Tetrahedron: *Asymmetry* 24 (2013) 37–42

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Enzymatic preparation of (1*S*,2*R*)- and (1*R*,2*S*)-stereoisomers of 2-halocycloalkanols

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ARTICLE INFO

Article history:
Received 16 October 2012
Accepted 19 November 2012

ABSTRACT

The stereoisomers of *cis*-2-halocycloalkanols were resolved by a kinetically controlled transesterification with vinyl acetate in the presence of lipases in organic media. High enantioselectivities (ee >98%) and good isolated yields were obtained for all substrates using the appropriate lipase. *Burkholderia cepacia* lipase was the most efficient enzyme for the resolution of these substrates. The enantiomeric purities of the compounds were defined by derivatization with Mosher's acid and the absolute configurations were determined by chemical correlation.

1. Introduction

Vicinal halogeno-cycloalkanol derivatives are common building blocks for a number of chiral natural and synthetic products. These compounds are important reagents for organic synthesis and are widely used for the preparation of various biologically active compounds, in particular, prostaglandins and leukotriene precursors.[1–4] 2-Substituted cyclohexanols can be converted into precursors of prostaglandin $F_2\alpha$, whereas 2-substituted cyclopentanols can be converted into L_7 leukotriene B_4, a conformationally-restricted leukotriene antagonist, used in the enantioselective total synthesis of (+)-Estron and Desogestrel.[5] The (1*R*,2*R*)- and (1*S*,2*S*)-enantiomers of *trans*-halogeno-cyclohexanols and *trans*-cyclopentanols have previously been reported on.[6–8] Kozma et al.[6] performed a one-pot, solid-state resolution of *trans*-2-iodocyclohexanol by *O*,*O*-dibenzoyl-(2*R*,3*R*)-tartaric acid. Hashimoto,[7a,7b] Haufe,[7c] and others prepared (1*R*,2*R*)-2-chloro-, bromo-, and fluorocyclohexan-1-ols by the *Pseudomonas Fluorescence* lipase catalyzed enantioselective transesterification of 2-substituted cyclohexanols. For this, Honig[8] used the hydrolysis of 2-substituted cyclohexyl butanoates catalyzed by *Candida cylindracea* and *Pseudomonas* sp. Lipases. However, to date (1*R*,2*S*)- and (1*S*,2*R*)-stereoisomers of *cis*-2-halogeno-cyclohexanols and *cis*-2-halogeno-cyclopentanols have not been resolved and their stereochemical properties have not been studied. Herein we report a chemoenzymatic approach for the preparation of the enantiomerically pure stereoisomers of (1*R*,2*S*)- and (1*S*,2*R*)-2-halogenocycloalkanols.

2. Results and discussion

2.1. Substrate preparation

We have prepared stereoisomers of halogenocycloalkanols by starting from cycloalkene oxides **1**,**2**.[9] The treatment of epoxides with lithium halogenides led to the formation of racemic, stereochemically pure, *trans*-2-halogenocycloalkanols **3**,**4** (Scheme 1). The racemic *trans*-2-halogenocyclohexanols **3** were then subjected to Swern oxidation[10a] while racemic *trans*-2-halogencyclopentanols **4** were subjected to Jones oxidation[10b] to give 2-halogenocycloalkanones **5**,**6** in good yields. Ketones **5**,**6** were reduced by sodium borohydride in methanol to give racemic *cis*-2-halogenocycloalkanols **7**,**8**. NMR analysis of the reaction mixtures showed that the *cis*-2-iodocycloalkanols were formed without *trans*-isomer impurities, although the *cis*-2-fluoro-, 2-chloro- and 2-bromocycloalkanols contained some amount of the *trans*-isomers (30%, 12%, and 5%, correspondingly) (Table 1).

The treatment of *cis*- and *trans*-2-chlorocycloalkanols with 10% aq NaOH proceeded with preferable hydrolysis of the *trans*-isomer leading to the formation of the pure *cis*-isomer, which was then additionally purified by recrystallization from hexane at 0 °C. The recrystallization of 2-bromocyclohexanol from hexane also yielded the pure *cis*-isomer. Analogously the *cis*-2-bromocyclopentanol was purified by low-temperature crystallization (at −30 to −40°C) in hexane and obtained as 100% of the *cis*-isomer. At the same time, the reduction of 2-fluorocycloalkanols with various reductants proceeded with low stereoselectivity: sodium borohydride in methanol yielded a mixture of *cis*- and *trans*-isomers in a ratio of 70:30, *i*-Bu_3B in a 75:25 ratio, and *i*-Bu_2AlH (H-DIBAL) in a 55:45 ratio.

The borohydride reductions of 2-substituted cyclohexanones depended on the conformational equilibrium of the axial and

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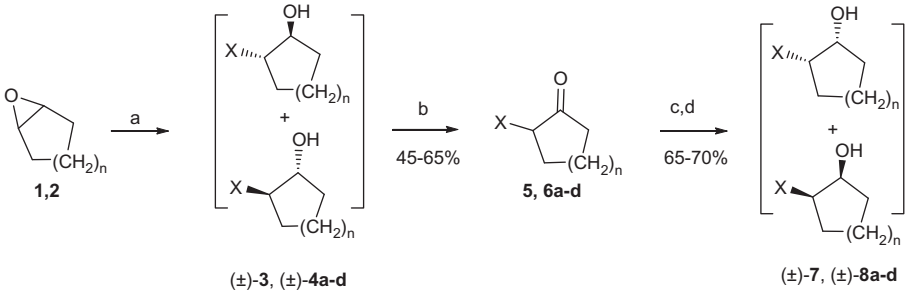
http://dx.doi.org/10.1016/j.tetasy.2012.11.011



n=2 **1,3,5,7**; 1 **2,4,6,8**; X=I **a**, Br **b**, Cl **c**, F **d**

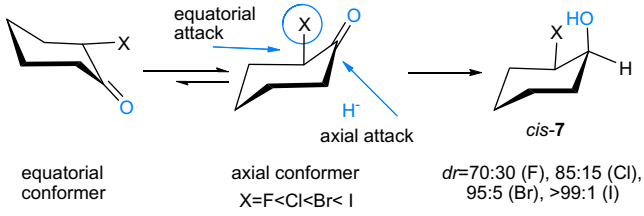
a) LiX/H_2O (Cl.Br,I) or Et_3N 3HF (X=F); b) DMSO/$(COCl)_2$/Et_3N;
c) $NaBH_4$/MeOH; d) 20% NaOH, 20°C, 2hr (X=Cl) or crystallization (X=Br, I)

Scheme 1. Synthesis of the racemic starting compounds.

Table 1
Preparation of racemic *cis*-2-halogenocycloalkanols

Compd	X	*n*	Reductant/solvent	Yields (%)	*cis*/*trans*
7a	I	2	$NaBH_4$/MeOH	70[b]	~100:0
7b	Br	2	$NaBH_4$/MeOH	65[b]	95:5
7c	Cl	2	$NaBH_4$/MeOH	70[a] (35[b])	88:12
7d	F	2	$NaBH_4$/MeOH	70[a]	70:30
7d	F	2	*i*-Bu_3B/THF	50[a]	75:25
7d	F	2	*i*-Bu_2AlH/toluene	50[a]	55:45
8a	I	1	$NaBH_4$/MeOH	80[b]	~99:1
8b	Br	1	$NaBH_4$/MeOH	65[b]	95:5
8d	F	1	$NaBH_4$/MeOH	70[a]	70:30

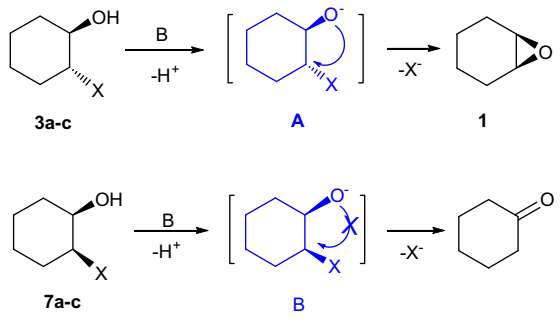
[a] Yields for the mixture of the *cis*- and *trans*-isomers.
[b] Yields for the purified *cis*-isomer.



Scheme 2. Sodium borohydride reduction of 2-halogen-substituted cyclohexanones.

equatorial forms: equatorial attack of the nucleophile leads to the formation of *trans*-alcohols while the axial attack provides the *cis*-alcohols.[11a–c] It has already been shown that the conformational equilibrium of 2-fluoro-, 2-chloro-, and 2-iodo-cyclohexanones is shifted toward the axial conformation and that the preference for the axial position increases with the size of the halogen atom: F < Cl < Br < I. The axial conformer is the prevailing form for the chloro- and bromocyclohexanones and is the major form for iodo-compounds in solvents.[11d–f] Therefore the conformationally mobile 2-halogencyclohexanones **5** give rise to the *cis*-2-halohydrins **7** through the conformation with the 2-substituent in the axial position (Scheme 2 and Table 1).

The *cis*-isomers of halogencycloalkanols are more stable toward hydrolysis than the *trans*-isomers. Unlike *trans*-isomers **3**, which upon alkali treatment easily convert into *cis*-epoxides **1**, *cis*-isomers **7** upon heating with alkali or with excess DBU convert to cyclohexanone. The *cis*-orientation of the oxygen and halogen atoms is unavailable for intramolecular S_N2 reaction with the formation of the epoxide. In this case, an alternative *anti*-conformation **B** (via a ring flip) is available for rearrangement via hydride migration and formation of the cyclohexanone (Scheme 3).



Scheme 3. Dehydrohalogenation of *cis*- and *trans*-2-halogencycloalkanols.

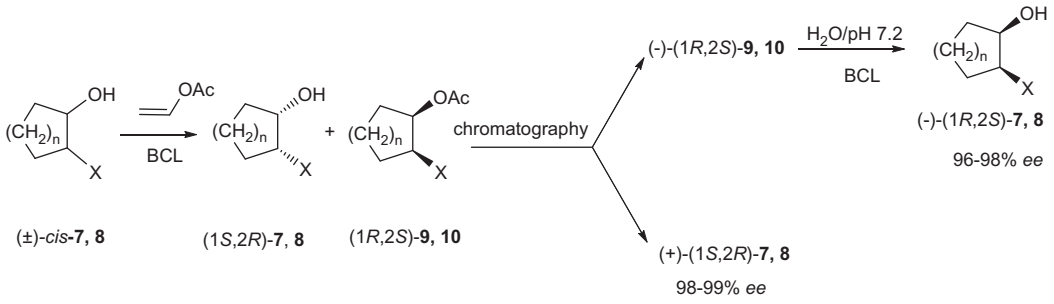
The NMR spectra allowed us to easily define the *cis*- and *trans*-isomers **3**,**4** and **7**,**8**. For example, in the ^1H NMR spectra of the *cis*-isomers the signals of the C*H*X protons are strongly shifted downfield.

2.2. Enzymatic resolution of 2-hydroxycycloalkanols

In order to obtain enantiomerically pure 2-halohydrins **7**,**8**, we tested a few lipases with well recognized stereoselective transesterification activity in organic solvents using vinyl acetate (VA) as the acyl transfer reagent. We tested *Candida antarctica* (CAL-B), *Pseudomonas cepacia* (PCL), and *Burkholderia cepacia* (BCL). The best results (highest ee) were obtained with BCL and therefore used this lipase.

Enzymatic esterification with vinyl acetate in the presence of BCL, immobilized on diatomite, allowed us to resolve the racemic *cis*-halogencycloalkanols into enantiopure optically active stereoisomers. The esterifications were carried out at room temperature and stopped at 50% conversion into the acetate. In all cases, the products were obtained with very good enantiomeric excesses (ee) (Scheme 4 and Table 2).

Generally with VA, slow esterifications of 15–18 h with 50% conversion into acetate **9** were observed. ^1H NMR spectroscopy was used to monitor the progress of the esterification (signal of C*H*OH and C*H*OAc). The enantiomeric purity and ee to the products of the enzymatic acylation were assigned by preparation of the Mosher esters with (*S*)-α-methoxy-α-trifluoromethylphenylacetic acid chloride [(*S*)-MTPA-Cl] according to a well established protocol.[11,12] For (1*S*,2*R*)-alcohols **7**, the ee (98–99%) of the enzymatic procedure was established by recording and analyzing the ^{19}F NMR spectra of the Mosher esters of each enzymatic preparation.

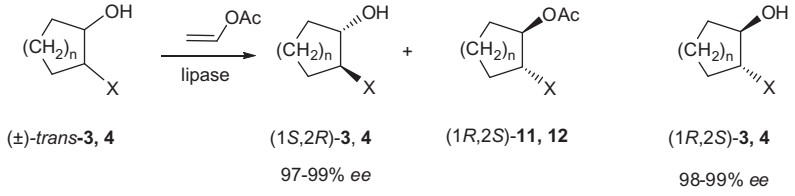


Scheme 4. Enzymatic resolution of *cis*-2-halogencycloalkanols **7**,**8**.

Table 2
Enzymatic resolution of vicinal halogencycloalkanes **3**,**4**,**7**,**8** through *Burkholderia cepacia* lipase-catalyzed esterification using vinyl acetate as an acyl donor

Substrate	Conversion (%)	τ (h)	Alcohol				Recovered alcohol				Acetate				E[a]
			Yield (%)	ee[b] (%)	$[\alpha]_D^{20}$[b]	Configuration	Yield (%)	ee[b] (%)	$[\alpha]_D^{20}$[b]	Configuration	Yield (%)	ee[c,d] (%)	$[\alpha]_D^{20}$	Configuration	
3a	50	16	45	99	+33.1	(1*S*,2*S*)	40	99	−32.0	(1*R*,2*R*)	45	98	−68.0	(1*R*,2*R*)	>100
3b	50	16	45	98	+32.0	(1*S*,2*S*)	42	99	−33.0	(1*R*,2*R*)	45	98	−68.0	(1*R*,2*R*)	>100
3c	50	15	40	97	+32.0	(1*S*,2*S*)	40	98	−30.0	(1*R*,2*R*)	44	96	−55.0	(1*R*,2*R*)	>100
4a	50	15	45	99	+33.0	(1*S*,2*S*)	44	98	−32.0	(1*R*,2*R*)	48	96	−52.0	(1*R*,2*R*)	>100
4b	50	15	46	98	+31.3	(1*S*,2*S*)	44	98	−33.2	(1*R*,2*R*)	48	96	−56.0	(1*R*,2*R*)	>100
7a	51	18	46	>99	−31.4	(1*S*,2*R*)	40	98	+31.1	(1*R*,2*S*)	48	98	+62.5	(1*R*,2*S*)	>100
7b	50	18	45	99	−31.7	(1*S*,2*R*)	42	99	+31.0	(1*R*,2*S*)	44	98	+61.0	(1*R*,2*S*)	>100
7c	50	16	45	98	−28.0	(1*S*,2*R*)	40	96	+30.0	(1*R*,2*S*)	44	96	+50.0	(1*R*,2*S*)	>100
8a	52	16	45	99	−31.5	(1*S*,2*R*)	40	98	+31.0	(1*R*,2*S*)	40	98	+62.6	(1*R*,2*S*)	>100
8b	50	16	45	99	−31.4	(1*S*,2*R*)	42	98	+30.9	(1*R*,2*S*)	48	98	+51.0	(1*R*,2*S*)	>100

[c] Obtained from the NMR spectra of the MTPA esters of the recovered alcohols, which were purified by recrystallization.
[a] Calculated by the acylated conversion and % ee of the product. $E = \ln[1 - c(1 + ee_p)]/\ln[(1 - c)(1 - ee_p)]$, where p = product.
[b] Determined by the ^{19}F NMR spectra of the respective MTPA esters.
[d] $[\alpha]_D$ and ee were defined for isolated and purified products.



Scheme 5. Enzymatic resolution of *trans*-2-halogencycloalkanols **3**,**4**.

After column chromatography separation, optically active alcohols (+)-(1*S*,2*R*)-**7** and acetates (−)-(1*R*,2*S*)-**9** were obtained with enantiomeric excesses of 96–99% and with an enantioselectivity factor of >100.

Acetates **9** were purified by vacuum distillation and then hydrolyzed in a phosphate buffer at pH 7.2 in the presence of BCL. Acetates **9**,**10** were also hydrolyzed by K_2CO_3 in methanol with the same ee and yields of hydrolyzed alcohols (1*R*,2*S*)-**7**,**8** (Table 2). From the hydrolysis, enantiomerically pure alcohols (+)-(1*S*,2*R*)-**7**,**8** and (−)-(1*R*,2*S*)-**7**,**8** were obtained. Additional low-temperature crystallization (at −20 °C) of the alcohols from hexane allowed us to obtain alcohols (+)-(1*S* 2*R*)-**7** and (−)-(1*R*, 2*S*)-**9** with de and ee >99%, which was determined by derivatization of the compounds by Mosher's acid.[11] Acylation of racemic *trans*-cyclohexanols **3**,**4** by vinyl acetate in the presence of BCL under kinetically controlled conditions (50% conversion of initial alcohol) led to the formation of alcohols (−)-(1*S*,2*R*)-**3** and (+)-(1*R*,2*S*)-acetates, which were separated by column chromatography (Scheme 5). Hydrolysis of the (+)-(1*R*,2*S*)-acetate in the phosphate buffer at pH 7.2 afforded the second stereoisomers of *trans*-cycloalkanols (+)-(1*R*,2*S*)-**3**,**4** with high enantiomeric purity (98–99% ee, after recrystallization in hexane). The enantiomerically pure 2-halogencycloalkanols were colorless low-melting compounds that were stable at room temperature or in a refrigerator. No racemization was observed during this work or storage.

2.3. Determination of the absolute configuration

Kazlauskas' rule[12] can be used for assignment of the absolute stereochemistry of the resolved halogencycloalkanols. Kazlauskas' rule is a simple empirical model based on the assumption that enantioselectivity is proportional to the size difference between the large (L) and medium-size (M) substituents in the substrate. According to Kazlauskas' rule, these substituents are located in two different pockets of the active site of an enzyme, in accordance with their sizes; this determines the absolute configuration of the products of the enzymatic reaction. According to Kazlauskas' rule, the biocatalytic acetylation of 2-halogencycloalkanols **3**,**4**,**7**,**8** should be (*R*)-selective (see Fig. 1). Consequently the biocatalytic transesterification of cycloalkanols should lead to the formation of (1*R*,2*S*)-acetates and (1*S*,2*R*)-cycloalkanols.

The absolute configuration of chiral acetates **9**,**10** was proven by dehydrohalogenation to give optically active 2-cycloalkenes (*R*)-**11**,**12** (Scheme 6).[13–15] Heating of the acetates at +70 °C in excess

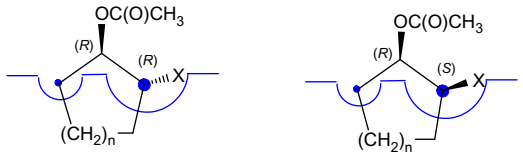
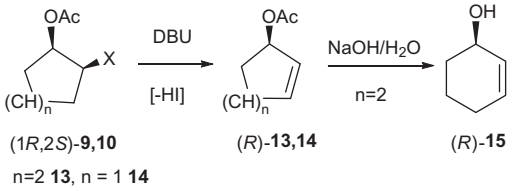


Figure 1. Kazlauskas' rule for the enantiopreference of BCL toward (±)-**3**,**4** (left) and (±)-**7**,**8** (right).



Scheme 6. Correlation of compounds **9**,**10a**–**c** with the 2-cycloalkenyl acetates **13**,**14**.

DBU for several hours led to the formation of enantiomerically pure cycloalkenyl acetates (+)-(*R*)-**13**,**14** in good yields, which were purified by vacuum distillation. The hydrolysis of (*R*)-**13** with 20% aq NaOH furnished (*R*)-cyclohexenol **15**.[8] The absolute configuration of compound (*R*)-**14** was assigned by comparison with the specific rotation of the known cyclopentenyl acetates.[13–16] From the absolute configuration of (*R*)-**13** and (*R*)-**14**, we were able to determine the absolute configuration of 2-halogencycloalkanols **7**,**8** by chemical correlation. Thereby, the biocatalytic esterification of racemic 2-cycloalkanols by vinyl acetate proceeded in accordance with Kazlauskas' rule.

3. Conclusion

In conclusion, enantiomerically pure (1*R*,2*S*)- and (1*S*,2*R*)-2-halogencycloalkanols were prepared via biocatalyzed kinetic resolution in good yields and with high enantiomeric excess. *Burkholderia cepacia* lipase showed excellent enantioselectivity as a biocatalyst for the transesterification of cyclohexanols with vinyl acetate. The absolute configuration of enantiomerically pure 2-halogencycloalkanols was determined by chemical correlation with known compounds. The biocatalytic esterification of 2-cycloalkanols with vinyl acetate proceeded in accordance with Kazlauskas' rule. In contrast to the chemo-catalyzed multi-step synthesis of chiral cyclic 2-halohydrins, the present methodology is straightforward, and uses commercially available lipases.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded in a $CDCl_3$ solvent on a 500 MHz spectrometer at ambient temperature. Chemical shifts (δ) are reported in ppm on a scale downfield from TMS as the internal standard. Signal patterns are as follows: s, singlet; d, doublet; dd, doublet of doublet; td, triplet of doublet; t, triplet; m, multiplet; br s, broad singlet. Coupling constants *J* are in Hertz. All reagents and solvents were reagent grade and used without further purification unless specified otherwise. Column chromatography was performed on Silica Gel 60 (70–230 mesh) using the specified eluents. Optical rotations were measured on a Perkin-Elmer 241 polarimeter (sodium D line at 20 °C). Melting points are uncorrected. All reactions were performed in flame-dried or oven-dried glassware with magnetic stirring. Lipase from *Burkholderia cepacia* (Amano PS) was purchased from Amano Pharmaceutical (Japan). The progress of the reactions and column chromatography separation of the resolved products was monitored by analytical thin layer chromatography (TLC) on pre-coated glass plates (silica gel 60 F_{254}-plate-Merck, Darmstadt, Germany) and the products were visualized by anisaldehyde. The purity of all compounds was verified by thin layer chromatography and NMR measurements.

4.2. Synthesis of racemic compounds

Racemic *trans*-2-chloro-, 2-bromo- and 2-iodocycloalkanols **7**,**8** were prepared according to earlier described methods, by the reaction of cyclohexene oxide or cyclopentene oxide with lithium halogenides.[9,17] *Trans*-2-fluorocyclohexanol and *trans*-2-fluorocyclopentanol were prepared by the reaction of cycloalkene oxides with triethylamine trihydrofluoride.[18]

4.2.1. Synthesis of racemic *cis*-halogencycloalkanols *rac*-7,8

Racemic *cis*-halogencycloalkanols were prepared by reduction of 2-halogencycloalkanones with sodium borohydride in methanol as described below.[19–21] The ^{1}H and ^{13}C NMR spectra allowed us to determine between the *cis*- and *trans*-isomers.

4.2.1.1. (a) Preparation of 2-halogencycloalkanone. To a solution of oxalyl chloride (2.9 g, 23 mmol) in 40 ml of methylene chloride were added dropwise 3.6 ml (50 mmol) of DMSO in 10 ml of methylene chloride at −70 °C. The *trans*-2-halogencycloalkanol (20 mmol) was added and the reaction mixture was stirred for 20 min. 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 hydrochloric acid solution. The water phase was separated and extracted with methylene chloride, the combined organic phases were washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was distilled under vacuum. *rac*-**5a**: yield 65%, bp 110 °C (10 mmHg).[22a] ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.40 (m, 1H, CH_2), 1.60 (m, 2H, CH_2), 1.90 (m, 1H, CH_2), 2.10–2.31 (m, 2H, CH_2), 2.45 (m, 2H, CH_2), 5.21 (m, 1H, CHI). *rac*-**5d**: yield 45%, bp 70 °C (10 mmHg).[22b] *rac*-**6a**: yield 65%, bp 100 °C (10 mmHg).[22c] *rac*-**5b**, *rac*-**5c**, *rac*-**6b**;[22c] were prepared by known methods.

(b) To halogencycloalkanones **5**,**6** (10 mmol) in 50 ml of methanol was added sodium borohydride (0.12 mol) at 0 °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 recrystallized from hexane. Spectroscopic data of **7b**–**d**; **8b**,**c** were in accordance with literature data.[20–22]

rac-**7a**. Yield 70%, mp 52–53 °C (hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (m, 2H, CH_2), 1.45–1.80 (m, 4H, CH_2), 1.19 (m, 2H, CH_2), 2.27 (m, 1H, OH), 3.16 (m, 1H, CHI), 4.71 (s, 1H, CHOH). ^{13}C NMR (125.74 MHz, $CDCl_3$): δ 21.93 (s, CH_2), 24.48 (s, CH_2), 32.23 (s, CH_2), 34.12 (s, CH_2), 46.51 (s, CHI), 71.01 (s, CHOH). Found (%): C, 31.38; H, 4.50. $C_6H_{11}IO$. Calculated (%): C, 31.88; H, 4.90.

rac-**7b**. Yield: 65%, bp 115 °C (12 mmHg). Mixture of *cis*- and *trans*-isomers **7b** and **3b** in ratio of 95:5. After crystallization in hexane at −20 °C the product was obtained as a pure *cis*-isomer of *rac*-**7b**. Colorless prisms. Mp 34 °C. (lit.[20,21], oil, bp 69 °C/14 mmHg) mixture of *cis*- and *trans*-isomers)

rac-**7c**. The product was obtained as a mixture of *cis*- and *trans*-isomers **7c** and **3c**. The mixture of **3c** and **7c** was treated with 1 M sodium hydroxide for 1.5 h at room temperature. The product was extracted with methylene chloride. The solvent was then evaporated. ^{1}H and ^{13}C NMR analyses of the residue showed the presence

of *cis*-2-chlorocyclohexanol **7c**, cyclohexene epoxide, cyclohexanone, and only trace amounts (~1%) of the *trans*-isomer **3c**. The residue was then distilled under vacuum, bp 70 °C (12 mmHg). After recrystallization from hexane the product was obtained as pure *cis*-**3c**. Yield 35%, colorless prisms, mp 30 °C (hexane, −20 °C), [lit. oil, bp 75 °C (8 mmHg), mixture of *cis* + *trans*-isomers].[21]

rac-**7d**. Yield 70%, bp 60 °C (12 mmHg). ^{1}H 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, 1 H, CH_2), 2.4 (br, 1 H, OH), 3.78 (d, 1H, J = 5, CHOH), 4.69 (dd, $J_{H,F}$ = 40 Hz, J = 3 Hz, 1 H, CHF), ^{13}C NMR (125.74 MHz, $CDCl_3$): 20.90 s, 22.00 s, 28.50 s, 30.10 s, 70.0 s, 92.87.[21,23]

rac-**8a**. Yield 80%, bp 70 °C (12 mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.61–1.54 (m, 1H), 1.84–1.78 (m, 2H), 2.15–2.01 (m, 2H), 2.39–2.32 (m, 1H), 4.05–4.01 (m, 1H), 4.45–4.42 (m, 1H). ^{13}C NMR (125.74 MHz, $CDCl_3$): δ 21.51 s, 23.31 s, 30.28 s, 34.63 s, 74.96 s. Found (%): C, 28.38; H, 4.50. C_5H_9IO. Calculated (%): C, 28.32; H, 4.28.

rac-**8b**. Yield 65%, ~100% de, mp ~0 °C (hexane, −50 °C) (lit.[20] mixture of *cis* + *trans*-isomers).

rac-**8d**. Yield of 70%. Bp 50 °C (12 mm Hg). lit.[21] mixture of *cis* + *trans*-isomers).

The preparation of pure *cis*-2-fluorocycloalkanols **7d**, **8d** and their resolution into enantiomers is currently underway.

4.3. Lipase-mediated resolution of racemic 2-halogencycloalkanols

4.3.1. General procedure

A solution of suitable 2-halogencycloalkanol (20 mmol), lipase (0.3 g), vinyl acetate, (10 ml) and *t*-BuOMe (10 ml) was stirred at +24 °C and the formation of the acetylated compounds was monitored by TLC and NMR analyses. The reaction mixture was stirred up to 50% conversion of the starting alcohol. The reaction mixture was filtered, concentrated under vacuum, and the resulting oil was purified by chromatography on silica gel using hexane–ethyl acetate (95:5–3:1) as eluent. Alcohols were additionally recrystallized in hexane. Acetates were distilled under vacuum.

Acetates **9**,**10** (10 mmol) were hydrolyzed by K_2CO_3 (2 g) in 20 ml of methanol with stirring at room temperature. The hydrolysis was monitored by TLC analysis. The solvent was removed and the residue was extracted with ethyl acetate. The extract was then evaporated and the residue was crystallized from hexane to afford the recovered alcohol. The 2-iodocyclohexyl acetate (1*R*,2*S*)-**9a** was also hydrolyzed in a phosphate buffered water solution using BCL and then recrystallized from hexane (See below).

4.3.2. Resolution of *cis*-2-iodocyclohexanol 7a

4.3.2.1. (−)-2-Iodocyclohexanol (1*S*,2*R*)-7a. Yield 46%, mp 52–53 °C (hexane), $[\alpha]_D^{20} = -31.4$ (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (m, 2H, CH_2), 1.45–1.80 (m, 4H, CH_2), 1.19 (m, 2H, CH_2), 2.27 (m, 1H, OH), 3.16 (m, 1H, CHI), 4.71 (s, 1H, CHOH). ^{13}C NMR (125.74 MHz, $CDCl_3$): δ 21.93 s, 24.48 s, 32.23 s, 34.12 s, 46.51 s, 71.01 s. Calculated (%): C, 31.88; H, 4.90. $C_6H_{11}IO$. Found (%): C, 31.38; H, 4.50.

4.3.2.2. (+)-2-Iodocyclohexyl acetate (1*R*,2*S*)-9a. Yield 48%, bp 115 °C (10 mmHg), $[\alpha]_D^{20} = +62.5$ (*c* 3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.40–1.65 (m, 4H, CH_2), 1.85 (m, 1H, CH_2), 2.00–2.10 (m, 4H, CH_2), 2.15 (s, 3H, CH_3), 2.45 (m, 1H, OH), 4.05 (m, 1H, CHI), 4.95 (m, 1H, C*H*OAc). ^{13}C NMR (125.74 MHz, $CDCl_3$): δ 21.30 s, 22.40 s, 23.77 s, 29.30 s, 34.44 s, 36.04 s, 72.95 s, 170.16 s. Calculated (%): C, 35.84; H, 4.89. $C_8H_{13}IO_2$. Found (%): C, 35.68; H, 4.71.

4.3.2.3. (+)-2-Iodocyclohexanol (1*R*,2*S*)-7a. Acetate **9a** (5 mmol) was hydrolyzed in a phosphate buffered water solution at a constant pH value of 7.2 using BCL as a biocatalyst (0.2 g) with stirring and room temperature. The hydrolysis was monitored by TLC analysis and ^{1}H NMR. The lipase was then filtered off and washed out with methylene chloride. The solvent was removed and the residue was extracted with ethyl acetate. The extract was evaporated and the residue was recrystallized from hexane to afford the recovered alcohol. Yield 60% (28% from starting *rac*-**7a**), mp 50 °C (hexane), $[\alpha]_D^{20} = +31.1$ (*c* 1, $CHCl_3$). ^{1}H and ^{13}C NMR spectra are similar to those of (1*S*,2*R*)-**7a**.

4.3.3. Resolution of *cis*-2-bromocyclohexanol 7b

4.3.3.1. (−)-2-Bromocyclohexanol (1*S*,2*R*)-7b. Yield 45%, mp 32–34 °C, $[\alpha]_D^{20} = -31.7$ (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.55–1.65 (3H, m), 1.75–1.85 (3H, m), 1.9–2.1 (1H, m), 2.15–25 (1H, m), 4.02 (1H, m), 4.32 (1H, m). ^{13}C NMR (125.74 MHz, $CDCl_3$): δ 24.3 s, 26.7 s, 33.8 s, 36.4 s, 61.9 s, 75.5 s. Calculated: C 40.25; H 6.19; Br 44.63 for C_6H_{11} BrO. Found: C 40.25; H 6.19; Br 44.63.

4.3.3.2. (+)-2-Bromocyclohexyl acetate (1*R*,2*S*)-9b. Yield 42%, bp 45 °C (0.1 mmHg). $[\alpha]_D^{20} = +61.0$ (*c* 5, $CHCl_3$). R_f 0.36 ($CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.4–1.5 (m, 2H), 1.6–1.8 (3H, m, CH_2), 1.8–1.9 (2H, m, CH_2), 2.27 (3H, s, CH_3CO), 4.5 (1H, s, CHBr), 4.72 (1H, s, CHOAc). ^{13}C NMR (125.74 MHz, $CDCl_3$): δ 22.06 s, 22.20 s, 28.06 s, 32.86 s, 34.35 s, 72.48 s, 170.02 s.

4.3.3.3. (+)-2-Bromocyclohexanol (1*R*,2*S*)-7b. Yield 42%, mp 32–34, $[\alpha]_D^{20} = +31.0$ (*c* 1, $CHCl_3$).

4.3.4. Resolution of *cis*-2-chlorocyclohexanol 7c

4.3.4.1. (−)-2-Chlorocyclohexanol (1*S*,2*R*)-7c. Yield 45%, mp 38 °C (hexane, −20 °C), bp 76–83 °C (13 mmHg) $[\alpha]_D^{20} = -28$ (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25–1.44 (3H, m), 1.6–1.88 (3H, m), 2.15 (1H, m), 2.35 (1H, m), 2.58 (1H, s), 3.62 (1H, m), 3.92 (1H, m). ^{13}C NMR (125.74 MHz, $CDCl_3$): δ 24.1 s, 25.8 s, 33.6 s, 35.3 s, 67.5 s, 75.5 s.

4.3.4.2. (+)-2-Chlorocyclohexyl acetate (1*R*,2*S*)-9c. Yield 44%, colorless oil, bp (10 mmHg), R_f 0.45 ($CHCl_3$), $[\alpha]_D^{20} = +50.0$ (*c* 5, $CHCl_3$). ^{1}H NMR ($CDCl_3$–500 MHz): δ 1.44–1.55 (2H, m), 1.65–1.8 (3H, m), 1.85–2.0 (2H, m), 2.15 (3H, s), 4.5 (1H, m), 4.85 (1H, m). ^{13}C NMR (125.74 MHz, $CDCl_3$): δ 20.84 s, 21.23 s, 27.24 s, 32.25 s, 38.73 s, 60.48 s, 72.63 s, 170.34 s.

4.3.4.3. (+)-2-Chlorocyclohexanol (1*R*,2*S*)-7c. Yield 40%, colorless prisms, mp 36 °C (hexane, −20 °C). $[\alpha]_D^{20} = +30$ (*c* 1, $CHCl_3$).

4.3.5. Resolution of *cis*-2-iodocyclopentanol 8a

4.3.5.1. (−)-2-Iodocyclopentanol (1*S*,2*R*)-8a. Yield 45%, mp ~0 °C. $[\alpha]_D^{20} = -31.5$ (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.61–1.54 (1H, m), 1.84–1.78 (2H, m), 2.15–2.01 (2H, m), 2.39–2.32 (1H, m), 4.05–4.01 (1H, m), 4.45–4.42 (1H, m). ^{13}C NMR ($CDCl_3$, 125.74 MHz): δ 21.51 s, 23.31 s, 30.28 s, 34.63 s, 74.96 s. Calculated (%): C, 28.32; H, 4.28 for C_5H_9IO. Found (%): C, 28.38; H, 4.50.

4.3.5.2. (+)-2-Iodocyclopentyl acetate (1*R*,2*S*)-10a. Yield 40%, $[\alpha]_D^{20} = +62.6$ (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30–1.40 (2H, m, CH_2), 1.7–1.8 (2H, m, CH_2), 1.9 (1H, m, CH_2), 2.10 (3H, m, CH_3), 4.1 (1H, m, CHBr), 5.20 (1H, m, CHOAc).

4.3.5.3. (+)-2-Iodocyclopentanol (1*R*,2*S*)-8a. Yield 42%, colorless oil at room temperature, mp ~0 °C (hexane, −20 °C), $[\alpha]_D^{20} = +31.0$ (*c* 1, $CHCl_3$).

4.3.6. Resolution of *cis*-2-bromocyclopentanol 8b

4.3.6.1. (−)-2-Bromocyclopentanol (1*S*,2*R*)-8b. Yield 45%, mp ~0 °C, $[\alpha]_D^{20} = -31.4$ (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ

1.45 (m, 2H, CH_2), 1.45–1.80 (m, 4H, CH_2), 1.19 (m, 2H, CH_2), 2.27 (m, 1H, OH), 3.16 (m, 1H, CHI), 4.71 (s, 1H, CHOH). ^{13}C NMR (125.74 MHz, $CDCl_3$): δ 21.93 s, 24.48 s, 32.23 s, 34.12 s, 46.51 s, 71.01 s.

4.3.6.2. (+)-2-Bromocyclopentyl acetate (1*R*,2*S*)-10b. Yield 42%, $[\alpha]_D^{20} = +51.0$ (*c* 1, $CHCl_3$), R_f 0.36 ($CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 1.3–1.45 m (2H, CH_2), 1.55–1.7 m (2H, CH_2), 1.8–2.0 m (2H,CH_2), 2.12 s (3H, CH_3), 4.46 m (1H, CHBr), 4.97 m (1H CHOAc). ^{13}C NMR (125.74 MHz, $CDCl_3$): δ 19.75 s, 20.92 s, 27.77 s, 33.50 s, 53.12 s, 75.70 s, 170.4 s.

4.3.6.3. (+)-2-Bromocyclopentanol (1*R*,2*S*)-8b. Yield 40%, mp <0, $[\alpha]_D^{20} = +30.9$ (*c* 1, $CHCl_3$).

4.3.7. Resolution of *trans*-2-halogencycloalkanols 3a–c

We carried out the biocatalytic kinetic resolution of *trans*-2-halogencyclohexanols with vinyl acetate in the presence of BCL. The resolution of these compounds was performed by biocatalytic hydrolysis of the acetates in the presence of *Candida cylindracea lipase*, *Pseudomonas* sp. *lipase*, and also by *trans*-esterification with vinyl acetate catalyzed by *Pseudomonas fluorescencia lipase* **7**,**8**. It was necessary for us to compare the results of the resolution for the *cis*- and *trans*-2-halogeno–hydrins under the same conditions. The results can be seen in Table 2. The data in Table 2 clearly show that the biocatalytic resolution of *cis*- and *trans*-2-halogenhydrins follows Kazlauskas' rule.

4.4. Determination of the enantiomeric purity of the compounds

The enantiomeric excesses of the compounds were determined by the formation of the Mosher esters of (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride [(*S*)-MTPA-Cl] with halogencycloalkanols: to a solution of an alcohol (0.1 mmol) and pyridine (0.2 mmol) in 0.5 ml of absolute THF was added a solution of MTPA-Cl (26 mg, 0.11 mmol) in 0.5 ml of THF at −70 °C. The temperature was increased to room temperature and the reaction mixture was centrifuged. The centrifugate was analyzed by ^{19}F NMR and ^1H NMR spectra. Two signals were discovered in racemic alcohols at −71–72 ppm (^{19}F) and 3.55–3.60 ppm (^1H, MeO-group) and only one signal was present in the kinetically resolved alcohols.

4.5. Determination of the absolute configuration of 2-halogencycloalkenols 7,8

The absolute configuration of the compounds was assigned by chemical correlation with the known 2-cyclohexenyl acetates and cyclopentenol as described below.

4.5.1. Correlation of compounds 7,8 a–c with the 2-cycloalkenyl acetates 13,14

4.5.1.1. 2-Cyclohexenyl acetate (*R*)-13. A mixture of (+)-(1*R*,2*S*)-2-iodo- or bromocyclohexyl acetate **9a**,**b** (2 g) and DBU (5 ml) was heated for 12 h at 70 °C, then the reaction mixture was diluted with ether, filtered, and washed with dilute hydrochloric acid and an aqueous solution of sodium bicarbonate. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography and bulb to bulb distillation to afford the 2-cyclohexenyl acetate (*R*)-**13.** Yield 45–50%, bp 60 °C (10 mmHg). $[\alpha]_D^{20} = +180$ (*c* 3, $CHCl_3$).[7b] ^1H NMR (500 MHz, $CDCl_3$): δ 2.02 (3H, s, CH_3), 2.29–1.63 (6H, m, CH_2), 5.73–5.67 (1H, m, OH), 5.99–5.92 (1H, m, CH═), 5.28–5.23 (1H, m, CH═).

4.5.1.2. 2-Cyclopentenyl acetate (*R*)-14. The evaporation in vacuo should be carried out with caution because of the volatility of the product. The 2-cyclopentenyl acetate was purified by flash chromatography (pentane–ether). Colorless oil. Yield 25%, $[\alpha]_D^{20} = +170$ (*c* 1, $CHC1_3$) {lit.[24a] $[\alpha]_D^{20} = -83.8$ (*c* 1.09, CH_2C1_2), 41% ee for the (*S*)-absolute configuration}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.09–6.07 (1H, m), 5.81–5.79 (1H, m), 5.68–5.65 (1H, m), 2.52–2.47 (1H, m), 2.31–2.23 (2H, m,), 2.01 (3H, s,), 1.81–1.75 (1H, m,). ^{13}C NMR (125.74 MHz, $CDCl_3$): δ 170.9, 137.5, 129.1, 80.4, 30.9, 29.6, 21.2.

4.5.1.3. 2-Cyclohexen-1-ol (*R*)-15. To a solution of 2-cyclohexenyl acetate (*R*)-**13** (1.1 g, 8.0 mmol) in 1.5 ml of methanol was added a solution of NaOH (1 M, 15 ml). The mixture was stirred overnight at room temperature. The mixture was then extracted with methylene chloride. The extract was evaporated and the residue was distilled under vacuum. Yield 0.60 g (80%), colorless oil, bp 96–97 °C (75 mmHg), $[\alpha]_D^{20} = +123.5$ (*c* 2, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 2.11–1.39 (7H, m), 4.29–4.03 (1H, m, CHOH), 5.97–5.58 (2H, m, CH═).[24b]

Acknowledgments

This work was financially supported by the State Foundation for Basic Research of Ukraine and the Russian Foundation for Basic Research (joint Project No. F40.3/034).

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