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# Crystal structure of 13-(*E*)-(2-aminobenzylidene)-parthenolide

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**Keywords:** crystal structure; parthenolide; 2-iodoaniline; Heck product.

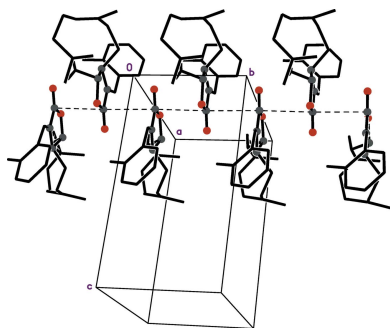
**CCDC reference:** 1869537

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

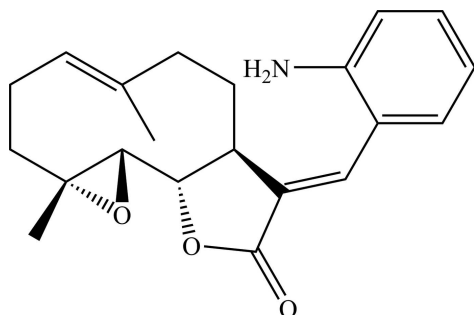
The title compound, C<sub>21</sub>H<sub>25</sub>NO<sub>3</sub> [systematic name: (1*aR*,4*E*,7*aS*,8*E*,10*aS*,10*bR*)-8-(2-aminobenzylidene)-1*a*,5-dimethyl-2,3,6,7,7*a*,8,10*a*,10*b*-octahydrooxireno[2',3':9,10]cyclodeca[1,2-*b*]furan-9(1*aH*)-one], was synthesized by the reaction of parthenolide [systematic name (1*aR*,7*aS*,10*aS*,10*bS*,*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 2-iodoaniline *via* Heck reaction conditions. The molecule is composed of fused ten-, five- (lactone), and three-membered (epoxide) rings. The lactone ring shows a flattened envelope-type conformation (r.m.s. deviation from planarity = 0.0477 Å), and bears a 2-aminobenzylidene substituent that is disordered over two conformations [occupancy factors 0.901 (4) and 0.099 (4)]. The ten-membered ring has an approximate chair–chair conformation. The dihedral angle between the 2-aminobenzylidene moiety (major component) and the lactone ring (mean plane) is 59.93 (7)°. There are no conventional hydrogen bonds, but there are a number of weaker C–H···O-type interactions.

## 1. Chemical context

Sesquiterpene lactones (SLs) are a large family of natural products that have been widely investigated for their anticancer activity. Parthenolide (PTL), a naturally occurring germacranolide SL (Minnaard *et al.*, 1999) isolated from the feverfew plant (*Tanacetum parthenium*) (Knight, 1995), has unique biological properties and selectively targets leukemia stem cells (LSC) compared to normal hematopoietic stem cells (Guzman *et al.*, 2005). PTL has been demonstrated to inhibit the NFκB pathway in LSCs, and also increases reactive oxygen species, and inhibits STAT3 (signal transduction and activation of transcription) (Mathema *et al.*, 2012). Synthetic analogues of SLs are also excellent sources of novel chemical entities for drug discovery, and over the last decade have been developed as efficacious anticancer drugs (Ghantous *et al.*, 2010). Previous work from our laboratory (Nasim & Crooks, 2008) reported the amino analogues of PTL as anti-leukemic agents, and moreover a water-soluble analogue of PTL, dimethylaminoparthenolide (DMAPT), has advanced into clinical studies (Ghantous *et al.*, 2010). Recently, Kempema *et al.* (2015) have reported C1 to C10-modified PTL analogues as anti-leukemic agents. Han *et al.* (2009) have also reported Heck products of PTL as anti-cancer agents. In continuing efforts from our group, Penthala *et al.* (2014*a*) reported Heck products of PTL and Melampomagnolide B as anti-cancer agents. Subsequently, Bommagani *et al.* (2015) reported the crystal structure of (*E*)-13-(pyrimidin-5-yl)-parthenolide, an



analog of PTL, which was found to have an *E*-configuration at C-13. The useful biological properties of PTL and its analogs directed our attention to design and synthesize novel bioactive analogs. In order to obtain detailed information on the structural conformation of the current molecule and to determine the geometry of the exocyclic double bond, a single-crystal X-ray structure determination has been carried out.

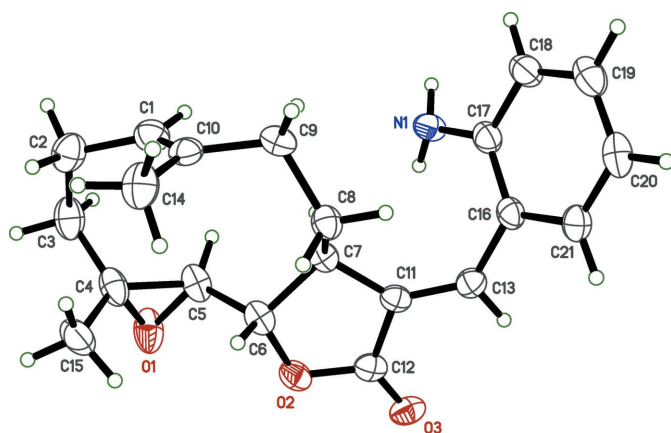


## 2. Structural commentary

The title compound (Fig. 1) is built from the PTL substructure, which contains a ten-membered carbocyclic ring (chair–chair conformation) merged to a lactone ring, and an epoxide ring, as previously reported (Castañeda-Acosta *et al.*, 1993). The lactone ring has a flattened envelope-type conformation, wherein atoms C6 and C7 reside 0.093 (4) and  $-0.105$  (4) Å above and below the mean plane through atoms C11, C12, O2, and O3. The molecule also contains a 2-aminobenzylidene group attached by an *E*-exocyclic C11=C13 olefinic bond. The 2-aminobenzylidene ring is twisted out of the plane of the furan ring, subtending a dihedral angle of 59.93 (7)°. All other bond lengths and angles are largely unremarkable.

## 3. Supramolecular features

There are no conventional hydrogen bonds in the crystal structure, although there are a number of weaker C–H···O-



**Figure 1**  
The molecular structure of the title compound with ellipsoids drawn at the 50% probability level.

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

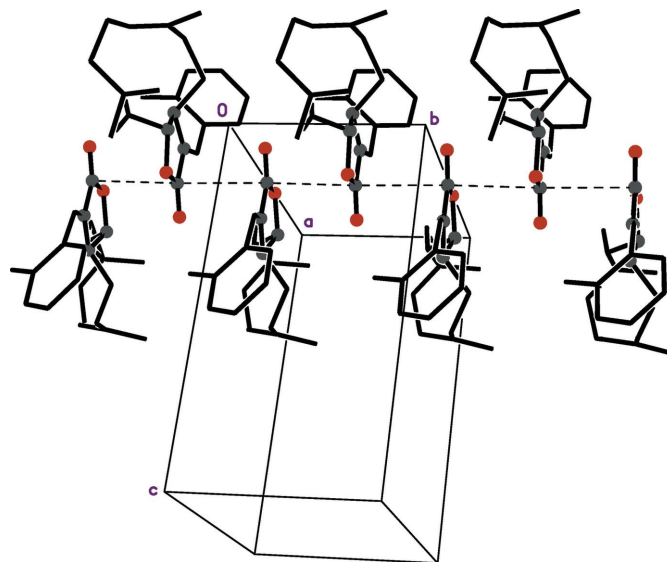
| <i>D</i> –H··· <i>A</i>     | <i>D</i> –H | H··· <i>A</i> | <i>D</i> ··· <i>A</i> | <i>D</i> –H··· <i>A</i> |
|-----------------------------|-------------|---------------|-----------------------|-------------------------|
| C5–H5···O3 <sup>i</sup>     | 1.00        | 2.59          | 3.268 (3)             | 125                     |
| C7–H7···O3 <sup>i</sup>     | 1.00        | 2.57          | 3.226 (3)             | 123                     |
| C15–H15A···O1 <sup>ii</sup> | 0.98        | 2.40          | 3.223 (3)             | 141                     |

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

type interactions (Table 1). The most striking packing feature consists of  $2_1$  screw-related  $(1 - x, \frac{1}{2} + y, -z)$  stacking of lactone groups parallel to the *b* axis (Fig. 2). The distance between planes of adjacent lactone rings is therefore half the *b*-axis length.

## 4. Database survey

A search of the November 2017 release (with three incremental updates) of the Cambridge Structure Database (Groom *et al.*, 2016) for the PTL substructure gave 30 hits. Three of these, PARTEN (Quick & Rogers, 1976), PARTEN01 (Bartsch *et al.*, 1983), and PARTEN02 (Long *et al.*, 2013) give the structure of PTL itself. One (EBOLOZ, Jamal *et al.*, 2014) is flagged in the CSD as a stereoisomer of parthenolide, though from the context it appears to be parthenolide with an incorrectly assigned absolute configuration. The remaining 26 are substituted variants of PTL. Of these, only six entries: HORZOF (Penthala *et al.*, 2014b), HUKLAB, HUKLEF (Han *et al.*, 2009), QILGEZ (Penthala *et al.*, 2013), RUTPON (Bommagani *et al.*, 2015), and BEMHIN (El Bouakher *et al.*, 2017) are substituted at the exocyclic double bond.



**Figure 2**  
A packing plot showing the stacking of  $2_1$  screw-related adjacent lactone groups. The stacking direction, shown by a dashed line, is parallel to the crystallographic *b* axis. For emphasis, lactone-group atoms are depicted as solid balls. For clarity, hydrogen atoms and minor disorder components are omitted.

**Table 2**  
Experimental details.

|  |  |
|--|--|
| Crystal data   |  |
| Chemical formula   | C <sub>21</sub> H <sub>25</sub> NO <sub>3</sub>  |
| <i>M<sub>r</sub></i>   | 339.42   |
| Crystal system, space group  | Monoclinic, <i>P</i> 2 <sub>1</sub>  |
| Temperature (K)  | 90   |
| <i>a</i> , <i>b</i> , <i>c</i> (Å)   | 11.6136 (3), 6.2403 (1), 12.6875 (3)   |
| β (°)  | 104.385 (1)  |
| <i>V</i> (Å <sup>3</sup> )   | 890.67 (3)   |
| <i>Z</i>   | 2  |
| Radiation type   | Cu Kα  |
| μ (mm <sup>-1</sup> )  | 0.67   |
| Crystal size (mm)  | 0.16 × 0.12 × 0.08   |
| Data collection  |  |
| Diffractometer   | Bruker X8 Proteum  |
| Absorption correction  | Multi-scan ( <i>SADABS</i> ;<br>Krause <i>et al.</i> , 2015)   |
| <i>T</i> <sub>min</sub> , <i>T</i> <sub>max</sub>  | 0.840, 0.942   |
| No. of measured, independent and<br>observed [ <i>I</i> > 2σ( <i>I</i> )] reflections                          | 24004, 2592, 2559  |
| <i>R</i> <sub>int</sub>  | 0.041  |
| (sin θ/λ) <sub>max</sub> (Å <sup>-1</sup> )  | 0.602  |
| Refinement   |  |
| <i>R</i> [ <i>F</i> <sup>2</sup> > 2σ( <i>F</i> <sup>2</sup> )], <i>wR</i> ( <i>F</i> <sup>2</sup> ), <i>S</i> | 0.032, 0.084, 1.08   |
| No. of reflections   | 2592   |
| No. of parameters  | 238  |
| No. of restraints  | 2  |
| H-atom treatment   | H atoms treated by a mixture of<br>independent and constrained<br>refinement   |
| Δρ <sub>max</sub> , Δρ <sub>min</sub> (e Å <sup>-3</sup> )   | 0.18, -0.14  |
| Absolute structure   | Flack <i>x</i> determined using 811<br>quotients [( <i>I</i> <sup>+</sup> ) - ( <i>I</i> <sup>-</sup> )] / [( <i>I</i> <sup>+</sup> ) + ( <i>I</i> <sup>-</sup> )]<br>(Parsons <i>et al.</i> , 2013), as<br>calculated by <i>PLATON</i> (Spek,<br>2009). |
| Absolute structure parameter   | 0.07 (7)   |

Computer programs: *APEX2* and *SAINT* (Bruker, 2006), *XP* in *SHELXTL* and *SHELXS97* (Sheldrick, 2008), *SHELXL2013* (Sheldrick, 2015) and *CIFFIX* (Parkin, 2013).

## 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), 2-iodoaniline (1.2 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, water was added to the reaction mass at room temperature, and the mixture was extracted into diethyl ether (2 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated and purified by silica gel column chromatography.

**Crystallization:** The title compound was recrystallized from a mixture of hexane and acetone (9:1), which gave colorless crystals upon slow evaporation of the solution at room temperature over 24 h. Melting point 457–459 K. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>d): δ 7.63 (*s*, 1H), 7.17 (*d*, *J* = 6.4 Hz, 2H), 6.78 (*dd*, *J* = 7.6 Hz, *J* = 18.4 Hz, 2H), 5.26 (*d*, *J* = 11.6 Hz, 1H), 3.97 (*s*, 2H), 3.92 (*t*, *J* = 7.6 Hz, *J* = 15.6 Hz, 1H), 2.87–2.83 (*m*, 2H), 2.42–2.38 (*m*, 1H), 2.20–2.08 (*m*, 4H), 2.08–1.96 (*m*, 1H),

1.74 (*d*, *J* = 18.0 Hz, 1H), 1.63 (*s*, 3H), 1.36–1.26 (*m*, 4H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>d) δ 171.17, 145.47, 135.37, 133.98, 131.11, 130.06, 129.05, 124.82, 118.93, 118.25, 116.21, 83.33, 66.91, 61.85, 47.42, 41.54, 36.49, 29.76, 24.42, 17.62, 17.54 ppm; (ESI): *m/z* C<sub>21</sub>H<sub>26</sub>NO<sub>3</sub> [*M* + *H*] 340.28.

## 6. Refinement details

Crystal data, data collection and structure refinement details are summarized in Table 2. H atoms were found in difference-Fourier maps. Carbon-bound hydrogens were subsequently placed at idealized positions with constrained distances of 0.98 Å (*RCH*<sub>3</sub>), 0.99 Å (*R*<sub>2</sub>CH<sub>2</sub>), 1.00 Å (*R*<sub>3</sub>CH) and 0.95 Å (*Csp*<sup>2</sup>H). Nitrogen-bound hydrogens on the major disorder component were refined freely, while those on the minor component were heavily restrained. *U*<sub>iso</sub>(H) values were set to either 1.2*U*<sub>eq</sub> or 1.5*U*<sub>eq</sub> (*RCH*<sub>3</sub>) of the attached atom.

To ensure satisfactory refinement of disordered groups in the structure, a combination of constraints and restraints were employed. The constraints (*SHELXL* commands EXYZ and EADP) were used to fix parameters of superimposed or partially overlapping fragments. Restraints (*SHELXL* command SADI) were used to maintain the integrity of ill-defined or disordered groups. Refinement progress was checked using *PLATON* (Spek, 2009) and by an *R*-tensor (Parkin, 2000).

The minor component of disorder of the amine was apparent in a difference map. Given the small occupancy factor (only about 10%), the geometry of the minor component is approximate, and its hydrogen atoms were included merely to achieve the correct atom count.

The conventionally calculated Flack parameter does not convincingly indicate the proper assignment of absolute configuration. An alternative formulation of the chirality parameter using Parsons quotients (Parsons *et al.*, 2013) [the so-called 'z' parameter = 0.07 (7)] as calculated by *PLATON* (Spek, 2009) is much more definitive.

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## References

- Castañeda-Acosta, J., Fischer, N. H. & Vargas, D. (1993). *J. Nat. Prod.* **56**, 90–98.
- Bartsch, H.-H., Jarchow, O. & Schmalte, H. W. (1983). *Z. Kristallogr.* **162**, 15–17.
- Bommagani, S., Penthalha, N. R., Parkin, S. & Crooks, P. A. (2015). *Acta Cryst.* **E71**, 1536–1538.
- Bruker (2006). *APEX2* and *SAINT*. Bruker AXS Inc., Madison, Wisconsin, USA.
- El Bouakher, A., Jismy, B., Allouchi, H., Duverger, E., Barkaoui, L., El Hakmaoui, A., Daniellou, R., Guillaumet, G. & Akssira, M. (2017). *Planta Med.* **83**, 661–671.
- Ghantous, A., Gali-Muhtasib, H., Vuorela, H., Saliba, N. A. & Darwiche, N. (2010). *Drug Discovery Today*, **15**, 668–678.

- Groom, C. R., Bruno, I. J., Lightfoot, M. P. & Ward, S. C. (2016). *Acta Cryst.* **B72**, 171–179.
- Guzman, M. L., Rossi, R. M., Karnischky, L., Li, X., Peterson, D. R., Howard, D. S. & Jordan, C. T. (2005). *Blood*, **105**, 4163–4169.
- Han, C., Barrios, F. J., Riofski, M. V. & Colby, D. A. (2009). *J. Org. Chem.* **74**, 7176–7179.
- Jamal, W., Bari, A., Mothana, R. A., Basudan, O., Mohammed, M. S. & Ng, S. W. (2014). *Asian J. Chem.* **26**, 5183–5185.
- Kempema, A. M., Widen, J. C., Hexum, J. K., Andrews, T. E., Wang, D., Rathe, S. K., Meece, F. A., Noble, K. E., Sachs, Z., Largaespada, D. A. & Harki, D. A. (2015). *Bioorg. Med. Chem.* **23**, 4737–4745.
- Knight, D. W. (1995). *Nat. Prod. Rep.* **12**, 271–276.
- Krause, L., Herbst-Irmer, R., Sheldrick, G. M. & Stalke, D. (2015). *J. Appl. Cryst.* **48**, 3–10.
- Long, J., Ding, Y.-H., Wang, P.-P., Zhang, Q. & Chen, Y. (2013). *J. Org. Chem.* **78**, 10512–10518.
- Mathema, V. B., Koh, Y. S., Thakuri, B. C. & Sillanpää, M. (2012). *Inflammation*, **35**, 560–565.
- Minnaard, A. J., Wijnberg, J. B. P. A. & de Groot, A. (1999). *Tetrahedron*, **55**, 2115–2146.
- 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.
- 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

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Crystal structure of 13-(*E*)-(2-aminobenzylidene)parthenolide

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## 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: *SHELXL2013* (Sheldrick, 2015); molecular graphics: *XP* in *SHELXTL* (Sheldrick, 2008); software used to prepare material for publication: *SHELX* (Sheldrick, 2008) and *CIFFIX* (Parkin, 2013).

(1*aR*,4*E*,7*aS*,8*E*,10*aS*,10*bR*)-8-(2-Aminobenzylidene)-1*a*,5-dimethyl-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

C<sub>21</sub>H<sub>25</sub>NO<sub>3</sub>

*M<sub>r</sub>* = 339.42

Monoclinic, *P*2<sub>1</sub>

*a* = 11.6136 (3) Å

*b* = 6.2403 (1) Å

*c* = 12.6875 (3) Å

β = 104.385 (1)°

*V* = 890.67 (3) Å<sup>3</sup>

*Z* = 2

*F*(000) = 364

*D<sub>x</sub>* = 1.266 Mg m<sup>-3</sup>

Cu *Kα* radiation, λ = 1.54178 Å

Cell parameters from 9958 reflections

θ = 3.9–68.2°

μ = 0.67 mm<sup>-1</sup>

*T* = 90 K

Block, colourless

0.16 × 0.12 × 0.08 mm

## Data collection

Bruker X8 Proteum  
diffractometer

Radiation source: fine-focus rotating anode

Detector resolution: 5.6 pixels mm<sup>-1</sup>

φ and ω scans

Absorption correction: multi-scan

(*SADABS*; Krause *et al.*, 2015)

*T<sub>min</sub>* = 0.840, *T<sub>max</sub>* = 0.942

24004 measured reflections

2592 independent reflections

2559 reflections with *I* > 2σ(*I*)

*R<sub>int</sub>* = 0.041

θ<sub>max</sub> = 68.2°, θ<sub>min</sub> = 3.6°

*h* = -13→13

*k* = -6→7

*l* = -15→15

## Refinement

Refinement on *F*<sup>2</sup>

Least-squares matrix: full

*R*[*F*<sup>2</sup> > 2σ(*F*<sup>2</sup>)] = 0.032

*wR*(*F*<sup>2</sup>) = 0.084

*S* = 1.08

2592 reflections

238 parameters

2 restraints

Primary atom site location: structure-invariant

direct methods

Secondary atom site location: difference Fourier  
map

Hydrogen site location: mixed

H atoms treated by a mixture of independent  
and constrained refinement

*w* = 1/[σ<sup>2</sup>(*F<sub>o</sub>*<sup>2</sup>) + (0.0449*P*)<sup>2</sup> + 0.1894*P*]

where *P* = (*F<sub>o</sub>*<sup>2</sup> + 2*F<sub>c</sub>*<sup>2</sup>)/3

(Δ/σ)<sub>max</sub> < 0.001

Δρ<sub>max</sub> = 0.18 e Å<sup>-3</sup>

Δρ<sub>min</sub> = -0.14 e Å<sup>-3</sup>

Absolute structure: Flack  $x$  determined using  
811 quotients  $[(F^-)-(F)]/[(F^+)+(F)]$  (Parsons *et al.*,  
2013), as calculated by PLATON (Spek, 2009).  
Absolute structure parameter: 0.07 (7)

### Special details

**Experimental.** The crystal was mounted with polyisobutene oil on the tip of a fine glass fibre, fastened in a copper mounting pin with electrical solder. It was placed directly into the cold stream of a liquid nitrogen based cryostat, according to published methods (Hope, 1994; Parkin & Hope, 1998).

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

**Geometry.** All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds 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 ( $\text{\AA}^2$ )

|     | <i>x</i>     | <i>y</i>   | <i>z</i>      | $U_{\text{iso}}^*/U_{\text{eq}}$ | Occ. (<1) |
|-----|--------------|------------|---------------|----------------------------------|-----------|
| O1  | 0.15259 (14) | 0.2877 (3) | -0.01598 (12) | 0.0449 (5)                       |           |
| O2  | 0.37973 (12) | 0.4845 (3) | 0.01116 (10)  | 0.0310 (3)                       |           |
| O3  | 0.57392 (13) | 0.4878 (3) | 0.08619 (10)  | 0.0338 (3)                       |           |
| C1  | 0.0887 (2)   | 0.3088 (4) | -0.34185 (17) | 0.0352 (5)                       |           |
| H1  | 0.1376       | 0.1884     | -0.3456       | 0.042*                           |           |
| C2  | -0.0258 (2)  | 0.2614 (4) | -0.31056 (19) | 0.0398 (6)                       |           |
| H2A | -0.0672      | 0.1415     | -0.3555       | 0.048*                           |           |
| H2B | -0.0781      | 0.3887     | -0.3256       | 0.048*                           |           |
| C3  | -0.0032 (2)  | 0.2016 (5) | -0.18904 (19) | 0.0408 (6)                       |           |
| H3A | -0.0797      | 0.1974     | -0.1680       | 0.049*                           |           |
| H3B | 0.0331       | 0.0573     | -0.1769       | 0.049*                           |           |
| C4  | 0.07850 (19) | 0.3630 (4) | -0.11934 (17) | 0.0353 (5)                       |           |
| C5  | 0.20641 (18) | 0.3246 (4) | -0.10509 (17) | 0.0328 (5)                       |           |
| H5  | 0.2251       | 0.1905     | -0.1407       | 0.039*                           |           |
| C6  | 0.29816 (17) | 0.4982 (4) | -0.09641 (14) | 0.0288 (4)                       |           |
| H6  | 0.2587       | 0.6418     | -0.1064       | 0.035*                           |           |
| C7  | 0.37413 (16) | 0.4677 (4) | -0.18048 (14) | 0.0262 (4)                       |           |
| H7  | 0.3626       | 0.3171     | -0.2080       | 0.031*                           |           |
| C8  | 0.34284 (18) | 0.6194 (4) | -0.28030 (15) | 0.0287 (5)                       |           |
| H8A | 0.3081       | 0.7530     | -0.2596       | 0.034*                           |           |
| H8B | 0.4167       | 0.6578     | -0.3014       | 0.034*                           |           |
| C9  | 0.25450 (18) | 0.5184 (4) | -0.37888 (14) | 0.0314 (5)                       |           |
| H9A | 0.2521       | 0.6076     | -0.4439       | 0.038*                           |           |
| H9B | 0.2840       | 0.3748     | -0.3924       | 0.038*                           |           |
| C10 | 0.12982 (17) | 0.4963 (4) | -0.36473 (13) | 0.0286 (4)                       |           |
| C11 | 0.49909 (17) | 0.4865 (4) | -0.11042 (13) | 0.0255 (4)                       |           |
| C12 | 0.49328 (19) | 0.4875 (4) | 0.00462 (15)  | 0.0280 (4)                       |           |
| C13 | 0.60415 (17) | 0.5038 (4) | -0.13427 (14) | 0.0282 (4)                       |           |



|      |              |            |               |            |           |
|------|--------------|------------|---------------|------------|-----------|
| H13  | 0.6711       | 0.5207     | -0.0742       | 0.034*     |           |
| C14  | 0.0631 (2)   | 0.7032 (4) | -0.37465 (19) | 0.0395 (6) |           |
| H14A | -0.0194      | 0.6752     | -0.3727       | 0.059*     |           |
| H14B | 0.0644       | 0.7725     | -0.4436       | 0.059*     |           |
| H14C | 0.1005       | 0.7976     | -0.3141       | 0.059*     |           |
| C15  | 0.0281 (2)   | 0.5807 (5) | -0.1117 (2)   | 0.0436 (6) |           |
| H15A | -0.0376      | 0.5705     | -0.0762       | 0.065*     |           |
| H15B | -0.0013      | 0.6402     | -0.1850       | 0.065*     |           |
| H15C | 0.0901       | 0.6745     | -0.0690       | 0.065*     |           |
| C16  | 0.62889 (16) | 0.5001 (4) | -0.24275 (14) | 0.0279 (4) |           |
| C17  | 0.58739 (18) | 0.3343 (4) | -0.31796 (15) | 0.0301 (4) | 0.901 (4) |
| N1   | 0.52374 (18) | 0.1616 (4) | -0.29365 (15) | 0.0308 (5) | 0.901 (4) |
| H1N  | 0.524 (3)    | 0.047 (5)  | -0.334 (2)    | 0.046*     | 0.901 (4) |
| H2N  | 0.530 (3)    | 0.136 (6)  | -0.225 (2)    | 0.046*     | 0.901 (4) |
| C17' | 0.58739 (18) | 0.3343 (4) | -0.31796 (15) | 0.0301 (4) | 0.099 (4) |
| H17' | 0.5450       | 0.2160     | -0.2992       | 0.036*     | 0.099 (4) |
| C18  | 0.61026 (19) | 0.3482 (5) | -0.42116 (16) | 0.0349 (5) |           |
| H18  | 0.5830       | 0.2377     | -0.4728       | 0.042*     |           |
| C19  | 0.67180 (19) | 0.5197 (5) | -0.44896 (16) | 0.0382 (6) |           |
| H19  | 0.6843       | 0.5279     | -0.5201       | 0.046*     |           |
| C20  | 0.71561 (19) | 0.6804 (4) | -0.37407 (18) | 0.0372 (5) |           |
| H20  | 0.7588       | 0.7973     | -0.3932       | 0.045*     |           |
| C21  | 0.69556 (18) | 0.6680 (4) | -0.27111 (17) | 0.0315 (5) | 0.901 (4) |
| H21  | 0.7275       | 0.7751     | -0.2188       | 0.038*     | 0.901 (4) |
| C21' | 0.69556 (18) | 0.6680 (4) | -0.27111 (17) | 0.0315 (5) | 0.099 (4) |
| N1'  | 0.7329 (16)  | 0.843 (3)  | -0.2219 (13)  | 0.0308 (5) | 0.099 (4) |
| H1N' | 0.7209       | 0.8389     | -0.1538       | 0.046*     | 0.099 (4) |
| H2N' | 0.8119       | 0.8571     | -0.2175       | 0.046*     | 0.099 (4) |

*Atomic displacement parameters (Å<sup>2</sup>)*

|     | $U^{11}$    | $U^{22}$    | $U^{33}$    | $U^{12}$     | $U^{13}$   | $U^{23}$    |
|-----|-------------|-------------|-------------|--------------|------------|-------------|
| O1  | 0.0318 (8)  | 0.0637 (13) | 0.0419 (8)  | 0.0018 (9)   | 0.0144 (6) | 0.0236 (8)  |
| O2  | 0.0381 (7)  | 0.0293 (8)  | 0.0295 (6)  | 0.0003 (8)   | 0.0160 (5) | 0.0015 (7)  |
| O3  | 0.0452 (8)  | 0.0288 (8)  | 0.0258 (6)  | -0.0091 (8)  | 0.0060 (6) | -0.0006 (7) |
| C1  | 0.0382 (12) | 0.0304 (13) | 0.0368 (10) | 0.0021 (11)  | 0.0093 (9) | -0.0045 (9) |
| C2  | 0.0356 (12) | 0.0331 (14) | 0.0491 (12) | -0.0049 (10) | 0.0075 (9) | 0.0010 (10) |
| C3  | 0.0324 (11) | 0.0388 (15) | 0.0542 (13) | 0.0006 (11)  | 0.0162 (9) | 0.0129 (11) |
| C4  | 0.0310 (11) | 0.0456 (15) | 0.0331 (10) | 0.0096 (11)  | 0.0154 (8) | 0.0133 (10) |
| C5  | 0.0325 (10) | 0.0298 (12) | 0.0401 (10) | 0.0067 (10)  | 0.0166 (8) | 0.0112 (10) |
| C6  | 0.0311 (10) | 0.0266 (11) | 0.0314 (9)  | 0.0056 (10)  | 0.0130 (7) | 0.0072 (9)  |
| C7  | 0.0269 (9)  | 0.0251 (11) | 0.0279 (8)  | 0.0011 (9)   | 0.0096 (7) | 0.0014 (8)  |
| C8  | 0.0277 (10) | 0.0315 (12) | 0.0282 (9)  | 0.0012 (9)   | 0.0094 (7) | 0.0052 (8)  |
| C9  | 0.0381 (11) | 0.0335 (13) | 0.0246 (8)  | 0.0022 (10)  | 0.0114 (7) | -0.0011 (9) |
| C10 | 0.0314 (10) | 0.0319 (12) | 0.0205 (8)  | 0.0005 (11)  | 0.0029 (7) | -0.0023 (9) |
| C11 | 0.0320 (10) | 0.0204 (10) | 0.0251 (8)  | 0.0004 (9)   | 0.0090 (7) | -0.0003 (8) |
| C12 | 0.0389 (10) | 0.0178 (10) | 0.0287 (8)  | -0.0027 (10) | 0.0110 (7) | 0.0005 (9)  |
| C13 | 0.0277 (9)  | 0.0281 (11) | 0.0276 (8)  | 0.0002 (10)  | 0.0048 (7) | -0.0002 (9) |

|      |             |             |             |             |            |              |
|------|-------------|-------------|-------------|-------------|------------|--------------|
| C14  | 0.0334 (11) | 0.0383 (15) | 0.0446 (12) | 0.0063 (11) | 0.0058 (9) | 0.0133 (11)  |
| C15  | 0.0393 (12) | 0.0528 (17) | 0.0417 (12) | 0.0142 (12) | 0.0161 (9) | -0.0052 (11) |
| C16  | 0.0221 (8)  | 0.0335 (12) | 0.0285 (8)  | 0.0047 (10) | 0.0071 (7) | 0.0024 (9)   |
| C17  | 0.0266 (9)  | 0.0338 (12) | 0.0314 (9)  | 0.0032 (10) | 0.0103 (7) | -0.0003 (9)  |
| N1   | 0.0382 (11) | 0.0292 (12) | 0.0270 (9)  | -0.0012 (9) | 0.0122 (7) | -0.0032 (8)  |
| C17' | 0.0266 (9)  | 0.0338 (12) | 0.0314 (9)  | 0.0032 (10) | 0.0103 (7) | -0.0003 (9)  |
| C18  | 0.0333 (10) | 0.0435 (15) | 0.0299 (9)  | 0.0041 (11) | 0.0119 (8) | -0.0012 (10) |
| C19  | 0.0331 (10) | 0.0509 (17) | 0.0332 (10) | 0.0071 (11) | 0.0134 (8) | 0.0107 (11)  |
| C20  | 0.0274 (10) | 0.0412 (15) | 0.0456 (12) | 0.0013 (11) | 0.0140 (8) | 0.0125 (11)  |
| C21  | 0.0225 (9)  | 0.0351 (13) | 0.0371 (10) | 0.0021 (9)  | 0.0075 (7) | 0.0011 (9)   |
| C21' | 0.0225 (9)  | 0.0351 (13) | 0.0371 (10) | 0.0021 (9)  | 0.0075 (7) | 0.0011 (9)   |
| N1'  | 0.0382 (11) | 0.0292 (12) | 0.0270 (9)  | -0.0012 (9) | 0.0122 (7) | -0.0032 (8)  |

*Geometric parameters (Å, °)*

|           |             |            |             |
|-----------|-------------|------------|-------------|
| O1—C5     | 1.440 (2)   | C9—H9B     | 0.9900      |
| O1—C4     | 1.456 (2)   | C10—C14    | 1.496 (3)   |
| O2—C12    | 1.342 (3)   | C11—C13    | 1.332 (3)   |
| O2—C6     | 1.458 (2)   | C11—C12    | 1.478 (2)   |
| O3—C12    | 1.211 (3)   | C13—C16    | 1.474 (2)   |
| C1—C10    | 1.323 (4)   | C13—H13    | 0.9500      |
| C1—C2     | 1.508 (3)   | C14—H14A   | 0.9800      |
| C1—H1     | 0.9500      | C14—H14B   | 0.9800      |
| C2—C3     | 1.544 (3)   | C14—H14C   | 0.9800      |
| C2—H2A    | 0.9900      | C15—H15A   | 0.9800      |
| C2—H2B    | 0.9900      | C15—H15B   | 0.9800      |
| C3—C4     | 1.510 (4)   | C15—H15C   | 0.9800      |
| C3—H3A    | 0.9900      | C16—C21    | 1.402 (3)   |
| C3—H3B    | 0.9900      | C16—C17    | 1.409 (3)   |
| C4—C5     | 1.471 (3)   | C17—N1     | 1.384 (3)   |
| C4—C15    | 1.492 (4)   | C17—C18    | 1.402 (3)   |
| C5—C6     | 1.504 (3)   | N1—H1N     | 0.88 (3)    |
| C5—H5     | 1.0000      | N1—H2N     | 0.87 (3)    |
| C6—C7     | 1.556 (2)   | C18—C19    | 1.381 (4)   |
| C6—H6     | 1.0000      | C18—H18    | 0.9500      |
| C7—C11    | 1.506 (3)   | C19—C20    | 1.388 (4)   |
| C7—C8     | 1.550 (3)   | C19—H19    | 0.9500      |
| C7—H7     | 1.0000      | C20—C21    | 1.385 (3)   |
| C8—C9     | 1.541 (3)   | C20—H20    | 0.9500      |
| C8—H8A    | 0.9900      | C21—H21    | 0.9500      |
| C8—H8B    | 0.9900      | N1'—H1N'   | 0.9100      |
| C9—C10    | 1.509 (3)   | N1'—H2N'   | 0.9100      |
| C9—H9A    | 0.9900      |            |             |
| C5—O1—C4  | 61.05 (13)  | C10—C9—H9B | 108.8       |
| C12—O2—C6 | 111.18 (13) | C8—C9—H9B  | 108.8       |
| C10—C1—C2 | 128.4 (2)   | H9A—C9—H9B | 107.7       |
| C10—C1—H1 | 115.8       | C1—C10—C14 | 125.06 (19) |

|              |             |               |             |
|--------------|-------------|---------------|-------------|
| C2—C1—H1     | 115.8       | C1—C10—C9     | 121.1 (2)   |
| C1—C2—C3     | 111.59 (19) | C14—C10—C9    | 113.8 (2)   |
| C1—C2—H2A    | 109.3       | C13—C11—C12   | 119.54 (17) |
| C3—C2—H2A    | 109.3       | C13—C11—C7    | 132.42 (16) |
| C1—C2—H2B    | 109.3       | C12—C11—C7    | 108.03 (16) |
| C3—C2—H2B    | 109.3       | O3—C12—O2     | 120.69 (17) |
| H2A—C2—H2B   | 108.0       | O3—C12—C11    | 128.95 (19) |
| C4—C3—C2     | 110.5 (2)   | O2—C12—C11    | 110.35 (16) |
| C4—C3—H3A    | 109.6       | C11—C13—C16   | 127.78 (17) |
| C2—C3—H3A    | 109.6       | C11—C13—H13   | 116.1       |
| C4—C3—H3B    | 109.6       | C16—C13—H13   | 116.1       |
| C2—C3—H3B    | 109.6       | C10—C14—H14A  | 109.5       |
| H3A—C3—H3B   | 108.1       | C10—C14—H14B  | 109.5       |
| O1—C4—C5     | 58.93 (13)  | H14A—C14—H14B | 109.5       |
| O1—C4—C15    | 112.9 (2)   | C10—C14—H14C  | 109.5       |
| C5—C4—C15    | 122.7 (2)   | H14A—C14—H14C | 109.5       |
| O1—C4—C3     | 117.2 (2)   | H14B—C14—H14C | 109.5       |
| C5—C4—C3     | 115.6 (2)   | C4—C15—H15A   | 109.5       |
| C15—C4—C3    | 116.50 (19) | C4—C15—H15B   | 109.5       |
| O1—C5—C4     | 60.02 (12)  | H15A—C15—H15B | 109.5       |
| O1—C5—C6     | 119.7 (2)   | C4—C15—H15C   | 109.5       |
| C4—C5—C6     | 124.6 (2)   | H15A—C15—H15C | 109.5       |
| O1—C5—H5     | 114.0       | H15B—C15—H15C | 109.5       |
| C4—C5—H5     | 114.0       | C21—C16—C17   | 119.53 (17) |
| C6—C5—H5     | 114.0       | C21—C16—C13   | 118.4 (2)   |
| O2—C6—C5     | 108.06 (16) | C17—C16—C13   | 122.1 (2)   |
| O2—C6—C7     | 106.71 (15) | N1—C17—C18    | 119.5 (2)   |
| C5—C6—C7     | 111.96 (18) | N1—C17—C16    | 122.18 (18) |
| O2—C6—H6     | 110.0       | C18—C17—C16   | 118.4 (2)   |
| C5—C6—H6     | 110.0       | C17—N1—H1N    | 115 (2)     |
| C7—C6—H6     | 110.0       | C17—N1—H2N    | 117 (2)     |
| C11—C7—C8    | 115.51 (17) | H1N—N1—H2N    | 115 (3)     |
| C11—C7—C6    | 102.31 (14) | C19—C18—C17   | 121.1 (2)   |
| C8—C7—C6     | 115.32 (17) | C19—C18—H18   | 119.4       |
| C11—C7—H7    | 107.7       | C17—C18—H18   | 119.4       |
| C8—C7—H7     | 107.7       | C18—C19—C20   | 120.67 (19) |
| C6—C7—H7     | 107.7       | C18—C19—H19   | 119.7       |
| C9—C8—C7     | 112.77 (18) | C20—C19—H19   | 119.7       |
| C9—C8—H8A    | 109.0       | C21—C20—C19   | 119.1 (2)   |
| C7—C8—H8A    | 109.0       | C21—C20—H20   | 120.4       |
| C9—C8—H8B    | 109.0       | C19—C20—H20   | 120.4       |
| C7—C8—H8B    | 109.0       | C20—C21—C16   | 121.1 (2)   |
| H8A—C8—H8B   | 107.8       | C20—C21—H21   | 119.4       |
| C10—C9—C8    | 113.94 (16) | C16—C21—H21   | 119.4       |
| C10—C9—H9A   | 108.8       | H1N'—N1'—H2N' | 109.5       |
| C8—C9—H9A    | 108.8       |               |             |
| C10—C1—C2—C3 | -107.8 (3)  | C8—C9—C10—C1  | -103.1 (2)  |

|               |              |                 |             |
|---------------|--------------|-----------------|-------------|
| C1—C2—C3—C4   | 49.0 (3)     | C8—C9—C10—C14   | 74.6 (2)    |
| C5—O1—C4—C15  | -115.5 (2)   | C8—C7—C11—C13   | -43.4 (4)   |
| C5—O1—C4—C3   | 104.9 (2)    | C6—C7—C11—C13   | -169.5 (3)  |
| C2—C3—C4—O1   | -151.63 (19) | C8—C7—C11—C12   | 135.47 (19) |
| C2—C3—C4—C5   | -85.0 (2)    | C6—C7—C11—C12   | 9.4 (2)     |
| C2—C3—C4—C15  | 70.2 (2)     | C6—O2—C12—O3    | 176.5 (2)   |
| C4—O1—C5—C6   | 115.1 (3)    | C6—O2—C12—C11   | -4.5 (3)    |
| C15—C4—C5—O1  | 98.8 (2)     | C13—C11—C12—O3  | -5.6 (4)    |
| C3—C4—C5—O1   | -107.7 (2)   | C7—C11—C12—O3   | 175.3 (2)   |
| O1—C4—C5—C6   | -107.3 (2)   | C13—C11—C12—O2  | 175.4 (2)   |
| C15—C4—C5—C6  | -8.5 (3)     | C7—C11—C12—O2   | -3.6 (3)    |
| C3—C4—C5—C6   | 145.1 (2)    | C12—C11—C13—C16 | 178.2 (2)   |
| C12—O2—C6—C5  | 131.12 (19)  | C7—C11—C13—C16  | -3.0 (4)    |
| C12—O2—C6—C7  | 10.6 (3)     | C11—C13—C16—C21 | 127.5 (3)   |
| O1—C5—C6—O2   | 44.4 (3)     | C11—C13—C16—C17 | -52.3 (3)   |
| C4—C5—C6—O2   | 116.6 (2)    | C21—C16—C17—N1  | 178.3 (2)   |
| O1—C5—C6—C7   | 161.60 (18)  | C13—C16—C17—N1  | -1.9 (3)    |
| C4—C5—C6—C7   | -126.2 (2)   | C21—C16—C17—C18 | -2.7 (3)    |
| O2—C6—C7—C11  | -11.8 (2)    | C13—C16—C17—C18 | 177.11 (19) |
| C5—C6—C7—C11  | -129.85 (19) | N1—C17—C18—C19  | 179.0 (2)   |
| O2—C6—C7—C8   | -138.03 (19) | C16—C17—C18—C19 | -0.1 (3)    |
| C5—C6—C7—C8   | 103.9 (2)    | C17—C18—C19—C20 | 1.8 (3)     |
| C11—C7—C8—C9  | 146.42 (18)  | C18—C19—C20—C21 | -0.8 (3)    |
| C6—C7—C8—C9   | -94.4 (2)    | C19—C20—C21—C16 | -2.0 (3)    |
| C7—C8—C9—C10  | 71.1 (2)     | C17—C16—C21—C20 | 3.8 (3)     |
| C2—C1—C10—C14 | -6.3 (4)     | C13—C16—C21—C20 | -176.0 (2)  |
| C2—C1—C10—C9  | 171.1 (2)    |                 |             |

*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> |
|--|-------------|---------------------|----------------------------|-------------------------------|
| C5—H5 $\cdots$ O3 <sup>i</sup>             | 1.00        | 2.59                | 3.268 (3)                  | 125                           |
| C7—H7 $\cdots$ O3 <sup>i</sup>             | 1.00        | 2.57                | 3.226 (3)                  | 123                           |
| C15—H15 <i>A</i> $\cdots$ O1 <sup>ii</sup> | 0.98        | 2.40                | 3.223 (3)                  | 141                           |

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