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tert-Butyl *N*-[(1*R**,2*R**,4*R**,5*S**)-*rel*-4-*tert*-butoxybicyclo[3.1.0]hex-2-yl]-*N*-hydroxycarbamate

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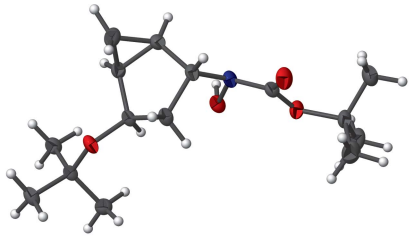
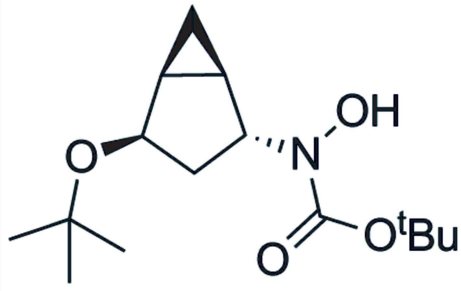
In the title compound, $C_{15}H_{27}NO_4$, the cyclopentane ring adopts an envelope conformation with the methylene group as the flap. The dihedral angle between the cyclopropane ring and the cyclopentane ring (all atoms) is 77.54 (13)°. In the crystal, molecules are linked *via* O—H···O hydrogen bonds, forming *C*(7) chains propagating along [010].

3D view



Chemical scheme



Structure description

Carbocyclic nucleosides are increasingly interesting compounds for their antiviral and antitumor effects (Ji & Miller, 2010). Replacing the oxygen atom of the parent furanose ring with a methylene unit increases stability towards certain cleaving enzymes but also decreases structural rigidity, which lowers bioactivity (Crimmons, 1998; Altona & Sundaralingam, 1972). The creation of structurally rigid carbocyclic nucleoside analogs are therefore synthetically useful targets. The cyclopropanation of 3-aza-2-oxabicyclic alkenes adds increased structural rigidity upon ring opening while creating new stereocenters to make diverse organic frameworks. The acid-catalysed ring-opening reaction (Fig. 1) of cyclopropanated 3-aza-2-oxabicylic **I** with an alcohol nucleophile thereby created the title fused bicyclic amino alcohol, **II**.

The molecular structure of **II** is shown in Fig. 2. In the arbitrarily chosen asymmetric molecule of the racemic crystal the stereogenic centres are as follows: C1 *R*; C2 S; C4 *R*; C5 *R*. The conformation of the cyclopentane ring is well described as an envelope on C6 (the methylene group), which lies to the same side of the C1/C2/C4/C5 plane as does C3. The dihedral angle between the cyclopropane ring (C2/C3/C4) and the cyclopentane ring (all atoms) is 77.54 (13)°. In the crystal, O—H···O hydrogen bonds link the molecules, forming *C*(7) chains propagating along [010] (Fig. 3, Table 1), with adjacent molecules related by translation.

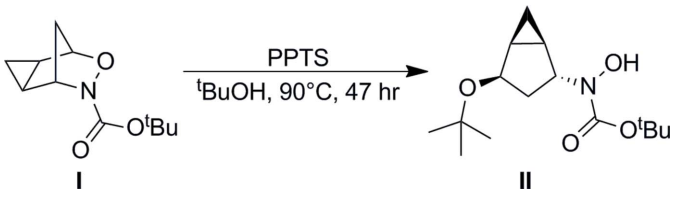


Figure 1
Acid-catalysed nucleophilic ring opening of cyclopropanated 3-aza-2-oxabicyclic substrate **I** with an alcohol.

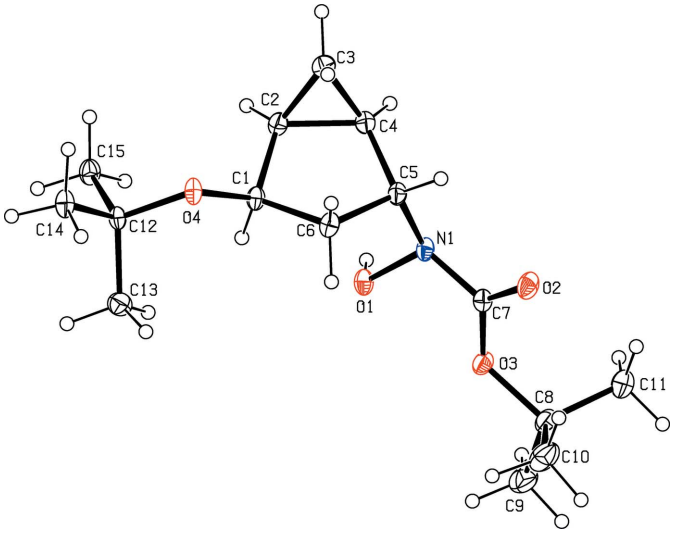


Figure 2
The molecular structure of **II**, with displacement ellipsoids shown at the 30% probability level.

Synthesis and crystallization

In a small screw-cap vial containing a stir bar, the catalyst pyridinium *p*-toluenesulfonate (PPTS) (4.4 mg, 0.018 mmol, 0.10 equiv) was added. The cyclopropanated 3-aza-2-oxabicyclic substrate **I** (35.1 mg, 0.166 mmol, 1.0 equiv) was added to the same vial and reagents were dissolved in the nucleophile *tert*-butyl alcohol (0.5 ml). The vial was sealed and heated to 90°C with continuous stirring for 47 h. The crude product was purified by column chromatography using a gradient (EtOAc:hexanes = 1:9 to 1:1), followed by recrystallization using slow evaporation of mixed solvents of 1:3 EtOAc:hexanes to give clear, colourless crystals of **II**.

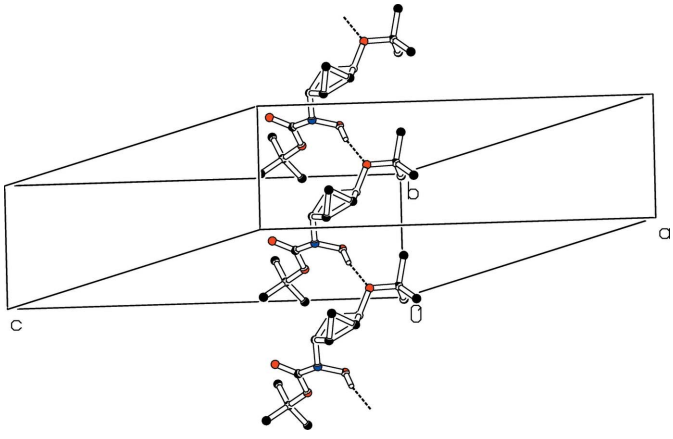


Figure 3
Part of the crystal structure of (II), with O—H···O hydrogen bonds shown as dashed lines.

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1—H1*O*···O4^{i}	0.94 (2)	1.87 (2)	2.7926 (12)	164.9 (17)

Symmetry code: (i) $x, y-1, z$.

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_{15}H_{27}NO_4$
M_r	285.37
Crystal system, space group	Monoclinic, *C*2/*c*
Temperature (K)	150
a, *b*, *c* (Å)	30.4330 (8), 6.0885 (2), 19.3949 (5)
β (°)	117.316 (1)
V (Å^3)	3192.97 (16)
Z	8
Radiation type	Cu *K*α
μ (mm^{-1})	0.69
Crystal size (mm)	0.20 × 0.02 × 0.02
Data collection	
Diffractometer	Bruker Kappa APEX DUO CCD
Absorption correction	Multi-scan (*SADABS*; Bruker, 2014)
T_{min}, T_{max}	0.669, 0.753
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	31096, 2841, 2438
R_{int}	0.046
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.598
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.032, 0.079, 1.04
No. of reflections	2841
No. of parameters	191
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.17, −0.19

Computer programs: *APEX2* and *SAINT* (Bruker, 2014), *SHELXT* (Sheldrick, 2015*a*), *SHELXL2016* (Sheldrick, 2015*b*), *PLATON* (Spek, 2009) and *SHELXTL* (Sheldrick, 2008).

Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2.

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full crystallographic data

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Crystal data

$C_{15}H_{27}NO_4$
M_r = 285.37
Monoclinic, $C2/c$
a = 30.4330 (8) Å
b = 6.0885 (2) Å
c = 19.3949 (5) Å
β = 117.316 (1)°
V = 3192.97 (16) Å^3
Z = 8
$F(000)$ = 1248
D_x = 1.187 Mg m^{-3}
Cu $K\alpha$ radiation, λ = 1.54178 Å
Cell parameters from 8804 reflections
θ = 3.3–66.5°
μ = 0.69 mm^{-1}
T = 150 K
Needle, colourless
0.20 × 0.02 × 0.02 mm

Data collection

Bruker Kappa APEX DUO CCD diffractometer
Radiation source: Bruker ImuS with multi-layer optics
φ and ω scans
Absorption correction: multi-scan (SADABS; Bruker, 2014)
T_{min} = 0.669, T_{max} = 0.753
31096 measured reflections
2841 independent reflections
2438 reflections with $I > 2\sigma(I)$
R_{int} = 0.046
θ_{max} = 67.2°, θ_{min} = 3.3°
h = −36→35
k = −6→7
l = −22→23

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.032
$wR(F^2)$ = 0.079
S = 1.04
2841 reflections
191 parameters
0 restraints
Primary atom site location: structure-invariant direct methods
Hydrogen site location: mixed
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0325P)^2 + 2.2411P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.17 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-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.

Refinement. H atoms were placed in calculated positions with C–H = 0.95–1.00\%A and included in the refinement with U_{iso}(H)=1.2U_{eq}(C) or 1.5U_{eq}(C_{methyl}).

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.62521 (3)	0.04110 (15)	0.55279 (5)	0.0254 (2)
O2	0.61508 (3)	0.12952 (16)	0.72223 (5)	0.0316 (2)
O3	0.57295 (3)	−0.08261 (14)	0.61525 (5)	0.0261 (2)
O4	0.66930 (3)	0.69189 (13)	0.51429 (4)	0.0235 (2)
N1	0.64312 (4)	0.08435 (17)	0.63300 (5)	0.0223 (2)
C1	0.66942 (5)	0.47437 (19)	0.54309 (7)	0.0213 (3)
H1A	0.647444	0.377948	0.498916	0.026*
C2	0.71989 (5)	0.3697 (2)	0.58472 (7)	0.0246 (3)
H2A	0.734864	0.301410	0.553512	0.030*
C3	0.75326 (5)	0.4479 (3)	0.66554 (8)	0.0347 (3)
H3A	0.743755	0.583547	0.683521	0.042*
H3B	0.789309	0.426698	0.685590	0.042*
C4	0.72183 (5)	0.2465 (2)	0.65364 (7)	0.0270 (3)
H4A	0.737951	0.098813	0.666975	0.032*
C5	0.67375 (4)	0.2832 (2)	0.65730 (7)	0.0227 (3)
H5A	0.680931	0.322490	0.711531	0.027*
C6	0.64988 (5)	0.4809 (2)	0.60336 (7)	0.0245 (3)
H6A	0.613378	0.468312	0.577668	0.029*
H6B	0.659443	0.619979	0.633065	0.029*
C7	0.60933 (4)	0.0513 (2)	0.66110 (7)	0.0222 (3)
C8	0.53621 (5)	−0.1602 (2)	0.63979 (7)	0.0282 (3)
C9	0.50339 (6)	−0.3055 (3)	0.57224 (9)	0.0459 (4)
H9A	0.488527	−0.217813	0.524572	0.069*
H9B	0.477189	−0.368744	0.582086	0.069*
H9C	0.523226	−0.423911	0.566358	0.069*
C10	0.50715 (6)	0.0317 (3)	0.64721 (10)	0.0455 (4)
H10A	0.528927	0.123914	0.691053	0.068*
H10B	0.479865	−0.023094	0.656027	0.068*
H10C	0.493823	0.118615	0.599364	0.068*
C11	0.56154 (6)	−0.2929 (3)	0.71356 (8)	0.0395 (4)
H11A	0.582298	−0.195949	0.756585	0.059*
H11B	0.582192	−0.406312	0.707037	0.059*
H11C	0.536558	−0.362710	0.724908	0.059*
C12	0.65385 (4)	0.71127 (19)	0.43108 (6)	0.0208 (3)
C13	0.60068 (5)	0.6342 (2)	0.38409 (8)	0.0311 (3)
H13A	0.580048	0.699460	0.405381	0.047*
H13B	0.599380	0.473737	0.386730	0.047*
H13C	0.588355	0.679736	0.329901	0.047*
C14	0.65735 (5)	0.9550 (2)	0.41865 (7)	0.0279 (3)
H14A	0.633297	1.034279	0.429788	0.042*
H14B	0.650232	0.981387	0.364683	0.042*
H14C	0.690773	1.006978	0.453451	0.042*

C15	0.68833 (5)	0.5845 (2)	0.40857 (7)	0.0276 (3)
H15A	0.722359	0.635327	0.439964	0.041*
H15B	0.678617	0.608928	0.353505	0.041*
H15C	0.686251	0.427409	0.417722	0.041*
H1O	0.6432 (7)	−0.081 (3)	0.5493 (11)	0.065 (6)*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0354 (5)	0.0249 (5)	0.0201 (4)	0.0002 (4)	0.0165 (4)	−0.0015 (3)
O2	0.0402 (5)	0.0366 (5)	0.0260 (5)	−0.0080 (4)	0.0220 (4)	−0.0063 (4)
O3	0.0281 (5)	0.0296 (5)	0.0254 (4)	−0.0057 (4)	0.0165 (4)	−0.0027 (4)
O4	0.0380 (5)	0.0170 (4)	0.0191 (4)	−0.0015 (4)	0.0162 (4)	0.0003 (3)
N1	0.0294 (5)	0.0227 (5)	0.0188 (5)	−0.0017 (4)	0.0144 (4)	−0.0003 (4)
C1	0.0290 (6)	0.0165 (6)	0.0216 (6)	0.0002 (5)	0.0145 (5)	0.0012 (5)
C2	0.0275 (6)	0.0257 (7)	0.0249 (6)	0.0004 (5)	0.0156 (5)	0.0023 (5)
C3	0.0276 (7)	0.0472 (9)	0.0280 (7)	−0.0095 (6)	0.0115 (6)	0.0013 (6)
C4	0.0257 (6)	0.0311 (7)	0.0246 (6)	0.0018 (5)	0.0119 (5)	0.0064 (5)
C5	0.0276 (6)	0.0229 (6)	0.0193 (6)	−0.0028 (5)	0.0122 (5)	0.0000 (5)
C6	0.0320 (7)	0.0205 (6)	0.0270 (7)	0.0008 (5)	0.0188 (6)	0.0010 (5)
C7	0.0264 (6)	0.0207 (6)	0.0217 (6)	0.0017 (5)	0.0130 (5)	0.0022 (5)
C8	0.0276 (7)	0.0311 (7)	0.0319 (7)	−0.0032 (5)	0.0188 (6)	0.0026 (6)
C9	0.0402 (8)	0.0558 (10)	0.0426 (9)	−0.0205 (8)	0.0198 (7)	−0.0073 (7)
C10	0.0408 (9)	0.0434 (9)	0.0669 (11)	0.0069 (7)	0.0372 (8)	0.0076 (8)
C11	0.0424 (8)	0.0388 (9)	0.0404 (8)	−0.0043 (7)	0.0218 (7)	0.0098 (7)
C12	0.0274 (6)	0.0205 (6)	0.0162 (6)	0.0009 (5)	0.0116 (5)	0.0007 (5)
C13	0.0283 (7)	0.0310 (7)	0.0309 (7)	0.0002 (6)	0.0109 (6)	0.0024 (6)
C14	0.0422 (8)	0.0215 (7)	0.0245 (6)	0.0000 (6)	0.0190 (6)	0.0020 (5)
C15	0.0338 (7)	0.0281 (7)	0.0259 (7)	0.0049 (5)	0.0179 (6)	0.0018 (5)

Geometric parameters (Å, º)

O1—N1	1.4172 (12)	C8—C11	1.5108 (19)
O1—H1O	0.94 (2)	C8—C10	1.511 (2)
O2—C7	1.2135 (14)	C8—C9	1.515 (2)
O3—C7	1.3333 (15)	C9—H9A	0.9800
O3—C8	1.4791 (14)	C9—H9B	0.9800
O4—C1	1.4367 (14)	C9—H9C	0.9800
O4—C12	1.4639 (13)	C10—H10A	0.9800
N1—C7	1.3818 (15)	C10—H10B	0.9800
N1—C5	1.4676 (15)	C10—H10C	0.9800
C1—C2	1.5097 (17)	C11—H11A	0.9800
C1—C6	1.5362 (16)	C11—H11B	0.9800
C1—H1A	1.0000	C11—H11C	0.9800
C2—C3	1.5013 (18)	C12—C14	1.5149 (17)
C2—C4	1.5098 (17)	C12—C15	1.5192 (17)
C2—H2A	1.0000	C12—C13	1.5218 (17)
C3—C4	1.5061 (19)	C13—H13A	0.9800

C3—H3A	0.9900	C13—H13B	0.9800
C3—H3B	0.9900	C13—H13C	0.9800
C4—C5	1.5139 (17)	C14—H14A	0.9800
C4—H4A	1.0000	C14—H14B	0.9800
C5—C6	1.5404 (17)	C14—H14C	0.9800
C5—H5A	1.0000	C15—H15A	0.9800
C6—H6A	0.9900	C15—H15B	0.9800
C6—H6B	0.9900	C15—H15C	0.9800

N1—O1—H1O	106.4 (11)	C11—C8—C10	112.95 (12)
C7—O3—C8	119.98 (9)	O3—C8—C9	101.77 (10)
C1—O4—C12	116.43 (9)	C11—C8—C9	110.72 (12)
C7—N1—O1	115.14 (9)	C10—C8—C9	110.57 (13)
C7—N1—C5	118.12 (10)	C8—C9—H9A	109.5
O1—N1—C5	111.94 (9)	C8—C9—H9B	109.5
O4—C1—C2	114.69 (10)	H9A—C9—H9B	109.5
O4—C1—C6	109.83 (9)	C8—C9—H9C	109.5
C2—C1—C6	104.95 (10)	H9A—C9—H9C	109.5
O4—C1—H1A	109.1	H9B—C9—H9C	109.5
C2—C1—H1A	109.1	C8—C10—H10A	109.5
C6—C1—H1A	109.1	C8—C10—H10B	109.5
C3—C2—C1	117.34 (11)	H10A—C10—H10B	109.5
C3—C2—C4	60.02 (9)	C8—C10—H10C	109.5
C1—C2—C4	107.47 (10)	H10A—C10—H10C	109.5
C3—C2—H2A	119.1	H10B—C10—H10C	109.5
C1—C2—H2A	119.1	C8—C11—H11A	109.5
C4—C2—H2A	119.1	C8—C11—H11B	109.5
C2—C3—C4	60.27 (8)	H11A—C11—H11B	109.5
C2—C3—H3A	117.7	C8—C11—H11C	109.5
C4—C3—H3A	117.7	H11A—C11—H11C	109.5
C2—C3—H3B	117.7	H11B—C11—H11C	109.5
C4—C3—H3B	117.7	O4—C12—C14	104.11 (9)
H3A—C3—H3B	114.9	O4—C12—C15	111.16 (9)
C3—C4—C2	59.71 (8)	C14—C12—C15	110.11 (10)
C3—C4—C5	115.60 (12)	O4—C12—C13	110.53 (10)
C2—C4—C5	108.80 (10)	C14—C12—C13	109.87 (11)
C3—C4—H4A	119.4	C15—C12—C13	110.86 (10)
C2—C4—H4A	119.4	C12—C13—H13A	109.5
C5—C4—H4A	119.4	C12—C13—H13B	109.5
N1—C5—C4	110.37 (10)	H13A—C13—H13B	109.5
N1—C5—C6	113.23 (10)	C12—C13—H13C	109.5
C4—C5—C6	104.36 (10)	H13A—C13—H13C	109.5
N1—C5—H5A	109.6	H13B—C13—H13C	109.5
C4—C5—H5A	109.6	C12—C14—H14A	109.5
C6—C5—H5A	109.6	C12—C14—H14B	109.5
C1—C6—C5	105.68 (10)	H14A—C14—H14B	109.5
C1—C6—H6A	110.6	C12—C14—H14C	109.5
C5—C6—H6A	110.6	H14A—C14—H14C	109.5

C1—C6—H6B	110.6	H14B—C14—H14C	109.5
C5—C6—H6B	110.6	C12—C15—H15A	109.5
H6A—C6—H6B	108.7	C12—C15—H15B	109.5
O2—C7—O3	126.50 (11)	H15A—C15—H15B	109.5
O2—C7—N1	121.89 (11)	C12—C15—H15C	109.5
O3—C7—N1	111.51 (10)	H15A—C15—H15C	109.5
O3—C8—C11	110.06 (10)	H15B—C15—H15C	109.5
O3—C8—C10	110.21 (11)		

C12—O4—C1—C2	102.14 (12)	C2—C4—C5—C6	−15.46 (13)
C12—O4—C1—C6	−139.98 (10)	O4—C1—C6—C5	−153.26 (10)
O4—C1—C2—C3	75.76 (13)	C2—C1—C6—C5	−29.48 (12)
C6—C1—C2—C3	−44.85 (14)	N1—C5—C6—C1	−92.48 (12)
O4—C1—C2—C4	140.48 (10)	C4—C5—C6—C1	27.59 (12)
C6—C1—C2—C4	19.87 (13)	C8—O3—C7—O2	−3.74 (19)
C1—C2—C3—C4	95.27 (12)	C8—O3—C7—N1	172.72 (10)
C2—C3—C4—C5	−97.70 (12)	O1—N1—C7—O2	−162.08 (11)
C1—C2—C4—C3	−111.98 (12)	C5—N1—C7—O2	−26.13 (17)
C3—C2—C4—C5	109.26 (12)	O1—N1—C7—O3	21.27 (14)
C1—C2—C4—C5	−2.72 (14)	C5—N1—C7—O3	157.22 (10)
C7—N1—C5—C4	154.03 (10)	C7—O3—C8—C11	−61.96 (15)
O1—N1—C5—C4	−68.71 (12)	C7—O3—C8—C10	63.27 (15)
C7—N1—C5—C6	−89.39 (12)	C7—O3—C8—C9	−179.40 (11)
O1—N1—C5—C6	47.87 (13)	C1—O4—C12—C14	179.81 (10)
C3—C4—C5—N1	171.18 (10)	C1—O4—C12—C15	−61.67 (13)
C2—C4—C5—N1	106.50 (11)	C1—O4—C12—C13	61.88 (13)
C3—C4—C5—C6	49.21 (13)		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1—H1*O*···O4^{i}	0.94 (2)	1.87 (2)	2.7926 (12)	164.9 (17)

Symmetry code: (i) *x*, *y*−1, *z*.