Pheromone Synthesis, CCV[‡]

Short Synthesis of Vesperal [(*S*)-10-Oxoisopiperitenone], the Female Sex Pheromone of the Longhorn Beetle (*Vesperus xatarti*), and of Its Enantiomer

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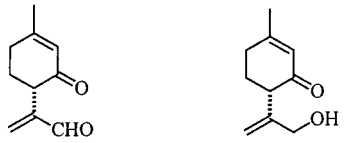
Vesperal [(*S*)-10-oxoisopiperitenone, **1**], the female sex pheromone of the longhorn beetle (*Vesperus xatarti*), was synthesized from (*R*)-limonene (**3**) in 6% overall yield (6 steps). The non-natural (*R*)-vesperal was also prepared from (*S*)-limonene.

The longhorn beetle (*Vesperus xatarti*) is a major pest of vineyards in Catalonia. In 1997, Boyer and co-workers isolated and identified two monoterpenes — vesperal [(*S*)-10-oxoisopiperitenone, **1**, Scheme 1] and vesperol [10-hydroxyisopiperitenone, **2**] — from the female-specific semiochemicals of *V. xatarti*.[1] They confirmed the proposed structures **1** and **2** by synthesis of their racemates.

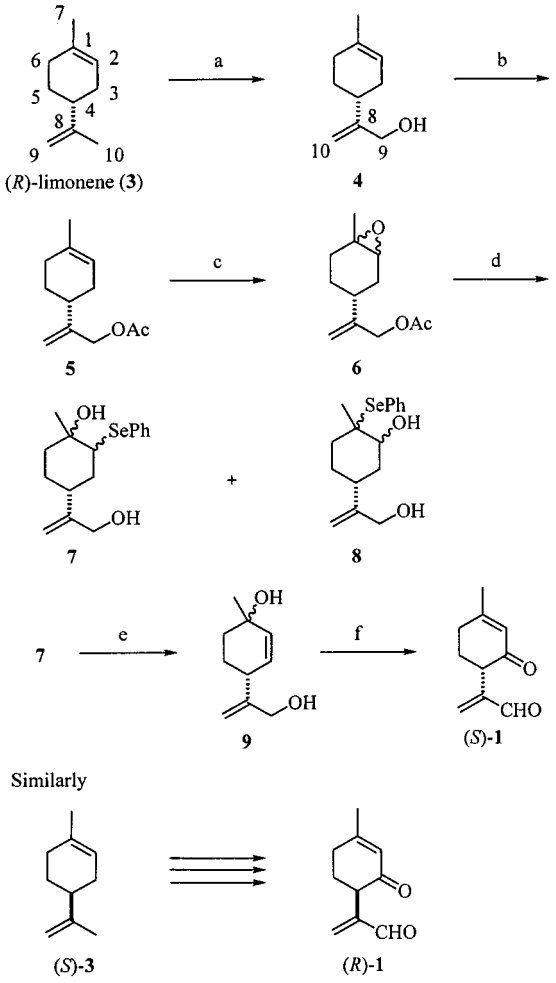


(*S*)-Vesperal (**1**) (*S*)-Vesperol (**2**)

Scheme 1. Structures of vesperal (**1**) and vesperol (**2**)

The *S* absolute configuration of vesperal (**1**) as shown in Scheme 1 was assigned on the basis of an HPLC comparison of natural **1** with the synthetic enantiomers of **1** derived from the resolved intermediates.[1] The absolute configuration of vesperol (**2**) might also be *S*, but that could not be proven. They then found that vesperal (**1**) alone was highly attractive to male beetles, whereas vesperol (**2**) was not.[1,2] Interestingly enough, Zagatti and co-workers observed that both enantiomers of vesperal (**1**) were bioactive when tested in the field.[2] We became interested in synthesizing the enantiomers [(*R*)- and (*S*)-**1**] of vesperal in an extremely pure state, as it was necessary to have them in hand so as to evaluate their bioactivity precisely.

In contrast to the nine-step synthesis of (±)-vesperal (**1**) by Boyer et al., who employed a Diels−Alder cycloaddition as their key reaction,[1] ours, as summarized in Scheme 2, is conceptually very simple. It is to make use of the abundant and cheap monoterpene limonene (**3**) as the C_{10}-template onto which the two oxygen functionalities may be attached.



Scheme 2. Synthesis of vesperal (**1**): reagents: (a) (i) *n*BuLi, TMEDA; (ii) O_2 (iii) 25% Na_2SO_3 aq. soln. (30%); (b) Ac_2O, C_5H_5N (quant.); (c) MCPBA, $NaHCO_3$, CH_2Cl_2 (86%); (d) Ph_2Se_2, $NaBH_4$, EtOH (70% of **7** and 17% of **8**); (e) 34% H_2O_2, THF/H_2O (65%); (f) PCC, NaOAc, CH_2Cl_2, (54%).

Another advantage of employing limonene (**3**) as the starting material is the fact that both (*R*)- and (*S*)-**3** are

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commercially available in acceptable enantiomeric purity [(*R*)-**3**: 98% *ee*; (*S*)-**3**: 88% *ee*].[3]

The first step of the synthesis was the introduction of the oxygen functionality at C-10 of (*R*)-(+)-limonene (**3**). For that purpose, the classical method of Crawford et al. was adopted: lithiating and then oxidizing the carbon at position 10, giving **4** in a moderate yield of 30% and with no racemization at C-4.[4] The next task was the introduction of the second oxygen functionality at C-3. This was achieved by employing a method previously developed by us, using organoselenium chemistry.[3] Accordingly, the acetate **5** (the *S* isomer of which is known[5]) derived from **4** by acetylation was epoxidized with *m*-chloroperbenzoic acid (MCPBA) to give epoxide **6** as a mixture of two diastereomers. Ring-opening of the epoxide **6** with the phenylselenide anion was executed according to Sharpless and Lauer[6] to give, with concomitant removal of the acetyl group, a mixture of **7** and **8**, which could be separated by silica gel chromatography. Compound **7**, which eluted sooner, was oxidized with hydrogen peroxide to effect the oxidative elimination reaction, giving the desired **9**. The formation of **9** indeed confirmed the structure **7** assigned to the earlier eluted material. Finally, oxidation of the bisallylic alcohol **9** with pyridinium chlorochromate (PCC) yielded (*S*)-vesperal (**1**) as the result of normal oxidation at C-10 and oxidation with an allylic rearrangement at C-3, generating the double bond at C-1. The overall yield of crystalline (*S*)-**1** was 6% based on (*R*)-limonene (**3**, 6 steps). Although the overall yield was rather low, this synthesis did afford (*S*)-**1** in a straightforward manner. After recrystallization from pentane/diethyl ether, our synthetic (*S*)-vesperal (**1**, m.p. 53°C) exhibited a specific rotation, $[\alpha]_D^{24}$ = +55.9 (CH_2Cl_2), higher than that {$[\alpha]_D$ = +31.9 (CH_2Cl_2)} reported by Boyer et al.[1] In the same manner, unnatural (*R*)-vesperal (**1**, m.p. 54°C; $[\alpha]_D^{24}$ = −54.8 (CH_2Cl_2) {ref.[1] $[\alpha]_D^{24}$ = −30.3 (CH_2Cl_2)}) was synthesized from (*S*)-(−)-limonene (**3**). Several recrystallizations were necessary to enhance the enantiomeric purity of (*R*)-**1**. The IR and ^1H and ^{13}C NMR spectra of our (*R*)- and (*S*)-**1** were identical with spectra of (±)-**1** sent to us by Dr. F.-D. Boyer. Our synthetic enantiomers of vesperal were enantiomerically pure (>99% *ee*) as measured by GC analysis on a chiral stationary phase (Chirasil-DEX CB). The final recrystallization of the synthetic enantiomers of **1** must have contributed to enriching their enantiomeric purity to make them purer than the starting materials (*R*)- and (*S*)-**3**.

In conclusion, enantiomerically pure (*R*)-vesperal (**1**) and its unnatural *S* isomer were synthesized. Their field bioassay will clarify whether or not both of them are really bioactive against the longhorn beetle (*V. xatarti*).

Experimental Section

Boiling points: uncorrected values. − IR: Jasco A-102. − ^1H NMR: Jeol JNM-EX 90A (90 MHz) and Bruker DPX 300 (300 MHz) (TMS at δ = 0.00 or $CHCl_3$ at δ = 7.26 as an internal standard). − ^{13}C NMR: Bruker DPX 300 (75.5 MHz) ($CDCl_3$ at δ = 77.0 as an internal standard). − MS: Jeol JMS-SX 102A and Hitachi M-80B. − CC: Merck Kieselgel 60 Art 1.07734. − TLC: 0.25 mm Merck silica gel plates (60F-254).

(*R*)-(+)-*p*-Mentha-1,8(10)-dien-9-ol [(*R*)-4]: This was prepared from (*R*)-**3** according to Crawford et al.[4] The product (*R*)-**4** was obtained in 30% yield as an oil; b.p. 68−72 °C/0.1 Torr. − n_D^{25} = 1.4146. − $[\alpha]_D^{22}$ = +104 (*c* = 1.0, C_2H_5OH) {ref.[4] $[\alpha]_D^{30}$ = +104 (*c* = 0.33, C_2H_5OH)}. − IR (film): $\tilde{\nu}_{max}$ = 3325 cm^{-1} (s, OH), 1640 (m, C=C), 1050 (s, C−O), 1020 (s, C−O), 900 (s, C=CH_2). − ^1H NMR (90 MHz, $CDCl_3$): δ = 1.3−2.3 (m, 7 H), 1.65 (s, 3 H, 1-Me), 4.14 (s, 2H, 9-H_2), 4.91 (s, 1 H), 5.05 (d, *J* = 1.2 Hz, 1 H), 5.41 (br. s, 1 H).

(*S*)-(−)-*p*-Mentha-1,8(10)-dien-9-ol [(*S*)-4]: The enantiomer (*S*)-**4** was obtained in 31% yield as an oil; b.p. 68−72 °C/0.1 Torr. − n_D^{25} = 1.4146. − $[\alpha]_D^{22}$ = −93 (*c* = 1.0, C_2H_5OH). − Its IR and ^1H NMR spectra were identical with those of the *R* isomer.

(*R*)-(+)-9-Acetoxy-*p*-mentha-1,8(10)-diene [(*R*)-5]: Acetic anhydride (6.0 g, 58.3 mmol) was added to a stirred and ice-cooled solution of (*R*)-**4** (5.0 g, 32.8 mmol) in dry pyridine (50 mL). The mixture was stirred for 2 h at room temperature, then poured into 1 M hydrochloric acid, and extracted with diethyl ether. The ethereal extract was washed successively with 1 M hydrochloric acid, a satd. copper(II) sulfate solution, water, a satd. sodium hydrogen carbonate solution and brine, dried with magnesium sulfate and concentrated in vacuo. The residue was purified by chromatography on silica gel (120 g, hexane/ethyl acetate, 100:1−50:1) to give 6.37 g (quant.) of (*R*)-**5** as an oil; b.p. 75−77 °C/12 Torr. − n_D^{25} = 1.4791. − $[\alpha]_D^{22}$ = +75.4 (*c* = 1.25, C_2H_5OH). − IR (film): $\tilde{\nu}_{max}$ = 2930 cm^{-1} (s), 1740 (s, C=O), 1650 (m, C=C), 1235 (s, C−OAc). − ^1H NMR (90 MHz, $CDCl_3$): δ = 1.1−2.3 (m, 7 H), 1.65 (s, 3 H, 1-Me), 2.09 (s, 3 H, 9-OAc), 4.58 (s, 2 H, 9-H_2), 4.97 (s, 1 H), 5.05 (d, *J* = 1.2 Hz, 1 H), 5.39 (br. s, 1 H, 2-H). − $C_{12}H_{18}O_2$ (194.3): calcd. C 74.19, H 9.34; found C 74.40, H 9.54.

(*S*)-(−)-9-Acetoxy-*p*-mentha-1,8(10)-diene [(*S*)-5]: In the same manner as described above, (*S*)-**4** (7 g, 46.0 mmol) yielded (*S*)-**5** (8.9 g, quant.) as an oil; b.p. 75−77 °C/12 Torr. − n_D^{25} = 1.4760. − $[\alpha]_D^{22}$ = −63.2 (*c* = 1.02, C_2H_5OH) {ref.[5] $[\alpha]_D^{20}$ = −73.1 (*c* = 1.35, $CHCl_3$)}. − Its IR and ^1H NMR spectra were identical with those of the *R* isomer.

(*R*)-(+)-9-Acetoxy-1(2)-epoxy-*p*-menth-8(10)-ene [(*R*)-6]: To a stirred and ice-cooled solution of MCPBA (70%, 3.6 g, 14.7 mmol) in CH_2Cl_2 (70 mL) was added (*R*)-**5** (2.6 g, 13.4 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred for 3 h at room temperature. It was then quenched with a satd. sodium thiosulfate solution and extracted with CH_2Cl_2. The organic layer was washed with a satd. sodium hydrogen carbonate solution, water and brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was purified by chromatography on silica gel (40 g, hexane/ethyl acetate, 50:1−30:1) to give 2.42 g (86%) of (*R*)-**6** as an oil; n_D^{25} = 1.4692. − $[\alpha]_D^{25}$ = +56.2 (*c* = 1.05, $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 1740 cm^{-1} (s, C=O), 1650 (m, C=C), 1230 (s, C−OAc). − ^1H NMR (90 MHz, $CDCl_3$): δ = 1.1−2.3 (m, 7 H), 1.30 (s, 3 H, 1-Me), 2.07 (s, 3 H, 9-OAc), 2.9−3.1 (m, 1 H), 4.51 (s, 2 H, 9-H_2), 4.97 (s, 1 H), 5.05 (d, *J* = 1.2 Hz, 1 H). − $C_{12}H_{18}O_3$ (210.3): calcd. C 68.54, H 8.63; found C 68.56, H 8.97.

(*S*)-(−)-9-Acetoxy-1(2)-epoxy-*p*-menth-8(10)-ene [(*S*)-6]: In the same manner as described above, (*S*)-**5** (10 g, 51.4 mmol) gave (*S*)-**6** (9.4 g, 87%) as an oil; n_D^{25} = 1.4694. − $[\alpha]_D^{25}$ = −46.5 (*c* = 1.20, $CHCl_3$). − Its IR and ^1H NMR spectra were identical with those

of the *R* isomer. − $C_{12}H_{18}O_3$ (210.3): calcd. C 68.54, H 8.63; found C 68.61, H 8.91.

(*R*)-(+)-2-Phenylselenyl-*p*-menth-8(10)-ene-1,9-diol [(*R*)-7]: To a stirred solution of diphenyl diselenide (4.1 g, 13.1 mmol) in dry EtOH (70 mL) was added $NaBH_4$ (991 mg, 26.2 mmol) under argon. The mixture turned colorless, and (*R*)-**6** (2.6 g, 12.4 mmol) in dry EtOH (5 mL) was then added dropwise. The mixture was stirred and heated under reflux for 2 h under argon. It was then quenched with 1 M hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with a satd. sodium hydrogen carbonate solution, water and brine, dried with magnesium sulfate and concentrated in vacuo. The residue was purified by chromatography on silica gel (60 g, hexane/ethyl acetate, 20:1−1:1) to give 3.05 g (75%) of (*R*)-**7** as an oil; $n_D^{25} = 1.5159$. − $[\alpha]_D^{24} = +54.3$ (c = 1.12, $CHCl_3$). − IR (film): $\tilde{\nu}_{max} = 3370\ cm^{-1}$ (s, -OH), 1650 (m, C=C), 1580 (m, arom. C=C). − ^1H NMR (90 MHz, $CDCl_3$): δ = 1.2−2.5 (m, 9 H), 1.40 (s, 3 H, 1-Me), 3.43 (m, 1 H), 4.03 (s, 2 H, 9-H_2), 4.89 (s, 1 H), 5.04 (br. s, 1 H), 7.2−7.7 (m, 5 H, Ph). − $C_{16}H_{22}O_2Se$ (325.3): calcd. C 59.07, H 6.82; found C 59.13, H 7.08.

(*S*)-(−)-2-Phenylselenyl-*p*-menth-8(10)-ene-1,9-diol [(*S*)-7]: In the same manner as described above, (*S*)-**6** (5 g, 23.8 mmol) yielded (*S*)-**7** (5.3 g, 69%) as an oil; $n_D^{26} = 1.5160$. − $[\alpha]_D^{25} = -45.0$ (c = 0.78, $CHCl_3$). − Its IR and ^1H NMR spectra were identical with those of the *R* isomer. − $C_{16}H_{22}O_2Se$ (325.3): calcd. C 59.07, H 6.82; found C 59.00, H 7.00.

(*R*)-(+)-*p*-Mentha-2,8(10)-diene-1,9-diol [(*R*)-9]: To a stirred and ice-cold solution of (*R*)-**7** (4.0 g, 12.3 mmol) in THF (150 mL) was added dropwise 34% H_2O_2 (12.3 mL, 123 mmol). Afterwards, the mixture was stirred at room temperature for 1 h, and then heated under reflux for 2 h. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried with potassium carbonate, and concentrated in vacuo. The residue was purified by chromatography on silica gel (100 g, hexane/ethyl acetate, 10:1−1:1) to give 1.3 g (63%) of (*R*)-**9** as an oil; $n_D^{26} = 1.5163$. − $[\alpha]_D^{24} = +89.2$ (c = 0.1, $CHCl_3$). − IR (film): $\tilde{\nu}_{max} = 3350\ cm^{-1}$ (s, -OH), 1650 (m, C=C), 1120 (s), 1040 (s), 925 (s), 775 (s). − ^1H NMR (90 MHz, $CDCl_3$): δ = 1.30 (s, 3 H, 1-Me), 1.4−2.1 (m, 6 H), 2.80 (br. s, 1 H, -OH), 4.15 (s, 2 H, 9-H_2), 4.94 (s, 1 H), 5.10 (br. s, 1 H), 5.70 (br. s, 2 H). − $C_{10}H_{16}O_2$ (168.2): calcd. C 71.39, H 9.59; found C 70.60, H 9.35.

(*S*)-(−)-*p*-Mentha-2,8(10)-diene-1,9-diol [(*S*)-9]: In the same manner as described above, (*S*)-**7** (3.0 g, 9.22 mmol) gave (*S*)-**9** (1.1 g, 71%) as an oil; $n_D^{25} = 1.5162$. − $[\alpha]_D^{25} = -45.0$ (c = 0.78, $CHCl_3$). − Its IR and ^1H NMR spectra were identical with those of the *R* isomer. − $C_{10}H_{16}O_2$ (168.2): calcd. C 71.39, H 9.59; found C 71.40, H 9.35.

(*S*)-(+)-Vesperal [(*S*)-1]: A solution of (*R*)-**9** (200 mg, 1.19 mmol) in CH_2Cl_2 (10 mL) was added to a stirred suspension of pyridinium chlorochromate (5.46 g, 24.8 mmol) and sodium acetate (80 mg) in CH_2Cl_2 (30 mL). The mixture was stirred at room temperature for 2 h, then diluted with diethyl ether and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel (10 g, hexane/ethyl acetate, 10:1−1:1) to give 105 mg (54%) of (*S*)-**1** as colorless needles; m.p. 53.5−54 °C. − $[\alpha]_D^{24} = +55.9$ (c = 1.02, CH_2Cl_2). − IR (CCl_4): $\tilde{\nu}_{max} = 1700\ cm^{-1}$ (s, C=O), 1680 (s, C=O), 1640 (m, C=C), 1435 (m), 1380 (m), 1315 (m), 1215 (m), 1020 (m), 945 (m), 880 (m). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.98 (s, 3 H, 1-Me), 2.0−2.5 (m, 4 H), 3.46 (dd, J = 4.6, 12.5 Hz, 1 H, 4-H), 5.96 (s, 1 H, 2-H), 6.20 (s, 1 H, 9-H′), 6.29 (s, 1 H, 9-H), 9.65 (s, 1 H, CHO). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3, 27.9, 30.7, 45.7, 126.5, 135.6, 148.4, 162.1, 193.3, 197.4. − MS (EI, 70 eV): m/z = 164[M^+], 149, 136, 135, 82 (100), 44. − $C_{10}H_{12}O_2$ (164.2): calcd. C 73.15, H 7.37; found C 73.00, H 7.62. − GC [column: Chirasil-DEX-CB, 0.25 mm × 25 m, 120 + 0.3°C/min: carrier gas: He, pressure 100 kPa]: t_R = 30.43 min [(*S*)-**1**, ca. 100%]. These IR and the ^1H and ^{13}C NMR spectra were identical with those of synthetic **1** kindly sent to us by Dr. F.-D. Boyer.

(*R*)-(−)-Vesperal [(*R*)-1]: In the same manner as described above, (*S*)-**9** (180 mg, 1.07 mmol) was converted into (*R*)-**1** (100 mg, 58%), isolated as colorless needles; m.p. 54.5−55 °C. − $[\alpha]_D^{22} = -54.8$ (c = 0.26, CH_2Cl_2). − Its IR and ^1H NMR spectra were identical with those of the *S* isomer. − $C_{10}H_{12}O_2$ (164.2): calcd. C 73.15, H 7.37; found C 73.28, H 7.66. − GC [under the same conditions for the analysis of (*S*)-**1**]: t_R = 30.96 min [(*R*)-**1**, ca. 100%].

Acknowledgments

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[1] F. -D. Boyer, C. Malosse, P. Zagatti, J. Einhorn, *Bull. Soc. Chim. Fr.* **1997**, *134*, 757−764.
[2] P. Zagatti, F.-D. Boyer, M. Guisset, I. De Cruz-Malosse, C. Malosse, C. Descoins, *Abstract of Papers, First Asia-Pacific Conference on Chemical Ecology*, Shanghai, China, **1999**, pp. 62−63.
[3] K. Mori, M. Kato, *Tetrahedron* **1986**, *42*, 5895−5900.
[4] R. J. Crawford, W. F. Erman, C. D. Broaddus, *J. Am. Chem. Soc.* **1972**, *94*, 4298−4306.
[5] H. Suemune, T. Kawahara, K. Sakai, *Chem. Pharm. Bull*. **1986**, *34*, 550−557.
[6] K. B. Sharpless, R. F. Lauer, *J. Am. Chem. Soc.* **1973**, *95*, 2697−2699.

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