c = 6.376 (2) Å for Z = 4. A total of 1053 reflections were measured by using a four-circle diffractometer and graphite monochromated radiation (λ = 1.5418 Å). Of these, 953 were observed ($I \geq 3\sigma I$) and corrected for Lorentz, polarization, and absorption effects. Application of a multisolution tangent formula approach to phase solution gave an initial model, which was subsequently refined by using Fourier methods and full-matrix least-squares analysis.[46] Positions and anisotropic temperature parameters were refined for the non-hydrogen atoms while just the positions for the hydrogens were refined. The function $\Sigma w(|F_o| - |F_c|)^2$ with $w = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual index of 0.034. Figure 1 is a perspective drawing of **11** showing the relative stereochemistry, while Tables I, II, and III contain the fractional coordinates, temperature parameters, bond distances, and bond angles.[47] The only short intermolecular contact is a hydrogen bond between O(11) and O(17) of length 2.82 Å.

Crystals of **19** formed as thick laths with internal symmetry $Pccn$ and unit cell constants of a = 7.150 (3), b = 38.433 (7), and c = 14.722 (6) Å for Z = 8. A total of 3174 reflections with $2\theta \leq 114°$ (λ = 1.5418 Å) were measured with a computer-controlled four-circle diffractometer using an ω scan technique. The 1719 diffraction maxima that were observed ($I \geq 3\sigma I$) were corrected for Lorentz and polarization effects. Application of direct methods and tangent formula refinement gave an initial model for the structure which was subsequently refined by using full-matrix least squares.[46] Isotropic temperature parameters were assigned to the hydrogen atoms by calculating the isotropic equivalent of the atoms to which they were bound. The final unweighted R factor was 0.057 after minimizing $\Sigma w(|F_o| - |F_c|)^2$ with $w = 1/(\sigma F_o)^2$. Figure 2[47] is a perspective drawing of **19** showing its relative stereochemistry. Tables IV–VI[47] contain the final fractional coordinates, temperature parameters, bond distances, and bond angles.

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Supplementary Material Available: Perspective drawings of **11** and **19** (Figures 1 and 2) and tables of final atomic parameters, bond lengths, and bond angles (Tables I–VI) for these compounds (8 pages). Ordering information is given on any current masthead page.

(46) The following library of crystallographic programs was used: MULTAN80, University of York, York, England (1980); Structure Determination Package V17.0, Enraf-Nonius Corp., Delft, Holland (1981) ORTEP-II, Oak Ridge National Laboratory, Oak Ridge, TN (1970).

(47) Supplementary material.