$- H_2O$), 594.2252; IR ($CHCl_3$) $\delta_{C=O}$ 1730, 1665 cm^{-1}; ^1H NMR (200 MHz) δ 0.70 (3 H, s), 0.84 (3 H, d, $J = 6.8$ Hz), 1.50 (3 H, s), 1.69 (1 H, br d, $J = 14$ Hz), 1.87 (3 H, s), 2.18 (1 H, br s), 2.35 (1 H, dd, $J = 14$ and 3.5 Hz), 4.15 (3 H, s), 4.31 (3 H, s), 4.47 (1 H, br s), 6.51 (1 H, d, $J = 8$ Hz), 6.63 (1 H, d, $J = 8$ Hz), 6.96 (2 H, d, $J = 8$ Hz), 7.18 1 H, t, $J = 8$ Hz), 7.24 (1 H, t, $J = 8$ Hz), 9.61 (1 H, br s), 10.16 (1 H, br s).

Feeding Experiments. A loopful culture of *Streptomyces pseudovenezuelae* strain AM-2947 on an agar slant was transferred into a 500-mL Sakaguchi Flask containing 100 mL of a medium (2% glycerol, 2% soybean meal, 0.3% NaCl and distilled water, pH 7.0) and incubated for 2 days at 27 °C to give a seed culture. One hundred test tubes (2 cm × 19 cm) each containing 10 mL of a production medium (1% glycerol, 1% soybeam meal, 0.3% NaCl and distilled water, pH 7.0) were inoculated with 0.5-mL aliquots of the seed culture and incubated at 27 °C with shaking. After 16 h, 0.5-mL portions of aqueous 2% [$1-^{13}C$]sodium acetate (90 atom % enriched) or 0.6% [$1,2-^{13}C_2$]sodium acetate (90 atom % enriched) solution was aseptically added to the cultures, which were incubated for an additional 2 days. Combined culture broth (1 L each) was extracted with ethyl acetate (1 volume) at pH 2.0 and the extract was evaporated to dryness under reduced pressure to give a crude powder. The crude sample was then purified by preparative layer chromatography on silica gel 60 F_{254} (Merck, 2-mm thickness), using chloroform-methanol (10:1) as solvent. The appropriate setomimycin band was scraped and extracted with chloroform-methanol (2:1). The extract was evaporated under reduced pressure to give a reddish orange residue, which was rechromatographed by preparative layer chromatography, using benzene-ethyl acetate (1:3) as solvent. The setomimycin band was again scraped, extracted with ethyl acetate, and stripped of solvent in vacuo to give 21.2 mg and 27.9 mg of setomimycin enriched from [$1-^{13}C$]- and [$1,2-^{13}C_2$]sodium acetate, respectively.

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Supplementary Material Available: ^{13}C NMR spectra of **1** and **3**, ^{13}C {^1H} low power decoupling spectra and ^{13}C {^{13}C} homonuclear decoupling spectra of the enriched **1** (5 pages). Ordering information is given on any current masthead page.

Stereocontrolled Total Synthesis of an α-Methylene Guaianolide in the 4,5-Epoxyosmitopsin Family

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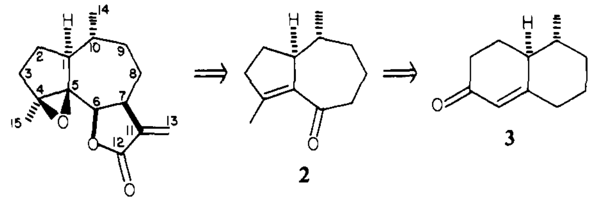
Abstract: Guaianolide **13** has been prepared in 19 steps and 7.9% overall yield from 1,3-cyclohexanedione. Two of the six chiral centers in racemic hydroazulene lactone **13** were introduced stereoselectively (4.5:1.0 ratio of stereoisomers), and the other four were introduced with virtually complete and remarkable stereocontrol. X-ray analysis of guaianolide **13** revealed *trans*-hydroazulene and *cis*-lactone ring fusions, and ^1H NMR showed an unusual chemical shift for one proton at δ 2.1. Decoupling experiments on α-methylene guaianolide **1** indicated that this characteristic downfield absorption is due quite unexpectedly to the C-8β hydrogen, which is situated close to the oxygen atom and in the plane of the 4β,5β-epoxide ring. Synthetic α-methylene guaianolide **1**, which shows significant antischistosomal activity, is the C-10 epimer of the structure reported for natural 4,5-epoxyosmitopsin.

Many hydroazulenic lactones have been isolated from plants and have been shown to possess high antitumor,[1] allergenic,[2] antischistosomal,[3] antihelminthic,[4] antifeedant,[5] contraceptive,[6] and root growth stimulatory and inhibitory[7] activities. Because of their high biological activity[8] and because they are available from natural sources often only in small quantities, some of these sesquiterpenes have been prepared in the laboratory. Although total syntheses of some *pseudoguaianolides* have recently been reported,[9] all of the published *guaianolide* hydroazulene syntheses have involved structural modifications of related naturally occurring decalin sesquiterpenes.[10] We recently reported the total synthesis and characterization of two stereoisomeric hydroazulenones,[11] and we record here the culmination of that project leading to the first, highly stereocontrolled, total synthesis of an α-methylene guaianolide which, although not itself a natural product, is structurally similar to natural 4,5-epoxyosmitopsin and which has some surprising NMR characteristics useful in assigning hydroazulene ring junction stereochemistry in guaianolides like **1** having a 4,5-epoxide group. Retrosynthetic analysis suggested octalone **3** as a precursor to hydroazulenone **2** which itself would be an intermediate for preparation of epoxyguaianolide **1**.



1 **2** **3**

Preparation of Octalone 3. Because pure octalone **3** was needed on at least a 10-g scale to initiate the multistep synthesis of

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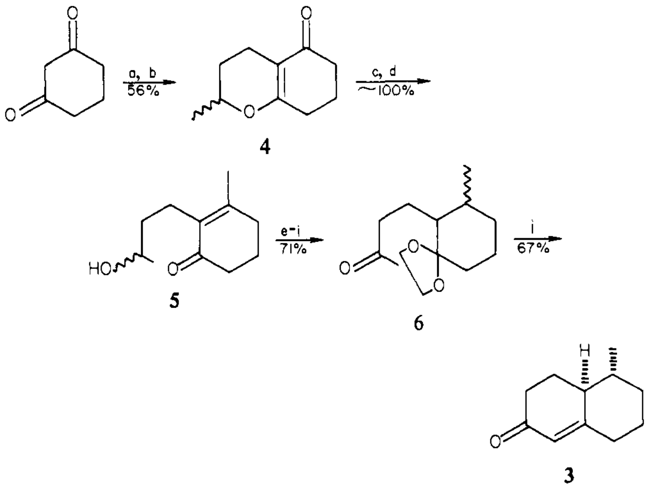
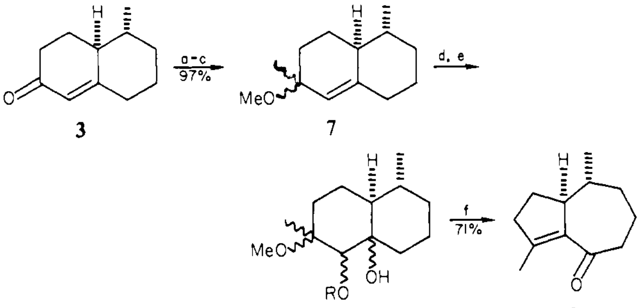
Scheme I



(a) CH$_2$=CHCOCH$_3$, (b) NaBH$_4$, (c) MeLi, (d) H$_3$O$^+$, (e) AcCl/pyridine, (f) H$_2$/Pd–C, (g) (HOCH$_2$)$_2$, *p*-TsOH, (h) KOH(aq), (i) pyridinium chlorochromate, (j) MeOH/HCl

Scheme II



8a, R = H (79%)
8b, R = SO$_2$Me (95%)

(a) MeLi, (b) H$_3$O$^+$, (c) NaH, MeI, (d) OsO$_4$, (e) MsCl, pyridine, (f) *t*-AmONa, benzene

guaianolide **1**, the literature procedures[11,12] were passed over in favor of the new, cheap, and reliable route shown in Scheme I.

Michael addition of 1,3-cyclohexanedione to methyl vinyl ketone followed directly by sodium borohydride reduction led to cyclic enol ether **4**.[13] Methyllithium addition followed by acidic aqueous workup produced cyclohexenone **5**. All attempts at hydrogenation and at dissolving metal reduction of cyclohexenone alcohol **5** failed. After acetylation of alcohol **5**, however, catalytic hydrogenation proceeded smoothly. Because attempts to remove the protecting acetate group in the presence of the free ketone produced mainly polymeric material, the corresponding ethylene ketal was formed. Saponification of the acetate ester and oxidation of the resulting alcohol under nonacidic conditions then led cleanly to ketone ketal **6**. Refluxing ketone ketal **6** in acidic aqueous methanol produced the desired octalone **3** along with its tetrasubstituted β,γ double bond isomer in 85:15 ratio. Low-temperature crystallization from hexane gave isomerically pure octalone **3** which was used immediately;[14] basic equilibration of the β,γ isomer produced more of desired octalone **3**, thus allowing efficient use of octalone **3** in the subsequent steps. We have shown previously that octalone **3** is stereochemically pure and that the angular hydrogen and adjacent methyl group are *syn* to each other.[11]

Preparation of Hydroazulenone 2. Because our original scheme leading from 11-carbon octalone **3** to 12-carbon hydroazulenone **2** had some delicate and troublesome steps,[11] especially introduction of the twelfth carbon atom, we developed a more direct and reliable route (Scheme II).

Addition of methyllithium to octalone **3**, followed by reaction of the corresponding sodium alkoxide with methyl iodide, led to tertiary allylic ether **7**. Osmium tetroxide oxidation of allylic ether **7** required vigorous hydrolysis conditions to liberate tertiary ether diol **8a** as a mixture of several diastereomers. Preparative TLC allowed separation of three solid diols. Although each one of these diols was converted separately into its corresponding secondary mesylate (**8b**) and subsequently rearranged to hydroazulene **2** in high yield, it was more convenient and efficient to mesylate and rearrange the crude diol mixture. Attempts to prepare diols **8a** using catalytic amounts of osmium tetroxide[15] or using potassium permanganate[16] failed, as did mercuric acetate[17] attempted oxidation. After diol monomesylates **8b** were exposed to sodium *tert*-amyloxide in benzene[18] for 30 s at 5 °C, TLC analysis indicated complete disappearance of mesylates **8b** and formation of a single product which was identified as hydroazulenone **2**. It seems probable, therefore, that this decalin → hydroazulene rearrangement produced β-methoxy ketone intermediates which very rapidly underwent loss of methanol to form enone **2**.

Conversion of octalone **3** into stereochemically pure hydroazulenone **2** via the six steps in Scheme II proceeded in an overall yield of 51.7%. As we showed recently,[11] both the ^{1}H and ^{13}C NMR chemical shifts of the C-14 methyl group and the coupling constant of its ^{1}H NMR doublet ($J_{10,14}$) distinguish 1,10-*syn*-hydroazulenone **2** from its 1,10-*anti*-epimer **2′**.

Preparation of Guaianolide 1. Kinetic deprotonation of hydroazulenone **2** was expected to involve removal of a C-7 proton thus alllowing C-7 attachment of the remaining three carbon atoms of the sesquiterpene skeleton.[19] Despite good literature analogies

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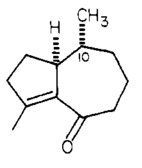
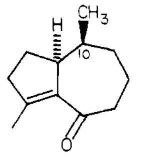


2

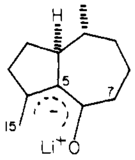
δ 0.96 (d, J = 5.0 Hz), 21.4 (^{13}C, q)



2'

δ 0.77 (d, J = 6.0 Hz), 12.1 (^{13}C, q)

for this type of kinetic deprotonation–alkylation in structurally similar tetrasubstituted α,β-ethylenic ketones (e.g., pulegone),[19c] treatment of hydroazulene **2** with lithium diisopropylamide and then with allyl bromide or with methyl bromoacetate led only to products alkylated at carbons 5 and 15, arising presumably via intermediacy of the corresponding dienolate **2a** which underwent α- and γ-alkylation. This tendency of hydroazulenone **2** to form dienolate **2a** seems to indicate either that kinetic enolate equilibration to the more thermodynamically stable dienolate **2a** is occurring or that in this case direct abstraction of a C-15 proton represents the kinetic as well as the thermodynamic site of deprotonation. Therefore removal or protection of the 4,5 double bond was necessary.

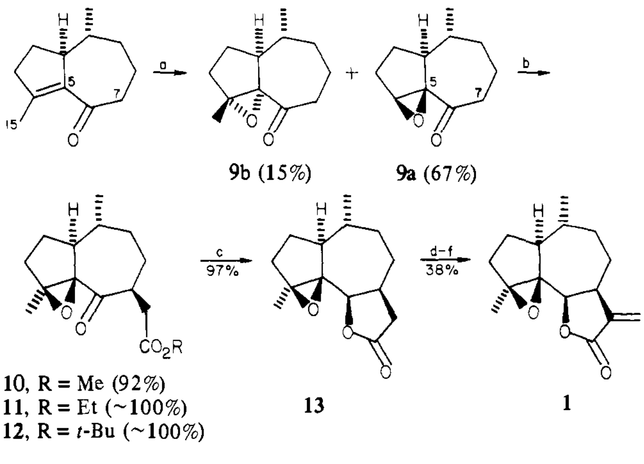


2a

Epoxidation of hydroazulenone **2** was chosen for several reasons: (1) the corresponding epoxy ketones **9a** and **9b** (Scheme III) can enolize only toward the desired C-7 position; (2) the stereochemistry of the hydroazulene ring fusion in epoxides **9a** and **9b** is established; (3) several natural guaianolides have either hydroxyl or epoxy groups at the C-5 ring junction carbon atom (e.g., parishin C,[20] eupatundin,[21] euparotin acatate,[21] eupachlorin,[21] hymenosignin,[22] and epoxyosmitopsin[23]); and (4) further functionalization of the cyclopentane ring is possible via epoxides **9**. Basic hydrogen peroxide epoxidation[24] of hydroazulenone **2** produced two stereoisomeric epoxy ketones, **9a** and **9b**, in 4.5:1.0 ratio.

Crude epoxides **9a** and **9b** were separated by *rapid* chromatography on florisil; *slow* elution caused hydrolysis of the minor epoxide **9b**. Chromatography on silica gel or on alumina caused hydrolysis (and dehydration) of both epoxide isomers **9a** and **9b**. Although sublimation of the minor epoxide resulted in its decomposition, sublimation of the major epoxide produced white crystalline solid **9a**, mp 69.8–70.6 °C. The main ^{1}H NMR spectroscopic differences between the major and minor epoxides **9a** and **9b** were as follows: **9a** showed C-14 CH_3 as a doublet at δ 0.92, C-15 CH_3 as a singlet at δ 1.36 (and as a ^{13}C quartet at δ 20.65), and a one-proton multiplet at δ 2.6; **9b** showed C-14 CH_3 as a doublet at δ 1.04 and C-15 CH_3 as a singlet at δ 1.42 (and as a ^{13}C quartet at δ 21.52) and did not show any unusual deshielded resonance below δ 2. At this point, however, it was not possible to assign stereochemistry to our epoxides **9a** and **9b** unambiguously. Because of the special downfield shift observed in the ^{1}H NMR spectrum of the major epoxide **9a**, we tentatively assigned it as having a *cis*-hydroazulene fusion with epoxide oxygen and C-1 H (shifted downfield) cis in analogy with other similar structural units and with other epoxyguaianes assigned in this way.[23,25,26] Only after X-ray analysis revealed synthetic guaianolide **13**, derived from the major epoxide, to have trans-fused hydroazulene stereochemistry, however, did it become evident that our major epoxide had structure **9a**. *Clearly, therefore, NMR spectral data alone are insufficient in this and many other epoxyhydroazulene cases*[23,25,26] *for unambiguous structural assignments.* Assigning the one-proton downfield ^{1}H NMR absorption to a specific proton in epoxyhydroazulenone **9a** was done at a later stage in the total synthesis.

Scheme III



9b (15%) **9a** (67%)

10, R = Me (92%)
11, R = Et (~100%)
12, R = t-Bu (~100%)

13

1

(a) H_2O_2, NaOH, (b) i-Pr_2NLi, XCH_2CO_2R, (c) $NaBH_4$, DMF, (d) i-Pr_2NLi, $CH_2{=}N^+Me_2\ I^-$, HMPA, (e) MeI, (f) $NaHCO_3$

Lithium diisopropylamide deprotonation of major epoxide **9a** at −78 °C followed by addition of methyl iodoacetate (or ethyl bromoacetate or *tert*-butyl iodoacetate) in hexamethylphosphoramide led to pure, alkylated epoxyhydroazulenone **10** (or **11** or **12**) in exceptionally good yield (90%) after florisil chromatography. This result stands in contrast to Marshall and Snyder's attempted alkylation of an analogous trans-fused pseudoguaiane ketone having carbon 10 sp^3-hybridized; in their case, only when C-10 was sp^2-hybridized was enolate alkylation at C-7 feasible.[9a] Epoxy keto methyl ester **10** showed only 15 carbon absorptions in its ^{13}C NMR spectrum, and addition of incremental amounts of the lanthanide shift reagent Eu(fod)$_3$ caused the C-15 CH_3 and the C-7 H to undergo downfield shifts of 10 ppm/equiv of shift reagent but did not cause appearance of two distinct C-15 CH_3, methyl ester, or C-7 H absorptions.[27] Apparently, therefore, methyl ester **10** is stereochemically pure, and the relative stereochemistry at C-7 in alkylated hydroazulenone **10** has been established with virtually complete stereocontrol. This stereochemically specific β alkylation is quite remarkable especially because of the well-known, conformational flexibility of cycloheptanones. Examination of Dreiding molecular models suggested that introduction of an alkyl group at C-7 would indeed occur preferentially (but not necessarily exclusively) from the β face

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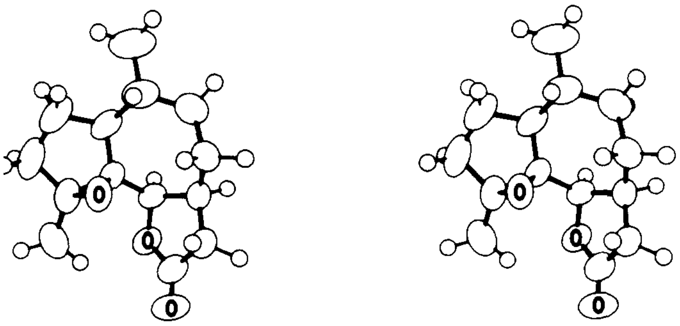


Figure 1. Sterodiagram of guaianolide **13** drawn by computer using the experimentally determined coordinates from an X-ray diffraction analysis of a single crystal. The small spheres represent hydrogen atoms, and the ellipsoids represent the thermal motion of the C and O atoms at a 50% probability level. One antipode was chosen arbitrarily; the substance occurs as a racemate and both hands are present in the crystal.

of a C-7 enolate intermediate and that basic equilibration of an initially formed alkylation product would also lead mainly to a pseudoequatorial (i.e., β oriented) alkyl group.

Although reduction of the C-6 carbonyl group with sodium borohydride in *methanol* led to a variety of hydroxyl-containing non-epoxide products, similar reduction in *dimethylformamide* produced cyrstalline epoxylactone **13** (homogeneous by TLC) directly in very high yield. The absence of any stereoisomeric lactone was shown unambiguously by the ^{13}C NMR spectrum of guaianolide **13** (only 14 absorptions) and by its 300-MHz ^{1}H NMR spectrum which showed very sharp absorptions for C-6 H (δ 4.94 (d, J = 8.0 Hz)), for C-15 CH_3 (δ 1.51 (s)), and for C-14 CH_3 (δ 0.91 (d, J = 6.0 Hz)); also a one-proton multiplet was observed at δ 2.1. Thus the sixth and last chiral center has been created with complete and remarkable stereocontrol, and guaianolide **13** has been prepared in 7.9% total yield over 19 steps starting with 1,3-cyclohexanedione.

At this point, however, unambiguous assignment of the lactone stereochemistry was not possible. Typical ^{1}H NMR coupling constants (J) for authenticated *cis*-lactones in the *pseudoguaiane* series have values between 7.0 and 9.5 Hz;[8-10] no authenticated *guaiane cis*-lactones were available for comparison. Typical J values for authenticated guaiane and pseudoguaiane *trans*-lactones fall between 8.0 and 10.5 Hz.[8-10] The measured J value of 8.0 Hz for synthetic guaiane lactone **13**, therefore, falls within the ranges of *both cis-* and *trans*-lactones. Therefore, a single-crystal X-ray analysis was performed. Figure 1 depicts a computer-generated perspective drawing of guaianolide **13**.

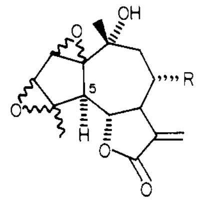
X-ray Data for Guaianolide 13. Guaianolide **13** ($C_{14}H_{20}O_3$) crystallized in the monoclinic space group $P2_1/n$ with a = 18.687 (4) Å, b = 5.909 (1) Å, c = 23.787 (5) A, β = 100.27 (2)°, and 8 molecules in the unit cell with a calculated density of 1.21 g/cm^3. Intensity data were collected by a computer-controlled, four-circle diffractometer with monochromatized Cu Kα radiation (λ = 1.541 78 Å) to a maximum value of 2θ = 112°. The structure was solved by the symbolic addition procedure[28] and refined by full-matrix least-squares refinement on all data within the 2θ = 112° sphere, a total of 3375 reflections. With coordinates and anisotropic thermal parameters varied for the C and O atoms and the positions of H atoms as found in the difference map held constant, the conventional agreement factor was 7.1% for 3067 reflections with intensities observed greater than zero.

The two independent molecules in the asymmetric unit, i.e., two molecules not related by crystallographic asymmetry, have identical configurations. The stereodiagram shown in Figure 1, computer drawn with coordinates from molecule B, can be superimposed on a similarly prepared stereodiagram for molecule A. The seven-membered ring has a chair conformation, while the two five-membered rings are not planar but assume a conformation between an envelope and a planar one. In the cis-fused lactone ring, C-7 is out of the approximate plane of the remaining atoms while in the cyclopentane ring, C-2 is out of the plane of the other four atoms. There are no unusual bond lengths or bond angles.

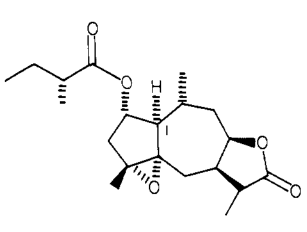
The proximity of the epoxide oxygen atom and the C-8β hydrogen atom is important in the interpretation of the NMR data of this guaianolide and related compounds. In **13**, this distance is 2.59 (3) Å in molecule A and 2.65 (3) Å in molecule B.

It is clear from Figure 1 that guaianolide **13** (and its mirror image) is a trans-fused hydroazulene with a *cis*-lactone ring oriented on the same face of the molecule as the epoxide ring. Furthermore, the X-ray data show that there are three protons which might be especially deshielded by the epoxide ring and therefore which might account for the unusual δ 2.1 absorption in the ^{1}H NMR spectrum of guaianolide **13**: (1) C-1 H, trans to the 4,5-epoxide ring;[26,29] (2) C-10 H, syn to the 4,5-epoxide; and (3) C-8β H, also syn to the epoxide ring.

Literature analogies seemed to suggest that hydroazulene angular hydrogens absorb at unusually low field when they are trans (but not cis) to epoxides at the hydroazulene ring junction [e.g., artecanin (**14-t**, C-5α H, δ 2.87),[26] but not canin (**14-c**, C-5α H, δ 2.35),[26] and yomogiartemin (**15-t**, C-5α H, δ 2.87),[29] but not hymenosignin (**16-c**, C-1α H, δ 1.88)[22]. We therefore tentatively assigned the δ 2.1 absorption in guaianolide **13** to C-1α H, *trans* to the 4β,5β-epoxide.



14-t, β-epoxides, R = H
14-c, α-epoxides, R = H
15-t, β-epoxides, R = OAc



16-c

α-Methylenation of *c*is-lactone **13** using Eschenmoser's dimethylmethyleneimmonium iodide procedure[30] gave sesquiterpene lactone **1** as a white solid, mp 69.5–70.5 °C, homogeneous by TLC in several solvent systems and by 300-MHz ^{1}H NMR. The unusual one-proton, low-field NMR absorption, however, changed from δ 2.1 in lactone **13** to δ 2.3 δ in α-methylene lactone **1**. Because this additional methylene unit on the lactone ring was not expected to cause any change in the environment of the remote C-1 H, we questioned whether indeed C-1 H was responsible for the δ 2.1–2.3 absorptions in guaianolides **13** and **1**.

^{1}H NMR (300-MHz) spin-decoupling experiments allowed unambiguous assignment of the δ 2.3 absorption to C-8β H in α-methylene guaianolide **1**. Irradiation at δ 2.3 caused no change in the C-14 methyl doublet at δ 0.91; the δ 2.3 absorption, therefore, is not due to the C-10 H. Irradiation at δ 3.3 (C-7 H), however, not only caused collapse of the C-6 and the lactone α-methylene doublets to singlets but also caused sharp decrease in the multiplicity of the signal at δ 2.3, which appeared now as a broad triplet, thus showing unambiguously that the proton absorbing at δ 2.3 (i.e., C-8β H and not C-1 H) was coupled with the C-7 H. Examination of the X-ray structure (Figure 1) does indeed show that the C-8 β proton is situated close to the oxygen atom and in the plane of the 4β,5β-epoxide ring; it is therefore expected to be deshielded.[31] Although the C-10 H is also situated

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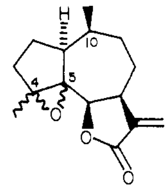
[29] Koreeda, M.; Matsueda, S.; Satomi, T. *Chem. Lett.* **1979**, 81.

[30] (a) Roberts, J. L.; Borromeo, P. S.; and Poulter, C. D. *Tetrahedron Lett.* **1977**, 1621. (b) Danishefsky, S.; Kitahara, T.; McKee, R.; Schuda, P. F. *J. Am. Chem. Soc.* **1976**, *98*, 6715. (c) Eschenmoser, A.; Schreiber, J.; Maag, H.; Hashimoto, N. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 330.

[31] (a) Bhacca, N. S.; Williams, D. H. "Applications of NMR Spectroscopy in Organic Chemistry"; Holden-Day: San Francisco, Calif., 1964; p 102. (b) Jeffries, P. R.; Rosich, R. S.; White, D. E. *Tetrahedron Lett.* **1963**, 1853. (c) Tori, K.; Kitahonaki, K.; Takano, Y.; Tanida, H.; Tsuji, T. *Tetrahedron Lett.* **1964**, 559.

close to the epoxide oxygen atom, the C-10 H is above the plane of the epoxide ring and is therefore expected to be shielded.[31]

Bohlmann and Zdero have recently isolated natural 4,5-epoxyosmitopsin and have assigned it as trans-fused guaiane **17-t** exclusively on the basis of ^{1}H NMR arguments.[23] They also prepared the isomeric epoxide and assigned it as cis-fused hydroazulene **17-c**. If the structure of natural 4,5-epoxyosmitopsin is indeed that of **17-t**, then this would be the first natural *cis*-lactone in the guaiane series ever isolated and then our synthetic α-methylene epoxyguaianolide **1** would be 10-epi-4,5-epoxyosmitopsin (**1** = 10-epi-**17-t**). Bohlmann and Zdero's guaianolide **17-t** may indeed be a *cis*-lactone. The lowest coupling constant ($J_{6,7}$) value for the many authenticated *trans*-lactones in the guaiane and the pseudoguaiane series is 8.0 Hz; guaianolide **17-t** has $J_{6,7}$ = 7.0 Hz, which strongly suggests a *cis*-lactone stereochemistry. Unambiguous confirmation of this structural argument by X-ray analysis of 4,5-epoxyosmitopsin **17** is extremely desirable.



17-t, 4β,5β-epoxy
17-c, 4α,5α-epoxy

Synthetic, racemic, α-methylene guaianolide **1** shows significant activity against schistosomal cercariae.[3,33] Synthesis of other biologically active guaianolides will certainly be facilitated by the chemical and stereochemical information reported in this stereocontrolled total synthesis of several conformationally mobile hydroazulenes.

Experimental Section

Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz., or by Galbraith Laboratories, Knoxville, Tenn. Melting points are uncorrected and were performed on Thomas-Hoover Melt Temp. Mass spectra were performed on a Hitachi Perkin-Elmer MU-6 at an ionizing voltage of 70 eV. Infrared spectra were recorded as solutions on a Perkin-Elmer 337 spectrophotometer, and NMR spectra were recorded on a Varian A-60A or JEOL MH-100 spectrophotometer and were standardized vs. tetramethylsilane (Me$_4$Si). Preparative VPC separations were obtained with a Varian Aerograph Model 90-P instrument equipped with a thermal conductivity detector and He as the carrier gas. The VPC column and conditions used were as follows: 10 ft × $^1/_8$ in. 5% SE-30 on 100–140 mesh chrom G, flow rate 20 cm^3 He/min.

All solvents were reagent grade. Anhydrous diethyl ether and tetrahydrofuran were distilled from benzophenone ketyl. Hexamethylphosphoramide (HMPA), tetramethylene sulfone (sulfolane), trimethylamine, and diisopropylamine (which were obtained from Aldrich) were purified by distillation from CaH$_2$ under nitrogen. Titration of alkyllithium reagents was accomplished by titration with diphenylacetic acid.[34] Methyllithium and *n*-butyllithium were used as 1.0–2.0 M solutions in ether and hexane, respectively. Drying solutions of crude products was done by using anhydrous sodium sulfate, unless noted otherwise.

Synthesis of Cyclic Enol Ether 4.[13] To a room temperature solution of 22.4 g (0.2 mol) of 1,3-cyclohexanedione in 250 mL of doubly distilled water (in an all glass apparatus) under nitrogen was added dropwise, over a 1-h period, 22.4 g (0.31 mol) of freshly distilled methyl vinyl ketone in 200 mL of distilled water. The reaction was maintained under nitrogen for 24 h. During this time, the reaction turned from nearly colorless to a deep amber. The reaction was then stirred vigorously under aspirator pressure for several hours to remove excess methyl vinyl ketone and then saturated with sodium chloride. The aqueous solution was extracted 4 times with 50 mL of methylene chloride. The combined organic layers were dried, and the solvent was removed by evacuation under reduced aspirator pressure followed by evacuation at 0.2mmHg for 48 h to give a thick syrup. The total yield was 39.5 g (88%).

To a −15 °C slurry of 1.9 g (0.05 mol) of sodium borohydride in 40 mL of absolute ethanol was added dropwise a solution of 10 g (~0.05 mol) of the crude Michael adducts prepared above at such a rate that the reaction temperature (monitored by internal thermometer) does not exceed −10 °C during the addition. Considerable amounts of hydrogen are evolved during addition. The reaction was stirred at −15 °C for 2 h and at room temperature for 3 h and then *carefully* quenched with water (~100 mL) followed by slow addition of 50 mL of 1 N HCl. The residue was concentrated at reduced pressure to remove ethanol solvent and then saturated with sodium chloride. The aqueous layer was extracted 4 times with 30 mL of methylene chloride, and the combined organic layers were dried. Removal of solvent at reduced pressure followed by distillation gave 4.69 g (56%) of cyclic enol ether **4** as a clear oil: bp 80 °C (0.2mmHg); ^{1}H NMR (CCl$_4$) δ 4.05 (b m, 1 H, -CHO-), 3.0–1.0 (b m, 10 H, skeletal H), 1.34 (d, 3 H, CH_3CH, J = 6 Hz); IR (CCl$_4$) $\nu_{C=O}$ 1655, 1620 cm^{-1}; mass spectrum (70 eV), *m/e* 166 (M$^+$), 151 (M − 15). These spectra are identical with those reported in the literature.[13]

Synthesis of Cyclohexenone 5. To a −40 °C solution of 10.0 g (60.2 mmol) of cyclic enol ether **4** in 50 mL of anhydrous ether under nitrogen was added dropwise over 20 min a solution of 35 mL (70.0 mmol) of 2.0 M methyllithium in ether. The mixture was stirred at −40 °C for 5 min, at 0 °C for 5 min, and at room temperature for 1 h. To this reaction mixture was then added solid ammonium chloride in small portions at 0 °C. Vigorous evolution of gas occurred over ~5-min period. Stirring was continued at room temperature for 10 min, and 30 mL of water was then added. The ether layer was removed after 5 min of stirring, and the aqueous layer was further extracted 2 times with 30 mL of ether. The combined organic layers were washed 1 time with aqueous sodium bicarbonate and dried over anhydrous potassium carbonate. Removal of solvent at reduced pressure gave 10.39 g of crude product. TLC (60:40 benzene/ethyl acetate on silica) showed one *major* (UV active) component at R_F = 0.3 plus some very minor component at R_F = 0.9. Attempts to purify this material by preparative TLC on silica lead to decomposition.

A solution of 100 mg of the crude tertiary alcohol prepared above in 25 mL of ether was stirred together with 25 mL of 1 N HCl for 10 min. The ether layer was separated and the aqueous layer extracted 2 times with 10 mL of ether. The combined organic layers were washed with aqueous sodium bicarbonate and dried over potassium carbonate. Removal of the solvent at reduced pressure gave ~100 mg (100%) of cyclohexenone **5** as a clear oil: ^{1}H NMR (CCl$_4$) δ 3.6 (b m, 2 H, OH and CHOH), 2.6–1.0 (b m, 10 H, skeletal H), 1.95 (s, 3 H, =CCH_3), 1.08 (d, 3 H, CHCH_3, J = 6.0 Hz); IR (CCl$_4$) 3460 (strong OH), 2920, 1655 ($\nu_{C=O}$), 1430, 1380, 1325, 1295, 1185, 1130, 1060, 1025, 960, 915 cm^{-1}. High-resolution mass spectrum (M − H$_2$O): calculated for $C_{11}H_{16}O$, 164.1201, found, 164.1199.

Synthesis of Ketone Ketal 6. Cyclohexenone alcohol **5** (8.19 g, 45.0 mmol) was acetylated in standard fashion by using acetyl chloride and pyridine in methylene chloride. The crude yellow, oily product was column chromatographed on silica gel (~500 g) with 20% ether/petroleum ether as eluant to give 8.81 g (87%) of the corresponding acetate as a clear water while oil. VPC analysis (165 °C) shows a single major component at 12.2-min retention time in >95% purity. An analytical sample was obtained by preparative TLC on silica gel with 1:1 ether/petroleum ether as eluant: ^{1}H NMR (CCl$_4$) δ 4.80 (sextet, 1 H, CHOAc, J = 6.4 Hz), 2.8–1.4 (b m, 10 H, ring and chain H), 2.00 (s, 3 H, COCH_3 or vinyl CH$_3$), 1.95 (s, 3 H, COCH_3 or vinyl CH$_3$), 1.22 (d, 3 H, -CHCH_3 J = 6.2 Hz); IR (CCl$_4$) 2930, 1730 (OAc), 1663 (unsaturated ketone), 1630, 1450, 1430, 1375, 1330, 1240, 1185, 1130, 1065, 1020, 960, 945 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 242 (14 800); mass spectrum (70 eV), *m/e* 224 (M$^+$), 164 (base peak). High-resolution mass spectral analysis: calculated for $C_{13}H_{20}O_3$, 224.1412, found, 224.1417.

A vigorously stirred solution of 8.65 g (38.6 mmol) of this keto acetate in 125 mL of absolute ethanol together with 100 mg of 10% Pd/C was degassed by alternately evacuating to aspirator pressure followed by flushing with nitrogen 4 times. A hydrogen atmosphere was then admitted and uptake at atmospheric pressure was monitored. Hydrogenation proceeded rapidly in less than 3 h. The mixture was filtered through a bed of Celite by suction, and the solid residue was washed several times with ethanol. Removal of solvent at reduced pressure gave a yellow oil which upon rapid chromatography on silica gel with 20% ether/petroleum ether gave 7.95 g (91%) of cyclohexanone acetate as a

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[32] Some cis-fused guaianes have been recently isolated: (a) Bohlmann, F.; Czerson, H. *Phytochem.* **1978**, *17*, 568; (b) Papano, G. Y.; Malakov, P. Y.; Bohlmann, F. *Phytochem.*, **1980**, *19*, 152; (c) Bohlmann, F.; Zitzkowski, P.; Suwita, A.; Fiedler, L. *Phytochem.* **1978**, *17*, 2101; (d) Herz, W.; Murari, R.; Govindan, V. *Phytochem.* **1979**, *18*, 1337. Some C-10 unfunctionalized guaianolides have also been isolated recently: Bovill, M.; Guy, M. H. P.; Sim, G. A.; White, D. N. J.; Herz, W. *J. Chem. Soc., Perkin Trans. 2* **1979**, 53; Alvarado, S.; Ciccio, J. F.; Calzada, J.; Zabel, V.; Watson, W. H. *Phytochem.* **1979**, *18*, 330.

[33] We thank Professor Ernest Beuding of the Department of Pathobiology, the Johns Hopkins University, School of Hygiene and Public Health, for performing these tests.

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[35] Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

clear, water white oil. An analytical sample was obtained by preparative TLC on silica 1:1 ether/petroleum ether: ^{1}H NMR (CCl$_4$) δ 4.88 (b m, CHOAc), 2.8–1.0 (b m, skeletal protons), 2.00 (s, OAc), 1.22 (d, -OCH*CH*$_3$, J = 6.6 Hz), 1.08 (d, CH*CH*$_3$, J = 4.4 Hz), 0.84 (d, CHC*H*$_3$, J = 7.6 Hz); IR (CCl$_4$) 2930, 1730 (shoulder of 1712 ketone carbonyl), 1712, 1445, 1370, 1240, 1125, 1040, 950 cm^{-1}. High-resolution mass spectral analysis (M-HOAc): calculated for $C_{11}H_{18}O$, 166.1358; found, 166.1355.

A mixture of 7.71 g (3.41 mmol) of this cyclohexanone acetate, 100 mg of toluenesulfonic acid monohydrate, and 15 mL of ethylene glycol in 100 mL of reagent grade benzene was stirred at reflux for 4.5 h with continuous removal of water by using a Dean-Stark trap. The heterogeneous mixture was cooled in an ice bath and quenched by the addition of 75 mL of saturated sodium bicarbonate. The benzene layer was separated after 10 min of stirring, and the aqueous layer was saturated with sodium chloride and extracted 3 times with 30 mL of ether. The combined organic layers were washed 2 times with aqueous NaCl, 1 time with saturated NaHCO$_3$, and dried. Removal of solvent gave 8.35 g (91%) of the corresponding ketal as a clear yellow oil. An analytical sample was obtained by preparative TLC on silica gel: ^{1}H NMR (CCl$_4$) δ 4.80 (b m, 1 H, CHOAc), 3.9 (b m, 4 H, ketal H), 1.98 (s, 3 H, OAc), 2.6–0.5 (b m, 12 H, ring and chain H), 1.16 (2 d, O–CH*CH*$_3$, J = 6.4 Hz), 0.9 (>2 d, CH*CH*$_3$); IR (CCl$_4$) 2930, 1728, 1450, 1370, 1240, 1160, 1050, 945, 850 cm^{-1}; mass spectrum (70 eV), *m/e* 270 (M$^+$), 255, 243 (M – CH$_3$CO) as base peak. High-resolution mass spectral analysis: calculated for $C_{15}H_{26}O_4$, 270.1831; found, 270.1821.

Standard potassium hydroxide saponification (5-h reflux) and workup of this ketal acetate (8.15 g, 30.0 mmol) gave 6.87 g (100%) of the corresponding ketal alcohol: ^{1}H NMR (CCl$_4$) δ 3.88 (m, -O–CH$_2$–CH$_2$–O–), 3.5 (m, C*H*OH and CHO*H*), 1.1 (d's, OCH–C*H*$_3$), 0.9 (d's, CH*CH*$_3$). The mass spectrum (70 eV) shows *m/e* 226 (M$^+$), 166 (M – CH$_2$CH$_2$O), and base peak at 151 (M – C$_4$H$_9$O). High-resolution mass spectral analysis: calculated for $C_{13}H_{22}O_3$, 226.1569; found, 226.1614.

To a room temperature slurry of 9.15 g (42.5 mmol) of pyridinium chlorochromate (PCC) in 30 mL of dry dichloromethane was added in one portion a solution of 6.41 g (28.1 mmol) of this ketal alcohol in 30.0 mL of dry dichloromethane. After 2 h of stirring at room temperature, an additional 3.1 g (13.2 mmol) of PCC was added. Stirring was continued for 2 h. Standard workup gave 6.25 g (98%) of ketal ketone **6**: ^{1}H NMR (CCl$_4$) δ 2.02 (COCH$_3$) and 3.87 (ketal H); IR (thin film) 1715 cm^{-1}, identical with that previously prepared by us.[36]

Synthesis of Octalone 3. To crude ketone ketal **6** (6.25 g, 30.0 mmol) was added 125 mL of absolute methanol and 25 mL of 3 N HCl. The mixture was degassed and a nitrogen atmosphere maintained throughout. The mixture was stirred at reflux for 6 h and cooled at room temperature. The methanol solvent was removed by evaporation at reduced pressure and the aqueous residue saturated with NaCl and extracted 3 times with 40 mL of ether. The combined organic layers were washed with saturated sodium bicarbonate and dried. The solvent was removed by evaporation at reduced pressure to yield 4.26 g of octalone **3**. This material was bulb-to-bulb distilled at 0.15mmHg at 90 °C to provide 3.85 g (67%) of a clear water white oil, whose ^{1}H NMR (CCl$_4$) (δ 5.73 (vinyl H), 1.06 (C-10 methyl)) and IR (CCl$_4$) ($\nu_{C=O}$ 1710 and 1675 cm^{-1}) were identical with the reported values for a 85:15 mixture of α,β-unsaturated ketone **3** and the corresponding β,γ-unsaturated ketone.[12b,36]

Synthesis of Allylic Ether 7. Separation of Octalone 3 from Its β,γ Isomer. A sample of octalone **3** and its β,γ isomer was dissolved in 5 times its volume of hexanes, in a Craig tube; the system was flushed thoroughly with nitrogen and the tube was sealed with a serum stopper. The tube was placed in a dry ice bath at -78 °C to effect crystallization. A precipitate soon formed and crystallization was judged complete after about 15 min. While still at -78 °C, the supernatant was removed via syringe and an equal volume of fresh hexanes was added. The tube was warmed at room temperature to effect dissolution, and the crystallization process was then repeated 3 times. In this matter, **3** could be obtained in a form nearly free of its β,γ isomer as judged by the near absence of $\nu_{C=O}$ 1710 cm^{-1} in the IR spectrum of the recrystallized material. This material was used immediately.

To a solution of 164 mg (1.0 mmol) of octalone **3** purified in this way in 7.0 mL of anhydrous ether under an atmosphere of nitrogen was added via syringe 2.0 mL (4.0 mmol) of 2.0 M methyllithium in ether. The resultant cloudy suspension was stirred at 0 °C for 15 min and at room temperature for 45 min and quenched by the dropwise addition of 20 mL of saturated ammonium chloride. Ether (10 mL) was added, and stirring was continued for several minutes. Standard workup gave the corresponding tertiary alcohol as a clear, water white oil: 173.9 mg (97%); ^{1}H NMR (CCl$_4$) δ 5.38 (b s, vinyl H), 3.5 (b s, OH), 1.20 (s, *CH*$_3$–C–OH), 0.98 (b s, C-10 CH$_3$'s); IR (CCl$_4$) 3600 (free OH), 3360 (H-bonded OH), 2920, 2850, 1600, 1445, 1365, 1240, 1190, 1150, 1130, 1105, 1090, 1060, 1040, 985, 955, 925, 900, 870, 835 cm^{-1}.

To a slurry of 230 mg (10.0 mmol) of NaH in 15 mL of anhydrous tetrahydrofuran under nitrogen atmosphere was added via syringe a solution of 370 mg (2.05 mmol) of this tertiary alcohol in 5 mL of anhydrous tetrahydrofuran followed by 11.4 g (80.0 mmol) of methyl iodide. The resulting mixture was stirred at room temperature until evolution of gas had ceased and then stirred at reflux for 5 h, cooled, and quenched by the *careful* addition of 25 mL of saturated sodium chloride solution and 20 mL of ether. After the solution was stirred for 10 min, the ether layer was separated and the organic layer extracted 3 times with 30 mL of ether, and the combined organic layers were dried. The solvent was removed by evaporation at reduced pressure to yield allylic ether **7** as a clear yellow oil: 407 mg (100%); (CCl$_4$) δ 5.3 (b s, vinyl H), 3.1 (s's, OCH$_3$), 3.6–0.5 (b m, skeletal protons), 1.22 (s, CH$_3$O–C–*CH*$_3$), 0.94 (d's, C-10 CH$_3$); IR (CCl$_4$) 3460 (weak OH), 2930, 1660, 1450, 1365, 1275, 1230, 1190, 1160, 1075, 950, 915, 865, 835 cm^{-1}. The mass spectrum (70 eV) shows *no* molecular ion at *m/e* 194 but a strong (M$^+$ – CH$_3$OH) at *m/e* 162. Tertiary allylic ether **7** can be purified by chromatography on Alcoa-F20 alumina, but significant loss usually occurs. Thus, this material was used without further purification.

Synthesis of Diols 8a. To a room temperature solution of 2.33 g (12.0 mmol) of allylic ether **7** in 7.0 mL of anhydrous pyridine was added a solution of 3.0 g (12.0 mmol) of osmium tetroxide in 7.0 mL of anhydrous ether. The mixture immediately turned deep brown. The flask was sealed and allowed to stand at room temperature for 24 h. The mixture was then diluted with 100 mL of absolute ethanol and 5 mL of water, and to it was added 5 g of sodium bisulfite. The reaction was then stirred at reflux for 20 h (the ether was allowed to distill away at the outset). At this point the reaction mixture consisted of a finely divided black suspension. The ethanol was then carefully removed by distillation until only a pasty mass remained in the distilling flask. The remainder of the ethanol was removed by addition of 50 mL of toluene and continued distillation until the distillation temperature was that of the boiling point of pure toluene and the reaction residue was a pasty mass. The contents of the flask were cooled and then diluted with 100 mL of ethyl acetate, and to this was added ~1 g of Norit. The mixture was stirred for 10 min and then filtered through a bed of Celite by suction filtration. The black solid residue was washed with ~150 mL of additional ethyl acetate. The combined filtrates were washed 2 times with 1 N HCl, 1 time with water, and 1 time with saturated sodium chloride and dried over magnesium sulfate. Removal of solvent at reduced pressure gave 2.15 g (79%) of diasteriomeric diols **8a** as a viscous golden oil. TLC of the residue (1:1 ether/petroleum ether on silica) revealed the presence of three desired products at R_F = 0.33, 0.23, and 0.17. ^{1}H NMR (CCl$_4$): δ 3.17 (s's, OCH$_3$), 1.26 (s's, CH$_3$O–C–*CH*$_3$), 0.86 (d's, C-10, CH$_3$'s). IR (CCl$_4$): 3580, 3450, 2930, 1450, 1375, 1335, 1260, 1165, 1070, 1020, 945, 905, 845 cm^{-1}.

Column chromatography on silica gel with 20% ether in petroleum ether gave three pure diols. The products were all solids and their ^{1}H NMR showed no olefinic proton signal.

(A) ^{1}H NMR (CCl$_4$): δ 3.36 (s's, OCH$_3$), 3.0–0.5 (b m, skeletal H), 1.37 (s, CH$_3$O–C–*CH*$_3$), 0.88 (d, C-10 CH$_3$, J = 7.0 Hz). IR (CCl$_4$) 3580 (st, free OH), 3450 (st, H-bonded -OH), 1700 (w), 1450, 1375, 1335, 1255, 1170, 1125, 1100, 1065, 1015, 990, 950 (d), 925, 910, 850, 680 cm^{-1}. The mass spectrum (70 eV) shows no molecular ion at *m/e* 228 but a strong (M$^+$ – CH$_3$OH) at *m/e* 196. An analytical sample was prepared by recrystallization twice from hexanes to give a white crystalline diol **8a**, mp 94.5–95.0 °C. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.25; H, 10.45.

(B) ^{1}H NMR (CCl$_4$): δ 3.37 (s, OCH$_3$), 3.0–0.5 (b m, skeletal H), 1.40 and 1.35 (s's, CH$_3$O–C–*CH*$_3$), 0.90 (overlapping d's, C-10 CH$_3$); IR (CCl$_4$) 3580 (free OH), 3450 (H-bonded OH), 1450, 1375, 1335, 1170, 1065, 1045, 1020, 985, 950 (d), 905, 865, 845, 680 cm^{-1}. The mass spectrum (70 eV) showed only (M – HOCH$_3$) at *m/e* 196.

(C) ^{1}H NMR (CCl$_4$): δ 4.45 (b s, C*H*OH or CHO*H*), 3.43 (s, OCH$_3$), 3.0–0.4 (b m, skeletal H), 1.31 (s, CH$_3$O–C–*CH*$_3$), 0.94 (d, C-10 CH$_3$, J = 4.0 Hz); IR (CCl$_4$) 3580 (free OH), 3470 (H-bond OH), 2920, 1700 (w), 1450, 1405, 1370, 1350, 1310, 1270, 1250, 1195, 1165, 1130, 1060, 1020, 960, 945, 930, 865 cm^{-1}. The mass spectrum shows (M – CH$_3$OH) at *m/e* 196.

Conversion of Diols 8a into Mesylates 8b. Each of these three diols was separately converted into the corresponding monohydroxymesylate **8b** by identical methods. The following is a representative procedure: To a room temperature solution of 157.5 mg (0.69 mmol) of the first diol **8a** in 5.0 mL of anhydrous pyridine was added 236 mg (2.07 mmol, 3 equiv) of distilled methanesulfonyl chloride. The reaction flask was sealed and stored at room temperature for 16 h. The reaction had darkened, and pyridinium hydrochloride had precipitated as long needles

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(36) Loomis, G. L. Ph.D. Thesis, The Johns Hopkins University, 1975.

in the reaction vessel. The mixture was then poured into excess 1 N HCl/ice slurry and then extracted 3 times with 30 mL of ether. The combined extracts were stirred vigorously together with 50 mL of 10% aqueous diethylenetriamine for 1 h to remove excess methanesulfonyl chloride. The ether layer was then separated and washed 1 time with 1 N HCl and 1 time with saturated sodium bicarbonate and dried over anhydrous magnesium sulfate. Removal of the solvent at reduced pressure gave 200.4 mg (95%) of **8b** as a viscous oil which solidified upon standing: ^{1}H NMR (CCl$_4$) δ 4.30 (b s, 1 H, CHOMs), 3.20 (s's, 3 H, OCH$_3$ or OMs), 3.10 (s's, 3 H, OCH$_3$ or OMs), 2.5–0.5 (b m, 12 H, skeletal H), 1.37 (s, 3 H, CH$_3$O–C–*CH$_3$*), 0.88 (d, 3 H, C-10 CH$_3$); IR (CCl$_4$) 3590 (free OH), 3500 (H-bonded OH), 2930, 1450, 1360, 1255, 1175, 1095, 1070, 1030, 950, 925, 915, 865, 845 cm^{-1}. An analytical sample was prepared by recrystallization (2×) from 5:1 petroleum ether/dichloromethane, mp 123.5–124.5 °C dec. Anal. Calcd for $C_{14}H_{26}O_5S$: C, 54.87; H, 8.55; S, 10.47. Found: C, 54.68; H, 8.47; S, 10.17.

Similarly, a mesylate was prepared from the second diol **8a**: ^{1}H NMR (CCl$_4$) 4.8 (m, CHOMs), 4.1 (m, CHOMs), 3.20, 3.10, 3.07 (s's, OMs, OCH$_3$), 2.8–0.4 (m, skeletal H), 1.3 (overlapping singlets, CH$_3$O–C–*CH$_3$*), 0.9 (overlapping doublets, C-10 methyl); IR (CCl$_4$) 3590, 3460, 2940, 1450, 1360, 1175, 1145, 1070, 1010, 975, 950, 910, 840 cm^{-1}.

A mesylate was also prepared from the third diol **8a**: (viscous oil) ^{1}H NMR (CCl$_4$) δ 4.63 (b s, 1 H, CHOMs), 3.33 (s, 3 H, OCH$_3$/OMs), 3.07 (s, 3 H, OCH$_3$/OMs), 2.5–0.5 (b m, 12 H, skeletal H), 1.33 (s, 3 H, *CH$_3$*–C–OCH$_3$), 0.87 (b d, 3 H, C-10 CH$_3$); IR (CCl$_4$) (no free OH at ~3600 °C) 3460, 2930, 1450, 1410, 1355, 1175, 1075, 950, 935, 840 cm^{-1}.

Pinacol Rearrangements of Hydroxymesylates 8b into Hydroazulenone 2. Each of the hydroxymesylates **8b** was transformed into hydroazulenic ketone **2** by treatment with sodium *tert*-amyloxide. The reaction of the first hydroxymesylate **8b** is representative.

In an all glass apparatus, oven dried and then thoroughly flushed with nitrogen, was placed 25 mL of anhydrous benzene, 5.5 mL (78.0 mmol) of *tert*-amyl alcohol, and 1.4 g (61.0 mmol) of sodium metal under a stream of nitrogen. Under a positive flow of nitrogen, the reaction was stirred at reflux for 2 days, cooled, and diluted with an equal volume of anhydrous benzene. Residual sodium was removed and the pale yellow solution of sodium *tert*-amyloxide titrated under nitrogen with standardized dilute hydrochloric acid. Concentration = 0.57 M in total base.

To a +5 °C solution of 177.0 mg (0.59 mmol) of the first mesylate **8b** in 12 mL of anhydrous benzene under nitrogen atmosphere was added dropwise via syringe 4.0 mL (2.32 mmol, 4 equiv) of 0.56 M sodium *tert*-amyloxide in benzene. Immediately, upon addition of the base the reaction mixture turned to a brilliant red color which persisted throughout the reaction. The mixture was then warmed to room temperature for 15 min. TLC (1:1 ether/petroleum ether on silica gel) showed *no* starting material at R_F = 0.54 and a single new (UV active) component at R_F = 0.80 (TLC, 9:1 ether/petroleum ether, also showed one material at R_F = 0.38). The reaction was quenched by the addition of 25 mL of aqueous sodium chloride. After being stirred for 5 min, the mixture was extracted 3 times with 25 mL of ether. The combined extracts were washed 1 time with saturated sodium bicarbonate and 1 time with saturated sodium chloride and dried over anhydrous magnesium sulfate. Removal of solvent gave 109.0 mg (100+%) of crude hydroazulenone **2**. Column chromatography on silica gel with 9:1 petroleum ether/ether gave 77 mg (71%) of hydroazulenone **2** as a clear water white oil. (Attempts to distill enone **34** at 1mmHg at 100 °C result in colored distillate and diminished yields, whereas the quality of the sample obtained after column chromatography was very acceptable.) ^{1}H NMR (CCl$_4$): δ 2.8–0.5 (b m, 12 H, skeletal H), 1.98 (s, 3 H, vinyl CH$_3$, fine allylic coupling observed with $J \leq 1$ Hz), 0.94 (d, 3 H, C-10 CH$_3$, J = 6.0 Hz). IR (CCl$_4$): 2920, 1670 (C═O), 1600, 1440, 1375, 1335, 1325, 1270, 1195, 1055, 960, 585 cm^{-1}. UV (EtOH): λ_{max} 254 (ϵ 7445).[11] High-resolution mass spectrum: calculated for $C_{12}H_{18}O$, 178.136; found, 178.135.

Synthesis of Epoxides 9a and 9b. To a –20 °C solution of 523.4 mg (2.94 mmol) of enone **2** in 20 mL of absolute methanol and 3.62 mL (29.4 mmol) of 30% hydrogen peroxide was added dropwise 0.24 mL (1.97 mmol) of 6 N sodium hydroxide. The reaction was stirred at –20 °C for 1 h, 0 °C for 1 h, and room temperature for 4 h. The reaction mixture was cooled in an ice bath, and to it was added slowly excess 10% aqueous sodium sulfite to destroy excess peroxide. After being stirred for 15 min at room temperature, the reaction mixture was extracted 5 times with 20 mL of dichloromethane. The resultant solution was then distilled at atmospheric pressure through a 30-cm vacuum-jacketed vigreux column. The temperature of the distillate remained constant at 38 °C. After ~90 mL had distilled, 50 mL of carbon tetrachloride were added, and distillation was continued. The boiling point of the distillate rapidly reached 56 °C. Enough carbon tetrachloride was replenished such that all methanol was removed as the azeotrope. This point was determined when the distillate temperature rose to 76 °C. The solution was then carefully concentrated to a volume of ~0.5 mL and column chromatographed on 50 g of florisil with 1:9 ether/petroleum ether. The two epoxides **9a** and **9b** were obtained as viscous oils; **9a** was further purified by sublimation at aspirator pressure at 55 °C to give 380 mg (67%) of a white crystalline product, mp 69.8–70.6 °C. The lower R_f *minor* epoxide (78 mg, 15%) was isolated as a clear oil. **9a**: ^{1}H NMR (CCl$_4$) δ 2.45 (M, COCH$_2$–), 2.8–0.4 (b m, skeletal H), 1.36 (s, $\overline{\mathrm{OCC}}$–CH$_3$), 0.92 (d, C-10 methyl, J = 6.0 Hz); IR (CCl$_4$) 2930, 1710 (C═O), 1450, 1400, 1375, 1330, 1275, 1185, 1065, 950, 915, 885, 855 cm^{-1}; ^{13}C NMR (CDCl$_3$) δ 197.8 (s), 72.83 (s), 72.28 (s), 47.03 (d), 43.57 (t), 38.83 (t), 35.53 (d), 32.06 (t), 24.86 (t), 23.92 (t), 20.65 (q), 14.86 (q). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.42; H, 9.32. **9b**: ^{1}H NMR (CCl$_4$) δ 2.56 (m, CO*CH$_2$*), 2.8–0.6 (b m, skeletal H), 1.42 (s,$\overline{\mathrm{OCC}}$–CH$_3$), 1.04 (d, C-10 methyl, J = 6.0 Hz); IR (CCl$_4$) 2940, 1705, 1450, 1380, 1320, 1155, 1035, 940, 885, 865 cm^{-1}; ^{13}C NMR (CDCl$_3$) δ 206, 71.30, 48.38, 42.05, 36.05, 34.98, 31.16, 29.75, 25.74, 22.41, 21.52, 15.03. The mass spectrum (70 eV) shows *m/e* 194 (M$^+$) and 116 (M – C═O). Anal. Calcd for $C_{12}H_{18}O_2$: 194.1307. Found: 194.1300.

Synthesis of Methyl Ester 10. Under nitrogen atmosphere, 0.93 mL (1.30 mmol) of a 1.4 M *n*-butyllithium solution in hexane was added via syringe to a 0 °C solution of 150 mg (1.50 mmol) of distilled diisopropylamine in 5.0 mL of tetrahydrofuran. The solution was stirred at 0 °C for 15 min and cooled to –78 °C in an acetone/dry ice bath. To this was then added via syringe, dropwise over a 3-min period, a solution of 194 mg (1.00 mmol) of *major* epoxide **9a**. This pale yellow solution was stirred at –78 °C for 45 min, and to it was added 600 mg (3.00 mmol) of methyl iodoacetate followed by 5.0 mL of anhydrous HMPA. The reaction was stirred at –78 °C for 1 h and at room temperature for 20 h. The reaction mixture was then quenched with excess aqueous sodium chloride (30 mL) followed by extraction 3 times with 30 mL of ether. The combined extracts were then stirred together with 50 mL of 5% aqueous diethylenetriamine for 1 h. The ether layer was separated, washed 1 time with ice cold 1 N HCl and 1 time with saturated sodium bicarbonate, and dried. Removal of solvent gave 292 mg of crude residue which was column chromatographed on 25 g of florisil with 1:9 ether/petroleum ether to give 239 mg (90%) of methyl ester **10** as a clear oil: ^{1}H NMR (CCl$_4$) δ 3.64 (s, 3 H, OCH$_3$), 3.25 (m, 1 H, C-7 H), 2.80 (dd, 1 H, COC*H*H, J = 8.5 and 17.0 Hz), 2.28 (dd, 1 H, COCH*H*, J = 5.0 and 17.0 Hz), 2.5–0.8 (b m, 10 H, skeletal H), 1.34 (s, 3 H, C-4 CH$_3$), 0.96 (d, 3 H, C-10 CH$_3$, J = 6 Hz); IR (CCl$_4$) 2930, 1735 (ester C═O), 1708 (ketone C═O), 1445, 1350, 1175 (v br), 1065, 995, 955, 905, 875 cm^{-1}; ^{13}C NMR (CDCl$_3$) (showed only 15 separate carbon signals) δ 206.71 (ketone C═O), 172.75 (ester C═O), 73.52 and 71.95 (epoxide carbon), 51.62, 47.32, 46.25, 38.70, 35.69, 34.17, 32.14, 30.91, 24.31, 20.31, 14.30. The mass spectrum shows *m/e* 255 (M$^+$ weak), 254 (M$^+$ – 18), 234, and 114 (base peak). High-resolution mass spectral analysis: calculated for $C_{15}H_{22}O_4$, 266.1523; found, 266.1523.

Synthesis of Guaianolide 13. To a –20 °C solution of 120 mg (0.45 mmol) of keto ester **10** in 5 mL of anhydrous dimethylformamide was added in one portion 100 mg of sodium borohydride. A drying tube was positioned to protect the mixture from atmospheric moisture, and the reaction was stirred at –20 °C for $^1/_2$ h and then at room temperature for $^1/_2$ h. The reaction was then quenched by addition of 5 mL of saturated sodium chloride and stired for 20 min. Slow evolution of gas was observed during this time. To this was then added *carefully* in small portions solid ammonium chloride (1 g). Vigorous evolution of gas occurred here. After ~15 min gas evolution ceased abruptly. The mixture was then extracted 5 times with 20 mL of petroleum ether. The combined extracts were washed 2 times with 10 mL of water and 1 time with saturated sodium chloride and dried. Removal of solvent at reduced pressure gave 103 mg (97%) of guaianolide **13** as a viscous oil which solidified upon standing, which was homogeneous by TLC, and which had spectral data identical with those of the analytical sample. This material was recrystallized 1 time from hexanes: mp 77.5–78.5 °C; ^{1}H NMR (CDCl$_3$ 300 MHz) δ 4.94 (d, 1 H, –CHO–, J = 8.0 Hz), 2.85 (m, 1 H, –OCH–C*H*), 2.42 (ABX m, 2 H, 0–C(═O)CH$_2$), 2.3–1.0 (b m, skeletal H, 10 H), 1.51 (s, 3 H, C-4CH$_3$), 0.91 (d, 3 H,C-10 CH$_3$, J = 6.7 Hz); IR (CCl$_4$) 2930, 1790 (lactone C═O), 1455, 1415, 1380 (d), 1325, 1310, 1290, 1255, 1165, 1045, 1015, 995, 910 (d), 895, 880, 840 cm^{-1}; ^{13}C NMR (CDCl$_3$) δ 176.69 (lactone C═O), 79.95 (C-6), 71.70 and 71.15 (epoxide carbons), 49.31, 40.69, 39.79, 35.08, 33.44, 32.61, 30.08, 28.37, 21.81, 17.62. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53; Found: C, 71.34; H, 8.52.

Synthesis of α-Methylene Guaianolide 1. Under a nitrogen atmosphere, 0.28 mL (0.4 mmol) of 1.45 M *n*-butyllithium was added to a 0 °C solution of 100 mg (1.0 mmol) of distilled diisopropylamine in 1.0 mL

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of THF. The reaction mixture was stirred at 0 °C for 30 min and then cooled to −78 °C in an acetone/dry ice bath. To this was then added, very slowly over a 2-min period, via syringe a solution of 23.6 mg (0.1 mmol) of guaianolide **13** in 7.5 mL of anhydrous THF. The reaction was stirred at −78 °C for 45 min, and to it was added under a blanket of nitrogen 370 mg (2.0 mmol) of dimethylmethyleneammonium iodide (Eschenmoser's Reagent).[30] The reaction was stirred at −78 °C for 30 min, warmed to −30 °C for 4 h, and then quenched at −30 °C by addition of 10 mL of saturated sodium bicarbonate solution. The mixture was then warmed to room temperature over a 30 min period and stirred at room temperature several hours. This was then extracted 3 times with 5 mL of ether. The combined organic layers were dried, and chromatography on florisil with 9:1 petroleum ether/ether gives 25.9 mg (88%) of the (dimethylamino)methyl lactone as an oil: ^{1}H NMR (CCl_4) δ 4.86 (d, $-CH-OC(=O)$, $J = \sim 8$ Hz), 3.0–0.8 (b m, skeletal H), 2.20 (s, NCH_3), 1.50 (s, C-4 CH_3), 0.95 (d's, C-10 CH_3); IR (CCl_4) 2940, 2770, 1775, 1465, 1425, 1385, 1335, 1315, 1270, 1170, 1050, 1015, 925, 895 cm^{-1}. High-resolution mass spectral analysis: calculated for $C_{17}H_{27}NO_3$, 293.1990; found: 293.1989.

To a solution of 25.0 mg of this tertiary amine in 2.0 mL of anhydrous THF was added 1.0 mL of methyl iodide. The solution was stirred at room temperature for 4 h and to it was added 5 mL of saturated sodium bicarbonate solution, and stirring was continued for another 3 h. This reaction mixture was then diluted with 10 mL of aqueous sodium chloride and 10 mL of ether. The organic layer was separated and the aqueous layer further extracted 3 times with 10 mL of ether. The combined ether layers were dried. Removal of solvent and recrystallization from 4:1 hexanes/ether give 9 mg (42.5%) of highly crystalline white solid **1**: mp 69.5–70.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.20 (d, 1 H, vinyl H, $J = 3.5$ Hz), 5.50 (d, 1 H, vinyl H, $J = 3.5$ Hz), 5.05 (d, 1 H, C-6 H, $J = 8.6$ Hz), 3.31 (m, 1 H, C-7 H), 2.30 (ABX m, 1 H, $C_{8\beta}$–H), 2.0–1.0 (b m, 9 H, skeletal H), 1.58 (s, 3 H, epoxide $-CH_3$), 0.94 (d, 3 H, C-10 CH_3, $J = 6.0$ Hz); IR (CCl_4) 2930, 1775 (α-methylene lactone), 1660, 1450, 1415, 1380, 1360, 1320, 1275, 1260, 1195, 1100, 1040, 1010, 940, 890 cm^{-1}.

High-resolution mass spectral analysis: calculated for $C_{15}H_{20}O_3$, 248.1412; found, 248.1413.

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Supplementary Material Available: Listings of observed and calculated structure factors as well as tables of anisotropic thermal parameters and fractional coordinates for the C and O and H atoms, listing of the structures and the $J_{10,14}$ coupling constants observed for the C-14 CH_3 doublets of four pairs of C-10 epimeric hydroazulenes, showing that in each case the 1,10 anti isomer has a higher $J_{10,14}$ coupling constant, and Figure 2, 300-MHz NMR spectrum of guaianolide **1** (20 pages). Ordering information is given on any current masthead page.

Total Synthesis of (+)-Furanomycin and Stereoisomers[1]

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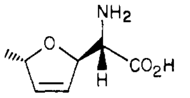
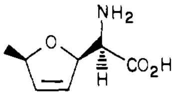
Abstract: The total synthesis of six stereoisomeric forms of α-amino-2,5-dihydro-5-methylfuranacetic acid is described. (+)-Furanomycin, the naturally occurring antibiotic of this series, was found to be identical with the isomer having the (αS,2R,5S) configuration, thereby requiring revision of the original (αR,2R,5R) assignment for this substance.

(+)-Furanomycin (**1**), an antibiotic α-amino acid containing a 2,5-dihydrofuran moiety, was first isolated by Katagiri and co-workers from the culture filtrate of *Streptomyces threomyceticus*. The structure of furanomycin was first assigned the (αR,2R,5R) configuration (**2**) based on a combination of spectroscopic and chemical degradation techniques.[3] This structural assignment rested largely on the coupling constants of the 2 and 5 protons ($J_{2,5}$). A large, long-range homoallylic coupling constant ($J_{2,5} = 5.7$ Hz) was observed for **1** and from this information it was concluded that the 2 and 5 protons were cis to each other.[3] Additional support for this assignment was provided by the total synthesis of *dl*-furanomycin reported by Masamune and Ono.[4a] These authors used as their starting material a 5-methyl-2,5-dihydro-2-furoic acid[4b] which exhibited a coupling constant $J_{2,5} = 6$ Hz and was therefore assigned the cis configuration, since elaboration of this substance produced an α-amino acid "identical in all respects" with the naturally occurring antibiotic. In contrast



1



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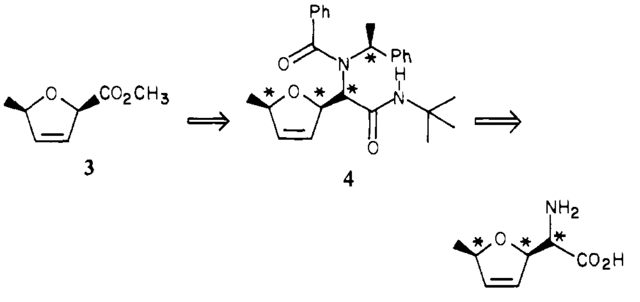
Scheme I



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[1] A preliminary account of this work was presented at the 178th National Meeting of the American Chemical Society, Washington, D.C., September 1979, ORG 124.

[2] (a) The synthetic studies of the cis stereoisomers of furanomycin were taken in part from the Ph.D. dissertation of J. Edward Semple, University of Pennsylvania, 1980; the synthetic investigations of the trans stereoisomers of furanomycin were taken in part from the Ph.D. dissertation of Pen C. Wang, University of Pennsylvania, 1980.

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[4] (a) Masamune, T.; Ono, M. *Chem. Lett.* **1975**, 625. (b) Masamune, T.; Ono, M.; Matsue, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 491.

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