Some would argue that the science/art of organic synthesis is a mature field, and that the pinnacle of achievement has already been reached. Such widely heralded landmark syntheses as Kishi’s total synthesis of palytoxin, and the quest by the Nicolaou group for the even larger marine natural product maitotoxin, weighing in at a burly 164 carbon atoms, 32 rings, and 98 stereocentres, serve as monuments to what can be accomplished in the laboratory. These molecules and other smaller yet comparably complex natural products still hold allure as total synthesis targets — showcases for the often elegant manner in which each individual molecule is realized through a unique and non-obvious retrosynthetic deconstruction.

Methodological advances in the areas of catalysis and C–H functionalization have further driven the field of synthesis towards a biomimetic sophistication in the approach to bond construction without the need for leveraging the brute-force, often highly reactive and largely stoichiometric methods of yesteryear. Most molecules that can be conceived of and are predicted by the basic principles of physics to be stable and isolable can be made, given adequate time and sufficient labour. Great strides towards scalability further speak to our collective mastery of the art of total synthesis. Yet, as powerful as the major technological and conceptual advances of the past half-century have been, small-molecule synthesis continues to be the rate-limiting bottleneck in biomedical research endeavours ranging from iterative cycles of lead optimization for low-molecular-weight drug molecules to the preparation of chemical probes and tools for answering fundamental biological questions.

Nature has evolved through 4.5 billion years to produce an incredibly diverse array of natural products of wide structural variation and amazing complexity. And yet ironically, unlike the myriad synthetic methods that for decades have adorned the pages of journals devoted to chemical synthesis, nature’s synthetic toolbox is surprisingly small and her arsenal for bond construction extremely limited when looked at from a retrosynthetic perspective. Nature makes peptides and proteins of seemingly endless diversity in structure and function using one simple amide-bond-forming reaction between amino acids fewer in number than there are letters of the alphabet, and we now direct such pursuits at the touch of a button. The same is true for oligonucleotide and oligosaccharide synthesis, yet small molecules and natural product synthesis is still largely relegated to the same basic strategy practised in the heyday of modern pioneers such as that used in R. B. Woodward’s classic synthesis of strychnine 60 years ago.

Martin Burke and co-workers now seek to bring the field a bold step closer to reducing complex natural product and small-molecule synthesis to an endeavour
potentially amenable to automation — a blueprint for synthesis on demand (Fig. 1). Writing in Nature Chemistry, they describe a conceptual strategy for the modular construction of natural products that draws clear parallels to what is now routine for the construction of the aforementioned classes of biomolecules. The methodology enabling this strategy is based on iterative cross-coupling chemistry of N-methyliminodiacetic acid (MIDA) boronates, an area pioneered by their research group. The MIDA protecting group for boronic acids effectively ties up the vacant p-orbital on boron, rendering the boronate inert to cross-coupling conditions, and resistant to reagents/reaction conditions used in a wide range of functional group transformations. Indeed such an iterative cross-coupling approach has been employed by Burke to greatly accelerate the preparation of key probe molecules to expeditiously elucidate the mechanism of action of the natural product and antifungal drug amphotericin B (ref. 9).

In the present work, Burke aims to systematize such an approach and apply it to broad classes of natural products. They first use an algorithm to retrosynthetically deconstruct the entirety of the nearly 3,000 known polyene natural products into fragments, which can then be made bifunctional (generally a halogen on one terminus and a MIDA boronate at the other terminus) by application of their methodology. They go on to show that such fragments can be readily stitched together to access the core structural motifs of 75% of this entire family from only twelve discrete building blocks. Burke and co-workers then further demonstrate the applicability of the methods through synthesis in the forward direction of fifteen common polyene natural product motifs using this iterative cross-coupling process. Finally, the authors apply this paradigm to the efficient total syntheses of three representative natural products spanning different subclasses: polyterpene, fatty acid and polyketide, using pre-constructed readily synthesized capping groups to complete each molecule.

Although, admittedly, the polyene subfamily of natural products may represent the low hanging fruit for illustration of the potential of this conceptual approach, the achievements here lay the groundwork for extension to other more complex families of natural products. Of key importance for robust application of this platform to a much wider scope of natural products will be improvements in the effectiveness of iterative enantiospecific sp² – sp³ cross-coupling methods, an area of significant ongoing investigation by many researchers in the field of synthetic chemistry. The ultimate potential of a platform such as that described in the paper by Burke and co-workers is yet to be determined, though the possibility of being able to quickly assemble natural products and low-molecular-weight drug candidates using complex building blocks is highly intriguing. Furthermore, one could readily imagine endless recombinations of nature’s building blocks in ways evolution has not yet realized in order to make unnatural products of comparable structural diversity and potential biological activity, with the possibility to greatly expedite the chemist’s ability to produce the molecules that will answer countless questions of biological significance.

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References

ATMOSPHERIC CHEMISTRY

Intermediates just want to react

Many of the rate parameters used in models of tropospheric chemistry are obtained through laboratory ozonolysis experiments. Now, results on the self-reaction of an important, but long-elusive, intermediate could alter many of those inferences.

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A substantial removal mechanism for alkenes from the Earth's troposphere is their reaction with ozone, which proceeds with the formation of reactive intermediate species, carbonyl oxides — often called Criegee intermediates (after Rudolf Criegee, who described their role in ozonolysis). Carbonyl oxides have been postulated to contribute to atmospheric HO₂ and NO₂ cycles and to participate in aerosol formation. However, it is only very recently — since the discovery of an efficient laboratory method for producing carbonyl oxides — that gas-phase Criegee intermediates could be studied directly. Most of our knowledge about their reactivity, and about their formation in ozonolysis, relies on a long series of careful but indirect measurements, determining the effect of changing reactant concentrations on the yields of stable ozonolysis products.

Ozonolysis involves a tremendously complex web of reactions (Fig. 1), so inference about any particular reaction depends on what is known or assumed about the rest of the web. Reactions that are inherent to the ozonolysis system are hence of particular importance in all indirect laboratory measurements of Criegee intermediate reactions. Now, Lin, Lee and colleagues have made measurements and calculations that show a surprisingly fast rate coefficient for one of these inherently important reactions: the self-reaction of the smallest Criegee intermediate, formaldehyde oxide (CH₂OO).

The reaction of CH₃ radicals with O₃ produces CH₂OO, the infrared absorption spectrum of which is known. Lin, Lee and colleagues now use time-resolved Fourier-transform infrared spectroscopy to monitor the CH₂OO production and decay following pulsed-laser formation of CH₃ radicals in the presence of O₃.