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Synthesis of all the four stereoisomers of (1′*S*)-1-ethyl-2-methylpropyl 3,13-dimethylpentadecanoate, the major component of the sex pheromone of Paulownia bagworm, *Clania variegata*

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ABSTRACT

All the four stereoisomers of (1′*S*)-1-ethyl-2-methylpropyl 3,13-dimethylpentadecanoate, the major component of the sex pheromone of *Clania variegata*, were synthesized by starting from (*R*)- or (*S*)-2-methylbutan-1-ol, (*R*)- or (*S*)-citronellal, and (*S*)-2-methylpentan-3-ol. Olefin cross metathesis was employed as the key reaction.

1. Introduction

The Paulownia bagworm, *Clania variegata* Snell (Lepidoptera: Psychidae), is a forest defoliator in managed forests in China. The major component of its sex pheromone was reported to be (1′*S*)-1-ethyl-2-methylpropyl 3,13-dimethylpentadecanoate (**1**, Fig. 1) by Gries et al.[1] As to the absolute configuration of this ester **1**, they assigned *S* configuration to the alcohol part by synthesis of both (1′*R*)- and (1′*S*)-**1** and their field trapping experiments in China.[1] The absolute configuration of the two remaining stereogenic centers of the carboxylic acid part of **1**, however, has remained unknown.

In continuation of our long-term studies on the absolute configuration of pheromones,[2] we became interested in clarifying the stereochemistry of the naturally occurring **1**. The standard method to achieve the goal is to synthesize all the possible stereoisomers of **1** and then to evaluate their pheromone activity. Usually the biologically active stereoisomer of **1** can be regarded as the naturally occurring **1**.[2] The ester **1** possesses four stereoisomers. We decided to employ olefin cross metathesis reaction as the key step to synthesize all the stereoisomers of **1** quickly without complication.[3]

Scheme 1 shows our retrosynthetic analysis of (3*R*,13*R*,1′*S*)-**1**. The ester **1** can be dissected to 3,13-dimethylpentadecane moiety

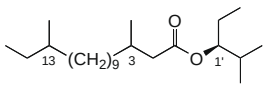

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Figure 1. Structure **1** of the major component of the sex pheromone of *Clania variegata*.

A and the alcohol moiety **B**. The olefinic acetate **A** might 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 obtainable from (*R*)-citronellal (**G**), and the alcohol part **B** must be available via asymmetric synthesis. This synthetic plan was put into practice as reported below.

2. Results and discussion

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.[4] 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

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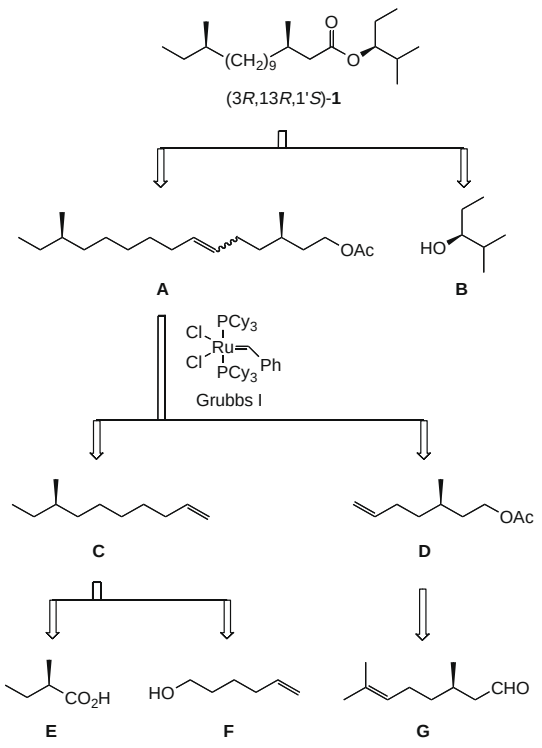
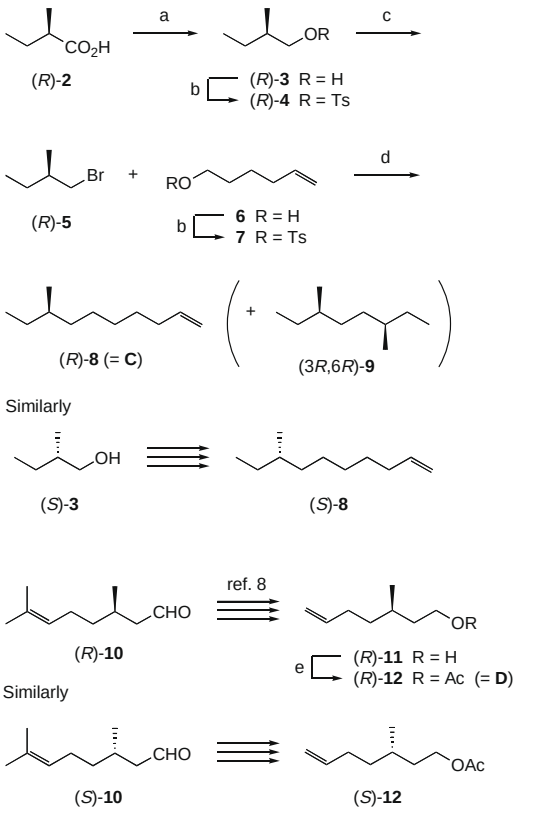


Scheme 1. Retrosynthetic analysis of (3*R*,13*R*,1′*S*)-**1**.

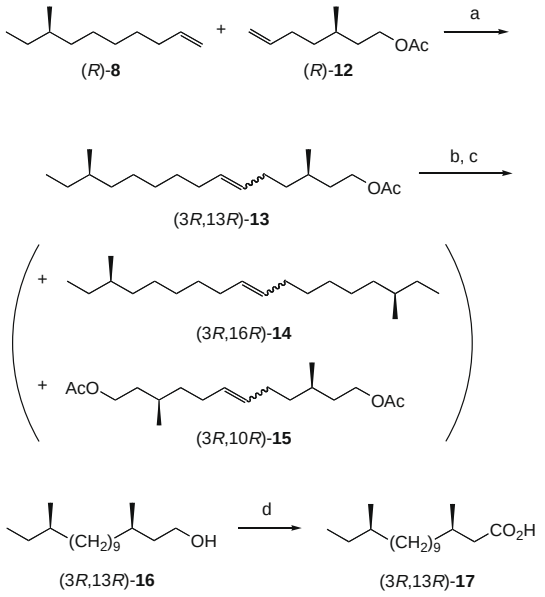
tosylate **7** (obtained by tosylation of commercially available **6**) in the presence of dilithium tetrachlorocuprate at −65 to −50 °C under the Schlosser conditions[5] to give (*R*)-**8**, bp 94–96 °C/48 Torr, $[\alpha]_D^{27}$ − 11.0 (*c* 3.40, pentane), in 42% yield based on (*R*)-**5**. Its GC–MS analysis 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 (*S*)-**8**, bp 110–115 °C/65 Torr, $[\alpha]_D^{26}$ + 10.6 (*c* 3.50, pentane), as a 93:7 mixture of (*S*)-**8** and (3*S*,6*S*)-**9**. 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.[6] The overall yield of (*R*)-**8** was 26% based on (*R*)-**2** (4 steps), while that of (*S*)-**8** was 22% based on (*S*)-**3** (3 steps).

The other partners of metathesis, (*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 intermediates in the synthesis of the pheromone of an Okinawan moth, *Lyclene dharma dharma*.[8] Their enantiomeric purities were 97.2% ee for both (*R*)-**12**, bp 130–134 °C/80 Torr, $[\alpha]_D^{26}$ +1.53 (*c* 3.41, Et_2O) and (*S*)-**12**, bp 122–125 °C/60 Torr, $[\alpha]_D^{25}$ −1.36 (*c* 3.12, Et_2O).[9] The overall yield of (*R*)-**12** was 46% based on (*R*)-**10** (7 steps), and that of (*S*)-**12** was 45% based on (*S*)-**10** (7 steps).

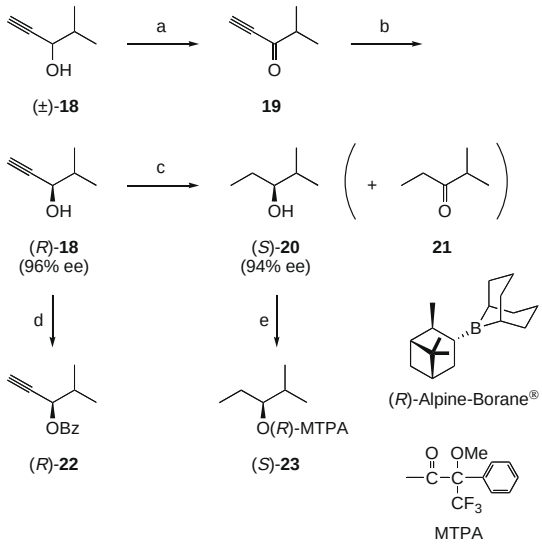
Scheme 3 shows the synthesis of the key acid (3*R*,13*R*)-**17** via the crucial step of olefin cross metathesis.[10–13] Because (*R*)-**8** could be prepared in shorter four steps than (*R*)-**12** (7 steps), 10 equiv of (*R*)-**8** was mixed with 1 equiv of (*R*)-**12** in dichloromethane. In the presence 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*,16*R*)-**14** [50% yield based on (*R*)-**8**] and then (3*R*,13*R*)-**13** contaminated with (3*R*,10*R*)-**15** in 88% yield based on (*R*)-**12**. Since complete removal of **15** from crude **13** was difficult, the crude (3*R*,13*R*)-**13** was subjected to alkaline hydrolysis and hydrogenation over 10% palladium–charcoal. Subsequent chromatographic purification gave (3*R*,13*R*)-**16**, $[\alpha]_D^{25}$ − 2.12 (*c* 7.64, hexane), in 53% yield based on the crude (3*R*,13*R*)-**13** (2 steps). Oxidation of (3*R*,13*R*)-**16** with Jones chromic acid afforded the desired acid (3*R*,13*R*)-**17**, $[\alpha]_D^{24}$ − 0.34 (*c* 1.39, $CHCl_3$), in 75% yield. The overall



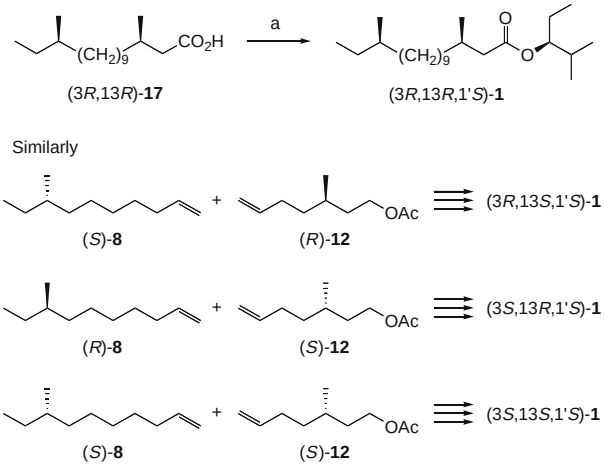
Scheme 2. Synthesis of the metathesis partners **8** and **12**. Reagents: (a) $LiAlH_4$, Et_2O; (b) TsCl, C_5H_5N (51% for **7**); (c) LiBr, DMF [63% based on (*R*)-**2**, 3 steps]; (d) (i) (*R*)-**5**, Mg, THF ; (ii) **7**, THF, Li_2CuCl_4 [42% based on (*R*)-**5** or 66% based on **7**]; (e) Ac_2O, DMAP, C_5H_5N (82%).



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. 10:1 in CH_2Cl_2, reflux, 6 h [88% based on (*R*)-**12**]; (b) NaOH, MeOH, aq THF, reflux, 1 h (92%); (c) H_2, 10% Pd–C, EtOH, then SiO_2 chromatog. (58%); (d) Jones CrO_3, acetone (75%).



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) (*S*)-MTPACl, C_5H_5N.



Scheme 5. Synthesis of the target esters **1**. Reagents: (a) (*S*)-**20**, EDC, DMAP, CH_2Cl_2 [83% based on (3*R*,13*R*)-**17**].

yield of (3*R*,13*R*)-**17** was 35% based on (*R*)-**12** (4 steps). Other stereoisomers of the acid **17** could be synthesized in the same manner.

The next task was the synthesis of (*S*)-2-methylpentan-3-ol (**20**). Gries et al. previously prepared (*S*)-**20** by kinetic resolution of (±)-4-methyl-1-penten-3-ol by Sharpless asymmetric epoxidation.[1] 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®[14] 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**, bp 119–121 °C, $[\alpha]_D^{25}$ − 0.96 (*c* 1.37, $CHCl_3$), in 47% yield. The enantiomeric purity of (*R*)-**18** was estimated as 96% ee by HPLC analysis of the corresponding benzoate (*R*)-**22**.[15] Hydrogenation of (*R*)-**18** over 10% palladium–charcoal in pentane afforded a 2:1 mixture of (*S*)-**20** and **21**. After chromatographic purification, highly volatile and pure (*S*)-**20**, bp 104–106 °C, $[\alpha]_D^{25}$ − 14.0 (*c* 1.10, $CHCl_3$), $[\alpha]_D^{25}$ − 20.1 (*c* 1.16, EtOH), Ref. 16 $[\alpha]_D^{23}$ − 16.9 (*c* 0.39, EtOH), could be secured in 16% yield. Its enantiomeric purity was estimated as 94.2% ee by GC analysis of the corresponding (*R*)-MTPA ester **23**.[17]

The final step as depicted in Scheme 5 was the esterification of the four stereoisomers of the acid **17** with (*S*)-**20**. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC, 1.6 equiv) was added to a solution of (3*R*,13*R*)-**17** (1 equiv), (*S*)-**20** (2 equiv), and 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 1.9 equiv) in dichloromethane to give (3*R*,13*R*,1′*S*)-**1** as an oil, $[\alpha]_D^{23}$ −5.38 (*c* 1.30, $CHCl_3$), in 83% yield. Its ^1H and ^{13}C NMR data[18] are in good accord with those published for (3*RS*,13*RS*,1′*S*)-**1**.[1] The MS of (3*R*,13*R*,1′*S*)-**1**[18] was also in accord with that of the naturally occurring pheromone component **1**.[1] 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* l.20, $CHCl_3$). The spectral data of these four isomers of **1** were virtually indistinguishable.[18] The overall yield of (3*R*,13*R*,1′*S*)-**1** was 13% based on (*R*)-**10** (12 steps).

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*. Future bioassay of these four stereoisomers of **1** will hopefully clarify the absolute configuration of the naturally occurring and bioactive component **1**. Olefin cross metathesis has been shown to be a useful reaction in pheromone synthesis, especially when a set of stereoisomers has to be prepared quickly and efficiently.

Acknowledgments

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6. (a) GC analysis of (*R*)-**8** [instrument: Agilent 7890; column: CHIRAMIX,® [7] 30 m × 0.25 mm i.d.; column temp.: 40–180 °C (+0.7 °C/min); carrier gas: He, 0.7 mL/min]: t_R 42 min (>99.9%, (*R*)-**8**], 47 min [<1.0%, (*S*)-**8**].; (b) GC analysis of (*S*)-**8** [same conditions as for (*R*)-**8**]: t_R 42 min [0.5%, (*R*)-**8**], 47 min [99.5%, (*S*)-**8**].
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15. HPLC analysis of (*R*)-**22** [column: Chiralcel® OJ-H, 25 cm × 4.6 mm i.d.; eluent: hexane/*i*-PrOH = 9:1; flow rate: 0.5 mL/min; column temp.: 10 °C; detection at 254 nm]: t_R 10.96 min [98.0%, (*R*)-**22**], 11.91 [2.0%, (*S*)-**22**].
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17. GC analysis of (*S*)-**23** [(*S*)-**23** was prepared from (*S*)-**20** employing (*S*)-MTPACl (Aldrich, ⩾99% ee). Instrument: Shimadzu GC-2014; column: DB-WAX,® 30 m × 0.25 mm i.d.; column temp.: 130 °C (1 min)–150 °C (+0.25 °C/min); carrier gas: He; press: 100 kPa]: t_R 29.92 min (97.1%), 30.12 min (2.9%). Diastereomeric purity of (*S*)-**23**: 94.2% de.
18. Spectral data of (3*R*,13*R*,1′*S*)-**1**: ν_{max} (film): 1735 (s, C=O), 1180 (m), 975 (m) cm^{-1}; 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 × 2), 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_a), 2.31 (1H, dd, *J* 6.0, 15, 2-H_b), 4.68 (1H, ddd, *J* 5.0, 5.0, 8.0, 1′-H) ppm; 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 ppm; GC–MS [Instrument: Agilent 19091S-433; column: HP-5MS, 5% phenylmethylsiloxane, 30 m × 0.25 mm i.d.; carrier gas: He; press: 60.7 kPa; temp.: 70–230 °C (+10 °C/min)]: t_R 17.513 min (1.63%), 19.608 (2.69%), 21.026 [93.4%; (3*R*,13*R*,1′*S*)-**1**]; MS (70 eV, EI): *m*/*z* 353 (very small, M^+-1), 339 (0.5, M^+-CH_3), 296 (2), 270 (37), 253 (63), 244 (4), 235 (5), 213 (3), 181 (4), 165 (1), 151 (1), 139 (3), 125 (5), 111 (6), 97 (10), 84 (100), 69 (35), 57 (36), 43 (38); HRMS calcd for $C_{17}H_{33}O$ $[M-C_6H_{13}O]^+$: 253.2531, found: 253.2529. Spectral data of other three isomers of **1** were identical to those of (3*R*,13*R*,1′*S*)-**1** within experimental errors. The diastereomers with remote stereogenic centers such as the isomers of **1** showed virtually identical spectral data, although they showed different specific rotations. GC retention times of all the isomers were also identical to that of (3*R*,13*R*,1′*S*)-**1** within experimental errors under the same conditions for the analysis of (3*R*,13*R*,1′*S*)-**1**: t_R 21.046 min [88.2%, (3*R*,13*S*,1′*S*)-**1**]; 21.039 [92.2%, (3*S*,13*R*,1′*S*)-**1**]; 21.058 [93.0%, (3*S*,13*S*,1′*S*)-**1**].