The optically active halodihydroindenols and dihydroindenediols are components of many biologically active natural compounds, being important pharmacophore groups. In the present work, to obtain the above compounds with a high degree of optical purity, the resolution of racemates into enantiomers using enzymes is proposed. Dihydroindenediols, which were reduced with sodium borohydride to dihydroindenols, were used as starting compounds. Burkholderia cepacia lipase (BCL) was used to separate racemic indenols. Racemic indenols were kinetically trans-esterificated with vinyl acetate in organic media in the presence of a BCL biocatalyst. As a result, acylated indenols of (R)-absolute configuration and unreacted indenol of (S)-configuration, which were separated into individual compounds by column chromatography, were obtained. The enzymatic resolution of halohydroindene acetates by hydrolysis in the presence of Candida antarctica B lipase immobilized on diatomite was also investigated. Enantiomerically enriched halohydroindene acetates and halohydroindene acetates were obtained when racemic halohydroindene acetates were treated with Novozym 435® in MTBE for 20—30 hours at 30—40 °C. The enantiomeric purity of the compounds was determined by the derivatization with Mosher acid. The absolute configuration of the compounds was established by the Kazlauskas method.

**Keywords:** 1,2-amino-cycloalkanols, 1,2-diaminocycloalkanes, enzymes, kinetic resolution, Burkholderia cepacia lipase, Candida antarctica lipase B.

The optically active halohydroindeneols and dihydroindenediols are components of many biologically active natural compounds. They attract close attention as synthetic blocks for the construction of important pharmaceutical preparations, peptide nucleic acids, and bioregulators. For example, indinavir is an oral drug used to treat human immunodeficiency virus infection [1]. This protease inhibitor, a highly active antiretroviral therapy product, is used to treat HIV infection and AIDS. Cis- and trans-indanediols are the key chiral synthones in the synthesis of indinavir 1 (Scheme 1) [2—4]. Therefore, the chiral derivatives of indanes attract great interest of many chemists, and various approaches to their preparation were developed. Some chiral derivatives of indanes are produced in industry. For example, in the industrial method for producing the chiral synthetic block indinavir — (1R,2S)-cis-aminoindanol, the bacterial cells of *Rhodocco-
cus sp. Living cells of *Rhodococcus* Sp capable to catalyze the bioconversion of indene to chiral cis and trans indanediols [5] are used.

Another important pharmaceutical product based on indanes is Ladostigil 2, a medicine for the treatment of Alzheimer’s disease and Parkinson’s disease, which can slow the development of clinical signs within a relatively short period [6—8]. It has a positive effect on symptoms of Alzheimer’s disease such as depression, increased anxiety, and various forms of imbecility (Scheme 1).

In the chemical literature, information on the synthesis of halogenindanediols is extremely limited, although a number of patents were devoted to the synthesis and properties of these compounds. In chemical journals, there is only one work of Japanese authors devoted to the synthesis and properties of indanediol derivatives, however, only racemates [9]. Therefore, it is undoubtedly interesting to use the methods of biocatalysis to obtain enantiomerically pure representatives of halodihydroindenol and dihydroindendiols.

The oxidative kinetic resolution of racemic indenols was previously described using acetone as a hydrogen acceptor in the presence of the organometallic catalyst [RuCl₂(PPh₃)(ferrocenyl oxazolidine phosphine)] [10]. The disadvantage of this method is the need to use a hard-to-reach and expensive ruthenium catalyst, as well as low yields and the insufficient enantiomeric purity of products. In addition, this method is carried out only on the milligram scale of starting reagents. In another method for the preparation of 1-indenol derivatives, the catalytic hydrogenation of indenones was applied with the use of the optically active Ru-PEG-BsDPEN catalyst [11] or the RuCl catalyst [(1S,2S)-p-tosyl-N-CH(C₆H₅)CH(C₆H₅)-NH₂(eta,6-p-cymene)/Bu₄NBr [12]. The asymmetric hydroxylation of OH and NH₂ substituted indenols with ethylbenzene dehydrogenase was studied in [13]. The resolution of racemic mixtures of indenols by means of preparative chromatography with the use of expensive precision instruments and chiral chromatographic columns [5], which are also hard-to-reach, was proposed in [6].

**Results and discussion.** The formulated problem was solved in that the kinetic resolution of racemic dihydro-1-indenols was carried out using the enzymatic trans-esterification with vinyl acetate in the presence of *Burkholderia cepacia* lipase [12].

An alternative method for the resolution of racemic mixtures into enantiomers of dihydro-1-indenols is the enzymatic hydrolysis of racemic dihydro-1-indenol acetates at the constant pH 7.2 buffer solution in the presence of *Candida Antarctica* lipase B. Therefore, we have developed a simple stereoselective method for the preparation of dihydro-1-indenols substituted in the aromatic ring, which provided the possibility of obtaining these substances in high yields and with high chemical purity.
Enzymatic deracemization of halogenated dihydroindenols and dihydroindenediols substituted in benzene ring

Synthesis of initial compounds. Starting from the halodihydroindenones 2a—c, racemic halodihydroindenols 3a—c were obtained. For this aim, halodihydroinden-1-ones were reduced with a insignificant excess of sodium borohydride in methanol, first with cooling to 0 °C and then at room temperature. The reaction was completed by a short reflux of the reaction mixture. As a result, 3a—c halodihydroindenols were obtained as colorless crystalline substances in good yields (Scheme 2).

Resolution of racemic indanols into stereoisomers. Racemic halodihydroindenols were separated into enantiomers by the lipase-catalyzed transesterification with vinyl acetate in diisopropyl ether in the presence of Burkholderia cepacia lipase (BCL). In this case, (R)-halodihydroindenols 3 were isolated in 45 % yield with 100 % ee (enantiomeric excess), and (S)-halodihydrindene acetates (+)-4 were obtained in 40 % yield with 93 % ee after column chromatography.

The resolution of halodihydrindien-1-ol into enantiomers was carried out by acylation with vinyl acetate under kinetic control in the presence of Burkholderia cepacia lipase (BCL). The reaction was led to 50 % conversion, then the reaction was stopped by filtration of the biocatalyst. As a result, a mixture of diol and acylated diol was obtained. The mixture was separated by column chromatography (Scheme 3).

As a result the enantiomerically and diastereomerically pure haloindanols with 99 % ee and the corresponding halodihydrindene acetates with 96 % ee were obtained. It turned out to be unexpected that dihydro-1-indendiol substituted in the benzene ring was regioselectively acylated only at the hydroxyl group located in the cyclopentane ring.

It was found that the tert-butyl methyl ether (MTBE) as a solvent, the Burkholderia cepacia as a biocatalyst, and a temperature of 35 °C are the optimal conditions for the kinetic resolution of halogenindenols. In this case, the completion of the reaction at 50 % conversion provided a smooth and unambiguous reaction between the reagents, which led to the formation of only one (R)-enantiomer of indenol acetate. As a result, unreacted indenol of the absolute configuration (S)- and acyl indenol of the (R)-configuration were obtained, which ensured the resolution of the stereoisomers of this mixture with high chemical yield and high optical purity. Further
hydrolysis of (R)-acyl indenol gives indenol of the (R)-configuration. Thus, it is possible to obtain both (S)- and (R)-enantiomers of indenol.

It is known that the solvent variation of the lipase-catalyzed kinetic resolution can influence the enantiomer or enantiotopic selectivity in many cases, as well as the reaction rate. Therefore, our next investigation was performed to find a more suitable solvent in this system. We found that dialkyl ethers were appropriate solvents for the enzymatic trans-esterification in the presence of the same lipase. Therefore, we have tested dibutyl ether (DBE), methyl t-butyllether (MTBE), and toluene. Among the solvent tested, MTBE exhibited the best results. When MTBE was used as a solvent, enantiomeric excess of (+)-3 was 96 % ee (45 % yield) and (–)-4 was 92 % ee (48 % yield), respectively. So, this solvent was shown to be more suitable than the others, although DBE is not much inferior to MTBE in efficiency. Interestingly, it was found that toluene was also applicable to this resolution, though with slightly lower efficiency.

The reaction of kinetic enzymatic hydrolysis of halodihydrinindene acetates was carried out in a two-phase system with a pH 7.2 buffer solution in MTBE medium in the presence of a CALB biocatalyst at 45 °C. The reaction was completed upon reaching 50 % conversion. As a result, the (R)-enantiomer of indenol and unreacted (S)-indenol acetate were obtained. The methodology ensured the resolution of stereomers of a racemic mixture in high chemical yield and with high optical purity. Further hydrolysis of unreacted (S)-indenol acetate gave (S)-indenol (Scheme 4).

Conveniently, Novozym 435® (immobilized lipase from Candida antarctica) has heat-resistant properties, so we examined the influence of the reaction temperature on the enantiomeric excess of the product under the same conditions using MTBE as a solvent. Decreasing the reaction temperature (30 °C) did not markedly influence the enantioselectivity or reaction rate. However, the raise of the reaction temperature (60 °C) showed a remarkable increase in the reaction rate, although the progress of the reaction seemed to be halted after 8 hours.

Since the reuse of a recovered enzyme is the most important problem to be overcome to establish a manufacturing process, the influence of the number of recycles on the resolution efficiency was investigated.

We found that lipase can be used up to three cycles without a noticeable decrease in the effectiveness of resolution. Only in the fourth cycle, a decrease in the efficiency of the biocatalyst was noted.

Under the optimal conditions (treated with Novozym 435® and in dibutyl ether for 20—30 hours at 30—40 °C), (–)-4 was converted to (1S)-3 (yield: 47 %, 94 % ee) and (R)-4 (yield: 49 %, 92 % ee), respectively (Scheme 2). The developed methodology provides the easy access to both (S)- and (R)-enantiomers of indeno-halohydrins with high optical purity. Using Burkholderia cepacia lipase and vinyl acetate, we resolved indandiol into enantiomers, which is a key intermediate in the synthesis of Ladostigil. These compounds can be easily converted to aminoinde-
Enzymatic deracemization of halogenated dihydroindenols and dihydroindenediols substituted in benzene ring

Enzymatic deracemization of halogenated dihydroindenols and dihydroindenediols substituted in benzene ring

Enzymatic deracemization of halogenated dihydroindenols and dihydroindenediols substituted in benzene ring

nols by the reaction with acetonitrile under the conditions of the Ritter reaction, giving enantio-
merically pure (1S, 2R)-cis-1-aminoindan-2-ol (Scheme 5) [14].

Chlorine and bromoindanols are colorless crystalline substances whose structure and che-

mical purity were confirmed by NMR spectra. Optical purity was established by the derivati-

zation with Mosher acid, as well as by chiral HPLC analysis on a Chiralpak OD-3 column

(hexane : IPA : MeOH = 95 : 2.5 : 2.5), flow rate = 0.6 mL/min, λ = 210 nm). After recrystall-

ization, the purity of synthesized bromindindanols was on the level of 99 % ee (Scheme 6).

The Kazlauskas rule was used to determine the absolute stereochemistry of enantiomerically
pure products. The Kazlauskas rule is an empirical model based on the postulate that the enan-
tioselectivity is proportional to the difference in size between large (L) and middle (M) substi-
tuents in the substrate. According to the Kazlauskas rule, these substitutes 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. Using this empiric rule, it was
found that biocatalytic acylation produces (R)-esters and (S)-halogenindanol remain unreacted.

The experiments performed show that the proposed biocatalyst allows one to obtain both
optical enantiomers of dihydro-1-indenols in high yields and high enantiomeric purity in a so-
lution of methyl tert-butyl ether at room temperature and a moderate amount of the biocatalyst,
using simple experimental conditions [5—8].

Experimental part. 1H NMR and 13C NMR spectra were recorded in a CDCl 3 solvent on a
500 MHz spectrometer at ambient temperature. Chemical shifts (δ) are shown in ppm in relation
to TMS as an internal standard. Signal multiplicity is shown as s — singlet; d — doublet; dd —
doublet of a doublet; t — triplet; m — multiplet; br s — wide singlet. The spin-spin coupling constants$J$ are
dicated in Hertz. Chiral HPLC analysis was done on an Agilent 1100 system equipped by a Chiralpak®-OD-3 column or Chiracel®
(Chiral Technologies) analytical columns with cellulose-based stationary phase. All reagents and solvents
were used without special purification, unless otherwise indicated. Column chromatography was
performed on silica gel 60 (70-230 mesh) using the indicated eluents. Optical rotations were
measured on a Perkin-Elmer 241 polarimeter (D sodium line at 20 °C). Melting points were
not corrected. All reactions were carried out in glassware dried on a fire or dried in a drying
chamber with stirring on a magnetic stirrer. Lipase from Burkholderia cepacia (Amano PS) was
purchased from Amano Pharmaceutical (Japan). The progress of the reactions was monitored
by analytical thin layer chromatography (TLC) on glass plates of silica gel 60 F254 (Merck,
Germany) and the products were visualized with anisaldehyde or UV. The purity of all com-
pounds was checked using thin layer chromatography and NMR measurements.

**(S)-5-Chloro-2,3-dihydro-1H-inden-1-ol (**(S)-3a).** A solution of racemic (R/S)-5-chloro-
2,3-dihydro-1H-inden-1-ol (1.7 g, 0.01 mol), Burkholderia cepacia lipase (0.1 g), vinyl acetate
(3 ml) in MTBE (3 ml) was stirred at 24 °C. Indenol acylation was monitored by TLC and NMR. The reaction mixture was stirred to 50 % conversion of the starting alcohol for 18 g. Then the reaction mixture was filtered, evaporated in vacuo, the resulting substance was chromatographed on column with silica gel using eluent hexane-ethyl acetate-ethanol (95 : 3 : 1). Indenol acetate of (R)-absolute configuration and unreacted indenol of (S)-absolute configura-
tion were obtained. The resulting (S)-indenol was further recrystallized in toluene. The yield of optically pure (S)-5-chloro-2,3-dihydro-1H-inden-1-ol is 50 %, mp 105 °C,
$[\alpha]_{D}^{20} +15$ (C = 3, CHCl$_3$) or +9 (C = 3, ethanol).

$^1$H NMR, (CDCl$_3$), δ, ppm (J, Hz): 1.95 m (1H, CH); 2.48 m (1H, CH); 2.80 m (1H, CH);
3.01 m (1H, CH); 5.19 t (1H, $J$ = 6.0 Hz, CHO$_2$); 7.18 m (2H, H-Ar); 7.32 m (1H, H-Ar).

$^{13}$C NMR, (CDCl$_3$), δ, ppm (J, Hz): δ$_{C}$ 30.1; 35.9; 76.1; 126; 127, 128.9; 133.8; 143; 143.1.

Found, %: C, 64.35; H, 5.34; Cl, 21.25. C$_9$H$_9$ClO. Calculated, %: C, 64.11; H, 5.38; Cl, 21.02.

**(R)-5-Chloro-2,3-dihydro-1H-inden-1-yl acetate (**(R)-4a).** Acetate obtained in the previous
experiment was purified by vacuum distillation.

Yield 45 %, bp 75 °C, $[\alpha]_{D}^{20} +76.36$ (C = 1, CHCl$_3$).

$^1$H NMR, (CDCl$_3$), δ, ppm (J, Hz): δ$_{H}$ 2.15 s (3H, CH$_3$CO); 2.13 m (1H, CH); 2.55 m (1H,
CH); 2.9 m (1H, CH); 3.1 m (1H, CH); 6.13 s (1H, CHO$_2$); 7.2 m (1H), 7.25 m (1H), 7.57 m
(1H, H-Ar).

$^{13}$C NMR, (CDCl$_3$), δ, ppm (J, Hz): δ$_{C}$ 21.1; 30.3; 32.2; 79.7; 125.5; 126.7; 129.1; 134.2; 139.1;
144.1; 170.4.


**(R)-5-Chloro-2,3-dihydro-1H-inden-1-ol (**(R)-3b.** Acetate 4a (2.1 g, 0.01 mol) was hydro-
lyzed by treatment with a solution of potash (2 g) in 20 ml of methanol with stirring at room
temperature. The progress of hydrolysis was monitored by TLC. The solvent was evaporated in vacuo, the residue was extracted with ethyl acetate. Then the extract was evaporated, and the residue was recrystallized in hexane. Pure (R)-indenol 3b was obtained.

Yield 45 %, mp. 105 °C, $[\alpha]_{D}^{20} = -15$ (C = 3, CDCl$_3$).
Enzymatic deracemization of halogenated dihydroindenols and dihydroindenediols substituted in benzene ring

\[ \text{ISSN 1025-6415. Допов. Нац. акад. наук Укр. 2020. № 3} \]

Enzymatic deracemization of halogenated dihydroindenols and dihydroindenediols substituted in benzene ring

\[ \text{1H NMR, (CDCl}_3\text{), } \delta, \text{ ppm (J, Hz): } \delta_1 1.95 \text{ m (1H, CH); 2.48 m (1H, CH); 2.80 m (1H, CH); 3.01 m (1H, CH); 5.19 t (1H, CHO); 7.18 m (2H, H-Ar); 7.32 m (1H, H-Ar).} \]

\[ \text{13C NMR, (CDCl}_3\text{), } \delta, \text{ ppm (J, Hz): } \delta_c 30.1; 35.9; 76.1; 126; 127, 128.9; 133.8; 143; 143.1. \]

\[ \text{Found, } \%: \text{ C, 64.02; H, 5.51. C}_9\text{H}_9\text{ClO. Calculated, } \%: \text{ C, 64.11; H, 5.38.} \]

(S)-5-Chloro-2,3-dihydro-1Н-inden-1-ol ((S)-3а). (S/R)-5-Chloro-2,3-dihydro-1H-inden-1-yl acetate was dissolved in MTBE, and phosphate buffer (0.05 M; pH = 7.2) and \textit{Candida Antarctica} lipase B (20 \% by weight of the substrate) were added. The reaction mixture was stirred for about 12—18 hours at room temperature. The progress of the reaction was monitored by NMR. When the reaction was completed, the biocatalyst was filtered off. The organic phase was separated from water. The water was washed 2 times with MTBE. The combined organic solutions were dried with sodium sulfate and evaporated. Optical purity was determined by NMR of the product derivatized with Mosher acid.

The yield of (R)-indenol is 45 \%. \[ \alpha_D^{20}–25 (C = 3, \text{CDCl}_3). \]

1H NMR (400 MHz, CDCl 3) \[ \delta_{1.95–1.89} (m, 1Н), 2.22 (s, 1Н), 2.50–2.44 (m, 1Н), 2.81–2.75 (m, 1Н), 3.02–2.96 (m, 1Н), 5.18–5.15 (m, 1Н), 7.20–7.18 (m, 2Н), 7.30–7.28 (m, 1Н), \]

13C NMR (100 MHz, CDCl 3) \[ \delta_{145.21, 143.36, 133.96, 126.86, 125.27, 124.99, 75.59, 35.96, 29.59}. \]

(S)-5-Bromo-2,3-dihydro-1Н-inden-1-ol ((S)-3b). The solution of (S/R)-5-Bromo-2,3-dihydro-1H-inden-1-ol (2.3 g, 0.01 mol), \textit{Burkholderia cepacia} lipase (0.2 g), and vinyl acetate (3 ml) in MTBE (10 ml) was stirred at +24 \degree C. The course of the reaction was monitored by TLC and NMR. The reaction mixture was stirred to 50 \% conversion of the starting alcohol for 18 hours. The reaction mixture was filtered and evaporated in vacuo, the residue was separated by silica gel column chromatography, eluent hexane-ethyl acetate-ethanol (95 : 53 : 1). The isolated (S)-dihydro-1H-inden-1-ol was recrystallized from toluene.

Yield 50 \%, mp 100 \degree C. \[ \alpha_D^{20} + 20 (C = 3, \text{CDCl}_3). \]

1H NMR, (CDCl 3), \[ \delta, \text{ ppm (J, Hz): } \delta_{1.88–1.99} (m, 2Н), 2.42–2.53 (m, 1Н), 2.74–2.85 (m, 1Н), 2.97–3.07 (m, 1Н), 5.18 (t, J = 6.6 Hz, 1Н), 7.26 (d, J = 2.7 Hz, 1Н), 7.34 (s, 1Н), 7.37 (d, J = 3.0 Hz, 1Н), \]

13C NMR, (CDCl 3) \[ \delta_{145.6, 143.9, 129.7, 128.0, 125.7, 122.2, 75.6, 35.9, 29.6}. \]


(R)-5-Bromo-2,3-dihydro-1H-inden-1-ol acetate ((R)-4b). The acetate obtained in the previous experiment was purified by vacuum distillation. Yield 40 \%. Bp. 100 \degree C (0.01 mmHg).

1H NMR, (CDCl 3), \[ \delta, \text{ ppm (J, Hz): } \delta_{2.05} c (3Н, \text{CH}_3\text{CO}); 2.55 m (1H, CH); 2.9 m (1H,CH); 3.1 m (1H, CH); 6.13 s (1H, CHO); 7.2 m (1H), 7.25 m (1H), 7.57 m (1H, H-Ar). \]

13C NMR, (CDCl 3), \[ \delta, \text{ ppm (J, Hz): } \delta_c 21.1; 29.5; 32.2; 79.7; 121.4; 123.2; 124.5; 131.6; 141.4; 143; 170.4}. \]

(R)-5-Bromo-2,3-dihydro-1H-inden-1-ol ((R)-3b). The acetate (0.01 mol) obtained in the previous experiment was hydrolyzed by treatment with potash (2 g) in 20 ml of methanol with stirring at room temperature. The progress of hydrolysis was monitored by TLC analysis. The solvent was evaporated, and the residue was extracted with ethyl acetate. Then the extract was evaporated, and the residue was recrystallized from hexane.

Yield 50 \%, mp. 105 \degree C. \[ \alpha_D^{20} = –20 (C = 3, \text{CDCl}_3). \]
(R)-5-Bromo-2,3-dihydro-1H-inden-1-ol ((R)-3b). (R)-5-Bromo-2,3-dihydro-1H-inden-1-yl acetate is dissolved in MTBE, and phosphate buffer (0.05 M; pH = 7.2) and CALB (20 % by weight of the substrate) were added. The reaction mixture was stirred for about 12—18 hours at room temperature. The progress of the reaction was monitored by NMR. When the reaction was completed, the biocatalyst was filtered. The organic phase was separated from water. The aqueous phase was washed 2 times with MTBE. The combined organic solutions were dried with sodium sulfate and evaporated. The optical purity was defined by NMR of the product derivatized by Mosher acid. The yield 45 %, [α]D 20 = −25 (C = 3, CDCl3).

The yield of unreacted (S)-acylindenol is 44 % [α]D 20 + 75 (C = 1, CDCl3).

(S)-4-Bromo-2,3-dihydro-1H-inden-1-ol ((S)-3c). The solution of (S/R)-4-Bromo-2,3-dihydro-1H-inden-1-ol (2.3 g, 0.01 mol), Burkholderia cepacia lipase (0.2 g) and vinyl acetate (3 ml) in MTBE (10 ml) was stirred at +24 °C. The course of the reaction was monitored by TLC and NMR. The reaction mixture was stirred up to 50 % conversion of the starting alcohol for 18 hours. The reaction mixture was filtered and evaporated in vacuo. The residue was separated into unreacted (S)-indenol and (R)-indenyl acetate by column chromatography with silica gel, eluent hexane-ethyl acetate-ethanol (95 : 53 : 1). Isolated (S)-bromo-dihydro-1H-inden-1-ol was recrystallized from toluene.

Yield 50 %, mp 85 °C, [α]D 20 = −19.00 (C = 0.25, EtOH).

(R)-4-Bromo-2,3-dihydro-1H-inden-1-ol ((R)-3c). Acetate 4c (0.01 mol) obtained in the previous experiment was hydrolyzed by potash (2 g) in 20 ml of methanol with stirring at room temperature. The progress of hydrolysis was monitored by TLC. The solvent was evaporated, and the residue was extracted with ethyl acetate. Then the extract was evaporated, and the residue was recrystallized from hexane.

Yield 50 %, mp 85 °C, [α]D 20 = +18.93 (C = 0.25, EtOH).


(R)-2,3-Dihydro-1H-inden-1,4-diol ((R)-3d). The solution of (S/R)-2,3-dihydro-1H-inden-1,4-diol 3d (1.5 g, 0.01 mol), Burkholderia cepacia lipase (0.2 g), vinyl acetate (10 ml) and MTBE (3 ml) were stirred at 24 °C. The formation of the acetylated product was monitored by TLC.
Enzymatic deracemization of halogenated dihydroindenols and dihydroindenediols substituted in benzene ring

and NMR. The reaction mixture was stirred to 50 % conversion of the starting alcohol, which took 18 hours. The reaction mixture was filtered and evaporated in vacuo, the resulting oil was purified by silica gel chromatography using eluent hexane-ethyl acetate-ethanol (95 : 53 : 1). Indendiols was recrystallized from toluene.

Yield 50 %, mp 135 °C, $[\alpha]_D^{20} = + 42.95$ (C = 1, CDCl$_3$).

$^1$H NMR, (CDCl$_3$), δ, ppm (J, Hz): δ$_H$ 2.0 m (1H, CH); 2.25 s (1H, OH); 2.5 m (1H, CH); 2.75 m (1H, CH); 3.0 m (1H, CH); 4.8 br (1H, OH); 5.25 m (1H, CHOH); 6.75 m (1H, H-Ar); 7.05 m (1H, H-Ar); 7.2 m (1H, H-Ar).

$^{13}$C NMR, (CDCl$_3$), δ, ppm (J, Hz): δ$_C$ 26.21 s (CH); 35.11 s (CH); 75.82 s (CHOH); 114.16 s (C-Ar); 115.39 s (C-Ar); 128.86 s (C-Ar); 128.99 s (C-Ar); 147.63 s (C-Ar); 153.25 s [C(OH)-Ar].

Found, %: C, 71.45; H, 6.82. C$_9$H$_{10}$O$_2$. Calculated, %: C, 71.98; H, 6.71.

(S)-5-hydroxy-2,3-dihydro-1H-inden-1-yl acetate ((S)-4d). Acetate obtained in the previous example was purified by vacuum distillation. Yield 40 %.

$^1$H NMR, (CDCl$_3$), δ, ppm (J, Hz): δ$_H$ 2.1 s (3H, CH$_3$CO); 2.2 m (1H, CH$_2$); 2.4 m (1H, CH$_2$); 2.7 m (2H, CH$_2$); 5.7 br (OH); 6.12 s (CHO); 6.56 s; 6.63 s; 7.15 s; 7.16 s (3H, H-Ar).

Found, %: C 68.45; H 6.19. C$_{11}$H$_{12}$O$_3$. Calculated, %: C 68.74; H 6.29.

(S)-2,3-Dihydro-1H-inden-1,4-diol ((S)-3d). (S)-2,3-dihydro-1H-indene-1,4-diol 1-acetate (14d) was hydrolyzed in a phosphate-buffered aqueous solution at a constant pH 7.2 using Burkholderia cepacia lipase (0.2 g) with stirring and room temperature. Hydrolysis was monitored by TLC and 1H NMR. Next, the lipase was filtered and washed with methylene chloride. The solvent was evaporated, and the residue was extracted with ethyl acetate. Then the extract was evaporated, and the residue was crystalized from hexane to give reduced alcohol.

Yield 42 %, mp 135 °C, $[\alpha]_D^{20} = – 42.95$ (C = 1, CDCl$_3$).

$^1$H NMR, (CDCl$_3$), δ, ppm (J, Hz): δ$_H$ 2.0 m (1H, CH); 2.25 s (1H, OH); 2.5 m (1H, CH); 2.75 m (1H, CH); 3.0 m (1H, CH); 4.8 m (1H, OH); 5.25 m (1H, CHOH); 6.75 m (1H, H-Ar); 7.05 m (1H, H-Ar); 7.2 m (1H, H-Ar).

$^{13}$C NMR, (CDCl$_3$), δ, ppm (J, Hz): δ$_C$ 26.21 s (CH); 35.11 s (CH); 75.82 s (CHOH); 114.16 s (C-Ar); 115.39 s (C-Ar); 128.86 s (C-Ar); 128.99 s (C-Ar); 147.63 s (C-Ar); 153.25 s [C(OH)-Ar].


REFERENCES


ФЕРМЕНТАТИВНА ДЕР АЦЕМІЗАЦІЯ ЗАМІЩЕНИХ У БЕНЗОЛЬНОМУ КІЛЬЦІ ГАЛОГЕНГІДРОІНДЕНОЛІВ І ДИГІДРОІНДЕНДІОЛІВ

Оптично активних галогенгідроінденолів і дигідроіндіенолів — компоненти багатьох біологічно активних природних сполук, є важливими фармантичними групами. У представленій роботі для отримання вищевказаних сполук з метою ступеня оптичної чистоти запропоновано поділ рацематів на енантиомери за допомогою ферментів. Дигідроінденоли, які відновлювали боргідридом натрію до дигідроінденолів, використовували як вихідні сполуки. Для поділу рацемічних інденолів використовували ліпазу Burkholderia cepacia (BCL). Рацемічні інденоли піддавали кінетичні переестерифікації в органічних середовищах у присутності іммобілізованої на діатоміті ліпази Candida Antarctica B. У результаті отримано енантіомерно чисті (S)-галогенінданоли і (R)-ацетоксигалогенінданоли. Запропонований біокаталізатор дає можливість одержувати обидва оптичні енантіомери дигідро-1-інденолів з високими виходами і високою енантіомерною чистотою у розчинні метил-трет-бутилового ефіру при кімнатній температурі і помірній кількості біокатализатора, що спрощує процес досягнення цих продуктів.
Енантіомерну чистоту сполук визначали шляхом дериватизації кислотою Мошера. Абсолютну конфігурацію сполук встановлювали за методом Казлаускаса.

**Ключові слова:** 1,2-аміноциклоалканоли, 1,2-діаміноциклоалканы, ферменти, кінетичне розділення, *Burkholderia cepacia* ліпаза, *Candida antarctica* ліпаза B.

Д.В. Присяжнюк, О.О. Колодяжна, О.И. Колодяжный
Институт біоорганічної хімії і нефтехімії ім. В.П. Кухаря НАН України, Київ
E-mail: oikol123@bpci.kiev.ua

**ФЕРМЕНТАТИВНАЯ ДЕРАЦЕМИЗАЦИЯ ЗАМЕЩЕННЫХ В БЕНЗОЛЬНОМ КОЛЬЦЕ ГАЛОГЕНДИГИДРОИНДЕНОЛОВ И ДИГИДРОИНДЕНДИОЛОВ**

Оптически активные галогендиgidроинденолы и дигидроиндендиолы — компоненты многих биологически активных природных соединений, являются важными фармацевтическими группами. В представленной работе для получения вышеуказанных соединений высокой степени оптической чистоты предложено разделение рацематов на энантиомеры с помощью ферментов. Дигидроинденолы, которые восстанавливали боргидридом натрия до дигидроинденолов, использовали в качестве исходных соединений. Для разделения рацемических инденолов использовали липазу *Burkholderia cepacia* (BCL). Рацемические инденолы подвергали кинетической переэстерификации винилацетатом в органических средах в присутствии биокатализатора ВСЛ. В результате получены ацилированный инденол, имеющий абсолютную конфигурацию (R), и непрореагировавший инденол конфигурации (S), которые были разделены на индивидуальные соединения колоночной хроматографией. Исследовано также ферментативное рассечеление ацетатов инден-галогенгидринов гидролизом в присутствии иммобилизованной на диатомите липазы *Candida antarctica* BCL. В результате получены энантиомерно чистые (S)-галогенинданолы и (R)-ацетогалиогенинданы. Предложенный биокатализатор позволяет получать оба оптических энантиомера дигидро-1-инденолов с высокими выходами и высокой энантиомерной чистотой в растворе метил-трет-бутилового эфира при комнатной температуре и умеренном количестве биокатализатора, что упрощает процесс достижения этих продуктов. Энантиомерную чистоту соединений определяли путем дериватизации кислотой Мошера. Абсолютную конфигурацию соединений устанавливаляли по методу Казлаускаса.

**Ключевые слова:** 1,2-аминоциклоклозанолы, 1,2-диаминоциклозаны, ферменты, кинетическое разделение, *Burkholderia cepacia* липаза, *Candida antarctica* липаза B.