DOI: 10.1002/ejoc.201403588

An Enantioselective Synthesis of (*R*)-5,6-Octadecadienoic Acid

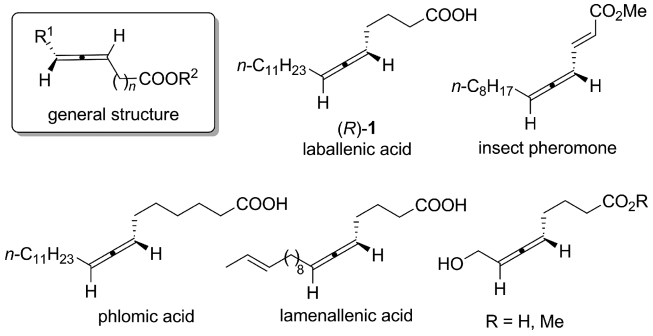
Qiong Yu[a] and Shengming Ma*[b,c]

Keywords: Total synthesis / Allenes / Enantioselectivity / Chiral auxiliaries

A convenient, scalable, and highly enantioselective total synthesis of (*R*)-5,6-octadecadienoic acid was developed by using the recently established ATA (allenylation of terminal alkynes) reaction of TBS-protected (TBS = *tert*-butyldimethylsilyl) propargyl alcohol with *n*-dodecanal in the presence of (*R*)-α,α-diphenylprolinol as the chiral source. The axial chirality of the allene unit withstood the many common organic transformations that were needed to achieve the total synthesis with a high *ee* (enantiomeric excess) value.

Introduction

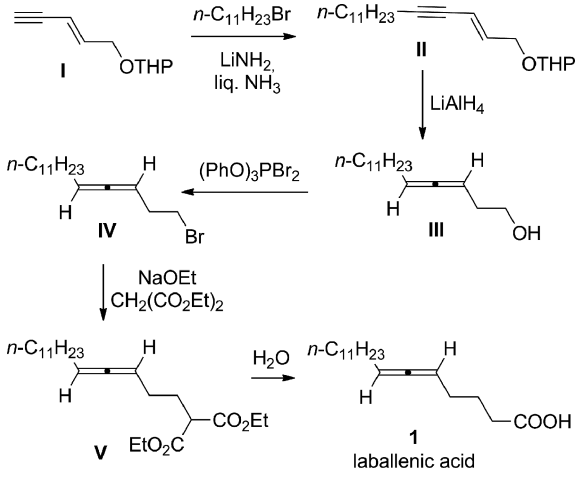
Approximately 150 natural products that contain an allenic unit have been isolated up to now.[1,2] Of particular interest, a large number of well-known natural products that contain a 1,3-disubstituted allene unit have been isolated from varied sources such as microorganisms, fungi, higher plants, and insects. Some typical natural 1,3-disubstituted allenes are listed in Scheme 1.[3]



Scheme 1. Typical examples of axially chiral natural 1,3-disubstituted allenes.

Because of the difficulty in constructing axial chirality, the enantioselective syntheses of these biologically active natural 1,3-disubstituted allenes are still a challenge. In 2005, Ogasawara and Hayashi reported the enantioselective synthesis of methyl (*R*,*E*)-(–)-tetradeca-2,4,5-trienoate with 76%*ee* by utilizing a Pd-catalyzed reaction of an alka-1,3-dien-3-yl bromide and malonate in the presence of a base and the atropisomeric biaryl bis(phosphine) (*R*)-segphos [5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole] as the ligand.[4] The synthesis of naturally occurring 8-hydroxy-5,6-octadienoate has been carried out with 94%*ee* (*ee* = enantiomeric excess) in 7 steps by starting from D-mannitol (based on chirality transfer strategy)[5] and 90%*ee* in 15 steps by starting from 5-TBSO-substituted pentanal (by enzymatic resolution and β-elimination, TBS = *tert*-butyldimethylsilyl),[6]

In this study, we focused on (*R*)-5,6-octadecadienoic acid [laballenic acid, (*R*)-**1**], which was isolated in 1964 by Wolff et al. from the seed oil of *Leonotis nepetaefolia* L. (R. Br.) of the family of Labiatae.[7] First, this compound was believed to be 2,3-methylene-4,5-heptadecadienoic acid,[7] which was later revised to (–)-5,6-octadecadienoic acid.[8] In 1966, Landor et al. identified the absolute configuration of the allene unit in laballenic acid as (*R*)[9] and realized its total synthesis in five steps by starting from the tetra-



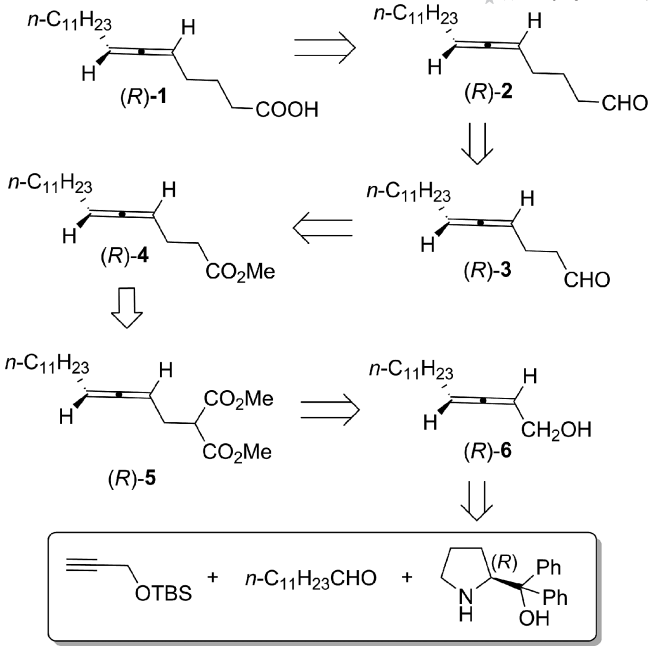
Scheme 2. Reported synthesis of laballenic acid.

[a] Shanghai Key Laboratory of Green Chemistry and Chemical Process, Department of Chemistry, East China Normal University,
3663 North Zhongshan Road, Shanghai 200062, P. R. China
E-mail: masm@sioc.ac.cn
[b] Department of Chemistry, Fudan University,
220 Handane Lu, Shanghai 200433, P. R. China
[c] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences,
345 Lingling Lu, Shanghai 200032, P. R. China
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201403588.

hydropyran (THP) ether of pent-4-yn-2-enol (see Scheme 2). The enantioselective synthesis relied on the asymmetric reduction of **II** by the 3-*O*-benzyl-1,2-*O*-cyclohexylidene-α-D-glucofuranose complex[10] to give the laballenic acid [(*R*)-**1**] with a very low *ee* value ($[a]_D^{20}$ = –3.0[9] vs. $[a]_D^{29}$ = –42.7 from our study with an *ee* value of 98%). Herein, we report the highly enantioselective synthesis of laballenic acid on a gram scale with an *ee* value of 98%.

Results and Discussion

On the basis of our recently developed *tert*-butyldimethylsilyl-directed highly enantioselective allenylation of propargyl alcohol with aliphatic aldehydes to afford axially chiral α-allenols,[11] we designed a retrosynthetic strategy for the synthesis of methyl (*R*)-5,6-octadecadienoic acid [laballenic acid, (*R*)-**1**] as outlined in Scheme 3. The axial chirality of the target molecule can be established by the synthesis of α-allenol (*R*)-**6**, which can be easily prepared by the $ZnBr_2$-catalyzed enantioselective allenylation of TBS-protected propargylic alcohol, the C_{12}-aldehyde, and (*R*)-α,α-diphenylprolinol followed by the removal of the stereodirecting TBS group. The acid functionality of the target molecule can be formed by reactions at the site of the malonate moiety in (2,3-butadienyl)malonate (*R*)-**5** (Scheme 3).



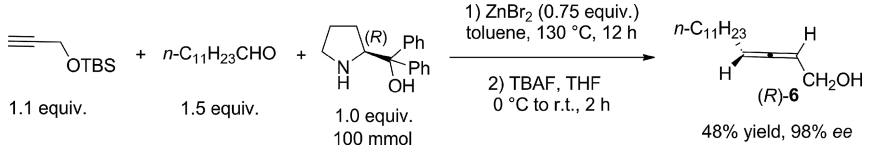
Scheme 3. Retrosynthetic analysis of laballenic acid.

With such a plan in mind, we began our study of the reaction of TBS-protected propargyl alcohol, *n*-dodecanal, and (*R*)-α,α-diphenylprolinol on a 100 mmol scale in the presence of 0.75 equiv. of $ZnBr_2$ in toluene.[11] The reaction was conducted at 130 °C for 12 h followed by flash chromatography on a silica gel column to afford the crude product, which upon desilylation yielded (*R*)-2,3-pentadecadien-1-ol [(*R*)-**6**] in 48% combined yield with 98%*ee*, see Equation (1).

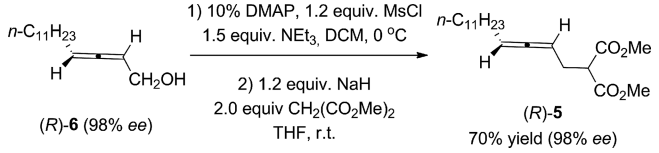
Next, the transformation of the axially chiral primary alcohol α-allenol (*R*)-**6** into optically active (2,3-butadienyl)malonate (*R*)-**5** was realized in two steps.[11] The treatment of (*R*)-**6** with mesyl chloride (MsCl) and triethylamine in the presence of 4-(dimethylamino)pyridine (DMAP) gave the corresponding α-allenyl mesylate, which underwent nucleophilic substitution, without further purification, by treatment with the dimethyl malonate anion to yield (*R*)-**5** in 70% yield with 98%*ee*, see Equation (2).

Direct decarboxylation was realized by the treatment of (*R*)-**5** with 2 equiv. of LiCl and 4 equiv. of H_2O in dimethyl sulfoxide (DMSO) at 180 °C (Krapcho method)[4,12,13] over 90 min to afford (*R*)-**4** in 73% yield with 98%*ee*. The conversion of (*R*)-**4** into (*R*)-**3** was successfully realized through the controlled reduction of the ester functionality by treatment with diisobutylaluminum hydride (DIBAL-H) to give an aldehyde unit (see Scheme 4).[14] The Wittig olefination of (*R*)-**3** with (methoxymethyl)triphenylphosphonium chloride in tetrahydrofuran (THF) gave methoxyalkene **IM1**, which without further purification was then treated with 30% H_2SO_4 to yield 5-allenal (*R*)-**2** (see Scheme 4).[15]

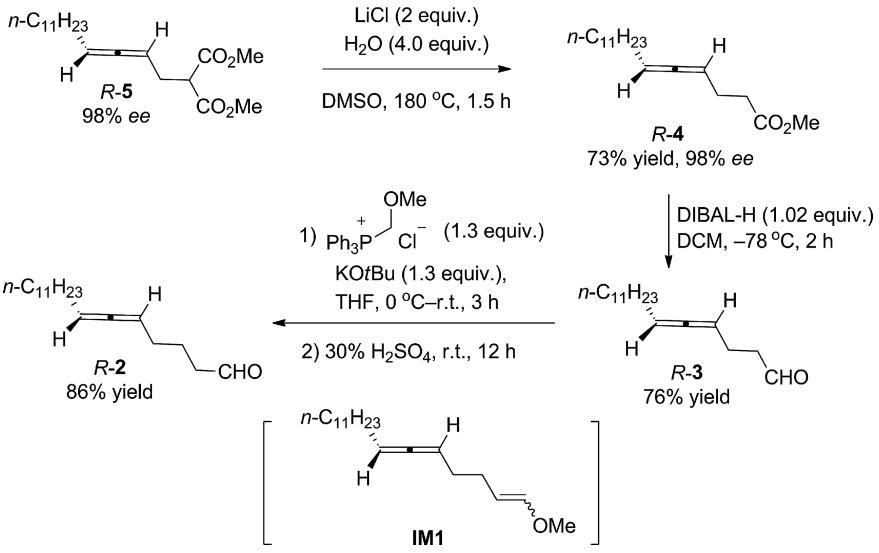
Finally, 5-allenal (*R*)-**2** was easily oxidized with Ag_2O on a 5 mmol scale to afford the final product laballenic ac-



(1)

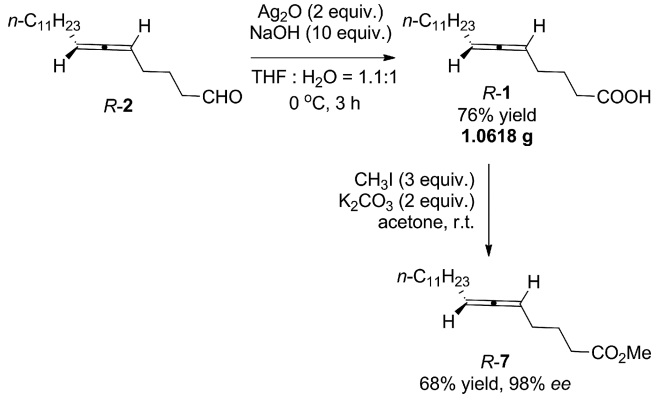


(2)



Scheme 4. Synthesis of (*R*)-**2** from (*R*)-**5** through a decarboxylation, reduction, and one-carbon elongation reaction (DCM = dichloromethane).

id[3d,10,16] (1.0618 g) in 73% yield with 98%*ee*, as determined by HPLC analysis of the corresponding (*R*)-methyl 5,6-octadecadienoate [(*R*)-**7**, see Scheme 5].



Scheme 5. Synthesis of (*R*)-**1** from (*R*)-**2** by oxidation.

The key step involved the construction of the axial chirality by the enantioselective allenylation of the protected propargyl alcohol with the aliphatic aldehyde in the presence of readily available (*R*)-α,α-diphenylprolinol as the chiral source. It was significant that such axial chirality survived common organic transformations such as acidic hydrolysis, basic treatment, nucleophilic substitution, decarboxylation, Wittig olefination, oxidation, reduction, and esterification. These reactions are essential for the syntheses of the other target molecules in Scheme 1, which have the carboxylic acid, carboxylate, C=C bond, and hydroxy functionalities, as well as the highly enantioselective syntheses of non-natural axially chiral allenes.[17] In addition, all the intermediate products (*R*)-**1**–(*R*)-**6** may be used as the starting materials for the syntheses of optically active cyclic compounds.[18,19]

Conclusions

In summary, we have developed a scalable total synthesis of the naturally occurring (*R*)-5,6-octadecadienoic acid [(*R*)-**1**] in 12% overall yield with 98%*ee* by starting from TBS-protected propargyl alcohol, *n*-dodecanal, and (*R*)-α,α-diphenylprolinol as the chiral source. The strategy presented herein may easily be applied to the syntheses of other target molecules.

Experimental Section

General Methods: The NMR spectroscopic data were recorded with a commercial Bruker-300 spectrometer (300 MHz for ^{1}H NMR, 75.4 MHz for ^{13}C NMR). The ^{1}H NMR chemical shifts were recorded in ppm relative to the residual $CHCl_3$ (δ = 7.26 ppm) or TMS (δ = 0.00 ppm) in $CDCl_3$. The ^{13}C NMR chemical shifts were recorded in ppm relative to $CDCl_3$ (δ = 77.0 ppm). The solvents that were distilled from a drying reagent prior to use are as follows: Na (benzophenone) for toluene and THF; CaH_2 for CH_2Cl_2. Other chemicals were used directly.

(*R*)-2,3-Pentadecadien-1-ol [(*R*)-6]: An oven-dried, three-necked 500 mL round-bottom flask that contained a magnetic stirring bar was equipped with a Dean–Stark trap. Anhydrous $ZnBr_2$ powder (17.1 g, 75 mmol) was added under argon, and the system was dried under vacuum by using a heat gun for about 1 min. After cooling to room temperature, (*R*)-α,α-diphenylprolinol (25.8 g, 100 mmol) and *tert*-butyldimethyl(2-propynyloxy)silane (18.7 g, 110 mmol) were added sequentially with stirring at room temperature under argon. The resulting suspension was stirred at room temperature for 5 min, and then freshly distilled toluene (150 mL) was added under argon. Freshly distilled *n*-dodecanal (d = 0.831 g·mL^{-1}, 33 mL, 27.6 g, 150 mmol) was added, and the addition funnel was rinsed with toluene (50 mL) under argon. The resulting mixture was stirred at room temperature for 3 min, during which time, freshly distilled toluene (8 mL) was added to fill the Dean–Stark trap. The flask was then placed in a preheated oil bath at 130 °C for

12 h with stirring. After cooling to room temperature, the resulting mixture was transferred into a 500 mL flask, and the precipitate was discarded after it was rinsed with ethyl ether (30 mL). After concentration by rotary evaporation, flash chromatography on silica gel (petroleum ether) afforded the product as an orange-red liquid. To a 500 mL flask was added a solution of the crude product in THF (200 mL), and the resulting mixture was cooled with an ice-water bath. To this was added tetra-*n*-butylammonium fluoride (TBAF, 26.3 g, 100 mmol) in batches in open air. The ice-water bath was then removed, and the resulting mixture was stirred at room temperature. The reaction reached completion after 2 h (monitored by TLC), and the resulting mixture was poured into a flask that contained ice water (150 mL). Ethyl ether (300 mL) was then added. The organic layer was separated, and the aqueous layer was extracted with ethyl ether (3× 50 mL). The combined organic layers were washed with brine (100 mL) and dried with anhydrous Na_2SO_4. The solvent was evaporated, and the residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate, 15:1) to afford (*R*)-**6** (11.0 g, 48% combined yield over two steps, 98%*ee*) as a liquid. HPLC (Chiralcel AD-H column; hexane/*i*PrOH, 200:1; 1.0 mL min^{-1}; λ = 214 nm): t_R= 11.4 min (major) and t_R = 12.3 min (minor). $[\alpha]_D^{26}$ = 47.6 (c = 0.98, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.35–5.21 (m, 2 H, CH=C=CH), 4.14–4.04 (m, 2 H, CH_2O), 2.06–1.93 (m, 2 H, CH_2Me), 1.78 (br. s, 1 H, OH), 1.45–1.15 (m, 18 H, 9 CH_2), 0.87 (t, J = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.0, 93.8, 91.6, 60.8, 31.9, 29.63 (2 C), 29.60, 29.4, 29.3, 29.10, 29.06, 28.6, 22.7, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 3322, 2923, 2853, 1963, 1465, 1211, 1056, 1012 cm^{-1}. MS (ESI): m/z = 225 [M + H]$^+$. $C_{15}H_{28}O$ (224.39): calcd. C 80.29, H 12.58; found C 80.03, H 12.54.

(*R*)-Dimethyl 2-(2,3-Pentadecadienyl)malonate [(*R*)-5]: To a flame-dried, three-necked 250 mL round-bottom flask were added DMAP (0.610 g, 5 mmol), anhydrous DCM (50 mL), anhydrous NEt_3 (d = 0.726 g mL^{-1}, 10.4 mL, 7.575 g, 75 mmol), (*R*)-**6** (11.200 g, 50 mmol, 98%*ee*), and dry DCM (50 mL) sequentially at room temp. under Ar. The reaction mixture was cooled to 0 °C, and a solution of MsCl (d = 1.475 g mL^{-1}, 4.6 mL, 6.84 g, 60 mmol) in anhydrous DCM (50 mL) was added dropwise within 30 min by an addition funnel. The resulting mixture was stirred at 0 °C for 1 h and the quenched with a saturated aqueous solution of $NaHCO_3$ (25 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (3× 50 mL). The combined organic layers were washed with brine (3× 50 mL) and dried with anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the mesylate residue was used in the next step without further purification. To another flame-dried, three-necked 250 mL round-bottom flask were added NaH (60%, 2.3961 g, 60 mmol) and anhydrous THF (80 mL). The reaction mixture was cooled to 0 °C, and dimethyl malonate (d = 1.151 g mL^{-1}, 12.6 mL, 110 mmol) was then added dropwise within 20 min under Ar by an addition funnel. The resulting mixture was stirred at room temp. for 60 min. The crude mesylate, which was prepared above, was then dissolved in dry THF (20 mL), and the resulting solution was then added dropwise at room temp. within 10 h by a syringe pump (2 mL per hour). After 10.5 h, the reaction reached completion (as monitored by TLC) and then was quenched with H_2O (20 mL). Et_2O (50 mL) was added, and the aqueous layer was extracted with Et_2O (3× 50 mL). The combined organic layers were washed with brine (100 mL) and dried with anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by chromatography on a silica gel column (petroleum ether/ethyl acetate, 30:1) to afford (*R*)-**5** (11.683 g, 70% yield over two steps, 98%*ee*) as a liquid. HPLC (Chiralcel OD-H column; hexane/*i*PrOH, 100:1; 0.7 mL min^{-1}; λ = 214 nm): t_R = 10.2 min (minor) and t_R= 10.7 min (major). $[\alpha]_D^{26}$ = –53.1 (c = 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.18–5.03 (m, 2 H, CH=C=CH), 3.72 (s, 6 H, 2 OCH_3), 3.49 (t, J = 7.4 Hz, 1 H, CH), 2.61–2.52 (m, 2 H, CH_2), 1.99–1.87 (m, 2 H, CH_2), 1.42–1.19 (m, 18 H, 9 CH_2), 0.86 (t, J = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.9, 169.4, 169.3, 93.0, 87.3, 52.5, 51.2, 31.9, 29.62, 29.59, 29.4, 29.3, 29.13, 29.06, 28.8, 28.0, 22.6, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2924, 2854, 1964, 1739, 1436, 1341, 1261, 1231, 1152, 1043 cm^{-1}. MS (EI): m/z (%) = 338 (6.17) [M]$^+$, 138 (100). HRMS: calcd. for $C_{20}H_{34}O_4$ [M]$^+$ 338.2457; found 338.2454.

(*R*)-Methyl Heptadeca-4,5-dienoate [(*R*)-4]: To a 100 mL flask were added LiCl (1.6797 g, 40 mmol), (*R*)-**5** (6.769 g, 20 mmol), DMSO (50 mL), and H_2O (d = 1.0 g mL^{-1}, 1.4 mL, 1.44 g, 80 mmol) sequentially at room temp. in air. The flask was then placed in a preheated oil bath at 180 °C, and the reaction mixture was stirred. After 1.5 h, the reaction reached completion (as monitored by TLC). After cooling to room temperature, H_2O (30 mL) and Et_2O (50 mL) were added, and the aqueous layer was extracted with Et_2O (3× 30 mL). The combined organic layers were washed with brine (3× 30 mL) and dried with anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by chromatography on a silica gel column (petroleum ether/ethyl acetate, 50:1) to afford (*R*)-**4** (4.072 g, 73% yield, 98%*ee*) as a liquid. HPLC (Chiralcel OD-H column; hexane/*i*PrOH, 100:0; 1 mL min^{-1}; λ = 214 nm): t_R = 8.9 min (minor) and t_R = 9.1 min (major). $[\alpha]_D^{29}$ = –50.2 (c = 0.99, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.18–5.08 (m, 2 H, CH=C=CH), 3.67 (s, 3 H, OCH_3), 2.47–2.38 (m, 2 H, CH_2), 2.34–2.23 (m, 2 H, CH_2), 2.01–1.88 (m, 2 H, CH_2), 1.43–1.18 (m, 18 H, 9 CH_2), 0.87 (t, J = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.6, 173.6, 92.6, 89.4, 51.5, 33.2, 31.9, 29.7, 29.6, 29.5, 29.3, 29.1, 28.9, 23.8, 22.7, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2925, 2854, 1963, 1744, 1464, 1437, 1362, 1251, 1198, 1161 cm^{-1}. MS (EI): m/z (%) = 280 (4.68) [M]$^+$, 80 (100). HRMS: calcd. for $C_{18}H_{32}O_2$ [M]$^+$ 280.2402; found 280.2404.

(*R*)-4,5-Heptadecadienal [(*R*)-3]: To a flame-dried, three-necked 100 mL round-bottom flask were added (*R*)-**4** (2.790 g, 10 mmol) and anhydrous DCM (30 mL). The reaction mixture was cooled to –78 °C, and DIBAL-H (1.5 M in toluene, 6.8 mL, 10.2 mmol, 1.02 equiv.) was then added slowly within 15 min under Ar by an addition funnel. After 2 h at –78 °C, the reaction reached completion (as monitored by TLC). A saturated aqueous solution of potassium sodium tartrate (10 mL) was added, and the mixture was warmed to room temperature. The resulting mixture was then stirred at room temperature for 2 h. The organic layer was separated, and the aqueous layer was extracted with DCM (3× 8 mL). The combined organic layers were washed with brine (3× 10 mL) and dried with anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by chromatography on a silica gel column (petroleum ether/ethyl acetate, 50:1) to afford (*R*)-**3** (1.903 g, 76% yield) as a liquid; $[\alpha]_D^{29}$ = –58.3 (c = 0.99, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.77 (s, 1 H, CHO), 5.19–5.10 (m, 2 H, CH=C=CH), 2.54 (t, J = 6.8 Hz, 2 H, CH_2), 2.36–2.26 (m, 2 H, CH_2), 2.00–1.90 (m, 2 H, CH_2), 1.43–1.20 (m, 18 H, 9 CH_2), 0.87 (t, J = 6.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.8, 202.1, 93.0, 89.3, 42.4, 31.9, 29.65, 29.62, 29.5, 29.3, 29.2, 29.1, 28.8, 22.7, 21.3, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2924, 2854, 2716, 1963, 1729, 1466, 1059 cm^{-1}. MS (EI): m/z (%) = 250 (2.27) [M]$^+$, 82 (100). HRMS: calcd. for $C_{17}H_{30}O$ [M]$^+$ 250.2297; found 250.2301.

(*R*)-5,6-Octadecadienal [(*R*)-2]: To a flame-dried, three-necked 50 mL round-bottom flask were added (methoxymethyl)triphenyl-

phosphonium chloride (2.677 g, 7.8 mmol) and anhydrous THF (10 mL). The reaction mixture was cooled to 0 °C, and a suspension of anhydrous potassium *tert*-butoxide (0.873 g, 7.8 mmol) in dry THF (5 mL) was then added slowly within 10 min under Ar by a syringe. The resultant solution was stirred at 0 °C for 1 h followed by the dropwise addition of a solution of (*R*)-**3** (1.501 g, 6 mmol) in THF (5 mL) within 15 min. The resulting mixture was warmed to room temp. and stirred for 3 h followed by quenching with water (5 mL). The mixture was then cooled to 0 °C, treated with 30% aqueous H_2SO_4 (1.5 mL), and then warmed to room temp. The resultant mixture was stirred for 12 h and then quenched by the slow addition of an aqueous solution of sodium hydrogen carbonate (15 mL). To the flask was then added Et_2O (15 mL), and the organic layer was separated. The aqueous layer was extracted with Et_2O (3× 5 mL), and the combined organic layers were washed with brine (3× 8 mL) and dried with anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by chromatography on a silica gel column (petroleum ether/ethyl acetate, 50:1) to afford (*R*)-**2** (1.358 g, 86% yield) as a liquid; $[\alpha]_D^{29}$ = –48.7 (*c* = 0.99, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.77 (t, *J* = 1.5 Hz, 1 H, CHO), 5.17–4.97 (m, 2 H, CH=C=CH), 2.47 (td, J_1 = 7.4 Hz, J_2 = 1.8 Hz, 2 H, CH_2), 2.08–1.92 (m, 4 H, 2 CH_2), 1.75 (quint, *J* = 7.3 Hz, 2 H, CH_2), 1.44–1.18 (m, 18 H, 9 CH_2), 0.87 (t, *J* = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.1, 202.5, 91.6, 89.7, 43.2, 31.9, 29.66, 29.63, 29.5, 29.3, 29.2, 29.1, 28.9, 28.2, 22.7, 21.4, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2924, 2854, 2714, 1962, 1728, 1464, 1170, 1075 cm^{-1}. MS (EI): *m*/*z* (%) = 264 (1.45) $[M]^+$, 80 (100). HRMS: calcd. for $C_{18}H_{32}O$ $[M]^+$ 264.2453; found 264.2455.

(*R*)-5,6-Octadecadienoic acid [(*R*)-1]: To a 50 mL Schlenk flask were added silver(I) oxide (2.3055 g, 10 mmol), H_2O (12 mL), THF (7 mL), and NaOH (2.010 g, 50 mmol) under Ar. The mixture was cooled to 0 °C and stirred, and a solution of (*R*)-**2** (1.311 g, 5 mmol) in THF (3.5 m) was added dropwise within 10 min by a syringe. After 3 h at 0 °C, the resulting mixture was treated with an aqueous solution of HCl (1 M) until the pH = 7. The resulting mixture was filtered, and the aqueous layer was extracted with ethyl ether (3× 10 mL). The combined organic layers were washed with brine (3× 8 mL) and dried with anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by chromatography on a silica gel column (petroleum ether/ethyl acetate, 10:1) to afford (*R*)-**1** (1.062 g, 76% yield) as a liquid. An *ee* value of 98% was determined by HPLC analysis of (*R*)-methyl 5,6-octadecadienoate [(*R*)-**7**]. $[\alpha]_D^{29}$ = –42.7 (*c* = 0.96, $CHCl_3$), $[\alpha]_{365}^{27}$ = –192.2 (*c* = 1.35, CH_3OH); which is consistent with ref.[16] $[\alpha]_{365}^{22}$ = –192 (*c* = 1.34, CH_3OH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.76 (br. s, 1 H, COOH), 5.16–4.98 (m, 2 H, CH=C=CH), 2.40 (t, *J* = 7.5 Hz, 2 H, CH_2), 2.09–1.91 (m, 4 H, 2 CH_2), 1.75 (quint, *J* = 7.4 Hz, 2 H, CH_2), 1.43–1.18 (m, 18 H, 9 CH_2), 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.0, 180.2, 91.6, 89.6, 33.3, 31.9, 29.7, 29.6, 29.5, 29.4, 29.2, 29.1, 28.9, 28.2, 24.0, 22.7, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 3095, 2923, 2853, 1962, 1709, 1457, 1240, 1158, 1072 cm^{-1}. MS (EI): *m*/*z* (%) = 280 (3.54) $[M]^+$, 140 (100). HRMS: calcd. for $C_{18}H_{32}O_2$ $[M]^+$ 280.2402; found 280.2404.

(*R*)-Methyl 5,6-Octadecadienoate [(*R*)-7]: A Schlenk tube that contained K_2CO_3 (55 mg, 0.40 mmol) was flame-dried and then filled with argon, and (*R*)-**1** (56 mg, 0.2 mmol), acetone (2 mL), and CH_3I (*d* = 2.3 g mL^{-1}, 37 μL, 85.2 mg, 0.6 mmol) were added sequentially. The resulting solution was stirred at room temp. The reaction reached completion after 5 h (as monitored by TLC), and the solvent was evaporated under vacuum. The residue was purified by chromatography on a silica gel column (petroleum ether/ethyl acetate, 30:1) to afford (*R*)-**7** (40 mg, 68% yield, 98% *ee*) as an oil. HPLC (Chiralcel OD-H column; hexane/*i*PrOH, 100:0; 0.5 mL min^{-1}; λ = 214 nm): t_R = 21.7 min (minor) and t_R = 22.8 min (major). $[\alpha]_D^{29}$ = –42.1 (*c* = 0.94, $CHCl_3$), which is consistent with ref.[8] $[\alpha]_D^{26}$ = –47.3 (*c* = 1.8, CH_3CH_2OH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.14–4.98 (m, 2 H, CH=C=CH), 3.67 (s, 3 H, CH_3), 2.35 (t, *J* = 7.7 Hz, 2 H, CH_2), 2.07–1.91 (m, 4 H, 2 CH_2), 1.74 (quint, *J* = 7.4 Hz, 2 H, CH_2), 1.41–1.20 (m, 18 H, 9 CH_2), 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.0, 174.1, 91.5, 89.8, 51.5, 33.4, 31.9, 29.70, 29.65, 29.5, 29.4, 29.24, 29.15, 29.0, 28.4, 24.3, 22.7, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2926, 2855, 1962, 1743, 1459, 1437, 1364, 1244, 1211, 1155, 1020 cm^{-1}. MS (EI): *m*/*z* (%) = 294 (3.49) $[M]^+$, 80 (100). HRMS: calcd. for $C_{19}H_{34}O_2$ $[M]^+$ 294.2559; found 294.2561.

Acknowledgments

Financial support from the National Natural Science Foundation of China (NSFC) (grant number 21232006) and the National Basic Research Program of China (2011CB808700) are greatly appreciated.

[1] A. Hoffmann-Röder, N. Krause, *Angew. Chem. Int. Ed.* **2004**, *43*, 1196–1216; *Angew. Chem.* **2004**, *116*, 1216–1236.
[2] a) S. R. Landor, *Naturally Occurring Allenes*, in: *The Chemistry of the Allenes* (Ed.: S. R. Landor), Academic Press, London, **1982**, p. 679; b) A. Claesson, *Biologically Active Allenes*, in: *The Chemistry of the Allenes* (Ed.: S. R. Landor), Academic Press, London, **1982**, p. 709; c) C. H. Robinson, D. F. Covey, *Biological Formation and Reactions*, in: *The Chemistry of Ketenes, Allenes and Related Compounds* (Ed.: S. Patai), Wiley, Chichester, UK, **1980**, p. 451.
[3] a) D. F. Horler, *J. Chem. Soc. C* **1970**, 859–862; for phlomic acid, see: b) K. Aitzetmüller, N. Tsevegsüren, K. Vosmann, *Fett/Lipid* **1997**, *99*, 74–78; for lamenallenic acid, see: c) K. L. Mikalaijczak, M. F. Rogers, C. R. Smith, I. A. Wolff, *Biochem. J.* **1967**, *105*, 1245–1249; d) J. S. Cowie, P. D. Landor, S. R. Landor, N. Punja, *J. Chem. Soc. Perkin Trans. 1* **1972**, 2197–2201; for a hydroxy acid, see: e) H. W. Sprecher, R. Maier, M. Barber, R. T. Holman, *Biochemistry* **1965**, *4*, 1856–1863; for a methyl hydroxy acid, see: f) H. Ohigashi, K. Kawazu, H. Egawa, T. Mitsui, *Agric. Biol. Chem.* **1972**, *36*, 1399–1403.
[4] M. Ogasawara, T. Nagano, T. Hayashi, *J. Org. Chem.* **2005**, *70*, 5764–5767.
[5] Y. Zhang, H. Hao, Y. Wu, *Synlett* **2010**, 905–910.
[6] O. W. Gooding, C. C. Beard, D. Y. Jackson, D. L. Wren, G. F. Cooper, *J. Org. Chem.* **1991**, *56*, 1083–1088.
[7] M. O. Bagley, C. R. Smith, I. A. Wolff, *Chem. Ind.* **1964**, 1861–1862.
[8] M. O. Bagby, C. R. Smith Jr., I. A. Wolff, *J. Org. Chem.* **1965**, *30*, 4227–4229.
[9] S. R. Landor, N. Punja, *Tetrahedron Lett.* **1966**, *40*, 4905–4507.
[10] S. R. Landor, B. J. Miller, A. R. Tatchell, *J. Chem. Soc. C* **1966**, 1822–1825.
[11] a) J. Ye, W. Fan, S. Ma, *Chem. Eur. J.* **2013**, *19*, 716–720; b) J. Ye, S. Ma, *Org. Synth.* **2014**, *91*, 233–247.
[12] a) A. P. Krapcho, A. J. Lovey, *Tetrahedron Lett.* **1973**, *14*, 957–960; b) A. P. Krapcho, E. G. E. Jahngen Jr., A. J. Lovey, F. W. Short, *Tetrahedron Lett.* **1974**, *15*, 1091–1094; c) A. P. Krapcho, J. F. Weimaster, J. M. Eldridge, E. G. E. Jahngen Jr., A. J. Lovey, W. P. Tephens, *J. Org. Chem.* **1978**, *43*, 138–147.
[13] W. R. Roth, T. Bastigkeit, *Liebigs Ann.* **1996**, 2171–2183.
[14] D. M. Hodgson, Y. K. Chung, J.-M. Paris, *J. Am. Chem. Soc.* **2004**, *126*, 8664–8665.

[15] a) G. Pattenden, S. J. Teague, *Tetrahedron* **1987**, *43*, 5637–6752; b) P. A. Evans, P. A. Inglesby, K. Kilbride, *Org. Lett.* **2013**, *15*, 1798–1801.
[16] F. Bohlmann, K.-M. Rode, M. Grenz, *Chem. Ber.* **1967**, *100*, 3201–3203.
[17] J. Ye, R. Lü, W. Fan, S. Ma, *Tetrahedron* **2013**, *69*, 8959–8963.
[18] Editorial: B. Alcaide, P. Almendros, *Progress in Allene Chemistry*, in: *Chem. Soc. Rev.* **2014**, vol. 43, p. 2886–2887.
[19] N. T. Patin, *Chem. Asian J.* **2012**, *7*, 2186–2194.

Received: December 8, 2014
Published Online: January 20, 2015

