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Chemoenzymatic construction of chiral alkenyl acetylenic alcohol, a key building block to access diastereoisomers of polyacetylenes

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Abstract

Background: Enzymatic kinetic resolution is proved as an efficient strategy of accessing chiral secondary alcohols in organic synthesis. Although several synthetic methods have been developed for the preparation of chiral acetylenic alcohol, biotransformation remains as a direct approach in the synthesis of polyacetylene lipids, which represent an intriguing class of marine natural products featuring interesting biological profiles.

Results: Novozym 435, a commercial lipase immobilized on macroporous acrylic resin, is utilized in the kinetic resolution of 1-yn-3-ol-4-(*E*)-ene (alkenyl acetylenic alcohol), which exists as terminus in recently isolated isofulvinol (**1**) both from the mollusk *Peltodoris atromaculata* and the sponge *Haliclona fulva*. The kinetic resolution enabled by Novozym 435 resulted in acetylenic alcohol and the corresponding acetate both in excellent enantiomeric excess and high isolated yield. The optimized reaction conditions allow us to realize the reaction at room temperature in toluene. The reaction is readily scaled up for synthetic use.

Conclusions: The current investigation builds up a platform for future exploration on stereoisomers of isofulvinol, synthetic intermediates with different chain length, and natural product analogs.

Keywords: Enzymatic catalysis; Novozym 435; Kinetic resolution; Polyacetylene; Total synthesis

Introduction

Over 100 polyacetylenes known so far are characterized from the extract of marine sponges of the genera *Petrosia*, *Xestospongia*, *Strongylophora*, etc. [1]. Characteristic of these natural products is a long chain that ranged from C44 to C47 that are bearing acetylenic, hydroxyl or keto, and isolated *cis/trans*-alkenes. Most polyacetylenic lipids have shown promising biological activities, such as antitumor, antimicrobial, and antiviral [2,3]. Very recently, Ciavatta and coworkers isolated several long-carbon-chain (C46) and fulvinol-like polyacetylenes from the ether extract of both the mollusk *Peltodoris atromaculata* and the sponge *Haliclona fulva* [4]. Among them, two compounds, isofulvinol (**1**) and hydroxydehydroisofulvinol (**2**)

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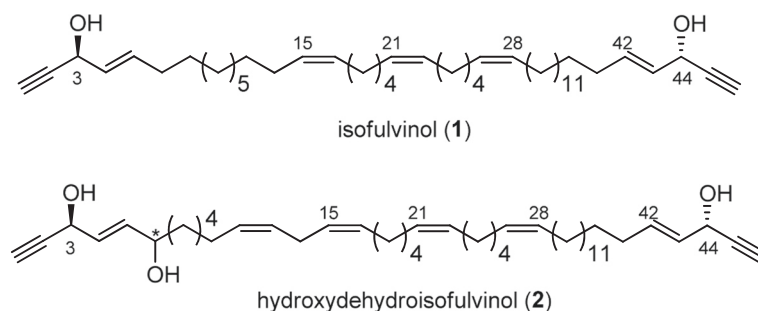Full list of author information is available at the end of the article

(Figure 1), showed *in vitro* promising growth inhibitory activity against a panel of six human cancer cell lines with the IC$_{50}$ values that ranged from 3 to 36 μM. It may also be essential for understanding some basic biological phenomena, including chemical defense mechanisms since *H. fulva* was reported as the nudibranch feeds for the mollusk *P. atromaculata* [5].

The rare resources of marine sponges as well as diverse biological profiles attract several total syntheses of selected targets [6-11]. These syntheses focused on the construction of acetylenic alcohols in a highly enantioselective manner through hydroboration, catalytic asymmetric hydrogenation, as well as enzymatic resolution. The direct acetylene addition of enal with chiral alkynylzinc complex was documented to be highly substrate dependent [8,12,13]. The enzymatic kinetic resolution in literature precedents revealed the power of achieving high enantioselectivity of the recovered acetylenic alcohols as well as the esterication product [7-11,14]. Lipase AK, Lipase PS, and Novozym 435 were proved as efficient biocatalysts for this type of substrates. However,

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**Figure 1 Isofulvinol (1) and hydroxydehydroisofulvinol (2).**

target-oriented synthesis (TOS) is limited to a specific target instead of developing a general approach to diversify structural features of polyacetylenes. Only two recent reports undertook this task and disclosed interesting biological profiles [13,14]. However, the chain length and levels of desaturation (numbers and geometry) as well as the chirality for adjusting biological activity remain elusive. Guided under this line, we initiated a synthetic effort to devise a unified and practical strategy for the future evaluation of the structure-and-activity relationship in terms of carbon chain length and chirality of acetylenic alcohols.

With the consideration of isolated *cis*-alkenes, the long carbon chain, and two identical chiral 1-yn-3-ol-4-(*E*)-ene terminuses, isofulvinol (**4**) is denoted as a good starting point to develop a general approach which may eventually guide us to synthesize its stereoisomers with different chain length using a flexible synthetic tactics. Retrosynthetically, *cis*-alkenyl bisaldehyde **5** can be derived from partial hydrogenation (Lindlar catalyst) of symmetric internal

alkyne **6** and stepwise Wittig olefination (Scheme 1). In order to collect both enantiomers of two 1-yn-3-ol-4-(*E*)-ene units **3** and **4**, an enzymatic kinetic resolution is envisioned to be an ideal option since both isomers are expected to achieve in high enantiomeric excess (e.e.). Moreover, this flexible tactics may offer an opportunity to establish the unknown chiral center in hydroxydehydroisofulvinol (**2**) (Figure 1) via introducing a hydroxyl group at C6 in **3** or its derivative.

Results and discussion

The synthesis of acetylenic alcohol *rac*-**3** was begun from the commercially available brominated alcohol **7** (Scheme 2). After standard Swern oxidation [15] and Wittig chain elongation, the corresponding ester **9** was further reduced by diisobutylaluminum hydride (DIBAL-H) and subsequent MnO_2 oxidation [16] to deliver enal **10**, which smoothly reacted with an acetylenic Grignard reagent to give acetylenic alcohol **3** in an impressively overall 76% yield for five straightforward steps. The corresponding
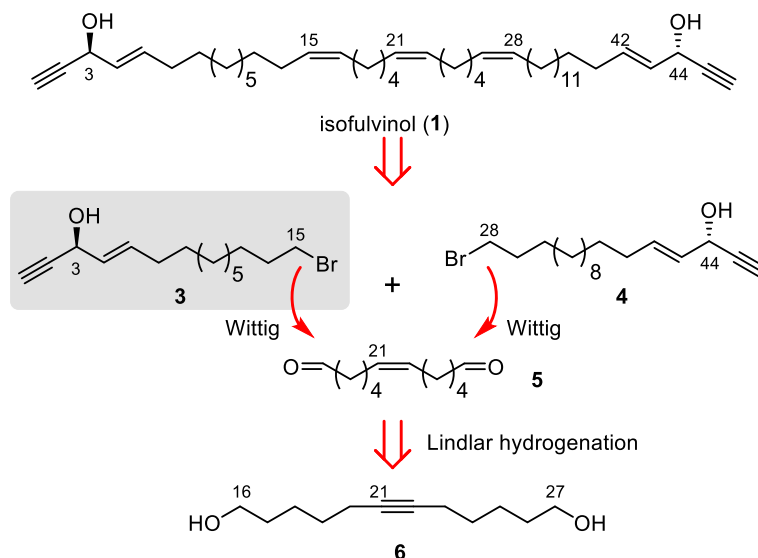
Scheme 1 Synthesis design of isofulvinol (1) (chiral moiety 3 was highlighted as the focus of the current research).

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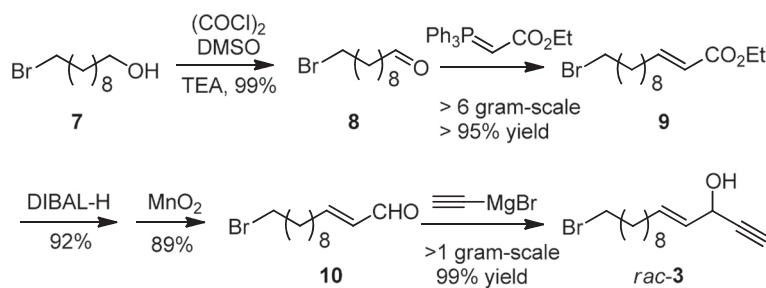
Scheme 2 Gram-scale synthesis of racemic acetylenic alcohol 3.

substance was readily cumulated in a gram scale. Three literature-known biocatalysts were screened, and only Novozym 435 gave a controllable conversion in 97% e.e. of the recovered alcohol (entry 2 in Table 1). For Lipase AK, the recovered alcohol was confirmed without a considerable enantiomeric excess during the reaction process (entry 1). Lipase PS gave a sluggish reaction and low selectivity ($E = 7$) (entry 3).

We then focused on solvent screening with the combination of Novozym 435. As shown in Table 2, enzymatic kinetic resolution was performed with a slow rate in polar solvents (entries 1 to 4). The activity of enzyme is correlated with the hydrophobicity of the solvent (Log P, P is the partition coefficient between 1-octanol and water) [17] (entries 1 to 9). In hexane and octane, however, the reaction was rather fast and not easy to maintain the alcohol 3 and the corresponding acetate 11 both in high enantioselectivities ($E = 17$ in entry 10 vs $E = 340$ in entry 8). Toluene was identified as the solvent of choice both for the reaction time and enantioselectivity (entry 7 vs 14). The resolution efficiency (E) for a synthetically useful scale (>200 mg) remains excellent (entry 15). The dramatic deterioration of activity in n-hexane during the increase of conversion[a] may be due to the conformational adjustment of biocatalyst [17] (entry 10 vs 8). Although the E number remains excellent when

the reaction was performed in octane (entry 11 vs 9), overesterification was found when the reaction was scaled up. The absolute configuration of the recovered chiral acetylenic alcohol 3 was determined to be R by the modified Mosher ester [18] (Additional file 1). Since the corresponding ester (S)-11 was not able to achieve a baseline separation on chiral HPLC columns, hydrolysis with K_2CO_3 in MeOH was performed and (S)-3 was obtained in good yield (Scheme 3). The corresponding acetylic alcohol was assigned as S by the comparison with the HPLC profile of the recovered (R)-3. Its enantiomeric excess is also impressively high as 97%. That means all diastereoisomers of isofulvinol (1) can be accessed in excellent enantiomeric purity by utilizing Novozym 435. Enzymatic resolution provided one pair of enantiomers in high e.e. which is suitable for further synthetic usage and derivatization[b] [19].

Conclusion

In summary, we devised an efficient protocol to access both enantiomers of the chiral acetylenic alcohol motif in high enantiomeric excess (both >97% e.e.). The synthesis design discussed in this work would allow us to access a series of isofulvinol stereoisomers and derivatives through the mutation of chain length and the alternation of the stereochemistry of secondary alcohols,

Table 1 Identification of biocatalyst for the resolution of rac-3

Entry	Biocatalyst	Time (h)	Conversion (%)[a]	(R)-3[b] % e.e.	(S)-11[b] % e.e.	E[c]
1	Lipase AK	0.5	>99	0	0	–
2	Novozym 435	0.5	56	96	97	340
3	Lipase PS	27.5	76	98	32	7

Reaction conditions: rac-3 (151 mg, 0.5 mmol), biocatalyst (250 mg, 165% w/w), vinyl acetate (307 μL, 6.6 equiv), n-hexane (5 mL), R.T. [a]Conversion was determined by HPLC (Chiralcel AS-H; flow rate: 0.50 mL/min; [i]PrOH/n-hexane: 1/99; temperature: 25°C; UV: $\lambda = 199$ nm); [b]the determination of enantiomeric excess (HPLC chiralcel AS-H) and the absolute configuration (Mosher ester) of 3 are illustrated in Additional file 1; [c]$E = \ln[(1 - e.e._S)(1 - C)]/\ln[(1 + e.e._S)(1 - C)]$, where e.e._S represents the enantiomeric excess of the recovered alcohol.

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Table 2 Solvent effect on the optimization of enzymatic kinetic resolution of acetylenic alcohol 3

Entry	Solvent	Log P	t (h)	Conversion (%)[a]	(R)-3[b] % e.e.	(S)-11[b] % e.e.	E[c]
1	Dioxane	−1.10	1.5	4	2.2	58.0	4
2	CH₃CN	−0.33	1.5	22	23.3	95.2	51
3	Acetone	−0.23	1.5	15	20.6	80[e]	11
4	THF	0.49	1.5	13	10.0	84.5	13
5	Et₂O	0.85	1.5	46.6	78.7	95.0	94
6	ᵗBuOMe	0.96	1.5	45	76.4	97.0	152
7	Toluene	2.50	1.5	49.3	91.1	96.6	185
8	n-Hexane	3.50	0.5	56	96.0	97.7	340
9	n-Octane	4.50	0.5	51.1	89.0	97.9	284
10	n-Hexane	3.50	6	60.0	96.0	64.2	17
11	n-Octane	4.50	6	54.3	98.4	96.2	300
12	Et₂O	0.85	6	52.9	97.7	89.2	78
13	ᵗBuOMe	0.96	6	52.4	98.4	91.6	109
14	Toluene	2.50	6	50.3	98.4	97.3	354
15[d]	Toluene	2.50	6	50.3	97.4	97.3	319

Reaction conditions: *rac*-3 (30 mg, 0.1 mmol), Novozym 435 (20 mg, 67% *w/w*, 1,000 U/mmol), vinyl acetate (62 μL, 6.6 equiv), solvent (1 mL), R.T. [a]Conversion (*C*) was determined by HPLC (Chiralcel AS-H; flow rate: 0.50 mL/min; ᶦPrOH/n-hexane: 1/99; temperature: 25°C; UV: λ = 199 nm); [b]the determination of enantioselectivity (HPLC Chiralcel AS-H) and the absolute configuration (Mosher's method) of 3 are illustrated in Additional file 1; [c]$E = \ln[(1 − e.e._s)(1 − C)]/\ln[(1 + e.e._s)(1 − C)]$, where e.e.$_s$ represents the enantiomeric excess of the recovered alcohol; [d]257 mg of *rac*-3 was applied, see the Experimental section for details; [e]since considerable side products were contaminated, the HPLC determination (80% e.e.) of (*R*)-3 was not calibrated.

which may further provide a comprehensive investigation of biological evaluation. Current investigation of total synthesis of the target molecule as well as its derivatization is underway in this laboratory and will be reported in due course.

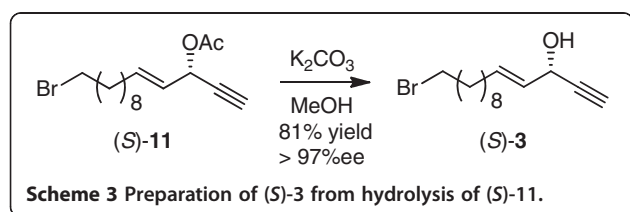## Experimental section
General procedure
All the reactions were carried out under N₂ atmosphere unless otherwise stated. Solvents utilized for reactions were dried using the standard procedure and distilled before use. All reagents were used after receiving albeit special treatment as indicated.

¹H NMR and ¹³C NMR were recorded on Bruker AM-400 (Bruker AXS, Inc., Madison, WI, USA) and Agilent NMR-vnmrs 400 (Agilent Technologies, Inc., Santa Clara, CA, USA) spectrometers in CDCl₃. ¹H NMR data were recorded as follows: multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, coupling constant in Hz, integration). IR spectra (cm⁻¹) were

recorded on a PerkinElmer 983 Digital FT-IR spectrometer (PerkinElmer, Waltham, MA, USA) or Bruker Tensor 27 (Bruker AXS, Inc., Madison, WI, USA). Mass spectra were determined on a Shimadzu LCMS-2010EV (ESI) mass spectrometer (Shimadzu Corporation, Kyoto, Japan) or Agilent G6100 LC/MSD (ESI) single Quand mass spectrometer (Agilent Technologies, Inc., Santa Clara, CA, USA). High-resolution mass spectra were recorded on Bruker Daltonics, Inc. APEXIII 7.0 TESLA FTMS (ESI) mass spectrometers (Bruker Daltonics, Inc., Billerica, MA, USA). Optical rotation was taken on JASCO P1030 (JASCO Analytical Instruments, Easton, MD, USA). Enantiomeric excess was determined by DIONEX Ulti-Mate 3000 chiral HPLC (Thermo Fisher Scientific, Inc., Waltham, MA, USA). Lipase from *Candida antarctica* (5,000 U/g) was used (Novozym 435, Sigma-Aldrich, Saint Louis, USA). The melting point was not calibrated.

Preparation of (E)-15-bromopentadec-4-en-1-yn-3-ol (rac-3)
11-Bromoundecanal (**8**): A solution of CH₂Cl₂ (25 mL) and oxalyl chloride (1.0 mL, 11 mmol) was added a solution of DMSO (1.7 mL, 22 mmol) in dry CH₂Cl₂ (5 mL) at −60°C. The corresponding mixture was stirred for 15 min, and then a solution of 11-bromo-1-undecanol (**7**) (2.512 g, 10 mmol) in CH₂Cl₂ (10 mL) was added dropwise over 5 min. After being stirred for 15 min, Et₃N (7.0 mL, 50 mmol) was added and then the

Scheme 3 Preparation of (S)-3 from hydrolysis of (S)-11.

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reaction mixture was gradually warmed up to room temperature. The reaction was quenched with water (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (2×25 mL). The combined organic layers were washed with HCl (aq., 1% *v/v*) and brine (3×40 mL) and then dried over anhydrous Na_2SO_4. After the removal of the organic solvent, the residue was subjected to purification by flash column chromatography (PE/EA = 50/1) to give **8** as colorless oil (2.473 g, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (t, *J* = 1.4 Hz, 1H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.42 (td, *J* = 7.3, 1.6 Hz, 2H), 1.81 to 1.89 (m, 2H), 1.59 to 1.65 (m, 2H), 1.38 to 1.44 (m, 2H), 1.27 to 1.34 (m, 10H).

(*E*)-ethyl 13-bromotridec-2-enoate (**9**): A solution of 11-bromoundecanal (**8**) (6.2 g, 25 mmol) and Ph_3P = CHCOOEt (9.135 g, 26.25 mmol) in toluene (125 mL) was refluxed about 3 h until the aldehyde was completely consumed. The reaction mixture was cooled to room temperature and diluted with petroleum ether (250 mL). A white precipitate was removed through a pad of Celite® (Shanghai Dahe Chemicals, Inc., Shanghai, China) and thoroughly washed with petroleum ether. The combined filtrate was concentrated under reduced pressure, and the residue was subjected to purification by flash column chromatography (PE/EA = 50/1) to afford **9** as yellow oil (7.15 g, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (dt, *J* = 15.6, 7.0 Hz, 1H), 5.81 (dt, *J* = 15.6, 1.4 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.41 (t, *J* = 6.9 Hz, 2H), 2.16 to 2.22 (m, 2H), 1.81 to 1.89 (m, 2H), 1.38 to 1.47 (m, 4H), 1.26 to 1.33 (m, 13H); LRMS-ESI: calcd. for $C_{15}H_{27}BrNaO_2$ [M + Na]$^+$: 341.1, found: 341.0.

(*E*)-13-bromotridec-2-enal (**10**): A solution of (*E*)-ethyl 13-bromotridec-2-enoate (**9**) (1.877 g, 5.88 mmol) in toluene (30 mL) was stirred at 0°C for 10 min. Then DIBAL-H (10.3 mL, 1.2 M in toluene) was added dropwise within 15 min, and the resulting mixture was stirred for additional 30 min. The reaction was quenched by H_2O (0.65 mL), and the resulting reaction mixture formed into gel; vigorous stirring was needed before the gel ages into a precipitate. The suspension was filtered by Celite® and washed with ethyl acetate. The filtrate was concentrated under reduced pressure, and the corresponding residue was subjected to purification by flash column chromatography (PE/EA = 10/1) to deliver (*E*)-13-bromotridec-2-en-1-ol as colorless oil (1.505 g, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.59 to 5.73 (m, 2H), 4.08 (m, 2H), 3.41 (t, *J* = 6.9 Hz, 2H), 2.03 (q, *J* = 7.2 Hz, 2H), 1.81 to 1.89 (m, 2H), 1.33 to 1.44 (m, 4H), 1.25 to 1.32 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.36, 128.81, 63.68, 34.01, 32.79, 32.17, 29.43, 29.40, 29.38, 29.12, 29.09, 28.72, 28.13; FT-IR: *ν* (cm^{-1}) 3,334 (br), 2,925, 2,853, 1,464, 1,438, 1,254, 1,089, 1,002, 969, 722, 645, 562; HRMS-ESI: calcd. for $C_{13}H_{25}BrNaO$ [M + Na]$^+$: 299.0986, found: 299.0981.

A suspension of above (*E*)-13-bromotridec-2-en-1-ol (1.45 g, 5.23 mmol) and MnO_2 (4.47 g, 52.3 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature. The reaction process was monitored by TLC. After completion, the mixture was filtered by Celite® and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure, and the residue was subjected to purification by flash column chromatography (PE/EA = 50/1) to give **10** as yellow oil (1.277 g, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.51 (d, *J* = 7.9 Hz, 1H), 6.85 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.12 (dd, *J* = 15.8 Hz, *J* = 7.8 Hz, 1H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.34 (q, *J* = 6.8 Hz, 2H), 1.81 to 1.89 (m, 2H), 1.47 to 1.54 (m, 2H), 1.39 to 1.44 (m, 2H), 1.27 to 1.36 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.06, 158.98, 132.90, 33.98, 32.76, 32.67, 29.31, 29.24, 29.06, 28.67, 28.09, 27.77; FT-IR: *ν* (cm^{-1}) 2,927, 2,854, 2,731, 1,692, 1,637, 1,460, 1,438, 1,256, 1,153, 1,009, 974, 722, 644, 561; HRMS-ESI: calcd. for $C_{13}H_{23}BrNaO$ [M + Na]$^+$: 297.0830, found: 297.0824.

(*E*)-15-bromopentadec-4-en-1-yn-3-ol (*rac*-**3**): A solution of (*E*)-13-bromotridec-2-enal (**10**) (1.164 g, 4.23 mmol) in tetrahydrofuran (THF) (30 mL) was stirred at 0°C for 10 min. Then ethynylmagnesium bromide (12.7 mL, 0.5 M in THF) was added dropwise, and the resulting reaction mixture was stirred for 3 h. The reaction was diluted with ether (50 mL) and quenched by addition of NH_4Cl (aq., 5 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2×15 mL). The combined organic layers were washed successively by $NaHCO_3$ (aq.), water, and brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to purification by flash column chromatography (PE/EA = 10/1) to deliver the corresponding alcohol (*rac*-**3**) as radial crystal (1.3 g, 99% yield). mp: 27°C to 28°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92 (dt, *J* = 15.2, 7.0 Hz, 1H), 5.60 (dd, *J* = 15.2, 6.4 Hz, 1H), 4.84 (t, *J* = 5.6 Hz, 1H), 3.41 (t, *J* = 6.9 Hz, 2H), 2.56 (d, *J* = 2.2 Hz, 1H), 2.06 (q, *J* = 7.6 Hz, 2H), 1.88 (d, *J* = 6.0 Hz, 1H), 1.81 to 1.89 (m, 2H), 1.36 to 1.46 (m, 4H), 1.26 to 1.33 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.36, 128.38, 83.40, 73.87, 62.65, 34.02, 32.79, 31.89, 29.40, 29.36, 29.11, 28.78, 28.71, 28.12; FT-IR: *ν* (cm^{-1}) 3371 (br), 3,305, 2,926, 2,854, 1,459, 1,438, 1,255, 1,089, 1,012, 968, 721, 647, 561; HRMS-ESI: calcd. for $C_{15}H_{25}BrNaO$ [M + Na]$^+$: 323.0986, found: 323.0981.

Enzymatic resolution of (E)-15-bromopentadec-4-en-1-yn-3-ol (rac-3)

(*R*)-15-bromopentadec-4-en-1-yn-3-ol ((*R*)-**3**) and (*S*)-15-bromopentadec-4-en-1-yn-3-yl acetate ((*S*)-**11**): A suspension of alcohol (*rac*-**3**) (257 mg, 0.853 mmol), Novozym 435 (172 mg, 5,000 U/g, recombinant, expressed in *Aspergillus niger*) and vinyl acetate (524 μL, 8.53 mmol) in toluene (8.5 mL) was stirred at room temperature. The

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reaction process was monitored by chiral HPLC. After completion (6 h), the mixture was filtered by Celite®. The filtrate was concentrated under reduced pressure, and the residue was subjected to purification by flash column chromatography (PE/EA = 50/1 to 10/1) to give (*R*)-**3** (125 mg, 48% yield) and (*S*)-**11** (150 mg, 51% yield).

(*R*)-**3**: $[\alpha]_D^{25}$ = −20.8 (c 1.00, CHCl$_3$); 97.4% e.e., HPLC (Chiralcel AS-H; flow rate: 0.50 mL/min; ^{i}PrOH/n-hexane: 1/99; temperature: 25°C; UV: λ = 199 nm); mp: 31°C to 32°C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.92 (dt, *J* = 15.2, 7.0 Hz, 1H), 5.60 (dd, *J* = 15.2, 6.4 Hz, 1H), 4.84 (t, *J* = 5.6 Hz, 1H), 3.41 (t, *J* = 6.9 Hz, 2H), 2.56 (d, *J* = 2.2 Hz, 1H), 2.06 (q, *J* = 7.6 Hz, 2H), 1.88 (d, *J* = 6.0 Hz, 1H), 1.81 to 1.89 (m, 2H), 1.36 to 1.46 (m, 4H), 1.26 to 1.33 (m, 10H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 134.36, 128.38, 83.40, 73.87, 62.65, 34.02, 32.79, 31.89, 29.40, 29.36, 29.11, 28.78, 28.71, 28.12; FT-IR: ν (cm^{-1}) 3,371 (br), 3,305, 2,926, 2,854, 1,459, 1,438, 1,255, 1,089, 1,012, 968, 721, 647, 561.

(*S*)-**11**: $[\alpha]_D^{25}$ = +22.3 (c 1.00, CHCl$_3$); 96.5% e.e., HPLC (Chiralcel AS-H; flow rate: 0.50 mL/min; ^{i}PrOH/n-hexane: 1/99; temperature: 25°C; UV: λ = 199 nm); ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.02 (dtd, *J* = 15.4, 6.8, 0.8 Hz, 1H), 5.83 (d, *J* = 5.6 Hz, 1H), 5.54 (ddt, *J* = 15.2, 6.8, 1.4 Hz, 1H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.56 (d, *J* = 2.2 Hz, 1H), 2.09 (s, 3H), 2.06 (m, 2H, overlap), 1.81 to 1.89 (m, 2H), 1.36 to 1.44 (m, 4H), 1.25 to 1.32 (m, 10H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.67, 137.15, 124.24, 79.85, 74.67, 64.05, 34.01, 32.79, 31.94, 29.39, 29.36, 29.33, 29.08, 28.72, 28.58, 28.13, 21.06; FT-IR: ν (cm^{-1}) 3,296, 2,927, 2,854, 1,743, 1,458, 1,437, 1,370, 1,228, 1,015, 968, 642; HRMS-ESI: calcd. for $C_{17}H_{27}BrNaO_2$ $[M + Na]^+$: 365.1092, found: 365.1087.

Hydrolysis of acetate to prepare (S)-15-bromopentadec-4-en-1-yn-3-ol ((S)-3)

A suspension of (*S*)-**11** (68.5 mg, 0.2 mmol) and anhydrous K$_2$CO$_3$ (276 mg, 2 mmol) in CH$_3$OH (1 mL) was stirred at room temperature. The reaction process was monitored by TLC. After completion, the mixture was diluted by Et$_2$O. The organic layer was washed successively by water and brine and dried over Na$_2$SO$_4$. After removal of the organic solvent, the residue was subjected to purification by flash column chromatography (PE/EA = 10/1) to deliver the corresponding alcohol (*S*)-**3** as radial crystal (48 mg, 81% yield). $[\alpha]_D^{25}$ = +24.0 (c 1.00, CHCl$_3$); 97.3% e.e., HPLC (Chiralcel AS-H; flow rate: 0.50 mL/min; ^{i}PrOH/n-hexane: 1/99; temperature: 25°C; UV: λ = 199 nm); mp: 27°C to 28°C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.92 (dt, *J* = 15.2, 7.0 Hz, 1H), 5.60 (dd, *J* = 15.2, 6.4 Hz, 1H), 4.84 (t, *J* = 5.6 Hz, 1H), 3.41 (t, *J* = 6.9 Hz, 2H), 2.56 (d, *J* = 2.2 Hz, 1H), 2.06 (q, *J* = 7.6 Hz, 2H), 1.88 (d, *J* = 6.0 Hz, 1H), 1.81 to 1.89 (m, 2H), 1.36 to 1.46 (m, 4H), 1.26 to 1.33 (m, 10H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 134.36,

128.38, 83.40, 73.87, 62.65, 34.02, 32.79, 31.89, 29.40, 29.36, 29.11, 28.78, 28.71, 28.12; FT-IR: ν (cm^{-1}) 3,371 (br), 3,305, 2,926, 2,854, 1,459, 1,438, 1,255, 1,089, 1,012, 968, 721, 647, 561.

Endnotes

[a]The conversions in Tables 1 and 2 were directly taken from the HPLC integration. This number should be adjusted since there are different absorption of alcohol (**3**) and the resulting acetate (**11**). This system error will not affect the qualitative comparison of enzymatic efficiency in different organic solvents.

[b]A recent elegant dynamic kinetic resolution of 1-yn-3-ol-4-ene utilizing Novozym 435 with acid resin as a racemization reagent was reported by Xu and coworkers (see [19]).

Additional file

Additional file 1: Supporting information available. The detailed information of the Mosher method for the absolute configuration identification of (*R*)-**3**, ^{1}H and ^{13}C NMR spectra of all unknown compounds, and HPLC profiles for compounds **3** and **11** are available free of charge via the Internet or directly from the authors.

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