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PREPARATION OF OPTICALLY ACTIVE SECONDARY ALCOHOLS BY COMBINATION OF ENZYMATIC HYDROLYSIS AND CHEMICAL TRANSFORMATION[1]

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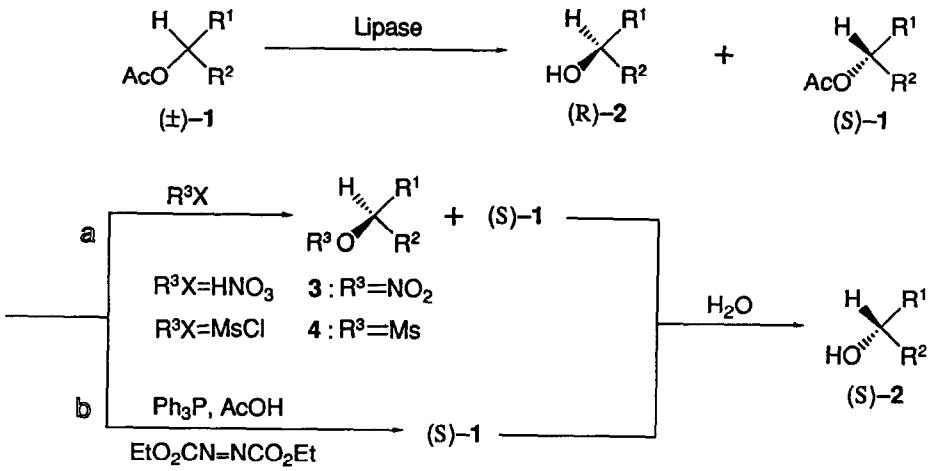
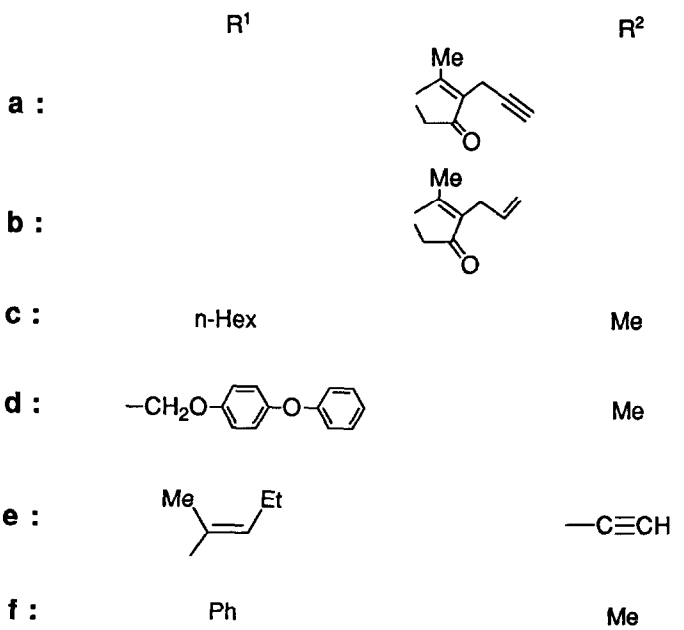
Abstract : Several kinds of optically active secondary alcohols (S)-**2**, which are important intermediates of bioactive compounds, were prepared from the corresponding racemic acetate (±)-**1** in high chemical and optical yields by combination of enzymatic hydrolysis and chemical transformation.

Optically active secondary alcohols are useful intermediates for preparation of bioactive compounds. Particularly, (S)-4-hydroxy-3-methyl-2-(2-propynyl)-2-cyclopenten-1-one ((S)-**2 a**) and (S)-4-hydroxy-3-methyl-2-(2-propenyl)-2-cyclopenten-1-one ((S)-**2 b**) are important alcohol moieties of optically active pyrethroid insecticides,[2] and (S)-1-(4-phenoxyphenoxy)-2-propanol ((S)-**2 d**) is an important intermediate of juvenile hormone mimics.[3] We recently demonstrated the strategy to prepare (S)-**2 a** from the corresponding racemic acetate (±)-**1 a** by combination of enzymatic hydrolysis and chemical transformation with inversion, and enzymatic hydrolysis of (±)-**1 a** was discussed.[4] As a part of our ongoing program, we examined the sequential chemical transformation of (R)-alcohol (R)-**2 a** and (S)-acetate (S)-**1 a** obtained by the enzymatic hydrolysis, and accomplished the route to prepare (S)-alcohol (S)-**2 a** in high chemical and optical yields, starting from the racemic acetate (±)-**1 a**.[1] By this success, our interest has been focussed on generalization of our methodology, and we have prepared several kinds of optically active secondary alcohols (S)-**2** in high chemical and optical yields (Scheme 1).

Scheme 1


Lipase
(±)–1
(R)–2
(S)–1
R³X
a
b
R³X=HNO₃ 3 : R³=NO₂
R³X=MsCl 4 : R³=Ms
Ph₃P, AcOH
EtO₂CN=NCO₂Et
(S)–1
H₂O
(S)–2

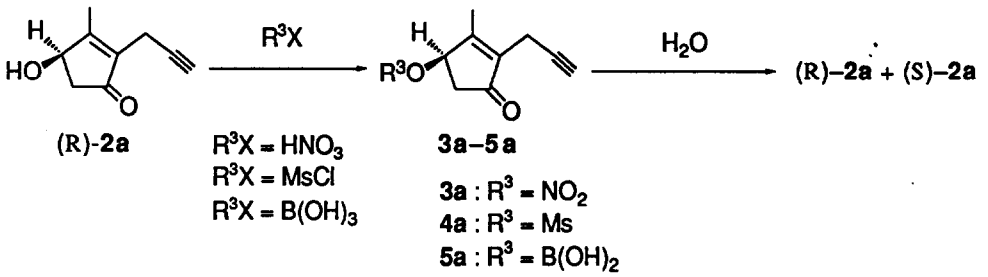

R¹
R²
a :
b :
c : n-Hex Me
d : Me
e : Me
Et
—C≡CH
f : Ph Me

Results and Discussion

Study on Methodology

We have investigated chemical transformations of (R)-alcohol (R)-**2 a** and (S)-acetate (S)-**1 a** obtained by the enzymatic hydrolysis in order to establish the route to prepare (S)-alcohol (S)-**2 a** starting from the racemic acetate (±)-**1 a** (Scheme 1-a). The racemic acetate (±)-**1 a** was hydrolyzed by using *Arthrobacter* lipase.[4] The crude product was purified by column chromatography on silica gel (30% EtOAc in hexane) to give optically pure (R)-**2 a** as pale yellow crystals in 46% yield, and optically pure (S)-**1 a** as white crystals in 46% yield.

Scheme 2



In order to convert (R)-**2 a** to (S)-**2 a**, several kinds of esters (**3 a** : nitrate, **4 a** : mesylate, **5 a** : borate) were prepared, and their hydrolysis under acidic or neutral conditions was examined (Scheme 2). The results are summarized in Table I. The yields of the resulting alcohols ((R)-**2 a** + (S)-**2 a**) and the isomeric ratios ((R)-**2 a** : (S)-**2 a**) were determined by GC and HPLC analysis, respectively. Borate **5 a** preferentially gave (R)-**2 a** with retention, which may be due to preferential B-O bond fission rather than C-O bond in this case (entry 7). On the other hand, the hydrolysis of nitrate **3 a** and mesylate **4 a** under neutral or acidic conditions proceeded with inversion to give preferentially (S)-alcohol (S)-**2 a**. For example, the rate of inversion was 86% for **3 a** and 94% for **4 a** in the presence of 1 eq. of $CaCO_3$ (entries 1 and 4). As the amount of $CaCO_3$ decreased, the rate of inversion decreased. In the absence of $CaCO_3$, the rate of inversion was 72% for **3 a** and 91% for **4 a** (entries 3 and 6). This tendency may be due to the larger contribution of S_N1 reaction as the reaction mixture becomes acidic. Thus, it was found that (S)-**2 a** can be obtained from (R)-**2 a** via S_N2 type hydrolysis of nitrate **3 a** and mesylate **4 a** under neutral or acidic conditions.

Next, the hydrolysis of (S)-acetate (S)-**1 a** under acidic conditions was investigated (Scheme 3). The results are summarized in Table II. Both aqueous H_2SO_4 and HNO_3 gave (S)-**2 a** quantitatively with retention of

Table I. Hydrolysis of Esters (3a–5a) [a]

Entry	Substrate	$CaCO_3$ for Neutralization (eq.)	Yield of 2a [b] (%)	Isomer Ratio [c] (R)-2a : (S)-2a
1	**3a**	1	85	14 : 86
2		0.2	84	19 : 81
3		—	90	28 : 72
4	**4a**	1	92	6 : 94
5		0.2	95	7 : 93
6		—	90	9 : 91
7	**5a**	0.2	99	98 : 2

[a]The esters (**3a-5a**) were prepared by using 10 mmol of (R)-**2a**, and the crude esters were hydrolyzed at 85 °C for 4 h in 30 mL of water. [b]Determined by GC (OV-101). [c]Determined by HPLC (Sumipax OA-4100).

Table II. Hydrolysis of (S)-Acetate ((S)-1a) [a]

Entry	Aq. Acid	Temp. (°C)	Time (h)	Yield of 2a [b] (%)	Isomer Ratio [c] (R)-2a : (S)-2a
1	2.5% H_2SO_4	80	3	96	0.7 : 99.3
2	2.5% HNO_3	80	1.5	100	0.8 : 99.2

[a]The hydrolysis was carried out on a 10 mmol scale in 30 mL of aqueous acid. [b]Determined by GC (OV-101). [c]Determined by HPLC (Sumipax OA-4100).

Scheme 3

configuration, the rate of retention being over 99% in both cases. Thus, it was confirmed that (S)-acetate (S)-**1 a** is hydrolyzed under acidic conditions to afford (S)-alcohol (S)-**2 a** with retention.

Thus, the method to prepare the desired (S)-alcohol (S)-**2** starting from the corresponding racemic acetate (±)-**1** in high chemical and optical yields has fallen into our hands.

Combination of Enzymatic Hydrolysis, Mesylation or Nitration, and Chemical Hydrolysis with Inversion

Our methodology to prepare (S)-alcohol (S)-**2** from the corresponding racemic acetate (±)-**1** was proved to be realized as follows. A crude mixture of (R)-alcohol (R)-**2** and (S)-acetate (S)-**1** obtained by the enzymatic hydrolysis of (±)-**1** was esterified with fuming HNO_3 or MsCl. Successively, a resultant crude mixture of the corresponding (R)-nitrate **3** or (R)-mesylate **4** and (S)-**1** was hydrolyzed to afford (S)-**2**, with inversion of **3** or **4** and retention of (S)-**1**. Several kinds of racemic acetates were employed for tests of the method, such as acetates of 4-hydroxy-2-cyclopenten-1-ones (**1 a** and **1 b**), aliphatic alcohols (**1 c** and **1 d**), allylic alcohol (**1 e**) and benzyl alcohol (**1 f**). An appropriate lipase was employed for enzymatic hydrolysis, and appropriate conditions for chemical hydrolysis were chosen, depending on substrates.

The enzymatic hydrolysis was carried out at 40 °C in 5% aq. KH_2PO_4 (pH 6) by using *Arthrobacter* or *Pseudomonas* lipase. The yields of hydrolyzed (R)-alcohol (R)-**2** and remaining (S)-acetate (S)-**1** were determined by GC analysis, and the enantiomeric excess (ee) of (R)-**2** was determined by HPLC analysis.[5] The ee of (S)-**1** was not determined. The results are summarized in Table III. *Arthrobacter* lipase exihibited high enantioselectivities for hydrolysis of racemic acetates ((±)-**1 a**, (±)-**1 b** and (±)-**1 f**) to give (R)-alcohols ((R)-**2 a**, (R)-**2 b** and (R)-**2 f**, respectively) in high optical yields (entries 1, 2 and 8). On the other hand, *Pseudomonas* lipase hydrolyzed (±)-**1 d** and (±)-**1 e** with high enantioselectivities to afford (R)-**2 d** and (R)-**2 e**, respectively (entries 5 and 7). In case of (±)-**1 c**, moderate ee of (R)-**2 c** was obtained (entry 3), which may be due that n-hexyl group of (±)-**1 c** is a flexible straight carbon-chain, and consequently is not recognized as a larger group than methyl group by the enzyme.

The crude mixture of (R)-**2** and (S)-**1** obtained by the enzymatic hydrolysis of (±)-**1** was esterified with fuming HNO_3 or MsCl, and without purification, the crude mixture of **3** or **4** and (S)-**1** was hydrolyzed under an appropriate condition. The crude product (S)-**2** was isolated by column chromatography on silica gel, and the ee was determined by HPLC analysis as mentioned above (Table IV).[5]

High optical and chemical yields were performed in cases of 4-hydroxy-2-cyclopenten-1-ones. Namely, (S)-**2 a** of 90%ee and 82%ee were obtained in 82% and 74% yields (based on (±)-**1 a**) by both mesylation and

Table III. Enzymatic Hydrolysis[a]

Entry	Substrate	Lipase (g)	Time / h	Yield[b] (R)-**2** / % (%ee)[c]	Yield[b] (S)-**1** / %[d]
1	(±)-**1a**	*Arthrobacter* (0.122)	17	50 (100.0)	50
2	(±)-**1b**	*Arthrobacter* (0.122)	17	43 (98.4)	53
3	(±)-**1c**	*Arthrobacter* (0.122)	39	50 (42.0)	46
4	(±)-**1d**	*Arthrobacter* (0.600)	24	28 (91.0)	72
5		*Pseudomonas* (0.600)	24	50 (97.4)	48
6	(±)-**1e**	*Arthrobacter* (2.00)	50	56 (74.0)	38
7		*Pseudomonas* (2.00)	50	52 (76.0)	39
8	(±)-**1f**	*Arthrobacter* (0.122)	44	43 (98.0)	53

[a]The enzymatic hydrolysis was carried out at 40 °C in 180 mL of 5% aq. KH_2PO_4 by using 20 g of a racemic acetate (±)-**1**. [b]Determind by GC analysis (OV-101). [c]The optical purity (ee) of (R)-**2** was determined by HPLC analysis (Sumipax OA-4100 for entries 1 and 2, OA-4000 (R) for entry 3, OA-1000 for entries 4 and 5, OA-2100 for entries 6 and 7, OA-2500I for entry 8). [d]The ee of (S)-**1** was not determined.

nitration, followed by hydrolysis under neutral condition (method A : at 85 °C in the presence of 1 eq. of $CaCO_3$) (entries 1 and 2). Similarly, (S)-**2b** of high ee was obtained in a reasonable yield via mesylation as well as nitration (entries 3 and 4). As an example of preparation of aliphatic alcohol, the crude mixture of (R)-**2d** and (S)-**1d** was used to find that a route via mesylation gave (S)-**2d** of high ee (93%ee and 83%ee, entries 5 and 6). In this route, two kinds of hydrolysis conditions (method B and C) were adopted in order to avoid elimination of mesylate (**4d**). In method B, hydrolysis was carried out stepwise at room temperature, that is, mesylate **4d** was first hydrolyzed in the presence of NaOAc under a neutral condition, followed by successive hydrolysis of resulting acetate (S)-**1d** in the presence of K_2CO_3 under a basic condition. In method C, hydrolysis was carried out at 80 °C in 2.5% aq. H_2SO_4. As an example of preparation of allylic (S)-alcohol, the crude mixture of (R)-**2e** and (S)-**1e** was employed for mesylation followed by hydrolysis. However, an isomerized alcohol was obtained from mesylate **4e** under any hydrolysis conditions examined (see Scheme 4). Finally, preparation of

Scheme 4

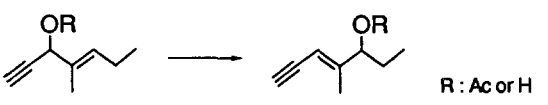


Table IV. Chemical Transformations of Mixture of (R)-2 and (S)-1 Obtained by Enzymatic Hydrolysis[a]

Entry	Starting Material	Reagent for Esterification	Method for Hydrolysis[b]	Yield of ((S)-**2** + (R)-**2**) / %[c]	Optical Yield of (S)-**2** / %ee[d]	$[\alpha]_D^{25}$
1	(±)-**1a**	MsCl	A	82	90.0	+19.2° (c 1.14, $CHCl_3$)
2		HNO_3	A	74	82.0	+17.7° (c 1.25, $CHCl_3$)
3	(±)-**1b**	MsCl	A	80	78.8	+11.9° (c 1.01, $CHCl_3$)
4		HNO_3	A	61	86.0	+13.0° (c 1.00, $CHCl_3$)
5	(±)-**1d**	MsCl	B	63	93.0	+16.6° (c 2.38, $CHCl_3$)
6		MsCl	C	64	83.0	+13.9° (c 2.07, $CHCl_3$)
7	(±)-**1e**	MsCl	A	isomerization	—	———
8		MsCl	B	isomerization	—	———
9	(±)-**1f**	MsCl	B	80	50.2	−27.5° (c 2.59, $CHCl_3$)
10		MsCl	C	17	1.1	———
11		HNO_3	B	79	67.2	−35.1° (c 3.10, $CHCl_3$)

[a]A crude mixture of (R)-**2** and (S)-**1** obtained by enzymatic hydrolysis (Table III) was esterified with MsCl or HNO_3, and successively hydrolyzed. The crude mixture (entry 5, Table III) was employed for entries 5 and 6, and the crude mixture (entry 7, Table III) was used for entries 7 and 8. [b]Method A : at 85 °C under neutral condition (1 eq. of $CaCO_3$). Method B : at room temperature, under neutral (NaOAc) and successively basic (K_2CO_3) conditions. Method C : 80 °C under acidic condition (2.5% aq. H_2SO_4). [c] Isolated yield based on the corresponding racemic acetate (±)-**1**. [d]Determined by HPLC analysis (see Table III).

(S)-benzyl alcohol was tested by using the crude mixture of (R)-**2f** and (S)-**1f**. Although a route via mesylation afforded (S)-**2f** of a low ee (50.2%ee, entry 9), the other route via nitration gave (S)-**2f** in an improved optical yield (67.2%ee entry 11). In both cases, hydrolysis was carried out by method B in order to avoid elimination and SN1 reaction. In fact, the reaction under an acidic condition gave essentially racemic alcohol, 1.1%ee (S)-**2f**, in 17% yield (entry 10).

Thus, our methodology was proved to be useful for preparation of (S)-alcohol from the corresponding racemic acetate with a high enantioselectivity in a high chemical yield, except for preparation of allylic alcohol.

Alternative Method by Mitsunobu Reaction

As an alternative to the method mentioned above, the adaptation of Mitsunobu reaction[6] was examined

(Scheme 1-**b**). The crude mixture of (R)-**2** and (S)-**1** obtained by the enzymatic hydrolysis (the same crude mixture as shown in Table III) was subjected to Mitsunobu reaction by using acetic acid, triphenylphosphine and diethyl azodicarboxylate. Without purification, the crude product was hydrolyzed under an appropriate condition. After purification by column chromatography on silica gel, the optical purity of (S)-**2** was determined by HPLC analysis (see Table III).[5] The results are shown in Table V. By combination of Mitsunobu reaction and successive hydrolysis under acidic conditions (at 80 °C in 2.5% aq. H_2SO_4), (S)-**2a** of 93.6%ee was obtained in 90% yield (entry 1). By switching the hydrolysis condition, from acidic to basic (at room temperature in the presence of K_2CO_3), (S)-**2d** of 94.6%ee and (S)-**2f** of 92.8%ee were also obtained in high yields (entries 2 and 4). Considering the facts that the chemical yield of (S)-**2d** and the optical yield of (S)-**2f** are improved drastically compared with the results obtained by the method via mesylation or nitration (see Table IV), the method via Mitsunobu reaction is preferable when there are possibilities of side-reactions such as elimination mentioned above. With regard to preparation of (S)-**2e**, we are still unsuccessful in getting a desired product because of isomerization, that is, an isomerized acetate was obtained as a major product by Mitsunobu reaction (see Scheme 4).

Table V. Mitsunobu Reaction of Mixture of (R)-2 and (S)-1 Obtained by Enzymatic Hydrolysis[a]

Entry	Starting Material	Yield of ((S)-**2** + (R)-**2**) / %[b]	Optical Yield of (S)-**2** / %ee[c]	$[\alpha]_D^{25}$
1	(±)-**1a**	90	93.6	+20.2° (c1.50, $CHCl_3$)
2	(±)-**1d**	96	94.6	+17.1° (c2.38, $CHCl_3$)
3	(±)-**1e**	isomerization	—	———
4	(±)-**1f**	84	92.8	−51.2° (c2.08, $CHCl_3$)

[a]A crude mixture of (R)-**2** and (S)-**1** obtained by enzymatic hydrolysis (Table III) was subjected to Mitsunobu reaction, and successively hydrolyzed. The crude mixture (entries 5 and 7, Table III) was used for entries 2 and 3, respectively. [b]Isolated yield based on (±)-**1**. [c]Determined by HPLC analysis (see Table III).

Conclusion

Various kinds of optically active secondary (S)-alcohols were prepared from the corresponding racemic acetate in high chemical and optical yields, by combination of enzymatic hydrolysis and chemical transformation, such as, mesylation or nitration followed by hydrolysis with inversion, or Mistunobu reaction. Further, these methods should be more useful by choosing an appropriate enzyme and an appropriate condition for hydrolysis.

A further study on another method is in progress, and will be published in the near future.

Experimental Section

General Procedures. Melting points are uncorrected. Optical rotations were taken on a JASCO DIP-140 digital polarimeter. ^{1}H NMR and ^{13}C NMR spectra were obtained at 60 MHz on a Hitachi R-24B and at 67.5 MHz on a JEOL JNM-270J, respectively. IR spectra were obtained on a Hitachi 260–10. High-resolution mass spectra (HRMS) were obtained on a Hitach M-80B under electron impact condition. HPLC were recorded on a Shimadzu LC-6A and GC were recorded on a Shimadzu CR-1A. *Arthrobacter* lipase (Shinnihon Chemical Co., Ltd.) and *Pseudomonas* lipase (Amano Pharmaceutical Co., Ltd.) were used for enzymatic hydrolysis. Other solvents and chemicals were used without purification.

Enzymatic Hydrolysis of (±)-4-Acetoxy-3-methyl-2-(2-propynyl)-2-cyclopenten-1-one ((±)-1 a). To a solution of 1 g of *Arthrobacter* lipase in 120 mL of 0.2M KH_2PO_4 was added 30 g (156 mmol) of (±)-**1 a**. The reaction mixture was adjusted to pH 6 and warmed to 40 °C. Vigorous stirring was continued at 40 °C for 17 h. After extraction with EtOAc (50 mL × 3), the organic phase was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (30% EtOAc in hexane) to give 10.8 g (46%) of (R)-**2 a** as pale yellow crystals : mp 43～5 °C ; $[\alpha]_D^{25}$ –21.6° (c 1.47, $CHCl_3$) [lit. (for (R)-**2 a** of 89.6%ee)[7] $[\alpha]_D^{23}$ –19.5° (c 1.42, $CHCl_3$)] ; IR (nujol) 3350, 3270, 2900, 1690, 1640, 1460, 1375 cm^{-1} ; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.98 (t, J=3 Hz, 1 H), 2.20 (s, 3H), 2.25 (dd, J=3, 18 Hz, 1H), 2.85 (dd, J=6, 18 Hz, 1H), 3.07 (d, J=3 Hz, 2H), 3.72 (br.s, 1H), 4.72 (br.d, J=6 Hz, 1H) ; ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 12.17, 13.85, 43.80, 68.80, 71.15, 79.51, 135.97, 172.00, 204.30. Similarly, chromatography on silica gel gave 13.9 g (46%) of (S)-**1 a** as white crystals : mp 45–6 °C ; $[\alpha]_D^{25}$ +39.4° (c 1.25, $CHCl_3$) [lit.[7] $[\alpha]_D^{20}$

+39.4° (c 1.25, $CHCl_3$)] ; IR (nujol) 3250, 2900, 1710, 1660, 1460, 1375, 1240 cm^{-1} ; ^1H NMR(60MHz,$CDCl_3$) δ 1.99 (t, J=3 Hz, 1H), 2.09 (s, 3H), 2.14 (s, 3H), 2.21 (dd, J=3, 18 Hz, 1H), 2.90 (dd, J=6, 18 Hz, 1H), 3.14 (d, J=3 Hz, 2H), 5.65 (br.d, J=6 Hz, 1H) ; ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 12.23, 13.93, 20.66, 41.17, 68.92, 72.65, 79.14, 138.17, 166.51, 170.44, 202.02. The absolute configurations of (R)-**2 a** and (S)-**1 a** have already been determined.[2,4]

(R)-2-Methyl-4-oxo-3-(2-propynyl)cyclopent-2-enyl nitrate (3 a). To 3.1 g (30 mmol) of acetic anhydride was added dropwise 1.05 g (15 mmol) of fuming HNO_3 (90%) at 0 °C. After stirring for 0.5 h, 1.5 g (10 mmol) of (R)-**2 a** obtained above was added to the solution, and the reaction mixture was kept at 0 °C for 1 h. The reaction mixture was poured into 30 mL of cold water, and extracted with toluene. The organic phase was washed with 5% aq. $NaHCO_3$ and water , and concentrated *in vacuo* to give 1.90 g (97%) of crude **3 a**. The crude product was employed for the next hydrolysis without purification.

For analysis, a small portion of the crude product was purified by column chromatography on silica gel (30% EtOAc in hexane) to give **3 a** as a pale yellow oil : $[\alpha]_D^{25}$ –103.1° (c 1.41, $CHCl_3$) ; IR (neat) 3290, 2120, 1715, 1650, 1630, 1280 cm^{-1} ; ^1H NMR (60 MHz, $CDCl_3$) δ 2.04 (t, J=3 Hz, 1H), 2.26 (s, 3H), 2.48 (dd, J=2, 18 Hz, 1H), 3.06 (dd, J=6, 18 Hz, 1H), 3.19 (d, J=3 Hz, 2H), 5.90 (br.d, J=6 Hz, 1H) ; MS m/e (rel intens) 195 (M^+, 18), 149 (45), 133 (43), 91 (51), 77 (100) ; HRMS for $C_9H_9NO_4$ (M^+), calcd 195.0530, found 195.0502.

(R)-2-Methyl-4-oxo-3-(2-propynyl)cyclopent-2-enyl mesylate (4 a). To a solution of 1.5 g (10 mmol) of (R)-**2 a** obtained above in 6 mL of acetone was added successively 0.65 g (13.5 mmol) of triethylamine and 0.62 g (11.5 mmol) of MsCl at –15 °C. After stirring at –15 °C for 2 h, the reaction mixture was poured into 30 mL of 1% aq. HCl, and extracted with dichloromethane. The organic phase was washed with water, and concentrated *in vacuo* to give 2.22 g (97%) of crude **4 a**. The crude product was used for the next hydrolysis without purification.

For analysis, a small portion of the crude product was purified by column chromatography on silica gel (50% EtOAc in hexane) to give **4 a** as yellow crystals : mp 75~6°C ; $[\alpha]_D^{23}$ –18.6° (c 1.25, $CHCl_3$) ; IR (nujol) 3280, 2120, 1700, 1650, 1350, 1170 cm^{-1} ; ^1H NMR (60 MHz, $CDCl_3$) δ 2.03 (t, J=3 Hz, 1H), 2.26 (s, 3H), 2.54 (dd, J=6, 18 Hz, 1H), 2.99 (dd, J=6, 18 Hz, 1H), 3.11 (s, 3H), 3.17 (d, J=3 Hz, 2H), 5.60 (br.d, J=6 Hz, 1H) ; MS m/e (rel intens) 228 (M^+, 20), 149 (23), 132 (100), 104 (69), 77 (100) ; HRMS for $C_{10}H_{12}O_4S$ (M^+), calcd 228.0455, found 228.0457.

(R)-2-Methyl-4-oxo-3-(2-propynyl)cyclopent-2-enyl borate (5 a). Azeotropic distillation was carried out by using 1.5 g (10 mmol) of (R)-**2 a** obtained above and 0.71 g (11.5 mmol) of boric acid in benzene. The reaction mixture was washed sequentially with water, 5% aq. $NaHCO_3$ and water, and concentrated *in vacuo* to give crude **5 a** (100%). The crude product was employed for the next hydrolysis without purification.

General Procedure for Hydrolysis of Esters (3 a – 5 a). The crude ester obtained above was hydrolyzed in 30 mL of water in the presence of an appropriate amount of $CaCO_3$ at 85 °C over 4 h. After neutralization with aq. $NaHCO_3$ and extraction with EtOAc, the organic phase was concentrated *in vacuo*. The yield of the resulting alcohol was determined by GC analysis (OV-101). The enantiomeric ratio ((R)-**2 a** : (S)-**2 a**) was determined by HPLC analysis (column, Sumipax OA-4100 ; eluent , hexane / 1,2-dichloroethane / ethanol = 800 / 100 / 10 ; flow rate, 1.0 mL / min ; detection, 254 nm light).

Acidic Hydrolysis of (S)-4-Acetoxy-3-methyl-2-(2-propynyl)-2-cyclopenten-1-one ((S)-1 a). 1.92 g (10 mmol) of (S)-**1 a** was heated in 30 mL of 2.5% aq. H_2SO_4 at 80 °C over 3 h. After neutralization with aq. $NaHCO_3$ and extraction with EtOAc, the organic phase was concentrated *in vacuo*. The yield and isomeric ratio of the resulting alcohols were determined in the same manner as described above.

Preparation of (S)-Alcohol (S)-2 from Corresponding Racemic Acetate (±)-1 via Mesylate 4.

(S)-4-Hydroxy-3-methyl-2-(2-propynyl)-2-cyclopenten-1-one ((S)-2 a). To a solution of 0.122 g of *Arthrobacter* lipase in 180 mL of 5% aq. KH_2PO_4 was added 20 g (104 mmol) of a racemic acetate (±)-**1 a**. The reaction mixture was warmed to 40 °C and vigorous stirring was continued at 40 °C for 17 h. After extraction with EtOAc, the organic phase was concentrated *in vacuo* to give 18.2 g of a crude mixture of (R)-**2 a** and (S)-**1 a** in 50% and 50% yields, respectively, which were determined by GC analysis (OV-101). The optical purity (ee) of (R)-**2 a** was found to be 100%ee, which was determined by HPLC analysis (column, Sumipax OA-4100 ; eluent, hexane / 1,2-dichloroethane / ethanol = 800 / 100 / 10 ; flow rate, 1.0 mL / min ; detection, 254 nm light). The ee of (S)-**1 a** was not determined.

2.5 g of the crude mixture obtained above and 1.06 g (9.25 mmol) of MsCl were dissolved in 10 mL of ether. To the solution was added 0.93 g (9.19 mmol) of triethylamine in 5 mL of ether stirring at 0 °C over 10 min, and the stirring was continued for 2 h at the same temperature. The reaction mixture was washed with 1% aq. HCl, and the aqueous phase was extracted with ether. The combined organic phase was washed with water,

and concentrated *in vacuo* to give a crude mixture of **4a** and (S)-**1a**.

The whole amount of the crude mixture obtained above was heated in 45 mL of water in the presence of 0.35 g (3.5 mmol) of $CaCO_3$ at 85 °C over 4 h. After neutralization with aq. $NaHCO_3$ and extraction with EtOAc, the organic phase was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (25～50% ether in hexane) to give 1.76 g (82% based on (±)-**1a**) of 90%ee (S)-**2a** as pale yellow crystals : mp 43～5 °C $[\alpha]_D^{25}$ +19.2 (c 1.14, $CHCl_3$) [lit.[8] $[\alpha]_D^{21}$ +22.4° (c 0.50, $CHCl_3$)] ; IR (nujol) 3350, 3270, 2900, 1690, 1640, 1460, 1375 cm^{-1} ; ^1H NMR (60 MHz, $CDCl_3$) δ 1.98 (t, J=3 Hz, 1H), 2.20 (s, 3H), 2.25 (dd, J=3, 18 Hz, 1H), 2.85 (dd, J=6, 18 Hz, 1H), 3.07 (d, J=3 Hz, 2H), 3.72 (br.s, 1H), 4.72 (br.d, J=6 Hz, 1H)

The ee of (S)-**2a** was determined by HPLC analysis as described above. The ^1H NMR and IR spectra of (S)-**2a** were identical with those of an authentic sample. The absolute configuration of (S)-**2a** has already been determined.[2]

(S)-4-Hydroxy-3-methyl-2-(2-propenyl)-2-cyclopenten-1-one ((S)-2b). The same procedure mentioned above was carried out on the same scale to give (S)-**2b** of 78.8%ee in 80% yield (based on (±)-**1b**) as a clear oil : bp 101～3 °C / 0.2 mmHg ; $[\alpha]_D^{25}$ +11.9° (c 1.01, $CHCl_3$) [lit.[9] $[\alpha]_D^{20}$ +15.0° (c 1.00, $CHCl_3$)] ; IR (neat) 3350, 2970, 2900, 1675, 1630, 1420, 1380, 1340, 1300, 1185 cm^{-1} ; ^1H NMR (60 MHz, $CDCl_3$) δ 2.09 (s, 3H), 2.39 (dd, J=3, 18 Hz, 1H), 2.62 (dd, J=6, 18 Hz, 1H), 2.91 (d, J=6 Hz, 2H), 3.90 (br.s, 1H), 4.66 (br.s, 1H), 4.91 (dd, J=1, 17 Hz, 1H), 4.96 (dd, J=1, 10 Hz, 1H), 5.62 (ddt, J=10, 17, 6 Hz, 1H). The ^1H NMR and IR spectra of (S)-**2b** were identical with those of an authentic sample. The absolute configuration of (S)-**2b** has already been determined.[2]

Hydrolysis of (±)-2-Octanol. Enzymatic hydrolysis of a racemic acetate (±)-**1c** was carried out on the same scale in the same manner given for (±)-**1a** to afford 17.4 g of a crude mixture of (R)-**2c** and (S)-**1c** in 50% and 46% yields, respectively, which were determined by GC analysis (OV-101). The ee of (R)-**2c** was determined to be 42.0%ee by HPLC analysis as a derivative of 3,5-dinitrophenyl isocyanate (**3,5-DNPI**) (column, Sumipax OA-4000 (R) ; eluent, hexane / 1,2-dichloroethane / ethanol = 100 / 20 / 1 ; flow rate, 1.0 mL / min ; detection, 254 nm light). The following procedure was not carried out because of low ee of (R)-**2c**.

(S)-1-(4-Phenoxyphenoxy)-2-propanol ((S)-2d). To a solution of 0.6 g of *Pseudomonas* lipase in 180 mL of 5% aq. KH_2PO_4 was added 20 g (69.4 mmol) of racemic acetate (±)-**1d**. The reaction mixture was stirred at 40 °C for 24 h. After extraction with CH_2Cl_2, the organic phase was concentrated *in vacuo* to give 18.2 g of a crude mixture of (R)-**2d** and (S)-**1d** in 50% and 48% yields, respectively, which was determined by GC analysis (OV-101). The ee of (R)-**2d** was determined to be 97.4%ee by HPLC analysis as a derivative of **3,5-**

DNPI (column, Sumipax OA-1000 ; eluent, hexane / 1,2-dichloroethane / ethanol = 100 / 100 / 1 ; flow rate, 0.8 mL / min ; detection, 254 nm light). The ee of (S)-**1 d** was not determined.

To 10 mL of ether were added 2.67 g of the crude mixture obtained above and 0.86 g (7.51 mmol) of MsCl. To this solution was added 0.77 g (7.61 mmol) of triethylamine in 5 mL of ether stirring at 0 °C over 10 min, and the stirring was continued at room temperature for 1.5 h. The reaction mixture was washed with 1% aq. HCl, and aqueous phase was extracted with ether. The combined organic phase was washed with water, and concentrated *in vacuo* to give a crude mixture of **4 d** and (S)-**1 d**.

The whole amount of the crude mixture obtained above was hydrolyzed in 35 mL of 50% aq. 1,4-dioxane in the presence of 2.1 g (25.6 mmol) of NaOAc at room temperature over 14 h. Then, 2.78 g (20.1 mmol) of K_2CO_3 and 20 mL of methanol were added, and the stirring was continued at room temperature for 21 h. After neutralization with 10% aq. HCl and extraction with EtOAc, the combined organic phase was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (25～50% ether in hexane) to give 1.57 g (63% based on (±)-**1 d**) of 93%ee (S)-**2 d** as white crystals : mp 71～2 °C ; $[\alpha]_D^{25}$ +16.6° (c 2.38, $CHCl_3$) [lit.[10] $[\alpha]_D^{23}$ +18.5° (c 1.00, $CHCl_3$)] ; IR (nujol) 3380, 2900, 1500, 1460, 1375, 1220, 1100, 830, 770 cm^{-1} ; ^1H NMR (60 MHz, $CDCl_3$) δ 1.10 (d, J=6 Hz, 3H), 2.63 (br.s, 1H), 3.61 (dd, J=3, 11 Hz, 1H), 3.65 (dd, J=6, 11 Hz, 1H) 3.6～4.4 (m, 1H), 6.65 (br.s, 4H), 6.5～7.1 (m, 5H). The ee of (S)-**2 d** was determined by HPLC analysis as described above. The ^1H NMR and IR spectra of (S)-**2 d** were identical with those of an authentic sample. The absolute configuration of (S)-**2 d** has already been determined.[3]

(E, S)-1-Ethynyl-2-methyl-2-penten-1-ol ((S)-2 e). Enzymatic hydrolysis of a racemic acetate (±)-**1 e** was carried out on the same scale in the same manner as preparation of (S)-**2 d** to give 15.7 g of a crude mixture of (R)-**2 e** and (S)-**1 e** in 52% and 39% yields, respectively, which were determined by GC analysis (OV-101). The ee of (R)-**2 e** was determined to be 76%ee by HPLC analysis as a derivative of **3,5-DNPI** (column, Sumipax OA-2100 ; eluent, hexane / 1,2-dichloroethane / ethanol = 800 / 100 / 10 ; flow rate, 1.0 mL / min ; detection, 254 nm light). The ee of (S)-**1 e** was not determined. The same mesylation and hydrolysis as those for preparation of (S)-**2 d** afforded an isomerized alcohol, 5-ethynyl-4-methyl-4-penten-3-ol, as a major product ; for the crude product, ^1H NMR (60 MHz, $CDCl_3$) δ 0.90 (t, J=6 Hz, 3H), 1.57 (dq, J=7, 6 Hz, 2H), 1.89 (s, 3H), 2.14 (br.s, 1H), 3.07 (d, J=3 Hz, 1H), 3.99 (t, J=7 Hz, 1H) 5.52 (d, J=3 Hz, 1H).

Preparation of (S)-Alcohol (S)-2 from Corresponding Racemic Acetate (±)-1 via Nitrate 3.

(S)-1-Phenylethanol ((S)-2f). The same enzymatic hydrolysis as that of (±)-**1 a** was carried out by

using 20 g (122 mmol) of (±)-**1f** to give 17.2 g of a crude mixture of (R)-**2f** and (S)-**1f** in 43% and 53% yields, respectively, which were determined by GC analysis (OV-101). The ee of (R)-**2f** was determined to be 98%ee by HPLC analysis (column, Sumipax OA-2500I ; eluent, hexane / ethanol = 300 / 1 ; flow rate, 1.0 mL / min ; detection, 254 nm light).

To 1.54 g (15.1 mmol) of acetic anhydride at 0 °C was added dropwise 0.50 g (7.1 mmol) of fuming HNO_3 (90%). After stirring for 0.5 h, 1.41 g of the crude mixture of (R)-**2f** and (S)-**1f** obtained above was added to the solution, and the reaction mixture was kept at 0 °C for 1 h. The reaction mixture was poured into 15 mL of cold water, and extracted with ether. The organic phase was washed with 5% aq. $NaHCO_3$ and water, and concentrated *in vacuo* to give a crude mixture of **3f** and (S)-**1f**.

The crude mixture obtained above was employed for the hydrolysis which had already been described in preparation of (S)-**2d** via the mesylate. The crude product was purified by column chromatography on silica gel (25～50% ether in hexane) to give 0.96 g (79% based on (±)-**1f**) of 67.2%ee (S)-**2f** as a clear oil : $[\alpha]_D^{25}$ −35.1° (c 3.10, $CHCl_3$) , $[\alpha]_D^{25}$ −38.0° (c 4.92, MeOH) [lit.[11] $[\alpha]_D^{20}$ −45.5° (c 4.91, MeOH)] ; IR (neat) 3300, 3040, 1490, 1370, 1205, 1075, 1005, 895, 760 cm^{-1} ; ^1H NMR (60 MHz, $CDCl_3$) δ 1.45 (d, J=7 Hz, 3H), 2.45 (br.s, 1H), 4.75 (q, J=7 Hz, 1H), 7.30 (br.s, 5H).

The ee of (S)-**2f** was determined by HPLC analysis as described above. The ^1H NMR and IR spectra of (S)-**2f** were identical with those of an authentic sample.

Preparation of (S)-Alcohol (S)-2 from Corresponding Racemic Acetate (±)-1 via Mitsunobu Reaction.

(S)-2a. The crude mixture of (R)-**2a** and (S)-**1a** obtained by the enzymatic hydrolysis described above was subjected to Mitsunobu reaction. To a solution of 2.5 g of the crude mixture, 2.81 g (10.7 mmol) of triphenylphosphine and 0.56 g (9.33 mmol) of acetic acid in 50 mL of THF at room temperature over 30 min was added 1.87 g (10.7 mmol) of diethyl azodicarboxylate in 10 mL of THF. The reaction mixture was stirred at room temperature overnight. After concentration *in vacuo*, the crude product was heated in 50 mL of 2.5% aq. H_2SO_4 at 80 °C for 3 h. After neutralization with aq. $NaHCO_3$ and extraction with EtOAc, the organic phase was washed with water, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (30% EtOAc in hexane) to give 1.93 g (90% based on (±)-**1a**) of 93.6%ee (S)-**2a** as pale yellow crystals : mp 43～5 °C ; $[\alpha]_D^{25}$ +20.2° (c 1.50, $CHCl_3$) [lit.[8] $[\alpha]_D^{21}$ +22.4° (c 0.50, $CHCl_3$)]. The ^1H NMR spectrum of (S)-**2a** was identical with that of an authentic sample.

(S)-2d. The crude mixture of (R)-**2d** and (S)-**1d** obtained by the enzymatic hydrolysis mentioned above was subjected to Mitsunobu reaction. To a solution of 2.66 g of the crude mixture, 2.63 g (10 mmol) of triphenylphosphine and 0.63 g (10.5 mmol) of acetic acid in 20 mL of ether at room temperature over 45 min was added 1.76 g (10.1 mmol) of diethyl azodicarboxylate in 10 mL of ether. The reaction mixture was stirred at room temperature for 8 h. After concentration *in vacuo*, the crude product was heated in 50 mL of 80% aq. MeOH in the presence of 2.8 g (20.3 mmol) of K_2CO_3 at room temperature for 21 h. After neutralization with 10% aq. HCl and extraction with ether, the organic phase was washed with water, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (25～50% ether in hexane) to give 2.37 g (96% based on (±)-**1d**) of 94.6%ee (S)-**2d** as white crystals : mp 71～2 °C ; $[\alpha]_D^{25}$ +17.1° (c 2.38, $CHCl_3$) [lit.[10] $[\alpha]_D^{23}$ +18.5° (c 1.00, $CHCl_3$)]. The ^1H NMR spectrum of (S)-**2d** was identical with that of an authentic sample.

(S)-2e. The crude mixture of (R)-**2e** and (S)-**1e** obtained by the enzymatic hydrolysis mentioned above was subjected to Mitsunobu reaction in the same manner as preparation of (S)-**2d**. An isomerized acetate, 5-ethynyl-4-methyl-4-penten-3-yl acetate, was obtained as a major product ; for the crude product, ^1H NMR (60 MHz, $CDCl_3$) δ 0.89 (t, J=6 Hz, 3H), 1.67 (dq, J=7, 6 Hz, 2H), 1.91 (s, 3H), 2.07 (s, 3H), 3.13 (d, J=2 Hz, 1H), 5.16 (t, J=7 Hz, 1H), 5.54 (d, J=2 Hz, 1H).

(S)-2f. The procedure given for preparation of (S)-**2d** was carried out in the same manner to afford (S)-**2f** of 92.8%ee in 84% yield (based on (±)-**1f**) as a clear oil : $[\alpha]_D^{25}$ −51.2° (c 2.08, $CHCl_3$) [lit.[11] $[\alpha]_D^{20}$ −45.5° (c 4.91, MeOH)]. The ^1H NMR spectrum of (S)-**2f** was identical with that of an authentic sample.

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5. The absolute configurations of (S)-**2a**[2], (S)-**2b**[2], (S)-**2d**[3] and (S)-**2e**[2] have already been determined. Authentic samples of (S)-**2c** and (S)-**2f** are commercially available.
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