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The Crystal and Molecular Structure of Epoxyisoacoragermacrone

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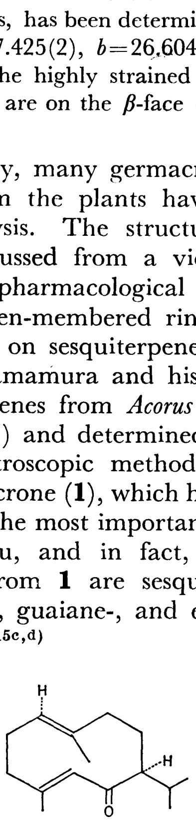
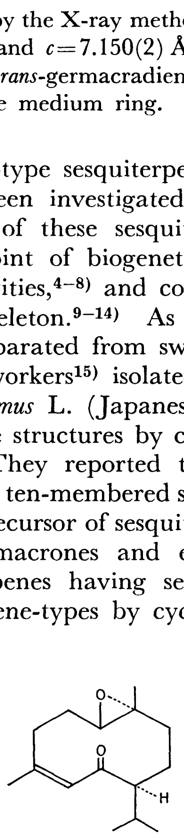
The crystal and molecular structure of epoxyisoacoragermacrone, which is an important derivative of acoragermacrone isolated from *Acorus calamus* L. for the study of the structural organic chemistry and biogenetic reactions, has been determined by the X-ray method. The crystal is orthorhombic, $P2_12_12_1$, with lattice parameters $a=7.425(2)$, $b=26.604(8)$, and $c=7.150(2)$ Å. The ten-membered ring is in a boat-chair conformation similar to the highly strained *cis, trans*-germacradiene system. The methyl groups take the axial and *syn* arrangement, and are on the β-face of the medium ring.

Recently, many germacrane-type sesquiterpenes isolated from the plants have been investigated by X-ray analysis. The structures of these sesquiterpenes were discussed from a viewpoint of biogenetic reactions,[1-3] pharmacological activities,[4-8] and conformations of ten-membered ring skeleton.[9-14] As a series of studies on sesquiterpenes separated from sweet flag oil,[15b] Yamamura and his coworkers[15] isolated many sesquiterpenes from *Acorus calamus* L. (Japanese name "Shyobu") and determined the structures by chemical and spectroscopic methods. They reported that acoragermacrone (**1**), which had a ten-membered skeleton, is one of the most important precursor of sesquiterpenes in Shyobu, and in fact, germacrones and epoxides derived from **1** are sesquiterpenes having selenane-, cadinane-, guaiane-, and elemene-types by cyclization reactions.[15c,d)]



1



2

Epoxyisoacoragermacrone (**2**), 6,7-epoxy-10-isopropyl-3,7-dimethyl-2-cyclodecen-1-one derived from **1**, seems to be an important model compound for the biogenetic model reactions,[15d] and we undertook its X-ray crystal structure analysis.

Experimental

The crystals are of transparent prismatic forms. The space group was determined as $P2_12_12_1$ from the systematic absences observed on the oscillation and Weissenberg photographs. The unit-cell parameters were determined by the least-squares method, using twelve reflections measured on a Hilger & Watts four circle diffractometer with Ni-filtered Cu $K\alpha$ radiation ($\lambda=1.5418$ Å) The intensity data were collected on the diffractometer with the 2θ-ω scanning mode ($2\theta\leqq144°$) using the crystal of $0.3\times0.2\times0.3$ mm sealed in a glass capillary. The intensities of three standard reflections were monitored after every 100 reflections. The standard reflections were stable within 1% fluctuation from their mean values. Neither absorption nor extinction correction was made. The crystal data are given in Table 1.

TABLE 1. CRYSTAL DATA

Chemical formula: $C_{15}H_{24}O_2$
M.W.: 236.36
Space group: $P2_12_12_1$; $Z=4$
$a=7.425(2)$, $b=26.604(8)$, $c=7.150(2)$ Å
$D_c=1.111$ g cm^{-3}
$\mu=5.67$ cm^{-1} (for Cu $K\alpha$ radiation)

Determination and Refinement of the Structure

The structure was determined by the direct method with the program MULTAN[16] using 128 reflections with $|E|\geqq1.40$. An E map computed from the phase set with the highest figure of merit ($FOM=1.43$) revealed the locations of all non-hydrogen atoms. Hydrogen atoms were found on the difference Fourier map. The refinement was performed by the block-diagonal least-squares method with 960 independent reflections of $|F_o|\geqq3\sigma$. R-index converged to 0.060 with an equal weight for each reflection. The atomic scattering factors were taken from "International Tables for X-Ray Crystallography."[17] The least-squares program used for the refinement was written by Katayama, one of the authors. The program ORTEP[18] was used for drawing of Figs. 1—3. A part of the computation was performed at the Nagoya University Computation

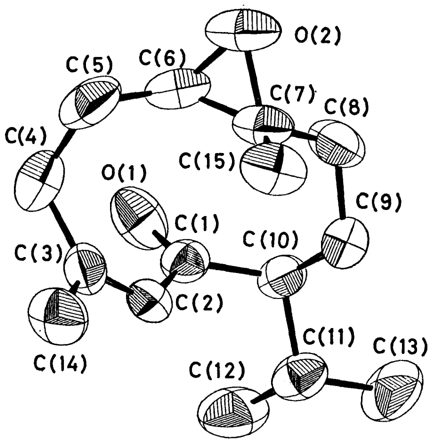


Fig. 1. The atomic numbering of **2**. Carbon and oxygen atoms are represented as thermal ellipsoids of a size such that the vibrating atoms have a 50% probability of being found them. The absolute configuration of the molecule was drawn to be in conformity with the established configuration by a chemical correlation method.

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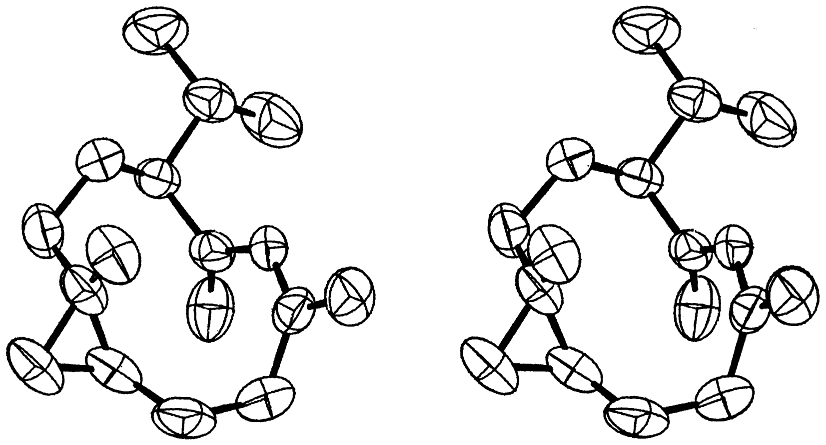

Fig. 2. A stereoscopic view of **2**. The absolute configuration and the criterion to the thermal ellipsoids of carbon and oxygen atoms are the same as in Fig. 1.

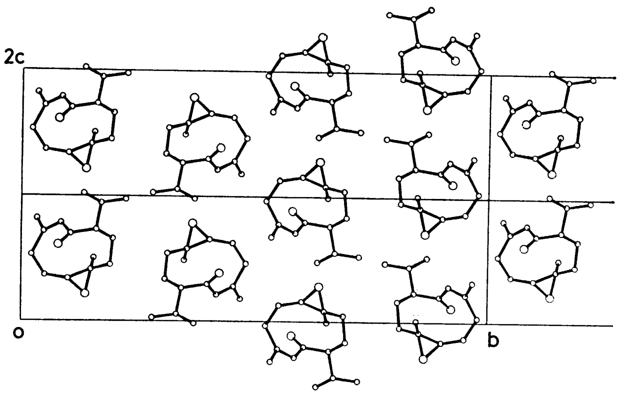

Fig. 3. The crystal structure projected along the a axis. Carbon atoms are depicted as small circles and oxygen atoms as large circles. The configuration is the same as in Fig. 1.

Center. The observed and calculated structure factors are given in Table 2.[19)]

Results and Discussion

The molecular structure with atomic numberings is shown in Fig. 1, where each atom is represented by thermal ellipsoid as having 50% probability. The positional and thermal parameters of non-hydrogen atoms with their standard deviations are given in Tables 3 and 4, respectively. The coordinates and isotropic thermal parameters of hydrogen atoms are given in Table 5. The bond lengths and angles with their standard deviations are listed in Tables 6 and 7, respectively.

The molecule takes a "boat-chair" conformation. An α,β-unsaturated ketone chromophore takes a cisoid configuration, which is not planar, the torsion angle around C(1)–C(2) bond being 33°. The double bond C(2)=C(3) and epoxide group, equivalent to a double bond, are *cis* and *trans* configuration, respectively.

The methyl groups of germacradiene-type sesquiterpenes including *cis*, *trans*-double bonds are *anti* arrangement,[6)] and of other ten-membered ring sesquiterpenes, shiromodiol[9)] and pregeijerene[10)] containing *trans*,*trans*-double bonds are *syn*, while those of melampodin[6)] and haliangine,[14)] *cis*,*trans*-double bonds, are *anti* arrangement. On the other hand, the conformations of the substituents of **2**, the epoxy and isopropyl groups, are semi equatorial and the two methyl groups are axial, *syn* arrangement, and β-orientation.

TABLE 3. ATOMIC COORDINATES AND THEIR STANDARD DEVIATIONS[a)] OF HEAVY-ATOMS

	x	*y*	*z*
O(1)	0.0487(6)	0.0782(2)	0.6129(6)
O(2)	0.4645(7)	0.1362(2)	0.2157(6)
C(1)	0.1535(8)	0.1044(2)	0.7017(8)
C(2)	0.3198(8)	0.0844(2)	0.7855(8)
C(3)	0.4251(8)	0.0481(2)	0.7192(8)
C(4)	0.3909(10)	0.0217(2)	0.5345(10)
C(5)	0.4788(11)	0.0500(2)	0.3698(9)
C(6)	0.3819(9)	0.0993(2)	0.3403(8)
C(7)	0.4475(9)	0.1479(2)	0.4159(8)
C(8)	0.3117(10)	0.1891(2)	0.4539(9)
C(9)	0.2592(9)	0.1944(2)	0.6223(9)
C(10)	0.1108(8)	0.1591(2)	0.7339(8)
C(11)	0.0671(9)	0.1696(2)	0.9442(8)
C(12)	−0.0635(11)	0.1322(3)	1.0197(10)
C(13)	−0.0074(11)	0.2215(2)	0.9734(11)
C(14)	0.5941(9)	0.0330(2)	0.8192(10)
C(15)	0.6282(9)	0.1538(2)	0.5078(9)

a) The standardard deviations are given in parentheses and refer to the last decimal position of respective values.

Ōsawa *et al.*[20)] estimated the ground state conformation for all possible geometrical isomers of hedycaryol, one of the germacradiene-type sesquiterpenes, by the molecular mechanics calculations, and proposed that all the isomer might have more than two stable conformations. Takeda *et al.*[21)] reported that several conformations of the ten-membered ring sesquiterpene should be considered in solution by temperature dependent NMR and NOE measurements. Yamamura *et al.*[15d)] reported the C_{14} methyl group in **2** and in a reaction product of **2** by thiophenol protrudes into α-face of the macrocycle, which is contrary to our results. Therefore, it seems likely that the molecule

Table 4. Anisotropic thermal factors$^{a)}$ ($\times 10^4$) and their standard deviations of heavy-atoms

	B_{11}	B_{22}	B_{33}	B_{12}	B_{23}	B_{31}
O(1)	226(9)	22(1)	359(13)	−25(5)	−58(6)	−14(22)
O(2)	329(12)	38(1)	161(10)	27(7)	1(6)	35(21)
C(1)	207(12)	16(1)	169(12)	−17(6)	−5(6)	85(25)
C(2)	217(13)	14(1)	175(12)	9(6)	18(6)	−18(24)
C(3)	251(14)	12(1)	246(15)	−2(6)	13(6)	76(29)
C(4)	335(18)	16(1)	346(19)	14(8)	−43(8)	25(39)
C(5)	354(20)	25(1)	258(17)	39(9)	72(8)	38(34)
C(6)	255(15)	29(1)	153(13)	2(8)	−28(7)	1(27)
C(7)	271(16)	25(1)	149(13)	10(8)	10(7)	63(28)
C(8)	313(18)	21(1)	206(15)	15(8)	39(7)	21(30)
C(9)	275(15)	14(1)	237(16)	3(7)	−12(7)	0(30)
C(10)	206(12)	16(1)	173(13)	24(6)	−17(6)	−49(24)
C(11)	199(13)	21(1)	213(14)	24(7)	−25(7)	−40(26)
C(12)	376(22)	34(2)	240(18)	−8(11)	−15(10)	182(37)
C(13)	398(23)	25(1)	350(20)	81(10)	−60(9)	29(42)
C(14)	263(16)	24(1)	301(18)	62(8)	21(9)	−20(35)
C(15)	198(14)	30(1)	262(17)	−35(8)	20(8)	−47(29)

a) The anisotropic thermal factors are of the form $\exp\{-(h^2B_{11}+k^2B_{22}+l^2B_{33}+hkB_{12}+hlB_{31}+klB_{23})\}$.

Table 5. Hydrogen atom parameters and their standard deviations

	x	y	z	B/Å^2
H(2)	0.357(7)	0.099(2)	0.880(7)	2.8(1.4)
H(4a)	0.448(8)	−0.014(2)	0.540(8)	3.7(1.4)
H(4b)	0.245(7)	0.019(2)	0.513(7)	2.4(1.3)
H(5a)	0.623(8)	0.055(2)	0.391(8)	4.9(1.6)
H(5b)	0.490(11)	0.026(2)	0.269(11)	9.8(2.3)
H(6)	0.251(7)	0.094(2)	0.325(8)	2.8(1.3)
H(8a)	0.361(9)	0.225(2)	0.422(9)	5.2(1.7)
H(8b)	0.205(8)	0.184(2)	0.387(8)	4.1(1.6)
H(9a)	0.212(8)	0.232(2)	0.678(8)	3.6(1.4)
H(9b)	0.376(8)	0.190(2)	0.725(8)	4.7(1.6)
H(10)	−0.012(8)	0.167(2)	0.662(7)	3.5(1.4)
H(11)	0.174(8)	0.169(2)	1.005(8)	4.1(1.5)
H(12a)	−0.089(9)	0.097(2)	0.995(9)	6.7(1.8)
H(12b)	−0.065(8)	0.134(2)	1.133(8)	5.1(1.7)
H(12c)	−0.202(8)	0.133(2)	0.970(9)	5.6(1.7)
H(13a)	−0.145(8)	0.227(2)	0.922(9)	5.0(1.7)
H(13b)	−0.023(9)	0.235(2)	1.071(9)	6.4(1.9)
H(13c)	0.050(9)	0.248(2)	0.903(8)	5.3(1.7)
H(14a)	0.588(9)	−0.008(2)	0.844(9)	6.4(1.9)
H(14b)	0.682(8)	0.030(2)	0.736(8)	4.4(1.6)
H(14c)	0.640(8)	0.056(2)	0.922(9)	5.2(1.7)
H(15a)	0.699(8)	0.121(2)	0.463(9)	5.4(1.7)
H(15b)	0.712(9)	0.189(2)	0.471(10)	7.3(2.0)
H(15c)	0.628(8)	0.147(2)	0.617(8)	3.6(1.5)

Table 6. Bond lengths and their standard deviations (Å)

O(1)-C(1)	1.223(7)	O(2)-C(6)	1.460(8)
O(2)-C(7)	1.471(8)	C(1)-C(2)	1.472(8)
C(1)-C(10)	1.506(8)	C(2)-C(3)	1.329(8)
C(3)-C(4)	1.517(10)	C(3)-C(14)	1.499(9)
C(4)-C(5)	1.544(11)	C(5)-C(6)	1.509(10)
C(6)-C(7)	1.484(9)	C(7)-C(8)	1.514(10)
C(7)-C(15)	1.502(9)	C(8)-C(9)	1.547(10)
C(9)-C(10)	1.535(9)	C(10)-C(11)	1.564(8)
C(11)-C(12)	1.490(10)	C(11)-C(13)	1.503(10)
C(i)-H(i)			
average	0.99		
range	0.80—1.15		

can take many conformations in solution.21) The conformation of the medium ring of **2** is same as a less stable geometrical isomer of hedycaryol.20)

Dunitz22) distinguished between the conformers of ten-membered ring in terms of the endocyclic torsion angles. The torsion angles of some compounds having ten-membered ring are shown in Table 8. Each torsion angle of **2** is very similar to that of melampodin6) and enhydrin,8) which belongs to a highly strained *cis,trans*-germacradiene system. In dihydromikanolide3) and pregeijerene,10) however, several bonds are distorted in the opposite directions by about same magnitude compared with **2**.

The bond lengths are all normal except the C(6)–C(7) bond in the epoxide ring being significantly shorter than a normal single bond and the bond angle C(5)–C(6)–C(7), 123.3(6)°, indicates a remarkable deformation due to the epoxide ring formation. The similar distortion of the endocyclic bond angle was found in the other ten-membered ring epoxide, agerol diepoxide (127.2(6) and 125.0(5)),1) dihydromikanolide (122.4(4)),3) and elephantol *p*-bromobenzoate (124(1)°).5)

Some of the non-bonded intramolecular distances are somewhat short, O(1)···C(6) being 3.199(8), C(1)···C(6), 3.094(9), C(1)···C(7), 3.206(9), C(2)···C(6), 3.240(9), and C(2)···C(7), 3.276(9)Å. A stereoview of the molecule is shown in Fig. 2, and the molecular packing in the crystal in Fig. 3. All intermolecular contacts are normal.

TABLE 7. BOND ANGLES AND THEIR STANDARD DEVIATIONS (°)

C(6)-O(2)-C(7)	60.8(4)	O(1)-C(1)-C(2)	122.6(5)
O(1)-C(1)-C(10)	119.7(5)	C(2)-C(1)-C(10)	117.7(5)
C(1)-C(2)-C(3)	127.7(6)	C(2)-C(3)-C(4)	123.2(6)
C(2)-C(3)-C(14)	121.2(6)	C(4)-C(3)-C(14)	115.5(6)
C(3)-C(4)-C(5)	111.5(6)	C(4)-C(5)-C(6)	109.2(6)
O(2)-C(6)-C(7)	117.9(6)	O(2)-C(6)-C(7)	59.9(4)
C(5)-C(6)-C(7)	123.3(6)	O(2)-C(7)-C(6)	59.2(4)
O(2)-C(7)-C(8)	122.7(5)	O(2)-C(7)-C(15)	111.8(5)
C(6)-C(7)-C(8)	118.6(6)	C(6)-C(7)-C(15)	122.9(6)
C(8)-C(7)-C(15)	116.1(6)	C(7)-C(8)-C(9)	113.9(6)
C(8)-C(9)-C(10)	116.5(5)	C(1)-C(10)-C(9)	112.8(5)
C(1)-C(10)-C(11)	111.3(5)	C(9)-C(10)-C(11)	111.1(5)
C(10)-C(11)-C(12)	111.4(5)	C(10)-C(11)-C(13)	112.0(5)
C(12)-C(11)-C(13)	108.9(6)		

TABLE 8. ENDOCYCLIC TORSION ANGLES (°)[a] OF SOME TEN-MEMBERED RING

	(A)[b]	(B)[b]	(C)[b]	(D)[b]	(E)[b]
ω(1-2)	148	132	125	128	116
ω(2-3)	−2	13	4	−2	−2
ω(3-4)	−87	−97	−56	−86	−90
ω(4-5)	69	75	14	58	73
ω(5-6)	−98	−92	−54	66[c]	57[c]
ω(6-7)	154	147	155	−165[c]	−153[c]
ω(7-8)	−101	−119	−101	101[c]	66[c]
ω(8-9)	84	95	76	−59[c]	−3[c]
ω(9-10)	−56	−63	−71	−82	55[c]
ω(10-1)	−59	−56	−44	−150	−163

a) The sign is negative if an anticlockwise rotation is required of atom(1) to eclipse atom(4) whilst looking down the (2)-(3) bond. b) (A) present work; (B) enhydrin, renumbered from Ref. 8; (C) melampodin, renumbered and inverted from Ref. 6; (D) 1:1 adduct of pregeijerene with silver nitrate, renumbered from Ref. 10; (E) dihydromikanolide, renumbered from Ref. 3. c) The rotations of these bonds are in the opposite directions compared to (A).

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