

The Chemistry of Algal Secondary Metabolism

J.A. Maschek and B.J. Baker(✉)

1.1 Introduction

Natural product chemistry is a branch of organic chemistry that touches upon many other fields of science, especially applied sciences such as medicine, agriculture, and engineering. It is fundamentally a basic science, involved in the discovery, characterization and cataloging of new chemical substances found in nature. Among other basic scientists, biologists and ecologists recognized some time ago that natural products might help explain species composition, distribution, and diversity in some settings, establishing the field of chemical ecology (Harborne 1989). The field has developed largely around collaborations of chemists and biologists, each bringing their own knowledge base to chemical ecological questions. This chapter is intended as an overview of natural product chemistry with an emphasis on the chemical aspects of algal defensive metabolites. It is our hope that algal ecologists will gain insight into the chemistry in the same manner that chemists will acquire a deeper understanding of the ecology from the remaining chapters of this book.

1.2 Conceptual Framework

1.2.1 *Natural Products*

Similar to those of other sessile organisms, successful life history strategies employed by algae must include adaptations to their biological communities. Such survival strategies may include behavioral, physical, or chemical means (Hay and Fenical 1988; Lobban and Harrison 1994; Dawes 1998; Stachowicz 2001). Chemical strategies, whereby an organism may produce a toxic defensive compound or an

J.A. Maschek

Department of Chemistry, University of South Florida, 4202 E. Fowler Ave CHE205, Tampa, FL 33620, USA

B.J. Baker

Department of Chemistry, University of South Florida, 4202 E. Fowler Ave CHE205, Tampa, FL 33620, USA. e-mail: bjbaker@cas.usf.edu

antifouling metabolite, utilize what chemists refer to as “natural products,” literally alluding to products made by living organisms. Defining what a natural product is can be a slippery slope; generally, we know one when we see it, but describing the identifying characteristics inevitably invites divisiveness. It is not the intent of our discussion here to devolve into the philosophy behind the concept, but rather to present typical characteristics observed among natural products.

The term natural product is used synonymously with “secondary metabolite,” the latter of which may have more obvious characteristics. In particular, “secondary” is used here in the context of functional significance, so that something that is secondary is less important than something that is primary. Indeed, primary metabolites are the nuts and bolts of a living system: amino acids, cofactors, and lipids, for example. Cellular function is not possible without primary metabolites. Similarly, organismal function is dependant on primary metabolism, extending “primacy” to large molecules, such as proteins, but perhaps enveloping other small molecules such as visual pigments and neurotransmitters. Primary metabolites tend to be ubiquitous; proteins and enzymes from all organisms are composed from a selection of 20-odd amino acids, and genes are built from combinations of four purine and/or pyrimidine bases. Thus primary metabolites are largely limited to several dozen small molecules, and polymers thereof, and drive all living systems, providing energy, structure, and reproductive capacity.

One of the ways to identify a secondary metabolite, then, is to establish that it is not a primary metabolite. For example, only a small group of red algae make C_{15} halogenated acetogenins (Sect. 1.3.1). These fatty-acid-derived compounds are not nuts and bolts, nor are they ubiquitous, and so they are clearly secondary. Consider, however, steroid derivatives produced by algae and plants known as phytosterols (Parish and Nes 1997). These sterols (cholesterol-like compounds) bear alkylation at C-24, differentiating them from animal sterols. They have roles in membrane structure, a primary characteristic, but they are often species-specific and usually fall under the guise of secondary metabolites. Most often, secondary metabolites are found to be associated with an organism’s interaction with its environment. Phlorotannins (Sect. 1.4.2), for example, can impart distastefulness to potential predators, which is a secondary characteristic even though phlorotannins can have primary roles in brown algal cell wall biosynthesis (Ragan and Glombitzka 1986; Amsler and Fairhead 2006). Thus, in the modern use of the term, when we speak of a secondary metabolite or a natural product, we are referring to compounds that are not involved in the development or maintenance of an organism, limited in their biological distribution, often species-specific, and most often produced by an organism for intervention in ecological interactions (Williams et al. 1989). Note that the lack of a demonstrated ecological role for a natural product does not mean one does not exist, and even the failure to identify a particular role is not sufficient to argue against ecological relevance. Careful and thorough investigations of the ecological roles for many natural products remain to be accomplished.

Chemical structure can often be used by itself to recognize a secondary metabolite because of their common biosynthetic origin. Terpenes and polyketides, for

example, account for most of the secondary metabolites (Buckingham 2002) and can be recognized as oligomers of the primary metabolites isoprene and acetate, respectively. An expert can discern arrangements of these oligomers and their associated source(s). Specific details of these chemical classes will be discussed in Sect. 1.3.

1.2.2 *Natural Product Names*

Like in other fields of science involved in characterizing and cataloging, natural product chemists name their discoveries. The International Union of Pure and Applied Chemistry (IUPAC) has rules of nomenclature, much to the chagrin of many a student of organic chemistry. However, systematic names of natural products, as IUPAC dictates, are inappropriate for common usage, bearing multiple nests of convoluted descriptions of functionalization (IUPAC 1976; Giles 1999; Favre et al. 2004). Common usage allows for nicknames, which are bestowed at the time a new compound is described in the literature, and are generally more succinct and easy to pronounce, and especially, more easily associated mentally with a chemical structure. As an example, most of us are aware of our personal cholesterol level, but few of us would fully comprehend the significance of our (3*S*,10*R*,13*R*,17*R*)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-1*H*-cyclopenta[*a*]phenanthren-3-ol level. Thus, a common naming system is critical for natural product chemists. Nonetheless, many scientists outside the field of natural products can be baffled by the odd amalgamation of terms that comprise the common names assigned, and perhaps worse, may still find difficulty in pronouncing them. A brief explanation is presented here to assist the nonspecialist.

A newly described natural product will normally be assigned a common name based either on its species of origin or, alternately, on a geographic characteristic associated with its acquisition. **Laurinterol** (Fig. 1.5a), for example, is a common name assigned to a compound first isolated from a red alga of the genus *Laurencia* (Irie et al. 1966), while **kahalalide** (Fig. 1.7e) describes a series of compounds isolated from a green alga (and its sacoglossan predator) from the **Kahala** district of O'ahu, Hawaii (Hamann and Scheuer 1993). Purists will argue the capriciousness of the latter, and certainly a natural product isolated from a Caribbean brown alga may one day turn up in another collected from Okinawan waters. However, as biological taxa undergo constant revision, genus and species names may become obsolete or their members reassigned, so that neither of these guidelines bestows durability or accuracy. Biologically based names can also suffer the discovery of a symbiotic or dietary source, such as the case for aplysiatoxin, which was first described from Hawaiian sea hares (Aplysiidae) (Watson and Rayner 1973; Kato and Scheuer 1974) but later proved to be of cyanobacterial origin. The ultimate aim in assigning a common name is to achieve uniqueness with some semblance of historical origin, be it biological or geographical.

The origin of the natural product occupies the part of the compound name that IUPAC refers to as the “parent” structure. Appended to the name of the parent is a suffix that indicates the primary chemical function (functional group) of the molecule. For instance, in the earlier-mentioned example, laurinterol has an alcohol functional group, which is denoted by IUPAC systematic nomenclature with the “-ol” ending. The “-ide” ending of kahalalide similarly identifies a lactone functionality. Caulerpenyne (Fig. 1.7a), isolated from the green algae *Caulerpa flexilix* (Amico et al. 1978), contains a carbon-carbon double bond, which is referred to as an alkene, as well as a carbon-carbon triple bond, known as an alkyne. Alternately, the suffix may convey biological activity information, or may categorize the structural class (Sect. 1.2) to which the natural product belongs. Aplysiatoxin (Fig. 1.8g), for example, is broadly cytotoxic and has been implicated in “swimmers itch” in shallow water environs of the South Pacific (Fujiki et al. 1985). Table 1.1 illustrates several other ways the suffix of a compound may provide further information.

There are exceptions to these guidelines. Ilimaquinone, for example, is a compound isolated from a Hawaiian sponge (Luibrand et al. 1979). The suffix, as guidelines suggest, imparts information about the chemical function present in the natural product, the quinone function. Ilima, rather than deriving from the species binomial or a geographical region, is the Hawaiian word for yellow, the characteristic color of the natural product. Putricine and menthol have obvious odoriferous characteristics associated with their constitution. Honorific names are rare among natural products (Herb et al. 1990; Cooray et al. 1988).

Nomenclature based on a parent term with an appended suffix accounts for most natural product names. However, as related compounds are identified, or even when a suffix has to denote multiple functional groups, a variety of modifying terms can be employed. For example, the common prefix “nor-” denotes the removal of a skeletal atom from the parent structure; the loss of two or more skeletal atoms is indicated by combining an appropriate numerical prefix with “nor-”, e.g., “dinor-”, “trinor-” (Giles 1999). Table 1.2 lists additional examples of commonly encountered modifying terms.

Table 1.1 Examples of natural product nomenclature suffix usage

Functional group	Structural class	Bioactivity	Biological origin
-al (aldehyde)	-sterol (steroid)	-toxin (toxin)	-mycin (Actinomycete)
-ol (alcohol)	-oside (sugar)	-statin (inhibitor)	-gorgin (gorgonian)
-one (ketone)	-ceramide (ceramide)	-lysin (lytic)	-spongins (sponge)

Table 1.2 Nomenclature modifying terms

Atom replacement	Bond rearrangements	Skeletal modifications
Aza (C → N)	Abeo (general rearrangement)	Apo (side chain loss)
Oxa (C → O)	Cyclo (cyclic rearrangement)	De (functional group loss)
	Iso (isomeric form)	Homo (add skeletal atom)
	Seco (bond removal)	Nor (skeletal atom loss)

The pronunciation of natural product names stresses the individual contributions. Thus, biological or geographical names incorporated into parent names of natural products are generally pronounced the way they are as biological or geographical names. Caulerpenyne, with its alkene and alkyne functionality described earlier, is pronounced to emphasize each of those three units: Caulerp en yne (kôl erp ěn ĩn). Isocyanopupukeanane (Burreson et al. 1975) looks like a mouthful, but when dissected into its functional group, the isocyano (ĩ sô sĩ an ôh) group, its geographical origin, Pupukea, Hawaii (pu pu kay a), and finally its structural class, an **alkane** (-ān), it is much more manageable: ĩsô sĩanôh pu pu kay ən ān. Structural classes can often combine some of the same terms, so that a diterpene (dĩ tũr pĕn) that has been metabolized to remove two carbon atoms from its skeleton becomes a “dinor” (dĩ nôr) diterpene or a dinorditerpene (dĩ nôr dĩ tũr pĕn). Select common names and terms used in this chapter will include phonetic pronunciation.

1.2.3 Bioactivity of Natural Products

Natural products are inherently bioactive. Bioactivity is a physiological response to a molecule or ion binding to a ligand, with downstream cascading consequences. Natural products are themselves products of enzymatic processes, demonstrating their ability to interact with receptors. Whether they bind other, nonsynthetic receptors likely depends on whether they have evolved in response to environmental pressures or whether they accumulate as a result of diverted primary metabolic pathways (Williams et al. 1989; Clardy 1995).

Receptor binding requires exquisite molecular organization, as generalized in Fig. 1.1. Proteins and enzymes present a plethora of functional groups on their surface, providing opportunity for molecular interactions. It is only when a potential binding molecule has its own array of functionality that complements those presented on the surface, or more likely in a pocket of an enzyme, that binding can take place. Binding, as measured by the ratio of bound to unbound natural product, is dependent on the strength of the molecular interactions depicted in Fig. 1.1 in order of decreasing strength: ionic bonds (**A**, structure II), hydrogen bonds (**B**, structure II), π -stacking interactions (**C**, structure II), which involve noncovalent aromatic interaction in which p-orbitals of flat aromatic molecules overlap and align parallel to each other, much like stacked coins, and, finally, van der Waals forces (**D**, structure II), also referred to as London dispersion forces.

The receptors of ecological interactions are still not well understood. In fact, many ecological studies have failed to demonstrate well-defined roles for natural products (Pawlik 1993). Most experimental evidence for natural product receptors derives from biomedical applications. Kahalalide F, for example, is a potent cytotoxic depsipeptide (see Sect. 1.3.2.3) initially found in the sacoglossan mollusc *Elysia rufescens* and later in the green alga it feeds upon (Hamann and Scheuer



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