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X-RAY STRUCTURE DETERMINATION OF EREMOPHILENOLIDE

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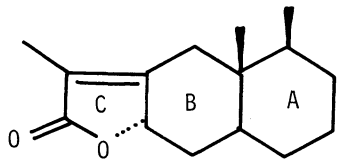
The structure of eremophilenolide is confirmed to be (1) by X-ray analysis. The cis-fused decalin system takes all chair "steroid-like conformation."

The structure and absolute stereochemistry of eremophilenolide, a naturally occurring sesquiterpenoid from *petasites officinalis* Moench, has been assigned as depicted in (1).[1] The total synthesis of the racemic modification of this compound has recently been reported by Piers *et al.*[2] In the course of our independent study on the synthesis of this compound,[3] it seems that the NMR coupling constants throw doubts on a reasonable interpretation of the α-orientation of the lactone ring. This may be due to the conformational flexibilities of A/B cis-fused decalin system. Therefore, in order to provide a complete configurational and conformational proof, we have undertaken a single-crystal X-ray analysis of eremophilenolide (I).



(1)

The crystals of (I), $C_{15}H_{22}O_2$, are orthorhombic with $P2_12_12_1$; a=12.378, b=15.218, c=7.036 Å, Dx=1.28 g.cm^{-3} (Z=4). The three-dimensional intensity data were collected on a Rigaku automatically controlled four-circle diffractometer using Mo-K_α radiation. The independent 1893 reflections ($\sin\theta/\lambda \leq 0.64$) were used in the following calculations. The structure was solved by a non-centrosymmetric direct method using the general principles described by Karle & Karle.[4] Three phases were assigned to define the origin; (1 0 1), E=3.05, $\phi=\pi/2$; (14 7 0), E=2.98, $\phi=0$; (5 17 0), E=2.67, $\phi=-\pi/2$. Phases for three additional reflections were assigned by symbols; (1 7 2), E=2.17, ϕ=a; (6 7 7), E=2.39, ϕ=b; (10 2 0), E=2.43, ϕ=c. In an application of Σ_2 formula, there were one or more strong indications that $a=\pm\pi/2$, b=0 or π, and c=0 or π. Eight different starting phase combinations were used as input data into the tangent formula.[5] Initial three cycles of calculation was carried out for the limited reflections with $|E| \geq 1.7$ and $\sin\theta/\lambda \leq 0.60$, and further recycling calculation was carried out for a total 245 of reflections with $|E| > 1.3$. About 220 phases were determined after six cycles of phase refinement calculation. Two sets of them had the highest consistency index ($\langle C \rangle = 0.61$) and the lowest residual index (R=0.38).[6] The sets corre-

Table 1 The final atomic coordinates

Atom	x/a	y/b	z/c	Atom	x/a	y/b	z/c
O(1)	0.0735	0.2755	0.6355	C(8)	-0.0020	0.3184	0.5046
O(2)	0.2422	0.2177	0.6101	C(9)	-0.0236	0.4101	0.5737
C(1)	-0.1012	0.5588	0.4969	C(10)	-0.0803	0.4649	0.4221
C(2)	0.0059	0.6117	0.5134	C(11)	0.1552	0.2824	0.3411
C(3)	0.0674	0.6126	0.3230	C(12)	0.1675	0.2540	0.5351
C(4)	0.0899	0.5188	0.2465	C(13)	0.1535	0.5263	0.0623
C(5)	-0.0202	0.4652	0.2283	C(14)	-0.0980	0.5073	0.0761
C(6)	0.0047	0.3685	0.1602	C(15)	0.2446	0.2727	0.1965
C(7)	0.0579	0.3224	0.3165				

spond to the starting phases of $a=2/\pi$, $b=\pi$ and $c=0$, and $a=\pm 2/\pi$, $b=0$ and $c=0$, respectively, and therefore one is the enantiomorph of the other. An almost complete structure was shown from the E-map. The 17 peaks in the range of 360-690 were correct and the highest spurious peak was only 210 in a relative scale. The model was refined by block-diagonal least-squares method. All of the hydrogen atoms were found by a difference Fourier synthesis. When the non-hydrogen atoms were assigned the anisotropic temperature factors and the hydrogen atoms the isotropic ones, the conventional R factor was reduced to 0.077. The final atomic parameters are listed in Table 1 and the perspective drawing of the molecule is shown in Figure 1.

The present X-ray analysis completely confirms the stereochemistry of eremophilenolide, (I). In this compound, a cis-fused decalin system is found in the expected all-chair "steroid-like" conformation (Figure 2).[7] Both A and B rings exist in a nearly undistorted chair form. The bond lengths and bond angles are normal (sp^3-sp^3 bond lengths; 1.52-1.57 Å and sp^3 bond angles; 109-111°). To reveal the degree of ring flattening, we calculated the displacement (d) of the atom from the plane through the central four carbon atoms (Figure 2). The values of 0.65-0.67 Å in A ring and will not deviate so largely from 0.73 Å in an idealized cyclohexane ring.[8]

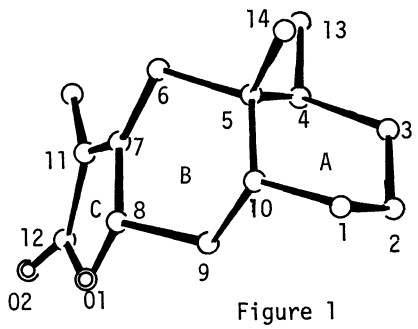


Figure 1

The perspective picture of (I)

The numbering is that normally employed for eremophilenolane-type sesquiterpenes.

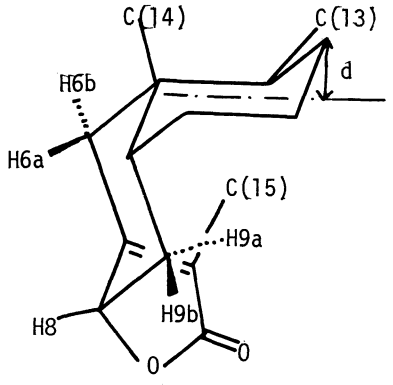


Figure 2

The conformational picture of (I)

In this molecule, a considerable constraint may exist at C(7) atom of B/C fused ring as indicated by its valence bond angles (Figure 3). An expansion of the C(6)C(7)C(11) angle (135°) will be due to the steric repulsive force between the methyl group, C(15), and the equatorial hydrogen atom, H6b, and while the C(8)C(7)C(11) angle is constracted to 108° by a construction of five-membered ring. By such angular distortions, the resulting rehybridization of bond orbitals with the changes of s- or p-character might explain a significant difference between the C(6)-C(7) and C(7)-C(8) bond lengths (1.462 Å and 1.518 Å).[9]

In α,β-unsaturated-γ-lactone ring, the bond lengths of C(11)-C(12) (1.440 Å) and C(11)=C(7) (1.361 Å) suggest a partial conjugation of this system. The observed bond shortening of C(12)-O(1) (1.403 Å), compared with C(8)-O(1) (1.465 Å), is similar to that in earlier reported γ-lactones.[10]

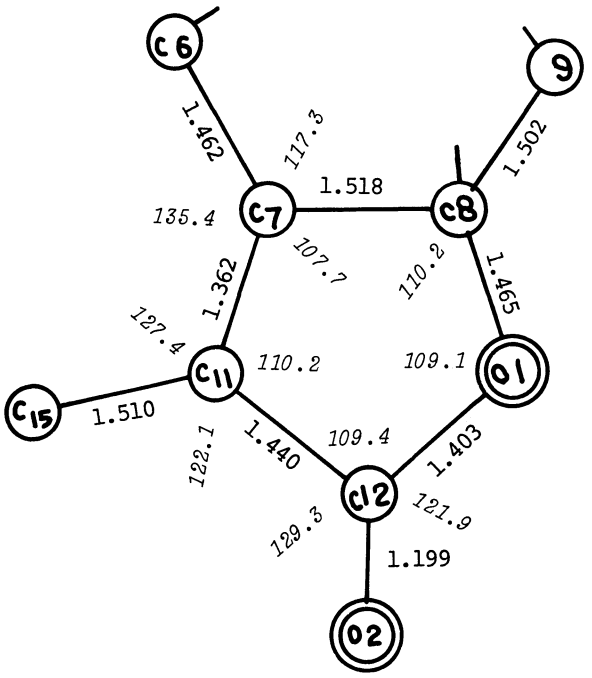


Figure 3 The bond lengths (Å) and angles (°) in the α,β-unsaturated γ-lactone moiety. The standard deviations are av. 0.009 Å and av. 0.8°.

Now having the crystallographic structure of eremophilenolide (I) in hand, we will discuss the NMR spectral data of it. The 100 Mc spectrum in $CDCl_3$ shows H8 as a doublet of doublets of doublets at δ4.65 [J(H8-H9b)=ca. 5 Hz; J(H8-H9a)= ca. 8 Hz; J(H8-H15)=1.5 Hz] (measured by decoupling experiments). The coupling constant (ca. 8 Hz) between H8 and H9a seemed to be small for the axial and axial protons in a chair form, and therefore, it was assumed that the B ring would be in a boat form. In the present geometry, the dihedral angles are 167° and 47° for H8-C(8)-C(9)-H9a and H8-C(8)-C(9)-H9b, respectively (Figure 2).

With respect to the preferred conformation of (I) in solution, the results of the nuclear Overhauser effects can provide conclusive proof. As shown in Table 2, the results suggest approaching of H6b proton to both methyl groups, C(13) and C(14), and this fact is compatible with the geometry in the present structure. Thus, since eremophilenolide is confirmed to have the α-oriented O(1) atom, it may be concluded that there will be no other than this all-chair steroid like conformation even in solution.

Table 2 Observed NOE values in NMR spectrum and distance for H---H in crystallographic structure

Proton irradiated	Proton observed	NOE (%) in integrated intensity	distance (Å) for C-H_3---H6b
C(15)H_3	H6b	17	2.3-2.7
C(13)H_3	H6b	9	2.8-3.2
C(14)H_3	H6b	8	2.7-3.2

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References and Footnotes

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5) This program was originally written by T. Ashida (Osaka Univ.) and modified by us, and all calculations were carried out by a NEAC 2200 computer in Tohoku University.

6) M. G. B. Drew, D. H. Templeton, and A. Zalkin, Acta Cryst., B, 25, 261 (1969).

7) We have also undertaken a single-crystal X-ray analysis of bromobenzoate (II) of 6-β-hydroxyeremophilenolide (III). The isolation and the characterization of (III) have been reported by H. Ishii et al.[9] Crystal data of (II), $C_{22}H_{23}O_4Br$, space group: $P2_12_12_1$, a=21.675, b=11.418, c=8.333 Å, Z=4. The molecular structure is consistent with that proposed previously.[11] As shown in a perspective picture of (II) (Figure 4), the carbon skeleton takes quite the same conformation as that of (I).

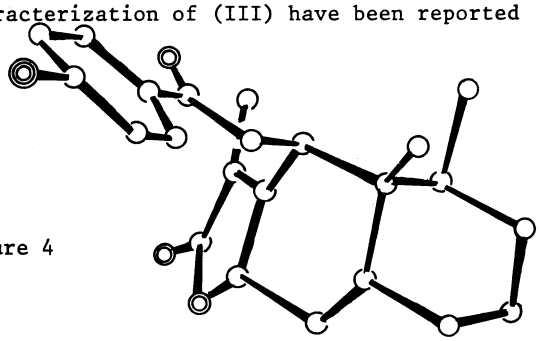

Figure 4

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