Acta Crystallographica Section E
**Structure Reports Online**
ISSN 1600-5368

# Redetermination of dihydroartemisinin at 103 (2) K

**Jerry P. Jasinski,[a]* Ray J. Butcher,[b] H. S. Yathirajan,[c] B. Narayana[d] and T. V. Sreevidya[d]**

[a]Department of Chemistry, Keene State College, 229 Main Street, Keene, NH 03435-2001, USA, [b]Department of Chemistry, Howard University, 525 College Street NW, Washington DC 20059, USA, [c]Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore 570006, India, and [d]Department of Studies in Chemistry, Mangalore University, Mangalagangotri 574199, India
Correspondence e-mail: jjasinski@keene.edu

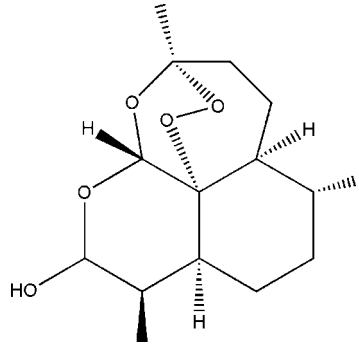
Received 18 November 2007; accepted 25 November 2007

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

Tthe structure of the title compound, $C_{15}H_{24}O_5$, 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 C–H···O and O–H···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

$C_{15}H_{24}O_5$
$M_r$ = 284.34
Orthorhombic, $P2_12_12_1$
$a$ = 5.5910 (6) Å
$b$ = 14.1309 (14) Å
$c$ = 18.8062 (19) Å
$V$ = 1485.8 (3) Å$^3$
$Z$ = 4
Mo $K\alpha$ radiation
$\mu$ = 0.09 mm$^{-1}$
$T$ = 103 (2) K
0.67 × 0.11 × 0.09 mm

### Data collection

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

### Refinement

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

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

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| O5—H5···O2$^{i}$ | 0.84 | 1.95 | 2.7799 (19) | 168 |
| C5—H5$A$···O4$^{ii}$ | 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*.

RJB acknowledges the Laboratory for the Structure of Matter at the Naval Research Laboratory, Washington DC, USA, for access to their diffractometers. BN thanks Strides Arco Labs, Mangalore, India, for a gift sample of the title compound.

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.* C**45**, 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.* B**51**, 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.* E**62**, 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.* A**46**, 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.* C**62**, o281–o282.

# supporting information

*Acta Cryst.* (2008). E**64**, o89–o90 [https://doi.org/10.1107/S1600536807063180]

## Redetermination of dihydroartemisinin at 103 (2) K

**Jerry P. Jasinski, Ray J. Butcher, H. S. Yathirajan, B. Narayana and T. V. Sreevidya**

### 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 artimisinine 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 inturn 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 $^1$H-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 $CDCl_3$ is reported (Karle & Lin, 1995). The crystal structure of artemisinin is reported (Lisgarten *et al.* 1998). The crystal structure of a dimer of $\alpha$- and $\beta$-dihydro-artemisinin (Yue *et al.* 2006) and that of 9,10-dehydrodeoxyartemisin 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). $\beta$-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). $\beta$-Artemether (AM), the *O*-methyl ether prodrug of di-hydroartemisinin (DHA), is an endoperoxide antimalarial (Maggs *et al.* 2000). In view of the importance of the title compound, (I) $C_{15}H_{24}O_5$, as n 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, $\theta$ and $\varphi$ 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, $\theta$ and $\varphi$ of 0.539 (2) Å, 2.7 (2)° and 227 (4)°, respectively. For an ideal chair $\theta$ 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, $\theta$ and $\varphi$ of 0.750 (2) Å, 85.26 (15)° and 96.58 (11)°, respectively. For an ideal twist-boat conformation, $\theta$ and $\varphi$ are 90° and (60$n$ + 30)°, 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 ($C_{15}H_{24}O_5$)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 $U_{iso}$(H) = 1.5$U_{eq}$(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 $U_{iso}$(H) = 1.17–1.22$U_{eq}$(C). The hydroxyl H was idealized with an O—H distance of 0.84Å and $U_{iso}$(H) = 1.21$U_{eq}$(O). Because no strong anomalous scattering atoms are present, the Friedel pairs were merged in the refinement.

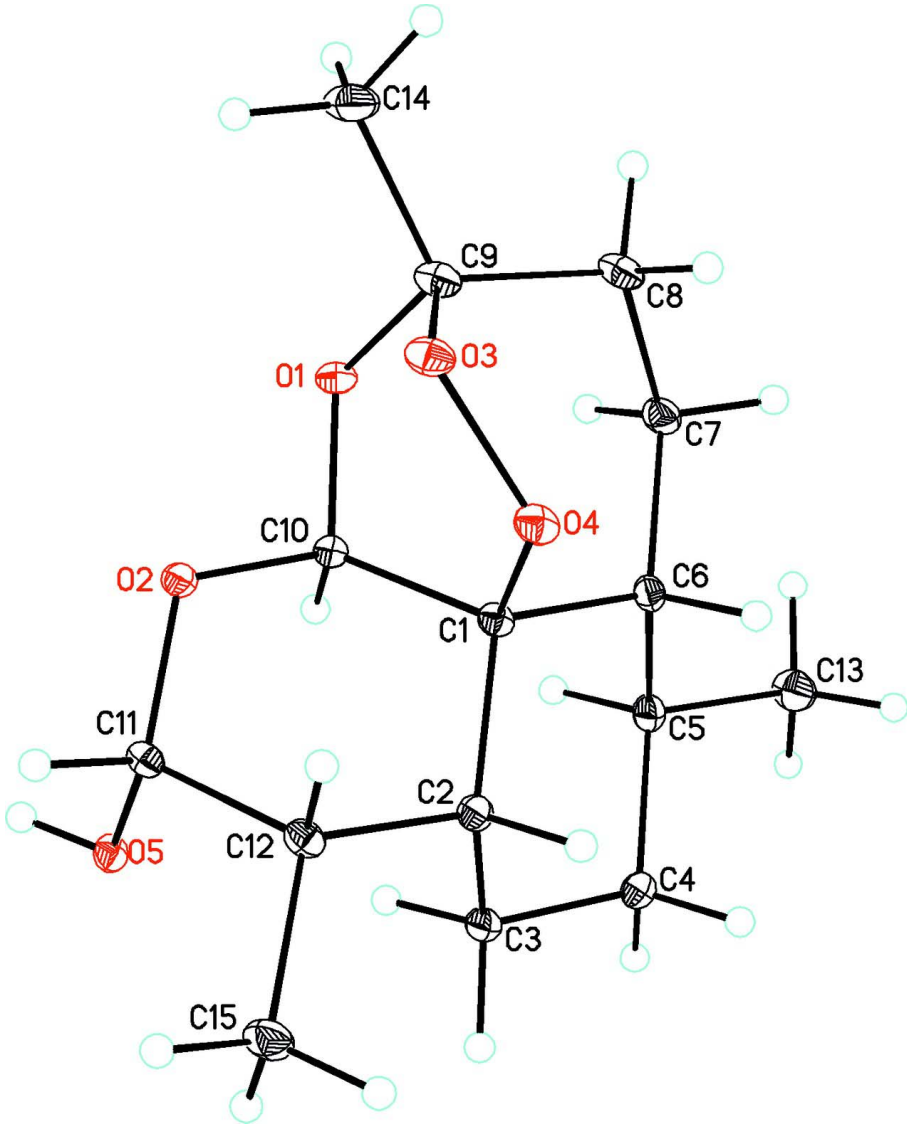



**Figure 1**

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

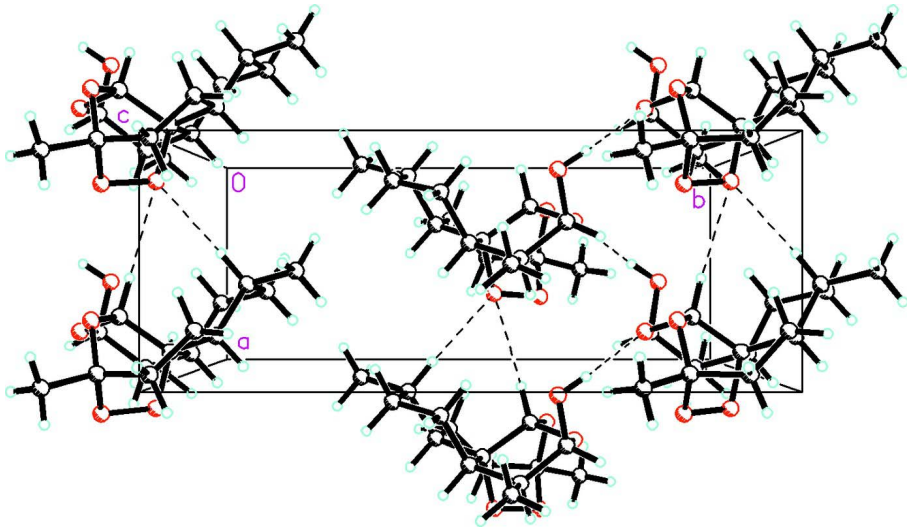



**Figure 2**

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
$V = 1485.8\ (3)$ Å$^3$
$Z = 4$
$F(000) = 616$
$D_x = 1.271$ 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 × 0.11 × 0.09 mm

*Data collection*

Bruker APEXII CCD area-detector diffractometer
Radiation source: fine-focus sealed tube
Graphite monochromator
$\varphi$ and $\omega$ 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 $I > 2\sigma(I)$
$R_{int} = 0.044$
$\theta_{max} = 30.5°$, $\theta_{min} = 1.8°$
$h = -5\rightarrow7$
$k = -19\rightarrow19$
$l = -26\rightarrow26$

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

$\Delta\rho_{max} = 0.37$ e Å$^{-3}$
$\Delta\rho_{min} = -0.22$ e Å$^{-3}$

*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 (Å$^2$)*

| | *x* | *y* | *z* | $U_{iso}$*/$U_{eq}$ |
|---|---|---|---|---|
| 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, º)*

| | | | |
|---|---|---|---|
| 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, º)*

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| O5—H5···O2$^{i}$ | 0.84 | 1.95 | 2.7799 (19) | 168 |
| C5—H5*A*···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*.