Stereochemistry of a Novel Sesquiterpene Lactone. *X*-Ray Determination of the Structure of Ursiniolide A Monohydrate ‡

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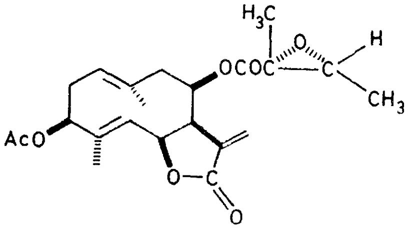
The crystal and molecular structure of ursiniolide A monohydrate has been determined by direct methods from intensity data collected on a diffractometer and refined by full-matrix least-squares to *R* 0.043 over 1 321 reflections. Crystals are tetragonal, space group $P4_1$, with $a = b = 13.921(2)$, $c = 11.187(1)$ Å, $Z = 4$. The cyclodeca-*trans,trans*-1(10),4-diene ring is in the chair-boat conformation with the two methyl groups at C(4) and C(10) in a *syn*-α orientation. The α-methylene-γ-lactone is *cis*-fused at C(6) and C(7) and adopts a distorted half-chair conformation. The water molecules and the molecules of ursiniolide A form a hydrogen-bonded array running along the 4_1 axis. The compound investigated is representative of a group of ursiniolides, the only germacranolides described so far with a lactone ring closed at C(6) and *cis*-annelated to a ten-membered homocycle.

THE isolation of three new sesquiterpene lactones from *Ursinia anthemoides* (L.) Poiret (Compositae, Anthemidae) [1] followed by complex chemical and spectroscopic investigations led to the suggestion that a novel stereochemical group of natural sesquiterpene lactones, germacra-1(10),4-diene-*cis*-6,12-olides has been discovered. To support this suggestion and, in particular, to solve the problem of the γ-lactone ring junction an *X*-ray analysis of ursiniolide A (I) was undertaken. The stereochemical results obtained have been reported briefly together with the results of ^{1}H n.m.r. and c.d. studies carried out for all three ursiniolides.[2] This paper reports details of the molecular conformation of ursiniolide A obtained by the *X*-ray method.



(I)

EXPERIMENTAL

Crystal Data.—$C_{22}H_{28}O_7,H_2O$, tetragonal, space group $P4_1$, $a = b = 13.921(2)$, $c = 11.187(1)$ Å, $U = 2\ 167.8$ Å^3, $D_m = 1.29$, $D_c = 1.29$ g cm^{-3}, $Z = 4$. Cu-K_α radiation, $\lambda = 1.54\ 18$ Å, μ(Cu-K_α) = 0.83 mm^{-1}.

Crystallographic Measurements.—Crystals of the compound suitable for structural analysis were crystallized from butyl alcohol. Precession photographs showed tetragonal symmetry and systematic absences $00l$, $l = 4n + 1$, indicated the $P4_1$ or $P4_3$ space group. A crystal of dimensions 0.3 × 0.3 × 0.4 mm was mounted on a Syntex $P2_1$ diffractometer (Cu-K_α radiation, graphite monochromator). Approximate cell parameters were refined by least-sqaures treatment of the setting angles of 15 reflections. 1 565 Independent reflections were measured in the θ–2θ scan mode up to $2\theta = 115°$. The scan speed varied from 1.8 to 29.3 ° min^{-1}. 1 323 Reflections were considered to be observed according to the criterion $I \geqslant 1.96\sigma(I)$. Background counts were measured at each end of the scan for half the scan time. All intensities were corrected for Lorentz and polarization effects, but not for absorption or extinction. Anomalous-dispersion corrections were applied to the scattering factors of the oxygen and carbon atoms.

Structure Analysis.—The calculations were carried out for an arbitrarily chosen $P4_1$ space group. The structure was solved with MULTAN.[3] An initial *E*-map showed 27 of the 30 C and O atoms. The three remaining atoms were located on a difference-synthesis map. Isotropic, followed by anisotropic, full-matrix least-squares refinement yielded an *R* of 0.075. Hydrogen atoms were located on two successive difference-Fourier maps by means of a nineteen-point electron-density interpolation. Although located on a difference map, the positions of the hydrogen atoms of the water molecule are not in good agreement with the theoretical distances. The structure was finally refined with anisotropic temperature factors for all the non-hydrogen atoms; hydrogen atoms were included as a fixed contribution with isotropic temperature factors one unit greater than the isotropic values for their carriers. The quantity minimized in the least-squares calculations was $\Sigma w(F_o - F_c)^2$ and statistical weights, $w = 1/\sigma_F{}^2$, were used. During the final cycles of refinement two strong, low-angle reflections, apparently suffering from extinction, were excluded from the least-squares calculations. The refinement converged to $R = 0.043$. All calculations were performed on a Nova minicomputer using original and locally modified (by M. Jaskólski) Syntex XTL programs.

RESULTS AND DISCUSSION

Lists of structure factors and anisotropic thermal parameters have been deposited as Supplementary Publication No. SUP 22970 (15 pp.).† Atomic parameters for non-hydrogen atoms are listed in Table 1 and those for hydrogen atoms in Table 2. Tables 3—5 list the bond lengths, valency angles and torsion angles.

X-Ray analysis establishes the structure and relative stereochemistry of ursiniolide A as shown in (I). Moreover, on the basis on c.d. studies [2] it can be assumed that (I) also represents the absolute stereochemistry and that the choice of the space group was correct. A view of the α-face of the molecule and the atom numbering scheme are shown in Figure 1. The conformation of the ten-membered ring closely resembles one of two frequently

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† See Notice to Authors No. 7 in *J. Chem. Soc., Perkin Trans. 2*, 1979, Index Issue.

TABLE 1

Positional parameters ($\times 10^4$) for non-hydrogen atoms

	x	y	z
C(1)	−1 390(4)	5 544(4)	4(6)
C(2)	−1 968(4)	6 312(4)	612(7)
C(3)	−1 729(4)	6 348(4)	1 971(7)
C(4)	−1 852(4)	5 362(4)	2 522(6)
C(5)	−1 179(4)	4 704(4)	2 414(6)
C(6)	−1 307(4)	3 652(4)	2 628(6)
C(7)	−1 067(4)	2 931(4)	1 592(6)
C(8)	−489(4)	3 269(4)	493(6)
C(9)	−994(4)	3 852(4)	−515(6)
C(10)	−1 672(4)	4 634(4)	−150(6)
C(11)	−518(4)	2 155(4)	2 250(7)
C(12)	−261(4)	2 503(4)	3 451(7)
C(13)	−259(4)	1 303(4)	1 880(7)
C(14)	−2 683(4)	4 313(4)	18(8)
C(15)	−2 860(4)	5 211(4)	3 014(7)
C(16)	−630(4)	7 631(4)	2 067(6)
C(17)	407(4)	7 924(5)	2 094(7)
C(18)	1 222(4)	3 574(4)	547(7)
C(19)	1 945(4)	4 176(4)	1 239(7)
C(20)	2 485(4)	3 694(4)	2 192(7)
C(21)	2 312(4)	2 677(5)	2 527(7)
C(22)	1 759(5)	5 242(5)	1 274(8)
O(23)	−656(3)	3 386(3)	3 630 *
O(24)	222(3)	2 125(3)	4 211(5)
O(25)	−748(2)	6 671(2)	2 084(5)
O(26)	−1 282(3)	8 197(3)	2 031(5)
O(27)	337(2)	3 809(2)	971(5)
O(28)	1 387(3)	2 990(3)	−189(5)
O(29)	2 916(2)	3 872(3)	1 025(5)
O(W)	4 485(3)	5 251(4)	1 206(6)

* Position fixed to define z co-ordinates in this polar space group.

TABLE 2

Positional parameters ($\times 10^3$) and isotropic B values (Å^2) for hydrogen atoms

	x	y	z	$B_{\text{iso.}}$
H(11)	−68	566	−11	4.3
H(21)	−179	701	32	4.9
H(22)	−277	622	62	4.9
H(31)	−224	694	233	4.3
H(51)	−45	492	218	3.8
H(61)	−204	350	311	3.7
H(71)	−167	257	120	3.8
H(81)	−26	263	10	4.3
H(91)	−132	341	−106	4.9
H(92)	−41	392	−104	4.9
H(131)	3	84	247	5.6
H(132)	−44	108	121	5.6
H(141)	−292	388	−48	4.8
H(142)	−319	479	15	4.8
H(143)	−269	386	88	4.8
H(151)	−348	526	238	4.6
H(152)	−311	457	326	4.6
H(153)	−292	583	376	4.6
H(171)	66	816	115	5.3
H(172)	68	795	295	5.3
H(173)	92	763	184	5.3
H(211)	185	249	316	5.3
H(212)	204	227	185	5.3
H(213)	282	233	259	5.3
H(221)	115	543	157	5.6
H(222)	183	554	47	5.6
H(223)	233	555	126	5.6
H(W1)	407	500	92	8.0
H(W2)	498	526	31	8.0
H(201)	274	413	289	5.2

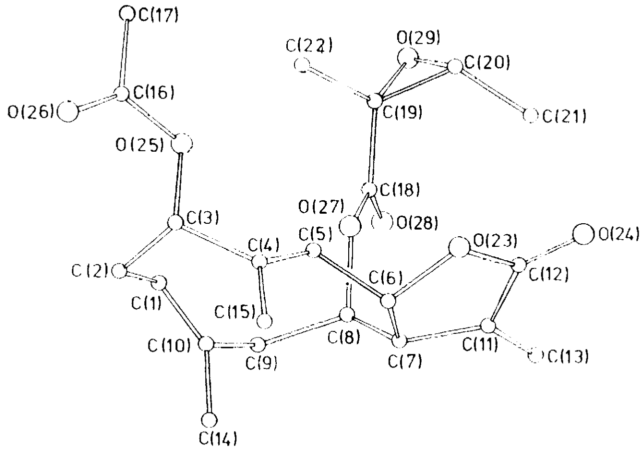

FIGURE 1 View of the α-face of the molecule and atom numbering scheme

occurring conformations for the cyclodeca-*trans*,*trans*-1(10),4-diene.[4] This conformation can be described as a chair-boat and is typified by dihydromikanolide,[5] shiromodiol,[6] and glaucolide A.[7] In all these sesquiterpenoids as well as in ursiniolide A the C(14) and C(15) carbon atoms carried by C(10) and C(4) are *syn* and on the α-face of the macrocycle. An attempt was made to compare the torsion angles of the ten-membered ring observed for ursiniolide A with the values obtained from

TABLE 3

Bond lengths (Å), with estimated standard deviations in parentheses

C(1)–C(2)	1.500(8)	C(11)–C(7)	1.515(8)
C(2)–C(3)	1.556(10)	C(7)–C(8)	1.542(9)
C(3)–C(4)	1.515(8)	C(8)–O(27)	1.474(7)
C(3)–O(25)	1.444(6)	O(27)–C(18)	1.359(7)
O(25)–C(16)	1.347(7)	C(18)–O(28)	1.180(8)
C(16)–O(26)	1.202(7)	C(18)–C(19)	1.522(9)
C(16)–C(17)	1.501(9)	C(19)–O(29)	1.436(7)
C(4)–C(5)	1.315(7)	C(19)–C(20)	1.466(10)
C(4)–C(15)	1.522(8)	C(19)–C(22)	1.507(9)
C(5)–C(6)	1.495(7)	C(20)–O(29)	1.457(9)
C(6)–C(7)	1.570(9)	C(20)–C(21)	1.485(9)
C(6)–O(23)	1.488(7)	C(8)–C(9)	1.556(9)
O(23)–C(12)	1.360(7)	C(9)–C(10)	1.497(8)
C(12)–C(11)	1.472(10)	C(10)–C(14)	1.488(8)
C(12)–O(24)	1.205(8)	C(10)–C(1)	1.338(8)
C(11)–C(13)	1.308(8)		

TABLE 4

Valency angles (°), with estimated standard deviations in parentheses

C(10)–C(1)–C(2)	125.2(6)	C(11)–C(7)–C(8)	110.0(5)
C(1)–C(2)–C(3)	110.6(5)	C(6)–C(7)–C(8)	120.3(5)
C(2)–C(3)–C(4)	110.1(5)	C(7)–C(8)–O(27)	105.9(5)
C(2)–C(3)–O(25)	107.3(5)	C(7)–C(8)–C(9)	120.1(5)
O(25)–C(3)–C(4)	110.7(5)	O(27)–C(8)–C(9)	110.5(5)
C(3)–O(25)–C(16)	115.0(5)	C(8)–O(27)–C(18)	117.3(5)
O(25)–C(16)–O(26)	124.0(6)	O(27)–C(18)–O(28)	125.8(6)
O(25)–C(16)–C(17)	112.7(5)	O(27)–C(18)–C(19)	106.9(5)
C(17)–C(16)–O(26)	123.3(6)	O(28)–C(18)–C(19)	127.2(6)
C(3)–C(4)–C(5)	120.9(5)	C(18)–C(19)–O(29)	112.1(5)
C(3)–C(4)–C(15)	112.1(5)	C(18)–C(19)–C(20)	117.2(5)
C(15)–C(4)–C(5)	126.4(6)	C(18)–C(19)–C(22)	116.2(6)
C(4)–C(5)–C(6)	125.6(5)	C(22)–C(19)–O(29)	117.2(5)
C(5)–C(6)–C(7)	118.9(5)	C(22)–C(19)–C(20)	121.3(6)
C(5)–C(6)–O(23)	107.0(4)	O(29)–C(19)–C(20)	60.3(4)
C(7)–C(6)–O(23)	105.5(4)	C(19)–C(20)–C(21)	122.5(6)
C(6)–O(23)–C(12)	111.1(4)	C(19)–C(20)–O(29)	58.8(4)
O(23)–C(12)–C(11)	109.5(5)	O(29)–C(20)–C(21)	117.1(5)
O(23)–C(12)–O(24)	121.1(6)	C(20)–O(29)–C(19)	60.9(4)
C(11)–C(12)–O(24)	129.4(6)	C(8)–C(9)–C(10)	117.8(5)
C(12)–C(11)–C(13)	121.4(6)	C(9)–C(10)–C(14)	114.4(5)
C(12)–C(11)–C(7)	109.4(5)	C(9)–C(10)–C(1)	122.6(6)
C(13)–C(11)–C(7)	129.2(6)	C(1)–C(10)–C(14)	123.0(6)
C(11)–C(7)–C(6)	101.8(5)		

Table 5

Torsion angles (°)

O(26)–C(16)–O(25)–C(3)	4.2
C(17)–C(16)–O(25)–C(3)	−175.7
C(16)–O(25)–C(3)–C(2)	84.6
C(16)–O(25)–C(3)–C(4)	−155.2
O(25)–C(3)–C(4)–C(15)	150.0
O(25)–C(3)–C(4)–C(5)	−38.2
C(2)–C(3)–C(4)–C(15)	−91.5
C(2)–C(3)–C(4)–C(5)	80.3
C(3)–C(4)–C(5)–C(6)	−163.2
C(15)–C(4)–C(5)–C(6)	7.3
C(4)–C(5)–C(6)–O(23)	−118.3
C(4)–C(5)–C(6)–C(7)	122.5
C(5)–C(6)–O(23)–C(12)	−142.5
C(7)–C(6)–O(23)–C(12)	−15.0
C(6)–O(23)–C(12)–O(24)	−173.6
C(6)–O(23)–C(12)–C(11)	7.0
O(23)–C(12)–C(11)–C(7)	4.4
O(23)–C(12)–C(11)–C(13)	−177.0
O(24)–C(12)–C(11)–C(7)	−175.0
O(24)–C(12)–C(11)–C(13)	3.7
C(12)–C(11)–C(7)–C(6)	−12.8
C(12)–C(11)–C(7)–C(8)	115.9
C(13)–C(11)–C(7)–C(6)	168.8
C(13)–C(11)–C(7)–C(8)	−62.6
C(11)–C(7)–C(6)–O(23)	16.2
C(11)–C(7)–C(6)–C(5)	136.1
C(8)–C(7)–C(6)–O(23)	−105.6
C(8)–C(7)–C(6)–C(5)	14.4
C(6)–C(7)–C(8)–O(27)	14.7
C(6)–C(7)–C(8)–C(9)	−78.7
C(11)–C(7)–C(8)–O(27)	−70.6
C(11)–C(7)–C(8)–C(9)	163.7
C(7)–C(8)–C(9)–C(10)	43.3
O(27)–C(8)–C(9)–C(10)	−80.3
C(8)–C(9)–C(10)–C(1)	91.3
C(8)–C(9)–C(10)–C(14)	−89.1
C(9)–C(10)–C(1)–C(2)	−166.2
C(14)–C(10)–C(1)–C(2)	14.3
C(10)–C(1)–C(2)–C(3)	91.3
C(1)–C(2)–C(3)–O(25)	66.9
C(1)–C(2)–C(3)–C(4)	−53.6
C(9)–C(8)–O(27)–C(18)	−98.4
C(7)–C(8)–O(27)–C(18)	130.2
C(8)–O(27)–C(18)–O(28)	1.8
C(8)–O(27)–C(18)–C(19)	−176.0
O(27)–C(18)–C(19)–O(29)	169.3
O(27)–C(18)–C(19)–C(22)	−51.8
O(27)–C(18)–C(19)–C(20)	102.8
O(28)–C(18)–C(19)–C(22)	130.4
O(28)–C(18)–C(19)–O(29)	−8.1
O(28)–C(18)–C(19)–C(20)	−75.0
C(22)–C(19)–O(29)–C(20)	112.3
C(18)–C(19)–O(29)–C(20)	−109.6
C(19)–O(29)–C(20)–C(21)	113.3
C(21)–C(20)–C(19)–C(18)	−3.0
C(21)–C(20)–C(19)–C(22)	150.2

force-field calculations carried out on dimethylcyclodeca-1(10),4-diene.[8] The relatively good agreement between both sets of data (theoretical and observed) is distorted in the vicinity of the C(6)–C(7) bond. The torsion angle C(5)–C(6)–C(7)–C(8) of 14.2° is markedly different from the calculated value (50°) and presumably reflects the adjustment necessary to accommodate a *cis*-fused α-methylene-γ-lactone. Also inspection of the C–C(sp^3)–C bond angles reveals considerable strain in the C(6)—C(9) region of the cyclodecadiene ring. The bond angles in this region average 119.3° while C(3) and C(2) display angles of *ca.* 110°. Moreover, the C(6)–C(7) bond length of 1.570(9) Å is the longest found in this structure.

It has been observed in several germacranolides that two double bonds in the ten-membered ring are not deformed to the same extent, C(4)–C(5) being more strained in nature. The C(3)–C(4)–C(5)–C(6) torsion angle is usually smaller than C(9)–C(10)–C(1)–C(2), the difference being *ca.* 10°.[4,9–12] Bovill *et al.*[4] have stated that this effect, absent in the isolated cyclic diene, is a feature of a germacranolide conformation. Unexpectedly, in ursiniolide A the torsion angles associated with the two double bonds differ by only 3°. It therefore seems possible that the differential distortion effect present in all germacranolides studied previously by *X*-ray diffraction and not observed in ursiniolide A is introduced to the germacradiene skeleton by a *trans*-fused γ-lactone ring.

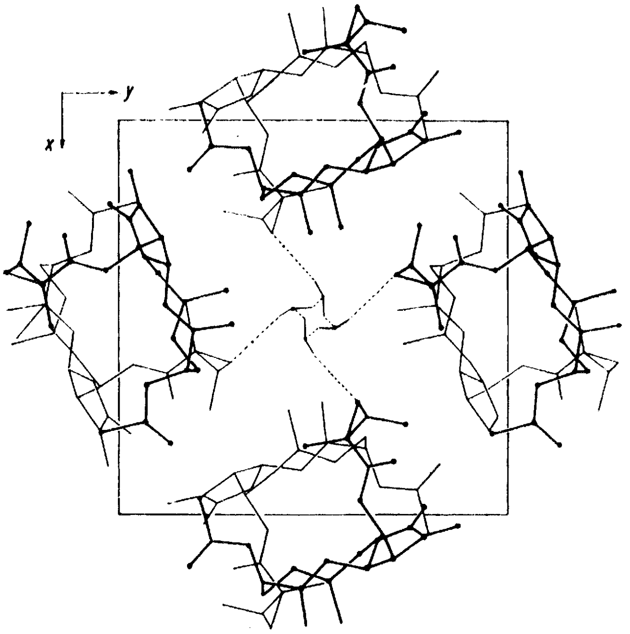

Figure 2 Projection of the structure along the *z* axis and hydrogen-bonding scheme

The γ-lactone ring, *cis*-fused at C(6) and C(7), more closely approximates to a half-chair conformation than to an envelope form. A pseudo-diad runs through C(12) and the midpoint of the C(6)–C(7) bond. The sum of the five endocyclic torsion angle moduli is 55.4° and the asymmetry parameters[13] are $\Delta C_2^{6,7} = 2.4$, $\Delta C_s^6 = 4.2$, and $\Delta C_s^7 = 7.9$. The conjugated exocyclic ethylene and carbonyl double bonds of the γ-lactone do not depart from planarity, the C(13)–C(11)–C(12)–O(24) torsion angle being only 3.7°.

The epoxide dimensions observed in the present structure are in the range of the values given by Foces-Foces *et al.*[14] and seem to support their conclusion that, independent of geometrical changes within the epoxide triangle, its area tends to have the constant value of *ca.* 0.914(2) Å^2. In the present structure this area is 0.912 Å^2.

In Figure 2 a projection of the structure along the *z* axis is given. The water molecule is situated so as to participate in hydrogen bonds with O(29) from the epoxide group of the ursiniolide molecule and with O(W) from the neighbouring water molecule. Thus each water molecule acts twice as a donor and once as an acceptor of a proton. The water molecules and the molecules of ursiniolide A form a helical hydrogen-bonded array along the 4_1 axis. The donor–acceptor distances are as follows: O(W) $\cdots$ O(29) 2.914(6) Å, O(W) $\cdots$ O(W′) at $y, -x + 1, z - 1/4$ 3.016(10) Å.

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Note added in proof. Since this paper was submitted, an account of the isolation and structure elucidation of three germacranolides which are also *trans,trans*-germacra-1(10),4-dien-*cis*-6,12-olides has appeared (W. Herz, S. V. Govindan, and J. F. Bloust, *J. Org. Chem.*, 1980, **45**, 1113.

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