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A semi-synthetic analog of the cembranoid sarcophine

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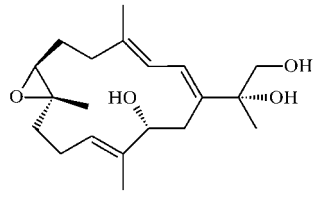
The title molecule, 2(*R*)-[(1*E*,3*E*,7*S*,8*S*,11*E*,13*R*)-13-hydroxy-4,8,12-trimethyl-7,8-epoxycyclotetradeca-1,3,11-trien-1-yl]propane-1,2-diol, $C_{20}H_{32}O_4$, is a semi-synthetic analog of sarcophine, the natural cembranoid of marine origin, isolated from the soft coral *Sarcophyton glaucum*. The conformation of the 14-membered ring differs substantially from that of sarcophine. The two OH groups of the propane-1,2-diol moiety form an unusual weak intramolecular hydrogen bond with an O···O distance of 2.788 (2) Å, and the molecules are linked into double chains by intermolecular hydrogen bonds with O···O distances of 2.772 (2) and 2.849 (2) Å.

Comment

Cembranoids, diterpenoids with a 14-membered ring, have been isolated from terrestrial and marine sources (Wahlberg & Eklund, 1992). Some cembranoids from soft corals have a remarkably wide spectrum of biological activities, including inhibitory activity against tumor promoters (Suganuma *et al.*, 1996; Tius, 1988). In order to obtain new compounds with chemopreventive activity, the marine natural product sarcophine, isolated from the soft coral *Sarcophyton glaucum*, was subjected to a series of chemical modifications (Katsuyama *et al.*, 2002). One of the products obtained as a result of such modifications was the title analog, (I). This compound displayed significant inhibitory activity against the tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA) in an Epstein–Barr virus early-antigen activation assay (Katsuyama *et al.*, 2002). We have undertaken the crystal structure analysis of (I) to confirm the structure and to establish the configuration of the stereogenic centers at atoms C13 and C15. The relative configuration of (I) compared with sarcophine allowed the determination of the configuration of these stereogenic centers on atoms C13 and C15 as *R*,*R*. This is the first case of the determination of the configuration of the stereogenic center in a propane-1,2-diol side chain attached to a Csp^2 atom, which is otherwise difficult to elucidate by spectroscopic methods.



(I)

The configuration and conformation of cembranoid (I) are illustrated in Fig. 1. The conformation of the 14-membered ring, described by the torsion angles in Table 1, differs substantially from that of sarcophine (Bernstein *et al.*, 1974; El Sayed *et al.*, 1998). Sarcophine lacks the OH group at C13 and has a γ-lactone at C1—C2 (*i.e.* a C1═C15 double bond), rather than the propane-1,2-diol substituent here. The differences are small in the portion of the ring carrying the epoxide, with the three endocyclic torsion angles in the C6—C7—C8—C9—C10—C11 sequence exhibiting a mean deviation of only 9.1°. However, in sarcophine, methyl group C18 is β-oriented (up in Fig. 1), while in (I), C18 points outward and the H atom at C3 points into the 14-membered ring. Likewise, the torsion angle about C10—C11, which determines the orientation of methyl group C20, is 177.26 (17)° in (I) and −95.7 (4)° in sarcophine. Thus, the 14-membered ring of (I) lies roughly in a plane, with an r.m.s. deviation of 0.37 Å and a maximum deviation of only 0.758 (2) Å for atom C5. The ring in sarcophine is slightly less planar, with an r.m.s. deviation of 0.49 Å and a maximum deviation of 0.825 (4) Å for atom C13.

The hydrogen bonding in (I) is illustrated in Fig. 2. Hydrogen bonds donated by atoms O1 and O4 link the molecules into double chains, which extend in the 2_1 direction. The

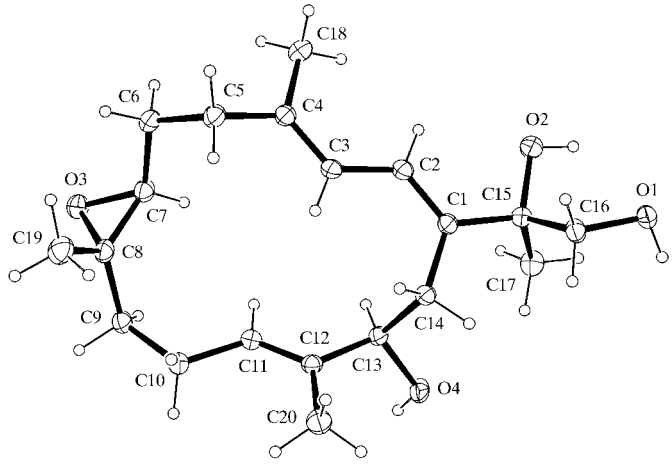


Figure 1
A view of the molecule of (I), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. The absolute configuration was assigned by comparison with sarcophine (see *Experimental*).

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chain-linking hydrogen-bonding unit contains 12 atoms, and involves three molecules and three intermolecular hydrogen bonds. The two OH groups of the propane-1,2-diol moiety form a weak intramolecular hydrogen bond, with atom O1 as acceptor. Although the O···O distance is not long, the five-membered ring imposes poor geometry on the donor and acceptor. This type of weak intramolecular hydrogen bond in propanediol substituents is somewhat unusual. They appear to be present only when stronger intermolecular bonding possibilities are unfavorable (André *et al.*, 1997), and are usually a component in bi- or trifurcated hydrogen bonds, where the other components are intermolecular (Kopf *et al.*, 1990; Jeffrey & Maluszynska, 1990; Jeffrey, 1997). The unusual weak intramolecular interaction in (I), unsupported by an intermolecular component, is similar to that in galactonic acid hydrazide (André *et al.*, 1997), in which the O···O distance is 2.748 (3) Å and the angle about H is 118 (4)°. Brock (2002) has recently examined crystal packing in vicinal diols, and has also noted the rarity of this type of intramolecular interaction. Yeh *et al.* (1994) and Dahlqvist *et al.* (1998) have calculated that, in the absence of intermolecular hydrogen bonding, the intramolecular hydrogen bond in vicinal diols causes the *gauche* conformer to be *ca* 8 kJ mol^{-1} lower in energy than the *anti* conformer.

A search of the Cambridge Structural Database (CSD; Allen, 2002) for the propane-1,2-diol side chain with atoms C1, C2 and C14 produced no hits. The most similar fragment in the CSD has the sp^2 atom C1 attached to two other Csp^2 atoms in a phenyl ring, rather than to the sp^2 C2 and sp^3 C14 atoms in (I). That fragment is found in only two compounds, two isomers of *endo*-2-{*o*-[(bicyclo[2.2.1]hept-5-en-2-yl)sulfinyl]-phenyl}propane-1,2-diol (refcodes WOFXEU and WOFXIY; Abe *et al.*, 1999), both of which are racemic. The conformations of the propane-1,2-diol side chain in WOFXEU and WOFXIY differ somewhat from that of (I), as they have C2—C1—C15—O2 torsion angles of −30.4 (4) and −38.4 (4)°, respectively, while in (I), it is nearly eclipsed, at 3.3 (2)°. This torsion angle appears to be controlled by the steric demands of the H atoms on atoms C14, C16 and C17. In (I), the nearest such distance is between H14*B* and H16*B*, at 2.08 Å. The O2—C15—C16—O1 torsion angle magnitude is 14.7 (4)° larger in WOFXEU and 11.1 (4)° larger in WOFXIY than the *gauche* angle of −56.53 (17)° in (I), probably as a result of the fact that, in both these compounds, atom O2 forms a normal intermolecular hydrogen bond rather than a weak intramolecular hydrogen bond. Thus, in (I), the conformation of the propane-1,2-diol side chain appears to result from two factors, the intramolecular H···H interactions and the intramolecular hydrogen bond.

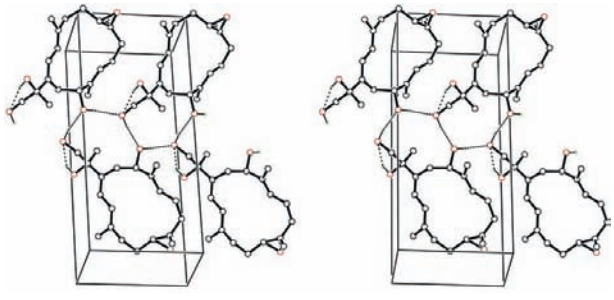

Figure 2
A stereoview of the unit cell of (I), showing the hydrogen bonding. The view is slightly oblique to *a*, with *b* horizontal.

Experimental

The preparation of the title compound from sarcophine has been described by Katsuyama *et al.* (2002). Crystals of (I) were grown from an hexane–acetone (1:1) solution.

Crystal data

$C_{20}H_{32}O_4$
M_r = 336.46
Monoclinic, $P2_1$
a = 5.858 (2) Å
b = 8.232 (2) Å
c = 19.241 (6) Å
β = 91.315 (10)°
V = 927.6 (5) Å^3
Z = 2
D_x = 1.205 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2443 reflections
θ = 2.5–30.0°
μ = 0.08 mm^{-1}
T = 100 K
Plate, pale yellow
0.32 × 0.22 × 0.05 mm

Data collection

Nonius KappaCCD area-detector diffractometer (with an Oxford Cryosystems Cryostream cooler)
ω scans with κ offsets
8313 measured reflections
2875 independent reflections
2647 reflections with $I > 2\sigma(I)$
R_{int} = 0.021
θ_{max} = 30°
$h = -8 \rightarrow 8$
$k = -11 \rightarrow 11$
$l = -26 \rightarrow 27$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.036
$wR(F^2)$ = 0.089
S = 1.04
2875 reflections
230 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0385P)^2 + 0.2001P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}
Absolute structure: not determined; Friedel pairs averaged

Table 1
Selected geometric parameters (Å, °).

O1—C16	1.436 (2)	C1—C2	1.348 (2)
O2—C15	1.442 (2)	C2—C3	1.452 (2)
O3—C7	1.449 (2)	C3—C4	1.347 (2)
O3—C8	1.455 (2)	C7—C8	1.474 (2)
O4—C13	1.446 (2)	C11—C12	1.332 (2)
C7—O3—C8	61.03 (11)		
C14—C1—C2—C3	5.8 (3)	C8—C9—C10—C11	−79.6 (2)
C1—C2—C3—C4	179.55 (18)	C10—C11—C12—C13	177.84 (16)
C2—C3—C4—C5	−169.72 (16)	C11—C12—C13—C14	115.01 (17)
C3—C4—C5—C6	−114.76 (18)	C2—C1—C14—C13	74.7 (2)
C4—C5—C6—C7	70.2 (2)	C12—C13—C14—C1	−129.46 (14)
C5—C6—C7—C8	90.3 (2)	C2—C1—C15—O2	3.3 (2)
C6—C7—C8—C9	−158.39 (16)	O2—C15—C16—O1	−56.53 (17)
C7—C8—C9—C10	88.63 (19)		

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

D—H···A	D—H	H···A	D···A	D—H···A
O1—H10···O4^{i}	0.88 (3)	1.92 (3)	2.772 (2)	162 (2)
O2—H20···O1	0.85 (3)	2.35 (3)	2.788 (2)	113 (2)
O4—H40···O1^{ii}	0.77 (3)	2.08 (3)	2.849 (2)	176 (3)

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

H atoms were placed in calculated positions, guided by difference maps, with C—H distances of 0.95–1.00 Å and U_{iso}(H) = 1.2U_{eq}(C) (1.5U_{eq} for methyl), and thereafter treated as riding. The coordinates of the hydroxy H atoms were refined. A torsional parameter was refined for each methyl group. The absolute configuration could not be established from the X-ray data, but was assigned based on the known configuration of sarcophine (Kashman, 1977). Friedel pairs were averaged.

Data collection: *COLLECT* (Nonius, 2000); cell refinement: *HKL SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *HKL DENZO* (Otwinowski & Minor, 1997) and *SCALEPACK*; program(s) used to solve structure: *SIR*97 (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 *for Windows* (Farrugia, 1997); 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: GA1004). Services for accessing these data are described at the back of the journal.

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