Pheromone Synthesis, CLXXVII[◇]

Synthesis of the Enantiomers of 2-Methyl-4-heptanol and 2-Methyl-4-octanol, the Pheromone Components of the West Indian Sugarcane Borer

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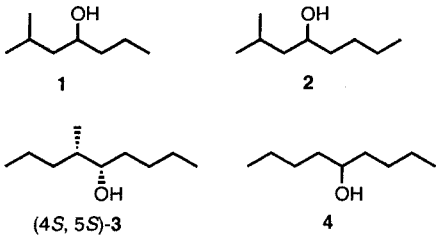
Both the enantiomers of 2-methyl-4-heptanol (**1**) and 2-methyl-4-octanol (**2**), the components of the male-produced aggregation pheromone of the West Indian sugarcane borer (*Metamasius hemipterus*), were synthesized by starting from the enantiomers of leucine.

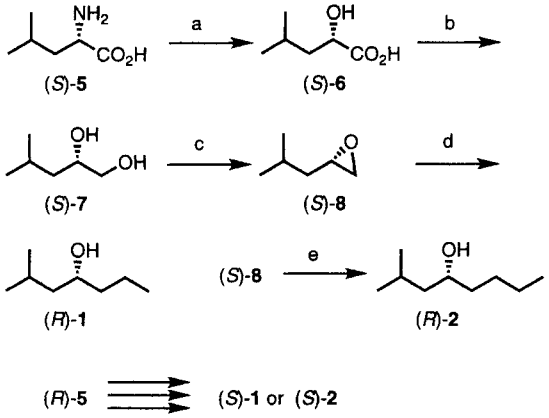
The West Indian sugarcane borer (*Metamasius hemipterus*) is a pest weevil against tropical crops such as sugarcane, bananas and palm trees. Four electroantennographically active compounds **1**–**4** (Scheme 1) were recently identified through analysis of the volatile extract of male *M. hemipterus* by Ramirez-Lucas et al.[1]. Of the four alcohols **1**–**4**, 4-nonanol (**4**) is an achiral compound, while the remaining three compounds are chiral. We previously determined the absolute configuration of the male-produced 3-methyl-4-nonanol [**3**, the major component (80%) of the pheromone] as (4*S*,5*S*) by the synthesis of the two enantiomers of **3** followed by gas-chromatographic analysis with a chiral stationary phase[2]. This paper describes the synthesis of the enantimers of 2-methyl-4-heptanol (**1**) and 2-methyl-4-octanol (**2**).

Scheme 1. Components of the male-produced aggregation pheromone of *Metamasius hemipterus*



Scheme 2 summarizes the synthesis of the enantiomers of **1** and **2**. The epoxide (*S*)-**8** was prepared from (*S*)-leucine (**5**) by the known method[3] via (*S*)-**6** and (*S*)-**7**. The original procedure[3] was slightly modified to convert **7** to **8** according to the method of Golding et al.[4]. Treatment of (*S*)-**8** with lithium diethylcuprate gave (*R*)-**1** in 6.2% overall yield based on (*S*)-leucine (**5**; 5 steps). Similarly, lithium di(*n*-propyl)cuprate converted (*S*)-**8** to (*R*)-**2** in 11% overall yield based on (*S*)-**5** (5 steps). The enantiomeric (*S*)-**1** and (*S*)-**2** were synthesized from (*R*)-leucine in the same manner as above.

Scheme 2. Synthesis of the enantiomers of **1** and **2**. – Reagents: (a) $NaNO_2$, dil. H_2SO_4 (43%). – (b) $LiAlH_4$, Et_2O (86%). – (c) i) 30% HBr in AcOH; ii) NaOMe, MeOH (39%). – (d) Et_2CuLi, Et_2O (43%). – (e) $n Pr_2CuLi$, Et_2O (76%)



Comparison of our synthetic samples with the natural products is under way in France, and the results will be reported in due course.

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Experimental

Boiling points: uncorrected values. – IR: Perkin-Elmer 1640. – ^1H NMR: Jeol JNM-EX 90A (90 MHz) and Jeol JMN-EX 270L (270 MHz) (TMS at $\delta = 0.00$ or $CHCl_3$ at $\delta = 7.26$ as an internal standard). – Optical rotations: Jasco DIP-1000. – GC analysis: Shimadzu GC-14B.

[◇] Part CLXXVI: H. Takikawa, Y. Shirai, M. Kobayashi, K. Mori, *Liebigs Ann.* **1996**, 1965–1970; following paper.

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(R)-2-Methyl-4-heptanol [(*R*)-**1**]: A solution of lithium diethylcuprate in diethyl ether was prepared by adding ethyllithium [prepared from lithium wire (3.47 g, 500 mmol) and ethyl bromide (15 ml, 200 mmol) in diethyl ether (50 ml)] to a suspension of CuI (2.86 g, 15.0 mmol) in diethyl ether (100 ml) at −30°C. A solution of (*S*)-**8** (528 mg, 5.27 mmol) in diethyl ether (30 ml) was added dropwise to the stirred and cooled solution of lithium diethylcuprate at −30°C under argon. After the addition, the reaction temperature was raised to 0°C and the mixture was stirred for 14 h in a refrigerator. Then a saturated aqueous NH_4Cl solution was added with cooling and the reaction mixture was extracted with diethyl ether. The ethereal solution was washed with water and brine, dried with K_2CO_3 and concentrated in vacuo. The residue was distilled to give 300 mg (44%) of (*R*)-**1**, b.p. 104−105°C/60 Torr. − n_D^{22} = 1.4220. − $[\alpha]_D^{22}$ = −11.9 (*c* = 1.04, CH_3OH). − IR: $\tilde{\nu}_{max}$ (film) = 3350 cm^{-1} (s, O−H), 2960 (s, C−H), 2930, 2870 (s, C−H), 1470 (m, C−H), 1370, 1230, 1150 (m, C−O), 1120, 1070. − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.80−1.05 (m, 3H, 7-H_3), 0.88 (d, *J* = 6.8 Hz, 3H, CHCH_3), 0.92 (d, *J* = 6.8 Hz, 3H, CHCH_3), 1.16−1.40 (m, 6H, 3,5,6-H_2), 1.45 (br., 1H, OH), 1.70 (m, 1H, 2-H), 3.69 (br., 1H, 4-H). − HRMS [$C_8H_{18}O^+-H_2O$]: calcd. 112.1253; found 112.1271. − Due to the volatility of the alcohols **1** and **2**, correct elemental analytical data could not be obtained.

(S)-2-Methyl-4-heptanol [(*S*)-**1**]: In the same manner as described above, (*R*)-**8** (1.00 g, 10.0 mmol) was converted to (*S*)-**1** (747 mg, 57%), b.p. 89−90°C/51 Torr. − n_D^{22} = 1.4220. − $[\alpha]_D^{22}$ = +13.3 (*c* = 1.11, CH_3OH). − IR: $\tilde{\nu}_{max}$ (film) = 3340 cm^{-1} (s, O−H), 2960 (s, C−H), 2930, 2870 (s, C−H), 1470 (m, C−H), 1370, 1150 (m, C−O), 1070, 1030. − ^1H NMR (270 MHz, $CDCl_3$): δ = 0.89−0.99 (m, 3H, 7-H_3), 0.90 (d, *J* = 6.8 Hz, 3H, CHCH_3), 0.93 (d, *J* = 6.8 Hz, 3H, CHCH_3), 1.17−1.46 (m, 6H, 3,5,6-H_2), 1.51 (br., 1H, −OH), 1.77 (sept, *J* = 2.4 Hz, 1H, 2-H), 3.65 (sept, *J* = 2.5 Hz, 1H, 4-H). − HRMS [$C_8H_{18}O^+-H_2O$]: calcd. 112.1253; found 112.1258.

(R)-2-Methyl-4-octanol [(*R*)-**2**]: A solution of lithium di(*n*-propyl)cuprate in diethyl ether was prepared by adding *n*-propyllithium [prepared from lithium wire (6.94 g, 1.00 mol) and *n*-propyl bromide (36 ml, 400 mmol) in diethyl ether (70 ml)] to a suspension of CuI (5.71 g, 30.0 mmol) in diethyl ether (100 ml) at −30°C. A solution of (*S*)-**8** (1.0 g, 10.0 mmol) in diethyl ether (30 ml) was added dropwise to the stirred and cooled solution of lithium di(*n*-propyl)cuprate at −30°C under argon. After the addition, the reaction temperature was raised to 0°C and the mixture was stirred for 14 h in a refrigerator. Then a saturated aqueous NH_4Cl solution was added with cooling and the reaction mixture was extracted with diethyl ether. The ethereal solution was washed with water and brine, dried with K_2CO_3 and concentrated in vacuo. The residue was distilled to give 1.09 g (76%) of (*R*)-**2**, b.p. 106−108°C/70 Torr. − n_D^{23} = 1.4248. − $[\alpha]_D^{23}$ = −10.5 (*c* = 1.17, CH_3OH). − IR: $\tilde{\nu}_{max}$ (film) = 3350 cm^{-1} (s, O−H), 2960 (s, C−H), 2930, 2870 (s, C−H), 1470 (m, C−H), 1370, 1150 (m, C−O), 1050. − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.80−1.10 (m, 3H, 8-H_3), 0.90 (d, *J* = 7.0 Hz, 3H, CHCH_3), 0.93 (d, *J* = 7.0 Hz, 3H, CHCH_3), 1.16−1.40 (m, 8H, 3,5,6,7-H_2), 1.41 (br., 1H, OH), 1.80 (m, 1H, 2-H), 3.69 (br., 1H, 4-H). − HRMS [$C_9H_{20}O^+-H_2O$]: calcd. 126.1409; found 126.1427.

(S)-2-Methyl-4-octanol [(*S*)-**2**]: In the same manner as described above, (*R*)-**8** (1.00 g, 10.0 mmol) was converted to (*S*)-**2** (865 mg, 60%), b.p. 101−102°C/41 Torr. − n_D^{21} = 1.4267. − $[\alpha]_D^{22}$ = +11.6 (*c* = 1.04, CH_3OH). − IR: $\tilde{\nu}_{max}$ (film) = 3340 cm^{-1} (s, O−H), 2960 (s, C−H), 2930, 2870 (s, C−H), 1470 (m, C−H), 1370, 1150 (m, C−O), 1030. − ^1H NMR (270 MHz, $CDCl_3$): δ = 0.88−0.96 (m, 3H, 8-H_3), 0.90 (d, *J* = 6.8 Hz, 3H, CHCH_3), 0.93 (d, *J* = 6.8 Hz, 3H, CHCH_3), 1.17−1.46 (m, 8H, 3,5,6,7-H_2), 1.51 (br., 1H, OH), 1.77 (sept, *J* = 2.4 Hz, 1H, 2-H), 3.65 (sept, *J* = 2.5 Hz, 1H, 4-H). − HRMS [$C_9H_{20}O^+-H_2O$]: calcd. 126.1409; found 126.1404.

Determination of the Enantiomeric Purity of **1** *and* **2**. − (a) (*R*) Isomer: The enantiomeric purity of (*R*)-**1** and (*R*)-**2** was determined by GC analysis of epoxide (*S*)-**8** on a chiral stationary phase [Chirasil-DEX CB, 0.25 mm × 25 m, DF = 0.25, at 40−60°C, 1°C/min, He, 110 kPa]: t_R = 11.66 min [(*R*)-**8**, 0.45%], 11.81 min [(*S*)-**8**, 99.55%]. The enantiomeric purity of (*R*)-**1** and (*R*)-**2** was therefore 99.1% e.e.

(b) (*S*) Isomer: The enantiomeric purity of (*S*)-**1** and (*S*)-**2** was determined by GC analysis of epoxide (*R*)-**8** on the same chiral stationary phase as described above. t_R = 11.48 min [(*R*)-**8**, 98.8%], 12.47 min [(*S*)-**8**, 1.2%]. The enantiomeric purity of (*S*)-**1** and (*S*)-**2** was therefore 97.6% e.e. There is no possibility of racemization when the epoxide (**8**) is converted to the desired alcohol (**1** or **2**). Thus, it is clear that the enantiomeric purity of the alcohol (**1** or **2**) was parallel to that of the epoxide (**8**).

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