Bull. Chem. Soc. Jpn., 72, 1093—1100 (1999) 1093

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

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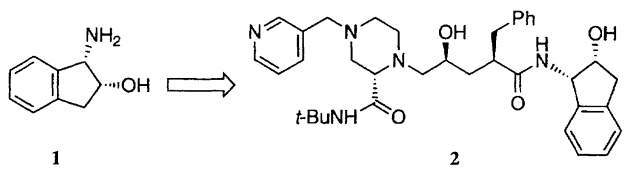
(Received November 26, 1998)

A synthesis of (1*S*,2*R*)-1-amino-2-indanol (**1**), a key component of an HIV protease inhibitor, was accomplished through (*R*)-2-hydroxy-1-indanone ((*R*)-**3**), which was prepared by an intramolecular Friedel–Crafts acylation of (*R*)-2-acetoxy-3-phenylpropanoic acid readily available from D-(*R*)-phenylalanine. Alternatively, (*R*)-**3** was obtained by an enzymatic resolution of (±)-2-acetoxy-1-indanone. Ketone (*R*)-**3** was converted into **1** through an oxime formation and diastereoselective hydrogenation.

Of the many potential therapeutic agents for the treatment of acquired immunodeficiency syndrome (AIDS), those which inhibit human immunodeficiency virus (HIV) protease still continue to be the most promising means.[1,2] A series of HIV protease inhibitors were prepared and tested, and an oligopeptide mimic containing (1*S*,2*R*)-1-amino-2-indanol (**1**) as a key component was found to exhibit a remarkably potent protease inhibition. The agent is called Indinavir (**2**) (Scheme 1).[1] Because of a wide applicability and effectiveness of Indinavir in medical treatment of AIDS, a practical and efficient method for the synthesis of **1** has been strongly desired.

In addition, because of the successful utilization of chiral amino alcohol **1** as a building block of chiral catalysts and as a chiral auxiliary for various asymmetric syntheses,[1,3] the search for a practical route to **1** is an attractive subject for synthetic chemists. To this end, various strategies involving asymmetric syntheses using a variety of chiral catalysts, optical resolution techniques, and chiral pool methods have been proposed and studied.[4] We also analyzed the synthetic problem to propose a strategy involving (*R*)-2-hydroxy-1-indanone ((*R*)-**3**) as a precursor of chiral amino alcohol **1**. Our retrosynthetic pathway is outlined in Scheme 2.

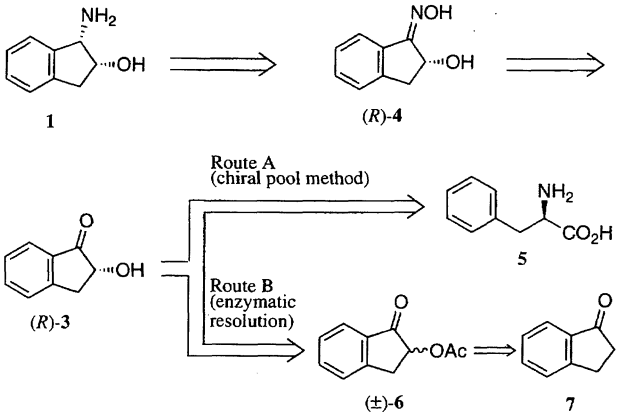


Scheme 1.

The target chiral amino alcohol **1** might be accessible by a diastereoselective hydrogenation of oxime (*R*)-**4**, which would be easily derived from enantiomerically pure (*R*)-**3**. Two routes are possible for the synthesis of (*R*)-**3**. One is Route A that starts with D-(*R*)-phenylalanine (**5**) as a chiral source. The other is Route B which utilizes an enzymatic resolution of racemic 2-acetoxy-1-indanone ((±)-**6**). In this paper we describe the details of the synthesis of **1** and (*R*)-**3** via the two routes.[5]

Results and Discussion

We first discuss the synthesis of amino alcohol **1** starting with D-(*R*)-phenylalanine (**5**) as shown in Scheme 3. The amino group of **5** was transformed in 82% yield to a hydroxy group with $NaNO_2$ and H_2SO_4 by a slightly modified procedure of Urban.[6] After protection of the hydroxy group in **8** with an acetyl group, the resulting α-acetoxy carbox-



Scheme 2.

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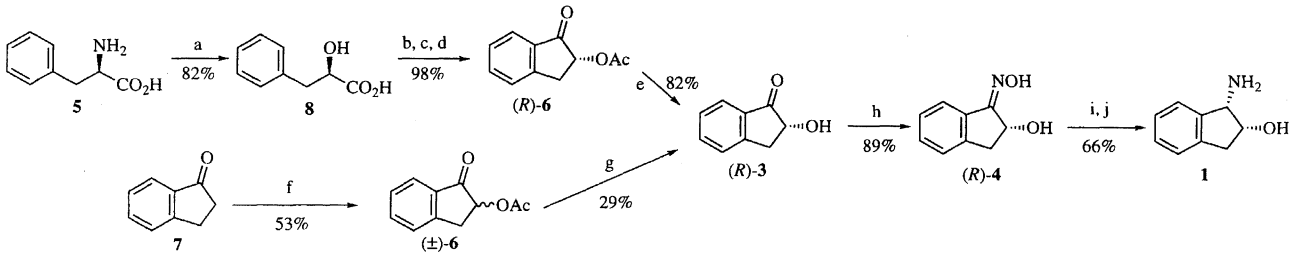


Scheme 3. Conditions: (a) $NaNO_2$, 2 M H_2SO_4, 0°C—r.t., 4 h; (b) Ac_2O/pyridine, 0 °C–r.t., 12 h; (c) $SOCl_2$, r.t.—50 °C, 3 h; (d) $AlCl_3/CH_2Cl_2$, r.t., 3 h; (e) $Sc(OTf)_3$ (20 mol%)/MeOH–H_2O, r.t., 61 h; (f) $Mn(OAc)_3$, reflux, 20 h; (g) lipase (*Pseudomonas sp.*), CH_3CN-buffer; (h) H_2NOH·HCl/pyridine; (i) Pd black, H_2, HBr; (j) aq $NaHCO_3$.

ylic acid was quantitatively converted into the corresponding acid chloride using thionyl chloride. An intramolecular Friedel–Crafts cyclization of the acid chloride smoothly proceeded at room temperature to give (*R*)-**6** quantitatively without any racemization. Hydrolysis of (*R*)-**6** using $Sc(OTf)_3$ proceeded with no loss of enantiomeric purity to give (*R*)-**3** in 82% yield.

An alternative synthesis of (*R*)-**3** was achieved via an enzyme-mediated kinetic resolution. Oxidation of 1-indanone (**7**) using $Mn(OAc)_3$ afforded a racemic ester (±)-**6** in 53% yield. Enzymatic hydrolysis of (±)-**6** with lipase of *Pseudomonas sp.* gave (*R*)-**3** in 29% yield. Details of the kinetic resolution will be discussed later.

Enantiomerically pure hydroxy ketone (*R*)-**3** was converted into oxime (*R*)-**4** as a mixture of (*E*)- and (*Z*)-isomers in 89% yield. Treatment of (*R*)-**4** (*E*:*Z*=65:35) in MeOH–HBr under an atmospheric pressure of molecular hydrogen in the presence of a Pd black catalyst afforded (1*S*, 2*R*)-**1** (92% yield) along with a small amount of *trans*-(1*R*,2*R*) isomer of **1** (*cis*:*trans*=96:4), both as hydrobromides. No such epimerization product as (1*R*,2*S*)-**1** or (1*S*,2*S*)-isomer was observed. Neutralization with aqueous $NaHCO_3$ followed by recrystallization from 2-propanol-isopropyl ether gave **1** (purity > 99%) in 66% yield.

Synthesis of (*R*)-3. We studied in more detail the synthesis of a key intermediate, chiral α-hydroxy ketone (*R*)-**3**. The first strategy (Route A as shown in Scheme 2) is a chiral pool method which utilizes D-(*R*)-phenylalanine (**5**) as a chiral source to give (*R*)-**3** via 5 steps without any racemization. D-(*R*)-Phenylalanine (**5**) is available as a by-product of the manufacture of Aspartame®, an artificial sweetener.

The other approach (Route B) starts from commercially available 1-indanone (**7**), which is oxidized to racemic acetate (±)-**6** whose enzymatic resolution gives enantiomerically pure α-hydroxy ketone (*R*)-**3**.

(a) Synthesis of (*R*)-3 via Route A. Although the transformation of L-(*S*)-phenylalanine to (*S*)-2-hydroxy-3-phenylpropanoic acid is well-established, the yield is not necessarily high enough.[6] We modified the procedure and could improve the yield up to 80% by slow and simultaneous addition of aqueous $NaNO_2$ and H_2SO_4. Thus, D-(*R*)-phenylalanine (**5**) was converted into (*R*)-**8** in 82% yield.

Although racemization occasionally accompanies the Friedel–Crafts acylation with an acid chloride having a chiral center at C-α,[7] we observed that (*R*)-2-acetoxy-3-phenylpropanoyl chloride underwent the Friedel–Crafts acylation in the presence of $AlCl_3$ without any racemization.

We first performed a basic hydrolysis of (*R*)-**6**. When the hydrolysis was conducted in the presence of K_2CO_3 or $Ba(OH)_2$, a complex mixture resulted, and alcohol **3** was not obtained. We also attempted the hydrolysis by use of LiOH, a reagent sometimes used for a moderate basic hydrolysis,[8] and obtained **3** in 75% yield. However, considerable racemization occurred; enantiomeric excess (ee) of **3** was estimated to be only 8%.

We next turned our attention to acid-catalyzed hydrolysis. When 20 mol% aqueous HCl, H_2SO_4, or trifluoromethanesulfonic acid (TFMSA) was used as a catalyst, racemization was suppressed at room temperature, but the reaction was too sluggish (21% yield after 48 h regardless of the kind of an acid). When the hydrolysis was conducted at 60 °C, the reaction rate was improved (20 mol% H_2SO_4, 75% yield after 48 h), but racemization occurred to some extent (86% ee). After screening acid catalysts for the hydrolysis of (*R*)-**6**, we found scandium(III) trifluoromethanesulfonate ($Sc(OTf)_3$) was a supreme catalyst for the particular hydrolysis of (*R*)-**6**: the reaction proceeded in the presence of 20 mol% of $Sc(OTf)_3$ at room temperature; the conversion reached to 95% after 48 h without any racemization. Although Inanaga recently reported that $Yb(OTf)_3$ is an excellent methanolysis catalyst for methoxyacetates,[9] $Sc(OTf)_3$ was more effective for the hydrolysis of (*R*)-**6** (88% conversion with $Yb(OTf)_3$). Such a high catalytic activity of $Sc(OTf)_3$ might be attributed to its strong Lewis acidity and coordination ability.

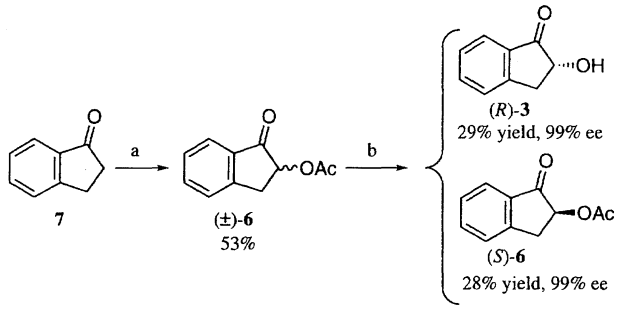
(b) Synthesis of (*R*)-3 via Route B. To exploit a short step synthesis of (*R*)-**3**, we next examined an enzymatic resolution of (±)-**6** (Scheme 4). Substrate (±)-**6** was prepared by the oxidation of 1-indanone (**7**) with $Mn(OAc)_3$[10] in 53% yield. Although the enzyme-catalyzed kinetic resolution of secondary alcohols or their carboxylates has been well-documented,[11] only a few examples are known concerning kinetic resolution of α-hydroxy or α-carboxy ketones.[12] To optimize the enzyme-mediated kinetic resolution, we screened 84 hydrolases including 4 acylases, 1 esterase, 54 lipases, and 25 proteases. The enzymes which showed relatively high E (> 10) and *c* values[13] (> 0.1) are listed in Table 1.

All of the enzymes that exhibited a good *E* value (> 10) were lipases. On the contrary, the tested acylases, esterase, and proteases exhibited poor selectivities. Except Fluka

Table 1. Enzymatic Hydrolysis of (±)-**6** in a pH 7.0 Phosphate Buffer–MeOH System[a)]

Enzyme	c[b)]	E[b)]	R/S[c)]
Fluka 62312 (*Pseudomonas fluorescens*)	0.43	97	*R*
Amano PS (*Pseudomonas sp.*)	0.37	75	*R*
Meito QL (*Aspergillus niger*)	0.43	70	*R*
Fluka 62293 (*Thermus aquaticus*)	0.36	31	*S*
Fluka 62291 (*Rhizomucor miehei*)	0.57	21	*R*
Fluka 62298 (*Mucor miehei*)	0.55	15	*R*
Fluka 62302 (*Candida cylindracea*)	0.12	15	*R*
Asahi Chemical LP (*Chromobacterium viscosum*)	0.65	11	*R*
Boehringer Mannheim L-2 (*Candida antactica*)	0.55	10	*R*
Amano CE (*Humicola langinosa*)	0.22	10	*R*

a) Conditions: A mixture of ester (±)-**6** (15 mg), enzyme (2.0 mg), a phosphate buffer (pH 7.0, 3.6 mL), and MeOH (1.2 mL) was stirred at 30 °C for 1 h, and the reaction was monitored by HPLC using a Daicel CHIRALCEL OB column. b) A c value means a conversion degree; an E value is a ratio of the specificity constant of each enantiomers calculated according to the Ref. 13. c) Stereochemical preference.



Scheme 4. Conditions: (a) $Mn(OAc)_3$/benzene, (b) *Pseudomonas sp.*/phosphate buffer (pH 7)–CH_3CN.

62293 (*Thermus aquaticus*), all the lipases listed in Table 1 showed an enantiomeric discrimination in favor of the desired (*R*)-isomer. These results encouraged us, because a lipase is stable in organic solvents and thus suitable for the transformation of organic compounds.[11,14)] We conducted the second screening in various organic solvent-phosphate buffer (pH 7.0) systems using three lipases that exhibited relatively high E and c values. The results are shown in Table 2.

In all the tested solvents, each enzyme recognized preferentially an (*R*)-enantiomer of **6**. The highest enantioselectivity (E = 250) was observed when Amano PS lipase was used in a CH_3CN–phosphate buffer system with c value being sufficiently high for an efficient transformation. An E value was strongly influenced by a solvent, but no obvious correlation between an E value and a hydrophobicity (log P) or polarity (ε) parameter was observed, in contrast to the suggestion by Nakamura et al.[15)]

We also envisioned an enzyme mediated transesterification of (±)-**6**. Since the stereoselectivity and activity of enzymes are strongly affected by a solvent, an enzyme mediated transesterification reaction in a non-aqueous solvent has a possibility to improve the selectivity and reaction rate.[11,14)] Transesterification reaction using Amano PS lipase was conducted in diisopropyl ether in the presence of an alcohol (30 mol amt.) as an acyl acceptor. Tested alcohols as well as E and c values are given in this order: 1-pentanol, E = 231, c = 0.15; 2-butanol, E = 41, c = 0.19; 9-fluorenylmethanol, E = 2, c = 0.43, and the lipase preferentially transformed (*R*)-isomer as was the case of the hydrolysis in an organic solvent-buffer system. The highest E value was obtained with 1-pentanol, but the c value was slightly inferior to that obtained in the hydrolysis. On the other hand, such a sterically congested alcohol as 9-fluorenylmethanol as an acyl acceptor showed the highest c value but a miserably low E value.

Table 2. Enzymatic Hydrolysis of (±)-**6** in a pH 7.0 Phosphate Buffer–Organic Solvent System[a)]

Enzyme	Organic solvent											
	CH_3CN		EtOAc		THF		i-Pr_2O		Dioxane		Toluene	
	c[b)]	E[b)]	c	E	c	E	c	E	c	E	c	E
Amano PS (*Pseudomonas sp.*)	0.32	250	0.20	168	0.28	178	0.42	159	0.48	108	0.20	219
Meito QL (*Alcaligenes sp.*)	0.28	158	0.15	122	0.16	38	0.31	101	0.48	114	0.19	149
Fluka 62312 (*Pseudomonas fluorescens*)	0.37	225	0.22	173	0.27	112	0.45	158	0.44	105	0.21	204

a) Conditions: A mixture of ester (±)-**6** (14 mg), enzyme (2 mg), a phosphate buffer (pH 7.0, 3.6 mL), and an organic solvent (1.2 mL) was stirred at 30 °C for 1 h, and the reaction was monitored by HPLC using a Daicel CHIRALCEL OB column. b) See footnote b in Table 1.

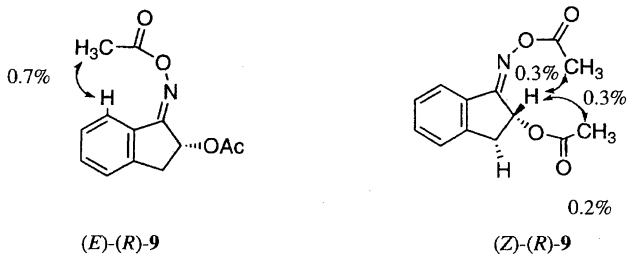
Based on the above results, the hydrolysis of (±)-**6** was conducted in a CH_3CN–phosphate buffer (pH 7.0) in the presence of Amano PS, under the conditions that afforded the highest *E* value. Treatment of (±)-**6** with Amano PS for 1 h at room temperature, followed by column chromatography on silica-gel, afforded the desired alcohol (*R*)-**3** (45% yield, 94% ee) and the recovered ester (*S*)-**6** (47% yield, 96% ee). Recrystallization from CH_2Cl_2–hexane afforded enantiomerically pure (*R*)-**3** in 29% yield based on (±)-**6**. In addition, (*S*)-enriched ester **6** was hydrolyzed using a catalytic amount of $Sc(OTf)_3$ to give rise to (*S*)-**3** (84% yield, 94% ee) and enantiomerically pure (*S*)-**3** was obtained after recrystallization from CH_2Cl_2–hexane (60% yield, > 99% ee). The excellent enantiomeric discrimination allowed us to isolate both enantiomers of **3** in high yields with high ee's.

Diastereoselective Hydrogenation of Oxime (*R*)-4: Synthesis of (1*S*,2*R*)-1-Amino-2-indanol (1). Treatment of (*R*)-**3** with $HONH_2$·HCl in pyridine afforded oxime (*R*)-**4** in 96% yield as a mixture of (*E*)- and (*Z*)-isomers without any racemization at C-2. Although it was reported that (*E*)- and (*Z*)-isomers of α-hydroxy oxime could be assigned by color spot test via complexation reaction with CuCl,[16] neither isomer of (*R*)-**4** was found to become colored. Thus the configuration of the isomers of (*R*)-**4** was assigned by NOE experiments after conversion to 2-acetoxy-1-acetoxyiminoindan (**9**). The results are shown in Fig. 1.

In this way, the ratio of (*E*)-**9** and (*Z*)-**9** in the above mixture was determined as 65 : 35. Although each isomer was interconverted upon a long term exposure to silica-gel, each isomer could be separated by quick silica-gel column chromatography.

We next studied diastereoselective hydrogenation of (*R*)-**4** to (1*S*,2*R*)-**1** using a conventional heterogeneous catalyst. First, the *cis*/*trans*-stereoselectivity was examined in the presence of an acid. In many cases, the presence of an acid affects the reactivity and selectivity of hydrogenation.[17] The results of the hydrogenation of (±)-**4** (*E* : *Z* = 65 : 35) using a Pd black catalyst are summarized in Table 3.

The hydrogenation in the absence of an acid was *trans*-selective (Run 1). However, thea use of 3 mol amounts of HCl drastically changed the *cis*/*trans*-selectivity (89% *cis*) and improved the yield (81%, Run 2). Addition of an acid in a large excess slightly improved the *cis*-selectivity (Run 3). Not only a protic acid but also a Lewis acid enhanced the *cis*-selectivity (Runs 11 and 12). Although the exact mechanism is not clear yet, we attribute the effect of an acid to a change



(*E*)-(*R*)-**9** (*Z*)-(*R*)-**9**

Fig. 1. The differential NOE of (*E*)-(*R*)-**9** and (*Z*)-(*R*)-**9**.

Table 3. Enantioselective Hydrogenation of (*R*)-**4**: Effect of Acid[a]

Run	Acid (mol amt.)	*cis*/%	Yield/%
1	—	41	59
2	HCl (3)	89	81
3	HCl (30)	91	>99
4	HCl (93)	91	95
5	47% aq HBr (3)	96	95
6	TFMSA[b] (3)	80	93
7	H_2SO_4 (3)	71	>99
8	TFA[c] (3)	68	98
9	H_3PO_4 (3)	60	>99
10	AcOH (3)	37	84
11	$Sc(OTF)_3$ (3)	82	93
12	BF_3·OEt_2 (3)	75	>99

a) Conditions: A mixture of (*R*)-**4** (20 mg), Pd black (5.0 wt%), and acid in MeOH was stirred at room temperature under H_2 (1 atm) for 20 h, and the mixture was analyzed by HPLC to determine *cis*-% and yield. b) Tfiluoromethanesulfonic acid. c) Trifluoroacetic acid.

in a chelation structure of oxime **4** on a palladium surface.[18]

We, we next studied the effect of the configuration of oxime **4** on the *cis*/*trans*-selectivity. In some cases, the configuration of α-hydroxy oxime influences the diastereoselectivity of hydrogenation reactions.[18] Each isomer of (*R*)-**4** was hydrogenated under H_2 (1 atm) in MeOH in the presence of Pd black (10 mol%) and 3 mol amounts of 47% aqueous HBr to give completely identical (96%) *cis*-selectivity. This was understood in terms of a rapid isomerization between (*E*)- and (*Z*)-isomers in an acidic medium. Accordingly, an isomeric mixture of **4** was used directly for the catalytic hydrogenation in an acidic medium.

The effect of hydrogen pressure was also studied. When the pressure was raised from 1 atm to 100 atm, the reaction time was dramatically shortened (from 20 h to 1 h) but with almost no change in *cis*-selectivity.

The hydrogenation reaction proceeded smoothly only in a protic solvent; the best *cis*-selectivity was obtained in MeOH (96% *cis*, 95% yield). The reaction proceeded in EtOH and 2-propanol and the *cis*-selectivity was > 99% *cis* (92% yield) and 90% *cis* (93% yield) respectively. To our surprise, no reaction took place in an aprotic solvent such as EtOAc, THF, dioxane, benzene, or DMF, common solvents used very often for many hydrogenation reactions.

The kind of a catalyst also influenced the results, as summarized in Table 4. Generally, a Pd catalyst exhibited high *cis*-selectivity; an optimum *cis*-selectivity and yield were achieved with Pd black (Run 1). Although iridium and rhodium catalysts showed good *cis*-selectivities, yields were disappointedly low (Runs 7 and 8). Addition of an acid increased the *cis*-selectivity in the case of a platinum catalyst, as was the case of a palladium catalyst, but the yields were unsatisfactory, due probably to the inhibition by a halide anion. Raney nickel also reduced **4** to amino alcohol **1**, but with a *cis*-selectivity inferior to other catalysts; the addition of an acid preferred a *trans*-selective reduction.

Table 4. Enantioselective Hydrogenation of (*R*)-**4**: Effect of Catalyst[a)]

Run	Catalyst	Additive	*cis*/%	Yield/%
1	Pd black	HCl	89	81
2	Pd/asbestos	HCl	88	88
3	PdO	HCl	88	4
4	Pd/C	HCl	87	88
5	$Pd(OH)_2$	HCl	85	>99
6	Pd/Al_2O_3	HCl	81	59
7	Ir black	47% aq HBr	89	31
8	Rh black	HCl	75	33
9	Rh/C	HCl	71	59
10	PtO_2	47% aq HBr	82	28
11	PtO_2	HCl	64	46
12	PtO_2	—	51	15
13	Raney Ni	—	57	90
14	Raney Ni	$Sc(OTf)_3$	27	34

a) Conditions: A mixture of (*R*)-**4** (20 mg), a catalyst (5.0 wt%), an additive (3.0 mol amt.) in MeOH was stirred at room temperature under H_2 (1 atm) for 20 h, and the mixture was analyzed by HPLC to determine *cis*-% and yield.

Conclusion

We achieved the synthesis of (1*S*,2*R*)-1-amino-2-indanol (**1**) by way of the key intermediate, (*R*)-2-hydroxyindanone ((*R*)-**3**). Both a chiral pool strategy and an enzyme mediated optical resolution were effective for the synthesis of (*R*)-**3**. The chiral pool strategy utilizes D-(*R*)-phenylalanine, a by-product of artificial sweetener Aspartame®, and highly efficiently gives rise to (*R*)-**3** without chromatographic purification. The enzyme-mediated resolution strategy allows a short step synthesis of (*R*)-**3** from commercially available 1-indanone (**7**) with an excellent enantiomeric discrimination. Both enantiomers of **3** are isolated in high yields with high ee's. The oxime formation and subsequent diastereoselective hydrogenation using a Pd black catalyst in HBr–MeOH affords the target *cis*-amino alcohol. The sequence of the reactions allows one to produce **1** in a large scale. In addition, enantiomerically pure 2-hydroxyindanone (**3**), a useful structural subunit of natural products and a valuable synthetic intermediate, is now readily available.

Experimental

All temperatures are uncorrected. Melting points were measured with a Mettler FP 62 auto melting point recorder. ^{1}H NMR spectra (TMS: 0 ppm as an internal standard) and ^{13}C NMR spectra ($CDCl_3$: 77.0 ppm as an internal standard) were measured on a Bruker AC-200 spectrometer (at 200 MHz for ^{1}H and at 50.3 MHz for ^{13}C) with chemical shifts being given in ppm. Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100A spectrometer. Optical rotations were recorded on a JASCO DIP-370 digital polarimeter in a 50 mm cell. Elemental analyses were carried out at Elemental Analysis Center, Tokyo Institute of Technology, using a Yanako MT2 CHN CORDER. Mass spectra were measured with a Finnigan MAT SSQ 7000 mass spectrometer using an ESI technique, with MeOH as a mobile phase. For thin-layer chromatography (TLC) analyses throughout this work, Merck precoated HPTLC plates (silica-gel 60 F_{254}) were used. Ee was determined by HPLC using a Daicel analytical chiral column (0.46 mm × 25 cm) at room temperature and a UV detector of 254 nm unless otherwise noted. Silica-gel column chromatography was carried out using Kanto Chemicals Silica-gel 60 (spherical, 140—325 mesh). Silica-gel preparative thin-layer chromatography was carried out using Merck Silica-gel 60 PF_{254}. Anhydrous MeOH was purchased from Merck Co., Ltd. Scandium(III) trifluoromethanesulfonate was purchased from Aldrich Chemical Inc. Dichloromethane was washed with H_2SO_4 and distilled and passed through an activated aluminum oxide (Wako Pure Chemical Industries, Ltd.) column prior to use.

An *E* value (a ratio of the specificity constant of each enantiomer) and a *c* value (a conversion degree) were calculated according to the method of Sih.[13)]

(*R*)-2-Hydroxy-3-phenylpropanoic Acid ((*R*)-8). This compound was synthesized according to the reported procedure[6)] after a slight modification. To a solution of D-(*R*)-phenylalanine (**5**) (1.0 g, 6.1 mmol) in H_2SO_4 (1 M, 20 mL, 1 M = 1 mol dm^{-3}) were added aqueous solutions of $NaNO_2$ (2.1 g, 30 mmol in 5 mL of H_2O) and H_2SO_4 (3.2 M aqueous solution, 5 mL) over 30 min at 0 °C. The reaction mixture was stirred for 75 min at 0 °C and extracted with EtOAc (10×5 mL). The organic layer was washed with brine (100×2 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by recrystallization (EtOAc–hexane) to give (*R*)-**8** (0.82 g, 82% yield, > 99.0% ee) as colorless prisms. Ee of (*R*)-**8** was determined after conversion to its methyl ester. To a solution of (*R*)-**8** (10 mg, 60 μmol) in benzene (1 mL) and MeOH (0.5 mL) was dropwise added (trimethylsilyl)diazomethane (1.0 M hexane solution, 0.6 mL). The resulting mixture was stirred at 25 °C for 1 min before concentration under reduced pressure; the residue was dissolved in EtOH and analyzed by HPLC using a Daicel CHIRALCEL OB column with EtOH in hexane (20 v/v%) as an eluent (0.5 mL min^{-1}). (*R*)-Isomer was eluted at t_R = 9.8 min and (*S*)-isomer at t_R = 10.3 min. Physical properties and spectroscopic data were identical with those of an authentic sample.

(*R*)-2-Acetoxy-3-phenylpropanoic Acid. A solution of (*R*)-**8** (50 g, 0.30 mol) in pyridine (500 mL) was mixed with acetic anhydride (34 mL, 0.36 mol) at 0 °C; the resulting solution was stirred at 25 °C for 12 h before concentration in vacuo. The residue redissolved in EtOAc (300 mL) was washed with 1 M HCl (100×2 mL), H_2O (150 mL), and with brine (300×3 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to give (*R*)-2-acetoxy-3-phenylpropanoic acid as an amber-colored oil (61 g, 97% yield). The crude product was used for the next reaction without further purification. IR, NMR, and MS spectra were in accord with those reported previously.[19)]

(*R*)-2-Acetoxy-1-indanone ((*R*)-6). A solution of (*R*)-2-acetoxy-3-phenylpropanoic acid (63 g, 0.30 mol) in thionyl chloride (180 g, 1.5 mol) was stirred at room temperature for 20 min and then heated at 50 °C for 3 h. Removal of all volatile materials under reduced pressure gave crude product (*R*)-2-acetoxy-3-phenylpropanoyl chloride (68 g) as an amber- colored oil. The crude material was used for the next step. To a solution of the obtained oil in CH_2Cl_2 (3 L) was added $AlCl_3$ (99 g, 0.74 mol) in one portion; the resulting mixture was stirred at 25 °C for 80 min and treated with ice-water (2.6 L). The organic layer was separated; the aqueous layer was extracted with CH_2Cl_2 (300×3 mL). The combined organic extracts were washed with H_2O (0.9 L) and brine (2.6 L), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by recrystallization (CH_2Cl_2–hexane) to give (*R*)-**6** (53 g, 93% yield, 98.3% ee) as an off-white solid. Ee of (*R*)-**6** was determined by HPLC using a Daicel CHIRALCEL OB column with EtOH in hexane (20 v/v%) as an eluent (0.5 mL min^{-1}). (*R*)-

Isomer was eluted with t_R = 23.7 min, and (*S*)-isomer with 26.3 min; mp 80.5—81.5 °C. IR (KBr) 1724, 1608, 1374, 1252, 1224, 1184, 1088, 1000, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.18 (s, 3H), 3.04 (dd, *J* = 5.0, 17.0 Hz, 1H), 3.65 (dd, *J* = 8.5, 17.0 Hz, 1H), 5.42 (dd, *J* = 5.0, 8.5 Hz, 1H), 7.38—7.61 (m, 2H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ = 21.3, 34.0, 74.6, 125.0, 127.2, 128.7, 135.0, 136.5, 151.0, 171.0, 201.2; MS *m/z* 189.2 $(M-H)^-$; $[\alpha]_D^{26} = -19.0°$ (*c* 1.0, MeOH). Found: C, 69.30; H, 5.34%. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30%.

(*R*)-2-Hydroxy-1-indanone ((*R*)-3).[20] To a solution of (*R*)-**6** (0.50 g, 2.6 mmol) in MeOH (20 mL) was added an aqueous solution of $Sc(OTf)_3$ (0.26 g, 0.53 mmol in 5 mL H_2O); the resulting mixture was stirred at 30 °C for 61 h and then concentrated in vacuo. The residue was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (10×3 mL). The organic layer was washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by recrystallization (CH_2Cl_2–hexane) to give (*R*)-**3** (0.32 g, 82% yield, 99.9% ee) as a colorless solid. Ee was determined by HPLC using a Daicel CHIRALCEL OB column with EtOH in hexane (20 v/v%) as an eluent (0.5 mL min^{-1}). For (*R*)-isomer, t_R = 13.4 min; for (*S*)-isomer, t_R = 18.1 min; Mp 82.4—83.7 °C. IR (KBr) 3460, 2880, 1706, 1608, 1582, 1464, 1388, 1289, 1210, 1206, 1104, 1090, 904, 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 3.02 (dd, *J* = 5.0, 16.5 Hz, 1H), 3.30 (s, 1H), 3.58 (dd, *J* = 8.0, 16.5 Hz, 1H), 4.56 (dd, *J* = 5.0, 8.0 Hz, 1H), 7.37—7.47 (m, 2H), 7.61—7.67 (m, 1H), 7.77 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ = 35.3, 74.2, 124.4, 126.9, 128.0, 134.0, 135.9, 151.0, 206.7; MS *m/z* 203.1 $(M+MeOH+Na)^+$; $[\alpha]_D^{25} = -57.0°$ (*c* 1.0, MeOH). Found: C, 72.60; H, 5.44%. Calcd for $C_9H_8O_2$: C, 72.96; H, 5.44%.

Alternative Hydrolysis of (*R*)-6. (a) Acid-Catalyzed Hydrolysis of (*R*)-6: To a solution of (*R*)-**6** (0.101 g, 0.53 mmol, > 99% ee) in MeOH (4 mL) was added hydrochloric acid (0.11 M, 1 mL, 0.11 mmol). The solution was stirred at 30 °C and analyzed by HPLC. The yield of (*R*)-**3** was 21% and ee was > 99% after 48 h. Sulfuric acid- or TFMSA-catalyzed hydrolysis of (*R*)-**6** conducted under the identical conditions gave (*R*)-**3** in 21% with > 99% ee regardless of the kind of acid. Hydrolysis of (*R*)-**6** with sulfuric acid (60 °C, 48 h) gave (*R*)-**3** in 75% yield with 86% ee.

(b) Base-Catalyzed Hydrolysis of (*R*)-6: A mixture of (*R*)-**6** (30 mg, 0.16 mmol, > 99% ee) in MeOH (3 mL) and $LiOH·H_2O$ (6.7 mg, 0.16 mmol in 1.4 mL H_2O) was stirred at 25 °C for 10 min. HPLC analysis showed 75% yield of (*R*)-**3** (7.8% ee) and 25% recovery of (*R*)-**6** (0.4% ee). Such a base as K_2CO_3 and $Ba(OH)_2$ caused decomposition of **6**, and **3** could not be obtained.

(±)-2-Acetoxy-1-indanone ((±)-6).[10] A mixture of 1-indanone (0.66 g, 5.0 mmol) and $Mn(OAc)_3$ (5.4 g, 23 mmol) in benzene (60 mL) was heated at reflux for 20 h; the reaction mixture was diluted with Et_2O (40 mL)–aqueous HCl (3 M, 40 mL) and filtered through a Celite® pad. The filtrate was extracted with EtOAc (20×5 mL); combined organic extracts were washed with H_2O (100 mL), aqueous $NaHCO_3$ (0.1 M, 40 mL), and brine (200 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by silica-gel column chromatography to give (±)-**6** (0.50 g, 53% yield) as a pale yellow solid.

Enzyme-Mediated Kinetic Resolution of (±)-6. Screening of Enzymes: (a) Hydrolysis of Ester (±)-6 in an Organic Solvent-Phosphate Buffer: An enzyme (2.0 mg) was added to a solution of (±)-**6** (15 mg, 76 μmol) in an appropriate organic solvent (1.2 mL, see Table 1)–phosphate buffer (pH 7.0, 3.6 mL). The reaction mixture was stirred at room temperature for 1 h before extraction with CH_2Cl_2 (2×2 mL). The combined organic layer was dried over anhydrous $MgSO_4$. The solution was concentrated in vacuo; *E* and *c* values were estimated by HPLC using a Daicel CHIRALCEL OB column.

(b) Transesterification of (±)-6 in an Organic Solvent: To a solution of (±)-**6** (5.0 mg, 26 μmol) in diisopropyl ether (1 mL) was added an enzyme (5.0 mg) and an alcohol solvent (1-pentanol, 2-butanol or 9-fluorenylmethanol, 0.79 mmol, 30 mol amt.); the resulting mixture was stirred for 1 h at room temperature before filtration through a membrane filter (pore size 0.45 μm). The filtrate was analyzed by HPLC (Daicel CHIRALCEL OB) to estimate *E* and *c* values.

Enzyme-Mediated Enantioselective Hydrolysis of (±)-6. (*R*)-2-Hydroxy-1-indanone ((*R*)-3): To a solution of (±)-**6** (0.19 g, 1.0 mmol) in a mixture of acetonitrile (12 mL)–phosphate buffer (pH 7.0, 36 mL) was added Amano PS (95 mg); the mixture was stirred for 1 h at room temperature and then saturated with ammonium sulfate. The suspension was filtered through a Celite® pad. The filtrate was extracted with EtOAc (20×10 mL); combined organic extracts were washed with brine (200 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give (*R*)-**3** (67 mg, 45% yield, 94% ee) as a colorless solid and (*S*)-**6** (90 mg, 47% yield, 96% ee) as a colorless solid. Enantiomerically pure (*R*)-**3** was obtained after recrystallization from CH_2Cl_2–hexane (44 mg, 29% yield, > 99% ee).

(*S*)-2-Hydroxy-1-indanone ((*S*)-3). Sc(OTf)$_3$-Catalyzed Hydrolysis of (*S*)-6: This was prepared in 60% yield with 99.6% ee by the procedure for the synthesis of (*R*)-**3** using $Sc(OTf)_3$: $[\alpha]_D^{25} = +57.1°$ (*c* 1.0, MeOH).

(*R*)-2-Hydroxy-1-indanone Oxime ((*R*)-4). To a solution of (*R*)-**3** (2.9 g, 20 mmol, > 99% ee) in pyridine (30 mL) was added hydroxyamine hydrochloride (1.39 g, 0.20 mol) in one portion at −15 °C. The reaction mixture was allowed to warm to 0 °C over 1 h. A second portion of hydroxyamine hydrochloride (1.39 g, 0.20 mol) was then added, and the solution was stirred for 15 h at room temperature. Pyridine was removed under reduced pressure to afford an yellow oil. The oil was suspended in brine (15 mL) and 10 wt% aqueous solution of citric acid (15 mL), and the mixture was extracted with EtOAc (20×3 mL). The combined organic extracts were washed with brine (50×2 mL), and dried over anhydrous $MgSO_4$, and concentrated. The resulting crystalline residue was recrystallized (EtOAc–hexane) to yield analytically pure (*R*)-**4** (2.9 g, 89% yield) as a colorless solid. The obtained oxime (*R*)-**4** was shown to be a 65 : 35 mixture of (*E*)- and (*Z*)-isomers by ^1H NMR. Ee of each isomer was > 99% as determined by HPLC. The configuration of (*R*)-**4** was determined by NOE experiments after conversion to (*R*)-2-acetoxy-1-acetoxyiminoindan (**9**). Ee of (*E*)-(*R*)-**4** was estimated by HPLC using Daicel CHIRALCEL OB column with 20 v/v% 2-propanol in hexane as an eluent (0.5 mL min^{-1}). (*R*)-Isomer, t_R = 14.7 min; (*S*)-isomer, t_R = 20.2 min. Analysis of (*Z*)-(*R*)-**4** was performed with a Daicel CHIRALPAK AD column and 14 v/v% 2-propanol in hexane as an eluent (0.7 mL min^{-1}). (*R*)-Isomer, t_R = 15.7 min; (*S*)-isomer, t_R = 13.7 min.

(*E*)-(*R*)-4: Mp 147.6—148.7 °C. IR (KBr) 3220, 2900, 1601, 1458, 1451, 1424, 1308, 1040, 1013, 976, 888, 734 cm^{-1}; ^1H NMR (DMSO-d_6) δ = 2.76 (dd, *J* = 2.5, 17.0 Hz, 1H), 3.28 (dd, *J* = 7.0, 17.0 Hz, 1H), 4.71 (m, 1H), 5.37 (d, *J* = 5.5 Hz, 1H), 7.24—7.41 (m, 3H), 8.24 (d, *J* = 8.0 Hz, 1H), 11.2 (s, 1H); ^{13}C NMR (DMSO-d_6) δ = 69.9, 125.6, 126.6, 128.5, 130.5, 132.2, 145.3, 159.0; $[\alpha]_D^{26} = -55.0°$ (*c* 1.0, MeOH). Found: C, 66.40; H, 5.33; N, 8.32%. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58%.

(*Z*)-(*R*)-4: Mp 124.9—125.5 °C. IR (KBr) 3540, 3108, 2784,

1644, 1601, 1474, 1464, 1426, 1380, 1332, 1308, 1236, 1209, 1092, 1040, 941, 933 cm^{-1}; ^1H NMR (5 v/v% of CD_3OD–$CDCl_3$) δ = 2.97 (dd, J = 3.0, 17.5 Hz, 1H), 3.43 (dd, J = 8.0, 17.5 Hz, 1H), 5.40 (dd, J = 3.0, 8.0 Hz, 1H), 7.22—7.39 (m, 3H), 7.62 (d, J = 8.0 Hz, 1H), 10.82 (s, 1H); ^{13}C NMR (5 v/v% of CD_3OD–$CDCl_3$) δ = 37.4, 69.1, 121.5, 125.5, 127.3, 130.9, 133.4, 145.2, 163.5; MS m/z 194.2 $(M+MeOH-H)^-$; $[\alpha]_D^{25} = -140.0°$ (c 1.0, MeOH). Found: C, 66.40; H, 5.38; N, 8.27%. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58%.

Isomerization between (*E*)-4 and (*Z*)-4 by an Acid: A 9 : 91 mixture of (*E*)-**4** and (*Z*)-**4** (6.2 mg, 38 μmol) was dissolved in a mixture of CD_3OD (35 μL) and $CDCl_3$ (0.67 mL) containing *p*-toluensulfonic acid monohydrate (0.5 mg, 2.7 μmol, 7.0 mol%) at room temperature, and the isomerization was monitored by ^1H NMR. After 19 h, the ratio of (*E*)-**4** and (*Z*)-**4** reached to an equilibrium of $E : Z$ = 43 : 57.

(*E*)-(*R*)-2-Acetoxy-1-acetoxyiminoindan ((*E*)-(*R*)-9). A mixture of (*E*)-(*R*)-**4** (50 mg, 0.31 mmol) and acetic anhydride (0.29 mL, 3.1 mmol) in pyridine (8 mL) was stirred at 25 °C for 20 h before concentration in vacuo. Purification of the residue by silica-gel column chromatography (0.3—0.4% MeOH in CH_2Cl_2) gave (*E*)-(*R*)-**9** (74 mg, 98% yield) as a colorless solid, mp 116.6—118.1 °C. IR (KBr) 1776, 1767, 1736, 1633, 1600, 1468, 1425, 1383, 1366, 1309, 1252, 1233, 1192, 1036, 999, 924, 892 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.12 (s, 3H), 2.33 (s, 3H), 3.04 (dd, J = 3.0, 17.5 Hz, 1H), 3.61 (dd, J = 3.0, 17.5 Hz, 1H), 5.92 (dd, J = 3.0, 7.5 Hz, 1H), 7.36—7.41 (m, 2H), 7.49—7.55 (m, 1H), 8.27 (dd, J = 1.5, 7.5 Hz, 1H); By irradiating at δ = 2.33 (Me of AcON) positive NOE at δ = 7.36—7.41 (Ph 0.7%) was observed; ^{13}C NMR ($CDCl_3$) δ = 19.5, 21.1, 37.3, 72.8, 126.0, 127.9, 129.8, 130.9, 133.3, 146.6, 163.1, 168.3, 170.3; MS m/z 270.1 $(M+Na)^+$, $[\alpha]_D^{26} = -90.0°$ (c 0.1, MeOH). Found: C, 63.03; H, 5.26; N, 5.28%. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66%.

(*Z*)-(*R*)-2-Acetoxy-1-acetoxyiminoindan ((*Z*)-(*R*)-9). This was prepared in 38% yield by the procedure as given above: Mp 111.3—112.2 °C. IR (KBr) 1784, 1730, 1640, 1604, 1467, 1424, 1374, 1250, 1248, 1208, 1072, 1043, 1014, 932, 707, 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.11 (s, 3H), 2.19 (s, 3H), 2.96 (dd, J = 2.5, 18.0 Hz, 1H), 3.55 (dd, J = 7.5, 18.0 Hz, 1H), 6.34 (dd, J = 2.5, 7.5 Hz, 1H), 7.31—7.34 (m, 2H), 7.45—7.51 (m, 1H), 7.92 (d, J = 8.0 Hz, 1H). Irradiation at δ = 2.11 (Me of AcOC) resulted in a positive NOE at δ = 2.96 (CH_2 0.2%) and at δ = 6.34 (methyne H of AcOCH 0.3%). Irradiation at δ = 2.19 (Me of AcON) induced a positive NOE at δ = 6.34 (methyne H of AcOCH 0.3%). ^{13}C NMR ($CDCl_3$) δ = 19.4, 20.7, 68.6, 123.5, 125.6, 127.9, 132.4, 133.0, 146.2, 165.9, 167.9, 169.6. $[\alpha]_D^{26} = -110.0°$ (c 0.1, MeOH). Found: C, 62.90; H, 5.25; N, 5.52%. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66%.

(1*S*,2*R*)-1-Amino-2-indanol (1). (a) Synthesis of 1 under the Optimized Conditions: To a solution of (*R*)-**4** ($E : Z$ = 65 : 35, 0.10 g, 0.61 mmol) in MeOH was added aqueous HBr (47% in H_2O, 0.32 g, 1.8 mmol); the resulting mixture was stirred under an atmospheric pressure of H_2 at ambient temperatures in the presence of Pd black (25 mg) for 20 h. Filtration of the catalyst and concentration afforded a hydrobromide of **1** as a 96 : 4 mixture of (1*S*,2*R*)-**1** and (1*R*,2*R*)-**1** in 96% yield. The crude product was dissolved in EtOAc (20 mL), neutralized with aqueous $NaHCO_3$ (1 M, 10 mL), and dried over anhydrous $MgSO_4$. Concentration under reduced pressure followed by recrystallization (diisopropyl ether-2-propanol), gave **1** (60 mg, 66% yield, > 99% ee, purity > 99%) as a gray solid. Ee of **1** was determined by HPLC using a Daicel CROWNPAK CR (+) column (0.46 mm, 15 cm) with aq $HClO_4$ (pH 2) as an eluent. (1*R*,2*S*)-**1** Had t_R = 7.39 min at a flow late of 0.8 mL min^{-1}, (1*S*,2*R*)-**1**, t_R = 20.2 min.

The purity of **1** was estimated also by HPLC with an ODS column and 5 v/v% MeOH in phosphoric acid aqueous solution (0.2 v/v%) as an eluent. (1*R*,2*R*)-**1** Had t_R = 4.46 min at a flow rate of 0.8 mL min^{-1}, (1*S*,2*R*)-**1**, t_R = 5.47 min. All physical and spectroscopic data of **1** were identical with those of an authentic sample. All spectral and analytical properties of synthetic (±)-*trans*-1-amino-2-indanol were consistent with an authentic sample synthesized by the reported procedure.[21]

(b) A General Procedure for Hydrogenation of (*R*)-4: A flask purged with argon was successively charged with oxime (*R*)-**4** ($E : Z$ = 65 : 35, 20 mg, 0.12 mmol), an additive, a solvent (5 mL), and a catalyst. The reaction flask was evacuated and was refilled with molecular hydrogen and then stirred at ambient temperatures. The progress of the reaction was monitored by HPLC.

Effect of a hydrogen pressure was examined under the following conditions: A mixture of (*R*)-**4** ($E : Z$ = 65 : 35, 20 mg, 0.12 mmol), 5 wt% of Pd black, and HCl (3 mol amt.) in MeOH (5 mL) was stirred at room temperature under an atmospheric pressure of H_2.

Solvent effect was examined under the following conditions: A mixture of (*R*)-**4** ($E : Z$ = 65 : 35, 20 mg, 0.12 mmol), 5 wt% of Pd black, and HCl (3 mol amt.) in an appropriate solvent (5 mL) was stirred at room temperature under an atmospheric pressure of H_2.

We thank Professors Yasuo Katoh (Biotechnology Research Center, Toyama Prefectural University), Kaoru Nakamura (Institute for Chemical Research, Kyoto University), and Takeshi Sugai (Department of Chemistry, Keio University) for their helpful suggestions. Thanks are due to Asahi Chemical Industry Co., Amano Pharmaceutical Co., Boehringer Mannheim GmbH, Nagase Biochemicals Co., Showa Denko K. K., Toyobo Co., Yakult Pharmaceutical Industry Co., and Meito Sangyo Co. for generous supply of various enzymes. We thank N. E. Chemcat Co. and Nikki Chemical Co. for supplying a variety of catalysts.

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