Tetrahedron: *Asymmetry* xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Total syntheses of 9-epoxyfalcarindiol and its diastereomer

Yun Zhou [a], Yanli Huang [b,c], Shuoning Li [a], Pengfei Yang [a], Jiangchun Zhong [a], Jingwei Yin [a], Kaijie Ji [a], Yanqing Yang [a], Ning Ye [d], Lifeng Wang [a], Mingan Wang [a], Min Wang [a], Qinghua Bian [a,*]

[a] *Department of Applied Chemistry, China Agricultural University, 2 West Yuanmingyuan Road, Beijing 100193, PR China*
[b] *School of Surveying and Land Information Engineering, Henan Polytechinic University, Jiaozuo, Henan 454000, PR China*
[c] *Institute of Soil and Water Conservation, Northwest A & F University, Yangling, Shanxi 454003, PR China*
[d] *Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA 02138, USA*

ARTICLE INFO

Article history:
Received 25 October 2016
Revised 30 November 2016
Accepted 6 December 2016
Available online xxxx

ABSTRACT

The first total syntheses of 9-epoxyfalcarindiol **1a** and its diastereomer **1b** have been achieved. Central to our approach were the Zn-cyclopropane-based amino alcohol catalyzed enantioselective alkynylation of acrolein, the diastereoselective addition of a diynic ester to an epoxy aldehyde, and the asymmetric Sharpless epoxidation of allylic alcohol catalyzed with *L*-(+)-diethyl tartrate and Ti(O*i*Pr)$_4$.

1. Introduction

9-Epoxyfalcarindiol **1a** (Fig. 1), also known as PQ-2, was first isolated in 1991 from American Ginseng (*Panax quinquefolium*),[1] a valuable anticancer herbal medicine.[2] It was also found to exist in other plants, such as *Hedera rhombea*,[3] *Panax notoginseng*,[4] *Angelica sinensis*,[5] and *Oenanthe fistulosa*.[6] Its structure was identified as 9,10-epoxy-heptadeca-1-ene-4,6-diyne-3,8-diol by analyses of spectroscopic data.[1] In 2009, the absolute configuration of 9-epoxyfalcarindiol was confirmed as (3*R*,8*R*,9*S*,10*R*) via the modified Mosher's method, and chemical correlation with (3*R*,8*S*)-falcarindiol **2** (Fig. 1).[6,7] The laboratory bioassays showed that 9-epoxyfalcarindiol exhibited cytotoxic activities against leukemia cells (L 1210)[1] and two pathogenic strains of *Mycobacterium tuberculosis* (H37R*v* and Erdman).[5b] The investigation of Shigemori et al. indicated that it could inhibit the shoot and root growth of rice, perennial ryegrass, cockscomb, lettuce, and cress.[3] Dall'Acqua et al. reported that 9-epoxyfalcarindiol was also able to inhibit the acetylcholinesterase (Ache).[8] In addition, Atanasov et al. observed that 9-epoxyfalcarindiol displayed the properties of selective partial peroxisome proliferator-activated receptor gamma (PPARγ), and was valuable for further exploration as pharmaceutical lead or dietary supplement.[9]

The enantioselective alkynylzinc addition to aldehydes is one of the most effective and convenient protocols to prepare optically active propargylic alcohols.[10–12] Recently, we have developed the highly enantioselective addition of 1,3-diynes to aldehydes catalyzed by zinc and our cyclopropane-based amino alcohol chiral ligands to afford optically active diynic alcohols.[13] Herein, we disclose the first total syntheses of 9-epoxyfalcarindiol **1a** and its diastereomer **1b** (Fig. 1) via implementing this strategy of alkynylation of acrolein and diastereoselective addition of epoxy aldehyde. Moreover, the chiral epoxy moiety of **1a** and **1b** was constructed with the enantioselective Sharpless epoxidation of allylic alcohol.

2. Results and discussion

The retrosynthetic analysis of 9-epoxyfalcarindiol **1a** is depicted in Fig. 2. The epoxy 1,3-diynic alcohol ester **17a** was envisioned to be obtained via the diastereoselective addition of diynic ester **10** to epoxy aldehyde **16**. The Zn-cyclopropane-based amino alcohol catalyzed enantioselective addition of TIPS diyne **3** to acrolein **4** was expected to afford chiral TIPS enynic diol **7**. On the other hand, we thought that the Sharpless asymmetric epoxidation of **14** could generate chiral epoxy alcohol **15**. Subsequent Dess-Martin oxidation of **15** would provide the key intermediate **16**.

Our study started with the preparation of diynic ester **10** (Scheme 1). TIPS diyne **3** was synthesized smoothly according to the procedure of Danheiser et al.,[14] subsequent enantioselective addition **3** to acrolein **4** catalyzed by zinc and our cyclopropane-based amino alcohol (1*S*,3*R*)-**L1** to afford (*R*)-8-methyl-8-((triisopropylsilyl)oxy)nona-1-en-4,6-diyn-3-ol **5** in 60% yield and with 81% ee.[13] For the determination of the absolute configuration of adduct **5**, a modified Mosher's method[15] was applied. The reaction of **5** with (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid chloride (MTPA-Cl) gave the (*S*)- and (*R*)-MTPA esters **18a** and **18b**, respectively. Analysis of the differences in ^{1}H chemical shifts ($\Delta\delta_H = \delta_S - \delta_R$) between the (*S*)- and (*R*)-MTPA of **5** favored its

* Corresponding author. Tel.: +86 010 62731356; fax: +86 010 62820325.
E-mail address: bianqinghua@cau.edu.cn (Q. Bian).

http://dx.doi.org/10.1016/j.tetasy.2016.12.008
0957-4166/

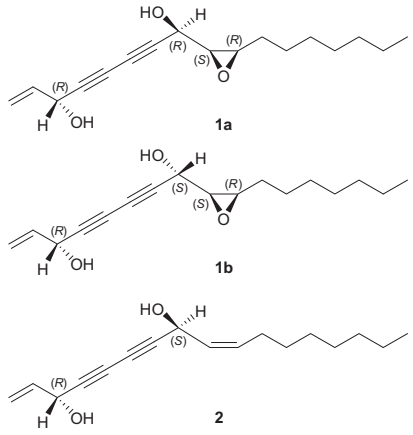
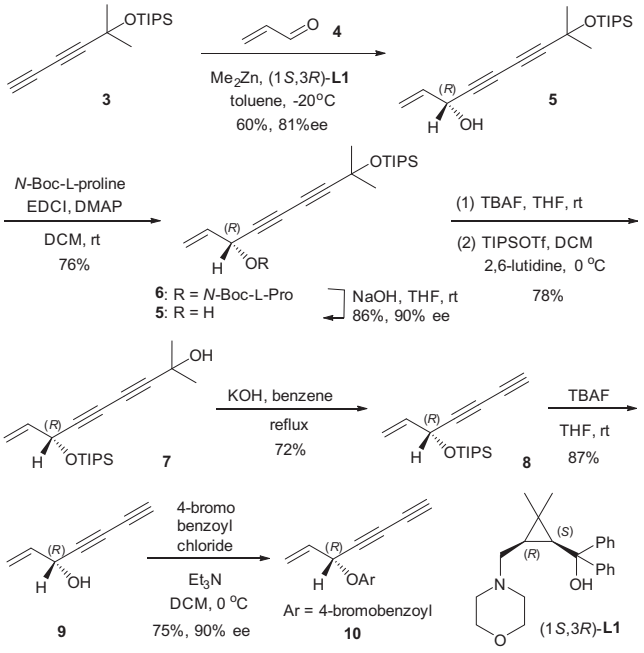


Figure 1. The structures of 9-epoxyfalcarindiol **1a**, its diastereomer **1b** and (+)-(3*R*,8*S*)-falcarindiol **2**.

absolute (*R*)-configuration (Fig. 3).[15] This result was consistent with the governing precedents of enantioselective addition between 1,3-diynes and aldehydes developed by our group.[13] Previous reports[16] demonstrated that *N-tert*-butoxycarbonyl-L-proline (Boc-L-proline) could resolve racemic secondary alcohols. To improve upon the enantiomeric optical of TIPS enynic alcohol **5**, the esterification of **5** with Boc-L-proline and the silica gel column chromatography separation were conducted sequentially, which provided enynic ester **6** in 76% yield. The resolving agent was then cleaved with NaOH in THF, and gave TIPS enynic alcohol **5** in 86% yield and with 90% ee.[16] After deprotection of the tertiary hydroxyl group at C-8 with TBAF, the secondary hydroxyl group at C-3 was protected with TIPSOTf to afford (*R*)-2-methyl-7-((triisopropylsilyl)oxy)nona-8-en-3,5-diyn-2-ol **7** in 78% yield over the two



Scheme 1. Synthesis of diynic ester **10**.

steps.[17] Upon exposure to KOH in refluxing toluene, TIPS enynic diol **7** was directly converted into TIPS enyne **8** in 72% yield.[18] Finally, deprotection of secondary hydroxyl group at C-3 with TBAF furnished (*R*)-hepta-1-en-4,6-diyn-3-ol **9** in 87% yield,[19] followed by the esterification of enynic alcohol **9** with 4-bromobenzoyl chloride to obtain diynic ester **10** in 75% yield and with 90% ee.[20]

Next, we focused on the synthesis of chiral epoxy aldehyde **16** (Scheme 2). The alkylation of propargyl alcohol **12** with

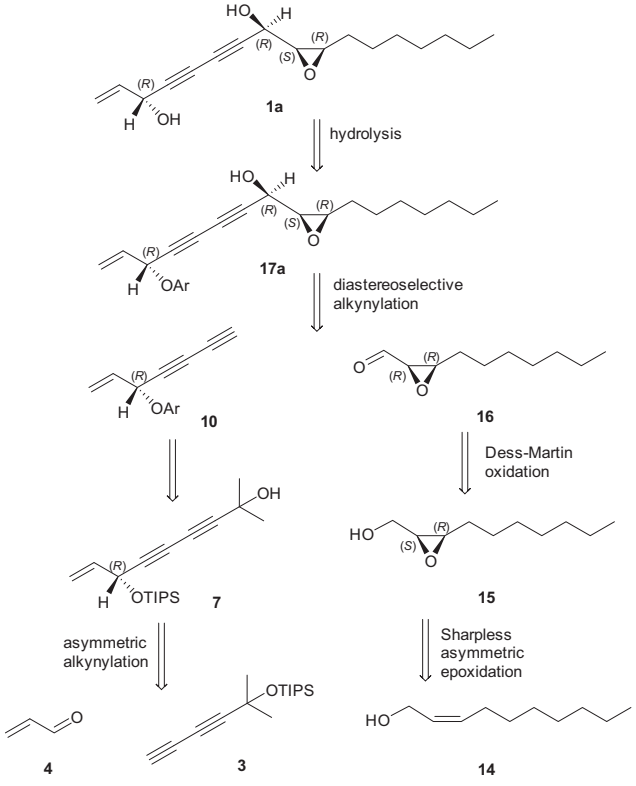


Figure 2. Retrosynthetic analysis of 9-epoxyfalcarindiol **1a**.

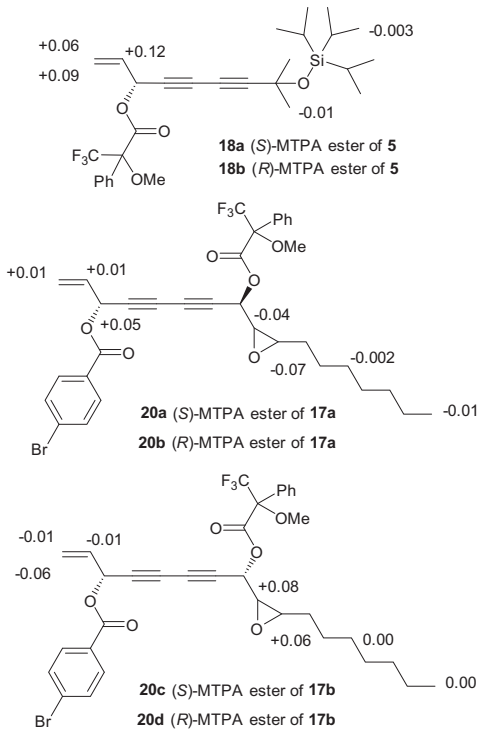
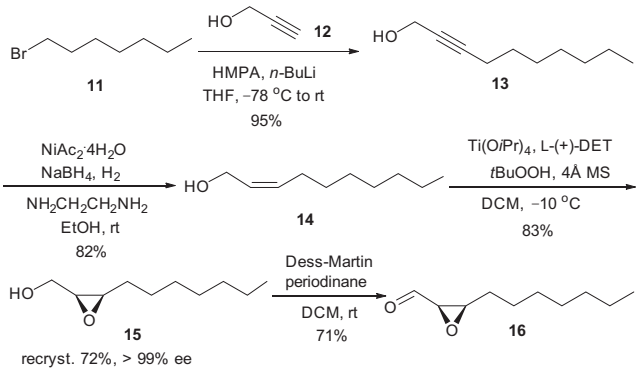
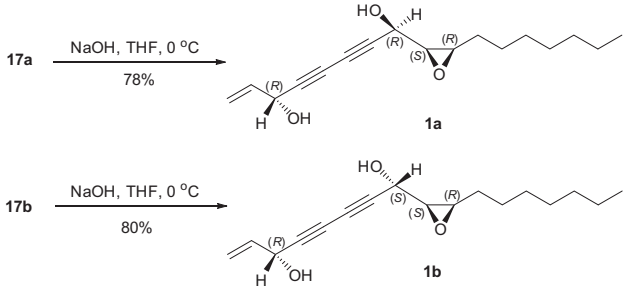


Figure 3. Confirmation of the absolute configurations of secondary alcohols **5**, **17a** and **17b** via the modified Mosher's method. $\Delta\delta_H$ ($\delta_S - \delta_R$) values are given in ppm.



Scheme 2. Synthesis of chiral epoxy aldehyde **16**.



Scheme 3. Synthesis of 9-epoxyfalcarindiol 1a and its diastereomer **1b**.

1-bromoheptane (**11**) afforded dec-2-yn-1-ol **13** in 95% yield,[21] which was reduced to (*Z*)-dec-2-en-1-ol **14** in 82% yield with Brown's P2-Ni system.[22] Sharpless asymmetric epoxidation of allylic alcohol **14** catalyzed with *L*-(+)-diethyl tartrate and Ti(O*i*Pr)$_4$ generated (2*S*,3*R*)-2,3-epoxy-1-decanol (**15**) in 83% yield.[23] Recrystallization of **15** from petroleum ether improved the ee to over 99%, which was determined by ^{1}H NMR and ^{13}C NMR analysis of (*S*)-MTPA ester of **15**.[15] The final Dess-Martin oxidation converted epoxy alcohol **15** into (2*R*,3*R*)-2,3-epoxy decanal **16** in 71% yield.[24]

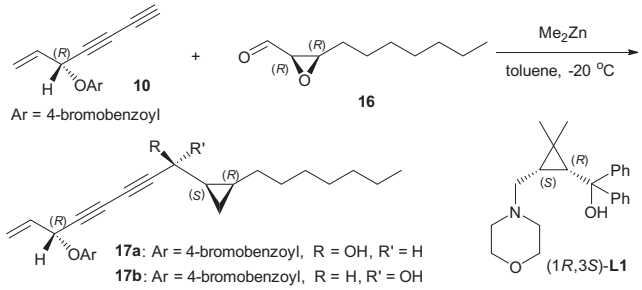
With the chiral building blocks **10** and **16** in hand, the diastereoselective addition of diynic ester **10** to epoxy aldehyde **16** was studied (Table 1). In the absence of a chiral ligand, the addition proceeded with a Felkin-Anh preference,[25] providing a 3:1 mixtures of **17a** and **17b** at −20 °C (entry 2). When chiral ligand (1*S*,3*R*)-**L1** was used, diastereomeric ratios of **1:6** showed that (1*S*,3*R*)-**L1** was the matched case (entry 4). However, in the presence of enantiomeric ligand (1*R*,3*S*)-**L1**, the addition gave a 1:1 mixtures of **17a** and **17b**, thus indicating that (1*R*,3*S*)-**L1** was a mismatched case (entry 6). A similar phenomenon was observed in the diastereoselective vinyl ether addition to enantioenriched *β*-hydroxy aldehydes by Walsh et al.[26] Furthermore, we found that increasing the temperature from −20 to 0 °C just increased the yield, but had almost had no effect on the diastereomeric ratio (entries 1,3,5 vs. 2,4,6). The same modified Mosher's method[15] was applied to assign the absolute configurations at C-8 of **17a** and **17b**. Analysis of the differences in the ^{1}H chemical shifts ($\Delta\delta_H = \delta_S - \delta_R$) between the (*S*)- and (*R*)-MTPA of **17a** suggested the *R* configuration (Fig. 3). The absolute configuration at C-8 of **17b** was confirmed as (*S*) by comparison of the chemical shifts of the protons ($\Delta\delta_H = \delta_S - \delta_R$) neighboring the oxygenated methine on the (*S*)- and (*R*)-MTPA of **17b** (Fig. 3).[15]

The final hydrolysis of **17a** with NaOH in THF afforded the target 9-epoxyfalcarindiol **1a** in 78% yield (Scheme 3).[20] The NMR spectroscopic data and specific rotation of synthetic **1a** were identical to those of the natural 9-epoxyfalcarindiol **1a** isolated from *Panax quinquefolium*.[1] The similar hydrolysis of **17b** gave the diastereomer of 9-epoxyfalcarindiol **1b** in 80% yield (Scheme 3), and its structure was character with ^{1}H NMR, ^{13}C NMR and HRMS spectra.

3. Conclusion

In conclusion, we have accomplished the total syntheses of 9-epoxyfalcarindiol **1a** and its diastereomer **1b** for the first time. The key steps of our approach include the asymmetric alkynylation of acrolein catalyzed by zinc and our cyclopropane-based amino alcohol chiral ligand, the diastereoselective addition of diynic ester to epoxy aldehyde, and the enantioselective Sharpless epoxidation of allylic alcohol. Moreover, the epoxy 1,3-diynic alcohols **1a** and **1b** synthesized herein are potentially useful in the development of antitumor drugs and dietary supplements.

Table 1
Diastereoselective addition of diynic ester **10** to epoxy aldehyde **16**[a]



Entry	Ligand	Temp. (°C)	Yield (%)[b]	Dr (**17a**:**17b**)[c]
1	No	0	48	3:1
2	No	−20	28	3:1
3	(1*S*,3*R*)-**L1**	0	63	1:5
4	(1*S*,3*R*)-**L1**	−20	60	1:6
5	(1*R*,3*S*)-**L1**	0	64	1:1
6	(1*R*,3*S*)-**L1**	−20	58	1:1

[a] Reactions were performed with **1** equiv epoxy aldehyde **16**, 3 equiv diynic ester **10** and Me_2Zn.
[b] Isolated yields after chromatographic purification.
[c] Determined by HPLC with a Daicel Chiralcel OJ-H column.

4. Experimental

4.1. General

Melting points were measured on a STUART-SMP3 Melt-Temp apparatus without correction. Optical rotations were obtained on a PERKIN ELEMER 341 Polarimeter. NMR spectra were recorded on a Bruker DP-X300 MHz spectrometer. Chemical shifts (δ) were relative to internal tetramethylsilane (TMS) for ^{1}H NMR (δ_H = 0.00 - ppm) and to $CDCl_3$ for ^{13}C NMR (δ_C = 77.00 ppm). High resolution mass spectra (HRMS) were conducted on an Agilent time-of-flight instrument. Enantiomeric excesses (ee) were determined on an Agilent 1200 HPLC system with a Daicel Chiralcel OJ-H chiral-phase column and elution with *n*-hexane and 2-propanol. All reactions were performed under an argon atmosphere, and the stated yields are isolated yields after chromatographic purification. Solvents were purified and dried according to the standard procedures before use. Unless otherwise stated, all commercially available reagents were used without further purification.

4.2. (*R*)-8-Methyl-8-((triisopropylsilyl)oxy)nona-1-en-4,6-diyn-3-ol 5

To a solution of cyclopropane-based amino alcohol (1*S*,3*R*)-**L1** (0.2106 g, 0.6 mmol, 0.2 equiv) in toluene (6 mL) was added TIPS diyne **3** (2.3802 g, 9 mmol, 3 equiv) at 0 °C under an argon atmosphere. A solution of Me_2Zn (7.5 mL, 1.2 M in toluene, 9 mmol, 3 equiv) was then added slowly via syringe at the same temperature. After the resulting mixture was stirred for 1.5 h at 0 °C, the mixture was cooled to −20 °C. Acrolein **4** (0.1682 g, 3 mmol, 1 equiv) was added slowly via syringe, and the reaction mixture was maintained for 48 h at −20 °C. The reaction was quenched with water (10 mL) and filtered through a Celite pad. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to get crude product. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate 10:1) to afford TIPS enynic alcohol **5** (0.5751 g, 60% yield, 81% ee, measured on chiral-phase HPLC analysis of its 3,5-dinitrobenzoate) as a yellow oil. Enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column (10% 2-propanol in *n*-hexane, 1.3 mL/min, 220 nm) minor (*S*)-enantiomer t_r = 9.76 min; major (*R*)-enantiomer t_r = 12.52 min. $[\alpha]_D^{24}$ = −2.1 (*c* 1.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.99 (ddd, *J* = 17.0, 10.1, 5.4 Hz, 1H), 5.54 (dd, *J* = 17.0, 0.5 Hz, 1H), 5.30 (dd, *J* = 10.1, 0.3 Hz, 1H), 5.01–4.97 (m, 1H), 2.01 (d, *J* = 6.5 Hz, 1H), 1.57 (s, 6H), 1.12–1.10 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 136.0, 117.2, 85.5, 77.5, 70.5, 66.6, 66.5, 63.6, 32.8, 18.3, 12.9; HRMS (ESI) *m*/*z* 321.2238 $[M+H]^+$ (calcd for $C_{19}H_{33}O_2Si$, 321.2250).

4.3. 1-(*tert*-Butyl)2-((*R*)-8-methyl-8-((triisopropylsilyl)oxy) nona-1-en-4,6-diyn-3-yl) (*S*)-pyrrolidine-1,2-dicarboxylate 6

Under an argon atmosphere, TIPS enynic alcohol **5** (0.4808 g, 1.5 mmol, 1 equiv) was added slowly to a solution of *N*-Boc-*L*-proline (0.3875 g, 1.8 mmol, 1.2 equiv), EDCI (0.3738 g, 1.95 mmol, 1.3 equiv), and DMAP (0.0916 g, 0.75 mmol, 0.5 equiv) in CH_2Cl_2 (6 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 h. The reaction was quenched with water (5 mL), and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain crude product. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate 20:1) to give enynic ester **6** (0.5900 g, 76% yield) as a yellow oil. $[\alpha]_D^{24}$ = −7.7 (*c* 0.68, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.02–5.82 (m, 2H), 5.58–5.52 (m, 1H), 5.37–5.33 (m, 1H), 4.28–4.24 (m, 1H), 3.59–3.40 (m, 2H), 2.24–2.20 (m, 1H), 1.99–1.86 (m, 3H), 1.53 (s, 6H), 1.43 (s, 9H), 1.15–1.06 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 171.7, 153.7, 131.9, 119.8, 85.7, 80.1, 73.8, 71.3, 66.5, 64.9, 59.0, 46.3, 32.8, 30.8, 28.4, 28.3, 23.6, 18.2, 12.9; HRMS (ESI) *m*/*z* 518.3297 $[M+H]^+$ (calcd for $C_{29}H_{48}NO_5Si$, 518.3302).

4.4. Hydrolysis of enynic ester 6 to TIPS enynic alcohol 5

At first, NaOH aqueous solution (1.1 mL, 2 M, 2.2 mmol, 2 equiv) and methanol (0.06 mL) were added to a solution of enynic ester **6** (0.5690 g, 1.1 mmol, 1 equiv) in THF (5 mL). The resulting mixture was warmed to room temperature, and stirred for 5 h. The reaction mixture was diluted with water (5 mL) and diethyl ether (5 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate 10:1) to obtain TIPS enynic alcohol **5** (0.3032 g, 86% yield, 90% ee, measured on chiral-phase HPLC analysis of its 3,5-dinitrobenzoate) as a yellow oil. Enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column (10% 2-propanol in *n*-hexane, 1.3 mL/min, 220 nm); minor (*S*)-enantiomer t_r = 9.61 min, major (*R*)-enantiomer t_r = 12.52 min.

4.5. (*R*)-2-Methyl-7-((triisopropylsilyl)oxy)nona-8-en-3,5-diyn-2-ol 7

To a solution of TIPS enynic alcohol **5** (0.2564 g, 0.8 mmol, 1 equiv) in THF (3 mL) was added TBAF (1.2 mL, 1.0 M in THF, 1.5 equiv) at 0 °C under an argon atmosphere. The resulting mixture was warmed to room temperature and stirred for 12 h. The reaction mixture was then cooled to 0 °C and quenched with water (3 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the crude enynic diol.

The crude enynic diol was dissolved in CH_2Cl_2 (6 mL), and cooled to 0 °C. 2,6-Lutidine (0.1114 g, 1.04 mmol, 1.3 equiv) and TIPSOTf (0.3187 g, 1.04 mmol, 1.3 equiv) were then added sequentially. After the reaction mixture was stirred for 1 h at 0 °C, the reaction was quenched with saturated aqueous NH_4Cl solution (4 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to get crude product. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate 10:1) to afford TIPS enynic diol **7** (0.1999 g, 78% yield) as a yellow oil. $[\alpha]_D^{24}$ +17.2 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.89 (ddd, *J* = 17.0, 10.1, 5.1 Hz, 1H), 5.41 (d, *J* = 17.0 Hz, 1H), 5.18 (d, *J* = 10.1 Hz, 1H), 5.01 (dd, *J* = 3.7, 1.4 Hz, 1H), 2.13 (s, 1H), 1.53 (s, 6H), 1.10–1.07 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 137.0, 115.4, 83.7, 79.3, 69.1, 66.6, 65.6, 64.0, 31.0, 17.9, 12.2; HRMS (ESI) *m*/*z* 321.2237 $[M+H]^+$ (calcd for $C_{19}H_{33}O_2S$, 321.2250).

4.6. (*R*)-(Hepta-1-en-4,6-diyn-3-yloxy)triisopropylsilane 8

To a suspension of powdered KOH (0.0617 g, 1.1 mmol, 2.2 equiv) in benzene (25 mL) was added slowly TIPS enynic diol

7 (0.5 mmol, 0.1603 g, 1 equiv) under an argon atmosphere. The resulting mixture was heated at reflux for 0.5 h, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad eluting with petroleum ether. The filtrate was concentrated under reduced pressure to obtain a crude product. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate 200:1) to give TIPS enyne **8** (0.0942 g, 72% yield) as a yellow oil. $[\alpha]_D^{24}$ = +2.1 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.90 (ddd, *J* = 17.0, 10.1, 5.1 Hz, 1H), 5.43 (dt, *J* = 17.0, 1.4 Hz, 1H), 5.21 (dt, *J* = 10.1, 1.4 Hz, 1H), 5.00 (dt, *J* = 4.0, 1.0 Hz, 1H), 2.2 (d, *J* = 1.0 Hz, 1H), 1.14–1.08 (m, 18H), 0.88–0.84 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 136.7, 115.6, 76.0, 69.4, 68.4, 67.6, 63.9, 17.9, 12.2; HRMS (ESI) *m*/*z* 263.1820 $[M+H]^+$ (calcd for $C_{16}H_{27}OSi$, 263.1831).

4.7. (*R*)-Hepta-1-en-4,6-diyn-3-ol 9

To a solution of TIPS enyne **8** (0.0787 g, 0.3 mmol, 1 equiv) in THF (1.5 mL) was added TBAF (0.45 mL, 1.0 M in THF, 0.45 mmol, 1.5 equiv) at 0 °C under an argon atmosphere. The resulting mixture was warmed to room temperature and stirred for 25 min. The reaction was then cooled to 0 °C and quenched with water (2 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate 10:1) to afford enynic alcohol **9** (0.0275 g, 87% yield) as a yellow oil. $[\alpha]_D^{20}$ = −38.2 (*c* 1.3, $CHCl_3$). Lit[6] $[\alpha]_D^{24}$ = −31.6 (*c* 0.75, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.93 (ddd, *J* = 17.0, 10.1, 5.4 Hz, 1H), 5.50 (dd, *J* = 17.0, 0.9 Hz, 1H), 5.27 (dd, *J* = 10.1, 0.3 Hz, 1H), 4.91 (s, 1H), 2.42 (br s, 1H), 2.23 (d, *J* = 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 135.6, 117.5, 74.7, 70.4, 69.0, 67.3, 63.3; HRMS(APCI-TOF) *m*/*z* 107.0506 $[M+H]^+$ (calcd for C_7H_7O, 107.0497).

4.8. (*R*)-Hepta-1-en-4,6-diyn-3-yl 4-bromobenzoate 10

To a solution of enynic alcohol **9** (0.0954 g, 0.9 mmol, 1 equiv) and triethylamine (0.1366 g, 1.35 mmol, 1.5 equiv) in CH_2Cl_2 (5 mL) was added 4-bromobenzoyl chloride (0.2350 g, 1.08 mmol, 1.2 equiv) in CH_2Cl_2 (3 mL) via a syringe pump over 3 h at 0 °C. The reaction solution was stirring for 3 h at the same temperature, and quenched with water (5 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate 200:1) to afford diynic ester **10** (0.1948 g, 75% yield, 90% ee) as a yellow oil. Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (1% 2-propanol in *n*-hexane, 1.0 mL/min, 220 nm); minor (*S*)-enantiomer t_r = 12.48 min, major (*R*)-enantiomer t_r = 13.32 min. $[\alpha]_D^{20}$ −69.3 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.91 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 6.12 (dd, *J* = 5.7, 1.1 Hz, 1H), 5.97 (ddd, *J* = 15.9, 10.0, 5.6 Hz, 1H), 5.63 (d, *J* = 16.9 Hz, 1H), 5.41 (d, *J* = 10.0 Hz, 1H), 2.25 (d, *J* = 0.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 164.3, 131.8, 131.7, 131.3, 128.75, 128.2, 120.2, 71.4, 71.1, 69.4, 67.1, 65.0; HRMS (ESI) *m*/*z* 288.9902 $[M+H]^-$ (calcd for $C_{14}H_{10}BrO_2$, 288.9864).

4.9. Dec-2-yn-1-ol 13

Under an argon atmosphere, *n*-BuLi (16 mL, 2.5 M in *n*-hexane, 40 mmol, 4 equiv) was added slowly to a stirred solution of propargyl alcohol **12** (1.1214 g, 20 mmol, 2 equiv) and HMPA (10.752 g, 60 mmol, 6 equiv) in THF (10 mL) at −78 °C. The resulting mixture was warmed to −30 °C and stirred for 3 h. 1-Bromoheptane **11** (1.7910 g, 10 mmol, 1 equiv) was then added slowly, and the reaction mixture was stirred for 30 min at −30 °C. After the reaction mixture was warmed to room temperature and stirred for 24 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 30 mL). The combined organic phases were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain a crude product. The crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate 10:1) to afford propargyl alcohol **13** (1.4647 g, 95% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.26 (dt, *J* = 6.0, 2.2 Hz, 2H), 2.22 (tt, *J* = 7.2, 2.2 Hz, 2H), 1.99 (t, *J* = 5.9 Hz, 1H), 1.52–1.50 (m, 2H), 1.33–1.28 (m, 8H), 0.90 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 86.6, 78.3, 51.4, 31.7, 28.8, 28.7, 28.6, 22.6, 18.7, 14.0; HRMS (APCI-TOF) *m*/*z* 155.1436 $[M+H]^+$ (calcd for $C_{10}H_{19}O$ 155.1436).

4.10. (*Z*)-Dec-2-en-1-ol 14

Under an H_2 atmosphere, a suspension of $NaBH_4$ (0.3594 g, 9.5 mmol, 1 equiv) in ethanol (10 mL) was added slowly to a stirred solution of $NiAc_2{\cdot}4H_2O$ (1.679 g, 9.5 mmol, 1 equiv) in ethanol (10 mL) at 25 °C. The resulting mixture was warmed to room temperature and stirred for 1 h. Ethylenediamine (2.2838 g, 38 mmol, 4 equiv) was then added and stirred for an additional 5 min. Next, propargyl alcohol **13** (1.4649 g, 9.5 mmol, 1 equiv) was added slowly. After the reaction mixture was maintained for another 6 h, the reaction mixture was filtered through a celite pad. The filtrate was concentrated under reduced pressure to get crude product. The crude product was purified by silica gel chromatography (petroleum ether) to afford allylic alcohol **14** (1.2153 g, 82% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.63–5.56 (m, 2H), 4.22–4.21 (m, 2H), 2.13–2.06 (m, 2H), 1.53 (br s, 1H), 1.40–1.30 (m, 10H), 0.91 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 133.0, 128.4, 58.5, 31.8, 29.6, 29.1, 29.0, 27.4, 22.6, 14.0; HRMS (APCI-TOF) *m*/*z* 157.1581 $[M+H]^+$ (calcd for $C_{10}H_{21}O$ 157.1592).

4.11. (2*S*,3*R*)-2,3-Epoxy-1-decanol 15

Under an argon atmosphere, L-(+)-diethyl tartrate (0.2245 g, 1.0887 mmol, 0.14 equiv) and $Ti(OiPr)_4$ (0.2210 g, 0.7777 mmol, 0.1 equiv) were added sequentially to a suspension of powdered activated 4 Å molecular sieves (0.6076 g) in CH_2Cl_2 (20 mL) at 0 °C. The resulting mixture was cooled to −23 °C, and *tert*-butyl hydroperoxide (TBHP) (2.8 mL, 5.5 M in decane, 15.4 mmol, 2 equiv) was then added slowly. After the mixture was stirred for 1 h at −23 °C, allylic alcohol **14** (1.2153 g, 7.7769 mmol, 1 equiv) was added. The reaction mixture was warmed to −10 °C and stirred for an additional 72 h, followed by quenching with water (10 mL) at 0 °C. After stirring for 1 h, NaOH aqueous solution (40 mL, 30%) was added and stirred vigorously until the phase separation was occurred at room temperature. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude product. The crude product was purified by silica gel chromatography (petroleum ether/diethyl ether 2:1) to afford epoxy alcohol **15** (1.1120 g, 83% yield) as a white solid. M.p. 43.0–44.0 °C; Recrystallization from petroleum ether (100 mL) provided a white solid (0.8006 g, 72% yield, >99% ee, determined by ^{1}H NMR analysis of the ester derived from (*R*)-MTPACl). $[\alpha]_D^{20}$ = −0.8 (*c* 0.48, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.84 (ddd, *J* = 11.7, 7.5, 4.0 Hz, 1H), 3.66 (ddd, *J* = 12.0, 6.9, 4.8 Hz, 1H), 3.14 (dt, *J* = 6.9, 4.2 Hz, 1H), 3.02 (dt, *J* = 6.9, 4.2 Hz, 1H), 1.86 (dd, *J* = 7.4, 4.8 Hz, 1H), 1.54–1.27

(m, 12H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, CD Cl$_3$) δ_C 60.9, 57.3, 56.8, 31.7, 29.4, 29.1, 27.9, 26.6, 22.6, 14.0; HRMS (APCI-TOF) 173.1533 [M+H]$^+$ (calcd for $C_{10}H_{21}O_2$ 173.1542).

4.12. (2*R*,3*R*)-2,3-Epoxy decanal 16

To a solution of epoxy alcohol **15** (0.1723 g, 1 mmol, 1 equiv) in CH_2Cl_2 (5 mL) at 0 °C, was added slowly Dess-Martin periodinane (0.5938 g, 1.4 mmol, 1.4 equiv). The reaction mixture was warmed to room temperature and stirred for 1 h. Next, the reaction was quenched with 5% $Na_2S_2O_3$ in saturated aqueous $NaHCO_3$ (15 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 25 mL). The combined organic phases were washed with brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain the crude product. The crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate 10:1) to afford epoxy aldehyde **16** (0.1208 g, 71% yield) as a colorless oil. $[\alpha]_D^{20}$ = +47.0 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.48 (d, J = 5.3 Hz, 1H), 3.35 (dd, J = 6.9, 4.8 Hz, 1H), 3.27 (dt, J = 6.9, 4.8 Hz, 1H), 1.77–1.64 (m, 4H), 1.39–1.30 (m, 8H), 0.90 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 199.0, 59.1, 57.9, 31.6, 29.1, 28.9, 28.1, 26.5, 22.5, 13.9; HRMS (APCI-TOF) *m*/*z* 171.1371 [M+H]$^+$ (calcd for $C_{10}H_{19}O_2$ 171.1385).

4.13. (3*R*,8*R*,9*S*,10*R*)-9,10-epoxy-8-hydroxyheptadeca-1-en-4,6-diyn-3-yl 4-bromobenzoate 17a and(3*R*,8*S*,9*S*,10*R*)-9,10-epoxy-8-hydroxyheptadeca-1-en-4,6-diyn-3-yl 4-bromobenzoate 17b

To a solution of cyclopropane-based amino alcohol (1*S*,3*R*)-**L1** (0.0014 g, 0.04 mmol, 0.2 equiv) in toluene (2 mL) was added epoxy aldehyde **16** (0.0341 g, 0.2 mmol, 1 equiv) at 0 °C under an argon atmosphere. A solution of Me_2Zn (0.5 mL, 1.2 M in toluene, 0.6 mmol, 3 equiv) was added slowly via syringe at the same temperature. After the resulting mixture was stirred for 1.5 h at 0 °C, diynic ester **10** (0.1735 g, 0.6 mmol, 3 equiv) was added slowly via syringe at −20 °C. The reaction mixture was then stirred for 48 h at the same temperature, and quenched with water (5 mL), followed by filtering through a Celite pad. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 8 mL). The combined organic layers were washed with brine (8 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to get the crude product. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate 5:1) to afford a mixture of two diastereoisomers **17a** and **17b** (0.0551 g, 60% yield, d.r. 1:6) as a yellow oil. The diastereoisomers were separated by silica gel column chromatography (*n*-hexane/ethyl acetate 15:1) to afford pure **17a** (0.0065 g) and **17b** (0.039 g). The diastereomeric ratio was determined by HPLC with a Daicel Chiralcel OJ-H column (5% 2-propanol in *n*-hexane, 1 mL/min, 220 nm); minor **17a** t_r = 16.68 min, major **17b** t_r = 21.83 min. **17a**: $[\alpha]_D^{20}$ = −85.3 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.96 (d, J = 8.6 Hz, 2H), 7.63 (d, J = 8.6 Hz, 2H), 6.19 (d, J = 5.9 Hz, 1H), 6.00 (ddd, J = 16.9, 10.0, 5.7 Hz, 1H), 5.67 (d, J = 16.9 Hz, 1H), 5.46 (d, J = 10.1 Hz, 1H), 4.32 (d, J = 7.5 Hz, 1H), 3.22 (dd, J = 7.5, 4.3 Hz, 1H), 3.09 (dt, J = 9.8, 4.9 Hz, 1H), 2.47 (br s, 1H), 1.61–1.52 (m, 2H), 1.40–1.30 (m, 10H), 0.91 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 164.4, 131.9, 131.7, 131.4, 128.7, 128.2, 120.2, 76.6, 75.1, 70.8, 70.5, 65.2, 62.1, 59.5, 57.4, 31.7, 29.3, 29.1, 28.1, 26.6, 22.6, 14.0. HRMS (APCI-TOF) *m*/*z* 459.1167 [M+H]$^+$ (calcd for $C_{24}H_{28}BrO_4$ 459.1171). **17b**: $[\alpha]_D^{20}$ +30.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.96 (d, J = 8.6 Hz, 2H), 7.64 (d, J = 8.6 Hz, 2H), 6.19 (d, J = 5.6 Hz, 1H), 6.00 (ddd, J = 16.9, 10.1, 5.7 Hz, 1H), 5.67 (d, J = 16.9 Hz, 1H), 5.45 (d, J = 10.1 Hz, 1H), 4.40 (dd, J = 6.9, 3.9 Hz, 1H), 3.17 (dd, J = 7.3, 3.9 Hz, 1H), 3.08 (dt, J = 5.7, 3.9 Hz, 1H), 2.28 (br s, 1H), 1.68–1.62 (m, 2H), 1.56–1.52 (m, 2H), 1.36–1.29 (m, 8H), 0.91 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 164.4, 131.8, 131.7, 131.4, 128.7, 128.3, 120.2, 78.5, 74.8, 71.0, 70.0, 65.2, 60.7, 58.0, 57.8, 31.5, 29.3, 29.1, 27.5, 26.5, 22.6, 14.0; HRMS (APCI-TOF) *m*/*z* 459.1176 [M+H]$^+$ (calcd for $C_{24}H_{28}BrO_4$ 459.1171).

4.14. (*S*)-MTPA ester 18a of 5

At first, TIPS enynic alcohol **5** (16.0 mg, 0.05 mmol, 1 equiv) was added slowly to a solution of DMAP (6.1 mg, 0.05 mmol, 1 equiv) and triethylamine (25.3 mg, 0.25 mmol, 5 equiv) in CH_2Cl_2 (2 mL) at 0 °C. (*R*)-(−)-α-Methoxy-α-(trifluoromethy1) phenylacetyl chloride (MTPACl) (25.3 mg, 0.1 mmol, 2 equiv) was then added, and the reaction mixture turned yellow. The reaction was maintained at 0 °C, and monitored by TLC. The reaction was quenched with water (3 mL), and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude product. The crude product was purified by thin layer chromatography to afford **18a** (15.2 mg, 57% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.54–7.52 (m, 2H), 7.43–7.41 (m, 3H), 6.13–6.11 (m, 1H), 5.94 (ddd, J = 16.9, 10.0, 6.0 Hz, 1H), 5.62 (dd, J = 16.9, 0.3 Hz, 1H), 5.43 (dd, J = 10.0, 0.06 Hz, 1H), 3.57 (s, 3H), 1.54 (s, 6H), 1.15–1.05 (m, 21H).

4.15. (*R*)-MTPA ester 18b of 5

According to the similar procedure of synthesis of **18a**, (*S*)-(−)-α-methoxy-α-(trifluoromethy1) phenylacetyl chloride (MTPACl) (25.3 mg, 0.1 mmol, 2 equiv) and TIPS enynic alcohol **5** (16.0 mg, 0.05 mmol, 1 equiv) gave **18b** (13.2 mg, 49% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.55–7.52 (m, 2H), 7.45–7.39 (m, 3H), 6.16–6.14 (m, 1H), 5.81 (ddd, J = 16.9, 10.1, 5.7 Hz, 1H), 5.53 (dd, J = 17.0, 0.7 Hz, 1H), 5.37 (dd, J = 10.1, 0.7 Hz, 1H), 3.61 (s, 3H), 1.55 (s, 6H), 1.12–1.06 (m, 21H).

4.16. (*S*)-MTPA ester 19 of 15

According to the similar procedure of synthesis of **18a**, (*R*)-(−)-α-methoxy-α-(trifluoromethy1) phenylacetyl chloride (MTPACl) (50.6 mg, 0.2 mmol, 2 equiv) and epoxy alcohol **15** (17.2 mg, 0.1 mmol, 1 equiv) gave **19** (20.2 mg, 52% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.59–7.56 (m, 2H), 7.46–7.44 (m, 3H), 4.55 (dd, J = 11.9, 4.6 Hz, 1H), 4.38 (dd, J = 11.9, 6.8 Hz, 1H), 3.61 (d, J = 1.2 Hz, 3H), 3.27 (dt, J = 6.9, 4.5 Hz, 1H), 3.06 (dt, J = 6.9, 4.5 Hz, 1H), 1.61–1.31 (m, 12H), 0.92 (t, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 166.5, 132.0, 129.7, 128.5, 127.3, 123.2 (q, J = 287.1 Hz), 84.7, 64.5, 56.6, 55.5, 53.0, 31.7, 29.3, 29.1, 27.9, 26.5, 22.6, 14.0. HRMS (APCI-TOF) *m*/*z* 389.1967 [M+H]$^+$ (calcd for $C_{20}H_{28}F_3O_4$ 389.1940).

4.17. (*S*)-MTPA ester 20a of 17a

According to the similar procedure of synthesis of **18a**, (*R*)-(−)-α-methoxy-α-(trifluoromethy1) phenylacetyl chloride (MTPACl) (11.1 mg, 0.04 mmol, 2 equiv) and **17a** (9.0 mg, 0.02 mmol, 1 equiv) gave **20a** (7.3 mg, 54% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.96 (d, J = 8.6 Hz, 2H), 7.65 (d, J = 8.6 Hz, 2H), 7.59–7.56 (m, 2H), 7.46–7.44 (m, 3H), 6.20 (d, J = 5.5 Hz, 1H), 6.04 (ddd, J = 17.0, 9.9, 5.7 Hz, 1H), 5.67 (d, J = 16.8 Hz, 1H), 5.51 (d, J = 5.4 Hz, 1H), 5.48 (d, J = 7.6 Hz, 1H), 3.63 (s, 3H), 3.30 (dd, J = 8.1, 4.3 Hz, 1H), 3.08 (dt, J = 10.9, 4.9 Hz, 1H), 1.32–1.29 (m, 12H), 0.89 (t, J = 7.9 Hz, 3H). HRMS (ESI) *m*/*z* 697.1369 [M+Na]$^+$ (calcd for $C_{34}H_{34}BrF_3NaO_6$ 697.1389).

Please cite this article in press as: Zhou, Y.; et al. *Tetrahedron: Asymmetry* (2016), http://dx.doi.org/10.1016/j.tetasy.2016.12.008

4.18. (*R*)-MTPA ester 20b of 17a

According to the similar procedure of synthesis of **18a**, (*S*)-(−)-α-methoxy-α-(trifluoromethy1) phenylacetyl chloride (MTPACl) (11.1 mg, 0.04 mmol, 2 equiv) and **17a** (9.1 mg, 0.02 mmol, 1 equiv) gave **20b** (6.7 mg, 50% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.96 (d, J = 8.6 Hz, 2H), 7.65 (d, J = 8.6 Hz, 2H), 7.57–7.56 (m, 2H), 7.46–7.44 (m, 3H), 6.19 (d, J = 5.7 Hz, 1H), 6.03 (ddd, J = 17.0, 10.1, 5.7 Hz, 1H), 5.67 (d, J = 17.0 Hz, 1H), 5.48 (d, J = 10.1 Hz, 1H), 5.43 (d, J = 8.4 Hz, 1H), 3.65 (s, 3H), 3.34 (dd, J = 8.5, 4.3 Hz, 1H), 3.15 (dt, J = 11.3, 6.2 Hz, 1H), 1.32–1.29 (m, 12H), 0.90 (t, J = 7.0 Hz, 3H). HRMS (ESI) m/z 675.1554 $[M+H]^+$ (calcd for $C_{34}H_{35}BrF_3O_6$ 675.1569).

4.19. (*S*)-MTPA ester 20c of 17b

According to the similar procedure of synthesis of **18a**, (*R*)-(−)-α-methoxy-α-(trifluoromethy1) phenylacetyl chloride (MTPACl) (5.4 mg, 0.02 mmol, 2 equiv) and **17b** (4.6 mg, 0.01 mmol, 1 equiv) gave **20c** (5.1 mg, 75% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.97 (dd, J = 6.8, 1.8 Hz, 2H), 7.64 (dd, J = 6.7, 1.8 Hz, 2H), 7.56–7.54 (m, 2H), 7.46–7.44 (m, 3H), 6.19 (d, J = 5.8 Hz, 1H), 6.02 (ddd, J = 16.8, 10.0, 5.8 Hz, 1H), 5.67 (d, J = 17.0 Hz, 1H), 5.47 (d, J = 10.1 Hz, 1H), 5.42 (d, J = 7.7 Hz, 1H), 3.58 (s, 3H), 3.33 (dd, J = 7.7, 3.8 Hz, 1H), 3.09 (dt, J = 8.6, 4.9 Hz, 1H), 1.30–1.28 (m, 12H), 0.91 (t, J = 6.2 Hz, 3H). HRMS (ESI) m/z 675.1546 $[M+H]^+$ (calcd for $C_{34}H_{35}BrF_3O_6$ 675.1569).

4.20. (*R*)-MTPA ester 20d of 17b

According to the similar procedure of synthesis of **18a**, (*S*)-(−)-α-methoxy-α-(trifluoromethy1) phenylacetyl chloride (MTPACl) (5.4 mg, 0.02 mmol, 2 equiv) and **17b** (4.6 mg, 0.01 mmol, 1 equiv) gave **20d** (4.9 mg, 73% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.97 (d, J = 8.6 Hz, 2H), 7.63 (dd, J = 8.6, 1.8 Hz, 2H), 7.54–7.53 (m, 2H), 7.45–7.43 (m, 3H), 6.20 (d, J = 5.7 Hz, 1H), 6.03 (ddd, J = 17.1, 10.1, 5.8 Hz, 1H), 5.73 (d, J = 16.9 Hz, 1H), 5.47 (d, J = 10.1 Hz, 1H), 5.42 (d, J = 7.9 Hz, 1H), 3.62 (s, 3H), 3.25 (dd, J = 7.9, 3.8 Hz, 1H), 3.03 (dt, J = 6.4, 3.1 Hz, 1H), 1.30–1.28 (m, 12H), 0.91 (t, J = 5.7 Hz, 3H). HRMS (ESI) m/z 675.1548 $[M+H]^+$ (calcd for $C_{34}H_{35}BrF_3O_6$ 675.1569).

4.21. (3*R*,8*R*,9*S*,10*R*) 9,10-Epoxy-heptadeca-1-en-4,6-diyn-3,8-diol 1a (9-epoxy-falcarindio1)

Aqueous solution NaOH (0.15 mL, 2 M, 3 mmol, 2 equiv) and methanol (0.03 mL) were added to a solution of **17a** (0.0707 g, 0.154 mmol, 1 equiv) in THF (2 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was diluted with water (5 mL) and diethyl ether (5 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude product. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate 3:1) to afford 9-epoxy-falcarindio1 **1a** (0.0330 g, 78% yield) as a yellow oil. $[\alpha]_D^{20}$ = +62 (*c* 0.07, CH_2Cl_2); lit[1] $[\alpha]_D$ = +86.9 (*c* 0.64, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.99 (ddd, J = 17.0, 10.3, 5.3 Hz, 1H), 5.52 (d, J = 17.1 Hz, 1H), 5.31 (d, J = 10.1 Hz, 1H), 4.99 (d, J = 5.1 Hz, 1H), 4.32 (d, J = 7.7 Hz, 1H), 3.22 (dd, J = 7.6, 4.4 Hz, 1H), 3.10 (dt, J = 9.7, 4.9 Hz, 1H), 2.63 (d, J = 10.7 Hz, 1H), 2.34–2.23 (m, 1H), 1.63–1.51 (m, 4H), 1.32–1.29 (m, 8H), 0.92 (t, J = 3.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 135.7, 117.4, 78.8, 76.4, 70.6, 69.8, 63.4, 62.1, 59.6, 57.5, 31.7, 29.3, 29.1, 28.1, 26.6, 22.6, 14.1; HRMS (APCI-TOF) m/z 277.1752 $[M+H]^+$ (calcd for $C_{17}H_{25}O_3$ 277.1804).

4.22. (3*R*,8*S*,9*S*,10*R*) 9,10-Epoxy-heptadeca-1-en-4,6-diyn-3,8-diol 1b (diastereomer of 9-epoxy-falcarindio1)

According to the similar procedure of synthesis of **1a**, 4-bromobenzoate **17b** (0.0689 g, 0.15 mmol, 1 equiv) and aqueous solution NaOH (0.15 mL, 2 M, 3 mmol, 2 equiv) gave the diastereomer of 9-epoxy-falcarindio1 **1b** (0.0332 g, 80% yield) as a yellow oil. $[\alpha]_D^{20}$ = −57 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.94 (ddd, J = 17.0, 10.2, 5.3 Hz, 1H), 5.48 (dd, J = 17.1, 0.9 Hz, 1H), 5.27 (dd, J = 10.2, 1.2 Hz, 1H), 4.94 (t, J = 4.6 Hz, 1H), 4.36 (dd, J = 7.2, 3.9 Hz, 1H), 3.14 (dd, J = 7.2, 3.9 Hz, 1H), 3.05 (dt, J = 7.2, 3.9 Hz, 1H), 2.17 (d, J = 4.5 Hz, 1H), 2.05 (d, J = 6.3 Hz, 1H), 1.56–1.46 (m, 4H), 1.32–1.24 (m, 8H), 0.88 (t, J = 3.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 135.7, 117.4, 78.6, 78.0, 70.2, 70.0, 63.5, 60.8, 58.0, 57.9, 31.7, 29.4, 29.1, 27.5, 26.5, 22.6, 14.0; HRMS (APCI-TOF) m/z 277.1797 $[M+H]^+$ (calcd for $C_{17}H_{25}O_3$ 277.1804).

Acknowledgments

We thank the National Key Technology Research and Development Program (No. 2015BAK45B01), National Training Program of Innovation and Entrepreneurship for Undergraduates (201510019142), and Beijing Training Program of Innovation and Entrepreneurship for Undergraduates (2015bj128 and 2015bj144) for the financial support.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2016.12.008.

References

1. Fujimoto, Y.; Satoh, M.; Takeuchi, N.; Kirisawa, M. *Chem. Pharm. Bull.* **1991**, *39*, 521–523.
2. (a) Peralta, E. A.; Murphy, L. L.; Minnis, J.; Louis, S.; Dunnington, G. L. *J. Surg. Res.* **2009**, *157*, 261–267; (b) Qi, L.-W.; Wang, C.-Z.; Yuan, C.-S. *Phytochemistry (Elsevier)* **2011**, *72*, 689–699; (c) Jee, H.-S.; Chang, K.-H.; Park, S.-H.; Kim, K.-T.; Paik, H.-D. *Food Rev. Int.* **2014**, *30*, 91–111.
3. Yamazoe, S.; Hasegawa, K.; Shigemori, H. Z. *J. Biosci.* **2006**, *61*, 536–540.
4. Komakine, N.; Okasaka, M.; Takaishi, Y.; Kawazoe, K.; Murakami, K.; Yamada, Y. *J. Nat. Med.* **2006**, *60*, 135–137.
5. (a) Deng, S.; Chen, S.-N.; Yao, P.; Nikolic, D.; van Breemen, R. B.; Bolton, J. L.; Fong, H. H. S.; Farnsworth, N. R.; Pauli, G. F. *J. Nat. Prod.* **2006**, *69*, 536–541; (b) Deng, S.; Wang, Y.; Inui, T.; Chen, S.-N.; Farnsworth, N. R.; Cho, S.; Franzblau, S. G.; Pauli, G. F. *Phytother. Res.* **2008**, *22*, 878–882.
6. Appendino, G.; Pollastro, F.; Verotta, L.; Ballero, M.; Romano, A.; Wyrembek, P.; Szczuraszek, K.; Mozrzymas, J. W.; Taglialatela-Scafati, O. *J. Nat. Prod.* **2009**, *72*, 962–965.
7. Ratnayake, A. S.; Hemscheidt, T. *Org. Lett.* **2002**, *4*, 4667–4669.
8. Dall'Acqua, S.; Maggi, F.; Minesso, P.; Salvagno, M.; Papa, F.; Vittori, S.; Innocenti, G. *Fitoterapia* **2010**, *81*, 1208–1212.
9. Atanasov, A. G.; Blunder, M.; Fakhrudin, N.; Liu, X.; Noha, S. M.; Malainer, C.; Kramer, M. P.; Cocic, A.; Kunert, O.; Schinkovitz, A.; Heiss, E. H.; Schuster, D.; Dirsch, V. M.; Bauer, R. *PLoS One* **2013**, *8*, e61755.
10. (a) Frantz, D. E.; Faessler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807; (b) Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143–4146; (c) Li, X.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636–12637; (d) Pu, L. *Acc. Chem. Res.* **2014**, *47*, 1523–1535.
11. (a) Trost, B. M.; Weiss, A. H.; von Wangelin, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 8–9; (b) Trost, B. M.; Burns, A. C.; Bartlett, M. J.; Tautz, T.; Weiss, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1474–1477; (c) Trost, B. M.; Bartlett, M. J. *Acc. Chem. Res.* **2015**, *48*, 688–701; (d) Lee, D.-S.; Gau, C.-W.; Chen, Y.-Y.; Lu, T.-J. *Appl. Organomet. Chem.* **2016**, *30*, 242–246.
12. (a) Zhong, J.-C.; Hou, S.-C.; Bian, Q.-H.; Yin, M.-M.; Na, R.-S.; Zheng, B.; Li, Z.-Y.; Liu, S.-Z.; Wang, M. *Chem.-Eur. J.* **2009**, *15*, 3069–3071; (b) Li, Z.-Y.; Wang, M.; Bian, Q.-H.; Zheng, B.; Mao, J.-Y.; Li, S.-N.; Liu, S.-Z.; Wang, M.-A.; Zhong, J.-C.; Guo, H.-C. *Chem.-Eur. J.* **2011**, *17*, 5782–5786.
13. Zheng, B.; Li, S.-N.; Mao, J.-Y.; Wang, B.; Bian, Q.-H.; Liu, S.-Z.; Zhong, J.-C.; Guo, H.-C.; Wang, M. *Chem.-Eur. J.* **2012**, *18*, 9208–9211.
14. Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776–5777.
15. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4409.

16. (a) Shen, L.; Wu, P.; Liu, F.; Zhou, Y.; Bian, Y. CN Patent 101735198, 2010.; (b) Sun, X.; Li, J.; Li, W.; Gao, Y.; Zhang, K. CN Patent 103664896A, 2014.
17. (a) Boyall, D.; Lopez, F.; Sasaki, H.; Frantz, D.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4233–4236; (b) Geary, L. M.; Woo, S. K.; Leung, J. C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 2972–2976.
18. Trost, B. M.; Chan, V. S.; Yamamoto, D. *J. Am. Chem. Soc.* **2010**, *132*, 5186–5192.
19. Mandel, A. L.; Bellosta, V.; Curran, D. P.; Cossy, J. *Org. Lett.* **2009**, *11*, 3282–3285.
20. Yang, Y.-Q.; Li, S.-N.; Zhong, J.-C.; Zhou, Y.; Zeng, H.-Z.; Duan, H.-J.; Bian, Q.-H.; Wang, M. *Tetrahedron: Asymmetry* **2015**, *26*, 361–366.
21. Chakor, N. S.; Musso, L.; Dallavalle, S. *J. Org. Chem.* **2009**, *74*, 844–849.
22. (a) Morandi, S.; Pellati, F.; Benvenuti, S.; Prati, F. *Tetrahedron* **2008**, *64*, 6324–6328; (b) Raghavan, S.; Sudheer Babu, V.; Sridhar, B. *J. Org. Chem.* **2011**, *76*, 557–565.
23. Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
24. Barrett, A. G. M.; Head, J.; Smith, M. L.; Stock, N. S.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1999**, *64*, 6005–6018.
25. (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199–2204; (b) Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840–10852.
26. Jeon, S.-J.; Chen, Y. K.; Walsh, P. J. *Org. Lett.* **2005**, *7*, 1729–1732.

Please cite this article in press as: Zhou, Y.; et al. *Tetrahedron: Asymmetry* (2016), http://dx.doi.org/10.1016/j.tetasy.2016.12.008