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Lipase-mediated kinetic resolution of *cis*-1,2-indandiol and the Ritter reaction of its mono-acetate

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Abstract—Lipase-mediated kinetic resolution of *cis*-1,2-indandiol **5** in the presence of lipase PS was examined. Enantiomerically enriched (1*S*,2*R*)-2-acetoxy-1-indanol **6a** was obtained when *cis*-1,2-indandiol **5** was treated with one equivalent of vinyl acetate. Treatment of **5** with two equivalents of vinyl acetate furnished a mixture of (1*R*,2*S*)-2-acetoxy-1-indanol **6a** and (1*R*,2*S*)-1-acetoxy-2-indanol **6b**. A route to both enantiomers of **1** was also developed by using the enantiomerically enriched mono-acetate thus obtained.

1. Introduction

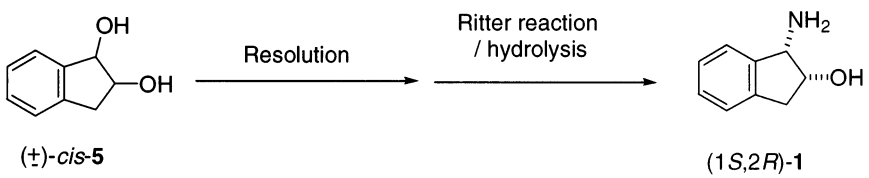
Many studies have provided several synthetic routes to *cis*-1-amino-2-indanol **1** in enantiomerically pure form in recent years, because (1*S*,2*R*)-**1** is a key component of the anti-HIV drug Indinavir[1] and both enantiomers of **1** are utilized as important components of chiral ligands[2] and auxiliaries[3] in asymmetric organic synthesis.

Several chiral compounds are shown to be the precursor of **1**. These include, for example, (1*S*,2*R*)-1,2-indene oxide **2** provided by asymmetric epoxidation using chiral manganese–salen complexes,[4] (1*S*,2*S*)-*trans*-1-azido-2-indanol **3** and (1*S*,2*S*)- or (1*R*,2*R*)-*trans*-2-bromo-1-indanol **4** prepared by lipase-catalyzed resolution.[5,6] These compounds have shown great promise for a large scale preparation of both enantiomers of aminoindanol **1**. Many of them are derivatized to enantiopure **1** using the Ritter reaction.[7] Herein, we report a new synthesis of **1** using lipase-catalyzed resolution of *cis*-1,2-indandiol **5** and subsequent Ritter reaction as shown in Scheme 1.

2. Results and discussion

We first examined the kinetic resolution of **5** with one equivalent of vinyl acetate in the presence of lipase PS (*Pseudomonas cepacia*, Amano). The results of this resolution study are summarized in Table 1.

The best result was obtained with lipase PS in *tert*-butyl methyl ether. In this case the optically enriched monoester (1*S*,2*R*)-**6a** was obtained in a yield of 47% with an e.e. of 91%. Formation of the regioisomer **6b** was not observed. The absolute configuration of **6a** was ascertained by its hydrolysis to the diol **5**, a compound of known absolute configuration, whilst its enantiomeric purity was determined by chiral HPLC after hydrolysis. With other solvents the yield and enantiomeric purity were reduced and longer reaction times were necessary.



(±)-*cis*-**5** (1*S*,2*R*)-**1**

Scheme 1.

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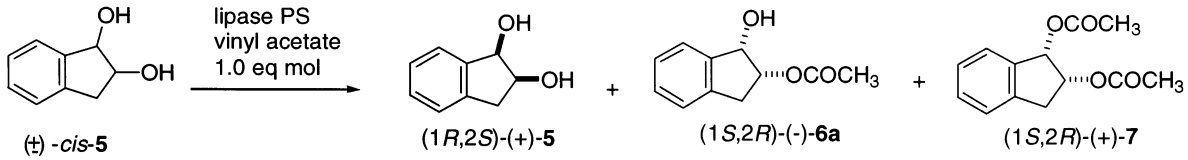
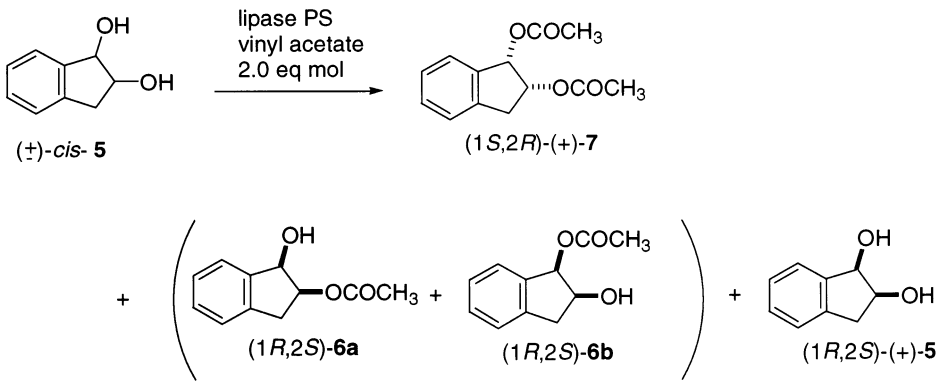
Table 1. Enzymatic transesterification of *cis*-1,2-indandiol **5** using lipase PS



Entry	Solvent/time (hours)	(1*R*,2*S*)-**5**		(1*S*,2*R*)-**6a**		(1*S*,2*R*)-**7**	
		Yield (%)[a]	E.e. (%)[b]	Yield (%)[a]	E.e. (%)[b]	Yield (%)[a]	E.e. (%)[b]
1	Hexane/4	68	4	14	–	11	89
2	THF/4	68	6	23	70	–	–
3	Benzene/4	52	59	37	46	4	89
4	IPE[c]/1	60	51	30	93	3	100
5	BME[d]/1	46	89	47	91	3	100
6	DBE[e]/1	56	31	29	71	2	92

[a] Isolated yield after silica gel column chromatography.
[b] Determined by chiral HPLC using Chiralcel OK (Daicel). Mono-acetate **6a** and di-acetate **7** were converted to indandiol **5** after hydrolysis with 25% aqueous NaOH.
[c] Di-*iso*-propyl ether.
[d] *tert*-Butyl methyl ether.
[e] Di-*n*-butyl ether.

Table 2. Enzymatic transesterification of *cis*-1,2-indandiol **5** using lipase PS

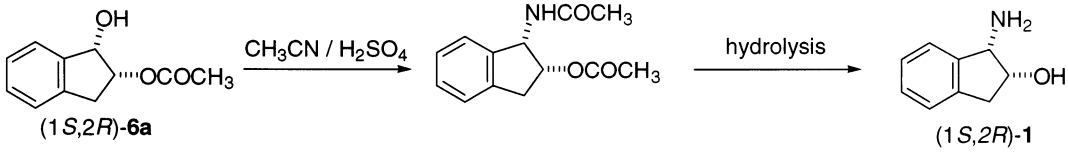


Entry	Solvent/time (hours)	(1*R*,2*S*)-**5**		(1*R*,2*S*)-**6a**/**6b**		(1*S*,2*R*)-**7**	
		Yield (%)[a]	E.e. (%)[b]	Yield (%)[a]	E.e. (%)[b]	Yield (%)[a]	E.e. (%)[b]
1	IPE[c]/24	10	100	36	100	38	100
2	BME[d]/24	4	100	50	74	44	82
3	DBE[e]/24	5	100	40	81	41	70

[a] Isolated yield after silica gel column chromatography.
[b] Determined by chiral HPLC using Chiralcel OK (Daicel). Mixture of **6a** and **6b** or di-acetate **7** was converted to indandiol **5** using 25% aqueous NaOH.
[c] Di-*iso*-propyl ether.
[d] *tert*-Butyl methyl ether.
[e] Di-*n*-butyl ether.

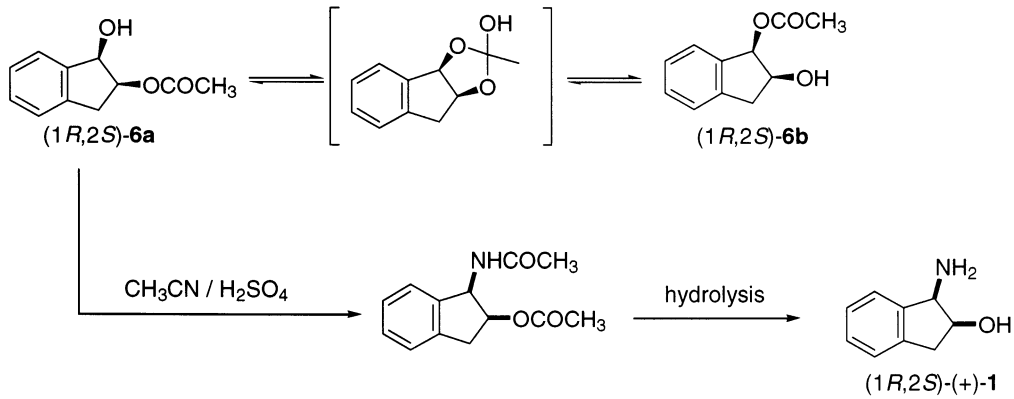
Under all conditions examined only the 2-acetoxy-1-indanol **6a** was obtained as the mono-esterified product. We further examined the enzymatic reaction of **5** with two equivalents of vinyl acetate. The results are summarized in Table 2.

This reaction was found to require more than double the reaction time than reactions in which only one equivalent of vinyl acetate was used, because the rate of the second esterification reaction was slower than that of the first. These reactions were terminated after 24 hours, and in this case mono-acetates were obtained as mixtures of **6a** and **6b**. Because it was difficult to separate **6a** and **6b** by silica gel column chromatography, absolute configuration and enantiomeric purity were measured as the mixture of **6a** and **6b** after hydrolysis to **5**. The best results were observed with di-*iso*-propyl ether as solvent. The mixture of (1*R*,2*S*)-



(1*S*,2*R*)-**6a** (1*S*,2*R*)-**1**

Scheme 2.



(1*R*,2*S*)-**6a** (1*R*,2*S*)-**6b** (1*R*,2*S*)-(+)-**1**

Scheme 3.

6a and (1*R*,2*S*)-**6b** was obtained in a yield of 36% with 100% e.e., and the regioisomeric ratio of **6a**:**6b** was 56:44. The enantiomerically pure **5** formed in 10% yield with 100% e.e., and **7** formed in 38% yield with 100% e.e. under the same conditions.

With the mono-acetates of both enantiomers in hand, we could then examine their behavior in the Ritter reaction. (1*S*,2*R*)-**6a** (Table 1, entry 5, 91% e.e.) was allowed to react with a large excess of CH_3CN in the presence of conc. H_2SO_4 (1.5 equiv. mol) at room temperature for 3 hours, followed by hydrolysis at 50°C for 8 hours to give (1*S*,2*R*)-**1** in 78% yield (with e.e. of 96%). In this case, the increase in enantiomeric purity results from the crystallization of (1*S*,2*R*)-**1** from the aqueous solution. This straightforward reaction of **6a** is in sharp contrast to the conversion of diol **5** to **1**, which required tightly controlled reaction conditions and gave only a moderate yield. The mono-acetate (1*S*,2*R*)-**6a** is one of the best precursors for (1*S*,2*R*)-**1** (Scheme 2).[7b,c]

In a similar manner, the reaction of the mixture of (1*R*,2*S*)-**6a** and (1*R*,2*S*)-**6b** (Table 2, entry 1, 100% e.e.) under the same reaction conditions gave (1*R*,2*S*)-**1** in 70% yield with 100% e.e. Lakshman and Zajc have reported regioselective preparation of aryl substituted *cis*-amino alcohols from the corresponding *cis*-glycols via oxirane intermediates.[8] We think it quite probable that this reaction took place by the intramolecular migration of the acetyl group followed by the formation of the same oxirane cation intermediate (Scheme 3).

In summary, the lipase-mediated kinetic resolution of **5** provides an efficient synthetic route to enantiomerically pure **1**. Additionally, this investigation shows the mono-acetate of **5** to be a good precursor for **1**.

3. Experimental

3.1. General

^{1}H NMR spectra were recorded on a JEOL GSX-270 (270 MHz). Chemical shifts are given in δ units with respect to TMS and coupling constants (J) are in Hz. Optical rotations were measured on a DIP 370 Jasco instrument. Enantiomeric purity of diol **5** was determined by chiral HPLC (Daicel Chiralcel OK column, hexane/isopropyl alcohol 9:1, 1 ml/min, 254 nm, 30°C; (1*R*,2*S*)-**5**, $t_r = 12.7$ min; (1*S*,2*R*)-**5**, $t_r = 14.8$ min). The optical purity of **1** was determined by chiral HPLC (Daicel Crownpack CR(–) column, aqueous $HClO_4$ pH 1.0, 0.6 ml/min, 210 nm, 30°C; (1*S*,2*R*)-**1**, $t_r = 19.2$ min; (1*R*,2*S*)-**1**, $t_r = 23.6$ min). All solvents and reagents were commercially available (reagent grade) and were used without further purification. Novozyme 435 was a gift from Novo-Nordisk Company.

3.2. Preparation of racemic *cis*-1,2-indandiol 5 and *cis*-2-acetoxyindan-1-ol 6a

Racemic *cis*-1,2-indandiol **5** was synthesized by the modification of the method reported by Winstein and Roberts.[9] The addition of silver acetate was unnecessary and no *trans*-isomer was formed.

trans-2-Bromo-1-indanol[10] (10.65 g, 0.05 mol) and acetic anhydride (6.38 g, 0.063 mol) were heated at 65°C for 5 hours to form *trans*-1-acetoxy-2-bromoindan. The pH of the reaction mixture was adjusted to 7–8 by addition of 25% aqueous sodium hydroxide solution. The heterogeneous reaction mixture was heated at 80°C for 2 hours and extracted with CH_2Cl_2 (2×50 ml). After evaporation of the solvent, the residue was purified by silica gel column chromatography using CH_2Cl_2 as the

eluent to give *cis*-2-acetoxyindan-1-ol **6a** (7.08 g, 74%) as pale yellow needles. This was the authentic sample to compare with the mixture of **6a** and **6b**. **6a**: mp 101–102°C; IR (KBr) = 3310, 1740, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, TMS): $\delta = 2.09$ (3H, s, CH_3), 2.29 (1H, br-d, $J = 7.4$ Hz, OH), 3.07 (1H, dd, $J = 16.8$, 3.0 Hz, CH_2), 3.21 (1H, dd, $J = 16.8$, 5.5 Hz, CH_2), 5.22 (1H, t, $J = 5.5$ Hz, CH) 5.46 (1H, td, $J = 5.5$, 3.0 Hz, CH), 7.22–7.48 (4H, m, arom.). When the pH was adjusted to more than 10, *cis*-1,2-indandiol **5** was obtained in a 90% yield from *trans*-2-bromo-1-indanol as off-white powder. **5**: mp 106–107°C; IR (KBr) = 3367 cm^{-1}; ^1H NMR ($CDCl_3$, TMS): $\delta = 3.12$ (1H, dd, $J = 16.1$, 5.7 Hz, CH_2), 3.24 (1H, dd, $J = 16.1$, 3.6 Hz, CH_2), 4.74 (1H, m, CH), 5.09 (2H, br-s, OH), 5.30 (1H, d, $J = 4.8$ Hz, CH), 7.21–7.71 (4H, m, arom.).

3.3. Lipase-catalyzed acetylation of *cis*-1,2-indandiol 5

A solution of **5** (1.51 g, 10 mmol) in the solvent of choice (30 ml, Table 1) was treated with lipase PS (1.51 g) and vinyl acetate (0.86 g, 10 mmol) and the resulting mixture was stirred at 35°C. The reaction was monitored by HPLC and stopped by filtering off the enzyme. The filtrate was concentrated under reduced pressure. The evaporation residue was then subjected to silica gel column chromatography (20 g, eluent: hexane/ethyl acetate (2:1)) The enantiomeric purities of **6a** and **7** were determined by their conversion to diols (10 mg of sample and 1 g of 25% NaOH were stirred at 60°C for 0.5 hours, and the reaction mixture was extracted with CH_2Cl_2 (10 ml)). After evaporation, **5** was obtained as white powder). The regioisomeric ratio of **6a** and **6b** was determined by ^1H NMR ($CDCl_3$, TMS) spectra, and the characteristic peak of the acetyl group CH_3 protons was observed at $\delta = 2.09$ for **6a** and $\delta = 2.15$ for **6b**.

3.4. Preparative acetylation of 5

Lipase PS (15.1 g) was added to a solution of **5** (15.1 g, 0.1 mol) and vinyl acetate (8.6 g, 0.1 mol) in *tert*-butyl methyl ether (300 ml). The mixture was stirred at 35°C for an hour until conversion reached ca. 50%. After filtering off the enzyme, evaporation of the solvent gave a residue which was subjected to chromatographic purification using hexane/ethyl acetate (2:1) to afford (1*R*,2*S*)-(+)-**5** (7.0 g, 46%, e.e. = 89%), $[\alpha]_D$ +51 (*c* 1.0, $CHCl_3$), (1*S*,2*R*)-(−)-**6a** (9.1 g, 47%, e.e. = 91%), $[\alpha]_D$ −61 (*c* 1.0, $CHCl_3$), and (1*S*,2*R*)-(+)-**7** (0.7 g, 3%, e.e. = 100%), $[\alpha]_D$ +69 (*c* 1.0, $CHCl_3$).

3.5. Preparation of (1*S*,2*R*)-*cis*-1-amino-2-indanol 1 from (1*S*,2*R*)-6a: typical procedure

(1*S*,2*R*)-**6a** 3.8 g (20 mmol, 91% e.e.) was dissolved in CH_3CN (20 ml) and 98% sulfuric acid (3.06 g, 30 mmol) was added dropwise to the solution at 15°C. After additional stirring at rt for 3 hours, H_2O (30 ml) was added. The mixture was stirred at 50°C for 8 hours. The reaction mixture was washed with CH_2Cl_2 (2×40 ml) and the aqueous layer was adjusted to pH 10 by the addition of 25% aqueous sodium hydroxide solution to form a slurry-like mixture. The mixture was filtered and filtrate was washed with CH_3CN (10 ml) and dried in vacuo to give (1*S*,2*R*)-1-amino-2-indanol **1** (2.67 g, 77%, e.e. = 96%), $[\alpha]_D$ −60 (*c* 1.0, $CHCl_3$), as a white powder.

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