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AN EFFICIENT SYNTHESIS OF NATURAL TRIBOLURE

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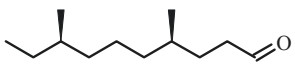
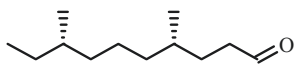
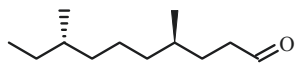
An efficient synthesis of natural tribolure has been achieved through an asymmetric methylation as a key step. Natural tribolure is a mixture of four stereoisomers, so racemic 2-methylbutan-1-ol was used as starting material. After a C5+C4 strategy and then a mixed Evan′s template inductive methylation, the key intermediate was obtained. Finally, the natural product tribolure (4:4:1:1 of stereoisomers, respectively) was obtained in 10 linear steps and in 34.2% overall yield.

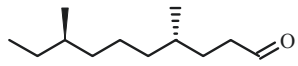
Keywords: aggregation pheromone, synthesis, Evan′s template, asymmetric alkylation.

Pheromones have been used for monitoring populations of pest insects or in pest control. As a matter of fact, more and more insect lures are in demand for "green agriculture." In the storage pantry, there two kinds of notorious flour beetles *Tribolium castanesum* and *Tribolium confusum*, which eat small fragments of cereal seeds and products thereof. In modern global times, the beetles may be spread by transportation all over the world. They secrete aggregation pheromones [1–3] to seduce both male and female insects, and the biological function might be a signal to share edible materials. Therefore, they may cause great waste of foodstuff during grain storage if big area explosion. Actually, this pheromone is secreted by several related kinds of flour beetles. The characteristics of natural tribolure are most interesting. The isomers are not enantiopure stereoisomers, and the ratio of the four stereoisomers (4*R*,8*R*)-**1**/(4*R*,8*S*)-**1**/(4*S*,8*R*)-**1**/(4*S*,8*S*)-**1** is 4/4/1/1 [4–10]. Comparing with other single stereoisomers, this mixture showed the strongest alluring activity. In 1987, Suzuki attributed a tribolure to 4,8-dimethyldecanal (**1**) which was discovered in another insect, *Tribolium freemanti* [11].


(4*R*,8*R*)-**1**, 40%


(4*S*,8*S*)-**1**, 10%


(4*R*,8*S*)-**1**, 40%


(4*S*,8*R*)-**1**, 10%

The pheromone synthesis has its difficulties in synthetic methodology. Most pheromones having one or more chiral carbon centers do not bear aromatic moieties, so it is not easy to detect it in synthesis. Even so, there have been a few reports on the synthesis of **1**, including stereospecific and racemic synthesis [12]. Suzuki reported the first synthesis and developed his synthesis after he discovered the pheromone [4]. Afterwards, the first asymmetric synthesis of all four stereoisomers of **1** was achieved in 1983 by the distinguished Japanese insect pheromone expert, Mori [13]. More syntheses on the asymmetric synthesis of 4,8-dimethyldecanal **1** [14–20] may be found in the literature. Most of the approaches use chiral starting materials or deracemization using an enzyme. There were some drawbacks to these methods. Extra steps are needed to utilize the chiral center of chiral natural products such as citronellal or limonene. On the other hand, deracemization of a bifunctional moiety will require more functional groups interconversions (FGIs). Moreover, in 2011, Mori disclosed the detailed composition of natural tribolure; therefore, a practical, easy-to-handle synthesis of natural tribolure is highly needed. As a continuation of our many years of endeavoring to synthesize agrochemicals [21], herein we wish to report a practical synthesis of natural tribolure.

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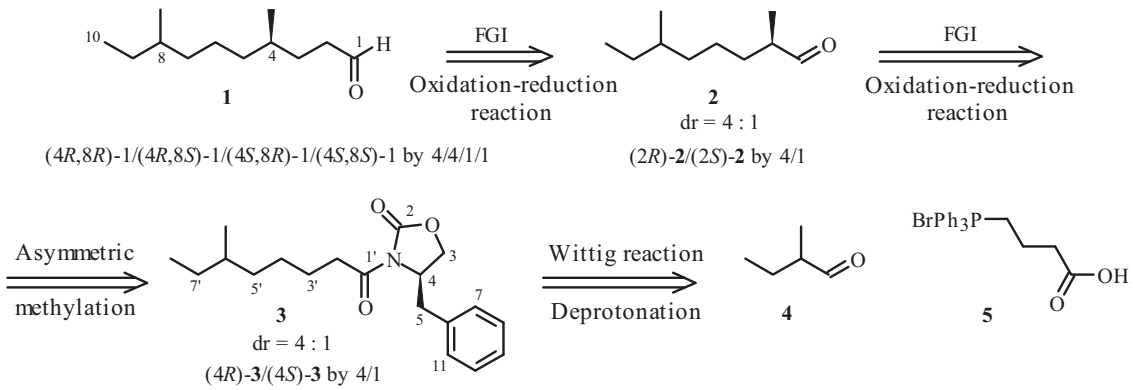
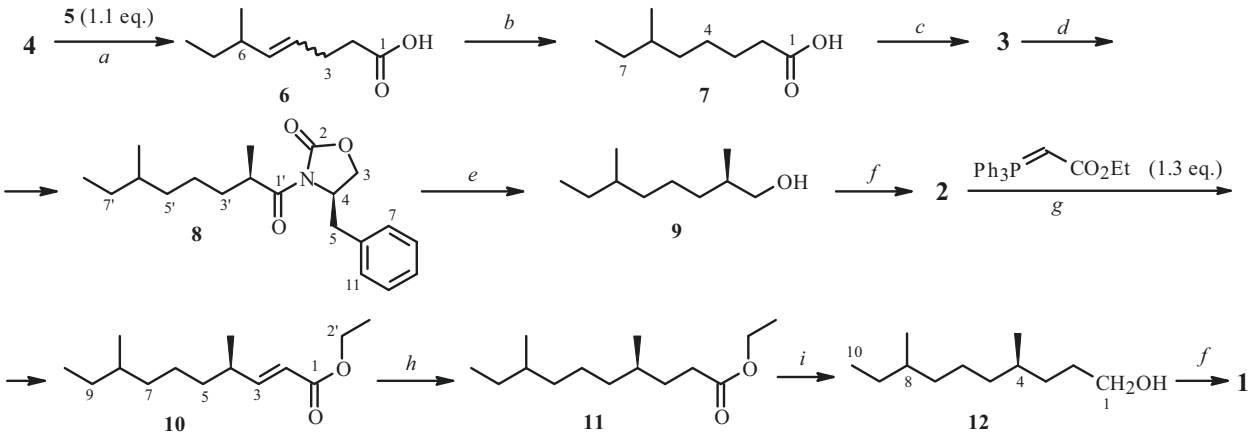


Scheme 1. The retrosynthesis of **1**.

The retro-synthesis is shown in Scheme 1. The molecule could be assembled through a linear C5+C4+C2 strategy. The carbon skeleton could be constructed through a Wittig reaction between **4** and **5** and then an asymmetric alkylation. Based on our previous papers [22–25], the asymmetric alkylation is highly effective, so, in order to obtain the dr = 4:1 mixture, a mixture of (*R*) and (*S*) 4-benzyl-2-oxazolidinone as chiral auxiliary (4/1) was used.

As planned, the synthesis commenced with 2-methylbutanal (**4**). The carbon chain was extended by a Wittig reaction effected with commercially available 4-(bromotriphenyl-λ^5-phosphanyl)butanoic acid (**5**), which gave compound **6** in 85% yield. From the NMR, the *E*/*Z* ratio is easily revealed in **1** (*E*)–**8** (*Z*). Then, the double bond was reduced by catalytic hydrogenation in 95% yield. After the acid **7** was produced, it was reacted with (*R*)-4-benzyl-2-oxazolidinone–(*S*)-4-benzyl-2-oxazolidinone (4:1) to afford compound **3**. Through chiral HPLC, the four stereoisomers could be observed in the peak areas in the ratio 1:1:4:4. Using 2.2 equivalents of Na-HMDS to deprotonate compound **3**, at –78 to –50°C, the corresponding methylated **8** could be obtained in 85% yield with the dr ratio = 4:1 (detected by HPLC). According to literature reports and our experience, the inducting effect should be reliable. After chiral HPLC analysis, the dr was confirmed to be 4:1 (see supporting information). Then the chiral auxiliary was removed by reduction and compound **9** was obtained in 95% yield. Compound **9** was subjected to pyridinium chlorochromate (PCC) oxidation to afford **2** in 90% yield. After another Wittig reaction between **2** and (carbethoxymethylene)-triphenylphosphorane in refluxing THF, compound **10** was obtained in 85% yield. This compound had the *trans*-configuration. As previous papers have pinpointed [21–22], 5% Pt/C was employed to remove the carbon-carbon double bond while preventing racemization, and compound **11** was obtained in 99% yield. Thus, the chain skeleton was completely constructed. After reduction, compound **12** was obtained in 92% yield, and after subsequent oxidization, natural tribolure **1** was obtained in 90% yield (Scheme 2).



a. Li-HMDS, (2.2 eq.), THF, –78°C – r.t., 12 h, 85%; *b*. 10% Pd/C, H_2, EtOAc, r.t., 24 h, 96%; *c*. Et_3N (2.4 eq.), PVCl (1.2 eq.), LiCl (3.0 eq.), Evan's oxazolidinone mixed *R*/*S* (1.0 eq.), THF, –78°C – r.t., 12 h, 92%; *d*. Na-HMDS (2.0 eq.), MeI (5.0 eq.), THF, –78°C – –50°C, 12 h, 85%; *e*. $LiAlH_4$ (4.0 eq.), THF, 0°C–r.t., 12 h, 95%; *f*. PCC (1.3 eq.), DCM, 0°C – r.t., 10 h, 90 %; *g*. THF, reflux, 10 h, 85%; *h*. 5% Pt/C, H_2, EtOAc, r.t., 24 h, 99%; *i*. $LiAlH_4$ (1.2 eq.), THF, 0°C – r.t., 12 h, 92%

Scheme 2. The synthesis of natural tribolure.

Based on a chiral Evan′s template induction strategy, an efficient way to synthesize natural tribolure, the aggregation pheromone of several notorious flour beetles has been achieved with an overall yield of 34.2%.

EXPERIMENTAL

General Methods. Tetrahydrofuran (THF) was dried by sodium and distilled before use. Dichloromethane was dried by calcium hydride (CaH_2) and distilled before use. The reactions were monitored by thin-layer chromatography (TLC) on glass plates coated with silica gel containing a fluorescent indicator. Flash chromatography was performed on silica gel (200–300 mesh) with ethyl acetate–petroleum ether (EtOAc/PE) as eluent. NMR spectra were recorded on an AC-500 MHz instrument (Bruker, Madison, WI, USA). Chemical shifts were reported in δ (ppm) and referenced to an internal TMS standard for ^{1}H NMR and $CDCl_3$ (77.16 ppm) for ^{13}C NMR. HR-MS spectra were measured on a LCMS-IT-TOF or LTQ-Orbitrap-XL apparatus. Optical rotations were measured on a polarimeter with a sodium lamp.

(4*R*)-4,8-Dimethyldecanal (1). To a solution of **12** (1.1 g, 6.2 mmol) in methylene chloride (40 mL) was added silica gel (100–200 mesh, 1.9 g) and PCC (1.9 g, 9.1 mmol). The reaction system was stirred for 12 h at 0°C. The mixture was filtered through a pad of Celite and concentrated. The crude product was purified by chromatography on silica gel (EtOAc–PE, 1:30) to give natural tribolure **1** as a colorless oil (904.0 mg, 82% yield); $[\alpha]_D^{25}$+1.01° (*c* 3.7, $CHCl_3$). ^{1}H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 9.81 (1H, t, J = 1.8, 1-CHO), 2.65–2.33 (2H, m, H-2), 1.72–1.67 (1H, m, H-4), 1.56–1.42 (2H, m, H-3), 1.42–1.40 (1H, m, H-8), 1.40–1.34 (2H, m, H-9), 1.34–1.03 (6H, m, H-5, 6, 7), 0.96–0.84 (9H, m, CH_3-4, 8, 9). ^{13}C NMR spectrum (126 MHz, $CDCl_3$, δ, ppm): 202.97, 41.73, 41.72, 37.05, 37.01, 36.86, 36.82, 34.41, 32.44, 32.42, 29.54, 29.44, 28.99, 28.91, 24.39, 19.38, 19.33, 19.23, 19.17, 11.39, 11.37. HR-MS-ESI *m/z* 185.1896 $[M + H]^+$ (calcd for $C_{12}H_{25}O$, 185.1900).

(2*R*)-2,6-Dimethyloctanal (2). To a solution of **9** (1.7 g, 10.5 mmol) in methylene chloride (40 mL) was added silica gel (100–200 mesh, 4.6 g) and PCC (4.6 g, 21.0 mmol) at 0°C. The reaction system was stirred for another 12 h. The mixture was filtered through a pad of Celite and concentrated. The crude product was purified by chromatography on silica gel (EtOAc–PE, 1:20) to give **2** as a colorless oil (1.5 g, 90% yield), $[\alpha]_D^{25}$ –15.06° (*c* 2.1, $CHCl_3$). ^{1}H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 9.64 (1H, d, J = 2.0, 1-CHO), 2.44–2.28 (1H, m, H-2), 1.81–1.59 (1H, m, H-6), 1.50–1.24 (6H, m, H-3, 4, 7), 1.24–1.19 (2H, m, H-5), 1.09–1.03 (3H, m, CH_3-2), 0.88 (6H, dd, J = 8.2, 6.7, CH_3-6, 7). ^{13}C NMR spectrum (126 MHz, $CDCl_3$, δ, ppm): 183.07, 39.39, 39.36, 36.43, 36.42, 34.25, 33.88, 33.83, 29.46, 29.44, 24.66, 24.63, 19.14, 16.88, 16.79, 11.37, 11.35. HR-MS-ESI *m/z* 157.1578$[M + H]^+$ (calcd for $C_{10}H_{21}O$, 157.158).

(4*R*)-4-Benzyl-3-(6-methyloctanoyl)oxazolidin-2-one (3). Under argon atmosphere, **7** (2.0 g, 12.6 mmol) was dissolved in anhydrous THF (50 mL) and the solution was cooled to –40°C. Then Et_3N (3.5 mL, 25.3 mmol) was added into the above reaction system, followed by pivaloyl chloride (PVCl) (1.9 mL, 15.2 mmol). After stirring for 10 min at –40°C, the reaction mixture was warmed to room temperature and stirred for 45 min. Then solid LiCl (1.6 g, 37.9 mmol) was added at room temperature. After 10 min, the mixture was cooled to –78°C, the anhydrous THF solution of (*R*)-4-benzyl-2-oxazolidinone (1.76 g, 10.08 mmol) and (*S*)-4-benzyl-2-oxazolidinone (0.44 g, 2.52 mmol) was added dropwise in 10 min, and the resulting mixture was slowly warmed to room temperature and stirred overnight. Then the reaction was quenched with H_2O, extracted with EtOAc (50 mL × 3), washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by chromatography on silica gel (EtOAc–PE, 1:5) to give compound **3** as a colorless oil (3.7 g, 92% yield); $[\alpha]_D^{25}$ –27.66° (*c* 2.6, $CHCl_3$). ^{1}H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 7.38 (2H, t, J = 7.3, H-8, 10), 7.31 (1H, dd, J = 9.5, 4.9, H-9), 7.25 (2H, d, J = 7.1, H-7, 11), 4.74–4.70 (1H, m, H-4), 4.25–4.20 (2H, m, H-3), 3.34 (1H, dd, J = 13.4, 3.2, H-5), 3.11–2.88 (2H, m, H-2′), 2.81 (1H, dd, J = 13.4, 9.6, H-5), 1.82–1.60 (2H, m, H-3′), 1.57–1.27 (4H, m, H-4′, 7′), 1.27–1.25 (1H, m, H-6′), 1.19–1.14 (2H, m, H-5′), 0.94–0.82 (6H, m, CH_3-6′, 7′). ^{13}C NMR spectrum (126 MHz, $CDCl_3$, δ, ppm): 173.47, 153.48, 135.38, 129.45, 128.97, 127.36, 66.17, 55.18, 37.99, 36.34, 35.61, 34.29, 29.48, 27.05, 26.68, 26.54, 24.65, 19.17, 11.40. HR-MS-ESI *m/z* 318.2065 $[M + H]^+$ (calcd for $C_{19}H_{28}NO_3$, 318.2064).

(*Z*/*E*)-6-Methyloct-4-enoic Acid (6). Under argon atmosphere, the solution of **5** (54.8 g, 0.127 mol) in anhydrous THF (100 mL) was cooled to –78°C and Li-HMDS (1.0 M in THF, 238 mL, 0.238 mol) was added into the above reaction system. The reaction was warmed to room temperature and stirred for another 60 min. The mixture was cooled to 0°C and the anhydrous THF solution of **4** (10.0 g, 0.116 mol) was added dropwise in 45 min. The reaction system was slowly warmed to rt and stirred for 15 h. When the aldehyde **4** was consumed, the mixture was cooled to 0°C and quenched with H_2O (500 mL). Then the solution was adjusted to pH 12, then extracted with CH_2Cl_2 (150 mL × 3). The water phase solution was cooled to 0°C and adjusted to pH 2, then extracted with EtOAc (150 mL × 3), washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by chromatography on silica gel (EtOAc–PE, 1:5) to give **6** as a pale-yellow

oil (15.0 g, 83%, a mixture of *Z*/*E*, 8:1, four carbons on olefins (137.99, 137.92, 125.88, 125.66) determined from ^{13}C NMR and peak area of ^{1}H NMR in supporting information). ^{1}H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 11.74 (1H, br.s, COOH-1), 5.29 (2H, t, J = 7.4, H-4, 5), 2.52–2.34 (4H, m, H-2, 3), 2.34–2.24 (1H, m, H-6), 1.41–1.10 (2H, m, H-7), 0.95–0.81 (6H, m, CH_3-6, 7). ^{13}C NMR spectrum (126 MHz, $CDCl_3$, δ, ppm): 179.94, 137.99, 137.92, 125.88, 125.66, 38.32, 34.44, 34.36, 33.47, 30.14, 29.70, 27.66, 22.82, 20.92, 20.24, 11.89, 11.65. HR-MS-ESI *m/z* 157.1223 $[M + H]^+$ (calcd for $C_9H_{17}O_2$, 157.1223).

6-Methyloctanoic Acid (7). Under hydrogen atmosphere, 10% catalyst Pd/C (1.5 g) was added into the EtOAc solution of **6** (15.0 g, 96.2 mmol) and the whole stirred at room temperature for 20 h. When the reaction was completed, the mixture was filtered through a pad of Celite and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc–PE, 1:10) to give **7** as a colorless oil (14.8 g, 97% yield). ^{1}H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 11.50 (1H, br.s, COOH-1), 2.35 (2H, t, J = 7.4, H-2), 1.65–1.56 (2H, m, H-3, 7), 1.34–1.30 (3H, m, H-3, 6, 7), 1.30–1.29 (2H, m, H-4), 1.18–1.07 (2H, m, H-5), 0.91–0.85 (6H, m, CH_3-6, 7). ^{13}C NMR spectrum (126 MHz, $CDCl_3$, δ, ppm): 180.94, 36.51, 34.57, 34.53, 29.77, 26.91, 25.34, 19.46, 11.68. HR-MS-ESI *m/z* 157.1382 $[M + H]^+$ (calcd for $C_9H_{19}O_2$, 159.1380).

(4*R*)-4-Benzyl-3-((2*R*)-2,6-dimethyloctanoyl)oxazolidin-2-one (8). Under argon atmosphere, the solution of **3** (4.0 g, 12.6 mmol) in anhydrous THF (100 mL) was cooled to –78°C and Na-HMDS (2.0 M in THF, 15.8 mL, 31.5 mmol) was added into the above reaction system. The reaction was stirred for another 30 min, methyl iodide (MeI) (3.9 mL, 63.0 mmol) was added dropwise, and the resulting mixture was stirred for another 1 h at –78°C. The reaction system was slowly warmed to –50°C and stirred for 15 h. When **3** was consumed, the mixture was cooled to –78°C and quenched with saturated NH_4Cl aqueous solution, extracted with EtOAc (50 mL × 3), washed with brine (60 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by chromatography on silica gel (EtOAc–PE, 1:5) to give compound **8** as a pale-yellow oil (3.6 g, 86% yield); $[\alpha]_D^{25}$–39.97° (*c* 2.4, $CHCl_3$). ^{1}H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 7.39–7.25 (5H, m, H-7–11), 4.68–4.64 (1H, m, H-4), 4.27–4.11 (2H, m, H-3), 3.71 (1H, d, J = 6.8, H-5), 3.27 (1H, d, J = 6.8, H-5), 2.77 (1H, dd, J = 13.4, 9.6, H-2′), 1.78–1.70 (1H, m, H-6′), 1.42–1.20 (8H, m, H-3′–5′, 7′), 1.19–1.11 (3H, m, CH_3-2′), 0.90–0.80 (6H, m, CH_3-6′, 7′). ^{13}C NMR spectrum (126 MHz, $CDCl_3$, δ, ppm): 177.26, 152.96, 135.26, 129.34, 128.82, 127.22, 65.90, 55.26, 37.83, 37.64, 37.63, 36.43, 36.41, 34.14, 33.63, 33.60, 29.33, 29.31, 24.63, 24.61, 19.03, 17.29, 17.21, 11.27, 11.24. HR-MS-ESI *m/z* 332.2222 $[M + H]^+$ (calcd for $C_{20}H_{30}NO_3$, 332.2220).

(2*R*)-2,6-Dimethyloctan-1-ol (9). Under argon atmosphere, an anhydrous THF (70 mL) solution of $LiAlH_4$ (1.5 g, 38.6 mmol) was cooled to 0°C. Then the solution of **8** (3.2 g, 9.7 mmol) in anhydrous THF (30 mL) was added portionwise to the above reaction system. The resulting mixture was allowed to warm slowly to room temperature and stirred overnight. After the starting material was consumed, the reaction was quenched with saturated $NaHCO_3$ aqueous solution, dried over anhydrous $MgSO_4$, and filtered under reduced pressure. The filtrate was evaporated, and the residue was purified by chromatography on silica gel (EtOAc–PE, 1:3) to afford **9** as a colorless oil (1.4 g, 89% yield); $[\alpha]_D^{25}$ +7.0° (*c* 1.9, $CHCl_3$). ^{1}H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm): 4.20 (1H, br.s, 1-OH), 3.57–3.54 (1H, m, H-1), 3.47–3.43 (1H, m, H-1), 1.68–1.62 (1H, m, H-2), 1.53–1.51 (1H, m, H-6), 1.51–1.24 (6H, m, H-3, 4, 7), 1.22–1.05 (2H, m, H-5), 0.99–0.83 (9H, m, CH_3-2, 6, 7). ^{13}C NMR spectrum (126 MHz, $CDCl_3$, δ, ppm): 68.49, 68.43, 36.91, 36.87, 35.83, 35.81, 34.40, 34.39, 33.52, 33.47, 29.57, 29.45, 24.45, 24.42, 19.25, 19.18, 16.65, 16.57, 11.42, 11.39. HR-MS-ESI *m/z* 159.1743 $[M + H]^+$ (calcd for $C_{10}H_{23}O$, 159.1743).

4,8-(4*R*,2*E*)-Ethyl 4,8-Dimethyldec-2-enoate (10). Under argon atmosphere, an anhydrous THF (40 mL) solution of ethyl-(triphenylphosphoranylidene)acetate (4.4 g, 12.5 mmol) was cooled to 0°C. Then the solution of **2** (1.5 g, 9.6 mmol) in anhydrous THF (30 mL) was added portionwise to the above reaction system. The resulting mixture was heated to reflux for 14 h. After cooling to room temperature, the reaction mixture was quenched with aqueous NH_4Cl, extracted with EtOAc, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by chromatography on silica gel (EtOAc–PE, 1:30) to give **10** as a colorless oil (1.7 g, 76% yield); $[\alpha]_D^{25}$ –19.92° (*c* 3.2, $CHCl_3$). ^{1}H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 6.91 (1H, ddd, J = 15.7, 7.9, 2.1, H-3), 5.81 (1H, dd, J = 15.7, 0.9, H-2), 4.23 (2H, q, J = 7.1, H-2′), 2.42–2.22 (1H, m, H-3), 1.56–1.49 (2H, m, H-9), 1.49–1.46 (1H, m, H-8), 1.46–1.23 (6H, m, H-5, 6, 7), 1.23–1.06 (6H, m, CH_3-4, 2′), 0.94–0.79 (6H, m, CH_3-8, 9). ^{13}C NMR spectrum (126 MHz, $CDCl_3$, δ, ppm): 167.01, 154.79, 154.76, 119.57, 119.54, 60.15, 36.61, 36.57, 36.54, 36.38, 36.36, 34.34, 29.50, 29.46, 24.69, 24.67, 19.45, 19.37, 19.20, 14.30, 11.40, 11.37. HR-MS-ESI *m/z* 227.2003 $[M + H]^+$ (calcd for $C_{14}H_{27}O_2$, 227.2006).

(4*R*)-Ethyl 4,8-Dimethyldecanoate (11). Under hydrogen atmosphere, 5% catalyst Pt/C (75.0 mg) was added into the EtOAc solution of **10** (1.5 g, 7.3 mmol) and the whole stirred at room temperature for 24 h. When the reaction was completed, the mixture was filtered through a pad of Celite and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc–PE, 1:10) to give **11** as a colorless oil (1.5 g, 91% yield); $[\alpha]_D^{25}$ +0.46° (*c* 2.3, $CHCl_3$). ^{1}H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 4.16 (2H, q, J = 7.1, H-2′), 2.39–2.28 (2H, m, H-2), 1.77–1.61 (1H, m, H-4), 1.51–1.42 (2H, m, H-3), 1.42–1.40 (1H, m, H-8), 1.40–1.22 (8H, m, H-5, 6, 7, 9), 1.21–1.04 (3H, m, CH_3-2′), 0.98–0.82

(9H, m, CH_3-4, 8, 9). ^{13}C NMR spectrum (126 MHz, $CDCl_3$, δ, ppm): 174.16, 60.16, 37.04, 37.00, 36.89, 36.85, 34.41, 32.47, 32.45, 32.20, 32.03, 31.94, 29.56, 29.46, 24.38, 19.27, 19.24, 19.19, 14.25, 11.40, 11.38. HR-MS-ESI *m/z* 229.2163 $[M + H]^+$ (calcd for $C_{14}H_{29}O_2$, 229.2162).

(4*R*)-4,8-Dimethyldecan-1-ol (12). Under argon atmosphere, an anhydrous THF (40 mL) solution of $LiAlH_4$ (374.0 mg, 9.9 mmol) was cooled to 0°C. Then the solution of **11** (1.5 g, 6.6 mmol) in anhydrous THF (10 mL) was added portionwise to the above reaction system. The resulting mixture was allowed to warm slowly to room temperature and stirred overnight. After the starting material was consumed, the reaction was quenched with saturated $NaHCO_3$ aqueous solution, dried over anhydrous $MgSO_4$, and filtered under reduced pressure. The filtrate was evaporated, and the residue was purified by chromatography on silica gel (EtOAc–PE, 1:5) to afford **12** as a colorless oil (1.2 g, 94% yield); $[\alpha]_D^{25}$ +1.92° (*c* 1.7, $CHCl_3$). ^1H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 4.17 (1H, br.s, 1-OH), 3.67 (2H, t, J = 6.7, H-1), 1.68–1.53 (2H, m, H-9), 1.55–1.52 (1H, m, H-4), 1.52–1.42 (2H, m, H-2), 1.42–1.40 (1H, m, H-8), 1.40–1.26 (4H, m, H-3, 6), 1.26–1.00 (4H, m, H-5, 7), 0.94–0.80 (9H, m, CH_3-4, 8, 9). ^{13}C NMR spectrum (126 MHz, $CDCl_3$, δ, ppm): 63.48, 37.36, 37.32, 36.97, 36.93, 34.43, 33.03, 32.95, 32.69, 32.66, 30.40, 30.39, 29.57, 29.48, 24.47, 19.68, 19.62, 19.27, 19.21, 11.42, 11.40. HR-MS-ESI *m/z* 373.4039 $[2M + H]^+$ (calcd for $C_{24}H_{53}O_2$, 373.4040).

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