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The mixed diol–dithiol 2,2-bis(sulfanylmethyl)propane-1,3-diol: characterization of key intermediates on a new synthetic pathway

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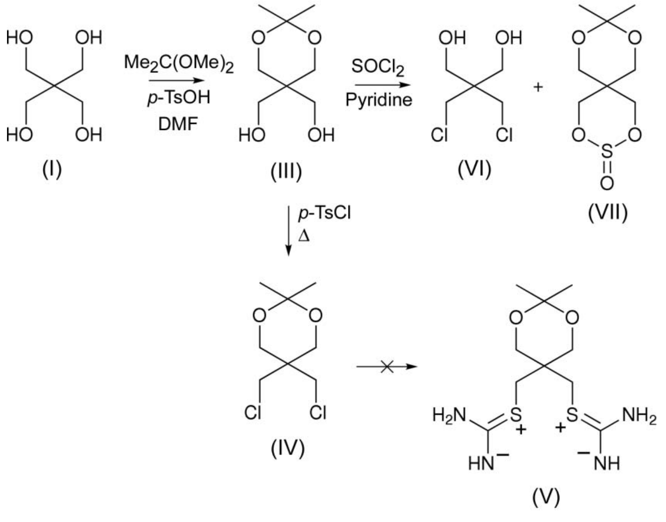
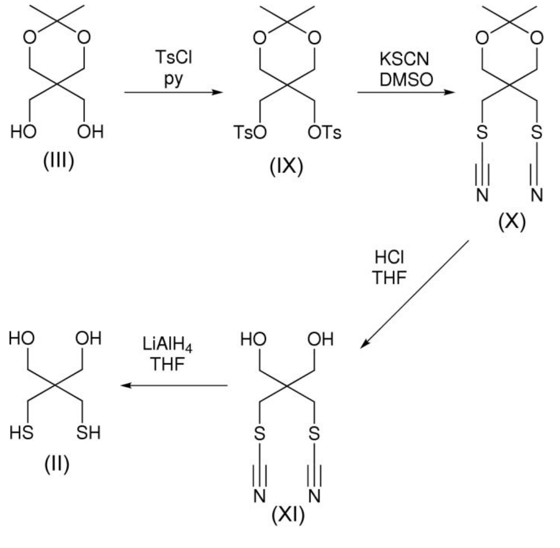
A new synthetic route to 2,2-bis(sulfanylmethyl)propane-1,3-diol, (II), is described starting from the commercially available 2,2-bis(hydroxymethyl)propane-1,3-diol. The structures of two intermediates on this route are described. 5,5-Dimethenyl-2,2-dimethyl-1,3-dioxane bis(thiocyanate) (systematic name: {[5-(cyanosulfanyl)-2,2-dimethyl-1,3-dioxan-5-yl]sulfanyl}formonitrile), $C_{10}H_{14}N_2O_2S_2$, (X), crystallizes in the space group $P2_1/c$ with no symmetry relationship between the two thiocyanate groups. There is a short intramolecular N$\cdots$S contact for one thiocyanate group, while the second group is positioned such that this type of interaction is not possible. 1,3-(Hydroxymethyl)propane-1,3-diyl bis(thiocyanate), $C_7H_{10}N_2O_2S_2$, (XI), also features a single short N$\cdots$S contact in the solid state. Hydrogen bonding between two molecules of compound (XI) results in the formation of dimers in the crystal, which are then linked together by a second hydrogen-bond interaction between the dimers. In addition, the structures of two intermediates from an unsuccessful alternative synthesis of (II) are reported. 2,2-Bis(chloromethyl)propane-1,3-diol, $C_5H_{10}Cl_2O_2$, (VI), crystallized as an inversion twin with a minor twin fraction of 0.43 (6). It forms a zigzag structure as a result of intermolecular hydrogen bonding. The structure of 9,9-dimethyl-2,4,8,10-tetraoxa-3λ^4-thiaspiro[5.5]undecan-3-one, $C_8H_{14}O_5S$, (VII), shows evidence for a weak S$\cdots$O contact with a distance of 3.2529 (11) Å.

Comment

The structure of 2,2-bis(hydroxymethyl)propane-1,3-diol ['pentaerythritol', (I), see Scheme 1] was first reported by Llewellyn *et al.* (1937), and a search of the Cambridge Structural Database (CSD, Version 5.31; Allen, 2002) reveals an additional 12 structural reports to date. This is unsurprising as (I) is a cheap commercially available material and exhibits a large degree of hydrogen bonding in the solid state. In contrast, the mixed diol–dithiol 2,2-bis(sulfanylmethyl)propane-1,3-diol, (II) (see Scheme 2), has received much less attention in the literature. The synthesis of (II) was first reported by Backer & Tamsma (1938), with further routes reported by Peppell & Signaigo (1946), Bladon & Owen (1950) and Nygård (1967). Compound (II) has clear potential as a starting material for functionalized dithiol ligands, and it is therefore highly surprising that there have been no reports of (II) in the literature since Nygård's paper. None of the reported syntheses of (II) involves a direct route from (I) and, given the availability of the latter, this seemed to be an obvious avenue to explore in producing large amounts of (II) with minimal synthetic effort.



Scheme 1: unsuccessful route to (II)



Scheme 2: successful route to (II)

The first strategy examined for the synthesis of (II) is outlined in Scheme 1. Conversion of (I) first to the acetal,

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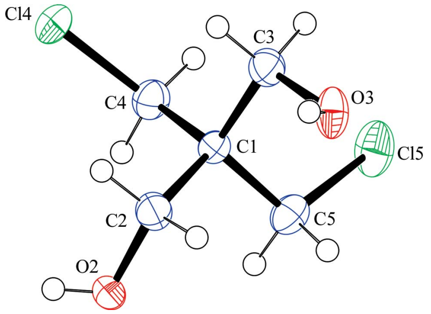


Figure 1
The structure of (VI), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

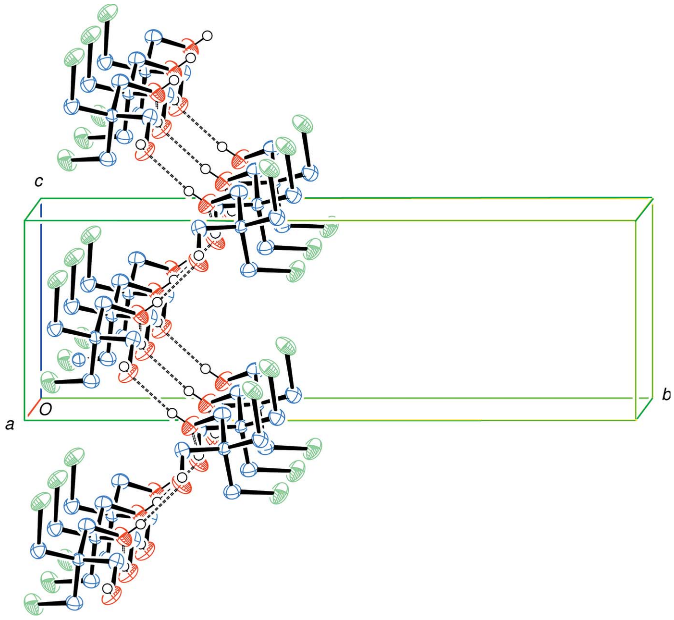


Figure 2
The two-dimensional hydrogen-bond network in (VI). H atoms, except for H2 and H3, have been omitted for clarity. The view is approximately along (100).

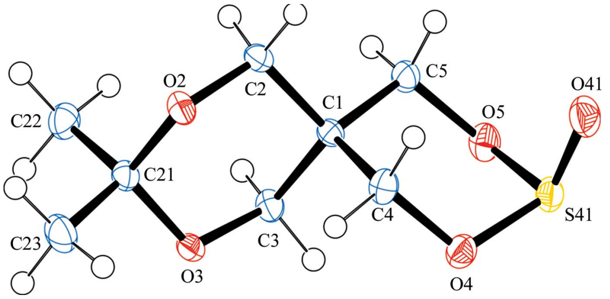


Figure 3
The structure of (VII), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

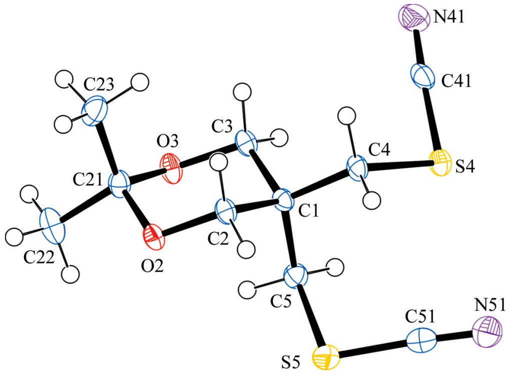
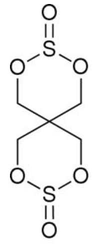


Figure 4
The structure of (X), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

(III), and then to the dichloride, (IV), was expected to be readily achieved. From (IV), the next target would be the bis(isothiouronium) salt, (V), with the intention of one-pot conversion of (V) to (II) in analogy to the formation of ethane-1,2-dithiol (Speziale, 1963).

Formation of acetal (III) from (I) presented no difficulties. However, the reaction of (III) with thionyl chloride ($SOCl_2$) was more challenging than initially anticipated. Reaction of (III) with $SOCl_2$ in pyridine at room temperature led to the isolation of two distinct crystalline solids after column chromatography. Both materials appeared to give spectroscopic data which would be consistent with the desired material. However, examination by X-ray methods revealed that the two solids were in fact (VI) and (VII) (Scheme 1). Presumably the formation of (VI) was due to hydrolysis of the desired material, (IV), on standing for crystallization (which took place in the air). Compound (VI) (Fig. 1) crystallizes in the space group *Cc* and the chosen crystal was found to exhibit inversion twinning, with a final occupancy for the minor component of 0.43 (6). The hydroxy groups in (VI) lead to an extended two-dimensional hydrogen-bonding network (Fig. 2 and Table 1), which links adjacent molecules to form a layer structure perpendicular to the *b* axis. This comprises a zigzag arrangement of hydrogen bonds, which hold the alternating molecules of (VI) together. The location of the hydrogen-bonding framework at the centre of the layer leaves the Cl atoms on the 'outside' of the layer.

The reaction to form a cyclic sulfur-containing ester, (VII) (Fig. 3), is similar to that reported by Rao *et al.* (2009), who showed that the reaction of (II) directly with $SOCl_2$ yields the bis(ester), (VIII) (see below). The geometry of compound (VII) is similar to that reported for (VIII) and is unremarkable. Both (VII) and (VIII) show evidence of weak intermolecular interactions. In (VII), there is a close contact between symmetry-related S=O groups, with an S41$\cdots$O41′ distance of 3.2529 (11) Å [symmetry code: (′) $2 - x$, $1 - y$,



(VIII)

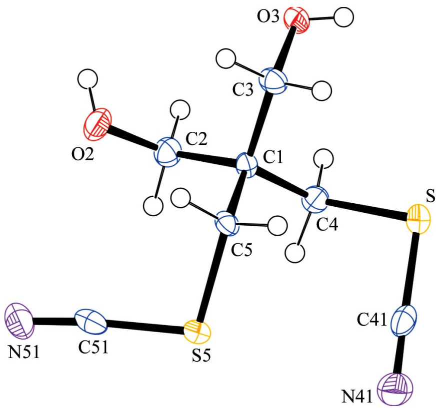


Figure 5
The structure of (XI), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

$2 - z$], while in (VIII) there are a number of S$\cdots$O distances in the range 3.308 (3)–3.315 (3) Å.

An alternative route to the desired chloride was explored by reacting (III) with 4-toluenesulfonyl chloride in pyridine. This led to a crystalline material with spectroscopic data fully in agreement with the structure of (IV). While a diffraction study on this new material showed the correct connectivity for (IV), high residual values prevented a satisfactory completion of the refinement; application of a twin law failed to improve the residual values obtained.

With (IV) available, reaction to form the desired salt, (V), was attempted. Reaction under a range of conditions failed to yield any material with spectroscopic characteristics matching those expected for the desired material. Given this failure, an alternative route to (II) was devised *via* the isothiocyanate compound, (XI) (see Scheme 2).

Starting from (III), the formation of (IX) by reaction with 4-toluenesulfonyl chloride in the presence of pyridine presented no significant difficulty. Compound (IX) could then be reacted with potassium thiocyanate in dimethyl sulfoxide (DMSO) to yield (X). This reaction proceeded much more readily in dimethyl sulfoxide than in the commonly employed dimethylformamide (DMF), presumably because of the differing basicity of the two solvents. Compound (X) could be crystallized as white needles from hexane–ethyl acetate (Fig. 4). Notably, compound (X) crystallizes in the space group $P2_1/c$ with no symmetry relationship between the two thiocyanate groups. In contrast, the only other reported bis(thiocyanate) structure, for methylene bis(thiocyanate), crystallizes in the space group $I2/c$ and does exhibit a symmetry relationship between the two groups (Konnert & Britton, 1971). The latter structure exhibits a short intermolecular N$\cdots$S contact [3.17 (1) Å]. In (X), there is one intramolecular contact [S4$\cdots$N51 = 3.2377 (16) Å], while the locations of S5 and N41 preclude contacts for these atoms. The molecular geometry of (X) is unremarkable.

Treatment with acid removed the acetal-protecting group from (X) to yield (XI) (Fig. 5). Compound (XI) crystallizes in the space group *Pbca* and as in (X) there is no symmetry relationship between the two thiocyanate groups. The intramolecular contact distance S5$\cdots$N41 of 3.264 (2) Å is similar to that in (X) and again larger than in the previously reported methylene bis(thiocyanate) (Konnert & Britton, 1971). Hydrogen bonding between molecules of (XI) occurs in two ways. Firstly, a pair of symmetry-related O—H$\cdots$O hydrogen bonds create 'dimers' of molecules. These dimers are then linked in an extended ribbon parallel to the *a* axis by a second set of symmetry-related hydrogen bonds between a hydroxy group and atom N51 of the thiocyanide group (Fig. 6 and Table 2). The ribbons are essentially flat without twists, and the ribbon plane lies parallel to (012).

Final reduction of (XI) to (II) with lithium aluminium hydride proceeded cleanly, and (II) was crystallized from

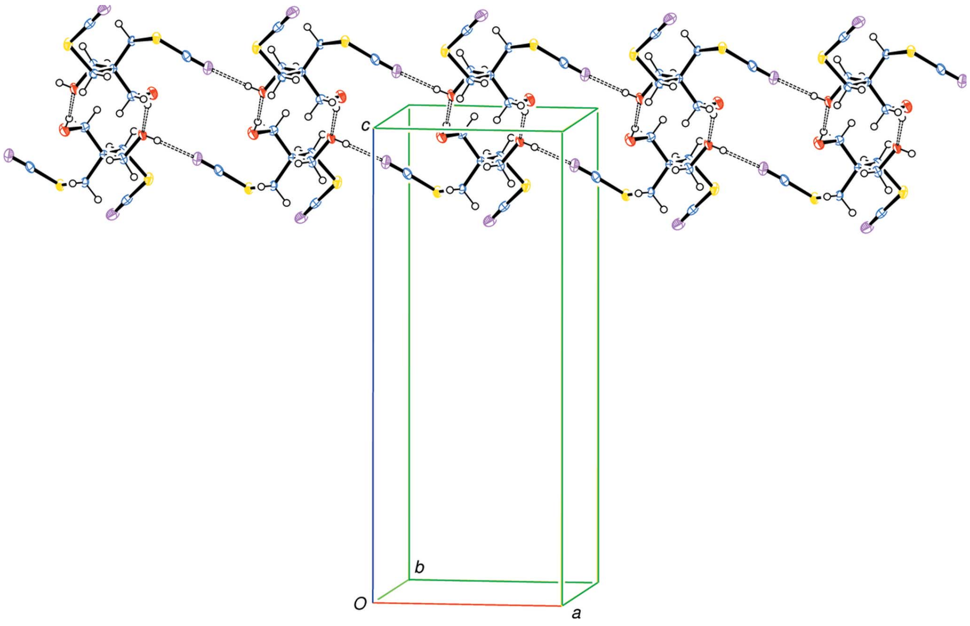


Figure 6
The hydrogen-bond network in (XI). H atoms, except for H2 and H3, have been omitted for clarity. The view is approximately along (010).

dichloromethane–diethyl ether. The resulting material gave spectroscopic data consistent with the formulation as (II).

In summary, a new synthesis of (II) has been disclosed starting from the commercial tetraol, (I). The structures of a number of key intermediates on this pathway have been presented.

Experimental

Compounds (VI) and (VII) were obtained by reaction of (III) with thionyl chloride in pyridine at 273 K. Column chromatography on silica (hexane–ethyl acetate 4:1 *v*/*v*) yielded two fractions, one of which was initially an oil and the other of which was a solid. The oil crystallized after standing in the air for several days to yield yellow crystals of (VI), while sublimation of the solid fraction at 1.3 Pa gave colourless crystals of (VII). Compound (X) was formed by the reaction of (IX) with potassium thiocyanate in dimethyl sulfoxide at 398 K. After aqueous work-up, column chromatography on silica (hexane–ethyl acetate 1:2 *v*/*v*) gave a clear oil which crystallized after standing overnight. Reaction of compound (X) with lithium aluminium hydride in tetrahydrofuran at 313 K followed by aqueous work-up gave (XI) as an off-white solid. This was recrystallized from hot chloroform. Full details of the syntheses of all the reported compounds and spectroscopic data are available in the archived CIF.

Compound (VI)

Crystal data

$C_5H_{10}Cl_2O_2$
M_r = 173.03
Monoclinic, *Cc*
a = 6.1635 (3) Å
b = 19.6495 (10) Å
c = 6.3889 (4) Å
β = 96.617 (5)°
V = 768.60 (7) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.77 mm^{-1}
T = 140 K
0.40 × 0.20 × 0.10 mm

Data collection

Oxford Diffraction Xcalibur 3/CCD diffractometer
Absorption correction: multi-scan (*CrysAlis Pro*; Oxford Diffraction, 2009)
$T_{\min}$ = 0.776, $T_{\max}$ = 1.000
5628 measured reflections
1707 independent reflections
1609 reflections with $I > 2\sigma(I)$
$R_{\rm int}$ = 0.028

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.028
$wR(F^2)$ = 0.075
S = 1.08
1707 reflections
91 parameters
2 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\max}$ = 0.46 e Å^{-3}
$\Delta\rho_{\min}$ = −0.23 e Å^{-3}
Absolute structure: Flack (1983), 825 Friedel pairs
Flack parameter: 0.43 (6)

Compound (VII)

Crystal data

$C_8H_{14}O_5S$
M_r = 222.25
Monoclinic, $P2_1/c$
a = 13.1287 (10) Å
b = 6.0588 (5) Å
c = 12.5024 (12) Å
β = 98.135 (8)°
V = 984.49 (15) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.32 mm^{-1}
T = 140 K
0.80 × 0.20 × 0.06 mm

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

D—H···A	D—H	H···A	D···A	D—H···A
O2—H2···O3$^{\rm i}$	0.77 (4)	1.91 (4)	2.653 (2)	165 (3)
O3—H3···O2$^{\rm ii}$	0.73 (3)	1.93 (3)	2.657 (2)	172 (3)

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

Data collection

Oxford Diffraction Xcalibur 3/CCD diffractometer
Absorption correction: multi-scan (*CrysAlis Pro*; Oxford Diffraction, 2009)
$T_{\min}$ = 0.771, $T_{\max}$ = 1.000
12831 measured reflections
2222 independent reflections
1805 reflections with $I > 2\sigma(I)$
$R_{\rm int}$ = 0.028

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.029
$wR(F^2)$ = 0.079
S = 1.06
2222 reflections
129 parameters
H-atom parameters constrained
$\Delta\rho_{\max}$ = 0.31 e Å^{-3}
$\Delta\rho_{\min}$ = −0.39 e Å^{-3}

Compound (X)

Crystal data

$C_{10}H_{14}N_2O_2S_2$
M_r = 258.35
Monoclinic, $P2_1/c$
a = 9.3934 (2) Å
b = 8.5696 (2) Å
c = 15.7918 (4) Å
β = 104.380 (2)°
V = 1231.38 (5) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.42 mm^{-1}
T = 140 K
0.70 × 0.08 × 0.08 mm

Data collection

Oxford Diffraction Xcalibur 3/CCD diffractometer
Absorption correction: multi-scan (*CrysAlis Pro*; Oxford Diffraction, 2009)
$T_{\min}$ = 0.840, $T_{\max}$ = 1.000
17624 measured reflections
2791 independent reflections
2222 reflections with $I > 2\sigma(I)$
$R_{\rm int}$ = 0.030

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.029
$wR(F^2)$ = 0.077
S = 1.01
2791 reflections
147 parameters
H-atom parameters constrained
$\Delta\rho_{\max}$ = 0.37 e Å^{-3}
$\Delta\rho_{\min}$ = −0.25 e Å^{-3}

Compound (XI)

Crystal data

$C_7H_{10}N_2O_2S_2$
M_r = 218.29
Orthorhombic, *Pbca*
a = 8.6971 (5) Å
b = 10.3972 (5) Å
c = 21.7280 (15) Å
V = 1964.8 (2) Å^3
Z = 8
Mo $K\alpha$ radiation
μ = 0.51 mm^{-1}
T = 140 K
0.39 × 0.13 × 0.01 mm

Data collection

Oxford Diffraction Xcalibur 3/CCD diffractometer
Absorption correction: multi-scan (*CrysAlis Pro*; Oxford Diffraction, 2009)
$T_{\min}$ = 0.926, $T_{\max}$ = 1.000
25270 measured reflections
2245 independent reflections
1498 reflections with $I > 2\sigma(I)$
$R_{\rm int}$ = 0.082

Table 2
Hydrogen-bond geometry (Å, °) for (XI).

$D-\text{H}\cdots A$	$D-\text{H}$	$\text{H}\cdots A$	$D\cdots A$	$D-\text{H}\cdots A$
$\text{O2}-\text{H2}\cdots\text{O3}^{\text{i}}$	0.78 (2)	1.97 (3)	2.744 (2)	170 (3)
$\text{O3}-\text{H3}\cdots\text{N51}^{\text{ii}}$	0.75 (2)	2.08 (2)	2.832 (2)	177 (3)

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

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.040$
$wR(F^2) = 0.069$
$S = 0.94$
2245 reflections
124 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\text{max}} = 0.31$ e Å^{-3}
$\Delta\rho_{\text{min}} = -0.26$ e Å^{-3}

All structure solutions and refinements were carried out from within the *WinGX* suite of programs (Farrugia, 1999). All C-bound H atoms were refined using a riding model (*SHELXL97*; Sheldrick, 2008), and with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$ for CH and CH_2 groups or $1.5U_{\text{eq}}(\text{C})$ for methyl groups. Methyl groups were allowed additional rotational freedom. In structures (VII) and (X), the oxygen-bound H atoms were initially positioned using the *CALC-OH* program (Nardelli, 1999), and both coordinates and U_{iso} values were freely refined. The chosen crystal of (VI) was found to exhibit inversion twinning and the refinement of the absolute structure parameter yielded a value of 0.43 (6) for the minor twin component.

For all compounds, data collection: *CrysAlis Pro* (Oxford Diffraction, 2009); cell refinement: *CrysAlis Pro*; data reduction: *CrysAlis Pro*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1993); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3* (Farrugia, 1997). Software used to prepare material for publication: *SHELXL97*, *enCIFer* (Allen *et al.*, 2004) and *publCIF* (Westrip, 2010) for (VI) and (VII); *SHELXL97*, *enCIFer* and *PARST* (Nardelli, 1995) for (X) and (XI).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3390). Services for accessing these data are described at the back of the journal.

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