Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Absolute structures and conformations of the spongian diterpenes spongia-13(16),14-dien-3-one, epispongiadiol and spongiadiol

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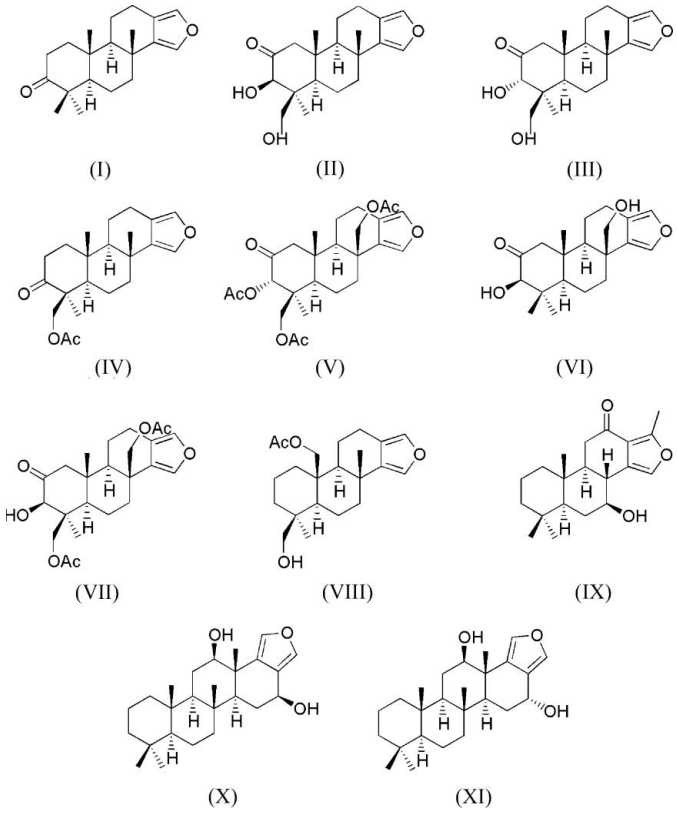
Received 6 March 2009
Accepted 10 March 2009
Online 25 March 2009

The absolute configurations of spongia-13(16),14-dien-3-one [systematic name: (3b*R*,5a*R*,9a*R*,9b*R*)-3b,6,6,9a-tetramethyl-4,5,5a,6,8,9,9a,9b,10,11-decahydrophenanthro[1,2-*c*]furan-7(3b*H*)-one], $C_{20}H_{28}O_2$, (I), epispongiadiol [systematic name: (3b*R*,5a*R*,6*S*,7*R*,9a*R*,9b*R*)-7-hydroxy-6-hydroxymethyl-3b,6,-9a-trimethyl-3b,5,5a,6,7,9,9a,9b,10,11-decahydrophenanthro-[1,2-*c*]furan-8(4*H*)-one], $C_{20}H_{28}O_4$, (II), and spongiadiol [systematic name: (3b*R*,5a*R*,6*S*,7*S*,9a*R*,9b*R*)-7-hydroxy-6-hydroxymethyl-3b,6,9a-trimethyl-3b,5,5a,6,7,9,9a,9b,10,11-decahydrophenanthro[1,2-*c*]furan-8(4*H*)-one], $C_{20}H_{28}O_4$, (III), were assigned by analysis of anomalous dispersion data collected at 130 K with Cu $K\alpha$ radiation. Compounds (II) and (III) are epimers. The equatorial 3-hydroxyl group on the cyclohexanone ring (*A*) of (II) is *syn* with respect to the 4-hydroxymethyl group, leading to a chair conformation. In contrast, isomer (III), where the 3-hydroxyl group is *anti* to the 4-hydroxymethyl group, is conformationally disordered between a major chair conformer where the OH group is axial and a minor boat conformer where it is equatorial. In compound (I), a carbonyl group is present at position 3 and ring *A* adopts a distorted-boat conformation.

Comment

Spongian diterpenoids [*e.g.* compounds (I)–(V)] are a group of tetracyclic compounds first isolated from Great Barrier Reef marine sponges of the genus Spongia (family Spongiidae, order Dictyoceratida) by Kazlauskas *et al.* (1979). Since then there have been a number of other reports of spongian diterpenes isolated from sponges of the orders Dictyoceratida and Dendroceratida (Keyzers *et al.*, 2006). Spongivorous molluscs belonging to the species *Glossodoris* have also yielded spongian diterpenes (Dilip de Silva *et al.*, 1982; Fontana *et al.*, 1997; Somerville *et al.*, 2006). In this paper, we report the crystal structures and absolute configurations of (+)-spongia-13(16),14-dien-3-one, (I) (Somerville *et al.*, 2006), (+)-epispongiadiol, (II), and (+)-spongiadiol, (III) (Kazlauskas *et al.*, 1979), isolated from the nudibranch *Glossodoris atromarginata*. Compounds (I)–(III) are structurally very similar, indeed (II) and (III) are epimers. Notwithstanding this similarity, the three diterpenes exhibit diversity in their solid-state structures, particularly in the conformation of the cyclohexanone ring.



The crystal structure of (I) was determined at 130 K. The compound crystallizes with two independent, but conformationally identical, molecules in the asymmetric unit. The tetracyclic structure of (I) is apparent in Fig. 1, where only one of the two molecules is displayed. A feature is the twisted-boat conformation of the cyclohexanone (*A*) ring. There are no classical hydrogen bonds in the structure and the six-

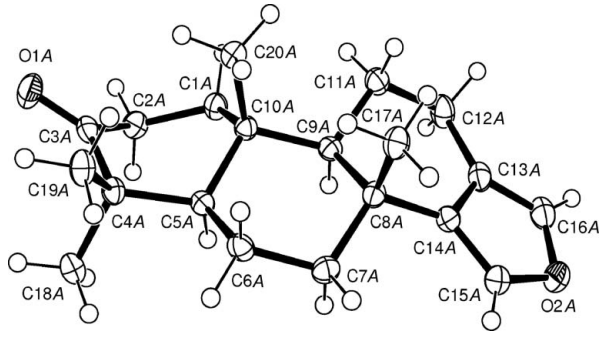


Figure 1
The molecular structure of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. Only one of the two independent molecules is shown.

 doi:10.1107/S0108270109008816

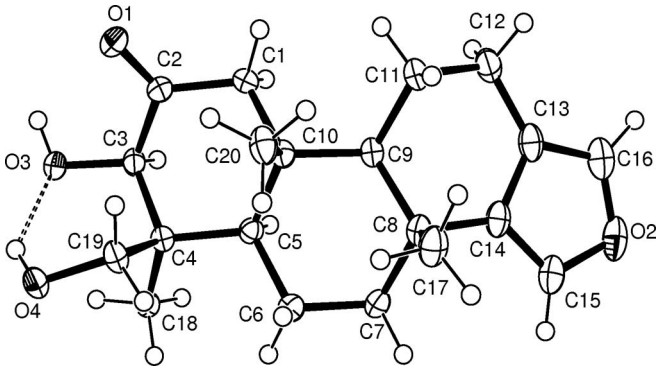


Figure 2
The molecular structure of (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

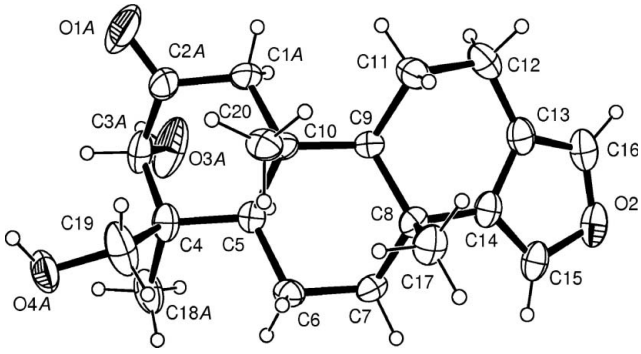


Figure 3
The molecular structure of the major conformer of (III), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

membered *B* and *C* rings adopt their expected chair conformations, while the inflexible furan ring (*D*) is necessarily planar. The only significant intermolecular contact is a nonclassical hydrogen bond donated by a furan H atom to the ketone O atom of an adjacent molecule [C16*A*—H···O1*A*$(1+x, y, z)$, with H···O = 2.49 Å]. The structure may be compared with that of 19-acetoxyspongia-13(16),14-dien-3-one, (IV) (Ponomarenko *et al.*, 2007), which exhibits a chair conformation of ring *A*. The two compounds only differ in the acetoxy group attached to C19 in (IV), which is absent in (I), yet this translates into a different conformation of ring *A*. Like (I), compound (IV) has no hydrogen-bond donors, so it appears that the two ring conformations are of very similar energy.

Compound (II) is structurally distinct in that the carbonyl group is at C2 on the cyclohexanone (*A*) ring, while hydroxyl groups appear on atoms C3 and C19. The OH group at C3 is equatorially disposed (Fig. 2) and ring *A* is in a conventional chair conformation. The hydroxymethyl group donates an intramolecular hydrogen bond to atom O3 (Table 1).

The crystal structure of compound (III) reveals disorder of ring *A*, comprising a dominant chair conformer (71% occupancy) with the 3-hydroxyl substituent in an axial position

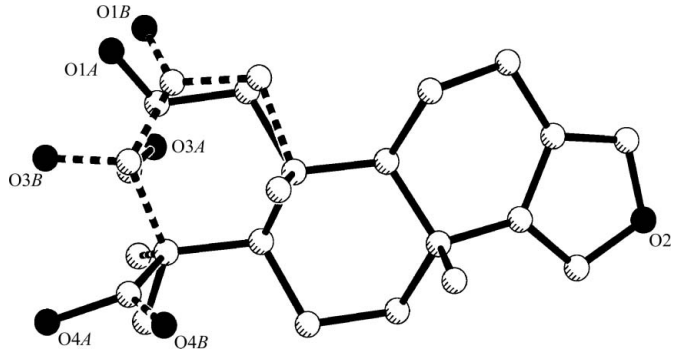


Figure 4
A plot of the disorder in (III). The minor conformer is shown with broken lines. H atoms have been omitted.

(Fig. 3). The minor contribution is a distorted-boat conformer where the hydroxyl group adopts an equatorial position. A superposition of the two conformers is shown in Fig. 4, where the distinct positions of all C atoms within ring *A* (except those fused with ring *B*) and their substituents are apparent. The two conformers display different hydrogen-bonding patterns (Table 2) due to the movement of the hydroxyl groups by more than 2.2 Å from one conformation to the other. This compound is most closely related to the acetylated analogue, (V), which exclusively exhibits a boat conformation of ring *A* (Kazlauskas *et al.*, 1979).

The absolute structures of (I), (II) and (III) were each determined by anomalous dispersion from an entire sphere of Cu $K\alpha$ data. Apart from the conventional Flack (1983) parameter, which is inconclusive for (II) and (III), the absolute structure was confirmed by the Bijvoet analysis of Hooft *et al.* (2008) implemented within the *PLATON* program (Version of 10 March 2009; Spek, 2009). In each case, the *P*2 parameter was 1.000 for the chosen enantiomorph and the Hooft y parameters were 0.04 (7), 0.02 (19) and 0.06 (8) for (I), (III) and (III), respectively.

All three spongian diterpenes, (I)–(III), have the same absolute configuration, 5*R*,8*R*,9*R*,10*R* for (I), 3*R*,4*S*,5*R*,8*R*,-9*R*,10*R* for (II) and 3*S*,4*S*,5*R*,8*R*,9*R*,10*R* for (III). The absolute structures of (−)-(IV) (Ponomarenko *et al.*, 2007) and (+)-(V) (Kazlauskas *et al.*, 1979) were assigned on the basis of circular dichroism (CD) data; Mo $K\alpha$ radiation was used for these crystal structure analyses, which only afforded relative stereochemistry. The absolute configurations of other spongian diterpenes, for example, (−)-(VI) (Searle & Molinski, 1994), (+)-(VII) (Fontana *et al.*, 1997) and (−)-(VIII) (Carroll *et al.*, 2008), have been deduced solely by Mosher ester analysis or by CD spectroscopy. So far, all the spongian diterpenes for which absolute configurations have been reported in the literature belong to the same enantiomeric series. This stereochemical uniformity is in contrast with the situation for sponge sesquiterpene metabolites, for which there are numerous reports of enantiomers in the literature, including recent examples from the furanosesquiterpenes (Gaspar *et al.*, 2008) and sesquiterpene quinones (Yong *et al.*, 2008).

The relative configuration of structurally related chamaetexane A, (IX), was reported from its crystal structure analysis (Barba *et al.*, 1992), but no absolute structure was reported. The pentacyclic sesterstatin epimers (X) and (XI) are somewhat different, but again their absolute configurations were not determined crystallographically (Pettit *et al.*, 1998).

There has been considerable interest in the synthesis of spongian diterpenes (González, 2008). Compound (I) has been previously reported as an intermediate in a diastereoselective synthesis starting from *S*-(+)-carvone (Arnó *et al.*, 1999). The optical rotation value for the crystallized natural product (I) ($[\alpha]_D$ +10.1°, *c* 0.37 $CHCl_3$) closely matches that of the synthetic intermediate (Arnó *et al.*, 1999; $[\alpha]_D$ +11.8°, *c* 3.8 $CHCl_3$).

The present study provides an important link between the absolute configuration of spongian diterpenes and their CD and optical rotation data, the latter being a somewhat ambiguous method for assigning chirality alone.

Experimental

Compounds (I)–(III) were obtained from an acetone extract of the nudibranch *G. atromarginata* collected from the Inner Gneerings Reef, Mooloolaba, Queensland, Australia. 23 specimens (25 g) of *G. atromarginata* were crushed and sonicated with acetone (20 ml). The solvent was then evaporated under reduced pressure to give an aqueous residue, which was partitioned with Et_2O (3 × 30 ml). The organic layer was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to give a dark-yellow oil (yield 70 mg, 0.28%). The organic extract was subsequently purified by reverse-phase high-performance liquid chromatography (50–100% MeOH–H_2O gradient over 40 min) to afford (+)-(I) (5.6 mg), (+)-(II) (2.7 mg) and (+)-(III) (3.7 mg), for which the $[\alpha]_D$ and NMR spectra and MS data concur with those published previously (Kazlauskas *et al.*, 1979; Somerville *et al.*, 2006). Slow recrystallization of (I) and (II) from MeOH (100%) and (III) from a 1:1 MeOH–MeCN mixture provided crystals suitable for X-ray analysis.

Compound (I)

Crystal data

$C_{20}H_{28}O_2$
M_r = 300.42
Monoclinic, $P2_1$
a = 12.3336 (1) Å
b = 7.4124 (1) Å
c = 18.2476 (1) Å
β = 101.930 (1)°
V = 1632.19 (3) Å^3
Z = 4
Cu *Kα* radiation
μ = 0.59 mm^{-1}
T = 130 K
0.3 × 0.3 × 0.1 mm

Data collection

Oxford Gemini S Ultra diffractometer
26930 measured reflections
5168 independent reflections
4826 reflections with $I > 2\sigma(I)$
R_{int} = 0.034
θ_{max} = 62.3°

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.027
$wR(F^2)$ = 0.070
S = 1.05
5168 reflections
406 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.17 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}
Absolute structure: Flack (1983), with 2344 Friedel pairs
Flack parameter: −0.06 (14)

Table 1
Hydrogen-bond geometry (Å, °) for (II).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O3—H3*A*···O4^{i}	0.84	1.94	2.760 (2)	166
O4—H4···O3	0.84	2.05	2.715 (2)	136

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

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O3*A*—H3*C*···O1*A*^{i}	0.84	1.97	2.709 (6)	146
O3*B*—H3*D*···O1*B*^{ii}	0.85	1.51	2.362 (13)	180

Symmetry codes: (i) $x-\frac{1}{2}, -y+\frac{5}{2}, -z+2$; (ii) $x+\frac{1}{2}, -y+\frac{5}{2}, -z+2$.

Compound (II)

Crystal data

$C_{20}H_{28}O_4$
M_r = 332.42
Monoclinic, $P2_1$
a = 9.5317 (1) Å
b = 7.8958 (1) Å
c = 11.6742 (1) Å
β = 101.734 (1)°
V = 860.24 (2) Å^3
Z = 2
Cu *Kα* radiation
μ = 0.71 mm^{-1}
T = 130 K
0.3 × 0.2 × 0.2 mm

Data collection

Oxford Gemini S Ultra diffractometer
16202 measured reflections
2624 independent reflections
2583 reflections with $I > 2\sigma(I)$
R_{int} = 0.024

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.045
$wR(F^2)$ = 0.119
S = 1.11
2624 reflections
222 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}
Absolute structure: Flack (1983), with 1160 Friedel pairs
Flack parameter: 0.2 (2)

Compound (III)

Crystal data

$C_{20}H_{28}O_4$
M_r = 332.42
Orthorhombic, $P2_12_12_1$
a = 6.1411 (1) Å
b = 12.7415 (3) Å
c = 21.6714 (5) Å
V = 1695.72 (6) Å^3
Z = 4
Cu *Kα* radiation
μ = 0.72 mm^{-1}
T = 130 K
0.5 × 0.5 × 0.15 mm

Data collection

Oxford Gemini S Ultra diffractometer
Absorption correction: multi-scan [*CrysAlis RED* (Oxford Diffraction, 2008); empirical (using intensity measurements) absorption correction using spherical harmonics implemented in SCALE3 ABSPACK scaling algorithm]
T_{min} = 0.640, T_{max} = 1.000 (expected range = 0.575–0.898)
26592 measured reflections
2683 independent reflections
2448 reflections with $I > 2\sigma(I)$
R_{int} = 0.038

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.056$
$wR(F^2) = 0.155$
$S = 1.09$
2683 reflections
253 parameters
9 restraints
H-atom parameters constrained
$\Delta\rho_{max} = 0.42$ e Å^{-3}
$\Delta\rho_{min} = -0.24$ e Å^{-3}
Absolute structure: Flack (1983), with 1100 Friedel pairs
Flack parameter: 0.1 (5)

Alkyl and heterocyclic H atoms were included at estimated positions using a riding model. Hydroxyl H atoms were constrained similarly but the H—O—C—C torsion angle was refined. For compound (III), disorder in ring *A* was identified and refined with two sets of atoms, *viz*. C1*A*/*B*, C2*A*/*B*, C3*A*/*B*, C18*A*/*B*, O1*A*/*B*, O3*A*/*B* and O4*A*/*B*. The *A* and *B* conformers were refined with complementary occupancies and the two rings were restrained to have similar bond lengths and angles. The major (71%) conformer of (III) has ring *A* in a chair conformer with the 3-hydroxyl group axial, while the minor conformer has the hydroxyl group equatorial and the ring in a twisted-boat conformation. For absolute structure determination, the analysis of Hooft *et al.* (2008) implemented within *PLATON* (Spek, 2009) was employed. Student's t statistics were used and the ν value of 15 was chosen.

For all three compounds, data collection: *CrysAlis CCD* (Oxford Diffraction, 2008); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2008); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXS86* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997) and *PLUTON* (Spek, 1991); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

Financial support from the University of Queensland and the Australian Research Council is gratefully acknowledged. A PhD scholarship to KWLY from the University of Queensland is also gratefully acknowledged. We also thank Professor R. Capon, Institute for Molecular Bioscience, University of Queensland, for assistance with the $[\alpha]_D$ measurements.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SQ3189). Services for accessing these data are described at the back of the journal.

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