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Enzymatic resolution of indene bromohydrin acetate using immobilized lipase

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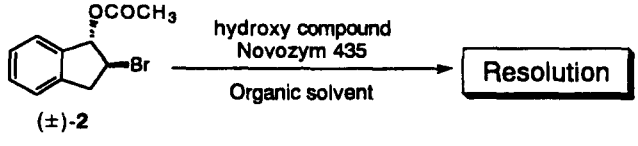
Abstract: Enzymatic resolution of indene bromohydrin acetate by hydrolysis or alcoholysis in the presence of immobilized lipase from *Candida antarctica* (Novozym 435®) has been investigated. Enantiomerically enriched (1*S*,2*S*)-(+)-2-bromoindan-1-ol and (1*R*,2*R*)-(−)-1-acetoxy-2-bromoindan were obtained when indene bromohydrin acetate was treated with Novozym 435® and cyclohexanol in dibutyl ether for 30 hours at 40°C.

Optically active indene bromohydrin is an important starting material for the synthesis of 1-aminoindan-2-ol[1] or 2-aminoindan-1-ol.[2] (1*S*,2*R*)-(−)-1-Aminoindan-2-ol is one of the key intermediates for the preparation of anti-HIV protease inhibitor, Indinavir (CRIXIVAN®).[3] Enantiomerically pure or enriched indene bromohydrin **1** can be obtained by HPLC separation of menthyloxyacetate diastereomers,[4] microbial reduction of 2-bromoindan-1-one,[5] microbial hydrolysis of corresponding acetate,[6] lipase-mediated transesterification,[7] or haloperoxydase bioconversion of indene.[8]

We recently found that racemic indene bromohydrin could be separated into its enantiomers by lipase catalysed transesterification with vinyl acetate in diisopropyl ether in the presence of Novozym 435® (immobilized SP 525® lipase from *Candida antarctica*).[9] In this case, (1*R*,2*R*)-indene bromohydrin (−)-**1** was isolated in 31% yield with 100% ee (enantiomeric excess) and (1*S*,2*S*)-indene bromohydrin acetate (+)-**2** was obtained in 35% yield with 93% ee after column chromatography. Our next interest was to examine the efficiency of this immobilized lipase under hydrolysis or alcoholysis condition of indene bromohydrin acetate (±)-**2**. Herein, we present the results of the kinetic resolution of (±)-**2** by Novozym 435® lipase-catalysed hydrolysis or alcoholysis in organic media (Scheme 1).



Scheme 1.

We first investigated the influence of hydroxy compounds in the resolution. Eight hydroxy compounds including water were tried in diisopropyl ether (IPE) in the presence of lipase (Table 1). In six cases, moderate resolution results were observed, and enantiomerically enriched (1*S*,2*S*)-(+)-**1** was formed. The absolute configuration of each chiral bromohydrin **1** and chiral bromohydrin acetate **2** was based on their specific rotations reported by Imuta.[6] On comparison of resolution efficiency, E values,[9,10] methanol, isopropanol, cyclohexanol and H_2O showed a good E value. But H_2O, methanol and isopropanol were unsuitable for hydroxy compounds, because addition of a small amount of these compounds led this immobilized lipase to a pulp. Therefore, we chose cyclohexanol (entry 8) as a hydroxy compound to establish the optimal conditions.

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Table 1. Hydroxy compound-dependent resolution of (±)-2[a]

Entry	hydroxy Compound	Time (h)	Alcohol (+)-1		Acetate (-)-2		E[d]
			Yield (%)[b]	ee (%)[c]	Yield (%)[b]	ee (%)[c]	
1	H_2O	50	37	95	60	56	0.70
2	Methanol	48	45	93	52	84	0.84
3	Isopropanol	49	44	91	55	74	0.80
4	n-Butanol	49	29	89	70	42	0.52
5	Ethoxy ethanol	48	21	25	65	N.D.[e]	0.11
6	Ethylene glycol	49	8	N.D.	85	N.D.	-
7	Phenol	48	19	N.D.	74	N.D.	-
8	Cyclohexanol	49	42	92	57	66	0.77

a) 10 mmol (2.55 g) of (±)-2, 50 ml of diisopropyl ether (IPE), 2.0 g of lipase (Novozym 435), hydroxy compound (10 mmol), 40 °C;
b) Determined by HPLC using diethyl phthalate as an internal standard.
c) Determined by chiral HPLC using CHIRALCEL OB (Daicel).
d) Defined as the product of the yield of alcohol based on half amount of the racemic alcohol and the ee of obtained alcohol.
e) Not determined.

Table 2. Solvent-dependent resolution of (±)-2[a]

Entry	Solvent	Time (h)	Alcohol (+)-1		Acetate (-)-2		E[d]
			Yield (%)[b]	ee (%)[c]	Yield (%)[b]	ee (%)[c]	
1	IPE[e]	25	34	94	63	52	0.64
2	IPE	49	42	92	57	66	0.77
3	DBE[f]	20	38	97	50	90	0.74
4	DBE	30	45	96	48	92	0.86
5	DBE	49	44	92	43	96	0.81
6	BME[g]	25	32	93	67	87	0.60
7	BME	34	44	92	55	93	0.81
8	BME	48	46	90	52	95	0.83
9	Toluene	49	39	97	52	76	0.76

a) 10 mmol (2.55 g) of (±)-2, 10 mmol (1.00 g) of cyclohexanol, 50 ml of solvent, 2.0 g of lipase (Novozym 435), 40 °C;
b) Determined by HPLC using diethyl phthalate as an internal standard.
c) Determined by chiral HPLC using CHIRALCEL OB (Daicel).
d) Defined as the product of the yield of alcohol based on half amount of the racemic alcohol and the ee of obtained alcohol.
e) diisopropyl ether f) dibutyl ether g) t-butyl methyl ether

It is known that solvent variation in many cases of lipase-catalysed kinetic resolution can influence the enantiomer or enantiotopic selectivity as well as the reaction rate.[11] 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 transacylation in the presence of same lipase.[9] From our experience, dibutyl ether (DBE), t-butyl methylether (BME), and toluene were tested (Table 2). Among the solvent tested, DBE exhibited the best results. When DBE was used as a solvent, enantiomeric excess of (+)-1 was 96% ee (45% yield) and (−)-2 was 92% ee (48% yield) respectively (entry 4), so this solvent was shown to be more suitable than the others. Interestingly, it was found that toluene was applicable for this resolution (entry 9).

Table 3. Temperature-dependent resolution of (±)-**2**[a)]

Entry	Temp. (℃)	Time (h)	Alcohol (+)-**1**		Acetate (-)-**2**		E[d)]
			Yield (%)[b)]	ee (%)[c)]	Yield (%)[b)]	ee (%)[c)]	
1	30	49	41	96	50	79	79
2	40	49	44	92	43	96	81
3	60	8	42	94	54	79	79
4	60	23	41	93	48	75	76
5	60	48	42	92	50	74	77

a) 10 mmol (2.55 g) of (±)-**2**, 10 mmol (1.00 g) of cyclohexanol, 50 ml of diisopropyl ether, 2.0 g of lipase (Novozym 435);
b) Determined by HPLC using diethyl phthalate as an internal standard.
c) Determined by chiral HPLC using CHIRALCEL OB (Daicel).
d) Defined as the product of the yield of alcohol based on half amount of the racemic alcohol and the ee of obtained alcohol.

Table 4. Recycle of lipase-dependent resolution of (±)-**2**[a)]

Entry	Temp. (℃)	Time (h)	Alcohol (+)-**1**		Acetate (-)-**2**		E[d)]
			Yield (%)[b)]	ee (%)[c)]	Yield (%)[b)]	ee (%)[c)]	
1	30	49	41	96	50	79	79
2	40	49	44	92	43	96	81
3	60	8	42	94	54	79	79
4	60	23	41	93	48	75	76
5	60	48	42	92	50	74	77

a) 10 mmol (2.55 g) of (±)-**2**, 10 mmol (1.00 g) of cyclohexanol, 50 ml of diisopropyl ether, 2.0 g of lipase (Novozym 435);
b) Determined by HPLC using diethyl phthalate as an internal standard.
c) Determined by chiral HPLC using CHIRALCEL OB (Daicel).
d) Defined as the product of the yield of alcohol based on half amount of the racemic alcohol and the ee of obtained alcohol.

Conveniently, Novozym 435® (immobilized lipase from *Candida antarctica*) has heat-resistant properties, so we examined the influence of reaction temperature on enantiomeric excess of the product under the same conditions described in Table 2 using IPE as a solvent (Table 3). Decreasing the reaction temperature (30°C) did not markedly influence the enantioselectivity or the reaction rate (entry 1).

However, elevation of the reaction temperature (60°C) showed a remarkable increase in the reaction rate (entry 3), although progress of the reaction seemed to be halted after 8 hours.

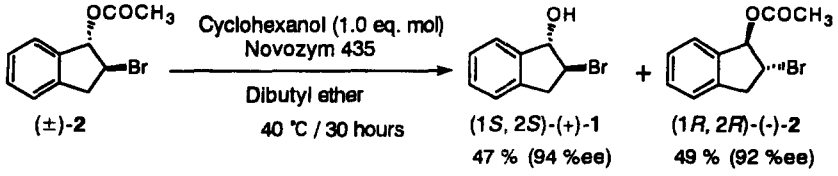
Since re-use of recovered enzyme is the most important problem to be overcome to establish a manufacturing process, the influence of the number of recycles on the resolution efficiency was investigated (Table 4).

Although re-use of lipase up to three cycles showed no remarkable decrease of its original efficiency, reaction was terminated on the fourth cycle.

Under the optimal conditions (treated with Novozym 435® and cyclohexanol in dibutyl ether for 30 hours at 40°C), (±)-**2** was converted to (1*S*,2*S*)-**1** (yield: 47%, 94% ee) and (1*R*,2*R*)-**2** (yield: 49%, 92% ee), respectively (Scheme 2).

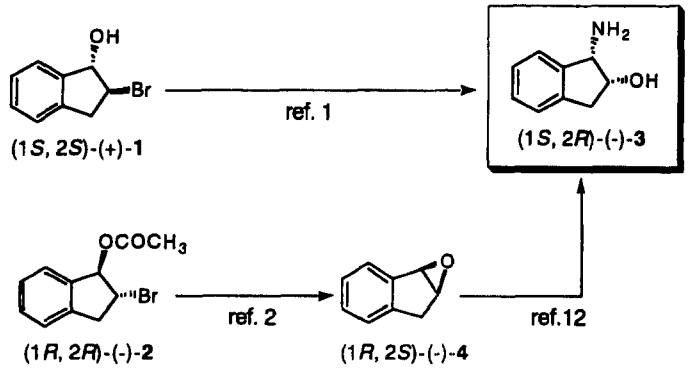
The described and reported procedures[9] represent simple access to both enantiomers of indene bromohydrin (1*S*,2*S*)- and (1*R*,2*R*)-**1** in enantiomerically enriched form.

Enantiomerically pure alcohol (+)-**1** was reacted with CH_3CN under the Ritter reaction conditions to



Scheme 2.

give enantiomerically pure (1*S*,2*R*)-*cis*-1-aminoindan-2-ol (−)-**3**.[1a,b] It has been reported that optically active acetate (−)-**2** was converted to corresponding (1*R*,2*S*)-epoxide (−)-**4**,[2a] which was also a precursor for the preparation of chiral (1*S*,2*R*)-aminoindanol (−)-**3**[12] (Scheme 3).



Scheme 3.

Experimental

Novozym 435® was a gift from Novo-Nordisk. All other reagents were standard laboratory grade without further purification.

The progress of the reaction could be monitored by HPLC analysis using diethyl phthalate as an internal standard (YMC pack C_8 A-202, 0.01 M KH_2PO_4:CH_3CN=55:45, 1 mL/min, 254 nm, 40°C). Optical purities of alcohol (+)-**1** was determined by chiral HPLC (Daicel CHIRALCEL OB, hexane:iso-propanol=95:5, 0.8 mL/min, 254 nm, 40°C). Enantiomeric excesses of acetate (−)-**2** were also determined by chiral HPLC (Daicel CHIRALCEL OB, hexane, 1.0 mL/min, 254 nm, 40°C).

Lipase catalysed resolution of indene bromohydrin acetate (±)-2: typical procedure

Novozym 435® (8.0 g) and cyclohexanol (4.00 g, 40 mmol) were added to a dibutyl ether solution (200 mL) of racemic indene bromohydrin acetate[13] (±)-**2** (10.39 g, 41 mmol), and the resulting mixture was stirred at 40°C. After the reaction (30 h), the mixture was filtered, and the filtrate was concentrated to give colorless semi-solid. Heptane (200 mL) was added to the residue with stirring followed by filtration at −15°C, and dried *in vacuo* to give (1*S*,2*S*)-2-bromoindan-1-ol (+)-**1** (4.00 g, yield: 47%, 94% ee) as colorless needles. Heptane solution was evaporated and purified by silica gel column chromatography using hexane:AcOEt (9:1) as an eluent to give (1*R*,2*R*)-2-bromo-1-acetoxyindan (−)-**2** (5.09 g, yield: 49%, 92% ee) as a yellow oil.

(1*S*,2*S*)-(+)-**1**: $[\alpha]_D^{30}$ +56.8 (c=0.5, EtOH) (lit.[7] $[\alpha]_D$ −57.8, EtOH ((1*R*,2*R*)-(−)-**1**)); mp 111.5–113.7°C (lit.[5] 116–118°C); IR (KBr)=3358, 1346, 1065, 752, 737 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ=2.41 (1H, d, *J*=5.4 Hz, OH), 3.22 (1H, dd, *J*=16.2, 7.8 Hz, CH_2), 3.58 (1H, dd, *J*=16.1, 7.0 Hz, CH_2), 4.28 (1H, m, CH), 5.32 (1H, t, *J*=5.8 Hz, CH), 7.21–7.40 (4H, m, H_{arom}).

(1*R*,2*R*)-(−)-**2**: $[\alpha]_D^{30}$ −168.5 (c=4.8, EtOH) (lit.[4] $[\alpha]_D$ −167.5, EtOH); IR (film)=1740, 1372, 1233, 1024, 754, 734 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ=2.11 (3H, s, CH_3), 3.28 (1H, dd, *J*=16.8, 4.5 Hz,

CH_2), 3.72 (1H, dd, J=17.1, 6.7 Hz, CH_2), 4.28 (1H, m, CH), 6.33 (1H, d, J=3.5, CH), 7.19–7.42 (4H, m, H_{arom}).

The ^{1}H-NMR spectrum of each product was in good agreement with reported data.[5]

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