A Platinum Open Access Journal for Organic Chemistry

Paper

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Synthesis of optically active vicinal fluorocyclopentanols and fluorocyclopentanamines by enzymatic deracemization

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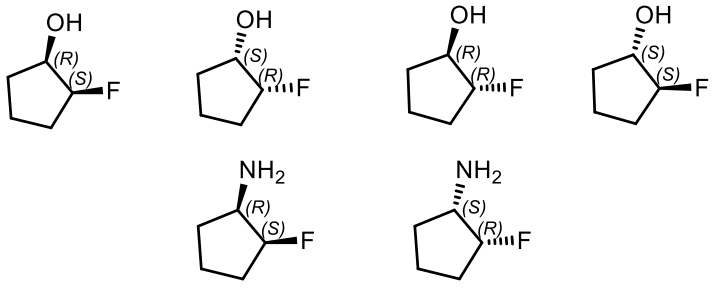
to Professor Gyorgy Keglevich on the occasion of his 65th birthday

Received 09-07-2021 **Accepted Manuscript** 10-28-2021 **Published on line** 11-24-2021

Abstract

All possible stereoisomers of *cis*- and *trans*-2-fluorocyclopentan-1-ols were obtained by kinetically controlled deracemization in the presence of lipases in organic media. High enantioselectivities and good yields of stereomers were obtained for all substrates. Optically pure 1,2-fluorocyclopentan-1-ols were converted to 2-fluoro-cyclopentan-1-amines using the Mitsunobu reaction. The absolute configurations were determined using the Kazlauskas rule and chemical correlation. The interaction of substrates with enzymes has considered using Koshland induced fit theory.



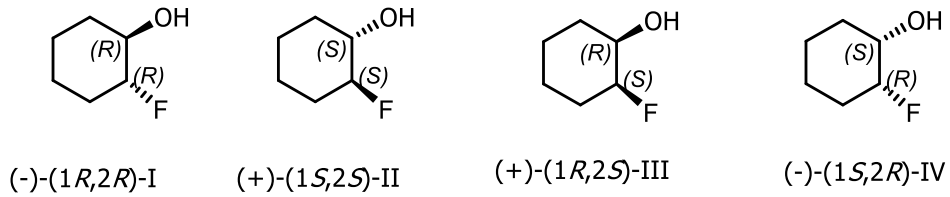
Keywords: Chiral 2-fluorocyclopentan-1-ols, 2-fluorocyclopentan-1-amines, enzymatic deracemisation, Mitsunobu reaction, Koshland induced fit theory

Introduction

The synthesis of fluorinated biologically active compounds of high enantiomeric purity (*ee*> 95%) has attracted much attention in recent years due to fluorine's ability to increase drugs' lipophilicity, selectivity and duration of action.[1] However, few methods are known for the synthesis of fluorine-containing compounds of high optical purity. For example, asymmetric metal complex catalysis only in some cases allows the achievement a high level of stereoselectivity in the preparation of chiral organofluorine compounds. Biocatalysis gives the best results. Optically active organofluorine compounds were obtained by such methods as yeast reduction of fluorinated ketones, hydrogenation of activated olefinic double bonds, and deracemization or desymmetrization of fluorinated compounds.[2-5]

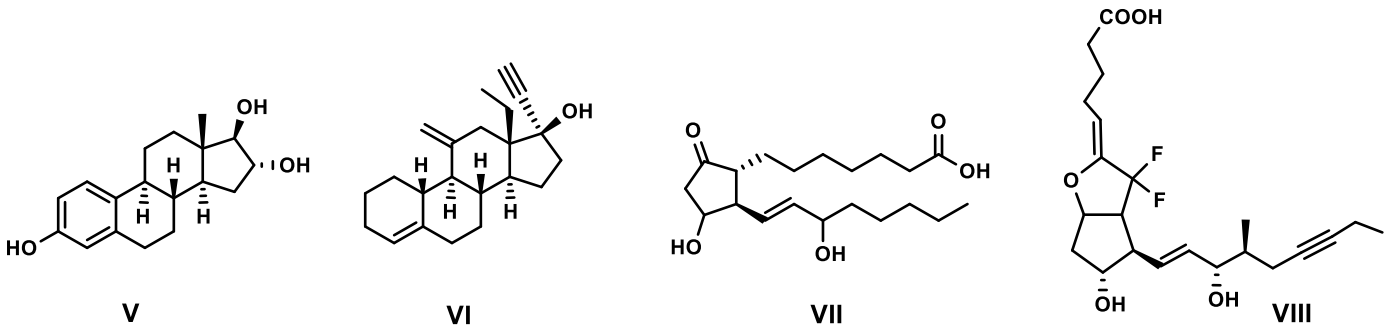
Vicinal halocyclopentanols are synthetic blocks for a number of chiral natural and synthetic products. These compounds are used to prepare various biologically active compounds, in particular, prostaglandins and precursors of leukotrienes.[6-10]

We have previously synthesized all possible stereoisomers of *cis*-halocyclohexanols (Hlg = I, Br, Cl, F) using the kinetic enzymatic resolution of corresponding racemates (Scheme 1). Haufe et al.[3] and Hashimoto et al.[4] described the enzymatic deracemization of *trans*-2-fluorocyclohexane-1-ols, 2-fluorocycloheptan-1-ols, and 2-fluorocyclooctan-1-ols using *Pseudomonas Fluorescence* lipase.



Scheme 1. Chiral 2-fluorocyclohexan-1-ols.

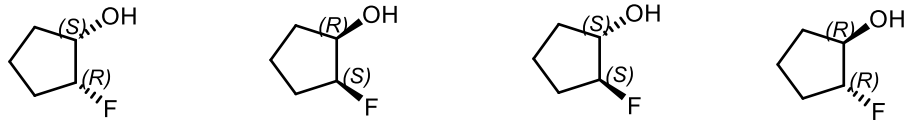
In connection with our studies of the influence of stereochemistry and fluorine atoms on the biological activity of compounds, we have synthesized all four optically pure *cis*- and *trans*-stereoisomers of 2-fluorocyclopentan-1-ols. These compounds are in demand as synthetic blocks for the preparation of many important biologically active products. For example, 2-substituted cyclopentanols can be converted into conformationally limited leukotriene antagonists, which can then be used in the enantioselective synthesis of (+)-Estron, Estriol, Desogestrel, Eicosanoids (V-VIII), and others (Scheme 2).[1]



Scheme 2. Natural compounds containing a cyclopentane ring.

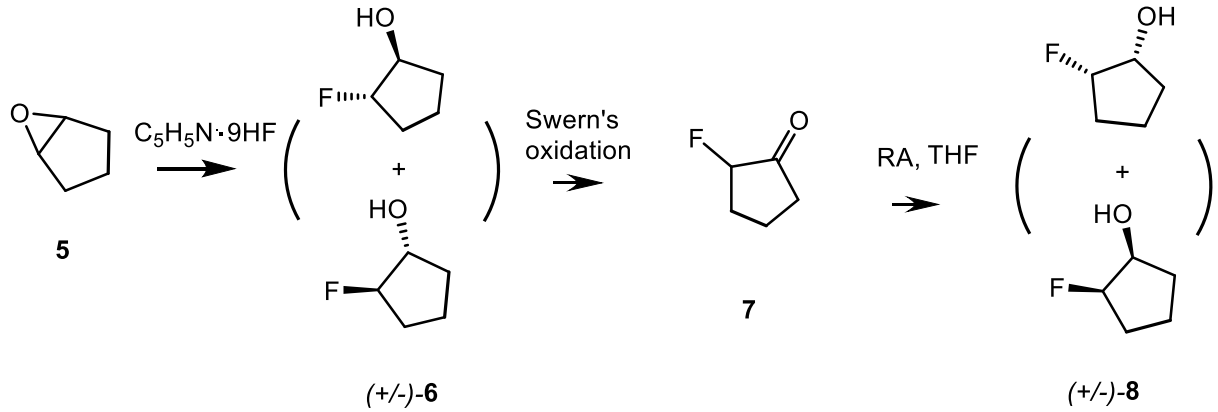
Results and Discussion

Stereoisomers of 2-fluorocyclopentan-1-ols are rarely studied compounds. Chiral stereoisomers of 2-fluorocyclopentan-1-ols (1*S*,2*R*)-**1,** (1*R*,2*S*)-**2**, and (1*R*,2*R*)-**4** have not been previously described and their stereochemical properties have not been studied. Only 2-fluorocyclopentan-1-ol (1*S*,2*S*)-**3** was obtained by Kalow and Doyle[2,11] with moderate stereoselectivity by asymmetric cleavage of mesomeric cyclopentene oxide with fluorine anions in the presence of chiral salen(Co) complexes. In this work, we report on an enzymatic approach to the preparation of enantiomerically pure stereoisomers of 2-fluorocyclopentan-1-ols (Scheme 3).



Scheme 3. Chiral 2-fluorocyclopentan-1-ols.

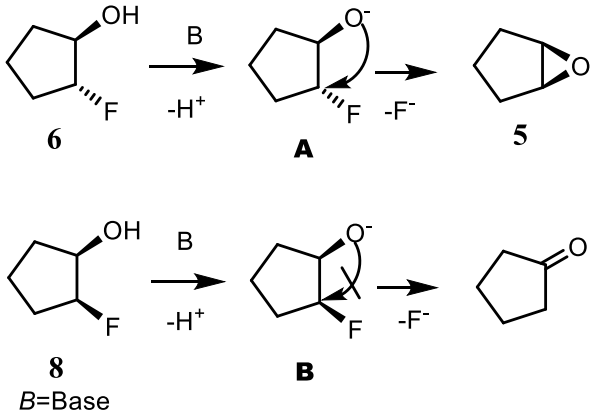
Racemic *trans*-2-fluorocyclopentan-1-ol (+/-)-**6** was synthesized from epoxides by opening the three-membered ring with hydrofluorinating agents (Scheme 4). Reactions with pure HF or HF in combination with bases such as tetrahydrofuran or pyridine are sometimes accompanied by rearrangements; however, such competing processes were not observed with less acidic but more nucleophilic reagents such as trimethylamine trishydrofluoride (Et_3N•3HF) or pyridinium poly(hydrogenfluoride) (C5H5N•9HF).[3] For the preparation of the desired fluorohydrins we have treated epoxide **5** with C_5H_5N•9HF. As a result, the racemic trans-2-fluorocyclopentanols (+/-)-**6** were obtained. Unlike racemates of *trans*-fluorocyclopentan-1-ol (+/-)-**6**, racemic *cis*-fluorocyclopentan-1-ol (+/-)-**8** was obtained with an admixture of the *trans*-isomer. To obtain pure *cis*-2-fluorocyclopentan-1-ols, we used the preparative method developed earlier by us (Scheme 4).[12]



Scheme 4. Synthesis of racemic *cis*- and *trans*-2-fluorocyclopentan-1-ols.

For this purpose, racemic *trans*-2-fluoro-substituted cyclopentanol (+/-)-**6** was underwent to Swern oxidation with the formation of 2-fluorocyclopentanone **7** in good yields. Ketone **7** was reduced with various reducing reagents, that led to the formation of *cis*-2-fluorocyclopentan-1-ol with an admixture of trans-isomers.

The best results were obtained with K-Selectride [(i-Bu_3BH)K], which gave a mixture of *cis*- and *trans*-isomers in a ratio of 75:25, reduction with sodium borohydride in methanol gave a ratio of 70:30, and the reduction with i-Bu_2AlH (H-DIBAL) resulted in a 55:45 ratio. Subsequent treatment of a mixture of *cis*- and *trans*-2-fluorocyclopentanols with base (DBU and others) proceeded with the preferential hydrolysis of the *trans*-isomer, that leads to the enrichment of mixture with the unreacted *cis*-isomer (Table 1). As a result, after additional low-temperature recrystallization in pentane or hexane, a pure *cis* isomer can be obtained. (Table 1). The reductions of 2-substituted fluoropentanones depended on the conformational equilibrium of the axial and equatorial forms: equatorial attack of the nucleophile leads to the formation of trans-alcohols while the axial attack provides the *cis*-alcohols. The *cis*-isomers of 2-halogencycloalkan-1-ols are more stable toward base-mediated HX-elimination than the *trans*-isomers. Unlike *trans*-isomers (+/-)-**6**, which upon alkali treatment easily convert into epoxide **5**, *cis*-isomers (+/-)-**8** with excess DBU converted into cyclopentanone. The *cis* orientation of the oxygen and halogen atoms is unavailable for intramolecular S_N2 reaction with the formation of the epoxide, because nucleophile cannot attack the stereocentre from the front side. In this case, an alternative anti-conformation **B** (*via* ring flip) is available for rearrangement *via* hydride migration and the cyclohexanone formation (Scheme 5).[12]



Scheme 5. Base-mediated reaction of *cis*- and *trans*-fluorocyclopentan-1-ols.

Table 1. Preparation of racemic *cis*-2-fluorocyclopentanols (+/-)-**8**

Compound	Reductant/solvent	Yields (%)[a)]	Yields (%)[b)]	*cis*/*trans*
7	$NaBH_4$/MeOH	70	38	70:30
7	[i-Bu_3BH]K/THF	50	33	75:25
7	i-Bu_2AlH/toluene	50	-	55:45

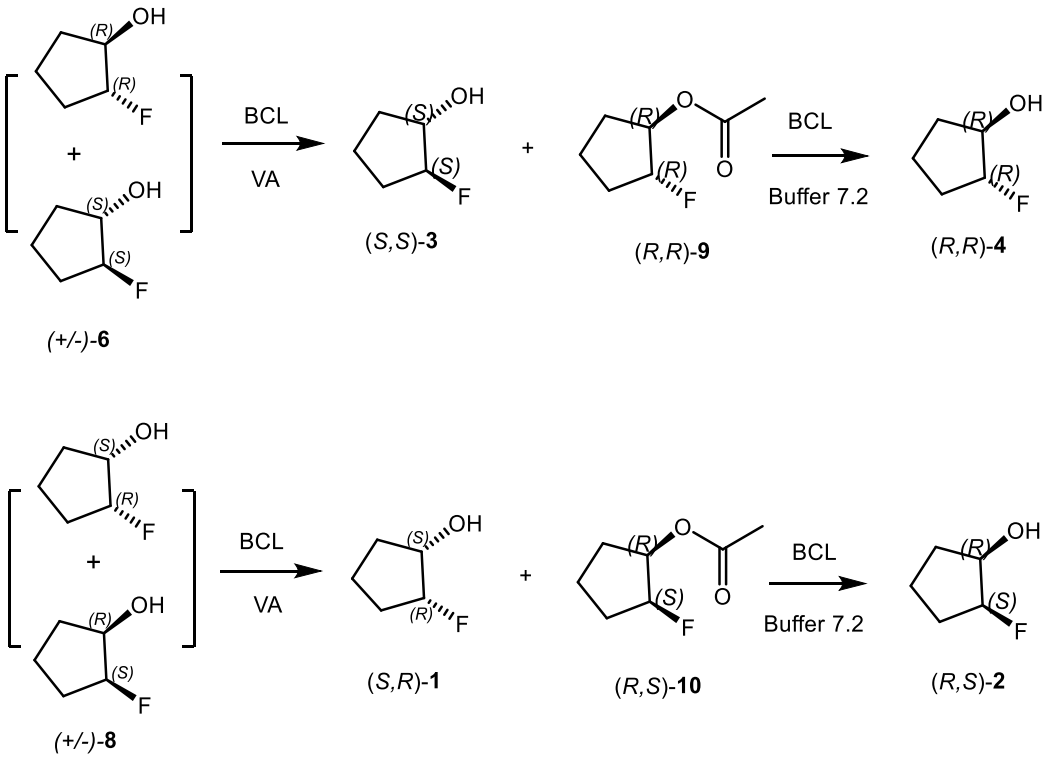
[a] Yields for the mixture of the *cis*- and *trans*-isomers.

[b] Yields for the purified *cis*-isomer (+/-)-**8**.

To deracemize 2-fluorocyclopentanols and obtain enantiomerically pure compounds, we used several lipases with well-known biocatalytic activity in organic solvents using vinyl acetate or isopropenylidene acetate as an acylating reagent. We tested *Candida antarctica* (CAL-B), *Pseudomonas cepacia* (PCL) and *Burkholderia cepacia* (BCL). The best results (highest *ee*) were obtained with BCL; therefore, this lipase was used. Enzymatic esterification in the presence of BCL immobilized on diatomaceous earth allowed separation of the racemic

fluorocyclopentanols into enantiomerically pure optically active stereoisomers. The esterification was carried out at room temperature and stopped at 50% conversion to acetate, which was achieved by filtration of the biocatalyst from the reaction mixture. In all cases, the products were obtained with very good enantiomeric excesses (*ee*).

The acylation of 2-fluorocyclopentanols (+/-)-**6** biocatalyzed by BCL proceeded with the highest enantioselectivity to provide (1*R*,2*R*)-**4** with 96% *ee* (Scheme 6). Acylation in the presence of the CALB biocatalyst proceeded faster, then with BCL, but the enantioselectivity of reaction was lower. In turn, the transesterification of the corresponding fluorocyclopentanols with vinyl acetate proceeded faster than with propenyl acetate. However, the enantioselectivity in this case was also slightly lower. Usually, esterification with vinyl acetate proceeds relatively slowly and within 15–18 hours leads to a 50% conversion of (+/-)-**6** to acetate (*R,R*)-**9**.



Scheme 6. Enzymatic deracemization of 2-*cis*- and *trans*-fluorocyclopentanols **6,8.**

The esterification process was monitored by ^{1}H NMR spectroscopy, evaluating the change in the intensity of the CHOAc (5.3 ppm) and CHOH (4.4 ppm) signals until they reached a 50:50 ratio. The enantiomeric purity of the products of enzymatic resolution was determined by derivatization of alcohols **1,2** with (*S*)-α-methoxy-α-trifluoromethylphenylacetic acid chloride [(*S*)-MTPA-Cl] proceeding with the formation of Mosher esters in accordance with the established protocol. Mosher esters were analyzed by ^{19}F NMR spectroscopy of each isolated stereoisomer of 2-fluorocyclopentan-1-ols. In the case of *cis*-2-fluorocyclopentan-1-ols, after separation by column chromatography, the optically active alcohols (+)-(1*S*,2*R*)-**7** and acetates (-)-(1*R*,2*S*)-**9** were obtained with an enantiomeric excess (*ee*) of 96–98% and enantioselectivity > 100.

Similarly, acylation of racemic *trans*-cyclopentanol with vinyl acetate in the presence of BCL under kinetically controlled conditions (50% conversion of the starting alcohol) led to the formation of alcohols (1*R*,2*S*)-**2** and acetates (1*R*,2*R*)-**9** that were isolated by column chromatography. Hydrolysis of (1*R*,2*R*)-**9** acetates in phosphate

buffer at pH 7.2 gave the second stereoisomer of (1*R*, 2*R*)-fluorocyclopentanol with high enantiomeric and diastereomeric purity.

Hydrolysis of the obtained acetates **9, 10** with BCL lipase in phosphate buffer at pH 7.2 led to the formation of the second stereoisomer of alcohols **2, 4** with high enantiomeric purity (98-99% *ee*). Acetates **9, 10** were also hydrolyzed with K_2CO_3 in methanol to afford the hydrolyzed alcohols **2, 4** with the same *ee* and yields (Table 2). Additional low-temperature (-20 ^{0}C) crystallization of alcohols in pentane made it possible to obtain enantiomerically pure alcohols (1*R*, 2*S*)-**2** and (1*R*, 2*R*)-**4** with *de* and *ee* >97-98%, that was determined by derivatization of the compounds with Mosher's acid. Enantiomerically pure 2-fluorocyclopentan-2-ols are colorless low-melting compounds or liquids that are stable at room temperature or in a refrigerator. No racemization was observed during operation with 2-fluorocyclopentan-1-ols or during storage.

Table 2. Enzymatic resolution of 2-fluorocyclopentan-1-ols **1-4** by *Burkholderia cepacia* lipase-catalyzed esterification using vinyl acetate as acyl donor

Entry	Conversion (%)[c]	τ (h)	Yield (%)	*ee*[b,c] (%)	$[\alpha]_D^{20}$ (EtOH)[d]	Configuration	E[a]
				Unreacted alcohol			
1	50	16	45	99	-20	(1*S*,2*R*)-**1**	>100
2	50	17	40	97	+25	(1*S*,2*S*)-**3**	>100
				Recovered alcohol			
3	50	16	40	99	+18	(1*R*,2*S*)-**2**	>100
4	50	17	40	98	-20	(1*R*,2*R*)-**4**	>100

[a] Calculated by the acylated conversion and% *ee* of the product. E = ln[1c(1 + ee_p)]/ln[(1c)(1ee_p)], where p = product.

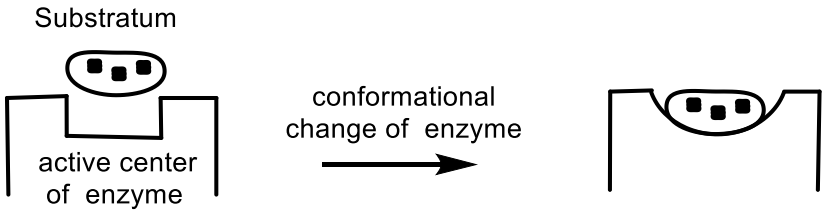
[b] Determined from the ^{19}F NMR spectra of the respective MTPA esters.

[c] Obtained from the NMR spectra of the MTPA esters of the recovered alcohols.

[d] $[\alpha]_D$ and *ee* were defined for isolated and purified products.

The nature of the solvents used had no significant effect on the enantioselectivity of the kinetic resolution. However, diisopropyl ether (DIPE) and methyl-tert-butyl ether (MTBE) or solvent-free vinyl acetate showed the highest *ee*, while the reaction proceeded faster in cyclohexane. In the case of *trans*-2-fluorocyclopentanol **(+/-)-6**, the reaction in the above-mentioned solvents took much longer and the enantioselectivity was slightly lower. The rate of acylation of 2-fluorocyclopentanols with vinyl acetate and PCL in DIPE was slightly higher compared to the corresponding reactions with isopropenylidene acetate. In all cases, (*R*)-selectivity was observed in accordance with the Kazlauskas' rule. Better solubility of most substrates in organic solvents and easy separation of immobilized lipases promote reactions in organic media. In accordance with the theory of Koshland ("induced fit model"), it is implied the flexibility of the active site of the deracemization reaction. The attachment of the substrate to the active center of the enzyme causes a change in the configuration of the catalytic center, as a result of which its shape matches the shape of the substrate ("hand-glove"). If this transformation contributes to better complementarity of the substrate and the active center, then this gives a gain in the reaction rate, i.e. provides a significant catalytic effect. Due to their mutual influence, when the substrate approaches the active

center of the enzyme, the structures of both reacting molecules are transformed. Thus, the polar interactions of different parts of the protein become stronger, and the enzyme becomes more rigid in conformational terms (Scheme 7).[13-15]

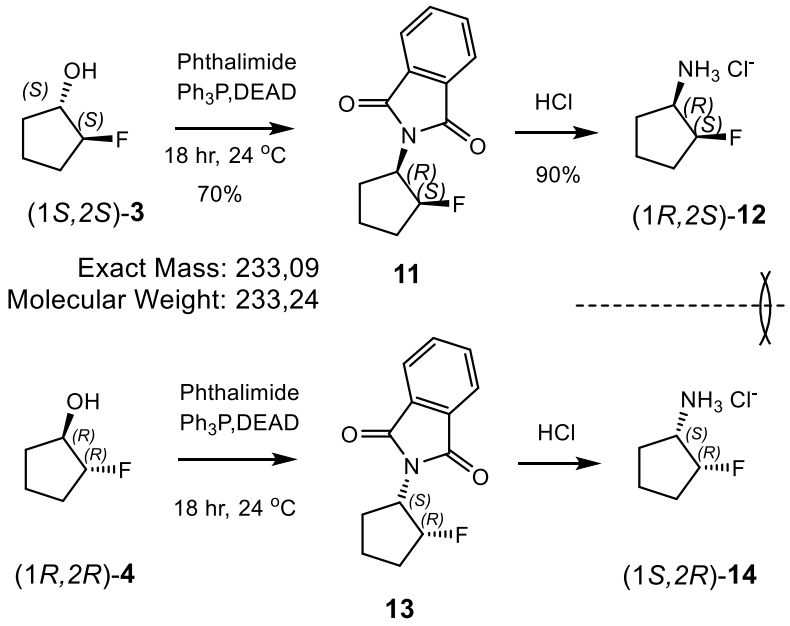


Scheme 7. Conformational change in the active centre of enzyme according to the "induced fit model".

The structure and purity of the reaction products were confirmed by physical-chemical methods. The ^{13}C NMR spectra of 2-fluorocyclopentanols show signals from all five carbon atoms split at the fluorine atom [$^{1}J_{CF}$ 177 Hz (C-F)]. In the proton resonance spectra, there are doublets of the signals of CHF and CHOH groups at 4.3 and 4.8 ppm, respectively. The signal of the fluorine atom was discovered at -185 ppm. The mass spectra contain signals of mass peaks. The purity of the compounds was confirmed by HPLC using a chiral column "Chiralcel OJ-H".

To confirm the structures and absolute configuration of 2-fluorocyclopropanols, we converted the (1*S*,2*S*)- and (1*R*,2*R*)-2-fluorocyclopentanols into enantiomers of (1*R*,2*S*)- and (1*S*,2*R*)-2-fluoro-1-aminocyclopentanols[16,17] using the Mitsunobu reaction. A solution of alcohol in THF was reacted with phthalimide in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD). The reaction proceeded with the inversion of the absolute configuration at the carbon atom containing the hydroxyl group. After the reaction was completed, the products were isolated by column chromatography **12,14**. The products were then treated with hydrochloric acid to form aminofluorocyclopentane hydrochloride. As a result, *trans*-1,2-fluorocyclopentanol was converted to *cis*-1,2-aminofluorocyclopentanes. Pure products were obtained with an enantiomeric excess of 95% *ee* (Scheme 8). 2-Fluorocyclopentyl-1-amines are of interest as intermediates for the synthesis of a number of important biologically active compounds: For example, they can be used in the synthesis of potent and selective opioid receptor-like antagonists.[15,16]

The resulting products **12,14** were separated by column chromatography. The yields of diones **11,13** and amines **12,14** were 70 and 90% correspondingly (Scheme 8).



Scheme 8. Synthesis of chiral 2-fluorocyclopentan-1-amine hydrochloride using Mitsunobu reaction.

The optical purities of the (*R,S*)- and (*S,R*)-2-fluorocyclopentan-1-amines **12, 14** were on the order of 96% determined by derivatization with Mosher's acid. The structures of amines were confirmed by NMR and mass-spectra. In the NMR spectra of the hydrochlorides the signals of NH_3^+ protons at 8.5 ppm, signals of CHF at 5.1 ppm, a doublet with $^2J_{HF}$ constant 55 Hz and CHN at 3.4 ppm, doublet, $^2J_{HF}$ 26 Hz, as well as the CH_2 protons were observed.[17]

The definition of absolute configuration. Kazlauskas rule[18] was used for determination of the absolute stereochemistry of the resolved 2-fluorocyclopentanols. According to the Kazlauskas rule, the enantioselectivity should be proportional to the size difference between the large (L) and medium-size (M) substituents in the substrate. The physical essence of the Kazlauskas rule is determined by structure of lipase active center, which has two pockets - one is larger and the other is smaller. In accordance with the structure of the active center, the orientation of the secondary alcohol occurs and the esterification/hydrolysis of the corresponding esters proceeds. According to the Kazlauskas rule, the biocatalytic acetylation of 2-fluorocyclopentan-1-ols should be (*R*)-selective, leading to the formation of (1*R*,2*S*)-acetates and (1*S*,2*R*)-unreacted alcohols in the case of the *cis*-fluorocyclopentanols and correspondingly to the formation of (1*R*,2*R*)-acetates and (1*S*,2*S*)-unreacted alcohols in case of *trans*-2-fluorocyclopentanols (Scheme 9).[19] Empirically, as shown earlier on a very large number of examples, trans-esterification of secondary alcohols in the presence of BCL, and as well as of many other lipases, always leads to the formation of (*R*)-acetate and unreacted (*S*)-alcohol. Therefore we have obtained the *cis*-(1*R*,2*S*)-**10** acetate and the *cis*-(1*S*,2*R*)-**3** alcohol, as well as *trans*-(1*R*,2*R*)-**9** acetate and *trans*-(1*S*,2*S*)-**2** alcohol. Enzymatic kinetic resolution is a fairly reliable method for the determining of absolute configuration.[20-22] In addition, we confirmed the results obtained on the basis of the Kazlauskas rule by independent synthesis of (1S, 2S) -fluorophosphonate **2** whose configuration is known.[2] The determination of absolute configuration of compound **2**, attained by two different methods was identical.

Scheme 9. Enzymatic transesterification of 2-fluorocyclopentan-1-ols according to the Kazlauskas rule.

Conclusions

Enantiomerically pure (1*R*,2*S*)-, (1*S*,2*R*)-, (1*S*,2*S*)- and (1*R*,2*R*)-2-fluorocyclopentanols were obtained by biocatalytic kinetic resolution in good yields and with high enantiomeric excesses. *Burkholderia cepacia* lipase has shown excellent enantioselectivity as a biocatalyst for the transesterification of 2-fluorocyclopentan-1-ols with vinyl acetate. The *trans*-2-fluorocyclopentan-1-ols were converted into (1*R*,2*S*)- and (1*S*,2*R*)-*cis*-2-fluorocyclopentane-1-amines using the Mitsunobu reaction. The absolute configuration of enantiomerically pure 2-fluorocyclopentan-1-ols was determined in accordance with Kazlauskas rule. In contrast to the multistage and difficult to access asymmetric metal complex synthesis of chiral 2-fluorocyclopentan-1-ols, the present methodology is simple and uses commercially available lipases.

Experimental Section

General. ^{1}H (500MHz) and ^{13}C (125 MHz) NMR spectra were recorded on Bruker Avance DRX 500 spectrometer in dimethylsulfoxide (DMSO-d_6) solution with tetramethylsilane (TMS) as an internal standard. Unless otherwise specified NMR spectra have been made in $CDCl_3$ Chemical shifts (δ) of ^{1}H and ^{13}C are reported in ppm relative to $CHCl_3$ (δ = 7.26 for ^{1}H and δ = 77.0for ^{13}C). J values are given in Hz. Proton (^{1}H) NMR information is given in the following format: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; sept; septet; m, multiplet, b, broad), coupling constant J, number of protons). Melting points were measured with a Büchi melting-point apparatus and are uncorrected. The chromatomass spectra were recorded on an Agilent 1100 Series high-performance liquid chromatograph equipped with a diode matrix with an Agilent LCnMSD SL mass selective detector, allowing fast switching of the ionization modes. The GC-MS studies were performed using an Agilent Technologies 1200 device. The HPLC was performed with Chiralcel OJ-H chiral column (250*4,6 mm, 5 mkm with Selector Celulose tris(4-methylbenzoate) coated on 5 mμ silica gel. The reaction progress was monitored by thin-layer chromatography (TLC) on silica gel $60F_{254}$ Merck and visualized under ultraviolet light (254 and 366 nm), or through spraying with 5% phosphomolybdic acid in EtOH, H_2SO_4 acidified by Anise aldehyde solution in EtOH or by placing in iodine vapor. Flash chromatography was performed with Merck silica gel 60 (230-400 mesh). Most part of the reactants were obtained from a commercially available source (Aldrich) and used without further purification. All solvents were purified by standard procedures or obtained from a Solvent Purification System (Braun SPS 800). Unless otherwise mentioned, all reactions were carried out under an atmosphere of dry argon.

***trans*-2-fluorocyclopentan-1-ol, [(+/-)-6].** To 6.00 mL (5.78 g, 0.069 moles) of cyclopenten oxide in 70 mL of 1.0 M triethylamine trihydrofluoride was added 20 mL of poly(hydrogen fluoride) pyridinium slowly via the polypropylene syringe at 0 °C at magnetic stirring. The mixture was left warmed to room temperature and then

stirred for 3 hours. The consecutive treatment with water and 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 distillation in vacuo. Yield 3.65 g (50%), bp 55-57 °C (20 mmHg). Lit. bp. 35-38 ^{0}C (15 mmHg).[24] bp. 55-57 ^{0}C (18 mmHg).[25,26]

^{1}H NMR (δ, ppm (*J*, Hz), CDC1$_3$): δ_H 1.3-2.00 (m, 6 H, CH_2); 2.0-2.1 (br.m, 1 H, OH); 4.30 (d, *J* 14, 1 H, CHOH); 4.90 (ddt, *J* 52.0, *J* 8.4 and *J* 2.8, 1H, CHF).^{13}C NMR (75.4 MHz, $CDCl_3$); δc: 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. Spectral data were in agreement with literature - reported values. [24]

cis*-2-Fluorocyclopentan-1-ol, [(+/-)-8].** *a) 2-Fluorocyclopentan-1-one* **7.* 3.6 mL (50 mmol) of DMSO in 10 mL of methylene chloride at -70 ° C was added dropwise to a solution of oxalyl chloride (2.9 g. 23 mmol) in 40 mL of methylene chloride.The *trans*-2-fluorocyclopentan-1-ol (2.1 g, 20 mmol) was added at the same temperature and the reaction mixture was stirred for 20 minutes. The temperature was then raised to −55 °C and 16 mL of triethylamine was added. The reaction mixture was stirred for 20 min., warmed to 0 °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 under atmospheric pressure with an effective column.

b) *Cis*-2-Fluorocyclopentanol was prepared from the fluorocyclopentanone **7** (1.1 g, 10 mmol) in 50 mL of methanol and sodium borohydride (3.5, 0.1 mol) at 0 °C according to general methodology earlier described by us.[12] Yield 50%, bp 55 °C (15mm Hg). Lit. bp 55-57 ^{0}C (18 mmHg).[25,26]

c) Racemic cis-2-fluorocyclopentanol can also be prepared similarly to the method developed by Basso for the reduction of 2-fluorocyclohexanone in anhydrous THF using K-selectride.[23] The product contains impurity of the *trans*-isomer as an impurity. Yield 45%, bp 55 ^{0}C/14 mm Hg.

^{1}H NMR (δ, ppm (*J*, Hz), CDC1$_3$): δ 1.25–1.35 (m, 2H, CH_2); 1.5–1.70 (m, 5H, CH_2CH_2); 2.0–2.1 (br.m, 1H, OH); 2.4 (br, 1 H, OH); 3.78 (d, 1H, *J* 5, CHOH); 4.69 (dd, J_{HF} 40 Hz. *J* 3 Hz, 1H, CHF); ^{13}C NMR (δ, ppm (*J*, Hz), $CDCl_3$):δc: 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. C_5H_9FO. Calculated, %: C 57.68; H 8.71.

(-)-(1S,2R)-**2-Fluorocyclopentane-1-ol, (1).** The racemic 2-fluorocyclopentane-1-ol (2,1 g, 20 mmol) was dissolved in MTBE and vinyl acetate (2.5 mL, 30 mml.) as the acylating agent. *Burkholderia cepacia* lipase immobilized on diatomite (0.5 g) was added as a biocatalyst. The reaction mixture was stirred at room temperature for 14-15 hours. The reaction was monitored by NMR. When the reaction passes above 50% completion, the lipase was filtered off and the solvent evaporated. The residue [a mixture of alcohol **1** (50%) and acetate **10** (50%)] was separated by column chromatography using hexane-ethyl acetate (95:5) as eluent. Acetate **10** (yield ~50%) was found in the first fraction and in the second fraction, (1*S*,2*R*)-fluorocyclopentane-1-ol (1*S*,2*R*)-**1**, yield ~50% (not purified state). The solvent was evaporated, and a colorless oil was obtained. The product was crystallized in pentane at low temperature. Yield 45%, $[\alpha]_D^{20}$=-20 (C-1, $CHCl_3$). Optical purity was determined by Mosher acid derivatization and HPLC with (Chiralcel OJ-H) chiral column.

^{1}H NMR (δ, ppm (*J*, Hz), CDC1$_3$): 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.m, 1 H, OH); 3.78 (d, 1H, *J* 5, CHOH); 4.69 (dd, J_{HF} 40 Hz, *J* 3 Hz, 1H, CHF).

^{13}C NMR (δ, ppm (*J*, Hz), CDC1$_3$): δc: 19.7; 27.0 (d, *J* 21.54); 31.0 (d, *J* 1.7); 56.0 (d, *J* 27.2); 94 (d, *J* 177);

^{19}F NMR, δ_F −180.5 ppm. Found, %: C 57.35; H 8.78. C_5H_9FO. Calculated, %: C 57.68; H 8.71.

(*+)-(1R,2S)*-**Fluorocyclopentane-1-ol, (2).** (1*R*,2*S*)-2-Fluorocyclopentyl acetate **10** (1.45 gr, 10 mmol) obtained in the precedent experiment was dissolved in MTBE, phosphate buffer (0.05 M, pH = 7.2) and Novozyme 435 lipase(0.2 molar equiv.) were added. Then the reaction mixture was stirred at room temperature for 14 hours. The course of reaction was monitored by NMR. When the reaction was completed the lipase was filtered off.

The organic phase was separated from water phase. The water phase was extracted with MTBE. The organic extracts were dried over sodium sulfate and evaporated. Optical purity was determined by Mosher acid derivatization (98% *ee*). Yield 45%. $[\alpha]_D^{20}$ = +18 (C=1, $CHCl_3$). ^{1}H NMR (δ, ppm (*J*, Hz), $CDC1_3$): δ_H 1.3-2.00 (m, 6 H, CH_2); 2.0-2.1 (br.m, 1 H, OH); 4.30 (d, *J* 14, 1 H, CHOH); 4.90 (ddt, *J* 52.0, *J* 8.5 and *J* 3.0, 1H, CHF); ^{13}C NMR (δ, ppm (*J*, Hz), $CDCl_3$): δ c: 19.7; 27.0 (d, *J* 21.54); 31.2, 57.0 (d, *J* 27.2.); 96.0 (d, *J* 177). ^{19}F NMR ($CDCl_3$); δ_F –181.95 ppm. Found, %: C 57.30; H 8.75. C_5H_9FO. Calculated, %: C 57.68; H 8.71.

m/z: 104.1 (M^+)

(+)-*(1S,2S)*- 2-Fluorocyclopentane-1-ol, (3). The racemic *trans*-2-fluorocyclopentane-1-ol (1.45 g, 10 mmol.) (+/-)-**6** was dissolved in MTBE and the vinyl acetate (3 molar equiv.) as acylating agent and *Burkholderia cepacia* lipase (0.1 molar equiv.) as biocatalyst were added. The reaction mixture was stirred at room temperature for 12-14 hours. 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 the alcohol and acetate) was separated by column chromatography. In the second fraction was found (1*S*,2*S*)-fluorocyclopentane-1-ol (1*S*,2*S*)-**3**. Yield 45%. The product was crystallized in pentane at low temperature. Yield 40%, m.p. 21 ^{0}C. $[\alpha]_D^{20}$ = +25 ($CHCl_3$); Lit. $[\alpha]^{22}_D$ = +10.3 ($CHCl_3$, C = 1.1).[2] Optical purity of the product was established by Mosher acid derivatization and confirmed by HPLC with chiral column 98% *ee*). Spectral data were in agreement with literature values.[2,11]

(-)-*(1R,2R)*-2-**Fluorocyclopentane-1-ol, (4).** (1*R*,2*R*)-2-Fluorocyclopentyl acetate **9** (10 mmol) obtained in the precedent experiment was dissolved in MTBE. Then phosphate buffer (0.05 M, pH = 7.2) and Novozyme 435[*)] (0.2 molar equiv.) was added and the reaction mixture was stirred at room temperature. 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 water phase. The water phase was extracted 2 times with MTBE. The combined organic extracts were dried over sodium sulfate and evaporated. Optical purity (98% *ee*) was determined by Mosher acid derivatization. Yield 45%. $[\alpha]_D^{20}$ = –20 (C=1, $CHCl_3$).

^{1}H NMR (δ, ppm (*J*, Hz), $CDC1_3$): δ_H 1.3-2.00 (m, 6 H, CH_2); 2.0-2.1 (br.m, 1 H, OH); 4.30 (d, *J* 12, 1 H, CHOH); 4.70 (ddt, *J* 55.0, *J* 8.5 and *J* 3.0, 1H, CHF). ^{13}C NMR (δ, ppm (*J*, Hz), $CDC1_3$): δ c: 21.7; 25.4 (d, *J* 21.54); 31.0; 50.4 (d, *J* 27.2); 95.0 (d, *J* 177). ^{19}F NMR, δ_F –181.9 ppm. Found, %: C 57.32; H 8.72. C_5H_9FO. Calculated, %: C 57.68; H 8.71. *m/z*: 104.1 (M^+).

[*)]The same yield and *ee* of **4** were obtained in the reaction with BCL instead of the Novozyme 435[*)]

(1R,2S)-**2-Fluorocyclopentyl) isoindoline -1,3-dione**, (**11)**

(1*S*,2*S*)-Fluorocyclopentan-1-ol **4** (2.1 g, 20 mmol) was dissolved in 10 mL of 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 while 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. Yield 70%. ^{1}H NMR (δ, ppm (*J*, Hz), $CDC1_3$): 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 (1H, *J* 5, CHOH); 5.2 (d, J_{HF} 50 Hz, 1H, CHF); 7.83; 7.91 (C_6H_4).

(+)-*(1R,2S)*- **2-fluorocyclopentan-1-aminium chloride, (12).**

(1*R*,2*S*)-2-Fluorocyclopentyl isoindolyl-1.3-dione **11** (2.3 g, 10 mmol)was dissolved in 6N hydrochloric acid and refluxed for 5 hours. When the reaction was completed, the precipitate (phthalic acid) was filtered off and the solvent was evaporated. Pure (1*R*,2*S*)-fluorocyclopentylphenamine hydrochloride was found in the residue. The optical purity of the product was determined by Mosher's acid derivatization. Yield 90%, 96% *ee*. $[\alpha]_D^{20}$ = +10.81 (C=0.1, Ethanol).

^{1}H NMR (δ, ppm, (*J*, Hz), DMSO-d_6): δ_H 1.6 m (2H, CH_2); 1.90 m (2H, CH_2); 2.0 m (2H, CH_2); 3.45 m (J_{HF} 26, 1H, $CHNH_2$,); 5.1 d (J_{HF} 55, CHF); 8.75 c (3H, NH_3^+); ^{13}C NMR (δ, ppm, (J, Hz), $CDCl_3$): 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}F NMR, δ_F -190 ppm.

MS-HRMS, *m/z*: 104.4 100%); 105.4 (10) (M+1).
Found, %: C 43.45; H 8.21. $C_5H_{11}ClFN$. Calculated, %: C 43.02; H 7.94.

(-)-(1*S*,2*R*)-2-Fluorocyclopentan-1-aminium chloride (14). To a solution of (1*R*,2*R*)-fluorocyclopentanol-1 (1.05 g, 10 mmol.) in dry THF, triphenylphosphine (1.2 molar equiv.), phthalimide (1,47 g, 10 mmol.) and DEAD were added while cooling in an ice-water bath. Then the reaction mixture was stirred overnight at room temperature. When the reaction was completed the solvent was evaporated and the residue was purified by column chromatography. (1*R*,2*S*)-2-Fluorocyclopentyl) isoindolyl-1,3-dione **13** was obtained in 70% yield. The product was dissolved in 6 N hydrochloric acid and refluxed for 5 hours. After the completion of the reaction, the precipitate of phthalic acid was filtered off. The mother liquor was evaporated. The residue contained the (1*S*,2*R*)-2-fluorocyclopentane-1-aminium chloride. The optical purity was monitored by HPLC with a chiral column and by derivatization with Mosher's acid.[27] Yield 90%, *ee* = 96%. $[\alpha]_D^{20}$ = -9.98 (C=0.1, Ethanol).
^{1}H NMR (DMSO-d_6), δ, ppm (*J*, Hz): δ 1.6 m (2H, CH_2); 1.85 m (2H, CH_2); 2.0 m (2H, CH_2); 3.5 d (J_{HF}26, 1H, $CHNH_2$); 5.15 d (J_{HF} 55, CHF); 8.55 s (3H, NH_3^+). ^{19}F NMR, δ_F -190 ppm.
MS-HRMS, *m/z*: 104.4 (100%); 105.4 (10) (M+1).
Found, %: C 43.42; H 8.20. $C_5H_{11}ClFN$. Calculated, %: C 43.02; H 7.94.

Supplementary Material

Copies of ^{1}H, ^{19}F and ^{13}C NMR spectra, mass spectra and HPLC, as well as the determination of optical purity by Mosher's acid derivatization, are provided in the Supplementary Material associated with this paper.

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