Allylsilane-Based Annulations. Direct Stereoselective Syntheses of (±)-Graveolide and (±)-Aromaticin[1]

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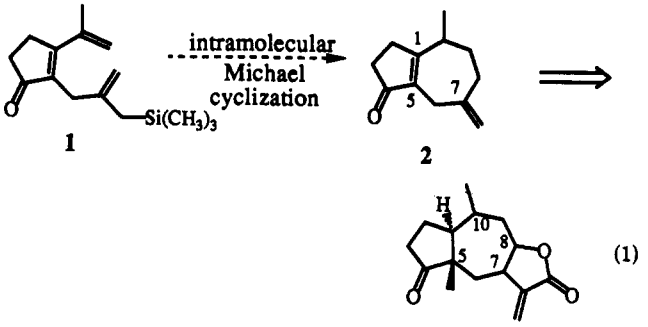
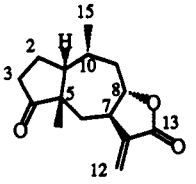
An allylsilane-based annulation was used to construct a functionalized perhydroazulene. The C(1), C(5), and C(10) stereocenters, characteristic of the helenanolides, were established using a reductive alkylation strategy. Stereoselective syntheses of the pseudoguaianolides graveolide and aromaticin were achieved.

Reactions of allylsilanes are becoming increasingly popular as a method for inter- and intramolecular carbon–carbon bond formation, due to their remarkable versatility and broad synthetic utility.[2,3] Our contributions to this active field have focused on developing new procedures using allylsilane chemistry to annulate seven- or eight-membered rings.[4-6] Thus we were confident that the 5,7-carbocyclic framework characteristic of the pseudoguaianolides could be formed by cyclizing a 2-isobutenyl dienone,[7] as shown in eq 1. Enone **2** is an attractive pseudoguaianolide precursor because the C(7) exocyclic methylene unit serves as a handle for the construction of a C(7),C(8)-α-methylene lactone, while the cyclopentenone moiety allows us to control the stereochemistry of the C(1) and C(5) chiral centers. Moreover, the pseudoguaianolides

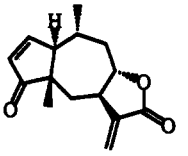


(1)

are subdivided into two families which differ primarily in the configuration at C(10) of the hydroazulene skeleton: the ambrosanolides, possessing a β-oriented methyl group, and the helenanolides with the methyl substituent residing on the α-face of the molecule.[8] We felt that enone **2** would function as a common intermediate for both the helenanolides and the ambrosanolides. Here we report the stereoselective synthesis of the helenanolides (±)-graveolide (**3**)[9] and (±)-aromaticin (**4**).[10]



graveolide (3)



aromaticin (4)

Results and Discussion

Placement of an allylsilane functionalized appendage onto the C(2) position of the conjugated dienone would be

(1) (a) This work was presented at the 201st National Meeting of the American Chemical Society in Atlanta, GA, April, 1991 [Abstract ORGN #189]. (b) Taken in part from the M.S. Thesis of Stephen M. Condon, The University of Georgia, 1990. (c) Taken in part from the Ph.D. Dissertation of Jee-Seop Song, The University of Georgia, 1991.

(2) For recent surveys of allylsilane chemistry, see: (a) Fleming, I.; Dunogues, J.; Smither, R. *Org. React.* **1989**, *37*, 57–575. (b) Majetich, G. Allylsilanes in Organic Synthesis in *Organic Synthesis, Theory, and Applications*, Hudlicky, T., Ed.; Jai Press, Inc.: Greenwich, CT; 1989; pp 173–240.

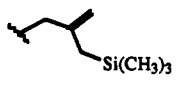
(3) For a review of intramolecular additions of allylsilanes to dienones, see: Majetich, G.; Hull, K.; Lowery, D.; Ringold, C.; Defauw, J. Intramolecular Additions of Allylsilanes to Dienones in *Selectivities in Lewis Acid-Promoted Reactions*; Schinzer, D., Ed.; Kluwer Academic Publishers Group: Dordrecht, Holland, 1989; pp 169–188.

(4) For cycloheptane annulations using allylsilanes, see: (a) Majetich, G.; Hull, K.; Defauw, J.; Desmond, R. *Tetrahedron Lett.* **1985**, *26*, 2747. (b) Majetich, G.; Ringold, C. *Heterocycles* **1987**, *25*, 271. (c) Majetich, G.; Defauw, J.; Ringold, C. *J. Org. Chem.* **1988**, *53*, 50. (d) Majetich, G.; Hull, K. *Tetrahedron* **1987**, *43*, 5621. (e) Majetich, G.; Song, J.-S.; Ringold, C. *J. Org. Chem.* **1991**, *56*, 3973.

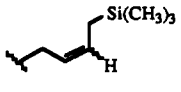
(5) For other examples using allylsilanes to construct cycloheptane-fused carbocycles, see: (a) Schinzer, D.; Steffen, J.; Solyom, S. *J. Chem. Soc., Chem. Commun.* **1986**, 829. (b) Lee, T. V.; Boucher, R. J.; Rockell, C. J. M. *Tetrahedron Lett.* **1988**, *29*, 689. (c) Molander, G. A.; Shubert, D. C. *J. Am. Chem. Soc.* **1987**, *109*, 6877. (d) Trost, B. M.; MacPherson, D. T. *Ibid.* **1987**, *109*, 3483.

(6) For cyclooctane annulations using allylsilanes, see: (a) Majetich, G.; Hull, K.; Desmond, R. *Tetrahedron Lett.* **1985**, *26*, 2751. (b) Majetich, G.; Lowery, D.; Khetani, V.; Song, J.-S.; Hull, K.; Ringold, C. *J. Org. Chem.* **1991**, *56*, 3988.

(7) We have developed several annulation methods to produce six-, seven-, and eight-membered rings based on the intramolecular addition of an allylsilane to a 3-vinylcycloalkenone. For convenience, we use the following conventions to describe these various cyclizations: (1) the suffix dienone describes the 3-vinylcycloalkenone unit; (2) a locant for the allylsilane appendage is stated; (3) the nature of the allylsilane side chain is defined either as an isoalkenyl or *n*-alkenyl substituent; and (4) geometric isomers or substitutions are ignored.



isoalkenyl



n-alkenyl

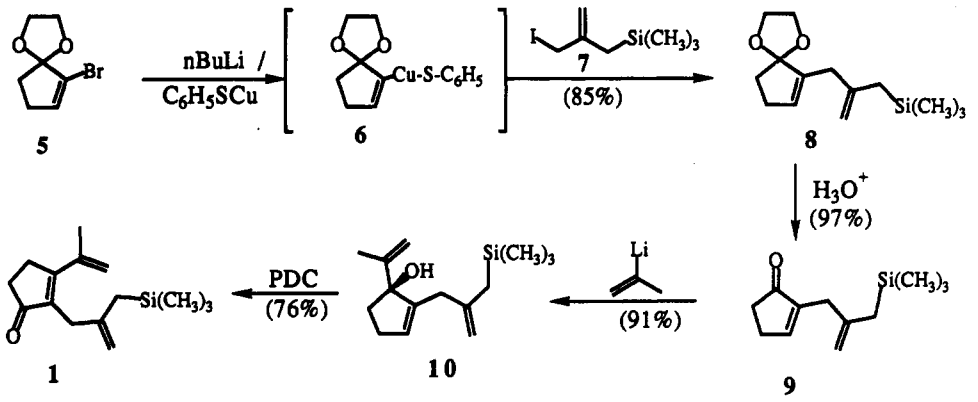
(8) For reviews on pseudoguaianolide syntheses prior to 1979, see: (a) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavan, F.; White, C. T. In *The Total Synthesis of Natural Products*, ApSimon, J., Ed.; Wiley: New York, 1983; Vol. 5, pp 347–377. (b) Vandewalle, M.; De Cerlg, P. *Tetrahedron* **1985**, *41*, 1767. For recent pseudoguaianolide syntheses, see: (c) Fang, J.-M. *J. Org. Chem.* **1982**, *47*, 3464. (d) Ziegler, F. E.; Fang, J.-M.; Tam. C. C. *J. Am. Chem. Soc.* **1982**, *104*, 7174. (e) Nagao, K.; Chiba, M.; Kim, S.-W. *Chem. Pharm. Bull.* **1983**, *31*, 414. (f) Heathcock, C. H.; Tice, C. M.; Germroth, T. C. *J. Am. Chem. Soc.* **1982**, *104*, 6081. (e) Heathcock, C. H.; DelMar, E. G.; Graham, S. L. *Ibid.* **1982**, *104*, 1907.

(9) Appendino, G.; Calleri, M.; Chiari, G.; Gariboldi, P.; Menichini, F. *Gazz. Chim. Ital.* **1986**, *116*, 637. Prior to its isolation from natural sources, graveolide was an advanced intermediate in Lansbury's synthesis of (±)-aromaticin.[10]

(10) (a) Lansbury, P. T.; Hangauer, D. G., Jr. *Tetrahedron* **1981**, *37*, 371. (b) Lansbury, P. T.; Hangauer, D. G., Jr.; Vacca, J. *J. Am. Chem. Soc.* **1980**, *102*, 3964.

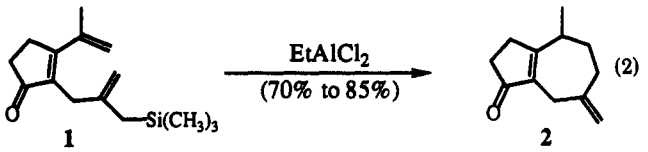
0022-3263/93/1958-1030$04.00/0

Scheme I



difficult to achieve using known methods,[11] so we developed a new dienone preparation (Scheme I).[12] First the Gilman reagent[13] derived from 2-bromo-2-cyclopenten-1-one ethylene ketal (**5**) was coupled with iodo silane **7**;[14] hydrolysis of the ketal then afforded α-alkylated enone **9**.[15] The next step involved a novel oxidative rearrangement.[16] In particular, 1,2-addition of 2-propenyllithium to **9** generated bis-allylic tertiary alcohol **10**, which when oxidized using excess pyridinium dichlorochromate (PDC) generated cyclization precursor **1**. Dienone **1** was prepared in 52% overall yield from ketal **5** using this four-step procedure. Each of these reactions could be carried out on greater than 10 g of substrate.

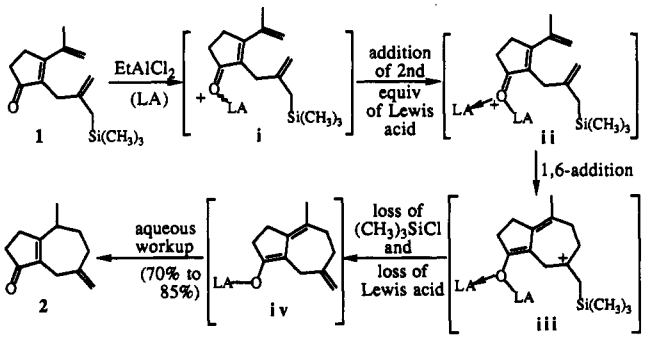
To our satisfaction, treatment of 100 mg of **1** with 2 or more equiv of ethylaluminum dichloride gave a 85% yield of hydroazulenone **2**, though cyclization was not observed with less than 2 equiv of Lewis acid. Enone **2** was produced in 70% yield on a 5-g-scale reaction (eq 2).



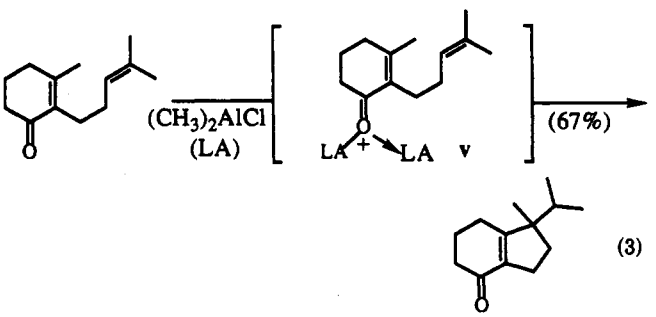
(2)

A mechanistic explanation for this cycloheptane annulation is presented in Scheme II. Addition of the first equivalent of ethylaluminum dichloride to **1** forms a 1:1 complex in which both 1,2- and 1,4-addition are geometrically precluded;[17] hence, intermediate **i** can react only in 1,6-fashion. Unlike 4-alkenyl dienone cyclizations, which occur using either a catalytic or stoichiometric amount of Lewis acid,[3,4] the cyclization of **1** (a 2-isobutenyl dienone) must involve the formation of a dienone–$[EtAlCl_2]_2$ complex, such as **ii**. Nucleophilic attack in 1,6-fashion by the allylsilane double-bond electrons to the doubly activated Michael acceptor produces ion **iii**,

Scheme II



containing a silicon-stabilized carbocation. Loss of the trimethylsilyl group generates the exocyclic methylene and chlorotrimethylsilane; aqueous workup then affords bicyclic enone **2**. Although the presence of chlorotrimethylsilane in the reaction mixture could result in formation of a silyl dienol ether, we did not detect this reactive intermediate. Support for the intermediacy of a 2:1 complex can be found in the intramolecular cyclizations of alkenes with simple enones by Snider and co-workers (eq 3).[18] Their studies demonstrated that β-substituted enones required the formation of an enone–$[EtAlCl_2]_2$ complex (**v**) before an intramolecular cyclization occurred.



(3)

After achieving an efficient preparation of enone **2**, we next sought to use it as a common intermediate for both families of pseudoguaianolides. Our plan to utilize **2** as an ambrosanolide precusor was based on the alkylation of

(11) For examples of the α-alkylation of cyclalkenones, see: (a) Suzuki, M.; Kawagashi, T.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 1809. (b) Baraldi, P. G.; Barco, A.; Benetti, M.; Pollini, G. P.; Zanirato, V. *Ibid.* **1984**, *25*, 4291. (c) Guaciaro, M. A.; Wovkulich, P. M.; Smith, A. B., III *Ibid.* **1978**, 4661. (d) Smith, A. B., III; Branca, S. J.; Pills, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1869.

(12) (a) All structures drawn herein represent racemates, only one enantiomer being drawn. (b) Reaction conditions have not been optimized. (c) All yields are isolated yields.

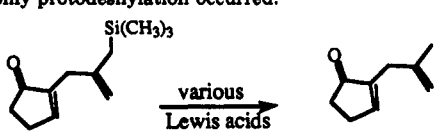
(13) Coupling of the lithio reagent derived from **5**[11c] with iodide **7** gave only the desilylated analogue of ketal **8** in low yield.

(14) Trost, B. M.; Curran, D. *J. Am. Chem. Soc.* **1981**, *103*, 7380.

(15) Majetich, G.; Leigh, A. J.; Condon, S. M. *Tetrahedron Lett.* **1991**, *32*, 605.

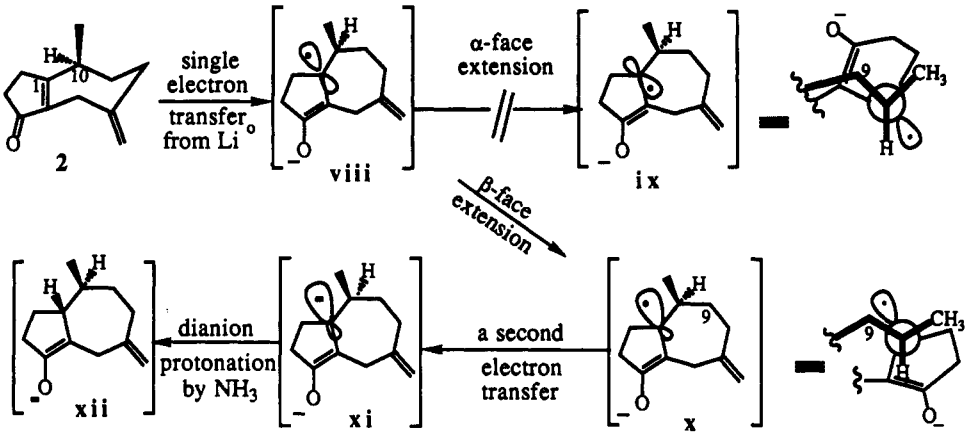
(16) Majetich, G.; Condon, S.; Hull, K.; Ahmad, S. *Tetrahedron Lett.* **1989**, *30*, 1033.

(17) Both 1,2- and 1,4-addition are possible in the example shown below. However, only protodesilylation occurred.

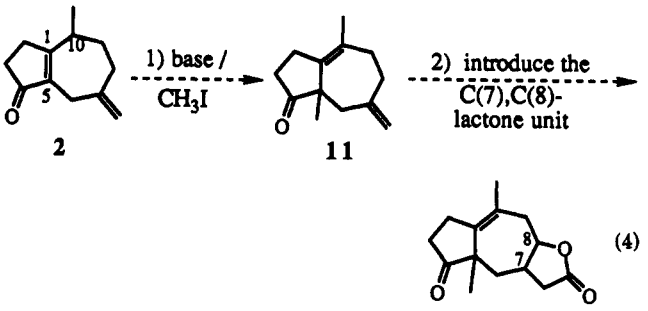


(18) Snider, B. B.; Rodini, D. J.; van Straten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5872.

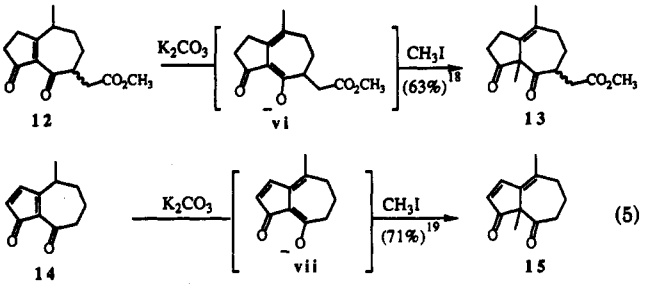
Scheme III



its thermodynamic enolate (eq 4), which introduces a methyl substituent at C(5) and a double bond between C(1) and C(10). Hydrogenation of this double bond would

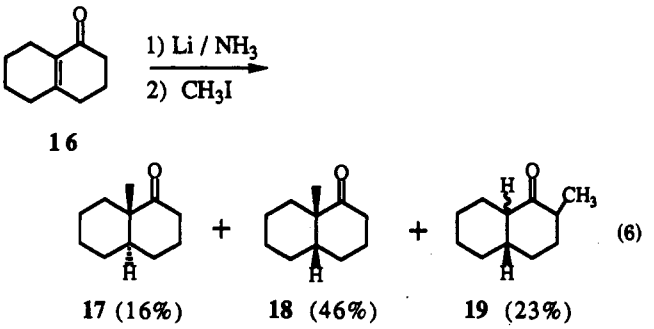


occur from the face opposite that of the angular methyl group, providing the required β-configuration at C(10) (cf. **11**). This alkylation strategy was first demonstrated by Kretchmer and Thompson in their pioneering synthesis of (±)-damsin.[19] This study showed that the dienolate of **12** could be alkylated with iodomethane to afford β,γ-unsaturated derivative **13** in 63% yield (eq 5). Schore



and co-workers recently methylated dione **14** to provide 1,3-diketone **15** in good yield.[20] However, under a variety of standard alkylating conditions, we were unable to effect the desired methylation of enone **2**. This conversion was not achieved because **2** enolizes through the cyclopentenone system, giving rise to a highly strained dienolate intermediate, whereas 1,3-diketones **12** and **14** enolize through the more flexible cycloheptenone system (cf. **vi** and **vii**). Since we were unable to take advantage of this known approach to the ambrosanolides, we sought another way to introduce the ring junction stereochemistry.

Previously, the reduction of α,β-unsaturated ketones with alkali metals in liquid ammonia has been used extensively for the control of ring fusion stereochemistry.[21] Although the regio- and stereoselective nature of these reactions has been thoroughly studied, the alkylation of the intermediate enolate and the stereochemistry of the resulting product have received little attention.[22] One of the first examples of this reductive alkylation strategy to control ring fusion stereochemistry is presented in eq 6.[23]



Normally, when the β-position of the conjugated system is located at a junction of six-membered rings, the dissolving metal reduction gives trans-fused ring products. Note, however, that the predominant product (**18**) in the reductive alkylation of 9-octalin-1-one (**16**) has a cis ring fusion.

We were curious whether a reductive alkylation sequence could be used to establish the C(1), C(10), and C(5) stereocenters of a helenanolide. The first intermediate to form during the course of a reductive alkylation is a 1,4-radical anion with a sp^2-hybridized β-carbon (cf. **viii**, Scheme III). Prior to the formation of a discrete dianionic species, the p orbital of the β-carbon distorts in order to minimize torsional strain in the σ-framework of the molecule or nonbonded interactions.[24] Molecular mechanics calculations on **2** indicated that the C(10)-methyl group resides in a pseudoaxial position (Scheme III).[25] Thus distortion of radical anion **viii** leads to either

(19) Kretchmer, R. A.; Thompson, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 3379.

(20) Sampath, V.; Lund, E. C.; Knudson, M. J.; Olmstead, M. M.; Schore, N. E. *J. Org. Chem.* **1987**, *52*, 3595.

(21) For reviews, see: (a) Caine, D. *Org. React.* **1976**, *23*, 1. (b) Pradhan, S. K. *Tetrahedron* **1986**, *42*, 6351 and references cited therein.

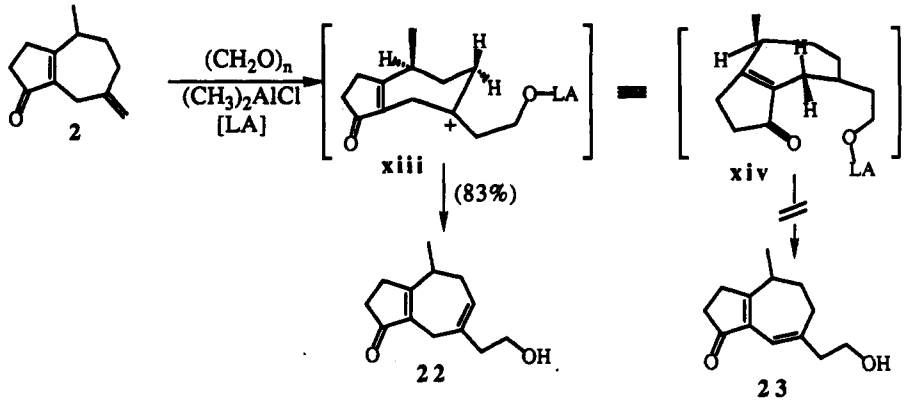
(22) House, H. O.; Giese, R. W.; Kronberger, K.; Kaplan, J. P.; Simeone, J. P. *J. Am. Chem. Soc.* **1970**, *92*, 2800.

(23) (a) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965**, *87*, 275. (b) Stork, G.; Darling, S. *J. Am. Chem. Soc.* **1964**, *86*, 1761.

(24) The expression "extended" to describe this distortion of the p orbital was first introduced by Fukui and co-workers. See: Fukui, K. *Theory or Orientation and Stereoselection*, Chapter 7.7; Springer Verlag: West Berlin, 1975.

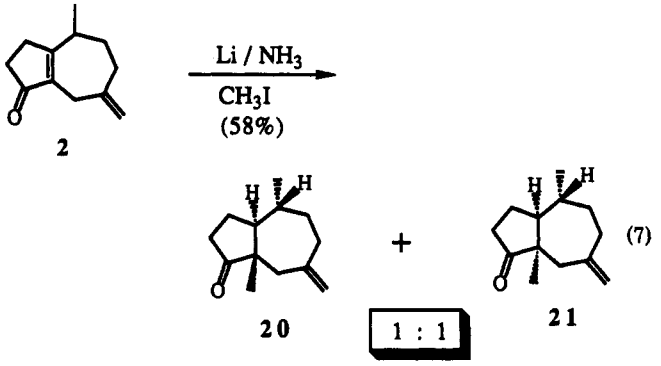
(25) St-Jacques and Vaziri have extensively studied the conformations of benzocycloheptenes and have determined by computer analysis of ^1H NMR spectra that these cycloalkenes favor a chair conformation, see: St-Jacques, M.; Vaziri, C. *Org. Magn. Reson.* **1972**, *4*, 77.

Scheme IV



conformer **x** having a staggared relationship between the pyramidalized p orbital and the C(9)-methylene or conformer **ix** in which these centers are eclipsed. We predicted that more stable conformer (**x**) would be reduced further to generate dianion **xi**. Protonation of **xi** produces enolate **xii** where the C(1) and C(10) hydrogens have the trans relationship characteristic of a helenanolide. Alkylation of this enolate with iodomethane was expected to produce the desired trans ring fusion.

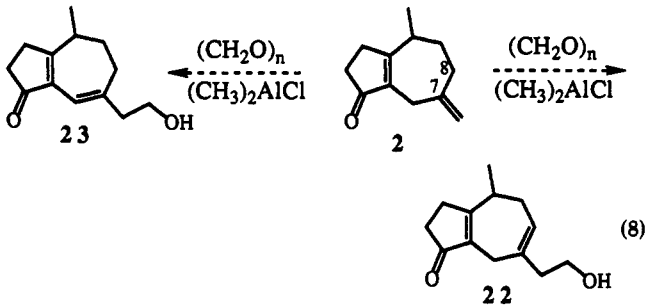
We found that treatment of enone **2** with lithium in liquid ammonia, followed by the addition of iodomethane, provided an inseparable 1:1 mixture of cis- and trans-fused diastereomers with a trans relationship between the C(1) and C(10) hydrogens (eq 7). This conclusion was



(7)

based on the chemical shift values of the angular methyl group for cis- and trans-fused systems[26] and the chemical shift of the C(10)-methyl. While our prediction that the stereochemistry of the C(1) and C(10) asymmetric centers proved to be correct, the fact that only half of the mixture consisted of the trans ring fused product was discouraging. Further scrutiny of models suggested that introduction of an sp^2 center at C(8) would make the cycloheptane ring more rigid, thereby favoring alkylation from the face of the molecule opposite the C(10)-methyl group. In order to test this we required a derivative of enone **2** having a C(7),C(8)-double bond.

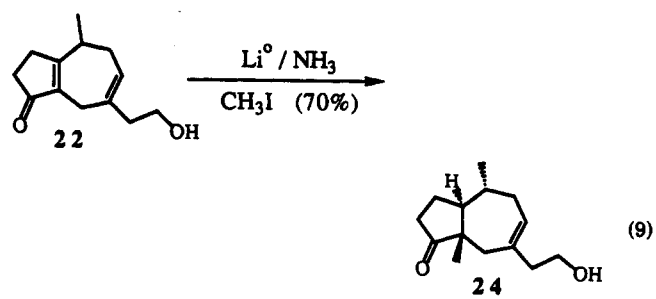
In theory, a Lewis acid-catalyzed ene reaction involving the C(7)-methylene would introduce the C(7),C(8)-double bond and the required C(13) carbon atom as a primary alcohol (cf. **22**).[27] However, an alternative ene product (isomeric homoallylic alcohol **23**) could also be formed (eq 8). We anticipated that alcohol **22** would be formed exclusively, based on steric arguments and the step-wise nature of this process.



(8)

In the first step complexation of the Lewis acid with formaldehyde forms the enophile. Coupling of the enophile and the ene component generates a zwitterionic intermediate, which can undergo a six-centered proton transfer to produce either alcohol **22** or **23** (Scheme IV). Inspection of Drieding models indicated that transition state **xiv** was more sterically congested than transition state **xiii**. Based on this analysis we were confident that homoallylic alcohol **22** would prevail. Indeed, the dimethylaluminum chloride-catalyzed ene reaction of **2** and paraformaldehyde proceeded smoothly to give the $\Delta^{7,8}$-homoallylic alcohol **22** in high yield.

Our efforts to prepare a conformationally less-flexible bicyclic enone were rewarded when the reduction methylation of **22** gave only ketone **24** having trans relationships between the C(1)-hydrogen and the C(5)-methyl group and the C(1),C(10)-hydrogens in 70% yield (eq 9).



(9)

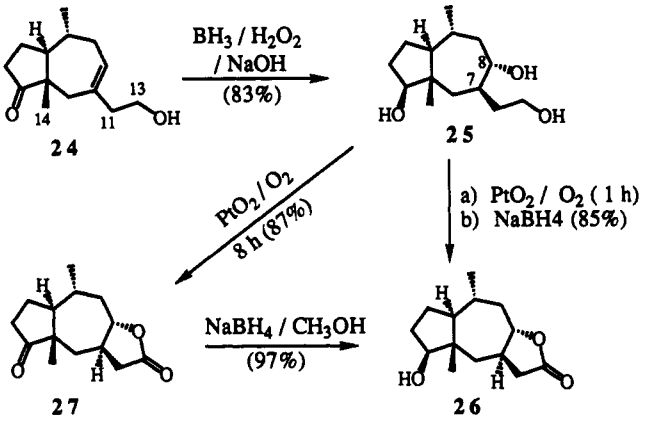
(26) These values are shown below [Snider, B. B.; Cartaya-Marin, C. P. *J. Org. Chem.* **1984**, *49*, 153]:

(27) For a review of Lewis acid-catalyzed ene reactions, see: (a) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426. See also: (b) Snider, B. B.; Rodini, D. J.; Kirk, T. C.; Cordova, R. *J. Am. Chem. Soc.* **1982**, *104*, 555. (c) Snider, B. B.; Rodini, D. J. *Tetrahedron Lett.* **1980**, *21*, 1815.

Once we had developed a means to control the C(5), C(1), and C(10) asymmetric centers, all that remained to complete a synthesis of the helenanolide graveolide (3) was to introduce a trans-fused α-methylene lactone at C(7),C(8). To do this required that we introduce an α-oriented hydroxy group at C(8), oxidize the C(13) carbon atom to a carboxylic acid, and then lactonize the intermediate hydroxy acid.[28]

Hydroboration of homoallylic alcohol 24 would occur from the α-face because of the steric effect of the C(14)-methyl group (Scheme V), thus dictating the C(7) and C(8) chirality. Indeed, Lansbury and co-workers observed a 4:1 preference for α-attack on a related system using this strategy.[29] Because diborane also reduces ketones, we were not surprised that treatment of 24 with diborane at −78 °C gave a single triol. Rather than rigorously prove the structure of triol 25, we chose to construct the lactone moiety first.

Scheme V

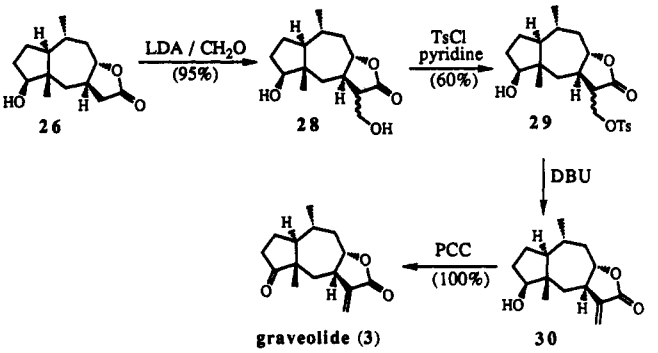


The selective oxidation of a primary alcohol in the presence of secondary hydroxy groups was first used in the context of a pseudoguaianolide synthesis by Kretchmer and Thompson in their synthesis of damsin.[18] The oxidation of 25 was carried out using an equal weight of PtO_2 in dilute aqueous acetone.[30] Oxygen was then bubbled through the suspension at 55 °C over an 8-h period. This experiment afforded an 87% yield of keto lactone 27 along with a trace of hydroxy lactone 26. An X-ray diffraction analysis of a single crystal of keto lactone 27 confirmed that we had established the five asymmetric centers required for a graveolide synthesis. While monitoring the reaction we observed that lactone formation was rapid, while longer reaction times resulted in the oxidation of the C(5) alcohol. Stopping this oxidation after only 1 h provided a 55% yield of hydroxy lactone 26 and a 40% yield of the "overoxidized" keto lactone 27. Selective reduction of the C(5) carbonyl of 27 was achieved using sodium borohydride in nearly quantitative yield.

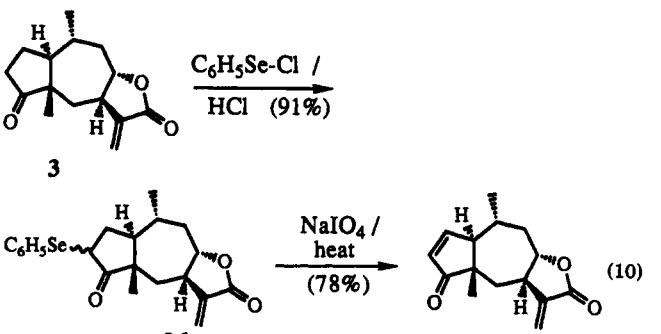
During the 1970s many methods were developed for the introduction of α-methylene groups adjacent to carbonyl units.[31] A three-step procedure, popularized by Grieco,[31c] involved the hydroxymethylation of a lactone enolate, followed by conversion of the hydroxymethyl group into a mesylate and subsequent elimination. Application of Greico's methylenation sequence to keto lactone 27 required that we protect the C(5) carbonyl unit in order to selectively form the lactone enolate. We recognized that the α-methylene unit could be introduced directly on unprotected hydoxy lactone 26, thereby avoiding the protection of the C(5) carbonyl.

As shown in Scheme VI, lactone 30 was prepared in 57% overall yield from lactone 26. Oxidation of cyclopentenol 30 with PDC completed a synthesis of (±)-graveolide, which was identical with an authentic sample of natural 3 kindly provided by Dr. Giovanni Appendino.[9]

Scheme VI



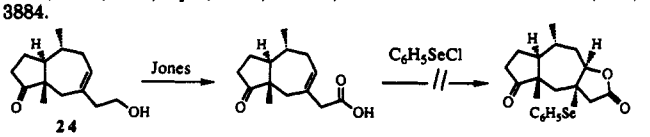
During Grieco's synthesis of ambrosin it was discovered that α-phenylselenation of the cyclopentanone ring could be carried out directly on damsin in ethyl acetate containing benzeneselenenyl chloride (1.0 equiv) in the absence of any base.[32] To our surprise, benzeneselenenyl chloride—in the absence of base—failed to react with graveolide despite lengthy reaction times. Moreover, addition of the weak base triethylamine also failed to promote the desired selenenation. These difficulties were overcome when the reaction medium was "spiked" with gaseous HCl, thereby leading to the desired functionalization (cf. 31) in high yield (eq 10).[10] Clearly, the presence



(10)

of an acid source in the reaction mixture favors the intermediacy of the enol of 3. We can only speculate that,

(28) We reasoned that phenselenolactonization would enable us to produce a β-oriented cis-fused C(7),C(8) lactone unit. However, in our hands this sequence failed. For successful applications, see: (a) Goldsmith, D.; Liotta, D.; Lee, C.; Zima, G. *Tetrahedron Lett.* **1979**, 4801. (b) Nicolaou, K. C.; Seitz, S. P.; Sipio, W. J.; Blount, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 3884.



(29) Lansbury, P. T.; Nickson, T. E.; Vacca, J. P.; Sindelar, R. D.; Messinger, J. M., II *Tetrahedron* **1987**, *43*, 5583.

(30) Fried, J.; Sih, J. C. *Tetrahedron Lett.* **1973**, 3899.

(31) (a) Grieco, P. A. *Synthesis* **1975**, 67. (b) Gammill, R. B.; Wilson, C. A.; Bryson, T. A. *Synth. Commun.* **1975**, *56*, 245. (c) Grieco, P. A.; Marinovic, N.; Miyashita, M. *J. Org. Chem.* **1975**, *40*, 1670. (d) Grieco, P. A.; Nishizawa, M.; Oquri, T.; Burke, S. D.; *Marinovic*, N. *J. Am. Chem. Soc.* **1977**, *99*, 5773.

(32) Grieco, P. A.; Ohfune, Y.; Majetich, G. *J. Am. Chem. Soc.* **1977**, *99*, 7393.

in contrast to the conversion of damsin to ambrosin [both of which have a C(6),C(7)-lactone unit],[32] the presence of the trans-C(7),C(8)-lactone in graveolide disfavors enolization of the C(4) ketone moiety. This unfavorable equilibrium was overcome using acid catalysis. The oxidative elimination followed published conditions[32] and afforded racemic aromaticin in good yield.

Thus, in the course of this project we have achieved (1) a new method for preparing conjugated dienones, (2) the reductive alkylation of a fused cycloalkenone, and (3) last—but not least—the synthesis of the helenanolides graveolide and aromoticin with complete stereocontrol.

Experimental Section

General. All reactions were run under an inert atmosphere of nitrogen and monitored by TLC analysis until the starting material was completely consumed. Unless otherwise indicated, all ethereal workups consisted of the following procedure: the reaction was quenched at rt with saturated aqueous ammonium chloride. The organic solvent was removed under reduced pressure on a rotary evaporator and the residue was taken up in ether, washed with brine, and dried over anhydrous $MgSO_4$. Filtration, followed by concentration at reduced pressure on a rotary evaporator and at 1 Torr to constant weight, afforded a crude residue which was purified by flash chromatography using NM silica gel 60 (230–400-mesh ASTM) and distilled reagent grade solvents. Microanalysis was performed by Atlantic Microlab, Inc., Atlanta, GA. Proton NMR chemical shifts were calibrated using trace $CHCl_3$ present (δ 7.27) as an internal reference.

6-[2-[(Trimethylsilyl)methyl]allyl]-1,4-dioxaspiro[4.4]non-6-ene (8). A solution of (phenylthio)copper(I) was prepared in the following manner: To a solution of 3.49 mL of thiophenol (30 mmol) in 200 mL of anhydrous ether at 0 °C was added 15.6 mL of 2.5 M *n*-BuLi (39 mmol) in hexane dropwise over a 10-min period. After an additional 30 min at 0 °C, 6.30 g of copper(I) iodide (33 mmol) dissolved in 80 mL of ether was added to the ethereal solution of (phenylthio)lithium. The resulting heterogeneous mixture of (phenylthio)copper(I) was stirred at 0 °C for 1 h and then cooled to −78 °C.

To a solution of 6.15 g of bromide **5** (30 mmol) in 60 mL of ether in a separate flask at −78 °C was added dropwise 13.2 mL of 2.5 M *n*-butyllithium (33 mmol) in hexanes over a 15-min period. The resulting solution of 2-lithio-2-cyclopenten-1-one ethylene ketal was stirred at −78 °C for a 25-min period.

The mixture of (phenylthio)copper(I) was added rapidly via cannula to the solution of 2-lithio-2-cyclopenten-1-one ethylene ketal and the reaction mixture was stirred for 30 min at −78 °C. 3-Iodo-2-[(trimethylsilyl)methyl]propene (**7**) (9.14 g, 36 mmol) was added in a single portion and the reaction mixture was stirred at −78 °C for 30 min and then warmed to −30 °C over a 30-min period. The resulting solution was stirred at −30 °C for an additional 30-min period. The reaction mixture was diluted at −30 °C with 200 mL of ether and 20 mL of 10% sodium carbonate solution and then stirred for 1.5 h at rt. The yellowish copper complex was removed via vacuum filtration. The organic phase was then separated from the filtrate. Standard etheral workup, followed by chromatography (H:E, 10:1) provided 6.72 g (85% yield) of ketal **8** which was homogeneous by TLC analysis [H:E, 5:1, R_f(**5**) = 0.48, R_f(**8**) = 0.54]: ^{1}H NMR (90 MHz) δ 0.00 (s, 9 H), 1.54 (br s, 2 H), 1.90–2.12 (m, 2 H), 2.18–2.42 (m, 2 H), 2.67 (br s, 2 H), 3.92 (s, 4 H), 4.54–4.73 (m, 2 H), 5.69–5.81 (m, 1 H); ^{13}C NMR (22.5 MHz) 145.2 (s), 141.1 (s), 132.2 (d), 119.9 (s), 109.0 (t), 65.0 (t), 65.0 (t), 35.6 (t), 34.7 (t), 27.7 (t), 26.0 (t), −1.4 (q) ppm; IR (film) 1640, 1425 cm^{-1}; mass spectrum, *m/z* 252 (M$^+$).

2-[2-[(Trimethylsilyl)methyl]allyl]-2-cyclopenten-1-one (9). A solution of 6.72 g of ketal **8** (26.6 mmol) in 50 mL of THF and 2 mL of 1 N aq sulfuric acid was stirred until TLC analysis revealed complete consumption of the starting material (approximately 5 min). The reaction was quenched by the addition of an equal volume of saturated aq $NaHCO_3$. Standard ethereal workup, followed by chromatography (H:E, 10:1), gave 5.1 g (97% yield) of enone **9** which was homogeneous by TLC analysis (H:E, 5:1, R_f(**8**) = 0.54, R_f(**9**) = 0.42): ^{1}H NMR (90 MHz) δ 0.00 (s, 9 H), 1.47 (s, 2 H), 2.28–2.44 (m, 2 H), 2.45–2.63 (m, 2 H), 2.78 (br s, 2 H), 4.55 (br s, 2 H), 7.23–7.37 (m, 1 H); ^{13}C NMR (62.5 MHz) 209.2 (s), 158.8 (d), 144.2 (s), 144.2 (s), 109.0 (t), 34.4 (t), 33.4 (t), 26.5 (t), 26.3 (t), −1.4 (q) ppm; IR (film) 1710, 1635 cm^{-1}; mass spectrum, *m/z* 208 (M$^+$). Anal. Calcd for $C_{12}H_{20}OSi$: C, 69.19; H, 9.68. Found: C, 68.82; H, 9.68.

1-(1-Methylethenyl)-2-[2-[(trimethylsilyl)methyl]allyl]-2-cyclopenten-1-ol (10). To a solution of 4.1 g of 2-bromopropene (33.6 mmol) in 150 mL of ether at −78 °C was added dropwise 39.5 mL of *tert*-butyllithium (1.7 M in pentane, 67.2 mmol). The solution was warmed to 0°C over a 1-h period and then recooled to −78 °C. To this solution of 2-lithiopropene was added 3.5 g of enone **10** (16.8 mmol) in 25 mL of ether. The reaction mixture was stirred 30 min at −78 °C and then slowly warmed to −30 °C. TLC analysis revealed complete consumption of the starting material. Standard ethereal workup, followed by chromatography (H:E, 20:1), gave 3.80 g (91% yield) of alcohol **10** which was homogeneous by TLC analysis (H:E, 5:1, R_f(**9**) = 0.42, R_f(**10**) = 0.60): ^{1}H NMR (250 MHz) δ 0.00 (s, 9 H), 1.56 (s, 2 H), 1.63 (s, 3 H), 1.78–2.55 (m, 5 H), 2.60 (s, 2 H), 4.59 (s, 1 H), 4.68 (s, 1 H), 4.90 (s, 1 H), 5.05 (s, 1 H), 5.62 (s, 1 H); ^{13}C NMR (62.5 MHz) 148.0 (s), 146.9 (s), 143.6 (s), 130.2 (d), 109.6 (t), 109.6 (t), 89.5 (s), 38.7 (t), 36.2 (t), 29.7 (t), 26.2 (t), 18.9 (q), −1.3 (q) ppm; IR (film) 3650–3250, 1635 cm^{-1}; mass spectrum, *m/z* 232 (M − 18). Anal. Calcd for $C_{15}H_{26}OSi$: C, 71.95; H, 10.47. Found: C, 71.66; H, 10.48.

3-(1-Methylethenyl)-2-[2-[(trimethylsilyl)methyl]allyl]-2-cyclopenten-1-one (1). To a suspension of 11.5 g of pyridinium dichromate (30.5 mmol) in 150 mL of anhydrous CH_2Cl_2 was added a solution of 3.81 g of alcohol **10** (15.2 mmol) in 25 mL of CH_2Cl_2 at 0 °C. The reaction mixture was then stirred for 3 h at 0 °C. Diethyl ether (150 mL) was added and the mixture was filtered through a plug of glass wool; the solids were washed with ether. Standard ethereal workup, followed by chromatography (H:E, 8:1), furnished 2.86 g (76% yield) of trienone **1** which was homogeneous by TLC analysis [H:E, 5:1, R_f(**10**) = 0.60, R_f(**1**) = 0.45]: ^{1}H NMR (250 MHz) δ 0.00 (s, 9 H), 1.56 (s, 2 H), 1.98 (s, 3 H), 2.36–2.44 (m, 2 H), 2.62–2.71 (m, 2 H), 2.92 (br s, 2 H), 4.21 (br s, 1 H), 4.48 (br s, 1 H), 5.19 (br s, 1 H), 5.29 (br s, 1 H); ^{13}C NMR (62.5 MHz) 209.3 (s), 169.8 (s), 144.7 (s), 140.8 (s), 137.9 (s), 118.0 (t), 107.3 (t), 33.7 (t), 32.5 (t), 28.6 (t), 28.1 (t), 21.3 (q), −1.3 (q) ppm; IR (film) 3080, 1700, 1630, 1595 cm^{-1}; mass spectrum, *m/z* 248 (M$^+$).

(±)-4-Methyl-7-methylene-3,4,5,6,7,8-hexahydroazulen-1(2*H*)-one (2). To a solution of 2.88 g of trienone **1** (11.60 mmol) in 90 mL of anhydrous toluene at −10 °C was added rapidly 25.8 mL of ethylaluminum dichloride (1.80 M in toluene, 46.42 mmol). The reaction mixture was warmed to rt, stirred for 1 h, and then quenched. Standard ethereal workup, followed by chromatography (H:E, 5:1), gave 1.57 g (77% yield) of enone **2** which was homogeneous by TLC analysis [H:E, 2:1, R_f(**1**) = 0.67, R_f(**2**) = 0.47]: ^{1}H NMR (250 MHz) δ 1.16 (d, 3 H, J = 7.2 Hz), 1.64–1.92 (m, 2 H), 2.32–2.70 (m, 7 H), 2.99 (s, 2 H), 4.66 (s, 1 H), 4.72 (s, 1 H); ^{13}C NMR (62.5 MHz) 208.8 (s), 178.2 (s), 146.4 (s), 138.2 (s), 111.3 (t), 36.9 (d), 34.4 (t), 34.1 (t), 32.4 (t), 30.7 (t), 29.1 (t), 17.6 (q) ppm; IR (film) 3060, 1680 cm^{-1}; mass spectrum, *m/z* 176 (M$^+$). Anal. Calcd for $C_{12}H_{26}O$: C, 81.76; H = 9.16. Found: C, 81.82; H = 9.22.

(±)-(3a*R,4*R**,8a*S**)-4,8a-Dimethyl-7-methylene-3,3aα,-4,5,6,7,8,8a-octahydroazulen-1(2*H*)-one (20)[12a] and (±)-(3a*R**,4*R**,8a*R**)-4,8a-Dimethyl-7-methylene-3,3a,4,5,6,7,8,-8a-octahydroazulen-1(2*H*)-one (21).**[12a] A 250-mL three-neck round-bottom flask was charged with 125 mL of dry, distilled liquid ammonia and 21 mg of finely divided lithium wire (3.03 mmol). To this solution was added 235 mg of enone **2** (1.34 mmol) in 25 mL of diethyl ether. The reaction mixture was stirred for 45 min, followed by the addition of 0.95 mL of iodomethane (15.3 mmol). After 30 min, the ammonia was evaporated. Standard ethereal workup, followed by chromatography (H:E, 15:1), provided 147 mg (58% yield) of an inseparable mixture of ketones **20** and **21** which were homogeneous by TLC analysis [H:E, 1:1, R_f(**2**) = 0.52, R_f(**20**/**21**) = 0.90]: ^{1}H NMR (250 MHz) δ 0.83 (s, 1.5 H), 0.94 (d, 1.5 H, J = 6.4 Hz), 0.97 (s, 1.5 H), 0.98 (d, 1.5 H, J = 6.7 Hz), 1.28–1.87 (m, 5 H), 1.95–2.45 (m, 6.5 H), 2.50 (s, 0.5 H, J = 15.4 Hz), 4.63 (br s, 0.5 H), 4.70 (br s, 1 H), 4.74–4.79 (m,

0.5 H); ^{13}C NMR (62.7 MHz) 224.0 (s), 222.3 (s), 147.4 (s), 145.3 (s), 114.3 (t), 37.0 (t), 36.1 (t), 35.9 (t), 33.7 (t), 33.5 (d), 33.0 (t), 26.8 (t), 26.5 (q), 24.1 (t), 22.4 (q), 20.9 (q), 16.0 (q) ppm; IR (film) 1740, 1640 cm^{-1}; mass spectrum, m/z 192 (M^+). These data represent a 1:1 mixture of diastereomers.

(±)-4-Methyl-1,2,3,4,5,8-hexahydro-1-oxoazulene-7-ethanol (22). To a suspension of 0.42 g of paraformaldehyde (14.0 mmol) and 1.23 g of enone **2** (7.0 mmol) in 150 mL of dry CH_2Cl_2 at 0 °C was added 28.0 mL of a 1.0 M solution of dimethylaluminum chloride in hexanes (28 mmol) all at once. The reaction mixture was warmed to ambient temperature and stirred for an additional 3 h. The reaction mixture was quenched with an aq solution of sodium bicarbonate and the aluminum salts were filtered and washed with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude alcohol was chromatographed on silica gel [elution with diethyl ether: ethyl acetate, 1:1] to provide 1.19 g (83% yield) of alcohol **22** which was homogeneous by TLC analysis [hexanes:ethyl acetate, 2:1, R_f(**2**) = 0.95, R_f(**22**) = 0.65]: ^{1}H NMR (300 MHz) δ 1.16 (d, 3 H, J = 7.1 Hz), 1.97 (br s, 1 H), 2.12–2.68 (m, 9 H), 2.91 (s, 2 H), 3.60 (t, 2 H, J = 6.7 Hz), 5.65 (t, 1 H, J = 6.9 Hz); ^{13}C NMR (75.5 MHz) 209.1 (s), 177.9 (s), 139.5 (s), 135.9 (s), 125.5 (d), 60.11 (t), 42.0, 35.5 (d), 33.0 (t), 32.1 (t), 29.1 (t), 25.2 (t), 18.9 (q) ppm; IR (film) 3460, 1700, 1633 cm^{-1}; mass spectrum, m/z 188 (M − 18). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.68; H, 8.80. Found: C, 75.58; H, 8.63.

(±)-(3a*R,4*R**,8a*S**)-4,8a-Dimethyl-1,2,3,3a,4,5,8,8a-octahydro-1-oxoazulene-7-ethanol (24).**[12a] A 250 mL three-neck round-bottom flask was charged with 100 mL of dry, distilled liquid ammonia and 119 mg of finely divided lithium wire (17 mmol). To this solution was added over a 5-min period 233 mg of enone **22** (1.13 mmol) in 20 mL of THF. The reaction mixture was stirred at −78 °C for 1 h, followed by the addition of 2.1 mL of iodomethane (34 mmol). After 3 h at −78 °C, the ammonia was evaporated. Standard ethereal workup, followed by chromatography (H:E, 19:1), gave 178 mg (70% yield) of ketone **24** which was homogeneous by TLC analysis [diethyl ether, R_f(**22**) = 0.50, R_f(**24**) = 0.84]: ^{1}H NMR (300 MHz), δ 0.79 (s, 3 H), 0.93 (d, 3 H, J = 7.1 Hz), 1.50–2.40 (m, 13 H), 3.63 (t, 2 H, J = 6.7 Hz), 5.65 (m, 1 H); ^{13}C NMR (75.5 MHz) 222.0 (s), 136.0 (s), 127.2 (d), 60.0 (t), 57.1 (d), 48.2 (s), 44.2 (t), 37.9 (t), 37.7 (t), 34.7 (t), 30.7 (d), 23.1 (t), 20.3 (q), 14.1 (q) ppm; IR (film) 3454, 1739, 1454 cm^{-1}; mass spectrum, m/z 204 (M − 18). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.62; H, 9.98. Found: C, 75.37; H, 10.30.

(±)-(3*R,3a*S**,5*R**,6*S**,8*R**)-1,6-Dihydroxy-3a,8-dimethyl-1,2,3,3a,4,5,6,7,8,8a-decahydroazulene-5-ethanol (25).**[12a] To 185 mg (0.84 mmol) of ketone **24** dissolved in 1.4 mL of dry THF, maintained at −78 °C, was added dropwise 2.25 mL of diborane (2.25 mmol, 1.0 M in THF, Aldrich). The mixture was stirred for 4 h at −78 °C and then 2 h at −50 °C and 10 h at 0 °C. The reaction mixture was then treated with 0.5 mL of methanol, and then 1.7 mL of 3 N sodium hydroxide (4.20 mmol) and 0.93 mL of 30% hydrogen peroxide (10.1 mmol) were added. The resulting solution was stirred for 2 h at 45 °C. Extraction of the aqueous phase with ethyl acetate (5 × 100 mL), followed by drying of the combined organic phases over anhydrous magnesium sulfate and removal of the solvent, provided 219 mg of a crude residue. Recrystallization from hexanes/CH_2Cl_2 gave 167 mg (83%) of pure triol **25**, a white amorphous solid which was homogeneous by TLC analysis [10% methanol/EtOAc, R_f(**24**) = 0.99, R_f(**25**) = 0.60]: ^{1}H NMR (300 MHz) δ 0.75 (s, 3 H), 0.90 (d, 3 H, J = 6.0 Hz), 1.20–2.00 (m, 16 H), 3.45 (t, 1 H, J = 8.7 Hz), 3.50–3.80 (m, 3 H); ^{13}C NMR (75.5 MHz) 81.8 (d), 77.2 (d), 62.3 (t), 55.8 (d), 47.4 (t), 47.0 (s), 42.9 (d), 40.4 (t), 40.3 (t), 34.2 (d), 28.9 (t), 25.9 (t), 21.9 (q), 13.7 (q) ppm; IR (film) 3400–3030 cm^{-1}; mass spectrum, m/z 224 (M − 18); mp 116–118 °C. Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.37; H, 10.82. Found: C, 69.67; H, 10.34.

(±)-(3a*R,4a*S**,5*R**,7a*S**,8*R**,9a*S**)-3a,4,4a,5,6,7,7a,8,9,9a-Decahydro-4a,8-dimethylazuleno[6,5-*b*]furan-2(3*H*)-one (27).**[12a] A 125-mL three-neck round-bottom flask was charged with 411 mg of platinum(IV) oxide (1.81 mmol) and 11 mL of distilled water. Hydrogen gas was bubbled through the mixture while the reaction mixture was sonicated for 30 min. Nitrogen gas was flushed through the reaction vessel to remove hydrogen gas. A solution containing 167 mg of triol **25** (0.69 mmol) in 54 mL of acetone was added to the catalyst solution. Oxygen was bubbled into the solution for 8 h at 50 °C. The oxygen was purged from the reaction vessel using a stream of nitrogen gas. The catalyst was removed by filtration through a small pad of Celite. The filtrate was then concentrated and chromatographed on silica gel (elution with H:E, 1:1) to afford 142 mg (87%) of keto lactone **27** which was homogeneous by TLC analysis [diethyl ether, R_f(**27**) = 0.70]: ^{1}H NMR (300 MHz) δ 1.03 (s, 3 H), 1.07 (d, 3 H, J = 5.1 Hz), 1.29–1.45 (m, 2 H), 1.80–1.98 (m, 2 H), 2.03–2.50 (m, 8 H), 2.65 (dd, 1 H, J = 12.7 Hz, 4.6 Hz), 4.33 (ddd, 1 H, J = 9.75, 7.5, 2.7 Hz); ^{13}C NMR (75.5 MHz) 222.4 (s), 175.7 (s), 83.1 (d), 50.2 (s), 48.2 (d), 44.1 (t), 41.0 (d), 37.3 (t), 36.7 (t), 35.1 (t), 29.3 (t), 22.0 (q), 19.9 (q) ppm; IR (neat) 1788, 1742, 1548 cm^{-1}; mp 95–97 °C; mass spectrum, m/z 236 (M^+).

Further elution afforded 2 mg (3%) of (±)-(3a*R**,4a*S**,5*R**,7a*S**,8*R**,9a*S**)-3a,4,4a,5,6,7,7a,8,9,9a-decahydro-5-hydroxy-4a,8-dimethylazuleno[6,5-*b*]furan-2(3*H*)-one (**26**) which was homogeneous by TLC analysis [diethyl ether, R_f(**26**) = 0.45]: ^{1}H NMR (300 MHz) δ 0.84 (s, 3 H), 0.92 (d, 3 H, J = 7.3 Hz), 1.13–1.45 (m, 4 H), 1.57 (dd, 1 H, J = 17.9, 9.7 Hz), 1.61–1.78 (m, 2 H), 1.79–2.0 (m, 3 H), 2.09 (dd, 1 H, J = 14.6, 5.4 Hz), 2.18–2.39 (m, 2 H), 2.55 (dd, 1 H, J = 16.3, 7.1 Hz), 3.70 (dd, 1 H, J = 8.9, 8.9 Hz), 4.20 (ddd, 1 H, J = 11.8, 9.2, 2.9 Hz); ^{13}C NMR (75.5 MHz) 176.3 (s), 84.1 (d), 83.5 (d), 47.3 (d), 44.8 (s), 44.3 (t), 41.3 (d), 40.3 (t), 37.5 (t), 29.8 (d), 28.6 (t), 25.3 (t), 20.4 (q), 17.4 (q) ppm; IR (neat) 3490, 1782, 1547 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.54; H, 9.31. Found: C, 70.69; H, 9.41.

Catalytic Oxidation Optimized for the Production of Keto Lactone 27. A 100-mL three-neck round-bottom flask was charged with 241 mg of platinum(IV) oxide (1.06 mmol) and 6.3 mL of distilled water. Hydrogen gas was bubbled through the mixture while the reaction mixture was sonicated for 30 min. Nitrogen gas was flushed through the reaction vessel to remove hydrogen gas. A solution containing 98 mg of triol **25** (0.40 mmol) in 32 mL of acetone was added to the catalyst solution. Oxygen was bubbled into the solution for 1 h at 50 °C. The oxygen was purged from the reaction vessel using a stream of N_2 gas. The catalyst was removed by filtration through a small pad of Celite. The filtrate was then concentrated and chromatographed on silica gel (elution with H:E, 1:1) to afford 38 mg (40%) of lactone ketone **27** which was identical to that characterized above. Further elution afforded 53 mg (55%) of hydroxy lactone **26** which was identical to that characterized above.

(±)-(3a*R,4a*S**,5*R**,7a*S**,8*R**,9a*S**)-3a,4,4a,5,6,7,7a,8,9,9a-Decahydro-5-hydroxy-4a,8-dimethylazuleno[6,5-*b*]furan-2(3*H*)-one (26).**[12a] To a solution of 124 mg (0.53 mmol) of keto lactone **27** in 10 mL of absolute methanol at −15 °C was added 20 mg (0.53 mmol) of sodium borohydride. The reaction mixture was stirred for 20 min and was then quenched with the addition of 3 drops of water. Standard ethereal workup provided an oil, which was purified by chromatography on silica gel (elution with diethyl ether) to afford 121 mg (97%) of hydroxy lactone **26**, which was identical to that characterized above.

(±)-(3a*R,4a*S**,5*R**,7a*S**,8*R**,9a*S**)-3a,4,4a,5,6,7,7a,8,9,9a-Decahydro-4a,8-dimethyl-5-hydroxy-3-methyleneazuleno-[6,5-*b*]furan-2(3*H*)-one (30).**[12a] To a solution of 0.23 mL of dry diisopropylamine (1.64 mmol) and 7 mL of THF was added 0.66 mL of 2.5 M *n*-BuLi (1.64 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and then allowed to cool to −78 °C. To the solution of LDA was added 129 mg of hydroxy lactone **26** (0.55 mmol) in 5 mL of THF at −78 °C dropwise over a 10-min period and then the mixture was stirred for 30 min at −78 °C. Gaseous formaldehyde, generated from 199 mg of paraformaldehyde (6.64 mmol) at 150 °C, was passed into the reaction mixture at −25 °C with the aid of a stream of dry nitrogen. After complete depolymerization, the reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride. The reaction mixture was diluted with 30 mL of ether and 30 mL of ethyl acetate and dried over anhydrous magnesium sulfate. Evaporation of the filtrate under reduced pressure provided 157 mg of crude residue which was purified on silica gel. Elution with diethyl ether/ethyl acetate (1:1) gave 9 mg of recovered hydroxy lactone **26** and 128 mg (88%, 95% based on the recovered starting material) of white crystalline lactone diol **28**, which consisted of a mixture of diastereomers (R_f(**26**) = 0.68, R_f(**28**) = 0.36, ethyl acetate): mp 111–112 °C; ^{1}H NMR (300 MHz) δ 0.83

(s, 3 H), 0.89 (d, 3 H, J = 6.4 Hz), 1.08–1.52 (m, 5 H), 1.52–1.82 (m, 3 H), 1.82–1.99 (m, 1 H), 2.12 (dd, 1 H, J = 14.3, 4.6 Hz), 2.20–2.54 (m, 3 H), 2.54–2.67 (m, 1 H), 3.64–4.09 (m, 4 H), 4.22–4.58 (m, 1 H); ^{13}C NMR (75.5 MHz) 179.1 (s), 177.5 (s), 84.1 (d), 83.3 (d), 82.7 (d), 82.5 (d), 59.3 (t), 58.6 (t), 53.3 (t), 50.7 (d), 47.5 (d), 47.1 (d), 45.1 (t), 44.5 (s), 44.2 (s), 44.0 (t), 42.3 (d), 42.4 (d), 38.9 (t), 33.8 (t), 29.7 (d), 29.6 (d), 28.0 (t), 25.2 (t), 25.1 (t), 20.3, (q), 17.3 (q) ppm; IR (film) 3358, 1762 cm^{-1}. These data represent a mixture of diastereomers.

A solution of diol **28** (55 mg, 0.21 mmol) in 2 mL of dry pyridine containing 47 mg of (0.25 mmol) of freshly recrystallized toluenesulfonyl chloride was allowed to stir for 2 h at rt for 10 h. The reaction mixture was poured into 2 mL of saturated aq sodium bicarbonate solution and extracted repeatedly with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated to leave 97 mg of crude residue. Chromatography on silica gel (elution with hexanes/ethyl acetate, 1:1) provided 41 mg (60%) of pure monotosylate **29** [R_f(**29**) = 0.82, ethyl acetate]: ^{1}H NMR (300 MHz) δ 0.86 (s, 3 H), 0.93 (d, 3 H, J = 6.4 Hz), 1.12–1.49 (m, 5 H), 1.50–1.86 (m, 4 H), 1.88–2.04 (m, 1 H), 2.17 (d, 1 H, J = 14.5, 5.2 Hz), 2.28–2.42 (m, 2 H), 2.45 (s, 3 H), 3.70–3.86 (m, 1 H), 4.06–4.38 (m, 3 H), 7.36 (d, 2 H, J = 8.0 Hz), 7.78 (d, 2 H, J = 8.2 Hz); ^{13}C NMR (75.5 MHz) 173.8, 145.3, 132.1, 129.9, 128.0, 83.0, 82.3, 66.2, 60.3, 48.1, 47.2, 44.7, 44.0, 43.0, 39.2, 29.8, 28.5, 25.3, 21.6, 20.4, 17.4 14.1 ppm; IR (film) 3460, 1769, 1597, 1459, 1362 cm^{-1}. Continued elution provided 23 mg of recovered diol **28** [R_f(**28**) = 0.36, ethyl acetate]. These data represent a mixture of diastereomers.

Some of the above tosylate (**29**) (12 mg, 0.03 mmol) was dissolved in 5 mL of dry benzene to which 8.5 μL (0.06 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) was added. After 10 h at rt, the reaction mixture was reduced to residue and chromatographed on silica gel [elution with diethyl ether] to give 7 mg (90% overall from **26**) of crystalline α-methylene lactone **30** which was homogeneous on TLC [note that the R_f(**29**) = 0.82 while the R_f(**30**) = 0.82]: ^{1}H NMR (300 MHz) δ 0.88 (s, 3 H), 0.95 (d, 3 H, J = 6.3 Hz), 1.20–1.86 (m, 8 H), 1.89–2.15 (m, 1 H), 2.25 (dd, 1 H, J = 14.5, 6.0 Hz), 2.70–2.90 (m, 1 H), 3.82 (dd, 1 H, J = 8.8, 8.8 Hz), 4.25 (ddd, 1 H, J = 10.4, 10.4, 3.1 Hz), 5.44 (d, 1 H, J = 3.2 Hz), 6.15 (d, 1 H, J = 3.5 Hz); ^{13}C NMR (75.5 MHz) 170.2 (s), 140.8 (s), 119.5 (t), 83.9 (d), 81.6 (d), 47.7 (d), 45.1 (d), 44.5 (s), 44.3 (t), 38.0 (t), 30.3 (d), 28.8 (t), 25.5 (t), 20.5 (q), 17.4 (q) ppm; IR (film) 3447, 1762 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.95; H, 8.86. Found: C, 72.14; H, 8.93.

(±)-Graveolide (3). To a suspension of 43 mg of pyridinium dichromate (0.11 mmol) in 1.5 mL of anhydrous CH_2Cl_2 was added a solution of 14 mg of alcohol **30** (0.06 mmol) in 1.5 mL of CH_2Cl_2. The reaction mixture was stirred for 10 h at rt. Diethyl ether (50 mL) was added and the mixture was filtered through a plug of glass wool; the solids were washed with ether. Recrystallization of the residue obtained by concentrating the ethereal extracts (hexanes/CH_2Cl_2, 4:1) furnished 12 mg (86% yield) of crystalline graveolide (**3**) which was homogeneous by TLC analysis [diethyl ether, R_f(**3**) = 0.65]: mp 123–124 °C; ^{1}H NMR (400 MHz) δ 1.02 (s, 3 H), 1.08 (d, 3 H, J = 6.0 Hz), 1.40 (dd, 1 H, J = 24.4, 11.8 Hz), 1.50 (dd, 1 H, J = 14.8, 11.8 Hz), 1.56–1.70 (m, 1 H), 1.86–1.98 (m, 2 H), 2.04–2.10 (m, 1 H), 2.16 (dd, 1 H, J = 19.5, 9.0 Hz), 2.40–2.48 (m, 2 H), 2.49 (dd, 1 H, J = 14.8, 6.4 Hz), 2.74–2.85 (m, 1 H), 4.26 (ddd, 1 H, J = 12.6, 9.8, 3.0 Hz), 5.49 (d, 1 H, J = 3.4 Hz), 6.16 (d, 1 H, J = 3.6 Hz); ^{13}C NMR (75.5 MHz) 209.4 (s), 169.8 (s), 140.1 (s), 120.0 (t), 80.7 (d), 49.9 (s), 48.6 (d), 44.6 (d), 43.9 (t), 35.1 (t), 34.4 (t), 29.5 (d), 24.0 (t), 21.9 (q), 19.9 (q) ppm; IR (film) 1762, 1700 cm^{-1}; mass spectrum, m/z 248 (M$^+$). These spectral data are identical to that obtained with an authentic sample of natural **3** provided by Dr. Giovanni Appendino.[9]

(±)-(3a*R,4a*S**,7a*S**,8*R**,9a*S**)-3a,4,4a,5,6,7,7a,8,9,9a-Decahydro-6-(phenylselenyl)-4a,8-dimethyl-3-methyleneazuleno[6,5-*b*]furan-2(3*H*)-one (31).**[12a] To 12 mg of synthetic graveolide (0.05 mmol) in 2 mL of freshly distilled ethyl acetate spiked with gaseous HCl was added 10.4 mg (0.053 mmol) of benzeneselenenyl chloride at rt. Over a 10-h period, the reddish reaction mixture turned pale yellow, whereupon the reaction was quenched with solid sodium bicarbonate and diluted with 50 mL of ethyl acetate. The organic phase was washed with brine, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to provide 47 mg of crude residue. Purification on silica gel (elution with H:E, 1:1) provided 17.7 mg (91%) of phenyl selenide **31** which was homogeneous by TLC analysis [diethyl ether, R_f(**3**) = 0.75, R_f(**31**) = 0.23]: ^{1}H NMR (300 MHz) δ 0.92–1.12 (m, 6 H), 1.20–1.28 (m, 1 H), 1.26–1.74 (m, 3 H), 1.72–2.04 (m, 2 H), 2.02–2.25 (m, 2 H), 4.26–4.32 (m, 1 H), 5.44–5.54 (m, 1 H), 6.18 (d, 1 H, J = 3.5 Hz), 7.28–7.38 (m, 3 H), 7.61–7.65 (m, 2 H); ^{13}C NMR (75.5 MHz) 212.3, 170.1, 140.1, 136.0, 129.2, 129.0, 127.5, 120.0, 80.3, 49.4, 47.6, 46.2, 44.6, 43.8, 43.3, 35.5, 32.8, 29.6, 29.3, 28.9, 22.7, 19.8 ppm.

Aromaticin (4). To a solution of 17.7 mg (0.005 mmol) of monoselenide **31** in 1 mL of a THF/water mixture (6:1) were added at rt 28 mg (0.13 mmol) of sodium periodate and 11 mg of sodium bicarbonate (0.13 mmol). The reaction mixture was stirred at rt for 16 h and then diluted with 100 mL of ethyl acetate and 5 mL of brine. The aqueous layer was extracted 2 × 25 mL portions of ethyl acetate and the combined organic extracts were dried over anhydrous magnesium sulfate and condensed. The oily residue obtained was purified on silica gel (elution with CH_2Cl_2 and 4% ethyl acetate) to afford 8.4 mg of white crystalline aromaticin **4** (78%) whose spectra and TLC behavior were identical with those of naturally occurring aromaticin: mp 178–180 °C (lit.[10a] mp 178–181 °C; racemic aromaticin): ^{1}H NMR (300 MHz) δ 1.19 (s, 3 H), 1.26 (d, 3 H, J = 6.5 Hz), 1.45 (dd, 1 H, J = 24.7, 11.9 Hz), 1.64 (dd, 1 H, J = 14.6, 11.2 Hz), 2.04–2.20 (m, 1 H), 2.47 (dd, 1 H, J = 14.6, 7.1 Hz), 2.50–2.59 (m, 1 H), 2.75 (ddd, 1 H, J = 10.5, 2.3, 2.2 Hz), 2.86–2.94 (m, 1 H), 4.50 (ddd, 1 H, J = 12.0, 9.3, 3.1 Hz), 5.52 (d, 1 H, J = 3.3 Hz), 6.13 (dd, 1 H, J = 6.0, 2.8 Hz), 6.19 (d, 1 H, J = 3.5 Hz), 7.63 (dd, 1 H, J = 6.0, 1.8 Hz); ^{13}C NMR (75.5 MHz) 213.6 (s), 169.5 (s), 161.5 (d), 140.2 (s), 130.3 (d), 120.1 (t), 79.5 (d), 54.1 (d), 51.1 (s), 46.4 (d), 44.1 (t), 32.0 (t), 27.9 (q), 27.1 (d), 19.8 (q) ppm; IR (film) 1765, 1709, 1646 cm^{-1}; mass spectrum, m/z 246 (M$^+$).

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Abbreviations. Aqueous (aq), room temperature (rt), hexanes:diethyl ether (H:E), and triethylamine (TEA).