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Synthesis Of The Enantiomers Of Lasiol, An Acyclic Monoterpene Alcohol In The Mandibular Gland Secretion Of The Male Ants, *Lasius meridionalis*†

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Abstract–(2*S*,3*S*)-(-)-Lasiol (2,3,6-trimethyl-5-hepten-1-ol, **1**) and its antipode were synthesized from *cis*-4,5-dimethylcyclohexene oxide (**3**) by employing asymmetric cleavage of the epoxy ring with a chiral lithium amide derived from **4** to give optically active *cis*-4,5-dimethyl-2-cyclohexen-1-ol (**5**) as the key-step.

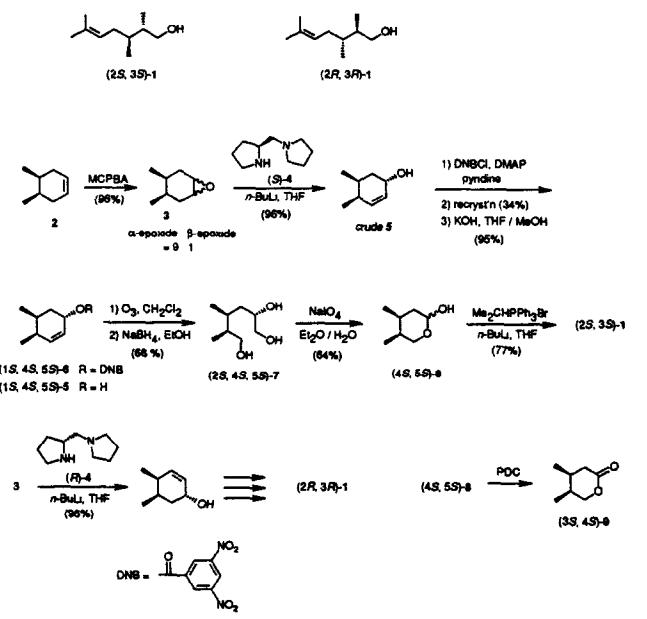
Introduction

In 1990 Lloyd *et al.* isolated a new monoterpene alcohol from mandibular glands of the male ants (*Lasius meridionalis*), named it lasiol, and determined its structure as *erythro*-2,3,6-trimethyl-5-hepten-1-ol (**1**) by a synthesis of (±)-**1**.[2] They suggested lasiol to be a sex attractant, because it was not found in extracts of females and workers of this species of ants.[2] We became interested in synthesizing both (2*S*,3*S*)- and (2*R*,3*R*)-**1** so as to clarify the absolute configuration of the natural product and also to investigate the behavioral role of the enantiomers of **1**.

Results and Discussion

Our synthesis of the enantiomers of **1** as shown in Scheme I started from the known *cis*-4,5-dimethylcyclohexene(**2**).[3] Oxidation of **2** with *m*-chloroperbenzoic acid (MCPBA) yielded epoxide **3** as an approximately 9:1 mixture of *trans*(epoxy ring *trans* to the methyl groups)- and *cis*-epoxides.[4] The next and the key step of the synthesis was the asymmetric cleavage of **3** according to Asami[5,6] by employing a chiral lithium amide derived from (*S*)-**4**.[7] The resulting crude allylic alcohol **5** could be purified by recrystallization of the corresponding 3,5-dinitrobenzoate (DNB ester **6**). The enantiomerically pure ester **6**, obtained in 32% yield from **3**, was hydrolyzed to give back pure (1*S*,4*S*,5*S*)-**5**. The assignment of 1*S*,4*S*,5*S*-stereochemistry to the product **5** was based on Asami's observation that cyclohexene oxide gave (*S*)-2-cyclohexen-1-ol, when treated with the lithium amide derived from (*S*)-**4**.[5]

The stereochemical course of the epoxide-cleavage reaction was carefully studied by employing both preparative and analytical HPLC techniques. The epoxide mixture **3** (= **3a** + **3b**, Scheme II) was treated with the lithium amide derived from (*R*)-**4** The resulting crude stereoisomeric mixture of allylic alcohols **5** was derivatized to give the corresponding mixture of 3,5-dinitrobenzoates **6**. The

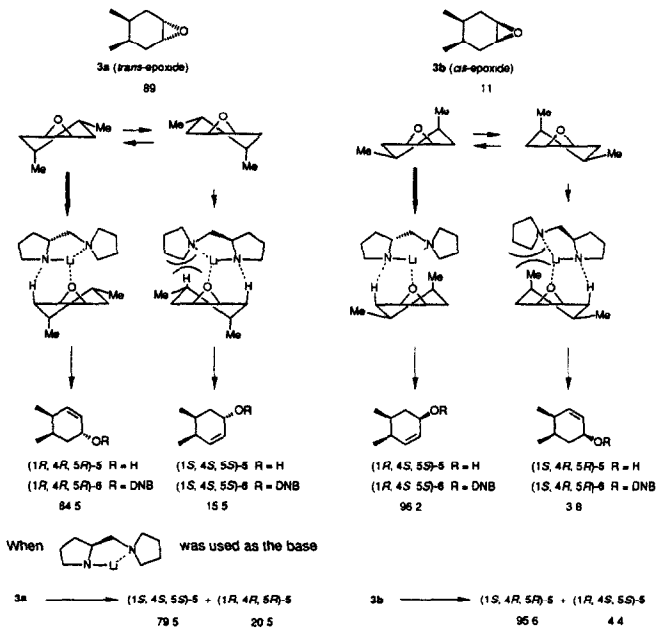


Scheme I. Synthesis of the enantiomers of lasiol

diastereomeric ratio of the products [i.e. (1*R**,4*R**,5*R**)-**6**:(1*R**,4*S**,5*S**)-**6**] could be estimated as 89:11, and the two diastereomers of **6** could be separated by preparative HPLC on an achiral stationary phase (Senshu Pak® Silica 1251N). The enantiomeric purity of each of the diastereomers of **6** was then estimated by analytical HPLC on a chiral stationary phase (Daicel Chiralcel® OJ). The major 3,5-dinitrobenzoate (1*R**,4*R**,5*R**)-**6** was thus found to be of 84.5 – 15.5 = 73.0% e.e. The reaction mechanism according to Asami as shown in Scheme II predicted the absolute configuration of the major alcohol to be (1*R*,4*R*,5*R*)-**5**. This prediction was later confirmed by the synthesis of (2*R*,3*R*)-**1** from the major alcohol (1*R*,4*R*,5*R*)-**5**. Subsequent analysis of (1*R**,4*S**,5*S**)-**6** on Chiralcel OJ revealed its enantiomeric purity to be 96.2 – 3.8 = 92.4% e.e. It was thus shown that the cleavage reaction of *cis*-epoxide **3b** was more selective because of

† Pheromone Synthesis, Part 150. For Part 149, see Ref. 1.

the steric hindrance caused by the axial methyl group of **3b**. By employing the amide derived from (*S*)-**4**, antipodal cleavage products could be obtained.



Scheme II. Asymmetric cleavage of epoxide **3**

Conversion of (1*S*,4*S*,5*S*)-**5** to (2*S*,3*S*)-lasiol(**1**) was straightforward (Scheme I). Ozonolysis of (1*S*,4*S*,5*S*)-**5** was followed by reductive work-up with sodium borohydride to give triol (2*S*,4*S*,5*S*)-**7**. Periodate oxidation of (2*S*,4*S*,5*S*)-**7** yielded hemiacetal (4*S*,5*S*)-**8**, which was treated with isopropylidenetriphenyl phosphorane to give (2*S*,3*S*)-lasiol(**1**), $[\alpha]_D^{22}$= -12.9° (n-hexane). The ^{1}H-NMR spectrum of our (2*S*,3*S*)-**1** was in good accord with that of (±)-**1**.[2] The enantiomeric purity of (2*S*,3*S*)-**1** was estimated as ~100% e.e. by 300 MHz ^{1}H-NMR analysis of the corresponding (*R*)- and (*S*)-α-methoxy-α-trifluoromethylphenylacetates (MTPA esters).[8] The high enantiomeric purity of the hemiacetal (4*S*,5*S*)-**8** was confirmed by its oxidation with pyridinium dichromate(PDC) to give the known lactone (3*S*,4*S*)-**9**, $[\alpha]_D^{22}$= -51.1° (MeOH) (Ref. 3 $[\alpha]_D^{22}$= -47.2° (MeOH) with a sample of 94% e.e.). For the synthesis of (2*R*,3*R*)-**1**, the epoxide **3** was treated with the lithium amide derived from (*R*)-**4**. The resulting (1*R*,4*R*,5*R*)-**5** yielded (2*R*,3*R*)-lasiol(**1**) of ~100% e.e., $[\alpha]_D^{22}$= +12.9° (n-hexane). After the completion of our synthesis, Kuwahara *et al.* reported another synthesis of the enantiomers of lasiol by starting from the known enantiomers of 3-methyl-4-butanolide.[9] Their synthesis unambiguously established the absolute configuration of (–)-lasiol as 2*S*, 3*S*, and that of the (+)-isomer as 2*R*, 3*R*.

In conclusion, the enantiomers of lasiol(**1**) were synthesized from *meso*-epoxide **3** in 10–15% overall yield after six steps. Biological works are in progress by Dr J. Tengö (Uppsala University) to clarify the role of lasiol in *Lasius meridionalis*.

Experimental

All m.p.s and b.p.s were uncorrected. ^{1}H-NMR spectra were recorded with TMS as an internal standard at 90 MHz on a Jeol JNM EX-90 spectrometer or at 300 MHz on a Bruker AC-300 spectrometer. ^{13}C-NMR spectra were recorded with $CDCl_3$ as an internal standard at δ=77.00 at 22.5 MHz on a Jeol JNM EX-90 spectrometer. IR spectra were recorded on a Jasco IRA-102 spectrometer. Optical rotations were measured on a Jasco DIP-371 polarimeter. HPLC analysis was performed on a Shimadzu LC-6A with an SPD-6A as a detector. Column chromatography was carried out on columns packed with Merck Kieselgel 60, Art. Nr. 7734.

(4S,5R*)-4,5-Dimethyl-1-cyclohexene oxide 3*

To a stirred and ice-cooled solution of (4*S**,5*R**)-4,5-dimethyl-1-cyclohexene (10.0 g, 0.091 mol) in CH_2Cl_2 (400 mL) was added $NaHCO_3$ (20.0 g, 0.238 mol) and MCPBA (20.0 g, 0.116 mol) portionwise at 0°C. After continuous stirring for 20 h at 0°C, to the mixture was added sat. aq. $Na_2S_2O_3$ (100 mL) and extracted with ether. The organic layer was washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, concentrated *in vacuo* and distilled under reduced pressure to give a diastereomeric mixture of **3** (9.62 g, 96 %);[4] b.p. 59°C/19 Torr ; IR(film) : ν = 1210 cm^{-1} (s, C–O), 830 (s, C–O), 760 (s, C–O); ^{1}H-NMR ($CDCl_3$, 90 MHz) : δ = 0.82 (d, 6H, J=5.4 Hz, $-CH_3$), 1.35–2.18 (m, 6H, 3,4,5,6-H), 3.12 (s, 2H, 1,2-H); Found: C, 75.86; H, 10.91; calc. for $C_8H_{14}O$: C, 76.14; H, 11.18. The ratio of the diastereomers was determined later by HPLC analysis of crude DNB ester **6**; HPLC (column, Senshu Pak® Silica 1251-N, 4.6 mmϕ x 250 mm; elution, n-hexane/THF (100:1), 2 mL/min) : R_t 17.2 min (major isomer **3a**, 89%, α-ODNB), 21.8 min (minor isomer **3b**, 11%, β-ODNB).

(1S,4S,5S)-4,5-Dimethyl-2-cyclohexen-1-ol (–)-5

To a stirred and ice-cooled solution of (*S*)-**4** (10.0 g, 65 mmol) in dry THF (200 mL) was added n-BuLi (36 mL, 1.68 M in n-hexane, 60 mmol) under Ar at 0°C. After stirring at 0°C for 30 min, it was cooled to -78°C and epoxide **3** (6.3 g, 50 mmol) in dry THF (50 mL) was added dropwise. After additional stirring for 16 h at 23°C, the reaction mixture was cooled to 0°C, quenched with ice-cooled sat. aq. NH_4Cl and extracted with Et_2O. The organic layer was washed with 2% HCl, water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel to give (–)-**5** (6.2 g, 98%) containing its enantio- and diastereoisomers as minor products. This was employed for the next step without further purification.

(1*R*,4*R*,5*R*)-Isomer (+)-**5** was prepared in the same manner

from epoxide **3** (1.61 g, 130 mmol) and amine (*R*)-**4** (4.0 g, 26 mmol); yield : 1.6 g (96%).

Purification of (–)-5

(a) (1S,4S,5S)-4,5-Dimethyl-2-cyclohexenyl 3,5-dinitrobenzoate (–)-6. To a stirred and ice-cooled solution of (–)-**5** (6. 2 g, 49 mmol) and 4-*N*,*N*-dimethylaminopyridine (DMAP) (0.40 g, 3.3 mmol) in pyridine (50 mL) was added 3,5-dinitrobenzoyl chloride (14 g, 61 mmol) at 0°C. After stirring for 10 h at 23°C, excess acid chloride was destroyed by the addition of water. The mixture was then acidified with 2N HCl and extracted with EtOAc. The organic layer was washed with 2N HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a mixture of (–)-**6** and its isomers (5.3 g, 97%). This was recrystallized five times from n-hexane/EtOAc (5 : 1) to give enantiomerically pure (–)-**6** as pale yellow needles (2.1 g, 34% recovery); m.p. 131.0–131.2°C; $[\alpha]_D^{22}$= -293° (c = 1.11, $CHCl_3$); IR(CCl_4) : ν = 3100 cm^{-1} (w, Ar–H), 1730 (s, C=O), 1630 (m, C=C), 1550 (s, N=O), 1460 (m, C=C), 1340 (s, N=O), 1270 (s, C–O), 1170 (s, C–O), 720 (w, Ar–H); ^{1}H-NMR ($CDCl_3$, 90 MHz) : δ = 0.92 (d, 3H, J = 7.5 Hz, 5-CH_3), 0.98 (d, 3H, J =7.0 Hz, 4-CH_3), 1.65–1.95 (m, 2H, 6-H_2), 1.95–2.58 (m, 2H, 4-H and 5-H), 5.56 (q, 1H, J =4.0 Hz, 1-H), 5.79 (dd, 1H, J=10 Hz, 4.0 Hz, 2-H), 6.06 (dd, 1H, J =10 Hz, 4.5 Hz, 3-H), 9.13 (m, 1H, *p*-H), 9.21 (m, 2H, *m*-H); Found: C, 56.02; H, 5.01; N, 8.73; calc. for $C_{15}H_{16}O_6N_2$: C, 56.25; H, 5.04; N, 8.75. Its enantiomeric excess was determined by HPLC (column, Daicel chiralcel® OJ, 4.6 mmϕ x 220 mm; elution, n-hexane/i-PrOH (60 : 1), 1 mL/min; detected at 254 nm) : R_t 26.5 min (single peak).

(1*R*,4*R*,5*R*)-Isomer (+)-**6** was prepared from (+)-**5** (1.61 g, 13 mmol) in the same manner; crude yield : 4.0 g (98%). This was recrystallized in the same condition to give 940 mg (26%) of enantiomerically pure (+)-**6** ; m.p. 131.2°C; $[\alpha]_D^{22}$= +292° (c = 1.05, $CHCl_3$). Its IR and ^{1}H-NMR spectra were identical with those of (1*S*,4*S*,5*S*)-**6**; HPLC (column , Daicel chiralcel® OJ; elution, n-hexane/i-PrOH (60: 1), 1 mL/min) : R_t 20.5 min (single peak); Found: C,56.31; H, 5.08; N, 8.75; calc. for $C_{15}H_{16}O_6N_2$: C, 56.25; H, 5.04; N, 8.75.

(b) (1S,4S,5S)-4,5-Dimethyl-2-cyclohexen-1-ol (–)-5. To a stirred and ice-cooled solution of (–)-**6** (3.2 g, 10 mmol) in THF (25 mL) and MeOH (11 mL) was added 1N KOH aq. (15 mL, 15 mmol) and stirring was continued for 30 min at 0°C. Then the mixture was extracted with Et_2O and the organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled under reduced pressure to give enantiomerically pure (–)-**5** (1.2 g, 95%); b.p. 89°C/27 Torr; n_D^{22} = 1.4728; $[\alpha]_D^{22}$= -277° (c = 1.24, MeOH); IR (film) : ν = 3400 cm^{-1} (s, O–H), 3030 (w, =C–H) 1650 (w, C=C), 1470 (m, CH_2), 1085, 1010 (s, C–O); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 0.83 (d, 3H, J =6.8 Hz, 5-CH_3), 0.91 (d, 3H, J =6.8 Hz, 4-CH_3), 1.20–1.78 (m, 3H, 6-H_2 and -OH), 1.78–2.38 (m, 2H, 4-H and 5-H), 4.17 (m, 1H, 1-H), 5.74 (t, 2H, 1.7 Hz, 2-H and 3-H); Found: C, 75.91; H, 11.10; calc. for $C_8H_{14}O$: C, 76.14; H, 11.18.

(1*R*,4*R*,5*R*)-Isomer (+)-**5** was prepared from (+)-**6** (830 mg, 2.6 mmol) in the same manner; crude yield : 320 mg (98%). A portion of this was distilled under reduced pressure to obtain analytical sample; n_D^{22} = 1.4752; $[\alpha]_D^{22}$= +276° (c = 0.88, MeOH). Its IR and ^{1}H-NMR spectra were identical with those of (1*S*,4*S*,5*S*)-**5**; Found: C, 75.74; H, 11.19; calc. for $C_8H_{14}O$: C, 76.14; H, 11.18.

(2S,4S,5S)-4,5-Dimethyl-1,2,6-hexanetriol (–)-7

Ozone was bubbled through a stirred and cooled solution of (–)-**5** (500 mg, 4.0 mmol) in CH_2Cl_2 (30 mL) at -78°C for 10 min. Excess ozone was removed by the bubbling of N_2. Then $NaBH_4$ (230 mg, 6.1 mmol) in EtOH (3 mL) was added dropwise and the mixture was gradually warmed to room temperature with continuous stirring overnight. It was then neutralized with 1N HCl and concentrated *in vacuo*. The residue was diluted with THF and the resulting suspension was dried over Na_2SO_4 and filtered through celite. The filter cake was washed with THF and the combined filtrate was concentrated *in vacuo* to give crude triol (–)-**7** (620 mg, 96%). It was distilled under reduced pressure to give pure (–)-**7** (428 mg, 66%); b.p. 126°C/1 Torr; n_D^{22} = 1.4725; $[\alpha]_D^{22}$ = -39.1° (c = 1.56, MeOH); IR (film) : ν = 3350 cm^{-1} (s, O–H), 1460 (s, CH_2), 1380 (s), 1040 (s, C–O); ^{1}H-NMR ($CDCl_3$, 90 MHz) : δ = 0.73 (d, 3H, J = 7.1 Hz, 4-CH_3), 0.92 (d, 3H, J =7.1 Hz, 5-CH_3), 0.98–2.08 (m, 4H, 3-H_2, 4-H and 5-H), 2.08–2.85 (br, 3H, 1-OH, 2-OH and 6-OH), 3.20–3.85 (m, 5H, 1-H_2, 2-H and 6-H_2); Found: C, 58.74; H, 11.19; calc. for $C_8H_{18}O_3$: C, 59.23; H, 11.18.

(2*R*,4*R*,5*R*)-Isomer (+)-**7** was prepared from (+)-**5** (320 mg, 2.5 mmol) in the same manner; crude yield: 402 mg (98%). A portion of this was distilled under reduced pressure to obtain an analytical sample; n_D^{22}= 1.4723; $[\alpha]_D^{22}$ = +39.1°(c = 0.46, MeOH). Its IR and ^{1}H-NMR spectra were identical with those of (2*S*,4*S*,5*S*)-**7**; Found: C, 58.95; H, 11.24; calc. for $C_8H_{18}O_3$: C, 59.23; H, 11.18.

(4S,5S)-4,5-Dimethyltetrahydropyran-2-ol (–)-8

$NaIO_4$ (565 mg, 3.2 mmol) was added portionwise to a stirred and ice-cooled solution of (–)-**7** (428 mg, 2.6 mmol) in Et_2O (30 mL) and H_2O (20 mL) and the stirring was continued for 1 h at 0°C. The solution was saturated with NaCl and extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was distilled under reduced pressure to give (–)-**8** (218 mg, 64%); b.p. 49°C/2 Torr; n_D^{22} = 1.4532; $[\alpha]_D^{22}$ = -86.7° (c = 1.40, $CHCl_3$); IR (film) : ν = 3400 cm^{-1} (s, O–H), 1450 (s, CH_2), 1120, 990 (s, C–O); ^{1}H-NMR ($CDCl_3$, 90 MHz) : δ = 0.88 (d, 3H, J = 6.8 Hz, 4-CH_3), 0.96 (d, 3H, J = 6.8 Hz, 5-CH_3), 1.05–2.40 (m, 4H, 3-H_2, 4-H and 5-H), 2.83 (br, 0.5H, OH), 3.30 (br,

0.5H, OH), 3.39 (dd, 0.5H, J = 11, 4.1 Hz, α-6-H (eq)),3.60 (dd, 0.5H, J = 9.3, 2.4 Hz, β-6-H (ax)), 3.80 (dd, 0.5H, J = 11, 2.4 Hz, β-6-H (eq)), 4.04 (dd, 0.5H, J = 11, 3.3 Hz, α-6-H (ax)), 4.80 (br, 0.5H, O-CH-O), 5.18 (br, 0.5H, O-CH-O); Found: C, 64.55; H, 10.88; calc. for $C_7H_{14}O_2$: C, 64.58; H, 10.83.

(4*R*,5*R*)-Isomer (+)-**8** was prepared from (+)-**7** (350 mg, 2.2 mmol) in the same manner; yield : 250 mg (87%); n_D^{22} 1.4542; $[\alpha]_D^{22}$ +88.3° (c = 0.70, $CHCl_3$). Its IR and ^{1}H-NMR spectra were identical with those of (4*S*,5*S*)-**8**; Found: C, 64.09; H, 10.92; calc. for $C_7H_{14}O_2$: C, 64.58; H, 10.83.

(2S,3S)-2,3,6-Trimethyl-5-hepten-1-ol [(–)-lasiol] 1

To a stirred and cooled suspension of i-propyltriphenylphosphonium bromide (1.7 g, 4.4 mmol) in dry THF (30 mL) was added n-BuLi (2.5 mL, 1.6 M in n-hexane, 4.1 mmol) dropwise at -20°C and the stirring was continued for 1 h. Then (–)-**8** (220 mg, 1.7 mmol) in dry THF (2 mL) was added dropwise at -20°C and the temperature was gradually raised to room temperature with continuous stirring for 2 h. Then the solution was poured into ice-cooled water and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with n-hexane/EtOAc (8 : 1) gave (–)-**1**. This was distilled under reduced pressure to give (–)-**1** (204 mg, 77%); b.p. 80°C/3 Torr; n_D^{22}= 1.4575; $[\alpha]_D^{22}$ = -12.9° (c = 1.02, n-hexane) [Ref.9 $[\alpha]_D^{22}$= -12.9° (c = 2.10, n-hexane)]; IR (film) : ν = 3340 cm^{-1} (s, O–H), 1660 (w, C=C), 1440 (s), 1370 (s), 1020 (s, C–O); ^{1}H-NMR ($CDCl_3$, 300 MHz) : δ = 0.874 (d, 3H, J = 6.6 Hz, CH–CH_3), 0.927 (d, 3H, J = 6.4 Hz, CH–CH_3), 1.21 (br.s, 1H, OH), 1.60 (s, 3H, 7-H_3), 1.70 (d, J = 0.99 Hz, 3H, 6-CH_3), 1.80 (dt, 1H, J = 14 Hz, 8.4 Hz, 4-H), 2.04 (dt, 1H, J = 14 Hz, 6.3 Hz, 4-H), 3.47 (dd, 1H, J = 9.7 Hz, 7.1 Hz, 1-H), 3.65 (dd, 1H, J = 9.7 Hz, 5.1 Hz, 1-H), 5.12 (m, 1H, 5-H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ = 13.8, 16.9, 17.8, 25.8, 31.5, 35.6, 40.2, 66.2, 123.6, 132.1; Found: C, 77.04; H, 12.96; calc. for $C_{10}H_{20}O$: C, 76.86; H, 12.90. (2*R*,3*R*)-Isomer (+)-**1** was synthesized from (+)-**8** (200 mg, 1.5 mmol) in the same manner; yield: 220 mg (91%); $_D^{22}$ = 1.4579; $[\alpha]_D^{22}$= +12.9° (c = 1.15, n-hexane) [Ref.9 $[\alpha]_D^{22}$= +12.4° (c = 2.02, n-hexane)]. Its IR, ^{1}H- and ^{13}C-NMR spectra were identical with those of (2*S*,3*S*)-**1**; Found: C, 76.57; H, 12.93; calc. for $C_{10}H_{20}O$: C, 76.86; H, 12.90.

Determination of the enantiomeric purity of lasiol

(–)-Lasiol was converted into the corresponding (*R*)- and (*S*)-MTPA esters by treatment with (*S*)- and (*R*)-MTPA chloride respectively in pyridine and analyzed by 300MHz ^{1}H-NMR spectroscopy in $CDCl_3$. The signals due to C-1 protons of (*S*)-MTPA ester appeared at δ = 4.18 (dd, J = 10.78, 7.44 Hz, 1H), and δ = 4.29 (dd, J = 10.78, 4.62 Hz, 1H), while the signals due to C-1 protons of (*R*)-MTPA ester were observed at δ = 4.11 (dd, J = 10.78, 7.56 Hz 1H) and δ = 4.37 (dd, J = 10.78, 5.33 Hz, 1H). In each spectrum, the signals due to the corresponding diastereomer were not observed. Therefore, (–)-lasiol was estimated to be almost 100% pure.

(+)-Lasiol was converted to corresponding (*R*)- and (*S*)-MTPA esters in the same manner. ^{1}H-NMR analysis showed that (+)-lasiol had almost 100% enantiomeric purity.

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4. α-Epoxide (*trans*-epoxide) was thought to be the major product due to the more crowded nature of the β-side owing to the β-oriented methyl groups. Direct GC analysis of the isomeric ratio of **3** could not be achieved.

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