

Redetermination of dihydroartemisinin at 103 (2) K

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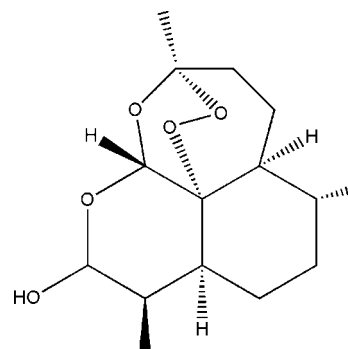
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Key indicators: single-crystal X-ray study; $T = 103$ K; mean $\sigma(\text{C}-\text{C}) = 0.003$ Å; R factor = 0.038; wR factor = 0.100; data-to-parameter ratio = 13.4.

The structure of the title compound, $\text{C}_{15}\text{H}_{24}\text{O}_5$, has been redetermined at 103 (2) K, with much improved precision. The title compound was first reported by Luo, Yeh, Brossi, Flippen-Anderson & Gillardi [*Helv. Chim. Acta* (1984), **67**, 1515–1522]. It is a derivative of the antimalaria compound artemisinin and consists primarily of three substituted ring systems fused together. A cyclohexane ring (with a distorted chair conformation), is fused to a tetrahydropyran group (also with a distorted chair conformation), and is adjacent to an oxacycloheptane unit containing an endoperoxide bridge. This gives the molecule a unique three-dimensional arrangement. The crystal packing is stabilized by intermolecular $\text{C}-\text{H}\cdots\text{O}$ and $\text{O}-\text{H}\cdots\text{O}$ interactions between an H atom from the cyclohexane ring and an O atom from the endoperoxide bridge, as well as between the hydroxyl H atom and an O atom from a tetrahydropyran ring.

Related literature

For crystal structures of similar compounds, see: Flippen-Anderson *et al.* (1989), Yue *et al.* (2006), Li *et al.* (2006); Karle & Lin (1995); Brossi *et al.* (1988). For the biological activity of artemisinin derivatives *in vitro* and *in vivo*, see: Li *et al.* (2001); Yang *et al.* (1997); Grace *et al.* (1998); Maggs *et al.* (2000). For endoperoxide sesquiterpene lactone derivatives, see: Venugopalan *et al.* (1995); Wu *et al.* (2001); Saxena *et al.* (2003). For the synthesis of artemisinin and its derivatives, see: Lui *et al.* (1979); Liu (1980); Robert *et al.* (2001). For related literature, see: Allen *et al.* (1987); Cremer & Pople (1975); Lisgarten *et al.* (1998); Qinghaosu Research Group (1980); Shen & Zhuang (1984); Wu & Li (1995); Luo *et al.* (1984).



Experimental

Crystal data

| | |
|--|-----------------------------------|
| $\text{C}_{15}\text{H}_{24}\text{O}_5$ | $V = 1485.8$ (3) Å ³ |
| $M_r = 284.34$ | $Z = 4$ |
| Orthorhombic, $P2_12_12_1$ | Mo $K\alpha$ radiation |
| $a = 5.5910$ (6) Å | $\mu = 0.09$ mm ⁻¹ |
| $b = 14.1309$ (14) Å | $T = 103$ (2) K |
| $c = 18.8062$ (19) Å | $0.67 \times 0.11 \times 0.09$ mm |

Data collection

| | |
|---|--|
| Bruker APEXII CCD area-detector diffractometer | 16573 measured reflections |
| Absorption correction: multi-scan (SADABS; Sheldrick, 1996) | 2475 independent reflections |
| $T_{\min} = 0.940$, $T_{\max} = 0.992$ | 2130 reflections with $I > 2\sigma(I)$ |
| | $R_{\text{int}} = 0.044$ |

Refinement

| | |
|---------------------------------|---|
| $R[F^2 > 2\sigma(F^2)] = 0.038$ | 185 parameters |
| $wR(F^2) = 0.100$ | H-atom parameters constrained |
| $S = 1.06$ | $\Delta\rho_{\text{max}} = 0.37$ e Å ⁻³ |
| 2475 reflections | $\Delta\rho_{\text{min}} = -0.22$ e Å ⁻³ |

Table 1

Hydrogen-bond geometry (Å, °).

| $D-\text{H}\cdots A$ | $D-\text{H}$ | $\text{H}\cdots A$ | $D\cdots A$ | $D-\text{H}\cdots A$ |
|---|--------------|--------------------|-------------|----------------------|
| $\text{O5}-\text{H5}\cdots\text{O2}^{\text{i}}$ | 0.84 | 1.95 | 2.7799 (19) | 168 |
| $\text{C5}-\text{H5A}\cdots\text{O4}^{\text{ii}}$ | 1.00 | 2.38 | 3.381 (3) | 175 |

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

Data collection: APEX2 (Bruker, 2006); cell refinement: APEX2; data reduction: SAINT (Bruker, 2006); program(s) used to solve structure: SHELXS97 (Sheldrick, 1990); 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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Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: FJ2084).

References

- Allen, F. H., Kennard, O., Watson, D. G., Brammer, L., Orpen, A. G. & Taylor, R. (1987). *J. Chem. Soc. Perkin Trans. 2*, pp. S1–19.
- Brossi, A., Venugopalan, B., Dominguez Gerpe, L., Yeh, H. J. C., Flippen-Anderson, J. L., Buchs, P., Luo, X. D., Milhousand, W. & Peters, W. (1988). *J. Med. Chem.* **31**, 645–650.
- Bruker (2000). *SHELXTL*. Version 6.10. Bruker AXS Inc., Madison, Wisconsin, USA.
- Bruker (2006). *APEX2*. Version 2.0-2. Bruker AXS Inc., Madison, Wisconsin, USA.
- Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
- Flippen-Anderson, J. L., George, C., Gilardi, R., Yu, Q.-S., Dominguez, L. & Brossi, A. (1989). *Acta Cryst.* **C45**, 292–294.
- Grace, J. M., Aguilar, A. J., Trotman, K. M. & Brewer, T. G. (1998). *Drug. Metab. Dispos.* **26**, 313–317.
- Karle, J. M. & Lin, Ai. J. (1995). *Acta Cryst.* **B51**, 1063–1068.
- Li, Y., Shan, F., Wu, J. M., Wu, G. S., Ding, J., Xiao, D., Yang, W. Y., Atassi, G., Leonce, S., Caignard, D. H. & Renard, P. (2001). *Bioorg. Med. Chem. Lett.* **11**, 5–8.
- Li, S.-H., Yue, Z.-Y., Gao, P. & Yan, P.-F. (2006). *Acta Cryst.* **E62**, o1898–o1900.
- Lisgarten, J., Potter, B. S., Bantuzeko, C. & Palmer, A. (1998). *J. Chem. Cryst.* **28**, 539–542.
- Liu, X. (1980). *Chin. Pharm. Bull.* **15**, 183–183.
- Lui, J.-M., Ni, M.-Y., Fan, Y.-E., Tu, Y.-Y., Wu, Z.-H., Wu, Y.-L. & Chou, W.-S. (1979). *Acta Chim. Sinica*, **37**, 129–141.
- Luo, X. D., Yeh, H. J. C., Brossi, A., Flippen-Anderson, J. L. & Gillardi, R. (1984). *Helv. Chim. Acta*, **67**, 1515–1522.
- Maggs, J. L., Bishop, L. P. D., Edwards, G., O'Neill, P. M., Ward, S. A., Winstanley, P. A. & Park, K. (2000). *Drug. Metab. Dispos.* **28**, 209–217.
- Qinghaosu Research Group (1980). *Sci. Sin. (Engl. Ed.)*, **23**, 380–396.
- Robert, A., Benoit-Vical, F., Dechy-Cabaret, O. & Meunier, B. (2001). *Pure Appl. Chem.* **73**, 1173–1188.
- Saxena, S., Pant, N., Jain, D. C. & Bhakuni, R. S. (2003). *Curr. Sci.* **85**, 1314–1329.
- Sheldrick, G. M. (1990). *Acta Cryst.* **A46**, 467–473.
- Sheldrick, G. M. (1996). *SADABS*. University of Göttingen, Germany.
- Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.
- Shen, C. C. & Zhuang, L. (1984). *Med. Res. Rev.* **4**, 57–59.
- Venugopalan, B., Karnik, P. J., Bapat, C. J., Chatterjee, D. K., Iyer, N. & Lepcha, D. (1995). *Eur. J. Med. Chem.* **30**, 697–706.
- Wu, Y.-L. & Li, Y. (1995). *Med. Chem. Res.* **5**, 569–586.
- Wu, J. M., Shan, F., Wu, G. S., Ying, L., Ding, J., Xiao, D., Han, J.-X., Atassi, G., Leonce, S., Caignard, D. H. & Renard, P. (2001). *Eur. J. Med. Chem.* **36**, 469–479.
- Yang, X. P., Pan, Q. C., Liang, Y.-G. & Zikang, Y.-L. (1997). *Cancer*, **16**, 186–187.
- Yue, Z.-Y., Li, S.-H., Gao, P., Zhang, J.-H. & Yan, P.-F. (2006). *Acta Cryst.* **C62**, o281–o282.

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Redetermination of dihydroartemisinin at 103 (2) K

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S1. Comment

Artemisinin and its derivatives, dihydroartemisinin, artemether, arteether and artesunate are antimalarial drugs which possess bioactivity with less toxicity (Wu & Li, 1995). Artemisinin is isolated from the leaves of plant *Artemisia annua* (Qinghao). It is a sesquiterpene lactone with an endoperoxide linkage. Artemisinin derivatives are more potent than artemisinin and are active by virtue of the endoperoxide. Their activity against strains of the parasite that had become resistant to conventional chloroquine therapy and the ability due to its lipophilic structure, to cross the blood brain barrier, it was particularly effective for the deadly cerebral malaria (Shen & Zhuang, 1984). Because of their shorter life time and decreasing activity, they are used in combination with other antimalarial drugs. The notable activity of artemisinin derivatives *in vitro* and *in vivo* has been reported in literature (Li *et al.* 2001 & Yang *et al.* 1997). However, some derivatives of artemisinin showed moderate cytotoxicity *in vitro*. The electronegativity and bulk of the substituents that attached to the aryl group plays an insignificant role in cytotoxicity. The antimalarial activity and cytotoxicity of some sesquiterpenoids has been reported in the literature (Venugopalan *et al.* 1995; Wu *et al.* 2001 and Saxena *et al.* 2003). The endoperoxide moiety present in these compounds plays an important role in antimalarial activity. Its 1,2,4 trioxane ring is unique in nature. After being opened in the plasmodium it liberates singlet oxygen and forms free radical which in turn produces oxidative damage to the parasites membrane. Artemisinin is hydrophobic in nature and are partitioned into the membrane of the plasmodium. The structures of the antimalarials dihydroqinghaosu, artemether and artesunic acid derived from qinghaosu were elaborated by ¹H-NMR spectroscopy, and supported with X-ray data have been reported (Luo *et al.* 1984). The crystal structure of an ether dimer of deoxydihydroqinghaosu, a potential metabolite of the antimalarial arteether is reported (Flippen-Anderson *et al.* 1989). The correlation of the crystal structures of diastereomeric artemisinin derivatives with their proton NMR spectra in CDCl₃ is reported (Karle & Lin, 1995). The crystal structure of artemisinin is reported (Lisgarten *et al.* 1998). The crystal structure of a dimer of α - and β -dihydroartemisinin (Yue *et al.* 2006) and that of 9,10-dehydrodeoxyartemisinin is recently reported (Li *et al.* 2006). The synthesis of artemisinin and its derivatives are described (Lui *et al.* 1979; Lui, 1980; Robert *et al.* 2001). The synthesis and antimalarial properties of arteether have been reported (Brossi *et al.* 1988). β -Arteether (AE) is an endoperoxide sesquiterpene lactone derivative currently being developed for the treatment of severe, complicated malaria caused by multidrug-resistant *Plasmodium falciparum* (Grace *et al.* 1998). β -Artemether (AM), the *O*-methyl ether prodrug of dihydroartemisinin (DHA), is an endoperoxide antimalarial (Maggs *et al.* 2000). In view of the importance of the title compound, (I) C₁₅H₂₄O₅, as an antimalarial drug, this paper reports a redetermination of the crystal structure first reported by Luo *et al.* (1984).

The six-membered cyclohexane ring (A, C1—C6) is a slightly distorted chair, with Cremer & Pople (1975) puckering parameters Q, θ and φ of 0.553 (2) Å, 4.8 (2)° and 170 (3)°, respectively. The tetrahydropyran group (D, C1—C2—C12—C11—O2—C10) is also a slightly distorted chair configuration with puckering parameters Q, θ and φ of 0.539 (2) Å, 2.7 (2)° and 227 (4)°, respectively. For an ideal chair θ has a value of 0 or 180°. Similar conformations for rings A and D

were found in 9,10-dehydrodeoxyartemisinin (Shu-Hui Li *et al.* 2006). The seven-membered ring B (C1/C6—C9/O1—C10) contains the important peroxy linkage [O3—O4 = 1.471 (2) Å]. The six-membered ring C (O1—C9—O3—O4—C1—C10) which contains both an oxygen bridge and a peroxy bridge is best described by a twist-boat conformation with puckering parameters Q , θ and φ of 0.750 (2) Å, 85.26 (15)° and 96.58 (11)°, respectively. For an ideal twist-boat conformation, θ and φ are 90° and $(60n + 30)^\circ$, respectively. This conformation is consistent with both 9,10-dehydrodeoxyartemisinin (Li *et al.* (2006) and dihydroartemisinin (Qinghaosu Research Group, 1980).

S2. Experimental

The title compound (C₁₅H₂₄O₅) was obtained in the pure form from Strides Arco Labs, Mangalore, India. X-ray diffraction quality crystals were grown from acetone-methylacetoacetate (1:1). (m.p.: 413 K).

S3. Refinement

All H atoms were initially located in a difference Fourier map. The methyl H atoms were then constrained to an ideal geometry with C—H distances of 0.98 Å and $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$, but each group was allowed to rotate freely about its C—C bond. All other H atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms with C—H distances in the range 0.98–1.00 Å and $U_{\text{iso}}(\text{H}) = 1.17\text{--}1.22U_{\text{eq}}(\text{C})$. The hydroxyl H was idealized with an O—H distance of 0.84 Å and $U_{\text{iso}}(\text{H}) = 1.21U_{\text{eq}}(\text{O})$. Because no strong anomalous scattering atoms are present, the Friedel pairs were merged in the refinement.

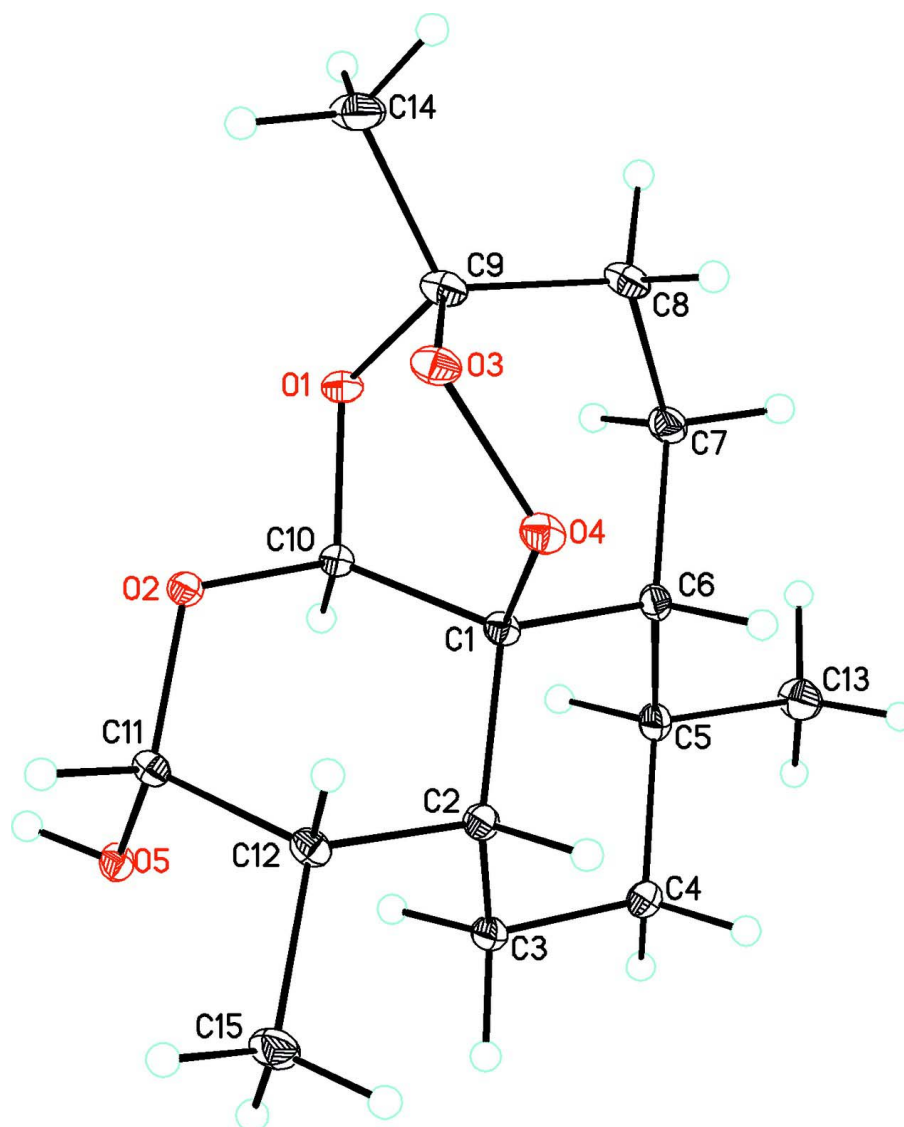


Figure 1

ORTEP view of dihydroartemisinin, (I), showing the atom numbering scheme and 50% probability displacement ellipsoids.

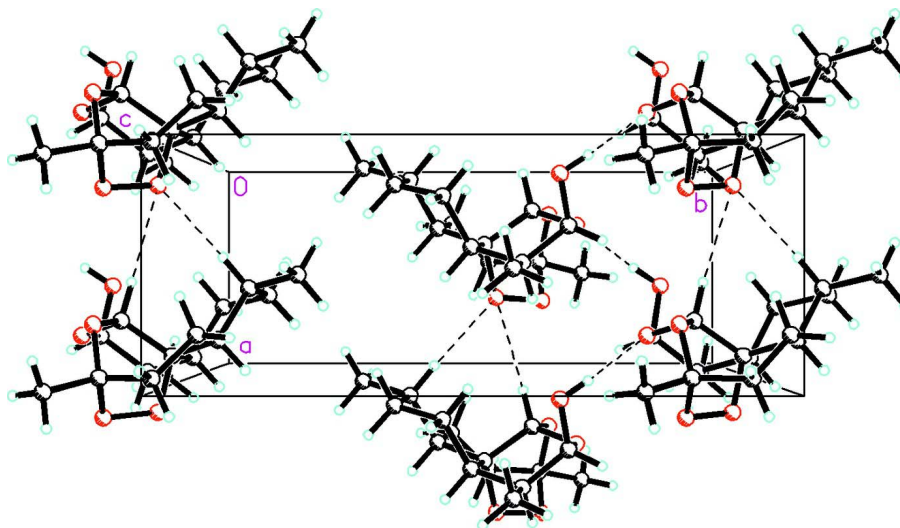


Figure 2

The molecular packing for I viewed down the *c* axis. Dashed lines indicate C–H⋯O and O–H⋯O intermolecular hydrogen bonds.

Dihydroartemisinin

Crystal data

$C_{15}H_{24}O_5$

$M_r = 284.34$

Orthorhombic, $P2_12_12_1$

Hall symbol: P 2ac 2ab

$a = 5.5910$ (6) Å

$b = 14.1309$ (14) Å

$c = 18.8062$ (19) Å

$V = 1485.8$ (3) Å³

$Z = 4$

$F(000) = 616$

$D_x = 1.271$ Mg m⁻³

Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å

Cell parameters from 4650 reflections

$\theta = 2.6$ – 29.6°

$\mu = 0.09$ mm⁻¹

$T = 103$ K

Needle, colorless

$0.67 \times 0.11 \times 0.09$ mm

Data collection

Bruker APEXII CCD area-detector
diffractometer

Radiation source: fine-focus sealed tube

Graphite monochromator

φ and ω scans

Absorption correction: multi-scan
(*SADABS*; Sheldrick, 1996)

$T_{\min} = 0.940$, $T_{\max} = 0.992$

16573 measured reflections

2475 independent reflections

2130 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.044$

$\theta_{\max} = 30.5^\circ$, $\theta_{\min} = 1.8^\circ$

$h = -5 \rightarrow 7$

$k = -19 \rightarrow 19$

$l = -26 \rightarrow 26$

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.038$

$wR(F^2) = 0.100$

$S = 1.06$

2475 reflections

185 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

$$w = 1/[\sigma^2(F_o^2) + (0.0434P)^2 + 0.5149P]$$

where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} = 0.002$

$$\Delta\rho_{\max} = 0.37 \text{ e } \text{\AA}^{-3}$$

$$\Delta\rho_{\min} = -0.22 \text{ e } \text{\AA}^{-3}$$

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 (\AA^2)

| | <i>x</i> | <i>y</i> | <i>z</i> | $U_{\text{iso}}^*/U_{\text{eq}}$ |
|------|-------------|--------------|--------------|----------------------------------|
| O1 | 0.2493 (3) | 0.35457 (10) | 0.85285 (7) | 0.0212 (3) |
| O2 | 0.1910 (3) | 0.31049 (9) | 0.96710 (6) | 0.0187 (3) |
| O3 | -0.1579 (3) | 0.36796 (11) | 0.87194 (7) | 0.0250 (3) |
| O4 | -0.1419 (3) | 0.45439 (10) | 0.91529 (7) | 0.0229 (3) |
| O5 | 0.4123 (3) | 0.34511 (9) | 1.06918 (7) | 0.0198 (3) |
| H5 | 0.4953 | 0.2959 | 1.0648 | 0.024* |
| C1 | 0.1042 (4) | 0.47570 (13) | 0.93520 (9) | 0.0178 (4) |
| C2 | 0.0886 (4) | 0.50052 (13) | 1.01511 (9) | 0.0195 (4) |
| H2A | -0.0458 | 0.5467 | 1.0205 | 0.023* |
| C3 | 0.3158 (4) | 0.55071 (13) | 1.04118 (10) | 0.0238 (4) |
| H3A | 0.2942 | 0.5701 | 1.0914 | 0.029* |
| H3B | 0.4523 | 0.5062 | 1.0390 | 0.029* |
| C4 | 0.3716 (5) | 0.63737 (13) | 0.99635 (10) | 0.0269 (5) |
| H4A | 0.5198 | 0.6674 | 1.0142 | 0.032* |
| H4B | 0.2398 | 0.6837 | 1.0012 | 0.032* |
| C5 | 0.4035 (4) | 0.61214 (13) | 0.91802 (10) | 0.0225 (4) |
| H5A | 0.5412 | 0.5673 | 0.9140 | 0.027* |
| C6 | 0.1797 (4) | 0.56209 (13) | 0.88957 (9) | 0.0195 (4) |
| H6A | 0.0459 | 0.6089 | 0.8925 | 0.023* |
| C7 | 0.2078 (4) | 0.53662 (14) | 0.81060 (9) | 0.0245 (4) |
| H7A | 0.1986 | 0.5957 | 0.7825 | 0.029* |
| H7B | 0.3697 | 0.5098 | 0.8035 | 0.029* |
| C8 | 0.0260 (5) | 0.46691 (15) | 0.78064 (10) | 0.0269 (5) |
| H8A | 0.0621 | 0.4558 | 0.7298 | 0.032* |
| H8B | -0.1353 | 0.4955 | 0.7836 | 0.032* |
| C9 | 0.0230 (4) | 0.37149 (15) | 0.81945 (10) | 0.0247 (4) |
| C10 | 0.2609 (4) | 0.38836 (12) | 0.92316 (9) | 0.0163 (4) |
| H10A | 0.4306 | 0.4051 | 0.9343 | 0.020* |
| C11 | 0.1826 (4) | 0.32865 (13) | 1.04225 (9) | 0.0184 (4) |
| H11A | 0.1159 | 0.2713 | 1.0663 | 0.022* |
| C12 | 0.0176 (4) | 0.41122 (14) | 1.05737 (9) | 0.0200 (4) |
| H12A | -0.1444 | 0.3922 | 1.0400 | 0.024* |

| | | | | |
|------|-------------|--------------|--------------|------------|
| C13 | 0.4636 (5) | 0.70119 (16) | 0.87466 (12) | 0.0342 (6) |
| H13A | 0.6048 | 0.7321 | 0.8950 | 0.051* |
| H13B | 0.3278 | 0.7450 | 0.8760 | 0.051* |
| H13C | 0.4967 | 0.6833 | 0.8253 | 0.051* |
| C14 | -0.0293 (6) | 0.28799 (17) | 0.77187 (11) | 0.0364 (6) |
| H14A | -0.0491 | 0.2310 | 0.8010 | 0.055* |
| H14B | 0.1039 | 0.2788 | 0.7387 | 0.055* |
| H14C | -0.1765 | 0.2999 | 0.7451 | 0.055* |
| C15 | -0.0068 (5) | 0.42857 (16) | 1.13739 (10) | 0.0299 (5) |
| H15A | -0.0695 | 0.3715 | 1.1604 | 0.045* |
| H15B | -0.1169 | 0.4814 | 1.1456 | 0.045* |
| H15C | 0.1503 | 0.4439 | 1.1574 | 0.045* |

Atomic displacement parameters (Å²)

| | U^{11} | U^{22} | U^{33} | U^{12} | U^{13} | U^{23} |
|-----|-------------|-------------|-------------|--------------|--------------|-------------|
| O1 | 0.0215 (8) | 0.0257 (6) | 0.0163 (5) | -0.0011 (6) | 0.0014 (6) | -0.0038 (5) |
| O2 | 0.0211 (7) | 0.0181 (6) | 0.0168 (6) | -0.0022 (6) | -0.0012 (6) | 0.0004 (5) |
| O3 | 0.0209 (8) | 0.0333 (7) | 0.0208 (6) | -0.0074 (6) | -0.0017 (6) | 0.0001 (6) |
| O4 | 0.0142 (7) | 0.0317 (7) | 0.0228 (6) | 0.0013 (6) | -0.0024 (5) | -0.0013 (6) |
| O5 | 0.0172 (7) | 0.0190 (6) | 0.0232 (6) | 0.0012 (5) | -0.0047 (6) | 0.0003 (5) |
| C1 | 0.0132 (9) | 0.0230 (8) | 0.0171 (8) | 0.0018 (7) | -0.0005 (7) | -0.0016 (7) |
| C2 | 0.0197 (10) | 0.0210 (8) | 0.0180 (8) | 0.0061 (8) | 0.0005 (8) | -0.0014 (6) |
| C3 | 0.0315 (12) | 0.0206 (8) | 0.0194 (8) | -0.0016 (9) | -0.0056 (9) | 0.0010 (7) |
| C4 | 0.0385 (13) | 0.0177 (8) | 0.0245 (9) | -0.0005 (9) | -0.0043 (9) | -0.0011 (7) |
| C5 | 0.0267 (11) | 0.0185 (8) | 0.0223 (8) | -0.0003 (8) | -0.0016 (8) | 0.0033 (7) |
| C6 | 0.0196 (10) | 0.0191 (8) | 0.0198 (8) | 0.0021 (7) | -0.0019 (8) | 0.0013 (7) |
| C7 | 0.0299 (12) | 0.0257 (9) | 0.0179 (8) | -0.0017 (9) | 0.0000 (8) | 0.0036 (7) |
| C8 | 0.0293 (13) | 0.0346 (11) | 0.0168 (8) | -0.0045 (10) | -0.0052 (8) | 0.0032 (8) |
| C9 | 0.0245 (11) | 0.0323 (10) | 0.0175 (8) | -0.0066 (9) | -0.0010 (8) | -0.0005 (8) |
| C10 | 0.0165 (9) | 0.0170 (7) | 0.0156 (7) | -0.0003 (7) | -0.0006 (7) | -0.0007 (6) |
| C11 | 0.0160 (9) | 0.0230 (8) | 0.0161 (7) | -0.0023 (8) | -0.0016 (7) | 0.0020 (7) |
| C12 | 0.0169 (10) | 0.0265 (9) | 0.0165 (8) | 0.0011 (8) | 0.0016 (7) | 0.0016 (7) |
| C13 | 0.0446 (15) | 0.0275 (10) | 0.0304 (10) | -0.0116 (11) | -0.0032 (11) | 0.0058 (9) |
| C14 | 0.0470 (17) | 0.0386 (12) | 0.0234 (10) | -0.0151 (12) | -0.0042 (11) | -0.0034 (9) |
| C15 | 0.0351 (14) | 0.0370 (11) | 0.0177 (9) | 0.0037 (10) | 0.0051 (9) | -0.0001 (8) |

Geometric parameters (Å, °)

| | | | |
|--------|-----------|--------|-----------|
| O1—C10 | 1.407 (2) | C6—C7 | 1.536 (3) |
| O1—C9 | 1.432 (3) | C6—H6A | 1.0000 |
| O2—C10 | 1.431 (2) | C7—C8 | 1.524 (3) |
| O2—C11 | 1.437 (2) | C7—H7A | 0.9900 |
| O3—C9 | 1.414 (3) | C7—H7B | 0.9900 |
| O3—O4 | 1.471 (2) | C8—C9 | 1.533 (3) |
| O4—C1 | 1.457 (2) | C8—H8A | 0.9900 |
| O5—C11 | 1.400 (2) | C8—H8B | 0.9900 |
| O5—H5 | 0.8400 | C9—C14 | 1.509 (3) |

| | | | |
|------------|-------------|---------------|-------------|
| C1—C10 | 1.531 (3) | C10—H10A | 1.0000 |
| C1—C2 | 1.546 (2) | C11—C12 | 1.514 (3) |
| C1—C6 | 1.551 (3) | C11—H11A | 1.0000 |
| C2—C3 | 1.535 (3) | C12—C15 | 1.531 (3) |
| C2—C12 | 1.543 (3) | C12—H12A | 1.0000 |
| C2—H2A | 1.0000 | C13—H13A | 0.9800 |
| C3—C4 | 1.519 (3) | C13—H13B | 0.9800 |
| C3—H3A | 0.9900 | C13—H13C | 0.9800 |
| C3—H3B | 0.9900 | C14—H14A | 0.9800 |
| C4—C5 | 1.526 (3) | C14—H14B | 0.9800 |
| C4—H4A | 0.9900 | C14—H14C | 0.9800 |
| C4—H4B | 0.9900 | C15—H15A | 0.9800 |
| C5—C6 | 1.533 (3) | C15—H15B | 0.9800 |
| C5—C13 | 1.537 (3) | C15—H15C | 0.9800 |
| C5—H5A | 1.0000 | | |
| | | | |
| C10—O1—C9 | 113.35 (15) | C7—C8—H8A | 108.9 |
| C10—O2—C11 | 116.08 (13) | C9—C8—H8A | 108.9 |
| C9—O3—O4 | 108.29 (14) | C7—C8—H8B | 108.9 |
| C1—O4—O3 | 111.82 (13) | C9—C8—H8B | 108.9 |
| C11—O5—H5 | 109.5 | H8A—C8—H8B | 107.7 |
| O4—C1—C10 | 109.63 (15) | O3—C9—O1 | 108.65 (14) |
| O4—C1—C2 | 104.10 (15) | O3—C9—C14 | 104.33 (18) |
| C10—C1—C2 | 111.04 (14) | O1—C9—C14 | 107.5 (2) |
| O4—C1—C6 | 106.12 (15) | O3—C9—C8 | 111.78 (19) |
| C10—C1—C6 | 113.38 (16) | O1—C9—C8 | 110.25 (17) |
| C2—C1—C6 | 112.01 (15) | C14—C9—C8 | 114.03 (16) |
| C3—C2—C12 | 115.21 (16) | O1—C10—O2 | 105.60 (13) |
| C3—C2—C1 | 111.63 (17) | O1—C10—C1 | 112.70 (14) |
| C12—C2—C1 | 109.25 (15) | O2—C10—C1 | 112.21 (15) |
| C3—C2—H2A | 106.8 | O1—C10—H10A | 108.7 |
| C12—C2—H2A | 106.8 | O2—C10—H10A | 108.7 |
| C1—C2—H2A | 106.8 | C1—C10—H10A | 108.7 |
| C4—C3—C2 | 111.42 (17) | O5—C11—O2 | 110.82 (16) |
| C4—C3—H3A | 109.3 | O5—C11—C12 | 111.27 (15) |
| C2—C3—H3A | 109.3 | O2—C11—C12 | 110.01 (15) |
| C4—C3—H3B | 109.3 | O5—C11—H11A | 108.2 |
| C2—C3—H3B | 109.3 | O2—C11—H11A | 108.2 |
| H3A—C3—H3B | 108.0 | C12—C11—H11A | 108.2 |
| C3—C4—C5 | 111.80 (16) | C11—C12—C15 | 111.25 (16) |
| C3—C4—H4A | 109.3 | C11—C12—C2 | 112.14 (16) |
| C5—C4—H4A | 109.3 | C15—C12—C2 | 113.47 (17) |
| C3—C4—H4B | 109.3 | C11—C12—H12A | 106.5 |
| C5—C4—H4B | 109.3 | C15—C12—H12A | 106.5 |
| H4A—C4—H4B | 107.9 | C2—C12—H12A | 106.5 |
| C4—C5—C6 | 110.45 (18) | C5—C13—H13A | 109.5 |
| C4—C5—C13 | 110.27 (16) | C5—C13—H13B | 109.5 |
| C6—C5—C13 | 111.78 (17) | H13A—C13—H13B | 109.5 |

| | | | |
|---------------|--------------|----------------|--------------|
| C4—C5—H5A | 108.1 | C5—C13—H13C | 109.5 |
| C6—C5—H5A | 108.1 | H13A—C13—H13C | 109.5 |
| C13—C5—H5A | 108.1 | H13B—C13—H13C | 109.5 |
| C5—C6—C7 | 111.22 (18) | C9—C14—H14A | 109.5 |
| C5—C6—C1 | 113.09 (15) | C9—C14—H14B | 109.5 |
| C7—C6—C1 | 112.24 (15) | H14A—C14—H14B | 109.5 |
| C5—C6—H6A | 106.6 | C9—C14—H14C | 109.5 |
| C7—C6—H6A | 106.6 | H14A—C14—H14C | 109.5 |
| C1—C6—H6A | 106.6 | H14B—C14—H14C | 109.5 |
| C8—C7—C6 | 116.15 (18) | C12—C15—H15A | 109.5 |
| C8—C7—H7A | 108.2 | C12—C15—H15B | 109.5 |
| C6—C7—H7A | 108.2 | H15A—C15—H15B | 109.5 |
| C8—C7—H7B | 108.2 | C12—C15—H15C | 109.5 |
| C6—C7—H7B | 108.2 | H15A—C15—H15C | 109.5 |
| H7A—C7—H7B | 107.4 | H15B—C15—H15C | 109.5 |
| C7—C8—C9 | 113.55 (17) | | |
| C9—O3—O4—C1 | -45.32 (18) | O4—O3—C9—C14 | -172.27 (16) |
| O3—O4—C1—C10 | -15.82 (18) | O4—O3—C9—C8 | -48.58 (19) |
| O3—O4—C1—C2 | -134.68 (13) | C10—O1—C9—O3 | -32.1 (2) |
| O3—O4—C1—C6 | 106.97 (15) | C10—O1—C9—C14 | -144.41 (16) |
| O4—C1—C2—C3 | -164.53 (15) | C10—O1—C9—C8 | 90.75 (18) |
| C10—C1—C2—C3 | 77.58 (19) | C7—C8—C9—O3 | 96.3 (2) |
| C6—C1—C2—C3 | -50.3 (2) | C7—C8—C9—O1 | -24.6 (2) |
| O4—C1—C2—C12 | 66.88 (19) | C7—C8—C9—C14 | -145.6 (2) |
| C10—C1—C2—C12 | -51.0 (2) | C9—O1—C10—O2 | 92.17 (17) |
| C6—C1—C2—C12 | -178.90 (17) | C9—O1—C10—C1 | -30.7 (2) |
| C12—C2—C3—C4 | 179.84 (17) | C11—O2—C10—O1 | -178.37 (16) |
| C1—C2—C3—C4 | 54.5 (2) | C11—O2—C10—C1 | -55.2 (2) |
| C2—C3—C4—C5 | -58.2 (3) | O4—C1—C10—O1 | 56.06 (19) |
| C3—C4—C5—C6 | 56.9 (2) | C2—C1—C10—O1 | 170.53 (16) |
| C3—C4—C5—C13 | -179.1 (2) | C6—C1—C10—O1 | -62.3 (2) |
| C4—C5—C6—C7 | 179.67 (16) | O4—C1—C10—O2 | -63.01 (18) |
| C13—C5—C6—C7 | 56.5 (2) | C2—C1—C10—O2 | 51.5 (2) |
| C4—C5—C6—C1 | -53.0 (2) | C6—C1—C10—O2 | 178.61 (14) |
| C13—C5—C6—C1 | -176.14 (18) | C10—O2—C11—O5 | -67.1 (2) |
| O4—C1—C6—C5 | 163.26 (15) | C10—O2—C11—C12 | 56.3 (2) |
| C10—C1—C6—C5 | -76.35 (19) | O5—C11—C12—C15 | -60.2 (2) |
| C2—C1—C6—C5 | 50.3 (2) | O2—C11—C12—C15 | 176.61 (17) |
| O4—C1—C6—C7 | -69.9 (2) | O5—C11—C12—C2 | 68.1 (2) |
| C10—C1—C6—C7 | 50.5 (2) | O2—C11—C12—C2 | -55.1 (2) |
| C2—C1—C6—C7 | 177.11 (18) | C3—C2—C12—C11 | -72.8 (2) |
| C5—C6—C7—C8 | 166.05 (18) | C1—C2—C12—C11 | 53.8 (2) |
| C1—C6—C7—C8 | 38.2 (3) | C3—C2—C12—C15 | 54.3 (2) |
| C6—C7—C8—C9 | -58.4 (3) | C1—C2—C12—C15 | -179.07 (18) |
| O4—O3—C9—O1 | 73.30 (18) | | |

Hydrogen-bond geometry (Å, °)

| <i>D</i> —H \cdots <i>A</i> | <i>D</i> —H | H \cdots <i>A</i> | <i>D</i> \cdots <i>A</i> | <i>D</i> —H \cdots <i>A</i> |
|----------------------------------|-------------|---------------------|----------------------------|-------------------------------|
| O5—H5 \cdots O2 ⁱ | 0.84 | 1.95 | 2.7799 (19) | 168 |
| C5—H5A \cdots O4 ⁱⁱ | 1.00 | 2.38 | 3.381 (3) | 175 |

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