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

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The title compound, C21H25NO3 [systematic name: (1aR,4E,7aS,8E,10aS,10bR)-8-(2-aminobenzylidene)-1a,5-dimethyl-2,3,6,7,8,9,10a,10b-octahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-9(1aH)-one], was synthesized by the reaction of parthenolide [systematic name (1aR,7aS,10aS,10bS,E)-1a,5-dimethyl-8-methylene-2,3,6,7,9,10a,10b-octahydroxireno[2',3':9,10]cyclodeca[1,2-b]furan-9(1aH)-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-aminobenzylidine 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 germacranoide 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 NFkB 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. (2014a) 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-

type interactions (Table 1). The most striking packing feature consists of 2i, screw-related (1 – x, 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.
5. Synthesis and crystalization

**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.

**Crystalization:** 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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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$_{21}$H$_{26}$NO$_3$ [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$_3$), 0.99 Å (R$_2$CH$_2$), 1.00 Å (R$_3$CH) and 0.95 Å (Csp$^3$H). Nitrogen-bound hydrogens on the major disorder component were refined freely, while those on the minor component were heavily restrained. $U_{iso}$(H) values were set to either 1.2$U_{eq}$ or 1.5$U_{eq}$ (RCH$_3$) 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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Computing details

Data collection: APiX2 (Bruker, 2006); cell refinement: SAINT (Bruker, 2006); data reduction: SAINT (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 CIPIX (Parkin, 2013).

\[\text{(1aR,4E,7aS,8E,10aS,10bR)-8-(2-Aminobenzylidene)-1a,5-dimethyl-2,3,6,7,7a,8,10a,10b-octahydrooxireno[2',3':9,10]cycloeca[1,2-b]furan-9(1aH)-one}\]

Crystal data

\[\text{C}_{21}\text{H}_{25}\text{NO}_3\]

\(M_r = 339.42\)

Monoclinic, \(P2_1\)

\(a = 11.6136 (3) \, \text{Å}\)

\(b = 6.2403 (1) \, \text{Å}\)

\(c = 12.6875 (3) \, \text{Å}\)

\(\beta = 104.385 (1) ^\circ\)

\(V = 890.67 (3) \, \text{Å}^3\)

\(Z = 2\)

Data collection

Bruker X8 Proteum diffractometer

Radiation source: fine-focus rotating anode

Detector resolution: 5.6 pixels mm\(^{-1}\)

\(\varphi\) and \(\omega\) scans

Absorption correction: multi-scan

\((\text{SADABS}; \text{Krause et al., 2015})\)

\(T_{\text{min}} = 0.840, T_{\text{max}} = 0.942\)

Refinement

Refinement on \(F^2\)

Least-squares matrix: full

\(R[F^2 > 2\sigma(F^2)] = 0.032\)

\(wR(F^2) = 0.084\)

\(S = 1.08\)

24004 measured reflections

2592 independent reflections

2559 reflections with \(I > 2\sigma(I)\)

\(R_{\text{int}} = 0.041\)

\(\theta_{\text{max}} = 68.2 ^\circ, \theta_{\text{min}} = 3.6 ^\circ\)

\(h = -13\rightarrow 13\)

\(k = -6\rightarrow 7\)

\(l = -15\rightarrow 15\)

Secondary atom site location: difference Fourier map

Hydrogen site location: mixed

H atoms treated by a mixture of independent and constrained refinement

\(w = 1/[\sigma^2(F_c^2) + (0.0449P)^2 + 0.1894P]\)

where \(P = (F_c^2 + 2F_s^2)/3\)

(\(\Delta/\sigma)_{\text{max}} < 0.001\)

\(\Delta\rho_{\text{max}} = 0.18\, \text{e} \, \text{Å}^{-3}\)

\(\Delta\rho_{\text{min}} = -0.14\, \text{e} \, \text{Å}^{-3}\)
Absolute structure: Flack $x$ determined using 811 quotients $[(I)-\langle I\rangle]/[\langle I\rangle+(I)]$ (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 ($\AA^2$)**

|   | $x$     | $y$     | $z$       | $U_{eq}$/$U_{eq}$ | 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)       |
### Atomic displacement parameters (\( \text{Å}^2 \))

|   | \( U_{11} \) | \( U_{22} \) | \( U_{33} \) | \( U_{12} \) | \( U_{13} \) | \( U_{23} \) |
|---|---|---|---|---|---|---|
| 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) | 0.0066 (11) | 0.0162 (9) | 0.0129 (11) |
| C4 | 0.0310 (11) | 0.0456 (15) | 0.0331 (10) | 0.0066 (11) | 0.0154 (8) | 0.0132 (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)  0.0322 (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, º)

| Bond/Distance          | Length (Å) | Angle (º)      |
|------------------------|------------|----------------|
| O1—C5                  | 1.440 (2)  | C9—H9B          |
| O1—C4                  | 1.456 (2)  | C10—C14          |
| O2—C12                 | 1.342 (3)  | C11—C13          |
| O2—C6                  | 1.458 (2)  | C11—C12          |
| O3—C12                 | 1.211 (3)  | C13—C16          |
| C1—C10                 | 1.323 (4)  | C13—H13          |
| C1—C2                  | 1.508 (3)  | C14—H14A         |
| C1—H1                  | 0.9500     | C14—H14B         |
| C2—C3                  | 1.544 (3)  | C14—H14C         |
| C2—H2A                 | 0.9900     | C15—H15A         |
| C2—H2B                 | 0.9900     | C15—H15B         |
| C3—C4                  | 1.510 (4)  | C15—H15C         |
| C3—H3A                 | 0.9900     | C16—C21          |
| C3—H3B                 | 0.9900     | C16—C17          |
| C4—C5                  | 1.471 (3)  | C17—N1           |
| C4—C15                 | 1.492 (4)  | C17—C18          |
| C5—C6                  | 1.504 (3)  | N1—H1N           |
| C5—H5                  | 1.0000     | N1—H2N           |
| C6—C7                  | 1.556 (2)  | C18—C19          |
| C6—H6                  | 1.0000     | C18—H18          |
| C7—C11                 | 1.506 (3)  | C19—C20          |
| C7—C8                  | 1.550 (3)  | C19—H19          |
| C7—H7                  | 1.0000     | C20—C21          |
| C8—C9                  | 1.541 (3)  | C20—H20          |
| C8—H8A                 | 0.9900     | C21—H21          |
| C8—H8B                 | 0.9900     | N1′—H1N′          |
| C9—C10                 | 1.509 (3)  | N1′—H2N′         |
| C9—H9A                 | 0.9900     |                  |

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C2—C1—H1 115.8
C1—C2—C3 111.59 (19)
C1—C2—H2A 109.3
C3—C2—H2A 109.3
C1—C2—C3 111.59 (19)
C1—C2—H2A 109.3
C3—C2—H2A 109.3
H2A—C2—C2 108.0
C4—C3—C2 110.5 (2)
C4—C3—H3A 109.6
C2—C3—H3A 109.6
C4—C3—H3B 109.6
C2—C3—H3B 109.6
H3A—C3—H3B 108.1
O1—C4—C5 58.93 (13)
O1—C4—C15 112.9 (2)
C5—C4—C15 122.7 (2)
O1—C4—C3 117.2 (2)
C5—C4—C3 115.6 (2)
C15—C4—C3 116.50 (19)
O1—C5—C4 60.02 (12)
C6—C5—C4 114.0
O2—C6—C5 108.06 (16)
C7—C6—C5 111.96 (18)
O2—C6—H6 110.0
C8—C7—C6 115.32 (17)
C9—C8—C7 115.51 (17)
C8—C7—H7 107.7
C9—C8—H8A 110.9
C7—C8—H8A 109.0
C9—C8—H8B 109.0
C7—C8—H8B 109.0
H8A—C8—H8B 107.8
C10—C9—C8 113.94 (16)
C10—C9—H9A 108.8
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)
O1—C4—C5—C6 −85.0 (2)  C7—C11—C12—O2 −3.6 (3)
C15—C4—C5—O1 −8.5 (3)  C13—C11—C12—O2 −175.4 (2)
C3—C4—C5—C6  145.1 (2)  C12—C11—C12—O3  178.2 (2)
C12—O2—C6—C5  131.12 (19)  C7—C11—C12—O3 −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—C21 −52.3 (3)
C4—C5—C6—O2  116.6 (2)  C11—C13—C16—C21 −178.3 (2)
C4—C5—C6—C7  161.60 (18)  C13—C16—C17—N1 −1.9 (3)
C4—C5—C6—C7 −126.2 (2)  C13—C16—C17—N1  179.0 (2)
C11—C7—C8—C12  −138.03 (19)  C16—C17—C18—C19 −0.1 (3)
C11—C7—C8—C12 −129.85 (19)  C16—C17—C18—C19  179.0 (2)
C5—C6—C7—C8  −126.2 (2)  C11—C7—C8—C9  −0.8 (3)
C5—C6—C7—C8 −146.42 (18)  C11—C7—C8—C9 −179.8 (2)
C6—C7—C8—C9 −94.4 (2)  C19—C20—C21—C20  1.8 (3)
C7—C8—C9—C10  71.1 (2)  C19—C20—C21—C20 −176.0 (2)
C2—C1—C10—C14 −6.3 (4)  C13—C16—C17—C18  177.11 (19)
C2—C1—C10—C9  171.1 (2)

Hydrogen-bond geometry (Å, °)

| D—H···A  | D—H | H···A | D···A  | D—H···A |
|----------|-----|------|-------|---------|
| C5—H5···O3i | 1.00 | 2.59 | 3.268 (3) | 125 |
| C7—H7···O3i | 1.00 | 2.57 | 3.226 (3) | 123 |
| C15—H154···O1ii | 0.98 | 2.40 | 3.223 (3) | 141 |

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