

12-2015

Crystal Structure of (*E*)-13-(pyrimidin-5-yl)parthenolide

Shobanbabu Bommagani
University of Arkansas for Medical Sciences

Narsimha Reddy Penthala
University of Arkansas for Medical Sciences

Sean Parkin
University of Kentucky, s.parkin@uky.edu

Peter A. Crooks
University of Arkansas for Medical Sciences

Right click to open a feedback form in a new tab to let us know how this document benefits you.

Follow this and additional works at: https://uknowledge.uky.edu/chemistry_facpub

 Part of the [Chemistry Commons](#)

Repository Citation

Bommagani, Shobanbabu; Penthala, Narsimha Reddy; Parkin, Sean; and Crooks, Peter A., "Crystal Structure of (*E*)-13-(pyrimidin-5-yl)parthenolide" (2015). *Chemistry Faculty Publications*. 63.
https://uknowledge.uky.edu/chemistry_facpub/63

This Article is brought to you for free and open access by the Chemistry at UKnowledge. It has been accepted for inclusion in Chemistry Faculty Publications by an authorized administrator of UKnowledge. For more information, please contact UKnowledge@lsv.uky.edu.

Crystal Structure of (*E*)-13-(pyrimidin-5-yl)parthenolide

Notes/Citation Information

Published by *Acta Crystallographica Section E: Crystallographic Communications*, v. 71, part 12, p. 1536-1538.

This is an open-access article distributed under the terms of the [Creative Commons Attribution \(CC-BY\) Licence](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original authors and source are cited.

Digital Object Identifier (DOI)

<https://doi.org/10.1107/S2056989015021507>



Crystal structure of (*E*)-13-(pyrimidin-5-yl)-parthenolide

Shobanbabu Bommagani,^a Narsimha R. Penthala,^a Sean Parkin^b and Peter A. Crooks^{a*}

Received 2 October 2015

Accepted 12 November 2015

Edited by G. Smith, Queensland University of Technology, Australia

Keywords: crystal structure; parthenolide; pyrimidine; Heck product

CCDC reference: 1436825

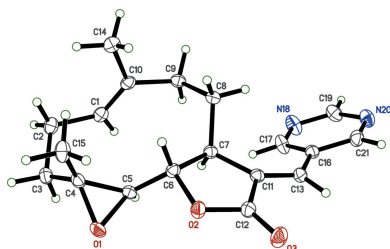
Supporting information: this article has supporting information at journals.iucr.org/e

^aDept. of Pharm. Sciences, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA, and ^bDept. of Chemistry, University of Kentucky, Lexington KY 40506, USA. *Correspondence e-mail: pacrooks@uams.edu

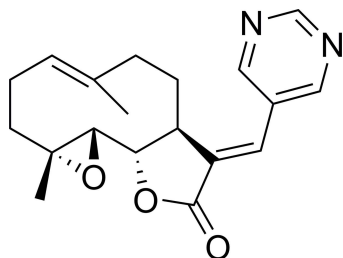
The title compound, C₁₉H₂₂N₂O₃, {systematic name (1*aR*,4*E*,7*aS*,8*E*,10*aS*,10*bR*)-1*a*,5-dimethyl-8-[(pyrimidin-5-yl)methylidene]-2,3,6,7,7*a*,8,10*a*,10*b*-octahydrooxireno[2',3':9,10]cyclodeca[1,2-*b*]furan-9(1*aH*)-one} was obtained from the reaction of parthenolide [systematic name (1*aR*,7*aS*,10*aS*,10*bR*,*E*)-1*a*,5-dimethyl-8-methylene-2,3,6,7,7*a*,8,10*a*,10*b*-octahydrooxireno[2',3':9,10]cyclodeca[1,2-*b*]furan-9(1*aH*)-one] with 5-bromopyrimidine under Heck reaction conditions, and was identified as an *E* isomer. The molecule possesses ten-, five- (lactone) and three-membered (epoxide) rings with a pyrimidine group as a substituent. The ten-membered ring displays an approximate chair–chair conformation, while the lactone ring shows a flattened envelope-type conformation. The dihedral angle between the pyrimidine moiety and the lactone ring system is 29.43 (7)°.

1. Chemical context

Parthenolide (PTL) is a sesquiterpene lactone known to significantly target cancer stem cells, which are the putative roots of all types of cancer (Gopal *et al.*, 2007). PTL has been isolated from several different plant species, feverfew leaf (*Tanacetum parthenium*) being one of the major sources (Awang, 1989). PTL exhibits a wide range of biological activities, such as anti-inflammatory, anti-bacterial, anti-fungal, and cytotoxic properties (Picman, 1986). Consequently, PTL was discovered to be capable of inducing robust apoptosis in primary acute myelogenous leukemia (AML) cells (Guzman *et al.*, 2007), proving to be equally effective among all subpopulations within primary AML specimens, including leukemia stem cells (LSCs). Gopal *et al.* (2007) reported that PTL specifically depletes HDAC1 protein without affecting other class I/II HDACs (histone deacetylases). Nasim *et al.* (2008) reported the anti-leukemic activity of aminoparthenolide analogues. Han *et al.* (2009) reported on bioactive derivatives of Heck products of PTL. Recently, Penthala *et al.* (2014*a*) reported the anti-cancer activity of PTL–Heck products. Recently we (Penthala *et al.*, 2014*b*) reported the crystal structure of 13-[4-[*Z*-2-cyano-2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl] parthenolide, an analog of PTL, which was found to have the *E* configuration at C-13. The interesting biological properties of PTL directed our attention to design and synthesize additional bioactive derivatives. In order to obtain detailed information on the structural conformation of the current molecule, including assignment of the absolute configuration of the four stereocentres, and to establish the geometry of the exocyclic double



bond, a single crystal X-ray structure determination has been carried out.



2. Structural commentary

The title compound is shown in Fig. 1. The PTL substructure of the molecule contains a ten-membered carbocyclic ring (chair–chair conformation) fused to a lactone ring (flattened envelope-type conformation), and an epoxide ring, as previously reported (Castañeda-Acosta & Fisher, 1993). The title compound contains an *E*-exocyclic olefinic bond C11=C13. The pyrimidine ring is twisted out of the plane of the furan ring, making a dihedral angle of 29.43 (7)°. The C11=C13–C16 bond angle of 127.89 (16)° deviates from the ideal value of 120°, but other bond lengths and angles are largely unremarkable. The four chiral carbon atoms in PTL were determined using 1354 quotients (Parsons *et al.*, 2013) as follows: C4(*R*), C5(*R*), C6(*S*), C7(*S*) for the arbitrary atom-numbering scheme used, and is consistent with previous studies (Penthala *et al.*, 2013).

3. Supramolecular features

There are no classical hydrogen bonds and no π – π interactions. There are a few C–H...N and C–H...O short contacts, but none that have the right geometry to be considered as non-classical hydrogen bonds. Intermolecular contacts thus appear to be limited to van der Waals interactions.

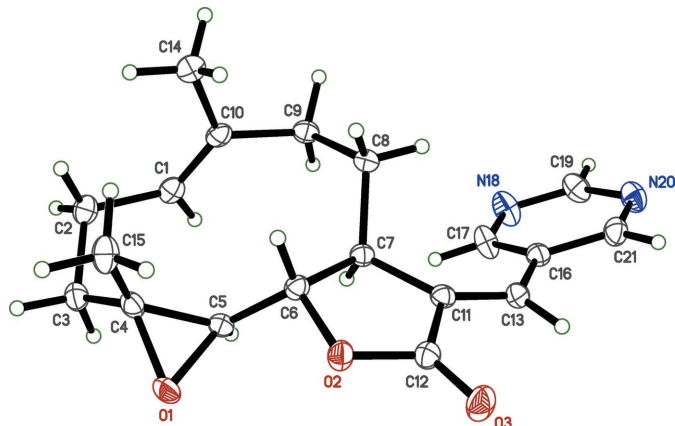


Figure 1

The molecular structure of the title compound with probability ellipsoids drawn at the 50% probability level.

4. Database survey

A search of the November 2014 release of the Cambridge Structure Database (Groom & Allen, 2014) for the PTL substructure gave 24 hits. Two of these (PARTEN: Quick & Rogers, 1976; PARTEN01: Bartsch *et al.*, 1983) give the structure of PTL itself, with the remaining 22 being substituted variants of PTL. Of these substituted parthenolides, only four CSD entries: HORZOF (Penthala *et al.*, 2014b), HUKLAB, HUKLEF (Han *et al.*, 2009) and QILGEZ (Penthala *et al.*, 2013), are substituted at the exocyclic double bond.

5. Synthesis and crystallization

Synthetic procedures: The title compound, containing the PTL substructure, was synthesized by the previously reported literature procedure (Han *et al.*, 2009). In brief, parthenolide (1 mmol), 5-bromopyrimidine (1.1 mmol), triethylamine (3.0 mmol) and 5 mol% of palladium acetate were charged into dimethylformamide (2 ml) at room temperature. The reactants were stirred at 333–343 K for 24 h. After completion of the reaction, the reaction mass was extracted into diethyl ether (2 × 30 ml). The combined organic layers were dried over anhydrous sodium sulfate, concentrated and purified by

Table 1
Experimental details.

Crystal data	
Chemical formula	C ₁₉ H ₂₂ N ₂ O ₃
<i>M_r</i>	326.38
Crystal system, space group	Monoclinic, <i>P</i> 2 ₁
Temperature (K)	90
<i>a</i> , <i>b</i> , <i>c</i> (Å)	10.3526 (2), 7.2612 (1), 11.9198 (2)
β (°)	108.1210 (6)
<i>V</i> (Å ³)	851.60 (2)
<i>Z</i>	2
Radiation type	Cu <i>K</i> α
μ (mm ⁻¹)	0.70
Crystal size (mm)	0.25 × 0.13 × 0.10
Data collection	
Diffractometer	Bruker X8 Proteum
Absorption correction	Multi-scan (<i>SADABS</i> ; Bruker, 2006)
<i>T</i> _{min} , <i>T</i> _{max}	0.850, 0.942
No. of measured, independent and observed [<i>I</i> > 2 σ (<i>I</i>)] reflections	11370, 3020, 3013
<i>R</i> _{int}	0.032
(<i>sin</i> θ / λ) _{max} (Å ⁻¹)	0.602
Refinement	
<i>R</i> [<i>F</i> ² > 2 σ (<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.027, 0.068, 1.05
No. of reflections	3020
No. of parameters	220
No. of restraints	1
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{\max}$, $\Delta\rho_{\min}$ (e Å ⁻³)	0.15, -0.14
Absolute structure	Flack <i>x</i> determined using 1354 quotients [(<i>I</i> ⁺) - (<i>I</i> ⁻)] / [(<i>I</i> ⁺) + (<i>I</i> ⁻)] (Parsons <i>et al.</i> , 2013).
Absolute structure parameter	-0.04 (3)

Computer programs: *APEX2* and *SAINT* (Bruker, 2006), *SHELXS97*, *SHELXTL* and *XP* in *SHELXTL* (Sheldrick, 2008), *SHELXL2014* (Sheldrick, 2015) and *CIFFIX* (Parkin, 2013).

column chromatography. The title compound was recrystallized from a mixture of hexane and acetone (9:1), which gave colourless needles upon slow evaporation of the solution at room temperature over 24 h.

6. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 1. H atoms were found in difference Fourier maps, but subsequently included in the refinement using riding models, with constrained distances set to 0.95 Å ($C_{sp^2}H$), 0.98 Å (RCH_3), 0.99 Å (R_2CH_2) and 1.00 Å (R_3CH). $U_{iso}(H)$ parameters were set to values of either $1.2U_{eq}$ or $1.5U_{eq}$ (RCH_3 only) of the attached atom. The absolute structure parameter [$-0.04(3)$] was determined directly from the diffraction data using 1354 Parsons quotients (Parsons *et al.*, 2013), with the four chiral carbon atoms assigned to be R,R,S,S for the arbitrarily numbered atoms C4, C5, C6, C7, respectively.

Refinement progress was checked using *PLATON* (Spek, 2009) and by an R -tensor (Parkin, 2000).

Acknowledgements

This work was supported by NIH/NCI grant CA158275.

References

- Awang, D. V. C. (1989). *Can. Pharm. J.* **122**, 266–270.
- Bartsch, H.-H., Jarchow, O. & Schmalle, H. W. (1983). *Z. Kristallogr.* **162**, 15–17.
- Bruker (2006). *APEX2*, *SAINT* and *SADABS*. Bruker-AXS Inc., Madison, Wisconsin, USA.
- Castañeda-Acosta, J., Fischer, N. H. & Vargas, D. (1993). *J. Nat. Prod.* **56**, 90–98.
- Gopal, Y. N. V., Arora, T. S. & Van Dyke, M. W. (2007). *Chem. Biol.* **14**, 813–823.
- Groom, C. R. & Allen, F. H. (2014). *Angew. Chem. Int. Ed.* **53**, 662–671.
- Guzman, M. L., Rossi, R. M., Neelakantan, S., Li, X., Corbett, C. A., Hassane, D. C., Becker, M. W., Bennett, J. M., Sullivan, E., Lachowicz, J. L., Vaughan, A., Sweeney, C. J., Matthews, W., Carroll, M., Liesveld, J. L., Crooks, P. A. & Jordan, C. T. (2007). *Blood*, **110**, 4427–4435.
- Han, C., Barrios, F. J., Riofski, M. V. & Colby, D. A. (2009). *J. Org. Chem.* **74**, 7176–7179.
- Nasim, S. & Crooks, P. A. (2008). *Bioorg. Med. Chem. Lett.* **18**, 3870–3873.
- Parkin, S. (2000). *Acta Cryst.* **A56**, 157–162.
- Parkin, S. (2013). *CIFFIX*. <http://xray.uky.edu/people/parkin/programs/ciffix>
- Parsons, S., Flack, H. D. & Wagner, T. (2013). *Acta Cryst.* **B69**, 249–259.
- Penthala, N. R., Bommagani, S., Janganati, V., MacNicol, K. B., Cragle, C. E., Madadi, N. R., Hardy, L. L., MacNicol, A. M. & Crooks, P. A. (2014a). *Eur. J. Med. Chem.* **85**, 517–525.
- Penthala, N. R., Bommagani, S., Janganati, V., Parkin, S. & Crooks, P. A. (2014b). *Acta Cryst.* **E70**, o1092–o1093.
- Penthala, N. R., Janganati, V., Parkin, S., Varughese, K. I. & Crooks, P. A. (2013). *Acta Cryst.* **E69**, o1709–o1710.
- Picman, A. K. (1986). *Biochem. Syst. Ecol.* **14**, 255–281.
- Quick, A. & Rogers, D. (1976). *J. Chem. Soc. Perkin Trans. 2*, pp. 465–469.
- Sheldrick, G. M. (2008). *Acta Cryst.* **A64**, 112–122.
- Sheldrick, G. M. (2015). *Acta Cryst.* **C71**, 3–8.
- Spek, A. L. (2009). *Acta Cryst.* **D65**, 148–155.

supporting information

Acta Cryst. (2015). E71, 1536-1538 [doi:10.1107/S2056989015021507]

Crystal structure of (*E*)-13-(pyrimidin-5-yl)parthenolide

Shobanbabu Bommagani, Narsimha R. Penthalala, Sean Parkin and Peter A. Crooks

Computing details

Data collection: *APEX2* (Bruker, 2006); cell refinement: *SAINTE* (Bruker, 2006); data reduction: *SAINTE* (Bruker, 2006); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL2014* (Sheldrick, 2015); molecular graphics: *XP* in *SHELXTL* (Sheldrick, 2008); software used to prepare material for publication: *SHELXTL* (Sheldrick, 2008) and *CIFFIX* (Parkin, 2013).

(1*aR*,4*E*,7*aS*,8*E*,10*aS*,10*bR*)-1*a*,5-** Dimethyl-8-[(pyrimidin-5-yl)methylidene]-2,3,6,7,7*a*,8,10*a*,10*b*-** octahydrooxireno[2',3':9,10]cyclodeca[1,2-*b*]furan-9(1*aH*)-one

Crystal data

C₁₉H₂₂N₂O₃

M_r = 326.38

Monoclinic, *P*2₁

a = 10.3526 (2) Å

b = 7.2612 (1) Å

c = 11.9198 (2) Å

β = 108.1210 (6)°

V = 851.60 (2) Å³

Z = 2

F(000) = 348

D_x = 1.273 Mg m⁻³

Cu *Kα* radiation, λ = 1.54178 Å

Cell parameters from 9908 reflections

θ = 4.5–68.2°

μ = 0.70 mm⁻¹

T = 90 K

Solvent-rounded block, colourless

0.25 × 0.13 × 0.10 mm

Data collection

Bruker X8 Proteum
diffractometer

Radiation source: fine-focus rotating anode

Detector resolution: 5.6 pixels mm⁻¹

φ and ω scans

Absorption correction: multi-scan

(*SADABS*; Bruker, 2006)

T_{min} = 0.850, *T_{max}* = 0.942

11370 measured reflections

3020 independent reflections

3013 reflections with *I* > 2σ(*I*)

R_{int} = 0.032

θ_{max} = 68.2°, θ_{min} = 4.5°

h = -12→10

k = -8→8

l = -14→13

Refinement

Refinement on *F*²

Least-squares matrix: full

R[*F*² > 2σ(*F*²)] = 0.027

wR(*F*²) = 0.068

S = 1.05

3020 reflections

220 parameters

1 restraint

Primary atom site location: structure-invariant

direct methods

Secondary atom site location: difference Fourier
map

Hydrogen site location: difference Fourier map

H-atom parameters constrained

w = 1/[σ²(*F_o*²) + (0.0326*P*)² + 0.1773*P*]

where *P* = (*F_o*² + 2*F_c*²)/3

(Δ/σ)_{max} < 0.001

Δρ_{max} = 0.15 e Å⁻³

Δρ_{min} = -0.13 e Å⁻³

Extinction correction: *SHELXL-2014*,

*Fc** = *kFc*[1 + 0.001 × *Fc*²λ³/sin(2θ)]^{-1/4}

Extinction coefficient: 0.010 (2)

Absolute structure: Flack x determined using
1354 quotients $[(F^+)-(F^-)]/[(F^+)+(F^-)]$ (Parsons *et al.*, 2013).

Absolute structure parameter: -0.04 (3)

Special details

Experimental. The crystal was mounted with polyisobutene oil on the tip of a fine glass fibre, which was fastened in a copper mounting pin with electrical solder. It was placed directly into the cold gas stream of a liquid nitrogen based cryostat, according to published methods.

Diffraction data were collected with the crystal at 90 K, which is standard practice in this laboratory for the majority of flash-cooled crystals.

The crystals were large, and could not be cut to size without inducing damage by crushing, leading to shattered, frayed ends. These damaged parts could easily be dissolved away, however, to give solvent-rounded undamaged pieces of optimal size for data collection.

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 progress was checked using *PLATON* (Spek, 2009) and by an R -tensor (Parkin, 2000). The final model was further checked with the IUCr utility *checkCIF*.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (\AA^2)

	x	y	z	$U_{\text{iso}}^*/U_{\text{eq}}$
O1	0.59428 (12)	0.24072 (19)	0.48957 (10)	0.0228 (3)
O2	0.30633 (12)	0.25486 (17)	0.43887 (10)	0.0195 (3)
O3	0.12397 (13)	0.29255 (19)	0.49855 (11)	0.0266 (3)
C1	0.57679 (17)	0.5285 (2)	0.19945 (14)	0.0185 (4)
H1A	0.5833	0.6439	0.2384	0.022*
C2	0.70386 (17)	0.4134 (3)	0.23289 (16)	0.0208 (4)
H2A	0.7809	0.4881	0.2257	0.025*
H2B	0.6915	0.3076	0.1781	0.025*
C3	0.73676 (17)	0.3417 (3)	0.36116 (15)	0.0202 (4)
H3A	0.8146	0.2554	0.3792	0.024*
H3B	0.7615	0.4460	0.4173	0.024*
C4	0.61322 (17)	0.2447 (2)	0.37345 (14)	0.0178 (4)
C5	0.51035 (16)	0.3615 (2)	0.40010 (13)	0.0165 (3)
H5A	0.5353	0.4948	0.4118	0.020*
C6	0.35977 (16)	0.3252 (2)	0.34753 (14)	0.0159 (3)
H6A	0.3445	0.2321	0.2829	0.019*
C7	0.27894 (16)	0.5036 (2)	0.29783 (13)	0.0149 (3)
H7A	0.3396	0.6113	0.3292	0.018*
C8	0.22800 (16)	0.5184 (3)	0.16174 (14)	0.0176 (4)
H8A	0.1434	0.5923	0.1376	0.021*
H8B	0.2058	0.3936	0.1278	0.021*
C9	0.33322 (17)	0.6078 (3)	0.11062 (14)	0.0185 (4)
H9A	0.2884	0.6358	0.0261	0.022*
H9B	0.3638	0.7258	0.1519	0.022*
C10	0.45591 (17)	0.4887 (2)	0.12176 (14)	0.0179 (4)
C11	0.16862 (16)	0.5027 (2)	0.35605 (14)	0.0159 (3)

C12	0.19100 (17)	0.3425 (3)	0.43718 (14)	0.0184 (4)
C13	0.06867 (17)	0.6212 (3)	0.35248 (14)	0.0179 (4)
H13A	0.0096	0.5872	0.3961	0.021*
C14	0.42876 (19)	0.3267 (3)	0.03864 (16)	0.0269 (4)
H14A	0.5140	0.2609	0.0473	0.040*
H14B	0.3908	0.3705	-0.0428	0.040*
H14C	0.3639	0.2434	0.0573	0.040*
C15	0.57578 (18)	0.0643 (2)	0.30934 (18)	0.0239 (4)
H15A	0.5012	0.0072	0.3311	0.036*
H15B	0.6548	-0.0179	0.3312	0.036*
H15C	0.5470	0.0861	0.2240	0.036*
C16	0.03901 (16)	0.7977 (2)	0.28928 (14)	0.0180 (4)
C17	0.13568 (18)	0.9097 (3)	0.26601 (18)	0.0244 (4)
H17A	0.2281	0.8719	0.2933	0.029*
N18	0.10538 (16)	1.0688 (2)	0.20684 (16)	0.0293 (4)
C19	-0.02533 (19)	1.1156 (3)	0.17269 (17)	0.0252 (4)
H19A	-0.0485	1.2265	0.1287	0.030*
N20	-0.12697 (15)	1.0248 (2)	0.19312 (14)	0.0256 (4)
C21	-0.09291 (18)	0.8673 (3)	0.25279 (15)	0.0219 (4)
H21A	-0.1621	0.7994	0.2713	0.026*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0188 (6)	0.0306 (7)	0.0176 (6)	0.0061 (5)	0.0035 (5)	0.0092 (5)
O2	0.0187 (6)	0.0200 (6)	0.0221 (6)	0.0038 (5)	0.0098 (5)	0.0064 (5)
O3	0.0242 (6)	0.0305 (8)	0.0303 (7)	0.0031 (6)	0.0162 (5)	0.0097 (6)
C1	0.0218 (8)	0.0163 (8)	0.0197 (8)	-0.0006 (7)	0.0100 (7)	0.0024 (7)
C2	0.0184 (8)	0.0208 (9)	0.0254 (9)	-0.0018 (7)	0.0101 (7)	-0.0001 (7)
C3	0.0157 (8)	0.0216 (9)	0.0228 (8)	0.0016 (7)	0.0053 (6)	-0.0004 (7)
C4	0.0163 (8)	0.0184 (8)	0.0174 (8)	0.0036 (7)	0.0031 (6)	0.0040 (7)
C5	0.0175 (8)	0.0173 (8)	0.0141 (7)	0.0020 (7)	0.0043 (6)	0.0031 (6)
C6	0.0173 (8)	0.0162 (8)	0.0154 (7)	0.0002 (6)	0.0068 (6)	0.0012 (6)
C7	0.0155 (7)	0.0147 (8)	0.0142 (7)	-0.0011 (6)	0.0041 (6)	-0.0008 (6)
C8	0.0172 (8)	0.0201 (8)	0.0143 (8)	0.0005 (7)	0.0034 (6)	0.0003 (7)
C9	0.0209 (8)	0.0195 (8)	0.0147 (7)	0.0018 (7)	0.0051 (6)	0.0044 (7)
C10	0.0221 (8)	0.0190 (9)	0.0150 (7)	0.0003 (7)	0.0092 (7)	0.0026 (7)
C11	0.0153 (7)	0.0170 (8)	0.0143 (7)	-0.0021 (7)	0.0031 (6)	-0.0010 (7)
C12	0.0166 (8)	0.0206 (9)	0.0187 (8)	0.0004 (7)	0.0065 (6)	0.0014 (7)
C13	0.0144 (8)	0.0213 (9)	0.0175 (8)	-0.0011 (7)	0.0044 (6)	-0.0018 (7)
C14	0.0258 (9)	0.0321 (11)	0.0219 (8)	0.0041 (8)	0.0061 (7)	-0.0061 (8)
C15	0.0206 (8)	0.0177 (9)	0.0346 (10)	0.0023 (7)	0.0105 (8)	0.0005 (7)
C16	0.0175 (8)	0.0190 (9)	0.0161 (7)	0.0009 (7)	0.0032 (6)	-0.0044 (7)
C17	0.0156 (8)	0.0189 (9)	0.0350 (10)	0.0005 (7)	0.0024 (8)	0.0019 (8)
N18	0.0209 (8)	0.0216 (9)	0.0409 (10)	-0.0014 (6)	0.0030 (7)	0.0062 (7)
C19	0.0240 (9)	0.0183 (9)	0.0288 (9)	0.0021 (8)	0.0016 (7)	0.0019 (8)
N20	0.0206 (8)	0.0232 (8)	0.0304 (8)	0.0042 (6)	0.0043 (6)	0.0003 (7)
C21	0.0194 (8)	0.0219 (9)	0.0253 (9)	0.0026 (7)	0.0084 (7)	-0.0024 (7)

Geometric parameters (Å, °)

O1—C5	1.444 (2)	C8—H8B	0.9900
O1—C4	1.457 (2)	C9—C10	1.508 (2)
O2—C12	1.348 (2)	C9—H9A	0.9900
O2—C6	1.4585 (19)	C9—H9B	0.9900
O3—C12	1.210 (2)	C10—C14	1.507 (3)
C1—C10	1.337 (2)	C11—C13	1.336 (2)
C1—C2	1.504 (2)	C11—C12	1.484 (2)
C1—H1A	0.9500	C13—C16	1.470 (2)
C2—C3	1.549 (2)	C13—H13A	0.9500
C2—H2A	0.9900	C14—H14A	0.9800
C2—H2B	0.9900	C14—H14B	0.9800
C3—C4	1.507 (2)	C14—H14C	0.9800
C3—H3A	0.9900	C15—H15A	0.9800
C3—H3B	0.9900	C15—H15B	0.9800
C4—C5	1.471 (2)	C15—H15C	0.9800
C4—C15	1.505 (3)	C16—C17	1.383 (3)
C5—C6	1.511 (2)	C16—C21	1.393 (2)
C5—H5A	1.0000	C17—N18	1.339 (2)
C6—C7	1.556 (2)	C17—H17A	0.9500
C6—H6A	1.0000	N18—C19	1.330 (2)
C7—C11	1.510 (2)	C19—N20	1.327 (3)
C7—C8	1.546 (2)	C19—H19A	0.9500
C7—H7A	1.0000	N20—C21	1.335 (3)
C8—C9	1.547 (2)	C21—H21A	0.9500
C8—H8A	0.9900		
C5—O1—C4	60.94 (10)	H8A—C8—H8B	107.8
C12—O2—C6	111.31 (12)	C10—C9—C8	113.70 (14)
C10—C1—C2	128.05 (17)	C10—C9—H9A	108.8
C10—C1—H1A	116.0	C8—C9—H9A	108.8
C2—C1—H1A	116.0	C10—C9—H9B	108.8
C1—C2—C3	110.73 (14)	C8—C9—H9B	108.8
C1—C2—H2A	109.5	H9A—C9—H9B	107.7
C3—C2—H2A	109.5	C1—C10—C14	124.58 (16)
C1—C2—H2B	109.5	C1—C10—C9	121.22 (16)
C3—C2—H2B	109.5	C14—C10—C9	114.20 (15)
H2A—C2—H2B	108.1	C13—C11—C12	119.20 (15)
C4—C3—C2	108.68 (14)	C13—C11—C7	132.19 (16)
C4—C3—H3A	110.0	C12—C11—C7	108.42 (13)
C2—C3—H3A	110.0	O3—C12—O2	121.43 (16)
C4—C3—H3B	110.0	O3—C12—C11	128.78 (16)
C2—C3—H3B	110.0	O2—C12—C11	109.75 (13)
H3A—C3—H3B	108.3	C11—C13—C16	127.89 (16)
O1—C4—C5	59.08 (10)	C11—C13—H13A	116.1
O1—C4—C15	112.05 (15)	C16—C13—H13A	116.1
C5—C4—C15	121.46 (15)	C10—C14—H14A	109.5

O1—C4—C3	118.08 (14)	C10—C14—H14B	109.5
C5—C4—C3	116.40 (15)	H14A—C14—H14B	109.5
C15—C4—C3	116.73 (15)	C10—C14—H14C	109.5
O1—C5—C4	59.97 (10)	H14A—C14—H14C	109.5
O1—C5—C6	120.41 (14)	H14B—C14—H14C	109.5
C4—C5—C6	122.16 (14)	C4—C15—H15A	109.5
O1—C5—H5A	114.5	C4—C15—H15B	109.5
C4—C5—H5A	114.5	H15A—C15—H15B	109.5
C6—C5—H5A	114.5	C4—C15—H15C	109.5
O2—C6—C5	109.48 (12)	H15A—C15—H15C	109.5
O2—C6—C7	106.97 (12)	H15B—C15—H15C	109.5
C5—C6—C7	112.07 (13)	C17—C16—C21	115.11 (16)
O2—C6—H6A	109.4	C17—C16—C13	124.52 (15)
C5—C6—H6A	109.4	C21—C16—C13	120.31 (15)
C7—C6—H6A	109.4	N18—C17—C16	123.19 (16)
C11—C7—C8	115.01 (13)	N18—C17—H17A	118.4
C11—C7—C6	102.45 (13)	C16—C17—H17A	118.4
C8—C7—C6	115.15 (13)	C19—N18—C17	115.52 (17)
C11—C7—H7A	107.9	N20—C19—N18	127.34 (18)
C8—C7—H7A	107.9	N20—C19—H19A	116.3
C6—C7—H7A	107.9	N18—C19—H19A	116.3
C7—C8—C9	112.99 (13)	C19—N20—C21	115.48 (15)
C7—C8—H8A	109.0	N20—C21—C16	123.23 (17)
C9—C8—H8A	109.0	N20—C21—H21A	118.4
C7—C8—H8B	109.0	C16—C21—H21A	118.4
C9—C8—H8B	109.0		
C10—C1—C2—C3	-110.99 (19)	C2—C1—C10—C14	-8.9 (3)
C1—C2—C3—C4	53.54 (19)	C2—C1—C10—C9	171.47 (16)
C5—O1—C4—C15	-114.44 (16)	C8—C9—C10—C1	-107.23 (18)
C5—O1—C4—C3	105.54 (17)	C8—C9—C10—C14	73.07 (19)
C2—C3—C4—O1	-152.28 (15)	C8—C7—C11—C13	-56.5 (2)
C2—C3—C4—C5	-84.95 (18)	C6—C7—C11—C13	177.78 (17)
C2—C3—C4—C15	69.54 (18)	C8—C7—C11—C12	128.73 (15)
C4—O1—C5—C6	111.94 (17)	C6—C7—C11—C12	3.06 (16)
C15—C4—C5—O1	98.43 (17)	C6—O2—C12—O3	172.90 (16)
C3—C4—C5—O1	-108.37 (16)	C6—O2—C12—C11	-9.33 (18)
O1—C4—C5—C6	-109.10 (17)	C13—C11—C12—O3	5.6 (3)
C15—C4—C5—C6	-10.7 (2)	C7—C11—C12—O3	-178.86 (18)
C3—C4—C5—C6	142.53 (15)	C13—C11—C12—O2	-171.94 (15)
C12—O2—C6—C5	132.85 (14)	C7—C11—C12—O2	3.59 (18)
C12—O2—C6—C7	11.21 (17)	C12—C11—C13—C16	172.57 (15)
O1—C5—C6—O2	36.7 (2)	C7—C11—C13—C16	-1.7 (3)
C4—C5—C6—O2	108.24 (17)	C11—C13—C16—C17	-29.8 (3)
O1—C5—C6—C7	155.20 (14)	C11—C13—C16—C21	153.17 (17)
C4—C5—C6—C7	-133.25 (15)	C21—C16—C17—N18	-3.7 (3)
O2—C6—C7—C11	-8.19 (16)	C13—C16—C17—N18	179.10 (17)
C5—C6—C7—C11	-128.18 (14)	C16—C17—N18—C19	1.1 (3)

O2—C6—C7—C8	-133.78 (14)	C17—N18—C19—N20	1.7 (3)
C5—C6—C7—C8	106.23 (15)	N18—C19—N20—C21	-1.4 (3)
C11—C7—C8—C9	153.12 (15)	C19—N20—C21—C16	-1.7 (3)
C6—C7—C8—C9	-88.08 (18)	C17—C16—C21—N20	4.0 (2)
C7—C8—C9—C10	69.71 (19)	C13—C16—C21—N20	-178.66 (16)
