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Candibirin A, a furanocoumarin dimer isolated from *Heracleum candicans* WALL.

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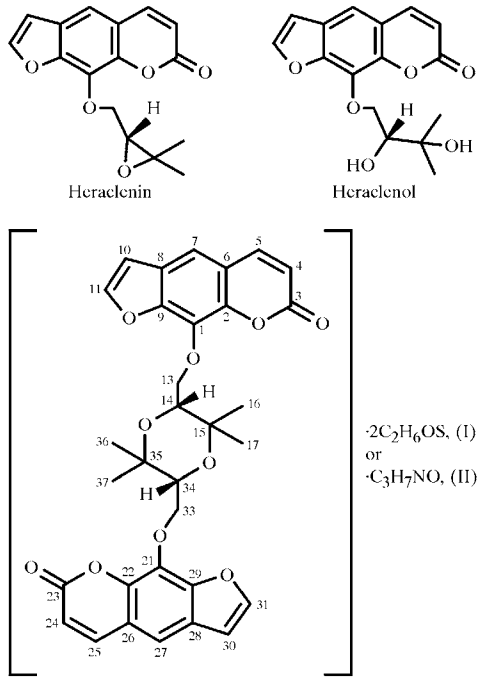
Candibirin A [systematic name: 9,9′-(1,4-dioxane-2,5-diyldimethylenedioxy)di(7*H*-furo[3,2-*g*]chromen-7-one)], a new furanocoumarin dimer, was isolated from *Heracleum candicans* WALL. ^{1}H NMR and MS spectra had indicated that the title compound was a dimer of heraclenin or heraclenol, but the linkage structure and its chirality were undetermined. The dioxane linkage, having the *R*,*R* configuration, has now been elucidated from dimethyl sulfoxide-solvated crystals, $C_{32}H_{28}O_{10}\cdot 2C_2H_6OS$. Candibirin A is thus a dimerization product from heraclenin formed by reaction at the epoxy group. Dimethylformamide-solvated crystals, $C_{32}H_{28}O_{10}\cdot C_3H_7NO$, adopt a different conformation, with a folded structure that differs from the extended structure in the dimethyl sulfoxide solvate. However, the puckering of the dioxane linker unit is very similar in the two conformers. This result shows that the rotation of the ether bonds, in the linker between the furanocoumarin and dioxane moieties, causes the conformational flexibility of (I).

Comment

Candibirin A is a new furanocoumarin dimer isolated from *Heracleum candicans* WALL., which is a herbal medicine used as an antipyretic. ^{1}H NMR and MS spectra indicated that candibirin A is a dimer of the previously reported furanocoumarin heraclenin, having an epoxy group (Bal-Tembe *et al.*, 1996), and heraclenol, having two hydroxy groups (Benkiki *et al.*, 2002). However, the linkage structure and its chirality are unknown since the dimerization pathway is unknown. We have therefore prepared dimethyl sulfoxide (DMSO)-solvated crystals, (I), with no chemical modification (DMSO form), and the absolute configuration was determined using the anomalous dispersion effects from the DMSO S atoms. A different solvate, (II), was obtained from a dimethylformamide (DMF) solution (DMF form), in which a second conformer of candibirin A was found.

The structure of DMSO form (I) is shown in Fig. 1. The two furanocoumarin moieties are linked by the dioxane ring. There are two DMSO molecules in the asymmetric unit, and



one of them is disordered over two sets of sites. The *R* configurations of atoms C14 and C34 are evidenced by Flack (1983) parameter calculations. This configuration agrees with those previously deduced for heraclenin (Bal-Tembe *et al.*, 1996) and heraclenol (Benkiki *et al.*, 2002). The presence of the dioxane ring and its configuration indicate that candibirin A is a dimerization product formed by reactions between the epoxy groups of heraclenin molecules.

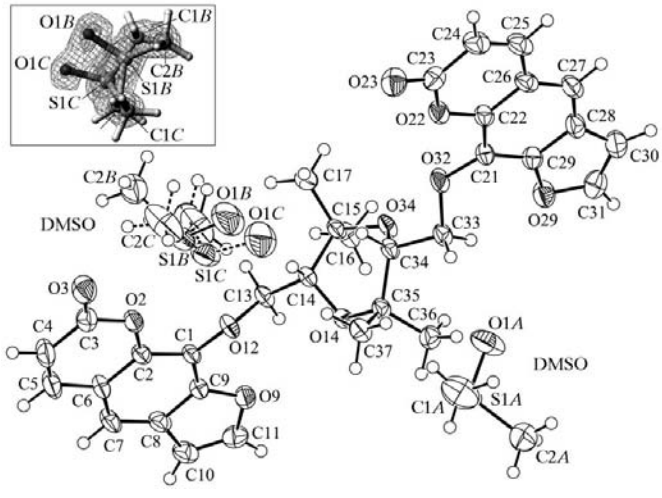


Figure 1
A view of candibirin A in the DMSO form. Displacement ellipsoids are drawn at the 50% probability level. There are two DMSO molecules in the asymmetric unit, and one DMSO molecule is disordered over two sites. The inset shows the electron density, drawn using *TURBO–FRODO* (Roussel *et al.*, 2002), around the disordered DMSO molecules at the 1σ and 2.5σ levels.

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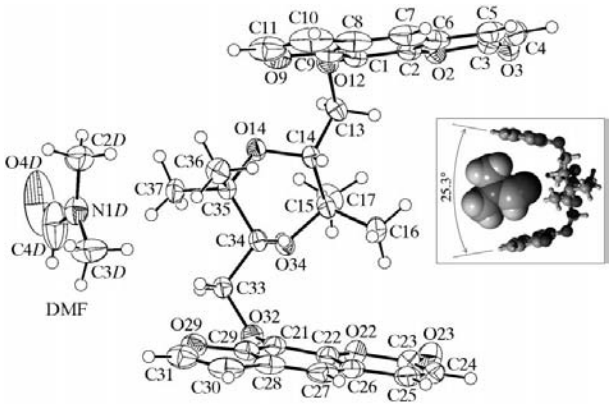

Figure 2
A view of candibirin A in the DMF form. Displacement ellipsoids are drawn at the 50% probability level. The inset shows the disposition of the DMF molecule and furanocoumarin moieties.

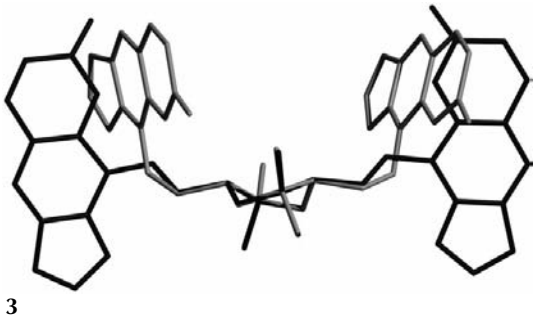

Figure 3
A superimposition of the structures of the DMSO and DMF forms of candibirin A drawn using *RASMOL* (Bernstein, 2000) and *POV-Ray* (POV-Team, 1991).

In the DMSO form, the two furanocoumarin rings are separated from one another, and the molecule is extended. Conversely, a folded molecule is observed in the DMF form (Fig. 2). The DMF molecule is held between the two furanocoumarin rings, with an angle of approximately 25.3° (Fig. 2, inset). The plane of the DMF molecule is approximately perpendicular to those of the furanocoumarin rings. The molecular conformations of the DMSO and DMF forms seem to be very different from one another. However, when the heat of formation was calculated using the semi-empirical AM1 method implemented in *MOPAC*2000 (Dewar *et al.*, 1985) (−851.7 and −870.8 kJ mol^{-1} for the DMSO and DMF forms, respectively), it was found that the energy gap between these structures is only −19.1 kJ mol^{-1}, despite the different disposition of the bulky furanocoumarin rings. To compare the conformations, molecular fitting was carried out (Fig. 3). The puckerings of the dioxane moieties are very similar to one another, and the conformational differences are mainly due to the differences between the respective values of the C1—O12—C21—O32 and C22—C21—O32—C33 torsion angles (Table 1).

Experimental

Acetone extracts were obtained from dried roots of *H. candicans* Wall., and candibirin A was purified by column chromatography as described previously (Xiao *et al.*, 1997). HR–EIMS *m*/*z*: 572.1681 $[M]^+$ (calculated for $C_{32}H_{28}O_{10}$: 572.1683); ^{1}H NMR ($CDCl_3$): δ_H 7.76 (2H, *d*, *J* = 9.6 Hz, C5/25—H), 7.69 (2H, *d*, *J* = 2.1 Hz, C11/31—H), 7.37 (2H, *s*, C7/27—H), 6.82 (2H, *d*, *J* = 2.1 Hz, C10/30—H), 6.36 (2H, *d*, *J* = 9.6 Hz, C4/24—H), 4.49 (2H, *dd*, *J* = 11.0 and 7.3 Hz, C13/33—H*A*), 4.43 (2H, *dd*, *J* = 11.0 and 3.9 Hz, C13/33—H*B*), 3.99 (2H, *dd*, *J* = 7.3 and 3.9 Hz, C14/34—H), 1.14 (12H, *s*, C16/36—H_3 and C17/37—H_3). Candibirin A (10 mg) was dissolved in either DMSO or DMF (0.1–0.2 ml), after which water (∼0.02 ml) was added to each solution. Crystals with different forms grew from the two solutions over a period of about a week.

DMSO form (I)

Crystal data

$C_{32}H_{28}O_{10}\cdot 2C_2H_6OS$
M_r = 728.80
Orthorhombic, $P2_12_12_1$
a = 10.903 (2) Å
b = 13.068 (2) Å
c = 24.400 (4) Å
V = 3476.5 (11) Å^3
Z = 4
D_x = 1.392 Mg m^{-3}
Mo *Kα* radiation
Cell parameters from 5833 reflections
θ = 2.3–28.2°
μ = 0.22 mm^{-1}
T = 200 (2) K
Needle, colourless
0.50 × 0.20 × 0.04 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
ω scans
Absorption correction: empirical (*SADABS*; Sheldrick, 1996)
T_{min} = 0.913, T_{max} = 1.0
30 564 measured reflections
7659 independent reflections
7041 reflections with $I > 2\sigma(I)$
R_{int} = 0.026
θ_{max} = 27.1°
h = −13 → 13
k = −16 → 16
l = −31 → 31
327 standard reflections
frequency: 240 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.037
$wR(F^2)$ = 0.099
S = 0.90
7659 reflections
498 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0729P)^2 + 0.5601P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.003
$\Delta\rho_{max}$ = 0.40 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}
Absolute structure: Flack (1983), 3379 Friedel pairs
Flack parameter = 0.04 (6)

DMF form (II)

Crystal data

$C_{32}H_{28}O_{10}\cdot C_3H_7NO$
M_r = 645.64
Monoclinic, $P2_1$
a = 8.2000 (7) Å
b = 16.2132 (14) Å
c = 11.6706 (10) Å
β = 97.244 (1)°
V = 1539.2 (2) Å^3
Z = 2
D_x = 1.393 Mg m^{-3}
Mo *Kα* radiation
Cell parameters from 7355 reflections
θ = 2.2–28.1°
μ = 0.10 mm^{-1}
T = 200 (2) K
Plate, colourless
0.50 × 0.40 × 0.04 mm

Data collection

Bruker SMART APEX area-detector diffractometer
ω scans
Absorption correction: empirical (*SADABS*; Sheldrick, 1996)
T_{min} = 0.932, T_{max} = 1.0
13 520 measured reflections
3516 independent reflections
3381 reflections with $I > 2\sigma(I)$
R_{int} = 0.017
θ_{max} = 27.1°
h = −10 → 10
k = −20 → 20
l = −14 → 14
213 standard reflections
frequency: 270 min
intensity decay: none

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0757P)^2 + 0.3442P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.042$	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2) = 0.116$	$\Delta\rho_{max} = 0.67$ e Å^{-3}
$S = 1.04$	$\Delta\rho_{min} = -0.38$ e Å^{-3}
3516 reflections	
430 parameters	
H-atom parameters constrained	

Table 1
Selected torsion angles (°).

	DMSO form (I)	DMF form (II)
Dioxane ring		
C35—O14—C14—C15	67.6 (2)	68.4 (3)
O14—C14—C15—O34	−38.0 (2)	−34.2 (3)
C14 —C15—O34—C34	−26.5 (2)	−31.4 (3)
C15—O34—C34—C35	66.1 (2)	68.4 (2)
O34—C34—C35—O14	−36.4 (2)	−34.3 (3)
C34—C35—O14—C14	−27.6 (2)	−31.4 (3)
Ether linkage		
C2—C1—O12—C13	−137.6 (2)	67.4 (3)
C1—O12—C13—C14	−170.7 (1)	75.1 (3)
O12—C13—C14—O14	79.4 (2)	66.3 (3)
C22—C21—O32—C33	−146.1 (2)	−125.4 (2)
C21—O32—C33—C34	−164.1 (2)	75.2 (3)
O32—C33—C34—O34	75.0 (2)	66.7 (3)

A full-sphere data set was collected for the DMSO form to aid in the determination of the absolute configuration of the structure. A full-sphere data set was also collected for the DMF form, but Friedel pairs were merged in the refinement because of the absence of significant anomalous scattering effects. The absolute configuration of the DMF form was assumed from that of the DMSO form. H atoms were placed at calculated positions [C—H = 0.95–1.00 Å, with $U_{iso}(H) = 1.5U_{eq}(C)$ for methyl H atoms and $1.2U_{eq}(C)$ for all other atoms] and were included in the structure-factor calculations.

For both forms, data collection: *SMART* (Bruker, 1998); cell refinement: *SMART*; data reduction: *SAINT-Plus* (Bruker, 1998); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2001); software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD1348). Services for accessing these data are described at the back of the journal.

References

Bal-Tembe, S., Joshi, D. D. & Lakdawala, A. D. (1996). *Indian J. Chem. Sect. B*, **35**, 518–519.
Benkiki, N., Benkhaled, M., Kabouche, Z. & Bruneau, C. (2002). Proceedings of the IUPAC International Conference on Biodiversity, Antalya, Turkey, 2001, pp. 303–307.
Bernstein, H. J. (2000). *Trends Biochem. Sci.* **25**, 453–455.
Bruker (1998). *SAINT-Plus* (Version 5) and *SMART* (Version 5). Bruker AXS Inc., Madison, Wisconsin, USA.
Dewar, M. J. S., Zoebisch, E. G., Healy, E. F. & Stewart, J. J. P. (1985). *J. Am. Chem. Soc.* **107**, 3902–3909.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
POV Team (1991). *POV-RAY*. Persistance of Vision Raytracer, Williamstown, Victoria, Australia. (URL: http://www.povray.org.)
Roussel, A., Legaigneur, P., Inisan, A. G. & Cambillau, C. (2002). *TURBO–FRODO*. Version Linux.1. Universite/Aix–Marseille II, Marrseille, France.
Sheldrick, G. M. (1996). *SADABS*. University of Göttingen, Germany.
Sheldrick, G. M. (1997). *SHELXS*97 and *SHELXL*97. University of Göttingen, Germany.
Spek, A. L. (2001). *PLATON*. Utrecht University, The Netherlands.
Xiao, Y.-Q., Liu, X.-H., Taniguchi, M. & Baba, K. (1997). *Phytochemistry*, **45**, 1275–1277.