

Chiral crystals from an achiral molecule: 4,6-di-*O*-benzyl-1,3-*O*-benzylidene-2-*O*-(4-methoxybenzyl)-*myo*-5-inosose

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Received 7 February 2012

Accepted 6 March 2012

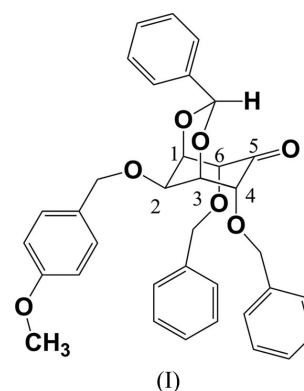
Online 6 April 2012

The title achiral compound, C₃₅H₃₄O₇, crystallizes in the chiral monoclinic space group *P*2₁. The molecules are densely packed to form a helical assembly along the crystallographic twofold screw axis *via* C—H···O and C—H···π interactions. Interestingly, the unit-translated helical chains are loosely connected *via* a rather uncommon edge-to-edge Ph—H···H—Ph short contact (H···H = 2.33 Å).

Comment

Among the various noncovalent interactions which govern the molecular arrangement in crystals (Desiraju, 1989), those involving the less acidic C—H group, *e.g.* C—H···O, C—H···π, C—H···N and C—H···X (X = F, Cl, Br), have been scrutinized intensely over the past 20–30 years (Desiraju & Steiner, 1999; Hobza & Havlas, 2000; Scheiner, 2005). Their role in molecular recognition, crystal packing and polymorphic modifications is well established in either the presence (Gonnade *et al.*, 2008; Krishnaswamy *et al.*, 2009) or absence (Gonnade *et al.*, 2010) of relatively strong conventional hydrogen-bonding interactions. *O*-Protected *myo*-inositol derivatives (Sureshan *et al.*, 2003) are important intermediates for the preparation of biologically relevant phosphoinositols. These molecules, which lack functional groups capable of forming conventional hydrogen bonds, provide opportunities to study the role of weaker noncovalent interactions of similar energies in molecular aggregation. Encouraged by the common polymorphic (Gonnade *et al.*, 2004, 2005, 2008, 2010; Bhosekar *et al.*, 2005; Manoj *et al.*, 2009) and solvatomorphic (Sureshan *et al.*, 2001; Gonnade *et al.*, 2004; Manoj *et al.*, 2006, 2012; Krishnaswamy *et al.*, 2010) behaviour exhibited by *myo*-inositol derivatives; the title compound, (I), was also screened for the same property. We reported previously the role of C—H···O interactions in

directing the molecular aggregation of a *meso* molecule, leading to the formation of chiral crystals under kinetic crystallization conditions (Gonnade *et al.*, 2004). We report here another such occurrence, where crystallization of the title *meso*-ketone (I) under a variety of conditions and solvents yielded chiral crystals belonging to the monoclinic space group *P*2₁ with one molecule in the asymmetric unit. Molecules of (I) form a helical chain along the *b* axis, linked *via* C—H···O and C—H···π interactions comprising polar groups clustering along the helical axis, whereas the nonpolar groups protrude perpendicular to the helical axis. Surprisingly, these neighbouring chains are loosely held along the *c* axis *via* relatively uncommon C—H···H—C short contacts (Bhosekar *et al.*, 2005).



The conformation of the molecule of (I) as observed in the crystal structure reveals a slight deviation of the inositol ring from a chair conformation, perhaps due to the presence of a planar carbonyl group at the C5 position. However, the C1/C2/C3/O3/C7/O1 acetal ring adopts a regular chair conformation (Fig. 1). All the benzyl groups adopt an extended conformation, pointing in the same direction but away from the fourth phenyl ring. This results in sandwiching of the hydrophilic inositol ring between hydrophobic benzene rings and facilitates the formation of a short intramolecular C2—H2···O6 hydrogen bond [H2···O6 = 2.43 Å, C2···O6 = 2.832 (6) Å and C2—H2···O6 = 104°].

Molecules of (I) form a helical assembly along the crystallographic twofold screw axis *via* one C—H···π and two C—H···O interactions exclusively involving the 4-methoxybenzyl (PMB) group (Fig. 2). Methylene atom C8 and ring atom C14 of the PMB group are involved in C—H···O contacts with atom O1 in the next molecule and O3 in the previous molecule of the chain, respectively (Table 1 and Fig. 2). The latter contact is shorter than the former, whereas the angles of approach in both cases are similar. This arrangement also brings the benzene C10—H10 group of PMB closer to the edge atoms C31, C32 and C33 of the C30—C35 acetal phenyl ring also in the next molecule of the chain, rather than pointing towards the centre of the π-cloud, generating an off-centred C—H···π contact [C10—H10···Cg2¹; Cg2¹ is the centroid of the C30—C35 ring; Table 1; symmetry code: (i) $-x + 2, y + \frac{1}{2}, -z + 2$]. This helical arrangement brings polar

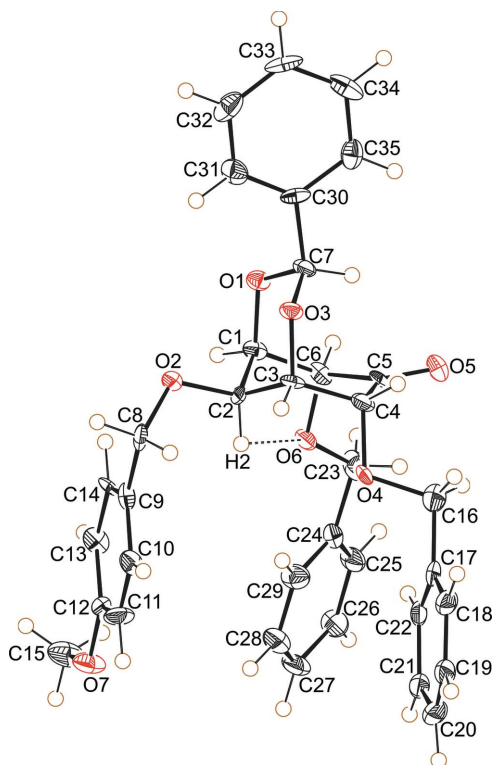


Figure 1
The molecular structure of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. The dashed line indicates the intramolecular C—H...O interaction. Only one conformation of the disordered benzyl group (C16–C22) is shown.

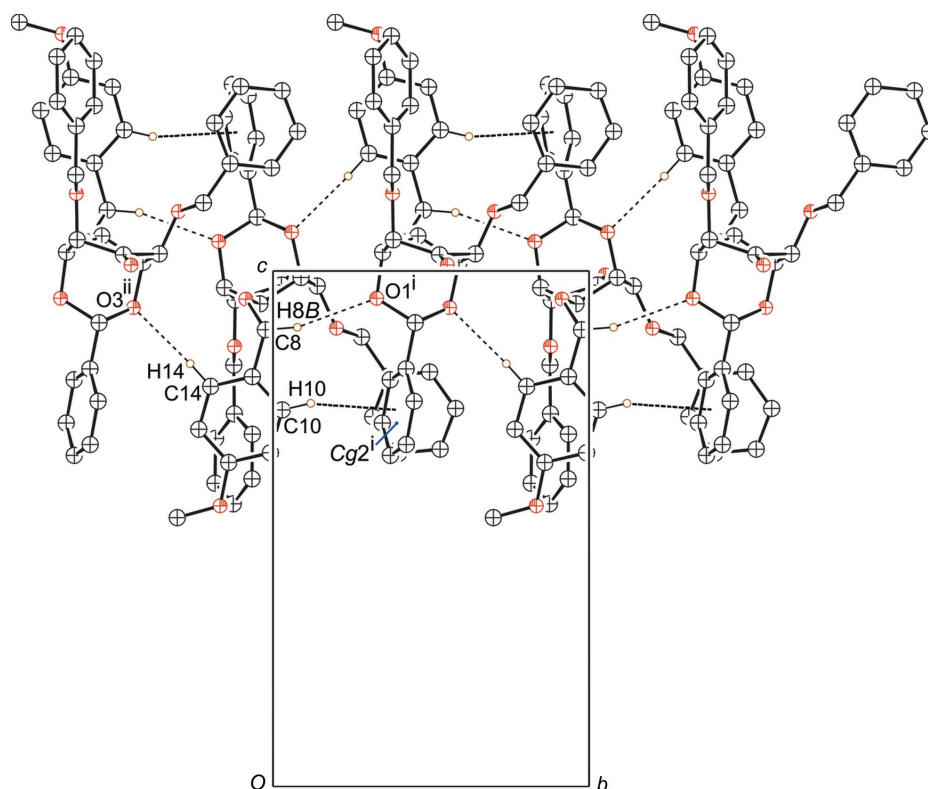
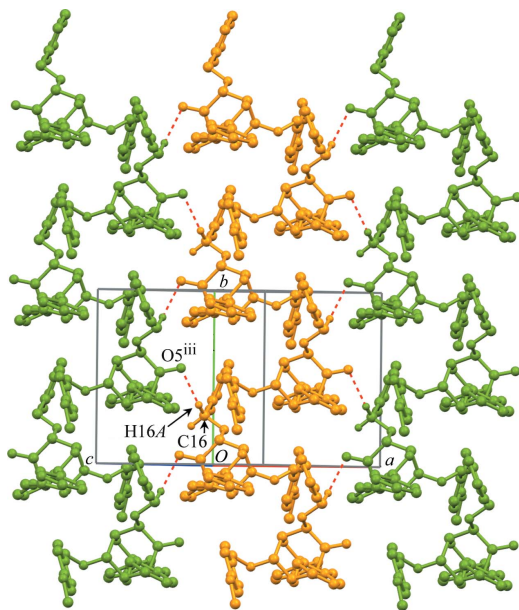


Figure 2
The molecular packing of (I), viewed down the *a* axis, showing the helical assembly of molecules along the crystallographic twofold screw axis (*b* axis). Dashed lines indicate intermolecular C—H...O and C—H... π interactions. H atoms not involved in hydrogen bonding have been omitted for clarity. [Symmetry codes: (i) $-x + 2, y + \frac{1}{2}, -z + 2$; (ii) $-x + 2, y - \frac{1}{2}, -z + 2$.]

segments of neighbouring molecules into close association, creating a hydrophilic layer between the hydrophobic layers formed by the benzene rings (see *Supplementary materials* for a space-filling model).

Neighbouring helices diagonal to the *ac* plane are held together *via* another C—H...O contact involving carbonyl atom O5 and the C16 methylene group of a benzyl group [C16—H16A...O5ⁱⁱⁱ; Table 1; symmetry code: (iii) $-x + 1, y + \frac{1}{2}, -z + 2$], thus generating a discrete packing of the helices throughout the crystal structure (Fig. 3). Viewed down the *a* axis, the molecular packing reveals the association of neighbouring unit-translated helices *via* hydrophobic forces; a somewhat uncommon edge-to-edge C—H...H—C contact [C33—H33...H26^{iv}—C26^{iv}, with H...H = 2.33 Å, C33...H26^{iv} = 3.27 Å, H33...C26^{iv} = 2.93 Å and C33—H33...H26^{iv} = 171°; symmetry code: (iv) $x + 1, y, z + 1$] joins adjacent helical chains (Fig. 4). Therefore, the cohesion of the two-dimensional layers in the *bc* plane seems to be only *via* short H...H contacts (although just at the boundary of the sum of the van der Waals radii of two H atoms, 2.35 Å; Batsanov, 2001), termed ‘dihydrogen bonds’ or ‘dihydrogen interactions’ (Echeverría *et al.*, 2011; Crabtree *et al.*, 1996; Crabtree, 1998; Custelcean & Jackson, 2001; Wang *et al.*, 2004). It is noteworthy that there are no significant aromatic π – π or C—H... π contacts between benzene rings of adjacent helical chains, although they are clustered together.

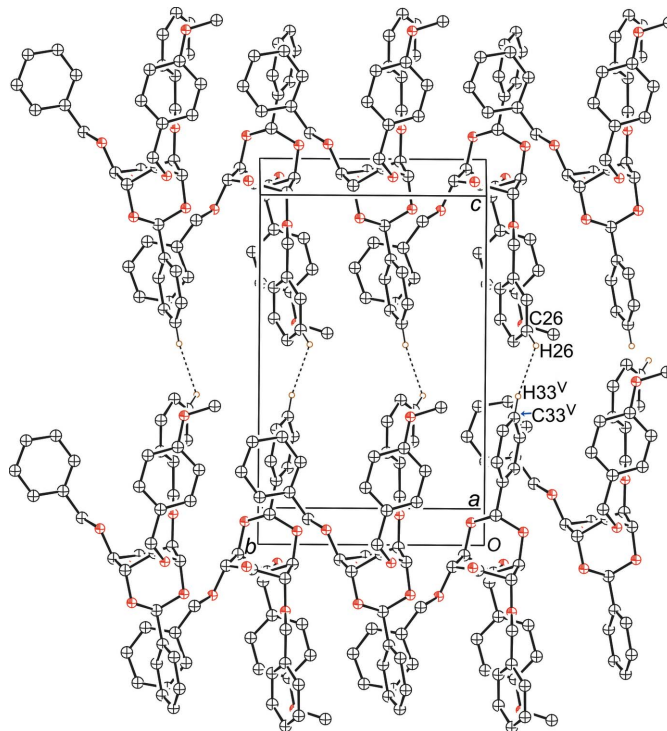
The computation of lattice energies (using the *Oprop* module of the *OPIX* program suite; Gavezzotti, 2007) by

**Figure 3**

The molecular packing of (I), viewed diagonal to the *ac* plane, revealing the association of discrete helices *via* C16—H16A...O5ⁱⁱⁱ interactions. H atoms not involved in hydrogen bonding have been omitted for clarity. [Symmetry code: (iii) $-x + 1, y + \frac{1}{2}, -z + 2$.]

summation of atom–atom pair-wise potential energies described by the UNI force field (Filippini & Gavezzotti, 1993; Gavezzotti & Filippini, 1994) gave a value of $-263.1 \text{ kJ mol}^{-1}$. The intermolecular interaction energies for the C14—H14...O3ⁱⁱ [symmetry code: (i) $-x + 2, y - \frac{1}{2}, -z + 2$] and H...H contacts were also estimated, giving values of -17.4 and 6.0 kJ mol^{-1} , respectively, suggesting that the former contact is attractive and the latter repulsive. However, an estimation of the intermolecular potentials [the sum of Coulombic, polarization, dispersion and repulsion terms, as defined in the PIXEL method (Gavezzotti, 1994) and implemented in the program *Mercury* (Macrae *et al.*, 2008)], gives the overall contribution from all the intermolecular forces (including van der Waals interactions) at the interface of the two helical chains (linked by the H...H contact) in the *bc* plane enveloped by hydrophobic groups as -3.8 kJ mol^{-1} . This suggests that, although the H...H contact is repulsive, the other forces contribute to this bridging and thence to the overall stability of the structure. The energies of the other weak interactions such as C—H... π could not be computed separately. However, using UNI force-field calculations, approximate energies for the intermolecular potentials were estimated. The intermolecular potential associated with two neighbouring molecules involved in helical chain formation is $-85.1 \text{ kJ mol}^{-1}$, with major contributions from C—H...O (C14—H14...O3ⁱⁱ and C8—H8B...O1ⁱ; symmetry codes as in Table 1) and C—H... π (C10—H10...Cg2ⁱ) interactions and other van der Waals forces.

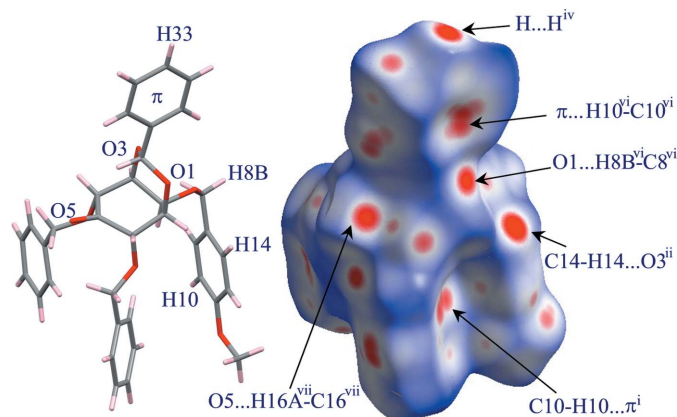
The intermolecular contacts in the crystal structure of (I) were quantified *via* Hirshfeld surface analysis (McKinnon *et al.*, 2004; Spackman & McKinnon, 2002) using *CrystalExplorer* (Wolff *et al.*, 2007). Hirshfeld surfaces are a novel tool for the

**Figure 4**

The molecular packing of (I), viewed down the *a* axis, showing the cohesion of the helical chains along the *c* axis *via* edge-to-edge C33—H33...H26—C26 short contacts. H atoms not involved in hydrogen bonding have been omitted for clarity. [Symmetry code: (v) $x - 1, y, z - 1$.]

visualization and understanding of intermolecular interactions (McKinnon *et al.*, 2007; Munshi *et al.*, 2008; Hathwar *et al.*, 2010). In the present study, the contacts responsible for the chiral crystal packing in (I) (C—H...O, C—H... π , H...H and others, *e.g.* O...O and C...C) were evaluated with respect to their contribution to the overall stability of the crystal structure. The percentage contributions of these interactions to the relative Hirshfeld surface areas reveal noticeable involvement of C—H... π (24.8%) and C—H...O (17.7%), whereas a more significant contribution comes from H...H contacts (56%), because of the considerable engagement of the hydrophobic groups in the molecular aggregation (see *Supplementary materials* for figures). However, it must be noted that these percentage contributions do not differentiate between close and distant contacts. The major C—H...O, C—H... π and H...H contacts are highlighted by conventional mapping of d_{norm} (normalized contact distance) on molecular Hirshfeld surfaces (Fig. 5). The dark spots (red in the electronic version of the paper) on the left and right surfaces of the plot are due to C—H...O and C—H... π interactions, while that on the top is from an H...H contact.

In conclusion, the spontaneous generation of chirality of an achiral molecule solely by the topology of weak interactions, as observed in the present case, is an enigmatic phenomenon which continues to fascinate crystal engineers and supramolecular chemists. Deeper insight into this phenomenon, especially in crystals formed from complex molecules, could


Figure 5

The Hirshfeld surface of (I) mapped with d_{norm} ; a molecule of (I) with a similar orientation has been added on the left-hand side for clarity. Selective atom labels on the left-hand side image indicate involvement of these atoms in intermolecular interactions. The dark spots indicated by arrows in the right-hand side image are attributed to the contribution of the d_{norm} map to the Hirshfeld surface by the specified intermolecular interactions. [Symmetry codes: (i) $-x + 2, y + \frac{1}{2}, -z + 2$; (ii) $-x + 2, y - \frac{1}{2}, -z + 2$; (iv) $x + 1, y, z + 1$; (vi) $-x + 2, y - \frac{1}{2}, -z + 2$; (vii) $-x + 1, y - \frac{1}{2}, -z + 2$.]

be of value in designing unconventional methods for asymmetric synthesis.

Experimental

To a solution of 4,6-di-*O*-benzyl-1,3-*O*-benzylidene-2-*O*-(4-methoxybenzyl)-*myo*-inositol (Gurale *et al.*, 2011; 1.80 g, 3.16 mmol) in ethyl acetate (20 ml) was added 2-iodoxybenzoic acid (IBX; 1.77 g, 6.32 mmol) and the resulting solution was refluxed for 3 h. The reaction mixture was filtered through a sintered glass funnel and the residue was washed with ethyl acetate (3 × 50 ml). The combined filtrate and washings were evaporated under reduced pressure, and the residue was dissolved in hot methanol and stored at ambient temperature. Colourless prismatic crystals of (I) were spontaneously obtained within 1 h (yield 1.70 g, 95%; m.p. 348.8–350.5 K). Thin-layer chromatography: $R_f = 0.5$ in 20% ethyl acetate/light petroleum. IR (CHCl₃, ν , cm⁻¹): 1716. ¹H NMR (CDCl₃, 400 MHz): δ 7.41–7.49 (*m*, 2H, Ar H), 7.20–7.40 (*m*, 15H, Ar H), 6.83–6.88 (*m*, 2H, Ar H), 5.66 (*s*, 1H, HCO₂), 4.67 (*s*, 2H, CH₂), 4.63 (*q*, 4H, $J = 11.8$ Hz, 2 × CH₂), 4.49 (*m*, 2H, Ins H), 4.23 (*t*, 1H, $J = 2.0$ Hz, Ins H), 4.17 (*d*, 2H, $J = 2.5$ Hz, Ins H), 3.79 (*s*, 3H, CH₃); ¹³C NMR (CDCl₃, 100.6 MHz): δ 201.0 (C=O), 159.3 (C_{arom}), 137.7 (C_{arom}), 136.6 (C_{arom}), 129.9 (C_{arom}), 129.7 (C_{arom}), 129.4 (C_{arom}), 128.4 (C_{arom}), 128.3 (C_{arom}), 128.1 (C_{arom}), 127.9 (C_{arom}), 126.2 (C_{arom}), 113.8 (C_{arom}), 93.9 (HCO₂), 79.4 (Ins C), 73.7 (Ins C), 71.9 (CH₂), 70.7 (CH₂), 66.0 (Ins C), 55.2 (CH₃). Analysis calculated for C₃₅H₃₄O₇: C 74.19, H 6.05%; found: C 74.36, H 6.04%. Crystallization from other common organic solvents like ethyl acetate, chloroform, dichloromethane and acetonitrile, as well as from the melt, also yielded chiral crystals spontaneously.

Crystal data

C ₃₅ H ₃₄ O ₇	$V = 1465$ (2) Å ³
$M_r = 566.62$	$Z = 2$
Monoclinic, $P2_1$	Mo $K\alpha$ radiation
$a = 9.492$ (8) Å	$\mu = 0.09$ mm ⁻¹
$b = 9.735$ (8) Å	$T = 133$ K
$c = 16.289$ (13) Å	$0.18 \times 0.13 \times 0.09$ mm
$\beta = 103.206$ (12)°	

Table 1

Hydrogen-bond geometry (Å, °).

Cg2 is the centroid of the C30–C35 ring.

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
C8–H8B ⁱ ⋯O1 ⁱ	0.99	2.62	3.572 (7)	160
C10–H10 ⁱ ⋯Cg2 ⁱ	0.95	2.76	3.588 (7)	146
C14–H14 ⁱⁱ ⋯O3 ⁱⁱ	0.95	2.52	3.430 (7)	161
C16–H16A ⁱⁱⁱ ⋯O5 ⁱⁱⁱ	0.99	2.49	3.336 (14)	144

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

Data collection

Bruker SMART APEX CCD area-detector diffractometer	7169 measured reflections
Absorption correction: multi-scan (SADABS; Bruker, 2003)	2741 independent reflections
$T_{\min} = 0.984, T_{\max} = 0.992$	2503 reflections with $I > 2\sigma(I)$
	$R_{\text{int}} = 0.047$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.073$	188 restraints
$wR(F^2) = 0.138$	H-atom parameters constrained
$S = 1.26$	$\Delta\rho_{\max} = 0.29$ e Å ⁻³
2741 reflections	$\Delta\rho_{\min} = -0.28$ e Å ⁻³
443 parameters	

All H atoms were placed in geometrically idealized positions (C–H = 1.00 Å for inositol ring H atoms and atom H7, C–H = 0.95 Å for aromatic H atoms, C–H = 0.99 Å for methylene H atoms and C–H = 0.98 Å for methyl H atoms) and constrained to ride on their parent atoms, with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$ or $1.5U_{\text{eq}}(\text{methyl C})$. In the absence of any significant anomalous scatterers in the molecule, the 1083 Friedel pairs were merged before the final refinement. The anisotropic displacement parameters (ADPs) for benzyl group C16–C22 were large in the initial refinement, indicating orientational disorder. A reasonable model was obtained by splitting the benzyl group into two components (C16–C22 and C16'–C22') each with equal (0.5) occupancies. The ADPs of these disordered atoms were restrained to be similar, as were the O4–C16 and O4–C16' bond lengths.

Data collection: *SMART* (Bruker, 2003); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 2003); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3* (Farrugia, 1997) and *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *SHELXL97*, *PLATON* (Spek, 2009) and *pubCIF* (Westrip, 2010).

BPG thanks the CSIR, New Delhi, for a Senior Research Fellowship. Financial support from the Department of Science and Technology, New Delhi, is gratefully acknowledged.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SF3168). Services for accessing these data are described at the back of the journal.

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