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(–)-Nomilin chloroform solvate

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The absolute stereochemistry of the title compound, $C_{28}H_{33}O_9\cdot CHCl_3$, has been determined by single-crystal X-ray diffraction by incorporation of the heavy-atom-containing solvent chloroform. The *A*/*B*, *B*/*C* and *C*/*D* ring junctions are all *trans*-fused. Five-membered ring *E* is equatorially attached to ring *D*. The crystal structure is stabilized by weak intermolecular C—H···O interactions.

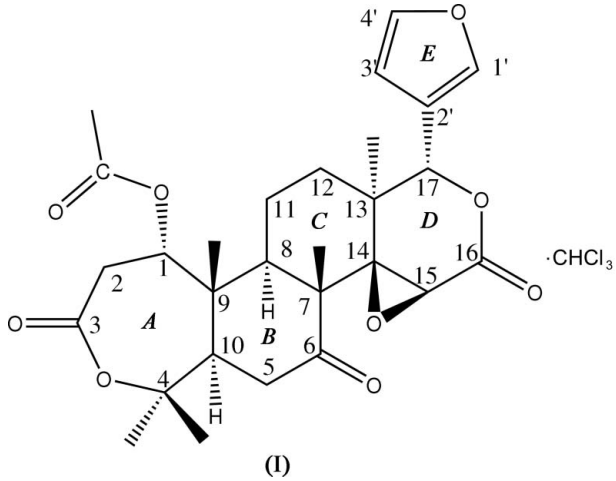
Key indicators

Single-crystal X-ray study
T = 298 K
Mean σ(C–C) = 0.007 Å
Disorder in solvent or counterion
R factor = 0.054
wR factor = 0.165
Data-to-parameter ratio = 13.3

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Comment

Limonoids, first reported in 1864 (Emerson, 1948), are a group of chemically related triterpene derivatives found in the Rutaceae and Meliaceae families (Bennett & Hasegawa, 1982; Hashinaga *et al.*, 1990). Nomilin is one of the most prevalent citrus limonoids. Many studies have shown that nomilin is biologically active, displaying anticarcinogenic activity, abirritation and antifeedant activity against insects (Bentley *et al.*, 1988; Lam *et al.*, 1989). Citrus plants from the Rutaceae family are the main source of the natural limonoids. Bergamot (*Citrus bergamia*), a hybrid of *Citrus aurantium* and *Citrus limon* L., has been used as a traditional Chinese medicine in the treatment of stomach-ache, emesia and anepithymia (Jin *et al.*, 2002). It contains coumarins, essential oils and limonoids as its main components.



(I)

The structure elucidation of nomilin is important for understanding its structure–activity relationships and biogenetic formation. The molecular structure of nomilin was first proposed by Barton *et al.* (1961). Several attempts were made to assign the stereochemistry of nomilin. The orientation of the acetoxy group at C1 is the most critical part in the stereochemistry determination. It was erroneously proposed to be in the β-configuration by NMR spectroscopy (Dreyer,

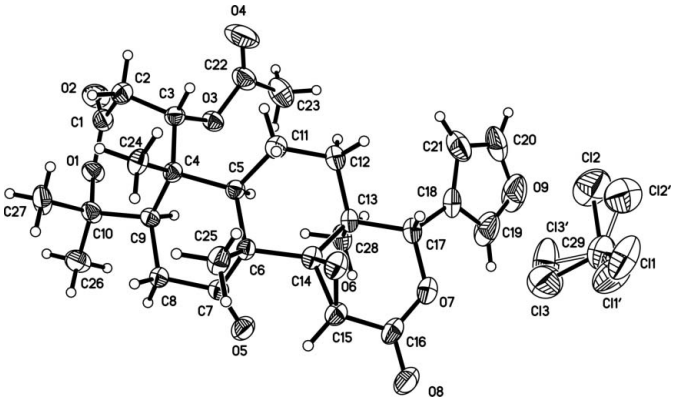


Figure 1
A view of the asymmetric unit of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. Both disorder components are shown for the chloroform molecule.

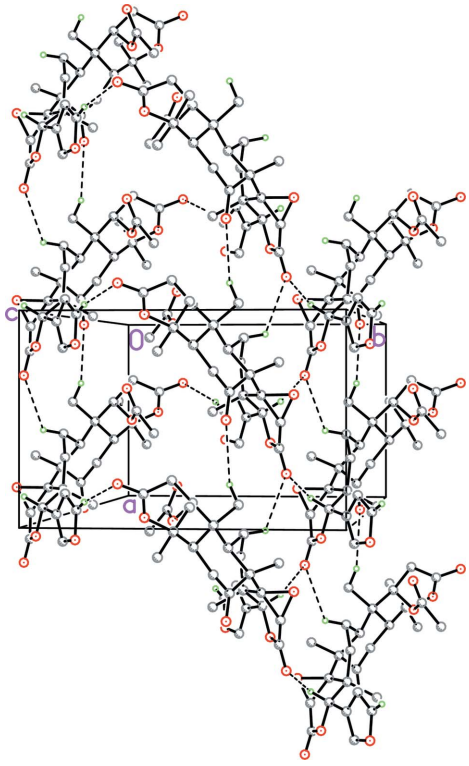


Figure 2
Part of the crystal structure of (I). Intermolecular C—H···O interactions are indicated by dashed lines. H atoms not involved in hydrogen bonding have been omitted.

1965). Then a systematic ORD and CD study of nomilin was reported (Dreyer, 1968). Recently, it was found that the configuration of the *A* ring is directly related to its biological activity (Mendel *et al.*, 1991; Ruberto *et al.*, 2002). In the present paper, the crystal structure of the title compound, (I) is presented. We have successfully incorporated heavy-atom-containing solvent into the crystal by using chloroform as a solvent during crystallization. Although the strict demanding criteria of Flack & Bernardinelli (2000) are not completely met, the absolute configuration is confirmed with reasonable confidence.

Compound (I) contains a four-ring *A*/*B*/*C*/*D* fused triterpenoid system and a furan ring *E* (Fig. 1). The bond lengths and angles in nomilin are comparable to the corresponding values in its analogue zapoterin (Argáez *et al.*, 2000). The seven-membered ring *A* (O1/C1–C4/C9/C10) exhibits a chair conformation, the plane being formed by C2/C3/C9/C10 with atoms C4 and C1/O1 displaced on opposite sides, as observed in its analogues 11β-hydroxycneorin G (Mitsui *et al.*, 2004) and 7-acetoxydihydronomilin (Ahmed *et al.*, 1978). Six-membered ring *B* (C4–C9) adopts a chair form, and rings *C* (C5/C11–C14/C6) and *D* (C13–C17/O7) screw-boat forms. The puckering parameters (Cremer & Pople, 1975) for rings *B*, *C* and *D* are Q = 0.574 Å, $q2$ = 0.057 Å, $q3$ = 0.571 Å, θ = 5.7°, Φ = 43.0°; Q = 0.779 Å, $q2$ = 0.771 Å, $q3$ = 0.112 Å, θ = 81.7°, Φ = 334.8°; and Q = 0.507 Å, $q2$ = 0.477 Å, $q3$ = −0.172 Å, θ = 109.8°, Φ= 93.9°, respectively. Five-membered ring *E* (O9/C18–C21) is equatorially attached to ring *D*. The *A*/*B*, *B*/*C* and *C*/*D* ring junctions are all *trans*-fused. The crystal structure is stabilized by intermolecular C—H···O weak interactions (Table 2 and Fig. 2).

Experimental

Dry fruit (18 kg) of bergamot, *Citrus bergamia*, collected in Jinhua city, Zhejiang province of China, authenticated by Dr Qing-Min Jian of the China Pharmaceutical University, were extracted with refluxing of 70% ethanol (3 × 30 l). The extract was concentrated and then extracted by ethyl acetate. The ethyl acetate was then evaporated from the combined filtrate and washings. The residue (350 g) was subjected to chromatography on a silica-gel column, eluting with a chloroform/methanol mixture (99:1 *v*/*v*) to give a colourless solid, nomilin (1.8 g, m.p. 549 K), which showed one spot on thin-layer chromatography. ESI–MS (*m*/*z*): 515 $[M+H]^+$. $[\alpha]_D^{24}$ = −122.87°. IR (KBr, ν, cm^{-1}): 2925, 1732 (C═O), 1713 (C═O), 1293, 1227, 1026. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09, 1.18, 1.33, 1.47, 1.56 (each 3H, *s*, –CH_3 × 5), 2.01 (3H, *s*, –$COOCH_3$), 3.80 (1H, *s*, 15-H), 5.01 (1H, *d*, *J* = 5.9 Hz, 1-H), 5.44 (1H, *s*, 17-H), 6.33 (1H, *t*, *J* = 1.5 Hz, furan ring α-H), 7.40 (2H, *d*, *J* = 1.5 Hz, furan ring α-H and furan ring β-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.67 (7-C), 169.20 (3-C), 169.05 (–Ac, C═O), 166.64 (16-C), 143.24 (furan ring α-C, 1′,4′-C), 120.08 (furan ring β-C, 2′-C), 109.62 (furan ring β-C, 3′-C), 84.30 (4-C), 78.00 (7-C), 70.72 (1-C), 65.45 (14-C), 53.43 (10-C), 52.86 (15-C), 51.00 (8-C), 44.34 (5-C), 44.19 (2-C), 38.80 (9-C), 37.50 (13-C), 35.34 (6-C), 33.44 (12-C), 20.80, 20.73, 17.20, 17.10, 16.50 (–CH_3 × 5). Crystals of (I) suitable for X-ray analysis were obtained from a chloroform solution by slow evaporation at room temperature.

Crystal data

$C_{28}H_{33}O_9 \cdot CHCl_3$
M_r = 632.91
Orthorhombic, $P2_12_12_1$
a = 8.599 (4) Å
b = 12.951 (6) Å
c = 27.252 (12) Å
V = 3035 (2) Å^3
Z = 4
D_x = 1.385 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.35 mm^{-1}
T = 298 (2) K
Prism, colourless
0.45 × 0.38 × 0.31 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2000)
T_{min} = 0.857, T_{max} = 0.898
16041 measured reflections
5361 independent reflections
3162 reflections with $I > 2\sigma(I)$
R_{int} = 0.050
θ_{max} = 25.0°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.054
$wR(F^2)$ = 0.165
S = 1.00
5361 reflections
404 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0796P)^2 + 0.9994P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.016
$\Delta\rho_{max}$ = 0.32 e Å^{-3}
$\Delta\rho_{min}$ = −0.29 e Å^{-3}
Absolute structure: Flack (1983), 2303 Friedel pairs
Flack parameter: −0.10 (14)

Table 1
Selected torsion angles (°).

O2—C1—C2—C3	−124.3 (5)	O5—C7—C8—C9	−124.5 (5)
C1—C2—C3—O3	48.8 (5)	C14—C15—C16—O8	−156.5 (4)

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

D—H···A	D—H	H···A	D···A	D—H···A
C24—H24C···O5^{i}	0.96	2.76	3.657 (6)	155
C11—H11B···O8^{i}	0.97	2.67	3.274 (6)	120
C20—H20A···O2^{ii}	0.93	2.57	3.489 (8)	168
C17—H17A···O8^{iii}	0.98	2.59	3.374 (6)	137

Symmetry codes: (i) $x-1, y, z$; (ii) $x+\frac{1}{2}, -y+\frac{1}{2}, -z+1$; (iii) $x-\frac{1}{2}, -y+\frac{3}{2}, -z+1$.

The chloroform molecule shows orientational disorder. It was assumed that atoms C29 and H29 are shared by the two possible sets of Cl atoms Cl1–Cl3 and Cl1′–Cl3′, the occupation factors being refined to 0.615 (19) and 0.385 (19). The methyl H atoms were constrained to an ideal geometry with C—H = 0.96 Å and U_{iso}(H) = 1.5U_{eq}(C), but were allowed to rotate freely about the C—C bonds. All remaining 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).

Data collection: *SMART* (Bruker, 2000); cell refinement: *SAINT* (Bruker, 2000); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 2000); software used to prepare material for publication: *SHELXTL*.

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