

5-Hydroxyalkyl derivatives of *tert*-butyl 2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate: diastereoselectivity of the Mukaiyama crossed-aldol-type reaction

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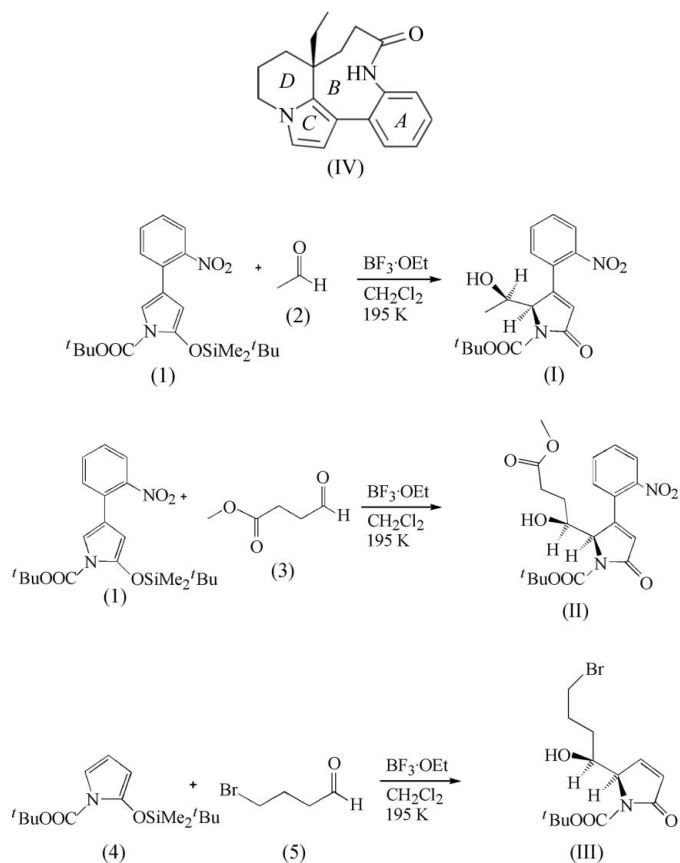
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The title compounds, *rac*-(1'*R*,2*R*)-*tert*-butyl 2-(1'-hydroxyethyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate, C₁₇H₂₀N₂O₆, (I), *rac*-(1'*S*,2*R*)-*tert*-butyl 2-[1'-hydroxy-3'-(methoxycarbonyl)propyl]-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate, C₂₀H₂₄N₂O₈, (II), and *rac*-(1'*S*,2*R*)-*tert*-butyl 2-(4'-bromo-1'-hydroxybutyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate, C₁₃H₂₀BrNO₄, (III), are 5-hydroxyalkyl derivatives of *tert*-butyl 2-oxo-2,5-dihydropyrrole-1-carboxylate. In all three compounds, the *tert*-butoxycarbonyl (Boc) unit is orientated in the same manner with respect to the mean plane through the 2-oxo-2,5-dihydro-1*H*-pyrrole ring. The hydroxyl substituent at one of the newly created chiral centres, which have relative *R,R* stereochemistry, is *trans* with respect to the oxo group of the pyrrole ring in (I), synthesized using acetaldehyde. When a larger aldehyde was used, as in compounds (II) and (III), the hydroxyl substituent was found to be *cis* with respect to the oxo group of the pyrrole ring. Here, the relative stereochemistry of the newly created chiral centres is *R,S*. In compound (I), O—H...O hydrogen bonding leads to an interesting hexagonal arrangement of symmetry-related molecules. In (II) and (III), the hydroxyl groups are involved in bifurcated O—H...O hydrogen bonds, and centrosymmetric hydrogen-bonded dimers are formed. The Mukaiyama crossed-aldol-type reaction was successful when using the 2-nitrophenyl-substituted hydroxypyrrole, or the unsubstituted hydroxypyrrole, and boron trifluoride diethyl ether as catalyst. The synthetic procedure leads to a *syn* configuration of the two newly created chiral centres in all three compounds.

Comment

The natural product (–)-rhazinilam, (IV), was first isolated by Linde in 1965 from *Melodinus australis* (Baudoin *et al.*, 2004). The tetracyclic structure was determined by a combination of X-ray analysis and chemical studies seven years later (De Silva *et al.*, 1972). Screening experiments have shown that (–)-rhazinilam has interesting pharmacological properties, due to its interference in the tubuline–microtubule equilibrium during mitosis. It has also been shown to have significant *in vitro* cytotoxicity, but no activity *in vivo* (Baudoin *et al.*, 2004). Several groups have reported their studies on the synthesis of this natural product and its analogues (Decor *et al.*, 2006; Baudoin *et al.*, 2002; Ghosez *et al.*, 2001; Rubio *et al.*, 2001; Dupont *et al.*, 2000; Alazard *et al.*, 1996). Our synthetic strategy was to replace the pyrrole ring by a corresponding

pyrrol-2(5*H*)-one ring or its protected 2-hydroxypyrrole tautomer (Vallat *et al.*, 2009).



In order to introduce the missing side chain needed for the formation of ring *B* of rhazinilam, we tested the known Mukaiyama crossed-aldol-type reaction (Mukaiyama *et al.*, 1974) of the protected 2-hydroxypyrrole with different aldehydes. This reaction was successful when using the 2-nitrophenyl-substituted hydroxypyrrole (1), or the unsubstituted hydroxypyrrole (4), and boron trifluoride diethyl ether as catalyst. The relative configuration at the two newly formed chiral centres could not be determined unequivocally using NMR methods. A literature search showed that the Boc-protected (Boc is *tert*-butoxycarbonyl) (*tert*-butyldimethylsilyloxy)pyrrole (1) had been used in a series of very elegant natural product syntheses (Battistini *et al.*, 2004; Rassa *et al.*, 2002, 2003; Barnes *et al.*, 2002; Casiraghi *et al.*, 1992; DeGoey *et al.*, 2002). The diastereoselectivity of the reaction with a series

of chiral aldehydes and imines has been carefully studied and was shown, for most of the reported processes, to be *syn*. However, the reaction using the imine has been reported to be *anti* selective (Barnes *et al.*, 2002; DeGoey *et al.*, 2002). The diastereoselectivity of the crossed-aldol-type reaction using a phenyl-substituted pyrrole has not been reported previously, to our knowledge. We report here the crystal structures of *rac*-(1'*R*,2*R*)-*tert*-butyl 2-(1'-hydroxyethyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate, (I), *rac*-(1'*S*,2*R*)-*tert*-butyl 2-[1'-hydroxy-3'-(methoxycarbonyl)propyl]-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate, (II),

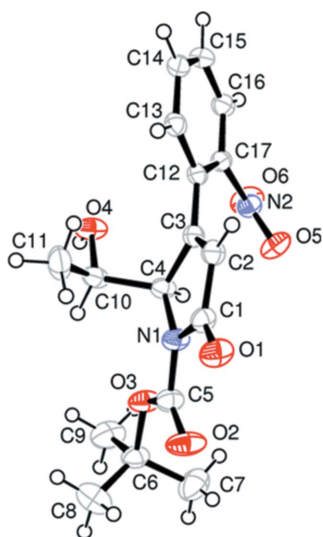


Figure 1
The molecular structure of compound (I), showing the atom-labelling scheme and displacement ellipsoids at the 50% probability level.

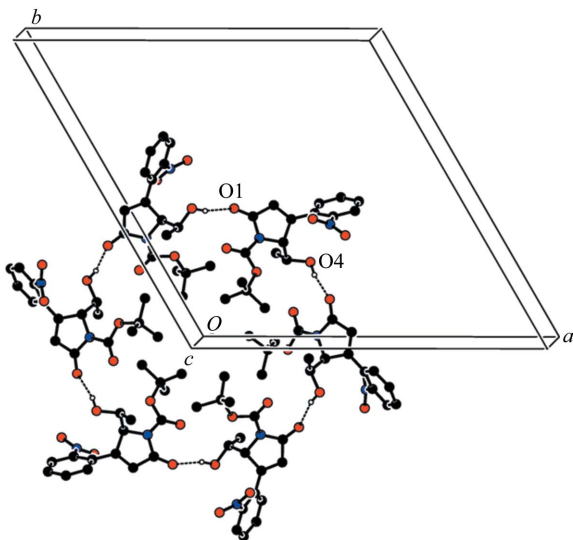


Figure 2
A partial cell view along the *c* axis of the crystal packing of compound (I), showing the formation of the hexagonal arrangement of symmetry-related hydrogen-bonded molecules (see Table 1 for details). Hydrogen bonds are shown as dotted lines and H atoms not involved in hydrogen bonding have been omitted for clarity.

and *rac*-(1'*S*,2*R*)-*tert*-butyl 2-(4'-bromo-1'-hydroxybutyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate, (III), which were studied to determine the diastereoselectivity of the Mukaiyama crossed-aldol-type reaction.

The molecular structures of compounds (I), (II) and (III) are illustrated in Figs. 1, 3 and 5, respectively. The crystal packing in compounds (I), (II) and (III), also showing the hydrogen bonding, are illustrated in Figs. 2, 4 and 6, respectively. The bond lengths and angles in all three compounds are in normal ranges (Allen *et al.*, 1987). Details of the hydrogen bonding are given in Tables 1, 2 and 3.

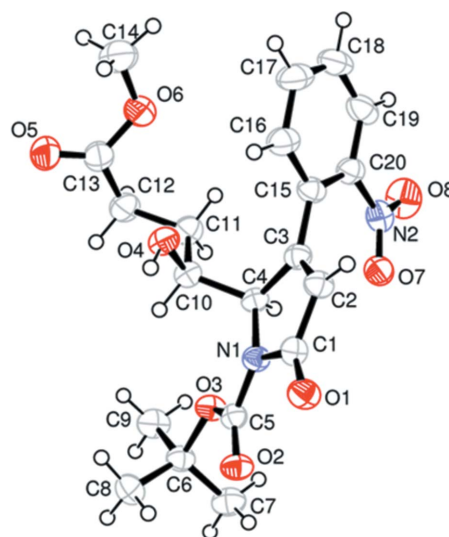


Figure 3
The molecular structure of compound (II), showing the atom-labelling scheme and displacement ellipsoids at the 50% probability level.

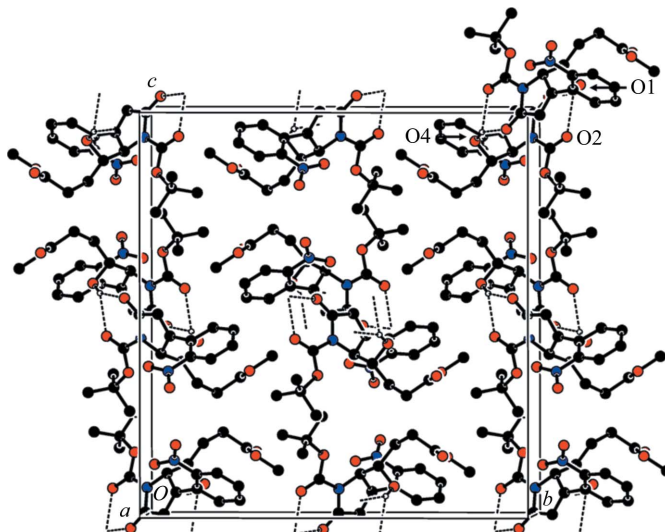


Figure 4
A view along the *a* axis of the crystal packing of compound (II), showing the bifurcated hydrogen bonds and the formation of the centrosymmetric hydrogen-bonded dimers (see Table 2 for details). Hydrogen bonds are shown as dotted lines and H atoms not involved in hydrogen bonding have been omitted for clarity.

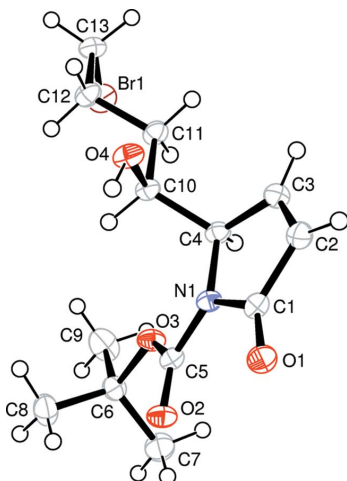


Figure 5
The molecular structure of compound (III), showing the atom-labelling scheme and displacement ellipsoids at the 50% probability level.

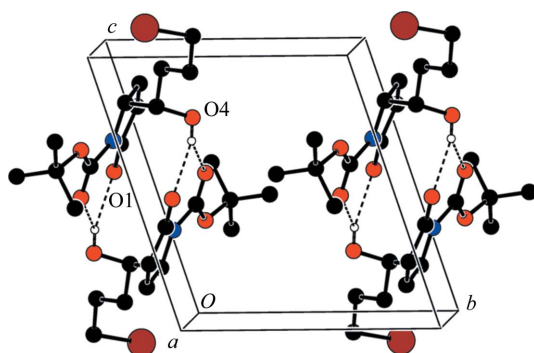


Figure 6
A cell view along the *a* axis of compound (III), showing the bifurcated hydrogen bonds and the formation of the centrosymmetric hydrogen-bonded dimers (see Table 3 for details). Hydrogen bonds are shown as dotted lines and H atoms not involved in hydrogen bonding have been omitted for clarity.

All three compounds contain 2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate units having very similar geometries. In compounds (I) and (II), the 2-nitrophenyl substituent at C3 is inclined to the best plane through the 2,5-dihydro-1*H*-pyrrole ring by 52.47 (6) and 71.25 (11)°, respectively. The orientation of the hydroxyl substituent at C10 in compound (I) (Fig. 1) is different to that in compounds (II) (Fig. 3) and (III) (Fig. 5). In (I), it lies *trans* with respect to the 2,5-dihydro-1*H*-pyrrole ring, and the C10–O4 bond makes an angle of 1.16 (9)° with the mean plane of the pyrrole ring. In compounds (II) and (III), however, it is *cis* with respect to the pyrrole ring, and here the C10–O4 bond is inclined to the pyrrole ring mean plane by 55.22 (11)° in (II) and 56.08 (11)° in (III).

In all three compounds, O–H···O hydrogen bonds play an important role. In the crystal structure of compound (I), a hexagonal arrangement ($\bar{3}$ symmetry) of symmetry-related molecules is formed (Fig. 2 and Table 1). In compounds (II) and (III), the hydroxyl group is involved in bifurcated O–H···O hydrogen bonds, and in both crystal structures

centrosymmetric hydrogen-bonded dimers are formed (Figs. 4 and 6, and Tables 2 and 3, respectively).

The relative stereochemistry of the newly created chiral centres in compound (I), at C4 and C10, is *R,R*. When a larger aldehyde was used, as in the case of compounds (II) and (III), the relative stereochemistry of the newly created chiral centres is *R,S*. The synthetic procedure used led to a *syn* configuration of the two newly created chiral centres in all three compounds, in close analogy to reports in the literature (Battistini *et al.*, 2004; Rassa *et al.*, 2002, 2003; Casiraghi *et al.*, 1992). Changing the Lewis acid, that is using BF₃ instead of SnCl₄, and introducing an aryl substituent at the carbon next to the nucleophilic centre, does not influence the diastereoselectivity of the process. An extended transition state respecting the Bürgi–Dunitz angle (Bürgi & Dunitz, 1974) is compatible with these results.

Experimental

For the preparation of compound (I), acetaldehyde (0.18 ml, 3.20 mmol) and BF₃·OEt₂ (0.47 ml, 3.78 mmol) were added dropwise to a solution of *tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-4-(2-nitrophenyl)-1*H*-pyrrole-1-carboxylate (1.22 g, 2.91 mmol) in dry CH₂Cl₂ (30 ml) at 195 K under argon. The colour of the solution changed from yellow to light yellow. The mixture was stirred at 195 K for 1 h. The reaction mixture was quenched at 195 K with a saturated aqueous solution of NaHCO₃ (20 ml) and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated. Purification of the residue by flash chromatography (silica gel, ethyl acetate–dichloromethane 4:6 *v/v*) afforded (I) as a white solid (yield 0.53 g, 52%). Crystals suitable for X-ray analysis were obtained by slow evaporation of an ether–hexane (1:1) solution.

For the preparation of (II), methyl 4-oxobutanoate (348 mg, 3.0 mmol) and BF₃·OEt₂ (0.38 ml, 2.3 mmol) were added dropwise to a solution of *tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-4-(2-nitrophenyl)-1*H*-pyrrole-1-carboxylate (966 mg, 2.3 mmol) in dry CH₂Cl₂ (20 ml) at 195 K under argon. The colour of the solution changed from yellow to light yellow. The mixture was stirred at 195 K for 1 h. The reaction mixture was quenched at 195 K with a saturated aqueous solution of NaHCO₃ (15 ml) and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated. Purification of the residue by flash chromatography (silica gel, ethyl acetate–diethyl ether 3:7 *v/v*) afforded (II) as a white solid (yield 815 mg, 93%). Crystals suitable for X-ray analysis were obtained by slow evaporation of an ether–hexane (1:1) solution.

For the preparation of (III), 4-bromobutanal (0.35 g, 2.31 mmol) and BF₃·OEt₂ (0.29 ml, 2.31 mmol) were added dropwise to a solution of *tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-1*H*-pyrrole-1-carboxylate (0.68 g, 2.31 mmol) in dry CH₂Cl₂ (20 ml) at 195 K under argon. The colour of the solution changed from yellow to light yellow. The mixture was stirred at 195 K for 1 h. The reaction mixture was quenched at 195 K with a saturated aqueous solution of NaHCO₃ (15 ml) and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated. Purification of the residue by flash chromatography (silica gel, ethyl acetate–dichloromethane 3:7 *v/v*) afforded (III) as a white solid (yield 0.30 g, 39%). Crystals suitable for X-ray analysis were obtained by slow evaporation of an ether–hexane (1:1) solution.

Compound (I)*Crystal data*

$C_{17}H_{20}N_2O_6$	$Z = 18$
$M_r = 348.35$	Mo $K\alpha$ radiation
Trigonal, $R\bar{3}$	$\mu = 0.10 \text{ mm}^{-1}$
$a = 21.1117 (8) \text{ \AA}$	$T = 173 \text{ K}$
$c = 20.3244 (9) \text{ \AA}$	$0.45 \times 0.45 \times 0.45 \text{ mm}$
$V = 7845.0 (5) \text{ \AA}^3$	

Data collection

Stoe IPDS-2 diffractometer	4041 reflections with $I > 2\sigma(I)$
39673 measured reflections	$R_{\text{int}} = 0.089$
4718 independent reflections	

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.039$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.098$	$\Delta\rho_{\text{max}} = 0.27 \text{ e \AA}^{-3}$
$S = 1.05$	$\Delta\rho_{\text{min}} = -0.17 \text{ e \AA}^{-3}$
4718 reflections	
235 parameters	

Compound (II)*Crystal data*

$C_{20}H_{24}N_2O_8$	$V = 4090.3 (6) \text{ \AA}^3$
$M_r = 420.41$	$Z = 8$
Orthorhombic, $Pbca$	Mo $K\alpha$ radiation
$a = 9.1439 (7) \text{ \AA}$	$\mu = 0.11 \text{ mm}^{-1}$
$b = 20.7113 (18) \text{ \AA}$	$T = 153 \text{ K}$
$c = 21.598 (2) \text{ \AA}$	$0.50 \times 0.45 \times 0.10 \text{ mm}$

Data collection

Stoe IPDS-2 diffractometer	2605 reflections with $I > 2\sigma(I)$
16666 measured reflections	$R_{\text{int}} = 0.078$
3856 independent reflections	

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.044$	277 parameters
$wR(F^2) = 0.110$	H-atom parameters constrained
$S = 0.95$	$\Delta\rho_{\text{max}} = 0.18 \text{ e \AA}^{-3}$
3856 reflections	$\Delta\rho_{\text{min}} = -0.22 \text{ e \AA}^{-3}$

Compound (III)*Crystal data*

$C_{13}H_{20}BrNO_4$	$\gamma = 101.367 (8)^\circ$
$M_r = 334.21$	$V = 719.57 (12) \text{ \AA}^3$
Triclinic, $P\bar{1}$	$Z = 2$
$a = 8.8340 (9) \text{ \AA}$	Mo $K\alpha$ radiation
$b = 9.0750 (9) \text{ \AA}$	$\mu = 2.87 \text{ mm}^{-1}$
$c = 10.7283 (10) \text{ \AA}$	$T = 173 \text{ K}$
$\alpha = 104.176 (7)^\circ$	$0.50 \times 0.50 \times 0.50 \text{ mm}$
$\beta = 113.759 (7)^\circ$	

Data collection

Stoe IPDS-2 diffractometer	9956 measured reflections
Absorption correction: multi-scan (<i>MULScanABS</i> in <i>PLATON</i> ; Spek, 2009)	3862 independent reflections
$T_{\text{min}} = 0.307$, $T_{\text{max}} = 0.472$ (expected range = 0.155–0.239)	3587 reflections with $I > 2\sigma(I)$
	$R_{\text{int}} = 0.031$

Table 1
Hydrogen-bond geometry (\AA , $^\circ$) for (I).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$O4-H4O\cdots O1^i$	0.852 (18)	1.930 (19)	2.7600 (15)	164.3 (19)

Symmetry code: (i) $y, -x + y, -z$.**Table 2**
Hydrogen-bond geometry (\AA , $^\circ$) for (II).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$O4-H4O\cdots O1^i$	0.84	2.15	2.903 (2)	149
$O4-H4O\cdots O2^i$	0.84	2.33	2.9696 (16)	134

Symmetry code: (i) $-x + 2, -y + 2, -z + 2$.**Table 3**
Hydrogen-bond geometry (\AA , $^\circ$) for (III).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$O4-H4O\cdots O1^i$	0.84	2.17	2.9138 (16)	148
$O4-H4O\cdots O2^i$	0.84	2.28	2.9225 (18)	134

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

$R[F^2 > 2\sigma(F^2)] = 0.027$	177 parameters
$wR(F^2) = 0.066$	H-atom parameters constrained
$S = 1.05$	$\Delta\rho_{\text{max}} = 0.43 \text{ e \AA}^{-3}$
3862 reflections	$\Delta\rho_{\text{min}} = -0.78 \text{ e \AA}^{-3}$

In compound (I), the hydroxyl H atom was located from a difference Fourier map and freely refined [$O-H = 0.852 (18) \text{ \AA}$]. For compounds (II) and (III), the hydroxyl H atoms were included in calculated positions and treated as riding [$O-H = 0.84 \text{ \AA}$ and $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{O})$]. The C-bound H atoms in all three compounds were included in calculated positions and treated as riding atoms [$C-H = 0.95-1.00 \text{ \AA}$ and $U_{\text{iso}}(\text{H}) = 1.2$ or $1.5U_{\text{eq}}(\text{C})$]. A small cusp of data is missing for structure (II); this problem is related to the image-plate diffractometer using only one azimuthal scan. A fraction of the reciprocal-lattice points never intersect the Ewald sphere and so a small cusp of data is missing. This has a small effect on the precision of the structure analysis, which can be seen when comparing the s.u. values of structure (II) with those of structures (I) and (III); for example, on average, the bond distances differ by 5 s.u., whereas for structures (I) and (III) they differ by only 2 s.u.

For all three compounds, data collection: *X-AREA* (Stoe & Cie, 2006); cell refinement: *X-AREA*; data reduction: *X-RED32* (Stoe & Cie, 2006); 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 *PLATON* (Spek, 2009); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GA3120). Services for accessing these data are described at the back of the journal.

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