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Complex molecules, clever solutions – Enzymatic approaches towards natural product and active agent syntheses

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ABSTRACT

Natural compounds are often structurally complex and their synthesis is still highly challenging. The review intends to give an overview on developments in biotechnology and their role for the production of natural products and active agents. *In vitro* and *in vivo* methods are presented side by side beginning with rather simple but smart single step conversions, followed by cascade reactions, and finishing with complex bio-, semi- and mutasynthesis endeavours. All the enzymatic approaches do obviously complement traditional synthetic methods; with their particular strengths, the combined repertoire will lead to an increased efficiency in natural product synthesis as well as in providing analogues.

Contents

1. Introduction

The ubiquitous competition of species for food, space to live, or mating partners, which Darwin called 'struggle for life',[1] evolved an incredible number of natural compounds working as specific signal molecules or as highly efficient poisons. Since every natural compound underwent a strict selection process, one can assume that they have biological activities by definition and have consequently served as pharmaceuticals since ancient times.[2–5] Nowadays, new natural compounds still have a great impact on lead structures for medicinal chemistry: Between 1981 and 2010 64% of new

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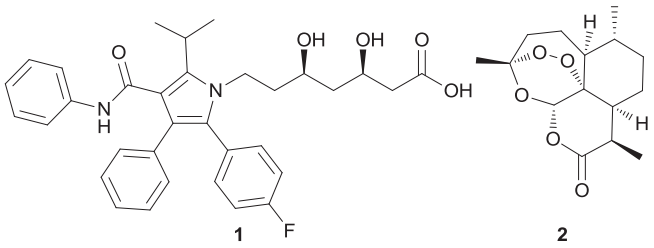


Fig. 1. Atorvastatin (**1**) and artemisinin (**2**).

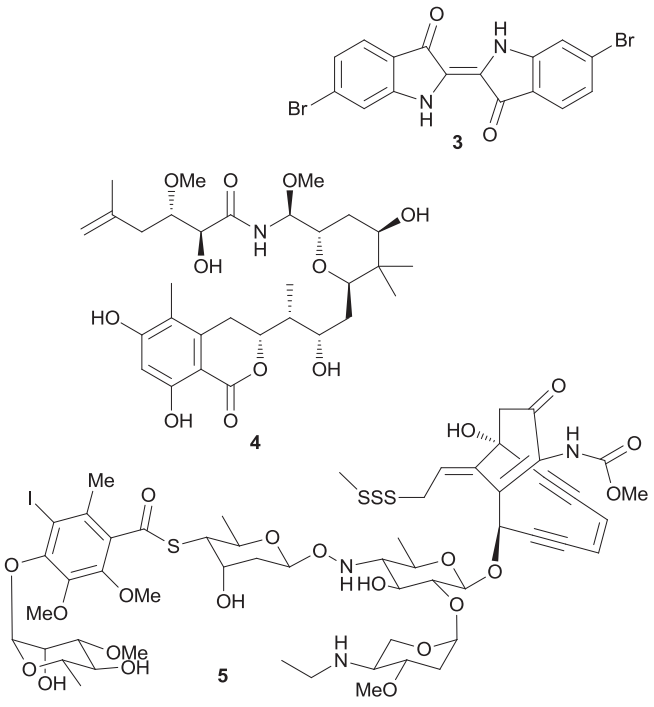
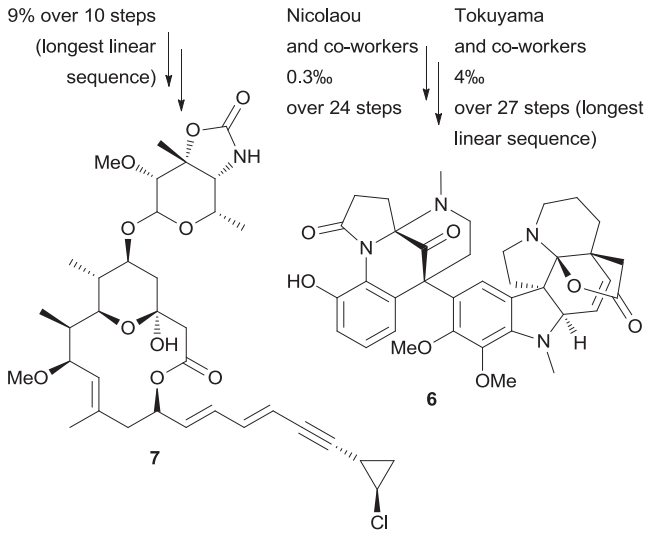


Fig. 2. 6,6′-Dibromoindigo (**3**), psymberin (**4**), and calicheamicin γ_1^1 (**5**).

chemical entities for pharmaceutical trials were natural products itself, derivatives of them or at least inspired by natural compounds.[6] Combinatorial chemistry on the other side did not come up with similar results, although considerable effort has been put into the field since the 1980s and the method is well established.[7–9] For example, the pharmaceutical block buster atorvastatin (**1**, Lipitor®/Pfizer) – a HMG-CoA-reductase inhibitor – is a compound, inspired by the natural product lovastatin from *Aspergillus terreus*, while the famous antimalarial compound artemisinin (**2**) is a natural compound (from *Artemisia annua*) itself (Fig. 1).[3,10,11]

The discovery of new natural compounds drastically expands the pharmacological space by means of new targets, new modes of action and new structures.[6,7] Van Valen described the co-evolution of prey-bait- or host-parasite/symbiont-relationships with an analogy to Lewis Carroll's 'Red Queen', who said 'it all the running you can do, to keep in the same place'.[12,13] And 'all the running' is exactly what created the cornucopia of natural compounds giving the chance to survive in a co-evolutionary competition also making them so attractive to human beings as potent pharmaceuticals, insecticides, cosmetics and so on. Beside these very attracting features, natural compounds have two significant drawbacks: On the one hand, many secondary metabolites are not available in sufficient amounts for industrial exploitations, because the species are not easy to cultivate or hardly accessible like marine organisms or more strikingly the content of the particular natural compound is very low. One example is given by the vast exploitation of the sea snail *Bolinus brandaris*: Beginning in the ages of the Phoenician and Roman Empire and being continued until modern times, this snail was the main source of the precious purple 6,6′-dibromoindigo dye (**3**) used for the colouration of Roman emperors' and Catholic cardinals' clothes (Fig. 2). To obtain one gram of this dye 10,000 snails had to be collected and extracted. Still visible signs for the insatiable thirst of the powerful towards this good are mountain like dumps of snail shells as the Monte Testaceo in Tarent (Italy), which was the centre of purple production in the Roman Empire. This natural compound finally lost its status as luxury product in 1856 as William Henry Perkin found the cheap surrogate aniline-purple or mauvein.[14,15] Assessing the structure of purple dye **3** one can deduce that it would be easy to synthesise, which is fully true. However, for most of the natural compounds this is not correct. Most of all secondary metabolites impress by their complexity in terms of numbers of functional moieties, their complex combination as well as the sheer number of stereogenic elements in one molecule. This can be seen exemplarily at psymberin ((Fig. 2) **4**) a generic polyketide from symbionts in the sponges *Psammocinia* sp. and *Ircinia ramose*, respectively: A rather small molecule having nine stereogenic centres in total combined with diverse hydroxyl moieties as well as two distinct ring systems (Fig. 2).[16] An even more astonishing example is the impressive calicheamicin γ_1^1 (**5**) from *Micromonospora echinospora* ssp. *calichensis* (Fig. 2): Decorated with a number of rare sugars, it contains a halogenated aromatic ring as well as an enediyne conjunction.[17]

This complexity makes natural product syntheses challenging in terms of the number of necessary steps and sophisticated protection strategies. The problem each synthesis is facing is that the overall yield of a synthesis is exponentially decreasing with each step. The longer the sequence is, the lower is the yield and protecting strategies, often necessary to implement chemo- and regioselectivity, elongate synthetic sequences even more. For example, Nicolaou as well as Tokuyama and co-workers published in 2009 the very impressive total syntheses of haplophytine (6), an anti-insecticidal compound from the flower *Haplophyton cimicidum*.[18,19] While both syntheses had good to very good yields in each step, the overall yields were between 0.3 and 4‰ (see Scheme 1). In addition to that, the atom efficiency is even worse



Scheme 1. Synthetically produced natural compounds haplophytine (**6**) and callipeltoside A (**7**).[18–21]