Functional Structure/Activity Relationships

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Synthesis and biological testing of ester pheromone analogues for two fruitworm moths (Carposinidae)

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ABSTRACT

A range of ester pheromone analogues for carposinid moths were synthesized and evaluated for biological activity. The analogues aimed to take advantage of the structural commonality of (7*Z*)-alken-11-ones found in this family. Analogues were tested on two pest species *Heterocrossa rubophaga* and *Coscinoptycha improbana*. Two of the analogues, (2*Z*)-nonenyl nonanoate and (4*Z*)-heptyl undecenoate, elicited significant electroantennogram responses. Only (4*Z*)-heptyl undecenoate gave consistent responses with both moth species in single sensillum recording. Field trapping trials were conducted with these two analogues both individually and in combination with the pheromone of each of the two moth species. No attraction was observed to either of the analogues alone, by either moth species. However, when (4*Z*)-heptyl undecenoate was coupled with the pheromone it produced a strong inhibitory effect in *H. rubophaga*, reducing male moth trap catch by over 95%. No inhibitory effect on male moth trap catch was observed in *C. improbana*.

KEYWORDS – Carposinidae, *Coscinoptycha improbana*, EAG, *Heterocrossa rubophaga*, pheromone inhibitor, sex pheromone analogues, SSR, synthesis

INTRODUCTION

Moths in the family Carposinidae, commonly known as “fruitworm moths”, are small to medium sized moths with a wingspan of 1 – 4 cm, whose larval stage are damaging to the fruit and growing shoots of plants.[1] There are thought to be about 279 species worldwide, with the majority found in Asia and the South Pacific regions.[1] Only three carposinid moth pheromones have been identified to date and all display an uncommon pheromone chemistry, falling outside the standard Type I (alkene acetates, alcohols or aldehydes) or Type II (polyene alkenes and associated epoxide/s) designation for moth pheromones, instead they are grouped in the Miscellaneous category.[2]

The first carposinid pheromone identified was that of the peach fruit moth, *Carposina sasakii*, (formerly *C. niponensis*) in the 1970s which was found to be a blend of two (7*Z*)-alken-11-ones (Figure 1): (7*Z*)-eicosen-11-one and (7*Z*)-nonadecen-11-one (please note historical names are used throughout the text to highlight the repeating nature of the structures).[3] The raspberry bud moth, *Heterocrossa rubophaga* (formerly *Carposina adreptella*) had its pheromone identified as a single component, (7*Z*)-nonadecen-11-one in the late 1990s,[4] while the guava moth, *Coscinoptycha improbana*'s pheromone was reported as a four component blend consisting of: (7*Z*)-tricosene, (7*Z*)-octadecen-11-one, (7*Z*)-nonadecen-11-one and (7*Z*)-tricosen-11-one in the early 2000s (Figure 1).[5] In recent years the main component of the peach fruit moth pheromone, (7*Z*)-eicosen-11-one, has been shown to attract some other carposinid moth species[6,7] and act as a mating disruption agent for guava moth.[8] This cross-species communication, along with the structural commonality of all compounds identified from this family, led us to investigate pheromone reception and possible analogues for moths in the Carposinidae. For the purposes of discussion in this article, pheromone analogues refer to chemicals of anthropomorphic origin that are not found in nature.

Since the identification of the silkworm pheromone bombykol by Butenandt et al.[9] chemists and biologists have been exploring the biological activity of structures related to pheromones.[10] These structural analogues may be preferred over the original compound because they offer greater stability, are cheaper to make or have an inhibitory effect on the insect.[10] Many pheromone analogues have been made for the typical Type I moth sex pheromones,[10] yet to the best of our knowledge no analogues have been made for carposinid moth pheromones. Analogues of the Type I moth pheromones include compounds with variations to the hydrocarbon chain length,[11] changes to the polar group(s),[12] halogenation,[13] and isosteric replacements within the hydrocarbon chain.[14] A sub-group of analogues within

these, are the formate ester analogues of aldehydes.[15,16] The formate analogues have shown varying effects from antagonistic[15] to cases where the analogue has been shown to be more attractive than the actual pheromone component itself.[16] Considering the related carbonyl of the ketone functional group in the Carposinidae, this was chosen as an area to investigate. Our study focused on two carposinid pests, with known pheromone components, that are economically impacting horticulture in New Zealand: the raspberry bud moth, a berry fruit crop pest[4,17] and the guava moth, a feijoa and macadamia pest.[18] The internal fruit and shoot feeding behavior of the larvae make these pests difficult to control with traditional pesticides.

The purpose of this study was to investigate the effects of pheromone analogues on raspberry bud moth and guava moth, expanding our knowledge of their pheromone perception, in the search for alternative pest management tools. Here we report the synthesis, electrophysiology and field testing of selected ester analogues (Figure 2.) of the (7*Z*)-alken-11-one pheromone component, (7*Z*)-nonadecen-11-one, which is common to the pheromone blend of all the three carposinid sex pheromones identified to date.

MATERIALS AND METHODS

General procedures. NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are reported relative to the solvent peak of chloroform and/or $CDCl_3$ (δ 7.3 for ^{1}H and δ 77.0 for ^{13}C, respectively). ^{1}H NMR data is reported as position (δ), relative integral, multiplicity (s, singlet; d, doublet; t, triplet; dt, double triplet; m, multiplet; br, broad peak), coupling constant (J, Hz), and the assignment of the atom. ^{13}C NMR data are reported as position (δ) and assignment of the atom. NMR assignments were performed using HSQC and HMBC experiments. Infrared (IR) spectra were recorded using a Perkin-Elmer Spectrum 1000 series Fourier Transform IR spectrometer. Absorption maxima are expressed in wave numbers (cm^{-1}). High-resolution mass spectroscopy (HRMS) was carried out by electrospray

ionization (ESI) on a MicroTOF-Q mass spectrometer. Analyses of all reaction products were conducted on an Agilent 7890B gas chromatograph (GC) coupled to an Agilent 5977A mass selective detector (MSD). The GC was equipped with a DB-5 ms column (30 m × 0.25 mm i.d. × 0.25 μm), and samples were analysed using methods previously reported.[19]

Synthesis reactions were monitored by thin layer chromatography (TLC). Premade silica gel on aluminium foil plates were purchased from Sigma-Aldrich. A developer solution of vanillin in acidified (H_2SO_4) ethanol and heat was used to visualize the spots.

Column chromatography was carried out using a medium pressure liquid chromatography (MPLC) system. Silica gel was purchased from Sigma-Aldrich, both standard 230 mesh and 10% $AgNO_3$ impregnated 230 mesh silica grades. The $AgNO_3$ columns were wrapped in aluminium foil to exclude light and increase the longevity of the $AgNO_3$. The $AgNO_3$ columns were re-used following back-flushing of the system with DCM.

Chemicals. Unless otherwise stated all chemical reagents and solvents were supplied by Sigma-Aldrich (St. Louis, MO, USA) and were used as received. All dry solvents were prepared by storing on 3Å molecular sieves and ethers were distilled over $LiAlH_4$ before use. Synthetic standards of the remaining guava moth pheromone components (7*Z*)-octadecen-11-one, (7*Z*)-tricosen-11-one and (7*Z*)-tricosene were gifts from Barry Bunn.

Synthetic procedures. Only procedures for novel compounds are reported in the text below. Synthetic procedures for previously reported compounds can be found in the Supporting Information. Scheme 1 shows the synthetic route to the pheromone component while Schemes 2 and 3 show the routes used to the ester and carbonate analogues respectively. Spectroscopic data is included for all compounds synthesized.

2-Hydroxytetrahydrofuran (1). δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.82-2.09 (4H, m, H-3, H-4), 3.13 (br s, 1H, OH), 3.83-3.88 (1H, m, H-5), 4.02-4.08 (1H, m, H-5), 5.53-5.55 (1H, m, H-2). The ^{1}H NMR data matched that reported in literature.[20]

(4Z)-Undecen-1-ol (2). δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.88 (3H, t, J = 6.9 Hz, H-11), 1.27-1.34 (9H, m, H-7, H-8, H-9, H-10, OH), 1.60-1.67 (2H, m, H-2), 2.01-2.06 (2H, m, H-6), 2.10-2.15 (2H, m H-3), 3.66 (2H, t, J = 6.5 Hz, H-1), 5.35-5.44 (2H, m, H-4, H-5). The ^{1}H NMR data matched that reported in literature.[21]

(4Z)-Undecenal (3). δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.88 (3H, t, J = 7.1 Hz, H-11), 1.27-1.32 (8H, m, H-7, H-8, H-9, H-10), 2.02-2.10 (2H, m H-6), 2.36-2.41 (2H, m, H-3), 2.46-2.48 (2H, m, H-2), 5.31-5.46 (2H, m, H-4, H-5), 9.77 (1H, t, J = 1.6 Hz, H-1). The ^{1}H NMR data matched that reported in literature.[22]

(7*Z*)-Nonadecen-11-ol (4). δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.88 (6H, t, J = 7.0 Hz, H-1, H-19), 1.28-1.55 (25H, m, H-2, H-3, H-4, H-5, H-10, H-12, H-13, H-14, H-15, H-16, H-17, H-18, OH), 2.02-2.07 (2H, m, H-6), 2.10-2.17 (2H, m, H-9), 3.59-3.63 (1H, m, H-11), 5.35-5.44 (2H, m, H-7, H-8). The ^{1}H NMR data matched that reported in literature.[22]

(7*Z*)-Nonadecen-11-one (5). δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.88 (3H, t, J = 7.1 Hz, H-1 or H-19), 0.88 (3H, t, J = 7.0 Hz, H-1 or H-19), 1.27-1.36 (18H, m, H-2, H-3, H-4, H-5, H-14, H-15, H-16, H-17, H-18), 1.54-1.58 (2H, m, H-13), 2.03 (2H, dt, J = 6.9 and J = 7.2 Hz, H-6), 2.27-2.32 (2H, m, H-9), 2.36-2.45 (4H, m, H-10, H-12), 5.27-5.33 (1H, m, H-8), 5.35-5.42 (1H, m, H-7). The ^{1}H NMR data matched that reported in literature.[23]

(7*E*)-Nonadecen-11-one (6). Isolated from $AgNO_3$ chromatography of (7Z)-nonadecen-11-one, isomeric purity > 99%. δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.88 (6H, t, J = 7.2 Hz, H-1, H-19), 1.27-1.31 (18H, m, H-2, H-3, H-4, H-5, H-14, H-15, H-16, H-17, H-18), 1.56-1.57 (2H,

m, H-13), 1.96 (2H, dt, J = 6.4 and J = 7.0 Hz, H-6), 2.25 (2H, dt, J = 6.9 and J = 7.3 Hz, H-9), 2.38 (2H, t, J = 7.5 Hz, H-12), 2.45 (2H, t, J = 7.7 Hz, H-10), 5.34-5.47 (2H, m, H-7, H-8). δ_C (100 MHz; $CDCl_3$) 14.1 (C-1, C-19), 22.6 (C-2, C-18), 23.8 (C-13), 26.9 (C-9), 28.8, 29.2, 29.3, 29.4, 29.5 (C-4, C-5, C-14, C-15, C-16) 31.7, 31.8 (C-3, C-17) 32.5 (C-6), 42.7 (C-10), 43.0 (C-12) 128.4 (C-8), 131.6 (C-7), 211.0 (C-11). IR: ν_{max}(film)/cm^{-1}; 2955, 2919, 2849, 1705, 1471, 1377, and 962. HRMS (ESI^+) found (MNa^+): 303.2653 $C_{19}H_{36}NaO$ requires 303.2658.

(4*Z*)-Undecenoic acid (7). δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.88 (3H, t, J = 7.2 Hz, H-11), 1.26-1.34 (8H, m, H-7, H-8, H-9, H-10), 2.04 (2H, dt, J = 6.8 and J = 7.2 Hz, H-6), 2.36-2.42 (4H, m, H-2, H-3), 5.32-5.37 (1H, m, H-5), 5.41-5.47 (1H, m, H-4). The ^{1}H NMR data matched that reported in literature.[24]

(4*Z*)-Heptyl undecenoate (8). To a solution of (4*Z*)-undecenoic acid **(7)** (88 mg, 0.48 mmol) in dry DCM (5 mL) at 0 °C, a solution of heptan-1-ol (124 mg, 1.07 mmol) in dry DCM (2 mL) was added with constant stirring. This was followed by the addition of a solution DMAP (23 mg, 0.19 mmol) in dry DCM (1 mL) and a solution of DCC (200 mg, 0.97 mmol) in dry DCM (2 mL). The resulting four component mixture was allowed to warm to room temperature and then left over night with constant stirring. Upon completion, as monitored by TLC, the dicyclohexylurea precipitate was filtered off and the filtrate was washed with 1M HCl (10 mL × 2), a saturated solution of $NaHCO_3$ (10 mL) then dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude product was purified by column chromatography (silica gel, DCM) to give (4*Z*)-heptyl undecenoate **(8)** (99 mg, 0.35 mmol, 73% yield, isomeric purity 99% by GC) as a clear colorless oil. δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.88 (3H, t, J = 6.5 Hz, H-11 or H-7′), 0.89 (3H, t, J = 7.5 Hz, H-11 or H-7′),1.27-1.32 (16H, m, H-7, H-8, H-9, H-10, H-3′, H-4′, H-5′, H-6′), 1.60-1.64 (2H, m, H-2′), 2.04 (2H, dt, J = 6.9 and J = 7.1 Hz,

H-6), 2.32-2.36 (4H, m, H-2, H-3), 4.06 (2H, t, J = 6.7 Hz, H-1′), 5.30-5.33 (1H, m, H-4), 5.34-5.38 (1H, m, H-5). δ_C (100 MHz; $CDCl_3$) 14.1 (C-11), 14.1 (C-7′), 22.6, 22.7 (C-10, C-6′), 22.9 (C-3), 25.9 (C-3′), 27.2 (C-6), 28.7 (C-2′), 28.9, 29.0 (C-7, C-4′), 29.6 (C-8), 31.7, 31.8 (C-9, C-5′), 34.5 (C-2), 64.6 (C-1′), 127.4 (C-4), 131.5 (C-5), 173.4 (C-1). IR: ν_{max}(film)/cm^{-1}; 2956, 2925, 2856, 1737, 1466, 1353, 1239, 1151, 1066, and 724. HRMS (ESI$^+$) found (MNa$^+$): 305.2444 $C_{18}H_{34}NaO_2$ requires 305.2451.

(2*Z*)-Nonenyl formate (9). To a stirred solution of formic acid (51 mg, 1.11 mmol) in dry DCM (5 mL), a solution of (2*Z*)-nonen-1-ol (174 mg, 1.22 mmol) in dry DCM (4 mL) was added. This was followed by the addition of a solution DMAP (48 mg, 0.39 mmol) in dry DCM (1 mL) and a solution of DCC (455 mg, 2.21 mmol) in dry DCM (4 mL). The resulting four component mixture was stirred overnight. Upon completion as monitored by TLC, the dicyclohexylurea precipitate was filtered off and the filtrate was washed with 1M HCl (15 mL × 2), a saturated solution of $NaHCO_3$ (15 mL) then dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude product was purified by column chromatography (silica gel, pentane: DCM gradient) to give (2*Z*)-nonenyl formate **(9)** (120 mg, 0.70 mmol, 64% yield, isomeric purity 97% by GC) as a clear colorless oil. δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.89 (3H, t, J = 7.0 Hz, H-9′), 1.27-1.57 (8H, m, H-5′, H-6′, H-7′, H-8′), 2.11 (2H, dt, J = 7.3 and J = 7.4 Hz, H-4′), 4.72 (2H, d, J = 6.9 Hz, H-1′), 5.51-5.58 (1H, m, H-2′), 5.65-5.72 (1H, m, H-3′), 8.07 (1H, s, H-1). δ_C (100 MHz; $CDCl_3$) 14.1 (C-9′), 22.6 (C-8′), 27.5 (C-4′), 28.9 (C-5′), 29.3 (C-6′), 31.7 (C-7′), 59.8 (C-1′), 122.6 (C-2′), 136.3 (C-3′), 161.0 (C-1). IR: ν_{max}(film)/cm^{-1}; 2926, 2857, 2120, 1725, 1460, 1378, 1275, 1156, 893 and 725. HRMS (ESI$^+$) found (MNa$^+$): 193.1200 $C_{10}H_{18}NaO_2$ requires 193.1199.

(2*Z*)-Nonenyl nonanoate (10). To a stirred solution of nonanoic acid (159 mg, 1.00 mmol) in dry DCM (5 mL), a solution of (2*Z*)-nonen-1-ol (159 mg, 1.12 mmol) in dry DCM (4 mL)

was added. This was followed by the addition of a solution DMAP (44 mg, 0.36 mmol) in dry DCM (1 mL) and a solution of DCC (413 mg, 2.00 mmol) in dry DCM (4 mL). The resulting four component mixture was stirred overnight. Upon completion as monitored by TLC, the dicyclohexylurea precipitate was filtered off and the filtrate was washed with 1M HCl (15 mL × 2), a saturated solution of $NaHCO_3$ (15 mL) then dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude product was purified by column chromatography (silica gel, DCM) to give (2*Z*)-nonenyl nonanoate **(10)** (195 mg, 0.69 mmol, 69% yield, isomeric purity 98% by GC) as a clear colorless oil. δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.86-0.90 (6H, m, C-9, C-9′), 1.27-1.38 (18H, m, H-4, H-5, H-6, H-7, H-8, H-5′, H-6′, H-7′, H-8′), 1.58-1.66 (2H, m, H-3), 2.10 (2H, dt, J = 7.2 and J = 7.5 Hz, H-4′), 2.30 (2H, t, J = 7.6 Hz, H-2), 4.62 (2H, d, J = 6.8 Hz, H-1′), 5.49-5.56 (1H, m, H-2′), 5.61-5.67 (1H, m, H-3′). δ_C (100 MHz; $CDCl_3$) 14.1 (C-9, C-9′), 22.6, 22.7 (C-8, C-8′), 25.0 (C-3), 27.6 (C-4′), 28.9, 29.1, 29.2, 29.2, 29.4 (C-4, C-5, C-6, C-5′, C-6′), 31.7, 31.8 (C-7, C-7′), 34.4 (C-2), 60.2 (C-1′), 123.4 (C-2′), 135.5 (C-3′), 173.8 (C-1). IR: ν_{max}(film)/cm^{-1}; 2960, 2924, 2856, 1737, 1460, 1378, 1161, 1109, 968, and 723. HRMS (ESI^+) found (MNa^+):305.2452 $C_{18}H_{34}NaO_2$ requires 305.2451.

Di-(2*Z*)-nonenyl carbonoate (11). To a stirred solution of (2*Z*)-nonen-1-ol (1.76 g, 12.4 mmol) in dry pyridine (4 mL) and dry THF (30 mL), a solution of triphosgene (642 mg, 2.16 mmol) in dry THF was added dropwise over 2 h. The solution was then stirred at room temperature for a further 4 h, after which, the solvent was removed *in vacuo*. The crude product was purified by column chromatography (silica gel, hexane: ethyl acetate gradient) to give di (2*Z*)-nonenyl carbonoate **(11)** (321 mg, 1.03 mmol, 48% yield, isomeric purity 93% by GC) as a clear colorless oil. δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.88 (6H, t, J = 7.1 Hz, H-9′, H-9″), 1.27-1.38 (16H, m, H-5′, H-6′, H-7′, H-8′, H-5″, H-6″, H-7″, H-8″), 2.11 (4H, dt, J = 7.1 and J = 7.5 Hz, H-4′ and H-4″), 4.68 (4H, d, J = 6.8 Hz, H-1′, H-1″), 5.52-5.59 (2H, m, H-2′, H-2″), 5.63-5.70 (2H, m, H-3′, H-3″). δ_C (100 MHz; $CDCl_3$) 14.1 (C-9′), 14,1 (C-9″), 22.6,

22.7 (C-8′, C-8″), 27.6 (C-4′, C-4″), 28.9, 29.4 (C-5′, C-6′, C-5″, C-6″), 31.6, 31.7 (C-7′, C-7″), 63.7 (C-1′, C-1″), 122.7 (C-2′, C-2″), 136.0 (C-3′, C-3″), 155.3 (C-1). IR: ν_{max}(film)/cm^{-1}; 2957, 2925, 2856, 1744, 1459, 1372, 1243, 941, 792, and 724. HRMS (ESI$^+$) found (MNa$^+$): 333.2403 $C_{19}H_{34}NaO_3$ requires 333.2400.

Insects. Raspberry bud moth larvae were collected from the canes and buds of wild blackberry plants in Chaney's Forest (43°25'52.8"S 172°39'59.2"E) Christchurch, New Zealand. Larvae were maintained on fresh blackberry leaves inside a mesh cage, while old leaves were provided for pupation. Guava moth larvae were collected from infested feijoa fruit from various locations in Auckland. Larvae were maintained on the feijoa fruit within a vented container lined with vermiculite for pupation. Pupae of both species were individually stored in humidified 30 mL plastic containers at 20 – 24 °C until emergence.

Electroantennogram recording (EAG). Antennal depolarisations of guava moth and raspberry bud moth were recorded in response to synthesis products using a Syntech IDAC-4 recording unit (Okenfels Syntech, GmbH, Kirchzarten, Germany). Healthy 1 – 6 day old virgin males were anaesthetised under CO_2, the antenna was excised adjacent to the scape, and the tip of the terminal segment was removed. The freshly excised antenna was mounted between two silver-silver chloride electrodes contained within saline filled glass capillaries. The antennal preparation was then placed in a charcoal filtered, humidified airstream with a flow rate of 600 mL/min. One mL solutions of synthesis products were prepared in DCM to give the desired amount of compound (1 ng, 10 ng, 100 ng, 1 µg, 10 µg, or 100 µg) in a 10 µL aliquot. A 10 µL aliquot of each solution was then added to a separate piece of filter paper (Whatman No.1, USA) with a surface area of approximately 1 cm^2 (2 cm × 0.5 cm). The filter paper with the test compound was left inside a fume hood for 5 min to allow the DCM to evaporate off. Each piece of filter paper containing a test compound was then transferred to

an individual Pasteur pipette to make an odour cartridge for testing on the antenna. The tip of the odour cartridge was then inserted into a small hole in the main airstream tube approximately 20 cm upwind from the antennal preparation. A stimulus controller (CS-55, Okenfels Syntech, GmbH, Kirchzarten, Germany) was then used to puff a 0.1 s pulse of air from the cartridge into the main airstream. Compounds were tested in a randomised order allowing at least 30 s between each puff for the antenna to stabilise. The maximum amplitude of the antenna depolarisation was recorded for each compound and dose using the Syntech IDAC-4 recording unit and Syntech EAG Pro software. Separate statistical analyses were run for each moth species. Individual antennal depolarization measurements for both raspberry bud moth and guava moth recordings were transformed by Log_{10} (μV+1) to stabilize variance and the transformed data were analysed by one-way ANOVA. Treatments were compared using Tukey's pairwise comparisons (P<0.05).

Single sensillum recording (SSR). Individual adult males of both guava moth and raspberry bud moth were anaesthetised under CO_2 before careful mounting on a Plasticine© block. Each moth was restrained using small copper wires. The restrained moth was then positioned in a charcoal filtered humidified airstream, ready for odour stimulation. The compounds for testing were prepared in the same manner as those for the EAG testing above. Once in the humidified airstream, a reference electrode was inserted into the soft membranous region separating segments of the abdomen of the moth. The reference electrode consisted of a silver-silver chloride wire housed in a pulled glass capillary (tip diameter < 10 μm) containing saline solution. The recording electrode was a chemically sharpened tungsten electrode (tip diameter < 0.1μm). The tungsten electrode was inserted into an olfactory sensillum in the antenna of the restrained moth using micromanipulators (MP-225, Sutter Instruments, USA) under a stereo microscope (Leica, Germany). Signals from individual sensillum were recorded on a Syntech IDAC-4 recording unit with a sampling rate of 12,000

signals per second. A stable contact between the tungsten electrode and the sensillum was indicated by the spontaneous firing of action potentials. Once a stable contact between the sensillum and tungsten electrode had been made a mixture of all the compounds to be tested was puffed over the antenna in the same manner as the EAG samples above. If the mixture elicited any electrophysiological response, all compounds were then tested individually on the connected sensillum. When testing the individual compounds at least 30 s was given between stimulus puffs for the sensilla to recover. The responsiveness of the sensilla was measured by the change in the number of action potentials before and after stimulation using the Syntech IDAC-4 recording unit and Syntech Autospike 32 software. Separate statistical analyses were run for each moth species. Untransformed spikes per second data measurements for both raspberry bud moth and guava moth from SSR recordings were analysed by one-way ANOVA. Treatments were compared using Tukey's pairwise comparisons ($P < 0.05$).

Field trapping trials. Pheromone and analogue dispensers were prepared using red rubber septa (West Pharmaceutical Services, Australia). The desired compound/s were added to the septa in a 100 µL volume of DCM. The DCM was allowed to evaporate off in a fume hood, then the septa were sealed in foil pouches and stored at -20 °C until use. Each treatment consisted of the relevant dispenser type on a white sticky base inside a red plastic delta trap (Etec Crop Solutions, Auckland, New Zealand).

Eight treatments were prepared for the raspberry bud moth using the optimum 300 µg dose reported by Foster and Thomas[4]: 1) blank (DCM only), 2) 300 µg (7Z)-nonadecen-11-one **(5)**, 3) 300 µg (2*Z*)-nonenyl nonanoate **(10)**, 4) 300 µg (4*Z*)-heptyl undecenoate **(8)**, 5) 300 µg (7*Z*)-nonadecen-11-one **(5)** plus 300 µg (2*Z*)-nonenyl nonanoate **(10)**, 6) 300 µg (7*Z*)-nonadecen-11-one **(5)** plus 300 µg (4*Z*)-heptyl undecenoate **(8)**, 7) 300 µg (7*Z*)-nonadecen-

11-one **(5)** plus 3 mg (2*Z*)-nonenyl nonanoate **(10)**, and 8) 300 µg (7*Z*)-nonadecen-11-one **(5)** plus 3 mg (4*Z*)-heptyl undecenoate **(8)**. These treatments were tested at four different sites within Chaney's Forest, (43°25'52.8"S 172°39'59.2"E) Christchurch, New Zealand over a two week period between 8 January and 22 January 2020. Each site consisted of a continuous blackberry transect at least 250 m long, with treatments randomly placed along the transect at 25 m intervals. Each transect was separated by at least 100 m. Trap bases were replaced weekly, lures were not replaced.

For the guava moth, eight treatments were also prepared in a similar manner where the 300 µg of (7Z)-nonadecen-11-one **(5)** above was replaced with the recommended 1 mg of the four component guava moth pheromone mix[5]: 650 µg of (7*Z*)-tricosene, 235 µg of (7*Z*)-octadecen-11-one, 15 µg of (7*Z*)-nonadecen-11-one **(5)** and 100 µg (7*Z*)-tricosen-11-one. The analogues were used at doses of 1 mg and 10 mg to keep the same ratios of 1:1 and 1:10 used above for the raspberry bud moth. For the guava moth, treatments were put out in a commercial feijoa orchard (36°56'04.3"S 174°36'30.9"E) Auckland, New Zealand, in a randomised block design 25 m apart, with five replicates of each treatment type dispersed throughout the orchard. The trial ran over a three week period between 10 February and 02 March 2020. Trap bases were replaced weekly, and lures were not replaced. The longer sampling period was used for the guava moth trial because of lower moth population and hence trap catch.

Separate statistical analyses were run for each moth species. During statistical analyses of the trapping trials, treatments that had a mean catch of zero and hence zero variance were omitted from statistical analyses to reduce the skewing of the data.[25] Testing for a difference between the pheromone and the empty unbaited control traps was conducted using a non-parametric test (Kruskal –Wallis) before the zero catch data were omitted. Individual trap catch data for

both raspberry bud moth and guava moth were transformed by Log_{10} (catch+1) after testing for normality to stabilize variance and the transformed data were analysed by one-way ANOVA. Treatments were compared using Tukey's pairwise comparisons ($P < 0.05$).

Statistical analysis. Homogeneity of variance was checked before analysis of data was performed. Where necessary, data were transformed to stabilize the variance. Details of the analysis conditions are outlined above for each set of experiments. All statistical calculations were performed using Minitab 18.

RESULTS AND DISCUSSION

Synthesis. Preparation of the pheromone component (7*Z*)-nondecen-11-one **(5)** (Scheme 1), was achieved following a route similar to that of Yang et al for the peach fruit moth pheromone.[26] Starting with the readily available 2,3-dihydrofuran, acid catalyzed hydration was carried out. Initial attempts using DCM reported by Yang et al. proved unsuccessful, so the more traditional aqueous approach of Kodato et al. was followed.[27] This method proved more reliable, and gave a satisfactory 55% yield of 2-hydroxytetrahydrofuran **(1)**, although purification of the product was more challenging, requiring multiple solvent washes to isolate the product. Next, was the alkene-forming Wittig reaction, where use of a non-stabilized ylide and Li-salt free conditions were chosen to favor the *Z*-alkene product.[28] The reaction proceeded well giving the (4*Z*)-undecen-1-ol **(2)** in 44% yield, with good isomeric purity. Dess-Martin oxidation of primary alcohol **(2)** afforded the corresponding aldehyde, (4*Z*)-undecenal **(3)**, with good yield (73%). The aldehyde **3** was then reacted with octylmagnesium bromide to give (7*Z*)-nonadecen-11-ol **(4)** in satisfactory yield (69%). Dess-Martin oxidation of the alcohol, provided the target compound (7*Z*)-nondecen-11-one **(5)** in good yield (89%) plus a small amount of the *E* isomer, which was able to be separated using silver nitrate impregnated silica gel. The small amount of isomerization observed during this synthetic

pathway turned out to be of benefit, as we had originally planned to synthesize a sample of the *E* isomer from the *Z* isomer using the method outlined by McGinn and Wheatley.[29] Whilst obtained in small amounts, (7*E*)-nondecen-11-one **(6)** was isolated in sufficient quality and quantity for both spectroscopic and electrophysiological testing.

The mild Steglich method was chosen for the ester syntheses (Scheme 2).[30] Synthesis of (4*Z*)-heptyl undecenoate **(8)** proceeded initially with silver oxide oxidation of the previously prepared (4*Z*)-undecenal **(3)** to the corresponding acid, (4*Z*)-undecenoic acid **(7)**, with a satisfactory yield (58%). The acid **7** was then subjected to reaction with DCC to form the *O*-acylisourea intermediate which was coupled with heptan-1-ol using DMAP as a catalyst, to give the target ester, (4*Z*)-heptyl undecenoate **(8)** in good yield (73%). Similarly, (2*Z*)-nonenyl formate **(9)** was prepared in 64% yield from the reaction of formic acid and (2*Z*)-nonen-1-ol, again using Steglich conditions. The (2*Z*)-nonenyl nonanoate **(10)**, was likewise prepared from nonanoic acid and (2*Z*)-nonen-1-ol in good yield (69%).

The carbonate **11** analogue was prepared via the reaction of (2*Z*)-nonen-1-ol with triphosgene, using pyridine as the base (Scheme 3).[31] This gave the di (2*Z*)-nonenyl carbonoate **(11)** in reasonable yield (48%), although the isomeric purity was only 93%. Due to inactivity of the carbonate with the moths, no attempts were made to improve the yield of this reaction or the isomeric purity of the product.

EAG testing. Electroantennogram testing began with dose response testing of both moth species to the pheromone component (7*Z*)-nondecen-11-one **(5)** (Figure 3). The guava moth appeared to be more sensitive, exhibiting significant EAG responses to the puff from the 100 ng cartridge ($F_{6,63} = 34.65$, $P < 0.001$). On the other hand, the raspberry bud moth started eliciting significant EAG responses at the 1 μg cartridge loading ($F_{6,35} = 36.23$, $P < 0.001$). Both species showed no difference in their EAG responses between the two highest doses of

(7*Z*)-nondecen-11-one **(5)**, 10 µg and 100 µg ($P > 0.05$). The somewhat higher sensitivity of the guava moth was unexpected since (7*Z*)-nondecen-11-one **(5)** alone is barely attractive to guava moth[5] yet is the principal component of the raspberry bud moth pheromone.[4] This sensitivity can perhaps be explained by the low percentage of (7*Z*)-nondecen-11-one **(5)** in the guava moth pheromone blend. It may be that there are specialized olfactory receptor neurons (ORN) for each chain length variant of the (7*Z*)-alken-11-ones, yet the work of Suckling et al (2013) showed there is a degree of plasticity in the pheromone receptors of guava moth to these (7*Z*)-alken-11-ones and were unable to tell if the 18 carbon and 19 carbon pheromone compounds used different ORNs.[8] Based on these results we chose a cartridge loading of 10 µg for screening the analogues for antennal activity.

Initial EAG testing of the analogues (Figure 4) showed that two of the esters, (2*Z*)-nonenyl nonanoate **(10)** and (4*Z*)-heptyl undecenoate **(8)** elicited significant EAG responses from raspberry bud moth compared with the DCM control puffs ($F_{6,35} = 24.05$, $P < 0.001$). Guava moth on the other hand, only showed significant responses to (4*Z*)-heptyl undecenoate **(8)** ($F_{6,35} = 13.01$, $P < 0.001$). Neither moth species showed a response to the geometric isomer (7*E*)-nonadecen-11-one **(6)**, the formate analogue **9** or the carbonate **11** ($P > 0.05$). The complete lack of response to (7*E*)-nonadecen-11-one **(6)** was a little surprising since it has been shown in numerous moth species that the related geometric isomer can be antagonistic,[32] even at very low levels.[33] It also suggests that these species are not using the geometric isomers to achieve sexual isolation from related species.[32,33] The lack of response from the (2*Z*)-nonenyl formate **(9)** is also informative, since the formate **9** with its greater volatility compared with the other analogues, would have been experienced at a much higher real dose on the antenna. This especially relates to the significant EAG activity induced by (2*Z*)-nonenyl nonanoate **(10)**, where the -H of the carbonyl in the formate **9** is replaced by the $-C_8H_{17}$ hydrocarbon tail. This suggests that the saturated hydrocarbon tail is important for the

fit of the pheromone molecule within the receptor protein in the ORN. Accordingly, only (2*Z*)-nonenyl nonanoate **(10)** and (4*Z*)-heptyl undecenoate **(8)** were taken forward for dose response testing and SSR testing.

Dose response testing of the two EAG active analogues showed similar responses for both moth species (Figure 5). Neither analogue was consistently detected at the cartridge loading of 1 µg, meaning the raspberry bud moth antennae were about 10 times less sensitive with the analogues, while the guava moth antennae were approximately 100 times less sensitive than to the pheromone component. Responses to the highest loading of each analogue, 100 µg, were not significantly different from the moth responses to 10 µg of the pheromone component (7*Z*)-nondecen-11-one **(5)** ($P > 0.05$). At the 10 µg loading of each analogue, the guava moth showed no difference in response from that of the pheromone component ($P > 0.05$). This was different to the original screening of analogues where the (2*Z*)-nonenyl nonanoate **(10)** was significantly different from the pheromone component for the guava moth. In the dose response trial, the increase in replicates (n = 10 compared with n = 6 in the screening) improved the sensitivity of the test showing a significant difference between the control, the 10 µg loading of (2*Z*)-nonenyl nonanoate **(10)** and the pheromone ($F_{13,126} = 30.79$, $P < 0.001$). The raspberry bud moth on the other hand, gave similar responses to those seen in the initial screening tests at the 10 µg loading of analogues with significant differences between the control and the 10 µg loadings of both analogues ($F_{13,70} = 28.23$, $P < 0.001$).

SSR testing. Single sensillum recording showed similar results to the EAG dose response testing. The pheromone component (7*Z*)-nondecen-11-one **(5)** and the 100 µg dose of (4*Z*)-heptyl undecenoate **(8)** elicited significant responses from the antennal ORNs in both species (raspberry bud moth $F_{5,36} = 9.91$, $P < 0.001$, guava moth $F_{5,60} = 17.18$, $P < 0.001$) (Figure 6).

For the guava moth the pheromone component elicited a mean of 139 ± 19 spikes sec^{-1} (± SEM) while the 100 µg dose of (4*Z*)-heptyl undecenoate **(8)** elicited a mean of 82 ± 15 spikes sec^{-1} (± SEM). The other treatments gave intermittent responses, sometimes causing the ORN to fire (Figure 7), while other times they did not respond at all. Only the pheromone component (7*Z*)-nondecen-11-one **(5)** and the 100 µg dose of (4*Z*)-heptyl undecenoate **(8)** consistently triggered responses from all the sensilla tested. The raspberry bud moth responded similarly. Here the pheromone component elicited a mean of 114 ± 25 spikes sec^{-1} (± SEM) while the 100 µg dose of (4*Z*)-heptyl undecenoate **(8)** elicited a mean of 86 ± 18 spikes sec^{-1} (± SEM). Again, the other treatments gave intermittent responses, sometimes causing the ORN to fire (Figure 8), while at other times they did not and hence were not significantly different from the control. For both species only one type of spikes was observed in the SSR testing so it was unclear whether or not more than one ORN was present in the sensilla recorded from. This intermittent ORN firing may have been due to different ORNs for each component of the pheromone on different sensilla. This may be especially true for the guava moth since its pheromone blend consists of at least three (7*Z*)-alken-11-ones. Concurrently, the shape of each analogue and its fit within the receptor protein will be determining the degree of response.

The shift of the ether oxygen position between the two ester analogues showed an effect on the ORNs of both species. Both moth species responded most strongly to the (4*Z*)-heptyl undecenoate **(8)** out of the analogues tested. This indicates that the original pheromone configuration between the *cis* double bond and carbonyl is the most important feature of the molecule with regard to its fit within the receptor protein. When the ether oxygen of the ester analogue was contained between the *cis* double bond and carbonyl as in the (2*Z*)-nonenyl nonanoate **(10)**, the response of both moth species was not significantly different to that of the solvent puff.

The test puff of the mixture of compounds to identify the active ORNs at the start of SSR testing did not inhibit responses to the individual compounds tested indicating that none of the compounds were binding irreversibly to the receptor proteins of either moth species.

Field testing. Trapping trials for raspberry bud moth recorded a total male moth catch of 1,362 across four replicates over two weeks. On the other hand, trapping trials for guava moth recorded a total male catch of only 308 moths across five replicates over three weeks. Both trials were hindered by patchy distribution of moths, while the guava moth trial was also affected by a low moth population, which reduced the statistical power of the analysis. A Kruskal-Wallis test was used to confirm that the pheromone and zero catch traps were indeed different for the guava moth ($P = 0.037$) before the zero catch treatments were omitted from the statistical calculations.

The pheromone traps for the raspberry bud moth had a mean catch of 148 ± 61 (± SEM) moths per trap while traps containing (2*Z*)-nonenyl nonanoate **(10)** or (4*Z*)-heptyl undecenoate **(8)** caught a total of zero moths. The zero catch here showed that neither analogue was attractive to the raspberry bud moth. Traps loaded with a 1:1 blend of (2*Z*)-nonenyl nonanoate **(10)** and pheromone had a mean catch of 63 ± 11 (± SEM) moths per trap while those loaded with a 1:1 blend of (4*Z*)-heptyl undecenoate **(8)** and pheromone had a mean catch of 63 ± 32 (± SEM) moths per trap. At the higher analogue dose of 10:1 the (2*Z*)-nonenyl nonanoate **(10)** and pheromone mix had a mean catch of 61 ± 26 (± SEM) moths per trap while the (4*Z*)-heptyl undecenoate **(8)** and pheromone mix had a mean catch of 6 ± 3 (± SEM) moths per trap. Only the 10:1 (4*Z*)-heptyl undecenoate **(8)** and pheromone mix catch per trap was significantly different from the mean pheromone catch per trap ($F_{4,15} = 5.48$, $P = 0.006$) (Figure 9).

453 The pheromone traps for the guava moth had a mean catch of 10 ± 4 (± SEM) moths per trap
454 while traps containing (2*Z*)-nonenyl nonanoate **(10)** or (4*Z*)-heptyl undecenoate **(8)** caught a
455 total of zero moths. The zero trap catch here was expected since the guava moth relies on a
456 four component blend for attraction.[5] Traps loaded with a 1:1 blend of (2*Z*)-nonenyl
457 nonanoate **(10)** and pheromone had a mean catch of 20 ± 11 (± SEM) moths per trap while
458 those loaded with a 1:1 blend of (4*Z*)-heptyl undecenoate **(8)** and pheromone had a mean
459 catch of 17 ± 8 (± SEM) moths per trap. At the higher analogue dose of 10:1 the (2*Z*)-
460 nonenyl nonanoate **(10)** and pheromone mix had a mean catch of 12 ± 7 (± SEM) moths per
461 trap while the (4*Z*)-heptyl undecenoate **(8)** and pheromone mix had a mean catch of 2 ± 1 (±
462 SEM) moths per trap. None of the treatments were significantly different from one another
463 ($F_{4,20} = 1.97$, $P = 0.138$) (Figure 9).

464 The trapping trials for the raspberry bud moth indicated that field behaviour aligned well with
465 the SSR testing, both showing that only the highest dose of (4*Z*)-heptyl undecenoate **(8)**
466 produced a significant result compared with control traps. The 10:1 ratio of (4*Z*)-heptyl
467 undecenoate **(8)** to the pheromone gave a reduction in trap catch of over 95% compared to the
468 pheromone alone, showing that the (4*Z*)-heptyl undecenoate **(8)** was having a strong
469 inhibitory effect on raspberry bud moth.

470 The guava moth showed similar results, with neither analogue alone showing any attraction.
471 We did expect an effect from the highest dose of the (4*Z*)-heptyl undecenoate **(8)** in
472 combination with the pheromone, yet its trap catch of two moths per trap was not
473 significantly different from the pheromone catch of 10 moths per trap. This may have been
474 due to the low overall trap catch of the trial failing to give sufficient sensitivity with
475 stochasticity at low density, or alternatively could have resulted from separate ORNs for each
476 component of the pheromone. If the latter is the case, then the receptors for the other (7*Z*)-

alken-11-ones of the guava moth pheromone may be receiving enough signal from those pheromone components for attraction. Or put another way, the (4*Z*)-heptyl undecenoate **(8)** may not be disrupting these other (7*Z*)-alken-11-one receptors as well as it is disrupting or binding to the (7*Z*)-nondecen-11-one **(5)** receptor.

The (4*Z*)-heptyl undecenoate **(8)** with its strong inhibitory effect on raspberry bud moth trap catch has potential as a mating disruption agent.[34,35] Demand for pesticide free fruit and more environmentally-friendly pest management techniques have seen mating disruption develop as a successful pest control tool based on pheromone technology.[36,37] Here the pheromone or analogue dispensers are placed throughout the orchard or crop, they are not sprayed directly on to the fruit like pesticide treatments, meaning the fruit has much lower residues from the pest management treatment. Mating disruption also has the added advantage of only targeting the pest species. It is hoped (4*Z*)-heptyl undecenoate **(8)** can now be investigated as a mating disruption tool for commercial berry fruit crops.

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607 **FIGURES**

608 **Legends**

609 Scheme 1. Synthesis of pheromone component (7*Z*)-nonadecen-11-one.

610 Scheme 2. Synthesis of ester analogues.

611 Scheme 3. Synthesis of carbonate analogue.

612 Figure 1. Pheromone components reported for carposinid moths.

613 Figure 2. Shared pheromone component and proposed analogue structures for guava moth
614 and raspberry bud moth.

615 Figure 3. Mean EAG responses (± SEM) of male guava moth (n = 10) and male raspberry
616 bud moth (n = 6) to varying doses of (7*Z*)-nonadecen-11-one. Separate statistical analyses
617 were run for each moth species. Bars within the species that do not have the same letter are
618 significantly different from each other (Tukey 95% confidence intervals).

619 Figure 4. Mean EAG responses (± SEM) of male guava moth (n = 6) and male raspberry bud
620 moth (n = 6) to 10 μg each of (7*Z*)-nonadecen-11-one, the four ester type analogues and the
621 geometric isomer, (7*E*)-nonadecen-11-one. Separate statistical analyses were run for each
622 moth species. Bars within the species that do not have the same letter are significantly
623 different from each other (Tukey 95% confidence intervals).

624 Figure 5. Mean EAG responses (± SEM) of male guava moth (n = 10) and male raspberry
625 bud moth (n = 6) to 10 μg of (*7*Z)-nonadecen-11-one and dose responses to (2Z)-nonenyl
626 nonanoate and (4Z)-heptyl undecenoate. Separate statistical analyses were run for each moth

627 species. Bars within the species that do not have the same letter are significantly different
628 from each other (Tukey 95% confidence intervals)

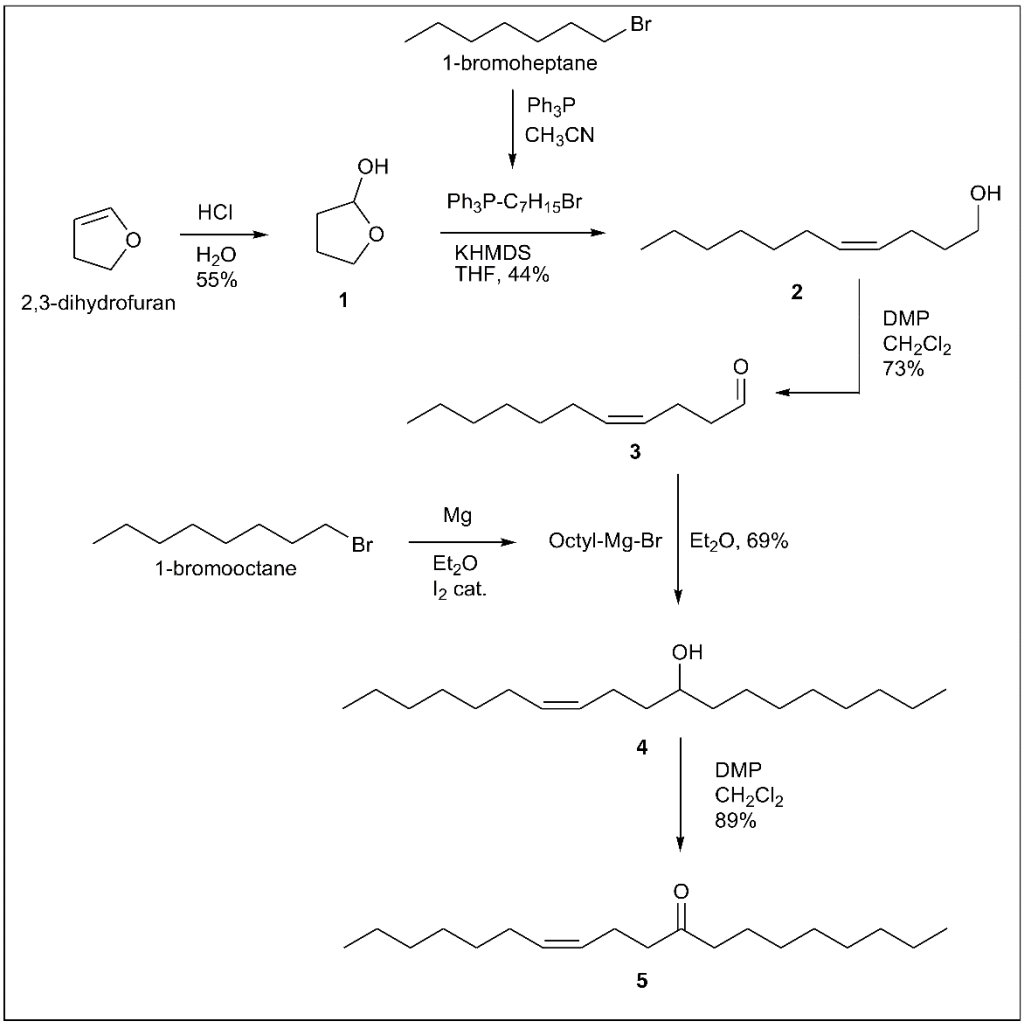
629 Figure 6. Mean number of spikes per second (± SEM) recorded from olfactory receptor
630 neurons (ORNs) of male guava moths (n = 11) and male raspberry bud moths (n = 7) to 10
631 µg of the pheromone component (7*Z*)-nonadecen-11-one and doses of (2*Z*)-nonenyl
632 nonanoate and (4*Z*)-heptyl undecenoate. Active ORNs were identified as those responding to
633 a mixture of the test compounds. Separate statistical analyses were run for each moth species.
634 Bars within the species that do not have the same letter are significantly different from each
635 other (Tukey 95% confidence intervals).

636 Figure 7. Example single sensillum action potentials of male guava moth to pheromone
637 component and analogues.

638 Figure 8. Example single sensillum action potentials of male raspberry bud moth to
639 pheromone component and analogues.

640 Figure 9. Mean catch per trap (± SEM) of guava moth males (total # males caught = 308) and
641 raspberry bud moth males (total # males caught = 1362) to sex pheromone and pheromone
642 analogues alone and in combination. '2*Z* + phero' = (2Z)-nonenyl nonanoate + the sex
643 pheromone while '4*Z* + phero' = (4Z)-heptyl undecenoate + the sex pheromone. Separate
644 statistical analyses were run for each moth species. Bars within the species that do not have
645 the same letter are significantly different from each other (Tukey 95% confidence intervals).
646 An * indicates a trap catch of zero for all traps of that treatment.

647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Br
Ph3P
CH3CN
2,3-dihydrofuran
HCl
H2O
55%
OH
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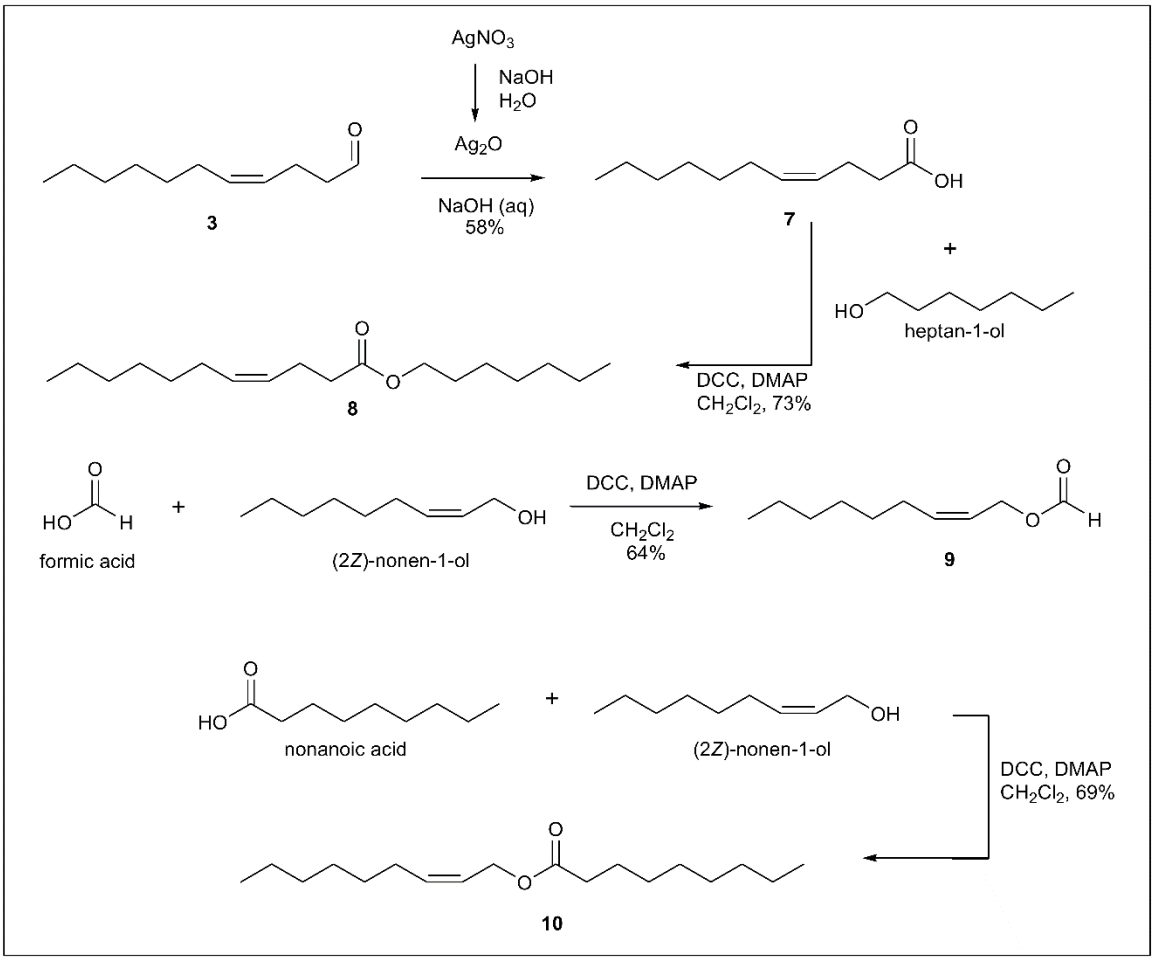
Ph3P-C7H15Br
KHMDS
THF, 44%
OH
2
DMP
CH2Cl2
73%
O
3
1-bromooctane
Br
Mg
Et2O
I2 cat.
Octyl-Mg-Br
Et2O, 69%
OH
4
DMP
CH2Cl2
89%
O
5

Scheme 1.



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652 Scheme 2.

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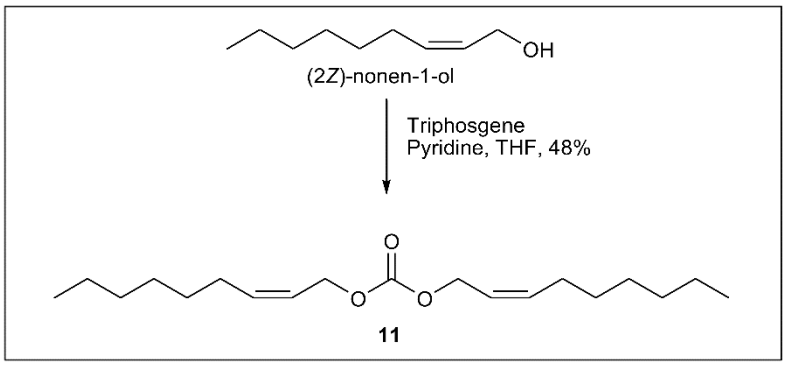

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656 Scheme 3.

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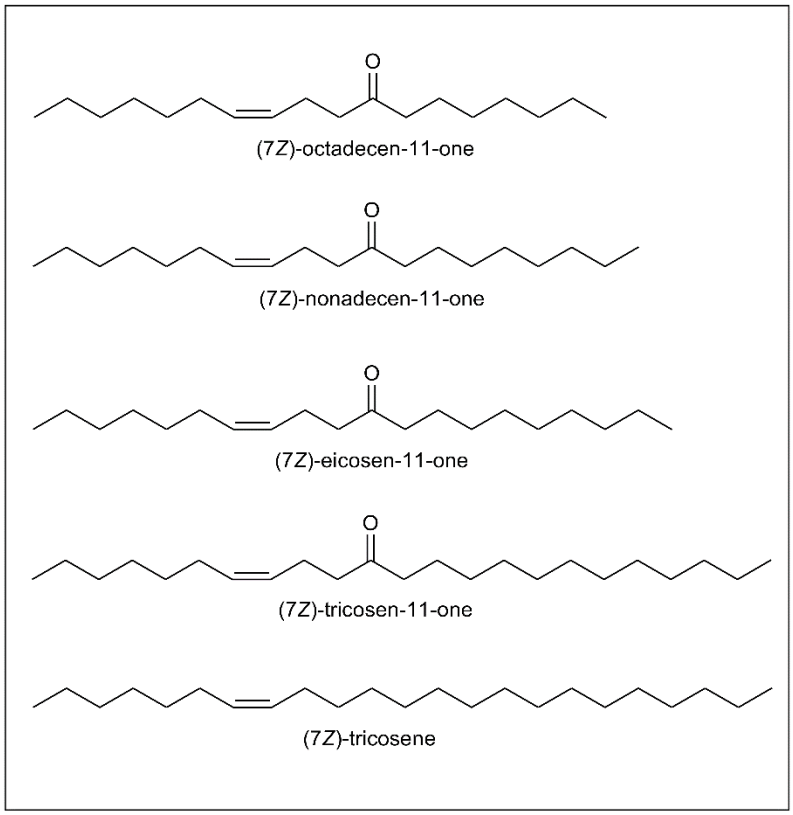

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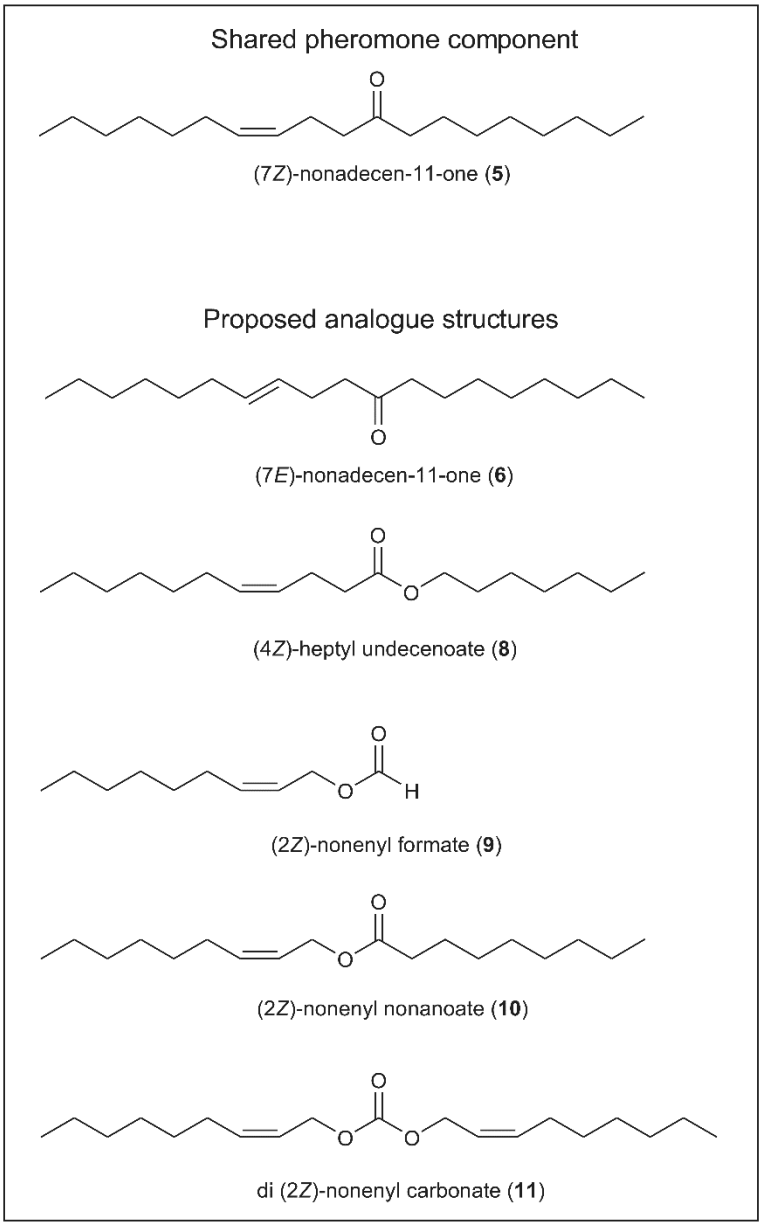

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661 Figure 2.

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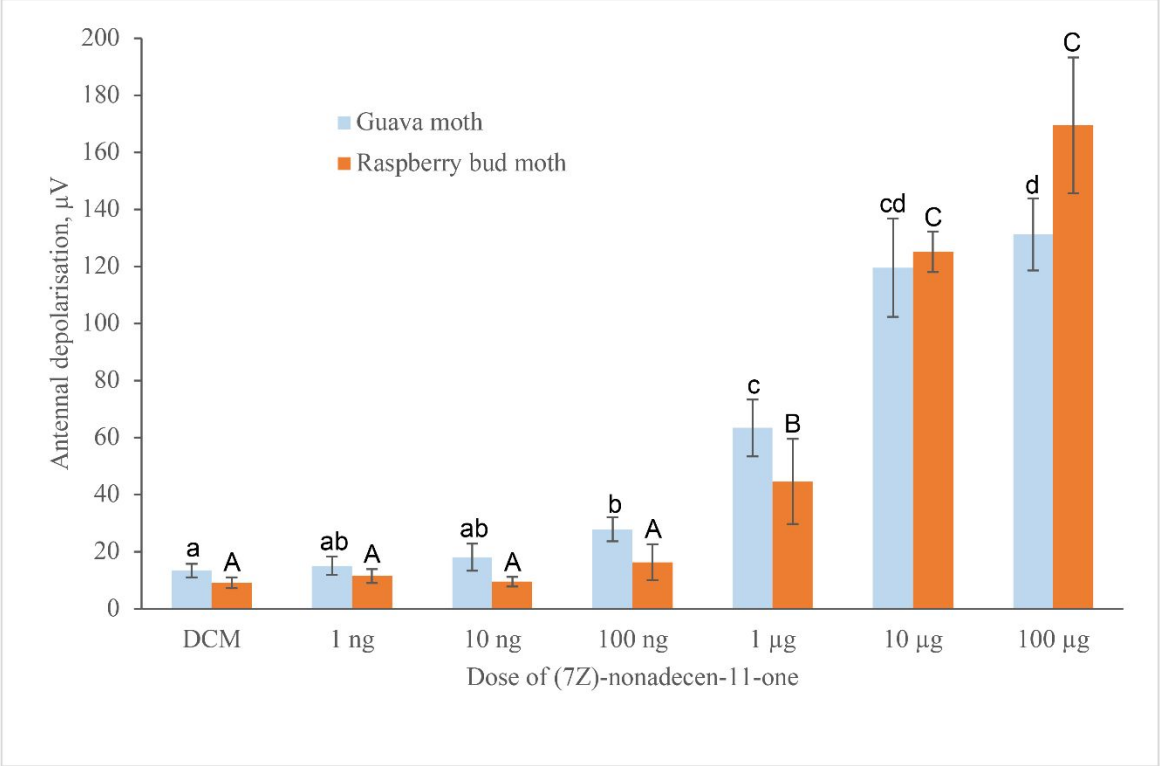

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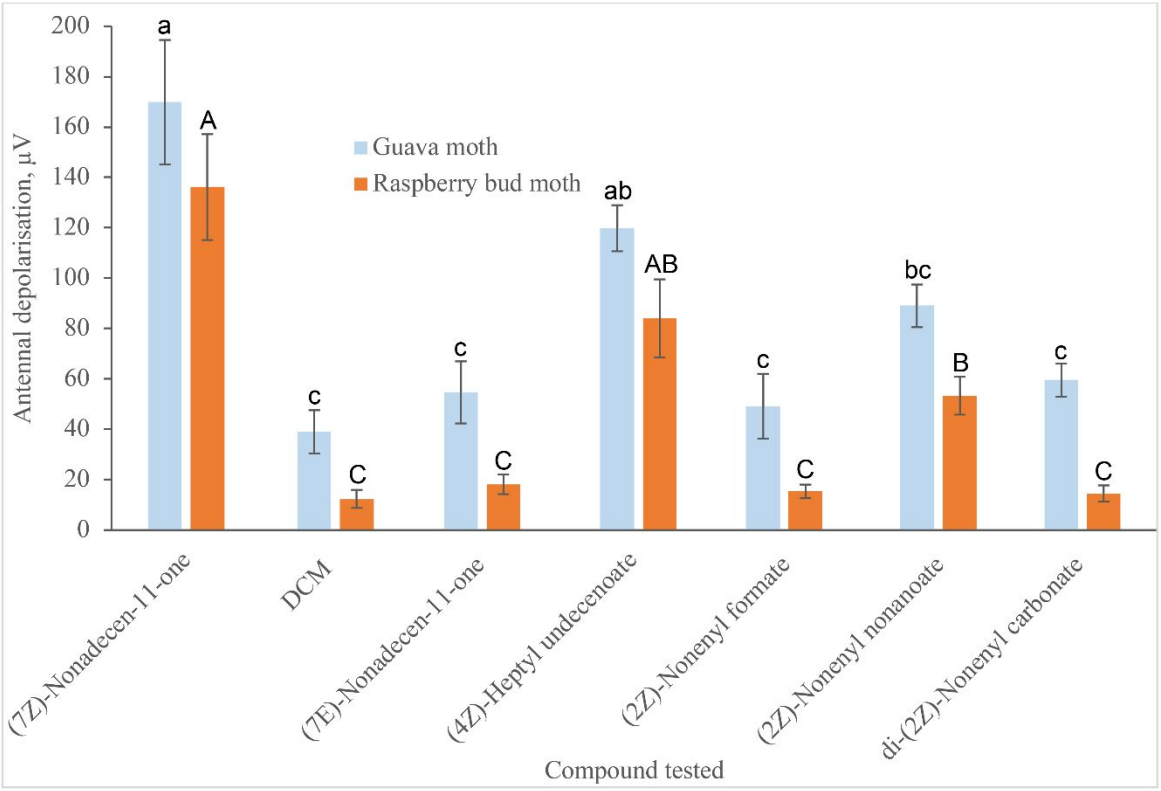
664 Figure 3.

665



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667 Figure 4.

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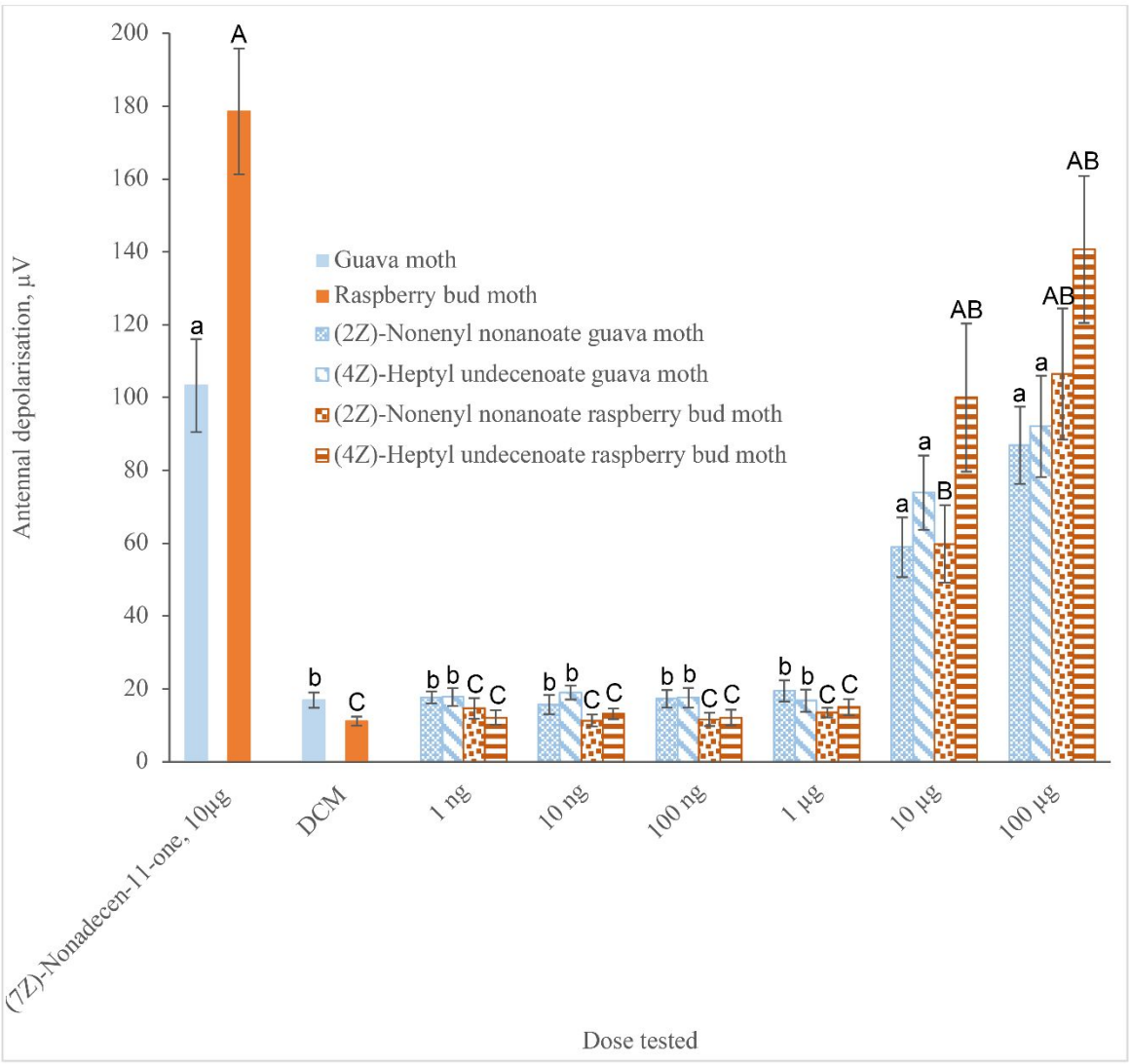

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670 Figure 5.

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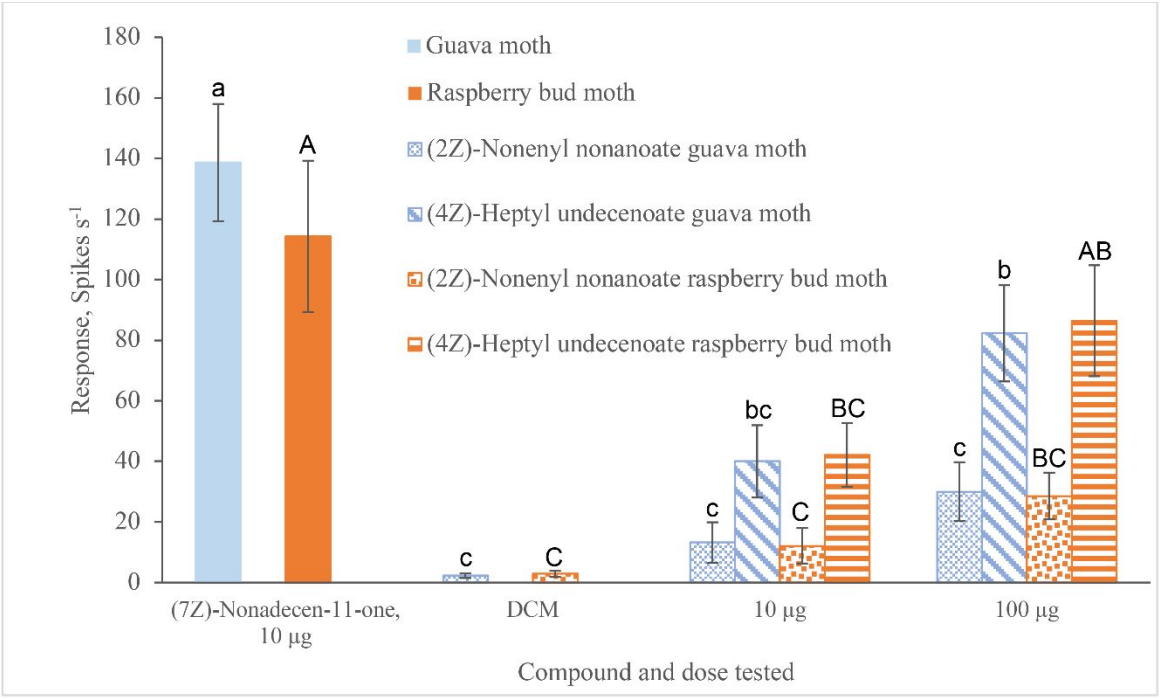

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673 Figure 6.

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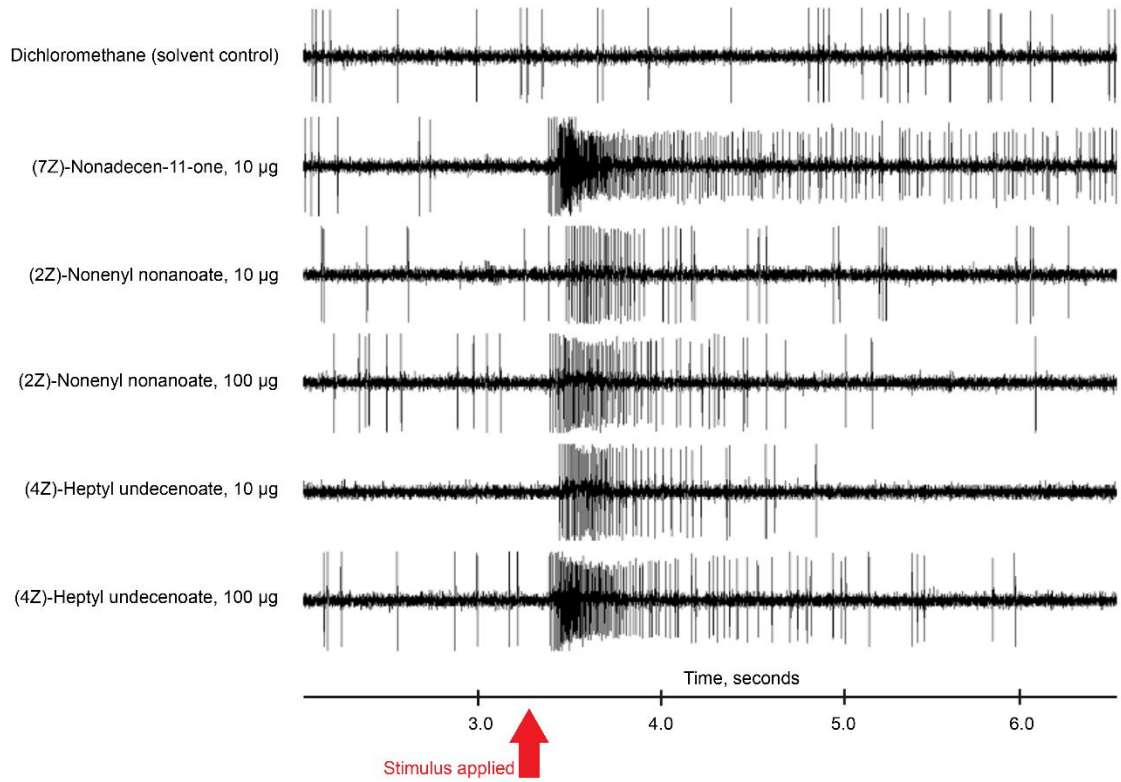

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676 Figure 7.

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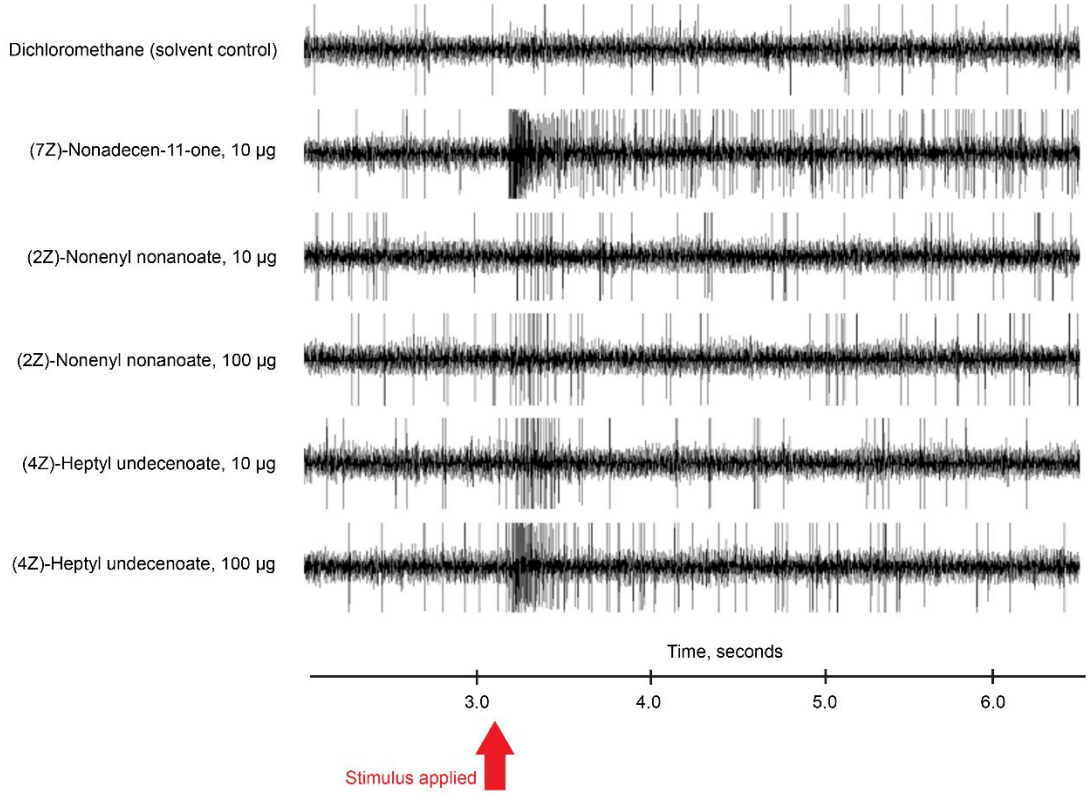

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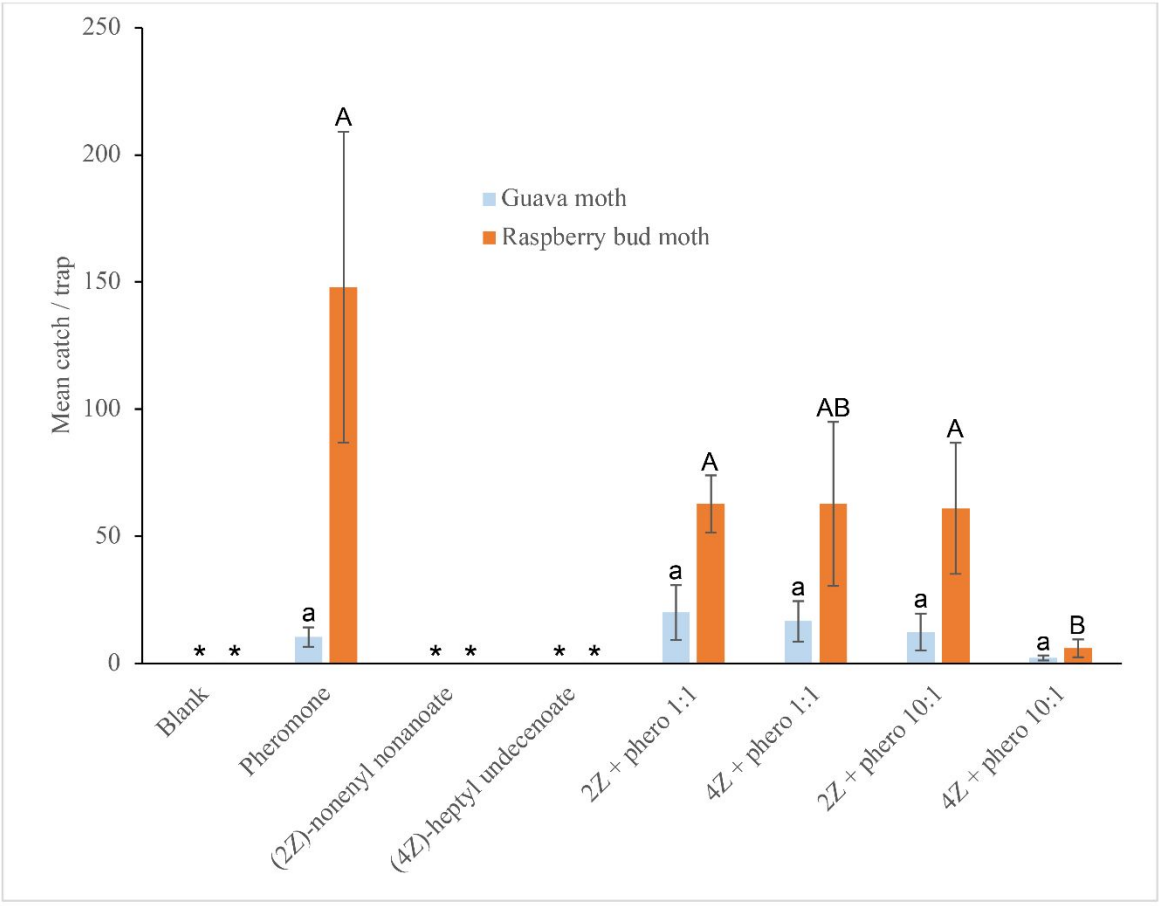

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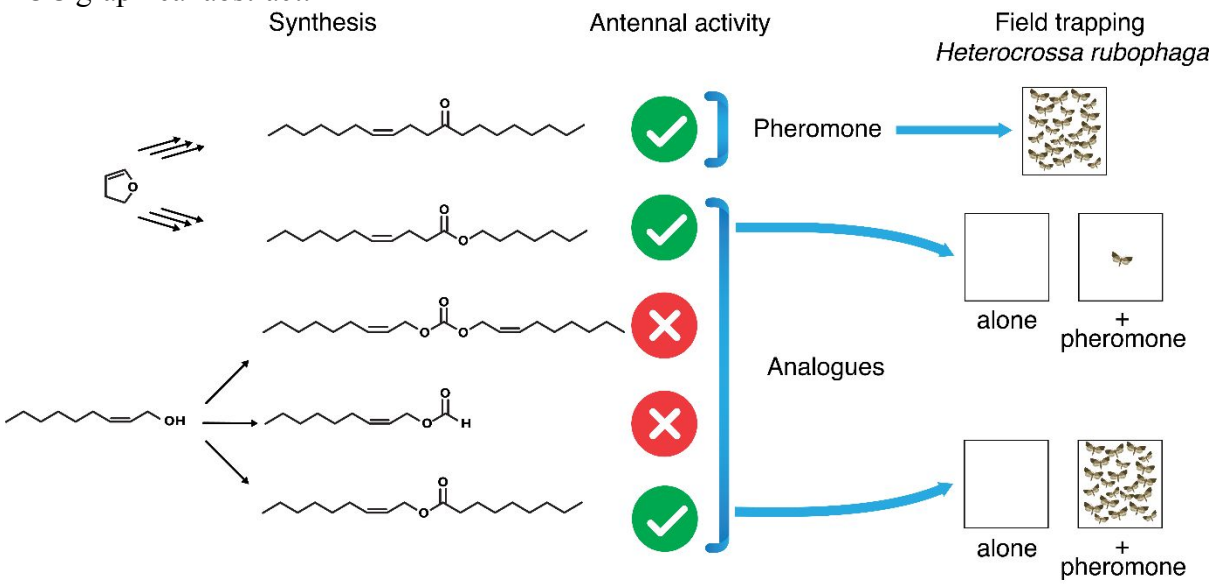
681 Figure 9.

682

683 TOC graphical abstract:



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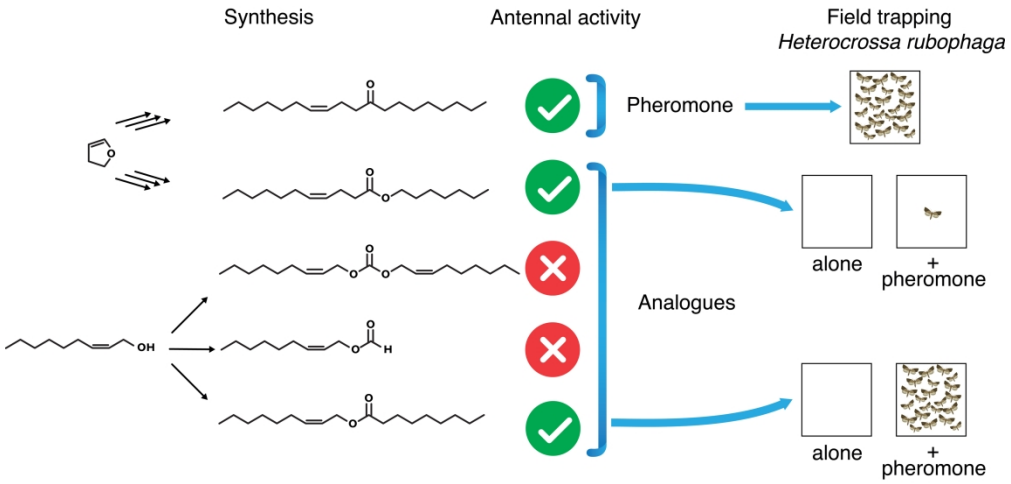

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