# Lipase-Mediated Resolution of Indene Bromohydrin

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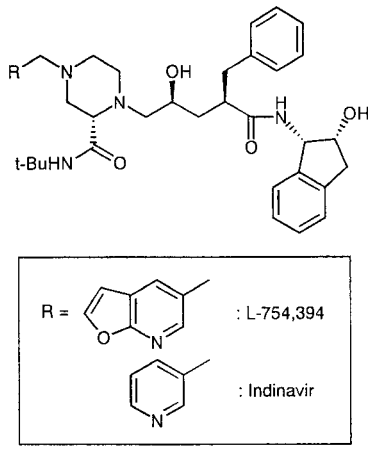
Lipase-mediated resolution of indene bromohydrin was examined, and we have found that immobilized CAL (*Candida antarctica* lipase SP525 immobilized on acurrell) was an efficient biocatalyst to resolve a readily available racemic indene bromohydrin (±)-**1**. Enantiomerically enriched (1*R*,2*R*)-2-bromoindan-1-ol (−)-**1** and its (1*S*,2*S*)-acetate (+)-**2** were obtained by this method.

Optically active 2-bromoindan-1-ol **(1)** has potential utility as a key starting material for the preparation of HIV-1 protease inhibitors, such as Indinavir[1] and L-754,394[2] (Figure). Recently, we have established that chiral *cis*-1-aminoindan-2-ol, which is an important intermediate for the above-mentioned drugs and a useful reagent for the preparation of various chiral compounds,[3] could be easily prepared employing the Ritter reaction of chiral indene bromohydrin.[4] However, synthesis of optically active bromohydrin **1** has been little studied; 1) A combination of HPLC separation/crystallization techniques of methyloxy acetate diastereomers;[5] 2) Microbial reduction of 2-bromoindan-1-one;[6] 3) Microbial hydrolysis of an acetate derivative;[7] but in all cases, the optical purity was unsatisfactory and the transformation was inappropriate for large scale preparation of optically pure bromohydrin **1**. Only one lipase-catalyzed preparation has been reported so far.[8] The preparation described was accomplished by kinetic transesterification of racemic (±)-**1** using lipase LP 237.87, however yield of (1*S*,2*S*)-(+)-**1** was low (20%) and optical purity of its acetate (1*R*,2*R*)-(−)-**2** was unsatisfactory (19% ee). We examined the resolution of racemic (±)-**1** to establish a more expedient procedure by employing easily available lipase-mediated kinetic transesterification. We wish to report here a new lipase-mediated procedure for the preparation of optically enriched **1**.




**Figure**

We first examined the kinetic transesterification of racemic (±)-**1** with vinyl acetate in the presence of various commercially available lipases such as lipase MY (from *Candida rugosa*), lipase PS (from *Pseudomonas cepacia*), lipase AK (from *Pseudomonas fluorescence*), lipase from *Mucor javanicus* and lipase from *Rhizopus niveus*. Only lipase PS and lipase AK catalyzed the reaction to give optically active products (1*S*,2*S*)-(+)-**1** and (1*R*,2*R*)-(−)-**2** (Scheme 1), the other lipases were not efficient. The absolute configuration of each chiral bromohydrin **1** and chiral bromohydrin acetate **2** were based on their optical rotations reported by Imuta.[6] We next examined reaction conditions using lipase PS (Table 1) in detail, and found that use of diisopropyl ether (IPE, solvent) and vinyl acetate (acyl donor) gave comparatively good results. For example, optically enriched acetate (−)-**2** was obtained in 41% yield (44% ee) (Run 1) and alcohol (+)-**1** was obtained in 15% yield (94% ee) (Run 9). However, no practically satisfactory results were observed due to low yield.

**Table 1.** Enzymatic Transesterification of *trans*-(±)-2-Bromoindan-1-ol **1** using Lipase PS (from *Pseudomonas cepacia*)

| Run[a] | Acyl Donor | Solvent | Products (Yield, %)[b] | % ee[c] | E[f] |
|---|---|---|---|---|---|
| 1 | vinyl acetate | IPE[d] | (−)-**2** 41 | 44 | |
| | | | (+)-**1** 37 | 63 | 47 |
| 2 | vinyl acetate | benzene | (−)-**2** 29 | 37 | |
| | | | (+)-**1** 45 | 15 | 14 |
| 3 | vinyl acetate | hexane | (−)-**2** 25 | 14 | |
| | | | (+)-**1** 49 | 6 | 6 |
| 4 | vinyl acetate | THF | no reaction | | |
| 5 | vinyl propionate | IPE | (−)-**2** 34 | n.d.[e] | |
| | | | (+)-**1** 45 | 27 | 24 |
| 6 | vinyl butyrate | IPE | (−)-**2** 20 | n.d.[e] | |
| | | | (+)-**1** 53 | 9 | 10 |
| 7 | vinyl benzoate | IPE | no reaction | | |
| 8 | vinyl acetate | IPE | (−)-**2** 49 | 35 | |
| | | | (+)-**1** 30 | 85 | 51 |
| 9 | vinyl acetate | IPE | (−)-**2** 56 | 28 | |
| | | | (+)-**1** 15 | 94 | 28 |

[a] Molar ratio of (acyl donor/substrate) were 1.0 except Run 8 (2.0) and Run 9 (3.0). All reaction were carried out at 35 °C for 35 h. Lipase (2.0 g) was used.

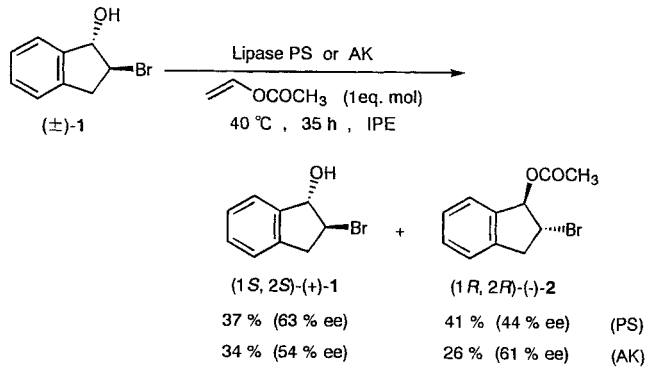
[b] Isolated yield.

[c] Determined by chiral HPLC.

[d] Diisopropyl ether.

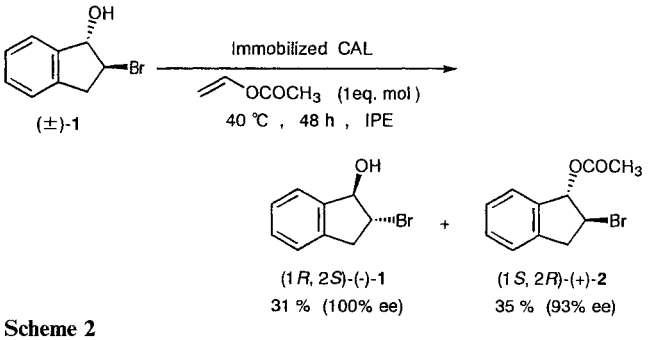
[e] Not determined.

[f] $E = \frac{\text{Yield of optically active alcohol (mol)}}{\text{Theoretical yield of (+)-2-bromoindan-1-ol (mol)}} \times \text{ee}(\%)$




**Scheme 1**

Our next investigation was performed to find a more efficient biocatalyst for the transesterification of racemic (±)-**1**. Recently, it was reported that immobilized lipase from *Candida antarctica* (recombinant DNA technology has been used)[9] was an efficient biocatalyst for the resolution of various racemic compounds such as alcohols,[10] hydroxy carboxylic acids[11] and amines.[12] We examined kinetic acylation of racemic (±)-**1** using immobilized CAL (Table 2). When vinyl acetate or isopropenyl acetate was used as acyl donor, enantiomerically enriched alcohol (1*R*,2*R*)-(−)-**1** and acetate (1*S*,2*S*)-(+)-**2** were obtained, respectively (Scheme 2). Interestingly, configuration of each product was contrary to that of each compound from transesterification using lipase PS. We found that dialkyl ethers such as IPE, dibutyl ether (DBE) and *tert*-butyl methyl ether (BME) were applicable solvents, however cyclic ethers such as THF and dioxane (DOX) were not applicable to this system. Conveniently, this lipase had good heat-resistant properties, so we examined the influences of reaction temperature on optical purity of products (Table 3). It showed that the reaction rate was accelerated according to increase in reaction temperature. The optical purities of each product prepared under heating were the same within the temperature range (35 °C–50 °C). When a reaction was carried out at 68 °C, although there was no change in the optical purity of alcohol (−)-**1** (it was suggested that an esterification was suspended), the optical purity of acetate (+)-**2** was decreased by an extension of the reaction time. From the above mentioned results, we established the most suitable reaction conditions, and tried to prepare optically active alcohol (−)-**1** and acetate (+)-**2**. Optically pure alcohol (−)-**1** was isolated in 31 % yield with 100 % ee and optically enriched acetate (+)-**2** was obtained in 35 % yield with 93 % ee after column chromatography.




**Scheme 2**

**Table 2.** Enzymatic Transesterification of *trans*-(±)-2-Bromoindan-1-ol **1** using Immobilized CAL

| Run[a] | Acyl Donor | Solvent[b] | Reaction Time (h) | Conversion (%) | % ee[c] |
|---|---|---|---|---|---|
| 1 | vinyl acetate | IPE | 48 | 49 | (+)-**2** 92<br>(−)-**1** 95 |
| 2 | vinyl acetate | DBE | 48 | 43 | (+)-**2** 96<br>(−)-**1** 85 |
| 3 | vinyl acetate | BME | 48 | 43 | (+)-**2** 93<br>(−)-**1** 90 |
| 4 | vinyl acetate | THF | 51 | 3 | (+)-**2** 69<br>(−)-**1** 5 |
| 5 | vinyl acetate | DOX | 48 | 6 | (+)-**2** 77<br>(−)-**1** 7 |
| 6 | isopropenyl acetate | IPE | 48 | 40 | (+)-**2** 96<br>(−)-**1** 80 |

[a] Acyl donor (mol)/Substrate (mol) = 1.0.
All reactions were carried out at 40 °C. Lipase (1.0 g) was used.
[b] IPE: Diisopropyl ether DBE: Dibutyl ether.
BME: *tert*.-Butyl methyl ether THF: Tetrahydrofuran
DOX: 1,4-Dioxane
[c] Determined by chiral HPLC.

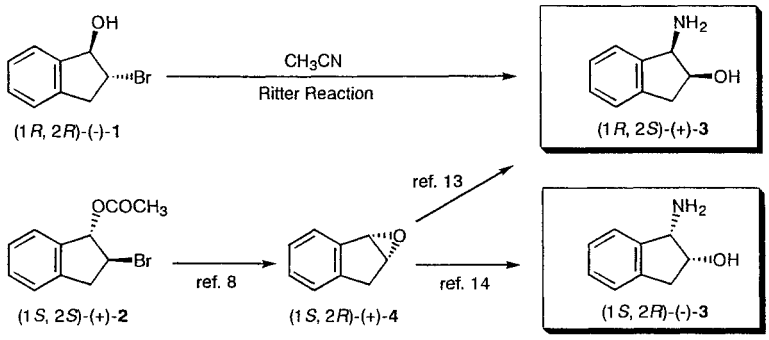
**Table 3.** Enzymatic Transesterification of *trans*-(±)-2-Bromoindan-1-ol **1** using Immobilized CAL at Various Temperatures.

| Run[a] | Temp. (°C) | Reaction Time (h) | Conversion (%) | % ee[b] |
|---|---|---|---|---|
| 1 | 30 | 49 | 41 | (+)-**2** 94<br>(−)-**1** 75 |
| 2 | 40 | 49 | 49 | (+)-**2** 92<br>(−)-**1** 95 |
| 3 | 68 | 24 | 44 | (+)-**2** 79<br>(−)-**1** 69 |

[a] Molar ratio of (vinyl acetate/substrate) = 1.0.
All reactions were carried out in diisopropyl ether. Lipase (1.0 g was used.
[b] Determined by chiral HPLC.

Optically pure alcohol (−)-**1** was reacted with $CH_3CN$ under the Ritter reaction conditions to give optically pure (1*R*,2*S*)-*cis*-1-aminoindan-2-ol (+)-**3**. It has been reported that optically active acetate (+)-**2** was converted to the corresponding (1*S*,2*R*)-epoxide (+)-**4**[8] which is also a precursor for the preparation of (+)-**3**[13] or (1*S*,2*R*)-*cis*-1-aminoindan-2-ol (−)-**3**[14], respectively (Scheme 3).

Racemic indene bromohydrin **1** was synthesized by a known method[15] and recrystallized from ethyl acetate. Lipase PS and Lipase AK were obtained from Amano Pharmaceutical Co.Ltd. Immobilized CAL was a gift from Novo-Nordisk. Lipase MY was purchased from Meitoh Sangyo Co.Ltd. Lipase from *Mucor javanicus* and Lipase from *Rhizopus niveus* were obtained from Fluka Fine Chemical Co.Ltd. All chemical reagents were used without further purification. All reactions were monitored by reversed phase HPLC (JASCO GULLIVER systems, YMC pack $C_8$ A-202, 0.01 M $KH_2PO_4$:$CH_3CN$ = 55:45, 1.0 mL/min., 254 nm, 40 °C). Optical purities of alcohol (1*R*,2*R*)-(−)-**1** and (1*S*,2*S*)-(+)-**1** were determined by chiral HPLC (Daicel CHIRALCEL OB, hexane:isopropanol = 95:5, 0.8 mL/min., 254 nm, 40 °C). Optical purities of ace-




Scheme 3

tate (1*R*,2*R*)-(−)-**2** and (1*S*,2*S*)-(+)-**2** were also determined by chiral HPLC (Daicel CHIRALCEL OB, hexane, 1.0 mL/min., 254 nm, 40 °C). Optical rotations were measured with a JASCO DIP-370 digital polarimeter. Silica gel for column chromatography was purchased from Merck (0.063–0.2 mm mesh). IR spectrometer (JASCO FT-IR 5300) and $^1$H NMR spectrometer (JEOL GSX-270, 270 MHz) were used to identify each products. Optical purity of (1*R*,2*S*)-*cis*-1-aminoindan-2-ol (+)-**3** was determined according to the literature method.[16]

**Lipase PS Catalyzed Resolution of Racemic (±)-1; General Procedure:**

Racemic indene bromohydrin (±)-**1** (2.13 g, 10 mmol), solvent (50 mL), acyl donor (10 mmol) and lipase (2.0 g) were mixed and stirred for 40–50 h at the chosen temperature. After the reaction, lipase was filtered and concentrated to give pale yellow semi-solid. The crude product was purified by silica gel column chromatography using hexane:$CH_2Cl_2$ = 50:50 as an eluent. The earlier fraction was concentrated in vacuo to give (1*R*,2*R*)-(−)-**2** as a yellow oil. The later fraction was concentrated in vacuo to give (1*S*,2*S*)-(+)-**1** as a colorless needles. The physicochemical properties of each products were in good agreement with reported data.[5,6]

**Immobilized CAL Catalyzed Resolution of Racemic (±)-1; Typical Procedure:**

Racemic indene bromohydrin (±)-**1** (2.13 g, 10 mmol), IPE (50 mL), vinyl acetate (0.86 g, 10 mmol) and lipase (1.0 g) were mixed and stirred for 48 h at 40 °C. After the reaction, lipase was filtered and concentrated to give pale yellow semi-solid. The crude product was purified using silica gel column chromatography using hexane:$CH_2Cl_2$ = 50:50 as an eluent. The earlier fraction was concentrated in vacuo to give 0.89 g (35%, 93% ee) of (1*S*,2*S*)-(+)-**2** as a yellow oil. The later fraction was concentrated in vacuo to give 0.65 g (31%, 100% ee) of (1*R*,2*R*)-(−)-**1** as a colorless needles. (1*S*,2*S*)-(+)-**2**: $[\alpha]_D$ +169.5 (*c* = 4.8, EtOH) (lit.[5] $[\alpha]_D$ −167.5, EtOH [(1*R*,2*R*)-(−)-**2**)]).

IR (Film): $\nu$ = 1740, 1372, 1233, 1024, 754, 734 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): $\delta$ = 2.11 (3 H, s, $CH_3$), 3.28 (1 H, dd, *J* = 16.8, 4.5 Hz, $CH_2$), 3.72 (1 H, dd, *J* = 17.1, 6.7 Hz, $CH_2$), 4.28 (1 H, m, CH), 6.33 (1 H, d, *J* = 3.5, CH), 7.19–7.42 (4 H, m, $H_{arom}$).

(1*R*,2*R*)-(−)-**1**: $[\alpha]_D$ −57.0 (*c* = 0.5, EtOH) (lit.[8] $[\alpha]_D$ −57.8, EtOH); mp 111.3–113.5 (lit.[5] 116–118 °C).

IR (KBr): $\nu$ = 3358, 1346, 1065, 752, 737 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): $\delta$ = 2.41 (1 H, d, *J* = 5.4 Hz, OH), 3.22 (1 H, dd, *J* = 16.2, 7.8 Hz, $CH_2$), 3.58 (1 H, dd, *J* = 16.1, 7.0 Hz, $CH_2$), 4.28 (1 H, m, CH), 5.32 (1 H, t, *J* = 5.8 Hz, CH), 7.21–7.40 (4 H, m, $H_{arom}$).

$^1$H NMR spectra of each product were in good agreement with reported data.[6]

**Preparation of (1*R*,2*S*)-*cis*-1-Aminoindan-2-ol [(+)-3] from (1*R*,2*R*)-(−)-1:**

Indene bromohydrin (1*R*,2*R*)-(−)-**1** (5.0 g, 24 mmol, 95% ee), $CH_3CN$ (1.93 g, 47 mmol) and dichloroethane (DCE, 10 mL) were mixed and 96% $H_2SO_4$ (3.59 g, 35 mL) was added dropwise at 20 °C for 40 min. After additional stirring at r.t. for 3 h, $H_2O$ (20 mL) was added. The mixture was stirred at 60 °C for 14 h and was treated in the usual way. Aqueous layer was washed with DCE (2 × 10 mL) and concentrated. 25% NaOH (15.3 g, 95 mmol) was added to the aqueous phase to form a slurry-like mixture. The mixture was filtered and washed with $CH_3CN$ (11 mL) to give (1*R*,2*S*)-1-aminoindan-2-ol (+)-**3** (2.66 g, 76%, 95% ee) as colorless plates.

$[\alpha]_D$ +25.2 (*c* = 1.0, 0.1 M HCl/MeOH); mp 117.9–118.8 °C (lit.[13] 114–115 °C).

IR (KBr): $\nu$ = 3343, 976, 735 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): $\delta$ = 2.30 (3 H, s, OH, $NH_2$), 2.93 (1 H, dd, *J* = 16.3, 3.0 Hz, $CH_2$), 3.09 (1 H, dd, *J* = 16.3, 5.4 Hz, $CH_2$), 4.30 (1 H, d, *J* = 5.4 Hz, CH), 4.37 (1 H, td, *J* = 5.4, 3.0 Hz, CH), 7.21–7.29 (4 H, m, $H_{arom}$).

$^1$H NMR spectra were in good agreement with literature.[13]

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