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Dibothrioclinin I and II, epimers from *Gerbera piloselloides* (L.) Cass

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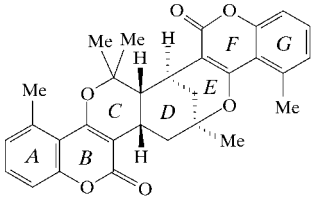
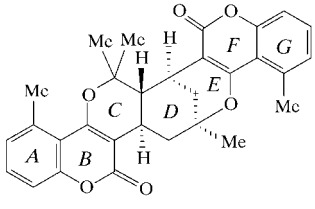
Dibothrioclinin I and II, namely (+)-(11*R*,12*S*,25*R*,27*S*)- and (±)-(11*RS*,12*RS*,25*RS*,27*SR*)-3,3,7,17,21-pentamethyl-4,12,-18,26-tetraoxaheptacyclo[15.11.1.$0^{2,15}$.$0^{5,14}$.$0^{6,11}$.$0^{19,28}$.$0^{20,25}$]-nonacosa-5(14),6,8,10,19(28),20,22,24-octaene-13,27-dione, respectively, are $C_{30}H_{28}O_6$ epimers which are derived from two bothrioclinin moieties joined so as to create an additional six-membered ring. Structurally, the epimers differ only by inversion at one C atom of a central ring junction and the corresponding six-membered rings have similar conformations in each molecule, except for one ring adjacent to this inversion site.

Comment

Most coumarins are widely distributed among higher plants, while only a few occur in animals and microorganisms, *e.g.* aflatoxin from *Aspergillus* and armillarisin from *Armillarialla tabescens*. Coumarins and their derivatives are active natural products which have many biological activities, such as anticoagulant or antimicrobial properties (Kwon *et al.*, 2002) and non-specific spasmolytic action (Oliveira *et al.*, 2001). In recent years, further investigations have indicated that they have anti-HIV activity (Yang, 2001). Therefore, these compounds are widely used in the fields of food, chemical engineering and medicine, and extensive future research into coumarin derivatives is likely.



(I)

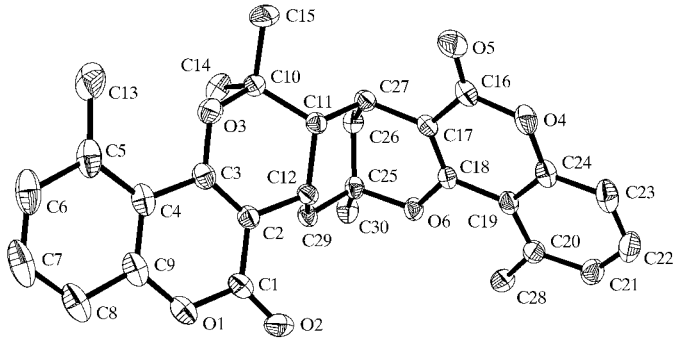


(II)

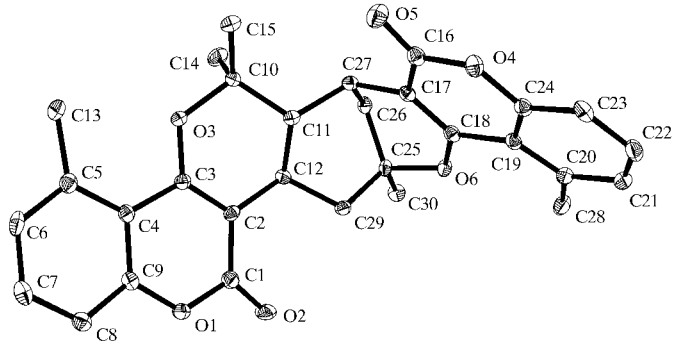
Gerbera piloselloides (L.) Cass has been used as an anti-pyretic and alexipharmic agent, and for regulating the flow of vital energy and the condition of the blood in traditional Chinese medicine (Jiangsu New Medical College, 1977). Besides 15 known compounds (Xiao *et al.*, 2002), two novel coumarin dimers, namely dibothrioclinin I and II, hereinafter (I) and (II), respectively, have been isolated from *Gerbera piloselloides* (L.) Cass. The structures and relative stereochemistries of these two compounds have been established by spectroscopy. The present study reports their crystal structures, which confirm the relative stereochemistries and establishes the conformations of all the rings in the molecules.

Dibothrioclinin I, (I) (Fig. 1*a*), is enantiopure ($[\alpha]_D$ = 24°, *c* 0.05, $CHCl_3$), although the absolute configuration has not been established, while dibothrioclinin II, (II) (Fig. 1*b*), is racemic. The compounds are epimers and their skeletons differ only by inversion of the configuration at C12, so that the stereochemistry of the ring *C*/*D* junction is *cis* in (I) and *trans* in (II). Each compound incorporates two structural units of bothrioclinin (Ferdinand & Christa, 1977) at opposite ends of the molecule. These units are dimerized by the formation of two single bonds, one of which is a direct connection between rings *C* and *E* *via* C11—C27, while the second connects ring *C*, *via* C12—C29, to one of the methyl substituents on ring *E*, thereby building a seventh six-membered ring, *D*.

The two coumarin skeletons in each structure, rings *A*/*B* and *F*/*G*, are each almost planar, with a mean deviation of 0.014 (3) Å in (I) and 0.019 (2) Å in (II). The dihedral angles between rings *A* and *B*, and between rings *F* and *G*, are 2.1 (1) and 3.7 (1)°, respectively, for (I), and 4.1 (1) and 3.7 (1)°,



(*a*)



(*b*)

Figure 1
The molecular structures and atomic numbering schemes for (*a*) (I) and (*b*) (II). Displacement ellipsoids are drawn at the 30% probability level and H atoms have been omitted for clarity.

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respectively, for (II). These properties are similar to those observed in the structure of ethuliacoumarin A (Larsen *et al.*, 1992).

The corresponding six-membered rings in each compound have similar conformations, except for differences in the conformations of rings *C*, *D* and *E* because of the effect of the inversion at C12. The 2*H*-dihydropyran ring *C* adopts a half-chair conformation in (I), with puckering parameters (Cremer & Pople, 1975) $Q = 0.444\ (3)$ Å, $\theta = 128.1\ (4)^\circ$ and $\varphi = 98.9\ (5)^\circ$ for the atom sequence O3/C3/C2/C12/C11/C10. In (II), ring *C* adopts a distorted envelope conformation, with puckering parameters for the corresponding atom sequence of $Q = 0.525\ (3)$ Å, $\theta = 122.1\ (3)^\circ$ and $\varphi = 46.5\ (3)^\circ$. The 2*H*-dihydropyran ring *E* has an almost ideal envelope form in (I), with puckering parameters $Q = 0.544\ (3)$ Å, $\theta = 55.1\ (3)^\circ$ and $\varphi = 240.0\ (4)^\circ$ for the atom sequence O6/C18/C17/C27/C26/C25. In (II), this ring is halfway between an envelope and a half-chair conformation, with puckering parameters for the corresponding atom sequence of $Q = 0.574\ (3)$ Å, $\theta = 53.9\ (3)^\circ$ and $\varphi = 259.8\ (3)^\circ$.

The greatest difference between the two compounds lies in the conformation of ring *D*. In (I), ring *D* has a slightly twisted chair conformation, owing to the *cis* fusion with ring *C*; the puckering parameters are $Q = 0.537\ (3)$ Å, $\theta = 13.5\ (4)^\circ$ and $\varphi = 241\ (2)^\circ$ for the atom sequence C11/C12/C29/C25/C26/C27. This is also indicated by the smaller C27—C11—C12—C29 and C11—C12—C29—C25 torsion angles of −41.7 (3) and 43.8 (4)°, respectively. The mean of the other four torsion angles is 55.7 (5)° (the torsion angle of the normal chair form of cyclohexane is 56°). In (II), the *trans C*/*D* ring junction imposes a conformation on ring *D* that is halfway between a boat and a twisted boat; the puckering parameters are $Q = 0.815\ (3)$ Å, $\theta = 87.4\ (2)^\circ$ and $\varphi = 255.5\ (2)^\circ$, for the same atom sequence as in (I). This is supported by the C12—C11—C27—C26 and C26—C25—C29—C12 torsion angles of 20.8 (3) and 13.6 (3)°, respectively. The mean of the other four torsion angles is 55.6 (4)° (the torsion angles of the normal boat form of cyclohexane are 0 and 56°).

Compounds (I) and (II) also exhibit different molecular stereostructures. The dihedral angle between the plane of rings *A*/*B* and the least-squares plane through ring *C* (including puckered atoms) is 4.8 (1)° for (I) and 16.8 (1)° for (II). The dihedral angle between the least-squares planes through rings *A*/*B*/*C* and *E*/*F*/*G* is 72.4 (1)° for (I) and 80.4 (1)° for (II). However, while the inversion at C12 influences the stereochemistry of the ring *C*/*D* junction, the stereostructure of rings *E*, *F* and *G* remains unaffected. This can be inferred from the dihedral angle between the plane of rings *F*/*G* and the least-squares plane through ring *E* (including puckered atoms), which is 8.9 (1)° for (I) and 10.9 (1)° for (II).

Experimental

The roots and rhizomes of *Gerbera piloselloides* (L.) Cass were collected from Dali, Yunnan Province, China. The air-dried roots and rhizomes (1 kg) were ground to a fine powder and extracted with ethanol, and the ethanol extract was partitioned between an aqueous solution and petroleum ether. The petroleum ether fraction was chromatographed repeatedly on silica gel, eluting with petroleum ether–acetyl acetate (9:1), and gave colourless crystals. Purification of the crystals on a preparative high-performance liquid chromatography column afforded compounds (I) (18 mg) and (II) (30 mg). Compound (I) was dissolved in methanol and chloroform (1:1) and stored at room temperature; transparent block-shaped crystals were obtained after 4 d. Compound (II) was dissolved in chloroform and stored at room temperature; transparent plate-like crystals were obtained after 7 d.

Compound (I)

Crystal data

$C_{30}H_{28}O_6$	$D_x = 1.321$ Mg m^{-3}
$M_r = 484.52$	Mo $K\alpha$ radiation
Monoclinic, $P2_1$	Cell parameters from 5888 reflections
$a = 11.001\ (2)$ Å	$\theta = 2.4$–27.3°
$b = 8.307\ (2)$ Å	$\mu = 0.09$ mm^{-1}
$c = 13.332\ (3)$ Å	$T = 296\ (1)$ K
$\beta = 90.39\ (3)^\circ$	Plate, colourless
$V = 1218.3\ (4)$ Å^3	0.4 × 0.2 × 0.1 mm
$Z = 2$	

Data collection

MAC DIP 2030 K area-detector diffractometer	$R_{int} = 0.024$
ω scans	$\theta_{max} = 27.3^\circ$
5888 measured reflections	$h = 0 \rightarrow 14$
2725 independent reflections	$k = 0 \rightarrow 10$
2715 reflections with $I > 2\sigma(I)$	$l = -17 \rightarrow 17$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0589P)^2 + 0.4086P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.054$	$(\Delta/\sigma)_{max} = 0.014$
$wR(F^2) = 0.138$	$\Delta\rho_{max} = 0.17$ e Å^{-3}
$S = 1.23$	$\Delta\rho_{min} = -0.26$ e Å^{-3}
2725 reflections	
325 parameters	
H-atom parameters constrained	

Compound (II)

Crystal data

$C_{30}H_{28}O_6$	$D_x = 1.377$ Mg m^{-3}
$M_r = 484.52$	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 15 334 reflections
$a = 15.517\ (3)$ Å	$\theta = 2.5$–27.4°
$b = 19.411\ (4)$ Å	$\mu = 0.10$ mm^{-1}
$c = 7.963\ (2)$ Å	$T = 296\ (2)$ K
$\beta = 102.90\ (3)^\circ$	Plate, colourless
$V = 2337.9\ (9)$ Å^3	0.5 × 0.3 × 0.1 mm
$Z = 4$	

Data collection

Rigaku R-AXIS RAPID area-detector diffractometer	$R_{int} = 0.070$
ω scans	$\theta_{max} = 27.4^\circ$
15 334 measured reflections	$h = -20 \rightarrow 19$
5186 independent reflections	$k = -25 \rightarrow 0$
2479 reflections with $I > 2\sigma(I)$	$l = 0 \rightarrow 10$

Refinement

Refinement on F^2	H-atom parameters constrained
$R[F^2 > 2\sigma(F^2)] = 0.057$	$w = 1/[\sigma^2(F_o^2) + (0.0719P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.161$	$(\Delta/\sigma)_{max} = 0.001$
$S = 0.84$	$\Delta\rho_{max} = 0.28$ e Å^{-3}
5186 reflections	$\Delta\rho_{min} = -0.30$ e Å^{-3}
325 parameters	

Due to the absence of any significant anomalous scatterers in (I), attempts to confirm the absolute structure by refinement of the Flack parameter (Flack, 1983) led to an inconclusive value (Flack & Bernardinelli, 2000) for this parameter. Therefore, the enantiomer used in the model was chosen arbitrarily and the Friedel pairs were merged before the final refinement. For both compounds, the methyl H atoms were constrained to an ideal geometry (C—H = 0.96 Å), with U_{iso}(H) = 1.5U_{eq}(C), but were allowed to rotate freely about the C—C bonds. All other H atoms were placed in geometrically idealized positions (C—H = 0.93–0.98 Å) and constrained to ride on their parent atoms, with U_{iso}(H) = 1.2U_{eq}(C).

For both compounds, data collection: *DENZO* (Otwinowski & Minor, 1997); cell refinement: *SCALE* (Otwinowski & Minor, 1997); data reduction: *SCALE*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976) and *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL*97 and *PLATON*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN1173). Services for accessing these data are described at the back of the journal.

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