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Lipase-catalyzed kinetic resolution of 3-butyn-2-ol

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Abstract

Optically active 3-butyn-2-ol, an important building block, was synthesized successfully using lipase-catalyzed kinetic resolution. Starting from the thus obtained 3-butyn-2-ol, several 4-aryl-substituted compounds were synthesized enantioselectively. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

Optically active 1-alkyn-3-ol **1** is an important material as a chiral building block as shown in Scheme 1.[1–8] Several methods for obtaining optically active **1** have been reported: resolution of a diastereomeric ether,[9] chemical[10,11] and enzymatic[12] asymmetric reductions of the corresponding ketone, asymmetric transesterification of the racemic alcohol[13] and asymmetric hydrolysis of the corresponding ester using biocatalysts.[14] Although the enzymatic resolution of 1-alkyn-3-ol with a long alkyl chain is successful, this method is difficult to apply to short alkyl chain analogs such as 3-butyn-2-ol because of poor enantioselectivities. This compound is an important building block as illustrated by the synthesis of a sex pheromone from a male mountain pine beetle, *Dendroctonus brevicomis* (Scheme 2).[7]

We report here highly selective lipase-catalyzed kinetic resolution of **2** by transesterification. Two strategies were employed for obtaining optically active 3-butyn-2-ol by transesterification: reaction of racemic alcohol with vinyl decanoate or reaction of racemic ester of the alcohol with an alkanol. Several 4-aryl-substituted compounds have been synthesized from optically active 3-butyn-2-ol using a Pd–Cu catalyst.[11,15] These compounds are important chiral building blocks for natural products such as Fenleuton which is a second generation 5-lipoxygenase inhibitor (Scheme 3).[8]

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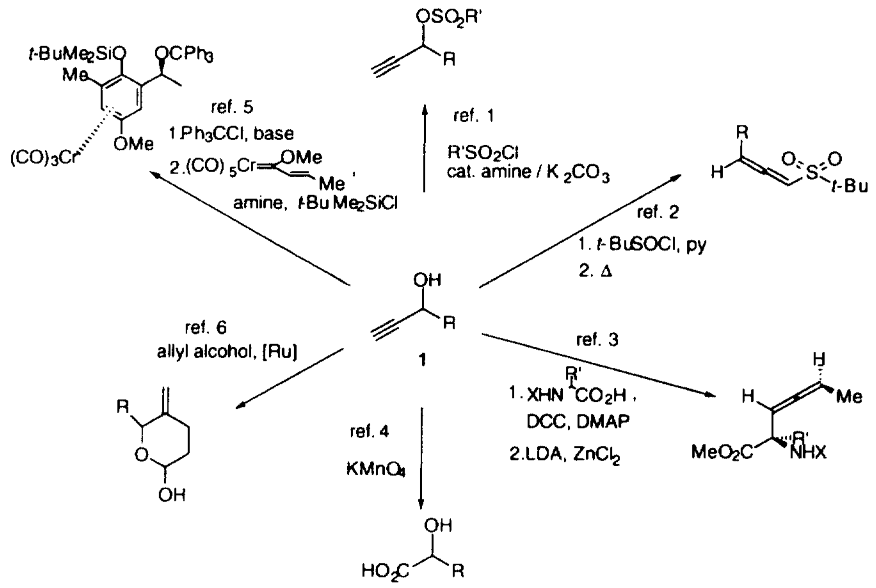
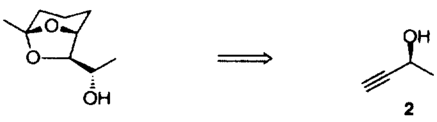
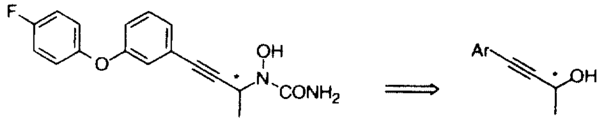


Scheme 1.



A volatile component from mountain pine beetle

Scheme 2.



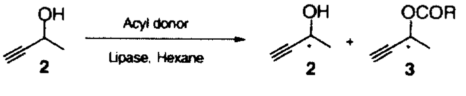
Fenleuton

Scheme 3.

2. Results and discussion

2.1. Reaction of racemic 3-butyn-2-ol with vinyl esters

Twenty-three lipases were subjected to an evaluation of selectivities in transesterification of **2** with vinyl acetate in hexane (Eq. 1). Results are summarized in Table 1. Most lipases (including a further 13 lipases which are not listed in Table 1) react selectively with the (*R*)-enantiomer while three lipases (LIP, LPL and OF) prefer to react with the (*S*)-enantiomer. Three lipases (Amano AK, AH and PS) were selected and employed for further studies, because they demonstrate relatively high selectivities and reactivities.



a : R = CH_3, **f** : R = C_9H_{19}
b : R = C_2H_5, **g** : R = CH_2Cl
c : R = C_3H_7, **h** : R = Ph
d : R = C_5H_{11}, **i** : R = $C(CH_3)_3$
e : R = C_7H_{15}, **j** : R = $(CH_2)_2CO_2H$

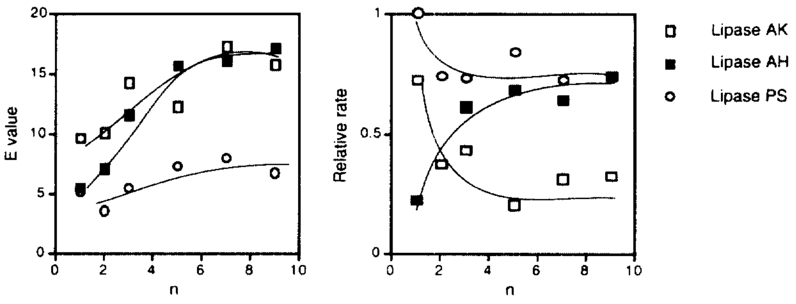
(1)

The length of the alkyl chain in an acyl donor greatly affects the enantioselectivity of transesterification as illustrated in Fig. 1 (AK, AH and PS). Selectivity (E value) increases as the number of carbon atoms

Table 1
Lipase-catalyzed transesterification of 3-butyn-2-ol **2** with vinyl acetates[a]

Lipase[b)]	Relative rate	E value	Reactive isomer
Amano AK	59	9.6	*R*
Amano AH	18	5.4	*R*
Amano PS	81	5.2	*R*
LIP	39	3.4	*S*
LPL	32	2.5	*S*
Novozym	100	1.5	*R*
QL	95	1.4	*R*
MY	20	1.3	*R*
OF	60	1.2	*S*
Amano F-AP	34	1.0	*R*

a) Reaction conditions : [**2**] = 72 mM, [lipase] = 5 mg, [vinyl acetate] = 0.58 M, [MS-4A] = 50 mg, [hexane] = 2 mL, stirred at 30 °C for 13 h. b) Origin : Amano AK ; *Pseudomonas fluorescens*, Amano AH ; *Pseudomonas cepacia*, Amano PS ; *Pseudomonas cepacia*, LIP ; *Pseudomonas aeruginosa*, LPL ; *Pseudomonas aeruginosa*, Novozym ; *Candida antarctica*, QL ; *Alcaligenes sp.*, MY ; *Candida rugosa*, OF ; *Candida rugosa*, Amano F-AP ; *Rhizopus javanicus*.



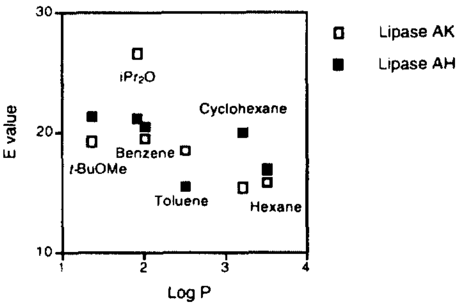
Reaction conditions : [**2**] = 72 mM, [lipase] = 5 mg, [vinyl carboxylate] = 0.58 M, [MS-4A] = 50 mg, [hexane] = 2 mL, stirred at 30 °C. E value was calculated from ee's of substrate remained and product.[16]

Figure 1. Effect of the length of carbon chain in acylating agent on selectivity in lipase-catalyzed transesterification of 3-butyn-2-ol **2**[16]

in the alkyl chain increases from acetyl (n=1) to hexanoyl (n=5) and becomes asymptotic at hexanoyl to decanoyl. The reaction rate of AH-catalyzed transesterification also increases with the increase in length of the alkyl chain in the acyl donor. In contrast, acetate reacts faster than hexanoate in the reactions of AK and PS.

The effect of solvent hydrophobicity on the selectivities of lipases AK and AH was investigated, employing vinyl decanoate as an acyl donor (Fig. 2). Transesterification in a hydrophobic solvent takes place faster than those in hydrophilic solvents (data not shown). Lipase AK shows high selectivity in diisopropyl ether but AH exerts no remarkable difference in the selectivity among the solvents tested.

The steric requirement of an acyl donor was tested. When vinyl chloroacetate is used as an acyl donor in hexane, both lipases AK and AH exert low selectivities. Bulky acylating agents such as vinyl benzoate and vinyl pivalate show poor reactivities. Succinic anhydride as an acyl donor affords high enantioselectivity in transesterification, both in diisopropyl ether and cyclohexane, as seen in Table 2.

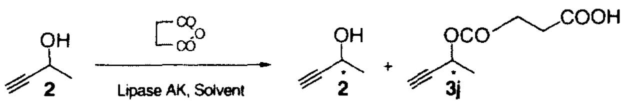


Reaction conditions : [2] = 72 mM, [lipase] = 5 mg, [vinyl decanoate] = 0.58 mM, [MS-4A] = 50 mg, [solvent] = 2 mL, stirred at 30 °C.
Log P : hydrophobicity parameter, logarithm of partition coefficient of a solvent between octanol and water.[17]

Figure 2. Correlation between hydrophobicity of solvent and E value[17]

Table 2

Lipase-catalyzed esterification of 3-butyn-2-ol **2** with succinic anhydride in various solvents[a]



Solvent	Time[b] / h	2 / %ee	3j / %ee	Conversion / %	E value
iPr$_2$O	8	91.1	72.9	55.0	19.8
Cyclohexane	48	87.7	76.3	53.5	21.1
Hexane	48	56.3	79.6	41.4	15.4
Benzene	24	94.8	65.3	59.2	16.8
CH$_2$Cl$_2$	48	83.1	67.1	55.3	1.9

a) Reaction conditions : [2] = 72 mM, [lipase AK] = 5 mg, [succinic anhydride] = 0.22 M, [MS-4A] = 50 mg, [solvent] = 2 mL, stirred at 30 °C. b) Reaction time.

Table 3 shows the effects of substrate concentration, amount of lipase and amount of vinyl decanoate on the enantioselectivity of the reaction. The selectivity is affected slightly by these factors. The conditions listed in entry 9 were employed for practical synthesis.

2.2. *Reaction of 3-decanoyl-1-butyne with an alkanol*

Two lipases, AH and AK, were used for alcoholysis of 3-decanoyloxy-1-butyne with propanol. Fig. 3 shows the solvent effect on the alcoholysis. In contrast to the reactions mentioned in the previous section, the enantioselectivity of the AH-catalyzed reaction is systematically affected by the solvent hydrophobicity and the lipase affords satisfactory selectivity with *t*-butyl methyl ether and diisopropyl ether, whereas selectivity of AK-catalyzed reactions are hardly affected by the difference in solvent hydrophobicity (E=7–11). Since the rate of alcoholysis is unaffected by the solvents of low hydrophobicity (Fig. 3), AH in *t*-butyl methyl ether was employed for experiments on a preparative scale.

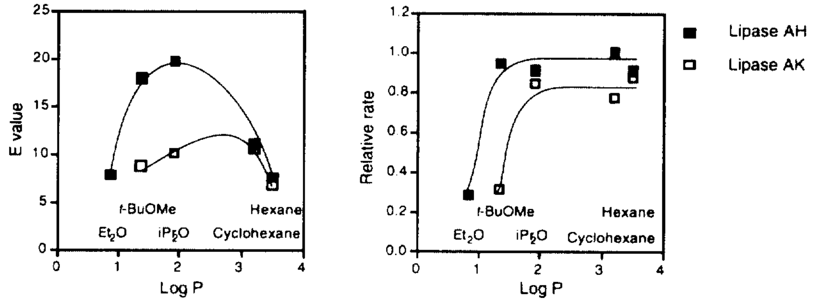
Table 4 demonstrates the effect of structure of alcohol on selectivity in alcoholysis. No remarkable difference in E value is seen except for when diethyl ether is the solvent. Practically, methanol in *t*-butyl methyl ether is the most preferable system, because the low boiling points of methanol and *t*-butyl methyl ether make it easy to retrieve **2** from the reaction mixture.

Table 5 shows the effects of substrate concentration and amount of lipase on the selectivity in the reaction. A high substrate concentration causes a slight decrease in enantioselectivity, and the amount of the lipase hardly influences the enantioselectivity.

Table 3
Effect of substrate concentration on lipase-catalyzed kinetic resolution of 3-butyn-2-ol **2**[a]

Entry	Substrate / mg	Lipase AK / mg	Vinyl decanoate / eq.	Time[b] / h	**2** / %ee	**3f** / %ee	Conversion / %	E value
1[c]	10	5	8	84	98.2	70.8	58.1	26.5
2	50	25	4	48	95.4	64.4	59.7	16.7
3	50	25	2	48	94.0	70.4	57.3	19.7
4	50	10	2	48	98.5	62.3	61.2	19.7
5	50	10	1.5	48	95.3	71.3	57.2	21.8
6	50	10	1	48	71.5	82.1	46.6	21.6
7	50	10	0.8	48	51.9	85.6	37.8[d]	21.6
8	100	20	1	24	67.6	80.1	45.8	18.2
9	200	40	1	24	78.9	79.6	50.0	21.0

a) Reaction conditions : [MS-4A] = 2.5 % (wt / v) , [diisopropyl ether] = 2 mL, stirred at 30 °C. b) Reaction time.
c) The same conditions as Fig. 2. d) No reaction proceeded further because no acyl donor remained at this moment.



Reaction conditions : [**3f**] = 23 mM, [lipase] = 20 mg, [PrOH] = 0.5 % (v / v), [solvent] = 2 mL, stirred at 30 °C for 24 h.

Figure 3. Effect of hydrophobicity of solvent on selectivity and relative rate

The enantioselectivity in methanolysis remains almost constant throughout the range of concentrations of methanol (0.5–25% (v/v)) studied. However, the reaction rate decreases as the concentration of methanol decreases.

2.3. *Isolation of chiral 3-butyn-2-ol*

For preparative purposes, racemic **2** was reacted with vinyl decanoate in diisopropyl ether under the catalysis by lipase AK. The reaction was quenched at 40 h, and (*R*)-**3f** in 82% ee was obtained in 30% chemical yield. The thus obtained (*R*)-**3f** was reacted with methanol in the presence of lipase AH in *t*-butyl methyl ether to isolate (*R*)-**2** in 96% ee with 64% chemical yield (Eq. 2).

Table 4
Lipase-catalyzed alcoholysis of 3-decanoyl-1-butyne **3f** with various alcohols[a]

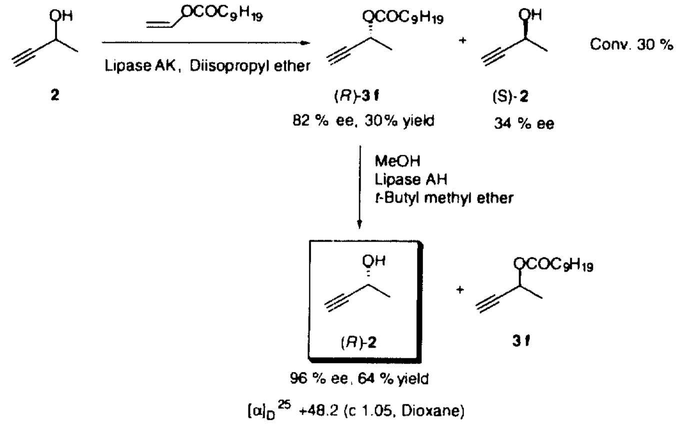
Solvent	R'OH	**3f** / % ee	**2** / % ee	Conv. / %	E value
Et_2O	MeOH	7.1	74.7	8.7	7.4
t-BuOMe	MeOH	65.9	82.1	44.5	20.1
iPr_2O	MeOH	82.9	73.8	52.9	16.9
iPr_2O	EtOH	87.4	74.5	54.0	19.2
iPr_2O	PrOH	85.8	75.8	53.1	19.7
iPr_2O	iPrOH	90.8	64.8	58.4	14.2
iPr_2O	BuOH	90.5	72.0	55.7	18.7
iPr_2O	*t*-BuOH	86.5	65.5	56.9	13.0

a) Reaction conditions : [**3f**] = 23 mM, [lipase AH] = 20 mg, [R'OH] = 0.5 % (v / v), [solvent] = 2 mL, stirred at 30 °C for 24 h.

Table 5
Lipase-catalyzed methanolysis of 3-decanoyloxy-1-butyne[a]

Substrate / mg	Lipase AH / mg	Time[b] / h	**3f** / % ee	**2** / % ee	Conversion / %	E value
10	20	24	65.9	82.1	44.5	20.1
100	200	24	72.3	77.4	48.3	16.8
100	100	48	81.2	74.1	52.3	16.6

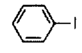
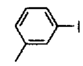
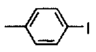
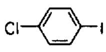
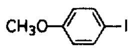
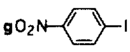
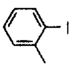
a) Reaction conditions : [**3f**] = 23 mM, [MeOH] = 0.5 % (v / v), [*t*-butyl methyl ether] = 2 mL, stirred at 30 °C.
b) Reaction time.



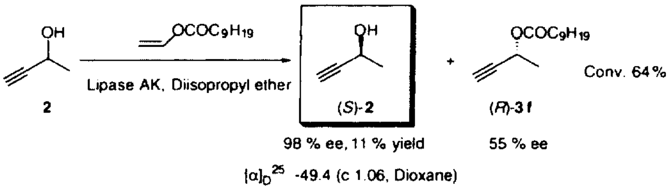
(2)

The antipode, (*S*)-**2**, was synthesized by AK-catalyzed transesterification of racemic **2** with vinyl decanoate. The reaction was quenched at 64% conversion (144 h) and (*S*)-**2** was obtained in 98% ee with 11% chemical yield (Eq. 3). Thus, both enantiomers of 3-butyn-2-ol were prepared in high ee.

Table 6
Syntheses of 4-aryl-3-butyn-2-ols[a]

Iodide		Config. / Yield / %	% ee[b)]	$[\alpha]_D^{25}$ (c 1.0, Et$_2$O)	Iodide		Config. / Yield / %	% ee[b)]	$[\alpha]_D^{25}$ (c 1.0, Et$_2$O)
4a		(*S*) / 84	97	−44.8[c)]	**4e**		(*S*) / 66[e)]	97	−41.3
4b		(*S*) / 62	97	−41.4	**4f**		(*R*) / 80	96	37.7
4c		(*S*) / 70	97	−35.1	**4g**		(*R*) / 80	96[f)]	37.5
4d		(*S*) / 45[d)]	97	−43.9					

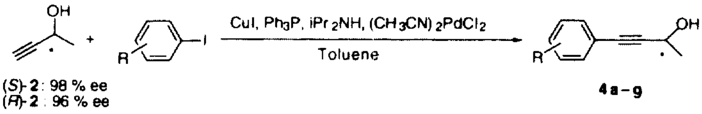
a) Reaction conditions : stirred at r.t. for 3 h. b) Determined by HPLC analysis (Chiralcel OD). c) Lit. for (*S*)-**4a** $[\alpha]_D^{25}$ −50.6° (c 1.475, Et$_2$O)[18]. d) Reaction time 24 h. e) Reaction time 12 h. f) Determined by HPLC analysis (Chiralpak AD).



(3)

2.4. Syntheses of chiral 4-aryl-3-butyn-2-ols

Several chiral 4-aryl-3-butyn-2-ols **4a–g** were synthesized from chiral 3-butyn-2-ol **2** which was obtained by lipase-catalyzed kinetic resolution. The Pd–Cu-catalyzed coupling reaction of chiral 3-butyn-2-ol (*S*: 98% ee and *R*: 96% ee) prepared according to Eqs. 2 and 3 with aryl iodides affords the desired product **4** successfully without loss of enantiomeric purity (Eq. 4). The results are listed in Table 6. Chemical yields of the products are satisfactory except for **4d**. The *ortho*-substituent seems to exert steric interference.



(4)

3. Experimental section

3.1. Instruments

Gas chromatographic analyses of ees of **2** and **3a–j** were performed using a Shimadzu GC-14A gas chromatograph with a Shimadzu C-R6A Chromatopac equipped with a chiral GC column (Chiraldex G-TA (Tokyo Kasei Kogyo Co., Ltd) or CP-Chirasil DEX-CB (Chrompack)). HPLC analyses of ees of **4a–g** were performed using a Hitachi 655 liquid chromatograph with a Hitachi D-2500 chromato-integrator and a spectrophotometer 852 III equipped with a chiral HPLC column (Chiralcel OD or Chiralpak AD (Daicel Chemical Ind., Ltd)). ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-

200 spectrometer. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. IR spectra were obtained from a JASCO FT/IR-5300. Elemental analyses were carried out with a Yanako MT-5 elemental analyzer. Melting points were measured using a Yanagimoto micromelting point apparatus and were uncorrected.

3.2. Materials

Lipases were supplied by Amano Pharmaceutical Co., Ltd. 3-Butyn-2-ol was purchased from Tokyo Kasei Kogyo Co., Ltd. Other materials were purchased from Nacalai Tesque, Inc., Tokyo Kasei Kogyo Co., Ltd, Wako Pure Chemical Industries, Ltd, and Aldrich Chemical Co., Inc. Solvents were dried over MS-4A before use.

*3.3. 3-Acetyloxy-1-butyne **3a***

Acetyl chloride (2.5 g, 31 mmol) was added to a pyridine (5 ml) solution of **2** (2.0 g, 29 mmol) at 0–5°C. The resulting mixture was stirred at room temperature for 2 h. Brine (30 ml) and then ether (30 ml) were added to the mixture. The organic phase was separated and washed with 5% aqueous HCl, saturated aqueous brine, saturated aqueous $NaHCO_3$, and saturated aqueous brine, successively. The organic phase was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified with silica gel column chromatography using hexane:dichloromethane (1:1) as an eluent to give a pale yellow oil. Yield 1.9 g (60%). 200 MHz ^1H NMR ($CDCl_3$) δ (ppm) 1.49 (3H, d, *J*=6.6 Hz), 2.07 (3H, s), 2.44 (1H, d, *J*=2.0 Hz) and 5.42 (1H, m). 50 MHz ^{13}C NMR ($CDCl_3$) δ (ppm) 169.8, 82.1, 72.8, 59.9, 21.1 and 21.0. IR (NaCl) ν=2122 and 1744 cm^{-1}. Anal. calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.07; H, 7.15.

*3.4. 3-Propionyloxy-1-butyne **3b***

Yield 3.3 g (61%). 200 MHz ^1H NMR ($CDCl_3$) δ (ppm) 1.16 (3H, t, *J*=7.5 Hz), 1.51 (3H, d, *J*=6.8 Hz), 2.36 (2H, q, *J*=7.6 Hz), 2.45 (1H, d, *J*=2.2 Hz) and 5.45 (1H, m). 50 MHz ^{13}C NMR ($CDCl_3$) δ (ppm) 173.3, 82.2, 72.7, 59.8, 27.5, 21.2 and 8.9. IR (NaCl) ν=2123 and 1744 cm^{-1}. Anal. calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.52; H, 8.15.

*3.5. 3-Butyryloxy-1-butyne **3c***

Yield 1.4 g (69%). 200 MHz ^1H NMR ($CDCl_3$) δ (ppm) 0.94 (3H, t, *J*=7.4 Hz), 1.49 (3H, d, *J*=6.6 Hz), 1.66 (2H, m), 2.30 (2H, t, *J*=7.5 Hz), 2.43 (1H, d, *J*=2.2 Hz) and 5.44 (1H, m). 50 MHz ^{13}C NMR ($CDCl_3$) δ (ppm) 172.3, 82.1, 72.6, 59.6, 36.0, 21.1, 18.2 and 13.4. IR (neat) ν=2124 and 1742 cm^{-1}. Anal. calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.34; H, 8.73.

*3.6. 3-Hexanoyloxy-1-butyne **3d***

Yield 1.6 g (81%). 200 MHz ^1H NMR ($CDCl_3$) δ (ppm) 0.88 (3H, br t), 1.29 (4H, m), 1.48 (3H, d, *J*=6.6 Hz), 1.61 (2H, m), 2.31 (2H, t, *J*=7.6 Hz), 2.43 (1H, d, *J*=2.2 Hz) and 5.43 (1H, m). 50 MHz ^{13}C NMR ($CDCl_3$) δ (ppm) 172.4, 82.1, 72.6, 59.6, 34.0, 31.1, 24.4, 22.2, 21.1 and 13.7. IR (neat) ν=2124 and 1742 cm^{-1}. Anal. calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.56. Found: C, 71.31; H, 9.63.

3.7. *3-Octanoyloxy-1-butyne **3e***

Yield 1.5 g (78%). 200 MHz ^{1}H NMR (CDCl$_3$) δ (ppm) 0.86 (3H, br t), 1.25 (12H, br), 1.48 (3H, d, *J*=6.8 Hz), 1.62 (2H, m), 2.30 (2H, t, *J*=7.5 Hz), 2.42 (1H, d, *J*=2.0 Hz) and 5.43 (1H, m). 50 MHz ^{13}C NMR (CDCl$_3$) δ (ppm) 172.6, 82.2, 72.6, 59.7, 34.2, 31.6, 28.9, 28.8, 24.8, 22.5, 21.2 and 14.0. IR (neat) ν=2124 and 1742 cm^{-1}. Anal. calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.26. Found: C, 73.22; H, 10.25.

3.8. *3-Decanoyloxy-1-butyne **3f***

Yield 2.9 g (91%). 200 MHz ^{1}H NMR (CDCl$_3$) δ (ppm) 0.86 (3H, br t), 1.26 (8H, m), 1.49 (3H, d, *J*=6.8 Hz), 1.59 (2H, m), 2.31 (2H, t, *J*=7.5 Hz), 2.43 (1H, d, *J*=2.0 Hz) and 5.43 (1H, m). 50 MHz ^{13}C NMR (CDCl$_3$) δ (ppm) 172.6, 82.2, 72.6, 59.6, 34.2, 31.8, 29.4, 29.2, 29.0, 24.8, 22.6, 21.2 and 14.0. IR (neat) ν=2124, 1742 cm^{-1}. Anal. calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.84; H, 10.96.

3.9. *Transesterification with 3-butyn-2-ol **2**; preparation of (R)-**3f***

A mixture of **2** (7.0 g, 100 mmol), Amano AK (1.4 g), vinyl decanoate (19.1 g, 100 mmol) and MS-4A (360 mg) in 70 ml of diisopropyl ether was shaken at 140 rpm at 30°C for 40 h. The lipase and molecular sieve MS-4A were removed by filtration and the solvent in the filtrate was evaporated under reduced pressure. The residue was purified with silica gel column chromatography using hexane:dichloromethane (1:1) as an eluent to give (*R*)-**3f** as a pale yellow oil. Yield 7.0 g (31%, 81.8% ee). 200 MHz ^{1}H NMR (CDCl$_3$) δ (ppm) 0.87 (3H, br t), 1.25 (8H, m), 1.49 (3H, d, *J*=6.8 Hz), 1.62 (2H, m), 2.33 (2H, m), 2.43 (1H, d, *J*=2.0 Hz) and 5.43 (1H, m). 50 MHz ^{13}C NMR (CDCl$_3$) δ (ppm) 172.6, 82.2, 72.6, 59.6, 34.2, 31.8, 29.4, 29.2, 29.0, 24.8, 22.6, 21.2 and 14.0. IR (neat) ν=2123 and 1742 cm^{-1}. Anal. calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.74; H, 10.99. The absolute configuration of **3f** thus obtained was determined by converting it to the corresponding alcohol, **2**.

3.10. *Enzymatic methanolysis of (R)-3-decanoyloxy-1-butyne (R)-**3f**; preparation of (R)-**2***

A mixture of (*R*)-**3f** (7.0 g, 31 mmol, 81.8% ee) obtained as described earlier, Amano AH (3.5 g) and methanol (1.3 ml) in 70 ml of *t*-butyl methyl ether was shaken at 140 rpm at 30°C for 48 h. The lipase was removed by filtration and the solvent in the filtrate was evaporated under reduced pressure. The residue was purified by distillation under reduced pressure, affording (*R*)-**2**. Yield 4.0 g (64%, 96% ee, bp 43°C/44 mmHg). $[\alpha]_D^{25}$ +48.2 (c 1.0, dioxane) (lit.[9] $[\alpha]_D^{20}$ +44 (c 1.2, dioxane)).

3.11. *Transesterification with 3-butyn-2-ol **2**; preparation of (S)-**2***

A mixture of **2** (16.0 g, 0.23 mol), Amano AK (3.2 g, 0.23 mol), vinyl decanoate (83.7 g, 0.46 mmol) and MS-4A (4.0 g) in 160 ml of diisopropyl ether was shaken at 140 rpm at 30°C for 144 h. The lipase and MS-4A were removed by filtration and the solvent in the filtrate was evaporated under reduced pressure. The residue was purified by distillation under reduced pressure, giving (*S*)-**2**. Yield 1.8 g (11%, 98% ee, bp 30°C/25 mmHg). $[\alpha]_D^{25}$ −49.4 (c 1.0, dioxane) (lit.[9] $[\alpha]_D^{20}$ −41 (c 3.45, dioxane)).

*3.12. Preparation of chiral 4-aryl-3-butyn-2-ols; (S)-(−)-4-phenyl-3-butyn-2-ol (S)-**4a***

A mixture of (*S*)-**2** (200 mg, 2.85 mmol, 98% ee) and *p*-iodobenzene (581 mg, 2.85 mmol) in toluene (1.5 ml) at room temperature was cooled to 0°C. To the solution were added diisopropylamine (288 mg, 2.85 mmol), copper(I) iodide (5.40 mg, 28.5 μmol), triphenylphosphine (8.20 mg, 31.4 μmol) and bis(acetonitrile)palladium(II) chloride (3.70 mg, 14.3 μmol) at 0°C. The mixture was stirred for 3 h at room temperature and then quenched by the addition of 10% aqueous ammonia. The organic phase was washed with saturated aqueous brine, 5% aqueous HCl, saturated aqueous Na_2CO_3 and brine, successively. The organic phase was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by silica gel (12 g) column chromatography using hexane:dichloromethane (1:1) as eluent to give (*S*)-**4a** as a pale yellow oil. Yield 348 mg (84%, 97% ee). $[\alpha]_D^{25}$ −44.8 (c 1.0, ether). 200 MHz ^{1}H NMR ($CDCl_3$) δ (ppm) 1.55 (3H, d, *J*=6.6 Hz), 2.13 (1H, d, *J*=5.0 Hz), 4.75 (1H, m), 7.31 (3H, m) and 7.42 (2H, m). 50 MHz ^{13}C NMR ($CDCl_3$) δ (ppm) 131.6, 128.3, 128.2, 122.5, 90.9, 83.9, 58.7 and 24.3. IR (NaCl) ν=3341 and 2232 cm^{-1}. Anal. calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 82.02; H, 6.96.

*3.13. (S)-(−)-4-*p*-Toluyl-3-butyn-2-ol (S)-**4b***

Yield 283 mg (62%, 97% ee, pale yellow solid). Mp 52–53°C. $[\alpha]_D^{25}$ −41.4 (c 1.0, ether). 200 MHz ^{1}H NMR ($CDCl_3$) δ (ppm) 1.56 (3H, d, *J*=6.6 Hz), 2.08 (1H, d, *J*=4.6 Hz), 2.35 (3H, s), 4.76 (1H, m), 7.11 (3H, m) and 7.33 (2H, m). 50 MHz ^{13}C NMR ($CDCl_3$) δ (ppm) 138.5, 131.5, 129.0, 119.4, 90.2, 84.1, 58.9, 24.4 and 21.4. IR (NaCl) ν=3430 and 2230 cm^{-1}. Anal. calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.51; H, 7.67.

*3.14. (S)-(−)-4-*p*-Methoxyphenyl-3-butyn-2-ol (S)-**4c***

Yield 349 mg (70%, 97% ee, pale yellow solid). Mp 44–45°C. $[\alpha]_D^{25}$ −35.1 (c 1.0, ether). 200 MHz ^{1}H NMR ($CDCl_3$) δ (ppm) 1.53 (3H, d, *J*=6.6 Hz), 2.00 (1H, d, *J*=4.8 Hz), 3.79 (3H, s), 4.73 (1H, m), 6.82 (2H, m) and 7.35 (2H, m). 50 MHz ^{13}C NMR ($CDCl_3$) δ (ppm) 159.6, 133.1, 114.6, 113.9, 89.6, 83.9, 58.9, 55.3 and 24.5. IR (NaCl) ν=3302, 2226 cm^{-1}. Anal. calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.82; H, 6.86.

*3.15. (S)-(−)-4-*o*-Toluyl-3-butyn-2-ol (S)-**4d***

Yield 153 mg (45%, 97% ee, pale yellow oil). $[\alpha]_D^{25}$ −43.9 (c 1.0, ether). 200 MHz ^{1}H NMR ($CDCl_3$) δ (ppm) 1.57 (3H, d, *J*=6.6 Hz), 2.08 (1H, br s), 2.42 (3H, s), 4.78 (1H, m), 7.19 (3H, m) and 7.39 (1H, d, *J*=7.6 Hz). 50 MHz ^{13}C NMR ($CDCl_3$) δ (ppm) 140.2, 132.0, 129.5, 128.5, 125.6, 122.4, 95.0, 82.9, 59.0, 24.6 and 20.7. IR (NaCl) ν=3353 and 2228 cm^{-1}. Anal. calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.25; H, 7.39.

*3.16. (S)-(−)-4-*m*-Toluyl-3-butyn-2-ol (S)-**4e***

Yield 151 mg (66%, 97% ee, pale yellow oil). $[\alpha]_D^{25}$ −41.3 (c 1.0, ether). 200 MHz ^{1}H NMR ($CDCl_3$) δ (ppm) 1.54 (3H, d, *J*=6.6 Hz), 2.02 (1H, br s), 2.31 (3H, s), 4.74 (1H, m) and 7.18 (4H, m). 50 MHz ^{13}C NMR ($CDCl_3$) δ (ppm) 137.9, 132.2, 129.2, 128.7, 128.1, 122.3, 90.6, 84.1, 58.8, 24.3 and 21.1. IR (NaCl) ν=3356 and 2238 cm^{-1}. Anal. calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.25; H, 7.39.

3.17. *(R)-(+)-4-p-Chlorophenyl-3-butyn-2-ol (R)-**4f***

Yield 205 mg (80%, 96% ee, pale yellow solid). Mp 65–66°C. $[\alpha]_D^{25}$ 37.7 (c 1.0, ether). 200 MHz ^{1}H NMR ($CDCl_3$) δ (ppm) 1.54 (3H, d, J=6.6 Hz), 2.09 (1H, d, J=5.2 Hz), 4.74 (1H, m) and 7.30 (4H, m). 50 MHz ^{13}C NMR ($CDCl_3$) δ (ppm) 134.4, 132.9, 128.6, 121.0, 91.8, 82.9, 58.8 and 24.3. IR (NaCl) ν=3299 and 2230 cm^{-1}. Anal. calcd for $C_{10}H_9OCl$: C, 66.49; H, 5.02. Found: C, 66.61; H, 5.02.

3.18. *(R)-(+)-4-p-Nitrophenyl-3-butyn-2-ol (R)-**4g***

Yield 217 mg (80%, 96% ee, pale yellow solid). Mp 119–120°C. $[\alpha]_D^{25}$ 37.5 (c 1.0, ether). 200 MHz ^{1}H NMR ($CDCl_3$) δ (ppm) 1.56 (3H, d, J=6.8 Hz), 2.12 (1H, s), 4.78 (1H, m), 7.54 (2H, m) and 8.16 (2H, m). 50 MHz ^{13}C NMR ($CDCl_3$) δ (ppm) 147.1, 132.4, 129.5, 123.5, 96.2, 82.2, 58.8 and 24.1. IR (NaCl) ν=3310 and 2230 cm^{-1}. Anal. calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74. Found: C, 62.59; H, 4.78.

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