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Novozym-435-catalyzed efficient preparation of (1*S*)-ethenyl and ethynyl 2,3-allenols and (1*R*)-ethenyl and ethynyl 2,3-allenyl acetates with high enantiomeric excess

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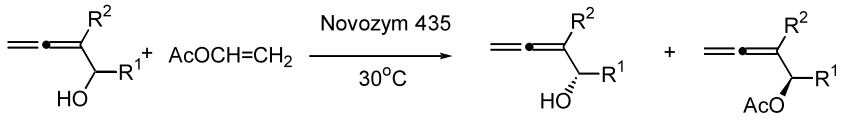
Abstract—Novozym-435 (a form of *Candida antarctica lipase B*) was found to be an effective biocatalyst for the kinetic resolution of a variety of racemic 1-ethenyl or ethynyl-substituted 2,3-allenols. The optically active 1-ethynyl-substituted 2,3-allenols can be subjected to Sonogashira coupling reactions and alkylations of terminal C–C triple bonds leading to the formation of 2,3-allenols, which cannot be directly prepared by Novozym 435-catalyzed kinetic resolution probably due to the steric hindrance.

1. Introduction

Allenes are a class of compounds with interesting properties such as unique reactivity and chirality owing to the presence of two cumulative carbon–carbon double bonds.[1] In recent years, much attention has been paid to the synthesis and reaction of functionalized allenes.[2] As a very important class of functionalized allenes, 2,3-allenols are highly versatile synthetic intermediates. They can be stereoselectively converted into compounds such as *syn*-1,2-diols,[3] oxiranes,[4] 2,5-dihydrofurans,[5] α-methylenelactones,[6] α- or γ-amino alcohols,[7] and α,β-unsaturated ketones,[8] which in turn can be used to prepare a variety of useful products. Moreover, some natural products, such as kumausallene,[9] also contain an allenol moiety. Thus the syntheses of optically active 2,3-allenols are of current interest. Optically active 2,3-allenols can be prepared by the reaction of the aldehyde with chiral allenylic or propargylic boron or tin reagents.[10] These protocols require more than stoichiometric amounts of enantiomerically pure chiral reagents or non-convenient reaction conditions. Biocatalytic methods are now well-established routes to enantiomerically pure or enriched alcohols with the advantages of easy availability of starting materials and the biocatalyst, providing that high stereoselectivity can be realized for both products. However, due to the notion that many allenes are harmful to the biocatalyst,[11] reports on the kinetic resolution of allenes using enzyme or microorganism as the catalyst are very limited.[12] During the course of our systemic studying of allenes, we found that Novozym-435 (a form of *Candida antarctica lipase B*) is an efficient biocatalyst for the kinetic resolution of a series of racemic 2,3-allenols affording (*S*)-2,3-allenols and (*R*)-2,3-allenyl acetates in high yields and excellent ees when R^1 is methyl or ethyl (Eq. (1)).[13]



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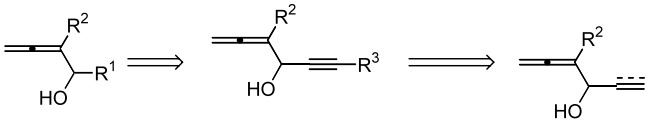
Further research found that when R^1 is *n*-propyl, *n*-butyl and benzyl, the reaction is extremely slow or does not even occur at all. Thus, it is a challenge to develop an alternative synthesis of optically active 2,3-allenols or acetates with R^1 having greater than two carbon atoms. Herein we report our recent results on the kinetic resolution of 1-ethenyl and 1-ethynyl-2,3-allenols leading to optically active 2,3-allenols o acetates, which may be precursors for the synthesis of optically active of 2,3-allenols with R^1 having more than 2 carbon atoms via subsequent coupling reactions or alkylations (Scheme 1).



Scheme 1.

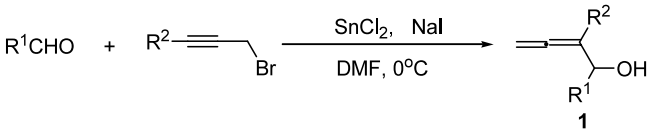
2. Results and discussion

2.1. Synthesis of starting racemic 2,3-allenols

The required racemic 2,3-allenols can be synthesized very conveniently via a one-step reaction of propargylic bromide with propenal or propynal with the mediation of $SnCl_2$ and NaI (Scheme 2).[14]

2.2. Kinetic resolution

Initially the resolution of **1a** using the literature conditions was studied,[13] and the results are excellent (Table 1). From the results shown in Table 1, it is obvious that this methodology can accommodate a range of different R^2 group. When R^1 is ethenyl, the reaction behaved similarly, however, when we turn to the allenols with R^1 being phenylethynyl or propargylic the usual problem appears: The reaction is too slow!



1a R^1 = ethynyl, R^2 = *n*-C_4H_9 **1f** R^1 = ethynyl, R^2= $PhCH_2CH_2$
1b R^1 = ethynyl, R^2 = allyl, **1g** R^1 = ethenyl, R^2= allyl
1c R^1= ethynyl, R^2 = *n*-C_6H_{13} **1h** R^1 = ethenyl, R^2 = *n*-C_4H_9
1d R^1 = ethynyl, R^2 = $PhCH_2$ **1i** R^1 = ethenyl, R^2 = $PhCH_2$
1e R^1 = ethynyl, R^2= $CH_2OCH_2CH_3$

Scheme 2. Synthesis of the racemic 1-ethenyl or ethynyl 2,3-allenols.

Candida antarctica lipase[15] demonstrated (*R*) stereoselectivity towards 2,3-allenols.[13] As shown in Figure 1, the allenyl moiety is the larger substitutent and the ethenyl or ethynyl is the smaller one. According to the empirical rule[12a,b,16] and our previous results,[13] the

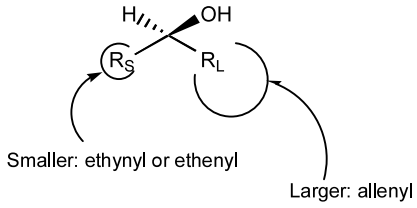
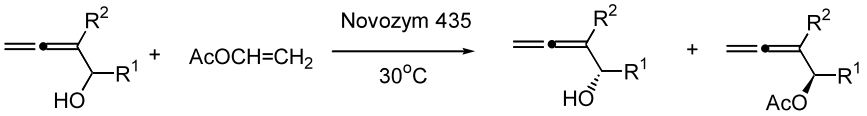


Figure 1.

Table 1. Novozym-435-catalyzed resolution of racemic 2,3-allenols[a]



1 (*S*)-**1** (*R*)-**2**

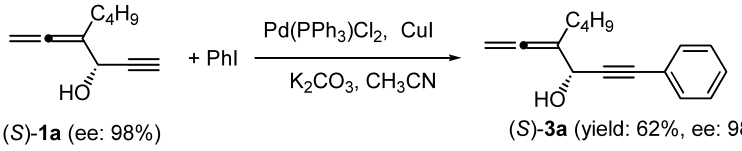
Entry	**1**		Time (h)	(*S*)-**1**		(*R*)-**2**	
	R^1	R^2		Yield[b] (%)	Ee[c] (%)	Yield[b] (%)	Ee[c] (%)
1	Ethynyl	C_4H_9 **1a**	95	41 **1a**	>99[d]	46 **2a**	97
2	Ethynyl	Allyl **1b**	96	55 **1b**	88[d]	40 **2b**	98
3	Ethynyl	C_6H_{13} **1c**	96	38 **1c**	97[e]	40 **2c**	>99[e]
4	Ethynyl	$PhCH_2$ **1d**	95	42 **1d**	>99[d]	43 **2d**	98
5	Ethynyl	CH_2OEt **1e**	94.5	44 **1e**	98[d]	42 **2e**	98
6	Ethynyl	$PhCH_2CH_2$ **1f**	94	40 **1f**	>99	44 **2f**	>99
7	Ethenyl	Allyl **1g**	79.5	39 **1g**	>99[d]	46 **2g**	98
8	Ethenyl	C_4H_9 **1h**	97	50 **1h**	98[d]	46 **2h**	98
9	Ethenyl	$PhCH_2$ **1i**	95	42 **1I**	>99[d]	42 **2i**	>99

[a] The reaction was carried out at 30°C using alcohol (~100 mg), vinyl acetate (5 mL), and Novozym-435 (70 mg).
[b] Isolated yield based on alcohol.
[c] Determined via GC or HPLC.
[d] Determined after its conversion to the corresponding acetate.
[e] Determined after its conversion to the corresponding benzoate.

absolute configuration of the obtained acetate was tentatively assigned as (*R*).

2.3. Preparation of allenols with high ee via the Sonogashira coupling reaction of 1-ethynyl-2,3-allenols

Since the 1-ethynyl-substituted 2,3-allenols with high ee could be easily obtained, we decided to study the corresponding Sonogashira coupling reaction.[17] The main problem is how to optimize the reaction conditions to avoid any racemization and thus obtain the product in a high yield. Our initial work began with the reaction of 2,3-allenol (*S*)-**1a** with iodobenzene in CH_3CN at room temperature using 5 mol% $Pd(PPh_3)_2Cl_2$, and 10 mol% CuI as the catalyst and K_2CO_3 (1.1 equiv.) as the base (Eq. (2)).



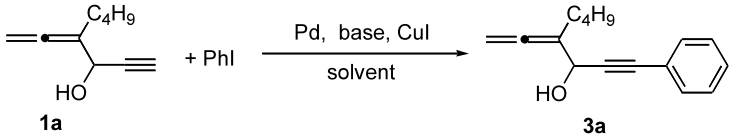
(*S*)-**1a** (ee: 98%) (*S*)-**3a** (yield: 62%, ee: 98%) (2)

The expected product was produced in 62% yield without obvious racemization. With these results in hand, we continued optimizing the reaction conditions using racemic 2,3-allenol **1a** as the substrate to improve the yield. A series of screening experiments were conducted, some typical results were listed in Table 2. The palladium catalyst, the base, the solvent and the reaction temperature are critical to the reaction. With $Pd(PhCN)_2Cl_2$ and $Pd(CH_3CN)_2Cl_2$, the reaction did not occur (Table 2, entries 1 and 2). Using NEt_3 or piperidine as the base and NEt_3, CH_3CN or 1,4-dioxane as the solvent, the yield of the product was essentially not improved (Table 2, entries 3, 4, 5, 6, 7). However, when the reaction was carried out in THF at room temperature using 2 mol% $Pd(PPh_3)_2Cl_2$ and 2 mol% CuI as the catalyst and *i*-Pr_2NH (1 equiv.) as the base, the yield of the product was improved to 82% (Table 2, entry 8). Furthermore, when the reaction was carried out at −2°C, the yield was ever higher (90%) (Table 2, entry 11). Decreasing the amount of the catalyst to 1 mol% $Pd(PPh_3)_2Cl_2$ and 1 mol% CuI, the product could also be obtained with 79% yield albeit with a longer time (Table 2, entry 10).

Subsequently, the Sonogashira coupling reactions of optically active 2,3-allenols **1a** with a number of differently substituted aryl iodides were performed using the standard conditions (Table 2, entry 10), the results are summarized in Table 3. Racemization was not observed. Both electron-donating and electron-withdrawing aryl iodides can be reacted to afford the corresponding products with good yields. The steric effect of the substituted group in aryl iodides has limited influence on the outcome of the reaction: the reaction of 2-iodotoluene and 4-iodotoluene with **1a** produced the corresponding products with similar yields (compare entry 4 with entry 8, Table 3). It is notable that (*R*)-**1a** could be obtained with good yield via the hydrolysis of (*R*)-**2a** using K_2CO_3 as the base and MeOH as the solvent, which makes it possible to get both (*R*)- and (*S*)-enantiomers.

The obtained (*S*)-**1a** could also be converted into the corresponding optically active allenols **4a** and **4b** via the

Table 2. Optimization of the Sonogashira coupling reaction of **1a** with iodobenzene

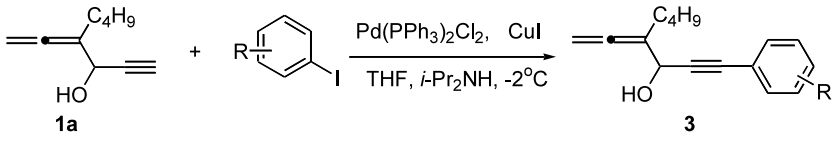


1a **3a**

Entry	Catalyst	Solvent	Base	T	Time (h)	Yield (%)
1[a]	$Pd(PhCN)_2Cl_2$	NEt_3	NEt_3	rt	33	NR
2[a]	$Pd(CH_3CN)_2Cl_2$	NEt_3	NEt_3	rt	33	NR
3[a]	$Pd(PPh_3)_2Cl_2$	NEt_3	NEt_3	rt	11.5	63
4[a]	$Pd(PPh_3)_2Cl_2$	1,4-Dioxane	NEt_3	rt	3.0	41
5[a]	$Pd(PPh_3)_2Cl_2$	1,4-Dioxane	Piperidine	rt	3.0	60
6[a]	$Pd(PPh_3)_2Cl_2$	1,4-Dioxane	*i*-Pr_2NH	rt	2.5	67
7[b]	$Pd(PPh_3)_2Cl_2$	CH_3CN	*i*-Pr_2NH	rt	5.5	68
8[b]	$Pd(PPh_3)_2Cl_2$	THF	*i*-Pr_2NH	rt	2.2	82
9[b]	$Pd(PPh_3)_2Cl_2$	THF	Piperidine	rt	3.5	59
10[c]	$Pd(PPh_3)_2Cl_2$	THF	*i*-Pr_2NH	rt	16.5	79
11[b]	$Pd(PPh_3)_2Cl_2$	THF	*i*-Pr_2NH	−2°C	5.0	90

[a] Pd (5 mol%) and CuI (10 mol%) were used.
[b] Pd (2 mol%) and CuI (2 mol%) were used.
[c] Pd (1 mol%) and CuI (1 mol%) were used.

Table 3. The Sonogarshira coupling reaction of **1a** with a variety of aryl iodide



Entry	1a		R	Time (h)	3	
	Configuration	Ee (%)			Yield (%)[a]	Ee (%)[b]
1	(*R*)-**1a**	99	H	5.0	86	98 **3a**
2	(*R*)-**1a**	99	*p*-COOMe	3.5	92	99 **3b**
3	(*R*)-**1a**	99	*p*-NO_2	6.0	86	99 **3c**
4	(*S*)-**1a**	98	*p*-Me	4.0	86	98 **3d**
5	(*S*)-**1a**	98	*p*-MeO	5.0	84	98 **3e**
6	(*S*)-**1a**	98	*p*-Br	4.0	80	98 **3f**
7	(*S*)-**1a**	98	*p*-CN	4.5	86	98 **3g**
8	(*R*)-**1a**	98	*o*-Me	21	87	97 **3h**

[a] Isolated yield based on **1a**.
[b] Determined by HPLC.

protection, alkylation and deprotection process in good yield (Scheme 3).

In conclusion, we have developed an efficient and facile method for the preparation of optically active 1-ethenyl or ethynyl-substituted-2,3-allenols under mild conditions. The obtained optically active 1-alkyn-4,5-dien-3-ols can be further elaborated by arylation or alkylation to afford the corresponding optically active allenols, which could not be directly obtained by Novozym 435-catalyzed kinetic resolution due to the steric reason. Due to the ready availability of both the catalyst and racemic allenols, this methodology should be useful in organic synthesis. Further studies on this reaction are being carried out in our laboratory.

3. Experimental

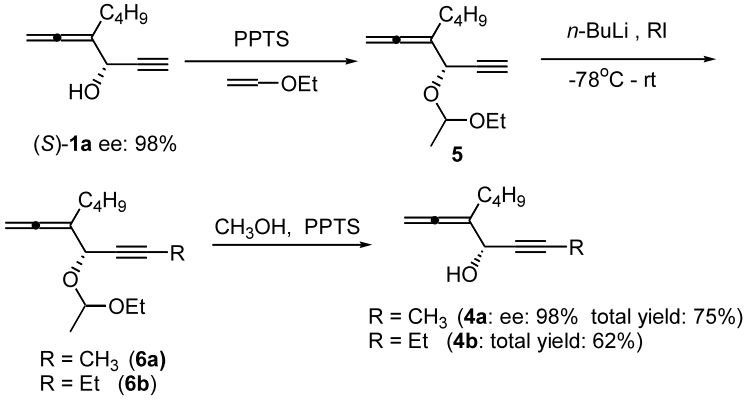
3.1. Synthesis of racemic 2,3-allen-ols 1a–l

The racemic 2,3-allenols were obtained via the reaction of propargylic bromide, aldehyde, and $SnCl_2$.[14]

3.1.1. Synthesis of (±)-4-(*n*-butyl)hexa-4,5-dien-1-yn-3-ol 1a: typical procedure. A suspension of stannous chloride (10.43 g, 55 mmol), 1-bromohept-2-yne (8.74 g, 50 mmol), sodium iodide (8.25 g, 55 mmol), and *N*,*N*-dimethylformamide (100 mL) was stirred at room temperature for 1 h. The reaction was then cooled to 0°C and propynal (2.18 g, 40 mmol) was added. The mixture was stirred at this temperature for 12 h, quenched with water and extracted with ether. The organic layer was washed with sat. NaCl solution and dried over anhydrous magnesium sulfate. After evaporation, the residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ether = 15/1) to afford **1a** (4.46 g, 59%).

3.1.2. Synthesis of (±)-4-allylhexa-4,5-dien-1-yn-3-ol 1b. Reaction of stannous chloride (4.17 g, 22 mmol), 5-hexen-2-ynyl bromide (3.17 g, 20 mmol), sodium iodide (3.30 g, 22 mmol), *N*,*N*-dimethylformamide (40 mL), and propynal (1.08 g, 20 mmol) afforded **1b** (1.32 g, 49%).

3.1.3. Synthesis of (±)-4-(*n*-hexyl)hexa-4,5-dien-1-yn-3-ol 1c. Reaction of stannous chloride (6.43 g, 34 mmol),



Scheme 3. Preparation of substituted 1,2-allenyl-1-alkynyl cabinols (*S*)-**4a** and **4b**.

1-bromonon-2-yne (6.23 g, 31 mmol), sodium iodide (5.08 g, 34 mmol), *N*,*N*-dimethylformamide (60 mL), and propynal (1.70 g, 31 mmol) afforded **1c** (4.04 g, 74%).

3.1.4. Synthesis of (±)-4-benzylhexa-4,5-dien-1-yn-3-ol 1d. Reaction of stannous chloride (2.30 g, 12 mmol), 4-phenylbut-2-ynyl bromide (2.26 g, 11 mmol), sodium iodide (1.82 g, 12 mmol), *N*,*N*-dimethylformamide (20 mL), and propynal (0.59 g, 11 mmol) afforded **1d** (1.27 g, 63%).

3.1.5. Synthesis of (±)-4-(ethoxymethyl)hexa-4,5-dien-1-yn-3-ol 1e. Reaction of stannous chloride (5.22 g, 28 mmol), 4-ethoxybut-2-ynyl bromide (4.43 g, 25 mmol), sodium iodide (4.13 g, 28 mmol), *N*,*N*-dimethylformamide (50 mL), and propynal (1.35 g, 25 mmol) afforded **1e** (2.58 g, 68%).

3.1.6. Synthesis of (±)-4-(2′-phenylethyl)hexa-4,5-dien-1-yn-3-ol 1f. Reaction of stannous chloride (2.30 g, 12 mmol), 5-phenylpent-2-ynyl bromide (2.54 g, 11 mmol), sodium iodide (1.84 g, 12 mmol), *N*,*N*-dimethylformamide (20 mL), and propynal (0.59 g, 11 mmol) afforded **1f** (1.27 g, 56%).

3.1.7. Synthesis of (±)-4-allylhexa-1,4,5-trien-3-ol 1g. Reaction of stannous chloride (4.17 g, 22 mmol), 5-hexen-2-ynyl bromide (3.15 g, 20 mmol), sodium iodide (3.38 g, 23 mmol), *N*,*N*-dimethylformamide (40 mL), and acrolein (1.12 g, 20 mmol) afforded **1g** (1.21 g, 44%).

3.1.8. Synthesis of (±)-4-(*n*-butyl)hexa-1,4,5-trien-3-ol 1h[18]. Reaction of stannous chloride (6.26 g, 33 mmol), 1-bromohept-2-yne (5.32 g, 31 mmol), sodium iodide (4.95 g, 33 mmol), *N*,*N*-dimethylformamide (60 mL), and acrolein (1.34 g, 24 mmol) afforded **1h** (2.43 g, 53%).

3.1.9. Synthesis of (±)-4-benzylhexa-1,4,5-trien-3-ol 1i. Reaction of stannous chloride (3.08 g, 16 mmol), 1-bromo-4-phenylbut-2-yne (2.35 g, 11 mmol), sodium iodide (1.88 g, 13 mmol), *N*,*N*-dimethylformamide (20 mL), and acrolein (0.63 g, 11 mmol) afforded **1i** (1.06 g, 51%).

3.2. Kinetic resolution of racemic 2,3-allenols 1a–i

3.2.1. Synthesis of (*S*)-(+)-4-(*n*-butyl)hexa-4,5-dien-1-yn-3-ol (*S*)-(+)-1a and (*R*)-(+)-4-(*n*-butyl)hexa-4,5-dien-1-yn-3-yl acetate (*R*)-(+)-2a. Typical procedure. To a racemic mixture of 4-(*n*-butyl)hexa-4,5-dien-1-yn-3-ol (l00 mg) and vinyl acetate (5 mL) was added Novozym 435 (70 mg). After stirring at 30°C for 95 h, the reaction mixture was worked up by filtration (ether). Evaporation and purification by flash chromatography on silica gel (eluent: petroleum ether/ether = from 40/1 to 10/1) afforded (*S*)-(+)-**1a** (41 mg, 41%) and (*R*)-(+)-**2a** (59 mg, 46%). (*S*)-(+)-**1a**: >99% ee (determined after its conversion to the corresponding acetate); $[\alpha]_D^{20}$ = +52.5 (2.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.00–4.90 (m, 2H), 4.90–4.78 (m, 1H), 2.51 (d, J = 2.1 Hz, 1H), 2.33 (bs, 1H), 2.18–2.00 (m, 2H), 1.50–1.20 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 204.4, 105.4, 82.7, 79.8, 73.5, 62.8, 29.5, 27.2, 22.3, 13.8; IR (neat): 3307, 2117, 1958 cm^{-1}; MS (m/z) 150 (M^+, 0.17), 79 (100.0); HRMS calcd for $C_{10}H_{14}O$ (M^+) 150.1045. Found 150.1088. (*R*)-(+)-**2a**: 97% ee (GC condition: Column: RT-βDEXcst (30 meters, 0.25 m ID, 0.25 μm DF); carrier: N_2, 12 psi; injector: 250°C; Detector (FID, H_2, 0.218 MPa): 250°C; Oven temperature: 100°C (30 min), then 1.0°C/min to 180°C); liquid; $[\alpha]_D^{20}$ = +31.7 (2.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.85–5.82 (m, 1H), 4.92–4.85 (m, 2H), 2.51 (d, J = 2.4 Hz, 1H), 2.07–1.98 (m, 2H), 2.06 (s, 3H), 1.50–1.22 (m, 4H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.4, 169.4, 101.5, 79.3, 78.8, 74.4, 64.5, 29.4, 27.2, 22.2, 20.8, 13.8; IR (neat): 2124, 1960, 1746 cm^{-1}; MS (m/z) 149 (M^+–$COCH_3$, 3.77), 150 (M^+–$COCH_2$, 28.60), 107 (100.0); HRMS calcd for $C_{10}H_{13}O$ (M^+–$COCH_3$) 149.0967. Found 149.0978.

3.2.2. Synthesis of (*S*)-(+)-4-allylhexa-4,5-dien-1-yn-3-ol (*S*)-(+)-1b and (*R*)-(+)-4-allylhexa-4,5-dien-1-yn-3-yl acetate (*R*)-(+)-2b. The reaction of racemic 3-(*n*-propyl)penta-3,4-dien-2-ol (100 mg) with Novozym 435 (70 mg) afforded (*S*)-(+)-**1b** (55 mg, 55%) and (*R*)-(+)-**2b** (52 mg, 40%). (*S*)-(+)-**1b**: 88% ee (determined after its conversion to the corresponding acetate); $[\alpha]_D^{20}$ = +15.0 (2.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.90–5.78 (m, 1H), 5.20–4.84 (m, 5H), 3.00–2.80 (m, 2H), 2.53 (d, J = 2.1 Hz, 1H), 2.45 (bs, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 204.9, 134.9, 116.6, 103.5, 82.4, 79.7, 73.9, 62.5, 32.6; IR (neat): 3299, 2117, 1958 cm^{-1}; MS (m/z) 134 (M^+, 0.93), 79 (100.0); HRMS calcd for $C_9H_{10}O$ (M^+) 134.0732. Found 134.0738. (*R*)-(+)-**2b**: 98% ee (GC condition: Column: RT-DEXcst (30 meters, 0.25 m ID, 0.25 μm DF); carrier: N_2, 8.5 psi; injector: 250°C; Detector (FID, H_2, 0.218 MPa): 250°C; Oven temperature: 100°C (20 min), then 1.0°C/min to 160°C (2 min) then 5.0°C/min to 180°C); $[\alpha]_D^{20}$ = +34.8 (2.60, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.94–5.78 (m, 2H), 5.20–5.08 (m, 2H), 5.02–4.96 (m, 2H), 2.96–2.82 (m, 2H), 2.58 (d, J = 2.4 Hz, 1H), 1.64 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.7, 169.3, 134.4, 116.6, 100.0, 79.0, 74.62, 74.60, 63.9, 32.6, 20.8; IR (neat): 2125, 1960, 1744, 1642 cm^{-1}; MS (m/z) 161 (M^+-Me, 6.51), 133 (M^+–$COCH_3$, 40.68), 43 (100.0); HRMS calcd for C_9H_9O (M^+–$COCH_3$) 133.0654. Found 133.0682.

3.2.3. Synthesis of (*S*)-(+)-4-(*n*-hexyl)hexa-4,5-dien-1-yn-3-ol (*S*)-1c and (*R*)-(+)-4-(*n*-hexyl)hexa-4,5-dien-1-yn-3-yl acetate (*R*)-2c. The reaction of racemic 4-(*n*-hexyl)hexa-4,5-dien-1-yn-3-ol (100 mg) with Novozym 435 (70 mg) afforded (*S*)-**1c** (38 mg, 38%) and (*R*)-**2c** (49 mg, 40%). (*S*)-**1c**: 97% ee (determined after its conversion to the corresponding benzoate. HPLC condition: ChiralPak AD Column (0.46 cmϕ×25 cm); λ 254 nm; rate: 0.7 mL/min; hexane/*i*-PrOH = 100/0.05); $[\alpha]_D^{20}$ = +41.6 (1.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10–4.90 (m, 2H), 4.90–4.78 (m, 1H), 2.53 (d, J = 2.4 Hz, 1H), 2.22–2.00 (m, 3H), 1.58–1.40 (m, 2H), 1.40–1.20 (m, 6H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 204.4, 105.4, 82.7, 79.9,

73.5, 62.8, 31.6, 28.9, 27.6, 27.4, 22.6, 14.0; IR (neat): 3310, 2111, 1959 cm^{-1}; MS (m/z) 178 (M^+, 0.31), 79 (100.0); HRMS calcd for $C_{12}H_{18}O$ (M^+) 178.1358. Found 178.1374. (*R*)-**2c**: >99% ee (determined after its conversion to the corresponding benzoate by hydrolysis and esterification); liquid; $[\alpha]_D^{20}=+26.2$ (2.65, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.82–5.78 (m, 1H), 4.94–4.82 (m, 2H), 2.48 (d, $J=1.8$ Hz, 1H), 2.05 (s, 3H), 2.05–1.90 (m, 2H), 1.50–1.30 (m, 2H), 1.30–1.10 (m, 6H), 0.82 (t, $J=6.9$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.3, 169.4, 101.5, 79.2, 78.7, 74.3, 64.5, 31.5, 28.7, 27.4, 27.2, 22.5, 20.8, 14.0; IR (neat): 2124, 1960, 1747 cm^{-1}; MS (m/z): 178 (M^++1-$COCH_3$, 9.39), 177 (M^+–$COCH_3$, 1.43), 43 (100.0); HRMS calcd for $C_{14}H_{20}O_2$ (M^+): 220.1463, Found: 220.1437.

3.2.4. Synthesis of (*S*)-(+)-4-benzylhexa-4,5-dien-1-yn-3-ol (*S*)-(+)-1d and (*R*)-4-benzylhexa-4,5-dien-1-yn-3-yl acetate (*R*)-2d. The reaction of racemic 4-benzylhexa-4,5-dien-1-yn-3-ol (100 mg) with Novozym 435 (70 mg) afforded (*S*)-(+)-**1d** (42 mg, 42%) and (*R*)-**2d** (53 mg, 43%). (*S*)-(+)-**1d**: >99% ee (determined after its conversion into the corresponding acetate); $[\alpha]_D^{20}=+25.1$ (1.45, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.08 (m, 5 H), 5.00–4.82 (m, 2H), 4.82–4.70 (m, 1H), 3.60–3.40 (m, 2H), 2.57 (d, $J=2.7$ Hz, 1H), 2.02 (d, $J=7.2$ Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 205.2, 138.4, 129.0, 128.2, 126.4, 104.8, 82.4, 79.6, 74.0, 62.0, 35.0; IR (neat): 3385, 2117, 1959, 1602 cm^{-1}; MS (m/z) 184 (M^+, 3.38), 183 (M–H^+, 22.21), 129 (100.0); HRMS calcd for $C_{13}H_{12}O$ (M^+) 184.0888. Found 184.0916. (*R*)-**2d**: 98% ee (HPLC: ChiralCel OD 0.46 cmϕ×25 cm); λ 254 nm; rate: 0.7 mL/min; hexane/*i*-PrOH = 100/1); liquid; $[\alpha]_D^{20}=+63.4$ (2.30, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.22–7.12 (m, 5H), 5.80–5.76 (m, 1H), 4.84–4.78 (m, 2H), 3.42–3.36 (m, 2H), 2.48 (d, $J=2.4$ Hz, 1H), 1.91 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 207.4, 169.4, 138.3, 128.9, 128.2, 126.4, 101.1, 79.1, 78.8, 74.8, 64.0, 35.1, 20.7; IR (neat): 2124, 1960, 1744, 1602 cm^{-1}; MS (m/z) 184 (M^++1-$COCH_3$, 28.73), 183 (M^+–$COCH_3$, 26.46), 165 (100.0); HRMS calcd for $C_{15}H_{14}O_2$ (M^+) 226.0994. Found 226.1017.

3.2.5. Synthesis of (*S*)-(–)-4-(ethoxymethyl)hexa-4,5-dien-1-yn-3-ol (*S*)-1e and (*R*)-(+)-4-(ethoxymethyl)hexa-4,5-dien-1-yn-3-yl acetate (*R*)-(+)-2e. The reaction of racemic 4-(ethoxymethyl)hexa-4,5-dien-1-yn-3-ol (100 mg) with Novozym 435 (70 mg) afforded (*S*)-**1e** (44 mg, 44%) and (*R*)-(+)-**2e** (53 mg, 42%). (*S*)-**1e**: 98% ee (determined after its conversion to the corresponding acetate); $[\alpha]_D^{20}=-66.6$ (1.80, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.15–4.84 (m, 3H), 4.34 (d, $J=10.8$ Hz, 1H), 4.09 (d, $J=10.8$ Hz, 1H), 3.60–3.30 (m, 3H), 2.54 (s, 1H), 1.19 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.0, 100.7, 82.3, 78.0, 73.6, 68.8, 65.6, 61.9, 14.8; IR (neat): 3310, 2117, 1959 cm^{-1}; MS (m/z) 123 (M^+–C_2H_5, 8.51), 52 (100.0); HRMS calcd for $C_9H_{12}O_2$ (M^+) 152.0837. Found 152.0858. (*R*)-(+)-**2e**: 98% ee (GC condition: Column: RT-βDEXcst (30 meters, 0.25 m ID, 0.25 μm DF); carrier: N_2, 10 psi; injector: 250°C; Detector (FID, H_2, 0.218 MPa): 250°C; Oven temperature: 120°C (20 min)); liquid; $[\alpha]_D^{20}=+2.4$ (1.65, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.98 (m, 1H), 5.03 (m, 2H), 4.11 (t, $J=2.1$ Hz, 2H), 3.49 (q, $J=6.9$ Hz, 2H), 2.75 (d, $J=2.1$ Hz, 1H), 2.10 (s, 3H), 1.20 (t, $J=6.9$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 207.0, 169.5, 98.9, 78.9, 78.7, 74.6, 67.9, 65.3, 61.9, 20.7, 14.8; IR (neat): 2126, 1960, 1745 cm^{-1}; MS (m/z) 194 (M^+, 0.13), 152 (M^++1-$COCH_3$, 10.40), 43 (100.0); HRMS calcd for $C_{11}H_{14}O_3$ (M^+) 194.0943. Found 194.0965.

3.2.6. Synthesis of (*S*)-(+)-4-(2′-phenylethyl)hexa-4,5-dien-1-yn-3-ol (*S*)-(+)-(1f) and (*R*)-(+)-4-(2′-phenylethyl)hexa-4,5-dien-1-yn-3-yl acetate (*R*)-(+)-2f. The reaction of racemic 4-(2′-phenylethyl)hexa-4,5-dien-1-yn-3-ol (100 mg) with Novozym 435 (70 mg) afforded (*S*)-(+)-**1f** (40 mg, 40%) and (*R*)-(+)-**2f** (53 mg, 44%). (*S*)-(+)-**1f**: >99% ee (HPLC condition: ChiralCel OJ Column (0.46 cmϕ×25 cm); λ 254 nm; rate: 0.7 mL/min; hexane/*i*-PrOH = 100/1.25); liquid; $[\alpha]_D^{20}=+18.7$ (1.90, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.18 (m, 5H), 5.08–4.98 (m, 2H), 4.90–4.80 (m, 1H), 2.81 (t, $J=8.1$ Hz, 2H), 2.54 (d, $J=2.4$ Hz, 1H), 2.50–2.40 (m, 2H), 2.20 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 204.7, 141.6, 128.4, 128.3, 125.9, 104.8, 82.5, 80.3, 73.8, 63.0, 33.8, 29.2; IR (neat): 3393, 2117, 1957, 1634 cm^{-1}; MS (m/z) 198 (M^+, 3.72), 91 (100.0); HRMS calcd for $C_{14}H_{14}O$ (M^+) 198.1045. Found 198.1056. (*R*)-(+)-**2f**: >99% ee (HPLC condition: ChiralCel OJ Column (0.46 cmϕ×25 cm); λ 254 nm; rate: 0.7 mL/min; hexane/*i*-PrOH = 100/0.05); liquid; $[\alpha]_D^{20}=+36.0$ (2.80, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.10 (m, 5H), 5.86 (d, $J=2.1$ Hz, 1H), 4.91 (dd, $J=3.6$ and 4.8 Hz, 2H), 2.74 (t, $J=8.1$ Hz, 2H), 2.49 (d, $J=2.1$, 1H), 2.49–2.24 (m, 2H), 2.03 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.5, 169.4, 141.4, 128.3, 128.2, 125.9, 101.0, 79.4, 79.1, 74.6, 64.5, 33.6, 29.2, 20.8; IR (neat): 2124, 1959, 1744, 1604 cm^{-1}; MS (m/z) 198 (M^+–$COCH_2$, 10.77), 197 (M^+–$COCH_3$, 10.80), 91 (100.0); HRMS calcd For $C_{14}H_{13}O$ (M^+–$COCH_3$) 197.0967. Found 197.0961.

3.2.7. Synthesis of (*S*)-(+)-4-allylhexa-1,4,5-trien-3-ol (*S*)-(+)-1g and (*R*)-(+) 4-allylhexa-1,4,5-trien-3-ol acetate (*R*)-(+)-2g. The reaction of racemic 4-allylhexa-1,4,5-trien-3-ol (101 mg) with Novozym 435 (70 mg) afforded (*S*)-(+)-**1g** (39 mg, 39%) and (*R*)-(+)-**2g** (61 mg, 46%). (*S*)-(+)-**1g**: >99% ee (determined after its conversion into the corresponding acetate); $[\alpha]_D^{20}=+71.3$ (1.85, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.90–5.70 (m, 2H), 5.40–5.00 (m, 4H), 5.00–4.90 (m, 2H), 4.45–4.40 (m, 1H), 2.80–2.65 (m, 2H), 2.17 (s, 1H), ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 204.7, 138.2, 135.2, 116.1, 115.6, 104.7, 78.8, 72.5, 32.7; IR (neat): 3379, 1957, 1641 cm^{-1}; MS (m/z) 136 (M^+, 2.35), 57 (100.0); HRMS calcd for $C_9H_{12}O$ (M^+) 136.0888. Found 136.0864. (*R*)-(+)-**2g**: 98% ee (GC condition: Column: RT-DEXcst (30 meters, 0.25 m ID, 0.25 μm DF); carrier: N_2, 8.0 psi; injector: 250°C; Detector (FID, H_2, 0.218 MPa): 250°C; Oven temperature: 100°C (10 min), then 1.0°C/min to 130°C (2 min), then 2.0°C/min to 160°C); liquid; $[\alpha]_D^{20}=+52.9$ (3.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.88–5.70 (m, 2H), 5.70–5.64 (m, 1H), 5.34–5.20 (m, 2H), 5.12–5.00 (m, 2H), 4.90–4.82 (m, 2H), 2.77–2.72 (m, 2H), 2.08 (s, 3H); ^{13}C NMR (75.4 MHz,

$CDCl_3$): δ 206.8, 170.1, 135.2, 134.6, 117.7, 116.6, 101.7, 78.6, 74.4, 33.4, 21.3; IR (neat): 1960, 1744, 1644 cm^{-1}; MS (m/z) 136 (M^++1-$COCH_3$, 23.70), 135 (M^+–$COCH_3$, 10.48), 43 (100.0); HRMS calcd for $C_9H_{11}O$ (M^+–$COCH_3$) 135.0810. Found 135.0789.

3.2.8. Synthesis of (*S*)-(+)-4-(*n*-butyl)hexa-1,4,5-trien-3-ol (*S*)-(+)-1h[18] and (*R*)-(+)-4-(*n*-butyl)hexa-1,4,5-trien-3-yl acetate (*R*)-(+)-2h. The reaction of racemic 4-(*n*-butyl)hexa-1,4,5-trien-3-ol (100 mg) with Novozym 435 (70 mg) afforded (*S*)-(+)-**1h** (50 mg, 50%) and (*R*)-(+)-**2h** (59 mg, 46%). (*S*)-(+)-**1h**: 98% ee (determined after its conversion into the corresponding acetate); $[\alpha]_D^{20}$ = +60.7 (2.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.90–5.76 (m, 1H), 5.29–5.22 (m, 1H), 5.18–5.10 (m, 1H), 4.92–4.80 (m, 2H), 4.52–4.44 (m, 1H), 2.09 (bs, 1H), 2.00–1.90 (m, 2H), 1.48–1.20 (m, 4H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 204.1, 138.7, 115.5, 106.8, 79.2, 72.9, 29.6, 27.6, 22.3, 13.8; IR (neat): 3367, 1956, 1630 cm^{-1}; MS (m/z) 152 (M^+, 0.21), 57 (100.0); HRMS calcd for $C_{10}H_{16}O$ (M^+) 152.1201. Found 152.1222. (*R*)-(+)-**2h**: 98% ee (GC condition: Column: RT-DEXcst (30 meters, 0.25 m ID, 0.25 μm DF); carrier: N_2, 8.0 psi; injector: 250°C; Detector (FID, H_2, 0.218 MPa): 250°C; Oven temperature: 100°C (10 min), then 1.0°C/min to 130°C (2 min), then 2.0°C/min to 160°C); liquid; $[\alpha]_D^{20}$ = +39.9 (2.85, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.90–5.74 (m, 1H), 5.60–5.58 (m, 1H), 5.30–5.16 (m, 2H), 4.85–4.78 (m, 2H), 2.06 (s, 3H), 2.00–1.88 (m, 2H), 1.44–1.24 (m, 4H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.1, 169.9, 134.6, 117.2, 103.0, 78.1, 74.6, 29.5, 27.7, 22.3, 21.1, 13.8; IR (neat): 1959, 1745, 1642 cm^{-1}; MS (m/z) 152 (M^++1-$COCH_3$, 44.15), 151 (M^+–$COCH_3$, 3.01), 43 (100.0); HRMS calcd for $C_{10}H_{15}O$ (M^+–$COCH_3$) 151.1112. Found 151.1120.

3.2.9. Synthesis of (*S*)-(+)-4-benzylhexa-1,4,5-trien-3-ol (*S*)-1i and (*R*)-(+)-4-benzylhexa-1,4,5-trien-3-yl acetate (*R*)-(+)-2i. The reaction of racemic 4-benzylhexa-1,4,5-trien-3-ol (100 mg) with Novozym 435 (70 mg) afforded (*S*)-**1i** (42 mg, 42%) and (*R*)-(+)-**2i** (51 mg, 42%). (*S*)-**1i**: >99% ee (determined after its conversion into the corresponding acetate); $[\alpha]_D^{20}$ = +69.2 (2.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.20 (m, 5H), 5.96–5.82 (m, 1H), 5.36–5.18 (m, 2H), 4.92–4.88 (m, 2H), 4.50 (S, 1H), 3.45 (dt, J = 15.0 and 2.7 Hz, 1H), 3.32 (dt, J = 15.0 and 2.7 Hz, 1H), 1.91 (d, J = 5.1 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 205.2, 138.9, 138.4, 128.9, 128.1, 126.2, 115.8, 106.1, 78.8, 72.1, 35.3; IR (neat): 3380, 1957, 1602 cm^{-1}; MS (m/z) 186 (M^+, 0.99), 185 (M^+-1, 5.98), 129 (100.0); HRMS calcd for $C_{13}H_{14}O$ (M^+) 186.1045. Found 186.0999. (*R*)-(+)-**2i**: >99% ee (HPLC condition: Chiral-Pak AD Column (0.46 cmϕ×25 cm); λ 254 nm; rate: 0.7 mL/min; eluent: hexane/*i*-PrOH = 100/0.5); liquid; $[\alpha]_D^{20}$ = +77.8 (2.40, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.24–7.10 (m, 5H), 5.84–5.70 (m, 1H), 5.61–5.56 (m, 1H), 5.24–5.10 (m, 2H), 4.80–4.68 (m, 2H), 3.26 (t, J = 3.0 Hz, 2H), 1.89 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 207.2, 169.8, 138.6, 134.3, 128.9, 128.1, 126.2, 117.4, 102.3, 78.0, 74.0, 35.6, 20.9; IR (neat): 1959, 1743, 1644, 1601 cm^{-1}; MS (m/z) 186 (M^+–$COCH_2$, 19.54), 185 (M^+–$COCH_3$, 5.99), 43 (100.0); HRMS calcd for $C_{13}H_{13}O$ (M^+–$COCH_3$) 185.0967. Found 185.0975.

3.2.10. Synthesis of (*R*)-(−)-4-(*n*-butyl)hexa-4,5-dien-1-yn-3-ol (*R*)-(−)-1a. To the solution of (*R*)-4-(*n*-butyl)hexa-4,5-dien-1-yn-3-yl acetate **2a** (0.49 g, 2.55 mmol, 99% ee) in MeOH (5 mL) was added K_2CO_3 (0.35 g, 2.55 mmol). The resulting mixture was stirred for 9 h at room temperature as monitored by TLC. After filtration, washing with ethyl ether, and evaporation, the residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl ether = 10/1) to afford (*R*)-**1a** (0.31 g, 82%, 99% ee); liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 5.00–4.90 (m, 2H), 4.90–4.78 (m, 1H), 2.51 (d, J = 2.1 Hz, 1H), 2.33 (s, 1H), 2.18–2.00 (m, 2H), 1.50–1.20 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H).

3.3. Sonogashira coupling of optically active 1a with differently substituted aryl iodides

3.3.1. Synthesis of (*R*)-(−)-1-phenyl-4-(*n*-butyl)hexa-4,5-dien-1-yn-3-ol (*R*)-(−)-3a: typical procedure. To a mixture of (*R*)-4-(*n*-butyl)hexa-4,5-dien-1-yn-3-ol **1a** (75 mg, 0.5 mmol, ee: 99%), CuI (2.2 mg, 0.01 mmol), $Pd(PPh_3)_2Cl_2$ (6.9 mg, 0.01 mmol) and PhI (0.08 mL, 0.7 mmol) in THF (2 mL) was added *i*-Pr_2NH (0.07 mL, 0.5 mmol) under nitrogen at −2°C. The resulting mixture was stirred at −2°C for 5 h as monitored by TLC. After filtration, washing with ethyl ether and evaporation, the residue was purified by flash chromatography on silica gel (eluent, 10:1 petroleum ether/ethyl ether, the column was washed with petroleum ether/*i*-Pr_2NH (100:1) before using) to afford 97 mg (86%) of (*R*)-(−)-**3a**. 98% ee (HPLC condition: Chiralpak As Column (0.46 cmϕ×25 cm); λ 254 nm; rate: 0.7 mL/min; eluent: hexane/*i*-PrOH = 100/1.2); liquid; $[\alpha]_D^{20}$ = −27.2 (1.85, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.50–7.40 (m, 2H), 7.35–7.28 (m, 3H), 5.07 (s, 1H), 5.01–4.97 (m, 2H), 2.23 (bs, 1H), 2.22–2.14 (m, 2H), 1.60–1.25 (m, 4H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 204.6, 131.7, 128.4, 128.2, 122.4, 105.8, 88.0, 85.4, 79.6, 63.5, 29.6, 27.4, 22.3, 13.9; IR (neat): 3331, 2200, 1959 cm^{-1}; MS (m/z) 226 (M^+, 1.76), 131 (100.0); HRMS calcd for $C_{16}H_{18}O$ (M^+) 226.1358. Found 226.1376.

3.3.2. Synthesis of (*R*)-(−)-(4′-methoxycarbonylphenyl)-4-(*n*-butyl)hexa-4,5-dien-1-yn-3-ol (*R*)-(−)-3b. The reaction of (*R*)-4-(*n*-buty)hexa-4,5-dien-1-yn-3-ol **1a** (44 mg, 0.29 mmol, ee: 99%), CuI (1.2 mg, 0.006 mmol), $Pd(PPh_3)_2Cl_2$ (4.1 mg, 0.006 mmol), *i*-Pr_2NH (0.04 mL, 0.3 mmol), *p*-(methoxycarbonyl)phenyl iodide (85 mg, 0.32 mmol), and THF (1.2 mL) afforded 76 mg (92%) of (*R*)-(−)-**3b**. 99% ee (HPLC condition: Chiralcel OJ Column (0.46 cmϕ×25 cm); λ 254 nm; rate: 0.7 mL/min; eluent: hexane/*i*-PrOH = 85/15); liquid; $[\alpha]_D^{20}$ = −39.9 (1.45, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 5.10–4.96 (m, 3H), 3.91 (s, 3H), 2.26–2.14 (m, 3H), 1.50–1.20 (m, 4H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 204.6, 166.5, 131.5, 129.5, 129.3, 127.2, 105.5, 91.1, 84.4, 79.6, 63.4, 52.2, 29.6, 27.4, 22.3, 13.8; IR (neat): 3430, 2200, 1952, 1726 cm^{-1}; MS (m/z) 283 (M^+-H, 2.87), 269 (M^+-CH_3, 5.60), 189 (100.0); HRMS calcd for $C_{18}H_{20}O_3$ (M^+) 284.1412. Found: 284.1380.

3.3.3. Synthesis of (*R*)-(−)-1-(4′-nitrophenyl)-4-(*n*-butyl)hexa-4,5-dien-1-yn-3-ol (*R*)-(−)-3c. The reaction of (*R*)-4-(*n*-butyl)hexa-4,5-dien-1-yn-3-ol **1a** (45 mg, 0.3 mmol, ee: 99%), CuI (1.2 mg, 0.006 mmol), $Pd(PPh_3)_2Cl_2$ (4.1 mg, 0.006 mmol), *i*-Pr_2NH (0.04 mL, 0.3 mmol), 4-nitrophenyl iodide (85 mg, 0.33 mmol), and THF (1.2 mL) afforded 70 mg (86%) of (*R*)-(−)-**3c**. 99% ee (HPLC condition: Chiralpak As Column (0.46 cmϕ×25 cm); λ 254 nm; rate: 0.7 mL/min; eluent: hexane/*i*-PrOH = 90/10); liquid; $[\alpha]_D^{20} = -50.1$ (1.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.17 (d, $J = 9.3$ Hz, 2H), 7.57 (d, $J = 9.3$ Hz, 2H), 5.09–4.96 (m, 3H), 2.28 (d, $J = 6.6$ Hz, 1H), 2.23–2.01 (m, 2H), 1.60–1.30 (m, 4H), 0.91 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 204.5, 147.0, 132.3, 129.3, 123.4, 105.2, 93.3, 83.3, 79.9, 63.4, 29.5, 27.4, 22.2, 13.8; IR (neat): 3385, 1958, 1595 cm^{-1}; MS (*m*/*z*) 270 (M^+–H, 1.34), 189 (100.0); HRMS calcd for $C_{16}H_{17}NO_3$ (M^+) 271.1208. Found 271.1208.

3.3.4. Synthesis of (*S*)-(+)-1-(4′-methylphenyl)-4-(*n*-butyl)hexa-4,5-dien-1-yn-3-ol (*S*)-(+)-3d. The reaction of (*S*)-4-(*n*-butyl)hexa-4,5-dien-1-yn-3-ol **1a** (40 mg, 0.27 mmol, ee: 98%), CuI (1.0 mg, 0.005 mmol), $Pd(PPh_3)_2Cl_2$ (4.0 mg, 0.006 mmol), *i*-Pr_2NH (0.04 mL, 0.3 mmol), 4-methylphenyl iodide (72 mg, 0.33 mmol), and THF (1 mL) afforded 55 mg (86%) of (*S*)-(+)-**3d**. 98% ee (HPLC condition: ChiralCel OJ Column (0.46 cmϕ×25 cm); λ 254 nm; rate: 0.7 mL/min; eluent: hexane/*i*-PrOH = 95/5); liquid; $[\alpha]_D^{20} = +81.5$ (2.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, $J = 8.1$ Hz, 2H), 7.11 (d, $J = 8.1$ Hz, 2H), 5.07 (s, 1H), 5.04–4.80 (m, 2H), 2.60–2.24 (m, 4H), 2.20–2.04 (m, 2H), 1.50–1.20 (m, 4H), 0.93 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 204.6, 138.5, 131.6, 128.9, 119.3, 105.8, 87.3, 85.5, 79.6, 63.5, 29.6, 27.4, 22.3, 21.4, 13.9; IR (neat): 3385, 2193, 1956 cm^{-1}; MS (*m*/*z*) 240 (M^+, 1.13), 145 (100.0); HRMS calcd for $C_{17}H_{20}O$ (M^+) 240.1514. Found 240.1515.

3.3.5. Synthesis of (*S*)-(+)-1-(4′-methoxyphenyl)-4-(*n*-butyl)hexa-4,5-dien-1-yn-3-ol (*S*)-(+)-3e. The reaction of (*S*)-4-(*n*-butyl)hexa-4,5-dien-1-yn-3-ol **1a** (47 mg, 0.31 mmol, ee: 98%), CuI (1.3 mg, 0.007 mmol), $Pd(PPh_3)_2Cl_2$ (4.2 mg, 0.006 mmol), *i*-Pr_2NH (0.05 mL, 0.36 mmol), 4-methoxylphenyl iodide (77 mg, 0.33 mmol), and THF (1 mL) afforded 67 mg (84%) of (*S*)-(+)-**3e**. 98% ee (HPLC condition: ChiralCel OJ Column (0.46 cmϕ×25 cm); λ 254 nm; rate: 0.7 mL/min; eluent: hexane/*i*-PrOH = 95/5); liquid; $[\alpha]_D^{20} = +32.1$ (2.40, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.38 (d, $J = 8.4$ Hz, 2H), 6.84 (d, $J = 8.4$ Hz, 2H), 5.10–4.95 (m, 3H), 3.81 (s, 3H), 2.28–2.08 (m, 3H), 1.60–1.38 (m, 4H), 0.93 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 204.5, 159.6, 133.1, 114.5, 113.8, 105.9, 86.6, 85.3, 79.5, 63.5, 55.2, 29.6, 27.4, 22.3, 13.9; IR (neat): 3385, 2230, 1952, 1606 cm^{-1}; MS (*m*/*z*) 255 (M^+–H, 3.37), 161 (100.0); HRMS calcd for $C_{17}H_{20}O_2$ 256.1463. Found 256.1423.

3.3.6. Synthesis of (*S*)-(+)-1-(4′-bromophenyl)-4-(*n*-butyl)hexa-4,5-dien-1-yn-3-ol (*S*)-(+)-3f. The reaction of (*S*)-4-(*n*-butyl)hexa-4,5-dien-1-yn-3-ol **1a** (48 mg, 0.32 mmol, ee: 98%), CuI (1.4 mg, 0.007 mmol), $Pd(PPh_3)_2Cl_2$ (5.0 mg, 0.007 mmol), *i*-Pr_2NH (0.05 mL, 0.36 mmol), 4-bromophenyl iodide (94 mg, 0.33 mmol), and THF (2 mL) afforded 78 mg (80%) of (*S*)-(+)-**3f**. 98% ee (HPLC condition: ChiralCel OJ Column (0.46 cmϕ×25 cm); λ 254 nm; rate: 0.7 mL/min; eluent: hexane/*i*-PrOH = 95/5); liquid; $[\alpha]_D^{20} = +65.7$ (2.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.4$ Hz, 2H), 5.10–4.98 (m, 3H), 2.30–2.04 (m, 3H), 1.58–1.36 (m, 4H), 0.92 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 204.6, 133.1, 131.4, 122.7, 121.3, 105.5, 89.1, 84.3, 79.7, 63.4, 29.6, 27.4, 22.3, 13.9; IR (neat): 3332, 2230, 1958 cm^{-1}; MS (*m*/*z*) 304 (M^+(^{79}Br), 3.70), 306 (M^+(^{81}Br), 3.80), 209 (100.0); HRMS calcd for $C_{16}H_{17}BrO$ (M^+(^{79}Br)) 304.0663. Found 304.0429.

3.3.7. Synthesis of (*S*)-(+)-1-(4′-cyanophenyl)-4-(*n*-butyl)hexa-4,5-dien-1-yn-3-ol (*S*)-(+)-3g. The reaction of (*S*)-4-(*n*-butyl)hexa-4,5-dien-1-yn-3-ol **1a** (43 mg, 0.29 mmol, ee: 98%), CuI (1.4 mg, 0.007 mmol), $Pd(PPh_3)_2Cl_2$ (4.3 mg, 0.006 mmol), *i*-Pr_2NH (0.05 mL, 0.36 mmol), 4-cyanophenyl iodide (75 mg, 0.33 mmol), and THF (1 mL) afforded 62 mg (86%) of (*S*)-(+)-**3g**. 98% ee (HPLC condition: Chiralpak As Column (0.46 cmϕ×25 cm); λ 254 nm; rate: 0.7 mL/min; eluent: hexane/*i*-PrOH = 90/10); liquid; $[\alpha]_D^{20} = +54.7$ (0.90, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, $J = 9.0$ Hz, 2H), 7.51 (d, $J = 9.0$ Hz, 2H), 5.12–4.98 (m, 3H), 2.22–2.12 (m, 3H), 1.60–1.38 (m, 4H), 0.92 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 204.6, 132.1, 131.9, 127.4, 118.3, 111.6, 105.3, 92.5, 83.6, 79.9, 63.3, 29.5, 27.4, 22.2, 13.8; IR (neat): 3473, 2233, 1959, 1603 cm^{-1}; MS (*m*/*z*) 250 (M^+–H, 1.14), 156 (100.0); HRMS calcd for $C_{17}H_{17}NO$ (M^+) 251.1310. Found 251.1328.

3.3.8. Synthesis of (*R*)-(−)-1-(2′-methylphenyl)-4-(*n*-butyl)hexa-4,5-dien-1-yn-3-ol (*R*)-(−)-3h. The reaction of (*R*)-4-(*n*-butyl)hexa-4,5-dien-1-yn-3-ol **1a** (73 mg, 0.49 mmol, ee: 98%), CuI (2.0 mg, 0.01 mmol), $Pd(PPh_3)_2Cl_2$ (7.0 mg, 0.01 mmol), *i*-Pr_2NH (0.07 mL, 0.5 mmol), 2-methylphenyl iodide (0.075 mL, 0.59 mmol), THF (2 mL) afforded 103 mg (87%) of (*R*)-(−)-**3h**. 97% ee (HPLC condition: ChiralCel OD Column (0.46 cmϕ×25 cm); λ 254 nm; rate: 0.7 mL/min; eluent: hexane/*i*-PrOH = 90/10); liquid; $[\alpha]_D^{20} = -23.4$ (4.75, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.42 (d, $J = 7.5$ Hz, 1H), 7.28–7.08 (m, 3H), 5.14–5.08 (m, 1H), 5.02–4.98 (m, 2H), 2.44 (s, 3H), 2.28–2.08 (m, 3H), 1.58–1.38 (m, 4H), 0.93 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 204.6, 140.3, 132.1, 129.4, 128.5, 125.5, 122.2, 106.0, 91.8, 84.3, 79.8, 63.7, 29.7, 27.6, 22.4, 20.7, 13.9; IR (neat): 3311, 2229, 1958 cm^{-1}; MS (*m*/*z*) 240 (M^+, 1.67), 145 (100.0); HRMS Calcd for $C_{17}H_{20}O$ (M^+) 240.1514. Found 240.1535.

3.4. The alkylation of optically active (*S*)-1a

3.4.1. Synthesis of (*S*)-(+)-3-(*n*-butyl)hepta-1,2-dien-5-yn-4-ol (*S*)-(+)-4a. Typical procedure. To a mixture of (*S*)-**1a** (73 mg, 0.49 mmol, ee: 98%) and vinyl ethyl ether (0.072 mL, 0.75 mmol) in CH_2Cl_2 (1 mL) was added PPTS (14 mg, 0.05 mmol) at room temperature.

The resulting mixture was stirred for 4.5 h as monitored by TCL. After evaporation, the residue was purified by flash chromatography on silica gel (eluent: 40:1 petroleum ether/ethyl ether) to afford compound **5**. To the solution of compound **5** in THF (1 mL) was added *n*-BuLi (0.31 mL, 1.6 M in hexane) under nitrogen at −78°C and the mixture was stirred for 1 h. Then, to the resulting mixture was added subsequently HMPA (10 μL) and CH_3I (0.75 mmol). After being stirred for 13.5 h at room temperature, the reaction was worked up by addition of saturated brine. After extraction with ethyl ether (20 mL×3), dried over anhydrous Na_2SO_4, and evaporation, the residue was purified by chromatography on silica gel to afford compound **6a**. To the solution of **6a** in CH_3OH (2 mL) was added PPTS (14 mg, 0.05 mmol). After being stirred for 3 h at room temperature and evaporation, the residue was purified by flash chromatography on silica gel (eluent: 10:1 petroleum ether/ethyl ether) to afford 60 mg (75%) of (*S*)-(+)-**4a**. 98% ee (GC condition: Column: ChiralDEX G-BP (20 m×0.25 mm); carrier: N_2, 10.0 psi; injector: 250°C; Detector (FID, H_2, 0.218 MPa): 250°C; Oven temperature: 110°C (20 min)); liquid; $[\alpha]_D^{20}=+49.6$ (1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.94 (dt, $J=2.1$ and 3.6 Hz, 2H), 4.84–4.75 (m, 1H), 2.20–2.00 (m, 2H), 2.00 (d, $J=6.0$ Hz, 1H), 1.87 (d, $J=1.8$ Hz, 3H), 1.50–1.30 (m, 4H), 0.91 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): 204.2, 106.1, 81.6, 79.4, 78.2, 63.1, 29.6, 27.1, 22.3, 13.8, 3.5; IR (neat): 3395, 2225, 1958 cm^{-1}; MS (*m*/*z*) 164 (M^+, 0.64), 67 (100.0); HRMS calcd for $C_{11}H_{16}O$ (M^+) 164.1201. Found 164.1158.

3.4.2. Synthesis of (*S*)-4-(*n*-butyl)oct-1,2-diene-5-yn-4-ol 4b. The reaction of (*S*)-**1a** (78 mg, 0.52 mmol, 98% ee), vinyl ethyl ether (0.08 mL, 0.83 mmol) and PPTS (14 mg, 0.05) in CH_2Cl_2 (1 mL) afforded compound **5**. The reaction of compound **5**, *n*-BuLi (0.33 mL, 1.6 M in hexane), HMPA (10 μL) and CH_3CH_2I (0.78 mmol) afforded compound **6b**. The reaction of **6b** and PPTS (14 mg, 0.05 mmol) in CH_3OH (1 mL) afforded (*S*)-**4b** (59 mg, 63%). liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 4.92 (dt, $J=2.4$ and 3.6 Hz, 2H), 4.84–4.75 (m, 1H), 2.28–2.06 (dq, $J=2.1$ and 7.5 Hz, 2H), 2.06–2.00 (m, 2H), 1.94 (d, $J=6.3$ Hz, 1H), 1.50–1.30 (m, 4H), 1.12 (t, $J=7.2$ Hz, 3H), 0.89 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): 204.3, 106.2, 87.6, 79.5, 78.4, 63.2, 29.7, 27.3, 22.3, 13.9, 13.7, 12.4; IR (neat): 3374, 2224, 1959 cm^{-1}; MS (*m*/*z*) 178 (M^+, 0.50), 83 (100.0); HRMS calcd for $C_{12}H_{18}O$ (M^+) 178.1358. Found 178.1360.

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