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The natural diterpenoid kamebanin

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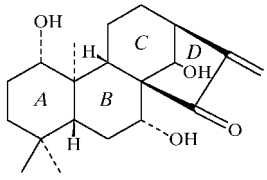
Kamebanin, alternatively called *rel*-(−)-(1*R*,4*R*,8*S*,9*R*,10*S*,13*S*,16*R*)-2,8,16-trihydroxy-5,5,9-trimethyl-14-methylenetetracyclo[11.2.1.0^{1,10}.0^{4,9}]hexadecan-15-one, $C_{20}H_{30}O_4$, is a natural diterpenoid which has cytotoxic and antibacterial activity. The molecule is composed of three six-membered rings, which all adopt chair conformations, and one five-membered ring, which adopts an envelope conformation. The conjugated α-methylenecyclopentanone ring is the active part in the molecule due to the ring strain. All three hydroxy groups serve as hydrogen-bond donors and acceptors, forming a continuous two-dimensional network.

Comment

The diterpenoid kamebanin, (I), has been previously isolated from the dry leaves of *Rabdosia kameba*, from which mebadonin was also isolated earlier (Hirotsu *et al.*, 1973). It possesses significant *in vitro* cytotoxicity (KB) and *in vivo* tumor inhibitory activity against Walker intramuscular carcinosarcoma in rats, and specific insecticidal activity against Lepidoptera larvae (Kubo *et al.*, 1977). Its cytotoxic activity against KB tissue culture (LD_{50}) was 5.1 μg ml^{-1} and the antibacterial activity against *Bacillus subtilis* was 10 μg ml^{-1} (Yamaguchi *et al.*, 1977). The structure was established from spectroscopic evidence (Kubo *et al.*, 1977) and has now been confirmed by X-ray diffraction.



(I)

The molecule of (I) (Fig. 1) contains three six-membered rings and one five-membered ring: ring *A* (C1–C5/C10) adopts a chair conformation, with puckering parameters (Cremer & Pople, 1975) Q = 0.571 (3) Å, θ = 179.5 (4)° and φ = 271 (17)°; ring *B* (C5–C10) also adopts a chair conformation, with Q = 0.598 (3) Å, θ = 168.7 (3)° and φ = 245.9 (15)°; ring *C* (C8/C9/C11–C14) adopts a chair conformation, with Q = 0.639 (3) Å, θ = 23.9 (3)° and φ = 289.4 (7)°; ring *D* (C8/C13–C16) adopts an envelope conformation, with the apex at C14, displaced by 0.657 (3) Å from the mean plane of the remaining four atoms.

Ring *D* is a conjugated α-methylenecyclopentanone ring and it has been found that this ring in *Rabdosia* diterpenes is highly reactive toward sulfhydryl (thiol) groups essential to enzyme function (Yamaguchi *et al.*, 1977). It is believed that steric strain within the five-membered ring helps to increase the reactivity of the conjugated double bond (Chen *et al.*, 1987). The extent of the deviation in the bond angles about C15 and C16 from ideal sp^2 angles (Table 1) shows that there must be significant strain within the five-membered ring. The deviation from ideal sp^3 angles around C8 shows the steric strain within ring *D* also.

Xindongnin B (Wang *et al.*, 1992; Fig. 2) has the same skeleton as kamebanin and its ring *D* adopts an envelope conformation with the apex at C14, displaced by 0.709 (7) Å from the mean plane of the remaining four atoms. The bond angle C16—C15—C8 is 109.3 (7)° and C15—C16—C13 is 105.0 (6)° (Wang *et al.*, 1992), similar to the corresponding angles in kamebanin (Table 1).

If an addition reaction takes place on the double bond of the α-methylenecyclopentanone ring, the ideal bond angles around C15 and C16 will approach a value of 109.5°, which is close to the ideal angle for a five-membered ring. The steric strain within the α-methylenecyclopentanone ring apparently

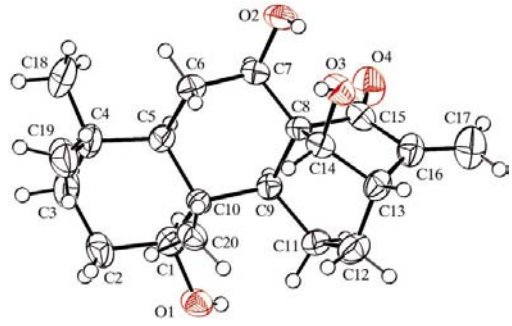


Figure 1
View of the molecule of kamebanin, showing 50% probability displacement ellipsoids.

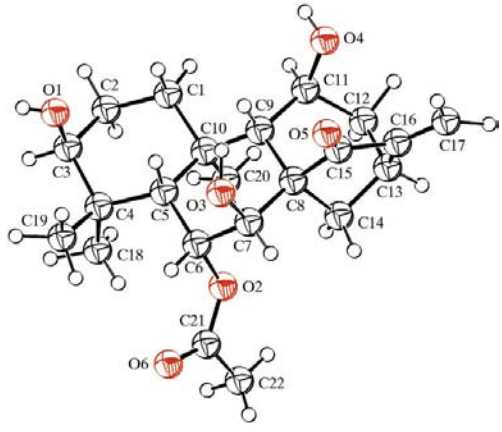


Figure 2
View of the molecule of xindongnin B, showing 50% probability displacement ellipsoids.

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increases the reactivity of the conjugated double bond, which may act *via* a similar 'Michael addition-type' reaction.

All three hydroxy groups in kamebanin serve as simultaneous hydrogen-bond donors and acceptors (Table 2), resulting in one intramolecular and two intermolecular O—H···O hydrogen bonds. An infinite two-dimensional network

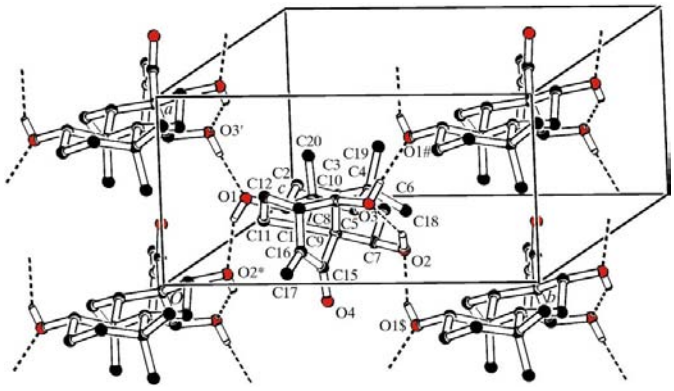

Figure 3
Part of the kamebanin crystal structure, showing the formation of a (001) sheet. For the sake of clarity, H atoms bonded to C atoms have been omitted. Atoms labelled with primes (′), asterisks (*), hashes (#) and dollar signs ($) are at the symmetry positions $(\frac{3}{2}+x, -\frac{1}{2}-y, -z)$, $(\frac{1}{2}+x, -\frac{1}{2}-y, -z)$, $(\frac{3}{2}+x, \frac{1}{2}-y, -z)$ and $(\frac{1}{2}+x, \frac{1}{2}-y, -z)$, respectively.

is formed parallel to (001) (Fig. 3). It is believed that the hydroxy groups help the molecule to bind to enzymes in the organism, and that these hydroxy groups, in addition to an α-methylenecyclopentanone group, are required for inhibitory activity (Yamaguchi *et al.*, 1977).

Experimental

Kamebarin was isolated (Hirotsu *et al.*, 1973) from the aerial parts of *Rabdosia leucophylla*, which were collected from wild plants growing in the Kangding region, Sichuan Province, People's Republic of China. Crystals suitable for single-crystal X-ray diffraction analysis were obtained by slow evaporation at room temperature of a solution in chloroform/methanol (1:1 *v*/*v*).

Crystal data

$C_{20}H_{30}O_4$
M_r = 334.44
Orthorhombic, $P2_12_12_1$
a = 6.568 (1) Å
b = 13.282 (3) Å
c = 20.801 (5) Å
V = 1814.6 (7) Å^3
Z = 4
D_x = 1.224 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 3.1–12.9°
μ = 0.08 mm^{-1}
T = 289 (2) K
Plate, colourless
0.66 × 0.54 × 0.08 mm

Data collection

Siemens *P*4 diffractometer
ω scans
2363 measured reflections
2176 independent reflections
1446 reflections with $I > 2\sigma(I)$
R_{int} = 0.016
θ_{max} = 26.5°
$h = 0 \rightarrow 8$
$k = 0 \rightarrow 16$
$l = -1 \rightarrow 26$
3 standard reflections
every 97 reflections
intensity decay: 0.4%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.045
$wR(F^2)$ = 0.105
S = 0.93
2176 reflections
224 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0514P)^2]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0071 (11)

Table 1
Selected geometric parameters (Å, °).

O1—C1	1.432 (3)	O3—C14	1.435 (3)
O2—C7	1.427 (3)	O4—C15	1.204 (4)
C15—C8—C14	101.3 (2)	C16—C15—C8	108.0 (3)
C7—C8—C14	117.1 (2)	C17—C16—C15	123.2 (3)
C16—C13—C14	102.6 (3)	C17—C16—C13	130.9 (3)
O4—C15—C16	125.4 (3)	C15—C16—C13	105.9 (3)
O4—C15—C8	126.6 (3)		

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

D—H···A	D—H	H···A	D···A	D—H···A
O2—H2O···O3	0.82	1.89	2.605 (3)	146
O1—H1O···O2^{i}	0.82	1.97	2.741 (3)	157
O3—H3O···O1^{ii}	0.82	1.88	2.692 (3)	173

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

The orientations of the hydroxy H atoms were determined initially from difference maps and were then refined by the *SHELXL*97 (Sheldrick, 1997) 'nearest acceptor' method. The H atoms were placed in geometrically calculated positions and were included in the final refinement as riding. Friedel reflections were merged before the final refinement and the relative stereochemistry is shown in the *Scheme* and figures. The absolute configuration is unknown.

Data collection: *XSCANS* (Siemens, 1994); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2002).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD1200). Services for accessing these data are described at the back of the journal.

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