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Synthesis of Enantiomerically Pure (1*S*, 2*R*)-Epoxy Indane and *cis*-(1*R*, 2*S*)-2-Amino-1-indanol.

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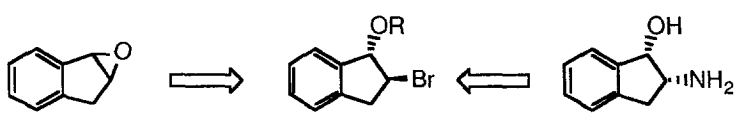
Abstract: Enantiomerically pure (1*S*, 2*R*)-epoxy indane and *cis*-(1*R*, 2*S*)-2-amino-1-indanol were synthesized via highly enantioselective lipase catalyzed transesterification of racemic *trans*-2-bromo-1-indanol.

Enantiomerically pure aminoindanol has recently been described as a highly efficient chiral ligand in titanium catalyzed asymmetric Diels Alder reactions[1] as well as a component of the inhibitor of a key enzyme in the human immunodeficiency virus (HIV).[2] Moreover, we have observed that 2-amino-1-indanol **5** as a metabolite[3] of dopamine β-hydroxylase (DBH),[4] a copper-containing monooxygenase which catalyses the transformation of dopamine into noradrenaline. In the course of these studies, the need for preparing useful quantities of enantiomerically active aminoindane **5** as well as the structurally related epoxy indane **4**[5] became apparent. Both, epoxy indane **4** and aminoindanol **5** can easily be obtained from bromohydrin **1** that we envisioned to obtain in enantiomerically pure form. Enantiomerically pure bromohydrin **1** has been obtained by: 1) a combination of HPLC separation/crystallization techniques of menthyloxyacetate diastereoisomers[6] 2) microbial reduction of 2-bromo-1-indanone[7] and 3) microbial hydrolysis of an acetate derivative.[8] But in all cases, the enantiomeric excess was unsatisfactory and the transformation was inappropriate to large scale preparations of enantiomerically pure bromohydrin **1**.



4 **1**, R = H; **2**, R = OAc; **3**, R = OOC(CH3)OAr **5**

We first studied the kinetic resolution of racemic *trans*-2-bromo-1-indanol **1** with different chiral carboxylic acids **6a-d** (ArOCHMeCOOH) derivatives of (*R*)-lactic acid, in the presence of dicyclohexyl carbodiimide (DCC) and catalytic amounts of 4-dimethylaminopyridine (DMAP) in THF at room temperature.[9] This reaction led to a mixture of the corresponding esters **3a-d** and the remaining bromohydrin **1** (Table 1), but unfortunately, the enantiomeric excess of remaining bromohydrin **1** did not exceed 15% (diastereoisomeric excess of esters **3a-d**: 24%).

Table 1. Kinetic resolution of racemic *trans*-bromohydrin **1** with chiral carboxylic acids **6a-d** (2:1 molar ratio).

Acids 6a-d	Esters 3a-d		Bromohydrin 1			
	Yields [i]	d. e. [ii]	Yields [i]	e. e.[iii]	$[\alpha]_D^{25}$	Config. [iv]
6a (Ar = 4-Cl-2-Me-Ph)	88%	24%	80%	14%	+ 8.1	(1*S*, 2*S*)
6b (Ar = 4-F-2-I-Ph)	78%	17%	81%	10%	+ 5.8	(1*S*, 2*S*)
6c (Ar = 4-F-2-Cl-Ph)	90%	20%	75%	15%	+ 8.5	(1*S*, 2*S*)
6d (Ar = 4-F-2-Br-Ph)	85%	16%	89%	13%	+ 8.0	(1*S*, 2*S*)

[i] Based on the starting carboxylic acid **6a-d**. [ii] Determined by ^{1}H NMR spectroscopy. [iii] Determined by HPLC using Chiralcel column OD-H (Daicel) with hexane/isopropyl alcohol (99:1) as eluant. [iv] From the $[\alpha]_D^{25}$ = - 64.4 in EtOH for (1*R*, 2*R*) enantiomer (Ref. 6).

The use of hydrolytic enzymes as catalysts for asymmetric hydrolysis has been well documented.[10] A preparative method using the kinetic resolution of racemic acetates **2** with four different lipases was now considered (Table 2). Unfortunately, even after two days in a phosphate buffer (*pH* = 7.5) the conversion and enantiomeric excess were very poor (< 5%). Next we used the lipase in a transesterification process with vinyl acetate as acyl donor.[11] As shown in figure 1 and table 2, after 8 days for 80% conversion, LP 237.87 lipase gave satisfactory and reproducible results which gave (1*S*, 2*S*)-bromohydrin **1** in extremely enantiomerically pure form (e. e. > 99%). When the reaction was stopped after 1 day (15% conversion) (1*R*, 2*R*)-acetate **4** was obtained with 70% enantiomeric purity.

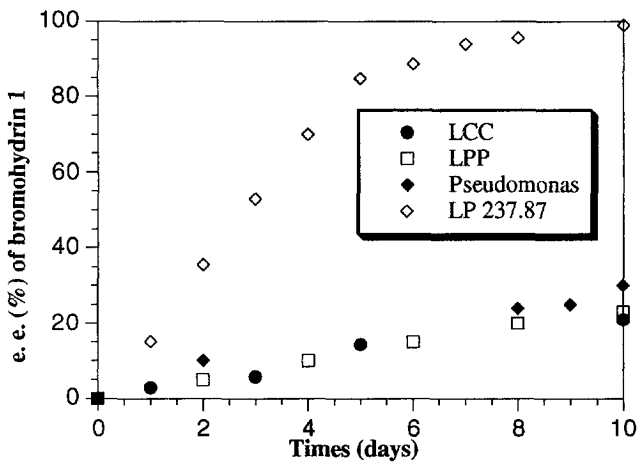
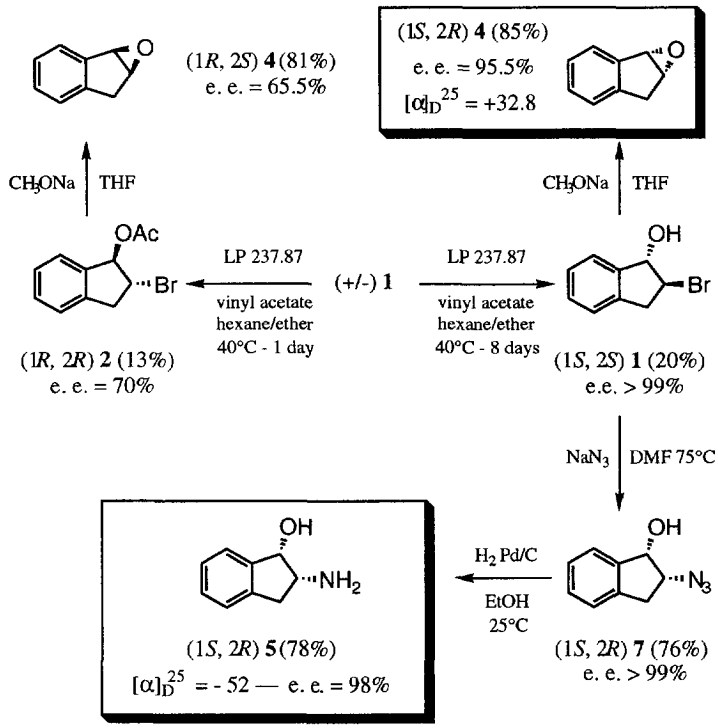


Figure 1. Kinetic resolution of racemic *trans*-bromohydrin **1** with lipases.

Table 2. Lipase catalyzed transesterification of racemic *trans*-bromohydrin **1**.

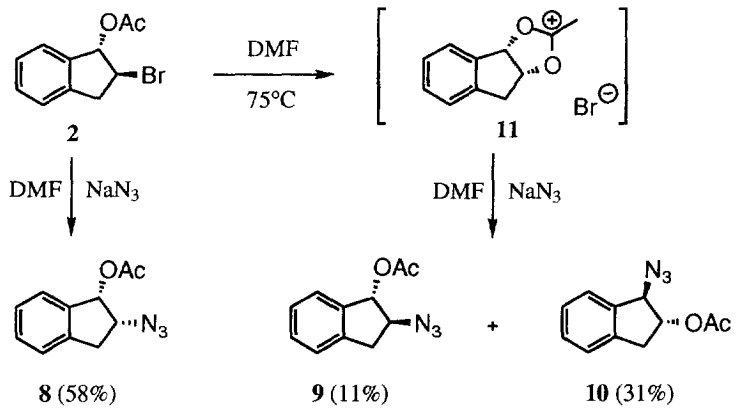
Lipases	Reaction Times in days	Acetate 4				Bromohydrin 1			
		Yields [i]	$[\alpha]_D^{25}$	Config. [ii]	e. e.	Yields [i]	$[\alpha]_D^{25}$	Config. [iii]	e. e. [iv]
LCC	10	58%	-51	(1*R*, 2*R*)	30%	38%	+11.8	(1*S*, 2*S*)	20%
P. fluorescens[vi]	10	62%	-53	(1*R*, 2*R*)	32%	35%	+15	(1*S*, 2*S*)	30%
LPP	10	58%	-55	(1*R*, 2*R*)	33%	39%	+12.6	(1*S*, 2*S*)	20%
LP 237.87[vii]	8	77%	-32	(1*R*, 2*R*)	19%	20%	+57.8	(1*S*, 2*S*)	> 99%
LP 237.87	1	13%	-117	(1*R*, 2*R*)	70%	87%	+6.2	(1*S*, 2*S*)	13%

[i] Yields based on isolated products after flash chromatography. [ii] From the $[\alpha]_D^{25}$ = - 167.5 in EtOH for (1*R*, 2*R*) enantiomer (Ref. 6). [iii] From the $[\alpha]_D^{25}$ = - 64.4 in EtOH for (1*R*, 2*R*) enantiomer (Ref. 6). [iv] Determined by HPLC using Chiralcel column OD-H (Daicel) with hexane/isopropyl alcohol (99:1) as eluant. [vi] Amano. [vii] Gist Brocades.



(1*S*, 2*R*)-Epoxy indane **4** was obtained in good yields (85%) and high enantiomeric excess (95.5%, determined by GLC at 120°C on a Macherey Nagel Lipodex A column) by reaction of *trans*-(1*S*, 2*S*)-2-bromo-1-indanol **1** with sodium methylate in THF (25°C, 2 h).[12] By the same way, *trans*-(1*R*, 2*R*)-1-acetoxy-2-bromo-indane **2** was converted into enantiomeric (1*R*, 2*S*)-epoxy indane **4**. By treatment with NaN_3 in DMF, *trans*-(1*S*, 2*S*)-2-bromo-1-indanol **1** was transformed into enantiomerically pure *cis*-(1*S*, 2*R*)-2-azido-1-

indanol **7** in 76% yield and > 99% e. e. (determined by HPLC on Daicel Chiralcel column OD-H with hexane/isopropyl alcohol (99:1) as eluant).[1] Hydrogenation catalyzed by palladium on charcoal gave *cis*-(1*S*, 2*R*)-2-amino-1-indanol **5** in 78% overall yield and > 99% e.e. The direct SN_2 azidation of the bromoacetate **2** (**2** ⇒ **8**) instead of bromohydrin **1** was less selective since the SN_2 process is in competition with the formation of cationic oxonium ion **11**. Nucleophilic attack of **11** lead to a mixture of *trans* azido acetate **9** and **10** (total 42%) as side products with retention of configuration.



In summary, enantioselective lipase catalyzed transesterification of indane bromohydrin provides epoxy indanes **4** and *cis*-(1*S*, 2*R*)-2-amino-1-indanol **5** in good yields and high enantiomeric excess complementary to the chemical resolution of racemic *cis*-2-amino-1-indanol **5** which gives the opposite enantiomer (1*S*, 2*R*).

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