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5-{[(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-Trimethylperhydro-3,12-epoxy-1,2-dioxepino[4,3-*i*]isochromen-10-yl]oxymethyl}benzene-1,3-diol

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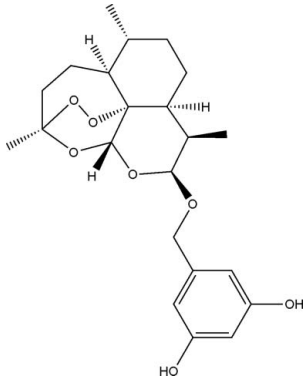
Key indicators: single-crystal X-ray study; T = 100 K; mean σ(C–C) = 0.002 Å; R factor = 0.026; wR factor = 0.069; data-to-parameter ratio = 13.6.

The title compound, $C_{22}H_{30}O_7$, is a fused five-ring system that is of interest for its anticancer and antimalarial activity. The six-membered C_6 and C_5O rings display chair conformations. The six-membered C_3O_3 ring containing the ether and peroxy functionalities has a distorted boat conformation, with a C—O—O—C torsion angle of 42.6 (1)° for the peroxy group. The seven-membered C_6O ring has a distorted boat-type conformation, while the seven-membered C_5O_2 ring has a very distorted chair-type conformation. The structure contains intermolecular O—H···O and O—H···(O,O) bonds that link the molecules into sheets parallel to the (100) planes.

Related literature

For the crystallographic analysis of artemisinin, see: Lisgarten *et al.* (1998). For antimalarial and antitumor activity of artemisinin, see Beekman *et al.* (1997, 1998); Pu *et al.* (1995); Zheng (1994).



Experimental

Crystal data

$C_{22}H_{30}O_7$
M_r = 406.46
Monoclinic, $P2_1$
a = 10.3088 (2) Å
b = 10.2844 (2) Å
c = 10.3218 (3) Å
β = 113.14 (1)°
V = 1006.29 (9) Å^3
Z = 2
Cu $K\alpha$ radiation
μ = 0.82 mm^{-1}
T = 100 (2) K
0.23 × 0.15 × 0.08 mm

Data collection

Bruker APEXII CCD diffractometer
Absorption correction: none
15943 measured reflections
3623 independent reflections
3604 reflections with $I > 2\sigma(I)$
R_{int} = 0.019

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.026
$wR(F^2)$ = 0.069
S = 1.08
3623 reflections
267 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.25 e Å^{-3}
$\Delta\rho_{min}$ = −0.22 e Å^{-3}
Absolute structure: Flack (1983), 1623 Friedel pairs
Flack parameter: 0.04 (10)

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

D—H···A	D—H	H···A	D···A	D—H···A
O6—H6···O7^{i}	0.82	1.99	2.7279 (14)	150
O7—H7···O2^{ii}	0.82	2.18	2.8409 (13)	138
O7—H7···O4^{ii}	0.82	2.22	2.9269 (13)	144

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

Data collection: *APEX2* (Bruker, 2005); cell refinement: *SAINT* (Bruker, 2005); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *SHELXTL* (Sheldrick, 2008); software used to prepare material for publication: *ORTEP-3 for Windows* (Farrugia, 1997).

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Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: BI2336).

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supplementary materials

Acta Cryst. (2009). E**65**, o358-o359 [**doi:10.1107/S1600536809002050**]

5-{[(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-Trimethylperhydro-3,12-epoxy-1,2-dioxepino[4,3-*i*]isochromen-10-yl]oxymethyl}benzene-1,3-diol

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Comment

The title compound, a new dihydroartemisinin acetal monomeric derivative, has been prepared by reacting dihydroartemisinin with 1,3-dihydroxy-5-hydroxymethyl benzene using $BF_3.Et_2O$ as the coupling catalyst. The compound exhibits anti-malarial, anti-cancer, and antiinfective activity.

Experimental

To a stirred solution of dihydroartemisinin (120 mg, 0.42 mmol) in dry ether (40 ml) was added dry 3,5-dihydroxybenzyl alcohol (28 mg), followed by $BF_3.OEt_2$ (32 ml). Stirring was continued for two and half hours, after which time the reaction was quenched by addition of 10 ml of 2% aqueous solution of $NaHCO_3$. The reaction mixture was then diluted with ether (50 ml), and transferred to a separatory funnel and extracted with ether (3 × 30 ml). The ether fractions were pooled, washed with water, and dried over Na_2SO_4. Removal of ether under reduced pressure left an oily crude product, which was purified over Si gel column using a gradient of EtOAc in hexanes (15% to 26%) to yield a colorless solid (35 mg, 28%).

Refinement

All H atoms were visible in difference maps, but were placed geometrically and treated as riding atoms for refinement, with the following constraints: C—H = 0.93 Å, U_{iso}(H) = 1.2U_{eq}(C) for Csp^2, C—H = 0.98 Å, U_{iso}(H) = 1.2U_{eq}(C) for CH, C—H = 0.97 Å, U_{iso}(H) = 1.2U_{eq}(C) for CH_2, C—H = 0.96 Å, U_{iso}(H) = 1.5U_{eq}(C) CH_3, O—H = 0.82 Å, U_{iso}(H) = 1.5U_{eq}(O) for OH.

Figures

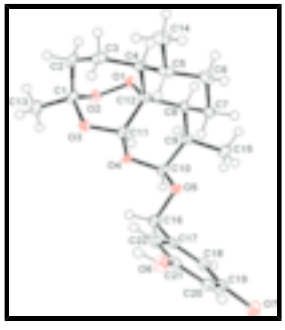


Fig. 1. Molecular structure of the title compound with displacement ellipsoids drawn at the 50% probability level for non-H atoms.

5-{[(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*, 12a*R*)-3,6,9-Trimethylperhydro-3,12-epoxy-1,2-dioxepino[4,3- *i*]isochromen-10-yl]oxymethyl}benzene-1,3-diol

Crystal data

$C_{22}H_{30}O_7$	F_{000} = 436
M_r = 406.46	D_x = 1.341 Mg m^{-3}
Monoclinic, $P2_1$	Cu $K\alpha$ radiation λ = 1.54178 Å
Hall symbol: P 2yb	Cell parameters from 9920 reflections
a = 10.3088 (2) Å	θ = 4.3–68.9º
b = 10.2844 (2) Å	μ = 0.82 mm^{-1}
c = 10.3218 (3) Å	T = 100 (2) K
β = 113.14 (1)º	Plate, colourless
V = 1006.29 (9) Å^3	0.23 × 0.15 × 0.08 mm
Z = 2	

Data collection

Bruker APEXII CCD diffractometer	3604 reflections with $I > 2\sigma(I)$
Monochromator: graphite	R_{int} = 0.019
T = 100(2) K	θ_{max} = 69.3º
φ and ω scans	θ_{min} = 4.7º
Absorption correction: none	h = −12→12
15943 measured reflections	k = −11→12
3623 independent reflections	l = −12→12

Refinement

Refinement on F^2	Hydrogen site location: inferred from neighbouring sites
Least-squares matrix: full	H-atom parameters constrained
$R[F^2 > 2\sigma(F^2)]$ = 0.026	$w = 1/[\sigma^2(F_o^2) + (0.0416P)^2 + 0.199P]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2)$ = 0.069	$(\Delta/\sigma)_{max} < 0.001$
S = 1.08	$\Delta\rho_{max}$ = 0.25 e Å^{-3}
3623 reflections	$\Delta\rho_{min}$ = −0.22 e Å^{-3}
267 parameters	Extinction correction: none
1 restraint	Absolute structure: Flack (1983), 1623 Friedel pairs
Primary atom site location: structure-invariant direct methods	Flack parameter: 0.04 (10)
Secondary atom site location: difference Fourier map	

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}
O4	0.24620 (9)	0.53498 (9)	0.32197 (9)	0.01671 (19)
O1	−0.02356 (10)	0.56559 (9)	0.09293 (9)	0.0177 (2)
O6	0.41598 (11)	0.67491 (10)	1.04175 (10)	0.0238 (2)
H6	0.3735	0.6057	1.0194	0.036*
O5	0.34731 (9)	0.70855 (9)	0.47383 (9)	0.01720 (19)
O3	0.07779 (9)	0.40591 (9)	0.33999 (9)	0.0184 (2)
O7	0.71639 (10)	0.95263 (9)	0.93260 (10)	0.0213 (2)
H7	0.7608	0.9578	0.8820	0.032*
O2	0.02421 (10)	0.42912 (9)	0.10142 (9)	0.0191 (2)
C18	0.58553 (13)	0.79300 (13)	0.75672 (13)	0.0177 (3)
H18	0.6249	0.8215	0.6946	0.021*
C1	−0.01197 (14)	0.36064 (14)	0.20186 (14)	0.0204 (3)
C20	0.56095 (14)	0.81251 (13)	0.97930 (13)	0.0178 (3)
H20	0.5828	0.8554	1.0646	0.021*
C10	0.31061 (13)	0.66001 (13)	0.33627 (13)	0.0172 (3)
H10	0.3973	0.6505	0.3195	0.021*
C8	0.06357 (14)	0.75832 (13)	0.22778 (13)	0.0166 (3)
H8	0.0018	0.7965	0.1376	0.020*
C4	−0.13890 (13)	0.62313 (15)	0.24865 (13)	0.0193 (3)
H4	−0.2079	0.6579	0.1599	0.023*
C11	0.11686 (13)	0.53590 (13)	0.34304 (13)	0.0158 (3)
H11	0.1353	0.5713	0.4368	0.019*
C12	0.00544 (13)	0.62013 (13)	0.23280 (13)	0.0161 (3)
C22	0.43232 (13)	0.64640 (13)	0.81424 (14)	0.0184 (3)
H22	0.3703	0.5763	0.7905	0.022*
C7	0.05456 (14)	0.84730 (14)	0.34327 (14)	0.0198 (3)
H7A	0.1191	0.8161	0.4346	0.024*
H7B	0.0834	0.9345	0.3305	0.024*
C5	−0.13896 (13)	0.71641 (15)	0.36552 (13)	0.0221 (3)
H5	−0.0685	0.6848	0.4551	0.026*
C15	0.28159 (15)	0.88607 (14)	0.23539 (15)	0.0233 (3)
H15A	0.3043	0.9221	0.3276	0.035*
H15B	0.2171	0.9428	0.1660	0.035*

H15C	0.3662	0.8771	0.2183	0.035*
C14	−0.28261 (14)	0.71858 (18)	0.37886 (15)	0.0297 (3)
H14A	−0.2827	0.7861	0.4430	0.044*
H14B	−0.2986	0.6362	0.4137	0.044*
H14C	−0.3561	0.7348	0.2881	0.044*
C17	0.48996 (13)	0.69005 (13)	0.72052 (13)	0.0174 (3)
C6	−0.09417 (15)	0.85158 (15)	0.34012 (14)	0.0231 (3)
H6A	−0.0971	0.9106	0.4123	0.028*
H6B	−0.1590	0.8836	0.2493	0.028*
C16	0.44908 (14)	0.62693 (14)	0.57838 (14)	0.0200 (3)
H16A	0.5318	0.6160	0.5566	0.024*
H16B	0.4087	0.5418	0.5788	0.024*
C9	0.21337 (13)	0.75281 (13)	0.22646 (13)	0.0178 (3)
H9	0.2017	0.7167	0.1347	0.021*
C21	0.46825 (13)	0.70848 (14)	0.94374 (13)	0.0186 (3)
C19	0.62111 (13)	0.85242 (13)	0.88701 (14)	0.0173 (3)
C3	−0.19196 (14)	0.48755 (15)	0.26635 (14)	0.0237 (3)
H3A	−0.1469	0.4632	0.3649	0.028*
H3B	−0.2925	0.4932	0.2432	0.028*
C2	−0.16688 (14)	0.37942 (15)	0.17856 (14)	0.0234 (3)
H2A	−0.2207	0.3982	0.0797	0.028*
H2B	−0.2024	0.2986	0.2004	0.028*
C13	0.02745 (16)	0.22097 (15)	0.19089 (15)	0.0262 (3)
H13A	−0.0393	0.1835	0.1055	0.039*
H13B	0.0267	0.1729	0.2703	0.039*
H13C	0.1201	0.2176	0.1899	0.039*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O4	0.0160 (4)	0.0163 (5)	0.0179 (4)	−0.0009 (3)	0.0068 (4)	−0.0024 (3)
O1	0.0225 (5)	0.0173 (5)	0.0130 (4)	−0.0007 (4)	0.0067 (4)	−0.0007 (4)
O6	0.0285 (5)	0.0254 (5)	0.0221 (5)	−0.0052 (4)	0.0149 (4)	0.0005 (4)
O5	0.0169 (4)	0.0187 (5)	0.0140 (4)	0.0006 (4)	0.0039 (3)	−0.0015 (3)
O3	0.0215 (5)	0.0181 (5)	0.0140 (4)	−0.0030 (4)	0.0051 (4)	−0.0005 (3)
O7	0.0232 (5)	0.0217 (5)	0.0232 (5)	−0.0058 (4)	0.0138 (4)	−0.0047 (4)
O2	0.0234 (5)	0.0183 (5)	0.0170 (4)	−0.0016 (4)	0.0094 (4)	−0.0024 (4)
C18	0.0191 (6)	0.0192 (7)	0.0165 (6)	0.0030 (5)	0.0088 (5)	0.0022 (5)
C1	0.0246 (7)	0.0215 (7)	0.0146 (6)	−0.0075 (5)	0.0072 (5)	−0.0028 (5)
C20	0.0185 (6)	0.0203 (7)	0.0145 (6)	0.0029 (5)	0.0063 (5)	−0.0002 (5)
C10	0.0165 (6)	0.0197 (7)	0.0162 (6)	−0.0034 (5)	0.0074 (5)	−0.0032 (5)
C8	0.0192 (6)	0.0167 (7)	0.0134 (6)	0.0021 (5)	0.0060 (5)	0.0014 (5)
C4	0.0149 (6)	0.0279 (7)	0.0146 (6)	0.0008 (5)	0.0052 (5)	0.0002 (5)
C11	0.0177 (6)	0.0158 (7)	0.0149 (6)	−0.0018 (5)	0.0075 (5)	−0.0022 (5)
C12	0.0176 (6)	0.0202 (7)	0.0109 (6)	−0.0015 (5)	0.0060 (5)	−0.0016 (5)
C22	0.0147 (6)	0.0170 (7)	0.0220 (6)	−0.0001 (5)	0.0055 (5)	0.0005 (5)
C7	0.0229 (7)	0.0170 (7)	0.0185 (6)	0.0017 (5)	0.0072 (5)	−0.0011 (5)
C5	0.0178 (6)	0.0329 (8)	0.0153 (6)	0.0039 (6)	0.0063 (5)	0.0005 (6)

C15	0.0253 (7)	0.0239 (8)	0.0213 (7)	−0.0053 (6)	0.0097 (6)	−0.0003 (6)
C14	0.0222 (7)	0.0464 (10)	0.0225 (7)	0.0053 (7)	0.0112 (6)	−0.0023 (7)
C17	0.0150 (5)	0.0182 (7)	0.0174 (6)	0.0050 (5)	0.0045 (5)	0.0015 (5)
C6	0.0249 (7)	0.0269 (8)	0.0177 (6)	0.0080 (6)	0.0086 (5)	−0.0015 (6)
C16	0.0190 (6)	0.0200 (7)	0.0190 (6)	0.0032 (5)	0.0053 (5)	0.0005 (5)
C9	0.0195 (6)	0.0209 (7)	0.0139 (6)	−0.0036 (5)	0.0075 (5)	−0.0016 (5)
C21	0.0159 (6)	0.0215 (7)	0.0189 (6)	0.0038 (5)	0.0075 (5)	0.0044 (5)
C19	0.0147 (6)	0.0164 (7)	0.0199 (6)	0.0019 (5)	0.0058 (5)	0.0023 (5)
C3	0.0178 (6)	0.0346 (8)	0.0196 (6)	−0.0045 (6)	0.0082 (5)	0.0006 (6)
C2	0.0227 (7)	0.0279 (8)	0.0190 (6)	−0.0101 (6)	0.0075 (5)	−0.0011 (5)
C13	0.0335 (7)	0.0225 (8)	0.0213 (7)	−0.0056 (6)	0.0094 (6)	−0.0031 (6)

Geometric parameters (Å, °)

O4—C10	1.4280 (16)	C11—H11	0.980
O4—C11	1.4328 (15)	C22—C17	1.3936 (19)
O1—C12	1.4660 (15)	C22—C21	1.3937 (19)
O1—O2	1.4785 (13)	C22—H22	0.930
O6—C21	1.3644 (16)	C7—C6	1.5214 (19)
O6—H6	0.820	C7—H7A	0.970
O5—C10	1.4092 (15)	C7—H7B	0.970
O5—C16	1.4423 (16)	C5—C6	1.520 (2)
O3—C11	1.3930 (17)	C5—C14	1.5403 (17)
O3—C1	1.4384 (15)	C5—H5	0.980
O7—C19	1.3730 (16)	C15—C9	1.5266 (19)
O7—H7	0.820	C15—H15A	0.960
O2—C1	1.4191 (16)	C15—H15B	0.960
C18—C19	1.3888 (18)	C15—H15C	0.960
C18—C17	1.3936 (19)	C14—H14A	0.960
C18—H18	0.930	C14—H14B	0.960
C1—C13	1.509 (2)	C14—H14C	0.960
C1—C2	1.5308 (19)	C17—C16	1.5052 (18)
C20—C21	1.3845 (19)	C6—H6A	0.970
C20—C19	1.3874 (18)	C6—H6B	0.970
C20—H20	0.930	C16—H16A	0.970
C10—C9	1.5190 (18)	C16—H16B	0.970
C10—H10	0.980	C9—H9	0.980
C8—C7	1.5344 (18)	C3—C2	1.520 (2)
C8—C9	1.5506 (17)	C3—H3A	0.970
C8—C12	1.5512 (18)	C3—H3B	0.970
C8—H8	0.980	C2—H2A	0.970
C4—C3	1.535 (2)	C2—H2B	0.970
C4—C5	1.5415 (19)	C13—H13A	0.960
C4—C12	1.5598 (16)	C13—H13B	0.960
C4—H4	0.980	C13—H13C	0.960
C11—C12	1.5289 (17)		
C10—O4—C11	113.64 (9)	C6—C5—H5	107.7
C12—O1—O2	111.75 (9)	C14—C5—H5	107.7
C21—O6—H6	109.5	C4—C5—H5	107.7

C10—O5—C16	112.09 (10)	C9—C15—H15A	109.5
C11—O3—C1	113.63 (10)	C9—C15—H15B	109.5
C19—O7—H7	109.5	H15A—C15—H15B	109.5
C1—O2—O1	109.72 (9)	C9—C15—H15C	109.5
C19—C18—C17	118.94 (12)	H15A—C15—H15C	109.5
C19—C18—H18	120.5	H15B—C15—H15C	109.5
C17—C18—H18	120.5	C5—C14—H14A	109.5
O2—C1—O3	108.18 (10)	C5—C14—H14B	109.5
O2—C1—C13	105.17 (11)	H14A—C14—H14B	109.5
O3—C1—C13	107.17 (11)	C5—C14—H14C	109.5
O2—C1—C2	112.33 (11)	H14A—C14—H14C	109.5
O3—C1—C2	109.88 (10)	H14B—C14—H14C	109.5
C13—C1—C2	113.79 (11)	C22—C17—C18	120.53 (12)
C21—C20—C19	119.65 (12)	C22—C17—C16	120.35 (12)
C21—C20—H20	120.2	C18—C17—C16	119.12 (12)
C19—C20—H20	120.2	C5—C6—C7	109.99 (11)
O5—C10—O4	110.67 (10)	C5—C6—H6A	109.7
O5—C10—C9	111.50 (10)	C7—C6—H6A	109.7
O4—C10—C9	110.18 (10)	C5—C6—H6B	109.7
O5—C10—H10	108.1	C7—C6—H6B	109.7
O4—C10—H10	108.1	H6A—C6—H6B	108.2
C9—C10—H10	108.1	O5—C16—C17	108.73 (10)
C7—C8—C9	113.15 (11)	O5—C16—H16A	109.9
C7—C8—C12	112.23 (10)	C17—C16—H16A	109.9
C9—C8—C12	111.46 (10)	O5—C16—H16B	109.9
C7—C8—H8	106.5	C17—C16—H16B	109.9
C9—C8—H8	106.5	H16A—C16—H16B	108.3
C12—C8—H8	106.5	C10—C9—C15	111.45 (11)
C3—C4—C5	111.25 (11)	C10—C9—C8	112.57 (10)
C3—C4—C12	113.19 (11)	C15—C9—C8	113.79 (11)
C5—C4—C12	112.84 (10)	C10—C9—H9	106.1
C3—C4—H4	106.3	C15—C9—H9	106.1
C5—C4—H4	106.3	C8—C9—H9	106.1
C12—C4—H4	106.3	O6—C21—C20	115.57 (12)
O3—C11—O4	105.56 (10)	O6—C21—C22	124.17 (12)
O3—C11—C12	113.63 (10)	C20—C21—C22	120.26 (12)
O4—C11—C12	111.25 (10)	O7—C19—C20	116.06 (11)
O3—C11—H11	108.8	O7—C19—C18	122.91 (11)
O4—C11—H11	108.8	C20—C19—C18	121.03 (12)
C12—C11—H11	108.8	C2—C3—C4	116.22 (11)
O1—C12—C11	108.60 (10)	C2—C3—H3A	108.2
O1—C12—C8	104.45 (9)	C4—C3—H3A	108.2
C11—C12—C8	110.91 (10)	C2—C3—H3B	108.2
O1—C12—C4	106.09 (10)	C4—C3—H3B	108.2
C11—C12—C4	113.69 (10)	H3A—C3—H3B	107.4
C8—C12—C4	112.48 (11)	C3—C2—C1	114.21 (11)
C17—C22—C21	119.54 (12)	C3—C2—H2A	108.7
C17—C22—H22	120.2	C1—C2—H2A	108.7
C21—C22—H22	120.2	C3—C2—H2B	108.7

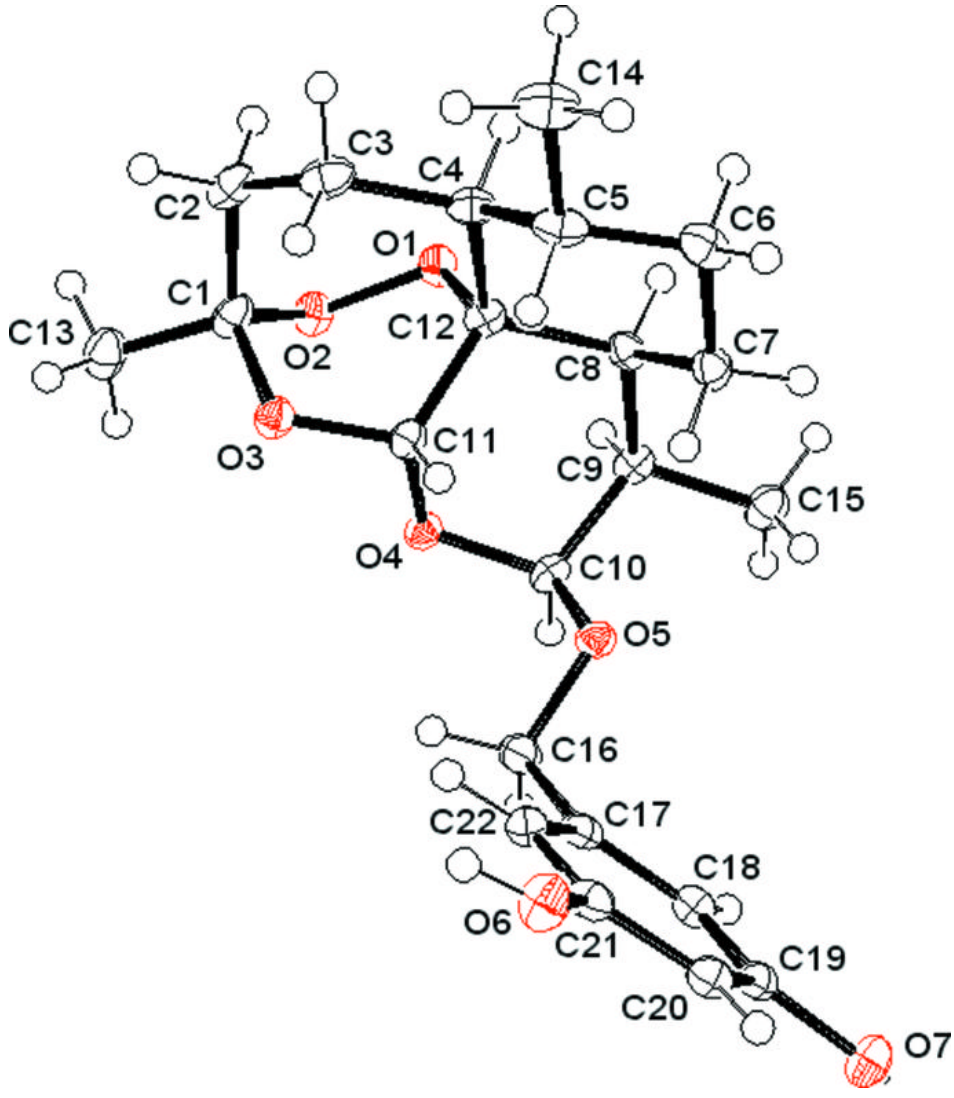
C6—C7—C8	111.64 (11)	C1—C2—H2B	108.7
C6—C7—H7A	109.3	H2A—C2—H2B	107.6
C8—C7—H7A	109.3	C1—C13—H13A	109.5
C6—C7—H7B	109.3	C1—C13—H13B	109.5
C8—C7—H7B	109.3	H13A—C13—H13B	109.5
H7A—C7—H7B	108.0	C1—C13—H13C	109.5
C6—C5—C14	111.72 (12)	H13A—C13—H13C	109.5
C6—C5—C4	109.92 (11)	H13B—C13—H13C	109.5
C14—C5—C4	112.02 (11)		

Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O6—H6···O7^{i}	0.82	1.99	2.7279 (14)	150
O7—H7···O2^{ii}	0.82	2.18	2.8409 (13)	138
O7—H7···O4^{ii}	0.82	2.22	2.9269 (13)	144

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

Fig. 1


C14
C3
C4
C2
C5
C6
O1
C1
C13
O2
C12
C8
C7
O3
C11
C9
C15
O4
C10
O5
C16
C22
C17
C18
O6
C21
C19
C20
O7