Application of Palladium-Catalyzed [3 + 2] Cycloaddition Technology to the Elaboration of Kempane Diterpenes. Stereocontrolled Synthesis of (±)-3α-Hydroxy-7β-kemp-8(9)-en-6-one and (±)-3β-Hydroxykemp-7(8)-en-6-one

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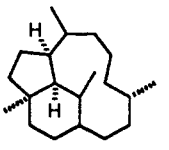
Abstract: The total synthesis of three hydroxykempenones (**8–10**) has been accomplished. The retrosynthetic elements of the strategy focused on setting four key stereocenters in rings A and B, followed by annulation of ring C and ultimate cyclization to construct the seven-membered ring, D. Since the target molecule carries eight contiguous stereogenic centers, proper attention to stereocontrolled processes was mandatory. The key features of the scheme include the palladium-catalyzed [3 + 2] cycloaddition of trimethylenemethane to an activated octalone with complete control of π-facial selectivity, fully regiospecific monooxidation of a diol with ammonium molybdate uniquely at the secondary site to provide a key hydroxy ketone, hydroxyl-directed hydride reduction of the latter intermediate in order to override a contrary kinetic preference for nucleophilic attack, avoidance of Grob fragmentation in diaxial, monofunctionalized 1,3-diols, and selective deoxygenation of a 1,3-diol. The stereochemical results featured in the cycloaddition step were elucidated preliminarily in experiments designed to probe cyclopentannulation in general. The striking kinetic stability of the α,β- and β,γ-unsaturated tetracyclic end products has been analyzed by means of molecular modeling.

Unlike lesser evolved termites that defend themselves physically by biting their foe with their mandibles, soldiers of the Nasutitermitinae subfamily avoid direct contact with the enemy by squirting an irritant secretion at them.[2] These gluelike materials, which are capable of immobilizing the most predacious assailants,[3] contain an impressive variety of structurally complex, irritant diterpenoids dissolved in monoterpene hydrocarbons.[4,5] Largely as a consequence of the extensive efforts of Prestwich,[6] Braekman,[7] Baker,[8] and Vrkoc,[9] many of the diterpene constituents have now been identified as containing a trinervitane (**1**), secotrinervitane (**2**), kempane (**3**), or rippertane (**4**) skeleton. The numerous oxygenation patterns, the richness in stereochemical variation, and the diversity of oxidation level engender admiration for the myriad ways in which the common precursor, cembrene A (**5**), can be biosynthetically manipulated.



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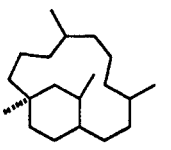

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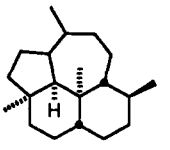

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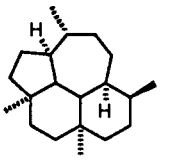

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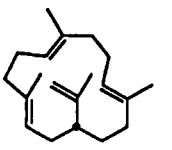

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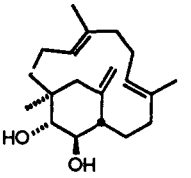
Despite the preeminent position held by this chemical cascade in the field of insect entomology, very little synthetic effort has been expended to meet the challenges offered by these discoveries. Kato et al. have reported a simple biogenetic route to racemic secotrinervitene-2β,3α-diol (**6**).[10] More recently, Dauben and his co-workers described an elegant scheme for the preparation of (±)-kempene 2 (**7**).[11]



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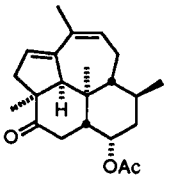

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Herein we report on a strategy that has resulted in the efficient acquisition of the hydroxykempenones **8–10**. These compounds are isomeric with 3β-hydroxy-7β-kemp-8(9)-en-6-one (**11**), a defense secretion agent of the neotropical species *Nasutitermes*

(1) (a) National Science Foundation Postdoctoral Fellow, 1990–1992. (b) Procter and Gamble Graduate Research Fellow, 1984–1985.

(2) Prestwich, G. D. *J. Chem. Ecol.* **1979**, *5*, 459. (b) Prestwich, G. D. *Sociobiology* **1979**, *4*, 127.

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(4) Prestwich, G. D. *Tetrahedron* **1982**, *38*, 1911.

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(7) (a) Braekman, J. C.; Daloze, D.; Dupont, A.; Pasteels, J.; Tursch, B.; Declercq, J. P.; Germain, G.; Van Meerssche, M. *Tetrahedron Lett.* **1980**, *21*, 2761. (b) Dupont, A.; Braekman, J. C.; Daloze, D.; Pasteels, J. M.; Tursch, B. *Bull. Soc. Chim. Belg.* **1981**, *90*, 485. (c) Braekman, J. C.; Daloze, D.; Dupont, A.; Arrieta, J. M.; Piccinni-Leopardi, C.; Germain, G.; Van Meerssche, M. *Bull. Soc. Chim. Belg.* **1983**, *92*, 111.

(8) (a) Wadhams, L. J.; Baker, R.; Howse, P. E. *Tetrahedron Lett.* **1974**, 1697. (b) Baker, R.; Briner, P. H.; Evans, D. A. *Chem. Commun.* **1978**, 410. (c) Baker, R.; Evans, D. A.; McDowell, P. G. *Tetrahedron Lett.* **1978**, 4073.

(9) (a) Vrkoc, J.; Ubik, K.; Dolejs, L.; Hrdy, L. *Acta Entomol. Bohemoslov.* **1973**, *70*, 74. (b) Vrkoc, J.; Budesinsky, M.; Sedmera, P. *Collect. Czech. Chem. Commun.* **1978**, *43*, 1225, 2478. (c) Vrkoc, J.; Ubik, K. *Tetrahedron Lett.* **1974**, 1463.

(10) Kato, T.; Hirukawa, T.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 977.

(11) Dauben, W. G.; Farkas, I.; Bridon, D. P.; Chueng, C.-P.; Henegar, K. E. *J. Am. Chem. Soc.* **1991**, *113*, 5883.

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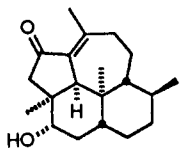
octopilis, whose structural assignment was fully corroborated by an X-ray diffraction analysis of the *p*-bromobenzoate derivative.[6d] The structural and stereochemical similarities of these four compounds suggested a common synthetic strategy and potentially a common chiral origin. In this way, useful information could be gained in support of the current quest for "biorationally designed" insect repellants.



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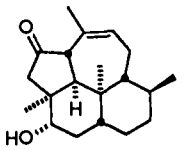

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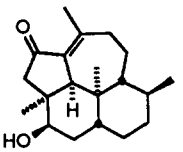

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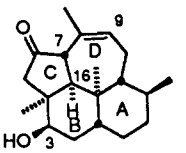

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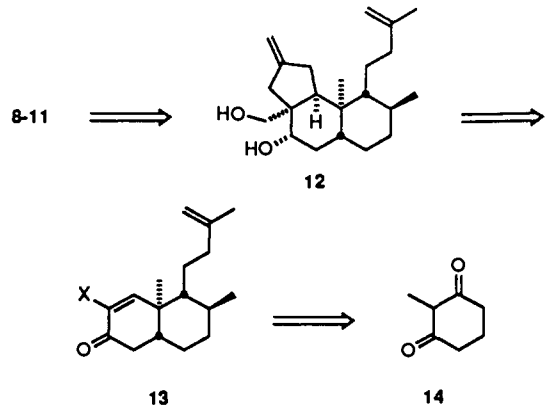
We note in advance that the concave conformational bias inherent to these dome-shaped diterpene systems introduces steric and electronic factors that preclude their chemical interconversion. From a retrosynthetic perspective, it was envisioned that our needs would be ideally served by presetting the seven contiguous stereogenic centers defined in diol **12**. Central to the construction of this intermediate was the previously recognized efficiency with which the transient trimethylenemethane–palladium(0) complex[12] cycloadds to activated 2-cyclohexenones.[13] From this point, the



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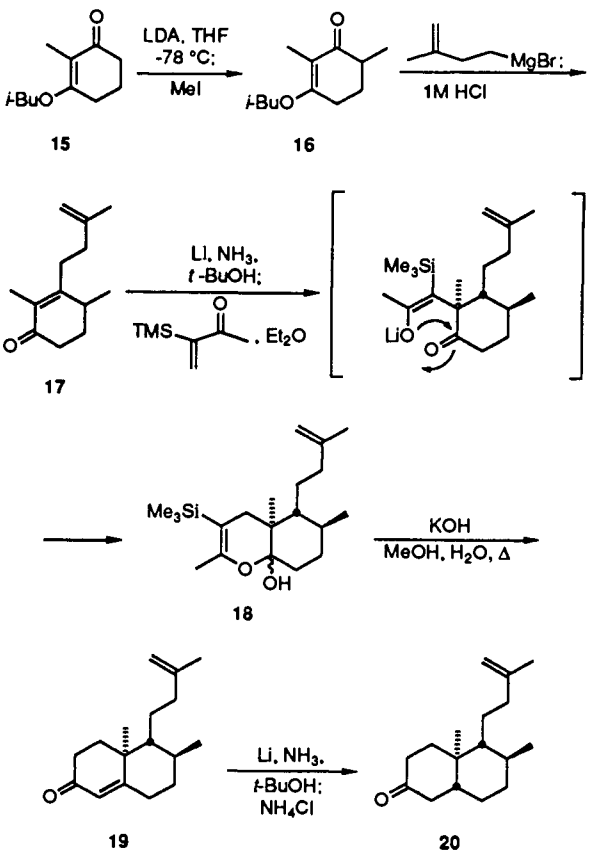
13 14

strategy reduced itself to the use of 2-methyl-1,3-cyclohexanedione (**14**) for obtaining **13**. Several features of this selection are important. First, diketone **14** is symmetric, eliminating the need to discriminate between its carbonyl groups. Second, recourse to a modified Robinson annulation reaction should conveniently accommodate the proper setting of the four chiral loci in ring A of the bicyclic keto ester. Finally, closure of ring D late in the sequence is not expected to suffer from adverse entropic effects since the two carbon atoms that are to be mutually bonded find themselves in relatively close proximity.

Results and Discussion

Construction of Functionalized Octalones. Advantage was first taken of the known propensity of 3-alkoxy-2-cyclohexenones for regiospecific α' deprotonation. Monomethylation of **15** according to Stork and Danheiser[14] afforded **16** in 92% yield (Scheme I). Condensation of **16** with the Grignard reagent derived from 4-bromo-2-methyl-1-butene[15] and in situ treatment of the adduct

Scheme I



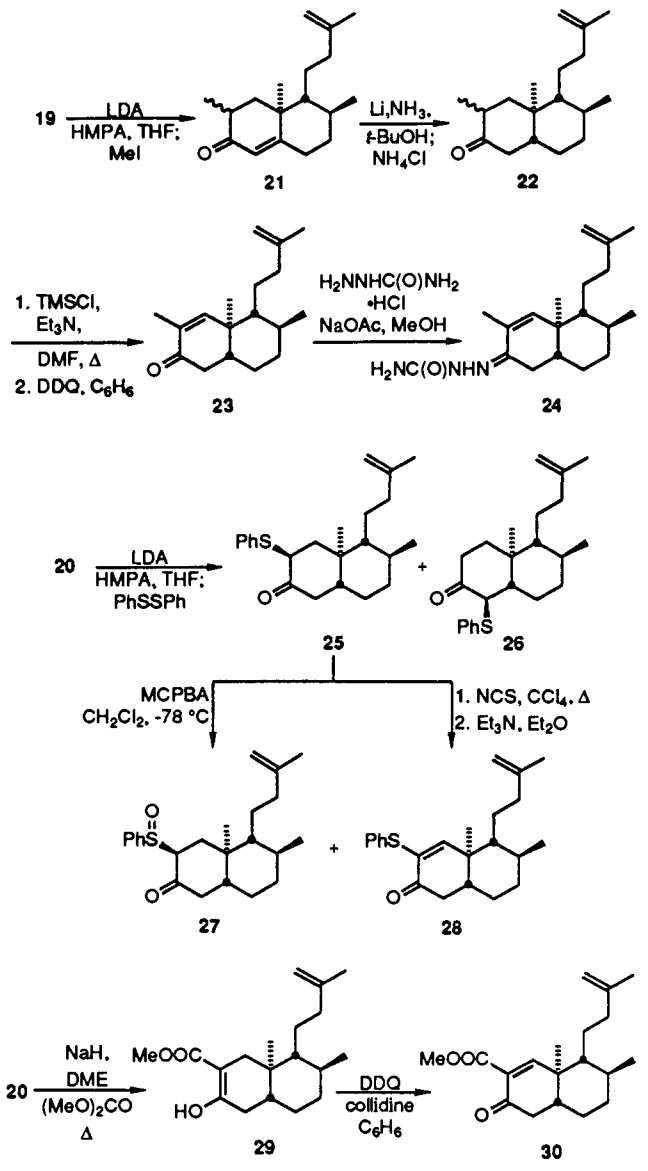
15 16 17 18 19 20

with dilute hydrochloric acid provided the desired **17** efficiently (72%). Subsequent reduction of **17** with lithium in liquid ammonia containing 0.8 equiv of *tert*-butyl alcohol was followed by replacement of the NH_3 with anhydrous ether and the introduction of α-(trimethylsilyl)vinyl methyl ketone.[16,17] Our expectation was that the initial Michael reaction would occur predominantly from that surface of the regiospecifically generated enolate opposite to that occupied by the isopentenyl substituent.[18] In actuality, enol hemiketal **18** was the major product formed under these conditions. Its conversion to **19** was smoothly accomplished with potassium hydroxide in refluxing aqueous methanol.[19] The latter enone was transformed readily into **20** by dissolving metal reduction. The assignment of ring-juncture stereochemistry in **20** was based on literature precedent.[20] With ample quantities of this bicyclic ketone in hand, attention was turned to activating the system for appendage of the methylene-functionalized cyclopentane ring.

In an effort to gain a reasonably panoramic appreciation of the ability of octalones of type **13** to engage in stereoselective cyclopentannulation, the three functionalized derivatives shown in Scheme II were prepared. Since the X substituent was ultimately to become a methyl group, it would be considered most expedient to undertake alkylation from the very outset. In practice, **23** can be acquired in straightforward fashion. Consideration of the enolate of **19** with methyl iodide leads to enone **21** in a very reasonable yield if HMPA is included in the reaction mixture.

(12) Review: Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1.
(13) Cleary, D. G.; Paquette, L. A. *Synth. Commun.* **1987**, *17*, 497.
(14) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.
(15) Ikan, R.; Markus, A.; Bergmann, E. D. *Isr. J. Chem.* **1971**, *9*, 259.
(16) (a) Stork, G.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 6152. (b) Stork, G.; Singh, J. *J. Am. Chem. Soc.* **1974**, *96*, 6181.
(17) (a) Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 6867. (b) Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 6179.
(18) Caine, D. In *Carbon-Carbon Bond Formation*; Augustine, R. L., Ed.; Marcel Dekker, Inc.: New York, 1979; Vol. 1, Chapter 2.
(19) Boeckman, R. K., Jr.; Blum, D. M.; Ganem, B. *Org. Synth.* **1978**, *58*, 158.
(20) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin, Inc.: Menlo Park, CA, 1972; Chapter 3.

Scheme II



Introduction of CH_3 at this stage quite clearly circumvents those potential problems with regiocontrol that might well materialize with the utilization of **20** (see below).

To set the stage for the needed oxidation, the double bond in **21** was saturated in a stereocontrolled fashion. Once generated, ketone **22** was heated with chlorotrimethylsilane and triethylamine in DMF[21] and subsequently exposed to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene at room temperature[22] to furnish **23** in 65% yield. Its nicely crystalline semicarbazone derivative **24** was subjected to X-ray diffraction analysis in order to assure that the several stereochemical assumptions advanced earlier were indeed correct. The ORTEP diagram seen in Figure 1 conclusively corroborates that the four contiguous stereogenic centers present in these intermediates had been installed in the requisite anti,syn,anti fashion.

Introduction of a phenylthio group at position X in **13** could be justified on several grounds, as will be discussed subsequently. For this purpose, serious consideration was accorded to the report that complete regiocontrol was realized in the sulfenylation of decalones (see below).[23] However, comparable treatment of **20**

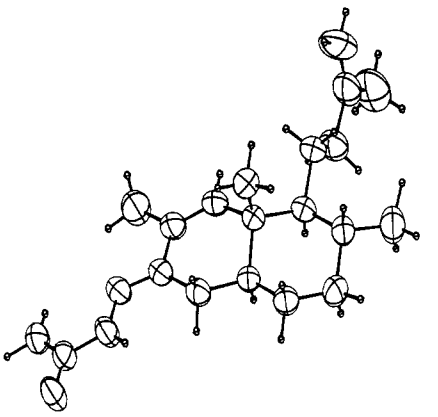
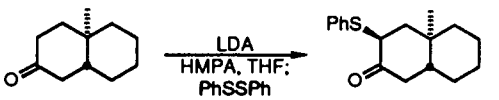


Figure 1. ORTEP drawing of **24**.

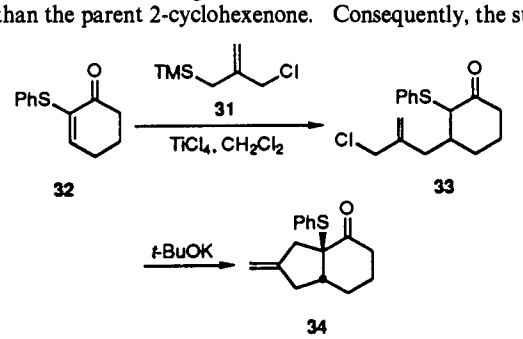
with LDA and diphenyl disulfide proceeded to generate the regioisomers **25** and **26** in a 2:1 ratio. The position and stereo-



chemical disposition of the SPh group in these products could be clearly delineated on the basis of ^1H NMR data. Thus, in **25** the proton geminal to sulfur appears at δ 3.93 in $CDCl_3$ as a doublet of doublets with coupling constants 5.9 and 13.3 Hz. These parameters reflect axial–equatorial and axial–axial couplings, respectively,[24] implying that the sulfur substituent in **25** is equatorial. The same proton in **26**, which resonates at δ 3.51, is seen as a doublet with J = 11.8 Hz attributable to an axial–axial interaction with the angular β hydrogen. Consequently, the sulfur substituent is again equatorially disposed. In an effort to reduce possible postequilibration, the enolate of **20** was introduced into an excess of diphenyl disulfide. Regiocontrol was not improved by this inverse protocol.

The preparation of keto ester **30** began by deprotonation of **20** with sodium hydride and condensation with dimethyl carbonate in refluxing 1,2-dimethoxyethane.[25] Under these conditions, no formation of the regioisomeric ester was observed. DDQ oxidation[26] of **29** led efficiently to **30**, which was utilized directly because of its relatively rapid deterioration on attempted storage.

Experiments Designed to Probe the Cyclopentannulation Process. The rationale underlying the acquisition of **28** had its roots in a report by Knapp that described the ability of allylsilane **31** to undergo conjugate addition to a variety of five- and six-membered cyclic enones in the presence of a Lewis acid.[27] Prominent among these was **32**, which undergoes overall conversion to **34** in higher yields than the parent 2-cyclohexenone. Consequently, the sulfur

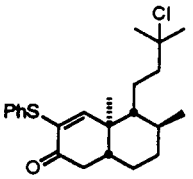


substituent is beneficial to the annulation process. Furthermore, dissolving metal reduction of substrates typified by **34** is a proven means for the regiospecific generation of enolates,[28] which in the

(21) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.
(22) Fleming, I.; Paterson, I. *Synthesis* **1979**, 736.
(23) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1967**, *98*, 4887.
(24) Hickmott, P. W.; Meth-Cohn, O. In *An Introduction to Spectroscopic Methods for Identification of Organic Compounds*; Scheinmann, F., Ed.; Pergamon Press: Oxford, 1970; Vol. 1, pp 59–70.
(25) Miller, R. B.; Nash, R. D. *Tetrahedron* **1974**, *30*, 2961.
(26) Review: Walker, D.; Hiebert, J. D. *Chem. Rev.* **1967**, *67*, 153.
(27) Knapp, S.; O'Connor, V.; Mobilis, D. *Tetrahedron Lett.* **1980**, *21*, 4557.

present circumstances could be trapped by methyl iodide to deliver the angular methyl group.

Although **28** and **31** did not enter into reaction in the presence of $TiCl_4$ at temperatures of −78 to −20 °C, enone **28** was completely consumed after 2 h at room temperature. However, the product was not that resulting from conjugate addition. Instead, hydrogen chloride had added across the isopentenyl double bond to generate **35**.[29] This single experiment proved to be indicative



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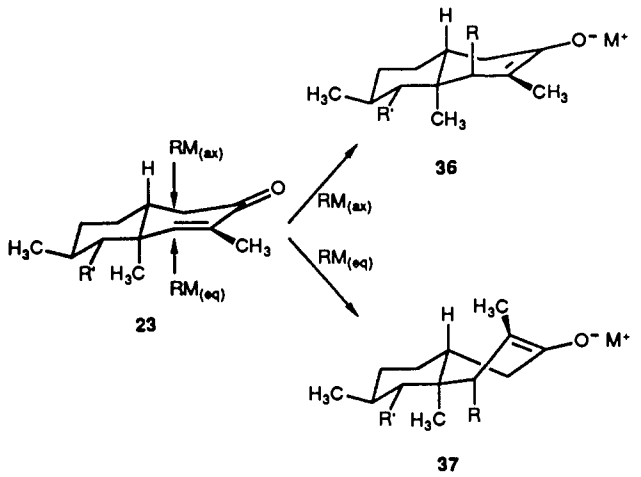
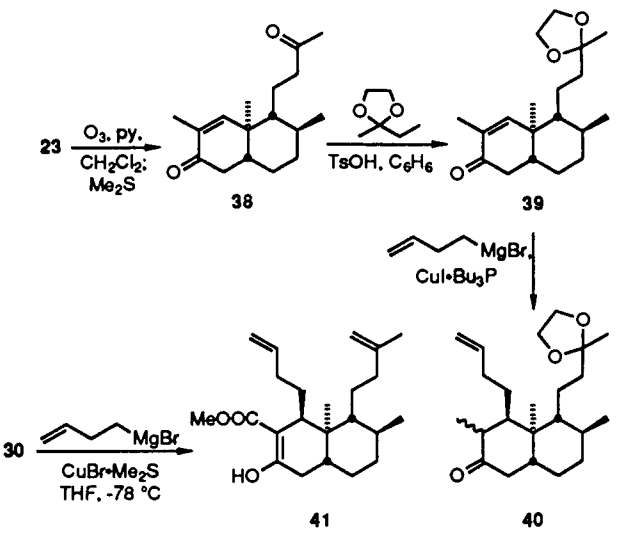
of two reactivity features of these functionalized octalones: (a) the potential of the isopentenyl double bond for facile generation of a tertiary carbocation precludes the utilization of any reagent or catalyst capable of liberating acid, and (b) the neopentyl character of the β carbon of the enone provides a level of steric shielding adequate to decelerate additions to that center. Allylsilane **31** is apparently rather sensitive to steric influences.[27]

In light of these developments, the ability of cuprate reagents to add to **23** (and **39**) was next evaluated. A predominantly axial mode of addition was anticipated on the basis of stereoelectronic and steric considerations.[30] Thus, approach from the top face delivers the chairlike enolate **36**, while the alternative bonding mode leads to the less stable boatlike enolate **37** and requires a trajectory that brings the incoming R group in close proximity to the bridgehead methyl. An analogy is available to support this prediction.[31]



Treatment of a cold (−78 °C) THF solution of the Grignard reagent prepared from 4-bromo-1-butene with the cuprous bromide–dimethyl sulfide complex[32] gave rise to a red-colored complex, to which **39**[33] was added. When no reaction was apparent at this temperature, the mixture was gradually warmed to −35 °C. Slow decomposition of the cuprate ensued, while **39** did not react. Substitution of cuprous iodide did not improve matters. On the other hand, the complex of cuprous iodide with tri-*n*-butylphosphine[34] and the butenyl Grignard proved to be stable

Scheme III



up to −20 °C. This increased range in operating temperature proved adequate to allow modest conversion to **40** (34%). However, the capricious nature of this reaction prompted an immediate switch to **30**. With this more electron-deficient system, a return to the original conditions was possible. Keto ester **41** was obtained as a single isomer in 75% yield (Scheme III).

The requisite angular methyl group could not be introduced by alkylation of **41**. Instead, O-methylation occurred to give **42** (86%, Scheme IV). Dibal-H reduction of **42** followed by hydrolysis with aqueous potassium sodium tartrate solution led rapidly to **43** via the unstable α-(hydroxymethyl) ketone (92% overall). This intermediate was subsequently reduced to afford a 1:1 mixture of **44** (axial methyl) and **45** (equatorial methyl). Complete conversion to **45** could be achieved by subsequent equilibration with potassium carbonate in methanol.

Since the stereochemistry at this center was to be set permanently during the aldol ring closure, the configuration of the α-methyl-substituted carbon was not viewed as significant. This proved to be the wrong perspective on the problem. Indeed, both stereoisomers could be successfully ozonolyzed to diketo aldehydes **46** and **47**, respectively. However, whereas **46** underwent rapid ring closure to tricyclic aldol **48** in the presence of dilute hydrochloric acid, **47** was resistant to the analogous reaction and only decomposed when conditions were made forcing. Since **48** is stable to the acidic environment in which it is produced, the difficulty appears to reside in the slow conversion of equatorial epimer **47** to its enol. In **46**, a 1,3-diaxial interaction is relieved on proceeding to the enol. This beneficial driving force is not available to **47**.

Enhancement in the relative proporation of the useful axial methyl epimer can be accomplished by several means. For example, substitution of *tert*-butyl alcohol for ammonium chloride as the quenching agent in the dissolving metal reduction of **43** invariably returned more **44** (49%) than **45** (27%). Further, the thermodynamic trimethylsilyl enol ether[21] of **45** is transformed predominantly into **44** following sequential exposure to methyllithium[35] and *tert*-butyl alcohol at −78 °C.

The regiochemistry of ring closure in **48** was confirmed by the appearance of the new bridgehead methyl group as a sharp singlet. The stereochemistry follows from the high improbability of generating a trans-fused ring juncture. Introduction of a C-ring double bond as in **49** proved more complicated than anticipated. However, heating the mesylate with lithium bromide in DMF afforded, in 77% yield, a 5:1 mixture of **49** and its double-bond regioisomer.

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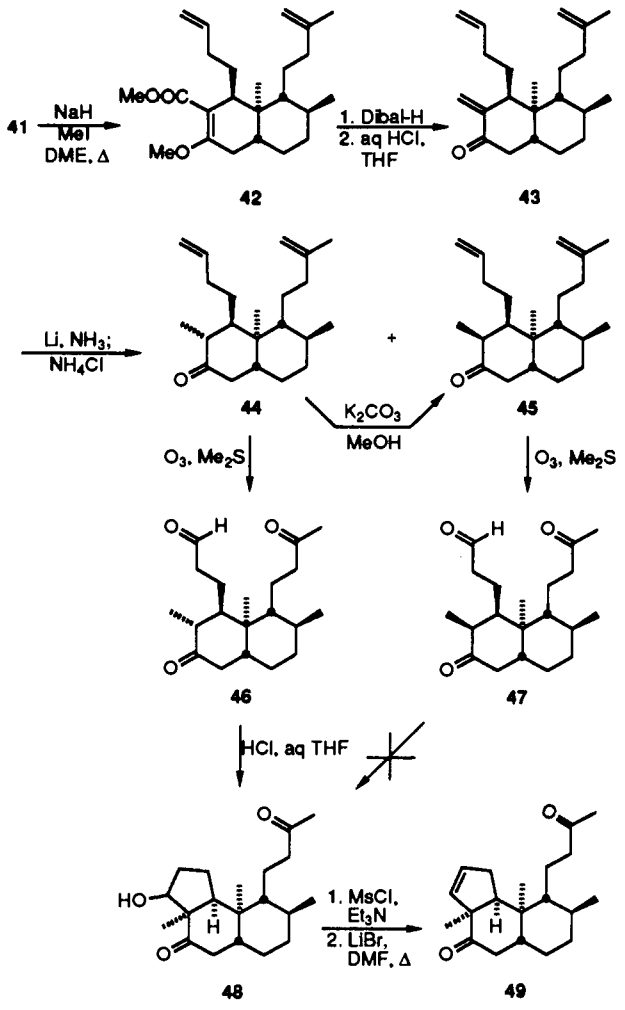
(32) House, H. O.; Chu, C.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460.
(33) Selective ozonolysis of **23** was best realized in the presence of pyridine [Slomp, G.; Johnson, J. L. *J. Am. Chem. Soc.* **1958**, *80*, 915] with ensuing reductive workup with dimethyl sulfide. Selective ketalization within **38** was similarly realized most efficaciously by dioxolane exchange [Dauben, H. J.; Löken, B.; Ringold, H. J. *J. Am. Chem. Soc.* **1954**, *76*, 1359].
(34) House, H. O.; Respess, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966**, *31*, 1460.
(35) Stork, G.; Hurdlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462.
(36) (a) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315. (b) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2326.

Scheme IV

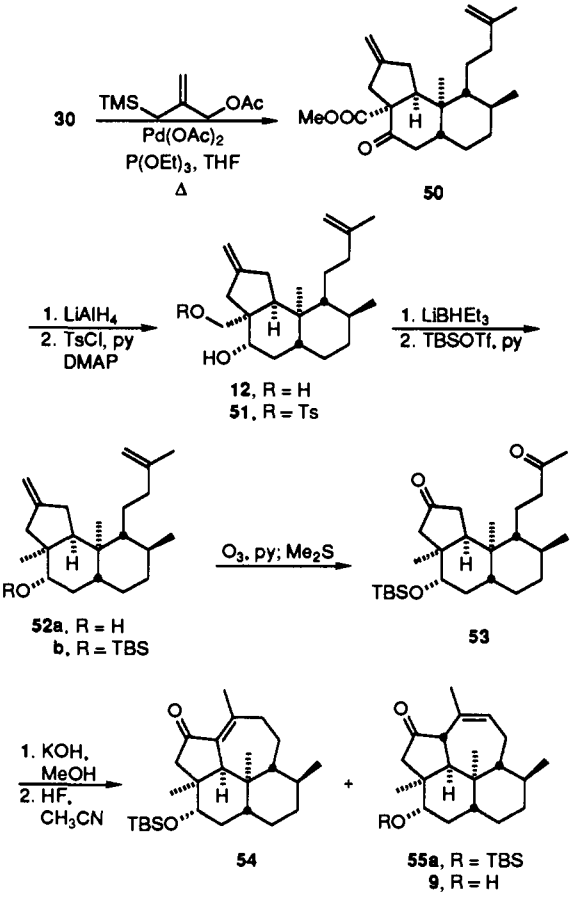


Implementation of the Pd-Catalyzed Trimethylenemethane Cycloaddition Protocol. The preceding studies established the feasibility of fusing a cyclopentane ring laterally to octalone **30**, especially from the fundamental perspective of stereochemistry. However, the further advance to an intermediate such as **12** by this pathway would obviously require an excessive number of steps. Of the various more direct methods considered for this task, one seemed uniquely qualified—the palladium(II)-mediated [3 + 2] cycloaddition of trimethylenemethane (TMM).[12,37] The problem, therefore, reduced itself to which, if any, of the octalones **23**, **28**, and/or **30** would prove to be sufficiently reactive toward this reagent system. In line with Trost and Chan's previous observation that 2-cyclohexenone reacts poorly if at all with TMM,[37a] **23** was almost totally unresponsive in our attempts to engage it in cycloaddition. On the other hand, the readiness with which 2-(methoxycarbonyl)cyclohexenone is known to react with [2-(acetoxymethyl)allyl]trimethylsilane in the presence of palladium acetate and triethyl phosphite[13] was mirrored by **30**. As shown in Scheme V, **50** was produced cleanly and in virtually quantitative yield (98%). Evidently, steric factors again conspire to force the TMM to approach exclusively from the β face. The octalone in Dauben's work[11] exhibited the same facial selectivity in a Diels–Alder reaction. The substantial rigidification of ring B that materializes during the conversion to **50** will be made evident during the course of ensuing transformations.

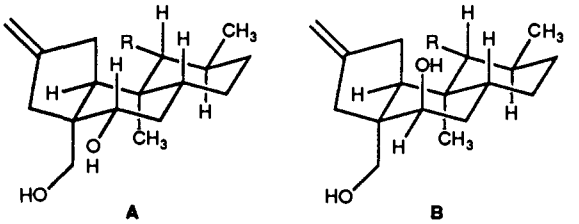
Lithium aluminum hydride reduction of **50** proceeded in a completely stereoselective manner to deliver diol **12**. The important point to note here is the overriding preference for kinetically controlled attack from the axial direction to orient the secondary hydroxyl equatorially (see **A**). The size of the reducing

(37) Cleary, D. Unpublished results.

Scheme V



agent (e.g., Dibal-H, $Zn(BH_4)_2$, $LiBEt_3H$, etc.), the nature of the solvent, and the reaction temperature had no impact on reversing the obviously strong bias for stereoselective approach to the ketone carbonyl.[37]

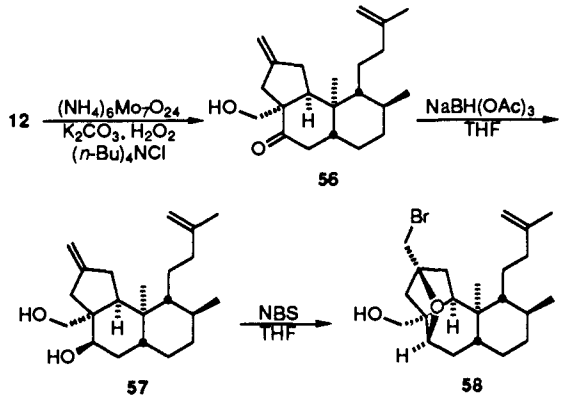


The monotosylation of **12** proved to be somewhat less regioselective than originally anticipated, a likely consequence of the axial disposition of the CH_2OH substituent. Small amounts of the ditosylate were invariably isolated alongside **51** (63%). Reduction of **51** for the purpose of setting the angular methyl group proceeded smoothly and efficiently, provided an excess of the boron hydride was utilized.

Alcohol **52a** could not be effectively ozonolyzed as long as its hydroxyl functionality was left unprotected. Once the conversion to **52b** had been accomplished, matters became far less troublesome, and **53** could be routinely obtained in 60% yield. When exposed to 1.5% KOH in *anhydrous* methanol, this diketone underwent intramolecular cyclization to give both **54a** and **55a** (5:1 ratio). The proportion of these double-bond isomers was seen to vary somewhat over the course of several experiments, although **54a** was always heavily dominant. More importantly, *no set of conditions was found to accomplish their interconversion.*

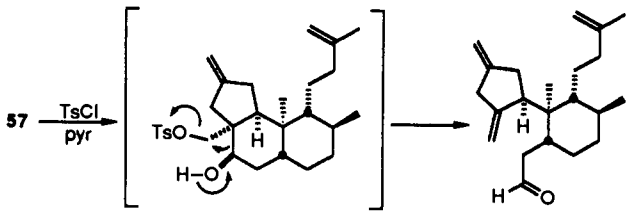
In order to effect epimerization at C-3, efforts were made to entice **52a** into the Mitsunobu reaction and its mesylate into S_N2 displacement with KO_2 and 18-crown-6 in HMPA solution. The failure of these pilot experiments revealed the level of steric crowding on the β face of this carbon atom to be high. It was

Scheme VI



therefore reasoned that advantage should be taken of hydroxyl-directed hydride delivery within the dehydro derivative **56**. To our delight, the action of hydrogen peroxide and ammonium molybdate[38] on **12** furnished the desired keto alcohol **56** in an amazingly selective fashion (Scheme VI). Although this oxidation requires the continuous slow infusion of hydrogen peroxide over 5 days, only **56** and the starting diol are ever visible by TLC analysis. Subsequent reduction of **56** with sodium triacetoxyborohydride[39] afforded **57** exclusively.

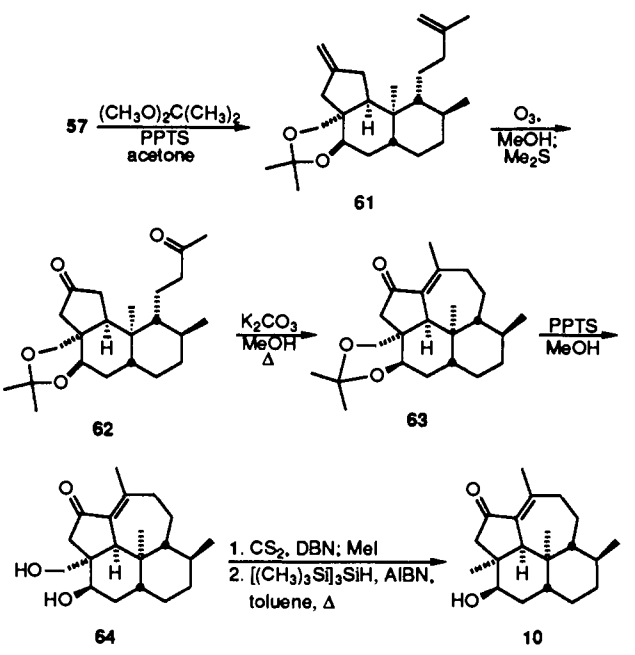
The close proximity of the secondary hydroxyl group in **57** to the methylenecyclopentane double bond was confirmed by bromoetherification to give **58**. The axial projection of the C-3 hydroxyl (see B) was manifested during attempted preparation of its monotosylate. The standard conditions for sulfonate ester formation also induced rapid Grob fragmentation[40] within **59** to give **60**.[37]



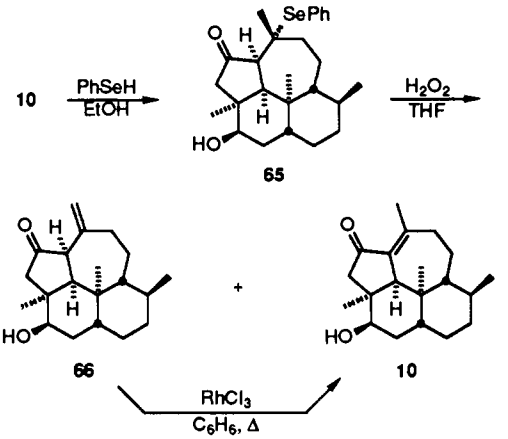
At this point, we speculated that a change in conformation of ring B might lend itself more suitably to our purposes. When **57** itself proved to be quite tolerant of acetonide formation (Scheme VII), **61** was subjected directly to ozonolysis. The subsequent ring closure of **62** was scrutinized with a selection of different bases. Of these, potassium carbonate (4–5 equiv) in refluxing methanol emerged as the reagent of choice. After 16 h of heating, **63** was isolated in 91% yield as the only detectable product. TLC monitoring of the cyclization as it proceeded provided no indication of the coproduction of the β,γ-unsaturated isomer.

The deprotection of **63** to give **64** proceeded without event. The subsequent regioselective conversion of **64** to the monoxanthate[41] could be accomplished consistently under reasonably mild conditions without obvious competition from Grob fragmentation. When this intermediate was heated in toluene with tris(trimethylsilyl)silane[42] in a modified Barton–McCombie reaction,[43]

Scheme VII



Scheme VIII



10 was produced in modest yield. As in the case of **58a**, all efforts to deconjugate this kempenone under either acidic or basic conditions were to no avail.[45] In all cases, the conditions selected led either to full recovery of **10** or, after prolonged periods, to partial decomposition.

As a final measure, an indirect isomerization route was probed (Scheme VIII). Satisfyingly, benzeneselenol in ethanol[45] added readily in conjugate fashion to **10**, providing a single adduct formulated stereochemically as **65**. In agreement with this assignment, oxidative elimination of the phenylselenyl substituent proceeded competitively in two directions (out of a possible three) to deliver **66** and **10**. When **66** was isomerized with rhodium trichloride in refluxing benzene,[46] only **10** was observed. Attempts to epimerize **65** in an effort to set the α-carbonyl proton β and drive the elimination toward **11** were unsuccessful.

Molecular Modeling Studies. The presence within the C-3 epimeric hydroxykempenones **9** and **11** of a trans-locked C/D arrangement is patently evident in their ^{1}H NMR spectra, with both compounds exhibiting a large value for $J_{7,16}$ (10.6–10.8 Hz). This particular stereochemical relationship imparts to these substances a remarkable inertness toward migration of the double bond into conjugation as in **8** and **10**, respectively. Prestwich

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(45) Miyashita, M.; Yoshikoshi, A. *Synthesis* **1980**, 664.

(46) Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 359.

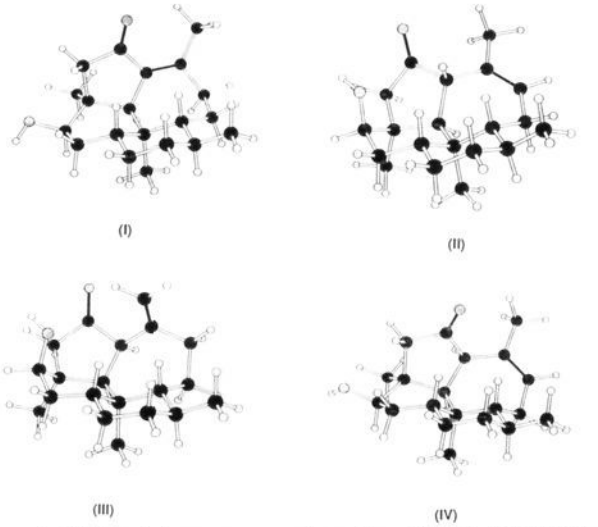


Figure 2. Global minimum energy conformations of (I) **10**, (II) **11**, (III) **66**, and (IV) **67** as determined by molecular mechanics calculations (Chem-3D output).

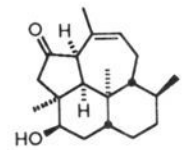
Table I. Computed Energies and Heats of Formation of **10**, **11**, **66**, and **67**

compd	ΔE_{strain}, kcal/mol	ΔH_f, kcal/mol	ΔE_{total}, kcal/mol
10	36.0	−105.71	48.0
11	31.7	−107.65	44.3
66	33.4	−104.15	46.4
67	43.2	−94.28	56.3

originally noted **11** to remain unchanged during chromatography on Florisil.[6d] Small amounts of material made available by him were subjected to strongly basic conditions without event. Efforts to cause isomerization in **55a** were met with the same response. All experiments designed to deconjugate **54a**, **8**, and **10** likewise returned unchanged to starting material.

To what might this unusual stability be attributed? To gain insight into this question, the global minimum energy conformations of **10**, **11**, and their exocyclic relative **66** were derived computationally by application of Allinger's MM2 force field.[47] Computer-generated drawings of the lowest energy structure in each instance, shown in Figure 2, have proven to be revealing of the underlying causes of their lack of interconvertibility. For example, neither of the C-9 protons in **10** is projected at an angle that provides for suitable stereoelectronic overlap with the π system of the α,β-unsaturated carbonyl chromophore (see I). It is therefore highly probable that enolization, when it does materialize, occurs either γ at the methyl group or at the α' carbon within the cyclopentanone ring. Unfortunately, insufficient supplies of either substrate precluded the direct experimental assessment of these points (e.g., by H–D exchange). Nonetheless, it is clear that formation of the extended intraring enolate is seriously impeded from the kinetic vantage point.

The inability of **11** to isomerize to **10** may arise from two factors. It so happens that **11** is less strained than **10** by approximately 4 kcal/mol (Table I). Accordingly, the thermodynamic bias resides in favor of **11** and to a significant degree. Also, as is clearly visible in II (Figure 2), the configuration at C-3 serves to project its β-oriented hydrogen to the interior of the molecule where it is rather sterically inaccessible. Consequently, the inability of a reagent as powerful as $RhCl_3$ to promote the conversion of **11** to **10** is precluded both thermodynamically and sterically. The latter restriction does not apply to **66** (see III). In this instance, approach from above the (π-allyl)rhodium species can materialize in either of two directions, since in-plane-oriented allylic hydrogens are available on either flank for participation in the oxidative addition. The option leading to **10** is followed exclusively, perhaps because the α-carbonyl proton is more activated and labile than the one at C-5. Alternative conversion to **67** does not appear to be a realistic option since this stereoisomer is severely twisted (see IV) and strained (Table I). Once **10** is formed, further isomerization to **11** is precluded for the reasons already presented.



67

Summary. The total syntheses of **8-10** described herein demonstrate the capability of [3 + 2] cycloaddition based on trimethylenemethane to serve as a useful scaffolding technique in natural products synthesis. The developed chemistry has allowed, for the first time, the preparation of a small group of hydroxykempenones such that direct comparison could be made with the chemical reactivity of the naturally occurring isomer **11**.

A number of useful tactics were utilized in the course of this work, including a means for skirting around the treacherous tendency of conformationally rigid, diaxial, monofunctionalized 1,3-diols for Grob fragmentation. The use of ammonium molybdate as a selective oxidizing agent emerged as a process of considerable importance. The coupling of this reaction with hydroxyl-directed hydride reduction was instrumental in setting β-hydroxyl stereochemistry at C-3. Molecular modeling proved to be useful in rationalizing the remarkable kinetic stability of the four tetracyclic isomers **8–11**. All of these developments have implications well beyond the present synthetic undertaking, and efforts to apply this information strategically in other contexts are currently in progress.

Experimental Section

Melting points were determined in open capillaries with a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded with Perkin-Elmer Model 467 and 1320 instruments. Proton magnetic resonance spectra were obtained with Varian T-60, Bruker WP-200, and Bruker WM-300 spectrometers. Carbon spectra were recorded with Bruker WP-80 and Bruker WM-300 instruments. Mass spectra were recorded on a Kratos MS-30 spectrometer at an ionization potential of 70 eV. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All solvents were predried by standard methods. All reactions involving nonaqueous solutions were performed under an inert atmosphere. Flash chromatography was performed on silica gel 60 (230–400 mesh, 60 Å) using the indicated solvents.

3-Isobutoxy-2-methyl-2-cyclohexen-1-one (15). A mixture of 2-methyl-1,3-cyclohexanedione (100 g, 0.79 mol), isobutyl alcohol (64.6 g, 0.87 mol), benzene (1000 mL), and *p*-toluenesulfonic acid monohydrate (1 g, 5.3 mmol) was placed in a 2-L one-necked flask equipped with a Dean–Stark trap and refluxed until 14.3 mL of water was removed (24–36 h). The solution was concentrated in vacuo, and the residue was dissolved in ether (1 L). The ether solution was washed with saturated $NaHCO_3$ solution (100 mL) and brine (100 mL), dried, and concentrated. Distillation of the residue under reduced pressure gave **15** as a pale yellow liquid (134.11 g, 93%): bp 95–99 °C/0.05 Torr; IR (neat, cm^{-1}) 1640, 1390, 1360, 1240, 1125, 1100; ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (d, J = 6.4 Hz, 2 H), 2.50 (dt, J = 1.4, 6.2 Hz, 2 H), 2.28 (t, J = 6.7 Hz, 2 H), 1.93 (m, 3 H), 1.66 (t, J = 1.5 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 6 H).

3-Isobutoxy-2,6-dimethyl-2-cyclohexen-1-one (16). *n*-Butyllithium in hexanes (0.201 mol) was added dropwise to a stirred solution of diisopropylamine (20.3 g, 0.201 mol) in THF (30 mL) at 0 °C. After being stirred at 0 °C for an additional 15 min, the mixture was cooled to −78 °C, treated dropwise with **15** (35 g, 0.192 mol) in THF (40 mL), and stirred at −78 °C for an additional 45 min prior to the addition of methyl iodide (28.6 g, 0.201 mol) in THF (35 mL) over 20 min. The reaction mixture was slowly warmed to ambient temperature and stirred for 12 h. Water (2 mL) was added, and the solvent was removed in vacuo. The residue was partitioned between ether (500 mL) and water (100 mL), and the ether solution was washed with brine (100 mL), dried, and

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evaporated under reduced pressure to give **16** as a yellowish liquid (34.77 g, 92%): bp 115–118 °C/0.08 Torr; IR (neat, cm^{-1}) 1645, 1620, 1380, 1235, 1095; ^1H NMR (60 MHz, $CDCl_3$) δ 3.7 (d, J = 6 Hz, 2 H), 2.7–1.5 (series of m, 6 H), 1.7 (t, J = 1 Hz, 3 H), 1.1 (d, J = 6 Hz, 3 H), 1.0 (d, J = 6 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 200.3, 170.1, 113.3, 39.0, 28.5, 28.4, 24.3, 18.6, 15.2, 7.2; MS m/z (M^+) 196.1463, obsd 196.1468.

4-Bromo-2-methyl-1-butene. Methallylmagnesium chloride was prepared by slow addition (over 3 h) of a solution of methallyl chloride (45 g, 0.5 mol) in ether (700 mL) to magnesium turnings (54 g, 2.25 mol) in ether (75 mL). Paraformaldehyde (15 g, 0.5 equiv) was added in one portion, and the mixture was refluxed for 12 h. After being cooled, the gray suspension was added to cold 1.2 M HCl (500 mL). The aqueous layer was extracted with additional ether (2 × 100 mL), and the combined ether layers were washed with saturated $NaHCO_3$ solution (200 mL) and brine (200 mL) prior to drying and solvent removal in vacuo. The residue was distilled at reduced pressure to give 2-methyl-1-buten-4-ol as a colorless liquid (26.59 g, 69%): bp 63–67 °C/50 Torr (lit.[15] bp 126–130 °C/760 Torr); IR (neat, cm^{-1}) 3340, 1440, 1375, 1040, 885; ^1H NMR (60 MHz, $CDCl_3$) δ 4.75 (m, 2 H), 3.65 (t, J = 6 Hz, 2 H), 3.15 (br s, 1 H), 2.25 (t, J = 6 Hz, 2 H), 1.75 (s, 3 H).

Methanesulfonyl chloride (10.08 g, 88 mmol) was added dropwise to a stirred, cooled (0 °C) solution of 2-methyl-1-buten-4-ol (6.88 g, 80 mmol), triethylamine (10.08 g, 88 mmol), and CH_2Cl_2 (400 mL). After being stirred at 0 °C for an additional 15 min, the mixture was transferred to a separatory funnel and washed with water (100 mL), cold 1.2 M HCl (100 mL), saturated $NaHCO_3$ solution (100 mL), and brine (100 mL). After drying and concentration in vacuo, the mesylate was obtained as a yellow oily residue, which was used without further purification (11.88 g, 91%): ^1H NMR (60 MHz, $CDCl_3$) δ 4.80 (m, 2 H), 4.30 (t, J = 6 Hz, 2 H), 3.00 (s, 3 H), 2.45 (t, J = 6 Hz, 2 H), 1.80 (s, 3 H).

A solution of anhydrous lithium bromide (13.88 g, 160 mmol) in acetone (80 mL) was added over a 10-min period to a refluxing solution of the above mesylate (11.88 g, 72.4 mmol) in acetone (60 mL). The mixture was refluxed for an additional 15 h, cooled to 0 °C, and filtered. Acetone was removed by distillation at atmospheric pressure through a 4-in. Vigreux column. Water (100 mL) was added to the residue, which was extracted with ether (300 mL). The ether phase was washed with water (75 mL), dried, and carefully concentrated on a rotary evaporator. The residue was distilled at reduced pressure to give the bromide as a colorless liquid (6.1 g, 57%): bp 55–58 °C/60 Torr (lit.[15] bp 60 °C/20 Torr); IR (neat, cm^{-1}) 1445, 890; ^1H NMR (300 MHz, $CDCl_3$) δ 4.85 (s, 1 H), 4.77 (s, 1 H), 3.47 (t, J = 7.4 Hz, 2 H), 2.58 (t, J = 7.4 Hz, 2 H), 1.75 (s, 3 H); MS m/z (M^+) calcd 149.9867, obsd 149.9871.

2,4-Dimethyl-3-(3-methyl-3-butenyl)-2-cyclohexen-1-one (17). A solution of 4-bromo-2-methyl-1-butene (21.6 g, 0.145 mol) in THF (100 mL) was added to magnesium turnings (3.52 g, 0.145 mol) in THF (20 mL) at a rate to maintain gentle reflux (the reaction was initiated with 1,2-dibromoethane). After being refluxed for an additional 30 min, the mixture was cooled to ambient temperature, and **16** (27.1 g, 0.138 mol) dissolved in THF (75 mL) was added dropwise. The solution was refluxed for 3 h, cooled, treated slowly with 1.2 M aqueous HCl(200 mL), stirred for 12 h, and extracted with ether (600 mL). The organic layer was washed with 3 M aqueous KOH (2 × 100 mL), saturated aqueous NH_4Cl solution (100 mL), and brine (100 mL) prior to drying. Solvent was removed in vacuo and the residue was purified either chromatographically (silica gel, elution with 10% ether in petroleum ether) or by distillation to furnish **17** (22.3 g, 84%) as a pale yellow oil: bp 112–115 °C/1.5 Torr; IR (neat, cm^{-1}) 1665; ^1H NMR (300 MHz, $CDCl_3$) δ 4.74 (s, 1 H), 4.71 (m, 1 H), 2.54–2.07 (series of m, 8 H), 1.76 (two s, 6 H), 1.75 (m, 1 H), 1.19 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$, ppm) 199.0, 162.6, 144.8, 130.5, 110.6, 35.7, 33.6, 31.8, 29.5, 22.3, 17.8, 10.7; MS m/z (M^+) calcd 192.1513, obsd 192.1513. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.77; H, 10.54.

(4a*R,5*S**,6*R**)-4,4a,5,6,7,8-Hexahydro-2,4a,6-trimethyl-5-(3-methyl-3-butenyl)-3-(trimethylsilyl)-8a*H*-1-benzopyran-8a-ol (18).** Lithium wire (3.23 g, 0.47 mol) was added to dry ammonia (400 mL) at −78 °C, and the resulting blue solution was stirred at −78 °C for 20 min. Enone **17** (15 g, 78.1 mmol) and *tert*-butyl alcohol (4.63 g, 62.5 mmol) in ether (300 mL) were added dropwise, and the mixture was stirred at −78 °C for 1.5 h. After the excess lithium was quenched with isoprene, the ammonia was removed in vacuo, and the residual white solid was suspended in ether (200 mL) and cooled to −78 °C. A solution of α-(trimethylsilyl)vinyl methyl ketone (15.13 g, 0.107 mol) in ether (300 mL) was introduced dropwise, and the mixture was allowed to warm to ambient temperature over 2 h before being quenched by addition of saturated NH_4Cl solution (200 mL). The organic layer was diluted with additional ether (400 mL), washed with brine (100 mL), dried, and evaporated. The residue was partially purified by chromatography on silica gel (elution with 10% ethyl acetate in petroleum ether) to give 18.4 g of a 2:1 mixture of **18** and 2,4-dimethyl-3-(3-methyl-3-butenyl)cyclohexan-1-one, which was used in the next step without further purification. For **18**: IR (neat, cm^{-1}) 3460, 1635, 1250, 1005, 845; ^1H NMR (300 MHz, $CDCl_3$) δ 4.77 and 4.66 (m, total 2 H), 1.81 (s, 3 H), 1.72 (s, 3 H), 2.50–1.70 (series of m, 6 H), 0.92 (s, 3 H), 0.91 (d, J = 5.7 Hz, 3 H), 1.64–0.86 (series of m, 7 H), 0.16–0.05 (several s, total 9 H); MS m/z (M^+) calcd 336.2484, obsd 336.2451.

(4a*R,5*S**,6*R**)-4,4a,5,6,7,8-Hexahydro-4a,6-dimethyl-5-(3-methyl-3-butenyl)-2(3*H*)-naphthalenone (19).** The mixture produced above (18.42 g) was dissolved in methanol (375 mL), and 4% aqueous KOH (75 mL) was added. After the mixture had refluxed for 4 h, solvent was removed in vacuo and the residue was dissolved in ether (500 mL). The ether solution was washed with saturated aqueous NH_4Cl solution (50 mL) and brine (50 mL), dried, and concentrated. Purification of the residue by chromatography on silica gel (elution with 10% ethyl acetate in petroleum ether) gave **19** as a light yellow oil (8.06 g, 42% from **17**): IR (neat, cm^{-1}) 1670; ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (d, J = 1.5 Hz, 1 H), 4.68 (s, 1 H), 4.66 (s, 1 H), 2.43–1.75 (series of m, 6 H), 1.72 (s, 3 H), 1.12 (s, 3 H), 0.97 (d, J = 6.5 Hz, 3 H), 1.71–0.75 (series of m, 8 H); ^{13}C NMR (20 MHz, $CDCl_3$, ppm) 199.4, 171.1, 145.9, 123.7, 110.0, 54.6, 40.0, 39.8, 35.8, 35.0, 34.3, 33.7, 33.0, 27.5, 22.4, 20.4, 17.7. Anal. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.43; H, 10.77.

(4a*R,5*R**,6*S**,8a*R**)-Octahydro-4a,6-dimethyl-5-(3-methyl-3-butenyl)-2(1*H*)-naphthalenone (20).** Lithium wire (1.40 g, 0.20 mol) was added to dry NH_3 (400 mL) at −78 °C, and the mixture was stirred at −78 °C for 20 min. A solution of **19** (5.0 g, 20 mmol) and *tert*-butyl alcohol (1.2 g, 16.3 mmol) in ether (50 mL) was added dropwise, and the blue mixture was stirred at −78 °C for an additional hour. Excess lithium was quenched with isoprene, ammonia was removed in vacuo, and solid NH_4Cl (6 g) was added. The white slurry was then partitioned between ether (600 mL) and water (100 mL). The water layer was saturated with NaCl and extracted with ether (200 mL), and the combined ether solutions were dried and concentrated. The residue was purified by chromatography on silica gel (elution with 10% ethyl acetate in petroleum ether) to give **20** as a colorless oil (3.98 g, 80%): IR (neat, cm^{-1}) 1710, 1440, 880; ^1H NMR (300 MHz, $CDCl_3$) δ 4.67 (s, 1 H), 4.65 (s, 1 H), 2.45–1.79 (series of m, 6 H), 1.71 (s, 3 H), 0.94 (s, 3 H), 0.92 (d, J = 6.4 Hz, 3 H), 1.70–0.83 (series of m, 10 H), 0.54 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 211.9, 146.2, 109.5, 54.7, 46.2, 44.7, 40.2, 38.0, 37.8, 37.1, 35.7, 34.2, 28.9, 27.8, 22.5, 20.7, 11.0. Anal. Calcd for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found: C, 82.09; H, 11.42.

(4a*R,5*S**,6*R**)-4,4a,5,6,7,8-Hexahydro-3,4a,6-trimethyl-5-(3-methyl-3-butenyl)-2(3*H*)-naphthalenone (21).** A solution of *n*-butyllithium in hexanes (3.98 mmol) was added dropwise to a stirred solution of diisopropylamine (0.40 g, 3.98 mmol) in THF (5 mL) cooled to 0 °C. After being stirred at 0 °C for an additional 15 min, the mixture was cooled to −78 °C, and **19** (0.89 g, 3.62 mmol) dissolved in HMPA (5.3 mL) and THF (18 mL) was added dropwise. The solution was stirred at −78 °C for 30 min, at which point methyl iodide (0.57 g, 3.98 mmol) in THF (18 mL) was added dropwise. The reaction mixture was warmed to ambient temperature over 3 h, stirred for 12 h, diluted with water (5 mL), and extracted with 1:1 ether–petroleum ether (500 mL). The organic phase was washed with water (2 × 20 mL), dried, and concentrated. The residue was purified by MPLC on silica gel (elution with 10% ethyl acetate in petroleum ether) to give **21** as an inseparable mixture of epimers (0.74 g, 79%). Treatment of this mixture with anhydrous K_2CO_3 in methanol (ambient temperature, 12 h) resulted in almost complete conversion to the equatorial methyl epimer: IR (neat, cm^{-1}) 1685; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (s, 1 H), 4.71 (s, 1 H), 4.68 (s, 1 H), 1.74 (s, 3 H), 1.17 (s, 3 H), 1.11 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.4 Hz, 3 H), 2.50–0.85 (series of m, 12 H), 0.78 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 201.7, 169.7, 146.0, 123.3, 109.8, 55.2, 44.4, 40.6, 39.7, 36.7, 35.5, 34.1, 32.6, 27.1, 22.5, 20.4, 17.6, 14.8; MS m/z (M^+) calcd 260.2140, obsd 260.2121.

(4a*R,5*R**,6*S**,8a*R**)-Octahydro-3,4a,6-trimethyl-5-(3-methyl-3-butenyl)-2(1*H*)-naphthalenone (22).** Lithium wire (1.70 g, 0.25 mol) was added to dry NH_3 (250 mL) at −78 °C, and the mixture was stirred at −78 °C for 20 min. A solution of **21** (3.18 g, 12.2 mmol) and *tert*-butyl alcohol (0.74 g, 10.0 mmol) in ether (60 mL) was added dropwise, and the mixture was stirred at −78 °C for an additional 90 min. Excess lithium was quenched with isoprene, ammonia was removed in vacuo, and the residue was partitioned between ether (500 mL) and saturated NH_4Cl solution (30 mL). The aqueous layer was saturated with NaCl and extracted with ether (100 mL), and the combined ethereal solutions were dried and concentrated. Purification on the residue by HPLC on silica gel (elution with 5% ethyl acetate in petroleum ether) gave **22** as an inseparable mixture of epimers (3.0 g, 93%). Treatment of this mixture with anhydrous K_2CO_3 in methanol (ambient temperature, 12 h) resulted in almost complete conversion to the equatorial methyl ep-

imer: IR (neat, cm^{-1}) 1720; ^1H NMR (300 MHz, $CDCl_3$) δ 4.68 (s, 1 H), 4.66 (d, J = 0.7 Hz, 1 H), 2.47 (m, 1 H), 2.28 (t, J = 13.8 Hz, 1 H), 2.11 (m, 3 H), 1.94 (m, 1 H), 1.73 (s, 3 H), 1.00 (d, J = 5.7 Hz, 3 H), 1.00 (s, 3 H), 0.92 (d, J = 6.4 Hz, 3 H), 1.71–0.92 (series of m, 9 H), 0.54 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 213.0, 146.4, 109.5, 54.8, 48.1, 47.6, 44.8, 40.8, 40.2, 38.0, 35.8, 34.1, 28.8, 27.8, 22.6, 20.8, 14.6, 12.1; MS m/z (M^+) calcd 262.2296, obsd 262.2289.

(4a*R,5*R**,6*S**,8a*R**)-4a,5,6,7,8,8a-Hexahydro-3,4a,6-trimethyl-5-(3-methyl-3-butenyl)-2(1*H*)-naphthalenone (23).** Ketone **22** (1.11 g, 4.24 mmol) in DMF (5 mL) was added to a solution of trimethylchlorosilane (1.15 g, 10.6 mmol) and triethylamine (2.13 g, 21.1 mmol) in DMF (10 mL). The mixture was refluxed for 12 h, cooled to ambient temperature, and dissolved in petroleum ether (150 mL). After being washed with cold, saturated $NaHCO_3$ solution (3 × 10 mL), the petroleum ether phase was dried and concentrated. The residue was purified by MPLC on silica gel (elution with 3% ethyl acetate in petroleum ether) to give the thermodynamic silyl enol ether as a colorless oil (1.19 g, 84%) contaminated with minor quantities of its regioisomer (0.06 g, 4%): IR (neat, cm^{-1}) 1244, 1190, 890, 850; ^1H NMR (300 MHz, $CDCl_3$) δ 4.68 (s, 2 H), 1.74 (s, 3 H), 1.54 (s, 3 H), 0.90 (d, J = 6.5 Hz, 3 H), 2.10–0.85 (series of m, 14 H), 0.69 (s, 3 H), 0.56 (m, 1 H), 0.16 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 146.8, 141.4, 110.0, 109.3, 54.8, 44.4, 42.3, 40.3, 36.7, 35.9, 35.1, 34.4, 28.7, 27.5, 22.6, 21.0, 16.6, 11.8, 0.7; MS m/z (M^+) calcd 334.2692, obsd 334.2706.

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.54 g, 2.4 mmol) in benzene (45 mL) was added dropwise to a stirred solution of the silyl enol ethers (0.83 g of a 95:5 mixture, 2.38 mmol of the major regioisomer) in benzene (30 mL). After being stirred at ambient temperature for 12 h, the mixture was partitioned between ether (300 mL) and saturated $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with additional ether (50 mL), and the combined organic phases were dried and concentrated. The residue was purified by MPLC on silica gel (elution with 8% ethyl acetate in petroleum ether) to give **23** as a faint yellow oil (0.40 g, 65%): IR (neat, cm^{-1}) 1670, 1445, 1370, 880; ^1H NMR (300 MHz, $CDCl_3$) δ 6.73 (d, J = 0.8 Hz, 1 H), 4.70 (m, 2 H), 2.37–1.80 (series of m, 4 H), 1.76 (s, 3 H), 1.73 (d, J = 1.3 Hz, 3 H), 1.72–0.98 (series of m, 8 H), 0.94 (d, J = 7.0 Hz, 3 H), 0.93 (s, 3 H), 0.74 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 199.9, 154.1, 145.9, 133.3, 109.8, 51.3, 44.4, 40.9, 40.3, 35.5, 34.6, 28.0, 27.5, 22.6, 20.9, 16.1, 13.0; MS m/z (M^+) calcd 260.2140, obsd 260.2131.

A mixture of **23** (100 mg, 0.38 mmol), semicarbazide hydrochloride (47 mg, 0.42 mmol), and sodium acetate (69 mg, 0.85 mmol) in methanol (0.5 mL) was stirred at ambient temperature for 12 h. The slurry was partitioned between ether (100 mL) and water (5 mL), and the ethereal phase was washed with additional water (5 mL) and dried. The solvent was removed in vacuo to give **24** as colorless crystals (90 mg, 75%): mp 193–195 °C (from ethanol); IR (KBr, cm^{-1}) 3470, 1695, 1575; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (br s, 1 H), 6.12 (s, 1 H), 4.72 (s, 2 H), 2.31–1.93 (series of m, 4 H), 1.84 (s, 3 H), 1.77 (s, 3 H), 1.81–1.02 (series of m, 8 H), 0.94 (d, J = 6.4 Hz, 3 H), 0.80 (s, 3 H), 0.70 (m, 1 H) (NH_2 not observed).

(3*S,4a*R**,5*R**,6*S**,8a*R**)-Octahydro-4a,6-dimethyl-5-(3-methyl-3-butenyl)-3-(phenylthio)-2(1*H*)-naphthalenone (25) and Its 1-Phenylthio Regioisomer 26.** *n*-Butyllithium in hexanes (2.9 mmol) was added dropwise to a stirred solution of diisopropylamine (0.30 g, 2.9 mmol) in THF (6 mL) at 0 °C. After being stirred at 0 °C for 15 min, the mixture was cooled to −25 °C, and a solution of **20** (0.30 g, 1.2 mmol) and HMPA (1.8 mL) in THF (2 mL) was added dropwise. Stirring was maintained at −25 °C for 30 min and at 0 °C for 30 min. A solution of diphenyl disulfide (0.63 g, 2.9 mmol) in THF (6 mL) was added dropwise, and the mixture was stirred at 0 °C for 20 min and at ambient temperature for 1 h. The solution was partitioned between ether (150 mL) and 1.2 M HCl (20 mL), and the ether layer was washed with saturated $NaHCO_3$ solution (20 mL) and dried. The solvent was removed in vacuo, and the residue was purified by MPLC on silica gel (elution with 6% ethyl acetate in petroleum ether) to give **25** as a yellow oil (0.20 g, 47%) along with regioisomer **26** (0.10 g, 23%).

For **25**: IR (neat, cm^{-1}) 1710, 1435; ^1H NMR (200 MHz, $CDCl_3$) δ 7.33 (m, 2 H), 7.19 (m, 3 H), 4.57 (s, 1 H), 4.50 (m, 1 H), 3.93 (dd, J = 5.9, 13.3 Hz, 1 H), 2.30–1.93 (series of m, 3 H), 1.55 (s, 3 H), 0.89 (s, 3 H), 0.84 (d, J = 6.4 Hz, 3 H), 1.85–0.83 (series of m, 11 H), 0.53 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 205.9, 147.9, 133.8, 132.4, 128.8, 127.2, 109.9, 54.5, 47.2, 46.8, 44.7, 40.2, 38.6, 35.5, 33.9, 28.5, 27.9, 22.2, 20.6, 11.9; MS m/z (M^+) calcd 356.2174, obsd 356.2201.

For **26**: ^1H NMR (200 MHz, $CDCl_3$) δ 7.39 (m, 2 H), 7.25 (m, 3 H), 4.68 (s, 1 H), 4.65 (m, 1 H), 3.51 (d, J = 11.8 Hz, 1 H), 2.64–1.91 (series of m, 6 H), 1.71 (s, 3 H), 0.95 (s, 3 H), 0.92 (d, J = 6.5 Hz, 3 H), 1.77–0.99 (series of m, 8 H), 0.58 (m, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$, ppm) 207.1, 146.2, 135.1, 132.1, 128.9, 127.2, 109.8, 59.8, 55.4, 51.1, 40.3, 38.7, 37.4, 36.6, 35.7, 34.2, 28.1, 27.1, 22.6, 20.7, 13.0; MS m/z (M^+) calcd 356.2174, obsd 356.2144.

(3*S,4a*R**,5*R**,6*S**,8a*R**)-Octahydro-4a,6-dimethyl-5-(3-methyl-3-butenyl)-3-(phenylsulfinyl)-2(1*H*)-naphthalenone (27).** *m*-Chloroperbenzoic acid (48 mg, 0.28 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a cooled (−78 °C) solution of **25** (0.1 g, 0.28 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at −78 °C for 20 min and partitioned between ether (20 mL) and 10% aqueous sodium sulfite solution (20 mL). The ether layer was washed with saturated $NaHCO_3$ solution (2 × 5 mL), dried, and concentrated. The resultant sulfoxide (**27**) was used without further purification (0.1 g crude): IR (neat, cm^{-1}) 1710, 1445, 1035; ^1H NMR (60 MHz, $CDCl_3$) δ 7.5 (m, 5 H), 4.65 (m, 2 H), 3.5 (dd, J = 6, 13 Hz, 1 H), 1.7 (s, 3 H), 0.9 (s and d, total 6 H), 2.8–0.5 (series of m, 15 H).

(4a*R,5*R**,6*S**,8a*R**)-4a,5,6,7,8,8a-Hexahydro-4a,6-dimethyl-5-(3-methyl-3-butenyl)-3-(phenylthio)-2(1*H*)-naphthalenone (28).** A solution of **25** (0.20 g, 0.56 mmol) and *N*-chlorosuccinimide (0.075 g, 0.56 mmol) in CCl_4 (9 mL) was refluxed for 90 min, cooled, and filtered. The filtrate was concentrated in vacuo, the residue was dissolved in ether (9 mL), and triethylamine (0.06 g, 0.56 mmol) was then added. After being stirred at ambient temperature for 12 h, this mixture was filtered, and the filtrate was diluted with additional ether (100 mL) and washed with 1.2 M HCl (10 mL), saturated $NaHCO_3$ solution (10 mL), and brine (10 mL). The ether solution was dried and concentrated, and the residue was purified by HPLC on silica gel (elution with 8% ethyl acetate in petroleum ether) to give **28** as a yellow oil (0.12 g, 60%): IR (neat, cm^{-1}) 1680; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35 (m, 5 H), 6.42 (s, 1 H), 4.59 (s, 1 H), 4.47 (s, 1 H), 2.40 (m, 2 H), 1.90 (m, 2 H), 1.68 (m, 1 H), 1.57 (s, 3 H), 0.92 (s, 3 H), 0.90 (d, J = 7.5 Hz, 3 H), 1.55–0.88 (series of m, 7 H), 0.63 (ddd, J = 2.1, 5.0, 10.8 Hz, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$, ppm) 195.4, 152.7, 145.7, 136.8, 134.2, 132.2, 129.6, 128.5, 109.8, 51.4, 44.0, 42.0, 41.3, 40.3, 35.4, 34.6, 28.4, 27.4, 22.4, 20.8, 13.0; MS m/z (M^+) calcd 354.2017, obsd 354.2035.

Methyl (4a*R,7*S**,8*R**,8a*R**)-Decahydro-7,8a-dimethyl-8-(3-methyl-3-butenyl)-3-oxo-2-naphthoate (29).** To a stirred suspension of sodium hydride (1.38 g, 57.5 mmol), dimethyl carbonate (21.6 g, 240 mmol), and dry 1,2-dimethoxyethane (90 mL) was added dropwise a solution of **20** (11.9 g, 48.0 mmol) in 1,2-dimethoxyethane (350 mL). The mixture was refluxed for 15 h, cooled to ambient temperature, and concentrated on a rotary evaporator. After the addition of water (30 mL) and acidification with 1.2 M HCl, the residue was extracted with ether (50 mL), dried, and concentrated. The residue was purified by chromatography on silica gel (elution with 4% ethyl acetate in petroleum ether) to give **29** as a light yellow oil, which solidified on standing (11.9 g, 81%). Recrystallization from 1:1 methanol–ether provided a white crystalline solid: mp 65–66 °C; IR (CH_2Cl_2, cm^{-1}) 1665, 1620, 1445, 1210; ^1H NMR (300 MHz, $CDCl_3$) δ 12.10 (s, 1 H), 4.70 (m, 2 H), 3.75 (s, 3 H), 2.43–1.81 (series of m, 5 H), 1.76 (s, 3 H), 1.72–0.95 (series of m, 9 H), 0.92 (d, J = 6.4 Hz, 3 H), 0.69 (s, 3 H), 0.61 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 173.2, 170.9, 146.5, 109.6, 96.0, 54.5, 51.3, 40.6, 40.1, 36.4, 36.2, 35.6, 34.3, 33.5, 28.3, 27.3, 22.5, 20.9, 11.5. Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.48; H, 9.90.

Methyl (4a*R,7*S**,8*R**,8a*R**)-3,4,4a,5,6,7,8,8a-Octahydro-7,8a-dimethyl-8-(3-methyl-3-butenyl)-3-oxo-2-naphthoate (30).** To a stirred solution of **29** (1.05 g, 3.42 mmol) in dry THF (15 mL) was added over 1 h a solution of freshly recrystallized DDQ (931 mg, 4.1 mmol) in THF (10 mL) via a syringe pump. The suspension was stirred for 2.5 h, treated with 100 μL of triethylamine, and concentrated. The crude material was taken up in ether–petroleum ether (1:9), filtered to remove insoluble solids, and freed of solvent. Repetition of this procedure provided a residue that was chromatographed on silica gel (elution with 10% ether in petroleum ether). There was isolated 703 mg (77%) of **30** as a labile golden oil that was used without further purification: IR (neat, cm^{-1}) 1745, 1730, 1690, 1270; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (s, 1 H), 4.72 (s, 1 H), 4.71 (s, 1 H), 3.80 (d, J = 0.7 Hz, 3 H), 2.45–1.85 (series of m, 5 H), 1.77 (s, 3 H), 1.73–1.04 (series of m, 7 H), 1.01 (d, J = 0.5 Hz, 3 H), 0.97 (d, J = 6.4 Hz, 3 H), 0.84 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 194.7, 165.6, 164.0, 145.5, 130.8, 110.3, 52.2, 50.4, 43.2, 41.4, 40.9, 40.0, 35.2, 34.5, 27.9, 27.2, 22.5, 20.8, 12.6; MS m/z (M^+) calcd 304.2038, obsd 304.2018.

(4a*R,5*R**,6*S**,8a*R**)-4a,5,6,7,8,8a-Hexahydro-3,4a,6-trimethyl-5-(3-oxobutyl)-2(1*H*)-naphthalenone (38).** A solution of **23** (100 mg, 0.39 mmol) and pyridine (30 mg, 0.39 mmol) in CH_2Cl_2 (50 mL) was cooled to −78 °C, and ozone was bubbled through until the starting material just disappeared (TLC analysis). After the mixture was purged with nitrogen, dimethyl sulfide (0.24 g, 3.9 mmol) was added, and the solution was warmed to ambient temperature, stirred for 12 h, and washed with saturated aqueous NH_4Cl solution (10 mL) and brine (10 mL). The solvent was removed from the dried organic phase, and the residue was purified by MPLC on silica gel (elution with 27% ethyl acetate in petroleum ether) to give **30** as a colorless oil (50 mg, 50%):

IR (neat, cm^{-1}) 1715, 1670; ^1H NMR (300 MHz, $CDCl_3$) δ 6.87 (s, 1 H), 2.63–2.19 (series of m, 4 H), 2.16 (s, 3 H), 1.75 (s, 3 H), 1.96–1.00 (series of m, 8 H), 0.94 (s, 3 H), 0.92 (d, J = 7.2 Hz, 3 H), 0.72 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 208.4, 200.0, 154.1, 133.4, 50.7, 45.6, 44.2, 40.8, 40.3, 35.3, 34.6, 29.9, 27.3, 23.0, 20.9, 16.0, 12.8. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.81; H, 9.99. Found: C, 77.39; H, 10.01.

(4a*R,5*R**,6*S**,8a*R**)-4a,5,6,7,8,8a-Hexahydro-3,4a,6-trimethyl-5-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2(1*H*)-naphthalenone (39).** *p*-Toluenesulfonic acid monohydrate (11 mg, 0.057 mmol) was added to a solution of **38** (0.15 g, 0.57 mol) and 2-methyl-2-ethyl-1,3-dioxolane (0.84 g, 5.7 mmol) in benzene (20 mL). The mixture was stirred at ambient temperature for 8 h, concentrated in vacuo, and dissolved in ether (100 mL). The ether solution was washed with saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), dried, and concentrated. The residue was purified by MPLC on silica gel (elution with 17% ethyl acetate in petroleum ether) to give **39** as a light yellow oil (0.15 g, 87%): IR (neat, cm^{-1}) 1675, 1375, 1050; ^1H NMR (300 MHz, $CDCl_3$) δ 6.78 (s, 1 H), 3.94 (m, 4 H), 2.36–2.14 (m, 2 H), 1.72 (d, J = 1.2 Hz, 3 H), 1.32 (s, 3 H), 0.97 (d, J = 5.8 Hz, 3 H), 0.91 (s, 3 H), 1.88–0.95 (series of m, 10 H), 0.68 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 200.2, 154.3, 133.3, 109.9, 64.6, 51.2, 44.3, 41.3, 40.8, 40.4, 35.4, 34.5, 27.3, 23.6, 23.5, 20.8, 16.1, 12.9; MS m/z (M^+) calcd 306.2195, obsd 306.2213.

Methyl (1*R,4a*R**,7*S**,8*R**,8a*R**)-1-(3-Butenyl)decahydro-7,8a-dimethyl-8-(3-methyl-3-butenyl)-3-oxo-2-naphthoate (41).** The requisite Grignard reagent was prepared in THF (35 mL) from 4-bromo-1-butene (2.41 g, 17.9 mmol) and magnesium turnings (0.43 g, 17.9 mmol). After a reflux period of 30 min, the solution was transferred to a dry three-necked flask and cooled to −78 °C. A cuprous bromide–dimethyl sulfide complex (0.61 g, 3.0 mmol) in dimethyl sulfide (25 mL) was added dropwise, and the resulting milky suspension was stirred at −78 °C for an additional 30 min. A solution of **30** (0.90 g, 3.0 mmol) in THF (65 mL) was added dropwise, and the bright yellow suspension was stirred for 30 min and warmed to −50 °C over 10 min. The reaction mixture was partitioned between ether (700 mL) and saturated NH_4Cl solution (50 mL). The ether layer was washed with additional NH_4Cl solution (2 × 50 mL) and brine (30 mL), dried, and concentrated. Purification of the residue by MPLC on silica gel (elution with 4% ethyl acetate in petroleum ether) gave **41** as a light yellow oil (0.80 g, 75%): IR (neat, cm^{-1}) 1655, 1615, 1440, 1270, 1220; ^1H NMR (300 MHz, $CDCl_3$) δ 11.90 (s, 1 H), 5.80 (m, 1 H), 4.94 (m, 2 H), 4.70 (s, 2 H), 3.75 (s, 3 H), 2.63–1.83 (series of m, 7 H), 1.76 (s, 3 H), 1.72–0.91 (series of m, 11 H), 0.95 (d, J = 6.4 Hz, 3 H), 0.70 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 173.5, 171.9, 146.8, 139.5, 114.1, 109.3, 102.0, 51.2, 48.1, 40.2, 40.1, 39.2, 35.6, 34.91, 34.88, 34.0, 32.1, 31.8, 29.0, 27.2, 22.6, 21.4, 14.2; MS m/z (M^+) calcd 360.2664, obsd 360.2685.

Methyl (1*R,4a*S**,7*R**,8*S**,8a*S**)-1-(3-Butenyl)-1,4,4a,5,6,7,8,8a-octahydro-3-methoxy-7,8a-dimethyl-8-(3-methyl-3-butenyl)-2-naphthoate (42).** To a stirred suspension of sodium hydride (53 mg, 2.2 mmol) in dry 1,2-dimethoxyethane (10 mL) was added dropwise a solution of **41** (0.61 g, 1.7 mmol) in 1,2-dimethoxyethane (20 mL). After this mixture had been refluxed for 5 min, methyl iodide (2.41 g, 17 mmol) was added by syringe, and the mixture was refluxed for an additional 15 min. Solvent was removed on a rotary evaporator, and the residue was dissolved in ether (200 mL). The ether solution was washed with saturated NH_4Cl solution (20 mL) and water (10 mL), dried, and concentrated. The residue was purified by MPLC on silica gel (elution with 15% ethyl acetate in petroleum ether) to give **42** as a colorless oil, which solidified on standing (0.54 g, 86%). Recrystallization from methanol provided a colorless crystalline solid: mp 54.5–55.5 °C; IR (KBr, cm^{-1}) 1710, 1640, 1450, 1370, 1255, 1210, 1050; ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (m, 1 H), 4.94 (m, 2 H), 4.76 (s, 2 H), 3.72 (s, 3 H), 3.66 (s, 3 H), 2.69 (dd, J = 3.0, 10.8 Hz, 1 H), 2.32 (dd, J = 5.8, 17.9, Hz, 1 H), 2.19–1.76 (series of m, 4 H), 1.73 (s, 3 H), 1.72–0.91 (series of m, 12 H), 0.95 (d, J = 6.4 Hz, 3 H), 0.73 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 169.5, 159.1, 146.7, 139.2, 114.2, 111.8, 109.4, 55.3, 51.3, 48.1, 43.4, 39.5, 39.2, 35.6, 35.2, 35.0, 31.9, 31.6, 30.8, 29.4, 27.2, 22.5, 21.4, 13.6. Anal. Calcd for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 76.78; H, 10.26.

(4*R,4a*S**,5*S**,6*R**,8a*S**)-4-(3-Butenyl)octahydro-4a,6-dimethyl-5-(3-methyl-3-butenyl)-3-methylene-2(1*H*)-naphthalenone (43).** A solution of **42** (1.04 g, 2.78 mmol) in dry CH_2Cl_2 (90 mL) was cooled to −78 °C, and Dibal-H in hexanes (7.0 mmol) was added dropwise by syringe. After the solution was stirred for 15 min at −78 °C, saturated potassium sodium tartrate solution (25 mL) was added, the mixture was warmed to ambient tmeperature, and the resulting milky emulsion was stirred until two layers formed (30 min). Additional CH_2Cl_2 (100 mL) and water (30 mL) were added, and the mixture was transferred to a separatory funnel. The organic layer was washed with water (30 mL) and concentrated. The residue was taken up in THF (90 mL) and 1.2 M hydrochloric acid solution (90 mL), stirred for 15 min, evaporated, and dissolved in ether (400 mL). The ether solution was washed with saturated $NaHCO_3$ solution (30 mL) and brine (30 mL), dried, and concentrated. The residue was purified by MPLC on silica gel (elution with 10% ethyl acetate in petroleum ether) to give **43** as a colorless oil (0.80 g, 92%): IR (neat, cm^{-1}) 1695; ^1H NMR (300 MHz, C_6D_6) δ 5.89 (d, J = 2.3 Hz, 1 H), 5.70 (m, 1 H), 4.98 (m, 2 H), 4.83 (s, 1 H), 4.81 (s, 1 H), 4.68 (d, J = 2.2 Hz, 1 H), 2.30–1.75 (series of m, 6 H), 1.69 (s, 3 H), 1.66–0.69 (series of m, 12 H), 0.84 (d, J = 6.5 Hz, 3 H), 0.64 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 203.3, 148.0, 146.4, 138.1, 120.9, 115.2, 109.5, 50.9, 47.9, 43.7, 40.3, 39.4, 37.6, 35.6, 34.5, 31.2, 29.0, 27.3, 26.7, 22.5, 21.2, 14.3; MS m/z (M^+) calcd 314.2609, obsd 314.2592.

(4*R,4a*R**,5*R**,6*S**,8a*R**)-4-(3-Butenyl)octahydro-3,4a,6-trimethyl-5-(3-methyl-3-butenyl)-2(1*H*)-naphthalenones (44 and 45).** Lithium wire (0.93 g, 0.136 mol) was added to dry liquid ammonia (100 mL) at −78 °C, and the resulting blue solution was stirred at −78 °C for 20 min. A 0.43-g (1.36 mmol) sample of **43** in ether (50 mL) was introduced dropwise, and the mixture was stirred at −78 °C for 1 h. After excess lithium had been quenched with isoprene, the ammonia was removed in vacuo, and the residue was suspended in dry ether (100 mL) and cooled to −78 °C. A solution of *tert*-butyl alcohol (5 mL) in ether (20 mL) was added dropwise, and the mixture was warmed to 0 °C and added to saturated NH_4Cl solution (20 mL) contained in a separatory funnel. The aqueous layer was removed, saturated with sodium chloride, and extracted with ether (100 mL). The combined ether phases were dried and concentrated. Purification of the residue by MPLC (elution with 10% ethyl acetate in petroleum ether) gave **44** (0.21 g, 49%) and **45** (0.11 g, 27%).

For **44**: IR (neat, cm^{-1}) 1700; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (m, 1 H), 5.04 (dd, J = 1.5, 17.1 Hz, 1 H), 4.98 (d, J = 10.2 Hz, 1 H), 4.69 (s, 1 H), 4.67 (s, 1 H), 2.35 (dd, J = 7.1, 17.4 Hz, 1 H), 2.28–1.77 (series of m, 7 H), 1.73 (s, 3 H), 1.24 (d, J = 7.3 Hz, 3 H), 0.95 (d, J = 6.4 Hz, 3 H), 1.64–0.71 (series of m, 11 H), 0.79 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 215.2, 145.8, 137.5, 114.3, 108.6, 49.5, 48.0, 47.2, 42.1, 40.1, 38.4, 36.9, 34.9, 33.6, 31.6, 29.7, 29.3, 26.8, 21.7, 20.6, 19.4, 14.4; MS m/z (M^+) calcd 316.2766, obsd 316.2737.

For **45**: IR (neat, cm^{-1}) 1705; ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (m, 1 H), 4.96 (m, 2 H), 4.69 (s, 1 H), 4.67 (s, 1 H), 2.87 (m, 1 H), 2.25–1.79 (series of m, 7 H), 1.74 (s, 3 H), 1.10 (s, 3 H), 1.04 (d, J = 6.7 Hz, 3 H), 0.97 (d, J = 6.3 Hz, 3 H), 1.69–0.79 (series of m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 213.2, 146.5, 138.2, 114.4, 109.3, 51.3, 48.5, 45.3, 45.1, 41.8, 41.3, 38.9, 36.3, 35.8, 34.8, 29.1, 27.7, 25.1, 22.7, 21.4, 15.1, 13.2; MS m/z (M^+) calcd 316.2766, obsd 316.2788.

Ozonolysis of 44. A solution of **44** (0.14 g, 0.43 mmol) in 1:1 methylene chloride–methanol (150 mL) was cooled to −78 °C, and ozone was bubbled through until a persistent blue color developed. After the solution was purged with nitrogen, dimethyl sulfide (5.3 g, 86 mmol) was introduced, and stirring was maintained for 1 h at −78 °C and for 10 h at 25 °C. The solvent was removed in vacuo, and the residue was dissolved in ether (150 mL). The ether solution was washed with water (20 mL), dried, and concentrated. The resulting colorless oil (**46**) was used without further purification (0.16 g crude): IR (CH_2Cl_2, cm^{-1}) 1720, 1715, 1700; ^1H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1 H), 3.52–2.15 (series of m, 5 H), 2.13 (s, 3 H), 1.23 (d, J = 7.5 Hz, 3 H), 0.92 (d, J = 6.4 Hz, 3 H), 0.80 (s, 3 H), 2.11–0.73 (series of m, 14 H).

Ozonolysis of 45. A solution of **45** (43.1 mg, 0.14 mmol) in 1:1 methylene chloride–methanol (40 mL) was cooled to −78 °C, and ozone was bubbled through until a persistent blue color developed. After the solution was purged with nitrogen, dimethyl sulfide (1.69 g, 27.3 mmol) was added, and stirring was maintained for 1 h at −78 °C and for 10 h at ambient temperature. The solvent was removed in vacuo, and the residue was dissolved in ether (100 mL) and washed with water (10 mL). The dried ether solution was concentrated, and the colorless residue (**47**) was used without further purification (46.1 mg): IR (neat, cm^{-1}) 1715, 1710; ^1H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 1 H), 2.10 (s, 3 H), 1.08 (s, 3 H), 0.99 (d, J = 6.7 Hz, 3 H), 0.89 (d, J = 6.2 Hz, 3 H), 2.88–0.71 (series of m, 19 H).

(3a*R,5a*R**,8*S**,9*R**,9a*R**,9b*S**)-Dodecahydro-3-hydroxy-3a,8,9a-trimethyl-9-(3-oxobutyl)-4*H*-benz[*e*]inden-4-one (48).** Unpurified **46** (0.16 g, 0.43 mmol) was dissolved in THF (100 mL), and a solution of 1.2 M HCl (20 mL) was added. The mixture was stirred for 30 min, concentrated, and dissolved in ether (200 mL). The ether layer was washed with saturated $NaHCO_3$ solution (20 mL), dried, and concentrated. The resulting **48** was used without further purification (0.16 g crude): IR (neat, cm^{-1}) 3590, 1705, 1680, 1090, 1010, 800; ^1H NMR (300 MHz, $CDCl_3$) δ 3.96 (m, 1 H), 2.71–2.35 (series of m, 3 H), 2.14 (s, 3 H), 1.16 (s, 3 H), 0.90 (d, J = 6.5 Hz, 3 H), 0.84 (s, 3 H), 2.25–0.75 (series of m, 16 H).

O-Silylation of 45 and Subsequent Hydrolysis. Equatorial methyl epimer **45** (93.5 mg, 0.30 mmol) in DMF (6 mL) was added to a solution of chlorotrimethylsilane (0.16 g, 1.48 mmol) and triethylamine (0.30 g, 2.96 mmol) in DMF (6 mL). The mixture was refluxed for 12 h, cooled, and diluted with petroleum ether (150 mL). The petroleum ether solution was washed with saturated $NaHCO_3$ solution (2 × 20 mL), dried, and concentrated. The residue was purified by MPLC on silica gel (elution with 10% ethyl acetate in petroleum ether) to give the thermodynamic silyl enol ether as a colorless oil (97.9 mg, 85%): IR (neat, cm^{-1}) 1680, 1250, 1175, 870, 845; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (m, 1 H), 4.96 (m, 2 H), 4.67 (s, 2 H), 2.21–1.76 (series of m, 6 H), 1.74 (s, 3 H), 1.64 (s, 3 H), 1.71–0.98 (series of m, 12 H), 0.94 (d, J = 6.4 Hz, 3 H), 0.71 (s, 3 H), 0.18 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 147.0, 142.4, 139.7, 115.4, 113.9, 109.2, 48.7, 48.3, 40.4, 39.2, 36.7, 35.9, 35.6, 35.0, 33.0, 30.8, 29.5, 27.5, 22.6, 21.6, 18.0, 14.1, 0.8; MS m/z (M^+) calcd 388.3161, obsd 388.3186.

The silyl enol ether (0.197 g, 0.51 mmol) in 1,2-dimethoxyethane (3 mL) was added to a solution of methyllithium (0.76 mmol) in 1,2-dimethoxyethane (2 mL). After being stirred at ambient temperature for 30 min, the mixture was cooled to −78 °C, *tert*-butyl alcohol (2 mL) in ether (3 mL) was added dropwise, and stirring was maintained at −78 °C for 15 min. The solution was warmed to 0 °C, added to saturated NH_4Cl solution (20 mL), and extracted with ether (2 × 50 mL). The ethereal solution was washed with water (5 mL), dried, and concentrated. The residue was purified by MPLC on silica gel (elution with 10% ethyl acetate in petroleum ether) to give **44** (47.1 mg, 30%) along with recovered **45** (20.9 mg, 13%). These products had spectral properties identical to those reported earlier.

(3a*R,5a*S**,8*R**,9*S**,9a*S**,9b*S**)-1,3a,5,5a,6,7,8,9,9a,9b-Decahydro-3a,8,9a-trimethyl-9-(3-oxobutyl)-4*H*-benz[*e*]inden-4-one (49).** Methanesulfonyl chloride (0.11 g, 1.04 mmol) was added by syringe to a solution of unpurified **48** (0.43 mmol) and triethylamine (0.13 g, 1.30 mmol) in CH_2Cl_2 (25 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min, diluted with CH_2Cl_2 (100 mL), and washed sequentially with 1.2 M HCl (10 mL), saturated $NaHCO_3$ solution (10 mL), and brine (10 mL) prior to drying. The solvent was removed in vacuo, and the residue was purified by MPLC on silica gel (elution with 75% ethyl acetate in petroleum ether) to give the mesylate as a single epimer (0.13 g, 76% from **44**): IR ($CHCl_3$, cm^{-1}) 1715, 1705, 1370, 1175, 910; ^1H NMR (300 MHz, $CDCl_3$) δ 5.15 (t, J = 5.4 Hz, 1 H), 3.00 (s, 3 H), 2.14 (s, 3 H), 1.29 (s, 3 H), 0.99 (s, 3 H), 0.88 (d, J = 6.3 Hz, 3 H), 2.69–0.78 (series of m, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 213.2, 208.2, 87.1, 57.4, 55.0, 49.1, 44.7, 41.5, 39.1, 38.7, 38.3, 35.4, 33.7, 30.1, 29.8, 28.8, 23.5, 21.9, 21.7, 21.0, 15.4; MS m/z ($M^+ - SO_3CH_3$) calcd 303.2324, obsd 303.2281.

Anhydrous lithium bromide (0.26 g, 3.0 mmol) was added in one portion to a solution of the above mesylate (0.12 g, 0.30 mmol) in DMF (10 mL), and the mixture was refluxed for 45 min. The cooled yellow solution was then added to 1:1 ether–petroleum ether (200 mL), washed with water (2 × 15 mL), and dried. The solvent was removed in vacuo, and the residue was purified by MPLC on silica gel (elution with 50% ethyl acetate in petroleum ether) to give an inseparable mixture of **49** and its 1,2 isomer in a 5:1 ratio (total 70.5 mg, 77%): IR (neat, cm^{-1}) 1695; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73 (m, 1 H), 5.38 and 5.33 (two m, total 1 H), 2.63–2.28 (series of m, 6 H), 2.16 and 2.14 (two s, total 3 H), 1.33 and 1.31 (two s, total 3 H), 0.91 and 0.89 (two s, total 3 H), 0.94 and 0.91 (two d, J = 7.0 and 7.7 Hz, total 3 H), 2.11–0.97 (series of m, 9 H), 0.83 (m, 1 H). For **49**: ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 215.4, 208.4, 136.3, 130.7, 60.9, 54.8, 49.6, 45.2, 41.9, 36.4, 35.6, 35.0, 33.9, 29.9, 29.3, 28.5, 27.8, 22.2, 21.2, 14.8; MS m/z (M^+) calcd 302.2246, obsd 302.2239. The separation of these regioisomers could be conveniently achieved following monoketalization.

p-Toluenesulfonic acid monohydrate (3.9 mg, 0.021 mmol) was added to the diketone mixture (74.5 mg, 0.206 mmol of **49**) and 2-methyl-2-ethyl-1,3-dioxolane (0.31 g, 2.06 mmol) in benzene (10 mL). The mixture was stirred at ambient temperature for 30 min and concentrated in vacuo. The residue was dissolved in ether (100 mL), and the ethereal solution was washed with saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), dried, and concentrated. The residue was purified by MPLC on silica gel (elution with 25% ethyl acetate in petroleum ether) to give the monoketal of **49** as a colorless oil (47.4 mg, 67%): IR (neat, cm^{-1}) 1695, 1060; ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (m, 1 H), 5.37 (m, 1 H), 3.94 (m, 4 H), 1.34 (s, 3 H), 1.31 (s, 3 H), 0.93 (d, J = 6.4 Hz, 3 H), 0.88 (s, 3 H), 2.49–0.90 (series of m, 15 H), 0.80 (m, 1 H); MS m/z (M^+) calcd 346.2508, obsd 346.2502.

Methyl (3a*R,5a*R**,8*S**,9*R**,9a*R**,9b*S**)-Dodecahydro-8,9a-dimethyl-9-(3-methyl-3-butenyl)-2-methylene-4-oxo-3a*H*-benz[*e*]indene-3a-carboxylate (50).** A solution of **30** (501 mg, 1.64 mmol), palladium acetate (87 mg, 0.39 mmol), and [2-(acetoxymethyl)allyl]trimethylsilane (650 μL, 3.06 mmol) in THF (15 mL) was treated dropwise with 310 μL (1.81 mmol) of triethyl phosphite. This mixture was heated at gentle reflux for 20 h, concentrated, and subjected to column chromatography on silica gel (elution with 10% ether in petroleum ether). There was isolated 576 mg (98%) of **50** as a colorless white solid: mp 87–88 °C (from hexane); IR (CH_2Cl_2, cm^{-1}) 1710, 1650; ^1H NMR (300 MHz, $CDCl_3$) δ 4.85 (d, J = 8.7 Hz, 2 H), 4.68 (d, J = 2.3 Hz, 2 H), 3.70 (s, 3 H), 3.39 (d, J = 16.2 Hz, 1 H), 3.12 (dd, J = 12.8, 8.1 Hz, 1 H), 2.66 (t, J = 14.2 Hz, 1 H), 2.44 (m, 2 H), 2.26–1.17 (series of m, 12 H), 1.73 (s, 3 H), 0.97 (s, 3 H), 0.91 (d, J = 6.4 Hz, 3 H), 0.74 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 206.1, 174.2, 146.2, 146.1, 109.5, 106.8, 63.9, 56.4, 52.4, 50.4, 43.8, 41.1, 40.7, 39.6, 38.9, 35.7, 34.1, 32.7, 28.5, 27.4, 22.5, 21.1, 14.2; MS m/z (M^+) calcd 358.2508, obsd 358.2518. Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.04; H, 9.65. Found: C, 77.20; H, 9.56.

(3a*R,4*R**,5a*S**,8*R**,9*S**,9a*S**,9b*R**)-Dodecahydro-4-hydroxy-8,9a-dimethyl-9-(3-methyl-3-butenyl)-2-methylene-3a*H*-benz[*e*]indene-3a-methanol (12).** To a cold (−78 °C), magnetically stirred solution of **50** (2.65 g, 7.37 mmol) in dry THF (50 mL) was added lithium aluminum hydride (1.2 g, 31.3 mmol). The suspension was stirred for 6 h, allowed to warm to room temperature, diluted with ether (15 mL), and treated sequentially with water (675 μL), 3 M NaOH (335 μL), and water (675 μL). The white granular solid was removed by filtration and rinsed with copious amounts of ether. The combined filtrates were evaporated, and the residue was recrystallized from hexane–CH_2Cl_2 (3:1) to give **12** as a white solid (2.66 g, 90%): mp 153–154 °C; IR (CH_2Cl_2, cm^{-1}) 3610; ^1H NMR (300 MHz, $CDCl_3$) δ 4.91 (d, J = 10.9 Hz, 1 H), 4.66 (s, 2 H), 4.38 (d, J = 10.9 Hz, 1 H), 3.75 (dd, J = 11.8, 4.5 Hz, 1 H), 3.32 (d, J = 10.8 Hz, 1 H), 2.85 (d, J = 16.7 Hz, 1 H), 2.50–0.79 (series of m, 18 H), 1.72 (s, 3 H), 0.90 (d, J = 6.3 Hz, 3 H), 0.81 (s, 3 H), 0.70 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 148.5, 146.7, 109.2, 107.0, 73.8, 69.5, 54.0, 51.2, 50.8, 42.5, 39.1, 39.0, 38.8, 36.1, 35.5, 34.4, 33.6, 28.3, 27.5, 22.7, 21.4, 16.3; MS m/z ($M^+ - H_2O$) calcd 314.2609, obsd 314.2569. Anal. Calcd for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91. Found: C, 79.35; H, 10.88.

(3a*R,4*R**,5a*S**,8*R**,9*S**,9a*S**,9b*R**)-Dodecahydro-4-hydroxy-8,9a-dimethyl-9-(3-methyl-3-butenyl)-2-methylene-3a*H*-benz[*e*]indene-3a-methanol 3a-*p*-Toluenesulfonate (51).** To a cold (0 °C), magnetically stirred solution of **12** (400 mg, 1.2 mmol), 4-(dimethylamino)pyridine (147 mg, 1.2 mmol), and triethylamine (840 μL, 6.0 mmol) in CH_2Cl_2 (10 mL) was added a solution of *p*-toluenesulfonyl chloride (251 mg, 1.32 mmol) in CH_2Cl_2 (6 mL) via syringe pump over 7 h. After overnight storage in a refrigerator, the reaction mixture was diluted with ether and washed with water, saturated cupric sulfate solution (2×), and water prior to drying and solvent evaporation. Chromatography of the residue on silica gel (elution with petroleum ether–ether 4:1) returned 43 mg (11%) of **12** and provided 343 mg (63%) of **51** as a colorless white solid: mp 56–58 °C; IR ($CHCl_3$, cm^{-1}) 3530, 1450, 1350, 1185, 1175, 950; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (AB q, $\Delta\nu$ = 135.4 Hz, J_{AB} = 8.2 Hz, 4 H), 4.87 (d, J = 8.0 Hz, 2 H), 4.67 (d, J = 6.8 Hz, 2 H), 4.19 (AB q, $\Delta\nu$ = 39.4 Hz, J_{AB} = 10.0 Hz, 2 H), 3.62 (m, 1 H), 2.53–0.81 (series of m, 18 H), 2.45 (s, 3 H), 1.72 (s, 3 H), 0.89 (d, J = 6.4 Hz, 3 H), 0.77 (s, 3 H), 0.68 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 147.3, 146.5, 144.7, 132.9, 129.8, 127.9, 109.3, 107.5, 72.1, 71.4, 60.4, 50.7, 49.4, 41.6, 39.1, 38.8, 38.7, 36.0, 34.7, 34.4, 33.0, 28.2, 27.3, 22.6, 21.6, 21.4, 15.4, 14.2; MS m/z (M^+) calcd 486.2804, obsd 486.2788.

(3a*R,4*R**,5a*S**,8*R**,9*S**,9a*S**,9b*R**)-Dodecahydro-4-hydroxy-3a,8,9a-trimethyl-9-(3-methyl-3-butenyl)-2-methylene-3a*H*-benz[*e*]indene (52a).** Into a cold (0 °C), magnetically stirred solution of **51** (40 mg, 0.082 mmol) in dry THF (5 mL) was added lithium triethylborohydride (0.98 mL of 1 M in THF, 0.98 mmol), and the resulting mixture was allowed to warm slowly to room temperature over 15 h. After the sequential addition of water (300 μL), 3 M NaOH (1.2 mL), and 30% hydrogen peroxide (1 mL), the mixture was stirred for 1 h, diluted with ether, washed with saturated $NaHCO_3$ solution (2 × 10 mL) and water (10 mL), dried, and evaporated. Column chromatography of the residue on silica gel (elution with petroleum ether–ethyl acetate 9:1) furnished **52a** as white crystals (24.4 mg, 94%): mp 76–78 °C; IR ($CHCl_3$, cm^{-1}) 3560; ^1H NMR (300 MHz, $CDCl_3$) δ 4.85 (d, J = 11.5 Hz, 2 H), 4.66 (s, 2 H), 3.52 (m, 1 H), 2.60–0.86 (series of m, 18 H), 1.73 (s, 3 H), 1.10 (s, 3 H), 0.92 (s, 3 H), 0.90 (d, J = 6.3 Hz, 3 H), 0.68 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 149.3, 147.0, 125.9, 109.1, 106.4, 72.0, 56.0, 50.8, 47.4, 46.5, 41.5, 39.8, 39.6, 38.9, 36.2, 35.2, 35.1, 34.2, 33.7, 28.9, 28.4, 27.5, 22.7, 21.53, 21.47, 16.2; MS m/z (M^+) calcd 316.2766, obsd 316.2758. Anal. Calcd for $C_{22}H_{36}O$: C, 83.48; H, 11.46. Found: C, 83.27; H, 11.75.

***tert*-Butyl[(3a*R**,4*R**,5a*S**,8*R**,9*S**,9a*S**,9b*S**)-dodecahydro-3a,8,9a-trimethyl-9-(3-methyl-3-butenyl)-2-methylene-1*H*-benz[*e*]inden-4-yloxy]dimethylsilane (52b).** Alcohol **52a** (107 mg, 0.339 mmol) was dissolved in THF (1.5 mL) containing triethylamine (0.124 mL, 0.542 mmol) and stirred at room temperature for 18 h. After dilution with ether (10 mL), the organic phase was washed with water (5 mL) and

saturated $NaHCO_3$ solution (5 mL) prior to drying and evaporation. Purification of the residue by silica gel chromatography (elution with hexane) gave **52b** as a colorless foam (131 mg, 94%): IR (neat, cm^{-1}) 1450, 1375, 1245, 1095, 1065, 1040; ^1H NMR (300 MHz, $CDCl_3$) δ 4.82 (br s, 2 H), 4.66 (s, 2 H), 3.46 (s, 2 H), 3.46 (dd, J = 10.4, 4.8 Hz, 1 H), 2.41 (m, 2 H), 2.15–0.77 (series of m, 18 H), 1.73 (s, 3 H), 1.06 (s, 3 H), 0.91 (d, J = 2.2 Hz, 3 H), 0.88 (s, 9 H), 0.66 (m, 1 H), 0.02 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 149.9, 147.0, 109.0, 106.0, 72.2, 55.7, 50.8, 47.8, 47.2, 39.6, 39.5, 38.9, 36.3, 35.5, 34.2, 33.6, 29.7, 28.6, 27.5, 25.9, 22.7, 22.2, 21.5, 18.1, 16.2, –3.5, –4.9; MS m/z (M^+) calcd 430.3645, obsd 430.3631.

(3a*R,4*R**,5a*S**,8*R**,9*S**,9a*S**,9b*R**)-4-(*tert*-Butyldimethylsiloxy)dodecahydro-3a,8,9a-trimethyl-9-(3-oxobutyl)-2*H*-benz[*e*]inden-2-one (53).** Ozone was bubbled through a cold (–78 °C), magnetically stirred solution of **52b** (50 mg, 0.116 mmol) and pyridine (100 μL) in CH_2Cl_2 until a blue color persisted. The reaction mixture was purged with nitrogen, quenched with dimethyl sulfide (5 mL), and allowed to warm to room temperature overnight. After concentration in vacuo, the residue was purified by column chromatography on silica gel (elution with petroleum ether–ether 3:1) to afford **53** (30 mg, 60%) as a colorless viscous oil: ^1H NMR (300 MHz, $CDCl_3$) δ 3.44 (dd, J = 11.3, 4.4 Hz, 1 H), 2.63–0.71 (series of m, 18 H), 2.12 (s, 3 H), 1.19 (s, 3 H), 1.01 (s, 3 H), 0.89 (d, J = 1.5 Hz, 3 H), 0.87 (s, 9 H), 0.56 (dd, J = 8.6, 6.9 Hz, 1 H), 0.03 (d, J = 6.4 Hz, 6 H); MS m/z (M^+) calcd 434.3216, obsd 434.3238.

Base-Promoted Cyclization of 53. Diketone **53** (37 mg, 0.086 mmol) was dissolved in methanol (10 mL), treated with potassium carbonate (321 mg, 3.77 mmol), and stirred at room temperature for 48 h. The solvent was evaporated, a saturated NH_4Cl solution was added, and the products were extracted into ether (3 × 10 mL). After drying and concentration, the residue was purified chromatographically on silica gel (elution with petroleum ether–ethyl acetate 97:3). There was isolated 17.6 mg (50%) of **54a** and 3.1 mg (9%) of **55l**.

For **54a**: viscous, pale yellow oil: IR (neat, cm^{-1}) 1700; ^1H NMR (300 MHz, $CDCl_3$) δ 3.49 (m, 1 H), 2.87 (d, J = 2.0 Hz, 1 H), 2.20 (AB q, J_{AB} = 16.3 Hz, 2 H), 2.12 (d, J = 2.0 Hz, 3 H), 1.76–0.77 (series of m, 13 H), 1.14 (s, 3 H), 1.05 (s, 3 H), 0.89 (s, 9 H), 0.82 (d, J = 6.3 Hz, 3 H), 0.05 (d, J = 4.2 Hz, 6 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 204.6, 148.2, 132.9, 74.1, 57.0, 52.8, 52.6, 41.7, 41.6, 40.6, 40.4, 35.9, 35.2, 31.2, 29.6, 24.9, 21.08, 21.05, 20.7, 18.3, 16.7, –3.8, –4.8; MS m/z (M^+) calcd 416.3110, obsd 416.3108.

For **55a**: colorless viscous oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.48 (br s, 1 H), 3.28 (dd, J = 11.4, 3.7 Hz, 1 H), 3.02 (d, J = 8.7 Hz, 1 H), 2.49–0.71 (series of m, 14 H), 1.73 (s, 3 H), 1.21 (s, 3 H), 1.03 (s, 3 H), 0.86 (s, 9 H), 0.82 (d, J = 6.3 Hz, 3 H), 0.03 (s, 6 H); MS m/z (M^+ – t-Bu) calcd 359.2406, obsd 359.2427.

(2a*R,3*R**,4a*S**,7*R**,7a*S**,10a*R**,10b*R**,10c*S**)-Dodecahydro-3-hydroxy-2a,7,10,10c-tetramethylnaphth[2,1,8-*cde*]azulen-1(2*H*)-one (9).** To a solution of **55a** (3.5 mg, 0.0084 mmol) in acetonitrile (1 mL) was added HF (0.5 mL of 20% solution in acetonitrile). After 1 h of stirring, saturated $NaHCO_3$ solution (1 mL) was introduced along with CH_2Cl_2 (2 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL), and the combined organic layers were dried and concentrated. Chromatography of the residue on silica gel (elution with petroleum ether–ethyl acetate 7:3) gave **9** as a clear oil that solidified on standing (2.2 mg, 87%): FTIR (neat, cm^{-1}) 3402, 1713; ^1H NMR (300 MHz, $CDCl_3$) δ 5.45 (m, 1 H), 3.35 (dd, J = 11.1, 4.1 Hz, 1 H), 3.02 (br d, J = 10.6 Hz, 1 H), 2.61 (dd, J = 16.6, 1.9 Hz, 1 H), 2.30 (d, J = 11.2 Hz, 1 H), 2.13 (d, J = 16.6 Hz, 1 H), 2.1–0.75 (m, 22 H), 1.73 (s, 3 H), 1.25 (s, 3 H), 1.04 (s, 3 H), 0.86 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 216.6, 135.5, 127.8, 73.5, 62.6, 53.6, 52.4, 50.6, 41.4, 35.9, 34.3, 30.1, 29.7, 29.4, 28.2, 25.8, 22.7, 21.7, 20.6, 16.1; MS m/z (M^+) calcd 302.2245, obsd 302.2236.

(3a*R,5a*S**,8*R**,9*S**,9a*S**,9b*R**)-Dodecahydro-3a-(hydroxymethyl)-8,9a-dimethyl-9-(3-methyl-3-butenyl)-2-methylene-4*H*-benz[*e*]-inden-4-one (56).** A mixture of **12** (166 mg, 0.5 mmol), potassium carbonate (830 mg, 6.0 mmol), ammonium molybdate tetrahydrate (680 mg, 0.55 mmol), and tetra-*n*-butylammonium chloride (175 mg, 0.77 mmol) in THF (6 mL) was treated dropwise with 30% hydrogen peroxide (2 mL) via a syringe pump over a period of 24 h. This addition was repeated four times, at which point the yellow homogeneous solution was diluted with ether (10 mL) and brine (5 mL). The separated aqueous phase was extracted with ether (4 × 10 mL), and the combined organic layers were dried and evaporated. The residue was chromatographed on silica gel (elution with petroleum ether–ethyl acetate 3:1) to give 120 mg (73%) of **56** and to return 31 mg of unreacted **12**.

For **56**: colorless solid, mp 119–120 °C; IR ($CHCl_3$, cm^{-1}) 3440, 1650; ^1H NMR (300 MHz, $CDCl_3$) δ 4.88 (m, 1 H), 4.68 (d, J = 5.6 Hz, 1 H), 3.59 (d, J = 11.0 Hz, 1 H), 3.34 (m, 1 H), 3.18 (m, 1 H), 2.63–0.82 (series of m, 20 H), 1.74 (s, 3 H), 0.94 (d, J = 6.5 Hz, 3 H), 0.74 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 217.5, 148.3, 146.9, 109.6, 67.8, 57.4, 52.4, 49.0, 42.1, 39.8, 39.6, 39.2, 35.7, 35.5, 34.9, 34.6, 29.9, 27.5, 22.8, 21.4, 15.0; MS m/z (M^+) calcd 330.2559, obsd 330.2568. Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.58; H, 10.41.

(3a*R,4*S**,5a*S**,8*R**,9*S**,9a*S**,9b*S**)-Dodecahydro-4-hydroxy-8,9a-dimethyl-9-(3-methyl-3-butenyl)-2-methylene-3a*H*-benz[*e*]indene-3a-methanol (57).** A solution of **56** (215 mg, 0.65 mmol) and sodium triacetoxyborohydride (275 mg, 1.3 mmol) in THF (10 mL) was stirred under nitrogen at room temperature for 48 h, evaporated, and directly chromatographed (silica gel, elution with petroleum ether–ethyl acetate, 3:2). There was isolated 206 mg (94%) of **57** as a white solid: mp 136–137 °C; IR ($CHCl_3$, cm^{-1}) 3260; ^1H NMR (300 MHz, $CDCl_3$) δ 4.86 (d, J = 9.2 Hz, 2 H), 4.67 (s, 2 H), 3.92 (t, J = 3.4 Hz, 1 H), 3.55 (AB q, J_{AB} = 10.6 Hz, 2 H), 2.74–0.77 (series of m, 20 H), 1.73 (s, 3 H), 0.92 (d, J = 6.4 Hz, 3 H), 0.82 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 150.6, 146.9, 109.1, 104.8, 71.2, 69.2, 50.8, 50.7, 49.5, 41.1, 38.8, 36.1, 35.7, 34.6, 34.2, 32.6, 28.7, 27.1, 22.7, 21.6, 16.2; MS m/z (M^+) calcd 332.2715, obsd 332.2704. Anal. Calcd for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91. Found: C, 79.28; H, 10.81.

(2*R,3a*R**,4*R**,4a*S**,5*S**,6*R**,8a*S**,9a*S**)-2-(Bromomethyl)-decahydro-4a,6-dimethyl-5-(3-methyl-3-butenyl)-2,4-methanonaphtho-[2,3-*b*]furan-3a(4*H*)-methanol (58).** A solution of **57** (12.4 mg, 0.037 mmol) in moist THF (2 mL) was cooled to –78 °C, treated with *N*-bromosuccinimide (6.5 mg, 0.037 mmol) dissolved in THF (1 mL), and stirred at this temperature for 4 h. Ether (5 mL) and $MgSO_4$ were added, and the mixture was filtered and evaporated. Purification of the residue was achieved by chromatography on silica gel (elution with petroleum ether–ethyl acetate, 3:2). There was isolated 13.5 mg (88%) of **58** as a crystalline white solid: mp 134–135 °C; IR ($CHCl_3$, cm^{-1}) 3690; ^1H NMR (300 MHz, $CDCl_3$) δ 4.66 (d, J = 5.6 Hz, 2 H), 4.04 (s, 1 H), 3.79 (m, 2 H), 3.59 (m, 2 H), 2.24 (m, 1 H), 2.12–0.6 (series of m, 18 H), 1.72 (s, 3 H), 0.91 (d, J = 6.3 Hz, 3 H), 0.81 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 146.6, 109.2, 83.5, 78.5, 63.7, 53.4, 50.7, 47.4, 43.5, 39.5, 38.5, 37.6, 35.8, 34.6, 34.2, 32.5, 30.5, 27.3, 26.9, 22.7, 21.1, 15.2; MS m/z (M^+) calcd 410.1794, obsd 410.1810.

(3a*R,7a*S**,8a*S**,11*R**,12*S**,12a*S**,12b*R**)-Dodecahydro-6,6,11,12a-tetramethyl-12-(3-methyl-3-butenyl)-2-methylene-4*H*-cyclopenta[3,4]naphtho[2,3-*d*]-*m*-dioxin (61).** A solution of **57** (400 mg, 1.20 mmol) in 30 mL of anhydrous acetone was treated with 2,2-dimethoxypropane (1.5 mL, 12 mmol) and pyridinium *p*-toluenesulfonate (75 mg, 0.30 mmol). The resulting mixture was stirred at ambient temperature for 12 h under a nitrogen atmosphere, quenched with K_2CO_3 (75 mg), and partitioned between 300 mL of ether and 20 mL of water. The organic layer was washed with brine (20 mL), dried, filtered, and concentrated. The residue was purified by flash chromatography on silica gel to yield 424.8 mg (95%) of **61** as a colorless syrup: ^1H NMR (300 MHz, $CDCl_3$) δ 4.83 (s, 2 H), 4.67 (s, 2 H), 4.38 (dd, J = 9.2, 8.1 Hz, 1 H), 3.6–3.4 (m, 2 H), 2.66–0.78 (series of m, 18 m), 1.73 (s, 3 H), 1.46 (s, 3 H), 1.39 (s, 3 H), 0.92 (s, 3 H), 0.91 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 150.8, 147.9, 109.3, 99.4, 71.9, 69.0, 50.0, 49.5, 46.8, 39.9, 37.8, 36.1, 35.5, 35.2, 34.5, 31.5, 31.1, 30.5, 30.4, 28.5, 23.0, 22.0, 20.5, 20.2; MS m/z (M^+) calcd 362.3028, obsd 372.3027. Anal. Calcd for $C_{25}H_{40}O_2$: C, 80.59; H, 10.82. Found: C, 80.52; H, 10.82.

(3a*R,7a*S**,8a*S**,11*R**,12*S**,12a*S**,12b*R**)-Decahydro-6,6,11,12a-tetramethyl-12-(3-oxobutyl)-4*H*-cyclopenta[3,4]naphtho[2,3-*d*]-*m*-dioxin-2(3*H*)-one (62).** A solution of **61** (37 mg, 0.099 mmol) dissolved in 20 mL of anhydrous methanol was cooled to –78 °C, and a stream of ozone was bubbled into the mixture until a blue color persisted. The reaction mixture was flushed with nitrogen for 5 min, treated with dimethyl sulfide (250 μL) at –78 °C, allowed to warm to ambient temperature overnight, and concentrated. Purification of the residue by flash chromatography on silica gel (elution with 30% EtOAc in petroleum ether) gave 32 mg (86%) of **62** as a colorless glass: ^1H NMR (300 MHz, $CDCl_3$) δ 4.36 (t, J = 8.7 Hz, 1 H), 3.75 (dd, J = 11.0, 2.0 Hz, 1 H), 3.50 (d, J = 11.0 Hz, 1 H), 2.65–2.11 (series of m, 6 H), 2.09 (s, 3 H), 1.92 (dd, J = 8.3, 3.9 Hz, 1 H), 1.60–1.48 (series of m, 5 H), 1.47 (s, 3 H), 1.34 (s, 3 H), 1.32–1.12 (series of m, 4 H), 0.96 (s, 3 H), 0.94–0.88 (m, 1 H), 0.84 (d, J = 6.4 Hz, 3 H), 0.76–0.71 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 218.1, 208.1, 99.5, 71.2, 68.4, 49.9, 46.2, 44.5, 43.9, 41.6, 40.8, 40.4, 36.5, 35.4, 34.5, 31.0, 30.5, 29.9, 29.7, 22.4, 21.2, 19.5, 19.2; MS m/z (M^+) calcd 376.2613, obsd 376.2596. Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.16; H, 9.63.

(2a*R,6a*S**,7a*S**,10*R**,10a*S**,13b*R**,13c*S**)-7,7a,8,9,10,10a,11,-12,13b,13c-Decahydro-5,5,10,13,13c-pentamethyl-2*H*,3*H*-azuleno-[1′,8′,7′:3,4,5]naphtho[2,3-*d*]-*m*-dioxin-1(6a*H*)-one (63).** A mixture of **62** (31 mg, 0.082 mmol), potassium carbonate (60 mg, 0.434 mmol), and methanol (20 mL) was heated to reflux under nitrogen for a period of 12 h, cooled to ambient temperature, concentrated, diluted with ether

(100 mL), washed with water (10 mL) and brine (10 mL), dried, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel to yield 26.8 mg (91%) of **63** as a colorless glass: IR (film, cm^{-1}) 1685; ^1H NMR (300 MHz, $CDCl_3$) δ 4.36 (t, J = 8.7 Hz, 1 H), 3.63 (dd, J = 11.1, 2.6 Hz, 1 H), 3.32 (d, J = 11.1 Hz, 1 H), 2.72 (d, J = 19.2 Hz, 1 H), 2.53 (dd, J = 19.2, 2.6 Hz, 1 H), 2.43–2.35 (m, 1 H), 2.32 (d, J = 1.6 Hz, 3 H), 2.18–2.12 (m, 2 H), 1.77–1.15 (series of m, 6 H), 1.55 (s, 2 H), 1.48 (s, 3 H), 1.38 (s, 3 H), 0.98 (s, 3 H), 0.95–0.85 (m, 2 H), 0.77 (d, J = 6.4 Hz, 3 H), 0.73–0.64 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 205.8, 153.6, 132.9, 99.4, 71.9, 68.5, 54.5, 48.7, 44.3, 39.9, 38.5, 36.5, 36.2, 35.9, 31.8, 31.0, 30.5, 29.8, 20.8, 20.7, 20.0, 19.2, 18.2; MS m/z (M^+) calcd 358.2508, obsd 358.2514. Anal. Calcd for $C_{23}H_{34}O_3 \cdot 0.5(C_2H_5)_2O$: C, 75.91; H, 9.94. Found: C, 75.95; H, 9.67.

(2a*R,3*S**,4a*S**,7*R**,7a*S**,10b*R**,10c*S**)-2a,3,4,4a,5,6,7,7a,8,9,-10b,10c-Dodecahydro-3-hydroxy-2a-(hydroxymethyl)-7,10,10c-trimethylnaphth[2,1,8-*cde*]azulen-1(2*H*)-one (64).** A mixture of **63** (36.5 mg, 0.1 mmol), pyridinium *p*-toluenesulfonate (15 mg, 0.06 mmol), and methanol (5 mL) was stirred at ambient temperature for 4 h, quenched with 10 drops of saturated $NaHCO_3$ solution, and concentrated. The residue was taken up in ether (25 mL), washed with brine (2 × 5 mL), dried, filtered, concentrated, and purified on a silica gel column to yield 32 mg (100%) of **64** as a colorless glass: IR ($CHCl_3$, cm^{-1}) 3610, 3470 (br), 1690; ^1H NMR (300 MHz, $CDCl_3$) δ 3.92 (d, J = 11.0 Hz, 1 H), 3.87 (dd, J = 13.4, 6.8 Hz, 1 H), 3.46 (br d, J = 11.0 Hz, 1 H), 3.29 (br s, 1 H), 2.96 (d, J = 1.6 Hz, 1 H), 2.87 (br s, 1 H), 2.56–2.46 (m, 2 H), 2.26–2.20 (m, 1 H), 2.17 (d, J = 2.1 Hz, 3 H), 1.85–1.23 (series of m, 10 H), 1.06 (s, 3 H), 0.98–0.87 (m, 1 H), 0.81 (d, J = 6.3 Hz, 3 H), 0.86–0.78 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 205.8, 152.5, 132.1, 73.3, 69.4, 52.2, 51.2, 47.9, 44.8, 40.2, 39.0, 38.5, 35.8, 35.3, 31.4, 29.4, 20.9, 20.8, 20.6, 15.9; MS m/z (M^+) calcd 318.2195, obsd 318.2172. Anal. Calcd for $C_{20}H_{30}O_3 \cdot 0.25H_2O$: C, 74.37; H, 9.52. Found: C, 74.22; H, 9.39.

(2a*R,3*S**,4a*S**,7*R**,7a*S**,10b*R**,10c*S**)-2a,3,4,4a,5,6,7,7a,8,9,-10b,10c-Dodecahydro-3-hydroxy-2a,7,10,10c-tetramethylnaphth[2,1,8-*cde*]azulen-1(2*H*)-one (10).** Diol **64** (20 mg, 0.06 mmol) and DBN (30 μL, 0.24 mmol) were dissolved in DMF (0.5 mL). Carbon disulfide (0.5 mL) was added, and the reaction mixture was stirred at ambient temperature under nitrogen for 1 h. After the introduction of methyl iodide (0.5 mL), stirring was continued for an additional hour prior to concentration in vacuo. The residue was partitioned between ethyl acetate (25 mL) and water (5 mL), and the organic phase was washed with brine (5 mL), dried, filtered, concentrated, and purified on a silica gel column to yield 18 mg (74%) of the xanthate as a light brown glass: ^1H NMR (300 MHz, $CDCl_3$) δ 4.86 (d, J = 11.1 Hz, 1 H), 4.44 (d, J = 11.1 Hz, 1 H), 3.90 (m, 1 H), 2.83 (br s, 1 H), 2.55 (s, 3 H), 2.50–2.30 (series of m, 3 H), 2.22 (d, J = 1.9 Hz, 3 H), 1.66–1.11 (series of m, 10 H), 1.07 (s, 3 H), 1.01–0.85 (series of m, 3 H), 0.80 (d, J = 6.4 Hz, 3 H).

To a solution of this xanthate (18 mg, 0.044 mmol) in 2 mL of toluene were added 21 μL (0.066 mmol) of tris(trimethylsilyl)silane and 2.5 mg (0.015 mmol) of AIBN. The mixture was stirred for 2 h at 110 °C under nitrogen, cooled, and evaporated in vacuo. The residue was purified on a silica gel column to yield 5 mg (38%) of **10** as a colorless syrup: IR ($CHCl_3$, cm^{-1}) 3475, 1690; ^1H NMR (300 MHz, $CDCl_3$) δ 4.05 (dd, J = 8.4, 7.9 Hz, 1 H), 2.59 (d, J = 18.3 Hz, 1 H), 2.44–2.36 (m, 1 H), 2.32 (s, 3 H), 2.20–2.17 (m, 1 H), 2.01 (d, J = 18.3 Hz, 1 H), 1.79–1.19 (series of m, 11 H), 1.15 (s, 3 H), 0.94–0.86 (m, 1 H), 0.90 (s, 3 H), 0.77 (d, J = 6.4 Hz, 3 H), 0.73–0.68 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 206.2, 153.2, 133.4, 72.0, 60.2, 49.1, 48.1, 41.7, 39.1, 36.6, 36.2, 36.0, 35.4, 31.7, 30.4, 30.3, 20.8, 20.8, 20.2, 17.6; MS m/z (M^+) calcd 302.2246, obsd 302.2241.

(2a*R,3*S**,4a*S**,7*R**,7a*S**,10a*S**,10b*R**,10c*S**)-Tetradecahydro-3-hydroxy-2a,7,10c-trimethyl-10-methylenenaphth[2,1,8-*cde*]azulen-1(2*H*)-one (66).** A solution of **10** (5 mg, 0.017 mmol) in absolute ethanol (2 mL) was cooled to 0 °C, treated with benzeneselenol in ethanol (100 μL of 0.52 M, 0.052 mmol), and stirred at this temperature for 1 h. The reaction mixture was partitioned between ether (100 mL) and water (10 mL), and the ether layer was washed with brine (10 mL), dried, concentrated, and redissolved in THF (10 mL). This yellow solution was cooled to 0 °C, treated with 100 μL of 30% hydrogen peroxide, and allowed to warm to room temperature over 12 h. Dilution with ether (50 mL) was followed by washing with saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), drying, and concentration. Chromatography of the residue on silica gel (elution with 25% ethyl acetate in petroleum ether) returned 1 mg of **10** along with 3 mg (60%) of **66** as a colorless syrup: IR ($CHCl_3$, cm^{-1}) 3500, 3320, 1730; ^1H NMR (300 MHz, $CDCl_3$) δ 5.60–5.45 (m, 2 H), 3.85 (s, 1 H), 3.58 (d, J = 10.5 Hz, 1 H), 2.29 (d, J = 14 Hz, 1 H), 2.12 (d, J = 14 Hz, 1 H), 1.75 (s, 1 H), 1.70–1.20 (series of m, 14 H), 1.23 (s, 3 H), 1.00 (s, 3 H), 0.01 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 217.3, 149.7, 117.1, 71.3, 61.7, 55.5, 53.1, 51.6, 40.8, 37.4, 36.2, 33.8, 33.1, 31.1, 29.4, 27.6, 25.1, 23.8, 20.6, 17.0.

Rhodium Trichloride-Catalyzed Isomerization of 66. A mixture of **66** (3 mg, 0.01 mmol) and rhodium trichloride heptahydrate (2 mg) in 1 mL of ethanol was heated to reflux for 3 h, cooled, diluted with ether (20 mL), and filtered through a small plug of silica gel to yield 1.25 mg of material identical to **10** by 300-MHz ^1H NMR.

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Supplementary Material Available: Crystallographic experimental procedure, solution and refinement of the structure, crystallographic details, tables of refined temperature factors, positional parameters, bond angles, and bond distances, and a diagram of the unit cell for **24** together with the final calculated (MM2) atomic coordinates for **10**, **11**, **66**, and **67** (21 pages). Ordering information is given on any current masthead page.

Stereocontrolled Access to the Most Highly Condensed Pentalenolactone Antibiotic. From Cycloheptatriene to Pentalenolactone P Methyl Ester

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Abstract: The first total synthesis of the title compound (**3b**) has been accomplished. Besides the immediate establishment of the trans cyclopropane–lactone relationship by an appropriate Diels–Alder reaction, other notable transformations include the regioselective chain-lengthening to generate **23**, oxadi-π-methane rearrangement, lactone ring construction by an intramolecular Michael reaction–oxidation sequence, and use of monomeric formaldehyde to introduce the final carbon atom. The chemistry outlined defines a strategy that is highly stereocontrolled and completely tolerant of a sterically congested cyclopropane ring that is carried through to the target from the very first step.

The assignment of structure and absolute configuration to pentalenolactone (**1**) was accomplished in 1969.[1] In the ensuing years, the broad spectrum of antibacterial,[2] antiviral,[3] and irreversible enzyme inactivator properties[4] of this sesquiterpene lactone

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