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RESEARCH ARTICLE

Synthesis of optically pure 3-heteroaryl-2-methylpropanoic and 3-heteroarylbutanoic acids by biocatalytic resolution

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Abstract: A new approach has been developed for synthesizing compounds with potential biological activity − enantiomerically pure 3-heteroaryl-2-methylpropanoic and 3-heteroarylbutanoic acids. The enzymatic dynamic kinetic enzymatic resolution methodology was applied at key synthesis stages. A dual biocatalytic purification method was employed to achieve a high degree of optical purity of the obtained products. The resulting amines are promising building blocks for the development of new pharmaceuticals and biologically active compounds.

Keywords: biocatalysis; chiral heterocyclic compounds; chiral 3-heterylbutanoic acids; 3-heteryl-2-methylpropanoic acids; lipase; enzymatic resolution; optical activity.

Introduction

Heterocyclic compounds play an extremely important role in pharmacology, as they form the basis of many pharmaceutical drugs. Approximately 75-90% of registered pharmaceutical compounds contain heterocyclic structures [1]. This is due to a range of properties and characteristics of heterocyclic compounds, such as a broad spectrum of biological activity, pharmacophoric nature, structural diversity, the ability to enhance drug solubility, penetration through biological membranes, and stability within the body [2, 3]. Heterocyclic aliphatic carboxylic acids represent an intriguing class of nitrogen-containing organic compounds that exhibit diverse biological and pharmacological activities. Among them there are important pharmaceutical agents such as antibiotics, non-steroidal anti-inflammatory drugs, antiviral agents, histamine antagonists, and GABA inhibitors [4-7]. They can also be used as precursors in the synthesis of many biologically significant compounds [8].

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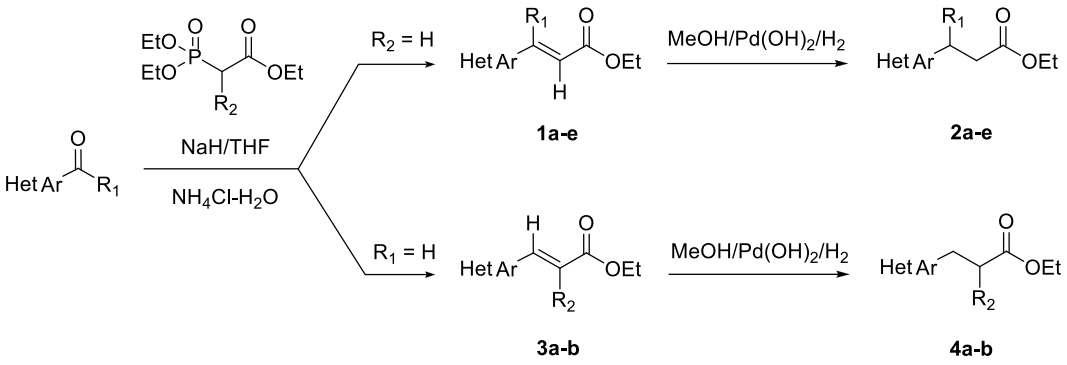
In recent years, there has been a significant increase in the use of chiral pharmaceutical agents. The regulatory requirements on this matter were published by the US Food and Drug Administration (FDA) as early as 1992 in a document titled *Development of New Stereoisomeric Drugs* [9, 10]. In accordance with these requirements, there has been a substantial shift toward the development of enantiomerically pure pharmaceuticals. As a result, the demand for enantiomerically pure drugs is growing annually by 13-15% [11, 12]. Therefore, the development of new, simple, accessible, cost-effective, and environmentally friendly methods for obtaining such compounds remains a highly relevant task in modern chemistry.

Chiral enantiomerically pure 3-heteroaryl-2-methylpropanoic acids and 3-heteroarylbutanoic acids are scarcely described in the literature. In their racemic form, they have been synthesized via the Horner-Wittig reaction, starting from the corresponding heterocarbonyl compounds [13]. In a stereochemically pure form, they were obtained through asymmetric hydrogenation using chiral cobalt-based catalysts, though the optical yields in this case remained moderate [14].

In our work, we have developed a method for obtaining stereochemically pure 3-heteroaryl-2-methylpropanoic and 3-heteroarylbutanoic acids through enzymatic kinetic resolution using lipases as biocatalysts.

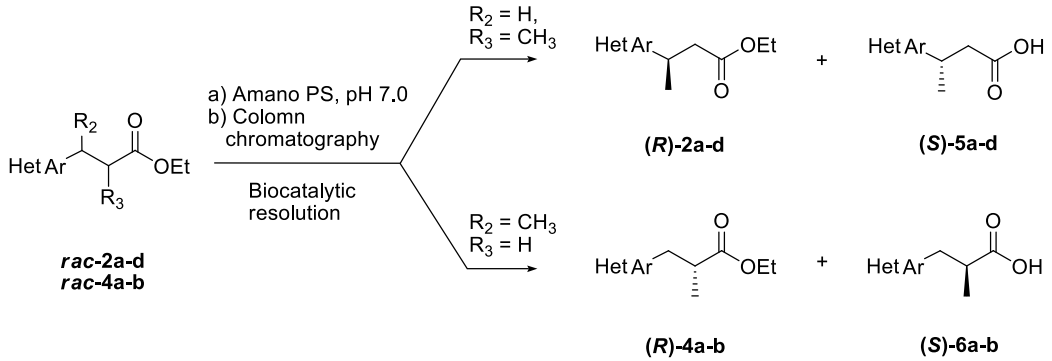


Compound	HetAr	R_1	R_2
2a	2-Pyridine	H	CH_3
2b	3-Pyridine	H	CH_3
2c	4-Pyridine	H	CH_3
2d	5-*N*-Me-Pyrazole	H	CH_3
4a	3-Pyridine	CH_3	H
4b	4-Pyridine	CH_3	H

Scheme 1. Synthesis of racemic esters of 3-heteroarylbutanoic acids and 3-heteroaryl-2-methylpropanoic acids.

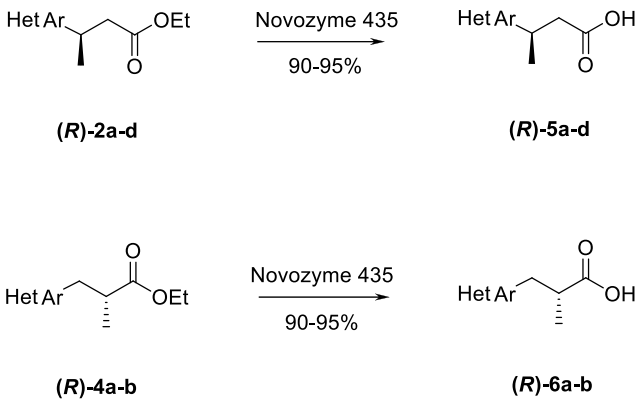
Results and Discussion

At the first stage of our work, racemic esters of 3-heteroaryl-2-methylpropanoic and 3-heteroarylbutanoic acids (**2a-e** and **4a-b**) were synthesized. To obtain them, we employed the approach previously described by us [15], following the two-step procedure shown in Figure 1.



Compound	(*R*)-Ester			Compound	(*S*)-Acid		E_a
	HetAr	Yield,%	*ee*, %		Yield,%	*ee*, %	
2a	2-Pyridine	40	97	**5a**	38		>100
2b	3-Pyridine	41	100	**5b**	40	100	>100
2c	4-Pyridine	38	97.5	**5c**	45	100	>100
2d	5-*N*-Me-Pyrazole	35	100	**5d**	37	100	>100
4a	3-Pyridine	39	100	**6a**	42	100	>100
4b	4-Pyridine	40	99	**6b**	40	97.5	>100

Scheme 2. Biocatalytic enantioselective resolution of heterocyclic carboxylic acid esters.



Scheme 3. Acid hydrolysis of (*R*)-heterocarboxylic acid esters.

Thus, by applying the Horner-Wittig reaction at a key stage, unsaturated heterocyclic carboxylic acids **1a-d** and **3a-b** were obtained from the corresponding substituted heterocyclic carbonyl compounds and ethyl 2-(diethoxy-phosphoryl)acetate. These intermediates were then hydro-genated in the presence of palladium hydroxide. As a result, racemic 3-heteroarylbutanoic acids **2a-e** and 3-heteroaryl-2-methylpropanoic acids **4a-b** were obtained in approximately 90% yields and were used in further transformations without additional purification.

The next stage involved obtaining enantiomerically pure isomers of heterylcarboxylic acids. To achieve this, enzymatic kinetic resolution was employed using lipases as biocatalysts. A selection of highly efficient and highly selective enzymes was tested, including lipases from *Burkholderia cepacia* (Amano PS), *Pseudomonas cepacia*, and *Candida antarctica* lipase B (CalB). Among these, Amano PS lipase proved to be the most effective in hydrolyzing racemic esters of heterocarboxylic acids.

The enzymatic hydrolysis was carried out in an aqueous medium using a phosphate buffer at pH 7.0 with Amano PS lipase [15-17]. All enantiomers of 3-heteryl-butanoic acids (**2a-d**) and 3-heteryl-2-methylpropanoic acids as (*R*)-esters (**2a-d**, **4a-b**) and (*S*)-acids (**5a-d**, **6a-b)** were obtained with yields of 52-60% and enantiomeric purity of 97-100% (Figure 2).

Table 1. 3-Phenylbutanoic acids and methyl-3-phenylpropanoic acids.

п/п	Compound	Optical Rotatory Power			HPLC		
		ee, %	$[\alpha]_D^{20}$	C (g/100 mL), solvent	τ (R) (min.)	τ (S) (min.)	Conditions
1	**(*R*)-5a**	97	-14.86	0.5, MeOH	12.362	9.606	a
2	**(*S*)-5a**	97.5	+15.36	0.5, MeOH	12,081	9.656	a
3	**(*R*)-5b**	100	-30.91	0.5, MeOH	12.682	-	b
4	**(*S*)-5b**	100	+32.36	0.5, MeOH	-	17.407	b
5	**(*R*)-5c**	97.5	-26.95	0.5, MeOH	7.465	6.278	c
6	**(*S*)-5c**	100	+29.97	0.5, MeOH	-	6.852	c
7	**(*R*)-5d**	100	-3.17	0.5, MeOH	17.947	-	d
8	**(*S*)-5d**	100	+2.22	0.5, MeOH	-	16.531	d
13	**(*S*)-6a**	100	-38.71	0.5, CH_2Cl_2	47.881	-	e
14	**(*R*)-6a**	100	+38.18	0.5, CH_2C_{l2}		41.411	e
15	**(*S*)-6b**	97.5	-28.26	0.5, $CHCl_3$	4,071	3.615	f
16	**(*R*)-6b**	99	+28.46	0.5, $CHCl_3$	-	3.442	f

Conditions: a) Column: Chiralpak AD-H (250 × 4.6 mm, 5 mkm) -3; Mobile Phase : Hexane : IPA : MeOH, 50:25:25; Flow Rate, 0.6 mL/min. b) Column: Chiralcel OJ-H (250 × 4.6 mm, 5 mkm) -3; Mobile Phase: Hexane (0.1%TFA) : IPA : MeOH, 70:15:15; Flow Rate, 0.6 mL/min. c) Column: Chiralpak AD-H (250 × 4.6 mm, 5 mkm -3; Mobile Phase: CO_2 : MeOH, 90:10; Flow Rate, 2.0 mL/min. d) Column: Chiralpak AD-H (250 × 4.6 mm, 5 mkm) - Mobile Phase: Hexane (0.1% TFA) : IPA, 90:10; Flow Rate, 0.6 mL/min. e) Column: Chiralcel OJ-H (250 × 4.6 mm, 5 mkm) - OJH0CE-UF008-3; Mobile Phase: Hexane (0.1%TFA) : IPA (0.1%TFA) : MeOH (0.1%TFA), 90:5:5; Flow Rate, 0.6 mL/min. f) Column: Chiralpak AD-H (250 × 4.6 mm, 5 mkm) -3; Mobile Phase: CO_2 : MeOH, 80:20 ; Flow Rate, 2.0 mL/min.

Next, the obtained (*R*)-esters **2a-d** and **4a-b** were subjected to acidic hydrolysis by heating ap to 40 °C for 3 days in deionized water in the presence Novozyme 435, yielding good, quantitative results without the need for additional purification (Figure 3). In all cases, the hydrolysis proceeded without racemization, preserving the absolute configuration of the compounds. As a result, all stereoisomers of 3-heteroarylbutanoic acids **5a-d** and 3-heteroaryl-2-methylpropanoic acids **6a-b** were obtained. They were characterized using available physicochemical methods (Table 1).

Conclusions

In this work, we obtained and described all optical isomers of 3-heteroarylbutanoic and 3-heteroaryl-2-methylpropanoic acids. For this purpose, a method of biocatalytic kinetic resolution of racemates of the esters of these acids was employed. Different lipases were used as biocatalysts, namely *Burkholderia cepacia* Amano PS lipase, *Pseudomonas cepacia* lipase, and *Candida antarctica* lipase B. The most effective lipase for the enzymatic hydrolysis of the esters of these acids was found to be Amano PS lipase. All optically active hetero-carboxylic acids were obtained with high chemical yields, optical purity >95%, and the preservation of the absolute configuration of the chiral center. These compounds were described and characterized using modern physicochemical methods.

Experimental section

All solvents were purified according to standard procedures. All starting materials were obtained from Enamine LTD. or other commercial sources. Melting points were measured using the MPA 100 OptiMelt, an automated melting point determination system. 1H and 13C NMR spectra were recorded in CDCl3 on a Bruker Avance III 500 MHz spectrometer (Germany) at ambient temperature. Chemical shifts (δ) are given in parts per million relative to tetramethylsilane (TMS) as the internal standard. Signal multiplicity is shown as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), m (multiplet), br (broad signal), q (quartet). Spin-spin coupling constants (*J*) are given in Hertz. Chiral HPLC analysis was carried out on an Agilent 1100 chromatographic system equipped with a Chiralpak OD-3 column or Chiracel analytical columns (Chiral Technologies) with a cellulose-based stationary phase. All reagents and solvents were used without further purification. Column chromatography was performed on silica gel 60 (70-230 mesh). Optical rotation was measured using a Perkin-Elmer polarimeter model 241 (sodium D line at 20 °C). Melting temperatures were not corrected. All reactions were carried out in glassware that was dried by flame or in a drying oven. *Burkholderia cepacia* lipase (Amano PS), *Pseudomonas cepacia* lipase from Amano Pharmaceutical (Japan), and *Candida antarctica* lipase B from Novozymes A/S (Denmark) were used. The progress of reactions was monitored by analytical thin-layer chromatography (TLC) on silica gel 60F254 plates (Merck, Germany), and products were visualized using anisaldehyde or UV light. The purity of all compounds was determined using TLC and NMR measurements.

Synthesis

*General Method for the Synthesis of (R) and (S) 3-heteroaryl-2-methylpropanoic and 3-heteroarylbutanoic acids **5a-d** and **6a-b**.*

A solution of 0.25 mol of racemic heteroarylcarboxylic acid ester **2a-d** or **4a-b** in 1500 mL of phosphate buffer pH 7.0. Add 20 g of Amano PS lipase. The mixture was stirred for 16 h at room temperature and then filtered. The filtrate was acidified with 2 M HCl to pH 2 and extracted with MTBE (3 × 300 mL). The organic extract was washed with 0.2 M aqueous potassium carbonate solution (2 × 300 mL), dried with sodium sulfate, and evaporated in a vacuum. (*R*)-Heteroarylcarboxylic acid esters **2a-d** or **4a-b** were obtained. Yield 38-41%; 93-100% *ee*. After extraction, the aqueous solution was acidified with 2 M HCl to a pH of 2, and then extracted with MTBE (3 × 500 mL). The extract was washed with sodium chloride solution, dried with sodium sulfate, and evaporated in a vacuum. (*S*)-Arylcarboxylic acids **5a-d** or **6a-b** were obtained. Yield 35-42%, 97-99% *ee*. To a 0.1 M solution of the corresponding enantiomerically pure (*R*)-heteroarylcarboxylic acid esters **2a-d** or **4a-b** (0.1 mol) in distilled water Novozyme 435 (0.1 g) was added in one portion. The mixture was heated to 40 °C and stirred at this temperature for 3 days. The mixture was filtered and concentrated. The residue was triturated in MTBE. The (*R*)-heteroarylcarboxylic acids **5a-d** or **6a-b** were obtained as a white powder. Yield 75-90%, 97-99% *ee*.

*(R)-Ethyl 3-(pyridin-2-yl)butanoate (**2a**).*

Pale yellow oil; yield 40%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.54-8.53 (d, *J* = 6.0 Hz, 1H), 7.62-7.58 (t, *J* = 9.5 Hz, 1H), 7.20-7.10 (dd, *J* = 37.5, 9.5 Hz, 1H), 4.10-4.04 (q, *J* = 8.5 Hz, 2H), 3.46-3.37 (m, 1H), 2.90-2.57 (dq, *J* = 138.5, 9.0 Hz, 2H), 1.35-1.33 (d, *J* = 8.5 Hz, 3H), 1.20-1.16 (t, *J* = 9.0, 3H).

*(R)-Ethyl 3-(pyridin-3-yl)butanoate (**2b**).*

Pale yellow oil; yield 41%. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.90-8.89 (d, *J* = 2.0 Hz, 1H), 8.77-8.76 (d, *J* = 7.0 Hz, 1H), 8.56-8.54 (d, *J* = 10.0 Hz, 1H), 8.01-7.97 (dd, *J* = 10.0, 7.0, Hz, 1H), 4.02-3.94 (m, 2H), 3.47-3.38 (m, 1H), 2.84-2.73 (m, 1H), 1.29-1.28 (d, *J* = 8.5 Hz, 3H), 1.10-1.07 (t, *J* = 9.5 Hz, 3H).

*(R)-Ethyl 3-(pyridin-4-yl)butanoate (**2c**).*

Pale yellow oil; yield 38%. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.83-8.81 (d, *J* = 7.0 Hz, 2H), 8.00-7.99 (d, *J* = 7.5 Hz, 2H), 4.03-3.97 (m, 2H), 3.49-3.43 (m, 1H), 2.87-2.75 (m, 2H), 1.30-1.28 (d, *J* = 8.5 Hz, 3H), 1.13-1.09 (t, *J* = 8.5 Hz, 3H).

*(R)-Ethyl 3-(pyrazol-5-yl)butanoate (**2d**).*

Pale yellow oil; yield 35%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (s, 1H), 5.98 (s, 1H), 4.10-4.04 (q, J = 9.0 Hz, 2H), 3.82 (s, 3H), 3.38-3.29 (m, 1H), 2.62-2.47 (dq, J = 9.0 Hz, 2H), 1.25-1.23 (d, J = 8.5 Hz, 3H), 1.20-1.16 (t, J = 8.5 Hz, 3H).

*(R)-Ethyl 2-methyl-3-(pyridin-3-yl)propanoate (**4a**).*

Pale yellow oil; yield 39%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.457 (s, 2H), 7.53-7.51 (d, J = 9.5 Hz, 1H), 7.24-7.21 (m, 1H), 4.12-4.07 (m, 2H), 3.02-2.97 (m, 1H), 2.74-2.70 (m, 2H), 1.21-1.18 (m, 5H).

*(R)-Ethyl 2-methyl-3-(pyridin-4-yl)propanoate (**4b**).*

Pale yellow oil; yield 40%. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.811 (s, 1H), 8.78-8.76 (d, J = 5.5 Hz, 1H), 8.43-8.42 (d, J = 8.0 Hz, 1H), 7.98-7.95 (m, 1H), 4.01-3.97 (q, J = 7.5 Hz, 2H), 3.06-2.97 (m, 3H), 1.09-1.06 (t, J = 7.0 Hz, 3H).

*(3S)-3-(Pyridin-2-yl)butanoic acid (**5a**).*

White solid; yield 41%; mp 89 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.50-8.47 (d, J = 4.5 Hz, 1H), 7.86-7.78 (t, J = 7.5 Hz, 1H), 7.32-7.29 (m, 2H), 3.38-3.32 (m, 1H), 2.94-2.80 (m, 2H), 1.43-1.42 (d, J = 7.0, 3H).

*(3R)-3-(Pyridin-2-yl)butanoic acid (**5a**).*

White solid; yield 37%; mp 88 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.50-8.49 (d, J = 4.5 Hz, 1H), 7.86-7.78 (t, J = 7.5 Hz, 1H), 7.32-7.29 (m, 2H), 3.38-3.32 (m, 1H), 2.94-2.80 (m, 2H), 1.43-1.42 (d, J = 7.0, 3H).

*(3S)-3-(Pyridin-3-yl)butanoic acid (**5b**).*

White solid; yield 40%; mp 90 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.46 (s, 1H), 8.38-8.37 (d, J = 4.5 Hz, 1H), 7.68-7.66 (d, J = 7.5 Hz, 1H), 7.30-7.28 (m, 1H), 3.18-3.14 (m, 1H), 2.54-2.53 (m, 2H), 1.21-1.21 (d, J = 7.0 Hz, 3H).

*(3R)-3-(Pyridin-3-yl)butanoic acid (**5b**).*

White solid; yield 40%; mp 90 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.46 (s, 1H), 8.38-8.37 (d, J = 4.5 Hz, 1H), 7.68-7.66 (d, J = 7.5 Hz, 1H), 7.30-7.28 (m, 1H), 3.18-3.14 (m, 1H), 2.54-2.53 (m, 2H), 1.21-1.21 (d, J = 7.0 Hz, 3H).

*(3S)-3-(Pyridin-4-yl)butanoic acid (**5c**).*

White solid; yield 34%; mp 170 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.44-8.43 (d, J = 6.0 Hz, 2H), 7.27-7.26 (d, J = 6.0 Hz, 2H), 3.14-3.09 (m, 1H), 2.54-2.52 (m, 2H), 1.19-1.18 (d, J = 7.0 Hz, 3H).

*(3R)-3-(Pyridin-4-yl)butanoic acid (**5c**).*

White solid; yield 36%; mp 172 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.44-8.43 (d, J = 6.0 Hz, 2H), 7.27-7.26 (d, J = 6.0 Hz, 2H), 3.14-3.09 (m, 1H), 2.54-2.52 (m, 2H), 1.19-1.18 (d, J = 7.0 Hz, 3H).

*(3S)-3-(1-Methyl-1H-pyrazol-5-yl)butanoic acid (**5d**).*

Light yellow solid; yield 39%; mp 127 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.407 (s, 1H), 6.06 (s,1H), 3.86 (s, 3H), 3.39-3.34 (m, 1H), 2.67-2.56 (m, 2H), 1.30-1.29 (d, J = 7.0 Hz, 3H).

*(3R)-3-(1-Methyl-1H-pyrazol-5-yl)butanoic acid (**5d**).*

Light yellow solid; yield 40%; mp 127 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 (s, 1H), 6.06 (s,1H), 3.86 (s, 3H), 3.39-3.34 (m, 1H), 2.70-2.56 (m, 2H), 1.30-1.29 (d, J = 7.0 Hz, 3H).

*(2S)-2-Methyl-3-(pyridin-3-yl)propanoic acid (**6a**).*

White solid; yield 41%; mp 88 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.21 (br s, 1H), 8.39 (s, 2H), 7.61-7.59 (d, J = 8.0 Hz, 1H), 7.29 (m, 1H), 2.89-2.83 (m, 1H), 2.68-2.62 (m, 2H), 1.04-1.03 (d, J = 7.0 Hz, 3H).

*(2R)-2-Methyl-3-(pyridin-3-yl)propanoic acid (**6a**).*

White solid; yield 42%; 89 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.21 (br s, 1H), 8.39 (s, 2H), 7.61-7.59 (d, J = 8.0 Hz, 1H), 7.29 (m, 1H), 2.89-2.83 (m, 1H), 2.68-2.62 (m, 2H), 1.04-1.03 (d, J = 7.0 Hz, 3H).

*(2S)-2-Methyl-3-(pyridin-4-yl)propanoic acid (**6b**).*

White solid; yield 38%; mp 160 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.233 (br s, 1H),8.44-8.43 (d, J = 4.5 Hz, 2H), 7.21-7.20 (d, J = 4.0 Hz, 2H), 2.90-2.85 (m, 1H), 2.71-2.61 (m, 2H), 1.04-1.03 (d, J = 7.0, 3H).

*(2R)-2-Methyl-3-(pyridin-4-yl)propanoic acid (**6b**).*

White solid; yield 42%; mp 160 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.23 (br s, 1H), 8.44-8.43 (d, J = 4.5 Hz, 2H), 7.21-7.20 (d, J = 4.0 Hz, 2H), 2.90-2.85 (m, 1H), 2.71-2.61 (m, 2H), 1.04-1.03 (d, J = 7.0, 3H).

Notes

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The authors declare no conflict of interest.

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Синтез оптично чистих 3-гетероарил-2-метилпропанових та 3-гетероарилбутанових кислот методом біокаталітичного розділення

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Резюме: Розроблено новий підхід до синтезу сполук з потенційною біологічною активністю − енантіомерно чистих 3-гетероарил-2-метилпропанових та 3-гетероарилбутанових кислот. На ключових етапах синтезу застосовано методологію ферментативного динамічного кінетичного розділення. Для досягнення високого ступеня оптичної чистоти отриманих продуктів використано метод подвійного біокаталітичного очищення. Отримані аміни є перспективними будівельними блоками для розробки нових фармацевтичних препаратів та біологічно активних сполук.

Ключові слова: біокаталіз; хіральні гетероциклічні сполуки; хіральні 3-гетерилбутанові кислоти; 3-гетерил-2-метилпропанові кислоти; ліпаза; ферментативне розділення; оптична активність.