

NATURAL PRODUCTS

Emulation illuminates biosynthesis

A concise synthesis of the fungal natural product epicolactone suggests that this highly stereochemically complex yet racemic natural product may come from a cascade reaction between two polyhydroxylated arenes.

Jaron A. M. Mercer and Noah Z. Burns

For synthetic organic chemists, inspiration frequently comes from nature. Small-molecule natural products remain the most important targets for chemical synthesis in academia, for the crucible of evolution ensures that such molecules are made for a purpose. Nature employs seemingly endless strategies for producing complex molecules, and emulating these approaches has been a rich source of chemical innovation. There are many remarkable examples of chemists mimicking biosyntheses, for example the reproduction of polyene cyclization logic to build terpene scaffolds^{1,2}. But biosynthetic hypotheses are typically uncoupled from attempts to synthesize the products in the laboratory. Although some of these ideas are not easily amenable to chemical synthesis, when the appropriate opportunities arise it can be highly enlightening. Writing in *Nature Chemistry*, Dirk Trauner and colleagues propose a biosynthesis, and describe the execution of a succinct chemical synthesis of the fungal natural product epicolactone. The efficiency of the synthesis gives credence to its possible relevance in nature³ (Fig. 1).

The majority of chiral natural products are isolated as single enantiomers. This is unsurprising given that the enzymes that make them are themselves chiral. When a natural product containing multiple stereocentres is isolated as a racemate, it subtly suggests that key biosynthetic steps may involve a spontaneous cascade reaction sequence from achiral starting materials; flagship examples of this include carpanone and the endiandric acids^{4,5}. In such instances, there is a true occasion for synthetic chemistry to inform our understanding of biosynthesis.

Epicolactone ((±)-**1**, Fig. 1) has multiple bridging rings, four tetrasubstituted carbons, and five contiguous stereogenic centres, but is isolated as a racemate. It has been isolated from two different species of *Epicoccum* fungi and demonstrates both antimicrobial and antifungal activity^{6,7}. Known metabolites from *Epicoccum* species include highly oxygenated arenes of polyketide origin, but even with these building blocks in

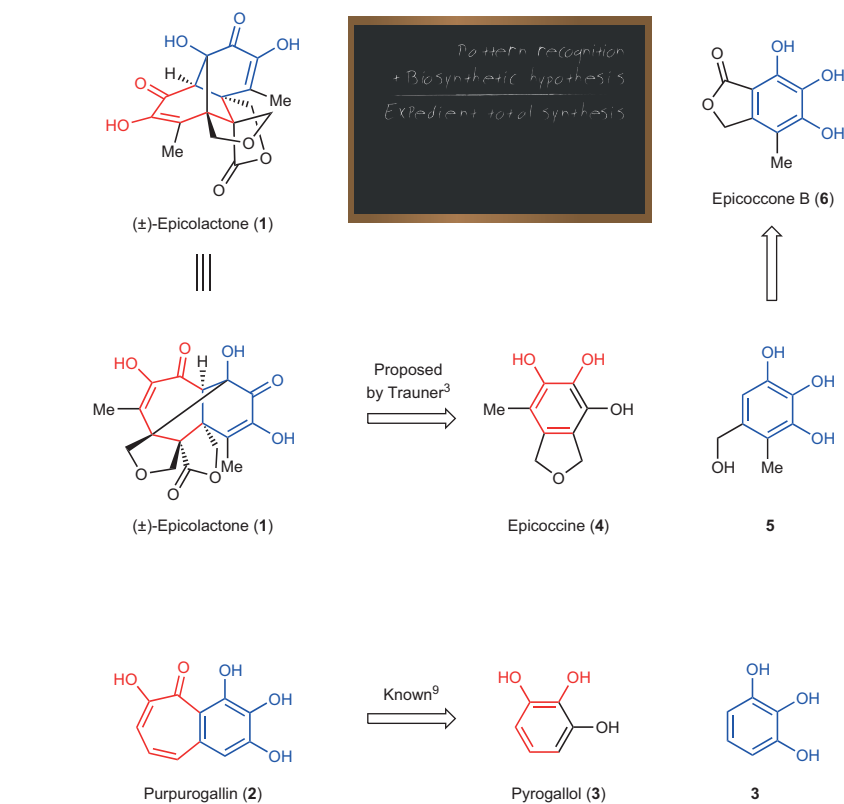


Figure 1 | The applications of pattern recognition and biosynthetic logic can be highly fruitful in natural product synthesis, both resulting in rapid molecular construction and informing practitioners of a molecule's potential origins. Examining the structure of epicolactone from different perspectives reveals its similarity to purpurogallin for which the biosynthesis is known. Trauner and co-workers then propose disconnections of epicolactone similar to those known for purpurogallin leading back to epicoccine and epicoccone. In the forward direction, a total synthesis of epicolactone was completed with the longest linear sequence being only eight steps.

mind, predicting which partners could come together to form a complex small molecule like epicolactone poses a great challenge. Trauner and co-workers applied a technique called pattern recognition in planning their synthesis⁸. The concept is simple in theory: given a target molecule, the chemist mentally scans and rescans the structure from different angles hoping to see a fragment or pattern that might reveal a synthetic opportunity. The challenge is ignoring the large numbers of seemingly good leads in favour of the best option,

an exercise in pure human chemical intuition. In the case of epicolactone, the key insight was identifying the 6–7-ring system (see alternative depiction in Fig. 1) and the pattern of five oxygen atoms that matched those of a smaller natural product, purpurogallin (**2**, Fig. 1).

Purpurogallin is the simplest member of a family of benzotropolones found commonly in black teas. The biosynthesis of this molecule has been known for decades: after enzymatic or chemical oxidation, two molecules of pyrogallol (**3**)

dimerize and subsequently rearrange spontaneously, incorporating a molecule of water and losing a molecule of carbon dioxide, to form purpurogallin⁹. Trauner and co-workers proposed that epicolactone might arise from an analogous oxidative dimerization of epicoccine (**4**), a known *Epicoccum* sp. metabolite, and a benzyl alcohol **5**, followed by a different sequence of rearrangements. While **5** has never been observed before (and indeed proved to be unstable in unprotected form), it could conceivably come from the hydrolysis and decarboxylation of the known *Epicoccum* sp. metabolite epicoccone B (**6**). In their report, Trauner and co-workers thus propose a hypothesis for the biosynthesis of **1** involving the oxidation and (5+2) cycloaddition of two highly oxygenated arenes followed by a series of rearrangements.

Excitingly, Trauner and his team prepared **4** and an *O*-methylated version of **5** in just

five and six steps, respectively. In support of their biosynthetic hypothesis, combination of the two pieces under oxidizing conditions led to the isolation of *O*-methylepicolactone, which could be unmasked to the natural product in a further single step. The entire synthesis is only eight steps in its longest linear sequence — truly remarkable for a molecule of this complexity.

Biomimetic cascade strategies such as this are inherently high-risk: the success of the route hinges on the success of a single cascade step. Even if a reaction occurs in nature without the guidance of an enzyme, there is no guarantee that it will work in a flask; finding the right conditions can be difficult or impossible. Indeed, previous work by the group to synthesize (±)-**1** via dimerization of **4** and **6** directly was unsuccessful¹⁰. A broad range of oxidants and protected versions of the arene coupling partners needed to be examined before Trauner's team arrived at a working

synthesis. Here the payoffs are substantial: it is difficult to imagine a more direct synthesis of this natural product. □

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LIGHT HARVESTING

Strike while the iron is cold

For many years, chemists have tried and failed to find efficient light-harvesting molecules based on Earth-abundant, environmentally friendly iron. Now, an iron complex has been developed with photoluminescent properties that are tuned to efficiently convert light to electrons.

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In the quest to produce electricity or high-energy chemicals using sunlight, solar-energy conversion devices made of light-absorbing molecules anchored to nanostructured metal-oxide semiconductors have long been studied^{1,2}. The light-to-energy conversion starts when a photoexcited chromophore, often called a dye or sensitizer, injects an electron into the semiconductor. Titanium dioxide is the semiconductor of choice, which, along with having useful charge-transport properties, is Earth-abundant, inexpensive and biocompatible. Also, the nanostructured films of it used in solar devices are easily prepared on a large scale. However, the dye molecules that are used do not tend to share these wholesome characteristics. Some of the most successful compounds used as dyes in dye-sensitized solar cells (DSCs) are polypyridine complexes of ruthenium³. Unfortunately, ruthenium is rare, expensive and toxic, making it unsuitable for solar devices on the scale needed to meet projected energy demands. Now, writing in *Nature Chemistry*, Kenneth Wärnmark and

colleagues have described the development of an alternative dye based on iron, which is a much more appropriate element to use from an industrial point of view⁴.

Iron was identified many years ago as a promising substitute for ruthenium: it is in the same group of the periodic table, is the fourth most abundant element in the Earth's crust, and is inexpensive and non-toxic. Furthermore, Fe(II)–polypyridine complexes are structurally similar to those of Ru(II) and are electrochemically reversible. They also have good light-absorption properties, with intense metal-to-ligand charge transfer (MLCT) bands in the visible region of the electromagnetic spectrum.

The first example of TiO₂ sensitization by a Fe(II) complex, *cis*-Fe(dcb)₂(CN)₂, was reported by Ferrere and Gregg in the late 1990s (ref. 5). The injection into TiO₂ was band selective, that is, sensitization occurred mostly from only one of the two MLCT absorbance bands of the iron complex. Unfortunately, it was very inefficient, with an injection yield of around 10%, resulting in low-performance DSCs. However, this

result suggested that suitably designed iron complexes may eventually replace ruthenium in solar devices.

Resolving the differences in the injection behaviour of iron complexes compared with ruthenium is the main challenge when considering their use as sensitizers. Ru(II)–polypyridines tend to have excited-state lifetimes in the microsecond range and injection quantum yields near unity, independent of the excitation wavelength. Conversely, Fe(II)–polypyridines display low injection quantum yields and exhibit very short-lived excited-states (<100 fs), resulting in a narrow window of time for electron injection into TiO₂. The origins of this behaviour have been studied by many groups, both experimentally and theoretically, and are now well understood, thanks to important early contributions by the McCusker group⁶ and, more recently, by Jakubikova and co-workers⁷. Briefly, the ¹MLCT and ³MLCT photoactive excited states in Fe(II)–polypyridines are efficiently deactivated on an ultrafast (sub-picosecond) timescale by intersystem crossing into