

Convergent method for the determination of the absolute configurations of 2,3-dihydro-1*H*-inden-1-ols

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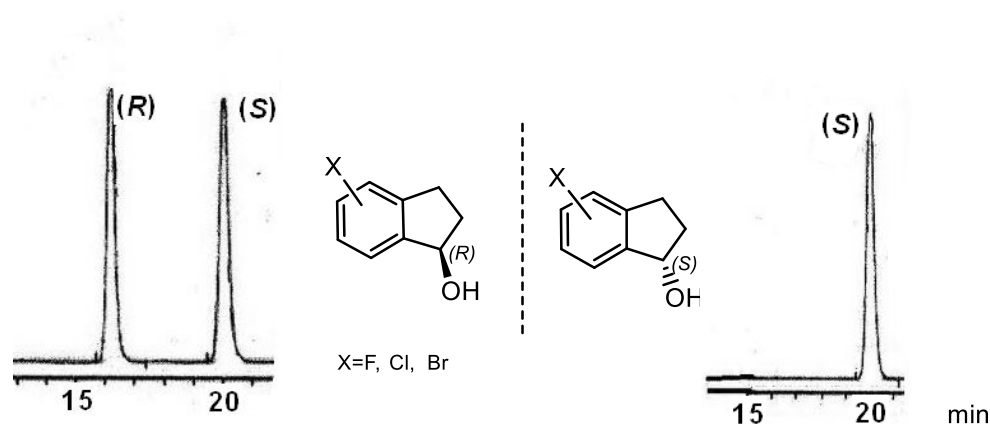
Received 07-19-2022

Accepted Manuscript 08-25-2022

Published on line 08-31-2022

Abstract

Racemic 2,3-dihydro-1*H*-inden-1-ols were resolved into enantiomers using kinetically controlled esterification of dihydroindenols by vinyl acetate with biocatalysis with *Burkholderia cepacia* lipase. The absolute configuration of halodihydroindenol enantiomers was defined by a convergent method of chiral HPLC analysis in combination with enzymatic analysis as well as single crystal X-Ray diffraction. The combined use of these methods increases the reliability in determining the absolute configurations of the studied compounds.



Keywords: Enzymatic deracemization, absolute configuration, enzymatic analysis, Kazlauskas rule, chiral HPLC

Introduction

Chiral HPLC has a number of extremely attractive properties, since it allows one to determine the optical purity of compounds in a short time and to carry out preparative resolution of enantiomers up to 100% *ee*.^{1,2} In addition, a very important advantage of this method is its use to determine the structure and absolute configuration of various natural and synthetic bioactive molecules. Biological compounds often contain multiple stereocenters, and in these situations classical methods may involve several complex and time-consuming steps. The solution to the absolute configuration problem can be effectively achieved using chiral HPLC, since it can be performed in a single step, starting by comparing the retention time of an unknown synthetic or natural sample with the retention time of reference enantiomers.

Results and Discussion

In this work, we investigated the possibility of determining the absolute configuration of optically active halogen-substituted dihydroindenols, which are components of various biologically active compounds, using chiral HPLC. In addition to chiral HPLC, we used enzymatic analysis of halo-2,3-dihydroinden-1-ols to establish the absolute configurations of the compounds, followed by comparison of the results of determining the configuration by two methods. Halo-2,3-dihydro-1*H*-inden-1-ols are synthetic building blocks for the creation of pharmaceuticals, insecticides, peptide nucleic acids, and bioregulators. For example, indinavir is an oral drug used to treat human immunodeficiency virus infection.³ *Cis*- and *trans*-indane derivatives are the key chiral synthons for the synthesis of indinavir.⁴⁻⁶ Another important pharmaceutical product based on indanes is Ladostigil, used for the treatment of Alzheimer's and Parkinson's diseases, which can slow down the development of clinical signs within a relatively short time. For the preparation of halo-2,3-dihydroinden-1-ols various methods have been used, mostly with metal complex catalysis.⁷⁻⁹

It should be noted that currently, the requirements for enantiomeric purity and unambiguity in determining the absolute configuration of biologically active compounds, especially pharmaceuticals, have increased significantly. Evidence of this is the recent FDA regulations and the growing proliferation of "Chiral Switch" methods.^{6,10} Of great importance in this case is the reliability of absolute configuration definitions, since errors occur in some cases. For example, errors were made in determining the configuration of some halo-2,3-dihydro-1*H*-inden-1-ols. There is still controversy over the specific stereochemistry of (*S*)-4-bromo-2,3-dihydro-1*H*-inden-1-ol, (*R*)-5-bromo-2,3-dihydro-1*H*-inden-1-ol, and (*R*)-5-chloro-2,3-dihydro-1*H*-inden-1-ol.⁷⁻⁹ To obtain enantiomerically pure halo-2,3-dihydro-1*H*-inden-1-ols, we have used the enzymatic resolution of these biologically active compounds with *Burkholderia cepacia* lipase, which had not previously been used for this purpose. Therefore, the development of convenient express methods for determining the absolute configuration of 2,3-dihydro-1*H*-inden-1-ols is undoubtedly an interesting and useful problem in practical terms. The chiral HPLC, enzymatic analysis and X-ray diffraction analysis allow the determination of the absolute configuration of halo-2,3-dihydro-1*H*-inden-1-ols to be convergent. The methods of biocatalytic resolution and chiral HPLC have much in common. First of all they are able to suggest how the deracemization of the secondary alcohol will occur. When using a Chiralcell OJ-H chiral column, (*S*)-alcohols are more strongly retained by the chiral stationary phase and therefore the alcohol having the (*R*)-configuration is eluted first. This is because the (*S*)-secondary alcohol forms a strong hydrogen bond with the chiral sugar contained in the stationary phase.^{11,12} In the case of enzymatic esterification of secondary alcohols catalyzed by lipases, the (*R*)-alcohol predominantly enters the esterification reaction and the (*R*)-ester is formed, while the (*S*)-alcohol

remains unreacted, as a result of which the reaction mixture can be easily separated by column chromatography. According to the Kazlauskas rule,¹³ the enantioselectivity of enzymatic deracemization should be proportional to the difference in size between the large (L) and medium (M) substituents in the substrate. The physical essence of the Kazlauskas rule is determined by the structure of the lipase active center, which has two pockets - one large, the other smaller, which determine the orientation of substrate substituents in the active center. Thus, in accordance with the structure of active center, the orientation of the secondary alcohol occurs during the esterification and hydrolysis of corresponding esters.^{14,15,16} Resolution of halo-2,3-dihydroinden-1-ols into enantiomers was carried out by acylation with vinyl acetate under kinetic control conditions in the presence of *Burkholderia cepacia* lipase. The reaction was brought to 50% conversion, then the reaction was stopped by filtration of the biocatalyst. The resulting mixture of unreacted alcohol and acetate was separated by column chromatography. For carrying out the kinetic transesterification of halo-2,3-dihydroindenols, *tert*-butyl methyl ether (MTBE) turned out to be the best solvent, and *Burkholderia cepacia*, at the temperature of 35 °C, turned out to be the best biocatalyst. In this case, completion of the reaction at 50% conversion resulted in acylation of only the (*R*)-enantiomer of the racemic mixture.¹⁷ As a result, unreacted (*S*)-2,3-dihydro-1*H*-inden-1-ol and (*R*)-2,3-dihydro-1*H*-inden-1-yl acetate were obtained in high chemical yield and high enantiomeric excess (*ee*). Subsequent hydrolysis of (*R*)-dihydroindenyl acetate gave dihydroindenol of (*R*)-configuration.¹⁴ Thus, both (*S*)- and (*R*)-enantiomers of halo-2,3-dihydroindenols were obtained (Figures 1, 2 and Table 1)

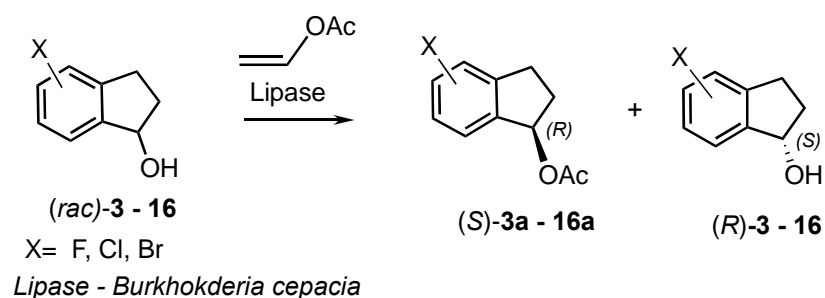


Figure 1. Resolution of racemic halo-2,3-dihydro-1*H*-indenols (*rac*)-3 - 16 via enzymatic esterification.

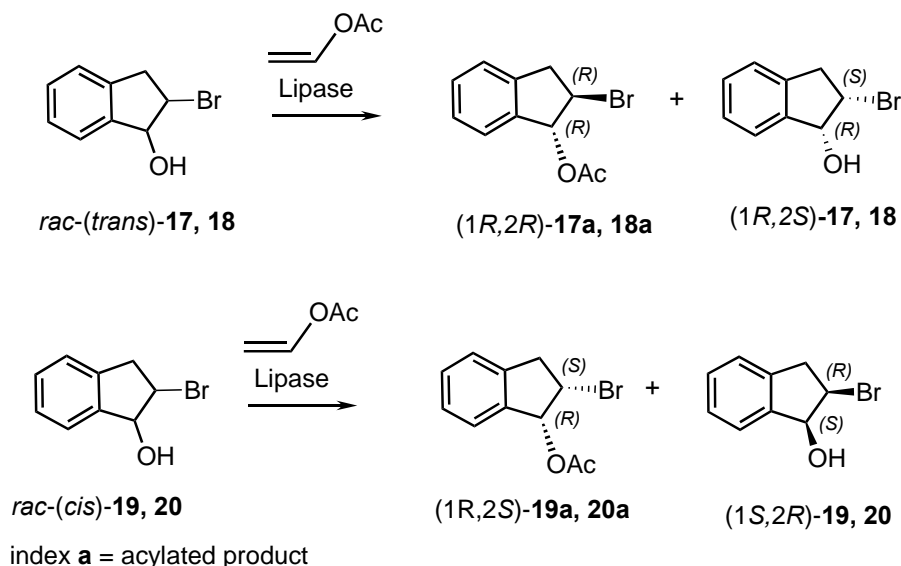


Figure 2. Resolution of *cis*- and *trans*-2-bromo-2,3-dihydro-1*H*-inden-1-ols 17, 18 and 19, 20.

The kinetic enzymatic hydrolysis of dihydroindenyl acetates was also carried out in a two-phase system with a pH 7.2 buffer solution in MTBE in the presence of a Novozyme 435[®] (CALB) biocatalyst at the temperature of 45 °C. The reaction was completed when 50% conversion was reached, which ensured the resolution of racemic mixture into stereoisomers in high chemical yield and high enantiomeric purity. Further hydrolysis of unreacted (*S*)-halo-2,3-dihydroindenyl acetate gave (*S*)-halo-2,3-dihydro-1*H*-inden-1-ol (Figure 3). The Novozym 435[®] (immobilized *Candida antarctica* B lipase) is heat resistant, so we investigated the effect of reaction temperature on the *ee* of product under the same conditions using diisopropyl ether (IPE) as solvent. Lowering the reaction temperature to 30 °C had no significant effect on enantioselectivity or reaction rate. Under optimal conditions, the treatment of acetates **3a-16a** with Novozyme 435[®] in dibutyl ether for 30 hours at 40 °C led to the conversion of (*rac*)-acetate to (*R*)-halo-2,3-dihydro-1*H*-inden-1-ol **3-16** in yield 49% and with 92% *ee*, respectively.¹⁶

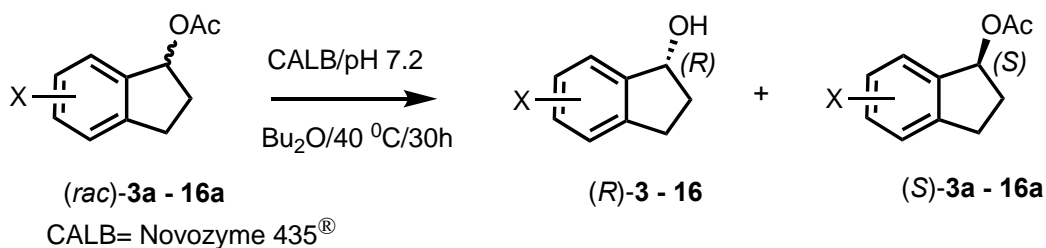


Figure 3. Resolution of haloindenyl acetates (*S/R*)-**3a - 16a** by enzymatic hydrolysis with Novozyme 435[®].

Thus, all samples of fluoro-, chloro-, bromo-2,3-dihydro-1*H*-inden-1-ols were resolved into (*S*)- and (*R*)-enantiomers isolated in pure form and characterized by physicochemical methods.¹⁷ Some compounds were synthesized by metal complex catalysis, although with a lower enantiomeric purity.⁹ The racemic and enantiomerically pure (*S*)- and (*R*)-enantiomers were then subjected to chiral HPLC analysis. Comparison of the stereochemical properties of the compounds obtained by enzymatic resolution, chiral HPLC, and compounds described in the literature confirmed the unambiguous determination of the absolute configuration in all cases.^{18,19} The results of these studies are shown in Figure 4 using (*rac*)-, (*S*)- and (*R*)-5-chloro-2,3-dihydro-1*H*-inden-1-ols as examples. As expected, the racemate was represented by two peaks of the (*S*)- and (*R*)-enantiomers, as well as single peaks of resolved enantiomers. This experiment confirmed that the acylation of a secondary alcohol with vinyl acetate catalyzed by *Burkholderia cepacia* lipase is strictly (*R*)-selective. In addition, the unambiguous resolution of enantiomers on a Chiralcel OJ-H chiral column was confirmed: the (*S*)-enantiomer is more strongly retained by the stationary phase than the (*R*)-enantiomer. In addition, as follows from the results shown in Figure 4, the resolution of racemic 2,3-dihydro-1*H*-inden-1-ols is extremely efficient and gives practically pure (*S*)- and (*R*)-enantiomers. Our developed methodology provides easy access to both (*S*)- and (*R*)-enantiomers of halo-2,3-dihydro-1*H*-inden-1-ols in high optical purity.

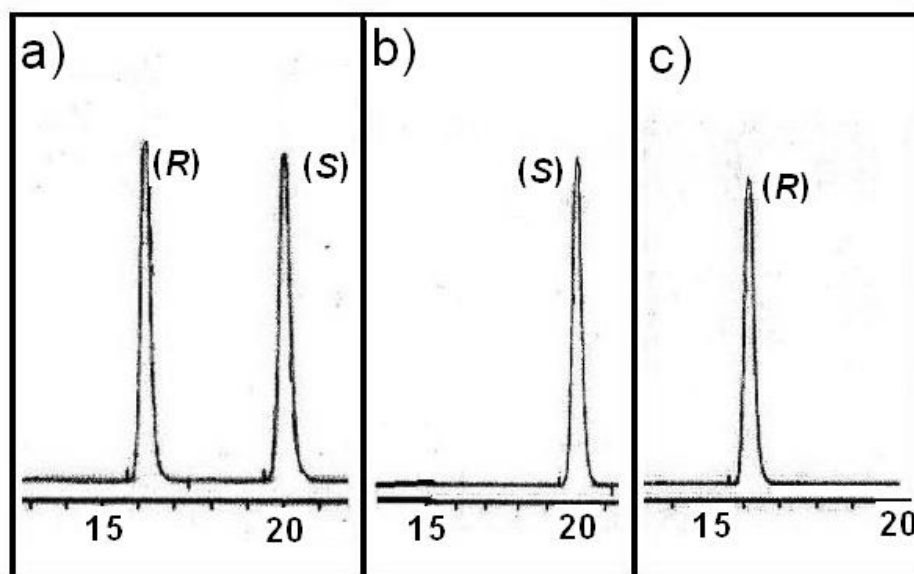
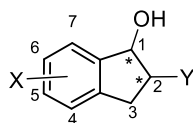


Figure 4. 5-Chloro-2,3-dihydro-1*H*-inden-1-ol analysis by chiral HPLC: a) racemate; b) (*S*)-**11**; c) (*R*)-**12**; (Chiralcel OJ-H chiral column (250x4.6 mm, with tris(4-methylbenzoate)cellulose selector applied to 5 μ m silica gel)).

Fluoro-, chloro- and bromo-2,3-dihydroindenols **3-20** resolved by enzymatic resolution were obtained as colorless crystalline substances, whose structure and chemical purity were confirmed by NMR, HRMS, HPLC. Optical purity was further established using Mosher acid derivatization and chiral liquid chromatography. In the general case, it was at the level of 96-99% *ee*.

Since the determination of absolute configuration has traditionally been limited to the relatively time-consuming method of X-ray crystallography, the development of alternative methods for the analysis of optically active substances to determine the absolute configuration will be very useful. An important aspect of the chiral HPLC method is that it can be used to determine the absolute configuration, even for a crude mixture of enantiomers. We have applied this method to determine the absolute configuration of halo-2,3-dihydro-1*H*-inden-1-ols and expect it to be generally applicable to various five-membered cyclic compounds (both 2,3-dihydroindenols and cyclopentane derivatives).

Table 1. Absolute configuration definition halo-2,3-dihydro-1*H*-indenols

Entry	Compound	X	Y	Mp (°C)	Configuration	$[\alpha]_D^{20}$	τ (minute)	HPLC	Note
1	3	4-F	H	100	<i>S</i>	+17.0 ^{a)}	18.5	c)	-
2	4	4-F	H	100	<i>R</i>	-17.0 ^{a)}	15.2	c)	-
3	5	5-F	H	100	<i>S</i>	+17.0 ^{a)}	17.83	c)	-
4	6	5-F	H	100	<i>R</i>	-17.0 ^{a)}	14.69	c)	-
5	7	6-F	H	100	<i>S</i>	+14.9 ^{a)}	14.1	c)	h)
6	8	6-F	H	100	<i>R</i>	-15.9	12.8	c)	-
7	9	4-Cl	H	105	<i>S</i>	+20.0 ^{a)}	10.58	d)	-
8	10	4-Cl	H	105	<i>R</i>	-20.0 ^{a)}	9.24 ^{b)}	d)	-
9	11	5-Cl	H	105	<i>S</i>	+28.0 ^{a)}	20.03	d)	i)
10	12	5-Cl	H	105	<i>R</i>	-28.0 ^{a)}	16.17 ^{c)}	d)	j).
11	13	4-Br	H	85	<i>S</i>	+19.0 ^{a)}	10.58	c)	k)
12	14	4-Br	H	102	<i>R</i>	-18.9 ^{a)}	9.24 ^{b)}	c)	-
13	15	5-Br	H	100	<i>S</i>	+20.0 ^{a)}	11.2	e)	-
14	16	5-Br	H	85	<i>R</i>	-25.0 ^{a)}	9.9	e)	l)
15	17	4-H	2-Br	113	1 <i>S</i> ,2 <i>S</i>	+63.2 ^{a)}	18.06	f)	-
16	18	4-H	2-Br	116	1 <i>R</i> ,2 <i>R</i>	-61.5 ^{a)}	12.43	f)	-
17	19	4-H	2-Br	103	1 <i>S</i> ,2 <i>R</i>	+61.5 ^{a)}	12.44	g)	-
18	20	4-H	2-Br	113	1 <i>R</i> ,2 <i>S</i>	-53.1 ^{a)}	17.98	g)	-

^{a-g)} Conditions of HPLC resolution: Chiralcel OJ-H chiral column (250*4.6 m μ) with tris(4-methylbenzoate) cellulose selector supported on 5 g of silica gel): ^{a)} CHCl₃, C= 0.1; ^{b)} EtOH; C=0.1; ^{c)} Hexane-*i*-Pr₂O 97:3; ^{d)} Hexane-*i*-Pr₂O-MeOH 95-2.5-2.5; ^{e)} Hexane-*i*-Pr₂O 97-3; ^{f)} Hexane-*i*-Pr₂O 90:10; ^{g)} Hexane-*i*-Pr₂O 80:20; ^{h)} $[\alpha]_D^{20} = +14.9$ (c 5.6, CHCl₃). ^{9 i)} $[\alpha]_D^{20} = +14.8$ (c 7.3, CHCl₃). ^{9 j)} $[\alpha]_D^{20} = -9.2$ (c 8.3, CHCl₃). ^{7 k)} $[\alpha]_D^{25} = +15.8$ (c 1.0, CHCl₃). ^{9 l)} $[\alpha]_D^{22} = -19.6$ (c 1.0, CHCl₃).

In general, it is impossible to determine the measured value with absolute accuracy.²⁰ Therefore, there is a probability of absolute and relative error, which in the case of determining the configuration of stereoisomers can be 50%, since one of the two values is determined, i.e. either (*R*)- or (*S*)-absolute configuration. Hence, errors arise in the determination of absolute configurations, which are often encountered. In this article, we

propose a simple method to improve the efficiency of determining the absolute configurations of stereoisomers of secondary alcohols, which include. carrying out convergent measurements by two sensitive methods. In particular, in the case of secondary alcohols, it is convenient to use enzymatic resolution in combination with the Kazlauskas rule and chiral HPLC.

As can be seen from the results in Table 1, the combined use of enzymatic kinetic resolution with chiral HPLC gives convergent results and is therefore a reliable method for determining the absolute configuration of secondary alcohols. The results of enzymatic kinetic resolution were confirmed by X-ray diffraction analysis of *cis*- and *trans*-stereoisomers of 2-bromo-2,3-dihydro-1*H*-inden-1-ol.¹⁴ These compounds contain an important heavy element, the bromine atom, which makes it possible to determine the configuration of these compounds by X-ray diffraction analysis.

Conclusions

The combined use of enzymatic analysis, Kazlauskas rules and chiral HPLC improves the accuracy of determining the absolute configurations of 2,3-dihydro-1*H*-indenols. The results of convergent determinations of absolute configuration are in complete agreement, which indicates that the proposed method is a reliable method that can be used in routine work with five-membered secondary alcohols. As a result, absolute configurations of a number of 2,3-dihydro-1*H*-indenols were determined, and additionally, errors in previously published determinations of absolute configurations were corrected

Experimental Section

General. ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ solvent on a 500 MHz spectrometer at ambient temperature. Chemical shifts (δ) are shown in ppm in relation to TMS as an internal standard. The Agilent Technologies 1200 chiral chromatograph column with a fixed phase tris(4-methylbenzoate)cellulose supported on 5 μ m silica gel was used.

Signal multiplicity is shown as c, singlet; e, doublet; dd, doublet doublet; td, triplet of doublets; t, triplet; m, multiplet; w, wide. The spin-spin constants *J* are given in Hertz. All reagents and solvents were used without special purification, unless otherwise indicated. Column chromatography was performed on SilicaGel 60 (70-230 mesh) using these eluents. Optical rotations were measured on a Perkin-Elmer 241 polarimeter (sodium D line at 20 °C). Melting points were not adjusted. All reactions were performed in a fire-dried or drying chamber in a glass vessel with stirring on a magnetic stirrer. Lipase from *Burkholderia cepacia* (Amano PS) was purchased from Amano Pharmaceutical (Japan). The reaction was monitored by analytical thin layer chromatography (TLC) on glass plates of SilicaGel 60 F₂₅₄ (Merck, Darmstadt, Germany) and the products were visualized with anisaldehyde or UV. The purity of all compounds was checked by thin layer chromatography and NMR measurements

Enzymatic kinetic resolution of halogenindenols (typical experiment)

(A) Enzymatic acylation of racemic 2,3-dehydroindanol. (S)-4-Fluoro-2,3-dihydro-1*H*-inden-1-ol (S)-(+)-(3). A solution of racemic 2,3-dihydro-1*H*-inden-1-ol (0.01 mol), *Burkholderia cepacia* lipase (0.1 g), vinyl acetate (3 ml) in MTBE (3 ml) was stirred at 24 °C. The acylation was monitored by TLC and NMR. The reaction mixture was stirred to 50% conversion of the original 2,3-dihydro-1*H*-inden-1-ol, which took about 18 hours. The

reaction mixture was then filtered, evaporated *in vacuo*, and the resulting substance was chromatographed on a silica gel column using the hexane-ethyl acetate-ethanol eluent (95:5-3:1). (*R*)-4-fluoro-dihydroindenyl acetate in 46% yield, and unreacted (*S*)-4-fluoro-1,2-dihydroindenol in 48% yield, which is recrystallized from toluene, were obtained. Yield of crystallized (*S*)-4-fluoro-2,3-dihydro-1*H*-inden-1-ol 42%, $[\alpha]_D^{20} +17.0$ (C 1, CHCl₃).

¹H NMR (CDCl₃): δ = 1.35 (m, 1H); 2.00 (m, 1H). 2.55 (m, 1H), 2.80 (m, 1H), 3.15 (m, 1H), 5.20 (qv, *J* 6.0 Hz, 1H), 6.90 (m, 1H), 7.30 (d, *J* 9.0 Hz, 1H), 7.45 (m, 1H). ¹³C NMR (CDCl₃): δ = 24.54, 40.50, 70.73, 115.9 (d, *J* 20.0 Hz), 117.9 (d, *J* 20.5 Hz), 129.7 (d, *J* 8.5 Hz), 144.8, 149.9 (d, *J* 7.5 Hz), 164.5 (d, *J* 250.0 Hz).

(B) Hydrolysis of resolved acetate. (*R*)-4-Fluoro-2,3-dihydro-1*H*-inden-1-ol (–)-(*R*)-(4). The acetate (0.01 mol) obtained in the previous experiment after chromatographic resolution was hydrolyzed by treatment with a solution of potash (2 g) in 20 ml of MeOH with stirring and at rt. The course of hydrolysis was monitored by TLC. The solvent was evaporated *in vacuo*, the residue was extracted with EtOAc. The extract was then evaporated and the residue was recrystallized in toluene. As a result, pure (*R*)-4-fluoro-2,3-dihydro-1*H*-inden-1-ol was obtained in ~45% yield. $[\alpha]_D^{20} -17.0$ (C 1, CHCl₃).

¹H NMR(CDCl₃): δ = 1.4 (m, 1H); 1.90 (m, 1H). 2.55 (m, 1H), 2.85 (m, 1H), 3.10 (m, 1H), 5.25 (qv, *J* 6.0 Hz, 1H), 6.95 (m, 1H), 7.30 (d, *J* 9.0 Hz, 1H), 7.35 (m, 1H). ¹³C NMR (CDCl₃) δ = 24.50, 40.45, 70.70, 115.8 (d, *J* 20.0 Hz,), 118.0 (d, *J* 20.5 Hz,), 129.0 (d, *J* 8.5 Hz,), 145.0, 140.0 (d, *J* 7.5 Hz,), 165.0 (d, *J* 250.0 Hz,).

Kinetic resolution by enzymatic hydrolysis of racemic halo-2,3-dihydro-1*H*-indenol acetates (typical experiment)

(*S*)-4-Bromo-2,3-Dihydro-1*H*-indenol (+)-(S)-(13). (*Rac*)-4-Bromo-2,3-dihydro-1*H*-indenol acetate (5 mmol) was hydrolyzed in phosphate-buffered aqueous solution at constant pH 7.2 using *Burkholderia cepacia* lipase (0.2 gr) with stirring at rt. Hydrolysis was monitored by TLC and ¹H NMR. The lipase was then filtered and washed with methylene chloride. The solvent was evaporated. The residue gave a mixture of (*R*)-4-bromo-2,3-dihydro-1*H*-indenyl 1-acetate and (*S*)-4-bromo-2,3-dihydro-1*H*-indenol, which was extracted with EtOAc. Then the extract was evaporated, the resulting mixture of products was separated on a chromatographic column with silica gel. Eluent: hexane-EtOAc-EtOH (95 : 5 : 1), which was recrystallized from toluene. Yield 42%, m. p. 100 °C, $[\alpha]_D^{20} = -20.00$ (C = 1, CDCl₃). The enantiomer ratio of 98:2 was determined by HPLC using a Chiralcel OJ-H column (95% hexane / 2propanol, 1.0 ml stream / min). *t_R* 9.5 min (minor); *t_R* 11.1 min (major).

¹H NMR (CDCl₃): δ = 1.75 (c, 1H, OH); 1.81 (m, 1H); 2.50 (m, 1H); 2.75 (m, 1H); 3.10 (m,1H); 3.12 – 3.03 (m, 1H); 5.25 (qv, *J* = 6.0 Hz, 1H); 7.35 (m, 1H), 7.35 (m, 1H), 7.45 (m, 2H), ¹³C NMR (CDCl₃): δ = 31.8. 35.9, 78.5, 120.6, 124.2, 129.6, 132.0, 144.6, 147.5. GSMS: 213.1000; 194.9020.

(*R*)-4-Bromo-2,3-Dihydro-1*H*-indenol (*R*)-(–)-(14). It was obtained by hydrolysis of (*R*)-acetate by potash treatment as described above.

Yield 42%, m.p. 100 °C, $[\alpha]_D^{20} = +20.00$ (C=1, CDCl₃). ¹H NMR (CDCl₃): δ = 1.75 (c, 1H, OH); 1.81 (m, 1H); 2.50 (m, 1H); 2.75 (m, 1H); 3.10 (m, 1H); 3.12 – 3.03 (m, 1H); 5.25 (q, *J* 6.0 Hz, 1H); 7.35 (m, 1H), 7.35 (m, 1H), 7.45 (m, 2H). ¹³C NMR (CDCl₃): δ = 31.8. 35.9, 78.5, 120.6, 124.2, 129.6, 132.0, 144.6, 147.5. GSMS: 213.1000; 194.9020.

The enantiomeric purity of resolved compounds was defined by derivatization with Mosher acid (See below).

MTPA Determination of optical purity of resolved stereoisomers of halo 2,1-dihydro-1*H*-indenols

To 4.7 mmol of racemic halo-2,1-dihydroindenol and 0.01 ml of triethylamine in 2 ml of Et₂O was added 13 mg (5.17 mmol) of Mosher acid chloride in the solution of 1 ml of Et₂O with stirring and cooling to –20 °C. After 10 min, the reaction mixture was centrifuged; the solvent was evaporated *in vacuo*. 1 ml of CDCl₃ was added to the residue, the solution was placed to NMR tube, ¹H and ¹⁹F NMR spectroscopic analyses were performed.

Chromatographic determination of the absolute configuration

The samples were dissolved in the mobile phase at a concentration of 0.1 mg / ml. *n*-Hexane with a modifier (MeOH, *i*-Pr₂O) of different concentrations was used as the mobile phase. All solutions were filtered (0.45 mm) and degassed in an ultrasonic bath before use. The mobile flow rate was 0.5 ml/min UV detection was performed at 230 nm. Chromatography was performed at 25 °C, unless otherwise indicated, to determine the temperature dependence of the enantiopartition. After each change in temperature or composition of the mobile phase, the column was equilibrated with the mobile phase for at least 2 h before the introduction of a new sample. The empty time of the column (t_0) was determined by introducing *n*-hexane and recording the first deviation of the baseline. Double injections were performed before each chromatographic experiment (Table 1).

Supplementary Material

Some ¹H, ¹³C NMR spectra of compounds **3-16** are described in our previous publication¹⁷ and also presented in the Supplementary part. The results of chiral chromatograms, HRMS and physico-chemical constants (m.p.) are given in Table 1 and presented in the Supplementary part

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