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Review

# Convergence in the biosynthesis of acetogenic natural products from plants, fungi, and bacteria

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ABSTRACT

This review deals with polyketides to which nature has developed different biosynthetic pathways in the course of evolution. The anthraquinone chrysophanol is the first example of an acetogenic natural product that is, in an organism-specific manner, formed via more than one polyketide folding mode: In eukaryotes, like e.g., in fungi, in higher plants, and in insects, it is synthesized via folding mode F, while in prokaryotes it originates through mode S. It has, more recently, even been found to be synthesized by a third pathway, named mode S′. Thus, chrysophanol is the first polyketide synthase product that originates through a divergent–convergent biosynthesis (depending on the respective producing organisms). A second example of a striking biosynthetic convergence is the isoquinoline alkaloids. While all as yet investigated representatives of this large family of plant-derived metabolites (more than 2500 known representatives!) are formed from aromatic amino acids, the biosynthetic origin of naphthylisoquinoline alkaloids like dioncophylline A is unprecedented in following a route to isoquinolines in plants: we have shown that such naphthylisoquinolines represent the as yet only known polyketidic di- and tetrahydroisoquinolines, originating from acetate and malonate units, exclusively. Both molecular halves, the isoquinoline part and the naphthalene portion, are even synthesized from a joint polyketide precursor, the first proven case of the F-type folding mode in higher plants. The biosynthetic origins of the natural products presented in this paper were elucidated by feeding $^{13}C_2$-labeled acetate (or advanced precursors) to the respective producing organisms, with subsequent NMR analysis of their $^{13}C_2$ incorporation patterns using the potent cryoprobe methodology, thus making the full polyketide folding pattern visible.


**Contents**



## 1. Introduction

Fused-ring aromatic polyketides constitute a large group of secondary metabolites with remarkable structural diversity and pharmacological properties, biosynthetically arising from small acyl units that get assembled by polyketide synthases (PKSs) (Rawlings, 1999; Staunton and Weissman, 2001; Thomas, 2004; Hertweck et al., 2007). In the past, polyketidic natural products have provided many promising leads for clinical and industrial development of important and widely used pharmaceutical agents or agrochemicals, and they still do represent a major source for structurally novel bioactive target molecules (Dewick, 2002; O'Hagan, 1991). They are widely distributed not only in fungi, lichens, and

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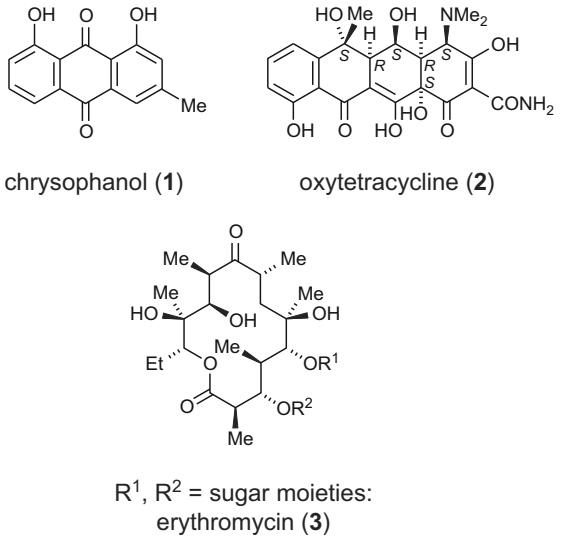


**Fig. 1.** Examples of bioactive polyketides: the tricyclic metabolite chrysophanol (**1**) and the more complex molecules oxytetracycline (**2**) and erythromycin (**3**).

higher plants, but also in animals, and, in particular, in soils, where they are mainly formed by microorganisms (Thomson, 1997). The variety of structural diversity ranges from simple aromatic metabolites, among them anthraquinones like chrysophanol (**1**), on which we report in more detail in this paper, to structurally complex tetracycline antibiotics like **2** (Thomas and Williams, 1983) and macrolides like **3** (Staunten and Wilkinson, 1998) (Fig. 1).

Biosynthetically, polyketides are usually built up by successive Claisen condensation of an acyl-CoA starter unit with extender units derived from malonyl-CoA in a manner related to fatty acid synthesis (Hopwood, 1997). Three types of polyketide synthases and several subtypes thereof have meanwhile been identified in diverse groups of organisms that catalyze the assembly and cyclization ('folding') of poly-β-ketoacyl intermediates (Austin and Noel, 2003; Hertweck et al., 2007; Shen, 2000; Staunton and Weissman, 2001). These PKSs consistently follow two different basic modes of how the linear polyketide building block is folded, thus giving rise to two structurally distinct groups of fused-ring aromatic structures (Thomas, 2001) as exemplified in Fig. 2. In eukaryotes (such as fungi, plants, and insects), the highly regioselective cyclization of the intermediate polyketide chain results in two intact $C_2$ units in the first aromatic ring of the final product (referred to as folding mode F, as typical of fungal producers) as for, e.g., dihydrofusarubin (**4**, Kurobane et al., 1980). In prokaryotes, by contrast, three such $C_2$-building blocks are incorporated into the first ring (mode S, as characteristic for *Streptomyces*) as exemplarily shown for hedamycin (**5**, Hertweck, 2009) (Fig. 2). The distribution of such intact (or cleaved) acetate-derived $C_2$ units in cyclic polyketides, and hence, the geometry of folding the linear reactive intermediates, can be determined by analysis of the respective $^{13}C$ incorporation patterns after feeding $^{13}C_2$-labeled acetate, and can, thus, be categorized using the modes S/F classification (Thomas, 2001).

Although it would be imaginable that identical basic structures might originate from different folding modes, no metabolite is as yet known to be formed from such different pathways, and there are, only few examples of particular polyketidic secondary metabolites that occur in both, eukaryotes and prokaryotes. One such candidate that might, in principle, be formed both, via F and S, could be chrysophanol (**1**), as already suggested by Thomas (2001) (see Fig. 3).

Chrysophanol (**1**) serves as a defense compound in several most diverse eukaryotic organisms (plants, lichens, fungi, insects) (Thomson, 1997). It had, however, never been found in prokaryotes until recently. Our discovery that chrysophanol (**1**) is also produced by

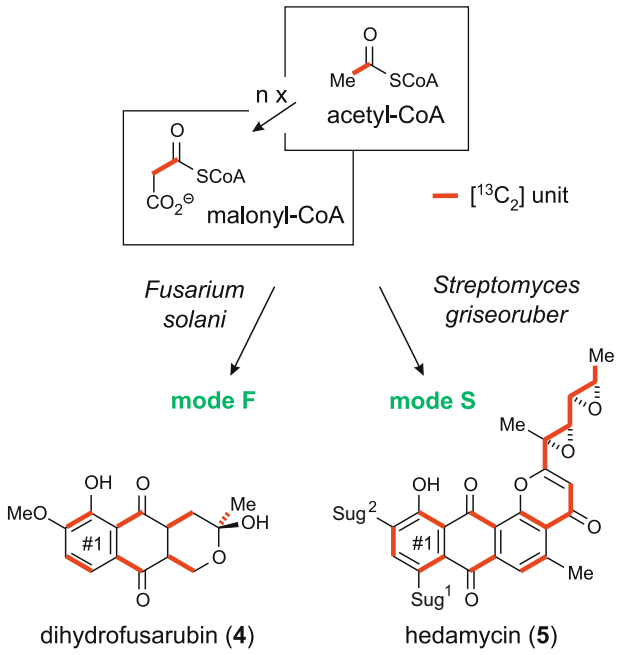


**Fig. 2.** Classification system of polyketides as introduced by Thomas (2001): mode F with two intact acetate units in the first aromatic ring as in dihydrofusarubin (**4**) and mode S with three such units in the first ring as in hedamycin (**5**).

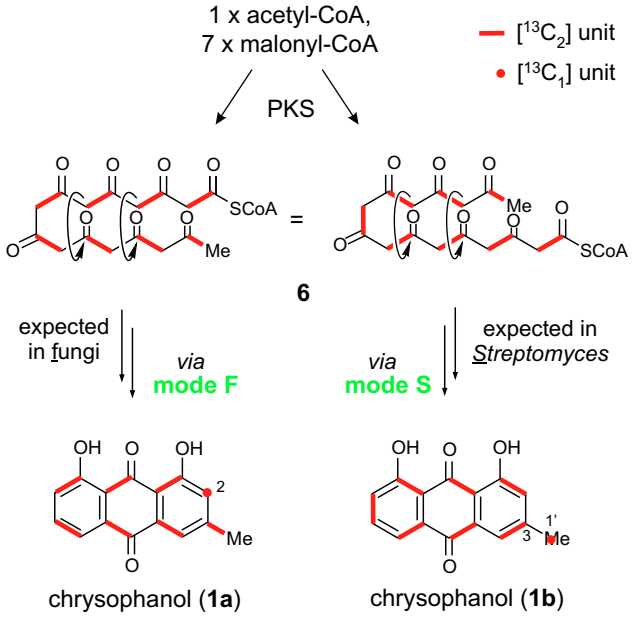


**Fig. 3.** The first possible example of convergence in polyketide biosynthesis in plants, fungi, and bacteria: two folding modes of one and the same polyketide chain, **6**, that might lead to chrysophanol (**1**).

a *Nocardia* strain, even as a main metabolite, allowed us to undertake a comparative biosynthetic study. Moreover, recent studies clearly revealed that there is even the possibility of two different prokaryotic polyketide folding modes, S and S′, all convergently leading to **1** in different prokaryotic species (Bringmann and Irmer, 2008), which will be described in the following paragraph.

Already from its unique structure the naphthylisoquinoline alkaloid dioncophylline A (**9**) (Fig. 4) from the tropical liana *Triphyophyllum peltatum* (Dioncophyllaceae) (Bringmann and Pokorny, 1995; Bringmann et al., 1998a, 2001) is a rewarding candidate to