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An Efficient Synthesis of (1*S*, 2*R*)-1-Amino-2-Indanol, A Key Intermediate of HIV Protease Inhibitor, Indinavir

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(1S,2R)-1-amino-2-indanol, a key component of an HIV protease inhibitor is synthesized in four steps starting from indanone. The $Mn(OAC)_3$ mediated acetoxylation of indanone followed by fungus catalyzed hydrolysis of acetoxyindanone furnished optically pure α-hydroxy indanone. Formation and enantioselective reduction of oxime ether of 2-hydroxyindanone afforded (1S, 2R)-1-amino-2-indanol in 97% *cis* selectivity.

Key Words: Manganese(III) oxidation, imine reduction, enantioselective hydrolysis, 1-amino-2-indanol

1. Introduction

Enantiomerically pure (1S, 2R)-1-amino-2-indanol **1** is used as a chiral auxiliary[1,2] for asymmetric synthesis and an important component of indinavir **2**, a potent inhibitor of the protease of human immunodeficiency virus[3] (HIV). For the efficient synthesis of **1**, it is required to prepare the *cis*-amino alcohol moiety with completely controlled regio-and stereochemistry and correct absolute configurations.

Several routes have been developed for the peraparation of optically pure (1S, 2R)-1-amino-2-indanol: Jacobsen's asymmetric epoxidation of indene followed by either a C-1 or C-2 chiral transfer process of the C-O bond of indene oxides resulting in enantiopure (1S)-amino-(2R)-indanol (**1**), and the Ritter reaction[4c] of racemic indene oxide or indane-1,2-diol and subsequent resolution achieved by Hiyama et. al. starting from *D*-phenylalanine and asymmetric synthesis using a variety of chiral catalysts.

2. Formulae 1 and 2

Recently we reported the $Mn(OAc)_3$ mediated acetoxylation of enones and aromatic ketones[5]; enzymes and fungus mediated resolution of acetoxy enones to obtain optically pure α-hydroxy ketones[6], and formation

and enantioselective reduction of oxime ethers[7]. Combining the above-mentioned reactions, we report herein a simple and efficient route to (1S, 2R)-1-amino-2-indanol.

3. Results and Discussion

In an initial reaction shown in the Scheme the oxidation of indanone **3** with four equivalents of manganese (III) acetate furnished the desired α-acetoxy indanone **4** in 82% yield. In connection with ongoing research[5a−h] we found that the source of manganese (III) acetate is very important for the yield of thereactions. The anhydrous manganese (III) acetate used in this oxidation was prepared from manganese (II) nitrate and acetic anhydride and dried using phosphorus pentoxide under vacuum prior to use[5i−k].

The enantioselective ester hydrolysis was performed using *Rhizopus oryzae*. The bioconversion was performed in EtOH and fungus was incubated in the presence of α- acetoxy indanone at 25°C. The reaction medium was neutralized with $CaCO_3$ solution during the conversion, and the conversion was monitored by TLC using authentic hydroxy ketone as reference. After 96 h about 45-50 % conversion of the product was observed. The product was separated using flash column chromatography, and hydroxy ketone 5 was isolated in 41 % yield and in 93 % ee. The configuration of the product was assessed as *(R)* by comparison of its specific rotation with data in the literature[8]. Under similar conditions termination of the reaction after 38-42 % conversion increases the ee to $>$ 97 %.

The ee is determined via its *(S)*-O-acetyllactylester derivative by GC (capillary column HP-5 crosslinked 5% PhMe-silicone[9]) and ^{1}H NMR spectroscopy (methyl proton arising from the *(S)*-O-acetyllactyl moiety of the diastereomeric esters gives signals as doublets in the range 1.54-1.63 ppm. The enantoimeric excess of the compounds is determined by resolving these signals). In an initial survey *Rhizopus* oryzae was shown to contain an esterase that can yield alcohols with configurations that appeared to exhibit a consistent pattern. The enantiomeric excesses of recovered acetoxy ketone *(S)*-**3** were 88 % (conversion: 47.5 %; E: 191[10]).

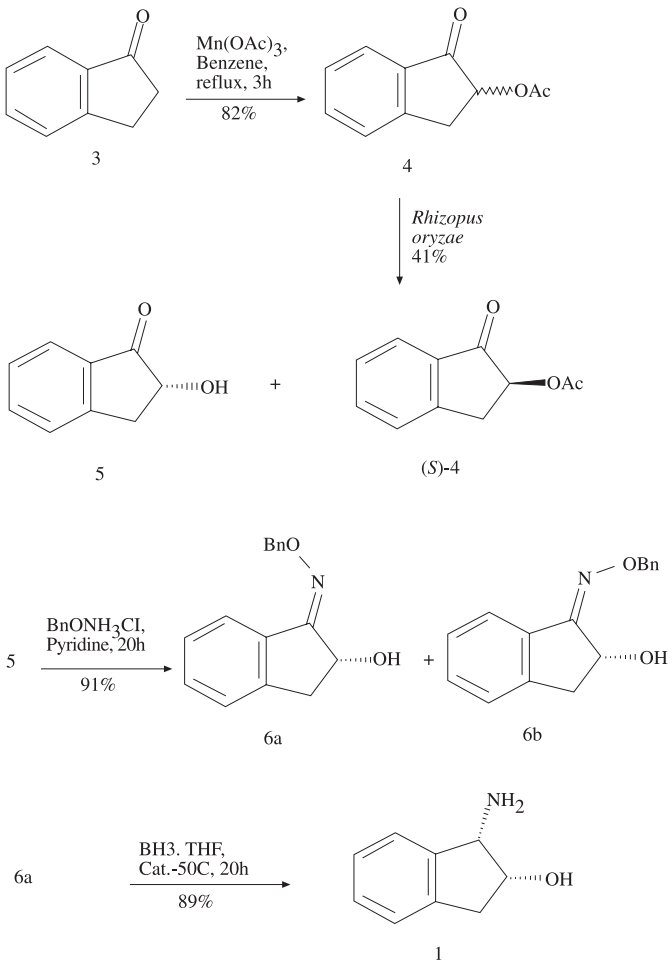
α-hydroxy indanone was converted to the corresponding α-hydroxybenzyl oxime **6a** and **6b** by treatment with 1.2 equivalent of benzyloxyamine hydrochloride in pyridine at RT for 20 h to give a mixture (4:1) of *E*- and *Z*- oxime ethers in 91 % isolated yield. The oxime ethers were separated by flash column chromatography (Rf: 0.57 for E- isomer; Rf: 0.68 for Z-isomer) using ethyl acetate and hexane (4:1) as the solvent system. The stereochemistry of oxime ethers **6a** and **6b** was determined by NOE experiments.

For the enantioselective reduction of *E*-oxime ether with BH_3. THF, in the presence of oxazaborolidine complexes prepared from different chiral amino alcohols shown in the Table, were used[11]. After reduction the crude product was purified using flash column chromatography and product **1** was isolated in 78-89 % yield. The reduction of *E*- oxime ether **6a** with **7-10** furnished *cis*-selectivity between 76-97 %, depending on the reaction conditions and catalysts. As shown the in Table the best optical yields were obtained using **9** and **10** as catalyst with the ratio of oxime ether: BH_3: catalysts 0.8:1.5. The assignment of stereochemistry and the optical purity in each case was made on the basis of the α-values of the product. The use of catalysts gave very low selectivity.

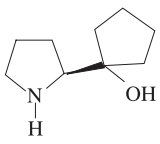
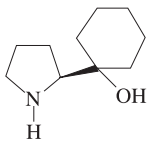
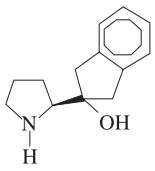
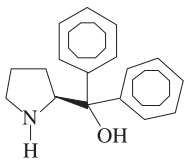
When the *E/Z*-isomeric mixture (4:1) was used as a substrate in reduction the ratio of *cis* and *trans* isomer was 62:38 with chiral catalyst and 58:42 without catalyst. Reduction of *E*-oxime ether uder conditions similar to those described above without chiral catalysts gave *cis*-product in excess (68:32). These selectivites could be explained as follows: The reaction of borane with α-hydroxy oxime ether first generates the alkoxy borane intermediate, activated by Lewis acid for oxime reduction, and subsequent reduction of oxime ether

occurs from the less hindered side (i.e. away from the bulky borane) to give *cis* amino alcohol. The formation of *cis* amino alcohol with high enantioselectivity using chiral oxazoborolidine as catalysts may be a result of double stereodifferentation in the reduction step.

In Summary, the method described in this report provides an efficient and convenient route to (1*S*, 2*R*)-1-amino-2-indanol.



Scheme

Anino alcohol	 7	 8	 9	 10
Product 1 de%	63	71	91	>97
Chem. Yield %	84	89	81	78

Table

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4. Experimental

All reagents were of commercial quality, and reagent quality solvents were used without further purification. IR spectra were determined on a Philips model PU9700 spectrometer. ^{1}H NMR spectra were determined on a Bruker AC 80 MHz FT, AC 200 MHz and Bruker DPX 400 MHz FT spectrometers. GC analyses were determined on a HP 5890 gas chromatograph. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter.

4.1. 2-Acetoxyindanone (4):

A mixture of (2.68 g, 10 mmol) of manganese (III) acetate and (0.33 g, 2.5 mmol) of ketone in benzene (50 mL) was refluxed (the reaction was monitored by TLC) under a Dean-Stark trap. The mixture was cooled to RT, diluted with ethyl acetate, was washed successively with 1M aqueous HC1 solution, saturated aqueous $NaHCO_3$ solution and brine, and dried over anhydrous $MgSO_4$. The crude product was chromatographed on flash silica gel in 1:3 ethyl acetate-hexane to afford 0.39 g (82 %) of colorless solid, mp: 80.5-82.0°C; Lit. [4]80.5-81.5°C.

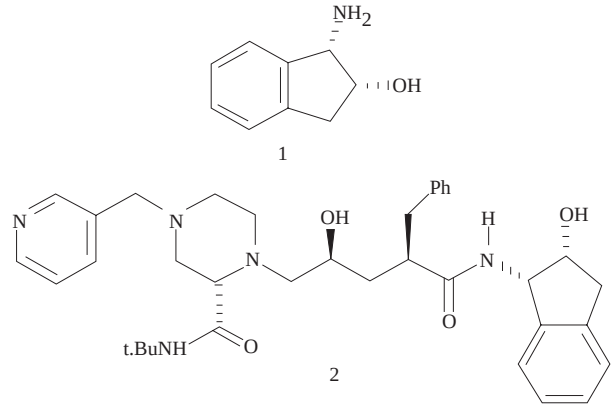
4.2. Hydrolysis of 2-acetoxyindanone:

Rhizopus oryzae (NRRL 395) was used for the experiments. It was cultivated on boiled rice and the fungal spores were transferred by loopfuls into the sterile flasks containing the medium and grown in a rotary shaker at 30°C for two days. The medium for fungal growth included 15.0 g glucose syrup, 1.0 g $(NH_4)_2SO_4$, 0.30 g KH_2PO_4, 0.12 g $MgSO_4$ and 0.02 g $ZnSO_4$ diluted to 500 ml by distilled water. The medium was divided into 5 and sterilized in an autoclave for 15 minutes. Spores from the main plate were transferred into an erlenmeyer flask containing 100 ml sterile medium. The fungus was inoculated at 30°C for two days in the rotary shaker and then the substrate (323 mg, 1.7 mmol) dissolved in 2 ml EtOH was added. Shaking was resumed until approximately 38-42% of the racemic acetate was hydrolyzed. During the hydrolysis the medium was neutralized with 10% $CaCO_3$ solution. The fungus was filtered out, washed with distilled water, and the combined aqueous phases extracted with ethyl acetate and the alcohol and unhydrolyzed acetate separated by flash column chromatography (EtOAc: hexane, 1:2). 5:Yield: 96 mg (38 %), mp 82-84°C (Lit. [4a]82.4-83.7°C). $[\alpha]_{D^{20}}$=-23.71(c=1.5, $CHCl_3$); $[\alpha]_{D^{20}}$=-23.1(c=1.5, $CHCl_3$)[4a,6]. *(S)*-**4**: Yield: 142 mg (44%), mp 80-82°C (Lit. [4a] 80.5-81.5°C), [α]=38.1 (c=0.5, CH_2Cl_2), Lit. For *(R)*-**4**:[8g] $[a]_{D^{22}}$=-37.8 (c=0.5, CH_2Cl_2).

4.3. 2-Hydroxyindanone *O*-benzyloxime ether (6):

To a solution of 148 mg (10 mmol) 2-hydroxyindanone (5) in 5 ml of pyridine was added 191 mg (12 mmol) solution of *O*-benzylhydroxylamine hydrochloride in 5 ml of pyridine under cooling in an ice bath. The reaction mixture was stirred for 14 h at RT and then concentrated. The residue was purified by column chromatography on silica gel using ethylacetate-hexane as an eluent. The product was obtained as viscose

oil, yield 230 mg 91 % [2e]. Separation of the isomers using flash column chromatography gave 168 mg *E*-oxime ether **6a** and 42 mg *Z*-oxime ether **6b**. ^{1}H NMR (**6a**) ($CDCl_3$): δ 3.03 (dd, J=16.5, 5.1 Hz, 1H), 3.58 (dd, J=16.5 Hz, 7.9 Hz, 1H), 4.54 (dd, J=7.9 Hz, 1H), 5.18 (s, 2H, CH_2), 7.23-7.48, 7.46-7.64 (m, 8H, aromatic H)[4,6,8g].



4.4. (1S, 2R)-(-)-cis-1-Amino-2-Indanol (1):

A solution of borane (20 mmol) in THF (20 ml) was added under argon dropwise to a 10 mmol amino alcohol solution in 10 ml of THF at -20°C. Then the resulting mixture was warmed to -5°C and stirring continued at this temperature for 10 h before 8 mmol (202 mg) of oxime ether **6a** in 10 ml THF was added dropwise. The resulting solution was stirred at RT for 48 h and was decomposed by slowly adding 2M-HC1. The mixture was extracted with ethyl acetate, and purification of crude product by recrystallization (EtOAc-hexane) furnished 106 mg (89%) of **1** in optically pure form. Mp 118-121°C (Lit. 118-121°C), NMR and IR spectras are identical with commercially available compound[4f].

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