

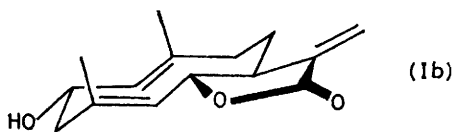
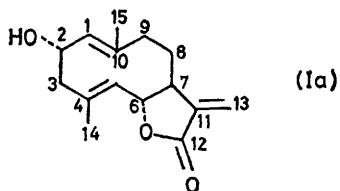
## Crystal and Molecular Structure of Tamaulipin-A, a *trans,trans*-Germacra-1(10),4-dienolide Sesquiterpene Lactone

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The crystal and molecular structure of tamaulipin-A (I),  $C_{15}H_{20}O_3$ , has been determined by single-crystal *X*-ray diffraction. Crystals are orthorhombic, space group  $P2_12_12_1$ ,  $a = 7.890(9)$ ,  $b = 11.957(13)$ ,  $c = 14.649(17)$  Å,  $Z = 4$ . The structure was solved from diffractometer data by direct phasing techniques and refined by full-matrix least-squares to  $R$  8.1% over 732 reflections. The cyclodecadiene ring is in the chair-chair conformation, the methyl groups attached to C(4) and C(10) are in the *syn*- $\beta$  orientation (absolute configuration inferred from independent data), and the  $\alpha$ -methylene- $\gamma$ -lactone is *trans*-fused at C(6) and C(7) with H(6) $\beta$  and H(7) $\alpha$ . Weak intermolecular hydrogen bonds exist between the hydroxy-group at C(2) and the lactone carbonyl [H  $\cdots$  O 2.2(1), O  $\cdots$  O 3.00(1) Å].

THE *trans,trans*-germacra-1(10),4-dienolide sesquiterpene lactone tamaulipin-A (I) was isolated by Fischer and

the known absolute configuration of a related compound, we believe (Ia) and (Ib) represent the absolute stereochemistry of tamaulipin-A.



Mabry<sup>1</sup> from certain Mexican populations of the common ragweed *Ambrosia confertiflora* DC. On the basis of physical and chemical evidence they postulated a structure and stereochemistry (Ia) which we have now confirmed by single-crystal *X*-ray analysis. On the basis of n.m.r. results, and by reason of consistency with

### EXPERIMENTAL

Tamaulipin-A was recrystallized from absolute ethanol, and a pale yellow crystal measuring *ca.*  $0.51 \times 0.42 \times 0.32$  mm<sup>3</sup> was mounted on a glass fibre. The crystal was bounded by faces of the orthorhombic forms {100}, {001}, {010}, and {011}. Preliminary Weissenberg, precession, and cone-axis photographs established space group  $P2_12_12_1$ . Intensity data were collected by use of Zr-filtered Mo- $K_{\alpha}$  radiation on an Enraf-Nonius PAD 3 diffractometer. The  $\theta$ - $2\theta$  scan technique, with  $4.5^\circ \leq \theta \leq 25^\circ$  [ $0.1104 \leq (\sin \theta)/\lambda \leq 0.5946$ ], was employed to measure the intensities of 1418 unique reflections in one octant. Throughout data collection, 3 reflections were measured periodically, but neither electronic nor crystal instabilities were detected.

The crystal scattered Mo radiation weakly and only 933 of the reflections had integrated intensities  $I > \sigma(I)$ . The variance was estimated as  $\sigma(I)^2 = I_t + I_b + 0.08I^2$ , where  $I_t$  and  $I_b$  are the total and estimated background counts in the scan. Lorentz and polarization (Lp) corrections were applied to yield structure amplitudes  $|F_o|$  and normalized

<sup>1</sup> N. H. Fischer and T. J. Mabry, *Tetrahedron*, 1968, **24**, 4091.

structure factors  $E$ . The variance of each structure amplitude was estimated as  $\sigma(|F_o|)^2 = \sigma(I)^2/(4ILp)$ .

**Crystal Data.**— $C_{15}H_{20}O_3$ ,  $M = 248$ . Orthorhombic,  $a = 7.890(9)$ ,  $b = 11.957(13)$ ,  $c = 14.649(17)$  Å,  $U = 1\,382$  Å<sup>3</sup>,  $D_m$  (floatation in aqueous NaBr) = 1.20,  $Z = 4$ ,  $D_c = 1.19$  g cm<sup>-3</sup>. Space group  $P2_12_12_1$ . Mo- $K_\alpha$  radiation,  $\lambda = 0.710\,7$  Å,  $\mu(\text{Mo-}K_\alpha) = 0.89$  cm<sup>-1</sup>.

**Structure Solution and Refinement.**—All structure invariant ( $\Sigma_2$ ) relationships<sup>2</sup> were determined for the 200 reflections with highest  $E$  values by means of the SINGEN link of the 'X-Ray '72' computing system.<sup>3</sup> The phases of three origin-defining reflections, an enantiomorph defining reflection and two arbitrary reflections were assigned

TABLE 1

Atomic positional ( $\times 10^4$ ) and thermal parameters ( $\times 10^3$ ) (H  $\times 10^3$  and  $\times 10^2$ )

Atom	X	Y	Z	U
C(1)	7 049(13)	6 186(8)	1 919(7)	48(2)
C(2)	8 389(13)	5 272(9)	1 851(7)	57(3)
C(3)	9 507(14)	5 494(8)	990(7)	50(3)
C(4)	10 179(11)	6 666(7)	1 032(6)	40(2)
C(5)	9 281(12)	7 483(7)	679(6)	40(2)
C(6)	9 343(12)	8 687(7)	917(7)	41(2)
C(7)	7 596(12)	9 216(8)	1 072(6)	50(3)
C(8)	6 846(16)	9 125(9)	2 042(8)	59(3)
C(9)	6 002(19)	8 004(13)	2 351(11)	80(5)
C(10)	7 091(12)	7 041(8)	2 455(6)	51(3)
C(11)	7 880(12)	10 363(8)	718(7)	52(2)
C(12)	9 323(14)	10 345(9)	118(7)	57(3)
C(13)	7 023(21)	11 300(13)	876(11)	86(4)
C(14)	11 702(17)	6 815(12)	1 610(10)	63(3)
C(15)	8 287(21)	7 167(17)	3 267(10)	88(4)
O(1)	7 684(11)	4 157(7)	1 788(7)	*
O(2)	10 130(7)	9 340(5)	184(4)	*
O(3)	9 888(12)	11 044(5)	-407(5)	*
H(1)	620(8)	615(5)	141(4)	2(2)
H(10)	718(13)	418(8)	127(6)	7(2)
H(2)	898(11)	520(6)	249(6)	7(2)
H(31)	889(9)	545(5)	41(5)	3(2)
H(32)	1 051(11)	490(6)	112(5)	8(3)
H(5)	827(9)	728(5)	299(4)	1(1)
H(6)	998(7)	888(4)	148(4)	1(1)
H(7)	662(14)	898(8)	59(7)	7(2)
H(81)	787(10)	922(6)	253(5)	3(2)
H(82)	617(16)	972(9)	202(7)	6(2)
H(91) †	512	781	189	6(2)
H(92) †	545	814	296	16(4)
H(131)	778(11)	1 182(7)	71(6)	4(2)
H(132)	627(13)	1 129(8)	131(7)	6(2)
H(141)	1 251(15)	659(9)	125(7)	9(3)
H(142)	1 202(10)	760(7)	160(5)	6(2)
H(143)	1 167(15)	661(9)	213(8)	7(2)
H(151) †	767	751	380	20(6)
H(152)	869(16)	641(11)	343(7)	12(4)
H(153) †	927	765	310	18(5)

\*  $T = \exp[-2\pi^2\sigma \cdot U \cdot \sigma]$ ,  $\sigma = ha^* + kb^* + lc^*$ ,  $U$  is a symmetric tensor with elements  $U_{ij}$ .

Atom	$U_{11}$	$U_{22}$	$U_{33}$	$U_{12}$	$U_{13}$	$U_{23}$
O(1)	89(6)	52(5)	110(7)	-11(5)	11(6)	24(5)
O(2)	60(4)	55(4)	58(4)	5(3)	12(4)	8(3)
O(3)	141(8)	57(4)	68(4)	-5(5)	11(5)	16(4)

† Fixed in calculated positions.

values and used in the tangent refinement process of TANGEN.<sup>3</sup> Of the four phase sets thus generated, the one with the highest figure-of-merit was used to calculate an  $E$  map, from which 13 of the 18 non-hydrogen atoms were located.

\*  $R' = (\Sigma w\Delta^2 / \Sigma w|F_o|^2)^{1/2}$ . Function minimized  $\Sigma w\Delta^2$  where  $\Delta = |F_o| - |F_c|$ .

† Error of fit is  $(\Sigma w\Delta^2 / N_o - N_v)^{1/2}$  where  $N_o$  and  $N_v$  are numbers of reflections and variables.

Successive least-squares and  $\Delta F$  procedures yielded the approximate positions of all 38 atoms.

With isotropic temperature factors for all atoms, weighted [ $w = \sigma(|F_o|)^{-2}$ ] full-matrix least-squares refinement yielded  $R$  9.5 and  $R'$  9.3%.\* With anisotropic temperature factors for the three oxygen atoms,  $R$  dropped to 8.3 and  $R'$  8.8%. However, it was noted that the two hydrogen atoms bonded to the C(9) methylene carbon, and two of the hydrogen atoms of the C(15) methyl group were in physically unreasonable positions. These four atoms were fixed in calculated positions for the last few cycles. The final  $R$  was 8.1 and  $R'$  8.7%, with 732 reflections contributing [ $I > 2\sigma(I)$ ] and an error-of-fit of 1.48.†

Atomic scattering factors for carbon and oxygen were from ref. 4 and for hydrogen from ref. 5.

TABLE 2

Interatomic distances (Å) and angles (°)

(a) Distances			
C(1)–C(2)	1.52(1)	C(7)–C(8)	1.54(1)
C(1)–C(10)	1.29(1)	C(7)–C(11)	1.48(1)
C(2)–C(3)	1.56(1)	C(8)–C(9)	1.56(2)
C(2)–O(1)	1.45(1)	C(9)–C(10)	1.44(2)
C(3)–C(4)	1.50(1)	C(10)–C(15)	1.53(2)
C(4)–C(5)	1.31(1)	C(11)–C(12)	1.44(1)
C(4)–C(14)	1.48(2)	C(11)–C(13)	1.33(2)
C(5)–C(6)	1.48(1)	C(12)–O(2)	1.36(1)
C(6)–C(7)	1.53(1)	C(12)–O(3)	1.22(1)
C(6)–O(2)	1.46(1)		
(b) Angles			
C(2)–C(1)–C(10)	126.2(9)	C(8)–C(7)–C(11)	116.4(8)
C(1)–C(2)–C(3)	108.8(8)	C(7)–C(8)–C(9)	119.4(10)
C(1)–C(2)–O(1)	113.4(9)	C(8)–C(9)–C(10)	117.4(11)
C(3)–C(2)–O(1)	108.8(8)	C(9)–C(10)–C(1)	123.6(10)
C(2)–C(3)–C(4)	108.9(8)	C(1)–C(10)–C(15)	124.7(11)
C(3)–C(4)–C(5)	119.2(8)	C(9)–C(10)–C(15)	111.8(11)
C(3)–C(4)–C(14)	115.0(9)	C(7)–C(11)–C(12)	108.6(8)
C(5)–C(4)–C(14)	125.0(9)	C(7)–C(11)–C(13)	129.9(11)
C(4)–C(5)–C(6)	127.7(8)	C(12)–C(11)–C(13)	121.5(11)
C(5)–C(6)–C(7)	114.0(8)	C(11)–C(12)–O(2)	109.8(8)
C(5)–C(6)–O(2)	111.1(7)	C(11)–C(12)–O(3)	131.6(10)
C(7)–C(6)–O(2)	105.6(7)	O(2)–C(12)–O(3)	118.6(9)
C(6)–C(7)–C(8)	116.8(8)	C(6)–O(2)–C(12)	108.9(7)
C(6)–C(7)–C(11)	101.2(7)		
(c) Interatomic contacts < 2.8 Å			
(i) Intramolecular			
H(1) ... H(10)	2.5(1)	H(6) ... H(142)	2.2(1)
H(2) ... H(152)	2.0(1)	H(7) ... H(91)	2.5(1)
H(31) ... H(5)	2.2(1)	H(81) ... H(151)	2.4(1)
H(31) ... H(10)	2.4(1)	H(81) ... H(153)	2.1(1)
H(5) ... H(7)	2.5(1)	H(82) ... H(132)	2.2(1)
H(6) ... H(81)	2.3(1)		
(ii) Intermolecular			
H(10) ... O(3)	2.2(1)	H(92) ... O(1)	2.4(1)
H(6) ... H(2)	2.3(1)	H(92) ... H(10)	2.3(2)
H(81) ... H(32)	2.5(1)		
H(92) ... O(3)	2.3(1)	O(1) ... O(3)	3.00(1)

## RESULTS AND DISCUSSION

Atomic parameters are listed in Table 1, molecular dimensions and significant contact distances in Table 2, and torsion angles in Table 3. Observed and calculated

<sup>2</sup> I. L. Karle and J. Karle, *Acta Cryst.*, 1963, **16**, 969.

<sup>3</sup> J. M. Stewart, G. J. Kruger, H. L. Ammon, C. Dickenson, and S. R. Hall, Technical Report TR 192, Computer Science Centre, University of Maryland, 1972.

<sup>4</sup> D. Cromer and J. Mann, *Acta Cryst.*, 1968, **A24**, 321.

<sup>5</sup> R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **42**, 3175.

structure factors ( $\times 10$ ) are deposited as Supplementary Publication No. SUP 22156 (5 pp.).\*

TABLE 3  
Torsion angles ( $^{\circ}$ )

C(10)-C(1)-C(2)-C(3)	-101
C(10)-C(1)-C(2)-O(1)	137
C(1)-C(2)-C(3)-C(4)	54
O(1)-C(2)-C(3)-C(4)	178
C(2)-C(3)-C(4)-C(5)	-89
C(2)-C(3)-C(4)-C(14)	82
C(3)-C(4)-C(5)-C(6)	156
C(14)-C(4)-C(5)-C(6)	-14
C(4)-C(5)-C(6)-C(7)	-132
C(4)-C(5)-C(6)-O(2)	109
C(5)-C(6)-C(7)-C(8)	87
C(5)-C(6)-C(7)-C(11)	-146
O(2)-C(6)-C(7)-C(8)	-151
O(2)-C(6)-C(7)-C(11)	-24
C(6)-C(7)-C(8)-C(9)	-79
C(11)-C(7)-C(8)-C(9)	161
C(7)-C(8)-C(9)-C(10)	67
C(8)-C(9)-C(10)-C(1)	-111
C(8)-C(9)-C(10)-C(15)	69
C(9)-C(10)-C(1)-C(2)	165
C(15)-C(10)-C(1)-C(2)	-14
C(6)-C(7)-C(11)-C(12)	21
C(6)-C(7)-C(11)-C(13)	-160
C(8)-C(7)-C(11)-C(12)	148
C(8)-C(7)-C(11)-C(13)	-32
C(7)-C(11)-C(12)-O(2)	-10
C(7)-C(11)-C(12)-O(3)	170
C(13)-C(11)-C(12)-O(2)	170
C(13)-C(11)-C(12)-O(3)	-10
C(11)-C(12)-O(2)-C(6)	-6
O(3)-C(12)-O(2)-C(6)	174
C(12)-O(2)-C(6)-C(7)	19
C(12)-O(2)-C(6)-C(5)	143

The unit cell contains four discrete molecules (Figure 1), each consisting of a cyclodecadiene ring (A) and a

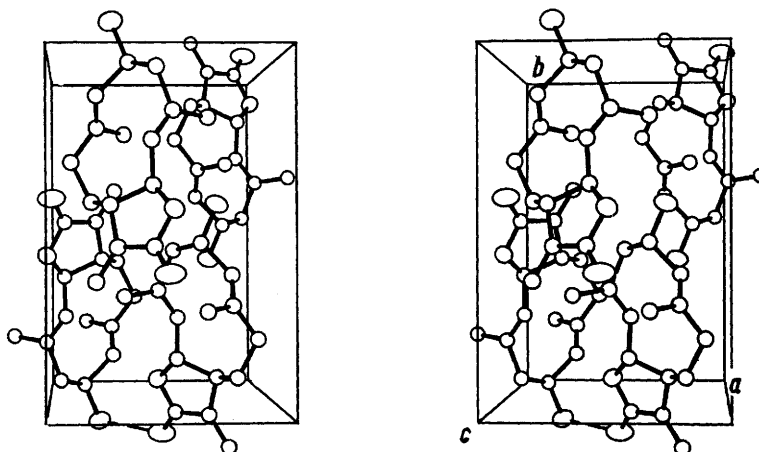


FIGURE 1 Stereodiagram of one unit cell of tamaulipin-A. The intermolecular hydrogen bond is displayed bottom foreground

five-membered  $\alpha$ -methylene- $\gamma$ -lactone ring (B) *trans*-fused to ring A at C(6) and C(7) (Figure 2). Although it was not possible to establish the absolute configuration

\* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1977, Index issue.

<sup>6</sup> F. Sorm, M. Suchy, M. Holub, A. Linek, I. Hadinec, and C. Novak, *Tetrahedron Letters*, 1970, 1893. The torsion angles calculated from the unrefined co-ordinates are those of the enantiomorph of costunolide.

<sup>7</sup> A. T. McPhail and G. A. Sim, *J.C.S. Perkin II*, 1972, 1313.

experimentally, we believe that (Ib) and Figure 2 represent the absolute stereochemistry by analogy with similar compounds of known stereochemistry, as discussed later.

*Ring A.*—The *trans,trans*-cyclodeca-1,5-diene ring is in extended chair or chair-chair conformation (+-+-+-+-) analogous to that of *trans*-decalin. Indeed, the conformations of six other germacranolide sesquiterpenes, for which detailed structural analyses have been carried out, can also be derived hypothetically from *trans*-decalin as follows. If the transannular bond [C(5)-C(10)] of *trans*-decalin were ruptured, and equatorial hydrogen atoms at C(1) and C(4) extracted, two mutually perpendicular *trans*-ethylenic bonds could be formed. As C(5) and C(10) move away from one another, the four axial positions at C(1), C(4), C(5), and C(10) would fall into the planes of the  $\pi$  systems with only minor alterations of their former positions. Substitution of carbon (usually methyl) groups at  $\beta$ -4 and  $\beta$ -10 would then produce the *syn*-configuration common to this class of germacranolides, and further substitution at equatorial or  $\beta$ -axial positions would yield costunolide,<sup>6</sup> elephantol<sup>7</sup> (as *p*-bromobenzoate), eupatolide,<sup>8</sup> germacratrione<sup>9</sup> (as AgNO<sub>3</sub> adduct), parthenolide,<sup>10</sup> pyrethrosin,<sup>11</sup> and tamaulipin-A (Ib) (see Tables 4 and 5). The stereochemistry of a tamaulipin-A derivative, dihydrotamaulipin-A acetate, was determined from NOE results by Bhacca and Fischer,<sup>12</sup> and is identical to the known absolute configuration of the related compound elephantol<sup>7</sup> (as the *p*-bromobenzoate). We are thus confident that (Ib) represents the absolute configuration of tamaulipin-A.

There is considerable strain in ring A, as judged by the C-C(*sp*<sup>3</sup>)-C bond angles, but it appears to be localized in

<sup>8</sup> A. T. McPhail and K. D. Onan, *J.C.S. Perkin II*, 1975, 1798.

<sup>9</sup> F. H. Allen and D. Rogers, *J. Chem. Soc. (B)*, 1971, 257.

<sup>10</sup> A. Quick and D. Rogers, *J.C.S. Perkin II*, 1976, 465. The configuration at C(7) is incorrectly quoted as 7(R), and should be 7(S).

<sup>11</sup> E. J. Gabe, S. Neidle, D. Rogers, and C. E. Nordman, *Chem. Comm.*, 1971, 559.

<sup>12</sup> N. S. Bhacca and N. H. Fischer, *Chem. Comm.*, 1968, 68.

the C(6) to C(9) region (mean  $117^\circ$ ) since C(2) and C(3) display angles near  $109^\circ$ . Endocyclic torsion about the C(10)-C(1) double bond is found in all known germacranolide structures of this class (Table 4, mean  $\omega_{10,1}$

positions 6 and 7 requires orientations H(6)  $\beta$  and H(7)  $\alpha$ . The endocyclic bond angles average  $107^\circ$ , and the sum of the endocyclic torsion angle moduli ( $80^\circ$ ) indicates significant non-planarity. The conformation of the ring

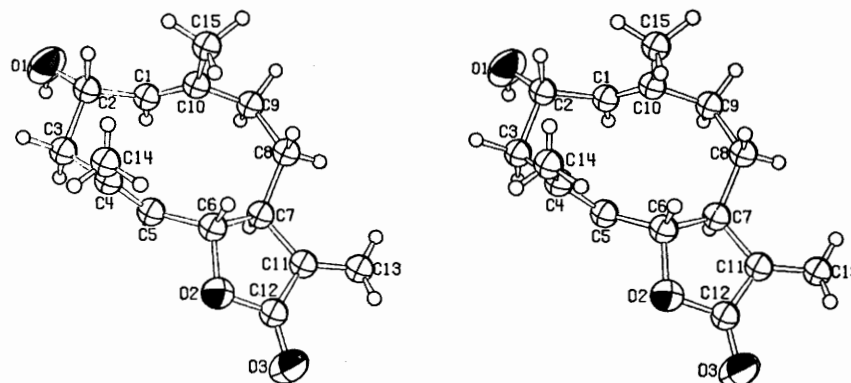


FIGURE 2 Stereodiagram of the  $\beta$ -face of tamaulipin-A

$165^\circ$ ) and is restricted to a narrow range of  $7^\circ$ . Of the four germacranolides with C(4)-C(5) double bonds, the average torsion from  $180^\circ$  is greater than  $\omega_{10,1}$  ( $159^\circ$ ) but so is the range ( $19^\circ$ ). As was observed for melampodin,<sup>13</sup>

is that of an envelope, with C(6) at the flap. Conjugation of the exocyclic methylene and carbonyl groups is perturbed somewhat by the  $-10^\circ$  torsion C(13)-C(11)-C(12)-O(3).

TABLE 4  
Comparative endocyclic torsion angles ( $^\circ$ )

Comp.*	$\omega_{10,1}$	$\omega_{1,2}$	$\omega_{2,3}$	$\omega_{3,4}$	$\omega_{4,5}$	$\omega_{5,6}$	$\omega_{6,7}$	$\omega_{7,8}$	$\omega_{8,9}$	$\omega_{9,10}$
(II)	180	-60	60	-60	180	-180	60	-60	60	-180
(III)	161	-91	53	-102	166	-125	79	-83	78	-119
(IV)	163	-104	42	-77	156	-108	82	-119	83	-89
(V)	167	-98	50	-86	155	-136	90	-76	67	-155
(VI)	168	-116	47	-91	160	-120	85	-113	96	-95
(VII)	168	-107	52	-88	147	-124	96	-89	75	-109
(I)	165	-101	54	-89	156	-132	87	-79	67	-111

\* Tamaulipin-A (I), idealized *trans*-decalin (II), costunolide (III), elephantol (IV), eupatolide (V), germacatriene (VI), and parthenolide (VII).

TABLE 5  
Correlation and specification of absolute stereochemistries

Compd.*	Chirality						$\beta$ -Substituents †				
	2	4	5	6	7	8	10	2	4	6	8
(III)				(R)	(S)		C(Me)	H	C(Me)	H	H
(IV)	(R)	(R)	(R)	(S)	(R)	(S)	C(Lac)-	O(Lac)	C(Me)	H	H
(V)				(R)	(R)	(R)	C(Me)	H	C(Me)	H	OH
(VI)							C(Me)	H	C(Me)	H	H
(VII)		(R)	(R)	(S)	(S)		C(Me)	H	C(Me)	H	H
(I)	(S)			(R)	(S)		C(Me)	H	C(Me)	H	H
Equatorial substituents											
	10	1	2	3	4	5	6	7	8	9	
(III)	$\Delta$	$-\Delta$	H	H	$\Delta$	$-\Delta$	O(Lac)-C(Lac)		H	H	
(IV)	$\Delta$	$-\Delta$	H	H	epoxide		OR	C(Lac-O(Lac))		H	
(V)	$\Delta$	$-\Delta$	H	H	$\Delta$	$-\Delta$	O(Lac)-C(Lac)		H	H	
(VI)	$\Delta$	$-\Delta$	H	H	$\Delta$	$-\Delta$	H	C(vinyl)		H	
(VII)	$\Delta$	$-\Delta$	H	H	epoxide		O(Lac)-C(Lac)		H	H	
(I)	$\Delta$	$-\Delta$	OH	H	$\Delta$	$-\Delta$	O(Lac)-C(Lac)		H	H	

\* See footnote to Table 4.

† All  $\alpha$ -oriented substituents are H.

these apparent torsions are composed of a true torsion and a bending of the  $sp^2$  bonds, but the relative contributions cannot be accurately deduced from X-ray data.

**Ring B.**—Fusion of the lactone ring at equatorial

**Interatomic Distances.**—The paucity of data precludes detailed analysis, but the mean C=C, C( $sp^2$ )-C( $sp^3$ ), and

<sup>13</sup> S. F. Watkins, N. H. Fischer, and I. Bernal, *Proc. Nat. Acad. Sci. U.S.A.*, 1973, **70**, 2434.

C( $sp^3$ )-C( $sp^3$ ) distances are as expected [1.31(1), 1.49(1), and 1.54(1) Å]. There is an intermolecular hydrogen bond between the hydroxy-group and the carbonyl

oxygen of the lactone ring [O(3) ···H(10) 2.2(1) Å], and the apparent length indicates the bond is weak.<sup>14</sup>

We thank N. H. Fischer for the crystalline sample and the University of Houston for facilities.

<sup>14</sup> W. C. Hamilton and J. A. Ibers, 'Hydrogen Bonding in Solids,' W. A. Benjamin, New York, 1967, p. 16, appendix.

[7/803 Received, 9th May, 1977]

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