Volatile isoprenoids that control insect behaviour and development

Alastair J. Hick, Mark C. Luszniak and John A. Pickett

BEC Dept., IACR-Rothamsted, Harpenden, Herts., UK AL5 2JQ

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1 Introduction

The volatile isoprenoids reviewed act as semiochemicals, a term derived from the Greek root “semeion” meaning signal or sign. Semiochemicals are chemicals that influence behaviour or initiate physiological processes, but by acting only as signals, and having no direct physiological effect beyond interaction with sensory or other forms of detection systems. Sometimes the term infochemical is used instead of the word semiochemical, but the authors consider that terminology to be inappropriate, both etymologically and scientifically. Included in semiochemicals are pheromones, which exclusively mediate intra-specific communication, allomones which favour the emitting organism and disfavour the recipient, kairomones which are the reverse of allomones, synomones which favour both emitter and receiver, and apneumones which are released from non-living sources.

Isoprenoids include the compounds known to be derived from isopentenyl pyrophosphate and dimethylallyl pyrophosphate, whether originally from mevalonic acid or deoxyxylulose. The biogenetic origin of isoprenoid semiochemicals is discussed in the final section of this review.

Volatile semiochemicals are those usually used for signalling over some distance and for isoprenoids this covers C_5 to C_{20} but with the diterpenes (C_{20}) usually as hydrocarbons only, so as to give sufficient volatility. Further structural aspects of volatile semiochemicals have been detailed.[1]

In this review the structure of the isoprenoid will be given and some information on the associated biological activity on insects (Arthropoda : Insecta). Unless relating directly to these issues, the use in pest control or in any other area of applied development will not be given. Recent developments in applied areas have been reviewed.[2,3] Many isoprenoid semiochemicals are generated by plants and this presents opportunities for their production by exploiting the associated genes or using the plants themselves as industrial crops.[4] However, practical aspects of these approaches will not be discussed further.

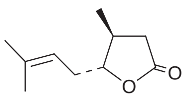
Several recent reviews cover aspects of the subject. For example, ‘Lower terpenoids as natural insect control agents’ from a symposium on ecological chemistry and biochemistry,[5] and an issue of the *Journal of Chemical Ecology* has been devoted to the role of terpenoids in chemical ecology.[6] An edition of *Bioorganic and Medicinal Chemistry*,[7] edited by guest editor K. Mori, considered the bioorganic chemistry of pheromones and includes a number of papers on isoprenoid pheromones. There is also a series of excellent reviews on ‘Advances in chemical ecology’ by Harborne in this journal, which cover the literature since 1982.[8–11] However, these focus on the diversity of chemical structures found in chemical ecology interactions, and not, as in this review, on the wide diversity of biological activities found for a biosynthetically related class of compounds, the isoprenoids. Semiochemicals employed by bark beetles (Scolytidae) are very frequently isoprenoids and have been reviewed by an important authority in this area, W. Francke.[12]

This review groups semiochemicals according to the type of behavioural effect involved. Many of the compounds referred to have simple structures, often without asymmetric carbon atoms. For those compounds with different isomers (geometric or stereochemical) the absolute stereochemistry is only included when it is defined in the original reference. However, only the first referenced isomer of each compound will be shown, with other isomers being designated by the compound number prefixed by the correct absolute stereochemistry. Since these simple compounds can be as important in their semiochemical role as more complex structures, they must be included and so structural novelty features relatively infrequently in this review. However, the increasing complexity of the interactions of these, sometimes simple molecules, justifies the attention paid to them. Some compounds, although simple in structure, mediate interactions between many different plant and insect species in many different ecological situations as will become apparent throughout the review.

2 Sex, aggregation and social interactions

Sex pheromones of moths (Lepidoptera) command a vast literature but are, in general, non-isoprenoid with most being derived from fatty acids. However, there are examples of isoprenoids playing a role in the chemical ecology of moths. The abdominal hair pencils of male moths produce secretions that can have pheromonal roles and often incorporate isoprenoids, as in the hair pencil secretion of the male African sugarcane borer, *Eldana saccharina* (Pyralidae), which includes amongst many fatty acid and amino acid metabolites, the *cis* and *trans* isomers of the isoprenoid eldanolide **1**.[13] This was shown to have activity with both male and female moths at the electrophysiological level (see Section 3.1).

Butterflies, also Lepidoptera, can use isoprenoid semiochemicals, and the male Japanese newspaper butterfly, *Idea leuconoe* (Danaidae), produces the rarely encountered viridifloric β-lactone **2** and the sulfur containing geranyl methyl thioether **3** as a component of a courtship pheromone.[14] The hair pencils of other danaid butterflies, *Euploea* spp., produce the novel isoprenoid 9,10-epoxytetrahydroedulan **4**.[15] The hair pencil pheromones produced by male Lepidoptera have usually only close range aphrodisiac-like activity, but those male butterflies from the genus *Euploea* also display their hair pencils during patrolling flights, suggesting other possible activities.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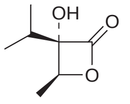

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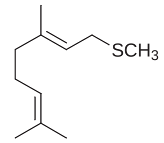

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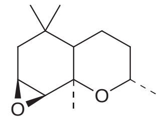
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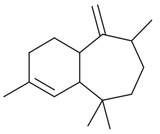
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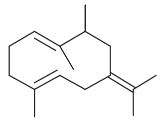
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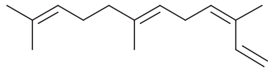
The quest for male-produced long range attractant pheromones which attract females, which would be of much greater value than pheromones that attract only males, has been answered in the Diptera. Two novel homosesquiterpene structures have been proposed for the sex pheromone attractants produced by male sandflies, *Lutzomyia longipalpis* (Psychodidae), an important disease vectoring species, as 3-methyl-α-himachalene **5**[16] and 9-methylgermacrene-B **6**.[17] The structures of these compounds are being confirmed by synthesis.

A range of isoprenoid volatiles can be emitted by the Caribbean and Mexican fruit flies, *Anastrepha suspensa* and *Anastrepha ludens* (Tephritidae).[18] These comprise the sesquiterpene hydrocarbons α-farnesene **7**, β-bisabolene **8** and α-*trans*-bergamotene **9**, but without the full stereochemistry having been assigned except for the β-bisabolene **8** from *A. suspensa* which was shown to have the *R* configuration. Also identified were three lactones: anastrephin **10**, epianastrephin *epi*-**10**, and suspenolide **11**, which are likely to be derived biosynthetically from farnesol **12**. *A. suspensa* also produces the monoterpene (*Z*)-β-ocimene **13**, whereas *A. ludens* produces limonene **14**.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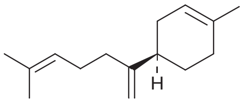

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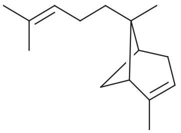
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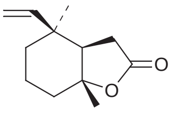
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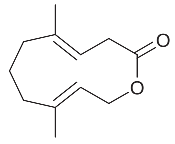
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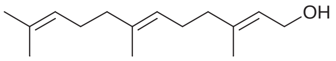

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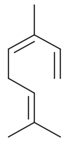
Although not strictly incorporated into this review since they are members of another arthropod class, the Arachnida, mites also produce isoprenoid sex pheromones. Recent characterisation of the sex pheromone for *Caloglyphus* spp. (Acaridiae), identified (2*R*,3*R*)-epoxyneral **15**, with the enantiomer (2*S*,3*S*)-epoxyneral 2*S*,3*S*-**15** being inactive, but in admixture there was no inhibition of the activity of the natural pheromone in bioassays, as is often the case for pheromone enantiomers.[19]

The true bugs are also known to employ sex pheromones, and the green stink bug, *Nezara viridula* (Heteroptera: Pentatomidae), incorporates *cis*- and *trans*-(*Z*)-α-bisabolene epoxide **16** as the main components of its sex pheromone.[20] The importance of the *cis* : *trans* ratio to maintain biological activity is also discussed. Closely related to true bugs are the aphids (Homoptera: Aphididae), and a considerable amount of attention has been directed to sex pheromones of the pest aphids in the subfamily Aphidinae, following the initial characterisation of two cyclopentanoids, a nepetalactone **17** and a nepetalactol **18**, with (4a*S*,7*S*,7a*R*) stereochemistry.[21] The stereochemistry for the lactol **18** was confirmed as having the (1*R*) configuration by subsequent X-ray crystallography on synthetic compounds.[22]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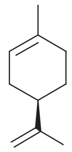
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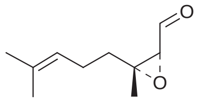

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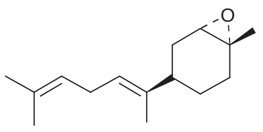

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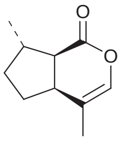

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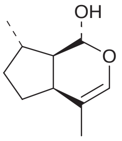

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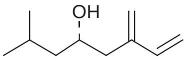
The interest in the use of aphid sex pheromones to control pest aphids[23] has resulted in further key identifications, for example, the major cereal pest, the American greenbug, *Schizaphis graminum* where the sex pheromone was shown to comprise the nepetalactol **18** exclusively.[24] For the damson hop aphid, *Phorodon humuli*,[25] different stereochemistry was found with activity shown for the diastereomeric mixture of nepetalactols **18** with (4a*R*,7*S*,7a*S*) stereochemistry.[25] In addition, long range attraction of aphids in the field was demonstrated for the first time with these pheromones, which are used by males searching for the true females, produced on the winter host, usually a woody plant, after autumn migration of the winged asexual females. The sex pheromone of the major European cereal aphid pest, the grain aphid, *Sitobion avenae*, was shown to have the nepetalactone **17** structure exclusively[26] and the horticultural pest of cruciferous plants, the cabbage aphid *Brevicoryne brassicae* had the same pheromone **17**.[27] However, species isolation is ensured by the taxonomic distance between host plants for these two aphid species.

The biology of the aphid sex pheromones has been discussed in detail,[28] the associated chemistry and attempts to elucidate the biosynthetic pathways have been described, together with the chemical characterisation of the pheromones for a further range of pest species.[29] Besides the long range attraction of male aphids to the sex pheromone, parasitoids and predators of aphids are attracted to the sex pheromone and this kairomonal role will be discussed in a later section.

Oxygenated isoprenoids are common components of the aggregation pheromones of bark beetles (Scolytidae), particularly in the genus *Ips*. These are often specific isomers of ipsenol **19**, ipsenone **20** and ipsdienol **21** with the stereochemistry known for many species. A newly investigated species, *I. schmutzenhoferi* releases principally ipsenol **19** but with traces of the other two compounds. The stereochemistry of the ipsenol **19** released by *I. schmutzenhoferi* was not determined, but the insects were attracted to the racemic mixture in bioassays and field studies.[30]



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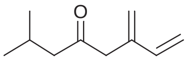

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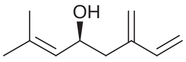

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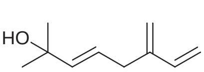

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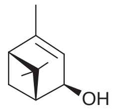

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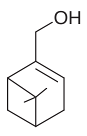

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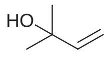

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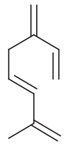
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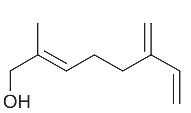
The exact compositions of the pheromones of two subspecies of *I. amatinus* have been investigated and were shown to contain significant quantities of (*S*)-ipsdienol **21**, along with amitinol **22**, *cis*-verbenol **23**, *trans*-verbenol *trans*-**23**, myrtenol **24** and traces of (*S*)-ipsenol **19**. The ratios of (*S*)-ipsdienol **21** and (*S*)-ipsenol **19** in these pheromones were determined in order to look for possible speciation.[31] On joining the males, female beetles also produced 2-methylbut-3-en-2-ol **25**, which is only produced by the males in trace amounts. In a similar study on *I. pini* two distinct regional variants of *I. pini* were found having different enantiomeric compositions of (*R*)- and (*S*)-ipsdienol **21**.[32] In addition to (*S*)-ipsdienol (**21**), (*S*)-ipsenol **19** and amitinol **22**, the aggregation pheromone of the European pine engraver, *I. mannsfeldi*, contains the unusual tetraene monoterpene ipstriene **26**.[33]

I. duplicatus also produces racemic ipsdienol **21** as its aggregation pheromone but in addition another, less common, oxygenated terpene (*E*)-myrcenol **27** is an important component, and this synergises the activity of ipsdienol **21**.[34] Opportunistic field studies with a mixture of monoterpenes including α-pinene **28**, (1*S*)-Δ^3-carene **29** and terpinolene **30** allowed catches of various bark beetles including *Tomicus piniperda*, *Hylurgops palliatus* and *Trypodendron domesticum*. This attraction was improved by addition of ethanol for *H. palliatus*. Attraction to ethanol alone was reduced for *T. domesticum* by addition of (1*S*,5*S*)-verbenone **31**, which is known in other cases to cause interruption of pheromone mediated attraction.[35] Recent studies demonstrating this effect of verbenone **31** on aggregation behaviour have been carried out with *I. latidens*, *I. pini*, and *Dendroctonus ponderosae*, where verbenone **31** significantly reduced catches to traps baited with aggregation pheromones.[36] Laboratory studies on *I. paraconfusus* have demonstrated that both (1*S*,5*S*)-verbenone **31** and (1*R*,5*R*)-verbenone 1*R*,5*R*-**31** decreased attractiveness of the aggregation pheromone, with the higher the enantiomeric purity of the verbenone the greater the effect.[37] Suppression of catches of the southern pine beetle *D. frontalis* on standing trees was also significantly reduced by verbenone **31** and this had no negative effect on natural enemies of this pest insect.[38] Verbenone **31** rapidly photo-isomerises in sunlight to chrysanthenone **32** and this has practical implications for attempts to use verbenone **31** to reduce colonisation of trees by bark beetles.[39]



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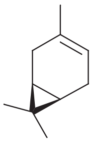

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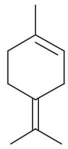

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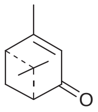

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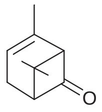

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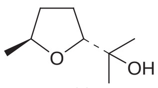
The female released aggregation pheromone of the white pine cone beetle, *Conophthorus coniperda*, has been identified as the degraded monoterpene (2*R*,5*S*)-pityol **33**.[40] The hemiterpene 3-methylbut-3-en-1-ol **34** has been shown to be the aggregation pheromone of the four-eyed spruce bark beetle, *Polygraphus rufipennis*[41] and this compound not only attracts *P. rufipennis*, but also the cylindrical bark beetle, *Lasconotus intricatus*. Addition of host terpenes including bornyl acetate **35** and β-pinene **36** to the 3-methylbut-3-en-1-ol **34** reduced the attraction of *L. intricatus* to pheromone traps in the field.[42] The ready availability of *cis*-verbenol **23** and 2-methylbut-3-en-2-ol **25** has allowed extensive field studies on the flight behaviour of *I. typographus* to be made.[43]



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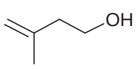

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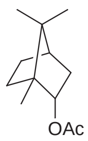

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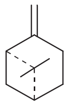

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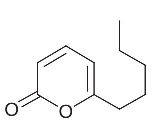
Social interactions of insects in the order Hymenoptera are often regulated by pheromones such as the trail pheromones used by ants. A recent study on the myrmicine ant, *Pristomyrmex pungens* (Myrmicinae), demonstrates that the trail pheromone, isolated from the poison gland, comprises the fatty acid product 6-*n*-pentyl-2-pyrone **37** together with a number of isoprenoids, including α-pinene **28**, camphene **38**, β-pinene **36**, β-myrcene **39**, α-phellandrene **40**, α-terpinene **41** and limonene **14**.[44] The isoprenoids were shown to increase locomotory activity, but the main trail pheromone activity was ascribed to the pyrone **37**. Two studies have been made on the volatile secretions of the Dufour glands of three species of New World army ants, *Eciton burchelli*, *Labidus coecus* and *Labidus praedator* (Ecitoninae), and the Old World army ant *Aenictus rotundatus* (Dorylinae). Compounds identified for the New World ants included numerous hydrocarbons as well as the isoprenoids geranylacetone **42**, geranyllinalool **43**, and (*E*)-β-ocimene *E*-**13**, which was identified for the first time in a Dufour gland secretion.[45] In the Old World ant, *A. rotundatus*, the main compound identified in the Dufour gland was geranylgeraniol **44** which comprised over 50% of the total secretion. Other isoprenoids including α-springene **45**, β-springene **46**, geranylneral **47** and geranylgeranial 2*E*-**47** were present at lower concentrations. Also found were a number of novel dioxabicyclo compounds thought to be isoprenoid in origin, although the exact structures have yet to be confirmed by synthesis, and a range of straight chain hydrocarbons.[46]



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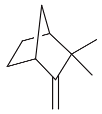

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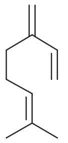

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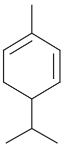

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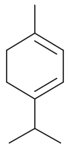

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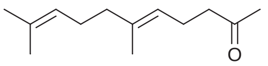

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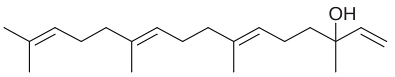

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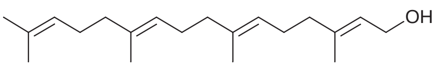

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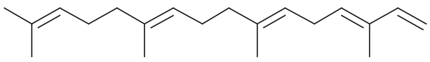

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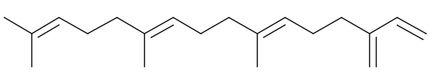

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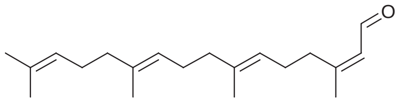

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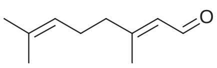
Honeybees, *Apis mellifera* (Apidae), produce a wide range of pheromonal secretions[47] and the Nasonov pheromone which can be used to attract honey bee swarms[48] continues to engender interest. The Nasonov gland responsible for the production of this pheromone has now been investigated structurally in detail and the function of the isoprenoid extracts containing geranial **48** and neral *Z*-**48**, (*E*,*E*)-farnesol **12**, nerol **49**, geraniol *E*-**49**,



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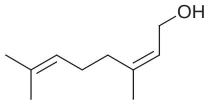

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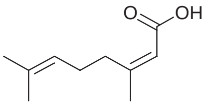

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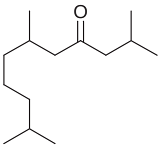

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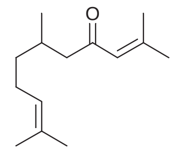
nerolic acid **50** and geranic acid *E*-**50** studied further.[49] The pheromonal cephalic secretion of the cuckoo bee, *Nomada lathburiana* (Anthophoridae), has been shown to contain a range of novel sesquiterpene ketones and norsesquiterpene ketones (**51–56**, *E*-**56** and *Z*-**54**) including as a major component the highly unstable oxygenated sesquiterpenoid (5*E*)-2,6,10-trimethylundecane-2,5,9-trien-4-one **54**.[50] In bumblebees the labial gland is responsible for a marking pheromone and for *Bombus pratorum* (Apidae) scent marking around the edges of birch leaves was found to contain farnesol **12**, geranylgeranyl acetate **57**, farnesyl acetate **58** and a number of fatty acid metabolites.[51] The labial gland secretions of the three North American bumblebees have been examined and show distinct species specificity, with each species containing a long chain fatty acid derived alcohol along with an isoprenoid component. Thus the secretions from *Bombus huntii* contain (*E*)-2,3-dihydrofarnesol **59**; *Psithyrus insularis* geranylcitronellol **60**; and *Bombus sonorus* geranylgeraniol **44**.[52]



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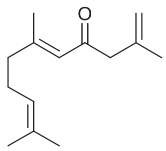

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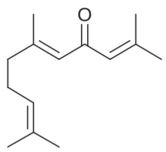

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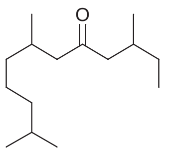

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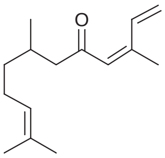

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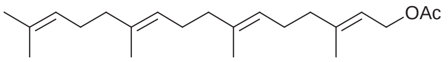

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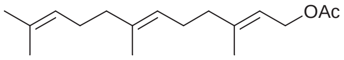

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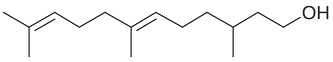

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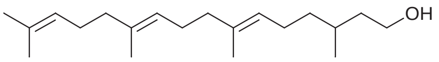

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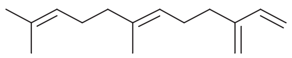
2.1 Pheromones interacting with plant semiochemicals

The first report of a pheromone being synergised by host plant chemicals was made in 1986.[53] This involved the aphid alarm pheromone component (*E*)-β-farnesene **61** being synergised by plant derived isothiocyanates released from the cruciferous host of the mustard aphid, *Lipaphis erysimi*, during feeding. In the full publication of this work,[54] it was shown that the response to the plant derived synergists results from a highly specific interaction with particular olfactory nerve cells in a similar manner to the pheromone component suggesting the possibility of a similar degree of sensitivity to plant derived compounds as to pheromones. Somewhat later other workers showed an enhancement of two commercially available insect pheromones, for the boll weevil, *Anthonomus grandis* (Curculionidae), and the bark beetle, *Scolytus multistriatus* (Scolytidae), with other plant compounds, this time the green leaf volatiles. In the same study volatiles from the Mediterranean fruit fly, *Ceratitis capitata* (Trypetidae), were also synergised by plant released green leaf volatiles.[55] The pheromone of the ambrosia beetle, *Trypodendron lineatum* (Scolytidae), lineatin **62** was found to be synergised by the plant component and isoprenoid α-pinene **28**.[56] A review covering aspects of this area, specifically examining the integration of sexual behaviour of phytophagous insects with their host plants has been published.[57]



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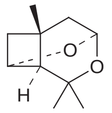

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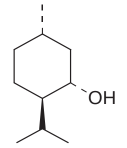
2.2 Analytical and stereochemical studies

When a correct identification of a pheromonal component has been made behavioural studies should then confirm the semiochemical role for the identified compound. However, it is still common to see papers with only electrophysiological activity reported, but where this is related to a particular sex or ecological system, this can be useful in initially defining a compound as a semiochemical. For example, female produced (*Z,E*)-α-farnesene **7** was found to be electrophysiologically active on the male antenna of a scarab beetle, *Maladera matrida* (Scarabaeidae), and female produced volatiles are known to be attractive to males, suggesting a semiochemical role for this compound.[58] However, further behavioural studies are now required to demonstrate real biological activity for the compound in this ecological system.

As stated earlier, pheromones can derive specificity from asymmetry, and the role of molecular asymmetry in pheromone science has been reviewed by the leading synthesis chemist in this area, K. Mori.[59] An extremely important technique in determining chirality of volatile semiochemicals is chiral GC used in conjunction with synthesised compounds or commercially available compounds of authentic stereochemistry. A number of studies have been made on bark beetle (Scolytidae) aggregation pheromones using a chiral stationary phase, based on a modified cyclodextrin, particularly involving the Hamburg group including W. Francke.[33,60–62] There are also now a number of GC chiral stationary phases based on modified cyclodextrins available from the major GC column manufacturers which, it is hoped, will result in an increased number of determinations of chirality in this area. A new strategy involving chiral amplification to determine the absolute configuration of non-readily available secondary alcohols and the analogous amines has been described and exemplified by showing the (*R*)-configuration for two non-isoprenoid components of the sex pheromone of the longhorn beetle, *Anaglyptus subfasciatus* (Cerambycide), and for various other compounds including the monoterpene menthol **63**.[63]

Although it is seldom possible to design very active analogues of semiochemicals because of the highly specific nature of the receptor system, there are still periodic studies of structure–activity relationships. For example, for the click beetles, *Agriotes* spp. (Elateridae), where the sex pheromone comprises various geranyl and (*E,E*)-farnesyl esters, a range of related compounds has been studied and some limited trends in activity discerned.[64] In a more sophisticated study on the much



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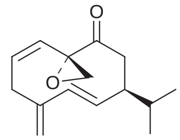

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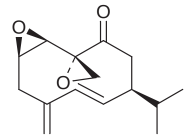

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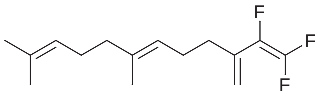

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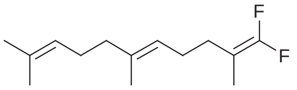

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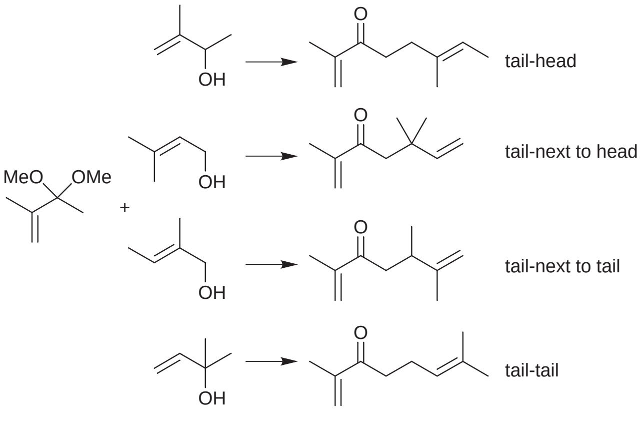
more difficult target of the sex pheromone of the American cockroach, *Periplaneta americana* (Blattidae), the components periplanone-A **64** and periplanone-B **65** and analogues have attracted combined molecular mechanical and molecular orbital studies, in order to evaluate biological activity from electronic and geometric properties. This has resulted in the refinement of a model used to predict biological activity. However, to date, no more readily synthesisable attractants have been identified.[65] Fluorine can, surprisingly, replace hydrogen with retention of relatively high levels of activity and this has been achieved with the aphid alarm pheromone (*E*)-β-farnesene **61**, providing analogues 1,1,2-trifluoro-(*E*)-β-farnesene **66** and a 1,1-difluoro-α-farnesene analogue **67**.[66]

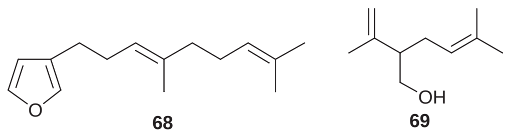
2.3 Synthesis

There is an excellent review on the synthesis of pheromones by the leading synthesis chemist in the area of semiochemicals, K. Mori, covering literature from 1979–1989, which includes chapters on the synthesis of isoprenoid pheromones.[67] He has also published an extensive review on the use of biochemical methods in the enantioselective synthesis of natural products, with a particular emphasis on pheromones, which contains the synthesis of many compounds of isoprenoid origin.[68]

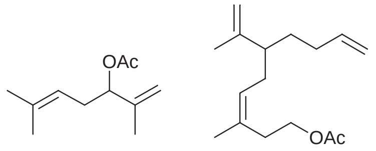
Two generic synthesis routes to isoprenoid pheromones and other semiochemical compounds have been published. One involves isoprenoid chain elongations by Claisen rearrangements[69] (Scheme 1) and this route has then been used to synthesise a number of all *trans* isoprenoid pheromone components including (*E*)-β-farnesene **61**,[70] (*E*,*E*)-β-springene **46** and dendrolasin **68**.[71] The other involves regio- and stereocontrolled processing of allyllithiums generated by reductive lithiation of allyl phenyl thioethers and has been used to synthesise lavandulol **69**, the sex pheromone **70** of the comstock mealybug, *Pseudococcus comstocki* (Pseudococcidae), and a California red scale, *Aonidiella aurantii* (Coccidae), sex pheromone component **71**.[72] The mealybug sex pheromone **70** has been synthesised using as the key step the deoxygenation of an α,β-unsaturated ketone **72** (Scheme 2), with a double bond migration which was carried out in one pot, without isolation of the intermediate tosylhydrazone.[73] A convenient synthesis of racemic ipsdienol **21** and racemic ipsenol **19**, the common bark beetle aggregation pheromone components, is reported starting from a readily prepared isoprenyl anion equivalent and the appropriate aldehyde or ketone.[74] The aggregation pheromone of the striped ambrosia beetle, *T. lineatum*, contains lineatin **62**, which can be used in its racemic form, and the racemate has been conveniently synthesised (Scheme 3) in 20% overall yield.[75]



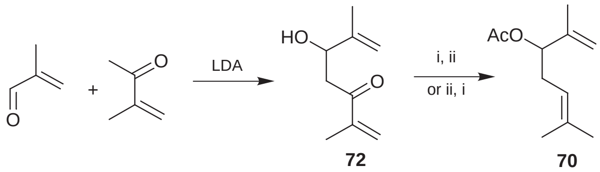
Scheme 1 Isoprenoid chain elongations *via* Claisen rearrangements.



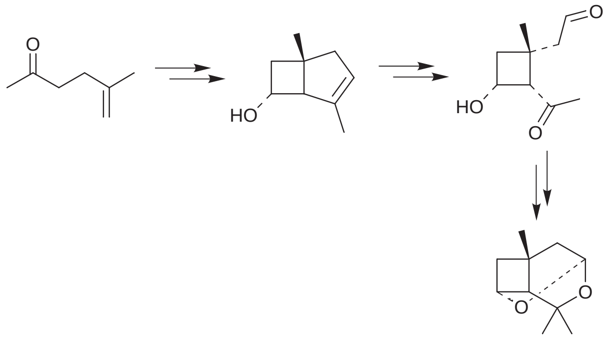
68 **69**



70 **71**

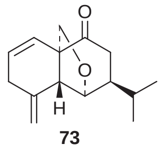


Scheme 2 Racemic synthesis of the comstock mealybug sex pheromone **70**. *Reagents and conditions*: i: *p*-TsNHNH$_2$, NaBH$_3$CN, AcOH; ii: Ac$_2$O, pyr.



Scheme 3 A summary of a synthesis of lineatin **62**.

There is also a synthesis of the racemic rearrangement product **73** obtained from the initially proposed structure for periplanone-A, from the sex pheromone of the American cockroach, *P. americana*.[76] This has been useful in clarifying the exact nature of the sex pheromone, which had been under investigation for some time.[77] However, the products from this synthesis are racemic and the most valuable synthesis developments are in the production of stereochemically pure products. For example, in continuation of the work on *P. americana* both enantiomers of Hauptmann's periplanone-A **64** and (3*S*,4*E*,8*R*,9*R*,10*R*)-periplanone-B **65** have been synthesised resulting in the correct characterisation of the components of this sex pheromone.[78,79]



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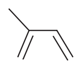
The ubiquitous (*R*)-ipsdienol *R*-**21** has been prepared by a periselective and enantioselective carbonyl-ene reaction of isoprene **74** with fluoroalkyl glyoxylate using a binaphthol–



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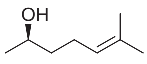

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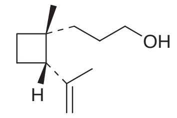

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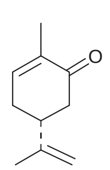

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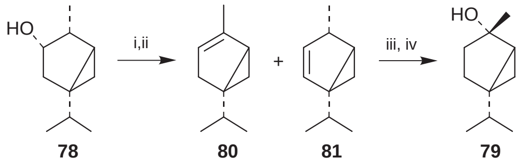
titanium catalyst in 59% overall yield.[80] Syntheses of this type, where the product is obtained enantiospecifically, are important in the synthesis of insect pheromones as different enantiomers can alter species specificity of the pheromone blend, as discussed above. Tandem asymmetric conjugate addition and stereospecific Meisenheimer rearrangement has been used for the asymmetric synthesis of a number of diols, as well as (*R*)-6-methylhept-5-en-2-ol **75** (sulcatol), which is of isoprenoid origin.[81] (3*S*,4*R*)-Eldanolide **1**, mentioned earlier as the sex pheromone component of the African sugar-cane borer, *E. saccharina*, has been synthesised in 92% enantiomeric excess by a homoaldol reaction.[82] (1*R*,2*S*)-Grandisol **76**, an aggregation pheromone component for the male cotton boll weevil, *A. grandis*, continues to attract considerable interest, and three papers have recently appeared describing new syntheses.[83–85] The construction of the cyclobutane ring is of considerable importance and this has been synthesised using an asymmetric [2 + 2] cycloaddition reaction catalysed by a chiral titanium reagent.[83] Both (1*R*,2*S*)-grandisol **76** and (1*R*,4*S*,5*R*,7*R*)-lineatin **62**, the female produced aggregation pheromone of *T. lineatum*, have been synthesised from a common intermediate.[84]

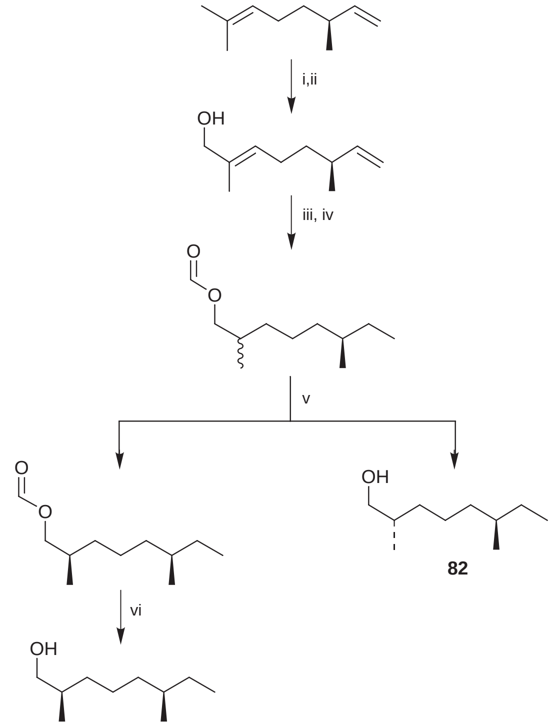
Stereochemically pure natural products are often valuable starting materials for the synthesis of chiral semiochemicals, and (1*R*,2*S*)-grandisol **76** has been synthesised in eighteen steps from (*R*)-carvone **77** in 2.6% overall yield.[85] Using (1*R*,3*S*,4*R*,5*R*)-3-thujol **78** as a starting material a clean generation of (1*R*,2*S*,5*R*)-sabinene hydrate (**79**, Scheme 4), a compound found in both insect–insect and insect–plant interactions, has been obtained by a highly selective ene reaction with singlet oxygen and unsaturated intermediates **80** and **81**.[86]



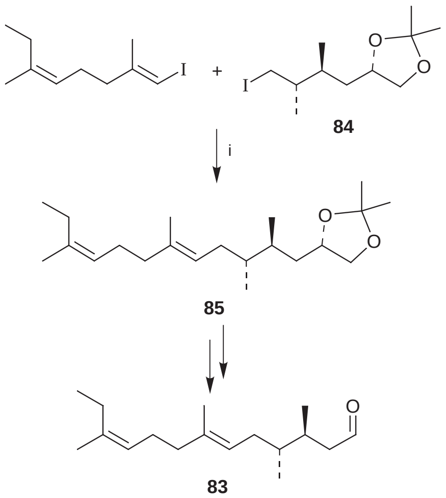
Scheme 4 Synthesis of *trans*-sabinene hydrate **79** from 3-thujol **78**. *Reagents and conditions*: i: MsCl, Et_3N; ii: KOH, 18-crown-6; iii: $^1O_2$; iv: H_2, Pd/C.

Lipases, such as porcine pancreatic lipase, can be used in a variety of ways to produce enantiomerically pure semiochemicals, for example saturated monoterpene alcohols such as (2*S*,6*R*)-2,6-dimethyloctanol (**82**, Scheme 5), the formate ester of which is an attractant for the smaller flour beetle, *Tribolium confusum* (Tenebrionidae).[87] The highly unstable straight chain sesquiterpene (3*S*,4*R*)-faranal (**83**, Scheme 6), the trail pheromone of the pharaohs ant, *Monomorium pharaonis* (Formicidae), has been synthesised by a purely chemical route with the key step being the asymmetric cleavage of an epoxide with a chiral lithium amide to generate the asymmetric centre in ketal **84**, which is further elaborated *via* **85** to afford **83**.[88,89] (*S*)-Geranylcitronellol **60** and the corresponding acetate **86** are produced as part of a marking pheromone by male bumblebees, *Bombus* spp. and *Psithyrus* spp., and have been synthesised *via* a conjugate addition reaction of a functionalised copper reagent to substituted bornyl crotonates.[90]

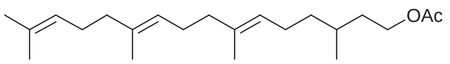
In the past many studies on the telomerization of isoprene have been made in Russia and a recent report[91] describes the telomerization of isoprene **74** with allyl, benzyl, 2-chloroethyl and methyl alcohols using a π-alkylpalladium complex as a catalyst to yield various isoprenoid type semiochemical components including the formate esters known to attract *T. confusum*.



Scheme 5 Chemo-enzymatic synthesis of optically pure saturated monoterpene alcohols. *Reagents and conditions*: i: SeO_2, *tert*-pentyl hydroperoxide; ii: $NaBH_4$; iii: H_2, Pt/C; iv: HCOOH; v: porcine pancreatic lipase, H_2O, pH 7.0, 37 °C; vi: KOH, MeOH.



Scheme 6 A summary of a synthesis of faranal **83**. *Reagents and conditions*: i: *tert*-butyllithium, Et_2O, THF.



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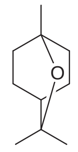
3 Host location

3.1 Plant hosts

An important technique in the identification of semiochemicals is electrophysiology, either using whole antennae, the usual site for interaction with volatile semiochemicals giving an electroantennogram (EAG), or preparations from a single cell or single sensilla on the antennae. This is usually coupled to a GC so that complex mixtures, typical of plant volatiles can be screened by the insect to determine the active compounds within the mixture. It is now clear that even for common plant derived semiochemicals and host derived semiochemicals generally, whether isoprenoids or not, there are usually highly specific interactions at the sensory nerve cell system.[92] Furthermore, it has recently been shown for some Coleoptera, for example the cabbage seed weevil, *Ceutorhynchus assimilis* (Curculionidae), that these highly specific cells can be located morphologically together in pairs or even sometimes in a pattern of three, as is the case for the pea and bean weevil, *Sitona lineatus* (Curculionidae) (Christine Woodcock, personal communication). Thus, in *C. assimilis* the cell specifically responding to 2-phenylethanol is found paired together with the cell responding to the monoterpene 1,8-cineole **87**.[92] It may be that the co-located cells allow the insect to determine relative proportions of semiochemicals arising from different biosynthetic pathways. This would allow insects to select between plants, not just on the basis of novel composition, but on specific relative proportions of more ubiquitous compounds, such as the isoprenoids.



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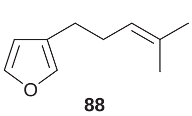

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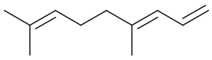

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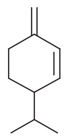
After tentative identification by mass spectrometry, authentic material should be provided for GC peak enhancement on columns of different polarity, thereby confirming the identification. However, there are still many reports where this is not the case, particularly for plant derived semiochemicals and this frequently leads to misidentifications. For example, since perillene **88** is in the major databases of mass spectrometry, whereas the homomonoterpene, (*E*)-4,8-dimethylnona-1,3,7-triene **89** is not, this often leads to the incorrect identification of (*E*)-4,8-dimethylnona-1,3,7-triene **89** as perillene **88** (Witko Francke, personal communication). There are many such examples proven, and many other likely cases, such as that by Kite and Leon,[93] which demonstrates the need for the authentic materials to be available for correct identifications to be made.

Although not dealing specifically with isoprenoid semiochemicals, a series of extremely valuable publications have appeared giving the release rates for various compounds, including a range of isoprenoids, from various plant sources.[94–97] For example, release of isoprene **74** ranges from $1.5\ \mathrm{ng\ g^{-1}\ h^{-1}}$ for the grape vine, *Vitis vinifera* (Vitaceae), to $614.4\ \mathrm{ng\ g^{-1}\ h^{-1}}$ for the oak, *Quercus robur* (Fagaceae); β-phellandrene **90** from 0.5 to 0 respectively, and limonene **14** from 1 to 104.9 respectively.[97] These data are useful in terms of examining the background levels of particular compounds and comparing these with amounts released in specific plant–insect interactions.



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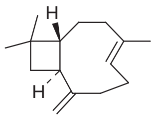

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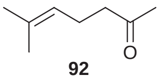


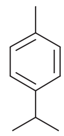
92

New biological roles continue to be found for β-caryophyllene **91**, including attraction of spring migrants of the damson-hop aphid *P. humuli*, to its summer host, the hop plant, *Humulus lupulus* (Cannabinaceae).[98]

Again, not directly tied to specific semiochemicals, but of interesting evolutionary significance, is a comparison of gymnosperm and angiosperm volatiles centring on four species of cycad (Cycadaceae).[99] Various isoprenoids and other compounds were released particularly by the insect-pollinated cycad species, with the overall suggestion of convergent evolution with regard to volatile components of the semiochemicals attracting pollinating insects for the gymnospermous cycads and the compared magnoliid angiosperms. The isoprenoid components released from a wide range of angiosperm flowers are also reported, although only presence or absence of a particular class of compound is given.[100] Post pollination changes in volatile production have been investigated in the orchid, *Ophyrus sphegodes* (Orchidaceae), and it was found that the pollinator *Andrena nigroaenea* (Andrenidae) is less attracted to flowers three days post pollination. This was attributed to changes in volatile production, including changes in the isoprenoids α-pinene **28**, 6-methylhept-5-en-2-one **92**, limonene **14**, and 1,8-cineole **87**.[101]

Besides taking the nectar produced by flowers, pollinating insects also collect pollen, and the volatile cues differentially produced by pollen and whole flowers have been compared in taxonomically unrelated species and a range of isoprenoids found. The field poppy, *Papaver rhoeas* (Papaveraceae), was found to contain mainly fatty acid derivatives with little isoprenoid component; as was dropwort, *Filpendula vulgaris* (Rosaceae); whereas lupin, *Lupinus polyphyllus* (Fabaceae), contained mainly isoprenoids, with high concentrations of (*E*)-β-farnesene **61** in both pollen and flowers, but with (*E*)-β-ocimene *E*-**13** found only in flowers, and 6-methylhept-5-en-2-one **92** and (*E*)-4,8-dimethylnona-1,3,7-triene **89** only in pollen.[102]

Hymenoptera and to some extent other orders, including Diptera, can be trained to respond to certain volatile cues when a reward is offered. In the case of the honeybee, *A. mellifera*, rewarding the insect by offering sucrose allows very precise training in, for example, foraging or proboscis extension. This has allowed an investigation into which individual components of a mixture, to which the honeybee is trained, are used by the insect in the learning process. Thus, by training a bee to total floral volatiles, the components can then be separated by GC and presented individually in the GC effluent to the trained bee. This has shown that a relatively small percentage of individual compounds are used by the bee in the learning process when the compounds are presented at realistic physiological levels. The bee employs a diverse range of compounds, with a number of isoprenoids, including α-pinene **28**, *p*-cymene **93**, α-terpinene **41**, linalool **94**, (1*S*)-Δ^3-carene **29** and (*E*,*E*)-α-farnesene *E*,*E*-**7**.[103] Furthermore, there was an indication that during the training process there was a physiological sensitisation to some of the compounds.[104]



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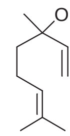
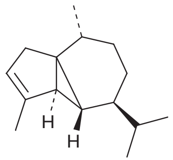


94

Herbivorous Hymenoptera such as leafcutting ants, also interact with plant-derived semiochemicals which act as attractants. Thus, needles from *Pinus caribaea* (Pinaceae), a host plant for the leafcutting ant, *Atta laevigata* (Formicidae), show intra-specific variation in isoprenoids that may play an important role in selection by the ant, with undefoliated trees showing lower levels of myrcene **39** and β-caryophellene **91**.[105] After four months, defoliated trees showed higher concentrations of α-cubebene **95**, α-copaene **96**, γ-muurolene **97** and β-cadinene **98**. Further studies have shown intraindividual variations in isoprenoid content which may be related to herbivory.[106] Variation in isoprenoids released during seasonal development of the Douglas fir, *Pseudotsuga menziesii* (Pinaceae), appears in two phases, with considerable implications for host–insect interactions, particularly with the western spruce budworm, *Choristoneura occidentalis* (Tortricidae). Thus,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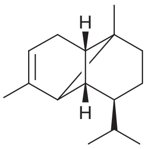
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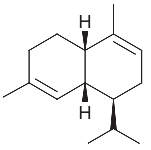
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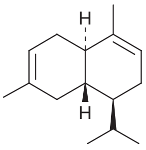
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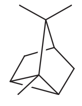
initially at the beginning of budbreak there is an accumulation of α-pinene **28**, tricyclene **99**, camphene **38** and bornyl acetate **35**, with the next phase being characterised by an increase of the minor components (*E*)-β-ocimene *E*-**13**, citronellal **100** and borneol **101**. In contrast, the levels of β-pinene **36**, myrcene **39** and terpinolene **30**, and the sesquiterpenes γ-cadinene **102**, α-bisabolene **103**, and an unknown oxygenated sesquiterpene, remain more or less at a constant background level.[107]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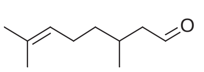
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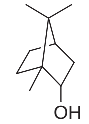
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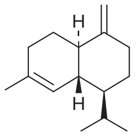
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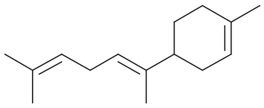
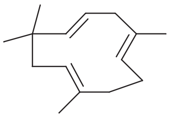

103

The major lepidopterous pest, the European corn borer, *Ostrinia nubilalis* (Pyralidae), employs a range of semiochemicals from its host plant maize, *Zea mays* (Poaceae), and 28 components and related analogues have been evaluated for initiating oviposition behaviour. The sesquiterpene components generally stimulated oviposition, with the most active being α-humulene **104**, α-farnesene **7**, β-farnesene **61** and β-caryophellene oxide **105**.[108] In an extension of this kind of study, 307 accessions from 73 different host plant species of another maize pest, *Helicoverpa zea* (Noctuidae), were analysed chemically and components investigated with *H. zea* for a role in oviposition and neonate larvae orientation bioassays. No compounds were found to act as oviposition deterrents, but a number of compounds including the isoprenoid acids curcumenoic acid **106**, β-bergamotenoic acid **107** and farnesoic acid **108** were found to act as oviposition stimulants. Among a number of other isoprenoids identified was a previously unknown sesquiterpene, 7-epizingiberene **109**, which unfortunately proved inactive at the level tested.[109] After similar investigations of components from the chickpea, *Cicer arietinum* (Fabaceae), a host for *Heliothis armigera* (Noctuidae), a synthetic plant-related kairomone was produced incorporating (1*S*)-Δ^3-carene **29** with α-pinene **28** and myrcene **39** together with pentan-1-ol, which proved to be attractive to the insect, from bioassay through to field studies.[110]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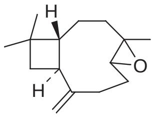
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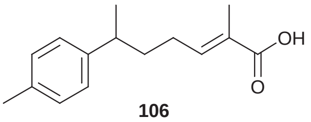
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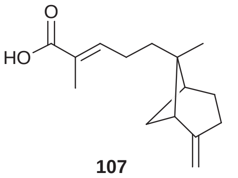
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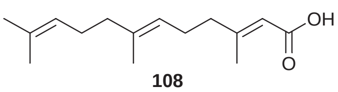
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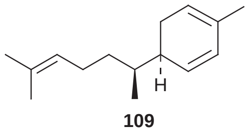
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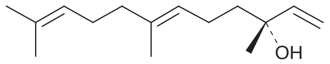
The bark beetle (Scolytidae) aggregation pheromones, although produced by insects, often interact with host semiochemicals in aggregation responses. Thus, for the spruce bark beetle, *I. typographus*, mixtures of (1*S*,5*S*)-α-pinene **28** and (*R*)-limonene **14** together with the aggregation pheromone, significantly increase attractiveness to the adults, whilst individual components are ineffective in increasing trap numbers. Application of myrcene **39** reduces pheromone baited trap catches, whilst (1*R*,5*R*)-α-pinene 1*R*,5*R*-**28** actually acts as a repellant.[111]

It is of great interest to understand the mechanisms by which insects detect and respond to mixtures of different semiochemicals such as those mentioned above, and in connection with isoprenoids involved in conifer–insect–pathogen interactions, a great number of quantitative and qualitative compositional differences have been investigated for various species and this has been comprehensively reviewed.[112]

The Japanese beetle, *Popillia japonica* (Scarabaeidae) is significantly more attracted by its host, the grape vine, *V. vinifera*, after overnight feeding with conspecifics. A range of fatty acid metabolites and isoprenoids, specifically (*E*)-β-ocimene *E*-**13**, linalool **94**, (*E*)-4,8-dimethylnona-1,3,7-triene **89**, (*E*,*E*)-α-farnesene *E*,*E*-**7** and nerolidol **110** were identified as the major compounds emitted in the beetle-damaged vines.[113]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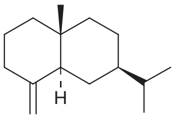
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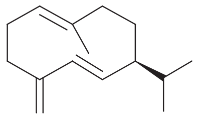
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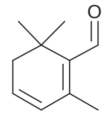
With the serious pest of potatoes, the Colorado potato beetle, *Leptinotarsa decemlineata* (Chrysomelidae), large undamaged potato plants, *Solanum tuberosum* (Solanaceae), attracted the beetle, but small plants did not. However, the small plants became extremely attractive following feeding damage by the beetle. Mechanical damage only resulted in short-term attraction, although damage by *Spodoptera exigua* (Noctuidae) also caused attraction by *L. decemlineata*. The effect persisted for some time after the damaging insects were removed, but only if considerable damage had initially taken place. Although the activity of individual components was not estimated, considerable variations between the damaged and undamaged plants were observed. Potato plants are well-known for producing a wide range of sesquiterpenes and these were amongst those compounds showing considerable variation under the various treatments. For example, the release of linalool **94** increased by a factor of 40 on damage caused by two hours of feeding and (1*R*,9*S*)-β-caryophyllene **91** by a factor of 15, whereas β-selinene **111** only increased by a factor of 1.5 with two hours feeding, but went up by a factor of 20 on twenty hours of feeding damage.[114] GC-EAG studies on *L. decemlineata* using volatiles from damaged potato plants has shown electrophysiological responses to a number of isoprenoids, including linalool **94**, β-myrcene **39** and the sesquiterpenes β-caryophellene **91** and germacrene-D **112**.[115]

3.2 Animal hosts

3.2.1 Invertebrate hosts. There are a number of examples of insect pheromones being used as kairomones by predators and parasitic organisms, or, more correctly, parasitoids, where death of the host is caused. Geranial **48** is the only isoprenoid in a list of 18 different compounds identified in species specific blends from the dorsal abdominal gland secretions of a number of stink bugs (Pentatomidae) which are responsible for parasitism by parasitic Diptera in the family Tachniidae and Hymenoptera in the Scelionida.[116] In the first publication of the identification of an aphid sex pheromone, it was suggested that this pheromone might act as an attractant for predators.[21] It took some considerable time before this was demonstrated, but recently the aphid sex pheromone components nepetalactone **17** and nepetalactol **18** have been shown to be to be attractants for the Far Eastern lacewing, *Chrysopa cognata*, (Neuroptera).[117] Somewhat earlier was the discovery, that wasp parasitoids of aphids, particularly *Praon volucre* (Braconidae), were attracted to sex pheromone components[118,119] and this was extended to other *Praon* spp. by further field studies.[120]

Other kairomones involved in attracting parasitoids are from the frass or faecal material of the host insect and are not normally pheromone components of the host. Thus for the cabbage white butterflies *Pieris rapae* and *P. brassicae* (Pieidae), a range of semiochemicals is emitted from the faeces comprising mostly fatty acid metabolites and amino acid catabolites, including the isothiocyanates, but also some isoprenoids; linalool **94**, safranal **113** and β-cyclocitral **114**.[121]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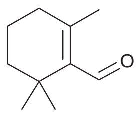
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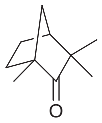
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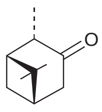
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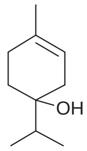
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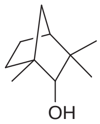
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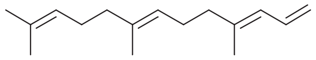
Frass from adult bark beetles such as the Eurasian bark beetle, *Dendroctonus micans*, and the red turpentine beetle, *D. valens*, causes attraction of the specific coleopterous predator *Rhizophagus grandis* (Rhizophagidae). In this situation a wide range of isoprenoids has been found to be involved with host location, with a mixture of (1*R*)-fenchone **115**, (1*S*,2*R*)-pinocamphone **116**, camphor **117**, terpinen-4-ol **118**, (1*S*)-borneol **101**, (1*R*)-fenchol **119** and (1*S*,5*S*)-verbenone **31** eliciting oviposition for *R. grandis*.[122]

3.2.2 Vertebrate hosts. Vertebrates produce a wide range of volatile semiochemicals which are employed as kairomones in locating such hosts by insects and have been studied particularly in the case of flies (Diptera). However, there are very few examples of isoprenoids having these roles except for the presumed monoterpene oxidation product 6-methylhept-5-en-2-one **92**, which has very recently been shown to modify fly load on cattle, particularly of *Hylobia irritans* (Melandryidae) and *Hemotobia irritans* (Muscidae) (Mike Birkett, personal communication).

3.3 Synomones

3.3.1 Plant derived synomones. The location of herbivorous hosts by means of the semiochemicals produced when the host plant of the herbivore is damaged is a valuable evolutionary strategy for parasitic and predatory organisms. The biochemical interactions between plant herbivores and parasitoids have been reviewed[123] with specific discussion of the semiochemicals employed by parasitoids[124] and also the mutualistic interactions involved.[125]

Significant advances have been made by the group of M. Dicke from Wageningen, Netherlands, studying model systems involving an important pest, the herbivorous non-insect spider-mite, *Tetranychus urticae* (Tetranychidae), on a host plant, Lima bean, *Phaseolus lunatus* (Fabaceae), and the mite *Phytoseiulus persimilis* (Phytoseiidae), which predates *T. urticae*.[126,127] This work has implicated the monoterpene (*E*)-β-ocimene *E*-**13** together with (*E*)-4,8-dimethylnona-1,3,7-triene **89** as synomone components. These compounds are released from the plant on damage by the herbivore and release continues even after the herbivore has been removed, maintaining the attraction and foraging stimulus role with the predatory mite. Indeed, it has been suggested that both this homoterpene and the homologous homosesquiterpene, (3*E*,7*E*)-4,8,12-trimethyltrideca-1,3,7,11-tetraene **120**, are important acyclic compounds indicating herbivory and thereby having value at the higher trophic level as synomone components for predators and parasitoids.[128] The Dutch group have also investigated similar interactions for various stem borer parasitoids, in the genus *Cotesia*, which attack the larvae of Noctuidae and Pyralidae moths that bore into the stems of cereals such as maize and sorghum.[129,130] Isoprenoids, with the homoterpenoids featuring prominently, are involved in host location by these parasitoids (Zia Khan, personal communication).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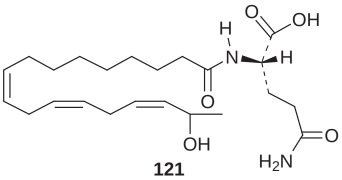

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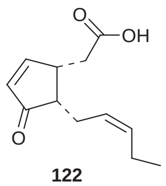
However, the main body of work on insect herbivore-induced plant odours attracting host-seeking parasitic wasps, comes from a group originally centring on Gainesville, Florida and Tifton, Georgia, with the key workers, T. Turlings, J. Tumlinson and W. Lewis coming together for a very valuable report in *Science*.[131] This includes the identification of various compounds, including fatty acid metabolites and isoprenoids, released by corn, *Zea mays* (Poacae), on damage by beet armyworm larvae, *S. exigua*, with the identified sesquiterpenes only appearing after periods of damage longer than two hours. These compounds were shown to be synomones attracting the larval parasitoid *Cotesia marginiventris* (Braconidae) which attacks various lepidopterous species including *S. frugiperda*, *S. exigua*, *Pseudoplusia includens* and *Heliothis* species (Noctuidae). The isoprenoids identified were linalool **94**, (*E*)-4,8-dimethylnona-1,3,7-triene **89**, α-*trans*-bergamotene **9**, (*E*)-β-farnesene **61**, (*E*)-nerolidol **110** and (3*E*,7*E*)-4,8,12-trimethyltrideca-1,3,7,11-tetraene **120**.[132] Further work showed that the same parasitoid would be attracted through a systemic release of signal chemicals after feeding by beet armyworm larvae, *S. exigua*.[133] Eventually, the compound causing this systemic effect from *S. exigua* mouth parts during larval feeding was elegantly identified as *N*-(17-hydroxylinolenoyl)-L-glutamine **121**. When applied to the plant this compound gives systemic release of β-caryophyllene **91**, α-*trans*-bergamotene **9**, (*E*)-β-farnesene **61**, (*E*)-nerolidol **110** and the (3*E*,7*E*)-4,8,12-trimethyltrideca-1,3,7,11-tetraene **120**.[134] This excellent work together with many other aspects, including extending the work to cotton, *Gossypium hirsutum* (Malvaceae), has appeared in two reviews.[135,136] In the full publication of the work on cotton the induced compounds are shown to be somewhat different from those released by corn, but a number of isoprenoids, specifically (*E*)-4,8-dimethylnona-1,3,7-triene **89**, are released in higher relative percentages in damaged plants than in undamaged plants. There is also an increase of 20 to 50 fold in the total amount of volatiles produced in damaged plants.[137] A range of cotton cultivars has been investigated to examine the volatiles produced on herbivore feeding, with no differences found in volatile production, for the different cultivars, although a naturalised cotton variety produced 7-fold more volatiles than the commercial cultivars.[138] The diurnal cycle of emission of induced isoprenoids by herbivore-injured cotton plants has been demonstrated with the main compounds showing such cycling being the acyclic terpenes (*E*)-β-ocimene *E*-**13** and (*E*)-β-farnesene **61**, which show a maximal release in the afternoon.[139] This continues after the herbivorous insect has been removed, at lower rates, whereas release of cyclic terpenes, such as α-pinene **28**, almost ceased after removal of the insects. The systemic release of volatiles from undamaged leaves has also been studied for cotton, where compounds released systemically when cotton is attacked by the beet armyworm *S. exigua* include (*E*)-β-ocimene *E*-**13**, linalool **94**, (*E*)-4,8-dimethylnona-1,3,7-triene **89**, (3*E*,7*E*)-4,8,12-trimethyltrideca-1,3,7,11-tetraene **120** and (*E*,*E*)-α-farnesene *E*,*E*-**7**.[140] The timescale in which the induced compounds are biosynthesised has been examined by some elegant $^{13}CO_2$ feeding studies that show the biosynthesis to be *de novo* for certain compounds, including the acyclic terpenes (*E*,*E*)-α-farnesene *E*,*E*-**7**, (*E*)-β-farnesene **61**, (*E*)-β-ocimene *E*-**13**, linalool **94**, (3*E*,7*E*)-4,8,12-trimethyltrideca-1,3,7,11-tetraene **120** and (*E*)-4,8-dimethylnona-1,3,7-triene **89**, as well as the tryptophan pathway product, indole. However, other volatile components including several cyclic isoprenoids, such as β-pinene **36** and α-humulene **104** are released from storage of synthesised products or stored intermediates following damage.[141,142]

In studies on a different system involving the pear psyllid, *Psylla pyricola* (Psyllidae), feeding on pear, *Pyrus communis* (Rosaceae), a number of compounds were released, including (*E*,*E*)-α-farnesene *E*,*E*-**7**, which attracted anthocorid predators such as *Anthocoris nemorum* and *Anthocoris nemoralis* (Cimicidae).[143]

Herbivore-induction of (*E*)-4,8-dimethylnona-1,3,7-triene **89** and (3*E*,7*E*)-4,8,12-trimethyltrideca-1,3,7,11-tetraene **120** from *P. lunatus* and *Z. mays* can also be triggered by a β-glucosidase or jasmonic acid **122**. A glucosidase could be released into the plant by herbivores with the latter compound generated by the octadecanoic acid pathway which is generally induced on damage.[144] In an extension of the studies on jasmonic acid it has been found that coronatin **123**, a natural jasmonic acid **122** analogue, can also cause induction of (3*E*,7*E*)-4,8,12-trimethyltrideca-1,3,7,11-tetraene **120** in tobacco, *Nicotiana tabacum* (Solanaceae).[145] Distribution and expression of (*E*)-4,8-dimethylnona-1,3,7-triene **89** has been examined in leaf and floral volatiles released from artificially damaged leaves of *Magnolia* spp. (Magnoliaceae). It was found that the time of release varied from immediately post-damage with *M. grandiflora* to 4-6 hours with *M. hypoleuca*. (*E*)-4,8-Dimethylnona-1,3,7-triene **89** was also found in flower volatiles at up to 30% of total flower volatile composition.[146]



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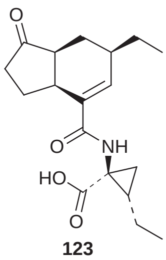

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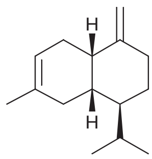

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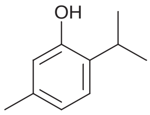
Beetles (Coleoptera) can also cause release of synomones that could be of value to organisms at higher trophic levels, and a range of compounds, including the isoprenoids, (*E*)-β-ocimene *E*-**13**, (*E*)-4,8-dimethylnona-1,3,7-triene **89**, linalool **94**, linalool oxide (isomer not designated) and (*E*,*E*)-α-farnesene *E*,*E*-**7**, have been found when the Japanese beetle, *P. japonica*, attacks crab apple leaves, *Malus domestica* (Rosaceae)[147]. The leafcutting ant, *A. laevigata* is also responsible on defoliation of the conifer *Pinus caribeae* for reduced levels of myrcene **39** and β-caryophyllene **91**, but even four months after the attack there were increased concentrations of the sesquiterpenes α-cubebene **95**, α-copaene **96**, γ-muurolene **124** and β-cadinene **98**, but the lower levels of myrcene **39** remained.[105]

A very interesting recent development has been the observation that some intact plants can imitate herbivore damaged plants by releasing compounds such as (*E*)-4,8-dimethylnona-1,3,7-triene **89** and thereby can cause attraction of parasitoids into the region without requiring herbivore damage.[148] This has now been put to practical use in controlling stemborers by increased parasitism in Africa (Zia Khan, personal communication).

3.3.2 Animal derived synomones. Just as plants have evolved to make use of synomones to protect themselves against herbivores, and parasitoids have evolved to find herbivorous hosts, so the situation is likely to be duplicated where insects feed on other animals. Indeed, one example has come to light in which the casemaking clothes moth, *Tinea pellionella* (Tineidae), feeds on rabbit, *Oryctolagus cuniculus* (Leporidae), and beaver, *Castor fiber* (Castoridae), pelts. This causes the release of synomones, including the isoprenoid geranylacetone **42**, which together with nonanal, serves to attract the parasitoid *Apanteles carpatus* (Braconidae).[149]

3.4 Oviposition deterrence

When eggs are laid by an insect on a host, it is often beneficial for the insects to employ an oviposition deterrent pheromone which can obviate over-colonisation. Furthermore, late oviposition can result in the earlier larvae cannibalising the later arrivals. Thus, from the larval frass of the Egyptian cotton leafworm, *Spodoptera littoralis*, (Noctuidae), an oviposition deterrent pheromone is released which includes thymol **125**, carvacrol **126**, nerolidol **110** and phytol **127**.[150] Studies on the oviposition behaviour of the European corn borer, *O. nubialis*, showed deterrence with farnesal **128**, farnesol **12** and methyl farnesoate **129**.[108] Dried leaves from two aromatic plants, *Artemesia tridentata* (Asteraceae) and *Monarda fistulosa* (Lamiaceae), have been shown to deter oviposition by the Mexican bean weevil, *Zabrotes subfasciatus* (Bruchidae). Analysis of the leaves showed the presence of many isoprenoids with the most abundant being camphor **117** and 1,8-cineole **87** for *A. tridentata* and carvacrol **126** for *M. fistulosa*.[151] However, further work is needed to ascertain which compounds are specifically responsible for the activity. Many other oviposition deterrents are known and have been studied but are seldom of isoprenoid character.



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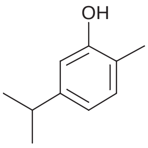

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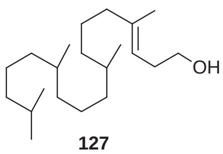

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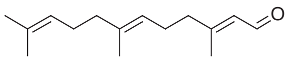

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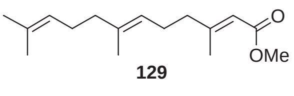

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3.5 Non-host avoidance

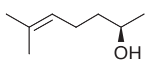
Non-host avoidance can be of a general nature, for example carnivorous animals tend to avoid chemistry particularly typical of plants, and this has given rise to a wide range of mosquito repellents, without individual components having a specific ecological role, and thereby seldom being very effective. However, specific avoidance of non-host plants is employed when insects could be particularly disadvantaged by attempts to feed on such non-hosts.

Various isoprenoids including the volatile (*S*)-carvone *S*-**77** were found to be used by the pales weevil, *Hylobius pales* (Curculionidae), to avoid colonisation when present at high levels.[152,153] The susceptibility of cultivars of crab apple, *Malus* spp., to the Japanese beetle, *P. japonica,* varies with the levels of (*E*)-β-ocimene *E*-**13**, β-caryophyllene **91**, germacrene-D **112** and (*E*,*E*)-α-farnesene *E*,*E*-**7**, which are found at significantly higher levels in susceptible cultivars, whereas the resistant cultivars produced greater amounts of (*E*)-4,8-dimethylnona-1,3,7-triene **89** and linalool **94**.[154] However, attractiveness of the host to the insect was not related to susceptibility of the host, with the attractiveness of particular cultivars correlating positively with linalool **94** when expressed as a percentage of the total volatiles released.

Various forms of stress can influence the susceptibility and value of plants to herbivores. Moisture stress on the river red gum, *Eucalyptus camaldulensis* (Myrtaceae), caused increased herbivory by various insect pests and it may be related to leaf morphology, as there were no significant changes in the level of the major isoprenoid 1,8-cineole **87**.[155] However, trees from two different populations showed differences in herbivory, with trees containing higher levels of the isoprenoid 1,8-cineole **87** showing reduced herbivory. Under nitrate-limiting conditions increased quantities of volatile terpenes were produced by the camphorweed, *Heterotheca subaxillaris* (Asteraceae), which reduced feeding by soybean looper larvae, *Pseudoplusia includens* (Noctuidae).[156] However, no information on the effect of specific isoprenoids within the overall mixture was reported. In the same way, there was a linear relationship between nitrogen availability provided by fertilisation and oviposition rate by the tarnished plant bug, *Lygus rugulipennis* (Miridae).[157] Compounds investigated included a range of terpenes, such as α-pinene **28**, myrcene **39**, and (1*S*)-Δ^3-carene **29**, which did not show a significant variation on fertilisation, whereas increased fertilisation resulted in decreased resin acids, suggesting that this was the cause of increased herbivory on fertilised seedlings.

In the case of the grey pine aphid, *Schizolachnus pineti,* in the sub-family Lachninae, feeding on *Pinus sylvestris* (Pinaceae), there was a positive correlation with foliar nitrogen content and feeding by the aphid. For some isoprenoids there was a relationship between fertilisation rate and isoprenoid content, with reduced levels of tricyclene **99**, α-pinene **28**, camphene **38**, limonene **14** and total monoterpenoids between no nitrogen added and a fertilisation rate of 16.7 g m^{-2}.[158]

As mentioned earlier, besides insects having specific olfactory sensory cells for host compounds, there is similar specificity for non-host compounds. This discovery was initially made in aphids by electrophysiological studies on the bird cherry-oat aphid, *Rhopalosiphum padi,*[159] and the black bean aphid, *Aphis fabae,*[160] where a role was being sought for the so-called redundant nerve cells encountered by many groups studying these species. In this work the function of these nerve cells was explained by responses to chemicals specifically produced by non-hosts which were as such of ecological significance to the aphids investigated. The presumed isoprenoids 6-methylhept-5-en-2-one **92**, and (*R*)- and (*S*)-6-methylhept-5-en-2-ol **130** and *S*-**130** were shown to be ecologically important for *R. padi,*[159] and (1*R*,5*S*)-myrtenal **131** for *A. fabae.*[160] Such specifically based non-host interactions gave rise to behavioural and successful field demonstration of the non-host compounds as repellents and this important development has been reviewed.[161] This phenomenon may provide the basis of the behavioural effects of various lower isoprenoids on the peach-potato aphid, *Myzus persicae*, where, for example, geraniol *E*-**49**, farnesol **12** and bisabola-2,10-dien-1-one **132** significantly inhibited settling by *M. persicae* on the sweet pepper, *Capsicum annuum* (Solanaceae).[162] This specificity of response to non-host compounds appears to be quite general and certainly extends to the Coleoptera, for example the pine shoot beetle, *Tomicus destruens* (Scolytidae).[163] The eucalyptus woodborer, *Phoracantha semipunctata,* (Cerambycidae) responds specifically to isoprenoids characteristic of non-hosts particularly *Pinus* spp. and the European olive, *Olea europaea* (Oleaceae) and different from its host *Eucalyptus* spp. (Myrtaceae) although these species produce very large amounts of an extremely wide range of isoprenoids (Eduardo Barata, personal communication).



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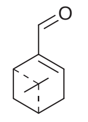

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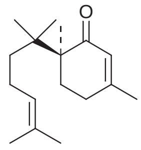

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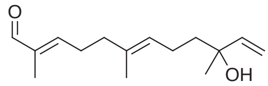
4 Predator avoidance

Insects can produce signals that act in defence as allomones, or that cause alarm within conspecifics and thereby allow insects to escape from an area where predators or parasitoids are foraging. Although in the past a great deal of work has been directed at the aphid alarm pheromone (*E*)-β-farnesene **61** which is released by aphids on attack, and which causes dispersal away from the site of attack,[28] new developments have taken place in this area. Defensive alarm pheromones from lace bugs (Tingidae), for example, *Corythucha* and *Gargaphia* spp. include fatty acid products as well as geraniol *E*-**49**, linalool **94** and nerolidol aldehyde **133**.[164] Larvae of the pine sawfly, *Neodiprion sertifer,* (Neodiprionidae) produce the defence compound germacra-1,6-dien-5-ol **134**.[165] The stick insect, *Megacrania tsudae* (Phasmatidae), also produces a defensive pheromone comprising various cyclopentanoids, with the major component being the cyclopentanoid actinidine **135** and minor components including boschniakine **136** and the degraded cyclopentanoid 1-acetyl-3-methylcyclopentane **137**.[166] The larvae of the monarch butterfly, *Danaus plexippus* (Danaidae), displays by physically waving its wings at passing Hymenoptera, including predatory wasps. It even does so to other related noises of human origin, for example, directly from shouting and even the noise of jet aircraft; a wasp flying nearby presumably giving similar noises to a jet flying far away. At the same time, it appears that volatile allomones are produced including (*E*,*E*)-α-farnesene *E*,*E*-**7**.[167] The burrowing bug, *Sehirus cinctus cinctus* (Cydnidae), produces a defensive secretion which deters various predators and this has been analysed and shown to contain a number of isoprenoids including, (1*R*,5*R*)-α-pinene 1*R*,5*R*-**28**, (1*S*,5*S*)-β-pinene **36**, β-myrcene **39**, (*R*)-limonene **14** and α-terpinolene **30**.[168]



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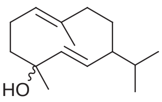

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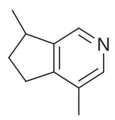

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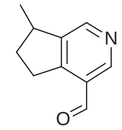

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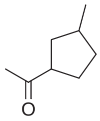

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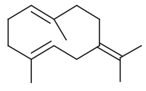
At a higher trophic level, a hyperparasitic wasp, *Alloxysta victrix* (Alloxystidae), which parasitises the aphid parasitoid *Aphidius uzbekistanicus* (Braconidae), releases 6-methylhept-

5-en-2-one **92**, which is then used by *A. uzbekistanicus* to avoid hyperparasitism by eliciting dispersal of the wasp from the area.[169]

5 Primer pheromones

Pheromones can act as primer signals that give rise to endocrine or other physiological changes within the organism. A recent report of a very interesting primer semiochemical produced by a plant has identified twelve compounds from the desert shrub *Commiphora quadricincta* (Burseraceae), including germacrene-B **138**, a series of monoterpenes, other often-encountered sesquiterpenes, and additionally alloaromadendrene **139** and spathulenol **140** as electrophysiologically active. These compounds presumably indicate that vegetation is available for the desert locust, *Schistocerca gregaria* (Acrididae), but instead of the effect being behavioural and, for example, attracting the herbivore, here we see a primer pheromone effect causing an increased rate of maturation in the insect.[170]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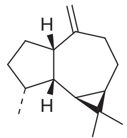

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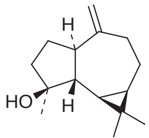

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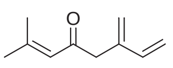
6 Biosynthesis

In this section, biosynthesis of insect metabolites acting as semiochemicals is discussed, with biosynthesis of semiochemicals in plants directed only to those compounds prominent in earlier sections.

6.1 Insects

A commonly-asked question after each new insect derived semiochemical is identified, particularly those of isoprenoid character, is, 'Is the compound sequestered or are precursors sequestered from a host plant?'. Although in the earlier literature sequestration was considered to be a common phenomenon, there are now fewer cases where this is believed to be the case. Some early examples have been re-worked showing that *de novo* synthesis is the more common route to isoprenoid semiochemicals, even when there is a close structural relationship between the insect pheromone and compounds abundant in the host plant. This is particularly true of the bark beetles, where it is now shown that ipsdienol **21** and (*E*)-myrcenol **27** are biosynthesised *de novo*[171] and that the possibility of sequestration of myrcene **39**, an obvious host plant compound which could act as a precursor, is definitely not the case with *I. duplicatus.*[172] Working with the congeneric species *I. paraconfusus* and *I. pini*, Seybold and others have shown unequivocally that acetate is converted *de novo* to (*S*)-ipsenol **19**, (*S*)-ipsdienol **21** and amitinol **22**.[173] In a further elegant extension of this work, it has been shown that the intermediates in this process are ipsdienone **141** and ipsenone **20**.[174]



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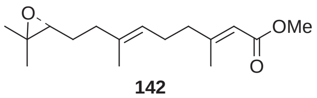

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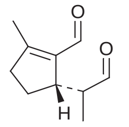
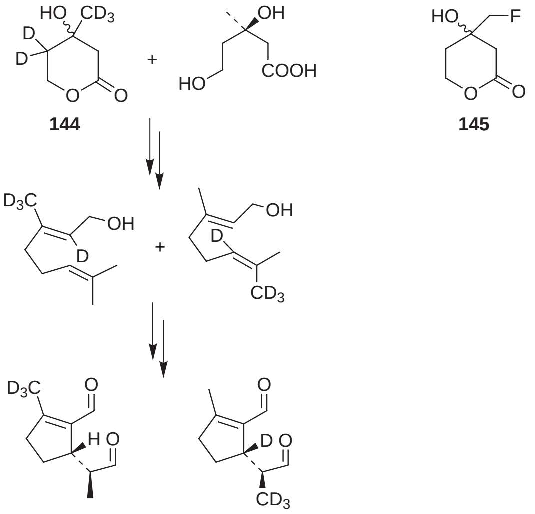
Mevalonic acid has also been shown to be a precursor in this biosynthetic pathway after acetate and is unaffected by addition of juvenile hormone III **142**, which can often affect biosynthetic yield of pheromones.[175]

Studies with *I. typographus* show the transformation of (1*S*,5*S*)-α-pinene **28**, possibly from the host tree, the common spruce, *Picea abies* (Pinaceae), into the aggregation pheromone (1*S*)-*cis*-verbenol **23**, whilst (1*R*,5*R*)-α-pinene 1*R*,5*R*-**28** is transformed into (1*S*)-*trans*-verbenol 1*S*-*trans*-**23**, which inhibits aggregation in field experiments.[176] It is thought that this transformation may be carried out by microorganisms in the intestinal tract of the insect, but just because this transformation can take place does not mean that this is the major source of the aggregation pheromone *in vivo* and further experiments need to be performed to establish the biosynthetic origin of the pheromone.

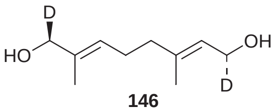
Cyclopentanoid or iridoid monoterpenoids are often encountered as insect metabolites, and because of their ubiquity in the plant kingdom have also been considered as products from possible sequestration. Initial studies on the defensive secretion of three species of leaf beetles (Chrysomelidae), showed that geraniol *E*-**49** was the starting material for the cyclopentanoids chrysomelidial **143** and epichrysomelidial *epi*-**143**, with similarities to the relevant pathways in plants, until cyclisation, when the mechanism was specific to each beetle species.[177,178] It was further demonstrated that *de novo* synthesis of this pathway was occurring by studies using deuterium labelled mevalonolactone **144** (Scheme 7) and a fluorine substituted mevalonate analogue **145** known to inhibit terpenoid biosynthesis.[179] Thus feeding experiments with racemic 4,4,6,6,6-D$_5$-mevalonolactone **144** gave the appropriate deuterium labelled product indicating *de novo* biosynthesis. Preliminary studies on plants using the same pathway have characterised the NADPH oxidoreductase responsible for oxidising the monoterpene primary alcohol on this pathway to a further oxidised compound prior to putative cyclization.[180] The same type of enzyme from the leaf beetle, *Phratora vitellinae*, (Chrysomelidae) was found to oxidise the substrate *Re*-specifically by using (1*R*,8*R*)-[^{2}H$_2$]-8-hydroxygeraniol **146** as a labelled precursor used in *in vitro* studies with six species of iridoid producing leaf beetles.[181]



143

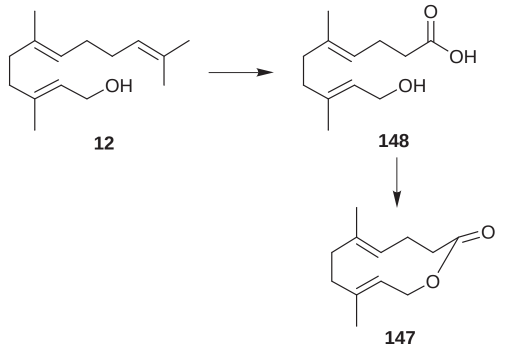


Scheme 7 Biosynthesis of iridoids from a deuterium labelled mevalonolactone **144**.



146

Cucujolide I (**147**, Scheme 8), an aggregation pheromone component from cucujid grain beetles is isoprenoidal in origin

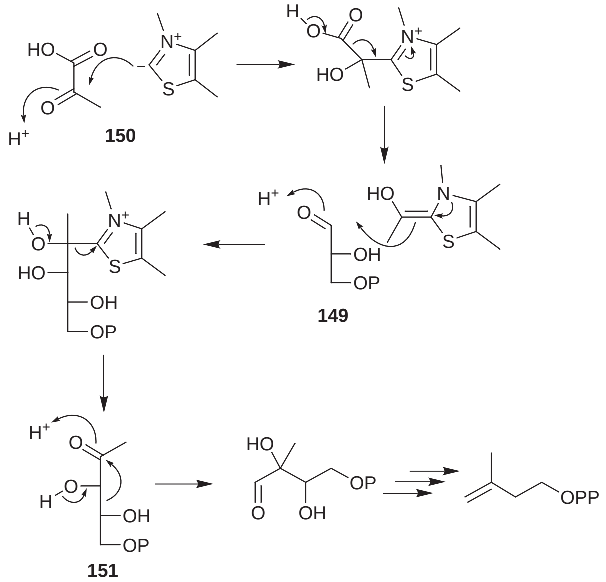


Scheme 8 Proposed biosynthesis of cucujolide I **147** from farnesol **12**.

and its biosynthesis has been demonstrated from exogenously, applied (*E,E*)-farnesol **12** in the rusty grain beetle, *Cryptolestes ferrugineus*, and the merchant beetle, *Oryzaephilus mercator* (Cucujidae). Dual labelling systems with deuterium and $^{18}O_2$ indicate conversion *via* the hydroxy acid **148** to cucujolide I **147** with retention of the hydroxyl oxygen.[182]

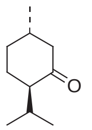
6.2 Plants

A range of volatile isoprenoids produced by plants have now been shown to be biosynthesised from the non-mevalonic pathway involving glyceraldehyde 3-phosphate (**149**, Scheme 9) and pyruvate **150** as precursors of isoprenoid pyrophosphates

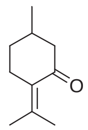


Scheme 9 Preliminary steps of isoprenoid biosynthesis from glyceraldehyde 3-phosphate **149** and pyruvic acid **150**.

produced *via* deoxyxylulose **151**. This pathway was originally elucidated for the isoprenoid side chain of the ubiquinones[183] then for volatile isoprenoids such as geraniol *E*-**49**, menthone **152**, pulegone **153** and thymol **125**, with labelling from [1-^{13}C]



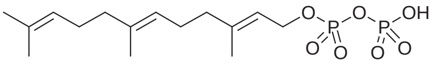
152



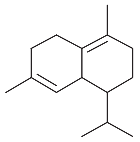
153

and [U-^{13}C]glucose in feeding studies with peppermint, *Mentha piperita* (Lamiaceae).[184]

Considerable progress has been made on the molecular biology and structure of isoprenoid cyclases. A number of monoterpenoid synthases have been identified from grand fir, *Abies grandis* (Pinaceae), by isolation of the gene and functional expression in *Escherichia coli*. These studies have identified a limonene synthase, a myrcene synthase and a pinene synthase that produces both α-pinene **28** and β-pinene **36**.[185] Higher isoprenoid cyclases including squalene cyclase,[186] 5-*epi*-aristolochene synthase,[187] and pentalene synthase[188] have been identified and the crystal structures determined, showing details of the active site involved in the depyrophosphorylation of the precursor farnesyl pyrophosphate **154** and the subsequent



154



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cyclisation mechanism. The first important semiochemical isoprenoid synthase isolated is that for (*E*)-β-farnesene **61**, the aphid alarm pheromone, the cDNA for which has been isolated from *M. piperita* and expressed in *E. coli*. This enzyme catalyses the formation of (*E*)-β-farnesene **61** from farnesyl pyrophosphate **154**, although there is production of small quantities of other sesquiterpenes including (*Z*)-β-farnesene *Z*-**61** and δ-cadinene **155**.[189] Further work on the grand fir, *A. grandis*, has identified two further sesquiterpene synthases which catalyse the production of a very wide range of predominantly cyclised sesquiterpenes from farnesyl pyrophosphate **154**. Named after the major products formed, δ-selinene synthase produces 34 different sequiterpenes, and γ-humulene synthase produces 52 different sesquiterpenes.[190]

In earlier sections the two homoterpenes, (*E*)-4,8-dimethylnona-1,3,7-triene **89** and (3*E*,7*E*)-4,8,12-trimethyltrideca-1,3,7,11-tetraene **120**, have been described as having many semiochemical roles. The Boland group has conducted a series of in-depth investigations into the origins of these compounds, and their ubiquity as plant-derived stress-related compounds. Labelled stereochemical studies demonstrated that for (*E*)-4,8-dimethylnona-1,3,7-triene **89** the precursor is nerolidol **110** and for (3*E*,7*E*)-4,8,12-trimethyltrideca-1,3,7,11-tetraene **120** the precursor is geranyllinalool **43** the reaction proceeding with an exclusive loss of H_s from C_5 of nerolidol **110**.[191] Further studies on mechanistic and biological aspects of this transformation followed[192] and elaboration of the labelling studies was completed.[193] The enzyme selectivity and absolute configuration of the nerolidol precursors was then elucidated.[194]

It is clear that for insects the generation of semiochemically active volatile metabolites is essential for completion of their life cycle. With plants there is a trade-off in terms of all secondary metabolism, hence other aspects of growth and nutrition and the metabolic costs of isoprenoid accumulation in higher plants has been reviewed.[195]

7 Acknowledgements

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