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Candida rugosa LIPASE-CATALYZED KINETIC RESOLUTION OF 3-(ISOBUTYRYLOXY)METHYL 4-[2-(DIFLUOROMETHOXY)PHENYL]-2-METHYL-5,5-DIOXO-1,4-DIHYDROBENZOTHIENO-[3,2-*b*]PYRIDINE-3-CARBOXYLATE

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The lipase-catalyzed kinetic resolution of 3-(isobutyryloxy)methyl 4-[2-(difluoromethoxy)phenyl]-2-methyl-5,5-dioxo-1,4-dihydrobenzothieno[3,2-b]pyridine-3-carboxylate has been performed. The most enantioselective reaction (E = 28) was transesterification with n-butanol in water-saturated toluene at 45°C.

Keywords: enantiopure 1,4-dihydropyridines, enzyme-catalyzed reaction, kinetic resolution, transesterification.

The pharmacological activities of drugs depend on their interaction with biological matrices (so-called drug targets). These drug targets, such as proteins (receptors, enzymes), nucleic acids, and biomembranes (phospholipids and glycolipids), have complex three-dimensional structures, which are capable of recognizing and binding specifically the ligand (drug) molecule in only one of the many possible arrangements in three-dimensional space [1, 2]. As a result of this direct correlation between drug stereochemistry and biological activity, the governing bodies that regulate the approval of new medicines in the USA [3, 4] and Europe [5] have issued specific rules pertaining to the development of stereoisomeric drugs [2, 6, 7].

Chirality plays an important role in the activity of 1,4-dihydropyridines (1,4-DHPs) and both quantitative and qualitative differences have been reported [8, 9]. The preferred method for the resolution of monocyclic 1,4-DHPs is enzymatic kinetic resolution, often assisted by the incorporation of an enzymatically labile group. This approach has been pioneered by the group of Sih [10] and Achiwa [11] and has been successfully used also by our research group [12-14]. Polycyclic 1,4-DHPs in enantiopure form are desired for extended pharmacological studies, since racemic 1,4-dihydrobenzothieno[3,2-*b*]pyridine 5,5-dioxides **1** [15] and 5-oxo-4,5-dihydro-1,4-indeno[1,2-*b*]pyridines **2** [16] have exhibited various biological activities. Many representatives of both classes of compounds (*e.g.*, **1** [R = phenyl, 4-bromophenyl, 4-nitrophenyl] and **2b**) show coronary dilating activities [17-19]. 1,4-DHPs **2a** and **2c** have exhibited anticancer activities [20].

Herein, we report the *Candida rugosa* lipase-catalyzed kinetic resolution of 3-(isobutyryloxy)methyl 4-[2-(difluoromethoxy)phenyl]-2-methyl-5,5-dioxo-1,4-dihydrobenzothieno[3,2-*b*]pyridine-3-carboxylate as a model compound for the resolution of these polycyclic 1,4-DHP derivatives.

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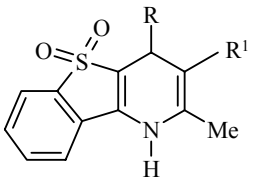
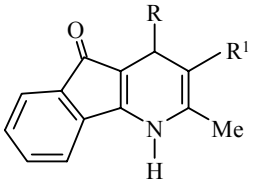


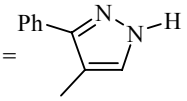
1

R = H, Me, Ph, C_6H_4Cl-4, C_6H_4OMe-4, C_6H_4OH-4, C_6H_4Br-4, $C_6H_3(OMe)_2$-2,3, $C_6H_4NO_2$-4, PhCH=CH

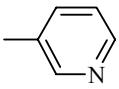
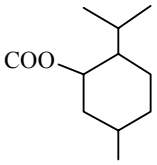
R^1 = COOAlk, COMe, CN, C(O)SEt, C(S)OEt, C(S)SEt



2

2a R =  , R^1 = COOMe

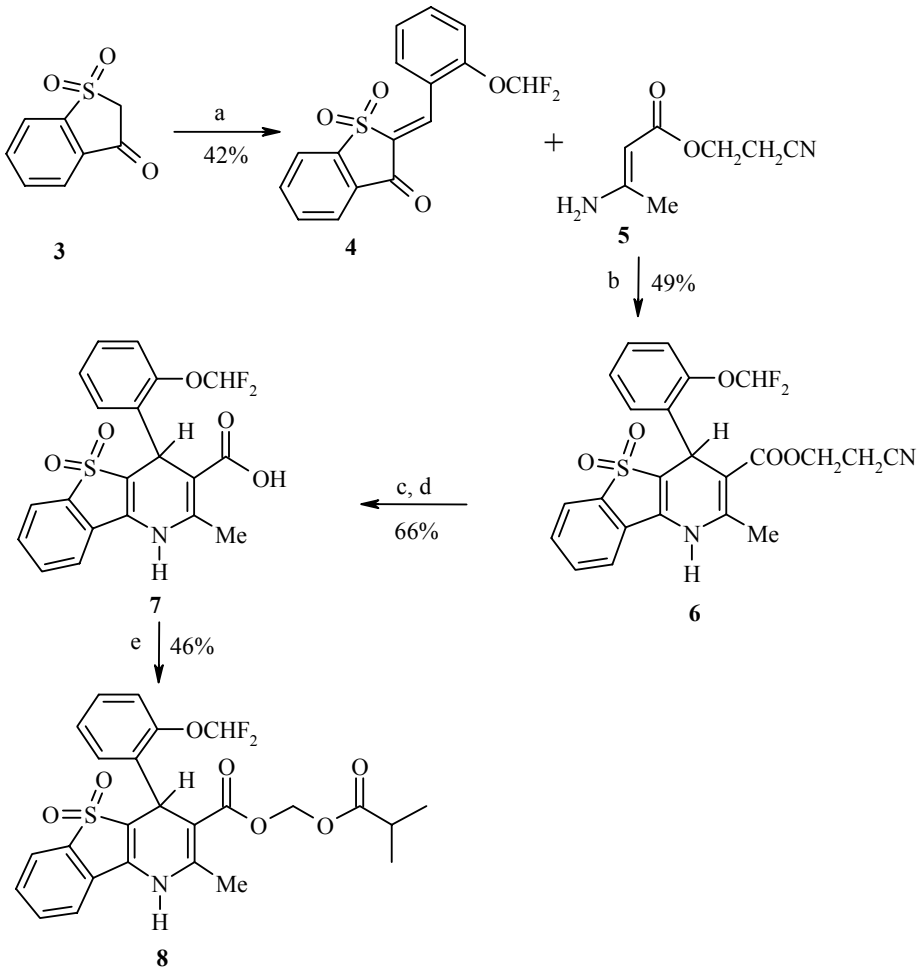
2b R = Ph, C_6H_4OH-2, $C_6H_4NO_2$-2 and -4;
R^1 = C(O)SEt, $C(O)SCH_2Ph$

2c R =  , R^1 = 

The synthesis of enantiopure polycyclic 1,4-DHPs has been performed *via* lipase-catalyzed kinetic resolution of the corresponding acyloxymethyl derivative **8**. The racemic acyloxymethyl ester **8** has been prepared in a four-step sequence as depicted in scheme 1. Thus, condensation of benzo[*b*]thiophen-3(2H)-one 1,1-dioxide (**3**) [21] with 2-(difluoromethoxy)benzaldehyde, followed by Hantzsch cyclization of the intermediate **4** with 2-cyanoethyl 3-aminocrotonate (**5**), furnished the polycyclic 1,4-DHP **6** framework according to the earlier reported method [15]. The hydrolysis of cyanoethyl ester **6** with KOH gave carboxylic acid **7**. The last step consists of the esterification of **7** with isobutyryloxymethyl chloride [13].

The choice of enzymes for primary screening was based on the previous work of our group [12-14, 22] and literature data [11, 23]. The primary screening was carried out in water-saturated diisopropyl ether (IPE) at 45°C. Of these tested hydrolases (Lipase PS and AH, *Candida antarctica* lipase B [Novozym 435® and Chirazyme L-2, c.-f., C3, lyo. (CAL-B)], *Rhizomucor miehei* lipase, *Burkholderia cepacia* lipase, and *Candida rugosa* lipase [CRL]), only CRL showed significant hydrolytic activity towards substrate **8**. CRL-Mediated hydrolysis of **8** in water-saturated IPE at 45°C (Table 1, entry 1) occurred with moderate enantioselectivity (E = 12 [24]). The very low solubility of the substrate in IPE and the moderate enantioselectivity of CRL led us to investigate other reaction conditions. The influence of the solvent on the enantioselectivity of CRL was studied in more detail and some examples are given in Table 1. It was found that the use of toluene as the solvent increased the solubility of substrate **8**. CRL-Catalyzed hydrolysis in toluene that was saturated with water at the reaction temperature occurred with moderate selectivity (Table 1, entry 2). CRL was found to be not active when toluene was used with *n*-butanol as nucleophile in the absence of water (Table 1, entry 3). Better results were obtained when 5-50 mmol/l *n*-butanol in water-saturated toluene was used as the reaction

Scheme 1



Reagents and conditions: a – 2-(difluoromethoxy)benzaldehyde, AcOH, piperidine, Δ, 3 h; b – EtOH : AcOH (20 : 1), Δ, 3 h; c – EtOH, KOH, room temperature, 3 h; d – H_2O, HCl; e – $ClCH_2OC(O)Pr$-*i*, K_2CO_3, DMF, room temperature, 3 h

medium (Table 1, entries 4-7). Using less *n*-butanol at higher temperatures appeared to give the most enantioselective reaction ($E = 28$) (Table 1, entry 6). The amount of water in the reaction mixture seems to be important for the enantioselectivity of CRL, as $E = 22$ for the reaction where the toluene was water-saturated at room temperature, whereas an $E = 28$ was obtained in the case where the toluene was water-saturated at 45°C (Table 1, entry 6). The experimentally determined water content in toluene was around 0.045 and 0.10% at 25 and 45°C, respectively.

The monoacid **7** and the remaining ester **8** were isolated after 2 h of reaction with CRL when the conversion reached ~30%, in order to have a good enantiomeric excess of the reaction product (ee_p). The enantiomerically pure monoacid **7** appeared to have an optical rotation of -61.4° (*c* 0.5, acetone) whereas the enantiomerically enriched remaining ester had an optical rotation of +29.1° (*c* 1.0, acetone). The remaining substrate (+)-**8** preferentially crystallises as a single enantiomer. After purification of (+)-**8** *via* crystallization from diluted methanol, the ee_p of the product was much higher than expected (94%).

TABLE 1. CRL-Catalyzed Kinetic Resolution of **8**

Entry	T, °C	Reaction medium	Conversion			E[a]
			Time, h	%	ee_p, %	
1	45	IPE/H_2O[b]	6	49	69	12.0±1.0
2	25	Toluene/H_2O[c]	20	25	82	14.0±0.8
3	45	50 mmol/l *n*-butanol in toluene[d]	4	—	—	—
4	45	50 mmol/l *n*-butanol in toluene/H_2O[e]	5.5	42	77	16.0±1.4
5	25	5 mmol/l *n*-butanol in toluene/H_2O[e]	6.0	41	83	23.0±1.6
6	45	5 mmol/l *n*-butanol in toluene/H_2O[e]	2.0	31	90	28.0±2.8
7	45	5 mmol/l *n*-butanol in toluene/H_2O[f]	4.5	25	89	22.0±2.7

[a] The enantiomeric ratio (E) was calculated using the computer program EIVFIT [25].

[b] A solution of 5 mg of **8** in 20 ml IPE that was water-saturated at room temperature with 5 mg of CRL was shaken at 250 revolutions per minute (rpm).

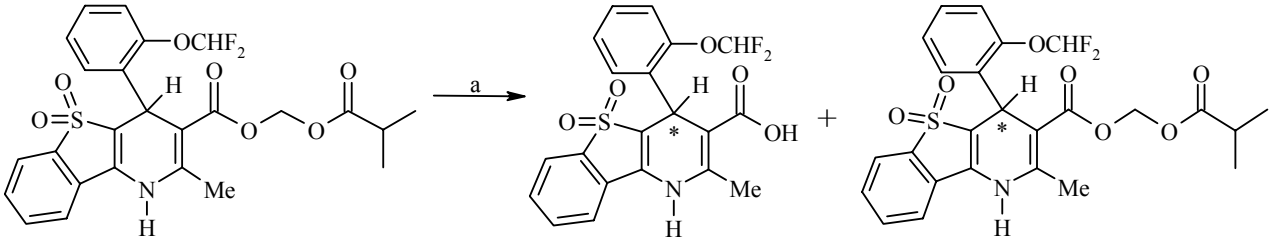
[c] A solution of 5 mg of **8** in 5 ml of toluene that was water-saturated at the reaction temperature with 5 mg of CRL was shaken at 250 rpm.

[d] A solution of 5 mg of **8** in 5 ml of 50 mmol/l *n*-butanol in toluene with 5 mg of CRL was shaken at 250 rpm.

[e] A solution of 5 mg of **8** in 5 ml of 5-50 mmol/l *n*-butanol in toluene that was water-saturated at the reaction temperature with 5 mg of CRL was shaken at 250 rpm.

[f] A solution of 5 mg of **8** in 5 ml of 5 mmol/l *n*-butanol in toluene that was water-saturated at room temperature with 5 mg of CRL was shaken at 250 rpm.

Scheme 2



rac-**8** → (-)-**7** 31% 91% *ee* + (+)-**8** 34% 94% *ee*

Reagents and conditions: a – *Candida rugosa* lipase, 5 mmol/l *n*-butanol solution in toluene that was water-saturated at the reaction temperature, 2 h at 45°C

In conclusion, the *Candida rugosa* lipase-catalyzed kinetic resolution of 3-(isobutyryloxy)methyl 4-[2-(difluoromethoxy)phenyl]-2-methyl-5,5-dioxo-1,4-dihydrobenzothieno[3,2-*b*]pyridine-3-carboxylate has been developed. The enantioselectivity of *Candida rugosa* lipase can be improved by changing the reaction medium and the temperature. The change of the reaction medium from water-saturated diisopropyl ether to

5 mmol/l solution of *n*-butanol in toluene resulted in a higher enantiomeric ratio (E = 28). This method shows that these tricyclic compounds are accepted by CRL and that enantiomeric recognition is feasible. This opens new avenues for the preparation of enantiopure fused 1,4-DHPs.

EXPERIMENTAL

All reagents were purchased from Aldrich, Acros or Merck and used without further purification. HPLC grade solvents were from Labscan (Dublin, Ireland). *Candida rugosa* lipase, (lipase (EC 3.1.1.3) Type VII from *Candida rugosa*, 875 U/mg) was purchased from Sigma. Lipase AH, and Lipase PS were gifts from Amano Pharmaceutical Co., Ltd. (Japan). Immobilized *Candida antarctica* lipase B (Novozym 435®) was a gift from Novo Nordisk A/S (Bagsvaerd, Denmark). *Rhizomucor miehei* lipase (Chirazyme L-9, c.-f, lyo.), *Candida antarctica* lipase B (Boehringer Mannheim, Chirazyme L-2, c.-f., C3, lyo.), and *Burkholderia cepacia* lipase (Chirazyme L-1, c.-f., lyo.) were gifts from Boehringer-Mannheim (Mannheim, Germany). Enzymatic reactions were carried out in a New Brunswick Scientific Innova 4080 incubatory orbital shaker at 250 rpm. Flash column chromatography was performed on Merck silica gel 60 (230-400 mesh or 70-230 mesh). TLC was performed on 20 × 20 cm Silica gel TLC-PET F_{254} foils (Fluka). ^{1}H NMR spectra were recorded on a Bruker WH 90/DC (90 MHz) or a Bruker AC-E 200 (200 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Bruker AC-E 200 (50 MHz). Mass spectral data were determined on a AEI MS-905 mass spectrometer. Melting points were determined on a Boetius apparatus and are uncorrected. Optical rotation values were measured with a Perkin–Elmer 241 digital polarimeter. Elemental analyses were determined on a Carlo-Erba elemental analyzer. The conversions and enantiomeric excesses of all enzymatic reactions were analyzed by HPLC on an enantioselective column Chirex 3011, 4.6 × 250 mm, 5 μm (Phenomenex) using a Ginkotek 580A pump (Germering, Germany) and an Applied Biosystems 759A absorbance detector at 254 nm or a LC-1110 pump and a LC-1200 UV/Vis detector at 254 nm, GBC (Dandenong, Australia). The eluent was 0.05 M ammonium acetate in MeOH at a flow rate of 1 ml/min. Peak areas were determined electronically with the Chromeleon chromatography data system, Dionex Softron GmbH (Germering, Germany) or DP-800, GBC (Dandenong, Australia). Water content in toluene was determined by gas chromatography, using a Hewlett Packard 5890 gas chromatograph equipped with a thermal conductivity detector (TCD) and a Porapak QS column.

2-[2-(Difluoromethoxy)benzylidene]benzo[*b*]thiophen-3(2H)-one 1,1-Dioxide (4). Benzo-[*b*]thiophen-3(2H)-one 1,1-dioxide **3** (1.64 g, 9 mmol), 2-(difluoromethoxy)benzaldehyde (1.55 g, 9 mmol), and piperidine (0.06 ml) in acetic acid (20 ml) were stirred under reflux for 3 h. After storing in the refrigerator the precipitated product was filtered to give 1.38 g of crude **4**. The precipitate was crystallized from methanol to give white crystals of **4** (1.27 g, 42%); mp 195-198°C. ^{1}H NMR spectrum (DMSO-d_6, 90 MHz), δ, ppm (J, Hz): 7.10-8.40 (m, 9H, Ar–H and =CH); 7.40 (t, 1H, J_{H-F} = 74.0, $OCHF_2$). MS: 336 $[M]^+$. Found, %: C 56.20; H 2.94. $C_{16}H_{10}F_2O_4S$. Calculated, %: C 57.14; H 3.00.

3-(2-Cyanoethyl) 4-[2-(Difluoromethoxy)phenyl]-2-methyl-5,5-dioxo-1,4-dihydrobenzothieno-[3,2-*b*]pyridine-3-carboxylate (6). To a solution of **4** (1.34 g, 4 mmol) in a mixture of ethanol (20 ml) and acetic acid (4 ml), 2-cyanoethyl 3-aminocrotonate **5** (0.62 g, 4 mmol) was added. The reaction mixture was stirred under reflux for 3 h. After refrigeration of the mixture, the orange precipitate was filtered off. The crude product was crystallized from methanol–acetic acid to give a yellow powder of **6** (0.92 g, 49%); mp 230-234°C. ^{1}H NMR spectrum (DMSO-d_6, 90 MHz), δ, ppm (J, Hz): 2.40 (s, 3H, CH_3, overlap with DMSO-d_6); 2.70 (t, 2H, J = 6.5, $CH_2\underline{CH_2}CN$); 4.05 (t, 2H, J = 6.5, $\underline{CH_2}CH_2CN$); 5.30 (s, 1H, CH); 6.90-8.10 (m, 8H, Ar-H); 6.97 (t, 1H, J_{H-F} = 76.0, $OCHF_2$); 9.80 (s, 1H, NH). MS: 472 $[M]^+$. Found, %: C 57.79; H 3.74; N 5.59; S 6.57. $C_{23}H_{18}F_2N_2O_5S$. Calculated, %: C 58.47; H 3.84; N 5.93; S 6.79.

4-[2-(Difluoromethoxy)phenyl]-2-methyl-5,5-dioxo-1,4-dihydrobenzothieno[3,2-*b*]pyridine-3-carboxylic Acid (7). Compound **6** (1.89 g, 4 mmol) in ethanol (20 ml) was heated under reflux until dissolution was complete, after which it was cooled down. Crushed KOH (0.28 g, 5 mmol) was added to the reaction

mixture at room temperature and this mixture was then stirred for 3 h at the same temperature before being evaporated. The residue was diluted with water. The ice-cooled solution was acidified with diluted aqueous HCl to pH 4.0-5.0. The precipitated product was filtered off, washed with water, and crystallized from methanol to give a yellow powder of **7** (1.11 g, 66%); mp 223-225°C. ^{1}H NMR spectrum (DMSO-d_6, 90 MHz), δ, ppm (*J*, Hz): 2.40 (s, 3H, CH_3, overlap with DMSO-d_6); 5.30 (s, 1H, CH); 6.98 (1H, t, $J_{H–F}$ = 76.0, $OCHF_2$); 7.04-8.10 (m, 8H, Ar–H); 9.55 (br. s, 1H, NH); 10.90 (br. s, 1H, COOH). Found, %: C 56.95; H 3.52; N 3.39; S 7.71. $C_{20}H_{15}F_2NO_5S$. Calculated, %: C 57.28; H 3.60; N 3.34; S 7.65.

3-(Isobutyryloxy)methyl 4-[2-(Difluoromethoxy)phenyl]-2-methyl-5,5-dioxo-1,4-dihydrobenzothieno[3,2-*b*]pyridine-3-carboxylate (8). To a solution of **7** (0.53 g, 1.3 mmol) in dry DMF (7 ml), K_2CO_3 (0.21 g, 1.5 mmol) was added at room temperature and the reaction mixture was stirred for 2 h, after which isobutyryloxymethyl chloride (0.22 g, 1.6 mmol) was added. The mixture was stirred for 3 h, poured into ice cold water, and extracted with $CHCl_3$. The organic layer was washed with water (three times) and brine, dried over $MgSO_4$, and evaporated. The remaining residue was crystallized from methanol to give 0.30 g (46%) of **8** as a yellow powder; mp 185-187°C. ^{1}H NMR spectrum ($CDCl_3$, 200 MHz), δ, ppm (*J*, Hz): 1.05 (d, 3H, *J* = 6.9, $CH\underline{CH_3}$); 1.07 (d, 3H, *J* = 6.9, $CH\underline{CH_3}$); 2.40 (septet, 1H, *J* = 6.9, $\underline{CH}(CH_3)_2$); 2.44 (s, 3H, CH_3); 5.43 (s, 1H, CH); 5.69 (ABq, 2H, OCH_2O); 6.54 (t, 1H, $J_{H–F}$ = 74.4, $OCHF_2$); 6.59 (br. s, 1H, NH); 7.00-7.64 (m, 8H, Ar–H). MS: 519 $[M]^+$. Found, %: C 57.64; H 4.35; N 2.64; S 6.26. $C_{25}H_{23}F_2NO_7S$. Calculated, %: C 57.80; H 4.46; N 2.70; S 6.17.

***Candida Rugosa* Lipase-catalyzed Kinetic Resolution of Racemic 8.** To a solution of **8** (85 mg, 0.16 mmol) in 5 mmol/l *n*-butanol in toluene (85 ml) that was water-saturated at 45°C was added *Candida rugosa* lipase (85 mg) and the resulting mixture was shaken for 2 h at 45°C. The reaction mixture was diluted with acetonitrile (200 ml), evaporated and directly flash chromatographed on silica gel with chloroform–petroleum ether (bp 40-60°C)–acetone–ethanol (9:7:2:2) to give (–)-**7** and (+)-**8**. The *ee*'s of both compounds were determined after crystallisation.

(–)-4-[2-(Difluoromethoxy)phenyl]-2-methyl-5,5-dioxo-1,4-dihydrobenzothieno[3,2-*b*]pyridine-3-carboxylic Acid ((–)-7). Yield 21 mg (31%) as a yellow powder from methanol–water; mp 166-167°C; 91% *ee*; $[\alpha]_D^{20}$ -61.4 (*c* 0.5, acetone). ^{1}H NMR spectrum (DMSO-d_6, 200 MHz), δ, ppm (*J*, Hz): 2.46 (s, 3H, CH_3); 5.36 (s, 1H, CH); 6.98 (t, 1H, $J_{H–F}$ = 74.3, $OCHF_2$); 7.03-7.34 (m, 4H, Ar–H); 7.58-8.08 (m, 4H, Ar–H); 9.71 (br. s, 1H, NH). ^{13}C NMR spectrum (DMSO-d_6, 50 MHz), δ, ppm (*J*, Hz): 18.35 (CH_3); 30.12 (CH); 102.07 (C); 110.16 (C); 116.82 (CH, t, $J_{C–F}$ = 250.0, $OCHF_2$); 116.83 (CH); 120.27 (CH); 121.20 (CH); 125.19 (CH); 126.04 (C); 128.07 (CH); 130.00 (CH); 130.65 (CH); 132.93 (CH); 135.36 (C); 135.75 (C); 137.86 (C); 146.22 (C); 148.31 (C); 167.75 (C). Found, %: C 56.72; H 3.40; N 3.37; S 7.75. $C_{20}H_{15}F_2NO_5S$. Calculated, %: C 57.28; H 3.60; N 3.34; S 7.65.

(+)-3-(Isobutyryloxy)methyl 4-[2-(Difluoromethoxy)phenyl]-2-methyl-5,5-dioxo-1,4-dihydrobenzothieno[3,2-*b*]pyridine-3-carboxylate ((+)-8). Yield 29 mg (34%) as a yellow powder from methanol–water; mp 85-86°C; 94% *ee*; $[\alpha]_D^{20}$ +29.1 (*c* 1.0, acetone). ^{1}H NMR (DMSO-d_6, 200 MHz), δ, ppm (*J*, Hz): 0.92 (d, 3H, *J* = 6.9, $CH\underline{CH_3}$); 0.97 (d, 3H, *J* = 6.9, $CH\underline{CH_3}$); 2.39 (septet, 1H, *J* = 6.9, $\underline{CH}(CH_3)_2$); 2.48 (s, 3H, CH_3); 5.34 (s, 1H, CH); 5.62 (ABq, 2H, *J* = 5.8, OCH_2O); 7.02 (t, 1H, $J_{H–F}$ = 74.2, $OCHF_2$); 7.07-7.32 (m, 4H, Ar–H); 7.60-8.09 (m, 4H, Ar–H); 9.99 (br. s, 1H, NH). ^{13}C NMR spectrum (DMSO-d_6, 50 MHz), δ, ppm (*J*, Hz): 18.00 (CH_3); 18.04 (CH_3); 18.69 (CH_3); 29.90 (CH); 32.61(CH); 78.26 (CH_2); 99.63 (C); 110.94 (C); 116.56 (CH); 116.75 (CH, t, $J_{C–F}$ = 255.1 Hz, $OCHF_2$); 120.38 (CH); 121.27 (CH); 125.02 (CH); 125.76 (C); 128.25 (CH); 129.87 (CH); 130.77 (CH); 133.03 (CH); 134.88 (C); 135.02 (C); 137.71 (C); 148.47 (C); 149.61(C); 164.50 (C); 174.58 (C). MS: 519 $[M]^+$. Found, %: C 57.50; H 4.31; N 2.62; S 6.29. $C_{25}H_{23}F_2NO_7S$. Calculated, %: C 57.80; H 4.46; N 2.70; S 6.17.

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REFERENCES

1. H. Y. Aboul-Enein and I. W. Wainer, *The Impact of Stereochemistry on Drug Development and Use*, John Wiley & Sons, 1997, 728 pp.
2. M. C. Hillier and P. J. Reider, *Drug Discovery Today*, **7**, 303 (2002).
3. M. Strong, *Food Drug Law J.*, **54**, 463 (1999).
4. FDA, *Chirality*, **4**, 338 (1992).
5. CPMP, *Note for Guidance: Investigation of Chiral Active Substances*, III/3501/91 (1993).
6. J. M. D. Daniels, E. R. Nestmann, and A. Kerr, *Drug Inf. J.*, **31**, 639 (1997).
7. P. Baldrick, *Drug Inf. J.*, **35**, 99 (2001).
8. S. Goldmann and J. Stoltefuss, *Angew. Chem., Int. Ed. Engl.*, **30**, 1559 (1991).
9. Y. Tokuma and H. Noguchi, *J. Chromatogr. A.*, **694**, 181 (1995).
10. X. K. Holdgrun and C. J. Sih, *Tetrahedron Lett.*, **32**, 3465 (1991).
11. K. Achiwa and T. Kato, *Curr. Org. Chem.*, **3**, 77 (1999).
12. A. Sobolev, M. C. R. Franssen, B. Vigante, B. Cekavicus, N. Makarova, G. Duburs, and Ae. de Groot, *Tetrahedron Asymmetry*, **12**, 3251 (2001).
13. A. Sobolev, M. C. R. Franssen, B. Vigante, B. Cekavicus, R. Zhalubovskis, H. Kooijman, A. L. Spek, G. Duburs, and Ae. de Groot, *J. Org. Chem.*, **67**, 401 (2002).
14. A. Sobolev, M. C. R. Franssen, J. Poikans, G. Duburs, and Ae. de Groot, *Tetrahedron Asymmetry*, **13**, 2389 (2002).
15. R. R. Dubure, B. A. Vigante, J. J. Ozols, G. J. Dubur, and G. I. Rozentale, *Khim. Geterotsikl. Soed.*, 1563 (1986).
16. V. Petrow, J. Saper, and B. Sturgeon, *J. Chem. Soc.*, 2134 (1949).
17. R. R. Dubure, R. O. Vitolina, J. J. Ozols, G. J. Duburs, A. A. Kimenis, and G. V. Zarins, USSR Inventor's certificate 1018396; *Chem. Abstr.*, **105**, 191950 (1986).
18. B. A. Vigante, J. J. Ozol, G. O. Sileniece, A. A. Kimenis, and G. J. Dubur, USSR Inventor's certificate 794006; *Chem. Abstr.*, **95**, 704 (1981).
19. B. A. Vigante, J. J. Ozol, R. O. Vitolina, G. O. Sileniece, A. A. Kimenis, and G. J. Dubur, Ger. Offen. 2909852; *Chem. Abstr.*, **94**, 15579 (1981).
20. E. A. Bisenieks, J. R. Uldrikis, G. J. Dubur, G. D. Tirzit, A. Z. Dauvarte, A. A. Zidermane, E. V. Ivanov, and T. V. Ponomareva, USSR Inventor's certificate 1050261; *Chem. Abstr.*, **124**, 333068 (1996).
21. M. A. Mackanova and G. J. Vanag, *Dokl. Akad. Nauk SSSR*, **132**, 615 (1960).
22. A. Sobolev, M. C. R. Franssen, N. Makarova, G. Duburs, and Ae. de Groot, *Tetrahedron Asymmetry*, **11**, 4559 (2000).
23. M. Chudik, V. Mastihuba, and B. Decroix, *Heterocycles*, **48**, 1943 (1998).
24. C. S. Chen, Y. Fujimoto, G. Girdaukas, and C. J. Sih, *J. Am. Chem. Soc.*, **104**, 7294 (1982).
25. J. A. Jongejan, J. B. A. van Tol, A. Geerlof, and J. A. Duine, *Recl. Trav. Chim. Pays-Bas*, **110**, 247 (1991).