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ENANTIOSELECTIVE SYNTHESIS OF BOTH ENANTIOMERS OF ETODOLAC *VIA* A LIPASE-CATALYZED KINETIC RESOLUTION

Shuji Akai,* Hiroyuki Nemoto, and Masahiro Egi

School of Pharmaceutical Sciences, University of Shizuoka
52-1, Yada, Suruga-ku, Shizuoka, Shizuoka 422-8526, Japan
E-mail: akai@u-shizuoka-ken.ac.jp

Abstract — The efficient preparation of both enantiomers of etodolac **1** was achieved by the lipase-catalyzed kinetic resolution of the racemic primary alcohol (±)-**2** followed by chemoselective oxidation.

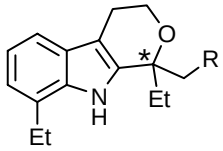
INTRODUCTION

Etodolac **1**, a nonsteroidal antiinflammatory drug with analgesic and antipyretic activities, has therapeutically been used as a racemate, while these pharmacological activities are known to be due to the (*S*)-isomer.[1] Recently, (*R*)-**1** was discovered to possess antitumor activities, and its clinical application to B-cell chronic lymphocytic leukemia[2] and multiple myeloma[3] is now under investigation. In order to further evaluate the differences in their biological profiles between the enantiomers, an effective production of the optically pure (*S*)- and (*R*)-**1** is required.

Various developed methods have mainly provided (*S*)-**1**, which included the fractional crystallization of the diastereomeric mixtures of the salts generated from (±)-**1** and optically pure amines, such as 1-phenylethylamine,[4] *N*-methyl glucamine,[5] and (–)-cinchonidine,[6] and that of the ester derived from optically pure (–)-isopinocamphenol.[6] The enrichment crystallization of (±)-**1** was also reported.[7] The HPLC separation of the diastereomeric mixture of the esters prepared from (–)-borneol[8] and the synthesis of (*S*)-**1** starting from either (*R*)-2,3-isopropylideneglyceraldehyde[9] or (–)-β-pinene derivatives[10] were developed as alternative approaches. Some of them afforded the optically pure (*S*)-**1** in fairly good yields,[4,5] while others were not very satisfactory because of their low yields and/or lengthy synthetic sequences. In addition, there are still few methods for the preparation of the optically pure (*R*)-**1**.[4,8]

The lipase-catalyzed kinetic resolution of racemic carboxylic esters and alcohols has been well acknowledged as a powerful means of producing optically pure compounds.[11] However, it has not yet

been successfully applied to the preparation of the optically pure **1**. Thus, Achiwa et al. investigated the hydrolase-catalyzed hydrolysis of a variety of esters derived from (±)-**1**; however, the best result obtained from the resolution of its pivaloyloxymethyl ester using *Alcaligenes sp.* lipase gave (*R*)-**1** (48% ee) in 58% yield, whose enantioselectivity, the E value,[12] was 6.3.[13] On the other hand, Brenna et al. reported the kinetic resolution of a racemic precursor **2** using *Candida cylindracea* lipase followed by oxidation to give (*S*)-**1**.[4] However, the resolution was not very efficient, whose E value was 5.3, therefore, they needed to repeat the resolution along with the recrystallization to improve the optical purity of the initial resolution product, (*S*)-**2** (33% ee).



Etodolac (**1**), R = CO_2H
2, R = CH_2OH

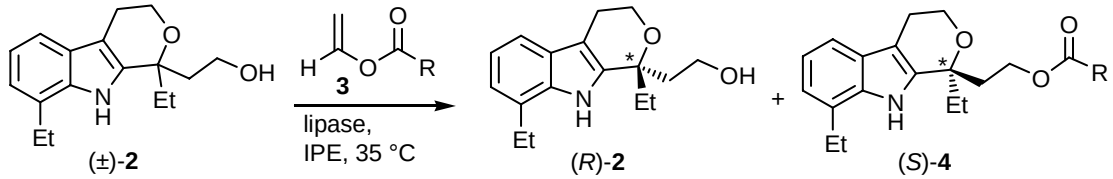
We now describe an improved preparation of both enantiomers of **1**, each in the optical pure form, which consists of the highly enantioselective resolution of (±)-**2** (E value = 89) using lipase R (*Penicillium roqueforti*, Amano) in cyclopentyl methyl ether (CPME) and the chemoselective oxidation of the primary hydroxyl group of the obtained (*R*)- and (*S*)-**2** without protecting the indole NH-group.

RESULTS AND DISCUSSION

Our first trial for the hydrolase-catalyzed kinetic resolution of (±)-**2** (3 mg) was carried out using vinyl acetate **3a** in diisopropyl ether (IPE) at 35 °C. Among the commercially available 46 enzymes, lipase R (*Penicillium roqueforti*, Amano) and lipase A12 (*Aspergillus niger*, Amano) were moderately effective for producing (*R*)-**2** and (*S*)-**4a** after 3 days [E = 6 by lipase R (Entry 1 in Table 1) and E = 4 by lipase A12 (Entry 6)]. Some lipases derived from the *Alcaligenes*, *Burkholderia, Candida*, *Mucor*, and *Pseudomonas* species catalyzed the reaction with poor enantioselectivities (E = <2), while others were not active at all.

The acyl moiety of **3** was found to have a significant effect on both the enantioselectivity and the reactivity.[14] Thus, the use of vinyl butyrate **3b** with lipase R gave a mixture of (*R*)-**2** and (*S*)-**4b** (E = 28) after 1 day (Entry 2), and that of vinyl hexanoate **3c** gave the products (E = 26) after 3 days (Entry 3), while that of vinyl decanoate **3d** and vinyl benzoate **3e** was not very effective (Entries 4 and 5). A similar increase in the enantioselectivities by changing **3** was also observed when lipase A12 was used (Entries 7–10). Among these results, the combination of lipase R and **3b** was thought to be the best based on the selectivity and the reaction rate.

Table 1. Lipase-catalyzed kinetic resolution of (±)-**2** using various kinds of acyl donors **3**.



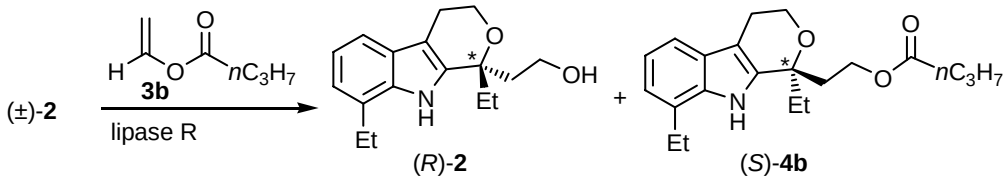
Entry	Lipase	**3**, R =	Time, day	Conv., %	E value	(*R*)-**2**, % ee[a]	(*S*)-**4**	
							R =	% ee[a]
1	R	Me (**3a**)	3	60	6	74	Me (**4a**)	49
2	R	nC$_3$H$_7$ (**3b**)	1	52	28	89	nC$_3$H$_7$ (**4b**)	81
3	R	nC$_5$H$_{11}$ (**3c**)	3	27	26	34	nC$_5$H$_{11}$ (**4c**)	90
4	R	nC$_9$H$_{19}$ (**3d**)	1	20	7	18	nC$_9$H$_{19}$ (**4d**)	70
5	R	Ph (**3e**)	4	10	19	10	Ph (**4e**)	89
6	A12	Me (**3a**)	3	48	4	45	Me (**4a**)	48
7	A12	nC$_3$H$_7$ (**3b**)	1	13	5	10	nC$_3$H$_7$ (**4b**)	66
8	A12	nC$_5$H$_{11}$ (**3c**)	10	29	35	37	nC$_5$H$_{11}$ (**4c**)	92
9	A12	nC$_9$H$_{19}$ (**3d**)	7	29	7	27	nC$_9$H$_{19}$ (**4d**)	67
10	A12	Ph (**3e**)	4	29	30	37	Ph (**4e**)	91

a) The optical purity was determined by HPLC analysis using Daicel CHIRALCEL OD-H.

Besides IPE, some ethereal solvents, such as *t*BuOMe (TBME) and cyclopentyl methyl ether (CPME), were equally useful (Entries 4 and 6 in Table 2), whereas the use of a cyclic ether, THF, caused no reaction (Entry 9). Toluene was another potent solvent that produced a good enantioselectivity (Entry 10); however, side reactions took place on a larger scale. Lowering the reaction temperature brought about a significant increase in the E value although the reaction rate decreased (Entries 3, 5, and 8).[15] Thus, the reaction using lipase R and **3b** in CPME at 5 °C (Entry 8) was determined to be the best (E = 131) among all the examined conditions.

The kinetic resolution of (±)-**2** (50 mg or 1.0 g) under the same conditions as Entry 8 in Table 2 suffered a low reproducibility of the reaction rate and the enantioselectivity, which was later found to be due to the fluctuation of the water content in the reaction media.[16] The trials under three different conditions by changing the water content between 0 to 0.3 w/w % revealed that the use of the solvent containing 0.1 w/w % was the most effective (Entries 1–3 in Table 3). The reproducibility of this method was confirmed by the resolution of 1.0 g of (±)-**2**, whose E value was 89, and (*R*)-**2** (99% ee, 43% isolated yield) and (*S*)-**4b** (89% ee, 52% isolated yield) were obtained (Entry 4). The absolute stereochemistries of the products were determined by the comparison of the optical rotation of the recovered alcohol **2** (99% ee){$[\alpha]_D^{20}$ +42.5 (*c* 0.17, $CHCl_3$)} to that of the reported value {$[\alpha]_D^{20}$ +42.4 (*c* 1.0, $CHCl_3$) for (*R*)-**2**}.[4]

Table 2. The effects of the solvent and the reaction temperature on the lipase-catalyzed kinetic resolution of (±)-**2** with **3b**.



Entry	Solvent[a]	Temp., °C	Time, day	Conv., %	E value	(*R*)-**2**, % ee[b]	(*S*)-**4b**, % ee[b]
1[c]	IPE	35	1	52	28	89	81
2	IPE	23	1	26	33	32	92
3	IPE	5	3	9	72	10	97
4	TBME	35	1	44	29	67	87
5	TBME	5	1	23	65	29	96
6	CPME	35	1	31	31	40	91
7	CPME	23	1	12	31	13	93
8	CPME	5	3	23	131	29	98
9	THF	35	7	<5	—	—	—
10	toluene	35	1	26	54	34	95

a) IPE: *i*Pr$_2$O, TBME: *t*BuOMe, CPME: Cyclopentyl methyl ether. b) The optical purity was determined by HPLC analysis using Daicel CHIRALCEL OD-H. c) Cited from Entry 2 in Table 1.

Table 3. The effect of the water content on the lipase-catalyzed kinetic resolution of (±)-**2**.[a]

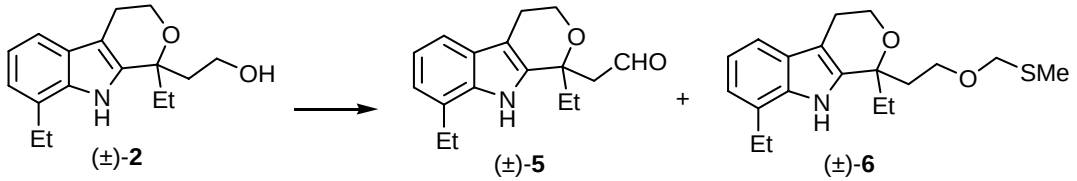
Entry	Amount of (±)-**2**	Water content, w/w %	Conv., %	E value	(*R*)-**2**, % ee[b]	(*S*)-**4b**, % ee[b]
1	50 mg	0	49	53	86	90
2	50 mg	0.1	35	82	51	96
3	50 mg	0.3	<5	—	—	—
4	1.0 g	0.1	53	89	99 (43%)[c]	89 (52%)[c]

a) Each reaction was carried out using lipase R in CPME at 5 °C for 3 days. b) The optical purity was determined by HPLC analysis using Daicel CHIRALCEL OD-H. c) Isolated yield is shown in parenthesis.

The other critical issue in this project was the oxidation of the primary hydroxyl group to the carboxyl group in the presence of the indole moiety. It is well known that the indoles without protection of the NH-group suffer easy oxidation under various conditions,[4] and only a few successful examples of the oxidation of alcohols or the aldehydes having a NH-free indole moiety were limited to the indoles having an electron-withdrawing substituent[17,18] and/or the oxidation at the reactive benzylic position.[18,19]

Because the development of an effective method for the protection-free synthesis has been requested from the standpoint of environmental consciousness,[20] we thoroughly investigated the direct oxidation of (±)-**2** as a preliminary substrate. Brenna et al. conducted the oxidation of (*S*)-**2** using DMSO and Ac_2O,[4] and their method was reproduced by our hand to give (±)-**5**. However, the methylthiomethyl ether (±)-**6** (27% yield) was also obtained as a side product just like they had mentioned (Entry 1 in Table 4). We found that the Parikh oxidation using DMSO and SO_3-pyridine dramatically depressed the formation of (±)-**6** and afforded (±)-**5** in 80% yield (Entry 2), while the Swern oxidation gave multiple products (Entry 3). The Ley oxidation using Pr_4NRuO_4 (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) was relatively effective (Entry 4), and the Margarita oxidation using 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) and $PhI(OAc)_2$[21] gave (±)-**5** in 25% yield (Entry 5). However, other methods were not useful thus resulting in either the formation of multiple products or no reaction (Entries 6–10).

Table 4. Oxidation of (±)-**2** to (±)-**5**.



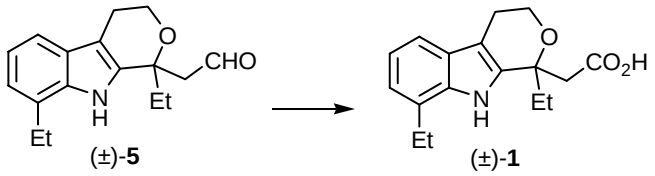
Entry	Reagents	Temp.	Reaction time	Products[a]
1	DMSO, Ac_2O	RT	8 h	**5** (56%), **6** (27%)
2	DMSO, SO_3·pyridine, Et_3N	RT	40 min	**5** (80%), **6** (5%)
3	DMSO, $(COCl)_2$, Et_3N	–78 °C	1 h	multiple products
4	TPAP, NMO	RT	1 h	**5** (66%)
5	TEMPO, $PhI(OAc)_2$[21]	0 °C	1 d	**5** (25%)
6	TEMPO, NaOCl, KBr[22]	0 °C	1 h	multiple products
7	Dess–Martin periodinane	0 °C	40 min	multiple products
8	$PhI(OAc)_2$, KBr	RT	4 h	multiple products
9	PhIO, KBr, MeOH	RT	5 min	multiple products
10	Ag_2CO_3, Celite	RT	4 d	no reaction

a) Isolated yield is shown in parenthesis.

The subsequent oxidation of the formyl group of (±)-**5** into the carboxyl group in the presence of the NH-unprotected indole moiety was more laborious. Although Brenna et al. reported the oxidation of (*S*)-**5** using nickel peroxide,[4] our trials always gave multiple products (Entry 1 in Table 5). The Pinnick oxidation ($NaClO_2$, 2-methyl-2-butene) was not available in this case (Entry 2), and 30% aqueous H_2O_2 did not cause any oxidation (Entry 3). On the contrary, the addition of 6 equiv. of K_2CO_3 to this reaction

gave the desired (±)-**1** in 7% yield (Entry 4). The improvement of the yield of (±)-**1** by the combination of H_2O_2 with various metal catalysts resulted in the formation of multiple products (Entries 5–8). After many unfruitful trials (some of them are shown in entries 9–11), we finally found that the Ley oxidation using TPAP and NMO with K_2CO_3 (1.0 mol equiv.) gave (±)-**1** in 56% yield (Entry 12). The addition of K_2CO_3[23] was inevitable for the chemoselective oxidation because a similar reaction in the absence of K_2CO_3 gave multiple products (Entry 11), while the co-oxidant, NMO, was not always necessary (Entry 13).

Table 5. Oxidation of (±)-**5** to (±)-**1**.



Entry	Reagents	Temp.	Reaction time	Products[a]
1	Nickel peroxide, aq. NaOH	RT	6 h	multiple products
2	$NaClO_2$, 2-methyl-2-butene	RT	1 h	multiple products
3	30% aq. H_2O_2	RT	1 d	no reaction
4	30% aq. H_2O_2, K_2CO_3	RT	1 d	**1** (7%)[b]
5	30% aq. H_2O_2, K_2CO_3, $CeCl_3 \cdot 7H_2O$	RT	1 d	multiple products
6	30% aq. H_2O_2, K_2CO_3, $(NH_4)_6Mo_7O_{24} \cdot H_2O$	RT	0.75 h	multiple products
7	30% aq. H_2O_2, K_2CO_3, cat. $(NH_4)_6Mo_7O_{24} \cdot H_2O$, $CeCl_3 \cdot 7H_2O$	RT	4 h	multiple products
8	30% aq. H_2O_2, SeO_2	RT	1.5 h	multiple products
9	Ag_2O	RT	4 h	multiple products
10	I_2, KOH[24]	0 °C	0.5 h	multiple products
11	TPAP, NMO, H_2O	RT	1 d	multiple products
12	TPAP, NMO, H_2O, K_2CO_3	RT	1 d	**1** (56%)
13	TPAP, H_2O, K_2CO_3	RT	1 d	**1** (58%)

a) Isolated yield is shown in parenthesis. b) An unidentified compound was obtained as a major product.

With these promising oxidation protocols in hand, we achieved the synthesis of both (*R*)- and (*S*)-**1** in optically pure forms. Thus, (*R*)-**2** (99% ee) was subjected to the Parikh oxidation followed by the Ley oxidation to give (*R*)-**1** (>98% ee) in 32% overall yield. Its enantiomer, (*S*)-**1** (>98% ee), was similarly produced from (*S*)-**2** (99% ee), obtained by the alkaline hydrolysis of (*S*)-**4b** (89% ee) followed by the second lipase-catalyzed kinetic resolution under the same reaction conditions (Scheme 1).

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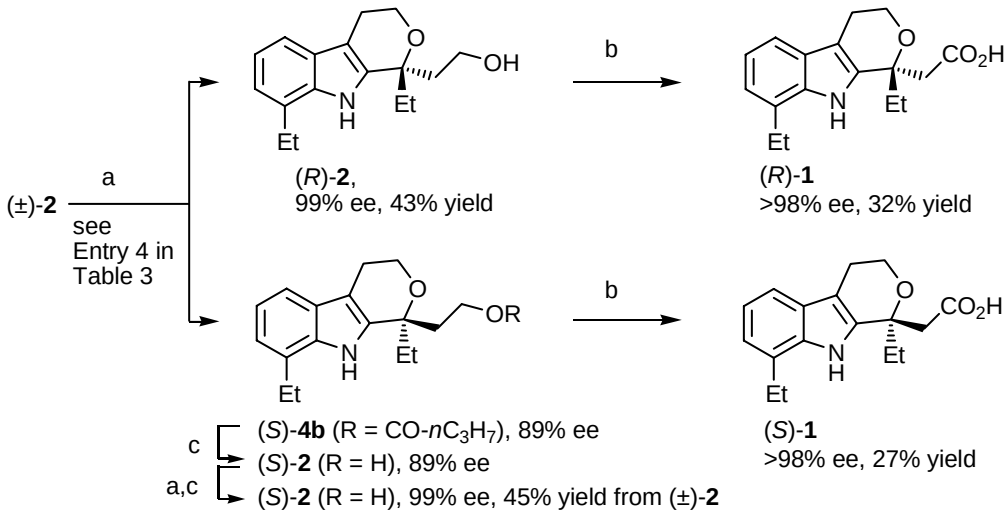

Scheme 1. Reagents and conditions: (a) **3b**, lipase R, CPME–H_2O (1000:1), 5 °C; (b) 1) DMSO, SO_3·pyridine, Et_3N, MeCN, RT, 2) TPAP, K_2CO_3, H_2O, MeCN, RT; (c) K_2CO_3, MeOH, RT.

CONCLUSION

Both enantiomers of the optically pure etodolac **1** were synthesized from the racemic precursor **2**. The following two accomplishments are worth noting: (1) The lipase-catalyzed kinetic resolution was found to be effective even for the primary alcohol **2** whose kinetic resolution has been thought to be difficult due to its unique structure; viz., the quaternary carbon as the sole stereogenic center and the highly flexible β-hydroxy ethyl group as the reactive site. (2) The proper choice of the reaction conditions achieved the chemoselective oxidation of the primary hydroxyl group into the carboxyl group without any protection of the indole NH-group. The application of this method to the preparation of the optically pure derivatives of **1**, such as SDX-308 and SDX-309,[25] is now under investigation in our laboratory.

EXPERIMENTAL

Typical Procedure for Hydrolase-Catalyzed Kinetic Resolution of (±)-2 Using 3a–e.

To a resealable vessel were added a hydrolase (3 mg), (±)-**2**[4] (3 mg, 0.01 mmol), an organic solvent (0.1 mL), and **3** (0.1 mL, 0.07 mmol). The reaction mixture was stirred at the designated temperature by monitoring the reaction with TLC. After the designated period of time, the reaction mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The residue was purified by preparative TLC (hexanes–EtOAc, 3:1) to give (*R*)-**2** and (*S*)-**4**. The reaction conditions, the conversion of the reaction, and the optical purity of the products are listed in Tables 1–3.

(*R*)-2-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)ethanol ((*R*)-2).

Under an argon atmosphere, a suspension of lipase R (1.0 g), (±)-**2**[4] (1.0 g, 3.7 mmol), **3b** (3.3 mL, 26 mmol) and distilled water (100 μL) in CPME (100 mL) was stirred at 5 °C for 3 days. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The residue was

purified by column chromatography (hexanes–EtOAc, 5:1→3:1 then EtOAc only) to give (*R*)-**2** (0.44 g, 43% yield, 99% ee) and (*S*)-**4b** (0.65 g, 52% yield, 89% ee). The optical purity of (*R*)-**2** was determined by HPLC analysis using Daicel CHIRALCEL OD-H (hexanes–*i*PrOH 90:10, flow rate 0.8 mL/min, 20 °C). Retention time: 7.0 min for (*R*)-**2** and 14.3 min for (*S*)-**2**. The optical purity of (*S*)-**4b** was determined by HPLC analysis using Daicel CHIRALCEL OD-H (hexanes–*i*PrOH 90:10, flow rate 0.8 mL/min, 20 °C). Retention time: 5.5 min for (*R*)-**4b** and 7.9 min for (*S*)-**4b**.

(*R*)-**2**: A colorless amorphous solid; $[\alpha]_D^{20}$ +42.5 (*c* 0.17, $CHCl_3$) {lit.,[4] $[\alpha]_D^{20}$ +42.4 (*c* 1.0, $CHCl_3$) for (*R*)-**2**}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.95 (3H, t, *J* = 7.5 Hz), 1.36 (3H, t, *J* = 7.5 Hz), 1.87–2.04 (2H, m), 2.05–2.24 (2H, m), 2.74–2.92 (4H, m), 3.62–3.72 (2H, m), 3.97–4.09 (2H, m), 7.03 (1H, d, *J* = 7.5 Hz), 7.10 (1H, t, *J* = 7.0 Hz), 7.38 (1H, d, *J* = 7.5 Hz), 7.97 (1H, br s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 7.9, 13.7, 22.4, 24.0, 31.3, 39.1, 59.6, 60.4, 78.1, 109.0, 115.9, 119.8, 120.4, 126.3, 126.5, 134.6, 136.0. IR (KBr): 3470 cm^{-1}. High resolution FAB-MS Calcd for $C_{17}H_{23}NO_2$ (M^+) *m/z*: 273.1729, found: 273.1754.

(*S*)-2-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)ethyl butyrate ((*S*)-4b).

A suspension of (*S*)-**4b** (0.65 g, 1.88 mmol, 89% ee) and K_2CO_3 (0.53 g, 3.8 mmol) in MeOH (10 mL) was stirred at room temperature for 3 h. The reaction mixture was filtered through a SiO_2 pad and the filtrate was concentrated in vacuo to give (*S*)-**2** (0.52 g, quant.). Under an argon atmosphere, a suspension of lipase R (0.50 g), the above obtained (*S*)-**2** (0.52 g, 1.88 mmol), **3b** (1.6 mL, 13.0 mmol) and distilled water (50 μL) in CPME (50 mL) was stirred at 5 °C for 3 days. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (hexanes–EtOAc, 5:1) to give (*S*)-**4b** (0.56 g, 87% yield, 99% ee) as white crystals; $[\alpha]_D^{20}$ –1.07 (*c* 0.95, $CHCl_3$), mp 81–83 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.86 (3H, t, *J* = 7.5 Hz), 0.90 (3H, t, *J* = 7.5 Hz), 1.37 (3H, t, *J* = 7.5 Hz), 1.50–1.57 (2H, m), 1.82–1.89 (1H, m), 1.91–1.97 (1H, m), 2.11 (2H, q, *J* = 7.5 Hz), 2.19–2.22 (2H, m), 2.72–2.83 (2H, m), 2.87 (2H, q, *J* = 7.0 Hz), 4.00 (2H, t, *J* = 6.0 Hz), 4.09–4.19 (2H, m), 7.02 (1H, d, *J* = 7.0 Hz), 7.07 (1H, t, *J* = 7.0 Hz), 7.35 (1H, d, *J* = 7.0 Hz), 7.72 (1H, br s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 7.9, 13.6, 13.8, 18.3, 22.3, 24.0, 31.9, 36.1, 36.7, 60.5, 60.8, 75.3, 109.0, 115.9, 120.0, 120.4, 126.3, 126.5, 134.6, 135.9, 173.9. IR (KBr): 3470, 1724 cm^{-1}. *Anal.* Calcd for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.08. Found: C, 73.40; H, 8.34; N, 4.10.

(*S*)-2-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)ethanol ((*S*)-2).

A suspension of (*S*)-**4b** (0.20 g, 0.58 mmol, 99% ee) and K_2CO_3 (163 mg, 1.18 mmol) in MeOH (3.0 mL) was stirred at room temperature for 15 h. The reaction mixture was filtered through a SiO_2 pad and concentrated in vacuo to give (*S*)-**2** (169 mg, quant., 99% ee) as a colorless amorphous solid. $[\alpha]_D^{20}$ –42.7 (*c* 0.87, $CHCl_3$). The NMR and IR data of this product were in full agreement with those of (*R*)-**2**.

(*R*)-2-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetaldehyde ((*R*)-5).

A solution of (*R*)-**2** (0.22 g, 0.81 mmol, 99% ee) and SO_3·pyridine (0.78 g, 4.9 mmol) in a mixture of

MeCN (1.1 mL), DMSO (1.1 mL), and Et_3N (1.1 mL) was stirred at room temperature for 40 min. The reaction mixture was poured into water, and the product was extracted with EtOAc. The combined organic layer was successively washed with 3% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexanes–EtOAc, 5:1) to give (*R*)-**5** (176 mg, 80% yield) as a colorless oil. The optical purity of (*R*)-**5** could not be determined by HPLC analysis using chiral columns due to the significant broadening of the peaks. $[\alpha]_D^{20}$ –28.5 (*c* 3.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.86 (3H, t, *J* = 7.5 Hz), 1.33 (3H, t, *J* = 7.5 Hz), 1.89–2.12 (2H, m), 2.78–2.85 (2H, m), 2.83 (2H, q, *J* = 7.5 Hz), 2.98 (1H, d, *J* = 18.0 Hz), 3.02 (1H, d, *J* = 18.0 Hz), 3.96–4.06 (2H, m), 7.00 (1H, d, *J* = 7.5 Hz), 7.06 (1H, t, *J* = 7.5 Hz), 7.35 (1H, d, *J* = 7.5 Hz), 8.44 (1H, s), 9.71 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 7.7, 13.7, 22.3, 24.0, 31.0, 51.8, 60.6, 74.8, 108.8, 116.0, 119.8, 120.6, 126.2, 126.5, 134.5, 135.1, 202.4. IR (KBr): 3466, 3431, 1720 cm^{-1}. High resolution FAB-MS Calcd for $C_{17}H_{21}NO_2$ (M^+) *m/z*: 271.1572, found: 271.1552.

(*S*)-2-(1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetaldehyde ((*S*)-5).

Similarly to the preparation of (*R*)-**5**, (*S*)-**5** (30 mg, 76% yield) was obtained from (*S*)-**2** (40 mg, 0.143 mmol, 99% ee). A colorless oil. $[\alpha]_D^{20}$ +31.6 (*c* 2.8, $CHCl_3$). The NMR and IR data of this product were in full agreement with those of (*R*)-**5**. High resolution FAB-MS Calcd for $C_{17}H_{22}NO_2$ [$(M+H)^+$] *m/z*: 272.1651, found: 272.1630.

(*R*)-Etodolac ((*R*)-1).

To a suspension of (*R*)-**5** (50 mg, 0.184 mmol) of MeCN (2.4 mL), K_2CO_3 (25 mg, 0.184 mmol), distilled water (two drops) and TPAP (19 mg, total 0.22 mmol) were added every 30 min for 4 times. The reaction mixture was filtered through a SiO_2 pad, the filtrate was concentrated in vacuo, and the residue was purified by column chromatography (hexanes–EtOAc–AcOH, 50:50:1) to give (*R*)-**1** (21 mg, 40% yield, >98% ee) as white crystals. The optical purity of this product was determined by HPLC analysis using Daicel CHIRALCEL OD (hexanes–*i*PrOH–AcOH 89:10:1, flow rate 0.8 mL/min, 20 °C). Retention time: 7.7 min for (*R*)-**1** and 9.6 min for (*S*)-**1**. $[\alpha]_D^{20}$ –67.8 (*c* 0.72, $CHCl_3$), mp 77–78 °C (138–140 °C after recrystallization from EtOAc){lit.,[4] $[\alpha]_D^{20}$ –66.8 (*c* 1, $CHCl_3$), lit.,[8] mp 139–141 °C}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 7.5 Hz), 1.34 (3H, t, *J* = 7.5 Hz), 2.01–2.15 (2H, m), 2.79–2.86 (4H, m), 3.03 (1H, d, *J* = 17.0 Hz), 3.05 (1H, d, *J* = 17.0 Hz), 4.04–4.13 (2H, m), 7.01 (1H, d, *J* = 7.5 Hz), 7.08 (1H, t, *J* = 7.5 Hz), 7.36 (1H, d, *J* = 7.5 Hz), 8.47 (1H, s), ^{13}C NMR (125 MHz, $CDCl_3$) δ: 7.7, 13.7, 22.1, 24.0, 30.9, 42.6, 60.9, 75.2, 108.5, 116.0, 119.8, 120.7, 126.0, 126.6, 134.5, 134.6, 175.8. IR (KBr): 3684, 1747 cm^{-1}. High resolution FAB-MS Calcd for $C_{17}H_{21}NO_3$ (M^+) *m/z*: 287.1521, found: 287.1531.

(*S*)-Etodolac ((*S*)-1).

Similarly to the preparation of (*R*)-**1**, (*S*)-**1** (20 mg, 35% yield, >98% ee) was obtained from (*S*)-**5** (54 mg, 0.20 mmol). $[\alpha]_D^{20}$ +70.1 (*c* 0.50, $CHCl_3$), mp 78–81 °C (138–141 °C after recrystallization from EtOAc)

{lit.,[4] $[\alpha]_D^{20}$ +65.6 (*c* 1, $CHCl_3$), lit.,[8] mp 138–140 °C}. High resolution FAB-MS Calcd for $C_{17}H_{23}NO_2$ (M^+) *m/z*: 287.1521, found: 287.1524.

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