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The Molecular and Crystal Structures of Two Derivatives of a Sesterterpene, Ophiobolin D

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The structures of two derivatives of a sesterterpene, ophiobolin D, were determined by X-ray crystallographic analyses. The final *R*-factors were 0.09 for both compounds. On the basis of their stereo-structures, it is suggested that the compounds are formed by different types of transannular reaction in an eight-membered ring, *i.e.*, a migration of a double bond and a cyclization to yield a novel ring system composed of four fused five-membered rings.

Keywords——sesterterpene; eight-membered ring; transannular reaction; pyrolytic decarboxylation; X-ray crystallography

Introduction

The structure of ophiobolin D (I), a sesterterpenic fungal metabolite, has previously been determined by the X-ray crystal structure analysis of a heavy atom derivative.[2]

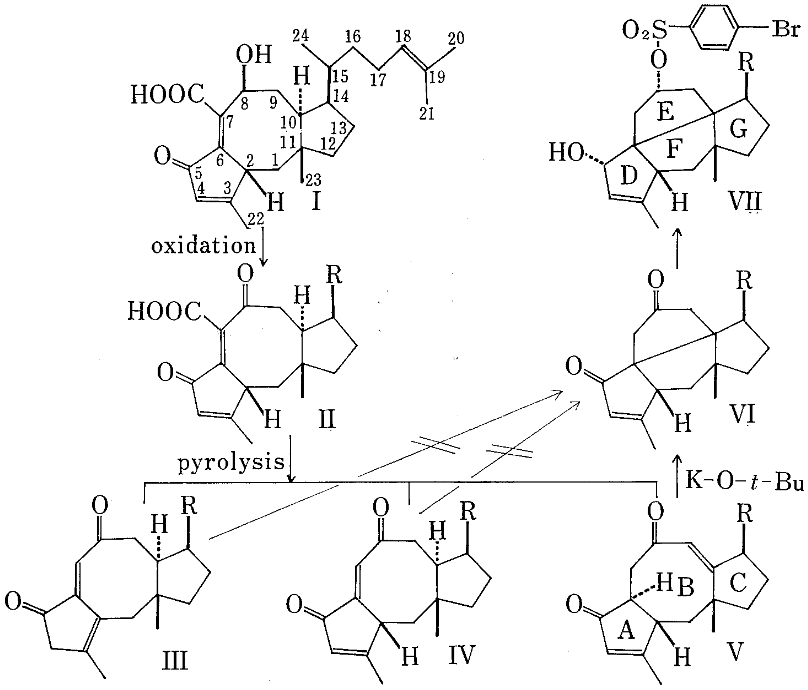

Fig. 1. Reaction Scheme and Chemical Structures together with Ring Designations

The structures of V, VI and VII are depicted on the basis of the present X-ray structure analyses.

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[1] Location: *a) Hongo, Bunkyo-ku, Tokyo*; *b) Aobayama, Sendai.*

[2] *a)* A. Itai, S. Nozoe, K. Tsuda, S. Okuda, Y. Iitaka, and Y. Nakayama, *Tetrahedron Lett.*, **1967**, 4111; *b)* A. Itai, S. Nozoe, S. Okuda, and Y. Iitaka, *Acta Cryst.*, **B25**, 872 (1969).

I was easily oxidized to dehydroophiobolin D (II) with an equimolar amount of Kiliani's reagent. As already reported,[3] II can be decarboxylated by heating to just above its melting point, to afford three products, III, IV, and V, all of which have the same molecular formulae. The structures of III and IV were determined physicochemically[4] as shown in Fig. 1, but the structure of V was left undetermined because its spectral properties were very different from those of the other two. Compound V is quantitatively converted to a tetracyclic compound VI by the addition of a trace of potassium *tert*-butoxide in *tert*-butyl alcohol. Neither III nor IV yields VI, even under more rigorous conditions.

We have carried out X-ray crystal and molecular structure analyses of V and VII, a heavy atom derivative of VI, making it possible to discuss the reaction mechanisms which lead to their formation. As a result, it is thought that two different types of transannular reaction of the eight-membered ring occur during the pyrolysis and the alkali treatment. Details of these reactions will be discussed in the following paper. This paper also includes a revision of the structure of compound V, which was erroneously assigned in our previous paper.[3] We had assigned the third pyrolysis product, yielding compound VI, as the C_2 epimer of compound IV.

Experimental

Crystal data are listed in Table I. Cell constants were determined from the precession photographs and intensity data were collected from multi-film equi-inclination Weissenberg photographs using Ni-filtered Cu *Kα* radiation. A microdensitometer was used for measuring the intensities on the films. The Weissenberg photographs were taken about the *a*-axis (0—3 rd layer) and *b*-axis (0—6 th layer) with the crystal of V, and about the *a*-axis (0—5 th layer) and *b*-axis (0—6 th layer) with that of VII.

TABLE I. Crystal Data for Compounds V and VII

	Compound V	Compound VII
Molecular formula	$C_{24}H_{34}O_2$	$C_{30}H_{41}BrO_4S$
Molecular weight	354.5	577.6
Color and habit	Colorless plates	Red-brown prism
Size, mm	0.3×0.2×0.1	0.2×0.1×0.1
Crystal system	Monoclinic	Monoclinic
a, Å	10.07±0.02	10.17±0.02
b, Å	8.28±0.02	8.56±0.02
c, Å	26.38±0.04	16.75±0.03
β, degree	97.1 ±0.3	90.4 ±0.3
Absent reflections	$(h\ k\ l)$; $h+k=2n+1$	$(0\ k\ 0)$; $k=2n+1$
Space group	$C2$	$P2_1$
Z	4	2
Density (measured), g/cm³	1.081	1.319
Density (calculated), g/cm³	1.077	1.315

In the case of V, the scalings between the reflections with h=odd and k=odd and those of h=even and k=even were carried out separately by calculating the scale factors with Wilson plots. The total numbers of independent and non-zero reflections were 1678 and 1264, respectively. These were corrected for Lorentz and polarization factors, but not for absorption or extinction.

The structure of V was solved by the direct method using the program MULTAN.[5] An E-map, calculated with 234 reflections of $E \geq 1.55$ taking into account even relatively weak $\sum 1$ relations to the starting phases, revealed the whole structure. The structure was refined by block-diagonal least-squares calculations. Eight hydrogens were located on a difference electron density map. Several cycles of refinement gave an

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3) S. Nozoe, A. Itai, and Y. Iitaka, *J. Chem. Soc.*, sect. D, **1971**, 872.

4) S. Nozoe, A. Itai, K. Tsuda, and S. Okuda, *Tetrahedron Lett.*, **1967**, 4113.

5) P. Main, M.M. Woolfson, and G. Germain (1971) *MULTAN*, A Computer Program for the Automatic Solution of Crystal Structures, Universities of York (England) and Leuven (Belgium).

R-index of 0.09, assuming anisotropic vibrations for non-hydrogen atoms and isotropic ones for hydrogen atoms. The weighting system was: $\sqrt{w}=0.7$ when $|Fo|<1.0$; $\sqrt{w}=1.0$ when $1.0\leq|Fo|<10.0$; $\sqrt{w}=10.0/|Fo|$ when $|Fo|\geq 10.0$. The final atomic parameters of V are listed in Table II(a).

The structure of VII was solved by the heavy atom method, as described in the previous paper,[3] and was refined anisotropically to a final *R*-index of 0.095. The unit weight was assumed for all reflections. The final atomic parameters of VII are listed in Table II(b). Atomic scattering factors for C and O atoms were those given in *International Tables for X-ray Crystallography* (1962)[6] and for H atoms they were those given by Stewart, Davidson and Simpson (1965).[7]

TABLE II. Fractional Coordinates and Temperature Factors ($\times 10^4$)
The anisotropic temperature factors are of the form:

$$T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$$

(a) Compound V

	x	y	z	$\beta11$	$\beta22$	$\beta33$	$\beta12$	$\beta13$	$\beta23$
O (1)	6818(5)	278(0)	4456(2)	156(7)	151(11)	23(1)	47(7)	−16(2)	17(3)
O (2)	2821(5)	−1336(7)	3168(2)	149(6)	89(9)	27(1)	−62(6)	6(2)	−9(3)
C (1)	4374(6)	4334(8)	3371(2)	94(6)	53(10)	13(1)	6(6)	−1(2)	−4(2)
C (2)	4623(5)	3374(8)	3866(2)	70(5)	72(11)	11(1)	17(6)	4(2)	0(2)
C (3)	5608(6)	4184(9)	4277(2)	93(6)	107(13)	12(1)	−19(7)	5(2)	−7(3)
C (4)	6484(6)	3144(10)	4523(2)	105(7)	168(16)	13(1)	−7(9)	−6(2)	0(3)
C (5)	6253(6)	1524(9)	4308(2)	101(7)	154(15)	12(1)	15(9)	−5(2)	12(3)
C (6)	5226(5)	1672(8)	3826(2)	67(5)	63(11)	12(1)	−2(6)	1(2)	5(2)
C (7)	4237(6)	239(9)	3767(3)	88(6)	91(12)	18(1)	14(7)	7(2)	12(3)
C (8)	3612(6)	−196(7)	3235(3)	78(6)	34(11)	19(1)	19(6)	6(2)	5(3)
C (9)	4049(5)	614(7)	2778(2)	83(5)	36(11)	14(1)	26(6)	1(2)	−1(2)
C (10)	4012(5)	2191(8)	2657(2)	61(5)	97(12)	12(1)	8(6)	−3(2)	−7(2)
C (11)	3361(5)	3575(8)	2936(2)	76(5)	45(10)	13(1)	33(6)	−4(2)	−5(2)
C (12)	3061(8)	4861(9)	2504(3)	180(10)	82(14)	13(1)	48(9)	−8(2)	6(3)
C (13)	4254(9)	4698(10)	2182(3)	211(12)	92(15)	16(1)	25(10)	1(3)	14(3)
C (14)	4579(6)	2861(9)	2188(2)	102(6)	122(13)	12(1)	10(7)	2(2)	5(3)
C (15)	4036(8)	1914(10)	1690(2)	184(10)	124(15)	12(1)	21(10)	11(2)	1(3)
C (16)	4627(10)	2472(15)	1203(3)	201(13)	348(27)	14(1)	52(15)	11(3)	9(5)
C (17)	6119(11)	2265(26)	1225(4)	182(14)	772(60)	22(2)	−17(25)	6(4)	38(9)
C (18)	6499(13)	2820(33)	679(5)	215(17)	1005(90)	30(3)	−36(33)	37(6)	5(13)
C (19)	7744(11)	2944(21)	569(4)	189(14)	565(45)	24(2)	−43(21)	23(4)	−11(8)
C (20)	8082(12)	3661(32)	45(5)	266(21)	821(66)	23(2)	−19(35)	25(5)	2(11)
C (21)	8938(11)	2653(21)	930(5)	181(14)	455(38)	34(2)	29(19)	10(5)	35(8)
C (22)	5533(8)	5964(10)	4386(3)	180(10)	94(13)	15(1)	10(9)	9(3)	−13(3)
C (23)	2028(6)	3069(9)	3149(3)	67(6)	138(15)	21(1)	33(7)	2(2)	−12(3)
C (24)	2456(10)	2030(16)	1570(4)	185(13)	339(27)	22(2)	−56(16)	−16(4)	−19(6)

(b) Compound VII

	x	y	z	$\beta11$	$\beta22$	$\beta33$	$\beta12$	$\beta13$	$\beta23$
BR	4422(3)	0(0)	10988(2)	131(3)	285(6)	71(1)	−11(5)	29(2)	46(3)
S	10064(6)	656(7)	9383(3)	119(7)	102(8)	21(2)	−2(7)	9(3)	11(4)
O (1)	9950(17)	7195(18)	7466(9)	172(23)	91(25)	39(6)	−25(22)	−2(10)	8(11)
O (2)	10104(13)	2261(16)	9035(7)	110(17)	89(21)	17(4)	2(17)	7(7)	−1(9)
O (3)	10180(18)	−494(18)	8758(8)	241(27)	114(29)	32(6)	−13(22)	32(10)	−13(10)
O (4)	10993(14)	686(20)	10003(8)	111(18)	205(31)	34(6)	−18(22)	−5(8)	42(13)
C (1)	8155(24)	2358(34)	6393(12)	120(30)	242(54)	20(8)	−42(37)	−4(13)	−18(19)
C (2)	7711(21)	4094(29)	6747(12)	116(29)	152(42)	25(8)	36(30)	−20(12)	3(16)
C (3)	7530(23)	5464(34)	6189(14)	132(29)	209(56)	46(10)	−67(37)	36(14)	−34(21)
C (4)	8106(26)	6777(27)	6454(14)	168(35)	86(40)	45(11)	−26(31)	35(16)	−4(17)

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6) "International Tables for X-ray Crystallography," Vol. III, Kynoch Press, Birmingham, 1962, p. 202.
7) R.F. Stewart, E.R. Davidson, and W.T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).

	x	y	z	β11	β22	β33	β12	β13	β23
C (5)	8762(25)	6422(29)	7286(13)	150(34)	124(40)	40(10)	−5(33)	32(15)	−0(17)
C (6)	8847(21)	4582(24)	7285(9)	157(29)	115(38)	1(5)	47(29)	5(10)	11(12)
C (7)	8811(20)	3952(28)	8171(10)	82(23)	163(39)	20(7)	68(28)	26(11)	5(15)
C (8)	9690(22)	2513(27)	8192(11)	115(27)	139(41)	21(8)	2(28)	10(12)	−16(15)
C (9)	10831(19)	3023(25)	7676(11)	62(21)	109(35)	22(7)	32(25)	7(11)	−1(13)
C (10)	10153(18)	3749(23)	6926(9)	79(22)	78(31)	11(6)	0(23)	23(10)	8(12)
C (11)	9635(21)	2544(25)	6305(9)	137(29)	118(38)	−0(5)	1(27)	−8(10)	3(12)
C (12)	9995(23)	3237(30)	5469(12)	136(32)	148(42)	28(9)	−36(32)	12(14)	4(16)
C (13)	11342(20)	3943(29)	5649(10)	102(26)	163(40)	14(7)	−29(30)	14(11)	−11(15)
C (14)	11104(18)	4956(31)	6421(10)	101(22)	106(32)	24(7)	29(30)	11(11)	−10(15)
C (15)	12365(20)	5519(27)	6831(12)	102(24)	113(38)	33(8)	43(28)	9(12)	−2(16)
C (16)	12732(27)	7017(28)	6331(13)	230(44)	76(39)	34(9)	49(34)	25(17)	−2(16)
C (17)	13969(25)	7991(36)	6678(17)	112(31)	265(62)	67(14)	120(40)	45(17)	63(25)
C (18)	13483(26)	8826(32)	7379(15)	162(37)	129(43)	53(12)	32(35)	−2(17)	−5(20)
C (19)	14301(26)	9823(33)	7845(14)	206(38)	105(40)	49(11)	−0(41)	27(17)	21(20)
C (20)	13791(31)	10644(33)	8593(14)	278(50)	143(45)	35(10)	−7(43)	−3(18)	5(20)
C (21)	15727(36)	10010(81)	7631(22)	259(56)	666(153)	91(21)	−201(105)	82(29)	−61(57)
C (22)	6711(25)	5320(60)	5425(15)	122(30)	576(115)	42(12)	−9(64)	−35(15)	−41(34)
C (23)	10223(30)	867(31)	6388(13)	239(43)	137(44)	27(9)	30(38)	24(16)	−13(17)
C (24)	13436(23)	4386(41)	6868(15)	94(27)	374(88)	51(12)	16(41)	13(15)	37(26)
C (25)	6126(20)	237(34)	10490(13)	96(25)	211(55)	47(10)	9(35)	1(13)	59(21)
C (26)	6506(29)	−1061(31)	10024(18)	184(41)	67(37)	85(16)	−27(34)	17(20)	−16(21)
C (27)	7698(29)	−852(28)	9650(13)	245(47)	84(39)	35(10)	32(35)	−28(17)	14(16)
C (28)	8394(19)	474(24)	9804(9)	108(23)	105(36)	7(5)	−11(27)	1(10)	23(12)
C (29)	8037(27)	1651(33)	10286(15)	185(40)	178(52)	42(11)	−32(38)	26(17)	−56(20)
C (30)	6833(29)	1443(42)	10699(16)	195(42)	343(74)	44(12)	−88(49)	66(19)	−74(25)

Discussion

The molecular structures of V and VII are shown in Fig. 2a and 2b as ORTEP drawings, referring to the absolute configuration determined for the crystal of methyl ophiobolin D bromoacetate (a heavy atom derivative of I).[2)] Chemical structures are illustrated in Fig. 1, together with the ring designations. Bond distances and bond angles along with the atomic numberings of V and VII are shown in Fig. 3a and 3b, respectively.

In V, the C_9 and C_{10} atoms are double-bonded unlike the C_6 and C_7 atoms in I, II, III, and IV; this is consistent with the shorter C_9—C_{10} bond length (1.343 Å) and the longer C_6—C_7

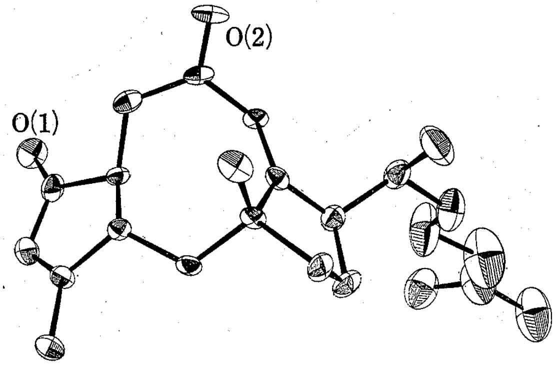

Fig. 2a. Perspective View of the Molecule of Compound V

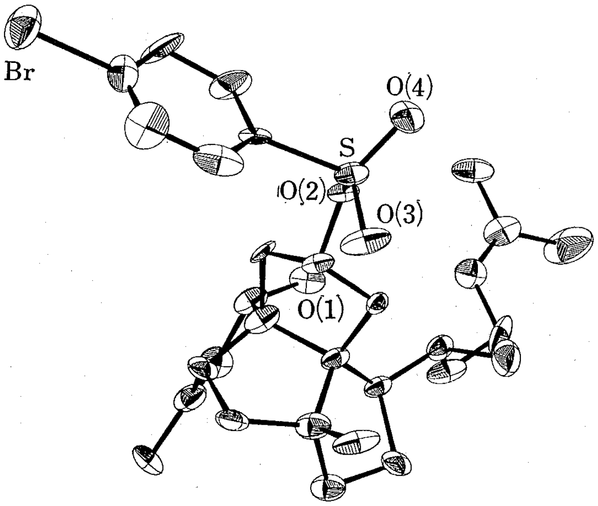

Fig. 2b. Perspective View of the Molecule of Compound VII

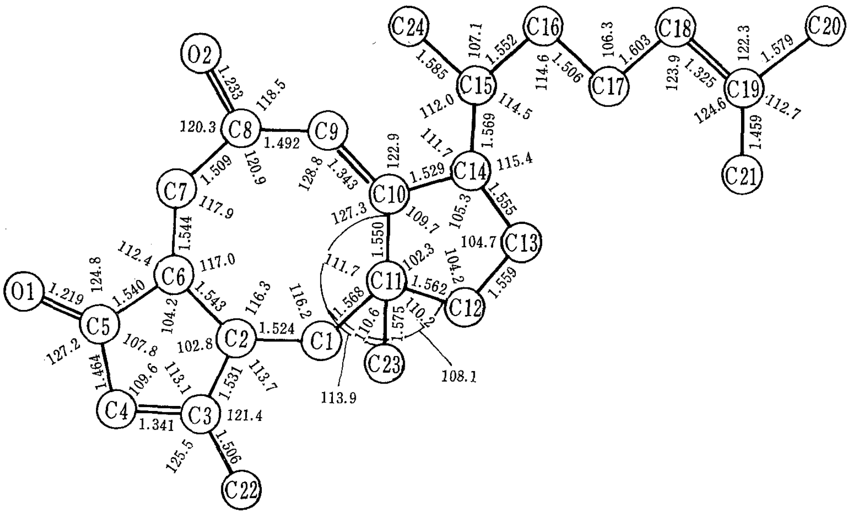

Fig. 3a. Bond Distances (Å) and Bond Angles (°) along with Atomic numbering in Compound V

The average estimated standard deviations of the values are 0.01 Å and 0.6°, respectively.

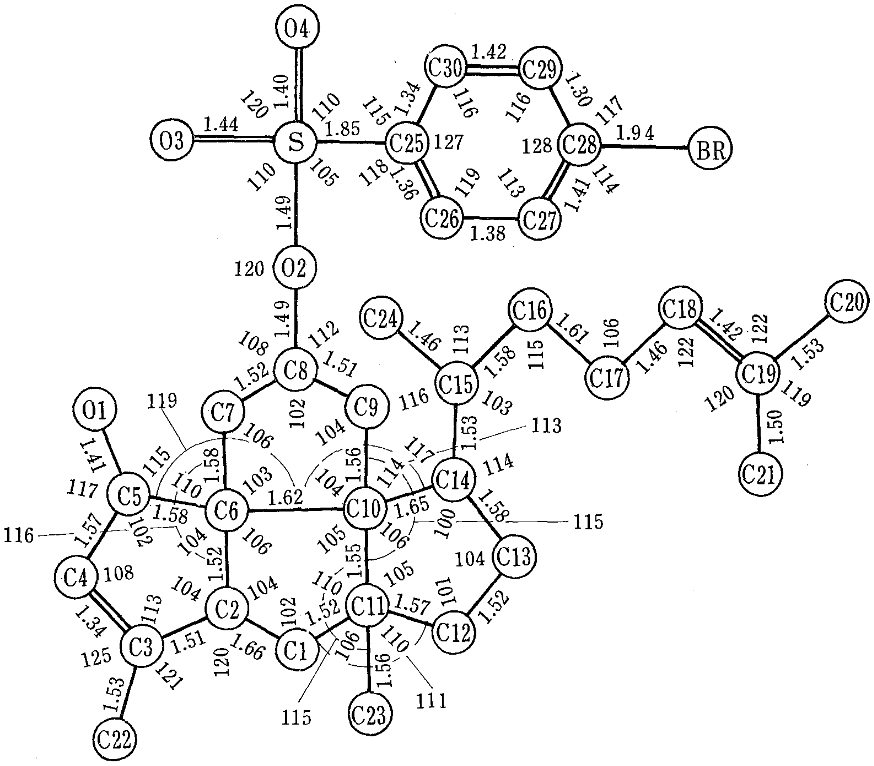

Fig. 3b. Bond Distances (Å) and Bond Angles (°) together with Atomic numbering in Compound VII

The average estimated standard deviations of the values are 0.03 Å and 1.5°, respectively.

bond (1.544 Å) as well as the larger C_8–C_9–C_{10} (128.8°) and C_9–C_{10}–C_{11} (127.3°) angles and the smaller C_2–C_6–C_7 (117.0°) and C_6–C_7–C_8 (117.9°) angles. It is also consistent with the UV spectra. The absorption maximum of V (λ_{max} 232 nm) is at considerably shorter wavelength than those of I (259 nm), II (258 nm) and IV (255 nm), all of which have cisoid type α,β-unsaturated ketone conjugation (O_1=C_5–C_6=C_7). Since the hydrogen atom at C_6 is in the α-orientation and the one at C_2 retains the β-orientation, the junction of the five-membered ring A and the eight-membered ring B should be *trans* in V. It was proved that compound VII has a novel ring system consisting of four fused five-membered rings, D, E, F, and G, and all the ring junctions (between D and F, E, and F, and F and G) are *cis*. The hydroxyl group at C_5 and the *p*-bromobenzene-sulfonyl group at C_8[8] are both in the α-orientation. The configurations of C_2, C_{11}, C_{14}, and C_{15} in both V and VII are the same as those in ophiobolin D (I).

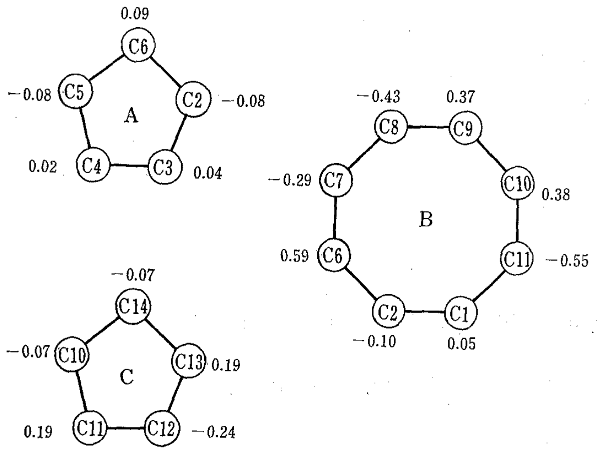

Fig. 4a. The Deviations (Å) of the Atoms from the Least-squares Planes of the Rings in Compound V

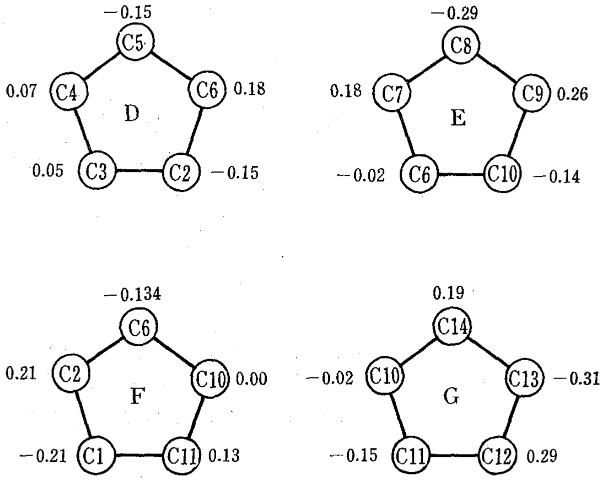

Fig. 4b. The Deviations (Å) of the Atoms from the Least-squares Planes of the Rings in Compound VII

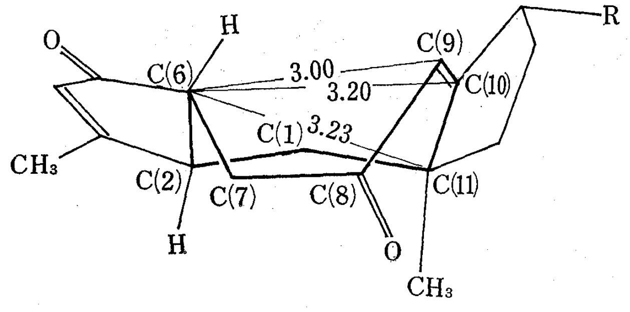

Fig. 5a. Schematic Drawing of the Conformation of the Eight-membered Ring in V, together with the Close Transannular Interatomic Distances (Å)

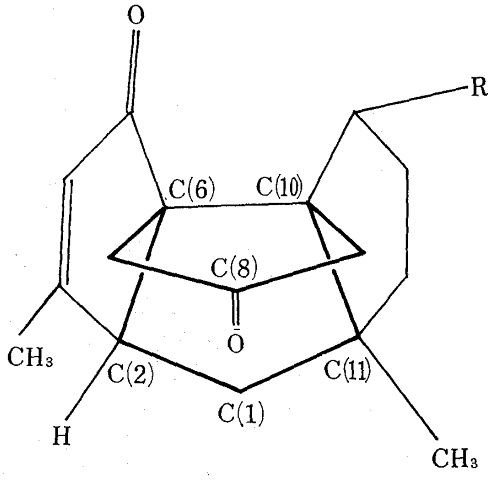

Fig. 5b. Structure Model of VI deduced from the Structure of VII

The numerical values in Fig. 4a and 4b indicate the deviations of each atom from the least-squares planes of the rings in V and VII, respectively. Ring A is almost planar, while ring C takes an envelope conformation with C_{12} serving as a flap corner. Ring D adopts an envelope conformation, while rings E, F, and G have half-chair conformation. The eight-membered ring B seems to take an unfavorable tub-like conformation, probably due to two five-membered rings, one of which (A) is fused *trans* and the other of which (C) is connected through an exocyclic double bond to ring B. Fig. 5a and 5b show schematic drawings of the conformation of ring B in V and a proposed structure for VI deduced from VII which accounts well for the quantitative conversion of V to VI by mild alkali treatment. The three carbons at C_6, C_9, and C_{10} in

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[8] The orientation of the *p*-bromobenzene-sulfonyl group in the chemical structure of compound VII, which was incorrectly drawn in our previous paper, should be revised to the α-orientation.

ring B project remarkably in the same direction from the ring plane formed by C_1, C_2, C_7, C_8, and C_{11}. The close transannular interatomic distances are also shown in Fig. 5a. The distances C6···C9 (3.00 Å), C6···C10 (3.20 Å) and C6···C11 (3.23 Å) are short enough to permit a facile transannular cyclization reaction. The active carbon at C_6 in V adjacent to the carbonyl (C_5=O_1) should be easily converted to a carbanion and may attack position 10 nucleophilically, while C_{10} has electrophilic properties induced by the carbonyl (C_8=O_2) and transmitted by the C_9–C_{10} double bond, resulting in the formation of the C_6–C_{10} bond in VI and VII. The reaction is considered to be accelerated by the ring strain of the eight-membered ring. The large strain

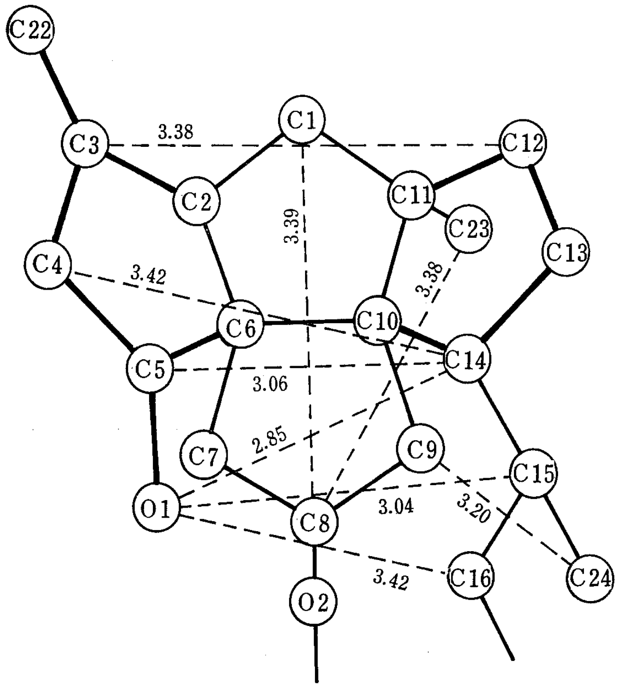

Fig. 6. Schematic Drawing of the Ring Skeleton of VII together with the Intramolecular Close Interatomic Distances (A)

Table III. Dihedral Angles between the Least-squares Planes of the Four Five-membered Rings in Compound VII

	D	E	F
E	92.0°		
F	114.1°	100.5°	
G	123.7°	94.6°	122.1°

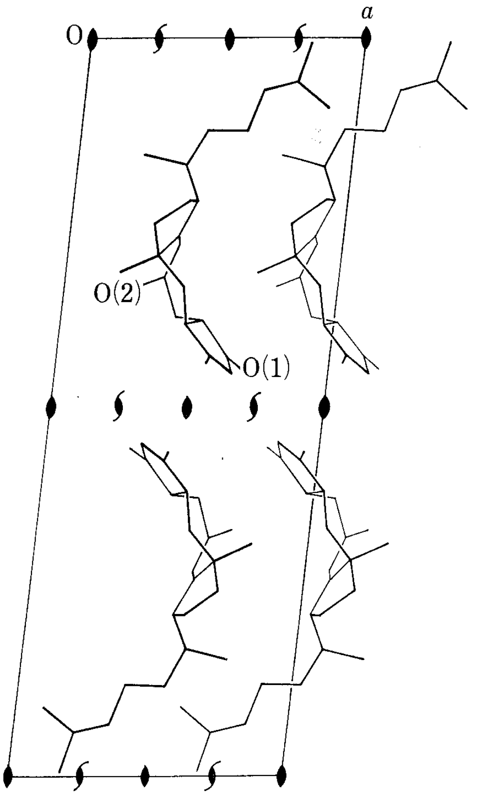

Fig. 7a. The Projection of the Crystal Structure along the *b*-axis in Compound V

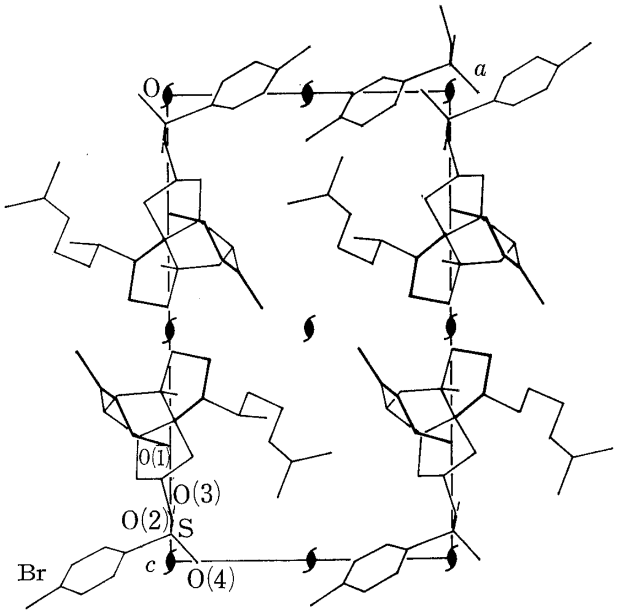

Fig. 7b. The Projection of the Crystal Structure along the *b*-axis in Compound VII

of the eight-membered ring may result in the lack of coplanarity of the α,β-unsaturated ketone (O_2=C_8–C_9=C_{10}). The O_2 atom is 0.86 Å away from the mean plane of the double bond composed of C_8, C_9, C_{10}, C_{11}, and C_{14}, in which there is no twisting. The dihedral angle of 53.1° between the two planes (C_8–C_9–C_{10} and O_2–C_8–C_9) is one of the largest reported so far among distorted α,β-unsaturated ketones.

In the molecule of VII, the atoms are close to each other due to the all-*cis* ring junctions, as shown in Fig. 6. The distances $O_1\cdots C_{14}$ (2.85 Å), $O_1\cdots C_{15}$ (3.04 Å) and $C_5\cdots C_{14}$ (3.06 Å) seem to be the shortest allowable as the sum of individual van der Waals radii. The interplanar angles between the mean planes of the five-membered rings are listed in Table III.

Thermal vibrations of atoms in the side chains are large, as shown in Fig. 2. The side chain of V extends in a *trans* zig-zag conformation, while that of VII takes a rather folded conformation due to the *gauche* angle of C_{15}–C_{16}–C_{17}–C_{18}, 72°.

Fig. 7a and 7b are the projections of the crystal structures of V and VII, respectively, along the *b*-axis. Molecules are packed by van der Waals contacts in V. However, in VII, the O_1–H$\cdots O_3$ hydrogen bonding between the hydroxyl and a sulfonyl group of the adjacent molecule translated along the *b*-axis ($O_1\cdots O_3$, 2.94 Å) links the molecules to form infinite chains along the *b*-axis.