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Pheromone synthesis. Part 243: Synthesis and biological evaluation of (3*R*,13*R*,1′*S*)-1′-ethyl-2′-methylpropyl 3,13-dimethylpentadecanoate, the major component of the sex pheromone of Paulownia bagworm, *Clania variegata*, and its stereoisomers☆

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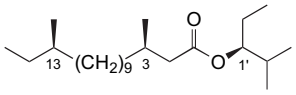
ABSTRACT

All of the four stereoisomers of (1′*S*)-1′-ethyl-2′-methylpropyl 3,13-dimethylpentadecanoate, the major component of the female sex pheromone of *Clania variegata*, were synthesized by employing olefin cross metathesis as the key reaction and starting from (*R*)- or (*S*)-2-methyl-1-butanol, (*R*)- or (*S*)-citronellal, and (*S*)-2-methyl-3-pentanol. Their bioassay revealed the (3*R*,13*R*,1′*S*)-isomer as the bioactive one, whose more efficient synthesis was achieved in two different ways by employing Wittig reaction as the key step.

1. Introduction

The Paulownia bagworm, *Clania variegata* Snell (Lepidoptera: Psychidae), is an economically important pest, and occurs in Asian countries such as China, India, Indonesia, Japan, Korea, Thailand, and Vietnam. The larvae feed on the foliage and young shoots of many plant species, including the Bishop wood (*Bischofia javanica* Blume) and the Princess tree (*Paulownia tomentosa* Thunb) causing serious damage to the growth and reduced timber yields. In addition, it causes significant defoliation of pine trees, *Pinus* spp., in naturally regenerating forests. It has only one generation per year in China, and the duration of adult activity is only two weeks.

The major component of its female-produced sex pheromone was reported to be 1′-ethyl-2′-methylpropyl 3,13-dimethylpentadecanoate (**1**, Fig. 1) by Gries et al.[2] in 2006. As to the absolute configuration of the pheromone **1**, they assigned *S* configuration to the alcohol part by synthesis of both (1′*R*)- and (1′*S*)-**1** followed by their field bioassay in China.[2] The absolute configuration of the two remaining stereogenic centers of the carboxylic part of **1**, however, remained unknown.



(3*R*,13*R*,1′*S*)-**1**

Figure 1. Structure of the major component of the sex pheromone of *Clania variegata*.

In continuation of our long-term studies on the absolute configuration of pheromones,[3] we became interested in clarifying the stereochemistry of the naturally occurring **1**. We therefore synthesized all of the four stereoisomers of (1′*S*)-**1** by means of olefin cross metathesis, which was reported as a preliminary communication in 2009.[4] The four isomers of (1′*S*)-**1** were bioassayed in China, and only a single isomer (3*R*,13*R*,1′*S*)-**1** was shown to be highly bioactive.

This paper describes in detail our metathesis-mediated synthesis of the four stereoisomers of (1′*S*)-**1** together with two additional syntheses of (3*R*,13*R*,1′*S*)-**1** by means of Wittig reaction. The new syntheses were more efficient than the metathesis-mediated one. As to the synthesis of (*S*)-2-methyl-3-pentanol, the

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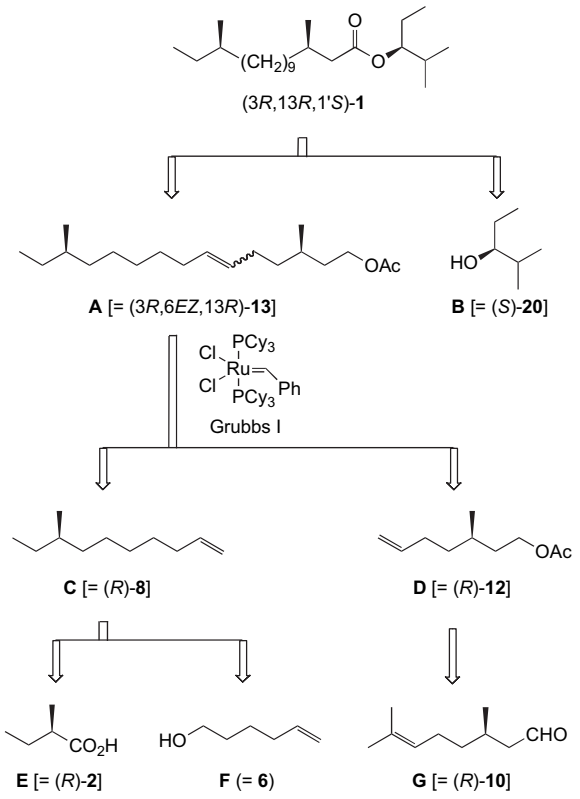
alcohol part of **1**, we will report both the details of the previous syntheses[4] and a new synthesis based on organozinc chemistry. Details of the bioassay in China will also be recorded.

2. Results and discussion

2.1. Metathesis-mediated synthesis of the four stereoisomers of (1′*S*)-1

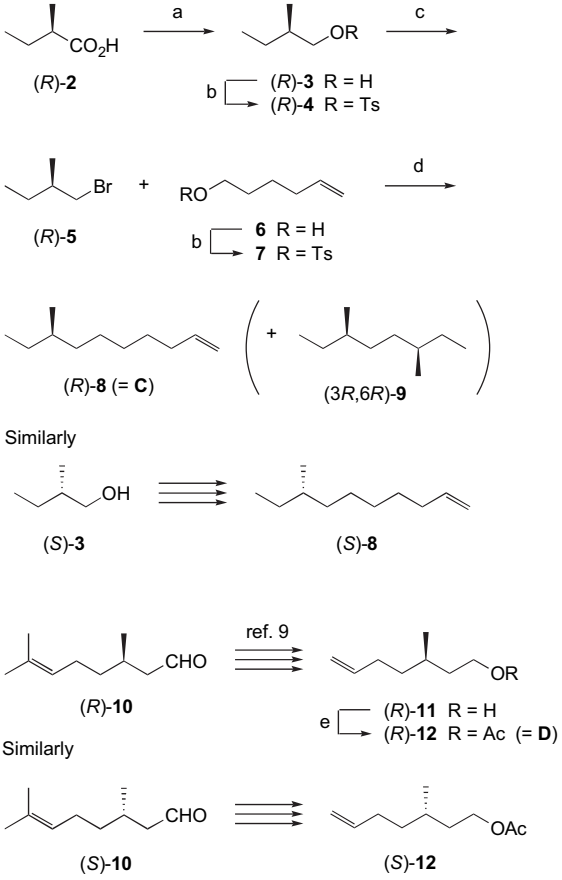
Since the absolute configuration of the natural pheromone was unknown at the outset of this work, we chose olefin cross metathesis as the key reaction to provide all the four isomers of (1′*S*)-**1** quickly without complication. Our synthesis is totally different from a synthesis reported by Wei et al. in the patent literature.[5]

Scheme 1 shows our retrosynthetic analysis of (3*R*,13*R*,1′*S*)-**1**. The ester **1** can be dissected to 1-acetoxy-3,13-dimethyl-6-pentadecene moiety **A** and the alcohol moiety **B**. The olefinic acetate **A** would be synthesized by cross metathesis of **C** with **D**, the two metathesis partners. The optically active olefin **C** would be prepared from (*R*)-2-methylbutanoic acid (**E**) and 5-hexen-1-ol (**F**). Another metathesis partner **D** would be obtained from (*R*)-citronellal (**G**), and the alcohol part **B** must be obtainable via asymmetric synthesis.



Scheme 1. Retrosynthetic analysis of (3*R*,13*R*,1′*S*)-**1**.

Synthesis of the metathesis partners, (*R*)-**8** (=**C**) and (*R*)-**12** (=**D**), is summarized in Scheme 2. The starting material for (*R*)-**8** was (*R*)-2-methylbutanoic acid (**2**, T. Hasegawa Co., >99.0% ee), which was obtained by treatment of (±)-**2** with *Pseudomonas* sp. TH-252-1.[6] Reduction of (*R*)-**2** with lithium aluminum hydride gave alcohol (*R*)-**3**, whose tosylate (*R*)-**4** was treated with lithium bromide in DMF to furnish (*R*)-2-methylbutyl bromide (**5**). The Grignard reagent prepared from (*R*)-**5** and magnesium in THF was coupled with tosylate **7** (obtained by tosylation of commercially available **6**) in the presence of dilithium tetrachlorocuprate at −65 to −50 °C under the Schlosser conditions[7] to give (*R*)-**8** in 42% yield based on (*R*)-**5**. GC–MS analysis of the product revealed it to be a 91.2:8.8 mixture of (*R*)-**8** and (3*R*,6*R*)-**9**. The latter must have been generated in the course of the preparation of the Grignard reagent. Similarly, commercially available (*S*)-**3** (Tokyo Kasei) afforded crude (*S*)-**8** as a 93:7 mixture of (*S*)-**8** and (3*S*,6*S*)-**9**. The contaminating hydrocarbon **9** could be removed after olefin metathesis. The enantiomeric purity of (*R*)-**8** was >98.0% ee, while that of (*S*)-**8** was 99.0% ee as determined by their GC analysis using CHIRAMIX®[8] as the chiral stationary phase. The overall yield of (*R*)-**8** was 32% based on (*R*)-**2** (four steps), and that of (*S*)-**8** was 22% based on (*S*)-**3** (three steps).

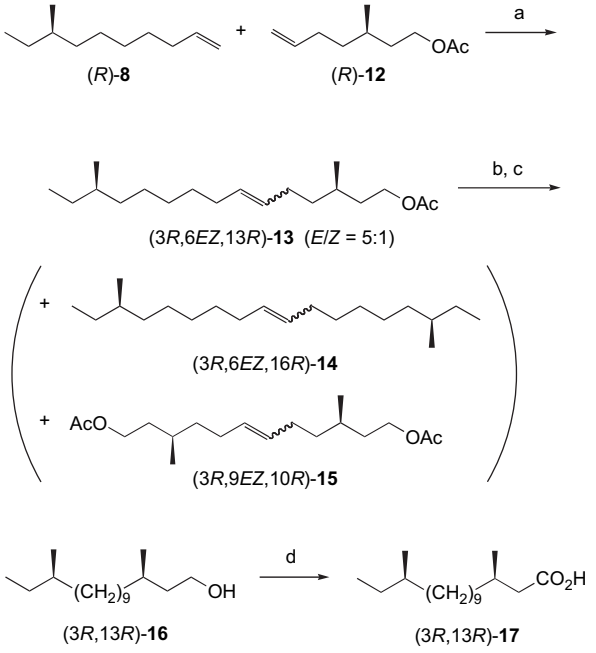


Scheme 2. Synthesis of the metathesis partners **8** and **12**. Reagents: (a) $LiAlH_4$, Et_2O; (b) TsCl, C_5H_5N (51% for **7**); (c) LiBr, DMF [78% based on (*R*)-**2**, three steps]; (d) (i) (*R*)-**5**, Mg, THF; (ii) **7**, THF, Li_2CuCl_4 [42% based on (*R*)-**5** or 66% based on **7**]; (e) Ac_2O, DMAP, C_5H_5N (82%).

The other partners of metathesis reaction, (*R*)- and (*S*)-**12**, were prepared by acetylation of (*R*)- and (*S*)-**11**. These alcohols (*R*)- and (*S*)-**11**, respectively, were synthesized from the enantiomers of citronellal (**10**, Takasago International Corporation, both 97% ee), and employed as the intermediates in the synthesis of the pheromone of an Okinawan moth, *Lyclene dharma dharma*.[9] Their enantiomeric purities were 97.2% ee for both (*R*)- and (*S*)-**12** by their GC analysis using octakis-(2,3-di-*O*-methoxymethyl-6-*O*-*tert*-butyldimethylsilyl)-γ-cyclodextrin as the chiral stationary phase.[9] The overall yield of (*R*)-**12** was 46% based on (*R*)-**10** (seven steps), and that of (*S*)-**12** was 45% based on (*S*)-**10** (seven steps).

Scheme 3 shows the synthesis of the key acid (3*R*,13*R*)-**17** via the crucial step of olefin cross metathesis.[10–14] Some applications of cross metathesis to pheromone synthesis have been reported by us and others.[1,9,14–16] Because (*R*)-**8** could be prepared in fewer steps (four) than (*R*)-**12** (seven steps), 3 equiv of (*R*)-**8** was mixed with 1 equiv of (*R*)-**12** in dichloromethane. In the presence of 5 mol % [based on (*R*)-**12**] of Grubbs' first generation catalyst, the mixture

was stirred and heated under reflux for 6 h under argon. Chromatographic purification of the product first gave (3*R*,9*EZ*,16*R*)-**14** [50% yield based on (*R*)-**8**], and then the desired (3*R*,6*EZ*,13*R*)-**13** contaminated with (3*R*,6*EZ*,10*R*)-**15** in 88% yield based on (*R*)-**12**.

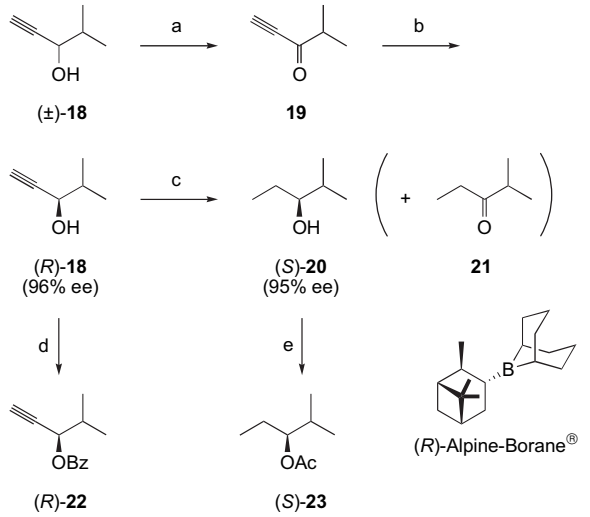


Scheme 3. Synthesis of the acid (3*R*,13*R*)-**17**. Reagents: (a) Grubbs I [ca. 5 mol % based on (*R*)-**12**], (*R*)-**8**/(*R*)-**12**=ca. 3:1 in CH_2Cl_2, reflux, 6 h [88% based on (*R*)-**12**]; (b) NaOH, MeOH, aq THF, reflux, 1 h (97%); (c) H_2, 10% Pd–C, EtOH; then SiO_2 chromatog. (58%); (d) Jones CrO_3, acetone (75%).

Since complete removal of **15** from **13** was difficult, the crude (3*R*,6*EZ*,13*R*)-**13** was subjected to alkaline hydrolysis and hydrogenation over 10% palladium/charcoal. Subsequent chromatographic purification gave (3*R*,13*R*)-**16** in 53% yield based on the crude (3*R*,13*R*)-**13** (two steps). Oxidation of (3*R*,13*R*)-**16** with Jones chromic acid afforded the desired acid (3*R*,13*R*)-**17** in 75% yield. The overall yield of (3*R*,13*R*)-**17** was 35% based on (*R*)-**12** (four steps). Other stereoisomers of the acid **17** could be synthesized in the same manner.

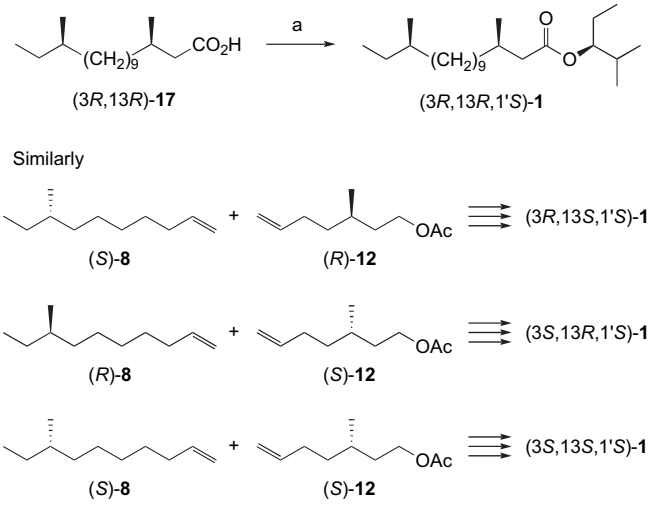
The next task was the synthesis of (*S*)-2-methyl-3-pentanol (**20**). Gries et al. previously prepared (*S*)-**20** by kinetic resolution of (±)-4-methyl-1-penten-3-ol by means of Sharpless asymmetric epoxidation.[2] As shown in Scheme 4, we synthesized (*S*)-**20** by asymmetric reduction of 4-methyl-1-pentyn-3-one (**19**) to (*R*)-**18** with Brown's (*R*)-Alpine-Borane®[17] as the key step. Commercially available (±)-4-methyl-1-pentyn-3-ol (**18**) was oxidized with Jones chromic acid to give ketone **19**. This was reduced with (*R*)-Alpine-Borane® to give highly volatile (*R*)-**18** in 47% yield. The enantiomeric purity of (*R*)-**18** was estimated as 96% ee by HPLC analysis of the corresponding benzoate (*R*)-**22**, employing Chiralcel® OJ-H as the chiral stationary phase. Hydrogenation of (*R*)-**18** over 10% palladium/charcoal in pentane afforded a 2:1 mixture of (*S*)-**20** and **21**. The ketone **21** must have been produced via 4-methyl-1-penten-3-one generated by palladium-catalyzed isomerization of **18**. A similar isomerization–hydrogenation has been observed in the past.[1] After chromatographic purification, highly volatile (*S*)-**20**; $[\alpha]_D^{25}$ −20.1 (*c* 1.16, EtOH) {Ref. 18: $[\alpha]_D^{23}$ −16.9 (*c* 0.39, EtOH)}, could be secured in 16% yield. Its enantiomeric purity was estimated as 95.0% ee by GC analysis of the corresponding acetate **23**. More efficient synthesis of (*S*)-**20** was later developed as described in Section 2.3.

The final step as depicted in Scheme 5 was the esterification of the four stereoisomers of acid **17** with (*S*)-**20**. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC, 1.5 equiv) was added to a solution of (3*R*,13*R*)-**17** (1 equiv), (*S*)-**20** (1.1 equiv), and



Scheme 4. Synthesis of the alcohol (*S*)-**20**. Reagents: (a) Jones CrO_3, acetone (73%); (b) (*R*)-Alpine-Borane® (47%); (c) H_2, 10% Pd–C, pentane (83%); (d) BzCl, DMAP, C_5H_5N; (e) Ac_2O, C_5H_5N.

4-(dimethylamino)pyridine (DMAP, 1.5 equiv) in dichloromethane to give (3*R*,13*R*,1′*S*)-**1** in 84% yield as an oil, $[\alpha]_D^{23}$ −5.38 (*c* 1.30, $CHCl_3$). Its ^1H and ^{13}C NMR data were in good accord with those published for (3*RS*,13*RS*,1′*S*)-**1**.[2] Similarly, we synthesized (3*R*,13*S*,1′*S*)-**1**, $[\alpha]_D^{23}$ +1.63 (*c* 1.32, $CHCl_3$), (3*S*,13*R*,1′*S*)-**1**, $[\alpha]_D^{23}$ −10.8 (*c* 1.31, $CHCl_3$), and (3*S*,13*S*,1′*S*)-**1**, $[\alpha]_D^{23}$ −3.42 (*c* 1.20, $CHCl_3$). The spectral data of these four isomers of **1** were virtually indistinguishable. The overall yield of (3*R*,13*R*,1′*S*)-**1** was 13% based on (*R*)-**10** (12 steps).



Scheme 5. Synthesis of the target esters **1**. Reagents: (a) (*S*)-**20**, EDC, DMAP, CH_2Cl_2 [84% based on (3*R*,13*R*)-**17**].

2.2. Evaluation of pheromone activity of the four stereoisomers of (1′*S*)-1 by field experiment

The four steroisomers of (1′*S*)-**1** were tested for the attraction of male *C. variegata* in the forest of *Platanus hispanica* Muench. in Yantai, Shandong Province, China, in June 2009.

As shown in Figure 2, the number of male *C. variegata* captured in traps was affected by the stereochemistry of (1′*S*)-**1**. Significantly more males were captured in traps baited with (3*R*,13*R*,1′*S*)-**1** than any other stereoisomer tested. An average of 43 males per trap were captured in traps baited with (3*R*,13*R*,1′*S*)-**1** over a 12-day period. Significantly fewer males (2.2 per trap) were captured in traps baited with (3*R*,13*S*,1′*S*)-**1**, while no male was captured in

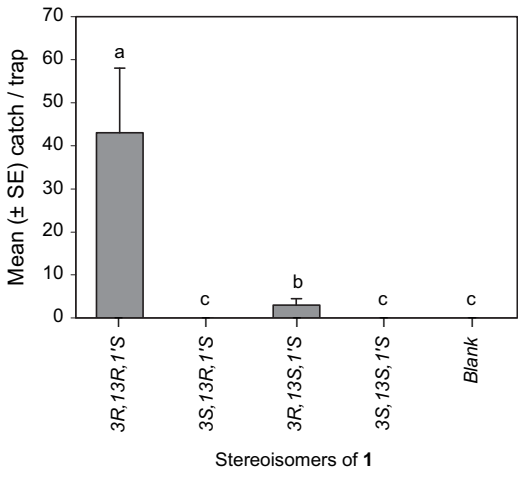


Figure 2. Mean catch ± standard error per trap over 12-day period of male Paulownia bagworm, *Clania variegata*, in traps baited with one of the four possible stereoisomers (100 μg) of (1′*S*)-1′-ethyl-2′-methylpropyl 3,13-dimethylpentadecanoate (**1**). Letters on columns indicate significant differences ($P<0.05$).

traps baited with either (3*S*,13*R*,1′*S*)- or (3*S*,13*S*,1′*S*)-**1** or in blank traps. The number of males captured in traps baited with (3*R*,13*R*,1′*S*)-**1** was sufficient to provide large and statistically significant differences between treatments. Unfortunately, because of the very short flight period of this insect (less than two weeks), it was neither possible to conduct additional experiments nor to investigate the behavioral activity of the other three stereoisomers of (1′*S*)-**1** on male attraction.

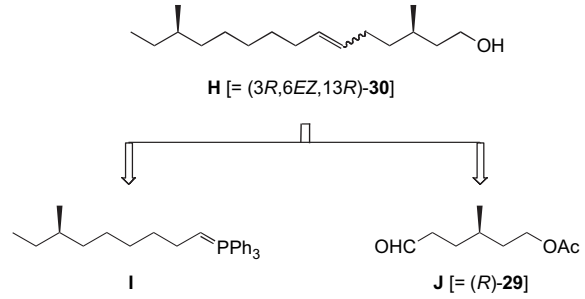
The results obtained from this single field experiment provide conclusive evidence that (3*R*,13*R*,1′*S*)-**1** is the active isomer among the four stereoisomers of (1′*S*)-**1** tested. This strongly suggests that (3*R*,13*R*,1′*S*)-**1** is the major component of the sex pheromone of *C. variegata*. On the other hand, the attraction of a much smaller number of males to traps baited with (3*R*,13*S*,1′*S*)-**1** could be due to the same configuration at C-3 of the acid part. Similarly, the lack of response to (3*S*,13*R*,1′*S*)- or (3*S*,13*S*,1′*S*)-**1** might indicate that chirality at C-3 of **1** is more important for the pheromone activity than that at C-13 of **1**.

The increase in catch in this study where the pure (3*R*,13*R*,1′*S*)-**1** was used, compared with the moderate catch in the previous study by Gries et al.,[2] could be due to difference in the population density in the two studies, or could more likely be due to one of the three other stereoisomers of (1′*S*)-**1** having an inhibitory effect. To address this point, further field trapping experiments are required to elucidate the biological activity of the three other isomers of (1′*S*)-**1**.

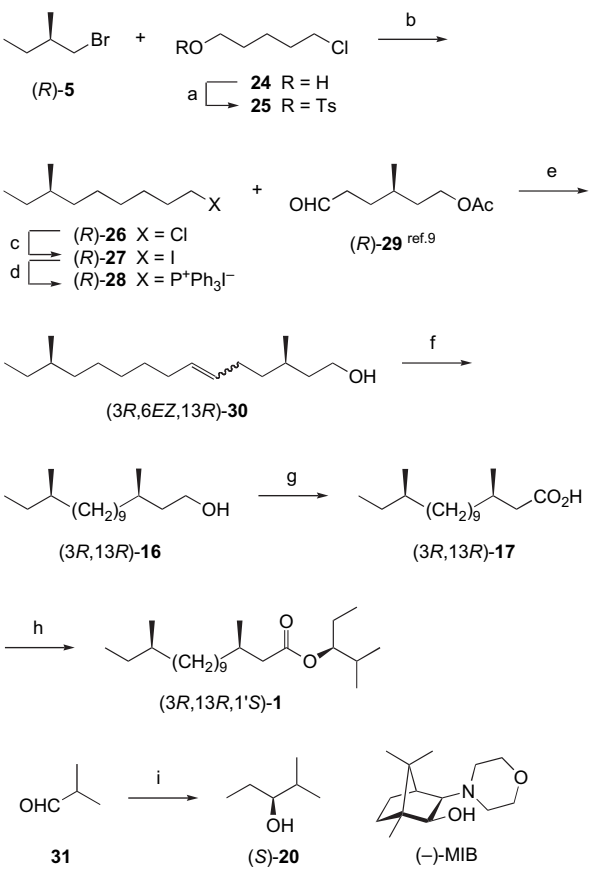
2.3. Wittig olefination-mediated synthesis of (3*R*,13*R*)-3,13-dimethylpentadecanoic acid (17) and its conversion to the pheromone

Determination of the absolute configuration of the bioactive isomer of **1** as 3*R*,13*R*,1′*S* prompted us to develop a more efficient synthesis of (3*R*,13*R*,1′*S*)-**1**. As shown in Scheme 6, our first attempt was to prepare **H** [=(3*R*,13*R*)-**30**] by Wittig reaction. Obvious bond disconnection of **H** demanded Wittig reagent **I** and aldehyde **J** as its precursors. This synthetic plan was executed as summarized in Scheme 7.

(*R*)-2-Methylbutyl bromide (**5**) served as the starting material for the Wittig reagent **I**. For the chain-extension of (*R*)-**5**, commercially available 5-chloro-1-pentanol (**24**) was tosylated to give **25**, which was coupled with the Grignard reagent prepared from (*R*)-**5** under the Schlosser conditions.[7] The resulting chloride (*R*)-**26** was treated with sodium iodide in acetone to give iodide (*R*)-**27**. Treatment of (*R*)-**27** with triphenylphosphine in hot toluene afforded phosphonium salt (*R*)-**28**. Addition of *n*-butyllithium to a solution of (*R*)-**28** in



Scheme 6. Retrosynthetic analysis of **H** [=(3*R*,6*EZ*,13*R*)-**30**].



Scheme 7. Synthesis of (3*R*,6*EZ*,13*R*)-**30** by Wittig reaction and its conversion to the pheromone. Reagents: (a) TsCl, DMAP, C_5H_5N (96%); (b) (i) (*R*)-**5**, Mg, THF; (ii) **25**, THF, Li_2CuCl_4 (71%); (c) NaI, DMF, Me_2CO (89%); (d) Ph_3P, toluene, heat (quant.); (e) (i) (*R*)-**28**, *n*-BuLi, THF; then (*R*)-**29**; (ii) NaOH, aq MeOH [43%, (*E*/*Z*=1:1.7)]; (f) H_2, 10% Pd–C, EtOAc (95%); (g) Jones CrO_3, acetone (94%); (h) (*S*)-**20**, EDC, DMAP, CH_2Cl_2 (84%); (i) Et_2Zn, (−)-MIB, toluene (45%).

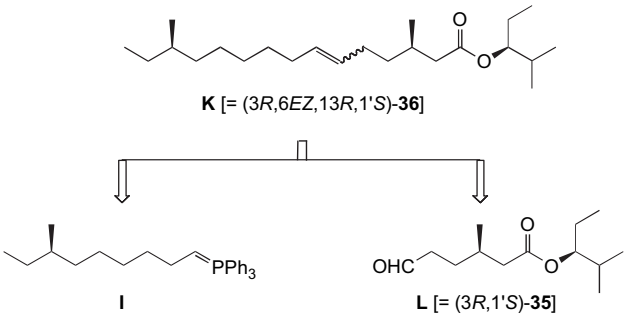
THF generated the Wittig reagent **I**. This was slowly added to a stirred and cooled solution of (*R*)-**29**[9] in THF. The product was treated with sodium hydroxide in aqueous methanol to give (3*R*,13*R*)-**30** in 43% yield based on (*R*)-**29**. The alkenol **30** was obtained as an *E*/*Z*-mixture (*E*/*Z*=1:1.7) as revealed by its GC–MS analysis. Hydrogenation of (3*R*,6*EZ*,13*R*)-**30** over 10% palladium/charcoal afforded (3*R*,13*R*)-**16**, which was oxidized with Jones chromic acid to give (3*R*,13*R*)-**17**. The overall yield of (3*R*,13*R*)-**17** was 19% based on (*R*)-**2** (nine steps).

Esterification of a gram-quantity of (3*R*,13*R*)-**17** to give (3*R*,13*R*,1′*S*)-**1** demanded the supply of a gram-quantity of (*S*)-**20**. Accordingly, we prepared (*S*)-**20** (96.8% ee as analyzed by the enantioselective GC of its acetate) in 45% yield by the addition of diethylzinc to isobutyraldehyde (**31**) in the presence of 2.5 mol % of (2*S*)-(−)-3-*exo*-(morpholino)isoborneol [(−)-MIB],[19] which was

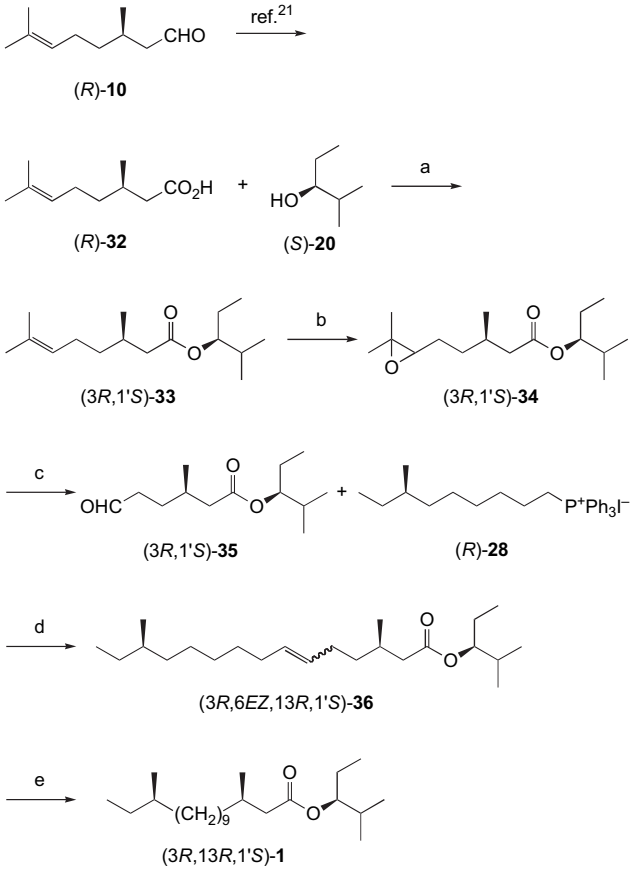
prepared by the method of Chen et al.[20] By using (*S*)-**20** thus prepared, 4.12 g of (3*R*,13*R*,1′*S*)-**1** could be synthesized from (3*R*,13*R*)-**17** in 16% overall yield based on (*R*)-**2** (10 steps).

2.4. Wittig olefination-mediated synthesis of (3*R*,6*EZ*,13*R*,1′*S*)-1′-ethyl-2′-methylpropyl 3,13-dimethyl-6-pentadecenoate (36) and its conversion to the pheromone

The most efficient synthesis of the pheromone (3*R*,13*R*,1′*S*)-**1** was finally achieved, basing on the retrosynthetic analysis as shown in Scheme 8. It is obvious that hydrogenation of **K** [=(3*R*,6*EZ*,13*R*,1′*S*)-**36**] affords (3*R*,13*R*,1′*S*)-**1**. Wittig reaction between the ylide **I** and aldo ester **L** [=(3*R*,1′*S*)-**35**] could give **K** in a single step. This simple idea was put into practice as shown in Scheme 9.



Scheme 8. Retrosynthetic analysis of **K** [=(3*R*,6*EZ*,13*R*,1′*S*)-**36**].



Scheme 9. Synthesis of (3*R*,6*EZ*,13*R*,1′*S*)-**36** by Wittig reaction and its conversion to the pheromone. Reagents: (a) EDC, DMAP, Et_2O, toluene, hexane [74% based on (*R*)-**32**]; (b) MCPBA, CH_2Cl_2 (quant.); (c) $HIO_4{\cdot}2H_2O$, THF, Et_2O (82%); (d) (*R*)-**28**, *n*-BuLi, THF; then (3*R*,1′*S*)-**35** (47%); (e) H_2, 10% Pd–C, EtOAc (96%).

(*R*)-Citronellal (**10**) was oxidized with pyridinium dichromate (PDC) in DMF to give (*R*)-citronellic acid (**32**) in 87% yield.[21] (*S*)-2-Methyl-3-pentanol (**20**) was prepared by asymmetric ethylation of isobutyraldehyde (**31**) with diethylzinc in the presence of (−)-MIB. After the work-up, a solution of (*S*)-**20** in hexane, toluene, and diethyl ether was used directly for the esterification of **32**, because isolation of (*S*)-**20** caused its substantial loss due to its high volatility. Accordingly, (*R*)-citronellic acid (**32**) and DMAP were dissolved into the above solution of (*S*)-**20**, to which was added EDC. This simplified version of esterification of (*R*)-**32** with (*S*)-**20** afforded (3*R*,1′*S*)-**33** in 74% yield. Epoxidation of **33** with *m*-chloroperbenzoic acid (MCPBA) furnished epoxy ester **34** quantitatively. Treatment of **34** with periodic acid dihydrate gave the desired aldo ester (3*R*,1′*S*)-**35** in 82% yield.

Wittig reaction of **35** with the ylide derived from (*R*)-**28** afforded (3*R*,6*EZ*,13*R*,1′*S*)-**36** in 47% yield. Finally, hydrogenation of **36** over 10% palladium/charcoal furnished (3*R*,13*R*,1′*S*)-**1** in 96% yield. The overall yield of this process was 22% based on (*R*)-**2** (eight steps) or 24% based on (*R*)-**10** (six steps). This final route to the pheromone was highly convergent and efficient. However, as to the consumption of the chiral alcohol part (*S*)-**20**, this route is less economical than the second route involving the final esterification step.

3. Conclusion

We synthesized all of the four stereoisomers of (1′*S*)-1′-ethyl-2′-methylpropyl 3,13-dimethylpentadecanoate (**1**), the major component of the sex pheromone of *C. variegata*. Olefin cross metathesis was shown to be a useful reaction in pheromone synthesis, particularly when a set of stereoisomers must be prepared quickly. The four stereoisomers of **1** were tested for attraction of male *C. variegata* in China to show (3*R*,13*R*,1′*S*)-**1** as the highly bioactive one, which must be the naturally occurring **1**. Two syntheses of (3*R*,13*R*,1′*S*)-**1** were achieved via Wittig olefination to provide more efficient preparative methods for the pheromone component.

The Paulownia bagworm, *C. variegata*, is not only an economically important insect in China and India, but also is potentially an invasive species in other parts of the world where the host tree is highly valued. Accordingly, the determination of the absolute configuration of the main sex pheromone component as (3*R*,13*R*,1′*S*)-**1** will enable not only monitoring and control of this insect in its native habitats but also detection and delimitation in any newly invaded habitat.

4. Experimental

4.1. General

Boiling points are uncorrected values. Refractive indices (n_D) were measured on an Atago DMT-1 refractometer. Optical rotations were measured on a Jasco P-1020 or P-1010 polarimeter. IR spectra were measured on a Jasco FT/IR-410 or 460 plus spectrometer. ^1H NMR spectra (400 MHz or 500 MHz, TMS at δ=0.00 as internal standard) and ^{13}C NMR spectra (100 MHz or 126 MHz, $CDCl_3$ at δ=77.0 as internal standard) were recorded on a Jeol JNM-AL 400 or Varian VNMRS-500 spectrometer. GC were recorded on a Shimadzu GC-2014 or an Agilent 7890 gas chromatograph. GC–MS were measured on an Agilent Technologies 5975 inert XL. HPLC was recorded on a Hitachi L-7110. HRMS were recorded on a Jeol JMS-SX102A. Column chromatography was carried out on Merck Kieselgel 60 Art 1.07734.

4.2. 2-Methylbutyl bromide 5

4.2.1. (R)-Isomer. A solution of (*R*)-**2** (T. Hasegawa Co., >99.9% ee, 13.0 g, 127 mmol) in dry Et_2O (20 mL) was added dropwise to an

ice-cooled and stirred suspension of $LiAlH_4$ (5.4 g, 128 mmol) in dry Et_2O (100 mL). The mixture was stirred for 1 h at 0–5 °C. The excess $LiAlH_4$ was destroyed by slowly adding water. The mixture was then acidified with ice and dil HCl, and extracted with Et_2O. The extract was successively washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated at atmospheric pressure to give crude (*R*)-**3** (11.8 g, quant) as an oil; ν_{max} (film): 3348 (OH, s), 1047 (s), 1016 (m); δ_H ($CDCl_3$): 0.912 (3H, t, *J* 7.2, CH_2CH_3), 0.915 (3H, d, *J* 6.4, $CHCH_3$), 1.19–1.25 (1H, m), 1.40–1.60 (2H, m), 3.40–3.55 (2H, m, CH_2OH). Powdered TsCl (30.0 g, 158 mmol) was added portionwise to an ice-cooled and stirred solution of (*R*)-**3** (11.8 g, 127 mmol) in dry pyridine (60 mL) at 0–5 °C. The mixture was stirred for 2 h at 0–5 °C. It was then poured into ice-water, and extracted with Et_2O. The extract was successively washed with dil. HCl, saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo to give (*R*)-**4** (29.2 g, 95%) as an oil; ν_{max} (film): 1599 (w, arom. C=C), 1360 (m), 1176 (s), 964 (m); δ_H($CDCl_3$): 0.83 (3H, t, *J* 7.6, CH_2CH_3), 0.87 (3H, d, *J* 6.8, $CHCH_3$), 1.10–1.22 (1H, m), 1.32–1.45 (1H, m), 1.65–1.75 (1H, m), 2.45 (3H, s, arom. CH_3), 7.34 (2H, d, *J* 8.8, arom. H), 7.78 (2H, d, *J* 8.8, arom. H). Powdered LiBr (20 g, 230 mmol) was added to a solution of (*R*)-**4** (29.2 g, 121 mmol) in dry DMF (70 mL) with shaking. The mixture became homogenous after exothermic reaction. It was then stirred and heated at 60 °C for 1.5 h. After cooling, the mixture was diluted with ice and water, and the heavy oil was separated. The aqueous layer was extracted with a small amount of pentane. The combined organic solution was washed with water and brine, dried ($MgSO_4$), and concentrated at atmospheric pressure. The residue was distilled to give 14.9 g [78% based on (*R*)-**2**, three steps] of (*R*)-**5** as a colorless oil, bp 117–119 °C (atm press); n_D^{22}=1.4434; $[\alpha]_D^{26}$ −3.72 (*c* 6.56, pentane); ν_{max} (film): 2964 (s), 2931 (m), 2875 (m), 1460 (m), 1381 (m), 1230 (m), 650 (m); δ_H ($CDCl_3$): 0.91 (3H, t, *J* 7.2, CH_2CH_3), 1.01 (3H, d, *J* 7.2, $CHCH_3$), 1.20–1.35 (1H, m), 1.40–1.55 (1H, m), 1.65–1.76 (1H, m), 3.30–3.45 (2H, m).

4.2.2. (S)-Isomer. In the same manner as described above (*S*)-**3** [Tokyo Kasei (TCI), 28.4 g, 322 mmol] yielded, via (*S*)-**4**, 38.0 g (78%, two steps) of (*S*)-**5**, bp 117–119 °C (atm press); n_D^{22}=1.4440; $[\alpha]_D^{25}$ +3.74 (*c* 4.76, pentane). Its spectral data were identical with those of (*R*)-**5**.

4.3. 5-Hexenyl *p*-toluenesulfonate 7

p-Toluenesulfonyl chloride (44.0 g, 231 mmol) was added portionwise to a stirred and ice-cooled solution of **6** (21.5 g, 215 mmol) in dry pyridine (100 mL). After stirring for 1 h, the mixture was left to stand 3 days in a refrigerator. Subsequent work-up as described for (*R*)-**4** gave **7** (26.6 g, 51%) as a colorless oil; ν_{max} (film): 3076 (m), 1641 (m), 1599 (m), 1360 (s), 1176 (s), 937 (s); δ_H ($CDCl_3$): 1.38–1.46 (2H, m), 1.60–1.70 (2H, m), 1.95–2.05 (2H, m), 2.45 (3H, s), 4.03 (2H, t, *J* 7.2, CH_2OTs), 7.34 (2H, d, *J* 8.4, arom. H), 7.88 (2H, d, *J* 8.4, arom. H). The low yield might have been due to the too long storage of the reaction mixture in the refrigerator. This was used for the next step without further purification.

4.4. 8-Methyl-1-decene 8

4.4.1. (R)-Isomer. A Grignard reagent was prepared from (*R*)-**5** (10.7 g, 71 mmol) and Mg (2.0 g, 80 mmol) in dry THF (70 mL) under Ar. A trace amount of I_2 was used as an initiator, and stirring and heating were continued for 30 min after the initial exothermic reaction caused by the dropwise addition of (*R*)-**5** in THF subsided. The Grignard reagent was added through a syringe to a stirred and cooled solution of **7** (11.4 g, 45 mmol) in dry THF (60 mL) at −65 to −50 °C under Ar. Then 0.1 M Li_2CuCl_4 in THF (3 mL, 0.3 mmol) was added to the mixture through a syringe, and the stirred mixture was left to stand overnight to bring it to the room temperature. The mixture was then added to ice-cooled NH_4Cl solution and extracted with a small amount of pentane. The pentane extract was washed with water and brine, dried ($MgSO_4$), and concentrated at atmospheric pressure. The residue was distilled to give (*R*)-**8** [4.61 g, 42% based on (*R*)-**5** or 66% based on **7**] as a colorless oil, bp 94–96 °C/48 Torr; n_D^{22}=1.4263; $[\alpha]_D^{27}$ −11.0 (*c* 3.40, pentane); ν_{max} (film): 3078 (w), 2927 (s), 1641 (m), 1462 (m), 1377 (m), 991 (m), 908 (s); δ_H ($CDCl_3$): 0.80–0.90 (6H, m, $CH_3\times2$), 1.05–1.18 (2H, m), 1.20–1.42 (9H, m), 2.04 (2H, q-like, *J* 7.2), 4.90–5.04 (2H, m, C=CH_2), 5.75–5.87 (1H, m, CH=C); GC–MS [Column: HP-5MS, 5% phenylmethylsiloxane, 30 m×0.25 mm i.d.; carrier gas: He; press: 52.8 kPa; temperature: 50–160 °C (+10 °C/min) −220 °C (+4 °C/min)]: t_R 6.07 min [8.8%, (3*R*,6*R*)-**9**], 8.16 min [91.2%, (*R*)-**8**]; MS of (3*R*,6*R*)-**9** (70 eV, EI): *m*/*z*: 142 (5) [M^+, $C_{10}H_{22}$], 113 (32), 112 (12), 85 (10), 71 (82), 57 (100), 56 (28), 43 (36), 41 (32); MS of (*R*)-**8** (70 eV, EI): *m*/*z*: 154 (1) [M^+, $C_{11}H_{22}$], 125 (34), 97 (20), 83 (68), 70 (100), 69 (65), 57 (45), 55 (67), 41 (53). Enantioselective GC: [instrument: Agilent 7890 GC; column: CHIRAMIX® 30 m×0.25 mm i.d.; column temperature: 40–180 °C (+0.7 °C/min); carrier gas: He, 0.7 mL/min]: t_R 42 min [>99.0%, (*R*)-**8**], 47 min [<1.0%, (*S*)-**8**]. Enantiomeric purity of (*R*)-**8** was >98.0% ee. HRMS calcd for $C_{11}H_{22}$: 154.1722, found: 154.1722.

4.4.2. (S)-Isomer. In the same manner as described above, (*S*)-**5** (18.2 g, 120 mmol), Mg (3.1 g, 130 mmol), and **7** (15.2 g, 60 mmol) afforded (*S*)-**8** [5.21 g, 28% based on (*S*)-**5** or 56% based on **7**] as a colorless oil, bp 110–115 °C/65 Torr; n_D^{22}=1.4263; $[\alpha]_D^{26}$ +10.6 (*c* 3.50, pentane); GC–MS [same conditions as described for (*R*)-**8**]: t_R 6.07 min [7.0%, (3*S*,6*S*)-**9**], 8.17 min [93%, (*S*)-**8**]. Its spectral data were identical with those of (*R*)-**8**. Enantioselective GC: [same conditions as described for (*R*)-**8**]: t_R 42 min [0.5%, (*R*)-**8**], 47 min [99.5%, (*S*)-**8**]. Enantiomeric purity of (*S*)-**8** was 99.0% ee. HRMS calcd for $C_{11}H_{22}$: 154.1722, found: 154.1722.

4.5. 3-Methyl-6-heptenyl acetate 12

4.5.1. (R)-Isomer. Acetic anhydride (15 mL, 16.2 g, 159 mmol) and DMAP (10 mg) were added to a stirred and ice-cooled solution of (*R*)-**11** (7.7 g, 60 mmol) in dry pyridine (30 mL). The mixture was left to stand overnight in a refrigerator. It was then poured into ice-water, and extracted with Et_2O. The organic extract was washed with dil HCl, saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give (*R*)-**12** (8.4 g, 82%) as a colorless oil, bp 130–134 °C/80 Torr; n_D^{25}=1.4314; $[\alpha]_D^{26}$ +1.53 (*c* 3.41, Et_2O); ν_{max} (film): 3078 (w), 1743 (s, C=O), 1641 (m, C=C), 1367 (m), 1240 (s), 1051 (m), 910 (m); δ_H($CDCl_3$): 0.92 (3H, d, *J* 6.0, $CHCH_3$), 1.20–1.30 (1H, m), 1.38–1.50 (2H, m), 1.52–1.62 (1H, m), 1.63–1.70 (1H, m), 2.04 (3H, s, $COCH_3$), 1.99–2.14 (2H, m), 4.04–4.16 (2H, m, CH_2OAc), 4.92–5.04 (2H, m), 5.74–5.86 (1H, m). Enantioselective GC: [instrument: Agilent 7890 GC; column: octakis-(2,3-di-*O*-methoxymethyl-6-*O*-*tert*-butyldimethylsilyl)-γ-cyclodextrin (MOMTB DMSGCD) 30 m×0.25 mm i.d.; column temperature: 40–180 °C (+0.7 °C/min); carrier gas: He, 0.7 mL/min]: t_R 77 min [98.6%, (*R*)-**12**], 78 min [1.4%, (*S*)-**12**]. The enantiomeric purity of (*R*)-**12** was 97.2% ee. HRMS calcd for $C_{10}H_{18}O_2$: 170.1307, found: 170.1305.

4.5.2. (S)-Isomer. In the same manner as described for (*R*)-**12**, (*S*)-**11** (5.0 g, 39 mmol) yielded 5.8 g (87%) of (*S*)-**12**, bp 122–125 °C/66 Torr; n_D^{25}=1.4312; $[\alpha]_D^{25}$ −1.36 (*c* 3.12, Et_2O). Its spectral data were identical with those of (*R*)-**12**. Enantioselective GC: [same conditions as described for (*R*)-**12**]: t_R 77 min [1.4%, (*R*)-**12**], 78 min

[98.6%, (*S*)-**12**]. The enantiomeric purity of (*S*)-**12** was 97.2% ee. HRMS calcd for $C_{10}H_{18}O_2$: 170.1307, found: 170.1299.

4.6. 3,13-Dimethyl-6-pentadecenyl acetate 13

4.6.1. (3R,6EZ,13R)-Isomer. Grubbs' first generation catalyst (Grubbs I, 92.8 mg, 0.11 mmol) was added to a solution of (*R*)-**8** (1.611 g, 10.5 mmol) and (*R*)-**12** (567 mg, 3.3 mmol) in dry CH_2Cl_2 (5 mL). The wine red solution was stirred and heated under reflux under Ar for 3 h. Then an additional amount of Grubbs I catalyst (30.0 mg, 0.04 mmol) was added, and the stirring was continued for another 3 h, when the evolution of ethylene ceased. The mixture was left to stand for 3 d, and concentrated in vacuo. The residue was chromatographed over SiO_2 (15 g). Elution with hexane gave (3*R*,9*EZ*,16*R*)-**14** [1.19 g; ν_{max} (film): 2923 (s), 1462 (s), 1377 (m), 966 (s)], and further elution with hexane/EtOAc (15:1) gave 866 mg [88% based on (*R*)-**12**] of crude (3*R*,6*EZ*,13*R*)-**13** contaminated with a small amount of (3*R*,6*EZ*,10*R*)-**15**. This crude product was used for the next step without further purification, because diol resulting from **15** can be separated from the desired (3*R*,13*R*)-**16** by chromatography. Properties of crude (3*R*,6*EZ*,13*R*)-**13**: ν_{max} (film): 1743 (s, C=O), 1462 (m), 1365 (m), 1238 (s), 1053 (m), 968 (m); δ_H ($CDCl_3$): 0.70–0.94 (9H, m, $CH_3\times3$), 1.00–1.50 (12H, m), 1.50–1.70 (2H, m), 1.92–2.10 (2H, m), 2.04 (3H, s, $COCH_3$), 4.03–4.15 (2H, m, CH_2OAc), 5.32–5.45 (2H, m, CH=CH); δ_C ($CDCl_3$): 11.4, 14.1, 19.3, 21.0, 22.6, 24.6, 26.9, 27.2, 29.3, 29.5, 29.6, 31.6, 32.6, 34.3, 35.4, 36.5, 36.9, 62.9, 129.3 and 129.9 [(*Z*)-isomer], 129.8 and 130.4 [(*E*)-isomer] (*Z*/*E*=1:4), 171.0; GC–MS [column: HP-5MS, 5% phenylmethylsiloxane, 30 m×0.25 mm i.d.; carrier gas, He: press: 60.7 kPa; 70–230 °C (+10 °C/min)]: t_R 17.74 min [16.3%, (*Z*)-**13**], 17.88 min [83.7%, (*E*)-**13**]; MS of these two peaks were almost identical; MS of (3*R*,6*E*,13*R*)-**13** (70 eV, EI): *m*/*z*: 296 [M^+, $C_{19}H_{36}O_2$], 236 (8, M^+−AcOH), 221 (5), 137 (7), 123 (12), 109 (37), 95 (35), 81 (100), 67 (30), 55 (28), 43 (42).

4.6.2. (3R,6EZ,13S)-Isomer. In the same manner as described for (3*R*,6*EZ*,13*R*)-**13**, (*S*)-**8** (1.561 g, 10 mmol) and (*R*)-**12** (522 mg, 3.1 mmol) were treated with Grubbs I catlyst (95 mg, 0.12 mmol) to give 780 mg [86% based on (*R*)-**12**] of (3*R*,6*EZ*,13*S*)-**13**. Its spectral data were identical with those of (3*R*,6*E*,13*R*)-**13**.

4.6.3. (3S,6EZ,13R)-Isomer. In the same manner as described for (3*R*,6*EZ*,13*R*)-**13**, (*R*)-**8** (1.563 g, 10 mmol) and (*S*)-**12** (537 mg, 3.2 mmol) were treated with Grubbs I catalyst (119.7 mg 0.15 mmol) to give (3*S*,6*EZ*,13*R*)-**13** [827 mg, 88% based on (*S*)-**12**]. Its spectral data were identical with those of (3*R*,6*EZ*,13*R*)-**13**.

4.6.4. (3S,6EZ,13S)-Isomer. In the same manner as described for (3*R*,6*EZ*,13*R*)-**13**, (*S*)-**8** (1.570 g, 10.2 mmol) and (*S*)-**12** (517 mg, 3.0 mmol) were treated with Grubbs I catalyst (116 mg, 0.14 mmol) to give (3*S*,6*EZ*,13*S*)-**13** [790 mg, 88% based on (*S*)-**12**]. Its spectral properties were identical with those of (3*R*,6*EZ*,13*R*)-**13**.

4.7. 3,13-Dimethyl-6-pentadecen-1-ol 30

4.7.1. (3R,6EZ,13R)-Isomer. A solution of (3*R*,6*EZ*,13*R*)-**13** (866 mg, 2.7 mmol) in THF (5 mL) was added to a solution of NaOH (0.6 g, 15 mmol) in H_2O (2 mL) and MeOH (5 mL). The mixture was stirred and heated under reflux for 1 h. It was then concentrated in vacuo, diluted with water, and extracted with hexane. The extract was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give 680 mg (97%) of crude (3*R*,6*EZ*,13*R*)-**30** as an oil; ν_{max} (film): 3330 (s, OH), 1059 (m), 966 (m); δ_H ($CDCl_3$): 0.80–0.92 (9H, m, $CH_3\times3$), 1.00–1.15 (2H, m), 1.18–1.45 (12H, m), 1.52–1.66 (3H, m), 1.90–2.10 (4H, m), 3.61–3.74 (2H, m), 5.30–5.44 (2H, m); δ_C ($CDCl_3$): 11.4, 19.2, 19.5, 24.6, 26.93, 26.96, 29.0, 29.47, 29.49, 30.0, 32.6, 34.3, 36.6, 37.0, 39.8, 61.0, 61.1, 129.5 and 129.9 [(*Z*)-isomer], 130.0 and 130.4 [(*E*)-isomer] (*Z*/*E*=1:4).

4.7.2. (3R,6EZ,13S)-Isomer. In the same manner as described for (3*R*,6*EZ*,13*R*)-**30**, (3*R*,6*EZ*,13*S*)-**13** (780 mg, 2.5 mmol) was treated with NaOH (0.5 g) to give crude (3*R*,6*EZ*,13*S*)-**30** (608 mg, 96%). Its spectral data were identical with those of (3*R*,6*EZ*,13*R*)-isomer.

4.7.3. (3S,6EZ,13R)-Isomer. In the manner as described for (3*R*,6*EZ*,13*R*)-**30**, (3*S*,6*EZ*,13*R*)-**13** (780 mg, 2.5 mmol) was treated with NaOH (0.6 g) to give crude (3*S*,6*EZ*,13*R*)-**30** (510 mg, 82%). Its spectral properties were identical with those of (3*R*,6*EZ*,13*R*)-isomer.

4.7.4. (3S,6EZ,13S)-Isomer. In the same manner as described for (3*R*,6*EZ*,13*R*)-**30**, (3*S*,6*EZ*,13*S*)-**13** (742 mg, 2.4 mmol) was treated with NaOH (0.5 g) to give crude (3*S*,6*EZ*,13*S*)-**30** (570 mg, 94%). Its spectral data were identical with those of (3*R*,6*EZ*,13*R*)-isomer.

4.8. 3,13-Dimethyl-1-pentadecanol 16

4.8.1. (3R,13R)-Isomer. To a solution of (3*R*,6*EZ*,13*R*)-3,13-dimethyl-6-pentadecen-1-ol (**30**, 680 mg, 2.7 mmol) in 99% EtOH (15 mL) was added 10% Pd–C (200 mg). The suspension was stirred under H_2 atmosphere for 1 h at room temperature. The mixture was filtered through Celite, and the Celite was washed with Et_2O. The organic filtrate was concentrated in vacuo, and the residue was chromatographed over SiO_2 (5 g). Elution with hexane/EtOAc (3:1) gave 391 mg (58%) of (3*R*,13*R*)-**16**; n_D^{22}=1.4514; $[\alpha]_D^{25}$ −2.12 (*c* 2.64, hexane); ν_{max} (film): 3334 (s, OH), 1057 (m, C–O), 721 (w); δ_H ($CDCl_3$): 0.80–0.92 (9H, m, $CH_3\times3$), 1.02–1.19 (3H, m), 1.20–1.41 (20H, m), 1.50–1.70 (2H, m), 3.61–3.72 (2H, m). HRMS (FAB) calcd for $C_{17}H_{36}ONa$: 279.2664, found: 279.2664.

4.8.2. (3R,13S)-Isomer. In the same manner as described for (3*R*,13*R*)-**16**, (3*R*,6*EZ*,13*S*)-**30** (590 mg, 2.3 mmol) in 99% EtOH (10 mL) was hydrogenated over 10% Pd–C (200 mg) to give 483 mg (82%) of (3*R*,13*S*)-**16** after chromatography over SiO_2 (5 g); n_D^{22}=1.4514; $[\alpha]_D^{25}$ +7.99 (*c* 3.26, hexane). Its spectral data were identical with those reported for (3*R*,13*R*)-**16**. HRMS (FAB) calcd for $C_{17}H_{36}ONa$: 279.2664, found: 279.2666.

4.8.3. (3S,13R)-Isomer. In the same manner as described for (3*R*,13*R*)-**16**, (3*S*,6*EZ*,13*R*)-**30** (510 mg, 2.0 mmol) in 99% EtOH (10 mL) was hydrogenated over 10% Pd–C (200 mg) to give 403 mg (79%) of (3*S*,13*R*)-**16** after chromatography over SiO_2 (5 g); n_D^{22}=1.4512; $[\alpha]_D^{25}$ −8.46 (*c* 3.07, hexane). Its spectral data were identical with those reported for (3*R*,13*R*)-**16**, HRMS (FAB) calcd for $C_{17}H_{36}ONa$: 279.2664, found: 279.2663.

4.8.4. (3S,13S)-Isomer. In the same manner as described for (3*R*,13*R*)-**16**, (3*S*,6*EZ*,13*S*)-**30** (550 mg, 2.2 mmol) in 99% EtOH (10 mL) was hydrogenated over 10% Pd–C (200 mg) to give 355 mg (65%) of (3*S*,13*S*)-**16** after chromatography over SiO_2 (5 g); n_D^{22}=1.4512; $[\alpha]_D^{25}$ +1.65 (*c* 1.89, hexane). Its spectral data were identical with those reported for (3*R*,13*R*)-**16**. HRMS (FAB) calcd for $C_{17}H_{36}ONa$: 279.2664, found: 279.2668.

4.9. 3,13-Dimethylpentadecanoic acid 17

4.9.1. (3R,13R)-Isomer. Jones chromic acid (2.67 M, 27.3 mL, 72.9 mmol) was added dropwise to an ice-cooled and stirred solution of (3*R*,13*R*)-**16** (3.75 g, 14.6 mmol) in acetone (300 mL) at 0 °C. The mixture was stirred for 3 h at room temperature, and then cooled to 0 °C. The reaction was quenched with *i*-PrOH (6.5 mL) at 0 °C. The resulting mixture was stirred for 1 h at room temperature.

It was then concentrated in vacuo. The residue was diluted with water and extracted with EtOAc. The combined organic solution was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (100 g). Elution with hexane/EtOAc (50:1) gave 3.73 g (94%) of (3*R*,13*R*)-**17** as a colorless oil; n_D^{23}=1.4493; $[\alpha]_D^{24}$ −0.34 (*c* 1.39, $CHCl_3$); ν_{max} (film): 3040 (br s, CO_2H), 1710 (s, C=O), 1410 (m), 1300 (br m), 940 (br m); δ_H (500 MHz, $CDCl_3$): 0.84 (3H, d, *J* 6.5), 0.85 (3H, t, *J* 7.0, CH_2CH_3), 0.96 (3H, d, *J* 7.0), 1.04–1.37 (21H, m), 1.91–2.00 (1H, m, 3-H), 2.14 (1H, dd, *J* 8.0, 15, 2-H_a), 2.35 (1H, dd, *J* 6.0, 15, 2-H_b), 11.44 (1H, br s, CO_2H); δ_C (126 MHz, $CDCl_3$): 11.4, 19.2, 19.7, 26.9, 27.1, 29.5, 29.62, 29.64, 29.706, 29.713, 30.0, 30.1, 34.4, 36.6, 36.7, 41.6, 179.8. HR-EIMS calcd for $C_{17}H_{34}O_2$ $[M]^+$: 270.2559, found: 270.2562.

4.9.2. (3R,13S)-Isomer. In the same manner as described above, (3*R*,13*S*)-**16** (303 mg, 1.18 mmol) was converted into 269 mg (84%) of (3*R*,13*S*)-**17** as a colorless oil, n_D^{25}=1.4484; $[\alpha]_D^{24}$ +9.46 (*c* 1.36, $CHCl_3$); ν_{max} (film): 3040 (br s, CO_2H), 1710 (s, C=O), 1410 (m), 1295 (br m), 940 (br m); δ_H (500 MHz, $CDCl_3$): 0.84 (3H, d, *J* 6.0), 0.85 (3H, t, *J* 7.0, CH_2CH_3), 0.96 (3H, d, *J* 6.5), 1.04–1.37 (21H, m), 1.91–2.00 (1H, m, 3-H), 2.14 (1H, dd, *J* 8.0, 15, 2-H_b), 2.35 (1H, dd, *J* 6.0, 15, 2-H_a), 11.38 (1H, br s, CO_2H); δ_C (126 MHz, $CDCl_3$): 11.4, 19.2, 19.7, 26.9, 27.1, 29.5, 29.62, 29.63, 29.70, 29.71, 30.0, 30.1, 34.4, 36.6, 36.7, 41.6, 179.7. These ^1H and ^{13}C NMR spectroscopic data are virtually identical to those of (3*R*,13*R*)-**17**. HR-EIMS calcd for $C_{17}H_{34}O_2$ $[M]^+$: 270.2559, found: 270.2552.

4.9.3. (3S,13R)-Isomer. In the same manner as described above, (3*S*,13*R*)-**16** (328 mg, 1.28 mmol) was converted into 310 mg (90%) of (3*S*,13*R*)-**17** as a colorless oil; n_D^{23}=1.4488; $[\alpha]_D^{24}$ −9.38 (*c* 1.28, $CHCl_3$). Its IR, ^1H and ^{13}C NMR spectra were identical with those of (3*R*,13*S*)-**17**. HR-EIMS calcd for $C_{17}H_{34}O_2$ $[M]^+$: 270.2559, found: 270.2547.

4.9.4. (3S,13S)-Isomer. In the same manner as described above, (3*S*,13*S*)-**16** (305 mg, 1.19 mmol) was converted into 267 mg (83%) of (3*S*,13*S*)-**17** as a colorless oil; n_D^{23}=1.4490; $[\alpha]_D^{24}$ +0.04 (*c* 1.12, $CHCl_3$). Its IR, ^1H and ^{13}C NMR spectra were identical with those of (3*R*,13*R*)-**17**. HR-EIMS calcd for $C_{17}H_{34}O_2$ $[M]^+$: 270.2559, found: 270.2559.

4.10. 4-Methyl-1-pentyn-3-one 19

Jones chromic acid (2.67 M, 74.2 mL, 198 mmol) was added dropwise to an ice-cooled and stirred solution of (±)-**18** (19.4 g, 198 mmol) in acetone (400 mL) at 0 °C. The mixture was stirred for 4 h at room temperature, and then cooled to 0 °C. The reaction was quenched with Na_2SO_3 (13 g) at 0 °C. The resulting mixture was diluted with water and extracted with Et_2O. The combined organic solution was successively washed with water, a saturated aqueous $NaHCO_3$ solution, and brine, dried (Na_2SO_4), and concentrated at atmospheric pressure. The residue was distilled to give 13.9 g (73%) of **19** as a colorless oil, bp 104–109 °C; n_D^{24}=1.4179; ν_{max} (film): 3260 (s, C≡CH), 2090 (s, C≡C) 1680 (br s, C=O), 1060 (br s); δ_H (500 MHz, $CDCl_3$): 1.21 (6H, d, *J* 7.0, CH_3×2), 2.68 (1H, sept., *J* 7.0, 4-H), 3.23 (1H, s, C≡CH). HR-EIMS calcd for C_6H_8O $[M]^+$: 96.0575, found: 96.0573.

4.11. (*R*)-4-Methyl-1-pentyn-3-ol (*R*)-18

(*R*)-Alpine-Borane® was prepared as follows: (1*R*)-(+)-α-pinene (Aldrich, 97% ee, 28.7 mL, 181 mmol) was added to 9-BBN (Aldrich, solid dimer, 20.1 g, 165 mmol) under Ar. After stirring for 6 h at 65 °C, the mixture was then cooled to room temperature.

The freshly prepared (*R*)-Alpine-Borane® (11.1 mL) was added to **19** (2.37 g, 24.7 mmol) at room temperature under Ar. The mixture was stirred for 4 h at room temperature. The liberated α-pinene was then evaporated in vacuo at 70 °C. The residue was diluted with Et_2O, and cooled to 0 °C. To this cooled mixture, 4 M aqueous NaOH solution (10 mL) and 30% aqueous H_2O_2 solution (10 mL) were successively added dropwise. After stirring for 1 h at 0 °C, the mixture was extracted with Et_2O. The combined organic solution was successively washed with saturated aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated at atmospheric pressure. The residue was purified by chromatography over SiO_2 [40 g, elution with pentane/Et_2O (10:1)] followed by distillation to give 1.15 g (47%) of (*R*)-**18** as a colorless oil, bp 119–121 °C; n_D^{24}=1.4357; $[\alpha]_D^{25}$ −0.96 (*c* 1.37, $CHCl_3$); $[\alpha]_D^{25}$ +12.7 (*c* 1.23, dioxane), lit. Ref. 17 $[\alpha]_D$ +14.6 (*c* 2, dioxane) 91% ee; ν_{max} (film): 3380 (br s, OH), 3310 (s, C≡CH), 2120 (w, C≡C), 1030 (br s, C–O); δ_H (500 MHz, $CDCl_3$): 1.00 (3H, d, *J* 6.5, CH_3), 1.02 (3H, d, *J* 6.5, CH_3), 1.85–1.94 (1H, m, 4-H), 1.99 (1H, br s, OH), 2.46 (1H, d, *J* 2.0, C≡CH), 4.18 (1H, dd, *J* 2.0, 5.5, 3-H); δ_C (126 MHz, $CDCl_3$): 17.3, 17.9, 34.3, 67.7, 73.6, 83.6. HR-EIMS calcd for C_6H_9O $[M-H]^+$: 97.0653, found: 97.0655.

A portion of (*R*)-**18** was converted to its benzoate (*R*)-**22** for determination of enantiomeric purity. HPLC (column: Chiralcel® OJ-H, eluent: hexane/*i*-PrOH=9:1, 0.5 mL/min; detection: 254 nm): t_R 10.96 min [98.0%, (*R*)-isomer], 11.91 min [2.0%, (*S*)-isomer], enantiomeric purity of (*R*)-**18**=96.0% ee.

4.12. (*S*)-2-Methyl-3-pentanol (*S*)-20

4.12.1. Hydrogenation of (R)-18. Palladium/charcoal (10%, Kawaken Co., 357 mg) was added to a solution of (*R*)-**18** (3.57 g, 36.4 mmol) in pentane (20 mL). The suspension was stirred under H_2 (balloon) for 3 h at room temperature. The suspension was filtered through a bed of Celite. The filtrate was concentrated in vacuo to give a mixture of (*S*)-**20** and **21** [3.09 g, 83%, (*S*)-**20**/**21**=2:1] as a colorless oil. The residue was purified by column chromatography on SiO_2 [40 g, elution with pentane/Et_2O (10:1)] followed by distillation to give 610 mg (16%) of (*S*)-**20** as a colorless oil, bp 104–106 °C; n_D^{24}=1.4180; $[\alpha]_D^{25}$ −14.0 (*c* 1.10, $CHCl_3$); $[\alpha]_D^{25}$ −20.1 (*c* 1.16, EtOH); ν_{max} (film): 3360 (br s, OH), 980 (br s); δ_H (500 MHz, $CDCl_3$): 0.91 (3H, d, *J* 7.0, CH_3), 0.92 (3H, d, *J* 7.0, CH_3), 0.96 (3H, t, *J* 7.0, 5-CH_3), 1.31 (1H, d, *J* 5.0, OH), 1.40 (1H, ddq, *J* 7.0, 8.5, 14, 4-H_b), 1.54 (1H, ddt, *J* 5.0, 7.0, 14, 4-H_a), 1.67 (1H, d-sept., *J* 5.0, 7.0, 2-H), 3.28 (1H, sext., *J* 5.0, 3-H); δ_C (126 MHz, $CDCl_3$): 10.3, 17.1, 18.9, 26.9, 33.1, 78.2. HR-EIMS calcd for $C_6H_{14}O$ $[M]^+$: 102.1045, found: 102.1044. A portion of (*S*)-**20** was (24 mg) was converted to its acetate (*S*)-**23** with Ac_2O in pyridine (12 h, at room temperature) for determination of enantiomeric purity. GC analysis of (*S*)-**23** [column: Cyclodex-β®, 30 m×0.25 mm i.d.; carrier gas: He, 100 kPa; temperature: 40 °C (1 min)+1.0 °C/min to 100 °C]: t_R 24.68 min [97.5%, (*S*)-**23**], 25.91 min [2.5%, (*R*)-**23**], enantiomeric purity of (*S*)-**23**=95.0% ee.

4.12.2. Asymmetric alkylation. A solution of diethylzinc (1.0 M in *n*-hexane, 100 mL, 100 mmol) was added dropwise to an ice-cooled and stirred solution of (2*S*)-(−)-3-*exo*-(morpholino)isoborneol [(−)-MIB, 598 mg, 2.50 mmol] and isobutyraldehyde (**31**, 4.56 mL, 50.0 mmol) in dry toluene (50 mL) under Ar at 0 °C. The mixture was stirred for 3 h at 0 °C. The reaction was then quenched with a saturated aqueous NH_4Cl solution. The resulting mixture was extracted with Et_2O, and the combined organic solution was successively washed with a 1 M aqueous HCl solution, water, a saturated aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated at atmospheric pressure. The residue was purified by chromatography over SiO_2 [80 g, elution with pentane/Et_2O (10:1)] followed by distillation to give 2.31 g (45%) of (*S*)-**20** as a colorless oil, bp 64–66 °C/125 Torr; n_D^{23}=1.4157. $[\alpha]_D^{26}$ −15.6 (*c* 1.86, $CHCl_3$); $[\alpha]_D^{26}$ −18.6 (*c* 1.10, EtOH). Its IR, ^1H and ^{13}C NMR spectra were

identical with those of (*S*)-**20** prepared by hydrogenation of (*R*)-**18**. HR-EIMS calcd for $C_6H_{14}O$ $[M]^+$: 102.1045, found: 102.1047. A portion of (*S*)-**20** (96 mg) was converted to its acetate with Ac_2O in pyridine (12 h, at room temperature) for determination of enantiomeric purity. GC analysis of the acetate [same conditions as described above]: t_R 24.32 min [98.4%, (*S*)-**23**], 25.99 min [1.6%, (*R*)-**23**]; enantiomeric purity of (*S*)-**20**=96.8% ee.

4.13. 1-Ethyl-2-methylpropyl 3,13-dimethylpentadecanoate 1

4.13.1. (3R,13R,1′S)-Isomer. EDC (3.95 g, 20.6 mmol) was added to an ice-cooled and stirred solution of (3*R*,13*R*)-**17** (3.72 g, 13.8 mmol), (*S*)-**20** (1.55 g, 15.2 mmol), and DMAP (2.52 g, 20.6 mmol) in dry CH_2Cl_2 (70 mL) at 0 °C. After stirring for 14 h at room temperature, the mixture was poured into water, and extracted with Et_2O. The combined organic solution was successively washed with water, a saturated aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (80 g). Elution with hexane/EtOAc (50:1) gave 4.12 g (84%) of (3*R*,13*R*,1′*S*)-**1** as a colorless oil. n_D^{23}=1.4448; $[\alpha]_D^{23}$ −5.38 (*c* 1.30, $CHCl_3$); ν_{max} (film): 1735 (s, C=O), 1180 (m), 975 (m); δ_H (500 MHz, $CDCl_3$): 0.84 (3H, d, *J* 7.0, CH_3), 0.85 (3H, d, *J* 7.0, CH_3), 0.87 (3H, t, *J* 7.0, CH_3), 0.89 (6H, d, *J* 7.0, $CH_3\times2$), 0.94 (3H, d, *J* 7.0, CH_3), 1.05–1.37 (21H, m), 1.48–1.62 (2H, m, 1″-H_2), 1.83 (1H, d-sept., *J* 5.0, 7.0, 2′-H), 1.91–2.01 (1H, m, 3-H), 2.11 (1H, dd, *J* 8.0, 15, 2-H_b), 2.31 (1H, dd, *J* 6.0, 15, 2-H_a), 4.68 (1H, ddd, *J* 5.0, 5.0, 8.0, 1′-H); δ_C (126 MHz, $CDCl_3$): 9.9, 11.4, 17.6, 18.6, 19.2, 19.7, 24.0, 26.9, 27.1, 29.5, 29.64, 29.65, 29.7, 29.8, 30.0, 30.4, 30.9, 34.4, 36.6, 36.8, 42.3, 79.4, 173.3. HR-EIMS calcd for $C_{17}H_{33}O$ $[M-C_6H_{13}O]^+$: 253.2531, found: 253.2529.

4.13.2. (3R,13S,1′S)-Isomer. In the same manner as described above, (3*R*,13*S*)-**17** (86 mg) was converted into 105 mg (93%) of (3*R*,13*S*,1′*S*)-**1** as a colorless oil; n_D^{23}=1.4439; $[\alpha]_D^{23}$ +1.63 (*c* 1.32, $CHCl_3$); ν_{max} (film): 1735 (s, C=O), 1180 (m), 975 (m); δ_H (500 MHz, $CDCl_3$): 0.84 (3H, d, *J* 7.0, CH_3), 0.85 (3H, d, *J* 7.0, CH_3), 0.87 (3H, t, *J* 7.0, CH_3), 0.89 (6H, d, *J* 7.0, $CH_3\times2$), 0.94 (3H, d, *J* 7.0, CH_3), 1.05–1.37 (21H, m), 1.48–1.62 (2H, m, 1″-H_2), 1.83 (1H, d-sept., *J* 5.0, 7.0, 2′-H), 1.91–2.01 (1H, m, 3-H), 2.11 (1H, dd, *J* 8.0, 15, 2-H_b), 2.31 (1H, dd, *J* 6.0, 15, 2-H_a), 4.68 (1H, ddd, *J* 5.0, 5.0, 8.0, 1′-H); δ_C (126 MHz, $CDCl_3$): 9.9, 11.4, 17.6, 18.6, 19.2, 19.7, 24.0, 26.9, 27.1, 29.5, 29.64, 29.65, 29.7, 29.8, 30.0, 30.4, 30.9, 34.4, 36.6, 36.8, 42.3, 79.4, 173.3. These ^1H and ^{13}C NMR spectroscopic data are virtually identical to those of (3*R*,13*R*,1′*S*)-**1**. HR-EIMS calcd for $C_{17}H_{33}O$ $[M-C_6H_{13}O]^+$: 253.2531, found: 253.2534.

4.13.3. (3S,13R,1′S)-Isomer. In the same manner as described above, (3*S*,13*R*)-**17** (128 mg) was converted into 153 mg (91%) of (3*S*,13*R*,1′*S*)-**1** as a colorless oil; n_D^{23}=1.4440; $[\alpha]_D^{23}$ −10.8 (*c* 1.31, $CHCl_3$); ν_{max} (film): 1735 (s, C=O), 1180 (m), 975 (m); δ_H (500 MHz, $CDCl_3$): 0.84 (3H, d, *J* 7.0, CH_3), 0.85 (3H, d, *J* 7.0, CH_3), 0.87 (3H, t, *J* 7.0, CH_3), 0.89 (6H, d, *J* 7.0, $CH_3\times2$), 0.94 (3H, d, *J* 7.0, CH_3), 1.05–1.37 (21H, m), 1.48–1.62 (2H, m, 1″-H_2), 1.83 (1H, d-sept., *J* 5.0, 7.0, 2′-H), 1.92–2.00 (1H, m, 3-H), 2.11 (1H, dd, *J* 8.0, 15, 2-H_b), 2.31 (1H, dd, *J* 6.0, 15, 2-H_a), 4.68 (ddd, *J* 5.0, 5.0, 8.0, 1′-H): δ_C (126 MHz, $CDCl_3$): 9.9, 11.4, 17.6, 18.6, 19.2, 19.8, 24.0, 26.9, 27.1, 29.5, 29.65, 29.70, 29.8, 30.0, 30.4, 30.8, 34.4, 36.6, 36.7, 42.3, 79.4, 173.3. These ^1H and ^{13}C NMR spectroscopic data are virtually identical to those of (3*R*,13*R*,1′*S*)-**1**. HR-EIMS calcd for $C_{17}H_{33}O$ $[M-C_6H_{13}O]^+$: 253.2531, found: 253.2533.

4.13.4. (3S,13S,1′S)-Isomer. In the same manner as described above, (3*S*,13*S*)-**17** (113 mg) was converted into 139 mg (94%) of (3*S*,13*S*,1′*S*)-**1** as a colorless oil; n_D^{23}=1.4451; $[\alpha]_D^{23}$ −3.42 (*c* 1.20, $CHCl_3$); ν_{max} (film): 1735 (s, C=O), 1180 (m), 975 (m); δ_H (500 MHz, $CDCl_3$): 0.84 (3H, d, *J* 7.0, CH_3), 0.85 (3H, d, *J* 7.0, CH_3), 0.87 (3H, t, *J* 7.0, CH_3), 0.89 (6H, d, *J* 7.0, $CH_3\times2$), 0.94 (3H, d, *J* 7.0, CH_3), 1.04–1.37 (21H, m), 1.48–1.62 (2H, m, 1″-H_2), 1.83 (1H, d-sept., *J* 5.0, 7.0, 2′-H), 1.92–2.00 (1H, m, 3-H), 2.11 (1H, dd, *J* 8.0, 15, 2-H_b), 2.31 (1H, dd, *J* 6.0, 15, 2-H_a), 4.68 (1H, ddd, *J* 5.0, 5.0, 8.0, 1′-H); δ_C (126 MHz, $CDCl_3$): 9.9, 11.4, 17.6, 18.6, 19.2, 19.8, 24.0, 26.9, 27.1, 29.5, 29.65, 29.71, 29.8, 30.0, 30.4, 30.8, 34.4, 36.6, 36.7, 42.3, 79.4, 173.3. These ^1H and ^{13}C NMR spectroscopic data are virtually identical to those of (3*R*,13*R*,1′*S*)-**1**. HRMS calcd for $C_{17}H_{33}O$ $[M-C_6H_{13}O]^+$: 253.2531, found: 253.2534.

4.14. 5-Chloropentyl tosylate 25

Tosyl chloride (19.0 g, 100 mmol) was added portionwise to a stirred and ice-cooled solution of **24** (9.8 g, 80 mmol) and DMAP (0.1 g) in dry pyridine (45 mL) at 0–5 °C. The mixture was stirred at 0–5 °C for 2 h, poured into ice-water, and extracted with Et_2O. The extract was successively washed with water, dil HCl, saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo to give 21.7 g (96%) of **25** as an oil. ν_{max} (film): 1599 (m), 1360 (s), 1188 (s), 1176 (s); δ_H ($CDCl_3$): 1.40–1.51 (2H, m), 1.60–1.75 (4H, m), 2.45 (3H, s, $ArCH_3$), 2.15 (2H, t, *J* 6.4, CH_2Cl), 4.04 (2H, t, *J* 6.4, CH_2OTs), 7.35 (2H, d, *J* 8.4, arom. H), 7.79 (2H, d, *J* 8.4, arom. H). This was employed in the next step without further purification.

4.15. (*R*)-7-Methylnonyl chloride 26

A Grignard reagent was prepared in the conventional manner by adding a solution of (*R*)-**5** (14.9 g, 99 mmol) in dry THF (60 mL) to a stirred suspension of Mg (2.6 g, 110 mmol) in dry THF (10 mL). After the addition of 5 mL of the solution of (*R*)-**5**, the reaction was initiated by the addition of a trace amount of I_2 while refluxing. The solution of (*R*)-**5** was added dropwise to maintain the refluxing of THF. The obtained Grignard reagent was cooled to room temperature, and added dropwise to a stirred and cooled solution of **25** (21.6 g, 78 mmol) in dry THF (60 mL) at −70 to −60 °C under Ar. Immediately after the addition, a solution of Li_2CuCl_4 in dry THF (0.1 M, 3 mL, 0.3 mmol) was added, and the stirred mixture was left to stand overnight under Ar with gradual warming to room temperature. The mixture was quenched with ice and NH_4Cl solution, and extracted with hexane. The hexane solution was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give (*R*)-**26** (12.5 g, 71%) as a colorless oil, bp 73–75 °C/4 Torr; n_D^{24}=1.4422; $[\alpha]_D^{26}$ −8.05 (*c* 6.84, pentane); ν_{max} (film): 2958 (s), 2929 (s), 2856 (s), 1462 (m), 1377 (m), 727 (m), 656 (m); δ_H ($CDCl_3$): 0.84 (3H, d, *J* 5.6, $CHCH_3$), 0.86 (3H, t, *J* 7.2, CH_2CH_3), 1.05–1.20 (2H, m), 1.20–1.73 (7H, m), 1.38–1.46 (2H, m), 1.77 (2H, m), 3.53 (2H, t, *J* 6.8, CH_2Cl): δ_C ($CDCl_3$): 11.4, 19.2, 26.9, 29.2, 29.5, 32.6, 34.3, 36.5, 45.1; GC–MS [column: HP-5MS, 5% phenylmethylsiloxane, 30 m×0.25 mm i.d.; press: 60.7 kPa; temperature: 70–230 °C (+10 °C/min)]: t_R 4.31 min [2.1%, (3*R*,6*R*)-3,6-dimethyloctane], 6.95 min (7.8%, 1-bromo-5-chloropentane), 8.85 min [85.8%, (*R*)-**26**]; MS of (*R*)-**26** (70 eV, EI): *m*/*z*: 176 (<1) [M^+, $C_{10}H_{21}Cl$], 147 (33), 111 (34), 105 (21), 69 (84), 57 (100), 41 (50). HRMS calcd for $C_{10}H_{21}Cl$: 176.1332, found: 176.1331.

4.16. (*R*)-7-Methylnonyl iodide 27

Sodium iodide (45.0 g, 300 mmol) was added to a solution of (*R*)-**26** (12.4 g, 70 mmol) and DMF (10 mL) in acetone (200 mL). The mixture was stirred and heated under reflux for 10 h. The initial solution soon became turbid, and NaCl precipitated. The mixture was concentrated in vacuo, diluted with water, and extracted with hexane. The hexane extract was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to give 16.8 g (89%) of (*R*)-**27** as a colorless oil, bp 96–98 °C/5 Torr; n_D^{22}=1.4958; $[\alpha]_D^{25}$ −5.42 (*c* 7.94, hexane); ν_{max} (film): 2958 (s), 2927

(s), 2871 (s), 2854 (s), 1462 (m), 1377 (m), 1200 (m), 1171 (m); δ_H ($CDCl_3$): 0.84 (3H, d, *J* 6.0, $CHCH_3$), 0.86 (3H, t, *J* 7.2, CH_2CH_3), 1.05–1.20 (2H, m), 1.20–1.45 (9H, m), 1.74–1.90 (2H, m), 3.19 (2H, t, *J* 7.2, CH_2I); δ_C ($CDCl_3$): 7.3, 11.4, 19.2, 26.8, 28.9, 29.4, 30.5, 33.5, 34.3, 36.4; GC–MS (same conditions as for (*R*)-**26**): t_R 11.16 min (12.0%, 1,5-diiodopentane), 11.35 min [86.0%, (*R*)-**27**]; MS of (*R*)-**27** (70 eV, EI): *m*/*z*: 268 (4) [M^+, $C_{10}H_{21}I$], 155 (15), 141 (16), 99 (15), 85 (73), 71 (63), 57 (100), 43 (46), 41 (39). HRMS calcd for $C_{10}H_{21}I$: 268.0688, found: 268.0684.

4.17. (*R*)-7-Methylnonyltriphenylphosphonium iodide 28

A solution of (*R*)-**27** [86% purity, 13.5 g, 43 mmol (containing 12% of 1,5-diiodopentane)] and triphenylphosphine (15.0 g, 57 mmol) in dry toluene (50 mL) was stirred and heated under reflux under Ar. After 10 min, the solution became turbid. Stirring and refluxing was continued for 3.5 h, and the mixture was cooled to separate into two layers. The lower layer solidified. Its recrystallization was unsuccessful presumably due to the contamination of the bisphosphonium salt resulting from 1,5-diiodopentane. The lower layer was washed four times with dry benzene by stirring followed by decantation to remove excess triphenylphosphine, and the remaining lower layer of crude (*R*)-**28** was used in the next step.

4.18. (*R*)-6-Acetoxy-4-methylhexanal 29

This was obtained by the known method[9] in 90% overall yield; ν_{max} (film): 2960 (m), 2931 (m), 2875 (m), 2725 (w, O=C–H), 1738 (vs, C=O), 1244 (s, C–O). This was used in the next step without further purification.

4.19. (3*R*,6*EZ*,13*R*)-3,13-Dimethyl-6-pentadecen-1-ol 30

A Wittig reagent was prepared by dropwise addition of *n*-BuLi in hexane (1.6 M, 30.5 mL, 49 mmol) to a stirred and cooled solution of (*R*)-**28** [prepared from 13.5 g of (*R*)-**27** (86% purity containing 12% of 1,5-diiodopentane), ca. 43 mmol] in dry THF (50 mL) at −30 to 0 °C under Ar. The resulting red solution was added dropwise to a stirred and cooled solution of (*R*)-**29** (7.0 g, 40 mmol) in dry THF (50 mL) at −60 to −50 °C under Ar. The red color soon disappeared, and the stirred mixture was left to stand overnight with gradual raise of the reaction temperature to room temperature. A solution of NaOH (5 g, 120 mmol) in MeOH (40 mL) and water (20 mL) was added, and the mixture was concentrated in vacuo. The residue was partitioned between hexane and aqueous MeOH [MeOH/H_2O=2:1 (v/v)]. The hexane layer was separated, washed with aqueous MeOH (MeOH/H_2O=2:1) containing 1 mL of 30% H_2O_2, which removed a trace of Ph_3P by oxidizing it to Ph_3PO. Even a trace amount of Ph_3P in **30** inhibits its hydrogenation over Pd–C. The hexane solution was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (100 g) in hexane. Elution with hexane/EtOAc (3:1) gave 4.4 g (43%) of (3*R*,6*EZ*,13*R*)-**30** as a colorless oil. ν_{max} (film): 3336 (br, OH), 2958 (s), 2873 (s), 2856 (s), 1462 (m), 1377 (m), 1057 (m), 966 (w); δ_H ($CDCl_3$): 0.84 (3H, d, *J* 7.6, $CHCH_3$), 0.85 (3H, t, *J* 8.0, CH_2CH_3), 0.91 (3H, d, *J* 6.4, $CHCH_3$), 1.04–1.18 (2H, m), 1.18–1.50 (13H, m), 1.52–1.68 (2H, m), 1.90–2.10 (4H, m), 3.60–3.74 (2H, m), 5.30–5.44 (2H, m); δ_C ($CDCl_3$): 11.4, 19.2, 19.5, 24.7, 26.93, 26.96, 27.2, 29.5, 29.6, 29.7, 32.6, 34.4, 36.6, 37.0, 37.1, 39.9, 61.1, 129.5 and 129.9 [(*Z*)-**30**], 130.0 and 130.4 [(*E*)-**30**; *Z*/*E*=2:1]. GC–MS [same conditions as for (*R*)-**26**]: t_R 16.69 min [60.5%, (*Z*)-**30**], 16.77 min [34.8%, (*E*)-**30**]; MS of (*Z*)- and (*E*)-**30** were identical (70 eV, EI): *m*/*z*: 254 (<1) [M^+, $C_{17}H_{34}O$], 236 (3), 221 (3), 208 (3), 151 (4), 137 (7), 123 (11), 109 (33), 95 (39), 81 (100), 71 (39), 69 (37), 68 (38), 55 (46), 41 (33). The spectral data of **30** prepared by this route was virtually identical to those of **30** prepared by metathesis (Section 4.7.1).

4.20. (3*R*,13*R*)-3,13-Dimethyl-1-pentadecanol 16

Pd–C (10%, 0.5 g) was added to a solution of (3*R*,6*EZ*,13*R*)-**30** (4.2 g, 16.5 mmol) in EtOAc (50 mL). The mixture was stirred under H_2 (balloon) for 1 h at room temperature, and filtered through Celite. The Celite layer was washed with hexane. The combined filtrate and washings were concentrated in vacuo to give 3.76 g (95%) of (3*R*,13*R*)-**16** as a colorless oil. n_D^{22}=1.4510; $[\alpha]_D^{26}$ −2.73 (*c* 4.40, hexane); ν_{max} (film): 3334 (br, OH), 2958 (s), 2925 (s), 2854 (s), 1464 (m), 1377 (m), 1059 (m), 721 (w); δ_H ($CDCl_3$): 0.80–0.93 (9H, m, $CH_3\times3$), 1.02–1.19 (3H, m), 1.20–1.45 (20H, m), 1.50–1.66 (2H, m), 3.61–3.72 (2H, m); δ_C ($CDCl_3$): 11.5, 19.3, 19.7, 27.0, 27.2, 29.5, 29.73, 29.75, 29.77, 30.0, 30.06, 30.15, 34.4, 36.7, 37.2, 40.0, 61.2; GC–MS [same conditions as for (*R*)-**26**]: t_R 16.92 min (91.5%, **16**); MS of (3*R*,13*R*)-**16** (70 eV, EI): *m*/*z*: 255 (<1) [M^+-1, $C_{17}H_{35}O$], 210 (5), 181 (6), 153 (4), 139 (10), 125 (16), 111 (30), 97 (54), 83 (55), 70 (100), 69 (50), 57 (56), 56 (36), 55 (58), 43 (34), 41 (32). The spectral data of the present **16** was identical to those of **16** prepared via the metathesis route (Section 4.8.1).

4.21. (*R*)-Citronellic acid 32

(*R*)-Citronellal (**10**, 21.0 g, 136 mmol) was oxidized with PDC as reported previously[21] to give 18.6 g (87%) of (*R*)-**32**. $[\alpha]_D^{26}$ +9.44 (*c* 2.98, $CHCl_3$).

4.22. (3*R*,1′*S*)-1-Ethyl-2-methylpropyl citronellate 33

In the same manner as described in Section 4.12.2, **31** (4.56 mL, 50.0 mmol) in dry toluene (50 mL) was reacted with diethylzinc (1.0 M solution in hexane, 100 mL, 100 mmol) in the presence of (−)-MIB (598 mg, 2.50 mmol) at 0 °C. After stirring for 3 h at 0 °C, the reaction was quenched with saturated aqueous NH_4Cl solution (50 mL). To this mixture, a 2 M aqueous HCl solution (120 mL, 240 mmol) was added slowly at 0 °C. After stirring for 30 min at room temperature, the mixture was diluted with Et_2O. The organic solution was washed twice with 2 M aqueous HCl solutions (30 mL×2). These acidic aqueous phases were combined. The organic solution was successively washed with water, a saturated aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and filtered to give a solution of crude (*S*)-**20**.

The combined acidic solution was made alkaline with a 4 M aqueous NaOH solution, and extracted with Et_2O. The combined organic solution was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (20 g). Elution with hexane/EtOAc (4:1) gave 533 mg (89%) of recovered (−)-MIB.

To the obtained solution of crude (*S*)-**20**, (*R*)-citronellic acid (**32**, 8.50 g, 49.9 mmol) and DMAP (9.16 g, 75.0 mmol) were added. The mixture was cooled to 0 °C. EDC (14.5 g, 75.6 mmol) was added to the mixture at 0 °C. After stirring for 12 h at room temperature, the mixture was poured into water, and extracted with EtOAc. The combined organic solution was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 [150 g, elution with hexane/EtOAc (25:1)] followed by distillation to give 9.44 g (74% based on **32**) of **33** as a colorless oil, bp 98–100 °C/0.2 Torr; n_D^{23}=1.4453; $[\alpha]_D^{22}$ −2.55 (*c* 1.20, $CHCl_3$); ν_{max} (film): 1730 (s, C=O), 1670 (w, C=C), 1190 (br s, C–O), 980 (br s); δ_H (500 MHz, $CDCl_3$): 0.87 (3H, t, *J* 7.0, 2″-H_3), 0.89 (6H, d, *J* 7.0, 2′-$CH_3\times2$), 0.96 (3H, d, *J* 7.0, 3-CH_3), 1.19–1.27 (1H, m, 4-H_a), 1.34–1.41 (1H, m, 4-H_b), 1.48–1.60 (2H, m, 1″-H_2), 1.60 (3H, br s, 7-CH_3), 1.68 (3H, br s, 7-CH_3), 1.79–1.87 (1H, m, 2′-H), 1.93–2.07 (3H, m, 3-H, 5-H_2), 2.12 (1H, dd, *J* 8.5, 15, 2-H_a), 2.33 (1H, dd, *J* 6.0, 15, 2-H_b), 4.69 (1H, ddd, *J* 5.0, 5.5, 8.0, 1′-H), 5.09 (1H, t-quint., *J* 7.0, 1.5, 6-H); δ_C (126 MHz, $CDCl_3$): 9.9, 17.6, 18.6, 19.6, 23.9, 25.4, 25.7, 30.0,

30.8, 36.8, 42.1, 79.4, 124.3, 131.4, 173.2. HR-EIMS calcd for $C_{16}H_{30}O_2$ $[M]^+$: 254.2246, found: 254.2234.

4.23. (3*R*,6*RS*,1′*S*)-1′-Ethyl-2′-methylpropyl 6,7-epoxycitronellate 34

MCPBA (65% purity, 2.5 g, ca. 10 mmol) was added portionwise to a stirred and ice-cooled solution of (3*R*,1′*S*)-**33** (2.20 g, 8.7 mmol) in dry CH_2Cl_2 (10 mL) at 0–5 °C. The mixture was stirred for 30 min at 0–5 °C to generate the paste of *m*-chlorobenzoic acid. It was then diluted with hexane, and filtered through a glass filter. The solid on the filter was washed with hexane. The combined filtrate and washings were washed with $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (20 g). Elution with hexane/EtOAc (10:1) gave 2.52 g (quant.) of **34** as a colorless oil; ν_{max} (film): 2964 (s), 2933 (s), 2877 (m), 1730 (s, C=O), 1462 (m), 1288 (m), 1250 (m), 1205 (m), 1167 (m), 1124 (m), 976 (m); δ_H ($CDCl_3$): 0.87 (3H, t, *J* 7.2, CH_2CH_3), 0.89 (6H, d, *J* 6.8, $CH(CH_3)_2$), 0.98 (3H, d, *J* 6.8, $CHCH_3$), 1.27 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.40–1.65 (6H, m), 1.78–1.88 (1H, m), 1.98–2.08 (1H, m), 2.12–2.21 (1H, m), 2.30–2.38 (1H, m), 2.71 (1H, t-like, *J* 5.6, OCH), 4.66–4.74 (1H, m, O=C–O-CH). This was employed in the next step without further purification.

4.24. (3*R*,1′*S*)-1′-Ethyl-2′-methylpropyl 3-methyl-6-oxohexanoate 35

A solution of **34** (2.35 g, 8.7 mmol) in Et_2O (10 mL) was added dropwise to a stirred and ice-cooled solution of $HIO_4 \cdot 2H_2O$ (2.30 g, 10.1 mmol) in THF (15 mL). The mixture was stirred for 0.5 h at 0–5 °C. HIO_3 separated from the solution as white precipitates. The mixture was diluted with water, and extracted with Et_2O. The extract was successively washed with water, $NaHCO_3$ solution, and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (2.47 g) was chromatographed over SiO_2 (20 g). Elution with hexane/EtOAc (10:1) gave 1.61 g (82%) of **35** as a colorless oil; n_D^{24}=1.4398; $[\alpha]_D^{23}$ −3.73 (*c* 2.40, hexane); ν_{max} (film): 2966 (s), 2935 (s), 2877 (s), 2823 (w), 2721 (w, O=C–H), 1728 (s, C=O), 1464 (m), 1383 (m), 1371 (m), 1255 (m), 1203 (m), 1165 (m), 1128 (m), 1099 (m), 976 (m); δ_H ($CDCl_3$): 0.87 (3H, t, *J* 7.6, CH_2CH_3), 0.882 [3H, d, *J* 6.8, $CH(CH_3)CH_3$], 0.890 [3H, d, *J* 6.8, $CH(CH_3)CH_3$], 0.98 [3H, d, *J* 6.8, $CHCH_3$], 1.48–1.61 (3H, m), 1.68–1.78 (1H, m), 1.79–1.88 (1H, m), 1.95–2.06 (1H, m), 2.12–2.22 (1H, m), 2.30–2.36 (1H, m), 2.42–2.52 (2H, m), 4.66–4.71 (1H, m), 9.78 (1H, t, *J* 1.6, O=C–H); GC–MS [same conditions as for (*R*)-**26**]: t_R 12.70 min (86.3%, **35**), 15.12 min (12.3%, unidentified); MS of **35** (70 eV, EI): *m*/*z*: 213 (<1) [M^+−15], 127 (100), 101 (10), 85 (24), 84 (22), 81 (47), 69 (20), 55 (14), 43 (26). HRMS calcd for $C_7H_{11}O_2$ [$C_{13}H_{24}O_3-C_6H_{13}O$ (alcohol part)]: 127.0759, found: 127.0743.

4.25. (3*R*,6*EZ*,13*R*,1′*S*)-1′-Ethyl-2′-methylpropyl 3,13-dimethyl-6-pentadecenoate 36

A Wittig reagent was prepared by the dropwise addition of *n*-BuLi in hexane (1.6 M, 6.9 mL, 11 mmol) to a stirred and cooled solution of (*R*)-**28** [prepared from 2.8 g of (*R*)-**27** (81% purity containing 12% of 1,5-diiodopentane), ca. 10 mmol] in dry THF (10 mL) at −30 to 0 °C under Ar. The resulting red solution was added dropwise to a stirred and cooled solution of (3*R*,1′*S*)-**35** (1.60 g, 7 mmol) in dry THF (10 mL) at −60 to −50 °C under Ar. The stirred mixture was left to stand overnight with gradual raise of the reaction temperature to room temperature. The reaction was quenched by adding MeOH (10 mL) and water (5 mL). H_2O_2 (30%, 1 mL) was added to the mixture to oxidize Ph_3P to Ph_3PO. The mixture was then extracted with hexane. The extract was washed with MeOH/H_2O (2:1, 20 mL) and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue (2.24 g) was chromatographed over SiO_2 (30 g). Elution with hexane/EtOAc (10:1) gave (3*R*,6*EZ*,13*R*,1′*S*)-**36** (1.15 g, 47%) as a colorless oil; n_D^{24}=1.4552; $[\alpha]_D^{23}$ −8.67 (*c* 3.51, hexane); ν_{max} (film): 2964 (s), 2927 (s), 2875 (m), 2856 (w), 1732 (s, C=O), 1462 (m), 1379 (m), 1200 (m), 1161 (m), 1128 (m), 974 (m); δ_H ($CDCl_3$): 0.80–0.90 (9H, m, $CH_3\times3$), 0.89 [6H, d, *J* 7.2, $CH(CH_3)_2$], 0.96 (3H, d, *J* 7.2, $CHCH_3$), 1.04–1.18 (2H, m), 1.20–1.48 (11H, m), 1.48–1.50 (2H, m), 1.78–1.88 (1H, m), 1.94–2.10 (5H, m), 2.10–2.18 (1H, m), 2.30–2.38 (1H, m), 4.65–4.72 (1H, m), 5.30–5.41 (2H, m); δ_C ($CDCl_3$): 9.9, 11.4, 17.7, 18.6, 19.6, 19.8, 24.0, 24.7, 27.0, 27.3, 29.5, 29.7, 29.9, 30.1, 30.9, 34.4, 36.6, 36.8, 42.1, 79.4, 129.1 and 130.1 [(*Z*)-**36**], 129.5 and 129.6 [(*E*)-**36**; *Z*/*E*=6:1], 172.9; GC–MS [same condition as for (*R*)-**26**]: t_R 18.32 min (5.2%, unidentified), 20.61 min [80.3%, (*Z*)-**36**], 20.80 min [13.1%, (*E*)-**36**]; MS of **36** (70 eV, EI) [Both (*E*)- and (*Z*)-**36** showed identical MS.]: *m*/*z*: 352 (<1) [M^+], 268 (12), 251 (50), 239 (11), 221 (9), 208 (21), 137 (8), 125 (9), 111 (10), 109 (10), 97 (15), 95 (15), 85 (100), 70 (44), 69 (34), 55 (27), 43 (50). HRMS calcd for $C_{17}H_{31}O$ [$C_{23}H_{44}O_2-C_6H_{13}O$ (alcohol part)]: 251.2375, found: 251.2364.

4.26. (3*R*,13*R*,1′*S*)-1′-Ethyl-2′-methylpropyl 3,13-dimethylpentadecanoate 1

Pd–C (10%, 0.22 g) was added to a solution of (3*R*,6*EZ*,13*R*,1′*S*)-**36** (1.05 g, 3 mmol) in EtOAc (20 mL). The mixture was vigorously stirred under H_2 (balloon) for 1.5 h at room temperature. The mixture was filtered through SiO_2 (10 g) in hexane, and the column was washed with hexane/EtOAc (5:1). The filtrate and washings were concentrated in vacuo to give (3*R*,13*R*,1′*S*)-**1** (1.01 g, 96%) as a colorless oil; n_D^{24}=1.4478; $[\alpha]_D^{25}$ −4.61 (*c* 2.52, $CHCl_3$); ν_{max} (film): 2964 (s), 2925 (s), 2875 (s), 2854 (s), 1734 (s, C=O), 1464 (m), 1379 (m), 1252 (m), 1180 (m), 1126 (m), 976 (m); δ_H ($CDCl_3$): 0.80–0.90 (9H, m, $CH_3\times3$), 0.89 [6H, d, *J* 6.8, $CH(CH_3)_2$], 0.94 (3H, d, *J* 6.4, $CHCH_3$), 1.02–1.12 (2H, m), 1.13–1.40 (18H, m), 1.48–1.65 (3H, m), 1.78–1.88 (1H, m), 1.90–2.00 (1H, m), 2.08–2.15 (1H, m), 2.25–2.45 (1H, m), 4.64–4.70 (1H, m); δ_C ($CDCl_3$): 9.97, 11.5, 17.7, 18.7, 19.3, 19.8, 24.0, 27.0, 27.2, 29.5, 29.7, 29.76, 29.85, 30.1, 30.4, 30.9, 34.4, 36.7, 36.8, 42.3, 79.4, 173.2; GC–MS [same condition as for (*R*)-**26**]: t_R 18.32 min (5.3%, unidentified), 21.04 min [92.5%, (3*R*,13*R*,1′*S*)-**1**]; MS of (3*R*,13*R*,1′*S*)-**1** (70 eV, EI): *m*/*z*: 339 (<1) [M^+−15], 271 (17), 270 (29), 253 (53), 81 (95), 84 (100), 69 (35), 57 (34), 43 (39).

4.27. Field experiment

The four stereoisomers (3*R*,13*R*,1′*S*)-, (3*R*,13*S*,1′*S*)-, (3*S*,13*R*,1′*S*)-, and (3*S*,13*S*,1′*S*)-**1** were tested for the attraction of male *C. variegata* in *P. hispanica* forests in Yantai, Shandong Province, China (121°59′E. 37°28′N) for 12-day period from the 1st of June to the 12th of June 2009, using a randomized complete block design. A red rubber septum was loaded with 100 μg of each the four stereoisomers dissolved in 200 μL of hexane, and the solvent was allowed to evaporate in a fume hood. The septa were stored at −20 °C until ready for use, except when shipped. Sticky traps were made from open-ended 2 L milk cartons coated inside with Entomological Glue (Huanxing Company, Guangdong Province, China), suspended from trees 10 m above ground. Traps were placed in five rows with five replications for each treatment at approximately 15–20 m spacing between trapping stations and treatment rows. Septa were placed in the center of the white sticky base lying on the sticky surface. Traps baited with blank septa were used as negative controls. One of each of the five treatments was randomly assigned to a trap tree within each row of trees. Every day, except when it rained, the numbers of moths captured were recorded and treatment positions were re-randomized.

4.27.1. Statistical analysis. The significance of the treatment effects in the field experiments was tested using ANOVA.[22] The mean captures obtained with each treatment were stabilized using $\sqrt{(x+1)}$ transformation. Significantly different means were identified post hoc using Fisher's Protected Least Significant Difference (α=0.05).

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