Synthesis of (1*R*,3*S*,5*S*)-1,3,8-Trimethyl-2,9-dioxabicyclo[3.3.1]non-7-ene, the Male Pheromone of a Hepialid Moth *Endoclita excrescens*, and Its Enantiomer

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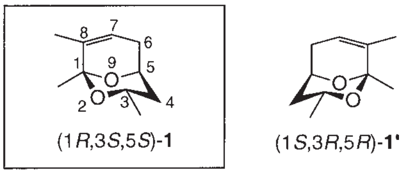
Both (1*R*,3*S*,5*S*)- and (1*S*,3*R*,5*R*)-isomers of 1,3,8-trimethyl-2,9-dioxabicyclo[3.3.1]non-7-ene were synthesized by starting from (*S*)- and (*R*)-isomers of ethyl 3-hydroxybutanoate, respectively. The (1*R*,3*S*,5*S*)-isomer was identified as the male sex pheromone of a Japanese hepialid moth, *Endoclita excrescens*.

Endoclita excrescens (Lepidoptera: Hepialidae) is a hepialid moth, which damages herbal and woody plants in Japan by boring into their stems and/or trunks. Nakashima recently reported the isolation of a compound from the hexane extract of brush organ on male hind legs of *E. excrescens*.[1] It induced an electroantennographic detection response in female antennae, and was found to be the pheromone of that moth. The chemical structure of the pheromone was proposed as 1,3,8-trimethyl-2,9-dioxabicyclo[3.3.1]non-7-ene (**1**, Figure 1) mainly on the basis of its mass spectral analysis.[1] By the request of Dr. Nakashima we synthesized both (1*R*,3*S*,5*S*)-**1** and (1*S*,3*R*,5*R*)-**1′** by starting from readily available (*S*)- and (*R*)-isomers of ethyl 3-hydroxybutanoate. Our synthetic (1*R*,3*S*,5*S*)-**1** indeed exhibited pheromone activity against *E. excrescens*. This Letter describes the synthesis of the pheromone **1** and its enantiomer **1′**.



(1*R*,3*S*,5*S*)-**1** (1*S*,3*R*,5*R*)-**1′**

Figure 1. Structure of the male pheromone (**1**) of *Endoclita excrescens*.

Scheme 1 summarizes our synthesis of **1** and **1′**. We chose the enantiomers **2** and **2′** of ethyl 3-hydroxybutanoate and commercially available 2,3-dimethylfuran as the starting materials. The strategy employed for the construction of 2,9-dioxabicyclo[3.3.1]non-7-ene system is that employed in 1980's by the research groups of Ziegler,[2] DeShong,[3] and Mori,[4] which involves conversion of a furan derivative **6** to a derivative **10** of 2,9-dioxabicyclo[3.3.1]non-7-ene via hemiacetal **9**.

Protection of the hydroxy group of the commercially available ethyl (*S*)-3-hydroxybutanoate (**2**, 96.7% ee) as *t*-butyldimethylsilyl (TBS) ether yielded (*S*)-**3**, which was reduced with diisobutylaluminum hydride (DIBAL-H) to give aldehyde (*S*)-**4**.[5] Addition of (*S*)-**4** to the anion generated from 2,3-dimethylfuran by treatment with *t*-butyllithium in THF/HMPA furnished a mixture of two diastereomeric alcohols **5** and **6** in a ratio of almost 1 : 1 as judged by ^{1}H NMR analysis, reflecting almost no *syn*/*anti*-stereoselection. Chromatographic purification of the mixture on spherical silica (Kanto Silica Gel 60 N: 40–50 μm) afforded pure **5** (27% yield) and **6** (35% yield),[6] whose stereochemistries were deduced by the later conversion of **6** to **10**.

Oxidation of **5** with *m*-chloroperbenzoic acid (MCPBA) provided oily hemiacetal **7** as an epimeric mixture. Neither hydrofluoric acid nor boron trifluoride etherate[4] could convert **7** to a 2,9-dioxabicyclo[3.3.1]non-7-ene derivative **8**, presumably because of the instability of **8** with severe 1,3-diaxial interactions between the methyl group at C-3 and the substituents at C-1 or C-5. We then executed the oxidation of **6** with MCPBA. In this case, the resulting hemiacetal **9** was obtained as a crystalline mixture of two epimers, m.p. 68–74 °C. Treatment of **9** with 48% hydrofluoric acid in acetonitrile[4] furnished the cyclization product **10** in 79% yield.[7] The equatorial nature of the methyl group at C-3 of **10** must have allowed the cyclization to take place readily.

In order to remove the oxygen function at C-6 of **10**, the ketone **10** was first reduced with sodium borohydride in the presence of cerium(III) chloride[8] to give allylic alcohol **11** in 94% yield. Although the splitting pattern of the ^{1}H NMR signal due to the proton at C-6 of **11** could not be analyzed, the NOE measurements as shown in the formula **11** suggested (*R*)-stereochemistry at C-6. Our plan was to remove the hydroxy group at C-6 of **11** by Barton's radical deoxygenation method.[9] Accordingly, alcohol **11** was converted to the corresponding methyl xanthate **12** by successive treatments of **11** with *n*-butyllithium, carbon disulfide and methyl iodide. Deoxygenation of **12** proceeded smoothly, when it was heated with tri-*n*-butyltin hydride in dry toluene in the presence of 2,2′-azobisisobutyronitrile (AIBN), furnishing the desired (1*R*,3*S*,5*S*)-**1** in 44% yield after chromatographic purification and distillation.[10] Gas chromatographic analysis of **1** on a chiral stationary phase revealed it to be of 96.8% ee.[10] The mass spectrum of **1** was in good agreement with that of the natural pheromone. The overall yield of (1*R*,3*S*,5*S*)-**1** was 8% based on (*S*)-**2** (8 steps). Similarly, (1*S*,3*R*,5*R*)-**1′** was synthesized from ethyl (*R*)-3-hydroxybutanoate (**2′**) in 7% overall yield (8 steps).[11] Electroantennographic and behavioral studies of **1** and **1′** by Nakashima revealed (1*R*,3*S*,5*S*)-**1** to be the naturally occurring pheromone.

In conclusion, (1*R*,3*S*.5*S*)-1,3,8-trimethyl-2,9-dioxabicyclo[3.3.1]non-7-ene (**1**) was proved to be the male pheromone of the moth *Endoclita excrescens*.

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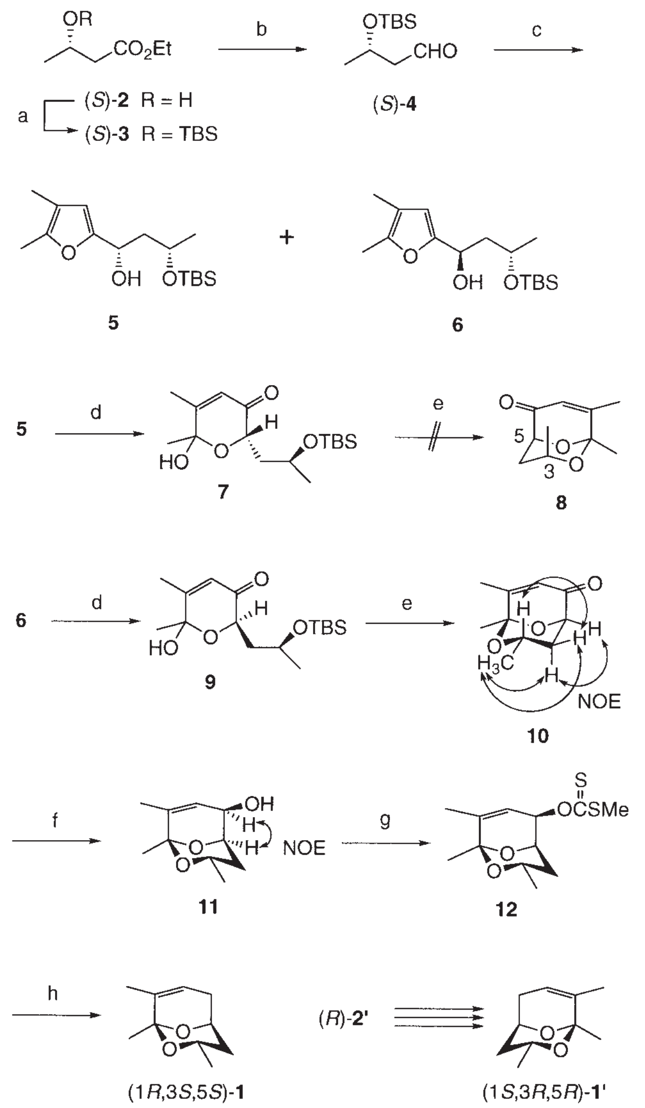
This Letter is dedicated to Professor Teruaki Mukaiyama on the occasion of his 75th birthday.



Scheme 1. Synthesis of the male pheromone (**1**) of *Endoclita excrescens* and its enantiomer (**1**): reagent: (a) TBSCl, imidazole, DMF (91%); (b) DIBAL-H,CH_2Cl_2 (88%); (c) 2,3-dimethylfuran, *t*-BuLi, Et_2O/HMPA (27% of **5** and 35% of **6**); (d) MCPBA, CH_2Cl_2 (96% for **7** and 89% for **9**); (e) 48% HF aq., MeCN (79%); (f) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH (94%); (g) *n*-BuLi, CS_2, MeI, THF (98%); (h) $(n\text{-Bu})_3SnH$, AIBN, toluene (44%).

References and Notes

1 T. Nakashima, 2nd Asia-Pacific Conference on Chemical Ecology, Penang, August 2001, Abstr., No 27.

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5 G. Solladié, F. Somny, and F. Colobert, *Tetrahedron: Asymmetry*, **8**, 801 (1997).

6 The structures of all new compounds in this Letter were supported by their spectral properties (IR, ^{1}H- and ^{13}C-NMR spectra) and also by elemental analyses (combustion or HRMS).

7 Properties of **10**: b.p. 114 °C/13 Torr; $n_D^{22} = 1.4909$; $[\alpha]_D^{22} = +372$ ($c = 1.07$, $CHCl_3$); IR: ν_{max} (film) cm^{-1} = 1690 (s, C=O), 1625 (w, C=C), 1125 (s, C–O), 1110 (s, C–O), 955 (s), 880 (s); NMR δ_H (400 MHz, $CDCl_3$): 1.19 (3 H, d, $J = 6.1$ Hz, 3-CH_3), 1.53 (3 H, s, 1-CH_3), 1.59 (1 H, ddd, $J = 13.6, 3.0, 1.4$ Hz, 4-H*a*), 1.85 (1 H, ddd, $J = 13.6, 12.0, 6.1$ Hz, 4-H*e*), 1.96 (3 H, d, $J = 1.4$ Hz, 8-CH_3), 3.89 (1 H, ddq, $J = 12.0, 3.0, 6.1$ Hz, 3-H), 4.30 (1 H, br.d, $J = 6.1$ Hz, 5-H), 6.14 (1 H, s, 7-H); NMR δ_C (100 MHz, $CDCl_3$): 19.5, 21.9, 24.8, 34.1, 64.2, 75.0, 96.0, 126.8, 156.9, 197.2.

8 A. L. Gemal and J.-L. Luche, *J. Am. Chem. Soc.*, **103**, 5454 (1981).

9 D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1574.

10 Properties of **1**: b.p. 93 °C/22 Torr; $n_D^{22} = 1.4690$; $[\alpha]_D^{22} = +116$ ($c = 1.04$, $CHCl_3$); IR: ν_{max} (film) cm^{-1} = 2970 (s), 2935 (s), 1435 (m), 1375 (s), 1350 (m), 1325 (m), 1295 (m), 1230 (s), 1200 (m), 1150 (m), 1125 (s), 1115 (s), 1095 (m), 1065 (m), 1005 (m), 955 (s), 875 (m), 855 (s), 795(m); NMR δ_H (400 MHz, $CDCl_3$): 1.16 (3 H, d, $J = 6.1$ Hz, 3-CH_3), 1.36 (1 H, ddd, $J = 13.4, 3.2, 1.2$ Hz, 4-H), 1.42 (3 H, s, 1-CH_3), 1.65 (3 H, dt, $J = 2.7, 1.2$ Hz, 8-CH_3), 1.78–1.91 (2 H, m, 4-H, 6-H), 2.64 (1 H, br.d, $J = 16.6$ Hz, 6-H), 4.03 (1 H, ddq, $J = 12.0, 3.2, 6.1$ Hz, 3-H), 4.29 (1 H, t, $J = 6.6$ Hz, 5-H), 5.75 (1 H, br.s, 7-H); NMR δ_C (100 MHz, $CDCl_3$): 18.6, 22.3, 24.7, 30.3, 38.2, 63.7, 66.5, 95.4, 123.4, 132.9; MS (EI) m/z (relative intensity): 43 (100), 71 (16), 81 (22), 93 (15), 109 (59), 125 (5), 153 (7), 168 (17); HRMS Found: $m/z = 168.1144$ (M^+). Calcd for $C_{10}H_{16}O_2$: 168.1150; GC (Column: Chirasil-DEX®, 0.25 mm × 25 m; Column temp: 100–250 °C, +3.0 °C/min; Carrier gas He at 1.0 kg/cm^2) t_R = 7.3 min (**1'**, 1.6%), 7.5 min (**1**, 98.4%; 96.8% ee).

11 Properties of **1'**: b.p. 86 °C/19 Torr; $n_D^{24} = 1.4671$; $[\alpha]_D^{23} = -116$ ($c = 1.01$, $CHCl_3$); HRMS Found: $m/z = 168.1156$ (M^+). Calcd for $C_{10}H_{16}O_2$: 168.1150; GC (under the same conditions as for **1**) t_R = 7.2 min (100%; ~100% ee).