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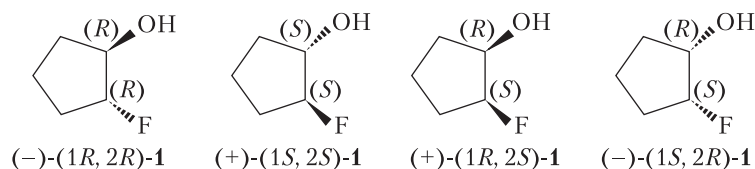
Enzymatic synthesis of enantiomerically pure 1,2-fluorocyclopentanols and 1,2-aminofluorocyclopentanes

Presented by Corresponding Member of the NAS of Ukraine O.I. Kolodiazhnyi

Vicinal fluorocyclopentanol are valuable chiral synthetic blocks for the preparation of a number of natural and synthetic biologically active substances. Racemic *cis*-2-fluorocyclopentanols were separated into enantiomers by the kinetically controlled transesterification with vinyl acetate in the presence of lipases in organic media. High enantioselectivity ($ee > 98\%$) and good yields of compounds were obtained for all substrates using *Burkholderia cepacia* lipase. The fluorocyclopentanols were converted into enantiomerically pure 1,2-aminofluorocyclopentanes using the Mitsunobu reaction. The enantiomeric purity of the compounds was determined by Mosher's acid derivatization method, and the absolute configurations were determined using the Kazlauskas rule.

Keywords: stereochemistry, biocatalysis, lipase *Burkholderia cepacia*, fluorocyclopentanols, aminofluorocyclopentanes, Kazlauskas rule.

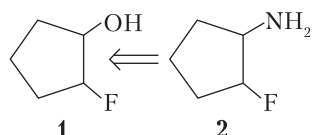
Vicinal fluorocyclopentanol are valuable chiral synthetic blocks for the preparation of a number of natural and synthetic biologically active substances [1]. These compounds are used to prepare various biologically active compounds, in particular, prostaglandins and precursors of leukotrienes [1–4]. 2-Fluorocyclopentanols can be converted to prostaglandin F_{2a} precursors, while 2-substituted cyclopentanols are the starting compounds for the preparation of L7 leukotriene B₄, a conformationally restricted leukotriene antagonist used in the enantioselective general synthesis of (+)-Estron and Desogestrel [5]. Previously, we reported on the biocatalytic method for the synthesis of chiral halogenocyclopentanols and halogenocyclopentanols, which were obtained by the chemoenzymatic transesterification of 2-halogenocyclopentanols [6] (Scheme 1).



Scheme 1

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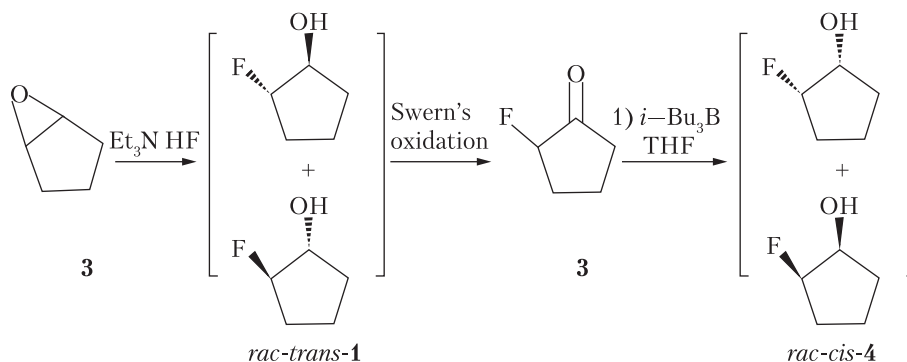
In the present work, we continued these studies using fluorocyclopentanols to synthesize new important synthetic blocks of biologically active compounds. First of all, we focused on the synthesis of enantiomerically pure aminofluorocyclopentane **2**, which we planned to obtain from the 1,2-fluorocyclopentanol **1** (Scheme 2).



Scheme 2

Results and discussion. *Synthesis of starting compounds.* The stereoisomers of 1,2-fluorocyclopentanols were synthesized from cyclopentane epoxides **3** [7]. With this end, the mixture of epoxide and triethylamine hydrofluoride was heated at 80 °C for several hours. As a result, a racemic mixture of *trans*-2-fluorocyclopentanol **1** without impurities of *cis*-isomer **4** was obtained in high yield (Scheme 3).

In the next step of the synthesis, *trans*-2-fluorocyclopentanols **1** was converted into racemic *cis*-2-fluorocyclopentanols **4**. For this, the compound *trans*-**1** was oxidized using the Swern methodology and treated at –80 °C with a mixture of dimethyl sulfoxide and oxalyl chloride for 1 h. Then it was treated with triethylamine, resulting in the formation of 2-fluorocyclopentanone **3** in high yield, 2-fluorocyclopentanone **3** was then reduced by triisobutylborane in THF to form racemic *cis*-2-fluorocyclopentanols. The analysis of NMR spectra of reaction mixtures showed that *cis*-2-fluoro-fluorocyclopentanol **4** contained minor impurities of *trans*-isomer **1** (Scheme 3).



Scheme 3

In addition, racemic *trans*-2-fluorocyclopentanol **1** was oxidized by the Johns method. As a result, 2-fluorocyclopentanone **4** was obtained in good yields. The ketones **3** were reduced by sodium borohydride in methanol, triisobutylborane in THF and H-Dibal. Recovery of 2-fluorocyclopentanone **3** with sodium borohydride in methanol yielded a mixture of *cis*- and *trans*-isomers in the ratio of 70 : 30. The reduction with triisobutylborane gave the diastereomers in the ratio of 75 : 25, and the reduction with H-Dibal resulted in the diastereomeric ratio of 55 : 45. The diastereomers were separated by column chromatography.

Resolution of 2-fluorocyclopentanols. Previously, chiral *cis*-2-fluorocyclopentanols **4** were not obtained, although the racemic isomers of 2-fluorocyclopentanols, as well as 2-fluorocyclopentanols, were described as the mixtures of *cis*- and *trans*- isomers [8, 9].

For the resolution of racemic 2-fluorohydrins **4**, we used several highly effective lipases, which were earlier used and showed the high effectivity on a number of transesterification reactions in organic solvents. Vinyl acetate or isopropylidene acetate were used as acylating agents. We have tested *Candida Antarctica* (CAL-B), *Pseudomonas cepacia* (PCL), and *Burholderia cepacia* (BCL) lipases as biocatalysts. The best results (the highest *ee*) were obtained with BCL, and, therefore, we chose this lipase. The enzymatic esterification with vinyl acetate in the presence of BCL resulted in the resolution of racemic *cis*-fluoro-cyclopentanols into enantiomerically pure, optically active stereoisomers. The esterification was performed at room temperature until the conversion attained 50 %. In all cases, the high enantiomeric excesses (*ee*'s) were obtained.

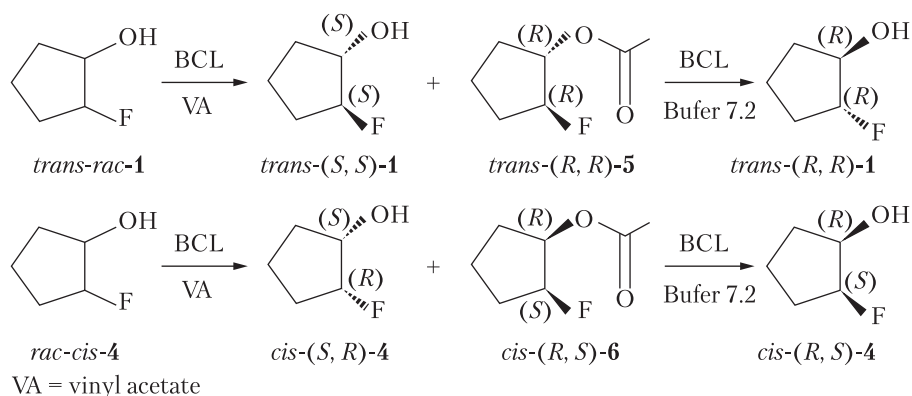
After the column chromatography, optically active alcohols and acetates were obtained with an optical purity of 98–99 % *ee*. Acetates **5** were hydrolyzed in a phosphate buffer at pH 7.2 in the presence of PCL lipase. As a result of hydrolysis, optically pure acetates **5** were obtained in contrast to the unreacted alcohols of the opposite configuration.

Transesterification with vinyl acetate proceeded for 6–12 h until the 50 % conversion into acetates **5**, **6**. One of the enantiomers in the racemic mixture reacted and turned into acetate, and the second enantiomer did not react with vinyl acetate. The optical purity of the acylated products was determined by the derivatization with (*R*)- or (*S*)-methoxy-trifluoromethylphenylacetic acid (Mosher's acid) according to the established protocol. For (*S*)-acetate, the achievement of 50 % conversion by the enzymatic acylation was established by analyzing the ¹H NMR spectra of the enzymatic separation esters. As a result of the enzymatic resolution and subsequent chromatography, optically active (–)-(1*R*, 2*S*)-fluorocyclopentanols and (–)-(1*R*, 2*R*)-acetates with an optical purity of 98–99 % were obtained.

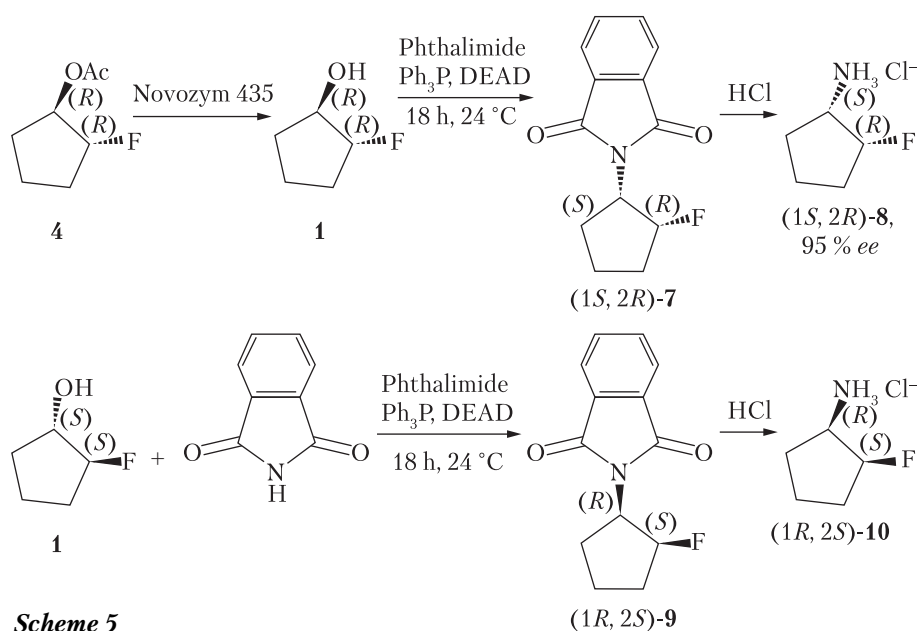
The acetates were purified by the distillation *in vacuo* and then hydrolyzed in a phosphate buffer at pH 7.2 in the presence of BCL. As a result of the hydrolysis, optically pure (+)-(1*R*, 2*S*) and (–)-(1*R*, 2*R*)-fluorocyclopentanols were obtained. The additional low-temperature crystallization of fluorocyclopentanols **4** in pentane allowed the preparation of optically pure alcohols (+)-(1*R*, 2*S*)-**4** and (–)-(1*R*, 2*R*)-**4**, which was established by the derivatization of the compounds with Mosher's acid. Similarly, the acylation of racemic *trans*-cyclopentanol with vinyl acetate in the presence of BCL under kinetically controlled conditions (50 % conversion of the α-fluorocyclopentanol) led to the formation of (–)-(1*R*, 2*S*)-alcohol and (+)-(1*R*, 2*R*)-acetate, which were purified by chromatography. The hydrolysis of (+)-(1*R*, 2*R*) acetate **5** in a phosphate buffer at pH 7.2 gave the second stereoisomer of *trans*-cyclopentanol (+)-(1*R*, 2*R*)-**1** with high optical purity. Optically pure 2-fluorocyclopentanols are colorless low-melting substances that are stable at room temperature or in the refrigerator. No racemization during the processing and storage was observed. The structure of the compounds was confirmed by spectroscopic studies. The NMR spectra allow us to easily identify the *cis*- and *trans*-isomers. For example, in the ¹H NMR spectra of *cis*-isomers, the signal of CHX protons was displaced to the weak field (Scheme 4).

We have used fluorocyclopentanols synthesized for the synthesis of aminofluorocyclopentanes of considerable interest as key reagents in the synthesis of a number of important biologically active compounds.

Optically pure 1,2-fluorocyclopentanols were converted into 2-fluorine aminocyclopentanes by the Mitsunobu reaction. The reaction proceeded with the inversion of the absolute configuration containing a hydroxyl group at the carbon atom. For the production of aminofluoro-



Scheme 4



Scheme 5

cyclopentanes, *cis*-(1*R*,2*R*)-fluorocyclopentanol **4** was dissolved in tetrahydrofuran and triphenylphosphine and phthalimide were added to the solution. After the cooling to 0 °C, diethyl azodicarboxylate (DEAD) was added, and the reaction mixture was stirred overnight at room temperature. Upon the completion of the reaction, the solvent was evaporated. 2-((1*R*,2*S*)-2-fluorocyclopentyl)isoindoline-1,3-diones **7**, **9** were purified by column chromatography. As a result, (*S*,*R*)-phthalimide was obtained in 70 % yield. Then phthalimides **7**, **9** were hydrolyzed with 6*N* hydrochloric acid to result in hydrochloride (*S*,*R*)-cyclopentylfluoramine **8** and hydrochloride (*R*,*S*)-cyclopentylfluoramine **10**. The optical purity was controlled by Mosher's acid derivatization method [10].

The products **7**, **9** were then treated with hydrochloric acid to form aminofluorocyclopentane hydrochlorides **8**, **10**. As a result, *trans*-1,2-fluorocyclopentanol **1** was converted into the *cis*-1,2-aminofluorocyclopentanes **8**, **10**. Pure products with an enantiomeric excess of 95 % were obtained (Scheme 5).

The Kazlauskas rule [11] was used to determine the absolute stereochemistry of enantiomerically pure products. The Kazlauskas rule is an empirical model based on the postulate that the enantioselectivity is proportional to the difference in size between large (L) and middle (M) substituents in the substrate. According to the Kazlauskas rule, these substituents are located in two different pockets of the active site of an enzyme, according to their size, which determines the absolute configuration of the products in the enzymatic reaction. According to the Kazlauskas rule, the biocatalytic acetylation of 2-fluorocyclopentanoles **1**, **4** should be (*R*)-selective. Consequently, the biocatalytic transesterification of cyclopentanoles should lead to the formation of (*1R*, *2S*)-acetates **5** and (*1S*, *2R*)-2-fluorocyclopentanoles **4**.

So in this work, racemic *cis*-2-fluorocyclopentanoles were resolved into enantiomers by the kinetically controlled biocatalytic transesterification with vinyl acetate in the presence of *Burkholderia cepacia* lipase in organic media. The high enantioselectivity (*ee* > 98 %) and good yields of compounds were obtained for all substrates. Fluorocyclopentanoles were converted into enantiomerically pure 1,2-aminofluorocyclopentanes using the Mitsunobu reaction. The enantiomeric purity of the compounds was determined by Mosher's acid derivatization method, and the absolute configurations were determined using the Kazlauskas rule [12, 13].

Experimental Part. ^1H NMR and ^{13}C NMR spectra were recorded in a CDCl_3 solvent on a 500 MHz spectrometer at ambient temperature. The chemical shifts (δ) are given in ppm with respect to TMS as the internal standard. Signals: s, singlet; d, doublet; dd, doublet of doublet; td, triplet of doublets; t, triplet; m, multiplet; br s, broad singlet. The constants of connection *J* are given in Hertz. All reagents and solvents were purchased from commercial firms and used without special purification, unless otherwise specified. Column chromatography was performed on silica gel 60 (70–230 mesh) using the indicated eluents. Optical rotations were measured on the Perkin-Elmer 241 polarimeter (sodium D line at 20 °C). Melting points are not corrected. All reactions were carried out in a carefully dried glass dish. Lipase isolated from *Burkholderia cepacia* (Amano PS) was purchased from Amano Pharmaceutical (Japan). Progression of the reactions and separation of the products by column chromatography were monitored by analytical thin layer chromatography (silica gel 60 F254-plate-Merck, Darmstadt, Germany), and the products were visualized with anisaldehyde. The purity of all compounds was verified using NMR measurements.

Rac-trans-2-fluorocyclopentanol (**1**). To 6.00 ml (5.78 g, 0.069 moles) of cyclopenten oxide in 70 ml of 1.0 M triethylamine trihydrofluoride, we added 20 ml of poly(hydrogen fluoride) pyridinium slowly via a polypropylene syringe, at 0 °C at the magnetic stirring. The mixture was left warmed to room temperature and then stirred for 3 h. The consecutive treatment with water, diethyl ether extraction, washing with aqueous sodium hydrogen carbonate, drying with anhydrous magnesium sulfate, and concentrating on a rotary evaporator gave an oil, which was purified by the distillation in vacuo. Yield 3.65 g (50 %), bp 55–57 °C (20 mmHg).

^1H NMR (300 MHz, CDCl_3): δ_{H} 1.3–2.00 (m, 6 H), 3.25 (br s, 1 H), 4.30 (d,m, *J* 14, 1 H), 4.90 (ddt, *J* 52.0, *J* 8.4 and *J* 2.8, 1H).

^{13}C NMR (75.4 MHz, CDCl_3), δ_{C} : 19.7 (d, *J* 1.7), 29.0 (d, *J* 21.54), 31.2 (d, *J* 1.7), 77.0 (d, *J* 27.2), 98.9 (d, *J* 177).

NMR ^{19}F , δ_{F} -185 ppm.

Found, %: C 57.35; H 8.78, $\text{C}_5\text{H}_9\text{FO}$, Calculated, %: C 57.68; H 8.71.

Rac-2-fluorocyclopentanone (3). 3.6 ml (50 mmol) of DMSO in 10 ml of methylene chloride at $-70\text{ }^{\circ}\text{C}$ was added dropwise to a solution of oxalyl chloride (2.9 g, 23 mmol) in 40 ml of methylene chloride. *Trans-2-fluorocyclopentanol (20 mmol)* was added at the same temperature, and the reaction mixture was stirred for 20 min. The temperature was then raised to $-55\text{ }^{\circ}\text{C}$, and 16 ml of triethylamine was added. The reaction mixture was stirred for 20 min, warmed to $0\text{ }^{\circ}\text{C}$, and poured into a 1 M aqueous solution of hydrochloric acid. The aqueous phase was separated and extracted with methylene chloride, the combined extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was distilled off at the atmospheric pressure with an effective column.

Synthesis of rac-cis-fluorocyclopentanols (4). To fluorocyclopentanone **3** (10 mmol) in 50 ml of methanol, we added sodium borohydride (0.12 mol) at $0\text{ }^{\circ}\text{C}$, and the reaction mixture was stirred for 2 h at room temperature. Next, NH_4Cl (11 mmol) was added and the reaction mixture was stirred for 0.5 h, filtered off, evaporated under reduced pressure, and the residue was extracted with methylene chloride. The extract was then dried over Na_2SO_4 . The solvent was removed under reduced pressure and the residue was distilled under vacuum. The yield 70 %, bp $55\text{ }^{\circ}\text{C}$ (15 mm Hg).

^1H NMR (500 MHz, CDCl_3): δ 1.25–1.35 (m, 2H, CH_2), 1.5–1.70 (m, 5H, CH_2CH_2), 2.0–2.1 (m, 1H, CH_2), 2.4 (br, 1 H), OH), 3.78 (d, 1H, $J = 5$, CHOH), 4.69 (dd, $J_{\text{H,F}} = 40\text{ Hz}$, $J = 3\text{ Hz}$, 1H, CHF).

^{13}C NMR (125.74 MHz, CDCl_3): 20.90 c, 22.00 c, 28.50 c, 30.10 c, 70.0 c, 92.87.

Chiral-1,2-fluorocyclopentanols. (*1R, 2R*)-2-Fluorocyclopentanol-1 (*1R, 2R*)-**1**. Racemic alcohol **1** (10 mmol) was dissolved in MTBE, vinyl acetate (30 mmol) was added as an acylating agent. Then the Amano PS (0.1 eq) was added, and the reaction mixture was stirred overnight at room temperature. The course of the reaction was monitored by NMR. When the reaction was completed, the lipase was filtered off, and the solvent was evaporated. The residue (mixture of cyclopentanol and acetate) was separated by column chromatography. Optical purity was controlled by Mosher's acid derivatization.

(*1R,2R*)-2-Fluorocyclopentyl acetate **5**: Yield 45 %.

(*1S, 2S*)-2-Fluorocyclopentanol-1 **1**, Yield 45 %, $[\alpha]_{\text{D}}^{20} = +12$ (CHCl_3).

(*1S,2S*)-Fluorocyclopentane-1-ol (*1S, 2S*)-**1**. Racemic alcohol obtained in the previous step (1 eq) was dissolved in MTBE and vinyl acetate (3 eq) as an acylating agent and Amano PS lipase (0.1 eq) as a biocatalyst were added. The reaction mixture was stirred at room temperature for 12–14 h. The reaction was monitored by NMR. When the reaction was completed, the lipase was filtered off, and the solvent was evaporated. The residue (mixture of alcohol and acetate) was separated by column chromatography. Optical purity of the product was established by the Mosher acid derivatization.

(*1S,2S*)-Fluorocyclopentanol: Yield 45 %, $[\alpha]_{\text{D}}^{20} = +11$ (CHCl_3).

(*1R,2R*)-2-Fluorocyclopentyl acetate: Yield 45 %.

(*1R,2R*)-2-Fluorocyclopentyl acetate (10 mmol) was dissolved in MTBE, phosphate buffer (0.05 M, pH = 7.2). Novozyme 435 (0.2 eq) was added, and the reaction mixture was stirred at room temperature for 14 h. The course of the reaction was monitored by NMR. When the reaction was completed, the lipase was filtered off. The organic phase was separated from the water phase. The water phase was extracted 2 times with MTBE. The combined organic extracts

were dried over sodium sulfate and evaporated. Optical purity was determined by the Mosher acid derivatization, The yield of (*R, R*)-alcohol was 95 %, $[\alpha]_D^{20} = -5.5$ (CHCl_3).

(*1S, 2S*)-2-Fluorocyclopentanol, $[\alpha]_D^{22} = +10.3$ (CHCl_3 , $c = 1.1$). Spectral data correspond to the literature data [6].

((*1R, 2S*)-2-Fluorocyclopentyl) isoindolyl-1,3-dione. (*1R, 2R*)-Fluorocyclopentan-1-ol (0.02 mol) was dissolved in absolute THF. Triphenylphosphine (0.024 mol) and phthalimide (0.02 mol) were added to the solution. Then the DEAD was added to the reaction mixture at the cooling with an ice-water bath, and the mixture was stirred overnight at room temperature. When the reaction was completed, the solvent was evaporated, and the residue was purified by column chromatography, The yield of (*S, R*)-phthalimide is 70 %.

$^1\text{H NMR}$ (500 MHz, CDCl_3): δ_{H} 1.75 (m, 2H, CH_2), 1.90 (m, 2H, CH_2CH_2), 2.6–2.8 (m, 2H, CH_2), 4.5 (d,m, 1H, $J = 5$, CHOH), 5.2 (d,m, $J_{\text{H,F}} = 50$ Hz, 1H, CHF), 7.83; 7.91 (C_6H_4).

(*1R,2S*)-1-Amino-2-fluorocyclopentane. ((*1R,2S*)-2-Fluorocyclopentyl) isoindolyl-1,3-dione was dissolved in 6N hydrochloric acid and refluxed for 5 h. When the reaction was completed, the precipitate (phthalic acid) was filtered off. The solvent was evaporated. In the residue, pure (*1S,2R*)-fluorocyclopentylphenamine hydrochloride was found. The optical purity of the product was determined by Mosher's acid derivatization. Yield of 90 %, $ee = 95$ %, $[\alpha]_D^{20} = -9.98$ ($C = 0.1$, Ethanol). Optical purity was controlled by Mosher's acid derivatization method.

$^1\text{H NMR}$ ($\text{DMSO}-d_6$), δ , ppm, (J , Hz): δ_{H} 1.9 m (2H, CH_2); 1.95 m (2H, CH_2); 2.3 m (2H, CH_2); 3.2 m (2H, CH_2); 4.5 m (CHNH_2 , 1H); 5.0 d ($J_{\text{HF}} = 55$, CHF); 6.78 c (2H, NH_3^+).

$^{13}\text{C NMR}$ (125.74 MHz, CDCl_3): δ_{C} : 19.90 c, 28.00 c, 30.50 c, 31.10 c, 77.0 d J 28, 98.0 d J 180 (C-F).

$^{19}\text{F NMR}$, δ_{F} -190 ppm.

Found, %: C 43.45; H 8.21. $\text{C}_5\text{H}_{11}\text{ClFN}$. Calculated, %: C, 43.02; H, 7.94.

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ФЕРМЕНТАТИВНИЙ СИНТЕЗ ЕНАНТИОМЕРНО ЧИСТИХ 1,2-ФТОРЦИКЛОАЛКАНОЛІВ І 1,2-АМІНОФТОРЦИКЛОАЛКАНІВ

Віцинальні фтороциклопентаноли є цінними хіральними синтетичними блоками для отримання ряду природних і синтетичних біологічно активних речовин. Ці сполуки використовують у синтезі різних біологічно активних сполук, зокрема простагландинів і прекурсорів лейкотрієнів. Для поділу рацемічних 2-фторгідринів були використані кілька високоефективних ліпаз, які в попередніх дослідженнях показали високу ефективність на багатьох реакціях переестерифікації в органічних розчинниках. Вінілацетат або ізопропіліден ацетат використовували як ацетилюючі агенти. Рацемічні *цис*-2-фторциклоалканоли були розділені на енантіомери в результаті кінетично контрольованої переестерифікації вінілацетату в присутності біокатализаторів. Високу енантіоселективність ($ee > 98\%$) і хороший вихід отримано для всіх субстратів з використанням ліпази *Burkholderia cepacia*. Фторциклоалканоли перетворили в енантіомерно чисті 1,2-амінофторциклоалкани з використанням реакції Міцунобу. Реакція відбувалася з інверсією абсолютної конфігурації на атомі вуглецю, що містить гідроксильну групу. Енантіомерну чистоту сполук визначено методом дериватизації кислотою Мошера, а абсолютну конфігурацію встановлено за методом Казлаускаса. Згідно з правилом Казлаускаса, біокаталітичне ацетилювання 2-фторциклопентанолів повинно бути (*R*)-селективним. Таким чином, енантіоселективність на рівні $ee > 98\%$ і вихід на рівні 90% отримано для всіх субстратів.

Ключові слова: стереохімія, біокатализ, ліпаза *Burkholderia cepacia*, фторциклоалканоли, амінофторциклоалкани, правило Казлаускаса.

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ФЕРМЕНТАТИВНИЙ СИНТЕЗ ЕНАНТИОМЕРНО ЧИСТИХ 1,2-ФТОРЦИКЛОАЛКАНОЛОВ И 1,2-АМІНОФТОРЦИКЛОАЛКАНОВ

Видинальные фтороциклопентаноли являются ценными хиральными синтетическими блоками для получения ряда природных и синтетических биологически активных веществ. Эти соединения используются в синтезе различных биологически активных соединений, в частности простагландинов и прекур-

соров лейкотриенов. Для разделения рацемических 2-фторгидринов были использованы несколько высокоэффективных липаз, которые в предыдущих исследованиях показали высокую эффективность на многих реакциях переэтерификации в органических растворителях. Винацетат или изопропилиден ацетат использовали в качестве ацилирующих агентов. Рацемические *цис*-2-фторциклоалканола были разделены на энантиомеры в результате кинетически контролируемой переэтерификации винацетатом в присутствии биокатализаторов. Высокая энантиоселективность ($ee > 98\%$) и хороший выход получены для всех субстратов с использованием липазы *Burkholderia cepacia*. Фторциклоалканола превратили в энантиомерно чистые 1,2-аминофторциклоалканы с использованием реакции Мицунобу. Реакция протекала с инверсией абсолютной конфигурации на атоме углерода, содержащего гидроксильную группу. Энантиомерная чистота соединений определена методом дериватизации кислотой Мошера, а абсолютная конфигурация установлена по методу Казлаускаса. Согласно правилу Казлаускаса, биокаталитическое ацетилирование 2-фторциклопентанолов 1,4 должно быть (*R*)-селективным. Таким образом, энантиоселективность на уровне $ee > 98\%$ и выход соединений на уровне 90 % получены для всех субстратов.

Ключевые слова: стереохимия, биокатализ, липаза *Burkholderia cepacia*, фторциклоалканола, аминофторциклоалканы, правило Казлаускаса.