A Practical Synthesis of (1*S*, 2*R*)-1-Amino-2-indanol, a Key Component of HIV Protease Inhibitor, Indinavir

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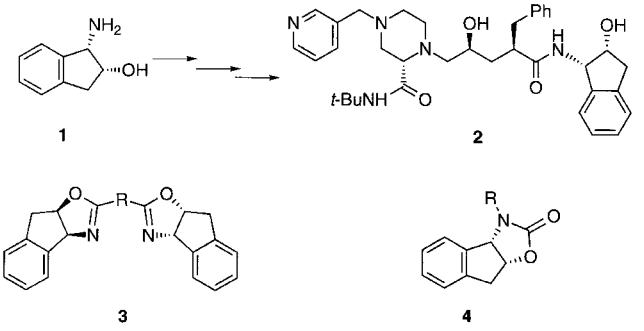
Abstract: The synthesis of (1*S*,2*R*)-1-amino-2-indanol, a key component of HIV protease inhibitor, is accomplished in eight steps from D-phenylalanine. The starting material is converted into 2-acetoxy-1-indanone in four steps involving intramolecular Friedel-Crafts cyclization. The stereochemically labile α-acetoxy ketone is hydrolyzed to 2-hydroxy-1-indanone using a catalytic amount of scandium triflate without any loss of the optical purity. Diastereoselective hydrogenation of α-hydroxy oxime, derived from the α-hydroxy ketone, gives the amino alcohol in 96% *cis*-selectivity. Optical purity of the starting material is perfectly retained throughout the transformations.

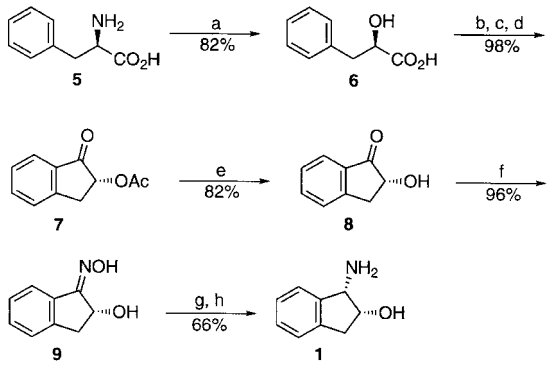
Enantiomerically pure (1*S*, 2*R*)-1-amino-2-indanol (**1**) is currently receiving considerable attention as the key component of indinavir (**2**), a potent inhibitor of the protease of human immunodeficiency virus (HIV).[1] Since indinavir is widely used in medical treatment for AIDS, inexpensive supply of **1** is strongly desired. In addition, **1** is the precursor of bisoxazoline **3**, a ligand for chiral catalysts,[2] and chiral auxiliary **4** is successfully utilized for various asymmetric syntheses.[3]



For the efficient synthesis of **1**, it is required to prepare the *cis*-amino alcohol moiety with completely controlled regio- and stereochemistry and with correct absolute configurations. Among various routes to **1**,[4] one of practical methods involves the Ritter reaction[4c] of racemic indene oxide or indane-1,2-diol and the subsequent resolution. The major drawback of optical resolution of racemic **1** or its precursor is that it leaves an equal amount of the undesired enantiomer.[5] Although asymmetric synthesis of **1** using a variety of chiral catalysts is feasible, the selectivities achieved are not high enough.[6]

To establish a practical synthetic route to **1** without optical resolution or asymmetric synthesis, we focused on i) use of a readily available chiral pool, ii) transformations without any loss of optical purity, and iii) induction of (1*S*, 2*R*) configuration of **1** from the chiral starting material. We have chosen D-phenylalanine as the starting material, because D-phenylalanine is co-produced in the industrial preparation of Aspartame®, an artificial sweetener. Our synthetic route is outlined in Scheme 1.

Treatment of D-phenylalanine (**5**) with $NaNO_2$-H_2SO_4[7,8] gave optically pure (*R*)-2-hydroxy-3-phenylpropanoic acid (**6**). The hydroxyl group of **6** was acetylated,[9] and the resulting α-acetoxy carboxylic acid was converted into the corresponding acid chloride with thionyl chloride.



Scheme 1. *Conditions:* (a) $NaNO_2$, 2M H_2SO_4, 0 °C-rt, 4 h; (b) Ac_2O / pyridine, 0 °C-rt, 12 h; (c) $SOCl_2$, rt-50 °C, 3 h; (d) $AlCl_3$ CH_2Cl_2, rt, 3 h; (e) $Sc(OTf)_3$ (20 mol%) / MeOH-H_2O, rt, 48 h; (f) $HONH_2$·HCl / pyridine, rt, 12 h; (g) H_2, Pd black (5 wt%), MeOH, HBr, rt, 15 h; (h) $NaHCO_3$ / H_2O

The intramolecular Friedel-Crafts reaction of the acid chloride using $AlCl_3$ in CH_2Cl_2 at room temperature proceeded smoothly to give **7** in quantitative yield without loss of the optical activity.[10,11] Our observation is striking in view that the Friedel-Crafts acylation of acid chlorides having a chiral center at α-position is often accompanied by racemization.[12]

Hydrolysis of 2-acetoxy-1-indanone (**7**) was first attempted with methanolic lithium hydroxide to give acyloin **8** in ca.70% yield with remarkable racemization: enantiomeric excess of **8** was estimated to be only 8%. Although the racemization was suppressed under acidic conditions (MeOH-H_2SO_4 or trifluoromethanesulfonic acid) at room temperature, the reaction took much longer time (21% yield after 48 h). When the hydrolysis was conducted at 60 °C under acidic conditions (MeOH-H_2SO_4), the conversion was improved (75% yield after 48 h) but by-products formed in considerable amounts and racemization occurred to a certain extent (86% ee). After screening the catalyst for hydrolysis of **7**, we found scandium triflate ($Sc(OTf)_3$) was the supreme catalyst. Hydrolysis of **7** in the presence of 20 mol% of $Sc(OTf)_3$ in H_2O-MeOH (1 : 4) at room temperature attained >95% conversion (>99% ee) in 48 h as determined by HPLC.[13] Work-up and recrystallization gave **8** in 82% yield with >99% ee as a colorless solid.[14] To the best of our knowledge, this is the first example of $Sc(OTf)_3$ as a hydrolysis catalyst.[15] Efficiency of the hydrolysis, we consider, is attributed to the coordination ability of $Sc(OTf)_3$ towards the α-acetoxy carbonyl moiety.[16] Indeed, hydrolysis of 2-acetoxyindan was much slower (30% yield, 48 h) than that of 2-acetoxy-1-indanone. Details will be described in due course.

Treatment of **8** with $HONH_2$·HCl in pyridine afforded oxime **9** in 96% yield as a 65 : 35 mixture of *E*- and *Z*-isomers.[17] The ee of each isomer was >99%.[18] Although the isomers could be easily separated by silica gel column chromatography, each isomer was found to rapidly isomerize in an acidic solution to reach a ratio of 43 : 57 at room temperature as revealed by ^{1}H NMR. Thus, an isomeric mixture of **9** was used for the next reduction.

We studied diastereoselective hydrogenation[19] of oxime **9** to our target molecule **1** using a variety of catalysts, additives, and solvents under various hydrogen pressures, and found an optimum *cis*-selectivity and yield were achieved with a Pd black catalyst and HBr.[20] Treatment of **9** (*E* : *Z* = 65 : 35) in MeOH-HBr under an atmospheric pressure of molecular hydrogen at ambient temperature in the presence of Pd black for 20 h afforded (1*S*, 2*R*)-**1** along with *trans*-(1*R*, 2*R*) isomer of **1** (*cis* : *trans*=96 : 4),[21] both as hydrobromides. During the hydrogenation, no epimerization at 2-position was observed. Neutralization with aqueous $NaHCO_3$ followed by recrystallization from MeOAc-hexane gave **1** in 66% yield.[22]

In summary, enantiomerically pure (1*S*, 2*R*)-1-amino-2-indanol (**1**) is obtained from D-phenylalanine in 8 steps without any chromatographic purification. This route allows us to produce **1** in a large scale. In addition, enantiomerically pure 2-hydroxy-1-indanone (**8**), a useful structural subunit of natural products and valuable synthetic intermediate, is now readily available.[23]

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References and Notes

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(11) Ee was determined by HPLC analysis using DAICEL CHIRALCEL OB analytical column (0.46 mm, 25 cm) with ethanol in hexane (20%) as an eluent. Mp 80.5-81.5 °C, $[\alpha]^{25}_D$ = -19 (c 1.0, MeOH).

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(13) $Lu(OTf)_3$ (73%), $Dy(OTf)_3$ (68%), $Ho(OTf)_3$ (65%) exhibit relatively good yield after 24 h.

(14) DAICEL CHIRALCEL OB analytical column (0.46 mm, 25 cm) with ethanol in hexane (20%) as an eluent was used. Mp 82.4-83.7 °C, $[\alpha]^{25}_D$ = -57 (c 1.0, MeOH) (lit. $[\alpha]^{25}_D$ = -62 (c 1.0, $CHCl_3$): See ref 6.

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(17) The geometry of **9** was determined by NOE experiments after conversion to 2-acetoxy-1-acetoxyiminoindanone.

(18) DAICEL CHIRALCEL OB analytical column (0.46 mm, 25 cm) with 20% 2-propanol in hexane as an eluent was used for *E*-**9**. The t_Rs observed at a flow rate of 0.5 mL·min-1 were as follows: 14.7 min (*R*-form), 20.2 min (*S*-form). Analysis of *Z*-**9** was performed by DAICEL CHIRALPAK AD analytical column (0.46 mm, 25 cm) with 14% 2-propanol in hexane as an eluent.

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(20) Such catalysts as Pt, Rh, Ru, Re, and Ir also were examined under the similar conditions. Relatively good *cis*-selectivity and the yield were obtained with PtO_2, Ir black and Rh black. Catalyst, cis%, and yield are given in this order: PtO_2, 82%, and 28%; Ir black, 89%, and 31%, and Rh black, 75%, and 33%.

(21) Even when the *E*- or *Z*-isomer was used respectively as a substrate, the ratio of *cis* and *trans* did not change, as might be expected on the basis of the isomerization experiment in an acidic solution.

(22) The amino alcohol obtained by this procedure was contaminated with 3% of (1*R*, 2*R*)-*trans* isomer of **1** as determined by HPLC (ODS column) with 5% methanol in aqueous phosphoric acid (0.2%) as an eluent. Enantiomeric ratio of the major isomer **1** was determined by HPLC using DAICEL CROWNPAK CR (+) analytical column (0.46 mm, 15 cm) with $HClO_4$ aq. (pH 2).

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