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Pheromone synthesis. Part 263: Synthesis of the racemate and the enantiomers of (*E*)-*cis*-6,7-epoxy-2-nonenal, the male-produced pheromone of the red-necked longhorn beetle, *Aromia bungii*

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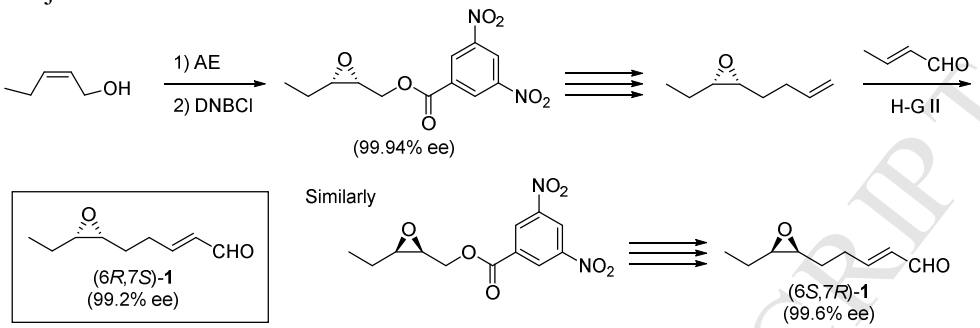

K. Mori, Graphical Abstract.

Pheromone synthesis. Part 263: Synthesis of the racemate and the enantiomers of (*E*)-*cis*-6,7-epoxy-2-nonenal, the male-produced pheromone of the red-necked longhorn beetle, *Aromia bungii*☆

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ABSTRACT

The racemate and the enantiomers of (*E*)-*cis*-6,7-epoxy-2-nonenal, the male pheromone of *Aromia bungii*, were synthesized by olefin cross metathesis between crotonaldehyde and (±)-, (+)- and (-)-*cis*-3,4-epoxy-7-octene. The epoxide was prepared by the Grignard coupling between allylmagnesium bromide and (±)-, (+)- and (-)-*cis*-2,3-epoxypentyl triflate. (±)-*cis*-2,3-Epoxy-1-pentanol was prepared by MCPBA epoxidation of (*Z*)-2-penten-1-ol, while its enantiomers were synthesized by the Sharpless asymmetric epoxidation of the allylic alcohol.

☆ For Part 262, see Ref.[1]

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1. Introduction

The red-necked longhorn beetle *Aromia bungii* (Faldermann) (Coleoptera: Cerambycidae) is a wood-boring beetle native to China, Korea, Mongolia and eastern Russia. It recently invaded and became established in Japan, and attacks mainly cherry, peach, plum and apricot trees, causing a big problem in both ornamental and horticultural trees.[2]

Its male-produced sex-aggregation pheromone was identified in 2017 as (*E*)-*cis*-6,7-epoxy-2-nonenal (**1**, Fig. 1) by Millar and co-workers.[3] The synthetic (±)-**1** was pheromonally active, and incorporated into effort to detect and manage the pest beetles in Japan. Millar's synthesis of (±)-**1** was straight-forward by epoxidation of the commercially available violet leaf aldehyde, (2*E*,6*Z*)-2,6-nonadienal (**A**)[3]. Millar and co-workers subsequently synthesized the enantiomers of **1**, and (6*R*,7*S*)-**1** was shown to be the naturally occurring one (J.G. Millar, personal communication, December 23, 2017).

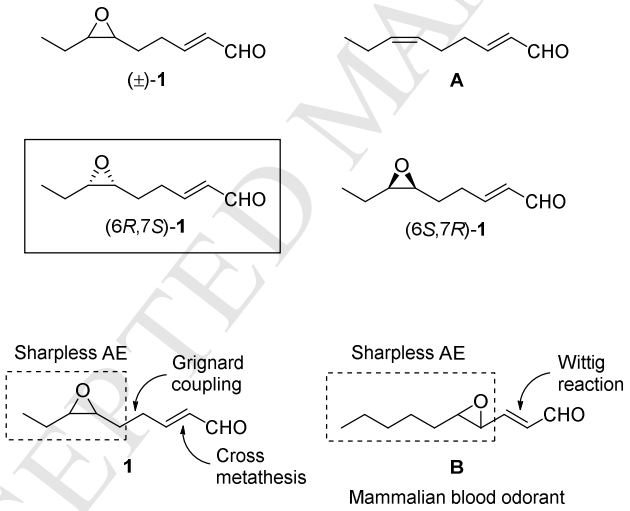


Fig.1. Structures of the pheromone [(6*R*,7*S*)-**1**] of *Aromia bungii* and related compounds.

This paper reports my own synthesis of the enantiomers of **1**, which is based on the Sharpless asymmetric epoxidation,[4] Grignard coupling, and olefin cross metathesis.[5] Our previous experience in the synthesis of the mammalian blood odorant **B** was advantageously utilized to introduce the chirality by the Sharpless procedure.[6]

2. Results and discussion

*2.1. Retrosynthetic analysis of (6R,7S)-**1***

Fig.2 shows the retrosynthetic analysis of (6*R*,7*S*)-**1**. The target pheromone (6*R*,7*S*)-**1** would be prepared by olefin cross metathesis of epoxyalkene **C** with crotonaldehyde **D**,[5,7] while **C** would be available by coupling of triflate **E**[8,9] with allylmagnesium bromide **F**. The epoxytriflate **E** would be prepared from **G**,[10] which is a known product of the Sharpless asymmetric epoxidation of (*Z*)-2-penten-1-ol **H**. The present work allowed the synthesis of the racemate as well as both the enantiomers of **1** in quantities sufficient for further biological works.

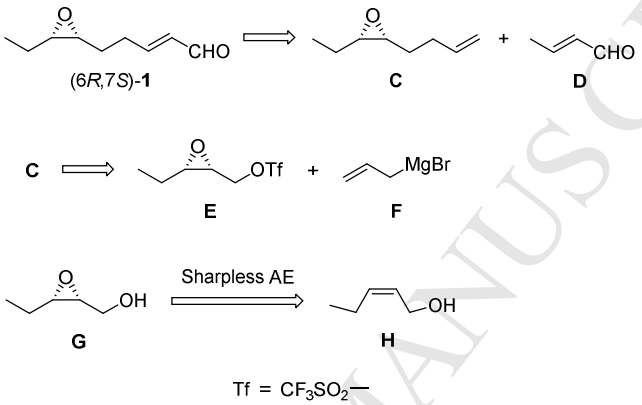


Fig.2. Retrosynthetic analysis of (6*R*,7*S*)-**1**.

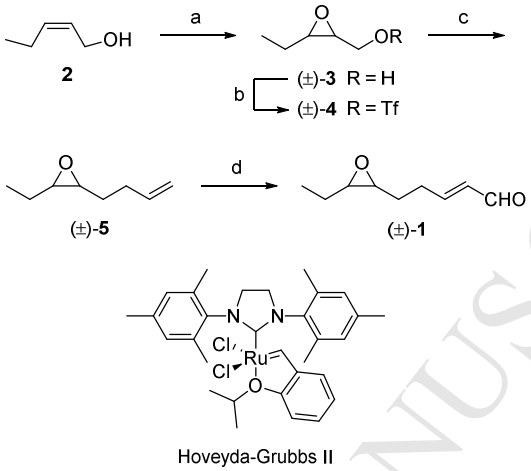
*2.2. Synthesis of (±)-**1***

Prior to the synthesis of the enantiomers of **1**, synthesis of (±)-**1** was first carried out as shown in Scheme 1 to find out the proper reaction conditions for each of the synthetic steps.

The known epoxy alcohol (±)-**3**[9] was prepared by epoxidation of (*Z*)-2-penten-1-ol (**2**) with *m*-chloroperbenzoic acid (MCPBA) in 58-70% yield. It was noticed in this step that the epoxy alcohol **3** was readily soluble in water, and its work-up should be executed by using a minimal amount of water. Otherwise, only a low yield (58%) of **3** was obtained.

Regioselective elongation of the carbon chain of **3** at C-1 without cleaving the epoxy ring was found to be possible in the course of the synthesis of chiral epoxyalkanes as pheromones. Copper-catalyzed Grignard coupling of epoxy tosylate (**4**, R=Ts instead of Tf) was proved to be successful in 1986.[11] However, it was later found that the corresponding triflate **4** showed greater reactivity at C-1 than the tosylate.[8,9] Accordingly, (±)-**3** was treated with *n*-BuLi and Tf_2O to give (±)-**4**, which was immediately coupled with allylmagnesium bromide in the presence of Li_2CuCl_4 to

give volatile and thermally unstable epoxide (±)-**5** in 41% yield based on (±)-**3**. Purification of (±)-**5** was first achieved by SiO_2 chromatography employing pentane/EtOAc as the eluent, and then by careful distillation below 100°C (bath temperature).



Scheme 1. Synthesis of (±)-**1**. Reagents: (a) MCPBA, CH_2Cl_2 (70%); (b) *n*-BuLi, Tf_2O, THF; (c) CH_2=$CHCH_2MgBr$, Li_2CuCl_4, THF, Et_2O (41%, 2 steps); (d) MeCH=CHCHO, Hoveyda-Grubbs II, CH_2Cl_2 (23% after chromatog. and distillation).

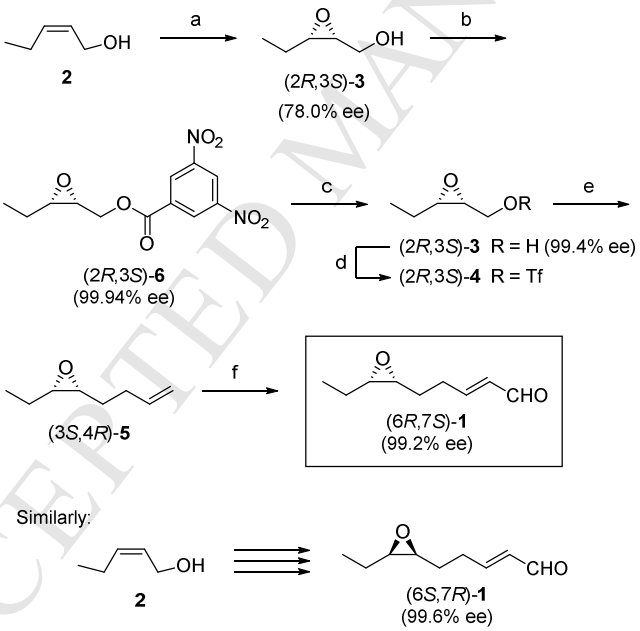
The final step of olefin cross metathesis between (±)-**5** and crotonaldehyde was successfully achieved employing Hoveyda-Grubbs second generation catalyst[12] to give (±)-**1**, which was thermally labile and obtained in 23% yield after chromatographic purification and distillation. The product was 96.8% pure (*E*)-**1** contaminated with 3.2% of its (*Z*)-isomer. More careful distillation in the cases of (+)- and (-)-**1** gave better yields (vide infra). The synthetic (±)-**1** showed ^{1}H and ^{13}C NMR and MS spectra identical with those of the natural pheromone and Millar's synthetic (±)-**1**. The overall yield of (±)-**1** was 6.6% based on **2** (4 steps).

*2.3. Synthesis of the enantiomers of **1***

Scheme 2 summarizes the synthesis of the enantiomers of **1**. Sharpless asymmetric epoxidation of **2** was reported by Baker and co-workers to give (2*S*,3*R*)-(-)-**3** of 80% ee {$[\alpha]_D^{20}$-11.8 (*c* 1.7, CH_2Cl_2)}.[10,13,14] Because the goal of the present work was to secure the pure enantiomers of **1** for bioassay, it was necessary to enrich the enantiomeric purities of both the enantiomers of **3**. For that purpose, purification of epoxy alcohols via their crystalline 3,5-dinitrobenzoates was quite useful.[6,11,13,14,15] With these past experience, the synthesis started from (*Z*)-2-penten-1-ol (**2**).

Catalytic asymmetric epoxidation[4] of **2** with D-(-)-diethyl tartrate (DET), $Ti(OPr^i)_4$

and *t*-BuOOH in CH_2Cl_2 was executed in the presence of powdered MS 3A for 24 h at -10°C to give (2*R*,3*S*)-**3**, $[\alpha]_D^{23}$+9.96 (*c* 3.05, CH_2Cl_2), (78.0% ee as determined by chiral GC) in 88% yield. Treatment of the oily (+)-**3** with 3,5-dinitrobenzoyl chloride (DNBCl) and pyridine afforded crystalline (2*R*,3*S*)-**6**. Its three recrystallizations from EtOAc/hexane gave pure 3,5-dinitrobenzoate (2*R*,3*S*)-**6**, mp 75-76°C, $[\alpha]_D^{23}$+30.2 (*c* 3.11, CH_2Cl_2) in 42% yield. The crystalline (2*R*,3*S*)-**6** was almost enantiomerically pure (99.94% ee) as determined by chiral HPLC. To recover the purified alcohol (+)-**3**, (+)-**6** was treated with K_2CO_3 in MeOH to effect methanolysis. Aqueous work-up at this stage gave a miserable yield (20% based on **6**) of (+)-**3** due to the water solubility of **3**. Accordingly, after methanolysis, the solution was concentrated in vacuo, and the residue was diluted with pentane. The insoluble K_2CO_3 and methyl 3,5-dinitrobenzoate were filtered off, and the filtrate was concentrated. The residue was distilled to give pure (2*R*,3*S*)-**3**, $[\alpha]_D^{19}$+14.3 (*c* 1.26, CH_2Cl_2), (99.4% ee as determined by chiral GC) in 67% yield.



Scheme 2. Synthesis of the enantiomers of **1**. Reagents: (a) D-(-)-DET, $Ti(OPr^i)_4$, *t*-BuOOH, MS 3A, CH_2Cl_2 (88%); (b) DNBCl, C_5H_5N, CH_2Cl_2, recryst'n (x 3) (42%); (c) K_2CO_3, MeOH (67%); (d) *n*-BuLi, Tf_2O, THF; (e) CH_2=$CHCH_2MgBr$, Li_2CuCl_4, THF, Et_2O (58%, 2 steps); (f) MeCH=CHCHO, Hoveyda-Grubbs II, CH_2Cl_2 (57%).

Chain-elongation of (2*R*,3*S*)-**3** was executed in the same manner as in the case of (±)-**3** to give (3*S*,4*R*)-**5** in 58% yield after chromatographic purification and distillation. The final cross metathesis between (3*S*,4*R*)-**5** and crotonaldehyde was followed by

chromatographic purification and distillation to give (6*R*,7*S*)-**1**, $[\alpha]_D^{22}$+12.8 (*c* 2.33, pentane), (99.2% ee as determined by chiral GC) in 57% yield. The product contained 3.3% of its (*Z*)-isomer. The spectroscopic data of (6*R*,7*S*)-**1** were identical with those of (±)-**1**. The overall yield of (6*R*,7*S*)-**1** was 8% based on **2** (six steps).

Similarly, by using L-(+)-diethyl tartrate as the catalyst for asymmetric epoxidation, (6*S*,7*R*)-**1**, $[\alpha]_D^{20}$-13.6 (*c* 2.33, pentane), (99.6% ee as determined by chiral GC) was obtained in 8% overall yield based on **2** (six steps). The product contained 1.3% of its (*Z*)-isomer. The amounts of the enantiomers of **1** thus synthesized was 1.96 g for (+)-**1** and 1.88 g for (-)-**1**.

3. Conclusion

The racemate as well as both the enantiomers of (*E*)-*cis*-6,7-epoxy-2-nonenal (**1**) were synthesized in amounts sufficient for biological works. Chirality was introduced by Sharpless asymmetric epoxidation, while the chain-elongation was executed by Grignard coupling and olefin cross metathesis. Nearly enantiopure (6*R*,7*S*)-(+)-**1** and (6*S*,7*R*)-(-)-**1** could be secured by enantiomer enrichment through recrystallization of the 3,5-dinitrobenzoate **6** of the epoxy alcohol **3** obtained by asymmetric epoxidation of **2**. Although the natural pheromone was known to be (6*R*,7*S*)-(+)-**1** whose pheromone activity was slightly stronger than that of (±)-**1** (J.G. Millar, personal communication, December 23, 2017 and H. Yasui, personal communication, October 3, 2017), the present synthesis provided materials sufficient for further biological works in Japan in the summer, 2018.

4. Experimental

4.1. General

All bps and mps are uncorrected values. Refractive indices were measured on an Atago DMT-1 refractometer. IR spectra were measured on a Jasco FT/IR-410 spectrometer. ^{1}H NMR spectra (400 MHz, TMS at δ=0.00 as the internal standard) and ^{13}C NMR spectra (100 MHz, $CDCl_3$ at δ=77.0 as the internal standard) were recorded on a Jeol JNM-ECZ 400S/L1 spectrometer. GC-MS were measured on Agilent Technologies 5975 inert XL. HRMS were recorded on Jeol JMS-700V or JMS-T100GCV. Silica gel column chromatography was carried out on Merck Kieselgel 60 Art 1.00734.

*4.2. cis-2,3-Epoxy-1-pentanol (**3**)*

4.2.1. Racemate

Epoxidation of **2** with MCPBA in CH_2Cl_2 as reported previously[9] gave (±)-**3** as a

colorless oil in 58-70% yield after distillation, bp 74-76°C/1 kPa. The product **3** is soluble in water, and excessive washing with aqueous $NaHCO_3$ solution in the course of work-up resulted in a reduced yield (58%) of **3**. Its IR, ^{1}H NMR and MS spectra were identical with those recorded in ref. 9. δ_C ($CDCl_3$): 10.74, 21.40, 57.20, 58.56,60.86.

4.2.2. (2R,3S)-(+)-Isomer by Sharpless asymmetric epoxidation

Activated (heating at 160°C under 0.1 kPa for 3 h) and powdered MS 3A(5.0 g) was added to dry CH_2Cl_2 (110 mL) under argon, and cooled to -10°C with a dry ice/CCl_4 bath. To this mixture were added with stirring and cooling a solution of D-(-)-DET (4.32 g, 21 mmol) in CH_2Cl_2 (20 mL), a solution of $Ti(OPr^i)_4$ (4.26 g, 15 mmol) in CH_2Cl_2 (20 mL) and a solution of *t*-BuOOH (5.5 M in nonane, 54.5 mL, 300 mmol) at -10°C. A solution of **2** (12.9 g, 150 mmol) in CH_2Cl_2 (20 mL) was added over 10 min to the stirred mixture at -20 to -10°C. Stirring was continued for 24 h at -10°C. The mixture was then warmed to 0°C. Subsequently, 30% NaOH solution (30 mL), 15% $Na_2S_2O_3$ solution (20 mL) and NaCl (10 g) were added to the stirred mixture under ice-cooling. After stirring for 10 min, the CH_2Cl_2 layer was separated, and aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 solution was dried ($MgSO_4$), filtered through a cotton plug, and the filtrate was concentrated under atmospheric pressure with a Vigreux column. The residue was distilled to give (2*R*,3*S*)-(+)-**3** (13.4 g, 88%) as a colorless oil, bp 72-74°C/0.8 kPa; n_D^{24}=1.4312; $[\alpha]_D^{23}$+9.96 (*c* 3.05, CH_2Cl_2); νmax (film); 3408 (br s), 2973 (s), 2936 (s), 2878 (m), 1460 (m), 1042 (s), 894 (m), 818 (m), 800 (m); δ_H ($CDCl_3$): 1.00 (3H, t, *J* = 7.2 Hz), 1.42-1.62 (2H, m), 2.48 (1H, br), 2.92-2.98 (1H, m), 3.10-3.15 (1H, m), 3.62-3.64 (1H, m), 3.79-3.82 (1H, m); δ_C ($CDCl_3$): 10.75, 21.41, 57.28, 58.57, 60.85; GC-MS [column: HP-5MS, 5% phenylmethylsiloxane, 0.25 mm i.d. x 30 m; carrier gas He; press 61 kPa; temp 70-230°C (+10°C/min)]: t_R 3.38 min (99.3%); MS (70 eV, EI): *m*/*z*: 102 (<1) [M^+], 60 (7), 59 (100), 57 (18), 45 (8), 44 (26), 43 (37), 42 (13), 41 (43), 39 (17), 31 (37).

4.2.3. (2S,3R)-(-)-Isomer by Sharpless asymmetric epoxidation

In the same manner as described above for (2*R*,3*S*)-(+)-**3** but by employing L-(+)-DET, **2** (12.9 g) gave 13.8 g (91%) of (2*S*,3*R*)-(-)-**3** as a colorless oil, bp 72-73°C/0.8 kPa; ; n_D^{24}=1.4320; $[\alpha]_D^{23}$-10.1 (*c* 2.31, CH_2Cl_2); {ref. 10. $[\alpha]_D^{20}$-11.8 (*c* 1.7, CH_2Cl_2); 80% ee}; GC-MS [same conditions as those used for (+)-**3**]: t_R 3.35 min (100%). Its IR, ^{1}H and ^{13}C NMR, and MS spectra were identical with those of (+)-**3**.

*4.3. cis-2,3-Epoxypentyl 3,5-dinitrobenzoate (**6**)*

4.3.1. (2R,3S)-(+)-Isomer

3,5-Dinitrobenzoyl chloride (DNBCl, 31.1 g, 135 mmol) was added portionwise to a stirred and ice-cooled solution of (2*R*,3*S*)-(+)-**3** (78.0% ee, 13.4 g, 131 mmol) in CH_2Cl_2

(100 mL) and C_5H_5N (40 mL) at 5-10°C. After the addition, the mixture was left to stand in a refrigerator for 3 d. It was then diluted with ice and water, and extracted with EtOAc. The extract was washed successively with $CuSO_4$ solution, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residual crystalline mass was recrystallized from EtOAc/hexane to give 22.3 g (57%) of (2*R*,3*S*)-**6**, mp 72-74°C; $[\alpha]_D^{22}$+29.2 (*c* 2.59, CH_2Cl_2). It was recrystallized again from EtOAc/hexane to give 17.6 g (45%) of purer (2*R*,3*S*)-**6**, mp 75-76°C, $[\alpha]_D^{25}$+30.1 (*c* 2.65, CH_2Cl_2). It was further recrystallized from EtOAc/hexane to give 16.5 g (42%) of pure (2*R*,3*S*)-**6** as pale yellow leaflets, mp 77-78°c; $[\alpha]_D^{23}$+30.2 (*c* 3.11, CH_2Cl_2); νmax (nujol); 3112 (w), 3094 (w), 1724 (s), 1629 (m), 1544 (s), 1348 (s), 1295 (s), 1178 (m), 1074 (m), 731 (m), 720 (m); δ_H ($CDCl_3$): 1.09 (3H, t, *J* = 7.6 Hz), 1.55-1.74 (2H, m), 3.08 (1H, dt, *J* = 4, 6 Hz), 3.53 (1H, dt, *J* = 4, 7.6 Hz), 4.38 (1H, dd, *J* = 8, 12 Hz), 4.71 (1H, dd, *J* = 3.6, 12 Hz); 9.17 (2H), 9.22 (1H); δ_C ($CDCl_3$): 10.86, 21.60, 53.57, 57.90, 65.47, 122.78, 129.72, 133.48, 148.81, 162.56; HRMS (APCI+) calc for $C_{12}H_{12}N_2O_7$ + H: 297.0723, found: 297.0723.

4.3.2. (2S,3R)-(-)-Isomer

In the same manner as described above for (2*R*,3*S*)-(+)-**6**, (2*S*,3*R*)-(-)-**3** (80.4% ee, 13.8 g) gave 19.2 g (47%) of pure (2*S*,3*R*)-(-)-**6** as pale yellow leaflets, mp 77-78°C; $[\alpha]_D^{17}$-30.7 (*c* 3.20, CH_2Cl_2). Its IR, ^1H and ^{13}C NMR data were identical with those of (+)-**6**. HRMS (APCI+) calc for $C_{12}H_{12}N_2O_7$ + H; 297.0723, found: 297.0729.

*4.4. Enantiomers of cis-2,3-epoxy-1-pentanol (**3**) by methanolysis of the enantiomers of **6***

4.4.1. (2R,3S)-(+)-Isomer

Potassium carbonate (1.60 g, 12 mmol) was added to a solution of (2*R*,3*S*)-(+)-**6** (16.5 g, 56 mmol) in THF (35 mL) and MeOH (90 mL). The mixture was stirred at 0-5°C for 1 h to give a dark red mixture, which was concentrated in vacuo at 30°C (bath temp). The residual semi-solid was triturated with pentane, and filtered to remove K_2CO_3 and methyl 3,5-dinitrobenzoate. The solid was washed thoroughly with pentane. The combined filtrate and washings were concentrated under atmospheric pressure with a Vigreux column. The residue was distilled to give 3.81 g (67%) of (2*R*,3*S*)-(+)-**3** as a colorless oil, bp 64-65°C/0.4 kPa; n_D^{21}=1.4344; $[\alpha]_D^{19}$+14.3 (*c* 1.26, CH_2Cl_2). Its IR, ^1H and ^{13}C NMR, and MS spectra were identical with those described in 4.2.2. GC-MS (same conditions as recorded in 4.2.2): t_R 3.36 min (100%). HRMS (isobutane CI+) calc for $C_5H_{10}O_2$ + H: 103.0759, found: 103.0760.

4.4.2. (2S,3R)-(-)-Isomer

In the same manner as described above for (2*R*,3*S*)-(+)-**3**, (2*S*,3*R*)-(-)-**6** (19.2 g)

gave 4.00 g (60%) of (2*S*,3*R*)-(-)-**3** as a colorless oil, bp 67-70°C/ 0.7 kPa; n_D^{23}= 1.4344; $[\alpha]_D^{22}$-14.0 (*c* 3.94, CH_2Cl_2). Its IR, ^1H and ^{13}C NMR, and MS spectra were identical with those described in 4.2.2. GC-MS (same conditions as recorded in 4.2.2): t_R 3.27 min (98.8%). HRMS (isobutane CI+) calc for $C_5H_{10}O_2$ + H: 103.0759, found: 103.0760.

*4.5. cis-3,4-Epoxy-7-octene (**5**)*

4.5.1. Racemate

A solution of *n*-BuLi (1.6 M in hexane, 20.2 mL, 32.4 mmol) was added dropwise over 15 min to a stirred and cooled solution of (±)-**3** (3.30 g, 32.4 mmol) in dry THF (60 mL) at -70 to -60°C under argon. The mixture was stirred for 15 min at -70°C to complete the formation of the lithium alkoxide. Then Tf_2O (9.13 g, 5.45 mL, 32.4 mmol) was added over 10 min to the stirred and cooled mixture at -60 to -50°C. After stirring for 15 min at -60°C to complete the formation of (±)-**4**, a solution of Li_2CuCl_4 (0.1 M in THF, 3 mL, 0.3 mmol) and allylmagnesium bromide (1.0 M in Et_2O, 32.4 mL, 32.4 mmol) were added over 10 min to the stirred and cooled mixture at -70°C to -60°C. The mixture was stirred for 30 min at -60°C, and left to stand at room temperature for 30 min. It was then poured into ice and NH_4Cl solution, and extracted with Et_2O. The Et_2O solution was washed successively with water, $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated under atmospheric pressure with a Vigreux column. the residue was further concentrated in vacuo (rotatory evaporator) for a short period (3-5 min). The residue (4.89 g) was chromatographed over SiO_2 (40 g). Elution with pentane gave hydrocarbon impurities (0.33 g). Further elution with pentane/EtOAc (50:1) gave 2.61 g (64%) of crude (±)-**5**. (Use of hexane for chromatography decreased the yield of (±)-**5** drastically due to the high volatility of **5**. Concentration of the eluted fractions was carried out under atmospheric pressure with a Vigreux column.). Distillation of crude (±)-**5** gave 1.69 g (41%) of pure (±)-**5** as a colorless oil, bp 63-65°C/3.0 kPa; n_D^{25}=1.4322; νmax (film): 3079 (w), 2973 (s), 2934 (m), 2878 (m), 1642 (m), 1457 (m), 996 (m), 911 (s), 816 (m), δ_H ($CDCl_3$): 1.04 (3H, t, *J* = 7.6 Hz), 1.45-1.70 (4H, m), 2.15-2.32 (2H, m), 2.85-2.91 (1H, m), 2.92-2.97 (1H, m), 4.90-5.10 (2H, m), 5.80-5.90 (1H, m); δ_C ($CDCl_3$): 10.73, 21.25, 27.25, 30.91, 56.94, 58.58; 115.30, 137.85; GC-MS (same conditions as reported in 4.2.2): t_R 4.02 min (94%); MS (70 eV, EI): *m*/*z*: 111 (3) [$(M-15)^+$], 97 (16), 85 (47), 67 (100), 59 (53), 41 (94). HRMS calc for $C_8H_{14}O$: 126.1045, found: 126.1056.

4.5.2. (3S,4R)-(-)-Isomer

In the same manner as described above for (±)-**5**, (2*R*,3*S*)-**3** (3.95 g) gave 2.82 g (58%) of (3*S*,4*R*)-(-)-**5** as a colorless oil, bp 62-65°C/2.4 kPa; n_D^{22}=1.4356; $[\alpha]_D^{20}$-8.53

(*c* 1.81, pentane). Its IR, ^{1}H and ^{13}C NMR, and MS spectra were identical with those of (±)-**5**. GC-MS (same conditions as reported in 4.2.2): t_R 4.01 (90.0%), 4.38 min (10.0%). HRMS calc for $C_8H_{14}O$: 126.1045, found: 126.1061.

4.5.3. (3R,4S)-(+)-Isomer

In the same manner as described above for (±)-**5**, (2*S*,3*R*)-**3** (3.99 g) gave 2.53 g (52%) of (3*R*,4*S*)-(+)-**5** as a colorless oil, bp 64-67°C/2.8 kPa; n_D^{18}=1.4350; $[\alpha]_D^{17}$+6.43 (*c* 1.28, pentane). Its IR, ^{1}H and ^{13}C NMR, and MS spectra were identical with those of (±)-**5**. GC-MS (same conditions as reported in 4.2.2): t_R 4.02 (94.4%), 4.38 min (5.6%). HRMS calc for $C_8H_{14}O$: 126.1045, found: 126.1066.

*4.6. (E)-cis-6,7-Epoxy-2-nonenal (**1**)*

4.6.1. Racemate

Hoveyda-Grubbs second generation catalyst (H-G II, 52 mg, 0.08 mmol, 0.6 mol% based on **5**) was added to a solution of (±)-**5** (1.69 g, 13 mmol) and MeCH=CHCHO (3.64 g, 52 mmol, 4 eq) in CH_2Cl_2 (30 mL) under argon. The solution was stirred and heated under reflux for 30 min until gas evolution ($MeCH=CH_2$) ceased. The slightly brown-colored solution was concentrated in vacuo, and the residue (4.8 g) was chromatographed over SiO_2 (20 g). Elution with hexane gave 0.37 g of hydrocarbon impurities. Further elution with hexane/EtOAc (20 : 1) gave 2.20 g (quant.) of crude (±)-**1**. The crude (±)-**1** (1.67 g) was distilled to give 470 mg (23% based on **5** or 30% based on crude **1** submitted to distillation) of pure (±)-**1** as a colorless oil (The product **1** was thermally unstable and polymerized to give residual oil or amorphons solid.), bp 91-93°C/0.1 kPa; n_D^{27}=1.4704; νmax (film): 2972 (s), 2937 (m), 2878 (m), 2819 (w), 2738 (w), 1692 (vs), 1637 (m), 1457 (m), 1390 (w), 1308 (w), 1273 (w), 1130 (m), 1095 (w), 1015 (w), 975 (m), 905 (m), 816 (m), 741 (w); δ_H ($CDCl_3$): 1.04 (3H, t, *J* = 7.2 Hz), 1.44-1.62 (2H, m), 1.63-1.72 (1H, m), 1.74-1.84 (1H, m), 2.44-2.62 (2H, m), 2.88-2.98 (2H, m), 6.12-6.20 (1H, m), 6.84-6.94 (1H, m), 9.50 (1H, dd, *J* = 2.8, 6.0 Hz); δ_C ($CDCl_3$): 10.69, 21.24, 26.35, 30.02, 56.41, 58.51, 133.48, 157.13, 194.02; GC-MS (same conditions as described in 4.2.2): t_R 9.31 [3.2%, (*Z*)-isomer], 9.57 min (96.8%); MS (70 eV, EI): *m*/*z*: 154 (<1) [M^+], 125 (3) 112 (4), 97 (37), 85 (60), 83 (32), 68 (86), 67 (85), 59 (56), 57 (36), 55 (40), 41 (100), 39 (55). [MS of the (*Z*)-isomer of (±)-**1** with t_R 9.31 min (70 eV, EI): *m*/*z*: 154 (<1) [M^+], 125 (9), 107 (8), 95 (48), 83 (29), 81 (44), 70 (32), 69 (33), 68 (100), 67 (57), 55 (62), 41 (71), 39 (49).]. HRMS calc for $C_9H_{14}O_2$: 154.0994, found: 154.0997.

4.6.2. (6R,7S)-(+)-Isomer

In the same manner as described above for (±)-**1**, (3*S*,4*R*)-**5** (2.80 g) gave 3.15 g (92%) of crude (6*R*,7*S*)-**1** after SiO_2 chromatography. This was distilled to give 1.96 g

(57%) of (6*R*,7*S*)-(+)-**1** as a colorless oil, bp 91-92°C/0.1 kPa: n_D^{23}=1.4742; $[\alpha]_D^{22}$+12.8 (*c* 2.33, pentane). Its IR, ^{1}H and ^{13}C NMR, and MS spectra were identical with those of (±)-**1**. GC-MS (same conditions as described in 4.2.2): t_R 9.31 [(3.3%), (*Z*)-isomer], 9.56 min (96.7%). HRMS calc for $C_9H_{14}O_2$: 154.0994, found: 154.0992.

4.6.3. (6S,7R)-(-)-Isomer

In the same manner as described above for (±)-**1**, (3*R*,4*S*)-**5** (2.50 g) gave 2.82 g (92%) of crude (6*S*,7*R*)-**1** after SiO_2 chromatography. This was distilled to give 1.88 g (62%) of (6*S*,7*R*)-(-)-**1** as a colorless oil, bp 91-92°C/0.1 kPa; n_D^{25}=1.4728; $[\alpha]_D^{20}$-13.6 (*c* 2.38, pentane). Its IR, ^{1}H and ^{13}C NMR, and MS spectra were identical with those of (±)-**1**. GC-MS (same conditions as reported in 4.2.2): t_R 9.32 [1.3%, (*Z*)-isomer], 9.55 min (98.7%). HRMS calc for $C_9H_{14}O_2$: 154.0994, found: 154.0997.

*4.7. Determination of the enantiomeric purities of the enantiomers of crude **3** obtained by AE, purified **3** obtained by methanolysis of **6**, **5** and **1** by enantioselective GC analysis*

*4.7.1. GC analysis of the enantiomers of crude **3***

Instrument: Agilent Technologies 7890A + 5975C (ionization voltage: 70 eV); column: heptakis-2,3-di-*O*-acetyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin (0.25 mm i.d. x 30 m); column temp: 40-180°C (+0.7°C/min); carrier gas, He; flow rate, 0.7 mL/min; detector, TIM. (2*R*,3*S*)-**3**: t_R 106.4 min; (2*S*,3*R*)-**3**: t_R 108.1 min. Ee of crude (2*R*,3*S*)-**3**: 78.0%; ee of crude (2*S*,3*R*)-**3**: 80.4%.

*4.7.2. GC analysis of the enantiomers of purified **3***

Same conditions as described in 4.7.1. Ee of purified (2*R*,3*S*)-**3**: 99.4%; ee of purified (2*S*,3*R*)-**3**: >99.8%.

*4.7.3. GC analysis of the enantiomers of **5***

Column: Chiramix®,[16] (0.25 mm i.d. x 30 m). Other conditions are same as described in 4.7.1. (3*S*,4*R*)-**5**: t_R 53.9 min; (3*R*,4*S*)-**5**: t_R 54.5 min. Ee of (3*R*,4*S*)-**5**; 98.8%; ee of (3*S*,4*R*)-**5**; 99.4%.

*4.7.4. GC analysis of the enantiomers of **1***

Same conditions as described in 4.7.1. (6*R*,7*S*)-**1**: t_R 159.9 min; (6*S*,7*R*)-**1**: t_R 163.6 min. Ee of (6*R*,7*S*)-**1**: 99.2%; ee of (6*S*,7*R*)-**1**: 99.6%.

*4.8. Determination of the enantiomeric purities of the enantiomers of 3,5-dinitrobenzoate **6** by enantioselective HPLC analysis*

System configuration (Shimadzu): system controller, CBM-20A; solvent delivery unit, LC-20ADSP; degassing unit, DGU-20A5R; auto injector, SIL-20Ac; column oven, CTO-20ACSP; PDA detector: SPD-M20A; column: Chiralpak® IA (4.6 x 250 mm, Daicel); temp: 30°C; mobile phase: *n*-hexane/EtOH= 60 : 40; flow rate: 1.0 mL/min;

detection: 254 nm. (2*R*,3*S*)-**6**: t_R 50.1 min; (2*S*,3*R*)-**6**: t_R 37.6 min. Ee of (2*R*,3*S*)-**6**: 99.94%; ee of (2*S*,3*R*)-**6**: 99.94%.

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Supplementary data

Supplementary data [IR, ^{1}H and ^{13}C NMR, and MS spectra of (±)-**1**, (6*R*,7*S*)-**1** and (6*S*,7*R*)-**1** and also MS of the (*Z*)-isomer of (6*R*,7*S*)-**1**] related to this article can be found at http://dx.doi.org/10.1016/j.tet.2018.00.000 as a PDF file.

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Legends of Figs. and Schemes

Fig.1. Structures of the pheromone [(6*R*,7*S*)-**1**] of *Aromia bungii* and related compounds.

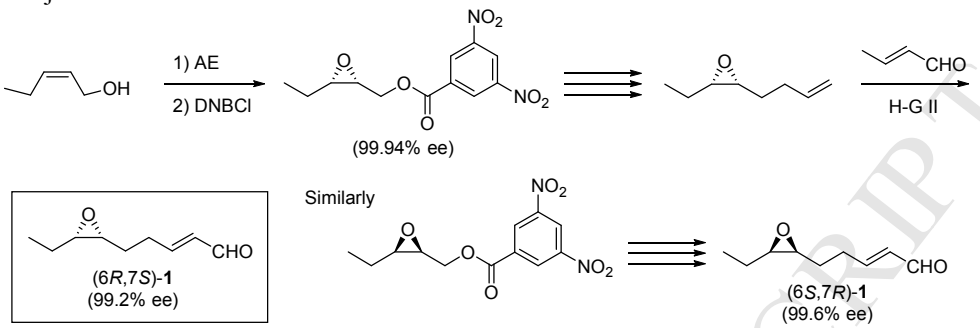
Fig.2. Retrosynthetic analysis of (6*R*,7*S*)-**1**.

Scheme 1. Synthesis of (±)-**1**. Reagents: (a) MCPBA, CH_2Cl_2 (70%); (b) *n*-BuLi, Tf_2O, THF; (c) CH_2=$CHCH_2MgBr$, Li_2CuCl_4, THF, Et_2O (41%, 2 steps); (d) MeCH=CHCHO, Hoveyda-Grubbs II, CH_2Cl_2 (23% after chromatog. and distillation).

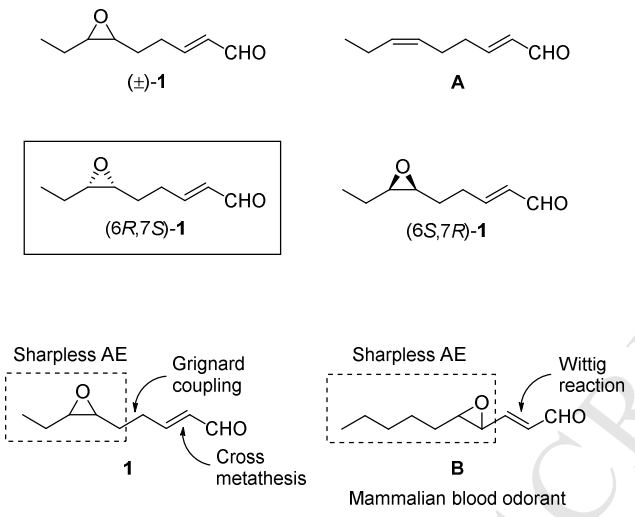
Scheme 2. Synthesis of the enantiomers of **1**. Reagents: (a) D-(-)-DET, $Ti(OPr^i)_4$, *t*-BuOOH, MS 3A, CH_2Cl_2 (88%); (b) DNBCl, C_5H_5N, CH_2Cl_2, recryst'n (x 3) (42%); (c) K_2CO_3, MeOH (67%); (d) *n*-BuLi, Tf_2O, THF; (e) CH_2=$CHCH_2MgBr$, Li_2CuCl_4, THF, Et_2O (58%, 2 steps); (f) MeCH=CHCHO, Hoveyda-Grubbs II, CH_2Cl_2 (57%).

Pheromone synthesis. Part 263: Synthesis of the racemate and the enantiomers of (*E*)-*cis*-6,7-epoxy-2-nonenal, the male-produced pheromone of the red-necked longhorn beetle, *Aromia bungii*

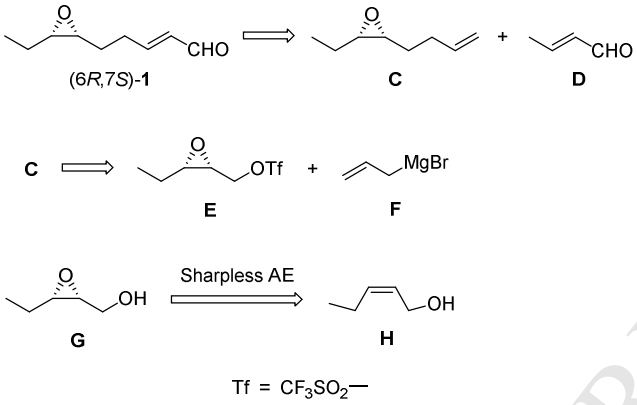
Kenji Mori



K. Mori, Graphical Abstract.



K. Mori, Fig. 1.



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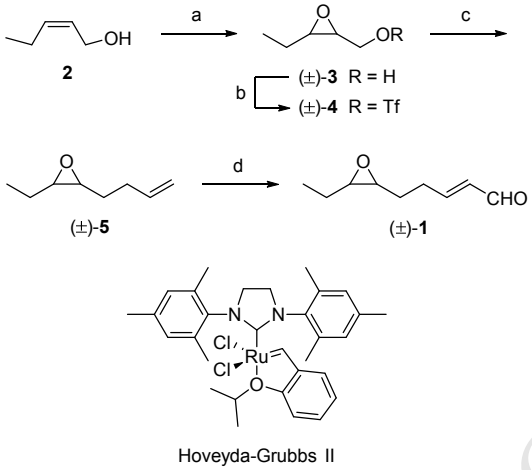
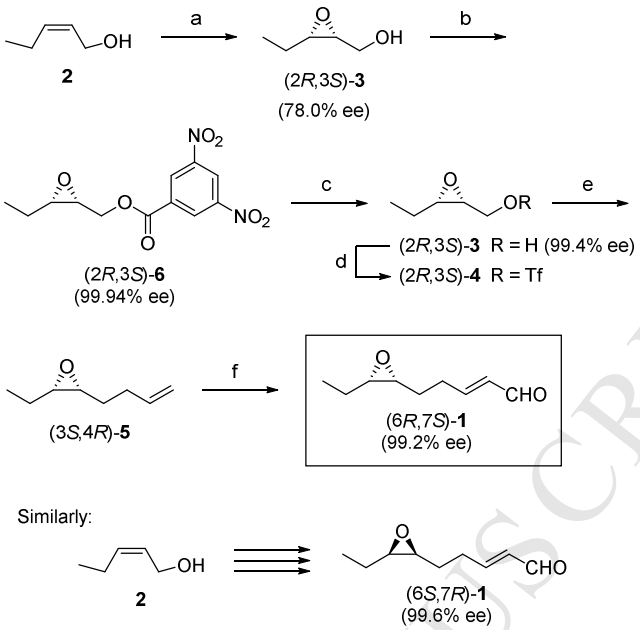


K. Mori, Scheme 1.



K. Mori, Scheme 2.