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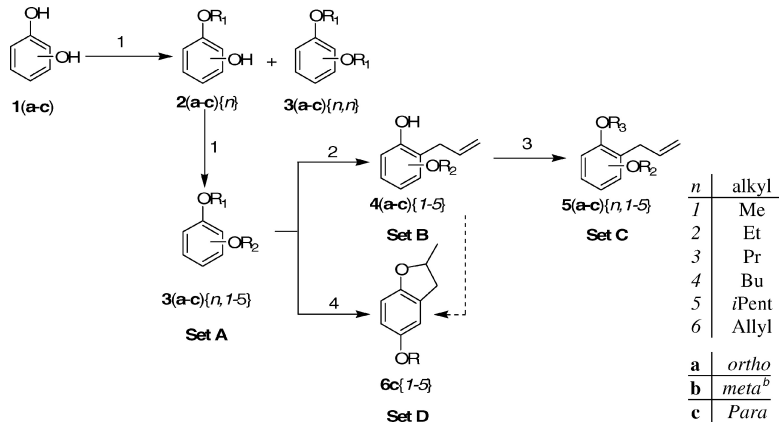

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Synthesis of Substituted Alkoxy Benzene Minilibraries, for the Discovery of New Insect Olfaction or Gustation Inhibitors

Peggy M. Paduraru,[†] Richard T. W. Popoff,[†] Ranjeet Nair,[†,‡] Regine Gries,[§] Gerhard Gries,[§] and Erika Plettner*[,†]

Department of Chemistry, Simon Fraser University, Burnaby, B. C. V5A 1S6, Canada, and Department of Biological Sciences, Simon Fraser University, Burnaby, B. C. V5A 1S6, Canada

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We describe methods for the rapid generation of minilibraries of substituted alkoxy benzenes (consisting of 4–5 compounds), for screening as insect olfaction or gustation inhibitors. Synthetic or commercially available monoalkoxy benzene compounds were mixed and reacted with various alkyl halides to afford a first set of minilibraries. A second and third set were generated from allyloxy minilibraries via the Claisen rearrangement and subsequent alkylation of the *ortho*-allyl phenols. We have chosen to prepare a collection of small libraries (as opposed to one large library) to test the response insects exhibit toward blends of compounds. We demonstrate how our minilibraries can be screened, both against insect antennae and against expressed pheromone-binding proteins from the gypsy moth, *Lymantria dispar*.

Introduction

Odors and tastes are important behavioral guides for many organisms. Insects, in particular, use chemical signals to find hosts,[1] assess the suitability of a host,[2,3] sense predators,[3,4] and locate mates.[5] The chemical senses (olfaction and gustation) in insects are highly sensitive and selective.[6] Chemical signals can encode information by the structure and concentration of individual components, as well as by the composition of blends. Blends are particularly important in the distinction between closely related potential hosts or mates, and sometimes, a small variation in the composition of several odor or tastant blends can elicit very different responses. The structural range of compounds insects can sense (both alone and as part of blends) is still not fully known, but appears to be large.[7]

The chemosensory system of insects consists of microscopic sensory hairs located on the mouthparts and appendages (antennae, legs, and wings). The hairs are innervated by sensory cell dendrites, which contain the odor and taste receptors. The dendrites are protected from the environment by an aqueous layer, rich in water-soluble binding proteins. These proteins belong to two families: the odorant-binding protein (OBP) family or the chemosensory-specific protein (CSP) family.[8]

The chemical information from odors and tastes is decoded at three levels in this system: (1) at the level of the OBPs or CSPs,[8] (2) at the level of the receptors on the dendrites,[9] and (3) in the brain, where neurons that function as logical gates accept or reject certain blends.[10] We are interested in developing simple analogs of known odorants that elicit certain behaviors in insects. We screen these analogs for interaction with binding proteins and for enhancement or inhibition of the natural antennal signal or of the behavior. Because insects are strongly dependent on their sense of smell, such analogs could become new species-selective insect pest control agents.

We have chosen to prepare low-molecular weight phenol derivatives, because phenolic odorants and tastants play important roles in the interaction between insects and their environment and these compounds can be produced in few steps from commodity chemicals, such as catechol **1a**, resorcinol **1b**, or hydroquinone **1c**. For example, phenol derivatives such as guaiacol (1-hydroxy-2-methoxybenzene), 1,2-dimethoxybenzene, 1-ethoxy-2-methoxybenzene, 1-propoxy-2-methoxybenzene, eugenol, and isoeugenol, occur in smoke[11–13] and are known to have insect-repellent and insecticidal activities.[14] Furthermore, smoke phenolics taste and smell pleasantly (to humans)[12] and many have antioxidant activity.[11] Eugenol (2-methoxy-4-(2-propenyl) phenol) is found in herbs (such as basil, *Ocimum suave* (Wild.)) and is known to have activity against grain beetles as a toxicant and deterrent.[15] Other benzene derivatives, such as benzyl alcohol, benzonitrile, phenylethanol, 4-methyl phenol, 4-ethylphenol, 2-methylphenol, and benzaldehyde are known components of human odor to which malaria mosquitoes respond.[16,17] In particular, female malaria mosquitoes have an olfactory receptor, AgOr1, that is expressed only when the females seek a blood meal from a human host and that responds strongly to 4-methyl phenol and weakly to 4-ethylphenol and 2-methyl phenol.[16]

In this paper, we describe the synthesis, purity control, and three screening approaches for substituted alkoxy benzene minilibraries. Each of these "minilibraries" contains only 4–5 compounds and has been checked thoroughly for

* Corresponding author. Tel.: 778-782-3586. Fax: 778-782-3765. E-mail: plettner@sfu.ca.
[†] Department of Chemistry, Simon Fraser University.
[‡] Current address: Indoco Remedies Ltd., R 92-93 TTC Area Rabale, M.I.D.C., Navi Mumbai 400 701, Maharashtra, India.
[§] Department of Biological Sciences, Simon Fraser University.

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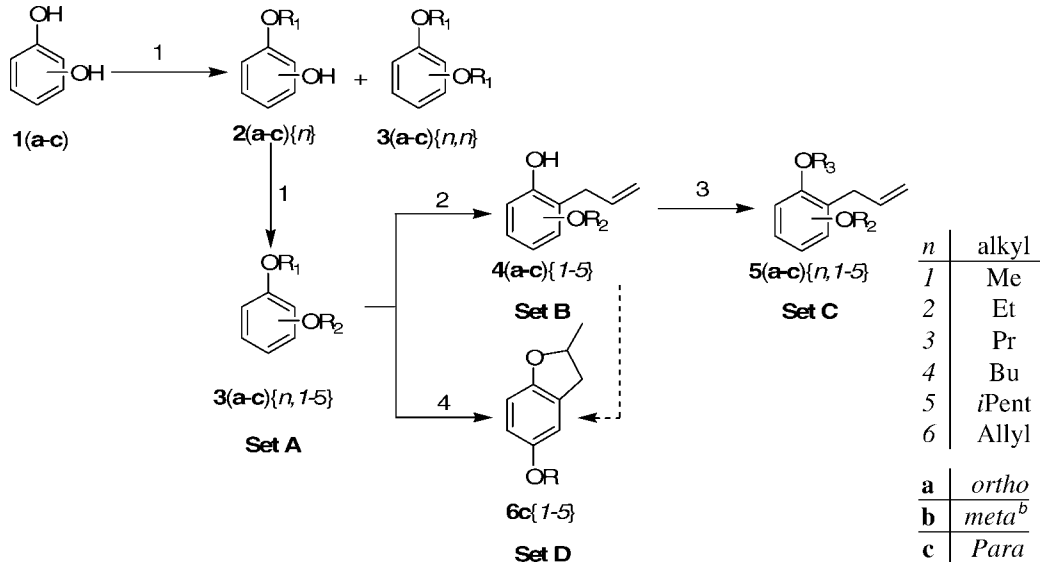
Scheme 1. General Approach for the Synthesis of Minilibraries[a]



[a] Reaction conditions: (1) base (NaH, K_2CO_3, or Cs_2CO_3), solvent (DMF or acetone), alkyl halide (MeI, EtI, PrI, BuBr, *i*PentBr, or AllylBr), room temperature or reflux; (2) for **3**(**a**−**c**){*6,1-5*} neat, 180 °C, 10 h (see Scheme 2); (3) K_2CO_3, alkyl halide, acetone, reflux; (4) for **3c**{*6,1-5*} neat, 180 °C, 30 h (Scheme 2). [b] The meta product from the Claisen rearrangement (Set B) results in two products and will be identified as: **4b**^{x}{*n*} for 5-alkoxy-2-allyl phenol and **4b**^{y}{*n*} for 3-alkoxy-2-allyl phenol (see Scheme 2) (similarly for their alkylated derivatives).

the identity and purity of individual components. The members of a library are obtained in a common, single reaction rather then individual, parallel reactions. Because blends are so important in taste and olfaction, one cannot simply screen libraries with hundreds or thousands of compounds mixed together. In order to facilitate interpretation of the results, the components of the test mixture need to be well-known. On the other hand, the screening assays are very laborious, so it is of great advantage to test a few compounds simultaneously. Systematic grouping of the compounds tested simultaneously, as well as testing of a few individual compounds, enables us to determine which substituent size and position may be most active in a particular insect species. The objectives of the work presented here were: (1) to develop ether syntheses to generate systematically varied sets of disubstituted alkoxybenzenes, (2) to expand chemical diversity of the alkoxybenzenes by studying the Claisen rearrangement of allyl ether sets, and (3) to demonstrate that these sets of compounds can be subjected to three types of biological assays: GC-electorantennographic detection (GC-EAD), electroantennogram (EAG) assays, and pheromone-binding protein (PBP) binding assays.

Results and Discussion

Chemistry. Synthesis. In preliminary studies, monoalkoxy phenols **2**(**b,c**){*n*} were obtained by enzymatic monoacetylation of resorcinol **1**(**b**) or hydroquinone **1**(**c**) followed by alkylation of the resulting phenol acetates and removal of the acetate group (see the Supporting Information). Subsequent experimental results led to the replacement of this initial route with a higher yielding direct alkylation approach. Ortho (**a**), meta (**b**) or para (**c**) substituted dihydroxy benzene **1**(**a**−**c**) was deprotonated and reacted with an alkyl halide to afford mono **2**(**a**−**c**){*n*} and dialkoxy **3**(**a**−**c**){*n,n*} products (Scheme 1). Tuning of the experimental conditions (base, solvent, and reaction time) allowed the preferential synthesis of either monoalkylated or dialkylated products. Mono- and dialkylated products were separated using their acid/base properties. The monoalkoxy compounds **2**(**a**−**c**){*n*} were necessary for the synthesis of libraries, and the dialkoxy compounds **3**(**a**−**c**){*n,n*} with identical alkyl groups were needed for characterization and biological testing (Table 1).

Table 1. Purity of Dialkoxy Compounds **3**(**a**−**c**){*n,n*} Synthesized for Characterization and Biological Evaluation

no.	compound	purity[a]	no.	compound	purity[a]
1	**3a**{*1,1*}	94	10	**3b**{*4,4*}	100
2	**3a**{*2,2*}	100	11	**3b**{*5,5*}	100
3	**3a**{*3,3*}	100	12	**3b**{*6,6*}	95
4	**3a**{*4,4*}	100	13	**3c**{*1,1*}	95
5	**3a**{*5,5*}	100	14	**3c**{*2,2*}	95
6	**3a**{*6,6*}	99	15	**3c**{*3,3*}	96
7	**3b**{*1,1*}	94	16	**3c**{*4,4*}	99
8	**3b**{*2,2*}	98	17	**3c**{*5,5*}	98
9	**3b**{*3,3*}	98	18	**3c**{*6,6*}	99

[a] Purity was determined by GC.

For the synthesis of the first set of minilibraries (Set A, Scheme 1 and Table 2), equimolar mixtures of monoalkoxy **2**(**a**−**c**){*n*} compounds were alkylated to afford chemsets of 4 or 5 members **3**(**a**−**c**){*n,1–5*}. In order to effect complete deprotonation of the monoalkoxy compounds **2**(**a**−**c**){*n*}, the alkylation was conducted with NaH as the base, in DMF, at room temperature. The reaction was monitored by GC, and it proceeded at similar rates for all the components, affording crude products of high purity (>90% by GC). However, the removal of DMF resulted in losses of material. Further, the more volatile dialkoxy members **3**(**a**−**c**){*n,1–5*} evaporated in sufficient quantities to introduce biases (e.g Table 2, entry 2). Following optimization, the K_2CO_3/acetone base/solvent system afforded better yields and much less bias (e.g., Table 2, entry 6).

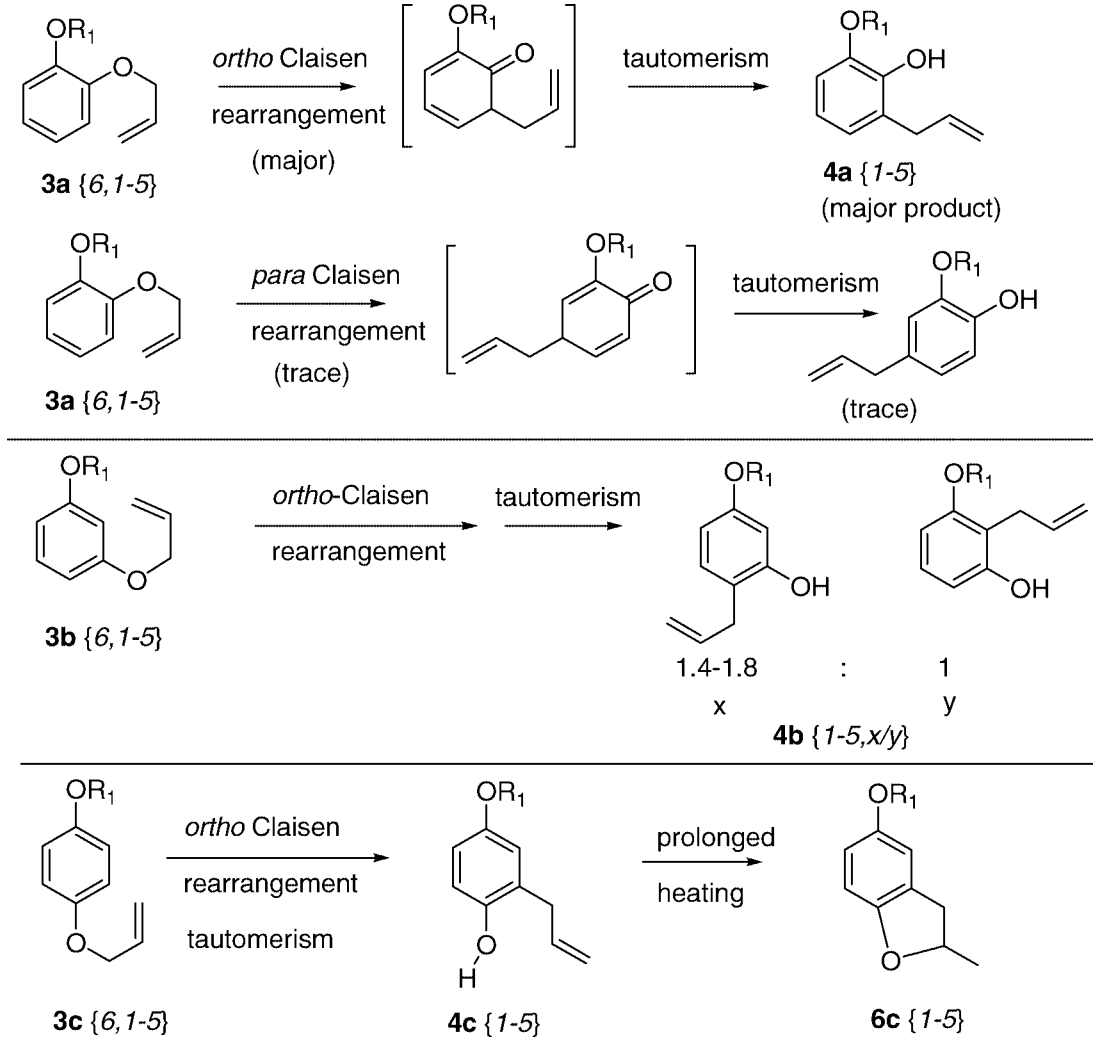
Further expansion of the libraries was accomplished via the ortho-Claisen rearrangement of chemsets **3**(**a**−**c**){*6,1–5*} at 180 °C and afforded pure libraries (Set B, Table 2). For

Table 2. Purity of the Libraries and Percent Distribution of the Members in Libraries

				distribution of members in library (%)[e]				
no.	library[b]	*n*	purity[c]	{*n*,1}[d]	{*n*,2}	{*n*,3}	{*n*,4}	{*n*,5}
				Set A				
1	**3a**{*1,1–5*}	1	100	13.7	13.0	16.9	26.0	30.4
2	**3a**{*2 1–5*}	2	99	7.0	8.8	15.3	32.5	35.0
3	**3a**{*3,1–5*}	3	99	9.7	12.3	20.2	25.8	30.7
4	**3a**{*4,1–5*}	4	99	9.0	14.7	18.8	27.9	27.2
5	**3a**{*5,1–5*}	5	99	7.7	12.9	17.9	31.2	29.6
6	**3a**{*6,1–5*}	6	100	13.2	15.9	19.2	27.3	24.3
7	**3b**{*1,1–5*}[a]	1	99	21.1	21.7	26.1		30.0
8	**3b**{*2,1–5*}[a]	2	95	16.2	20.4	26.4		32.3
9	**3b**{*3,1–5*}[a]	3	97	12.0	16.2	28.6		39.7
10	**3b**{*4,1–5*}[a]	4	100	19.1	20.7	27.7		32.2
11	**3b**{*5,1–5*}[a]	5	97	22.5	22.9	27.3		24.3
12	**3b**{*6,1*}	6	100	100				
13	**3b**{*6,2–3*}	6	97		62	38		
14	**3b**{*6,4–5*}	6	97				59	41
15	**3c**{*1,1–5*}[a]	1	97	15.1	20.2	23.2		38.2
16	**3c**{*2,1–5*}[a]	2	98	20.1	23.6	23.9		30.7
17	**3c**{*3,1–5*}[a]	3	96	19.7	18.6	24.9		32.9
18	**3c**{*4,1–5*}[a]	4	97	24.6	23.0	24.7		24.8
19	**3c**{*5,1–5*}[a]	5	95	22.7	21.2	24.5		26.7
20	**3c**{*6,1–5*}	6	100	10.1	13.6	18.6	23.8	33.9
				Set B				
21	**4a**{*1–5*}		95	13.7	17.3	18.9	23.1	22.0
22	**4b**{*1*}[f]		100	61/39				
23	**4b**{*2–3*}[f]		100		22/20	32/27		
24	**4b**{*4–5*}[f]		100				26/24	28/22
25	**4c**{*1–5*}		100	9.1	14.3	20.6	22.9	33.1
				Set C				
26	**5a**{*1,1–5*}	1	92	12.9	14.5	17.2	24.1	23.7
27	**5a**{*2,1–5*}	2	93	14.3	15.5	17.0	23.2	23.1
28	**5a**{*3,1–5*}	3	94	14.0	15.2	17.6	23.7	23.1
29	**5a**{*4,1–5*}	4	90	16.7	16.7	15.7	22.3	18.5
30	**5a**{*5,1–5*}	5	90	19.9	20.7	15.6	19.7	14.5
31	**5a**{*6,1–5*}	6	96	17.6	21.5	18.0	22.5	16.4
32	**5b**{*1,1*}[f]	1	99	60/40				
33	**5b**{*1,2–3*}[f]	1	96		23/16	38/24		
34	**5b**{*1,4–5*}[f]	1	100				34/20	29/17
35	**5b**{*2,1*}[f]	2	100	62/38				
36	**5b**{*2,2–3*}[f]	2	98		24/16	38/22		
37	**5b**{*2,4–5*}[f]	2	100				36/20	27/17
38	**5b**{*3,1*}[f]	3	100	61/39				
39	**5b**{*3,2–3*}[f]	3	100		25/16	35/23		
40	**5b**{*3,4–5*}[f]	3	100				35/19	31/15
41	**5b**{*4,1*}	4	98	62/38				
42	**5b**{*4,2–3*}[f,g]	4	98		34/20	31/15		
43	**5b**{*4,4–5*}[f,g]	4	95				30/18	32/20
44	**5b**{*5,1*}[f,g]	5	99	62/38				
45	**5b**{*5,2–3*}[f,g]	5	100		34/20	31/15		
46	**5b**{*5,4–5*}[f,g]	5	99				30/19	31/20
47	**5b**{*6,1*}[f,g]	6	94	61/39				
48	**5b**{*6,2–3*}[f,g]	6	94		36/21	26/17		
49	**5b**{*6,4–5*}[f,g]	6	88				29/20	30/21
50	**5c**{*1,1–5*}	1	99	11.0	14.0	19.9	23.7	30.0
51	**5c**{*2,1–5*}	2	100	12.6	16.5	22.8	21.3	26.8
52	**5c**{*3,1–5*}	3	100	12.5	15.9	21.9	22.7	26.9
53	**5c**{*4,1–5*}	4	100	9.8	14.5	23.1	24.1	28.5
54	**5c**{*5,1–5*}	5	99	16.5	18.9	22.0	20.3	21.3
55	**5c**{*6,1–5*}	6	100	14.1	21.5	27.5	18.6	18.3
				Set D				
56	**6a**{*1–5*}		100	10.5	15.1	19.9	24.6	29.9

[a] These libraries do not contain the {*n*,4} member. [b] The sequence of alkyl substituents in the brackets is interchangeable: e.g., member **3a**{*1,2*} is identical with member **3a**{*2,1*}. [c] Purity was determined by GC. [d] "*n*" has the same significance as in Scheme 1, and it corresponds to the first number in the bracket of the respective chemset. [e] Percent distribution of the library members was determined by GC and validated by NMR and GC-MS data. [f] Meta compounds undergoing a Claisen rearrangement yielded two products, and the "5-alkoxy-2-allyl phenol" (*x*) is listed first; the same format holds for the alkylated derivatives of the meta-Claisen rearrangement products. [g] The initial lot of starting material, **4b**{*n*}, was used completely and resynthesized as a second lot.

Scheme 2. Reactions Observed for the Thermal Claisen Rearrangement of Ortho, Meta, and Para Allyl Ethers **3a**, **3b**, and **3c**{*6,1−5*}[a]



[a] The thermal ortho-Claisen rearrangement is believed to be concerted,[22–24] and the para-Claisen rearrangement is thought to proceed via charged pairs or via a Cope rearrangement preceding tautomerism.[19,21] The product ratio of the ortho-Claisen rearrangement of the meta-substituted starting compounds **3b**{*6,1−5*} is similar to the ratio observed or predicted in mechanistic studies.

the ortho library, **4a**{*1–5*}, traces (2−5%) of the para-Claisen rearrangement products were detected (Scheme 2). For the meta **4b** libraries, no para-Claisen rearrangement was detected, and for para **4c** libraries, the para-Claisen rearrangement was not possible and not observed (Scheme 2). Under thermal conditions, the para-Claisen rearrangement of allyl phenyl ethers is not an important pathway.[18] Under selected Lewis acid or metal catalysis conditions, and when the ortho positions are blocked, the para-Claisen rearrangement can be significant.[19–21] The meta compounds **3b**{*6,1–5*} yielded two products: 5-alkoxy-2-allylphenol, *x*, and 3-alkoxy-2-allylphenol, *y* (Table 2, Scheme 2) upon ortho-Claisen rearrangement. The rearrangement to the less sterically hindered side was slightly more prevalent (1.4–1.8×) than the alternative rearrangement to the hindered position, consistent with previous literature on the thermal Claisen rearrangement of meta-substituted allyl phenol ethers.[18,22,23]

The Claisen rearrangement introduced an *OH* group, which was further alkylated to afford Set C of trisubstituted minilibraries **5**(**a**−**c**){*n,1–5*}. The **4**(**a**−**c**){*1–5*} and **5**(**a**−**c**){*n,1–5*} minilibraries can be considered as eugenol (2-methoxy-4-(2-propenyl) phenol) analogues. In one instance, prolonged heating of the **4c**{*1–5*} minilibrary afforded the minilibrary of racemic dihydrobenzofurans **6c**{*1–5*} which was isolated in 60% yield and 100% purity. Despite many attempts, the ortho and meta sets did not undergo this cyclization reaction upon prolonged heating.

Characterization. The identity of the members in each library was confirmed by ^{1}H NMR and GC-MS techniques. The increment of one carbon between the members of a chemset was reflected in very well-resolved peaks in both GC and GC-MS. Members of chemsets belonging to Sets A and C have a common alkyl group, *n*, and a variable second alkyl group, *1−5* (see Scheme 1 for naming). Each chemset contains a member with identical alkyl groups, and these members were synthesized as single compounds and fully identified (^{1}H NMR, ^{13}C NMR, and GC-MS). These individual compounds are helpful during screening assays, to obtain information about the molecular mass range and substitution pattern that are best for activity (see below). Data from the ^{1}H NMR spectra of these dialkylated compounds **3**(**a**−**c**){*n,n*} and of the monoalkylated phenol compounds

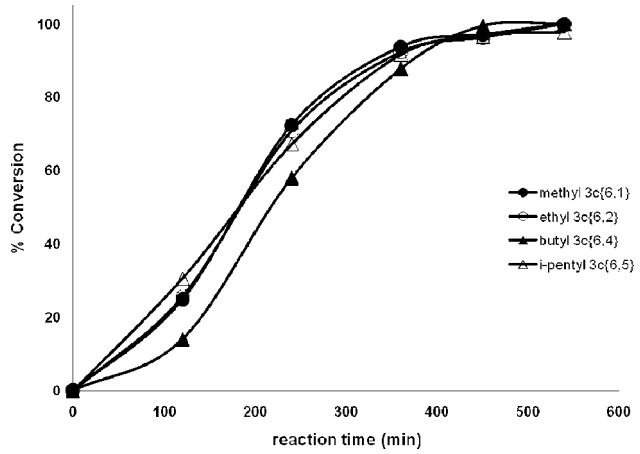


Figure 1. Progress of the Claisen rearrangement reaction of the **3c**{*6,1–5*} library.

2(**a**−**c**){*n*} was used to assign at least one characteristic signal for each member of a chemset. The proportion of each compound in a set, obtained from the integration of these characteristic signals, was the same as the proportion of that compound obtained by GC. This congruence of ^{1}H NMR and GC data validates the composition of the libraries (Table 2). Each library composition was further confirmed during GC-MS calibrations (with 1-methoxy-4-methyl-benzene as internal standard) that were part of the PBP binding assays of the compounds and libraries (see the Biological Evaluation section).

Reaction Rates of Components in the Libraries. Within each set, **2a**{*1–5*}, **2b**{*1–5*}, or **2c**{*1–5*}, the rates of the second alkylation were similar for all compounds in the mixture, suggesting that the size of the substituent did not influence the rate of the reaction. This was especially surprising in the case of the ortho-substituted substrates for which, regardless of the differences in size of the alkyl substituent or alkyl halide reagent (methyl to *iso*-pentyl), complete conversion was achieved at the same time for all the members of the set.

To determine whether the Claisen rearrangement of the **3(a-c)**{*6,1–5*} libraries was also independent of substituent size, the rearrangement was monitored by GC at regular time intervals. For the para library, **3c**{*6,1–5*}, the GC peaks corresponding to the substrates were better resolved and the percent conversion of four of the starting materials was calculated and plotted against time (Figure 1). The graph confirms that the size of the substituent did not influence the reaction progress and that complete conversion of all compounds in a set was achieved after about 9 h of reaction time. A similar behavior was also obtained for the ortho and meta libraries **3**(**a**,**b**){*6,1–5*}. A previous kinetic study of the Claisen rearrangement of various para-substituted allyl phenyl ethers also suggested that the rate of the rearrangement is mildly dependent on the nature of the substituents; electron-releasing groups accelerated the reaction. The methoxy and ethoxy members of that study gave the same rates of rearrangement.[25]

Comparison between the conversion profile of ortho-, meta-, and para-substituted library members showed differences in the half-time to total conversion, but not in the total

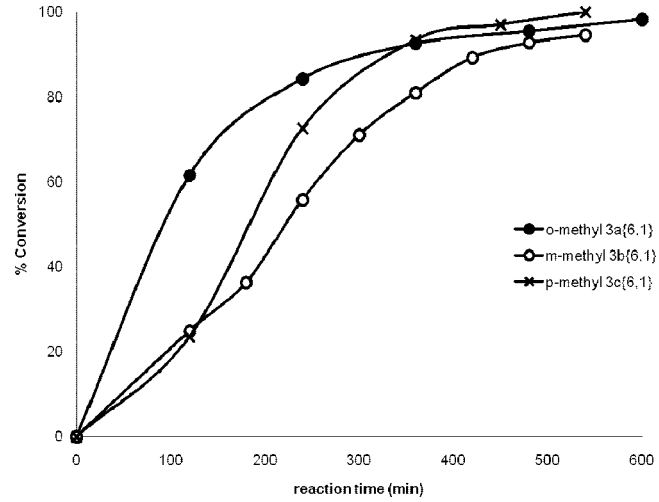


Figure 2. Progress of the Claisen rearrangement reaction: comparison between the ortho methoxy **3a**{*6,1*}, meta methoxy **3b**{6,1}, and para methoxy **3c**{*6,1*} library members.

reaction time. Members of the ortho library **3a**{*6,1–5*} achieved 50% conversion in 1 h while it took 3 and 4 h for the members of the para library **3c**{*6,1–5*} and meta library **3b**{*6,1–5*}, respectively, to reach the same point. The time necessary to achieve total conversion was not dependent upon the substitution pattern. For clarity, only data for one member in each library are shown (Figure 2). In a previous kinetic study, the rearrangement of para and meta methoxy substituted allyl phenyl ether had the same rate constants.[25]

Dihydrobenzofuran Formation. When the para library **3c**{*6,1–5*} was heated three times longer (30 h) than required for the completion of the Claisen rearrangement, dihydrobenzofurans **6c**{*1–5*} were obtained. Reported spectral data for the known compound, **6c**{*1*}, was used to confirm the identity of the products.[26] As a further proof we synthesized **6c**{*3*} as a single compound, and its spectra as well as GC retention time matched the data for the respective library member. Interestingly, cyclization occurred only on the para substituted compounds **3c**{*6,1–5*} and not on the ortho **3a**{*6,1–5*}or meta **3b**{6,1–5} substituted ones. Ortho and meta allyl ethers began decomposing when heated longer than was necessary to complete the Claisen rearrangement. Further, we learned that the cyclization reaction followed the Claisen rearrangement and, therefore, library **6c**{*1–5*} could also be obtained directly from the **4c**{*1–5*} library. The cyclization reaction proceeded in a Markovnikov sense, and this selectivity has been observed also with (3′-methyl)-2′-butenyl (dimethylallyl) substituents.[20] In previous literature, allyl aryl ethers were rearranged and cyclized to dihydrobenzofurans in the presence of a copper (II) triflate catalyst,[27] an iridium (III)/silver triflate catalyst,[26] aluminum-containing mesoporous molecular sieves,[28] a gold (I)-catalyst,[29] or a bismuth triflate catalyst.[20] These studies also suggest that the Claisen rearrangement occurs first, followed by the Markovnikov addition of the new phenol OH to the allyl double bond.[29] In fact, few catalysts promoted the tandem reaction; some only catalyzed the Claisen reaction, and others caused decomposition. Further, the allyl phenyl ethers that cyclized best generally had electron-releasing groups or no additional substituents on the benzene ring.

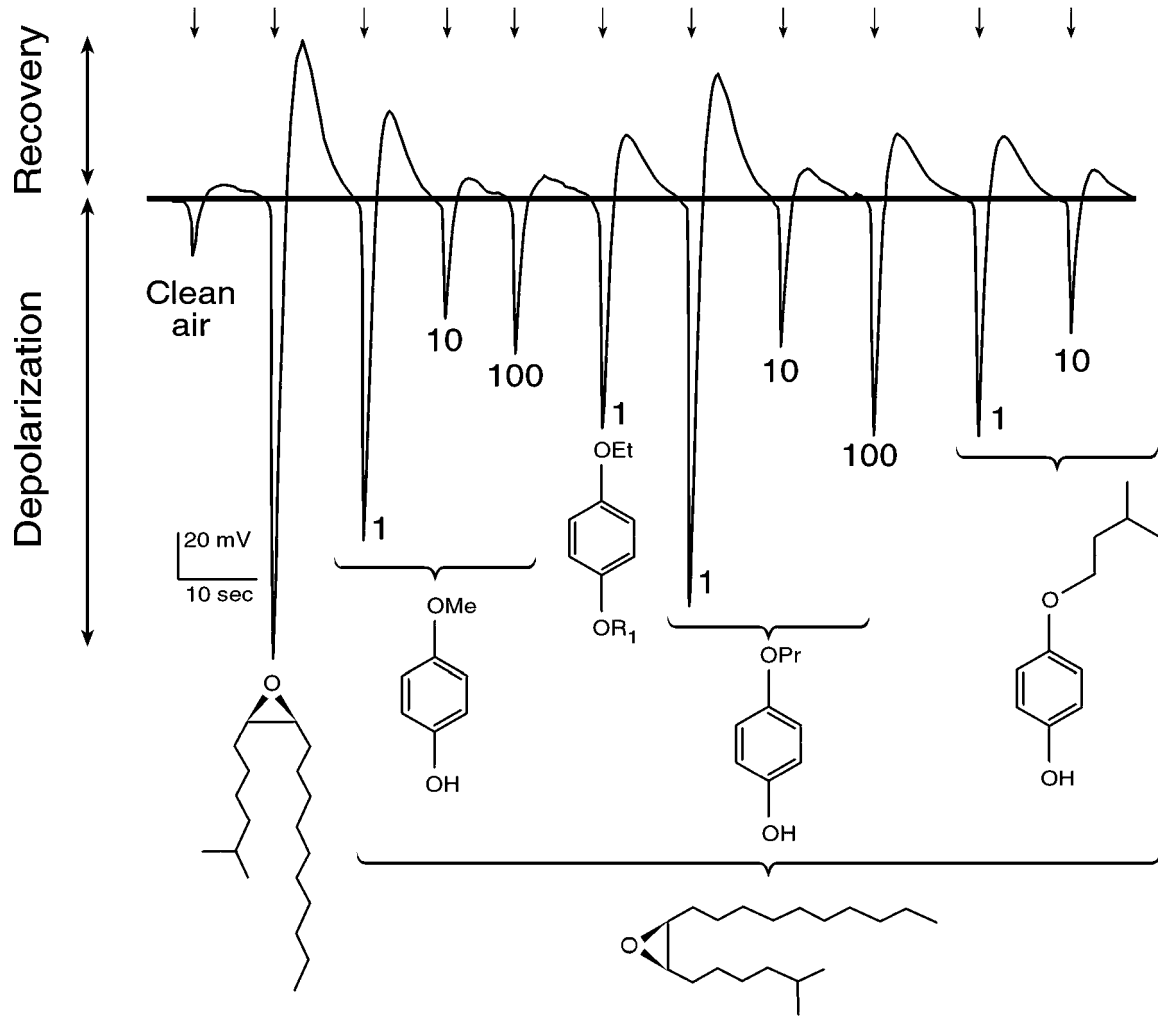


Figure 3. Competitive electroantennogram (EAG) assay, with an antenna of a male gypsy moth, *Lyamantria dispar*, responding to puffs of clean air or to chemicals delivered in puffs of air. In this assay, libraries and individual compounds are tested for their ability to inhibit the antennal response to the sex attractant pheromone of the gypsy moth, (7*R*,8*S*) 2-methyl-7,8-epoxyoctadecane, also known as (+)-disparlure. The controls consisted of a puff of clean air (negative) or of air passed over a cartridge impregnated with (+)-disparlure (100 ng) (positive). The treatments consisted of 100 ng of (+)-disparlure in combination with a compound or library at 1, 10, or 100 μg, on a cartridge over which the air puff was passed. The small arrows above the trace denote the times where the air was puffed over the antenna.

Consistent with our observation that in the noncatalyzed tandem Claisen-cyclization only para-substituted and non-substituted aryl allyl ethers cyclized, the highest yield for the $IrCl_3$/AgOTf-catalyzed reaction was reported for 1-allyloxy-4-methoxy (**3c**{*1,6*}).[26] Strongly electron-withdrawing groups appear to inhibit the cyclization, perhaps because the phenol is less nucleophilic in those cases.[27]

Biological Evaluation

We used three screening methods in this study, all applied to the gypsy moth *Lymantria dispar*: (1) electroantennogram detection of GC traces (GC-EAD), (2) competitive electroantennograms (EAG), in which we assayed libraries and individual compounds for inhibition of the antennal responses to the sex pheromone *cis*-(7*R*,8*S*)-7,8-epoxy-2-methyloctadecane of *L. dispar* (also known as (+)-disparlure), and (3) in vitro screen for pheromone-binding protein (PBP) binding activity. As an example, we present results with compounds **2c**{*n*}, **2c**{*n,n*}, and minilibraries **3c**{*n,1–4*}. All the other compounds discussed here are in the process of being screened, and the results from that work will be published elsewhere.

Gas Chromatorgaphic-Electroantennographic Detection (GC-EAD). In GC-EAD assays, the analyte is processed by gas chromatography (GC). The column effluent is split, such that molecules of each chromatographic peak arrive simultaneously at the flame ionization detector of the GC and at an anectomized but otherwise intact insect antenna as the biological detector. This procedure detects specific compounds in the analyte that elicit an electrical potential from the antenna. The results of GC-EAD indicated that compounds and minilibraries tested **2c**{*n*}, **2c**{*n,n*}, and **3c**{*1–5*} elicited almost no antennal response by themselves. This is desirable, as it implies that the moths cannot detect these compounds with their antennae.

Pheromone EAG Assays. We performed EAG competitive assays to investigate whether our diethers inhibit the response of *L. dispar* antennae to the main component of the sex attractant pheromone *cis*-(7*R*,8*S*)-epoxy-2-methyloc-

Table 3. Inhibitory Activity of Para Compounds **2c**{*n*}, **2c**{*n,n*}, and Libraries **3c**{*n,1–5*}[a]

compound/library	dose (μg)	activity	compound/library	activity
2c{*1*}	1	10 ± 5 (15)	**3c**{*1,1*}	4 ± 6 (4)
	10	55 ± 11 (15)		−8 ± 9 (5)
	100	43 ± 12 (15)		38 ± 7 (4)
2c{*2*}	1	49 ± 10 (22)	**3c**{*2,2*}	4 ± 13 (5)
	10	64 ± 9 (6)		45 ± 6 (6)
	100	45 ± 8 (6)		−3 ± 13 (5)
2c{*3*}	1	17 ± 14 (16)	**3c**{*3,3*}	5 ± 16 (5)
	10	43 ± 14 (16)		55 ± 7 (6)
	100	35 ± 12 (16)		−3 ± 15 (6)
2c{*5*}	1	38 ± 17 (16)	**3c**{*5,5*}	63 ± 12 (12)
	10	38 ± 27 (16)		38 ± 22 (13)
	100	19 ± 20 (14)		64 ± 11 (11)
3c{*1,1–5*}[a]	100[b]	**73 ± 9** (14)	**3c**{*4,1–5*}[a]	**90 ± 6** (12)
3c{*2,1–5*}[a]	100	**86 ± 11** (14)	**3c**{*5,1–5*}[a]	**74 ± 6** (12)
3c{*3,1–5*}[a]	100	**89 ± 6** (13)		

[a] These libraries no not contain the {*n,4*} member. Data are for percent inhibition of the EAG response to the sex attractant pheromone of the gypsy moth (+)-disparlure (eq 1); means ± SE. The number of replicates is shown in parenthesis. Signals were corrected for a clean air background. Entries in bold showed >70% inhibition of the (+)-disparlure signal. The dose is the amount of material placed on a paper cartridge, over which a puff of air is passed to stimulate the insect antenna. Responses are corrected relative to the antennal response to a puff of clean air. [b] Response of the libraries to 1 and 10 μg doses was not determined.

tadecane [(+)-disparlure] (Figure 3). In EAG assays, an anectomized, responsive antenna is mounted between electrodes and subjected to specific chemical stimuli. The stimuli are delivered in an air stream passing over the antennal preparation. The monoalkoxy phenols **2c**{*n*} and the para-substituted dialkoxybenzenes were tested for this study. The results (Table 3) showed that there was some selectivity in the inhibitory activity of the tested compounds. The monoalkyl phenols showed moderate or weak inhibition of antennal pheromone responses at any dose. Among the bisphenol ethers **2c**{*n,n*}, some moderate inhibitory activity was seen with **2c**{*3,3*} and with **2c**{*5,5*}. This suggested that a certain minimal compound size was required for activity. Three minilibraries showed robust inhibitory activity (>80% inhibition). Interestingly, the activity was moderate when the common alkyl group was either methyl **3c**{*1,1–5*} or isopentyl **3c**{*5,1–5*} and strong when the common group was either ethyl **3c**{*2,1–5*}, propyl **3c**{*3,1–5*}, or butyl **3c**{*4,1–5*}. This suggests that there is a certain minimal and maximal compound size required. Further, the activity of compound **3c**{*5,5*} was lower than that of the **3c**{*5,1–5*} minilibrary, and the activity of compound **3c**{*3,3*} was significantly lower than that of **3c**{*3,1–5*} or **3c**{*4,1–5*} minilibraries, suggesting that at least one of the ether moieties in the diethers needs to be medium-sized (propyl, butyl) and straight-chain. Therefore, our study showed that in order to design compounds with high activity toward gypsy moth, these should probably incorporate one isopentyl group and either an ethyl, propyl, or butyl group.

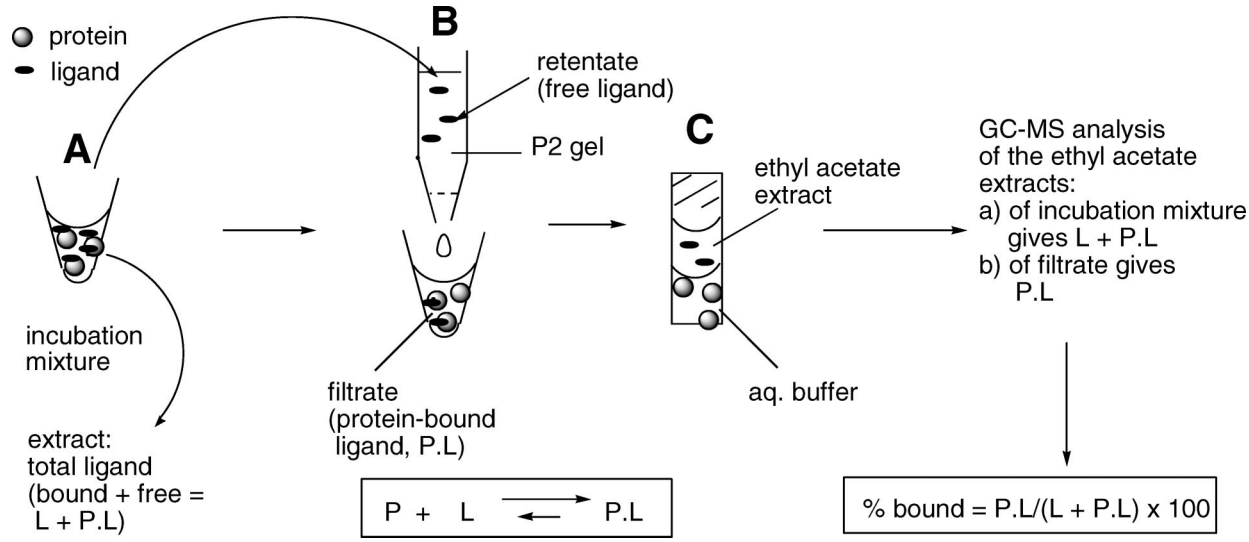
Pheromone-Binding Protein (PBP) Binding Assays. These assays were performed as described in Scheme 3. The members of each minilibrary were separated cleanly by GC; therefore, it was possible to monitor binding of individual members to PBP1 or PBP2, the two known PBPs in the gypsy moth, by extraction from the aqueous incubation mixture, followed by GC analysis of the extract (Scheme 3). Interestingly, PBPs exhibit nonlinear behavior in the presence of blends.[21] In this study, blend effects manifested themselves as different binding affinities for one compound, depending on the composition of the minilibrary tested (Table 4). For example, **3c**{*1,2*} bound to PBP1 and PBP2 as a member of the **3c**{*2,1–5*} ethyl library more strongly than as a member of the **3c**{*1,1–5*} methyl library. Similarly, **3c**{*2,3*} bound more strongly to PBP2 as a member of the **3c**{*2,1–5*} ethyl library than as a member of the **3c**{*3,1–5*} propyl library. Further, the pure compounds **3c**{*1,1*}, **3c**{*2,2*}, and **3c**{*3,3*} bound more strongly to PBP1 by themselves than as part of the minilibraries that contain these compounds. Interestingly, for PBP2 binding of the pure compounds with identical alkyl group, **3c**{*n,n*} was either weaker or the same as in the libraries. We have noticed previously that PBP2 is less discriminating and exhibits lesser blend effects than PBP1.[30,31]

Overall, binding was strongest to both PBPs in the **3c**{*2,1–5*} ethyl library and binding became weaker as the average molecular size in the series increased. These results suggest that there is a minimal and a maximal size requirement for binding. There was no correlation between the percentage bound of the single compounds or the strongest binder from the minilibraries and the EAG inhibition activity ($R^2 < 0.2$). There were moderate negative correlations between PBP binding of **3c**{*2,2*}, **3c**{*3,3*}, and **3c**{*5,5*}, as well as binding of individual isopentyl members of the libraries **3c**{*1,5*}, **3c**{*2,5*}, **3c**{*3,5*}, **3c**{*4,5*}, and **3c**{*5,5*} and the EAG inhibitory responses of the **3c**{*n,n*} compounds or the minilibraries (correlations: $R^2 = 0.57$, PBP1; $R^2 = 0.81$, PBP2). This suggests that, for some of the compounds, the stronger the PBP binding, the weaker the EAG inhibition activity. Further assays with the other compounds described herein and with various insects will be presented elsewhere.

Conclusions

In this paper, we present a high-yielding method for generating libraries of substituted alkoxy benzenes or their derivatives, for testing as odorants or tastants. The chemical sensing process of insects is highly complex and nonlinear: the sensation and resulting behavior of the insect are dependent on both concentration of a chemical signal and blend composition. On the other hand, tests with insect chemosensory systems are laborious. Thus, we have prepared small libraries of alkoxy benzenes (with 4–5 compounds),

Scheme 3. Insect Pheromone-Binding Protein (PBP) Ligand Binding Assay[a]



[a] (**A**) The protein and ligand are incubated in buffer (see the Experimental Details section) overnight. (**B**) For half of the incubation mixture, the free ligand (L) is separated from the protein-bound ligand (PL) by size-exclusion chromatography on P2 Gel (BioRad, exclusion limit 2000 Da). The protein elutes from the small column bed, with its ligand bound (see the Experimental Details section and refs 30 and 31), while the free ligand is retained on the column.[31] (**C**) The remaining half of the incubation mixture and the filtrate are transferred to glass vials and extracted with ethyl acetate, containing an internal standard (see the Experimental Details section). The extract from the filtrate (**B**) contains the protein-bound ligand and the extract from the incubation mixture (**A**) contains all the ligand (bound and free) present in the aqueous phase. The extracts are analyzed by GC-MS, to obtain values for total ligand in solution (L + P·L) and for protein-bound ligand (P·L). These can then be used to calculate the percent bound (Table 4).

Table 4. Binding Affinity of Two Pheromone-Binding Proteins (PBPs) from Gypsy Moth toward Members in the Para **3c**{*n,1–5*}[a] Libraries and Para Dialkoxy **3c**{*n,n*} Compounds

		(% bound)[b]	
library/compound	member	PBP1	PBP2
(+)-disparlure		54 ± 16	71 ± 23
3c{*1,1–5*}[a]	**3c**{*1,1*}	24 ± 0.3	19 ± 0.9
	3c{*1,2*}	15 ± 0.4	12 ± 1.5
	3c{*1,3*}	7 ± 0.5	5 ± 2.1
	3c{*1,5*}	1 ± 0.7	2 ± 2.5
3c{*1,1*}		40 ± 2.5	13 ± 2.1
3c{*2,1–5*}[a]	**3c**{*2,1*}	30 ± 0.2	40 ± 0.1
	3c{*2,2*}	14 ± 0.5	33 ± 0.6
	3c{*2,3*}	10 ± 0.3	22 ± 0.3
	3c{*2,5*}	4 ± 0.2	14 ± 0.2
3c{*2,2*}		28 ± 0.1	19 ± 0.2
3c{*3,1–5*}[a]	**3c**{*3,1*}	13 ± 0.3	7 ± 0.2
	3c{*3,2*}	13 ± 0.3	6 ± 0.2
	3c{*3,3*}	4 ± 0.3	3 ± 0.1
	3c{*3,5*}	1 ± 0.2	nd
3c{*3,3*}		15 ± 0.7	5 ± 0.2
3c{*4,1–5*}[a]	**3c**{*4,1*}	20 ± 0.4	nd
	3c{*4,2*}	10 ± 0.4	nd
	3c{*4,3*}	4 ± 0.3	nd
	3c{*4,5*}	4 ± 0.4	nd
3c{*4,4*}		4 ± 0.1	8 ± 0.3
3c{*5,1–5*}[a]	**3c**{*5,1*}	7 ± 0.1	5 ± 0.1
	3c{*5,2*}	2 ± 0.1	3 ± 0.03
	3c{*5,3*}	3 ± 0.1	2 ± 0.02
	3c{*5,5*}	5 ± 0.1	1 ± 0.1
3c{*5,5*}		9 ± 0.7	8 ± 0.2

[a] These libraries do not contain the {*n,4*} member. [b] Percentage of compound bound to the protein, according to eq 4. Data shown are means ± SE for 4 replicates. nd = not detected in the GC-MS quantitations.

whose members separate easily by GC and can therefore be monitored during assays. Sets of known composition and total purity with respect to the compounds of interest have been prepared by three reactions: (1) alkylation of 1-hydroxy-2,3, or 4-alkoxybenzenes, (2) thermal ortho-Claisen rearrangement of 1-allyloxy, 2, 3 or 4-alkoxybenzenes, and (3) a second alkylation of the rearrangement products. Reactions of all three types worked well for ortho, meta, and para compounds, while minimal (in the case of ortho-) or no para-allyl migration occurred. The Claisen rearrangement of the para compounds was followed by a cyclization to dihydrobenzofurans upon prolonged heating.

None of the para-substituted compounds assayed here elicited antennal responses by themselves. However, when puffed simultaneously with the sex attractant pheromone of the gypsy moth, compounds with two medium-sized alkoxy groups (one ethyl-, propyl-, or butyl- and one isopentyl group) gave significant inhibition of the antennal response to the pheromone at high doses. None of the para compounds tested here bound strongly to either of the two pheromone-binding proteins (PBPs) of the gypsy moth. *Para*-dialkoxybenzenes with small substituents (methyl, ethyl) bound slightly more strongly to PBPs than compounds with larger substituents.

Experimental Details

General. All solvents used were of analytical grade. Resorcinol monoacetate was from Aldrich. Gas chromatography was done on Hewlett-Packard 5890 using a SPB-5 column Supelco, 30 m, 0.25 mm i.d., (0.25 μm film), programmed at 100 °C (5 min), 10 °C/min, 200 °C (0 min), 50 °C/min, and 250 °C (14 min). The gas chromatographic data are reported as retention indices (RI). NMR spectra were taken on a Varian 500 MHz instrument using $CDCl_3$ as solvent. Mass spectra were recorded on a Varian Saturn 2000 MS coupled to a CP 300 GC, equipped with a SPB-5 GC column (same type as above). Both EI (70 eV) and CI (isobutane) modes of ionization were used.

Procedures and Data for Minilibraries in Set A and Set C. Method A. A mixture of monoalkoxy phenols (1 equiv) in DMF (2 mL) was added to a suspension of NaH

(5 equiv) in DMF (3 mL). The alkylating reagent (MeI, EtI, PrI, BuBr, bromo-3-methyl butane, or allyl bromide, 3 equiv) was then added, and the reaction mixture was stirred at room temperature and monitored by GC. When the reaction was complete (between 1 and 4 h), a solution of saturated NH_4Cl (25 mL) was slowly added and the aqueous phase was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with water (4 × 25 mL) and brine (2 × 25 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography using hexane:EtOAc (4:1) to afford the corresponding library as pure oil. (note: the 1,3-dialkoxy benzene libraries required a second purification by flash column chromatography, with hexanes:EtOAc, 4:1).

Method B. A mixture of monoalkoxy phenols (1 equiv) in acetone (5 mL) was added to a suspension of K_2CO_3 (10 equiv) in acetone (20 mL), and the mixture was stirred at room temperature for 2 h. The alkylating reagent (MeI, EtI, PrI, BuBr, 1-bromo-3-methylbutane, or allyl bromide, 3 equiv) was then added, and the reaction mixture was heated at reflux and monitored by GC. When the reaction was complete, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue obtained was diluted with $CHCl_3$ (30 mL) and water (20 mL). The layers were separated; the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the corresponding library as pure oil. For compound sets **5b**{*n,n*}, the oils were decolorized with flash chromatography (5% EtOAc in hexane), even though GC analysis indicated that the compounds were pure.

Method C. A mixture of monoalkoxy phenols (1 equiv) in acetone (5 mL) was added to a suspension of Cs_2CO_3 (2 equiv) in acetone (15 mL), and the mixture was stirred at room temperature for 2 h. The alkylating reagent (3 equiv) was then added, and the reaction mixture was heated at reflux and monitored by GC. When the reaction was complete, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue obtained was diluted with $CHCl_3$ (30 mL) and water (20 mL). The layers were separated; the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the corresponding library as pure oil.

Data for the compounds synthesized are presented here for one representative minilibrary. Data for all the other compounds and minilibraries prepared can be found in the Supporting Information.

3a{*1,1–5*} methyl library (method A, 27% yield; method C, 72% yield): ^{1}H NMR δ: 0.95–0.99 (m, 8.9H), 1.04 (t, J = 7.5 Hz, 3H, CH_3 (Pr)), 1.45–1.52 (m, 5H), 1.75 (q, J = 7.0 Hz, 2H, CH_2 (*i*-pent)), 1.80–1.91 (m, 5.4H), 3.86, 3.865, 3.87 (s, 8.5H), 3.88 (s, 3H, OCH_3 (Me)), 3.89 (s, 6H, OCH_3 (Me)), 3.98 (t, J = 6.9 Hz, 2H), 4.01–4.06 (m, 4.3H), 4.11 (q, J = 7.0 Hz, 2H, OCH_2 (Et)), 6.88–6.94 (m, 19H, Ar *H*). GC RI MS *m/z* (relative intensity, %) 1,2-dimethoxy benzene **3a**{*1,1*} 1145 139 (M^+ + H, 29), 138 (M^+, 100), 123 (44); 1-ethoxy-2-methoxy benzene **3a**{*1,2*} 1190 153 (M^+ + H, 23), 152 (M^+, 100), 124 (58), 109 (91); 1-methoxy-2-propoxy benzene **3a**{*1,3*} 1280 167 (M^+ + H, 18), 166 (M^+, 100), 124 (66), 109 (76); 1-butoxy-2-methoxy benzene **3a**{*1,4*} 1377 181 (M^+ + H, 15), 180 (M^+, 100), 124 (57), 109 (52); 1-methoxy-2-(3-methyl-butoxy) benzene **3a**{*1,5*} 1434 195 (M^+ + H, 15), 194 (M^+, 100), 124 (68), 109 (46).

3a{*2,1–5*} ethyl library (method A, 57% yield), **3a**{*3,1–5*} propyl library (method A, 67% yield), **3a**{*4,1–5*} butyl library (method A, 62% yield), **3a**{*5,1–5*} isopentyl library (method A, 43% yield), **3a**{*6,1–5*} allyl library (method B, 94% yield): ^{1}H NMR and GC-MS data Supporting Information pp S15−S16.

3b{*1,1–5*} methyl library (method A, 85% yield): ^{1}H NMR δ 0.97 (d, J = 6.6 Hz, 6H, CH_3 (*i*-pent)), 1.04 (t, J = 7.4 Hz, 3H, CH_3 (Pr)), 1.42 (t, J = 7.0 Hz, 3H, CH_3 (Et)), 1.68 (apparent q, J = 6.8 Hz, 2H, CH_2 (*i*-pent)), 1.78–1.87 (m, 3H), 3.79–3.80 (m, 15H, OCH_3), 3.91 (t, J = 6.6 Hz, 2H, OCH_2 (Pr)), 3.98 (t, J = 6.7 Hz, 2H, OCH_2 (*i*-pent)), 4.02 (q, J = 7.0 Hz, 2H, OCH_2 (Et)), 6.47–6.53 (m, 9.6H, ArH), 7.18 (t, J = 8.2 Hz, 3H, Ar*H*). GC RI MS *m/z* (relative intensity, %) 1,3-dimethoxy benzene **3b**{*1,1*} 1180 138 (M^+, 100); 1-ethoxy-3-methoxy benzene **3b**{*1,2*} 1253 153 (M^+ + H, 25), 152 (M^+, 100); 1-methoxy-3-propoxy benzene **3b**{*1,3*} 1345 167 (M^+ + H, 32), 166 (M^+, 100), 124 (22); 1-methoxy-3-(3-methyl-butyloxy) benzene **3b**{*1,5*} 1508 195 (M^+ + H, 30), 194 (M^+, 100).

3b{*2,1–5*} ethyl library (method A, 66% yield), **3b**{*3,1–5*} propyl library (method A, 53% yield), **3b**{*4,1–5*} butyl library (method A, 69% yield), **3b**{*5,1–5*} isopentyl library (method A, 72% yield), **3b**{*6,1*} (method B, % yield), **3b**{*6,2–3*} (method B, % yield), **3b**{*6,4–5*} (method B, % yield): ^{1}H NMR and GC-MS data Supporting Information pp S16−S18.

3c{*1,1–5*} methyl library (method A, 65% yield): ^{1}H NMR δ 0.96 (d, J = 6.7 Hz, 9H, CH_3 (*i*-pent)), 1.03 (t, J = 7.4 Hz, 3.3H, CH_3 (Pr)), 1.39 (t, J = 6.7 Hz, 4H, CH_3 (Et)), 1.66 (apparent q, J = 6.7 Hz, 3H, CH_2 (*i*-pent)), 1.77–1.85 (m, 3H), 3.77, 3.78 (s, 15H, OCH_3), 3.87 (t, J = 6.6 Hz, 2H, CH_2 (Pr)), 3.94 (t, J = 6.6 Hz, 3H, CH_2 (*i*-pent)), 3.98 (q, J = 7.1 Hz, 3H, CH_2(Et)), 6.83–6.85 (m, 16H, Ar *H*). GC RI MS *m/z* (relative intensity, %) 1,4-dimethoxy benzene **3c**{*1,1*} 1122 139 (M^+ + H, 80), 138 (M^+, 100); 1-ethoxy-4-methoxy benzene **3c**{*1,2*} 1188 153 (M^+ + H, 73), 152 (M^+, 100); 1-methoxy-4-propoxy-benzene **3c**{*1,3*} 1281 167 (M^+ + H, 48), 166 (M^+, 100); 1-methoxy-4-(3-methyl-butyloxy) benzene **3c**{*1,5*} 1442 195 (M^+ + H, 48), 194 (M^+, 100).

3c{*2,1–5*} ethyl library (method A, 31% yield), **3c**{*3,1–5*} propyl library (method A, 82% yield), **3c**{*4,1–5*} butyl library (method A, 76% yield), **3c**{*5,1–5*} isopentyl (3-methyl-butyloxy) library (method A, 82% yield), **3c**{*6,1–5*} allyl library (method B, 95% yield): ^{1}H NMR and GC-MS data Supporting Information pp S18−S19.

Procedure and Data for Minilibraries in Set B. The allyloxy-alkoxy minilibrary **3**(**a**−**c**){*6,1–5*} was heated at 180 °C in a sealed tube, under a nitrogen atmosphere. Reaction progress was monitored by GC. In order to remove the color, the crude libraries were passed through a silica column (top charcoal layer, chloroform as eluent).

4a{*1–5*}95% yield: ^{1}H NMR δ 0.97–1.00 (m, 7.3H), 1.05 (t, J = 7.4 Hz, 3H, CH_3 (Pr)), 1.44 (t, J = 7.0 Hz, 3.8H, CH_3 (Et)), 1.50 (q, J = 7.6 Hz, 1.7H), 1.71 (apparent q, J =

6.8 Hz, 1.5H, CH_2 (*i*-pent)), 1.77–1.88 (m, 4.4H), 3.42 (d, J = 6.6 Hz, 9.3H), 3.89 (s, 3.7H, OCH_3 (Me)), 3.99 (t, J = 6.5 Hz, 2H, OCH_2 (Pr)), 4.02–4.07 (m, 3.8H), 4.10 (q, J = 7.0 Hz, 2.7H, OCH_2 (Et)), 5.04–5.11 (m, 10.2H), 1.69 (s, 1.2H, O*H*), 5.73 (s, 0.5H, O*H*), 5.74 (s, 0.8H, O*H*), 5.75 (s, 1.8H, O*H*), 5.98–6.06 (m, 4H), 6.70–6.86 (m, 13.8H, Ar*H*). GC RI MS *m*/*z* (relative intensity, %) 2-allyl-6-methoxy phenol **4a**{*1*} 1358 165 (M^+ + H, 23), 164 (M^+, 100); 2-allyl-6-ethoxy phenol **4a**{*2*} 1413 179 (M^+ + H, 25), 178 (M^+, 100); 2-allyl-6-propoxy phenol **4a**{*3*} 1504 193 (M^+ + H, 22), 192 (M^+, 100); 2-allyl-6-butoxy phenol **4a**{*4*} 1603 207 (M^+ + H, 22), 206 (M^+, 100); 2-allyl-6-(3-methyl-butoxy) phenol **4a**{*5*} 1664 221 (M^+ + H, 21), 220 (M^+, 100).

4b^{x,y}{*1*} 82% yield: ^{1}H NMR δ 3.35 (m, 3.8H, CH_2 (allyl^x)), 3.47 (m, 2H, CH_2 (allyl^y)), 3.77 (s, 6.6H, OCH_3 (Me^x)), 3.81 (s, 3H, OCH_3 (Me^y)), 5.01 (s, 1H, OH^y), 5.04 (s, 1.7H, OH^x), 5.08–5.13 (m, 2.1H), 5.14–5.18 (m, 3.8H), 5.95–6.04 (m, 2.6H), 6.42 (d, J = 2.5 Hz, 1.7H, ArH^x), 6.46 (dd, J = 2.5 and 8.3 Hz, 1.7H, ArH^x), 6.50 (dd, J = 6.5 and 7.9 Hz, 2H, ArH^y), 7.00 (d, J = 8.3 Hz, 1.7H, ArH^x), 7.08 (t, J = 8.2 Hz, 1H, ArH^y). GC RI MS *m*/*z* (relative intensity, %) 2-allyl-5-methoxy phenol **4b**^{x}{*1*} 1393 165 (M^+ + H, 30), 164 (M^+, 100); 2-allyl-3-methoxy phenol **4b**^{y}{*1*} 1446 165 (M^+ + H, 37), 164 (M^+, 100).

4b^{x,y}{*2–3*} 64% yield: ^{1}H NMR δ 1.01–1.06 (m, 10.9H, CH_3 (Pr)), 1.38–1.42 (m, 7.7H, CH_3 (Et)), 1.75–1.84 (m, 7.6H, C H_2CH_3 (Pr)), 3.34–3.35 (m, 7.3H), 3.47–3.49 (m, 4.2H), 3.86–3.92 (m, 7.5H, OCH_2 (Pr)), 3.97–4.04 (m, 5.4H, OCH_2 (Et)), 5.06–5.09 (m, 7.4H), 5.11–5.12 (m, 1.3H), 5.13–5.15 (m, 6.5H), 5.17–5.18 (m, 2H), 5.94–6.04 (m, 5.6H), 6.41–6.49 (m, 11.5H, Ar*H*), 6.98 (m, 3.5H, ArH^x), 7.05 (m, 2H, ArH^y). GC RI MS *m*/*z* (relative intensity, %) 2-allyl-5-ethoxy phenol **4b**^{x}{*2*} 1455 179 (M^+ + H, 54), 178 (M^+, 100); 2-allyl-3-ethoxy phenol **4b**^{y}{*2*} 1517 179 (M^+ + H, 38), 178 (M^+, 100); 2-allyl-5-propoxy phenol **4b**^{x}{*3*} 1549 193 (M^+ + H, 62), 192 (M^+, 100); 2-allyl-3-propoxy phenol **4b**^{y}{*3*} 1615 193 (M^+ + H, 47), 192 (M^+, 100).

4b^{x,y}{*4–5*} 31% yield: ^{1}H NMR δ 0.94–0.99 (m, 30.1H), 1.44–1.53 (m, 8.5H, C H_2CH_3 (Bu)), 1.61–1.87 (m, 17.6H), 3.34–3.35 (m, 9.5H), 3.46–3.48 (m, 4.4H), 3.90–3.98 (m, 14.6H), 5.01–5.03 (m, 6.0H), 5.06–5.09 (m, 2.2H), 5.10–5.12 (m, 1.1H), 5.13–5.18 (m, 10.1H), 5.93–6.04 (m, 6.1H), 6.41–6.50 (m, 13.6H), 6.97–6.98 (m, 4.4H, ArH^x), 7.03–7.07 (m, 2H, ArH^y). GC RI MS *m*/*z* (relative intensity, %) 2-allyl-5-butoxy phenol **4b**^{x}{*4*} 1649 207 (M^+ + H, 11), 206 (M^+, 54), 135 (M – 71, 100); 2-allyl-3-butoxy phenol **4b**^{y}{*4*} 1721 207 (M^+ + H, 17), 206 (M^+, 94), 149 (M – 57, 100); 2-allyl-5- *iso*pentoxy phenol **4b**^{x}{*5*} 1706 221 (M^+ + H, 11), 220 (M^+, 54), 135 (M – 85, 100); 2-allyl-3-(3-methyl-butoxy) phenol **4b**^{y}{*5*} 1786 221 (M^+ + H, 17), 220 (M^+, 90), 150 (M – 70, 100).

4c{*1–5*}97% yield: ^{1}H NMR δ 0.97–0.99 (m, 8.8H), 1.03 (t, J = 7.4 Hz, 3.7H, CH_3 (Pr)), 1.39 (t, J = 7.0 Hz, 4.2H, CH_3 (Et)), 1.45–1.53 (m, 2H), 1.66 (apparent q, J = 6.8 Hz, 2H, CH_2 (*i*-pent)), 1.72–1.86 (m, 5.4H), 3.37–3.40 (m, 11.5H), 3.77 (s, 4.3H, OCH_3 (Me)), 3.86 (t, J = 6.6 Hz, 2.5H, OCH_2 (Pr)), 3.89–3.95 (m, 3.5H), 3.98 (q, J = 7.0 Hz, 2.6H, OCH_2 (Et)), 5.21 (broad s, 5.2H, O*H*), 5.13–5.17 (m, 10.6H), 5.98–6.06 (m, 5H), 6.66–6.77 (m, 16H, Ar*H*). GC RI MS *m*/*z* (relative intensity, %) 2-allyl-4-methoxy phenol **4c**{*1*} 1432 165 (M^+ + H, 31), 164 (M^+, 100); 2-allyl-4-ethoxy phenol **4c**{*2*} 1494 179 (M^+ + H, 31), 178 (M^+, 100); 2-allyl-4-propoxy phenol **4c**{*3*} 1587 193 (M^+ + H, 31), 192 (M^+, 100); 2-allyl-4-butoxy phenol **4c**{*4*} 1687 207 (M^+ + H, 29), 206 (M^+, 100); 2-allyl-4-(3-methyl-butoxy) phenol **4c**{*5*} 1750 221 (M^+ + H, 31), 220 (M+, 100).

Procedure and Data for Minilibraries in Set C. **5a**{*1,1–5*} allyl-methyl library (method B, 90% yield): ^{1}H NMR δ 0.96–1.00 (m, 8.4H), 1.06 (t, J = 7.4, 3.2H, CH_3 (Pr)), 1.44–1.47 (m, 4.4H), 1.50–1.55 (m, 2.3H), 1.73 (apparent q, J = 6.8 Hz, 1.7H, CH_2 (*i*-pent)), 1.79–1.91 (m, 5.9H), 3.40–3.43 (m, 10H), 3.81, 3.82, 3.83, 3.834, 3.84 (s, 15.2H, O*CH*$_3$), 3.86 (s, 4.8H, O*CH*$_3$), 3.95 (t, J = 6.5 Hz, 2H, OCH_2 (Pr)), 3.98–4.03 (m, 4.4H), 4.07 (q, J = 7.0 Hz, 2.7H, OCH_2 (Et)), 5.02–5.09 (m, 10H), 5.94–6.02 (m, 5H), 6.71–6.82 (m, 12H, Ar*H*), 6.95–7.01 (m, 5H, Ar*H*). GC RI MS *m*/*z* (relative intensity, %) 1-allyl-2,3-dimethoxy benzene **5a**{*1,1*} 1333 179 (M^+ + H, 50), 178 (M^+, 100); 1-allyl-3-ethoxy-2-methoxy benzene **5a**{*1,2*} 1386 193 (M^+ + H, 79), 192 (M^+, 100); 1-allyl-2-methoxy-3-propoxy benzene **5a**{*1,3*} 1481 207 (M^+ + H, 65), 206 (M^+, 100); 1-allyl-2-butoxy-3-methoxy benzene **5a**{*1,4*} 1578 221 (M^+ + H, 66), 220 (M^+, 100); 1-allyl-2-methoxy-3-(3-methyl-butoxy) benzene **5a**{*1,5*} 1632 235 (M^+ + H, 62), 234 (M^+, 100).

5a{*2,1–5*} allyl-ethyl library (method B, 91% yield), **5a**{*3,1–5*} allyl-propyl library (method B, 96% yield), **5a**{*4,1–5*} allyl-butyl library (method B, 92% yield), **5a**{*5,1–5*} allyl-*i*pentyl library (method B, 90% yield), **5a**{*6,1–5*} allyl-allyl library (method B, 90% yield): ^{1}H NMR and GC-MS data Supporting Information pp S19−S21.

5b^{x,y}{*1,1*} allyl-methyl library A (method B, 90% yield): ^{1}H NMR δ 3.30–3.31 (m, 3.9H, CH_2 (allyl^x)), 3.41 (dt, J = 1.6 and 6.1 Hz, 2H, CH_2 (allyl^y)), 3.79 (s, 6H (Me^y)), 3.80 (s, 5.4H (Me^x)), 3.81 (s, 5.4H (Me^x)), 4.91–4.95 (m, 1.6H), 4.97–5.04 (m, 4.2H), 5.91–6.01 (m, 2.8H), 6.42–6.45 (m, 3.7H, ArH^x), 6.55 (d, J = 8.3 Hz, 2H, ArH^y), 7.03 (d, J = 8.1 Hz, 1.7H, ArH^x), 7.15 (t, J = 8.3 Hz, 1H, ArH^y). GC RI MS *m*/*z* (relative intensity, %) 2-allyl-1,3-dimethoxy benzene **5b**^{y}{*1,1*} 1378: 179 (M^+ + H, 30), 178 (M^+, 100), 1-allyl-2,4-dimethoxy benzene **5b**^{x}{*1,1*} 1411: 179 (M^+ + H, 28), 178 (M^+, 100).

5b^{x,y}{*1,2–3*} allyl-methyl library B (method B, 61% yield): ^{1}H NMR δ 1.02–1.06 (m, 11.4H, CH_3 (Pr)), 1.38–1.42 (m, 7.6H, CH_3 (Et)), 1.77–1.84 (m, 7.9H, CH_2 (Pr)), 3.30–3.31 (m, 7.1H), 3.42–3.44 (m, 4.4H), 3.80 (m, 10.4H (Me^x)), 3.81 (m, 6.1H (Me^y)), 3.89–3.93 (m, 7.8H), 4.00–4.05 (m, 4.9H), 4.91–4.93 (m, 2.1H), 4.98–5.04 (m, 8.8H), 5.91–6.01 (m, 5.2H), 6.42–6.46 (m, 7.3H, ArH^x), 6.52–6.54 (m, 4.2H, ArH^y), 7.00–7.01 (m, 3.2H, ArH^x), 7.10–7.13 (m, 2.0H, ArH^y). GC RI MS *m*/*z* (relative intensity, %) 2-allyl-1-ethoxy-3-methoxy benzene **5b**^{y}{*1,2*} 1435 193 (M^+ + H, 30), 192 (M^+, 70), 163 (M – 29, 100); 1-allyl-4-ethoxy-2-methoxy benzene **5b**^{x}{*1,2*} 1480 193 (M^+ + H, 41), 192 (M^+, 100), 163 (M – 29, 28); 2-allyl-1-methoxy-3-propoxy benzene **5b**^{y}{*1,3*} 1527 207 (M^+ + H, 62), 206 (M^+, 100),

177 (M – 29, 68); 1-allyl-2-methoxy-4-propoxy benzene **5b**^{x}{*1,3*} 1573 207 (M^+ + H, 52), 206 (M^+, 100), 177 (M – 29, 1).

5b^{x,y}{*1,4–5*} allyl-methyl library C (method B, 77% yield): ^{1}H NMR δ 0.95–0.99 (m, 30.7H), 1.45–1.54 (m, 8.7H, CH_2 (Bu)), 1.65–1.69 (m, 6.4H), 1.73–1.90 (m, 11.8H), 3.29–3.31 (m, 8.3H), 3.41–3.42 (m, 4.4H), 3.80 (m, 11.7H (Me^x)), 3.81 (m, 6.0H (Me^y)), 3.93–3.99 (m, 14.4H), 4.90–4.93 (m, 2.1H), 4.96–5.04 (m, 10.1H), 5.90–6.01 (m, 5.6H), 6.41–6.45 (m, 8.6H, ArH^x), 6.52–6.54 (m, 4.2H, ArH^y), 6.99–7.01 (m, 3.8H, ArH^x), 7.10–7.14 (m, 2H, ArH^y). GC RI MS *m/z* (relative intensity, %) 2-allyl-3-methoxy-1-butoxy benzene **5b**^{y}{*1,4*} 1624 221 (M^+ + H, 36), 220 (M^+, 100), 191 (M – 29, 79); 1-allyl-2-methoxy-4-butoxy benzene **5b**^{x}{*1,4*} 1672 221 (M^+ + H, 34), 220 (M^+, 100), 191 (M – 29, 1); 2-allyl-1-methoxy-3-(3-methyl-butoxy) benzene **5b**^{y}{*1,5*} 1680 235 (M^+ + H, 32), 234 (M^+, 100), 205 (M – 29, 47); 1-allyl-2-methoxy-4-(3-methyl-butoxy) benzene **5b**^{x}{*1,5*} 1731 235 (M^+ + H, 31), 234 (M^+, 100), 205 (M – 29, 0).

5b^{x,y}{*2,1*} allyl-ethyl library A (method B, 70% yield), **5b**^{x,y}{*2,2–3*} allyl-ethyl library B (method B, 80% yield), **5b**^{x,y}{*2,4–5*} allyl-ethyl library C (method B, 48% yield), **5b**^{x,y}{*3,1*} allyl-propyl library A (method B, 88% yield), **5b**^{x,y}{*3,2–3*} allyl-propyl library B (method B, 80% yield), **5b**^{x,y}{*3,4–5*} allyl-propyl library C (method B, 62% yield), **5b**^{x,y}{*4,1*} allyl-butyl library A (method B, 81% yield), **5b**^{x,y}{*4,2–3*} allyl-butyl library B (method B, 52% yield), **5b**^{x,y}{*4,4–5*} allyl-butyl library C (method B, 64% yield), **5b**^{x,y}{*5,1*} allyl-*i*pentyl library A (method B, 64% yield), **5b**^{x,y}{*5,2–3*} allyl-*i*pentyl library B (method B, 74% yield), **5b**^{x,y}{*5,4–5*} allyl-*i*pentyl library C (method B, 82% yield), **5b**^{x,y}{*6,1*} allyl-allyl library A (method B, 67% yield), **5b**^{x,y}{*6,2–3*} allyl-allyl library B (method B, 53% yield), **5b**^{x,y}{*6,4–5*} allyl-allyl library C (method B, 76% yield): ^{1}H NMR and GC-MS data Supporting Information pp S21−S25.

5c{*1,1–5*} allyl-methyl library (method B, 98% yield): ^{1}H NMR δ 0.95–0.99 (m, 8.6H), 1.03 (t, J = 7.5, 3.2H, CH_3 (Pr)), 1.38 (t, J = 7.0 Hz, 4H), 1.45–1.52 (m, 2H), 1.65 (apparent q, J = 6.7 Hz, 2H, CH_2 (*i*-pent)), 1.71–1.86 (m, 5.2H), 3.35–3.36 (m, 10.8H), 3.76 (s, 4H, OC H_3), 3.78–3.79 (m, 16.5H, OC H_3), 3.86 (t, J = 6.6 Hz, 2.3H, OCH_2 (Pr)), 3.89–3.94 (m, 3.6H), 3.97 (q, J = 7.0 Hz, 2.4H, OCH_2 (Et)), 5.04–5.08 (m, 10H), 5.94–6.02 (m, 4.7H), 6.70–6.80 (m, 15.6H, Ar*H*). GC RI MS *m/z* (relative intensity, %) 1-allyl-2,5-dimethoxy benzene **5c**{*1,1*} 1397 179 (M^+ + H, 28), 178 (M^+, 100); 1-allyl-5-ethoxy-2-methoxy benzene **5c**{*1,2*} 1462 193 (M^+ + H, 32), 192 (M^+, 100); 1-allyl-2-methoxy-5-propoxy benzene **5c**{*1,3*} 1557 207 (M^+ + H, 33), 206 (M^+, 100); 1-allyl-5-butoxy-2-methoxy benzene **5c**{*1,4*} 1650 221 (M^+ + H, 32), 220 (M^+, 100); 1-allyl-2-methoxy-5-(3-methyl-butoxy) benzene **5c**{*1,5*} 1709 235 (M^+ + H, 29), 234 (M^+, 100).

5c{*2,1–5*} allyl-ethyl library (method B, 89% yield), **5c**{*3,1–5*} allyl-propyl library (method B, 95% yield), **5c**{*4,1–5*} allyl-butyl library (method B, 95% yield), **5c**{*5,1–5*} allyl-*i*pentyl library (method B, 95% yield): ^{1}H NMR and GC-MS data Supporting Information pp S26–S27.

Procedure and Data for Set D. The **3c**{*6,1–5*} minilibrary (2.7224 g) was heated at 180 °C in a sealed tube, under a nitrogen atmosphere, for 30 h. The viscous dark black oil was purified by column chromatography with chloroform to afford 1.6334 g of the pure **6c**{*1–5*} library in 60% yield.

^{1}H NMR δ 0.92–0.97 (m, 9.5H), 1.02 (t, J = 7.4 Hz, 3.6H), 1.37 (t, J = 7.0 Hz, 4.2H), 1.45 (d, J = 6.2 Hz, 15.7H), 1.57–1.58 (m, 1.4H), 1.64 (q, J = 6.8 Hz, 2H), 1.70–1.85 (m, 5.7H), 2.77–2.82 (m, 4.8H), 3.24–3.30 (m, 5H), 3.75 (s, 3.4H, OC H_3), 3.85 (t, J = 6.6 Hz, 2.2H), 3.87–3.92 (m, 3.9H), 3.96 (q, J = 7.0 Hz, 2.3H), 4.85–4.93 (m, 4.2H), 6.63–6.82 (m, 17.6H, Ar*H*). GC RI MS *m/z* (relative intensity, %) 5-methoxy-2-methyl-2,3-dihydro benzofuran **6c**{*1*} 1365 165 (M^+ + H, 24), 164 (M^+, 100), 149 (65); 5-ethoxy-2-methyl-2,3-dihydro benzofuran **6c**{*2*} 1434 179 (M^+ + H, 22), 178 (M^+, 100), 149 (25); 5-propoxy-2-methyl-2,3-dihydro benzofuran **6c**{*3*} 1533 193 (M^+ + H, 22), 192 (M^+, 100); 5-butoxy-2-methyl-2,3-dihydro benzofuran **6c**{*4*} 1634 207 (M^+ + H, 22), 206 (M^+, 100); 5-(3-methyl-butoxy)-2-methyl-2,3-dihydro benzofuran **6c**{*5*} 1699 221 (M^+ + H, 22), 220 (M^+, 100).

Gas Chromatographic-Electroantennographic Detection (GC-EAD). Coupled gas chromatographic-electroantennographic detection (GC-EAD) analyses were conducted employing a Hewlett-Packard (HP) 5890 gas chromatograph fitted with a GC-column (30 m × 0.32 mm i.d.) coated with DB-5 (J&W Scientific, Folsom, CA). For GC-EAD recordings, an antenna was carefully dislodged from a male moth's head, and the antennal base was placed into the opening of a glass capillary electrode (0.58 mm i.d. × 65 mm length) (A-M Systems, Inc., Carlsborg, WA) filled with saline solution.[32] The tip of the antenna was removed by spring microscissors (Fine Science Tools Inc., North Vancouver, BC, Canada) and then placed into the opening of the recording electrode mounted on a portable micromanipulator and positioned in front of a constant stream of warm air (Praxair Canada Inc., Mississauga, ON, Canada) which delivered the GC column eluent. Antennal receptor potentials (measured in millivolts) elicited by specific compounds were recorded by a HP 3392A chart recorder. Identical retention times of compounds detected by the flame ionization detector of the GC and by the insect antenna allowed assignment of antennal responses to specific compounds in the eluent.

Electroantennogram (EAG) Competitive Screen. For EAGs, a male moth antenna was mounted as above and placed in front of a stimulus-delivery glass tubing (160 mm × 5 mm i.d.) with a side orifice (2 mm diameter) near (2 cm) the distal opening. The tubing was connected to one port of an apparatus (Stimulus Controller CS-05, Syntech Research and Equipment, NL-1200BM Hilversum, The Netherlands) that generated a constant stream of clean air (300 mL/min). The second port of the apparatus was connected to a Pasteur pipet inserted through the side orifice of the stimulus-delivery tubing. The test stimulus was applied to a disk of Whatman no. 1 filter paper inside the Pasteur pipet and was discharged through a 0.3-s pulse of air (600 mL/min). Receptor potentials of the antennae in response to test stimuli were recorded with a Syntech IDAC probe, amplifier, and interfaced board and were analyzed with EAG Syntech Software version 2.4 (1996). Inhibition (%) was calculated as

$$\% \text{ inhibition} = (D_d - D_s)/D_d \times 100 \quad (1)$$

where D_d is the depolarization observed with pure disparlure (corrected for the clean air background) and D_s is the depolarization with disparlure + sample. See Figure 3 for a representative EAG inhibition assay trace.

Assay of Binding Protein Activity. For these assays, *L. dispar* PBP 1 or PBP 2 was incubated with the test compound or minilibrary. The PBP and the ligand(s) (L) were left to equilibrate (eq 2) overnight. The nonbound ligand was then separated from the protein-bound material (PBP·L) by size-exclusion chromatography. By determining the total ligand in solution at equilibrium (eq 3) and the protein-bound ligand, it is possible to estimate the percentage of ligand bound to the protein at equilibrium (eq 4). This assay is possible because dissociation of the ligand from the internal binding site of the PBP is very slow ($t_{1/2} \geq 2$ h),[8] so no significant dissociation occurrs during the size-exclusion chromatography. This binding assay has been validated extensively in previous studies.[31] The components of each minilibrary separated cleanly by GC, so it was possible to monitor binding of individual components.

$$\text{PBP} + \text{L} \rightleftarrows \text{PBP} \cdot \text{L} \quad (2)$$

$$[\text{L}]_{tot} = [\text{L}] + [\text{PBP} \cdot \text{L}] \quad (3)$$

$$\% \text{ bound} = 100 \times [\text{PBP} \cdot \text{L}]/[\text{L}]_{tot} \quad (4)$$

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Supporting Information Available. Detailed methods and summary of the early synthesis of the monoalkoxy phenols (via acetate protection/deprotection). This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Raffa, K. F.; Aukema, B. H.; Erbilgin, N.; Klepzig, K. D.; Wallin, K. F. *Recent Adv. Phytochem.* **2005**, *39*, 79–118.
(2) Martin, D.; Bohlmann, J. *Recent Adv. Phytochem.* **2005**, *39*, 29–56.
(3) Micha, S. G.; Wyss, U. *Chemoecology* **1996**, *7*, 132–139.
(4) DeMoraes, C. M.; Lewis, W. J.; Pare, P. W.; Alborn, H. T.; Tumlinson, J. H. *Nature* **1998**, *393*, 570–573.
(5) Mandava, N. B.; Morgan, E. D. *Insect Attractants and Repellents*, 2nd ed.; CRC Press: Boca Raton, FL, 1988; Vol. 6.
(6) Plettner, E. The peripheral pheromone olfactory system in insects: targets for species-selective insect control agents. In *Insect Pheromone Biochemistry and Molecular Biology*; Blomquist, G., Vogt, R., Eds.; Elsevier: London, 2003; pp 477–507.
(7) Mustaparta, H.; Stranden, M. *Recent Adv. Phytochem.* **2005**, *39*, 269–292.
(8) Honson, N. S.; Gong, Y.; Plettner, E. Structure and Function of Insect Odorant and Pheromone-Binding Proteins (OBPs and PBPs) and Chemosensory-Specific Proteins (CSPs). In *Chemical Ecology and Phytochemistry of Forest Ecosystems*; Romeo, J. T., Ed.; Elsevier Ltd.: Oxford, 2005; Vol. 39, pp 227–268.
(9) Jacquin-Joly, E.; Merlin, C. *J. Chem. Ecol.* **2004**, *30*, 2359–2397.
(10) Hildebrand, J. G. *J. Comp. Physiol. A* **1998**, *178*, 5–19.
(11) Bortolomeazzi, R.; Sebastianutto, N.; Toniolo, R.; Pizzariello, A. *Food Chem.* **2006**, *100*, 1481–1489.
(12) DaPorto, C.; Moret, S.; Soldera, S. *Anal. Chim. Acta* **2006**, *563*, 396–400.
(13) Guillen, M. D.; Manzanos, M. J. *Flavour Fragrance J.* **2005**, *20*, 676–685.
(14) Murugan, K.; Murugan, P.; Noortheen, A. *Bioresour. Technol.* **2006**, *98*, 198–201.
(15) Obeng-Ofori, D.; Reichmuth, C. H. *Int. J. Pest Manage.* **1997**, *43*, 89–94.
(16) Hallem, E. A.; Fox, A. N.; Zwiebel, L. J.; Carlson, J. R. *Nature* **2004**, *427*, 212–213.
(17) Meijerink, J.; Braks, M. A. H.; Brack, A. A.; Adam, W.; Dekker, T.; Posthumus, M. A.; VanBeek, T. A.; VanLoon, J. J. A. *J. Chem. Ecol.* **2000**, *26*, 1367–1382.
(18) Ito, F.; Fusegi, K.; Kumamoto, T.; Ishikawa, T. *Synthesis* **2007**, *12*, 1785–1796.
(19) Kuntz, E.; Amgoune, A.; Lucas, C.; Godard, G. *J. Mol. Catal. A* **2006**, *244*, 124–138.
(20) Ollevier, T.; Mwene-Mbeja, T. M. *Synthesis* **2006**, *23*, 3963–3966.
(21) Yadav, G. D.; Lande, S. V. *Synth. Commun.* **2007**, *37*, 941–946.
(22) Gozzo, F. C.; Fernandes, S. A.; Rodrigues, D. C.; Nogueira-Eberlin, M.; Marsaioli, A. J. *J. Org. Chem.* **2003**, *68*, 5493–5499.
(23) White, W. N.; Slater, C. D. *J. Org. Chem.* **1961**, *26*, 3631–3638.
(24) White, W. N.; Gwynn, D.; Schlitt, R.; Girard, C.; Fife, W. *J. Am. Chem. Soc.* **1958**, *80*, 3271–3277.
(25) Goering, H. L.; Jacobson, R. R. *J. Am. Chem. Soc.* **1958**, *80*, 3277–3285.
(26) Grant, V. H.; Liu, B. *Tetrahedron Lett.* **2005**, *46*, 1237–1240.
(27) Ito, Y.; Kato, R.; Hamashima, K.; Kataoka, Y.; Oe, Y.; Ohta, T.; Furukawa, I. *J. Organomet. Chem.* **2007**, *692*, 691–697.
(28) Mathew, N. T.; Khaire, S.; Mayadevi, S.; Jha, R.; Sivasanker, S. *J. Catal.* **2004**, *229*, 105–113.
(29) Reich, N. W.; Yang, C.-G.; Shi, Z.; He, C. *Synlett* **2006**, *8*, 1278–1280.
(30) Honson, N.; Johnson, M. A.; Oliver, J. E.; Prestwich, G. D.; Plettner, E. *Chem. Senses* **2003**, *28*, 479–489.
(31) Plettner, E.; Lazar, J.; Prestwich, E. G.; Prestwich, G. D. *Biochemistry* **2000**, *39*, 8953–8962.
(32) Staddon, B. W.; Everton, I. J. *Comp. Biochem. Physiol. A* **1980**, *65*, 371–374.

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