Tetrahedron Letters 49 (2008) 4820–4823

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

(9*Z*)-9,13-Tetradecadien-11-ynal, the sex pheromone of the avocado seed moth, *Stenoma catenifer*

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ARTICLE INFO

Article history:
Received 7 May 2008
Revised 30 May 2008
Accepted 4 June 2008
Available online 10 June 2008

Keywords:
(9*Z*)-9,13-Tetradecadien-11-ynal
(9*Z*)-9,13-Tetradecadien-11-yn-1-ol
Pheromone
Conjugated dienyne

ABSTRACT

The highly unsaturated aldehyde (9*Z*)-9,13-tetradecadien-11-ynal and the corresponding alcohol were identified as possible sex pheromone components of the avocado seed moth, *Stenoma catenifer*. The aldehyde as a single component attracted more male moths than caged virgin female moths, and addition of the analogous alcohol and/or acetate decreased attraction. A stereospecific synthesis of the pheromone is described.

The avocado seed moth, *Stenoma catenifer*, is one of the most serious pests of commercial avocado production in areas in which avocados and *S. catenifer* are endemic. The current range of this insect extends from Mexico to South America, and damage from *S. catenifer* infestations can be so severe that it has been reported to limit and even prevent commercial avocado cultivation in some areas.[1] This insect has not yet become established in avocado production areas of the United States in southern California, Florida, or Hawaii, but US Department of Agriculture risk assessments conducted over the past decade have identified *S. catenifer* as one of the most serious potential threats to the US avocado industry.[2] As part of an effort to provide growers, exporters, and regulatory agencies with a sensitive and reliable method for detection of *S. catenifer*, we report here the identification, synthesis, and preliminary testing of the novel sex pheromone of this insect.

Insects were obtained from naturally infested fruit collected from commercial Hass avocado orchards and non-Hass avocados in Guatemala, and used to start a colony. Colony-reared pupae and pupae from infested avocados were packed singly in ventilated plastic vials with cotton wool, and shipped by courier to the University of California, Riverside quarantine facility from Guatemala for pheromone analysis (USDA-APHIS permit #P526P-06-01565). Pheromone glands were dissected from 1 to 2-day-old unmated adult females. Groups of excised glands were soaked in pentane (~20 µl per gland) for ~1 h, and the composite extracts were transferred to clean conical vials and concentrated under a stream of nitrogen for analyses. Aliquots of extracts were analyzed by coupled GC–electroantennogram detection (GC–EAD) on nonpolar (DB-5) and polar (DB-WAX) columns,[3] and by GC–MS (Hewlett–Packard 5973 mass selective detector interfaced to an H–P 6890 GC, DB-5MS column, 30 m × 0.25 mm ID × 0.25 µm film, 40 °C/1 min, 10°/min to 280 °C, hold 15 min; electron impact ionization, 70 eV).

In GC–EAD analyses of pheromone gland extracts on the DB-WAX column, two compounds consistently elicited large responses from antennae of male moths (Fig. 1, peaks A and C). These

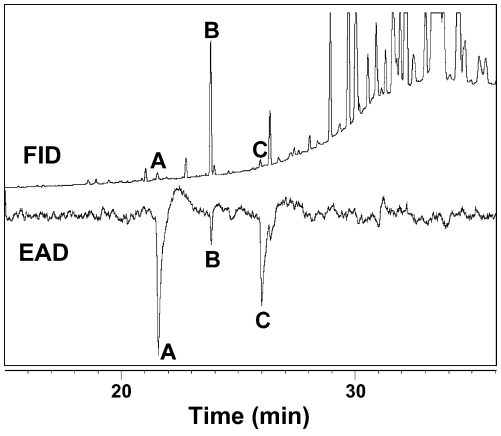

Figure 1. Coupled gas chromatography–electroantennogram analysis (DB-WAX column) of a composite extract of pheromone glands of female *Stenoma catenifer*. Upper trace shows the GC detector response, lower, inverted trace shows the response from a male *S. catenifer* antenna.

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0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.06.019

compounds had retention times in the ranges typical of 14-carbon conjugated, multiply unsaturated aldehydes and alcohol standards, respectively (Kovats index [KI] values vs hydrocarbon standards; on polar DB-WAX column, 2231 and 2472, respectively; on nonpolar DB-5 column, compound A, KI = 1654; compound C, KI = 1718).[4] GC–MS analyses confirmed these results with the mass spectrum of the first compound showing an unusual and distinctive base peak at *m*/*z* 78. This is in marked contrast to the mass spectra of many other polyunsaturated lepidopteran pheromones, fatty acids, and related compounds which typically show a strong *m*/*z* 79 ion (e.g., [9*Z*,11*E*,13]-tetradecadienal).[5] It was also unusual that the molecular ion was very weak; lepidopteran pheromones with conjugated double-bonds typically show medium to quite strong molecular ions, even for alcohols.[6] The highest mass ion seen in the spectrum obtained from the small amount of compound A in the extract was *m*/*z* 189, which was followed by a regular series of losses of 14 amu down to *m*/*z* 91. These data supported a possible molecular weight of *m*/*z* 204, corresponding to an aldehyde with 4 carbon–carbon double bond equivalents. The base peak at *m*/*z* 78 could be accommodated by a terminal, conjugated dienyne fragment, and the presence of a triple bond also explained the very weak molecular ion.[7] Analysis of a standard of (11*E*)-11,13-tetradecadien-9-ynal, available from a previous project,[5] determined that its retention time was approximately correct, but its mass spectrum was entirely different, with a base peak at *m*/*z* 91, and a relatively small *m*/*z* 78 ion. However, the mass spectrum (Fig. 2) and retention times on both polar (DB-WAX) and nonpolar (DB-5) columns matched those of a synthetic standard of (9*Z*)-9,13-tetradecadien-11-ynal (vide infra). There was no uncertainty as to which stereoisomer was present because the corresponding (*E*)-isomer eluted a full minute later on the DB-5 column under the GC conditions used. Furthermore, the retention times and mass spectra of the third possibility, isomers of 9,11-tetradecadien-13-ynal, also were markedly different.[8]

The mass spectrum of the second compound that elicited a strong electroantennogram response from the antennae of male moths (Fig. 1, peak C) also showed a base peak at *m*/*z* 78, and the spectrum was quite similar to that of (9*Z*)-9,13-tetradecadien-11-ynal. This compound eluted later than (9*Z*)-9,13-tetradecadien-11-ynal on both the DB-5 and DB-WAX columns. The difference in the Kovats indices between the two columns (241 KI units later on the polar DB-WAX) was analogous to the difference in KI values for two model compounds, (*E*8,*E*10)-8,10-tetradecadien-1-ol and (*E*8,*E*10)-8,10-tetradecadienal, respectively (KI difference 245 units), suggesting that the second compound was the alcohol analog of (9*Z*)-9,13-tetradecadien-11-ynal. This was confirmed by retention time matches of the insect-produced compound with a synthetic standard of (9*Z*)-9,13-tetradecadien-11-yn-1-ol on both GC columns, and a good match between the mass spectra. As with the aldehyde, the large difference in the retention times of the (*E*)- and (*Z*)-isomers rendered the stereochemistry unequivocal. A third compound (Fig. 1, peak B) that elicited only weak electroantennogram responses from antennae of male moths, despite being present in much larger amounts than the other two components, was tentatively identified as (*Z*6,*Z*9)-6,9-tricosadiene from its molecular ion at *m*/*z* 348 and diagnostic fragments in its mass spectrum. The identification was confirmed by matches of its retention times on polar and apolar columns and its mass spectrum with those of an authentic standard.

Because we did not initially know which stereoisomer of the dienynal was produced by the insects, our synthesis was designed to produce either isomer simply by changing the stereochemistry of one intermediate (Fig. 3). It was also deemed prudent to use a synthesis in which the two alkene substructures were inserted in the correct degree of unsaturation and with fixed and known stereochemistry, rather than using a route based on selective partial reductions of one or two acetylene units, with the possibility of generating under- or over-reduced contaminants that might be difficult to remove. Thus, 9-decyn-1-ol **1** was hydroborated with catecholborane, and the resulting boronic acid intermediate **2** was regiospecifically and stereoselectively converted to the (*Z*)-vinyl iodide **3**.[9] After protection of the alcohol as the THP derivative **4**, the iodide was coupled with propargyl alcohol, with Pd and CuI catalysis, giving alcohol **5**.[10] Oxidation of the propargylic alcohol gave aldehyde **6**, and subsequent Wittig reaction with methylenetriphenylphosphorane placed the terminal double bond. The synthesis of the basic structure was completed by removal of the protecting group, giving (9*Z*)-9,13-tetradecadien-11-yn-1-ol **7**. Straightforward acetylation or oxidation of **7** gave (9*Z*)-9,13-tetradecadien-11-yn-1-yl acetate **8** and (9*Z*)-9,13-tetradecadien-11-ynal **9**, respectively.[11] The former compound was prepared for testing in field trials, in case it proved to be either a synergist or an antagonist. Samples of the (*E*)-isomers of **7** and **9** were prepared by the same route by starting with (9*E*)-10-iododecen-1-ol instead of the (*Z*)-vinyl iodide **3**.

In preliminary field trials in avocado orchards in Guatemala, (9*Z*)-9,13-tetradecadien-11-ynal **9** (0.1 mg doses on grey rubber septum lures) as a single component was attractive to male moths (baited traps, mean ± standard error, 7.2 ± 2.1 moths; controls, zero moths). In a second trial run in an orchard with low populations due to heavy insecticide use, 0.1 mg doses of the aldehyde attracted male moths (total of 28 moths in 11 traps), whereas three traps baited with caged virgin female moths caught no moths. Addition of (9*Z*)-9,13-tetradecadien-11-yn-1-ol, (9*Z*)-9,13-tetra-

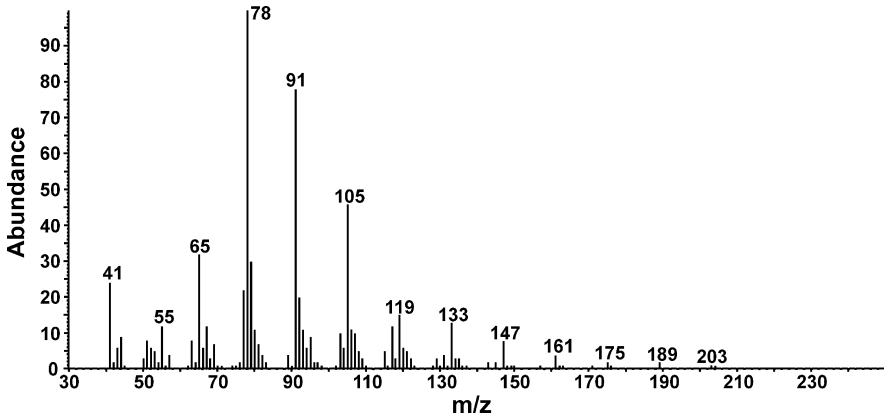

Figure 2. Electron impact (70 eV) mass spectrum of (9*Z*)-9,13-tetradecadien-11-ynal.

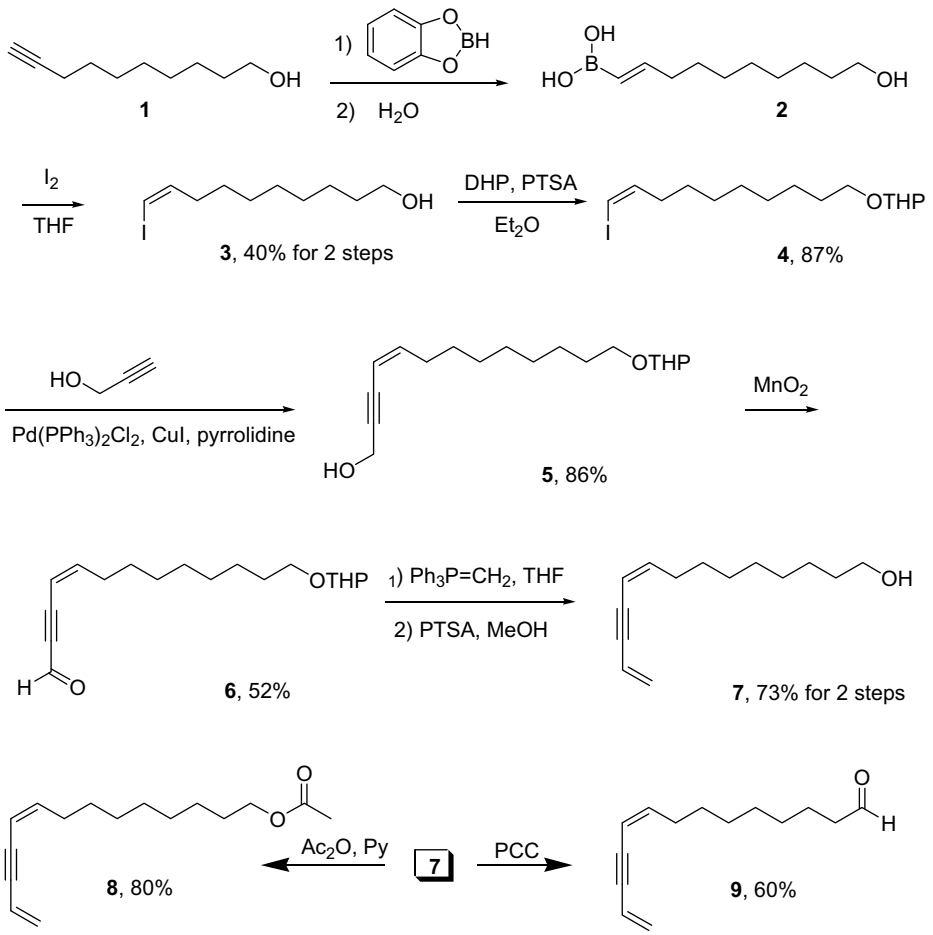

Figure 3. Synthesis of (9*Z*)-9,13-tetradecadien-11-yn-1-ol, and the corresponding aldehyde and acetate.

decadien-11-yn-1-yl acetate, or both, significantly decreased the attraction, suggesting that these components are not part of the pheromone. Furthermore, blends of (*Z*6,*Z*9)-6,9-tricosadiene with (9*Z*)-9,13-tetradecadien-11-ynal over a range of ratios were no more attractive than (9*Z*)-9,13-tetradecadien-11-ynal as a single component. Thus, this species appears to use a single-component pheromone. Comprehensive field trials testing a full range of doses, blends, and the field longevity of formulations are in progress, and will be reported in due course.

The dienyne structure of this pheromone is remarkable, both in terms of the presence of the alkyne, which is a very unusual functional group in lepidopteran pheromones,[7] and in terms of the overall high degree of unsaturation, with five double bond equivalents within a fourteen carbon chain. To our knowledge, (9*Z*)-9,13-tetradecadien-11-ynal **9** is a new natural product, and the terminal conjugated dienyne motif appears to have no precedent among known natural products. However, as is often the case with lepidoptera, closely related species use similar pheromone compounds, and (9*Z*,11*E*)-9,11,13-tetradecatrienal has been identified from the congeneric species *Stenoma cecropia*,[12] as well as from a more distantly related pyralid moth species, *Ectomyelois ceratoniae*.[13] In fact, (9*E*)-9,13-tetradecadien-11-yn-1-ol and (9*E*)-9,13-tetradecadien-11-yn-1-yl acetate, the 9*E* isomers of **7** and **8** respectively, have been reported as intermediates in a synthesis of (9*E*,11*Z*)-9,11,13-tetradecatrienal.[14]

Overall, the identification of an attractive pheromone for this notorious pest species will benefit avocado producers worldwide by providing an effective method for monitoring adult moth populations and population cycles. The pheromone will also be of substantial benefit to regulatory agencies charged with the detection of this potentially invasive species, and in reliably certifying specific orchards and even entire geographic areas as being free of this insect, so that avocado shipments can be made without fear of introducing a noxious pest into new areas or countries.

Acknowledgments

We thank the California Avocado Commission and the Hansen Trust for financial support of this work. We are indebted to our cooperators in Guatemala for their assistance and wish to thank Hector Leal, Oscar Coy, Peter Grant, Richard and Eugenia West, and members of Anaguacate for location of study sites, and for providing unlimited access to orchards.

References and notes

1. (a) Ebeling, W. *Subtropical Fruit Pests. Division of Agricultural and Natural Resources*; University of California: Berkeley, 1959; (b) Boscan de Martinez, N.; Godoy, F. J. *Agron. Tropical* **1985**, *34*, 205–208; (c) Miller, C. E.; Green, A. S.; Harabin, V.; Stewart, R. D. Risk analysis of a systems approach for Mexican avocados. US Dept. of Agriculture-Animal and Plant Health Inspection Service, Riverdale MD, 1995.; (d) Ventura, M. U.; Destro, D.; Lopes, E. C. A.; Montalvan, R. *Fl. Entomol* **1999**, *82*, 625–631.
2. Miller, C. E. *Risk management analysis: a systems approach for Mexican avocado*. Animal and Plant Health Inspection Service, US Dept. of Agriculture, Riverdale, MD, 1995.
3. McElfresh, J. S.; Millar, J. G. *J. Chem. Ecol.* **1999**, *25*, 687–709.
4. For example, Kovats index of (9*Z*,11*E*,13)-9,11,13-tetradecatrienal = 1692 on DB-5 column.
5. Millar, J. G. *Agric. Biol. Chem.* **1990**, *54*, 2473–2476.
6. (a) Ando, T.; Koike, M.; Uchiyama, M.; Kuroko, H. *Agric. Biol. Chem.* **1987**, *51*, 2691–2694; (b) Löfstedt, C.; Odham, G. *Biomed. Mass Spectrom.* **1984**, *11*, 106–113.

7. Millar, J. G.; McElfresh, J. S.; de Assis Marques, F. *J. Econ. Entomol.* **2002**, *95*, 692–698.
8. (9*E*,11*Z*)-9,11-Tetradecadien-13-ynal and (9*E*,11*E*)-9,11-tetradecadien-13-ynal were synthesized for comparison purposes, by Wittig reaction of the THP derivative of (*E*)-11-hydroxyundec-2-enal (available from other studies) with (3-trimethylsilyl-2-propynyl)triphenylphosphonium bromide. After removal of the protecting groups and oxidation, the mass spectra of the resulting aldehydes were sufficiently different from that of (9*Z*,13)-tetradecadien-11-ynal that it was not deemed necessary to synthesize the (9*Z*,11*Z*)-tetradecadien-13-ynal and (9*Z*,11*E*)-tetradecadien-13-ynal isomers for additional comparisons.
9. Brown, H. C.; Subrahmanyam, C.; Hamaoka, T.; Ravindran, N.; Bowman, D. H.; Misumi, S.; Unni, M. K.; Somayaji, V.; Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6068–6075.
10. Chen, M.-J.; Narkunan, K.; Liu, R.-S. *J. Org. Chem.* **1999**, *64*, 8311–8318.
11. Spectral data for (9*Z*,13)-tetradecadien-11-ynal: ^{1}H NMR: δ 9.75 (t, J = 2.0 Hz, 1H), 5.92 (m, 2H), 5.60 (dd, J = 17.6, 2.4 Hz, 1H), 5.56 (dd, J = 11.2, 1.6 Hz, 1H), 5.45 (dd, J = 11.2, 1.6 Hz, 1H), 2.41 (td, J = 7.4, 2.0 Hz, 2H), 2.30 (qd, J = 7.3, 1.6 Hz, 2H), 1.62 (m, 2H), 1.44–1.28 (m, 8H). ^{13}C NMR: δ 203.0 (CH), 144.4 (CH), 126.2 (CH_2), 117.6 (CH), 109.1 (CH), 92.4 (C), 87.2 (C), 44.1 (CH_2), 30.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 22.2 (CH_2). IR (neat): 3018, 2928, 2856, 2719, 1724, 1599, 1464, 1414, 1392, 1164, 971, 917, 738, 674 cm^{-1}. HRMS (ESI/APCI) calcd for $C_{14}H_{21}O$ $[M+H]^{+}$: 205.1592, found 205.1589.
12. Zagatti, P.; Lucas, P.; Genty, P.; Arango, S.; Malosse, C.; Tellier, F. *J. Chem. Ecol.* **1996**, *22*, 1103–1121.
13. Baker, T. C.; Francke, W.; Millar, J. G.; Lofstedt, C.; Hansson, B.; Du, J.-W.; Phelan, P. L.; Vetter, R. S.; Youngman, R.; Todd, J. L. *J. Chem. Ecol.* **1991**, *17*, 1973–1988.
14. Tellier, F.; Déscoins, C. *Tetrahedron Lett.* **1991**, *47*, 7767–7774.