

## 68. The Structure and Absolute Configuration of Arteannuin B

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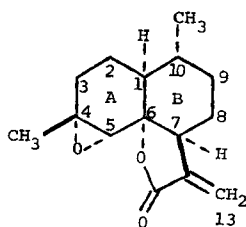
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The recent publication of *Stefanović et al.* [1] describing the structure of arteannuin B prompted us to disclose our results, which also produced a structure of this compound. A generous sample of arteannuin B, isolated from *Artemisia annua* L. [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  $[\alpha]_D^{25} = -72.2^\circ$  ( $c = 1.025$ ,  $\text{CH}_3\text{OH}$ )<sup>1</sup>. 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 $\alpha$ , 5 $\alpha$ -epoxy-6 $\alpha$ -hydroxy-10 $\alpha$ -cadin-11(13)-en-12-oic acid lactone] for this natural product.

The IR. spectrum in chloroform exhibited absorptions for a  $\gamma$ -lactone at 1775, an epoxide at 950–1200, and a double bond at 1665  $\text{cm}^{-1}$ . The last functionality was also indicated to be part of a conjugated lactone grouping by an UV. absorption at 204 nm ( $\epsilon = 13,700$ )<sup>2</sup>. The presence of the unsaturated  $\gamma$ -lactone and its absolute configuration were supported by rotational data: ORD. (0.11% solution in  $\text{CH}_3\text{OH}$ )  $\Phi_{\min}^{256} = -2801^\circ$ ,  $\Phi^{255} = 0^\circ$ ,  $\Phi_{\max}^{214} = +9018^\circ$ ; CD. (the same solution)  $\Theta_{\min}^{256} = -4545^\circ$ . These data compare favorably with the *trans*-fused  $\alpha$ -methylene- $\gamma$ -butyrolactone moiety characteristic of many naturally occurring sesquiterpenes [3].

The *trans*-configuration of the lactone was also evident from NMR. spectrum [ $\text{CDCl}_3$ , 220 MHz,  $(\text{CH}_3)_4\text{Si}$ ,  $\delta$ -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.

<sup>1</sup>) Reported [1]:  $[\alpha]_D^{20} = -6^\circ$  (no solvent indicated).

<sup>2</sup>) Reported [1]: 215 nm ( $\epsilon$  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 10 $\alpha$ -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.

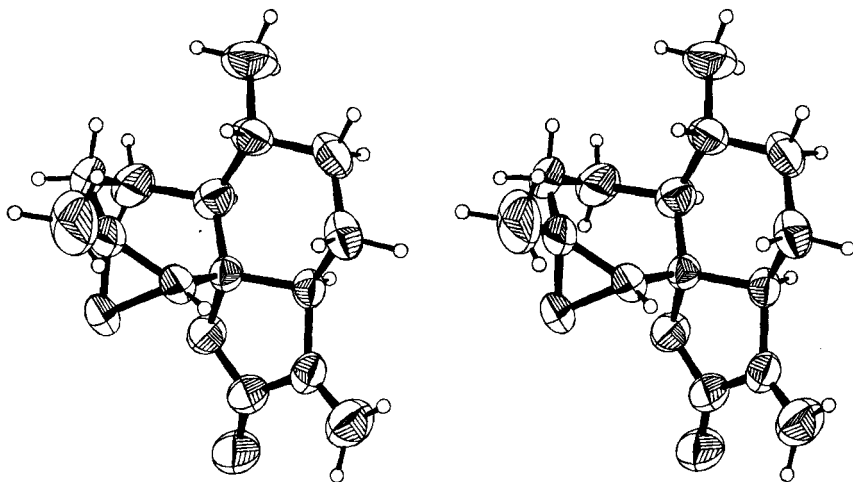


Fig. 1. Stereodrawing of **1**. The anisotropic atoms are shown scaled to the 50% probability level. The hydrogens are shown as spheres of an arbitrary size.

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 *Hülgner-Watts* model Y290 four circle diffractometer. Nickel filtered Cu K $\alpha$  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  $0.2 \text{ e } \text{\AA}^{-3}$  in magnitude.

## REFERENCES

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

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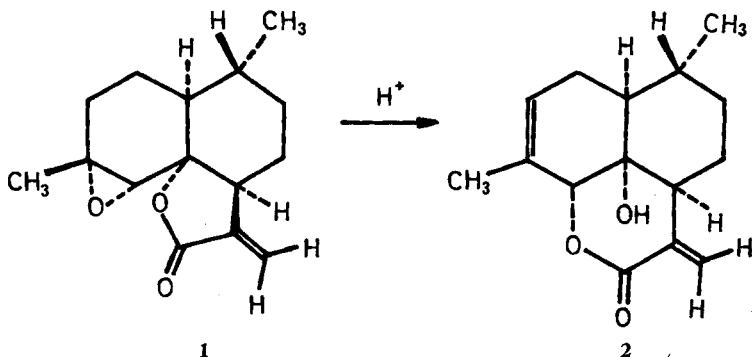
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*Zusammenfassung.* Die Struktur des Sesquiterpen- $\gamma$ -Laktons Arteannuin B (**1**) wurde röntgenographisch und diejenige seines Hydrolyseproduktes (**2**) durch eine vollständige Analyse des NMR.-Spektrums ermittelt.

**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 compounds<sup>2)</sup>, which confirm these structure proposals. First a detailed argument will be presented for the structure of the acid hydrolysis product **2**, based



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