

Received 13 April 2017

Accepted 19 April 2017

Edited by H. Stoeckli-Evans, University of  
Neuchâtel, Switzerland**Keywords:** crystal structure; pharmacopoeia  
reference standard; hydrogen bonding..**CCDC reference:** 1544853**Supporting information:** this article has  
supporting information at journals.iucr.org/e

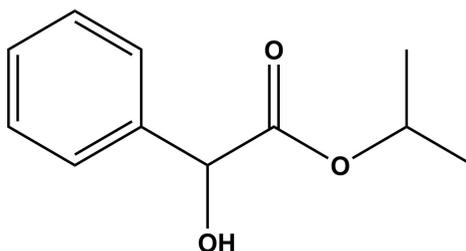
# Crystal structure of isopropyl 2-hydroxy-2-phenylacetate: a pharmacopoeia reference standard

Ivan Isaiev,<sup>a\*</sup> Svitlana Shishkina,<sup>b</sup> Igor Ukrainets<sup>c</sup> and Elena Bevz<sup>c</sup><sup>a</sup>V. N. Karazin Kharkiv National University, 4 Svobody Sq., Kharkiv 61077, Ukraine, <sup>b</sup>SSI 'Institute for Single Crystals', National Academy of Sciences of Ukraine, 60 Nauky Ave., Kharkiv 61001, Ukraine, and <sup>c</sup>National University of Pharmacy, 4 Valentynivska St., Kharkiv 61168, Ukraine. \*Correspondence e-mail: swhtlover@gmail.com

The title compound, C<sub>11</sub>H<sub>14</sub>O<sub>3</sub>, is used as a pharmacopoeia reference standard for determining impurities in the drug Pregabalin, used for the treatment of epilepsy and diabetic neuropathic pain. The molecule is far from being planar, with the dihedral angle between the planes of the aromatic ring and the carboxyl fragment (O—C=O) being 76.1 (6)°. The isopropyl substituent is located in a synperiplanar position relative to the C=O bond and is turned so that the C—O—C—H torsion angle is −43.7°. In the crystal, bifurcated O—H···(O,O) hydrogen bonds, enclosing R<sub>1</sub><sup>2</sup>(5) ring motifs, lead to the formation of chains propagating along the *c*-axis direction. Inversion-related chains are linked by the C—H···O hydrogen bonds, forming undulating layers lying parallel to the *bc* plane.

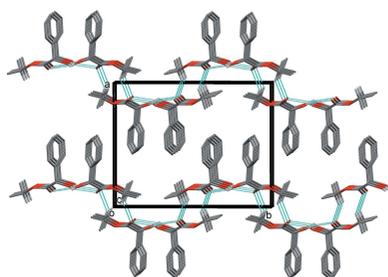
## 1. Chemical context

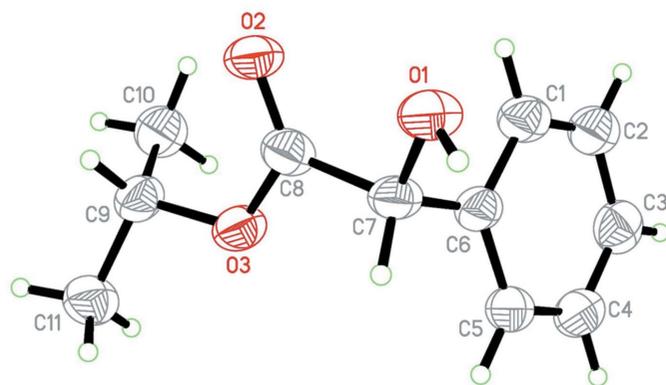
Pharmacopoeia reference standards are used widely for identification and quantitative determination of an active ingredient and undesirable impurity contents in many drug substances (European Pharmacopoeia Supplement, 2017). The title compound is used as the pharmacopoeia reference standard for the determining the level of impurities in Pregabalin (European Pharmacopoeia Supplement, 2016). This drug, sold under the trade mark 'Lyrica' (Silverman, 2016) is used for the treatment of epilepsy and diabetic neuropathic pains. Until now, its molecular and crystal structure were unknown.



## 2. Structural commentary

The molecular structure of the title compound is shown in Fig. 1. The hydroxyl group is situated in the *-sc* position relative to the C1—C6 endocyclic bond; torsion angle C1—C6—C7—O1 being −46.2 (6)°. The ester substituent at atom C7 has a *+sc*-orientation with respect to bond C1—C6 bond, with torsion angle C1—C6—C7—C8 = 71.2 (6)°, and it is turned in such way that the dihedral angle between the planes




**Figure 1**

The molecular structure of the title compound, showing the atom labelling. Displacement ellipsoids are drawn at the 50% probability level.

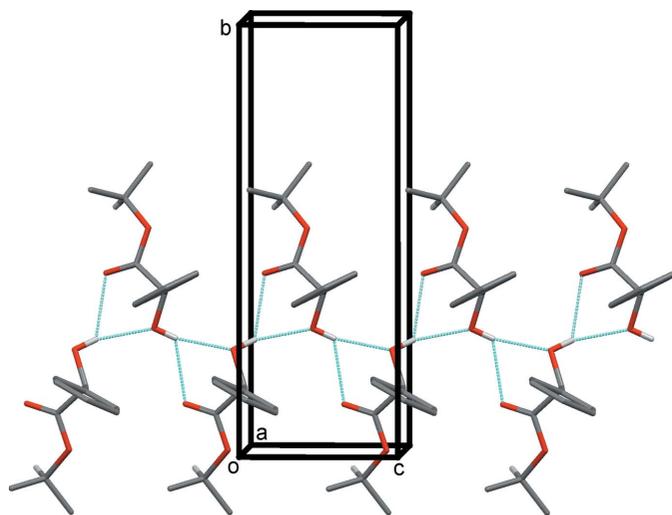
of the aromatic ring (C1–C6) and the carboxyl fragment (O3–C8=O2) is  $76.1(6)^\circ$ . The isopropyl substituent is located in a *syn*-periplanar position relative to the C8=O2 bond and is turned so that the C8–O3–C9–H9 torsion angle is  $-43.7^\circ$ .

### 3. Supramolecular features

In the crystal, molecules are linked by bifurcated O–H···(O,O) hydrogen bonds, forming chains propagating along [001] and enclosing  $R_1^2(5)$  ring motifs (Fig. 2 and Table 1). Neighbouring chains are linked by C–H···O hydrogen bonds, forming undulating layers lying parallel to the *bc* plane (Table 1 and Fig. 3).

### 4. Database survey

A search in the Cambridge Structural Database (Version 5.38, update February 2017; Groom *et al.*, 2016) for substructure


**Figure 2**

A partial view along the *a* axis of the crystal packing of the title compound, with the hydrogen bonds shown as dashed lines (see Table 1). For clarity, only H atoms H1O and H9 have been included.

**Table 1**

Hydrogen-bond geometry (Å, °).

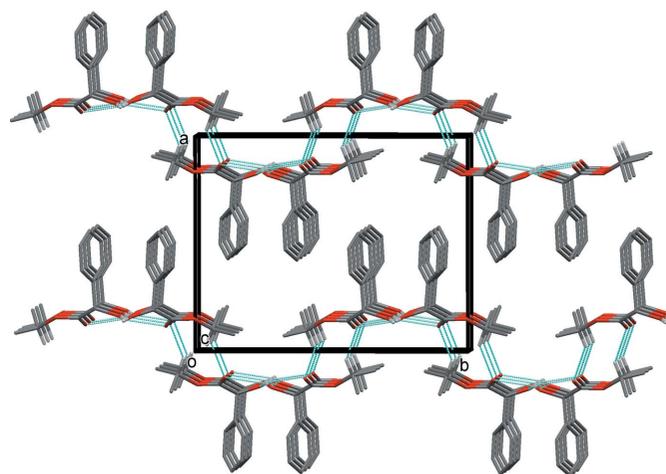
<i>D</i> –H··· <i>A</i>	<i>D</i> –H	H··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> –H··· <i>A</i>
O1–H1O···O1 <sup>i</sup>	0.83 (6)	2.12 (5)	2.903 (2)	158 (5)
O1–H1O···O2 <sup>i</sup>	0.83 (6)	2.38 (6)	2.930 (5)	124 (5)
C9–H9···O2 <sup>ii</sup>	1.00	2.53	3.379 (7)	142

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

isopropyl 2-hydroxy-2-phenylacetate yielded three hits, *viz.* isopropyl 2,2-bis(4-bromophenyl)-2-hydroxyacetate (EFAFEY; Smith, 2012), 1-isopropyl 4-methyl 2-hydroxy-2-[2-[(methoxycarbonyl)amino]phenyl] succinate (MAZJAA; Suárez-Castillo *et al.*, 2012) and *syn*-isopropyl 2,3-dihydroxy-4-methyl-2-phenylpentanoate (MERRIL; Scholtis *et al.*, 2006). In the crystals of these three compounds, molecules are linked by pairs of O–H···O hydrogen bonds, forming inversion dimers.

### 5. Synthesis and crystallization

To a solution of (*2RS*)-2-hydroxy-2-phenylacetic acid (15.22 g, 0.1 mol; racemic mandelic acid) in 50 ml propan-2-ol was added 0.5 ml of concentrated H<sub>2</sub>SO<sub>4</sub>, and the mixture was refluxed for 5 h (Fig. 4). The excess of propan-2-ol was removed *in vacuo*. The reaction mixture was diluted with cold water and Na<sub>2</sub>CO<sub>3</sub> was added to adjust the pH to 8. The solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 30 ml). The organic layers were combined and the solvent extracted by distillation (at reduced pressure at the end). The residue was distilled *in vacuo*, and a fraction with a boiling point of 361–363 K/4 mm Hg was taken, and then left for several hours in the refrigerator at *ca* 278 K, giving finally the title compound as colourless needle-like crystals (yield of 17.67 g, 91%; m.p. 306.9–307.3 K).


**Figure 3**

A view along the *c* axis of the crystal packing of the title compound, with the hydrogen bonds shown as dashed lines (see Table 1). For clarity, only H atoms H1O and H9 have been included.

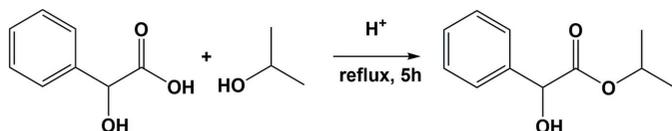


Figure 4  
Reaction scheme

## 6. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2. All of the H atoms could all be located from difference-Fourier maps. The hydroxyl H atom was refined with  $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{O})$ . The C-bound H atoms were included in calculated positions and treated as riding: C–H = 0.93–0.97 Å, with  $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C-methyl})$  and  $1.2U_{\text{eq}}(\text{C})$  for other H atoms.

## References

- Agilent (2012). *CrysAlis PRO*. Agilent Technologies, Yarnton, England.  
 European Pharmacopoeia Supplement (2016). pp. 5801–5803. Strasbourg: Council of Europe.  
 European Pharmacopoeia Supplement (2017). pp. 733–736. Strasbourg: Council of Europe.  
 Farrugia, L. J. (2012). *J. Appl. Cryst.* **45**, 849–854.  
 Groom, C. R., Bruno, I. J., Lightfoot, M. P. & Ward, S. C. (2016). *Acta Cryst.* **B72**, 171–179.  
 Macrae, C. F., Bruno, I. J., Chisholm, J. A., Edgington, P. R., McCabe, P., Pidcock, E., Rodriguez-Monge, L., Taylor, R., van de Streek, J. & Wood, P. A. (2008). *J. Appl. Cryst.* **41**, 466–470.  
 Scholtis, S., Ide, A. & Mahrwald, R. (2006). *Org. Lett.* **8**, 5353–5355.  
 Sheldrick, G. M. (2008). *Acta Cryst.* **A64**, 112–122.  
 Sheldrick, G. M. (2015). *Acta Cryst.* **C71**, 3–8.  
 Silverman, R. B. (2016). *Technol. Innov.* **17**, 153–158.  
 Smith, G. (2012). *Acta Cryst.* **E68**, o3276.  
 Spek, A. L. (2009). *Acta Cryst.* **D65**, 148–155.

Table 2

Experimental details.

Crystal data	
Chemical formula	$\text{C}_{11}\text{H}_{14}\text{O}_3$
$M_r$	194.22
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	100
$a, b, c$ (Å)	11.872 (3), 15.165 (4), 5.6079 (11)
$\beta$ (°)	91.41 (2)
$V$ (Å <sup>3</sup> )	1009.3 (4)
$Z$	4
Radiation type	Mo $K\alpha$
$\mu$ (mm <sup>-1</sup> )	0.09
Crystal size (mm)	0.20 × 0.08 × 0.06
Data collection	
Diffractometer	Agilent Xcalibur Sapphire3
Absorption correction	Multi-scan ( <i>CrysAlis RED</i> ; Agilent, 2012)
$T_{\text{min}}, T_{\text{max}}$	0.357, 1.000
No. of measured, independent and observed [ $I > 2\sigma(I)$ ] reflections	5292, 1761, 922
$R_{\text{int}}$	0.101
$(\sin \theta/\lambda)_{\text{max}}$ (Å <sup>-1</sup> )	0.594
Refinement	
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.090, 0.255, 1.03
No. of reflections	1761
No. of parameters	132
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\text{max}}, \Delta\rho_{\text{min}}$ (e Å <sup>-3</sup> )	0.30, -0.26

Computer programs: *CrysAlis CCD* and *CrysAlis RED* (Agilent, 2012), *SHELXS2014* (Sheldrick, 2008), *SHELXL2014* (Sheldrick, 2015), *ORTEP-3 for Windows* (Farrugia, 2012), *Mercury* (Macrae *et al.*, 2008), *PLATON* (Spek, 2009) and *publCIF* (Westrip, 2010).

Suárez-Castillo, R., Bautista-Hernández, C. I., Sánchez-Zavala, M., Meléndez-Rodríguez, M., Sierra-Zenteno, A., Morales-Ríos, M. S. & Joseph-Nathan, P. (2012). *Heterocycles*, **85**, 2147–2171.  
 Westrip, S. P. (2010). *J. Appl. Cryst.* **43**, 920–925.

## supporting information

*Acta Cryst.* (2017). E73, 771-773 [https://doi.org/10.1107/S2056989017005862]

## Crystal structure of isopropyl 2-hydroxy-2-phenylacetate: a pharmacopoeia reference standard

Ivan Isaiev, Svitlana Shishkina, Igor Ukrainets and Elena Bevz

### Computing details

Data collection: *CrysAlis CCD* (Agilent, 2012); cell refinement: *CrysAlis CCD* (Agilent, 2012); data reduction: *CrysAlis RED* (Agilent, 2012); program(s) used to solve structure: *SHELXS2014* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL2014* (Sheldrick, 2015); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 2012) and *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *SHELXL2014* (Sheldrick, 2015), *PLATON* (Spek, 2009) and *publCIF* (Westrip, 2010).

### Isopropyl 2-hydroxy-2-phenylacetate

#### Crystal data

$C_{11}H_{14}O_3$

$M_r = 194.22$

Monoclinic,  $P2_1/c$

$a = 11.872$  (3) Å

$b = 15.165$  (4) Å

$c = 5.6079$  (11) Å

$\beta = 91.41$  (2)°

$V = 1009.3$  (4) Å<sup>3</sup>

$Z = 4$

$F(000) = 416$

$D_x = 1.278$  Mg m<sup>-3</sup>

Mo  $K\alpha$  radiation,  $\lambda = 0.71073$  Å

Cell parameters from 403 reflections

$\theta = 4.3$ – $21.1$ °

$\mu = 0.09$  mm<sup>-1</sup>

$T = 100$  K

Needle, colourless

$0.20 \times 0.08 \times 0.06$  mm

#### Data collection

Agilent Xcalibur Sapphire3  
diffractometer

Radiation source: Enhance (Mo) X-ray Source

Detector resolution: 16.1827 pixels mm<sup>-1</sup>

$\omega$ -scan

Absorption correction: multi-scan  
(*CrysAlis RED*; Agilent, 2012)

$T_{\min} = 0.357$ ,  $T_{\max} = 1.000$

5292 measured reflections

1761 independent reflections

922 reflections with  $I > 2\sigma(I)$

$R_{\text{int}} = 0.101$

$\theta_{\max} = 25.0$ °,  $\theta_{\min} = 3.2$ °

$h = -14 \rightarrow 13$

$k = -17 \rightarrow 18$

$l = -5 \rightarrow 6$

#### Refinement

Refinement on  $F^2$

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.090$

$wR(F^2) = 0.255$

$S = 1.03$

1761 reflections

132 parameters

0 restraints

Primary atom site location: structure-invariant  
direct methods

Secondary atom site location: difference Fourier  
map

Hydrogen site location: difference Fourier map

H atoms treated by a mixture of independent  
and constrained refinement

$$w = 1/[\sigma^2(F_o^2) + (0.1022P)^2]$$

where  $P = (F_o^2 + 2F_c^2)/3$   
 $(\Delta/\sigma)_{\max} < 0.001$

$$\Delta\rho_{\max} = 0.30 \text{ e } \text{\AA}^{-3}$$

$$\Delta\rho_{\min} = -0.26 \text{ e } \text{\AA}^{-3}$$

*Special details*

**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.

*Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ( $\text{\AA}^2$ )*

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
O1	0.8289 (3)	0.2748 (2)	0.4019 (6)	0.0456 (10)
H1O	0.845 (4)	0.252 (4)	0.534 (10)	0.068*
O2	0.8740 (3)	0.4013 (2)	0.0966 (6)	0.0476 (11)
O3	0.8375 (3)	0.5068 (2)	0.3667 (6)	0.0455 (10)
C1	0.5984 (5)	0.3361 (3)	0.3003 (9)	0.0443 (14)
H1	0.6314	0.3108	0.1638	0.053*
C2	0.4827 (5)	0.3407 (3)	0.3113 (9)	0.0479 (14)
H2	0.4368	0.3171	0.1856	0.057*
C3	0.4332 (5)	0.3801 (3)	0.5079 (9)	0.0492 (15)
H3	0.3535	0.3852	0.5142	0.059*
C4	0.4998 (5)	0.4111 (3)	0.6910 (9)	0.0467 (14)
H4	0.4658	0.4367	0.8262	0.056*
C5	0.6154 (5)	0.4061 (3)	0.6831 (9)	0.0419 (13)
H5	0.6600	0.4286	0.8122	0.050*
C6	0.6684 (4)	0.3679 (3)	0.4857 (8)	0.0387 (13)
C7	0.7937 (4)	0.3603 (3)	0.4744 (8)	0.0403 (13)
H7	0.8283	0.3743	0.6343	0.048*
C8	0.8399 (4)	0.4230 (3)	0.2895 (9)	0.0416 (13)
C9	0.8869 (5)	0.5744 (3)	0.2113 (9)	0.0452 (14)
H9	0.9599	0.5521	0.1494	0.054*
C10	0.8087 (5)	0.5957 (4)	0.0050 (9)	0.0565 (16)
H10A	0.7346	0.6120	0.0649	0.085*
H10B	0.8009	0.5440	-0.0989	0.085*
H10C	0.8394	0.6451	-0.0856	0.085*
C11	0.9094 (5)	0.6527 (3)	0.3724 (9)	0.0528 (15)
H11A	0.9489	0.6329	0.5183	0.079*
H11B	0.8378	0.6802	0.4136	0.079*
H11C	0.9562	0.6956	0.2897	0.079*

*Atomic displacement parameters ( $\text{\AA}^2$ )*

	$U^{11}$	$U^{22}$	$U^{33}$	$U^{12}$	$U^{13}$	$U^{23}$
O1	0.074 (3)	0.030 (2)	0.0327 (19)	0.0060 (18)	0.0021 (18)	0.0017 (15)
O2	0.074 (3)	0.040 (2)	0.0298 (19)	-0.0036 (18)	0.0078 (18)	-0.0039 (15)
O3	0.068 (3)	0.035 (2)	0.0337 (19)	-0.0031 (18)	0.0107 (17)	-0.0007 (15)
C1	0.062 (4)	0.039 (3)	0.031 (3)	0.000 (3)	-0.003 (2)	0.003 (2)

C2	0.064 (4)	0.042 (3)	0.038 (3)	-0.001 (3)	-0.003 (3)	0.005 (2)
C3	0.055 (4)	0.046 (3)	0.047 (3)	-0.001 (3)	-0.001 (3)	0.009 (3)
C4	0.063 (4)	0.036 (3)	0.041 (3)	0.004 (3)	0.010 (3)	0.001 (2)
C5	0.065 (4)	0.027 (3)	0.033 (3)	-0.004 (3)	0.001 (2)	0.003 (2)
C6	0.055 (4)	0.033 (3)	0.029 (3)	-0.004 (2)	0.003 (2)	0.003 (2)
C7	0.060 (4)	0.031 (3)	0.030 (3)	-0.001 (3)	0.003 (2)	-0.004 (2)
C8	0.055 (4)	0.034 (3)	0.036 (3)	-0.002 (3)	-0.003 (2)	-0.002 (2)
C9	0.061 (4)	0.038 (3)	0.037 (3)	-0.006 (3)	0.012 (2)	0.001 (2)
C10	0.081 (4)	0.051 (4)	0.038 (3)	-0.015 (3)	0.001 (3)	0.010 (3)
C11	0.074 (4)	0.039 (3)	0.045 (3)	-0.008 (3)	0.002 (3)	-0.001 (2)

*Geometric parameters (Å, °)*

O1—C7	1.424 (6)	C3—C4	1.364 (8)
O2—C8	1.211 (5)	C4—C5	1.376 (8)
O3—C8	1.343 (6)	C5—C6	1.412 (7)
O3—C9	1.476 (6)	C6—C7	1.495 (7)
C1—C2	1.378 (7)	C7—C8	1.519 (7)
C1—C6	1.401 (7)	C9—C10	1.501 (8)
C2—C3	1.397 (7)	C9—C11	1.512 (7)
C8—O3—C9	117.1 (4)	O1—C7—C6	112.4 (4)
C2—C1—C6	121.6 (5)	O1—C7—C8	105.2 (4)
C1—C2—C3	119.8 (5)	C6—C7—C8	110.9 (4)
C4—C3—C2	119.6 (6)	O2—C8—O3	123.8 (5)
C3—C4—C5	121.1 (5)	O2—C8—C7	125.0 (4)
C4—C5—C6	120.8 (5)	O3—C8—C7	111.2 (4)
C1—C6—C5	117.0 (5)	O3—C9—C10	111.0 (4)
C1—C6—C7	121.0 (5)	O3—C9—C11	105.0 (4)
C5—C6—C7	121.9 (5)	C10—C9—C11	112.9 (5)
C6—C1—C2—C3	1.9 (8)	C1—C6—C7—C8	71.2 (6)
C1—C2—C3—C4	-2.1 (8)	C5—C6—C7—C8	-109.5 (5)
C2—C3—C4—C5	1.4 (8)	C9—O3—C8—O2	-4.3 (8)
C3—C4—C5—C6	-0.5 (7)	C9—O3—C8—C7	176.1 (4)
C2—C1—C6—C5	-0.9 (7)	O1—C7—C8—O2	15.9 (7)
C2—C1—C6—C7	178.4 (5)	C6—C7—C8—O2	-105.9 (6)
C4—C5—C6—C1	0.2 (7)	O1—C7—C8—O3	-164.5 (4)
C4—C5—C6—C7	-179.1 (4)	C6—C7—C8—O3	73.7 (5)
C1—C6—C7—O1	-46.2 (6)	C8—O3—C9—C10	76.8 (6)
C5—C6—C7—O1	133.0 (5)	C8—O3—C9—C11	-160.9 (5)

*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>
O1—H1O $\cdots$ O1 <sup>i</sup>	0.83 (6)	2.12 (5)	2.903 (2)	158 (5)

---

O1—H1O···O2 <sup>i</sup>	0.83 (6)	2.38 (6)	2.930 (5)	124 (5)
C9—H9···O2 <sup>ii</sup>	1.00	2.53	3.379 (7)	142

---

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