

**(*S,S*)-Lactoyllactic acid and (*S,S,S*)-
lactoyllactoyllactic acid**Martin Lutz^{a*} and Jan van Krieken^b^aBijvoet Center for Biomolecular Research, Crystal and Structural Chemistry, Faculty of Science, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands, and^bPurac, Arkelsedijk 46, 4206 AC Gorinchem, The Netherlands

Correspondence e-mail: m.lutz@uu.nl

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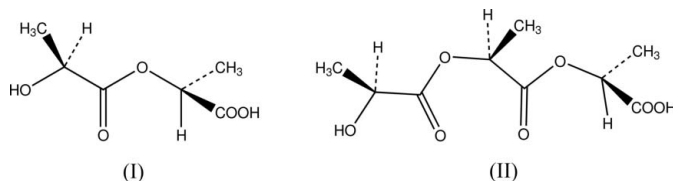
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The dimeric condensation product of lactic acid, namely (*S,S*)-2-[(2-hydroxypropanoyl)oxy]propanoic acid, C₆H₁₀O₅, (I), crystallizes with two independent molecules in the asymmetric unit, which both have an essentially planar backbone. The trimeric condensation product, namely (*S,S,S*)-3-hydroxybut-3-en-2-yl 2-[(2-hydroxypropanoyl)oxy]propanoate, C₉H₁₄O₇, (II), has one molecule in the asymmetric unit and consists of two essentially planar parts, with the central C—O bond in a *gauche* conformation. Both molecules of the dimer are involved in intermolecular hydrogen bonds, forming chains with a *C*(8) graph set. These chains are connected by *D*(2) hydrogen bonds to form a two-dimensional layer. The trimer forms hydrogen-bonded *C*(10) and *C*₂²(6) chains, which together result in a two-dimensional motif. The Hooft method [Hooft, Straver & Spek (2008). *J. Appl. Cryst.* **41**, 96–103] was successfully applied to the determination of the absolute structure of (I).

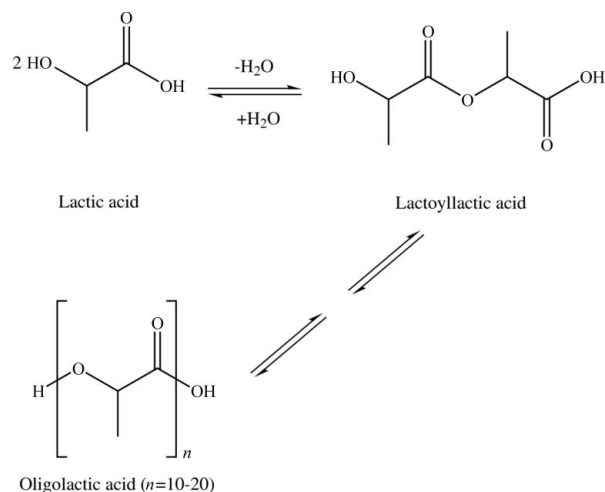
Comment

Lactic acid is the simplest 2-hydroxy acid with a chiral C atom. Hydroxy acids are known to form condensation polymers upon heating and removal of water (Probst *et al.*, 1977). The crystal structures of the dimer, (I), and the trimer, (II), are reported here.



Today lactic acid is produced in general by fermentation. Both enantiomeric forms can be produced in this way: (*S*)-lactic acid, which is the natural form, but also (*R*)-lactic acid. Pure monomeric (*S*)-lactic acid has a melting point of 326 K (Borsook *et al.*, 1933). However, due to the hygroscopicity of crystalline (*S*)-lactic acid, its high solubility in water and the

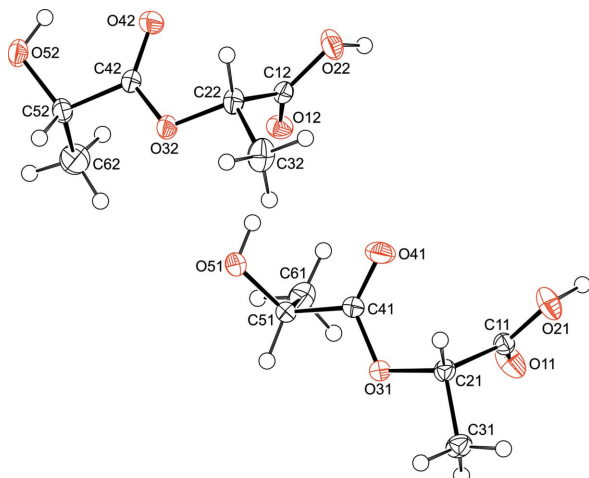
phenomenon of condensation polymerization, the commercial product is not a solid, but a concentrated solution in water. A commercial solution of 90 wt% lactic acid at equilibrium and 293 K contains about 65 wt% of monomeric lactic acid, 15–20 wt% of dimer and about 5 wt% of higher oligomers. The crystal structure of lactic acid (Schouten *et al.*, 1994) shows an almost planar molecule, with the hydroxy group coplanar with the carboxylic acid group.



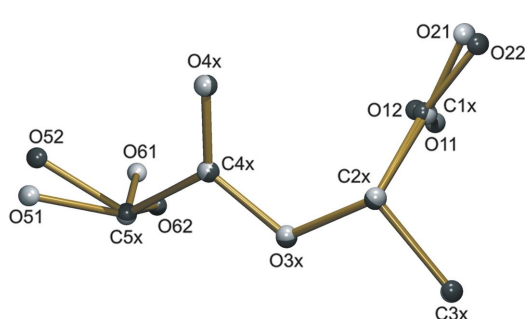
Lactic acid and its derivatives are used in a wide range of applications (Datta, 2005). Lactic acid and its alkali metal salts are used in food applications for reasons of pH control, taste and antimicrobial activity (Bogaert & Naidu, 2000; Shelef, 1994). Apart from food applications, lactic acid and its derivatives are also used in technical applications (*e.g.* lactic acid in household cleaning and ethyl lactate as a solvent in electronics), medical applications (*e.g.* sodium lactate in infusion liquor) and cosmetic applications. In the last decade, the application of lactic acid as monomer in the synthesis of poly(lactic acid) (PLA) has gained importance. PLA is used as a biobased polymer in packaging, but also in other polymer applications (Jem *et al.*, 2010).

The condensation polymerization of lactic acid occurs at room temperature. The process starts with the formation of a dimer (lactoyllactic acid), followed by a trimer, *etc.* (Holten, 1971). At high temperatures (473 K) and reduced pressure, a degree of polymerization of 10–20 can be achieved. As far as we know, no data on the pure solid dimer or trimer of (*S*)-lactic acid have been published previously.

Compound (I) crystallizes with two independent molecules in the asymmetric unit (*Z'* = 2). A plot of these molecules is shown in Fig. 1. The backbone of both molecules is essentially planar, with the torsion angles about C4_x—O3_x and O3_x—C2_x indicating *trans* conformations (Table 1; *x* = 1 or 2). The main differences between the two molecules are the conformations of the end groups, which are both involved in intermolecular hydrogen bonding (see below), and the differences can thus be ascribed to crystal-packing effects. The torsion angles about C1_x—C2_x differ by about 15° between the two molecules; the torsion angles about C4_x—C5_x differ by about 25°. These differences can also be seen in an overlay plot of


Figure 1

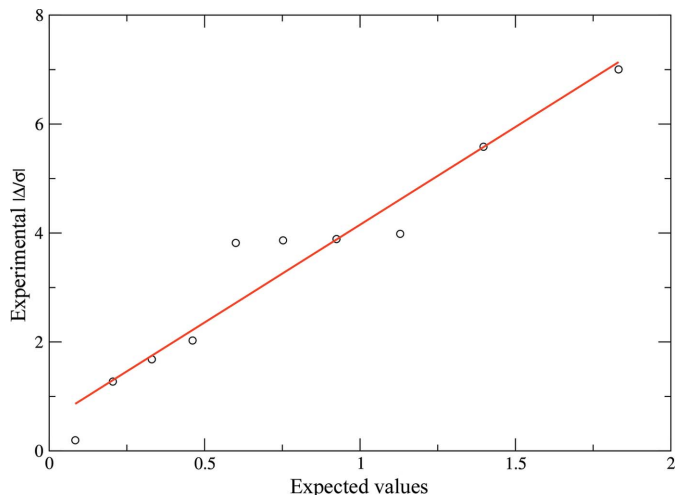
A view of the asymmetric unit of (I), showing the two independent molecules and the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. (In the electronic version of the paper, O atoms are drawn in red.)


Figure 2

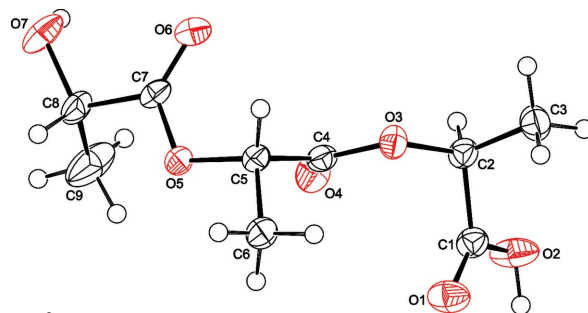
A quaternion fit of the two independent molecules in (I) ($x = 1, 2$), calculated by *PLATON* (Spek, 2009) using an algorithm of Mackay (1984). The fit is based on all non-H atoms, except for O1x, O2x, O5x and C6x, resulting in an r.m.s. fit of 0.027 Å for the seven fitted atoms.

the two molecules (Fig. 2). Thermal motion analysis using the *THMA11* program (Schomaker & Trueblood, 1998) reveals that the second molecule is more rigid than the first, with $R_{\text{thma}} = 0.167$ versus 0.280 ($R_{\text{thma}} = \{[\sum(w\Delta U)^2]/[\sum(wU_{\text{obs}})^2]\}^{1/2}$). A possible explanation is the presence of an intramolecular O—H...O interaction in the second molecule, which makes the molecule more rigid. A comparison of the bond lengths in both molecules using a half-normal probability plot (Abrahams & Keve, 1971) is shown in Fig. 3 and reveals that the largest difference is 7.00 σ . This difference is between the C41—C51 bond in the first molecule and C42—C52 in the second. The latter bond is part of the five-membered ring formed by the intramolecular hydrogen bond.

Compound (II) crystallizes with one independent molecule in the asymmetric unit ($Z' = 1$), which is shown in Fig. 4. The molecule consists of two essentially planar parts, with the torsion angles about C2—O3, O3—C4, C4—C5 and O5—C7 corresponding to *trans* conformations. The central C5—O5 bond adopts a *gauche* conformation (Table 3). If a segmented model is applied in the rigid-body analysis in *THMA11* and the molecule is allowed to move about this C5—O5 bond,


Figure 3

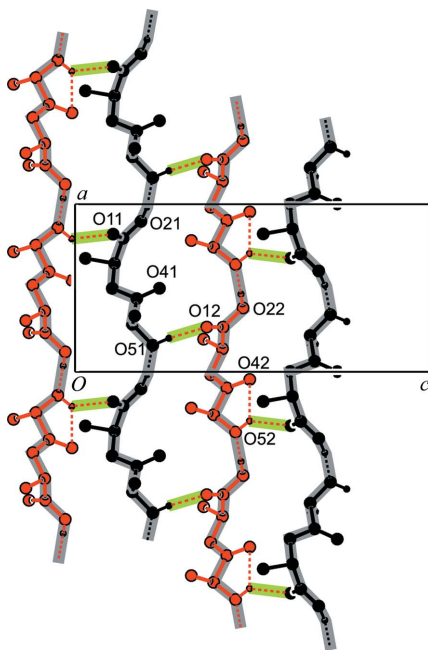
A half-normal probability plot (Abrahams & Keve, 1971) of the bond distances in the two independent molecules of (I). The slope is 3.59 and the intercept is 0.56.


Figure 4

A view of the asymmetric unit of (II), 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. (In the electronic version of the paper, O atoms are drawn in red.)

R_{thma} drops from 0.263 to 0.148. Segmentation about other bonds of the molecule does not lead to such a large improvement. We therefore consider this as a strong indication that the two planar parts of the molecule are independent rigid groups.

The two independent molecules in (I) form hydrogen-bonded chains in the direction of the crystallographic *a* axis. Carboxylic acid atom O21 acts as donor and ester atom O51 of the translated molecule is the acceptor (Table 2). An identical situation is found for the second residue, and the graph-set descriptors (Bernstein *et al.*, 1995) for the two chains are consequently both *C*(8). The two chains are linked, with hydroxy groups O51 and O52 as donors and carboxylic acid atoms O12 and O11 of the other chain as acceptors, best described with the graph-set descriptor *D*(2). The overall pattern formed by intermolecular hydrogen bonding is thus a two-dimensional network in the *ac* plane (Fig. 5). The hydroxy group at O52 is actually bifurcated, with an angle sum of 357 (2)° at H52O. This additionally forms an intramolecular hydrogen bond with atom O42 as acceptor, thereby imparting molecular rigidity (see above); here the graph-set notation is *S*(5). The corresponding interaction at O51 is considered

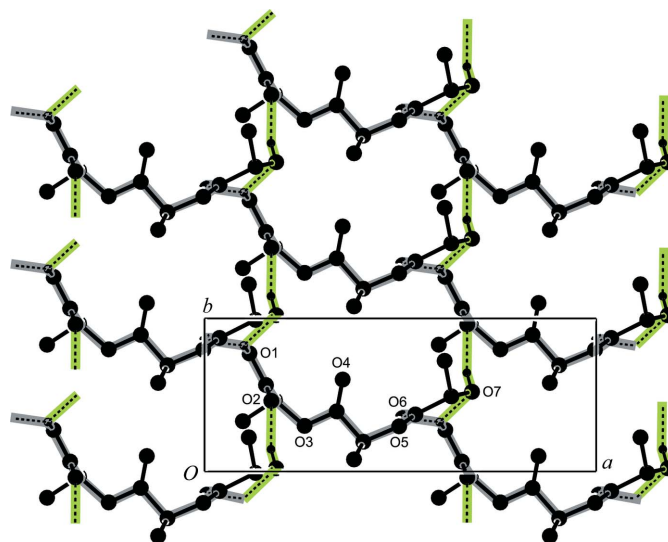
**Figure 5**

A view of the two-dimensional hydrogen-bonding pattern in (I), viewed along the *b* axis. C-bound H atoms have been omitted for clarity. Chains with graph set $C(8)$ (coloured grey in the electronic version of the paper) run along *a* axis. Hydrogen bonds forming connections along the *c* direction (coloured green in the electronic version of the paper) have graph set $D(2)$. Hydrogen-bond geometry and symmetry operations are given in Table 2.

much weaker, due to an O—H...O angle of only 94.9 (12)° and a very long H...O distance of 2.625 (16) Å.

In (II) we also find a two-dimensional hydrogen-bonding pattern (Fig. 6). Chains with graph-set descriptor $C(10)$ run along the $[\bar{1}10]$ diagonal. Carboxylic acid atom O2 is the hydrogen-bond donor and ester atom O6 the acceptor (Table 4). Atom H2O is bifurcated, with an angle sum of 361 (5)°, and also involved in a hydrogen-bonded chain in the *b* direction. In this chain, atom O2 is the donor and hydroxy group O7 the acceptor. In a co-operative fashion, atom O7 is then also a donor, with carboxylic atom O1 as acceptor. Consequently, the graph-set descriptor here is $C_2^2(6)$. Combination of the $[\bar{1}10]$ and $[010]$ chains results in a two-dimensional network in the *ab* plane.

Both molecules (I) and (II) only consist of the very weak anomalous scatterers C, H and O. For Mo $K\alpha$ radiation, the *a priori* estimation of the Bijvoet differences (Flack & Shmueli, 2007) results in the very low value of Friedel = 7 for both structures. The standard uncertainties in the Flack parameters (Flack, 1983), $x = 0.0$ (3) for (I) and $x = -0.1$ (8) for (II), were so large that the absolute structure could not be determined reliably by this method (Flack & Bernardinelli, 2000). For the least-squares refinement of both structures, the Friedel pairs have therefore been averaged. Interestingly, using the method of Hooft *et al.* (2008) on the unmerged data allowed the absolute structure of (I) to be confirmed. Here, the absolute structure is not determined during the least-squares refinement as with the Flack parameter, but likelihood calculations are applied on the Bijvoet differences. For (I), the Hooft

**Figure 6**

A view of the two-dimensional hydrogen-bonding pattern in (II), viewed along the *c* axis. C-bound H atoms have been omitted for clarity. Chains with graph-set notation $C(10)$ (coloured grey in the electronic version of the paper) run along the $[\bar{1}10]$ direction. Chains in the *b* direction (coloured green in the electronic version of the paper) have graph-set notation $C_2^2(6)$. Hydrogen-bond geometry and symmetry operations are given in Table 4.

parameter yields a value of $y = -0.02$ (9) based on all 3024 Bijvoet pairs and assuming a Gaussian distribution of errors. The probability that the absolute configuration is correct is 1.000. In the case of (II), the standard uncertainty in the Hooft parameter $y = 0.2$ (2) is too high to draw reliable conclusions. Here, a probability of 0.987 for the correct absolute structure is only attained by making the assumption that the crystal is enantiomerically pure. Allowing the possibility of an inversion twin reduces the probability to 0.536.

Experimental

For the preparation of (*S,S*)-lactoyllactic acid, (I), (*S,S*)-lactide (401 g) was mixed with demineralized water (100 g) and acetone (161 g). The mixture was refluxed for 5 h and afterwards cooled to about 313 K. The excess water, the acetone and some monomeric lactic acid were then removed by means of a short-path distillation (KDL-4, UIC). The resulting product contained about 90 wt% of (*S,S*)-lactoyllactic acid. The crude product (398 g) was mixed with diisopropyl ether (112 g), cooled to 288 K and seeded. After 2.5 h at 288 K the crystals were separated off using a filtering centrifuge. The crystals were dried *in vacuo* at room temperature. The yield was 177 g of dried solids (differential scanning calorimetry m.p. 318.7 K; heat of fusion 93 kJ kg⁻¹).

For the preparation of (*S,S,S*)-lactoyllactoyllactic acid, (II), (*S,S*)-lactide (637 g) was mixed with (*S*)-lactic acid (230 g). The mixture was heated to 423 K, allowed to react for 1 h and then cooled rapidly to 353 K. Further overnight cooling to room temperature resulted in crystallization of the excess lactide. The viscous suspension was separated by means of a filtering centrifuge, resulting in a viscous filtrate containing lactic acid and oligomers up to a degree of polymerization of about 12, and some lactide. The viscous liquid was separated by means of a short-path distillation at low pressure (1 mbar; 1 bar = 100 000 Pa) to remove lactic acid, lactide and some

of the lactoyllactic acid. After distillation, the residue, containing about 25% of trimer, was used for further processing by means of preparative chromatography (Sepacor, Buchi). Separation of the oligomer mixture was achieved with a solvent gradient from water-methanol 85:15 (v/v) to methanol-acetonitrile 40:60 (v/v). The fractions containing the (S)-lactic acid trimer were combined and evaporated to dryness at 303 K and 20 mbar. Each 10 g of crude oligomer mixture resulted in 2.2 g of pure (S)-lactic acid trimer after chromatography. The product crystallized slowly after concentration and had a purity of 95–97% [differential scanning calorimetry m.p. 346.2 K (onset); heat of fusion 83 kJ kg⁻¹].

Compound (I)

Crystal data

C ₆ H ₁₀ O ₅	V = 1565.70 (3) Å ³
M _r = 162.14	Z = 8
Orthorhombic, P2 ₁ 2 ₁ 2 ₁	Mo Kα radiation
a = 7.94437 (7) Å	μ = 0.12 mm ⁻¹
b = 11.71472 (17) Å	T = 150 K
c = 16.82348 (12) Å	0.38 × 0.36 × 0.24 mm

Data collection

Nonius KappaCCD area-detector diffractometer	69491 measured reflections
Absorption correction: multi-scan (SADABS; Sheldrick, 2008a)	3856 independent reflections
T _{min} = 0.703, T _{max} = 0.747	3674 reflections with I > 2σ(I)
	R _{int} = 0.026

Refinement

R[F ² > 2σ(F ²)] = 0.026	H atoms treated by a mixture of independent and constrained refinement
wR(F ²) = 0.076	Δρ _{max} = 0.31 e Å ⁻³
S = 1.07	Δρ _{min} = -0.20 e Å ⁻³
3856 reflections	
219 parameters	

Table 1

Selected geometric parameters (Å, °) for (I).

C41–C51	1.5231 (12)	C42–C52	1.5117 (11)
C41–O31–C21–C31	171.34 (7)	C42–O32–C22–C32	171.42 (7)
O11–C11–C21–O31	-41.75 (10)	O12–C12–C22–O32	-27.49 (10)
C21–O31–C41–C51	178.52 (7)	C22–O32–C42–C52	178.90 (6)
O31–C41–C51–O51	135.58 (8)	O32–C42–C52–O52	160.08 (7)

Table 2

Hydrogen-bond geometry (Å, °) for (I).

D–H...A	D–H	H...A	D...A	D–H...A
O21–H21O...O51 ⁱ	0.94 (2)	1.73 (2)	2.6617 (10)	169.4 (19)
O51–H51O...O12	0.869 (18)	1.902 (18)	2.7650 (9)	171.7 (17)
O22–H22O...O52 ⁱ	0.912 (19)	1.698 (19)	2.6006 (10)	169.6 (18)
O52–H52O...O42	0.857 (19)	2.168 (18)	2.6730 (9)	117.4 (15)
O52–H52O...O11 ⁱⁱ	0.857 (19)	2.090 (19)	2.7785 (11)	136.9 (16)

Symmetry codes: (i) x + 1, y, z; (ii) -x + ½, -y + 1, z + ½.

Table 3

Selected torsion angles (°) for (II).

C4–O3–C2–C3	173.83 (14)	O3–C4–C5–O5	169.56 (12)
C2–O3–C4–C5	170.40 (13)	C5–O5–C7–C8	175.50 (16)
C7–O5–C5–C4	-71.28 (18)		

Table 4

Hydrogen-bond geometry (Å, °) for (II).

D–H...A	D–H	H...A	D...A	D–H...A
O2–H2O...O6 ⁱ	0.89 (3)	2.00 (3)	2.7986 (19)	149 (3)
O2–H2O...O7 ⁱ	0.89 (3)	2.37 (3)	3.049 (2)	134 (3)
O7–H7O...O1 ⁱⁱ	0.83 (3)	2.03 (3)	2.843 (2)	166 (3)

Symmetry codes: (i) x - ½, y + ½, z; (ii) x + ½, y + ½, z.

Compound (II)

Crystal data

C ₉ H ₁₄ O ₇	V = 1134.71 (7) Å ³
M _r = 234.20	Z = 4
Monoclinic, C2	Mo Kα radiation
a = 17.3594 (5) Å	μ = 0.12 mm ⁻¹
b = 5.62712 (17) Å	T = 150 K
c = 13.9888 (6) Å	0.48 × 0.12 × 0.09 mm
β = 123.861 (1)°	

Data collection

Nonius KappaCCD area-detector diffractometer	19858 measured reflections
Absorption correction: multi-scan (SADABS; Sheldrick, 2008a)	1443 independent reflections
T _{min} = 0.707, T _{max} = 0.746	1358 reflections with I > 2σ(I)
	R _{int} = 0.028

Refinement

R[F ² > 2σ(F ²)] = 0.028	H atoms treated by a mixture of independent and constrained refinement
wR(F ²) = 0.069	Δρ _{max} = 0.17 e Å ⁻³
S = 1.07	Δρ _{min} = -0.15 e Å ⁻³
1443 reflections	
156 parameters	
1 restraint	

Friedel pairs were merged prior to refinement. H atoms were located in difference Fourier maps. Thereafter, hydroxy H atoms were refined freely with isotropic displacement parameters and all other H atoms were refined using a riding model, with C–H = 0.98 Å for methyl H atoms or 1.00 Å for the other H atoms, and with U_{iso}(H) = 1.5U_{eq}(C) for methyl H atoms or 1.2U_{eq}(C) for the other H atoms.

For both compounds, data collection: COLLECT (Nonius, 1999); cell refinement: PEAKREF (Schreurs, 2005); data reduction: EVAL15 (Schreurs et al., 2010) and SADABS (Sheldrick, 2008a); program(s) used to solve structure: SHELXS97 (Sheldrick, 2008b); program(s) used to refine structure: SHELXL97 (Sheldrick, 2008b); molecular graphics: PLATON (Spek, 2009); software used to prepare material for publication: manual editing of CIF from SHELXL97.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM3098). Services for accessing these data are described at the back of the journal.

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