Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

7β-Hydroxyartemisinin

Paulo B. Carvalho,[a] Bo Liu,[a] Yunshan Wu,[a] John S. Williamson[a] and Mitchell A. Avery[a,b,c]*

[a]Department of Medicinal Chemistry, University of Mississippi, 417 Faser Hall, University, MS 38677, USA, [b]National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, University, MS 38677, USA, and [c]Department of Chemistry and Biochemistry, University of Mississippi, University, MS 38677, USA
Correspondence e-mail: mavery@olemiss.edu

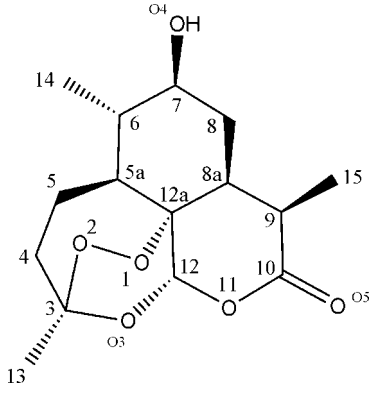
Received 19 December 2007; accepted 3 January 2008

Key indicators: single-crystal X-ray study; T = 296 K; mean σ(C–C) = 0.002 Å; R factor = 0.029; wR factor = 0.073; data-to-parameter ratio = 12.7.

Crystals of the title compound [systematic name: (3*R*,6*R*,7*S*,8a*R*,9*R*,12a*R*)-7-hydroxy-3,6,9-trimethyloctahydro-3,12-epoxy[1,2]dioxepino[4,3-*i*]isochromen-10(3*H*)-one], $C_{15}H_{22}O_6$, were obtained from microbial transformation of artemisinin by a culture of *Cunninghamella elegans*. The stereochemistry of the compound is consistent with the spectroscopic findings in previously published works. A weak O—H···O hydrogen bond occurs in the crystal structure, together with intermolecular C—H···O hydrogen bonds.

Related literature

For related literature, see: Blasko & Cordell (1988); Chen & Yu (2001); Liu *et al.* (2006); Parshikov *et al.* (2004, 2005, 2006); Zhan, Zhang *et al.* (2002); CDC (2007); Klayman (1985); TDR (2007); Zhan, Guo *et al.* (2002).



Experimental

Crystal data

$C_{15}H_{22}O_6$
M_r = 298.33
Orthorhombic, $P2_12_12_1$
a = 6.3047 (2) Å
b = 9.1266 (2) Å
c = 24.5309 (6) Å
V = 1411.52 (6) Å^3
Z = 4
Cu $K\alpha$ radiation
μ = 0.90 mm^{-1}
T = 296 (2) K
0.23 × 0.15 × 0.12 mm

Data collection

Bruker SMART CCD diffractometer
Absorption correction: none
12572 measured reflections
2464 independent reflections
2456 reflections with $I > 2\sigma(I)$
R_{int} = 0.020

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.028
$wR(F^2)$ = 0.072
S = 1.08
2464 reflections
194 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}
Absolute structure: Flack (1983), with 990 Friedel pairs
Flack parameter: 0.11 (14)

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

D—H···A	D—H	H···A	D···A	D—H···A
O4—H4···O4^{i}	0.82	2.48	3.2488 (18)	156
C5A—H5A1···O3^{ii}	0.98	2.53	3.4731 (16)	161
C5—H5B···O2^{iii}	0.97	2.53	3.4571 (17)	159
C13—H13B···O2^{iv}	0.96	2.44	3.3703 (18)	164

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

Data collection: *SMART* (Bruker, 2002); cell refinement: *SAINT* (Bruker, 2002); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *SHELXTL* (Bruker, 2002); software used to prepare material for publication: *SHELXTL*.

The authors thank Dr K. Hardcastle for his helpful advice. The authors also thank the Center for Disease Control and Prevention, USA, for providing financial assistance (CDC cooperative agreements 1UO1 CI000211-03 and 1UO1 CI000362-01). This investigation was conducted in a facility constructed with support from Research Facilities Improvement Program grant No. C06 Rr-14503-01 from the National Center for Research Resources, National Institutes of Health.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: HB2682).

References

Blasko, G. & Cordell, G. (1988). *J. Nat. Prod.* **51**, 1273–1276.
Bruker (2002). *SMART*, *SAINT* and *SHELXTL*. Bruker AXS Inc., Madison, Wisconsin, USA.
CDC (2007). *Malaria treatment and diagnosis*, http://www.cdc.gov/malaria/diagnosis_treatment/treatment.htm, accessed 15 March 2007.
Chen, Y. & Yu, B. (2001). *Yaowu Shengwu Jish*, **8**, 90–93.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Klayman, D. L. (1985). *Science*, **228**, 1049–1055.

Liu, J., Chen, Y., Yu, B. & Chen, Y. (2006). *Bioorg. Med. Chem. Lett.* **16**, 1909–1912.
Parshikov, I. A., Miriyala, B., Muraleedharan, K. M., Avery, M. A. & Williamson, J. S. (2006). *J. Ind. Microbiol. Biotechnol.* **33**, 349–352.
Parshikov, I. A., Miriyala, B., Muraleedharan, K. M., Illendula, A., Avery, M. A. & Williamson, J. S. (2005). *Pharm. Biol.* **43**, 579–582.
Parshikov, I. A., Muraleedharan, K. M., Avery, M. A. & Williamson, J. S. (2004). *Appl. Microbiol. Biotechnol.* **64**, 782–786.
Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.
TDR (2007). *Malaria*, http://www.who.int/tdr/diseases/malaria/default.htm, accessed 15 March 2007.
Zhan, J., Guo, H., Han, J., Zhang, Y. & Guo, D. (2002). *Zhongcaoyao*, **33**, 869–872.
Zhan, J., Zhang, Y., Guo, H., Han, J., Ning, L. & Guo, D. (2002). *J. Nat. Prod.* **65**, 1693–1695.

supporting information

Acta Cryst. (2008). E**64**, o395–o396 [doi:10.1107/S1600536808000251]

7*β*-Hydroxyartemisinin

Paulo B. Carvalho, Bo Liu, Yunshan Wu, John S. Williamson and Mitchell A. Avery

S1. Comment

The natural occurring sesquiterpene lactone endoperoxide artemisinin has been the subject of extensive research for its effective therapeutic action against multidrug-resistant *Plasmodium falciparum* strains (Klayman, 1985). Some of the reasons for this are the increasing number of people under risk of contracting malaria, the alarming spread of drug-resistant parasites (TDR, 2007) and the relatively complicated treatment protocols, with so many variables and no effective cure for the several strains of *Plasmodium* causing the disease (CDC, 2007).

One of the strategies used for increasing the bioavailability of artemisinin is its semi-synthetic transformation through microorganisms (Chen & Yu, 2001; Zhan, Guo *et al.*, 2002; Zhan, Zhang *et al.*, 2002; Liu *et al.*, 2006). The metabolites resulting from the action of several enzymes in selected strains of fungi can be further transformed in dimers or attached to other moieties for selective action and/or delivery.

Our group has been studying the microbial transformation of artemisinin for some years (Parshikov *et al.*, 2005; 2006) and we follow the numbering system of Blasko & Cordell (1988), and the CA Index Name. Some authors follow a different numbering system and call the title compound, (I), 9*β*-hydroxyartemisinin, rather than 7*β*-hydroxyartemisinin. Several well established methods of one-dimensional and two-dimensional NMR have already determined the configuration of artemisinin and most of its derivatives. The crystallographic data confirm the assignment of the chiral centers proposed in a previously published paper (Parshikov *et al.*, 2004). The configuration of the chiral centers in (I) are: C3 *R*, C5A S, C6 S, C7 S, C8A S, C9 *R*, C12 S, C12A *R*.

In the crystal of (I), a weak intermolecular O—H···O hydrogen bond links the molecules into chains and some short C—H···O contacts occur (Table 1).

S2. Experimental

7*β*-Hydroxyartemisinin was obtained following a method previously published by our group (Parshikov *et al.*, 2004). Well developed fungal mycelia of *Cunninghamella elegans* ATCC 9245 were removed from the surface of agar slants, suspended in 100 ml of sterilized water, and used to inoculate 1 liter of medium (400 g Sabouraud-dextrose, 300 g sucrose, 200 g peptone, in 20 liters of deionized water) in 4 liter shake flasks. The pH was adjusted to 6.5 using 0.1 N NaOH. Cultures were grown for 48 h on a rotary shaker at 301 K with shaking at 180 rpm. The resulting biomass was used as inocula for 1,000 ml of medium contained in 4 liter shake flasks that were again incubated for 48 h. 10 g of Artemisinin (Mediplantex, Vietnam) were dissolved in 400 ml of methanol (MeOH), filter-sterilized, and 20 ml were added to each flask to make the final concentration 500 mg/l. The cultures were returned to the shaker incubators (180 rpm) for an additional 14 days at 301 K. The cultures were harvested and the broth and mycelia were separated using coarse filter paper in a Büchner funnel. The mycelia were washed with water and discarded. The culture broth was extracted with three equal volumes of ethyl acetate (EtOAc) and evaporated under vacuum. The residues were dissolved in MeOH for analysis.

Thin layer chromatography (TLC) was performed on precoated silica gel G and GP Uniplates (Analtech, Newark, Del.) in EtOAc/hexanes (*v*/*v* 50:50). TLC plates were visualized with iodine, and *p*-anisaldehyde stain. Metabolites were purified by semi-preparative flash-chromatography carried out on silica gel 60 (SCI Adsorbents, Louisville, Ky.) using the EtOAc/hexanes solvent system in a gradient mode, eluting from 10–40% EtOAc, collecting 50 ml fractions with a flow rate of 30 ml/min.

Colourless needles of (I) were grown by slow evaporation of a solution in absolute ethanol.

S3. Refinement

The hydrogen atoms were placed in idealized locations (C—H = 0.96–0.98 Å, O—H = 0.82 Å) and refined as riding with U_{iso}(H) = 1.2U_{eq}(C) or 1.5U_{eq}(methyl C, O).

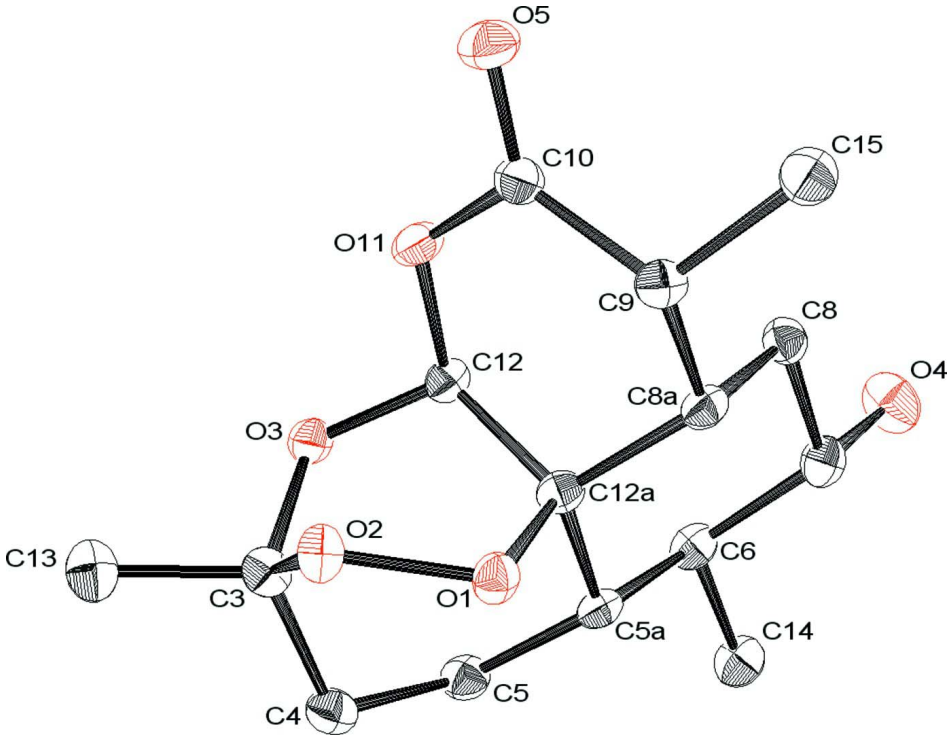


Figure 1

View of the molecular structure of (**I**) with displacement elipsoids drawn at the 50% probability level. Hydrogen atoms are omitted for clarity.

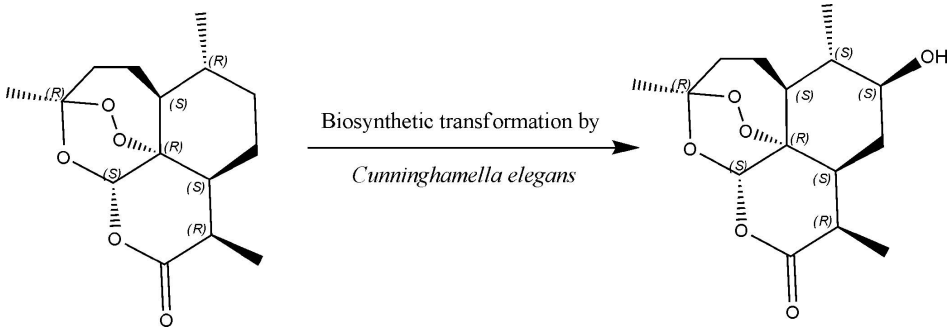


Figure 2

The formation of the title compound.

(3*R*,6*R*,7*S*,8aR,9*R*,12aR)-7-hydroxy-3,6,9-trimethyloctahydro-3,12- epoxy[1,2]dioxepino[4,3-*i*]isochromen-10(3*H*)-one

Crystal data

$C_{15}H_{22}O_6$
$M_r = 298.33$
Orthorhombic, $P2_12_12_1$
Hall symbol: P 2ac 2ab
$a = 6.3047$ (2) Å
$b = 9.1266$ (2) Å
$c = 24.5309$ (6) Å
$V = 1411.52$ (6) Å^3
$Z = 4$
$F(000) = 640$
$D_x = 1.404$ Mg m^{-3}
Cu $K\alpha$ radiation, $\lambda = 1.54178$ Å
Cell parameters from 9907 reflections
$\theta = 3.6$–66.0°
$\mu = 0.90$ mm^{-1}
$T = 296$ K
Needle, colourless
0.23 × 0.15 × 0.12 mm

Data collection

Bruker SMART CCD diffractometer
Radiation source: fine-focus sealed tube, Siemens KFF Cu 2 K90
Graphite monochromator
ω scans
12572 measured reflections
2464 independent reflections
2456 reflections with $I > 2\sigma(I)$
$R_{int} = 0.020$
$\theta_{max} = 66.5°$, $\theta_{min} = 3.6°$
$h = -7\rightarrow7$
$k = -10\rightarrow10$
$l = -28\rightarrow29$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.028$
$wR(F^2) = 0.072$
$S = 1.08$
2464 reflections
194 parameters
0 restraints
Primary atom site location: structure-invariant direct methods
Secondary atom site location: difference Fourier map
Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0408P)^2 + 0.3857P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.24$ e Å^{-3}
$\Delta\rho_{min} = -0.16$ e Å^{-3}
Absolute structure: Flack (1983), 990 Friedel pairs
Absolute structure parameter: 0.11 (14)

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit *S* are based on F^2, conventional *R*-factors *R* are based on *F*, with *F* set to zero for negative F^2. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on *F*, and *R*-factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.61177 (15)	1.07519 (10)	0.80390 (4)	0.0180 (2)
O2	0.80303 (16)	1.07108 (10)	0.76947 (4)	0.0196 (2)
O5	1.06564 (17)	1.28606 (12)	0.91615 (4)	0.0257 (2)
O11	1.00751 (15)	1.07562 (11)	0.87615 (4)	0.0202 (2)
O3	0.96938 (15)	0.88540 (11)	0.81679 (4)	0.0179 (2)
O4	0.3981 (2)	0.79291 (13)	0.99868 (4)	0.0312 (3)
H4	0.5183	0.7748	1.0095	0.047*
C10	0.9351 (2)	1.20070 (15)	0.90000 (5)	0.0180 (3)
C8A	0.5644 (2)	1.08876 (15)	0.89973 (5)	0.0164 (3)
H8A	0.4185	1.1175	0.8910	0.020*
C15	0.6384 (2)	1.33349 (16)	0.94762 (6)	0.0231 (3)
H15A	0.6812	1.2917	0.9818	0.035*
H15B	0.4877	1.3486	0.9477	0.035*
H15C	0.7091	1.4256	0.9424	0.035*
C6	0.4729 (2)	0.76793 (15)	0.90164 (6)	0.0196 (3)
H6	0.6086	0.7227	0.9114	0.024*
C7	0.4095 (2)	0.87131 (16)	0.94816 (6)	0.0211 (3)
H7	0.2672	0.9086	0.9401	0.025*
C3	0.8719 (2)	0.92375 (15)	0.76551 (5)	0.0189 (3)
C13	1.0455 (3)	0.92467 (16)	0.72317 (6)	0.0244 (3)
H13A	0.9850	0.9423	0.6879	0.037*
H13B	1.1165	0.8316	0.7232	0.037*
H13C	1.1456	1.0007	0.7315	0.037*
C5	0.5912 (2)	0.74642 (15)	0.80360 (6)	0.0205 (3)
H5A	0.6983	0.6846	0.8203	0.025*
H5B	0.4763	0.6831	0.7919	0.025*
C9	0.6978 (2)	1.22918 (15)	0.90130 (6)	0.0177 (3)
H9	0.6651	1.2817	0.8675	0.021*
C14	0.3095 (2)	0.64461 (16)	0.89482 (6)	0.0241 (3)
H14A	0.2810	0.6009	0.9296	0.036*
H14B	0.3647	0.5716	0.8705	0.036*
H14C	0.1806	0.6842	0.8801	0.036*
C4	0.6880 (2)	0.81822 (16)	0.75307 (6)	0.0207 (3)
H4A	0.5777	0.8717	0.7340	0.025*
H4B	0.7389	0.7419	0.7289	0.025*
C12A	0.6419 (2)	0.98999 (15)	0.85346 (6)	0.0164 (3)
C12	0.8748 (2)	0.95112 (15)	0.86157 (6)	0.0166 (3)

H12	0.8821	0.8810	0.8918	0.020*
C8	0.5571 (2)	1.00298 (15)	0.95338 (5)	0.0185 (3)
H8B	0.6987	0.9698	0.9627	0.022*
H8C	0.5074	1.0665	0.9824	0.022*
C5A	0.5049 (2)	0.85116 (16)	0.84744 (5)	0.0171 (3)
H5A1	0.3644	0.8832	0.8352	0.021*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0161 (5)	0.0194 (5)	0.0185 (5)	0.0033 (4)	0.0003 (4)	0.0022 (4)
O2	0.0198 (5)	0.0179 (5)	0.0212 (5)	0.0016 (4)	0.0043 (4)	0.0019 (4)
O5	0.0209 (5)	0.0243 (5)	0.0318 (5)	−0.0053 (5)	−0.0020 (4)	−0.0077 (4)
O11	0.0135 (5)	0.0206 (5)	0.0266 (5)	−0.0006 (4)	−0.0026 (4)	−0.0048 (4)
O3	0.0156 (4)	0.0185 (5)	0.0196 (5)	0.0031 (4)	−0.0004 (4)	−0.0017 (4)
O4	0.0419 (7)	0.0276 (6)	0.0240 (5)	−0.0063 (5)	0.0054 (5)	0.0044 (5)
C10	0.0188 (7)	0.0186 (7)	0.0166 (6)	−0.0016 (6)	−0.0004 (5)	−0.0003 (5)
C8A	0.0130 (6)	0.0155 (6)	0.0208 (6)	0.0007 (6)	−0.0018 (5)	−0.0004 (5)
C15	0.0225 (7)	0.0183 (7)	0.0283 (7)	−0.0007 (6)	0.0008 (6)	−0.0034 (6)
C6	0.0174 (7)	0.0171 (7)	0.0244 (7)	−0.0005 (6)	−0.0004 (6)	0.0021 (6)
C7	0.0194 (7)	0.0214 (7)	0.0225 (7)	−0.0011 (6)	0.0033 (6)	0.0025 (6)
C3	0.0213 (7)	0.0165 (7)	0.0189 (6)	0.0020 (6)	−0.0004 (6)	−0.0002 (5)
C13	0.0279 (8)	0.0201 (7)	0.0253 (7)	0.0001 (6)	0.0054 (6)	−0.0001 (6)
C5	0.0205 (7)	0.0174 (6)	0.0234 (7)	−0.0033 (6)	−0.0011 (6)	−0.0029 (6)
C9	0.0178 (7)	0.0160 (7)	0.0192 (6)	0.0006 (6)	−0.0018 (5)	0.0000 (5)
C14	0.0235 (7)	0.0193 (7)	0.0295 (8)	−0.0029 (7)	0.0009 (6)	0.0020 (6)
C4	0.0226 (7)	0.0200 (7)	0.0196 (6)	0.0004 (6)	−0.0024 (6)	−0.0023 (5)
C12A	0.0157 (7)	0.0159 (6)	0.0175 (6)	0.0009 (6)	−0.0024 (5)	0.0018 (5)
C12	0.0146 (6)	0.0154 (6)	0.0198 (7)	−0.0007 (5)	−0.0002 (5)	0.0003 (5)
C8	0.0189 (7)	0.0184 (7)	0.0181 (6)	0.0012 (6)	0.0009 (6)	−0.0014 (5)
C5A	0.0126 (6)	0.0186 (7)	0.0202 (6)	−0.0006 (5)	−0.0027 (5)	−0.0004 (5)

Geometric parameters (Å, º)

O1—C12A	1.4556 (16)	C7—C8	1.525 (2)
O1—O2	1.4727 (13)	C7—H7	0.9800
O2—C3	1.4164 (17)	C3—C13	1.509 (2)
O5—C10	1.2003 (18)	C3—C4	1.538 (2)
O11—C10	1.3615 (17)	C13—H13A	0.9600
O11—C12	1.4558 (17)	C13—H13B	0.9600
O3—C12	1.3866 (17)	C13—H13C	0.9600
O3—C3	1.4429 (16)	C5—C4	1.529 (2)
O4—C7	1.4328 (17)	C5—C5A	1.5383 (19)
O4—H4	0.8200	C5—H5A	0.9700
C10—C9	1.5193 (19)	C5—H5B	0.9700
C8A—C12A	1.5297 (18)	C9—H9	0.9800
C8A—C8	1.5320 (18)	C14—H14A	0.9600
C8A—C9	1.5333 (19)	C14—H14B	0.9600

C8A—H8A	0.9800	C14—H14C	0.9600
C15—C9	1.5289 (19)	C4—H4A	0.9700
C15—H15A	0.9600	C4—H4B	0.9700
C15—H15B	0.9600	C12A—C12	1.5234 (19)
C15—H15C	0.9600	C12A—C5A	1.5405 (19)
C6—C7	1.5336 (19)	C12—H12	0.9800
C6—C14	1.535 (2)	C8—H8B	0.9700
C6—C5A	1.5444 (18)	C8—H8C	0.9700
C6—H6	0.9800	C5A—H5A1	0.9800

C12A—O1—O2	111.00 (9)	C5A—C5—H5A	108.2
C3—O2—O1	108.33 (9)	C4—C5—H5B	108.2
C10—O11—C12	124.56 (11)	C5A—C5—H5B	108.2
C12—O3—C3	113.74 (10)	H5A—C5—H5B	107.4
C7—O4—H4	109.5	C10—C9—C15	111.29 (12)
O5—C10—O11	117.15 (13)	C10—C9—C8A	113.38 (11)
O5—C10—C9	123.87 (13)	C15—C9—C8A	113.89 (11)
O11—C10—C9	118.85 (12)	C10—C9—H9	105.8
C12A—C8A—C8	110.23 (11)	C15—C9—H9	105.8
C12A—C8A—C9	109.62 (11)	C8A—C9—H9	105.8
C8—C8A—C9	114.95 (11)	C6—C14—H14A	109.5
C12A—C8A—H8A	107.2	C6—C14—H14B	109.5
C8—C8A—H8A	107.2	H14A—C14—H14B	109.5
C9—C8A—H8A	107.2	C6—C14—H14C	109.5
C9—C15—H15A	109.5	H14A—C14—H14C	109.5
C9—C15—H15B	109.5	H14B—C14—H14C	109.5
H15A—C15—H15B	109.5	C5—C4—C3	114.09 (11)
C9—C15—H15C	109.5	C5—C4—H4A	108.7
H15A—C15—H15C	109.5	C3—C4—H4A	108.7
H15B—C15—H15C	109.5	C5—C4—H4B	108.7
C7—C6—C14	110.94 (12)	C3—C4—H4B	108.7
C7—C6—C5A	111.84 (11)	H4A—C4—H4B	107.6
C14—C6—C5A	110.77 (11)	O1—C12A—C12	111.07 (11)
C7—C6—H6	107.7	O1—C12A—C8A	105.26 (10)
C14—C6—H6	107.7	C12—C12A—C8A	110.38 (11)
C5A—C6—H6	107.7	O1—C12A—C5A	106.63 (10)
O4—C7—C8	110.58 (12)	C12—C12A—C5A	111.18 (11)
O4—C7—C6	110.46 (12)	C8A—C12A—C5A	112.12 (11)
C8—C7—C6	112.84 (12)	O3—C12—O11	106.56 (11)
O4—C7—H7	107.6	O3—C12—C12A	114.31 (11)
C8—C7—H7	107.6	O11—C12—C12A	113.85 (11)
C6—C7—H7	107.6	O3—C12—H12	107.2
O2—C3—O3	107.52 (10)	O11—C12—H12	107.2
O2—C3—C13	105.32 (11)	C12A—C12—H12	107.2
O3—C3—C13	107.01 (11)	C7—C8—C8A	110.41 (11)
O2—C3—C4	112.14 (12)	C7—C8—H8B	109.6
O3—C3—C4	110.01 (11)	C8A—C8—H8B	109.6
C13—C3—C4	114.44 (12)	C7—C8—H8C	109.6

C3—C13—H13A	109.5	C8A—C8—H8C	109.6
C3—C13—H13B	109.5	H8B—C8—H8C	108.1
H13A—C13—H13B	109.5	C5—C5A—C12A	112.32 (11)
C3—C13—H13C	109.5	C5—C5A—C6	110.02 (11)
H13A—C13—H13C	109.5	C12A—C5A—C6	113.30 (11)
H13B—C13—H13C	109.5	C5—C5A—H5A1	106.9
C4—C5—C5A	116.20 (12)	C12A—C5A—H5A1	106.9
C4—C5—H5A	108.2	C6—C5A—H5A1	106.9

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O4—H4···O4^{i}	0.82	2.48	3.2488 (18)	156
C5*A*—H5*A*1···O3^{ii}	0.98	2.53	3.4731 (16)	161
C5—H5*B*···O2^{iii}	0.97	2.53	3.4571 (17)	159
C13—H13*B*···O2^{iv}	0.96	2.44	3.3703 (18)	164

Symmetry codes: (i) $x+1/2, -y+3/2, -z+2$; (ii) $x-1, y, z$; (iii) $-x+1, y-1/2, -z+3/2$; (iv) $-x+2, y-1/2, -z+3/2$.