Synthesis of Sesquiterpene Antitumor Lactones. 10. Total Synthesis of (±)-Parthenin[1]

Clayton H. Heathcock,* Colin M. Tice, and Ted C. Germroth

Contribution from the Department of Chemistry, University of California, Berkeley, California 94720. *Received March 8, 1982*

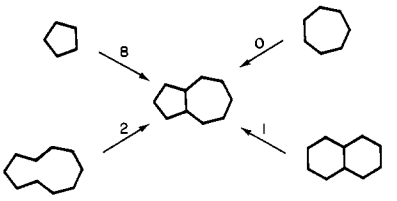
Abstract: (±)-Parthenin (**1**) has been prepared in 22 steps from cyclohexenone. The synthetic strategy employed involves annelation of the five-membered ring onto a preexisting cycloheptane precursor (**5** → **21** → **3**). Alkylation of the lithium enolate of cis-fused hydroazulenone **22** gives entirely the desired 7β-oriented isomer **23**. Base-catalyzed equilibration of **23** provides the 7α epimer **24**. Conformational analysis of this equilibrium, using the Allinger MM1 force field, suggests that a part of the reason for the predominance of **24** is the fact that it has two conformations that are of equal energy while **23** is restricted to a single conformation. Reduction of **23** by diisobutylaluminum hydride in ether gives isomers **30** and **31** in a ratio of 13:1. Compound **30** is converted into the keto lactone **2** by ozonolysis, deprotection, and oxidation. The complete stereostructure of compound **2** was established by single-crystal X-ray analysis. The cyclopentane ring is functionalized as shown in Scheme V. Ketalization of enone **42** affords unsaturated lactone **43**, which is epoxidized by *m*-chloroperoxybenzoic acid to obtain epoxide **48**. The α-methylene unit is introduced by the use of Stiles' reagent, via carboxy lactone **52**. The final step in the synthesis is acid-catalyzed hydrolysis of the ketal in **54**, which leads directly to (±)-parthenin (**1**). The synthesis provides interesting information on the stereochemistry of cis-fused pseudoguaianolide precursors, a class of compounds not extensively investigated heretofore.

In the previous paper in this series[1] we discussed four basic strategies for construction of the hydroazulene ring system characteristic of the pseudoguaianolides. In the eleven published synthetic approaches to these interesting sesquiterpenes, three of these strategies have been examined (Scheme I). In this paper, we report an application of the fourth method, which involves fusion of the five-membered ring onto a preexisting cycloheptane ring, in a total synthesis of the interesting sesquiterpene parthenin (**1**), the substance largely responsible for the allergic contact dermatitis caused by the bitter herb *Parthenium hysterophorus*.[2,3]

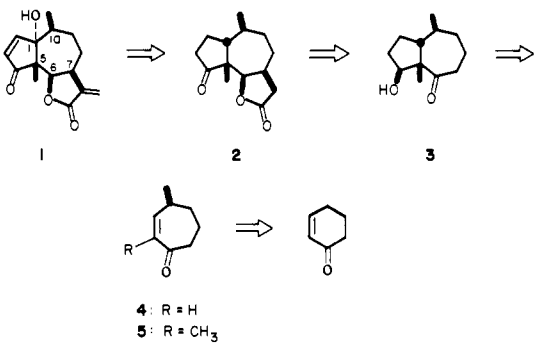
The synthetic strategy is summarized in Scheme II. The proposed cyclopentane annelation (**4** or **5** → **3**) was to be carried out along the lines previously developed in this laboratory and was expected to afford a cis-fused hydroazulenone having the correct relative stereostructure at the two methyl centers (future C_5 and C_{10}).[4] Although this strategy must proceed through intermediates having the unnatural configuration at C_1,[5] this is of no consequence in a synthesis of parthenin, since this position must eventually be oxidized. In addition, the approach summarized in Scheme II offered an opportunity to evaluate the efficacy of cis-fused hydroazulenones for establishing the desired sense of chirality at C_6 and C_7. As will be seen, the approach offers certain advantages in this regard.

The required cycloheptenones were prepared as summarized in Scheme III.[6] As previously described[5] **4**-methylcyclohept-2-en-1-one (**4**) is obtained in 54% overall yield from cyclohexenone by the method of Ito and Saegusa.[7] Enone **4** was employed in the developmental stages of the synthesis. Recently Conia and co-workers reported a convenient synthesis of 2,4-dimethylcyclohept-2-en-1-one (**5**, 70% overall from cyclohexenone)[8] that

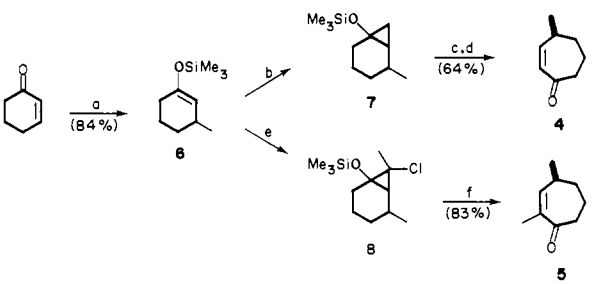
Scheme I



Scheme II



Scheme III



a. Me_2CuLi, Me_3SiCl, Et_3N; b. CH_2I_2, Zn(Cu); c. $FeCl_3$, pyridine, DMF; d. NaOAc, MeOH; e CH_3CHCl_2, *n*-BuLi, Et_2O, -20°C; f. Et_3N, MeOH, Δ.

was used in the final version of our work.

Previous studies had shown that cycloheptenone **4** reacts with organocuprate reagents to give predominantly *trans*-3,4-dialkylcycloheptanones.[5] Thus, treatment of **4** with the Grignard reagent prepared from bromo acetal **9**[4] in the presence of cuprous iodide affords a 4:1 mixture of ketones **10** in 57% yield. Acid-catalyzed hydrolysis of the acetal is accompanied by aldolization

(1) For part 9, see: C. H. Heathcock, E. G. DelMar, and S. L. Graham, *J. Am. Chem. Soc.*, **104**, 1907 (1982).

(2) (a) H. V. Arny, *J. Pharm.*, **121** (1890); **169** (1897). (b) W. Herz, and H. Watanabe, *J. Am. Chem. Soc.*, **81**, 6088 (1959). (c) W. Herz, H. Watanabe, M. Miyazaki, and Y. Kishida, *ibid.*, **84**, 2601 (1962). (d) M. T. Emerson, C. N. Caughlan, and W. Herz, *Tetrahedron Lett.*, 6151 (1966). (e) E. Rodriguez, G. H. N. Towers, and J. C. Mitchell, *Phytochemistry*, **15**, 1573 (1976).

(3) For a previous total synthesis of parthenin, see: P. Kok, P. De Clercq, and M. Vandewalle, *Bull. Soc. Chim. Belg.*, **87**, 615 (1978).

(4) D. N. Brattesani and C. H. Heathcock, *J. Org. Chem.*, **40**, 2165 (1975).

(5) C. H. Heathcock, T. C. Germroth, and S. L. Graham, *ibid.*, **44**, 4482 (1979).

(6) Although only one enantiomer is depicted in each case, all compounds in this paper are racemates.

(7) Y. Ito, S. Fujii, and T. Saegusa, *J. Org. Chem.*, **41**, 2073 (1976).

(8) (a) L. Blanco, N. Slougi, G. Rousseau, and J. M. Conia, *Tetrahedron Lett.*, **22**, 645 (1981). (b) L. Blanco, P. Amice, and J. M. Conia, *Synthesis*, 289 (1981).

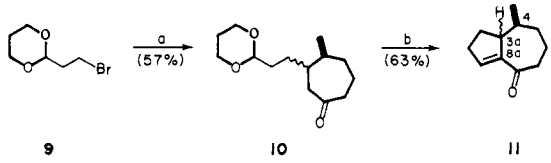
0002-7863/82/1504-6081$01.25/0

Table I. Hydrolysis-Aldolization of Keto Acetal 13

entry	solvent[a]	temp, °C	time, h	product distribution 14	3	15	other	yield, %[b]
1	A	30	20	60	0	0	40[c]	
2	A	reflux	22	0	57	43	0	60
3	A	reflux	55	0	42	58	0	62
4	B	30	2.5	61	32	0	7[d]	
5	B	30	48	0	100	0	0	64
6	B	reflux	0.4	0	100	0	0	50
7	B	reflux	1	0	70	30	0	60

[a] Solvent A = 5:1 mixture of EtOH and 10% aqueous HCl; solvent B = 5:1 mixture of HOAc and 10% aqueous HCl. [b] Yield of isolated, purified mixture of 3 and 15. [c] Diethyl acetal of keto aldehyde 14. [d] Keto acetal 13.

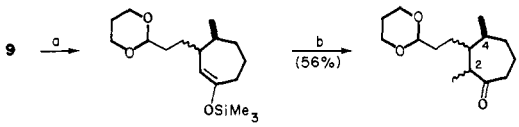
and dehydration, providing a similar 4:1 ratio of hydroazulenones **11**. As shown by subsequent transformation, the major isomer



9 10 11

a Mg, THF, enone **4**, CuI; b. 5% HCl, EtOH, reflux, 1 hr.

of **11** is the one having the methyl group at C_4 and the hydrogen at C_{3a} cis. Attempts to methylate **11** at C_{8a} with methyl iodide and various bases (NaH, Me_2SO; *t*-BuOK, *t*-BuOH; KH, THF) failed to give useful amounts of methylated products. We were also unable to methylate the magnesium enolate resulting from conjugate addition to enone **4**. However, silylation of the conjugate addition product provides an enol ether (**12**), which may be treated



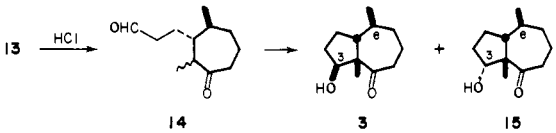
12 13

a. Mg, THF, CuI, enone **4**; Me_3SiCl, Et_3N. b. MeLi, DME; MeI, 5°C

with methyllithium in 1,2-dimethoxyethane (DME) to form the corresponding lithium enolate. Methylation of this species affords ketone **13** in an overall yield of 56%.[9]

Although **13** is produced as a diastereomeric mixture, the methylation actually occurs with considerable stereoselectivity. The two C_2 epimers (each a **4**:1 epimeric mixture at C_4) are produced in a ratio of 9:1 (^{13}C NMR spectroscopy, HPLC, isolation).

When keto acetal **13** is treated with HCl in aqueous ethanol or aqueous acetic acid the acetal group is hydrolyzed and the resulting keto aldehyde **14** cyclizes to a mixture of hydroxy ketones



14 3 15

3 and **15**.[10] The ratio of **3**:**15** is found to be dependent on the conditions under which the hydrolysis–cyclization is carried out. Results are shown in Table I. (When aqueous acetic acid is employed, there is some acetylation of the initial hydroxy ketone products. In this case, acid treatment is followed by saponification with methanolic sodium methoxide.) The data in the table clearly

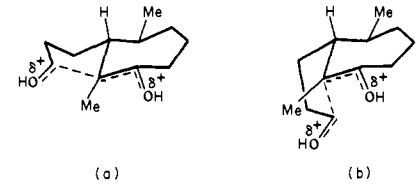
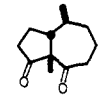


Figure 1. Transition states leading from keto aldehyde **14** to *trans*- and *cis*-hydroazulenes.

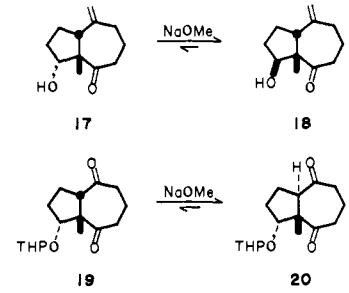
show that acetal hydrolysis is more rapid than aldolization (entries 1 and 4). It also establishes that isomer **3** is the kinetic product of aldolization and that isomer **15** results from subsequent equilibration (entires 2 and 3, 6 and 7), presumably via keto aldehyde **14**. That **3** and **15** are isomeric at the secondary alcohol position was shown by the fact that they give the same dione (**16**)



16

upon oxidation. The cis fusion of the two rings was assigned on the basis of examination of molecular models, which show that there is more torsional strain involved in bringing the propionaldehyde chain from one side of the cycloheptane ring to the other (Figure 1a) than in the analogous transition state leading to the cis-fused product (Figure 1b). This hypothesis was verified by single-crystal X-ray analysis of a subsequent conversion product of **3**. The relative configurations of the C_3 hydroxy groups in **3** and **15** are assigned on the basis of the infrared spectra of the two hydroxy ketones. In the kinetic product, the OH stretch appears as a sharp absorption at 3595 cm^{-1} at 2% concentration in CCl_4 and as a broad band at 3500 cm^{-1} at 10% concentration. For the thermodynamic product the OH stretch is a broad band at 3550 cm^{-1} at all concentrations. Drieding stereomodels of **3** and **15** indicate that the latter is capable of intramolecular H bonding while the former is not.

It is interesting to speculate why equilibration of **3** and **15** does not lead to a trans-fused aldol, since *trans*-hydroazulenes are usually more stable than their cis isomers.[1,11,12] A similar equilibration (**17** ⇌ **18**) has been observed by Vandewalle and



17 18

19 20

co-workers.[13] In this case, only cis-fused aldols are detected, even though the closely related dione **19** yields principally the trans-fused isomer **20** upon equilibration.[12] This behavior is consistent with a hypothesis that there is a substantial difference in the energies of the two transition states depicted in Figure 1, such that there is an effective kinetic barrier to formation of the trans-fused isomers by intramolecular aldolization.

Although the annelation sequence leading from cycloheptane **4** to hydroazulene **3** is reasonably brief, it proceeds in an overall yield of only 36% at best and is often unreliable in large-scale application. Some of the loss in yield is obviously incurred in the process of introducing the C_2 methyl group, which requires three separate operations. For this reason, the use of enone **5** is par-

(9) The procedure is that of Coates and Sandefur (R. M. Coates and L. O. Sandefur, *J. Org. Chem.*, **39**, 275 (1974)).

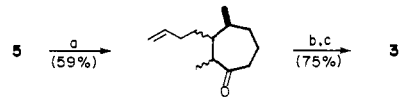
(10) Compounds **3** and **15** are each produced as a 4:1 mixture of epimers at C_8, of which only the major isomer is depicted in each case.

(11) J. A. Marshall, *Synthesis*, 517 (1972).

(12) P. De Clercq and M. Vandewalle, *J. Org. Chem.*, **42**, 3447 (1977).

(13) M. Vandewalle, private communication.

ticularly appealing. However, attempts to bring about conjugate addition of the Grignard reagent derived from halide **9** to enone **5** failed; only recovered starting material and its 1,2-addition product were obtained. Similar results were obtained with 3-butenyl-1-magnesium bromide. The reluctance of enones bearing alkyl substituents at C_2 or C_3 to react with cuprate reagents is well precendented.[14] A solution to this dilemma is found in the use of Yamamoto's reagent.[15] Thus, the complex formed by adding first 1 equiv of cuprous iodide and then 1 equiv of boron trifluoride etherate to 3-butenyl-1-magnesium bromide adds smoothly to enone **5** to give adduct **21** as a diastereomeric mixture

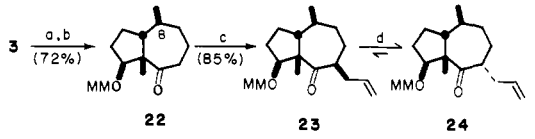


21

a. CH_2=$CHCH_2CH_2Cu \cdot BF_3$, THF, −78°C; b. O_3, MeOH, CH_2Cl_2, −78°C; Me_2S. c. HCl, H_2O, HOAc, 30°C, 52 hr; NaOMe, MeOH, 30°C, 1 hr.

in 59% yield. Unfortunately, the Grignard reagent obtained from halide **9** is not effective in this reaction.[16] Ozonolysis of **21** in methanolic methylene chloride, followed by dimethyl sulfide workup, gives a mixtue of keto aldehyde **14** and its dimethyl acetal. When this mixture is stirred at room temperature with HCl in aqueous acetic acid for 52 h (cf. Table I, entry 5) hydroazulene **3** is formed in 75% overall yield. The modified synthesis via cycloheptenone **5** provides **3** in six steps and 31% overall yield from cyclohexenone as compared to eight steps and 19% overall yield for the synthesis via cycloheptenone **4**. In addition, the Yamamoto procedure for conjugate addition is more stereoselective (5:1 vs. 4:1), presumably because it is carried out at −78 °C rather than at −20 °C.

With a reliable synthesis of **3** in hand, it was next necessary to introduce a suitable alkyl group and fashion the γ-butyrolactone ring with the desired relative configuration at the eventual C_6 and C_7 positions. For investigation of this operation without the possible complication of reverse aldolization, the secondary alcohol was protected as the methoxymethyl ether (**22**). At this point the C_8 epimers are easily separated by chromatography; the remaining operations are carried out with pure **22**. Alkylation of the lithium enolate of ketone **22** with allyl bromide gives a single



22 **23** **24**

a. CH_3OCH_2Cl, $(i\text{-}Pr)_2EtN$, CH_2Cl_2; b. chromatographic separation of C_8 epimers; c. LDA, DME; CH_2=$CHCH_2Br$, 30°C, 3 hrs. d. $NaOCH_3$, CH_3OH, reflux, 12 hrs.

product (**23**) in 85% yield. Analysis of this alkylation product by ^{13}C NMR spectroscopy, TLC, and analytical HPLC established its homogeneity. The indicated stereostructure was elucidated by single-crystal X-ray analysis of a conversion product. Base-catalyzed equilibration of **23** provides a 1:9 mixture of **23** and its isomer **24**.

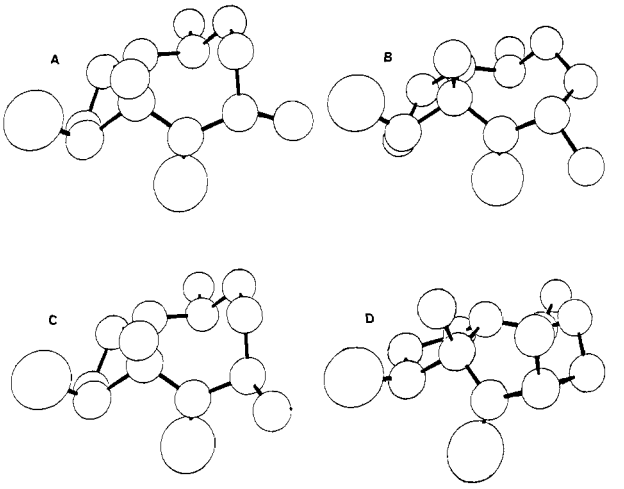
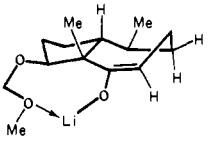


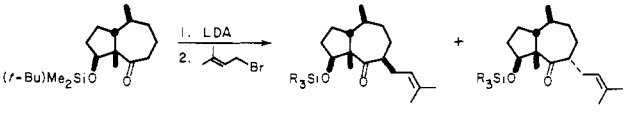
Figure 2. Perspective drawings of minimum energy conformations of hydroazulenes **28** and **29**. (A) **29**, twist-boat, (B) **29**, twist-chair, (C) **28**, twist-boat, (D) **28**, twist-chair.

The highly stereoselective alkylation of ketone **22** is explicable in terms of steric hindrance to approach to the α face of the enolate **22a**:



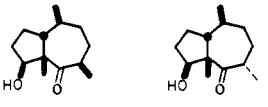
22a

The hypothesis that chelation of the lithium cation by the β-oxygen of the methoxymethyl group is important is based on a study of the alkylation of the related keto ether **25** with prenyl bromide; isomers **26** and **27** are produced in a ratio of 3:1.[18]



25 **26** **27**

House and co-workers have shown that the Allinger MM1 force field[19] successfully reproduces strain energies in cycloheptane derivatives.[20] Therefore, we evaluated the equilibrium **23** ⇌ **24** in this manner. To facilitate the analysis, we calculated strain energies for various conformations of the model keto alcohols **28** and **29**. For compound **29**, two low-energy conformations, one



28 **29**

a twist-boat (Figure 2A) and the other a twist-chair (Figure 2B), were found. The calculated strain energies for these two conformations are 14.7 and 14.8 kcal mol^{-1}, respectively. For isomer **28** there is only one low-energy conformation, a twist-boat (Figure 2C), with a calculated strain energy of 14.6 kcal mol^{-1}. The twist-chair conformation of **28** is destabilized by a serious methyl–methyl interaction (Figure 2D) and has a calculated strain energy of 16.3 kcal mol^{-1}. Although the force-field calculations do not predict an enthalpy difference between isomers **28** and **29**, they do predict that isomer **29** will be favored over isomer **28** for entropic reasons.

(14) (a) G. H. Posner, *Org. React.* (*N.Y*), **19**, 1 (1972). (b) H. O. House, *Acc. Chem. Res.*, **9**, 59 (1976).

(15) Y. Yamamoto and K. Maruyama, *J. Am. Chem. Soc.*, **100**, 3240 (1978).

(16) The failure of this reaction is apparently due to the failure of the Grignard reagent to form a stoichiometric cuprate upon addition of the CuI. When a Grignard solution is treated with CuI, formation of the cuprate is normally evidenced by the production of a black suspension. In this case the solution remains pale yellow.

(17) A similar increase in stereoselectivity under the Yamamoto conditions is seen in addition of methylcopper, *n*-propylcopper, and 3-butenylcopper to enone **4**.[18]

(18) For full details, see C. M. Tice, Ph.D. Thesis, University of California, Berkeley, 1981.

(19) N. L. Allinger and D. H. Wertz, *Tetrahedron*, **30**, 1579 (1974), and previous papers cited in this reference.

(20) H. O. House, C. C. Yau, and D. VanDerveer, *J. Org. Chem.*, **44**, 3031 (1979).

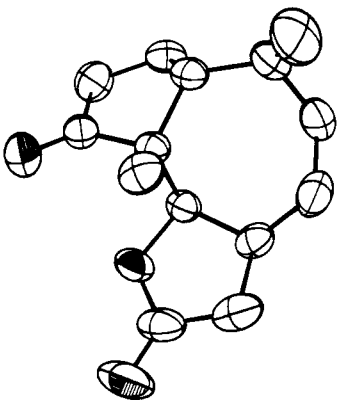


Figure 3. ORTEP stereoplot of keto lactone **2**.

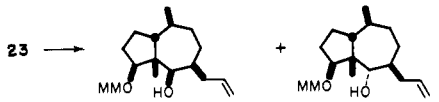
Table II. Reduction of Ketone **23**[a]

reducing agent	solvent	**30**:**31**	yield, %
$LiAlH_4$	ether	42:58	89
$LiAl(OMe)_3H$	ether	50:50	92
$(i\text{-}C_4H_9)_2AlH$[b]	hexane	72:28	88
$(i\text{-}C_4H_9)_2AlH$[b]	ether	93:7	92
$(i\text{-}C_4H_9)_2AlH$[b]	THF	71:29	78[c]
$(i\text{-}C_4H_9)_2AlH$[b]	DME	89:11	89

[a] All reductions were carried out at −78 °C. [b] The reagent is used as a 1.0 M solution in hexane. [c] In this case 20% of starting material is also obtained.

To complete the stereoselective elaboration of the cis-fused γ-butyrolactone ring, it is necessary to reduce the carbonyl group of **23** from the face opposite the methyl and allyl appendages. To evaluate the probability of success, we applied Wipke's steric congestion analysis[21] to the twist-boat conformation of compound **28** (Figure 2C). The computation predicts that the top face of the carbonyl is more hindered than the bottom. On a quantitative basis, the relative steric hindrance ratio is found to be 96:4.

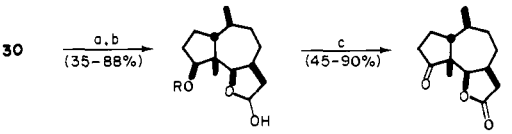
Compound **23** was treated with a variety of hydride reducing agents to obtain alcohols **30** and **31**. The results of a series of



30 **31**

reductions are summarized in Table II. The data show that stereoselectivity increases as the effective bulk of the reducing reagent increases ($LiAlH_4$ < $LiAl(OMe)_3H$ < $(i\text{-}C_4H_9)_2AlH$ in hexane < $(i\text{-}C_4H_9)_2AlH$ in ethereal solvents). In addition, the major isomer is that predicted by the steric congestion analysis.

Ozonolysis of unsaturated alcohol **30** in methanol, followed by

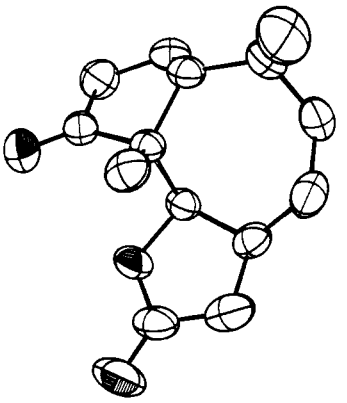


32: R = $MeOCH_2$
33: R = H
2

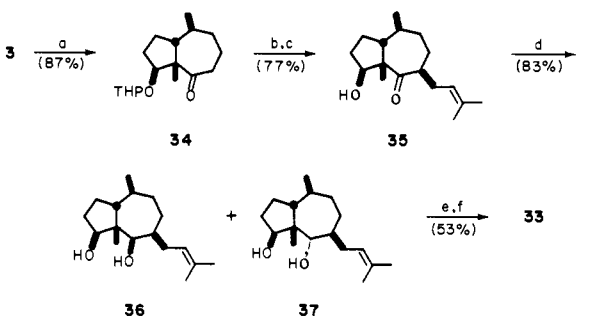
a. O_3, MeOH, -78°C; Me_2S; HCl, H_2O, THF, 25°C, 30 sec. b. HCl, H_2O, THF, 100°C, 30 min. c. H_2CrO_4, acetone, 30°C, 20 min.

dimethyl sulfide workup and brief treatment with mild acid, affords a hemiacetal (**32**) which is deprotected by refluxing with a 1:1 mixture of THF and 5% aqueous HCl. The resulting diol (**33**) is oxidized by Jones' reagent to the crystalline keto lactone **2**. The full stereostructure of **2**, as well as of all interemdiates leading to it, was elucidated by single-crystal X-ray analysis. An ORTEP stereoplot of the structure is shown in Figure 3.

(21) W. T. Wipke and P. Gundy, *J. Am. Chem. Soc.*, **98**, 8017 (1976).



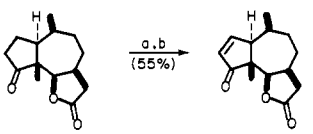
Scheme IV



a. Dihydropyran, p-TsOH, CH_2Cl_2. b. LDA, THF; $(CH_3)_2C{=}CHCH_2Br$. c. HCl, H_2O, THF, dioxane, 25°C, 16 hr. d. $(i\text{-}C_4H_9)_2AlH$, ether, -100°C. e. O_3, MeOH, CH_2Cl_2, Me_2S. f. HCl, H_2O, THF, 25°C.

The five-step conversion of hydroxy ketone **3** into keto lactone **2** establishes a viable method for constructing the γ-butyrolactone ring with the desired configuration at the two new asymmetric centers. However, it leaves something to be desired in terms of overall yield, particularly in large-scale runs. The problems lie with the deprotection and oxidation steps (**32** → **2**). Although both of these operations can be achieved in about 90% yield on small scale (<1 mM), the yields fall drastically on scale-up. To partially alleviate this problem, we examined protecting groups that can be removed under more gentle conditions. We also changed the alkylating agent from allyl bromide to prenyl bromide on the basis of the hypothesis that a trisubstituted alkene would undergo ozonolysis more readily than an allyl group. Of a number of variations that were investigated,[18] the sequence of operations outlined in Scheme IV turns out to be most reliable in large-scale applications. In this manner, compound **3** may be converted into keto lactone **2** on a several-gram scale in an overall yield of about 15%.

In order to insert the required oxygen at C_1, it is necessary to introduce the C_2–C_3 double bond. Vandewalle and co-workers accomplished this task in the trans-fused series by acid-catalyzed selenylation (**38** → **39**).[3] However, application of this method

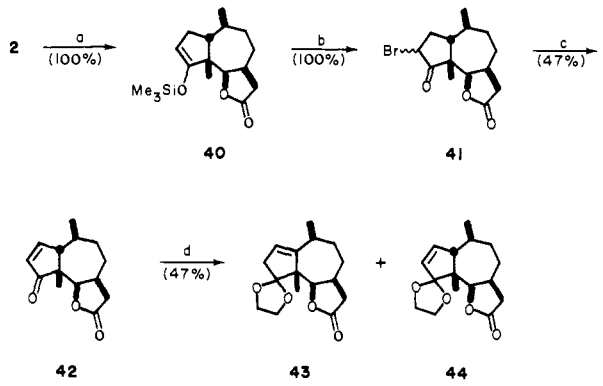


38 **39**

a. C_6H_5SeCl, EtOAc. b. O_3, CH_2Cl_2, C_5H_5N.

to keto lactone **2** affords a mixture of mono- and diselenylated products, along with unreacted starting material. Deprotonation of **2** with LDA at 78 °C, followed by selenylation of the resulting enolate, also gives a mixture of products. After evaluating a number of other methods for introduction of the C_2–C_3 double bond,[18,22] we settled on the method shown in Scheme V. Although

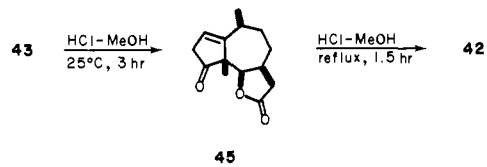
Scheme V



a. Me_3SiOTf, Et_3N, C_6H_6. b. NBS, THF, 0°C. c. $CaCO_3$, DMAC. d. β-$NpSO_3H$, $(CH_2OH)_2$, C_6H_6, reflux.

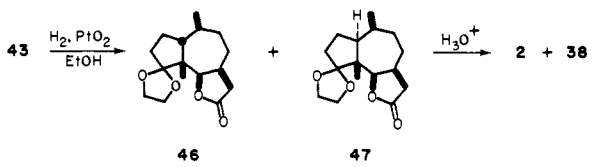
the enolate of compound **2** can be trapped with trimethylsilyl chloride at 78 °C, silyl ether **40** is more conveniently obtained by the use of trimethylsilyl triflate.[23] Direct oxidation of enol ether **40** to enone **42** can be achieved with palladium acetate,[24] but the yield is usually no more than 20%. However, bromination of **40** with *N*-bromosuccinimide in THF[25] affords bromo ketones **41** as a 1:1 mixture of diastereomers in quantitative yield. Dehydrobromination of this mixture using the conditions of Green and Long[26] provides enone **42** in 47% overall yield.

Ketalization of enone **42** proved to be unexpectedly difficult. Vandewalle and co-workers found that trans-fused enone **39** is smoothly converted into the isomerized ketal **43** in 82% yield. However, under the best conditions found, **42** gives a 70:30 mixture of ketals **43** and **44** in only 47% yield based on unreacted starting material. Under more forcing conditions, the ratio of **43**:**44** improves but the yield diminishes. The reluctance of cis-fused enone **42** to undergo ketalization, relative to its trans-fused isomer **39**, is probably due to the fact that **42** is considerably more stable than **39**. Indeed, gentle hydrolysis of **43** provides the deconjugated



enone **45**, which reacts with HCl in methanol to regenerate **42**; none of isomer **39** is formed in this reaction. Although the trans-fused isomer is normally more stable than the cis in simple hydroazulenes,[1,11,12] this order of stability is known to be reversed when there is a butyrolactone moiety fused to the seven-membered ring.[27]

Catalytic hydrogenation of unsaturated ketal **43** gives a 1:1



mixture of cis-fused and trans-fused ketals **46** and **47**. The latter is known from the work of Kretchmer,[28] and the former is obtained

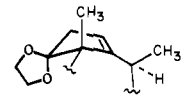
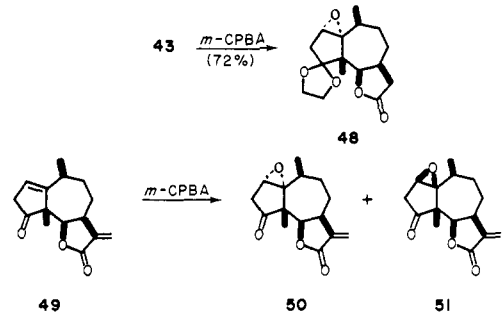


Figure 4. Perspective view of the cyclopentene ring of unsaturated ketal **43**.

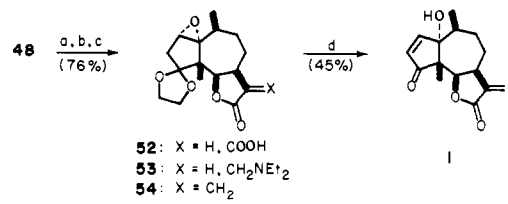
by ketalization of ketone **2**. Hydrolysis of the mixture of **46** and **47** provides a mixture of ketones **2** and **38**. On the other hand, hydrogenation of enone **45** under identical conditions gives ketones **2** and **38** in a ratio of 1:3. Examination of a Dreiding stereomodel of ketal **43** reveals that the ketal oxygen on the bottom face of the molecule hinders this face of the double bond, apparently counterbalancing the steric effect of angular methyl group (Figure 4).

Epoxidation of ketal **43** with *m*-chloroperoxybenzoic acid affords



a single epoxide, subsequently shown to have the desired C_1–C_2 α configuration (**48**). This result is in contrast to the observation by Vandewalle and co-workers that epoxidation of neoambrosin (**49**) gives a 70:30 mixture of epoxides **50** and **51**.[3] The difference is clearly due to the same α-directed ketal oxygen in **43** (see Figure 4), which must facilitate α-face epoxidation by hydrogen bonding to the oxidizing agent.

The final stage of the synthesis, introduction of the methylene group into the lactone ring, was accomplished with the Stiles' reagent methodology used by Schlessinger and co-workers in their pseudoguaianolide work.[29] Thus, treatment of lactone **48** with



a. $MeOMgOCO_2Me$, DMF, 140°C, 3 hr. b. HCHO, Et_2NH, NaOAc, H_2O, HOAc. c. MeI, MeOH; $NaHCO_3$, H_2O, EtOAc d HCl, MeOH, 25°C, 3 hr

Stiles' reagent gives carboxy lactone **52**,[30] which is subjected to Mannich conditions to obtain 22% of (diethylamino)methyl lactone **53** and 65% of methylene lactone **54**. Quaternization and elimination of the former product provide more of unsaturated lactone **54**; the total yield is 76% from compound **48**. Treatment of **54**

(22) For full details, see T. C. Germroth, Ph.D. Thesis, University of California, Berkeley, 1979.
(23) (a) G. Simchen and W. Korber, *Synthesis*, 259 (1976). (b) R. D. Miller and D. R. McKean, *ibid.*, 730 (1979).
(24) Y. Ito, T. Hirao, and T. Saegusa, *J. Org. Chem.*, **42**, 3787 (1977).
(25) R. H. Ruess and A. Hassner, J. *Org. Chem.*, **39**, 1785 (1974).
(26) G. F. H. Green and A. G. Long, *J. Chem. Soc.*, 2532 (1961).
(27) (a) W. Herz, M. V. Lakshikantham, and R. N. Mirrington, *Tetrahedron*, **22**, 1709 (1966). (b) A. Romo de Vivar, L. Rodriquez-Hahn, J. Romo, M. V. Lakshimikantham, R. N. Mirrington, J. Kagan, and W. Herz, *ibid.*, **22**, 3279 (1966).
(28) (a) R. A. Kretchmer and W. Schafer, *J. Org. Chem.*, **38**, 95 (1973). (b) R. A. Kretchmer and W. J. Thompson, *J. Am. Chem. Soc.*, **98**, 3379 (1976).
(29) (a) M. R. Roberts and R. H. Schlessinger, *J. Am. Chem. Soc.*, **101**, 7626 (1979). (b) G. J. Quallich and R. H. Schelssinger, *ibid.*, **101**, 7627 (1979).
(30) A curious observation was made in the course of developing this carboxylation. On some occasions treatment of **48** with Stiles' reagent produced small amounts of methylene lactone **54** (up to 20%) *directly*, without treatment with formaldehyde and diethylamine. The mechanism of formation of **54** under these conditions is obscure. It may be that small amounts of formaldehyde and dimethylamine are produced by reduction of DMF by residual particles of magnesium left over from formation of the reagent. Alternatively, a Cannizzaro-type reduction of DMF, promoted by residual methoxide in the Stiles' reagent, may produce formaldehyde and dimethylamine.

with concentrated HCl in methanol at room temperature provides (±)-parthenin (**1**), mp 157–158 °C.

In summary, this work establishes the viability of the cyclopentane annelation strategy for synthesis of pseudoguaianolides. The approach requires the use of cis-fused hydroazulene intermediates, a group of compounds not extensively studied heretofore. The use of these compounds confers some advantages from the standpoint of establishing the desired relative stereochemistry about the cycloheptane ring. On the other hand, the late stages of the current synthesis (those steps associated with introduction of unsaturation into the five-membered ring and ketalization of enone **42**) do not proceed as smoothly as in the Vandewalle approach via trans-fused intermediates. In all, the current synthesis requires 22 steps from cyclohexenone and delivers (±)-parthenin in an overall yield of 0.25%.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Ether, 1,2-dimethoxyethane (DME), and tetrahydrofuran (THF) were distilled from sodium/benzophenone immediately prior to use. Triethylamine, pyridine, diisopropylamine, acetonitrile, *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMAC), and trimethylsilyl chloride were distilled from calcium hydride prior to use. Dichloromethane was distilled from phosphorus pentoxide. All reactions involving organometallic reagents were conducted under a nitrogen atmosphere. Boiling points and melting points (Pyrex capillary) are uncorrected. IR spectra were determined with a Perkin-Elmer Model 297 infrared recording spectrophotometer. ^{1}H NMR spectra were determined on the following spectrometers: Varian T-60, Varian EM-390, UCB-180, UCB-200, or UCB-250 (superconducting 180-, 200-, and 250-MHz FT instruments). Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^{1}H NMR data are tabulated in order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant(s) in hertz. ^{13}C NMR spectra were measured at 25.14 MHz with a Nicolet TT-23 spectrometer, at 45.28 MHz on the UCB-180, or at 63.07 MHz on the UCB-250. Mass spectra were obtained with Atlas MS-12 and Consolidated 12-110B mass spectrometers. Mass spectral data are tabulated as *m/e* (intensity expressed as percent total ion current). Gas–liquid partition chromatography (GLC) was done with Varian Aerograph A-90P, 920, and 940 gas chromatographs. High-performance liquid chromatography (HPLC) was done with a Waters PrepLC/System 500 (preparative) with Porasil columns. Analytical HPLC was done with a Waters Model ALC/GPC-244 liquid chromatograph. Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley.

4-Methylcyclohept-2-en-1-one (4) was prepared from cyclohexenone as previously described.[5]

2,4-Dimethylcyclohept-2-enone (5). To a solution of 36.80 g (0.20 mol) of silyl enol ether **6**[5] and 51.06 g (0.52 mol) of 1,1-dichloroethane in 800 mL of ether at −40 °C was added 280 mL of 1.58 M *n*-BuLi in hexane (0.44 mol) dropwise over a period of 6 h. The temperature was maintained between −20 and −40 °C during the course of the addition. The cooling bath was removed, and the mixture was allowed to warm to room temperature. The mixture was washed with 700 mL of water. The aqueous layer was separated and extracted with 500 mL of ether. The combined ether extracts were washed with 300 mL of brine and dried over $MgSO_4$. The solvent was removed to leave 59.30 g of crude (chloromethyl)cyclopropanes **8**.

A solution of this crude product in a mixture of 425 mL of methanol and 75 mL of triethylamine was heated at reflux for 30 h. The bulk of the solvent was removed, the residue was diluted with 1 L of water and extracted with three 500-mL portions of ether. The combined ether extracts were washed sucessively with 300 mL of 5% aqueous HCl, 300 mL of saturated aqueous sodium bicarbonate, and 300 mL of brine and dried over $MgSO_4$. Removal of the solvent left 36.38 g of crude enone **5**. The crude product was distilled (0.5 torr) to afford 22.87 g (83%) of **5**: bp 45–58 °C; ^{1}H NMR ($CDCl_3$) δ 1.15 (3 H, d, J = 7.1), 1.83 (3 H), 6.24 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 18.9, 20.4, 22.0, 32.6, 33.1, 42.1, 136.9, 146.9, 204.1; IR (film) 1665 cm^{-1}; mass spectrum, 138 (3.45), 95 (6.61), 67 (7.33). An analytical sample was obtained by preparative HPLC (8% SE-30, 10 ft × 0.25 in., 130 °C). Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.04; H, 10.13.

4-Methyl-3-(3-(trimethylenedioxy)propyl)cycloheptanone (10). To a suspension of 0.800 g of magnesium turnings (33.3 mmol) in 8 mL of dry THF at room temperature was added 6 drops of β-bromopropionaldehyde trimethylene acetal (part of 4.64 g, 22.2 mmol) and a small crystal of iodine. The solution was stirred at room temperature until the violet color rapidly disappeared (1–10 min) before 42 mL of THF was added. The remaining β-bromopropionaldehyde trimethylene acetal was added dropwise over a 40-min period to the reaction mixture, which was maintained at 25 °C. The reaction mixture was stirred for 10 min.

A titration for active Grignard was then performed. The total base was determined by adding 1.00 mL of reaction mixture to 10 mL of water and titrating this solution with 3.84 mL of a 0.100 N aqueous HCl solution to a phenolphthalein end point. The non-Grignard base was determined by adding 0.20 mL of 1,2-dibromoethane to 1.00 mL of reaction mixture and stirring for 10 min at room temperature. This solution was added to 10 mL of water and titrated with 0.88 mL of 0.100 N aqueous HCl solution to a phenolphthalein end point. These titrations showed 17.2 mmol of total active Grignard in the reaction mixture.

The solution was stirred at 0 °C for 20 min and then cooled to −20 °C, and 317 mg of purified copper(I) iodide (1.66 mmol) was added. After 5 min, 1.92 g of 4-methylcyclohept-2-enone (15.5 mmol) in 2 mL of dry THF was added dropwise over a 30-min period. After 5 min, the reaction mixture was warmed to room temperature over a 15-min period and poured into a rapidly stirring mixture of 200 mL of a 4:1 ammonia buffer[31] and 300 mL ether. The organic phase was separated, washed twice with 100 mL of the ammonia buffer and then with 100 mL of brine, and dried over $MgSO_4$.

Removal of solvent in vacuo yielded 4.06 g of a yellow liquid. Thin-layer chromatographic analysis (40% ether in hexanes) showed three spots by iodine development with R_f 0.17 (very weak), 0.14 (strong), and 0.07 (moderate). The crude product was purified by preparative HPLC (45% ether in hexanes) to yield 2.106 g (8.77 mmol, 57%) of a colorless liquid that gave satisfactory analysis. Analytical HPLC (40% water/MeOH, μ-C_{18}, 30 cm × 3.9 mm, flow rate 1.5 mL/min) showed one peak at 13 min: ^{1}H NMR ($CDCl_3$) δ 1.00 (3 H, d, J = 6 Hz), 3.57 (2 H, br t, J = 10 Hz), 4.00 (2 H, dd, J = 5, 12 Hz), 4.32 (1 H, br t); IR (neat) 1700, 1400, 1375 cm^{-1}; ^{13}C NMR ($CDCl_3$) trans isomer 20.5, 20.6, 25.7, 28.3, 31.7, 35.2, 38.0, 41.4, 43.5, 46.0, 66.6, 102.1, 213.6 ppm; cis isomer 14.2, 26.7, 33.2, 35.4, 36.4, 38.7 ppm. Anal. Calcd for $C_{14}H_{24}O_3$: C, 70.01; H, 10.00. Found: C, 69.61; H, 9.93.

2,3,3a,4,5,6-Hexahydro-4-methylazulen-8(7*H*)-one (11). A solution of 285.8 mg of 4-methyl-3-(3-(trimethylenedioxy)propyl)cycloheptanone (1.19 mmol) in 7 mL of 10% aqueous HCl and 40 mL of absolute ethanol was brought rapidly to reflux and was maintained at reflux for 55 min. The reaction mixture was cooled to room temperature over a period of 1 h and poured into 300 mL of water and 200 mL of ether. The aqueous phase was washed with 200 mL of ether. The organic phases were combined, washed with 200 mL of saturated aqueous $NaHCO_3$, and dried over $MgSO_4$.

Removal of solvent in vacuo yielded 179.5 mg (1.09 mmol, 92%) of a yellow liquid. Thin-layer chromatographic analysis (12% ether in hexanes) showed only one spot by H_2SO_4 development with R_f 0.22 that is UV active. The crude product was purified by column chromatography on silica gel (10% ether in hexanes) to yield 123.4 mg (0.752 mmol, 63%) of a colorless liquid. Both ^{1}H NMR and ^{13}C NMR spectra show a cis/trans ratio of 22/78. Several attempts to obtain a satisfactory elemental analysis were unsuccessful. However, the IR, ^{1}H NMR, ^{13}C NMR, TLC, and GLC of the purified material exhibit no evidence of contamination: ^{1}H NMR (CCl_4) δ 0.80 (3 H, d, J = 7 Hz), 0.95 (4.7 H, m), 6.60 (1 H, br d, J = 2 Hz); IR (neat) 1675, 1605, 1325, 1195 cm^{-1}; UV (MeOH) λ_{max} 247 (log ϵ 3.75); ^{13}C NMR ($CDCl_3$) major isomer 21.0, 23.7, 30.8, 39.9, 44.1, 50.5, 143, 148, 200; minor isomer 11.5, 19.2, 29.5, 31.7, 36.1, 37.1, 44.7, 48.6, 142, 200; high-resolution mass spectrum calcd for $C_{11}H_{16}O$, 164.1201; obsd, 164.1204.

4-Methyl-3-(3-(trimethylenedioxy)propyl)-1-(trimethylsiloxy)cycloheptene (12). A solution of Grignard reagent was prepared as described for the preparation of compound **10** from 0.243 g of magnesium turnings (10.0 mmol) and 1.73 g of β-bromopropionaldehyde trimethylene acetal (8.87 mmol). The light gray Grignard solution (not titrated) was cooled to −20 °C, and 95.2 mg of copper(I) iodide (0.50 mmol) was added. The reaction mixture was stirred at −20 °C for 30 min, and 1.00 g of 4-methylcyclohept-2-enone (8.06 mmol) in 4 mL of dry THF was then added over a 20-min period to the now black reaction mixture. When the addition was complete, 1.40 mL of triethylamine (1.01 g, 10.0 mmol) and then 1.52 mL of chlorotrimethylsilane (1.30 g, 120. mmol) were added. The reaction mixture was allowed to warm to room temperature over a 30-min period and was then poured into 150 mL of saturated aqueous $NaHCO_3$ solution and 400 mL of ether. The organic phase was separated, washed with 100 mL of saturated aqueous $NaHCO_3$ solution and 100 mL of brine, and then dried over $MgSO_4$.

Removal of solvent in vacuo yielded 2.70 g (9.52 mmol, 118%) of a yellow liquid. Thin-layer chromatographic analysis (10% ether in hex-

(31) This refers to a 4:1 mixture of saturated aqueous ammonium chloride and concentrated aqueous ammonium hydroxide.

anes) showed two spots with R_f 0.25 and 0.76, with the latter being UV active. Preparative HPLC separation yielded 876.3 mg (2.81 mmol, 35%) of a colorless liquid that gave a satisfactory combustion analysis: ^{1}H NMR (CCl_4) δ 0.9 (3 H, m), 3.68 (2 H, br t, J = 11 Hz), 4.05 (2 H, dd, J = 4, 12 Hz), 4.40 (1 H, br t), 4.75 (1 H, m); IR (neat) 1663, 1383, 1259 cm^{-1}; ^{13}C NMR ($CDCl_3$) trans isomer 0.19, 20.4, 21.9, 25.8, 28.0, 32.9, 34.7, 34.9, 35.7, 41.1, 66.7, 102.4, 111.3, 153.7 ppm. Anal. Calcd for $C_{17}H_{32}O_3Si$: C, 65.38; H, 10.25. Found: C, 65.05; H, 10.4.

2,4-Dimethyl-3-(3-(trimethylenedioxy)propyl)cycloheptenone (13). A. From Purified enol ether 12. To a solution of 786.3 mg of purified enol ether **12** (2.52 mmol) in 5 mL of DME at room temperature was added 2.04 mL of 1.30 M methyllithium in ether (2.65 mmol) over a 2-min period. The mixture was stirred at room temperature for 45 min and then cooled to 5 °C in an ice bath, and 3.58 g of iodomethane (2.52 mmol) was added rapidly. The mixture was stirred at 5 °C for 15 min and then poured into a mixture of 100 mL of saturated aqueous $NaHCO_3$ and 180 mL of ether. The organic layer was separated, washed with 100 mL of water and 100 mL of brine, and dried over $MgSO_4$. Thin-layer chromatographic analysis (40% ether in hexanes) showed two spots by H_2SO_4 development with R_f 0.25 (strong) and 0.32 (weak).

Removal of the solvent in vacuo yielded 683.1 mg (2.71 mmol, 108%) of a yellow liquid. The crude product was purified by column chromatography (40% ether in hexanes) to yield 51.2 mg (0.203 mmol, 8%) of one C-2 epimer (R_f 0.31) and 450.0 mg (1.79 mmol, 71%) of the other C-2 epimer of the title compound. Fraction 1: ^{1}H NMR (CCl_4) δ 1.02 (6 H, d, J = 7 Hz), 3.65 (2 H, br t, J = 11 Hz), 4.04 (2 H, dd, J = 5, 11 Hz), 4.40 (1 H, br t); IR (neat) 1704, 1460, 1380, 1242, 1145 cm^{-1}. Fraction 2: ^{1}H NMR (CCl_4) δ 0.91 (3 H, d, J = 7 Hz), 1.03 (3 H, d, J = 7 Hz), 3.65 (2 H, br t, J = 11 Hz), 4.04 (2 H, dd, J = 5, 11 Hz), 4.40 (1 H, br t); IR (neat) 1702, 1460, 1380, 1242, 1145 cm^{-1}; ^{13}C NMR ($CDCl_3$) 15.9, 20.7, 20.8, 25.3, 25.6, 30.6, 33.9, 36.6, 42.5, 46.3, 48.0, 66.6, 102.2, 215.7 ppm. Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.88; H, 10.24. Found: C, 70.71; H, 10.27.

B. **From Unpurified Enol Ether 12.** To a solution of 5.18 g of enol ether **12** (16.57 mmol) in 100 mL of DME at 5 °C was added rapidly 13.9 mL of 1.25 M methyllithium in ether (17.40 mmol). Cleavage of the enol ether (3–10 min) was monitored by TLC (10% ethyl acetate in benzene) by observing the disappearance of the spot with R_f 0.58 and the appearance of two spots at R_f 0.12 and 0.03. The reaction mixture was transferred by cannula to another flask containing 11.76 g of iodomethane (5.16 mL, 2.85 mmol) in 60 mL of DME at 5 °C. The transfer required 3 min. Precipitation of lithium iodide was immediate. The mixture was stirred at 5 °C for 15 min and was then poured into a beaker containing 300 mL of rapidly stirring cold (5 °C) saturated aqueous NH_4Cl and 200 mL of ether. The mixture was transferred to a separatory funnel, and the organic phase was separated, washed with 200 mL of saturated aqueous $NaHCO_3$ and 200 mL of brine, and then dried over $MgSO_4$. Thin-layer chromatographic analysis (40% ether in hexanes) showed three spots by H_2SO_4 development with R_f 0.35 (moderate), 0.30 (strong), and 0.02 (weak).

Removal of solvent in vacuo yielded 3.54 g (14.04 mmol, 85%) of a yellow liquid. The crude produce was purified by preparative HPLC (40% ether in hexanes) to yield 2.32 g (9.20 mmol, 56% from enone **4**) of **13** as a colorless liquid that gave satisfactory combustion analysis. Analytical HPLC (50% MeOH in water, C_{18} and 25% ether in hexanes, μ-Porasil) and analytical GLC (154 °C, 10 ft × $^1/_8$ in., 8% Carbowax) were able to separate the C-2 epimers but not the C-4 epimers. The NMR and IR spectra of this material were identical with those reported above.

3aβ,8-Dimethyl-3-hydroxy-1,2,3,3a,6,7,8,8aβ-octahydroazulen-4-(5*H*)-one (3 and 15). Method A (HCl–EtOH). A solution of 103.6 mg of keto acetal **13** (0.411 mmol) in 3 mL of 10% aqueous hydrochloric acid and 16 mL of absolute ethanol was stirred at room temperature for 50 min and then placed in an oil bath (110 °C) and refluxed for 30 min. The solution was cooled to room temperature and poured into a mixture of 200 mL of ether and 150 mL of water, and the layers were separated. The aqueous phase was extracted with 100 mL of ether. The organic phases were combined, washed with 100 mL of water, 100 mL of saturated aqueous $NaHCO_3$, and 100 mL of brine, and dried over $MgSO_4$. Removal of the solvent in vacuo yielded 60.0 mg (0.309 mmol, 75%) of a yellow liquid. Thin-layer chromatographic analysis (40% ether in hexanes) showed two spots with R_f 0.28 and 0.22. The crude products were purified and separated by column chromatography on silica gel (40% ether in hexanes) to yield two fractions. Fraction 1 contained 20.3 mg (0.13 mmol, 25%) of 3aβ,8-dimethyl-3α-hydroxy-1,2,3,3a,6,7,8,8aβ-octahydroazulen-4(5*H*)-one (**15**) as a colorless liquid. Fraction 2 contained 27.0 mg (0.139 mmol, 34%) of a 3aβ,8-dimethyl-3β-hydroxy-1,2,3,3a,6,7,8,8aβ-octahydroazulen-4(5*H*)-one (**3**) as a colorless liquid. These reaction conditions thus yielded a 60% yield of a 57:43 mixture of **3** and **15**. When the same conditions were used except for a longer reflux period of 55 h, a 42:58 mixture of **3** and **15** was obtained in 62% yield. The IR spectrum of **15** remains invariant over a concentration range of 2–10% (w/v in CCl_4) while that of **3** changes dramatically in the hydroxyl region from a sharp absorbance at 3595 cm^{-1} in a 2% solution to a broad absorbance at 3500 cm^{-1} in a 10% solution. These data indicate that intramolecular hydrogen bonding is present in **15** but not in **3**.

Fraction 1 (**15**): ^{1}H NMR (CCl_4) δ 0.89 (3 H, d, J = 6 Hz), 1.05 (3 H, s), 4.00 (1 H, br t, J = 7 Hz); IR (2% in CCl_4) 3550, 1682, 1460, 1380 cm^{-1}; ^{13} NMR ($CDCl_3$) 8β isomer 11.4, 15.2, 21.0, 22.4, 24.6, 25.9, 35.2, 39.4, 44.0, 47.1, 65.8 ppm. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.42; H, 10.27. Found: C, 73.06; H, 10.37.

Fraction 2 (**3**): ^{1}H NMR (CCl_4) δ 0.87 (3 H, d, J = 6 Hz), 1.18 (3 H, s), 4.35 (1 H, dd, J = 7, 11 Hz); IR (2% in CCl_4) 3595, 1692, 1460, 1380 cm^{-1}; ^{13}C NMR ($CDCl_3$) 8β isomer 20.5, 21.9, 25.1, 25.2, 28.9, 38.3, 38.4, 40.5, 52.7, 74.2 ppm. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.42; H, 10.27. Found: C, 73.18; H, 10.19.

Method B (HCl–HOAc). A solution of 1.80 g of keto acetal **13** (7.14 mmol) in a mixture of 19 mL of 10% aqueous hydrochloric acid and 70 mL of glacial acetic acid was stirred at 30 °C for 48 h. Removal of the solvent in vacuo yielded 2.03 g of a crude yellow oil. Thin-layer chromatographic analysis (40% ether in hexanes) showed three spots by H_2SO_4 development with R_f 0.36, 0.25, and 0.10. [The identity of these spots was determined (^{1}H NMR, ^{13}C NMR, and IR spectroscopy) in an earlier reaction with identical reaction conditions. In that case column chromatography had allowed separation of the three compounds, which were found to be 1,3-diacetoxypropane, the acetate of compound **3**, and compound **3**, respectively.] The crude reaction mixture was dissolved in 40 mL of methanol, and 315.0 mg of anhydrous sodium methoxide (5.83 mmol) was added. The resulting mixture was stirred at room temperature for 2 h while the course of reaction was monitored by TLC. The mixture was poured into 400 mL of ether and 200 mL of cold (5 °C) 5% aqueous HCl and separated. The aqueous layer was extracted with 300 mL of ether, and the layers were separated. The organic phases were combined, washed with 300 mL of water, 250 mL of saturated aqueous $NaHCO_3$, and 300 mL of brine, and dried over $MgSO_4$. Removal of the solvent in vacuo yielded 1.87 g (134%) of a yellow liquid. Thin-layer chromatographic analysis (10% ethyl acetate in benzene) showed one spot by H_2SO_4 development with R_f 0.16. The crude reaction product was purified by preparative HPLC (40% ether in hexanes) to yield 888.9 mg (4.54 mmol, 64%) of **3** as a colorless liquid that gave a satisfactory combustion analysis. ^{1}H NMR and IR spectra of this material were identical with those of the material prepared in method A (fraction 2).

3aβ,8-Dimethyl-1,3a,6,7,8,8aβ-hexahydroazulen-3(2*H*),4(5*H*)-dione (16). To a solution of 80.7 mg of pyridine (82.2 μL, 1.02 mmol) in 1.5 mL of dichloromethane was added 50.8 mg of chromium trioxide (0.508 mmol) in one portion at room temperature. After 15 min, 16.6 mg of hydroxy ketone **3** (85 μmol) in 2 mL of dichloromethane was added rapidly to the burgundy-colored reaction mixture. Reaction was monitored by TLC (10% ethyl acetate in benzene). After 8 min the starting material spot (R_f 0.13) had completely disappeared and was replaced by a single spot at R_f 0.35. The reaction mixture was stirred for 19 min, 8 mL of ether was added, and the mixture was filtered through 10 g of Florisil. The reaction flask was washed several times with ether and the ether filtered through the Florisil pad. After 100 mL of ether had been put through the Florisil pad, the filtrate was added to a mixture of 100 mL of ether and 100 mL of cold (5 °C) 5% aqueous HCl, and the layers were separated. The organic phase was washed with 100 mL of a 1:1 mixture of saturated aqueous $NaHCO_3$ and water and then with 100 mL of brine and dried over $MgSO_4$. Thin-layer chromatographic analysis (40% ether in hexanes) showed one spot by H_2SO_4 development with R_f 0.29.

Removal of the solvent in vacuo yielded 12.1 mg (62.4 μmol, 73%) of a light yellow liquid. The crude product was purified by column chromatography (6 g of silica gel, 40% ether in hexanes) to yield one fraction containing 10.3 mg (53.1 μmol, 62%) of the title compound as a colorless liquid that crystallized upon standing to afford a white solid: mp 50.5–51.5 °C; ^{1}H NMR (CCl_4) δ 1.05 (3 H), 1.30 (3 H, s); IR (5 μM in $CHCl_3$) 1741, 1690, 1380 cm^{-1}; ^{13}C NMR ($CDCl_3$) 21.5, 23.5, 23.9, 26.5, 32.1, 37.8, 38.4, 40.4, 52.8 ppm; high-resolution mass spectrum, calcd for $C_{12}H_{18}O_2$, 194.1206; obsd, 194.1307.

Oxidation of 10.5 mg of hydroxy ketone **15** under similar conditions gave 9.3 mg of the same dione, identified by melting point, TLC, and ^{1}H and ^{13}C NMR spectroscopy.

3-(3-Butenyl)-2,4-dimethylcycloheptanone (21). To a well-stirred suspension of 48.3 g (0.25 mol) of purified copper(I) iodide in 150 mL of THF at 5 °C was added 600 mL of 0.42 M 3-butenylmagnesium bromide (0.25 mol) in THF dropwise over a period of 2 h. After stirring for 0.5 h at 5 °C, the mixture was cooled to −78 °C and 30.8 mL (0.25 mol) of boron trifluoride etherate was added dropwise over a 1-h period.

The mixture was stirred for 1 h at −70 °C, and 17.04 g (0.123 mol) of enone **5** in 30 mL of THF was added dropwise over a 0.5-h period. After stirring for an additional 1 h at −78 °C, the cooling bath was removed and stirring was continued for 1 h. The mixture was poured into 1 L of a 4:1 ammonia buffer[31] and extracted with two 1-L portions of ether. The combined ether extracts were washed with 500 mL of brine and dried over $MgSO_4$. Removal of the solvent afforded 27.44 g of crude product (115%). Distillation (0.03 torr) furnished 13.85 g of **21** (59%), bp 60–80 °C. The product was a 1:1 mixture of epimers at C-2. No attempt was made to assign the stereochemistry of the two epimers: ^1H NMR ($CDCl_3$) δ 0.92 (3 H, d, J = 6.8), 1.08 (3 H, d, J = 6.8), 4.95 (2 H, m), 5.75 (1 H, m), and 1.02 (3 H, d, J = 6.8), 1.13 (3 H, d, J = 7.1), 4.95 (2 H, m), 5.75 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 14.9, 16.3, 17.3, 19.3, 20.7, 21.0, 27.9, 29.6, 30.8, 31.4, 32.0, 32.1, 33.8, 36.8, 42.5, 43.4, 46.5, 46.6, 48.7, 114.3, 114.6, 138.2, 138.5; IR (film) 1700 cm^{-1}; mass spectrum, 194 (0.62), 179 (0.39), 139 (2.85), 122 (2.98). Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.60; H, 11.35.

3aβ,8-Dimethyl-3β-hydroxy-1,2,3,3a,6,7,8,8aβ-octahydroazulen-4-(5*H*)-one (3). A solution of 12.70 g (66 mmol) of keto olefin **21** in a mixture of 200 mL of dichloromethane and 70 mL of methanol was cooled to −78 °C, and a stream of ozone in oxygen was bubbled through until a blue color appeared. The solution was purged with nitrogen, 20 mL (250 mmol) of dimethyl sulfide was added, and the mixture was allowed to warm to room temperature. After the solution was allowed to stand overnight, the solvent was evaporated to leave 20.10 g of crude product.

This material was dissolved in a mixture of 500 mL of glacial acetic acid and 150 mL of 10% aqueous HCl and stirred at room temperature for 52 h. The mixture was poured into 1 L of aqueous sodium chloride and extracted with two 1-L portions of ether. The combined ether extracts were washed with concentrated aqueous sodium hydroxide to remove acetic acid. The combined aqueous phases were made basic with sodium hydroxide and extracted with 500 mL of ether. The combined ether extracts were washed with 500 mL of saturated aqeuous sodium bicarbonate and 50 mL of brine and dried over $MgSO_4$. The solvent was evaporated to afford 12.90 g of an oil. This material was taken up in 500 mL of methanol, and 3.84 g (71 mmol) of commercial sodium methoxide was added. The mixture was stirred at room temperature for 4 h. The bulk of the solvent was evaporated, and the residue was taken up in 1 L of water and extracted with two 800-mL portions of ether. The combined ether extracts were washed with 500 mL of brine and dried over $MgSO_4$. The solvent was removed to leave 10.94 g (84%) of a yellow oil that was purified by flash chromatography[32] on 100 g of silica gel, eluting with 50% ether in hexanes, to afford 9.72 g of **3** (75% from **21**). ^1H and ^{13}C NMR spectra of this product were identical with those of the material obtained as described above.

3a,β,8-Dimethyl-3β-(methoxymethoxy)-1,2,3,3a,6,7,8,8a-octahydroazulen-4(5*H*)-one (22). To a solution of 221.1 mg of keto alcohol **3** (1.13 mmol) and 199.1 mg of *N,N*-diisopropylethylamine (0.296 mL, 1.71 mmol) in 3 mL of dichloromethane at room temperature was added 137.4 mg of chloromethyl methyl ether (0.130 mL, 1.71 mmol). The mixture was allowed to stir at room temperature for 23 h. Reaction was monitored by TLC (40% ether in hexanes), which showed the disappearance of starting material after 12 h. The reaction mixture was poured into 80 mL of concentrated ammonium hydroxide and 150 mL of ether. The organic phases were combined, washed with 80 mL of cold (5 °C) aqueous 5% HCl and 80 mL of saturated aqueous $NaHCO_3$, and dried over $MgSO_4$.

Removal of the solvent in vacuo yielded 294.5 mg (1.04 mmol, 92%) of a yellow liquid. Thin-layer chromatographic analysis (15% ether in hexanes) showed two spots by H_2SO_4 development with R_f 0.15 and 0.12. The crude products were separated and purified by column chromatography on silica gel (15% ether in hexanes) to yield two fractions. Fraction 1 contained 195.5 mg (0.815 mmol, 72%) of pure **22** as a colorless oil. Analytical HPLC (15% H_2O in MeOH, μ-C_{18}, 30 cm × 3.9 mm, flow rate 1.4 mL/min) showed one peak at 3.6 min. Fraction 2 contained 48.3 mg (0.201 mmol, 18%) of a mixture of **22** and its C-10 epimer. This mixture could be separated by repeated column chromatography to yield analytical samples of both isomers. 8α (minor) Isomer: ^1H NMR (CCl_4) δ 0.92 (3 H, d, J = 6 Hz), 1.03 (3 H, s), 2.42 (2 H, m), 3.22 (3 H, s), 4.15 (1 H, dd, J = 5, 7 Hz), 4.42 (2 H, s); IR (neat) 1692, 1455, 1150, 1110, 1040 cm^{-1}; ^{13}C NMR ($CDCl_3$) 19.5, 22.0, 22.5, 25.3, 31.2, 32.2, 34.4, 39.4, 40.8, 53.4, 55.3, 81.4, 95.9 ppm. Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.96; H, 10.07. Found: C, 69.58; H, 9.95. 8β (major) Isomer: ^1H NMR (CCl_4) 0.86 (3 H, d, J = 5 Hz), 1.24 (3 H, s), 2.78 (1 H, m), 3.20 (3 H, s), 4.42 (1 H, m), 4.45 (2 H, dd, J = 8, 14 Hz); IR (neat) 1694, 1460, 1380, 1325, 1145, 1120, 1055, 1038 cm^{-1}; ^{13}C NMR ($CDCl_3$) 22.4, 23.0, 26.1, 28.0, 30.3, 37.2, 39.2, 39.9, 55.8, 59.4, 79.9, 96.7, 214.5 ppm. Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.75; H, 9.80.

3aβ,8-Dimethyl-3β-(methoxymethoxy)-1,2,3,3a,6,7,8,8a-octahydro-5β-(2-propenyl)azulen-4(5*H*)-one (23). To a solution of 178.2 mg of *N,N*-diisopropylamine (1.71 mmol, 0.249 mL) in 16 mL of DME at −10 °C to −20 °C was added 1.18 mL of a 1.50 M hexane solution of *n*-butyllithium (1.77 mmol) dropwise over a 5-min period. The solution was stirred for 15 min. To this solution, maintained at −20 °C, was added 378.1 mg of keto acetal **22** (1.57 mmol) in 4 mL of DME over a 40-min period. The mixture was stirred at −15 °C for 30 min, warmed to room temperature, and stirred for an additional 90 min. At this time 209.6 mg of 3-bromopropene (1.54 mL, 17.7 mmol) was added rapidly. The mixture was stirred at room temperature for 3 h and then poured into a mixture of 50 mL of cold (5 °C) aqueous 5% HCl and 200 mL of ether. The organic phase was removed, washed with 50 mL of saturated aqueous $NaHCO_3$, and dried over $MgSO_4$.

Removal of solvent in vacuo yielded 373.7 mg (1.33 mmol, 85%) of **23** as a colorless liquid. Thin-layer chromatographic analysis showed one spot by H_2SO_4 development with R_f 0.17. The crude reaction product required no purification since it was shown to be pure by TLC and analytical HPLC (25% H_2O in acetonitrile, μ-C_{18}, 30 cm × 3.9 mm, flow rate 2.0 mL/min, retention time 4.0 min) chromatography and ^1H NMR, ^{13}C NMR, and IR spectroscopy. These analytical techniques also showed the presence of only one stereoisomer (>95% 5β). An analytical sample was prepared by column chromatography (10% ether in hexanes) on silica gel: ^1H NMR (CCl_4) δ 0.88 (3 H, d, J = 7 Hz), 1.00 (3 H, s), 2.48 (1 H, m), 2.72 (1 H, m), 3.17 (3 H, s), 4.10 (1 H, dd, J = 7, 11 Hz), 4.92 (2 H, m), 5.62 (1 H, m); IR (neat) 1692, 1640, 1445, 1380, 1150, 1115, 1040 cm^{-1}; ^{13}C NMR ($CDCl_3$) 20.8, 21.4, 28.9, 29.2, 31.4, 32.0, 36.5, 37.3, 48.6, 55.1, 56.1, 59.6, 82.0, 96.4, 117, 137, 216 ppm. Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 9.99. Found: C, 72.43; H, 9.86.

3aβ,8-Dimethyl-3β-(methoxymethoxy)-1,2,3,3a,6,7,8,8a-octahydro-5α-(2-propenyl)azulen-4(5*H*)-one (24). A solution of 8.1 mg of keto olefin **23** (28.9 μmol) and 15.6 mg of sodium methoxide (0.286 mmol) in 4 mL of methanol was refluxed gently for 12 h. Analytical HPLC analysis (25% H_2O in MeOH, μ-C_{18}, 30 cm × 3.9 mm, flow rate 1.5 mL/min, retention times 7.8 and 9.3 min) indicated a 2:1 mixture of starting material **23** and product **24**. The product was resubmitted to exactly the original conditions and refluxed vigorously for 24 h. Analytical HPLC analysis under the conditions reported above indicated a 9:1 mixture of product **24** and starting material **23**. The reaction mixture was worked up by pouring into a mixture of 40 mL of cold (5 °C) aqueous HCl and 200 mL of ether. The organic layer was separated, washed with 50 mL of water and 50 mL of saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. Removal of solvent in vacuo yielded 4.9 mg (17.5 μmol, 85%) of a light yellow liquid. The crude product was pure by TLC (20% ether in hexanes, R_f 0.38) and analytical HPLC. Analysis by both ^1H and ^{13}C NMR spectroscopy showed a 9:1 mixture of the 5α:5β (**24**:**23**) epimers: ^1H NMR (CCl_4) δ 0.70 (3 H, d, J = 6 Hz), 1.25 (3 H, s), 3.15 (3 H, s), 4.42 (3 H, m), 4.90 (2 H, m), 5.55 (1 H, m); IR (neat) 1694, 1640, 1450, 1375, 1150, 1035, 918 cm^{-1}; ^{13}C NMR ($CDCl_3$) 2.22, 22.3, 27.2, 29.5, 33.7, 36.8, 38.8, 47.3, 55.6, 55.9, 58.9, 79.5, 95.9, 116, 136 ppm; mass spectrum, 230(0.07), 235 (5.3), 223(2.3), 147(0.44), 109(1.6), 45(8.8); high-resolution mass spectrum, calcd for $C_{17}H_{28}O_3$, 280.2038; obsd, 280.2049.

8aα-Decahydro-3aβ,8β-dimethyl-4-hydroxy-3β-(methoxymethoxy)-7β-(2-propenyl)azulene (30 and 31). To a solution of 1.36 mL of a 1.0 M hexane solution of diisobutylaluminum hydride (1.36 mmol) in 10 mL of ether at −78 °C was added 129.8 mg of keto olefin **23** (0.463 mmol) in 2 mL of ether dropwise over a 15-min period. The internal temperature was carefully maintained below −72 °C during the addition. The mixture was stirred at a temperature below −72 °C for 1 h. Thin-layer chromatographic analysis (20% ether in hexane) showed only one spot by H_2SO_4 development with R_f 0.16 and no trace of starting material (R_f 0.36). The mixture was allowed to warm to −20 °C over a 10-min period and poured into 80 mL of water and 150 mL of ether. The aqueous layer was separated and washed with two 70-mL portions of ether. The organic phases were combined, washed with 70 mL of water, 70 mL of cold (5 °C) aqueous 5% HCl, and 70 mL of saturated aqueous $NaHCO_3$, and dried over $MgSO_4$.

Removal of the solvent in vacuo yielded 123.9 mg (0.439 mmol, 95%) of a colorless liquid. The crude reaction product required no purification since it was shown to be pure by TLC and analytical HPLC (25% water in acetonitrile, μ-C_{18}, 30 cm × 3.9 mm, flow rate 2.0 mL/min) chromatography and ^1H NMR, ^{13}C NMR, and IR spectroscopy. Analytical HPLC showed two peaks with retention times of 4.0 and 4.6 min in a ratio of greater than 9:1. The major product was the 4β alcohol **30**. The minor component was never isolated in a pure form but is believed to be the 4α alcohol **31**. The ^1H NMR and ^{13}C NMR data show a 93:7 mixture of the two products. The crude product was purified by column

(32) W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).

chromatography on silica gel (20% ether in hexanes) to yield 109.5 mg (0.388 mmol, 84%) of a colorless oil, which gave satisfactory elemental analysis. However, this chromatography failed to separate the epimers. Minor product (**31**): ^{1}H NMR (CCl_4) δ 1.10 (3 H, s), 3.30 (3 H, s), 4.07 (1 H, dd, J = 7, 11 Hz); ^{13}C NMR ($CDCl_3$) 20.8, 24.4, 27.5, 29.2, 31.2, 35.8, 38.2, 29.9, 54.0, 55.5, 79.0, 79.7, 81.2, 94.8, 115, 138 ppm. Major product (**30**): ^{1}H NMR (CCl_4) δ 0.92 (3 H, d, J = 5 Hz), 0.95 (3 H, s), 3.29 (3 H, s), 3.60 (1 H, s), 3.66 (1 H, m), 4.53 (2 H, dd, J = 7.5, 10 Hz), 4.80 (1 H, br s), 4.97 (1 H, br d, J = 5 Hz), 5.68 (1 H, m); IR (neat) 3450, 1638, 1380, 1153, 1118, 1040, 910 cm^{-1}; ^{13}C NMR ($CDCl_3$) 21.5, 22.6, 27.0, 27.4, 28.3, 32.8, 36.9, 37.0, 40.3, 50.2, 54.5, 55.6, 79.3, 85.0, 95.7, 116, 139 ppm. Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.63. Found: C, 72.09; H, 10.43.

2,9β-Dihydroxy-6β,9aβ-dimethyl-2,3,3aβ,4,5,6,6aβ,7,8,9,9a,9b-dodecahydroazuleno[4,5-*b*]furan (33). Method A. Into a solution of 137.1 mg of a 93.7 mixture of alcohols **30** and **31**, in a mixture of 30 mL of dichloromethane and 10 mL of anhydrous methanol at −78 °C, was bubbled ozone from a Welsbach ozonater (O_3 in O_2 stream; settings were 60 V, 0.01 mL/min, and 6 psi) until a blue color appeared (approximately 8 min). The solution was then removed from the ozonater, and gaseous nitrogen was bubbled through the mixture at −78 °C. Dimethyl sulfide (1 mL, 846 mg, 13.62 mmol) was added at −78 °C, and the solution was warmed to room temperature over a 30-min period. The mixture was poured into a mixture of 100 mL of dichloromethane and 40 mL of water, and the aqueous phase was separated and extracted with 100 mL of dichloromethane. The organic phases were combined and dried over $MgSO_4$. Thin-layer chromatographic analysis (50% ether in hexanes) showed several spots by H_2SO_4 development with R_f 0.59 (strong), 0.45 (weak), 0.30 (weak), 0.18 (moderate). When this crude product was treated with aqueous acid (see below) for 30 s, TLC analysis (75% ether in hexanes) showed only one spot by H_2SO_4 development with R_f 0.41. Removal of solvent in vacuo yielded 140.4 mg (0.494 mmol, 102%) of **32** as a colorless oil: ^{1}H NMR ($CDCl_4$) δ 0.84 (3 H, d, J = 6 Hz), 0.97 (3 H, s), 3.28 (3 H, s), 3.67 (1 H, dd, J = 6, 10 Hz), 4.16 (1 H, d, J = 9 Hz), 4.50 (2 H, dd, J = 7, 24 Hz), 5.34 (1 H, d, J = 4 Hz); IR (neat) 3420, 1462, 1220, 1155, 1118 cm^{-1}.

The crude product (140.4 mg, 0.494 mmol) was dissolved in 7 mL of THF, 7 mL of 5% aqueous HCl was added, and the reaction flask was immediately placed in an oil bath heated to 120 °C. The solution began to reflux within 10 min. Reaction was monitored by TLC which showed complete disappearance of starting material after 25 min. After 30 min the mixture was cooled in an ice–water bath for 10 min and then poured into 40 mL of water and 150 mL of dichloromethane. The aqueous phase was separated and washed with 50 mL of dichloromethane. The organic phases were combined and washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$.

Removal of solvent in vacuo yielded 118.1 mg (0.492 mmol, 101%) of a colorless, viscous liquid. The crude product was purified by column chromatography (66% ether in hexanes) to obtain 103.0 mg (0.429 mmol, 88% from **30**) of a colorless, viscous liquid that gave satisfactory combustion analysis. This material crystallized on standing to give a white solid: mp 100–103 °C; ^{1}H NMR (CCl_4) δ 0.80 (3 H, d, J = 4 Hz), 0.95 (3 H, s), 3.79 (1 H, dd, J = 6, 10 Hz), 4.32 (1 H, d, J = 9 Hz), 5.38 (1 H, d, J = 5 Hz); IR (neat) 3620, 3400, 1472, 1350, 1200 cm^{-1}. Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.18; H, 9.86.

Method B. A solution of 2.70 g (10.1 mmol) of diol **31** in 90 mL of dichloromethane and 30 mL of methanol was cooled to −70 °C, and a stream of ozone in oxygen was bubbled through until the solution became blue. The solution was purged with air, and 5 mL (68 mol) of dimethyl sulfide was added. The cooling bath was removed and the mixture was allowed to stand at room temperature overnight. Removal of the solvent left 3.25 g of an oil. Flash chromatography[32] of this product on 50 g of silica gel, eluting with 30% ether in hexanes, afforded 1.37 g of the methyl acetal of compound **33** (53%): ^{1}H NMR ($CDCl_3$) δ 0.80 (3 H, d, J = 5.7 Hz), 1.00 (3 H, s), 3.32 (3 H, s), 3.96 (1 H, dd, J = 5.6, 9.4 Hz), 4.38 (1 H, d, J = 9.4 Hz), 4.98 (1 H, d, J = 4.7 Hz); IR (film) 3650 cm^{-1}; mass spectrum, 254 (0.01), 252 (0.02), 236 (0.36), 222 (1.30), 204 (0.93). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 71.03; H, 10.12.

A solution of 1.12 g (4.4 mmol) of this material in 100 mL of THF and 50 mL of 0.1 N HCl was stirred at room temperature for 18 h. The mixture was poured into 250 mL of water and extracted with three 100-mL portions of ether. The combined ether extracts were washed with 100 mL of saturated aqueous $NaHCO_3$ and 100 mL of brine and dried over $MgSO_4$. Removal of the solvent furnished 1.08 g of diol **33** (102%). The spectra of this material were the same as those of the material prepared in part A.

6β,9aβ-Dimethyl-2,3,3aα,4,5,6,6aβ,7,8,9,9a,9bα-dodecahydroazuleno-[4,5-*b*]furan-2,9-dione (2). To a cooled (5 °C) solution of 20.3 mg of diol **33** (84.6 μmol) in 1 mL of acetone was added dropwise over a 2 min period 94.9 μL of a 2.65 M solution of Jones' reagent (0.254 mmol). The solution was stirred in an ice bath for 20 min and 0.5 mL of isopropyl alcohol was added. Reaction was monitored by TLC (ether), which showed disappearance of starting material (R_f 0.37), the appearance and disappearance of an intermediate (R_f 0.40, subsequently shown to be the hydroxy lactone; vida infra) and, finally, the appearance of product **2** (R_f 0.49). The mixture was stirred at 5 °C for 5 min after addition of isopropyl alcohol, during which time the color of the solution changed from burgundy to green. The mixture was poured into a mixture of 100 mL of dichloromethane and 50 mL of cold (5 °C) aqueous 5% HCl. The reaction flask was washed alternately with dichloromethane and cold (5 °C) aqueous 5% HCl until all the residue was removed. The washes were combined with reaction mixture and solvent and extracted. The aqueous phase was separated and washed with 70 mL of dichloromethane. The organic phases were combined, and washed with 40 mL of cold (5 °C) saturated aqueous $NaHCO_3$, and dried over $MgSO_4$.

Removal of the solvent in vacuo gave 19.7 mg (83.6 μmol, 98%) of a nearly colorless, viscous liquid. The crude product was purified by column chromatography (66% ether in hexanes) to yield 18.3 mg (77.7 μmol, 92%) of a viscous, colorless liquid. This material could be crystallized from 5–10% ether in hexane to give 17.9 mg (76.1 μmol, 90%) of a white solid, mp 77.5–79.5 °C, which gave satisfactory elemental analysis: ^{1}H NMR ($CDCl_3$) δ 1.05 (3 H, d, J = 6.4 Hz), 1.33 (3 H, s), 4.76 (1 H, d, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) 22.1, 22.8, 25.1, 29.2, 30.4, 33.9, 36.4, 36.8, 37.7, 50.7, 55.3, 84.4, 176.2, 217.6; IR (neat) 1783, 1742, 1462, 1182 cm^{-1}; mass spectrum, 236 (0.43), 221 (2.5), 194 (1.0), 179 (1.7), 97 (7.0). Anal. Calcd for $C_{14}H_{26}O_3$: C, 71.16; H, 8.53. Found: C, 70.98; H, 8.59.

On a larger scale, this oxidation gives lower yields of keto lactone. The following procedure is typical. A solution of 1.08 g (4.5 mmol) of **33** in 50 mL of ether was cooled to 0 °C, and 9 mL of cooled 2 M chromic acid (18 mmol) was added dropwise over a 15-min period. The mixture was stirred at 0 °C for 20 min, poured into 150 mL of water, and extracted with two 100-mL portions of dichloromethane. The combined organic extracts were washed with 50 mL of saturated aqueous sodium bicarbonate and 50 mL of brine and dried over $MgSO_4$. Removal of the solvent left 0.84 g (79%) of an oil. This material was purified by flash chromatography[32] on 50 g of silica gel, eluting with 60% ether in hexanes, to give 0.481 g (45%) of keto lactone **2**.

On one occasion, chromatography of the oxidation mixture afforded a minor product resulting from partial oxidation. The spectral characteristics of this material are consistent with the hypothesis that it is a hydroxy lactone: ^{1}H NMR ($CDCl_3$) δ 0.84 (3 H, d, J = 5.9 Hz), 1.09 (3 H, s), 4.03 (1 H, dd, J = 5.6, 9.0 Hz), 4.80 (1 H, d, J = 9.0 Hz); IR ($CHCl_3$) 3600, 1700 cm^{-1}; mass spectrum, 238 (0.28), 220 (1.34), 205 (0.25), 179 (4.53), 97 (4.83), 69 (9.77). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.64; H, 9.23.

3aβ,8β-Dimethyl-3β-(tetrahydropyranyloxy)-1,2,3,3a,6,7,8,9a-octahydroazulen-4(5*H*)-one (34). To a solution of 9.72 g (49.7 mmol) of hydroxy ketone **3** and 15 mL (165 mmol) of dihydropyran in 500 mL of dichloromethane was added 20 mg (0.1 mmol) of toluenesulfonic acid. The mixture was stirred for 1 h at room temperature, washed with 300 mL of saturated aqueous sodium bicarbonate, and dried over $MgSO_4$. Removal of the solvent afforded 17.72 g of crude product. Purification by flash chromatography[32] on 100 g of silica gel, eluting with 15% ether in hexanes, furnished 12.15 g (87%) of **34**. The product consisted of approximately equal amount of two diastereomers resulting from the asymmetric carbon in the protecting group. Spectral data are given for the mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 0.87 (3 H, d, J = 6.6 Hz), 1.29 (3 H, s), 1.34 (3 H, s), 3.47 (1 H, m), 3.87 (1 H, m), 4.62 (1 H, m), 4.73 (1 H, dd, J = 6.0, 10.9 Hz); IR (neat) 1695 cm^{-1}. Anal. Calcd for (mixture of stereoisomers) $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.91; H, 9.89.

3aβ,8β-Dimethyl-3β-hydroxy-5β-(3-methyl-2-butenyl)-1,2,3,3a,6,7,8,8aβ-octahydroazulen-4(5*H*)-one (35). To a solution of 13.4 mL (96.0 mmol) of *N*,*N*-diisopropylamine in 1.2 L of THF at 5 °C was added 61 mL of 1.57 M *n*-BuLi (96.0 mmol) in hexane dropwise over a period of 5 min. The resulting solution was stirred for 45 min and a solution of 24.30 g (87.0 mmol) of THP-protected aldol **34** in 50 mL of THF was added, dropwise, over a period of 1 h. The cooling bath was removed, the mixture was stirred for 3.5 h at room temperature and 20 mL of 1-bromo-3-methyl-2-butene was added. The mixture was stirred overnight, poured into 2 L of water, and extracted with three 600-mL portions of ether. The combined ether extracts were washed with 500 mL of 5% aqueous HCl, 500 mL of saturated aqueous $NaHCO_3$, and 500 mL of brine and dried over $MgSO_4$. Removal of the solvent left 33.12 g of a yellow oil which was approximately a 1:1 mixture of epimers at the center on the THP ring. This material was partially purified by chromatography on 200 g of silica gel, eluting with 8% ether in hexanes to obtain 24.45 g (81%) of oily product. Spectral data are given for the

mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 0.90 (3 H, d, J = 6.5 Hz), 1.11 (3 H, s), 1.16 (3 H, s), 1.62 (3 H, s), 1.68 (3 H, s), 3.43 (1 H, m), 3.67 (1 H, m), 4.35 (2 H, m), 5.11 (1 H, t, J = 6.4 Hz); IR (film) 1695 cm^{-1}; mass spectrum, 348 (0.20), 291 (0.21), 264 (2.65), 207 (3.71), 85 (18.40). An analytical sample was obtained by column chromatography on silica gel, eluting with 5% ether in hexanes. Anal. Calcd for (mixture of stereoisomers) $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.66; H, 10.18.

A solution of 6.28 g (17.8 mmol) of this THP ether in 150 mL of methanol, 50 mL of dioxane, and 50 mL of 1% aqueous HCl was stirred at room temperature for 16 h. The mixture was poured into 1 L of brine and extracted with three 400-mL portions of ether. The combined organic extracts were washed with 400 mL of brine and dried over $MgSO_4$. Removal of the solvent left 4.53 g of **35** as a yellowish oil (97%): ^{1}H NMR ($CDCl_3$) δ 0.89 (3 H, d, J = 6.1 Hz), 1.15 (3 H, s), 1.61 (3 H, s), 1.68 (3 H, s), 4.28 (1 H, m), 5.06 (1 H, t, J = 8.0 Hz); IR (thin film) 3450, 1690 cm^{-1}; mass spectrum, 264 (1.15), 246 (1.29), 231 (0.48), 207 (1.03). Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.54; H, 10.65.

3β,4β-Dihydroxy-3aβ,8β-dimethyl-5β-(3-methyl-2-butenyl)decahydroazulene (36) and 3β,4α-Dihydroxy-3aβ,8β-dimethyl-5β-(3-methyl-2-butenyl)decahydrozaulene (37). To a mixture of 80 mL of diisobutylaluminum hydride (80 mmol) in hexane and 400 mL of ether at −100 °C was added a solution of 4.53 g (13.0 mmol) of hydroxy ketone **35** in 30 mL of ether dropwise over a period of 40 min. The mixture was stirred at −100 °C for 1 h, warmed to −40 °C, and poured into a mixture of 500 mL of 10% aqueous HCl and 200 mL of ether. The aqueous layer was separated and extracted with two 400-mL portions of ether. The combined ether extracts were washed with 400 mL of 10% aqueous HCl and 400 mL of saturated aqueous sodium bicarbonate and dried over $MgSO_4$. Removal of the solvent left 4.36 g of an oil. This material was purified by flash chromatography[32] on 100 g of silica gel, eluting with 50% ether in hexanes to furnish 2.70 g of a 9:1 mixture of **36** and **37** (78%). Samples of the pure diols were obtained by careful chromatography on silica gel.

Cis diol **36** displayed the following spectral characteristics: ^{1}H NMR ($CDCl_3$) δ 0.86 (3 H, d, J = 5.7 Hz), 1.04 (3 H, s), 1.63 (3 H, s), 1.70 (3 H, s), 3.94 (2 H, m), 5.06 (1 H, t, J = 7.6 Hz); IR (film) 3400, 740 cm^{-1}; mass spectrum, 266 (1.01), 248 (1.07). Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.45; H, 11.17.

Trans diol **37** gave these spectral data: ^{1}H NMR ($CDCl_3$) δ 0.97 (3 H, d, J = 6.0 Hz), 1.15 (3 H, s), 1.64 (3 H, s), 1.72 (3 H, s), 3.70 (1 H, dd, J = 3.7, 9.5 Hz), 4.26 (1 H, m), 5.24 (1 H, t, J = 6.9 Hz); IR (CCl_4) 3550 cm^{-1}; mass spectrum, 266 (0.22), 248 (1.22); high-resolution mass spectrum, calcd for $C_{17}H_{30}O_2$, 266.2244; obsd, 226.2236.

6β,9aβ-Dimethyl-3,3aβ,4,5,6,6aβ,9a,9bβ-octahydroazuleno[4,5-*b*]furan-2,9-dione (42). To a solution of 2.234 g (9.5 mmol) of keto lactone **2** in 60 mL of benzene at room temperature were added 1.6 mL (11.5 mmol) of triethylamine and 1.95 mL (10.5 mmol) of trimethylsilyl triflate. The mixture was stirred for 16 h, diluted with 150 mL of dichloromethane, washed with 50 mL of cold saturated aqueous sodium bicarbonate, and dried over $MgSO_4$. Removal of the solvent left 2.980 g (102%) of **40** as a yellow oil. No attempt was made to purify this intermediate: ^{1}H NMR ($CDCl_3$) δ 0.22 (9 H, s), 0.92 (3 H, d, J = 6.1 Hz), 1.25 (3 H, s), 4.53 (1 H, t, J = 2.4 Hz), 4.71 (1 H, d, J = 8.4 Hz); IR (film) 1775, 1650 cm^{-1}.

To a solution of 2.980 g (9.5 mmol) of silyl enol ether **40** in 200 mL of the THF at 5 °C was added 1.870 g (19.5 mmol) of *N*-bromosuccinimide. The mixture was stirred for 30 min at 5 °C, poured into 300 mL of saturated aqueous sodium bicarbonate, and extracted with two 300-mL portions of dichloromethane. The combined organic extracts were washed with 100 mL of brine and dried over $MgSO_4$. Removal of the solvent left 3.166 g (106%) of crude bromo ketones **41**. Spectral data are given for the mixture of diastereomers: ^{1}H NMR ($CDCl_3$) 1.06 (3 H, d, J = 6.1), 1.32/1.49 (each 3 H, s), 4.40 (1 H, m), 4.74/4.94 (each 1 H, d, J = 7.3 Hz).

To a well-stirred, refluxing slurry of 6.15 g (61.5 mmol) of powdered calcium carbonate in 80 mL of *N,N*-dimethylacetamide (DMAC) was added a solution of 3.166 g (9.5 mmol) of bromo ketones **41** in 15 mL of DMAC over a period of 2 min. The mixture was maintained at reflux for 8 min and allowed to cool to room temperature. The calcium carbonate was removed by filtration, and the solvent was removed by distillation (2.5 torr). Chromatography of the residue on 60 g of silica gel, eluting with 80% ether in hexanes, afforded 1.037 g of enone **42** (47%) as a white solid. Recrystallization from ethyl acetate–hexanes gave white crystals: mp 189–90 °C; ^{1}H NMR ($CDCl_3$) δ 1.08 (3 H, d, J = 8.3 Hz), 1.26 (3 H, s), 4.76 (1 H, d, J = 8.7 Hz), 6.14 (1 H, dd, J = 1.8, 5.9 Hz), 7.68 (1 H, dd, J = 3.0, 5.9 Hz); ^{13}C NMR ($CDCl_3$) 19.9, 20.7, 26.8, 33.5, 34.5, 34.9, 36.9, 51.1, 55.8, 80.7, 129.8, 164.7, 175.9; IR ($CHCl_3$) 1770, 1705, 1600 cm^{-1}; mass spectrum, 234 (1.00), 219 (1.18), 175 (1.80). In spite of several attempts, satisfactory analytical data were not obtained for this compound. High-resolution mass spectrum, calcd for $C_{14}H_{18}O_3$, 234.1257; obsd, 234.1256.

6β,9aβ-Dimethyl-3,3aα,4,5,6,8,9a,9bβ-octahydroazuleno[4,5-*b*]furan-2,9-dione 9-Ethylene Ketal (43) and 6β,9aβ-Dimethyl-3,3aα,4,5,6,6aβ,9a,9bα-octahydroazuleno[4,5-*b*]furan-2,9-dione 9-Ethylene Ketal (44). A mixture of 0.457 g (1.95 mmol) of enone lactone **42**, 27 mg (0.12 mmol) of naphthalenesulfonic acid, 1.0 mL of ethylene glycol, and 15 mL of benzene was heated at reflux with a Dean–Stark trap for 9 h. The mixture was allowed to cool, diluted with 80 mL of dichloromethane, washed with 30 mL of saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. Removal of the solvent left 0.470 g of crude product (87%). This material was purified by chromatography on 10 g of silica gel, eluting first with 50% ether in hexanes to furnish 0.21 g (40%) of a 2.5:1 mixture of **43** and **44** and then with pure ether to afford 0.067 g of recovered enone **42** (15%). More careful column chromatography allowed partial separation of **43** and **44**.

The α,β-unsaturated ketal **44** was recrystallized from ether–hexanes to give white needles: mp 127–28 °C; ^{1}H NMR ($CDCl_3$) δ 0.91 (3 H, d, J = 6.3 Hz), 1.16 (3 H, s), 4.05 (4 H, m), 5.34 (1 H, d, J = 9.3 Hz), 5.61 (1 H, dd, J = 1.6, 5.9 Hz), 5.98 (1 H, dd, J = 3.2, 5.9 Hz); ^{13}C NMR ($CDCl_3$) 19.1, 21.1, 26.9, 32.1, 35.3, 35.7, 36.1, 37.9, 51.1, 57.0, 65.4 (double height), 81.4, 120.6, 130.2, 136.3, 176.7; IR ($CHCl_3$) 1780 cm^{-1}; mass spectrum, 278 (6.67), 263 (0.93), 179 (2.16), 139 (6.30), 112 (4.67), 99 (5.62). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.02; H, 8.03.

The β,γ-unsaturated ketal **43** was recrystallized from ether–hexanes to furnish white crystals: mp 102–105 °C (lit. mp 108–110 °C); ^{1}H NMR ($CDCl_3$) δ 1.18 (3 H, d, J = 7.3 Hz), 1.28 (3 H, s), 4.0 (4 H, m), 4.68 (1 H, d, J = 7.4 Hz), 5.53 (1 H, t, J = 2.1 Hz); ^{13}C NMR ($CDCl_3$) 17.6, 22.6, 26.5, 28.7, 36.3, 27.1, 39.1, 40.0, 56.8, 64.8 (double height), 82.7, 124.8; IR ($CHCl_3$) 1775 cm^{-1}; mass spectrum, 278 (3.41), 263 (0.82), 249 (0.21), 139 (2.20), 99 (3.56), 86 (5.14). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.79; H, 7.84.

6β,9aβ-Dimethyl-3,3aα,4,5,6,8,9a,9bα-octahydroazuleno[4,5-*b*]furan-2,9-dione (45). To a solution of 27 mg (0.97 mmol) of ketal **43** in 4 mL of methanol was added 2 mL of 10% aqueous HCl. The mixture was stirred for 3 h at room temperature, diluted with 40 mL of dichloromethane, washed with 15 mL of saturated aqueous sodium bicarbonate, and dried over $MgSO_4$. Removal of the solvent left 24 mg (106%) of a solid. Recrystallization from ethyl acetate–hexanes gave white crystals: mp 159–160 °C; ^{1}H NMR ($CDCl_3$) δ 1.21 (3 H, d, J = 7.4 Hz), 1.35 (3 H, s), 4.41 (1 H, d, J = 8.0 Hz), 5.92 (1 H, t, J = 2.1 Hz); IR ($CHCl_3$) 1775, 1750 cm^{-1}; mass spectrum, 234 (3.17), 219 (0.53), 206 (0.53), 191 (0.60), 174 (0.81); high-resolution mass spectrum, calcd for $C_{14}H_{18}O_3$, 234.1255; obsd, 234.1247.

Hydrogenation of Ketal 43. To a solution of 4.0 mg (0.017 mmol) of ketal **43** in 2 mL of 95% ethanol was added 2 mg of platinum oxide. The mixture was stirred under hydrogen for 1 h. TLC showed complete consumption of starting material. The mixture was filtered to remove the catalyst and the solvent was removed to leave 3.2 mg of a 1:1 mixture of ketals **46** and **47** (67%), as determined by ^{1}H NMR spectroscopy. The ketal mixture was dissolved in 20 drops of methanol, and 10 drops of water and 6 drops of concentrated HCl were added. After stirring for 2 h, the mixture was diluted with 40 mL of dichloromethane, washed with 20 mL of saturated aqueous sodium bicarbonate, and dried over $MgSO_4$. Removal of the solvent left 2.0 mg (50%) of a 1:1 mixture of keto lactones **2** and **38**, as determined by ^{1}H NMR spectroscopy.

Hydrogenation of Enone 45. To a solution of 8 mg (0.034 mmol) of enone **45** in 3 mL of ethanol was added 2 mg of platinum oxide. The mixture was stirred under a hydrogen atmosphere for 1 h. The mixture was filtered through a pad of diatomaceous earth, and the solvent was removed to leave 7 mg of a 3:1 mixture of keto lactones **2** and **38** (87%), as determined by ^{1}H NMR spectroscopy.

Reconjugation of Enone 45. A solution of 8 mg (0.034 mmol) of enone **45** in 3 mL of methanol and 2 mL of concentrated HCl was heated at reflux for 1.5 h. The mixture was allowed to cool, poured into 20 mL of saturated aqueous sodium bicarbonate, and extracted with two 20-mL portions of dichloromethane. The combined organic extracts were washed with 20 mL of saturated aqueous sodium bicarbonate and dried over $MgSO_4$. Removal of the solvent left 6 mg (75%) of a white solid, shown by ^{1}H NMR spectroscopy to be enone **42**.

4β,9bβ-Dimethyl-2,3,4,5,6,6aα,9aα,9b-octahydro-1*H*-oxireno[1,8a]azuleno[4,5-*b*]furan-1,8(4*H*)-dione 1-Ethylene Ketal (50). To a solution of 0.362 g (1.30 mmol) of a 2:1 mixture of ketals **43** and **44** in 35 mL of dichloromethane at room temperature was added 0.412 g (2.02 mmol) of *m*-chloroperoxybenzoic acid. The mixture was stirred for 3 h at room temperature, diluted with 100 mL of dichloromethane, washed with 60 mL of saturated aqueous $NaHSO_3$ and 60 mL of saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. Removal of the solvent left 0.47 g of

a mixture of epoxide **48** and ketal **44**. Separation was achieved by chromatography on 20 g of silica gel, eluting with 50% ether in hexanes to furnish 0.103 g of **44** (29%) and with pure ether to afford 0.198 g of epoxide **48** (52%, 72% based on recovered **44**) as a white solid. Recrystallization of **48** from ethyl acetate–hexanes gave white crystals: mp 173–174 °C; ^{1}H NMR ($CDCl_3$) 1.20 (3 H, d, J = 7.5 Hz), 1.21 (3 H, s), 2.13 (2 H, s), 3.20 (1 H, s), 3.95 (4 H, m), 5.10 (1 H, d, J = 9.7 Hz); ^{13}C NMR ($CDCl_3$) 14.1, 18.1, 24.2, 28.3, 35.6, 38.3, 38.6 (double height), 54.6, 58.2, 64.1, 65.2, 69.1, 80.9, 116.0, 176.3; IR ($CHCl_3$) 1780 cm^{-1}; mass spectrum, 294 (0.96), 279 (0.12), 266 (0.36). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.30; H, 7.54.

(±)-Parthenin (1). A solution of 82 mg (0.28 mmol) of epoxy lactone **48** in 4 mL of 2 M methyl methoxymagnesium carbonate in DMF (8.0 mmol) was heated at 140 °C for 3 h. The mixture was cooled, poured into 80 mL of cold 5% aqueous HCl, and extracted with three 30-mL portions of dichloromethane. The combined organic extracts were washed with 20 mL of water and dried over $MgSO_4$. Removal of the solvent left 108 mg (130%) of **52** as a brownish solid. No attempt was made to purify this intermediate: ^{1}H NMR ($CDCl_3$) δ 1.22 (3 H, s), 1.22 (3 H, d, J = 7.4 Hz), 3.27 (1 H, s), 3.95 (4 H, m), 5.04 (1 H, d, J = 8.6 Hz). A mixture of 51 mg (0.62 mmol) of sodium acetate, 0.5 mL (4.8 mmol) of diethylamine, 1.5 mL (20.0 mmol) of formalin, and 2.0 mL of glacial acetic acid was prepared and added to 108 mg (0.28 mmol) of crude **52**. The mixture was heated on a steam bath for 15 min. After cooling, the mixture was diluted with 80 mL of dichloromethane, washed successively with 30 mL of water, 30 mL of 5% aqueous HCl, and 30 mL of saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. Removal of the solvent left 53 mg (62%) of α-methylenated compound **54** as a yellowish oil.

The water and acid washes were made basic by addition of solid sodium carbonate and extracted with three 30-mL portions of dichloromethane. The combined organic extracts were dried over $MgSO_4$. Removal of the solvent left 230 mg (22%) of (diethylamino)methyl compound **53**: ^{1}H NMR ($CDCl_3$) δ 1.47 (6 H, t, J = 7.1 Hz), 3.03 (4 H, q, J = 7.1 Hz), 3.9 (4 H, m), 5.07 (1 H, d, J = 9.5 Hz).

The basic material **53** (23 mg, 0.068 mmol) was dissolved in 2 mL of methanol, and 4 mL of methyl iodide was added. The mixture was stirred for 23 h at room temperature. The volatiles were removed at reduced pressure, and 7 mL of ethyl acetate, 0.5 mL of water, and 7 mg (0.083 mmol) of $NaHCO_3$ were added to the residue. The mixture was stirred for 3 h, diluted with 25 mL of ethyl acetate, washed with 10 mL of brine, and dried over $MgSO_4$. Removal of the solvent left 12 mg (14%) of **54**.

The total yield of **54** was 76%. This intermediate was not generally purified. ^{1}H NMR ($CDCl_3$) δ 1.07 (3 H, s), 1.19 (3 H, d, J = 7.4 Hz), 3.23 (1 H, s), 4.0 (4 H, m), 5.30 (1 H, d, J = 9.5 Hz), 5.49 (1 H, d, J = 3.4 Hz), 6.21 (1 H, d, J = 3.9 Hz); IR ($CDCl_3$) 1750, 1600 cm^{-1}; mass spectrum, 306 (0.50), 291 (0.06), 278 (0.58). Satisfactory analytical data were not obtained for this compound. High-resolution mass spectrum, calcd for $C_{17}H_{22}O_5$, 306.1467; obsd, 306.1473.

To a solution of 65 mg (0.21 mmol) of **54** in 4.5 mL of methanol was added 1.5 mL of concentrated HCl. The mixture was stirred at room temperature for 3 h. The mixture was poured into 20 mL of saturated aqueous $NaHCO_3$ and extracted with three 15-mL portions of dichloromethane. The combined organic extracts were washed with 15 mL of saturated aqueous sodium bicarbonate and dried over $MgSO_4$. Removal of the solvent left 52 mg (71% from **48**) of crude (±)-parthenin (**1**). This material was chromatographed on 3 g of silica gel, eluting with 75% ether in hexanes to furnish 33 mg (45% from **48**) of **1** as a white solid, mp 150–154 °C. This material was recrystallized from ethyl acetate–hexanes to give white needles: mp 157–158 °C (lit.[3] mp 151–155 °C); ^{1}H NMR ($CDCl_3$) δ 1.13 (3 H, d, J = 5.6 Hz), 1.30 (3 H, s), 3.53 (1 H, m), 5.01 (1 H, d, J = 8.0 Hz), 5.60 (1 H, d, J = 2.4 Hz), 6.21 (1 H, d, J = 5.9 Hz), 6.30 (1 H, d, J = 2.7 Hz), 7.50 (1 H, d, J = 5.9 Hz); IR ($CHCl_3$) 3575, 1755, 1720 cm^{-1}; mass spectrum, 262 (0.43), 244 (1.15), 229 (0.47), 216 (1.01), 123 (2.50), 111 (4.27), 53 (4.63). The ^{1}H NMR spectrum is identical with that reported by Vandewalle.[3]

Acknowledgment. This work was supported by a research grant from the U.S. Public Health Service (CA 12617). Force-field calculations and the Wipke steric congestion analysis on hydroxy ketones **28** and **29** were carried out at the University of California at Santa Cruz. We thank Dr. C. T. Buse and Professor W. T. Wipke for assistance with these calculations. The X-ray structure of keto lactone **2** was carried out by Dr. Fred Hollander of the Berkeley Crystallography Lab.

Registry No. 1, 69401-55-4; **2**, 83096-43-9; **2** hydroxy lactone, 83096-76-8; **3**, 83096-44-0; **4**, 83096-45-1; **5**, 83096-46-2; **6**, 83149-31-9; **7**, 83096-47-3; **8**, 83096-48-4; **9**, 33884-43-4; *cis*-**10**, 83096-49-5; *trans*-**10**, 83096-77-9; *cis*-**11**, 83096-50-8; *trans*-**11**, 83096-78-0; *trans*-**12**, 83096-51-9; **13** (isomer 1), 83096-52-0; **13** (isomer 2), 83149-34-2; **14**, 83096-53-1; **15**, 83096-54-2; **16**, 83096-55-3; **21**, 83096-56-4; 8α-Me-**22**, 83096-57-5; 8β-Me-**22**, 83096-79-1; **23**, 83096-58-6; **24**, 83096-59-7; **30**, 83096-60-0; **31**, 83096-61-1; **32**, 83096-62-2; **33**, 83096-63-3; **33**, 2-methyl ether, 83096-80-4; **34** (isomer 1), 83149-32-0; **34** (isomer 2), 83149-35-3; **35**, 83096-64-4; **35** THP ether (isomer 1), 83096-81-5; **35** THP ether (isomer 2), 83096-82-6; **36**, 83096-65-5; **37**, 83096-66-6; **38**, 60090-71-3; **39**, 69363-03-7; **40**, 83096-67-7; **41** (isomer 1), 83096-68-8; **41** (isomer 2), 83096-83-7; **42**, 83096-69-9; **43**, 69363-04-8; **44**, 83096-70-2; **45**, 83096-71-3; **46**, 83149-33-1; **47**, 60090-72-4; **48**, 83096-72-4; **49**, 69401-54-3; **50**, 69401-57-6; **51**, 69401-58-7; **52**, 83096-73-5; **53**, 83096-74-6; **54**, 83096-75-7.