Reaction of 1-Trimethylsilyl-1,2-epoxy-3-alkanols with Alkynes and Application to the Synthesis of 18-HEPE

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Experimental section

**General Methods.** The $^1$H (300 or 400 MHz) and $^{13}$C NMR (75 or 100 MHz) spectroscopic data were recorded in CDCl$_3$ using Me$_4$Si ($\delta = 0$ ppm) and the centerline of the triplet ($\delta = 77.1$ ppm), respectively, as internal standards. Signal patterns are indicated as br s (broad singlet), s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants ($J$) are given in Hertz (Hz). Chemical shifts of carbons are accompanied by minus (for C and CH$_2$) and plus (for CH and CH$_3$) signs of the attached proton test (APT) experiments. High-resolution mass spectroscopy (HRMS) was performed with a double-focusing mass spectrometer with an ionization mode of positive FAB or EI as indicated for each compound. The solvents that were distilled prior to use are THF (from Na/benzophenone), Et$_2$O (from Na/benzophenone), and CH$_2$Cl$_2$ (from CaH$_2$). After the reactions were completed, the organic extracts were concentrated by using an evaporator, and then the residues were purified by chromatography on silica gel (Kanto, spherical silica gel 60N).

Intermediates were synthesized by published methods$^{S1,S2}$ and the summaries are shown in Schemes S1 and 2.

![Scheme S1](image)

**Scheme S1** Synthesis of the intermediate 9

![Scheme S2](image)

**Scheme S2** Synthesis of the intermediates ($R$)-1b (anti) and ($S$)-8
General procedure for the epoxide ring opening of the TMS-substituted epoxylcohols with acetylene anions

\((E)-1-(\text{Trimethylsilyl})\text{dec-3-en-1-yn-5-ol (3a) from alcohol [1a (anti)] (Table 1, entry 5)}\)

To an ice-cold solution of trimethylsilylacetylene \((2a) (0.40 \text{ mL, 2.89 mmol})\) in THF \((0.1 \text{ mL})\) was added \(n\)-BuLi \((1.55 \text{ M in hexane, 1.60 mL, 2.48 mmol})\) dropwise. After 30 min of stirring at \(0 \text{ °C}\), HMPA \((0.95 \text{ mL, 5.44 mmol})\) and a solution of epoxy alcohol \(1a\) (anti) \((65 \text{ mg, 0.30 mmol})\) in THF \((0.2 \text{ mL})\) were added. The solution was stirred at rt for 3 h and diluted with saturated \(\text{NH}_4\text{Cl}\) at \(0 \text{ °C}\). The mixture was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over MgSO\(_4\), and concentrated. Chromatography of the residue on silica gel \((\text{hexane/EtOAc})\) afforded enyne \(3a\) \((41 \text{ mg, 60%})\) and a small amount of the starting material \((4 \text{ mg, 6%})\). Enyne \(\text{rac-3}: \text{liquid}; \text{R}f = 0.43 \text{ (hexane/EtOAc 9:1); }^1\text{H NMR} \text{ (300 MHz, CDCl}_3) \delta \text{ 0.19 (s, 9 H), 0.88 (t, } J = 6.9 \text{ Hz, 3 H), 1.20–1.66 (m, 9 H), 4.08–4.22 (m, 1 H), 5.72 (dd, } J = 15.9 \text{ Hz, 1.5 Hz, 1 H), 6.20 (dd, } J = 15.9, 6.3 \text{ Hz, 1 H); }^{13}\text{C–APT NMR} \text{ (75 MHz, CDCl}_3) \delta \text{ –0.05 (+), 14.1 (+), 22.6 (–), 25.0 (–), 31.8 (–), 36.9 (–), 72.3 (+), 95.1 (–), 103.2 (–), 109.8 (+), 147.0 (+); HRMS} \text{ (FAB\(^+\)) calcd for } C_{13}H_{24}OSiNa [(M+Na)]^+ 247.1494, \text{ found 247.1490.}\)

\((E)-1-(\text{Trimethylsilyl})\text{dec-3-en-1-yn-5-ol (3a) from alcohol [1a (syn)]}\)

\(\text{Method A in THF (Table 1, entry 6): To an ice-cold solution of trimethylsilylacetylene (2a) (0.20 mL, 1.45 mmol) in THF (0.5 mL) was added } n\text{-BuLi (1.55 M in hexane, 0.62 mL, 0.96 mmol) dropwise. After 30 min}\)
1a (syn) (52 mg, 0.24 mmol) in THF (0.5 mL) were added. The solution was stirred at rt for 4 h and diluted with saturated NH₄Cl at 0 °C. The mixture was extracted twice with EtOAc. The combined organic layers were dried over MgSO₄, and concentrated. Chromatography of the residue on silica gel (hexane/EtOAc) afforded enyne 3a (32 mg, 59%). The ¹H NMR spectrum was consistent with that obtained from 1a (anti).

**Method B in THF-HMPA (Table 1, entry 7):** According to the general procedure, epoxy alcohol 1a (syn) (70 mg, 0.32 mmol) in THF (0.4 mL) was added to a mixture of trimethylsilylacetylene (2a) (0.20 mL, 1.45 mmol), n-BuLi (1.55 M in hexane, 0.80 mL, 1.24 mmol), and HMPA (0.50 mL, 2.87 mmol) in THF (0.5 mL). The mixture was stirred at 0 °C for 3.5 h to afford enyne 3a (47 mg, 65%). The ¹H NMR spectrum was consistent with that obtained from 1a (anti).

(E)-7-(Trimethylsilyl)hept-4-en-6-yn-3-ol (3b)

According to the general procedure, epoxy alcohol 1b (anti/syn) (491 mg, 2.82 mmol) in THF (2 mL) was added to a mixture of 2a (2.60 mL, 18.8 mmol), n-BuLi (1.55 M in hexane, 11.1 mL, 17.1 mmol), and HMPA (6.0 mL, 34 mmol) in THF (2 mL). The mixture was stirred at rt for 3 h to afford enyne 3b (384 mg, 75%): liquid; Rf = 0.53 (hexane/EtOAc 9:1); ¹H NMR (300 MHz, CDCl₃) δ 0.19 (s, 9 H), 0.94 (t, J = 7.5 Hz, 3 H), 1.49–1.62 (m, 3 H), 4.02–4.15 (m, 1 H), 5.73 (d, J = 15.9 Hz, 1.5 Hz, 1 H), 6.20 (dd, J = 15.9 Hz, 6.0 Hz, 1 H); ¹³C–APT NMR (75 MHz, CDCl₃) δ -0.1 (+), 9.6 (+), 29.7 (−), 73.3 (+), 94.9 (−), 103.2 (−), 109.8 (+), 146.7 (+). The ¹H NMR and ¹³C NMR spectra were consistent with those reported.⁵³

(S,3E,7Z)-1-(Trimethylsilyl)deca-3,7-dien-1-yn-5-ol (3c)
According to the general procedure, epoxy alcohol 1c (anti) (82 mg, 0.38 mmol) in THF (0.5 mL) was added to a mixture of 2a (0.35 mL, 2.53 mmol), n-BuLi (1.55 M in hexane, 1.50 mL, 2.33 mmol), and HMPA (0.80 mL, 4.60 mmol) in THF (0.5 mL). The mixture was stirred at rt for 4 h to afford enyne 3c (59 mg, 69%): liquid; Rf = 0.45 (hexane/EtOAc 5:1); 1H NMR (300 MHz, CDCl3) δ 0.18 (s, 9 H), 0.97 (t, J = 7.5 Hz, 3 H), 1.67 (d, J = 4.5 Hz, 1 H), 2.06 (quint., J = 7.5 Hz, 2 H), 2.31 (t, J = 6.3 Hz, 2 H), 4.14–4.26 (m, 1 H), 5.26–5.39 (m, 1 H), 5.53–5.66 (m, 1 H), 5.76 (dd, J = 15.9 Hz, 1.5 Hz, 1 H), 6.22 (dd, J = 15.9 Hz, 5.7 Hz, 1 H); 13C–APT NMR (75 MHz, CDCl3) δ −0.05 (+), 14.2 (+), 20.8 (−), 34.8 (−), 71.5 (+), 95.3 (−), 103.2 (−), 109.9 (+), 123.1 (+), 135.9 (+), 146.1 (+); HRMS (FAB+) calcd for C13H22OSiNa [(M+Na)+] 245.1338, found 245.1340.

(R,3E,7Z,10Z)-1-(Trimethylsilyl)trideca-3,7,10-trien-1-yn-5-ol (3d)

According to the general procedure, epoxy alcohol 1d (anti) (76 mg, 0.30 mmol) in THF (0.5 mL) was added to a mixture of 2a (0.30 mL, 2.17 mmol), n-BuLi (1.55 M in hexane, 1.20 mL, 1.86 mmol), and HMPA (0.62 mL, 3.56 mmol) in THF (0.5 mL). The mixture was stirred at rt for 3.5 h to afford enyne 3d (50 mg, 64%): liquid; Rf = 0.67 (toluene/EtOAc 9:1); 1H NMR (300 MHz, CDCl3) δ 0.19 (s, 9 H), 0.97 (t, J = 7.4 Hz, 3 H), 1.65 (d, J = 4.5 Hz, 1 H), 2.06 (quint., J = 7.4 Hz, 2 H), 2.34 (t, J = 6.6 Hz, 2 H), 2.80 (t, J = 7.2 Hz, 2 H), 4.14–4.28 (m, 1 H), 5.23–5.46 (m, 3 H), 5.52–5.64 (m, 1 H), 5.76 (dd, J = 15.9 Hz, 1.5 Hz, 1 H), 6.22 (dd, J = 15.9 Hz, 5.4 Hz, 1 H); 13C–APT NMR (75 MHz, CDCl3) δ −0.05 (+), 14.3 (+), 20.6 (−), 25.8 (−), 34.9 (−), 71.4 (+), 95.3 (−), 103.1 (−), 110.0 (+), 124.1 (+), 126.6 (+), 132.3 (+), 132.4 (+), 146.0 (+); HRMS (FAB+) calcd for C16H26OSiNa [(M+Na)+] 285.1651, found 285.1655.

(E)-1-[(tert-Butyldimethylsilyl)oxy]-8-(trimethylsilyl)oct-5-en-7-yn-4-ol (3e)
According to the general procedure, epoxy alcohol 1e (anti/syn) (191 mg, 0.60 mmol) in THF (0.5 mL) was added to a mixture of 2a (0.57 mL, 4.12 mmol), n-BuLi (1.55 M in hexane, 2.30 mL, 3.57 mmol), and HMPA (1.25 mL, 7.18 mmol) in THF (0.5 mL). The mixture was stirred at rt for 3.5 h to afford enyne 3e (96 mg, 50%): liquid; Rf = 0.62 (toluene/EtOAc 9:1); 1H NMR (300 MHz, CDCl3) δ 0.07 (s, 6 H), 0.18 (s, 9 H), 0.90 (s, 9 H), 1.52–1.78 (m, 4 H), 3.03 (d, J = 4.5 Hz, 1 H), 3.65 (t, J = 5.7 Hz, 2 H), 4.14–4.26 (m, 1 H), 5.77 (dd, J = 16.0 Hz, 1.5 Hz, 1 H), 6.21 (dd, J = 16.0 Hz, 5.4 Hz, 1 H); 13C–APT NMR (75 MHz, CDCl3) δ –5.4 (+), –0.02 (+), 18.4 (–), 26.0 (+), 28.6 (–), 34.4 (–), 63.4 (–), 71.5 (+), 94.8 (–), 103.5 (–), 109.4 (+), 147.2 (+); HRMS (FAB+) calcd for C_{17}H_{34}O_{2}Si_{2}Na [(M+Na)^+] 349.1995, found 349.1998.

(E)-Pentadec-7-en-9-yn-6-ol (3f)

According to the general procedure, epoxy alcohol 1a (anti) (80 mg, 0.37 mmol) in THF (0.5 mL) was added to a mixture of 1-heptyne (2b) (0.43 mL, 3.4 mmol), n-BuLi (1.55 M in hexane, 1.90 mL, 2.95 mmol), and HMPA (1.15 mL, 6.61 mmol) in THF (0.5 mL). The mixture was stirred at rt for 20 h to afford enyne 3f (61 mg, 75%): liquid; Rf = 0.61 (toluene/EtOAc 9:1); 1H NMR (300 MHz, CDCl3) δ 0.88 (t, J = 6.9 Hz, 3 H), 0.90 (t, J = 6.9 Hz, 3 H), 1.22–1.60 (m, 15 H), 2.29 (dt, J = 1.8, 7.2 Hz, 2 H), 4.06–4.18 (m, 1 H), 5.67 (dm, J = 15.9 Hz, 1 H), 6.04 (dd, J = 15.9, 6.3 Hz, 1 H); 13C–APT NMR (75 MHz, CDCl3) δ 14.0 (+), 14.1 (+), 19.4 (–), 22.3 (–), 22.6 (–), 25.0 (–), 28.5 (–), 31.1 (–), 31.8 (–), 37.0 (–), 72.6 (+), 78.4 (–), 91.3 (–), 110.5 (+), 144.3 (+).

(E)-1-Phenyldec-3-en-1-yn-5-ol (3g)
According to the general procedure, epoxy alcohol 1a (anti) (80 mg, 0.37 mmol) in THF (0.5 mL) was added to a mixture of phenylacetylene (2c) (364 mg, 3.56 mmol), n-BuLi (1.55 M in hexane, 2.04 mL, 3.16 mmol), and HMPA (1.23 mL, 7.11 mmol) in THF (0.5 mL). The mixture was stirred at rt for 3 h to afford enyne 3g (65 mg, 77%): liquid; Rf = 0.39 (toluene/EtOAc 9:1); 1H NMR (300 MHz, CDCl3) δ 0.90 (t, J = 6.9 Hz, 3 H), 1.21–1.64 (m, 9 H), 4.21 (q, J = 6.2 Hz, 1 H), 5.93 (dd, J = 16.0, 1.2 Hz, 1 H), 6.24 (dd, J = 16.0 Hz, 6.2 Hz, 1 H), 7.28–7.36 (m, 3 H), 7.39–7.46 (m, 2 H); 13C–APT NMR (75 MHz, CDCl3) δ 14.1 (+), 22.7 (+), 25.0 (–), 31.8 (–), 37.1 (–), 72.5 (+), 87.5 (–), 90.1 (–), 109.9 (+), 123.3 (–), 128.2 (+), 128.4 (+), 131.5 (+), 145.9 (+); HRMS (FAB+) calcd for C16H20O (M)+ 228.1514, found 228.1515.

Methyl 10-hydroxydeca-5,8-diynoate (S3)

To a suspension of K2CO3 (1.01 g, 7.31 mmol), NaI (1.48 g, 9.87 mmol), and Cul (1.89 g, 9.92 mmol) in DMF (7 mL) was added solutions of methyl 5-hexynoate (S2) (732 mg, 5.80 mmol) in DMF (1 mL) and propargylic chloride S1S2 (509 mg, 4.87 mmol) in DMF (2 mL). The mixture was stirred at rt for 7 h and diluted with saturated NH4Cl. The resulting mixture was extracted with Et2O three times. The combined extracts were washed with brine, dried over MgSO4, and concentrated in vacuo to leave an oil, which was purified by chromatography on silica gel (hexane/EtOAc) to afford S3 (767 mg, 81%): liquid; Rf = 0.28 (hexane/EtOAc 2:1); 1H NMR (300 MHz, CDCl3) δ 1.61–1.79 (m, 1 H), 1.81 (quint., J = 7.1 Hz, 2 H), 2.23 (tt, J = 7.1, 2.2 Hz, 2 H), 2.43 (t, J = 7.5 Hz, 2 H), 3.17 (quint., J = 2.2 Hz, 2 H), 3.68 (s, 3 H), 4.26 (br s, 2 H); 13C–APT NMR (75 MHz, CDCl3) δ 9.6 (–), 17.9 (–), 23.6 (–), 32.7 (–), 50.7 (–), 51.5 (+), 74.4 (–), 78.6 (–), 79.5 (–), 79.9 (–), 173.8 (–). The 1H NMR and 13C NMR spectra were consistent with those reported. S1,S2
Methyl 10-bromodeca-5,8-diynoate (S4)

To an ice-cold solution of alcohol S3 (2.00 g, 10.3 mmol) and PPh₃ (3.24 g, 12.4 mmol) in CH₂Cl₂ (20 mL) was added CBr₄ (4.10 g, 12.4 mmol). The solution was stirred at 0 °C for 1 h and diluted with saturated NaHCO₃. The resulting mixture was extracted with CH₂Cl₂ twice. The combined extracts were dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to afford bromide S4 (2.11 g, 80%): liquid; Rf = 0.63 (hexane/EtOAc 2:1); ¹H NMR (300 MHz, CDCl₃) δ 1.81 (quint., J = 7.2 Hz, 2 H), 2.24 (tt, J = 6.9, 2.4 Hz, 2 H), 2.43 (t, J = 7.5 Hz, 2 H), 3.21 (quint., J = 2.4 Hz, 2 H), 3.68 (s, 3 H), 3.91 (t, J = 2.4 Hz, 2 H); ¹³C–APT NMR (75 MHz, CDCl₃) δ 9.8 (–), 14.7 (–), 17.9 (–), 23.6 (–), 32.6 (–), 51.4 (+), 73.7 (–), 75.2 (–), 79.8 (–), 81.6 (–), 173.3 (–). The ¹H NMR and ¹³C NMR spectra were consistent with those reported.¹¹,¹²

Methyl 13-hydroxytrideca-5,8,11-triynoate (S6)

To a suspension of K₂CO₃ (957 mg, 6.92 mmol), NaI (1.41 g, 9.41 mmol), and CuI (1.78 g, 9.35 mmol) in DMF (7 mL) was added propargyl alcohol (S5) (0.33 mL, 5.71 mmol) and a solution of propargylic bromide S4 (1.18 g, 4.59 mmol) in DMF (3 mL). The mixture was stirred at rt for 14 h and diluted with saturated NH₄Cl. The resulting mixture was extracted with EtOAc twice. The combined extracts were washed with brine, dried over MgSO₄, and concentrated in vacuo to leave an oil, which was purified by chromatography on silica gel (hexane/EtOAc) to afford S6 (850 mg, 80%): liquid; Rf = 0.10 (hexane/EtOAc 5:1); ¹H NMR (300 MHz, CDCl₃) δ 1.62–1.88 (m, 1 H), 1.81 (quint., J = 7.2 Hz, 2 H), 2.23 (tt, J = 6.9, 2.4 Hz, 2 H), 2.43 (t, J = 7.5 Hz, 2 H), 3.12 (quint., J = 2.1 Hz, 2 H), 3.20 (quint., J = 2.1 Hz, 2 H), 3.68 (s, 3 H), 4.26 (t, J = 2.1 Hz, 2 H); ¹³C–APT NMR (75 MHz, CDCl₃) δ 9.7 (–), 9.9 (–), 18.2 (–), 23.8 (–), 32.9 (–), 51.1 (–), 51.7 (+), 73.9 (–), 74.7 (–), 75.3 (–), 78.8 (–), 79.6 (–), 79.8 (–), 173.8 (–). The ¹H NMR and ¹³C NMR spectra were consistent
with those reported.

**Methyl 13-bromotrideca-5,8,11-triynoate (9)**

![Chemical Structure](image)

To an ice-cold solution of alcohol S6 (1.15 g, 4.95 mmol) and PPh₃ (1.56 g, 5.95 mmol) in CH₂Cl₂ (10 mL) was added CBr₄ (1.97 g, 5.94 mmol). The solution was stirred at 0 °C for 1 h and diluted with saturated NaHCO₃. The resulting mixture was extracted with CH₂Cl₂ twice. The combined extracts were dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to afford bromide 9 (894 mg, 61%): liquid; Rf = 0.59 (hexane/EtOAc 2:1); ¹H NMR (300 MHz, CDCl₃) δ 1.81 (quint., J = 7.3 Hz, 2 H), 2.23 (tt, J = 6.9, 2.4 Hz, 2 H), 2.43 (t, J = 7.5 Hz, 2 H), 3.13 (quint., J = 2.4 Hz, 2 H), 3.23 (quint., J = 2.4 Hz, 2 H), 3.67 (s, 3 H), 3.90 (t, J = 2.4 Hz, 2 H); ¹³C–APT NMR (75 MHz, CDCl₃) δ 9.7 (–), 10.1 (–), 14.7 (–), 18.1 (–), 23.8 (–), 32.8 (–), 51.6 (+), 73.3 (–), 74.5 (–), 75.5 (–), 75.6 (–), 79.6 (–), 81.2 (–), 173.6 (–). The ¹H NMR and ¹³C NMR spectra were consistent with those reported.

**[(R)-1][(2R,3R)-3-(Trimethylsilyloxiran-2-yl)propan-1-ol [(R)-1b] and (S,E)-1-(trimethylsilyl)pent-1-en-3-ol [(S)-8]**

![Chemical Structure](image)

To an ice-cold solution of Ti(O-i-Pr)₄ (0.30 mL, 1.01 mmol) in CH₂Cl₂ (4 mL) was added D-(−)-DIPT (0.27 mL, 1.29 mmol). The solution was stirred at 0 °C for 30 min and cooled to −15 °C. A solution of rac-8 (159 mg, 1.00 mmol) in CH₂Cl₂ (1 mL) was added to the solution. After 30 min of stirring at −15 °C, the solution was cooled to −40 °C and t-BuOOH (4.34 M in CH₂Cl₂, 0.38 mL, 1.65 mmol) was added dropwise. The reaction was continued at −20 °C for 8 h and terminated by adding Me₂S (0.40 mL, 5.4 mmol). After 30 min of stirring at −20 °C aqueous 10% tartaric acid (0.1 mL), NaF (301 mg, 7.17 mmol), and Celite (150 mg) were added. The mixture was stirred vigorously at rt and filtered.
through a pad of Celite with CH₂Cl₂. The filtrate was mixed with 1 N NaOH (10 mL, 10 mmol). The mixture was stirred at rt for 30 min and extracted with CH₂Cl₂ twice. The combined extracts were washed with brine, dried over MgSO₄, and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to produce epoxy alcohol \((R)\)-1b (anti) (70 mg, 40%) and allylic alcohol \((S)\)-8 (65 mg, 41%). Enantiomeric excesses of \((R)\)-1b (anti) and \((S)\)-8 were determined to be 99% and >99%, respectively, by ¹H NMR spectroscopy of the derived MTPA esters. Epoxy alcohol \((R)\)-1b (anti): liquid; \(R_f\) = 0.40 (hexane/EtOAc 5:1); ¹H NMR (300 MHz, CDCl₃) \(\delta\) 0.07 (s, 9 H), 1.01 (t, \(J = 7.5\) Hz, 3 H), 1.45–1.72 (m, 2 H), 1.86 (br s, 1 H), 2.37 (d, \(J = 3.8\) Hz, 1 H), 2.88 (t, \(J = 3.8\) Hz, 1 H), 3.77–3.86 (m, 1 H). Allylic alcohol \((S)\)-8: liquid; \(R_f\) = 0.47; ¹H NMR (300 MHz, CDCl₃) \(\delta\) 0.07 (s, 9 H), 0.92 (t, \(J = 7.5\) Hz, 3 H), 1.49–1.64 (m, 3 H), 3.96–4.07 (m, 1 H), 5.84 (dd, \(J = 18.7, 1.2\) Hz, 1 H), 6.03 (dd, \(J = 18.7, 5.3\) Hz, 1 H). The ¹H NMR spectra of \((R)\)-1b (anti) and \((S)\)-8 were identical with those reported.¹²

\(\text{(R,E)-7-(Trimethylsilyl)hept-4-en-6-yn-3-ol [(R)-3b]}\)

\[
\begin{array}{c}
\text{TMS} & \text{TMS-} & \text{TMS-} \\
\text{O} & \text{C≡C-H (2a)} & \text{OTBS} \\
\text{(R)-1b (anti)} & \text{(R)-3b} & \text{(R)-6} \\
\end{array}
\]

According to the general procedure, epoxy alcohol \((R)\)-1b (anti) (398 mg, 2.28 mmol) in THF (2 mL) was added to a mixture of 2a (2.20 mL, 15.9 mmol), \(n\)-BuLi (1.55 M in hexane, 8.75 mL, 13.6 mmol), and HMPA (4.80 mL, 27.6 mmol) in THF (2 mL). The mixture was stirred at rt for 4 h to afford enyne \((R)\)-3b (302 mg, 73%): >99% by ¹H NMR spectroscopy of the derived MTPA esters. The ¹H NMR spectrum was identical with that of racemic 3b synthesized above.

\(\text{(R,E)-tert-Butyl(hept-4-en-6-yn-3-yloxy)dimethylsilane [(R)-7]}\)

\[
\begin{array}{c}
\text{TMS} & \text{TMS-} & \text{TMS-} \\
\text{O} & \text{OH} & \text{OTBS} \\
\text{(R)-3b} & \text{(R)-6} & \text{(R)-7} \\
\end{array}
\]

To a solution of \((R)\)-3b (231 mg, 1.27 mmol) and imidazole (213 mg, 3.13 mmol) in
CH$_2$Cl$_2$ (2 mL) was added TBSCl (233 mg, 1.55 mmol). The solution was stirred at rt for 1 h and diluted with saturated NaHCO$_3$. The resulting mixture was extracted with CH$_2$Cl$_2$ twice. The combined extracts were washed with brine, dried over MgSO$_4$, and concentrated to leave a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford (R)-6 (329 mg, 88%): liquid; $R_f$ = 0.73 (hexane/EtOAc 9:1); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.19 (s, 9 H), 0.87 (t, $J$ = 7.5 Hz, 3 H), 0.90 (s, 9 H), 1.45–1.56 (m, 2 H), 4.07–4.15 (m, 1 H), 5.69 (dd, $J$ = 15.9 Hz, 1.8 Hz, 1 H), 6.18 (dd, $J$ = 15.9 Hz, 4.8 Hz, 1 H); $^{13}$C–APT NMR (75 MHz, CDCl$_3$) $\delta$ –4.8 (+), –4.5 (+), 9.3 (+), 18.3 (–), 25.9 (+), 30.7 (–), 73.4 (+), 94.2 (–), 103.8 (–), 108.8 (+), 147.4 (+).

To a solution of (R)-6 (313 mg, 1.06 mmol) in MeOH (2 mL) was added K$_2$CO$_3$ (229 mg, 1.66 mmol). The mixture was stirred at rt for 1.5 h and diluted with saturated NH$_4$Cl. The resulting mixture was extracted with EtOAc twice. The combined extracts were washed with brine, dried over MgSO$_4$, and concentrated to leave a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford enyne (R)-7 (206 mg, 87%): liquid; $R_f$ = 0.38 (hexane); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.03 (s, 3 H), 0.05 (s, 3 H), 0.87 (t, $J$ = 7.5 Hz, 3 H), 0.90 (s, 9 H), 1.46–1.58 (m, 2 H), 2.86 (d, $J$ = 2.1 Hz, 1 H), 4.07–4.18 (m, 1 H), 5.65 (dm, $J$ = 15.9 Hz, 1 H), 6.23 (dd, $J$ = 15.9 Hz, 5.1 Hz, 1 H); $^{13}$C–APT NMR (75 MHz, CDCl$_3$) $\delta$ –4.8 (+), –4.5 (+), 9.3 (+), 18.3 (–), 25.9 (+), 30.6 (–), 73.4 (+), 77.3 (–), 82.2 (–), 107.7 (+), 148.2 (+). The $^1$H NMR and $^{13}$C NMR spectra were consistent with those reported.$^{3b}$

**Methyl (R,E)-18-[(tert-butyldimethylsilyl)oxy]icos-5,8,11,14-tetraynoate [(R)-10]**

![Chemical Structure](image)

To a mixture of CuI (196 mg, 1.03 mmol), Cs$_2$CO$_3$ (252 mg, 0.773 mmol), and NaI (154 mg, 1.03 mmol) in DMF (1 mL) were added enyne (R)-7 (122 mg, 0.544 mmol) in DMF (0.5 mL) and bromide 9 (151 mg, 0.511 mmol) in DMF (0.5 mL). After being stirred at rt for 7 h, the mixture was diluted with saturated NH$_4$Cl. The resulting mixture was extracted...
with EtOAc twice. The combined extracts were washed with brine, dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to afford acetylene \((R)-10\) (141 mg, 63%): liquid; \(R_l = 0.33\) (hexane/EtOAc 9:1); \([\alpha]_D^{20} +13\) (c 1.18, CHCl₃); IR (neat) 1738, 1319, 1255, 837, 759 cm⁻¹; \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 0.02 (s, 3 H), 0.04 (s, 3 H), 0.86 (t, \(J = 7.5\) Hz, 3 H), 0.89 (s, 9 H), 1.43–1.57 (m, 2 H), 1.81 (quint., \(J = 7.2\) Hz, 2 H), 2.24 (t, \(J = 7.0\) Hz, 2 H), 2.43 (t, \(J = 7.5\) Hz, 1 H), 3.10–3.19 (m, 4 H), 3.26–3.32 (m, 2 H), 3.68 (s, 3 H), 4.04–4.13 (m, 1 H), 5.62 (d, \(J = 15.9\) Hz, 1 H), 6.09 (dd, \(J = 15.9, 5.1\) Hz, 1 H); \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta\) –4.9 (+), –4.6 (+), 9.2 (+), 9.7 (–), 9.8 (–), 10.4 (–), 18.1 (–), 18.2 (–), 23.8 (–), 25.8 (+), 30.6 (–), 32.8 (–), 51.5 (+), 73.5 (+), 74.1 (–), 74.4 (–), 74.5 (–), 74.7 (–), 75.0 (–), 79.0 (–), 79.5 (–), 83.3 (–), 108.4 (+), 146.2 (+), 173.6 (–); HRMS (FAB⁺) calcd for C₂₇H₃₉O₃Si [(M+H)⁺] 439.2668, found 439.2660.

**Methyl \((R,5Z,8Z,11Z,14Z,16E)-18-[(tert-butylidimethylsilyl)oxy]icos-5,8,11,14,16-pentaenoate \([(R)-11]\)**

To an ice-cold suspension of Ni(OAc)₂·4H₂O (105 mg, 0.42 mmol) in EtOH (0.5 mL) was added NaBH₄ (20 mg, 0.53 mmol). The flask was purged with hydrogen and ethylenediamine (0.050 mL, 0.74 mmol) was added. After 10 min of stirring at rt, acetylene \((R)-10\) (149 mg, 0.34 mmol) in EtOH (0.5 mL) was added. The mixture was stirred at rt for 90 min and filtered through a pad of Celite with EtOAc and the filtrate was concentrated in vacuo to leave an oil, which was purified by chromatography on silica gel (hexane/EtOAc) to afford a mixture of \((R)-11\) and \((R)-12\) (94 mg, 62%): liquid; \(R_l = 0.55\) (hexane/EtOAc 9:1). The ratio of \((R)-11/\(12\) was 4 : 1 by peak height calculation of the \(^{13}\)C NMR signals.

To a slurry of Zn (2.0 g, 31 mmol) in H₂O (6 mL) was added Cu(OAc)₂ (200 mg, 1.1 mmol) and the mixture was stirred at rt for 15 min. AgNO₃ (202 mg, 1.19 mmol) was added to the mixture, which was stirred at rt for further 30 min and filtered using a Hirsch funnel. The remaining solids were washed successively with H₂O (5 mL x 2), MeOH (5 mL x 2),
acetone (5 mL x 2), and Et₂O (5 mL x 2) and added to a solution of \((R)-11\) and \(-12\) (4:1, 64 mg, 0.143 mmol) in MeOH (2 mL) and H₂O (1 mL) under nitrogen. The mixture was stirred at 40–45 °C for 12 h and filtered through a pad of Celite with EtOAc. The filtrate was washed with brine, dried over MgSO₄, and concentrated to afford a residual oil, which was purified by chromatography on silica gel (hexane/EtOAc) to afford \((R)-11\) (57 mg, 89%): liquid; \(R_f = 0.55\) (hexane/EtOAc 9:1); \(^1\)H NMR (300 MHz, CDCl₃) \(\delta 0.03\) (s, 3 H), 0.05 (s, 3 H), 0.87 (t, \(J = 7.2\) Hz, 3 H), 0.90 (s, 9 H), 1.51 (quint., \(J = 7.0\) Hz, 2 H), 1.70 (quint., \(J = 7.2\) Hz, 2 H), 2.03–2.18 (m, 2 H), 2.32 (t, \(J = 7.5\) Hz, 2 H), 2.71–2.88 (m, 4 H), 2.95 (t, \(J = 5.9\) Hz, 2 H), 3.66 (s, 3 H), 4.10 (q, \(J = 6.0\) Hz, 1 H), 5.28–5.48 (m, 7 H), 5.65 (dd, \(J = 15.0, 6.0\) Hz, 1 H), 5.99 (t, \(J = 11.0\) Hz, 1 H), 6.45 (dd, \(J = 15.0, 11.0\) Hz, 1 H); \(^{13}\)C–APT NMR (75 MHz, CDCl₃) \(\delta –4.7\) (–), –4.3 (–), 9.7 (+), 18.3 (–), 24.8 (–), 25.7 (–), 26.0 (+), 26.1 (–), 26.6 (–), 31.2 (–), 33.5 (–), 51.5 (+), 74.4 (+), 124.2 (+), 128.0 (+), 128.1 (+), 128.3 (+), 128.4 (+), 128.5 (+), 128.9 (+), 129.0 (+), 129.1 (+), 137.3 (+), 174.1 (–); HRMS (FAB⁺) calcd for C₂₇H₄₅O₃Si [(M–H)⁺] 445.3138, found 445.3136.

**Methyl (R,5Z,8Z,11Z,14Z,16E)-18-hydroxyicosa-5,8,11,14,16-pentaenoate [(R)-13]**

To an ice-cold solution of TBS ether \((R)-11\) (56 mg, 0.125 mmol) in THF (0.3 mL) was added Bu₄NF (TBAF) (1.0 M in THF, 0.40 mL, 0.40 mmol). The solution was stirred at rt for 5 h and diluted with saturated NH₄Cl. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over MgSO₄, and concentrated to give a residual oil, which was purified by chromatography on silica gel (hexane/EtOAc) to afford alcohol \((R)-13\) (28 mg, 67%): liquid; \(R_f = 0.26\) (hexane/EtOAc 5:1); \(^1\)H NMR (400 MHz, CDCl₃) \(\delta 0.93\) (t, \(J = 7.6\) Hz, 3 H), 1.49–1.63 (m, 2 H), 1.64–1.74 (m, 3 H), 2.11 (q, \(J = 6.8\) Hz, 2 H), 2.32 (t, \(J = 7.2\) Hz, 2 H), 2.80 (t, \(J = 5.6\) Hz, 2 H), 2.84 (t, \(J = 5.2\) Hz, 2 H), 2.96 (t, \(J = 6.0\) Hz, 2 H), 3.66 (s, 3 H), 4.10 (q, \(J = 6.4\) Hz, 1 H), 5.30–5.46 (m, 7 H), 5.69 (dd, \(J = 15.2, 6.4\) Hz, 1 H), 6.00 (t, \(J = 11.2\) Hz, 1 H), 6.52 (dd, \(J = 15.2, 11.2\) Hz, 1 H); \(^{13}\)C–APT NMR (100 MHz, CDCl₃) \(\delta 9.8\) (+), 24.8 (–), 25.68 (–),

S13
25.72 (−), 26.2 (−), 26.6 (−), 30.2 (−), 33.5 (−), 51.6 (+), 74.1 (+), 125.6 (+), 127.7 (+), 128.0 (+), 128.1 (+), 128.4 (+), 128.6 (+), 128.9 (+), 129.0 (+), 130.2 (+), 136.4 (+), 174.2 (−); HRMS (FAB+) calcd for C_{21}H_{32}O_{3}Na [(M+Na)^+] 355.2249, found 355.2256. The \(^{13}\)C NMR spectrum was consistent with that reported,\textsuperscript{55} and the \(^1\)H NMR was revised.

\((18R)-\text{HEPE} \, [(R)-5]\)

\[
\begin{align*}
\text{(R)-13} & \rightarrow \text{(18R)-HEPE} \, [(R)-5]
\end{align*}
\]

To a solution of ester (R)-13 (10.0 mg, 0.030 mmol) in THF (0.2 mL) and MeOH (0.2 mL) was added aqueous LiOH (2.0 N, 0.15 mL, 0.30 mmol). The mixture was stirred at rt for 1 h and diluted with McIlvaine's phosphate buffer (pH 5.0) and the resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over MgSO\(_4\), and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to afford (R)-5 (5.4 mg, 56%): liquid; \(R_f = 0.33\) (CH\(_2\)Cl\(_2\)/THF 9:1); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.93 (t, \(J = 7.6\) Hz, 3 H), 1.52–1.64 (m, 2 H), 1.71 (quint., \(J = 7.4\) Hz, 2 H), 2.13 (q, \(J = 7.0\) Hz, 2 H), 2.36 (t, \(J = 7.2\) Hz, 2 H), 2.82 (t, \(J = 5.8\) Hz, 2 H), 2.85 (t, \(J = 5.5\) Hz, 2 H), 2.98 (t, \(J = 6.4\) Hz, 2 H), 4.14 (q, \(J = 6.6\) Hz, 1 H), 5.1–6.6 (m, 2 H), 5.32–5.46 (m, 7 H), 5.69 (dd, \(J = 15.2, 6.6\) Hz, 1 H), 6.00 (t, \(J = 11.0\) Hz, 1 H), 6.54 (dd, \(J = 15.2, 11.0\) Hz, 1 H); \(^{13}\)C–APT NMR (100 MHz, CDCl\(_3\)) \(\delta\) 9.8 (+), 24.5 (−), 25.7 (−), 25.8 (−), 26.2 (−), 26.5 (−), 30.2 (−), 33.2 (−), 74.2 (+), 125.7 (+), 127.7 (+), 128.0 (+), 128.1 (+), 128.3 (+), 128.6 (+), 128.9 (+), 129.1 (+), 130.4 (+), 135.9 (+), 178.0 (−); HRMS (FAB\(^+\)) calcd for C_{20}H_{30}O_{3}Na [(M+Na)^+] 341.2093, found 341.2097. The \(^1\)H and \(^{13}\)C NMR spectra were consistent with the reported data.\textsuperscript{56} The reported spectra\textsuperscript{57} were updated.

\((S,E)-7\)-(Trimethylsilyl)hept-4-en-6-yn-3-ol [(S)-3b]

\[
\begin{align*}
\text{(S)-8} & \rightarrow \text{(S)-1b} \rightarrow \text{(S)-3b}
\end{align*}
\]

To an ice-cold mixture of (S)-8 (1.49 g, 9.40 mmol) and NaHCO\(_3\) (1.97 g, 23.5 mmol) in
CH$_2$Cl$_2$ (20 mL) was added m-CPBA (70% purity, 2.81 g, 11.4 mmol). The mixture was stirred at rt for 5 h and quenched by addition of Me$_2$S (1.5 mL, 21 mmol). The mixture was diluted with saturated NaHCO$_3$, and the resulting mixture was extracted with EtOAc twice. The combined organic layers were dried over MgSO$_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford (S)-1b (anti/syn) (1.36 g, 83%) as a 40:60 mixture of the anti and syn isomers: $R_f = 0.38$, 0.28 (hexane/EtOAc 5:1); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.07 (s, 9 H), 0.98 and 1.01 (2t, $J = 7.5$ and 7.5 Hz, total 3 H), 1.48–1.69 (m, 2 H), 1.85–2.14 (br s, 1 H), 2.23 (d, $J = 3.6$ Hz, 0.6 H), 2.37 (d, $J = 3.6$, 0.4 H), 2.81 (dd, $J = 5.4$, 3.6 Hz, 0.6 H), 2.88 (dd, $J = 3.6$, 3.3 Hz, 0.4 H), 3.26–3.36 (m, 0.6 H), 3.77–3.86 (m, 0.4 H).

According to the general procedure, epoxy alcohol (S)-1b (anti/syn) (290 mg, 1.66 mmol) in THF (1 mL) was added to a mixture of trimethylsilylacetylene (2a) (1.50 mL, 10.8 mmol), n-BuLi (1.55 M in hexane, 6.50 mL, 10.1 mmol), and HMPA (3.5 mL, 20.1 mmol) in THF (2 mL). The mixture was stirred at rt for 4 h to afford enyne (S)-3b (221 mg, 73%): $R_f = 0.55$ (toluene/EtOAc 9:1). The $^1$H NMR (300 MHz, CDCl$_3$) spectrum was consistent with that of (R)-3b synthesized above.
References for SI


$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (75 MHz, CDCl$_3$)
**1H NMR (300 MHz, CDCl₃)**

**13C NMR (75 MHz, CDCl₃)**
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (75 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (75 MHz, CDCl$_3$)

S20
1H NMR (300 MHz, CDCl₃)

13C NMR (75 MHz, CDCl₃)
$\text{3f}$

$\text{1H NMR (300 MHz, CDCl}_3$}

$\text{13C NMR (75 MHz, CDCl}_3$}
H NMR (300 MHz, CDCl₃)

\[ \text{HO}_{\text{S3}} \rightarrow \text{CO}_2\text{Me} \]

\[^1\text{H NMR (300 MHz, CDCl₃)}\]

\[^{13}\text{C NMR (75 MHz, CDCl₃)}\]

S3
Br≡≡≡CO₂Me

S4

¹H NMR (300 MHz, CDCl₃)

Br≡≡≡CO₂Me

S4

¹³C NMR (75 MHz, CDCl₃)
S6

$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (75 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (75 MHz, CDCl$_3$)
(R)-1b (anti)

$^1$H NMR (300 MHz, CDCl$_3$)

(S)-8

$^1$H NMR (300 MHz, CDCl$_3$)
(R)-MTPA ester of (R)-1b (anti)

$^1$H NMR (300 MHz, CDCl$_3$)

See next page for expansion and % ee calculation.

(S)-MTPA ester of (R)-1b (anti)

$^1$H NMR (400 MHz, CDCl$_3$)


See next page for expansion.
Expansion of $^1$H NMR (300 MHz, CDCl$_3$)

(TMS)$\overset{\text{O}}{\text{O}}$-(R)-MTPA

(R)-MTPA ester of (R)-1b (anti)

ee = (149.41 - 1.00) x 100 / (149.41 + 1.00)

= 98.7%

= 99% ee

isomer

Expansion of $^1$H NMR (400 MHz, CDCl$_3$)

(TMS)$\overset{\text{O}}{\text{O}}$-(S)-MTPA

(S)-MTPA ester of (R)-1b (anti)


isomer
See next page for expansion and % ee calculation.

1H NMR (300 MHz, CDCl$_3$)

TMS$\rightarrow$O-(R)-MTPA

(R)-MTPA ester of (S)-8


See next page for expansion.

TMS$\rightarrow$O-(S)-MTPA

(S)-MTPA ester of (S)-8
Expansion of $^1$H NMR (300 MHz, CDCl$_3$)

TMS\(\text{-}\)(R)-MTPA

(R)-MTPA ester of (S)-8

\(\text{ee} = >99\%\)

isomer

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Expansion of $^1$H NMR (300 MHz, CDCl$_3$)

TMS\(\text{-}\)(S)-MTPA

(S)-MTPA ester of (S)-8


isomer

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See next page for expansion and % ee calculation.

\[
\text{TMS} \quad \text{O-}\text{(S)-MTPA}
\]

crude (S)-MTPA ester of (R)-3b

\(^1\text{H NMR (400 MHz, CDCl}_3\)}

See next page for expansion and % ee calculation.

\[
\text{TMS} \quad \text{O-}\text{(R)-MTPA}
\]

crude (R)-MTPA ester of (R)-3b

\(^1\text{H NMR (400 MHz, CDCl}_3\)}
crude (S)-MTPA ester of (R)-3b
$^1$H NMR (400 MHz, CDCl$_3$)

>99% ee

Both of two possible sites of the peaks are not corresponding to the isomer. See below for clearer conclusion.

Peaks are not the isomer.
\(^1\text{H NMR (300 MHz, CDCl}_3\)\)

\(^{13}\text{C NMR (75 MHz, CDCl}_3\)\)
1H NMR (300 MHz, CDCl₃)

13C NMR (75 MHz, CDCl₃)

OTBS

(R)-7

OTBS

(R)-7
$^{1}$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (75 MHz, CDCl$_3$)

(R)-10

CO$_2$Me

OTBS

CO$_2$Me

OTBS

H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (75 MHz, CDCl$_3$)
(R)-11

$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (75 MHz, CDCl$_3$)
\( (R)-13 \)

**\(^1\)H NMR (400 MHz, CDCl\(_3\))**

**\(^{13}\)C NMR (100 MHz, CDCl\(_3\))**
(18R)-HEPE [(R)-5]

$^1$H NMR (400 MHz, CDCl$_3$)

(18R)-HEPE [(R)-5]

$^{13}$C NMR (75 MHz, CDCl$_3$)