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IDENTIFICATION AND ENANTIOSELECTIVE SYNTHESIS OF (Z,Z)-6,9-*CIS*-3S,4R-EPOXYNONADECADIENE, THE MAJOR SEX PHEROMONE COMPONENT OF *BOARMIA SELENARIA*

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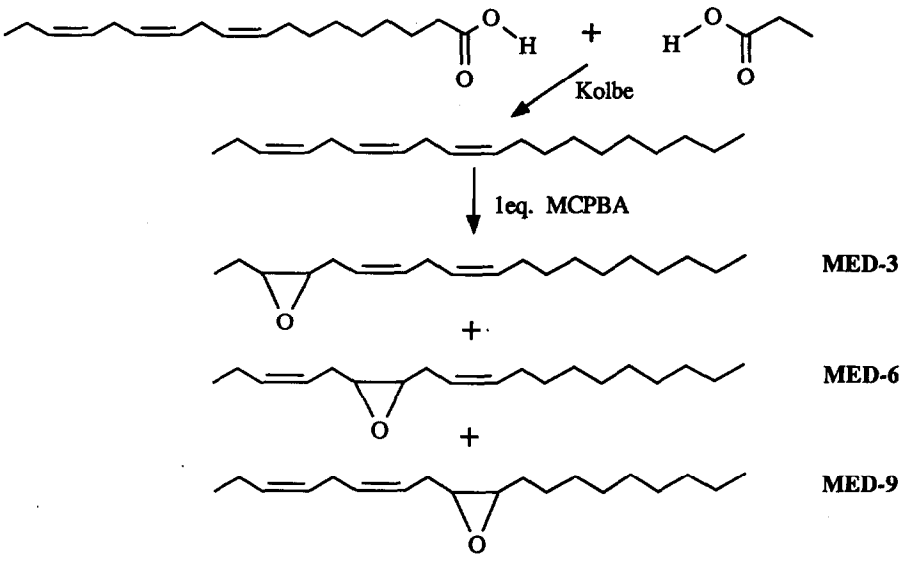
Summary: (Z,Z)-6,9-*cis*-3S,4R-Epoxynonadecadiene has been identified as the major sex pheromone component of the Geometrid *Boarmia selenaria*. A short and efficient synthesis of the chiral methylene-interrupted diene-epoxide has been developed for both enantiomers.

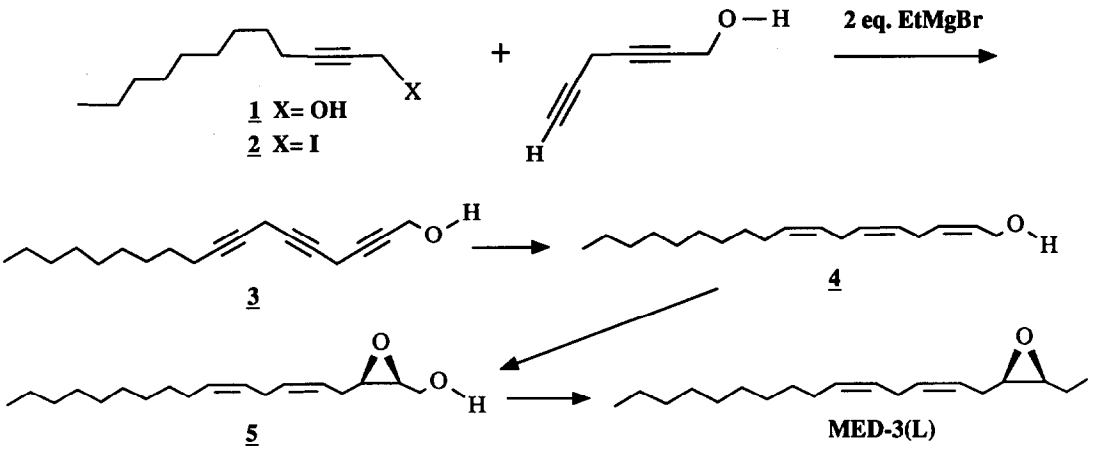
The Giant Looper, *Boarmia (Ascotis) selenaria* (Lepidoptera: Geometridae), is a widely distributed pest affecting important crops, such as coffee in Kenya, tea in India, peanuts in Madagascar, citrus in South Africa, and avocado and pecan in Israel.[1] One component, (Z,Z,Z)-3,6,9-nonadecatriene, was previously identified in extracts of virgin female ovipositor tips.[2] However, this triene failed to attract any male moths in the field. We have now identified an additional compound which appears to be the major component in the sex pheromone of this moth.

A crude pheromone extract was obtained by extracting ovipositor tips of one-day-old calling virgin females. The females were obtained from a laboratory colony of field-collected larvae, which had been reared on an artificial diet.[3] The components were separated either by preparative GC or by chromatography over silica gel. Bioassays were performed by electroantennograph (EAG) and wind tunnel tests. It was found that the fraction which should contain compounds of polarity, such as ketones, aldehydes or epoxides[4] had the highest biological activity. By running qualitative micro-reactions like bromination, reduction and oxidation and testing the products by EAG, the presence of carbonyl functionality could be ruled out, and that of unsaturated bonds could be established in the active compound. (Z,Z,Z)-3,6,9-Nonadecatriene is present in ovipositor extracts of virgin females and hence it was our intention to test whether monoepoxides of this triene are active as well. The triene was prepared[5] and epoxidized randomly by meta-chloroperbenzoic acid as described in Scheme I to give a mixture of three monoepoxides (MED). This mixture was found to be much more active than the triene in the bioassay tests and it showed the same retention time (GC) and polarity (LC on silica gel) as the active fraction. We could separate MED-6 from the mixture by preparative GC; however it was not active in wind tunnel tests. A mixture of MED-3 and MED-6 was prepared by random epoxidation of (Z,Z)-3,6-nonadecadiene[6], and showed activity in the bioassays. Buser[7] has identified (Z,Z)-6,9-nonadecadien-3-one as one component of the sex pheromone of *Boarmia rhomboidaria*. Hence it appeared that MED-3 could be the active compound and its synthesis was undertaken.



Scheme I

The synthesis of methylene-interrupted Z-polyenes has attracted the interest of organic chemists because these are important units of prostaglandin precursors. The most common approach for this unit is based on reduction of methylene-interrupted polyacetylenes. Recently this method has been used successfully by Mori in syntheses of (Z,Z)-3,6-*cis*-9S,10R-epoxyheneicosadiene[8a], (Z,Z)-1,3,6-*cis*-9S,10R-epoxyheneicosatriene[8b] and (Z,Z)-1,3,6-*cis*-9S,10R-epoxyeicosatriene[8b], sex pheromone components of *Estigmene acrea* and *Hyphantria cunea*. We have modified his sequence for the synthesis of MED-3. 2-Dodecyn-1-ol was prepared by condensation of a protected propargyl alcohol and 1-bromononane (THF, HMPA, BuLi). The protecting ethyl vinyl ether was cleaved by mild acid catalysis (2 ml of conc. HCl in 20 ml of methanol at RT) to give the alcohol **1** (90°C/0.01 mm Hg) in 88% yield . This alcohol was converted into the corresponding 1-iodo-2-dodecyne **2** (CH_3CN, I_2, Ph_3P, imidazole)[9] in 85% yield. Two units of protected propargyl alcohol were added in five steps: 1) condensation of the first unit with **2** (1 eq. of EtMgBr), 2) hydrolysis; 3) conversion of the alcohol to the corresponding iodide, 4) condensation with the second unit, 5) hydrolysis; giving the triacetylene alcohol **3** in 36% yield from **2**. **3** was found to be unstable if exposed to light or air, and Lindlar reduction failed when unpurified material was used. All our efforts to improve the yield and obtain pure triacetylene failed. An alternative synthesis of **3** in 58% yield was found, by a one-step sequence from **2** through condensation with 2,5-hexadiyne-1-ol[10] as described in Scheme II. Here triacetylene **3** could be obtained crystalline from the crude reaction mixture in cold hexane (0°C). This material was reduced (H_2, 1 atm., hexane) over Lindlar catalyst to give **4** in quantitative yield. From **4** it was possible to prepare the two enantiomers of the epoxide **5** applying a Sharpless[11] epoxidation. In our laboratory the best yield for the chiral epoxydiene alcohol **5**(L) was obtained by using an excess of oxidizing reagent (5 eq. Bu^tOOH, 1 eq. $Ti(OPr^i)_4$, 1 eq. L(+) dimethyl tartrate, -20°C, 2 days). The crude mixture was chromatographed over silica gel column



Scheme II

eluted by hexane:methylene chloride 1:2 to give pure 5(L) in 77% yield[12]. The epoxydiene alcohol 5(L) was converted to chiral MED-3(L) in two steps: 1) tosylation (pyridine, 4°C, overnight), and 2) $(CH_3)_2CuLi$ (ether, -20°C, 2 h) in 75% yield. The use of D(-) diethyl tartrate enabled us to prepare MED-3(D). In EAG tests with one nanogram doses and 8 replicates of each enantiomer, MED-3(L) was significantly more active than MED-3(D), this was confirmed by wind tunnel experiments (see Table 1). Final proof has been obtained from preliminary field tests where only traps baited with MED-3(L) attracted males. It was shown that calling females release MED-3, and that this is the major component of the pheromone; by co-injection (on three capillary columns) of MED-3 with airborne volatiles collected from a single female.

Based on the results we can conclude that the major component of the sex pheromone of the Giant Looper *Boarmia selenaria* is Z,Z-6,9-*cis*-3S,4R-epoxynonadecadiene, MED-3(L).

Table 1. Behavior of *B. selenaria* males in response to two concentrations of MED-3(L) and MED-3(D) loaded on rubber septa dispensers.

Treatment	n	% Response[e]	% Wingfanning[e]	% Upwindflight[e]	% Landing on source[e]
MED-3(L) 1000µg	37	100[a]	100[a]	86[a]	49[a]
MED-3(L) 250µg	15	87[ab]	87[ab]	53[b]	13[bc]
MED-3(D) 1000µg	15	100[a]	100[a]	80[ab]	40[ab]
MED-3(D) 250µg	15	80[b]	67[b]	6[d]	0[c]

[e]percentages which have no letter in common are significantly different according to χ^2 (P<0.05)

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12) All our efforts to verify the enantiomeric purity by the known methods failed. Based on similar studies applying the Sharpless epoxidation we can assume enantiomeric purity of 80-92 ee%.
13) All new compounds were fully characterized. ^{1}H NMR analysis is based on high resolution COSY-45, the protons are identified by nomenclature numbering.

    4: HRMS calcd. for $C_{18}H_{32}O$ 264.2453, found 264.2462; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (1H, m, =C-H 2), 5.52 (1H, m, =C-H 3), 5.33 (4H, m, =C-H 5,6,8,9), 4.20 (2H, d J = 7Hz, C-H 1), 2.82 (2H, t J = 7 Hz, C-H 4), 2.78 (2H, t J = 7 Hz, C-H 7), 2.02 (2H, q, C-H 10), 1.24 (12H, s, C-H 11-17), 0.85 (3H, t, C-H 18).

    5: HRMS calcd. for $C_{18}H_{32}O_2$ 280.2403, found 280.2393; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (1H, m, =C-H 5), 5.39 (2H, m, =C-H 6,8), 5.27 (1H, m, =C-H 9), 3.81 (1H, bd J = 15 Hz, C-H 1), 3.68 (1H, dd J = 15, J = 7 Hz, C-H 1), 3.15 (1H, m, C-H 2), 3.04 (1H, m, C-H 3), 2.75 (2H, t, C-H 7), 2.44 (1H, m, C-H 4), 2.25 (1H, m, C-H 4), 2.0 (2H, q, C-H 10), 1.22 (14H, s, C-H 11-17), 0.84 (3H, t, C-H 18).

    MED-3(L): HRMS calcd. for $C_{19}H_{34}O$ 278.2609, found 278.2594; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.5-5.42 (2H, m, =C-H 6,7), 5.42-5.3 (2H, m, =C-H 9,10), 2.93 (1H, m, C-H 4), 2.87 (1H, m, C-H 3), 2.79 (2H, t, C-H 8), 2.39 (1H, m, C-H 5), 2.2 (1H, m, C-H 5), 2.02 (2H, q, C-H 11), 1.57 (2H, m, C-H 2), 1.35 (2H ,m, C-H 12), 1.25 (12H, s, C-H 13-18), 1.04 (3H, t, C-H 1), 0.86 (3H, t, C-H 19).

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