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Synthesis of enantiomers of indanoxazolidinone based on the lipase-catalyzed resolution of the corresponding *N*-carbamylamino derivative

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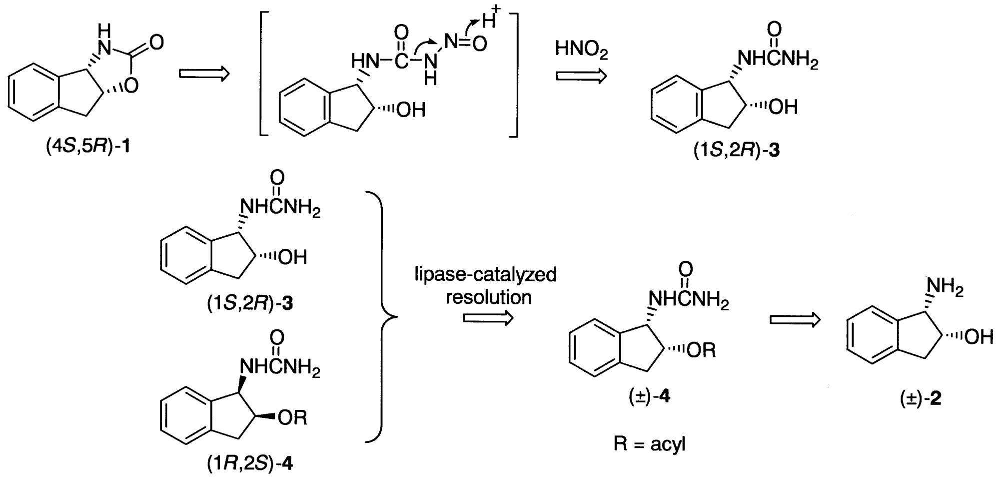
Abstract—Enantiomerically enriched (4*R*,5*S*)- and (4*S*,5*R*)-indano[1,2-*d*]oxazolidinones were enzymatically prepared from (±)-1-amino-2-indanol. Racemic 1-(*N*′-chloroacetyl-*N*-carbamylamino)-2-indanol *O*-chloroacetate was hydrolyzed with immobilized *Pseudomonas cepacia* lipase in the presence of *β*-cyclodextrin in acetone-buffer solution, to afford (1*S*,2*R*)-1-(*N*′-chloroacetyl-*N*-carbamylamino)-2-indanol (90%*e.e.*) and the unreacted (1*R*,2*S*)-substrate (97%*e.e.*), in nearly quantitative yields. The deprotection provided enantiomers of 1-*N*-carbamylamino-2-indanol, the precursor of indanoxazolidinone, via nitrosation-deaminocyclization reaction. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Enantiomerically enriched forms of indanoxazolidinone (**1**) [for example, (4*S*,5*R*)-form, Scheme 1] have been developed as a unique and highly efficient chiral auxiliary for the asymmetric aldol reaction.[1] Many efforts have so far been devoted toward the enantiomerically enriched forms of *cis*-1-amino-2-indanol (**2**), the framework of **1**.[1a,b,2–4] Other pioneering work in asymmetric syntheses has also been carried out based on the open chain derivatives of **2** itself.[5] Furthermore, the amino alcohol [(1*S*,2*R*)-**2**] has another importance as the component of Crixivan®, a potent protease inhibitor of HIV.[2,6]

Here we present an approach based on the enantiomeric resolution of 1-*N*-carbamylamino-2-indanol (**3**), the direct precursor of **1** through nitrosation-deaminocyclization reaction,[7] by way of lipase-catalyzed enantioselective hydrolysis of the corresponding acyl precursor [(±)-**4**], starting from racemic 1-amino-2-indanol [(±)-**2**].[8]



Scheme 1.

Keywords: enzymes and enzyme reactions; hydrolysis; nitroso compounds; oxazolidinones.

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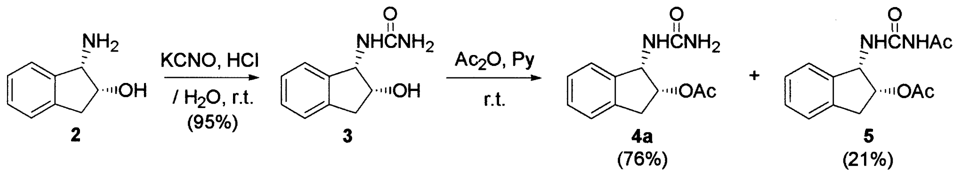
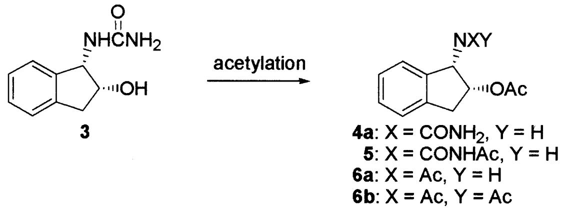


Scheme 2.

Table 1. Attempts for bisacetylation of *N*-carbamylamino indanol (**3**)



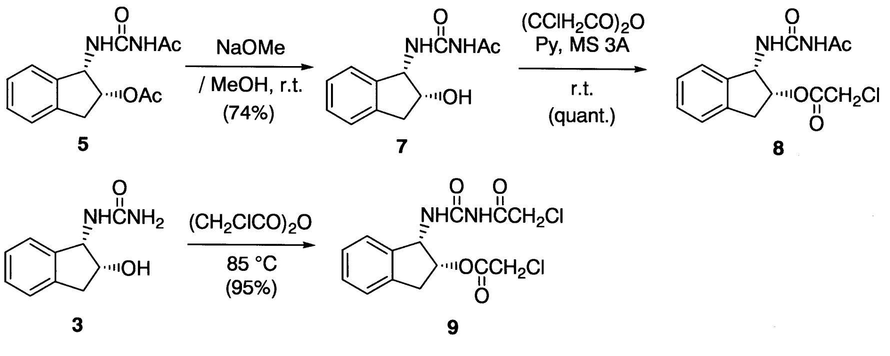
Entry	Reagent	Temp.	Time	Yield of **5** (%)	Major product
1	Ac_2O, Py	r.t.	32 h	21	**4a**
2	Ac_2O, Py, DMAP	r.t.	20 h	62	**5**
3	Ac_2O, Et_3N/DMF	r.t.→50°C	11 h	10	**4a**
4	Ac_2O, AcONa	reflux	5 min	79	**5**
5	Ac_2O, AcOk	reflux	5 min	79	**5**
6	Ac_2O	reflux	1.5 h	–	**5**

2. Results and discussion

A number of works have so far been reported in regard to enzyme-catalyzed kinetic resolutions of related intermediates. Most of them adopted the acylation of 2-indanols bearing hydroxyl-,[3a] *N*-acetamido-[3c] and azido[3g] group on the 1-position. Our plan as illustrated in Scheme 1 would have advantages in the following points. The resolution of direct precursors can exclude any loss of isomeric and chemical purity of the resolved objectives. In this sense, only one related example has been reported, however, the yield was not satisfactory.[3d] In addition, the remarkable advantage of enzyme-catalyzed hydrolysis, compared to the reverse reaction such as acylation and/or transesterification,[9] is the essentially high specific activity of enzymes in aqueous media as well as the irreversibility of the reaction.

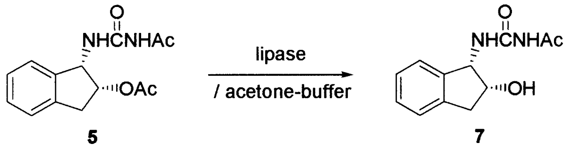
Our initial candidate for the enzyme substrate was the carbamylamino acetate (**4a**). Toward this end, the carbamylamino alcohol (**3**) was submitted to acetylation in a conventional manner, as shown in Scheme 2. The yield of **4a** was, however, as low as 76%, and besides this, an *N′*,*O*-bisacetylated by-product (**5**) was obtained in 21% yield. The improved lipophilicity and lower melting point (see experimental) of **5** compared to **4a**, however, were attractive, so that bisacetate would work as an alternative as the substrate for lipase-catalyzed hydrolysis. This situation prompted us to optimize the reaction conditions to obtain an enhanced yield of **5**.

Table 1 summarizes the attempts toward efficient *N′*,*O*-bisacetylation. In the initial trial, the rate of reaction was still very slow even when molar equivalent DMAP was added. Moreover, further reacted side-products were given (entry 2). In this reaction, these unexpected by-products were revealed to be *N*-decarbamylated derivatives (**6a** and **6b**). To suppress the formation of the undesired materials, the reaction condition was modified by modulating the nucleophilicity and basicity of reagents. A brief treatment of **3** with acetic anhydride and sodium or potassium acetate[10] (entries 4 and 5) at a raised temperature was effective to give as high as 79% yield of **5**. Without a base (entry 6), the reaction was slower than those observed in entries 4 and 5, and the ratio of the desired product (**5**) did not improve, judging from its TLC analysis.



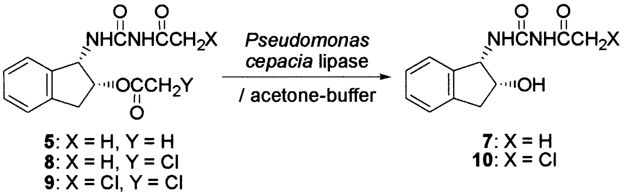
Scheme 3.

Table 2. The lipase-catalyzed hydrolysis of bisacetate (**5**)



Entry	Lipase	Substrate	Time (day)				
			1	2	3	4	5
1	*Candida antarctica*	(1*S*,2*R*)-**5**	±	±	+	+	+
2		(1*R*,2*S*)-**5**	−	−	−	−	−
3	*Pseudomonas cepacia*	(1*S*,2*R*)-**5**	±	±	±	+	+
4		(1*R*,2*S*)-**5**	−	−	−	−	−

Table 3. The effect of the electron-withdrawing group on the lipase-catalyzed hydrolysis



Entry	Substrate	Product	Conversion (%)	Final pH
1	(1*S*,2*R*)-**5**	**7**	2.7	6.3
2	(1*S*,2*S*)-**8**	**7**	52.9	3.4
3	(1*S*,2*R*)-**9**	**10**	67.1	3.1
4	(1*R*,2*S*)-**8**	**7**	1.8	5.6
5	(1*R*,2*S*)-**9**	**10**	2.1	5.7

Under the same protocol, chloroacetates (**8**) and (**9**), which would have enhanced reactivity toward lipase-catalyzed hydrolysis,[11] were prepared (Scheme 3). Selective de-*O*-acetylation of (**5**) provided *N*′-acetylcarbamylamino alcohol (**7**), which was then chloroacetylated to give *N*′-acetyl-*O*-chloroacetylated substrate (**8**). On the other hand, a direct treatment of carbamylamino alcohol (**3**) with chloroacetic anhydride gave *N*′,*O*-bischloroacetate (**9**) in 95% yield. Under either condition for the chloroacetylation as above, no decarbamylation was observed even under as high as 85°C.

With the substrates in hand, the rates of lipase-catalyzed hydrolysis between the enantiomers were compared. The results are shown in Table 2. Although we confirmed the large differences between the enantiomers of acetate (**5**) on both *Pseudomonas cepacia* lipase and *Candida antarctica*-lipase, which had been successfully applied to the lipase-catalyzed transesterification on the structurally related substrates,[3] the rates of reaction were very low.

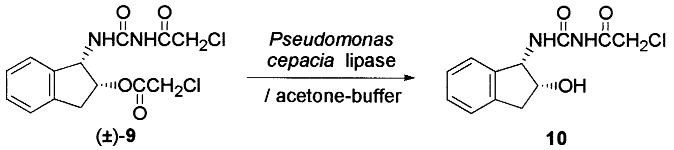
As expected, the introduction of an electron-withdrawing group[11] was very effective, as exemplified in such as chloroacetates **8** and **9**, and the hydrolysis of the (1*S*,2*R*)-isomers was highly accelerated (entries 2 and 3). Fortunately, still a large difference in the rates of hydrolysis between the enantiomers was observed (entries 2 and 4, 3 and 5). From these results, in the practical sense, chloroacetates were expected for lipase-catalyzed kinetic resolution of racemate. Further investigation was continued with racemic *N*′,*O*-bischloroacetate [(1*R**,2*S**)-**9**] as the substrate.

As a considerable lowering of pH was observed even in an acetone-buffer in the preliminary experiments (Table 3), due to the liberation of a strong acid (chloroacetate), the racemic substrate (**9**) was incubated under pH-controlling condition (at 7.0–8.0). The reaction, however, was sluggish and even after 3 days, the conversion was as low as 25%. The reason for such low reactivity was ascribable to the very low solubility of the racemate of **9**. The melting point of the racemate (172.9–173.4°C) was much higher than that of the pure enantiomer (123.4–123.9°C). An X-ray crystallographic analysis revealed a large difference in the hydrogen-bonding network between the racemate and the enantiomerically pure form, which led to a denser packing of molecules in the racemic crystal.[12]

The hydrolysis of (±)-**8** was faster than that of (±)-**9**, as expected from its lower melting point (164.2–164.8°C) compared to **9** (see the previous paragraph). Due to the accessibility of bischloroacetate [(±)-**9**] by the simple preparation from (±)-**3**, however, the substrate was fixed to be (±)-**9**, and the reaction conditions were extensively elaborated as shown in Table 4 to overcome the problem caused by this low solubility.

First, the ratio of a co-solvent (acetone) to water was increased, expecting enhanced dissolution of the substrate (entries 2 and 3). The medium range of concentration of acetone (42–67%) only resulted in a loss of activity of lipase. At a higher ratio (83%), however, the reaction

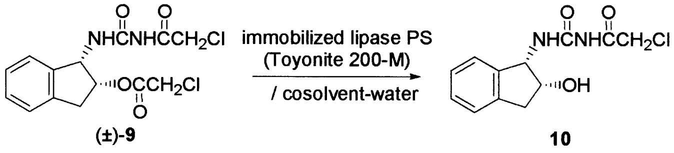
Table 4. The effect of the organic co-solvent on the lipase-catalyzed hydrolysis



Entry	Sub. conc. (w/v%)	Acetone/buffer	State	Reaction time (h)	Conversion (%)
1	4.2	1:14	Susp.	71	25.1
2	2.0	1:1.0	Susp.	66	25.9
3	2.7	1:0.5	Susp.	68	11.6
4	3.3	1:0.2	Sol.	72	47.9
5	4.2	1:1.4	Susp.[a]	37	3.2

[a] DMF precipitation.[13]

Table 5. The effect of additives on the lipase-catalyzed hydrolysis



Entry	Sub. conc. (w/v%)	Cosolvent	Cosolvent-water	Additive	Effect
1	2.7	Acetone	1:0.13	None	
2	10.0	DMF	1:0.14	None	No reaction
3	3.0	Acetone	1:0.13	Triton X-100	−
4	2.7	Acetone	1:0.13	β-cyclodextrin	+

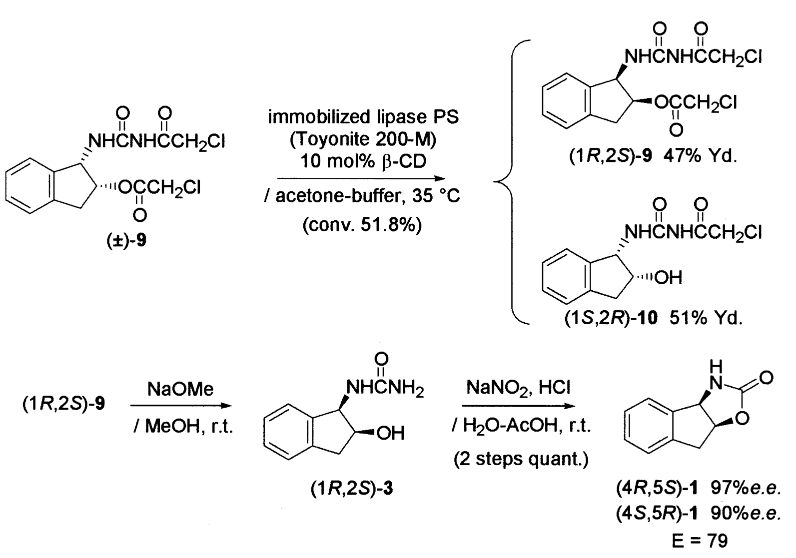
smoothly proceeded, as expected from the homogeneity of the reaction mixture (entry 4). In the present example, the state of substrates, the completely dissolved form, was important and the efficiency was not affected by the surface of the solid substrate. Indeed, pre-treatment of the substrate with DMF (DMF aggregate amorphous formation)[13] had no effect in our present case (entry 5).

Further attempts for the enhancement of the rate of hydrolysis were continued, as the retention of high enzyme activity in organic solvent was indexed as shown in Table 5. From this standpoint, the immobilization of *Pseudomonas* lipase on Toyonite 200-M[14] was very effective (entry 1). Changing the co-solvent from acetone to DMF, which would lower the limit of the organic solvent to make a homogeneous state, however, caused the complete denaturation of enzyme (entry 2).[15] At this stage, as a different approach, the effect of additives was also examined, expecting an efficient transfer of the substrate which stayed in the organic solvent to the hydrophilic surroundings of the enzyme.[16] In contrast to a detergent such as Triton X-100 (entry 3),[17] the addition of *β*-cyclodextrin (0.1–1.0 equiv.),[18] had a remarkable accelerating effect (entry 4).

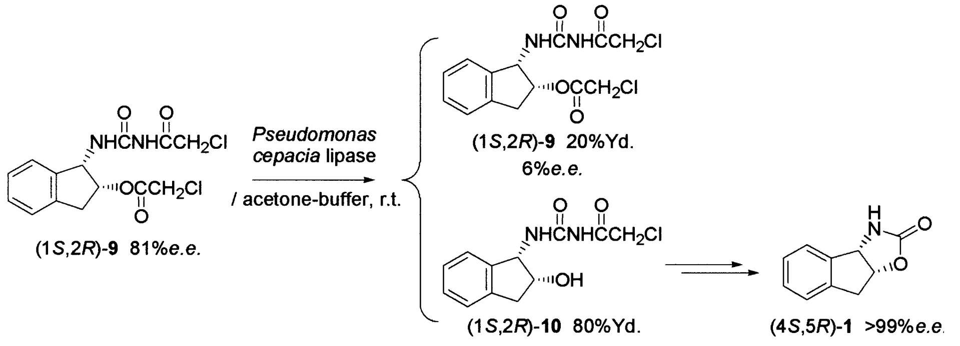
Based on the above-mentioned elaborated condition, upscaling of the reaction (substrate: 2 g) was attempted. The unreacted starting material (1*R*,2*S*)-**9**, and the corresponding alcohol (1*S*,2*R*)-**10** were obtained in 47 and 51% yield, respectively. Both products were efficiently converted to the enantiomers of **3**, the precursor for cyclization, by treatment with a sodium methoxide-methanol solution. After the nitrous-acid catalyzed cyclization reaction,[7] the *e.e.*s were determined at the stage of the oxazolidinones (**1**) by the GLC analysis.[19] The *e.e.*s of (1*R*,2*S*)-**9** (97%) and (1*S*,2*R*)-**10** (90%) indicated that the conversion and E value[20] of the *Pseudomonas* lipase-catalyzed reaction were 51.8 and 79, respectively (Scheme 4).

As we mentioned earlier, pure (4*S*,5*R*)-enantiomer of indanoxazolidinone (**1**) has more importance as the building block of Crixivan®. The enantiomerically enriched alcohol, (1*S*,2*R*)-**10** (for example, 81%*e.e.*) was allowed to give the desired product by reacylation and the subsequent hydrolysis with *P. cepacia* lipase as shown in Scheme 5. In this case, due to the low melting point of the substrate (115.5–116.4°C), the hydrolysis proceeded more smoothly, even under the low concentration of an organic co-solvent and with native (non-immobilized) lipase.

In summary, both enantiomers of indanoxazolidinone were synthesized from racemic 1-amino-2-indanol via immobilized lipase PS-catalyzed kinetic resolution. The highly crystalline nature of the substrate of the enzymatic



Scheme 4.



Scheme 5.

hydrolysis brought about the very low reactivity under conventional conditions, and elaboration of the reaction conditions, especially in regard to the dissolution of the substrate, overcame this problem.

3. Experimental

3.1. General

All mps were uncorrected. IR spectra were measured as films for oils and KBr disks for solids, on a JASCO FT/IR-410 spectrometer. ^{1}H NMR spectra were measured at 270 MHz on a JEOL JNM EX-270 or at 400 MHz on a JEOL JNM GX-400 spectrometer. ^{13}C-NMR spectra were measured at 100 MHz on a JEOL JNM GX-400 spectrometer. Mass spectra were recorded on Hitachi M-80B spectrometer at 70 eV. GLC data were recorded on a GC-353 (GL Sciences Inc.) gas chromatograph. Optical rotations were recorded on a JASCO DIP 360 polarimeter. Wako Gel B-5F and silica gel 60 K070-WH (70-230 mesh) of Katayama Chemical Co. were used for preparative TLC and column chromatography, respectively.

3.1.1. (1*R,2*S**)-(±)-1-*N*-Carbamylamino-2-indanol 3.** To a solution of (1*R**,2*S**)-(±)-1-amimo-2-indanol (**2**, 1.00 g, 6.70 mmol) in 2 M HCl (4.36 mL, 8.71 mmol) was added potassium cyanate (0.82 g, 10.05 mmol). The mixture was stirred at room temperature for 5 min, a white solid was deposited. After stirring for another 30 min, the precipitate was filtered and washed with ice-cooled water. The carbamylamino alcohol (**3**) was obtained in 95% yield. Mp 235.2–235.5°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.12 (m, 4H), 6.14 (d, 1H, J=8.8 Hz), 5.74 (s, 2H), 5.09 (d, 1H, J=3.9 Hz), 4.98 (m, 1H), 4.35 (dd, 1H, J=3.9, 8.8 Hz), 2.99 (dd, 1H, J=4.9, 16.1 Hz), 2.75 (d, 1H, J=16.1 Hz); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 39.8, 57.4, 72.3, 123.7, 124.7, 126.0, 126.8, 140.2, 143.5, 158.6; IR (KBr) 3441, 3328, 1649, 1629, 1457, 1381, 1297, 1177, 1052 cm^{-1}. Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.40; H, 6.33; N, 14.59. The enantiomers [(1*S*,2*R*)- and (1*R*,2*S*)-form] were prepared in the same manner.

3.1.2. (1*R*,2*S*)-1-(*N*'-Acetyl-*N*-carbamylamino)-2-indanol *O*-acetate 5. To a refluxing suspension of potassium acetate (0.37 g, 3.80 mmol) in acetic anhydride (15.0 mL) was added *N*-carbamylamino alcohol [(1*R*,2*S*)-**3**, 1.00 g, 5.20 mmol]. After stirring for 5 min at reflux, the reaction mixture was poured into ice, and the mixture was stirred for 30 min to destroy excess acetic anhydride. The mixture was concentrated in vacuo, then toluene was added and further evaporated until the trace of AcOH was removed. The residue was purified by silica gel column chromatography (150 g). Elution with hexane-AcOEt (2:3 to 3:7) afforded **5** (79% yield). Recrystallization from Et_2O provided colorless prisms. Mp 128.0–128.4°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 9.03 (d, 1H, J=8.3 Hz), 7.30 (m, 4H), 5.68–5.61 (m, 2H), 3.25 (dd, 1H, J=4.9, 17.1 Hz), 3.06 (d, 1H, J=17.1 Hz), 2.15 (s, 3H), 2.06 (s, 3H); IR (KBr) 3300, 3239, 3115, 2981, 2944, 1738, 1715, 1691, 1550, 1510, 1375, 1259, 1243, 1040 cm^{-1}. Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.87; H, 5.86; N, 10.16.

In the course of the preparation of **5**, 1-*N*-carbamylamino-2-indanol *O*-acetate (**4a**), 1-acetamide-2-indanol *O*-acetate (**6a**) and 1-*N*,*N*-diacetylamino-2-indanol *O*-acetate (**6b**) were obtained as by-products. **4a** (Fine needles from AcOEt-EtOH): mp 190.2–191.0°C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.23 (m, 4H), 5.55 (m, 1H), 5.36 (d, 1H, J=4.9 Hz), 3.18 (dd, 1H, J=5.4, 17.1 Hz), 2.95 (dd, 1H, J=1.5, 17.1 Hz), 2.00 (s, 3H); IR (KBr) 3491, 3335, 3291, 1734, 1720, 1653, 1597, 1566, 1376, 1245, 1041 cm^{-1}. Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.18; H, 6.04; N, 11.62. **6a** (Colorless solid): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 4H), 5.98 (d, 1H, J=9.3 Hz), 5.68 (dd, 1H, J=5.4, 9.3 Hz), 5.55 (ddd, 1H, J=1.5, 5.4, 5.4 Hz), 3.21 (dd, 1H, J=5.4, 17.1 Hz), 3.01 (dd, 1H, J=1.5, 17.1 Hz), 2.10 (s, 3H), 2.02 (s, 3H); IR (KBr) 3303, 3072, 1732, 1651, 1550, 1377, 1288, 1244, 1211, 1043 cm^{-1}. ^{1}H NMR spectrum was identical with an authentic sample prepared from (1*S*,2*R*)-aminoindanol (**2**). **6b** (Colorless oil): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (m, 3H), 7.09 (d, 1H, J=7.3 Hz), 5.92 (d, 1H, J=8.3 Hz), 5.53 (m, 1H), 3.31 (dd, 1H, J=7.8, 16.8 Hz), 3.25 (dd, 1H, J=5.4, 16.8 Hz), 2.22 (br s, 6H), 1.96 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.8, 27.0, 38.3, 60.7, 72.7, 123.8, 125.7, 127.8, 129.1, 139.2, 140.5, 171.3, 175.0; IR (NaCl) 3023, 2937, 1738, 1704, 1432, 1368, 1239, 1070 cm^{-1}. Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.44; H, 6.24; N, 5.16.

In the same manner as described above, (1*S*,2*R*)-**5** was obtained from (1*S*,2*R*)-**3**. ^{1}H NMR spectrum was identical with that of (1*R*,2*S*)-**5**.

3.1.3. (1*S*,2*R*)-1-(*N*'-Acetyl-*N*-carbamylamino)-2-indanol 7. To a solution of (1*S*,2*R*)-**5** (400 mg, 1.45 mmol) in MeOH (4.0 mL) was added NaOMe solution (0.11 M in MeOH, 1.33 mL, 0.15 mmol) dropwise at 0°C. After stirring for 1 h at room temperature, the reaction was quenched with aqueous NH_4Cl and extracted with AcOEt three times. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (14 g). Elution with AcOEt afforded (1*S*,2*R*)-**7** (74% yield). Recrystallization from hexane-EtOH provided colorless needles. Mp 181.5–181.9°C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.94 (d, 1H, J=7.4 Hz), 7.24 (m, 4H), 5.24 (dd, 1H, J=5.2, 7.4 Hz), 4.59 (br s, 1H), 3.11 (dd, 1H, J=5.2, 16.5 Hz), 2.92 (dd, 1H, J=1.5, 16.5 Hz), 2.59 (br s, 1H), 2.03 (s, 3H); IR (KBr) 3518, 3406, 3230, 3241, 3133, 2964, 1690, 1676, 1571, 1536, 1255, 1044 cm^{-1}. Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.45; H, 6.01; N, 11.96.

3.1.4. (1*S*,2*R*)-1-(*N*'-Acetyl-*N*-carbamylamino)-2-indanol *O*-chloroacetate 8. The mixture of (1*S*,2*R*)-**7** (81 mg, 0.35 mmol), chloroacetic anhydride (117 mg, 0.69 mmol), pyridine (1.4 mL) and MS 3A (ca. 400 mg) was stirred for 1 h at room temperature. After quenching with pH 7.0 phosphate buffer, the reaction mixture was filtered to remove insoluble materials, and the filtrate was extracted with AcOEt three times. The combined organic layer was concentrated in vacuo. To the residue was added toluene and evaporated in vacuo until pyridine was removed. The residue was purified by silica gel column chromatography (13 g). Elution with hexane-AcOEt (2:3) afforded (1*S*,2*R*)-**8** (quant.). Recrystallization from hexane-AcOEt provided colorless plates. Mp 119.6–120.1°C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.97 (d, 1H, J=8.9 Hz), 7.31 (m, 4H), 5.77 (dd, 1H, J=5.1, 5.2 Hz), 5.66 (dd, 1H, J=5.2, 8.9 Hz), 4.08 (dd, 2H, J=15.3 Hz), 3.30 (dd, 1H, J=5.1, 17.2 Hz), 3.11 (d, 1H, J=17.2 Hz), 2.16 (s, 3H); IR (KBr) 3231, 3118, 2960, 1765, 1691, 1550, 1481, 1239, 1173, 1037 cm^{-1}. Anal. Calcd. for $C_{14}H_{15}ClN_2O_4$: C, 54.11; H, 4.87; N, 9.02. Found: C, 54.01; H, 4.68; N, 9.00.

In the same manner as described above, (1*R*,2*S*)-**8** was obtained. Its ^{1}H NMR spectrum was identical with that of (1*S*,2*R*)-**8**.

3.1.5. (1*R,2*S**)-(±)-1-(*N*'-Chloroacetyl-*N*-carbamylamino)-2-indanol *O*-chloroacetate 9.** A mixture of *N*-carbamylamino alcohol (**3**, 4.50 g, 23.4 mmol) and chloroacetic anhydride (17.0 g, 99.5 mmol) was heated at 85°C and stirred for 10 min. The reaction mixture was poured into pH 7.0 phosphate buffer and stirred for 1 h, white solids were gradually deposited. The precipitate was filtered and washed with aqueous $NaHCO_3$ and water to give **9** (95% yield). This was employed for the next step without further purification. Analytical sample (±)-**9** (colorless needles from AcOEt): mp 172.9–173.4°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (br s, 1H), 8.56 (d, 1H, J=8.8 Hz), 7.23 (m, 4H), 5.70 (m, 1H), 5.60 (dd, 1H, J=5.4, 8.8 Hz), 4.07 (s, 2H), 4.03 (d, 1H, J=15.1 Hz), 3.97 (d, 1H, J=15.1 Hz), 3.23 (dd, 1H, J=4.9, 17.1 Hz), 3.04 (d, 1H, J=17.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 37.2, 41.0, 42.5, 56.5, 77.1, 123.9, 125.0, 127.5, 128.6, 138.8, 139.3, 152.6, 166.8, 167.6; IR (KBr) 3300, 3235, 3112, 2973, 1753, 1724, 1694, 1561, 1513, 1404, 1316, 1250, 1200, 1176, 1042 cm^{-1}. Anal. Calcd. for $C_{14}H_{14}Cl_2N_2O_4$: C, 48.71; H, 4.09; N, 8.12. Found: C, 48.75; H, 4.02; N, 8.07.

In the same manner, (1*S*,2*R*)-**9** was prepared. Recrystallization from hexane-AcOEt provided colorless needles; mp. 123.4–123.9°C; $[\alpha]_D^{20}$=−37.2 (c 1.01, $CHCl_3$); IR (KBr) 3291, 3245, 3141, 2953, 1751, 1728, 1702, 1550, 1499, 1405, 1316, 1248, 1199, 1173, 1057 cm^{-1}. ^{1}H NMR spectrum was same as (±)-**9**.

The enantiomer [(1*R*,2*S*)-form] was also prepared in the same manner. ^{1}H NMR spectrum was identical with that of (±)-**9**.

3.2. Chirazyme® L-2 and lipase PS catalyzed hydrolysis of (1*R**,2*S**)-5

The rates of hydrolyses of both enantiomers of **5** with *C. antarctica*lipase (Chirazyme® L-2) and *P. cepacia* lipase (Amano PS) were compared as follows.

To a solution of *N*′,*O*-diacetyl-*N*-carbamylamino alcohol [(1*S*,2*R*)- or (1*R*,2*S*)-**5**, each 50 mg] in acetone (0.4 mL) and pH 7.0 phosphate buffer (0.1 M, 0.6 mL) was added lipase (10 mg). The reaction mixture was stirred at room temperature. The conversion was roughly estimated on the basis of TLC analysis (AcOEt, R_f=0.56 for the substrate **5**, 0.30 for the product **7**).

3.3. Comparison the rate of lipase PS catalyzed hydrolysis between (1*S*,2*R*)-5, (1*R**,2*S**)-8 and (1*R**,2*S**)-9

The substrate (50 mg), acetone (0.5 mL), pH 7.0 phosphate buffer (0.1 M, 0.7 mL) and lipase PS (10 mg) were mixed and stirred for 24 h at room temperature. To the reaction mixture was added brine and extracted with AcOEt 3–5 times. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in $CDCl_3$ and its ^{1}H NMR spectrum was measured. The ratios between expecting products **7**, **10** and the starting materials respectively, were estimated by comparing the signals of the substrates [H-1 and H-2 (δ 5.68–5.61 for **5**, 5.77 and 5.66 for **8,** 5.70 and 5.60 for **9**)] with those of the products (δ 5.24 and 4.59 for **7**, 5.29 and 4.63 for **10**).

3.4. Immobilization of lipase PS on toyonite 200-M

A suspension of commercial lipase PS (12.50 g) in pH 7.0 phosphate buffer (0.1 M, 50.0 mL) was stirred for 30 min. The mixture was centrifuged, and the supernatant was passed through an Amicon YM10 ultrafiltration membrane (62 mmϕ) until the volume of the solution inside the cell reached 7.6 mL. To this concentrated protein solution was added Toyonite 200-M (268 mg) and the mixture was shaken for 14 h at 25°C under argon. It was filtered and the residue was allowed to dry in vacuo to afford immobilized lipase PS (300 mg). The weight of protein retained on the support was estimated to be 23 mg by the CBB method, being calibrated with γ-globulin as the standard.

3.5. Effect of additives in immobilized lipase PS catalyzed hydrolysis

To a mixture of (±)-**9** (400 mg, 1.16 mmol) and an additive (Triton X-100 or β-CD) in acetone-water, was added immobilized lipase PS (17 mg). While keeping its pH above 6.6 by a pH controller, the reaction mixture was stirred at room temperature until ca. 50% conversion. The conversion was checked by ^{1}H NMR analysis ($CDCl_3$) of a small portion of the reaction mixture, in the same manner as described above.

3.6. Upscaling of the hydrolysis of (±)-9 with immobilized lipase PS

To a solution of (±)-**9** (2.00 g, 5.79 mmol) and β-CD (0.66 g, 0.58 mmol) in acetone (65.0 mL) and pH 7.0 phosphate buffer (0.01M, 6.6 mL), was added immobilized lipase PS (200 mg). While keeping its pH above 6.9 by a pH controller, the reaction mixture was stirred for 15 h at 35°C. The immobilized lipase was filtered off and the filtrate was evaporated in vacuo to remove acetone. The mixture was extracted with AcOEt five times. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (300 g). Elution with $CHCl_3$-AcOEt (1:0 to 1:9) afforded (1*R*,2*S*)-**9** (47% yield) and (1*S*,2*R*)-**10** (51% yield). Both products were converted to indanoxazolidinones (**1**) without further purification and the *e.e.*s were determined. (1*S*,2*R*)-**10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.62 (d, 1H, J=7.2 Hz), 7.22 (m, 4H), 5.29 (dd, 1H, J=5.4, 7.2 Hz), 4.63 (dddd, 1H, J=2.4, 5.4, 5.4, 5.4 Hz), 3.14 (dd, 1H, J=5.4, 16.6 Hz), 2.93 (dd, 1H, J=2.4, 16.6 Hz), 1.98 (d, 1H, J=5.4 Hz); MS m/z=269 (M^+). Recrystallization from AcOEt gave an analytical sample as colorless needles. Anal. Calcd. for $C_{12}H_{13}ClN_2O_3$: C, 53.64; H, 4.88; N, 10.43. Found: C, 53.79; H, 4.89; N, 10.31.

3.6.1. (4*S*,5*R*)-Indano[1,2-*d*]oxazolidinone 1. To a solution of (1*S*,2*R*)-**10** (75 mg, 0.28 mmol) in MeOH (3.0 mL) was added NaOMe solution (0.11 M, 0.25 mL, 0.03 mmol) at room temperature. The reaction mixture was stirred overnight and quenched with H_2O. After evaporating the organic solvent in vacuo, 2 M HCl (1.5 mL, 3.0 mmol) and AcOH (7.0 mL) were added to the residue. To the solution was added $NaNO_2$ (31 mg, 0.45 mmol) and the mixture was stirred for 1 h at room temperature. To the reaction was added aqueous KOH until the pH of the mixture was reached 10 and the mixture was extracted with $CHCl_3$ three times. The combined organic layer was washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated in vacuo. (4*S*,5*R*)-Oxazolidinone (**1**) was obtained (2 steps, quant.) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 4H), 6.80 (br s, 1H), 5.42 (ddd, 1H, J=1.7, 6.3, 7.3 Hz), 5.18 (d, 1H, J=7.3 Hz), 3.41 (dd, 1H, J=6.3, 17.8 Hz), 3.33 (dd, 1H, J=1.7, 17.8 Hz); IR (KBr) 3249, 3141, 2922, 1752, 1706, 1484, 1393, 1331, 1233, 1053 cm^{-1}. Its NMR spectrum was identical with that reported previously.2 On the basis of GLC analysis, the *e.e.* was estimated to be 90.1%.[19] GLC (column, BETA DEX™ 225; 0.25 mm×30 m; 230°C; press 80 kPa): t_R=19.9 min for (4*S*,5*R*)-**1**, 22.3 min for (4*R*,5*S*)-**1**.

In the procedure described above, (1*R*,2*S*)-*N*′,*O*-bischloroacetyl-*N*-carbamylamino alcohol **9** was converted to (4*R*,5*S*)-**1** (2 steps, quant.). On the basis of GLC analysis, the *e.e.* was estimated to be 96.7%.

3.7. Enhancement of the *e.e.* of (1*S*,2*R*)-10 by repetition of lipase-catalyzed hydrolysis

An enantiomerically enriched form of (1*S*,2*R*)-**10** (80.9%*e.e.*), which obtained by the lipase-catalyzed hydrolysis as mentioned above, was chloroacetylated again to give (1*S*,2*R*)-**9**. This (50 mg, 0.14 mmol) was suspended in acetone (0.5 mL) and pH 7.0 phosphate buffer (0.1 M, 0.7 mL), and was added native (non-immobilized) lipase PS (10 mg). While controlling its pH about 6 by addition of aqueous KOH, the reaction mixture was stirred for 20 h at room temperature. Conventional workup and chromatographic separation [hexane-AcOEt (2:3)] afforded (1*S*,2*R*)-**9** (5.5%*e.e.*, 20% yield) and (1*S*,2*R*)-**10** (99.9%*e.e.*, 80% yield). The *e.e.*s were determined at the stage of oxazolidinones, in the same manner as described above.

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References

1. (a) Senanayake, C. H. *Aldrichimica Acta* **1998**, *31*, 3–15. (b) Ghosh, A. K.; Fidanze, S.; Senanayake, C. H. *Synthesis* **1998**, 937–961. (c) Davies, I. W.; Senanayake, C. H.; Castonguay, L.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7619–7622. (d) Ghosh, A. K.; Duong, T. T.; McKee, S. P. *J. Chem. Soc., Chem. Commun.* **1992**, 1673–1674.
2. Ghosh, A. K.; Kincaid, J. F.; Haske, M. G. *Synthesis* **1997**, 541–544.
3. (a) Nakano, S.; Igarashi, Y.; Nohira, H. *Tetrahedron: Asymmetry* **2001**, *12*, 59–62. (b) Demir, A. S.; Hamamci, H.; Doganel, F.; Ozgul, E. *J. Mol. Catal. B: Enz.* **2000**, *9*, 157–161. (c) Anilkumar, A. T.; Goto, K.; Takahashi, T.; Ishizaki, K.; Kaga, H. *Tetrahedron: Asymmetry* **1999**, *10*, 2501–2503. (d) Luna, A.; Maestro, A.; Astorga, C.; Gotor, V. *Tetrahedron: Asymmetry* **1999**, *10*, 1969–1977. (e) Igarashi, Y.; Otsutomo, S.; Harada, M.; Nakano, S.; Watanabe, S. *Synthesis* **1997**, 549–552. (f) Igarashi, Y.; Otsutomo, S.; Harada, M.; Nakano, S. *Tetrahedron: Asymmetry* **1997**, *8*, 2833–2837. (g) Takahashi, M.; Ogasawara, K.

Synthesis **1996**, 954–958. (h) Boyd, D. R.; Sharma, N. D.; Bowers, N. I.; Goodrich, P. A.; Groocock, M. R.; Blacker, A. J.; Clarke, D. A.; Howard, T.; Dalton, H. *Tetrahedron: Asymmetry* **1996**, *7*, 1559–1562. (i) Mitrochkine, A.; Eydoux, F.; Martres, M.; Gil, G.; Heumann, A.; Réglier, M. *Tetrahedron: Asymmetry* **1995**, *6*, 59–62. (j) Didier, E.; Loubinoux, B.; Ramos Tombo, G. M.; Rihs, G. *Tetrahedron* **1991**, *47*, 4971–4958.

4. Thompson, W. J.; Fitzgerald, P. M. D.; Holloway, M. K.; Emini, E. A.; Darke, P. L.; McKeever, B. M.; Schleif, W. A.; Quintero, J. C.; Zugay, J. A.; Tucker, T. J.; Schwering, J. E.; Homnick, C. F.; Nunberg, J.; Springer, J. P.; Huff, J. R. *J. Med. Chem.* **1992**, *35*, 1685–1701.
5. (a) Ghosh, A. K.; Fidanze, S. *Org. Lett.* **2000**, *2*, 2405–2407. (b) Ghosh, A. K.; Fidanze, S. J. *J. Org. Chem.* **1998**, *63*, 6146–6152. (c) Ghosh, A. K.; Fidanze, S.; Onishi, M.; Hussain, K. A. *Tetrahedron Lett.* **1997**, *38*, 7171–7174. (d) Ghosh, A. K.; Onishi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2527–2528.
6. (a) Vacca, J. P.; Dorsey, B. D.; Schleif, W. A.; Levin, R. B.; McDaniel, S. L.; Darke, P. L.; Zugay, J.; Quintero, J. C.; Blahy, O. M.; Roth, E.; Sardana, V. V.; Schlabach, A. J.; Graham, P. I.; Condra, J. H.; Gotlib, L.; Holloway, M. K.; Lin, J.; Chen, I.-W.; Vastag, K.; Ostovic, D.; Anderson, P. S.; Emini, E. A.; Huff, J. R. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4096–4100. (b) Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Gaure, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I.-W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1994**, *37*, 3443–3451.
7. Suzuki, M.; Yamazaki, T.; Ohta, H.; Shima, K.; Ohi, K.; Nishiyama, S.; Sugai, T. *Synlett* **2000**, 189–192.
8. (a) Senanayake, C. H.; Roberts, F. E.; DiMichele, L. M.; Ryan, K. M.; Liu, J.; Fredenburgh, L. E.; Foster, B. S.; Douglas, A. W.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 3993–3996. (b) Senanayake, C. H.; DiMichele, L. M.; Liu, J.; Fredenburgh, L. E.; Ryan, K. M.; Roberts, F. E.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7615–7618. (c) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045–4048.
9. (a) Carrea, G.; Riva, S. *Angew. Chem. Int. Ed.* **2000**, *39*, 2226–2254. (b) Fang, J.-M.; Wong, C.-H. *Synlett.* **1994**, 393–402. (c) Faber, K.; Riva, S. *Synthesis* **1992**, 895–910.
10. Brown, G. B.; Davoll, J.; Lowy, B. A. *Biochem. Prepn.* **1955**, *4*, 70–76.
11. (a) Mizuno, H.; Domon, K.; Masuya, K.; Tanino, K.; Kuwajima, I. *J. Org. Chem.* **1999**, *64*, 2648–2656. (b) Schwartz, A.; Madan, P.; Whitesell, J. K.; Lawrence, R. M. *Org. Synth.* **1990**, *69*, 1–9.
12. Eishima, M.; Ohba, S.; Suzuki, M.; Nagasawa, C.; Sugai, T. *Acta Cryst.* **2000**, *C56*, 1391–1393.
13. Kometani, T.; Sakai, Y.; Matsumae, H.; Shibatani, T.; Matsuno, R. J. *Ferment. Bioeng.* **1997**, *84*, 195–199.
14. Kamori, M.; Hori, T.; Yamashita, Y.; Hirose, Y.; Naoshima, Y. *J. Mol. Catal. B: Enz.* **2000**, *9*, 269–274.
15. Kvittingen, L. *Tetrahedron* **1994**, *50*, 8253–8274.
16. Okahata, Y.; Mori, T. *Yukigosei Kagaku Kyokaishi (J. Synth. Org. Chem., Jpn.)* **1998**, *56*, 931–939.
17. Bakke, M.; Takizawa, M.; Sugai, T.; Ohta, H. *J. Org. Chem.* **1998**, *63*, 6929–6938.
18. (a) Murata, T.; Usui, T. *Biosci. Biotech. Biochem.* **1997**, *61*, 1059–1066. (b) Nakamura, K.; Kondo, S.; Ohno, A. *Bioorg. Med. Chem.* **1994**, *2*, 433–437. (c) Nakamura, K.; Kondo, S.; Kawai, Y.; Ohno, A. *Tetrahedron: Asymmetry* **1993**, *4*, 1253–1254.
19. Armstrong, D. W.; Lee, J. T.; Chang, L. W. *Tetrahedron: Asyemtry* **1998**, *9*, 2043–2064.
20. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.