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Dialkoxybenzene and Dialkoxyallylbenzene Feeding and Oviposition Deterrents against the Cabbage Looper, *Trichoplusia ni*: Potential Insect Behavior Control Agents

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The antifeedant, oviposition deterrent, and toxic effects of individual dialkoxybenzene compounds/sets and of hydroxy- or alkoxy-substituted allylbenzenes, obtained through Claisen rearrangement of substituted allyloxybenzenes, were assessed against the cabbage looper, *Trichoplusia ni*, in laboratory bioassays. Most of the compounds/sets strongly deterred larval feeding, with some exhibiting mild toxic and oviposition deterrent effects as well. Some of the compounds/sets were more active than the commercial insect repellent, DEET (*N,N*-diethyl-*m*-toluamide), as both feeding and oviposition deterrents against the cabbage looper. On the basis of the obtained oviposition data a general hypothesis was proposed regarding the oviposition sites: one binding mode with the alkyl and allyl groups on the same side of the benzene ring resulted in deterrence, the other with alkyl and allyl groups on opposite sides of the benzene ring resulted in stimulation. The results suggest some structure−activity relationships useful in improving the efficacy of the compounds and designing new, nontoxic insect control agents for agriculture.

KEYWORDS: Dialkoxybenzene; DEET; feeding deterrence; toxicity; oviposition sites; cabbage looper; structure-activity; insect control agents

INTRODUCTION

For the past 40 years there has been an increased interest in the behavioral manipulation of insect pests for their management, as an alternative to broad-spectrum insecticides. Of particular interest are nontoxic compounds that show some selectivity toward a pest insect but not toward its natural enemies, pollinators, and the environment. Successful manipulation of pest behavior could provide protection of the resource (crop plant) through the use of stimuli that either enhance or inhibit a particular behavior and ultimately change its expression. The choice of a stimulus for behavioral manipulation is usually dependent upon a number of factors including accessibility, reproducibility, specificity, and practicality (*1*).

Various short- or long-range stimuli, involved in behavioral manipulation of insects, are perceived through contact chemoreceptors or olfactory receptors, respectively. These stimuli can either stimulate feeding or oviposition, keeping the insect at the host plant, or inhibit those behaviors, resulting in the insect abandoning the plant. Examples of feeding stimulants include carbohydrates, proteins, or fats (*2*) that are ubiquitous in plants, whereas oviposition stimulants can be highly species-specific. Feeding stimulants can be used in conjunction with toxins in "attract and kill" strategies (*2*), occasionally employed in crop protection. A deterrent can be applied to a host plant to prevent feeding or oviposition. Therefore, deterrents have potential value in crop protection, in combination with other strategies such as "attract and kill" (*3*).

Most natural plant defensive chemicals discourage insect herbivory, either by deterring feeding and oviposition or by impairing larval growth, rather than by killing insects outright. Insect feeding deterrents can be found among all the major classes of plant secondary metabolites: alkaloids, phenolics, and terpenoids (*4*). Especially well studied in this group are triterpenes such as the limonoids from neem (*Azadirachta indica*), chinaberry (*Melia azedarach*), and *Citrus* species and diterpenes, including the clerodanes and the abietanes (*5*). Apart from terpenes, another important class of compounds involved in the defense of plants against herbivores and pathogens, as well as in attracting pollinators, are the compounds often derived from aromatic amino acids, phenolics (*6*).

Phenolic compounds can be short-range (polyphenols) or long-range stimuli (phenylpropanoids) and are divided into hydrolyzable tannins (gallic acid esters of glucose and other sugars) and phenylpropanoid-derived conjugates such as lignins, flavonoids, and condensed tannins. The best studied polyphenols are the flavonoids including flavonols, flavones, catechins, flavanones, anthocyanidins, coumarins, and isoflavonoids (*7*, *8*). Phenylalanine-derived phenolics include flavonoids, *trans*-cinnamic acid and its derivatives, such as caffeic and ferulic acids, vanillin, eugenol, and anethole (*6*, *9*). Eugenol is a volatile member of the phenylpropanoids from essential oils of many spices, particularly

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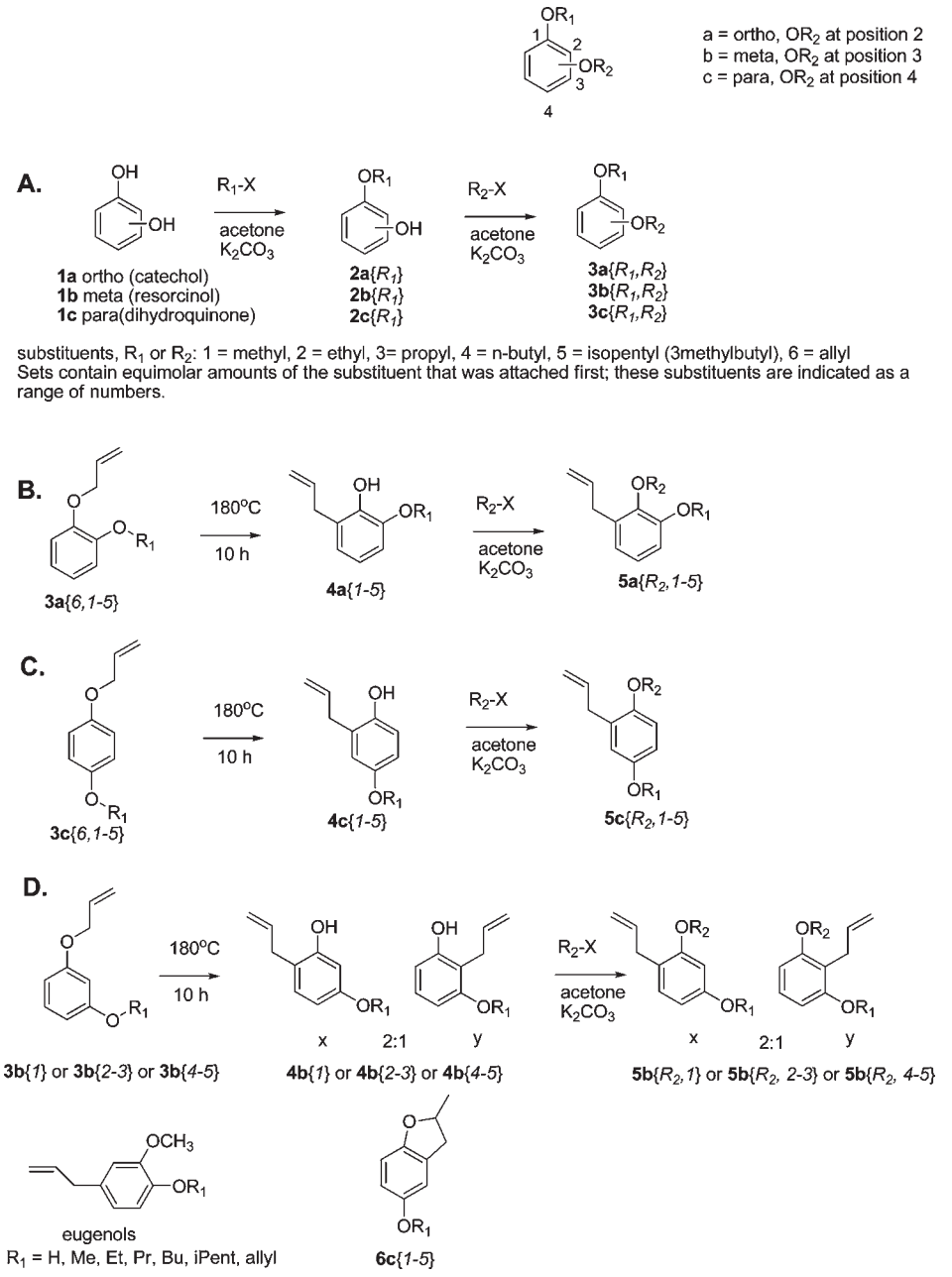


Figure 1. (**A**) Synthesis of dialkoxybenzenes from catechol (**1a**), resorcinol (**1b**), or dihydroquinone (**1c**). Details of the synthesis and analyses have been described previously (*17*). (**B**) Synthesis of Claisen rearranged products from 1-allyl-2-alkoxybenzenes. (**C**) Synthesis of Claisen rearranged products from 1-allyl-4-alkoxybenzene. (**D**) Synthesis of Claisen rearranged products from 1-allyl-3-alkoxybenzene.

clove (*9*). Cloves are useful in the home as moth deterrents (personal observation), and the main odorant from cloves, eugenol, is known to be perceived as a long-range stimulus by several lepidopterans (*10*). One problem with phenylpropanoids such as eugenol and compounds with a cinnamyl framework is that they can produce toxic metabolites after benzylic/allylic oxidation by certain cytochrome P450 enzymes (*9*).

Several polyphenolic compounds are also known for their toxic/insecticidal effects (*11*). Flavonoids isolated from *Annona squamosa* (*12*), *Ricinus communis* (*13*), and *Calotropis procera* (*14*) are toxic to the pulse beetle, *Callosobruchus chinensis*, and *R. communis* also caused oviposition deterrent and ovicidal effects in addition to toxicity. Larvicidal activity of lignans, leptostachyol acetate, and analogues from the roots of *Phryma leptostachya* have been reported against three mosquito species (*Culex pipiens pallens*, *Aedes aegypti*, and *Ocheratatos togoi*) (*15*).

The purpose of the present study was to assess the antifeedant, oviposition deterrent, and toxic effects of candidate compounds or compound sets including the individual candidate dialkoxybenzenes (**Figure 1A**) based on our previous structure−activity work (*16*) indicating that compounds with intermediate group sizes were the best lead compounds for oviposition and feeding deterrent effects. Furthermore, the presence of a free hydroxyl group as well as a methyl group served to reduce feeding deterrent effects in all series of compounds, and replacement of a methyl group with larger alkyl substituents increased the feeding deterrent effects (in most cases) and substituted allylbenzene sets generated by Claisen rearrangement of substituted allyloxybenzenes and subsequent alkylation (**Figure 1B**−**D**) (*17*). The cabbage looper, *Trichoplusia ni*, was chosen as a model insect for our study. The cabbage looper is one of the most destructive insect pests of vegetable crops. It feeds on a variety of crops including lettuce,

beet, pea, celery, tomato, crucifers, certain ornamentals, and weedy plants (*18*). Annual losses and the cost of control measures make the cabbage looper an economically important pest (*19*). Even though there are several natural enemies of cabbage looper, chemical control is recommended in most situations (*20*). Because *T. ni* has evolved resistance against many synthetic insecticides (*19*) and the microbial insecticide *Bacillus thuringiensis* (*21*), there is a need to develop new methods that could protect crops in integrated pest management systems.

Here we have chosen to investigate relatively nontoxic compounds that mimic naturally occurring bioactive odorants and tastants and that are relatively easily prepared from commodity chemicals. Because host plant detection is essential to the larval and adult stages of this moth species (*22*), consequently leading to crop damage, we target this chemical communication system with aromatic odorants that interfere with larval feeding or the oviposition behavior of adult moths, without causing acute toxic effects to the insect.

MATERIALS AND METHODS

Plant Material. Cabbage plants (*Brassica oleraceae* var. Stonehead) used in the bioassays were grown in plastic pots with a mixture of sandy loam soil and peat moss (4:1) in a greenhouse at the University of British Columbia (UBC), Vancouver, BC, Canada. Leaves used in the bioassays were collected from 5−6-week-old cabbage plants.

Test Insects. *T. ni* larvae and moths were obtained from a long-established colony (>50 generations) maintained on an artificial diet, Velvetbean Caterpillar Diet (Bio-Serv Inc., Frenchtown, NJ) in the insectary of UBC. It is therefore possible that our insects may respond differently from wild conspecifics. The diet was supplemented with finely ground alfalfa, to improve acceptability, and vitamins (Bio-Serv Inc.).

Test Compounds. Dialkoxybenzene compounds were synthesized from catechol (**1a**), resorcinol (**1b**), or dihydroxyquinone (**1c**) as shown in **Figure 1**. Synthesis of Claisen rearrangement products from 1-allyl-2-alkoxybenzenes (**B**), 1-allyl-4-alkoxybenzenes (**C**), and 1-allyl-3-alkoxybenzenes (**D**) are shown in **Figure 1** (*17*). Isomers *x* and *y* from the Claisen rearrangement of meta-substituted allyloxybenzenes were separated by flash chromatography on $AgNO_3$−silica as described below.

General Information about the Spectrometers and the Conditions Used To Determine ^{1}H and ^{13}C NMR Spectra. Commercial grade solvents were distilled under nitrogen prior to use with the following exceptions: dried THF was obtained from a MBRAUN LTS 350 solvent purification system, and HPLC grade acetone was used without further treatment. Reagents were used without further purification. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker 400 or 600 MHz spectrometers. GC was run on a Hewlett-Packard 5890 using an SPB column (Supelco, 30 m, 0.25 mm i.d., 0.25 μm film), programmed at 100 °C (5 min) and raised at 10 °C /min to 250 °C (4.0 min). The gas chromatographic data on the DB-5 column are reported as retention indices (RI). GC mass spectra were recorded on a Varian Saturn 2000 MS coupled to a CP 300 GC, equipped with an SPB-5 GC column (same type as above), programmed as above. Mass spectra were acquired in EI mode [2 μscans (0.55 s/scan), emission current (30 μamp), scanning single ion storage SIS (m/z 49−375)]. HRMS was recorded on a 6210 series time-of-flight LC-MS system.

Preparation of Compounds. The general procedures for the synthesis of test compounds for the present study have been described earlier (*17*). For the meta compounds, the Claisen rearrangement gave two isomers. For the alkoxy substituents we are using, the isomer in which the allyl group migrates to position 4 (isomer *x*) is slightly favored thermodynamically over the isomer in which the allyl group migrates to position 2 (isomer *y*) (*23*). Typical ratios of compounds *x*/*y* range from 2.3:1 to 1.2:1. The two isomers *x* and *y* were separated for selected cases of series **5b** (**Table 4**). Briefly, 1% (w/v) $AgNO_3$ was dissolved in water and silica gel was added to it, forming a thick slurry. The slurry dried overnight (120 °C), before being packed into the column. Care was taken not to expose the silver nitrate silica to light by wrapping the beaker with the slurry and later the column with aluminum foil. The silver−silica column was equilibrated with hexane/toluene 99:1, and the loaded compounds were eluted with 90:10 hexane/toluene. To monitor the separation, 1% $AgNO_3$ TLC plates were prepared by running the silver nitrate solution up the plates and drying them. The plates could be stained with anisaldehyde solution. Isomer *y* ran more quickly than *x*, and it was possible to obtain several fractions that contained pure *y*. However, *y* also tailed into the *x* peak, so that it was difficult to obtain fractions with 100% *x* by FCC. Alternatively, **5b**{*3,1*}*y* and **5b**{*3,1*}*x* as well as **5b**{*3,2*}*y* and **5b**{*3,2*}*x* could be separated by preparative TLC (100% hexanes) with multiple developments.

The more compact isomer *y* was more volatile than *x*, eluting usually 0.5−1 min earlier from the GC (DB-5 column). Also, in general, isomer *y* formed an M + 1 ion in the mass spectrum more readily and fragmented more extensively (for example, to the tropylium ion m/z 91) than isomer *x*.

Data for the individual compounds and ^{1}H NMR data of new, pure **3a**, **3b**, and **3c** compounds that have not been published previously (*17*) are given in the Supporting Information.

General Testing Procedure for the Bioassays. Initial screening for feeding deterrent effects was conducted at 50 μg/cm^2 in feeding deterrent choice bioassays. Compounds exhibiting >50% feeding deterrence at this concentration were subjected to further testing for oviposition deterrent effects and contact toxicity at 0.25% of the test substance. For compounds exhibiting >50% values for feeding deterrence, DC_{50} values (concentration causing 50% feeding deterrence compared with the control) were determined, on the basis of bioassays involving a minimum of four concentrations (<3.12−25 μg/cm^2).

Feeding Deterrent Bioassays. Leaf disk choice bioassays (*16*) were conducted to determine feeding deterrent effects of the synthetic compounds using freshly molted third-instar larvae starved for 4−5 h prior to each bioassay. Larvae were given the choice of feeding on two leaf disks, one treated with 10 μL of a solution of the test substance painted on each side and the other treated with a carrier solvent alone. The number of larvae was 25 per treatment. Bioassays were terminated when ∼50% of the control disk had been eaten (normally 3−5 h).

Areas of control and treated leaf disks consumed by the larvae were measured using Scion Image software, and feeding deterrence was calculated (*16*) using the formula

$$[(C - T)/(C + T)] \times 100$$

where *C* and *T* are areas consumed of the control and treated leaf disks, respectively.

Oviposition Deterrent Bioassays. Oviposition response of *T. ni* moths was measured according to our previously described oviposition choice bioassay (*16*). A pair of moths (one male and one female) was introduced into an oviposition cage with a control and a treated cabbage leaf. Each leaf (approximately 100−110 cm^2) was sprayed with 0.5 mL of MeOH or a methanolic solution of the test chemical on each side. Eggs were counted on each cabbage leaf after 48 h. The oviposition deterrence index (ODI) was calculated using the formula

$$\mathrm{ODI} = [(C - T)/(C + T)] \times 100$$

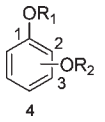
where *C* and *T* are the numbers of eggs laid on the control and treated leaf disks, respectively (*16*).

Contact Toxicity Bioassays. Mortality was determined 24 h after larvae had been sprayed directly with 0.25% of the test solutions (*16*). Third-instar *T. ni* larvae were sprayed in 90 mm × 15 mm Petri dishes (Falcon) lined with Fisher Scientific filter paper (90 mm diameter). Small plastic hand spraying bottles (50 mL capacity) were used. Larvae were then transferred to Petri dishes (90 mm × 15 mm) with a small piece of artificial diet. Each Petri dish contained 10 larvae. Three replicates, each consisting of 10 larvae, were used per treatment. Controls were sprayed with MeOH only.

Comparison of Toxicity and Oviposition and Feeding Deterrence Values. The mortality for each test material was plotted against its respective oviposition deterrence value (determined at 0.25%) to explore the relationship between the two bioassays using correlation analysis. Similarly, feeding deterrence was plotted against oviposition deterrence and mortality (*16*).

Data Analysis. Feeding deterrence data (percent) from the initial screening concentration were analyzed by analysis of variance (ANOVA) after arcsine transformation using statistics software (*24*). When significant *F* values were found, Tukey's HSD multiple-comparison tests were used to test for significant differences between individual treatments.

Table 1. Feeding Deterrent, Oviposition Deterrent, and Toxic Bioactivities of Individual Compounds or Compound Sets to the Cabbage Looper, Based on Previous Structure−Activity Work (*16*) or Precursor Sets for the Claisen Rearrangements and Subsequent Alkylations



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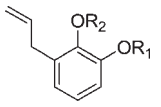
a = ortho, OR_2 at position 2
b = meta, OR_2 at position 3
c = para, OR_2 at position 4

compound/set	R_1[a]	R_2[a]	FD[b] (%) (mean ± SE, N = 25)	DC_{50}[c] (μg/cm^2) (R^2, N = 25)	mortality[d] (%) (N = 3 × 10)	OD[d] (%) (mean ± SE, N = 35−40)
3a{*3,6*}	allyl	propyl	96 ± 3 ^{A}	12 (0.98)	17	28 ± 13
3a{*3,6*}	allyl	propyl	97 ± 15 ^{A}	16 (0.92)	10	12 ± 13
3a{*4,6*}	allyl	butyl	92 ± 6 ^{A}	17 (0.96)	19	35 ± 17
3a{*3,4*}	propyl	butyl	98 ± 2 ^{A}	21 (0.97)	19	37 ± 14
3a{*6,1−5*}	allyl	Me, Et, Pr, Bu, iPent	68 ± 12 ^{AB}	30 (0.90)	23	67 ± 15
3a{*5,6*}	allyl	iPent	−[e]	−	−	26 ± 13.5
3b{*3,5*}	propyl	iPent	97 ± 3 ^{A}	17 (0.98)	10	9 ± 17
3b{*1,5*}	methyl	iPent	89 ± 7 ^{A}	29 (0.96)	30	30 ± 14
3b{*1,6*}	methyl	allyl	66 ± 12 ^{AB}	34 (0.89)	33	9 ± 14
3b{*6,2−3*}	allyl	Et, Pr	64 ± 12 ^{AB}	42 (0.93)	65	−9 ± 14
3b{*6,4−5*}	allyl	Bu, iPent	69 ± 11 ^{AB}	32 (0.89)	40	−1 ± 15
3b{*6,6*}	allyl	allyl	97 ± 3 ^{A}	20 (0.98)	13	26 ± 16
3b{*5,6*}	allyl	iPent	−	−	−	10 ± 13
2b{*6*}	H	allyl	36 ± 10 ^{B}	−	−	5 ± 13
3c{*6,1−5*}	allyl	Me, Et, Pr, Bu, iPent	100 ± 0 ^{A}	9 (0.99)	7	46 ± 15
3c{*1,6*}	methyl	allyl	62 ± 15 ^{AB}	30 (0.96)	6	13 ± 13
3c{*2,6*}	ethyl	allyl	73 ± 12 ^{AB}	30 (0.98)	−5	17 ± 14
3c{*3,6*}	propyl	allyl	100 ± 0 ^{A}	0.5 (0.98)	−11	21 ± 14
3c{*5,6*}	ipent	allyl	−	−	−	−25 ± 12
3c{*2,3*}	ethyl	propyl	100 ± 0 ^{A}	33.3 (0.99)	17	10 ± 13
DEET		not applicable	60 ± 15 ^{AB}	47 (0.98)	7	23 ± 14

[a] Me = methyl, Et = ethyl, Pr = propyl, Bu = *n*-butyl, iPent = isopentyl (= 3-methylbutyl). [b] Feeding deterrent effects (mean ± SE) at 50 μg/cm^2 are expressed in %. Means followed by the same capital letters within a column do not differ significantly (one-way ANOVA, $F_{18, 462}$ = 4.4, p < 0.0001; Tukey's test, p < 0.05). [c] DC_{50} values (concentrations causing 50% feeding deterrence compared with the control) were calculated for samples showing >50% feeding deterrence in initial screening concentration (50 μg/cm^2), using Excel. Linear regression analysis was conducted for all dose−response experimental data. The R^2 values for the linear regressions are shown in parentheses after the number. [d] Mortality and oviposition deterrent (OD) effects were determined at 0.25% for samples showing >50% feeding deterrence in initial screening. [e] −, not tested.

Table 2. Feeding Deterrent, Oviposition Deterrent, and Toxic Bioactivities of Libraries of Ortho Claisen Rearrangement Products from 1-Allyloxy-2-alkoxybenzenes



compound/set	R_2[a]	FD[b] (%) (mean ± SE, N = 25)	DC_{50}[c] (μg/cm^2) (R^2, N = 25)	mortality[d] (%) (N = 3 × 10)	OD[d] (%) (mean ± SE, N = 35−40)
4a{*1−5*}	H	100 ± 0 ^{A}	20.6 (0.92)	17	7 ± 15
5a{*1,1−5*}	Me	100 ± 0 ^{A}	15.5 (0.86)	17	32 ± 15
5a{*2,1−5*}	Et	100 ± 0 ^{A}	20.0 (0.91)	27	31 ± 15
5a{*3,1−5*}	Pr	31 ± 15 ^{B}	−[e]	47	−
5a{*4,1−5*}	Bu	6 ± 17 ^{B}	−	1	−
5a{*5,1−5*}	iPent	22 ± 16 ^{B}	−	7	−
5a{*6,1−5*}	allyl	22 ± 18 ^{B}	−	7	−

[a] Me = methyl, Et = ethyl, Pr = propyl, Bu = *n*-butyl, iPent = isopentyl (= 3-methylbutyl). For **5a** sets, the code is **5a**{R_2,R_1} (**Figure 1**). [b] Feeding deterrent effects (mean ± SE) at 50 μg/cm^2 are expressed in %. Means followed by the same capital letters within a column do not differ significantly (one-way ANOVA, $F_{6, 173}$ = 12.5, p < 0.0001; Tukey's test, p < 0.05). [c] DC_{50} values (concentrations causing 50% feeding deterrence compared with the control) were calculated for samples showing >50% feeding deterrence in initial screening concentration (50 μg/cm^2), using Excel. Linear regression analysis was conducted for all dose−response experimental data. The R^2 values for the linear regressions are shown in parentheses after the number. [d] Mortality and oviposition deterrent (OD) effects were determined at 0.25% for samples showing >50% feeding deterrence in initial screening. [e] −, not tested.

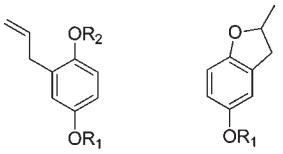
RESULTS

Feeding Deterrent, Toxicity, and Oviposition Deterrent Effects. *Individual Compounds or Compound Sets, Based on Previous Structure−Activity Work (16).* DC_{50} values varied from 0.5 to 42.1 μg/cm^2 (**Table 1**). The compound 1-allyloxy-4-propoxybenzene, **3c**{*3,6*}, had the lowest DC_{50} value (0.5 μg/cm^2) followed by the 1-allyloxy-4-alkoxybenzene set **3c**{*6,1−5*}, (8.5 μg/cm^2), which contains compound **3c**{*3,6*}. DEET showed a DC_{50} value of 46.7 μg/cm^2 (**Table 1**).

At 0.25% the 1-allyloxy-3-ethoxy/-propoxybenzene set **3b**{*6,2−3*} was the most toxic (65% mortality,) followed by the 1-allyloxy-3-butoxy/isopentoxybenzene set **3b**{*6,4−5*} (40% mortality) (**Table 1**). 1-Allyloxy-4-ethoxybenzene **3c**{*2,6*} was the least toxic (6.7% mortality) in this group.

At 0.25% the 1-allyloxy-2-alkoxybenzene set **3a**{*6,1−5*} showed the strongest oviposition deterrent effect (66.7%) (**Table 1**). Interestingly, members of set **3c**{*6,1−5*} with small alkoxy substituents (**3c**{*1,6*}, **3c**{*2,6*}, and **3c**{*3,6*}) were poor oviposition deterrents

Table 3. Feeding Deterrent, Oviposition Deterrent, and Toxic Bioactivities of Libraries of Ortho Claisen Rearrangement Products from 1-Allyloxy-4-alkoxybenzenes



5c{R_2,*1-5*} **6c**{*1-5*}

compound/set	R_2[a]	FD[b] (%) (mean ± SE, N = 25)	DC_{50}[c] ($\mu g/cm^2$) (R^2, N = 25)	mortality[d] (%) (N = 3 × 10)	OD[d] (%) (mean ± SE, N = 35−40)
4c{*1−5*}	H	51 ± 18^{ABC}	57 (0.92)	3.3	51 ± 17
5c{*1,1*}	Me, R_1 = Me	80 ± 11^{AB}	20 (0.88)	39	14 ± 12
5c{*1,1−5*}	Me	68 ± 12^{ABC}	19 (0.94)	17	37 ± 15
5c{*2,1−5*}	Et	66 ± 14^{ABC}	22 (0.95)	3.3	64 ± 17
5c{*3,1*}	Pr, R_1 = Me	92 ± 6^{A}	9.4 (0.90)	6.4	7 ± 15
5c{*3,1−5*}	Pr	65 ± 11^{ABC}	33 (0.98)	17	21 ± 14
5c{*4,1−5*}	Bu	23 ± 16^{C}	−[e]	−	-14 ± 13
5c{*5,1−5*}	iPent	83 ± 12^{AB}	15 (0.85)	27	20 ± 15
5c{*6,1−5*}	allyl	29 ± 11^{BC}	−	−	−
6c{*1−5*}	cyclic	100 ± 0^{A}	16 (0.95)	1.0	-12 ± 13

[a] Me = methyl, Et = ethyl, Pr = propyl, Bu = *n*-butyl, iPent = isopentyl (= 3-methylbutyl). For **5c** sets, the code is **5c**{R_2,R_1} (**Figure 1**). [b] Feeding deterrent effects (mean ± SE) at 50 $\mu g/cm^2$ are expressed in %. Means followed by the same capital letters within a column do not differ significantly (one-way ANOVA, $F_{9\text{-}241} = 4.3$, $p < 0.0001$; Tukey's test, $p < 0.05$). [c] DC_{50} values (concentrations causing 50% feeding deterrence compared with the control) were calculated for samples showing >50% feeding deterrence in initial screening concentration (50 $\mu g/cm^2$), using Excel. Linear regression analysis was conducted for all dose−response experimental data. The R^2 values for the linear regressions are shown in parentheses after the number. [d] Mortality and oviposition deterrent (OD) effects were determined at 0.25% for samples showing >50% feeding deterrence in initial screening. [e] −, not tested.

(< 30%). The meta-substituted dialkoxybenzenes (**3b** compounds) were generally weak, with the strongest congeners being the ones with a molecular volume of 250−260 $Å^3$ and either an allyloxy or an isopentyloxy group **3b**{*1,5*} and **3b**{*6,6*} (25−30% oviposition deterrence).

Libraries of Ortho Claisen Rearrangement Products from 1-Allyloxy-2-alkoxybenzenes. The **5a**{*1,1−5*} minilibrary had the lowest DC_{50} value (16 $\mu g/cm^2$) followed by **5a**{*2,1−5*} and **4a**{*1−5*} (~20 $\mu g/cm^2$) (**Table 2**). A structure−activity relationship was clear among these compounds: small R_2 groups (H, methyl, or maximally ethyl) gave high feeding deterrence. This activity was lost significantly with a one or more carbon increase in the size of group R_2.

Set **5a**{*3,1−5*} was the most toxic (**Table 2**) at 0.25% (47% mortality). A structure−activity relationship could be seen, with R_2 = propyl being most toxic and R_2 groups smaller or larger than that being less toxic. At 0.25% the sets **5a**{*1,1−5*}and **5a**{*2,1−5*} caused ~30% oviposition deterrence (**Table 2**).

Libraries of Ortho Claisen Rearrangement Products from 1-Allyloxy-4-alkoxybenzenes. Set **5c**{*3,1*} had the lowest DC_{50} value (9 $\mu g/cm^2$), whereas **4c**{*1−5*} had the highest DC_{50} value (57 $\mu g/cm^2$). There was a moderate structure−activity relationship among the sets **5c**{R_2,*1−5*}, with R_2 = butyl or allyl being less active than R_2 = methyl, ethyl, propyl, or isopentyl. Compounds **5c**{*3,1*} and **5c**{*1,1*} were more active than the entire **5c**{*3,1−5*} or **5c**{*1,1−5*} sets, respectively.

At 0.25% set **5c**{*1,1*} was the most toxic with 38.9% mortality followed by **5c**{*5,1−5*} (**Table 3**). Other members in the group exhibited < 26% mortality (**Table 3**). Set **5c**{*2,1−5*} demonstrated strong oviposition deterrent activity (63.6%) followed by **4c**{*1−5*} (51.4%) and **5c**{*1,1−5*} (37%). There was some structure−activity relationship with respect to oviposition deterrence, with the optimal R_2 alkyl group being ethyl: smaller or larger was less effective. Set **6c**{*1−5*} acted as a moderate oviposition stimulant. All other libraries had only modest oviposition deterrent activities (**Table 3**).

Libraries of Ortho Claisen Rearrangement Products from 1-Allyloxy-3-alkoxybenzenes. Set **5b**{*5,1*}, a mixture of two isomeric compounds (**Table 4**), exhibited the lowest DC_{50} value (4 $\mu g/cm^2$), in one trial. A different lot of set **5b**{*5,1*} exhibited a higher DC_{50} value (16 $\mu g/cm^2$). With respect to feeding deterrence there were clear structure−activity relationships. For group R_2, propyl gave the best results, and the smaller (methyl, ethyl, or allyl) or larger (butyl or isopentyl) groups gave lower feeding deterrence. For group R_1 the structure−activity relationship was clear: within each group with R_2 constant, there was a decrease in activity in going from R_1 = methyl to the larger groups. For cases in which isomers *x* and *y* were separated, the more compact isomer *y* was more active as a feeding deterrent than isomer *x*.

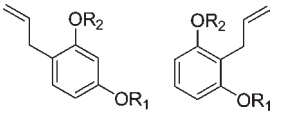
Compound **4b**{*2−3*} was the most toxic, causing 70% mortality at 0.25% (**Table 4**). Thus, group R_2 = H or methyl gave high mortality. For the larger R_2 sets, mortality was lower, and there was a slight pattern with respect to group R_1 within each group with constant R_2 (ethyl or propyl): the set with R_1 = ethyl/propyl was more toxic than the set with R_1 = methyl.

5b{*5,1*} and **5b**{*6,1*} demonstrated the strongest oviposition deterrent effects (50%). Set **5b**{*2,4−5*} acted as a mild oviposition stimulant (**Table 4**). There were clear structure−activity patterns in the oviposition data. Among the **4b** sets, oviposition deterrence increased with increasing size of group R_1. Also in the **5b** sets when R_2 = methyl, ethyl, or propyl, there was an increase in oviposition deterrence going from R_1 = methyl to R_1 = ethyl/propyl, but when R_2 = isopentyl or allyl, there was a decrease in oviposition deterrence going from R_1 = methyl to R_1 = ethyl/propyl or butyl/isopentyl. In the R_2 = butyl sets, oviposition deterrence was the same for all R_1 groups.

Eugenol and Alkylated Derivatives of Eugenol. Butyl and eugenol exhibited the lowest DC_{50} value (12 $\mu g/cm^2$) followed by allyleugenol (15 $\mu g/cm^2$). There was an increase in feeding deterrence (and a decrease in DC_{50}), with increasing size of group R_1 from methyl to butyl. The larger isopentyl group gave slightly lower feeding deterrence (higher DC_{50}) (**Table 5**).

Methyleugenol was the most toxic, causing 41% mortality at 0.25% (**Table 5**). All others exhibited < 37% mortality. There was a structure−activity relationship for toxicity as well, with an increase from R_1 = H (eugenol) to methyleugenol, but then a

Table 4. Feeding Deterrent, Oviposition Deterrent, and Toxic Bioactivities of Libraries of Ortho Claisen Rearrangement Products from 1-Allyloxy-3-alkoxybenzenes



compound/set[a]	R_1[a]	R_2[a]	FD[b] (%) (mean ± SE, N = 25)	DC_{50}[c] (μg/cm^2) (R^2, N = 25)	mortality[d] (%) (N = 3 × 10)	OD[d] (%) (mean ± SE, N = 35−40)
4b{*1*}	Me	H	74 ± 11 ABC	25 (0.98)	20	12 ± 12
4b{*2−3*}	Et, Pr	H	73 ± 11 ABC	33 (0.99)	70	31 ± 14
4b{*4−5*}	Bu, iPent	H	66 ± 13 ABC	26 (0.96)	50	45 ± 15
5b{*1,1*}	Me	Me	77 ± 9 ABC	25 (0.99)	50	−5 ± 13
5b{*1,2−3*}	Et, Pr	Me	74 ± 11 ABC	23 (0.98)	65	19 ± 15
5b{*1,4−5*}	Bu, iPent	Me	41 ± 16 ABC	—[h]	—	—
5b{*2,1*}	Me	Et	93 ± 5 AB	24 (0.89)	3.6	−2 ± 13
5b{*2,2−3*}	Et, Pr	Et	79 ± 10 ABC	17 (0.99)	20	28 ± 14
5b{*2,4−5*}	Bu, iPent	Et	81 ± 11 ABC	15 (0.95)	10	−24 ± 13
5b{*3,1*}	Me	Pr	100 ± 0 A	16 (0.90)	3.6	−11 ± 15
5b{*3,2−3*}	Et, Pr	Pr	93 ± 5 AB	8.7 (0.85)	10	5 ± 13
5b{*3,4−5*}	Bu, iPent	Pr	33 ± 16 BC	—	—	34 ± 15
5b{*3,2*}	Et	Pr	92 ± 6 AB	17 (0.79)	0.6	25 ± 13
5b{*4,1*}	Me	Bu	60 ± 16 ABC	27 (0.90)	10	13 ± 14
5b{*4,2−3*}	Et, Pr	Bu	54 ± 16 ABC	49 (0.96)	6.7	9 ± 13
5b{*4,4−5*}	Bu, iPent	Bu	26 ± 16 C	—	—	18 ± 14
5b{*5,1*}	Me	iPent	71 ± 14 ABC	19 (0.93)	16	51 ± 14
5b{*5,2−3*}	Et, Pr	iPent	79 ± 9 ABC	24 (0.98)	6.7	15 ± 14
5b{*5,4−5*}	Bu, iPent	iPent	41 ± 17 ABC	—	—	—
5b{*6,1*}	Me	allyl	76 ± 12 ABC	21 (0.97)	25	50 ± 14
5b{*6,2−3*}	Et, Pr	allyl	90 ± 8 AB	16 (0.96)	33	8 ± 13
5b{*6,4−5*}	Bu, iPent	allyl	57 ± 15 ABC	43 (0.96)	33	19 ± 13
second lots and purified isomers of **5b**{*n,1*} or **5b**{*3,2*} compounds						
5b{*1,1*}[e]	Me	Me	58 ± 15 ABC	39 (0.97)	−2.9	10 ± 15
5b{*3,1*}[e]	Me	Pr	91 ± 6 AB	26 (0.96)	10	7 ± 11
5b{*3,1*}*y* (100% *y*)	Me	Pr	100 ± 0 A	14 (0.98)	−4.2	17 ± 14
5b{*3,1*}*x* (68% *x*, 32% *y*)	Me	Pr	68 ± 12 ABC	24 (0.76)	−32	0
5b{*3,2*}[g]	Et	Pr	92 ± 6 AB	17 (0.79)	0.6	25 ± 13
5b{*3,2*}*y* (100% *y*)	Et	Pr	74 ± 14 ABC	28 (0.99)	0	−6.4 ± 11.4
5b{*3,2*}*x* (82% *x*, 18% *y*)	Et	Pr	95 ± 3 AB	25 (0.98)	0	26 ± 8
5b{*5,1*}[e]	Me	iPent	99 ± 1 A	4 (0.98)	6.0 ±	32 ± 12
5b{*6,1*}[e]	Me	allyl	92 ± 6 AB	23 (0.92)	−1.6 ±	10 ± 14

[a] Me = methyl, Et = ethyl, Pr = propyl, Bu = *n*-butyl, iPent = isopentyl (= 3-methylbutyl). For **5b** sets, the code is **5b**{R_2,R_1} (**Figure 1**). The compounds are a mixture of isomers *x* and *y* in a ratio of *x*/*y* 2:1. [b] Feeding deterrent effects (mean ± SE) at 50 μg/cm^2 are expressed in %. Means followed by the same capital letters within a column do not differ significantly (one-way ANOVA, $F_{27, 684}$ = 3.2, p < 0.0001; Tukey's test, p < 0.05). [c] DC_{50} values (concentrations causing 50% feeding deterrence compared with the control) were calculated for samples showing >50% feeding deterrence in initial screening concentration (50 μg/cm^2), using Excel. Linear regression analysis was conducted for all dose−response experimental data. The R^2 values for the linear regressions are shown in parentheses after the number. [d] Mortality and oviposition deterrent (OD) effects were determined at 0.25% for samples showing >50% feeding deterrence in initial screening. [e] These lots were prepared on a larger scale than previously (*17*), and the ratios of *x*/*y* were as follows: **5b**{*1,1*}, 1.8:1; **5b**{*3,1*}, 1.2:1; **5b**{*3,2*}, 2.3:1; **5b**{*5,1*} 1.8:1; **5b**{*6,1*}, 2.3:1. [f] The isomers were separated on a column of silica/silver nitrate (see Materials and Methods). [g] Same set as listed above with the sets, provided for convenience. [h] —, not tested.

general decrease with increasing group size from methyl to butyl. The larger isopentyleugenol was again slightly more toxic.

Butyl and eugenol demonstrated the strongest oviposition deterrent effect (34%) followed by propyl and eugenol (29%) when tested at 0.25%. Methyl and eugenol acted as an oviposition stimulant (**Table 5**). There was a structure−activity pattern here, too: as the alkyl group increased, oviposition deterrence generally increased, up to butyleugenol. Isopentyleugenol and allyleugenol were less active in this category.

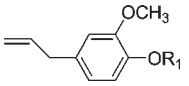
Comparison of Toxicity and Oviposition and Feeding Deterrence. There was no correlation between toxicity and oviposition deterrence ($y = -0.0738x + 20.582$, $R^2 = 0.0044$) within the data sets. Similarly, there was no correlation between feeding deterrence and oviposition deterrence ($y = -0.2005x + 25.333$, $R^2 = 0.0368$) within the data sets. Furthermore, there was no correlation between toxicity and feeding deterrence ($y = -0.0235x + 20.565$, $R^2 = 0.0006$).

Comparison of Feeding Deterrence with Long-Term EAG Inhibition of Sex Attractant Pheromone Responses in Male Gypsy Moth (Another Lepidopteran Species). To our surprise, we found a correlation between larval feeding deterrence in third-instar *T. ni* larvae and long-term EAG inhibition of sex attractant pheromone responses in male gypsy moth, *Lymantria dispar* ($y = 2.0x - 2.9$, $R^2 = 0.66$, **Figure 2**) (*25*) for some of the compounds. Compounds that were active in both insects are (in order of decreasing activity) **3c**{*2,3*}, **3c**{*3,1−5*}, **3c**{*4,1−5*}, **3a**{*4,4*}, **3b**{*3,3*}, **3c**{*5,1−5*}, **3c**{*3,6*}, **2a**{*4*}, **3b**{*1,1−5*}, **5a**{*3,1−5*}, **2b**{*5*}, **2c**{*1*}, **2c**{*3*}, **2a**{*1*}, **3c**{*3,3*}, and **2b**{*2*}.

DISCUSSION

Our results have demonstrated that most of the compounds and libraries are effective feeding deterrents, with minimal toxicity in most cases. We are focusing on compounds that are behaviorally active without acute toxicity to the insects as we anticipate that

Table 5. Feeding Deterrent, Oviposition Deterrent, and Toxic Bioactivities of Eugenol and Alkylated Derivatives of Eugenol



compound	R_1[a]	FD[b] (%) (mean ± SE, $N = 25$)	DC_{50}[c] ($\mu g/cm^2$) (R^2, $N = 25$)	mortality[d] (%) ($N = 3 \times 10$)	OD[d] (%) ($N = 35-40$)
eugenol	H	44 ± 16^A	56 (0.89)	30	–[e]
methyleugenol	Me	64 ± 15^A	26 (0.90)	41	-22 ± 14
ethyleugenol	Et	51 ± 18^A	50 (0.88)	35	18 ± 12
propyleugenol	Pr	84 ± 11^A	19 (0.92)	37	29 ± 15
allyleugenol	allyl	86 ± 9^A	15 (0.94)	18	16 ± 16
n-butyleugenol	Bu	92 ± 8^A	12 (0.89)	15	34 ± 14
isopentyleugenol	iPent	86 ± 10^A	25 (0.99)	28	9 ± 14

[a] Me = methyl, Et = ethyl, Pr = propyl, Bu = *n*-butyl, iPent = isopentyl (= 3-methylbutyl). [b] Feeding deterrent effects (mean ± SE) at 50 $\mu g/cm^2$ are expressed in %. Means followed by the same capital letters within a column do not differ significantly (one-way ANOVA, $F_{6,171} = 2.07$, $p > 0.06$; Tukey's test, $p < 0.05$). [c] DC_{50} values (concentrations causing 50% feeding deterrence compared with the control) were calculated for samples showing >50% feeding deterrence in initial screening concentration (50 $\mu g/cm^2$), using Excel. Linear regression analysis was conducted for all dose–response experimental data. The R^2 values for the linear regressions are shown in parentheses after the number. [d] Mortality and oviposition deterrent (OD) effects were determined at 0.25% for samples showing >50% feeding deterrence in initial screening. [e] –, not tested.

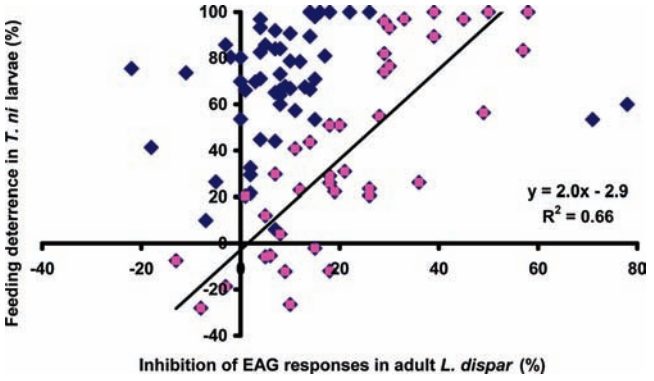


Figure 2. Correlation of the activities of compounds from this and a previous (*16*) study: feeding deterrence (%) against *T. ni* larvae versus long-term inhibition of EAG responses to the sex pheromone in *L. dispar* males (*25*). Compounds for which the two activities paralleled are shown in pink, and the line shown refers to these compounds.

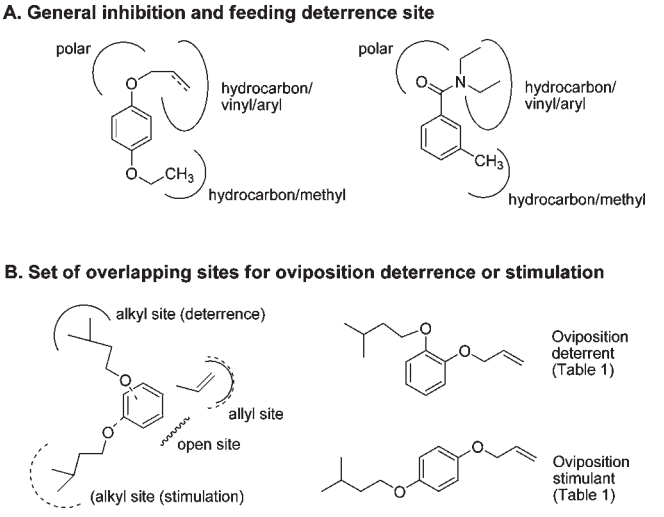


Figure 3. (**A**) "Site" defined by structure–activity relationships for feeding deterrence of *T. ni* third-instar larvae (this study and ref *16*) and on the inhibition of the EAG responses to the sex pheromone of *L. dispar* males (*25*). (**B**) Set of overlapping "sites" defined by structure–activity relationships for oviposition deterrence of *T. ni* adult females.

these will have low impact on nontarget arthropods and fewer regulatory obstacles. Most of them possess low or medium oviposition deterrent effects, and a few act as oviposition stimulants. The highest feeding deterrence was seen for compound **3c**{*3,6*}. It was considered to be the best candidate for manipulating larval feeding, as it exhibited low toxicity and oviposition deterrence to the cabbage looper larvae and female moths, respectively. Compounds **5c**{*3,1*} and **5c**{*1,1*} were more active than the entire **5c**{*3,1–5*} or **5c**{*1,1–5*} sets, respectively. Because sets and compounds were tested at the same concentration by weight, this result suggests that the activity detected for the sets came mostly from the most active component, and there is probably little or no synergy or antagonism within these sets. Overall, the structure–activity suggests that good feeding deterrents in the **5c** group have an odd-numbered (methyl or propyl) or branched (isopentyl) R_2 alkyl group and a small R_1 (methyl) group. Compound set **6c**{*1–5*} was formed during the synthesis of **5c** libraries (in cases when the Claisen reaction was left too long) (*17*). The cyclic portion of compounds **6c**{*1–5*} resembles a branched chain and could fit the same type of site as the **5c** compounds.

The highest oviposition deterrence was seen with set **3a**-{*6,1–5*}, and this set may exhibit synergistic effects, because compound **3a**{*5,6*} in isolation showed some oviposition deterrence, but lower than that of the full set. Sets **4c**{*1–5*}, **4b**{*4–5*}, and **5b**{*5,1*} also had high oviposition deterrence activity, and of these **4c**{*1–5*} had the lowest toxicity. All of these oviposition deterrents were moderate or poor feeding deterrents, so these candidates would target only the oviposition behavior. Finally, set **5a**{*1,1–5*} and the compound butyleugenol were not the best overall in any of the activities tested, but they best combined all three desirable properties in one: high feeding deterrence, high oviposition deterrence, and low toxicity.

One important aspect of our study is that many of the pure compounds and libraries were more active than a commercial insect repellent, DEET, as feeding and/or oviposition deterrents against *T. ni* larvae and adult female moths, respectively. DEET exhibited the highest DC_{50} value (47 $\mu g/cm^2$) in the whole group (**Table 1**) as opposed to the low DC_{50} value of 0.5 $\mu g/cm^2$ exhibited by **3c**{*3,6*}. DEET is a highly effective (*26*) and widely used insect repellent. We used DEET as a positive control in our study. The advantage of having compared our results to DEET is that one target site for DEET is known in the dipterans: DEET interacts with the conserved olfactory coreceptor OR83b (*27*). The lepidopteran orthologue of this protein has been designated OR2 (*28*). Interaction of DEET with OR83b and other olfactory

components, such as the specific OR for a particular set of odors (*27*, *28*), causes the inhibition of behavioral attraction to food odors in *Drosophila melanogaster* and *Anopheles gambiae* (*29*).

Because our leading candidate compound for feeding deterrence, **3c**{*3,6*}, has some resemblance to DEET and appears to be highly active on more than one species and more than one life stage of Lepidoptera (see above), there is a possibility that this compound also acts on one of the widespread, conserved components of the olfactory system.

The most active feeding deterrents overlap on a site that could also accommodate DEET (**Figure 3A**). Such a site could be located on a single protein or at a protein/protein interface needed for the olfactory response. Interactions between various dendritic membrane components have been shown to be important for olfactory responses in insects. For example, it has been shown with *Drosophila* that the coreceptor OR83b interacts very closely with the sensory neuron membrane protein (SNMP) (*30*) and with the odorant receptor (OR) itself (*29*).

Compounds and sets **3a**{*3,1*−*5*}, **3a**{*4,1*−*5*}, **3b**{*4,1*−*5*}, **3b**{*5,1*−*5*}, **3c**{*6,6*}, **3c**{*1,1*−*5*}, **3c**{*2,1*−*5*}, **4b**{*1*}, **5a**{*1,1*−*5*}, **5a**{*2,1*−*5*}, **5b**{*2,4*−*5*}, **5b**{*3,2*−*3*}, **5b**{*6,2*−*3*}, **5b**{*3,1*}, **5b**{*6,1*}, **5c**{*5,1*−*5*}, allyleugenol, propyleugenol, and butyleugenol showed strong feeding deterrence activity in *T. ni* larvae in the present study, but were not active as inhibitors of pheromone perception in *L. dispar* adult males (*25*). These compounds or sets may be perceived more specifically as "unpleasant" general odorants or tastants by *T. ni* larvae. Finally, the oviposition deterrents seem to target a set of overlapping sites (**Figure 3B**) that cause deterrence if occupied by the alkyl and allyl groups on the same side of the benzene ring (ortho positions) and oviposition stimulation if occupied by the alkyl and allyl groups on opposite sides of the benzene ring (meta and para positions).

On the basis of antifeedant activity, our compounds/libraries possess levels of activity that compare favorably to some of the most active botanical insecticides in current use. Compound **3c**{*3,6*} in the group is as active as pyrethrum (DC_{50} = 0.9 $\mu g/cm^2$) in the feeding deterrence bioassay with *T. ni* larvae (*31*). Similarly, other compounds/sets including **5c**{*3,1*}, **3c**{*6,1*−*5*}, **5b**{*3,2*−*3*}, and **5b**{*5,1*}*x* + y were more active than rotenone against third-instar *T. ni* larvae. All of the candidate compounds/sets were more active than rosemary oil (DC_{50} = 158 $\mu g/cm^2$), clove leaf oil (DC_{50} = 217 $\mu g/cm^2$), *Melia azedarach* (DC_{50} = 288 $\mu g/cm^2$), *Trichilia americana* (DC_{50} = 190 $\mu g/cm^2$), and *Ryania* (DC_{50} = 725 $\mu g/cm^2$) (*31*).

Most of the compounds were identified as strong feeding deterrents with low to moderate toxic and oviposition deterrent effects. Some of the compounds exhibited toxic effects against cabbage looper larvae. Because most of the compounds and libraries (set **5a**{*1,1*−*5*} and the compound butyleugenol) possess both feeding deterrent and oviposition deterrent properties, they could constitute a "dual defense" against different cabbage looper life stages (*16*).

Our study indicates a general lack of correlation between feeding deterrence and oviposition deterrence, consistent with other results (*16*) and consistent with the idea that the two activities are mediated through chemosensory sites of different selectivities.

There was a lack of correlation between toxicity and oviposition deterrence in the compounds and minilibraries. Interestingly, most of these libraries had strong feeding deterrent effects, but only a few had strong deterrent as well as toxic properties. The structure−activity relationship of the toxicity and feeding deterrence was also generally dissimilar, which suggests that the deterrent effect of our compounds was not linked to a toxic effect. The nontoxic deterrents found here could be used in combined strategies, in which the larvae or the females are deterred from the crop and attracted to traps or refuge areas, as shown in a previous study (*32*).

In conclusion, we have described the activity of synthetic aromatic compounds that mediate the feeding and oviposition behavior of cabbage looper larvae and adult female moths, respectively. On the basis of their comparable efficacy to azadirachtin and other commercial feeding deterrents, many of the compounds/libraries have potential for development as commercial insect control agents with selectivity toward Lepidoptera.

However, the demonstration of bioactivity in the laboratory is simply the first step in the development of a commercial product, and numerous other criteria must be satisfied before the true commercial potential can be realized (*33*). Empirical tests are needed to confirm low nontarget toxicity (especially low mammalian toxicity), and persistence under field conditions needs to be assessed. Persistence and other aspects of field performance can be partly addressed through proper formulation, provided that solvents and adjuvants used are compatible with conventional application equipment and can maintain a cost to the end-user that is competitive with that of other pest management products. The failure to meet one or more of these criteria accounts for the dearth of alternative insect control products (i.e., those not based on neurotoxins). The next step in our research will be focused on determining the efficacy of the compounds in a greenhouse environment.

ACKNOWLEDGMENT

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Supporting Information Available: Data for the individual compounds and ^{1}H NMR data of new, pure **3a**, **3b**, and **3c** compounds that have not been published previously (*17*). This material is available free of charge via the Internet at http://pubs.acs.org.

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