

# Polymorphism and phase transition behavior of 6,6'-bis(chloromethyl)-1,1',4,4'-tetramethyl-3,3'-(*p*-phenylenedimethylene)bis(piperazine-2,5-dione)

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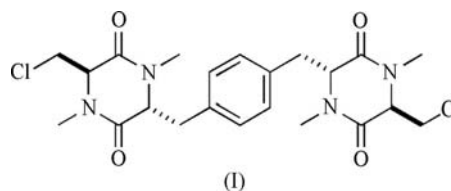
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A crystallographic investigation of the title compound,  $C_{22}H_{28}Cl_2N_4O_4$ , using crystals obtained under different crystallization conditions, revealed the presence of two distinct polymorphic forms. The molecular conformation in the two polymorphs is very different: one adopts a 'C' shape, whereas the other adopts an 'S' shape. In the latter, the molecule lies across a crystallographic twofold axis. The 'S'-shaped polymorph undergoes a reversible orthorhombic-to-monoclinic phase transition on cooling, whereas the structure of the 'C'-shaped polymorph is temperature insensitive.

## Comment

Sporidesmins are a diverse class of natural products containing molecules with one or two epidithiodioxopiperazine (ETP) rings that display a wide variety of biological activities (Waksman & Bugie, 1944; Saito *et al.*, 1988; Fujimoto *et al.*, 2004; Gardiner *et al.*, 2005; Li *et al.*, 2006). While toxic to mammalian cells, studies have suggested that certain sporidesmins, namely bis-ETPs chetomin (Waksman & Bugie, 1944) and chaetocin (Hauser *et al.*, 1970), may possess anticancer activity due to their ability to suppress neovascularization (Waksman & Bugie, 1944; Hauser *et al.*, 1970; McInnes *et al.*, 1976; Brewer *et al.*, 1978; Kung *et al.*, 2004). In order to understand better the chemistry and biology of the bridged bis-ETPs, diketopiperazines (1,4-piperazine-2,5-diones, DKPs) (Martins & Carvalho, 2007) and bridged bis-DKP structures lacking a disulfide bridge must also be studied. Even in the absence of the disulfide bridge many compounds of this class exhibit a broad spectrum of interesting biological activity. Natural products, such as ditryptophenaline (Springer *et al.*, 1977), WIN-64821, WIN-64745 (Barrow *et al.*, 1993; Popp *et al.*,

1994) and leptosin S (Yamada *et al.*, 2004) incorporate a 3a,3a'-bispyrrolidinoindoline core with contiguous stereogenic quaternary carbons and display cytotoxicity in various cell lines. Perhaps the most interesting is a  $C_2$ -symmetrical piperazine-2,5-dione (WIN-64821), which is a competitive substance-P antagonist against the human NK1 receptor at submicromolar concentrations (Barrow *et al.*, 1993; Popp *et al.*, 1994; Oleynek *et al.*, 1994; Sedlock *et al.*, 1994) and also serves as an antagonist of the cholecystokinin type-B receptor (Hiramoto *et al.*, 1994). The title compound, (I), was synthesized as part of a wider project to develop new synthetic methods for the preparation of bridged bis-DKPs (Polaske *et al.*, 2009). Unlike other model compounds, which we observed to crystallize consistently in one form only, this compound crystallizes as at least two polymorphic forms, obtained by different methods of crystallization. The molecular structures of the polymorphs are very different: one adopts a 'C' shape, (1), while the other adopts an 'S' shape, (2). The 'S'-shaped polymorph also undergoes a reversible orthorhombic-to-monoclinic phase transition upon cooling (the 'C'-shaped structure is insensitive to temperature).



The molecular structure of polymorph (1) is shown in Fig. 1. The 'C' shape is supported by weak distorted intra- and intermolecular C—H...O interactions (Table 1) and by Cl...Cl interactions (Fig. 2). The Cl1...Cl2<sup>i</sup> [symmetry code: (i)  $x - 1, y, z - 1$ ] distance is 3.445 (4) Å and the pertinent angles are C5—Cl1...Cl2<sup>i</sup> = 143.9 (4)° and C22<sup>i</sup>—Cl2<sup>i</sup>...Cl1 = 168.9 (5)°. This is slightly longer than the mean Cl...Cl distance of 3.38 Å obtained by a search of the Cambridge Structural Database (CSD, Version 5.30 plus three updates; Allen, 2002) for Cl...Cl contact distances between two Cl atoms (not including those reported structures with Cl...Cl interactions between dichloromethane and chloroform),

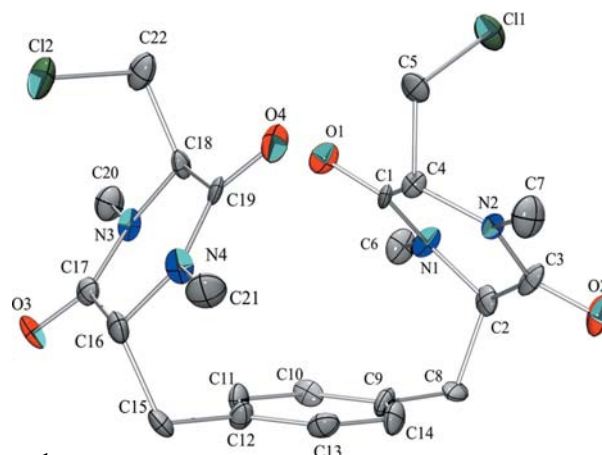
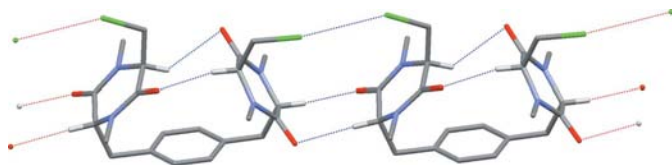


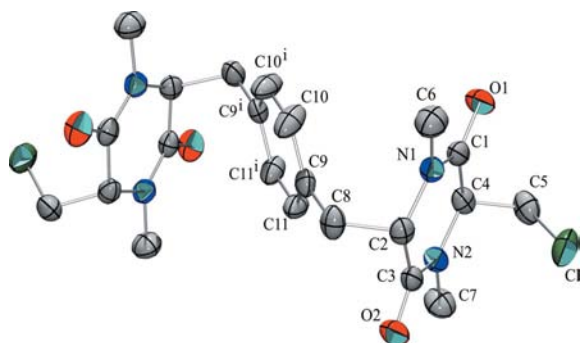
Figure 1

The 'C'-shaped molecular structure of polymorph (1), with displacement ellipsoids at the 30% probability level and H atoms omitted.

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**Figure 2**

Weak C—H...O (dotted blue lines in the electronic version of the paper) and Cl...Cl (dotted green lines) link adjacent molecules of polymorph (1) into a chain. (In the electronic version of the paper, red dotted lines indicate continuation of the interactions.)

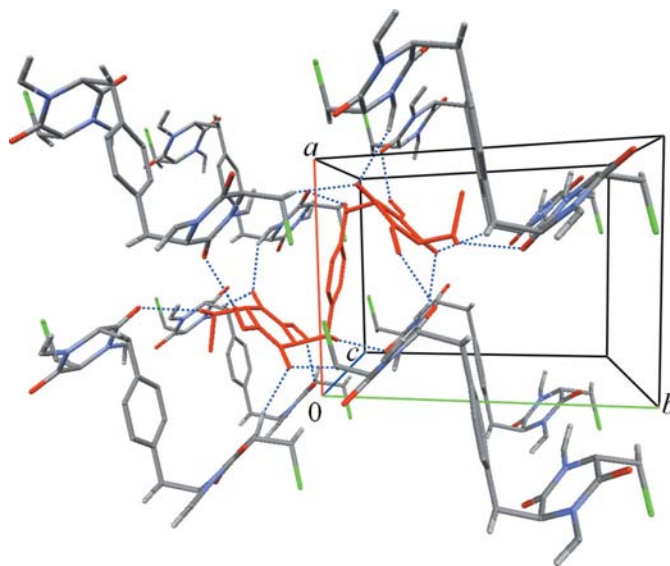
**Figure 3**

The 'S'-shaped molecular structure of room-temperature polymorph (2rt), with displacement ellipsoids at the 30% probability level and H atoms omitted. [Symmetry code (twofold rotation): (i)  $-x + 1, -y, z$ .]

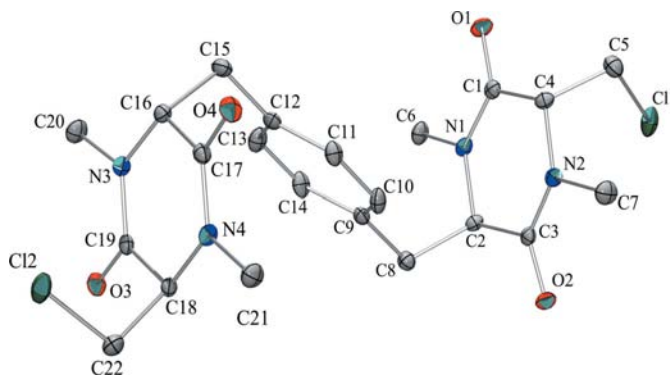
yielding 774 hits. Two  $R_2^2(8)$  rings, one intermolecular and one intramolecular, are formed by C—H...O interactions. In all cases, the C—H...O interactions are weak, with poorly activated H atoms, long H...O distances and the motif is rather distorted. Nevertheless, these motifs represent the favorable arrangement of mildly electropositive and electronegative sites such as to maximize electrostatic interaction; they are not a direct cause of the 'C' shape, nor are they merely an effect of the shape.

The molecular structure of the polymorph determined at room temperature, (2rt), is shown in Fig. 3. The 'S'-shaped molecule has crystallographic twofold rotational symmetry and as with polymorph (1) the crystal packing is dominated by an extensive network of weak intermolecular C—H...O interactions (Table 2) with all O atoms acting as bifurcated 'acceptors' although as in the case of polymorph (1) the geometry of the interactions and the poorly acidic nature of each donor H atom are indicative of very weak hydrogen bonding. In this structure, but here the Cl1...Cl1<sup>i</sup> [symmetry code: (i)  $2 - x, 1 - y, z$ ] distance, at 3.319 (1) Å, is shorter than that observed in (1). The arrangement of C—H...O interactions is difficult to visualize with one simple diagram; contacts from the discrete crystallographically unique molecule touch eight adjacent molecules but do not form small cyclic motifs as in (1) and this is most easily seen by considering a perspective *c*-axis plot (Fig. 4). In Fig. 4, the discrete unique molecule is shown at the centre of the plot and hydrogen-bonding contacts have been expanded to show all eight acceptor molecules.

The structural behavior of polymorph (2) was first noted by comparison of experimental X-ray powder diffraction

**Figure 4**

A perspective *c*-axis plot of part of the crystal packing of room-temperature polymorph (2rt). The discrete unique molecule in the centre of the plot (colored red in the electronic version of the paper) is surrounded by eight hydrogen-bonding acceptor molecules, although hydrogen bonding does not form small cyclic motifs as in polymorph (1).

**Figure 5**

The 'S'-shaped molecular structure of low-temperature polymorph (2lt), with displacement ellipsoids at the 30% probability level and H atoms omitted.

patterns, which were measured at room temperature, with calculated X-ray powder diffraction patterns based on a low-temperature (100 K) single-crystal structure. The two did not match and it was then that a room-temperature single-crystal analysis was carried out. Although we have not carried out a systematic variable-temperature study of this compound, flash cooling to 100 K produces a single-crystal structure, (2lt), with some striking differences when compared with (2rt). The compound undergoes an orthorhombic-to-monoclinic phase transition; the obvious effect of this reduction in symmetry is loss of the twofold axis and consequently loss of crystallographically imposed symmetry on the discrete molecule (Fig. 5). Although the molecule retains an 'S' shape, the two piperazinedione rings are able to twist further away from the central benzene ring. In (2lt), the torsion angles about the methylene linker are 109.9 (3) (C2—C8—C9—C14) and

94.2 (4)° (C13—C12—C15—C16), whereas in (2rt) the equivalent torsion angle is 76.0 (3)°. This reduction in symmetry also causes the onset of nonmerohedral twinning in the monoclinic structure; this is typical behavior in such situations. The crystal packing of (2lt) is not significantly different from that of (2rt) except that the twisting of the piperazinedione rings causes a change in the weak hydrogen-bonding geometry (Table 3), resulting in shorter H···O distances. For example, in (2rt), the approximate distance between H2 and O1<sup>i</sup> [symmetry code: (i)  $\frac{1}{2} + x, \frac{1}{2} - y, 1 - z$ ] is approximately 2.81 Å; in (2lt) the equivalent distance, H2···O3<sup>vi</sup> [symmetry code: (vi)  $-x, \frac{1}{2} + y, 1 - z$ ] is approximately 2.56 Å. The Cl1···Cl2<sup>ii</sup> [symmetry code: (ii)  $x, \frac{1}{2} + y, z - 1$ ] distance in (2lt) is the shortest of all three structures at 3.2414 (11) Å. This behaviour of polymorph (2) was found to be reversible and the crystal suffered no physical defects (*e.g.* cracking) as a result of the phase change.

In summary, two polymorphs of the title compound have been identified. Both polymorphs differ entirely in their molecular conformation and consequently in the crystal packing. 'C'-shaped monoclinic polymorph (1) is insensitive to temperature change; 'S'-shaped polymorph (2) is orthorhombic at room temperature but forms a monoclinic nonmerohedrally twinned structure when flash cooled to 100 K. The weak inter- and intramolecular interactions in (1) are more conducive to retaining the 'C' shape as is and probably prevent such temperature-induced behavior.

## Experimental

To a suspension of 6,6'-dihydroxy-1,1',4,4'-tetramethyl-3,3'-(*p*-phenylenedimethylene)bis(piperazine-2,5-dione) (Polaske *et al.*, 2009) (45 mg, 0.10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml), triphenylphosphine (130 mg, 0.50 mmol) and hexachloroacetone (76 µl, 0.50 mmol) were added. After stirring at room temperature for 18 h, the solvent was removed and the residue resuspended in a 1:1 mixture of acetonitrile and water (5 ml). The solids were filtered off and the filtrate was purified by semipreparative HPLC using a 5–95% gradient of 0.05% trifluoroacetic acid in acetonitrile, yielding crystals of form (1) as small colorless rods. Recrystallization of (1) from ethanol yielded crystals of form (2) (26 mg, 54% yield) as colorless prisms. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 6.95 (4H, *s*), 4.28 (2H, *br t*, *J* = 2.5 Hz), 4.02 (2H, *dd*, *J* = 12.5 Hz and 1.5 Hz), 3.74 (2H, *dd*, *J* = 12.5 Hz and 3.5 Hz), 3.43 (2H, *dd*, *J* = 14 Hz and 2.5 Hz), 3.24 (2H, *br s*), 3.11 (2H, *dd*, *J* = 14 Hz and 5 Hz), 3.06 (6H, *s*), 2.88 (6H, *s*). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 165.6, 163.6, 134.2, 129.8, 69.24, 60.52, 44.19, 37.16, 32.63, 30.68. HRMS (FAB, [*M* + *H*]<sup>+</sup>) found: 483.1570, C<sub>22</sub>H<sub>28</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>4</sub> requires 483.1566.

## Polymorph (1)

### Crystal data

C <sub>22</sub> H <sub>28</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>4</sub>	<i>V</i> = 1215.3 (4) Å <sup>3</sup>
<i>M<sub>r</sub></i> = 483.38	<i>Z</i> = 2
Monoclinic, <i>P</i> 2 <sub>1</sub>	Mo <i>K</i> α radiation
<i>a</i> = 8.4158 (17) Å	<i>μ</i> = 0.30 mm <sup>−1</sup>
<i>b</i> = 14.779 (3) Å	<i>T</i> = 150 K
<i>c</i> = 10.438 (2) Å	0.32 × 0.13 × 0.07 mm
<i>β</i> = 110.58 (3)°	

### Data collection

Nonius KappaCCD diffractometer	1649 independent reflections
Absorption correction: multi-scan ( <i>SADABS</i> ; Sheldrick, 1996)	1123 reflections with <i>I</i> > 2σ( <i>I</i> )
<i>T</i> <sub>min</sub> = 0.664, <i>T</i> <sub>max</sub> = 0.917	<i>R</i> <sub>int</sub> = 0.128
8536 measured reflections	<i>θ</i> <sub>max</sub> = 22.5°

### Refinement

<i>R</i> [ <i>F</i> <sup>2</sup> > 2σ( <i>F</i> <sup>2</sup> )] = 0.080	1 restraint
<i>wR</i> ( <i>F</i> <sup>2</sup> ) = 0.134	H-atom parameters constrained
<i>S</i> = 1.18	Δ <i>ρ</i> <sub>max</sub> = 0.30 e Å <sup>−3</sup>
1649 reflections	Δ <i>ρ</i> <sub>min</sub> = −0.29 e Å <sup>−3</sup>
293 parameters	

## Polymorph (2) at room temperature, (2rt)

### Crystal data

C <sub>22</sub> H <sub>28</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>4</sub>	<i>V</i> = 1159.75 (9) Å <sup>3</sup>
<i>M<sub>r</sub></i> = 483.38	<i>Z</i> = 2
Orthorhombic, <i>P</i> 2 <sub>1</sub> 2 <sub>1</sub> 2	Mo <i>K</i> α radiation
<i>a</i> = 9.7566 (5) Å	<i>μ</i> = 0.32 mm <sup>−1</sup>
<i>b</i> = 12.7626 (6) Å	<i>T</i> = 296 K
<i>c</i> = 9.3138 (4) Å	0.20 × 0.15 × 0.09 mm

### Data collection

Bruker Kappa APEXII DUO CCD diffractometer	15349 measured reflections
Absorption correction: numerical ( <i>SADABS</i> ; Sheldrick, 1996)	2288 independent reflections
<i>T</i> <sub>min</sub> = 0.641, <i>T</i> <sub>max</sub> = 0.745	1847 reflections with <i>I</i> > 2σ( <i>I</i> )
	<i>R</i> <sub>int</sub> = 0.025

### Refinement

<i>R</i> [ <i>F</i> <sup>2</sup> > 2σ( <i>F</i> <sup>2</sup> )] = 0.037	H-atom parameters constrained
<i>wR</i> ( <i>F</i> <sup>2</sup> ) = 0.102	Δ <i>ρ</i> <sub>max</sub> = 0.22 e Å <sup>−3</sup>
<i>S</i> = 1.03	Δ <i>ρ</i> <sub>min</sub> = −0.18 e Å <sup>−3</sup>
2288 reflections	Absolute structure: Flack (1983)
148 parameters	Flack parameter: −0.03 (8)

## Polymorph (2) at low temperature, (2lt)

### Crystal data

C <sub>22</sub> H <sub>28</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>4</sub>	<i>V</i> = 1129.6 (3) Å <sup>3</sup>
<i>M<sub>r</sub></i> = 483.38	<i>Z</i> = 2
Monoclinic, <i>P</i> 2 <sub>1</sub>	Mo <i>K</i> α radiation
<i>a</i> = 9.2208 (13) Å	<i>μ</i> = 0.33 mm <sup>−1</sup>
<i>b</i> = 12.6517 (19) Å	<i>T</i> = 100 K
<i>c</i> = 9.6894 (15) Å	0.19 × 0.16 × 0.10 mm
<i>β</i> = 92.123 (2)°	

### Data collection

Bruker Kappa APEXII DUO CCD diffractometer	2919 measured reflections
Absorption correction: multi-scan ( <i>TWINABS</i> ; Sheldrick, 1996)	2919 independent reflections
<i>T</i> <sub>min</sub> = 0.632, <i>T</i> <sub>max</sub> = 0.746	2603 reflections with <i>I</i> > 2σ( <i>I</i> )
	<i>R</i> <sub>int</sub> = 0.034

### Refinement

<i>R</i> [ <i>F</i> <sup>2</sup> > 2σ( <i>F</i> <sup>2</sup> )] = 0.035	H-atom parameters constrained
<i>wR</i> ( <i>F</i> <sup>2</sup> ) = 0.085	Δ <i>ρ</i> <sub>max</sub> = 0.32 e Å <sup>−3</sup>
<i>S</i> = 1.02	Δ <i>ρ</i> <sub>min</sub> = −0.23 e Å <sup>−3</sup>
2919 reflections	Absolute structure: Flack (1983)
294 parameters	Flack parameter: 0.07 (7)
1 restraint	

**Table 1**

Hydrogen-bond geometry (Å, °) for polymorph (1).

<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>
C2—H2...O3 <sup>i</sup>	1.00	2.49	3.487 (14)	173
C4—H4...O4	1.00	2.64	3.379 (13)	131
C18—H18...O1	1.00	2.39	3.372 (14)	167

Symmetry code: (i)  $x - 1, y, z - 1$ .**Table 2**

Hydrogen-bond geometry (Å, °) for polymorph (2rt).

<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>
C6—H6C...O1 <sup>i</sup>	0.96	2.42	3.255 (4)	145
C8—H8B...O1 <sup>ii</sup>	0.97	2.68	3.463 (3)	138
C5—H5B...O2 <sup>iii</sup>	0.97	2.67	3.323 (3)	125
C7—H7C...O2 <sup>iv</sup>	0.96	2.50	3.415 (4)	158

Symmetry codes: (i)  $x + \frac{1}{2}, -y + \frac{1}{2}, -z + 1$ ; (ii)  $-x + \frac{3}{2}, y - \frac{1}{2}, -z + 1$ ; (iii)  $-x + \frac{3}{2}, y + \frac{1}{2}, -z$ ; (iv)  $x - \frac{1}{2}, -y + \frac{1}{2}, -z$ .**Table 3**

Hydrogen-bond geometry (Å, °) for polymorph (2lt).

<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>
C2—H2...O3 <sup>i</sup>	1.00	2.56	3.362 (4)	137
C4—H4...O4 <sup>ii</sup>	1.00	2.56	3.296 (4)	130
C5—H5A...O2 <sup>iii</sup>	0.99	2.52	3.167 (4)	123
C6—H6B...O3 <sup>i</sup>	0.98	2.30	3.215 (4)	154
C7—H7B...O4 <sup>ii</sup>	0.98	2.43	3.361 (4)	159
C8—H8A...O1 <sup>iv</sup>	0.99	2.68	3.539 (4)	145
C15—H15A...O3 <sup>v</sup>	0.99	2.60	3.307 (4)	129
C20—H20B...O1 <sup>vi</sup>	0.98	2.33	3.246 (4)	154
C21—H21B...O2 <sup>vii</sup>	0.98	2.40	3.353 (4)	165
C22—H22A...O2 <sup>viii</sup>	0.99	2.63	3.302 (4)	125
C22—H22A...O4 <sup>viii</sup>	0.99	2.70	3.371 (4)	125

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

Polymorph (1) showed surprisingly weak diffraction, necessitating exposures of 120 s per frame and even this was sufficient only to yield data with an  $R\sigma < 30\%$  cutoff of  $2\theta = 45^\circ$ . Owing to this, the value of the Flack absolute structure parameter (Flack, 1983) is indeterminate and Friedel pairs were merged, while polymorph (2rt) has a Flack parameter of  $-0.03$  (8) from 953 Friedel pairs, while polymorph (2lt) has a Flack parameter of  $0.07$  (7) from 2657 Friedel pairs and a nonmerohedral twin scale factor of  $0.447$  (3). For all structures, H atoms were either placed geometrically [for (1)] or first located in a difference map [for (2)] and then refined with  $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$  for methyl H atoms and  $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$  for all other H atoms. Fixed C—H distances of  $0.95$  (aryl),  $0.98$  (methyl and  $R_3\text{CH}$ ) and  $0.99$  Å (methylene) were used.

Data collection: *COLLECT* (Nonius, 1998) for (1); *APEX2* (Bruker, 2007) for (2). Cell refinement: *EVALCCD* (Duisenberg *et al.*, 2003) for (1); *SAINT* (Bruker, 2007) for (2rt); *CELL\_NOW* (Sheldrick, 2004) and *SAINT* for (2lt). Data reduction: *EVALCCD* for (1); *SAINT* for (2). For all compounds, program(s) used to solve structure: *SHELXTL* (Sheldrick, 2008); program(s) used to refine structure: *SHELXTL*; molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997) and *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *SHELXTL*, *publCIF* (Westrip, 2009) and local programs.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3332). Services for accessing these data are described at the back of the journal.

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