The Crystal and Molecular Structure of the Pseudoguaianolide Autumnolide[1]

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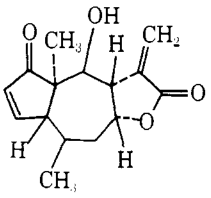
Abstract: A crystal structure analysis of the pseudoguaianolide autumnolide (**3**) has revealed a conformation of the seven-membered ring that is markedly different from that found for the very similar bromohelenalin. The principal difference between the two conformations involves a drastic twist of 111.0° about C6–C7 and associated rotations about all contiguous bonds. As a consequence of this molecular conformation, there is an unusual OH–pπ interaction in autumnolide which is not found in the other pseudoguaianolides. The structure was solved by direct methods analysis of data from a crystal with space group $P2_1$ and $a = 7.595 \pm 0.004$, $b = 13.380 \pm 0.009$, $c = 6.870 \pm 0.006$ Å, $\beta = 92.87 \pm 0.06°$, $Z = 2$, and density $\rho_{\text{calcd}} = 1.336$ g/cm^3. An anisotropic full-matrix least-squares refinement converged to a conventional residual of $R = 0.058$ for 2086 reflections recorded with Mo Kα radiation on an automatic four-circle diffractometer.

The common sneezeweed of Oregon, *Helenium autumnale* L. var. montanum (Nutt.) Fern. (Compositae), has been found to contain the pseudoguaianolide[2,3] helenalin (**1**), an antineoplastic agent with substantial in vitro and in vivo activity.[4,5] Another prominent component of this plant, autumnolide, was tentatively assigned structure **2** by Herz and colleagues.[6] Autumnolide was also found to inhibit (ED$_{50}$ 3.1) growth of the National Cancer Institute's KB cell culture (human epidermoid carcinoma of the nasopharynx). However, unlike helenalin, no effect on progression of the murine P-388 lymphocytic leukemia was noted over the dose range 6 to 25 mg/kg.[5] Because of this wide variation of in vivo activity and the seemingly close structural relationship with helenalin, we have undertaken a structure analysis of autumnolide. Moreover, the presence of a large number of high quality diffraction data provide the opportunity to establish with considerable precision the molecular parameters for this representative pseudoguaianolide.



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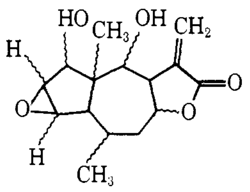

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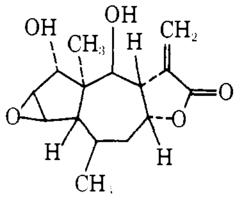

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Experimental Section

Autumnolide[5] ($C_{15}H_{20}O_5$) crystallized as well formed tabular prisms from acetone-hexane (mp 199–201°; mass spec M$^+$ 280). The CD spectrum in methanol gave a negative lactone Cotton effect with a molar ellipticity [θ] of -5626 at 256 nm. X-Ray diffraction photographs displayed monoclinic symmetry with only the systematic extinction $0k0$, $k = 2n + 1$, and conformed to the noncentrosymmetric space group $P2_1$. A total of 15 reflections within the angular range $5.3 \leq 2\theta \leq 16.5$ for Mo Kα radiation were automatically centered on a Syntex $P\bar{1}$ autodiffractometer; a least-squares refinement of the angular settings yielded the lattice parameters $a = 7.595 \pm 0.004$, $b = 13.380 \pm 0.009$, $c = 6.870 \pm 0.006$ Å, $\beta = 92.87 \pm 0.06°$ which for $Z = 2$ gives $\rho_{\text{calcd}} = 1.336$ g/cm^3 ($\rho_{\text{obsd}} = 1.335$ g/cm^3).

The diffraction intensities were measured on a 0.38 × 0.41 × 0.29 mm wedge-shaped crystal using Zr filtered Mo Kα radiation with the diffractometer operating in the variable speed θ–2θ scan mode. For each reflection, the scan speed, between 1 and 8°/min, was determined from the intensity found in a rapid sampling scan. The scans were taken over the range $2\theta\text{K}\alpha_1 - 1.0°$ to $2\theta\text{K}\alpha_2 + 1.0°$ with background counts for 0.25 of the scan time taken at each end of the scan. A total of 2411 reflections were investigated ($2\theta \leq 60°$) of which 2086 were retained as objectively observed with $|F_o| \geq 0.675\,\sigma_F$; $\sigma_F = 0.025|F_o| + (C + k^2B)^{1/2}R/(2|F_o|\text{Lp})$ where C is the total count in a scan taken at the rate R, and k is the ratio of scanning time to the time for the total background count B. Periodic monitoring of three reflections showed a maximum 2% random variation in intensity during the time of data collection. Corrections were applied for Lorentz and polarization effects, but absorption and extinction effects proved to be negligible. An average thermal parameter (2.71 Å^2) and a scale factor (1.00) required for the calculation of normalized structure factors $|E_{hkl}|$, were obtained from a Wilson analysis.[7]

Structure Determination and Refinement

A partial structure was obtained by application of the generalized tangent formula[8] to 303 reflections starting with values of ϕ_{hkl} and $2\phi_{hkl}$ obtained from the Σ_2[9] and squared-tangent formulas.[8,10,11] The complete structure of

Table I. Atomic Fractional Coordinates[a]

Atom	x	y	z
C1	−0.0733 (3)	0[b]	0.2096 (3)
C2	−0.2284 (3)	0.0629 (3)	0.2694 (4)
O23	−0.2974 (2)	0.0282 (3)	0.4513 (3)
C3	−0.1751 (4)	0.1109 (3)	0.4538 (5)
C4	0.0144 (4)	0.0814 (3)	0.5084 (4)
O4	0.0971 (3)	0.1618 (3)	0.6114 (3)
C5	0.0893 (3)	0.0551 (2)	0.3071 (3)
C5a	0.1279 (4)	0.1520 (3)	0.1979 (5)
C6	0.2598 (3)	−0.0077 (3)	0.3293 (3)
O6	0.3442 (2)	0.0177 (2)	0.5130 (3)
C7	0.2288 (3)	−0.1218 (3)	0.3170 (4)
C8	0.1527 (4)	−0.1595 (4)	0.1141 (5)
C9	0.1059 (4)	−0.0823 (3)	−0.0420 (4)
C10	−0.0646 (4)	−0.0245 (3)	−0.0073 (4)
C10a	−0.2278 (5)	−0.0827 (4)	−0.0794 (5)
C11	0.3976 (4)	−0.1811 (3)	0.3462 (5)
C11a	0.5069 (5)	−0.1884 (4)	0.5008 (7)
C12	0.4245 (5)	−0.2406 (3)	0.1684 (6)
O12	0.5417 (4)	−0.2972 (3)	0.1358 (5)
O13	0.2902 (3)	−0.2236 (3)	0.0369 (3)

[a] The estimated standard deviations from the last least-squares are shown in parentheses. [b] y coordinate is arbitrary.

Table II. Thermal Parameters[a]

Atom	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}	B_{iso}[b]
C1	2.07 (8)	2.37 (9)	2.35 (9)	−0.17 (8)	−0.19 (7)	0.06 (8)	2.25
C2	2.19 (9)	3.47 (12)	3.87 (12)	0.29 (10)	−0.24 (9)	−0.02 (10)	3.07
O23	2.08 (7)	5.84 (13)	4.35 (10)	−0.32 (8)	0.72 (7)	−0.45 (9)	3.67
C3	2.57 (11)	3.68 (13)	4.71 (15)	0.62 (10)	0.41 (10)	−0.76 (11)	3.43
C4	2.06 (9)	3.41 (12)	3.05 (10)	−0.02 (9)	0.30 (8)	−0.78 (9)	2.71
O4	3.32 (9)	4.97 (12)	4.82 (11)	−0.17 (9)	0.07 (8)	−2.53 (10)	3.88
C5	1.94 (8)	2.12 (9)	2.39 (9)	−0.23 (7)	0.25 (7)	0.03 (8)	2.12
C5a	3.86 (13)	2.67 (11)	3.99 (12)	−0.65 (10)	0.22 (11)	0.72 (10)	3.34
C6	1.85 (8)	2.56 (10)	2.39 (9)	−0.14 (8)	0.24 (7)	−0.13 (8)	2.23
O6	1.92 (6)	4.47 (10)	3.48 (8)	−0.12 (7)	−0.32 (6)	−1.03 (7)	3.01
C7	2.05 (9)	2.68 (10)	2.54 (10)	−0.12 (8)	0.04 (7)	0.04 (8)	2.41
C8	2.96 (11)	2.77 (11)	3.06 (11)	−0.12 (9)	0.15 (9)	−0.53 (9)	2.89
C9	3.88 (13)	3.54 (13)	2.25 (9)	−0.24 (11)	0.16 (9)	−0.38 (9)	3.12
C10	3.31 (11)	3.29 (12)	2.54 (10)	−0.18 (10)	−0.49 (9)	0.12 (9)	2.99
C10a	4.18 (15)	5.20 (18)	4.24 (14)	−0.59 (15)	−1.27 (12)	−1.33 (14)	4.19
C11	2.45 (10)	2.56 (11)	4.75 (15)	0.05 (9)	0.10 (10)	0.36 (10)	3.09
C11a	4.02 (14)	3.82 (15)	7.81 (23)	0.99 (13)	−2.03 (15)	−0.33 (15)	4.60
C12	3.80 (14)	3.29 (13)	5.67 (17)	0.56 (12)	1.50 (13)	0.25 (13)	3.96
O12	5.42 (14)	5.61 (14)	8.35 (18)	2.56 (13)	2.07 (13)	−0.09 (13)	5.59
O13	5.38 (13)	4.46 (11)	4.42 (10)	1.53 (10)	0.67 (10)	−1.12 (9)	4.40

[a] Numbers in parentheses are estimated standard deviations in the last significant figure. The relation between B_{ij} Å^2 and the dimensionless β_{ij} used during refinement is $B_{ij} = 4\beta_{ij}/a_i{}^*a_j{}^*$. [b] Isotropic thermal parameter calculated from $B_{iso} = 4[V^2 det(\beta_{ij})]^{1/3}$.

Table III. Hydrogen Atomic Parameters[a]

Atom bound to	x	y	z	Bond, Å
C1	−0.082	−0.062	0.281	0.97
C2	−0.309	0.092	0.175	0.95
C3	−0.205	0.179	0.478	0.95
C4	0.023	0.019	0.591	1.01
O4	0.203	0.143	0.642	0.86
C5a	0.231	0.189	0.261	0.95
C5a	0.155	0.137	0.065	0.96
C5a	0.028	0.195	0.189	1.01
C6	0.336	0.011	0.225	0.97
O6	0.451	0.011	0.495	0.83
C7	0.146	−0.143	0.410	0.96
C8	0.041	−0.205	0.127	1.05
C9	0.088	−0.119	−0.164	0.97
C9	0.208	−0.038	−0.051	0.97
C10	−0.069	0.038	−0.078	0.96
C10a	−0.222	−0.098	−0.219	0.98
C10a	−0.233	−0.147	−0.011	0.98
C10a	−0.334	−0.043	−0.052	0.99
C11a	0.606	−0.232	0.493	0.96
C11a	0.476	−0.148	0.624	1.04

[a] Reasonable estimates of the error in the fractional coordinates and the bond lengths are ~0.003 and ~0.03 Å, respectively.

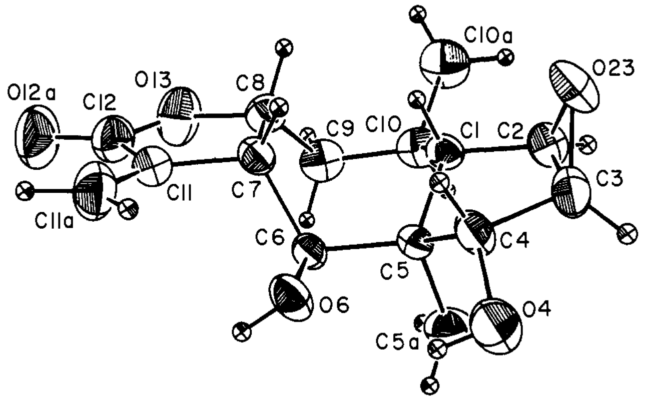

Figure 1. A perspective representation of the structure of autumnolide. A hydrogen atom on C5a, C6, and C10a is hidden from view.

20 atoms was obtained after tangent refinement of phases calculated from this partial structure.[12]

The model was refined with isotropic thermal parameters by full-matrix least-squares[13] analysis (initial $R = 0.34$) with each reflection assigned a weight, $w = 1/\sigma_F{}^2$, and with atomic scattering factors for C^0 and O^0 calculated by Cromer and Mann.[14] At convergence, the standard residual was $R = 0.129$, and the weighted residual, $R_w = (\Sigma_w(|F_o| - |F_c|)^2/\Sigma_w|F_o|^2)^{1/2}$, was 0.141. Guided by a difference Fourier synthesis based on these results, all the hydrogen atoms were placed in idealized positions 1.00 Å from their respective heavy atoms and assigned a temperature factor of $B = 3.0$ Å^2. The model with anisotropic thermal motion of the nonhydrogen atoms was then refined by full-matrix least-squares and with the hydrogen atoms fixed to give residuals of $R = 0.064$ and $R_w = 0.064$ for 180 parameters. The positions of the hydrogen atoms were then refined with all other parameters fixed, and then the refinement of the nonhydrogen atom parameters was repeated. The residuals for this final refinement were $R = 0.058$ and $R_w = 0.057$. The estimated error in a reflection of unit weight was 1.068.[15]

Results

Final atomic coordinates and thermal parameters for autumnolide are presented in Tables I, II, and III along with the estimated standard deviations derived from the least-squares analysis. The perspective view shown in Figure 1 displays the essential configurational and conformational features of the molecule. In addition, a stereodiagram of the unit cell is shown in Figure 2. Each atom is represented by an ellipsoid consistent with the anisotropic thermal parameters in Table II. Because of the great similarily with the asymmetric centers of helenalin (vide infra), whose absolute configuration has been assigned[16] on the basis of an extended correlation with tenulin, autumnolide is shown in the same enantiomorphic form. The configurations of the nine chiral centers are (S)-C1, (R)-C2, (S)-C3, (S)-C4, (R)-C5, (S)-C6, (S)-C7, (R)-C8, and (R)-C10.

Bond lengths and angles within the molecule are systematically recorded in Table IV. The selected set of dihedral angles listed in Table V fully characterizes all the conformational features of the molecule; a similar set for the closely related bromohelenalin,[17] is provided for comparison.

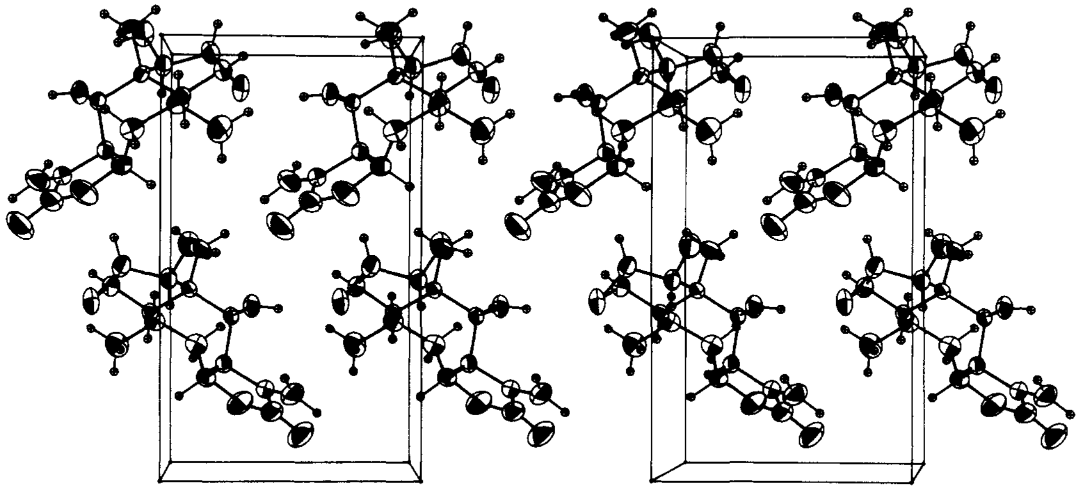

Figure 2. A stereodiagram of the unit cell for autumnolide and two adjacent molecules. The axial directions are a → and b ↑.

Table IV. Bond Distances and Angles in Autumnolide[a]

Atom	Bond	Distance, Å	Angle, deg
C1	C1–C2	1.519 (4)	C2–C1–C5, 103.2 (2)
	C1–C5	1.558 (3)	C2–C1–C10, 116.9 (2)
	C1–C10	1.528 (4)	C5–C1–C10, 116.6 (2)
C2	C2–C3	1.458 (4)	C1–C2–C3, 107.0 (2)
	C2–O23	1.453 (4)	C1–C2–O23, 111.8 (2)
			O23–C2–C3, 59.5 (2)
C3	C2–O23	1.444 (4)	C2–O23–C3, 60.4 (2)
	C3–C4	1.519 (4)	C2–C3–O23, 60.1 (2)
			O23–C3–C4, 113.8 (3)
			C2–C3–C4, 108.5 (2)
C4	C4–O4	1.416 (4)	C3–C4–O4, 108.4 (2)
	C4–C5	1.559 (4)	C3–C4–C5, 102.8 (2)
			O4–C4–C5, 116.3 (2)
C5	C5–C5a	1.533 (4)	C1–C5–C4, 99.9 (2)
	C5–C6	1.543 (3)	C1–C5–C5a, 110.9 (2)
			C1–C5–C6, 115.2 (2)
			C4–C5–C5a, 109.1 (2)
			C4–C5–C6, 112.0 (2)
			C5a–C5–C6, 109.2 (2)
C6	C6–O6	1.426 (3)	C5–C6–C7, 114.0 (2)
	C6–C7	1.546 (4)	C5–C6–O6, 107.2 (2)
			O6–C6–C7, 110.1 (2)
C7	C7–C8	1.564 (4)	C6–C7–C8, 114.6 (2)
	C7–C11	1.511 (4)	C6–C7–C11, 112.7 (2)
			C8–C7–C11, 102.8 (2)
C8	C8–C9	1.517 (4)	C7–C8–C9, 118.1 (2)
	C8–O13	1.468 (4)	C7–C8–O13, 105.8 (2)
			O13–C8–C9, 106.8 (2)
C9	C9–C10	1.535 (4)	C8–C9–C10, 113.8 (2)
C10	C10–C10a	1.524 (4)	C1–C10–C9, 109.6 (2)
			C1–C10–C10a, 110.6 (2)
			C9–C10–C10a, 111.7 (3)
C11	C11–C11a	1.317 (5)	C7–C11–C11a, 129.9 (3)
	C11–C12	1.479 (5)	C7–C11–C12, 108.9 (3)
			C11a–C11–C12, 121.2 (3)
C12	C12–O13	1.345 (4)	C11–C12–O12, 128.9 (4)
	C12–O12	1.198 (4)	C11–C12–O13, 109.3 (3)
			O12–C12–O13, 121.8 (3)
			C12–O13–C8, 112.6 (2)

[a] Numbers in parentheses are estimated standard deviations in last significant figure.

Table V. Selected Dihedral Angles (in Deg)[a]

	Autumnolide[b]	Bromohelenalin[c]
C1-C2-C3-C4	1.7	2.0
C2-C3-C4-C5	24.5	9.0
C3-C4-C5-C1	-39.6	-15.6
C4-C5-C1-C2	41.0	16.4
C5-C1-C2-C3	-27.3	-12.3
C1-C5-C6-C7	-19.4	60.6
C5-C6-C7-C8	65.0	-36.0
C6-C7-C8-C9	-4.1	58.7
C7-C8-C9-C10	-74.7	-81.2
C8-C9-C10-C1	40.4	31.6
C9-C10-C1-C5	53.5	52.9
C10-C1-C5-C6	-69.2	-77.0
C7-C8-O13-C12	7.9	-30.0
C8-O13-C12-C11	-4.9	9.4
O13-C12-C11-C7	-0.2	15.7
C12-C11-C7-C8	4.7	-33.0
C11-C7-C8-O13	-7.3	37.8

[a] An arbitrary but self-consistent set defined for the sequence *a–b–c–d* as the positive clockwise rotation from *a* to *d* in the projection of the array down the line *b–c*. [b] The estimated error for the coordinates from which these angles were calculated is ~0.003 Å. [c] The angles reported here have been calculated from the coordinates provided in ref 17, with an estimated error given as ~0.01 Å.

Discussion

The molecular structure of autumnolide, except for stereochemistry, is in accord with that proposed by Herz, et al.[6] In addition, careful examination of the six chiral centers C1, C5, C7, C8, and C10 that are in common with those of bromohelenalin[17] shows that they have the same relative configurations in both molecules. Hence, the only differences between the present structure and bromohelenalin, apart from the bromine atom, are the presence of an epoxide at C2-C3 instead of a double bond and the replacement of the carbonyl at C4 with a hydroxyl group.

Despite the great similarity in stereochemistry, the two compounds display considerably different molecular conformations. In autumnolide, the seven-membered ring takes on a symmetrical boat arrangement composed of three accurate planes; the central plane C5-C6-C9-C10 (average deviation ±0.064 Å) makes dihedral angles of 125.9 and 120.6° with the outer planes C5-C1-C10 and C6-C7-C8-C9 (average deviation ±0.015 Å), respectively. However, this ring in bromohelenalin is in a deformed chair conformation. The difference is most apparent from a comparison of the dihedral angles (Table V) in the sequence C1-C5-C6-C7-C8; in particular, the bond C6-C7 is twisted by 111.0° in the transition between the two conformers. All of the interior angles, 109.6-118.1°, of this ring fall in the range expected for a seven-membered ring with the largest angles occurring at the ring junctions. The bond distances, 1.517-1.564 Å, in the ring take on the expected values for C-C single bonds, although those in the ring junctions are slightly longer. Similar angles and distances were reported for the other pseudoguaianolides.[17-19]

The lactone ring system is nearly flat with an average deviation of ±0.034 Å from the plane for all seven atoms. As a result, the two π systems at C11-C11a and C12-O12 are coplanar permitting the formation of the conjugated system C11a-C11-C12-O12. As a result, the C11-C12 bond, 1.479 Å, is considerably shorter than a C-C single bond. In bromohelenalin[17] and the closely related bromomexicanin-E,[18] the different molecular conformations require a twist of 15° in this bond which prevents any conjugation between the two double bonds on C11 and C12. In these compounds, the C11-C12 bond, 1.52 and 1.55 Å, respectively, is a normal C-C single bond. The other bonds and angles are similar for all three structures. In particular for autumnolide, the bonds C12-O12 (1.345 Å), C12-O13 (1.198 Å), and O13-C8 (1.468 Å) are very characteristic of an ester linkage, the bond C11-C11a (1.317 Å) is a normal double bond, and C7-C11 (1.511) is typical for a C-C bond next to a double bond. The angular requirements of the five-membered ring have reduced the interior angles at the two sp^2 carbon atoms, C11 (108.9°) and C12 (109.3°), to much less than the normal 120°. This is accommodated by an unequal increase in the exterior angles, where one is ~121° and the other is ~129° at both C11 and C12. Despite these distortions, the sp^2 atom and the three attached atoms remain in a plane in both cases (maximum deviation 0.018 Å). The same effect on the sp^2 atoms in the lactone ring can also be seen in the structures of bromohelenalin and bromomexicanin-E.

At the other end of the molecule, the rather normal epoxide forms a nearly perfect equilateral triangle. It and the attached five-membered ring are in a symmetrical chair conformation. The atoms C1, C2, C3, and C4 form an exact plane (average deviation ±0.007 Å) with C5 out of the plane by 0.66 Å. The epoxide ring makes a dihedral angle of 106.5° with this plane. The symmetry of this group is accurately preserved in the bond distances; the bonds C1-C2 and C3-C4 are identical (1.519 Å) as are the bonds C1-C5 and C4-C5 (1.558 Å). The deviation of these bonds from the normal C-C single bond length is probably due to the electronegativity of the epoxide group.

The molecular conformation of autumnolide permits the formation of the hydrogen bond, O4-H-O6, which cannot be present in either bromohelenalin or bromomexicanin-E. The O4-O6 distance (2.797 Å) is normal for a hydrogen bond, and the hydrogen atom was found to lie in between the two oxygen atoms. The orientation of the other hydroxyl, O6-H, suggests the possibility of a hydrogen bond to the π system at C11-C11a; the oxygen, O6, is 2.56 Å from the plane containing the π orbitals and is 1.34 Å above the C11-C11a-H_2 plane. However, the O6-H bond appears to be canted away from the double bond with the hydrogen 1.75 Å above the C11-C11a-H_2 plane and 2.70 Å away from C11a. In addition, careful examination of the packing diagram (Figure 2) reveals an intermolecular hydrogen bond between O6-H and the epoxide, O23, on an adjacent molecule. The O6-O23 distance, 2.779 Å, is normal for a hydrogen bond, and the hydrogen atom is almost directly between the two oxygen atoms. Hence, it is difficult to assess the significance of the possible OH-pπ interaction observed in this structure.

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Supplementary Material Available. A table of observed and calculated structure amplitudes from the final refinement will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24X reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for \$4.50 for photocopy or \$2.50 for microfiche, referring to code number JACS-75-5256.

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