2.04 Insect Natural Products

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2.04.1 Introduction

With greater than 1 million described species, arthropods comprise more than 80% of all known animal species, and by some estimates make up roughly two-thirds of all extant species.[1,2] The phylum Arthropoda includes insects, spiders, ticks, lice, centipedes, shrimp, and crabs, as well as several less well-known groups. Arthropods are virtually ubiquitous worldwide, and many species play dominant roles in the ecology of their habitats. One commonly cited factor in the arthropod's 'phyletic dominance,' as termed by Meinwald and Eisner,[3] is their extensive use of small-molecule chemical signals. Arthropods use chemical signals for mate attraction and selection, for defense against predators and pathogens, and for the acquisition of prey. In fact, the extent to which the ecological interactions of arthropods are facilitated by small-molecule metabolites is only now becoming clear, and many novel types of chemical interactions remain to be identified.

Arthropod natural products are structurally diverse, including compounds derived from fatty acid, polyketide, terpenoid, nucleoside, and amino acid pathways, although the biosynthesis of most of these compounds has not yet been studied in detail (**Figure 1**). The biosynthesis of defensive metabolites among beetles and ants has been reviewed recently,[4] and a monograph devoted to insect natural product biosynthesis, *Biosynthesis in Insects*, by Morgan,[5] has recently become available. In addition to covering biosynthetic aspects, Morgan's text provides

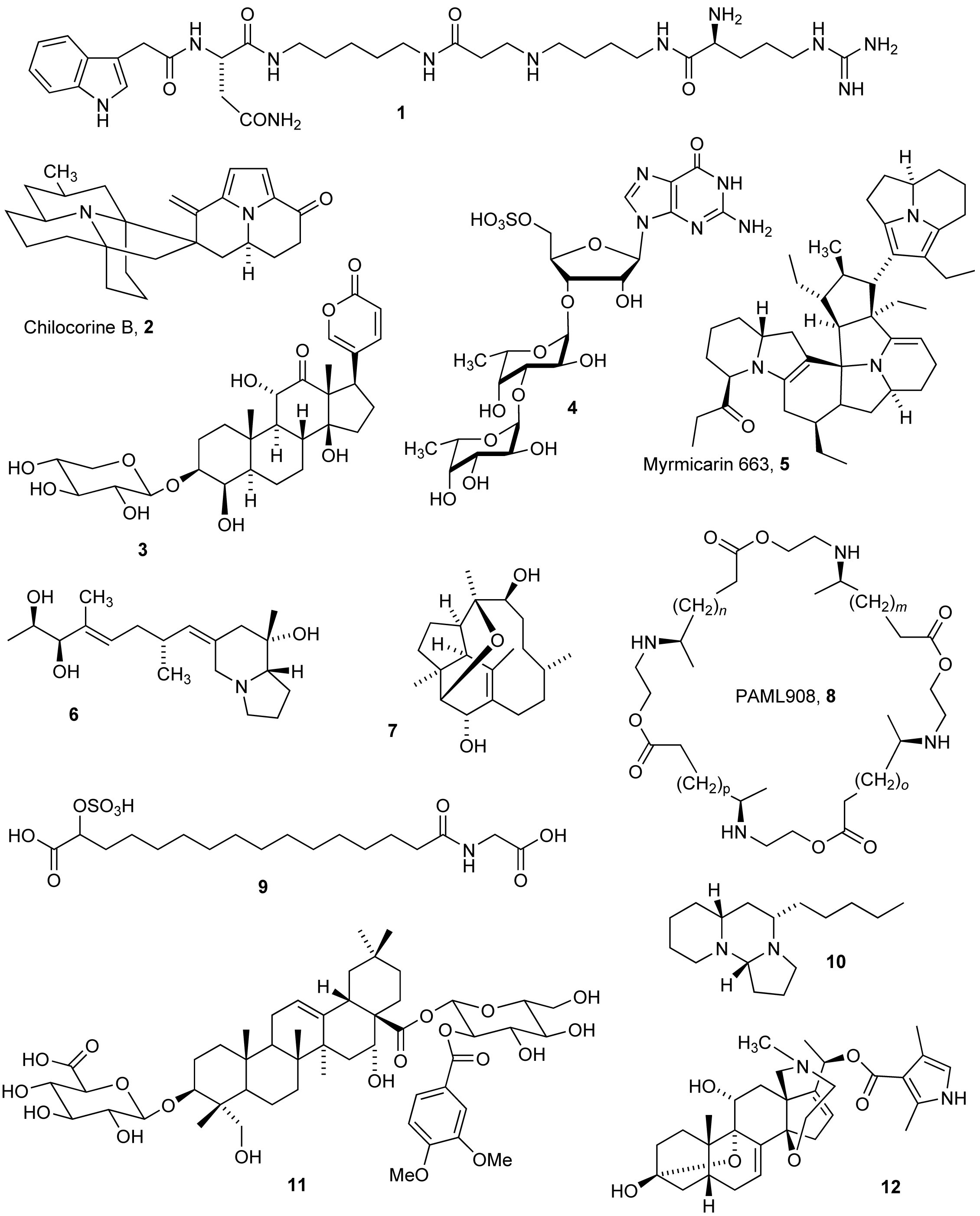


Figure 1 Examples of arthropod natural products from spiders (**1**, **4**), mites (**6**), ants (**5**, **7**, **10**), fireflies (**3**), termites (**7**), grasshoppers (**9**), and beetles (**2**, **8**, **11**, **12**).

an excellent overview of insect natural products, including many older examples that are not dealt with in this chapter. Compared to fungi and bacteria, arthropods generally produce less polar compounds, which mostly are of polyacetate or fatty acid origin, with structures derived from polyketide (or polypropanoid) pathways being less common. Furthermore, arthropod-derived compounds are more likely to possess carbocyclic ring systems and chemically reactive functional groups such as ketones or enamines. An additional layer of structural complexity is introduced in the biosynthesis of complex arthropod alkaloids such as the chilocorines and myrmicarins or the macrocyclic polyamines. These compounds are derived from oligomerization of several polyacetate- or fatty acid-derived building blocks resulting in unique oligocyclic or macrocyclic structures, for example, chilocorine B (**2**), myrmicarin 663 (**5**), and PAML908 (**8**) (**Figure 1**). Arthropod metabolic capabilities often vary greatly, even among closely related species, as well as within individual species between different life stages. In coccinellid beetles, for example, larvae, pupae, and adults are often found to produce very different types of defensive alkaloids (see Section 2.04.6.1).

Today, our knowledge of the structures and functions of small-molecule secondary metabolites in arthropods remains uneven. A few groups of organisms, including some species of ants, beetles, butterflies, moths, and spiders, have been chemically scrutinized in considerable detail, and as a result a relatively great number of structures have been identified from these species. However, most species of insects and other groups of arthropods, for example, crustaceans, remain largely unexplored. It is worthy of note that even for those cases where chemical analyses have led to the identification of new and often chemically fascinating structures, the biological roles of the identified compounds, perhaps with the exception of sex pheromones, have rarely been explored comprehensively. In most cases, the identified compounds have been assigned generic attributes such as 'irritant' or 'defensive,' without a detailed analysis of either their full ecological context or their molecular mode of action. In what Blum has termed 'semiochemical parsimony,' individual arthropod secondary metabolites frequently serve multiple ecological functions,[6] and our current understanding of many seemingly well-studied chemical–ecological interactions involving arthropods may in fact be largely incomplete. Furthermore, our understanding of the biochemical pathways involved in arthropod secondary metabolite regulation lags far behind that for other groups, such as plants, bacteria, and fungi. Only recently have chemical ecologists and chemical biologists begun to fully address these questions, and perhaps the current state of arthropod natural product chemistry can be best described as one of the change, where purely structure-oriented chemical prospecting is being supplanted by a focus on elucidation of the detailed molecular mechanisms underlying chemical–ecological interactions.[7]

The most well-known functions of secondary metabolites among arthropods include the use of pheromones for intraspecific communication, the employment of antipredatorial defensive agents, and the offensive use of paralytic and/or toxic agents, such as in the form of venoms, for the acquisition of prey. In recent years, considerable insight has been gained in all three categories, as well as in the discovery of heretofore unknown interactions (see Section 2.04.4.1). Fossil evidence of chemical defense in the insects reaches as far back as the Early Cretaceous period.[8] The chemical defense of insects has been reviewed as recently as 2005,[9] and earlier works dealing with chemical defense of ants,[10] beetles,[11–13] as well as of arthropods in general,[14–16] also exist.

In this chapter, arthropod pheromones and hormones will not be considered, except for a few example structures of important compound classes. These topics are dealt with in detail in Chapters 4.03 and 4.04. Our primary focus will be the defensive and venom chemistry of terrestrial arthropods, as well as any additional structures discovered as a result of general chemical prospecting in these animals. Biosynthetic origin and biological roles of the described compounds, as far as they are known, will be summarized briefly; however, for more extensive information on ecological functions or biosynthesis the reader should consult some of the many excellent reviews and monographs referenced. Throughout we will make an effort to point out indirect effects and benefits that can or have been gained through the study of arthropod natural products.

This chapter is organized primarily based on a classification of arthropod-derived compounds according to their putative biogenetic origin ('terpenoids,' 'polyketides') or specific structural features ('alkaloids,' 'nucleosides'). This approach allowed us to emphasize chemical characteristics and peculiarities that distinguish arthropod-derived compounds from other groups of natural products. Phylogenetic relationships are discussed only in specific cases where they directly relate to similarities in natural product profiles. With respect to our classification of arthropod natural products as terpenoids, fatty acid derivatives, or polyketides, it should be noted that for most arthropod natural products, assignments of biogenetic origin remain tentative at best because few biosynthetic routes have been confirmed experimentally.

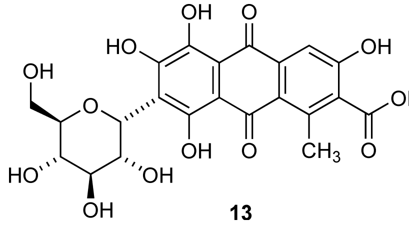
2.04.2 Challenges in Arthropod Natural Products Chemistry

One of the oldest known human uses of an insect natural product is that of carminic acid (**13**) as the active color ingredient of the natural dye cochineal.[17] Produced from the scale insect, *Dactylopius coccus*, cochineal dye was once a geopolitically important commodity. The semisynthetic derivative carmine later found applications as a biological stain and as a food coloring. As was generally the case with early use of natural products, little to no consideration was given to the compound's ecological significance. Only much later, scientific studies showed that carminic acid benefits *D. coccus* by acting as a deterrent to predation,[18] but could also be sequestered by predaceous insects that feed on *D. coccus* for their own defense.[19] The ability to sequester defensive metabolites is particularly widespread among arthropods, although sequestration of dietary toxins has also been observed for marine gastropods,[20] as well as for some birds,[21] reptiles,[22] and amphibians. In the case of many tropical poisonous frogs, the sequestered toxins are in fact derived from arthropod prey species, and extensive research in this area has had the indirect effect of revealing much about the defensive alkaloids of many species of arthropods (**Figure 2**).[23–27]

The widespread occurrence of sequestration adds to the challenges intrinsic to arthropod natural product research. The sheer number of species promises a virtually unlimited pool of organisms for future analyses, whose genetic diversity – or that of associated microorganisms – probably encodes a correspondingly diverse collection of small-molecule metabolites. Frequently, different life stages of species have vastly different metabolomes, and careful inspection of a species' lifecycle and ecology can often lead to the discovery of additional groups of metabolites. However, precise identification of species and life stages often requires the enlistment of collaborators with specific taxonomic expertise. This poses a considerable challenge for the systematic screening of arthropod species for new natural products, because for many, if not most groups of arthropods biological knowledge is extremely limited.

Another problem is posed by the fact that the number of known species that can be collected in large quantities (often those species considered pests) represents only a small fraction of overall arthropod species diversity. Most arthropod species are rare, and can only be collected sporadically, often with dramatic seasonal or yearly variations in availability. It is unfortunately all too common to identify what appears to be a promising species for further research, often with considerable investment of time in collecting preliminary data, only to realize subsequently that additional specimens cannot be obtained. This problem is compounded by the fact that many insect species are difficult or even impossible to raise in captivity. Such instances bring to the foreground what may be the biggest challenge in insect natural products research: lack of sufficient sample amounts for detailed analyses.

Because arthropods, like most other vertebrates and invertebrates, live in close, often symbiotic association with various types of microorganisms, it cannot generally be assumed that the isolated compounds have been biosynthesized by the arthropod. Some compounds isolated from arthropods may be of microbial origin, or result from mixed biogenesis including participation of both the host organism and its associated microfauna. In a few cases, for example, the coleopteran defensive polyketide pederin (**14**),[28] bacterial origin has been demonstrated, and it is probable that many more so-called arthropod natural products are in fact the products of microbial symbionts.[29,30] Furthermore, as previously mentioned, many arthropods sequester small-molecule metabolites from their diet – plants, other arthropods, or fungi. Such sequestered compounds frequently undergo additional modification. The ultimate biosynthetic origin of compounds isolated from arthropods is



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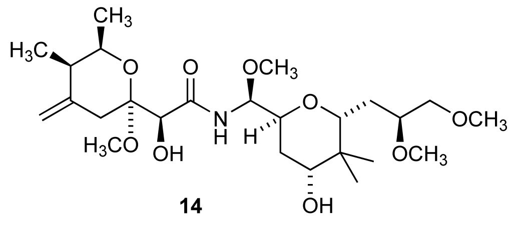

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Figure 2 Carminic acid (**13**) and pederin (**14**).