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Lipase-mediated resolution of *cis*-1-amino-2-indanol, the key component of the HIV protease inhibitor indinavir

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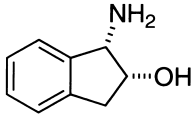
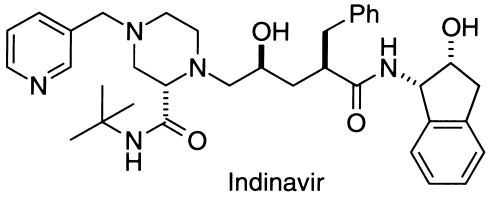
Abstract

The efficient and direct resolution of *cis*-1-amino-2-indanol using *Candida antarctica* lipase B catalyzing the alcoholysis of its *N*,*O*-diacetyl derivative is reported.

Recently, much attention has been paid to the synthesis of enantiomerically pure *cis*-1-amino-2-indanol **1** as a key component of the HIV protease inhibitor, indinavir (Merck's Crixivan®).[1] In the commercial synthesis of indinavir,[2] (1*S*,2*R*)-1-amino-2-indanol ((1*S*,2*R*)-**1**) is used as a key component and also plays an important role in the asymmetric control of the two central stereocenters. In addition, chiral ligands and auxiliaries derived from both enantiomers of **1** have proven to be very effective in a number of asymmetric reactions.[3]



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



Indinavir

In order to obtain enantiomerically pure **1**, many efforts have been attempted, e.g. asymmetric synthesis via Jacobsen's epoxidation of indene,[4] synthesis from D-phenylalanine[5] and various chemoenzymatic approaches.[6–11] Resolution of the racemate is one of the most important and convenient methods for preparing enantiomerically pure compounds, and the resolution of cyclic 1,2-aminoalcohols such as 2-aminocyclopentanol and 2-aminocyclohexanol has been achieved using enzymes.[12] Although classical methods have been developed for the resolution of racemic **1**,[13] no effort has been made to resolve (±)-**1** enzymatically. We now report the efficient and direct kinetic resolution of *cis*-1-amino-2-indanol through CAL-B (*Candida antarctica* lipase B) mediated alcoholysis in an organic solvent (Scheme 1).

Racemic **1** was prepared from 2-bromo indanol via the Ritter reaction.[8] A preliminary attempt for the irreversible acylation of (±)-**1** using vinyl acetate as the acyl donor was examined. However, no reaction

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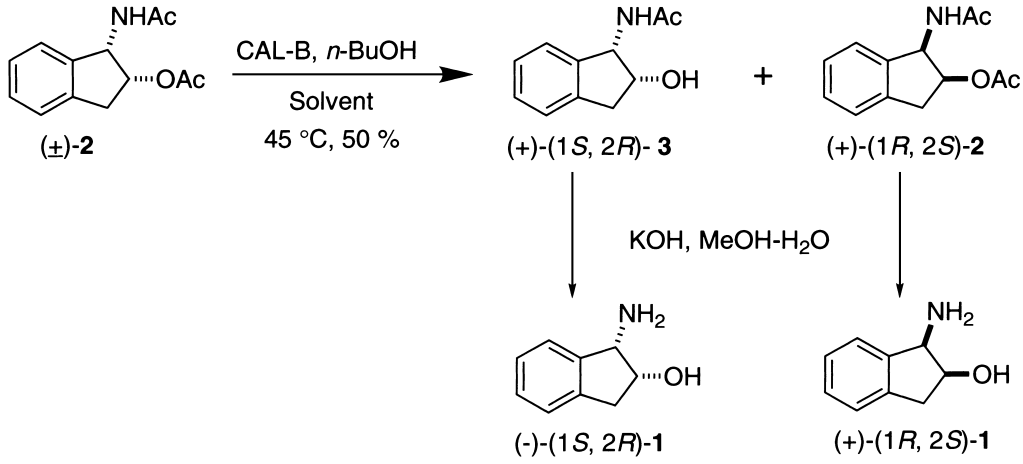

Scheme 1.

occurred when using lipases such as CAL-B, lipase PS, PPL, etc. By using ethyl acetate as the acyl donor and also the solvent, we obtained three acylated products with extremely low enantioselectivity. This was expected because free aminoalcohols are not generally used as suitable substrates in a transesterification reaction. Thus, the enzyme catalyzed alcoholysis of the *N*,*O*-diacetyl derivative of (±)-**1** ((±)-**2**) in organic solvent was considered, as shown in Scheme 1. Since (±)-**2** was barely soluble in DIPE and toluene, common organic solvents for enzymatic reactions, we examined several solvents as listed in Table 1.

Table 1
CAL-B catalyzed alcoholysis of (±)-**2** in organic solvents[a]

Entry	Solvent	Reaction time (h)	Conversion[b] %	Substrate (**2**) % ee[c]	Product (**3**) % ee[c]	E[d]
1	Dioxane	70	49	96	>99	>500
2	DIPE/Dioxane (1:1)	76	50	98	>99	>500
3	THF	115	47	88	>99	>500
4	Acetone	115	49	94	>99	>500
5	$CHCl_3$	115	47	90	>99	>500
6	$CHCl_3$/Toluene (1:3)	84	49	96	>99	>500
7	$CHCl_3$/DIPE (1:2)	84	50	97	>99	>500

[a] (±)-**2**, 0.21 mmol; *n*-BuOH, 1.05 mmol; CAL-B, 50 mg; solvent, 6 ml; temp., 45 °C.
[b] Determined by GC.
[c] Determined by chiral HPLC (Chiralcel OD, *i*-PrOH/hexane = 1:9).
[d] Defined in ref. 15.

Commercially available lipases (CAL-A, CAL-B, lipase PS, lipase AY, lipase AK, PPL) were examined for the alcoholysis of (±)-**2** with *n*-BuOH in $CHCl_3$. CAL-B (Chirazyme® L-2, c.-f. C2, lyo) efficiently catalyzed the alcoholysis, while the reaction hardly proceeded using other enzymes. In general, water-immiscible lipophilic solvents such as hexane, toluene and DIPE are widely used for enzymatic reactions as they retain an enzyme's catalytic activity.[14] On the contrary, water-miscible hydrophilic solvents such as dioxane, acetone and THF, in which most enzymes are denatured and deactivated, are rarely used.

As listed in Table 1, not only in water-immiscible solvents (entries 5–7) but also in water-miscible ones (entries 1–4), both the unreacted substrate **2** and product **3** are obtained in high enantiomeric purity.

Furthermore, the enantiomeric ratio (E value)[15] was calculated to be >500, showing excellent kinetic resolution. Thus, this result shows that CAL-B is an exceptionally stable enzyme in the solvents examined for the alcoholysis of (±)-**2**. As for the alcoholysis rate, solvents such as THF, acetone and $CHCl_3$ (entries 3–5), which require a relatively longer reaction time to attain 50% conversion, are somewhat less preferable.

A preparative reaction was carried out as follows. To a solution of (±)-**2** (250 mg, 1.07 mmol) and *n*-BuOH (0.4 ml, 4.32 mmol) in DIPE:dioxane (1:1, 16 ml) was added CAL-B (200 mg). The mixture was shaken at 45°C and the progress of the reaction was monitored by GC. When the conversion reached 50%, the lipase was filtered off. The products were purified by silica gel column chromatography to provide (+)-(1*S*,2*R*)-**3** [89 mg, 43% yield, >99% ee, $[\alpha]_D^{20}$ +38.3 (*c* 0.84, EtOH)] and (+)-(1*R*,2*S*)-**2** [120 mg, 48% yield, 99% ee, $[\alpha]_D^{20}$ +76.2 (*c* 1.35, $CHCl_3$)]. The absolute configurations of the resolved products were assigned after their conversion into the corresponding aminoalcohols and comparison of the specific rotations with the literature values.[7] Thus, the basic hydrolysis of (+)-**2** and (+)-**3** provided (+)-(1*R*,2*S*)-**1** and (−)-(1*S*,2*R*)-**1**, respectively, without any racemization, establishing their absolute configurations as shown in Scheme 1.

In conclusion, the present procedure represents a direct and practical access to both enantiomers of *cis*-1-amino-2-indanol (−)-(1*S*,2*R*)- and (+)-(1*R*,2*S*)-**1**, a medicinally and chemically useful component, in an enantiomerically pure form through CAL-B-mediated alcoholysis.

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