Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Mikanolide from Jamaican *Mikania micrantha*

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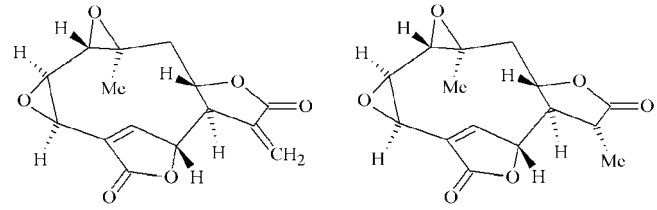
Received 9 June 2004
Accepted 20 July 2004
Online 9 October 2004

Mikanolide [systematic names: 1,10:2,3-diepoxy-6,8-dihydroxy-11-vinylgermacr-4-ene 12,14-di-γ-lactone and 7,10a-dimethyl-1a,1b,2a,6a,7,9a,10,10a-octahydro-4*H*-6,3-methenofuro[3,2-*c*]bisoxireno[*f*,*h*]oxacycloundecin-4,8(6*H*)-dione], $C_{15}H_{14}O_6$, derived from a variety of *Mikania micrantha* growing in Portland, Jamaica, contains a methylcyclodecane ring fused to an unsaturated planar α,γ-lactone, an envelope-type near-planar vinyl-β,γ-lactone and two epoxide moieties. The crystal packing shows stacks of mikanolide molecules interlocked *via* a network of non-classical C—H···O hydrogen bonds between the lactone units.

Comment

Mikanolide, (I), is a sequiterpene dilactone isolated from a variety of *Mikania* species abundant in many regions. It is used locally as a folk medicine and has attracted the attention of natural products chemists because of its antibacterial, antitumor, antimicrobial, cytotoxic and phytotoxic activities (Ahmed *et al.*, 2001; Aguinaldo *et al.*, 1995; Bohlmann *et al.*, 1984; Facey *et al.*, 1999; Gutierrez *et al.*, 1985; Pickman, 1986; Valdes *et al.*, 1998). Although structural studies of (I) and dihydromikanolide (1,10:2,3-diepoxy-6,8-dihydroxygermacr-4-ene-12,14-di-γ-lactone, $C_{15}H_{16}O_6$), (II), from *Mikania scandens* (L.) Willd have been published by Herz *et al.* (1970) and the crystal structure of (II) has been reported (Cox & Sim, 1974), to our knowledge the solid-state structure of (I) has never been investigated. As part of an effort to explore structure–activity relationships of natural products isolated from medicinal plants that are used as alternative medicines in Jamaican society, we report here the structure of mikanolide isolated from *Mikania micrantha* Kunth from Port Antonio, Portland, Jamaica, and compare the results with those reported for dihydromikanolide from *Mikania scandens* (L.) Willd. The leaves of the *M. micrantha*, commonly known as 'guaco', are used to make a poultice for snake bites and scorpion stings. A decoction of the leaves is used to bathe rashes, skin itches, athlete's foot and as wound dressings (Ayensu, 1981). In Jamaica, its most popular uses are for wound dressings and to promote the healing of sores. An extract of *Mikania micrantha* was tested for antimicrobial activity against five common pathogens, namely *Staphylococcus aureus, Streptococcus* group A, *Escherichia coli, Proteus mirabilis* and *Pseudomonas aeruginosa*. The extract exhibited activity against the first three of these. Activity-directed chemical isolation studies led to the isolation of two known sesquiterpenes, (I) and (II). These studies revealed that the antibacterial activity of the extract was due to the presence of (I) and (II) and that (I) shows higher activity than (II).



Structural comparators including space group, unit-cell parameters, atomic composition and fractional coordinates shows that an isomorphous relationship exists between (I) and (II). A closely related set of fractional coordinates is obtained when the *a* and *c* cell axes of (II) are interchanged and an origin shift of $(\frac{1}{2},y,\frac{1}{2})$ is applied. The enantiomer shown in the scheme has the same relative stereochemistry as that reported for dihydromikanolide (Cox & Sim, 1974). A displacement ellipsoid plot of (I) (Fig. 1) shows a methyl-substituted cyclodecane ring fused to a planar unsaturated α,γ-lactone, a nearly planar envelope-type vinyl-β,γ-lactone and two epoxide moieties. The conformations of the cyclodecane ring and epoxide units in (I) are very similar to those reported for (II) (Cox & Sim, 1974), although subtle differences were noted. The similarities are evident from the appearance of the methyl group attached to atom C10 on the same face of the macrocycle as atom C14 of the α,γ-lactone group and in the bond distances, valence angles and endocyclic torsion angles of the cyclodecane ring, which are comparable to the corresponding angles in (II) (see Table 1). The same is true of the epoxide groups at C1—C10 and C2—C3 and of the near-planar α,γ-lactone group at C4—C5—C6. The dihedral angle between the epoxide rings is nearly identical for the two

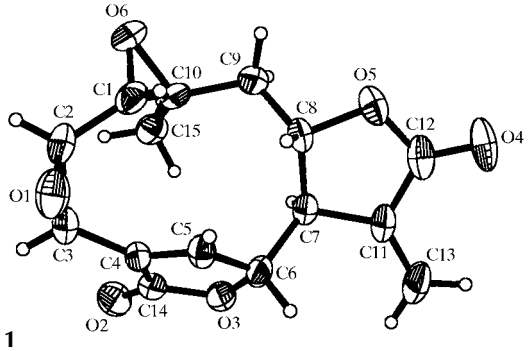


Figure 1
The molecular structure of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

 © 2004 International Union of Crystallography DOI: 10.1107/S0108270104017809

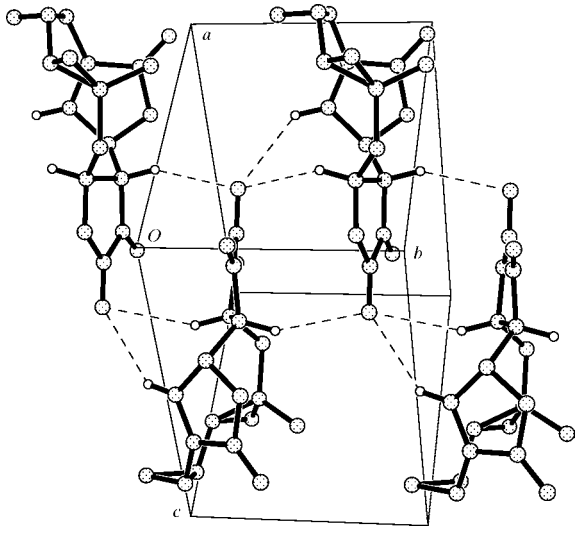
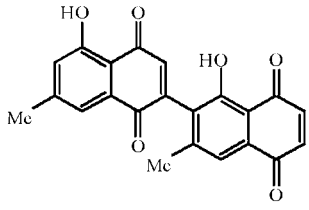


Figure 2
A view of the packing in (I), showing stacks of molecules running along the *b* axis. C—H···O hydrogen bonds are indicated by dashed lines.

compounds, its value being 36.1 (4)° in (I) and 34.4 (7)° in (II). An exception is the endocyclic C5—C6—C7—C8 torsion angle, which has a value of 10.2 (4)° in (I) and −2.0 (2)° in (II). Although the C4═C5 double bond of the α,γ-lactone group in (I) shows the same strain as that in (II), slight variations in the conformations of the α,γ-lactone groups in (I) and (II) were noted, as is apparent from the torsion angles around the α,γ-lactone rings. For example, in (I), the C14—O3—C6—C5 and C3—C4—C14—O2 torsion angles are 6.3 (3) and −10.7 (6)°, respectively, while in (II), these values are 2.0 (7) and −17.0 (7)°. The major structural and conformational differences between (I) and (II) occur in the β,γ-*trans*-fused γ-lactone group at C7—C8, which is a more planar five-membered lactone ring in (I), with endocyclic torsion angles approximately half the values of those in the saturated γ-lactone group of (II). In (I), C6—C7—C11—C13, C13—C11—C12—O5 and C13—C11—C12—O4 torsion angles of 35.7 (6), −172.4 (4) and 7.1 (7)°, respectively, were observed, while corresponding values of 77.0 (7), 148.0 (7) and −34.0 (7)° have been reported for (II).

Molecules of (I) are stacked along the *b* axis; they are linked by a network of C—H···O hydrogen bonds between the lactone units of neighbouring molecules related by a 2_1 screw axis (see Table 2 and Fig. 2). The geometric parameters for these non-classical hydrogen bonds are normal and similar to those reported for a variety of compounds containing such bonds, for example, diospyrin [1′,5-dihydroxy-3′,7-dimethyl-2,2′-binaphthalene-1,4,5′,8′-tetrone, $C_{22}H_{14}O_6$, (III) (Harrison & Musgrave, 2004)].

In conclusion, the structural determination of (I) is the first for an unsaturated mikanolide and reveals a near-planar β-lactone unit that may allow for intercalation of mikanolide into the minor groove of DNA, a feature that provides a possible explanation for its biological activity. In view of the use of folk medicinal plants as a guide to the development of new pharmaceuticals, studies are currently in progress in our laboratories to explore the structure–activity relationships of natural products isolated from a variety of common native Jamaican plants.



(III)

Experimental

Mikanolide extracted from *Mikania micrantha* Kunth (from Port Antonio, Portland, Jamaica) was isolated as described by Facey *et al.* (1999). Crystals were obtained when an extract in hexane–ethyl acetate (1:3) was allowed to stand at room temperature for several days.

Crystal data

$C_{15}H_{14}O_6$
$M_r = 290.26$
Monoclinic, $P2_1$
$a = 8.9090$ (12) Å
$b = 7.1840$ (8) Å
$c = 10.4940$ (11) Å
$\beta = 98.830$ (9)°
$V = 663.60$ (14) Å^3
$Z = 2$
$D_x = 1.452$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 43 reflections
$\theta = 9.5$–24.3°
$\mu = 0.11$ mm^{-1}
$T = 293$ (2) K
Rectangular prism, colourless
0.4 × 0.3 × 0.2 mm

Data collection

Bruker *P*4 diffractometer
$2\theta/\omega$ scans
1782 measured reflections
1483 independent reflections
1269 reflections with $I > 2\sigma(I)$
$R_{int} = 0.028$
$\theta_{max} = 25.0°$
$h = -10 \rightarrow 1$
$k = -8 \rightarrow 1$
$l = -12 \rightarrow 12$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.037$
$wR(F^2) = 0.098$
$S = 1.04$
1483 reflections
191 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.049P)^2 + 0.069P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.13$ e Å^{-3}
$\Delta\rho_{min} = -0.11$ e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.028 (6)

Table 1
Selected torsion angles (°).

C14—O3—C6—C5	6.3 (3)	C6—C7—C11—C13	35.7 (6)
C3—C4—C14—O2	−10.7 (6)	C13—C11—C12—O4	7.1 (7)
C5—C6—C7—C8	10.2 (4)	C13—C11—C12—O5	−172.4 (4)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C5—H5···O4^{i}	0.93	2.50	3.282 (4)	141
C7—H7···O4^{ii}	0.98	2.49	3.396 (4)	153
C8—H8···O4^{i}	0.98	2.54	3.409 (4)	147

Symmetry codes: (i) $2-x, y-\frac{1}{2}, -z$; (ii) $2-x, \frac{1}{2}+y, -z$.

All H atoms were assigned by assuming an idealized geometry, with C—H distances of 0.98, 0.96, 0.97 and 0.93 Å for tertiary CH, methyl CH_3, secondary CH_2 and terminal $=CH_2$ atoms, respectively, and with U_{iso}(H) values of $1.5U_{eq}$(C) for methyl H atoms and $1.2U_{eq}$(C) for all other H atoms. The absolute structure of mikanolide is not known, but we have adopted the same relative stereochemistry as that assigned for dihydromikanolide by Cox & Sim (1974).

Data collection, cell refinement and data reduction: *XSCANS* (Bruker, 1997); structure solution: *SHELXS*97 (Sheldrick, 1990); structure refinement: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 1997) and *PLATON* (Spek, 2003).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM1574). Services for accessing these data are described at the back of the journal.

References

Aguinaldo, A. M., Abe, F., Yamauchi, T. & Padolina, W. G. (1995). *Phytochemistry*, **38**, 1441–1443.
Ahmed, M., Rahman, M. T., Alimuzzaman, M. & Shilpi, J. A. (2001). *Fitoterapia*, **72**, 919–921.
Ayensu, E. S. (1981). *Medicinal Plants of the West Indies*. USA: Reference Publishers Inc.
Bohlmann, F., Tsankova, E., King, R. M. & Robinson, H. (1984). *Phytochemistry*, **23**, 1099–1101.
Bruker (1997). *SHELXTL*. Version 5.1. Bruker AXS Inc., Madison, Wisconsin, USA.
Cox, P. J. & Sim, G. A. (1974). *J. Chem. Soc. Perkin Trans.* 2, pp. 1355–1359.
Facey, P. C., Pascoe, K. O., Porter, R. B. & Jones, A. D. (1999). *J. Pharm. Pharmacol.* **51**, 1455–1460.
Gutierrez, A. B., Oberti, J. C., Kulanthaivel, P. & Herz, W. (1985). *Phytochemistry*, **24**, 2967–2971.
Harrison, W. T. A. & Musgrave, O. C. (2004). *Acta Cryst.* C**60**, o399–o401.
Herz, W., Subramaniam, P. S., Santhanam, P. S., Aota, K. & Hall, A. L. (1970). *J. Org. Chem.* **35**, 1453–1463.
Pickman, A. K. (1986). *Biochem. Syst. Ecol.* **14**, 255–281.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1997). *SHELXL*97. University of Göttingen, Germany.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
Valdes, D. A., Bardon, A., Catalan, C. A. N., Gedris, T. E. & Herz, W. (1998). *Biochem. Syst. Ecol.* **26**, 685–689.