Insect-Plant Interactions – Metabolism of Plant Compounds to Pheromones and Allomones by Lepidoptera and Leaf Beetles

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Pyrrolizidine alkaloids are taken up from plants by various butterflies and moths belonging to the Danainae, Ithomiinae, and Arctiidae, which use them for defence and for the production of male pheromones. A complex distribution scheme of these plant alkaloids by the insect has been established in some species. The transformations involved include conversion into insect alkaloids, metabolism to male pheromones, and transfer of alkaloids from males to females and further into eggs. While these lepidoptera selectively sequester certain compounds from plants in a complex pattern, the leaf beetle *Chrysomela lapponica* follows a different strategy. Glycosidically bound alcohols present in leaves of their host-plants are liberated and transformed into esters, which are used for defence. Related beetles rely on host-derived single compounds such as salicyl aldehyde or de novo synthesized iridoid monoterpenes. Several aspects of these insect-plant relations, including biosynthetic transformations of plant compounds by the insects, are discussed herein.

Introduction

Insects very often have close relationships with plants: They use them among other things as living habitat and as food source. Plant chemicals may play an important role in such relationships. Some examples of chemical interactions between plants and insects are given in this microreview, while references to other aspects can be found elsewhere.[1–3]

Plants utilize a wide array of methods to protect themselves from consumption by herbivores. One of the strategies hinges on secondary metabolites that are toxic to potential herbivores.[1] While these compounds may be avoided by most plant feeders, others may be able to cope with them. This opens a new food source for such specialists, for which they may have fewer competitors. The benefit of being a tolerant herbivore may lead to the disadvantage of total dependence on one or few foodplants. A close evolution between herbivores and plants can be expected. Plants might try to deter herbivores by refining their arsenal of chemicals, while the latter try to adapt to such changes.[2][4] This leads to monophagous, oligophagous, and polyphagous feeding strategies of herbivores.

Pyrrolizidine Alkaloids and Lepidoptera

Pyrrolizidine alkaloids (PA) have been identified in more than 560 plant species, belonging mostly to the families Apocynaceae, Asteraceae, Boraginaceae, Fabaceae, and Orchadaceae. They consist of a necic base part containing the

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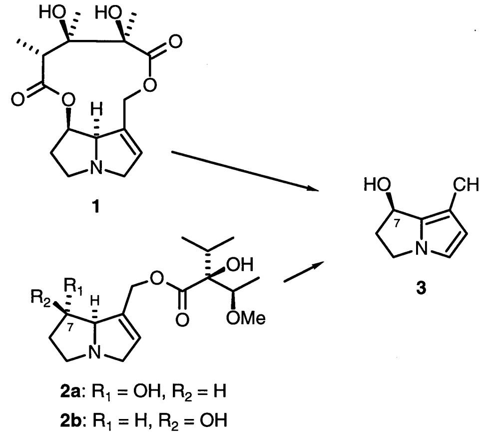
pyrrolizidine ring system, which is esterified with a mono- or diacid (necic acid) (see e. g. **1, 2**). Almost 400 different PA have been identified in these plants.[5] One of their functions seems to be the deterrence of generalist herbivorous insects.[5][6] Some insect species from different orders are able to tolerate these alkaloids and even use them for their own defence.[5]

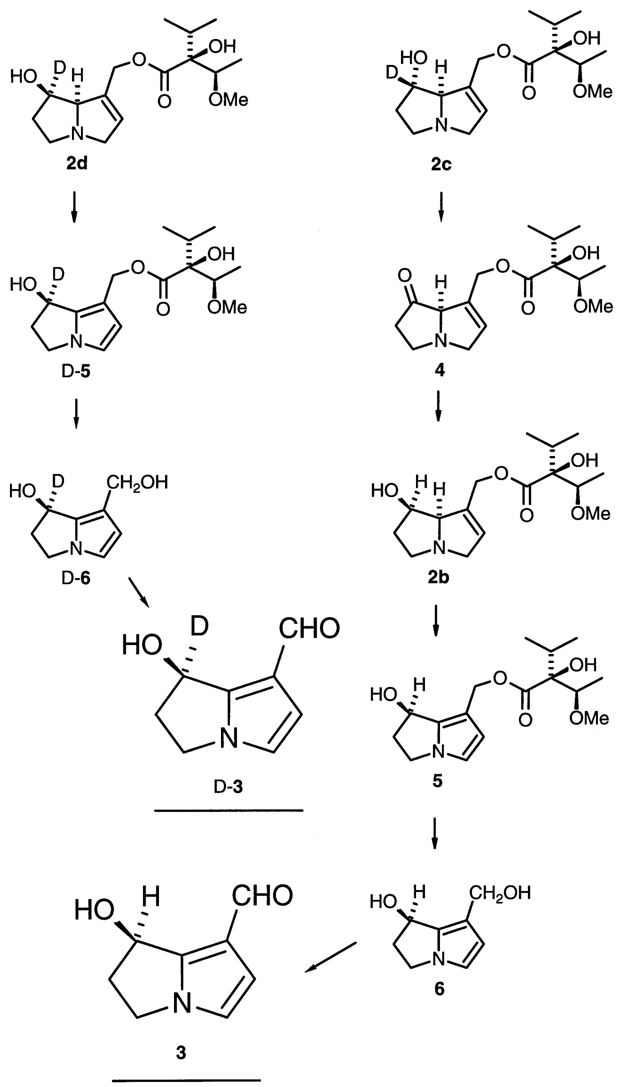
Scheme 1



Larvae of the arctiid moth *Creatonotos transiens* even ingest pure PA (pharmacophagy: sequestration of compounds for non-nutritional purposes[7]). Males metabolize these compounds to the related dihydropyrrolizine hydroxydanaidal (**3**), a pheromone of the adult males.[8] When the larvae are fed with the pyrrolizidine alkaloid monocrotaline (**1**), with (*R*)-configuration at C-7, (*R*)-**3** is formed by the insect. Surprisingly, the feeding of heliotrine (**2a**) with (*S*)-configuration at C-7 also leads to formation of (*R*)-**3** by *C. transiens*.[9] In the bodies of the respective larvae, a mixture of **2a** and its 7-epimer **2b** could be found.[10] To elucidate the biosynthetic pathways underlying these transformations, we performed feeding experiments with deuterated heliotrine (**2c**) and deuterated 7-epiheliotrine (**2d**). These alkaloids were prepared by Swern oxidation of the commercially available **2a** to yield the unstable ketone **4**. Immediate reduction with sodium borodeuteride furnished the pure epimeric alkaloids after chromatographic separation.[11] By feeding these and other alkaloids to *C. transiens* and analysis of the larvae, the pupae, and the adults, the biosynthetic pathway from **2a** to **3** could be deduced.[11] In summary, heliotrine is epimerized at C-7 by an oxidation-reduction process with the ketone **4** as intermediate. The involved enzymes selectively recognize 7(*S*)-configured alkaloids, because no loss of the deuterium label is observed after feeding of **2d**. Just prior to eclosion of the pupae, the unstable pyrrole **5** is formed from **2b**. This is followed by cleavage of the ester group to yield (*R*)-dehydroretronecine [(*R*)-**6**] which is finally oxidized to **3**.[11]

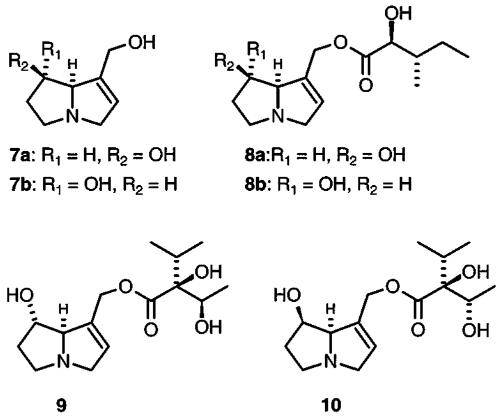
The necine bases retronecine (**7a**) and heliotridine (**7b**) are not intermediates of the biosynthesis. When **7a** is fed, the insect alkaloid creatonotine (**8a**) is formed by esterification with an insect derived necic acid,[11][12] which in turn is transformed into **3**. Esterification also occurs after feeding **7b** with 7(*S*)-configuration, and the resulting alkaloid is epimerized. Thus, the two epimeric alkaloids creatonotine (**8a**) and isocreatonotine (**8b**) are present in the insects. Because all PA are oxidized to PA-*N*-oxides after uptake by insects,[13] the transformations leading to **5** are most likely to proceed with the alkaloids in the *N*-oxidized state in *Creatonotos*. As *Creatonotos*, the day flying ithomiine butterfly *Mechanitis polymnia* is able to epimerize C-7 as well as C-3′ of the necic acid to form its major defensive alkaloid, lycopsamine (**10**), when fed e. g. with rinderine (**9**).[14]

Scheme 2



The function of the pheromone **3** is perhaps best understood in another arctiid moth, *Utetheisa ornatrix*. The males expand their coremata (scent emitting organs found exclusively on males of a species) at close range during courtship, thus disseminating their pheromone. The amount of **3** on the coremata is directly correlated to the amount of PA ingested during the larval stage.[15][16] The male transfers PA to the female during copulation, and alkaloids originating from both parents are then deposited in the eggs to protect them from predators.[17] The female seems to choose

Scheme 3



males depending on their load of PA, because these protective alkaloids are not available to the larvae in unlimited amounts. The chemical ecology of PA and insects has been reviewed in more detail in several excellent articles.[5][16][18][19]

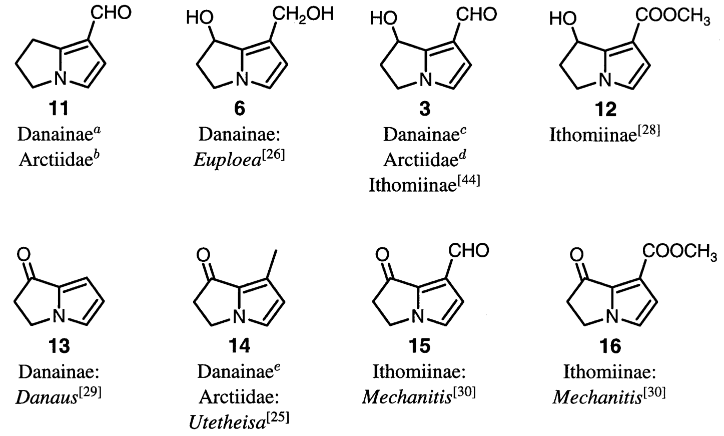
A behavior modifying function of dihydropyrrolizines occurring in male pheromone glands has been established only in a few cases. For the arctiids *Phragmatobia fuliginosa* and *Phyrractia isabella*, a short display of coremata containing **3** during courtship at close range is essential for success.[20] In contrast, *Creatonotos* seems to attract conspecifics with **3** over a longer range.[21] The amount of PA ingested determines even the size of the coremata and the amount of **3** produced in this species.[22] The queen butterfly, *Danaus gilippus* (Danainae), uses the related dihydroyrrolizine danaidone (**14**) as courtship pheromone,[23] and, like *Utetheisa*, transfers PA to the female during copulation.[16] In another danaine, *Idea leuconoe*, it has been show that **14** and some other compounds (see below) can attract females over a range of several meters.[24]

Other Lepidoptera belonging to the Arctiidae, Danainae and Ithomiinae also pharmacophagously take up PA for defence and for the production of male pheromone gland constituents. The function of these compounds has not been tested. A list of the dihydropyrrolizines from butterfly pheromone glands identified so far is given in Scheme 4. Male arctiid moths use either hydroxydanaidal (**3**) or the related compound danaidal (**11**), while danaine butterflies can also contain danaidone (**14**). The only exception from this rule is *Utetheisa pulchelloides*, the pheromone glands of which contain a 100 : 1 mixture of (*R*)-**3** and **14**.[25] The unstable diol **6** has been identified in silylated extracts of pheromone glands of *Euploea* spp. (Danainae),[26] but this may be an artefact because PA-*N*-oxides, possibly present in the extracts, are known to form **6** under silylating conditions.[27] The ithomiine butterflies, closely related to the Danainae, also use **3**, as well as methyl hydroxydanaidoate (**12**).[28] Recently we identified some new dihydropyrrolizines. Nordanaidone (**13**) occurs as a minor component in the hairpencils of *Danaus affinis* besides **3**, **11**, and **14**.[29] The keto derivatives oxodanaidal (**15**) and methyl oxodanaidoate (**16**) are present in the wing scent glands of *Mechanitis* spp. (Ithomiinae).[30] In all cases investigated, only the (*R*)-enantiomer of **3** occurs naturally.[31]

Most Lepidoptera that use PA for pheromone production employ only the necine base as precursor. The exception are some ithomiines and some of the related danaines. Several ithomiine butterflies use the lactone ithomiolide A (**17**), besides the PA derivatives **3** and **12**, as male pheromone component.[28][32] Minor amounts of the keto derivative ithomiolide B (**18**) are also present in at least one species.[33] The lactone **17** has been proposed to act as a male attractant[34] or as an intra- and interspecific repellent.[32] Ithomiolide A may well be a derivative of the necic acids of PA such as **9** or **10**. Hydroxylation of one of the methyl groups of the isopropyl side chain and lactone formation leads to this structure. Because at least three of the four possible stereoisomers of 2,3-dihydroxy-2-(1-methylethyl)butanoic acid (viridifloric and trachelanthic acids, **19a-d**) occur in PA naturally,[5] the absolute configuration of **17** was unknown. By synthesis of pure enantiomers starting from (*S*)-3-methyl-4-butanolide and gas chromatographic separations on a chiral cyclodextrin phase (chiral gas chromatography, CGC) the absolute configuration of ithomiolide A in the ithomiine *Prittwitzia hymaenea* could be determined to be (1′*S*, 2*S*, 3*R*).[33] Thus, the pheromone is derived from PA containing (−)-viridifloric acid (**19a**), like **10**, the major alkaloid of many Ithomiinae.[35] Interestingly, other alkaloids can be converted by the butterflies to just this compound (see above).[14]

Males of the giant white danaine *Idea leuconoe* possess, like other danaines, so-called hairpencils, which are used during courtship. These glands contain a complex mixture of volatile compounds embedded in a lipidic matrix consisting of alcohols, ketones, alkenes and alkanes.[36] Among the volatiles are danaidone (**14**), the first dihydropyrrolizine isolated from an insect,[37] and the β-lactone **20**.[24][36] The absolute configuration of **20** could be established by synthesis and CGC to be (2*S*, 3*S*).[38] Thus, this β-lactone can easily be formed by lactonization from the necic acid (−)-viridifloric acid (**19a**). Lycopsamine (**10**) and other alkaloids containing **19** as the necic acid part are ingested by the larvae when feeding on ist host, *Parsonsia laevigata*.[39] Minor amounts of the β-lactone **21**, originating from the corresponding necic acid present in the host alkaloids, could also be detected in the pheromone glands. Females are visually attracted to the males and show an acceptance behavior if the male pheromone is present. To elicit this response, a mixture of **19**, **14**, and the unusual thioterpene geranyl methyl thioether (**22**) is necessary.[24] An even better response could be obtained by using a mixture of twelve compounds identified from the pheromone glands. Besides **20**, **14**, and **22**, this mixture contained phenol, *p*-cresol, benzoic acid, (*E,E*)-farnesol, (*Z*)-9-tricosene, (*R*)-mellein (**23**), and a series of 6-hydroxy-4-alkanolides ranging from C_{10} to C_{13}. The adult butterflies are attracted to mellein, which is produced by the endophytic fungus, *Lasiodiplodia theobromae*, living in the butterfly hostplants. This fungus has also been isolated from the butterfly surface.[40] A similar relationship has been established for the bumblebee wax

Scheme 4



11 Danainae[a] Arctiidae[b]

6 Danainae: *Euploea*[26]

3 Danainae[c] Arctiidae[d] Ithomiinae[44]

12 Ithomiinae[28]

13 Danainae: *Danaus*[29]

14 Danainae[e] Arctiidae: *Utetheisa*[25]

15 Ithomiinae: *Mechanitis*[30]

16 Ithomiinae: *Mechanitis*[30]

[a] *Danaus*,[26][48][65–67] *Tirumala*[25][68]

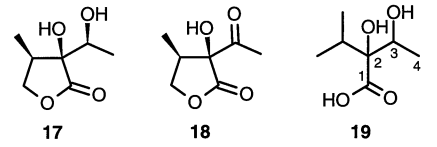
[b] *Panaxia*,[69] *Phragmatobia*,[70][71] *Pyrrharctia*,[70][71] *Teracotona*,[47] *Utetheisa*[72]

[c] *Amauris*,[48] *Danaus*,[26][28][65][68] *Euploea*,[26][28][66–68] *Ideopsis*,[25][68][73] *Parantica*,[25][65][67][68] *Tirumala*[25][66–68]

[d] *Cisseps*,[20] *Creatonotos*,[9][74] *Estigmene*,[25][71] *Panaxia*,[69] *Pareuchaetes*,[75] *Phragmatobia*,[70][71] *Pyrrharctia*,[70][71] *Teracotona*,[47] *Utetheisa*[25][72][76]

[e] *Amauris*,[48][77][78] *Danaus*,[26][28][48][65–68][77][79] *Euploea*,[28] *Idea*,[24][36] *Ideopsis*,[73] *Lycorea*,[25][37] *Parantica*,[25][43][65][68] *Tirumala*[25][48][65–68][77]

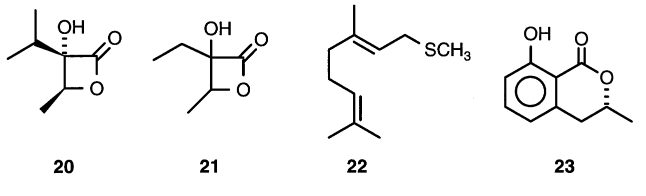
Scheme 5



a: (−)-viridifloric acid (2*S*,3*S*)
b: (+)-trachelantic acid (2*S*,3*R*)
c: (−)-trachelantic acid (2*R*,3*S*)
d: (+)-viridifloric acid (2*R*,3*R*)

moth, *Aphomia sociella*, which uses **23** as male pheromone, and the fungus *Aspergillus ochraceus*.[41] Mellein is also used as trail pheromone by some ants.[42]

Scheme 6

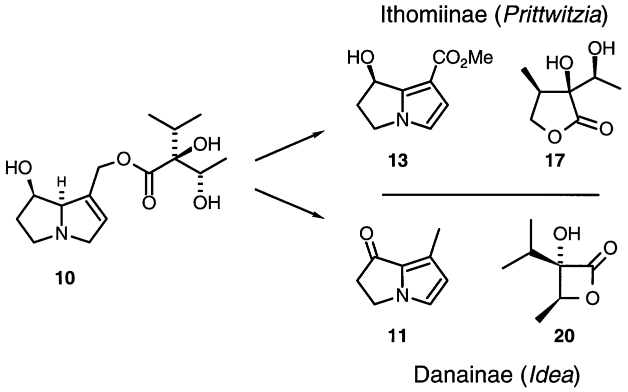


The use of both parts of the PA leads to different products in danaines and ithomiines. For example, *Prittwitzia hymaenea* and the danaine *Idea leuconoe* both use lycopsamine as a precursor for male pheromone components. While *P. hymaenea* pheromone glands contain a mixture of the γ-lactone **17** and the dihydropyrrolizine **12**, the respective glands of *I. leuconoe* contain the γ-lactone **20** and danaidone (**14**).

In many ithomiine species **3**, **12**, or **17** occur, together with other species-specific components, in male pheromone glands. The Ithomiinae are a family with more than 300 species in about 50 genera. Recently a phylogeny of these butterflies has been published.[43] During our investigations more than 30 species have been analyzed,[44][45] and PA derivatives identified in 15 genera. From these and literature data[28][32] it looks as though the ancestral genera belonging to the Melinaeini and Mechanitini only use dihydropyrrolizines derived from the necine bases such as **3** or **12**. The most recent genera belonging to the Godyrini use the lactone **17**, derived from necic acids, instead, while the intermediate genera contain both types of compounds. This shift toward the lactone can be explained by the need for unique signals. Dihydropyrrolizines like **3** can also be produced by plants[46] or by degradation of PA.[47] On the other hand, the lactone is not formed by plants or during degradation, and thus has a higher degree of uniqueness compared to the dihydropyrrolizines. Species specificity can be added to such a signal by biological separation (e. g. different habitats, dial activity, and so on) or by additional compounds. The latter is often observed in the pheromone gland composition of male butterflies.

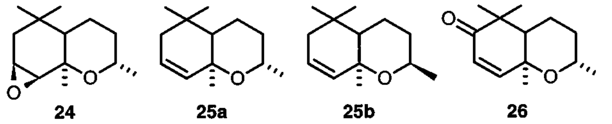
The pheromone bouquets of danaine butterflies contain complex mixtures with up to 150 components consisting of terpenes, acetogenins, aromatic compounds, and the mentioned alkaloids.[36][48] Some of these compounds may also be taken up by feeding or pharmacophagously like methyl *p*- and *o*-hydroxybenzoates by *Idea leuconoe*.[49] Certain *Euploea* species contain a main component in their hairpencils, which could be identified by synthesis and CGC to be (1*R*, 3*S*, 6*R*, 9*S*, 10*S*)-9,10-epoxytetrahydroedulan (**24**).[50]

Scheme 7



Recently, a synthesis of the pure enantiomer has been published.[51] The butterflies do not use the hairpencils only during courtship as other danaines, but also during patrolling flights. The exact function of the compound is still unknown. The epoxide **24** may be formed by oxidation of the dihydroedulan **25a**. The two diastereomers **25a** and **25b** have been identified in plants[52] and are both present in the scent glands of *E. klugii*, but only one is metabolized to **24**. It seems plausible that the dihydroedulans **25** are taken up by the butterfly from plants. Unfortunately, the foodplants of the adult butterfly are not known.[53] The North American Monarch butterfly, *Danaus plexippus*, contains the related (1*RS*, 3*SR*, 6*RS*)-8-oxodihydroedulan (**26**) as the main constituent of the hairpencils.[50][54] This species is the only danaine known that does not use a dihydropyrrolizine as a pheromone component. Although the butterflies have been observed on a wealth of plants, none has been investigated for the presence of **25**.

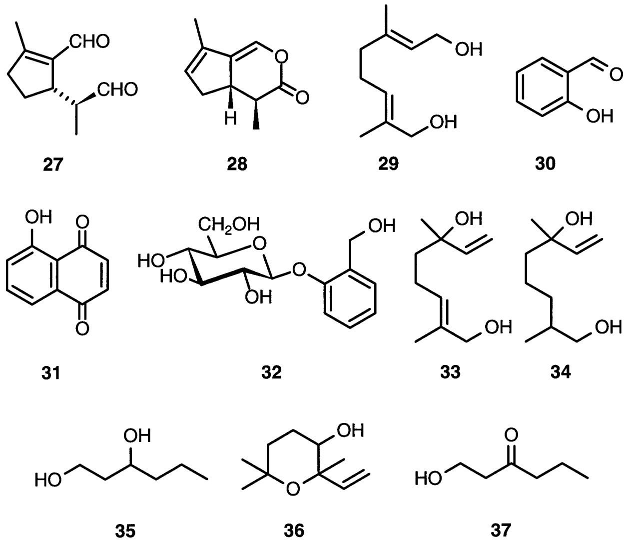
Scheme 8



Leaf Beetles and Their Hosts

Leaf beetles (Chrysomelidae), a large family with over 35 000 species, use a wide variety of chemicals to defend themselves against predators.[55] Many larvae of the Chrysomelina, Phyllodectina, Gonioctenina, and Paropsina use exocrine volatile secrections emitted by eversible dorsal glands to deter predators. The secretion can be retrieved, so that an economic use is assured. A number of species use iridoid monoterpenes such as the dialdehyde chrysomelidial (**27**) or the lactone plagiolactone (**28**).[55] These compounds are produced de novo by the beetles starting from 8-hydroxygeraniol (**29**).[56][57] Another group relies on the deterrent properties of single compounds, namely salicylaldehyde (**30**), benzaldehyde, or juglone (**31**). The larvae of *Chrysomela tremulae* lives on willow trees and ingests salicin (**32**) from it during feeding. By the action of a glucosidase and an oxidase, **30** is formed.[58] Similarly, **31** may be derived from glucosides of 1,4,5-trihydroxynaphthalene present in walnut trees, on which *Gastrolina depressa* feeds.[59]

Scheme 9



A different strategy is used by the larvae of *Chrysomela lapponica.* This species occurs in Central Europe on both willow and birch trees. Thus, one can observe the influences of the host plant on the composition of the defensive chemicals. Surprisingly, the secretion is totally different from the types described so far. This species uses a mixture of more than 60 volatile components to deter predators, which could be identified by GC-MS and synthesis of reference compounds.[60] The bouquet of larvae feeding on birch consists of isobutyric and (*S*)-2-methylbutyric acids and esters of these acids with a wide variety of alcohols. Most prominent compounds are esters with benzyl alcohol, 2-phenylethanol, and 8-hydroxylinalool (**33**) esterified at C-8. Diol esters are also present, the most prominent of which is 1,3-hexanediol (**35**), accompanied by glycol, 1,2-propanediol, and 1,4-hexanediol esters. Other minor esters are those formed with (*Z*)-3-hexen-1-ol, and the pyranoid linalool oxides **36**. Larvae feeding on willow showed a similar mixture, but contained additionally benzoic acid and the respective esters, while esters of **36** and 1,4-hexanediol were absent. In addition, esters of geraniol could be identified as minor constituents.[60]

The origin of the defensive compounds was investigated by analysis of plant constituents and feeding experiments with laballed precursors.[61] Application of $[D_8]$valine to the beetles led to labelled isobutyrates, showing that isobutyric acid is formed by the beetles from this amino acid. The acids are esterified with alcohols that originate mostly from the hostplant. Both glycosidically-bound and free alcohols can be present in leaves. In addition, enzymatic action may form additional alcohols during disruption of the leaves, as has been shown for the common leaf alcohol, (*Z*)-3-hexen-1-ol. This alcohol is formed from linolenic acid by the action of a lipoxygenase during cell damage.[62] When leaves of *Betula pendula* were macerated and stirred for 12 hours in water, large amounts of benzyl alcohol, 2-phenylethanol, (*E*)- and (*Z*)-8-hydroxylinalool (**33**) and their dihydro derivative **34**, as well as several C_6 green leaf compounds such as (*Z*)-3-hexen-1-ol, 1-hexanol, and the hitherto undescribed 1-hydroxy-3-hexanone (**37**) could be identified. These were accompanied by phenolics and carotenoid degradation products. The analysis of leaves in which the enzymes were deactivated prior to maceration showed that these alcohols occur glycosidically-bound, with the exception of most of the C_6 compounds. The same components are present in *Salix fragilis*, but are accompanied by several unique low molecular weight cyclic alcohols such as 6-hydroxy-2-cyclohexenone.

Feeding experiments with [D_5]-(*Z*)-3-hexen-1-ol showed that the larvae indeed take up alcohols from leaves and transform them into esters. However, this is not the only pathway leading to defensive components. When laballed phenylalanine is fed, small amounts of labelled 2-phenylethyl esters can be detected, showing the ability of the larvae to synthesize some alcohols themselves. Feeding of deuterated **37** led to highly labelled 1,3-hexanediyl esters. The larvae obviously reduce the hydroxyketone **37** to the diol **35** and then form the hexanediyl esters.

As an overall pattern, primary and secondary alcohols are esterified by the larvae, while tertiary and of the latter compounds phenolic hydroxyl groups remain free. Derivatives are not normally transferred into the defensive glands. Specific alcohols such as **35** are synthesized by conversion of suitable precursors such as **37** by the larvae.

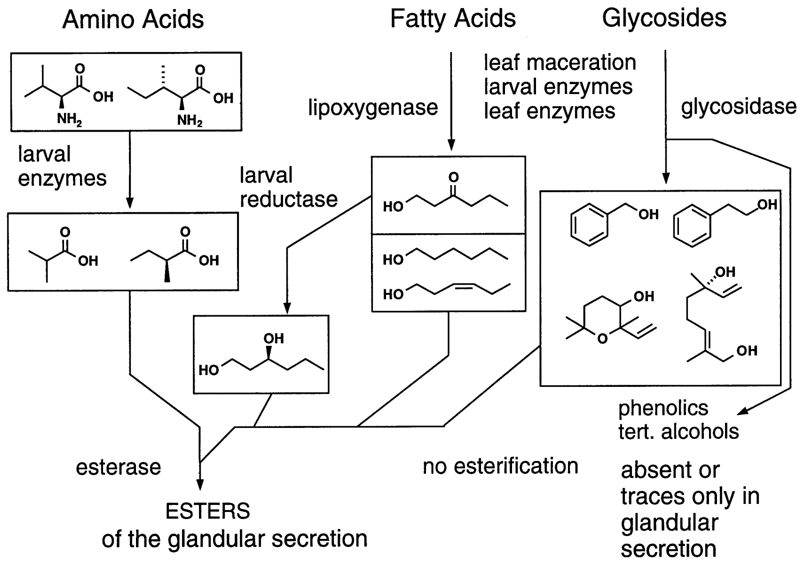
Additionally, specific uptake pathways must exist, because some alcohols fitting in this scheme are not transformed into defensive esters. This is exemplified by 1,2-cyclohexanediol, which occurs in large amounts glycosidically-bound in leaves of *S. fragilis*,[61] but respective esters could not be detected in the defensive secretion. Also, some differences in the enantiomeric composition of leaf alcohols and defensive secretions can be observed. While the (*R*)/(*S*) ratio of the terpene diol **33** of *B. pendula* is 3:2 and that of *S. fragilis* 7:3, the corresponding esters in the defensive secretion exhibits an 7:3 excess of the (*S*)-enantiomer.[60] Clearly, the larvae can form their arsenal of defensive compounds using two different host plants that share some common compounds.

The secretion of larvae fed on willow also contained large amounts of free salicyl alcohol, but only traces of salicylaldehyde (**30**). No esters of salicyl alcohol could be found. Surprisingly, *C. lapponica* larvae from Finland feeding in willow were found to contain only small amounts of the esters, but large amounts of **30** instead.[63] Despite the fact that our strain originating from the Czech Republic had access to willow leaves containing the precursor of **30**, salicin, they produced the former aldehyde only in minute amounts. Thus, the defense system of *C. lapponica* seems to be related to that of other leaf beetles using **30** as a defensive compound. Nevertheless, some chemical relations to leaf beetles using de novo synthesized iridoid monoterpenes are also obvious. Their biosynthesis starts from geraniol, which is oxidized to 8-hydroxygeraniol (**29**),[56][57] the β-glucoside of which has also been identified in the defensive secretion of some beetle larvae.[64] Small amounts of glycosidically bound **29** are also present in leaves of *Salix fragilis* and it has been suggested that the larvae may obtain **29** from their foodplants, too. Allylic transposition of the hydroxy group can readily transform 8-hydroxylinalool into **29**, showing the close connection between the two terpenediols.

Conclusion

In this article different strategies of plant compound use by insects have been described. The mentioned Lepidoptera use specific compounds, PA, and communicate chemically to each other about it. They can even convert alkaloids to

Figure 1. Transformation of plant compounds by feeding larvae of *Chrysomela lapponica*



structures best suiting their needs. Leaf beetles have envolved different strategies including costly development of their own compounds (iridoids), reliance on a single effective compound (salicylaldehyde), or generation of an arsenal of compounds leading to a potentially broader acting defence. The case of *C. lappon*ica is also a nice example of natural combinatorial chemistry. The combination of two (or three) acids with alcohols and especially diols leads to a large number of compounds. The presented examples increase expectations that other striking examples of the use of chemicals in nature are waiting to be uncovered.

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