

Huub Kooijman,^{a*} Anthony L. Spek,^a Arkadij Sobolev,^{b†} Hugo Jongejan^c and Maurice C. R. Fransen^c^aBijvoet Center for Biomolecular Research, Department of Crystal and Structural Chemistry, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands, ^bLatvian Institute of Organic Synthesis, Aizkraukles 21, Riga LV-1006, Latvia, and ^cLaboratory of Organic Chemistry, Wageningen University, Dreijenplein 8, 6703 HB Wageningen, The Netherlands

† Visiting scientist at Wageningen University.

Correspondence e-mail:
h.kooijman@chem.uu.nl

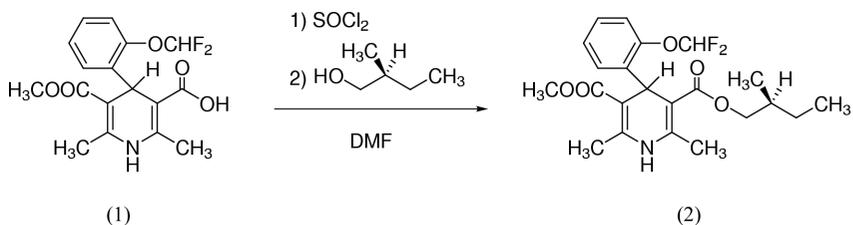
Key indicators

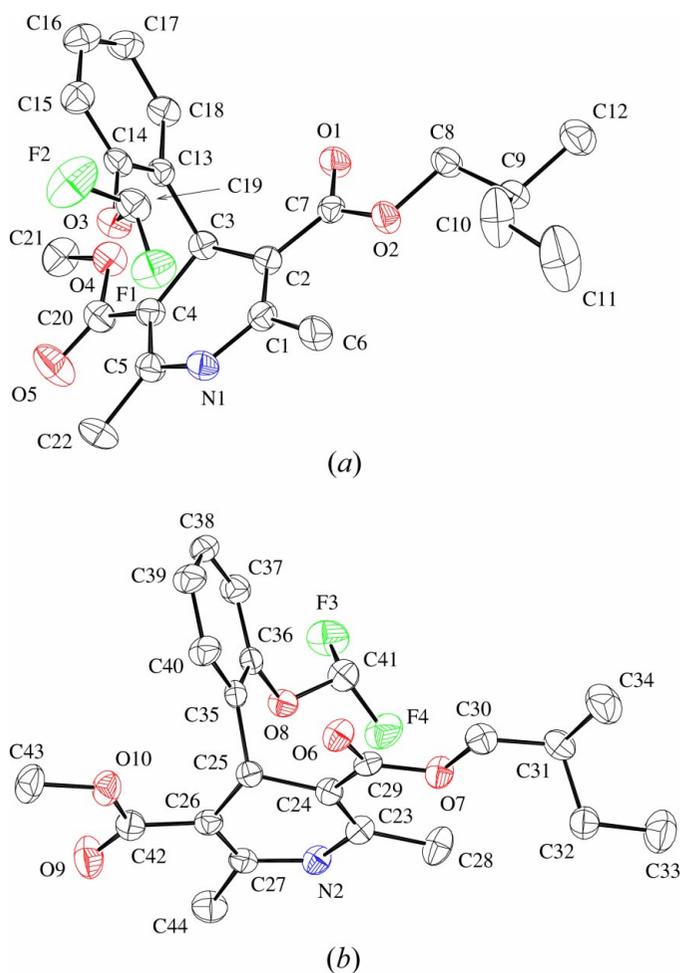
Single-crystal X-ray study
T = 150 K
Mean $\sigma(C-C)$ = 0.005 Å
R factor = 0.046
wR factor = 0.095
Data-to-parameter ratio = 8.4For details of how these key indicators were automatically derived from the article, see <http://journals.iucr.org/e>.

3-Methyl 5-[(S)-2-methylbutyl] 4-[2-(difluoromethoxy)phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

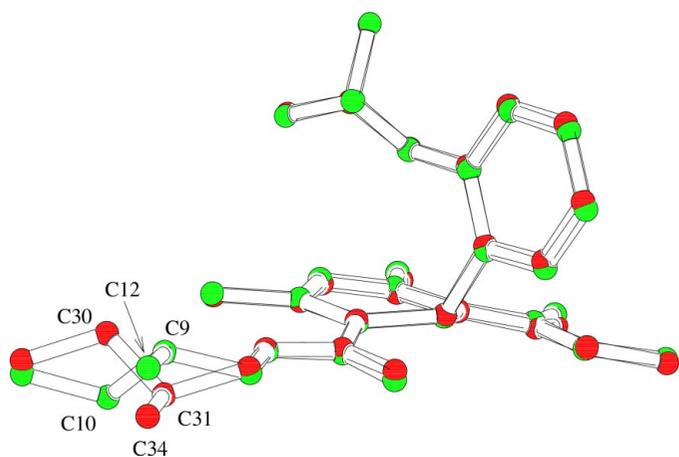
The crystal structure of the title compound, C₂₂H₂₇F₂NO₅, contains two diastereomers, related by a pseudo-glide plane. Owing to the addition of the difluoromethoxyphenyl moiety, the dihydropyridine ring is somewhat deformed from planarity. The packing involves a two-dimensional network created by C—H···O and N—H···O hydrogen bonds.Received 27 March 2002
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Comment

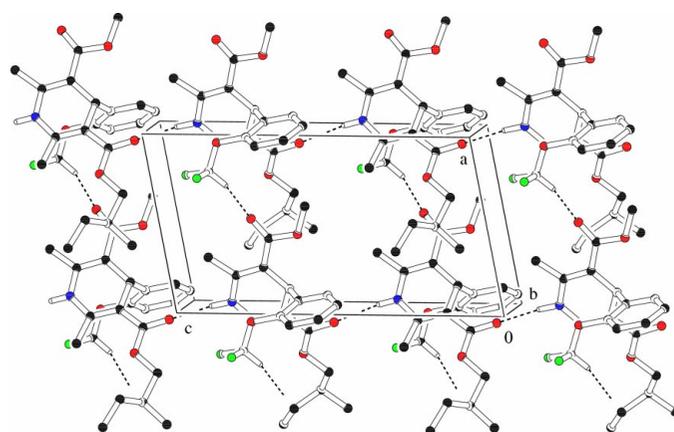
In order to investigate the stereochemical course of the *Candida rugosa* lipase mediated kinetic resolution of 3-acyloxymethyl-4-aryl-1,4-dihydropyridine-3,5-dicarboxylates, a derivative containing a second chiral centre of known configuration was prepared. This would allow the determination of the relative configuration of the chiral centre at C⁴ (labelled C3 and C25 in Fig. 1). The enzymatically prepared carboxylic acid (1) was esterified to (S)-2-methyl-1-butanol, giving the title compound, (2), whose crystal structure has been determined. However, since the starting material was not entirely stereochemically pure, there was a risk that the two diastereomers would preferentially crystallize together. This indeed proved to be the case, as is shown in Fig. 1. Later, compound (2) was prepared in stereochemically pure form. Unfortunately, we could not obtain crystals suitable for a structure determination from this material.The asymmetric unit contains two molecules, which are diastereomers with configuration (*R,S*) and (*S,S*) at (C3,C9) and (C25,C31), respectively. These configurations have been assigned with reference to the known (*S*)-configuration of atoms C9 and C31. The diastereomers have adopted conformations which are related by an inversion operation, with the exception of the 2-methylbutyl moiety. This is illustrated in Fig. 2, which displays a fit of molecule (1) and the inverted molecule (2). In the crystal, the molecules are related by a pseudo-*c*-glide plane, with the exception of the 2-methylbutyl moiety. The unit cell displays a pseudo-monoclinic geometry, with the pseudo-glide plane parallel to the *a* and *c* axes. The best-fit between the molecules is obtained by a rotation of -176° over the rotary-inversion axis [$-0.018, -1.000, 0.042$], combined with a shift of 7.226 Å (*i.e.* 0.48*c*) in the direction

**Figure 1**

View of the title compound, with the atom-numbering scheme. H atoms have been omitted for clarity. Displacement ellipsoids for non-H atoms are drawn at the 50% probability level. (a) molecule (1), the (*R,S*)-stereoisomer; (b) molecule (2), the (*S,S*)-stereoisomer.

**Figure 2**

Fit of molecule (1) [configuration (*R,S*), green] on the inverted molecule (2) [configuration (*R,R*), red; NB this configuration is not present in the crystal]. H atoms have been omitted for clarity.

**Figure 3**

N-H...*O* bonded chains (parallel to *c*) of alternating diastereomers, linked into a two-dimensional network by soft *C*-H...*O* interactions (parallel to *a*).

[0.002, -0.096, -1.000]. The unit weight r.m.s. fit is 0.31 Å, with the largest deviations for atoms C9, C10 and C12 of molecule (1).

Addition of the difluoromethoxyphenyl moiety to the dihydropyridine ring results in a slight deformation from planarity towards a sofa conformation in both diastereomers. The relevant asymmetry parameters (Duax & Norton, 1975) are $\Delta C_s[N1] = 2.2$ (4°) for molecule (1) and $\Delta C_s[N2] = 1.8$ (4°) for molecule (2); all other asymmetry parameters are at least 10° . The total puckering amplitude (Cremer & Pople, 1975) of the dihydropyridine ring is 0.177 (3) Å in molecule (1) and 0.173 (3) Å in molecule (2). The phenyl rings show total puckering amplitudes of 0.029 (3) and 0.019 (3) for molecules (1) and (2), respectively. For these rings, all asymmetry parameters are less than 5° . Hydrogenation of the pyridine N atom apparently has no influence on its hybridization (sp^2) or the planarity of this part of the six-membered ring. The bond distances in the dihydropyridine rings indicate delocalization of the formal double bonds of the $C=C-N-C=C$ fragment (see Table 1).

Crystal packing involves the formation of chains, parallel to the *c* axis, consisting of molecules connected by *N*-H...*O* hydrogen bonds (see Fig. 3 and Table 2). Each chain consists of an alternation of both diastereomers. The unitary graph set is *DD*, the binary graph set is $C_2^2(12)$ (Bernstein *et al.*, 1995). Two neighbouring chains are connected by *C*-H...*O* hydrogen bonds linking the F_2OCH moiety to the $O=C$ acceptor of the carboxylate moiety. These hydrogen bonds form links between equal stereoisomers. Both types of hydrogen bond together create a two-dimensional network of hydrogen-bonded molecules, with main axes *a* and *c*.

Experimental

The title compound was prepared from 284 mg (0.808 mmol) of 4-[2-(difluoromethoxy)phenyl]-5-(methoxycarbonyl)-2,6-dimethyl-1,4-dihydro-3-pyridinecarboxylic acid, (1), by reaction of its acid chloride with 0.262 ml (2.41 mmol) of (*S*)-2-methyl-1-butanol, using the

method of Sobolev *et al.* (2002). The crude product was flash chromatographed on silica gel with ethyl acetate/petroleum ether (b.p. 313–333 K, 1:3), purified again on silica gel with petroleum ether (b.p. 313–333 K)/chloroform/isopropyl alcohol (20:5:2) and crystallized from ethanol to give 276 mg (81%) as pale-yellow crystals: m.p. 406–407 K; $^1\text{H NMR}$ (CDCl_3 , 200 MHz): δ 0.83 (*t*, 3H, $J = 7.3$ Hz, CH_3), 0.85 (*d*, 3H, $J = 7.4$ Hz, CH_3), 0.95–1.16 (*m*, 1H, CH_2), 1.19–1.40 (*m*, 1H, CH_2), 1.60–1.76 (*m*, 1H, CH), 2.28 (*s*, 3H, CH_3), 2.30 (*s*, 3H, CH_3), 3.59 (*s*, 3H, CH_3), 3.77 (*dd*, 1H, $J = 10.8, 6.9$ Hz, CH_2), 3.89 (*dd*, 1H, $J = 10.8, 6.4$ Hz, CH_2), 5.25 (*s*, 1H, CH), 5.60 (*br s*, 1H, NH), 6.46 (*dd*, 1H, $J_{\text{H-F}} = 75.6, 75.8$ Hz, OCHF_2), 6.95–7.13 (*m*, 3H, Ar-H), 7.35 (*dd*, 1H, $J = 2.2, 7.3$ Hz, Ar-H). MS *m/z*: 423 (M^+ , 9), 352 (10), 336 (5), 308 (9), 284 (6), 281 (15), 280 (100), 211 (4), 210 (36); HRMS calculated for $\text{C}_{22}\text{H}_{27}\text{F}_2\text{O}_5$: 423.1857, found 423.1853. Crystals suitable for X-ray analysis were obtained by recrystallization from hexane containing a small amount of methanol.

Crystal data

$\text{C}_{22}\text{H}_{27}\text{F}_2\text{NO}_5$	$Z = 2$
$M_r = 423.45$	$D_x = 1.330 \text{ Mg m}^{-3}$
Triclinic, $P1$	MoK α radiation
$a = 8.2340$ (16) Å	Cell parameters from 367 reflections
$b = 8.7827$ (18) Å	$\theta = 1.6\text{--}25.0$
$c = 14.9145$ (18) Å	$\mu = 0.11 \text{ mm}^{-1}$
$\alpha = 89.299$ (11)°	$T = 150 \text{ K}$
$\beta = 78.697$ (11)°	Needle, colourless
$\gamma = 89.906$ (7)°	$0.3 \times 0.1 \times 0.1 \text{ mm}$
$V = 1057.6$ (3) Å 3	

Data collection

Nonius KappaCCD area-detector diffractometer	3257 reflections with $I > 2\sigma(I)$
φ scans, and ω scans with κ offsets	$R_{\text{int}} = 0.084$
Absorption correction: none	$\theta_{\text{max}} = 27.5^\circ$
21160 measured reflections	$h = -10 \rightarrow 10$
4617 independent reflections	$k = -11 \rightarrow 11$
	$l = -19 \rightarrow 19$

Refinement

Refinement on F^2	H atoms treated by a mixture of independent and constrained refinement
$R[F^2 > 2\sigma(F^2)] = 0.046$	$w = 1/[\sigma^2(F_o^2) + (0.0468P)^2]$
$wR(F^2) = 0.095$	where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.02$	$(\Delta/\sigma)_{\text{max}} = 0.002$
4617 reflections	$\Delta\rho_{\text{max}} = 0.17 \text{ e \AA}^{-3}$
549 parameters	$\Delta\rho_{\text{min}} = -0.23 \text{ e \AA}^{-3}$

Table 1 Selected geometric parameters (Å, °).

N1—C1	1.381 (4)	N2—C23	1.372 (4)
N1—C5	1.374 (5)	N2—C27	1.371 (4)
C1—C2	1.354 (4)	C23—C24	1.362 (4)
C2—C3	1.532 (5)	C24—C25	1.522 (5)
C3—C4	1.521 (5)	C25—C26	1.520 (5)
C4—C5	1.360 (4)	C26—C27	1.356 (4)
C7—O2—C8—C9	−159.7 (3)	C29—O7—C30—C31	−170.7 (3)
O2—C8—C9—C10	−57.5 (4)	O7—C30—C31—C32	−60.9 (3)
C8—C9—C10—C11	173.1 (4)	C30—C31—C32—C33	174.9 (3)

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

$D\text{—}H\cdots A$	$D\text{—}H$	$H\cdots A$	$D\cdots A$	$D\text{—}H\cdots A$
N1—H1 \cdots O6 ⁱ	0.96 (4)	2.13 (4)	3.080 (4)	171 (4)
N2—H2 \cdots O1	0.88 (4)	2.19 (4)	3.060 (3)	171 (4)
C19—H19 \cdots O4 ⁱⁱ	1.00	2.20	3.155 (5)	159
C41—H41 \cdots O9 ⁱⁱ	1.00	2.24	3.160 (4)	153

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

Owing to the absence of significant anomalous dispersion, the absolute configurations could not be determined reliably. The configuration of C9 and thereby also that of C31 was set equal to *S*, consistent with the starting materials used. The measured reflections reduced to 9040 unique reflections with an R_{int} of 0.074. After merging of the Friedel pairs, the 4617 reflections reported above remained. H atoms of the N—H moieties were located in a difference Fourier map and their coordinates and isotropic displacement parameters were refined. All other H atoms were included at calculated positions, riding on their carrier atoms. Isotropic displacement parameters of H atoms bonded to C atoms were coupled to the equivalent isotropic displacement parameter of their carrier atoms by a fixed factor of 1.5 (methyl H atoms) or 1.2 (other H atoms).

Data collection: COLLECT (Nonius, 1998); cell refinement: DENZO (Otwinowski & Minor, 1997); data reduction: DENZO; program(s) used to solve structure: SHELXS86 (Sheldrick, 1985); program(s) used to refine structure: SHELXL97 (Sheldrick, 1997); molecular graphics: PLATON (Spek, 2002); software used to prepare material for publication: PLATON.

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