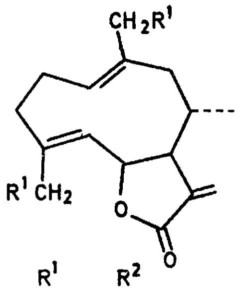
Sesquiterpenoids. Part XXIII.[1] X-Ray Crystallographic Determination of the Molecular Conformation of the Germacranolide Alatolide Monohydrate

By **Philip J. Cox** *† and **George A. Sim**, Chemistry Department, University of Glasgow, Glasgow G12 8QQ

Alatolide (1), a germacrane sesquiterpenoid lactone has been studied by X-ray diffraction and the conformation shown to be similar to that of costunolide. The torsion angles about the double bonds in the cyclodeca-1,5-diene ring are C(3)–C(4)–C(5)–C(6) 154 and C(2)–C(1)–C(10)–C(9) 167°. The negative $n\rightarrow\pi^*$ Cotton effect of the α-methylene γ-lactone is consistent with the *trans*-fusion of the lactone at C(6)–C(7) but the C=C–C=O chromophore is planar and, hence, non-chiral in the crystal. The hydroxy-groups at C(14) and C(15) are associated in an intramolecular hydrogen bond. The compound crystallized as a hydrate, with a = 13.175(2), b = 12.495(2), c = 11.663(4) Å, space group $P2_12_12_1$, and Z = 4. The crystal structure was determined by direct-phasing methods and the atomic parameters were refined by least-squares calculations to R 6.4% over 1 560 diffractometer reflections.

ALATOLIDE, a germacrane sesquiterpenoid lactone, was isolated from the leaves of *Jurinea alata*. Chemical and spectroscopic studies led to the proposal of the stereochemistry shown in (1).[2] We undertook an X-ray analysis to obtain details of the molecular conformation.



	R¹	R²
(1)	OH	O·CO·CHMe₂
(2)	H	H
(3)	OH	O·CO·CMe = CH·CH₂·OH

The crystal structure of alatolide monohydrate was elucidated by direct-phasing procedures and least-squares adjustment of the atomic parameters converged to R 6.4% over 1 560 independent reflections measured with Cu-K_α radiation on a four-circle diffractometer. The resultant molecular structure is shown in Figure 1, and the packing of the molecules in the unit cell in Figure 2. Atomic co-ordinates are listed in Table 1, bond lengths, valency and torsion angles are in Tables 2—4.

The water molecule is situated so as to participate in hydrogen bonds with O(6) and O(1) in one molecule and O(2) in another. There is also an intramolecular hydrogen bond O(2) ··· O(1) (see Table 5). Intermolecular distances are listed in Table 6.

The conformation of the macrocycle is closely similar to the conformations of germacratriene,[3] elephantol,[4] and

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† *Present address:* School of Pharmacy, Robert Gordon's Institute of Technology, Schoolhill, Aberdeen AB9 1FR.

[1] Part XXII, P. J. Cox and G. A. Sim, *J.C.S. Perkin II*, 1976, 990.

[2] B. Drożdż, Z. Samek, M. Holub, and V. Herout, *Coll. Czech. Chem. Comm.*, 1973, **38**, 727.

[3] F. H. Allen and D. Rogers, *J. Chem. Soc.* (*B*), 1971, 257.

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

costunolide (2),[5] where C(14) and C(15) are *cis* and on the β-face of the molecule. The torsion angles C(3)–C(4)–C(5)–C(6) (154°) and C(2)–C(1)–C(10)–C(9) (167°) are markedly different from the ideal value of 180°, and the *trans* double bonds are clearly subject to some strain. Similar distortions are found in other germacranolides.[4,6] Since ω(3–4–5–6) — ω(14–4–5–6) is 174° and ω(2–1–10–9) — ω(2–1–10–15) is 181°, out-of-plane bending at C(4) and C(10) is not large, and twisting about the double bonds is an important component of the distortion. The ring displays the customary short C(1) · · · C(5) transannular separation (2.88 Å).

TABLE 1

Fractional atomic co-ordinates with standard deviations in parentheses

Atom	*x*	*y*	*z*
O(1)	0.672 4(3)	0.340 5(3)	0.120 7(3)
O(2)	0.469 9(3)	0.382 6(3)	0.096 1(3)
O(3)	0.668 3(2)	0.717 8(3)	0.052 8(3)
O(4)	0.770 7(3)	0.837 6(3)	−0.029 2(3)
O(5)	0.941 6(2)	0.542 6(2)	0.211 5(2)
O(6)	0.976 0(3)	0.387 0(3)	0.130 8(4)
O(7)	0.836 6(3)	0.269 8(3)	−0.002 7(3)
C(1)	0.624 0(4)	0.450 7(4)	0.375 0(4)
C(2)	0.513 8(4)	0.423 5(5)	0.365 2(4)
C(3)	0.456 0(4)	0.517 0(5)	0.307 2(5)
C(4)	0.512 3(4)	0.549 9(4)	0.197 0(4)
C(5)	0.589 5(3)	0.615 0(4)	0.205 9(4)
C(6)	0.677 6(3)	0.622 9(4)	0.125 0(4)
C(7)	0.781 6(3)	0.632 5(4)	0.186 6(4)
C(8)	0.834 0(3)	0.523 7(4)	0.204 5(4)
C(9)	0.803 8(4)	0.462 9(4)	0.317 0(4)
C(10)	0.701 9(4)	0.410 8(4)	0.314 5(4)
C(11)	0.835 8(4)	0.712 6(4)	0.111 0(4)
C(12)	0.758 8(4)	0.763 4(4)	0.036 0(4)
C(13)	0.930 7(4)	0.748 8(4)	0.110 4(6)
C(14)	0.479 8(4)	0.495 8(5)	0.087 4(4)
C(15)	0.691 4(5)	0.312 1(4)	0.242 1(5)
C(16)	1 005 2(4)	0.469 5(4)	0.169 8(4)
C(17)	0.113 1(4)	0.503 2(5)	0.175 1(5)
C(18)	0.142 1(4)	0.539 1(6)	0.297 5(5)
C(19)	1.183 5(4)	0.419 4(5)	0.127 4(6)
H(O1)	0.722(5)	0.281(5)	0.084(5)
H(O2)	0.555(4)	0.366(5)	0.097(5)
H(O7A)	0.860(4)	0.197(4)	−0.032(5)
H(O7B)	0.895(5)	0.300(5)	0.028(6)
H(1)	0.631(3)	0.524(3)	0.410(4)
H(2A)	0.502(3)	0.356(3)	0.326(3)
H(2B)	0.478(6)	0.404(6)	0.421(6)
H(3A)	0.384(3)	0.489(3)	0.300(3)
H(3B)	0.439(5)	0.582(5)	0.350(5)
H(5)	0.602(4)	0.660(4)	0.266(4)
H(6)	0.679(3)	0.554(3)	0.078(3)
H(7)	0.773(3)	0.676(3)	0.267(4)
H(8)	0.822(3)	0.478(3)	0.146(3)
H(9A)	0.862(3)	0.402(3)	0.323(3)
H(9B)	0.803(3)	0.526(3)	0.368(4)
H(13A)	0.986(4)	0.716(4)	0.159(5)
H(13B)	0.942(4)	0.827(5)	0.077(5)
H(14A)	0.404(3)	0.519(3)	0.070(3)
H(14B)	0.532(3)	0.518(4)	0.032(4)
H(15A)	0.764(3)	0.266(3)	0.244(4)
H(15B)	0.623(4)	0.263(4)	0.267(4)
H(17)	1.114(4)	0.578(4)	0.121(4)
H(18A)	1.093(4)	0.611(4)	0.330(5)
H(18B)	1.142(4)	0.454(5)	0.349(5)
H(18C)	1.217(4)	0.577(5)	0.311(5)
H(19A)	1.260(4)	0.439(5)	0.126(5)
H(19B)	1.168(5)	0.342(5)	0.158(6)
H(19C)	1.167(7)	0.383(7)	0.048(8)

Cotton effects at 221 nm (+ve) and 199 nm (−ve) in the c.d. spectrum of jurineolide (3), which differs from alatolide only in the *O*-acyl group at C(8), and similar features in the spectra of the related germacranolides albicolide and costunolide, are believed to originate in the exciton splitting of degenerate π→π* absorption bands associated with the double bonds in the ten-

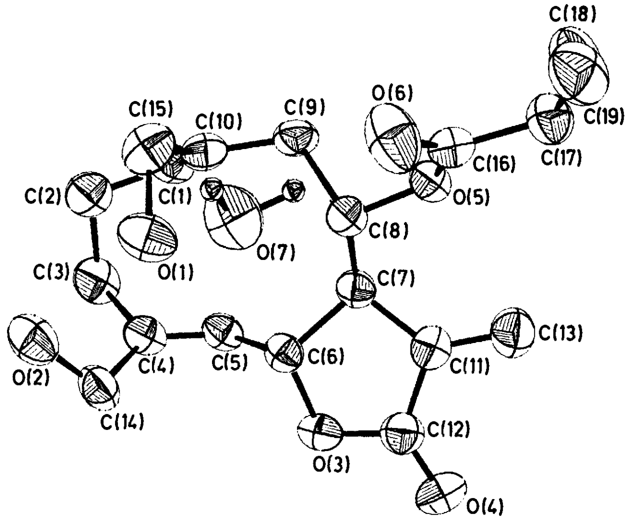

FIGURE 1 The atomic arrangement

TABLE 2

(*a*) Bond lengths (Å), with standard deviations in parentheses

O(1)–C(15)	1.481(6)	O(2)–H(O2)	1.14(6)
O(2)–C(14)	1.424(7)	O(7)–H(O7A)	1.02(6)
O(3)–C(6)	1.459(6)	O(7)–H(O7B)	0.93(6)
O(3)–C(12)	1.336(6)	C(1)–H(1)	1.01(4)
O(4)–C(12)	1.209(6)	C(2)–H(2A)	0.97(4)
O(5)–C(8)	1.439(5)	C(2)–H(2B)	0.86(7)
O(5)–C(16)	1.332(6)	C(3)–H(3A)	1.01(4)
O(6)–C(16)	1.191(6)	C(3)–H(3B)	0.98(6)
C(1)–C(2)	1.496(7)	C(5)–H(5)	0.92(5)
C(1)–C(10)	1.341(7)	C(6)–H(6)	1.02(3)
C(2)–C(3)	1.550(8)	C(7)–H(7)	1.08(4)
C(3)–C(4)	1.539(7)	C(8)–H(8)	0.91(3)
C(4)–C(5)	1.307(7)	C(9)–H(9A)	1.09(4)
C(4)–C(14)	1.508(7)	C(9)–H(9B)	0.98(4)
C(5)–C(6)	1.500(6)	C(13)–H(13A)	1.01(5)
C(6)–C(7)	1.551(6)	C(13)–H(13B)	1.05(6)
C(7)–C(8)	1.539(6)	C(14)–C(14A)	1.06(4)
C(7)–C(11)	1.513(7)	C(14)–H(14B)	0.98(4)
C(8)–C(9)	1.567(7)	C(15)–H(15A)	1.12(4)
C(9)–C(10)	1.491(7)	C(15)–H(15B)	1.13(5)
C(10)–C(15)	1.502(7)	C(18)–H(18A)	1.16(5)
C(11)–C(12)	1.482(7)	C(18)–H(18B)	1.22(6)
C(11)–C(13)	1.330(7)	C(18)–H(18C)	1.10(6)
C(16)–C(17)	1.484(7)	C(19)–H(19A)	1.03(6)
C(17)–C(18)	1.544(8)	C(19)–H(19B)	1.06(7)
C(17)–C(19)	1.505(8)	C(19)–H(19C)	1.07(11)
O(1)–H(O1)	1.08(7)		

(*b*) Some intramolecular non-bonded separations (Å)

O(1) · · · O(2)	2.735	C(5) · · · C(10)	3.211
C(1) · · · C(4)	2.831	O(4) · · · C(13)	2.885
C(1) · · · C(5)	2.884	O(5) · · · C(13)	2.837
C(4) · · · C(10)	3.338		

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[5] F. Šorm, M. Suchý, M. Holub, A. Linek, I. Hadinec, and C. Novák, *Tetrahedron Letters*, 1970, 1893; K. Tori, I. Horibe, Y. Tamura, and H. Tada, *J.C.S. Chem. Comm.*, 1973, 620.

[6] P. J. Cox and G. A. Sim, *J.C.S. Perkin II*, 1974, 1355.

membered ring.[7] The similarity of these spectra indicates that these compounds have the same absolute stereochemical arrangement of double bonds in their cyclodeca-1,5-diene rings. Since the $\pi \rightarrow \pi^*$ transition in ethylene is polarized along the C=C axis, the mutual orientation of the double bonds defines the mutual orientation of the transition moments of the ethylenic chromophores in the cyclodeca-1,5-diene ring. Our results establish that the torsion angle C(4)–C(5) · · · C(1)–C(10) in alatolide is 110°, and that the separation between the centres of the double bonds is 2.93 Å.

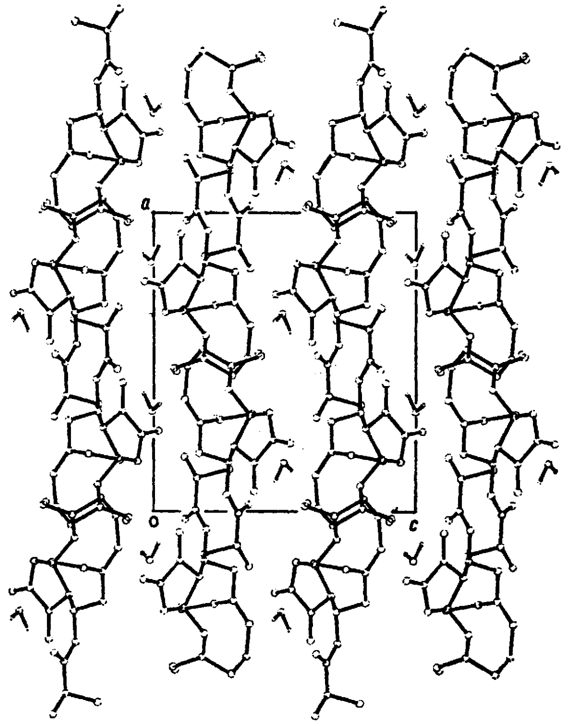

FIGURE 2 The crystal structure

TABLE 3

Valency angles (°) with standard deviations in parentheses

C(10)–C(1)–C(2)	128.2(3)	C(9)–C(10)–C(1)	121.1(4)
C(3)–C(2)–C(1)	109.8(4)	C(15)–C(10)–C(1)	122.0(4)
C(4)–C(3)–C(2)	109.2(3)	C(13)–C(11)–C(12)	119.6(3)
C(5)–C(4)–C(3)	118.4(3)	C(12)–C(11)–C(7)	107.7(3)
C(14)–C(4)–C(3)	116.8(3)	C(13)–C(11)–C(7)	132.3(3)
C(14)–C(4)–C(5)	124.6(4)	O(4)–C(12)–O(3)	122.3(3)
C(6)–C(5)–C(4)	126.4(3)	C(11)–C(12)–O(3)	110.0(3)
C(7)–C(6)–C(5)	113.4(3)	C(11)–C(12)–O(4)	127.6(4)
C(5)–C(6)–O(3)	110.6(3)	C(4)–C(14)–O(2)	114.2(3)
C(7)–C(6)–O(3)	106.1(3)	C(10)–C(15)–O(1)	110.9(4)
C(8)–C(7)–C(6)	113.0(3)	O(6)–C(16)–O(5)	122.0(2)
C(11)–C(7)–C(6)	101.4(3)	C(17)–C(16)–O(5)	113.2(3)
C(11)–C(7)–C(8)	116.9(3)	C(17)–C(16)–O(6)	124.8(4)
C(9)–C(8)–C(7)	115.4(3)	C(18)–C(17)–C(16)	110.9(4)
C(7)–C(8)–O(5)	107.7(3)	C(19)–C(17)–C(16)	112.1(4)
C(9)–C(8)–O(5)	106.4(3)	C(19)–C(17)–C(18)	113.1(4)
C(10)–C(9)–C(8)	115.1(3)	C(12)–O(3)–C(6)	110.9(3)
C(15)–C(10)–C(9)	116.9(3)	C(16)–O(5)–C(8)	119.1(3)

Alatolide has a negative Cotton effect at 262 nm, attributable to the $n \rightarrow \pi^*$ transition of the α-methylene γ-lactone chromophore.[2] According to the correlation established by Stöcklin *et al.*,[8] the negative Cotton effect is characteristic of a C(6), C(7)-*trans*-lactone with the

TABLE 4

Torsion angles (°)*

C(12)–O(3)–C(6)–C(5)	142	C(5)–C(6)–C(7)–C(11)	−141
C(12)–O(3)–C(6)–C(7)	18	C(6)–C(7)–C(8)–O(5)	154
C(6)–O(3)–C(12)–O(4)	173	C(6)–C(7)–C(8)–C(9)	−87
C(6)–O(3)–C(12)–C(11)	−9	C(11)–C(7)–C(8)–O(5)	37
C(16)–O(5)–C(8)–C(7)	−146	C(11)–C(7)–C(8)–C(9)	156
C(16)–O(5)–C(8)–C(9)	90	C(6)–C(7)–C(11)–C(12)	14
C(8)–O(5)–C(16)–O(6)	−3	C(6)–C(7)–C(11)–C(13)	−173
C(8)–O(5)–C(16)–C(17)	176	C(8)–C(7)–C(11)–C(12)	138
C(10)–C(1)–C(2)–C(3)	−107	C(8)–C(7)–C(11)–C(13)	−50
C(2)–C(1)–C(10)–C(9)	167	O(5)–C(8)–C(9)–C(10)	−165
C(2)–C(1)–C(10)–C(15)	−14	C(7)–C(8)–C(9)–C(10)	76
C(1)–C(2)–C(3)–C(4)	50	C(8)–C(9)–C(10)–C(1)	−108
C(2)–C(3)–C(4)–C(5)	−83	C(8)–C(9)–C(10)–C(15)	73
C(2)–C(3)–C(4)–C(14)	92	C(1)–C(10)–C(15)–O(1)	97
C(3)–C(4)–C(5)–C(6)	154	C(9)–C(10)–C(15)–O(1)	−83
C(14)–C(4)–C(5)–C(6)	−20	C(7)–C(11)–C(12)–O(3)	−4
C(3)–C(4)–C(14)–O(2)	−47	C(7)–C(11)–C(12)–O(4)	173
C(5)–C(4)–C(14)–O(2)	127	C(13)–C(11)–C(12)–O(3)	−178
C(4)–C(5)–C(6)–O(3)	104	C(13)–C(11)–C(12)–O(4)	0
C(4)–C(5)–C(6)–C(7)	−137	O(5)–C(16)–C(17)–C(18)	53
O(3)–C(6)–C(7)–C(8)	−145	O(5)–C(16)–C(17)–C(19)	−180
O(3)–C(6)–C(7)–C(11)	−19	O(6)–C(16)–C(17)–C(18)	−129
C(5)–C(6)–C(7)–C(8)	93	O(6)–C(16)–C(17)–C(19)	−1

* The sign is negative if an anticlockwise rotation is required of atom (1) to eclipse atom (4) whilst looking down the (2)–(3) bond. Mean standard deviation of torsion angles 0.7°.

TABLE 5

Distances (Å) and angles (°) associated with hydrogen bonds

O(1) · · · O(2)	2.735, O(1) · · · H(O2) 1.61, H(O2)–O(2) 1.14, O(1) · · · H(O2)–O(2) 170
O(1) · · · O(7)	2.745, O(7) · · · H(O1) 1.82, H(O1)–O(1) 1.08, O(7) · · · H(O1)–O(1) 141
O(2)* · · · O(7)	2.810, O(2)* · · · H(O7A) 1.91, H(O7A)–O(7) 1.02, O(7)–H(O7A) · · · O(2)* 146
O(6) · · · O(7)	2.817, O(6) · · · H(O7B) 1.93, H(O7B)–O(7) 0.93, O(6) · · · H(O7B)–O(7) 158

* Co-ordinates transformed by $\frac{1}{2} + x, \frac{1}{2} - y, -z$.

TABLE 6

Intermolecular separations (<3.85 Å)

O(2) · · · C(19^{I})	3.819	O(7) · · · C(5^{III})	3.816
C(1) · · · C(11^{II})	3.467	C(6) · · · C(9^{III})	3.757
C(1) · · · C(12^{II})	3.614	C(12) · · · C(15^{III})	3.616
C(1) · · · C(13^{II})	3.778	C(14) · · · C(18^{III})	3.768
C(2) · · · C(13^{II})	3.653	O(4) · · · C(14^{IV})	3.519
C(10) · · · C(11^{II})	3.819	O(2) · · · O(7^{V})	2.810
C(10) · · · C(12^{II})	3.418	O(7) · · · C(19^{V})	3.432
O(3) · · · C(9^{III})	3.578	O(3) · · · C(13^{VI})	3.687
O(3) · · · C(10^{III})	3.637	O(4) · · · C(17^{VI})	3.341
O(4) · · · C(10^{III})	3.618	O(4) · · · C(19^{VI})	3.443
O(4) · · · C(15^{III})	3.296	O(3) · · · C(2^{VII})	3.644
O(6) · · · C(1^{III})	3.841		

Roman numeral superscripts refer to the following transformations of the atomic co-ordinates:

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

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[7] M. Suchý, L. Dolejš, V. Herout, F. Šorm, G. Snatzke, and J. Himmelreich, *Coll. Czech. Chem. Comm.*, 1969, **34**, 229.

[8] W. Stöcklin, T. G. Waddell, and T. A. Geissman, *Tetrahedron*, 1970, **26**, 239.

absolute configuration as shown in (1), *i.e.* with β-H(6) and α-H(7). Beecham has suggested that the sign of the Cotton effect is determined by the chirality of the C=C–C=O chromophore [9] and *X*-ray results have shown that in lactones with a C(6), C(7)-*trans*-ring junction the C=C–C=O group generally has left-handed chirality (negative torsion angle).[10] In alatolide, however, the torsion angle C(13)–C(11)–C(12)–O(4) is 0°, though the corresponding angle in the closely related germacranolide costunolide is –10°.[11] Molecular mechanics calculations for an isolated molecule of this type indicate that the C=C–C=O angle should be negative,[11] and the spread of crystallographic results suggests a measure of molecular flexibility. Figure 3 shows that the exocyclic C=C–C=O and endocyclic C_α–C_β–C_γ–O torsion angles in α-methylene γ-lactones in the solid state are roughly correlated; the angles are frequently paired in sign and the endocyclic angle is generally rather larger than the exocyclic. The relationship is by no means exact, however, and since the C=C–C=O angles of 0 and –10° in alatolide and costunolide, respectively, correspond to C_α–C_β–C_γ–O angles of –19 and –25°, the sign of the Cotton effect may be more effectively related to the sign of the C_α–C_β–C_γ–O angle than to the sign of the C=C–C=O angle. Indeed, the greater consistency of Stöcklin's correlation, contrasted with the range of crystallographic results for the C=C–C=O torsion angle, suggests that we cannot ignore the possibility that the asymmetric perturbation of the lactone chromophore by the substitution pattern of the lactone may contribute substantially to the generation of the Cotton effect.

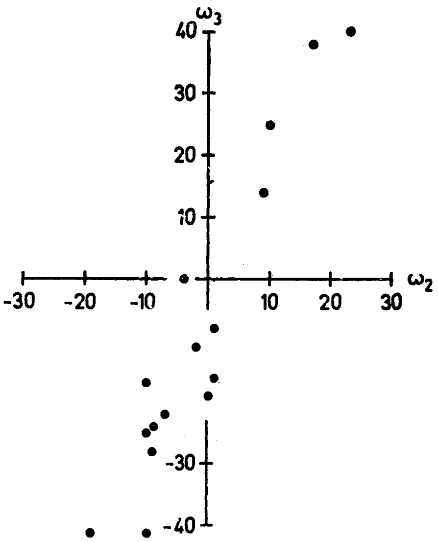

Figure 3 The relationship between the torsion angles (°) C=C–C=O (ω_2) and C_α–C_β–C_γ–O (ω_3) in α-methylene γ-lactones

EXPERIMENTAL

Crystal Data.—Alatolide monohydrate, $C_{19}H_{26}O_6,H_2O$, $M = 368.4$. Orthorhombic, $a = 13.175(2)$, $b = 12.495(2)$, $c = 11.663(4)$ Å, $U = 1\,920$ Å^3, $D_m = 1.27$, $Z = 4$, $D_c = 1.27$ g cm^{-3}, $F(000) = 792$. Space group $P2_12_12_1(D_2^4)$. Cu-K_α radiation, $\lambda = 1.5418$ Å; μ(Cu-K_α) = 8.12 cm^{-1}.

Crystallographic Measurements.—Final values of the cell dimensions were determined by least-squares analysis of the angular settings of twelve reflections, measured on a Hilger and Watts computer-controlled four-circle diffractometer, at θ(Cu-K_α) *ca.* 32°. The reflections in the octant *hkl* were measured in the range $\theta \leqslant 68°$, with θ–ω scans of 60 steps of 0.02° s^{-1}, background counts of 15 s being taken at each end of the scan range. Of 1 968 independent reflections surveyed, the intensities of 1 560 having $I > 3\sigma(I)$ were considered observed. No absorption correction was applied.

Structure Analysis.—The crystal structure was elucidated by direct-phasing procedures from the '*X*-Ray' suite of programs.[12] Based on an overall isotropic temperature parameter B 3.76 Å^2, $|E|$ values were derived and Σ_2 relationships generated for the 249 reflections with $|E| \geqslant 1.46$. The initial set of phases comprised three to define the origin,[13] one to define the enantiomorph, and two to which values of $\pm\pi/2$ were given (see Supplementary Publication). This procedure yielded four sets of phases characterized by R_K 0.23 and 0.31—0.34, and an *E*-map calculated from the phases with the lowest value of R_K yielded positions for all the carbon and oxygen atoms. An initial structure-factor calculation gave R 33.2% and subsequent least-squares calculations with isotropic thermal parameters lowered R to 13.3%. The carbon and oxygen atoms were next assigned anisotropic thermal parameters and R reduced to 10.1%. A difference electron-density distribution revealed the hydrogen atom positions and further least-squares refinement, with anisotropic thermal parameters for the carbon and oxygen atoms and isotropic thermal parameters for the hydrogen atoms, converged to R 6.4, R' 5.3%. The weighting scheme adopted in the closing stages of the calculations was $w = AB$, where A and B were chosen so as to minimize the deviation from constant $w\Delta^2$ over the range of sin θ and $|F_o|$, the final parameters being defined by: $A = \sin\theta/0.562$ for $\sin\theta < 0.562$, $A = 1$ for $\sin\theta \geqslant 0.562$, $B = 59.5/|F_o|$ for $|F_o| > 59.5$, $B = 1$ for $|F_o| \leqslant 59.5$.

The absolute configuration of the molecule could not be determined reliably by the anomalous-dispersion method. Observed and calculated structure amplitudes and the initial set of phases are included in Supplementary Publication No. SUP 21890 (15 pp., 1 microfiche).*

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

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