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SYNTHESIS OF (2R,3R)-EPOXYNERAL, A SEX PHEROMONE OF THE ACARID MITE, Caloglyphus sp. (ASTIGMATA: ACARIDAE)¹

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Abstract: (2R,3R)-Epoxy-3,7-dimethyl-6-octenal [(2R,3R)-epoxyneral] **1a**, was identified from an acarid mite Caloglyphus sp. (Astigmata: Acaridae) as the sex pheromone, although its antipode (2S,3S)-epoxyneral **1b** is known as a component from a few mite species without an obvious function. Both enantiomers were synthesized by asymmetric epoxidation of nerol and subsequent oxidation to aldehydes. Optical purity of each epoxynerol was improved by recrystallization of its 3,5-dinitrobenzoate. The purest **1a** and **1b** were unexpectedly obtained from the mother liquor during the recrystallization process.

Astigmatid mites possess a pair of opisthonotal glands at the opisthosoma². *n*-Hydrocarbons, monoterpenoids and aromatic compounds have been identified in the secretion from 20 mite species belonging to 7 families, and several compounds function as alarm, aggregation and sex pheromones³. In the present paper, (2R,3R)-epoxyneral **1a** is identified as the female sex pheromone of an unidentified species of the genus *Caloglyphus* (Astigmata: Acaridae), whose phoretic hypopus was collected from the June beetle, *Melolontha japonica* (Coleoptera: Scarabaeidae). The antipode (2S,3S)-epoxyneral **1b** is known as a component of the mite *Tyrophagus perniciosus* (Astigmata: Acaridae) and its distribution is restricted to a few species without an obvious biological function⁴, which function is chemo-taxonomically important for identifying the species.

Caloglyphus sp.were raised by feeding on dry yeast under a humid condition at an ambient temperature. Males demonstrated sexual excitation upon exposure to the mite's hexane extract, suggesting the presence of a female sex pheromone in the species. Details of the purification and the bioassay will be discussed elsewhere. The active principle $(2 \ \mu g)$ was isolated from 100 mites as the 10% ether-in-hexane eluate of an SiO₂ column. GC/MS of the compound gave the same retention time⁵ and fragmentation pattern as those of (2S,3S)-epoxyneral⁴. In order to confirm the sex pheromone activity and the stereochemistry, both enantiomers were synthesized.



Sharpless asymmetric epoxidation⁶ of nerol gave, after usual work-up, (2S,3R)-epoxynerol **2a** (80% yield) and (2R,3S)-epoxynerol **2b** (74% yield) with low enatiomeric excess⁷ (77% e.e., each, determined by GLC of epoxynerals after oxidation of **2a** and **2b** with PDC⁸, using a capillary column⁹ with chiral stationary phase). 3,5-Dinitrobenzoylation of an epoxyalcohol is successfully directed for (+)-disparlure synthesis, to improve optical purity by recrystallization⁷. The same procedure was applied to **2a** and **2b** to give the corresponding benzoates¹⁰. Repeated recrystallization from *n*-hexane-ether (5:1) gave crystalline

2,3-epoxy-3,7-dimethyl-6-octenyl 3,5-dinitrobenzoate 3a {m.p. 66.5-67.5°C, 18% yield, [α]₀²⁷-14.0° (c 0.90, benzene)} and oily benzoate 3'a {54% yield, $[\alpha]_D^{30}$ -52.1° (c 1.14, benzene)} from the mother liquor after chromatographic purification. Ester derived from 2b was similarly treated to give crystalline 3b {m.p. 66.5-67°C, 13% yield, $[\alpha]_D^{27}$ +13.4° (c 0.90, benzene)} and oily **3'b** {50% yield, $[\alpha]_D^{28}$ +52.6° (c 1.06, benzene)}. Portions of both crystalline esters 3a and 3b were each hydrolyzed by K₂CO₃-MeOH to **2a** { $[\alpha]_D^{27}$ -3.56° (c 0.84, hexane)} and **2b** { $[\alpha]_D^{24}$ +4.46° (c 1.44, hexane)}. The resulting alcohols¹¹ were oxidized with PDC. Enantiomeric excess of epoxyneral from 3a was revealed to be unexpectedly as low as 26% e.e.; likewise, that from 3b was 24% e.e. On the other hand, 2a { $[\alpha]_{D}^{27}$ - 18.1° (c 1.12, hexane) and 2b $\{[\alpha]_D^{30} + 17.2^\circ (c 0.97, hexane)\}$ from each of the mother liquors 3'a and 3'b were fairly pure in 97% e.e and 96% e.e., respectively. The 77% e.e. of 2a benzoate (2.16g, 72% yield) before recrystallization corresponded to a mixture of (2S,3R)-enantiomer (1.91g) and (2R,3S)-enantiomer (0.248g). When both enantiomers of **3a** [0.562g, 26% e.e. (corresponding to 2S,3R: 0.354g and 2R,3S: 0.208g)] are removed by crystallization, the resulting enantiomeric excess of the mother liquid 3'a (1.60g) is calculated as 95% e.e. (observed 97% e.e.). Likewise, from the benzoate of 2b after removal of 3b (24% e.e.), the resultant enantiomeric excess of 3'b was 91% e.e. (observed 96% e.e.). These values accorded well with those observed.

Physical and spectral data of epoxyneral were as follows; **1a**: $[\alpha]_D^{28} + 127.9^{\circ}$ (*c* 1.12, hexane) and **1b**: $[\alpha]_D^{28} - 128.2^{\circ}$ (*c* 0.89, hexane); IR v_{max} 2950(m), 2900(m), 2850(m), 1720(s), 1450(m), 1350(m) cm⁻¹; ¹H-NMR δ (CDCl₃) 1.42(3H, s), 1.59(3H, br.s), 1.66(3H, br.s), 1.7-2.3(4H, m), 3.14(1H, d, *J*=5.3Hz), 5.04(1H, m), 9.41(1H, d, *J*=5.3Hz); ¹³C-NMR δ (CDCl₃) 17.6, 22.2, 24.2, 25.6, 33.5, 64.5, 64.6, 122.5, 133.3, 198.8; MS m/z 153(M⁺-CH₃, 0.9%), 150(M⁺-H₂O, 1.5%), 109(44%), 69(78%), 41(100%); (Found: C, 71.10; H, 9.83. Calc for C₁₀H₁₆O₂: C, 71.40; H, 9.59 %). The natural pheromone gave the same retention time as that of (2*R*.3*R*)-epoxyneral **1a** by GLC using the column with chiral stationary phase. Synthetic **1a** revealed the sex pheromone activity at a 0.1ng-dose.

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- 2,3-Epoxy-3,7-dimethyl-6-octenyl 3,5-dinitrobenzoate: IR ν_{max} 3080(m), 1730(s), 1540(s), 1340(s), 1260(s), 1150(s) cm⁻¹; ¹H-NMR δ(CDCl₃) 1,41(3H, s), 1.64(3H, br.s), 1.70(3H, br.s), 1.6-2.3(4H, m), 3.17(1H, dd, J=3.7, 7.4Hz), 4.36(1H, dd, J=7.4, 12.1Hz), 4.76(1H, dd, J=3.7, 12.1Hz), 5.13(1H, m), 9.20(3H, m); ¹³C-NMR δ(CDCl₃) 17.7, 22.0, 24.2, 25.7, 33.4, 60.5, 61.2, 65.8, 122.6, 123.0, 129.5, 132.8, 133.6, 148.9, 162.5, 198.8; MS m/z 364(M⁺, 1.0%), 346(M⁺-H₂O, 5.2%), 239(44.8%), 195(100%), 149(70.9%), 109(77.1%).
- 2,3-Epoxynerol: IR ν_{max} 3400(br.), 2900(s), 1440(m), 1350(m), 1050(s) cm⁻¹; ¹H-NMR δ(CDCl₃) 1.34(3H, s), 1.62 (3H, br.s), 1.70(3H, d, J=1.1Hz), 1.6-2.1(4H, m), 2.47(1H, m), 2.96(1H, dd, J=4.8, 6.6Hz), 3.73(2H, m), 5.09(1H, m); ¹³C-NMR δ(CDCl₃) 17.6, 22.2, 24.2, 25.6, 33.2, 61.3, 61.5, 64.4, 123.4, 132.5; MS m/z 155(M⁺-CH₃, 1.0%), 152(M⁺-H₂O, 2.3%), 109(80.6%), 69(80.5%), 41(100%).

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