

68. The Structure and Absolute Configuration of Arteannuin B

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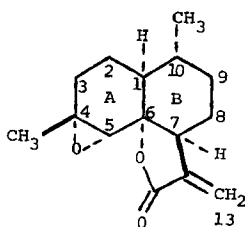
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The recent publication of *Stefanović et al.* [1] describing the structure of arteannuin B prompted us to disclose our results, which also produced a structure of this compound. A generous sample of arteannuin B, isolated from *Artemisia annua* L. [1], was received from Prof. *Stefanović* for a collaborative effort in structural investigation. After recrystallization from ether, the sample (m.p. 152–152.5°) exhibited a rotation of $[\alpha]_D^{25} = -72.2^\circ$ ($c = 1.025$, CH_3OH)¹). The high resolution mass spectrum (m/e 248.1418, M^+) and elemental analysis (C 72.35, H 8.09%) indicated that the molecular formula was $\text{C}_{15}\text{H}_{20}\text{O}_3$. Spectral evidence including an X-ray analysis and consideration of the biogenetic scheme proposed by *Andersen* [2] led to the structure and absolute configuration **1** [4 α , 5 α -epoxy-6 α -hydroxy-10 α -cadin-11(13)-en-12-*oic* acid lactone] for this natural product.

The IR. spectrum in chloroform exhibited absorptions for a γ -lactone at 1775, an epoxide at 950–1200, and a double bond at 1665 cm^{-1} . The last functionality was also indicated to be part of a conjugated lactone grouping by an UV. absorption at 204 nm ($\epsilon = 13,700$)²). The presence of the unsaturated γ -lactone and its absolute configuration were supported by rotational data: ORD. (0.11% solution in CH_3OH) $\Phi_{\text{min}}^{256} = -2801^\circ$, $\Phi^{255} = 0^\circ$, $\Phi_{\text{max}}^{214} = +9018^\circ$; CD. (the same solution) $\Theta_{\text{min}}^{256} = -4545^\circ$. These data compare favorably with the *trans*-fused α -methylene- γ -butyrolactone moiety characteristic of many naturally occurring sesquiterpenes [3].

The *trans*-configuration of the lactone was also evident from NMR. spectrum [CDCl_3 , 220 MHz, $(\text{CH}_3)_4\text{Si}$, δ -values]: 2.72 for allylic C(7)-proton, a doublet of quartets, with $J_{7,8\beta} = 12$ Hz (axial-axial), $J_{7,8\alpha} = 3$ Hz (axial-equatorial), $J_{7,13} = 3$ Hz



(perpendicular allylic, confirmed by decoupling); 5.44 and 6.14 for C(13)-methylene protons, two doublets each with $J_{7,13} = 3$ Hz. Since no NMR. signal for a proton on a carbon bearing the ether oxygen of the lactone was observed, the carbon atom C(6) had to be tertiary.

¹) Reported [1]: $[\alpha]_D^{30} = -6^\circ$ (no solvent indicated).

²) Reported [1]: 215 nm (ϵ 5820).

The NMR. spectrum also indicated a secondary methyl group at 0.98 as a doublet with $J = 6$ Hz; a methyl group on the epoxide ring at 1.32 as a singlet; and a proton on the epoxide ring at 2.67. Since the last proton exhibited a singlet, it was assigned to a carbon linked to two other carbons bearing no protons.

These data led us to postulate the structure **1** for arteannuin B without specifying the stereochemistry at C(1), C(4), C(5), and C(10). The AB-ring junction and the configuration of the C(10) methyl group were subsequently established by an analysis of the NMR. signal for the C(1) proton. This proton gave a doublet of quartets at 2.05 resulting from one large and three small coupling constants: $J_{1,10\beta} = 12.5$ Hz (axial-axial), $J_{1,2\beta} = 3$ Hz (equatorial-equatorial), $J_{1,2\alpha} = 3$ Hz (equatorial-axial), and $J_{1,3\alpha} = 3$ Hz (W-coupling). This pattern is compatible only with a *cis*-ring junction and a 10α -methyl group. The $1,3\alpha$ -W coupling is indicative of a half-chair conformation of the Ring A. The stereochemistry of the last two centers, C(4) and C(5), could only be established by an X-ray analysis. A stereodrawing of the molecule is presented in the figure.

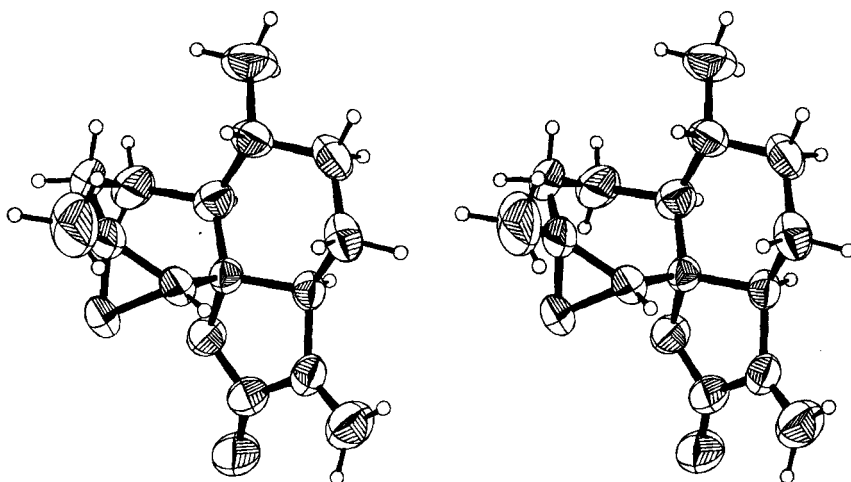


Fig. 1. Stereodrawing of **1**. The anisotropic atoms are shown scaled to the 50% probability level. The hydrogens are shown as spheres of an arbitrary size.

Crystals of **1** are orthorhombic, space group $P2_12_12_1$, with unit cell parameters $a = 9.034$ (12), $b = 12.266$ (12), $c = 12.290$ (15) Å. The calculated density is $D_c = 1.211$ g cm⁻³ for $Z = 4$. Three dimensional intensity data were measured on a *Hilger-Watts* model Y290 four circle diffractometer. Nickel filtered Cu K α radiation and pulse height discrimination were used. The approximate dimensions of the crystals were $0.20 \times 0.20 \times 0.45$ mm; no absorption corrections were made ($\mu = 6.8$ cm⁻¹). Of the 1610 accessible reflections with $\theta < 76^\circ$, 1091 had intensities significantly greater than background.

The structure was solved by a multiple solution procedure [4]. All non-hydrogen atoms were located from the E-map calculated for the phase set with the highest figure-of-merit. The hydrogen atom positions were obtained from a difference *Fourier* calculated after preliminary refinement of the structure. The final refine-

ment was carried out by full matrix least squares with anisotropic thermal parameters for all atoms except the hydrogens which have isotropic temperature factors. The final unweighted R index is 0.041 for the 1091 observed reflections. A difference *Fourier* based on the final parameters has no features greater than $0.2 \text{ e } \text{Å}^{-3}$ in magnitude.

REFERENCES

- [1] D. Jeremić, A. Jokić, A. Behbud, & M. Stefanović, *Tetrahedron Letters* 1973, 3039.
 [2] N. H. Andersen, *Phytochemistry* 9, 145 (1970).
 [3] T. G. Waddell, W. Stöcklin, & T. A. Gassman, *Tetrahedron Letters* 1969, 1313.
 [4] G. Germain, P. Main & M. M. Woolfson, *Acta Cryst. B* 26, 274 (1970).

69. The Structure of Arteannuin B and its Acid Hydrolysis Product

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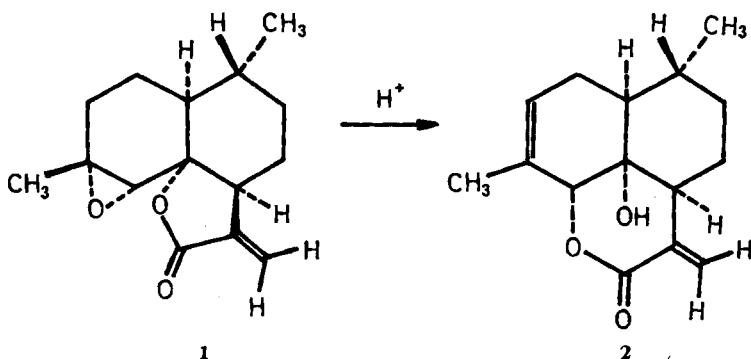
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Zusammenfassung. Die Struktur des Sesquiterpen- γ -Laktons Arteannuin B (**1**) wurde röntgenographisch und diejenige seines Hydrolyseproduktes (**2**) durch eine vollständige Analyse des NMR.-Spektrums ermittelt.

1. Introduction. – The isolation of the sesquiterpene lactone arteannuin B from *Artemisia Annuua* L. and several conversions including the formation of an acid hydrolysis product have recently been reported by *Stefanović et al.* [1]. Certain arguments were presented there in preliminary form which led to a proposal of structures **1** and **2** for arteannuin B and its hydrolysis product. We report here our own investigation of these two compounds²⁾, which confirm these structure proposals. First a detailed argument will be presented for the structure of the acid hydrolysis product **2**, based



¹⁾ Royal Society Post-doctoral Fellow, 1972–73.

²⁾ We thank Prof. *Stefanović* for the samples of Arteannuin B and its hydrolysis product.