combined acetonitrile layers were concentrated in vacuo to afford 2.68 g of a pale-yellow oil. The oil was chromatographed first over 50 g of silica gel (ethyl acetate–hexane, 25:75, followed by ethyl acetate–hexane, 1:1, and finally ethyl acetate) and then over a Lobar size C column (ethyl acetate–hexane, 25:75, followed by ethyl acetate) to yield 241 mg (8%) of unreacted starting material **34** as a pale-yellow oil. Continued elution gave a fraction which was recrystallized from 4 mL of hexane to yield 627 mg (30%) of one diastereoisomer of **37** as a white solid: mp 93.5–94.5 °C; IR ($CCl_4$) 1700 $cm^{-1}$; NMR ($CDCl_3$, 200 MHz) $\delta$ 0.13 (s, 9 H, $SiMe_3$), 1.24–2.71 (m, 8 H), 2.82 (dt, $J$ = 11, 5 Hz, 1 H, NCH), 3.95 (dd, $J$ = 11, 5 Hz, NCH), 4.25 (ddd, $J$ = 11, 7, 5 Hz, 1 H, angular NCH), 7.10–7.40 (m, 5 H, ArH). Exact mass calcd for $C_{17}H_{25}NOSSi$: $m/e$ 319.1426. Found: $m/e$ 319.1447.

Anal. Calcd for $C_{17}H_{25}NOSSi$: C, 63.90; H, 7.89. Found: C, 64.00; H, 8.07.

The mother liquor was concentrated in vacuo to give 86.6 mg (4%) of a colorless oil composed of **37** and **40** (35:65, respectively, by NMR). Characteristic signals of **40**: NMR ($CDCl_3$) $\delta$ 3.30–3.45 (two overlapping t's, $J$ = 7 Hz, at 3.35 and 3.40, 4 H, $NCH_2$), 6.55 (t, $J$ = 7 Hz, 1 H, =CH). Further elution gave 445 mg (25%) of a mixture of **38** and **39** (3:2, respectively, by NMR). A small amount of pure **38** was obtained by further chromatography over a Lobar column as a colorless oil: IR ($CCl_4$) 1695 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.19 (s, 9 H, $SiMe_3$), 1.37–2.75 (m, 8 H), 3.15 (br t, $J$ = 12 Hz, 1 H, NCH), 3.54 (dt, $J$ = 12, 8 Hz, 1 H, NCH), 3.80 (td, $J$ = 9, 7 Hz, 1 H, angular NCH), 7.13–7.40 (m, 5 H, ArH). Exact mass calcd for $C_{17}H_{25}NOSSi$: $m/e$ 319.1426. Found: $m/e$ 319.1474. Only an enriched sample of **39** could be obtained: NMR ($CDCl_3$, 200 MHz) $\delta$ 3.00 (ddd, $J$ = 11, 8, 5 Hz, 1 H, NCH), 3.56 (td, $J$ = 11, 8 Hz, 1 H, NCH), 3.96 (q, $J$ = 6 Hz, 1 H, angular NCH).

Final elution gave 596 mg (28%) of the most polar diastereoisomer of **37** as a white solid: mp 87–88.5 °C; IR ($CCl_4$) 1695 $cm^{-1}$; NMR ($CDCl_3$, 200 MHz) $\delta$ 0.18 (s, 9 H, $SiMe_3$), 1.42–2.05 (m, 4 H), 2.13–2.71 (m, 4 H), 2.93 (td, $J$ = 12, 7 Hz, 1 H, NCH), 3.78 (ddd, $J$ = 12, 8, 5 Hz, 1 H, NCH), 4.01 (td, $J$ = 9, 7 Hz, 1 H, angular NCH), 7.11–7.50 (m, 5 H, ArH). Exact mass calcd for $C_{17}H_{25}NOSSi$: $m/e$ 319.1426. Found: $m/e$ 319.1452.

Anal. Calcd for $C_{17}H_{25}NOSSi$: C, 63.90; H, 7.89. Found: C, 63.86; H, 7.69.

**Acknowledgment.** We thank Mr. Richard Weisenberger for recording mass spectra at The Ohio State University Chemical Instrument Center. Financial support from the NIH (GM-27647) and NSF (CHE-8205878) are gratefully acknowledged. We also thank the NIH for a grant (GM-27431) to Ohio State University in support of the acquisition of a Bruker WM-200 NMR spectrometer used during the course of this research.

**Registry No.** (±)-**4**, 18929-90-3; (±)-**5**, 92845-54-0; **6a**, 92844-96-7; (±)-**6b**, 92844-97-8; **7a**, 92844-98-9; (±)-**7b**, 92844-99-0; **8a**, 92845-00-6; (±)-**8b**, 92845-01-7; (±)-**9a**, 92845-02-8; **9b**, 70255-35-5; (±)-**10a**, 92845-03-9; **10b**, 92845-04-0; **11a**, 92845-05-1; (±)-**11b**, 92845-06-2; **12a**, 92845-07-3; (±)-**12b**, 92845-15-3; (±)-**13b**, 92845-16-4; (±)-**14b**, 92845-14-2; (±)-**15a**, 92845-08-4; **15b**, 92845-13-1; (±)-**16** (isomer 1), 92845-09-5; (±)-**16** (isomer 2), 92845-10-8; (±)-**17**, 92845-11-9; (±)-**18**, 92845-12-0; **19**, 5615-85-0; **20a**, 35000-38-5; **20c**, 16640-68-9; (*Z*)-**21a**, 92845-17-5; (*E*)-**21a**, 92845-18-6; (±)-(*E*)-**21a**-ol, 92845-47-1; (±)-(*Z*)-**21a**-ol, 92845-48-2; (*Z*)-**21b**, 92845-19-7; (*E*)-**21b**, 92845-20-0; **21b**-ol, 92845-49-3; (*Z*)-**21c**, 92845-21-1; (*E*)-**21c**, 92845-22-2; (±)-(*E*)-**21c**-ol, 92845-50-6; (±)-(*Z*)-**21c**-ol, 92845-51-7; (±)-(*Z*)-**22a**, 92845-23-3; (±)-(*E*)-**22a**, 92845-24-4; **22b**, 92845-25-5; (*Z*)-**22c**, 92845-26-6; (*E*)-**22c**, 92845-27-7; (±)-**23a**, 92845-29-9; **23b**, 92845-33-5; (±)-**23c**, 92845-35-7; (±)-**24a**, 92845-28-8; (±)-**24c**, 92845-34-6; **25a**, 92845-30-2; (±)-**26**, 92845-31-3; (±)-**27**, 92845-32-4; (±)-**29**, 89922-81-6; **30**, 62761-90-4; (±)-(*E*)-**31**, 92845-36-8; (±)-(*Z*)-**31**, 92845-37-9; (*E*)-**32**, 92845-38-0; (*Z*)-**32**, 92845-39-1; (*E*)-**33**, 92845-40-4; (*Z*)-**33**, 92845-41-5; (±)-(*E*)-**34**, 92845-42-6; (±)-(*Z*)-**34**, 92845-43-7; (*Z*)-**35**, 88695-24-3; (*E*)-**35**, 88850-04-8; (*E*)-**35**-ol, 92845-52-8; (*Z*)-**35**-ol, 92845-53-9; (*Z*)-**36**, 92900-58-8; (*E*)-**36**, 92900-59-9; **37**, 92845-44-8; **39**, 92845-46-0; **40**, 92845-45-9; (1*R*,2*S*,5*R*)-2-(2-phenyl-2-propyl)-5-methylcyclohexanol, 65253-04-5; (1*R*,2*S*,5*R*)-2-(2-phenyl-2-propyl)-5-methylcyclohexanol bromoacetate, 80595-59-1; acetaldehyde, 75-07-0; paraformaldehyde, 30525-89-4; succinimide, 123-56-8; thiophenol, 108-98-5; bromoacetic acid, 79-08-3.

**Supplementary Material Available:** Experimental procedures for the preparation of **6b–11b** and **20b** (6 pages). Ordering information is given on any current masthead page.

# Total Synthesis of Guaianolides: (±)-Dehydrocostus Lactone and (±)-Estafiatin

**James H. Rigby* and JoAnn Zbur Wilson**

*Contribution from the Department of Chemistry, Wayne State University, Detroit, Michigan 48202.* *Received April 12, 1984*

**Abstract:** The total synthesis of two guaianolide sesquiterpenes, (±)-dehydrocostus lactone and (±)-estafiatin, is described. The synthesis starts with 2,4,6-cycloheptatrien-1-one (tropone) and introduces the elements of the five-membered ring through a 1,8-addition of the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxolane. A stereocontrolled Lewis acid mediated cyclization reaction generates the requisite cis-fused hydroazulene intermediate. Regio- and stereoselective γ-butyrolactone formation via epoxide opening with dilithioacetate followed by the introduction of three exocyclic methylene groups completes the synthesis of (±)-dehydrocostus lactone in twelve steps from tropone. (±)-Estafiatin is constructed in two additional steps from dehydrocostus lactone.

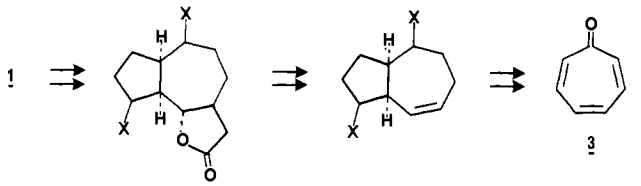
The guaianolides comprise one of the largest and most widely distributed groups of naturally occurring sesquiterpene lactones.[1] A majority of these species feature a cis-fused hydroazulene skeleton in which a trans-fused γ-butyrolactone moiety is appended to the seven-membered carbocycle. With approximately 200 representatives currently identified, the great structural diversity exhibited by this class of natural products stems principally from the level and variety of functionalization that can be located at a number of positions in the molecules. Many guaianolides are endowed with an impressively rich spectrum of biological activity. Tumor inhibitory[2] and schistosomicidal[3] as well as plant growth

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

(2) (a) Jolad, S. D.; Wiedhopf, R. M.; Cole, J. R. *J. Pharm. Sci.* **1974**, *63*, 1321. (b) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *14*, 1147. (c) Lee, K.-H.; Huang, E.-S.; Piantadosi, C.; Pagano, J. S.; Geissman, T. A. *Cancer Res.* **1971**, *31*, 1649.

0002-7863/84/1506-8217$01.50/0 

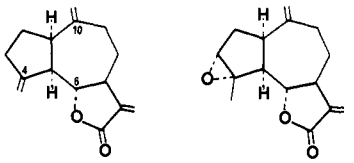
**Scheme I**



regulatory activity[4] are common among members of this group of compounds.

In spite of the many obvious attractions these natural products present, the literature currently reveals a conspicuous paucity of synthetic successes. Until recently the only synthetic efforts directed toward the guaianolides were in the form of relay syntheses involving eudesmane and germacrane sesquiterpenes as starting points.[5] To date only two groups have successfully assembled guaianolide species by total synthesis,[6,7] and a third group has recently disclosed a novel approach to a closely related guaiane species.[8] This lack of activity in the guaianolide series is in stark contrast to the prodigious synthetic output devoted to the closely related pseudoguaianolides.[9]

Described herein is the first total synthesis of the guaianolide (±)-dehydrocostus lactone (**1**)[10] and its subsequent conversion into the somewhat more highly functionalized (±)-estafiatin (**2**).[6a] At



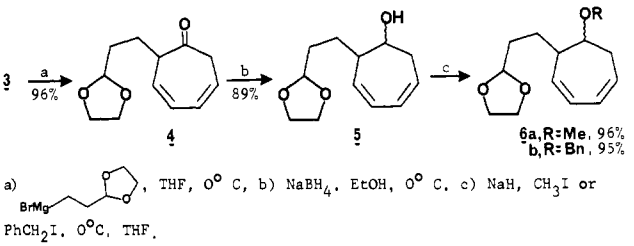
the outset of this investigation, compound **1** and related species were viewed as attractive penultimate synthetic targets from which other more highly oxygenated members of this class of compounds could be conveniently accessed.

Our fundamental strategy initially addressed the problems associated with the construction of an appropriately functionalized cis-fused hydroazulene intermediate. As noted by Heathcock,[9d] at least four complementary strategies for assembling the hydroazulene skeleton can be envisioned. These include transannular cyclization of a ten-membered ring, skeletal rearrangement of a decalin precursor, introduction of a seven-membered ring onto a five-membered ring, and elaboration of a five-membered ring onto a preexisting seven-membered carbocycle. Many of these approaches have been extensively exploited for hydroazulenic sesquiterpene synthesis.[1] Surprisingly, the last approach has not received much attention.[9g]

We envisaged that a strategy based on fusing the elements of a five-membered ring onto a preformed, highly functionalized seven-membered ring system offered a potentially efficient and versatile entry into *cis*-perhydroazulenes which in turn could be transformed into guaianolides. The limited availability of appropriate starting materials has certainly contributed to the shortage of strategies starting from seven-membered ring species. However, we were particularly intrigued with the possibility of utilizing the high degree of functionalization and unique reactivity exhibited by 2,4,6-cycloheptatrien-1-one (tropone) (**3**) and its derivatives for the construction of perhydroazulenes (Scheme I). Although the cycloheptatrienones have been the subject of extensive investigation,[12] their potential for application to synthetic problems has not been extensively explored until recently.[13] Tropone itself is readily available from cycloheptatriene, which is the least expensive functionalized seven-membered ring compound available commercially.[14]

The unusual propensity for tropone to undergo 1,8-addition with Grignard reagents[15] was viewed as the key carbon–carbon bond forming operation in the initial stages of our synthesis. The resulting dihydrotropone would retain a substantial degree of functionality for further manipulation, and the use of a terminally functionalized three-carbon chain Grignard reagent would provide a handle for subsequent closure to the requisite five-membered ring.[16]

Slow addition of tropone to 2 equiv of the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxolane[17] at 0 °C in THF resulted in a nearly quantitative conversion to the sensitive 2-substituted cyclohepta-3,5-dienone **4**.[18] Since related adducts



are prone to double bond migration,[15,19] dienone **4** was usually not purified but immediately subjected to careful reduction to dienol **5** with sodium borohydride at 0 °C. Facile 1,5-H shifts that normally characterize the dihydrotropone species appear to

(3) (a) Baker, P. M.; Fortes, C. C.; Fortes, E. G., Gassinelli, G.; Gilbert, B.; Lopes, J. N. C.; Pellegrino, J.; Tomassini, T.; Vichnewski, W. *J. Pharm. Pharmacol.* **1972**, *24*, 853. (b) Vichnewski, W.; Sarti, S. J.; Gilbert, B.; Herz, W. *Phytochemistry* **1976**, *15*, 191. (c) Herz, W.; Kumar, N.; Vichnewski, W.; Blount, J. F. *J. Org. Chem.* **1980**, *45*, 2503.

(4) (a) Rodriguez, E.; Towers, G. H. N.; Mitchell, J. C. *Phytochemistry* **1976**, *15*, 1573. (b) Asakawa, Y.; Takemoto, T. *Phytochemistry* **1979**, *18*, 285.

(5) (a) Ando, M.; Yamaoka, H.; Takase, K. *Chem. Lett.* **1982**, 501. (b) Edgar, M. T.; Greene, A. E.; Crabbé, P. *J. Org. Chem.* **1979**, *44*, 159. (c) Ando, M.; Akahane, A.; Takase, K. *Chem. Lett.* **1978**, 727. (d) Ogura, M.; Cordell, G. A.; Farnsworth, N. R. *Phytochemistry* **1978**, *17*, 957. (e) Ando, M.; Ono, A.; Takase, K. *Chem. Lett.* **1984**, *493*.

(6) (a) Devreese, A. A.; Demuynck, M.; De Clercq, P. J.; Vandewalle, M. *Tetrahedron* **1983**, *39*, 3049. (b) Demuynck, M.; Devreese, A. A.; De Clercq, P. J.; Vandewalle, M. *Tetrahedron Lett.* **1982**, *23*, 2501. (c) Devreese, A. A.; De Clercq, P. J.; Vandewalle, M. *Tetrahedron Lett.* **1980**, *21*, 4767.

(7) Posner, G. H.; Babiak, K. A.; Loomis, G. L.; Frazee, W. J.; Mittal, R. D.; Karle, I. L. *J. Am. Chem. Soc.* **1980**, *102*, 7498.

(8) Jacobi, P. A.; Selnick, H. G. *J. Am. Chem. Soc.* **1984**, *106*, 3041.

(9) For an excellent review of the approaches to the pseudoguainolides through 1980, see: Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In "The Total Synthesis of Natural Products"; ApSimon, J. W., Ed.; Wiley: New York, 1982; Vol. 5. For some recent developments, see: (a) Ziegler, F. E.; Fang, J.-M. *J. Org. Chem.* **1981**, *46*, 825. (b) Grieco, P. A.; Majetich, G. F.; Ohfune, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4226. (c) Grieco, P. A.; Ohfune, Y.; Majetich, G. F.; Wang, C.-L. J. *J. Am. Chem. Soc.* **1982**, *104*, 4233. (d) Heathcock, C. H.; Del Mar, E. G.; Graham, S. L. *J. Am. Chem. Soc.* **1982**, *104*, 1907 and references therein. (e) Ziegler, F. E.; Fang, J.-M.; Tam, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 7174. (f) Schultz, A. G.; Motyka, L. A. *J. Am. Chem. Soc.* **1982**, *104*, 5800. (g) Heathcock, C. H.; Tice, C. M.; Germroth, T. C. *J. Am. Chem. Soc.* **1982**, *104*, 6081.

(10) (a) Ito, K.; Iida, T.; Kobayashi, T. *Phytochemistry* **1984**, *23*, 188. (b) Mathur, S. B.; Hiremath, S. V.; Kulkarni, G. H.; Kelkar, G. R.; Bhattacharyya, S. C.; Simonovic, D.; Rao, A. S. *Tetrahedron* **1965**, *21*, 3575.

(11) For other recent hydroazulene approaches, see: (a) Devreese, A. A.; Demuynck, M.; De Clercq, P. J.; Vandewalle, M. *Tetrahedron* **1983**, *39*, 3039. (b) Hudlicky, T.; Reddy, D. B.; Govindan, S. V.; Kulp, T.; Still, B.; Sheth, J. P. *J. Org. Chem.* **1983**, *48*, 3422. (c) Kozikowski, A. P.; Mugrage, B. B.; Wang, B. C.; Xu, Z. *Tetrahedron Lett.* **1983**, 3705. (d) Metz, P.; Schäfer, H.-J.; Henkel, G.; Krebs, B. *Tetrahedron Lett.* **1983**, 1959. (e) Posner, G. H.; Loomis, G. L. *Tetrahedron Lett.* **1978**, 4213.

(12) For an excellent review of the chemistry of the cycloheptatrienones, see: Pietra, F. *Chem. Rev.* **1973**, *73*, 293.

(13) For some recent uses of tropone and its derivatives in synthesis, see: (a) Garst, M. E.; Roberts, V. A.; Prussin, C. *J. Org. Chem.* **1982**, *47*, 3969. (b) Rigby, J. H.; Sage, J.-M.; Raggon, J. *J. Org. Chem.* **1982**, *47*, 4815. (c) Greene, A. E.; Teixeira, M. A.; Barreiro, E.; Cruz, A.; Crabbe, P. *J. Org. Chem.* **1982**, *47*, 2553. (d) Uyehara, T.; Ogata, K.; Yamada, J.; Kato, T. *J. Chem. Soc., Chem. Commun.* **1983**, 17.

(14) Radlick, P. *J. Org. Chem.* **1964**, *29*, 960. We have been able to double the reported yield of tropone by carefully monitoring the reaction temperature and stirring the reaction mixture.

(15) (a) Nozoe, T.; Mukai, T.; Tezuka, J. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 619. (b) Chapman, O. L.; Pasto, D. J.; Griswold, A. A. *J. Am. Chem. Soc.* **1962**, *84*, 1213.

(16) For a preliminary account of part of this work, see: Rigby, J. H. *Tetrahedron Lett.* **1982**, 1863.

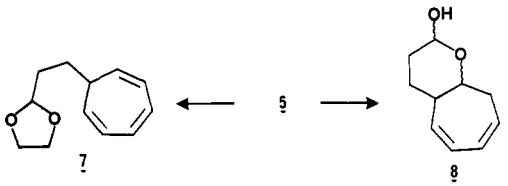
(17) Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122.

(18) Two equivalents of reagent appear to be necessary to obtain maximum yields of adducts.

(19) Ter Borg, A. P.; Kloosterziel, H. *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 741.

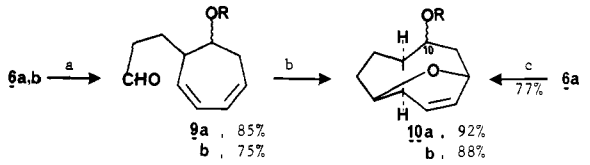
be minimized in the absence of the carbonyl group, and the regiochemical integrity of the diene could be maintained over a number of steps.

Our attention then turned to the conversion of the acetal on the three-carbon side chain into a form suitable for closure to the five-membered ring. The need for protecting the alcohol became immediately apparent when all efforts to expose the aldehyde directly from **5** generated only the lactol **8**. After considerable




experimentation methyl and benzyl ethers were chosen as viable forms of alcohol-group protection. This selection was initially predicated on the expectation that these groups would be able to survive a number of operations intact.

Although the introduction of the methyl ether proceeded without incident to provide **6a** in 85% yield, the benzylation was more troublesome. Only poor yields of **6b** were obtained with benzyl chloride or bromide as the alkylating agent. The major product of these reactions proved to be substituted cycloheptatriene **7**.[20] The use of the more reactive benzyl iodide as the alkylating agent gave excellent yields of **6b**. In contrast to the situation in the absence of alcohol protection, removal of the acetal now proceeded smoothly on the protected alcohols **6a,b** with 5% aqueous TFA in acetone to give the key aldehydes **9a,b** in excellent yields.




a) 5% aq TFA, acetone, b) $BF_3 \cdot Et_2O$, 0° C, $CH_2Cl_2$, c) 50% aq TFA, $CH_2Cl_2$.

The stage was set for examining the means for effecting a closure to the five-membered ring. Of critical importance to the successful implementation of this strategy for guaianolide synthesis was the ability to efficiently prepare a *cis-fused* hydroazulene system since the trans ring fusion is often favored in an equilibrium process in simple perhydroazulene species.[21]

It was initially anticipated that a mixture of hydroazulenic diene alcohols would be the principal products resulting from an acid-catalyzed cyclization of **9**.[22] However, on treatment with 2 equiv of $BF_3 \cdot Et_2O$ at 0 °C in $CH_2Cl_2$, aldehyde **9a** was rapidly (<5 min) consumed and cyclic ether **10a** was formed as a 2:1 mixture of epimers at $C_{10}$ (guaianolide numbering) in 92% yield. No trace of any diene alcohol products could be located, and the cyclization to **10b** in the benzyl series proceeded with only slightly less efficiency.[23]

Table I documents the cyclization results with a variety of acid catalysts. Clearly, $BF_3 \cdot Et_2O$ emerges as the most effective reagent; however, the result in entry 5 was intriguing and suggested the possibility of simultaneously hydrolyzing the acetal in **6** and effecting cyclization in a single operation. To our delight, treatment of acetal **6a** with 50% aqueous TFA in acetone at ambient temperature gave **10a** directly in 77% yield. This remarkable one-step process provided the key cyclic ether in yields competitive with the original two-step sequence.

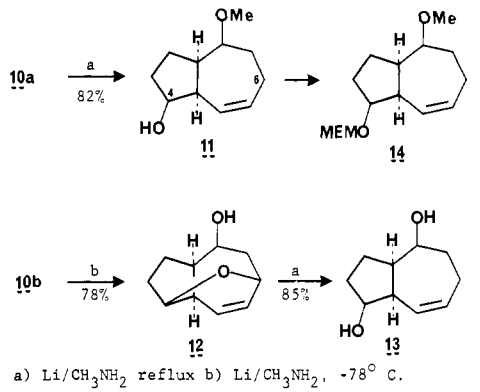
**Table I.** Effect of Acid on the Cyclization of Aldehyde **9a**

| entry | acid[a] | no. of equiv | temp, °C | time | yield of **10a**, %[b] |
|---|---|---|---|---|---|
| 1 | $Et_2AlCl$ | 2 | 0 | 10 min | 60 |
| 2 | $SnCl_4$ | 2 | −78 | 10 min | 62 |
| 3 | $ZnBr_2$ | 2 | 25 | 4 days | 44 |
| 4 | $BF_3 \cdot Et_2O$ | 2 | 0 | 5 min | 92 |
| 5 | concn TFA | 2 | 25 | 1.5 h | 75 |

[a] Freshly distilled $CH_2Cl_2$ was used as solvent in all cases. [b] Yield of isolated, purified cyclic ether **10a**.

The geometrical constraints placed on the approach of the tethered aldehyde to the diene during the formation of cycloadduct[24] **10** ensure that the resulting hydroazulene portion of the molecule possesses a cis fusion.[25] In addition, this process fixes the configuration at $C_4$ relative to the ring fusion, thus providing a potential stereochemical control element for future use. Finally, a fourth asymmetric center at $C_8$ is also present, which may prove useful in the synthesis of members of the $C_8$-oxygenated series of guaianolides. Thus, this novel protocol provides an efficient entry into the requisite hydroazulene series if the cyclic ether can be manipulated to reveal the hydroazulene moiety itself in a useful form.[26]

Reductive fission of allylically activated oxygen–carbon bonds has substantial precedent in the literature.[27] Treatment of **10a** with lithium in methylamine at reflux resulted in the expected smooth scission of the $C_8$ carbon–oxygen bond (guaianolide numbering) to give alcohol **11** in 82% yield. Of critical importance to the subsequent utility of **11** as a guaianolide precursor was the observation that only one of the two possible double-bond regioisomers was isolated from this transformation. Decoupling experiments ascertained that the 6,7-double bond was the isomer




a) $Li/CH_3NH_2$ reflux b) $Li/CH_3NH_2$, −78° C.

(20) Compound **7** was shown to be identical with an authentic sample prepared by addition of the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxolane to tropylium fluoborate.

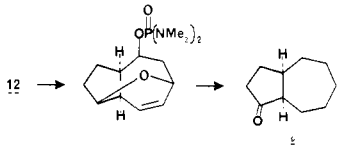
(21) (a) Concannon, P. W.; Ciabattoni, J. *J. Am. Chem. Soc.* **1973**, *95*, 3284. (b) Marshall, J. A.; Huffman, W. F. *J. Am. Chem. Soc.* **1970**, *92*, 6358. (c) House, H. O.; Yau, C. C.; VanDerveer, D. *J. Org. Chem.* **1979**, *44*, 3031. (d) De Clercq, P.; Vandewalle, M. *J. Org. Chem.* **1977**, *42*, 3447.

(22) Marshall, J. A.; Wuts, P. G. M. *J. Org. Chem.* **1977**, *42*, 1794.

(23) After the initial phase of this work was completed, *inter*molecular Lewis acid mediated cyclocondensations of aldehydes and electron-rich diene systems were reported: (a) Danishefsky, S.; Kerwin, J. F.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358. (b) Danishefsky, S.; Kato, N.; Askin, D.; Kerwin, J. F. *J. Am. Chem. Soc.* **1982**, *104*, 360.

(24) The use of the term cycloadduct in this context is a structural designation and not necessarily a mechanistic implication.

(25) The presence of a cis fusion in the hydroazulenes produced by this method was demonstrated by converting **12** into the known ketone *i*, which was shown to be identical with an authentic sample kindly provided by Professor C. D. Gutsche.




(26) In order to carry stereochemically homogeneous material into succeeding reactions the epimers at $C_{10}$ in cyclic ether **10a** were separated by column chromatography. The major epimer, which was assummed to possess the β-configuration at this point, was employed in subsequent reactions during the developmental stages of the synthesis. Material comprised a mixture of $C_{10}$ epimers was often used in preparative scale runs.

(27) (a) Mongrain, M.; Lafontaine, J.; Belanger, A.; Deslongchamps, P. *Can. J. Chem.* **1970**, *48*, 3273. (b) Fanta, W. I.; Erman, W. F. *J. Org. Chem.* **1968**, *33*, 1656. (c) Hallsworth, A. S.; Henbest, H. B.; Wrigley, T. I. *J. Chem. Soc.* **1957**, 1969.

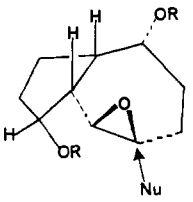



**Figure 1.** Direction of attack of nucleophiles on epoxide **15**.

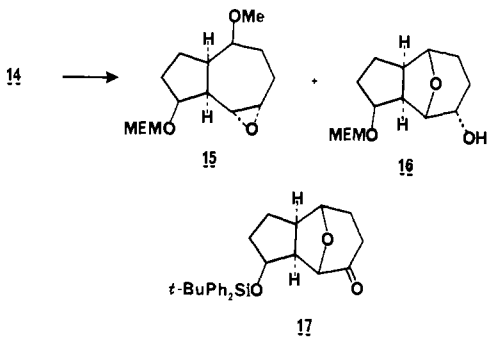
generated.[28] Interestingly, the benzyl ether in **10b** could be selectively severed at −78 °C with Li/$MeNH_2$ to give **12** in 78% yield. Further opening of the dihydropyran ring could be accomplished at reflux to give diol **13**. These results clearly expand the versatility of the benzyl series for subsequent functional group manipulations.

Although the route through the benzyl-protected series appeared quite attractive, we elected to carry the methyl series through to our target molecule. Several practical factors influenced this decision. The yields of each step in the methyl series were uniformly superior to those in the benzyl series. The selective benzyl-group removal, although interesting, added steps to the sequence and ultimately proved to be a somewhat capricious reaction. Although methyl ethers are reputed to be stubborn in removal, recent developments in this area suggested that conditions could be identified which would permit manipulation of the $C_{10}$ position at a later stage in the synthesis. Proceeding on this assumption, the $C_4$ alcohol in **11** was masked as the (methoxyethoxy)methyl (MEM) derivative **14** in quantitative yield.[29] *Thus the key cis-hydroazulene intermediate* ***14*** *can be prepared in only six steps and in over 52% yield from tropone* (***3***).

Hydroazulene **14** possesses several features that are of considerable significance to the success of our synthetic endeavors. Most importantly, the β-oriented substituent at $C_4$ should act as a potential stereochemical control element which could aid in the subsequent introduction of additional substituents. The oxygen substituents at $C_4$ and $C_{10}$ would also serve as masked ketone equivalents, ensuring against possible premature equilibration to the thermodynamically preferred but unwanted *trans*-hydroazulene throughout much of the remaining portion of the synthetic sequence.[30]

The fortuitous double bond regioselection obtained from the dissolving metal reduction of cyclic ether **10a** greatly simplified the task of elaborating the *trans*-γ-butyrolactone. It was planned that the lactone could be introduced via an epoxide opening with an appropriate carbon nucleophile. The correct configuration at $C_6$ would then be established at the epoxidation stage. This epoxidation was anticipated to occur primarily from the more accessible convex face of **14**, and the point of attack on the epoxide would be dictated by approach of the nucleophile from the sterically least congested direction (Figure 1).

Surprisingly, treatment of hydroazulene **14** with *m*-chloroperoxybenzoic acid gave two products in a ratio of about 2:1 in 82% yield. The major product was shown to be the desired epoxide **15**, but the more polar species appeared to possess structure **16** on the basis of $^1H$ NMR and IR data. Only a trace amount of the β-epoxide was isolated from this reaction. The structural assignment for **16** was unambiguously established by single-crystal X-ray analysis on ketone **17** which was prepared




from the corresponding 4-*tert*-butyldiphenylsilyl-protected hydroazulene by treatment with *m*-chloroperoxybenzoic acid followed by oxidation.[31] The facility of this cyclization reflects the conformational mobility of the *cis*-hydroazulene ring system, and, in fact, a number of natural products have recently been isolated that feature tetrahydrofuran systems not unlike the one found in compounds **16** and **17**.[32]

An extensive search was mounted to identify epoxidation conditions that could circumvent this interesting but annoying side reaction. It was quickly learned that using a substrate bearing a methyl group on the $C_{10}$ oxygen in this reaction yielded the minimum amount of **16**. As would be expected, performing this epoxidation on a mixture of $C_{10}$ epimers resulted in increased yields of epoxide products as well. This tactic was employed in subsequent preparative scale runs since the configuration at $C_{10}$ is irrelevant to our ultimate purposes. To date, no conditions have been found that completely avoid the formation compound **16**.

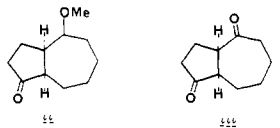
Epoxide **15**, which was easily separated from the other product, was then treated with a large excess of dilithioacetate in DME in order to introduce the final two-carbon portion of the requisite γ-butyrolactone.[33] This transformation proceeded without incident at 60 °C over a period of 4 to 5 days to give lactone **18** as the only identifiable product in 78% yield.[34] Attempting the same reaction under the identical conditions on the corresponding epoxide having a *tert*-butyldimethylsilyl group on the $C_4$ alcohol gave no discernable reaction after 6 days. The same reaction was completed in about 2 days employing a substrate with methyl ether protection at $C_4$ and $C_{10}$, but 10–15% of the product resulting from carbanion attack at $C_6$ was isolated in addition to the expected lactone regioisomer.

At this juncture in the synthetic scheme, our attention was directed to the introduction of the necessary exocyclic methylene groups at $C_4$ and $C_{10}$. Initially a strategy designed for sequential elaboration of the olefins was pursued and lactone **18** provided an attractive intermediate for this purpose. Efforts to selectively remove the (methoxyethoxy)methyl ether at $C_4$ using standard procedures were, on the whole, unsuccessful. After some developmental work, we were able to cleanly and efficiently deprotect the (methoxyethoxy)methyl ether with $Me_3SiCl$/NaI at −20 °C in acetonitrile to generate lactone alcohol **19** in 79% yield.[35] Swern oxidation then produced keto lactone **20** in 90% yield. This compound was the first intermediate in our sequence that was potentially susceptible to ring fusion equilibration. However, it has been previously noted[6a,36] that a butyrolactone moiety ap-

(28) Other methods of breaking this carbon–oxygen bond do not proceed with as high a degree of regioselectivity. Results on these observations will be reported in due time.

(29) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

(30) The thermodynamic preference for the trans fusion in this series has been confirmed by equilibration studies on compounds ii and iii. In each case




ii iii

the trans isomer prevailed at equilibrium in a ratio of approximately 85:15. The isomers were easily separated by flash chromatography.

(31) The β-configuration of the major $C_{10}$ epimer in this series was confirmed by this X-ray data.

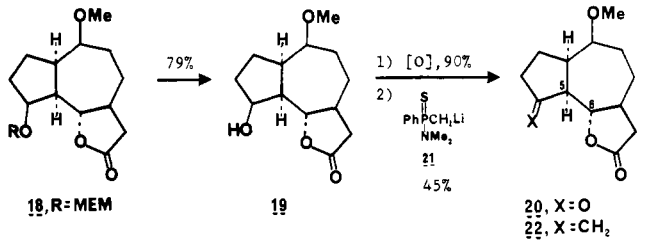
(32) (a) Battaglia, R.; De Bernardi, M.; Fronza, G.; Mellerio, G.; Vidari, G.; Vita-Finsi, P. *J. Nat. Prod.* **1980**, *43*, 319 (b) Amico, V.; Oriente, G.; Piatelli, M.; Trignali, C. *Phytochemistry* **1979**, *18*, 1895.

(33) Danishefsky, S.; Schuda, P. F.; Kitahara, T.; Etheredge, S. J. *J. Am. Chem. Soc.* **1977**, *99*, 6066.

(34) The regio- and stereochemistry assigned to the newly formed lactone was substantiated by the diagnostic downfield chemical shift of $H_6$ (δ 4.45) indicative of a β-electronegative substituent at $C_{10}$: Vichnewski, W.; Welbaneide, F.; Machado, L.; Rabi, J. A.; Murari, R.; Herz, W. *J. Org. Chem.* **1977**, *42*, 3910.

(35) Rigby, J. H.; Wilson, J. Z. *Tetrahedron Lett.* **1984**, *25*, 1429.

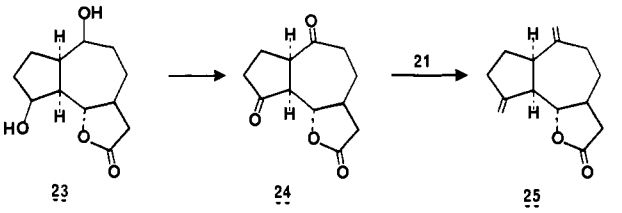
(36) (a) Herz, W.; Lakshmikantham, M. V.; Mirrington, R. N. *Tetrahedron* **1966**, *22*, 1709. (b) Romo de Vivar, A.; Rodriquez-Hahn, L.; Romo, J.; Lakshmikantham, M. V.; Mirrington, R. N.; Kagan, J.; Herz, W. *Tetrahedron* **1966**, *22*, 3279.




pended to the seven-membered ring of a hydroazulene often reverses the trend seen in simpler hydroazulene systems in which the trans fusion is more stable. Consequently, the 1,3-disposition of the $C_4$ carbonyl group and the $C_6$ lactone oxygen in **20** provided greater reason for concern. Enolization at this point could irreversibly disrupt the carefully developed relative stereochemistry at $C_5$ and $C_6$. Indeed, attempted reaction via the usual assortment of methylenation methods (Wittig, Peterson, etc.) led only to the anticipated $\beta$-elimination process.[37] In contrast, exposure of **20** to (lithiomethyl)phosphinothioic dimethyl amide **21**[38] followed by adduct collapse with methyl iodide and pyridine provided a satisfactory return of ene lactone **22**.

Unfortunately, we were unable at this point to remove the methyl group at $C_{10}$ and, at the same time, retain the regiochemical integrity of the $C_4$ exocyclic double bond. The unsaturation moved rapidly into the ring on attempted demethylation. This event was not entirely unexpected since similar observations in related species have been made previously.[39] Having established reliable methodology for the introduction of the potentially troublesome $C_4$ methylene group, the possibility of simultaneous elaboration of both olefins was considered. This approach would be particularly advantageous in terms of economizing on the number of steps necessary for completion of the synthesis.

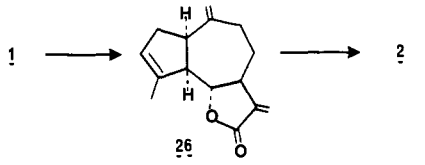
We were gratified when both ether protecting groups could be cleanly removed in one pot simply by exposing lactone **18** to excess $Me_3SiCl/NaI$ at ambient temperature for several hours. Scrupulously dried materials were essential to the success of this double deprotection. This is in contrast to the selective removal of the (methoxyethoxy)methyl ether in **18** in which reagents used "out of the bottle" were satisfactory. The resulting diol **23** was immediately oxidized under Swern conditions to give dione lactone **24** in an overall yield of 42% for the two steps.




Treatment of this material with 2 equiv of reagent **21** followed by adduct decomposition under conditions identical with those of the previous case provided the key diene lactone **25** in modest yield. In this particular instance the addition of the organolithium reagent proceeded cleanly, but all of the resulting adduct could not be efficiently converted into the corresponding diene. Other methylenation procedures that were examined proved to be totally ineffectual with substrate **24**.

The final stage of the synthesis, introduction of the methylene group onto the lactone, was achieved by using methodology employing Eschenmoser's salt as the source of the methylene carbon.[40] After quaternization and elimination of trimethylamine, dehydrocostus lactone (**1**) was obtained in 71% yield. The synthetic material, obtained in only 12 steps from tropone (**3**), was identical with an authentic sample of natural dehydrocostus lactone by comparison of IR, $^1H$ NMR, and TLC data.

Finally, the dehydrocostus lactone produced by this scheme was treated with 1 equiv of $BF_3 \cdot Et_2O$ in benzene to give diene lactone **26** in 68% yield.[39] Regio- and stereoselective epoxidation[6a]




proceeded smoothly to give (±)-estafiatin (**2**), which exhibited $^1H$ NMR and TLC data identical with those of estafiatin prepared in the same fashion from authentic dehydrocostus lactone.

The syntheses outlined herein demonstrate that tropone-based strategies are both efficient and potentially general entries into intermediates that are suitably functionalized for elaboration into a wide range of hydroazulenic sesquiterpenes.

## Experimental Section

**General Experimental.** All reactions were run under an atmosphere of dry nitrogen. Solvents were freshly distilled prior to use: tetrahydrofuran (THF) was distilled from sodium benzophenone; dimethoxyethane (DME) was distilled from lithium aluminum hydride followed by distillation from sodium benzophenone; acetonitrile was distilled from calcium hydride; dimethyl sulfoxide ($Me_2SO$) was distilled from potassium hydroxide. Unless otherwise noted, all reaction mixtures were dried, after workup, over anhydrous sodium sulfate.

**2-[2-(1,3-Dioxolan-2-yl)ethyl]-3,5-cycloheptadien-1-one (4).** To a suspension of 24 g (1.0 mol) of magnesium turnings in 600 mL of dry. THF were added one crystal of iodine, *ca.* 0.5 mL of 1,2-dibromoethane, and several drops of a solution of 2-(2-bromoethyl)-1,3-dioxolane[17] (180 g, 1.0 mol) in 200 mL of dry THF from an addition funnel. The stirred mixture was gently warmed with a heat gun to initiate the reaction. As the reaction proceeded, the 2-(2-bromoethyl)-1,3-dioxolane solution was added slowly, 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 for an additional 1 h at room temperature and then cooled to 0 °C. Tropone (**3**)[14] (53 g, 0.5 mol) in 50 mL of dry THF was then added slowly from an addition funnel. As the tropone was added a transient red-orange color was observed. When the addition was complete, the reaction mixture was stirred for 30 min at 0 °C, after which time a precipitate appeared. The mixture was quenched at 0 °C by the addition of 130 mL of a 10% aqueous HCl solution. Upon quenching, the precipitate disappeared, the reaction mixture went from a greenish yellow to deep orange, and this mixture was poured into 1 L of ether. The organic phase was washed with one 600-mL portion of water, three 500-mL portions of a saturated aqueous sodium bicarbonate solution, and then brine. The organic layer was dried and the solvent evaporated in vacuo to yield 100 g (96%) of the ketone **4** which was used in the next step without further purification: IR ($CCl_4$) $\nu$ 3025, 2960, 2880, 1720, 1600, 1140, 1045 $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$ 1.3–2.2 (m, 4 H), 2.7–3.2 (m, 3H), 3.6–4.0 (m, 4 H), 4.8 (t, $J$ = 4 Hz, 1 H), 5.4–6.5 (m, 4 H).

**2-[2-(1,3-Dioxolan-2-yl)ethyl]-3,5-cycloheptadien-1-ol (5).** A solution of the crude ketone **4** (100 g, 0.483 mol) in 480 mL of absolute methanol was cooled to 0 °C, and solid sodium borohydride was added in small portions until TLC analysis showed the reaction to be complete. The reaction mixture was then carefully quenched by a slow addition of a 10% aqueous HCl solution until foaming ceased. The methanol was removed under reduced pressure, and the resulting two-phase residue was taken up in 1 L of ether. The organic layer was separated and washed with two 500-mL portions of a saturated aqueous sodium bicarbonate solution and one 500-mL portion of brine. The ether layer was dried and the solvent evaporated under reduced pressure to give a brown oil which was purified by column chromatography on 1.5 kg of silica gel, eluting with 3:1 ether/hexanes. This yielded 90 g (89%) of the alcohol **5**: $R_f$ 0.2 (1:1 ether/hexanes); IR ($CCl_4$) $\nu$ 3560, 3500, 3010, 2980, 2900, 1615, 1440, 1400, 1150, 1040 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.27–1.91 (m, 4 H), 2.23–2.61 (m, 4 H), 3.75–4.20 (m, 5 H), 4.87 (m, 1 H), 5.50–5.98 (m, 4 H); mass spectrum, $m/e$ (%) 210 (5), 148 (7), 130 (8), 122 (16), 99 (30), 73 (100), 130 (8); high-resolution mass spectrum, calcd for $C_{12}H_{18}O_3$, 210.125 58; found, 210.125 43.

**1-Methoxy-2-[2-(1,3-dioxolan-2-yl)ethyl]-3,5-cycloheptadiene (6a).** To a stirred suspension of 23 g (476 mmol) of a 50% sodium hydride dispersion (washed with two 100-mL portions of dry pentane before use)

(37) Cyclopentanones are often prone to enolization during Wittig methylenation: (a) Sondheimer, F.; Mechoulam, R. *J. Am. Chem. Soc.* **1957**, *79*, 5029. (b) Wittig, G.; Böll, W.; Krück, K.-H. *Chem. Ber.* **1962**, *95*, 2514.
(38) Johnson, C. R.; Elliot, R. C. *J. Am. Chem. Soc.* **1982**, *104*, 7041.
(39) Macaira, L. A.; Garcia, M.; Rabi, J. A. *J. Org. Chem.* **1977**, *42*, 4207.
(40) Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 330.
(41) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

in 140 mL of dry THF at 0 °C was added a solution of alcohol **5** (50 g, 238 mmol) in 100 mL of THF. The reaction mixture was allowed to stir at 0 °C for 30 min, and then 23 mL (357 mmol) of methyl iodide was added. The cooling bath was removed, and the reaction was allowed to stir at room temperature for an additional 30 min, then cooled to 0 °C, and quenched with water. The mixture was diluted with 1 L of ether, washed with brine, and dried. Evaporation of the solvent afforded a crude oil, which was purified by column chromatography on 1.0 kg of silica gel (elution with 3:7 ether/hexanes) to yield 102 g (96%) of the methyl ether **6a**: $R_f$ 0.66 (1:1 ether/hexanes); IR ($CCl_4$) $\nu$ 3020, 2970, 2950, 2910, 1440, 1150, 1100, 1050 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.60–1.70 (m, 4 H), 2.50–2.60 (m, 3 H), 3.30 (s, 3 H), 3.58 (m, 1 H), 3.85 (m, 4 H), 4.83 (t, $J$ = 5 Hz, 1 H), 5.77 (m, 4 H); mass spectrum, $m/e$ (%) 224 (13), 209 (6), 193 (24), 192 (27), 131 (54), 99 (94), 73 (100). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99; Found: C, 69.47; H, 8.93.

**1-(Phenylmethoxy)-2-[2-(1,3-dioxolan-2-yl)ethyl]-3,5-cycloheptadiene (6b).** To a stirred suspension of 50% sodium hydride dispersion (5.3 g, 111.4 mmol, washed with two 50-mL portions of dry pentane prior to use) in 35 mL of dry THF at 0 °C was added a solution of alcohol **5** (11.7 g, 55.7 mmol) in 20 mL of THF. The reaction mixture was stirred at 0 °C for 30 min, and then 14.6 g (66.8 mmol) of benzyl iodide (**Caution**: **severe lachrymator!**) was added. The reaction mixture was allowed to stir for an additional 3.5 h and then quenched with 100 mL of water. The resulting two-phase mixture was diluted with 300 mL of ether, and the organic layer separated and washed with brine. Drying and evaporation of the solvent gave the crude benzyl ether **6b** which was purified by flash chromatography on 250 g of silica gel (3:7 ether/hexanes as eluent). This gave 16.0 g (95%) of benzyl ether **6b**: $R_f$ 0.75 (1:1 ether/hexanes); IR ($CCl_4$) $\nu$ 3100, 3025, 2980, 2900, 1620, 1500, 1460, 1420, 1370, 1150, 1110, 1080, 920 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.07–2.03 (m, 4 H), 2.20–2.75 (m, 3 H), 3.71–4.03 (m, 5 H), 4.40 (s, 2 H), 4.88 (m, 1 H), 5.65–6.00 (m, 4 H), 7.29 (s, 5 H); mass spectrum, $m/e$ (%) 300 (50), 299 (20), 270 (18), 259 (40), 238 (40), 210 (70), 209 (100), 192 (60), 179 (50); high-resolution mass spectrum, calcd for $C_{19}H_{24}O_3$, 300.172 53; found, 300.173 30.

**1-Methoxy-2-[3-(1-oxopropyl)]-3,5-cycloheptadiene (9a).** To 43.0 g (192 mmol) of methyl ether **6a** were added 86 mL of a 5% aqueous solution of trifluoroacetic acid and enough acetone (ca. 250 mL) to make the reaction mixture homogeneous. After stirring at room temperature for 5 days, the acetone was evaporated under reduced pressure, and the two-phase mixture was diluted with 800 mL of ether. The organic layer was washed with two 400-mL portions of a saturated aqueous sodium bicarbonate solution followed by brine. After the solvent was dried and evaporated, column chromatography on 1.0 kg of silica gel (3:7 ether/hexanes as eluent) yielded 29 g (85%) of the aldehyde **9a**: $R_f$ 0.61 (1:1 ether/hexanes); IR ($CCl_4$) $\nu$ 3010, 2925, 2900, 2820, 2725, 1725, 1615, 1460, 1400, 1100 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.40–2.00 (m, 3 H), 2.25–2.60 (m, 4 H), 3.32 (s, 3 H), 3.48 (m, 1 H), 5.60–5.90 (m, 4 H), 9.74 (m, 1 H); mass spectrum, $m/e$ (%) 180 (4), 148 (9), 136(16), 137 (12), 130 (25), 121 (20), 104 (60), 91 (100), 79 (59); high-resolution mass spectrum, calcd for $C_{11}H_{16}O_2$, 180.115 01; found, 180.114 51.

**1-(Phenylmethoxy)-2-[3-(1-oxopropyl)]-3,5-cycloheptadiene (9b).** To 16.0 g of benzyl ether **6b** were added 32 mL of a 5% aqueous solution of trifluoroacetic acid and enough acetone to make the solution homogeneous (ca. 100 mL). After stirring at room temperature for 5 days, the acetone was removed under reduced pressure and the residue taken up in 500 mL of ether. The ether layer was washed with 200 mL of a saturated aqueous sodium bicarbonate solution and then with brine. Drying followed by evaporation of the solvent gave the crude aldehyde **9b**. After flash chromatography on 500 g of silica gel (1:2 ether/hexanes), 10.3 g (75%) of **9b** was obtained: $R_f$ 0.72 (1:1 ether/hexanes); IR ($CCl_4$) $\nu$ 3095, 3050, 2950, 2900, 2720, 1730, 1625, 1500, 1460, 1100, 1080, 1040 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.10–2.81 (m, 7 H), 3.87 (m, 1 H), 4.51 (s, 2 H), 5.62–5.95 (m, 4 H), 7.31 (s, 5 H), 9.71 (brs, 1 H); mass spectrum, $m/e$ (%) 256 (2), 165 (17), 148 (11), 122 (15), 94 (28), 92 (100); high-resolution mass spectrum, calcd for $C_{17}H_{20}O_2$, 256.146 31; found, 256.146 01.

**4$\beta$-Methoxy-1$\alpha$,2,3,3a$\alpha$,4$\alpha$,5,6$\alpha$,8a$\alpha$-octahydro-1,6-epoxyazulene (10a).** To a solution of the aldehyde **9a** (27 g, 151 mmol) in 600 mL of $CH_2Cl_2$ cooled to 0 °C was added 37 mL (302 mmol) of freshly distilled boron trifluoride etherate complex via syringe. During the addition the reaction mixture turned a deep purple color. 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 removal of the solvent under reduced pressure gave the cyclic ether **10a** as a pale yellow oil which was purified by column chromatography on 800 g of silica gel (1:4 ether/hexanes as eluent), yielding 16.5 g of the $\beta$-$C_{10}$ epimer and 8.3 g of the $\alpha$ epimer of **10a** (92% combined yield).

$\beta$ epimer: $R_f$ 0.61 (1:1 ether/hexanes); IR ($CCl_4$) $\nu$ 2940, 2890, 2820, 1460, 1100, 1040 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.60–2.00 (m, 6 H), 2.69 (m, 2 H), 3.15 (m, 1 H), 3.27 (s, 3 H), 3.93 (br s, 1 H), 4.37 (br s, 1 H), 6.23 (m, 2 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 21.58, 34.24, 39.87, 42.39, 55.82, 68.14, 77.50, 78.36, 128.63, 131.95; mass spectrum, $m/e$ (%) 180 (33), 148 (16), 137 (16), 121 (44), 104 (54), 91 (91). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95; Found: C, 73.35; H, 8.96.

$\alpha$ epimer: $R_f$ 0.52 (1:1 ether/hexanes); $^1H$ NMR ($CDCl_3$) $\delta$ 1.47 (m, 1H), 1.73 (m, 1 H), 2.02 (m, 4 H), 2.56 (m, 1 H), 2.71 (m, 1 H), 3.17 (m, 1 H), 3.24 (s, 3 H), 3.95 (t, $J$ = 4 Hz, 1 H), 4.36 (m, 1 H), 6.28 (m, 2 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 27.16, 34.63, 35.48, 42.43, 42.82, 56.20, 70.37, 78.23, 81.87, 129.49, 131.83.

The cyclization can also be achieved in one step from acetal **6a** using the following procedure:

To 2.2 g of acetal **6a** were added 6.6 mL of a 50% aqueous solution of trifluoroacetic acid and enough acetone to make the solution homogeneous (ca. 20 mL). After the mixture was stirred at room temperature for 5 days, the acetone was evaporated under reduced pressure, and the resulting two-phase residue was diluted with ether. The ether layer was washed with a saturated aqueous sodium bicarbonate solution followed by brine. Removal of the solvent under reduced pressure followed by flash chromatography of the resulting oil on 100 g of silica gel (3:7 ether/hexanes) gave 1.36 g (77%) of the cyclic ether **10a** as a mixture of $C_{10}$ epimers.

**4-(Phenylmethoxy)-1$\alpha$,2,3,3a$\alpha$,4$\alpha$,5,6$\alpha$,8a$\alpha$-octahydro-1,6-epoxyazulene (10a).** To a stirred solution of aldehyde **9b** (2.08 g, 8.13 mmol) in 30 mL of $CH_2Cl_2$ cooled to 0 °C was added freshly distilled boron trifluoride etherate complex (2.0 mL, 16.25 mmol). After being stirred for 5 min, the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution. The two-phase mixture was diluted with 300 mL of ether, and the organic layer was separated and washed with several portions of saturated aqueous sodium bicarbonate solution followed by brine. The ether layer was dried and the solvent removed in vacuo. Purification of the resulting oil (flash chromatography on 100 g of silica gel eluting with 1:2 ether/hexanes) gave 1.83 g (88%) of **10b** as an inseparable mixture of $C_{10}$ epimers: $R_f$ 0.59 (1:1 ether/hexanes); IR ($CCl_4$) $\nu$ 3050, 3030, 2925, 1490, 1450, 1380, 1350, 1170, 1090, 1050, 1035 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.42–2.40 (m, 6 H), 2.63 (m, 2 H), 3.36 (m, 1 H), 3.93 (m, 1 H), 4.34 (m, 1 H), 4.43 (s, 2 H), 6.08–6.34 (m, 2 H), 7.2, (s, 5 H); mass spectrum, $m/e$ (%) 256 (11), 238 (4), 212 (3), 174 (8), 165 (100), 147 (43), 121 (87), 91 (98). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.66; H, 7.87; Found: C, 79.65; H, 7.83.

**4-Methoxy-1$\alpha$,2,3,3a$\alpha$,4$\alpha$,5,6,8a$\alpha$-octahydroazulen-1-ol (11).** Anhydrous monomethylamine (1.5 L) was condensed into a flask equipped with a dry ice condenser. The cyclic ether **10a** (17.2 g, 95.6 mmol) in 200 mL of dry diethyl ether was added to the amine, and the rapidly stirred reaction mixture was allowed to come to reflux (~6 °C). Freshly cleaned lithium metal (1.4 g, 191.2 mmol) was added in small pieces. Each piece was allowed to react completely before the next piece was added. When the addition was complete the reaction mixture turned a deep blue. At this point the contents of the flask were cooled to −78 °C, and the reaction was quenched with solid ammonium chloride (until color paled). The cooling bath was removed, and the amine was allowed to evaporate under a constant stream of nitrogen. Ether (1 L) and then water (500 mL) were added to the pale yellow residue. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and dried. Evaporation of the solvent under reduced pressure followed by flash chromatography on 350 g of silica gel (1:1 ether/hexanes as eluent) afforded 14.2 g (82%) of the alcohol **11**: $R_f$ 0.43 (1:1 ether/hexanes); IR ($CCl_4$) $\nu$ 3450, 3000, 2915, 2830, 2815, 1670, 1450, 1430, 1420, 1160, 1100, 1080, 1040, 1000, 955, 900 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.44–1.87 (m, 5 H), 1.93–2.45 (m, 4 H), 2.64 (m, 1 H), 3.13 (s, 3 H), 3.37 (m, 1 H), 3.86 (m, 1 H), 5.43 (m, 2 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 23.72, 28.00, 34.24, 45.09, 49.64, 57.42, 75.50, 82.26, 127.22, 129.95; mass spectrum $m/e$ (%) (no $M^+$) 150 (7), 132 (8), 119 (42), 131 (64), 116 (53), 105 (94), 103 (97), 90 (100). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95; Found: C, 72.50; H, 10.00.

**4-Hydroxy-1$\alpha$,2,3,3a$\alpha$,4$\alpha$,5,6$\alpha$,8a$\alpha$-octahydro-1,6-epoxyazulene (12) and 1,4-Dihydroxy-1$\alpha$,2,3,3a$\alpha$,4$\alpha$,5,6,8a$\alpha$-octahydroazulene (13).** Anhydrous monomethylamine (1 L) was condensed into a cooled (−78 °C) flask equipped with a dry ice condenser. Cyclic ether **9b** (11.3 g, 44.14 mmol) in 150 mL of ether was introduced, and freshly cleaned lithium metal (0.618 g, 88.28 mmol) was added in small pieces to the rapidly stirred reaction mixture. Each piece was allowed to react completely before the next piece was added. When the addition was complete, the reaction mixture was quenched by the addition of solid ammonium chloride. The cooling bath was removed, and the amine was allowed to evaporate under a constant stream of nitrogen. The pale yellow residue was taken up in 1 L of ether, washed with brine, and dried. Evaporation of the solvent followed by flash chromatography on 200 g of silica gel

(ether as eluent) gave 5.72 g (78%) of the alcohol **12** and 0.740 g (10%) of the diol **13**. Alcohol **12**: $R_f$ 0.31 (ether); IR ($CCl_4$) $\nu$ 3620, 3400, 3060, 2940, 1460, 1440, 1380, 1170, 1045, 910 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 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.

Diol **13** can be obtained as the sole product of the reaction by employing the following procedure:

To 600 mL of anhydrous monomethylamine, cooled to −78 °C, was added cyclic ether **9b** (6.8 g, 26.56 mmol) in 100 mL of ether. The cooling bath was removed, and the amine solution allowed to come to reflux (−6 °C). Lithium metal (0.743 g, 106.25 mmol) was added in small pieces, allowing each piece to react completely prior to the addition of the next piece. When the addition was complete, the reaction mixture turned a deep blue color which paled upon quenching with solid ammonium chloride at −78 °C. The amine was allowed to evaporate under a constant stream of nitrogen. The crude residue was taken up in 800 mL of ether, washed with brine, and dried. Evaporation of the solvent followed by flash chromatography on 150 g of silica gel (ether as eluent) yielded 3.8 g (85%) of diol **13**: $R_f$ 0.51 (ether); IR ($CCl_4$) $\nu$ 3620, 3300, 2940, 1460, 1440, 1170, 1110, 1050, 910 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.50–2.08 (m, 8 H), 2.10–2.54 (m, 3 H), 2.78 (m, 1 H), 3.95 (m, 1 H), 4.16 (m, 1 H), 5.62 (m, 1 H), 5.88 (m, 1 H); mass spectrum, *m/e* (%) 151 (8), 133 (20), 118 (15), 107 (100), 105 (80), 92 (60), 80 (40); high-resolution mass spectrum, calcd for ($M^+$ − 18), 150.104 45; found, 150.105 29.

**4-Methoxy-1-[(2-methoxyethoxy)methoxy]-1α,2,3,3aα,4α,5,6,8aα-octahydroazulene (14).** To 14.2 g (78.0 mmol) of alcohol **11** in 78 mL of $CH_2Cl_2$ were added 16.3 mL (93.6 mmol) of diisopropylethylamine and 10.6 mL (93.6 mmol) of (2-methoxyethoxy)methyl chloride.[29] The reaction mixture was stirred at room temperature for 2 h and then poured into 600 mL of ether. The ether mixture was washed quickly with 200 mL of a 5% aqueous HCl solution, 200 mL of saturated aqueous sodium bicarbonate solution, and brine. The organic layer was dried and the solvent removed under reduced pressure. Flash chromatography on 300 g of silica gel (1:4 ether/hexanes as eluent) gave 20.4 g (97%) of (methoxyethoxy)methyl ether **14**: $R_f$ 0.55 (1:1 ether/hexanes); IR ($CCl_4$) $\nu$ 3015, 2920, 2895, 2810, 1660, 1465, 1455, 1370, 1200, 1095, 970 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.45–2.00 (m, 7 H), 2.20 (m, 1 H), 2.45 (m, 1 H), 2.70 (br s, 1 H) 3.35 (s, 3 H), 3.42 (s, 3 H), 3.48 (m, 1 H), 3.59 (m, 2 H), 3.72 (m, 2 H), 4.10 (m, 1 H), 4.68 (s, 2 H), 5.70 (m, 1 H), 5.86 (m 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 19.30, 24.95, 26.77, 27.61, 41.26, 41.91, 56.33, 58.93, 66.99, 71.86, 79.98, 83.82, 94.92, 127.28, 131.70; mass spectrum, *m/e* (%) (no $M^+$) 199 (3), 195 (6), 194 (9), 164 (45), 132 (25), 91 (39), 89 (100). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69; Found: C, 66.71; H, 9.85.

**4β-Methoxy-1β-[(2-methoxyethoxy)methoxy]-1α,2,3,3aα,4α,5,6,-7β,8β,8aα-decahydro-7,8-epoxyazulene (15).** The (methoxyethoxy)-methyl ether **14** (12.5 g, 46.30 mmol) in 200 mL of $CH_2Cl_2$ was cooled to 0 °C, and 10.0 g (46.30 mmol) of 85% *m*-chloroperoxybenzoic acid was added. The cooling bath was removed, and the reaction was allowed to warm to room temperature. After 1 h, the reaction mixture was poured into 500 mL of chloroform and washed with 300 mL of a 10% aqueous sodium sulfite solution followed by saturated aqueous sodium bicarbonate solution and brine. The chloroform layer was dried and the solvent evaporated to give a 2:1 mixture of the desired epoxide **15** and the alcohol **16**. These were separated by flash chromatography on 250 g of silica gel (5:1 ether/hexanes as eluent) to yield 7.15 g (54%) of epoxide **15** and 3.54 g (28%) of the alcohol **16**. Epoxide **15**: $R_f$ 0.63 (ether); IR ($CCl_4$) $\nu$ 2950, 2900, 2820, 1460, 1180, 1140, 1100, 1050, 850 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.40 (m, 5 H), 1.40–2.10 (m, 4 H), 2.28 (m, 2 H), 2.98 (t, $J$ = 5 Hz, 1 H), 3.09 (m, 1 H), 3.21 (s, 3 H), 3.35 (s, 3 H), 3.50 (m, 2 H), 3.66 (m, 1 H), 4.23 (m, 1 H), 4.73 (s, 2 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 19.87, 22.47, 24.61, 28.57, 40.37, 41.36, 54.15, 55.39, 56.42, 58.96, 67.14, 71.81, 80.19, 83.05, 94.99; mass spectrum, *m/e* (%) (no $M^+$) 197 (25), 181 (20), 180 (25), 165 (15), 166 (20), 149 (38), 148 (37), 147 (18), 131 (35), 130 (52), 89 (100). Anal. Calcd for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15; Found: C, 62.93; H, 9.34.

Alcohol **16**: $R_f$ 0.22 (ether); IR ($CCl_4$) $\nu$ 3480, 2950, 2880, 1130, 1100 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.36–1.89 (m, 8 H), 2.37 (m, 1 H), 2.60 (m, 1 H), 2.76 (t, $J$ = 8 Hz, 1 H), 3.38 (s, 3 H), 3.57 (m, 4 H), 3.73 (m, 1 H), 3.85 (m, 1 H), 3.98 (br s, 1 H), 4.40 (m, 1 H), 4.77 (s, 2 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 26.12, 29.37, 29.69, 31.97, 44.38, 45.87, 58.99, 67.25, 67.70, 71.99, 78.55, 81.22, 83.43, 99.64; mass spectrum, *m/e* (%) (no $M^+$) 183 (3), 152 (10), 111 (5), 89 (34), 70 (62), 61 (100). Anal. Calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88; Found: C, 61.69; H, 8.88.

**9-[(2-Methoxyethoxy)methoxy]-6-methoxy-3aα,4,5,6α,6aα,7,8,9α,-9aα,9bβ-decahydroazuleno[4,5-*b*]furan-2(3*H*)-one (18).** To a solution of diisopropylamine (58.7 mL, 419.6 mmol) in 200 mL of DME at −78 °C was added 262.3 mL (419.6 mmol) of *n*-BuLi (1.6 M in hexanes) from a thoroughly dried addition funnel. The reaction mixture was allowed to warm to −40 °C, and 12.0 mL of glacial acetic acid (distilled from $KMnO_4$, then from $P_2O_5$ prior to use) in 30 mL of DME was added. The cooling bath was removed, and the reaction mixture was allowed to slowly warm to 60 °C. After the mixture was stirred for 2 h at this temperature, 3.0 g (10.50 mmol) of the epoxide **15** in 20 mL of DME was added. The reaction was maintained at 60 °C for 4 days, then cooled to 0 °C, and quenched by the slow addition of 100 mL of water. The DME was evaporated in vacuo, and the remaining yellow solution was diluted with water and extracted twice with ethyl acetate. The combined ethyl acetate fractions were back-extracted twice with a 5% aqueous NaOH solution. The combined aqueous phases were acidified to pH 2 by the careful, dropwise addition of concentrated HCl. Ethyl acetate was then added, and the two-phase solution was stirred for 2 h. After the ethyl acetate layer was separated, it was washed with water, several portions of saturated aqueous sodium bicarbonate solution, and brine. Drying over anhydrous sodium sulfate followed by evaporation of the solvent yielded the crude lactone **18** which was purified by flash chromatography on 100 g of silica gel (ether as eluent). This gave 2.69 g (78%) of lactone **18**: $R_f$ 0.54 (1:4 ethyl acetate/ether); IR ($CCl_4$) $\nu$ 2950, 2830, 1790, 1460, 1100, 1080, 1040 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.17 (m, 1 H), 1.43 (m, 1 H), 1.69–1.81 (m, 5 H), 2.17 (dd, $J$ = 12, 17 Hz, 1 H), 2.55 (dd, $J$ = 8, 17 Hz, 1 H) 2.66 (m, 1 H), 2.86 (m, 1 H), 3.30 (m, 1 H), 3.33 (s, 3 H), 3.39 (s, 3 H), 3.54 (m, 2 H), 3.64 (m, 2 H), 4.22 (dd, $J$ = 15.5, 10.5 Hz, 1 H), 4.45 (t, $J$ = 5 Hz, 1 H), 4.69 (s, 2 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 24.33, 28.61, 30.12, 31.84, 36.77, 39.70, 41.75, 42.02, 56.65, 58.99, 67.18, 71.76, 80.22, 82.56, 86.43, 94.39, 176.26; mass spectrum, *m/e* (%) (no $M^+$) 254 (25), 253 (10), 240 (40), 224 (95), 203 (25), 193 (45), 192 (60), 191 (48), 165 (30), 89 (100). Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.18; H, 8.59; Found: C, 62.00; H, 8.71.

**9-Hydroxy-6-methoxy-3aα,4,5,6α,6aα,7,8,9α,9aα,9bβ-decahydroazuleno[4,5-*b*]furan-2(3*H*)-one (19).** Lactone **18** (4.0 g, 12.2 mmol) was dissolved in 200 mL of dry acetonitrile and cooled to −20 °C. Sodium iodide (1.8 g, 12.2 mmol) and trimethylsilyl chloride (1.5 mL, 12.2 mmol) were added to the reaction flask. After 15 min an additional 1.8 g (12.2 mmol) of sodium iodide and 1.5 mL (12.2 mmol) of trimethylsilyl chloride were added. The reaction mixture was stirred at −20 °C for an additional 15 min and then quenched with 25 mL of absolute methanol. The solvents were removed under reduced pressure, and the residue was taken up in 600 mL of ethyl acetate. The ethyl acetate mixture was washed with two 150-mL portions of a 10% aqueous sodium thiosulfate solution followed by brine. The organic layer was dried and the solvent removed. Flash chromatography on 100 g of silica gel (eluting with ether) gave 2.3 g (79%) of the alcohol **19**: mp 125–126 °C; $R_f$ 0.45 (1:4 EtOAc/ether); IR ($CCl_4$) $\nu$ 3600, 3400, 2925, 2860, 1775, 1440, 1415, 1340, 1320, 1280, 1260, 1225, 1180, 1140, 1120, 1060, 1075, 1010 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.23–1.36 (m, 1 H), 1.63–2.00 (m, 9 H), 2.15 (dd, $J$ = 17, 12 Hz, 1 H), 2.43 (m, 1 H), 2.58 (m, 1 H), 2.66 (dd, $J$ = 17, 8 Hz, 1 H), 3.42 (s, 3 H), 3.49 (m, 1 H), 4.44 (dd, $J$ = 10.8, 5.5 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 24.95, 26.65, 26.96, 32.28, 36.52, 37.75, 43.53, 45.42, 57.24, 73.42, 81.61, 84.79, 176.27; mass spectrum, *m/e* (%) 240 (1), 222 (3), 208 (3), 190 (12), 164 (26), 97 (23), 79 (22), 71 (100); high-resolution mass spectrum, calcd for $C_{13}H_{20}O_4$, 240.136 15; found, 240.136 50.

**6-Methoxy-3aα,4,5,6α,6aα,7,8,9bβ-octahydroazuleno[4,5-*b*]furan-2-(3*H*),9(9aα*H*)-dione (20).**[41] Oxalyl chloride (164 μL, 1.88 mmol) in 3 mL of $CH_2Cl_2$ was cooled to −78 °C, and dry $Me_2SO$ (291 μL, 4.10 mmol) in 2 mL of $CH_2Cl_2$ was added dropwise via syringe. After stirring for 15 min, the alcohol **19** (409 mg, 1.71 mmol) in 1 mL of $CH_2Cl_2$ was added slowly to the reaction mixture. Stirring was continued for an additional 30 min, at which time triethylamine (2.4 mL, 17.1 mmol) was added. The cooling bath was removed, and 5 mL of water was added when the reaction mixture had warmed to room temperature. After 10 min, the resulting two-phase mixture was separated, and the aqueous phase was extracted twice with $CH_2Cl_2$. The combined organic phases were washed with brine and dried. Evaporation of the solvent followed by flash chromatography on 20 g of silica gel (eluting with 1:9 EtOAc/ether) gave 365 mg (90%) of the ketone **20**: mp 118–120 °C; $R_f$ 0.32 (1:4 EtOAc/ether); IR ($CDCl_3$) $\nu$ 2920, 2840, 1780, 1745, 1465, 1450, 1420, 1370, 1250, 1180, 1090, 1030, 1010 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.30–1.39 (m, 1 H), 1.63 (m, 1 H), 1.89–2.35 (m, 7 H), 2.58 (m, 1 H), 2.74 (dd, $J$ = 17, 8.5 Hz, 1 H), 2.61 (m, 1 H), 3.03 (dd, $J$ = 9.5, 4 Hz, 1 H), 3.32 (s, 3 H), 3.56 (dd, $J$ = 8, 3 Hz, 1 H), 4.42 (dd, $J$ = 10, 4 Hz, 1 H); mass spectrum, *m/e* (%) 238 (3), 220 (8), 206 (11), 188 (13), 178 (15), 170 (13), 164 (32), 155 (72), 123 (23), 105 (24), 95 (27), 83 (100); high-resolution mass spectrum, calcd for $C_{13}H_{18}O_4$, 238.120 49; found, 238.120 90.

**6-Methoxy-9-methylene-3aα,4,5,6α,6aα,7,8,9,9aα,9bβ-decahydroazuleno[4,5-*b*]furan-2(3*H*)-one (22).** To a solution of 139 mg (0.699

mmol) of *N,N,P*-trimethyl-*P*-phenylphosphinothioic amide[38] in 5 mL of THF cooled to −78 °C was added 503 μL (0.699 mmol) of *n*-BuLi (1.39 M in hexanes). After 30 min, ketone **20** (138 mg, 0.583 mmol) in 5 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 dried. Evaporation of the solvent under reduced pressure left a crude residue which was taken up in 3.5 mL of acetone. Pyridine (94 μL, 1.17 mmol) and methyl iodide (67 μL, 1.05 mmol) were added, and the reaction mixture was stirred at room temperature for 18 h during which time a white precipitate formed. The precipitate was filtered off, and evaporation of the filtrate followed by flash chromatography of the residue on 15 g of silica gel (1:1 ether/hexanes) yielded 62 mg (45%) of **22**: $R_f$ 0.75 (1:4 EtOAc/ether); IR ($CDCl_3$) $\nu$ 2980, 2930, 2880, 1780, 1450, 1385, 1075, 1100 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.10–2.57 (m, 12 H), 2.67 (m, 1 H), 3.33 (s, 3 H), 3.50 (m, 1 H), 4.2 (dd, $J$ = 4, 6.5 Hz, 1 H), 5.15 (m, 2 H).

**3aα,4,5,7,8,9bβ-Hexahydroazuleno[4,5-*b*]furan-2(3*H*),6(6a*αH*),9-(9a*αH*)-trione (24).** To a solution of 2.29 g (6.98 mmol) of the lactone **18** in 13.2 mL of dry acetonitrile were added 6.28 g (41.88 mmol) of dried NaI and 5.31 mL (41.88 mmol) of freshly distilled trimethylsilyl chloride. The reaction mixture was allowed to stir at room temperature for 3 h and then quenched with 20 mL of absolute methanol. After the solvent was removed in vacuo the residue was taken up in 1 L of ethyl acetate and washed with two 200-mL portions of a 10% aqueous sodium thiosulfate solution followed by brine. Drying over anhydrous sodium sulfate followed by removal of the solvent left 1.45 g of the crude diol **23**, which was carried onto the next step without purification.

Oxalyl chloride (1.23 mL, 14.12 mmol) in 20 mL of $CH_2Cl_2$ was cooled to −78 °C. Dry $Me_2SO$ (2.0 mL, 28.24 mmol) in 10 mL of $CH_2Cl_2$ was added dropwise via syringe. When the addition was complete, the reaction mixture was stirred for 15 min followed by the dropwise addition of the crude diol **23** (1.45 g) in 25 mL of $CHCl_3$. After 30 min, triethylamine (8.9 mL, 64.3 mmol) was added and the cooling bath removed. When the reaction mixture had warmed to room temperature, 35 mL of water was added. Stirring was continued for 10 min, and then the organic layer was separated. The aqueous layer was extracted several times with $CH_2Cl_2$, and the combined organic layers were washed with brine and dried. Evaporation of the solvent under reduced pressure followed by flash chromatgraphy on 100 g of silica gel (1:1 ether/hexanes as eluent) yielded 650 mg (42% from lactone **18**) of the very polar dione **24**: mp 184–189 °C dec; $R_f$ 0.30 (1:1 EtOAc/ether, two elutions); IR ($CHCl_3$) $\nu$ 3050, 2930, 1790, 1750, 1710, 1200, 1000 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.95–2.10 (m, 4 H), 2.26–2.75 (m, 8 H), 3.07 (m, 1 H), 4.10 (t, $J$ = 10 Hz, 1 H), 4.10 (t, $J$ = 10 Hz; 1 H); mass spectrum, $m/e$ (%) 222 (75), 194 (100), 153 (80); high-resolution mass spectrum, calcd for $C_{12}H_{14}O_4$, 222.089 19; found, 222.0887.

**6,9-Dimethylene-3aα,4,5,6,6aα,7,8,9,9aα,9bβ-decahydroazuleno[4,5-*b*]furan-2(3*H*)-one (25).** *N,N,P*-Trimethyl-*P*-phenylphosphinothioic amide (448 mg, 2.25 mmol) in 5 mL of THF was cooled to −78 °C, and 1.62 mL (2.25 mmol) of *n*-BuLi (1.39 M in hexanes) was added. After 30 min, 250 mg (1.13 mmol) of dione **24** in 3 mL of $CH_2Cl_2$ was added. The reaction mixture was allowed to stir for an additional 30 min, then warmed to 0 °C, and quenched with 1 mL of a saturated aqueous ammonium chloride solution. The mixture was diluted with ether, and the two phases were separated. The organic phase was dried over anhydrous sodium sulfate, and the solvent was removed in vacuo. The crude residue was taken up in 4 mL of acetone, and pyridine (364 μL, 4.50 mmol) and methyl iodide (215 μL, 3.38 mmol) were added. After the mixture was stirred at room temperture for 48 h a white precipitate developed. The precipitate was filtered off. Evaporation of the filtrate gave the crude diene **25**, which was purified by flash chromatography on 50 g of silica gel (1:1 ether/hexanes as eluent) to yield 38 mg (15%) of diene **25**: $R_f$ 0.46 (1:1 ether/hexanes); IR ($CHCl_3$) $\nu$ 3080, 2950, 2900, 2830, 1790, 1460, 1420, 1100, 950, 880 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.50–2.00 (m, 5 H), 2.10–2.65 (m, 8 H), 3.91 (t, $J$ = 9.5 Hz, 1 H), 4.85 (br s, 1 H), 4.96 (br s, 1 H), 5.05 (br s, 1 H), 5.30 (br s, 1 H); mass spectrum, $m/e$ (%) 218 (80), 203 (20), 190 (30), 189 (15), 176 (25), 163 (32), 158 (32), 149 (25), 147 (25), 143 (25), 116 (35), 104 (35), 90 (100); high-resolution mass spectrum, calcd for $C_{10}H_{18}O_2$, 218.130 66; found, 218.130 53.

**(±)-Dehydrocostus Lactone (1).** To a solution of diisopropylamine (28 μL, 0.202 mmol) in 1 mL of THF at −78 °C was added 135 μL (0.202 mmol) of *n*-BuLi (1.5 M in hexanes). After the mixture was stirred at −78 °C for 30 min, 8.8 mg (0.040 mmol) of diene **25** was added. The reaction mixture was stirred at −78 °C for an additional 45 min and then transferred via syringe to a suspension of 50 mg (0.269 mmol) of Eschenmoser's salt[40] in 0.50 mL of THF. The cooling bath was removed, and the reaction mixture was warmed to room temperature. After the mixture was stirred for 15 min, a 5% aqueous solution of HCl was added until a pH of 2 was reached. The solution was then made basic by the addition of solid potassium carbonate and extracted five times with ethyl acetate. The combined organic layers were dried, and the solvent was removed under reduced pressure. The resulting residue was dissolved in 0.5 mL of absolute methanol, and 250 μL (3.93 mmol) of methyl iodide was added. The reaction mixture was allowed to stir at room temperature for 18 h after which time the solvents were removed in vacuo. Ethyl acetate was added to the residue followed by 1 mL of a saturated aqueous sodium bicarbonate solution. The mixture was then stirred until the residue dissolved, and the two phases were separated. The aqueous phase was extracted with ethyl acetate, the combined organic phases were dried, and the solvent was evaporated. Flash chromatography of the crude product (5 g of silica gel eluting with 1:4 ether/hexanes) yielded 6.3 mg (71%) of dehydrocostus lactone (**1**): IR ($CCl_4$) 2940, 1770, 1640, 1260, 1000 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.42 (m, 1 H), 1.90 (m, 2 H), 2.20 (m, 2 H), 2.55 (m, 3 H), 2.90 (m, 3 H), 3.89 (t, $J$ = 10 Hz, 1 H), 4.83 (s, 1 H), 4.95 (s, 1 H), 5.08 (s, 1 H); 5.28 (s 1 H), 5.48 (d, $J$ = 3.5 Hz, 1 H), 6.21 (d, $J$ = 3.5 Hz, 1 H), mass spectrum, $m/e$ (%) 230 (32), 215 (18), 201 (20), 175 (19); high-resolution mass spectrum, calcd for $C_{15}H_{18}O_2$, 230.13067; found, 230.13137.

**3,6-Dimethylene-9-methyl-3a,4,5,6,6aα,7,9aα,9bβ-octahydroazuleno-[4,5-*b*]furan-2(3*H*)-one (26).**[39] To a stirred solution of dehydrocostus lactone (15 mg, 0.0652 mmol) in 1.4 mL of benzene was added 8.0 μL of freshly distilled boron trifluoride etherate complex. The reaction mixture was stirred at room temperature for 3 h during which time the mixture gradually turned red. The reaction mixture was quenched by the dropwise addition of a saturated aqueous sodium bicarbonate solution. The two-phase mixture was diluted with ether, and the organic layer was washed with saturated aqueous sodium bicarbonate solution followed by brine. Drying of the ether layer followed by solvent removal left a crude residue which was purified by flash chromatography on 2 g of silica gel (1:1 ether/hexanes) to give 10.2 mg (68%) of diene lactone **26**: $R_f$ 0.71 (1:1 ether/hexanes); IR ($CCl_4$) $\nu$ 2940, 2860, 1780, 1660, 1640, 1255, 1140, 1130, 1050, 935, 900 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.42 (m, 1 H), 1.85 (s, 3 H), 2.12 (m, 1 H), 2.25 (m, 1 H), 2.46 (m, 3 H), 2.82 (m, 2 H), 3.15 (m, 1 H), 4.04 (t, $J$ = 10 Hz, 1 H), 4.87 (s, 1 H), 4.88 (s, 1 H), 5.48 (d, $J$ = 3 Hz, 1 H), 5.54 (s, 1 H), 6.20 (d, $J$ = 3.5 Hz, 1 H).

**(±)-Estafiatin (2).**[6a] To a stirred solution of diene lactone **26** (10 mg, 0.0435 mmol) in 500 μl of $CH_2Cl_2$ cooled to 0 °C was added 7.5 mg (0.0435 mmol) of 85% *m*-chloroperoxybenzoic acid in 100 μL of $CH_2Cl_2$. After being stirred for 2.5 h, the reaction mixture was diluted with ether and washed with a saturated aqueous ammonium chloride solution. Drying of the ether layer followed by evaporation of the solvent and chromatography on 1 g of silica gel (1:1 ether/hexanes) gave 5.5 mg (51%) of (±)-estafiatin: $R_f$ 0.38 (1:1 ether/hexanes); $^1H$ NMR ($CDCl_3$) $\delta$ 1.52 (m, 1 H), 1.61 (s, 3 H), 1.82 (m, 1 H), 2.07 (m, 1 H), 2.22 (m, 2 H), 2.80–3.02 (m, 2 H), 3.39 (s, 1 H), 4.04 (dd, $J$ = 8, 10 Hz), 4.86 (s, 1 H), 4.95 (s, 1 H), 5.48 (d, $J$ = 3 Hz), 6.21 (d, $J$ = 3 Hz).

**Acknowledgment.** We thank the National Institutes of Health (GM-30771) for support of this research and Dr. W. Rahman (Wayne State University) for obtaining the crystal structure of ketone **17**. We also are grateful to Professor K. Ito (Meijo University, Nagoya, Japan) for kindly providing a sample of natural dehydrocostus lactone and to Ms. Joung Yon Lee for helpful experimental assistance.

**Registry No.** (±)-**1**, 93219-83-1; (±)-**2**, 83150-86-1; **3**, 539-80-0; (±)-**4**, 93111-80-9; **5**, 93111-81-0; **6a**, 93111-82-1; **6b**, 82830-55-5; **9a**, 93111-83-2; **9b**, 93111-84-3; (±)-**10a** (isomer 1), 93111-85-4; (±)-**10a** (isomer 2), 93219-87-5; (±)-**10b** (isomer 1), 93219-84-2; (±)-**10b** (isomer 2), 93219-88-6; (±)-**11**, 93111-86-5; (±)-**12**, 93219-85-3; (±)-**13**, 93111-87-6; (±)-**14**, 93111-88-7; (±)-**15**, 93111-89-8; (±)-**16**, 93111-90-1; (±)-**18** (R = MEM), 93111-91-2; (±)-**19**, 93219-86-4; (±)-**20**, 93111-92-3; (±)-**22**, 93111-93-4; (±)-**24**, 93111-94-5; (±)-**25**, 93111-95-6; (±)-**26**, 83150-85-0; $CH_3I$, 74-88-4; $PhCH_2I$, 620-05-3; 2-(2-bromoethyl)-1,3-dioxolane, 18742-02-4; Eschenmoser's salt, 33797-51-2; lithium methylamide, 37123-26-5; (2-methoxyethoxy)methyl chloride, 3970-21-6.