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High yield of natural products

Biologically active small molecules isolated from natural sources remain an important focus of chemical biology research. Small molecules released by organisms are used for communication within and between species. Progress in identifying these pheromones enriches our understanding of ecology and may provide avenues for controlling pests. Natural products are also a well-known resource for the pharmaceutical industry. During the 1980s and 1990s, 28% of new drugs approved by the US Food and Drug Administration (FDA) were natural products or derived from natural products (*Nature* **432**, 829–837, 2004). The challenges of natural product identification have led to a gradual shift away from these biologically made chemicals in favor of the more rapidly accessible synthetic chemical libraries. However, a number of recent papers in *Nature Chemical Biology* highlight the central importance of natural products to both chemists and biologists.

A striking example of natural products chemistry is found in this month's issue of *Nature Chemical Biology*. Sorensen, Hoye and their colleagues report the isolation and characterization of the migratory pheromone of the sea lamprey (p. 324). Sea lampreys are parasitic fish that have invaded the Great Lakes of North America and devastated stocks of salmon and trout. These organisms have a complex natural history, including a migration from large open waters to rivers for spawning. To guide them to spawning grounds, sea lampreys have evolved specialized chemical sensors that can detect subpicomolar quantities of pheromones produced by larvae. The authors identified and characterized a mixture of larval steroid-like compounds that attract adult sea lampreys to suitable spawning grounds. As discussed by Dittman (News & Views, p. 316), these studies have potentially great ecological impact: deployment of this pheromone could be used to reduce the population of economically devastating invasive sea lampreys.

Bacteria also use secreted chemicals to communicate with each other. For example, during infection, when strength in numbers is required, individual bacteria produce small molecules known as autoinducers. By sensing the concentration of these 'quorum-sensing' molecules, bacteria coordinate expression of virulence factors only at high population density. One particular autoinducer, AI-2, is produced by a broad range of bacterial species, including both Gram-positive and Gram-negative strains. Recently Xavier and Bassler found that the AI-2 quorum sensing of one bacterial species can be disrupted by another bacterial species. This result is highlighted in this issue by Richard Novick in a News and Views article (p. 321). Increased understanding of how pathogenic bacteria use these small molecules could influence the design of new antibiotics. Another newly identified quorum-sensing molecule was reported our launch issue. Sakagami, Dubnau and colleagues (*Nat. Chem. Biol.* **1**, 23–24, 2005) identified a peptide containing a novel tryptophan modification that is involved in communication among *Bacillus subtilis*.

The importance of natural products as drug leads is nicely illustrated by a paper from Sakamoto and colleagues in this issue (p. 333), reporting on work in which a metabolite produced by a fungus isolated from fallen leaves in Japan was found to inhibit the replication of hepatitis C virus (HCV). Remarkably, this molecule acted not by inhibiting a HCV process, but by targeting host-cell sphingolipid biosynthesis. Besides providing a new target for drug efforts, this study reveals a requirement for host sphingolipids in targeting HCV to the cell membrane during replication.

As these examples illustrate, the isolation and characterization of minute quantities of biologically active compounds from a complex mixture remains a challenging and labor-intensive process. Furthermore, confirmatory chemical synthesis is required to provide sufficient material for biological activity validation and structural characterization. Owing to the structural and stereochemical complexity of most natural products, total synthesis efforts continue to rely on advances in asymmetric synthetic methodologies.

Tools from chemical biologists offer potential to aid natural product isolation and synthesis. A paper by Challis and coworkers (*Nat. Chem. Biol.* **1**, 265–269, 2005) provides one new route for identifying natural products. Genome mining of microbial biosynthetic genes guided the authors to the isolation and characterization of a new iron-chelating small molecule and the elucidation of its biosynthetic pathway. Biosynthetic engineering approaches (see, for example, *Nat. Chem. Bio.* **1**, 122–124, 2005) provide an efficient method to overcome the challenges of total chemical synthesis of complex natural products by harnessing the stereoselectivity and rate accelerations inherent in enzymatic pathways. Given their involvement as signaling molecules, probes of biological systems and leads for drug discovery, natural products will continue to attract the attention of chemists and biologists. ■