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Asymmetric Synthesis of Both Enantiomers of Disparlure

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Starting from propargyl alcohol (**12**), and on the basis of Zhou's modified Sharpless asymmetric epoxidation, the sex pheromone of the Gypsy moth, disparlure (+)-**8** and its enantiomer (−)-**8** have been synthesized, each in six steps, with overall yields of 29% for (+)-**8** and 27% for (−)-**8** (*ee*>98%). The use of the sequential coupling tactic renders the method flexible, which is applicable to the synthesis of other *cis*-epoxy pheromones.

Keywords Gypsy moth, pheromones, Sharpless asymmetric epoxidation, asymmetric synthesis, epoxides

Introduction

Sex pheromones are signal substances released or emitted by plants and insects for communication between individuals within the same species. With the advantages of being active at very low concentration, non-toxic, and species-specific, pheromones of many pests are used to monitor insects and protect plants against those pests. However, making on practice of such efficient and sustainable insect management strategies is largely limited by the availability of pheromones since generally, only μg to ng scales of the pheromones are available from natural sources. This also constitutes an obstacle for both unequivocal determination of relative and absolute stereochemistries, and profound bioactivity-related studies. Thus, enantioselective synthesis of pheromones have attracted much interest of ecologists and synthetic organic chemists.[1]

Among the sex pheromones identified so far, many are characterized by the c*is*-epoxy substructure. For example, epoxides **1**—**3** (Figure 1) are pheromone components of the fall webworm moth, *Hyphantria cunea*;[2] epoxide **1** was also identified as the major pheromone component of the saltmarsh caterpillar moth *Estigment acrea* Drury;[3] epoxide **4** is a pheromone of the pink moth (the rosy Russian gypsy moth, *Lymantria mathura* Moore);[4] alkenyl epoxides **5**—**7** are the sex pheromones of the elm spanworm *Ennomus subsignaria* (Hübner),[5] the painted apple moth, *Teia anartoides* Walker,[6] and the ruby tiger moth, *Phragmatobia fuliginosa* (L.).[7]

Gypsy moth, *Porthetria dispar* L. is a class of widespread and harmful pests with a very broad diet which causes severe forest losses during outbreaks. Its larva can spread with the wind, firstly expanding from Europe to Asia, and then North America, now worldwide existing. It is also one of the most harmful pests that damages forest, garden, sericulture and fruiter. In 1970, Bierl and co-workers identified disparlure as the sex pheromone of the female gypsy moth and the structure was elucidated as *cis*-7,8-epoxy-2-methyloctadecane (**8**).[8] The absolute configuration of disparlure was established by synthesis of both enantiomers,[9a] which also allowed the conclusion that natural (+)-disparlure is more active than the (−)-enantiomer.[9a] Studies towards disparlure (**8**) has attracted much attention from both biological[10] and synthetic communities. Up to now more than twenty approaches have been reported for the enantioselective synthesis of

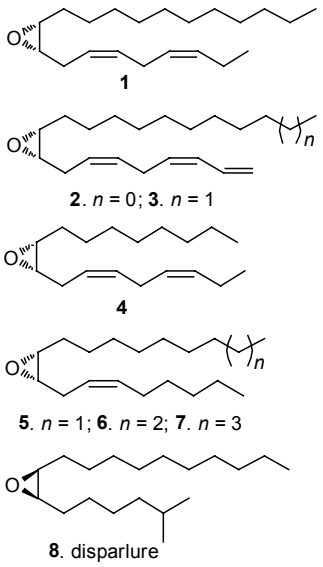

Figure 1 Sex pheromones of several species of moth.

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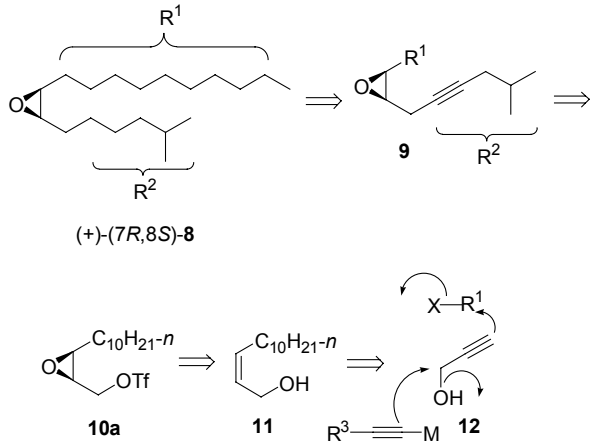
(+)-disparlure,[9,11-17] and eight for (−)-disparlure.[18] The reported methods are based on either chiral pools,[9] or asymmetric synthesis.[11-17] Although nine used the Sharpless asymmetric epoxidation as the key step,[11] there are drawbacks in those approaches, such as use of uncommon starting materials,[11f,11g] the need of a derivatization for enantiomer enrichment,[11c,11f-11h] low enantiomeric purity of the final product,[11i] low overall yield or multiple steps required for the chain elongation.[11a,11b,11d,11e] In short, although a number of methods have been reported to access both enantiomers of disparlure, short and efficient ones without using expensive starting material and toxic reagents are still demanding.

In recent years, we have been engaged in the asymmetric synthesis of pheromones.[19] We recently reported a divergent synthesis of the two main pheromone components of the fall webworm moth, *Hyphantria cunea*.[19b] As an extension of the latter synthetic strategy, we now report the syntheses of both enantiomers of disparlure (**8**, Scheme 1).

Scheme 1 Retrosynthetic analysis of (+)-(7*R*,8*S*)-disparlure **(8)**

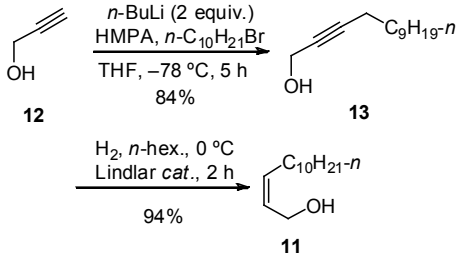


On the basis of our previous work,[19b] and in view of a general access to epoxy pheromones, our retrosynthetic analysis of disparlure (**8**) is displayed in Scheme 1. Given the chiral epoxide as the key structural feature of **8**, the Sharpless asymmetric epoxidation (AE) was selected as a convenient method for the enantioselective formation of the epoxy group.[20] In view of the unsatisfactory enantioselectivity of the Sharpless AE with *cis*-allylic alcohols,[11] longer chain (R^1) at the epoxy carbon was planned to be introduced first, which would allow an enrichment of the major enantiomer by recrystallization of the epoxide formed. Installation of the shorter chain (R^2) by means of alkynylation would allow the access to both alkyl or alkenyl epoxy pheromones after reduction or controlled *cis*-selective reduction.

Results and Discussion

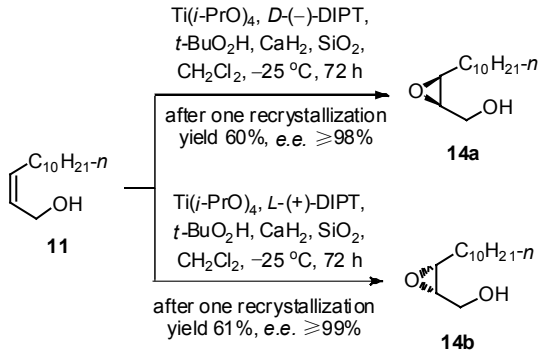
On the basis of the retrosynthetic analysis, the synthesis started with the preparation of (*Z*)-allylic alcohol **11** by Ames's procedure[21] (Scheme 2). In the event, treatment of 1-bromodecane with $LiC{\equiv}CCH_2OLi$ in a mixed solvent system HMPA/THF produced propargylic alcohol **13** in 84% yield. Partial hydrogenation of propargylic alcohol **13** over Lindlar catalyst (H_2, 5% $Pd/CaCO_3$, poisoned with 3.5% Pb, *n*-hex., 0 ℃) gave (*Z*)-allylic alcohol (**11**) in 94% yield.

Scheme 2 Synthesis of (*Z*)-dodec-2-en-1-ol **(11)**



With allylic alcohol **11** in hand, we proceeded to investigate its enantioselective epoxidation to prepare epoxide **14a** via the Sharpless asymmetric epoxidation. In this context, many successful examples of asymmetric epoxidation methods have been documented in the literatures,[20] and Zhou's modified Sharpless catalytic system[22] was adopted according to our previous results.[19b] Thus, in the presence of $Ti(O\textit{i}\text{-}Pr)_4$, CaH_2, SiO_2 and *D*-(−)-DIPT, allylic alcohol **11** was treated with *t*-BuO_2H in CH_2Cl_2 to produce the corresponding epoxide **14a** in 80% *ee*.[23] Moderate enantioselectivity of Sharpless epoxidation for (*Z*)-allylic alcohol has been observed.[11,24] Fortunately epoxy **14a** is solid and could be enriched to 98%—99% *ee* in 60% yield after one recrystallization from petroleum ether (Scheme 3).

Scheme 3 Syntheses of epoxide **14a** and **14b**



The next task was the activation of the hydroxyl group in **14a**. Thus **14a** was converted into the corresponding triflate **10a** by treating with triflic anhydride (Tf_2O, NEt_3, CH_2Cl_2, −78 to −45 ℃, yield 88%) (Scheme 4).

With the fragment **10a** available, its coupling reaction was undertaken. Treatment of the organometallic

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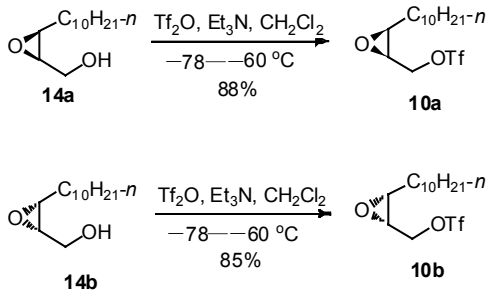
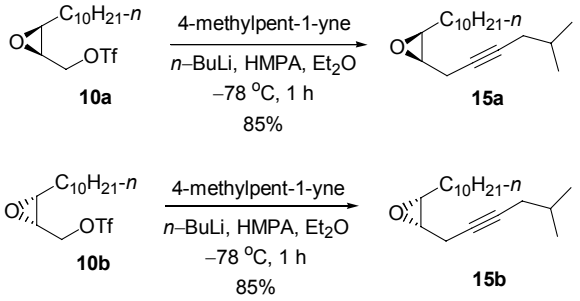
species generated from 4-methylpent-1-yne and *n*-BuLi with triflate **10a** gave the desired propargyl alcohol **15a** in 85% yield (Scheme 5).

Scheme 4 Syntheses of epoxy triflate **10a** and **10b**

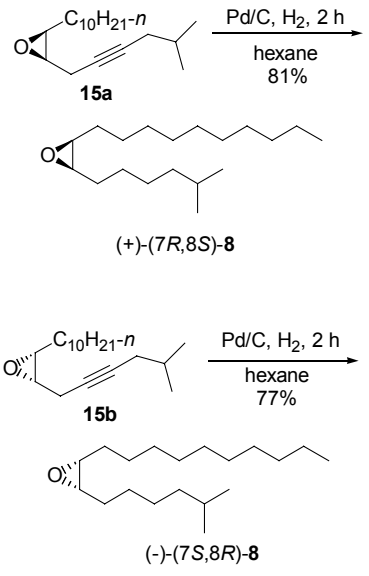


Scheme 5 Coupling reactions of triflate **10a** and **10b** with the lithium alkynide



Finally, chemoselective hydrogenation of **15a** in the presence of 5% Pd—C in dry *n*-hexane under 10^5 Pa of hydrogen at r.t. for 2 h produced the desired target compound (+)-**8** in 81% yield (Scheme 6).

Scheme 6 Syntheses of compounds (+)-**8** and (−)-**8**



We next turned to the synthesis of (−)-**8**. For this purpose, allylic alcohol **11** was converted to the epoxide **14b** under the same condition for **14a** except *D*-(−)-DIPT was replaced with *L*-(+)-DIPT (Scheme 3). In such a manner, **14b** was obtained in 61% yield and ＞99% *ee* after recrystallization. Using the procedures described for (+)-**8** (Schemes 4—6), compound **14b** was converted to (−)-**8** in 3 steps with yield of 85%, 85%, and 77%, respectively.

In summary, a new and expeditious six-step approach for the synthesis of the sex pheromone of the Gypsy moth, disparlure (+)-**8** and its enantiomer (−)-**8** has been developed, which features the use of Zhou's Sharpless asymmetric epoxidation of allylic alcohol **11** as the key step. Starting from propargyl alcohol **12**, (+)-(7*R*,8*S*)-**8** and its enantiomer (−)-**8** have been synthesized with overall yields of 29% and 27%, respectively. The *ee* values of the final products (+)-**8** and (−)-**8** are at least 98%. Our strategy is flexible, and could also be used for the synthesis of other insect pheromones having similar *cis*-epoxy substructure, such as the sex pheromones **4**—**7**. Further research is in progress.

Experimental

General methods Melting points were determined on a micro melting point apparatus and were uncorrected. Infrared spectra were measured with a FT-IR spectrometer using film KBr pellet techniques. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz respectively. Chemical shifts are expressed in δ units downfield from TMS. Mass spectra were recorded with a liquid chromatography-mass spectrum apparatus (direct injection). Optical rotations were measured with a polarimeter. Silica gel (300—400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60—90 ℃) mixture. Ether and THF were distilled over sodium benzophenone ketyl under N_2. Dichloromethane was distilled over calcium hydride under N_2.

Tridec-2-yn-1-ol (13) To a cooled (−78 ℃) solution of propynyl alcohol **12** (280 mg, 5 mmol) in THF (50 mL) was added *n*-butyllithium (4.7 mL, 10.5 mmol, 2.2 mol/L in hexane) under an argon atmosphere. After being stirred for 60 min, a solution of 1-bromodecane (1.1 mL, 5.5 mmol) in hexamethylphosphoramide (HMPA, 2.3 mL) was added. After being stirred for another 5 h, the reaction was quenched with 0.5 mol/L aqueous Na_2CO_3 solution (10 mL), diluted with diethyl ether (20 mL). The aqueous phase was back-extracted with diethyl ether (20 mL×2) and the organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (R_f 0.2, ethyl acetate∶petroleum ether=1∶10) to afford compound **13** (823 mg, 84%) as a white solid. m.p. 30—31 ℃ (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, J=6.8 Hz, 3H),

1.22—1.42 (m, 14H), 1.46—1.56 (m, 3H), 2.21 (tt, J= 7.1, 2.1 Hz, 2H), 4.25 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 18.7, 22.7, 28.6, 28.9, 29.1, 29.3, 29.5, 29.6, 31.9, 51.4, 76.7, 86.7; IR (film) ν_{max}: 3326 (OH), 2927, 2853, 2219 (w, C≡C), 1464, 1375, 1138, 1016 cm^{-1}; MS (ESI) m/z: 219.1 ($M+Na^+$). HRMS (ESI) calcd for $C_{13}H_{24}NaO^+$ [$M+Na^+$] 219.1719, found 219.1713.

(*Z*)-Tridec-2-en-1-ol (11) To a round-bottomed flask was added Lindlar catalyst (Pd, 15% on $CaCO_3$ poisoned with 3.5% Pb, 5 mg), and the flask was filled with H_2 and cooled to 0 ℃. Compound **13** (30 mg, 0.15 mmol) in 2 mL distilled *n*-hexane was added to the resultant mixture. After stirring for 2 h at 0 ℃, the product was filtered through silica gel to remove the catalyst and then concentrated to give **11** (28.5 mg, 94%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, J= 6.8 Hz, 3H), 1.24—1.37 (m, 17H), 2.02—2.10 (m, 2H), 4.19 (d, J=6.1 Hz, 2H), 5.50—5.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.7, 27.4, 29.2, 29.3, 29.47, 29.59 (2C), 29.68, 31.9, 58.6, 128.3, 133.3; IR (film) ν_{max}: 3329 (br s, OH), 3015, 2927, 2847, 1658 (w, C= C), 1466, 1384, 1015, 721 cm^{-1}; MS (ESI) m/z (%): 221.2 ($M+Na^+$, 100). HRMS (ESI) calcd for $C_{13}H_{26}NaO^+$ [$M+Na^+$] 221.1876, found 221.1878.

(2*R*,3*S*)-2,3-Epoxy-tridecan-1-ol (14a) To a mixture of titanium tetraisopropoxide (4.9 mL, 16.7 mmol), 63 mg of calcium hydride and 83 mg of silica gel in 128 mL of anhydrous CH_2Cl_2 was injected a solution of *D*-(−)-diisopropyl tartrate (4.20 g, 18.0 mmol) in anhydrous CH_2Cl_2 (5 mL) via syringe under N_2 at −25 ℃. After being stirred for 30 min, a solution of (*Z*)-tridec-2-en-1-ol (**11**) (2.74 g, 13.8 mmol) in anhydrous CH_2Cl_2 (5 mL) was added. After being stirred for another 30 min, 5.5 mL (30.4 mmol) of anhydrous *tert*-butyl hydroperoxide (TBHP, 5.5 mol/L) was then injected at −25 ℃. The resultant mixture was allowed to stir at −25 ℃ for 3 d. The reaction was quenched with 40 mL of 10% aqueous solution of tartaric acid. The mixture was stirred at −25 ℃ for 1 h, then warmed to room temperature until the aqueous layer became clear. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (50 mL×2) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (R_f 0.3, ethyl acetate∶petroleum ether=1∶3) to afford epoxide **14a**, which was recrystallized from petroleum ether to give 1.78 g (60%) of epoxide **14a**. m.p. 62—63 ℃ (petroleum ether) (lit.[11a] m.p. 62—63 ℃); $[\alpha]_D^{20}$ −7.9 (*c* 1.0, EtOH) [lit.[11a] $[\alpha]_D^{20}$ −7.8 (*c* 1.0, EtOH)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, J=6.9 Hz, 3H), 1.20—1.60 (m, 18H), 1.61—1.68 (m, 1H), 3.03 (ddd, J=6.6, 5.5, 4.2 Hz, 1H), 3.16 (ddd, J=6.9, 4.2, 4.2 Hz, 1H), 3.68 (ddd, J=11.8, 6.9, 4.9 Hz, 1H), 3.86 (ddd, J=11.8, 7.6, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.7, 26.6, 27.95, 29.3, 29.4, 29.48, 29.51, 29.55, 31.9, 56.7, 57.3, 60.9; IR (film) ν_{max}: 3427 (br s, OH), 2911, 2850, 1634, 1469, 1042 cm^{-1}; MS (ESI) m/z (%): 237.2 ($M+Na^+$, 100). HRMS (ESI) calcd for $C_{13}H_{26}NaO_2^+$ [$M+Na^+$] 237.1825, found 237.1829. The enantiomeric excess (*ee*) of epoxide (2*R*,3*S*)-**14a** was determined by HPLC analysis of the corresponding 3,5-dinitrobenzoyl ester (column, Chiralpak AD-H 4.6 mm×250 mm; *n*-hexane∶ethanol=60∶40; flow rate, 1.0 mL/min) t_R (min): the product after one recrystallization, (2*R*,3*S*)-ester: *ee*=98.2%.

(2*R*,3*S*)-2,3-Epoxy-tridecyl trifluoroacetate (10a) To a vigorously stirred suspension of epoxide **14a** (250 mg, 1.17 mmol) in anhydrous CH_2Cl_2 (65 mL) was added dropwise triethylamine (0.6 mL, 4.21 mmol) and trifluoromethanesulfonic anhydride (0.58 mL, 3.5 mmol) under an argon atmosphere at −78 ℃. The suspension was allowed to warm slowly to about −60 ℃ and stirred. Once the solution became clear, the reaction was recooled to −78 ℃ and stirred for 30 min, then the reaction was quenched with an aqueous NH_4Cl solution (5.0 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL×2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel (R_f 0.25, ethyl acetate∶petroleum ether=1∶50) to afford crude triflate **10a** (354 mg, 88%) as a colorless oil, which was used in the subsequent step without further purification.

(7*R*,8*S*)-7,8-Epoxy-2-methyloctadecane-4-yne (15a) A solution of *n*-BuLi (2.2 mol/L in hexane, 0.83 mL, 1.82 mmol) was added dropwise to a solution of 4-methylpent-1-yne (0.24 mL, 2.0 mmol) in anhydrous diethyl ether (15 mL) at −78 ℃ under an argon atmosphere. After being stirred for 10 min, a solution of triflate (2*R*,3*S*)-**10a** (350 mg, 1.0 mmol) in anhydrous diethyl ether (2 mL) and anhydrous HMPA (0.4 mL) was added. After being stirred for 1 h at the same temperature, the reaction was quenched with an aqueous NH_4Cl solution (1.0 mL). The aqueous layer was extracted with EtOAc (10 mL×3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (R_f 0.25, ethyl acetate∶petroleum ether=1∶50) to afford compound **15a** (236 mg, 85%) as a colorless oil. $[\alpha]_D^{20}$ −47.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, J=6.9 Hz, 3H), 0.95 (d, J=6.6 Hz, 6H), 1.20—1.60 (m, 18H), 1.77 (sept, J=6.6 Hz, 1H), 2.04 (dt, J=6.5, 2.4 Hz, 2H), 2.23 (ddt, J=16.9, 7.4, 2.4 Hz, 1H), 2.57 (ddt, J=16.9, 5.0, 2.4 Hz, 1H), 2.94 (dt, J=4.2, 5.9 Hz, 1H), 3.10 (ddd, J=7.4. 5.0, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 18.7, 21.9 (2C), 22.6, 26.4, 27.5, 27.9, 28.1, 29.3, 29.47, 29.51 (2C), 29.6, 31.9, 55.4, 57.0, 75.7, 81.2; IR (film) ν_{max}: 2957, 2924, 2850, 2278 (w, C≡C), 1592, 1464, 1384, 1022 cm^{-1}; MS (ESI) m/z (%): 301.2 ($M+Na^+$, 100). HRMS (ESI) calcd for $C_{19}H_{34}NaO^+$ [$M+Na^+$] 301.2502, found 301.2506.

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(7*R*,8*S*)-7,8-Epoxy-2-methyloctadecane [(+)-8] To a round-bottomed flask was added Pd/C (6 mg, 10%), and filled with H_2. Compound **15a** (57 mg, 0.2 mmol) in 1 mL distilled *n*-hexane was added to the resultant mixture. After being stirred for 2 h at room temperature, the product was filtered through silica gel to remove the catalyst and then concentrated. The residue was purified by flash column chromatography on silica gel (R_f 0.25, ethyl acetate∶petroleum ether=1∶100) to afford compound (+)-**8** (47 mg, 81%) as a colorless oil. $[\alpha]_D^{20}$ +1.0 (*c* 1.0, CCl_4) {lit.[14] $[\alpha]_D$ +0.9 (*c* 1.1, CCl_4)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.84—0.91 (m, 9H), 1.15—1.59 (m, 27H), 2.84—2.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.57, 22.58, 22.7, 26.6, 26.8, 27.3, 27.81, 27.84, 27.87, 29.3, 29.54, 29.58, 31.9, 38.9, 57.2; IR (film) ν_{max}: 2951, 2924, 2854, 1464, 1378, 1263, 1098, 1021, cm^{-1}; MS (ESI) *m*/*z* (%): 305.3 (M+Na^+, 100). HRMS (ESI) calcd for $C_{19}H_{38}NaO^+$ [M+Na^+] 305.2815, found 305.2811.

(2*S*,3*R*)-2,3-Epoxy-tridecan-1-ol (14b) To a mixture of titanium tetraisopropoxide (5.6 mL, 18.2 mmol), 71 mg of calcium hydride, and 95 mg of silica gel in 148 mL of anhydrous CH_2Cl_2 was injected a solution of *L*-(+)-diisopropyl tartrate (4.80 g, 20.6 mmol) in anhydrous CH_2Cl_2 (5 mL) via syringe under N_2 at −25 ℃. After being stirred for 30 min, a solution of (*Z*)-tridec-2-en-1-ol (**11**) (3.14 g, 15.8 mmol) in anhydrous CH_2Cl_2 (5 mL) was added. After being stirred for another 30 min, 6.3 mL (34.9 mmol) of anhydrous TBHP (5.5 mol/L) was then injected at −25 ℃. The resultant mixture was allowed to stir at −25 ℃ for 3 d. The reaction was quenched with 40 mL of 10% aqueous solution of tartaric acid. The mixture was stirred at −25 ℃ for 1 h, then warmed to room temperature until the aqueous layer became clear. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (50 mL×2) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (R_f 0.3, ethyl acetate∶petroleum ether=1∶3) to afford epoxide **14b**, which was recrystallized from petroleum ether to give 2.06 g (61%) of epoxide **14b**. m.p. 62—63 ℃ (petroleum ether) (enantiomer lit.[11a] m.p. 62—63 ℃); $[\alpha]_D^{20}$ +7.9 (*c* 1.0, EtOH) {enantiomer lit.[11a] $[\alpha]_D^{23}$ −7.8 (*c* 1.0, EtOH)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, *J*=6.9 Hz, 3H), 1.20—1.60 (m, 18H), 1.85—1.97 (m, 1H), 3.03 (ddd, *J*=6.6, 5.5, 4.2 Hz, 1H), 3.16 (ddd, *J*=7.0, 4.2, 4.2 Hz, 1H), 3.67 (ddd, *J*=11.8, 7.0, 4.7 Hz, 1H), 3.86 (ddd, *J*=11.8, 7.6, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.6, 26.6, 27.95, 29.3, 29.4, 29.48, 29.50, 29.55, 31.9, 56.8, 57.3, 60.9; IR (film) ν_{max}: 3427 (br s, OH), 2911, 2850, 1634, 1469, 1042 cm^{-1}; MS (ESI) *m*/*z* (%): 237.2 (M+Na^+, 100). HRMS (ESI) calcd for $C_{13}H_{26}NaO_2^+$ [M+Na^+] 237.1825, found 237.1828. The enantiomeric excess (*ee*) of epoxide (2*S*,3*R*)-**14b** was determined by HPLC analysis of the corresponding 3,5-dinitrobenzoyl ester (column, Chiralpak AD-H 4.6 mm × 250 mm; *n*-hexane∶ethanol=60∶40; flow rate, 1.0 mL/min) t_R (min): the product after one recrystallization, (2*S*,3*R*)-ester: *ee*>99%.

(2*S*,3*R*)-2,3-Epoxy-tridecyl trifluoroacetate (10b) To a vigorously stirred suspension of epoxide **14b** (100 mg, 0.47 mmol) in anhydrous CH_2Cl_2 (26 mL) was added dropwise triethylamine (0.24 mL, 1.68 mmol) and trifluoromethanesulfonic anhydride (0.23 mL, 1.40 mmol) under an argon atmosphere at −78 ℃. The suspension was allowed to warm slowly to about −60 ℃ and stirred. Once the solution became clear, the reaction was recooled to −78 ℃ and stirred for 30 min, then the reaction was quenched with an aqueous NH_4Cl solution (5.0 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL×2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel (R_f 0.25, ethyl acetate∶petroleum ether=1∶50) to afford crude triflate **10b** (138 mg, 85%) as a colorless oil, which was used in the subsequent step without further purification.

(7*S*,8*R*)-7,8-Epoxy-2-methyloctadecane-4-yne (15b) A solution of *n*-BuLi (2.2 mol/L in hexane, 0.23 mL, 0.50 mmol) was added dropwise to a solution of 4-methylpent-1-yne (0.07 mL, 0.56 mmol) in anhydrous diethyl ether (3 mL) at −78 ℃ under an argon atmosphere. After being stirred for 10 min, a solution of triflate (2*S*,3*R*)-**10b** (100 mg, 0.28 mmol) in anhydrous diethyl ether (1 mL) and anhydrous HMPA (0.11 mL) was added. After being stirred for another 1 h at the same temperature, the reaction was quenched with an aqueous NH_4Cl solution (1.0 mL). The aqueous layer was extracted with EtOAc (10 mL×3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (R_f 0.25, ethyl acetate∶petroleum ether=1∶50) to afford compound **15b** (66 mg, 85%) as a colorless oil. $[\alpha]_D^{20}$ +47.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, *J*=6.8 Hz, 3H), 0.95 (d, *J*=6.6 Hz, 6H), 1.20—1.60 (m, 18H), 1.76 (sept, *J*=6.6 Hz, 1H), 2.04 (dt, *J*=6.5, 2.4 Hz, 2H), 2.23 (ddt, *J*=16.9, 7.4, 2.4 Hz, 1H), 2.57 (ddt, *J*=16.9, 5.0, 2.4 Hz, 1H), 2.94 (dt, *J*=4.2, 5.9 Hz, 1H), 3.10 (ddd, *J*=7.4, 5.0, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 18.8, 21.9 (2C), 22.7, 26.5, 27.5, 27.9, 28.1, 29.3, 29.49, 29.53 (2C), 29.6, 31.9, 55.4, 57.0, 75.7, 81.3; IR (film) ν_{max}: 2957, 2924, 2850, 2278 (w, C≡C), 1592, 1464, 1384, 1022 cm^{-1}; MS (ESI) *m*/*z* (%): 301.2 (M+Na^+, 100). HRMS (ESI) calcd for $C_{19}H_{34}NaO^+$ [M+Na^+] 301.2502, found 301.2504.

(7*S*,8*R*)-7,8-Epoxy-2-methyloctadecane [(−)-8] To a round-bottomed flask was added Pd/C (2 mg, 10%), and filled with H_2. Compound **15b** (18 mg, 0.064 mmol) in 1 mL distilled *n*-hexane was added to the resultant mixture. After being stirred for 2 h at room temperature,

the product was filtered through silica gel to remove the catalyst and then concentrated. The residue was purified by flash column chromatography on silica gel (R_f 0.25, ethyl acetate: petroleum ether=1∶100) to afford compound (−)-**8** (14 mg, 77%) as a colorless oil. $[\alpha]_D^{20}$ −1.0 (*c* 1.0, CCl_4) {lit.[14] $[\alpha]_D$ −0.9 (*c* 0.21, CCl_4)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.84—0.91 (m, 9H), 1.17—1.56 (m, 27H), 2.84—2.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.6, 22.7, 26.6, 26.8, 27.3, 27.81, 27.85, 27.88, 29.3, 29.54, 29.58, 31.9, 38.9, 57.2; IR (film) ν_{max}: 2951, 2924, 2854, 1464, 1378, 1263, 1098, 1021 cm^{-1}; MS (ESI) *m*/*z* (%): 305.3 (M+Na$^+$, 100). HRMS (ESI) calcd for $C_{19}H_{38}NaO^+$ [M+Na$^+$] 305.2815, found 305.2824.

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