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A Concise, Protection-Free and Divergent Approach for the Enantioselective Syntheses of Two Pheromonal Epoxide Components of the Fall Webworm Moth and Other Species

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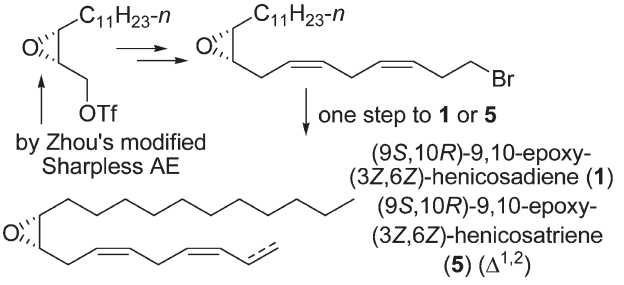

On the basis of Zhou's modified Sharpless asymmetric epoxidation, sequential coupling reactions, and a divergent strategy, the *protection-free* syntheses of two main pheromonal components **1** and **5**, found in the fall webworm moth, *Hyphantria cunea*, and other species have been accomplished in 10 steps (for two compounds). The overall yields are 31% for **1**, 28% for **5**, and 25% for both **1** and **5**, respectively. The ee values of the final products **1** and **5** are at least 99%.

The fall webworm moth, *Hyphantria cunea*, also known as the American white moth and Amerika-Shirohitori, is a notorious pest widely distributed throughout the northern hemisphere and in many Asian countries such as Japan and China. Its larva attacks many crops, fruit trees, and ornamental trees. A total of five pheromone components (**1**−**5**, Figure 1) have been identified with three of them being optically active epoxides.[1,2] Interestingly, some of these pheromones have been found in other species. For example, (3*Z*,6*Z*)-*cis*-9,10-epoxy-3,6-henicosadiene (**1**) is also identified as the major pheromone component of the saltmarsh caterpillar moth *Estigment acrea* Drury.[3] Further study on the female arctiids has uncovered this same 21-carbon

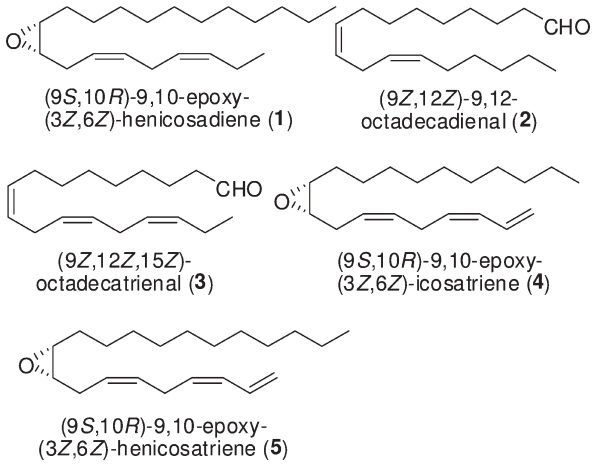

FIGURE 1. Structures of the pheromone of the fall webworm moth (*Hyphantria cunea*).

epoxide in at least five species.[4] Moreover, epoxides **1** and **5** were also two pheromonal components of *Diacrisia obliqua* (Bihar hairy caterpillar, Arctiidae), a polyphagous pest attacking as many as 33 host plants particularly oil seed crops.[5] This pest has been recorded in many Asian countries including Indian, China, and Japan. Roelofs and co-workers suggested (9*S*,10*R*) absolute configuration for pheromones of *E. acrea*.[3] Arn and co-workers showed that the synthetic (9*S*,10*R*)-enantiomers of **4** and **5** were biologically active, while the (9*R*,10*S*) forms were inactive.[2] Thus the (9*S*,10*R*)-enantiomers are the natural and biologically active pheromones. Field tests showed that a mixture of synthetic **1**−**5** in the approximate proportions found in the *H. cunea*[2] and *Diacrisia obliqua* female attracted males.[5b] Latter, Senda and co-workers found that a blend of **1**, **3**, and **5** was able to attract *H. cunea*, and this blend was commercialized for *H. cunea* monitoring.[6]

It has been demonstrated that the **1**, **3**, and **5**-containing blend of female *H. cunea* and *Diacrisia obliqua* is active in the field test, and the epoxide components **1** and **5** play a key role for the biological activity. Because component **3** can be prepared readily from linolenic acid,[1,7] the synthesis of these pheromonal components were focused on the asymmetric synthesis of epoxides components **1**[5b,8] and **5**,[2,5,8g,9] respectively. Nevertheless, considering the synthesis of both

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SCHEME 1. Retrosynthetic Analysis of the Pheromonal Components 1 and 5

components **1** and **5**, the known approaches are inefficient, because the two triene and diene side chains in both components **1** and **5** need to be synthesized separately. On the basis of these considerations, we decided to develop an inherently divergent approach to the key pheromonal components **1** and **5**, and the results are reported herein.

Considering the structural similarity of epoxides **1** and **5**, bromide **6** was designed as a common precursor. Accordingly, the retrosynthetic analysis of both components **1** and **5** is outlined in Scheme 1. Given the epoxide as the key structural feature of both **1** and **5**, the Sharpless asymmetric epoxidation (AE)[10] appeared to be a convenient method for their asymmetric synthesis. A direct use of the Sharpless asymmetric epoxidation (AE) has been reported by Mori,[8b] and adopted by Kovalev and co-workers[2] for the synthesis of components **1**, **4**, and **5**. The drawback of the approach, featuring the first installation of the shorter unsaturated side chain, resided in the fact that the enantiomeric excess (% ee) of the AE product was only 87−88% that required additional steps including derivation, repeated recrystallizations, and release of the hydroxyl group. This was expected to be avoided by using allylic alcohol **9**, bearing a longer side chain, as a substrate for the AE.[10] Indeed, in the synthesis of another pheromone, Mori and co-workers showed that the enantiomeric purity of the AE product of **9** can be enriched simply by one recrystallization.[11] However, a low yield (42%) was obtained in the subsequent coupling reaction via tosylate derivative. Thus triflate **8** was selected as our key intermediate.

Our synthesis started with propargyl alcohol (**10**), which was converted to (*Z*)-allylic alcohol **9** by Ames's procedure.[11,12] In the event, treatment of 1-bromoundecane with LiC≡CCH$_2$OLi in a mixed solvent system HMPA/THF produced propargylic alcohol **11** in 92% yield. Partial hydrogenation of propargylic alcohol **11** over Lindlar catalyst (H$_2$, 5% Pd/CaCO$_3$, poisoned with 3.5% Pb, *n*-hex., 0−5 °C) gave (*Z*)-allylic alcohol **9** in 98% yield. The *Z*/*E* ratio of **9** was at least 49:1 as determined by GC analysis of the crude product. For the asymmetric epoxidation of (*Z*)-allylic alcohol[10,11] **9**, Zhou's modified Sharpless asymmetric oxidation (AE) conditions[13] [Ti(O*i*Pr)$_4$, L-(+)-DIPT, *t*-BuO$_2$H, CaH$_2$, SiO$_2$, CH$_2$Cl$_2$, −25 °C, 4 days) turned out to give a better result (Scheme 2). In such a manner, the epoxide **12** was obtained in at least 85% ee and 92% yield, which was enriched to >99% ee after one recrystallization from *n*-hexane. The enantiomeric excess of epoxide alcohol **12** was determined by chiral HPLC analysis of its 3,5-dinitrobenzoyl ester. The racemic epoxide (±)-**12** for comparison was obtained by epoxidation of allylic alcohol **9** with mCPBA. For an efficient coupling of epoxide **12** with propargyl alcohol, the former was converted into the corresponding triflate[14] **8** by treating with triflic anhydride (Tf$_2$O, NEt$_3$, CH$_2$Cl$_2$, −78 to −45 °C, yield 98%).

SCHEME 2

Successive treatment of propargyl alcohol TMS ether **13**[15] with *n*-BuLi and triflate **8** in a mixed HMPA/Et$_2$O solvent system at −78 °C afforded the desired coupling product, which, without purification, was treated with K$_2$CO$_3$ in MeOH to give the propargylic alcohol **14** in 85% yield over two steps (Scheme 3). It was found that when 2 equiv of *n*-BuLi was used, the coupling of triflate **8** with propargyl alcohol (**10**) proceeded chemoselectively[8g] to produce directly the coupling product **14** in 84% yield.

SCHEME 3

Chemoselective bromination of propargylic alcohol **14** by Appel−Lee reaction[16] (CBr$_4$, PPh$_3$, CH$_2$Cl$_2$, rt) gave

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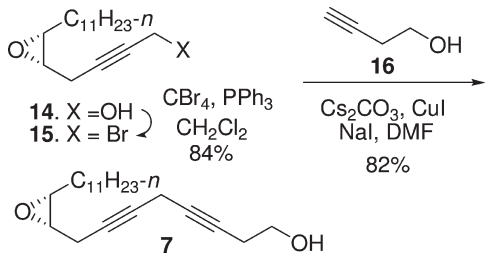
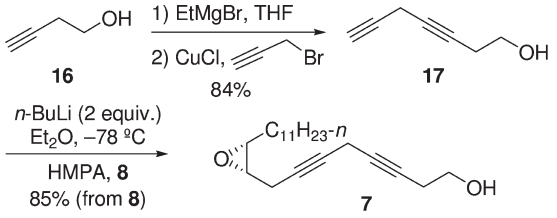
SCHEME 4



SCHEME 5

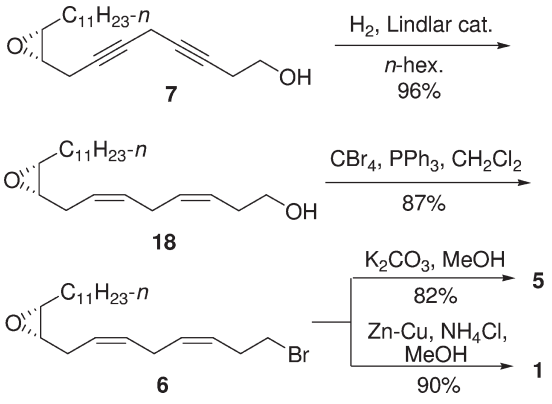


bromide **15** in 84% yield without affecting the epoxide[8g,9b] (Scheme 4). Further chemoselective coupling of propargyl bromide **15** with 3-butynyl alcohol (**16**) was achieved by using Spinella's conditions[17] (Cs_2CO_3, CuI, NaI, DMF, rt), which afforded the coupling product **7** in 82% yield.

Alternatively, a convergent coupling approach was also explored. For this purpose, the requisite diyne **17** was prepared from 3-butynyl alcohol (**16**) by deprotonation with ethyl magnesium bromide, followed by CuCl-mediated chemoselective coupling[8a] with propargyl bromide (Scheme 5). The coupling of triflate **8** with the alkynide generated in situ from diyne **17** and 2 mol equiv of *n*-BuLi at −78 °C produced the desired coupling product **7** in 85% yield. To prove the chemoselectivity of the reaction, the coupling of **8** with the lithium alkynide, derived in situ from *O*-TMS protected **17** and 1 equiv of *n*-BuLi at −78 °C, was also tested. After cleavage of TMS with K_2CO_3 in MeOH compound **7** was obtained.

Chemoselective partial hydrogenation of the diyne **7** was achieved by using the Lindlar catalyst (H_2, 5% Pd-$CaCO_3$, poisoned with 3.5% Pb, *n*-hexane, 18−19 °C, 35 min), which gave the known diene[9b] **18** in 96% yield (Scheme 6). Chemoselective bromination[8g] of alcohol **18** afforded bromide **6** in 87% yield. Compound **6** was considered to be a ready precursor of both **1** and **5**. Indeed, treatment of bromide **6** with K_2CO_3 in MeOH at rt for 24 h[9b] gave the desired triene **5** in 82% yield. The physical {$[\alpha]^{28}_D$ −0.9 (*c* 1.9, $CHCl_3$); lit.[8g] $[\alpha]^{21}_D$ −0.38 (*c* 1.04, $CHCl_3$); lit.[9b] $[\alpha]^{25}_D$ −0.6 (*c* 3.0, $CHCl_3$)} and spectral data of the synthetic compound were identical with those reported.[2,5,8g,9] On the other hand, cleavage of the C−Br bond in **6** with Zn−Cu/NH_4Cl[18] in MeOH at 68 °C for 40 min afforded diene **1** in 90% yield. The physical {$[\alpha]^{28}_D$ + 3.9 (*c* 1.8, CCl_4); lit.[8g] $[\alpha]^{22}_D$ +4.0 (*c* 1.6, CCl_4)} and spectral data of the synthetic compound were identical with those reported.[5b,8]

SCHEME 6



In summary, we have developed a strategically convergent and product divergent, yet *protection−deprotection-free* approach to the two pheromone principle components of *H. cunea* and *Diacrisia obliqua*, which are also present in several other species. Considering the total steps (10 steps) required for the synthesis of the two most active and challenging pheromone components of the useful blend, this approach is quite efficient. The concept of developing a divergent synthesis in the last step in a target-oriented synthesis (TOS) is of value in organic synthesis.

Experimental Section

(2*S*,3*R*)-2,3-Epoxytetradecan-1-ol (12). To a mixture of titanium tetraisopropoxide (10.9 mL, 35.8 mmol), 150 mg of calcium hydride, and 200 mg of silica gel in 280 mL of anhydrous CH_2Cl_2 was injected L-(+)-diisopropyl tartrate (9.8 g, 41.1 mmol) dissolved in anhydrous CH_2Cl_2 (15 mL) via syringe under N_2 in a cooling bath (−35 °C). After stirring for 30 min, (*Z*)-tetradec-2-en-1-ol (**9**, 6.6 g, 31.1 mmol) dissolved in anhydrous CH_2Cl_2 (15 mL) was injected. After stirring for another 30 min, 12.5 mL (68.5 mmol) of anhydrous TBHP (5.5 M) was then injected at −35 °C. The resulting mixture was allowed to stir at −30 °C for 3 days. The reaction was quenched with 80 mL of 10% aq tartaric acid. The mixture was stirred at −20 °C 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 (2 × 50 mL) 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 0.25, eluent: ethyl acetate: petroleum ether = 1:5) to afford epoxide **12** (6.55 g, 92%) as a white solid, which was recrystallized from petroleum ether to give 4.62 g (65%) of epoxide **12**. Mp 69−70 °C (petroleum ether) (lit.[11] mp 62.5−63.5 °C); $[\alpha]^{28}_D$ −4.2 (*c* 1.0, $CHCl_3$) {enantiomer lit.[19] $[\alpha]_D$ +4 (*c* 1.3, CH_2Cl_2)}; $[\alpha]^{22}_D$ +8.4 (*c* 2.0, EtOH) {lit.[11] $[\alpha]^{23}_D$ +8.3 (*c* 0.7, EtOH)}; IR (film) ν_{max} 3301 (br, OH), 2914, 2849, 1470, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.20−1.62 (m, 20H), 2.12 (dd, *J* = 4.6, 7.5 Hz, 1H), 3.01−3.06 (ddd, *J* = 6.7, 5.5, 4.4 Hz, 1H), 3.16 (ddd, *J* = 3.9, 4.4, 7.0 Hz, 1H), 3.67 (ddd, *J* = 4.6, 7.0, 11.9 Hz, 1H), 3.86 (ddd, *J* = 3.9, 7.5, 11.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 26.6, 27.9, 29.3, 29.4, 29.48, 29.5, 29.58, 29.59, 31.9, 56.9, 57.3, 60.9 ppm; MS (ESI) *m*/*z* 251.2 ($M + Na^+$, 100%). Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.66; H, 12.36. The enantiomeric excess (ee) of epoxide (2*S*,3*R*)-**12** was determined by HPLC analysis of the

(17) For copper-mediated coupling of 1-alkynes and propargylic halides, see: Caruso, T.; Spinella, A. *Tetrahedron* **2003**, *59*, 7787–7790. and references cited therein.

(18) This reagent is efficient for the debromination of α-bromo ketones: Takaya, H.; Makino, S.; Hayakawa, Y.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1765–1777.

(19) Soulié, J.; Boyer, T.; Lallemand, J. Y. *Tetrahedron: Asymmetry* **1995**, *6*, 625–636.

corresponding 3,5-dinitrobenzoyl ester (column, Chiralpak AD-H 4.6 × 250 mm; *n*-hexane/ethanol = 60:40; flow rate, 1.0 mL/min) t_R (min): the product before recrystallization, (2*R*,3*S*)-ester: 19.9 (5.4%), (2*S*,3*R*)-ester: 24.2 (94.6%), ee 89.0%; the product after one recrystallization, (2*R*,3*S*)-ester: 19.9 (0.2%), (2*S*,3*R*)-ester: 24.0 (99.8%), ee 99.5%.

(2*S*,3*R*)-2,3-Epoxytetradecyl Trifluoroacetate (8). To a vigorously stirred suspension of epoxide **12** (502 mg, 2.2 mmol) in anhydrous CH_2Cl_2 (146 mL) were added dropwise triethylamine (1.1 mL, 7.9 mmol) and trifluoromethanesulfonic anhydride (1.1 mL, 6.6 mmol) under argon atmosphere at −78 °C. The suspension was allowed to warm slowly to about −35 °C and stirred. Once the solution became clear, the reaction was recooled to −78 °C and stirred for 30 min, then quenched with an aqueous NH_4Cl solution (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (R_f 0.33, eluent: ethyl acetate:petroleum ether = 1:40) to afford crude triflate **8** (775 mg, 98%) as a colorless oil, which was used in the subsequent step without further purification.

(9*S*,10*R*)-9,10-Epoxyhenicosan-3,6-diyn-1-ol (7). Method 1: A solution of *n*-BuLi (1.6 M in hexane, 5.1 mL, 8.2 mmol) was added slowly to a solution of freshly prepared 3,6-heptadiyn-1-ol (**17**, 444 mg, 4.1 mmol) in anhydrous diethyl ether (60 mL) at −78 °C under argon. After stirring for 30 min at the same temperature, a solution of (2*S*,3*R*)-**8** (755 mg, 2.1 mmol) in anhydrous diethyl ether (5 mL) and anhydrous HMPA (1.4 mL) were added. After stirring for 60 min at −78 °C, the reaction was quenched with a saturated aqueous NH_4Cl solution. The aqueous layer was extracted with diethyl ether (3 × 30 mL). 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, eluent: ethyl acetate:petroleum ether = 1:4) to give (9*S*,10*R*)-**7** (567 mg, 85%) as a white solid. Mp 72−73 °C (ethyl acetate/*n*-hexane) (lit.[9b] mp 48−50 °C); $[\alpha]^{28}_D$ +32.5 (*c* 1.0, $CHCl_3$) {lit.[9b] $[\alpha]^{25}_D$ +23.5 (*c* 1, $CHCl_3$)}; IR (film) ν_{max} 3311 (br, OH), 2954, 2916, 2849, 2285 (w, C≡C), 1470, 1318, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.20−1.55 (m, 20H), 1.72 (t, J = 6.3 Hz, 1H), 2.28 (ddt, J = 17.0, 7.0, 2.4 Hz, 1H), 2.45 (tt, J = 6.2, 2.4 Hz, 2H), 2.55 (ddt, J = 17.0, 5.7, 2.4 Hz, 1H), 2.96 (dt, J = 4.2, 5.9 Hz, 1H), 3.12 (ddd, J = 4.2, 5.7, 7.0 Hz, 1H), 3.16 (ddt, J = 2.4, 2.4, 2.4 Hz, 2H), 3.71 (dt, J = 6.3, 6.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.8, 14.1, 18.7, 22.6, 23.0, 26.4, 27.5, 29.3, 29.4, 29.5 (2C), 29.59, 29.6, 31.9, 55.0, 57.1, 61.0, 75.7, 76.22, 76.23, 77.1 ppm; MS (ESI) m/z 341.3 ($M + Na^+$, 100%), 357.3 ($M + K^+$, 70%). Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.95; H, 11.03.

(9*S*,10*R*)-9,10-Epoxy-(3*Z*,6*Z*)-henicosa-1,3,6-triene (5). To a solution of (9*S*,10*R*)-**6** (66 mg, 0.17 mmol) in 2 mL of anhydrous methanol was added anhydrous K_2CO_3 (70 mg) with stirring at room temperature. After 48 h, the reaction mixture was filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (R_f 0.35, eluent: ethyl acetate:petroleum ether = 1:50) to give (9*S*,10*R*)-**5** (44 mg, 82%) as a colorless oil. $[\alpha]^{28}_D$ −0.9 (*c* 1.9, $CHCl_3$) {lit.[8g] $[\alpha]^{21}_D$ −0.38 (*c* 1.04, $CHCl_3$); lit.[9b] $[\alpha]^{25}_D$ −0.6 (*c* 3.0, $CHCl_3$)}; IR (film) ν_{max} 3014, 2924, 2854, 1635 (w, C=C), 1466, 1080, 1051, 1035, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.20−1.57 (m, 20H), 2.24 (dt, J = 14.5, 6.4 Hz, 1H), 2.40 (dt, J = 14.5, 6.4 Hz, 1H), 2.90−3.00 (m, 4H), 5.13 (d, J = 10.1 Hz, 1H), 5.22 (d, J = 16.8 Hz, 1H), 5.41 (dt, J = 10.4, 8.0 Hz, 1H), 5.45−5.58 (m, 2H), 6.03 (dd, J = 10.8, 10.4 Hz, 1H), 6.65 (ddd, J = 16.8, 10.8, 10.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 26.25, 26.28, 26.6, 27.8, 29.3, 29.55, 29.63, 31.9, 56.3, 57.2, 117.7, 124.9, 129.5, 129.83, 129.88, 131.8 ppm; MS (ESI) m/z 327.2 ($M + Na^+$, 100%). Anal. Calcd for $C_{21}H_{36}O$: C, 82.83; H, 11.92. Found: C, 82.94; H, 11.63.

(9*S*,10*R*)-9,10-Epoxy-(3*Z*,6*Z*)-henicosa-3,6-diene (1). To a stirring aqueous solution (20 mL) of $CuSO_4$ (400 mg) was added Zn dust (3.0 g). The resulting couple was allowed to settle, the supernatant was decanted, and the residue was washed successively with water and MeOH. The couple was suspended in NH_4Cl saturated MeOH (15 mL), and (9*S*,10*R*)-**6** (77 mg, 0.20 mmol) was added. The mixture was refluxed with stirring for 40 min. The mixture was filtered through Celite, and the filter cake was washed with diethyl ether. The combined filtrates were concentrated, washed with water (5 mL), and extracted with diethyl ether (3 × 5 mL). 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 0.35, eluent: ethyl acetate:petroleum ether = 1:50) to give (9*S*,10*R*)-epoxide **1** (55 mg, 90%) as a colorless oil. $[\alpha]^{28}_D$ +3.9 (*c* 1.8, CCl_4) {lit.[8g] $[\alpha]^{22}_D$ +3.99 (*c* 1.65, CCl_4)}; IR (film) ν_{max} 3012, 2960, 2925, 2854, 1648 (w, C=C), 1463, 1381, 1069, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H), 1.20−1.60 (m, 20H), 2.08 (quint, J = 7.4 Hz, 2H), 2.22 (dt, J = 15.1, 6.4 Hz, 1H), 2.40 (dt, J = 15.1, 6.4 Hz, 1H), 2.81 (t, J = 7.0 Hz, 2H), 2.90−2.97 (m, 2H), 5.26−5.56 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.2, 20.5, 22.7, 25.7, 26.2, 26.6, 27.8, 29.3, 29.5, 29.6, 29.61, 31.9, 56.4, 57.2, 124.2, 126.7, 130.7, 132.2 ppm; MS (ESI) m/z 329.2 ($M + Na^+$, 100%). Anal. Calcd for $C_{21}H_{38}O$: C, 82.28; H, 12.50. Found: C, 82.52; H, 12.33.

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Supporting Information Available: Experimental procedures, characterization for all new compounds, and copies of ^1H, ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.