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α-Artemether

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Key indicators: single-crystal X-ray study; T = 103 K; mean σ(C–C) = 0.002 Å; R factor = 0.033; wR factor = 0.087; data-to-parameter ratio = 8.3.

The title compound, $C_{16}H_{26}O_5$, a derivative of the antimalaria compound artesunate, consists primarily of three substituted ring systems fused together. A cyclohexane ring (distorted chair configuration) fused to a tetrahydropyran group (normal chair) is adjacent to an oxacycloheptane unit containing an endoperoxide bridge, giving the molecule a unique three-dimensional arrangement.

Related literature

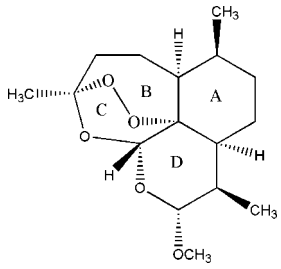
For crystal structures of similar compounds, see: Flippen-Anderson *et al.* (1989); Yue *et al.* (2006); Li *et al.* (2006); Karle & Lin (1995).

For 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 synthesis of artemisinin and its derivatives, see: Lui *et al.* (1979); Liu (1980); Robert *et al.* (2001).

For related literature and structure interpretation tools, see: Allen *et al.* (1987); Cremer & Pople (1975); Lisgarten *et al.* (1998); Qinghaosu Research Group (1980); Shen & Zhuang (1984); Wu & Li (1995).



Experimental

Crystal data

$C_{16}H_{26}O_5$
M_r = 298.37
Orthorhombic, $P2_12_12_1$
a = 10.315 (2) Å
b = 13.620 (3) Å
c = 11.073 (2) Å
V = 1555.6 (5) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 103 K
0.84 × 0.47 × 0.34 mm

Data collection

Bruker APEX II CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.926, T_{max} = 0.969
17053 measured reflections
2434 independent reflections
2305 reflections with $I > 2\sigma(I)$
R_{int} = 0.029

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.033
$wR(F^2)$ = 0.087
S = 1.12
2434 reflections
294 parameters
All H-atom parameters refined
$\Delta\rho_{max}$ = 0.38 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}

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: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *SHELXTL* (Bruker, 2000).

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Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: NC2038).

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.
Bruker (2000). *SHELXTL*. Version 6.10. Bruker AXS Inc., Madison, Wisconsin, USA.
Bruker (2006). *APEX2* (Version 2.0-2) and *SAINT*. Bruker AXS Inc., Madison, Wisconsin, USA.
Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
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, S.-H., Yue, Z.-Y., Gao, P. & Yan, P.-F. (2006). *Acta Cryst.* E**62**, o1898–o1900.
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.
Lisgarten, J., Potter, B. S., Bantuzeko, C. & Palmer, A. (1998). *J. Chem. Crystallogr.* **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.
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.

 doi:10.1107/S1600536807029108

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, 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.
Wu, Y.-L. & Li, Y. (1995). *Med. Chem. Res.* **5**, 569–586.
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.

supplementary materials

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α-Artemether

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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. Because of their activity against strains of the parasite that has become resistant to conventional chloroquine therapy and due to the ability due to its lipophilic structure to cross the blood brain barrier, they are particularly effective for the deadly cerebral malaria (Shen & Zhuang, 1984). With their shorter life time and decreasing activity, they are used in combination with other antimalarial drugs. However, some derivatives of artimisinine showed moderate cytotoxicity *in vitro*. The electronegativity and bulk of the substituents attached to the aryl group plays an insignificant role in cytotoxicity. The endoperoxide moiety present in some sesquiterpenoids 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 radicals which in turn produces oxidative damage to the parasites membrane. Artemisinin is hydrophobic in nature and is partitioned into the membrane of the plasmodium. In view of the importance of the title compound (I), $C_{23}H_{24}O_5$, as an antimalarial drug, this paper reports its crystal structure.

The six-membered cyclohexane ring (A, C1—C6) is a slightly distorted chair, with Cremer & Pople (1975) puckering parameters Q, θ and φ of 0.5395 (13) Å, 172.41 (14)° and 314.6 (10)°, respectively. The tetrahydropyran group (D, C1—C2—C12—C11—O2—C10) has a normal chair configuration with puckering parameters Q, θ and φ of 0.5512 (11) Å, 177.68 (11)° and 124 (3)°, 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 = 1.4745 (14) 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 0.7460 (11) Å, 94.05 (8)° and 276.11 (7)°, respectively. For an ideal twist-boat conformation, θ and φ are 90° and (60*n* + 30)°, respectively. This conformation is consistent with both 9,10-dehydrodeoxyartemisinin (Shu-Hui Li *et al.*,(2006) and dihydroartemisinin (Qinghaosu Research Group, 1980).

Experimental

α-Artemether ($C_{16}H_{26}O_5$) was obtained in the pure form from Strides Arco Labs, Mangalore, India. X-ray diffraction quality crystals were grown from acetone (m.p.: 361 K).

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) = 1.5U_{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 0.95–1.00 Å and U_{iso}(H) = 1.2U_{eq}(C). The amine H was idealized with an N—H distance of 0.86 Å and U_{iso}(H) = 1.2U_{eq}(N). Because no strong anomalous scattering atoms are present, the Friedel pairs were merged in the refinement.

Figures

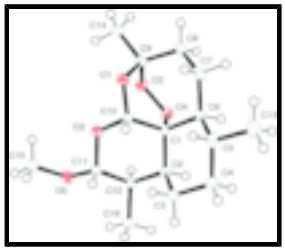

Fig. 1. *ORTEP* view of α-artemether, (I), showing the atom numbering scheme and 50% probability displacement ellipsoids.

α-Artemether

Crystal data

$C_{16}H_{26}O_5$	D_x = 1.274 Mg m^{-3}
M_r = 298.37	Mo $K\alpha$ radiation λ = 0.71073 Å
Orthorhombic, $P2_12_12_1$	Cell parameters from 7832 reflections
a = 10.315 (2) Å	θ = 2.4–29.3º
b = 13.620 (3) Å	μ = 0.09 mm^{-1}
c = 11.073 (2) Å	T = 103 K
V = 1555.6 (5) Å^3	Chunk, colorless
Z = 4	0.84 × 0.47 × 0.34 mm
F_{000} = 648	

Data collection

Bruker APEX II CCD area-detector diffractometer	2434 independent reflections
Radiation source: fine-focus sealed tube	2305 reflections with $I > 2\sigma(I)$
Monochromator: graphite	R_{int} = 0.029
T = 103 K	θ_{max} = 29.4º
φ and ω scans	θ_{min} = 2.4º
Absorption correction: multi-scan (SADABS; Sheldrick, 1996)	h = −14→14
T_{min} = 0.926, T_{max} = 0.969	k = −18→18
17053 measured reflections	l = −15→15

Refinement

Refinement on F^2	Secondary atom site location: difference Fourier map
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites

$R[F^2 > 2\sigma(F^2)] = 0.033$	All H-atom parameters refined
$wR(F^2) = 0.087$	$w = 1/[\sigma^2(F_o^2) + (0.0581P)^2 + 0.1127P]$ where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.12$	$(\Delta/\sigma)_{max} = 0.010$
2434 reflections	$\Delta\rho_{max} = 0.38$ e Å^{-3}
294 parameters	$\Delta\rho_{min} = -0.18$ e Å^{-3}
Primary atom site location: structure-invariant direct methods	Extinction correction: none

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	0.03875 (10)	0.94372 (8)	0.46788 (9)	0.0190 (2)
O2	0.06904 (10)	0.86438 (8)	0.29146 (9)	0.0185 (2)
O3	0.25631 (10)	0.96669 (7)	0.41839 (9)	0.0190 (2)
O4	0.29685 (9)	0.86551 (7)	0.44698 (9)	0.0178 (2)
O5	0.09732 (10)	0.80257 (9)	0.10277 (9)	0.0226 (2)
C1	0.18559 (12)	0.80176 (10)	0.46874 (12)	0.0153 (2)
C2	0.21488 (13)	0.70667 (10)	0.39781 (13)	0.0169 (3)
H2A	0.3047 (19)	0.6846 (15)	0.4181 (18)	0.023 (5)*
C3	0.12631 (15)	0.62201 (11)	0.43812 (14)	0.0217 (3)
H3A	0.032 (2)	0.6358 (17)	0.417 (2)	0.032 (5)*
H3B	0.154 (2)	0.5623 (17)	0.397 (2)	0.029 (5)*
C4	0.13763 (17)	0.60375 (12)	0.57331 (15)	0.0245 (3)
H4A	0.219 (3)	0.584 (2)	0.585 (2)	0.052 (8)*
H4B	0.081 (2)	0.5502 (16)	0.5970 (19)	0.025 (5)*
C5	0.10231 (14)	0.69445 (12)	0.64718 (14)	0.0221 (3)
H5A	0.008 (2)	0.7114 (16)	0.6347 (18)	0.026 (5)*
C6	0.18230 (13)	0.78510 (11)	0.60788 (12)	0.0179 (3)
H6A	0.274 (2)	0.7701 (16)	0.6266 (19)	0.029 (5)*
C7	0.14016 (15)	0.87730 (12)	0.67833 (13)	0.0216 (3)
H7A	0.049 (2)	0.8827 (16)	0.6777 (19)	0.026 (5)*
H7B	0.169 (2)	0.8672 (16)	0.762 (2)	0.029 (5)*
C8	0.19185 (15)	0.97536 (12)	0.63154 (13)	0.0216 (3)
H8A	0.282 (2)	0.9778 (17)	0.640 (2)	0.034 (5)*
H8B	0.1549 (19)	1.0310 (15)	0.6778 (18)	0.023 (5)*

C9	0.15630 (14)	0.99552 (11)	0.49904 (13)	0.0190 (3)
C10	0.06182 (13)	0.85073 (10)	0.41870 (13)	0.0160 (3)
H10A	−0.0143 (17)	0.8105 (14)	0.4358 (16)	0.013 (4)*
C11	0.08704 (13)	0.77595 (11)	0.22462 (12)	0.0174 (3)
H11A	0.0109 (18)	0.7349 (14)	0.2375 (15)	0.011 (4)*
C12	0.21300 (13)	0.72559 (10)	0.26021 (12)	0.0176 (3)
H12A	0.2810 (19)	0.7722 (13)	0.2414 (16)	0.015 (4)*
C13	0.1210 (2)	0.67245 (16)	0.78169 (16)	0.0353 (4)
H13A	0.074 (2)	0.6122 (19)	0.804 (2)	0.041 (6)*
H13B	0.088 (2)	0.7235 (19)	0.835 (2)	0.044 (7)*
H13C	0.208 (3)	0.664 (2)	0.800 (2)	0.054 (8)*
C14	0.13381 (18)	1.10288 (11)	0.46909 (15)	0.0247 (3)
H14A	0.128 (2)	1.1111 (14)	0.3787 (19)	0.023 (5)*
H14B	0.204 (2)	1.1413 (17)	0.499 (2)	0.033 (6)*
H14C	0.054 (2)	1.1227 (19)	0.508 (2)	0.040 (6)*
C15	−0.01422 (18)	0.85153 (13)	0.05639 (15)	0.0274 (3)
H15A	0.001 (2)	0.8640 (18)	−0.025 (2)	0.037 (6)*
H15B	−0.023 (2)	0.9115 (18)	0.093 (2)	0.036 (6)*
H15C	−0.093 (2)	0.8117 (19)	0.070 (2)	0.040 (6)*
C16	0.23452 (16)	0.63220 (12)	0.18597 (15)	0.0255 (3)
H16A	0.308 (2)	0.5962 (16)	0.214 (2)	0.034 (6)*
H16B	0.249 (2)	0.6487 (17)	0.102 (2)	0.036 (6)*
H16C	0.162 (2)	0.5883 (17)	0.194 (2)	0.032 (6)*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0164 (4)	0.0208 (5)	0.0198 (5)	0.0027 (4)	−0.0010 (4)	−0.0062 (4)
O2	0.0221 (5)	0.0187 (5)	0.0148 (4)	0.0025 (4)	−0.0020 (4)	−0.0035 (4)
O3	0.0203 (5)	0.0174 (5)	0.0195 (4)	−0.0003 (4)	0.0030 (4)	0.0000 (4)
O4	0.0128 (4)	0.0173 (4)	0.0233 (5)	−0.0006 (4)	0.0008 (4)	0.0007 (4)
O5	0.0253 (5)	0.0278 (5)	0.0146 (4)	0.0030 (4)	−0.0013 (4)	−0.0020 (4)
C1	0.0119 (5)	0.0184 (6)	0.0157 (6)	−0.0011 (5)	0.0001 (5)	−0.0007 (5)
C2	0.0142 (6)	0.0176 (6)	0.0189 (6)	0.0006 (5)	0.0007 (5)	−0.0013 (5)
C3	0.0236 (7)	0.0178 (6)	0.0238 (7)	−0.0032 (5)	0.0012 (6)	−0.0003 (5)
C4	0.0261 (7)	0.0221 (7)	0.0253 (7)	−0.0017 (6)	0.0003 (6)	0.0055 (6)
C5	0.0201 (6)	0.0266 (7)	0.0198 (6)	−0.0046 (6)	0.0014 (6)	0.0022 (6)
C6	0.0142 (6)	0.0244 (7)	0.0151 (6)	−0.0022 (5)	−0.0014 (5)	0.0009 (5)
C7	0.0203 (7)	0.0286 (7)	0.0158 (6)	−0.0024 (6)	0.0008 (5)	−0.0027 (5)
C8	0.0234 (7)	0.0249 (7)	0.0165 (6)	−0.0031 (6)	−0.0017 (6)	−0.0046 (5)
C9	0.0187 (6)	0.0203 (6)	0.0181 (6)	−0.0007 (5)	0.0000 (5)	−0.0043 (5)
C10	0.0131 (5)	0.0190 (6)	0.0158 (6)	0.0011 (5)	−0.0007 (5)	−0.0032 (5)
C11	0.0184 (6)	0.0184 (6)	0.0152 (6)	0.0009 (5)	−0.0003 (5)	−0.0037 (5)
C12	0.0154 (6)	0.0192 (6)	0.0182 (6)	0.0005 (5)	0.0022 (5)	−0.0033 (5)
C13	0.0449 (11)	0.0397 (10)	0.0215 (7)	−0.0108 (8)	0.0022 (8)	0.0063 (7)
C14	0.0302 (8)	0.0199 (7)	0.0240 (7)	0.0018 (6)	−0.0002 (6)	−0.0043 (6)
C15	0.0338 (8)	0.0284 (8)	0.0200 (7)	0.0081 (7)	−0.0053 (7)	−0.0011 (6)
C16	0.0272 (7)	0.0245 (7)	0.0248 (7)	0.0052 (6)	0.0035 (6)	−0.0072 (6)

Geometric parameters (Å, °)

O1—C10	1.3990 (17)	C6—H6A	0.99 (2)
O1—C9	1.4447 (17)	C7—C8	1.529 (2)
O2—C10	1.4231 (16)	C7—H7A	0.94 (2)
O2—C11	1.4258 (17)	C7—H7B	0.98 (2)
O3—C9	1.4198 (17)	C8—C9	1.537 (2)
O3—O4	1.4745 (14)	C8—H8A	0.94 (2)
O4—C1	1.4591 (16)	C8—H8B	0.99 (2)
O5—C11	1.4011 (17)	C9—C14	1.517 (2)
O5—C15	1.426 (2)	C10—H10A	0.976 (18)
C1—C10	1.5434 (18)	C11—C12	1.5211 (19)
C1—C2	1.5445 (19)	C11—H11A	0.974 (19)
C1—C6	1.5576 (19)	C12—C16	1.531 (2)
C2—C3	1.537 (2)	C12—H12A	0.969 (19)
C2—C12	1.5454 (19)	C13—H13A	0.98 (3)
C2—H2A	1.00 (2)	C13—H13B	0.97 (3)
C3—C4	1.522 (2)	C13—H13C	0.92 (3)
C3—H3A	1.02 (2)	C14—H14A	1.01 (2)
C3—H3B	0.97 (2)	C14—H14B	0.95 (2)
C4—C5	1.526 (2)	C14—H14C	0.97 (3)
C4—H4A	0.89 (3)	C15—H15A	0.93 (3)
C4—H4B	0.97 (2)	C15—H15B	0.92 (2)
C5—C13	1.531 (2)	C15—H15C	0.99 (2)
C5—C6	1.547 (2)	C16—H16A	0.96 (2)
C5—H5A	1.01 (2)	C16—H16B	0.97 (2)
C6—C7	1.541 (2)	C16—H16C	0.97 (2)
C10—O1—C9	113.10 (10)	C9—C8—H8B	105.4 (11)
C10—O2—C11	114.23 (11)	H8A—C8—H8B	107.7 (19)
C9—O3—O4	109.24 (10)	O3—C9—O1	108.94 (11)
C1—O4—O3	111.62 (9)	O3—C9—C14	103.90 (12)
C11—O5—C15	114.01 (12)	O1—C9—C14	106.87 (12)
O4—C1—C10	109.52 (11)	O3—C9—C8	112.19 (12)
O4—C1—C2	105.14 (10)	O1—C9—C8	109.93 (12)
C10—C1—C2	109.97 (11)	C14—C9—C8	114.66 (12)
O4—C1—C6	105.50 (10)	O1—C10—O2	106.03 (11)
C10—C1—C6	113.58 (11)	O1—C10—C1	113.09 (11)
C2—C1—C6	112.65 (11)	O2—C10—C1	111.63 (10)
C3—C2—C12	113.82 (11)	O1—C10—H10A	107.2 (11)
C3—C2—C1	111.41 (11)	O2—C10—H10A	107.9 (10)
C12—C2—C1	111.05 (11)	C1—C10—H10A	110.7 (11)
C3—C2—H2A	105.1 (12)	O5—C11—O2	106.93 (11)
C12—C2—H2A	106.5 (12)	O5—C11—C12	107.55 (11)
C1—C2—H2A	108.6 (12)	O2—C11—C12	110.95 (11)
C4—C3—C2	111.26 (12)	O5—C11—H11A	110.5 (10)
C4—C3—H3A	109.5 (13)	O2—C11—H11A	107.6 (10)
C2—C3—H3A	111.2 (13)	C12—C11—H11A	113.1 (11)
C4—C3—H3B	107.2 (13)	C11—C12—C16	111.06 (12)

C2—C3—H3B	108.6 (14)	C11—C12—C2	109.96 (11)
H3A—C3—H3B	109.0 (18)	C16—C12—C2	112.90 (12)
C3—C4—C5	112.13 (13)	C11—C12—H12A	105.5 (11)
C3—C4—H4A	105.5 (18)	C16—C12—H12A	108.9 (11)
C5—C4—H4A	112.9 (18)	C2—C12—H12A	108.2 (10)
C3—C4—H4B	110.0 (12)	C5—C13—H13A	110.0 (15)
C5—C4—H4B	108.6 (13)	C5—C13—H13B	113.9 (15)
H4A—C4—H4B	108 (2)	H13A—C13—H13B	106 (2)
C4—C5—C13	109.45 (15)	C5—C13—H13C	111.1 (17)
C4—C5—C6	111.58 (12)	H13A—C13—H13C	109 (2)
C13—C5—C6	111.26 (14)	H13B—C13—H13C	107 (2)
C4—C5—H5A	110.0 (12)	C9—C14—H14A	109.5 (11)
C13—C5—H5A	107.4 (12)	C9—C14—H14B	109.8 (14)
C6—C5—H5A	107.0 (12)	H14A—C14—H14B	109.2 (19)
C7—C6—C5	110.94 (12)	C9—C14—H14C	107.5 (15)
C7—C6—C1	112.84 (12)	H14A—C14—H14C	111 (2)
C5—C6—C1	113.96 (12)	H14B—C14—H14C	110 (2)
C7—C6—H6A	109.3 (13)	O5—C15—H15A	107.2 (15)
C5—C6—H6A	106.6 (13)	O5—C15—H15B	109.5 (15)
C1—C6—H6A	102.5 (12)	H15A—C15—H15B	107 (2)
C8—C7—C6	116.24 (12)	O5—C15—H15C	110.8 (14)
C8—C7—H7A	106.1 (13)	H15A—C15—H15C	113 (2)
C6—C7—H7A	109.9 (13)	H15B—C15—H15C	110 (2)
C8—C7—H7B	109.7 (13)	C12—C16—H16A	111.5 (14)
C6—C7—H7B	106.2 (13)	C12—C16—H16B	110.2 (14)
H7A—C7—H7B	108.5 (18)	H16A—C16—H16B	108 (2)
C7—C8—C9	113.35 (12)	C12—C16—H16C	110.5 (14)
C7—C8—H8A	110.1 (15)	H16A—C16—H16C	105.7 (17)
C9—C8—H8A	109.1 (15)	H16B—C16—H16C	111 (2)
C7—C8—H8B	111.0 (11)		
C9—O3—O4—C1	43.92 (13)	O4—O3—C9—C8	49.83 (14)
O3—O4—C1—C10	16.81 (13)	C10—O1—C9—O3	30.95 (16)
O3—O4—C1—C2	134.93 (10)	C10—O1—C9—C14	142.63 (12)
O3—O4—C1—C6	−105.80 (11)	C10—O1—C9—C8	−92.36 (13)
O4—C1—C2—C3	164.58 (11)	C7—C8—C9—O3	−95.08 (15)
C10—C1—C2—C3	−77.60 (14)	C7—C8—C9—O1	26.31 (17)
C6—C1—C2—C3	50.20 (15)	C7—C8—C9—C14	146.71 (14)
O4—C1—C2—C12	−67.41 (13)	C9—O1—C10—O2	−91.32 (12)
C10—C1—C2—C12	50.41 (14)	C9—O1—C10—C1	31.32 (15)
C6—C1—C2—C12	178.20 (11)	C11—O2—C10—O1	−177.53 (10)
C12—C2—C3—C4	177.13 (12)	C11—O2—C10—C1	58.91 (14)
C1—C2—C3—C4	−56.37 (16)	O4—C1—C10—O1	−57.04 (14)
C2—C3—C4—C5	58.87 (17)	C2—C1—C10—O1	−172.11 (11)
C3—C4—C5—C13	−177.72 (14)	C6—C1—C10—O1	60.61 (15)
C3—C4—C5—C6	−54.13 (18)	O4—C1—C10—O2	62.43 (14)
C4—C5—C6—C7	176.82 (12)	C2—C1—C10—O2	−52.64 (14)
C13—C5—C6—C7	−60.62 (18)	C6—C1—C10—O2	−179.92 (11)
C4—C5—C6—C1	48.15 (17)	C15—O5—C11—O2	−60.39 (15)
C13—C5—C6—C1	170.71 (14)	C15—O5—C11—C12	−179.62 (12)

O4—C1—C6—C7	71.41 (14)	C10—O2—C11—O5	−177.65 (11)
C10—C1—C6—C7	−48.55 (15)	C10—O2—C11—C12	−60.64 (14)
C2—C1—C6—C7	−174.43 (11)	O5—C11—C12—C16	−61.73 (15)
O4—C1—C6—C5	−160.89 (11)	O2—C11—C12—C16	−178.35 (12)
C10—C1—C6—C5	79.14 (15)	O5—C11—C12—C2	172.58 (11)
C2—C1—C6—C5	−46.73 (16)	O2—C11—C12—C2	55.96 (15)
C5—C6—C7—C8	−168.34 (12)	C3—C2—C12—C11	74.34 (14)
C1—C6—C7—C8	−39.08 (17)	C1—C2—C12—C11	−52.34 (15)
C6—C7—C8—C9	57.24 (17)	C3—C2—C12—C16	−50.30 (17)
O4—O3—C9—O1	−72.13 (13)	C1—C2—C12—C16	−176.99 (11)
O4—O3—C9—C14	174.24 (10)		

Fig. 1