Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

(6*S*)-6-Isobutylpiperidine-2,4-dione and (4*R*,6*S*)/(4*S*,6*S*)-4-hydroxy-6-isobutylpiperidin-2-one

Claude Didierjean,[a] Julien Marin,[b] Emmanuel Wenger,[a] Jean-Paul Briand,[b] André Aubry[a]* and Gilles Guichard[b]

[a]Laboratoire de Cristallographie et Modélisation des Matériaux Minéraux et Biologiques (LCM3B), UMR No. 7036, Groupe Biocristallographie, Université Henri Poincaré, Nancy I, Faculté des Sciences, BP 239, 54506 Vandoeuvre lès Nancy CEDEX, France, and [b]Immunologie et Chimie Thérapeutiques, UPR 9021 CNRS, Institut de Biologie Moléculaire et Cellulaire, 15 Rue Descartes, 67000 Strasbourg, France
Correspondence e-mail: aubry@lcm3b.uhp-nancy.fr

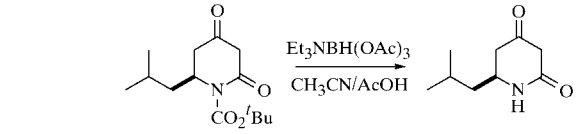
Received 16 July 2003
Accepted 8 January 2004
Online 10 February 2004

The crystal structure of (6*S*)-6-isobutylpiperidine-2,4-dione, $C_9H_{15}NO_2$, shows that the keto tautomer is favoured in the solid state. The reduction of the keto functionality leads to the corresponding 4-hydroxy-6-isobutylpiperidin-2-one, $C_9H_{17}NO_2$, with an 84:16 *cis*/*trans* ratio, containing the 4*R*,6*S* and 4*S*,6*S* isomers; the ratio of the two isomers was determined by NMR analysis of the reaction mixture. Crystals obtained from the mixture of both isomers have been studied and shown to contain the isomers in a 86:14 ratio. Hence, both X-ray and NMR analyses show that crystallization does not select the major diastereomer formed by the reduction. In both crystal structures, the two independent molecules dimerize through an $R_2^2(8)$ hydrogen-bond motif between adjacent amide groups.

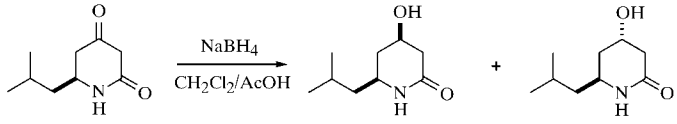
Comment

As part of a programme to synthesize enantiopure monohydroxylated δ-lactams, we recently introduced 6-substituted-2,4-dioxopiperidine-1-carboxylates as novel chiral adducts for the asymmetric synthesis of 4-hydroxy-6-substituted-2-oxopiperidine-1-carboxylate. In these series, the pseudo-axial orientation of the side chain at the 6-position [resulting from minimization of the allylic $A(1,3)$ strain] is believed to account for the high stereoselectivity observed in the reduction of the 4-oxo group. A variety of reductive agents and conditions have been explored. Treatment of lactam (I) (see scheme), bearing an isobutyl side chain at atom C6, with $NaBH_4$ in a mixture of CH_2Cl_2 and 10% acetic acid affords the desired 4-hydroxy derivative in 93% yield, with a 90:10 *cis*/*trans* ratio (Didierjean *et al.*, 2004).

Surprisingly, the attempt to reduce (I) with tetramethylammonium triacetoxyborohydride in a mixture of MeCN and 15% acetic acid resulted exclusively in removal of the Boc (butoxycarbonyl) protecting group and afforded (6*S*)-6-isobutyl-2,4-dioxopiperidine, (II), in 84% yield. Subsequent reduction of (II) with $NaBH_4$ in a mixture of CH_2Cl_2 and acetic acid (9:1) gave the corresponding 4-hydroxy-6-isobutyl-2-oxopiperidine, in an 84:16 *cis*/*trans* ratio; the 4*R*,6*S* and 4*S*,6*S* isomers are denoted (III) and (IV), respectively. The overall yield was 62% and the ratio of isomers was determined by NMR analysis of the reaction mixture. The reduction of (II) is driven by torsional effects that favour attack of the hydride reagent across the axial face of the C=O bond. A similar selectivity (85:15 *cis*/*trans*) was reported by Davis *et al.* (2000) in the reduction of the related enantiopure (*R*)-6-phenylpiperidine-2,4-dione. We present here the results of the X-ray crystallographic analyses of (II), (III) and (IV).



(I) (II)



(II) (III) (IV)

Compound (II) crystallizes with two independent molecules, (II*A*) and (II*B*), in the asymmetric unit, in a triclinic cell. A view of the independent molecules with the atom-numbering schemes is shown in Fig. 1. All bond distances and angles fall within normal limits (Allen *et al.*, 1987) and are in agreement with the geometry of similar piperidine rings (Bocelli & Grenier-Loustalot, 1981; Tomas *et al.*, 1996; Marin *et al.*, 2002; Didierjean *et al.*, 2004). The *S* configuration of the C atom at the 6-position of the piperidine ring was assumed from the precursor Boc-β-L-Leu-OH compound (Seebach *et al.*, 1996). Both independent molecules, (II*A*) and (II*B*), reveal that the keto tautomer is favoured over the enol tautomer in the solid state. This preference is evident from the observed C3—C4 and C4—O2 bond distances in (II*A*) [C13—C14 and C14—O12 in (II*B*)], which are consistent with single and double bonds, respectively (Table 1). Molecules (II*A*) and (II*B*) show a similar conformation (Table 1). Both independent piperidine rings adopt a twisted-boat conformation, with the isobutyl group in an equatorial orientation. The C3—C4—C5—C6 and C13—C14—C15—C16 torsion angles [−43.9 (4) and −21.6 (5)°, respectively] reveal that the conformation is more twisted in (II*A*) than in (II*B*).

X-ray analysis of crystals obtained from the mixture of (III) and (IV) reveals a monoclinic cell, with two independent molecules in the asymmetric unit. In one of the two independent molecules, the C atoms at the 4- and 5-positions and the hydroxy group of the piperidine ring are disordered, leading to a mixture of (III) and (IV) in a 0.712 (8):0.288 (8) ratio. No detectable disorder was observed in the other

  DOI: 10.1107/S0108270103024065

independent molecule, which is the major diastereomer formed by the reduction of (II), *i.e.* the 4*R*,6*S* diastereomer. Thus, the asymmetric unit of the crystal consists of a unit-occupancy and a 0.712 (8)-occupancy 4*R*,6*S* diastereomer (Figs. 2 and 3), and a 0.288 (8)-occupancy 4*S*,6*S* diastereomer (Fig. 4). The ratio of 4*R*,6*S* to 4*S*,6*S* isomers in the crystals, determined by crystallographic refinement, is thus 1.712:0.288 (or 86:14), in very good agreement with NMR analysis of the reaction mixture. NMR measurements for the dissolved crystals confirmed that a mixture of the 4*R*,6*S* and 4*S*,6*S* isomers was present in the solid state. In the three structures, the hydroxy group at the 4-position and the isobutyl side chain at the 6-position of the piperidine ring assume an equatorial orientation (Table 3). The two structures of (III) have similar piperidine ring conformations, close to a half-chair. The C atom at the 5-position is displaced by 0.693 (6) Å [0.610 (3) Å] from the mean plane defined by atoms N1, C2, C3, C4 and C6 (N11, C12, C13, C14 and C16). The six-membered ring of (IV) adopts a sofa conformation, with the C atom at the 4-position displaced by 0.70 (2) Å from the mean plane defined by the other five atoms of the ring. The positions of the hydroxy O atoms in the 0.712 (8)-occupancy molecule of (III) and the 0.288 (8)-occupancy molecule of (IV) are separated by 0.46 (1) Å. Both hydroxy groups are thus involved in the same intermolecular hydrogen bonds (Table 4).

In both structures, a typical amide–amide hydrogen-bond motif (Rychlewska & Warzajtis, 2000) is observed, joining the two independent molecules *via* two intermolecular N—H···O═C hydrogen bonds (Figs. 5 and 6, and Tables 2 and 4). The amide H atoms, which are obviously *cis* to the amide

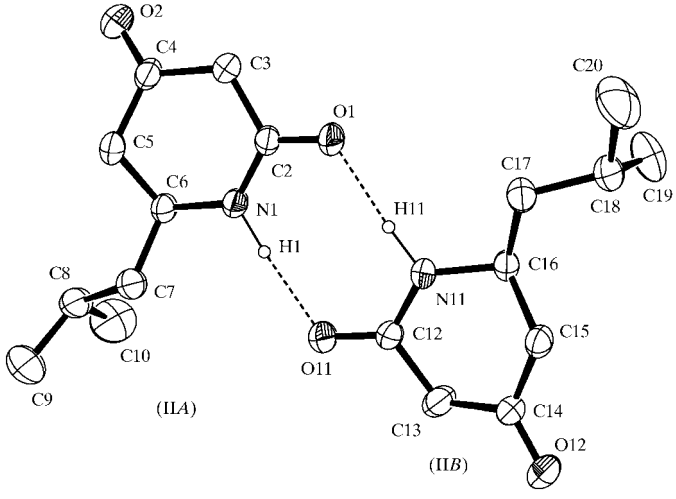


Figure 1
A view of the asymmetric unit of (II), with the atom-numbering scheme and 25% probability displacement ellipsoids. H atoms, except for those of the NH groups, have been omitted for clarity. The intermolecular hydrogen bonds are marked as dashed lines.

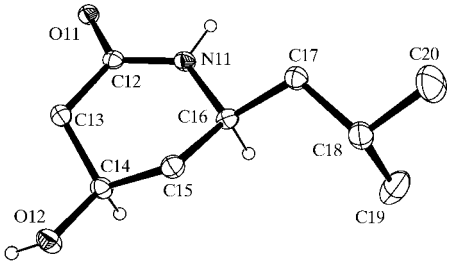


Figure 2
A view of the unit-occupancy molecule of (III), with the atom-numbering scheme and 25% probability displacement ellipsoids. H atoms, except for those of the hydroxy and NH groups and the asymmetric C atoms, have been omitted for clarity.

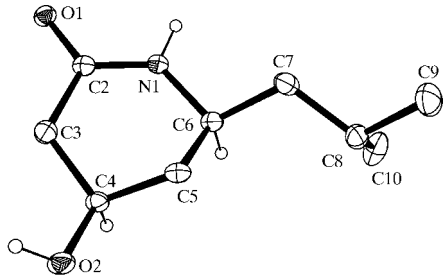


Figure 3
A view of the 0.712 (8)-occupancy molecule of (III), with the atom-numbering scheme and 25% probability displacement ellipsoids. H atoms, except for those of the hydroxy and NH groups and the asymmetric C atoms, have been omitted for clarity.

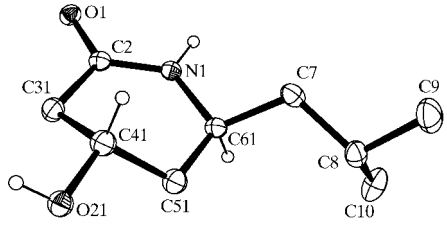


Figure 4
A view of the 0.288 (8)-occupancy molecule of (IV), with the atom-numbering scheme and 25% probability displacement ellipsoids. H atoms, except for those of the hydroxy and NH groups and the asymmetric C atoms, have been omitted for clarity.

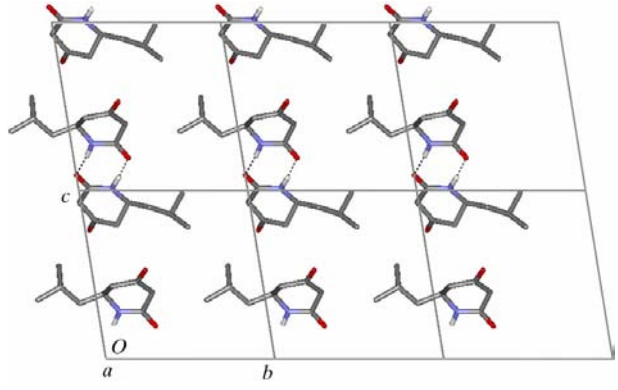


Figure 5
A packing diagram for (II), viewed along the *a* axis. The intermolecular hydrogen bonds are marked as dashed lines.

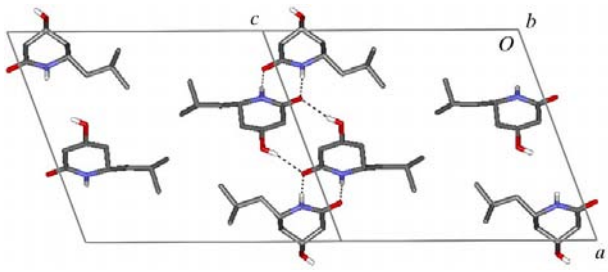


Figure 6
A packing diagram for (III/IV), viewed along the *b* axis. The intermolecular hydrogen bonds are marked as dashed lines. The 0.288 (8)-occupancy molecules of (IV) have been omitted for clarity.

carbonyl O atom, form an eight-membered ring, leading to the graph-set motif $R_2^2(8)$ (Bernstein *et al.*, 1995). Both crystals show a similar molecular packing, which can be described as a regular stacking of bilayers with the isopropyl groups on the surfaces (Figs. 5 and 6). In each bilayer, the hydrogen-bonded independent dimers (Tables 2 and 4) pack together, the packing involving mainly van der Waals interactions in the crystal of (II). In the crystal of (III/IV), a three-dimensional hydrogen-bond network between the dimers is observed, involving the hydroxy and carbonyl groups of the piperidine rings (Table 4 and Fig. 6). It is interesting to note that the crystals of the *N*-Boc-protected molecules of (II) and (III) show similar stacking of bilayers, with hydrophobic heads on the surface (Didierjean *et al.*, 2004). Nevertheless, the molecular packing mode inside a bilayer is different. Indeed, strong OH···O=C hydrogen bonds lead to infinite chains packed in a parallel fashion, *via* van der Waals interactions, to form a bilayer.

Experimental

For the preparation of (6*S*)-6-isobutylpiperidine-2,4-dione, (II), tetramethylammonium triacetoxyborohydride (293 mg, 1.11 mmol) was added to a stirred solution of (I) (100 mg, 0.37 mmol) in a mixture of acetonitrile and 15% *v*/*v* acetic acid at room temperature. After 48 h, the mixture was quenched with water. Acetonitrile was evaporated under reduced pressure and replaced with ethyl acetate, which was extracted using water and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated to afford a residue that was purified by flash chromatography (ethyl acetate) to give pure (II) (53 mg, 84%). Colourless single crystals of (II), suitable for X-ray analysis, were grown from a mixture of dichloromethane and diisopropyl ether (1:3) (m.p. 395–397 K). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (*bs*, 1H), 3.80–3.65 (*m*, 1H), 3.32 (*d*, J = 19.8 Hz, 1H), 3.20 (*d*, J = 19.8 Hz), 2.68 (*dd*, J = 16.3 and 4.2 Hz, 1H), 2.31 (*dd*, J = 16.3 and 8.8 Hz, 1H), 1.82–1.62 (*m*, 1H), 1.57–1.27 (*m*, 2H), 0.90 (*d*, J = 2.1 Hz, 3H), 0.87 (*d*, J = 2.1 Hz, 3H). For the preparation of 4-hydroxy-6-isobutylpiperidin-2-one, (III/IV), sodium borohydride (67 mg, 1.77 mmol) was added to a stirred solution of (II) (100 mg, 0.59 mmol) in a mixture of dichloromethane and 10% *v*/*v* acetic acid at room temperature. After 72 h, the mixture was quenched with water. Dichloromethane was evaporated under reduced pressure and replaced with ethyl acetate, which was extracted using water and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated to afford a residue that was purified by flash chromatography (ethyl acetate–acetic acid, 95:5), giving a 84:16 mixture (63 mg, 62%) of (III) and the corresponding 4*S*,6*S* diastereomer, (IV). Colourless single crystals of (III/IV) suitable for X-ray analysis were grown from a mixture of dichloromethane and diisopropyl ether (1:3); the ratio between (III) and (IV) changed to 75:25 (determined by NMR) (m.p. 418–420 K). Spectroscopic analysis of the major diastereomer, (III), ^{1}H NMR (300 MHz, CD_3OD): δ 4.03–3.93 (*m*, 1H), 3.49–3.40 (*m*, 1H), 2.61 (*ddd*, J = 17.2, 5.6 and 2.2 Hz, 1H), 2.20–2.11 (*m*, 2H), 1.79–1.68 (*m*, 1H), 1.50–1.41 (*m*, 1H), 1.39–1.22 (*m*, 2H), 0.94 (*d*, J = 3.8 Hz, 3H), 0.92 (*d*, J = 3.8 Hz, 3H).

Compound (II)

Crystal data

$C_9H_{15}NO_2$
M_r = 169.22
Triclinic, *P*1
a = 5.0760 (2) Å
b = 10.0760 (4) Å
c = 10.1210 (5) Å
α = 95.691 (1)°
β = 102.529 (1)°
γ = 103.730 (2)°
V = 484.65 (4) Å^3
Z = 2
D_x = 1.16 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 7698 reflections
θ = 2.1–26.3°
μ = 0.08 mm^{-1}
T = 293 (2) K
Prism, colourless
0.2 × 0.1 × 0.1 mm

Data collection

Nonius KappaCCD diffractometer
ω scans
7698 measured reflections
1959 independent reflections
1334 reflections with $I > 2\sigma(I)$
R_{int} = 0.040
θ_{max} = 26.3°
$h = -5 \rightarrow 6$
$k = -12 \rightarrow 12$
$l = -12 \rightarrow 12$

Refinement

Refinement on F^2
$R(F)$ = 0.043
$wR(F^2)$ = 0.118
S = 0.94
1959 reflections
217 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0747P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.14 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}

Table 1
Selected geometric parameters (Å, °) for (II).

C3—C4	1.489 (5)	C13—C14	1.494 (5)
C4—O2	1.210 (4)	C14—O12	1.204 (4)
N1—C2—C3—C4	12.6 (5)	N11—C12—C13—C14	27.0 (6)
C2—C3—C4—C5	11.0 (5)	C15—C14—C13—C12	−16.2 (6)
C3—C4—C5—C6	−43.9 (5)	C16—C15—C14—C13	−21.6 (5)
C4—C5—C6—N1	52.7 (4)	N11—C16—C15—C14	47.2 (4)
C2—N1—C6—C5	−32.1 (5)	C12—N11—C16—C15	−40.1 (4)
C6—N1—C2—C3	−1.1 (5)	C16—N11—C12—C13	3.0 (5)
C4—C5—C6—C7	174.8 (3)	C17—C16—C15—C14	167.2 (3)

Table 2
Hydrogen-bonding geometry (Å, °) for (II).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O11	0.86	2.04	2.899 (3)	176
N11—H11···O1	0.86	2.05	2.878 (3)	161

Compound (III/IV)

Crystal data

$C_9H_{17}NO_2$	Mo $K\alpha$ radiation
M_r = 171.24	Cell parameters from 2173 reflections
Monoclinic, $P2_1$	θ = 1.0–26.4°
a = 12.9121 (6) Å	μ = 0.08 mm^{-1}
b = 5.3871 (3) Å	T = 100 (2) K
c = 14.8945 (7) Å	Prism, colourless
β = 109.692 (2)°	0.2 × 0.1 × 0.1 mm
V = 975.45 (8) Å^3	
Z = 4	
D_x = 1.166 Mg m^{-3}	

Data collection

Nonius KappaCCD diffractometer	R_{int} = 0.079
ω scans	θ_{max} = 26.3°
18 084 measured reflections	$h = -16 \rightarrow 16$
2196 independent reflections	$k = -6 \rightarrow 6$
1760 reflections with $I > 2\sigma(I)$	$l = -18 \rightarrow 17$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0769P)^2 + 0.0386P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R(F)$ = 0.043	$(\Delta/\sigma)_{max}$ = 0.002
$wR(F^2)$ = 0.114	$\Delta\rho_{max}$ = 0.16 e Å^{-3}
S = 1.01	$\Delta\rho_{min}$ = −0.19 e Å^{-3}
2196 reflections	
236 parameters	
H-atom parametes constrained	

Table 3
Selected torsion angles (°) for (III/IV).

N11—C12—C13—C14	−22.1 (3)	C5—C6—N1—C2	−25.1 (4)
C12—C13—C14—C15	49.3 (3)	C2—C3—C4—O2	165.2 (4)
C13—C14—C15—C16	−62.7 (3)	C4—C5—C6—C7	172.2 (3)
C14—C15—C16—N11	46.8 (2)	N1—C2—C31—C41	23.3 (6)
C15—C16—N11—C12	−19.8 (3)	C2—C31—C41—C51	−55 (1)
C16—N11—C12—C13	7.5 (3)	C31—C41—C51—C61	63 (1)
C12—C13—C14—O12	169.41 (19)	C41—C51—C61—N1	−35 (1)
C14—C15—C16—C17	167.86 (18)	C51—C61—N1—C2	2.7 (7)
N1—C2—C3—C4	−10.8 (4)	C61—N1—C2—C3	3.6 (4)
C2—C3—C4—C5	40.1 (4)	C2—C31—C41—O21	−175.2 (8)
C3—C4—C5—C6	−61.8 (4)	C2—N1—C61—C7	−142.6 (2)
C4—C5—C6—N1	53.9 (4)		

Table 4
Hydrogen-bonding geometry (Å, °) for (III/IV).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O11	0.88	2.05	2.925 (3)	172
N11—H11···O1	0.88	2.01	2.888 (3)	172
O12—H12···O11^{i}	0.84	1.95	2.769 (2)	164
O2—H2···O1^{ii}	0.84	1.98	2.821 (5)	177
O21—H21···O1^{ii}	0.84	1.98	2.797 (14)	163

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

Because of the lack of any significant anomalous dispersion effects, the absolute configuration could not be determined from the diffraction experiment, so Friedel pairs were merged prior to refinement. All H atoms were placed at calculated positions and treated using a riding model, with C—H distances of 0.93–0.97 Å, an N—H distance of 0.88 Å and an O—H distance of 0.82 Å. The U_{iso}(H) parameters were fixed at $1.2U_{eq}$(C,N) for methyl, methylene and NH groups, and at $1.5U_{eq}$(C,O) for methyl and OH groups. In the (III/IV) crystal structure, the distances between Csp^3 atoms in the disordered piperidine rings were restrained to 1.50 (2) Å. The parameters for atoms C41, O21 and C51 of the 0.288 (8)-occupancy molecule of (IV) were refined isotropically.

For both compounds, data collection: *COLLECT* (Nonius, 1998); cell refinement: *COLLECT*; data reduction: *HKL* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 *for Windows* (Farrugia, 1997) and *WebLab ViewerPro* (MSI, 1999); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

We thank the Service Commun de Diffraction X sur Monocristaux (Université Henri Poincaré, Nancy I) for providing access to crystallographic experimental facilities.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1125). Services for accessing these data are described at the back of the journal.

References

Allen, F. H., Kennard, O., Watson, D. G., Brammer, L., Orpen, A. G. & Taylor, R. (1987). *J. Chem. Soc. Perkin Trans.* 2, pp. S1–19.

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.

Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.

Bocelli, G. & Grenier-Loustalot, M. F. (1981). *Acta Cryst.* B**37**, 1302–1304.

Davis, F. A., Fang, T., Chao, B. & Burns, D. M. (2000). *Synthesis*, pp. 2106–2112.

Didierjean, C., Marin, J., Wenger, E., Briand, J.-P., Aubry, A. & Guichard, G. (2004). *Acta Cryst.* C**60**, o200–o203.

Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.

Farrugia, L. J. (1999). *J. Appl. Cryst.* **32**, 837–838.

Marin, J., Didierjean, C., Aubry, A., Briand, J.-P. & Guichard, G. (2002). *J. Org. Chem.* **67**, 8440–8449.

MSI (1999). *WebLab ViewerPro*. Version 3.5. Molecular Simulation Inc., 9685 Scranton Road, San Diego, CA 92121, USA.

Nonius (1998). *COLLECT*. Nonius BV, Delft, The Netherlands.

Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.

Rychlewska, U. & Warzajtis, B. (2000). *Acta Cryst.* B**56**, 833–848.

Seebach, D., Ciceri, P. E., Overhand, M., Jaun, B., Rigo, D., Oberer, L., Hommel, U., Amstutz, R. & Widner, H. (1996). *Helv. Chim. Acta*, **79**, 2043-2066.

Sheldrick, G. M. (1997). *SHELXL*97. University of Göttingen, Germany.

Tomas, A., Lemoine, P., Viossat, B., Robin, S., Zhu, J. & Galons, H. (1996). *Acta Cryst.* C**52**, 199–201.