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Chemoenzymatic synthesis of (1*S*,2*R*)-1-amino-2-indanol, a key intermediate of HIV protease inhibitor, indinavir

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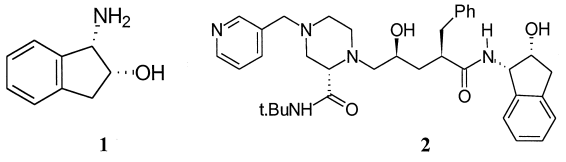
Abstract

The synthesis of (1*S*,2*R*)-1-amino-2-indanol, a key component of HIV protease inhibitor is accomplished in four steps starting from indanone efficiently and with high levels of diastereo- and enantioselectivity. The starting material is converted into 2-acetoxy-1-indanone involving Manganese (III) acetate oxidation . The 2-acetoxyketone is hydrolyzed to 2-hydroxy-1-indanone enantioselectively using *Rhizopus oryzae*. Selective reduction of 2-hydroxyoxime derivative, derived from the 2-hydroxyketone, gives the amino alcohol up to 98% diastereo- and enantioselectivity.

Keywords: Biotransformation; 1-Amino-2-indanol; *Rhizopus oryzae*; Enantioselective hydrolysis; Enantioselective reduction

1. Introduction

Enantiomerically pure (1*S*,2*R*)-1-amino-2-indanol, **1**, is used as chiral auxiliary [1–5] for asymmetric synthesis and is an important component of indinavir, **2**, a potent inhibitor of the protease of human immunodeficiency virus [4,5] (HIV). For the efficient synthesis of **2**, it is required to prepare the *cis*-amino alcohol moiety with completely controlled regio- and stereochemistry and correct absolute configurations (Scheme 1).



1 **2**

Scheme 1.

Several routes have been developed for the preparation of optically pure (1*S*,2*R*)-1-amino-2-indanol [1–3]: 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 (1*S*,2*R*)-1-amino-2-indanol **(1)**, and the Ritter reaction of racemic indene oxide or indane-1,2-diol and subsequent resolution. Eight steps synthesis

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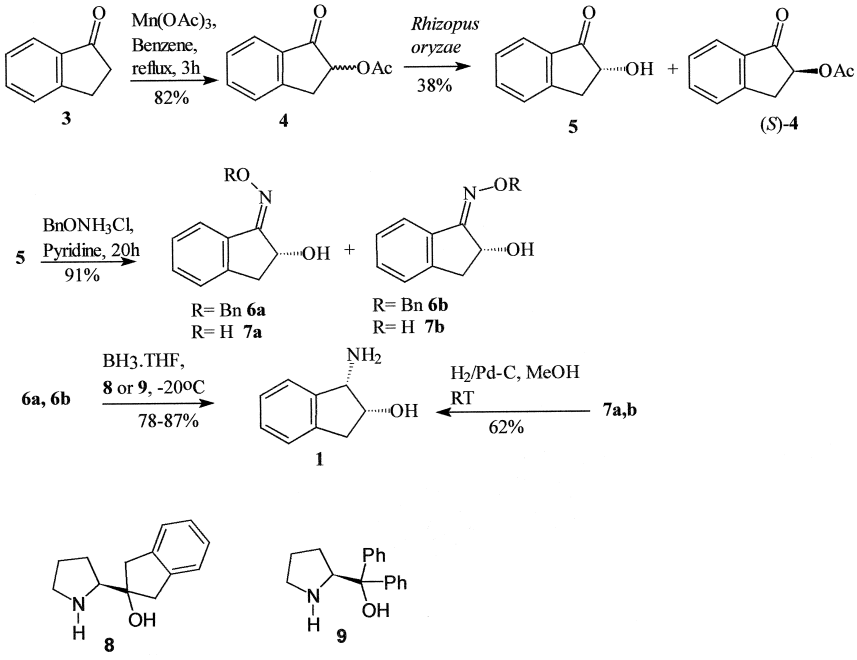
achieved by Kajiro et al. starting from D-phenylalanine [3].

2. Results and discussion

Recently, we have reported the $Mn(OAc)_3$ mediated acetoxylation of enones and aromatic ketones [6–9]; enzymes and fungus-mediated resolution of acetoxy enones to obtain optically pure α-hydroxyketones [10], and formation and enantioselective reduction of oxime ethers [11]. Combining our above-mentioned reactions, we report herein a simple and efficient route to (1*S*,2*R*)-1-amino-2-indanol.

In an initial reaction shown in Scheme 2, the oxidation of indanone **3** with four equivalents of Manganese (III) acetate furnished the desired α-acetoxy indanone **4** in 82% yield. 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 hydroxyketone as reference. After 96 h about 45%–50% conversion of the product was observed. The product was separated using flash column chromatography, and hydroxyketone, **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 Refs. [2,3]. 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 [12]) and ^{1}H-NMR spectroscopy (methyl proton arising from the (*S*)-*O*-acetyllactyl moiety of the diastereomeric esters gives signals as doublet in the range 1.54–1.63 ppm. The enantiomeric excess of the compounds is determined by resolving these signals). In an initial survey, *R. oryzae* shows to contain an esterase that can yield alcohols with configurations that appeared to exhibit a consistent pattern. The enantiomeric



Scheme 2.

excesses of recovered acetoxyketone (*S*)-**4** was 88% (conversion: 47.5%; E: 191 [13]).

α-Hydroxy indanone was converted to the corresponding α-hydroxybenzyloxime, **6a** and **6b**, by treatment with 1.2 equivalent of benzyloxyamine hydrochloride in pyridine at RT for 20 h to give mixture (4:1) of *E*- and *Z*-oxime ethers in 91% isolated yield. The oxime ethers are 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 $BH_3 \cdot THF$, in the presence of oxazaborolidine complexes prepared from different chiral amino alcohols and $BH_3 \cdot THF$ shown in Table 1, are used [14–16]. Slow addition of oxime ether to chiral inducer and $BH_3 \cdot THF$ at -20°C was applied in all runs. After reduction, the crude product was purified using flash column chromatography and the product **1** was isolated in 78%–84% yield. The reduction of *E*-oxime ether **6a** with **8** and **9** furnished *cis*-selectivity between 71% and 99%, depending on the reaction conditions and chiral inducers. As shown in Table 1, the best optical yields are obtained with the ratio of oxime ether:BH_3: chiral inducers, 1:4:2. Catalytic amounts of chiral inducers (5%–15% of BH_3–oxazaborolidine complex and two equivalents of $BH_3 \cdot THF$) gave low selectivity (70%–73% *cis*). Reduction of *E*-oxime ether under similar conditions described above without chiral inducer gave *cis*-product in excess (68:32). As shown in Table 1, the reduction of *Z*-oxime ether with and without chiral inducer furnished *cis*-product in excess but in low selectivity. The assignment of stereochemistry and the optical purity in each case was made using ^{1}H-NMR, HPLC and on the basis of optical rotation values of the product. The *cis*-stereochemistry of the product was demonstrated by a ^{1}H-NMR spectrum where CH protons showed a coupling constant of 3.7 Hz from *cis*-orientation. The 2-methylpyrrol derivative of the amino alcohol , which was synthesized according to the literature procedure [17], showed excellent separation properties on the chiral HPLC column. In each case, the optical purity of the isomers was determined via their 2-methylpyrrol derivative using HPLC. The results are compared with 2-methylpyrrol derivative of *rac*- and optically pure commercially available (+)-*cis*, (−)-*cis*-**1**.

Table 1
Reduction of oxime ethers **6a** and **6b** with different chiral inducers

Oxime ether:borane: chiral inducer	Ratio	1-Amino-2-indanol **1**	
		cy (%)	*cis* (1*S*,2*R*): *trans* (1*R*,2*R*)[a]
6a:BH_3:**8**	1:4:2	81	96:4
6a:BH3:**9**		78	99:1
6a:BH_3:**8**	1:2:0.05	84	70:30
6a:BH3:**9**		82	71:29
6a:BH_3:**8**	1:2:0.15	84	71:29
6a:BH3:**9**		83	73:27
6b:BH_3:**8**	1:4:2	79	63:37
6b:BH_3:	1:4:–	85	64:36
6a:BH_3:	1:4:–	87	68:32

[a]The physical and spectroscopic data of the product are in agreement with commercial available data. The isomeric ratio is determined by chiral HPLC analysis (Chiralpack AD column, UV detection at 220 nm, 90:10 *i*-hexane/isopropanol, flow rate 0.75 ml/min) comparing of chiral and *rac* 2-methylpyrrol derivative of the amino alcohols. Configurations were determined by comparsion of the specific rotations with literature values.

These selectivities could be explained based on the following suggestion: The reaction of borane with α-hydroxy oxime ether first generates the alkoxy borane intermediate, which act as a Lewis acid internally activated for oxime ether reduction. The 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 diastereo- and enantioselectivity by using chiral oxazaborolidine as chiral inducers may be a result of double stereodifferentation in the reduction step.

The synthesis of amino alcohol **1** was also carried out starting from the oxime derivative, **7**, of hydroxy ketone **5**. Treatment of **5** with $HONH_2 \cdot HCl$ in pyridine afforded oxime **7** in

95% yield as a 70:30 mixture of *E*- and *Z*-isomers. The isomers are separated by flash column chromatography according to the procedure of Kajiro et al. [3]. The *E*-oxime **7a** was hydrogenated by using 5% palladium on charcoal in methanol at RT and at atmospheric pressure and the target amino alcohol (1*S*,2*R*)-**1** was isolated in 62% yield and in 88% de. The results obtained in the hydrogenation of the *Z*-oxime and *E*-, *Z*-mixture were similar to those of corresponding *E*-oxime (84%–86% de). It looks like that both *E*- and *Z*-oximes could be hydrogenated in chelated form and in intramolecular hydrogen bonded form, respectively. The steric bulkiness around the diastereomeric face of the *E*-oxime forming the five-membered chelated structure with the catalyst is almost the same as that of the corresponding *Z*-oxime forming the six-membered intramolecular hydrogen bonding.

In summary, the method described a short and efficient route to (1*S*,2*R*)-1-amino-2-indanol using chemical and biotransformations in high diastereo- and enantioselectivity.

3. 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.

*3.1. 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) using a Dean–Stark trap. The mixture was cooled to RT, diluted with ethyl acetate, was washed successively with 1 M aqueous HCl 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°C–82.0°C; Ref. [10] 80.5°C–81.5°C.

3.2. Hydrolysis of 2-acetoxyindanone

R. 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 rotary shaker at 30°C for 2 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 five and sterilized in the autoclave for 15 min. Spores from the main plate were transferred into the Erlenmeyer flask containing 100 ml sterile medium. The fungus was inoculated at 30°C for 2 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 (96 h). 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°C–84°C (Ref. [10] 82.4°C–83.7°C), $[\alpha]_D^{20} = -23.71$ ($c = 1.5$, $CHCl_3$); $[\alpha]_D^{20} = -23.1$ ($c = 1.5$, $CHCl_3$) [10]). (*S*)-**4**: Yield: 142 mg (44%), mp 80°C–82°C (Ref. [10], 80.5°C–81.5°C), $[\alpha]_D^{22} = 38.1$ ($c = 0.5$, CH_2Cl_2), For (*R*)-**4**: Refs. [14,15], $[\alpha]_D^{22} = -37.8$ ($c = 0.5$, CH_2Cl_2).

*3.3. 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) a solution of *O*-benzylhydroxylamine hydrochloride in 5 ml of pyridine under cooling in an ice bath. The reaction mixture was stirred for 20 h at RT and then concentrated. The residue was purified by column chromatography on silica gel using ethyl acetate–hexane as an eluent. The product was obtained as viscous oil, yield 230 mg, 91% [18]. 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, $J = 16.5$, 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) [17]. Anal. Calcd. for $C_{16}H_{15}NO_2$ (253.3): C, 75.87, H, 5.97, N, 5.53. Found: C, 75.58, H, 5.86 N, 5.56.

*3.4. (1S,2R)-(−)-cis-1-Amino-2-indanol (**1**)*

(a) 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 was continued at this temperature for 10 h before 8 mmol (202 mg) of oxime ether **6a** in 10 ml of THF was added dropwise. The resulting solution was stirred at RT for 48 h and was decomposed by slowly adding 2 M HCl. The mixture was extracted with ethyl acetate, and purification of crude product by recrystallization (EtOAc–hexane) furnished 87 mg (81%) of **1** in optically pure form. $[\alpha]_D^{20} = -61$ ($c = 0.5$, $CHCl_3$); Refs. [1–3]: $[\alpha]_D^{20} = -61$ ($c = 0.5$, $CHCl_3$). Mp 118°C–121°C (Lit. 118°C–121°C), NMR and IR spectra are identical with commercially available compound. (b) The oxime **7** (80 mg, 0.5 mmol) was hydrogenated by using 5% palladium on charcoal (25 mg) in a 5-ml methanol at RT and at atmospheric pressure for 20 h. After hydrogenation, the solvent was removed and the residue was dissolved in ethyl acetate and purified as described above. The amino alcohol was obtained in 62% yield.

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References

[1] C.H. Senanayake, Synthesis of *cis*-amino alcohol, Aldrichimica Acta 31 (1998) 3.
[2] A. Ghosh, S. Fidanze, C.H. Senanayake, Synthesis of *cis*-amino alcohol, Review, Synthesis (1998) 937.
[3] H. Kajiro, S. Mitamura, A. Mori, T. Hiyama, Synthesis of *cis*-amino alcohol, Synlett (1998) 51.
[4] J.P. Vacca, B.D. Dorsey, W.A. Schleif, R.B. Levin, S.L. McDaniel, P.L. Darke, J. Zugay, J.C. Quintero, O.M. Blahy, E. Roth, V.V. Sardana, A.J. Schlabach, P.I. Graham, J.H. Condra, L. Gotlieb, M.K. Holloway, J. Lin, I.-W. Chen, K. Vastag, D. Ostovic, P.S. Anderson, E.A. Emini, J.R. Huff, Proc. Natl. Acad. Sci. U.S.A. 91 (1994) 4096.
[5] J.P. Vacca, B.D. Dorsey, W.A. Schleif, R.B. Levin, S.L. McDaniel, P.L. Darke, J. Zugay, J.C. Quintero, O.M. Blahy, E. Roth, V.V. Sardana, A.J. Schlabach, P.I. Graham, J.H. Condra, L. Gotlieb, M.K. Holloway, J. Lin, I.-W. Chen, K. Vastag, D. Ostovic, P.S. Anderson, E.A. Emini, J.R. Huff, J. Med. Chem. 37 (1994) 3443, and references.
[6] A.S. Demir, N. Camkerten, Z. Gercek, N. Duygu, O. Reis, E. Arikan, Tetrahedron 55 (1999) 2441.
[7] A.S. Demir, A. Jeganathan, Synthesis (1992) 235.
[8] A.S. Demir, N. Çamkerten, H. Akgün, C. Tanyeli, A.S. Mahasneh, D.S. Watt, Synth. Commun. 20 (15) (1990) 2279.
[9] A.S. Demir, C. Tanyeli, V. Gülbeyaz, H. Akgün, Turk. J. Chem. 20 (1996) 244.
[10] A.S. Demir, H. Hamamci, C. Tanyeli, I.M. Akhmedov, F. Doganel, Tetrahedron: Asymmetry 9 (1998) 1673.
[11] A.S. Demir, C. Tanyeli, A. Cagir, M.N. Tahir, D. Ulku, Tetrahedron: Asymmetry 9 (1998) 1035.
[12] A. Monsadi, M. Gessner, G. Gunther, W. Deger, G. Singer, J. High Resolut. Chromatogr. Chromatogr. Commun. 10 (1987) 67.
[13] C.-S. Chen, Y. Fujimoto, G. Girdaukas, C.H. Sih, J. Am. Chem. Soc. 104 (1982) 7294.
[14] A.S. Demir, Pure Appl. Chem. 69 (1997) 108.
[15] S. Itsuno, Y. Sakurai, K. Ito, A. Hirao, S. Nakahama, Bull. Chem. Soc. Jpn. 60 (1987) 395.
[16] A.S. Demir, I.M. Akhmedov, C. Tanyeli, V. Gulbeyaz, Tetrahedron: Asymmetry 7 (1996) 3359.
[17] A.S. Demir, I.M. Akhmedov, C. Tanyeli, Z. Gercek, R.A. Gadzhili, Tetrahedron: Asymmetry 8 (1997) 753.
[18] A.K. Ghosh, S.P. Mckee, W.M. Sanders, Tetrahedron Lett. 32 (1991) 711.