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Synthesis and absolute configuration of the male aggregation pheromone of the stink bug *Erysarcoris lewisi* (Distant), (2*Z*,6*R*,1′*S*,5′*S*)-2-methyl-6-(4′-methylenebicyclo[3.1.0]hexyl)hept-2-en-1-ol ☆

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ABSTRACT

The structure including the absolute configuration of the male-produced aggregation pheromone of the stink bug *Erysarcoris lewisi* (Distant) was determined to be (2*Z*,6*R*,1′*S*,5′*S*)-2-methyl-6-(4′-methylenebicyclo[3.1.0]hexyl)hept-2-en-1-ol **1** by bioassay and comparison of the ^{1}H NMR spectrum of the natural pheromone with those of (2*Z*,6*R*,1′*S*,5′*S*)- and (2*Z*,6*R*,1′*R*,5′*R*)-isomers. These two diastereomers were synthesized from the corresponding ketones (6*R*,1′*S*,5′*R*)- and (6*R*,1′*R*,5′*S*)-**2**, which were prepared by lipase-catalyzed asymmetric acetylation of a mixture of (6*R*,1′*S*,4′*S*,5′*R*)- and (6*R*,1′*R*,4′*R*,5′*S*)-7′-norsesquisabinen-4′-ol **3**. The absolute configuration of ketone **2** was assigned by its CD comparison with (1*R*,5*S*)-sabina ketone **4**. An alternative synthesis of (2*Z*,6*R*,1′*S*,5′*S*)-**1** was achieved without recourse to enzyme by employing Hodgson's diastereoselective intramolecular cyclopropanation as the key step.

1. Introduction

In continuation of our ongoing project to study the significance of chirality in pheromone science,[2] we became interested in determining the absolute configuration of a new pheromone **1** (Scheme 1) with a bicyclo[3.1.0]hexane ring by synthesizing the pheromone itself.[3]

Pecky rice (rice grain damaged by insects) is a serious economic problem in Japanese rice production.[4] A stink bug, *Erysarcoris lewisi* (Distant) is known as one of the major species of rice bugs that causes pecky rice in northern Japan.[5] It usually lives in meadows and fields, and comes to the rice paddy fields and attacks rice plants at the time of their grain formation. The possibility of using its pheromone for the purpose of monitoring its population was examined by Takita et al.[6,7] Takita then proposed the structure of the male-produced aggregation pheromone of *E. lewisi* as (*E*)-2-methyl-6-(4′-methylenebicyclo[3.1.0]hexyl)hept-2-en-1-ol **1** [(*E*)-sesquisabinen-1-ol, Scheme 1].[8] Isolation and characterization of the pheromone have recently been reported in detail.[9] A crude extract containing 60,200 male equivalents (a male equivalent = volatiles obtained from a single male within a day) was used for the characterization.[9] However, Mori's synthetic work in 2007, in which citronellal was employed as the starting material, revealed the male pheromone of *E. lewisi* to be (2*Z*,6*R*)-2-methyl-6-(4′-methylenebicyclo[3.1.0]hexyl)hept-2-en-1-ol **1**.[10]

Herein we report in detail the determination of the absolute configuration of the natural pheromone as (2*Z*,6*R*,1′*S*,5′*S*)-**1**, which has been published as a preliminary communication.[3] The key to this result was reduction, followed by lipase-catalyzed asymmetric acetylation, of a diastereomeric mixture of sesquisabina ketone (6*R*,1′*RS*,5′*SR*)-**2**. Reduction of the ketone (6*R*,1′*RS*,5′*SR*)-**2** gave a mixture of alcohols (6*R*,1′*S*,4′*S*,5′*R*)-**3** and (6*R*,1′*R*,4′*R*,5′*S*)-**3**, the former of which remains intact after enzymatic acetylation while the latter is acetylated. Oxidation of (6*R*,1′*S*,4′*S*,5′*R*)-**3** gave sesquisabina ketone (6*R*,1′*S*,5′*R*)-**2**, whose absolute configuration could be assigned by its CD comparison with (1*R*,5*S*)-sabina ketone **4**. Herein, we also describe an asymmetric synthesis of the natural pheromone (2*Z*,6*R*,1′*S*,5′*S*)-**1** without recourse to an enzyme by employing Hodgson's diastereoselective intramolecular cyclopropanation[11] as the key step (see Scheme 4).

2. Results and discussion

2.1. Determination of the absolute configuration of the natural pheromone by enzymatic asymmetric synthesis

Scheme 2 summarizes the synthesis of (6*R*,1′*S*,5′*R*)- and (6*R*,1′*R*,5′*S*)-**2** via lipase-catalyzed asymmetric acetylation. A diastereomeric mixture of the key intermediate, sesquisabina ketone (6*R*,1′*RS*,5′*SR*)-**2** was prepared from (*R*)-citronellal **5** (Takasago International Corporation, 97% ee) via diazoketone (*R*)-**6** as reported previously.[10] Reduction of **2** with lithium tri(*sec*-butyl)borohydride (L-Selectride®) was followed by treatment with alkaline hydrogen peroxide to give a diastereomeric mixture of

☆ Pheromone synthesis, Part 237. For Part 236, see Ref. 1.

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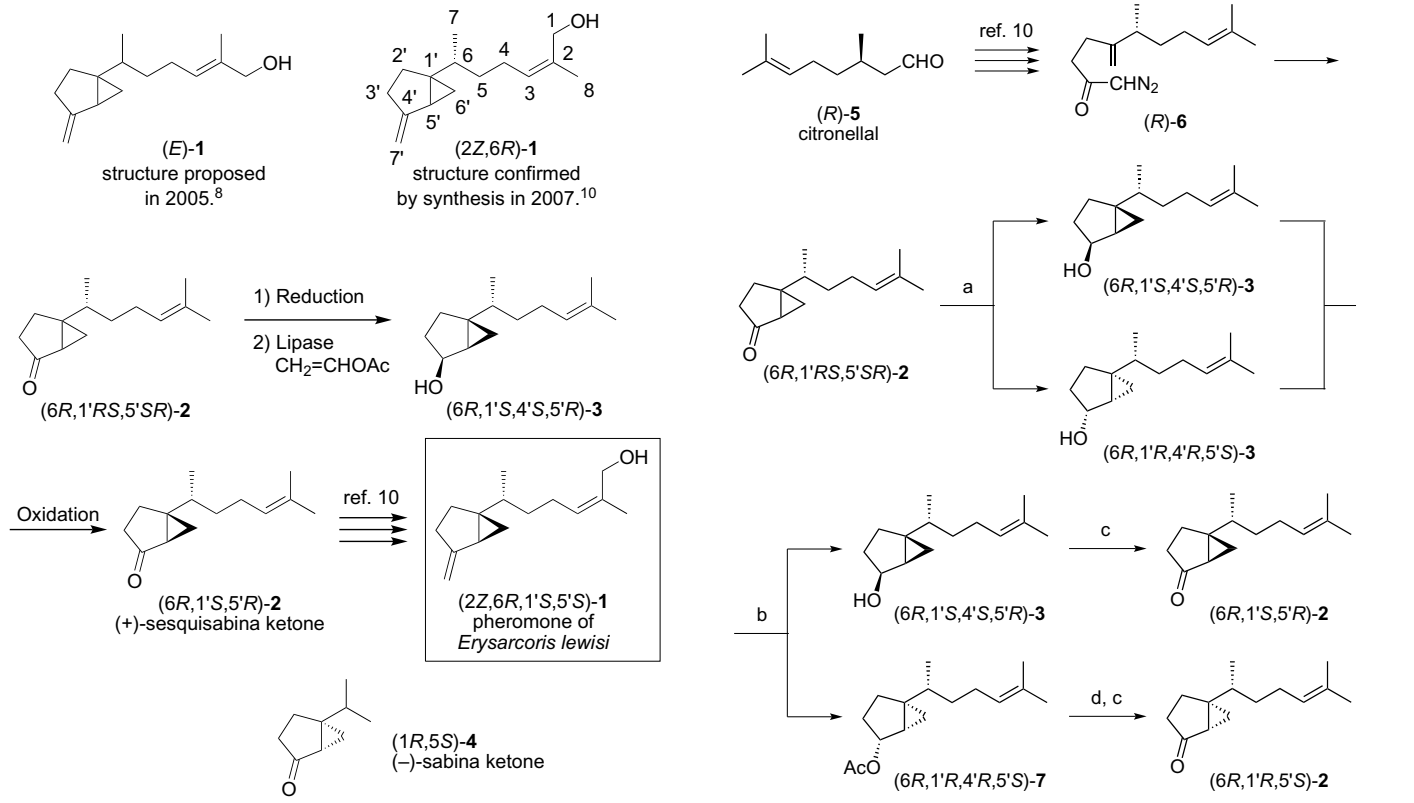


Scheme 1. Structure and synthetic plan for the pheromone of *Erysarcoris lewisi* (Distant), (2*Z*,6*R*,1′*S*,5′*S*)-**1**.

Scheme 2. Synthesis of (6*R*,1′*S*,5′*R*)- and (6*R*,1′*R*,5′*S*)- sesquisabina ketone **2**. Reagents and conditions: (a) LiB(*sec*-Bu)$_3$H, THF, −60 °C to −20 °C, 5 h; then 3 M NaOH aq soln, 30% H_2O_2, 5 °C to room temperature, 2 h (94%); (b) lipase PS-D (Amano), CH_2=CHOAc, Et_2O, room temperature, 10 h, repeated three times [32% for (6*R*, 1′*S*,4′*S*,5′*R*)-**3** and 11% for (6*R*,1′*R*,4′*R*,5′*S*)-**7**]; (c) TPAP, NMO, powdered MS 4 Å, CH_2Cl_2, room temperature, 1.5 h (95% ∼ quant.); (d) K_2CO_3, MeOH, room temperature (26% after purification).

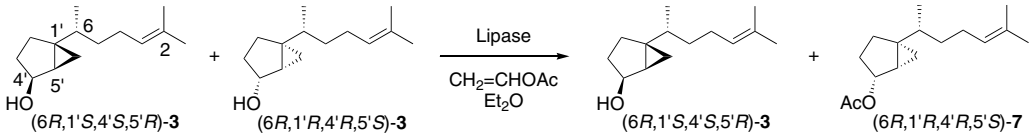
alcohols (6*R*,1′*S*,4′*S*,5′*R*)- and (6*R*,1′*R*,4′*R*,5′*S*)-**3** in 94% yield. The hydride anion of the reducing agent approached from the opposite side of the cyclopropane ring to avoid steric hindrance. The configuration of the newly generated hydroxy group of **3** was assigned as depicted in the formula on the basis of the ^{1}H NMR analysis of **3**, since the proton at C-4′ absorbed at δ 4.52 with ddd, $J_{H4',H5'}$ = 8.4 Hz (dihedral angle $\Phi_{H4',H5'}$ = 36° as calculated by MM2).[12] When (±)-sabina ketone **4** was reduced with L-Selectride®, two alcohols were obtained in a ratio of 78:22. The more polar one (78%) showed NMR signals due to C*H*OH at δ 4.50 as ddd, $J_{H4,H5}$ = 8.0 Hz ($\Phi_{H4,H5}$ = 33°),[12] while the less polar one (22%) exhibited the corresponding signal due to C*H*OH at δ 4.17 as br d, $J_{H4,H5}$ = ca. 0 Hz ($\Phi_{H4,H5}$ = 83°).[12] In the case of the reduction of **2**, the more sterically demanding side chain at C-1′ must have fixed the conformation of the bicyclo[3.1.0]hexane ring of **2** over the course of the reduction to give *endo*-alcohol **3** predominantly (>95%). The stable conformations of these compounds are shown in Figure 3.[12]

For separation of the diastereomeric mixture of alcohols (6*R*,1′*S*,4′*S*,5′*R*)- and (6*R*,1′*R*,4′*R*,5′*S*)-**3**, we applied lipase-catalyzed asymmetric acetylation, which is one of the most practical methods for that purpose. Enzymatic acetylation of the diastereomeric mixture of **3** was carried out with vinyl acetate in the presence of lipase PS-D (Amano) I (lipase of *Burkholderia cepacia*). This enzyme was selected after preliminary screening with lipases PS, PS-C, PS-D, AK, and AH-S (see Table 1). Three repetitions of the enzymatic asymmetric acetylation yielded the recovered (6*R*,1′*S*,4′*S*,5′*R*)-**3** {dr = 14:1 as revealed by its ^{1}H NMR analysis (400 MHz, $CDCl_3$) observing the intensity of the signals of the cyclopropane at δ 0.25 [due to a (6*R*,1′*S*,4′*S*,5′*R*)-**3**] and δ 0.34 [due to (6*R*,1′*R*,4′*R*,5′*S*)-**3**]} in 32% yield and a (6*R*,1′*R*,4′*R*,5′*S*)-**7** (dr = 18:1) in 11% yield, respectively. As to the absolute configuration of the two products of asymmetric acetylation, (6*R*,1′*S*,4′*S*,5′*R*)-configuration was tentatively assigned to the recovered alcohol **3**, while (6*R*,1′*R*,4′*R*,5′*S*)-configuration was given to acetate **7**, in analogy with the result of a similar asymmetric acetylation [(±)-**A** → (*S*)-**A** + (*R*)-**B**] in the case of our strigol synthesis.[13]

The recovered alcohol (6*R*,1′*S*,4′*S*,5′*R*)-**3** was then oxidized with tetra(*n*-propyl)ammonium perruthenate (TPAP) in the presence of *N*-methylmorpholine *N*-oxide (NMO) to give (6*R*,1′*S*,5′*R*)-**2**. Acetate **7** was deacetylated, and the resulting (6*R*,1′*R*,4′*R*,5′*S*)-**3** was oxidized to give (6*R*,1′*R*,5′*S*)-**2**. The tentatively assigned stereostructure of the diastereomers of **2** was confirmed at this stage by circular dichroism (CD) spectroscopy. The CD spectrum of (6*R*,1′*S*,5′*R*)-**2**, designated as enzymatic, in MeOH as $\Delta\varepsilon$ = +6.2 (282.4 nm) and −16.3 (204.7 nm) was nearly antipodal to that [$\Delta\varepsilon$ = −7.9 (282.6 nm) and +17.9 (205.5 nm)] of (1*R*,5*S*)-sabina ketone **4** {$[\alpha]_D^{20}$ = −41.2 (EtOH); 96.6% ee as estimated by GC on Chiramix}, while (6*R*,1′*R*,5′*S*)-**2**, designated as enzymatic, showed CD spectrum [$\Delta\varepsilon$ = −9.8 (282.3 nm) and +22.3 (204.8 nm)] as almost the same as that of (1*R*,5*S*)-**4** (see Fig. 1). It should be noted that (−)-sabina ketone **4** is known to possess the (1*R*,5*S*) absolute configuration as elucidated by many people[14] including Ohloff et al.[15]

The two diastereomers of ketone **2** were converted to the two diastereomers of (2*Z*,6*R*)-**1** according to the previously reported

Table 1
Lipase-catalyzed asymmetric acetylation of diastereomeric (6*R*)-**3**[a,b]



Lipase	Time (h)[c]	(6*R*,1′*S*,4′*S*,5′*R*)-**3**		(6*R*,1′*R*,4′*R*,5′*S*)-**7**	
		Yield[d] (%)	de[e] (%)	Yield[d] (%)	de[e] (%)
PS	48	61	40	31	47
PS-C(I)	9.5	63	35	26	43
PS-D(I)	7	63	38	25	44
AK	24	68	24	28	16
AH-S	4	57	28	42	−7[f]

[a] Conditions: To a solution of diastereomeric (6*R*)-**3** (50 mg) in diethyl ether (2 mL) and vinyl acetate (0.5 mL) was added each lipase (100 mg) at room temperature. The enzymes were the generous gift of Amano Enzyme, Inc. (Lipase AK from *Pseudomonas fluorescens;* Lipase AH from *Burkholderia cepacia;* Lipase PS from *Burkholderia cepacia;* PS-C = PS on Celite; PS-D = PS on diatomaceous earth).
[b] The diastereomeric ratio of the starting alcohol (6*R*,1′*S*,4′*S*,5′*R*)-**3**:(6*R*,1′*R*,4′*R*,5′*S*)-**3** was 1.4:1.
[c] Acetylation was monitored by TLC.
[d] Yields were based on the starting diastereomeric (6*R*)-**3**.
[e] Determined by ^{1}H NMR analysis (400 MHz) of **3** and **7**.
[f] In this case, undesired (6*R*,1′*S*,4′*S*,5′*R*)-**7** was the major product.

procedure (Scheme 3).[10] Oxidation of (6*R*,1′*S*,5′*R*)-**2** with osmium tetroxide and sodium periodate gave (6*R*,1′*S*,5′*R*)-**8** in 72% yield. Olefination of **8** with Ando's *Z*-selective Horner–Wadsworth–Emmons reagent, ethyl 2-(di-*o*-tolylphosphono)propanoate,[10,16] furnished (2*Z*,6*R*,1′*S*,5′*R*)-**9** in 77% yield. The ratio of the geometrical isomers was determined by ^{1}H NMR (400 MHz), and shown to be *Z*:*E* = 21:1. These isomers were separated by silica gel column chromatography. Methylenation of **9** under conventional Wittig conditions afforded (2*Z*,6*R*,1′*S*,5′*S*)-**10** in 58% yield. Finally, treatment of ester **10** with diisobutylaluminum hydride gave (2*Z*,6*R*,1′*S*,5′*S*)-**1** (60.7 mg), $[\alpha]_D^{27} = -37.9$ (*c* 1.19, hexane), in 91% yield [dr = 10.5:1 (analyzed by ^{1}H NMR spectrum at 400 MHz)]. The overall yield of (2*Z*,6*R*,1′*S*,5′*S*)-**1** was 3.3% (17 steps) based on

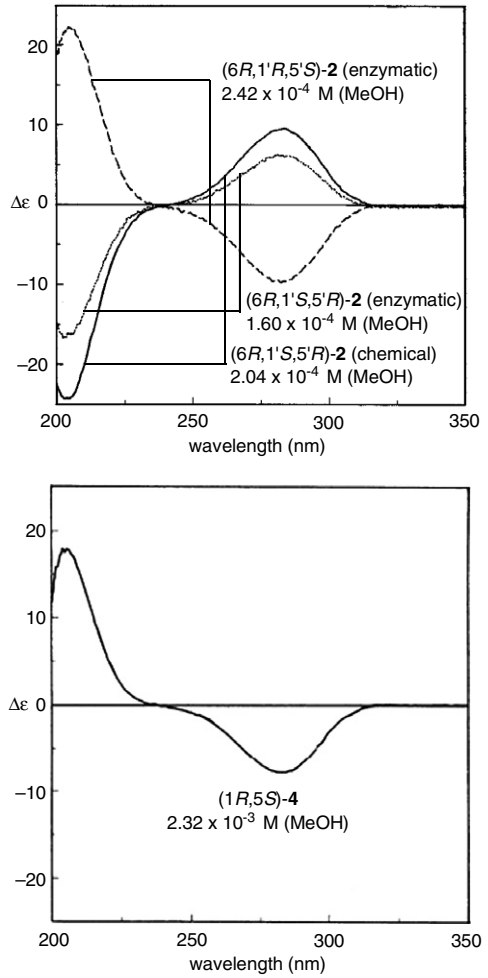
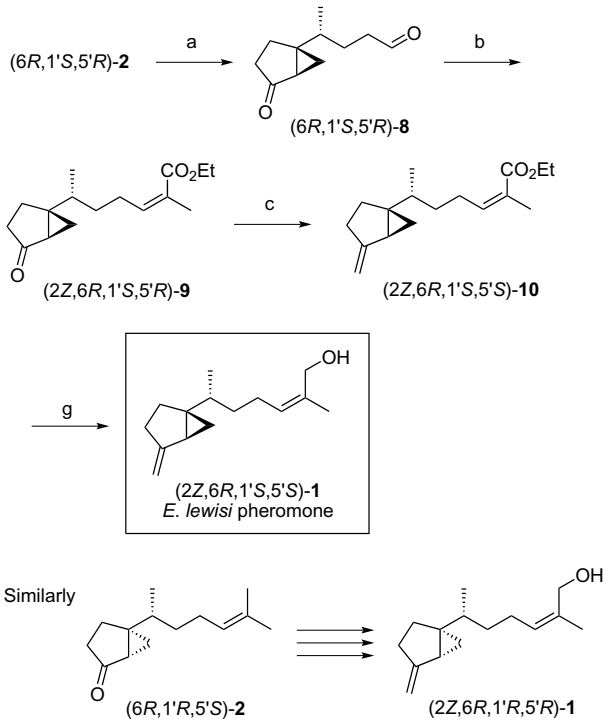


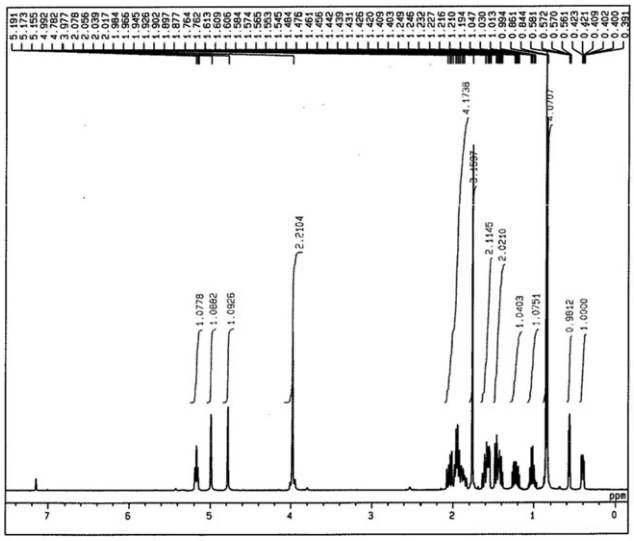
Figure 1. CD spectra of (6*R*,1′*R*,5′*S*)-**2** (enzymatic), (6*R*,1′*S*,5′*R*)-**2** (enzymatic), (6*R*,1′*S*,5′*R*)-**2** (chemical), and (1*R*,5*S*)-**4**.



Scheme 3. Synthesis of the pheromone of *Erysarcoris lewisi* (Distant) (2*Z*,6*R*,1′*S*,5′*S*)-**1** and its diastereomer (2*Z*,6*R*,1′*R*,5′*R*)-**1**. Reagents and conditions: (a) OsO_4, $NaIO_4$, THF, H_2O, room temperature, 19 h (72%); (b) (*o*-$MeC_6H_4O)_2P(O)CHMeCO_2Et$, NaH, THF, −78 °C, 1 h, then 0 °C, 0.5 h (77%); (c) $(C_6H_5)_3PMeBr$, *n*-BuLi, THF, 0 °C, 5 min (58%); (d) $(i\text{-Bu})_2AlH$, toluene, CH_2Cl_2, −78 °C, 0.5 h, then 0 °C, 0.5 h (91%).

(*R*)-citronellal **5**. Similarly, the diastereomeric ketone (6*R*,1′*R*,5′*S*)-**2** afforded (2*Z*,6*R*,1′*R*,5′*R*)-**1** (14.1 mg), $[\alpha]_D^{27} = +59.8$ (*c* 0.61, hexane) [dr = 18:1 (^{1}H NMR, 400 MHz)].

The ^{1}H NMR spectra at 400 MHz of these two diastereomers of **1** were slightly different, especially at the high field region due to



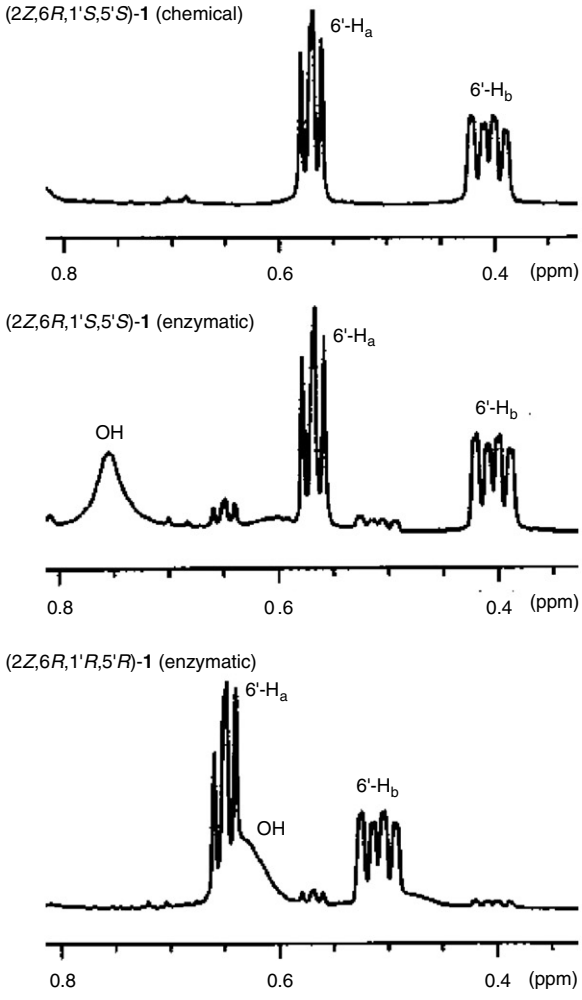


Figure 2. ^{1}H NMR spectrum of (2*Z*,6*R*,1′*S*,5′*S*)-**1** (chemical) and ^{1}H NMR spectra (cyclopropyl protons) of (2*Z*,6*R*,1′*S*,5′*S*)-**1** (chemical), (2*Z*,6*R*,1′*S*,5′*S*)-**1** (enzymatic), and (2*Z*,6*R*,1′*R*,5′*R*)-**1** (enzymatic) (400 MHz, C_6D_6).

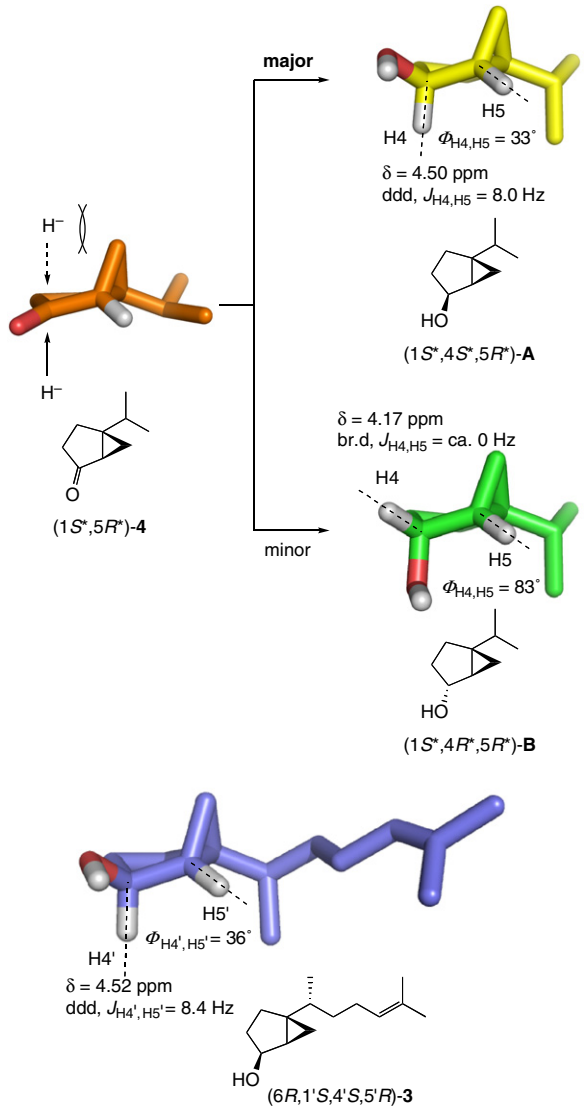


Figure 3. The stable conformations of (1*S**,4*S**,5*R**)-**A**, (1*S**,4*R**,5*R**)-**B**, and (6*R*,1′*S*,4′*S*,5′*R*)-**3**.

cyclopropane protons, while (2*Z*,6*R*,1′*S*,5′*S*)-**1** had ^{1}H and ^{13}C NMR spectra identical to those of the natural pheromone.[9] Figure 2 shows the ^{1}H NMR spectra of our synthetic samples of **1**. The identity of (2*Z*,6*R*,1′*S*,5′*S*)-**1** with the natural pheromone was also confirmed by GC analysis on a CP-Chirasil-DEX CB column (25 m × 0.25 mm i.d.) at 60 °C (1 min)→6 °C/min→200 °C. The retention time of the natural pheromone was 22.13 min, while that of the synthetic (2*Z*,6*R*,1′*S*,5′*S*)-**1** was 22.12 min and that of (2*Z*,6*R*,1′*R*,5′*R*)-**1** was 22.47 min.

The field bioassay of our synthetic products, (2*Z*,6*R*,1′*S*,5′*S*)-**1** and (2*Z*,6*R*,1′*R*,5′*R*)-**1** was carried out at the Yamagata Prefectural Agricultural Research Center. As reported previously, the results of the bioassay definitely confirmed the attractancy of (2*Z*,6*R*,1′*S*,5′*S*)-**1** against *E. lewisi*.[3] Another experiment carried out by Yoshimura indicates that (2*Z*,6*S*)-**1** is neither bioactive nor inhibitory.[17]

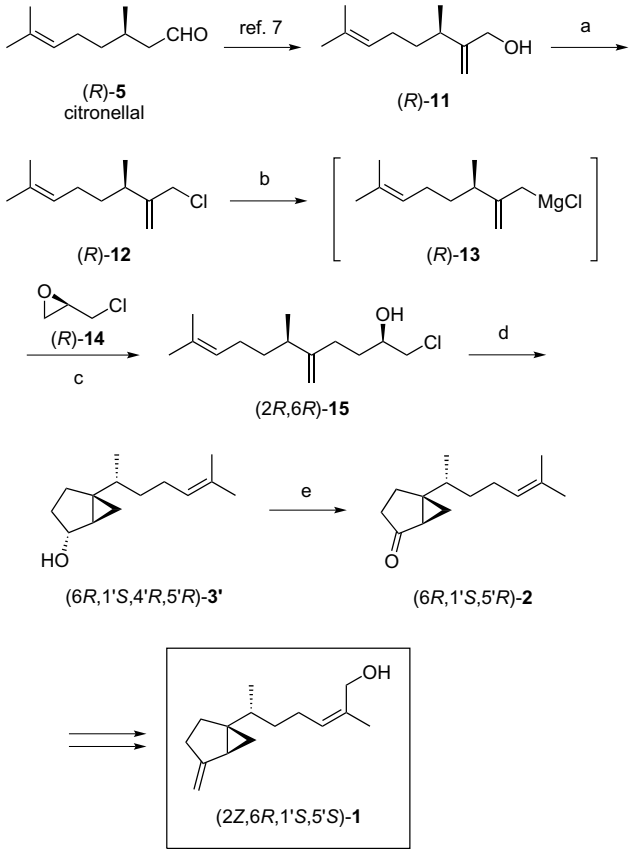
2.2. Chemical asymmetric synthesis of (2*Z*,6*R*,1′*S*,5′*S*)-1

In order to synthesize the natural pheromone (2*Z*,6*R*,1′*S*,5′*S*)-**1** in a sufficient amount, there was a need to develop a more efficient and diastereoselective synthetic route. For this purpose, we chose

Hodgson's regioselective intramolecular cyclopropanation procedure employing unsaturated chlorohydrin **15** (Scheme 4).[11] Alcohol **11**, which was prepared from (*R*)-citronellal in two steps,[10] was treated with methanesulfonyl chloride in the presence of pyridine to give allyl chloride **12** in 85% yield.[18] Conversion of **12** into the corresponding Grignard reagent **13**, was followed by treatment with (*R*)-epichlorohydrin **14** in the presence of CuI to give the key intermediate **15** in 50% yield.[19] Chlorohydrin **15** was subjected to Hodgson's intramolecular cyclopropanation by treatment with lithium 2,2,6,6-tetramethylpiperidide to afford (6*R*,1′*S*,4′*R*,5′*R*)-**3**′ in 95% yield as a single diastereomer.[11,19] Oxidation of (6*R*,1′*S*,4′*R*,5′*R*)-**3**′ with TPAP furnished the ketone (6*R*,1′*S*,5′*R*)-**2** in quantitative yield. The CD spectrum of this ketone (6*R*,1′*S*,5′*R*)-**2**, designated as chemical, is depicted in Figure 1. The newly obtained (6*R*,1′*S*,5′*R*)-**2** was diastereomerically pure judging from its ^{1}H NMR spectrum, while its overall yield from (*R*)-citronellal **5** was improved to 31% (6 steps), while in the enzymatic synthesis it was 11% (13 steps).

In the same manner as described above for the conversion of (6*R*,1′*S*,5′*R*)-**2** (enzymatic) to (2*Z*,6*R*,1′*S*,5′*S*)-**1**, the ketone (6*R*,1′*S*,5′*R*)-**2** (chemical) was converted to (2*Z*,6*R*,1′*S*,5′*S*)-**1** (364 mg), $[\alpha]_D^{22} = -52.7$ (*c* 1.14, hexane). Judging from its ^{1}H NMR spectrum, the resulting (2*Z*,6*R*,1′*S*,5′*S*)-**1**, designated as chemical, was diastereomerically pure (see Fig. 2). This new synthesis was considerably shorter (10 steps) than the previous one (17 steps).

As a by-product of the present study, an interesting observation could be made as follows: the acetate, $[\alpha]_D^{24} = -39.5$ (*c* 0.2, $CHCl_3$), isolated from an African plant *Haplocarpha scaposa* (Harv.) and identified as the acetate of **1** by Bohlmann and Wallmeyer in 1982,[20] turned out to be the acetate of the present pheromone, because the acetate prepared from (2*Z*,6*R*,1′*S*,5′*S*)-**1** (chemical) showed $[\alpha]_D^{22} = -51.6$ (*c* 1.10, $CHCl_3$). The reason why the African plant produces the acetate of the pheromone of *E. lewisi* remains a mystery in chemical ecology.



Scheme 4. Chemical asymmetric synthesis of (2*Z*,6*R*,1′*S*,5′*S*)-**1**. Reagents and conditions: (a) MsCl, pentane, −5 °C, 0.5 h; then pyridine, room temperature, 20 h (85%); (b) Mg, $(CH_2Br)_2$, THF, room temperature, 2 h; (c) CuI, THF, −78 °C to 0 °C, 1 h (50%); (d) *n*-BuLi, 2,2,6,6-tetramethylpiperidine, *tert*-BuOMe, −78 °C to room temperature, 12 h (95%); (e) TPAP, NMO, powdered MS 4 Å, CH_2Cl_2, room temperature, 2 h (95%).

3. Conclusion

The stereostructure of the male-produced aggregation pheromone of the stink bug *E. lewisi* (Distant) was established as (2*Z*,6*R*,1′*S*,5′*S*)-2-methyl-6-(4′-methylenebicyclo[3.1.0]hexyl)hept-2-en-1-ol **1** by using enzymatic acetylation as the key step. We also developed a more efficient route for the synthesis of the natural pheromone by employing Hodgson's intramolecular cyclopropanation reaction.

4. Experimental

4.1. General

Refractive indices (n_D) were measured on an Atago 1T refractometer. Optical rotations were measured on a Jasco P-1010 polarimeter. IR spectra were recorded on a Jasco FT/IR-460 plus spectrometer. ^{1}H NMR spectra (270 MHz or 400 MHz, TMS at δ 0.00 or $CHCl_3$ at δ 7.26 as internal standard) and ^{13}C NMR spectra (100 MHz, $CHCl_3$ at δ 77.0 as internal standard) were recorded on a JNM-AL270 or a JNM-A400 spectrometers. CD spectra were measured on a Jasco J-720. HRMS were recorded on a JMS-SX102A. Column chromatography was performed on Merck Kieselgel 60 Art 1.07734.

4.2. (6*R*)-2-Methyl-6-(4′-hydroxybicyclo[3.1.0]hexyl)hept-2-ene (6*R*,1′*S*,4′*S*,5′*R*)- and (6*R*,1′*R*,4′*R*,5′*S*)-3

A solution of L-Selectride® in THF (1 M, 33 mL, 33 mmol) was added dropwise to a stirred and cooled solution of (6*R*,1′*RS*,5′*SR*)-**2** (5.1 g, 25 mmol) in dry THF (15 mL) at −60 °C under N_2. The reaction mixture was slowly warmed up to −20 °C over 5 h. Subsequently, an aqueous solution of NaOH (1 M, 33 mL, 33 mmol) and 30% H_2O_2 in water (30 mL) were added dropwise, and the mixture was stirred for 2 h at 0–5 °C to room temperature. It was then diluted with water and extracted with Et_2O. The extract was washed with water and brine, dried over K_2CO_3, and concentrated in vacuo to give 5.7 g of crude (6*R*)-**3** as an oil. This was chromatographed over SiO_2 (75 g). Elution with hexane/EtOAc (15:1–10:1) afforded 4.8 g (94%) of (6*R*)-**3** as a colorless oil, δ_H (400 MHz, $CDCl_3$): 0.25, 0.33 (total 1H, m), 0.70, 0.78 (total 1H, m), 0.89, 0.92 (total 3H, each d, *J* = 6.8 Hz), 1.05–1.15 (2H, m), 1.18–1.32 (3H, m), 1.35–1.46 (2H, m), 1.60 (3H, s), 1.60–1.68 (1H, m), 1.68 (3H, s), 1.85–2.05 (3H, m), 4.51 (1H, m), 5.09 (1H, m). The obtained alcohol (6*R*)-**3** was immediately used in the next step without further purification.

4.3. (6*R*,1′*S*,4′*S*,5′*R*)-2-Methyl-6-(4′-hydroxybicyclo[3.1.0]hexyl)-hept-2-ene and (6*R*,1′*R*,4′*R*,5′*S*)-2-methyl-6-(4′-hydroxybicyclo[3.1.0]hexyl)hept-2-ene (6*R*,1′*S*,4′*S*,5′*R*)- and (6*R*,1′*R*,4′*R*,5′*S*)-3

To a stirred solution of a mixture of (6*R*,1′*S*,4′*S*,5′*R*)- and (6*R*,1′*R*,4′*R*,5′*S*)-**3** (1.74 g, 8.35 mmol) and vinyl acetate (15 mL) in Et_2O (60 mL) was added Lipase PS-D Amano I (Amano Enzyme, Inc., 3.51 g) at room temperature. After stirring at room temperature for 10 h, the mixture was then filtered through a bed of Celite and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel [40 g, hexane/EtOAc = 20:1 for (6*R*,1′*R*,4′*R*,5′*S*)-**7**, and 8:1 for (6*R*,1′*S*,4′*S*,5′*R*)-**3**] to give (6*R*,1′*R*,4′*R*,5′*S*)-**7** (738 mg, 34%, 45% de) and

(6*R*,1′*S*,4′*S*,5′*R*)-**3** (1.18 g, 66%, 49% de) as a colorless oil. The diastereomeric purities of (6*R*,1′*R*,4′*R*,5′*S*)-**7** and (6*R*,1′*S*,4′*S*,5′*R*)-**3** were determined by ^{1}H NMR analysis (400 MHz).

(6*R*,1′*S*,4′*S*,5′*R*)-**3**: Enzymatic acetylation described above was repeated for the alcohol (6*R*,1′*S*,4′*S*,5′*R*)-**3** (1.15 g, 5.52 mmol) twice more to give unreacted alcohol (6*R*,1′*S*,4′*S*,5′*R*)-**3** [first: 801 mg, 72% de; second: 536 mg, 87% de; 32%, based on diastereomeric (6*R*)-**3**, 3 steps] as a colorless oil, ν_{max} (film): 3330 (br s, OH), 3060 (w), 1670 (w, C=C), 1060 (br s, C–O) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.26 (1H, dd, *J* = 4.8, 7.6 Hz), 0.70 (1H, t, *J* = 4.8 Hz), 0.90 (3H, d, *J* = 6.8 Hz), 1.04–1.16 (2H, m), 1.17–1.32 (2H, m), 1.36–1.48 (1H, m), 1.60 (3H, s), 1.57–1.68 (2H, m), 1.68 (3H, s), 1.86–2.03 (3H, m), 3.54 (1H, br s), 4.52 (1H, br ddd, *J* = 4.4, 8.0, 12 Hz), 5.03–5.15 (1H, m); HRMS (EI$^+$) calcd for $C_{14}H_{24}O$ (M^+) 208.1827; found, 208.1808. The obtained (6*R*,1′*S*,4′*S*,5′*R*)-**3** was used immediately in the next step without further purification.

(6*R*,1′*R*,4′*R*,5′*S*)-**3**: The separated (6*R*,1′*R*,4′*R*,5′*S*)-**7** (686 mg, 2.74 mmol) was then methanolyzed with K_2CO_3 (34 mg, 0.25 mmol) in MeOH (15 mL). After stirring at room temperature for 21 h, the mixture was concentrated in vacuo. The residue was diluted with Et_2O, and the mixture was filtered through a bed of Celite. The filtrate was concentrated in vacuo to give the diastereomerically enriched crude alcohol (6*R*,1′*R*,4′*R*,5′*S*)-**3** (567 mg). This procedure, enzymatic resolution followed by methanolysis as described above, was repeated twice for the resulting alcohol to give diastereomerically enriched alcohol (6*R*,1′*R*,4′*R*,5′*S*)-**3** [first: 265 mg, 78% de; second: 48 mg, 90% de; 2.9%, based on diastereomeric (6*R*)-**3**, 6 steps] as a colorless oil, ν_{max} (film): 3340 (br s, OH), 3060 (w), 1670 (w, C=C), 1060 (br s, C–O) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.34 (1H, dd, *J* = 4.8, 8.0 Hz), 0.78 (1H, dd, *J* = 3.6, 4.8 Hz), 0.92 (3H, d, *J* = 6.4 Hz), 1.05–1.16 (2H, m), 1.17–1.25 (2H, m), 1.33–1.43 (1H, m), 1.61 (3H, s), 1.58–1.70 (2H, m), 1.68 (3H, s), 1.93 (1H, dt, *J* = 8.0, 13 Hz), 2.00 (2H, br q, *J* = 7.2 Hz), 3.50 (1H, br s), 4.48–4.54 (1H, m), 5.06–5.15 (1H, m); HRMS (EI$^+$) calcd for $C_{14}H_{24}O$ (M^+) 208.1827; found, 208.1822. The obtained alcohol (6*R*,1′*R*,4′*R*,5′*S*)-**3** was immediately used in the next step without further purification.

4.4. (*R*)-3,7-Dimethyl-2-methylene-6-octenyl chloride (*R*)-12

To a stirred solution of (*R*)-**11**[10] (7.41 g, 44.0 mmol) in pentane (120 mL), methanesulfonyl chloride (5.1 mL, 65.9 mmol) was added over 5 min at −5 °C. The mixture was stirred at −5 °C for 30 min. A solution of pyridine (7.1 mL, 87.8 mmol) in pentane (30 mL) was added dropwise over 10 min to this mixture at −5 °C. After stirring at room temperature for 20 h, the reaction was quenched with water. The separated organic phase was successively washed with water, aqueous 1 M HCl solution, water, saturated aqueous $NaHCO_3$ solution and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (100 g, pentane) to give (*R*)-**12** (6.95 g, 85%) as a colorless oil. The analytical sample was distilled for further purification, bp 77–80 °C/5 Torr; $n_D^{23} = 1.4711$; $[\alpha]_D^{20} = -18.7$ (*c* 1.56, $CHCl_3$); ν_{max} (film): 1670 (w, C=C), 1640 (m, C=C), 1260 (s), 910 (s), 750 (s) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.08 (3H, d, *J* = 6.8 Hz), 1.36 (1H, dq, *J* = 6.8, 14 Hz), 1.52 (1H, dq, *J* = 6.8, 14 Hz), 1.59 (3H, s), 1.69 (3H, s), 1.96 (2H, q, *J* = 7.2 Hz), 2.34 (1H, sext., *J* = 6.8 Hz), 4.06 (2H, s), 5.00 (1H, s), 5.10 (1H, tq-like, *J* = 1.2, 7.6 Hz), 5.18 (1H, s); HRMS (EI$^+$) calcd for $C_{11}H_{19}Cl$ (M^+) 186.1175; found, 186.1182.

4.5. (2*R*,6*R*)-1-Chloro-6,10-dimethyl-5-methylene-9-undecen-2-ol (2*R*,6*R*)-15

To a stirred suspension of magnesium (541 mg, 22.3 mmol) and 1,2-dibromoethane (3 drops) in dry THF (5 mL), a solution of (*R*)-**12** (1.88 g, 10.1 mmol) in dry THF (10 mL) was added dropwise at room temperature. After stirring at room temperature for 2 h, this solution of Grignard reagent (*R*)-**13** was added dropwise to the mixture of CuI (191 mg, 1.00 mmol) and (*R*)-epichlorohydrin [(*R*)-**14**, 0.80 mL, 10.2 mmol] in dry THF (5 mL) at −78 °C. The reaction temperature was gradually warmed up to 0 °C over 90 min, and the mixture was then stirred at 0 °C for further 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with ether. The combined organic phase was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (40 g, hexane/EtOAc = 20:1) to give (2*R*,6*R*)-**15** (1.23 g, 50%) as a colorless oil; $n_D^{21} = 1.4860$; $[\alpha]_D^{20} = -9.7$ (*c* 1.21, $CHCl_3$); ν_{max} (film): 3400 (br s, OH), 1670 (w, C=C), 1640 (s, C=C), 1060 (br s, C–O), 890 (s), 745 (s) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.02 (3H, d, *J* = 6.8 Hz) 1.26–1.35 (1H, m), 1.42–1.51 (1H, m), 1.59 (3H, s), 1.68 (3H, s), 1.65–1.72 (1H, m), 1.92 (2H, q, *J* = 7.2 Hz), 2.03–2.23 (4H, m), 3.51 (1H, dd, *J* = 7.6, 11 Hz), 3.66 (1H, dd, *J* = 3.2, 11 Hz), 3.79–3.87 (1H, m), 4.74 (1H, br d-like, *J* = 1.2 Hz), 4.79 (1H, br s), 5.12–5.06 (1H, m); HRMS (EI$^+$) calcd for $C_{14}H_{25}ClO$ (M^+) 244.1594; found, 244.1593.

4.6. (6*R*,1′*S*,4′*R*,5′*R*)-2-Methyl-6-(4′-hydroxybicyclo[3.1.0]-hexyl)hept-2-ene (6*R*,1′*S*,4′*R*,5′*R*)-3′

To a stirred solution of (*R*)-**15** (3.70 g, 15.1 mmol) and 2,2,6,6-tetramethylpiperidine (6.4 mL, 37.9 mmol) in *tert*-BuOMe (120 mL), a solution of *n*-BuLi (1.55 M in *n*-hexane, 34.1 mL, 52.9 mmol) was added dropwise at −78 °C under argon. The reaction temperature was gradually warmed up to room temperature with stirring. After stirring for 12 h at room temperature, the reaction was quenched with MeOH (3 mL). The mixture was diluted with ether, and the separated organic phase was successively washed with water, aqueous 1 M HCl solution, water, saturated aqueous $NaHCO_3$ solution and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (150 g, hexane/EtOAc = 50:3) to give (6*R*,1′*S*,4′*R*,5′*R*)-**3**′ (2.98 g, 95%) as a pale yellow oil, $n_D^{21} = 1.4883$; $[\alpha]_D^{21} = +11.7$ (*c* 1.04, $CHCl_3$); ν_{max} (film): 3340 (br s, OH), 3060 (w), 1670 (w, C=C), 965 (m), 925 (m), 820 (m) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.20 (1H, dd, *J* = 3.6, 4.8 Hz) 0.33 (1H, dd, *J* = 4.8, 8.0 Hz), 0.94 (3H, d, *J* = 6.8 Hz), 1.13–1.59 (7H, m), 1.61 (3H, s), 1.68 (3H, s), 1.82 (1H, dt, *J* = 9.2, 12 Hz), 1.94–2.10 (2H, m), 4.19 (1H, t, *J* = 4.4 Hz), 5.10 (1H, br t-like, *J* = 7.2 Hz); HRMS (EI$^+$) calcd for $C_{14}H_{24}O$ (M^+) 208.1827; found, 208.1819.

4.7. (6*R*,1′*S*,5′*R*)-2-Methyl-6-(4′-oxobicyclo[3.1.0]hexyl)hept-2-ene (6*R*,1′*S*,5′*R*)-2 (enzymatic)

To a stirred solution of (6*R*,1′*S*,4′*S*,5′*R*)-**3** (487 mg, 2.34 mmol) in dry CH_2Cl_2 (20 mL) were added *N*-methylmorpholine-*N*-oxide (548 mg, 4.68 mmol), powdered MS 4 Å (727 mg), and tetra-*n*-propylammonium perruthenate (44 mg, 0.13 mmol) at room temperature. After stirring for 90 min at room temperature, the mixture was diluted with ether. The resulting suspension was filtered through a column of silica gel (40 g, ether) to give (6*R*,1′*S*,5′*R*)-**2** (481 mg, quant.) as a colorless oil, $n_D^{22} = 1.4860$; $[\alpha]_D^{26} = +18.9$ (*c* 1.16, $CHCl_3$); ν_{max} (film): 3070 (w), 1730 (br s, C=O), 1180 (m), 915 (m) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.97 (3H, d, *J* = 6.8 Hz), 1.07 (1H, dd, *J* = 3.2, 4.8 Hz), 1.13 (1H, dd, *J* = 4.8, 8.8 Hz), 1.25–1.37 (2H, m), 1.42–1.56 (1H, m), 1.59 (3H, s), 1.68 (3H, s), 1.63–1.70 (1H, m), 1.86–2.06 (4H, m), 2.06–2.19 (2H, m), 5.06 (1H, br t-like, *J* = 6.8 Hz); CD (*c* = 1.60 × 10^{-4} M, MeOH): $\lambda_{ext.}$ 282.4 ($\Delta\varepsilon$ = +6.2), 204.7 ($\Delta\varepsilon$ = −16.3) nm; HRMS (EI$^+$) calcd for $C_{14}H_{22}O$ (M^+) 206.1671; found 206.1673. This was immediately used in the next step without further purification.

4.8. (6*R*,1′*S*,5′*R*)-2-Methyl-6-(4′-oxobicyclo[3.1.0]hexyl)hept-2-ene (6*R*,1′*S*,5′*R*)-2 (chemical)

In the same manner as described above, (6*R*,1′*S*,4′*R*,5′*R*)-**3**′ (348 mg, 1.67 mmol) was converted into (6*R*,1′*S*,5′*R*)-**2** (329 mg, 95%) as a colorless oil, $n_D^{21} = 1.4856$; $[\alpha]_D^{21} = +23.5$ (*c* 1.12, $CHCl_3$); Its IR and ^1H NMR spectra were identical with those of **2** (enzymatic); CD (*c* 2.04×10^{-4} M, MeOH): $\lambda_{ext.}$ 284 ($\Delta\varepsilon = +9.5$), 203 ($\Delta\varepsilon = -24.3$) nm; HRMS ($EI^+$) calcd for $C_{14}H_{22}O$ (M^+) 206.1671; found 206.1680. This was immediately used in the next step without further purification.

4.9. (6*R*,1′*R*,5′*S*)-2-Methyl-6-(4′-oxobicyclo[3.1.0]hexyl)hept-2-ene (6*R*,1′*R*,5′*S*)-2

In the same manner as described above, (6*R*,1′*R*,4′*R*,5′*S*)-**3** (86 mg, 0.41 mmol) was converted into (6*R*,1′*R*,5′*S*)-**2** (81 mg, 95%) as a colorless oil, $n_D^{26} = 1.4862$; $[\alpha]_D^{25} = -30.1$ (*c* 1.06, $CHCl_3$); ν_{max} (film): 3060 (w), 1730 (br s, C=O), 1180 (m), 910 (m) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.98 (1H, d, *J* = 6.4 Hz), 1.16 (1H, dd, *J* = 3.6, 4.8 Hz), 1.19 (1H, dd, *J* = 4.8, 8.8 Hz), 1.23–1.36 (2H, m), 1.42–1.50 (1H, m), 1.59 (1H, dd, *J* = 3.6, 8.8 Hz), 1.62 (3H, s), 1.69 (3H, s), 1.86–2.20 (5H, m), 5.06–5.11 (1H, m); CD (*c* 2.42×10^{-4} M, MeOH): $\lambda_{ext.}$ 282.3 ($\Delta\varepsilon = -9.8$), 204.8 ($\Delta\varepsilon = +22.3$) nm; HRMS ($FAB^+$) calcd for $C_{14}H_{23}O$ [$(M+H)^+$] 207.1749; found, 207.1767. This was immediately used in the next step without further purification.

4.10. (4*R*,1′*S*,5′*R*)-4-(4′-Oxobicyclo[3.1.0]hexyl)pentanal (4*R*,1′*S*,5′*R*)-8 (enzymatic)

To a stirred solution of (6*R*,1′*S*,5′*R*)-**2** (enzymatic, 384 mg, 1.86 mmol) in THF (3 mL) and H_2O (1 mL) were added a solution of OsO_4 (1 g/100 mL in *t*-BuOH, 1 mL) and $NaIO_4$ (1.22 g, 5.70 mmol) at room temperature. After stirring at room temperature for 19 h, the mixture was diluted with ether and water. The separated organic phase was successively washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo to give (4*R*,1′*S*,5′*R*)-**8** (240 mg, 72%) as a yellow oil, ν_{max} (film): 3070 (w), 2700 (w, CHO), 1720 (br s, C=O), 1180 (m), 915 (w), 780 (m) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.98 (3H, d, *J* = 6.8 Hz), 1.09 (1H, dd, *J* = 3.2, 4.8 Hz), 1.13 (1H, dd, *J* = 4.8, 8.8 Hz), 1.35–1.41 (1H, m), 1.53–1.67 (1H, m), 1.70 (1H, dd, *J* = 3.2, 8.8 Hz), 1.78–1.91 (1H, m), 1.93–2.04 (2H, m), 2.08–2.17 (2H, m), 2.38–2.59 (2H, m), 9.78 (1H, t, *J* = 1.2 Hz). Due to its high volatility, this was immediately used in the next step without further purification.

4.11. (4*R*,1′*S*,5′*R*)-4-(4′-Oxobicyclo[3.1.0]hexyl)pentanal (4*R*,1′*S*,5′*R*)-8 (chemical)

In the same manner as described above, (6*R*,1′*S*,5′*R*)-**2**′ (chemical, 269 mg, 1.30 mmol) was converted into (4*R*,1′*S*,5′*R*)-**8**′ (181 mg, 77%) as a colorless oil, ν_{max} (film): 3070 (w), 2720 (w, CHO), 1720 (br s, C=O), 1180 (m), 910 (m), 780 (w) cm^{-1}; δ_H (270 MHz, $CDCl_3$): 0.98 (3H, d, *J* = 7.0 Hz), 1.04–1.18 (2H, m), 1.32–1.42 (1H, m), 1.53–1.73 (2H, m), 1.77–1.91 (1H, m), 1.93–2.03 (2H, m), 2.03–2.18 (2H, m), 2.38–2.60 (2H, m), 9.78 (1H, br s). Due to its high volatility, this was immediately used in the next step without further purification.

4.12. (4*R*,1′*R*,5′*S*)-4-(4′-Oxobicyclo[3.1.0]hexyl)pentanal (4*R*,1′*R*,5′*S*)-8

In the same manner as described above, (6*R*,1′*R*,5′*S*)-**2** (74 mg, 0.36 mmol) was converted into (4*R*,1′*R*,5′*S*)-**8** (50 mg, 77%) as a colorless oil, ν_{max} (film): 3070 (w), 2720 (m, CHO), 1720 (br s, C=O), 1180 (m), 910 (m), 775 (m) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.02 (3H, d, *J* = 6.8 Hz), 1.17–1.24 (1H, m), 1.24–1.30 (1H, m), 1.39 (1H, d, *J* = 1.6 Hz), 1.58–1.69 (1H, m), 1.76–1.92 (2H, m), 1.97–2.06 (2H, m), 2.09–2.19 (2H, m), 2.52–2.57 (2H, m), 9.81 (1H, t, *J* = 1.2 Hz). Due to its high volatility, this was immediately used in the next step without further purification.

4.13. Ethyl (2*Z*,6*R*,1′*S*,5′*R*)-2-methyl-6-(4′-oxobicyclo[3.1.0]-hexyl)hept-2-enoate (2*Z*,6*R*,1′*S*,5′*R*)-9 (enzymatic)

To a stirred solution of ethyl 2-(di-*o*-tolylphosphono)propanoate (486 mg, 1.34 mmol) in dry THF (20 mL), NaH (60% mineral oil suspension, 58 mg, 1.33 mmol) was added at 0 °C. After stirring at 0 °C for 30 min, the mixture was cooled to −78 °C. To this mixture, a solution of (4*R*,1′*S*,5′*R*)-**8** (enzymatic, 236 mg, 1.31 mmol) in dry THF (10 mL) was added dropwise at −78 °C. The resulting mixture was stirred for 1 h at −78 °C, and then for 30 min at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl solution, and the mixture was diluted with ether. The separated organic phase was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo (*Z*:*E* = 21:1, determined by 400 MHz ^1H NMR). The residue was purified by column chromatography on silica gel (15 g, hexane/EtOAc = 10:1) to give (2*Z*,6*R*,1′*S*,5′*R*)-**9** (268 mg, 77%) as a colorless oil [containing unreacted ethyl 2-(di-*o*-tolylphosphono)propanoate]. The undesired *E*-isomer could be removed by column chromatography. ν_{max} (film): 3060 (w), 1720 (br s, C=O), 1645 (w, C=C), 1180 (br s, C–O), 950 (br m), 760 (br m) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.98 (3H, d, *J* = 6.4 Hz), 1.07 (1H, dd, *J* = 2.8, 4.8 Hz), 1.13 (1H, dd, *J* = 4.8, 8.8 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 1.33–1.46 (2H, m), 1.67 (1H, dd, *J* = 2.8, 8.8 Hz), 1.89 (3H, d, *J* = 0.8 Hz), 1.96–2.00 (2H, m), 2.07–2.28 (3H, m), 2.37–2.56 (2H, m), 4.19 (2H, q, *J* = 7.2 Hz), 5.87 (1H, dt, *J* = 0.8, 7.6 Hz). The ester was immediately used in the next step without further purification.

4.14. Ethyl (2*Z*,6*R*,1′*S*,5′*R*)-2-methyl-6-(4′-oxobicyclo[3.1.0]-hexyl)hept-2-enoate (2*Z*,6*R*,1′*S*,5′*R*)-9 (chemical)

In the same manner as described above, (4*R*,1′*S*,5′*R*)-**8** (chemical, 181 mg, 0.25 mmol) was converted into (2*Z*,6*R*,1′*S*,5′*R*)-**9** (142 mg, 54%) as a colorless oil [contaminated with unreacted ethyl 2-(di-*o*-tolylphosphono)propanoate], ν_{max} (film): 3060 (w), 1730 (br s, C=O), 1720 (br s, C=O), 1645 (w, C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.98 (3H, d, *J* = 6.8 Hz), 1.08 (1H, dd, *J* = 2.8, 4.8 Hz), 1.14 (1H, dd, *J* = 4.8, 9.2 Hz), 1.30 (3H, t, *J* = 6.8 Hz), 1.33–1.47 (2H, m), 1.50–1.62 (1H, m), 1.67 (1H, dd, *J* = 2.4, 9.6 Hz), 1.89 (3H, s), 1.94–2.00 (2H, m), 2.07–2.15 (2H, m), 2.20–2.28 (1H, m), 2.37–2.53 (2H, m), 4.19 (2H, q, *J* = 6.8 Hz), 5.87 (1H, br t-like, *J* = 7.2 Hz). The ester was immediately used in the next step without further purification.

4.15. Ethyl (2*Z*,6*R*,1′*R*,5′*S*)-2-methyl-6-(4′-oxobicyclo[3.1.0]-hexyl)hept-2-enoate (2*Z*,6*R*,1′*R*,5′*S*)-9

In the same manner as described above, (4*R*,1′*R*,5′*S*)-**8** (45 mg, 0.25 mmol) was converted into (2*Z*,6*R*,1′*R*,5′*S*)-**9** (38 mg, 58%) as a colorless oil [contaminated with unreacted ethyl 2-(di-*o*-tolylphosphono)propanoate], ν_{max} (film): 3060 (w), 1720 (br s, C=O), 1645 (w, C=C), 1180 (br s, C–O), 950 (br m), 765 (br m) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.00 (3H, d, *J* = 6.8 Hz), 1.15–1.20 (1H, m), 1.25 (1H, t, *J* = 7.6 Hz), 1.31 (3H, t, *J* = 7.2 Hz), 1.34–1.45 (1H, m), 1.49–1.57 (1H, m), 1.69 (1H, dd, *J* = 7.6, 19 Hz), 1.90 (3H, d, *J* = 1.6 Hz), 1.92–2.18 (2H, m), 2.19–2.29 (1H, m), 2.54 (2H, br q, *J* = 7.2 Hz), 4.20 (2H, q, *J* = 7.2 Hz), 5.90 (1H, dq, *J* = 1.2, 7.2 Hz). The ester was immediately used in the next step without further purification.

4.16. Ethyl (2*Z*,6*R*,1′*S*,5′*S*)-2-methyl-6-(4′-methylenebicyclo-[3.1.0]hexyl)hept-2-enoate (2*Z*,6*R*,1′*S*,5′*S*)-10 (enzymatic)

To a stirred suspension of methyltriphenylphosphonium bromide (500 mg, 1.40 mmol) in dry THF (5 mL), a solution of *n*-BuLi (1.57 M in hexane, 0.89 mL, 1.4 mmol) was added dropwise at 0 °C under argon. After stirring at 0 °C for 10 min, a solution of (2*Z*,6*R*,1′*S*,5′*R*)-**9** (enzymatic, 174 mg, 0.660 mmol) in dry THF (5 mL) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 5 min, and then the reaction was quenched with water. The resulting mixture was extracted with EtOAc. The combined extract was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (15 g, hexane/EtOAc = 20:1) to give (2*Z*,6*R*,1′*S*,5′*S*)-**10** (100 mg, 58%) as a colorless oil, ν_{max} (film): 3080 (w), 1715 (s, C=O), 1650 (m, C=C), 1190 (br s, C–O), 1145 (br s, C–O), 860 (s) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.59 (1H, dd, *J* = 4.4, 8.0 Hz), 0.67 (1H, dd, *J* = 3.6, 4.4 Hz), 0.93 (3H, d, *J* = 6.8 Hz), 1.24 (1H, q, *J* = 6.8 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 1.33–1.42 (1H, m), 1.50–1.58 (1H, m), 1.60 (1H, dd, *J* = 3.6, 8.0 Hz), 1.64–1.78 (2H, m), 1.88 (3H, d, *J* = 1.2 Hz), 1.93–2.08 (1H, m), 2.14 (1H, dd, *J* = 8.4, 16 Hz), 2.33–2.53 (2H, m), 4.19 (2H, q, *J* = 7.2 Hz), 4.62 (1H, s), 4.80 (1H, s), 5.89 (1H, dq, *J* = 1.2, 8.0 Hz); HRMS (FAB^+) calcd for $C_{17}H_{27}O_2$ [$(M+H)^+$] 263.2011; found, 263.1992.

4.17. Ethyl (2*Z*,6*R*,1′*S*,5′*S*)-2-methyl-6-(4′-methylenebicyclo-[3.1.0]hexyl)hept-2-enoate (2*Z*,6*R*,1′*S*,5′*S*)-10 (chemical)

In the same manner as described above, (2*Z*,6*R*,1′*S*,5′*R*)-**9** (chemical, 127 mg, 0.480 mmol) was converted into (2*Z*,6*R*,1′*S*,5′*S*)-**10** (55 mg, 43%) as a colorless oil, ν_{max} (film): 3080 (w), 1720 (s, C=O), 1650 (m, C=C), 1190 (br s, C–O), 1025 (m), 860 (s) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.59 (1H, dd, *J* = 4.8, 8.4 Hz), 0.67 (1H, dd, *J* = 3.2, 4.8 Hz), 0.93 (3H, d, *J* = 6.8 Hz), 1.19–1.28 (1H, m), 1.30 (3H, t, *J* = 7.2 Hz), 1.33–1.42 (1H, m), 1.51–1.62 (2H, m), 1.63–1.77 (2H, m), 1.89 (3H, s), 1.94–2.05 (1H, m), 2.14 (1H, dd, *J* = 8.4, 16 Hz), 2.32–2.53 (2H, m), 4.19 (2H, q, *J* = 7.2 Hz), 4.63 (1H, s), 4.80 (1H, s), 5.90 (1H, br t, *J* = 7.6 Hz); HRMS (EI^+) calcd for $C_{17}H_{26}O_2$ (M^+) 262.1933; found, 262.1935.

4.18. Ethyl (2*Z*,6*R*,1′*R*,5′*R*)-2-methyl-6-(4′-methylenebicyclo-[3.1.0]hexyl)hept-2-enoate (2*Z*,6*R*,1′*R*,5′*R*)-10

In the same manner as described above, (2*Z*,6*R*,1′*R*,5′*S*)-**9** (38 mg, 0.14 mmol) was converted into (2*Z*,6*R*,1′*R*,5′*R*)-**10** (24 mg, 64%) as a colorless oil, ν_{max} (film): 3080 (w), 1715 (s, C=O), 1650 (m, C=C), 1185 (br s, C–O), 1140 (br s, C–O), 860 (s) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.65 (1H, dd-like, *J* = 4.4, 8.4 Hz), 0.75 (1H, dd, *J* = 3.6, 4.4 Hz), 0.95 (3H, d, *J* = 6.8 Hz), 1.19 (1H, q, *J* = 6.8 Hz), 1.30 (3H, t, *J* = 7.2 Hz), 1.34 (1H, q, *J* = 8.0 Hz), 1.46–1.53 (1H, m), 1.53 (1H, dd, *J* = 3.6, 8.4 Hz), 1.62 (1H, dd, *J* = 7.2, 11 Hz), 1.73–1.82 (1H, m), 1.89 (3H, q, *J* = 1.2 Hz), 1.96–2.06 (1H, m), 2.15 (1H, dd, *J* = 9.2, 16 Hz), 2.50 (2H, dq-like, *J* = 1.2, 7.6 Hz), 4.20 (2H, q, *J* = 7.2 Hz), 4.62 (1H, s), 4.80 (1H, s), 5.90 (1H, dt-like, *J* = 1.2, 7.6 Hz); HRMS (EI^+) calcd for $C_{17}H_{26}O_2$ (M^+) 262.1933; found, 262.1927.

4.19. (2*Z*,6*R*,1′*S*,5′*S*)-2-Methyl-6-(4′-methylenebicyclo[3.1.0]-hexyl)hept-2-en-1-ol (2*Z*,6*R*,1′*S*,5′*S*)-1 (enzymatic)

To a stirred solution of (2*Z*,6*R*,1′*S*,5′*S*)-**10** (enzymatic, 80 mg, 0.30 mmol) in dry CH_2Cl_2 (5 mL), a solution of $(i\text{-Bu})_2AlH$ (0.99 M in toluene, 3.1 mL, 3.1 mmol) was added dropwise at −78 °C under argon. The mixture was stirred at −78 °C for 30 min and 0 °C for 30 min. The reaction was then quenched with MeOH (3 mL) at 0 °C, and the mixture was stirred at room temperature for 30 min. The mixture was diluted with ether, and filtered through a bed of Celite. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (10 g, hexane/EtOAc = 10:1) to give (2*Z*,6*R*,1′*S*,5′*S*)-**1** (61 mg, 91%) as a colorless oil, $n_D^{27} = 1.5040$; $[\alpha]_D^{27} = -37.9$ (*c* 1.19, hexane); ν_{max} (film): 3330 (s, OH), 1650 (s, C=C), 1450 (s), 1375 (m), 1010 (br s, C–O), 865 (s) cm^{-1}; δ_H (600 MHz, C_6D_6): 0.40 (1H, ddd, *J* = 1.2, 4.8, 7.8 Hz), 0.53 (1H, t, *J* = 5.4 Hz), 0.57 (1H, dd, *J* = 3.6, 4.8 Hz), 0.85 (3H, d, *J* = 6.6 Hz), 1.01 (1H, q, *J* = 7.2 Hz), 1.19–1.26 (1H, m), 1.40–1.47 (2H, m), 1.56 (1H, dd, *J* = 3.0, 8.4 Hz), 1.57–1.62 (1H, m), 1.75 (3H, d, *J* = 1.2 Hz), 1.84–1.92 (1H, m), 1.92–2.00 (2H, m), 2.05 (1H, dd, *J* = 9.0, 16 Hz), 3.93–3.98 (2H, m), 4.79 (1H, s), 5.00 (1H, s), 5.17 (1H, t, *J* = 7.2 Hz); δ_C (150 MHz, C_6D_6): 16.2, 18.3, 21.3, 25.8, 26.5, 29.0, 31.7, 35.2, 36.4, 38.0, 61.4, 102.5, 128.1, 135.0, 153.8. These ^1H and ^{13}C NMR spectra were identical with those of the natural pheromone except for signal due to contamination with a small amount of (2*Z*,6*R*,1′*R*,5′*R*)-**1** (see Ref. 9); δ_H (400 MHz, $CDCl_3$): 0.57 (1H, dd, *J* = 4.8, 8.4 Hz), 0.67 (1H, dd, *J* = 3.6, 4.8 Hz), 0.93 (3H, d, *J* = 6.8 Hz), 1.19 (1H, q, *J* = 6.8 Hz), 1.20–1.36 (2H, m), 1.41–1.55 (1H, m), 1.59 (1H, dd, *J* = 3.6, 8.4 Hz), 1.62–1.76 (2H, m), 1.79 (3H, d, *J* = 1.2 Hz), 1.94–2.09 (3H, m), 2.14 (1H, dd, *J* = 8.0, 16 Hz), 4.12 (2H, s), 4.63 (1H, s), 4.81 (1H, s), 5.28 (1H, t, *J* = 6.8 Hz); δ_C (100 MHz, $CDCl_3$): 16.1, 18.0, 21.2, 25.6, 26.5, 28.7, 31.2, 34.9, 36.5, 37.8, 61.6, 101.9, 128.8, 134.0, 154.1; HRMS (EI^+) calcd for $C_{15}H_{24}O$ (M^+) 220.1827; found, 220.1829.

4.20. (2*Z*,6*R*,1′*S*,5′*S*)-2-Methyl-6-(4′-methylenebicyclo[3.1.0]-hexyl)hept-2-en-1-ol (2*Z*,6*R*,1′*S*,5′*S*)-1 (chemical)

In the same manner as described above, (2*Z*,6*R*,1′*S*,5′*S*)-**10** (chemical, 573 mg, 2.18 mmol) was converted into (2*Z*,6*R*,1′*S*,5′*S*)-**1** (364 mg, 76%) as a colorless oil, $n_D^{23} = 1.5060$; $[\alpha]_D^{22} = -52.7$ (*c* 1.14, hexane); ν_{max} (film): 3340 (s, OH), 3070 (w), 1650 (s, C=C), 1455 (br s), 1375 (m), 1010 (br s, C–O), 865 (s) cm^{-1}; δ_H (400 MHz, C_6D_6): 0.41 (1H, ddd, *J* = 0.8, 4.8, 8.4 Hz), 0.57 (1H, dd, *J* = 3.3, 4.6 Hz), 0.85 (3H, d, *J* = 6.8 Hz), 1.01 (1H, sext., *J* = 6.8 Hz), 1.17–1.27 (1H, m), 1.39–1.49 (2H, m), 1.56 (1H, dd, *J* = 3.2, 8.4 Hz), 1.57–1.64 (1H, m), 1.76 (3H, d, *J* = 0.8 Hz), 1.83–1.93 (1H, m), 1.96 (2H, br q, *J* = 7.6 Hz), 2.05 (1H, dd, *J* = 8.8, 16 Hz), 3.98 (2H, s), 4.78 (1H, s), 4.99 (1H, s), 5.17 (1H, t, *J* = 7.2 Hz); δ_C (100 MHz, C_6D_6): 16.2, 18.3, 21.4, 25.8, 26.5, 29.0, 31.7, 35.2, 36.5, 38.0, 61.4, 102.5, 128.1, 135.0, 153.8. These ^1H and ^{13}C NMR spectra were completely identical with those of the natural pheromone (see Ref. 9); δ_H (400 MHz, $CDCl_3$): 0.57 (1H, dd, *J* = 4.4, 8.4 Hz), 0.68 (1H, dd, *J* = 2.8, 5.2 Hz), 0.93 (3H, d, *J* = 6.8 Hz), 1.21 (1H, sext., *J* = 7.2 Hz), 1.25 (1H, br s), 1.33 (1H, dq, *J* = 14, 7.6 Hz), 1.44–1.53 (1H, m), 1.59 (1H, dd, *J* = 3.2, 8.0 Hz), 1.62–1.74 (2H, m), 1.79 (3H, d, *J* = 1.6 Hz), 1.94–2.02 (1H, m), 2.03 (2H, br q, *J* = 7.6 Hz), 2.14 (1H, dd, *J* = 7.6, 16 Hz), 4.12 (2H, s), 4.63 (1H, s), 4.81 (1H, s), 5.28 (1H, t, *J* = 7.2 Hz); δ_C (100 MHz, $CDCl_3$): 16.1, 18.0, 21.2, 25.5, 26.5, 28.7, 31.2, 34.8, 36.5, 37.8, 61.6, 101.8, 128.8, 134.0, 154.1; HRMS (EI^+) calcd for $C_{15}H_{24}O$ (M^+) 220.1827; found, 220.1822.

4.21. (2*Z*,6*R*,1′*R*,5′*R*)-2-Methyl-6-(4′-methylenebicyclo[3.1.0]-hexyl)hept-2-en-1-ol (2*Z*,6*R*,1′*R*,5′*R*)-1

In the same manner as described above, (2*Z*,6*R*,1′*R*,5′*R*)-**10** (24 mg, 0.092 mmol) was converted into (2*Z*,6*R*,1′*R*,5′*R*)-**1** (14 mg, 70%) as a colorless oil, $n_D^{25} = 1.5033$; $[\alpha]_D^{25} = +59.8$ (*c* 0.61, hexane); ν_{max} (film): 3330 (s, OH), 1650 (s, C=C), 1455 (s), 1375 (m), 1010 (br s, C–O), 860 (s) cm^{-1}; δ_H (600 MHz, C_6D_6): 0.51 (1H, ddd, *J* = 1.2, 6.0, 7.2 Hz), 0.53 (1H, t, *J* = 5.4 Hz), 0.65 (1H, dd, *J* = 3.6, 4.2 Hz), 0.87 (3H, d, *J* = 6.6 Hz), 0.99 (1H, q, *J* = 6.6 Hz), 1.12–1.28

(2H, m), 1.31–1.38 (1H, m), 1.43 (1H, dd, J = 8.4, 11 Hz), 1.47(1H, dd, J = 3.0, 7.8 Hz), 1.65 (1H, dq, J = 1.8, 10 Hz), 1.76 (3H, d, J = 0.6 Hz), 1.87–1.94 (1H, m), 1.98 (1H, dt, J = 7.8, 15.6 Hz), 2.06 (1H, dd, J = 9.0, 16 Hz), 3.94 (2H, d, J = 5.4 Hz), 4.79 (1H, s), 5.01 (1H, s), 5.19 (1H, t, J = 7.2 Hz); δ_C (150 MHz, C_6D_6): 17.6, 18.4, 21.3, 26.0, 26.4, 29.2, 30.1, 35.8, 36.7, 38.1 61.4, 102.4, 128.2, 134.9, 153.9; δ_H (400 MHz, $CDCl_3$): 0.65 (1H, ddd, J = 1.2, 4.4, 8.4 Hz), 0.75 (1H, dd, J = 3.2, 4.4 Hz), 0.94 (3H, d, J = 6.8 Hz), 1.14–1.31 (3H, m), 1.38–1.47 (1H, m), 1.53 (1H, dd, J = 3.2, 8.4 Hz), 1.61 (1H, dd, J = 8.8, 12 Hz), 1.72–1.80 (1H, m), 1.79 (3H, d, J = 1.2 Hz), 1.95–2.13 (3H, m), 2.15 (1H, dd, J = 8.8, 16 Hz), 4.14 (2H, s), 4.62 (1H, s), 4.81 (1H, s), 5.29 (1H, t, J = 6.8 Hz); δ_C (100 MHz, $CDCl_3$): 17.4, 18.3, 21.2, 25.7, 26.2, 28.9, 29.7, 35.5, 36.7, 38.0, 61.6, 101.7, 128.8, 134.0, 154.3; HRMS (EI+) calcd for $C_{15}H_{24}O$ (M^+) 220.1827; found, 220.1825.

4.22. (2*Z*,6*R*,1′*S*,5′*S*)-2-Methyl-6-(4′-methylenebicyclo[3.1.0]-hexyl)hept-2-enyl acetate (2*Z*,6*R*,1′*S*,5′*S*)-17

To a stirred solution of (2*Z*,6*R*,1′*S*,5′*S*)-**1** (chemical, 40 mg, 0.18 mmol) in pyridine (3 mL), acetic anhydride (52 μL, 0.55 mmol) and a catalytic amount of DMAP (20 mg, 0.16 mmol) were added at 0 °C. After stirring at 0 °C for 2 h, the reaction was quenched with water. The resulting mixture was diluted with EtOAc, and then the separated organic phase was successively washed with water, saturated aqueous $CuSO_4$ solution, water, saturated aqueous $NaHCO_3$ solution and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (10 g, hexane/ethyl acetate = 25:1) to give (2*Z*,6*R*,1′*S*,5′*S*)-**17** (39 mg, 82%) as a colorless oil, $n_D^{22} = 1.4888$; $[\alpha]_D^{22} = -51.6$ (*c* 1.10, $CHCl_3$); ν_{max} (film): 3080 (w), 1740 (s, C=O), 1650 (s, C=C), 1235 (br s), 1020 (s, C–O), 865 (s) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.57 (1H, dd, J = 4.4, 8.0 Hz), 0.67 (1H, dd, J = 3.2, 4.4 Hz), 0.92 (3H, d, J = 6.8 Hz), 1.21 (1H, sext., J = 6.8 Hz), 1.27–1.37 (1H, m), 1.44–1.54 (1H,m), 1.59 (1H, dd, J = 3.2, 8.0 Hz), 1.62–1.73 (2H, m), 1.74 (3H, d, J = 0.8 Hz), 1.94–2.08 (3H, m), 2.07 (3H, s), 2.14 (1H, dd, J = 8.0, 16 Hz), 4.57 (2H, s), 4.63 (1H, br s), 4.80 (1H, br s), 5.39 (1H, br t, J = 7.2 Hz); HRMS (EI+) calcd for $C_{17}H_{26}O_2$ (M^+) 262.1933; found, 262.1935.

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