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Natural Compounds for Pest and Weed Control

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The control of insect pests and invasive weeds has become more species-selective because of activity-guided isolation, structure elucidation, and total synthesis of naturally produced substances with important biological activities. Examples of isolated compounds include insect pheromones, antifeedants, and prostaglandins, as well as growth regulators for plants and insects. Synthetic analogues of natural substances have been prepared to explore the relationships between chemical structure and observed biological activity. Recent scientific advances have resulted from better methods for the chemical synthesis of target compounds and better analytical methods. The capability of analytical instrumentation continues to advance rapidly, enabling new insights.

KEYWORDS: Pyrethrins; caffeine; azadirachtin; allelopathic agents; phytoalexins; spinosyns; loline alkaloids; pheromones; prostaglandins

INTRODUCTION

Although synthetic chemistry is the dominant approach to pesticide or herbicide discovery, conventional insecticides are often highly toxic to many living organisms and to the environment (*1*). Insects also evolve effective resistance mechanisms that reduce the efficacy of conventional insecticides (*2*). Consequently, new biorational and more specific approaches to pest or weed control have been developed (*3*–*6*).

Many of the hundreds of thousands of secondary products generated by plants, microbes, and animals are the result of coevolution of the producing organism with other organisms (*7*). Nature is full of bioactive compounds with unexploited properties. Some of these compounds potentially can be used directly as pest or weed control agents (*8*).

Once a promising source for new natural products is found, it must be fractionated into bioactive components and compounds (*9*–*14*). Fractionation generally proceeds by initially partitioning an extract from the identified biological source between polar and nonpolar solvents. Aliquots are tested for biological activity (e.g., insect toxicity or phytotoxicity), and further fractionation is pursued on the fraction or fractions for which activity is demonstrated. Column chromatography usually follows, and eluates (subfractions) are collected and tested for their biological activity. Chromatographic workup on the bioactive eluate (subfraction) is carried out until a pure compound is obtained. Structure elucidation is conducted by spectroscopic methods and examination of the physical properties of the compound. This whole process, which constitutes a bioassay-directed isolation, has resulted in many leads in the discovery of bioactive constituents from medicinal plants (*15*). Natural products research can result in improved strategies for the cost-effective management and control of native and invasive insect, mite, and weed pests while minimizing impacts on the environment and human health.

Natural compounds or preparations may require less regulatory scrutiny for registration than synthetic compounds (*1*), thus reducing the cost of commercializing the product. In some market niches, such as the home garden, the claim that a pesticide is "natural" will appeal to consumers.

Natural products can also serve as lead compounds or as templates for pest or weed control agents. The recent high level of investment in combinatorial chemical synthesis and high-throughput screening has reinforced this approach (*16*).

This review presents a brief sampling of some natural products for pest and weed control; this paper was not separated into pest and weed control because some classes of natural products can serve both purposes. We have divided discussion of research efforts into four topics: natural products isolated from plants and microbes and their synthetic analogues, semiochemicals and pheromones, the biochemistry of prostaglandins related to insects, and promising future directions of research efforts.

NATURAL PRODUCTS AND ANALOGUES

Contact Poisons. Contact poisons must actually touch the insect pest to be effective (*17*, *18*). These agents can be applied as dusts, sprays, aerosols, or residual sprays. Nicotine and pyrethrins are examples of natural contact poisons (**Figure 1**).

Nicotine (**Figure 1**, compound **1**) is a pyridine-type alkaloid obtained from cured tobacco, *Nicotiana tabacum* L. (*17*, *18*). The hydrochloride or sulfate salts of the alkaloid are highly soluble in water. Nicotine sulfate dust has been sold as Black Leaf 40 and is highly effective against aphids, but nicotine is also highly toxic to pets and people.

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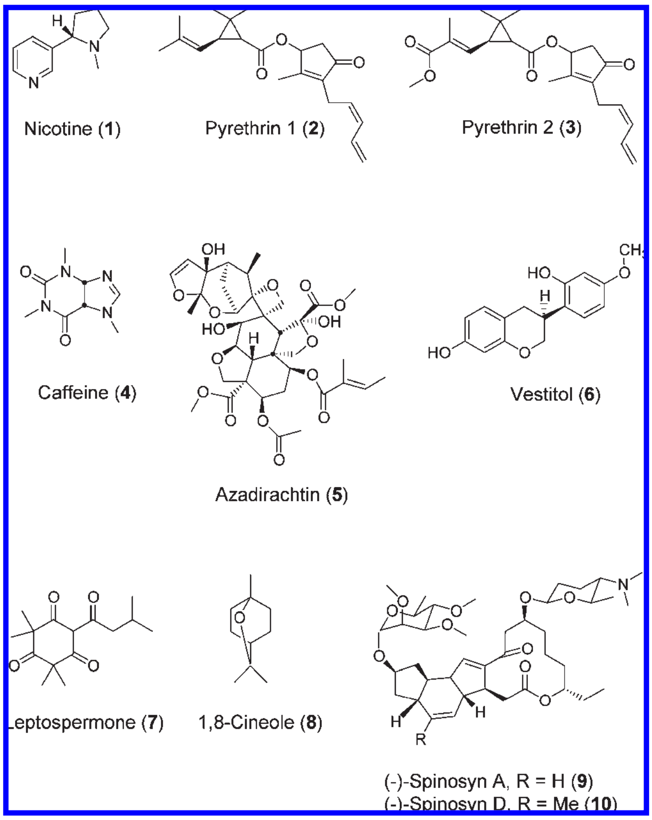


Figure 1. Natural pest and weed control agents.

Pyrethrum flowers consist of dried flower heads of certain species of chrysanthemums, such as *Chrysanthemum cinerariaefolium* Vis (*17*, *18*). Sprays derived from chrysanthemums contain pyrethrins 1 and 2 (**Figure 1**, compounds **2** and **3**). Pyrethrins are noteworthy because of their quick "knockdown" of flies and mosquitoes (*17*, *18*). These compounds function by attacking the nervous systems of insects and are gradually replacing more toxic organophosphates and organochlorides as a pesticides. Pyrethrins are much less toxic to pets and people than nicotine and are considered to be among the safest insecticides for use around food; however, the EPA classifies pyrethrin-I as a Restricted Use Pesticide (RUP). RUPs may be purchased and used only by certified applicators (*19*).

Caffeine. Caffeine (**Figure 1**, compound **4**) is an abundant and safe natural product found in coffee and tea. Coffee seeds contain 1−2% of the alkaloid by weight (*17*). Caffeine has been approved as a food additive, especially for beverages. Caffeine, in solution, was found to act as both a repellent and a toxicant against slugs and snails (*20*). Slugs and snails were killed when drenched with a 2% aqueous solution of caffeine, whereas lower concentrations caused slugs to exit treated soil. Caffeine solutions, as low as 0.01%, applied to cabbage significantly reduced slug feeding. A 2% caffeine drench applied to the media of potted orchids killed 95% of snails and provided better control than a commercial liquid metaldehyde product. Because of low mammalian toxicity, caffeine may prove useful for protecting home-grown food crops and greenhouse plants from slugs and snails.

Azadirachtin. Seeds of the Indian neem tree, *Azadirachta indica* A. Juss., and the related chinaberry tree, *Melia azadirachta* L., contain a compound called azadirachtin (**Figure 1**, compound **5**). The compound was discovered by using bioassay-guided fractionation and isolation techniques (*21*). Azadirachtin is a strong feeding deterrent and growth and development disruptor and has general toxicity to insect tissues (*22*). Azadirachtin is valuable for insect pest control because it is biodegradable and shows very low toxicity to mammals (*21*, *22*).

The probing and settling behaviors of both aphid species, *Rhopalosiphum padi* (L.) and *Sitobion avenae* (F.), were strongly biased toward the untreated seedlings or those treated with concentrations of azadirachtin of 50 ppm (*23*). The reduction in probing activity was related to a concomitant increase in locomotory activity (*23*).

Neem seeds contain 0.2−0.8% by weight of azadirachtin. A simplified extractive/chromatography-based isolation procedure has been developed, resulting in the isolation of >5 g of pure azadirachtin from 2 kg of neem seeds (*24*).

Analogues of the compound are being designed and prepared to probe relationships between chemical structure and biological activity (*25*). Researchers hope to be able to design a simpler compound with approximately the same biological activity and low mammalian toxicity.

Phytoalexins. Plants can defend themselves or "fight back" against insect pests and microbes by induced production and accumulation of low molecular weight secondary metabolites (*26*). These compounds are classified as phytoalexins and can be thought of as "natural antibiotics produced by plants" (*27*). Phytoalexin production can also be induced by weather-related environmental stress.

An example of a phytoalexin is 3*R*-(−)-vestitol (**Figure 1**, compound **6**), which was found by activity-guided isolation from the root of the resistant pasture legume *Lotus pedunculatus* Cav. The compound is an insect feeding deterrent for larvae of the grub beetle *Costelytra zealandica* White (*28*). This compound was also identified in feeding deterrent active *L. pedunculatus* leaf extracts.

Recent work has focused on the ability to induce phytoalexin production in the laboratory. The influence of nutrients, visible light, UV light, amount of water, temperature, plant growth regulators, and the elicitation response to pathogenic fungi on plants or plant tissue cultures has been studied (*29*, *30*).

Allelopathic Agents. Allelopathy is chemically mediated interactions between plants (*31*). Plants have evolved ways to minimize competition for nutrients and sunlight with other plant species. Plants produce a very large number of phytotoxins with potential use as herbicides. For example, leptospermone (**Figure 1**, compound **7**) is an allelochemical from which the triketone class of herbicides was developed (*32*). This is perhaps the most successful development of a commercial herbicide from a phytochemical.

Monoterpene cineoles are natural products commonly found in the essential oils from aromatic plants such as *Laurus nobilis* L., *Salvia* spp., *Eucalyptus* spp., and *Artemisia* spp. (*33*). Some volatile monoterpenes are phytotoxic. Of those compounds, eucalyptol, also known as 1,8-cineole (**Figure 1**, compound **8**), has been shown to be active against both weeds and insects.

Eucalyptol caused a reduction of seed germination to 34% for barnyard grass, *Echinochloa crus-galli* L., and 49% for sicklepod, *Cassia obtusifolia* L., at a concentration of just 10 μg/g of sand (*33*). Eucalyptus oil contains 85−95% eucalyptol and is a GRAS (Generally Recognized as Safe) compound, which can be used to inhibit potato tuber sprouting and the growth of fungal mycelia in laboratory-scale flow chamber experiments with a headspace concentration of just 1.05 mg/L (*34*).

Eucalyptol was also insecticidal against *Rhyzopertha dominica* (F.) and *Tribolium castaneum* (Herbst) ingesting wheat grain. The LC_{50} values were 0.69 and 0.98 mg/g, respectively (*35*). Eucalyptol may also partially account for the suppression of local mosquito populations in northern California, by the volatile oil released from *Hemizonia fitchii* A.Gray (Asteraceae) (*36*).

Spinosyns. The spinosyns (**Figure 1**, compounds **9** and **10**) are a new class of fermentation-derived insect control agents that are effective against a variety of chewing insect pests (*37*). Spinosad, which contains the active compound, has been introduced into the agricultural marketplace for commercial pest control (*37*). The mode of action of spinosad is the activation of insect acetylcholinesterase and a prolongation of acetylcholine responses (*38*). A concise synthesis of spinosyns has been reported (*39*), and efforts have been made to develop analogues with improved physical characteristics, stability to sunlight exposure, and activity against a broader spectrum of insect pests under field conditions (*40*). A second-generation spinosyn called spinetoram (XDE-175) was launched in late 2007 (*41*). It has the advantage of improved insecticidal activity, enhanced duration of control, and an expanded pest spectrum (*41*). Both spinosad and spinetoram are classified as "reduced risk" compounds by the U.S. Environmental Protection Agency (*41*,*42*) and do not require certified training for handlers, on the basis of potential hazards.

Loline Alkaloids. The loline alkaloids are a group of pyrrolizidine alkaloids (**Figure 2**, compounds **11**−**17**) found in some grasses, such as tall fescue (*Festuca arundinacea* Schreb.), infected with a fungal endophyte such as a *Neotyphodium* species (anamorphic Clavicipitaceae). Greater than 35 million acres are planted in tall fescue pasture grass (*43*), and some insects avoid eating the grass. Loline alkaloids are especially important because of their abundance and the crop source is already in place.

Loline alkaloids known to be feeding deterrents against sucking insects, such as aphids (*Rhopalosphum pali* L. and *Skizophis graminum* Rondani) include *N*-formyl-loline, *N*-acetyl-loline, and *N*-methyl-loline (**12**−**14**). Synthetic pathways to the other loline alkaloids, from loline (**11**), are shown in **Figure 2** (*43*). Loline alkaloids, from *Adenocarpus* species, lack the *N*-methyl group and thus are called norlolines (compounds **15**−**17**).

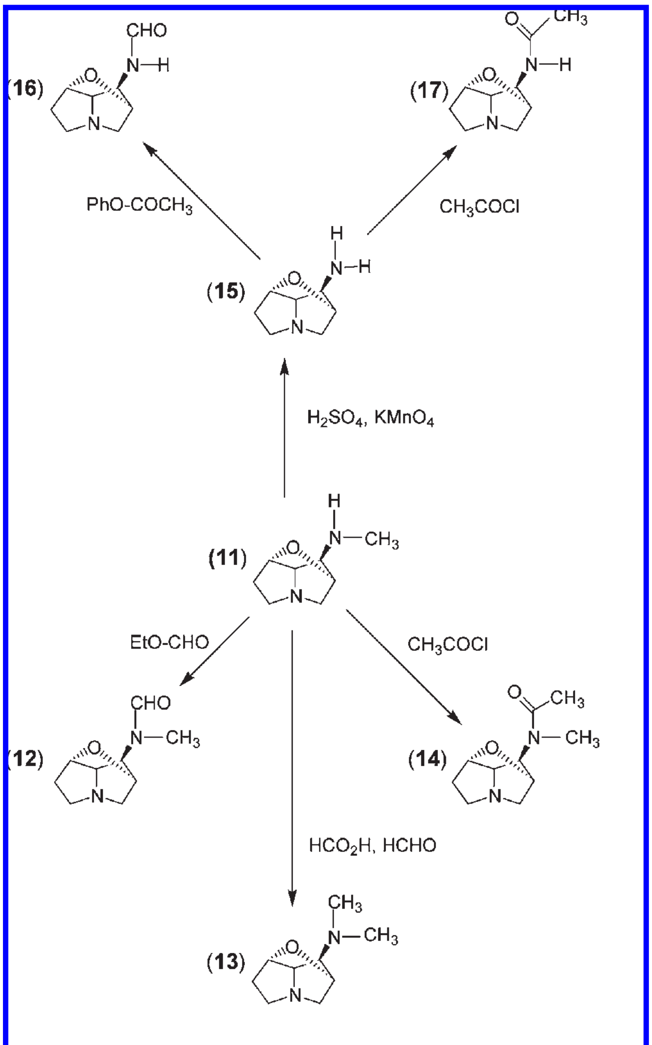
Loline alkaloids have low mammalian toxicity because they do not behave like typical pyrrolizidine alkaloids. This is due to the ether bridge, which prevents metabolism to a toxic pyrrole byproduct (*43*). Analysis and isolation of the compounds are not difficult, and loline can be easily stored in a salt form (*44*,*45*). The potential of these compounds, for home greenhouse or home garden use in selective pest or weed control (*46*−*48*), warrants further investigation because about 200,000 kg of loline alkaloids goes to waste every year (*43*).

The potential of loline or norloline, as starting materials for the preparation of new pharmaceuticals, is still unexplored. This investigation should be done because of the novel rigid structure of the compounds and low mammalian toxicity.

SEMIOCHEMICALS AND PHEROMONES

Semiochemicals are natural substances produced and used by animals and plants to communicate, by the exchange of chemical messages between members of the same or different species (*49*). The term "semio" comes from the Greek and means "sign". Whereas humans use sight and sound to perceive the world around them, insects have developed olfactory systems with an acute level of sensitivity and selectivity (*49*). A pheromone is a natural semiochemical substance produced by an insect to communicate with members of its own species.

Insect-produced pheromones are detected against a background of odorous molecules released by host and nonhost plants (*50*). Plants can be signal sources guiding insects to find and accept a potential host. The combination of an insect pheromone and host plant volatile compounds often results in increased levels of attractiveness (*51*). A synthetic food-related attractant can also serve to increase attraction to the aggregation pheromone. Pheromones can be of use in enhancing a beneficial activity of the insects such as pollination (*52*).

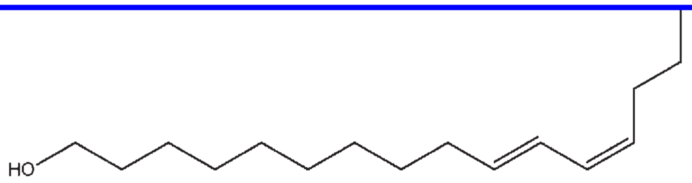


oline **11**, *N*-Formylloline **12**, *N*-Methylloline **13**, *N*-Acetylloline **1**
orloline **15**, *N*-Formylnorloline **16**, *N*-Acetylnorloline **17**

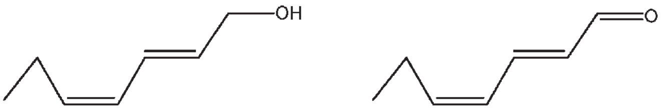
Figure 2. Synthetic conversions of loline alkaloids.

The study of semiochemicals and their influence on insect behavior promises methods of pest control as alternatives to the exclusive use of broad-spectrum toxicants (*53*). Traps baited with a combination of host-plant attractants and pheromones can be used to monitor pest populations, thereby allowing accurate timing of pesticide treatments. Trap crops can also be used to manipulate pest behavior (*53*). Pest populations can be reduced by the combined use of semiochemicals with selective insecticides or biological control agents, such as microorganisms and other insects (*53*). Use of semiochemicals should be combined with other approaches in integrated management strategies because semiochemicals, when employed alone, often give ineffective or insufficiently robust pest control. Semiochemicals and pheromones are classified as "biochemical pesticides" by the Environmental Protection Agency because these naturally-occurring substances control pests by nontoxic mechanisms (*1*). Use of these agents, in agriculture, is not restricted to certified applicators.

Because pheromones are isolated in such small quantities (nanograms to micrograms), complete structural assignment by the standard spectroscopic methods of structure elucidation, is not always possible (*49*, *50*). Only through chemical synthesis can a semiochemical be obtained in an amount sufficient for confirmation of the structure and decisive biological evaluation. The best way to determine absolute stereochemistry of a semiochemical is

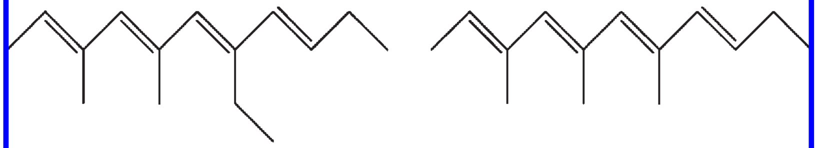


Bombykol, (*E*,*Z*)-10,12-Hexadecadien-1-ol (**18**)



(19) **(20)**

Composition of *Diorhabda elongata* pheromone blend



(21) **(22)**

Composition of *Carpophilus lugubris* aggregation pheromone blend

Figure 3. Insect pheromones.

by rigorous enantioselective synthesis of the compounds to provide pure enantiomers, starting from compounds of known absolute configuration. The chiroptical properties of the natural and synthetic pheromone are then compared. Relationships, between chemical structure and observed biological activity, reveal the diversity in the stereochemical aspects of pheromone and other semiochemical communications.

Bombykol. The first pheromone to be isolated and characterized was bombykol, (*E*,*Z*)-10,12-hexadecadien-1-ol, which is a sex pheromone (**Figure 3**, compound **18**) released by the female silkworm moth, *Bombyx mori* L., to attract mates (*54*). The substance was named after the moth's genus name *Bombyx*. Efforts have since been made to improve the synthetic pathway to bombykol (*55*−*59*). The receptor for the sex pheromone has been characterized recently (*60*).

Saltcedar Leaf Beetle Pheromone. *Diorhabda elongata* Brulle (Coleoptera: Chrysomelidae) is being used for the biological control of saltcedar (*Tamarix* spp), which is an invasive weedy tree found along rivers in the western United States (*61*). The compounds (2*E*,4*Z*)-2,4-heptadien-1-ol (**Figure 3**, compound **19**) and (2*E*,4*Z*)-2,4-heptadienal (**Figure 3**, compound **20**) are a major part of the pheromone of *D. elongata* and have potential use in monitoring dispersal of this species from sites of release (*62*).

A mixture of aggregative semiochemicals, including host plant attractants and sex pheromones, stimulate colonization of pests on trap crops or invasive weeds (*53*). Availability of the *D. elongata* pheromone, by an efficient synthesis (*63*), enabled this approach to be successfully applied to the control of saltcedar (*64*).

Sap Beetle Pheromones. Most species of sap beetles (*Carpophilus* species, Coleoptera: Nitidulidae) are attracted to the wounds of trees, where they feed on sap. However, the habits of various sap beetles are quite variable (*65*). Sap beetles have been found in various habitats feeding on flowers, fruits, sap, fungi, decaying and fermenting plant tissues, or dead animal tissue (*66*).

Although there are many species of sap beetles, only several species are agricultural pests of field and stored products. These include the dusky sap beetle *Carpophilus lugubris* Murray, on field and sweet corn; the corn sap beetle *Carpophilus dimidiatus*, on field corn; the complex *Carphphilus dimidiatus* (F.), *Carpophilus freemani* Dobson, and *Carpophilus mutilatus* Erichson, on stored maize (*66*); and the driedfruit beetle *Carpophilus hemipterus* (L.).

Sap beetles can also vector mycotoxin-producing fungi to corn and strawberries (*67*). Maize sap beetles appear to be well adapted for vectoring mycotoxigenic fungi, including species in the genera *Aspergillus*, *Penicillium*, and *Fusarium*. The adults feed on corn plant residues left in the field after harvest. These residues usually contain spores of *Aspergillus* or *Fusarium*, which not only damage crops but produce toxins harmful to humans and animals. They have also been implicated as vectors of forest pathogens causing wood rots (*68*). Some species, such as the dusky sap beetle, *C. lugubris*, and the beetles in the genus *Glischrochilus*, are implicated as vectors of tree diseases such as oak wilt, *Ceratocystis fagacearum* (*69*, *70*).

Sap beetles are strongly attracted to certain volatile plant compounds in ripening or decaying fruits and themselves produce pheromones/kairomones (chemicals advantageous to receivers and disadvantageous to donors) that elicit an aggregating behavior (*71*−*75*). Baits using such material can be effective in trapping and monitoring sap beetle populations and, hence, determine when treatment is necessary. Ready availability of sap beetle pheromones, for use in trapping and monitoring of sap

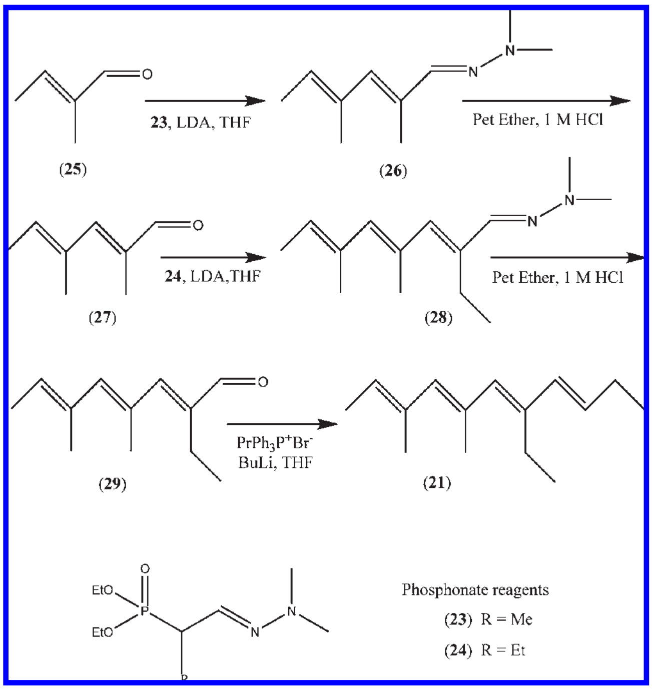


Figure 4. Synthesis of pheromone for *Carpophilus lugubris.*

beetle populations coupled with monitoring the spread of harmful bacterial or fungal organisms, would permit an early warning of a potential agricultural bioterrorist attack against some field and stored crops including corn.

Sap beetles have male-produced aggregation pheromones consisting of conjugated triene and tetraene hydrocarbons, which are attractive to both sexes (*71*). One species, the dusky sap beetle, *C. lugubris* Murray, uses a pheromone blend composed of (2*E*, 4*E*,6*E*,8*E*)-3,5-dimethyl-7-ethyl-2,4,6,8-undecatetraene (**Figure 3**, compound **21**) and (2*E*,4*E*,6*E*,8*E*)-3,5,7-trimethyl-2,4,6,8-undecatetraene (**Figure 3**, compound **22**), in a ratio of 10 to 1 (*71*–*73*). Using new phosphonate reagents (*76*, *77*), diethyl ethylformyl-2-phosphonate dimethylhydrazone (**Figure 4**, compound **23**) and diethyl 1-propylformyl-2-phosphonate dimethylhydrazone (**Figure 4**, compound **24**), compound **21** was prepared on a 10 g scale in just five steps (two condensation/deprotection cycles plus a final Wittig olefination) from commercially available (2*E*)-2-methyl-2-butenal (**Figure 4**, compound **25**) with compounds **26**–**29** as synthetic intermediates (**Figure 4**). This is a two-step improvement over the previous method using standard ester-based phosphonate reagents (*74*, *77*).

Pheromone Analogues. The possibility of disrupting the chemical communication of insect pests has initiated the development of man-made analogues of semiochemicals (*78*). Analogues are produced with modification of the carbon chain and/or at a polar group. These compounds are structurally related to natural pheromone or semiochemical components, but can act as pheromone mimics, synergists, and agonists, or else pheromone antagonists, antipheromones.

Some pheromone analogues induce subtle modifications of behavior that need to be analyzed in more detail. A better knowledge of these subtle effects may also provide insights for the development of new bioactive molecules. Pheromone analogues have been used in quantitative structure–activity relationship studies of insect olfaction (*79*–*83*).

PROSTAGLANDINS

Prostaglandins (PGs) and other eicosanoids are oxygenated metabolites of arachidonic acid (AA; **Figure 5**, compound **30**) and two other C20 polyunsaturated fatty acids, 20:3n-6 and 20:5n-3. Three major groups of eicosanoids are recognized. These are the PGs (COX products, **Figure 5**, compounds **31**–**36**), the epoxyeicosatrienoic acids, and the many lipoxygenase (LOX) metabolites. The chemical structures and outlines of eicosanoid biosynthesis have been published elsewhere (*84*, *85*). PGs were first discovered during research into human reproductive physiology, and they are named from their original discovery in the human prostate gland (*86*). It would now be very difficult to exaggerate the significance of these compounds in contemporary biomedicine. The primary PGs include PGA2, PGE2, PGD2, and PGF2α (**Figure 5**, compounds **32**, **34**, **35**, and **36**). Looking beyond mammals, in the past 25 years we have seen tremendous progress into understanding the biological significance of PGs and other eicosanoids in lower vertebrates, invertebrates, and many eukaryotic microbes. PGs and other eicosanoids act in several aspects of insect reproduction, in ion transport physiology, and in insect immunity. We have focused on PGs and one of their crucial actions in insects, mediation of cellular immunity (*84*,*85*). Cellular defense reactions involve direct interactions between invading organisms and circulating hemocytes; these reactions take place immediately after an infection is registered. The cellular immune effector mechanisms include microaggregation and nodulation (**Figure 6**) and, in the case of foreign bodies too large for single-cell reactions (such as parasitoid eggs), encapsulation. Microaggregation is a step in the nodulation process, in which hemocytes with attached bacterial cells form small aggregates of 10–20 hemocytes (**Figure 6B**). The microaggregates continue to grow, finally forming nodules (**Figure 6A**).

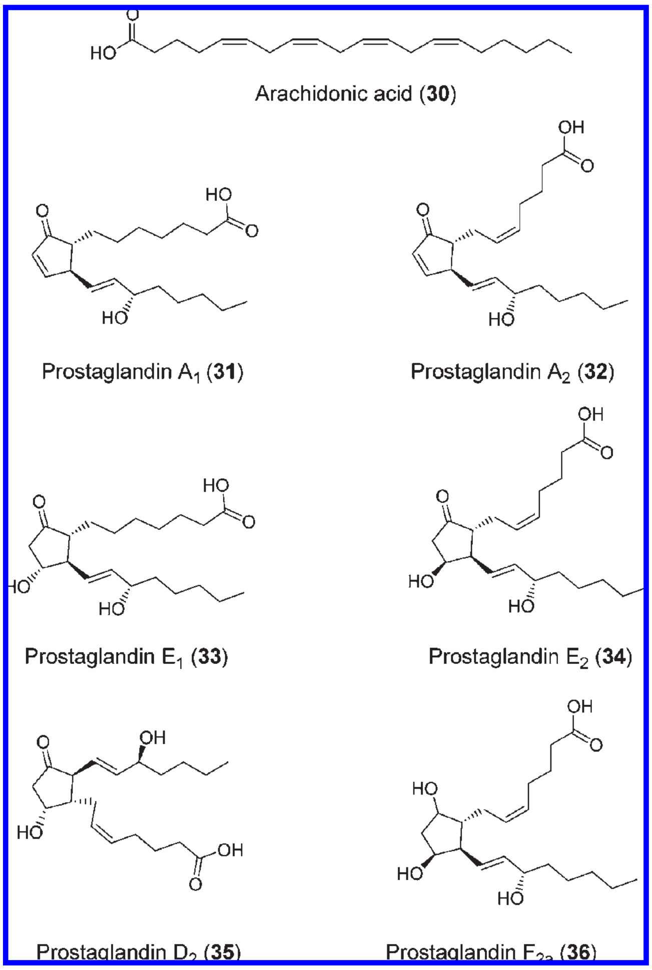


Figure 5. Structures of arachidonic acid and some prostaglandins.

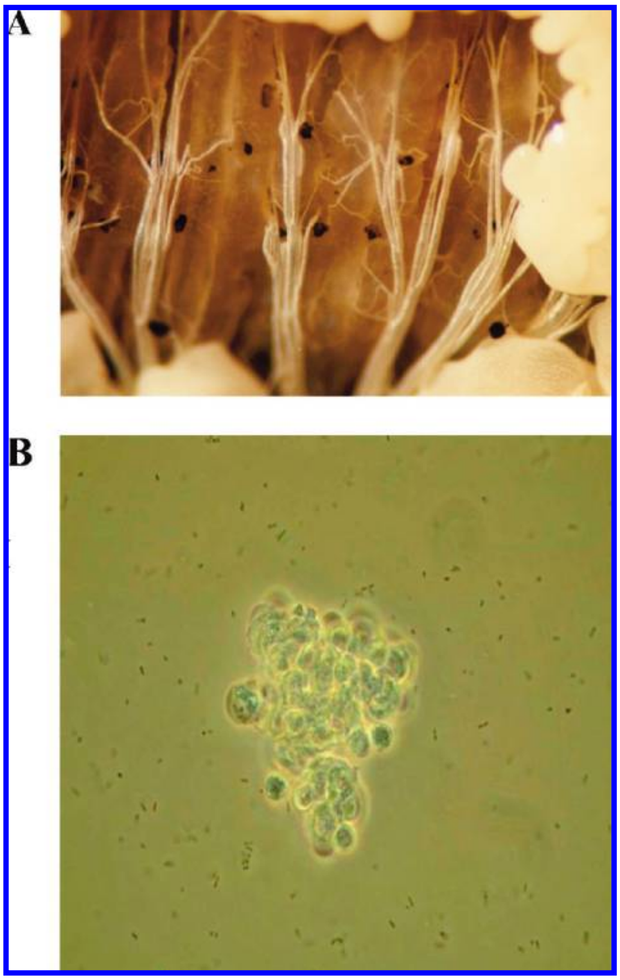


Figure 6. Microaggregation and nodulation: (**A**) photomicrograph (40×) of mature, melanized nodules attached to internal organs of a tobacco hornworm, *Manduca sexta* L.; (**B**) photomicrograph (400×) of a hemocyte microaggregate at 1 h postinfection.

These nodules are completed with a final layer of hemocytes, which undergo a melanization reaction, creating darkened nodules. The nodulation process is responsible for clearing the bulk of bacterial infections from circulation. Encapsulation of invaders, such as parasitoid eggs, that are very much larger than individual hemocytes is a process of adding successive layers of hemocytes; these are finally melanized, and the invaders are topologically removed from circulation. PGs are responsible for mediating and coordinating all of these cellular defense steps. Specifically, PGs mediate hemocyte migration toward sites of wounding and infection, microaggregation, cell spreading, and nodulation (*87*).

The research on hemocyte migration is interesting because the ability to migrate is a fundamental property of cells (*88*). Migration is essential for cellular migration toward sites of infection and toward wounds. The research was carried out using Boyden chambers (**Figure 7**), in which a potential chemoattractant was placed in solution in the lower chamber and hemocytes were placed in the upper chamber. For these experiments the bacterial-specific blocked tripeptide formy-methionine−leucine−phenylalanine (fMLP), a potent attractant for human neutrophils, was used as a chemoattractant. Insect hemocytes prepared from tobacco hornworms, *Manduca sexta*, recognized fMLP and migrated across the membranes toward fMLP. In a second series of experiments, treating hemocytes with various COX inhibitors led to substantial reductions in hemocyte migration toward fMLP. The influence of the glucocordicoid dexamethasone was reversed by treating hemocytes with AA. These results supported our hypotheses that insect hemocytes are competent to migrate to a bacterial signal molecule and that PGs mediate the migration process.

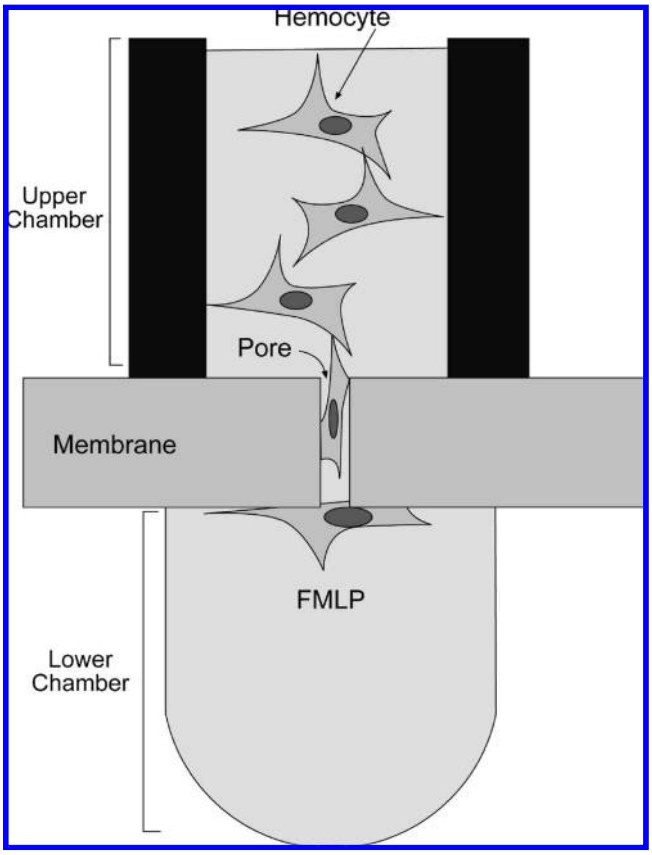


Figure 7. Cartoon representing a Boyden blind-well chamber. Although the original work was conducted using a single-well device (4.5 mL capacity), we used the Neuroprobe 48-well block (25 μL capacity per well). The cartoon shows a lower well filled with buffer amended with fMLP covered with a membrane with 8 μm laser-cut pores. The upper chamber is loaded with a hemocyte suspension.

We are now focusing on the intracellular mechanisms of PG action in insect cells (*89*). **Figure 8** shows three two-dimensional gels of cellular proteins, after 12 h treatments with PG vehicle (controls), PGE1 and PGA1. These treatments altered the expression of approximately 33 proteins; of these, a heat-shock protein (HSP70) was increased in expression by 18-fold. We infer from these data that one mode of PG action in insect cells is via their influence on gene expression.

In the years since the first suggestion that eicosanoids act in insect immunity, the biochemistry of eicosanoid biosynthesis has been characterized in immunity-conferring tissues, the hypothesis has been supported by experiments with a phylogenetically wide range of insect species and a wide range of infecting agents, including a parasitoid wasp, and several specific eicosanoid-mediated cellular actions have been identified. In research on the biochemical modes of PG actions, the influence of PGs on gene expression in insect cells has been recorded, linking PG actions to specific proteins. Very recent work indicates the *Drosophila* Pxt may be a gene encoding an insect COX, and this opens new possibilities for experimentation. The number of known biomolecules acting in insect immunity is increasing, and this will also open possibilities to investigate the interaction of these different moieties in immune reactions.

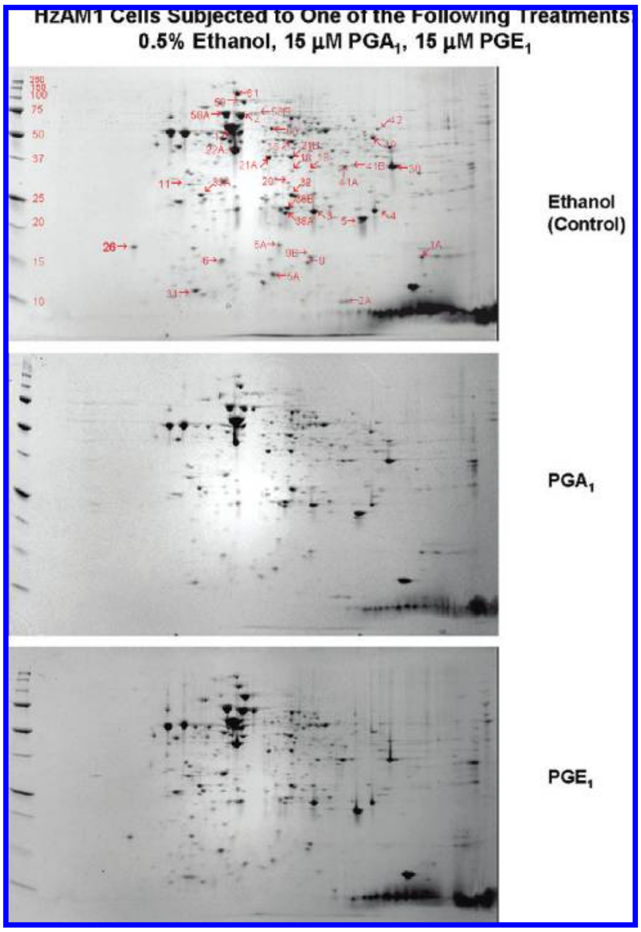


Figure 8. Influence of two prostaglandin treatments on protein expression in an established insect cell line, HzAM1 cells.

This work represents another approach to insect control technology, in which specific enzymes or receptors are targeted for specific inhibition. In this case, identification of insect-specific inhibitors of COX and LOX pathways can lead to compounds that cripple insect immune reactions.

FUTURE DIRECTIONS

Advances in computer sciences and instrument design will extend the reach of scientists. Recent advances in the ability to acquire both mass spectral and infrared spectral data from a gas chromatographic sample enable faster structure elucidation of compounds found in complex mixtures (*90*). The science behind the total synthesis of complex natural products continues to advance rapidly (*91*, *92*). Better enantioselective catalysts, new resin-bound reagents, easier reaction workups, and greener chemistry will become predominant in the future (*93*−*96*). Previously difficult separation and identification of compounds have been overcome with improved gas and liquid chromatographic methods (*97*). Isolation of desired substances from complex mixtures continues to attract intensive research efforts. The use of high-throughput screening with direct input of acquired data into state-of-the-art statistical analysis programs has enabled rapid elucidation of subtle structure−activity relationships (*98*, *99*). This technology continues to improve.

The combination of the above advances will enable solving previously impossible tasks. New agents for ecologically friendly pest and weed control, either directly from or based on natural product templates, will certainly result. There is no shortage of fertile fields of research endeavor. We need to continue to protect the world's food and horticultural plant supply from emerging pests, invasive weeds, and even agricultural bioterrorism.

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