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Chemical Signalling in Beetles

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Abstract This chapter reviews chemical structures of biologically active, volatile compounds in beetles. Techniques used for structure elucidation are briefly discussed as well as facts and speculations on the biosynthesis of target compounds. Syntheses of selected substances are cursorily presented. The order of sections follows taxonomic classifications. Depending on the biological significance of relevant compounds in certain taxa, the corresponding sections are again subdivided into "attractive compounds" (mostly intraspecifically active pheromones) and "defensive compounds" (mostly interspecifically active allomones).

Keywords Beetles · Attractive compounds · Pheromones · Defensive compounds · Biosynthesis · Identification techniques · Structure elucidation

1 Introduction

Beetles (Coleoptera) comprise the most species-rich insect order. About 350,000 species have been described today, about 10% of the estimated actual amount. Apart from open oceans, beetles are colonizing almost every habitat and are able

to cope with extreme climatic conditions. Their body size ranges from very small (some feather-winged beetles – Ptiliidae – show a body length below 0.1 mm) to gigantic (some scarabs – Scarabaeidae – and longhorn beetles – Cerambycidae – are up to 15–20 cm big), and some species truly look bizarre.

In beetles, the front pairs of wings are transformed into hardened wing covers under which the soft hind wings are folded when not in use. This hard cover provides protection which may be a major reason for the successful evolution of this largest order in the animal kingdom.

Beetles pass a holometabolous development with several larval instars, pupae (often poorly known), and completely transformed adults. Larvae show biting mouth parts and often possess abdominal cerci-like structures which are absent in adults. The usually short heads of adults may be elongated to form a snout (as in weevils). Antennae and legs, especially the tarsomeres, may vary strongly with species and are taxonomically useful.

A large number of phytophagous beetles is economically important as pests on crops, forests, and stored products, and they are vectors of fungi and viral plant diseases. On the other hand, many species have beneficial functions in the detritus cycle, and carnivorous species may feed on herbivorous insects.

Apart from optical, acoustical, and tactile cues, transfer of information by volatile compounds plays a pivotal role in the transfer of information between living beings. In insects, intra- and interspecific chemical communication is particularly widespread and important.

Similar to the beetles' global distribution as well as their very different appearance and habitats, the chemical structures that beetles use as signals and their biological significance are highly diverse. They comprise a wide range of volatiles including low boiling carboxylic acids, carbonyl compounds, alcohols as well as simple aromatic compounds, derivatives of amino acids, oxygen containing heterocycles showing several stereogenic centres, and (high boiling, unsaturated, branched) hydrocarbons.

Aiming at the development of integrated pest management systems, research on beetle pheromones has predominantly been carried out with economically important species. In contrast, investigations on the defence chemistry of beetles has largely been phenomenologically oriented. Pheromones of beetles have been listed [1] and presented in a more general context [2] as well as discussed under specific aspects including some biological background [3–7]. The evolution of chemical defence as well as compounds involved in defence chemistry have been reviewed [8, see also the chapter by Laurent et al., this volume]. Valuable data on defensive substances from insect eggs have recently been compiled [9].

Syntheses of pheromones have been comprehensively treated by Mori [10–14]. The role of synthesis in the research on semiochemicals, the importance of stereochemistry in chemical signalling, and the significant relations between enantiomeric composition and biological activity of chiral semiochemicals have been thoroughly discussed by Mori [15–17]. In the present context, presentation of pheromone synthesis plays a minor role; syntheses

leading to mixtures of stereoisomers or to non-natural stereoisomers are not included.

2
Isolation and Structure Elucidation

Techniques in isolation and structure elucidation of (volatile) semiochemicals from beetles are the same as in other insects. Problems are mainly due to the often very small amounts of target compounds, embedded in large amounts of non-active substances which form a kind of "cosmetic formulation" for the biologically active principle. Comprehensive reviews of analytical approaches have been published [18–20].

There is no optimal method for sample preparation. Solvent extraction of crushed insects is certainly a most "dirty" method, as extremely large amounts of body lipids are obtained as contaminants which may cause serious problems during further separation steps. Nevertheless, extraction of dissected glands and of faeces, frass or gnawings as well as short time surface washings are frequently used as standard operations. Headspace techniques using adsorption of emitted volatiles on charcoal or porapak etc. including closed loop stripping, cryo-focussing, and purge-and-trap may largely avoid contamination and greatly facilitate the detection of compounds that are truly released by the investigated organism. Solid sample injection (dissected glands, tissue [21]) and solid-phase-micro-extraction (SPME) [22] avoid any solvent; however, the sample is usually used up during one analytical run, and no derivatives of target components can be prepared (see below). The non-invasive SPME-technique has become almost routine in many labs [23, 24], as it is particularly suitable to follow continuously changes in the production and release of semiochemicals in the same animal depending on time, food, and other parameters.

Tracing biologically active compounds that are perceived by the insects' antennae may be greatly facilitated by on-line linking of gas chromatographic separation (GC) with electrophysiological detection (EAD) [25]. This technique combines high resolution at the separation site with high specificity and high sensitivity at the detector site [18, 20, 26].

Structure elucidation of semiochemicals by modern NMR-techniques (including HPLC/NMR) is often hampered by the very small amounts of available material and problems in the isolation of pure compounds from the complex mixtures they are embedded in. Thus, the combination of gas chromatography and mass spectrometry, GC/MS, is frequently the method of choice. Determination of the molecular mass of the target compound (by chemical ionisation) and its atomic composition (by high resolution mass spectrometry) as well as a careful use of MS-libraries (mass spectra of beetle pheromones and their fragmentation pattern have been described [27]) and gas chromatographic retention indices will certainly facilitate the identification procedure. In addition, the combination of gas chromatography with Fourier-transform infrared spec-

trometry (GC-/FT-IR) may provide important information. As the fragmentation of organic compounds does not always follow strict rules, the interpretation of mass spectra does not always unambiguously enable the deduction of a definite structure. Similarly, infrared spectroscopy provides information on the nature of functional groups rather than on carbon skeletons. Structure elucidation (especially in the case of entirely new compounds) will inevitably need proof through independent synthesis of the proposed structure and comparison of the analytical data of the synthetic compound with those of the natural product.

Microreactions followed by GC/MS-investigations of the reaction products may provide additional information on the chemical structures of target compounds [21, 22]. There are two major areas where micro reactions can be particularly helpful: investigations on the carbon skeleton of a target compound and on the nature of its functional groups. In contrast to NMR-investigations which largely base on the interpretation of signals caused by the influence of functional groups, structure assignment of carbon skeletons by mass spectrometry is limited and often not facilitated by functional groups. This is predominantly due to the formation of stable fragments formed upon α- or β-cleavage, while other signals are of very minor abundance. As a consequence, removal of functional groups or their transformation into groups that do not stabilize the charge may be advantageous. The following micro-reactions proved to be particularly successful in structure elucidation of semiochemicals.

1. Investigations on the carbon skeleton.

Information on the number of double bonds and the number of rings through:
– Removal of double bonds upon hydrogenation (including deuterium)

Location of double bonds through:
– Cleavage of double bonds upon ozonization
– Addition of thiomethyl groups to double bonds upon the reaction with dimethyl disulfide
– Diels-Alder reaction of conjugated double bonds with suitable dienophiles
– Replacement of carbonyl groups or hydroxy groups by hydrogen (including deuterium)
– Transformation of carboxylic acids, esters, alcohols, or ethers into nitriles [28] or other nitrogen containing derivatives [29]
– Investigations on the nature of functional groups

Gas chromatographic separation may be facilitated, and important structural information may be obtained upon the formation of:
– Silylation or (trifluoro)acetylation of hydroxy- or amino groups
– Derivatization of carbonyl groups (reduction or formation of *N,N*-dimethylhydrazones or oximes)
– Transformation of carboxyl groups (esterification or reduction).

The sensitivity of modern mass spectrometers enables subsequent employment of micro reactions even if the yields per step are only moderate. Here an

example: A methyl ketone showing a long carbon chain with several methyl branchings (as indicated by its retention index) was detected among a huge cluster of unseparable hydrocarbons. The mass spectrum of the ketone was strongly dominated by the fragment produced upon McLafferty-rearrangement and did not provide any hints about the branching points. Reduction of the ketone with lithium aluminium deuteride, followed by mesylation and a second reduction step with again lithium aluminium deuteride yielded a di-deuterated hydrocarbon with two deuteriums replacing the oxygen of the former carbonyl group. Its mass spectrum could be easily distinguished from the accompanying non-deuterated hydrocarbons, and its substitution pattern could be assigned according to the literature [30]. Despite the fact that hydride reduction of mesylates of secondary alcohols are proceeding with low yield, the three-step reaction sequence was successfully carried out with less than 50 ng of the target compound [31].

Investigations on the stereochemistry of chiral semiochemicals may be carried out by (gas) chromatographic separation of stereoisomers using chiral stationary phases, e.g. modified cyclodextrins [32]. Alternatively, formation of diastereomers (e.g. Mosher's ester or derivatives involving lactic acid etc.) may be followed by separation on conventional achiral stationary phases. Assignment of the absolute configuration of the natural product will again need comparison with an authentic (synthetic) reference sample.

Another approach ("biogenetic analyses") involves considerations of a reasonable biogenesis of a target compound. Reflections on relationships of components which belong to the same odour bouquet or which have already been known from related species may suggest structures to be expected and, thus, be helpful in the identification process.

3
Biosynthesis and Structural Principles

The biosynthesis and endocrine regulation of pheromone production in beetles has been reviewed [33, 34]. Nevertheless, some more general pathways will be briefly discussed here. As corresponding structures are widespread among insects [2], the examples shown here are selected mostly from taxa other than beetles. Structures representing beetle pheromones will be shown in the context of the discussion of the corresponding species.

Acetogenins. Acetogenins are produced upon chain elongation with activated acetate units (or malonate followed by loss of carbon dioxide). A simplified sketch of this sequence is given in Fig. 1. During the first steps, a Claisen-type condensation of two acyl precursors yields a β-ketoacyl intermediate **A**. Upon reduction to **B** and dehydration to **C**, followed by hydrogenation to **D** and hydrolysis, the chain elongated fatty acid **E** is produced. The next cycle will add another two carbons to the chain. Similarly, a reversed sequence leads to chain

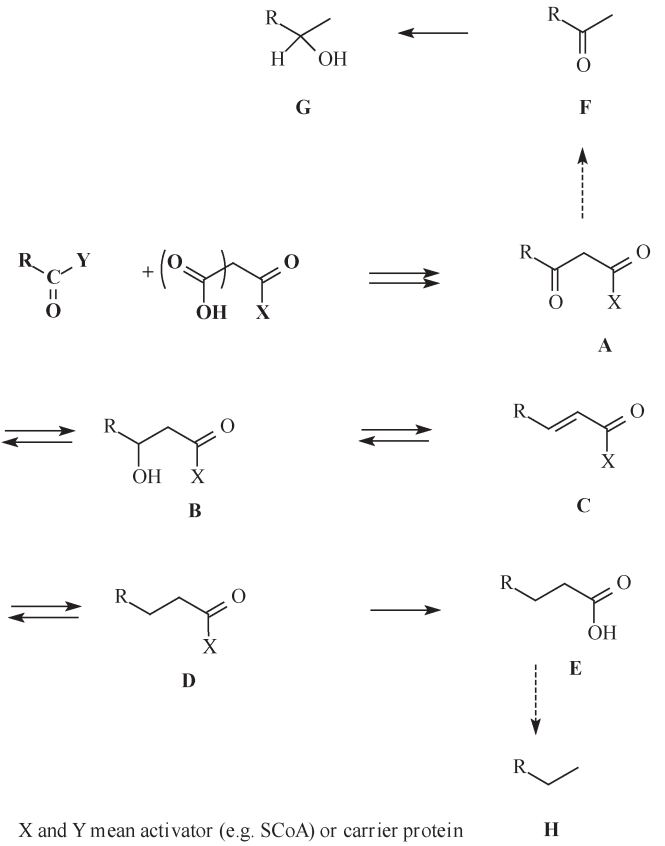


Fig. 1 Sketch of the biosynthesis of simple acetogenins

shortening. Further reactions like decarboxylation of the β-ketoacyl intermediate (obtained after hydrolysis) will yield a methyl ketone **F** which may be reduced to the corresponding (chiral) carbinol **G.** Acetogenins typically form long chain, unbranched compounds, which, according to the general principles of their biosyntheses, occur as characteristic rows of bishomologues with even numbers of carbon atoms (Fig. 1). Classical representatives are saturated fatty acids. Upon decarboxylation, even numbered fatty acids will yield uneven numbered hydrocarbons **H** which are particularly widespread constituents of insect cuticular lipids.

During chain formation, retention of double bonds or oxygen containing functional groups (as remnants of catabolic mechanisms) or introduction of functional groups in the course of secondary reactions (as a result of catabolic processes) may form complex molecules including cyclic and bicyclic structures [35]. Many beetle pheromones originate from the "acetate pool" [2]. The "classical" sex pheromones of moths are represented by straight chain unsat-

urated aldehydes, alcohols or corresponding acetates. In some cases, esters of fatty acids with short chain alcohols have been identified [36]. As shown in Fig. 1, chain elongation as well as chain shortening will pass β-ketoacyl units which, upon loss of the carboxyl carbon, will yield methyl ketones which may be reduced to chiral alcohols. Both classes of compounds have been identified as pheromones in moths [37] and beetles (see below).

Propanogenins and Related Compounds. When during chain formation along a polyketide route acetate units (or malonate) are replaced by propanoate (or methylmalonate), a distinct methyl branching in the final product will be the result. Already Chuman has pointed to close structure relations among a group of pheromones that formally involve propanoate units [38]. When the chain is exclusively formed by a formal condensation of propanoate, the chain will start with a straight chain C3-unit after which every second carbon will carry a methylene group (Fig. 2). During biosynthesis, some or all of the oxygens may be removed, leaving a polymethylated fatty acid like **I**, which has been found in the preen-gland wax of the domestic goose, *Anser a. f. domesticus* [39]. Four propanoate units (including removal of two oxygens) form the lactone **II**, invictolide, a pheromone component of several ant species [40]. The biosynthesis of this compound in *Camponotus* ants has been carefully followed up using isotope-labelling [41]. Formal condensation of five propanoate units and further derivatization is realized in the pyrone **III**, supellapyrone, the female produced sex pheromone of the cockroach *Supella longipalpa* [42].

According to Fig. 2, one of the steps in chain formation with propanoate will result in the formation of an α-methyl-β-ketoacyl moiety **A′**, which, similarly to an acetogenin (Fig. 1), may be converted to the acid precursor **D′**, via reduction to **B′** and dehydration to **C′**, followed by hydrogenation. Alternatively, after another two cycles, decarboxylation would provide an ethyl ketone like 4,6-dimethylnonan-3-one, **III**, a component of the pheromone bouquet of caddis flies, *Potamophylax* spp. [43].

Ethyl ketones may, in general, originate from the decarboxylation of an α-methyl-β-ketoacid as has been shown for 9-methyldecan-3-one, a volatile produced by the myxobacterium *Myxococcus xanthus* [44]. In contrast, a methylketone or a methyl carbinol moiety may originate from a β-ketoacid, produced during chain elongation with acetate (malonate etc.) instead of propanoate as the last step in chain formation (see above). However, an alternative mechanism, proven by isotope labelling, is oxidative decarboxylation of a polymethylated precursor formed from propanoate units [45] to yield compounds like **V**, the pheromone of the mite *Lardoglyphus konoi* [46] (compare structures **I** and **V**). The biosynthesis of the unique branched polyenes which make up the male-produced pheromones of sap beetles, *Carpophilus* spp. has been carefully studied by Bartelt and coworkers using isotope labelled precursors [47, 48]. The carbon skeleton of the tetraene **VI**, the major pheromone component of *C. hemipterus* and *C. brachypterus* is formally made up by an acetate unit as a starter and four propanoate units (the last of which is losing

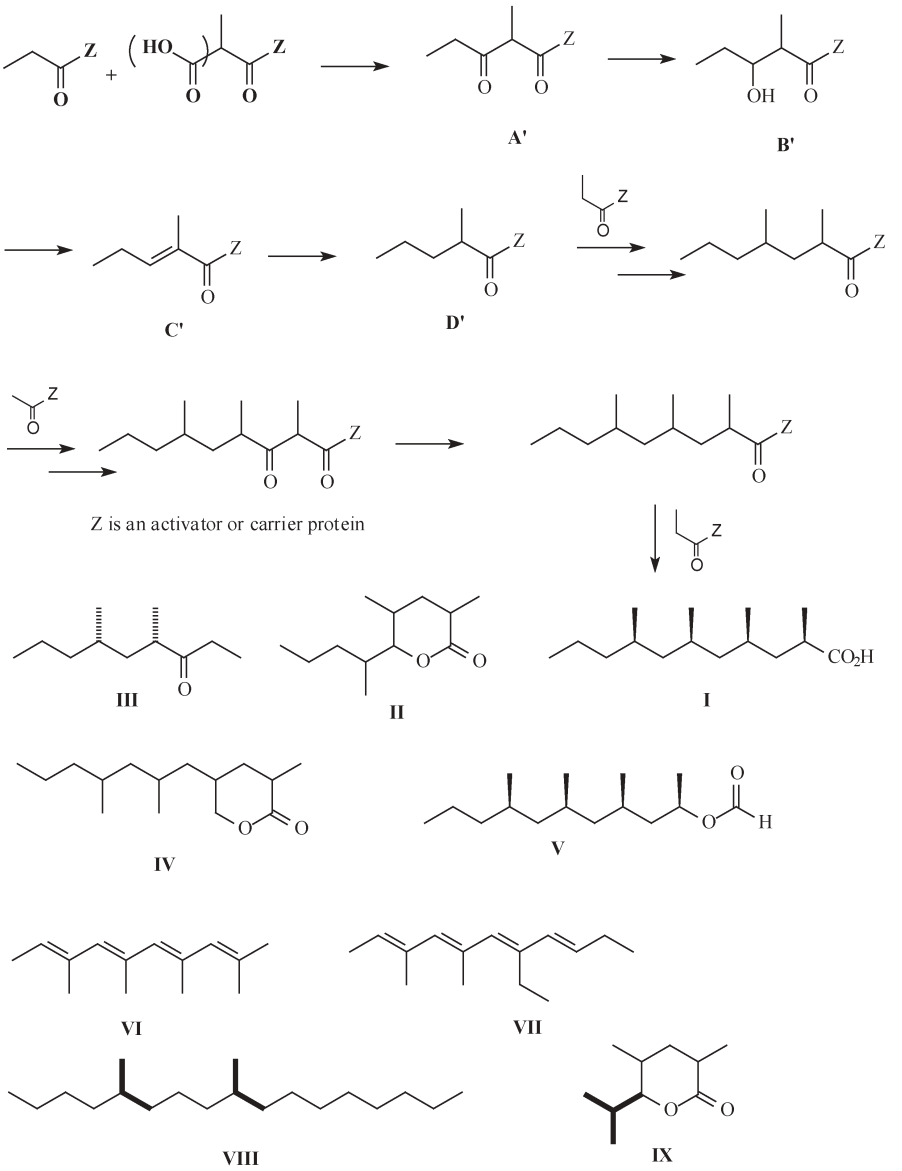


Fig. 2 Sketch of the biosynthesis of simple polyketides made up of propanoate units and some exemplary structures

carbon dioxide).The biosynthesis of the tetraene **VII**, major pheromone component of *C. lugubris*, again starts with acetate, but is continued with two propanoate and two butanoate units (again loss of one carbon through decarboxylation).

The system discussed here is highly versatile: reduction of carbonyl groups and elimination of water will yield (poly)unsaturated structures with characteristic 1,3-dimethyl branching (as in the sap beetles) which may be (partially) hydrogenated. Formation of ethyl branching along the chain through incorporation of butanoate has been described for insects [48] and marine natural products [49]. In mixed biosynthesis, chain elongation may include several acetate units, leading to an uneven number of methylene groups between the methyl branchings as in the hydrocarbon **VIII**, the sex pheromone of the leaf miner moth, *Leucoptera scitella* [50] (formal propanoate units in bold).Various building blocks, including amino acids, may serve as starters for branched compounds: valine may be involved in the biosynthesis of **IX** – possible starter unit in bold – a pheromone identified from a parasitic wasp [51]. Terminal branching has also been described to originate from a leucine starter [2, 44]. Consequently, isoleucine (or a sequence of acetate and propanoate) should give ante-iso branching. Finally, the formation of methyl branching provides stereoisomerism as another disposable variant in the formation of unique signals. Indeed, stereoisomeric composition of chiral compounds plays an important role in chemical communication.

Biogenetic principles involving propanoate as shown in Fig. 2 seem to be very widespread among insects [2]. Similar ways have been described for marine organisms a well as for microorganisms [44, 52–54]. It would be interesting to investigate whether insect volatiles showing polypropanoate structures are truly produced by the insects or whether they result from activities of yet unknown (endo)symbionts.

Isoprenoids. The biosynthesis of isoprenoids has been thoroughly investigated, particularly in plants [55]. The "classical" way involves the diphosphate of mevalonate, (*R*)-3,5-dihydroxy-3-methylpentanoate **a**, which is formed from three acetate units. Elimination of water and carbon dioxide yields 3-methyl-3-butenyl diphosphate **d**, which forms an equilibrium with 3-methyl-2-butenyl diphosphate **e** by the action of an isopentenyl diphosphate isomerase. Coupling of these two C_5 units yields geranyl diphosphate **f**, the parent compound of monoterpenes (Fig. 3). Apart from this "mevalonate" pathway, amino acids such as valine or leucine **b** may serve as starters for the formation of **d** and **e** (for a review see [56]). Another "non-mevalonate" pathway leading to monoterpenes has been discovered in eubacteria, green algae and higher plants [57–61]. Glyceraldehyde-3-phosphate and a C_2 unit derived from pyruvate decarboxylation are the precursors of **d** and **e** via a deoxy-D-xylulose **c** [62–65].

Almost all types of signals, from sex pheromones to highly potent defence substances, are found among the isoprenoids. Many of these compounds seem to be directly sequestered from plants or represent simple transformation

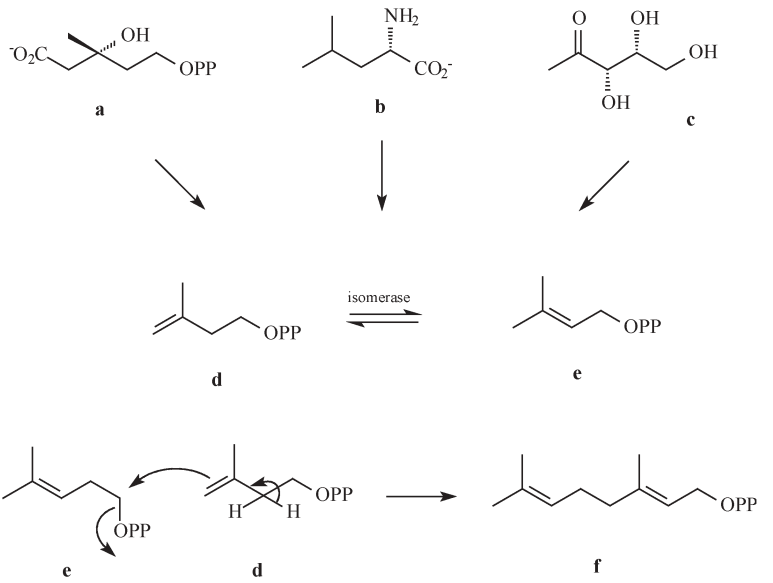


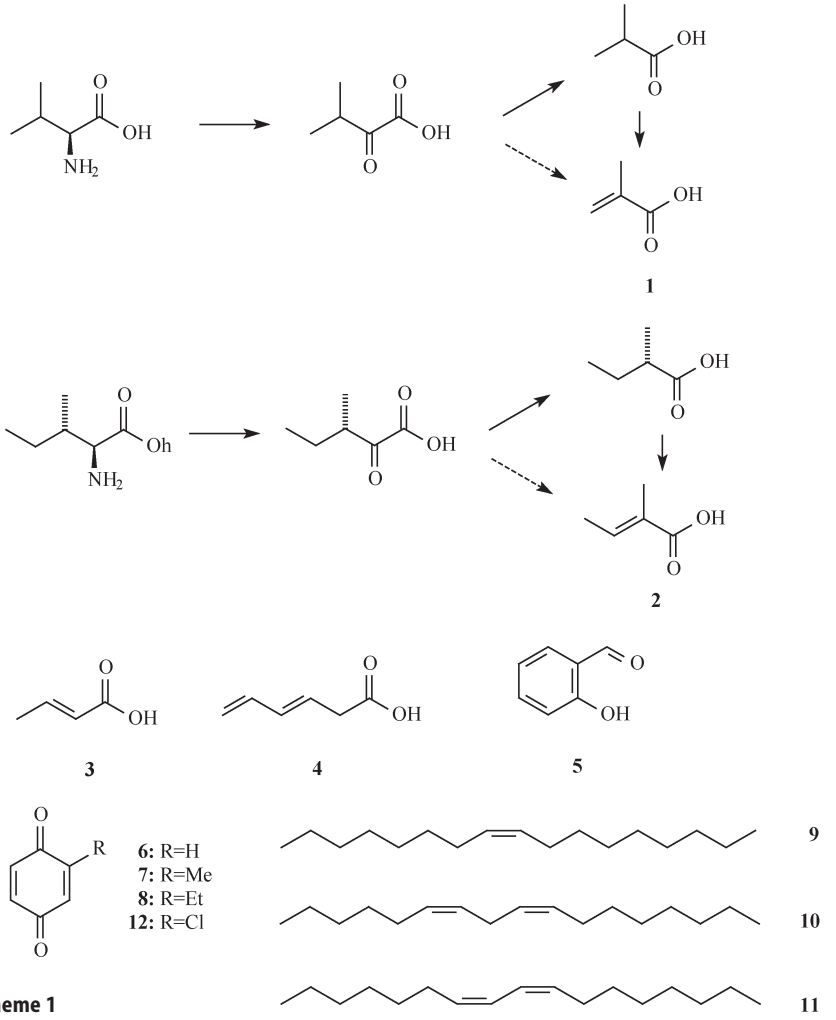
Fig. 3 Sketch of the biosynthesis of terpenoids

products thereof. It has been shown, however, that de novo syntheses may also take place [66–70]. De novo production of isoprenoids has been demonstrated in endothelial cells in the anterior mid gut of bark beetles [71]. Sometimes associated microorganisms play an important role in the production of terpenoids: they may be involved in de novo synthesis and also in secondary transformations of plant compounds [72, 73].

This chapter reviews the structures of beetle produced, intraspecifically active sex-attractants and aggregation pheromones as well as volatile substances that are used for interspecific signalling and for defence. In addition, some metabolites from microorganisms, which have been isolated from beetles and which might have a function in defence, are reported. Compounds identified in beetles but without a proven biological or physical function are mentioned only exceptionally. In the following review, the order of the sections has been arranged according to taxonomical classifications [74, 75]. In each family, relevant volatiles are grouped into subtopics "Attractive Compounds" and "Defence Compounds". In some taxa only defence compounds are known while in others only attractive compounds have been identified. As may be seen, in a given species attractants are frequently made up by only a few compounds while defence chemistry is represented by an array of compounds including solvents and surfactants.

4
Carabidae (Ground Beetles)

Defensive Compounds. The chemistry of pygidial glands has been studied in more than 350 species of ground beetles [8]. Since Blum's important compilation [76] data were reported from a lot of species including representatives of Cicindelidae (see Cicindelidae) and other Carabidae especially bombardier beetles from the Paussinae and Brachinitae families. In *Oodes americanus* (Oodini, Callistitae) a striking sexual dimorphism was revealed [77]: Whereas the unsaturated methacrylic acid **1**, tiglic acid **2**, and crotonic acid **3** are exclusively found in females, males only produce the corresponding saturated analogs. In other



Scheme 1

species such as *Pasimachus subsulcatus* no sexual differences in the carboxylic acid patterns were found [78, 79]. Obviously, these acids are derived from amino acids via the α-ketoacid intermediates [80, 81] (see Scheme 1). It seems probable that males lack the desaturases and that these secretions may also play a pheromonal role. The genera *Oodes* (Oodini) and *Moriosomus* (Morionini) also contain benzoic acid and (*E*)-2-octenoic acid as was found in water beetles [79, 82]. Hexanoic acid, (*E*)-3-hexenoic acid, (*E*)-3,5-hexadienoic acid **4**, and octenoic acids are typical acetogenins. Pygidial gland acids could be characterized as pentafluorobenzyl derivatives [80]. The production of formic acid, typical for many ground beetles, was studied in detail in *Galerita lecontei* [83], where the gland contains formic acid in amounts of up to 3% of the body mass, enough for more than six ejections. The secretory output of formic acid may reach as much as 5% of the gland volume per hour. Formic acid is probably produced from the amino acids L-serine and glycine, via N^5-formyltetrahydrofolate. The separated glands of *Helluomorphoides clairvillei* contain a mixture of compounds including carboxylic acids, aliphatic esters, and hydrocarbons [84]. *Oodes amaroides* (Oodini) secretes salicylic aldehyde **5** from its pygidial glands, while other species produce nonyl acetate, various other acetogenic acetates, formates, hexanoates and 2-pentadecanone.

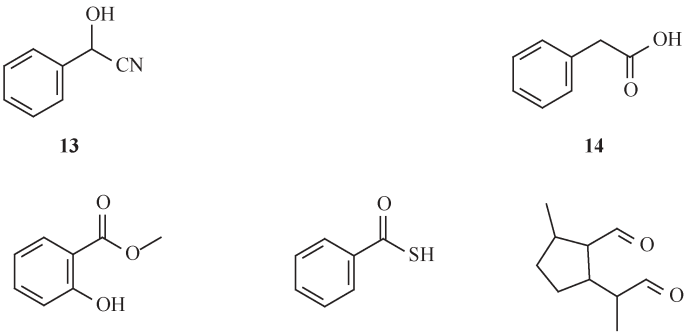
A detailed predator-prey analysis of the chemical relations between the carabid *Pasimachus subsulcatus* and the skink *Eumeces inexpectus* proved that the latter were repelled by constituents of the carabids' secretions, indicating that the beetles are chemically protected from attacks by the lizards [85].

In abdominal defensive glands of carabid beetles, two lineages exhibiting a bombarding mechanism can be observed: the brachinoid (Brachinini with worldwide 14 genera, Crepidogastrini) and the paussoid (Paussini, Ozaenini, Mystropomini, Metriini) lineage. Discharging mechanisms and aiming techniques vary between the two lines. Brachinini rotate their abdominal tips whereas Paussini use their elytral flanges. According to Eisner et al. [86] both groups are characterized by bicompartmented glands and a hot, audible discharge of quinones, i.e. 1,4-benzoquinone **6**, as well as 2-methyl-1,4-benzoquinone **7**, and 2-ethyl-1,4-benzoquinone **8**.

The ability to bombard either evolved only once in Carabidae or independently in both lineages. The glands contain 1,4-benzoquinones and various straight chain or methylbranched alkanes, alkenes and alkadienes such as pentadecane, (*Z*)-8-heptadecene **9** or (6*Z*,9*Z*)-6,9-heptadecadiene **10** and (7*Z*,9*Z*)-7,9-heptadecadiene **11**. In *Metrius contractus* the secretion contains small amounts of 2-chloro-1,4-benzoquinone **12**. As compared to alkanes, the slightly more polar alkenes are better solvents for the quinones and for spreading of the secretion over the beetles [87, 88]. The *Z,Z*-configuration of conjugated dienes of bombardier beetles seems to prohibit a Diels-Alder reaction of these "solvent components" with the active defence compounds, benzoquinones [89].

5
Cicindelidae (Tiger Beetles)

Defensive Compounds. Many tiger beetle species from several genera [90] (about 90 species: *Megacephala, Neocollyris, Odontocheila, Pentacomia, Cicindela*) release benzaldehyde and hydrogen cyanide which are produced from the cyanogenic precursor, mandelonitrile **13** (Scheme 2), which is probably synthesized de novo from phenylalanine. In addition, several species contain benzoic and phenyl acetic acid **14** (as in Hydradephaga and a few Carabidae), methyl salicylate **15** [91], thiobenzoic acid **16**, tridecane and pentadecane [90, 92], tetradecyl acetate, and hexadecyl acetate [90], heptadecanol [92] and even iridodial isomers **17**. As a whole, phylogenetic factors as evidenced by DNA-comparison may predominantly influence the pygidial gland chemistry pattern of tiger beetles [90, 93]. In *Cicindela*, aposematic coloration was restricted to a phylogenetic group producing large amounts of the benzaldehyde. Species previously thought to lack benzaldehyde were later shown to produce small but detectable amounts [92].



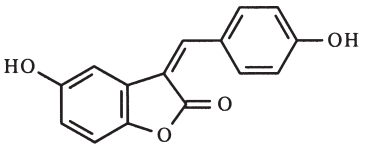
13 14 15 16 17

Scheme 2

6
Dytiscidae (Predaceous Diving Beetles)

Defensive Compounds. As all other terrestrial and aquatic adephagan beetles, dytiscids are characterized by paired pygidial glands which are found laterally behind the eighth abdominal tergites. Chemically the secretions are characterized either by phenylacetic acid (Hydroporinae, Noteridae, Haliplidae) or by benzoic acid, hydroxybenzaldehyde and related compounds (Dytiscinae, Colymbetinae; [8, 82]). The secretion exhibits a pronounced antimicrobial activity and protects from adhering bacteria and fungi [94]. Moreover, the beetle may modify the wettability of their body surface [82, 95].

Marginalin [96] **18** (Scheme 3), a yellow pigment from pygidial glands of *Dytiscus marginalis*, was found to fix solidly on a variety of supports. When



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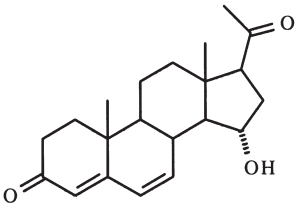

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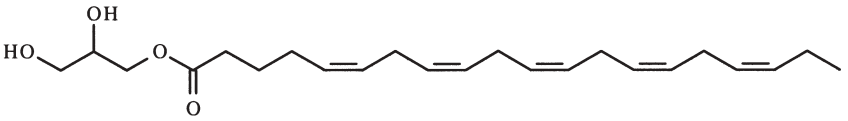

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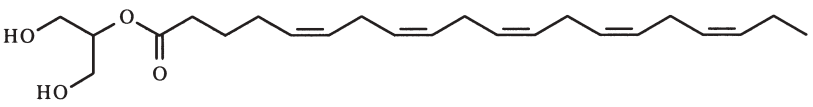

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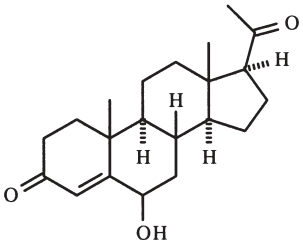

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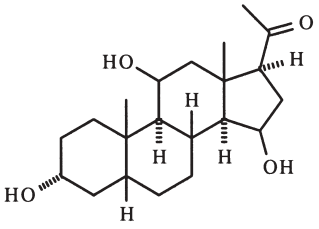

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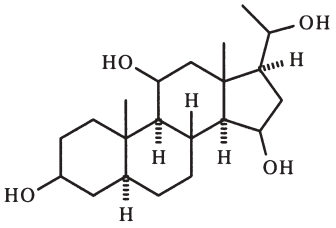

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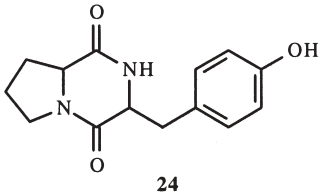

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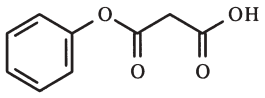

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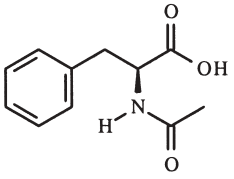

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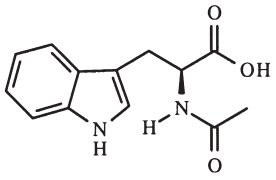

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Scheme 3

in contact with bacteria and fungi, marginalin may react with the proteins at the cell surface [97]. *Z*-Marginalin has been synthesized by base-catalysed condensation of *p*-hydroxybenzaldehyde with 2,5-dihydroxyphenylacetic acid [98].

Paired prothoracic defence glands opening behind the prothoracic margin are present in Dytiscidae and Hygrobiidae. The secretions are targeted against predatory vertebrates (esp. fish, amphibians) and contain both toxic anaesthetic and odorous substances [8]. Various steroids were found in high amounts. Several constituents are discussed in the chapter by Laurent et al., this volume. In addition, 15α-hydroxypregna-4,6-dien-3,20-dione **19** was identified in prothoracic defensive glands of *Agabus affinis* along with four 1- or 2- monoglycerides of a polyunsaturated fatty acid: 1- or 2-[(5*Z*,8*Z*,11*Z*,14*Z*)-5,8,11,14-icosatetraenoyl]glycerol and 1- or 2-[(5*Z*,8*Z*,11*Z*,14*Z*,18*Z*)-5,8,11,14,18-icosapentaenoyl]-glycerol **20a/20b**. Since the 2-acylated monoglycerides showed only a weak activity as feeding deterrents against minnows, their possible role as cannabimimetics needs to be investigated [99].

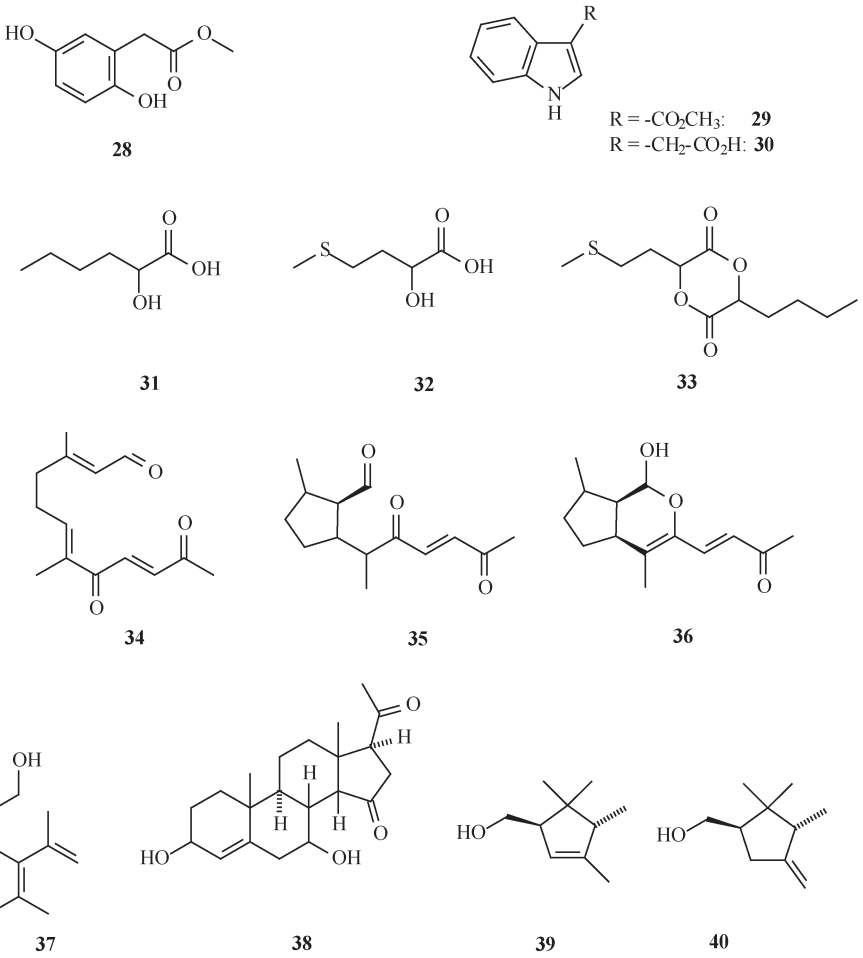
In the prothoracic gland secretion of *Agabus guttatus* testosterone and estradiol as well as nine higher oxygenated pregnane derivatives could be identified [100]: 3α-hydroxy-5β-pregnane-20-one, 3α,11β-dihydroxy-5β-pregnane-20-one, 5β-pregnane-20-one, 3β,20α-dihyroxypregn-5-ene, 6β-hydroxypregn-4-en-3,20-dione **21**, 3α,20α-dihydroxy-5α-pregnane, 3α,11β,15β-trihydroxy-5β-pregnane-20-one **22**, 16α,20β-dihydroxypregn-4-ene, 3β,11β,15β,20β-tetrahydroxy-5α-pregnane **23**, and 3β,11β,15α-trihydroxy-5α-pregnane-20one.

Since the predatory water beetles cannot biosynthesise the steroid skeleton de novo, steroidal precursors must be obtained from exogenous sources. *Bacillus*-strains, isolated from the foregut of the water beetle *Agabus affinis*, were tested for their ability to transform steroids [101]. After incubation with androst-4-en-3,17-dione two *Bacillus* strains produced 13 different transformation products. Hydroxylation took place at C6, C7, C11 and C14 resulting in the formation of 6β-, 7α-, 11α-, and 14α-hydroxyandrost-4-en-3,17-diones. After incubation with pregnenolone the two *Bacillus* strains produced a variety of steroids among which 7α-hydroxypregnenolone was the major product [102].

From the fore gut of *Laccophilus minutus*, a *Bacillus pumilus* strain was isolated which produced maculosin, the diketopiperazine formed from proline and tyrosine [103] **24**, phenyl malonate **25**, *N*-acetylphenylalanine **26**, *N*-acetyltryptophane **27** and 3,4-dihydroxybenzoic acid [103]. Maculosin which has also been isolated from several microorganisms and sponges shows phytotoxic and cytotoxic properties [103], 3,4-dihydroxybenzoic acid shows antioxidant properties and was already found in pygidial defensive glands of several dytiscid beetles.

7
Amphizoidae (Trout Stream Beetles)

Defensive Compounds. Pygidial glands of *Amphizoa lecontei* contain dimethyldisulfide, methyl *p*-hydroxybenzoate, methyl homogentisate **28** (Scheme 4), methyl indole-3-carboxylate **29**, and the pigment marginalin **18** [96]. Beetles may use the aromatic compounds as both antimicrobic and fungicide agents to keep their body surface clean, which may explain why they leave the water in order to distribute their pygidial gland secretion over the body surface [95].



Scheme 4

8
Noteridae (Burrowing Water Beetles)

Defensive Compounds. The sweetish smell of *Noterus* species is due to the presence of phenyl acetic acid **14** as the main constituent of the pygidial gland secretion. Furthermore, some additional aromatics and 3-indole acetic acid **30** could be identified [82, 104].

9
Hygrobiidae=Pelobiidae (Squeak Beetles)

Defensive Compounds. The pygidial gland secretion of *Hygrobia hermanni* contains unusual 2-hydroxy acids such as 2-hydroxyhexanoic **31** acid and 2-hydroxy-4-(methylthio)butanoic acid **32.** The compounds may form lactides **33**, which are the oxygen-analogues of diketopiperazins. Traces of benzoic acid and *p*-hydroxybenzaldehyde could be identified [104].

10
Haliplidae (Crawling Beetles)

Defensive Compounds. Crawling beetles of the genera *Haliplus* and *Brychius* contain pygidial gland secretions with phenyl acetic acid **14** as the main constituent [8]. Secretion grooming was observed which may serve for distributing the antimicrobics on the body surface and for modifying the wettability of the surface [82, 95].

11
Gyrinidae (Whirligig Beetles)

Defensive Compounds. In the stinking pygidial gland secretion of these beetles [8], 3-methylbutanal and the corresponding alcohol are present [8]. In addition, the secretions of *Gyrinus* and *Dineutes* contain the toxic sesquiterpenes, gyrinidal **34**, gyrinidione **35**, and gyrinidone **36** [105–108] (Scheme 4).

Captive fish, *Micropterus slamoides*, rejected both the beetle *Dineutes hornii* and mealworms after topical treatment with gyrinidal. The fish also exhibited an intensive and dose dependent oral flushing behaviour to get rid of gyrinidal [109].

Borg-Karlsson et al. [110] showed that the pygidial gland secretions of certain *Gyrinus* species may contain volatiles which act as intra- and interspecific alarm signals.

12
Silphidae (Carrion Beetles)

Defensive Compounds. Carrion beetles may spray defensive secretions from their anal region which are usually mixed with faecal material [8, 111]. Apart from ammonia, the material contains fatty acids, lavandulol **37**, and ketopregnanes such as 15β-hydroxyprogesterone [8, 111]. Two new pregnanes could be identified from *Silpha novaboracensis* [111]: 3α,7β-dihydroxy-14β-pregn-4-en-15,20-dione **38** (major defensive steroid) and 3α,7β,20-trihydroxy-14β-pregn-4-en-15-one (configuration at C-20 remains unassigned; minor constituent) [111]. Bioassays with the unusual cylopentanoid terpenes α- and β-necrodol **39,40** identified from *Necrodes surinamensis* [112], proved these compounds to be repellent for *Monomorium*-ants as well as topically irritant against the cockroach *Periplaneta americana* and the fly *Phormia regina*.

13
Staphylinidae (Rove Beetles)

Attractive Compounds. In contrast to defence chemistry, little is known about the pheromone systems of rove beetles.

In the sternal gland secretion of males of *Aleochara curtula*, 1-methylethyl (*Z*)-9-hexadecenoate was identified. The compound was attractive to males and females and acts as an aggregation pheromone [113].

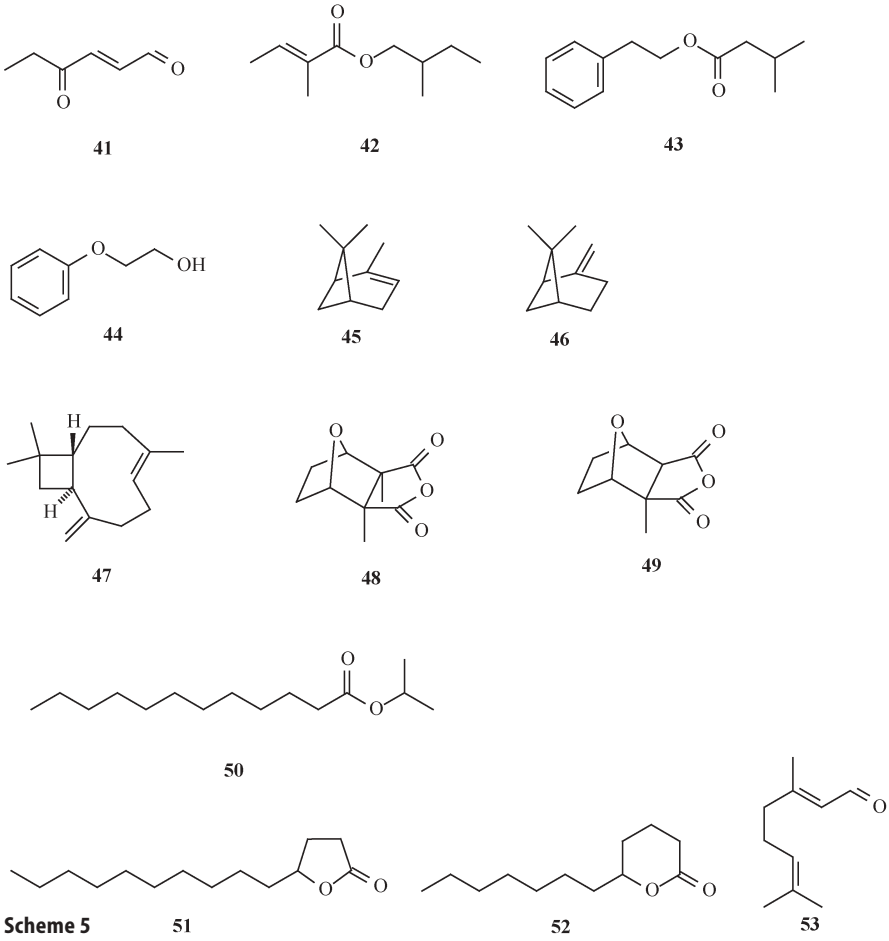
The female produced sex pheromone of *Aleochara curtula* has been described to consist of a mixture of (*Z*)-7-henicosene and (*Z*)-7-tricosene [114]. The same compounds are reported to be used by young males as a kind of camouflage to avoid aggression from older males. Similarly, chemical camouflage by using hydrocarbons plays a role in the relations between the myrmecophilous staphylinid beetle *Zyras cones* and the ant *Lasius fuliginosus*. The host worker ants never attack these beetles which show the same profiles of cuticular hydrocarbons as the ants [115].

The neotropical staphylenid *Leistrotrophus versicolor* use volatile compounds secreted from their abdominal tips to attract their prey, drosophilid and phorid flies [116]. The structures of the active compounds are yet unknown, however, it has been speculated that actinidine or other iridoids, typically found in the defensive gland which are located at the abdominal tips of these beetles, may be key components [117].

Defensive Compounds. Many data on chemical defences of rove beetles have been compiled by Dettner [118]. Recent taxonomic compilations indicate that this beetle family with its omaliine, oxyteline, tachyporine and staphylinine subgroups consists of about 60,000 species, worldwide [119]. Within all four groups, chemical defensive systems evolved independently, because free living rove bee-

tles have an usually soft unsclerotized abdomen which is completely unprotected from predatory attack.

Representatives of the subfamilies Omaliinae and Proteininae (*omaliine group*) possess an abdominal defensive gland reservoir that opens out between sternite 7 and 8 [120]. The multi-component mixtures contained in these glands are used for defence. In Omaliinae and Proteininae the secretion is characterized by mixtures of acids (e.g. 2-methylpropanoic acid, hexanoic acid, 2-octenoic acid, 2-methylbutanoic acid, 3-methylbutanoic acid, butyric acid, and tiglic acid), aldehydes ((*E*)-2-hexenal, heptanal, octanal, nonanal), ketoaldehydes such as 4-oxo-2-hexenal **41** (Scheme 5), 6-methyl-5-hepten-2-one, alcohols (octanol, (*E*)-2-hexen-1-ol, 2-methylbutan-1-ol), alkanes (nonadecane), esters (2-methylbutyl tiglate **42**, various propanoates, 2-hexenyl 3-methylbutanoate, 2-methylbutyl 2-methylbutanoate, octanoates, butanoates), and aromatic compounds (e.g. 2-phenethyl 3-methylbutanoate **43**). Unusual compounds are 2-



Scheme 5

phenoxyethanol **44** and benzonitrile as well as α-pinene **45**, β-pinene **46**, and β-caryophyllene **47**.

In species of the genera *Omalium, Lathrimaeum, Phyllodrepa, Eusphalerum, Phleonomus,* and *Proteinus* the secretions are characterized by acids, corresponding aldehydes and alcohols, ketones and the corresponding esters. In several *Eusphalerum*-species and *Anthophagus,* esters seem to be replaced by hydrocarbons.

Specimens of the pollen-feeding staphylinid beetle *Eusphalerum minutum* were found in cantharidin traps, which indicates that they are canthariphilous [121]. In addition, they contain small amounts of cantharidin **48**, which is accompanied by palasonin **49**. Palasonin has been previously only known from seeds and fruits of the Indian shrub *Butea frondosa* (Leguminaceae; [122]).

In the *oxyteline group*, considerable knowledge has accumulated concerning the morphology and chemistry of the paired 8/9 th tergite gland system within Oxytelinae and Pseudopsinae [118]. All the 1700 worldwide known species of Oxytelinae share this defensive gland which contains *p*-toluquinone **7** as the active principle (see Fig. 4). The solvents range from esters of 2-propanol

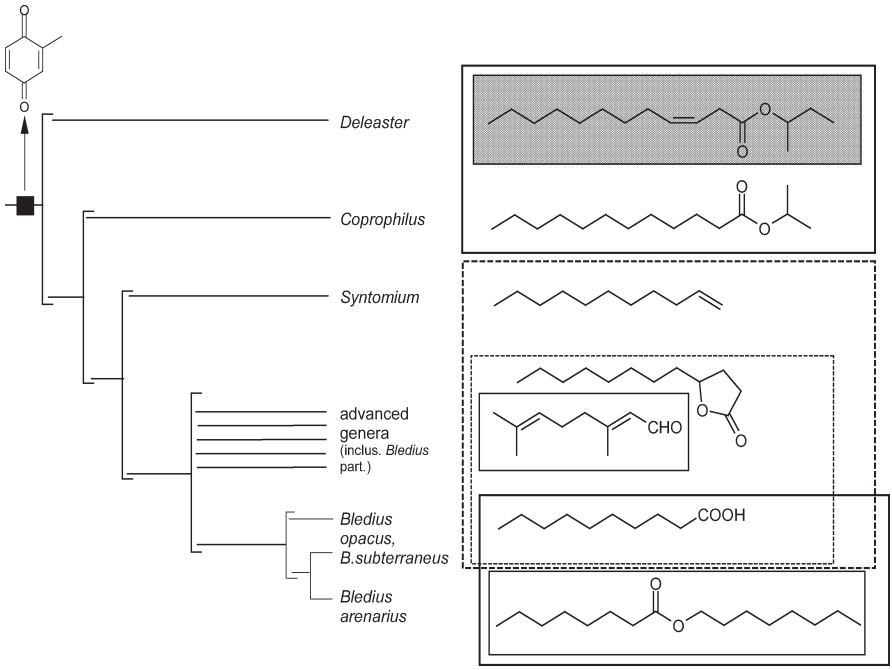


Fig. 4 Evolution of solvents and solvent-mixtures in the defensive secretion of Oxytelinae (Staphylinidae) beetles. The secretions of all worldwide investigated species are saturated with the toxic compound *p*-toluquinone (*left*). The topical irritancy of the mixtures is continuously increased from primitive to advanced taxa. The cladogram on the left side includes the most important primitive (*Deleaster, Coprophilus, Syntomium*) and several advanced genera [117, 122]

or 2-butanol (e.g. 1-methylethyl dodecanoate, **50**) in the primitive genera such as *Deleaster* and *Coprophilus* to 1-alkenes and γ-lactones (e.g. γ-tetradecalactone **51**) in more advanced genera including many *Bledius*-species (Fig. 4). Advanced species additionally produce δ-lactones (e.g. δ-dodecalactone **52**), citral (a mixture of geranial **53** and its *cis*-isomer, neral), various acetates and esters such as hexyl decanoate.

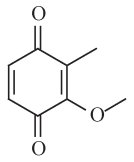
It is astonishing that *Bledius arenarius* represents the only species which does not fit into this concept, because its toluquinone is dissolved only in decanoic acid and octyl octanoate (Fig. 4). However, *B. opacus* and *B. subterraneus* keep an intermediate position because they secret both alkenes/lactones and acids which are also found in *B. arenarius* [123].

Interestingly, the defensive secretion of Oxytelinae is optimised by replacing mixtures of physicochemically similar solvents such as esters of 2-propanol or 2-butanol by mixtures of physicochemically different compounds as 1-alkenes and γ-lactones [87]. Only in the second case it is possible to vary both physicochemical and biological parameters of the mixture, and the topical irritancy of the quinone containing mixture against arthropod targets is significantly improved from primitive to advanced beetles due to a quasi-synergistic effect. Moreover, it was found that the beetles maintain a certain solvent ratio of about one part of lactone and five parts of alkenes. Through this defined mixture the beetles achieve an optimal topical efficiency and can, thus, reduce the amounts of the toxic quinone as was shown by the *Calliphora*-constriction test. Finally, the optimal response of target organisms is due to the fact that maximal amounts of the toxic quinone penetrate the lipophilic cuticle of the target arthropod organism [118]. It was shown that the abdominal gland secretion represents an optimal defence against predators [124] and that the solvent ratio of various *Bledius* species is optimally adapted to their natural targets such as earwigs, ants, flies, carabid beetles, and wading-birds [125].

With respect to the biosynthesis of the solvents it has been speculated on the basis of quantitative data and the identification of β,γ-unsaturated acids in primitive oxytelid beetles that pairs of 1-alkenes and γ-lactones are synthesized from corresponding 3-alkenoic acids by either lactonization or by decarboxylation [118].

Among aleocharine larvae (tachyporine group) two bark-inhabiting representatives of the genera *Leptusa* and *Bolitochara* were investigated [118, 126]. They possess an unpaired abdominal defensive gland reservoir with few polyploidous gland cells associated with the eighth abdominal tergite. Upon molestation, the larvae generate a toxic defensive secretion which is topically active. The secretions contain *p*-toluquinone **7** and 3-methoxytoluquinone **54** (Scheme 6) as active principles which are dissolved in ethyl esters, isopropyl esters, and alkanes. In addition, the antimicrobic benzyl propanoate **55** and methyl 4-hydroxybenzoate **56** were identified.

Apart from the primitive Deinopsini and Gymnusini, adult Aleocharinae show unpaired tergal glands situated between tergites 6 and 7 [127]. Up to now, chemical data of the topically active defensive secretions are available from



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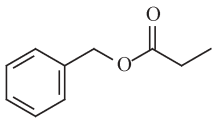

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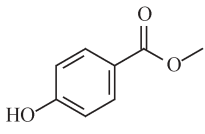

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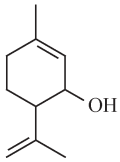

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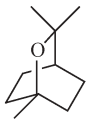

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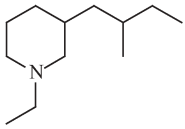

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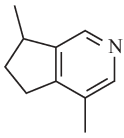

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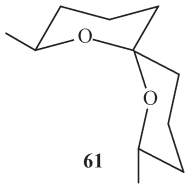

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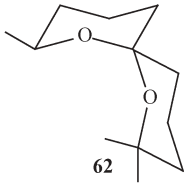

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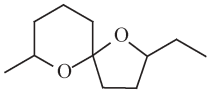

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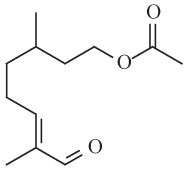

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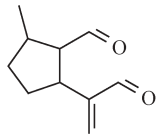

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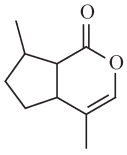

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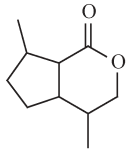

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Scheme 6

about 30 species. One group of species including representatives of Aleocharini, Myrmedoniini, Athetini, and Oxypodini contain hydrocarbons from nonane to heptadecane (undecane as the main component), aldehydes (decanal, dodecanal, tetradecanal, tetradec-5-enal, tetradec-5,8-dienal), short-chain fatty acids like isobutyric acid and isovaleric acid as well as esters such as dodecyl acetate as solvents for *p*-toluquinone **7**, the methoxyquinone **54** and sometimes 1,4-benzoquinone **6**. All quinones are accompanied by the corresponding hydroquinones. The genus *Dinarda* and Bolitocharini predominantly contain long-chain fatty acid esters (ethyl octadecanoate to ethyl octadecadienoate, and ethyl hexadecanoate; group 2) and isoamyl propionate whereas the third group is characterized by *p*-toluquinone and 2-heptanone (Placusini). Within the fourth group of aleocharine beetles (*Falagria*, *Autalia*) only aqueous alkylquinone-solutions could be recorded from small gland reservoirs.

The following chemically defended taxa belong to the staphylinine group: Steninae, Paederinae, Staphylininae, and Xantholininae, sometimes also Silphidae (see above) are incorporated in this group.

Adults of the Steninae possess paired eversible abdominal defensive gland reservoirs [119, 128]. When the beetles walk on the water surface the spreading secretion propels the beetle forward which represents an unique escape mechanism. The secretion contains isopiperitenole **57**, 1,8-cineole **58**, 6-methyl-5-hepten-2-one and the unique spreading alkaloid stenusine, *N*-ethyl-3-(2-methylbutyl)piperidine **59**. Natural stenusine was found to be a mixture of all four stereoisomers in a ratio of (*S, S*):(*S, R*):(*R, R*):(*R, S*)=43:40:13:4. An enantioselective synthesis of stenusine has been carried out via an Enders-approach [129].

Representatives of certain adult Paederinae (Paederus, Paederidus) possess a median complex gland which is situated at the front margin of the fourth sternite [130]. In the genus *Rugilus* even two glands are located at the front margin of sternites 4 and 5. The constituents of abdominal glands of *Paederus*/*Paederidus* have not been be fully elucidated but the presence of various alkenes seems probable. Whether the *Paederus*-glands are able to externalise the hemolymphtoxin pederin has to be investigated. Further data on the microbial-derived insect toxin pederin and the defensive chemistry of Paederinae can be found in the chapter by Laurent et al., this volume.

The paired defensive gland reservoirs of Staphylininae are situated between tergites 8/9 and may be everted upon molestation. Therefore, the secretion acts topically. The chemistry varies considerably between species. While Staphylinina use terpenoids as solvents for, e.g. iridodial 17, representatives of Philonthina produce a lot of acetates and hydrocarbons as solvents for actinidin **60** [8, 118].

Recordings from Staphylininae [115] include: 3-methylbutanal, the corresponding alcohol, and its acetate, various ketones such as 4-methyl-3-hexanone, 4-methyl-3-heptanone, 5-methyl-3-hexanone (and the corresponding alcohol), 2-heptanone, 6-methyl-2-heptanone, 6-methyl-5-hepten-2-one as well as methylcyclopentene and methylfuran. In addition, the secretions of *Ontholestes murinus* contain the spiroacetals (2*S*,6*R*,8*S*)-2,8-dimethyl-1,7-dioxaspiro[5,5]-

undecane, **61**, (in *Ontholestes tesselatus* largely racemic), (6*R*,8*S*)-2,2,8-trimethyl-1,7-dioxaspiro[5,5]-undecane **62**, and (*E*,*E*)- as well as (*Z, E*)-2-ethyl-7-methyl-1,6-dioxaspiro[4,5]-decane **63** [131–133]. Further gland constituents are α-pinene **45**, neral and its E-isomer, geranial **53**, nerol, citronellol and esters such as (*E*)-8-oxocitronellyl acetate **64**, ethyl hexadecenoate, and ethyl octadecenoate. Several iridoids were reported, sometimes of unknown stereochemistry: actinidine **60** [119], various iridodial-isomers **17**, dolichodial **65**, nepetalactone **66** and dihydronepetalactone **67**.

There was proposed a detailed account of iridoid biosynthesis in rove beetles which resembles the biosynthesis in leaf beetle larvae but exhibits distinct stereochemical differences [134], see also the chapter by Laurent et al., this volume.

Within Quediini defensive glands are either present (*Algon*) or are lacking (*Quedius* [8, 118]). In the first case the paired glands contain hexanoic acid, hexanal, and (*E*)-2-hexenal which may be sprayed upon disturbance.

Representatives of Xantholininae possess an unpaired nonreversible anal gland reservoir at their abdominal tip. As already reported, the secretion contains iridodial, actinidin, terpenoid aldehydes, ketones, limonene, and isopulegol [8, 118].

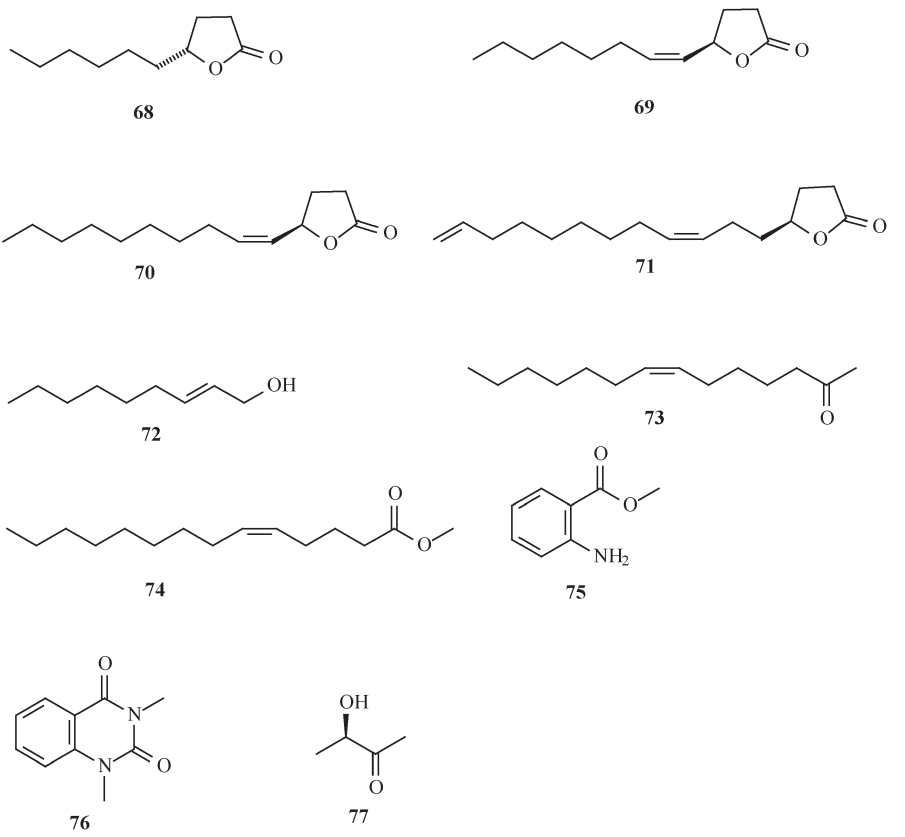
14
Scarabaeidae (Scarab Beetles, Chafers, Dung Beetles)

Attractive Compounds. Though the first report on the identification of a pheromone from a scarabaeid beetle dates back more than 30 years – phenol as an attractant for males of the gras grub beetle *Costelytra zealandica* [135] which turned out to be produced by beetle associated bacteria [136] – most of the pheromone structures known today have been elucidated during the last decade [3, 137, 138].

Pheromone chemistry in scarab beetles, chafers, and dung beetles covers a wide range of structures, including esters of amino acids and aromatics as well as branched and straight chain aliphatic compounds, among which a row of γ-lactones forms a most characteristic group.

The male released pheromone of *Osmoderma eremita* is (*R*)-5-hexyloxacyclopentan-2-one **68** [139] (Scheme 7). In contrast, in other scarab species, pheromones are mostly produced by females.

Females of several species use (*R*)-5-[(1*Z*)-1-octenyl]oxacyclopentan-2-one, buibuilactone **69** [140–144]. The first γ-lactone identified from a scarab beetle was (*R*)-5-[(*Z*)-1-decenyl]oxacyclopentan-2-one, japonilure **70**, the female produced sex pheromone of the Japanese beetle *Popillia japonica* [145]. Both **69** and **70** are components of specific blends of several species [140–143]. The Japanese beetle is extremely sensitive to the non-natural enantiomer of his pheromone: as little as 1% of the (*S*)-enantiomer inhibits the attractiveness of the pheromone [145]. With respect to species discrimination, this is particularly



Scheme 7

interesting on an evolutionary point of view. The closely related species *Anomala osakana* uses this very compound, (*S*)-5-[(*Z*)-1-decenyl]oxacyclopentan-2-one as the pheromone [146] and, in turn, the species is repelled by the pheromone of the Japanese beetle. For scarab beetles, olfactory discrimination of enantiomers at the level of odorant binding proteins as well as enantiomeric anosmia has been described [138, 147, 148]. The biosynthesis of those γ-lactones proceeds via an enantioselective 8-hydroxylation of fatty acids and chain shortening, followed by ring closure [149]. Another γ-lactone, (*R*)-5-[(*Z*)-dodeca-3,11-dienyl]oxacyclopentan-2-one **71** is the sex pheromone of the yellowish elongate chafer, *Heptophylla picea* [150, 151]. In this case, only the (*R*)-enantiomer showed attractiveness, while its activity was not inhibited by the presence of its antipode [152].

Several syntheses of optically active japonilure and related lactones involve enzyme-catalysed transformations [153]; however, recently, it has been efficiently prepared in high enantiomeric purity via boronic esters of 1,2-dicyclohexyl-1,2-ethanediol [154] (Fig. 5).

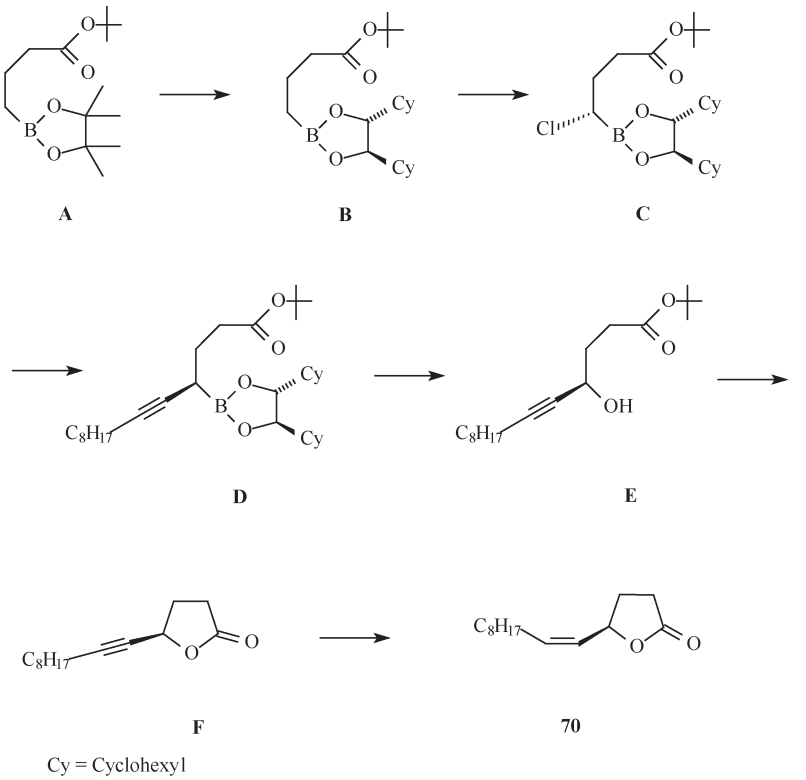


Fig. 5 Reaction scheme for the synthesis of optically active japanilure **70**

The boronic acid ester **B** was synthesized by transesterification of the corresponding pinacolester **A** with (1*R*,2*R*)-1,2-dicyclohexyl-1,2-dihydroxyethane. Stereoselective chlorination of **B** was carried out with (dichloromethyl) lithium and zinc chloride. Reaction of the obtained chloroboronic ester **C** with lithio 1-decyne followed by oxidation of the intermediate **D** with alkaline hydrogen peroxide afforded the propargylic alcohol **E**. Treatment with acid to saponify the *tert*-butyl ester moiety and to achieve ring closure, produced lactone **F**. Finally, Lindlar-hydrogenation provided japonilure **70** in an excellent yield and high enantiomeric purity.

In some species, (*E*)-2-nonenol **72** represents a second pheromone component along with the lactone **69** [141, 144], while in *Anomala schönfeldti* **72** is the only attractive component [155]. The alcohol **72**, the corresponding aldehyde, lactone **69** and methyl benzoate make up the pheromone of *Anomala albopilosa albopilosa* [144].

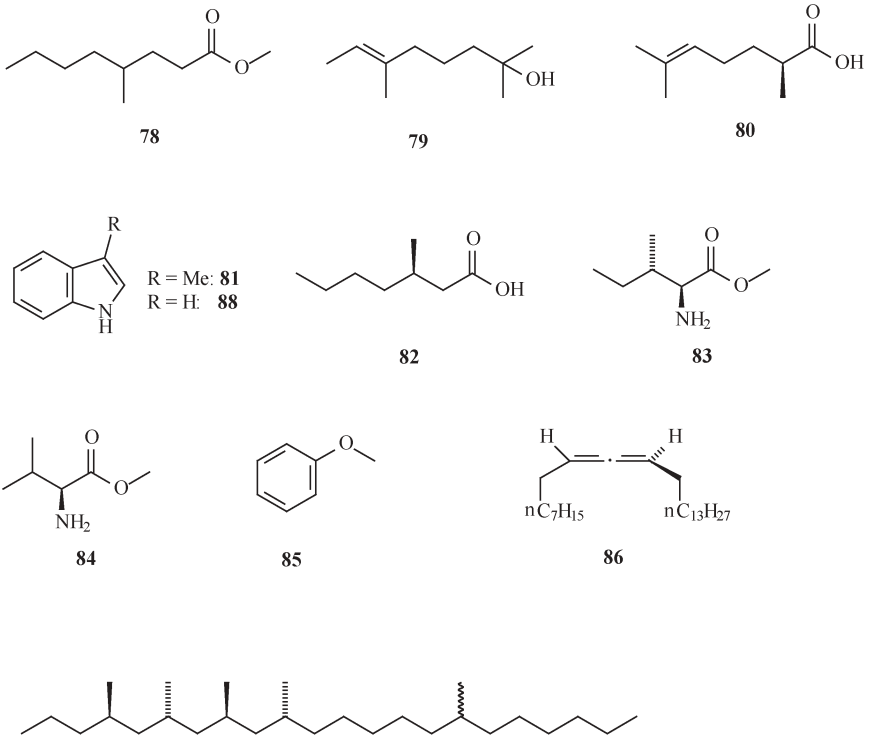
A cluster of straight chain aldehydes and methyl ketones was identified from airborne volatiles collected from females of *Hoplia equina*. While all compounds were perceived by the males' antennae, only tetradecane-2-one proved to be

attractive, and none of the other compounds enhanced its activity [156]. A mixture of (*Z*)- and (*E*)-7-tetradecen-2-one are components of the pheromone of the Oriental beetle, *Exomala orientalis* (=*Blitophertha orientalis*=*Phyllopertha orientalis*=*Anomala orientalis*) [157, 158]. The (*Z*)-isomer **73** proved to be attractive in the field. Its activity was neither synergized nor inhibited by the presence of the (*E*)-isomer. The pheromone of the soybean beetle, *Anomala rufocuprea* is methyl (*Z*)-5-tetradecenoate **74**, the biosynthesis of which may show a certain relationship to those of the γ-lactones [159].

Some scarab species are strongly attracted by plant volatiles which may optimise both host finding and/or mate finding. In the case of *Anomala rufocuprea* methyl anthranilate **75** was even more attractive to males than the female produced pheromone. In addition, it caught substantial amounts of females [160]. Interestingly, anthranilic acid has been described as the pheromone of the black chafer *Holotrichia loochooana loochooana* [161]. It should be noted that the unique pheromone of *Phyllopertha diversa* [162] 1,2,3,4-tetrahydro-1,3-dimehtylchinazolin-2,4-dione, **76**, shows the same substitution pattern at the benzene ring as anthranilic acid. *Phyllopertha diversa* displays specificity and sensitivity to so called green leaf volatiles as (*Z*)-3-hexen-1-ol, the corresponding acetate, and (*E*)-2-hexenal etc [163]. The forest cockchafer *Melolontha hippocastani* is strongly attracted to (*Z*)-3-hexen-1-ol released from damaged leaves [164] and so is the European cockchafer *Melolontha melolontha* [165]. Surprisingly, 1,4-benzoquinone **6**, a typical and widespread insect defence compound, is the female produced sex pheromone of the forest chafer [166]. The combined odour of green leaf volatiles and the quinone allows the males to discriminate sites where females feed from those with unspecific leaf damage.

The antennae of both males and females of the summer chafer *Amphimallon solstitiale* react well to green leaf volatiles [167]. Both sexes produce acetoin of high enantiomeric purity, and the corresponding 2,3-butanediols; however, females do not perceive these compounds. While (*R*)-acetoin **77** proved to be highly attractive to swarming males, neither the racemate nor the 2,3-butanediols showed a behaviour mediating capacity. The same set of small molecules was also found in other scarab beetles [168]. Males of the Melanesian rhinoceros beetle *Scapanes australis* also produce acetoin with high enantiomeric excess, along with 2-butanol as a second important component, showing an enantiomeric composition of (*R*):(*S*)=2:1. Racemic acetoin and racemic 2-butanol in a ratio of 5:90 proved to be highly attractive in the field [169].

Two related scarab species produce ethyl 4-methyloctanoate **78** (Scheme 8) as an aggregation pheromone: the African rhinoceros beetle *Oryctes monoceros* [170] and the coconut rhinoceros beetle *Oryctes rhinoceros* [171, 172]. The latter is readily attracted to the racemate. Its secretion was found to contain the free acid as well as ethyl 4-methylheptanoate [171]. Similarly to other cases, the attractiveness of ethyl 4-methyloctanoate is enhanced by host compounds, i.e. coconut wood [173]. The date palm fruit stalk borer, *Oryctes elegans*, uses 4-methyloctanoic acid as a male produced pheromone [174]. Structurally



78 79 80 82 83 84 85 86 87

Scheme 8

related compounds such as its ethyl ester **78**, the corresponding methyl ester or 4-methyloctanol and its acetate, which were found to be additionally present, did not increase the attractivity of the acid. However, addition of crushed date palm tissue dramatically increased trap catches.

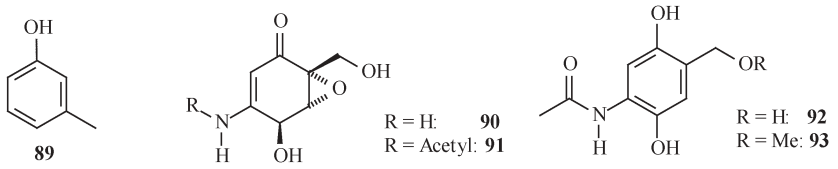
Dung beetles, *Kheper* species, use branched aliphatic compounds as semiochemicals: males of *Kheper subaeneus* produce (*E*)-2,6-dimethyl-6-octen-2-ol, (*E*)-subaeneol, **79.** The compound is active on the antennae of both males and females; (*S*)-(+)-2,6-dimethyl-5-heptenoic acid **80** is the main component of the secretion [175]. Earlier, this acid (absolute configuration not assigned) had been described as a volatile compound in a closely related species, *Kheper lamarcki*, along with hexadecanoic acid and skatole **81**. Three components of the abdominal sex-attracting secretion of male *Kheper nigroaeneus* are well perceived by males and females. Two of them could be identified to be (*R*)-(+)-3-methylheptanoic acid **82** and (the possibly tryptophane derived) skatole **81** [177]. Interspecific attraction in dung beetles has been described by Burger [178].

Females of several other species of scarab beetles use methyl esters of L-isoleucine **83** and L-valine **84** as sex pheromones [179, 180]. In *Phyllophaga elenans*, apart from **83**, the corresponding *N*-formyl- and *N*-acetyl derivatives have been

identified, however, these amides do not seem to play a role as intraspecific attractants [181]). In contrast to *Holotrichia parallela* that uses **83** as the pheromone [177], the related *Holotrichia consanguinea* and *Holotrichia reynaudi* use anisol [182, 183] **85**.

Recently, two new facets have been added to scarab chemistry. A suite of unusual $\Delta^{9,10}$-allenic hydrocarbons like **86** has been identified among the cuticular hydrocarbons from several Australian melolonthine scarab beetles [184]. Though very low-level components in the related cane beetle *Antitrogus parvulus*, the major cuticular hydrocarbons in this species proved to be oligomethyldocosanes like **87**. Only the relative configurations of these compounds could be determined [185]. Whether these interesting hydrocarbons have a function as pheromones needs to be established.

Defensive Compounds. Some species of dung beetles emit an odorous secretion when attacked by vertebrates. Representatives of the genus *Canthon* have two small glands on the posterior margin of the elytra and contain indole **88**, *m*-cresol **89** (Scheme 9), and phenol [186]. As a rule, species of this genus possess paired pygidial glands at sternite 8 which produce intensely smelling defence compounds [187, 188]. The dung beetle *Oniticellus egregius* flips onto its back, exhibits thanatosis, and releases a brown odorous fluid containing methyl salicylate **15** and 1,4-benzoquinone **6** from the lateral edges of the anterior abdominals segments [189].



Scheme 9

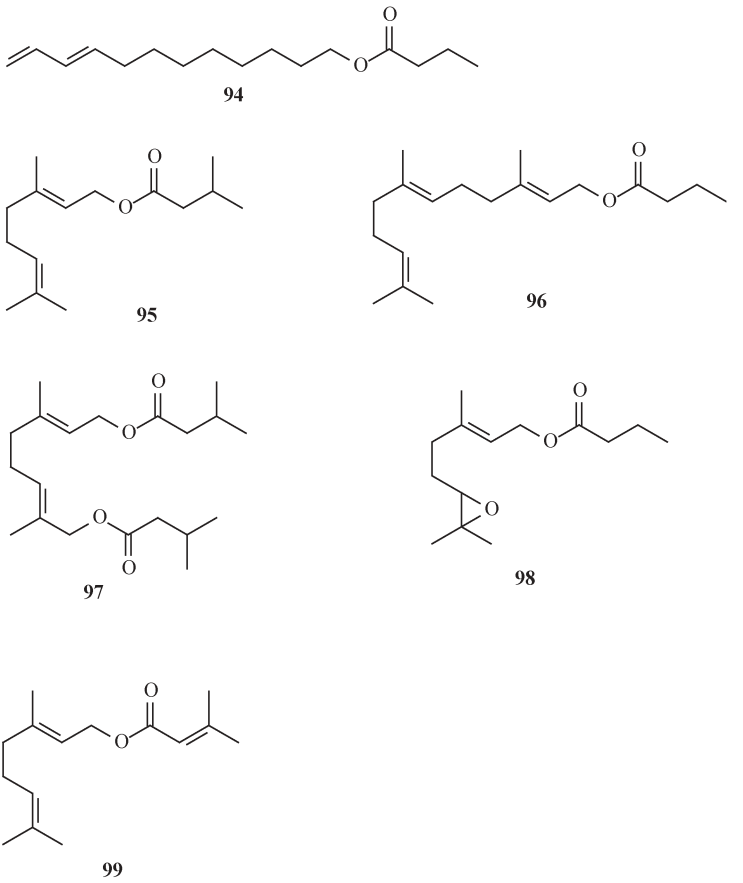
From the hind gut of *Cetonia aurata* an *Actinomyces* species was isolated which produces the new cytotoxic epoxy quinoles [190] named cetoniacytone A **90** and B **91**. In addition, the structurally related aromatic compounds 2,5-dihydroxy-4-hydroxymethylacetanilide **92** and 2,5-dihydroxy-4-methoxymethylacetanilide **93** were found in minor amounts.

15
Elateridae (Click Beetles)

Attractive Compounds. Larvae of several click beetle species (wire worms) can be serious pests in agriculture and forestry. In a few cases, sex pheromones produced in a female specific abdominal gland, have been identified.

The first biologically active compounds identified from click beetles were hexanoic acid and pentanoic acid from *Limonius canus* and *L. californicus*, respectively [191].

The structures of the female produced pheromones of the sugar cane wire worms *Melanotus sakishimensis* and *M. okinawensis* look much more like "conventional" moth pheromones: While in the latter species it simply is dodecyl acetate, *M. sakishimensis* uses a mixture of (*E*9,11)-dodecadienyl butyrate **94** (Scheme 10) and the corresponding hexanoate [192].



Scheme 10

In females of the genus *Agriotes,* several esters of acyclic terpenes have been identified as pheromone components. Typical examples are geranyl 3-methylbutyrate **95**, the first pheromone identified from an *Agriotis* species [193] or (*E*,*E*)-farnesyl butyrate **96**, which together with geranyl butyrate is the major component of the sex pheromone of *A. brevis* [194]. In *A. lineatus*, the activity

of the main component, geranyl octanoate, is strongly synergised by geranyl butyrate [194]. The main components in the bouquet of *A. obscurus* are geranyl hexanoate and geranyl octanoate [195–199].

In *Agriotes,* the biogenetic principle in the formation of unique blends of specific pheromone components seems to be based on the combination (esterification) of acyclic isoprenoid alcohols with short chain acids. Disposable variants in relevant structures are provided by the number of isoprene subunits (mono-, sesqui-, di-terpenes) and double-bond configurations at the terpene site as well as on chain length and methyl branching at the acid moieties [199]. Other features are the introduction of an additional oxygen at the terpene site forming either a second alcohol group followed by esterification as in **97** [200, 201] or an epoxide. Apart from geranyl butyrate, 6,7-epoxygeranyl butyrate (unknown stereochemistry) **98** is the second major component in the secretion of the abdominal gland of females of *A. sputator* [201]. The acids, representing substructures of terpene esters may be unsaturated as in geranyl 3-methyl-3-butenoate or geranyl 3-methyl-2-butenoate **99**, minor components in the abdominal secretion of *A. litigiosus*. The latter acids may represent *hemi*-terpenes. Mechanisms accounting for species specificity need to be clarified in some species.

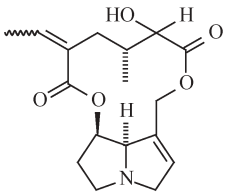
Defensive Compounds. *Agrypnus (=Lacon=Adelocera) murinus* possess paired abdominal defensive glands which are everted on molestation during thanatosis [8]. The four stink gland constituents are indole **88** dimethylsulfide, dimethyldisulfide, dimethyltrisulfide, and dimethyltetrasulfide.

16
Lampyridae (Lightningbugs or Fireflies)

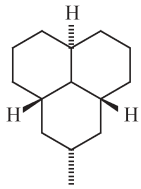
Defensive Compounds. The developmental stages of fireflies are poisonous due to the presence of steroidal pyrones called lucibufagins. Recently it became evident that exotic reptiles and amphibians from habitats without the poisonous fireflies, e.g. the Australian lizard *Pogona*, are killed immediately if they ingest just one firefly.

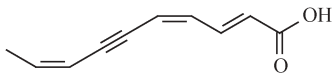
17
Cantharidae (Soldier Beetles)

Defensive Compounds. The aposematically coloured *Chauliognathus fallax* which feed on *Senecio brasiliensis* (Asteraceae) sequester the four pyrrolizidine alkaloids senecionine (**100** main compound), integerrimine (**101** main compound), retrorsine **102**, and usaramine **103** [203] (Scheme 11). Other *Chauliognathus*-species may contain either precoccinelline **104** and related alkaloids (*C. pulchelus*) or *Z*-dihydromatricaria acid **105** (*C. pennsylvanicus*).



(*Z*,*R*): **100**
(*E*,*R*): **101**
(*Z*,*S*): **102**
(*E*,*S*): **103**





Scheme 11 **104** **105**

18
Dermestidae (Skin Beetles)

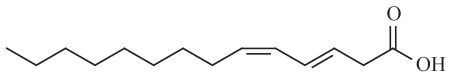
Attractive Compounds. Pheromones of dermestid beetles were among the first ones identified from insects. Almost all have been described as "one-component-systems", and re-investigations employing refined techniques, especially GC-EAD and sensitive GC-MS, may reveal the presence of additional and important compounds, which may lead to improved activity of synthetic lures, and under natural conditions may account for species specificity etc.

The female produced sex pheromone of the black carpet beetle, *Attagenus unicolor* (formerly called *A. megatoma* or *A. piceus*) has been identified as early as 1967 to be (3*E*,5Z)-3,5-tetradecadienoic acid, megatomoic acid **106** [204, 205] (Scheme 12). The (3*Z*)-isomer of megatomoic acid was found to be the major male attracting component in the female produced pheromone of A. *brunneus* (formerly *A. elongatulus*) [206].

Virgin females of the furniture carpet beetle, *Anthrenus flavipes*, produce (*Z*)-3-decenoic acid as a sex pheromone **107** [207]. In contrast, the female-produced sex pheromone of the varied carpet beetle *Anthrenus verbasci* is a two component mixture of (*Z*)-5-undecenoic acid **108** and its (E)-isomer [208]. Recent investigations showed the presence of additional electrophysiologically active components, however, no behaviour tests have been carried out [209].

The sex pheromone of the Guernsey carpet beetle, *Anthrenus sarnicus*, contains 1-decanol and its butyrate **109** in almost equal amounts [210].

Fatty acid esters also play a role in the communication system of the hide beetle, *Dermestes maculatus*. In a sex specific gland, situated at the ventral side of the fourth sternite, males produce a bouquet of isopropyl esters of fatty acids showing 12, 14, 16, and 18 carbon atoms [211]. Apart from the esters of the four saturated acids and isopropyl (*Z*)-hexadec-9-enoate as well as isopropyl oleate,



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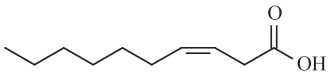

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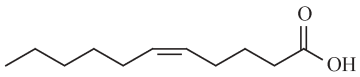

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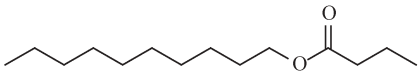
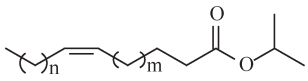
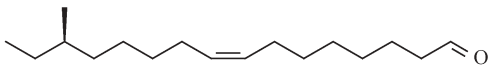


109



m = 1, 3, 5
n = 5, 3, 1

110



111

Scheme 12

esters of three dodecenoic acids **110** and three tetradecenoic acids, each showing (*Z*)-configured double bonds at positions 5, 7, and 9, make up a complex mixture [212, 213]. The unsaturated esters, especially the lower boiling ones, evoked high olfactory receptor potentials in *D. maculatus* but also in the related species *D. lardarius* and *D. ater*. Behaviour studies led to the conclusion that the gland secretion represents a male recognition signal releasing aggregation behaviour. The mixture of synthetic esters was found to be considerably less active than the natural secretion and, in fact, a reinvestigation revealed a much more complex composition showing the presence of several doubly unsaturated esters [214].

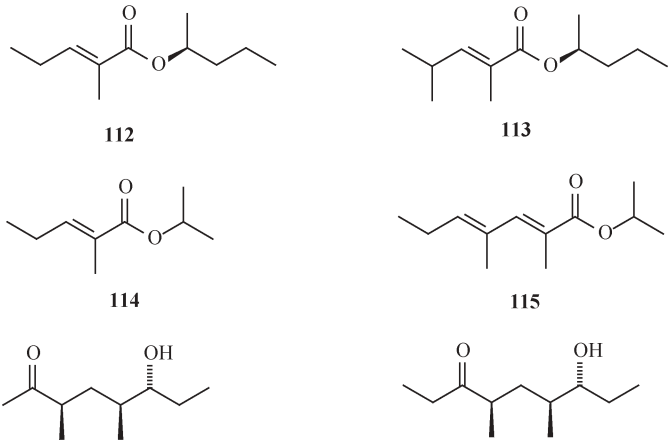
Structure elucidation of the female-produced sex pheromones of *Trogoderma* spp. has a rather confused history. Extracts of females of *T. inclusum* were shown to contain (*Z*)-14-methyl-8-hexadecenol and the methyl ester of the respective carboxylic acid [215]. The corresponding compounds showing (*E*)-configuration were shown to be present and behaviourally active in *T. inclusum* [216]. Finally, investigations of head space collections, obtained with live females, revealed the presence of 14-methyl-8-hexadecenal, an aldehyde

which was not detected in extracts of females. In *T. inclusum* and *T. variabile* this proved to be the (*Z*)-isomer **111** while in *T. glabrum* it was shown to be the (*E*)-isomer, and in *T. granarium* a ca. 9:1 (*Z*):(*E*)-mixture was found [217–220]. Because of its constant occurrence as a pheromone in *Trogoderma* species, 14-methyl-8-hexadecenal was termed trogodermal [221]. Determination of the absolute configuration of trogodermal was again accompanied by some confusion. The available amounts of naturally produced trogodermal were too small to determine its rotation value. Enantiomeric separation by enantio-selective gas chromatography was impossible. Even today trogodermal cannot be resolved on chiral columns as the stereogenic centre appears too far away from the functional group (ozonolysis and enantiomeric separation of the produced 6-methyloctanal may, however, be worth a trial). In contrast to the aldehyde, the alcohol could be isolated in sufficient amounts to measure its rotation value. Finally, Mori carried out unambiguous syntheses of both enantiomers of (*Z*)-14-methyl-8-hexadecenal via the corresponding alcohols [222]. Comparison of rotation values of the synthetic material with that of naturally occurring (*Z*)-14-methyl-8-hexadecenol showed that the beetle produced compound and the corresponding pheromone aldehyde keep the (*R*)-configuration in *T. granarium*. This was supported in bioassays where the (*S*)-enantiomer of trogodermal elicited a response at dosages 100–1000 times lower than the (*R*)-enantiomer [223]. Corresponding results were found during tests with *T. glabrum*, *T. inclusum*, and *T. variabile* [224]. During recent years, only very few syntheses of dermestid pheromones have been reported [225].

19
Bostrychidae (Powder-Post Beetles)

Attractive Compounds. Pheromones of three Bostrychid species have been identified. Males of the lesser grain borer, *Rhizopertha dominica*, produce (*S*)-1-methylbutyl (*E*)-2-methyl-2-pentenoate (dominicalure 1) **112** and (*S*)-1-methylbutyl (*E*)-2,4-dimethyl-2-pentenoate (dominicalure 2) **113** (Scheme 13). Both compounds induce aggregation of males and females; however, the mixture does not show synergistic effects [226]. Pheromone release and inter-male variation as well as effects of different hosts and the presence of conspecific females on pheromone production by males of *Rhizopertha* have been recently investigated [227, 228].

Similar to *R. dominica*, a two-component male produced pheromone accounts for the aggregation of both sexes of another Bostrychid, *Prostephanus truncatus*. 1-Methylethyl (*E*)-2-methyl-2-pentenoate (trunc-call 1, T1) **114** shows the same acid moiety as dominicalure 1 [229]. The second (slightly more active [230]) component proved to be 1-methylethyl (2*E*,4*E*)-2,4-dimethyl-2,4-heptadienoate (trunc-call 2, T2) **115**. In this species, synergistic effects of the two compounds have been reported [229]. The effect of age and sex on the response of walking *P. truncatus* to its pheromone has been investigated [230]. Inter-



112 **113**

114 **115**

116 **117**

Scheme 13

male variation in pheromone release [231], the effect of age and sex [232], as well as other factors influencing response to the aggregation pheromone have been described [233]. Obviously, apart from attracting both sexes, the male produced signal also acts as a sex pheromone and plays a role in sexual selection [234]. In contrast, males of a predator of grain borers, *Teretriosoma nigrescens*, while using the *Prostephanus* pheromone as a kairomone, were slightly more responsive than females [230].

The Bostrychid *Dinoderus bifoveolatus* is a serious pest on cassava, the dried roots of manioc. Again, this species shows male specific volatiles, two of which were found to produce intense signals in the antennae of conspecific males and females. The minor component proved to be (3*R*,5*S*,6*R*)-3,5-dimethyl-6-hydroxyoctan-2-one **116**, while the major one was shown to be its homologue, (4*R*,6*S*,7*R*)-4,6-dimethyl-7-hydroxy-nonan-3-one **117** [235].

As already pointed out by Chuman et al. [38] structures like **112, 114, 115,** and **117** are very likely biosynthesised from propanoate units, see Fig. 2. Three propanoate units (keeping one oxygen) would yield 2,4-dimethyl-5-hydroxyheptanoate, while a propanoate-stopper (and loss of carbon dioxide) would complete the formation of the ethylketone **117**. Correspondingly, an acetate-stopper would give rise to the formation of the methylketone **116.** In the biosynthesis of **113**, the starting unit contributing four carbon atoms and producing iso-branching, may well originate from an amino acid, e.g. valine.

As depicted in Fig. 6, syntheses of enantiomerically pure **116** and **117** have been carried out [236]. Lipase AK-catalysed asymmetric acetylation of *meso*-2,4-dimethyl-1,5-pentanediol **A** yielded (2*R*,4*S*)-5-acetoxy-2,4-dimethylpentanol **B**. Protection of the free hydroxy group as the *tert*-butyldimethylsilyl (TBS) ether, saponification of the acetate, and oxidation furnished the aldehyde **C.** Reaction of **C** with ethylmagnesium bromide gave a diastereomeric mixture of the corresponding secondary alcohols which could be resolved by asym-

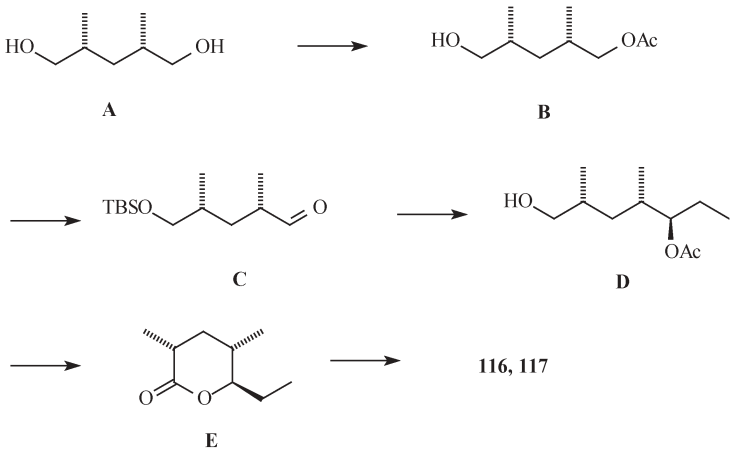


Fig. 6 Reaction scheme for the synthesis of pheromone components of male *Dinoderus bifoveolatus* **116** and **117**

metric acetylation with vinyl acetate and lipase PS-D (Amano). Chromatographic separation followed by deprotection at the primary alcohol side yielded **D.** After saponification of **D** to the corresponding diol, oxidation of the primary hydroxy group with tetra(*n*-propyl)ammonium perruthenate produced lactone **E.** Reaction of **E** with either methylmagnesium bromide or ethylmagnesium bromide gave the target compounds **116** or **117**, respectively.

First bioassays with synthetic compounds were highly promising [235]. Interestingly, the major component **117** is a stereoisomer of serricornin **118**, the sex pheromone of the cigarette beetle, *Lasioderma serricorne* (see below). The pheromone of this anobiid beetle shows, however, (4*S*,6*S*,7*S*)-configuration [38, 237, 238]. Whether such differences in the stereochemistry of pheromones may have played a role in species discrimination during earlier times when *Dinoderus* and *Lasioderma* may have lived in the same habitat, awaits further investigations (see also the above mentioned mutual agonistic-antagonistic activities of pheromones of the scarab beetles *Popillia japonica* and *Anomala osakana* [146]). The structural similarities between the Bostrychid pheromones and those of the Anobiidae (next section) may serve as a further proof for the close relationship between the two families.

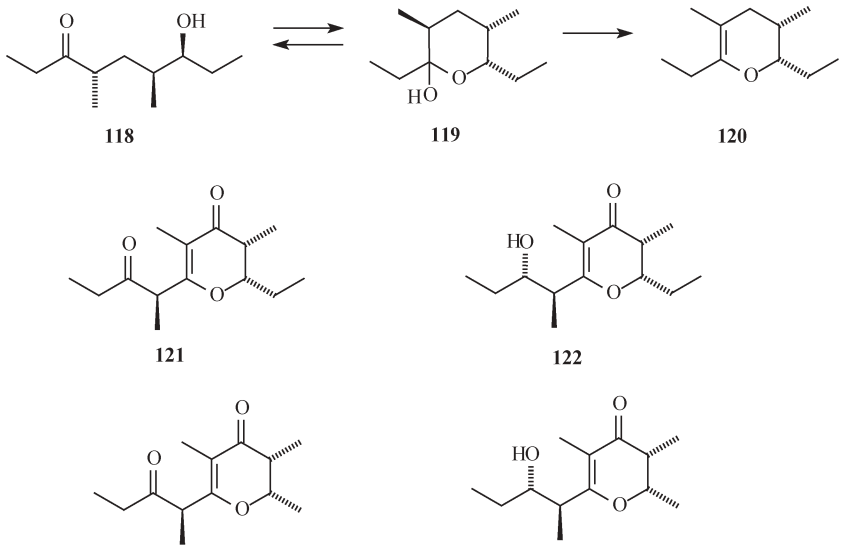
20
Anobiidae (Cigarette Beetles, Drugstore Beetles)

Attractive Compounds. Only little is known about the systems of chemical communication in anobiid beetles. Investigations have been mainly concerned with two economically important species, the cigarette beetle, *Lasioderma serricorne,* and the drugstore beetle, *Stegobium paniceum*.

(4*S*,6*S*,7*S*)-7-Hydroxy-4,6-dimethylnonan-3-one **118** (serricornin) is the female produced sex pheromone of the cigarette beetle [38, 237, 238]. The pheromone is produced in a female specific gland located at the second abdominal segment [239]. Serricornin forms a 1:3 equilibrium with its cyclic hemiacetal **119** [240, 241]. Its attractivity is strongly inhibited by the non-natural (4*S*,6*S*,7*R*)-diastereomer [242]. The dihydropyrane **120** representing the dehydrated **119** which had been described as highly attractive [243], proved to be biologically inactive after careful reinvestigation [244].

Additional compounds found in the pheromone gland of female cigarette beetles are (2*S*,3*R*,1′*R*)-2,3-dihyro-2-ethyl-3,5-dimethyl-6-(1′-methyl-2′-oxobutyl)-4*H*-pyran-4-one **121** (β-serricorone), its (1′*S*)-epimer (α-serricorone), and its reduction product, serricorole, **122** which shows (1′*S*,2′*S*)-configuration [245–247]. These compounds showed only weak attractivity [245], however, they obviously act as oviposition deterrents [248, 249].

The interesting structures of the *Lasioderma* compounds have been the subject of many syntheses, serving as models for stereocontrolled approaches. More recent syntheses of serricornin form two groups: those using chiral auxiliaries (oxazolidinone [250], boronic esters [251], and SAMP/RAMP [252]) and those involving chemoenzymatic steps ([253–255]).



Scheme 14

The pheromone produced by females of the drugstore beetle was the first to be identified in an anobiid beetle: 2,3-dihydro-2,3,5-trimethyl-6-(1′-methyl-2′-oxobutyl)-4*H*-pyran-4-one (stegobinone) [256] which by independent synthesis [257] was shown to keep (2*S*,3*R*,1′*R*)-configuration **123.** A second compound

which, however, seems to be of minor importance in the communication system of the drugstore beetle was found to be (2*S*,3*R*,1′*S*,2′*S*)-2,3-dihydro-2,3,5-trimethyl-6-(2′-hydroxy-1′-methylbutyl)-4*H*-pyran-4-one **124** (stegobiol) [258, 259]. A non-natural stereoisomer, 1′-*epi*-stegobinone showing (2*S*,3*R*,1′*S*)-configuration strongly inhibits response [260]. The compound is easily formed from stegobinone upon enolization. Crystalline (2*S*,3*R*,1′*R*)-stegobinone was synthesized by careful oxidation of crystalline stegobiol, and its absolute configuration was confirmed by X-ray analysis [261, 262].

The furniture beetle *Anobium punctatum*, a death-watch beetle, seems to use the same communication system as the drugstore beetle [263, 264].

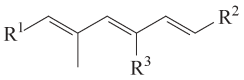
Comparison of the structures of the *Lasioderma* compounds **121** and **122** with the *Stegobium* compounds **123** or **124** reveals strong similarities even with respect to the stereochemistry. The biosyntheses may be very similar involving a C3-unit as the stereotypic building block. As already mentioned above (see introduction and Fig. 2) the skeletons of **123** and **124** would be formed when the methylmalonate (or propanoate) unit terminating the chain elongation of **121** and **122** would be replaced by malonate (or acetate), respectively.

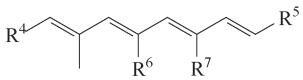
21
Cleridae (Checkered Beetles)

Defensive Compounds. Clerid beetles such as *Trichodes apiarius* were found to contain considerable amounts of cantharidin **48**, accompanied by small to minute amounts of palasonin **49** [122, 265]. Previously, the latter has been known only from seeds and fruits of the Indian shrub, *Butea frondosa* (Leguminaceae). It is suggested that these predatory beetles feed on cantharidin producing oedemerid and meloid beetles, see below. Several clerid species are canthariphilous [266, 267].

22
Nitidulidae (Sap Beetles)

Attractive Compounds. The male-produced pheromones of sap beetles, known so far, show the rather stereotypic structures **125–147** (Scheme 15): methyl- and ethyl-branched hydrocarbons with three or four (*E*)-configured conjugated double bonds [4]. Up to now, 23 compounds could be identified, forming species specific mixtures. Major components in the bouquets are (2*E*,4*E*,6*E*)-5-ethyl-3-methyl-2,4,6-nonatriene, **128**, in *Carpophilus davidsoni* [268] as well as in *C. freemani* [269], (2*E*,4*E*,6*E*)-4,6-dimethyl-2,4,6-nonatriene, **129**, in *C. truncatus* [270], (3*E*,5*E*,7*E*)-5-ethyl-methyl-3,5,7-undecatetraene, **132**, in *C. mutillatus* [271], (2*E*,4*E*,6*E*,8*E*)-3,5,7-trimethyl-2,4,6,8-decatetraene, **134**, in *C. hemipterus* [272] as well as *C. brachypterus* [273], (2*E*,4*E*,6*E*,8*E*)-3,5,7-tri-





	R^1	R^2	R^3
125	Me	Me	Me
126	Me	Me	Et
127	Me	Et	Me
128	Me	Et	Et
129	Et	Me	Me
130	Et	Et	Me
131	Et	Et	Et
132	Pr	Et	Et

	R^4	R^5	R^6	R^7
133	Me	Me	Me	Me
134	Me	Et	Me	Me
135	Me	Me	Et	Me
136	Me	Me	Me	Et
137	Et	Me	Me	Me
138	Me	Et	Et	Me
139	Me	Et	Me	Et
140	Me	Me	Et	Et
141	Et	Me	Et	Me
142	Et	Me	Me	Et
143	Et	Et	Me	Me
144	Me	Et	Et	Et
145	Et	Et	Me	Et
146	Et	Et	Et	Et
147	Pr	Et	Et	Et

Scheme 15

methyl-2,4,6,8-undecatetraene, **134**, in *C. obsoletus* [274], (*E*2,*E*4,*E*6,*E*8)-7-ethyl-3,5-dimehtylundecatetraene, **139**, in *C. lugubris* [275], and (*E*3,*E*5,*E*7,*E*9)-6,8-diethyl-4-methyldodeca-3,5,7,9-tetraene **146** in *C. antiquus* [276] as well as in *C. dimidiatus* [277]. The major components are accompanied by several homologues as minor components, and cross-attraction between species has been frequently observed [278]. Response of sap beetles to their natural pheromones is strongly inhibited by the (*Z*)-configured analogues [279, 280]. In contrast, pheromones are synergized by food and host volatiles [281, 282].

The biosyntheses of the sap beetle pheromones has been carefully investigated by Bartelt and his co-workers [47, 48]. The typical methyl-branching of the compounds originates from propanoate (or methylmalonate) units that form the principal structures (see Fig. 2). Replacement of propanoate by butyrate during chain elongation yields ethyl-branching. In about half of the compounds (**125–128**, **133–136**, **138–140**, and **144**) the structures suggest acetate to act as a starter while in **133** and **147** the starter should be butyrate. The chains

are built up by sequences of Claisen-type condensations of subunits, while in the final step decarboxylation provides the hydrocarbon structure.

Syntheses follow a kind of bio-mimetic approach [283, 284] in building up the chain during a sequence of Wittig-type reactions or Horner-Wadsworth-Emmons olefination, adding two carbons to the chain at a time with either methyl- or ethyl-branches. As the final products need to be highly pure (*E*)-stereoisomers, reaction steps and purification need to be carefully controlled.

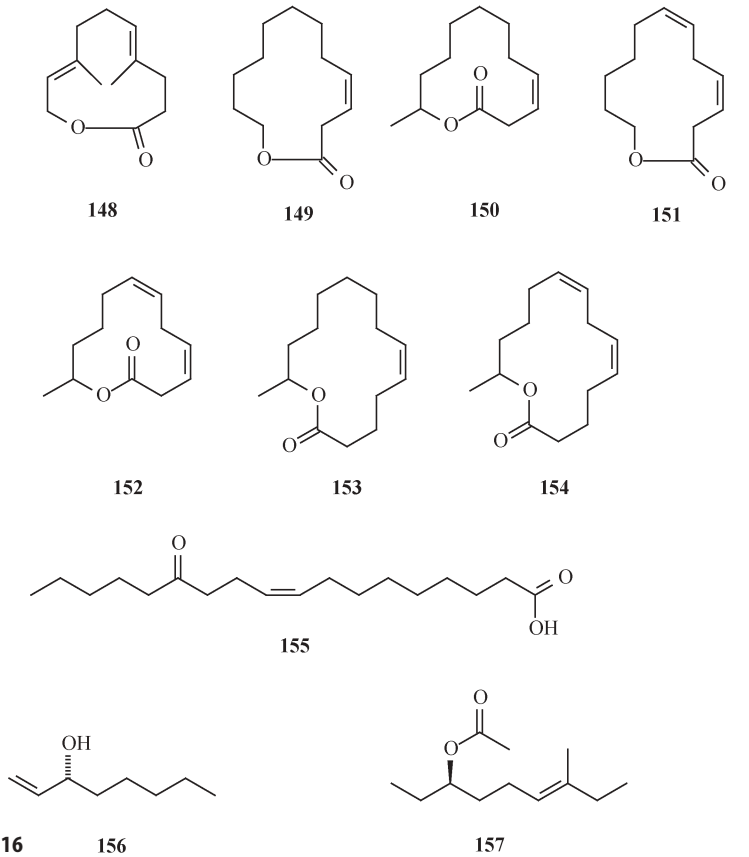
23
Cucujidae, Silvanidae/Laemophloeidae (Flat Bark Beetles, Grain Beetles)

Attractive Compounds. Macrocyclic lactones are typical components of the male produced aggregation pheromones of cucujid beetles [285]. Males and females are attracted to species-specific mixtures of these compounds, which have been given the trivial name cucujolides [286]. The following compounds have been identified: (4*E*,8*E*)-4,8-dimethyl-4,8-decadien-10-olide, cucujolide I **148** (formerly termed ferrulactone I), (*Z*)-3-dodecen-12-olide, cucujolide VIII **149** (Scheme 16), (*Z*)-3-dodecen-11-olide, cucujolide II **150** (formerly termed ferrulactone II), (3*Z*,6*Z*)-3,6-dodecadien-12-olide, cucujolide IX **151**, (3Z,6Z)-3,6-dodecadien-11-olide, cucujolide IV **152**, (*Z*)-5-tetradecen-13-olide, cucujolide III **153**, and (5*Z*,8*Z*)-5,8-tetradecadien-13-olide, cucujolide V **154**.

The biosynthesis of cucujolides has been investigated by Vanderwel et al. [287, 288]. With the exception of **148**, which shows a branched carbon skeleton, the compounds are biosynthesised from unsaturated fatty acids like oleic acid or linoleic acid. Chain-shortening and oxidation at the ω- or ω-1 position will furnish monounsaturated or doubly unsaturated lactones after ring closure. In the case of ω-1 oxidation, ring closure proceeds with high enantioselectivity. As shown by isotope labelling, **148** is of isoprenoid origin: oxidative cleavage of the last double bond of (*E*,*E*)-farnesol, followed by ring closure, yields cucujolide I.

The structures of (*Z*)-13-oxooctadec-9-enoic aid **155** and its bis-homologue (*Z*)-15-oxoicos-11-enoic acid (and their – doubly unsaturated? – precursors) are certainly related to the cucujolides, as corresponding sequences of chain shortening will provide unsaturated C12- or C14-acids. The two oxygenated fatty acids were identified in wheat flour infested by *Oryzaephilus surinamensis* but found to be absent in non-infested material. They seem to act as arrestants [289]. Similarly, 3-ketosteroids, cholestan-3-one, ergostan-3-one, and stigmastan-3-one were identified in wheat flour infested by *O. surinamensis* and described to be arrestant [290].

As already mentioned, the cucujolides form species specific mixtures of at least two compounds per species. Depending on the species, some of the compounds are active per se while others act as synergists. Species specificity also includes enantiomeric composition. While cucujolides II and III show (*S*)-configuration in *C. ferrugineus* and *C. pusillus*, respectively, cucujolies II, IV, and V



Scheme 16

show (*R*)-configuration in *O. mercator* and *O. surinamensis*. The pheromone of *C. turcicus* keeps a position in between, as cucujolide V shows an enantiomeric ratio of (*R*):(*S*)=85:15 synergized by cucujolide III of (*R*):(*S*)=35:65. Pure enantiomers of cucujolides V and III proved to be inactive in this species [286, 291]. For details see [7, 285].

The key step in Fürstner's elegant synthesis of racemic **153** furnishing a *Z*:*E*=7:3 mixture, used an intramolecular metathesis reaction of the ester **A** [292]. Employing optically active 9-decene-2-ol will certainly produce the desired enantiomer (Fig. 7).

A synthesis of **149**, cucujolide VIII, proceeded via the *tert*-butyldimethylsilyl-(TBS)-ether of methyl (*E*)-12-hydroxydodec-4-enoate **B** [293] (Fig. 7). Deprotonation in α-position and reaction with di(4-methoxyphenyl)diselenide furnished **C**. This was transformed to the macrolide **E** after saponification of the ester moiety, deprotection of the hydroxy group, and Mitsunobu lactonization. Alternatively, the unsaturated lactone **F** was synthesized from **B** following a sequence similar to that from **C** to **D**. Oxidative elimination of the arylseleno group

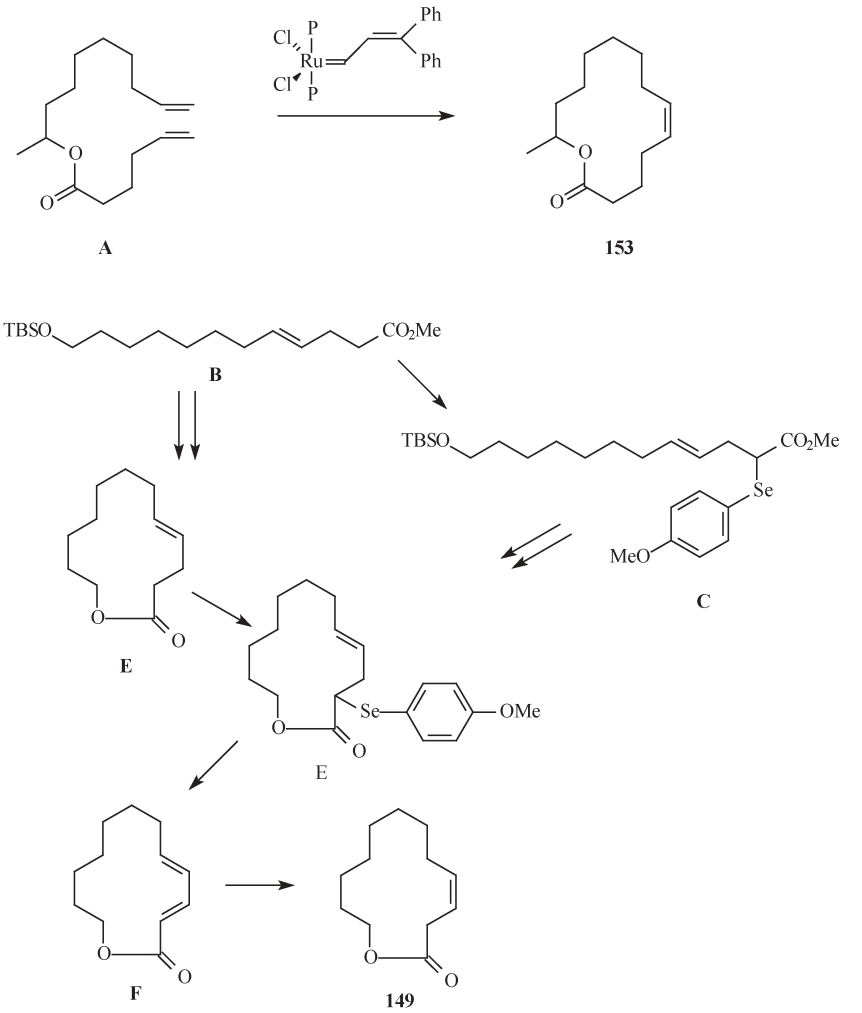


Fig. 7 Reaction scheme for the syntheses of cucujolide III **153** and cucujolide VIII **149**

in **D** gave (2,4)-dodecadiene-12-olide **G.** Subsequently, 1,4-*cis*-hydrogenation over (η 6-naphthalene) tricarbonylchromium afforded the target compound, **149.** Similarly, organoselenium chemistry and Mitsunobu lactonization have been applied in the synthesis of racemic **149** from commercially available methyl 10-undecenoate [294].

In addition to the cucujolides, (*R*)-1-octen-3-ol **156** has been described as a pheromone compound in *O. mercator* and *O. surinamensis* [295]. The alcohol is produced by both sexes at low population densities, and during a later stage of adulthood. It is reported to be attractive at low concentrations (supporting the attractivity of the cucujolies) but strongly repellent at high dosages. The

same alcohol has been reported as an aggregation pheromone, produced by both sexes of the foreign grain beetle *Ahasverus advenes* [296]. At this stage it should be noted that 1-octen-3-ol is a particularly wide-spread natural volatile, mostly associated with fungal activities.

The male-produced aggregation pheromone of the square-necked grain beetle, *Cathartus quadricollis* has been identified to be (3*R*,6*E*)-3-acetoxy-7-methylnon-6-ene **157** [297]. The compound, termed quadrilure, is attractive to both sexes, however, females are more sensitive at low concentrations. The (*S*)-enantiomer is biologically inactive.

Syntheses of both enantiomers of **157** are depicted in Fig. 8. Both approaches involve enzymatically controlled reactions during asymmetric syntheses.

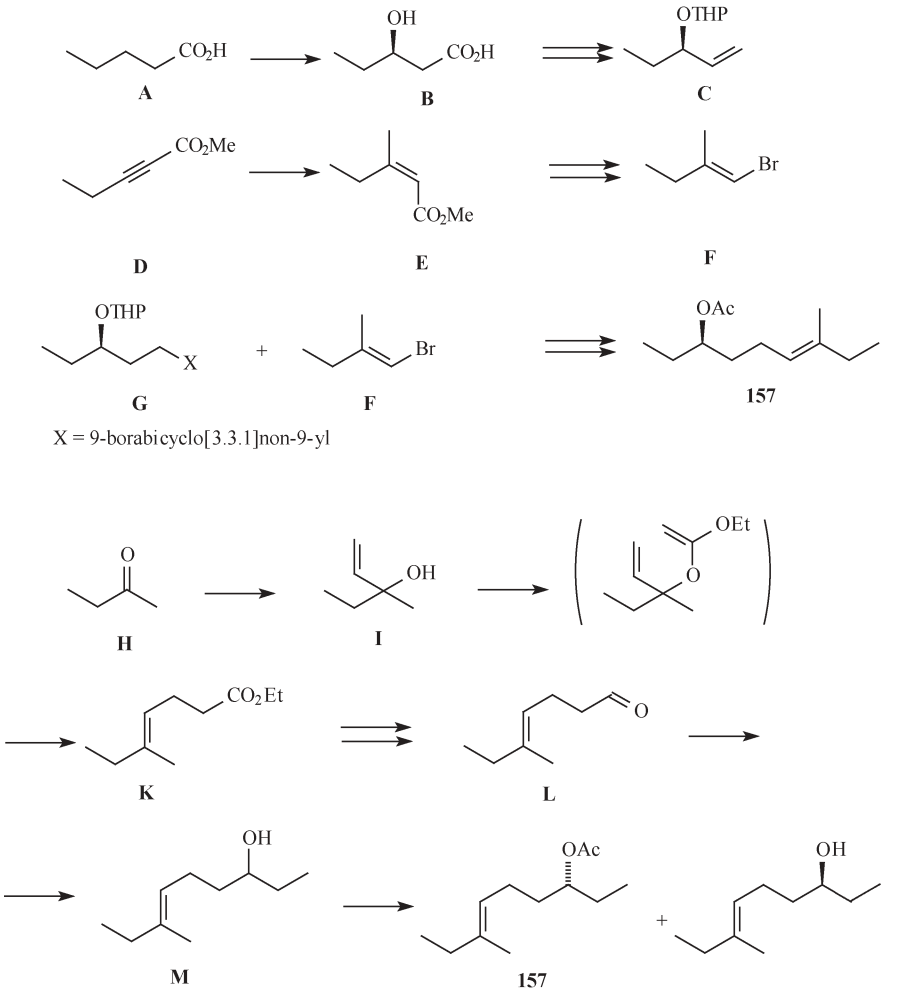


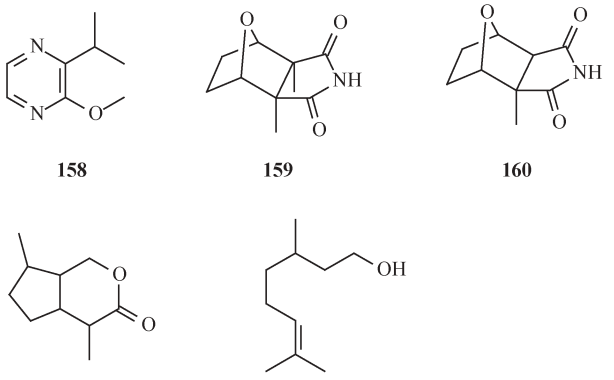
Fig. 8 Reaction scheme for the syntheses of optically active quadrilure **157**

Mori started with the early introduction of the chiral centre [298] in using β-oxidation of pentanoic acid **A** by the yeast, *Candida rugosa*, IFO 0750 [299]. The obtained (*R*)-3-hydroxypentanoic acid **B** was transformed into **C** in a few conventional steps. The second building block was prepared from methyl 2-pentynoate **D**: conjugate addition of lithium dimethyl cuprate yielded **E**, which was further converted into the *trans*-configured vinyl bromide **F**. Hydroboration of **C** yielded **G** which upon Suzuki's palladium catalysed cross-coupling with **F** furnished **157** after treatment of the reaction product with hydrochloric acid followed by chromatographic purification. The synthesis of *ent*-**157** used (*S*)-3-hydroxypentanoic acid.

In contrast to Mori's synthesis, Pawar and Chattapadhyay used enzymatically controlled enantiomeric separation as the final step [300]. Butanone **H** was converted into 3-methylpent-1-en-3-ol **I**. Reaction with trimethyl orthoacetate and subsequent Claisen-orthoester rearrangement yielded ethyl (*E*)-5-methylhept-4-enoate **K**. Transformation of **K** into the aldehyde **L**, followed by reaction with ethylmagnesium bromide furnished racemic (*E*)-7-methylnon-6-ene-3-ol **M**. Its enzyme-catalysed enantioselective transesterification using vinylacetate and lipase from *Penicillium* or *Pseudomonas* directly afforded **157**, while its enantiomer was obtained from the separated alcohol by standard acetylation.

24
Coccinellidae (Ladybird Beetles)

Attractive Compounds. While the defence chemistry of ladybird beetles has been extensively investigated, little is known about intraspecific communication. The role of chemical and behavioural cues has been described in mate recognition in *Adalia bipunctata*. Cuticular hydrocarbons, especially 7- and 9-methyltricosane seem to play an important role [301]. In *Coccinella septempunctata*, 2-isopropyl-3-methoxypyrazine **158** (see Scheme 17) accounting for the dis-



158 159 160

161 162

Scheme 17

tinctive odour of the secretion that these beetles release after molestation, was found to act as an aggregation pheromone of adult males and females [302]. The compound had previously been identified from several butterfly species as well as from coccinellids and has been described as alerting odour or warning signal to carnivores, announcing potent defence chemistry [303]. In some coccidophagous species, larvae produce chemical signals that prohibit ovipositon by adult conspecifics [304, 305]. In *Adalia bipunctata* this pheromone seems to consist of a mixture of hydrocarbons with *n*-pentacosane as the major component [305].

Defensive Compounds. The defensive chemistry of ladybird beetles was treated in the chapter by Laurent et al. in this volume.

25
Oedemeridae (False Blister Beetles)

Defensive Compounds. All developmental stages of oedemerid beetles contain and produce cantharidin as a defensive substance. The total amount of the terpenoid anhydride increases in successive instars [306]. Moreover, by using deuterium-labelled cantharidin it was found that males of *Oedemera femorata* transfer no or only very small amounts of cantharidin **48** to females during copulation. False blister beetles cause a severe dermatitis, i.e. blisters with burning and itching sensation a few hours after contact with oedemerid haemolymph [307].

26
Pyrochroidae (Fire-coloured Beetles)

Almost 30% of the world's pyrochroid genera are canthariphilous which indicates that most of these species may gain considerable amounts of cantharidin **48** from exogenous sources [121]. In the European genus *Schizotus* [306] and the North American genus *Neopyrochroa* [308, 309] an intersexual transfer of cantharidin during copulation from male to females was shown. In *Schizotus* the transfer was followed up by isotope techniques. Analyses of eggs and first instar larvae showed that a paternal allocation of cantharidin to developmental stages exists. In addition, males possess special head glands where cantharidin is excreted. During courtship, females test cantharidin titres of individual males and accept only those which contain elevated amounts of this nuptial gift [306, 308, 309].

27
Meloidae (Blister Beetles)

Defensive Compounds. Apart from cantharidin **48** and palasonin **49** the corresponding non-toxic imides cantharidinimide **159** and palasoninimide **160** could be identified in various bodyparts of the meloid beetle, *Hycleus lunata* [310, 311].

While the Indian shrub *Butea frondosa*, contains (*S*)-(–)-palasonin of high enantiomeric purity, palasonin from *Hycleus lunata* shows *a* low ee with the (*R*)-(+)-enantiomer (20–50 *ee*) prevailing. Despite this difference between the insect-derived and the plant-produced product, an uptake of palasonin from hitherto unknown plant sources in the environment of *Hycleus* appears to be highly unlikely, however, palasonin may be produced by oxidative demethylation of cantharidin [122].

The cantharidin titres of male and female specimens of *Epicauta occidentalis*, dead and live beetles as well as specimens stored under different conditions, were measured in detail [312].

Several predation tests especially with spiders and blister beetles [121, 313, 314], show that spiders exhibit a wide range of sensitivities to meloid beetles as prey. In the racoon *Procyon lotor* it was shown that they quickly form an aversion to blister beetle prey, which is induced by cantharidin [314].

28
Anthicidae (Antlike Flower Beetles)

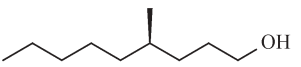
Defensive Compounds. Just as many male meloid beetles, both sexes of many anthicids possess paired mesothoracic gland reservoirs which open ventrally through an unpaired mesothoracic pore [315]. The reservoir surface is covered by secretory glands. The secretion has been shown to deter ants of the genera *Lasius* and *Myrmica*, and in addition, it shows a topical irritancy. Chemical constituents of the secretion were identified in the genera *Formicomus* and *Microhoria* and are represented by iridoids such as iridodial **17**, dolidodial **65**, iridomyrmecin **161**, dihydronepetalactone **67**, and actinidine **60**. Apart from citronellol **162**, citronellal, and isopropyl hexadecanoate the mesothoracic secretions contain alkanes ranging from tridecane to nonadecane (main constituents: pentadecane and heptadecane), 1-alkanols from 1-undecanol to 1-pentadecanol and 1-alkenes from 1-tridecene to 1-heptadecene.

Many anthicid species are known to be cantharipholous [121]. After take up, males store the toxin in the accessory glands and transfer it as a kind of nuptial gift to the females. Many male anthicid species are characterized by elytral exocrine glands which serve for excretion of cantharidin depending on the cantharidin titre. Similar to Pyrochroidae (see there) females test the cantharidin load of males before copulation and select those males which previously were able to incorporate this precious defensive compound from exogenous sources.

It has been stated that the biologically active gland secretion protects the adults whereas the haemolymph toxin which is transferred to females may serve for protection of both larvae and eggs.

29
Tenebrionidae (Darkling Beetles, Flower Beetles)

Attractive Compounds. The female-produced sex pheromone of the yellow mealworm beetle, *Tenebrio molitor*, is (*R*)-4-methyl-1-nonanol [316] **163** (Scheme 18). Careful investigations on the biosynthesis of this compound [317] revealed that it is produced through a modification of normal fatty acid biosynthesis (Fig. 1, Fig. 2): propanoate serves as the starter, while formal chain elongation with acetate, propanoate, and acetate (accompanied by removal of the oxygens) produces 4-methylnonanoate which yields the pheromone alcohol after reduction. The structures and role of proteins that are present in the hemolymph or secreted by the tubular accessory glands of *T. molitor*, and that may carry lipophilic chemical messengers (like pheromones) are under investigation [318, 319].



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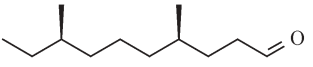

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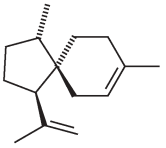

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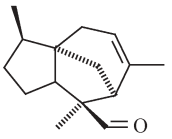

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Scheme 18

The male-produced sex pheromone of the red flour beetle, *Tribolium castaneum*, has been identified to be (4*R*,8*R*)-4,8-dimethyldecanal **164** (tribolure) [320, 321]. During bioassays, a mixture of the (4*R*,8*R*)- and (4*R*,8*S*)-stereoisomers proved to be more active than the pure (4*R*,8*R*)-enantiomer [322]. The exact enantiomeric composition of the natural product remains as yet unknown. 4,8-Dimethyldecanal was found in other *Tribolium* species, too [323]. Factors affecting the pheromone production in *T. castaneum* have been described by Hussain et al. [324].

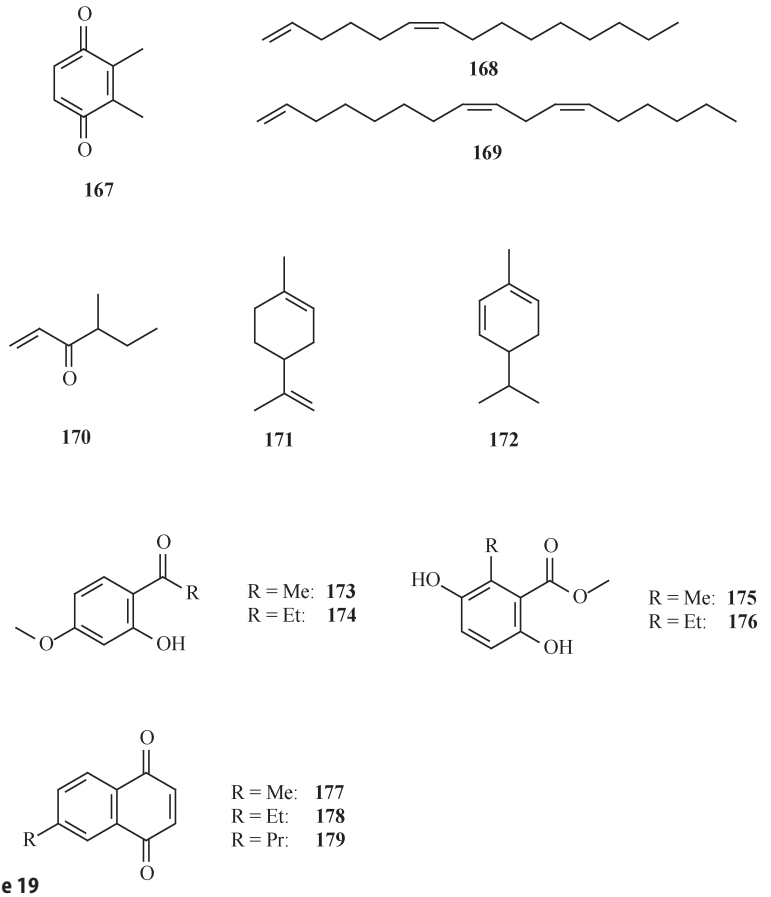
While the structure of 4,8-dimethyldecanal may suggest a tris-norsesquiterpene, produced upon degradation of a farnesol-precursor, it appears more likely that its biosynthesis follows a way similar to that of 4-methylnonanol: starting

with acetate followed by chain elongation with a sequence of propanoate-acetate-propanoate-acetate would yield 4,8-dimethyldecanoate which could be easily transformed to the corresponding aldehyde (see also Fig. 2).

The biological significance of 1-pentadecene and 1,6-pentadecadiene which have been shown to be common volatiles among flour beetles [323] remains to be investigated.

While the pheromones of *Tenebrio* and *Tribolium* originate from a mixed biosynthesis, those produced by males of the broad horned flour beetle, *Gnathocerus cornutus,* represent true terpenes. Initially, the configuration of this new pheromone had been erroneously proposed to be (1*R*,4*R*,5*S*) α-acoradiene [325]; however, independent syntheses of pure stereoisomers [326, 327] proved the correct structure to show (1*S*,4*R*,5*R*)-configuration **165**. The scope of the synthesis is shown by Mori (see chapter by Mori in volume 1 and [15]). A minor component of the *G. cornutus* was reported to be α-cedren-14-al **166** [328].

Defensive Compounds. Since the last review [8], secretions of another 88 species from 63 Australian tenebrionid genera and 23 tribes [329] as well as 10 species of Triboliini [330] have been analysed. They usually contain constituents previously identified from American and European species [329]. Most species produce toluquinone **7**, as well as the ethyl- and propyl-homologue. In addition, Australian species may contain 2,3-dimethyl-1,4-benzoquinone **167** (Scheme 19) or 2-methoxy-3-methyl-1,4-benzoquinone **54** admixed with a row of straight chain uneven numbered 1-alkenes from C_9-C_{19} as well as pentadecadiene, heptadecadiene and nonadecadiene. In *Palorus ratzeburgi* and various *Tribolium*-species, structures of polyenes were determined to be (1,6*Z*)-1,6-pentadecadiene **168**, (1,7*Z*)-1,7-hexadecadiene, (1,8*Z*)-1,8-heptadecadiene, and (1,8*Z*,11*Z*)-1,8,11-heptadecatriene **169**. The biosynthesis of the uneven numbered 1-alkenes starts with fatty acids. The process involves an enantiospecific cleavage of the C-H bond of the pro-(*S*) hydrogen at C3 and simultaneous decarboxylation of the acid form an 1-alkene and carbon dioxide via an *anti*-periplanar transition state geometry (*anti*-elimination). The stereochemistry of this biotransformation was shown to be identical in all respects with the same reaction in higher plants [331]. Further defensive compounds of Australian species are ethylbenzene, *m*-cresol **89**, 4-methyl-3-hexanone, 4-methylhex-1-en-3-one **170**, limonene **171**, α-pinene **45**, α-phellandrene **172**, hexadecyl acetate and tetradecyl acetate. The defensive glands of *Tribolium* additionally contained 2-hydroxy-4-methoxyacetophenone **173**, 2-hydroxy-4-methoxypropiophenone **174**, methyl 2,5-dihydroxy-6-methylbenzoate **175** and methyl 2,5-dihydroxy-6-ethylbenzoate **176**. The defensive secretion of *Blaps mucronata* was analysed in detail [332]. Most compounds correspond to substances of Australian tenebrionids; unusual components are tridecanone, pentadecanone and octanoic acid. As in staphylinid beetles [265] irritancies caused by tenebrionid secretion were determined by using bioassays with ants and cockroaches. Hydrocarbons of *Blaps*-secretions may serve as surfactants that promote spreading of the secretion over the beetles' body [332].



Scheme 19

In Australian tenebrionid beetles, defensive compounds and their patterns seem to be of only low chemotaxonomic value. However, the aforementioned aromatic compounds are restricted to the genus *Tribolium*. Abdominal defensive compounds were used as chemosystematic characters in order to construct a phylogenetic tree for the genus *Tribolium* [330]. The defensive secretion of adults of *Tenebrio molitor* was shown to contain toluquinone **7** and *m*-cresol **89** [333]. The quantification of benzoquinones in single individuals of *Tribolium castaneum* at different days after adult eclosion indicates that the amount of toxic quinone only shows a maximum subsequent to cuticle sclerotization. Obviously, there is a need for an adequate cuticular barrier for self-protection from these defensive compounds [334].

In order to determine whether the defensive compounds of hybrids of the two *Tribolium*- species *T. freemani* and *T. castaneum* represent simple mixtures of the parental phenotypes, different glandular samples were compared by GC-MS [335]. Concerning the qualitative and quantitative data of the quinones,

hydroquinones, propiophenone and alkenes/alkadienes (main compounds) only small differences could be observed. However, the pattern of saturated branched and straight chain hydrocarbons showed significant quantitative differences.

Acidic methanolic extracts of larvae of *Tenebrio molitor* contain toxic substances, so-called paralysins, which exhibit immediate paralytic effects on other insects upon injection [336].

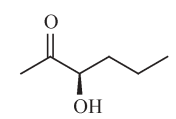
Larvae of the tenebrionid beetle *Hypophloeus versipellis* were shown to possess an unpaired defensive gland reservoir with an opening situated at the anterior border of the ninth tergite [126]. The secretion contains methyl-1,4-benzoquinone **7**, ethyl-1,4-benzoquinone **8**, ethylhydroquinone, and acetophenone as well as 6-methyl-1,4-naphthoquinone **177**, 6-ethyl-1,4-naphthoquinone **178**, and 6-propyl-1,4-naphthoquinones **179**. Several alkenes (probably 1-alkenes) like 1-tridecene, 1-tetradecene, 1-pentadecene (main constituent), 1-hexadecene, and 1-heptadecene may function as solvents for the solid biologically active compounds.

The secretion of *Hypophloeus* caused considerable amounts of mortalities when tested with co-occurring sciarid larvae and probably acts as a bactericide, fungicide, and as a fumigant [337]. 6-Alkyl-1,4-naphthoquinones are erratically distributed among arthropods but also occur in non-homologous paired defensive glands of adult darkling beetles of the genus *Argoporis* (see [8]).

30
Cerambycidae (Longhorn Beetles)

Attractive Compounds. Structures of pheromone components of longhorn beetles are surprisingly diverse (Scheme 20).

Various unbranched α-hydroxyketones were found in several species: (*R*)-3-hydroxy-2-hexanone **180** is the most important compound in the male-specific pheromone blend of the old house borer *Hylotrupes bajulus* and in *Pyrrhidium sanguineum* [338]. Additional compounds are 2-hydroxy-3-hexanone **181** (possibly an artefact produced from **180** upon hydrogen shift) and the reduction products (2*R*,3*R*)-hexanediol, (2*S*,3*R*)-2,3-hexanediol, the corresponding diketone, and 2-butanol. The latter compounds have consequently not been tested with respect to their biological activity; however, the diols appear to be important. The hydroxyketone **181** and its *bis*-homologue (*R*)-3-hydroxy-2-octanone **183** are male released pheromone constituents of *Anaglyptus subfasciatus* [339, 340]. The attractivity of a 25:1 blend of **180** and **182** is significantly enhanced by the addition of the floral attractant methyl phenylacetate [341]. The sex pheromones of *Xylotrechus* spp. consist of (2*S*,3*S*)-2,3-octanediol **183** and (*S*)-2-hydroxy-3-octanone [342, 343]. Structures of pheromone components in the coffee white stem borer, *Xylotrechus quadripes*, seem to follow the scheme of other *Xylotrechus* spp: (*S*)-2-hydroxy-3-decanone **184** (accompanied by the corresponding dione) was found to be weakly attractive



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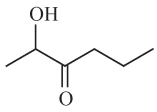

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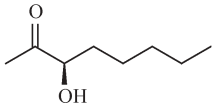

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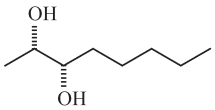

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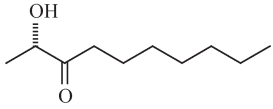

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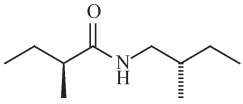

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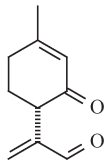

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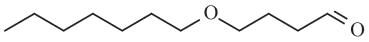

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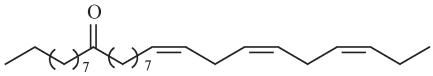

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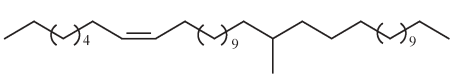


Scheme 20 **189**

[344]. All these compounds represent a row of bishomologues of acetoin **77**, the pheromone of the chafer *Amphimallon solstitiale* [167].

The female produced long range sex pheromone of *Migdolus fryans* is *N*-[(2′*S*)-2-methylbutyl]-(2*S*)-2-methylbutyramide **185** [345]. The acyl part as well as the alkyl part may be derived from isoleucine. Interestingly, this amide is accompanied by the ethyl ester of *N*-formyl isoleucine, which is also known from the scarab beetle, *Phyllophaga elenans* [181]. This amino acid derivative proved to be not attractive for both species; its biological significance remains to be clarified.

In contrast to the doubly oxygenated acetogenins **180–184** and the branched amide **185**, female specific semiochemicals of *Vesperus xytarti* are monoter-

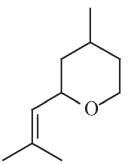
penes. The oxygenated isopiperitenone derivatives **186** and the corresponding primary alcohol were called vesperal and vesperol [346]. Independent syntheses proved the natural compounds to show (*S*)-configuration [346, 347] while bioassays established the role of **186** as the decisive pheromone component.

Two male specific volatiles of *Anoplophora glabripennis* were found to elicit strong electrophysiological responses in the antenna of both males and females. The very unusual 4-(*n*-heptyloxy)butanal **187** and the corresponding alcohol form a 1:1 mixture [348]. A synthetic blend proved to be attractive in laboratory bioassays.

While these functionalized ethers may be long range signals, long chain unsaturated ketones, isolated from the elytra of females of the related species *Anoplophora malasiaca*, act as contact pheromones. The mixture of 10-heptacosanone, (*Z*)-18-heptacosen-10-one, (18*Z*,21*Z*)-18,21-heptacosadien-10-one and (18*Z*,21*Z*,24*Z*)-18,21,24-heptacosatrien-10-one **188** proved to show pronounced biological activity [349].

Another contact sex pheromone was identified as a component of the cuticular lipids of females of *Psacothea hilaris* [350, 351]. Extracts of the elytra contained (*Z*)-21-methyl-8-pentatriacontene **189**. The synthetic compounds (both enantiomers were synthesized [352, 353]) induced precopulatory behaviour in males, however, its biological activity was considerably lower than that of the natural extract.

Defensive Compounds. In Cerambycinae, paired metasternal glands are situated in the thorax, while associated reservoirs open near the hind coxae [8]. Rose oxide **190** (Scheme 21) and iridodial **17** were identified from *Aromia moschata*



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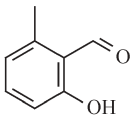

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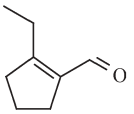

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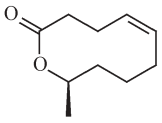

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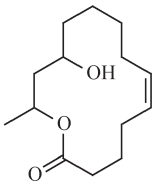

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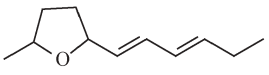


195

Scheme 21

[354]. *Phoracantha* species contained 6-methylsalicylic aldehyde **191**, the disubstituted cyclopentene phoracanthal **192**, the corresponding alcohol, phoracanthol, and the (*E*)- and (*Z*)-stereoisomers of the saturated system. In addition, methyl and ethyl esters of 2-methylbutyric acid and isovaleric acid as well as the macrocyclic lactones decan-9-olide (=phoracantholide I), (*Z*)-dec-4-en-9-olide (=phoracantholide J) **193**, and 11-hydroxytetradec-5-en-13-olide **194** [8, 355, 356]. As shown by independent syntheses of both enantiomers, the natural phoracantholides show (*R*)-configuration [357].

From the metasternal gland secretion of the locust tree borer *Megacyllene robiniae* Wheeler et al. [358] identified 2-(1,3-hexadienyl)-5-methyltetrahydrofuran **195** (no stereochemistry provided), hexadecyl acetate, octadecyl acetate, and 1-phenylethanol.

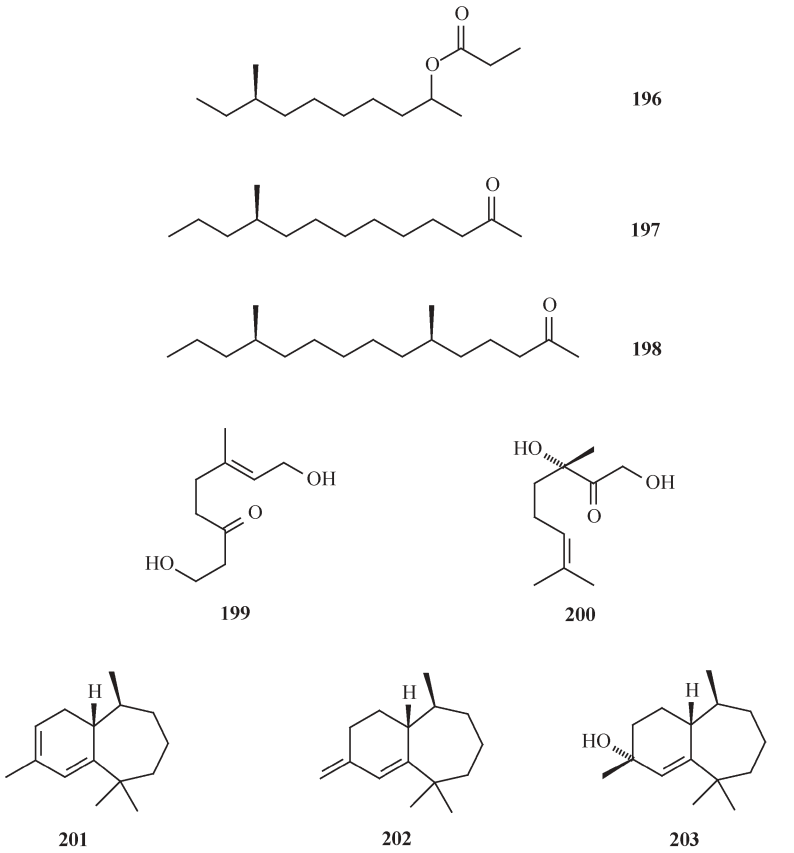
31
Chrysomelidae (Leaf Beetles)

Attractive Compounds. Despite the fact that defence chemistry and insect-plant interactions have been extensively investigated in many leaf beetle species, not too much is known about the chemical background of intraspecific communication.

1,7-Dimethylnonyl propanoate **196** (Scheme 22), the female produced sex pheromone of several corn root worm species, *Diabrotica* spp. keeps (*R*)-configuration at the methyl branching, whereas the stereochemistry at the oxygen function may vary with species (including the formation of mixtures) [359, 360]. The structure of the pheromone of the southern corn root worm *D. undecimpunctata*, (*R*)-10-methyltridecan-2-one **197**, is closely related to **196** [361, 362]. Compared with **196** and **197**, (6*R*,12*R*)-6,10-dimethylpentadecan-2-one **198**, the sex pheromone of *D. balteata* shows similar structural features [363, 364].

A more recent synthesis of **197** [365] is shown in Fig. 9. Enders introduced the stereogenic centre of (*S*)-lactic acid into the crucial position 10 in **197**. The vinylsulfone **B**, readily available from lactic acid, was transformed into the planar chiral phenylsulfonyl-substituted (η^3-allyl)tetracarbonyliron(+1) tetrafluoroborate **C** showing (1*R*,2*S*,3*R*)-configuration. Addition of allyltrimethyl silane yielded the vinyl sulfone **D** which was hydrogenated to **E**. Alkylation with the dioxolane-derivative of 1-bromoheptan-6-one (readily available from 6-bromohexanoic acid) afforded **F**. Finally, reductive removal of the sulfonyl group and deprotection of the carbonyl group furnished **197**. A similar approach was used for the synthesis of **198** [366].

The biosyntheses of these compounds may follow similar principles involving propanonate (methylmalonate) and acetate (malonate) units; however, the sequence seems to be less clear than in other branched chain structures. According to Fig. 2, incorporation of propanoate followed by chain elongation with acetate (including termination by either propanoate or acetate) would lead to an even number of methylene groups between the methyl branching



Scheme 22

and the oxygen function – which is not the case in the *Diabrotica* pheromones. However, a sequence of acetate-propanoate-acetate-acetatepropanoate followed by oxidative decarboxylation of the acyl-intermediate (see also remarks concerning the biosynthesis of lardolure [45]) and esterification would definitely yield **196**. Similarly, the introduction of oxygen into **197** and **198** may be introduced upon oxidative decarboxylation of an α-methyl acyl-precursor.

Another unusual structure was identified from cereal leaf beetles, *Oulema melanopus*: (*E*)-8-hydroxy-6-methyl-6-octen-3-one **199** was found to be a male-specific volatile. Electrophysiological investigations showed a sensitive detection of **199** by both sexes which is consistent with a male-produced aggregation pheromone [367]. The behaviour mediating capacity of the compound needs to be proven.

While the existence of a female produced sex pheromone in the Colorado potato beetle *Leptinotarsa decemlineata* has been the subject of controversy for many years (for a discussion see [368]) a male produced pheromone has

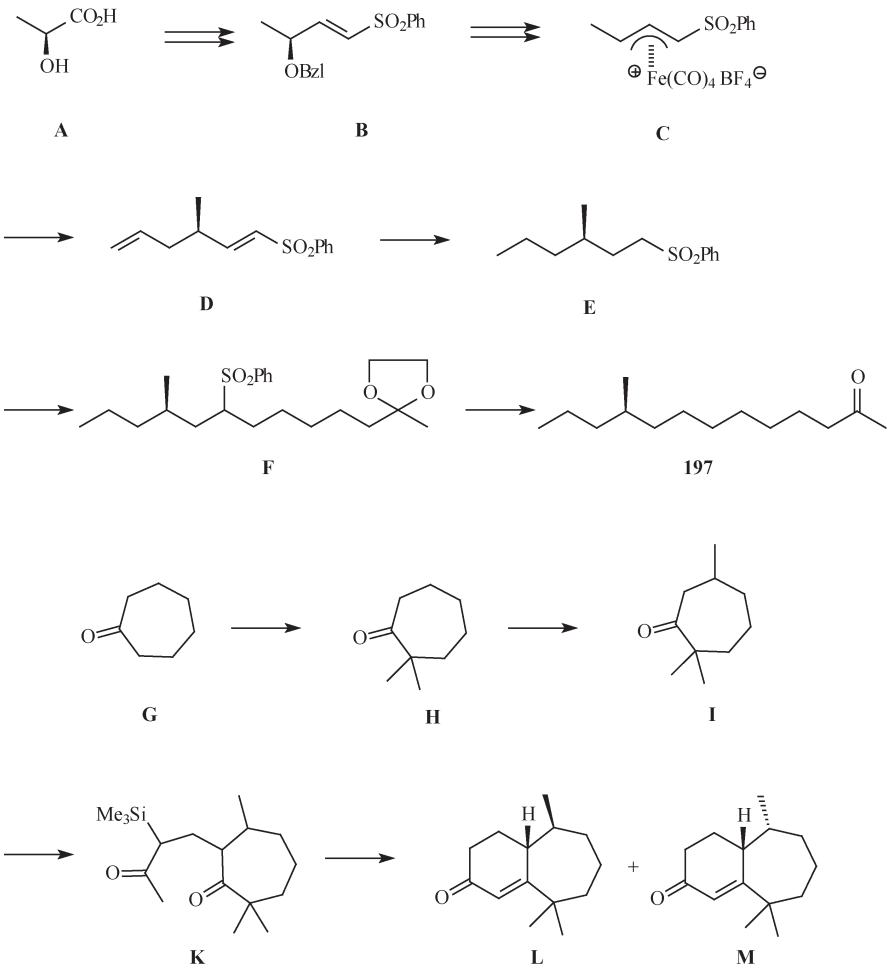


Fig. 9 Reaction schemes for the syntheses of (*R*)-10-methyltridecan-2-one and the sesquiterpenes of *Phyllotreta* and *Aphtona* spp.

recently been identified: (*S*)-3,7-dimethyl-2-oxo-6-octene-1,3-diol **200**. The structure suggests a highly oxygenated monoterpene [369]. Only the natural (S)-enantiomer proved to be active. Corresponding syntheses have been shown by Mori [15, 16]. It is obvious that **199** and **200** may share an isoprene subunit.

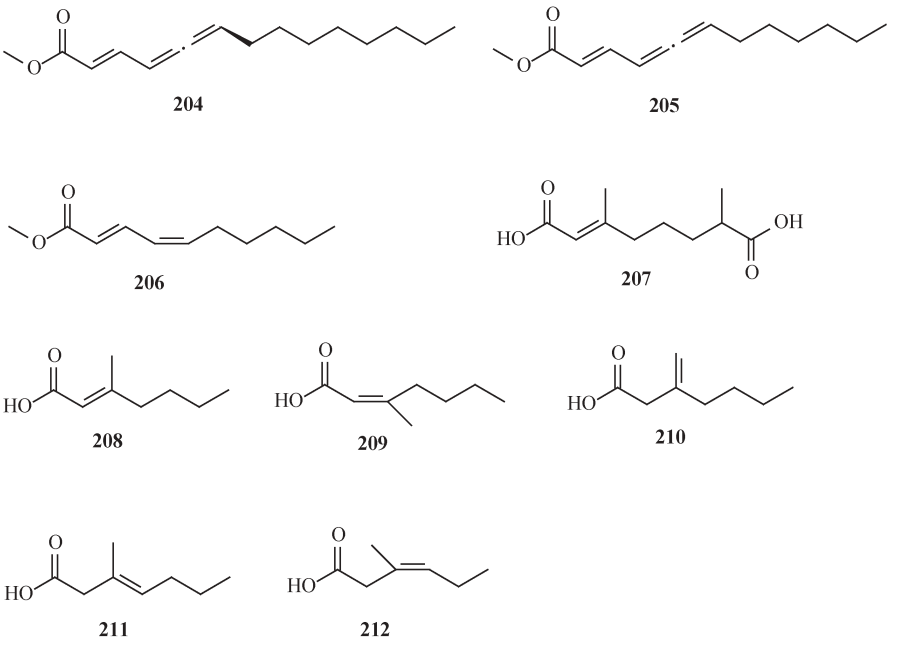
In some flea beetles, *Phyllotreta* and *Aphthona* spp., species specific, male produced blends of himachalene derivatives like **201, 202,** and **203** were identified. Structure elucidation was carefully carried out on the basis of spectroscopic methods, micro reactions, and independent syntheses [370, 371]. Compounds **201, 202, 203** are perceived by both male and female antennae, as would be expected for an aggregation pheromone. Investigations on the behaviour mediating capacity of the compounds are ongoing.

Syntheses of diastereomerically pure racemates of himachalene derivatives started from cycloheptanone **G** (Fig. 9). The sequence to **I** involved dimethylation to yield **H** followed by bromination/dehydrobromination and conjugate methylation using cuprate chemistry. The sequence furnishing **L** and **M** follows a Robinson-annelation type: Reaction of **I** with 3-(trimethylsilyl)but-3-en-2-one yielded **K**. Refluxing **K** with potassium hydroxide in ethanol removed the silyl group and cyclized the diketone to form a 97:3 mixture of racemic **L** and **M**. Occurring as a volatile in *A. flava*, **L** served as a versatile intermediate in the syntheses of other *Aphthona* compounds.

Defensive Compounds. The defensive chemistry of leaf beetles was treated in the chapter by Laurent et al., this volume.

32
Bruchidae (Bean Weevils, Seed Beetles)

Attractive Compounds. The male produced sex pheromone of the dried bean beetle, *Acanthoscelides obtectus*, is an unusual methyl ester, methyl (*R*,2*E*)-2,4,5-tetradecatrienoate **204** [372] (Scheme 23). The compound was among the first pheromones identified from male beetles, and only very recently other insect volatiles showing allenic structures have been described [184]. Careful head



Scheme 23

space analyses of volatiles released by males of *A. obtectus* confirmed the presence of **204** as a major component but showed also other compounds like methyl 2,4,5-dodecatrienoate **205** and methyl (2*E*,4*Z*)-decadienoate **206** to be present [373]. No bioassays have been carried out with **205** or **206**.

While the unbranched **204–207** clearly originate from the acetate pool, the structure of (*E*)-3,7-dimethyl-2-octene-1,8-dioic acid, callosobruchusic acid **207**, a female produced copulation releasing pheromone of the azuki bean weevil, *Callosobruchus chinensis* [374] points to a terpenoid structure. The synthetic enantiomers [375] proved to be equally effective in releasing copulation behaviour in males.

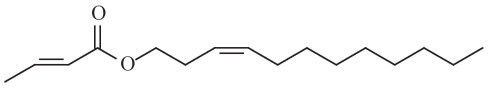
Females of the cowpea weevil, *Callosobruchus maculatus*, release a male attracting pheromone from the tip of their abdomen. The volatile signal contains five unsaturated, branched C8-acids **208–212** [376, 377]. Individual compounds proved to be active while mixtures showed additive effects. Similarly, compounds **208** and **209** have been identified as the female produced sex pheromone of *C. subinnotatus* [378], while **209** had been described as the sex pheromone of *C. analis* [379]. However, GC-MS analyses of female produced volatiles of *C. analis* failed to detect any of the *C. maculatus* compounds, but did find an unidentified C8-acid with a retention time different from any of the *C. maculatus* acids [377].

It is interesting to note that the *C. maculatus* compounds show an "isoprene sub-unit" which bears the unsaturation and the carboxylic moiety just like callosobruchusic acid **207**. A propanoate (or methylmalonate) starter would formally complete the biogenesis of the structures.

33
Curculionidae (Snout Beetles, Weevils)

Attractive Compounds. With the exception of (*Z*)-3-dodecenyl (*E*)-2-butenoate **213** (Scheme 24), the female produced sex pheromone of the sweetpotato weevil *Cylas formicarius* [389], the structures of weevil pheromones are represented by oxygenated monoterpenes, polyketides produced from propanoate units, and branched alcohols and ketones, probably originating from a mixed acetate-propanoate biosynthesis [5].

The male produced sex pheromone of the boll weevil, *Anthonomus grandis*, was the first weevil pheromone identified [381]. The bouquet is made up by four compounds, the tri-substituted cyclobutane **214**, grandisol (main component), and the cyclohexane derivatives (*Z*)-3,3-dimethyl-$\Delta^{1,\beta}$-cyclohexanethanol, (*Z*)-ochtoden-1-ol **215** (main component), **216**, and **217** (minor components). Upon comparison with synthetic samples, natural grandisol proved to show (1*R*,2*S*)-configuration [382, 383], its enantiomer is behaviourally inactive [384]. A close relative of the boll weevil, the pepper weevil, *Anthonomus eugenii*, does not produce grandisol but the three cyclohexane derivatives **215–217** and **218** as well as geraniol and geranic acid **219** [385].



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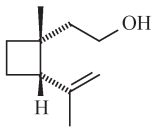

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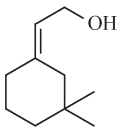

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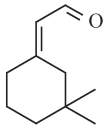

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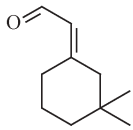

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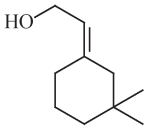

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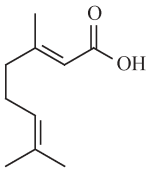

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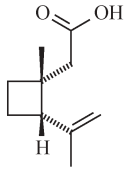

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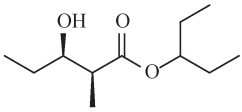

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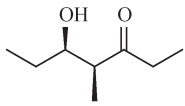

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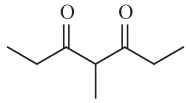

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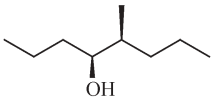

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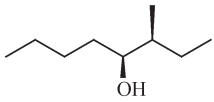

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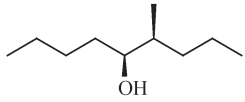

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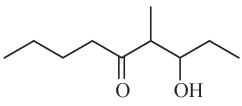

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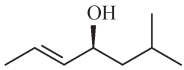

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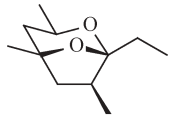


229

Scheme 24

The pheromone bouquet of the pecan weevil, *Curculio caryae* is similar to that of the boll weevil; however, it also contains (1*S*,2*R*)-grandisol. The quantitative composition of the blend determines whether it is more attractive to the pecan weevil or to the boll weevil [386]. In some pine weevils, *Pissodes* species, grandisol and the corresponding aldehyde, grandisal, are components of a male produced pheromone. In *Pissodes nemorensis* and *Pissodes strobi* grandisol

shows almost 100% (1*R*,2*S*)-configuration. In contrast, *Pissodes nemorensis* releases nearly 100% pure (1*S*,2*R*)-grandisal, while in *Pissodes strobi* this enantiomer dominates only with 20% enantiomeric excess [387]. Finally, (1*R*,2*S*)-grandisoic acid **220** was identified as a component of the male produced aggregation pheromone of the plum curculio *Conotrachelus nenuphar* [388]. The male produced pheromone of the strawberry blossom weevil, *Athonomus rubi* consists of (1*R*,2*S*)-grandisol **214**, (*Z*)-ochtoden-1-ol **215**, and lavandulol **37** [389].

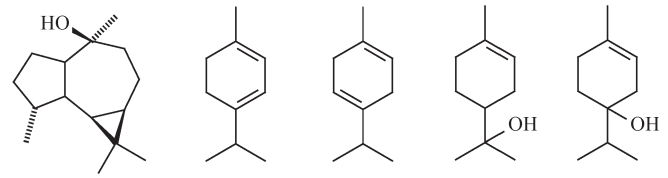
Two propanoate units (see Fig. 2) seem to be coupled in 1-ethylpropyl (2*S*,3*R*)-2-methyl-3-hydroxypropanoate **221**, the male produced aggregation pheromone of the granary weevil, *Sitophilus granarius* [390–393]. Even the ester-moiety may origin from two propanoate units after decarboxylation and reduction Three propanoate units (and decarboxylation, see Fig. 2) may produce (4*S*,5*R*)-5-hydroxy-4-methyl-3-heptanone, sitophilure **222**, the aggregation pheromone of the rice weevil, *Sitophilus oryzae* [394, 395]. The same carbon skeleton is present in the achiral 4-methylheptan-3,5-dione **223**, the pheromone of the pea weevil, *Sitona lineatus* [396–398].

Simple branched secondary alcohols have been identified as male-produced aggregation pheromones of *Rhynchophorus* and related species. With only few exceptions the compounds are not species specific. The pheromone of the palmetto weevil, *Rhynchophorus cruentatus* is (4*S*,5*S*)-5-methyl-4-octanol, cruentol, **224** [399, 400] whereas its isomer, (3*S*,4*S*)-3-methyl-4-octanol, phoenicol, **225**, is the pheromone of the African palm weevil, *Rhynchophorus phoenicis* [399–402]. The homologue of **225**, (4*S*,5*S*)-4-methyl-5-nonanol, ferruginol, **226**, was identified in the African palm weevil, *Rhynchophorus ferrugineus*, and several related species including *Dynamis borassi* [403–405]. Ferruginol is also the most important pheromone component of the sugar cane weevil, *Metamasius hemipterus*, where it is accompanied by 2-methyl-4-heptanol, 2-methyl-4-octanol, the corresponding ketones, 5-nonanol, and 3-hydroxy-4-methyl-5-nonanone **227** [406–408]. No bioassays with these minor components have been reported. The pheromone of the American palm weevil, *Rhynchophorus palmarum* is (2E,4*S*)-methyl-2-hepten-4-ol, rhynchophorol, **228** [409–411]. The corresponding epoxide was also found to be present [412], but no bioassays have been reported.

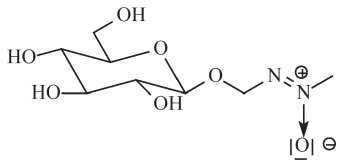
Weevils do not seem to be very sensitive to the presence of non-natural stereoisomers of their pheromones, since racemic mixtures proved to be active in the field. This greatly facilitates their use in large-scale integrated pest management. Some species also contain ketones, corresponding to the pheromone alcohols; however, they do not show behavioural activity.

A higher degree of oxygenation along the chain is represented in (1*S*,3*R*,5*R*,7*S*)-1-ethyl-3,5,7-trimethyl-2,8-dioxabicyclol[3.2.1]octane, sordidin, **229**, the aggregation pheromone of the banana weevil, *Cosmopolites sordidus* [413–415]. It is interesting to note, that the (1*R*,3*S*,5*S*,7*S*)-stereoisomer of sordidin is a biologically active compound in cadddisfly species (Trichoptera) [416].

The biological activity of the banana weevil pheromone and those of related palm weevil species is strongly enhanced by host plant volatiles [399, 417–419].



230 **231** **232** **233** **234**



Scheme 25 **235**

Defensive Compounds. Larvae of the weevil *Oxyops vitiosa* produce a shiny orange secretion that covers their integument and probably acts as deterrent against ants [420]. The composition of the secretion resembles the terpenoid pattern of the host foliage (*Melaleuca quinquenervia*) from where it is sequestered (concentration about twice that of the host foliage). It contains the sesquiterpene (+)-viridoflorol **230** (Scheme 25), the monoterpene hydrocarbons α-pinene **45**, β-pinene **46**, limonene **171**, α-terpinene **231**, and γ-terpinene **232** as well as the oxygenated monoterpenes1,8-cineole **58**, α-terpineol **233**, and terpinen-4-ol **234**.

In males and females of the weevil *Rhopalotria mollis* the sequestration of cycasin **235** known from the Mexican cycad *Zamia furfuracea* was reported [421].

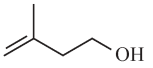
34
Scolytidae (Bark Beetles)

Attractive Compounds. Among the Coleoptera, bark beetles are the most intensively investigated family. Guided by chemical signals they typically colonize their host trees in large amounts (mass attack) to overcome jointly its resistance which is prerequisite for a successful breeding. In this context, typical sex pheromones produced by one sex to attract exclusively the other play a minor role. In contrast, intraspecific communication is mainly based on aggregation pheromones that attract both sexes. These aggregation pheromones are released by so-called pioneer beetles after landing on a host tree while mate-finding of the attracted conspecifics on the host tree surface seems to be a matter of close range orientation and statistics. In general, females of monogamous species select individual host trees while in polygamous species it is the males.

Host selection is largely influenced by the physical condition of the tree as well as by its inventarium of volatile and non-volatile compounds. In coniferous species, the composition of monoterpene hydrocarbons seems to be a major olfactory clue in bark beetle orientation (primary attraction); however, details are still not understood. The chemical signal is specified by pheromones (secondary attraction) which may serve as intraspecific attractants and interspecific repellents for species that compete for the same breeding place. At the same time predators may locate their prey by using the corresponding pheromones as kairomones. With a few exceptions, bark beetle species that have been investigated with respect to their communication systems attack coniferous trees. The intriguing mechanisms of host colonization as well as intra- and interspecific communication in bark beetles have been extensively reviewed [422–425]. This paragraph is focussed on chemical structures of compounds that are used in bark beetle communication rather than on pheromone biology, i.e. the intruding mechanisms of host selection, mate finding, and interspecific competition etc.

The hemiterpene 3-methyl-3-buten-1-ol **236** (Scheme 26), one of the two C5-building blocks of monoterpenes, is a pheromone of the larch bark beetle *Ips cembrae* [426]. While the other principal building block of monoterpenes, 3-methyl-2-buten-1-ol does not play a decisive role as a bark beetle pheromone, 2-methyl-3-buten-2-ol, **237**, the product of its allylic rearrangement is the main aggregation pheromone of several *Ips* and related species [427, 428]. In *Ips typographus* it proved to be synthesized de novo [429]. A higher oxygenated isoprenoid 3-hydroxy-3-methylbutan-2-one **238**, is a volatile constituent of ambrosia beetles [430] and induces an extremely high electrophysiological response in the antenna of *Xyloterus lineatus* [431].

The almost ubiquitous terpenoid 6-methyl-5-hepten-2-one may be produced either by degradation of a geranial precursor (oxidative cleavage of the allylic-double bond or a retroaldol type reaction) or by chain elongation of β,β-dimethylalkyl pyrophosphate with acetoacetate followed by decarboxylation. Reduction of 6-methyl-5-hepten-2-one yields the corresponding alcohol, sulcatol **239**, which is the aggregation pheromone of *Gnathotrichus* spp [432–434]. These ambrosia beetles produce species specific mixtures of the sulcatol enantiomers, and the natural proportions are essential for maximum response. Oxidation at the double bond of sulcatol (e.g. epoxidation) followed by ring closure will yield either 2-(1-hydroxy-1-methylethyl)-5-methyltetrahydrofuran, pityol **240**, or 2,2,6-trimethyl-3-hydroxytetrahydropyran, vittatol **241**. The elm bark beetle *Pteleobius vittatus* uses *cis*-pityol and *cis*-vittatol of as yet unknown absolute configuration as part of its aggregation pheromone [435]. Males of *Pityophthorus pityographus* release trans-pityol showing (2*R*,5*S*)-configuration [436]. The same stereoisomer is part of the aggregation pheromones of other *Pityophthorus* species: in *Pityophthorus carmeli* it is produced by the males and in *Pityophthorus nitidulus* as well as in *Pityophthorus setosus* by the females [437]. Moreover, females of cone beetles, *Conophthorus* spp, also produce (2*R*,5*S*)-pityol as an aggregation pheromone [438, 439]. The structural relations



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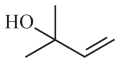

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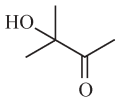

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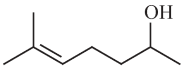

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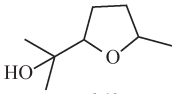

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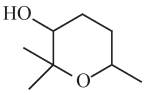

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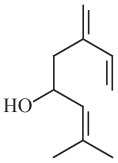

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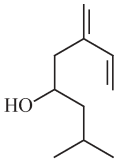

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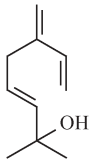

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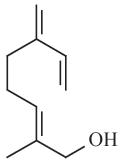

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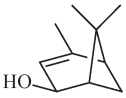

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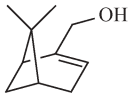

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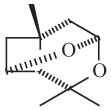

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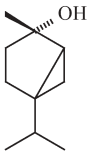

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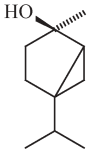

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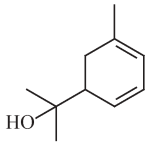

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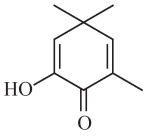

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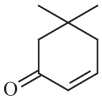

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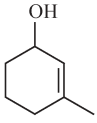

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Scheme 26

between **239**, **240**, and **241** are essentially the same as those between linalool and the furanoid or pyranoid forms of linalool oxide.

Monoterpenes play a particularly important role in host selection and mass aggregation of bark beetles. Insects attacking conifers have to overcome both physical and chemical obstacles as sticky and toxic oleoresin is involved in the defence mechanisms of trees. Bark beetles developed a series of strategies to survive which include detoxification through oxygenation. These oxygenation products may in turn be used as chemical signals indicating the attempts of an individual insect to attack a tree. Allylic oxygenation or hydration of unsaturated monoterpene hydrocarbons followed by secondary reactions such as further oxidation, hydrogenation, or rearrangement seem to be important mechanisms in the generation of bark beetle pheromones [440, 441] (Scheme 26).

Whereas some species oxidize host terpenes more randomly, producing an array of rather unspecific volatiles with little information, others use highly selective enzyme systems for the production of unique olfactory signals. However, apart from transformations of monoterpene hydrocarbons of host trees, oxygenated monoterpenes may well be biosynthesized de novo by the beetles (see below).

None of the monoterpene pheromones of bark beetles is represented by a specific compound per se; however, species specificity of the signal is accomplished by qualitatively and quantitatively fine-tuned mixtures including enantiomeric proportions.

The myrcene derivatives ipsdienol **242**, and ipsenol **243**, the first pheromone components identified from bark beetles [442], are typical male-specific aggregation pheromones of many Ips species, but they also play a role in host colonization by other species such as *Pityokteines* [443, 444] or *Xylocleptes bispinus* [445] (which attacks *Clematis vitalba* and is, thus, no truly conifer-breeder). Enantiomeric composition of these monoterpene alcohols is instrumental with respect to the behaviour mediating capacity of the signal [446], even in different populations of the same species [447]. The corresponding ketones, ipsdienone and ipsenone, were found in several *Ips* species, however, their biological significance is not yet clear. They may well be involved in transformation reactions leading from ipsdienol to ipsenol [448, 449]. The tertiary alcohol amitinol **244**, represents a product of an allylic rearrangement of ipsdienol [450, 451]. Another product of a formally allylic oxidation of myrcene, *trans*-myrcenol **245**, was also identified as a pheromone of *Ips* species [452].

While earlier it was generally thought that the acyclic monoterpene alcohols **242–245** are derived from the host tree's oleoresin component, myrcene [453], more recent results clearly show that at least in some species they are produced de novo [454–456].

Oxygenated monoterpenes which are found in almost every bark beetle species attacking coniferous trees, include *cis*-verbenol **246**, *trans*-verbenol **247**, and myrtenol **248**, representing primary products of allylic oxidation of the host terpene α-pinene **45**. Further oxidation of **247** or **248** leads to the

corresponding carbonyl compounds verbenone and myrtenal, which, too, are common bark beetle volatiles. 1,4-Elimination of water from verbenol yields verbenene **249**, which was found as a behaviour-mediating volatile emitted by females of *Dendroctonus rufipennis* [457]. Among the bicyclic terpenes, *cis*-verbenol is a particularly important component in the aggregation pheromones of *Ips* spp., whereas *trans*-verbenol is used by *Dendroctonus* spp. Both sexes of *Ips* species oxidise α-pinene enantioselectively [458, 459]: (4*S*)-*cis*-verbenol **246** is produced from (–)-α-pinene, whereas (+)-α-pinene yields (4*S*)-*trans*-verbenol **247**. Verbenone, which in bark beetles appears to be largely formed from verbenols due to the action of associated microorganisms [460, 461] seems to act as a general inhibiting signal which the beetles use to avoid overpopulation and which induces shifting of the attack to another tree [442, 462].

The close relationships between weevils and bark beetles becomes evident in the fact that (*E*)-ochtodenol **218**, and grandisol **214**, are components of the pheromone bouquet of *Pityogenes quadridens* [463]. In related *Pityogenes* species as well as in *Pityophthorus pityographus* grandisol shows (1*R*,2*S*)-configuration. The tricyclic acetal, lineatin **250**, a higher oxygenated derivative of grandisol (showing an additional oxygen at the position complementory to carbon 4 in ipsdienol) is an aggregation pheromone of several ambrosia beetles, *Xyloterus* (*Trypodendron*) spp. The natural product was shown to be the (1*S*,4*R*,5*S*,8*S*)-enantiomer [465, 466].

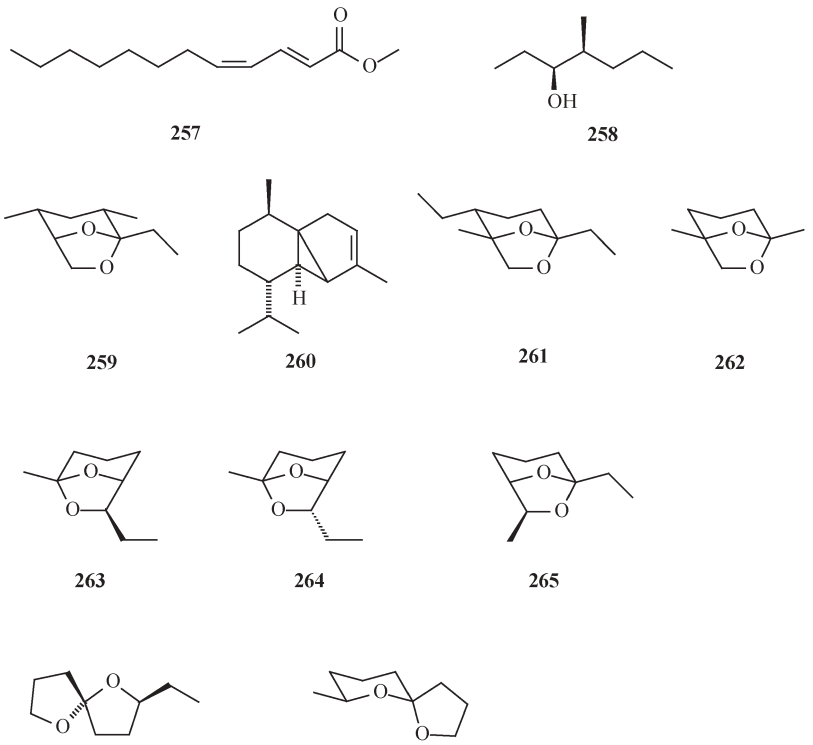
In *Polygraphus poligraphus* the (4*R*)-enantiomer of terpinen-4-ol **234**, acts as an aggregation pheromone [467]. The compound is accompanied by the thujanols **251** and **252** which may be biogenetically close to terpinen-4-ol and keep the same configuration at C4 [440].

The interesting *m*-menthadienol (3*S*)-1-methyl-5-(1-hydroxy-1-methylethyl)-1,3-cyclohexadiene **253**, is produced by *Ips sexdentatus*, boring under stress in 3-carene-rich, highly resinous pine trees and possibly released as a kind of warning signal to conspecifics to keep off [463].

2-Hydroxy-4,4,6-trimethyl-2,5-hexadien-1-one, lanierone, **254**, is a component of the complex aggregation signal of male *Ips pini* [468]. The carbon skeleton of **254** is the same as in isophorone **255**, which has been identified as a volatile constituents of females of *Ips typographus*. Whether these compounds are degradation products of higher terpenes awaits further investigations.

Another cyclohexane derivative is represented by 3-methyl-2-cyclohexen-1-ol seudenol **256**, a component of the female produced aggregation pheromone of Douglas-fir beetles, *Dendroctonus pseudotsugae* [470]. Enantiomeric compositions of the natural compound are reported to range between (*R*):(*S*)=2:1 and almost racemic [471]. Again, the product of an allylic rearrangement, 1-methyl-2-cyclohexen-1-ol, has been identified as an accompanying attractive compound [472]. The biosynthesis of **256**, and that of the corresponding ketone which acts as an intraspecific repellent (similar to verbenone in other species) is unknown, however, a simple acetogenin like 2,6-heptandione (derived from a fatty acid?) would easily produce 3-methyl-2-cyclohexen-1-one upon intramolecular aldol condensation.

An open chain fatty acid derivative is methyl (2*E*,4*Z*)-dodecadienoate **257**, an important component of the male produced aggregation pheromone of *Pityogenes chalcographus* [473]. A behaviour releasing capacity of ethyl dodecanoate, which has been found in several other *Pityogenes* spp [463], needs to be tested. Compounds with a chain length similar to the ester **257** are undecanal and decanal as well as 2-undecanone, 2-decanone, and 2-nonanone which apart from α- and β-pinene **45**, **46** were identified as attractive components of the olive bark beetle *Phloeotribus scarabaeoides* [474]. Nonanal fits to this row; it was found to be present in many bark beetle species; however, no significant behaviour mediating capacity of this compound has been reported. Somewhat shorter is 2-heptanol a principal pheromone constituent produced by female *Dendroctonous jeffreyi* [475]. The structure of (3*S*,4*S*)-4-methyl-3-heptanol **258**, strongly suggests a biosynthesis involving three propanoate units according to Fig. 2. The compound is an important component in the aggregation pheromones of several *Scolytus* species [476], whereas its (3*R*,4*S*)-diastereomer acts as a trail pheromone of the ant *Leptogenys diminuta* [477]. The corresponding ketone was also identified in *Scolytus* spp.; however, it did not decisively contribute to the biological activity of the pheromone bouquet [478].



257 258 259 260 261 262 263 264 265 266 267

Scheme 27

A group of bark beetle pheromones is represented by alkylated 6,8-dioxabicyclo[3.2.1]octanes. The biological significance, mass spectrometric fragmentation, and syntheses of these bicyclic acetals have been extensively reviewed [479]. An important pheromone component of several *Scolytus* species is (1*S*,2*R*,4*S*,5*R*)-multistriatus **259** [480, 481]. In the smaller European elm bark beetle, *Scolytus multistriatus*, it forms the aggregation signal along with (3*S*,4*S*)-4-methyl-3-heptanol **258** and the host tree sesquiterpene (–)-a-cubebene **260**. Similar to the alcohol **258**, the biosynthesis of the acetal **259** may involve propanoate units.

The male produced aggregation pheromone of the beech bark beetle, *Taphrorychus bicolor* is (1*S*,2*R*,5*R*)-bicolorin **261** [482, 483]. Its carbon skeleton may represent a rearranged terpene.

Frontalin **262** is a widespread pheromone of *Dendroctonus* species [285]. In those cases where the enantiomeric composition of naturally occurring frontalin is known, the (1*S*,5*R*)-enantiomer is always dominating. In females of *Dendroctonus frontalis*, it shows an enantiomeric excess of 70% [481] while males of *Dendroctonus simplex* produce it in high enantiomeric purity [483]. The biosynthesis of frontalin may involve 6-methyl-6-hepten-2-ol as precursor which upon epoxidation and ring closure would yield **262** [483]. The beetles produce the compound de novo along a mevalonate pathway [486, 487]. Interestingly, frontalin (unknown configuration) has been identified in the temporal gland secretion of male Asian elephant [488] and in the *Alnus* spp. red alder and Sitka alder [489].

Other important *Dendroctonus* pheromones are *exo*-brevicomin **263** [481, 490] as well as endo-brevicomin **264** [490]. In the monogamous *Dendroctonus* species, frontalin and brevicomin are part of intriguing dialogues between the sexes: attracted to the resin components of host trees, females of the southern pine beetle, *Dendroctonus frontalis*, release frontalin and the oxygenated monoterpene *trans*-verbenol **247** to attract both males and females [491]. The males joining the females strongly increase the attractivity of the system by contributing (1*R*,5*S*,7*S*)-*endo*-brevicomin [492, 493]. In contrast, females of the western pine beetle, *Dendroctonus brevicomis*, produce (1*R*,5*S*,7*R*)-*exo*-brevicomin which also attracts both sexes with a preponderance of males; after arrival, these release (1*S*,5*R*)-fontalin which is predominantly attractive to females [494]. As may be seen, brevicomin and frontalin are not always produced by the same sex. Brevicomin frequently occurs as a mixture of diastereomers with a large excess of the *exo*-isomer. In the mountain pine beetle, *Dendroctonus ponderosae*, males produce highly pure (1*R*,5*S*,7*R*)-*exo*-brevicomin [481, 495, 496]; however, the enantiomeric excess in the accompanying (1*R*,5*S*,7*S*)-*endo*-brevicomin ranged only between 65–70% depending on the population. The brevicomins were also identified in *Dryocoetes* species. Males of the European *Dryocoetes autographus* release the attractive compounds upon feeding [497]. Again, *exo*-brevicomin proved to be the very pure (1*R*,5*Z*,7*R*)-isomer, while *endo*-brevicomin showed an enantiomeric excess of only 63%. The American *Dryocoetes confusus* uses *exo*-brevicomin [498], and the same is true for

Dryocoetes affaber [499]. In the case of brevicomin, bark beetles seem to make use of all degrees of freedom which are opened by a compound showing two chiral centres: species specific mixtures may be generated by differences in relative proportions of enantiomers and diastereomers as well as by release of different absolute amounts. It is interesting to note that the parent carbon skeleton of the brevicomins is represented by (1*R*,5*S*)-6,8-dioxabicyclo[3.2.1]octane, while the other bicyclic acetal pheromones are alkylated enantiomers thereof. The biological significance of oxygenated brevicomins that have been identified in volatiles of the mountain pine beetle, *Dendroctonus ponderosae* [500], needs to be clarified. The same is true for an "*iso*-*exo*-brevicomin" **265** which compared to natural *exo*-brevicomin shows a kind of reverse substitution pattern and keeps (1*S*,5*R*,7*S*)-configuration, basically the opposite configuration of **263** [500]. The biosynthesis of *exo*-brevicomin has been thoroughly investigated in *Dendroctous ponderosae* [501, 502]. There is strong evidence that the compound is derived from the fatty acid pool and produced via an unsaturated ketone, 6-nonen-2-one, through epoxidation and ring closure. Similar to frontalin, the occurrence of brevicomin is not restricted to beetles as (1*R*,5*S*,7*S*)-*endo*-brevicomin (only 30% enantiomeric excess) was found among the volatiles of the orchid, *Ophrys speculum* [503].

Apart from those reviewed in the chapter written by Mori and in reference 479 of this chapter, only a few syntheses of the bicyclic acetals mentioned above have been published [504–506].

The spiroacetal **266**, chalcogran, is an important component in the male produced aggregation pheromone of spruce beetle, *Pityogenes* spp. [22, 507]. In *Pityographus chalcographus* it occurs as a pair of diastereomers showing (2S,5R)- and (2S,5S)-configuration [508, 509]. The weak biological activity of chalcogran is dramatically enhanced by the ester **257** [510, 511]. Field tests with pure stereoisomers of chalcogran showed that the biological activity rests with the (2*S*,5*R*)-enantiomer while its (2*S*,5*S*)-diastereomer is inactive. Racemic chalcogran proved to be strongly attractive to a predator, the Ostomid beetle, *Nemosoma elangatum* [512]. Similar to some bicyclic acetals, **266** was found to be a component of flower volatiles [513]. The spiroacetal conophthorin **267**, an isomer of chalcogran, plays a dual role in bark beetle-communication. The biological significance, mass spectrometric fragmentation and syntheses of volatile spiroacetals, has been extensively reviewed [514]. Apart from bark beetles, the relatively widespread **267** was found in the poison glands of wasps, in fruit flies, orchids, and in a couple of tree species [512]. In general, naturally occurring conophthorin shows (2*S*,5*S*)-configuration of rather high enantiomeric purity. In several bark beetle species, the male produced **267** shows a repellent effect as in *Leperisinus varius* and *Cryphalus piceae* [514] as well as in pine cone borers, *Conophthorus* spp. [438, 439], and in *Pityophthorus* spp. [437]. This may be interpreted as a "spacer" signal used during male-male competition and to ensure enough space for a successful establishment of the new brood system. In *Pityophthorus carmeli* conophtorin **267** and pityol **240** make up the male produced aggregation pheromone [437].

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