CHEMISTRY LETTERS, pp. 81-84, 1979. Published by the Chemical Society of Japan

STRUCTURE OF YOMOGIARTEMIN, A NOVEL SESQUITERPENE α-METHYLENE-γ-LACTONE FROM *Artemisia feddei*

Masato KOREEDA*[1]

Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218
and Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109, USA

Sumu MATSUEDA* and Takehiro SATOMI

Department of Chemistry, University of Hirosaki, Hirosaki 036

and

Ken HIROTSU and Jon CLARDY*

Department of Chemistry, Cornell University, Ithaca, New York 14853, USA

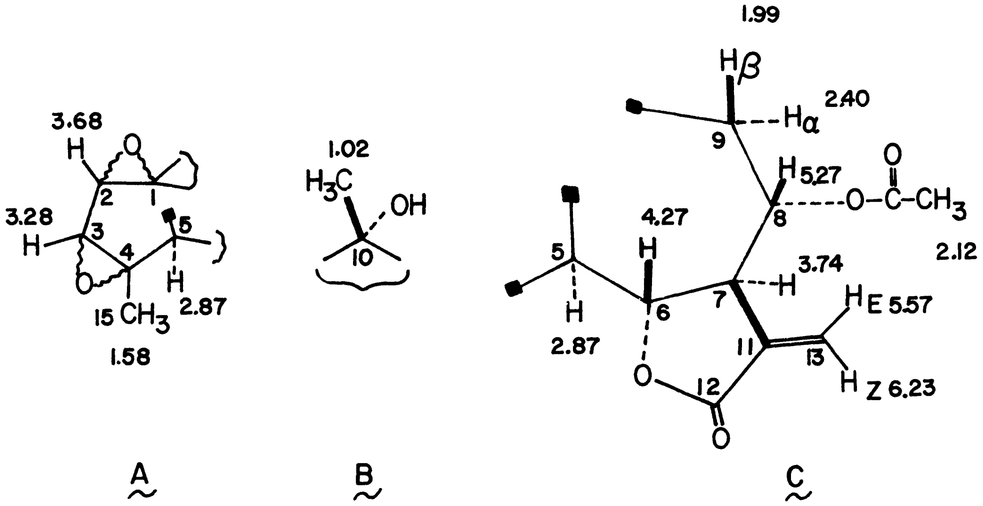
A novel diepoxy-guaianolide sesquiterpene α-methylene-γ-lactone, yomogiartemin 1, has been isolated from *Artemisia feddei* of the *Compositae* family. The structure was determined by both spectroscopic mehtods and x-ray analysis.

Our efforts to search natural sources for highly oxygenated α-methylene lactones as possible anti-tumor and/or cytotoxic compounds[2,3] have resulted in the isolation of a new guaianolide sesquiterpene lactone, yomogiartemin 1, from *Artemisia feddei* of the *Compositae* family.[2] We now wish to report its molecular structure.

Chloroform extracts of 17.7 Kg of pulverized *A. feddei* Lev et Van ("hime-yomogi" in Japanese)[4] were purified by silica gel chromatography and recrystallized from ethyl acetate providing 20 mg of pure yomogiartemin 1; mp. 240 - 242°C, $C_{17}H_{20}O_7$, ms (chemical ionization, NH_3 gas): $[M + 18]^+$ at m/e 354, ir (KBr): 3450, 1760, and 1735 cm^{-1}, uv (MeOH): λ_{max} 214 nm (ε 11,000). The presence of an α-methylene-γ-lactone in yomogiartemin 1 was readily assigned from its ir and uv spectroscopic properties. Extensive proton nmr analysis of 1 led to the proposal of the two partial structures A and C and one *tert*-methyl group B for 1, accounting for all seventeen carbon atoms present in 1 (Figure 1). This was further corroborated by its C-13 nmr spectrum in $CDCl_3$;[5] δ (ppm) 20.31 (q), 21.31 (q), 26.71 (q), 29.72 (d), 44.06 (t), 44.77 (d), 49.00 (d), 56.94 (d), 58.59 (d), 70.06 (s), 71.35 (s), 71.59 (d), 76.47 (s), 121.45 (t), 137.50 (s), 169.21 (s), and 169.90 (s).

It was not, however, possible to unequivocally distinguish between a perhydroazulene and an

Figure 1. Partial Structures of Yomogiartemin 1 and its ^1H-nmr Data.[a,b]



Coupling constants:[c]

$^3J_{2,3}$ = 1.2 Hz

$^3J_{5,6}$ = 10.0 Hz

$^3J_{6,7}$ = 10.0 Hz

$^3J_{7,8}$ = 10.0 Hz

$^4J_{7,13Z}$ = $^4J_{7,13E}$ = 3.0 Hz

$^3J_{8,9\alpha}$ = 7.0 Hz

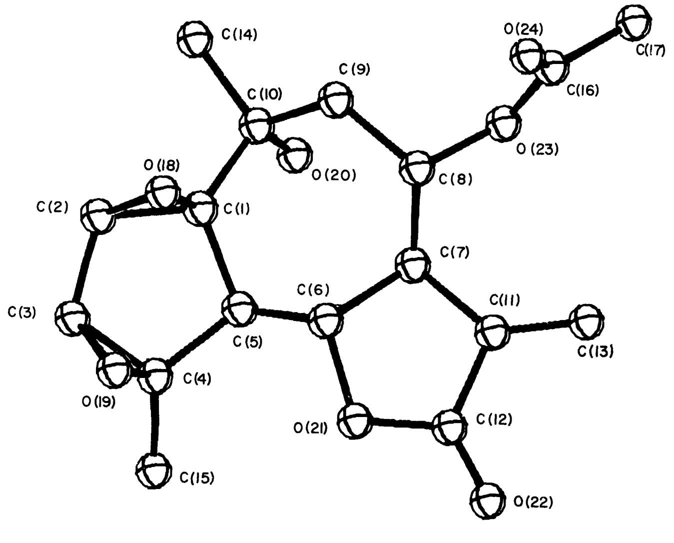
$^3J_{8,9\beta}$ = 2.5 Hz

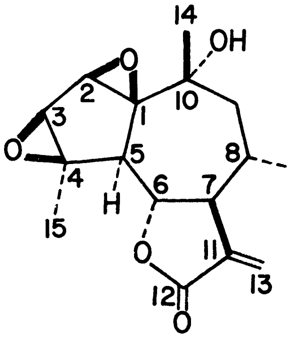
$^2J_{9\alpha,9\beta}$ = 16.0 Hz

- a. Nmr spectrum was measured on a Jeol MH-100 and a Varian HA-100 in $CDCl_3$ and chemical shifts given in the Figure are in parts per million down-field from the internal reference, tetramethylsilane.
- b. ■ denotes a fully substituted quaternary carbon.
- c. Small long-range coupling ($|J| < 0.75$ Hz) was detected between protons in the following pairs as ascertained by decoupling experiment:

  3 - H/15 - H and 5 - H/15 - H.

Figure 2. A Computer-generated Perspective Drawing of Yomogiartemin 1. Hydrogens are omitted for clarity.





1

eudesmane skeleton of yomogiartemin 1 based solely on nmr. Thus, a single crystal x-ray analysis was carried out to elucidate its molecular structure. Yomogiartemin crystallized in the orthorhombic crystal class with a = 8.980 (4), b = 10.371 (4), and c = 17.492 (9) Å. Systematic extinctions and an observed density of ~1.37 g/cc indicated one molecule of composition $C_{17}H_{20}O_7$ in the common chiral space group $P2_12_12_1$. All unique diffraction maxima with $2\theta \leq 114^o$ were collected on a computer controlled four-circle diffractometer with graphite monochromated CuKα radiation (1.54178 Å) and a variable speed ω-scan technique. Of the 1293 reflections surveyed in this manner, 1272 (98%) were judged observed after correction for Lorentz, polarization, and background effects. A phasing model was reduced using a multisolution weighted tangent formula approach.[6] Full-matrix least-squares refinements with anisotropic temperature for the non-hydrogen atoms and isotropic hydrogens have converged to a conventional crystallographic residual of 0.053 for the observed reflections.[6]

Figure 2 is a computer-generated perspective drawing of the final x-ray model without hydrogen atoms. The x-ray experiment defined only the relative configuration and the enantiomer displayed represents an arbitrary choice. The cyclopentane ring [C(1), C(2), C(3), C(4), and C(5)] is planar within 0.02 Å and the γ-lactone ring is intermediate between an envelope and a half-chair form. The cycloheptane ring is approximately in a chair form [C(7)-C(8)-C(9)-C(10)-dihedral angle ~ 7^o]. In general, bond distances and angles agree well with generally accepted values.[7] There are no intermolecular contacts less than van der Waals distances with the exception of the O(20)H····O(18) distance of 2.88 Å.

Interestingly, the structure of a closely related sesquiterpene, chrysantemin B,[8] isolated from a *Chrysanthemum* species, has recently been revised and shown to possess the same diepoxyguaianolide skeleton as yomogiartemin 1.[9] The pharmacological properties of this highly oxygenated α-methylene-γ-lactone, yomogiartemin 1, are currently under investigation.

Acknowledgments. The authors wish to thank Mr. I. Miura (Columbia University) for his nmr decoupling experiments. This research was supported in part by NIH Grants CA 18580 and ES 02133 (to MK).

References and Notes.

1. Present address: Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109.

2. W. Herz, Recent Advances in Phytochemistry, ed. by T. J. Marby, R. E. Alston, and V. C. Runeckles, Appleton-Century-Crofts, New York, Vol. 1, 1968, pp.229 - 269.

3. For the biological activities of sesquiterpene lactones, see: (a) K. H. Lee, E. S. Huang, C. Piantadosi, J. S. Pagano, and T. A. Geissman, Cancer Res., **31**, 1649 (1971), (b) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, J. Med. Chem., **14**, 1147 (1971), and (c) K. H. Lee, T. Ibuka, R. Y. Wu, and T. A. Geissman, Phytochem., **16**, 1177 (1977).

4. This plant is often confounded with another similar species *A. lavavdulaefolia* DC. which carries the identical Japanese name.

5. The carbon-13 nmr spectrum was obtained on a Varian CFT-20 and chemical shifts are reported in parts per million down field from the internal reference, tetramethylsilane. Notations in the parenthesis (i.e., s, d, t, and q) represent the signal multiplicity of each carbon (singlet, doublet, triplet, and quartet, respectively) measured in an off-resonance mode.

6. All crystallographic calculations were done on a Prime 400 computer operated by the Materials Science Center and the Department of Chemistry, Cornell University. The principal programs used were: REDUCE and UNIQUE, data reduction programs, M. E. Leonowicz, Cornell University, 1978; BLS, block diagonal least squares refinement, K. Hirotsu, Cornell University, 1978; ORFLS (modified), full-matrix least squares, W. R. Busing, K. O. Martin, and H. S. Levy, Oak Ridge, ORNL-TM-305; ORTEP, crystallographic illustration program, C. Johnson, Oak Ridge, ORNL-3794, BOND, structural parameters and errors, K. Hirotsu, Cornell University, 1978; MULTAN-76, direct methods and fast fourier transform, G. Germain, P. Main, and M. Woolfson, University of York.

7. Tables of fractional coordinates and thermal parameters, bond distances, bond angles, and observed and calculated structure factors are available from J. C.

8. J. Romo, A. Romo de Vivar, R. Trevino, P. Joseph-Nathan, and E. Diaz, Phytochem., **9**, 1615 (1970).

9. T. Osawa, D. Taylor, A. Suzuki, and S. Tamura, Tetrahedron Lett., 1169 (1977). See also: T. Osawa, A. Suzuki, and S. Tamura, Agr. Biol. Chem., **35**, 1966 (1971). Two stereoisomers of chrysantemin B (H instead of the acetoxyl group in **1**) have also been reported.[8,10]

10. K. H. Lee, R. F. Simpson, and T. A. Geissman, Phytochem., **8**, 1515 (1969).

(Received November 6, 1978)