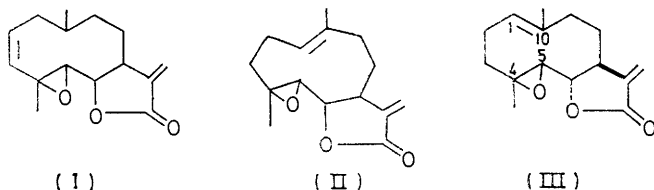


## Crystal and Molecular Structure of Parthenolide [4,5-Epoxygermacra-1(10),11(13)-dien-12,6-olactone]†

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The crystal structure of the title compound has been determined from single-crystal X-ray data by direct methods. Crystals are orthorhombic.  $a = 11.929(1)$ ,  $b = 12.267(2)$ ,  $c = 18.761(2)$  Å. space group  $P2_12_12_1$ ,  $Z = 8$ , *i.e.* two independent molecules per asymmetric unit. Full-matrix least-squares refinement based on 2 330 independent reflections has reached  $R$  0.047. The double bond C(1)–C(10) and the equivalent double bond C(4)–C(5) are both *trans*, both methyl groups are  $\beta$ , and the ten-membered ring has a conformation typical of several germacranolides.

THE sesquiterpenic lactone, parthenolide, isolated from *Chrysanthemum parthenium* (L), was originally assigned the structure (I).<sup>1</sup> The same compound was isolated from the trunk bark of *Michelia champaca* and its structure revised to (II)<sup>2</sup> from a study of its n.m.r. spectrum and chemical reactions. The absolute configuration of the molecule has been determined and it was shown that parthenolide can be represented by the stereoformula (III).<sup>3</sup>



The present crystal structure, part of a series of studies of ten-membered ring compounds, was undertaken to show the conformation of the epoxide ring and also the orientation of the methyls at C(4) and C(10).

### EXPERIMENTAL

The crystals were colourless plates.

*Crystal Data.*— $C_{15}H_{20}O_3$ ,  $M = 248.3$ , Orthorhombic.  $a = 11.929(1)$ ,  $b = 12.267(2)$ ,  $c = 18.761(2)$  Å,  $U = 2\,745.4$  Å<sup>3</sup>,

† Reprints are not available.

<sup>1</sup> M. Souček, V. Herout, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1961, **26**, 803.

<sup>2</sup> T. R. Govindachari, B. S. Joshi, and V. N. Kamat, *Tetrahedron*, 1965, **21**, 1509.

$D_m = 1.19(2)$  (by flotation),  $Z = 8$ ,  $D_c = 1.20$  g cm<sup>-3</sup>. Space group  $P2_12_12_1$  (No. 19) uniquely from systematic absences. Cu- $K\alpha$  radiation  $\lambda = 1.5418$  Å;  $\mu(\text{Cu-}K\alpha) = 6.71$  cm<sup>-1</sup>.

A crystal *ca.*  $0.50 \times 0.51 \times 0.05$  mm<sup>3</sup> was mounted along its *b* direction and data were measured on a Siemens off-line automatic four-circle diffractometer, with filtered Cu- $K\alpha$  radiation. A total of 2 330 independent reflections (to  $\theta = 60^\circ$ ) were measured by use of the  $\theta$ – $2\theta$  scan technique with the 'five-value' measuring procedure.<sup>4</sup> Of these 463 reflections were judged to be unobserved, *i.e.* having  $I < 2.58\sigma(I)$ .<sup>4</sup> The net count of the 3,0,9 reflection, measured as a reference every 50 reflections, did not alter significantly during data collection (*ca.* 6 days). Data were scaled by use of this reflection and Lorentz and polarization corrections were applied.

The structure was solved by direct methods using the program MULTAN<sup>5</sup> and starting with 209 reflections having normalized structure factors  $|E| \geq 1.57$ . The *E* map, calculated from the solution with the highest combined figure of merit, gave plausible positions for 28 non-hydrogen atoms of the structure. These refined with isotropic temperature factors to  $R$  0.34. A difference electron-density map computed at this stage showed the remaining eight non-hydrogen atoms. The solution refined with isotropic temperature factors to  $R$  0.135. A second

<sup>3</sup> A. S. Bawdekar, G. R. Kelkar, and S. C. Bhattacharyya, *Tetrahedron Letters*, 1966, 1225.

<sup>4</sup> F. H. Allen, D. Rogers, and P. G. H. Troughton, *Acta Cryst.*, 1971, **B27**, 1325.

<sup>5</sup> G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst.*, 1971, **A27**, 368.

difference map showed no major unassigned peaks. The structure was then refined anisotropically reducing  $R$  to 0.094. A difference-Fourier now showed the positions of all 40 hydrogen atoms, and these were assigned the equivalent

isotropic temperature factors of their parent atoms. When these atoms were included in the block-diagonal least-squares refinement with fixed isotropic temperature factors and the remaining atoms were refined anisotropically,  $R$  dropped to 0.047. Unit weights were used

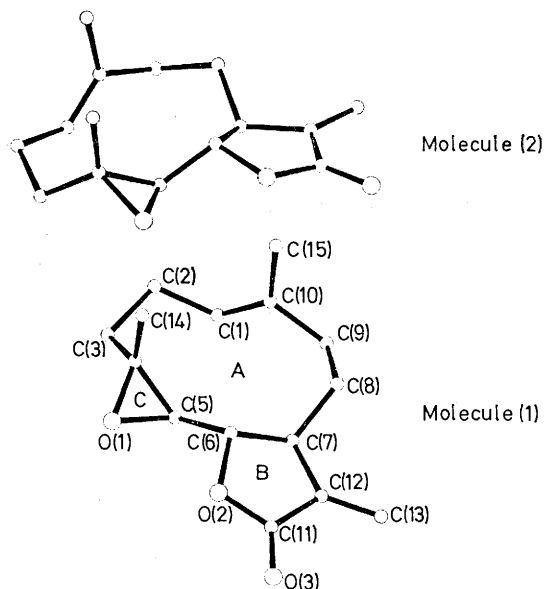


FIGURE 1 A representative pair of independent molecules, showing the atomic numbering used

TABLE I

Fractional co-ordinates ( $\times 10^4$ ) for the non-hydrogen atoms with estimated standard deviations in parentheses

Atom	$x$	$y$	$z$
(a) Molecule (1)			
C(101)	-52(4)	2 228(4)	5 694(3)
C(102)	-79(4)	2 716(5)	6 418(3)
C(103)	647(5)	2 036(5)	6 943(3)
C(104)	1 822(4)	1 870(4)	6 630(2)
C(105)	1 977(4)	906(4)	6 174(2)
C(106)	2 723(4)	844(4)	5 542(2)
C(107)	2 152(4)	566(4)	4 836(2)
C(108)	1 791(4)	1 492(4)	4 341(2)
C(109)	579(4)	1 911(4)	4 460(3)
C(110)	451(4)	2 624(4)	5 111(3)
C(111)	3 744(4)	-586(4)	5 069(3)
C(112)	2 995(4)	-201(4)	4 499(3)
C(113)	3 086(5)	-532(5)	3 833(3)
C(114)	2 494(5)	2 878(4)	6 553(3)
C(115)	930(5)	3 733(4)	5 039(3)
O(101)	2 415(3)	948(3)	6 885(2)
O(102)	3 541(2)	-27(3)	5 677(2)
O(103)	4 457(3)	-1 293(3)	5 053(2)
(b) Molecule (2)			
C(201)	2 277(4)	6 179(4)	7 416(3)
C(202)	3 133(5)	6 056(5)	7 991(3)
C(203)	4 186(5)	5 449(5)	7 720(3)
C(204)	4 597(4)	5 977(5)	7 046(3)
C(205)	4 096(4)	5 635(4)	6 363(3)
C(206)	3 921(4)	6 344(4)	5 736(2)
C(207)	2 698(3)	6 334(4)	5 454(2)
C(208)	1 910(4)	7 241(4)	5 710(2)
C(209)	1 297(4)	6 999(5)	6 407(3)
C(210)	2 025(4)	7 075(4)	7 053(2)
C(211)	4 050(4)	5 989(4)	4 524(3)
C(212)	2 869(4)	6 329(4)	4 658(2)
C(213)	2 228(5)	6 572(6)	4 134(3)
C(214)	5 110(6)	7 087(6)	7 129(3)
C(215)	2 409(6)	8 188(4)	7 210(3)
O(201)	5 219(3)	5 287(4)	6 543(2)
O(202)	4 579(3)	5 914(3)	5 150(2)
O(203)	4 483(4)	5 760(3)	3 969(2)

TABLE 2

Fractional co-ordinates ( $\times 10^3$ ) of the hydrogen atoms with estimated standard deviations in parentheses, numbered according to the carbon atoms to which they are bonded

Atom	$x$	$y$	$z$
(a) Molecule (1)			
H(1011)	-38(3)	144(3)	568(2)
H(1021)	10(4)	369(3)	654(2)
H(1022)	-81(4)	277(3)	660(2)
H(1031)	77(3)	235(3)	750(2)
H(1032)	28(3)	123(3)	703(2)
H(1051)	141(3)	37(3)	612(2)
H(1061)	310(3)	164(3)	553(2)
H(1071)	154(3)	10(3)	491(2)
H(1081)	235(3)	214(3)	445(2)
H(1082)	187(3)	109(3)	379(2)
H(1091)	41(3)	239(3)	395(2)
H(1092)	9(3)	123(3)	452(2)
H(1131)	362(4)	-129(3)	367(2)
H(1132)	267(4)	-22(4)	332(2)
H(1141)	253(3)	329(3)	711(2)
H(1142)	311(3)	275(3)	643(2)
H(1143)	213(3)	345(3)	623(2)
H(1151)	74(3)	420(3)	552(2)
H(1152)	188(3)	370(3)	501(2)
H(1153)	72(3)	408(3)	455(2)
(b) Molecule (2)			
H(2011)	201(3)	536(3)	735(2)
H(2021)	328(3)	683(3)	824(2)
H(2022)	275(4)	561(3)	846(2)
H(2031)	475(4)	546(3)	808(2)
H(2032)	419(4)	465(3)	752(2)
H(2051)	353(3)	499(3)	647(2)
H(2061)	421(3)	715(3)	579(2)
H(2071)	243(3)	555(3)	559(2)
H(2081)	235(3)	798(3)	577(2)
H(2082)	140(3)	733(3)	538(2)
H(2091)	77(3)	768(3)	646(2)
H(2092)	111(3)	613(3)	647(2)
H(2131)	240(4)	660(3)	340(2)
H(2132)	162(4)	675(3)	418(2)
H(2141)	484(4)	767(4)	765(2)
H(2142)	578(4)	692(4)	711(2)
H(2143)	494(4)	757(4)	664(2)
H(2151)	220(4)	905(4)	687(2)
H(2152)	213(4)	866(3)	752(2)
H(2153)	300(4)	816(4)	746(2)

Each hydrogen atom was given the equivalent isotropic  $B$  factor of its parent atom.

throughout the refinements. No absorption corrections were applied. A final difference map showed no significant peaks. Scattering factors for carbon and oxygen were taken from ref. 6 and those for hydrogen from ref. 7. Allowance for anomalous scattering<sup>8</sup> by the oxygen atoms was applied to all the non-zonal reflections for both chiralities, but it was not possible to determine the absolute configuration as both chiralities refined to the same  $R$  value.

The crystal structure calculations system 'X-Ray '70,'<sup>9</sup> was used to refine the structure. Calculations were carried

<sup>6</sup> D. T. Cromer and J. T. Waber, *Acta Cryst.*, 1965, **18**, 104.

<sup>7</sup> R. F. Steward, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **42**, 3175.

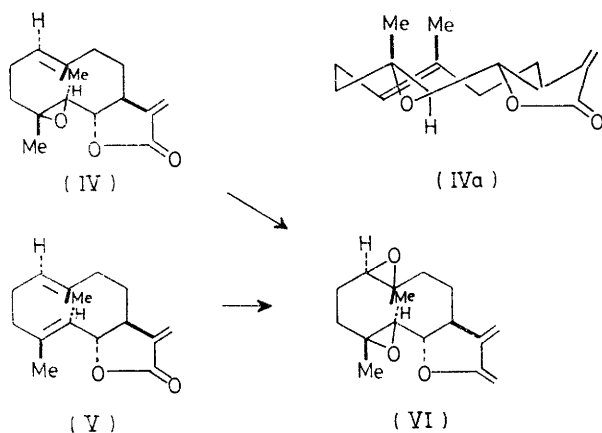
<sup>8</sup> D. T. Cromer, *Acta Cryst.*, 1965, **18**, 17.

<sup>9</sup> 'X-Ray '63' System of Crystallographic Programs, University of Maryland, Technical Report TR 646, revised version, 1970.

out on the Imperial College CDC 6400 and the University of London CDC 6600 and 7600 computers. Figure 1 shows the atom numbering used. Table 1 lists the final co-ordinates of the non-hydrogen atoms and Table 2 gives the co-ordinates of the hydrogen atoms. Observed and calculated structure factors are listed in Supplementary Publication No. SUP 21586 (14 pp., 1 microfiche),\* together with the anisotropic thermal parameters of the carbon and oxygen atoms.

#### DESCRIPTION AND DISCUSSION OF THE STRUCTURE

The two independent molecules have essentially the same geometry and absolute stereochemistry which can be depicted by (IV) or (IVa). This confirms the



proposed formula (III) and completes the stereochemical specification. Thus the two methyl groups are  $\beta$ -oriented; both the double bond C(1)-C(10) and the double bond equivalent of C(4)-C(5) are *trans*; the ten-membered ring has the same flattened conformation [with the two double bonds crossed as in (IVa)] as was found in pyrethrosin,<sup>10</sup> shiromodiol,<sup>11</sup> and elephantol,<sup>11</sup> which are typical germacranolides, and, from the known absolute configuration, the configurations at the asymmetric atoms prove to be 4(*R*), 5(*R*), 6(*S*), 7(*R*). The

TABLE 3

Bond lengths ( $\text{\AA}$ ) and bond angles ( $^\circ$ ), with standard deviations in parentheses

(a) Distances

	Molecule (1) <i>M</i> = 1	Molecule (2) <i>M</i> = 2
C(M01)-C(M02)	1.485(8)	1.492(8)
C(M01)-C(M10)	1.338(7)	1.327(7)
C(M02)-C(M03)	1.554(8)	1.547(8)
C(M03)-C(M04)	1.532(7)	1.502(8)
C(M04)-C(M05)	1.472(7)	1.475(7)
C(M04)-C(M14)	1.481(7)	1.501(9)
C(M04)-O(M01)	1.418(6)	1.469(7)
C(M05)-C(M06)	1.485(6)	1.477(7)
C(M05)-O(M01)	1.435(6)	1.446(6)
C(M06)-C(M07)	1.530(6)	1.552(6)
C(M06)-O(M02)	1.468(6)	1.450(6)
C(M07)-C(M08)	1.538(6)	1.534(6)
C(M07)-C(M12)	1.509(6)	1.506(6)
C(M08)-C(M09)	1.551(6)	1.527(7)
C(M09)-C(M10)	1.511(7)	1.495(7)
C(M10)-C(M15)	1.482(7)	1.470(8)
C(M11)-C(M12)	1.472(7)	1.491(7)
C(M11)-O(M02)	1.352(6)	1.337(6)
C(M11)-O(M03)	1.215(6)	1.197(6)
C(M12)-C(M13)	1.317(7)	1.280(7)

TABLE 3 (Continued)

(b) Angles

	Molecule (1) <i>M</i> = 1	Molecule (2) <i>M</i> = 2
C(M02)-C(M01)-C(M10)	127.7(5)	127.5(5)
C(M01)-C(M02)-C(M03)	110.6(5)	111.5(4)
C(M02)-C(M03)-C(M04)	109.8(4)	109.5(5)
C(M03)-C(M04)-C(M05)	116.4(4)	118.4(5)
C(M03)-C(M04)-C(M14)	114.9(5)	115.9(5)
C(M03)-C(M04)-O(M01)	115.7(4)	117.1(5)
C(M05)-C(M04)-C(M14)	123.1(4)	120.9(5)
C(M05)-C(M04)-O(M01)	59.5(3)	58.8(3)
C(M14)-C(M04)-O(M01)	115.4(4)	112.6(5)
C(M04)-C(M05)-C(M06)	125.6(4)	125.5(4)
C(M04)-C(M05)-O(M01)	58.4(3)	60.4(3)
C(M06)-C(M05)-O(M01)	121.8(4)	119.4(4)
C(M05)-C(M06)-C(M07)	115.8(4)	113.6(4)
C(M05)-C(M06)-O(M02)	107.3(4)	108.2(4)
C(M07)-C(M06)-O(M02)	106.1(4)	104.4(4)
C(M06)-C(M07)-C(M08)	118.4(4)	117.6(4)
C(M06)-C(M07)-C(M12)	102.0(4)	102.2(3)
C(M08)-C(M07)-C(M12)	113.1(4)	113.4(4)
C(M07)-C(M08)-C(M09)	114.9(4)	114.9(4)
C(M08)-C(M09)-C(M10)	113.7(4)	113.9(4)
C(M01)-C(M10)-C(M09)	119.8(5)	119.8(5)
C(M01)-C(M10)-C(M15)	125.5(5)	126.6(5)
C(M09)-C(M10)-C(M15)	114.8(4)	113.6(5)
C(M12)-C(M11)-O(M02)	109.9(4)	108.5(4)
C(M12)-C(M11)-O(M03)	129.5(5)	128.4(5)
O(M02)-C(M11)-O(M03)	120.6(5)	123.0(5)
C(M07)-C(M12)-C(M11)	107.3(4)	107.2(4)
C(M07)-C(M12)-C(M13)	130.0(5)	132.3(5)
C(M11)-C(M12)-C(M13)	122.7(5)	120.5(5)
C(M04)-O(M01)-C(M05)	62.1(3)	60.8(3)
C(M06)-O(M02)-C(M11)	110.1(4)	121.6(4)

TABLE 4

Torsion angles

	<i>M</i> = 1	<i>M</i> = 2
Ring a		
C(M01)[C(M02)-C(M03)]C(M04)	52.5	51.3
C(M02)[C(M03)-C(M04)]C(M05)	-89.5	-85.7
C(M03)[C(M04)-C(M05)]C(M06)	145.8	147.8
C(M04)[C(M05)-C(M06)]C(M07)	-121.3	-126.8
C(M05)[C(M06)-C(M07)]C(M08)	95.8	95.7
C(M06)[C(M07)-C(M08)]C(M09)	-91.6	-87.5
C(M07)[C(M08)-C(M09)]C(M10)	76.4	74.2
C(M08)[C(M09)-C(M10)]C(M01)	-105.8	-111.2
C(M09)[C(M10)-C(M01)]C(M02)	167.9	168.7
C(M10)[C(M01)-C(M02)]C(M03)	-109.7	-105.1
Ring b		
C(M06)[O(M02)-C(M11)]C(M12)	-5.9	-9.3
O(M02)[C(M11)-C(M12)]C(M07)	-8.6	-6.1
C(M11)[C(M12)-C(M07)]C(M06)	18.3	17.2
C(M12)[C(M07)-C(M06)]O(M02)	-21.5	-21.9
C(M07)[C(M06)-O(M02)]C(M11)	17.7	20.2
Ring c		
C(M07)[C(M06)-C(M05)]O(M01)	167.2	160.7
C(M02)[C(M03)-C(M04)]O(M01)	-156.0	-152.5
Ring d		
C(M02)[C(M01)-C(M10)]C(M15)	-10.9	-9.9
C(M08)[C(M09)-C(M10)]C(M15)	73.1	67.6
C(M08)[C(M07)-C(M12)]C(M13)	-35.7	-33.5
O(M02)[C(M11)-C(M12)]C(M13)	173.1	172.2
C(M06)[C(M07)-C(M12)]C(M13)	-163.6	-160.8
C(M06)[O(M02)-C(M11)]O(M03)	174.4	174.3
C(M07)[C(M12)-C(M11)]O(M03)	171.1	170.0
C(M13)[C(M12)-C(M11)]O(M03)	-7.2	-11.7
C(M02)[C(M03)-C(M04)]C(M14)	65.2	70.8
C(M06)[C(M05)-C(M04)]C(M14)	-6.6	-7.6
C(M05)[O(M01)-C(M04)]C(M14)	-114.9	-113.8

\* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1975, Index issue.

<sup>10</sup> E. J. Gabe, S. Neidle, D. Rogers, and C. E. Nordman, *Chem. Comm.*, 1971, 559.

<sup>11</sup> R. J. McClure, G. A. Sim, P. Coggon, and A. T. McPhail, *Chem. Comm.*, 1970, 128.

geometry of the epoxide shows the molecule is directly related to costunolide (V),<sup>12</sup> so it follows that the di-epoxide described by Bawdekar *et al.* as derivable from

double bonds [C(1)-C(10) 1.333 Å]. The torsion angles about the  $\Delta^{1(10)}$  double bond is 168° and for C(3)-C(4)-C(5)-C(6) is 147°, again typical of the strains encountered

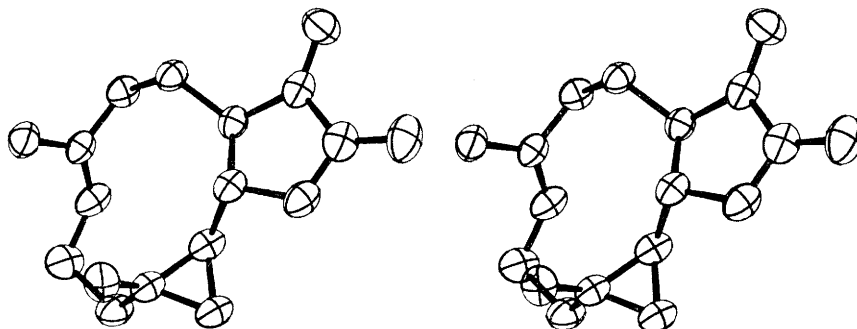


FIGURE 2 Stereoview of one molecule of parthenolide

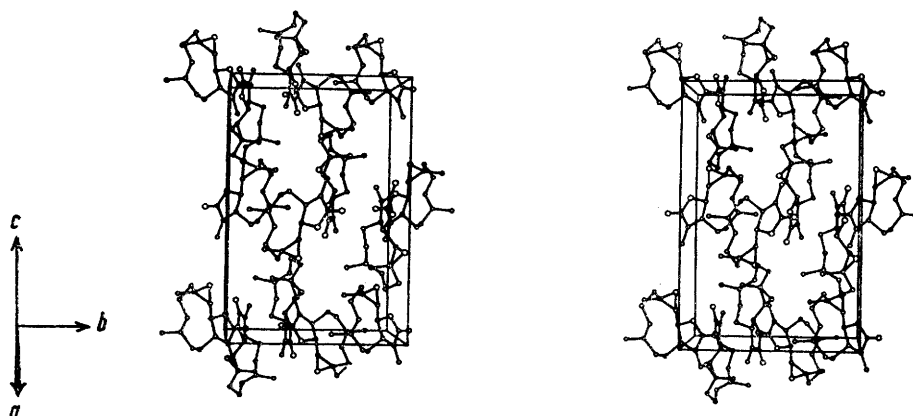


FIGURE 3 A stereoscopic view showing the molecular packing

both (IV) and (V) must be represented by (VI). This geometry agrees well with n.o.e. results.<sup>13</sup> The mean C( $sp^3$ )-C( $sp^3$ ) (1.542 Å) and C( $sp^3$ )-C( $sp^2$ ) distances (1.498 Å) are typical. So, too, is the mean of the two

in germacranolides. Individual bond lengths, and valence and torsion angles are given in Tables 3 and 4,

TABLE 5

Mean planes through various sets of atoms

(a) Deviations (in Å × 10<sup>3</sup>) of atoms from the planes

	$A_1$		$A_2$		$B_1$		$B_2$	
	$M = 1$	$M = 2$	$M = 1$	$M = 2$	$M = 1$	$M = 2$	$M = 1$	$M = 2$
C(M01)	-384	-373	C(M07)	-26	-19			
C(M02)	26	32	C(M11)	-47	-33			
C(M03)	-187	-185	C(M12)	43	31			
C(M04)	503	463	O(M02)	29	21			
C(M05)	-310	-319	C(M06) *	316	339			
C(M06)	214	251						
C(M07)	-421	-418						
C(M08)	298	267						
C(M09)	-151	-146						
C(M10)	413	427						

(b) Equations to the planes in the form  $Ax + By + Cz - D = 0$

	A	B	C	D
$A_1$	7.016	9.906	-0.841	2.915
$A_2$	4.862	11.113	2.155	7.787
$B_1$	7.207	9.242	-4.871	4.604
$B_2$	2.845	11.913	-0.093	8.373

\* Not included in derivation of plane.

TABLE 6

Selected intramolecular contacts (Å)  $\leq 3.50$  Å

	$M = 1$	$M = 2$
C(M03) ... C(M01)	2.50	2.51
C(M04) ... C(M01)	2.88	2.86
C(M05) ... C(M01)	3.05	3.01
C(M05) ... C(M02)	3.34	3.30
C(M14) ... C(M02)	3.09	3.13
C(M15) ... C(M02)	3.12	3.12
C(M10) ... C(M04)	3.41	3.35
C(M10) ... C(M05)	3.43	3.30
C(M11) ... C(M05)	3.48	3.48
C(M14) ... C(M06)	3.15	3.11
O(M03) ... C(M06)	3.46	3.46
C(M10) ... C(M07)	3.29	3.24
C(M13) ... C(M08)	3.07	3.09
C(M15) ... C(M08)	3.22	3.10
O(M03) ... C(M13)	2.96	2.89
O(M02) ... O(M01)	2.89	2.83

TABLE 7

Selected intermolecular contacts (Å)  $\leq 3.50$  Å

C(206) ... C(103 <sup>I</sup> )	3.23	O(201) ... C(108 <sup>II</sup> )	3.32
C(215) ... O(101 <sup>I</sup> )	3.44	O(103) ... C(208 <sup>II</sup> )	3.46
O(202) ... O(103 <sup>I</sup> )	3.43	O(201) ... C(109 <sup>II</sup> )	3.32
		C(111) ... C(115 <sup>II</sup> )	3.46

Roman numerals indicate the following equivalent positions relative to the reference molecule at  $x, y, z$ :

$$\text{I } x, 1 + y, z \quad \text{II } \frac{1}{2} + x, \frac{1}{2} - y, -1 - z$$

<sup>12</sup> F. Šorm, M. Suchý, M. Holub, A. Lfnek, I. Hadinec, and C. Novák, *Tetrahedron Letters*, 1970, 1893.

<sup>13</sup> T. A. Geissman, personal communication.

and the concordance between the two molecules is evidently close. Examination of the torsion angles round the ten-membered ring shows wide variations, but a fair approximation to a diad axis runs between the midpoints of bonds C(2)-C(3) and C(7)-C(8), despite the strains and asymmetries imposed by the substituents and fusion to smaller rings. The planes of atoms C(9)-C(10)-C(1)-C(2) and C(3)-C(4)-C(5)-C(6) are as usual roughly perpendicular to the macrocycle. Ring B is an envelope, with atom C(6) deviating most (see Table 5); the remaining atoms are reasonably planar.

Selected intra- and inter-molecular contact distances are given in Tables 6 and 7 respectively. The packing is depicted in the stereopair (Figure 3),<sup>14</sup> and is fairly open: only van der Waals contacts occur.

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<sup>14</sup> C. K. Johnson, ORTEP Thermal Ellipsoid plotting program, Oak Ridge National Laboratory Report ORNL 3794, 1965.

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