Structures of the racemate and (*S*)-enantiomer of 7,8-difluoro-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine

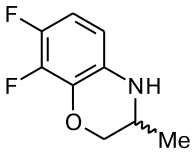
P. A. Slepukhin, D. A. Gruzdev, E. N. Chulakov, G. L. Levit, V. P. Krasnov, and V. N. Charushin*

I. Ya. Postovsky Institute of Organic Synthesis, Russian Academy of Sciences, 22/20 ul. S. Kovalevskoi, 620990 Ekaterinburg, Russian Federation. Fax: +7 (343) 374 1189. E-mail: slepukhin@ios.uran.ru

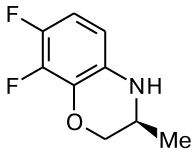
The comparative X-ray diffraction study of racemic and (*S*)-enantiomer of 7,8-difluoro-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine was carried out. The both forms of benzoxazine are crystallized in the orthorhombic crystal system, the (*S*)-enantiomer is crystallized in the chiral space group $P2_12_12_1$, while the racemate is crystallized in the centrosymmetric *Pbca* space group. The bond lengths and bond and torsional angles in the both molecules are almost equal. The packing of the racemate is characterized by a closer interaction of polar NH...O groups.

Key words: X-ray diffraction analysis, enantiomers, racemates, 2,3-dihydro-4*H*-[1,4]benzoxazines, organofluorine compounds.

Racemic (*RS*)-7,8-difluoro-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine (*rac*-**1**) and its (*S*)-enantiomer ((*S*)-**1**) are key intermediates in the synthesis of antibacterial drugs ofloxacin and levofloxacin, respectively.[1—3]



rac-**1**



(*S*)-**1**

Racemic benzoxazine *rac*-**1** is usually synthesized by the reductive ring closure of 5,6-difluoro-2-nitrophenol derivatives.[1,4—6]

The known methods for the synthesis of enantiomer (*S*)-**1** can be divided into two main groups. The first group includes the methods for asymmetric synthesis: (a) asymmetric reduction of imines by the action of chiral reducing agents[7] and chiral catalysts based on the Ir^I complexes and (b) asymmetric synthesis using chiral synthones, *viz.*, diols[9] and alaninol derivatives.[10,11]

The second group of the methods for synthesis of enantiomer (*S*)-**1** is based on the resolution of racemic benzoxazine *rac*-**1** and its derivatives. There are described methods for microbiological and enzymatic hydrolytic resolution of *N*-acyl derivatives of racemic benzoxazine[12,13] and optical resolution *via* diastereomeric salts and amides of chiral acids, including the developed by us method for kinetic resolution *via* acylation with the chiral resolving agent.[14]

The crystal structure of hydrochloride (*S*)-**1** has been studied earlier,[2] and no structures of the free forms of benzoxazine **1** (both the racemic and enantiomerically pure forms) were described.[15] It has previously been reported[7—14] that the (*S*)-enantiomer is a yellow oil. We succeeded to obtain for the first time compound (*S*)-**1** in the crystalline form and to perform the comparative crystallographic study of racemic and enantiomerically pure 7,8-difluoro-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine.

Results and Discussion

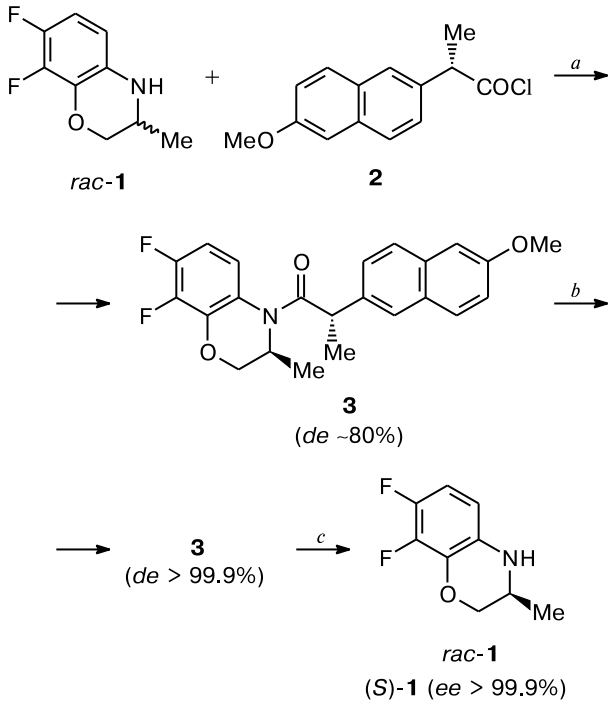
We synthesized racemic 7,8-difluoro-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine (*rac*-**1**) using the known procedure of reductive intramolecular ring closure of 2-acetonyloxy-3,4-difluoronitrobenzene on the Raney Ni catalyst.[1] Subsequent recrystallization from hexane gave chemically pure racemate *rac*-**1** as colorless crystals. The structure of compound **1** was confirmed by ^1H and ^{19}F NMR spectroscopy and elemental analysis, and the enantiomeric composition was determined by HPLC on the chiral stationary phase (Chiralcel OD-H).

To obtain enantiomerically pure benzoxazine (*S*)-**1** (*ee* >99.9%), we used the earlier developed method based on the kinetic resolution of racemate *rac*-**1** (2 equiv.) by acylation with (*S*)-naproxen chloride (**2**) (1 equiv.) followed by the recrystallization of the obtained diastereomerically enriched (*S*,*S*)-amide **3** and its subsequent acidic hydrolysis (Scheme 1).[14] The enantiomeric purity of benzoxazine (*S*)-**1** was determined by HPLC on Chiralcel OD-H. Although it was reported that benzoxazine (*S*)-**1** is a yellow oil, we succeeded to obtain this compound in the crystalline form (colorless prisms, m.p. 29—30 °C) by spontaneous crystallization from the melt. This is likely

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 5, pp. 932—936, May, 2011.

due to the fact that the method developed by us allows one to obtain the target compound of high enantiomeric purity (*ee* >99.9%).

Scheme 1



Reagents and conditions: *a*. CH_2Cl_2, –20 °C; *b*. Recrystallization; *c*. HCl, AcOH, Δ.

We carried out the comparative X-ray diffraction study of the racemic and enantiomerically pure forms of compound **1**. As follows from the X-ray diffraction data (Table 1), the both forms of benzoxazine **1** are crystallized in the orthorhombic crystal system ($\alpha = \beta = \gamma = 90°$), (*S*)-**1** is crystallized in the chiral crystal system, and *rac*-**1** is crystallized in the centrosymmetric space group of symmetry. The empirical formulas are the same for the both structures: $C_9H_9F_2NO$ (M = 185.17 g mol^{-1}), *F*(000) = 768, *Z* = 8. In the both experiments, the obtained values of bond lengths and bond and torsional angles are almost the same (Figs 1 and 2). The molecules exist in the conformation "pseudo-twist" and are characterized, in the both cases, by the pseudo-equatorial arrangement of the methyl groups.

The molecular packing of compound *rac*-**1** is formed by oppositely directed chains of molecules extended along the axis 0*a*. The orientation of the molecules in the chains is achieved due to shortened polar contacts NH...O, which can also be considered as weak intermolecular hydrogen bonds (Table 2). Other intermolecular contacts with the distance shorter than the sum of van der Waals radii are absent in the packing. The planes of benzene rings of the

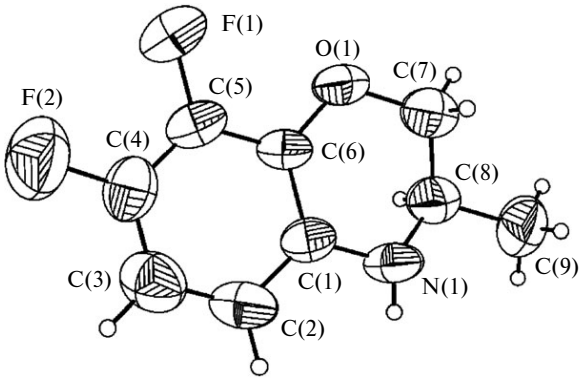


Fig. 1. General view and the numbering scheme of atoms in compound *rac*-**1** accepted in structural experiment (thermal ellipsoids of 50% probability are shown).

molecules in the chain form the dihedral angle $L_2 = 78.9°$, which makes it possible to avoid steric hindrances and approach the polar atoms N and O by approximately 0.4 Å compared to the structure of enantiomer (*S*)-**1**. This presumably allows one to stabilize the packing and increase the melting point of the racemate over that of the studied (*S*)-enantiomer. The fragment of the molecular packing of compound *rac*-**1** is shown in Fig. 3.

The crystalline molecular packing of enantiomer (*S*)-**1** is formed by two crystallographically independent molecules of similar configurations (additional index A was ascribed to the atoms of the second crystallographically independent molecule).

A molecule of (*S*)-**1** contains no atoms heavier than atoms of the 2nd period, which does not allow one to determine the absolute configuration by the anomalous scattering effect; the configuration was specified from the value of the rotation angle of the polarization plane and from the HPLC data. The molecular packing is formed by oppositely directed chains of molecules extended along

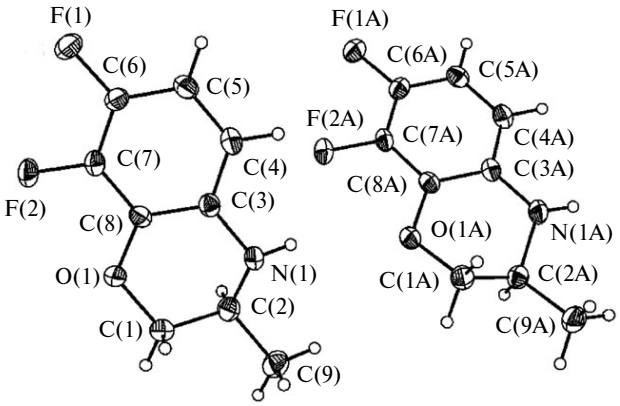


Fig. 2. General view and the numbering scheme of atoms in enantiomer (*S*)-**1** (thermal ellipsoids of 50% probability are shown).

Table 1. Crystallographic characteristics and experimental and refinement data for the crystal structures of (*S*)-**1** and *rac*-**1**

Parameter	(*S*)-**1**	*rac*-**1**
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	*Pbca*
a/Å	7.9259(5)	11.687(5)
b/Å	12.4943(8)	10.175(5)
c/Å	16.7049(13)	15.387(3)
V/Å^3	1654.3(2)	1829.8(12)
Z	8	8
d_{calc}/g cm^{-3}	1.487	1.344
μ/mm^{-1}	0.128	0.116
Sample size/mm	0.25×0.15×0.10	0.35×0.27×0.15
$\theta_{min}/\theta_{max}$/deg	2.84/30.51	2.97/26.04
Number of collected reflections	10341	4448
Number of independent reflections	2858 (R_{int} = 0.0276)	1752 (R_{int} = 0.0374)
Number of reflections with $I > 2\sigma(I)$	1976	633
Completeness (for θ/deg)	99.8% (30.51)	96.8% (26.04)
Weighing scheme	$w = 1/[s^2(F_o^2) + (0.0155P)^2]$, $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[s^2(F_o^2) + (0.04P)^2]$, $P = (F_o^2 + 2F_c^2)/3$
S on F^2	1.008	1.003
R_1 ($I > 2\sigma(I)$)	0.0332	0.0361
wR_2 ($I > 2\sigma(I)$)	0.0733	0.0614
R_1 (all reflections)	0.0527	0.1069
wR_2 (all reflections)	0.0762	0.0650
$(\Delta\rho_{max}/\Delta\rho_{min})$/e·Å^{-3}	0.239/−0.186	0.135/−0.122

the axis 0*b*, whose formation involves the both independent molecules. The planes of benzene rings of the crystallographically independent molecules in the chain form the dihedral angle $L_1 = 42.5°$. The orientation of molecules in the chains is achieved due to the shortened polar contacts (weak intermolecular hydrogen bonds) NH...O (see Table 2). The interatomic distances N...O are 0.4—0.5 Å longer than those in molecules *rac*-**1** and the angle N—H—O is considerably more strongly deviated from 180°. It is most likely that the formation of full intermolecular hydrogen

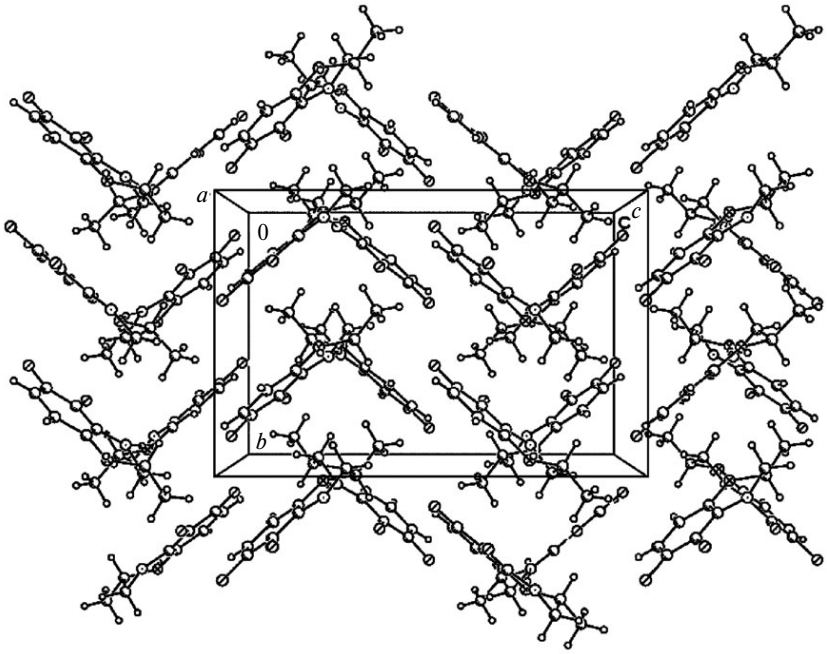


Fig. 3. Fragment of the molecular packing of compound *rac*-**1**.

Table 2. Contacts N—H...O in the packing of compounds (*S*)-**1** and *rac*-**1**

Compound	Bond N—H	*d*(N—H)/Å	*d*(H...O)/Å	Angle N—H...O/deg	*d*(N...O)/Å	Atom O
(*S*)-**1**	N(1)—H(1)	0.82(2)	2.65(2)	163(1)	3.448(2)	O(1A)
	N(1A)—H(1A)	0.86(2)	2.83(2)	146(1)	3.582	O(1) [x, $1+y$, z]
rac-**1**	N(1)—H(1)	0.82(2)	2.28(2)	170(1)	3.090(2)	O(1) [$x-1/2$, y, $-z+1/2$]

bonds is impossible because of steric hindrances. In particular, the structure is characterized by a series of shortened contacts C...F and H...F. The contacts C..F can be considered as contacts of the π—π type between the aromatic system and p-electrons of the F atom. The deviation from the sum of van der Waals radii for these contacts does not exceed 0.05 Å: minimum distance *d*(C(7)...F(1A) [$1-x, -1/2+y, 1/2-z$]) — 3.126(2) Å, *d*(F(1)...C(8A) [$2-x, -1/2+y, 1/2-z$]) — 3.121(2) Å. The length of the shortest contacts C—F...H *d*(F(1)...H(4A) [$2-x, -1/2+y, 1/2-z$]) (2.545 Å) and *d*(F(1A)...H(4AA) [$1-x, -1/2+y, 1/2-z$]) (2.463 Å) agrees well with the value $d = 2.54$ Å obtained earlier.[16] Significance of these contacts is indicated, in particular, by the observed decrease in the C—F bond lengths by 0.015—0.020 Å compared to that in a molecule of *rac*-**1** (Table 3), whereas the discrepancy is substantially smaller for the bond lengths found for the benzoxazine cycle. In addition, the calculated density of crystalline (*S*)-**1** (1.487 g cm^{-3}) significantly exceeds the density of *rac*-**1** (1.344 g cm^{-3}), which is probably explained by the thermal compression of the structure and also by the greater role of shortened contacts that affect the molecular packing geometry. However, taking into account that the value of van der Waals radii and inaccuracies of determination of atomic coordinates are conventional, we may hardly unambiguously conclude about the role of these or other contacts in the accomplishment of this molecular packing. The fragment of the molecular packing of enantiomer (*S*)-**1** is shown in Fig. 4.

Thus, we obtained the unit cell parameters and studies specific features of the molecular packings of the racemic and enantiomerically pure forms of 7,8-difluoro-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine. It was shown that the packing of the racemate is characterized by the closer interaction of the polar groups NH...O of the molecules, whereas the packing of the (*S*)-form is characterized by shortened intermolecular contacts.

Experimental

The melting point was determined on an SMP3 instrument (Barloworld Scientific, UK). The enantiomeric purity was analyzed by HPLC on a Knauer Smartline-1100 chromatograph: column Chiralcel OD-H (250×4.6 mm), detection at 230 nm, eluent flow rate 1 mL min^{-1}, and hexane—Pr^{i}OH (40 : 1) as a mobile phase. Optical rotations were determined on a Perkin Elmer M-341 instrument. Elemental analyses of the compounds were carried out on an Euro EA 3000 analyzer (Eurovector, Italy). ^{1}H and ^{19}F NMR spectra were recorded on a Bruker DRX-400 spectrometer (400.13 and 376.43 MHz, respectively using $SiMe_4$ and hexafluorobenzene, respectively, as internal standards.

The X-ray diffraction studies of the compounds were carried out according to a standard procedure on an Xcalibur 3 diffractometer equipped with a CCD detector (λ(Mo-Kα) = 0.71073 Å, graphite monochromator, ω/2θ scan mode, scanning increment

Table 3. Measured bond lengths in molecules of compounds (*S*)-**1** and *rac*-**1**

Bond	*d*/Å	Bond	*d*/Å	Bond	*d*/Å	Bond	*d*/Å
rac-**1**		*rac*-**1**		(*S*)-**1**		(*S*)-**1**	
F(1)—C(5)	1.3697(18)	C(2)—C(3)	1.383(2)	C(1)—C(2)	1.514(2)	N(1A)—C(3A)	1.392(2)
F(2)—C(4)	1.378(2)	C(4)—C(3)	1.374(3)	C(3)—C(4)	1.394(2)	C(2A)—C(9A)	1.518(2)
O(1)—C(7)	1.461(2)	(*S*)-**1**		C(3)—C(8)	1.403(2)	C(1A)—C(2A)	1.510(2)
O(1)—C(6)	1.3797(19)			C(7)—C(8)	1.381(2)	C(3A)—C(4A)	1.389(2)
N(1)—C(8)	1.464(2)	F(2)—C(7)	1.3537(18)	C(6)—C(7)	1.374(2)	C(3A)—C(8A)	1.405(2)
N(1)—C(1)	1.409(2)	F(1)—C(6)	1.3633(18)	C(4)—C(5)	1.384(2)	C(7A)—C(8A)	1.382(2)
C(8)—C(9)	1.527(2)	O(1)—C(1)	1.444(2)	C(5)—C(6)	1.377(2)	C(6A)—C(7A)	1.373(2)
C(8)—C(7)	1.478(2)	O(1)—C(8)	1.3739(19)	F(2A)—C(7A)	1.3532(19)	C(4A)—C(5A)	1.382(2)
C(1)—C(2)	1.404(2)	N(1)—C(2)	1.455(2)	F(1A)—C(6A)	1.3579(19)	C(5A)—C(6A)	1.375(2)
C(1)—C(6)	1.400(2)	N(1)—C(3)	1.404(2)	O(1A)—C(1A)	1.445(2)		
C(6)—C(5)	1.395(2)	C(2)—C(9)	1.510(2)	O(1A)—C(8A)	1.3737(19)		
C(5)—C(4)	1.381(2)	C(2)—C(9)	1.510(2)	N(1A)—C(2A)	1.453(2)		

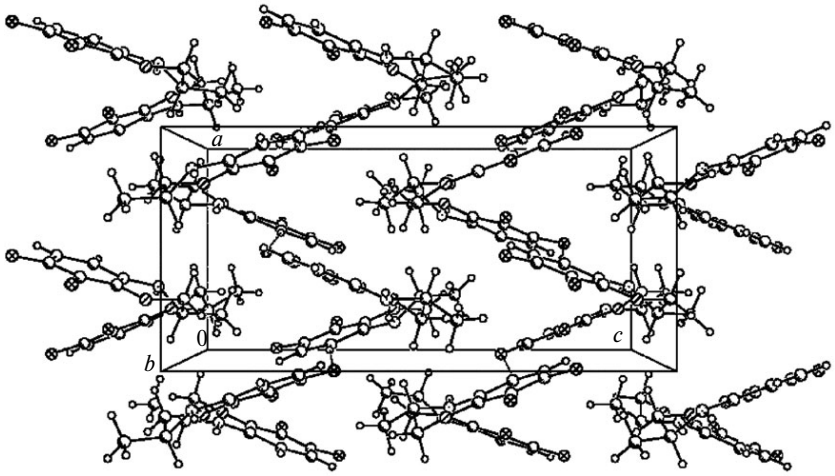


Fig. 4. Fragment of the molecular packing of enantiomer (*S*)-**1**.

size 1°, and time of frame measuring 20 s). Colorless irregular pieces were used for the analysis of the compounds. Since enantiomer (*S*)-**1** is easily melted, it was studied at reduced temperatures (125(2) K), while for compound *rac*-**1** the experiment was carried out at 295(2) K. No absorption correction was applied because of its negligibility. The structure was solved by a direct method using the SHELXS97 program and refined using the SHELXL97 program[17] by least squares on F^2 in the anisotropic full-matrix approximation for non-hydrogen atoms. The hydrogen atoms of the CH bonds were added to the geometrically calculated positions and included into refinement in the isotropic approximation with dependent thermal parameters in the riding model, and the hydrogen atoms of the NH groups were independently refined in the isotropic approximation. Selected parameters of X-ray diffraction experiments are listed in Table 1, and hydrogen bonding parameters are given in Table 2.

(*RS*)-7,8-Difluoro-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine (*rac*-1) was synthesized according to the known procedure.[1] The recrystallization of 150 g of *rac*-**1** was performed from 600 mL of hexane. Compound *rac*-**1** was obtained as colorless prisms in a yield of 120 g (80%), m.p. 53 °C. Found (%): C, 58.34; H, 4.91; N, 7.48. $C_9H_9F_2NO$. Calculated (%): C, 58.38; H, 4.90; N, 7.56. ^{1}H NMR (400 NHz, $CDCl_3$), δ: 1.20 (d, 3 H, Me, J = 6.5 Hz); 3.51 (dqd, 1 H, C(3)H, J = 8.1 Hz, J = 6.5 Hz, J = 2.7 Hz); 3.79 (dd, 1 H, $C(2)H_B$, J = 10.5 Hz, J = 8.1 Hz); 4.28 (dd, 1 H, $C(2)H_A$, J = 10.5 Hz, J = 2.7 Hz); 6.27 (ddd, 1 H, C(5)H, J = 9.0 Hz, J = 4.6 Hz, J = 2.3 Hz); 6.55 (ddd, 1 H, C(6)H, J = 10.0 Hz, J = 9.0 Hz, J = 8.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$), δ: 0.92 (ddd, F(7), J = 21.0 Hz, J = 8.1 Hz, J = 2.3 Hz); 11.9 (ddd, F(7), J = 21.0 Hz, J = 10.0 Hz, J = 4.6 Hz).

(*S*)-7,8-Difluoro-3-methyl-2,3-dihydro-4*H*-[1,4]benzoxazine (*S*)-1 was synthesied from the racemate as described earlier.[14] The crystalline sample as colorless prisms was obtained by the spontaneous crystallization of the melt, m.p. 29—30 °C, *ee* >99.95% (HPLC: the main enantiomer, τ_R 14.80 min; the minor enantiomer, τ_R 11.98 min), $[\alpha]_D$ −7.7 (*c* 2, $CHCl_3$). Found (%): C, 58.29, H, 4.84, N, 7.71. $C_9H_9F_2NO$. Calculated (%): C, 58.38; H, 4.90; N, 7.56.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 10-03-00084), the Council on Grants at the President of the Russian Federation (Program for State Support of Leading Scientific Schools, Grant NSh-65261.2010.3), the Ministry of Education and Science of the Russian Federation (State Contract No. 02.522.12.2011), and the Ural Branch of the Russian Academy of Sciences (Project Nos 09-P-3-2001 and 09-I-3-2004).

* The full set of crystallographic data of the compounds was deposited with the Cambridge Crystallographic Data Centre (CCDC Nos 821 014 and 821 015) and is available at www.ccdc.cam.ac.uk/conts/retrieving.html (or CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

References

1. I. Hayakawa, S. Atarashi, S. Yokohama, M. Imamura, K.-I. Sakano, M. Furukawa, *Antimicrob. Agents Chemother.*, 1986, **29**, 163.
2. S. Atarashi, S. Yokohama, K. Yamazaki, K. Sakano, M. Imamura, I. Hayakawa, *Chem. Pharm. Bull.*, 1987, **35**, 1896.
3. L. A. Mitsher, P. N. Sharma, D. T. W. Chu, L. L. Shen, A. G. Pernet, *J. Med. Chem.*, 1987, **30**, 2283.
4. I. Hayakawa, T. Hiramitsu, Y. Tanaka, *Chem. Pharm. Bull.*, 1984, **32**, 4907.
5. M. J. Joung, J. H. Ahn, H. M. Kim, J. H. Kang, S. J. Lee, N. M. Yoon, *J. Heterocycl. Chem.*, 2002, **39**, 1065.
6. R. A. Bunce, D. M. Herron, L. Y. Hale, *J. Heterocycl. Chem.*, 2003, **40**, 1031.
7. S. Atarashi, H. Tsurumi, T. Fujiwara, J. Hayakawa, *J. Heterocycl. Chem.*, 1991, **28**, 329.
8. K. Satoh, M. Inenaga, K. Kanai, *Tetrahedron: Asymmetry*, 1998, **9**, 2657.

9. S. B. Kang, E. J. Ahn, Y. Kim, Y. H. Kim, *Tetrahedron Lett.*, 1996, **37**, 9317.
10. J. F. Bower, P. Szeto, T. Gallagher, *Org. Lett.*, 2007, **9**, 3283.
11. M. K. Parai, G. Panda, *Tetrahedron Lett.*, 2009, **50**, 4703.
12. K. Sakano, S. Yokohama, I. Hayakawa, S. Atarashi, S. Kadoya, *Agricult. Biol. Chem.*, 1987, **51**, 1265.
13. A. Miyadera, A. Imura, *Tetrahedron: Asymmetry*, 1999, **10**, 119.
14. V. N. Charushin, V. P. Krasnov, G. L. Levit, M. A. Korolyova, M. I. Kodess, O. N. Chupakhin, M. H. Kim, H. S. Lee, Y. J. Park, K.-Ch. Kim, *Tetrahedron: Asymmetry*, 1999, **10**, 2691.
15. *Cambridge Structural Database. Version 5.31, 2010 release.* Cambridge Crystallographic Data Centre (CCDC), UK.
16. R. S. Rowland, R. Taylor, *J. Phys. Chem.*, 1996, **100**, 7384.
17. G. M. Sheldrick, *Acta Crystallogr.*, *Sect. A*, 2008, **64**, 112.

Received November 10, 2010;
in revised form January 18, 2011