organic compounds

(1S)-1-Phenylethanaminium 4-{[(1S,2S)-1-hydroxy-2,3-dihydro-1H,1'H-[2,2'-biinden]-2-yl]methyl}-benzoate

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The title molecular salt, $C_8H_{12}N^+ \cdot C_{26}H_{21}O_3^-$, contains a dimeric indane pharmacophore that demonstrates potent anti-inflammatory activity. The indane group of the anion exhibits some disorder about the α-C atom, which appears common to many structures containing this group. A model to account for the slight disorder was attempted, but this was deemed unsuccessful because applying bond-length constraints to all the bonds about the α-C atom led to instability in the refinement. The absolute configuration was determined crystallographically as S,S,S by anomalous dispersion methods with reference to both the Flack parameter and Bayesian statistics on Bijvoet differences. The configuration was also determined by an *a priori* knowledge of the absolute configuration of the (1S)-1-phenylethanaminium counter-ion. The molecules pack in the crystal structure to form an infinite two-dimensional hydrogen-bond network in the (100) plane of the unit cell.

Comment

The indane pharmacophore occurs in many different bioactive molecules, including the nonsteroidal anti-inflammatory indane sulindac (Clinoril, Merck) (Scheper *et al.*, 2007; Shiff *et al.*, 1995) and the protease inhibitor indinavir (Crixivan, Merck), used as a component of highly active antiretroviral therapy (HAART) (Vacca *et al.*, 1994; Lin, 1999). As part of our drug-discovery programme, we have identified a number of indanes that demonstrate smooth-muscle relaxation and inhibit mediator release (Sheridan *et al.*, 1990, 1999a,b). More recently, we have synthesized and characterized a series of dimeric indanes that demonstrate potent anti-inflammatory activity (Frankish *et al.*, 2004; Sheridan, Walsh, Cogan *et al.*,

2009; Sheridan, Walsh, Jordan *et al.*, 2009). The title compound, (I), a single enantiomer, is the 1-phenylethanaminium salt of 4-{[(1S,2S)-1-hydroxy-2,3-dihydro-1H,1'H-[2,2'-biinden]-2-yl]methyl}benzoic acid (PH46) and represents a first-in-class anti-inflammatory indane scaffold with potential therapeutic use in the treatment of inflammatory bowel disease (Frankish & Sheridan, 2012). The crystal structure and absolute stereochemistry determination of (I) are described here.
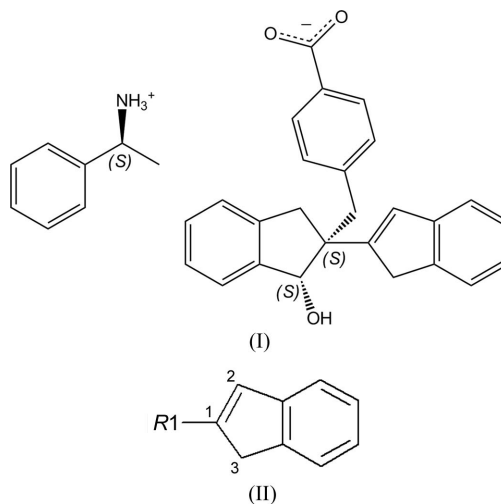
The structure of (I) is shown in Fig. 1. The inden-2-yl group, defined by atoms C18–C26, demonstrates disorder in the position of the C—C and C=C bonds in the five-membered ring. The disorder manifests itself in the appearance of three
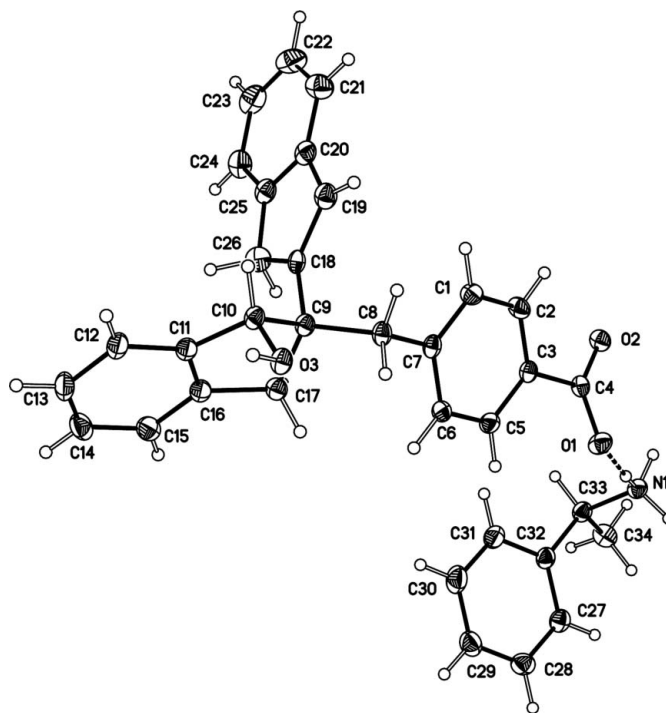

Figure 1
The molecular structure of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level for non-H atoms. The dashed line indicates a hydrogen bond.
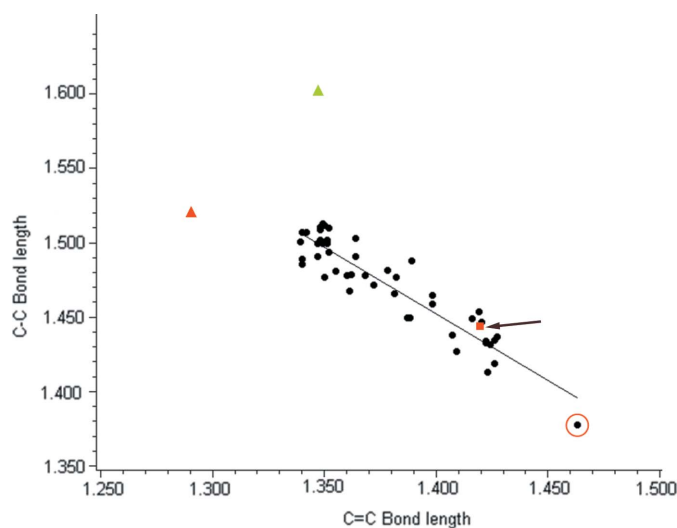
Figure 2
A scatterplot of C≡C *versus* C—C bond lengths for inden-2-yl fragments in the CSD. See the *Comment* for an explanation of the symbols.

potential H-atom positions in a difference Fourier synthesis about each of atoms C19 and C26, both α to atom C18. The potential disorder in this group was also revealed through a Hirshfeld rigid-bond test (Hirshfeld, 1976), where the differences in the components of the anisotropic displacement parameters along the C18—C19 and C18—C26 bonds exceed 6 s.u.

A simple *Conquest* (Macrae *et al.*, 2008) search of the Cambridge Structural Database (CSD, Version 5.33; Allen, 2002) for inden-2-yl fragments as shown in (II) (see Scheme), where $R1$ is defined as any substituent other than hydrogen, returned a total of 33 entries. The disorder present in the inden-2-yl fragment was documented in a number of structures and the use of a two-part disorder model to separate the two components was attempted [see, for example, CSD refcodes APOVUX (Nikitin *et al.*, 2010), CORBOB (Nikitin *et al.*, 2009), OGEKAN (Nikulin *et al.*, 2008) and TENBAP (Li *et al.*, 1996)], although in the case of APOVUX it was specifically noted that the disorder model failed. A scatterplot of C—C distances *versus* C≡C distances is shown in Fig. 2. The correlation between these two parameters is clear, such that for structures where there is no disorder present, or where the disorder model has been successfully implemented, the values of the C≡C and C—C bond lengths are clearly different, *ca* 1.35 and 1.50 Å, respectively (*e.g.* OGEKAN), whereas for structures that demonstrate the disorder phenomenon these two bond lengths appear to be correlated and ultimately equilibrate to a value of *ca* 1.42 Å. The outlier point circled in Fig. 2 (QUGWUK; Basavaiah *et al.*, 2001) is due to the incorrect assignment of the C-atom type when geometrically placing the H atoms; the 1.378 and 1.463 Å bond lengths should be assigned as C≡C and C—C bonds, respectively, and not *vice versa*. The complete list of structures contained within this data set is available in the *Supplementary materials*.

In keeping with the findings above, the C≡C and C—C bond lengths (C18≡C19 and C18—C26, respectively) in (I)

refined to values of 1.420 (3) and 1.443 (2) Å, respectively (shown as a square in Fig. 2, indicated with an arrow). A disorder model incorporating the two different components, with the sum of the occupancies constrained to unity, was attempted. However, in order for the refinement to converge successfully, the displacement parameters for the α-C atom C18 and its disordered component C18A had to be constrained as isotropic. The model converged, yielding occupancies of the two inden-2-yl components of 0.57 (2) and 0.43 (2). The resulting C≡C and C—C bond lengths about C18/C18A were 1.29 (2)/1.52 (2) Å for component 1 and 1.35 (2)/1.60 (3) Å for component 2 (lower and upper triangles in Fig. 2, respectively). Further refinement cycles in which additional bond-length constraints were applied to all bonds about the α-C atom led to instability in the refinement. From this analysis it was concluded that the disorder model was insufficient and so the data presented here is based on the ordered model.

For the inden-2-yl moiety, the five-membered C18–C20/C25/C26 ring is planar, with C18—C19—C20—C25 and C20—C25—C26—C18 torsion angles of 1.36 (16) and −0.69 (16)°, respectively, whereas the five-membered C9–C11/C16/C17 ring of the indan-2-yl moiety adopts an envelope conformation or *E* form, with atom C9 displaced by 0.478 (2) Å from the mean plane defined by the other four atoms.

The absolute configuration of (I), *viz. S, S* and *S* at the chiral centres C9, C10 and C33, respectively, was determined by reference to the *a priori* knowledge of the chirality of the (*S*)-(−)-methylbenzylamine used in the salt-formation step and by anomalous dispersion methods (Flack, 1983). The determination of the absolute configuration of (I) by anomalous dispersion methods was likely to be challenging, given that the molecular formula and asymmetric unit contain only a single N and three O atoms. To maximize the likelihood of success, a full sphere of data was collected using Cu $K\alpha$ radiation to a maximum resolution of 0.80 Å. A total of 25 532 reflections were collected, yielding a Flack parameter x and standard uncertainty u for this structure of 0.00 (15) based on 2343 Friedel pairs. The value of u is slightly beyond the limit of enantiopure-sufficient distinguishing power (Flack & Bernardinelli, 1999, 2000), and for further confirmation of the absolute configuration a determination using Bayesian statistics on Bijvoet differences (Hooft *et al.*, 2008), as implemented in the program *PLATON* (Spek, 2009), was performed. This gave probability values $p3(ok)$, $p3(twin)$ and $p3(wrong)$ of 1.000, 0.000 and 0.000, respectively. The calculation was based on 2343 Bijvoet pairs. The absolute structure parameter and standard uncertainty calculated using this method was 0.11 (4). An improvement in the absolute structure parameter can be made using a Student t distribution rather than a Gaussian distribution (Hooft *et al.*, 2010), giving −0.03 (13) for a v parameter of 9.79. The overall $p3$ probability values calculated using this method remain unchanged at 1.000, 0.000 and 0.000.

The packing arrangement for (I) is best descibed as an infinite two-dimensional hydrogen-bond network in the (100) plane of the unit cell. The primary building block of this
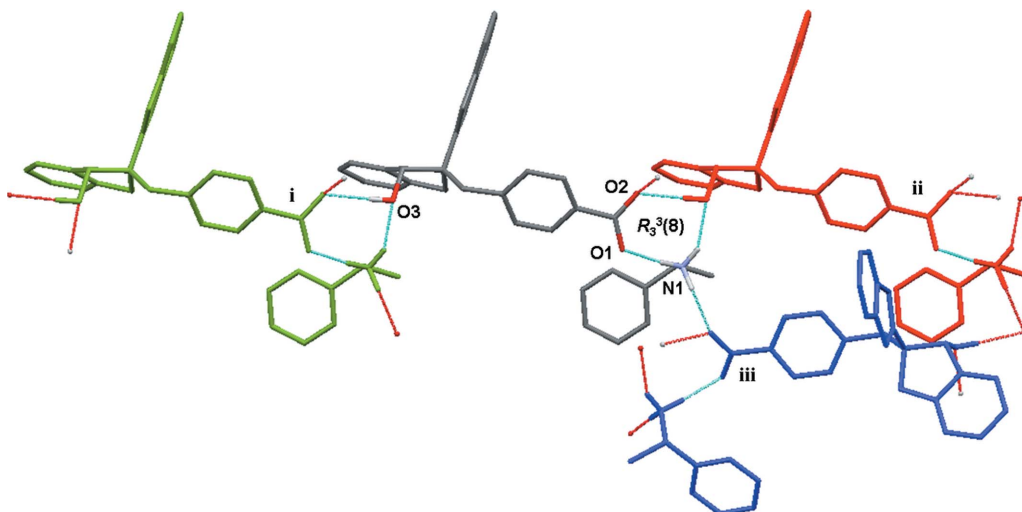
Figure 3
A view of part of the crystal packing of (I). The figure shows the four hydrogen-bond interactions (thin lines) and the formation of the $R_3^3(8)$ ring. [In the electronic version of the paper, molecules generated by the symmetry codes (i), (ii) and (iii) are represented by the colours green, red and blue, respectively, with hydrogen bonds shown as thin turquoise lines and incomplete hydrogen bonds as thin red lines.] For clarity, only H atoms attached to heteroatoms are shown. (The symmetry codes are as given in Table 1.)

network is the formation of an infinite chain of PH46 anions through a translational symmetry operation along the *c* axis of the unit cell. This interaction is formed by a single hydrogen bond from the hydroxy group of the substituted indenyl group, acting as donor, to a carbonyl O atom of the benzoate group, acting as acceptor [O3—H3A···O2^i = 2.7113 (14) Å; see Table 1 for hydrogen-bond geometry and symmetry codes]. The hydrogen-bond network is extended by the formation of three further interactions linking the PH46 anion to the (1*S*)-1-phenylethanaminium cation. These three interactions are formed by the –NH$_3^+$ ammonium group acting as donor to O atoms of three different PH46 anions acting as acceptors. Two of these interactions bridge the infinite chain along the *c* axis to form an $R_3^3(8)$ ring (Bernstein *et al.*, 1995); N1—H1···O1 = 2.6697 (16) Å and N1—H1C···O3^{ii} = 2.8799 (18) Å. The –NH$_3^+$ ammonium group of the cation makes a further donor

interaction with the carbonyl O atom of a PH46 anion to form a larger overall two-dimensional network in the (100) plane; N1—H1D···O2^{iii} = 2.7991 (17) Å. Fig. 3 shows the four hydrogen-bond interactions described above. An overall view of the crystal packing down the *a* axis of the unit cell is shown in Fig. 4. All potential hydrogen-bond donors are utilized in the hydrogen-bonding arrangement, thus concurring with Etter's first rule of hydrogen bonding for organic compounds, which states that all good H-atom donors and acceptors are used in hydrogen bonding (Etter, 1990).

Experimental

To an ethanol (7.5 ml) suspension of 4-{[(1*S*,2*S*)-1-hydroxy-2,3-dihydro-1*H*,1′*H*-[2,2′-biinden]-2-yl]methyl}benzoic acid (PH46; 0.5 g, 1.31 mmol) was added (*S*)-(−)-α-methylbenzylamine (0.2 ml, 1.5 mmol, 1.1 equivalents) portionwise. This reaction mixture was stirred for 2 h at 323 K and then left overnight at room temperature. Since no solid material was obtained, the solution was then concentrated under reduced pressure and diethyl ether (2 ml) was added to the flask. A white solid was immediately observed, which was further washed with diethyl ether (3 × 4 ml). The organic solvent was removed using a Pasteur pipette and the remaining white solid was dried in a vacuum oven at 313 K (yield 0.56 g, 85%). Crystals of the salt, (I), were obtained by dissolving the crude material (*ca* 100 mg) in MeOH (3 ml) in a flat-bottomed sample tube, followed by the addition of diethyl ether (6 ml), which was added until the sample solution became slightly cloudy. The solution was filtered and placed in a dry-box at room temperature. A small amount of tetrahydrofuran (*ca* 0.5 ml) was added to the diethyl ether–methanol solution. After 5 d, colourless crystals of (I) were obtained (m.p. 467.2–467.9 K). ^{1}H NMR (100 MHz, d_6-DMSO): δ 1.33 (*d*, 3H, *J* = 6.7 Hz), 2.68 (*d*, 1H, *J* = 13.5 Hz), 2.94, (*d*, 1H, *J* = 15.5 Hz), 2.99 (*d*, 1H, *J* = 15.5 Hz), 3.17 (*d*, 1H, *J* = 13.6 Hz), 3.44 (*d*, 1H, *J* = 23.0 Hz), 3.58 (*d*, 1H, *J* = 23.0 Hz), 4.12 (*q*, 1H, *J* = 6.7 Hz), 5.05 (*s*, 1H), 5.85 (*br s*, 1H), 6.41 (*s*, 1H), 6.86 (*d*, 2H, *J* = 8.2 Hz), 7.08 (*td*, 1H, *J* = 7.3, 1.3 Hz), 7.14–7.44 (*m*, aromatic 12H), 7.65 (*d*, 2H, *J* = 8.2 Hz).
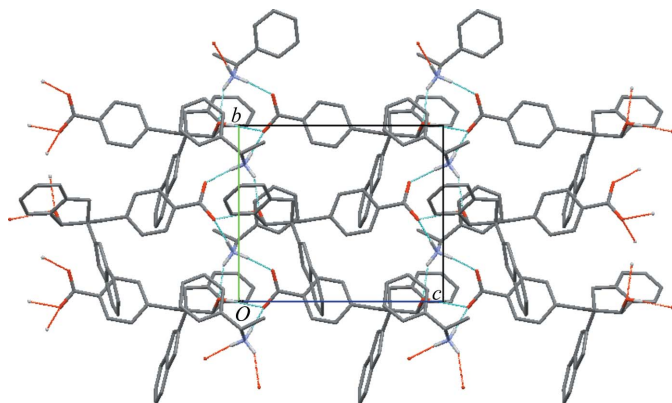

Figure 4
The packing of (I), viewed down the *a* axis, with hydrogen bonds shown as thin lines. (In the electronic version of the paper, hydrogen bonds are shown as thin turquoise lines and incomplete hydrogen bonds as thin red lines.) For clarity, only H atoms attached to heteroatoms are shown.

organic compounds

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

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$O3-H3A\cdots O2^{i}$	0.85 (2)	1.86 (2)	2.7113 (14)	177 (2)
$N1-H1B\cdots O3^{ii}$	0.91 (2)	2.05 (2)	2.8799 (18)	151 (2)
$N1-H1C\cdots O2^{iii}$	0.92 (2)	1.88 (2)	2.7991 (17)	178 (2)
$N1-H1D\cdots O1$	0.91 (2)	1.77 (2)	2.6697 (16)	174 (2)

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

Crystal data

$C_8H_{12}N^+ \cdot C_{26}H_{21}O_3^-$
$M_r = 503.61$
Monoclinic, $P2_1$
$a = 11.0350$ (3) Å
$b = 10.1713$ (3) Å
$c = 11.8533$ (3) Å
$\beta = 93.678$ (2)°

$V = 1327.68$ (6) Å^3
$Z = 2$
Cu $K\alpha$ radiation
$\mu = 0.63$ mm^{-1}
$T = 100$ K
$0.50 \times 0.47 \times 0.42$ mm

Data collection

Agilent SuperNova Dual
 diffractometer, with Cu at zero
 and an Atlas detector
Absorption correction: multi-scan
 (*CrysAlis PRO*; Agilent, 2011)
 $T_{min} = 0.749$, $T_{max} = 1.000$

25532 measured reflections
5221 independent reflections
5157 reflections with $I > 2\sigma(I)$
$R_{int} = 0.026$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.035$
$wR(F^2) = 0.098$
$S = 1.01$
5221 reflections
362 parameters
1 restraint

H atoms treated by a mixture of
 independent and constrained
 refinement
$\Delta\rho_{max} = 0.21$ e Å^{-3}
$\Delta\rho_{min} = -0.21$ e Å^{-3}
Absolute structure: Flack (1983),
 with 2343 Friedel pairs
Flack parameter: 0.00 (15)

H atoms bonded to heteroatoms were located in a difference map and refined. Other H atoms were positioned geometrically and refined using a riding model (including free rotation about the methyl C—C bond), with C—H = 0.95–0.99 Å and $U_{iso}(H) = 1.5U_{eq}(C)$ for methyl groups or $1.2U_{eq}(C)$ otherwise.

Data collection: *CrysAlis PRO* (Agilent, 2011); cell refinement: *CrysAlis PRO*; data reduction: *CrysAlis PRO*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 2008); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL* and *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *SHELXTL* and *Mercury*.

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supplementary materials

(1*S*)-1-Phenylethanaminium 4-{[(1*S*,2*S*)-1-hydroxy-2,3-dihydro-1*H*,1′*H*-[2,2′-biinden]-2-yl]methyl}benzoate

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(1*S*)-1-Phenylethanaminium 4-{[(1*S*,2*S*)-1-hydroxy-2,3-dihydro-1*H*,1′*H*- [2,2′-biinden]-2-yl]methyl}benzoate

Crystal data

$C_8H_{12}N^+ \cdot C_{26}H_{21}O_3^-$	$D_x = 1.260$ Mg m^{-3}
$M_r = 503.61$	Melting point: 467.5 K
Monoclinic, $P2_1$	Cu $K\alpha$ radiation, $\lambda = 1.54178$ Å
$a = 11.0350$ (3) Å	Cell parameters from 17123 reflections
$b = 10.1713$ (3) Å	$\theta = 3.7$–75.9°
$c = 11.8533$ (3) Å	$\mu = 0.63$ mm^{-1}
$\beta = 93.678$ (2)°	$T = 100$ K
$V = 1327.68$ (6) Å^3	Block, yellow
$Z = 2$	$0.50 \times 0.47 \times 0.42$ mm
$F(000) = 536$	

Data collection

Agilent SuperNova Dual diffractometer, with Cu at zero and an Atlas detector	$T_{min} = 0.749$, $T_{max} = 1.000$
	25532 measured reflections
	5221 independent reflections
Radiation source: SuperNova (Cu) X-ray Source	5157 reflections with $I > 2\sigma(I)$
	$R_{int} = 0.026$
Mirror monochromator	$\theta_{max} = 74.5°$, $\theta_{min} = 3.7°$
Detector resolution: 10.5598 pixels mm^{-1}	$h = -13 \rightarrow 13$
ω scans	$k = -11 \rightarrow 12$
Absorption correction: multi-scan (*CrysAlis PRO*; Agilent, 2011)	$l = -14 \rightarrow 14$

Refinement

Refinement on F^2	H atoms treated by a mixture of independent and constrained refinement
Least-squares matrix: full	
$R[F^2 > 2\sigma(F^2)] = 0.035$	$w = 1/[\sigma^2(F_o^2) + (0.075P)^2 + 0.250P]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.098$	
$S = 1.01$	$(\Delta/\sigma)_{max} < 0.001$
5221 reflections	$\Delta\rho_{max} = 0.21$ e Å^{-3}
362 parameters	$\Delta\rho_{min} = -0.21$ e Å^{-3}
1 restraint	Extinction correction: *SHELXTL* (Sheldrick, 2008), Fc*=kFc[1+0.001xFc$^2\lambda^3$/sin(2θ)]$^{-1/4}$
Primary atom site location: structure-invariant direct methods	Extinction coefficient: 0.0021 (4)
Secondary atom site location: difference Fourier map	Absolute structure: Flack (1983), with 2343 Friedel pairs
Hydrogen site location: inferred from neighbouring sites	Flack parameter: 0.00 (15)

Special details

Experimental. CrysAlisPro, Agilent Technologies, Version 1.171.35.19 (release 27-10-2011 CrysAlis171 .NET) (compiled Oct 27 2011,15:02:11) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($Å^2$)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.97227 (10)	0.67327 (12)	0.83449 (8)	0.0226 (2)
O2	0.92573 (9)	0.46529 (11)	0.87703 (8)	0.0191 (2)
O3	0.89439 (9)	0.51048 (11)	0.09869 (8)	0.0182 (2)
H3A	0.9027 (19)	0.499 (2)	0.029 (2)	0.033 (6)*
C1	0.91707 (13)	0.37857 (15)	0.52630 (12)	0.0194 (3)
H1A	0.9223	0.2909	0.4994	0.023*
C2	0.92760 (13)	0.40249 (15)	0.64190 (12)	0.0192 (3)
H2A	0.9402	0.3312	0.6931	0.023*
C3	0.91987 (11)	0.52948 (15)	0.68328 (11)	0.0156 (3)
C4	0.94029 (12)	0.55850 (15)	0.80808 (11)	0.0158 (3)
C5	0.89799 (13)	0.63239 (15)	0.60755 (11)	0.0185 (3)
H5A	0.8904	0.7196	0.6349	0.022*
C6	0.88715 (13)	0.60794 (15)	0.49189 (12)	0.0193 (3)
H6A	0.8714	0.6790	0.4411	0.023*
C7	0.89896 (11)	0.48130 (15)	0.44897 (11)	0.0161 (3)
C8	0.90019 (12)	0.45817 (16)	0.32278 (10)	0.0174 (3)
H8A	0.9452	0.3758	0.3104	0.021*
H8B	0.9459	0.5308	0.2895	0.021*
C9	0.77439 (12)	0.44829 (15)	0.25795 (11)	0.0161 (3)
C10	0.79016 (12)	0.43611 (15)	0.12766 (11)	0.0168 (3)
H10A	0.7962	0.3421	0.1039	0.020*
C11	0.67726 (12)	0.50009 (15)	0.07553 (11)	0.0181 (3)
C12	0.63315 (13)	0.49669 (17)	−0.03744 (12)	0.0219 (3)
H12A	0.6692	0.4411	−0.0904	0.026*
C13	0.53492 (14)	0.57693 (18)	−0.07056 (13)	0.0257 (3)
H13A	0.5038	0.5765	−0.1472	0.031*
C14	0.48202 (13)	0.65749 (18)	0.00710 (15)	0.0275 (3)
H14A	0.4147	0.7111	−0.0169	0.033*
C15	0.52649 (13)	0.66076 (17)	0.12012 (14)	0.0238 (3)
H15A	0.4900	0.7157	0.1732	0.029*
C16	0.62537 (12)	0.58175 (15)	0.15320 (12)	0.0185 (3)
C17	0.69704 (13)	0.57468 (15)	0.26644 (12)	0.0185 (3)
H17A	0.6422	0.5681	0.3291	0.022*
H17B	0.7495	0.6530	0.2786	0.022*
C18	0.70480 (12)	0.32897 (15)	0.29625 (11)	0.0166 (3)
C19	0.75503 (14)	0.20146 (16)	0.31348 (12)	0.0226 (3)
H19A	0.8364	0.1762	0.3031	0.027*
C20	0.65735 (13)	0.11507 (16)	0.35061 (11)	0.0205 (3)
C21	0.65690 (16)	−0.01722 (18)	0.37918 (13)	0.0278 (3)
H21A	0.7294	−0.0677	0.3798	0.033*
C22	0.54745 (18)	−0.07482 (19)	0.40716 (14)	0.0320 (4)

H22A	0.5454	−0.1657	0.4256	0.038*
C23	0.44189 (16)	−0.0006 (2)	0.40821 (14)	0.0318 (4)
H23A	0.3683	−0.0413	0.4270	0.038*
C24	0.44272 (14)	0.13288 (18)	0.38206 (13)	0.0269 (3)
H24A	0.3709	0.1840	0.3843	0.032*
C25	0.55085 (14)	0.18992 (16)	0.35255 (11)	0.0210 (3)
C26	0.57753 (14)	0.32620 (17)	0.31758 (13)	0.0239 (3)
H26A	0.5273	0.3500	0.2484	0.029*
H26B	0.5602	0.3890	0.3783	0.029*
N1	0.90975 (11)	0.78051 (13)	1.02795 (10)	0.0189 (3)
H1B	0.9082 (19)	0.710 (2)	1.0743 (19)	0.025 (5)*
H1C	0.966 (2)	0.840 (2)	1.0589 (18)	0.028 (5)*
H1D	0.933 (2)	0.749 (2)	0.961 (2)	0.031 (5)*
C27	0.81467 (13)	1.06674 (17)	0.92266 (13)	0.0221 (3)
H27A	0.8446	1.0993	0.9942	0.026*
C28	0.80522 (14)	1.15072 (17)	0.82987 (14)	0.0253 (3)
H28A	0.8271	1.2406	0.8386	0.030*
C29	0.76376 (14)	1.10320 (18)	0.72436 (14)	0.0273 (3)
H29A	0.7576	1.1604	0.6609	0.033*
C30	0.73157 (15)	0.9727 (2)	0.71210 (13)	0.0303 (4)
H30A	0.7041	0.9399	0.6399	0.036*
C31	0.73922 (14)	0.88904 (18)	0.80497 (13)	0.0253 (3)
H31A	0.7161	0.7995	0.7961	0.030*
C32	0.78069 (12)	0.93597 (16)	0.91144 (12)	0.0198 (3)
C33	0.78543 (13)	0.84192 (16)	1.01074 (12)	0.0200 (3)
H33A	0.7257	0.7699	0.9927	0.024*
C34	0.75416 (15)	0.90403 (17)	1.12179 (13)	0.0256 (3)
H34A	0.6714	0.9394	1.1140	0.038*
H34B	0.8114	0.9754	1.1413	0.038*
H34C	0.7595	0.8374	1.1816	0.038*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0316 (5)	0.0215 (6)	0.0148 (4)	−0.0046 (4)	0.0014 (4)	−0.0027 (4)
O2	0.0244 (5)	0.0211 (6)	0.0119 (4)	0.0015 (4)	0.0020 (3)	0.0013 (4)
O3	0.0196 (5)	0.0244 (6)	0.0107 (4)	−0.0016 (4)	0.0024 (3)	−0.0004 (4)
C1	0.0247 (7)	0.0182 (7)	0.0154 (7)	0.0024 (6)	0.0016 (5)	−0.0028 (5)
C2	0.0256 (7)	0.0192 (8)	0.0130 (6)	0.0025 (6)	0.0021 (5)	0.0036 (5)
C3	0.0147 (6)	0.0202 (7)	0.0119 (6)	−0.0012 (5)	0.0010 (4)	−0.0004 (5)
C4	0.0155 (6)	0.0199 (7)	0.0121 (6)	0.0017 (5)	0.0015 (4)	−0.0004 (5)
C5	0.0224 (6)	0.0174 (7)	0.0153 (6)	−0.0019 (5)	−0.0010 (5)	−0.0007 (5)
C6	0.0244 (7)	0.0183 (7)	0.0147 (6)	−0.0030 (5)	−0.0036 (5)	0.0037 (5)
C7	0.0140 (5)	0.0218 (8)	0.0123 (6)	−0.0024 (5)	0.0006 (4)	0.0000 (5)
C8	0.0169 (6)	0.0230 (8)	0.0122 (6)	−0.0015 (5)	0.0004 (5)	0.0010 (5)
C9	0.0182 (6)	0.0191 (7)	0.0110 (5)	−0.0007 (5)	0.0011 (5)	−0.0005 (5)
C10	0.0195 (6)	0.0201 (7)	0.0109 (6)	−0.0022 (5)	0.0008 (5)	−0.0004 (5)
C11	0.0188 (6)	0.0191 (7)	0.0163 (6)	−0.0042 (5)	0.0002 (5)	0.0022 (5)
C12	0.0224 (7)	0.0258 (8)	0.0170 (6)	−0.0065 (6)	−0.0021 (5)	0.0016 (6)
C13	0.0229 (7)	0.0319 (9)	0.0212 (7)	−0.0076 (6)	−0.0074 (5)	0.0068 (6)

C14	0.0184 (7)	0.0290 (9)	0.0341 (8)	−0.0009 (6)	−0.0055 (6)	0.0099 (7)
C15	0.0190 (6)	0.0235 (8)	0.0287 (7)	−0.0008 (6)	0.0004 (6)	0.0034 (6)
C16	0.0186 (6)	0.0198 (8)	0.0171 (6)	−0.0030 (5)	0.0008 (5)	0.0020 (5)
C17	0.0214 (6)	0.0198 (7)	0.0145 (6)	0.0008 (5)	0.0019 (5)	0.0000 (5)
C18	0.0184 (6)	0.0217 (7)	0.0093 (5)	−0.0004 (5)	−0.0013 (5)	−0.0009 (5)
C19	0.0232 (7)	0.0265 (9)	0.0180 (6)	−0.0027 (6)	0.0004 (5)	0.0026 (6)
C20	0.0257 (7)	0.0243 (8)	0.0115 (6)	−0.0025 (6)	0.0010 (5)	−0.0007 (5)
C21	0.0378 (9)	0.0250 (9)	0.0212 (7)	0.0013 (7)	0.0062 (6)	0.0033 (6)
C22	0.0513 (10)	0.0242 (9)	0.0213 (7)	−0.0089 (7)	0.0085 (7)	0.0025 (6)
C23	0.0354 (9)	0.0367 (10)	0.0237 (7)	−0.0149 (7)	0.0042 (6)	0.0030 (7)
C24	0.0241 (7)	0.0343 (9)	0.0224 (7)	−0.0045 (6)	0.0029 (5)	0.0057 (7)
C25	0.0240 (7)	0.0264 (8)	0.0126 (6)	−0.0035 (6)	0.0016 (5)	−0.0006 (6)
C26	0.0275 (8)	0.0260 (8)	0.0188 (6)	−0.0008 (6)	0.0068 (5)	0.0001 (6)
N1	0.0235 (6)	0.0185 (7)	0.0145 (6)	−0.0017 (5)	0.0002 (4)	−0.0015 (5)
C27	0.0195 (6)	0.0261 (8)	0.0207 (7)	−0.0024 (6)	0.0022 (5)	0.0000 (6)
C28	0.0230 (7)	0.0236 (9)	0.0297 (8)	−0.0021 (6)	0.0043 (6)	0.0042 (6)
C29	0.0241 (7)	0.0313 (9)	0.0262 (7)	−0.0014 (6)	−0.0007 (6)	0.0087 (7)
C30	0.0306 (8)	0.0383 (10)	0.0212 (7)	−0.0053 (7)	−0.0051 (6)	0.0020 (7)
C31	0.0274 (7)	0.0253 (8)	0.0226 (8)	−0.0048 (6)	−0.0038 (6)	0.0000 (6)
C32	0.0159 (6)	0.0231 (8)	0.0204 (7)	−0.0026 (5)	0.0006 (5)	0.0013 (6)
C33	0.0188 (6)	0.0211 (8)	0.0200 (7)	−0.0029 (5)	0.0009 (5)	0.0005 (6)
C34	0.0280 (7)	0.0276 (9)	0.0220 (7)	0.0029 (6)	0.0072 (6)	0.0024 (6)

Geometric parameters (Å, º)

O1—C4	1.2534 (19)	C18—C26	1.443 (2)
O2—C4	1.2686 (18)	C19—C20	1.479 (2)
O3—C10	1.4365 (17)	C19—H19A	0.9500
O3—H3A	0.85 (2)	C20—C21	1.388 (2)
C1—C2	1.389 (2)	C20—C25	1.402 (2)
C1—C7	1.396 (2)	C21—C22	1.401 (2)
C1—H1A	0.9500	C21—H21A	0.9500
C2—C3	1.386 (2)	C22—C23	1.389 (3)
C2—H2A	0.9500	C22—H22A	0.9500
C3—C5	1.390 (2)	C23—C24	1.393 (3)
C3—C4	1.5111 (17)	C23—H23A	0.9500
C5—C6	1.3910 (19)	C24—C25	1.391 (2)
C5—H5A	0.9500	C24—H24A	0.9500
C6—C7	1.394 (2)	C25—C26	1.482 (2)
C6—H6A	0.9500	C26—H26A	0.9900
C7—C8	1.5152 (17)	C26—H26B	0.9900
C8—C9	1.5463 (17)	N1—C33	1.5092 (19)
C8—H8A	0.9900	N1—H1B	0.91 (2)
C8—H8B	0.9900	N1—H1C	0.92 (2)
C9—C18	1.521 (2)	N1—H1D	0.91 (2)
C9—C17	1.550 (2)	C27—C32	1.386 (2)
C9—C10	1.5701 (17)	C27—C28	1.391 (2)
C10—C11	1.5029 (19)	C27—H27A	0.9500
C10—H10A	1.0000	C28—C29	1.391 (2)
C11—C16	1.390 (2)	C28—H28A	0.9500

C11—C12	1.3956 (19)	C29—C30	1.379 (3)
C12—C13	1.393 (2)	C29—H29A	0.9500
C12—H12A	0.9500	C30—C31	1.390 (2)
C13—C14	1.389 (3)	C30—H30A	0.9500
C13—H13A	0.9500	C31—C32	1.399 (2)
C14—C15	1.397 (2)	C31—H31A	0.9500
C14—H14A	0.9500	C32—C33	1.515 (2)
C15—C16	1.391 (2)	C33—C34	1.520 (2)
C15—H15A	0.9500	C33—H33A	1.0000
C16—C17	1.5153 (19)	C34—H34A	0.9800
C17—H17A	0.9900	C34—H34B	0.9800
C17—H17B	0.9900	C34—H34C	0.9800
C18—C19	1.420 (2)		
C10—O3—H3A	107.5 (15)	C19—C18—C9	124.88 (13)
C2—C1—C7	121.07 (14)	C26—C18—C9	125.69 (13)
C2—C1—H1A	119.5	C18—C19—C20	107.47 (13)
C7—C1—H1A	119.5	C18—C19—H19A	126.3
C3—C2—C1	120.60 (13)	C20—C19—H19A	126.3
C3—C2—H2A	119.7	C21—C20—C25	120.44 (15)
C1—C2—H2A	119.7	C21—C20—C19	131.50 (15)
C2—C3—C5	119.03 (12)	C25—C20—C19	108.06 (14)
C2—C3—C4	121.31 (13)	C20—C21—C22	118.68 (16)
C5—C3—C4	119.60 (13)	C20—C21—H21A	120.7
O1—C4—O2	125.47 (12)	C22—C21—H21A	120.7
O1—C4—C3	116.64 (12)	C23—C22—C21	120.73 (17)
O2—C4—C3	117.87 (13)	C23—C22—H22A	119.6
C3—C5—C6	120.15 (14)	C21—C22—H22A	119.6
C3—C5—H5A	119.9	C22—C23—C24	120.69 (16)
C6—C5—H5A	119.9	C22—C23—H23A	119.7
C5—C6—C7	121.38 (14)	C24—C23—H23A	119.7
C5—C6—H6A	119.3	C25—C24—C23	118.71 (16)
C7—C6—H6A	119.3	C25—C24—H24A	120.6
C6—C7—C1	117.70 (12)	C23—C24—H24A	120.6
C6—C7—C8	120.71 (13)	C24—C25—C20	120.73 (16)
C1—C7—C8	121.47 (13)	C24—C25—C26	130.50 (15)
C7—C8—C9	115.85 (11)	C20—C25—C26	108.76 (13)
C7—C8—H8A	108.3	C18—C26—C25	106.28 (14)
C9—C8—H8A	108.3	C18—C26—H26A	110.5
C7—C8—H8B	108.3	C25—C26—H26A	110.5
C9—C8—H8B	108.3	C18—C26—H26B	110.5
H8A—C8—H8B	107.4	C25—C26—H26B	110.5
C18—C9—C8	110.97 (11)	H26A—C26—H26B	108.7
C18—C9—C17	110.60 (11)	C33—N1—H1B	111.0 (13)
C8—C9—C17	113.23 (12)	C33—N1—H1C	111.2 (14)
C18—C9—C10	108.70 (11)	H1B—N1—H1C	108.5 (18)
C8—C9—C10	109.95 (10)	C33—N1—H1D	109.9 (14)
C17—C9—C10	103.03 (11)	H1B—N1—H1D	105 (2)
O3—C10—C11	109.20 (12)	H1C—N1—H1D	110.8 (19)

O3—C10—C9	109.55 (11)	C32—C27—C28	120.48 (15)
C11—C10—C9	103.24 (11)	C32—C27—H27A	119.8
O3—C10—H10A	111.5	C28—C27—H27A	119.8
C11—C10—H10A	111.5	C29—C28—C27	120.09 (16)
C9—C10—H10A	111.5	C29—C28—H28A	120.0
C16—C11—C12	121.13 (14)	C27—C28—H28A	120.0
C16—C11—C10	110.62 (12)	C30—C29—C28	119.79 (15)
C12—C11—C10	127.79 (14)	C30—C29—H29A	120.1
C13—C12—C11	118.24 (15)	C28—C29—H29A	120.1
C13—C12—H12A	120.9	C29—C30—C31	120.25 (15)
C11—C12—H12A	120.9	C29—C30—H30A	119.9
C14—C13—C12	120.76 (14)	C31—C30—H30A	119.9
C14—C13—H13A	119.6	C30—C31—C32	120.36 (16)
C12—C13—H13A	119.6	C30—C31—H31A	119.8
C13—C14—C15	120.86 (15)	C32—C31—H31A	119.8
C13—C14—H14A	119.6	C27—C32—C31	119.01 (15)
C15—C14—H14A	119.6	C27—C32—C33	122.40 (13)
C16—C15—C14	118.51 (15)	C31—C32—C33	118.59 (14)
C16—C15—H15A	120.7	N1—C33—C32	110.62 (11)
C14—C15—H15A	120.7	N1—C33—C34	108.06 (12)
C11—C16—C15	120.49 (13)	C32—C33—C34	114.33 (13)
C11—C16—C17	110.15 (12)	N1—C33—H33A	107.9
C15—C16—C17	129.23 (14)	C32—C33—H33A	107.9
C16—C17—C9	103.90 (12)	C34—C33—H33A	107.9
C16—C17—H17A	111.0	C33—C34—H34A	109.5
C9—C17—H17A	111.0	C33—C34—H34B	109.5
C16—C17—H17B	111.0	H34A—C34—H34B	109.5
C9—C17—H17B	111.0	C33—C34—H34C	109.5
H17A—C17—H17B	109.0	H34A—C34—H34C	109.5
C19—C18—C26	109.40 (13)	H34B—C34—H34C	109.5
C7—C1—C2—C3	0.2 (2)	C15—C16—C17—C9	167.53 (15)
C1—C2—C3—C5	1.8 (2)	C18—C9—C17—C16	−88.29 (13)
C1—C2—C3—C4	−175.44 (12)	C8—C9—C17—C16	146.44 (11)
C2—C3—C4—O1	156.52 (14)	C10—C9—C17—C16	27.72 (13)
C5—C3—C4—O1	−20.69 (18)	C8—C9—C18—C19	−44.49 (17)
C2—C3—C4—O2	−22.41 (19)	C17—C9—C18—C19	−171.03 (12)
C5—C3—C4—O2	160.38 (13)	C10—C9—C18—C19	76.54 (16)
C2—C3—C5—C6	−1.6 (2)	C8—C9—C18—C26	137.40 (13)
C4—C3—C5—C6	175.68 (12)	C17—C9—C18—C26	10.86 (18)
C3—C5—C6—C7	−0.6 (2)	C10—C9—C18—C26	−101.57 (15)
C5—C6—C7—C1	2.6 (2)	C26—C18—C19—C20	−1.81 (15)
C5—C6—C7—C8	−173.49 (13)	C9—C18—C19—C20	179.82 (12)
C2—C1—C7—C6	−2.4 (2)	C18—C19—C20—C21	−179.67 (14)
C2—C1—C7—C8	173.66 (13)	C18—C19—C20—C25	1.36 (16)
C6—C7—C8—C9	−83.83 (17)	C25—C20—C21—C22	1.6 (2)
C1—C7—C8—C9	100.22 (16)	C19—C20—C21—C22	−177.31 (14)
C7—C8—C9—C18	−64.37 (17)	C20—C21—C22—C23	−1.1 (2)
C7—C8—C9—C17	60.70 (16)	C21—C22—C23—C24	−0.4 (3)

C7—C8—C9—C10	175.34 (13)	C22—C23—C24—C25	1.3 (2)	
C18—C9—C10—O3	−155.39 (11)	C23—C24—C25—C20	−0.9 (2)	
C8—C9—C10—O3	−33.73 (16)	C23—C24—C25—C26	177.79 (15)	
C17—C9—C10—O3	87.25 (13)	C21—C20—C25—C24	−0.6 (2)	
C18—C9—C10—C11	88.37 (13)	C19—C20—C25—C24	178.51 (13)	
C8—C9—C10—C11	−149.97 (12)	C21—C20—C25—C26	−179.50 (13)	
C17—C9—C10—C11	−28.99 (14)	C19—C20—C25—C26	−0.40 (16)	
O3—C10—C11—C16	−96.36 (13)	C19—C18—C26—C25	1.56 (15)	
C9—C10—C11—C16	20.12 (16)	C9—C18—C26—C25	179.92 (12)	
O3—C10—C11—C12	75.84 (19)	C24—C25—C26—C18	−179.46 (15)	
C9—C10—C11—C12	−167.68 (15)	C20—C25—C26—C18	−0.69 (16)	
C16—C11—C12—C13	−0.4 (2)	C32—C27—C28—C29	−1.3 (2)	
C10—C11—C12—C13	−171.84 (14)	C27—C28—C29—C30	0.3 (2)	
C11—C12—C13—C14	−0.4 (2)	C28—C29—C30—C31	0.7 (3)	
C12—C13—C14—C15	0.4 (2)	C29—C30—C31—C32	−0.6 (3)	
C13—C14—C15—C16	0.2 (2)	C28—C27—C32—C31	1.3 (2)	
C12—C11—C16—C15	1.0 (2)	C28—C27—C32—C33	−177.95 (13)	
C10—C11—C16—C15	173.84 (13)	C30—C31—C32—C27	−0.4 (2)	
C12—C11—C16—C17	−175.21 (13)	C30—C31—C32—C33	178.92 (14)	
C10—C11—C16—C17	−2.40 (17)	C27—C32—C33—N1	−86.92 (17)	
C14—C15—C16—C11	−0.9 (2)	C31—C32—C33—N1	93.78 (15)	
C14—C15—C16—C17	174.50 (15)	C27—C32—C33—C34	35.32 (19)	
C11—C16—C17—C9	−16.65 (15)	C31—C32—C33—C34	−143.97 (14)	

Hydrogen-bond geometry (Å, º)

D—H···A	D—H	H···A	D···A	D—H···A
O3—H3*A*···O2ⁱ	0.85 (2)	1.86 (2)	2.7113 (14)	177 (2)
N1—H1*B*···O3ⁱⁱ	0.91 (2)	2.05 (2)	2.8799 (18)	151 (2)
N1—H1*C*···O2ⁱⁱⁱ	0.92 (2)	1.88 (2)	2.7991 (17)	178 (2)
N1—H1*D*···O1	0.91 (2)	1.77 (2)	2.6697 (16)	174 (2)

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