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Dimethylprolinol Versus Diphenylprolinol in $CuBr_2$-Catalyzed Enantioselective Allenylation of Terminal Alkynols

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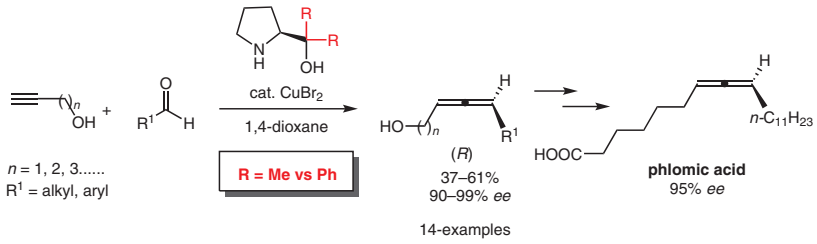

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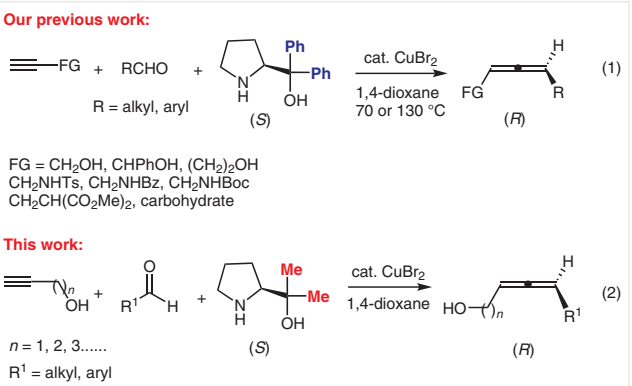
Abstract The $CuBr_2$-catalyzed enantioselective allenylation of terminal alkynols with carbon chains of different lengths has been developed. Compared with (*S*)-α,α-diphenylprolinol, the reaction using (*S*)-α,α-dimethylprolinol as the chiral amine afforded optically active 1,3-disubstuted allenols with higher *ee*-values. Both aliphatic and aromatic aldehydes could be applied. The naturally occurring phlomic acid was synthesized in four steps from commercially available hex-5-yn-1-ol.

Key words $CuBr_2$, enantioselective allenylation, terminal alkynols, (*S*)-α,α-diphenylprolinol, (*S*)-α,α-dimethylprolinol, phlomic acid

Optically active 1,3-disubstituted allenes[1] are the key unit in some natural products or bioactive compounds, such as marasin,[2] (*R*)-(–)-adenallene,[3] and (*R*)-(–)-cytallene.[4] Allenols are potential precursors for a series of 1,3-disubstituted allenic natural products.[5] Owing to the rich reactivity of the alcohol functionality towards other synthetically useful functional groups, including aldehydes, esters, amides, amines, halides, malonates, etc., chiral allenols are very useful starting materials in organic synthesis. So far, transition metal-catalyzed cyclization of allenols has been a powerful tool for the construction of oxa-cyclic compounds.[6] In addition, the axial chirality of allenes may be transferred to central chirality under suitable reaction conditions.[7] Thus, the highly enantioselective synthesis of 1,3-disubstituted allenols is of high interest.

Recently, significant advances on the synthesis of axially chiral allenes with functionalized groups such as boronates, alcohols, esters, amides, malonates, etc. have been achieved.[1,8] In 2015, we reported the $CuBr_2$-catalyzed highly enantioselective synthesis of optically active allenes from terminal alkynes, aldehydes, and (*R*)- or (*S*)-α,α-diphenylprolinol (Scheme 1, Equation 1).[9] However, the enantioselectivity for some α-allenols with longer carbon chains between the allene moiety and alcohol functionality is not satisfactory (see also the data in Table 1). To our delight, when (*S*)-α,α-dimethylprolinol was used instead of (*S*)-α,α-diphenylprolinol, the enantioselectivity could be improved to a satisfactory level.[10] Reported methods for the preparation of optically active 1,3-disubstituted allenols usually suffered from lengthy steps, harsh conditions, limited scopes, and low enantioselectivity, etc.[1b,11] Particularly, reports on the preparation of optically active allenols with longer carbon chains than γ-allenols are rare. Herein, we wish to report our recent investigations on developing a general access to these 1,3-disubstituted allenols with a practical enantioselectivity from the readily available terminal alkynols (Scheme 1, Equation 2).[12]



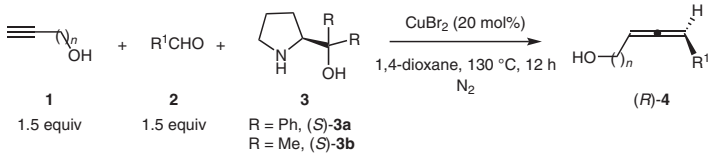
Scheme 1 $CuBr_2$-catalyzed enantioselective allenylation of terminal alkynes

Different terminal alkynols **1a–f** were reacted with undecanal (**2a**) under $CuBr_2$ (20 mol%) in the presence of (*S*)-α,α-diphenylprolinol [(*S*)-**3a**] and (*S*)-α,α-dimethylprolinol [(*S*)-**3b**], respectively. As a result, the reactions promoted by (*S*)-**3b** afforded higher *ee* values (93–96% *ee*) than those by (*S*)-**3a** (85–93% *ee*) in all cases (Table 1, entries 1–6). When

n >1, the difference in enantioselectivity is much larger. In most cases, the yields are also higher (entries 2–6). Besides *n*-alkyl aldehyde **2a**, the bulkier *sec*-alkyl aldehydes could also be applied. The reactions using (*S*)-**3b** also gave chiral allenols in higher yields and *ee*s than those using (*S*)-**3a** (entries 7–9).

Among the three reactants of the allenylation reaction, terminal alkynols **1** are usually not commercially available, and should be generally considered as the limiting reagent. Thus, the reaction was further optimized for this purpose. At first, we attempted the reaction with the ratio of **1c**/**2a**/(*S*)-**3b** being 1:1.5:1.1. As a result, the yield of (*R*)-**4ca** was 51% and the *ee*-value was 94% (Table 2, entry 2), both of which were slightly lower than that of reactions using **1c**/**2a**/(*S*)-**3b** (ratio: 1.5:1.5:1) (entry1). On the basis of the results, the effect of the loading of **2a** was screened (entries 2–5): When the ratio of **1c**/**2a**/(*S*)-**3b** was 1:1.4:1.1, (*R*)-**4ca** was obtained in 46% yield with the highest *ee* of 95% (entry 3). Increasing the loading of (*S*)-**3b** to 1.2 equivalents led to an improved yield of 49% with the same *ee* (entry 6). Thus, the best conditions for this reaction could also be defined as **1** (1.0 equiv) and **2** (1.4 equiv) reacted with (*S*)-**3b** (1.2

Table 1 Allenylation of Different Terminal Alkynols **1** with Aliphatic Aldehydes **2**: (*S*)-**3a** vs (*S*)-**3b**[a]

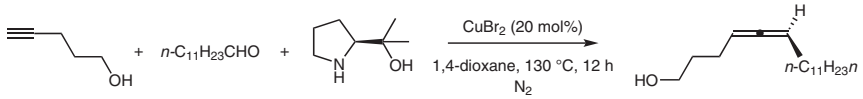


1 1.5 equiv | **2** 1.5 equiv | **3** R = Ph, (*S*)-**3a**; R = Me, (*S*)-**3b** | (*R*)-**4**

Entry	**1**	**2**	(*R*)-**4** from (*S*)-**3a**		(*R*)-**4** from (*S*)-**3b**	
	n	R	Yield (%)[b]	*ee* (%)	Yield (%)[b]	*ee* (%)
1	1 (**1a**)	*n*-$C_{11}H_{23}$(**2a**)	60[c] [(*R*)-**4aa**]	93[c]	61 [(*R*)-**4aa**]	96
2	2 (**1b**)	*n*-$C_{11}H_{23}$(**2a**)	49 [(*R*)-**4ba**]	86	51 [(*R*)-**4ba**]	95
3	3 (**1c**)	*n*-$C_{11}H_{23}$(**2a**)	56 [(*R*)-**4ca**]	85	53 [(*R*)-**4ca**]	95
4	4 (**1d**)	*n*-$C_{11}H_{23}$(**2a**)	51 [(*R*)-**4da**]	88	57 [(*R*)-**4da**]	93
5	5 (**1e**)	*n*-$C_{11}H_{23}$(**2a**)	46 [(*R*)-**4ea**]	87	52 [(*R*)-**4ea**]	96
6	6 (**1f**)	*n*-$C_{11}H_{23}$(**2a**)	53 [(*R*)-**4fa**]	88	50 [(*R*)-**4fa**]	95
7	4 (**1d**)	Cy (**2b**)	45 [(*R*)-**4db**]	93	46 [(*R*)-**4db**]	97
8	4 (**1d**)	*i*-Pr (**2g**)	40 [(*R*)-**4dg**]	92	49 [(*R*)-**4dg**]	96
9	4 (**1d**)	Et_2CH (**2h**)	34 [(*R*)-**4dh**]	94	53 [(*R*)-**4dh**]	99

[a] The reaction was conducted using **1** (1.5 mmol), **2** (1.5 mmol), (*S*)-**3a** or (*S*)-**3b** (1.0 mmol), and $CuBr_2$ (20 mol%) in 1,4-dioxane (3 mL) at 130 °C for 12 h.
[b] Isolated yield.
[c] Data reported in entry 12 of Table 2 in Ref. 9a.

Table 2 Reaction of **2a** with Pent-4-yn-1-ol (**1c**) as the Limiting Reagent[a]



1c | **2a** | (*S*)-**3b** | (*R*)-**4ca**

Entry	**1c**/**2a**/(*S*)-**3b**	(*R*)-**4ca**	
		Yield (%)[b]	*ee* (%)
1	1.5:1.5:1	53	95
2	1:1.5:1.1	51	94
3	1:1.4:1.1	46	95
4	1:1.45:1.1	46	94
5	1:1.6:1.1	50	93
6	**1:1.4:1.2**	**49**	**95**

[a] The reaction was conducted using **1c**, **2a**, (*S*)-**3b**, and $CuBr_2$ (20 mol%) in 1,4-dioxane (3 mL) on 1 mmol scale at 130 °C for 12 h.
[b] Isolated yield.

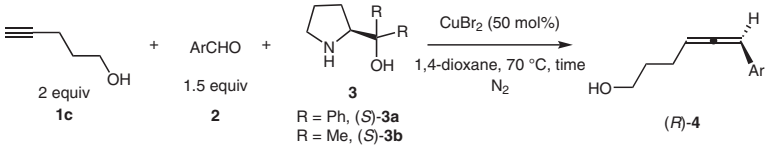
equiv) catalyzed by $CuBr_2$ (20 mol%) at 130 °C in 1,4-dioxane when terminal alkynols were considered as the limiting reagent.

With the optimized conditions in hand, the reaction was then carried out on a gram scale. The allenol (*R*)-**4da** was obtained smoothly in 55% yield with 97% *ee* (Scheme 2).

The reactions of aromatic aldehydes were also tested. Pent-4-yn-1-ol (**1c**; 2 equiv) reacted with benzaldehyde (**2c**; 1.5 equiv) under $CuBr_2$ (50 mol%) in the presence of (*S*)-**3a** at 70 °C in 1,4-dixoane to give (*R*)-**4cc** in 45% yield with 95% *ee*. Under the same conditions, (*S*)-**3b**-promoted reaction afforded (*R*)-**4cc** in 37% yield with 98% *ee* (Table 3, entry 1). For 4-bromobenzaldehyde (**2d**), (*S*)-**3b**-promoted reaction gave better *ee* than (*S*)-**3a**. However, the yield was lower (entry 2). When 4-methylbenzaldehyde (**2e**) was applied under the same conditions, better yield and *ee* were obtained in the presence of (*S*)-**3b**. Nevertheless, the enantioselectivity for (*R*)-**4ce** was 90%, which was not satisfactory (entry 3). Gladly, the reaction using **1c**/**2e**/(*S*)-**3b** (ratio 1:1.4:1.4) gave a better result, affording (*R*)-**4ce** with 93% *ee* albeit in a yield of 41% (entry 4). For 4-nitrobenzaldehyde (**2f**), the reaction using (*S*)-**3b** afforded (*R*)-**4cf** with a slightly better *ee*, but a lower yield than that using (*S*)-**3a** (entry 5). The reaction of *o*-chlorobenzaldehyde (**2i**) using (*S*)-**3a** and (*S*)-**3b** afforded the corresponding allenol (*R*)-**4ci** in 6% and 12% NMR yield, respectively (Scheme 3).

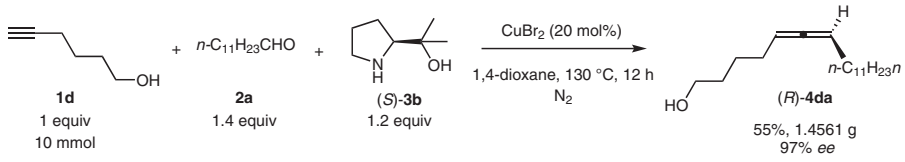
Several transformations were conducted to illustrate the synthetic potentials of these optically active allenols. Aerobic oxidation of (*R*)-**4ca** afforded chiral allenal (*R*)-**5** with the same *ee* under the catalysis of 20 mol% each of $Fe(NO_3)\cdot 9H_2O$, TEMPO, and NaCl in DCE (Scheme 4A).[13] Allenol (*R*)-**4da** could undergo a Mitsunobu reaction[14] to afford chiral allenyl amide (*R*)-**6** without any racemization (Scheme 4B).

Table 3 Some Typical Examples with Aromatic Aldehydes[a]

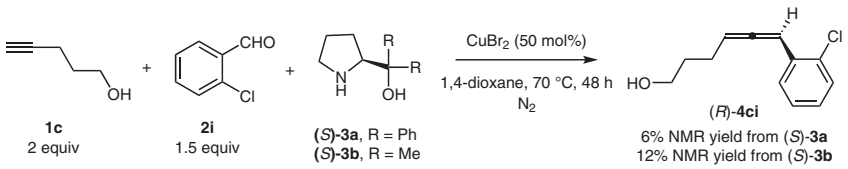


Entry	**2**	(*R*)-**4** from (*S*)-**3a**			(*R*)-**4** from (*S*)-**3b**		
	Ar	Time (h)	Yield (%)[b]	*ee* (%)	Time (h)	Yield (%)[b]	*ee* (%)
1	Ph (**2c**)	46.5	45 [(*R*)-**4cc**]	95	46.5	37 [(*R*)-**4cc**]	98
2	4-BrC_6H_4(**2d**)	44.5	51 [(*R*)-**4cd**]	90	45.5	41 [(*R*)-**4cd**]	94
3	4-MeC_6H_4(**2e**)	46.5	49 [(*R*)-**4ce**]	76	47.5	56 [(*R*)-**4ce**]	90
4[c]	4-MeC_6H_4(**2e**)	–	–	–	42	41 [(*R*)-**4ce**]	93
5	4-$NO_2C_6H_4$ (**2f**)	43	47 [(*R*)-**4cf**]	95	43	39 [(*R*)-**4cf**]	96

[a] The reaction was conducted using **1c** (2 mmol), **2** (1.5 mmol), (*S*)-**3a** or (*S*)-**3b** (1 mmol), and $CuBr_2$ (50 mol%) in 1,4-dioxane (3 mL) at 70 °C.
[b] Isolated yield.
[c] The reaction was conducted using **1c** (1 mmol), **2e** (1.4 mmol), (*S*)-**3b** (1.4 mmol), and $CuBr_2$ (50 mol%) in 1,4-dioxane (3 mL) at 70 °C.



Scheme 2 Gram-scale synthesis of allenol (*R*)-**4da**



Scheme 3 Reaction of *o*-chlorobenzaldehyde with pent-4-yn-1-ol

Finally, we applied this chemistry to the convenient synthesis of naturally occurring phlomic acid (*R*)-**9**.[10,15] Starting from (*R*)-**4da**, iodide (*R*)-**7** was obtained by the treatment of PPh_3, imidazole, and I_2.[16] Then, the diester (*R*)-**8** was formed in 61% yield with 96% *ee* by alkylation with diethyl malonate in the presence of NaH as the base. By the treatment with aqueous NaOH in MeOH, followed by heating in AcOH at 120 °C, natural product phlomic acid [(*R*)-**9**] was obtained in 78% yield and 95% *ee* (Scheme 4C).

As proposed in our previous work,[9a] the reaction between the in situ generated alkynylmetal species **IN-1** and the iminium ion **11** via 1,2-attack of the alkynyl entity from the back-side of the dimethylhydroxymethyl or diphenylhydroxymethyl group would generate propargylic amine (*S*,*S*)-**12**, which undergoes highly stereoselective $CuBr_2$-mediated intramolecular 1,5-hydride transfer followed by *anti*-β-elimination to deliver the *R*-allene unit. The reaction using (*S*)-dimethylprolinol may afford optically active propargylic amine (*S*,*S*)-**12** with higher de, resulting in higher *ee* for 1,3-disubstituted allenols (Scheme 5).

In conclusion, we have developed a general allenylation of terminal alkynols with aliphatic or aromatic aldehydes using (*S*)-α,α-dimethylprolinol instead of (*S*)-α,α-diphenylprolinol, affording a series of optically active 1,3-disubstituted allenols with high enantioselectivity in one-pot. The synthetic potentials of these allenols prepared have also been demonstrated by oxidation to aldehyde and conversion to amide, as well as a different approach for the naturally occurring phlomic acid.

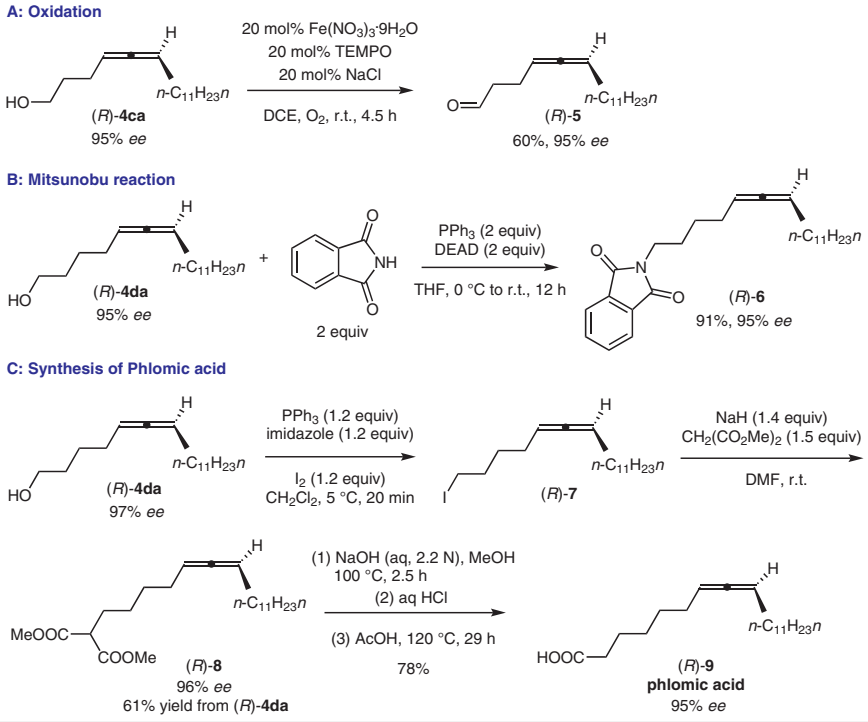
^1H and ^{13}C NMR spectra were recorded with a Bruker AM 300 MHz spectrometer. IR spectra were recorded on a PerkinElmer 983G instrument. Elemental analyses were measured with a Carlo-Erba EA1110 elementary analysis instrument. Mass spectrometry was performed with an HP 5989A system. High-resolution mass spectrometry was taken with a Finnigan MAT 8430 or Bruker APEXIII instrument. $CuBr_2$ was purchased from J & K. 1,4-Dioxane was distilled from Na using benzophenone as indicator under N_2 before use. Et_2O and THF were distilled from Na wire using benzophenone as indicator under N_2 before use. CH_2Cl_2 and DMF were distilled from CaH_2 under N_2 before use. Petroleum ether (PE) used had a boiling range of 60–90 °C. All liquid aldehydes were freshly distilled before use. Unless otherwise indicated, chemicals and solvents were purchased from commercial suppliers.

(*S*)-α,α-Dimethylprolinol[17] and oct-7-yn-1-ol (**1f**)[12] were prepared following the literature methods.

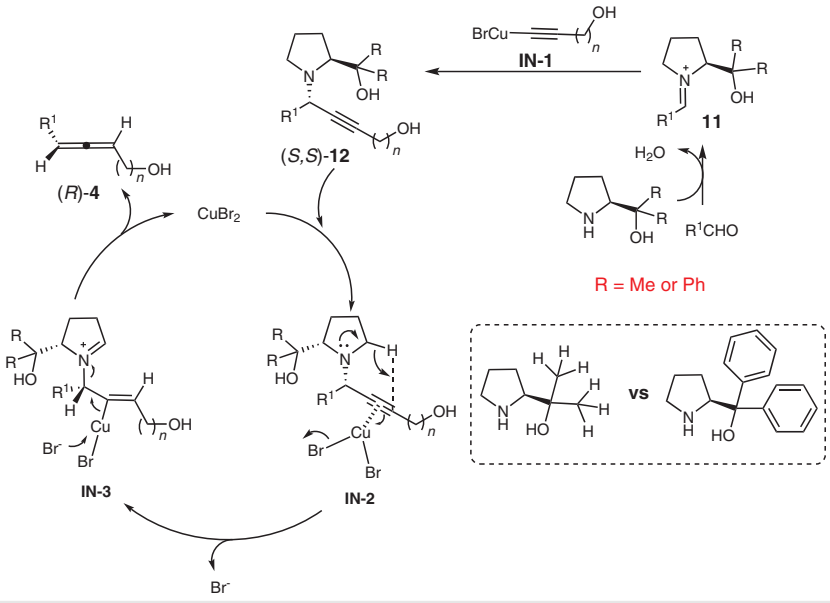
Synthesis of Optically Active 1,3-Disubstuted Allenols via Enantioselective Allenylation of Terminal Alkyne (EATA) Reaction Using (*S*)-α,α-Diphenylprolinol and (*S*)-α,α-Dimethylprolinol

Synthesis of (*R*)-Pentadeca-2,3-dien-1-ol [(*R*)-4aa] Using (*S*)-3b; Typical Procedure I

To a flame-dried Schlenk tube with a polytetrafluoroethylene plug were added $CuBr_2$ (0.0453 g, 0.2 mmol), (*S*)-**3b** (0.1299 g, 1.0 mmol), prop-2-yn-1-ol (**1a**; 0.0846 g, 1.5 mmol, dissolved in 1.5 mL of 1,4-dioxane), and dodecanal (**2a**; 0.2762 g, 1.5 mmol, dissolved in 1.5 mL



Scheme 4 Synthetic applications



Scheme 5 Proposed mechanism

of 1,4-dioxane) sequentially under N_2. The Schlenk tube was then sealed by screwing the polytetrafluoroethylene plug tightly with the outlet being closed. Then the reaction mixture was heated in an oil bath preheated at 130 °C with stirring. After 12 h, the reaction was complete as monitored by TLC and the mixture was cooled to r.t. Afterwards, the resulting mixture was diluted with Et_2O (30 mL) and washed with aq HCl (3 M, 20 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (20 mL) and dried (anhyd Na_2SO_4). After filtration and evaporation, the residue was purified by chromatography on silica gel (PE/EtOAc 8:1, 720 mL) to afford (*R*)-**4aa**;[9a] yield: 0.1372 g (61%); pale yellow liquid; $[\alpha]_D^{20}$ –50.6 (*c* 1.025, $CHCl_3$) {Lit.[9a] 93% *ee*; $[\alpha]_D^{25.9}$ –52.1 (*c* 0.99, $CHCl_3$)}.

HPLC: Chiralcel AS-H column, *n*-hexane/*i*-PrOH (200:1), 1.0 mL/min, λ = 214 nm; t_R (major) = 19.6 min, t_R (minor) = 21.3 min; 96% *ee*.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.38–5.24 (m, 2 H, 2 × =CH), 4.16–4.07 (m, 2 H, OCH_2), 2.09–1.96 (m, 2 H, CH_2), 1.54–1.19 (m, 19 H, 9 × CH_2 + OH), 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.9, 94.1, 91.7, 60.8, 31.9, 29.65, 29.62, 29.4, 29.3, 29.12, 29.07, 28.7, 22.7, 14.1.

Synthesis of (*R*)-Hexadeca-3,4-dien-1-ol [(*R*)-4ba]

*Using (S)-**3a***: Following the Typical Procedure I, the reaction of but-3-yn-1-ol (**1b**; 0.1048 g, 1.5 mmol), dodecanal (**2a**; 0.2762 g, 1.5 mmol), (*S*)-**3a** (0.2585 g, 1 mmol), and $CuBr_2$ (0.0451 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (*R*)-**4ba** (PE/EtOAc 8:1, 450 mL) was used for the first round to afford impure (*R*)-**4ba**, which was further purified by chromatography on silica gel (eluent: CH_2Cl_2, 200 mL for the second round); yield: 0.1161 g (49%); pale yellow liquid; $[\alpha]_D^{20}$ –44.9 (*c* 1.01, $CHCl_3$).

HPLC: Chiralcel IC column, *n*-hexane/*i*-PrOH (200:1), 0.6 mL/min, λ = 214 nm; t_R (minor) = 23.4 min, t_R (major) = 25.3 min; 86% *ee*.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.20–5.04 (m, 2 H, 2 × =CH), 3.70 (q, *J* = 5.7 Hz, 2 H, OCH_2), 2.24 (qd, J_1 = 6.3 Hz, J_2 = 3.0 Hz, 2 H, CH_2), 1.99 (qd, J_1 = 7.0 Hz, J_2 = 3.2 Hz, 2 H, CH_2), 1.66 (br s, 1 H, OH), 1.46–1.20 (m, 18 H, 9 × CH_2), 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.6, 91.7, 87.1, 62.1, 32.3, 31.9, 29.65, 29.63, 29.5, 29.3, 29.2, 29.1, 28.9, 22.7, 14.1.

*Using (S)-**3b***: Following the Typical Procedure I, the reaction of but-3-yn-1-ol (**1b**; 0.1059 g, 1.5 mmol), dodecanal (**2a**; 0.2770 g, 1.5 mmol), (*S*)-**3b** (0.1298 g, 1 mmol), and $CuBr_2$ (0.0451 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (*R*)-**4ba** (PE/EtOAc 8:1, 900 mL); yield: 0.1227 g (51%); pale yellow liquid; $[\alpha]_D^{20}$ –51.3 (*c* 0.970, $CHCl_3$).

HPLC: Chiralcel IC column, *n*-hexane/*i*-PrOH (200:1), 0.6 mL/min, λ = 214 nm; t_R (minor) = 22.9 min, t_R (major) = 25.1 min; 95% *ee*.

IR (neat): 3334, 2954, 2923, 2853, 1963, 1466, 1378, 1341, 1286, 1178, 1050 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.20–5.02 (m, 2 H, 2 × =CH), 3.69 (t, *J* = 6.5 Hz, 2 H, OCH_2), 2.24 (qd, J_1 = 6.4 Hz, J_2 = 3.0 Hz, 2 H, CH_2), 1.99 (qd, J_1 = 6.9 Hz, J_2 = 3.1 Hz, 2 H, CH_2), 1.86 (br s, 1 H, OH), 1.47–1.14 (m, 18 H, 9 × CH_2), 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.6, 91.6, 87.1, 62.0, 32.3, 31.9, 29.63, 29.60, 29.4, 29.3, 29.2, 29.1, 28.8, 22.6, 14.1.

MS (70 eV, EI): *m*/*z* (%) = 238 (M^+, 1.87), 68 (100).

HRMS: *m*/*z* calcd for $C_{16}H_{30}O$ (M^+): 238.2297; found: 238.2294.

Synthesis of (*R*)-Heptadeca-4,5-dien-1-ol [(*R*)-4ca]

*Using (S)-**3a***: Following the Typical Procedure I, the reaction of pent-4-yn-1-ol (**1c**; 0.1307 g, 1.5 mmol), dodecanal (**2a**; 0.2769 g, 1.5 mmol), (*S*)-**3a** (0.2589 g, 1 mmol), and $CuBr_2$ (0.0449 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (*R*)-**4ca** (PE/EtOAc 8:1, 450 mL) for the first round to afford impure (*R*)-**4ca**, which was fur-

ther purified by chromatography on silica gel (eluent: CH_2Cl_2, 200 mL for the second round); yield: 0.1405 g (56%); colorless liquid; $[\alpha]_D^{20}$ –44.1 (*c* 1.04, $CHCl_3$).

HPLC: Chiralcel IC column, *n*-hexane/*i*-PrOH (400:1), 0.6 mL/min, λ = 214 nm; t_R (minor) = 35.9 min, t_R (major) = 37.9 min; 85% *ee*.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.15–5.05 (m, 2 H, 2 × =CH), 3.69 (t, *J* = 6.3 Hz, 2 H, OCH_2), 2.11–2.02 (m, 2 H, CH_2), 2.02–1.90 (m, 2 H, CH_2), 1.75–1.63 (m, 2 H, CH_2), 1.48–1.21 (m, 19 H, 9 × CH_2 + OH), 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.8, 91.5, 90.1, 62.4, 31.95, 31.91, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 28.9, 25.2, 22.7, 14.1.

*Using (S)-**3b***: Following the Typical Procedure I, the reaction of pent-4-yn-1-ol (**1c**; 0.1306 g, 1.5 mmol), dodecanal (**2a**; 0.2774 g, 1.5 mmol), (*S*)-**3b** (0.1298 g, 1 mmol), and $CuBr_2$ (0.0449 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (*R*)-**4ca** (PE/EtOAc 8:1, 900 mL); yield: 0.1345 g (53%); yellow liquid; $[\alpha]_D^{20}$ –50.0 (*c* 0.975, $CHCl_3$).

HPLC: Chiralcel IC column, *n*-hexane/*i*-PrOH (400:1), 0.6 mL/min, λ = 214 nm; t_R (minor) = 39.5 min, t_R (major) = 42.2 min; 95% *ee*.

IR (neat): 3333, 2923, 2853, 1962, 1466, 1378, 1350, 1293, 1167, 1058 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.16–5.05 (m, 2 H, 2 × =CH), 3.68 (t, *J* = 6.6 Hz, 2 H, OCH_2), 2.13–1.90 (m, 4 H, 2 × CH_2), 1.77–1.55 (m, 3 H, CH_2 + OH), 1.45–1.18 (m, 18 H, 9 × CH_2), 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.9, 91.5, 90.1, 62.4, 32.0, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 28.9, 25.2, 22.7, 14.1.

MS (70 eV, EI): *m*/*z* (%) = 253 [$(M^+ + 1)^+$, 3.87], 252 (M^+, 1.22), 79 (100).

HRMS: *m*/*z* calcd for $C_{17}H_{32}O$ (M^+): 174.1045; found: 174.1051.

Synthesis of (*R*)-Octadeca-5,6-dien-1-ol [(*R*)-4da]

*Using (S)-**3a***: Following the Typical Procedure I, the reaction of hex-5-yn-1-ol (**1d**; 0.1512 g, 1.5 mmol), dodecanal (**2a**; 0.2772 g, 1.5 mmol), (*S*)-**3a** (0.2589 g, 1 mmol), and $CuBr_2$ (0.0449 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (*R*)-**4da** (PE/EtOAc 8:1, 810 mL); yield: 0.1363 g (51%); yellow liquid; $[\alpha]_D^{20}$ –41.4 (*c* 1.105, $CHCl_3$).

HPLC: Chiralcel PA-2 column, *n*-hexane/*i*-PrOH (200:1), 1.0 mL/min, λ = 214 nm; t_R (major) = 14.3 min, t_R (minor) = 15.9 min; 88% *ee*.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.12–5.01 (m, 2 H, 2 × =CH), 3.65 (t, *J* = 6.3 Hz, 2 H, OCH_2), 2.08–1.91 (m, 4 H, 2 × CH_2), 1.68–1.56 (m, 2 H, CH_2), 1.56–1.19 (m, 21 H, 10 × CH_2 + OH), 0.88 (t, *J* = 6.6 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.8, 91.2, 90.5, 62.8, 32.2, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 29.0, 28.7, 25.3, 22.7, 14.1.

*Using (S)-**3b***: Following the Typical Procedure I, the reaction of hex-5-yn-1-ol (**1d**; 0.1516 g, 1.5 mmol), dodecanal (**2a**; 0.2774 g, 1.5 mmol), (*S*)-**3b** (0.1290 g, 1 mmol), and $CuBr_2$ (0.0452 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (*R*)-**4da** (PE/EtOAc 8:1, 450 mL); yield: 0.1508 g (57%); yellow liquid; $[\alpha]_D^{20}$ –47.0 (*c* 1.055, $CHCl_3$).

HPLC: Chiralcel PA-2 column, *n*-hexane/*i*-PrOH (200:1), 1.0 mL/min, λ = 214 nm; t_R (major) = 14.3 min, t_R (minor) = 15.9 min; 93% *ee*.

IR (neat): 3334, 2924, 2853, 1962, 1465, 1378, 1341, 1295, 1159, 1061 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.12–5.01 (m, 2 H, 2 × =CH), 3.65 (t, *J* = 6.3 Hz, 2 H, OCH_2), 2.08–1.91 (m, 4 H, 2 × CH_2), 1.71–1.56 (m, 2 H, CH_2), 1.56–1.19 (m, 21 H, 10 × CH_2 + OH), 0.88 (t, *J* = 6.6 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.8, 91.2, 90.5, 62.8, 32.2, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 29.0, 28.7, 25.3, 22.7, 14.1.

MS (70 eV, EI): *m*/*z* (%) = 267 [$(M + 1)^+$, 3.25], 266 (M^+, 1.94), 82 (100).

HRMS: *m*/*z* calcd for $C_{18}H_{34}O$ (M^+): 266.2610; found: 266.2613.

Synthesis of (*R*)-4da Using (*S*)-3b on a Gram-Scale

To a flame-dried Schlenk tube with a polytetrafluoroethylene plug were added $CuBr_2$ (0.4476 g, 2.0 mmol), (*S*)-**3b** (1.6336 g, 95% purity, 12 mmol), hex-5-yn-1-ol (**1d**; 1.0125 g, 97% purity, 10 mmol, dissolved in 15 mL of 1,4-dioxane), and dodecanal (**2a**; 2.7202 g, 95% purity, 14 mmol, dissolved in 15 mL of 1,4-dioxane) sequentially under N_2. The Schlenk tube was then sealed by screwing the polytetrafluoroethylene plug tightly with the outlet being closed. Then the reaction mixture was heated in an oil bath preheated at 130 °C with stirring. After 12 h, the reaction was complete as monitored by TLC. The mixture was cooled to r.t., diluted with Et_2O (150 mL), and washed with aq HCl (3 M, 150 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with brine (200 mL) and dried (anhyd Na_2SO_4). After filtration and evaporation, the residue was purified by chromatography on silica gel (PE/EtOAc 10:1, 1000 mL) to afford (*R*)-**4da**; yield: 1.4561 g (55%); colorless liquid; $[\alpha]_D^{20}$ –47.1 (*c* 1.065, $CHCl_3$).

HPLC: Chiralcel PA-2 column, *n*-hexane/*i*-PrOH (200:1), 1.0 mL/min, λ = 214 nm; t_R (major) = 19.9 min, t_R (minor) = 23.0 min; 97% *ee*.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.12–5.01 (m, 2 H, 2 × =CH), 3.64 (t, *J* = 6.5 Hz, 2 H, OCH_2), 2.07-1.90 (m, 5 H, 2 × CH_2 + OH), 1.69–1.54 (m, 2 H, CH_2), 1.54–1.18 (m, 20 H, 10 × CH_2), 0.88 (t, *J* = 6.5 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.8, 91.1, 90.4, 62.7, 32.1, 31.9, 29.6, 29.5, 29.3, 29.2, 29.1, 28.9, 28.6, 25.2, 22.6, 14.1.

Synthesis of (*R*)-Nonadeca-6,7-dien-1-ol [(*R*)-4ea]

*Using (S)-**3a***: Following the Typical Procedure I, the reaction of hept-6-yn-1-ol (**1e**; 0.1730 g, 1.5 mmol), dodecanal (**2a**; 0.2763 g, 1.5 mmol), (*S*)-**3a** (0.2587 g, 1 mmol), and $CuBr_2$ (0.0452 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (*R*)-**4ea** (PE/EtOAc 8:1, 450 mL for the first round; CH_2Cl_2, 200 mL for the second round); yield: 0.1303 g (46%); colorless solid with a very low mp (0–20 °C); $[\alpha]_D^{20}$ –39.0 (*c* 1.065, $CHCl_3$).

HPLC: Chiralcel PA-2 column, *n*-hexane/*i*-PrOH (200:1), 1.0 mL/min, λ = 214 nm; t_R (major) = 16.7 min, t_R (minor) = 18.6 min; 87% *ee*.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.11–5.00 (m, 2 H, 2 × =CH), 3.63 (t, *J* = 6.6 Hz, 2 H, OCH_2), 2.06–1.89 (m, 4 H, 2 × CH_2), 1.71 (br s, 1 H, OH), 1.62–1.52 (m, 2 H, CH_2), 1.50–1.17 (m, 22 H, 11 × CH_2), 0.88 (t, *J* = 6.6 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.8, 91.0, 90.6, 62.9, 32.6, 31.9, 29.6, 29.5, 29.3, 29.2, 29.1, 29.0, 28.91, 28.89, 25.2, 22.7, 14.1.

*Using (S)-**3b***: Following the Typical Procedure I, the reaction of hept-6-yn-1-ol (**1e**; 0.1739 g, 1.5 mmol), dodecanal (**2a**; 0.2771 g, 1.5 mmol), (*S*)-**3b** (0.1284 g, 1 mmol), and $CuBr_2$ (0.0451 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (*R*)-**4ea** (PE/EtOAc 8:1, 610 mL for the first round; CH_2Cl_2, 200 mL for the second round); yield: 0.1447 g (52%); colorless solid with a very low mp (0–20 °C); $[\alpha]_D^{20}$ –43.4 (*c* 1.110, $CHCl_3$).

HPLC: Chiralcel PA-2 column, *n*-hexane/*i*-PrOH (200:1), 1.0 mL/min, λ = 214 nm; t_R (major) = 17.4 min, t_R (minor) = 19.0 min; 96% *ee*.

IR (neat): 3346, 2922, 1961, 1463, 1378, 1350, 1292, 1152, 1072, 1053 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.11–5.00 (m, 2 H, 2 × =CH), 3.63 (t, *J* = 6.5 Hz, 2 H, OCH_2), 2.06–1.89 (m, 4 H, 2 × CH_2), 1.79–1.51 (m, 3 H, CH_2 + OH), 1.49–1.17 (m, 22 H, 11 × CH_2), 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.8, 91.0, 90.6, 62.9, 32.6, 31.9, 29.6, 29.5, 29.3, 29.2, 29.1, 29.0, 28.91, 28.89, 25.2, 22.7, 14.1.

MS (70 eV, EI): *m*/*z* (%) = 281 [(M + 1)$^+$, 1.80], 280 (M$^+$, 1.62), 93 (100).

HRMS: *m*/*z* calcd for $C_{19}H_{36}O$ (M$^+$): 280.2766, found: 280.2762.

Synthesis of (*R*)-Icosa-7,8-dien-1-ol [(*R*)-4fa]

*Using (S)-**3a***: Following the Typical Procedure I, the reaction of oct-7-yn-1-ol (**1f**;[12] 0.1893 g, 1.5 mmol), dodecanal (**2a**; 0.2760 g, 1.5 mmol), (*S*)-**3a** (0.2583 g, 1 mmol), and $CuBr_2$ (0.0450 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (*R*)-**4fa** (PE/EtOAc 8:1, 450 mL for the first round; CH_2Cl_2, 200 mL for the second round); yield: (0.1558 g, 53%); colorless solid with a very low mp (0–20 °C); $[\alpha]_D^{20}$ –36.2 (*c* 1.205, $CHCl_3$).

HPLC: Chiralcel PA-2 column, *n*-hexane/*i*-PrOH (200:1), 0.7 mL/min, λ = 214 nm; t_R (major) = 28.5 min, t_R (minor) = 30.4 min; 88% *ee*.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.10–5.00 (m, 2 H, 2 × =CH × 2), 3.64 (t, *J* = 6.6 Hz, 2 H, OCH_2), 2.04–1.90 (m, 4 H, 2 × CH_2), 1.64–1.50 (m, 2 H, CH_2), 1.48–1.21 (m, 25 H, 12 × CH_2 + OH), 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.8, 91.0, 90.7, 63.0, 32.7, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 29.0, 28.9, 28.8, 25.6, 22.7, 14.1.

*Using (S)-**3b***: Following the Typical Procedure I, the reaction of oct-7-yn-1-ol (**1f**;[12] 0.1894 g, 1.5 mmol), dodecanal (**2a**; 0.2769 g, 1.5 mmol), (*S*)-**3b** (0.1290 g, 1 mmol), and $CuBr_2$ (0.0450 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (*R*)-**4fa** (PE/EtOAc 8:1, 450 mL for the first round; CH_2Cl_2, 200 mL for the second round); yield: 0.1473 g (50%); colorless solid with a very low mp (0–20 °C); $[\alpha]_D^{20}$ –39.3 (*c* 1.000, $CHCl_3$).

HPLC: Chiralcel PA-2 column, *n*-hexane/*i*-PrOH (200:1), 0.7 mL/min, λ = 214 nm; t_R (major) = 22.1 min, t_R (minor) = 24.7 min; 95% *ee*.

IR (neat): 3334, 2925, 2854, 1962, 1464, 1377, 1056 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.10–5.00 (m, 2 H, 2 × =CH), 3.64 (t, *J* = 6.5 Hz, 2 H, OCH_2), 2.04–1.90 (m, 4 H, 2 × CH_2), 1.64–1.50 (m, 2 H, CH_2), 1.48–1.17 (m, 25 H, 12 × CH_2 + OH), 0.88 (t, *J* = 6.6 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.9, 91.0, 90.7, 63.0, 32.8, 31.9, 29.67, 29.66, 29.5, 29.3, 29.2, 29.15, 29.13, 29.0, 28.92, 28.87, 25.6, 22.7, 14.1.

MS (70 eV, EI): *m*/*z* (%) = 294 (M$^+$, 5.54), 81 (100).

HRMS: *m*/*z* calcd for $C_{20}H_{38}O$ (M$^+$): 294.2923; found: 294.2922.

Synthesis of (*R*)-7-Cyclohexylhepta-5,6-dien-1-ol [(*R*)-4db]

*Using (S)-**3a***: Following the Typical Procedure I, the reaction of hex-5-yn-1-ol (**1d**; 0.1534 g, 96% purity, 1.5 mmol), cyclohexanecarbaldehyde (**2b**; 0.1692 g, 1.5 mmol), (*S*)-**3a** (0.2585 g, 1 mmol), and $CuBr_2$ (0.0451 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (*R*)-**4db** (PE/EtOAc 20:1, 300 mL to 10:1, 300 mL); yield: 0.0870 g (45%); yellow liquid; $[\alpha]_D^{20}$ –81.2 (*c* 0.96, $CHCl_3$).

HPLC: Chiralcel PA-2 column, *n*-hexane/*i*-PrOH (200:1), 0.6 mL/min, λ = 214 nm; t_R (major) = 30.8 min, t_R (minor) = 32.4 min; 93% *ee*.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.16–5.04 (m, 2 H, 2 × =CH), 3.66 (t, *J* = 6.5 Hz, 2 H, OCH_2), 2.11–1.87 (m, 3 H, CH_2 + CH), 1.82–1.56 (m, 7 H, 3 × CH_2 + 1 H from CH_2), 1.55–1.40 (m, 2 H, CH_2), 1.37–0.98 (m, 6 H, 2 × CH_2 + 1 H from CH_2 + OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.6, 97.2, 91.4, 62.6, 37.2, 33.1, 33.0, 32.1, 28.7, 26.1, 26.0, 25.3.

*Using (S)-**3b***: Following the Typical Procedure I, the reaction of hex-5-yn-1-ol (**1d**; 0.1523 g, 1.5 mmol), cyclohexanecarbaldehyde (**2b**; 0.1685 g, 1.5 mmol), (*S*)-**3b** (0.1289 g, 1 mmol), and $CuBr_2$ (0.0452 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (*R*)-**4db** (PE/EtOAc 8:1, 720 mL for the first round; CH_2Cl_2, 200 mL for the second round); yield: 0.0900 g (46%); yellow liquid; $[\alpha]_D^{20}$ –87.6 (*c* 1.045, $CHCl_3$).

HPLC: Chiralcel AD-H column, *n*-hexane/*i*-PrOH (200:1), 0.7 mL/min, λ = 214 nm; t_R (major) = 36.4 min, t_R (minor) = 39.1 min; 97% *ee*.

IR (neat): 3334, 2923, 2851, 2658, 1960, 1448, 1361, 1347, 1303, 1258, 1229, 1213, 1159, 1058 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.17–5.00 (m, 2 H, 2 × =CH), 3.64 (t, *J* = 6.5 Hz, 2 H, OCH_2), 2.09–1.87 (m, 3 H, CH_2 + CH), 1.84 (s, 1 H, OH), 1.79–1.55 (m, 7 H, 3 × CH_2 + 1 H from CH_2), 1.53–1.41 (m, 2 H, CH_2), 1.36–0.98 (m, 5 H, 2 × CH_2 + 1 H from CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.6, 97.2, 91.4, 62.7, 37.2, 33.11, 33.05, 32.2, 28.8, 26.1, 26.0, 25.3.

MS (70 eV, EI): *m*/*z* (%) = 195 [(M + 1)$^+$, 1.63], 194 (M$^+$, 2.17), 79 (100).

HRMS: *m*/*z* calcd for $C_{13}H_{22}O$ (M$^+$): 194.1671; found: 194.1669.

Synthesis of (*R*)-8-Methylnona-5,6-dien-1-ol [(*R*)-4dg]

*Using (S)-**3a***: Following the Typical Procedure I, the reaction of hex-5-yn-1-ol (**1d**; 0.1524 g, 1.5 mmol), isobutyraldehyde (**2g**, 0.1090 g, 1.5 mmol), (*S*)-**3a** (0.2582 g, 1 mmol), and $CuBr_2$ (0.0451 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (*R*)-**4dg** (PE/EtOAc 10:1, 500 mL); yield: 0.0615 g (40%); colorless liquid; $[\alpha]_D^{20}$ = –63.8 (*c* 0.765, $CHCl_3$).

HPLC: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH (100:1), 1.0 mL/min, λ = 214 nm; t_R (minor) = 11.0 min, t_R (major) = 11.6 min; 92% *ee*.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.18–5.07 (m, 2 H, 2 × =CH), 3.65 (t, *J* = 6.5 Hz, 2 H, OCH_2), 2.36–2.19 (m, 1 H, CH), 2.08–1.96 (m, 2 H, CH_2), 1.68–1.56 (m, 2 H, CH_2), 1.55–1.33 (m, 3 H, CH_2 + OH), 1.00 (d, *J* = 6.9 Hz, 6 H, 2 × CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.3, 98.7, 91.8, 62.8, 32.2, 28.8, 27.9, 25.3, 22.5.

*Using (S)-**3b***: Following the Typical Procedure I, the reaction of hex-5-yn-1-ol (**1d**; 0.1515 g, 1.5 mmol), isobutyraldehyde (**2g**; 0.1084 g, 1.5 mmol), (*S*)-**3b** (0.1362 g, 1 mmol), and $CuBr_2$ (0.0455 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (*R*)-**4dg** (PE/EtOAc 10:1, 500 mL); yield: 0.0752 g (49%); colorless liquid; $[\alpha]_D^{20}$ –65.3 (*c* 0.995, $CHCl_3$).

HPLC: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH (100:1), 1.0 mL/min, λ = 214 nm; t_R (minor) = 12.0 min, t_R (major) = 12.9 min; 96% *ee*.

IR (neat): 3344, 2960, 2925, 2867, 1960, 1458, 1381, 1362, 1298, 1059, 1034 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.19–5.07 (m, 2 H, 2 × =CH), 3.66 (t, *J* = 6.6 Hz, 2 H, OCH_2), 2.35–2.20 (m, 1 H, CH), 2.08–1.96 (m, 2 H, CH_2), 1.72–1.55 (m, 2 H, CH_2), 1.55–1.41 (m, 2 H, CH_2), 1.36 (br s, 1 H, OH), 1.00 (d, *J* = 6.6 Hz, 6 H, 2 × CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.3, 98.7, 91.8, 62.8, 32.2, 28.8, 27.9, 25.3, 22.5.

MS (70 eV, EI): *m*/*z* (%) = 155 [(M + 1)$^+$, 8.3], 154 (M$^+$, 4.6), 81 (100).

HRMS: *m*/*z* calcd for $C_{10}H_{18}O$ (M$^+$): 154.1358; found:154.1361.

Synthesis of (*R*)-8-Ethyldeca-5,6-dien-1-ol [(*R*)-4dh]

*Using (S)-**3a***: Following the Typical Procedure I, the reaction of hex-5-yn-1-ol (**1d**, 0.1510 g, 1.5 mmol), 2-ethylbutanal (**2h**; 0.1509 g, 1.5 mmol), (*S*)-**3a** (0.2586 g, 1 mmol), and $CuBr_2$ (0.0454 g, 0.2 mmol) in

1,4-dioxane (3 mL) at 130 °C for 12 h afforded (*S*)-**4dh** (PE/EtOAc 10:1, 495 mL); yield: 0.0619 g (34%); colorless liquid; $[\alpha]_D^{20}$ –66.7 (*c* 0.780, $CHCl_3$).

HPLC: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH (200:1), 1.0 mL/min, λ = 214 nm; t_R (minor) = 11.3 min, t_R (major) = 11.9 min; 94% *ee*.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.08 (qd, J_1 = 6.5 Hz, J_2 = 2.0 Hz, 1 H, =CH), 4.95–4.84 (m, 1 H, =CH), 3.66 (t, *J* = 6.5 Hz, 2 H, OCH_2), 2.11–1.96 (m, 2 H, CH_2), 1.92–1.74 (m, 2 H, CH + OH), 1.68–1.18 (m, 8 H, 4 × CH_2), 0.894 (t, *J* = 7.4 Hz, 3 H, CH_3), 0.886 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.7, 94.9, 90.4, 62.8, 42.9, 32.2, 28.9, 27.7, 27.5, 25.4, 11.7, 11.5.

*Using (S)-**3b***: Following the Typical Procedure I, the reaction of hex-5-yn-1-ol (**1d**; 0.1509 g, 1.5 mmol), 2-ethylbutanal (**2h**; 0.1502 g, 1.5 mmol), (*S*)-**3b** (0.1369 g, 1 mmol), and $CuBr_2$ (0.0455 g, 0.2 mmol) in 1,4-dioxane (3 mL) at 130 °C for 12 h afforded (*S*)-**4dh** (PE/EtOAc 10:1, 495 mL); yield: 0.0980 g (53%); colorless liquid; $[\alpha]_D^{20}$ –73.6 (*c* 0.975, $CHCl_3$).

HPLC: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH (200:1), 1.0 mL/min, λ = 214 nm; t_R (minor) = 11.4 min, t_R (major) = 12.2 min; 99% *ee*.

IR (neat): 3328, 2962, 2933, 2874, 1961, 1456, 1377, 1341, 1283, 1065, 1036 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.07 (qd, J_1 = 6.5 Hz, J_2 = 1.5 Hz, 1 H, =CH), 4.92–4.85 (m, 1 H, =CH), 3.66 (t, *J* = 6.5 Hz, 2 H, OCH_2), 2.07–1.97 (m, 2 H, CH_2), 1.89–1.74 (m, 2 H, CH + OH), 1.70–1.20 (m, 8 H, 4 × CH_2), 0.893 (t, *J* = 7.5 Hz, 3 H, CH_3), 0.886 (t, *J* = 7.4 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.7, 94.9, 90.4, 62.8, 42.9, 32.2, 28.9, 27.7, 27.5, 25.4, 11.7, 11.5.

MS (70 eV, EI): *m*/*z* (%) = 183 [(M + 1)$^+$, 0.4], 182 (M^+, 1.2), 93 (100).

HRMS: *m*/*z* calcd for $C_{12}H_{22}O$ (M^+): 182.1671; found: 182.1670.

Synthesis of (*R*)-6-Phenylhexa-4,5-dien-1-ol [(*R*)-4cc]

Synthesis of (*R*)-4cc Using (*S*)-3a; Typical Procedure II

To a flame-dried Schlenk tube were added $CuBr_2$ (0.1135 g, 0.5 mmol), (*S*)-**3a** (0.2589 g, 1.0 mmol), prop-2-yn-1-ol (**1c**; 0.1733 g, 2 mmol, dissolved in 1.5 mL of 1,4-dioxane), and benzaldehyde **2c** (0.1592 g, 1.5 mmol, dissolved in 1.5 mL of 1,4-dioxane) sequentially under N_2. The resulting mixture was heated in an oil bath preheated at 70 °C with stirring. After 46.5 h, the reaction was complete as monitored by TLC. The mixture was cooled to r.t., diluted with Et_2O (30 mL), and washed with aq HCl (3 M, 20 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (20 mL) and dried (anhyd Na_2SO_4). After filtration and evaporation, the residue was purified by chromatography on silica gel (CH_2Cl_2/Et_2O 100:1, 300 mL) to afford (*R*)-**4cc**; yield: 0.0783 g (45%); pale yellow liquid; $[\alpha]_D^{20}$ –224.2 (*c* 1.035, $CHCl_3$).

HPLC: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH (80:1), 0.8 mL/min, λ = 214 nm; t_R (major) = 60.7 min), t_R (minor) = 66.7 min; 95% *ee*.

IR (neat): 3354, 3082, 3062, 3030, 2937, 2876, 1948, 1597, 1495, 1459, 1264, 1057 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.23 (m, 4 H, ArH), 7.22–7.13 (m, 1 H, ArH), 6.18–6.12 (m, 1 H, =CH), 5.59 (q, *J* = 6.6 Hz, 1 H, =CH), 3.67 (t, *J* = 6.6 Hz, 2 H, OCH_2), 2.20 (qd, J_1 = 7.1 Hz, J_2 = 3.0 Hz, 2H , CH_2), 1.91–1.67 (m, 3 H, OH + CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.1, 134.8, 128.5, 126.7, 126.5, 95.0, 94.4, 62.1, 31.8, 24.8.

MS (70 eV, EI): *m*/*z* (%) = 174 (M^+, 16.58), 130 (100).

HRMS: *m*/*z* calcd for $C_{12}H_{14}O$ (M^+): 174.1045; found: 174.1051.

Synthesis of (*R*)-4cc Using (*S*)-3b; Typical Procedure III

To a flame-dried Schlenk tube were added $CuBr_2$ (0.1132 g, 0.5 mmol), (*S*)-**3b** (0.1296 g, 1.0 mmol, dissolved in 1 mL of 1,4-dioxane), prop-2-yn-1-ol (**1c**; 0.1733 g, 2 mmol, dissolved in 1 mL of 1,4-dioxane), and benzaldehyde (**2c**; 0.1596 g, 1.5 mmol, dissolved in 1 mL of 1,4-dioxane) sequentially under N_2. The resulting mixture was heated in an oil bath preheated at 70 °C with stirring. After 46.5 h, the reaction was complete as monitored by TLC. The mixture was cooled to r.t. and diluted with Et_2O (30 mL) and washed with aq HCl (3 M, 20 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (20 mL) and dried (anhyd Na_2SO_4). After filtration and evaporation, the residue was purified by chromatography on silica gel (CH_2Cl_2/Et_2O 100:1, 300 mL) to afford (*R*)-**4cc**; yield: 0.0644 g (37%); pale yellow liquid; $[\alpha]_D^{20}$ –245.2 (*c* 1.100, $CHCl_3$).

HPLC: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH (80:1), 0.8 mL/min, λ = 214 nm; t_R (major) = 60.8 min), t_R (minor) = 66.4 min; 98% *ee*.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.23 (m, 4 H, ArH), 7.22–7.12 (m, 1 H, ArH), 6.17–6.10 (m, 1 H, =CH), 5.59 (q, *J* = 6.5 Hz, 1 H, =CH), 3.67 (t, *J* = 6.5 Hz, 2 H, OCH_2), 2.25–2.14 (m, 2 H, CH_2), 1.96–1.67 (m, 3 H, OH + CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.1, 134.8, 128.5, 126.7, 126.5, 95.0, 94.4, 62.1, 31.8, 24.8.

Synthesis of (*R*)-6-(4-Bromophenyl)hexa-4,5-dien-1-ol [(*R*)-4cd]

*Using (S)-**3a***: Following the Typical Procedure II, the reaction of pent-4-yn-1-ol (**1c**; 0.1729 g, 2 mmol), 4-bromobenzaldehyde (**2d**; 0.2831 g, 1.5 mmol), (*S*)-**3a** (0.2580 g, 1 mmol), and $CuBr_2$ (0.1141 g, 0.5 mmol) in 1,4-dioxane (3 mL) at 70 °C for 44.5 h afforded (*R*)-**4cd** (CH_2Cl_2/Et_2O 40:1, 280 mL); yield: 0.1300 g (51%); yellow liquid; $[\alpha]_D^{20}$ –209.0 (*c* 1.02, $CHCl_3$).

HPLC: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH (50:1), 1.0 mL/min, λ = 214 nm; t_R (minor) = 28.9 min, t_R (major) = 40.5 min; 90% *ee*.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.7 Hz, 2 H, ArH), 7.13 (d, *J* = 8.4 Hz, 2 H, ArH), 6.13–6.04 (m, 1 H, =CH), 5.59 (q, *J* = 6.6 Hz, 1 H, =CH), 3.67 (t, *J* = 6.3 Hz, 2 H, OCH_2), 2.26–2.13 (m, 2 H, CH_2), 190 (br s, 1 H, OH), 1.83–1.64 (m, 2 H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.2, 133.8, 131.6, 128.0, 120.3, 94.9, 94.2, 62.1, 31.7, 24.7.

*Using (S)-**3b***: Following the Typical Procedure II, the reaction of pent-4-yn-1-ol (**1c**; 0.1730 g, 2 mmol), 4-bromobenzaldehyde (**2d**; 0.2839 g, 1.5 mmol), (*S*)-**3b** (0.1290 g, 1 mmol), and $CuBr_2$ (0.1131 g, 0.5 mmol) in 1,4-dioxane (3 mL) at 70 °C for 45.5 h afforded (*R*)-**4cd** (CH_2Cl_2/Et_2O, 40:1, 280 mL); yield: 0.1065 g (41%, purity 97%); yellow liquid; $[\alpha]_D^{20}$ –241.5 (*c* 0.995, $CHCl_3$).

HPLC: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH (50:1), 1.0 mL/min, λ = 214 nm; t_R (minor) = 29.2 min, t_R (major) = 41.8 min; 94% *ee*.

IR (neat): 3354, 2936, 1948, 1899, 1587, 1487, 1444, 1387, 1258, 1230, 1197, 1174, 1069, 1009 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.4 Hz, 2 H, ArH), 7.13 (d, *J* = 8.4 Hz, 2 H, ArH), 6.13–6.02 (m, 1 H, =CH), 5.59 (q, *J* = 6.5 Hz, 1 H, =CH), 3.67 (t, *J* = 6.5 Hz, 2 H, OCH_2), 2.27–2.14 (m, 2 H, CH_2), 1.90 (br s, 1 H, OH), 1.80–1.66 (m, 2 H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.2, 133.8, 131.6, 128.0, 120.2, 94.9, 94.2, 62.0, 31.7, 24.7.

MS (70 eV, EI): *m*/*z* (%) = 254 (M^+, ^{81}Br), 1.77), 252 (M^+, ^{79}Br), 1.54), 31 (100).

HRMS: *m*/*z* calcd for $C_{12}H_{13}O^{79}Br$ (M^+): 252.0150; found: 252.0145.

Synthesis of (*R*)-6-(*p*-Tolyl)hexa-4,5-dien-1-ol [(*R*)-4ce]

*Using (S)-**3a***: Following the Typical Procedure II, the reaction of pent-4-yn-1-ol (**1c**; 0.1732 g, 2 mmol), 4-methylbenzaldehyde (**2e**; 0.1795 g, 1.5 mmol), (*S*)-**3a** (0.2584 g, 1.0 mmol), and $CuBr_2$ (0.1141 g, 0.5 mmol) in 1,4-dioxane (3 mL) at 70 °C for 46.5 h afforded (*R*)-**4ce** (CH_2Cl_2/Et_2O 40:1, 320 mL); yield: 0.0920 g (49%); pale yellow liquid; $[\alpha]_D^{20}$ –225.7 (*c* 1.055, $CHCl_3$).

HPLC: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH (80:1), 0.8 mL/min, λ = 214 nm; t_R (minor) = 59.4 min, t_R (major) = 75.4 min; 76% *ee*.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.1 Hz, 2 H, ArH), 7.09 (d, *J* = 7.8 Hz, 2 H, ArH), 6.16–6.07 (m, 1 H, =CH), 5.57 (q, *J* = 6.5 Hz, 1 H, =CH), 3.67 (t, *J* = 6.5 Hz, 2 H, OCH_2), 2.31 (s, 3 H, CH_3), 2.25–2.12 (m, 2 H, CH_2), 1.88–1.64 (m, 3 H, OH + CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.7, 136.4, 131.7, 129.2, 126.4, 94.8, 94.3, 62.1, 31.8, 24.9, 21.1.

*Using (S)-**3b***: Following the Typical Procedure II, the reaction of pent-4-yn-1-ol (**1c**; 0.1738 g, 2 mmol), 4-methylbenzaldehyde (**2e**; 0.1810 g, 1.5 mmol), (*S*)-**3b** (0.1293 g, 1.0 mmol), and $CuBr_2$ (0.1142 g, 0.5 mmol) in 1,4-dioxane (3 mL) at 70 °C for 47.5 h afforded (*R*)-**4ce** (CH_2Cl_2/Et_2O, 40:1, 280 mL); yield: 0.1046 g (56%); pale yellow liquid.

HPLC: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH (50:1), 1.0 mL/min, λ = 214 nm; t_R (minor) = 32.5 min, t_R (major) = 41.2 min; 90% *ee*.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.1 Hz, 2 H, ArH), 7.09 (d, *J* = 7.5 Hz, 2 H, ArH), 6.16–6.08 (m, 1 H, =CH), 5.57 (q, *J* = 6.6 Hz, 1 H, =CH), 3.67 (t, *J* = 6.6 Hz, 2 H, OCH_2), 2.31 (s, 3 H, CH_3), 2.25–2.12 (m, 2 H, CH_2), 1.81–1.63 (m, 3 H, OH + CH_2).

*Using (S)-**3b**; by changing the ratio of starting materials **1c**/**2e**/(S)-**3b** to 1:1.4:1.4)*: Following the Typical Procedure II, the reaction of pent-4-yn-1-ol (**1c**; 0.0871 g, 1 mmol), 4-methylbenzaldehyde (**2e**; 0.1683 g, 1.4 mmol), (*S*)-**3b** (0.1810 g, 1.4 mmol), and $CuBr_2$ (0.1130 g, 0.5 mmol) in 1,4- dioxane (3 mL) at 70 °C for 42 h afforded (*R*)-**4ce** (CH_2Cl_2/Et_2O 40:1, 200 mL); yield: 0.0778 g (41%); pale yellow liquid; $[\alpha]_D^{20}$ –266.1 (*c* 0.975, $CHCl_3$).

HPLC: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH (50:1), 1.0 mL/min, λ = 214 nm; t_R (minor) = 38.5 min, t_R (major) = 46.1 min; 93% *ee*.

IR (neat): 3354, 3022, 2936, 2865, 1947, 1902, 1513, 1446, 1395, 1379, 1349, 1313, 1294, 1264, 1212, 1199, 1177, 1113, 1057, 1019 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21–7.13 (m, 2 H, ArH), 7.09 (d, *J* = 8.1 Hz, 2 H, ArH), 6.15–6.08 (m, 1 H, =CH), 5.56 (q, *J* = 6.5 Hz, 1 H, =CH), 3.66 (t, *J* = 6.5 Hz, 2 H, OCH_2), 2.31 (s, 3 H, CH_3), 2.24–2.12 (m, 2 H, CH_2), 1.93 (br s, 1 H, OH), 1.79–1.66 (m, 2 H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.7, 136.4, 131.7, 129.2, 126.4, 94.8, 94.3, 62.1, 31.7, 24.9, 21.1.

MS (70 eV, EI): *m*/*z* (%) = 188 (M^+, 11.85), 129 (100).

HRMS: *m*/*z* calcd for $C_{13}H_{16}O$ (M^+): 188.1201, found: 188.1198.

Synthesis of (*R*)-6-(4-Nitrophenyl)hexa-4,5-dien-1-ol [(*R*)-4cf]

*Using (S)-**3a***: Following the Typical Procedure II, the reaction of prop-2-yn-1-ol (**1c**; 0.1733 g, 2 mmol), 4-nitrobenzaldehyde (**2f**; 0.2332 g, 1.5 mmol), (*S*)-**3a** (0.2590 g, 1 mmol), and $CuBr_2$ (0.1130 g, 0.5 mmol) in 1,4-dioxane (3 mL) at 70 °C for 43 h afforded (*R*)-**4cf** (CH_2Cl_2/Et_2O 80:1, 400 mL); yield: 0.1041 g (47%); pale yellow liquid; $[\alpha]_D^{20}$ –317.6 (*c* 1.175, $CHCl_3$).

HPLC: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH (90:10), 1.0 mL/min, λ = 214 nm; t_R (major) = 20.1 min, t_R (minor) = 22.9 min; 95% *ee*.

IR (neat): 3375, 3107, 3075, 2935, 2872, 1946, 1594, 1515, 1494, 1445, 1392, 1342, 1202, 1177, 1109, 1057 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.7 Hz, 2 H, ArH), 7.40 (d, *J* = 9.0 Hz, 2 H, ArH), 6.26–6.19 (m, 1 H, =CH), 5.74 (q, *J* = 6.6 Hz, 1 H, =CH), 3.72 (t, *J* = 6.5 Hz, 2 H, OCH_2), 2.33–2.23 (qd, J_1 = 7.2 Hz, J_2 = 3.0 Hz, 2 H, CH_2), 1.90–1.50 (m, 3 H, CH_2 + OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.1, 146.3, 142.3, 126.9, 124.0, 95.5, 94.1, 62.0, 31.7, 24.5.

MS (70 eV, EI): *m*/*z* (%) = 219 (M^+, 12.43), 128 (100).

HRMS: *m*/*z* calcd for $C_{12}H_{13}NO_3$(M^+): 219.0895; found: 219.0893.

*Using (S)-**3b***: Following the Typical Procedure III, the reaction of prop-2-yn-1-ol (**1c**; 0.1741 g, 2 mmol), 4-nitrobenzaldehyde (**2f**; 0.2332 g, 1.5 mmol), (*S*)-**3b** (0.1287 g, 1 mmol), and $CuBr_2$ (0.1130 g, 0.5 mmol) in 1,4-dioxane (3 mL) at 70 °C for 43 h, afforded (*R*)-**4cf** (CH_2Cl_2/Et_2O 80:1, 400 mL); yield: 0.0852 g (39%); pale yellow liquid; $[\alpha]_D^{20}$ –331.1 (*c* 1.025, $CHCl_3$).

HPLC: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH (90:10), 1.0 mL/min, λ = 214 nm; t_R (major) = 20.1 min), t_R (minor) = 23.0 min; 96% *ee*.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.7 Hz, 2 H, ArH), 7.40 (d, *J* = 8.7 Hz, 2 H, ArH), 6.27–6.19 (m, 1 H, =CH), 5.74 (q, *J* = 6.6 Hz, 1 H, =CH), 3.73 (t, *J* = 6.5 Hz, 2 H, OCH_2), 2.33–2.23 (m, 2 H, CH_2), 1.85–1.65 (m, 2 H, CH_2), 1.50 (br s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.1, 146.3, 142.3, 126.9, 124.0, 95.5, 94.2, 62.1, 31.7, 24.6.

Synthetic Applications

Synthesis of (*R*)-Heptadeca-4,5-dienal [(*R*)-5] via Fe-Catalyzed Aerobic Oxidation of (*R*)-4ca[13]

To a flame-dried Schlenk tube were added $Fe(NO_3)_3$·$9H_2O$ (0.0703 g, 0.17 mmol), TEMPO (0.0272 g, 0.17 mmol), NaCl (0.0102 g, 0.17 mmol), and DCE (3 mL) sequentially at r.t. with stirring. Then (*R*)-**4ca** (0.2150 g, 0.85 mmol) and DCE (1 mL) were added. After that, the air was extruded out of the reaction mixture by a gas bag filled with O_2. The reaction mixture was stirred at r.t. After 4.5 h, the reaction was complete as monitored by TLC. Filtration through a short column of silica gel [eluent: Et_2O (3 × 20 mL)], evaporation, and column chromatography on silica gel (PE/CH_2Cl_2 4:1, 700 mL) afforded (*R*)-**5**;[5i] yield: 0.1270 g (60%); colorless liquid; $[\alpha]_D^{20}$ –59.2 (*c* 1.015, $CHCl_3$) {Lit.[5i] $[\alpha]_D^{29}$ –58.9 (*c* 0.99, $CHCl_3$), 98% *ee*}.

IR (neat): 2955, 2923, 2853, 2716, 1963, 1731, 1466, 1445, 1409, 1387, 1378, 1352, 1284, 1255, 1219, 1184, 1117, 1070, 1057 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.78 (t, *J* = 1.7 Hz, 1 H, CHO), 5.21–5.10 (m, 2 H, 2 × =CH), 2.59–2.50 (m, 2 H, CH_2), 2.38–2.27 (m, 2 H, CH_2), 2.02–1.90 (m, 2 H, CH_2), 1.45–1.19 (m, 18 H, 9 × CH_2), 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.8, 202.1, 93.0, 89.3, 42.4, 31.9, 29.63, 29.61, 29.4, 29.3, 29.13, 29.12, 28.8, 22.7, 21.3, 14.1.

MS (70 eV, EI): *m*/*z* (%) = 250 (M^+, 22.11), 79 (100).

The *ee* Determination of (*R*)-5

The *ee* of (*R*)-**5** was determined after reduction with $LiAlH_4$ to (*R*)-**4ca**.

(*R*)-4ca

To a flame-dried Schlenk tube were added $LiAlH_4$ (0.0235 g, 0.6 mmol) and anhyd Et_2O (1 mL) under N_2. Then the resulting mixture was cooled to 0 °C in an ice-water bath with stirring. After that, (*R*)-**5** (0.1008 g, 0.4 mmol) and anhyd Et_2O (1 mL) were added. Then the reaction mixture was warmed up to r.t. After 16.5 h, the reaction was complete as monitored by TLC. The mixture was cooled to 0 °C in an ice-water bath, quenched with H_2O (3 mL), and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried (anhyd Na_2SO_4). After filtration and evaporation, the residue was purified by chromatography on silica gel [PE (redistilled)/EtOAc 8:1, 450 mL] to afford (*R*)-**4ca**; yield: 0.0896 g (88%); colorless liquid; $[\alpha]_D^{20}$ –50.1 (*c* 1.02, $CHCl_3$).

HPLC: Chiralcel IC column, *n*-hexane/*i*-PrOH (400:1), 0.6 mL/min, λ = 214 nm; t_R (minor) = 44.5 min, t_R (major) = 47.6 min; 95% *ee*.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.17–5.04 (m, 2 H, 2 × =CH), 3.69 (t, *J* = 6.6 Hz, 2 H, OCH_2), 2.13–2.02 (m, 2 H, CH_2), 2.02–1.91 (m, 2 H, CH_2), 1.76–1.63 (m, 2 H, CH_2), 1.61 (s, 1 H, OH), 1.44–1.19 (m, 18 H, 9 × CH_2), 0.88 (t, *J* = 6.6 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.8, 91.5, 90.1, 62.3, 31.90, 31.88, 29.6, 29.5, 29.3, 29.2, 29.1, 28.9, 25.2, 22.6, 14.1.

Synthesis of (*R*)-2-(Octadeca-5,6-dienyl)isoindoline-1,3-dione [(*R*)-6] via Mitsunobu Reaction;[14] Typical Procedure IV

To a flame-dried Schlenk tube were added (*R*)-**4da** (0.2661 g, 1 mmol) and anhyd THF (5 mL) under N_2. Then PPh_3 (0.5240 g, 2 mmol) and phthalimide (0.2970 g, 2 mmol) were added. The reaction mixture was cooled to 0 °C in an ice-water bath with stirring. After that, DEAD (320 μL, *d* = 1.106 g/cm^3, 0.3554 g, 2 mmol) was added dropwise over 2 min. The reaction mixture was then warmed up to r.t. After 12 h, the reaction was complete as monitored by TLC. After evaporation, the residue was purified by chromatography on silica gel (PE/EtOAc 15:1, 480 mL) to afford (*R*)-**6**; yield: 0.3611 g (91%); colorless liquid; $[\alpha]_D^{20}$ –42.1 (*c* 1.10, $CHCl_3$).

HPLC: Chiralcel PC-4 column, *n*-hexane/*i*-PrOH (400:1), 1.0 mL/min, λ = 214 nm; t_R (minor) = 28.6 min, t_R (major) = 30.7 min; 95% *ee*.

IR (neat): 2924, 2853, 1961, 1771, 1714, 1615, 1467, 1456, 1435, 1393, 1372, 1361, 1337, 1232, 1212, 1188, 1171, 1116, 1088, 1071, 1039 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88–7.78 (m, 2 H, ArH), 7.75–7.66 (m, 2 H, ArH), 5.13–4.97 (m, 2 H, 2 × =CH), 3.69 (t, *J* = 7.4 Hz, 2 H, CH_2), 2.09–1.88 (m, 4 H, 2 × CH_2), 1.79–1.66 (m, 2 H, CH_2), 1.51–1.17 (m, 20 H, 10 × CH_2), 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.8, 168.4, 133.8, 132.1, 123.1, 91.3, 90.2, 37.8, 31.9, 29.6, 29.5, 29.3, 29.2, 29.1, 28.9, 28.4, 28.0, 26.3, 22.7, 14.1.

MS (70 eV, EI): *m*/*z* (%) = 396 [(M + 1)$^+$, 6.28], 395 (M$^+$, 1.24), 108 (100).

HRMS: *m*/*z* calcd for $C_{26}H_{37}NO_2$(M$^+$): 395.2824; found: 395.2827.

Synthesis of *rac*-6 for *ee* Determination (Scheme 6)

Following the Typical Procedure IV, the reaction of *rac*-**4da** (0.2666 g, 1 mmol), PPh_3 (0.5243 g, 2 mmol), phthalimide (0.2970 g, 2 mmol), and DEAD (320 μL, *d* = 1.106 g/cm^3, 0.3554 g, 2 mmol) in THF (5 mL) at r.t. for 8.5 h afforded *rac*-**6** (PE/EtOAc 15:1, 480 mL); yield: 0.3126 g (79%); colorless liquid.

IR (neat): 2923, 2853, 1961, 1771, 1714, 1615, 1467, 1435, 1394, 1372, 1232, 1212, 1188, 1171, 1116, 1088, 1071, 1039 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85–7.80 (m, 2 H, ArH), 7.75–7.66 (m, 2 H, ArH), 5.12–4.98 (m, 2 H, 2 × =CH), 3.69 (t, *J* = 7.4 Hz, 2 H, CH_2), 2.09–1.88 (m, 4 H, 2 × CH_2), 1.79–1.65 (m, 2 H, CH_2), 1.51–1.17 (m, 20 H, 10 × CH_2), 0.87 (t, *J* = 6.6 Hz, 3 H, CH_3).

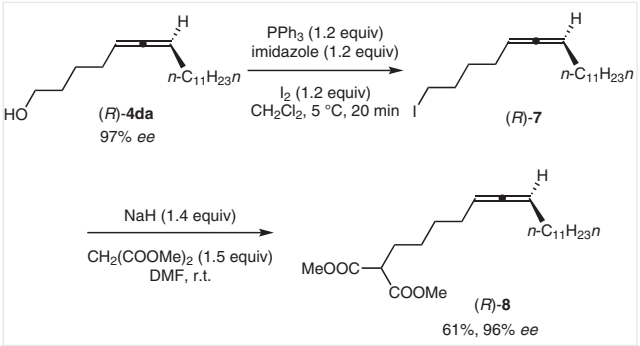
^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.8, 168.3, 133.7, 132.1, 123.0, 91.3, 90.2, 37.8, 31.9, 29.6, 29.4, 29.3, 29.2, 29.1, 28.9, 28.4, 28.0, 26.3, 22.6, 14.1.

MS (70 eV, EI): *m*/*z* (%) = 396 [(M + 1)$^+$, 6.28], 395 (M$^+$, 1.09), 108 (100).

HRMS: *m*/*z* calcd for $C_{26}H_{37}NO_2$(M$^+$): 395.2824, found: 395.2831.

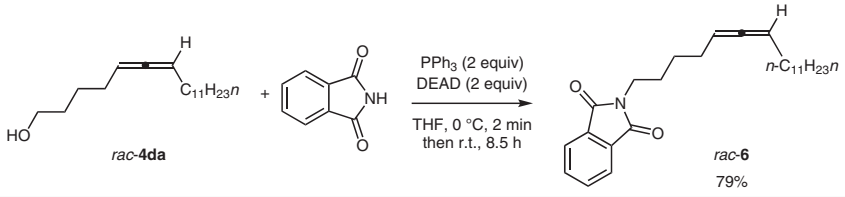
Synthesis of Phlomic Acid [(*R*)-9]

Step 1: Synthesis of Dimethyl (*R*)-2-(Octadeca-5,6-dien-1-yl)malonate [(*R*)-8][16] (Scheme 7)



Scheme 7 Synthesis of dimethyl (*R*)-2-(octadeca-5,6-dien-1-yl)malonate [(*R*)-**8**]

To a flame-dried Schlenk tube were added (*R*)-**4da** (0.8790 g, 3.3 mmol) and CH_2Cl_2 (30 mL) under N_2. Then PPh_3 (1.0390 g, 3.96 mmol) and imidazole (0.2725 g, 3.96 mmol) were added sequentially. After cooling the reaction mixture to 5 °C, I_2 (1.0060 g, 3.96 mmol) and CH_2Cl_2 (3 mL) were added. Then the resulting mixture was stirred at this temperature for 20 min until the reaction was complete as monitored by TLC. Filtration through a short column of silica gel [eluent: PE (3 × 20 mL)] for the first time, evaporation, and filtration through a



Scheme 6 Synthesis of *rac*-**6**

short column of silica gel [eluent: PE (3 × 50 mL)] for the second time afforded (*R*)-**7** as a liquid, which was used directly in the next step without further purification.

To a flame-dried Schlenk flask were added NaH (0.1586 g, 3.96 mmol, 60% in mineral oil) and anhyd DMF (17 mL) under N_2 and the reaction mixture was stirred at r.t. Dimethyl malonate (507 μL, d = 1.14 g/cm^3, 0.5783 g, 4.29 mmol) was added dropwise in 5 min. After that, the resulting mixture was stirred at r.t. for another 10 min. A solution of (*R*)-**7** (prepared as above) in anhyd DMF (16 mL) was added dropwise to the reaction mixture in 5 min and the resulting mixture was stirred at r.t. After 9.75 h, the reaction was complete as monitored by TLC. The resulting mixture was cooled to 0 °C in an ice-water bath, quenched with sat. aq NH_4Cl (50 mL), and extracted with Et_2O (3 × 30 mL). The combined organic layers were was washed with H_2O (20 mL), brine (20 mL), and dried (anhyd Na_2SO_4). After filtration and evaporation, the residue was purified by chromatography on silica gel (PE/EtOAc 40:1, 1200 mL) to afford (*R*)-**8**; yield: 0.7706 g (61% over two steps); colorless liquid; $[\alpha]_D^{20}$ –38.0 (*c* 1.095, $CHCl_3$).

HPLC: Chiralcel PA-2 column, MeCN/H_2O (90:10), 0.7 mL/min, λ = 214 nm; t_R (major) = 10.7 min, t_R (minor) = 12.3 min; 96% *ee*.

IR (neat): 2952, 2925, 2854, 1961, 1759, 1739, 1462, 1435, 1343, 1269, 1252, 1228, 1200, 1150, 1077, 1014 cm^{-1}.

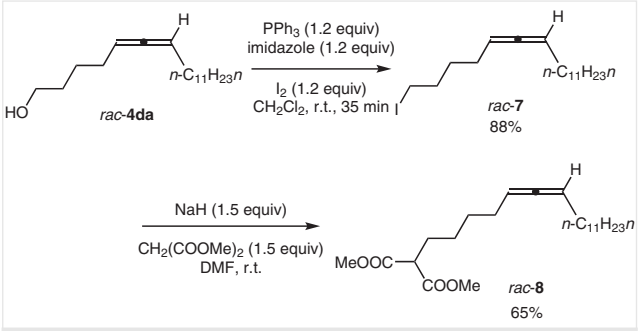
^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.12–4.99 (m, 2 H, 2 × =CH), 3.74 (s, 6 H, 2 × OCH_3), 3.36 (t, J = 7.5 Hz, 1 H, CH), 2.03–1.86 (m, 6 H, 3 × CH_2), 1.50–1.19 (m, 22 H, 11 × CH_2), 0.88 (t, J = 6.8 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.8, 169.8, 91.2, 90.3, 52.4, 51.6, 31.9, 29.6, 29.5, 29.3, 29.2, 29.1, 28.9, 28.7, 28.6, 26.8, 22.7, 14.1.

MS (70 eV, EI): *m*/*z* (%) = 380 (M$^+$, 1.03), 148 (100).

HRMS: *m*/*z* calcd for $C_{23}H_{40}O_4$(M$^+$): 380.2927; found: 380.2930.

Synthesis of *rac*-8 for *ee* Determination[16] (Scheme 8)



Scheme 8 Synthesis of *rac*-**8**

rac-7

To a flame-dried Schlenk tube were added *rac*-**4da** (0.3989 g, 1.5 mmol), CH_2Cl_2 (12 mL), PPh_3 (0.4725 g, 1.8 mmol), and imidazole (0.1239 g, 1.8 mmol) sequentially under N_2. I_2 (0.4568 g, 1.8 mmol) and CH_2Cl_2 (3 mL) were added at r.t. with stirring. The resulting mixture was kept stirring at r.t. for 35 min until the reaction was complete as monitored by TLC. After filtration through a short column of silica gel [eluent: PE (3 × 20 mL)] and evaporation of the solvent, the residue was purified by chromatography on silica gel (eluent: PE, 400 mL) to afford *rac*-**7**; yield: 0.4982 g (88%); colorless liquid.

IR (neat): 2955, 2923, 2852, 1962, 1463, 1456, 1435, 1377, 1367, 1340, 1278, 1243, 1224, 1207, 1166, 1120 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.15–4.99 (m, 2 H, 2 × =CH), 3.19 (t, J = 7.1 Hz, 2 H, ICH_2), 2.07–1.92 (m, 4 H, 2 × CH_2), 1.92–1.81 (m, 2 H, CH_2), 1.58–1.45 (m, 2 H, CH_2), 1.45–1.20 (m, 18 H, 9 × CH_2), 0.88 (t, J = 6.8 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.9, 91.4, 90.1, 32.9, 31.9, 29.9, 29.67, 29.65, 29.5, 29.4, 29.2, 29.1, 29.0, 27.8, 22.7, 14.1, 6.7.

MS (70 eV, EI): *m*/*z* (%) = 376 (M$^+$, 6.53), 109 (100).

HRMS: *m*/*z* calcd for $C_{18}H_{33}I$ (M$^+$): 376.1627; found: 376.1623.

rac-8

To a flame-dried Schlenk flask were added NaH (0.0603 g, 1.5 mmol, 60% in mineral oil) and anhyd DMF (5 mL) under N_2 and the reaction mixture was stirred at r.t. Dimethyl malonate (177 μL, d = 1.14 g/cm^3, 0.2018 g, 1.5 mmol) was added dropwise over 5 min. After that, the resulting mixture was stirred at r.t. for another 30 min and treated with a solution of *rac*-**7** (0.3751g, 1 mmol) in anhyd DMF (5 mL) dropwise over 5 min. Then the reaction mixture was stirred at r.t. After 11.7 h, the reaction was complete as monitored by TLC. The resulting mixture was cooled to 0 °C in an ice-water bath, quenched with sat. aq NH_4Cl (15 mL), and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with H_2O (15 mL), brine (15 mL), and dried (anhyd Na_2SO_4). After filtration and evaporation, the residue was purified by chromatography on silica gel (PE/EtOAc 50:1, 650 mL) to afford *rac*-**8**; yield: 0.2469 g (65%); colorless liquid.

IR (neat): 2952, 2925, 2854, 1961, 1755, 1738, 1462, 1456, 1435, 1344, 1269, 1252, 1228, 1201, 1150, 1077, 1014 cm^{-1}.

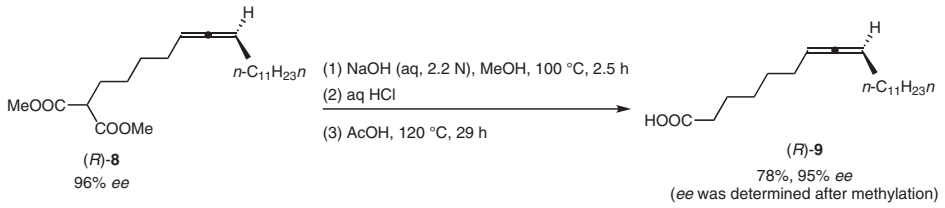
^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.13–4.98 (m, 2 H, 2 × =CH), 3.74 (s, 6 H, 2 × OCH_3), 3.36 (t, J = 7.7 Hz, 1 H, CH), 2.03–1.86 (m, 6 H, 3 × CH_2), 1.50–1.19 (m, 22 H, 11 × CH_2), 0.88 (t, J = 6.8 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.8, 169.8, 91.2, 90.3, 52.4, 51.6, 31.9, 29.6, 29.4, 29.3, 29.2, 29.1, 28.9, 28.65, 28.55, 26.8, 22.6, 14.1.

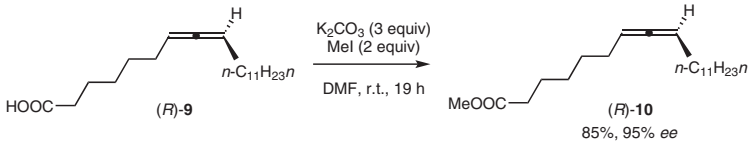
MS (70 eV, EI): *m*/*z* (%) = 380 (M$^+$, 1.11), 148 (100).

HRMS: *m*/*z* calcd for $C_{23}H_{40}O_4$(M$^+$): 380.2927; found: 380.2932

Step 2: Hydrolysis of (*R*)-8 to Phlomic Acid (Scheme 9)



Scheme 9 Hydrolysis of (*R*)-**8** to phlomic acid



Scheme10 Esterification of (*R*)-**9**

Phlomic Acid [(*R*)-9][10]

To a flame-dried Schlenk tube were added (*R*)-**8** (0.2669 g, 0.7 mmol), MeOH (2 mL), and aq 2.2 N NaOH (1.3 mL) under N_2. The resulting mixture was stirred in a pre-heated (100 °C) oil bath. After 2.5 h, the reaction was complete as monitored by TLC. The reaction mixture was cooled to r.t., acidified to pH 1 with aq 1 N HCl, and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (5 mL) and dried (anhyd Na_2SO_4). After filtration and evaporation, the residue was used in the next step without further purification.

To a flame-dried Schlenk tube were added the product prepared as above and AcOH (4.2 mL) under N_2. The resulting mixture was stirred in a pre-heated (120 °C) oil bath. After 29 h, the reaction was complete as monitored by TLC. After evaporation, the residue was purified by chromatography on silica gel (PE/EtOAc 3:1, 400 mL) to afford (*R*)-**9**;[10] yield: 0.1692 g (78%); pale yellow solid with a very low mp (0–20 °C); $[\alpha]_D^{20}$ –38.7 (*c* 1.035, $CHCl_3$) {Lit.[10] $[\alpha]_D^{30.5}$ –40.7 (*c* 1.03, $CHCl_3$)}.

IR (neat): 2924, 2854, 2673, 1962, 1713, 1463, 1439, 1413, 1377, 1278, 1237, 1145, 1085 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 11.53 (s, 1 H, CO_2H), 5.18–4.99 (m, 2 H, 2 × =CH), 2.36 (t, *J* = 7.5 Hz, 2 H, CH_2), 2.05–1.90 (m, 4 H, 2 × CH_2), 1.72–1.58 (m, 2 H, CH_2), 1.50–1.20 (m, 22 H, 11 × CH_2), 0.88 (t, *J* = 6.6 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.8, 180.4, 91.1, 90.5, 34.1, 31.9, 29.7, 29.5, 29.4, 29.2, 29.1, 29.0, 28.73, 28.71, 28.5, 24.5, 22.7, 14.1.

MS (70 eV, EI): *m*/*z* (%) = 308 (M^+, 7.20), 67 (100).

The *ee* Determination of (*R*)-9

The *ee* of (*R*)-**9** was determined after esterification to (*R*)-**10** (Scheme 10).

(*R*)-10

To a flame-dried Schlenk tube were added (*R*)-**9** (0.0624 g, 0.2 mmol) and anhyd DMF (2 mL) and the resulting mixture was stirred at r.t. After that, K_2CO_3 (0.0831 g, 0.6 mmol) was added. MeI (25 µL, *d* = 2.28 g/mL, 0.0568 g, 0.4 mmol) was added dropwise over 2 min and the resulting mixture was stirred at r.t. After 19 h, the reaction was complete as monitored by TLC. The resulting mixture was quenched with sat. aq NH_4Cl (4 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried (anhyd Na_2SO_4). After filtration and evaporation, the residue was purified by chromatography on silica gel (PE/EtOAc 30:1, 360 mL) to afford (*R*)-**10**;[10] yield: 0.0554 g (85%); colorless liquid; $[\alpha]_D^{20}$ –37.3 (*c* 1.05, $CHCl_3$) {Lit.[10] $[\alpha]_D^{30.5}$ –39.9 (*c* 0.99, $CHCl_3$); 96% *ee*}.

HPLC: Chiralcel PA-2 column, *n*-hexane/*i*-PrOH (100:0), 1.0 mL/min, λ = 214 nm; t_R (major) = 24.6 min, t_R (minor) = 32.3 min; 95% *ee*.

IR (neat): 2925, 2854, 1961, 1744, 1463, 1436, 1377, 1363, 1258, 1200, 1170, 1088, 1012 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.11-4.99 (m, 2 H, 2 × =CH), 3.67 (s, 3 H, OCH_3), 2.31 (t, *J* = 7.5 Hz, 2 H, CH_2), 2.03–1.91 (m, 4 H, 2 × CH_2), 1.69–1.57 (m, 2 H, CH_2), 1.49–1.19 (m, 22 H, 11 × CH_2), 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.8, 174.2, 91.1, 90.6, 51.4, 34.0, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 29.0, 28.7, 28.6, 24.8, 22.7, 14.1.

MS (70 eV, EI): *m*/*z* (%) = 322 (M^+, 1.28), 150 (100).

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Supporting Information

Please see the copies of 1H NMR, 13C NMR, and HPLC spectra in Supporting Information.Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1592007.

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