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The Structure of Glaucolide-D, $C_{23}H_{28}O_{10}$. A Sesquiterpene Lactone*

BY I. F. TAYLOR JR AND W. H. WATSON
FASTBIOS Laboratory, Texas Christian University, Fort Worth, Texas 76129, *U.S.A.*

AND M. BETKOUSKI, W. G. PADOLINA AND T. J. MABRY
The Cell Research Institute and Department of Botany, The University of Texas, Austin, Texas 78712, *U.S.A.*

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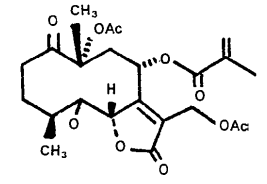
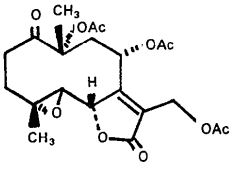
Glaucolide-D, $C_{23}H_{28}O_{10}$, is a germacranolide-type sesquiterpene lactone isolated from *Vernonia uniflora*. The material crystallizes in space group $P2_12_12_1$ with cell dimensions $a=21{\cdot}57(1)$, $b=12{\cdot}49(1)$ and $c=8{\cdot}45(1)$ Å with $Z=4$. The crystal decomposes slowly upon exposure to X-rays. Counter techniques were used to collect 1721 independent reflections of which 1440 had intensities greater than $3\sigma(I)$. Phases for the 403 $|E|$'s greater than 1·2 were calculated by *MULTAN* and all 33 nonhydrogen atoms were located in the E map. The structure was refined by block-diagonal least-squares techniques to a final R of 0·044. The ten-membered ring contains a *trans* double bond at the 1–10 position and a *trans* epoxide at the 3–4 position. The conformation and configuration of the ten-membered ring is such that the C(14) and C(15) methyl groups lie on the β-face of the molecule.

Introduction

Several new, highly oxygenated germacranolides have been isolated from members of the genus *Vernonia* (Compositae). Three compounds [glaucolide-A (I) and -B (II) (Padolina, 1973; Padolina *et al.*, 1974*b*; Watson, Wu, Monti, Davis, Mabry & Padolina, 1974) and marginatin (III) (Padolina, Nakatani, Yoshioka, Mabry & Monti, 1974*a*)], have been isolated from North American species and structurally identified. One of these bitter principles, glaucolide-A, recently was shown to be an insect feeding deterrent and growth inhibitor for several species of lepidoptera (Burnett, Jones, Mabry & Padolina, 1974). Here we report the structure of another member of this series of sesquiterpene lactones, glaucolide-D (IV), isolated from *Vernonia uniflora* Sch.-Bip. collected in Oaxaca, Mexico. The discovery of glaucolide-D in this species supports the treatment of *Eremosis* (to which *V. uniflora* belongs) as a section of the genus *Vernonia* (Mabry, Abdel-Baset, Padolina & Jones, 1975).



(I)



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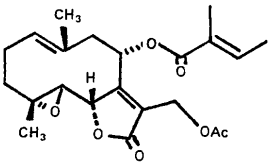

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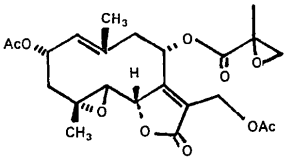

(IV)

* FASTBIOS Contribution No. 22.

Experimental

A crystal of dimensions $0{\cdot}50\times0{\cdot}30\times0{\cdot}75$ mm was mounted with the c axis coincident with the rotation axis. The unit cell was found to be orthorhombic and room temperature cell dimensions were determined from calibrated precession photographs.

Crystal data

$C_{23}H_{28}O_{10}$, M.W. 464·474, $a=21{\cdot}57(1)$, $b=12{\cdot}49$ (1), $c=8{\cdot}45$ (1) Å. $P2_12_12_1$ (D_2^4, No. 19). $Z=4$, $F(000)=984$, $V=2276{\cdot}5$ Å^3, D_{exp} (flotation) $=1{\cdot}360$, $D_{cal}=1{\cdot}355$ g cm^{-3}, $\mu=9{\cdot}1$ cm^{-1}.

The intensity data, $hk0$ through $hk7$, were collected with a Philips Pailred diffractometer using equi-inclination geometry and the continuous ω-scan technique. A scan range of 3·6 to 5·2° at 2·5° min^{-1} was used. A background count was taken for 20 s on either side of the ω-scan range. 1721 independent reflections were measured and 1440 had intensities greater than $3\sigma(I)$. The intensities of the reference reflections decreased by 19% during data collection and a separate linear correction was applied to each level. Lorentz and polarization corrections were applied, but no absorption correction was made. Structure-factor magnitudes, $|F_o|$, and normalized structure factor magnitudes, $|E_h|$, were computed. The scattering factors of Cromer & Waber (1965) were used for the carbon and oxygen atoms while those of Stewart, Davidson & Simpson (1965) were used for the hydrogen atoms.

Structure determination and refinement

MULTAN (Germain, Main & Woolfson, 1971) was used to calculate phases for the 403 $|E|$'s greater than 1·2. The E map with the largest combined figure of merit yielded the positions of all 33 nonhydrogen atoms. The parameters were refined by block-diagonal least

squares techniques to an R of 0·062 using anisotropic temperature factors. Positions of all hydrogen atoms except for C(14) and C(22) methyl groups were located in a difference Fourier map. The contributions of the hydrogen atoms to the structure factors were included in several more least-squares calculations, but the hydrogen atom parameters were not refined. The refinement was terminated at $R=0{\cdot}044$ and $R_w=0{\cdot}061$ where $R=\sum||F_o|-|F_c||/\sum|F_o|$ and $R_w=[\sum W(|F_o-|F_c|)^2/(\sum wF_o)^2]^{1/2}$. The function minimized was $w(F_o-F_c)^2$ where $w=1/(\Delta F)^2$ is an empirical weighting factor derived from a least-squares fit of $\Delta F=a+bF$ with constants $a=0{\cdot}248$ and $b=0{\cdot}04568$. The final three-dimensional difference Fourier map contained positive density of approximately 0·5 e $Å^{-3}$ around C(14) and C(22) methyl groups. The estimated standard deviations were calculated from the inverse of the normal-equations matrix. All shifts of the parameters during the final cycle were less than 0·03 of the estimated standard deviation.

The atomic and thermal parameters along with the estimated standard deviations are given in Table 1.*

Discussion

Fig. 1 shows a projection of the unit-cell contents onto the *ab* plane, and Fig. 2 indicates the numbering sys-

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31167 (8 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 1. *Atomic positional* ($\times 10^4$) *and thermal* ($\times 10^3$) *parameters*

Anisotropic thermal parameters have the form $\exp[2\pi^2(U_{11}h^2a^{*2}+U_{22}k^2b^{*2}+U_{33}l^2c^{*2}+2U_{12}hka^*b^*+2U_{13}hla^*c^*+2U_{23}klb^*c^*)]$. The isotropic thermal parameter for all H atoms is 3·0 $Å^2$.

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	947 (2)	1649 (4)	8382 (6)	32 (2)	31 (3)	29 (3)	0 (2)	4 (2)	−2 (2)
C(2)	328 (2)	1911 (4)	9095 (6)	36 (3)	38 (3)	32 (3)	−4 (2)	4 (2)	3 (2)
C(3)	329 (2)	3076 (4)	9664 (7)	36 (3)	46 (3)	44 (4)	0 (3)	20 (2)	0 (3)
C(4)	556 (2)	3825 (4)	8395 (7)	36 (3)	28 (3)	50 (3)	6 (2)	8 (3)	−4 (3)
C(5)	1233 (2)	4029 (4)	8382 (7)	36 (3)	31 (3)	41 (3)	5 (2)	8 (2)	−8 (3)
C(6)	1614 (2)	4368 (4)	6963 (7)	30 (2)	30 (3)	44 (3)	0 (2)	2 (2)	0 (2)
C(7)	2049 (2)	3523 (4)	6302 (6)	31 (2)	28 (3)	27 (3)	2 (2)	0 (2)	2 (2)
C(8)	1833 (2)	2587 (4)	5327 (6)	30 (2)	32 (3)	25 (3)	1 (2)	6 (2)	−1 (2)
C(9)	1713 (2)	1532 (4)	6250 (6)	37 (3)	32 (3)	32 (3)	0 (2)	8 (2)	−6 (2)
C(10)	1057 (2)	1490 (4)	6866 (7)	34 (3)	29 (3)	40 (3)	−9 (2)	4 (2)	−2 (2)
C(11)	2631 (2)	3817 (4)	6613 (6)	37 (3)	24 (3)	32 (3)	−1 (2)	5 (2)	−3 (2)
C(12)	2623 (2)	4867 (4)	7419 (7)	42 (3)	33 (3)	44 (3)	2 (3)	10 (3)	0 (3)
C(13)	3242 (2)	3299 (4)	6298 (7)	29 (3)	33 (3)	52 (4)	0 (2)	3 (2)	−9 (3)
C(14)	149 (2)	3928 (5)	6938 (8)	39 (3)	61 (4)	72 (5)	7 (3)	−4 (3)	23 (4)
C(15)	573 (2)	1276 (5)	5589 (7)	45 (3)	79 (5)	34 (3)	−18 (3)	2 (3)	−13 (3)
O(16)	2027 (2)	5197 (3)	7550 (5)	39 (2)	26 (2)	62 (3)	0 (2)	10 (2)	−11 (2)
O(17)	3052 (2)	5398 (3)	7881 (6)	46 (2)	45 (2)	86 (3)	−10 (2)	0 (2)	−27 (2)
O(18)	808 (2)	4837 (3)	8966 (5)	55 (2)	39 (2)	57 (3)	5 (2)	18 (2)	−15 (2)
O(19)	3188 (1)	2184 (3)	6646 (4)	29 (2)	36 (2)	46 (2)	9 (2)	3 (2)	5 (2)
C(20)	3698 (2)	1600 (5)	6631 (8)	39 (3)	54 (4)	57 (4)	10 (3)	−1 (3)	−4 (3)
O(21)	4192 (2)	1969 (4)	6266 (8)	47 (3)	66 (3)	168 (6)	17 (2)	14 (3)	0 (4)
C(22)	3560 (3)	442 (5)	6980 (11)	76 (4)	40 (4)	109 (6)	20 (3)	5 (4)	21 (4)
O(23)	245 (1)	1201 (3)	10462 (4)	30 (2)	51 (2)	31 (2)	2 (2)	5 (1)	11 (2)
C(24)	−340 (2)	982 (4)	10872 (7)	35 (3)	41 (3)	36 (3)	−2 (2)	5 (2)	0 (2)
O(25)	−784 (2)	1366 (4)	10246 (5)	35 (2)	80 (3)	58 (3)	7 (2)	0 (2)	23 (2)
C(26)	−373 (2)	179 (5)	12173 (7)	44 (3)	55 (4)	52 (4)	2 (3)	6 (3)	16 (3)
O(27)	2323 (1)	2382 (3)	4185 (4)	33 (2)	44 (2)	19 (2)	2 (2)	1 (2)	−3 (2)
C(28)	2147 (2)	2175 (4)	2685 (6)	49 (3)	37 (3)	27 (3)	−8 (2)	−2 (2)	−2 (2)
O(29)	1624 (1)	2158 (4)	2230 (5)	44 (2)	88 (3)	38 (2)	−10 (2)	−10 (2)	−15 (2)
C(30)	2716 (2)	1954 (5)	1695 (6)	53 (3)	60 (4)	23 (3)	−6 (3)	3 (3)	−10 (3)
C(31)	3253 (3)	1442 (7)	2435 (9)	65 (4)	133 (7)	67 (5)	47 (5)	2 (4)	−22 (5)
O(32)	2564 (2)	1567 (5)	143 (5)	78 (3)	129 (5)	38 (3)	−28 (3)	15 (2)	−38 (3)
C(33)	2790 (3)	2625 (7)	313 (8)	65 (4)	105 (6)	39 (4)	−27 (4)	10 (3)	5 (4)

	x	y	z		x	y	z
H(1)	1385	1757	9080	H(13′)	3558	3703	6960
H(2)	−58	1702	8210	H(15)	580	1987	4570
H(3)	0	3162	10150	H(15′)	192	1459	5920
H(3′)	654	3108	10750	H(15″)	800	459	5290
H(5)	1500	3620	9240	H(31)	3481	1838	3040
H(6)	1385	4684	6090	H(31′)	3615	1216	2000
H(8)	1442	2973	4985	H(31″)	3135	676	3220
H(9)	1827	892	5650	H(33)	2450	3297	150
H(9′)	2019	1432	7030	H(33′)	3173	2838	80
H(13)	3404	3378	5290				

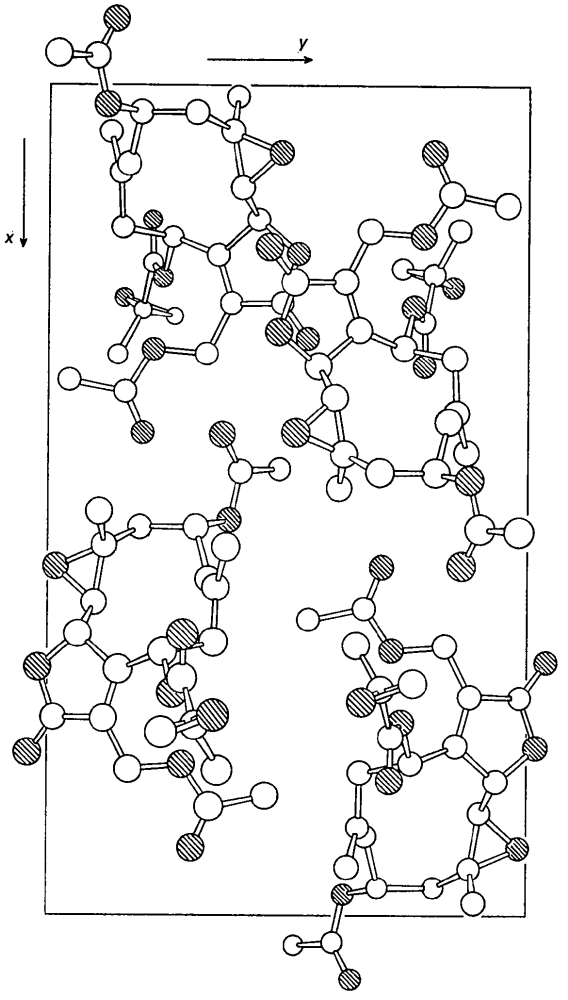

Fig. 1. Projection of the unit-cell contents onto the *ab* plane for glaucolide-D.

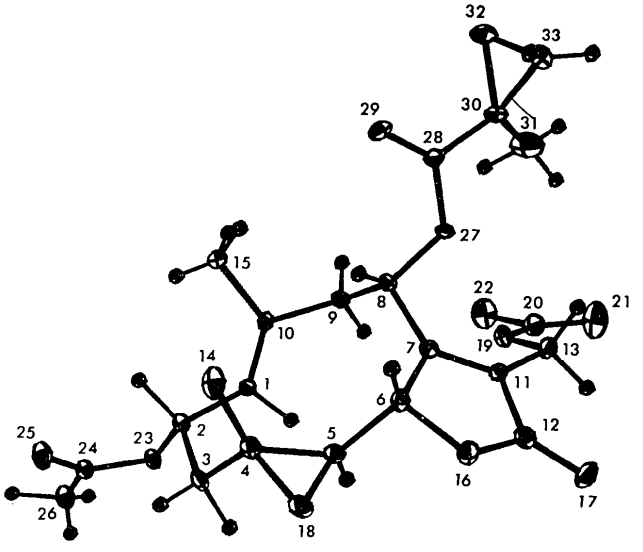

Fig. 2. Molecular structure of glaucolide-D and numbering system used in all the tables.

tem used in all the tables. Table 2 lists bond distances and bond angles while Table 3 presents torsion angles for glaucolide-D and several related sesquiterpenes.

It is assumed that the absolute configuration at C(6) is the same for all germacranolides (Neidle & Rogers, 1972) and is designated as *S* for glaucolide-D. The torsion angles correspond to this choice of stereochemistry. The conformation of the ten-membered ring differs considerably from that of glaucolide-A (Padolina *et al.*, 1974*b*) and dihydrodesacetoxyglaucolide-A (Watson *et al.*, 1974). This is due to a keto function at C(1) in glaucolide-A instead of the C(1)–C(10) double bond found in glaucolide-D. The conformation is such that the C(14) and C(15) methyl groups lie *syn* on the β-face and the C(10)–C(1) and C(4)–C(5) bonds are in a crossed orientation.

The endocyclic double bond at C(7)–C(11) is typical of the glaucolide series of germacranolides and the five-membered γ-lactone ring is almost planar with no internal torsion angle greater than 5°. The shift of the C(11)–C(13) double bond found in most germacranolides to C(7)–C(11) in the glaucolide series is responsible for the lack of significant cytotoxic activity of these molecules (Watson, Reinecke & Hitt, 1975); however, at least one member in the series is an insect feeding deterrent and growth inhibitor for several species of lepidoptera (Burnett *et al.*, 1974).

The torsion angle O(17)C(12)C(11)C(13) is 0° while the angle C(13)C(11)C(7)C(8) is −7° indicating planarity in this portion of the molecule. All bond lengths are normal and the internal consistency is quite good. The four C=O distances average 1·198 Å with an average deviation of 0·003 Å while the four C–O bonds adjacent to the carbonyl average 1·337 Å with an average deviation of 0·001 Å. The six bonds in the two epoxide groups average 1·436 Å with an average deviation of 0·015 Å, and all angles are within 3 σ of 60°. The high density of 1·361 g cm^{-3} indicates a well packed structure which is consistent with an *R* value of 0·044 and well behaved thermal parameters. The shortest intermolecular interactions occur between H(5)–H(33), 2·2 Å, and H(33′)–O(25), 2·47 Å. The interactions H(1)–O(32), H(1)–O(29), H(3′)–O(29) and H(6)–O(25) fall between 2·71 and 2·76 Å. These and additional interactions between 2·80 and 2·95 Å restrict the movements of the side chains and the motions of the methyl groups C(15), C(26) and C(31). The hydrogen atoms on methyl groups C(14) and C(22) could not be located in difference Fourier maps and their rotations are not restricted.

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Table 2. *Bond distances* (Å) *and bond angles* (°)

C(1)—C(2)	1·501 (7)	C(12)–O(16)	1·354 (6)	C(2)—O(23)	1·466 (6)
C(2)—C(3)	1·533 (7)	C(12)–O(17)	1·202 (7)	O(23)–C(24)	1·337 (6)
C(3)—C(4)	1·505 (8)	O(16)–C(6)	1·453 (6)	C(24)–O(25)	1·196 (6)
C(4)—C(5)	1·483 (7)	C(4)—C(14)	1·517 (9)	C(24)–C(26)	1·489 (8)
C(5)—C(6)	1·515 (7)	C(4)—O(18)	1·458 (6)	C(8)–O(27)	1·454 (5)
C(7)—C(8)	1·504 (7)	C(5)—O(18)	1·450 (6)	O(27)–C(28)	1·348 (6)
C(8)—C(9)	1·553 (7)	C(10)–C(15)	1·524 (8)	C(28)–O(29)	1·193 (6)
C(9)—C(10)	1·509 (7)	C(11)–C(13)	1·492 (7)	C(28)–C(30)	1·511 (7)
C(10)–C(1)	1·318 (7)	C(13)–O(19)	1·428 (6)	C(30)–C(31)	1·464 (9)
C(7)—C(11)	1·335 (6)	O(19)–C(20)	1·319 (6)	C(30)–O(32)	1·436 (7)
C(11)–C(12)	1·477 (7)	C(20)–O(21)	1·201 (7)	C(30)–C(33)	1·446 (9)
O(32)–C(33)	1·415 (10)	C(20)–C(22)	1·506 (9)	C(2)—H(2)	1·15
C(3)—H(3)	0·83	C(3)—H(3′)	1·16	C(5)—H(5)	1·06
C(6)—H(6)	0·97	C(8)—H(8)	1·01	C(9)—H(9)	0·98
C(9)—H(9′)	0·94	C(1)—H(1)	1·12	C(13)–H(13)	0·93
C(13)–H(13′)	1·02	C(15)–H(15)	1·24	C(15)–H(15′)	0·90
C(15)–H(15″)	1·16	C(26)–H(26)	1·10	C(26)–H(26′)	0·77
C(26)–H(26″)	0·74	C(31)–H(31)	0·86	C(31)–H(31′)	0·91
C(31)–H(31″)	1·19	C(33)–H(33)	1·12	C(33)–H(33′)	0·89
C(6)—C(7)	1·518 (7)				

Bond angles (°). Standard deviations range from 0·4 to 0·6°.

1–2–3	109·3	5–6–7	115·6	7–11–13	132·5	8–27–28	116·9
1–2–23	107·1	7–6–16	104·0	11–12–16	108·6	27–28–29	125·0
3–2–23	109·0	6–7–8	123·4	11–12–17	129·0	27–28–30	109·1
2–3–4	111·5	6–7–11	108·5	16–12–17	122·4	28–30–31	119·1
3–4–5	115·6	11–7–8	127·8	12–16–6	109·7	28–30–32	112·5
3–4–14	116·3	7–8–9	115·8	11–13–19	108·3	28–30–33	115·6
3–4–18	115·1	7–8–27	105·9	13–19–20	118·0	31–30–32	115·0
5–4–14	123·3	27–8–9	107·8	19–20–21	122·1	31–30–33	120·8
14–4–18	114·2	8–9–10	111·1	19–20–22	111·3	30–32–33	61·0
5–4–18	59·1	9–10–1	119·9	21–20–22	126·4	32–33–30	60·2
4–5–18	59·6	9–10–15	113·8	2–23–24	116·3	32–30–33	58·8
4–18–5	61·3	15–10–1	126·3	23–24–25	124·0	12–11–13	118·5
4–5–6	126·1	10–1–2	125·6	23–24–26	112·0	29–28–30	125·9
18–5–6	114·7	7–11–12	108·9	25–24–26	124·0		

Table 3. *Torsion angles* (°)

	D	P	A	DA
C(1)—C(2)	−109	−106	143	141
C(2)—C(3)	50	59	−55	−54
C(3)—C(4)	−90	−82	−55	−60
C(4)—C(5)	155	150	149	152
C(5)—C(6)	−109	−128	−102	−99
C(6)—C(7)	15	2	57	53
C(7)—C(8)	85	86	−103	−103
C(8)—C(9)	−88	−59	148	152
C(9)—C(10)	−105	−66	−61	−59
C(10)–C(1)	163	165	−68	−68
C(11)–C(12)	−1			
C(7)—C(11)	−2			
C(6)—C(7)	5			
C(16)–C(6)	−5			
C(12)–C(16)	4			

D = glaucolide-D, P = pregijerene, A = glaucolide-A, DA = dihydrodesacetoxyglaucolide-A.

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