The inherent strength of carbon nanotubes and graphene (or nanocomposites containing them) make them well suited to use in bone regrowth, where matching the mechanical properties of an implant with that of the bone to be regrown is critical. Another attractive feature is that they can be processed at high temperature, enabling composites to be formed with melt-extrudable materials that are known to be biocompatible.

The bionic materials store is well and truly stacked, and many tools are available to characterize and use the contents. The challenge lies in determining the most appropriate electrode materials for a particular application. For medical bionic applications involving tissue engineering—such as implants for peripheral nerve, spinal cord repair, or muscle regeneration—the ability to produce biodegradable and bioabsorbable materials with appropriate function and lifetime profiles will be critical. For bionic prosthetics, challenges include reducing power requirements, finding natural (biological) power supplies, and extending device lifetime. In the case of bionic repair systems, devices should be biodegradable. Our increasing understanding of the properties of new electrodes and of how to design and control the electrode-cellular interface promises exciting advances in medical bionics.

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CHEMISTRY

Total Chemical Synthesis Peers into the Biosynthetic Black Box

Key steps in a natural product synthesis route may relate to nature's strategies and catalysts.

Scott J. Miller

The structures, endemic roles, biosynthetic origins, and chemical reactivities of complex natural products contribute to their allure as enduring subjects of scientific inquiry (*1*). Embedded in each molecular framework is an evolutionary history, a functional role to be unveiled in a complex biological milieu, and deep mystery with respect to the reaction sequences that might lead to the assembly of the structure, either in nature or in the laboratory (*2*). Such is the narrative in the study by Kim *et al.* on page 238 of this issue (*3*). The authors have achieved a chemical synthesis of the highly complex molecule (+)-11,11′-dideoxyverticillin A (see the figure), a natural product isolated from the fungus *Shiraia bambusicola* (*4*) that possesses anticancer activity (*5*). Their laboratory synthesis, inspired by an analysis of the possible biosynthetic route, reveals much about chemical reactivity in a highly complex molecular environment.

The key reactions used by the authors lead to barely stable structures that might otherwise only be seen under the auspices of biosynthetic enzymes. The synthetic achievement thus raises provocative questions about the biosynthetic enzymes involved in the natural production of (+)-11,11′-dideoxyverticillin A. Such questions may now fuel further inquiry, and the insights gained by the authors may assist in the annotation of the biosynthetic gene cluster connected to (+)-11,11′-dideoxyverticillin A, which contains several proteins of unassigned function (*6*).

The structure of (+)-11,11′-dideoxyverticillin A is extremely complex, with many sterically congested, contiguous stereogenic centers as well as acid- and base-labile and redox-sensitive functionality. Any synthetic strategy must take into account that advanced synthetic intermediates may be unstable. The strategy must therefore include plausible intermediates that are sufficiently stable to survive a range of reaction conditions. Consideration of this type of structure also compels the chemist to turn to the biosynthetic pathway for clues as to how it might be synthesized in the laboratory.

Molecules such as (+)-11,11′-dideoxyverticillin A have some analogy in other natural products, including dithiodiketopiperazines (*7*–*13*). However, (+)-11,11′-dideoxyverticillin A is dimeric, increasing the magnitude of the synthetic challenge. Issues of diastereomerism, steric congestion, and the union of the two complex domains heighten the sensitivity of intermediates toward decomposition and greatly restrict options for assembly. It is even more difficult to execute a tetraoxidation reaction, followed by tetrathiolation/disulfide bond formation. Selective oxidations of the type found in the synthesis of Kim *et al.* would be challenging to achieve with selectivity and efficiency individually; to achieve them all at the same time is another matter altogether. Multisite reactions (*12*) set the stage for devastating losses of material due to the multiplicative amplification of fractional yields in such polyfunctionalization reactions.

Essentially every step in this synthesis is of interest. The authors use few protecting-group manipulations to mask undesired reactivity, and little extraneous oxidation state adjustment. The cobalt-based chemistry underlying the key dimerization step stands on the pioneering work of the authors' laboratory (*13*). The tetraoxidation chemistry, one of the key aspects of the synthesis, is conducted under carefully optimized conditions with a unique manganese-based reagent. In one approach to the final step to form (+)-11,11′-dideoxyverticillin A, the authors use a hafnium-mediated tetrathiolation/oxidation sequence. The reduction of these difficult steps to practice reveals not only the viability of a daring biosynthetically inspired strategy, but also the power of

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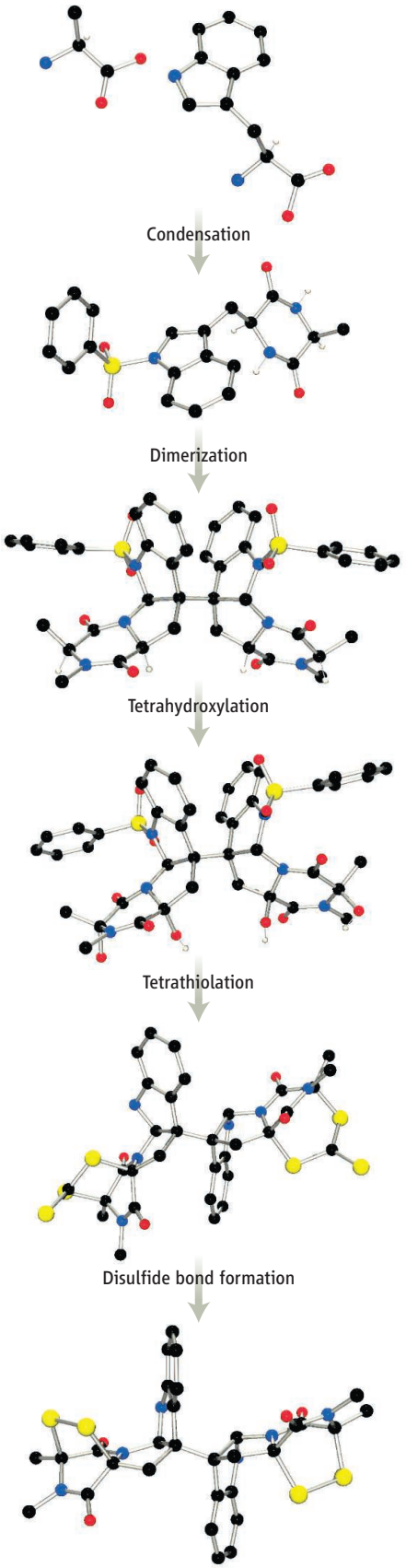

Rising to the challenge. Kim *et al.* report a striking total synthesis of the highly complex natural product (+)-11,11′-dideoxyverticillin A.

remote reaches of the periodical table for diverse bond-forming processes.

Kim *et al.*'s successful strategy for assembly of (+)-11,11′-dideoxyverticillin A suggests that the biosynthetic route may also rely on sophisticated, near-simultaneous multisite oxidation reactions (*3*). But how might such reactions be achieved biosynthetically? The authors point to work by Kirby *et al.* (*14*) and by Fox and Howlett (*6*), who have studied the biosynthesis and the gene cluster responsible for the production of related natural products. Proteins of unassigned function in this cluster bear homologous analogy to p450 oxidase enzymes; the unassigned proteins may be oxidases that mediate multisite oxidations of the type postulated and demonstrated by the current authors.

Kim *et al.* have achieved a remarkable chemical synthesis of a truly complex molecule. Although the final strategy makes the whole endeavor look straightforward, the chemical sophistication of the work is very high. Furthermore, the chemistry has stimulated detailed thinking about the biosynthetic pathway and the biosynthetic genes. In this way, complex molecule synthesis and complex chemical reactivity serve as central intellectual constructs in driving the fields of chemistry and biology forward.

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GENETICS

Leishmania Exploit Sex

Michael A. Miles, Matthew Yeo, Isabel L. Mauricio

Leishmania are the last of the three major groups of trypanosomatid parasites to give up their secret—a healthy capacity for genetic exchange.

Protozoan parasites of the genus *Leishmania* (*Kinetoplastida: Trypanosomatidae*) cause widespread and devastating human diseases. Visceral leishmaniasis is responsible for overwhelming fatal epidemics, and cutaneous leishmaniasis can lead to destructive and life-threatening mucocutaneous lesions (*1*). Since the discovery of these disease agents more than a century ago, there has been debate as to whether they reproduce entirely clonally or undergo genetic exchange, although naturally occurring putative hybrids have been described (*2*). That debate is now over. On page 265 of this issue, Akopyants *et al.* (*3*) provide evidence for genetic exchange in *Leishmania*. This represents the latest in a series of discoveries of sexual cycles operating in eukaryotic pathogens previously thought to be asexual (*4*).

Leishmania infect phagocytic cells of their mammalian hosts, where they are visible as tiny, ovoid cells (amastigotes) with a nucleus and a kinetoplast. The kinetoplast contains a network of minicircle and maxicircle mitochondrial DNA and is a distinctive feature of both *Leishmania* and *Trypanosoma* (a related genus of trypanosomatid parasites). In the sand fly vectors of *Leishmania*, morphology is somewhat more diverse than in the mammal, with various flagellated forms (promastigotes). Yet no distinct male and female gametes or sexual cycle have been described.

Despite the apparent morphological simplicity of *Leishmania*, their taxonomy is complex. They have been divided into two subgenera, *Leishmania* and *Viannia*, and numerous species, partly based on the clinical presentation of infection. Molecular markers have

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