

THE STEREOCHEMISTRY AND SOLID STATE CONFORMATION OF 1,10 β -EPOXYACHILLIN¹

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ABSTRACT.—The stereochemistry and solid state conformation of the natural guaianolide 1,10-epoxyachillin [**1**], isolated from *Artemisia assoana*, has been definitively established on the basis of an X-ray analysis. The epoxide ring is β oriented and the seven-membered ring shows a chair conformation with the pseudo plane of symmetry through C-7 (guaiane numbering). The lactone ring adopts an envelope conformation with pseudo symmetry plane through C-7, and the cyclopentenone ring is almost flat. This geometry is practically identical to that predicted by a computer program for conformational analysis.

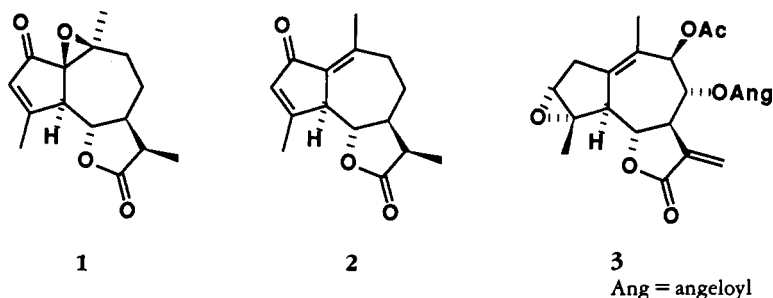
Among natural compounds, sesquiterpene lactones are highly interesting for their remarkable biological properties (1) and their usefulness as taxonomic markers (2). They are concentrated in a few specific plant families, mainly Compositae (3) and Umbelliferae (4). Many of these lactones exhibit a guaiane skeleton (guaianolides) and are very frequent in most Compositae tribes (3). Among these, the tribes Carduceae, Veronnieae, Eupatorieae, and Anthemideae include most of the known examples of guaianolides bearing oxirane rings.

The stereochemical assignment of epoxide rings in complex natural structures is not always easy, especially in tetrasubstituted oxiranes. Use has been made of the effect of the epoxide ring upon both ¹H-nmr chemical shifts and coupling constants (5–9). Because, however, the anisotropic effects of the epoxide ring have to be applied to an assumed conformation, caution is recommended in systems with some degree of conformational flexibility (10). In the case of 1,10-epoxyguaianolides, the influence of the epoxide ring on the chemical shift of H-6 or H-8 has been often utilized for stereochemical assignments (9, 11, 12) but it has recently been shown (13) that a secure stereochemical assignment cannot be taken for granted with this criterion, even if both diastereoisomeric epoxides (1,10 α and 1,10 β) are available.

¹³C-nmr chemical shifts have also been utilized for stereochemical assignments of epoxides (14–16). Diagnostically interesting are the γ upfield shifts caused by the oxirane ring on carbon atoms having an hydrogen atom *syn* to the three-membered heterocycle. Nevertheless, a recent paper (17) has shown that this criterion may occasionally lead to erroneous conclusions.

1,10-Epoxyachillin [**7**] was first isolated by González *et al.* (18) from *Artemisia lanata* Willd. The configuration of the epoxide ring was left undetermined. Some years later, the same group succeeded in chemically correlating **1** with achillin [**2**] and assigned a β configuration to the epoxide ring in the former (19). Their stereochemical as-

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signments, however, were based again on ^1H -nmr chemical shift differences between pairs of diastereoisomers, rather than on completely stereoselective transformations. On the other hand, it has been recently shown by X-ray analysis (13) that a 1,10-epoxyderivative of 8α -hydroxyachillin has a β oriented epoxide ring. In this way, the authors corrected an earlier erroneous assignment by Liu and Mabry (20), who had isolated this latter product from *Artemisia frigida* Willd. In the present paper, we report the complete assignment of the signals in both ^1H - and ^{13}C -nmr spectra of **1** and **2** as well as single crystal X-ray diffraction studies of **1**. The geometry of **1** deduced from these experiments is also compared with that predicted by a computer program for conformational analysis developed by one of us (21).

RESULTS AND DISCUSSION

We have recently isolated **1** and **2** from *Artemisia assoana* Willd. (Compositae) (22).

TABLE 1. ^1H -Nmr Data of Sesquiterpene Lactones **1** and **2**.^a

Proton	Compound	
	1	2
3	6.18 dq	6.10 dq
5	3.02 br d	3.37 br d
6	4.22 dd	3.75 dd
7	1.90 dddd	2.38 dddd
8α	1.62 dddd	1.81 dddd
8β	1.53 dddd	1.37 dddd
9α	2.18 ddd	2.40 ddd
9β	2.03 ddd	2.25 ddd
11	2.59 dq	2.64 dq
13	1.14 d	1.08 d
14	1.73 s	2.36 s
15	2.34 dd	2.23 dd

^aRun at 27° in CDCl_3 solution (300.13 MHz) with the solvent signal as reference (δ 7.25 ppm). Coupling constants (Hz) for compound **1**: $J_{3,5} = 2.3$, $J_{3,15} = 1.3$, $J_{5,6} = 10.2$, $J_{5,15} = 1.3$, $J_{6,7} = 10.2$, $J_{7,8\alpha} = 3.1$, $J_{7,8\beta} = 11.5$, $J_{7,11} = 7.6$, $J_{8\alpha,8\beta} = 13.9$, $J_{8\alpha,9\alpha} = 3.0$, $J_{8\alpha,9\beta} = 5.3$, $J_{8\beta,9\alpha} = 11.7$, $J_{8\beta,9\beta} = 2.5$, $J_{9\alpha,9\beta} = 15.6$, $J_{11,13} = 7.6$. For compound **2**: $J_{3,5} = 1.4$, $J_{3,15} = 1.3$, $J_{5,6} = 10.3$, $J_{5,15} = 1.3$, $J_{6,7} = 10.3$, $J_{7,8\alpha} = 2.3$, $J_{7,8\beta} = 11.6$, $J_{7,11} = 7.6$, $J_{8\alpha,8\beta} = 13.8$, $J_{8\alpha,9\alpha} = 2.2$, $J_{8\alpha,9\beta} = 6.9$, $J_{8\beta,9\alpha} = 12.3$, $J_{8\beta,9\beta} = 1.9$, $J_{9\alpha,9\beta} = 14.4$, $J_{11,13} = 7.6$.

An analysis of their ^1H -nmr spectra at 300 MHz permitted the unequivocal assignment of all hydrogens in both molecules (Table 1). Comparison of the chemical shift values of the seven-membered ring protons in **1** and **2** shows all these hydrogens in **1** resonating at higher field compared to the respective protons in **2**, except for H-6 and H-8 β . Indeed, the marked downfield shifts experienced by these atoms may point to a β stereochemistry of the oxirane ring in **1**. Moreover, the upfield shifts observed in the ^{13}C -nmr signals of C-6 and C-8 in **1** with respect to **2** (Table 2) should also lead to the same conclusion. Nevertheless, the above-mentioned comments about the uncertainty of such correlations led us to carry out an X-ray analysis of a single crystal of **1**, in order to unequivocally establish the configuration of the molecule.

TABLE 2. ^{13}C -Nmr Data of Sesquiterpene Lactones **1** and **2**.^a

Carbon	Compound	
	1	2
1	67.00 ^b	131.65
2	200.97	195.86
3	133.16	135.39
4	176.69	170.07
5	49.67	52.82
6	79.67	83.40
7	51.76	51.81
8	19.80	23.48
9	34.60	37.49
10	65.21 ^b	152.17
11	39.30	39.25
12	179.10	178.43
13	9.91	9.85
14	18.86	21.46
15	20.93	19.71

^aRun at 27° in CDCl_3 solution (75.47 MHz) with the solvent signal as reference (δ 77 ppm).

^bAssignments may be interchanged.

A perspective view of the molecule is shown in Figure 1, and its atomic coordinates (for the non-hydrogen atoms) are listed in Table 3. As can be seen, the seven-membered ring adopts in the solid state conformation of **1** a chair conformation with the pseudo plane of symmetry through C-7; the lactone ring shows an envelope conformation with pseudo symmetry plane through C-7; and the cyclopentenone ring is almost flat. The last point is evidenced by the small deviations of the carbon atoms C-1 to C-5 from the least-square plane, as calculated for this ring (Table 4). Essentially the same overall conformation is predicted by the systematic conformation analysis (SCA) program (21), as revealed by Table 5. These results can be now compared with the data of achillin [**2**], the X-ray structure of which has been very recently published (23). The values of the torsion angles (Table 5) for the hydrogens H-5, H-6, H-7, H-8 α/β , H-9 α/β , and H-11 in **1** and **2** are quite close and the shapes of both molecules are very similar (23). Another structurally related case is that of berlandin [**3**] (24). Here too, the seven-membered ring adopts a chair conformation. The marked resemblance of the seven-membered chair conformations in **1** and **3** is revealed in this case by the comparison of the endocyclic torsion angles of the seven-membered ring in both compounds (Table 5).

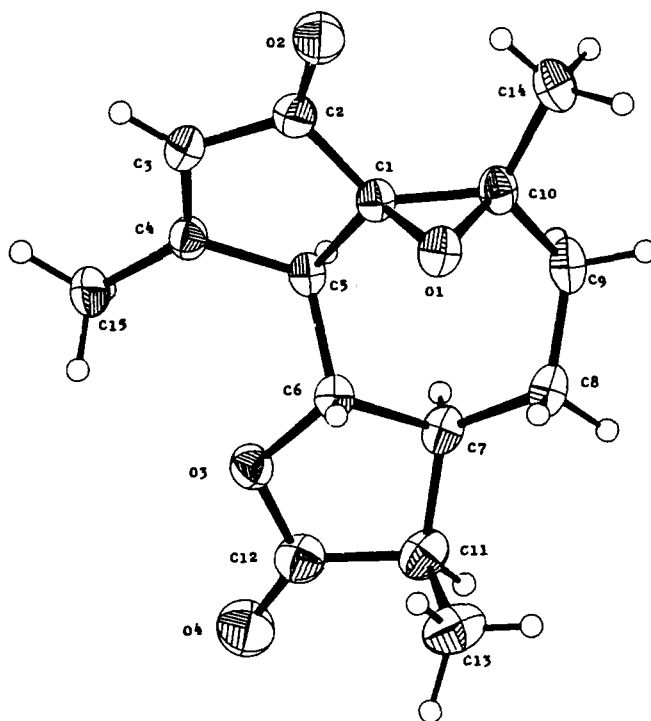


FIGURE 1. Molecular structure of compound 1.

TABLE 3. Final Atomic Coordinates of 1,10 β -Epoxyachillin [1].^a

Atom	x	y	z
C-1	0.9955(3)	0.4456(1)	0.3490(1)
C-2	1.0777(4)	0.3870(1)	0.4215(1)
C-3	0.9281(4)	0.3009(1)	0.4251(1)
C-4	0.7628(3)	0.3020(1)	0.3679(1)
C-5	0.7697(3)	0.3959(1)	0.31933(9)
C-6	0.7662(3)	0.3868(1)	0.2284(1)
C-7	0.6991(3)	0.4823(1)	0.1868(1)
C-8	0.8916(3)	0.5602(1)	0.1864(1)
C-9	0.9322(4)	0.6064(1)	0.2684(1)
C-10	1.0718(3)	0.5461(1)	0.3291(1)
C-11	0.6047(4)	0.4444(2)	0.1065(1)
C-12	0.4881(4)	0.3499(2)	0.1323(1)
C-13	0.7934(5)	0.4247(2)	0.0425(1)
C-14	1.2159(4)	0.6063(2)	0.3862(1)
C-15	0.5774(4)	0.2264(1)	0.3571(1)
O-1	1.1901(2)	0.46200(9)	0.29425(8)
O-2	1.2456(3)	0.4060(1)	0.46438(9)
O-3	0.5822(2)	0.31948(9)	0.20300(8)
O-4	0.3374(3)	0.3031(1)	0.1000(1)

^aEstimated standard deviations in the least significant digit are shown in parentheses. Only the non-hydrogen atoms are included. For atom numbering, see Figure 1.

TABLE 4. Distances from the Least-Square Plane for the Atoms of the Cyclopentenone Ring (estimated SD in parentheses).^a

Atom	x	y	z	Distance (Å)
C-1	5.6131	6.0914	5.8276	0.057 (0.002)
C-2	6.0766	5.2901	7.0373	-0.037 (0.002)
C-3	5.2332	4.1127	7.0968	-0.001 (0.002)
C-4	4.3008	4.1286	6.1427	0.038 (0.002)
C-5	4.3398	5.4117	5.3317	-0.057 (0.002)

^aThe equation of the plane is of the form: $Ax + By + Cz - D = 0$, where A, B, C and D are constants and x, y and z are orthogonalized coordinates. The values of the constants are A = 0.5981, B = -0.4918, C = -0.6328, and D = -3.3826.

Furthermore, if we consider again the data in Table 1, we note the great similarity in several coupling constants for **1** and **2**, which strongly suggests the same seven-membered ring conformation in solution for these products. This means that the introduction of the epoxide ring (which is practically symmetrical) causes only minor alterations in the geometry of the molecule. Especially informative are the large values obtained for the *trans* and *anti* oriented H-5/H-6 (10.2–10.3 Hz), H-6/H-7 (10.2–10.3 Hz), H-7/H-8 β (11.5–11.6 Hz), and H-8 β /H-9 α (11.7–12.3 Hz). These coupling patterns are consistent with a chair conformation as present in the solid state of **1**. Very similar values have also been measured in the ¹H nmr spectrum of **3** (24), thus indicating a very close resemblance in the solution conformation of all three lactones. With regard to H-7, H-8, and H-9 we should emphasize here that in **1** and **2** only the apparent coupling constants are measured. The closeness of the two signals from H-7 and H-9 α in **2** could disturb the resonance patterns, but as non-neighboring protons are concerned, the disturbances are from a long range origin and thus minimal.

TABLE 5. Comparison of Some Selected Torsion Angles (°) in 1,10 β -Epoxyachillin [**1**], Achillin [**2**], and Berlandin [**3**].

Angle	1 ^a	1 ^b	2 ^c	3
H-5-C-5-C-6-H-6	162.5		169.3	176 ^d
H-6-C-6-C-7-H-7	-167.0		-153.5	-176 ^d
H-7-C-7-C-8-H-8 α	-77.8		-71.3	
H-7-C-7-C-8-H-8 β	166.6		169.5	175 ^d
H-7-C-7-C-11-H-11	42.1		35.0	
H-8 α -C-8-C-9-H-9 α	75.2		74.2	
H-8 α -C-8-C-9-H-9 β	-42.1		-43.9	
H-8 β -C-8-C-9-H-9 α	-163.9		-166.6	-169 ^d
H-8 β -C-8-C-9-H-9 β	78.9		75.3	
C-10-C-1-C-5-C-6	61.3	61		64 ^e
C-5-C-1-C-10-C-9	-5.6	0		-6 ^e
C-8-C-9-C-10-C-1	-54.2	-61		-73 ^e
C-7-C-8-C-9-C-10	76.6	77		76 ^e
C-6-C-7-C-8-C-9	-71.9	-63		-57 ^e
C-5-C-6-C-7-C-8	74.3	63		64 ^e
C-1-C-5-C-6-C-7	-78.6	-77		-82 ^e

^aX-ray.

^bComputed by SCA, see text.

^cX-ray data from Martinez *et al.* (23).

^d¹H-nmr data from Cox *et al.* (24).

^eX-ray data from Cox *et al.* (24).

EXPERIMENTAL

Compounds **1** and **2** were isolated from *A. assoana* as described (22).

NMR MEASUREMENTS.—¹H- and ¹³C-nmr spectra were measured in CDCl₃ solution at 25° on a Bruker AM-300 spectrometer. Assignments of signals were carried out by careful analysis of the coupling constants, aided by 2D-COSY correlation spectra (25).

CRYSTAL DATA.—Compound **1**: C₁₅H₁₈O₄ (M = 262.31), orthorhombic, a = 5.638(1), b = 13.670(2), c = 16.696(4) Å, V = 1286.89 Å³ (by least-squares technique involving diffractometer 2θ angles for 25 automatically centered reflections, λ = 0.71069 Å), space group P2₁2₁2₁ (No. 19), Z = 4, D_{calc} = 1.344 g/cm³. Colorless needles, sealed in Lindemann capillaries. Crystal dimensions: 0.20 × 0.24 × 0.35 mm, μ (Mo-Kα) = 0.90 cm⁻¹.

DATA COLLECTION.—Data for unit cell determination and also for the structural studies were collected utilizing an Enraf-Nonius CAD-4 diffractometer. A total of 2046 reflections were measured at room temperature with graphite-monochromated MoKα radiation up to θ = 27°, using an ω-2θ scan mode with ω scan width = 0.70 + 0.35 tan θ and ω scan speed 1.1 deg/min. After data reduction, 1621 reflections with I ≥ 2σ(I) were taken as observed.

STRUCTURE ANALYSIS AND REFINEMENT.—The structure was solved by direct methods (MULTAN11/82) (26); hydrogen atoms were obtained from a difference Fourier map. The following full-matrix least-squares refinement with anisotropic thermal parameters for all non-hydrogen atoms and isotropic thermal parameters for hydrogen atoms led to R = 0.036 and R_w = 0.043 for 244 variables [weighting scheme: w⁻¹ = σ²(F) + (p|F|)² with p = 0.04]. The final difference Fourier map showed no significant features. Scattering factors are from Cromer and Waber (27). All crystallographic calculations were performed by using the Enraf-Nonius SDP package (28).²

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²Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

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