Structures and Conformations of the Fourteen-membered Ring Diterpene Ovatodiolide and Its Acid Cyclization Product: Nuclear Overhauser Effect Studies in Solution and *X*-Ray Crystal Structure Analyses of Ovatodiolide and Ovatodiolic Acid

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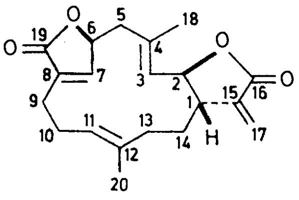
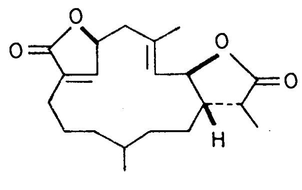
The conformation and relative stereochemistry of ovatodiolide (1), a fourteen-membered ring diterpene dilactone isolated from *Anisomeles ovata*, have been elucidated by ^{1}H n.m.r. spectroscopy including intramolecular nuclear Overhauser effect measurements. The structure of ovatodiolic acid (3), an acid cyclization product of (1) has also been investigated. Single-crystal *X*-ray analyses have confirmed the structural and stereochemical assignments of (1) and (3) both of which crystallize in the orthorhombic system, space group $P2_12_12_1$, with $a = 12.798(8)$, $b = 13.255(8)$, $c = 10.950(8)$ Å, $Z = 4$, for (1), and $a = 12.994(8)$, $b = 14.435(9)$, $c = 9.432(8)$ Å, $Z = 4$, for (3). The crystal structures were solved by direct non-centrosymmetric phase-determining procedures and atomic parameters refined from diffractometer data by full-matrix least-squares calculations to *R* 0.071 [1 280 reflections (1)] and 0.074 [1 399 reflections, (3)]. The trisubstituted *trans* double bonds in (3) are distinctly distorted from planarity.

OVATODIOLIDE, $C_{20}H_{24}O_4$, a crystalline macrocyclic diterpene dilactone isolated from *Anisomeles ovata* was earlier assigned structure (1) with undefined stereochemistry.[1] In view of the increasing importance of cembrene-type fourteen-membered ring diterpenes in Nature,[2] we have further investigated the stereochemistry of (1). The present paper describes the results of conformational and configurational studies of (1) and tetrahydro-ovatodiolide (2) by intramolecular nuclear Overhauser effect (n.o.e.) measurements which lead to definition of the total relative stereochemistry as represented by structure (1). Also reported here are structural investigations on ovatodiolic acid (3) which was obtained by cyclization of (1) in the presence of acid. The results of single-crystal *X*-ray analyses performed on (1) and (3) are in complete accord with the structural assignments and provide details of the solid-state conformations.



(1)



(2)

Stereochemistry and Conformation of Ovatodiolide (1).— The 100 MHz ^{1}H n.m.r. spectra of (1) were examined in

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[1] H. Immer, J. Polonsky, R. Toubiana, and H. D. An, *Tetrahedron*, 1965, **21**, 2117; H. D. An, R. Toubiana, and E. Lederer, *Bull. Soc. chim. France*, 1963, 1192.

[2] For a leading ref., see W. G. Dauben, G. H. Beasley, M. D. Broadhurst, B. Muller, D. J. Peppard, P. Pesnelle, and C. Suter, *J. Amer. Chem. Soc.*, 1974, **96**, 4724; 1975, **97**, 4973.

both [^{2}H]chloroform and [$^2H_6$]benzene. Detailed spin-decoupling and INDOR experiments revealed signal assignments indicated which are illustrated in the Supplementary Publication (see later); δ and J values are given in Table 1. Double irradiation of the H(1) multiplet at *ca.* δ 2.45 caused no enhancement in any signals at lower fields; this fact suggested a *trans*-relationship between H(1) and H(2). Upon double irradiation of the H(18) and H(20) methyl signals no increase was observed in the integrated intensities of the H(3) and H(11) multiplets and consequently *trans*-configurations were indicated for the C(3):C(4) and C(11):C(12) double bonds;[3b] however, in this same experiment n.o.e. values CH_3(18)→(2) of 20—25% and CH_3 (18)→(7) of 6—8% were noted (see Figure 1). When these observations are considered along with the ^3J[H(2),H(3)] (10.0) and ^3J[H(5),H(6)] (4.0 and 3.7 Hz) values obtained, the relative stereochemistry of ovatodiolide may be defined as in (1) and the solution conformation approximately as shown in Figure 1 where other observed n.o.e. values are also provided. It should be noted that long-range spin-couplings ^5J[H(2), H(17A)] (*ca.* 0.3 Hz) and ^4J[H(3),H(5A)] (*ca.* 0.8 Hz) were observed but no discernible couplings were found for ^5J[H(2),H(17B)] or ^4J[H(3),H(5B)].

TABLE 1

^{1}H n.m.r. spectral data on ovatodiolide(1) and tetrahydro-ovatodiolide (2)

	(1)			(2)		
H	δ [a]	δ [b]	ASIS [c]	δ [a]	δ [b]	ASIS [c]
1	~2.45	~2.35	~−0.10			
2	4.85	4.63	−0.22	4.52	4.08	−0.44
3	5.15	5.10	−0.05	5.35	5.22	−0.13
5A	2.86	2.36	−0.50	2.83	2.41	−0.42
5B	2.29	1.56	−0.73	2.41	1.61	−0.80
6	5.10	4.36	−0.74	5.11	4.30	−0.81
7	7.03	6.08	−0.95	7.00	6.00	−1.00
11	4.90	4.70	−0.20			
17A	6.20	6.13	−0.07			
17B	5.60	5.13	−0.47	1.25	1.02	−0.23
18	1.74	1.27	−0.47	1.74	1.21	−0.53
20	1.62	1.46	−0.16	0.88	0.86	−0.02

(1) |J|/Hz	(2) |J|/Hz
1,2 1.8; 1,17A 2.0; 1,17B 1.8; 2,3 10.0; 2,17A ≈ 0.3; 2,17B <0.1; 3,5A 0.8; 3,5B <0.1; 3,18 1.3; 5A,5B 14.2; 5A,6 4.0; 5A,7 ≈ 0.3; 5B,6 3.7; 5B,7 <0.1; 6,7 ≈ 1; 17A,17B <0.1	1,2 9.6; 2,3 9.0; 3,5A 0.8; 3,5B < 0.3; 3,18 1.3; 5A,5B 14.0; 5A,6 4.5; 5A,7 ≈ 0.3; 5B,6 4.0; 5B,7 <0.1; 6,7 ≈ 1; 12,20 6.8; 15,17 6.8

[a] $CDCl_3$. [b] C_6D_6. [c] Δδ/p.p.m.

The 100 MHz spectra of (2) were also examined in both solvents in order to confirm the foregoing results; δ and J values are included in Table 1. Complete saturation of the H(18) methyl signal caused increases in the integrated intensities of the H(2) and H(7) signals by *ca.* 20 and 10%, respectively, but did not enhance the H(3) or H(6) signals. Other n.o.e. values similar to those observed for (1) were obtained. Both (1) and (2) appear to be completely mobile in solution around C(9)—C(14) but the C(1)—C(8) skeleton apparently adopts a fairly rigid conformation.

Aromatic-solvent induced shifts (ASIS) with benzene[4] for (1) and (2) are also listed in Table 1. The fairly small upfield shift (−0.10 p.p.m.) of the H(1) signal implies that H(1) is situated to the same side of the OC(19)–O grouping[4b] as the OC(16)–O grouping and this results in cancellation of the expected large upfield shift of the H(1) signal due to the latter.[4b] Furthermore, the small upfield shifts of the H(3) signals in (1) (−0.05) and (2) (−0.13 p.p.m.) indicate that this olefinic proton is located approximately equidistant from the OC(16)–O and OC(19)–O reference planes. Both observations are consistent with the stereochemistry and conformation of (1) as shown in Figure 1.

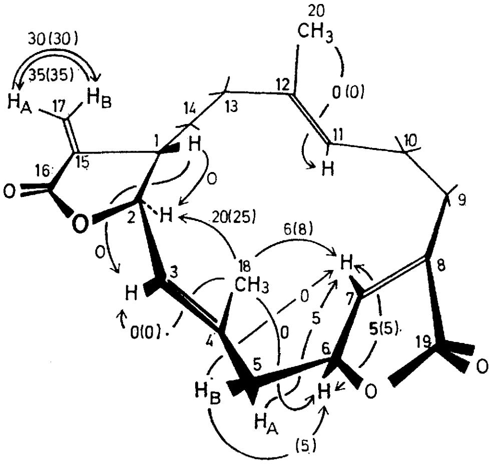

FIGURE 1 Conformation and stereochemistry of (1) and the results of n.o.e. measurements in [^{2}H]chloroform, % values in parentheses are n.o.e. values obtained in [^{2}H]benzene; *i*-H→*j*-H indicates that an n.o.e. was observed on the *j*-H signal when the *i*-H signal was completely saturated by double irradiation

The results of a single-crystal X-ray analysis of (1) confirmed that it is a $\Delta^{3,4}$*trans*, $\Delta^{7,8}$*trans*, $\Delta^{11,12}$*trans*-triene dilactone of the cembrane class of diterpenoids. Figure 2 is a view of the solid-state conformation and this corresponds closely with that derived from the solution n.m.r. studies. Final atomic co-ordinates and thermal parameters are listed in Tables 2 and 3, interatomic distances and valency angles between the non-hydrogen atoms in Table 4, and torsion angles in Table 5.

The means of chemically equivalent bonds are in good agreement with accepted values:[5] $C(sp^3)-C(sp^3)$ 1.529, $C(sp^3)-C(sp^2)$ 1.509, $C(sp^2)-C(sp^2)$ 1.459, $C(sp^2)=C(sp^2)$ 1.330, $C(sp^3)-O$ 1.463, $C(sp^2)-O$ 1.378, $C(sp^2)=O$ 1.203, C–H 1.02 Å.

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[3] (*a*) J. H. Noggle and R. E. Schirmer, 'The Nuclear Overhauser Effect,' Academic Press, New York and London, 1971; (*b*) K. Takeda, K. Tori, I. Horibe, H. Minato, N. Hayashi, S. Hayashi, and T. Matsuura, *J. Chem. Soc.* (*C*), 1970, 985, and references therein.

[4] (*a*) For a leading recent reference, see K. Nikki, N. Nakawaga, and Y. Takeuchi, *Bull. Chem. Soc. Japan*, 1975, **48**, 2902, and references therein; (*b*) J. D. Connolly and R. McCrindle, *Chem. and Ind.*, 1965, 2066; C. R. Narayanan and N. K. Venkatasubramanian, *J. Org. Chem.*, 1968, **33**, 3156.

[5] *Chem. Soc. Special Publ.*, No. 11, 1958; No. 18, 1965.

In the fourteen-membered macrocyclic ring the mean endocyclic valency angle at 117.7° is intermediate between those of 116.1° in crassin *p*-iodobenzoate[6] (two *trans* double bonds) and 116.7° in eupalmerin acetate[7] (one *trans* double bond, one epoxide), and that of 119.4° in cembrene[8] (three *trans*, one *cis* double bonds). Thus the value is correlated with the degree of unsaturation of the ring. The only noteworthy transannular separations in the macrocyclic ring occur in the vicinity of the C(3)–C(4) and C(7)–C(8) double bonds where the large difference between the short C(4) · · · C(7) separation (2.99 Å), and the much larger C(3) · · ·

TABLE 2

Fractional atomic co-ordinates (× 10^4) for the non-hydrogen atoms, with estimated standard deviations in parentheses *

Atom	*x*	*y*	*z*
(*a*) Ovatodiolide (1)			
C(1)	−1 354(4)	3 858(4)	1 678(5)
C(2)	−1 506(4)	3 139(4)	2 790(5)
C(3)	−931(5)	3 469(4)	3 916(5)
C(4)	−335(4)	2 894(5)	4 634(5)
C(5)	209(5)	3 339(5)	5 737(5)
C(6)	1 232(5)	3 858(5)	5 429(5)
C(7)	1 957(4)	3 329(5)	4 596(5)
C(8)	2 153(4)	3 884(4)	3 598(5)
C(9)	2 821(5)	3 660(5)	2 489(6)
C(10)	2 261(4)	3 799(4)	1 288(5)
C(11)	1 285(5)	3 165(4)	1 178(5)
C(12)	619(5)	3 204(5)	264(5)
C(13)	−385(5)	2 621(6)	272(6)
C(14)	−1 341(5)	3 290(6)	454(6)
C(15)	−2 269(5)	4 537(5)	1 786(7)
C(16)	−3 043(5)	4 061(5)	2 545(6)
C(17)	−2 440(7)	5 427(7)	1 290(13)
C(18)	−184(6)	1 757(5)	4 394(8)
C(19)	1 564(5)	4 839(4)	3 724(5)
C(20)	784(7)	3 901(8)	−844(7)
O(1)	−2 627(3)	3 208(3)	3 078(4)
O(2)	−3 927(4)	4 298(6)	2 767(6)
O(3)	1 016(3)	4 804(3)	4 804(4)
O(4)	1 548(4)	5 562(3)	3 053(5)
(*b*) Ovatodiolic acid (3)			
C(1)	9 486(4)	3 354(3)	−6 352(5)
C(2)	9 536(4)	3 389(3)	−4 718(5)
C(3)	8 829(4)	4 143(3)	−4 170(5)
C(4)	8 125(4)	4 047(4)	−3 104(5)
C(5)	7 671(5)	4 904(5)	−2 441(6)
C(6)	8 497(5)	5 427(4)	−1 527(5)
C(7)	9 225(5)	4 775(4)	−876(5)
C(8)	10 132(4)	4 814(3)	−1 525(5)
C(9)	11 003(4)	4 146(4)	−1 571(5)
C(10)	10 781(4)	3 313(3)	−2 575(5)
C(11)	10 620(4)	3 548(3)	−4 140(5)
C(12)	11 378(4)	3 833(4)	−4 963(5)
C(13)	11 230(5)	4 078(4)	−6 527(6)
C(14)	10 114(5)	4 146(3)	−6 968(5)
C(15)	9 790(4)	2 411(3)	−6 973(4)
C(16)	9 452(5)	2 282(3)	−8 481(5)
C(17)	10 266(5)	1 746(4)	−6 305(5)
C(18)	7 858(5)	3 141(5)	−2 413(7)
C(19)	10 085(5)	5 610(3)	−2 519(6)
C(20)	12 488(5)	3 952(5)	−4 451(8)
O(1)	9 858(4)	1 539(3)	−9 077(4)
O(2)	8 847(4)	2 782(3)	−9 080(4)
O(3)	9 132(3)	5 983(2)	−2 467(4)
O(4)	10 735(3)	5 938(3)	−3 265(5)

* Standard deviations quoted in parentheses throughout are in terms of the least significant digit quoted.

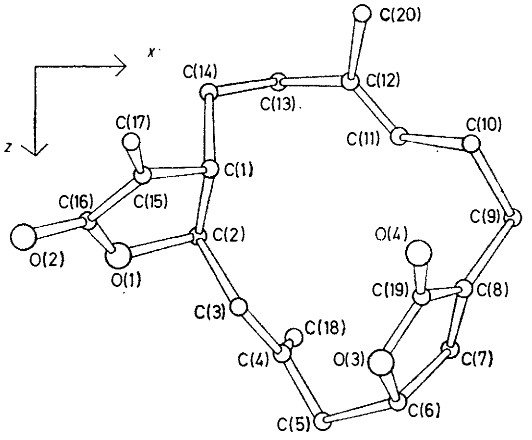

FIGURE 2 Atomic arrangement and conformation of ovatodiolide (1) in the solid state

TABLE 3

Hydrogen atom fractional co-ordinates (× 10^3), isotropic thermal parameters, and distances (Å) to their bonded carbon or oxygen atoms; estimated standard deviations are in parentheses

Atom	*x*	*y*	*z*	B/Å^2	d/Å
(*a*) Ovatodiolide (1)					
H(1)	−66(5)	427(5)	162(6)	3.3(14)	1.05(7)
H(2)	−138(5)	240(4)	249(5)	1.6(14)	1.04(6)
H(3)	−112(5)	420(5)	419(6)	2.2(13)	1.04(6)
H(5A)	32(5)	286(6)	639(7)	4.0(17)	0.97(7)
H(5B)	−24(6)	378(6)	622(8)	4.5(19)	0.98(8)
H(6)	159(6)	396(6)	612(8)	5.3(21)	0.89(8)
H(7)	216(7)	259(7)	464(8)	8.0(26)	1.01(9)
H(9A)	308(6)	288(6)	246(7)	6.1(19)	1.09(8)
H(9B)	344(8)	406(6)	228(8)	8.1(26)	0.98(10)
H(10A)	275(6)	359(5)	76(7)	2.7(17)	0.90(7)
H(10B)	197(6)	452(5)	124(7)	4.2(17)	1.03(7)
H(11)	108(5)	266(5)	188(6)	3.5(15)	1.06(7)
H(13A)	−39(5)	207(4)	100(6)	1.7(13)	1.08(6)
H(13B)	−45(5)	222(5)	−66(6)	3.1(16)	1.15(7)
H(14A)	−195(6)	276(6)	29(7)	5.9(20)	1.07(8)
H(14B)	−136(6)	380(6)	−12(7)	4.0(16)	0.93(8)
H(17A)	−188(7)	562(7)	55(8)	6.3(23)	1.11(9)
H(17B)	−307(7)	581(6)	135(8)	8.1(23)	0.95(9)
(*b*) Ovatodiolic acid (3)					
H(1)	869(4)	345(4)	−668(7)	1.3(12)	1.08(6)
H(2)	930(5)	279(4)	−430(7)	2.1(7)	1.00(7)
H(3)	905(5)	468(5)	−469(7)	1.9(13)	0.96(7)
H(5A)	740(8)	536(7)	−325(12)	3.7(17)	1.07(7)
H(5B)	703(5)	473(5)	−180(9)	6.1(25)	1.06(7)
H(6)	813(7)	582(7)	−73(11)	8.4(25)	1.06(10)
H(7)	907(7)	436(6)	8(12)	3.5(24)	1.10(11)
H(9A)	1 180(6)	434(6)	−183(9)	6.7(23)	1.10(8)
H(9B)	1 095(7)	379(6)	−37(11)	3.1(11)	1.24(10)
H(10A)	1 142(4)	289(4)	−247(6)	0.7(11)	1.03(6)
H(10B)	1 004(4)	302(4)	−225(6)	1.4(12)	1.10(5)
H(13A)	1 155(6)	470(6)	−660(9)	3.0(9)	1.00(8)
H(13B)	1 152(6)	355(5)	−720(8)	3.4(19)	1.06(7)
H(14A)	990(7)	479(6)	−694(12)	11.6(32)	1.06(7)
H(14B)	1 016(9)	415(7)	−825(15)	6.0(24)	0.97(9)
H(17A)	1 041(7)	117(7)	−665(12)	5.4(21)	0.91(9)
H(17B)	1 052(7)	184(6)	−525(12)	6.0(23)	1.06(9)
H(O1)	968(7)	139(6)	−1 012(11)	4.6(23)	1.03(10)

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[6] M. B. Hossain and D. van der Helm, *Rec. Trav. chim.*, 1969, **88**, 1413.

[7] S. E. Ealick, D. van der Helm, and A. J. Weinheimer, *Acta Cryst.*, 1975, **B31**, 1618.

[8] M. G. B. Drew, D. H. Templeton, and A. Zalkin, *Acta Cryst.*, 1969, **B25**, 261.

C(8) distance (4.00 Å) gives a measure of the non-parallel orientation of these bonds which reduces the severity of their π–π interactions; the dihedral angle between the normals to the C(2)—(5),C(18) and C(6)—(9),C(19) least-squares planes is 117°. Torsion angles around the trisubstituted double bonds lie close to the strain-free 180 and 0° values, and accordingly, the atoms in the individual moieties may be regarded as being coplanar.

In the unsaturated γ-lactone ring the sum of the moduli of the endocyclic torsion angles, $\Sigma|\omega|$ 4°, indicates that the atoms are coplanar. The conformation of the *trans*-fused α-methylene-γ-lactone ring approximates to a half-chair (C_2) with C(1) and C(2) displaced by 0.21 and 0.15 Å to opposite sides of the least-squares plane through C(15),C(16),O(1), and O(2). In accord with previous observations [9] for such rings, the C(15)–C(1)–C(2)–O(1) torsion angle (22°) has its sign paired with the C(17)–C(15)–C(16)–O(2) torsion angle (7°), and is *ca.* 3 times its magnitude.

The arrangement of molecules in the crystal is illustrated in Figure 3; the shorter intermolecular separations (Table 4) all involve oxygen atoms and correspond to normal van der Waals type interactions.

The absolute configuration of (1) could not be assigned from the c.d. spectra of (1) ($[\theta]_{215}$ −6000; $[\theta]_{235}$ +13 700) and (2) ($[\theta]_{216}$ +14 900) in methanol since the interpretation is complicated by the presence of two γ-lactone rings and their possible interactions with the C(3):C(4) and/or C(11):C(12) double bonds.

Structure and Stereochemistry of Ovatodiolic Acid (3), *a Cyclization Product of* (1).—Ovatodiolide (1) when heated under reflux in formic acid or in benzene in the presence of toluene-*p*-sulphonic acid afforded a new crystalline compound, $C_{20}H_{24}O_4$, for which structure (3) is suggested to accord with the following data. The i.r. spectrum showed a γ-lactone band at 1 740 cm^{-1} and a carboxy-band at 1 710 cm^{-1}, the latter being absent in the spectrum of (1). The ^{1}H n.m.r. spectrum of (3) in [^{2}H]chloroform showed a resonance at δ 10.9, not present in the spectrum of (1) and characteristic of a carboxylic proton. Other spectral differences are apparent. In particular, the region between δ 4.6 and 5.3 of the spectrum of (3) showed the presence of one proton of the *H*–C–O type and one olefinic proton in contrast to the

TABLE 4

Interatomic distances (Å) and angles (deg.) with estimated standard deviations in parentheses

	(1)	(3)
(*a*) Bond lengths		
C(1)–C(2)	1.559(8)	1.543(6)
C(1)–C(14)	1.538(8)	1.521(7)
C(1)–C(15)	1.482(8)	1.534(6)
C(2)–C(3)	1.502(8)	1.515(7)
C(2)–C(11)		1.528(7)
C(2)–O(1)	1.471(7)	
C(3)–C(4)	1.334(8)	1.366(7)
C(4)–C(5)	1.514(8)	1.506(8)
C(4)–C(18)	1.542(9)	1.502(8)
C(5)–C(6)	1.517(9)	1.571(8)
C(6)–C(7)	1.478(8)	1.468(8)
C(6)–O(3)	1.455(7)	1.453(7)
C(7)–C(8)	1.341(8)	1.329(8)
C(8)–C(9)	1.513(8)	1.488(8)
C(8)–C(19)	1.480(8)	1.483(7)
C(9)–C(10)	1.509(9)	1.558(7)
C(10)–C(11)	1.510(8)	1.529(7)
C(11)–C(12)	1.316(8)	1.319(7)
C(12)–C(13)	1.499(9)	1.529(7)
C(12)–C(20)	1.540(10)	1.531(8)
C(13)–C(14)	1.524(10)	1.511(8)
C(15)–C(16)	1.438(9)	1.500(7)
C(15)–C(17)	1.316(12)	1.304(7)
C(16)–O(1)	1.379(8)	1.321(7)
C(16)–O(2)	1.199(8)	1.207(8)
C(19)–O(3)	1.376(7)	1.351(7)
C(19)–O(4)	1.207(7)	1.198(7)

TABLE 4 (*Continued*)

	(1)	(3)
(*b*) Valency angles		
C(2)–C(1)–C(14)	112.5(5)	109.5(4)
C(2)–C(1)–C(15)	102.2(4)	113.6(4)
C(14)–C(1)–C(15)	112.0(5)	112.5(4)
C(1)–C(2)–C(3)	113.7(4)	109.8(4)
C(1)–C(2)–C(11)		113.6(4)
C(1)–C(2)–O(1)	104.5(4)	
C(3)–C(2)–O(1)	106.4(4)	
C(3)–C(2)–C(11)		109.2(4)
C(2)–C(3)–C(4)	126.7(5)	125.8(4)
C(3)–C(4)–C(5)	120.7(6)	119.0(5)
C(3)–C(4)–C(18)	122.0(5)	124.2(5)
C(5)–C(4)–C(18)	117.3(5)	116.4(5)
C(4)–C(5)–C(6)	113.3(5)	110.8(5)
C(5)–C(6)–C(7)	117.7(5)	111.2(5)
C(5)–C(6)–O(3)	109.3(5)	108.6(4)
C(7)–C(6)–O(3)	103.8(4)	104.1(5)
C(6)–C(7)–C(8)	111.1(5)	110.5(4)
C(7)–C(8)–C(9)	130.7(5)	131.3(5)
C(7)–C(8)–C(19)	107.3(5)	106.7(5)
C(9)–C(8)–C(19)	122.0(5)	121.0(4)
C(8)–C(9)–C(10)	114.0(5)	112.1(4)
C(9)–C(10)–C(11)	113.2(5)	116.2(4)
C(2)–C(11)–C(10)		115.9(4)
C(2)–C(11)–C(12)		121.7(4)
C(10)–C(11)–C(12)	125.1(5)	122.3(5)
C(11)–C(12)–C(13)	122.1(6)	123.0(5)
C(11)–C(12)–C(20)	122.2(6)	123.6(5)
C(13)–C(12)–C(20)	115.6(6)	113.4(5)
C(12)–C(13)–C(14)	112.9(6)	113.7(5)
C(1)–C(14)–C(13)	114.1(5)	111.1(4)
C(1)–C(15)–C(16)	108.9(5)	113.4(4)
C(1)–C(15)–C(17)	130.0(7)	126.2(4)
C(16)–C(15)–C(17)	121.1(7)	120.4(4)
C(15)–C(16)–O(1)	109.8(5)	112.8(5)
C(15)–C(16)–O(2)	130.7(7)	124.1(5)
O(1)–C(16)–O(2)	119.5(6)	123.1(5)
C(8)–C(19)–O(3)	108.1(5)	108.9(5)
C(8)–C(19)–O(4)	129.1(6)	130.4(5)
O(3)–C(19)–O(4)	122.8(5)	120.6(5)
C(16)–O(1)–C(2)	109.7(4)	
C(6)–O(3)–C(19)	109.7(4)	108.8(4)

(*c*) Intermolecular distances <3.6 Å between non-hydrogen atoms

(*a*) Ovatodiolide (1)			
C(7) ··· O(1$^{\mathrm{I}}$)	3.31	O(4) ··· C(2$^{\mathrm{II}}$)	3.54
C(10) ··· O(3$^{\mathrm{III}}$)	3.31	O(4) ··· C(18$^{\mathrm{II}}$)	3.57
C(6) ··· O(1$^{\mathrm{I}}$)	3.51		
(*b*) Ovatodiolic acid (3)			
O(4) ··· O(2$^{\mathrm{IV}}$)	2.76	C(19) ··· O(2$^{\mathrm{IV}}$)	3.48
C(7) ··· O(1$^{\mathrm{V}}$)	3.37	C(17) ··· C(18$^{\mathrm{VI}}$)	3.57
C(18) ··· O(1$^{\mathrm{V}}$)	3.44	C(14) ··· O(2$^{\mathrm{IV}}$)	3.59

Roman numeral superscripts refer to the following transformations of the reference molecule at x, y, z:

I $\frac{1}{2} + x, \frac{1}{2} - y, 1 - z$
II $-x, \frac{1}{2} + y, \frac{1}{2} - z$
III $\frac{1}{2} - x, 1 - y, -\frac{1}{2} + z$
IV $2 - x, \frac{1}{2} + y, -\frac{3}{2} - z$
V $x, y, 1 + z$
VI $\frac{1}{2} + x, \frac{1}{2} - y, -1 - z$

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[9] A. T. McPhail and G. A. Sim, *Tetrahedron*, 1973, **29**, 1751.

two *H*–C–O and two olefinic proton signals found in this region of the spectrum of (1). Other signals for (3) were similar to those of (1): that of H(7) appeared at δ 6.82 as a multiplet; those of H(17A) and H(17B) were at 5.58 and 6.32; two double-bond methyl signals occurred as doublets at 1.58 and 1.75.

TABLE 5

Torsion angles (°), estimated standard deviation *ca.* 1°. The angle A–B–C–D is defined as positive if, when viewed along the B–C bond, atom A must be rotated clockwise to eclipse atom D

	(1)	(3)
C(14)–C(1)–C(2)–C(3)	146	77
C(14)–C(1)–C(2)–C(11)		−46
C(14)–C(1)–C(2)–O(1)	−99	
C(15)–C(1)–C(2)–C(3)	−94	−156
C(15)–C(1)–C(2)–C(11)		81
C(15)–C(1)–C(2)–O(1)	22	
C(2)–C(1)–C(14)–C(13)	−68	60
C(15)–C(1)–C(14)–C(13)	177	−67
C(2)–C(1)–C(15)–C(16)	−19	163
C(2)–C(1)–C(15)–C(17)	162	−15
C(14)–C(1)–C(15)–C(16)	102	−72
C(14)–C(1)–C(15)–C(17)	−77	110
C(1)–C(2)–C(3)–C(4)	−133	131
O(1)–C(2)–C(3)–C(4)	113	
C(11)–C(2)–C(3)–C(4)		−103
C(1)–C(2)–C(11)–C(10)		−163
C(3)–C(2)–C(11)–C(10)		74
C(1)–C(2)–C(11)–C(12)		14
C(3)–C(2)–C(11)–C(12)		−109
C(1)–C(2)–O(1)–C(16)	−18	
C(3)–C(2)–O(1)–C(16)	103	
C(2)–C(3)–C(4)–C(5)	179	165
C(2)–C(3)–C(4)–C(18)	−2	−7
C(3)–C(4)–C(5)–C(6)	−83	−70
C(18)–C(4)–C(5)–C(6)	98	103
C(4)–C(5)–C(6)–C(7)	−45	−33
C(4)–C(5)–C(6)–O(3)	73	81
C(5)–C(6)–C(7)–C(8)	121	106
O(3)–C(6)–C(7)–C(8)	0	−10
C(5)–C(6)–O(3)–C(19)	−127	−110
C(7)–C(6)–O(3)–C(19)	−1	8
C(6)–C(7)–C(8)–C(9)	−179	−160
C(6)–C(7)–C(8)–C(19)	1	8
C(7)–C(8)–C(9)–C(10)	128	76
C(19)–C(8)–C(9)–C(10)	−52	−91
C(7)–C(8)–C(19)–O(3)	−1	−3
C(7)–C(8)–C(19)–O(4)	177	175
C(9)–C(8)–C(19)–O(3)	178	167
C(9)–C(8)–C(19)–O(4)	−3	−15
C(8)–C(9)–C(10)–C(11)	−57	62
C(9)–C(10)–C(11)–C(2)		−113
C(9)–C(10)–C(11)–C(12)	175	70
C(2)–C(11)–C(12)–C(13)		3
C(2)–C(11)–C(12)–C(20)		−177
C(10)–C(11)–C(12)–C(13)	−174	180
C(10)–C(11)–C(12)–C(20)	2	0
C(11)–C(12)–C(13)–C(14)	108	11
C(20)–C(12)–C(13)–C(14)	−69	−169
C(12)–C(13)–C(14)–C(1)	−62	−44
C(1)–C(15)–C(16)–O(1)	9	170
C(1)–C(15)–C(16)–O(2)	−172	−13
C(17)–C(15)–C(16)–O(1)	−172	−12
C(17)–C(15)–C(16)–O(2)	7	165
C(15)–C(16)–O(1)–C(2)	6	
O(2)–C(16)–O(1)–C(2)	−173	
C(8)–C(19)–O(3)–C(6)	1	−4
O(4)–C(19)–O(3)–C(6)	−177	178

Preparation of the series of derivatives shown in Scheme 1 (see Experimental section) indicated a structure for (3) in which the fourteen-membered ring had been modified to a bicyclic system with the following functional groups: four double bonds, two of which were conjugated, one αβ-unsaturated carboxy-group, and one αβ-unsaturated γ-lactone. Single-crystal *X*-ray analysis confirmed this structure and completely defined the stereochemistry (*vide infra*).

The allylic character of the C(2)–O γ-lactone bond renders (1) susceptible to opening of this ring by acid catalysis in a manner similar to that reported for the ψ-santonin (9) to ψ-santonic acid (10) transformation [10,11] which has been viewed as proceeding through an allylic carbonium ion intermediate. For the transformation of (1) to (3), stabilization of the carbonium-ion intermediate occurs by intramolecular Markownikoff-type cyclization [12] involving the C(11):C(12) double bond and leads to contraction of the fourteen-membered ring of (1) to produce the bicyclic form found in acid (3) (see Scheme 2).

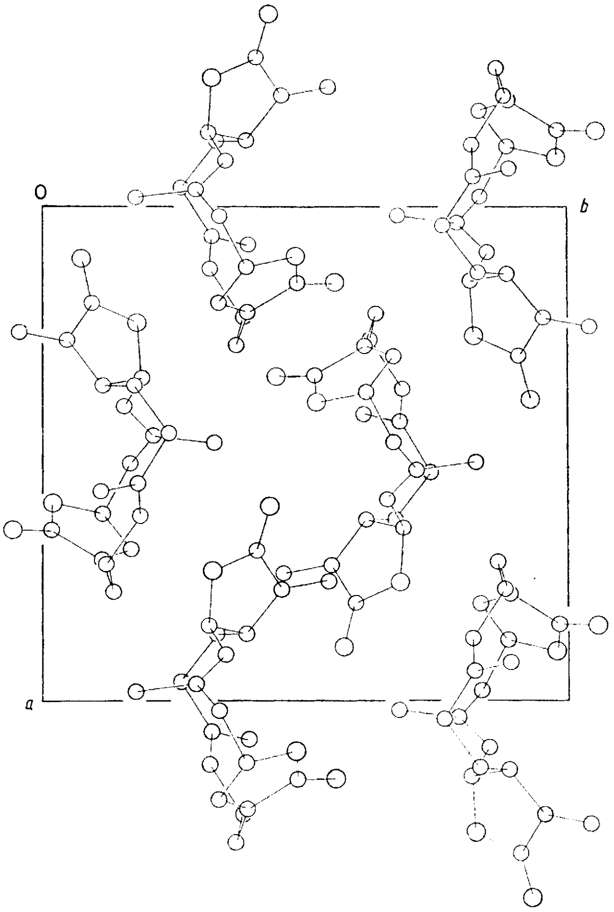

FIGURE 3 Molecular packing in crystals of ovatodiolide (1), viewed in projection along the *c* axis

X-Ray crystal-structure analysis of acid (3) confirmed the constitution and relative stereochemistry to be as

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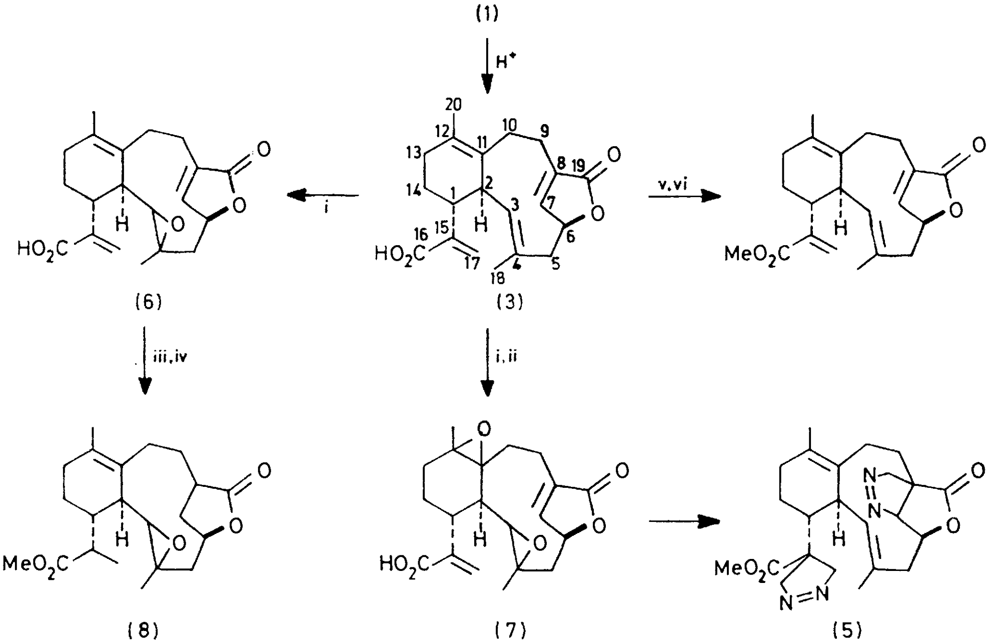
[10] W. G. Dauben, P. D. Hance, and W. K. Hayes, *J. Amer. Chem. Soc.*, 1955, **77**, 4609.

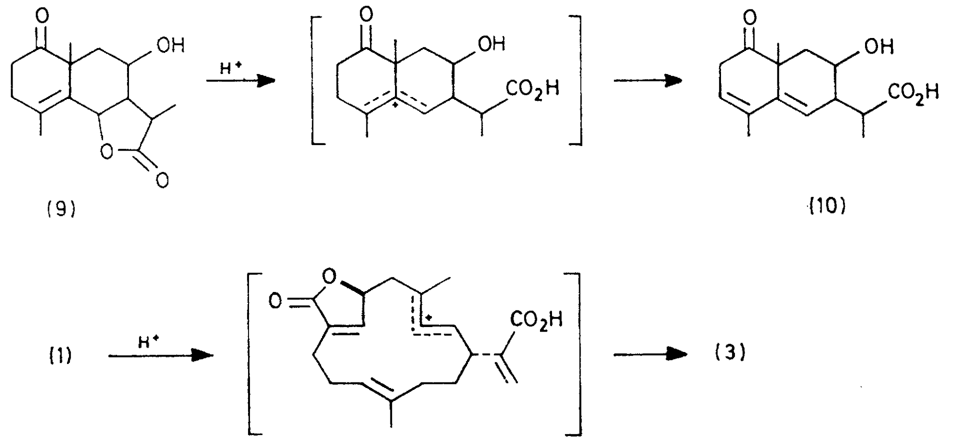
[11] N. M. Chopra, W. Cocker, J. T. Edward, T. B. H. McMurry, and E. R. Stuart, *J. Chem. Soc.*, 1956, 1828.

[12] W. Parker, J. S. Roberts, and R. Ramage, *Quart. Rev.*, 1967, **21**, 331.

shown. Figure 4 illustrates the molecular conformation and shows the atom numbering scheme. Final atomic co-ordinates and thermal parameters are listed in Tables 2 and 3. Interatomic distances, valency and torsion angles are included for comparison alongside the corresponding ovatodiolide values in Tables 4 and 5.



SCHEME 1 Reagents: i, *p*-nitroperbenzoic acid; ii, excess; iii, CH_2N_2; iv, H_2-Pt; v, $AgNO_3$; vi, MeI



SCHEME 2

Contraction from the fourteen-membered macrocyclic ring in (1) to the *trans,trans*-cyclodeca-1,5-diene ring in (3) introduces considerable strain which is reflected in the significant elongation of the C(5)–C(6) bond in (3) to 1.571(8) from 1.517(9) Å in (1). A similar bond-length extension [1.573(13) Å], has been found at the corresponding cyclodeca-1,5-diene bond of eupatolide.[13] Around the C(3):C(4) and C(7):C(8) double bonds the ring strain in (3) is evident from the highly significant departures of the torsion angles around these bonds from their ideal values. The short C(3) $\cdots$ C(7) and C(3) $\cdots$ C(8) transannular separations (3.28 and 3.16 Å) and their associated C(2)–C(3)–C(4)–C(5) and C(6)–C(7)–C(8)–C(9) torsion angles (165 and −160°) are similar to the corresponding values found in the medium rings of germacranolide sesquiterpenoids.[13-15] The similar magnitude of the C(4) $\cdots$ C(7) and C(3) $\cdots$ C(8) distances (2.75 and 3.16 Å) in (3) means that the double bonds are more nearly parallel than in (1) and an increased amount of π–π interaction must be present; the dihedral angle (35°) between the normals to the least-squares planes through C(2)—(5), C(18) and through C(6)—(9), C(19) is consequently much smaller than the corresponding value in (1) (116°). The C(2)–C(3)–C(4)–C(18) and C(6)–

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[13] A. T. McPhail and K. D. Onan, *J.C.S. Perkin II*, 1975, 1798.

[14] R. J. McClure, G. A. Sim, P. Coggon, and A. T. McPhail, *Chem. Comm.*, 1970, 128.

[15] A. T. McPhail and G. A. Sim, *J.C.S. Perkin II*, 1972, 1313.

C(7)–C(8)–C(19) torsion angles (−7 and 8°) indicate that the distortion at each of the trisubstituted double bonds is due to approximately equal contributions arising from true twist around the double bonds and departure from planar trigonal geometry at C(4) and C(8).

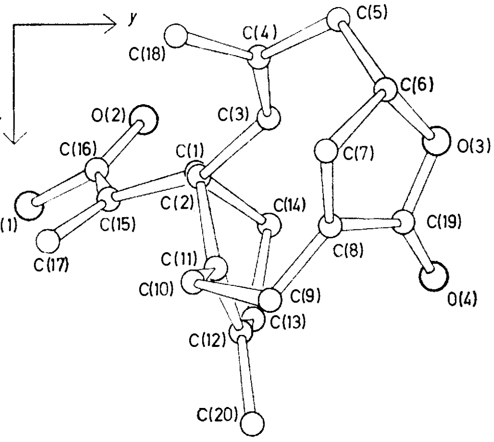

FIGURE 4 Atomic arrangement and conformation of ovatodiolic acid (3)

In contrast to the planar unsaturated γ-lactone ring geometry in (1) ($\Sigma|\omega|$ 4°), the corresponding ring in (3) is puckered ($\Sigma|\omega|$ 35°) as a consequence of the strain around the C(7):C(8) double bond already described. The ring adopts a very flattened half-chair (C_2) conformation in which C(6) and C(7) are displaced by 0.07 and 0.08 Å to opposite sides of the least-squares plane through C(8), C(19), O(3), and O(4). The degree of puckering of this ring, as revealed by the sum of the moduli of the torsion angles, is not dissimilar to that encountered in the strained unsaturated γ-lactone ring of elephantol *p*-bromobenzoate [15] where $\Sigma|\omega|$ is 33°.

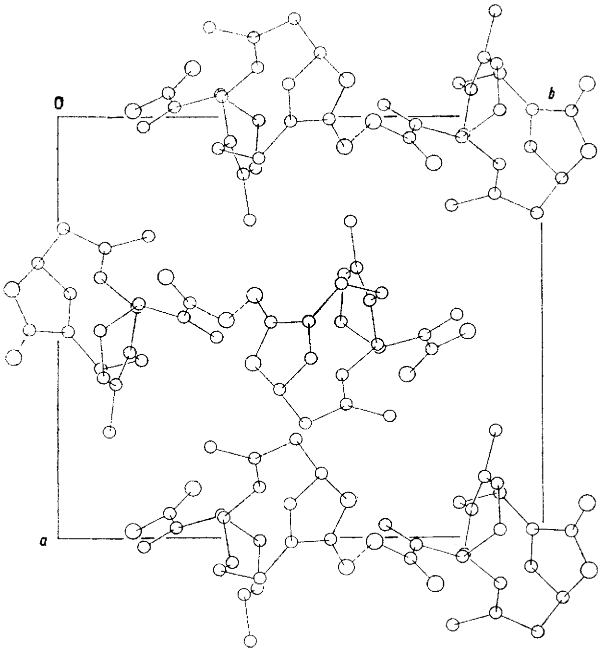

FIGURE 5 Arrangement of ovatodiolic acid molecules in the crystal as viewed in projection along the *c* axis; O–H · · · O hydrogen bonds are denoted by broken lines

The conformation of the cyclohexane ring approximates to a half-chair (C_2) in which C(1) and C(14) are displaced by 0.44 and 0.32 Å to opposite sides of the least-squares plane through C(2), C(10)—(13), and C(20). The C(1) substituent has a quasi-axial orientation.

In the α-methylene carboxylic acid moiety the planar C(1), C(15)—(17) and C(15), C(16), O(1), O(2) groups are twisted by a small amount (12°) about the C(15)–C(16) bond. The C=O bond is *anti* with respect to the C=CH$_2$ bond and is *syn*-oriented with respect to the C(1)–H(1) bond, the latter being similar to the conformation usually associated with secondary esters.[16]

The packing of ovatodiolic acid molecules in the crystal is shown in Figure 5; the shortest intermolecular distance (Table 4) involves the lactone carbonyl group of the reference molecule and the acid hydroxy-group of a molecule related by the 2_1 screw axis along the *b* direction [O(4) · · · O(2) 2.76 Å], and it is typical for an OH · · · O hydrogen bond. Other intermolecular separations correspond to normal van der Waals interactions.

EXPERIMENTAL

All m.p.s were measured with a Kofler apparatus and are corrected. Specific rotations were determined by use of an electronic Roussel–Jouan polarimeter and the c.d. spectra of (1) and (2) were run on a JASCO UV CD 6. Mass spectra were measured on an MS 9 spectrograph, u.v. and i.r. spectra with Perkin-Elmer 202 and 257 spectrophotometers, respectively. N.m.r. spectra were taken with a Varian A 60 spectrometer for CDCl$_3$ solutions, with Me$_4$Si as internal standard unless otherwise noted.

Measurements of N.o.e.—The 100 MHz n.m.r. spectra of (1) and (2) were recorded on a Varian HA 100 spectrometer in CDCl$_3$ and C$_6$D$_6$ in the frequency-swept and internal-tetramethylsilane-locked mode. Errors of δ and J are ±0.01 and ±0.1 Hz, respectively. N.o.e. experiments were carried out by measuring the integrated intensities of a signal with and without irradiation at the resonance frequency of another signal at a sweep rate of 0.4 Hz s^{-1}; at least four measurements were made. Care was taken that the audio phase-sensitive detector of the spectrometer was not overloaded.[3] The enhancement is expressed in %; accuracy is ±2%.

Crystal Data.—*Ovatodiolide* (1). $C_{20}H_{24}O_4$, m.p. 148—150 °C, M = 328.41. Orthorhombic, a = 12.798(8), b = 13.255(8), c = 10.950(8) Å, U = 1 857.5 Å^3, D_m (flotation) = 1.18, Z = 4, D_c = 1.17 g cm^{-3}, $F(000)$ = 7.4. Cu-K_α radiation, λ = 1.541 8 Å; μ(Cu-K_α) = 6.60 cm^{-1}. Space group $P2_12_12_1(D_2^4)$ uniquely from systematic absences.

(*b*) *Ovatodiolic acid* (3). $C_{20}H_{24}O_4$, m.p. 222—225 °C, M = 328.41. Orthorhombic, a = 12.994(8), b = 14.435(9), c = 9.432(8) Å, U = 1 769.1 Å^3, D_m (flotation) = 1.21, Z = 4, D_c = 1.23 g cm^{-3} $F(000)$ = 7.4. μ(Cu-K_α) = 6.93 cm^{-1}. Space group $P2_12_12_1(D_2^4)$ uniquely from systematic absences.

Crystallographic Measurements.—Preliminary cell dimensions and space-group data for (1) and (3) were obtained from oscillation and Weissenberg photographs taken with

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[16] A. McL. Mathieson, *Tetrahedron Letters*, 1965, 4137.

Cu-K_α radiation. Crystals of dimensions *ca.* 0.5 × 0.2 × 0.2 for (1) and *ca.* 0.3 × 0.3 × 0.3 mm for (3) were oriented on glass fibres such that their crystallographic *a* axes were parallel to the ϕ axis of an Enraf-Nonius CAD 3 automated diffractometer (Ni-filtered Cu-K_α radiation, take-off angle 3°). Improved cell parameters were obtained in both cases by least-squares treatment of the θ, χ, and ϕ values of 40 accurately centred reflections widely separated in reciprocal space. For each crystal, one octant of intensity data up to θ 67° was collected by the θ—2θ scanning technique with scanwidths $(1.0 + 0.50\tan\theta)°$ for (1) and $(0.90 + 0.45\tan\theta)°$ for (3). Attenuators were inserted automatically to ensure that counting rates were not $>2\,500$ counts s^{-1}; attenuation factors were derived experimentally. Stationary-background measurements for a time equal to half the scan period were made at each end of the scan range. For each crystal the intensity of a standard reflection re-examined after each batch of 99 reflections showed no significant variation during data collection. From these measurements 1 280 reflections from (1) and 1 399 reflections from (3) for which $I > 2.0\sigma(I)$, where $\sigma(I) = (\text{scan count} + \text{total background count})^{\frac{1}{2}}$, were used in the structure analysis and refinement. Absorption corrections were established experimentally from the ϕ-dependence of the intensity of the 800 reflections from each crystal measured at χ 90°. Data were corrected for Lorentz, polarization, and absorption effects.

Structure Analysis.—Both structures were solved by direct non-centrosymmetric phase-determining procedures by use of the MULTAN[17] programme package and $|E|$ values >1.30. For (1) there were eight reflections in the starting set and for (3) there were nine. In each case an E map computed with that set of phases which gave the highest figure-of-merit and lowest residual revealed clearly positions for all the carbon and oxygen atoms.

Refinement of both structure models by full-matrix least-squares calculations, at first with isotropic and then with anisotropic temperature factors, proceeded smoothly to R 0.090 for (1) and 0.104 for (3). At this point computed positions for all hydrogen atoms, except those of the methyl groups, which could not be located unambiguously, were confirmed to correspond with sites of significant positive electron-density in difference Fourier maps. Further least-squares adjustment of the positional and thermal parameters (anisotropic C,O; isotropic H) brought the refinement to convergence at R 0.071 for (1) and 0.074 for (3). Observed and calculated structure factors together with Figures illustrating 100 MHz n.m.r. spectra for both (1) and (3) have been deposited in Supplementary Publication No. SUP 21814 (22 pp., 1 microfiche).*

In the structure-factor calculations scattering factors were taken from ref. 18 for carbon and oxygen, for hydrogen from ref. 19. The weighting scheme used in the least-squares calculations was of the form $\sqrt{w} = 1$ when $|F_o| < K$, $\sqrt{w} = K/|F_o|$ when $|F_o| > K$ [$K = 11.0$ for (1), 8.0 for (3)] and $\Sigma w\Delta^2$ was minimised. No systematic dependence of $\langle w\Delta^2\rangle$ was noted when analysed in ranges of $|F_o|$ and $\sin\theta$.

Tetrahydro-ovatodiolide (2).—Ovatodiolide (1) (120 mg) was hydrogenated in the presence of palladium–BaCO$_3$ (5%) to give a tetrahydro-derivative (2) (75 mg), $C_{20}H_{28}O_4$, m.p. 155—159 °C (from acetone–isopropyl ether), $[\alpha]_D^{20}$ $-8.6 \pm 0.8°$ (*c* 0.582, CHCl$_3$); *m/e* 332(M^+); $\nu_{max.}$ (CHCl$_3$) 1 760 and 983 cm^{-1}; n.m.r. (see Table 1).

Ovatodiolic Acid (3).—A solution of (1) (2.45 g) in 80 ml of benzene containing 1.65 g of toluene-*p*-sulphonic acid was refluxed for one hour. The solvent was removed and chloroform was added. The extraction was carried out in alkaline conditions. The yields were 450 mg of a neutral substance and 1.87 g of acid (3), $C_{20}H_{24}O_4$ (from MeOH), $[\alpha]_D^{20}$ $-63°$ (*c* 1, CHCl$_3$); *m/e* 328(M^+); n.m.r. (see text). (Found: C, 73.12; H, 7.33. $C_{20}H_{24}O_4$ requires C, 73.14; H 7.33%).

Methyl Ovatodiolate (4).—Ovatodiolic acid (60 mg) was dissolved in 95% ethanol (4 ml) and neutralized with 0.1N-methanolic potassium hydroxide (2.5 ml) (end-point determined with phenolphthalein). To the resulting solution of potassium ovatodiolate was added a 2% solution (2.2 ml) of silver nitrate in ethanol. The mixture was centrifuged and dried to yield silver ovatodiolate (28 mg) which was then dissolved in benzene (2 ml) and heated under reflux for 2 h in the presence of methyl iodide (2 ml). Precipitated silver iodide was removed and the remaining solution treated in the usual manner to give methyl ester (4) (25 mg), $C_{21}H_{26}O_4$, m.p. 125—128 °C (from chloroform–isopropyl ether), $[\alpha]_D^{20}$ $-55°$ (*c* 1, CHCl$_3$); *m/e* 342(M^+); n.m.r. δ 1.58 [d, H(18)], 1.75 [s, H(20)], 3.70 [s, CO$_2$Me], 5.45, 6.15 [m, H(17A,B)], and 6.80 [m, H(7)]; (Found: C, 73.56; H, 7.76. $C_{21}H_{26}O_4$ requires C, 73.66; H, 7.66%).

Dipyrazoline (5).—To a methanol solution of (3) (339 mg) was added a solution of diazomethane until a yellow colour persisted. This solution was left at 4 °C until crystals formed; these were subsequently isolated and dried *in vacuo*. (230 mg); $C_{23}H_{30}N_4O_4$, m.p. 230—235 °C (from MeOH), $[\alpha]_D^{20}$ $+53°$ (*c* 1, dioxan); *m/e* 426(M^+); (Found: C, 64.03; H, 7.10; N, 13.38. $C_{23}H_{30}N_4O_4$ requires C, 64.06; H, 6.84; N, 13.58%).

Monoepoxyovatodiolic Acid (6).—To a solution of (3) (200 mg) in chloroform (10 ml) *p*-nitrobenzoic acid (120 mg) was added and the mixture stirred overnight at room temperature. After filtration solvent was evaporated and the product chromatographed on silica gel (Merck) (16 g). Elution with chloroform–methanol (18 : 2) gave monoepoxide (5) (115 g), $C_{20}H_{24}O_5$, m.p. 272—277 °C (from MeOH), $[\alpha]_D^{20}$ $-20°$ (*c* 1, CHCl$_3$); *m/e* 344(M^+); n.m.r. δ 1.35 [s, H(18)], 1.80 [s, H(20)], 2.85 [d, H(3)], 5.15 [m, H(6)], 5.32, 6.25 [m, H(17A, B)], 7.25 [m, H(7)], and 9.08 [br s, COOH]; (Found: C, 69.83; H, 6.88. $C_{20}H_{24}O_5$ requires C, 69.75; H, 7.02%).

Diepoxyovatodiolic Acid (7).—To (3) (300 mg) dissolved in chloroform (20 ml) was added *p*-nitrobenzoic acid (600 mg) and the mixture stirred overnight at room temperature. After filtration solvent was evaporated and the product chromatographed on silica gel (45 g) (Merck). Elution with chloroform–methanol (98 : 2) afforded diepoxide (7) (130 mg), $C_{20}H_{24}O_6$, m.p. 244—249 °C (from MeOH), $[\alpha]_D^{20}$ $-18°$ (*c* 1, dioxan); *m/e* 360(M^+); n.m.r. δ (pyridine) 1.45 [s, H(18)], 1.68 [s, H(20)], 3.20 [d, H(3)], 5.22 [m, H(6)], 5.78, 6.50 [m, H(17A,B)], 7.50 [m, H(7)], and 8.75 (br s, COOH); (Found: C, 66.78; H, 6.63. $C_{20}H_{24}O_6$ requires C, 66.65: H, 6.71%).

Methyl Tetrahydromonoepoxyovatodiolate (8).—Monoepoxyovatodiolic acid (6) (1 g) dissolved in acetic acid (10 ml)

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

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was hydrogenated in the presence of platinum (500 mg). After the usual treatment and diazomethane esterification, a product (950 mg) was obtained and run on silica gel (30 g) (Merck). After elution with methylene chloride–diethyl ether, methyl ester (8) (450 mg) was obtained, $C_{21}H_{30}O_5$, m.p. 110—113 °C (from diethyl ether–light petroleum), $[\alpha]_D^{20}$ $-72°$ (*c* 1, $CHCl_3$); *m/e* 362(M^+); n.m.r. δ 1.10 [d, H(17)], 1.42 [s, H(18)], 1.72 [s, H(20)], 3.02 [d, H(3)], 3.55 [s, CO_2Me], and 4.60 [m, H(7)]; (Found: C, 69.59; H, 8.39. $C_{21}H_{30}O_5$ requires C, 69.58; H, 8.34%).

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