ether. The ether extract was dried over Na_2SO_4 and concentrated in vacuo. Column chromatography of the crude residue on 50 g of silica gel with 2.5% EtOAc/petroleum ether provided 0.350 g (70%) of 1-vinyl-4-methoxybenzocyclobutene (**15**): R_f (10% EtOAc/hexane) 0.5; ^{1}H NMR 2.86 (d, J = 7.5, 2 H), 3.37 (dd, J = 7.7, 1 H), 3.75 (s, 3 H), 4.96–6.12 (m, 3 H), 6.65–7.0 (3H); ^{13}C NMR 36.4 (t), 45.3 (d), 55.2 (q), 108.9 (d), 113.4 (d), 113.8 (t), 123.4 (d), 138.8 (s), 139.6 (d), 144.1 (s), 160.2 (s); IR 3040, 2960, 2910, 2880, 2790, 1610, 1580, 1565, 1450, 1300, 1250, 1140 cm^{-1}.

This olefin was converted to the iodide **9** by the method of Kabalka.[25] The olefin (0.56 g, 3.5 mmol) in 3.5 mL of THF was cooled to 0 °C. To this solution was added BH_3·THF (1.3 equiv), and stirring was continued for 3 h. Methanolic sodium acetate (2 equiv, 1 M), aqueous sodium iodide (2 equiv, 1 M), and methanolic chloramine-T (2 equiv, 0.5 M) were added sequentially to the organoborane solution at 25 °C. The mixture was stirred for 5 min at 25 °C and then quenched by adding aqueous sodium thiosulfate (1 M) and HCl (1 N). The mixture was diluted with water and extracted with 2 × 20 mL of pentane. The pentane extract was dried over Na_2SO_4 and evaporated. The residue was chromatographed on 50 g of silica gel with petroleum ether. The first 200 mL was concentrated in vacuo to recover unreacted olefin (0.15 g). The next 400 mL was concentrated in vacuo to give the iodie **16** [0.395 g (54% based on unrecovered starting olefin)] as a colorless oil: R_f (10% EtOAc/hexane) 0.59; ^{1}H NMR 2.0–2.4 (m, 2 H), 2.44–3.64 (m, 5 H), 3.75 (s, 3 H), 6.7–7.07 (m, 3 H); ^{13}C NMR 3.9 (t), 35.1 (t), 38.7 (t), 43.3 (d), 55.6 (q), 109.4 (d), 113.6 (d), 123.1 (d), 139.7 (s), 144.3 (s), 160.1 (s); IR 3100, 2960, 2890, 1625, 1580, 1450, 1400, 1240, 900 cm^{-1}.

Preparation of 12. The dianion alkylation was carried out by the method of Schlessinger.[20] Thus, 2.5 equiv of LDA were prepared in a flame-dried flask at 0 °C by dropwise addition of n-BuLi (0.9 mmol, 2.3 M) to diisopropylamine (0.9 mmol) in 1 mL of THF. The β-keto ester **11** (0.060 g, 0.35 mmol) in 0.5 mL of THF was added dropwise. The reaction mixture was then warmed to 40 °C for 3 h to complete the formation of the dianion. The solution was cooled to 0 °C, and the iodide **16** (0.53 mmol, 1.5 equiv) and HMPA (0.35 mmol, 1 equiv) were added. The reaction mixture was stirred for 4 h, then diluted with saturated aqueous NH_4Cl, and extracted with 3 × 20 mL of ether. The combined ether extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on 5 g of silica gel with 4% EtOAc/petroleum ether. The first 50 mL was discarded. The next 70 mL was concentrated in vacuo to give **12**: 0.061 g (55%); R_f (EtOAc/hexane) 0.19; ^{1}H NMR 0.92 (s, 3 H), 1.4–3.7 (m, 11 H), 3.76 (s, 3 H), 3.79 (s, 3 H), 5.05–5.87 (m, 3 H), 6.64–7.05 (m, 3 H); ^{13}C NMR 18.3 (q), 28.5 (t), 29.6 (t), 34.2 (t), 35.4 (t), 42.5 (d), 45.0 (d), 46.8 (s), 52.5 (q), 54.9 (d), 55.4 (q), 109.1 (d), 113 (t), 117.5 (d), 122.8 (s), 136.1 (d), 140.9 (s), 144.5 (s), 159.6 (s), 169.7 (s), 214.6 (s); IR 3040, 2920, 2890, 1735, 1710, 1630, 1560, 1545, 1450, 1315, 1250, 1220 cm^{-1}; MS 342 (32), 311 (10), 186 (11), 173 (16), 172 (22), 161 (100), 160 (86), 147 (17), 145 (23); exact mass for $C_{21}H_{26}O_4$, calcd 342.183, obsd 342.182.

Preparation of (+)-Estrone Methyl Ether (1). Decarbomethoxylation was effected by the method of Krapcho.[26] Thus, a mixture of **12** (0.061 g, 0.178 mmol), NaCl (0.89 mmol, 5 equiv), and H_2O (0.06 mL, 5 equiv) in 0.5 mL of Me_2SO was heated at 165 °C for 45 min. The mixture was cooled and extracted with 6 × 5 mL of petroleum ether. The combined petroleum ether extracts were washed with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was chromatographed on 2.5 g of silica gel with 3.5% EtOAc/petroleum ether. The first 20 mL was discarded. The next 20 mL was concentrated in vacuo to give the ketone: 0.035 g (69%); R_f (10% EtoAc/hexane) 0.27; ^{1}H NMR 0.88 (s, 3 H), 1.3–3.35 (m, 12 H), 3.78 (s, 3 H), 5.05–5.95 (m, 3 H), 6.60–7.03 (m, 3 H); ^{13}C NMR 14.1 (q), 24.4 (t), 29.3 (t), 29.6 (t), 29.7 (t), 34.1 (t), 35.5 (d), 37.3 (s), 42.7 (d), 55.5 (q), 109.1 (q), 113.1 (t), 116.6 (d), 122.8 (d), 137.3 (d), 138.1 (s), 144.3 (s), 159.1 (s), 212.2 (s); IR 2920, 2890, 1720, 1610, 1540, 1520, 1485, 1240, 1180, 800 cm^{-1}; MS 284 (12), 161 (45), 160 (11), 98 (17); exact mass for $C_{19}H_{24}O_2$, calcd 284.1776, obsd 284.177.

A solution of the ketone (25 mg) in 3 mL of distilled o-dichlorobenzene was stirred under nitrogen for 8 h at 180 °C. The solvent was removed in vacuo, and the residue was chromatographed on 1 g of silica gel with 3% EtOAc/petroleum ether. The first 10 mL was discarded. Concentration of the next 15 mL gave the product **1** [0.015 g (41% from **12**)] as a thick viscous material. This was recrystallized from methanol to give white crystals: mp 163–165 °C (lit. mp 164–165 °C); R_f (10% EtOAc/hexane) 0.19; ^{1}H NMR 0.91 (s, 3 H), 1.4–2.6 (m, 14 H), 2.89 (br t, J = 4.3, 1 H), 3.78 (s, 3 H), 6.65–7.28 (m, 3 H); ^{13}C NMR 13.7 (q), 21.4 (t), 25.7 (t), 26.3 (t), 29.5 (t), 31.5 (t), 35.6 (t), 38.2 (d), 43.5 (d), 47.8 (s), 50.2 (d), 55.1 (q), 111.1 (d), 113.7 (d), 125.8 (d), 131.8 (s), 137.7 (s), 157.4 (s), 213.1 (s); IR 2900, 2820, 2790, 1720, 1630, 1610, 1580, 1520, 1470, 1430, 1250, 1230, 1030, 790 cm^{-1}; MS 284 (24), 199 (6), 186 (4), 160 (6), 32 (13), 28 (43), 19 (1000); exact mass for $C_{19}H_{24}O_2$, calcd 284.186, obsd 284.187. The proton and carbon NMR and IR spectra of the synthetic estrone methyl ether were found to be congruent with those of authentic (+)-estrone methyl ether: $[\alpha]^{27}_D$ = +146° (c 0.002 86, $CHCl_3$); $[\alpha]_D$ +160° ($CHCl_3$) for authentic material.

Acknowledgment. We thank the National Institutes of Health (Grant GM 32027), the National Science Foundation (Grant CHE 8306692), the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the University of Delaware Research Foundation for support of this work. D.F.T. thanks ICI Americas for an unrestricted research grant.

A General Approach to the Synthesis of C_8-Oxygenated Guaianolides†

James H. Rigby* and Jo Ann Zbur Wilson

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

Received July 17, 1986

Preparation of an advanced intermediate for the synthesis of several highly oxygenated members of the guaianolide family of sesquiterpene lactones is described. The key hydroxy lactone species is constructed from the readily available hydroazulene **3** via thiophenol-mediated cyclic ether opening followed by a convergent epoxidation–lactonization sequence.

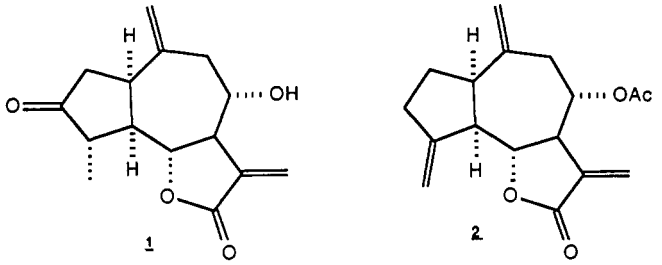
The guaianolides comprise one of the largest and most widely distributed groups of naturally occurring sesquiterpene lactones.[1] In addition to the simple members of this family, a number of species bearing an oxygen substituent at the C_8 position have been identified. Many of these compounds display significant biological activity as well as complex molecular architecture and as such are intriguing candidates for synthetic investigation. To date,

† Taken, in part, from the Ph.D. Thesis of J.Z.W., Wayne State University, 1986.

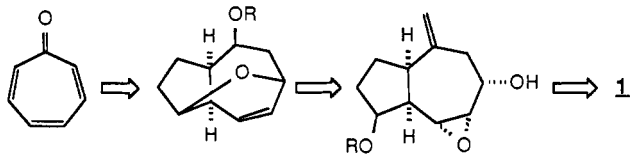
(1) Fischer, N. H.; Olivier, E. J.; Fischer, H. D. *Fortschr. Chem. Org. Naturst.* **1979**, *38*, 47.

0022-3263/87/1952-0034$01.50/0

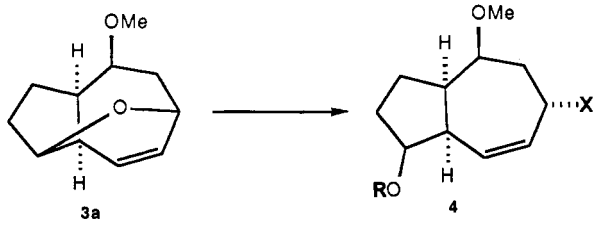
no members of this subgroup of the guaianolide family have yielded to total synthesis.[2] Although the disposition of the critical C_8 oxygen substituent can be of either the α or β orientation, compounds exhibiting the α configuration, as exemplified by grosshemin (1) and 8α-acetoxydehydrocostus lactone (2), appear to be the prevalent variety. The regio- and stereocontrolled introduction of this additional functionality coupled with the intrinsic difficulties associated with guaiane synthesis makes the C_8-oxygenated series particularly challenging targets.



An interesting approach into these molecules would entail the expanded exploitation of the functionality and stereochemistry available in the unique cycloadduct 3, which we have previously established as a useful and readily available precursor to the simpler (less oxygenated) guaianolides.[3] It was envisioned at the outset that the

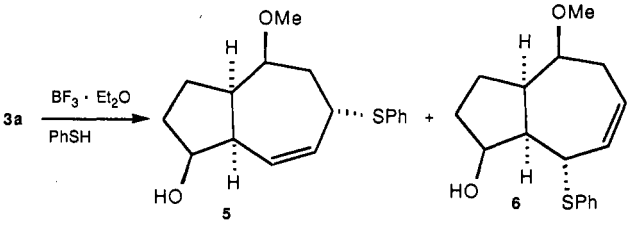


β-oriented carbon–oxygen bond at C_8 (guaianolide numbering) in cycloadduct **3a** could serve as an ideal template from which the *α-oriented* hydroxyl group found in the target molecules could be introduced. Selective displacement of the allylically activated oxygen substituent with inversion by an oxygen or "oxygen-equivalent" nucleophile would establish the desired functional group array directly as in **4**. Epoxidation and lactone formation



as achieved in our earlier synthesis would complete the strategy.[3] Clearly, simple oxygen nucleophiles would not be satisfactory reagents for the displacement process. It was anticipated that Lewis acid activation of the allylic ether would be a minimum requirement for effecting the desired transformation. Unfortunately, direct introduction of the C_8 oxygen under these conditions failed.[4]

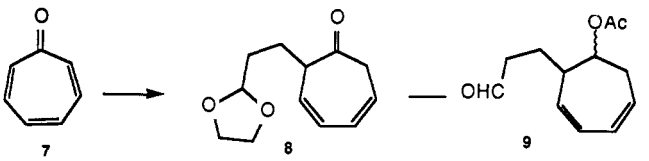
The use of an appropriate sulfur nucleophile in the displacement process presented some fascinating possibilities since several methods are currently available for converting carbon–sulfur bonds into carbon–oxygen bonds.[5] Furthermore, thiols are well-known to cleave a variety of ethers under the influence of Lewis acid.[6] Treatment of the hydroazulene **3a** with excess BF_3·Et_2O in thiophenol as solvent yielded two products in a ratio of nearly 1:1. These were tentatively assigned structures **5** and **6** on the basis of ^1H NMR data. Single-crystal X-ray



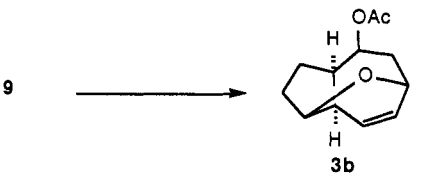
analysis of the highly crystalline isomer **6** confirmed our initial structural assignment in this case. Although it was reasonable to assume that compound **5** was the regioisomeric sulfide, the critical configuration at C_8 could not be established unambiguously by NMR arguments alone. All attempts to prepare a crystalline derivative of **5** were unsuccessful, and efforts to effect a chemical correlation of allylic sulfides **5** and **6** failed. Final verification of the structure assigned to **5** had to await a further development.

With a viable method in hand for the introduction of a useful heteroatom at an appropriate location in the hydroazulene system, our attention turned to the detailed logistics of the synthetic plan of attack. In view of the problems that heteroatom substitution at C_{10} presented in our previous guaianolide work,[3] in which transannular side reactions were common, early elaboration of the requisite exocyclic methylene group at that position became a key provision of the current strategy. The sulfur-mediated ring-opening technology should afford the maximum latitude in the means for achieving this task.

As in our previous work,[3] 1,8 addition of the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxolane to tropone **7** provided the key building block, dihydrotropone **8**. Reduction with sodium borohydride and protection of the resulting alcohol as the acetate followed by careful acetal hydrolysis gave aldehyde **9** in 76% overall yield.



Treatment of **9** with 2 equiv of BF_3·Et_2O at 0 °C gave the adduct **3b** in 86% yield as a 2:1 mixture of β- and α-C_{10} epimers. This preparative sequence proceeded without incident as in previous cases to provide convenient access to large quantities of the critical hydroazulenic species upon which the strategy rested.



The required C_{10} methylene was now easily incorporated by saponification of the acetate in **3b** followed by Collins

(2) For other approaches to guaianolides, see: (a) Devreese, A. A.; Demunck, M.; DeClerq, P. S.; Vandewalle, M. *Tetrahedron* **1983**, *19*, 3054. (b) Jacobi, P. A.; Selnick, H. G. *J. Am. Chem. Soc.* **1984**, *106*, 3041.

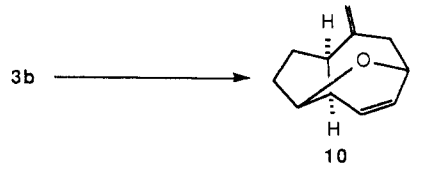
(3) Rigby, J. H.; Wilson, J. Z. *J. Am. Chem. Soc.* **1984**, *106*, 8217 and references cited therein.

(4) Ganem, B.; Small, V. R. *J. Org. Chem.* **1974**, *39*, 3728.

(5) (a) Via sulfoxide rearrangement: Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147. (b) Via Pummerer rearrangement: Block, E. *Reactions of Organosulfur Compounds*; Academic: New York, 1978.

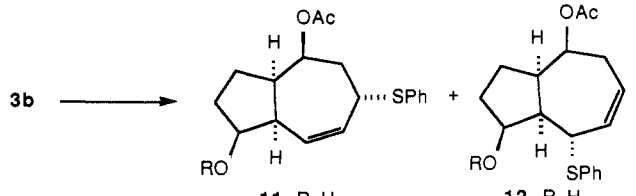
(6) (a) Nale, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1980**, *45*, 4275. (b) Node, M.; Nishide, K.; Sai, L. M.; Ichikawa, K.; Fuji, K.; Fujita, E. *Chem. Lett.* **1979**, 97. (c) Node, M.; Hori, H.; Fujita, E. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2237.

oxidation and methylenation with *P*-(lithiomethyl)-*N*,*N*-dimethyl-*P*-phenylphosphinothioic amide[7] to give compound **10**. Unfortunately, attempts to convert this material into the corresponding allylic sulfides by exposure to the thiophenol and $BF_3 \cdot Et_2O$ conditions were unsuccessful due, apparently, to competitive thiol addition to the exocyclic unsatuation. This transformation was not further investigated in any detail. Clearly, this olefin would have to be added subsequent to the cleavage of the cyclic ether.



10

At this point the C_{10} epimers of **3b** were separated, and the remaining operations described below were performed on the major β epimer to simplify subsequent product mixtures. Treatment of the major epimer of **3b** with $PhSH/BF_3 \cdot Et_2O$ again led to the formation of two isomeric allylic sulfides, **11** and **12**, in a 2:1 ratio in 62% combined yield. In this instance the major sulfide **11** proved to be crystalline and yielded to single-crystal X-ray analysis, which confirmed our initial structural assignment. To verify the structure assigned to the minor sulfide, it was converted into the methoxy derivative **6** whose structure had been previously determined by X-ray analysis. Similarly, the major acetoxy sulfide **11** was converted into the corresponding methyl derivative **5**, thus confirming the initial structural assignment for that compound as well.

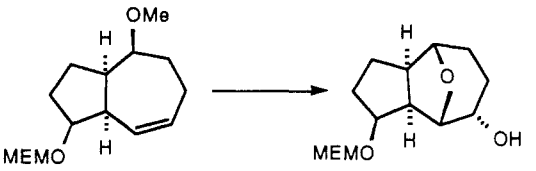


11, R=H
13, R=MEM
12, R=H
14, R=MEM

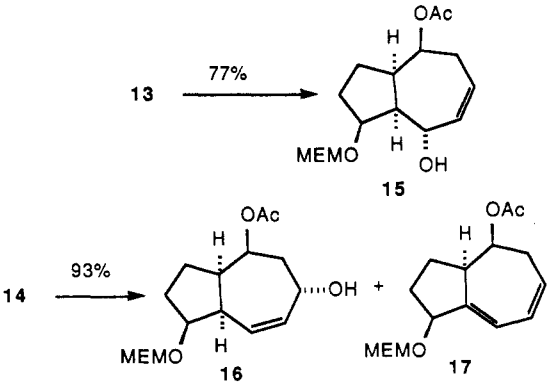
With the structures of key sulfides **11** and **12** firmly in hand, conversion into the corresponding MEM ethers **13** and **14**, respectively, followed in nearly quantitative yields.[8]

At this juncture in the synthesis, a problematic aspect of the newly developed method for allylic sulfide formation became manifest. Of the two allylic sulfides provided by the cyclic ether cleavage reaction, only the *minor* isomer can be converted into an allylic alcohol (via allylic sulfoxide rearrangement) with regiochemistry consistent with the initial synthetic design. If this novel reaction is to be employed in the synthetic scheme in a useful fashion, a way must be identified to utilize both regioisomeric sulfides. It was anticipated that the butyrolactone unit would again be fabricated by regioselective epoxide opening using the dianion of acetic acid as the source of the two-carbon side chain. The question became whether a way could be devised such that both regioisomeric epoxy alcohols would give rise to the same hydroxy lactone product. Observations made previously by a number of workers, in particular in the vernolepin series, suggested that the answer to the question posed above would be in the affirmative. Most pertinent to the situation at hand, Danishefsky reported that attack of dilithioacetate on cyclic *syn*-epoxy alcohols occurred preferentially at the epoxide carbon adjacent to the *syn*-hydroxyl group in several cases.[9] With this information and a ready supply of necessary starting materials, the possibility of achieving a *regioconvergent* synthesis, that is one in which two regioisomeric series merge into a single product at a particular stage in a synthesis, stimulated further investigation.

Scheme I



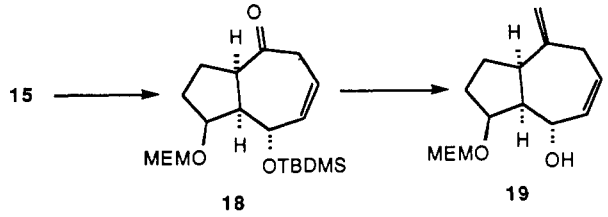
Persuant to these goals the isomeric allylic sulfides **13** and **14** were each exposed to *m*-chloroperoxybenzoic acid at −40 °C to provide the corresponding sulfoxides, which, without further purification, were subjected to the rearrangement conditions [$(CH_3O)_3P$/MeOH, 50 °C]. This process proceeded without incident in the case of allylic sulfide **13** to provide the allylically transposed alcohol **15** in 77% yield. In contrast, when the minor sulfide isomer underwent the same series of reactions two products were isolated in a ratio of 3.5:1. The major product proved to be the expected alcohol **16**, and the minor product was shown to be the diene **17**, which presumably arose from a sulfoxide elimination process. Attempts to suppress the formation of this product were unsuccessful. Elimination occurred even when the reaction was run at room temperature. It is tempting to suggest that the ratio of rearrangement product to elimination product reflects in some fashion the diastereomer ratio of the sulfoxides; however, this contention remains only speculative at this point since it was very difficult to determine this ratio by either spectroscopic or chromatographic means.

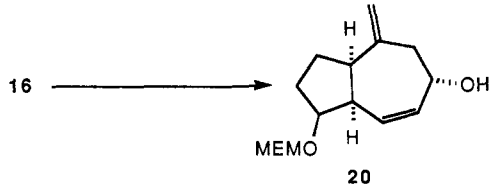


We then turned our attention to introducing the exocyclic methylene group required at the C_{10} position in the two allylic alcohols. As mentioned previously, early introduction of this group was deemed prudent in the face of the difficulties experienced at this juncture in our earlier guaianolide synthesis.[3] Epoxidation of an intermediate similar in nature to **16** invariably yielded substantial quantities of a product resulting from internal opening of the initially formed epoxide.[3,10] (See Scheme I.) The presence of an sp^2 center at C_{10} during the epoxidation step should preclude this type of side reaction. Furthermore, regioselective epoxidation of the double bond adjacent to the alcohol would be expected in this instance.

(7) Johnson, C. R.; Elliot, R. C. *J. Am. Chem. Soc.* **1982**, *104*, 7041.
(8) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.
(9) (a) Danishefsky, S.; Schuda, P. F.; Kitahara, T.; Etheredge, S. J. *J. Am. Chem. Soc.* **1979**, *99*, 6066. (b) Danishefsky, S.; Tsai, M. Y.; Kitahara, T. *J. Org. Chem.* **1977**, *42*, 394.
(10) This type of side reaction appears to be general for *cis*-hydroazulenes: Hudlicky, T.; Govendan, S. V.; Frazier, J. O. *J. Org. Chem.* **1985**, *50*, 4166.

Temporary protection of the free hydroxyl group at C_6 in compound **15** as the *tert*-butyldimethylsilyl ether (TBDMS) followed by saponification of the acetate and Collins oxidation provided ketone **18**. Attempts to methylenate this ketone using conventional Wittig methodology or "Johnson's" reagent[7] were unsuccessful due to the enhanced enolizability of the β,γ-unsaturated ketone. Excellent results, however, were realized when the reaction was performed with Lombardo's modification[11a] of technology developed by Oshima.[11b] This easily prepared reagent was reported to add to carbonyl groups with a minimum of concomitant enolization and in this case provided the requisite species in 99% purified yield. Fluoride-induced desilylation generated allylic alcohol **19** in 77% overall yield from alcohol **15**. A similar sequence starting from **16** gave the isomeric alcohol **20** with nearly equal efficiency.

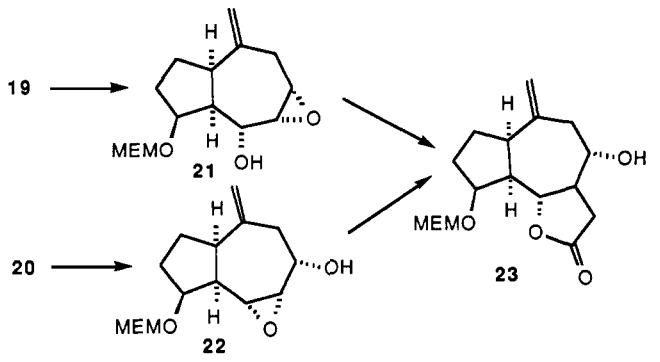




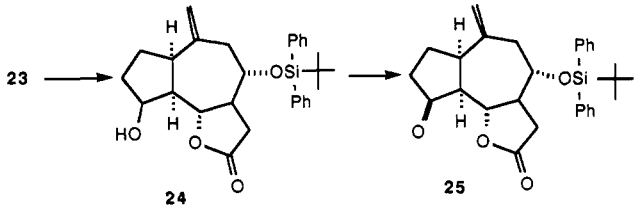
At this stage of the synthesis our concept of regioconvergency as applied to guaianolide synthesis is finally put to the test, pending successful regio- and stereoselective epoxidation of each allylic alcohol. The results are outlined in Scheme II. Directed epoxidation[12] of compound **19** with *tert*-butylhydroperoxide (TBHP) and $VO(acac)_2$ proceeded very slowly. Maximum yields of **21** required the use of anhydrous solutions of TBHP. In contrast, the minor alcohol **20** was converted without difficulty into the corresponding epoxide **22**. The stage was now set to test the proposition that both epoxides **21** and **22** could yield a single hydroxy lactone on exposure to dilithioacetate. Treatment of the C_8 hydroxy epoxide **22** with the dianion of acetic acid at 60 °C for several hours led to a single lactone in 76% yield which was assigned structure **23** on the basis of ^1H NMR data. The possibility that the product was the result of lactonization toward the C_8 oxygen was rejected on the basis of the coupling pattern exhibited by the proton attached to the carbon bearing the lactone oxygen. Furthermore, we were indeed gratified when the C_6 hydroxy epoxide **21** afforded a single lactone in 79% yield, which was shown to be identical, by all of the usual criteria, with compound **23**. None of the product resulting from attack at the C_8 position could be detected in the reaction mixture. Clearly, the directing effect of the syn hydroxy group observed in six-membered rings is operative in our substrate since molecular models indicate that the C_7 and C_8 positions in epoxide **21** are nearly equally accessible to an incoming nucleophile.

All that remained was the elaboration of the appropriate substitution pattern in the five-membered carbocycle and routine introduction of the exocyclic methylene on the butyrolactone portion of the molecule. To demonstrate the versatility of this strategy, our plan called for the initial synthesis of the relatively simple 8α-acetoxydehydrocostus lactone (**2**) and then proceeded onto the somewhat more intricate conversion of lactone **23** into grosshemin (**1**).

Scheme II



Prior to the introduction of the carbon at C_4, the C_8 hydroxyl group was masked as the reasonably robust *tert*-butyldiphenylsilyl (TBDPS)[13] group and the MEM ether was removed without incident with NaI/TMSCl, a method developed in our laboratory in conjunction with our early guaianolide work,[3,14] to give hydroxy lactone **24** in 95% overall yield. Careful oxidation of this alcohol with pyridinium dichromate (PDC) produced the extremely sensitive ketone **25**, which very readily eliminated the lactone moiety, even on attempted purification on silica gel. All efforts to methylenate the crude ketone were unsuccessful. Even Lombardo's reagent[11a] failed to provide more than a trace of the desired methylene compound.



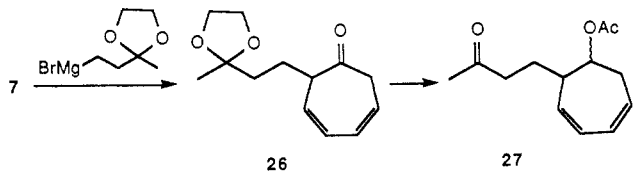
When a ketone is present at the C_4 position, base-induced elimination of the lactone moiety is a recurring problem in the guaianolide series. This is in stark contrast to the situation in the pseudoguaianolide family. In this case the five-membered ring and the seven-membered ring are "insulated" by a methyl group situated at the ring fusion.[15]

These results and observations prompted us to consider the introduction of the requisite C_4 carbon at an earlier stage in the synthesis, thus avoiding the risky manipulation of a ketone functionality at that position late in the synthesis. The elaboration of carbon substitution at this position in the guaiane skeleton is a persistent problem, and a general solution was sought. An attractive possibility could involve incorporating a methyl group at the terminus of the three-carbon side chain in the initial construction of the hydroazulene system. This approach would necessitate the cyclization of a methyl ketone onto the diene system of the dihydrotropone intermediate. While isolated examples have appeared in which ketones have been used as enophiles[16] and initiators in cation–olefin cyclizations,[17]

(11) (a) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293. (b) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2417.
(12) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63.
(13) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.
(14) Rigby, J. H.; Wilson, J. Z. *Tetrahedron Lett.* **1984**, *25*, 1429.
(15) For some synthetic approaches to the pseudoguaianolides, see: Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavec, W.; White, C. T. In *The Total Synthesis of Natural Products*; Apsimon, J. W., Ed.; Wiley: New York, 1982; Vol. 5.

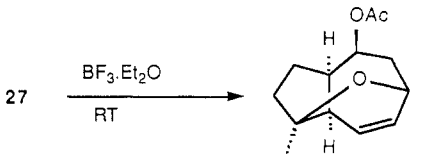
they had not been reported to participate as heterodienophiles in intramolecular "cycloaddition" reactions.

The methyl ketone adduct **27** was prepared in a fashion completely analogous to that employed for the corresponding aldehyde series. Slow addition of tropone to 2



26 27

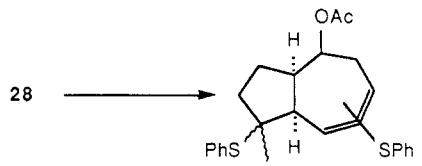
equiv of the Grignard reagent derived from 2-[(2-bromoethyl)-2-methyl]-1,3-dioxolane[18] led to dihydrotropone **26**, which was usually carried on without purification. Reduction of the cycloheptanone carbonyl group, protection of the resulting alcohol as the acetate, and mild ketal hydrolysis gave ketone **27** in good overall yield. Ketone **27** obligingly provided cycloadduct **28** as a single C_{10} ep-



28

imer in 73% yield on treatment with 2 equiv of BF_3·Et_2O at room temperature.[19] The unreacted minor α epimer of the starting material was recovered unchanged.[20] Attempts to induce the minor isomeric ketone to cyclize by prolonged exposure to the reaction conditions led only to decomposition of the starting material.

This efficient cyclization provided a relatively simple potential solution to the chronic problem of the introduction of a carbon at the C_4 position in the guaianolides. Unfortunately, efforts to cleave the allylic carbon–oxygen bond using our thiophenol/BF_3·Et_2O protocol did not give the expected sulfides in synthetically useful yields. Apparently, further reaction can occur under these conditions, presumably through the intermediacy of a tertiary carbocation when the C_4 position is substituted. A variety of Lewis acid catalysts and reaction conditions were examined in an attempt to attenuate the reactivity at C_4. Competitive substitution of the C_4 carbon–oxygen bond occurred in all cases examined in which reaction occurred.



These results, along with the inability to introduce the requisite exocyclic methylene unit through the intermediacy of the C_4 ketone, indicate that an alternate strategy must be developed. Work in this direction is under way and will be reported in due time.

Experimental Section

General Experimental Procedures. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on either a Perkin-Elmer 282 B or 237 B grating infrared spectrometer or on a Nicolet 20-DX Fourier transform infrared spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at either 60 MHz on a Varian T-60 spectrometer or at 300 MHz on a Nicolet NT-300 or QE-300 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as an internal standard. Multiplicities are abbreviated as follows: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants are reported in hertz (Hz). Carbon NMR were recorded on either a JEOL JNM-FX-60 or a Nicolet QE-300 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane as an internal standard. Mass spectra were obtained on either a Kratos MS-80RFA spectrometer or an AEI-MS-902 spectrometer. Microanalyses were performed by either Galbraith Laboratories, Inc., Knoxville, TN, or by Spang Microanalytical Laboratories, Eagle Harbor, MI. Analytical thin-layer chromatography (TLC) was routinely used to monitor reactions. Plates precoated with E. Merck silica gel 60 F_{254} of 0.25-mm thickness were used. Column chromatography was performed using Baker silica gel (60–200 mesh). Flash chromatography was performed according to the procedure of Still[21] using E. Merck silica gel 60 (230–400 mesh).

All reactions were run in flame-dried vessels under an atmosphere of dry nitrogen. Solvents were freshly distilled prior to use: tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl; dimethoxyethane (DME) was distilled from lithium aluminum hydride followed by distillation from sodium–benzophenone ketyl; acetonitrile was distilled from calcium hydride; *N,N*-dimethylformamide (DMF) was stirred with potassium hydroxide and then distilled from calcium oxide; methylene chloride was distilled from calcium hydride. Nomenclature for compounds in this section is based on the hydroazulene numbering system following the convention of *Chemical Abstracts*.

4-Acetoxy-1α,2,3,3aα,4,5,6α,8aα-octahydro-1,6-epoxyazulene (3b). To a stirred solution of 20 g (96 mmol) of aldehyde **9** in 500 mL of methylene chloride cooled to 0 °C was added freshly distilled boron trifluoride etherate complex (24 mL, 192 mmol). After 5 min the reaction was quenched with saturated aqueous sodium bicarbonate solution. The two-phase mixture was diluted with ether and washed with several portions of saturated aqueous sodium bicarbonate solution and then with brine. Drying of the organic layer followed by evaporation of the solvent under reduced pressure gave the cyclic ether **3b**, which was purified by column chromatography on 800 g of silica gel (1:3 ether/hexanes) to give 11.5 g of the β-C_{10} epimer and 5.7 g of the α epimer (86% combined yield).

β Epimer: mp 91–92 °C; R_f 0.57 (1:1 ether/hexanes); IR (CCl_4) ν 3053, 2936, 2856, 1735, 1465, 1438, 1372, 1242, 1170, 1058, 1030, 915.3 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.6–2.0 (m, 6 H), 2.0 (s, 3 H), 2.67 (m, 2 H), 3.93 (m, 1 H), 4.37 (m, 1 H), 4.74 (m, 1 H), 6.26 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.216, 21.705, 33.118, 33.582, 40.380, 42.031, 67.599, 71.472, 77.911, 128.470, 130.780, 170.376; mass spectrum, *m/e* (%) 208 (3), 166 (2), 148 (17), 130 (6), 119 (13), 104 (32), 91 (33), 81 (26), 43 (100); high-resolution mass spectrum for $C_{12}H_{16}O_2$, calcd 208.1099, found 208.1102. Anal. Calcd for $C_{12}H_{16}O_2$: C, 69.21; H, 7.74. Found: C, 69.16; H, 7.62.

α Epimer: R_f 0.53 (1:1 ether/hexanes); ^{1}H NMR ($CDCl_3$) δ 1.56 (m, 1 H), 1.75 (m, 2 H), 1.88–2.10 (m, 2 H), 2.18 (ddd, J = 2.2, 5.6, 16.2 Hz, 1 H), 1.98 (s, 3 H), 2.57 (m, 2 H), 3.95 (t, J = 3.4 Hz, 1 H), 4.35 (m, 1 H), 4.75 (dd, J = 0.8, 5.5 Hz, 1 H), 6.27 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.447, 26.636, 34.281, 36.288, 42.227, 43.666, 69.866, 73.547, 78.190, 129.463, 131.729, 170.341.

4-Methoxy-6-(thiophenoxy)-1α,2,3,3aα,4α,5,6b,8aα-octahydroazulen-1-ol (5) and 4-Methoxy-8-(thiophenoxy)-1α,2,3,3aα,4α,5,8β,8aα-octahydroazulen-1-ol (6). To a solution of 3.01 g (16.73 mmol) of cyclic ether **3a**[3] in 26 mL of freshly distilled thiophenol was added 8.2 mL (66.93 mmol) of freshly distilled boron trifluoride etherate complex. The reaction mixtue

(16) (a) Jackson, A. C.; Goldman, B. E.; Snider, B. B. *J. Org. Chem.* **1984**, *49*, 3988. (b) Anupitan, A. J.; Scovell, E. G.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans. 1* **1983**, 755. (c) Trost, B. M.; McDougal, P. G. *J. Am. Chem. Soc.* **1982**, *104*, 6110. (d) Wender, P. A.; Hubbs, J. C. *J. Org. Chem.* **1980**, *45*, 365.

(17) Thomas, A. F.; Ozainne, M *J. Chem. Soc., Chem. Commun.* **1977**, 120.

(18) Ponaras, A. A. *Tetrahedron Lett.* **1976**, 3105.

(19) For a preliminary account of this cyclization, see: Rigby, J. H.; Wilson, J. Z.; Senanayake, C. J. *Tetrahedron Lett.* **1986**, 3329.

(20) The identities of the major a nd minor epimers in the system were unambiguously established in earlier work in our laboratory; see ref 3.

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

was allowed to stir at room temperature for 1 h and then diluted with 300 mL of ether. The excess boron trifluoride etherate complex was then quenched by the careful addition of saturated aqueous sodium bicarbonate solution. The organic layer was separated and washed with several 200-mL portions of a saturated sodium bicarbonate solution followed by two 200-mL portions of a 5% aqueous sodium hydroxide solution and, finally, with brine. The organic layer was dried and the solvent evaporated under reduced pressure. The resulting oil was purified by flash chromatography on 150 g of silica gel (3:7 ether/hexanes) to give 1.45 g of the C_6 sulfide **6** and 1.07 g of the C_8 sulfide **5** (52% combined yield).

5: R_f 0.49 (1:1 ether/hexanes); IR (CCl_4) ν 3460, 2940, 2880, 2840, 1590, 1480, 1440, 1310, 1260, 1170, 1090, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64 (m, 4 H), 1.87 (m, 1 H), 2.33 (m, 1 H), 2.56 (m, 1 H), 2.72 (m, 1 H), 3.33 (s, 3 H), 3.38 (m, 1 H), 3.90 (m, 1 H), 4.00 (m, 1 H), 5.56 (m, 1 H), 5.80 (m, 1 H), 7.23 (m, 3 H), 7.40 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 15.269, 27.613, 34.306, 34.826, 43.727, 45.222, 49.380, 58.086, 75.760, 80.438, 127.152, 127.801, 129.909, 131.377, 132.220, 134.886; mass spectrum, *m/e* (%) 290 (1), 240 (1), 219 (4), 218 (28), 181 (13), 149 (33) 131 (64) 130 (22) 121 (14), 109 (62), 91 (73) 84 (100); high-resolution mass spectrum for $C_{17}H_{22}SO_2$, calcd 290.1340, found 290.1339.

6: mp 98–99 °C; R_f 0.51 (ether/hexanes); IR (CCl_4) ν 3460, 3080, 3030, 2960, 1590, 1480, 1440, 1170, 1080, 1040, 1020, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (m, 2 H), 1.50 (m, 1 H), 1.70 (m, 2 H), 1.93 (m, 1 H), 2.33 (m, 2 H), 2.65 (m, 1 H), 3.40 (s, 3 H), 3.43 (m, 1 H), 4.20 (br s, 1 H), 4.33 (m, 1 H), 5.35 (m, 1 H), 5.80 (m, 1 H), 7.20 (m, 3 H), 7.35 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 28.783, 31.382, 34.241, 42.558, 43.663, 52.694, 57.242, 73.876, 81.282, 125.852, 126.242, 128.711, 130.920, 134.16, 135.988; mass spectrum, m/e (%) 290 (7), 181 (19), 163 (13), 149 (47), 132 (10), 131 (100), 129 (11), 121 (12), 111 (25), 110 (26), 91 (58), 79 (36), 71 (60); high-resolution mass spectrum for $C_{17}H_{22}SO_2$, calcd 290.1340, found 290.1338. Anal. Calcd for $C_{17}H_{22}SO_2$: C, 70.31; H, 7.64; S, 11.04. Found: C, 70.35; H, 7.66; S, 11.10.

1-Acetoxy-2-(3-oxopropyl)-3,5-cycloheptadiene (9). To 70 g (0.33 mol) of 2-[2-(1,3-dioxolan-2-yl)ethyl]-3,5-cycloheptadien-1-ol[3] in 500 mL of methylene chloride cooled to 0 °C were added 37.7 mL (0.40 mol) of acetic anhydride, 55.6 mL (0.40 mol) of triethylamine, and 2.0 g (16.5 mmol) of 4-(*N,N*-dimethylamino)pyridine. After 30 min, the cooling bath was removed, and stirring was continued at room temperature for an additional 30 min. The reaction mixture was then poured into 1 L of ether and washed successively with two 600-mL portions of a saturated aqueous sodium bicarbonate solution followed by one 600-mL portion of brine. The organic layer was dried and the solvent removed under reduced pressure. Column chromatography of the resulting residue on 1.5 kg of silica gel (1:4 ether/hexanes) yielded 84 g (99%) of the acetoxy acetal: R_f 0.52 (1:1 ether/hexanes); IR (CCl_4) ν 3025, 2979, 2956, 2878, 1716, 1438, 1370, 1239, 1142, 1123, 1023 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4–1.8 (m, 4 H), 2.03 (s, 3 H), 2.44–2.65 (m, 3 H), 3.80–4.00 (m, 4 H), 4.85 (m, 1 H), 5.18 (m, 1 H), 5.58–5.98 (m, 4 H); mass spectrum, *m/e* (%) 252 (0.5), 210 (2.7), 192 (5.5), 148 (5.6), 130 (19.4), 104 (80.5), 91 (50.3), 73 (100); high-resolution mass spectrum for $C_{14}H_{20}O_4$, calcd 252.1361, found 252.1357. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.51; H, 8.06.

To 78 g (0.31 mol) of 1-acetoxy-2-[2-(1,3-dioxolan-2-yl)-ethyl]-3,5-cycloheptadiene were added 156 mL of a 5% aqueous solution of trifluoroacetic acid and enough acetone to make the reaction mixture homogeneous. After the mixture was allowed to stir at room temperature for 5 days, the acetone was removed under reduced pressure and the two-phase mixture was diluted with 1 L of ether. The organic layer was separated and washed with two 600-mL portions of a saturated aqueous sodium bicarbonate solution and then with brine. Drying and evaporation of the solvent gave the crude aldehyde, which was purified by column chromatography on 1.5 kg of silica gel (3:7 ether/hexanes). This gave 58 g (90%) of the pure aldehyde **9**: R_f 0.52 (1:1 ether/hexanes); IR (CCl_4) ν 3040, 2960, 2900, 2820, 2720, 1740, 1435, 1415, 1370, 1235, 1135, 1050, 1015, 970 cm^{-1}; ^1H NMR (CCl_4) δ 1.6–2.4 (m, 3 H), 2.2 (s, 3 H), 2.5–2.8 (m, 4 H), 5.3 (m, 1 H), 5.8–6.1 (m, 4 H); mass spectrum, *m/e* (%) (no M^+), 192 (1), 164 (2), 162 (2), 136 (3), 130 (6), 104 (27), 99 (14), 91 (23), 79 (11), 73 (44), 43 (100).

4-Methylene-1α,2,3,3aα,4,5,6α,8aα-octahydro-1,6-epoxyazulene (10). To a stirred solution of 3.70 g (17.8 mmol) of acetate **3b** in 18 mL of anhydrous methanol was added 4.90 g (35.6 mmol) of anhydrous potassium carbonate. The reaction mixture was allowed to stir for 4 h, and then the methanol was removed under reduced pressure. The residue was diluted with 300 mL of ether and washed with water followed by brine. The ether layer was dried over sodium sulfate and the solvent evaporated in vacuo to give the crude alcohol which was purified by flash chromatography on 150 g of silica gel (ether as eluent). This afforded 2.60 g (88%) of pure 1α,2,3,3aα,4,5,6α,8aα-octahydro-1,6-epoxyazulen-4-ol: R_f 0.31 (ether); IR (CCl_4) ν 3620, 3400, 3060, 2940, 1460, 1440, 1380, 1170, 1045, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04–2.85 (m, 8 H), 3.44–3.75 (m, 1 H), 3.86 (m, 1 H), 4.29 (m, 1 H), 6.12 (m, 2 H); mass spectrum, *m/e* (%) 166 (38), 149 (72), 120 (40), 105 (60), 92 (100), 80 (84), 68 (90). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.27; H, 8.49. Found: C, 72.13; H, 8.47.

To an ice-cold solution of 6.40 mL (78.4 mmol) of pyridine in 70 mL of methylene chloride was added 3.90 g (39.2 mmol) of chromium trioxide. The ice bath was removed, and the reaction mixture was allowed to stir at room temperature for 1 h after which time 1.30 g (7.83 mmol) of 1α,2,3,3aα,4,5,6α,8aα-octahydro-1,6-epoxyazulen-4-ol in 10 mL of methylene chloride was added. After 5 h, the reaction mixture was diluted with ether and suction filtered through a pad of silica gel. The filtrate was washed quickly with a 5% aqueous HCl solution followed by a saturated aqueous sodium bicarbonate solution and, finally, with brine. The ether layer was dried over sodium sulfate, and the solvent was removed under reduced pressure. Flash chromatography of the resulting product on 100 g of silica gel (3:1 ether/hexanes) afforded 1.10 g (86%) of the pure 1α,2,3,3aα,4,5,6α,8aα-octahydroazulen-4-one: R_f 0.71 (ether); IR (CCl_4) ν 3054, 2946, 1705, 1462, 1440, 1406, 1380, 1318, 1237, 1165, 1047, 945.2 cm^{-1}; ^1H NMR ($CDCl_3$ δ 1.80–2.20 (m, 4 H), 2.40 (ddd, J = 2.2, 3.5, 16.5 Hz, 1 H), 2.81 (m, 1 H), 3.05 (dd, J = 3.0, 16.7 Hz, 1 H), 3.13 (m, 1 H), 4.15 (t, J = 3.8 Hz, 1 H), 4.54 (m, 1 H), 6.39 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 26.286, 34.082, 42.399, 48.106, 57.633, 66.418, 78.545, 129.700, 133.938, 210.862; mass spectrum, *m/e* (%) 164 (32), 147 (2), 136 (7), 135 (3), 122 (8), 121 (10), 108 (15), 107 (27), 95 (11), 94 (23), 93 (26), 91 (31), 80 (30), 77 (34), 67 (100); high-resolution mass spectrum for $C_{10}H_{12}O_2$, calcd 164.0837, found 164.0841.

To a solution of 513 mg (2.58 mmol) of *N,N,P*-trimethyl-*P*-phenylphosphinothioic amide in 8 mL of THF, cooled to −78 °C, was added 995 μL (2.58 mmol) of *n*-butyllithium (2.6 M in hexanes). The reaction mixture was allowed to stir at −78 °C for 30 min after which time the 1α,2,3,3aα,4,5,6α,8aα-octahydroazulen-4-one (424 mg, 2.58 mmol) in 2 mL of THF was added. The reaction mixture was stirred for an additional 30 min and then warmed to 0 °C at which time 5 mL of a saturated aqueous ammonium chloride solution was added. The two-phase mixture was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried, and the solvent was evaporated under reduced pressure. The remaining residue was taken up in 5 mL of dry acetone. Pyridine (277 μL, 3.43 mmol) and methyl iodide (164 μL, 2.58 mmol) were added, and the reaction mixture was allowed to stir at room temperature for 18 h during which time a precipitate formed. The precipitate was filtered off and the filtrate evaporated under reduced pressure to give the crude product. Flash chromatography on 40 g of silica gel (1:6 ether/hexanes) afforded 301 mg (72%) of pure olefin **10**: R_f 0.80 (1:1 ether/hexanes); IR (CCl_4) ν 3073, 3053, 2931, 2903, 1638, 1549, 1458, 1439, 1422, 1384, 1250, 1216, 1200, 1167, 1045, 1006, 978.0, 953.9 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67–1.83 (m, 2 H), 1.92 (m, 1 H), 2.02 (m, 1 H), 2.26 (ddd, J = 1.5, 4.58 15.6 Hz, 1 H), 2.63 (m, 2 H), 3.02 (m, 1 H), 3.99 (t, J = 4.1 Hz, 1 H), 4.41 (m, 1 H), 4.55 (t, J = 2.3 Hz, 1 H), 4.69 (t, J = 2.3 Hz, 1 H), 6.23 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 27.864, 34.448, 40.064, 43.987, 49.813, 70.202, 78.201, 112.370, 129.389, 131.452, 148.567.

4-Acetoxy-6-(thiophenoxy)-1α,2,3,3aα,4α,5,6β,8aα-octahydroazulen-1-ol (11) and 4-Acetoxy-8-(thiophenoxy)-1α,2,3,3aα,4α,5,8β,8aα-octahydroazulen-1-ol (12). Cyclic ether **3b** (13.8 g, 66.35 mmol) was dissolved in 100 mL of freshly distilled thiophenol, and 24.5 mL (199 mmol) of freshly distilled boron trifluoride etherate complex was added. The reaction mixture was allowed to stir at room temperature for 8 h and then was poured into 1 L of ether. The excess boron trifluoride etherate

was then quenched by the careful addition of saturated aqueous sodium bicarbonate solution. The organic layer was separated and washed with several portions of saturated aqueous sodium bicarbonate solution followed by two 500-mL portions of a 5% aqueous sodium hydroxide solution and, finally, with brine. The ether layer was dried and the solvent evaporated under reduced pressure. Flash chromatography of the crude product on 400 g of silica gel (3:7 ether/hexanes) afforded 3.4 g of sulfide **12** and 9.5 g of sulfide **11** (62% combined yield).

12: R_f 0.40 (1:1 ether/hexanes); IR (CCl_4) ν 3558, 3074, 3025, 2959, 1740, 1651, 1585, 1477, 1440, 1374, 1236, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5–1.9 (m, 4 H), 2.11 (s, 3 H), 2.40–2.55 (m, 4 H), 2.56–2.70 (m, 1 H), 4.31 (dd, J = 4.0, 8.5 Hz), 4.50 (m, 1 H), 5.31 (m, 1 H), 5.44 (m, 1 H), 5.89 (m, 1 H), 7.20–7.40 (m, 5 H); ^{13}C NMR δ 21.445, 27.876, 33.672, 33.946, 42.526, 44.413, 51.101, 73.013, 74.900, 126.675, 128.975, 130.819, 132.780, 170.338; mass spectrum, m/e (%) 318 (23), 259 (41), 241 (12), 209 (82), 149 (100), 131 (95), 105 (40), 91 (43); high-resolution mass spectrum for $C_{18}H_{22}SO_3$, calcd 318.1289, found 318.1294. Anal. Calcd for $C_{18}H_{22}SO_3$: C, 67.89; H, 6.97. Found: C, 67.80; H, 7.17.

11: mp 118–119 °C; R_f 0.24 (1:1 ether/hexanes); IR (CCl_4) ν 3636, 3561, 3063, 3022, 2961, 1740, 1585, 1481, 1439, 1368, 1240, 1025, 963, 945 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6–1.9 (m, 5 H), 2.06 (s, 3 H), 2.10 (m, 1 H), 2.60 (m, 2 H), 2.89 (m, 1 H), 3.90 (m, 1 H), 5.33 (ddd, J = 1.6, 3.8, 9.0 Hz, 1 H), 5.67 (ddd, J = 1.6, 4.8, 12.4 Hz, 1 H), 5.91 (ddd, J = 2.1, 4.4, 12.4 Hz, 1 H), 7.2–7.5 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 21.039, 25.280, 32.841, 33.841, 43.395, 44.887, 46.892, 72.515, 75.371, 127.714, 127.392, 128.922, 131.615, 132.569, 169.880; mass spectrum, m/e (%) 318 (0.8), 258 (5), 209 (5), 167 (6), 149 (58), 131 (100), 110 (49), 105 (45), 91 (99); high-resolution mass spectrum for $C_{18}H_{22}SO_3$, calcd 318.1289, found 318.1287. Anal. Calcd for $C_18H_{22}SO_3$: C, 67.89; H, 6.97; S, 10.07. Found: C, 67.52; H, 7.02; S, 10.25.

4-Acetoxy-1-[(2-methoxyethoxy)methoxy]-6-(thiophenoxy)-1α,2,3,3aα,4α,5,6β,8aα-octahydroazulene (13). To 8.6 g (27 mmol) of alcohol **11** in 30 mL of methylene chloride were added 5.6 mL (32.5 mmol) of diisopropylethylamine and 3.7 mL (32.5 mmol) of (2-methoxyethoxy)methyl chloride. The reaction mixture was stirred at room temperature for 12 h and then poured into 500 mL of ether. The ether mixture was washed quickly with a 300-mL portion of a 5% aqueous HCl solution, 300 mL of saturated aqueous sodium bicarbonate solution, and then brine. The ether solution was dried and the solvent removed in vacuo to leave the crude MEM ether, which was purified by flash chromatography on 300 g of silica gel (1:1 ether/hexanes). This gave 10.9 g (99%) of the pure MEM ether **13**: R_f 0.83 (ether); IR (CCl_4) ν 3025, 2942, 2885, 2818, 1738, 1586, 1467, 1440, 1367, 1241, 1048, 1025, 908 cm^{-1}; ^1H NMR δ 1.5–1.9 (m, 5 H), 1.99 (s, 3 H), 2.27 (m, 1 H), 2.45 (m, 1 H), 2.90 (m, 1 H), 3.39 (s, 3 H), 3.55 (m, 2 H), 3.68 (m, 2 H), 3.96 (m, 1 H), 4.08 (m, 1 H), 4.71 (m, 2 H), 5.76 (ddd, J = 2.9, 4.7, 10.8 Hz, 1 H), 5.80 (dd, J = 12.0, 3.2 Hz, 1 H), 5.93 (ddd, J = 12.0, 6.8, 2.5 Hz, 1 H), 7.30 (m, 3 H), 7.50 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.318, 21.140, 28.159, 31.770, 41.981, 45.056, 58.985, 67.004, 71.312, 71.743, 79.564, 94.766, 127.387, 128.859, 129.227, 130.288, 132.959, 134.815, 169.899; mass spectrum, m/e (%) (no M^+) 347 (3), 331 (19), 271 (37), 257 (13), 237 (8), 221 (6), 191 (17), 179 (36), 161 (28), 149 (62), 133 (25), 131 (100), 89 (99).

4-Acetoxy-1-[(2-methoxyethoxy)methoxy]-8-(thiophenoxy)-1α,2,3,3aα,4α,5,8β,8aα-octahydroazulene (14). To 3.3 g (10.38 mmol) of alcohol **12** in 30 mL of methylene chloride were added 2.2 mL (12.45 mmol) of diisopropylethylamine and 1.4 mL (12.45 mmol) of (2-methoxyethoxy)methyl chloride. The reaction mixture was stirred at room temperature for 12 h and then poured into 200 mL of ether. The ether mixture was washed quickly with 150 mL of a 5% aqueous HCl solution, 150 mL of saturated aqueous sodium bicarbonate solution, and then brine. The ether solution was dried and evaporated under reduced pressure to give the crude MEM ether. Flash chromatography on 150 g of silica gel (1:2 ether/hexane) afforded 4.1 g (97%) of pure **14**: R_f 0.40 (1:2 ether/hexanes); IR (CCl_4) ν 3078, 3024, 2935, 2888, 2818, 1737, 1653, 1586, 1481, 1439, 1363, 1242, 1228, 1104, 1041, 908.5 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (m, 1 H), 1.80 (m, 3 H), 2.09 (s, 3 H), 2.50 (m, 4 H), 3.35 (s, 3 H), 2.45 (2 H), 2.53 (m, 2 H), 4.19 (m, 1 H), 4.61 (m, 1 H), 4.70 (m, 2 H), 5.40 (m, 2 H), 5.84 (ddt, J = 12.0, 4.2, 2.1 Hz, 1 H), 7.20–7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 21.447, 27.663, 31.242, 34.839, 42.216, 44.006, 50.759, 58.927, 66.914, 71.730, 72.547, 80.934, 95.218, 126.051, 126.118, 128.811, 130.274, 132.528, 136.168, 170.769; mass spectrum, m/e (%) (no M^+) 347 (8), 332 (13), 331 (57), 271 (26), 221 (12), 191 (14), 179 (42), 161 (25), 149 (67), 133 (20), 132 (14), 131 (91), 123 (30), 89 (100).

4-Acetoxy-1-[(2-methoxyethoxy)methoxy]-1α,2,3,3aα,-4α,5,8β,8aα-octahydroazulen-8-ol (15). To a solution of 8.5 g (20.9 mmol) of sulfide **13** in 200 mL of methylene chloride cooled to −40 °C was added 3.0 g (20.9 mmol) of 85% m-chloroperoxybenzoic acid in small portions. The reaction mixture was monitored closely by TLC, and when there was no evidence of starting material remaining, the reaction mixture was diluted with 300 mL of chloroform. The chloroform mixture was washed with 200 mL of a saturated aqueous sodium bicarbonate solution, 200 mL of a 5% aqueous sodium hydroxide solution, and finally brine. Drying of the organic layer followed by evaporation of the solvent gave the crude sulfoxide, which was then dissolved in 200 mL of absolute methanol. Trimethyl phosphite (25 mL, 209 mmol) was added, and the methanol solution was warmed to 50 °C. After 12 h, the methanol was removed under reduced pressure and the residue taken up in 500 mL of ethyl acetate. The ethyl acetate solution was washed with 300 mL of a saturated aqueous sodium bicarbonate solution followed by brine. Drying over anhydrous sodium sulfate followed by evaporation of the solvent gave the allylic alcohol **15**, which was purified by flash chromatography on 200 g of silica gel (ether as eluent) to give 5.06 g (77% from sulfide **13**) of pure allylic alcohol **15**: R_f 0.45 (ether); IR (CCl_4) ν 3515, 2942, 2891, 1737, 1368, 1363, 1246, 1234, 1136, 1119, 1104, 1043, 978 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6 (m, 1 H), 1.8 (m, 3 H), 2.05 (s, 3 H), 2.30 (m, 2 H), 2.45 (m, 1 H), 2.55 (m, 1 H), 3.40 (s, 3 H), 3.59 (m, 2 H), 3.65 (m, 1 H), 3.80 (m, 2 H), 4.24 (m, 1 H), 4.75 (m, 2 H), 5.01 (m, 1 H), 5.12 (m, 1 H), 5.37 (m, 1 H), 5.72 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.343, 26.366, 29.982, 33.319, 41.557, 53.226, 58.966, 66.320, 67.400, 71.694, 72.170, 80.839, 94.633, 122.160, 136.354, 170.708; mass spectrum, m/e (%) (no M^+) 238 (2), 225 (1), 179 (3), 177 (17), 165 (8), 148 (20), 147 (13), 120 (11), 91 (15), 89 (32), 79, (14), 59 (100). Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.33. Found: C, 61.21; H, 8.30.

4-Acetoxy-1-[(2-methoxyethoxy)methoxy]-1α,2,3,3aα,-4α,5,6β,8aα-octahydroazulen-6-ol (16). A solution of 3.0 g (7.39 mmol) of sulfide **14** in 70 mL of methylene chloride was cooled to −40 °C, and m-chloroperoxybenzoic acid (1.59 g, 7.39 mmol) was added in small portions. The reaction was monitored closely by TLC, and when the starting material was consumed, the reaction mixture was diluted with 100 mL of chloroform. The chloroform mixture was washed with 75 mL of a saturated aqueous sodium bicarbonate solution, 75 mL of a 5% aqueous sodium hydroxide solution, and finally brine. The organic layer was dried and evaporated under reduced pressure. The crude sulfoxide thus obtained was dissolved in 70 mL of anhydrous methanol. Trimethyl phosphite (8.7 mL, 73.90 mmol) was added, and the reaction mixture was warmed to 55 °C. After 16 h the methanol was evaporated under reduced pressure. The residue was taken up in 200 mL of ethyl acetate. This solution was washed with 150 mL of a saturated aqueous sodium bicarbonate solution followed by brine. The organic layer was dried over anhydrous sodium sulfate and then evaporated. The resulting oil was flash chromatographed on 85 g of silica gel (4:1 ether/hexanes) to give 1.66 g (72% from sulfide) of the allylic alcohol **16** along with 460 mg (21% from sulfide) of diene **17**.

16: R_f 0.35 (ether); IR (CCl_4) ν 3623, 3498, 2944, 2887, 1735, 1450, 1367, 1243, 1046, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) 1.6–1.9 (m, 5 H), 2.03 (s, 3 H), 2.40 (ddd, J = 3.5, 10.3, 13.9, Hz, 1 H), 2.52 (br s, 1 H), 2.60 (m, 1 H), 2.88 (m, 1 H), 3.39 (s, 3 H), 3.55 (m, 2 H), 3.67 (m, 2 H), 4.08 (dt, J = 5.2, 5.3 Hz, 1 H), 4.38 (dt J = 5.0, 3.9 Hz, 1 H), 4.70 (m, 2 H), 5.37 (ddd, J = 2.2, 4.9, 10.1 Hz, 1 H), 5.70 (dd, J = 5.1, 12.4 Hz, 1 H), 5.84 (dd, J = 4.9, 12.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.200, 22.436, 29.690, 35.218, 42.437, 43.402, 58.938, 66.126, 66.824, 70.461, 71.692, 79.842, 94.541, 127.667, 132.975, 170.701; mass spectrum, m/e (%) (no M^+) 179 (1), 178 (1), 166 (2), 165 (3), 149 (2), 148 (6), 130 (26), 104 (48), 92 (14), 89 (48), 59 (100). Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.33. Found: C, 60.41; H, 8.61.

17: R_f 0.43 (1:1 ether/hexanes); IR (CCl_4) ν 3019, 2964, 2934, 2887, 2817, 1736, 1455, 1438, 1417, 1374, 1366, 1241, 1225, 1237, 1106, 1037, 982.8 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68–1.95 (m, 4 H),

1.99 (s, 3 H), 2.57 (m, 2 H), 2.79 (m, 1 H), 3.41 (s, 3 H), 3.58 (m, 2 H), 3.67 (m, 1 H), 3.80 (m, 1 H), 4.45 (m, 1 H), 4.70–5.00 (m, 2 H), 5.36 (m, 1 H), 5.69 (m, 1 H), 5.95 (m, 1 H), 6.06 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.134, 27.645, 32.775, 36.008, 46.190, 58.959, 66.695, 71.729, 72.709, 78.607, 91.998, 122.363, 125.380, 129.531, 143.375, 171.038; mass spectrum, m/e (%) (no M^+) 192 (2), 191 (13), 161 (4), 160 (4), 148 (9), 147 (9), 132 (16), 131 (100), 130 (76), 91 (21), 89 (77), 59 (90).

8-[(*tert*-Butyldimethylsilyl)oxy]-1-[(2-methoxyethoxy)methoxy]-1α,2,3,3aα,8β,8aα-hexahydroazulen-4(5*H*)-one (18). To a stirred solution of 3.12 g (9.94 mmol) of alcohol **15** in 15 mL of freshly distilled DMF was added 1.01 g (14.9 mmol) of *tert*-butyldimethylsilyl chloride. The reaction mixture was stirred at room temperature for 16 h and then washed quickly with 100 mL of a 10% aqueous HCl solution, 200 mL of a saturated aqueous sodium bicarbonate solution, and then brine. The organic layer was dried and the solvent evaporated to leave the crude silyl ether, which was purified by flash chromatography on 170 g of silica gel (1:1 ether/hexanes). This afforded 4.3 g (100%) of the pure 4-acetoxy-8-[(*tert*-butyldimethylsilyl)oxy]-1-[(2-methoxyethoxy)methoxy]-1α,2,3,3aα,4α,5,8β,8aα-octahydroazulene: R_f 0.58 (1:1 ether/hexanes); IR (CCl_4) ν 3027, 2953, 2929, 2888, 2858, 1738, 1472, 1442, 1423, 1370, 1362, 1246, 1233, 1181, 1174, 1106, 1069, 1043 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.047 (s, 3 H), 0.087 (s, 3 H), 0.905 (s, 9 H), 1.35 (m, 1 H), 1.68–1.84 (m, 2 H), 2.02 (m, 1 H), 2.08 (s, 3 H), 2.22–2.50 (m, 4 H), 3.39 (s, 3 H), 3.53 (m, 3 H), 3.78 (m, 1 H), 4.01 (t, J = 3.1 Hz, 1 H), 4.78 (s, 2 H), 5.04 (m, 1 H), 5.28 (m, 2 H), 5.66 (ddt, J = 12.4, 2.7, 2.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ −4.931, −4.024, 17.956, 21.528, 25.586, 25.908, 27.962, 31.955, 35.317, 40.772, 55.374, 58.954, 66.942, 67.204, 71.727, 72.601, 82.426, 96.845, 122.337, 136.458, 170.874; mass spectrum, m/e (%) (no M^+) 370 (1), 369 (4), 353 (4.1), 323 (8), 294 (9), 293 (39), 279 (10), 263 (23), 223 (19), 179 (15), 161 (20), 149 (23), 133 (56), 131 (78), 117 (13), 89 (100), 59 (57).

To a stirred solution of 4-acetoxy-8-[(*tert*-butyldimethylsilyl)oxy]-1-[(2-methoxyethoxy)methoxy]-1α,2,3,3aα,4α,5,8β,-8aα-octahydroazulene (4.4 g, 10.23 mmol) in 50 mL of absolute methanol was added 5.6 g (40.93 mmol) of anhydrous potassium carbonate. The reaction mixture was stirred at room temperature for 12 h after which time the methanol was evaporated under reduced pressure. The resulting residues was taken up in 300 mL of ether and washed with water followed by brine. Drying, followed by evaporation of the ether, afforded the crude alcohol, which was purified by flash chromatography on 120 g of silica gel (1:1 ether/hexanes). The 8-[(*tert*-butyldimethylsilyl)oxy]-1-[(2-methoxyethoxy)methoxy]-1α,2,3,3aα,4α,5,8β,8aα-octahydroazulen-4-ol (3.7 g) was obtained in 93% yield: R_f 0.37 (1:1 ether/hexanes); IR (CCl_4) ν 3478, 2957, 2930, 2890, 2858, 1473, 1462, 1418, 1363, 1256, 1109, 1073, 1046, 1025, 901.8, 873.8 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.033 (s, 3 H), 0.070 (s, 3 H), 0.892 (s, 9 H), 1.40 (m, 1 H), 1.76 (m, 2 H), 2.00–2.50 (m, 4 H), 3.39 (s, 3 H), 3.54–3.66 (m, 3 H), 3.83–3.93 (m, 2 H), 3.99 (br s, 1 H), 4.10 (t, J = 2.7 Hz, 1 H), 4.86 (s, 2 H), 4.98 (m, 1 H), 5.30 (m, 1 H), 5.58 (ddt, J = 1.8, 2.4, 12.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ −4.892, −4.042, 17.875, 25.824, 28.636, 31.391, 37.733, 40.632, 56.194, 58.977, 66.856, 67.848, 71.338, 71.602, 51.923, 96.122, 123.795, 135.492; mass spectrum, m/e (%) (no M^+) 311 (1), 297 (4), 293 (7), 279 (6), 263 (9), 253 (7), 235 (4), 224 (6), 223 (31), 180 (14), 179 (100), 149 (38), 133 (40), 131 (46), 89 (99), 75 (24), 73 (20), 59 (85).

To an ice-cold solution of 7.5 mL (92.8 mmol) of pyridine in 200 mL of methylene chloride was added 4.6 g (46.4 mmol) of chromium trioxide. The ice bath was removed, and the reaction mixture was stirred at room temperature for 45 min after which time the 8-[(*tert*-butyldimethylsilyl)oxy]-1-[(2-methoxyethoxy)methoxy]-1α,2,3,3aα,4α,5,8β,8aα-octahydroazulen-4-ol in 25 mL of methylene chloride was added. After 16 h the contents of the reaction flask were diluted with 300 mL of ether, and the resulting solution was suction filtered through a pad of silica gel. The filtrate was quickly washed with 200 mL of a 5% aqueous HCl solution to remove the pyridine, 300 mL of a saturated aqueous sodium bicarbonate solution, and finally brine. The ether layer was dried and evaporated under reduced pressure. The crude ketone was purified by flash chromatography on 100 g of silica gel (3:7 ether/hexanes) to give 3.0 g (84%) of pure **18**: R_f 0.60 (1:1 ether/hexanes); IR (CCl_4) ν 2954, 2930, 2987, 2859, 1711, 1551, 1472, 1463, 1390, 1361, 1253, 1095, 1047, 873.5, 838.1 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 6 H), 0.0860 (s, 9 H), 1.40–1.63 (m, 2 H), 2.24 (m, 1 H), 2.46–2.66 (m, 2 H), 2.90 (ddd, J = 0.3, 7.8, 20.0 Hz, 1 H), 3.00 (m, 1 H), 3.15 (m, 1 H), 3.39 (s, 3 H), 3.54 (m, 3 H), 3.96 (m, 2 H), 4.63 (m, 1 H), 4.70 (m, 2 H), 5.55 (dddd, J = 2.4, 3.2, 7.8, 10.9 Hz, 1 H), 5.91 (ddd, J = 3.0, 4.7, 10.7 Hz, 1 H); ^{13}C NMR δ −5.047, −4.357, 17.871, 21.517, 25.693, 31.695, 43.750, 49.510, 58.757, 58.911, 66.922, 67.068, 71.794, 80.573, 95.831, 119.844, 139.800, 209.363; mass spectrum, m/e (%) (no M^+) 310 (2), 309 (9), 295 (3), 280 (7), 279 (30), 251 (5), 223 (3), 221 (5), 147 (8), 133 (36), 89 (100), 75 (17), 73 (18), 59 (96).

Preparation of Lombardo's Reagent.[11a] To a stirred suspension of zinc dust (14.4 g, 220 mmol) and methylene bromide (5.0 mL, 71.0 mmol) in 125 mL of freshly distilled THF, cooled to −40 °C, was added 5.75 mL of $TiCl_4$ slowly via syringe. The reaction mixture was allowed to warm to 0 °C and maintained with stirring at that temperature for 3 days. The stock solution thus prepared is stable up to 2 months if stored at 0 °C.

1-[(2-Methoxyethoxy)methoxy]-4-methylene-1α,2,3,3aα,4,5,8β,8aα-octahydroazulen-8-ol (19). To a stirred solution of 567 mg (1.47 mmol) of ketone **18** in 3 mL of methylene chloride was added Lombardo's reagent in small portions via pipet. The reaction was monitored by TLC, and when the starting material had been consumed, the reaction mixture was diluted with 100 mL of ether. The ether mixture was shaken in a separatory funnel with 100 mL of a saturated aqueous sodium bicarbonate solution until the organic layer was clear. The aqueous phase was then back-extracted with several 100-mL portions of ether. The combined organic layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure to give the crude product. Flash chromatography on 20 g of silica gel (1:3 ether/hexanes) afforded 557 mg (99%) of pure 8-[(*tert*-butyldimethylsilyl)oxy]-1-[(2-methoxyethoxy)methoxy]-4-methylene-1α,2,3,3aα,4α,5,8β,8aα-octahydroazulene: R_f 0.89 (1:1 ether/hexanes); IR (CCl_4) ν 3026.5, 2955, 2929, 2892, 2859, 2817, 1653, 1646, 1472, 1462, 1389, 1360, 1264, 1257, 1171, 1114, 1079, 1048, 882.5, 838.1 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 6 H), 0.85 (s, 9 H), 1.49 (m, 1 H), 1.88 (m, 1 H), 2.04–2.28 (m, 2 H), 2.33 (dd, J = 4.0, 11.0 Hz, 1 H), 2.68 (m, 1 H), 2.82 (m, 1 H), 3.03 (dddd, J = 2.7, 2.7, 2.7, 18.6 Hz, 1 H), 3.42 (s, 3 H), 3.59 (m, 3 H), 3.90 (m, 1 H), 4.00 (m, 1 H), 4.75 (m, 3 H), 4.97 (br s, 1 H), 5.00 (br s, 1 H), 5.31 (dddd, J = 2.7, 2.7, 5.2, 11.6 Hz, 1 H), 5.56 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ −4.850, −4.085, 17.898, 25.884, 27.547, 32.483, 41.716, 42.076, 58.183, 58.976, 67.083, 67.268, 71.833, 82.937, 96.884, 109.846, 123.777, 137.391, 148.042; mass spectrum, m/e (%) (no M^+) 365 (3), 335 (1), 325 (1), 319 (4), 308 (7), 307 (27), 293 (8), 289 (5), 279 (2), 278 (5), 277 (18), 249 (14), 176 (17), 175 (100), 157 (45), 147 (44), 146 (14), 145 (95), 133 (33), 89 (38).

The 8-[(*tert*-butyldimethylsilyl)oxy]-1-[(2-methoxyethoxy)methoxy]-4-methylene-1α,2,3,3aα,4α,5,8β,8aα-octahydroazulene (976 mg, 2.54 mmol) and 5.08 mL of tetrabutylammonium fluoride (1 M in hexanes) were allowed to stir for 5 h at room temperature. The reaction mixture was then diluted with 50 mL of ether and washed with a 30-mL portion of a saturated sodium bicarbonate solution followed by brine. The ether layer was dried and evaporated under reduced pressure. The crude product was purified by flash chromatography on 25 g of silica gel (1:4 ether/hexanes) to give 680 mg (100%) of pure allylic alcohol **19**: R_f 0.51 (ether); IR (CCl_4) ν 3514, 3087, 3026, 2894, 2829, 1661, 1644, 1435, 1369, 1260, 1243, 1201, 1137, 1107, 1047, 973.2, 896.0 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 1 H), 1.80 (m, 1 H), 1.90–2.15 (m, 2 H), 2.45 (dt, J = 10.77, 5.04 Hz, 1 H), 2.68 (m, 1 H), 2.80 (m, 1 H), 3.00 (m, 1 H), 3.40 (s, 3H), 3.55 (m, 3 H), 3.63–3.81 (m, 2 H), 4.26 (m, 1 H), 4.74 (m, 3 H), 4.88 (d, J = 1.2 Hz, 1 H), 4.92 (d, J = 0.6 Hz, 1 H), 5.43 (m, 1 H), 5.62 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.052, 30.0908, 41.033, 43.544, 55.162, 58.985, 66.497, 67.512, 71.720, 81.158, 94.568, 110, 249, 124.787, 135.111, 147.228; mass spectrum, m/e (%) (no M^+) 252 (2), 251 (15), 233 (3), 193 (7), 192 (16), 191 (9), 176 (10), 175 (77), 163 (17), 162 (19), 157 (29), 147 (16), 146 (15), 145 (100), 89 (70).

1-[(2-Methoxyethoxy)methoxy]-4-methylene-1α,2,3,3aα,4,5,6β,7β,8β,8aα-decahydro-6,7-epoxyazulen-8-ol (21). To a stirred solution of 500 mg (1.87 mmol) of allylic alcohol **19** in 2 mL of methylene chloride were added 49 mg (0.187 mmol) of $VO(acac)_2$ and 2.3 mL of an anhydrous solution (4.1 M in dichloroethane) of *tert*-butyl hydroperoxide. The reaction mixture was allowed to stir at room temperature for 8 h after which time

it was diluted with an additional 50 mL of methylene chloride. A 50-mL portion of a 10% aqueous sodium sulfite solution was added, and the resulting two-phase mixture was allowed to stir for 1 h. The organic layer was separated and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure followed by flash chromatography of the resulting oil on 10 g of silica gel (ether as eluent) gave 282.6 mg (53%) of pure epoxide **21**: R_f 0.27 (ether); IR (CCl_4) ν 3503, 2962, 2946, 2933, 2889, 2819, 1550, 1364, 1262, 1101, 1046, 1019 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50–1.80 (m, 2 H), 1.92 (m, 2 H), 2.34 (dt, J = 4.9, 10.4 Hz, 1 H), 2.58 (m, 1 H), 2.72 (dd, J = 3.0, 0.8 Hz, 1 H), 3.19 (m, 1 H), 3.29 (d, J = 4.6 Hz, 1 H), 3.40 (s, 3 H), 3.56 (m, 2 H), 3.66 (m, 1 H), 3.78 (m, 1 H), 3.87 (d, J = 3.7 Hz, 1 H), 4.30 (m, 2 H), 4.74 (m, 2 H), 4.85 (br s, 1 H), 4.88 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.007, 30.833, 37.507, 41.964, 47.182, 53.205, 59.032, 61.555, 66.930, 67.482, 71.761, 81.224, 94.468, 111.465, 144.628; mass spectrum, m/e (%) 284 (0.05), 208 (9), 179 (5), 161 (5), 149 (9), 133 (12), 131 (14), 121 (11), 105 (15), 91 (23), 89 (51), 79 (13), 59 (100); high-resolution mass spectrum for $C_{15}H_{24}O_5$, calcd 284.1623, found 284.1611.

1-[(2-Methoxyethoxy)methoxy]-4-methylene-1α,2,3,3aα,4,5,6β,8aα-octahydroazulen-6-ol (20). Imidazole (325 mg, 4.78 mmol) and *tert*-butyldimethylsilyl chloride (716 mg, 4.78 mmol) were added to a room temperature solution of 1.0 g (3.18) of allylic alcohol **16** in 5 mL of freshly distilled DMF. The reaction mixture was allowed to stir at room temperature of 1.5 h and was then diluted with 200 mL of ether. The ether mixture was washed quickly with a 5% aqueous HCl solution, then with 100 mL of a saturated aqueous sodium bicarbonate solution, and finally with brine. The organic layer was dried and evaporated under reduced pressure to give the crude product, which was purified by flash chromatography on 50 g of silica gel. This afforded 1.31 g (96%) of pure 4-acetoxy-6-[(*tert*-butyldimethylsilyl)oxy]-1-[(2-methoxyethoxy)methoxy]-1α,2,3,3aα,4α,5,6β,8aα-octahydroazulene: R_f 0.58 (1:1 ether/hexanes); IR (CCl_4) ν 2955, 2930, 2887, 2858, 1738, 1472, 1437, 1369, 1243, 1087, 1046, 1024, 908.6, 836.7 cm^{-1}; ^1H NMR δ 0.036 (s, 3 H), 0.058 (s, 3 H), 0.889 (s, 9 H), 1.50–1.82 (m, 4 H), 1.88 (ddd, J = 3.3, 7.0, 13.3 Hz, 1 H), 2.01 (s, 3 H), 2.08 (m, 1 H), 2.44 (m, 1 H), 2.90 (m, 1 H), 3.39 (s, 3 H), 3.54 (m, 2 H), 3.68 (m, 2 H), 4.08 (dt, J = 6.1, 5.9 Hz, 1 H), 4.38 (m, 1 H), 4.72 (m, 2 H), 5.54 (m, 1 H), 5.68 (dd, J = 4.0, 12.2 Hz, 1 H), 5.81 (ddd, J = 2.05, 5.5, 12.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ −5.019, −4.642, 18.103, 21.225, 21.422, 25.769, 28.843, 35.947, 42.033, 42.692, 59.011, 65.737, 66.962, 70.916, 71.735, 79.887, 94.778, 127.515, 134.343, 170.105; mass spectrum, m/e (%) (no M^+) 354 (2), 353 (8), 294 (16), 293 (67), 263 (14), 237 (5), 179 (6), 161 (14), 149 (33), 133 (15), 132 (11), 131 (100), 89 (12).

A solution of 1.30 g (3.0 mmol) of 4-acetoxy-6-[(*tert*-butyldimethylsilyl)oxy]-1-[(2-methoxyethoxy)methoxy]-1α,2,3,3aα,4α,5,6β,8aα-octahydroazulene and 1.70 g of anhydrous potassium carbonate (12.0 mmol) in 5 mL of absolute methanol was allowed to stir at room temperature for 16 h. When the reaction was complete, the methanol was evaporated under reduced pressure and the residue was dissolved in 200 mL of ether. The organic layer was washed once with a 150-mL portion of distilled water and then with brine. The ether layer was dried and the solvent removed under reduced pressure to give the crude alcohol. Flash chromatography on 40 g of silica gel (1:1 ether/hexanes) gave 1.00 g (86%) of pure 6-[(*tert*-butyldimethylsilyl)oxy]-1-[(2-methoxyethoxy)methoxy]-1α,2,3,3aα,4α,5,6β,-8aα-octahydroazulen-4-ol: R_f 0.65 (ether); IR (CCl_4) ν 3449, 2953, 2930, 2888, 2857, 1472, 1463, 1409, 1361, 1343, 1255, 1201, 1109, 1072, 1058 1047, 1026, cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.081 (s, 3 H), 0.086 (s, 3 H), 0.900 (s, 9 H), 1.68 (m, 2 H), 1.92 (m, 3 H), 2.27 (m, 1 H), 2.52 (m, 1 H), 2.76 (m, 1 H), 3.39 (s, 3 H), 3.53–3.78 (m, 5 H), 3.88 (m, 1 H), 4.18 (m, 1 H), 4.58 (m, 1 H), 4.76 (m, 2 H), 5.50 (ddd, J = 2.0, 5.2, 12.7, 1 H), 5.75 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ −4.836, −4.775, 18.103, 25.817, 26.946, 30.885, 42.155, 45.759, 48.327, 58.943, 67.006, 67.296, 69.305, 71.585, 80.786, 93.697, 124.662, 136.969; mass spectrum, m/e (%) (no M^+) 329 (3), 311 (3), 298 (2), 297 (8), 293 (7), 281 (8), 280 (11), 279 (8), 263 (10), 253 (8), 223 (26), 179 (38), 161 (14), 153 (26), 149 (27), 133 (49), 131 (66), 89 (98), 75 (35), 59 (100).

To an ice-cold solution of 2.4 mL (14.7 mmol) of pyridine in 50 mL of methylene chloride was added 1.47 g (14.7 mmol) of chromium trioxide. The ice bath was removed, and the mixture was allowed to stir at room temperature for 45 min. At this time the 6-[(*tert*-butyldimethylsilyl)oxy]-1-[(2-methoxyethoxy)methoxy]-1α,2,3,3aα,4α,5,6β,8aα-octahydroazulen-4-ol in 10 mL of methylene chloride was added. After 5 h the reaction mixture was diluted with 100 mL of ether and suction filtered through a pad of silica gel. The filtrate was quickly washed with 100 mL of a 5% aqueous HCl solution, followed by 100 mL of a saturated aqueous sodium bicarbonate solution and then brine. The ether layer was dried and evaporated under reduced pressure to leave the crude ketone, which was purified by flash chromatography on 30 g of silica gel. This afforded 862.4 mg (91%) of pure 6-[(*tert*-butyldimethylsilyl)oxy]-1-[(2-methoxyethoxy)methoxy]-1α,2,3,3aα,4α,5,6β,8aα-octahydroazulen-4-one: R_f 0.35 (1:1 ether/hexanes); IR (CCl_4) ν 2956, 2931, 2888, 2859, 1713, 1472, 1463, 1362, 1257, 1122, 1072, 1052, 908.5, 866.1 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.084 (s, 6 H), 0.890 (s, 9 H), 1.42–1.64 (m, 3 H), 2.20 (m, 1 H), 2.69 (dd, J = 4.5, 12.3 Hz, 1 H), 3.06 (dd, J = 8.7, 12.3 Hz, 1 H), 3.16 (m, 1 H), 3.25 (m, 1 H), 3.41 (s, 3 H), 3.55 (m, 2 H), 3.68 (m, 2 H), 4.10 (dt, J =5.8, 5.3 Hz, 1 H), 4.33 (m, 1 H), 4.70 (m, 2 H), 5.81 (m, 1 H), 5.88 (dd, J = 3.3, 12.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ −4.94, −4.78, 17.97, 21.49, 25.68, 29.15, 43.96, 51.06, 52.86, 58.89, 66.53, 66.88, 71.66, 79.28, 94.27, 128.42, 133.60, 208.52;

The 6-[(*tert*-butyldimethylsilyl)oxy]-1-[(2-methoxyethoxy)-methoxy]-1α,2,3,3aα,4α,5,6β,8aα-octahydroazulen-4-one (850 mg, 2.2 mmol) was dissolved in 5.0 mL of methylene chloride. Lombardo's reagent was added in small portions via pipet until TLC analysis showed the reaction to be complete. The mixture was then diluted with 200 mL of ether and shaken in a separatory funnel with a 150-mL portion of a saturated aqueous sodium bicarbonate solution until the organic layer was clear. The aqueous layer was back-extracted several times with ether. The combined organic layers were dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure and flash chromatography of the crude product on 30 g of silica gel (1:5 ether/hexanes) gave 798 mg (94%) of pure 6-[(*tert*-butyldimethylsilyl)oxy]-1-[(2-methoxyethoxy)methoxy]-4-methylene-1α,2,3,3aα,4α,5,6β,8aα-octahydroazulene: R_f (1:1 ether/hexanes); ^1H NMR ($CDCl_3$) δ 0.94 (s, 6 H), 0.903 (s, 9 H), 1.62 (m, 2 H), 1.90 (m, 2 H), 2.51 (m, 2 H), 2.80 (m, 1 H), 3.19 (m, 1 H), 3.40 (s, 3 H), 3.56 (m, 2 H), 3.70 (m, 2 H), 4.10 (m, 1 H), 4.17 (m, 1 H), 4.74 (m, 2 H), 4.77 (br s, 1 H), 4.90 (br s, 1 H), 5.59 (m, 1 H), 5.74 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ −4.609, 25.894, 26.445, 28.930, 42.222, 43.185, 45.485, 59.009, 66.973, 71.712, 72.694, 79.161, 94.766, 122.190, 125.700, 133.038.

To a stirred solution of 780 mg (2.0 mmol) of 6-[(*tert*-butyldimethylsilyl)oxy]-1-[(2-methoxyethoxy)methoxy]-4-methylene-1α,2,3,3aα,4α,5,6β,8aα-octahydroazulene in 1 mL of freshly distilled THF was added 2.0 mL of a 1 M solution of tetra-*n*-butylammonium fluoride in THF. The reaction mixture was allowed to stir for 1 h and then diluted with 100 mL of ether. The ether mixture was washed with a 75-mL portion of a saturated aqueous sodium bicarbonate solution followed by brine. The ether layer was dried and evporated under reduced pressure to give the crude allylic alcohol. Flash chromatography on 25 g of silica gel (1:1 ether/hexanes) afforded 534 mg (99%) of the pure allylic alcohol **20**: R_f 0.55 (ether); IR (CCl_4) ν 3520, 3080, 2900, 2815, 1630, 1425, 1250, 1220, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70 (m, 2 H), 1.86 (m, 2 H), 2.02 (d, J = 6.97 Hz, 1 H), 2.42 (dd, J = 12.29, 9.12 Hz, 1 H), 2.78 (dd, J = 12.28, 5.32, 1 H), 2.84 (m, 1 H), 3.12 (m, 1 H), 3.40 (s, 3 H), 3.56 (m, 2 H), 3.70 (m, 2 H), 4.10 (m, 1 H), 4.18 (br s, 1 H), 4.74 (m, 2 H), 4.81 (t, J = 1.8 Hz, 1 H), 4.89 (m, 1 H), 5.72 (m, 1 H), 5.78 (dd, J = 3.42, 12.08 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 26.975, 29.257, 41.587, 43.414, 46.266, 58.986, 66.936, 70.640, 71.791, m..416, 94.790, 112.782, 127.304, 132.104, 147.172.

1-[(2-Methoxyethoxy)methoxy]-4-methylene-1α,2,3,3aα,4,5,6β,8aα-octahydro-7,8-epoxyazulen-6-ol (22). To a stirred solution of 300 mg (1.12 mmol) of allylic alcohol **20** in 1.0 mL of methylene chloride was added 30 mg (0.112 mmol) of $VO(acac)_2$ and 1.4 mL (5.6 mmol) of a 4.1 M anhydrous solution of *tert*-butyl hydroperoxide. The reaction mixture was allowed to stir at room temperature for 1 h after which time it was diluted with an additional 20 mL of methylene chloride and stirred for 1 h with 20 mL of a 10% aqueous sodium sulfite solution. The organic layer was separated and dried over anhydrous sodium sulfate. Evaporation of the solvent and flash chromatography of the crude product on 8 g of silica gel (ether as eluent) gave 205.5 mg (65%) of pure epoxide **22**: R_f 0.27 (ether); IR (CCl_4) ν 3590,

3476, 3085, 2945, 2881, 2818, 1640, 1469, 1457, 1450, 1402, 1365, 1120, 1042, 908.5 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (m, 2 H), 1.96 (m, 1 H), 2.12 (d, J = 7.99 Hz, 1 H), 2.24 (dd, J = 8.42, 12.67 Hz, 1 H), 2.54 (dd, J = 4.56, 12.88 Hz, 1 H), 2.70 (m, 2 H), 3.29 (m, 1 H), 3.36 (m, 1 H), 3.40 (s, 3 H), 3.56 (m, 2 H), 3.70 (m, 2 H), 4.12 (m, 1 H), 4.30 (m, 1 H), 4.74 (m, 2 H), 4.82 (br s, 1 H), 4.87 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.159, 30.335, 40.075, 45.008, 46.184, 56.557, 58.449, 59.030, 67.051, 69.399, 71.797, 78.909, 94.517, 112.845, 145.570; mass spectrum, m/e (%) (no M^+) 255 (1), 237 (1), 209 (3), 195 (3), 191 (6), 179 (11), 161 (17), 155 (10), 149 (18), 133 (15), 119 (12), 91 (12), 89 (82), 59 (100).

4-Hydroxy-9-[(2-methoxyethoxy)methoxy]-6-methylene-3aα,4β,5,6,6aα,7,8,9α,9aα,9bα-decahydroazuleno[4.5-*b*]furan-2(3*H*)-one (23). To a solution of 12.22 mL (87.32 mmol) of diisopropylamine in 80 mL of DME, cooled to −78 °C, was added 34.9 mL (87.32 mmol) of *n*-BuLi (2.5 M in hexanes). The reaction mixture was allowed to slowly warm to −40 °C and then 2.50 mL (43.66 mmol) of glacial acetic acid (distilled from $KMnO_4$ and then from P_2O_5 prior to use) in 5.0 mL of DME was added. The cooling bath was removed, the reaction mixture was slowly warmed to 60 °C, the resulting yellow suspension was allowed to stir at that temperature for 2 h, and then epoxide **21** (310 mg, 1.09 mmol) in 2.0 mL of DME was added. After 2.5 h the reaction mixture was cooled to 0 °C and quenched by the careful addition of 20 mL of water. The DME was evaporated in vacuo, and the remaining yellow solution was diluted with 100 mL of water and extracted with two 60-mL portions of ethyl acetate. The combined ethyl acetate fractions were then back-extracted with three 70-mL portions of a 5% aqueous sodium hydroxide solution. The combined aqueous layers were acidified to pH 2 by the careful dropwise addition of concentrated HCl. Ethyl acetate (300 mL) was added to the acidified aqueous layers, and the resulting two-phase mixture was stirred for 20 min at room temperature. The ethyl acetate layer was separated, and the aqueous phase was extracted with 200 mL of ethyl acetate. The combined organic layers were washed with one 300-mL portion of water, several portions of a saturated aqueous sodium bicarbonate solution, and finally brine. Drying of the organic layer over anhydrous sodium sulfate followed by evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash chromatography on 20 g of silica gel (ether as eluent). This afforded 280 mg (79%) of pure lactone **23**: R_f 0.34 (1:1 EtOAc/ether); IR (CCl_4) ν 3629, 3476, 2963, 2928, 1785, 1262, 1218, 1181, 1161, 1101, 1043, 1024, 903.7 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (m, 1 H), 1.50 (m, 1 H), 1.82 (m, 1 H), 2.05 (m, 1 H), 2.25–2.52 (m, 3 H), 2.75–2.85 (m, 3 H), 3.33 (s, 3 H), 3.57 (m, 3 H), 3.71 (m, 2 H), 4.25 (m, 1 H), 4.34 (t, J = 10.2 Hz, 1 H), 4.74 (m, 2 H), 5.04 (s, 1 H), 5.08 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.678, 31.592, 35.236, 44.028, 49.125, 50.155, 51.509, 58.854, 66.819, 71.722, 75.030, 78.931, 79.387, 94.334, 114.488, 142.674, 175.869; mass spectrum, m/e (%) (no M^+) 252 (15), 251 (9), 237 (5), 221 (5), 219 (6), 203 (13), 145 (9), 133 (13), 119 (10), 91 (5), 89 (100), 59 (81).

The lactone **23** was also prepared from the regioisomeric epoxide **22** following this same procedure. Addition of epoxide **22** (190 mg, 0.670 mmol) to a suspension of 28.17 mmol of dilithioacetate generated according to the procedure described above gave, after 16 h, 166 mg (76%) of lactone **23** which was identical (300-MHz NMR, ^{13}C NMR, IR, mass spectrum, TLC) with that obtained from epoxide **21**.

4-[(*tert*-Butyldiphenylsilyl)oxy]-9-hydroxy-6-methylene-3aα,4β,5,6,6aα,7,8,9α,9aα,9bβ-decahydroazuleno-[4,5-*b*]furan-2(3*H*)-one (24). To a solution of 189 mg (0.580 mmol) of hydroxy lactone **23** in 1.0 mL of freshly distilled DMF was added 48.0 mg (0.696 mmol) of imidazole and 181 μL (0.696 mmol) of *tert*-butyldiphenylsilyl chloride. The reaction mixture was stirred for 22 h at room temperature and then diluted with 70 mL ether. The ether mixture was washed successively with one 40-mL portion of a 5% aqueous HCl solution, two 40-mL portions of a saturated aqueous sodium bicarbonate solution, and one 40-mL portion of brine. The organic layer was dried over anhydrous sodium sulfate and the solvent removed in vacuo to give the crude product, which was purified by flash chromatography on 20 g of silica gel (1:4 ether/hexanes). This afforded 323 mg (99%) of pure 4-[(*tert*-butyldiphenylsilyl)oxy]-9-[(2-methoxyethoxy)methoxy]-6-methylene-3aα,4β,5,6,6aα,7,8,9α,9aα,9bβ-decahydroazuleno[4,5*b*]furan-2(3*H*)-one: R_f 0.84 (ether); ^1H NMR ($CDCl_3$) 1.07 (s, 9 H), 1.40 (m, 1 H), 1.70 (m, 1 H), 1.95 (m, 3 H), 2.05 (m, 2 H), 2.65 (m, 1 H), 2.83 (dd, J = 7.7, 17.1 Hz, 1 H), 3.37 (s, 3 H), 3.50 (m, 3 H), 3.65 (m, 2 H), 4.15 (t, J = 10.48 Hz, 1 H), 4.20 (m, 1 H), 4.36 (s, 1 H), 4.65 (m, 2 H), 4.83 (s, 1 H), 7.40 (m, 6 H), 7.65 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 19.315, 26.940, 27.465, 31.483, 36.107, 44.074, 48.991, 51.103, 51.211, 58.978, 66.835, 71.749, 78.890, 79.414, 94.293, 114.165, 127.586, 127.870, 129.795, 130.083, 133.92, 135.854, 142.580, 175.76; mass spectrum, m/e (%) (no M^+) 508 (7), 507 (18), 403 (5), 325 (3), 257 (14), 225 (6), 213 (12), 200 (11), 199 (58), 197 (10), 135 (18), 91 (10), 89 (91), 77 (10).

To a solution of 320 mg (0.567 mmol) of 4-[(*tert*-butyldiphenylsilyl)oxy]-9-[(2-methoxyethoxy)methoxy]-6-methylene-3aα,4β,5,6,6aα,7,8,9α,9aα,9bβ-decahydroazuleno[4,5-*b*]furan-2-(3*H*)-one in 12.0 mL of dry acetonitrile, cooled to −20 °C, were added 170.2 mg (1.13 mmol) of sodium iodide and 144 μL (1.13 mmol) of trimethylsilyl chloride. The reaction mixture was stirred at −20 °C for 1 h and then quenched by the addition of 2 mL of absolute methanol. The solvents were removed under reduced pressure, and the resulting residue was taken up in 100 mL of ethyl acetate. The ethyl acetate mixture was washed with two 50-mL portions of a saturated aqueous sodium thiosulfate followed by brine. The organic layer was dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The crude product was flash chromatographed on 132 g of silica gel (1:4 ether/hexanes) to give 259 mg (96%) of hydroxy lactone **24**: R_f 0.84 (ether); IR (CCl_4) ν 3611, 3532, 3074, 2962, 2932, 2861, 1787, 1473, 1428, 1391, 1262, 1211, 1182, 1114, 1105, 1086, 988.6, 904.9 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (2, 9 H), 1.4–2.0 (m, 6 H), 2.23 (m, 2 H), 2.55 (m, 3 H), 2.85 (dd, J = 7.6, 17.2 Hz, 1 H), 3.45 (m, 2 H), 4.10 (t, J = 10.6 Hz, 1 H), 4.25 (s, 1 H), 4.50 (m, 1 H), 4.85 (s, 1 H), 7.40 (m, 5 H), 7.65 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 19.315, 29.956, 27.493, 34.079, 35.868, 45.246, 48.070, 51.159, 51.867, 74.362, 79.640, 114.244, 127.64, 127.90, 129.86, 130.14, 135.85, 142.81, 175.63; mass spectrum, m/e (%) (no M^+) 420 (2), 419 (7), 272 (10), 271 (37), 213 (39), 200 (18), 199 (100), 193 (19), 183 (11), 77 (15).

4-[(*tert*-Butyldiphenylsilyl)oxy]-6-methylene-3aα,4,5,6,6aα,7,8,9bβ-octahydroazuleno[4,5-*b*]furan-2-(3*H*),9(9aα*H*)-dione (25). To a solution of hydroxy lactone **24** (250 mg, 0.527 mmol) in 10 mL of methylene chloride was added 1.18 g (3.16 mmol) of PDC. The reaction mixture was allowed to stir at room temperature for 48 h and then diluted with 20 mL of ether. The resulting heterogeneous mixture was quickly suction filtered through a short pad of silica gel. The filtrate was evaporated under reduced pressure to give the crude keto lactone **25**: R_f 0.71 (ether); IR (CCl_4) ν 3074, 2963, 2933, 2860, 1793, 1753, 1473, 1463, 1428, 1262, 1113, 1105, 1089, 1014 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (s, 9 H), 1.88–2.32 (m, 6 H), 2.38 (dd, J = 4.9, 12.5 Hz, 1 H), 2.62 (m, 3 H), 3.00 (m, 1 H), 3.39 (m, 2 H), 3.80 (t, J = 9.91 Hz, 1 H), 4.39 (s, 1 H), 4.58 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.233, 25.729, 26.884, 35.096, 36.051, 42.799, 47.884, 49.684, 56.071, 77.600, 114.483, 127.611, 127.886, 129.877, 130.157, 135.771, 144.005, 174.942, 215.362; mass spectrum, m/e (%) (no M^+) 272 (8), 271 (30), 213 (39), 200 (19), 199 (100), 193 (14), 183 (10), 181 (7), 77 (14).

2-(2-Bromoethyl)-2-methyl-1,3-dioxolane.[18] Anhydrous HBr was bubbled into 178 mL of ethylene glycol cooled to 0 °C until 77 g (0.96 mol) had been added. Methyl vinyl ketone (52.0 mL, 0.64 mol) was added slowly to the vigorously stirred ethylene glycol mixture. When the addition was complete, the reaction mixture was allowed to stir for 30 min at 0 °C, and then the ice bath was removed and stirring was continued for 30 min. The reaction mixture was extracted several times with petroleum ether, and the combined organic extracts were washed with a saturated aqueous sodium bicarbonate solution. The petroleum ether mixture was dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to give the crude product, which was distilled under high vacuum to give 97.8 g (79%) of pure bromo ketal: bp 44 °C (0.5 mm); ^1H NMR (CCl_4) δ 1.1 (s, 3 H), 2.1 (m, 2 H), 3.4 (m, 2 H), 4.0 (br s, 4 H).

2-[2-(2-Methyl-1,3-dioxolan-2-yl)ethyl]-3,5-cycloheptadien-1-one (26). To a stirred suspension of 7.26 g (302.6 mmol) of magnesium turnings in 200 mL of dry THF were added a small crystal of iodine, ca. 0.2 mL of 1,2-dibromoethane, and several drops of a solution of 58.7 g (302.6 mmol) of 2-(2-bromoethyl)-2-methyl-1,3-dioxolane in 50 mL of dry THF from an addition funnel. The reaction mixture was warmed gently with

a heat gun to initiate the reaction. As the reaction proceeded, the 2-(2-bromoethyl)-2-methyl-1,3-dioxolane solution was added in small portions while the reaction temperature was carefully maintained between 20 and 30 °C with the use of an ice bath. When the addition was complete, the reaction mixture was allowed to stir at room temperature for an additional 1 h and then cooled to 0 °C. Tropone (16.0 g, 151.3 mmol) in 50 mL of dry THF was added slowly from an addition funnel. As the tropone was added, a transient red-orange was observed. When the addition was complete, the reaction mixture was allowed to stir at 0 °C for 30 min and then quenched by the careful addition of 50 mL of a 10% aqueous HCl solution. The reaction mixture was poured into 1 L of ether and washed with several portions of a saturated aqueous sodium bicarbonate solution followed by brine. The organic layer was dried and the solvent evaporated in vacuo to give the crude ketone **26**, which was used in the next step without purification: IR (CCl_4) ν 3030, 2990, 2930, 2880, 1725, 1380, 1250, 1220, 1070, 945 cm^{-1}; ^1H NMR (CCl_4) δ 1.3 (s, 3 H), 1.2–2.0 (m, 4 H), 2.8–3.2 (m, 3 H), 3.8–4.0 (m, 4 H), 5.4–6.2 (m, 4 H).

1-Acetoxy-2-(3-oxobutyl)-3,5-cycloheptadiene (27). To a solution of the crude ketone **26** in 300 mL of absolute methanol, cooled to 0 °C, was added solid sodium borohydride in small portions until TLC analysis showed the reaction to be complete. The reaction mixture was then quenched by the slow addition of a 10% aqueous HCl solution until foaming ceased. The methanol was then evaporated under reduced pressure, and the resulting residue was taken up in 800 mL of ether. The ether layer was washed with two 400-mL portions of a saturated aqueous sodium bicarbonate solution followed by brine. After the ether layer was dried and evaporated, the crude product was purified by column chromatography on 500 g of silica gel (7:3 ether/hexanes). This gave 28.4 g (84% from tropone) of pure 2-(3-oxobutyl)]-3,5-cycloheptadien-1-ol: R_f 0.27 (1:1 ether/hexanes); IR (CCl_4) ν 3580, 3500, 3020, 3000, 2960, 2840, 1380, 1250, 1220, 1140, 1070, 1060, 950, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (s, 3 H), 1.60–1.78 (m, 5 H), 2.40 (m, 1 H), 2.54 (m, 2 H), 3.93 (m, 4 H), 4.09 (br s, 1 H), 5.51 (m,1 H), 5.73 (m, 1 H), 5.90 (m, 2 H).

To an ice-cold solution of 15.5 g (69.20 mmol) of 2-(3-oxobutyl)]-3,5-cycloheptadien-1-ol in 100 mL of methylene chloride were added 11.6 mL (83.04 mmol) of triethylamine, 7.8 mL (83.04 mmol) of acetic anhydride, and 84 mg (0.692 mmol) of 4-(*N*,*N*-dimethylamino)pyridine. After 30 min the ice bath was removed, and the reaction mixture was allowed to stir at room temperature for 1 h and then poured into 500 mL of ether. The ether mixture was washed with 300 mL of a 10% aqueous HCl solution, two 300-mL portions of a saturated aqueous sodium bicarbonate solution, and then brine. The organic layer was dried and the solvent removed in vacuo to give the crude product, which was purified by column chromatography on 300 g of silica gel (1:1 ether/hexanes) to give 17.3 g (94%) of pure 1-acetoxy-2-(3-oxobutyl)]-3,5-cycloheptadiene: R_f 0.55 (1:1 ether/hexanes); ^1H NMR ($CDCl_3$) δ 1.29 (s, 3 H), 1.44–1.85 (m, 4 H), 2.05 (s, 3 H), 2.54 (m, 3 H), 3.92 (m, 4 H), 5.00–5.20 (m, 1 H), 5.60–6.00 (m, 4 H); mass spectrum, *m/e* (%) 266 (0.9), 251 (8), 224 (4), 207 (20), 191 (8), 163 (7), 162 (9), 147 (11), 146 (15), 145 (80), 144 (38), 129 (12), 104 (85), 91 (44), 87 (100). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.32. Found: C, 67.39; H, 8.23.

To 10.3 g (38.72 mmol) of the 1-acetoxy-2-(3-oxobutyl)]-3,5-cycloheptadiene was added 20 mL of a 5% aqueous trifluoroacetic acid solution and enough acetone to make the reaction mixture homogeneous (ca. 60 mL). The reaction mixture was stirred at room temperature for 2 h, and then the acetone was evaporated under reduced pressure. The resulting two phase mixture was taken up in 400 mL of ether and washed with several 300-mL portions of a saturated aqueous sodium bicarbonate solution followed by brine. The organic layer was dried and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on 200 g of silica gel (2:3 ether/hexanes) gave 6.8 g (79%) of the pure ketone **27**: R_f 0.52 (1:1 ether/hexanes); IR (CCl_4) ν 3025, 2958, 2895, 1740, 1723, 1431, 1370, 1240, 1160, 1022, 974.1, 959.7 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (m, 1 H), 1.84 (m, 1 H), 2.05 (s, 3 H), 2.15 (s, 3 H), 2.52 (m, 5 H), 4.93 and 5.17 (2 m, ratio 1:2, 1 H total), 5.57–6.00 (m, 4 H).

4-Acetoxy-1-methyl-1,2,3,3aα,4α,5,6α,8aα-octahydro-1,6-epoxyazulene (28). To a solution of 6.3 g (28.38 mmol) of ketone **27** in 200 mL of methylene chloride was added 10.5 mL (85.14 mmol) of freshly distilled boron trifluoride etherate complex. The reaction mixture was allowed to stir for 1.5 h at room temperature, then cooled to 0 °C, and quenched by the careful addition of a saturated aqueous sodium bicarbonate solution. The mixture was diluted with 300 mL of ether, and the organic layer was separated and washed with several portions of a saturated aqueous sodium bicarbonate solution followed by brine. Drying of the ether layer followed by evaporation under reduced pressure gave the crude product. Flash chromatography on 150 g of silica gel (1:3 ether/hexanes) gave 4.6 g of the cyclic ether **28** (73%, 93% based on recovered starting material) and 1.37 g (22%) of the α epimer of the starting ketone.

Cyclic Ether 28: mp 44–46 °C; R_f 0.61 (1:1 ether/hexanes); IR (CCl_4) ν 3052, 2971, 2931, 2857, 1736, 1466, 1442, 1372, 1241, 1177, 1147, 1056, 1029, 981.8 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 3 H), 1.60–2.00 (m, 6 H), 2.00 (s, 3 H), 2.48 (m, 1 H), 2.68 (m, 1 H), 4.34 (m, 1 H), 4.76 (ddd, J = 5.09, 6.61, 11.03 Hz, 1 H), 6.23 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.25, 21.44, 25.42, 33.10, 39.48, 40.99, 46.87, 67.86, 71.74, 83.88, 128.55, 130.19, 170.42; mass spectrum, *m/e* (%) 222 (6), 162 (39), 147 (14), 144 (22), 134 (25), 133 (25), 119 (34), 105 (33), 104 (100), 94 (76), 91 (83), 81 (90); high-resolution mass spectrum for $C_{13}H_{18}O_3$, calcd 222.1256, found 222.1250.

Acknowledgment. We thank the National Institutes of Health (Grant GM-30771) for support of this research and Prof. John Oliver for obtaining the crystal structures of compounds **6** and **11**.