Crystal and Molecular Structure of Eupatolide, the Major Cytotoxic Principle from *Eupatorium formosanum* HAY

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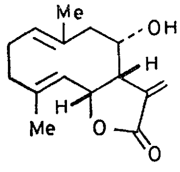
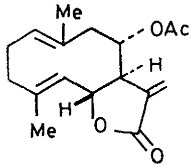
Single-crystal *X*-ray analysis of eupatolide [8β-hydroxygermacra-1(10),4,11(13)-trien-12,6α-olactone] has established the detailed molecular conformation and the absolute configuration follows from the known sign of the Cotton effect of the $n\rightarrow\pi^*$ transition of the C=C–C=O chromophore. Crystals are orthorhombic, space group $P2_12_12_1$, with $a = 10.04(1)$, $b = 13.82(1)$, $c = 9.68(1)$ Å, $Z = 4$. The structure was solved by direct phase-determining methods and refined by full-matrix least-squares calculations to R 0.074 over 957 statistically significant reflections from diffractometer measurements. The *trans,trans*-cyclodecadiene ring is in a chair,chair-conformation with the C(4) and C(10) methyl groups *syn*-oriented on the β-face of the molecule. Analysis of deviations from ideal geometry at the trisubstituted double-bond carbon atoms reveals that in both cases the majority of the distortion arises from twist around the double bond.

EUPATOLIDE, $C_{15}H_{20}O_3$, a cytotoxic sesquiterpene lactone, was first obtained by Dolejš and Herout [1] from base hydrolysis of eupatoriopicrin and formulated as (I). The more recent isolation and subsequent determination of the structure and stereochemistry of tulipinolide (II) and epitulipinolide (III) by Doskotch and El-Feraly [2] resulted in revision of the eupatoriopicrin structure to (IV) from which it followed that that of eupatolide must be modified to (V). Searches among Formosan plant sources for potential antitumor or cytotoxic agents [3] have recently yielded eupatolide as the naturally-occurring major cytotoxic principle of *Eupatorium formosanum* HAY. As part of our continuing interest in the detailed structure and stereochemistry of sesquiterpene lactones we have performed a single-crystal *X*-ray analysis of eupatolide to define accurately the molecular geometry of this lightly substituted germacranolide α-methylene-γ-lactone.



(I)



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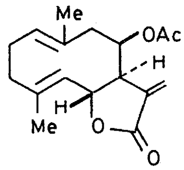
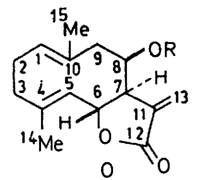
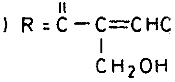


(III)



(IV) R =



$$\overset{\displaystyle O}{\overset{\|}{C}}-\underset{\displaystyle CH_2OH}{\underset{|}{C}}=CHCH_2OH$$

(V) R = H

EXPERIMENTAL

Crystal Data.—$C_{15}H_{20}O_3$, $M = 248.4$. Orthorhombic, $a = 10.04(1)$, $b = 13.82(1)$, $c = 9.68(1)$ Å, $U = 1\,359$ Å^3, D_m (flotation) = 1.20, $Z = 4$, $D_c = 1.214$, $F(000) = 536$, Mo-K_α radiation, $\lambda = 0.7107$ Å; $\mu(\text{Mo}K_\alpha) = 0.90$ cm^{-1}. Space group $P2_12_12_1$ (D_4^2) from systematic absences: $h00$ when $h \neq 2n$, $0k0$ when $k \neq 2n$, and $00l$ when $l \neq 2n$.

Crystallographic Measurements.—A crystal of dimensions *ca.* 0.40 × 0.40 × 0.45 mm was oriented with the *a* axis parallel to the ϕ axis of an Enraf-Nonius CAD 3 diffractometer (Zr-filtered Mo-K_α radiation; 3° take-off angle). Initial cell dimensions obtained from precession photographs were refined by automatically centring 32 high-order reflections on the diffractometer. One octant of data up to 2θ 55° was collected by use of the θ—2θ scanning technique as described previously.[4] A standard reflection, measured once every hundred reflections to monitor crystal and instrument stability, showed no significant variation over the collection period. Of 1 490 measurements, 957 reflections with $I > 2\sigma(I)$ were corrected for Lorentz and polarization effects. No corrections were made for absorption, the effects of which would be very small.

Structure Analysis.—The structure was solved by direct phase-determining methods using MULTAN [5] with 166 reflections having $|E| > 1.30$. Reflections in the starting set were 0,17,2; 1,0,2; 5,0,7; 4,1,6; 4,3,3; 6,9,0; and 8,14,2. The first three of these were origin defining and the fourth was used for enantiomer specification. In the E map computed by use of that set of phases which produced the lowest residual and the highest figure of merit, all the non-hydrogen atom positions were revealed clearly. A structure-factor calculation based on these eighteen atom positions yielded R 0.199. Four cycles of full-matrix least-squares refinement of the positional and isotropic thermal parameters reduced R to 0.119.

A three-dimensional difference Fourier synthesis was then evaluated and significant positive electron-density was found at calculated hydrogen atom positions. Inclusion of the hydrogen-atom contributions into the subsequent structure-factor calculation decreased R to 0.096. Several further cycles of least-squares calculations during which anisotropic thermal parameters for the carbon and oxygen atoms were varied and the hydrogen atoms were refined with isotropic thermal parameters brought the refinement to convergence at R 0.074.

For the structure-factor calculations scattering factor curves of ref. 6 were used for carbon and oxygen, and of

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[1] L. Dolejš and V. Herout, *Coll. Czech. Chem. Comm.*, 1962, **27**, 2654.

[2] R. W. Doskotch and F. S. El-Feraly, *J. Org. Chem.*, 1970, **35**, 1928.

[3] K. H. Lee, H. C. Huang, E. S. Huang, and H. Furukawa, *J. Pharm. Sci.*, 1972, **61**, 629.

[4] D. L. McFadden and A. T. McPhail, *J.C.S. Dalton*, 1974, 363.

[5] G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst.*, 1971, **A27**, 368.

[6] D. T. Cromer and J. T. Waber, *Acta Cryst.*, 1965, **18**, 104.

TABLE 1

(*a*) Fractional atomic co-ordinates ($\times 10^4$) and anisotropic thermal parameters ($\times 10^4$),* with estimated standard deviations in parentheses

Atom	*x*	*y*	*z*	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
C(1)	447(8)	7 014(6)	−330(9)	88(10)	42(5)	114(10)	−15(13)	19(20)	39(13)
C(2)	531(9)	7 684(7)	874(10)	129(11)	13(5)	165(11)	−9(15)	56(21)	−14(15)
C(3)	−643(9)	7 480(6)	1 910(9)	122(9)	24(5)	125(10)	−35(13)	68(19)	−48(13)
C(4)	−693(8)	6 407(6)	2 223(9)	77(8)	38(5)	89(9)	−1(13)	26(18)	−43(12)
C(5)	−1 371(7)	5 840(5)	1 366(8)	74(8)	26(4)	75(8)	20(11)	19(15)	−15(11)
C(6)	−1 134(7)	4 793(5)	1 154(8)	69(7)	33(4)	74(8)	−2(11)	−7(16)	7(10)
C(7)	−1 150(8)	4 471(5)	−373(8)	78(8)	32(4)	72(8)	28(11)	−2(17)	12(12)
C(8)	196(8)	4 495(5)	−1 162(8)	110(8)	44(4)	61(9)	16(10)	49(16)	−25(12)
C(9)	708(9)	5 496(6)	−1 161(10)	121(10)	54(5)	60(11)	37(14)	80(21)	1(15)
C(10)	1 111(8)	6 196(5)	−503(8)	74(8)	55(4)	70(9)	−19(12)	62(17)	68(12)
C(11)	−1 727(7)	3 474(5)	−252(7)	79(7)	40(4)	71(8)	26(10)	−41(15)	−17(10)
C(12)	−2 488(8)	3 434(5)	1 043(8)	86(8)	22(4)	118(8)	0(10)	−23(17)	−24(11)
C(13)	−1 620(8)	2 713(6)	−1 055(8)	98(9)	60(4)	93(9)	−20(11)	9(18)	−25(12)
C(14)	183(8)	6 044(6)	3 369(9)	104(9)	70(5)	105(10)	−53(13)	−35(20)	−42(14)
C(15)	2 276(8)	5 909(6)	404(9)	54(10)	60(5)	165(10)	−7(14)	13(20)	22(14)
O(16)	−2 236(5)	4 223(4)	1 793(5)	115(6)	45(3)	98(6)	−39(8)	56(11)	−14(8)
O(17)	−3 249(6)	2 821(4)	1 479(6)	143(7)	43(3)	134(8)	−88(10)	75(14)	−30(10)
O(18)	1 190(6)	3 994(4)	−377(6)	88(6)	37(4)	184(7)	56(10)	−4(14)	−36(10)

* In the form $B \sin^2 \theta/\lambda^2 = b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl$.

ref. 7 for hydrogen. In the least-squares calculations, $\Sigma w(|F_o| - |F_c|)^2$ was minimized with weights w being assigned $\sqrt{w} = 1$ for $|F_o| \leqslant 14.0$ and $\sqrt{w} = 14.0/|F_o|$ for $|F_o| > 14.0$. With this scheme, no systematic dependence of $\langle w\Delta^2 \rangle$ was found when the values were analysed in ranges of $|F_o|$.

Final atomic positional and thermal parameters are in Tables 1 and 2. Observed and calculated structure factors are listed in Supplementary Publication No. SUP 21507 (8 pp., 1 microfiche).*

TABLE 2

Fractional atomic co-ordinates ($\times 10^3$) and isotropic thermal parameters for hydrogen atoms, with estimated standard deviations in parentheses. Atoms are labelled according to the carbon or oxygen atoms to which they are bonded

Atom	*x*	*y*	*z*	B/Å^2
H(1)	−16(9)	707(7)	−85(10)	5(2)
H(2α)	40(7)	832(5)	62(7)	2(2)
H(2β)	133(9)	769(7)	154(10)	6(2)
H(3α)	−154(9)	770(6)	143(9)	6(2)
H(3β)	−37(7)	779(6)	283(8)	3(2)
H(5)	−191(7)	614(5)	62(8)	3(2)
H(6)	−28(6)	457(4)	156(6)	1(1)
H(7)	−182(8)	481(6)	−80(8)	3(2)
H(8)	−1(7)	415(5)	−204(6)	1(2)
H(9α)	−6(13)	572(9)	−227(13)	9(4)
H(9β)	144(8)	527(6)	−229(9)	4(2)
H(13α)	−196(9)	216(7)	−88(11)	6(3)
H(13β)	−122(9)	281(7)	−187(10)	7(2)
H(14α)	104(7)	622(5)	329(7)	3(2)
H(14β)	34(13)	544(8)	346(14)	1(4)
H(14γ)	−19(9)	632(6)	420(9)	5(2)
H(15α)	207(8)	531(6)	111(10)	6(3)
H(15β)	260(12)	641(9)	93(13)	9(3)
H(15γ)	306(8)	580(6)	−9(8)	5(2)
H(18)	120(7)	351(5)	−66(7)	3(2)

RESULTS AND DISCUSSION

The *X*-ray analysis confirms that the structure and relative stereochemistry of eupatolide are correctly represented by the revised structure (V).[1] Moreover, when the results are considered in conjunction with the known sign of the Cotton effect[8] of the α-methylene-γ-lactone chromophore (*vide infra*) they establish that (V) also represents the absolute stereochemistry. A view of the molecular conformation in the solid state and the atom numbering scheme are shown in Figure 1. Interatomic distances, valency and torsion angles are in Table 3.

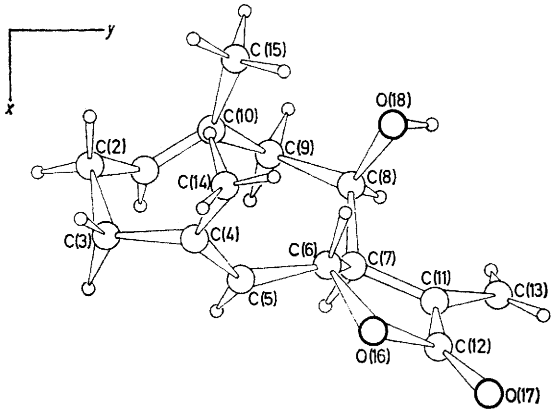

FIGURE 1 Molecular conformation and numbering scheme for the carbon and oxygen atoms; small circles denote hydrogen atoms

The *trans,trans*-cyclodeca-1,5-diene ring of eupatolide adopts a chair, chair conformation in which the methyl groups at C(4) and C(10) are in a *syn*-orientation on the β-face of the molecule. Recognition of the common occurrence of similar *syn*-related methyl groups or their equivalents in pregeijerine,[9] germacratriene,[10] elephantol,[11] and shiromodiol,[12] has prompted the postulate that

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* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1974, Index issue.

[7] R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **42**, 3175.

[8] W. Stöcklin, T. G. Waddell, and T. A. Geissman, *Tetrahedron*, 1970, **26**, 2397.

[9] P. Coggon, A. T. McPhail, and G. A. Sim, *J. Chem. Soc.* (*B*), 1970, 1024.

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

[11] A. T. McPhail and G. A. Sim, *J.C.S. Perkin II*, 1972, 313.

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

this probably represents the energetically favoured form. The results of the present *X*-ray analysis and those on costunolide,[13] pyrethrosin,[14] and dihydromikanolide,[15] add further examples to this group.

In eupatolide the C(1) · · · C(5) and C(10) · · · C(5) transannular separations although distinctly short (2.94 and 3.12 Å) are in accord with the corresponding distances in a number of *trans,trans*-germacradienes, *e.g.* 2.98 and 3.13 in pregeijerine–silver nitrate,[9] 2.98 and 3.36 in elephantol *p*-bromobenzoate,[11] and 3.05 and 3.51 Å in shiromodiol acetate *p*-bromobenzoate.[12] The anomalous u.v. spectra found for several unsaturated germacranes in the 210 mμ region have been rationalized in terms of this transannular proximity of double bonds,[16] and eupatolide, not unexpectedly, exhibits a similar effect. In each of the compounds cited the methyl groups or their equivalents at C(4) and C(10) are noticeably bent away from each other to reduce transannular non-bonded interactions and yield more normal C(14) · · · C(15) distances: 3.56 in eupatolide, 3.49 in pregeijerine–silver nitrate,[9] 3.32 in elephantol *p*-bromobenzoate,[11] and 3.88 Å in shiromodiol acetate *p*-bromobenzoate.[12]

TABLE 3

Interatomic distances (Å) and angles (°), with estimated standard deviations in parentheses

(*a*) Bond lengths

C(1)–C(2)	1.491(13)	C(7)–C(11)	1.500(10)
C(1)–C(10)	1.323(11)	C(8)–C(9)	1.538(12)
C(2)–C(3)	1.573(13)	C(8)–O(18)	1.433(10)
C(3)–C(4)	1.515(12)	C(9)–C(10)	1.501(12)
C(4)–C(5)	1.329(11)	C(10)–C(15)	1.515(11)
C(4)–C(14)	1.502(12)	C(11)–C(12)	1.469(10)
C(5)–C(6)	1.481(10)	C(11)–C(13)	1.312(11)
C(6)–C(7)	1.544(11)	C(12)–O(16)	1.335(9)
C(6)–O(16)	1.492(9)	C(12)–O(17)	1.216(10)
C(7)–C(8)	1.553(11)		
C(1)–H(1)	0.80(10)	C(9)–H(9β)	1.04(8)
C(2)–H(2α)	0.92(7)	C(13)–H(13α)	0.86(9)
C(2)–H(2β)	1.03(10)	C(13)–H(13β)	0.90(9)
C(3)–H(3α)	1.06(9)	C(14)–H(14α)	0.90(7)
C(3)–H(3β)	1.03(8)	C(14)–H(14β)	0.85(12)
C(5)–H(5)	1.00(8)	C(14)–H(14γ)	0.96(9)
C(6)–H(6)	0.99(6)	C(15)–H(15α)	1.09(9)
C(7)–H(7)	0.92(8)	C(15)–H(15β)	0.92(12)
C(8)–H(8)	1.00(6)	C(15)–H(15γ)	0.93(8)
C(9)–H(9α)	1.05(13)	O(18)–H(18)	0.72(7)

(*b*) Valency angles

C(2)–C(1)–C(10)	126.9(8)	C(7)–C(8)–O(18)	109.6(6)
C(1)–C(2)–C(3)	110.2(7)	C(9)–C(8)–O(18)	110.6(6)
C(2)–C(3)–C(4)	109.1(7)	C(8)–C(9)–C(10)	117.9(7)
C(3)–C(4)–C(5)	118.0(7)	C(1)–C(10)–C(9)	120.4(7)
C(3)–C(4)–C(14)	117.1(7)	C(1)–C(10)–C(15)	122.7(7)
C(5)–C(4)–C(14)	124.3(8)	C(9)–C(10)–C(15)	116.9(7)
C(4)–C(5)–C(6)	125.5(7)	C(7)–C(11)–C(12)	107.6(6)
C(5)–C(6)–C(7)	114.4(6)	C(7)–C(11)–C(13)	131.2(7)
C(5)–C(6)–O(16)	109.9(6)	C(12)–C(11)–C(13)	121.2(7)
C(7)–C(6)–O(16)	103.7(6)	C(11)–C(12)–O(16)	109.6(6)
C(6)–C(7)–C(8)	117.1(6)	C(11)–C(12)–O(17)	130.4(7)
C(6)–C(7)–C(11)	101.2(6)	O(16)–C(12)–O(17)	120.0(7)
C(8)–C(7)–C(11)	113.2(6)	C(6)–O(16)–C(12)	110.3(5)
C(7)–C(8)–C(9)	116.7(6)		
C(2)–C(1)–H(1)	119(7)	O(18)–C(8)–H(8)	111(4)
C(10)–C(1)–H(1)	113(7)	C(8)–C(9)–H(9α)	101(7)
C(1)–C(2)–H(2α)	112(5)	C(8)–C(9)–H(9β)	98(5)
C(1)–C(2)–H(2β)	123(5)	C(10)–C(9)–H(9α)	116(7)
C(3)–C(2)–H(2α)	103(5)	C(10)–C(9)–H(9β)	117(5)
C(3)–C(2)–H(2β)	101(5)	H(9α)–C(9)–H(9β)	103(8)
H(2α)–C(2)–H(2β)	106(7)	C(11)–C(13)–H(13α)	124(7)
C(2)–C(3)–H(3α)	108(5)	C(11)–C(13)–H(13β)	116(6)
C(2)–C(3)–H(3β)	106(4)	H(13α)–C(13)–H(13β)	119(9)
C(4)–C(3)–H(3α)	110(5)	C(4)–C(14)–H(14α)	114(5)
C(4)–C(3)–H(3β)	104(4)	C(4)–C(14)–H(14β)	121(9)
H(3α)–C(3)–H(3β)	119(6)	C(4)–C(14)–H(14γ)	105(5)
C(4)–C(5)–H(5)	119(4)	H(14α)–C(14)–H(14β)	96(10)
C(6)–C(5)–H(5)	113(4)	H(14α)–C(14)–H(14γ)	110(7)
C(5)–C(6)–H(6)	113(3)	H(14β)–C(14)–H(14γ)	112(10)
C(7)–C(6)–H(6)	107(3)	C(10)–C(15)–H(15α)	114(5)
O(16)–C(6)–H(6)	108(3)	C(10)–C(15)–H(15β)	113(8)
C(6)–C(7)–H(7)	107(5)	C(10)–C(15)–H(15γ)	114(5)
C(8)–C(7)–H(7)	114(5)	H(15α)–C(15)–H(15β)	107(9)
C(11)–C(7)–H(7)	103(5)	H(15α)–C(15)–H(15γ)	111(7)
C(7)–C(8)–H(8)	103(4)	H(15β)–C(15)–H(15γ)	96(9)
C(9)–C(8)–H(8)	105(4)	C(8)–O(18)–H(18)	105(6)

(*c*) Intermolecular distances <3.7 Å

O(18) · · · O(17$^{\mathrm{I}}$)	2.78	C(2) · · · O(16$^{\mathrm{II}}$)	3.54
C(13) · · · O(17$^{\mathrm{I}}$)	3.49	C(8) · · · O(17$^{\mathrm{I}}$)	3.58
O(18) · · · C(13$^{\mathrm{I}}$)	3.51	O(18) · · · C(12$^{\mathrm{I}}$)	3.67

Roman numeral superscripts refer to the following transformations of the co-ordinates of Table 1:

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

TABLE 3 (*Continued*)

(*d*) Torsion angles

C(10)–C(1)–C(2)–C(3)	−97.5	C(11)–C(7)–C(8)–O(18)	−66.3
C(1)–C(2)–C(3)–C(4)	50.4	C(6)–C(7)–C(11)–C(12)	23.2
C(2)–C(3)–C(4)–C(5)	−85.7	C(6)–C(7)–C(11)–C(13)	−155.2
C(2)–C(3)–C(4)–C(14)	86.1	C(8)–C(7)–C(11)–C(12)	149.4
C(3)–C(4)–C(5)–C(6)	155.0	C(8)–C(7)–C(11)–C(13)	−28.9
C(14)–C(4)–C(5)–C(6)	−16.2	C(7)–C(8)–C(9)–C(10)	66.6
C(4)–C(5)–C(6)–C(7)	−136.0	O(18)–C(8)–C(9)–C(10)	−59.5
C(4)–C(5)–C(6)–O(16)	107.9	C(8)–C(9)–C(10)–C(1)	−115.4
C(5)–C(6)–C(7)–C(8)	89.9	C(8)–C(9)–C(10)–C(15)	63.3
C(5)–C(6)–C(7)–C(11)	−146.5	C(9)–C(10)–C(1)–C(2)	166.6
O(16)–C(6)–C(7)–C(8)	−150.5	C(15)–C(10)–C(1)–C(2)	−12.1
O(16)–C(6)–C(7)–C(11)	−26.9	C(7)–C(11)–C(12)–O(16)	−10.5
C(5)–C(6)–O(16)–C(12)	145.4	C(7)–C(11)–C(12)–O(17)	169.8
C(7)–C(6)–O(16)–C(12)	22.7	C(13)–C(11)–C(12)–O(16)	168.0
C(6)–C(7)–C(8)–C(9)	−75.7	C(13)–C(11)–C(12)–O(17)	−11.7
C(6)–C(7)–C(8)–O(18)	51.0	C(6)–O(16)–C(12)–C(11)	−8.1
C(11)–C(7)–C(8)–C(9)	167.1	C(6)–O(16)–C(12)–O(17)	171.7

It is well-established that endocyclic *trans*-double-bonds in medium-ring olefins are subject to considerable strain[17] and consequently it is not surprising to find that both the C(2)–C(1)–C(10)–C(9) and C(3)–C(4)–C(5)–C(6) torsion angles (167 and 155°) depart significantly from the ideal 180°. These values are similar to the corresponding angles in other germacradienes studied previously by *X*-ray diffraction.[9,12] Since both the 1(10) and 4(5) double-bonds are trisubstituted the results of the present study may be used to resolve the magnitudes of two component parts of the distortion, *viz.* twist around the double bond itself and departure from trigonal bonding at the sp^2 carbon atom bearing the methyl group. In the case of the C(1)–C(10) double bond, the principal source of the apparent twist (13°) is not the out-of-plane dis-

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[13] F. Šorm, M. Suchý, M. Holub, A. Línek, I. Hadinec, and C. Novák, *Tetrahedron Letters*, 1970, 1893.

[14] E. J. Gabe, S. Neidle, D. Rogers, and C. E. Nordman, *Tetrahedron Letters*, 1971, 559.

[15] P. J. Cox, G. A. Sim, J. S. Roberts, and W. Herz, *Chem. Comm.*, 1973, 428.

[16] F. Šorm in ' Progress in the Chemistry of Organic Natural Products,' vol. 19, L. Zechmeister, ed., Springer, Vienna, 1961, p. 1; N. H. Fischer and T. J. Mabry, *Chem. Comm.*, 1967, 1235; N. H. Fischer, T. J. Mabry, and H. B. Kagan, *Tetrahedron*, 1968, **24**, 4091; R. V. H. Jones and M. D. Sutherland, *Austral. J. Chem.*, 1968, **21**, 2255.

[17] V. Prelog, K. Schenker, and W. Kung, *Helv. Chim. Acta*, 1953, **36**, 471; V. Prelog, K. Schenker, and H. H. Gunthardt, *ibid.*, 1952, **35**, 1602; F. H. Allen, E. D. Brown, D. Rogers, and J. K. Sutherland, *Chem. Comm.*, 1967, 1116.

placement of bonds at C(10), the angle between the C(9)–C(10)–C(1) and C(15)–C(10)–C(1) planes being only 1°, but rather a true twist about the C(1)–C(10) double bond as measured by the C(15)–C(10)–C(1)–C(2) torsion angle of −12°. A like conclusion holds at the C(4)–C(5) double bond where the C(14)–C(4)–C(5)–C(6) torsion angle of −16° establishes that most of the 25° distortion is again due to a true twist about the C(4)–C(5) bond.

The γ-lactone, *trans*-fused at C(6) and C(7), approximates to a half-chair conformation with C(6) and C(7) displaced to opposite sides of the least-squares plane through C(11), C(12), O(16), and O(17) by 0.20 and 0.26 Å, respectively. In accord with earlier observations[18] for *trans*-fused α-methylene-γ-lactones, the signs of the C(13)–C(11)–C(12)–O(17) and C(11)–C(7)–C(6)–O(16) torsion angles are paired with the magnitude of the latter (−27°) being about twice that of the former (−12°). The sum of the moduli of the torsion angles of the γ-lactone ring in eupatolide (92°) indicates that this ring is much more puckered than either of the γ-lactone rings in elephantol *p*-bromobenzoate[11] where the corresponding values are only 11 and 33°.

From measurements of the sign of the Cotton effect of the $n\rightarrow\pi^*$ transition of the α-methylene-γ-lactone chromophore in a number of sesquiterpene lactones Stöcklin *et al.*[8] were able to establish that, although there were some exceptions, 6,7-*cis*-fused lactones generally gave rise to a positive Cotton effect whereas a negative Cotton effect was found when the lactone ring was *trans*-fused across the 6,7-bond. More recently Beecham[19] has generalized these observations and related the sign of the Cotton effect to the chirality of the C=C–C=O chromophore. For eupatolide, with its *trans*-fused 6,7-lactone ring, the experimentally determined Cotton effect[8] is negative in agreement with the Stöcklin *et al.* correlation and it implies a negative chirality of the C=C–C=O group. Moreover, eupatolide represented by (V) has a C=C–C=O torsion angle of −12° from which we conclude that (V) must also represent the absolute configuration which consequently makes the C-7 hydrogen atom α-oriented as in all known sesquiterpene lactones from higher plants.

The mean lengths of chemically equivalent bonds compare well with accepted values:[20] C(sp^3)–C(sp^3) 1.552(13), C(sp^3)–C(sp^2) 1.501(13), C(sp^2)–C(sp^2) 1.469(10), C(sp^2)=C(sp^2) 1.321(11), C(sp^3)–O(hydroxy) 1.433(10), C(sp^3)–O(lactone) 1.492(9), C(sp^2)–O 1.335(9) and C=O(lactone) 1.216(10), C–H 0.96(8), and O–H 0.72(7) Å.

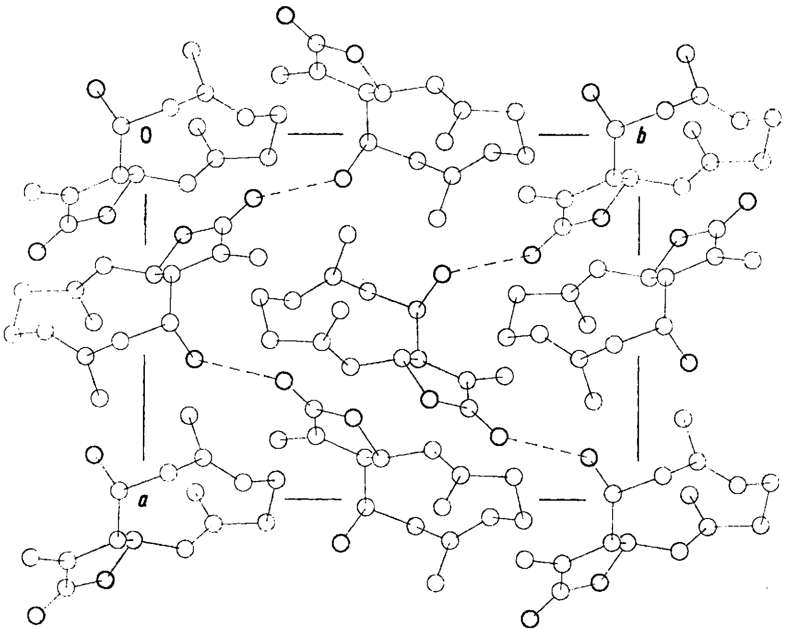

FIGURE 2 Crystal structure viewed in projection along the *c* axis; O–H · · · O hydrogen bonds are denoted by the broken lines

The crystal structure viewed in projection along the *c* axis is shown in Figure 2. The shortest intermolecular separation quoted in Table 3 (2.78 Å) occurs between the C(8)-hydroxy group of one molecule and the C(12) carbonyl oxygen of a molecule related by the 2_1 screw axis along the *a* direction and it is typical for an OH · · · O hydrogen bond. The other intermolecular distances correspond to normal van der Waals' interactions.

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

[19] A. F. Beecham, *Tetrahedron*, 1972, **28**, 5543.

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