The art and science of constructing the molecules of nature

Embedded within this issue of PNAS is a Special Feature* comprising 3 Perspectives and 25 research articles dealing with the theme of natural product synthesis—the art and science of constructing the molecules of nature in the laboratory.

The birth of this discipline coincides with the synthesis of urea by Friedrich Wöhler from ammonium cyanate in 1828, because this compound is a naturally occurring substance. Besides giving birth to organic synthesis, that landmark event served to "demystify" nature by burying, once and for all, the myth that the synthesis of nature's molecules is her exclusive domain. These days, the discipline of natural product synthesis, both total and partial (semisynthesis), is an important field of investigation whose dividends stretch from new scientific knowledge to practical applications. Considered by many as the flagship of organic synthesis, natural product synthesis symbolizes the power of chemical synthesis at any given time and defines its scope and limitations. It also serves to sharpen the tool of chemical synthesis by attempting to push its frontiers into higher molecular complexity, diversity, and efficiency.

The field of natural product synthesis has been recognized with the Nobel Prize in Chemistry with constant periodicity over the entire history of the award. Included among these prizes are those given to E. Fischer (in 1902; for his work on sugar and purine syntheses), H. Fischer (in 1930; for his researches into the constitution of haemin and chlorophyll and especially for his synthesis of haemin), R. Robinson (in 1947; for his investigations on plant products of biological importance, especially the alkaloids), R. B. Woodward (in 1965; for his outstanding achievements in the art of organic synthesis), and E. J. Corey (in 1990; for his development of the theory and methodology of organic synthesis). These days, the field appears as vigorous as ever, and its future looks as promising as its past has been rewarding. There are many reasons why natural product synthesis withstood the test of time as an enabling and rewarding science and technology, not to mention its attractiveness as an intellectual and creative endeavor offering opportunities for discovery and invention.

Although the theme of natural product synthesis is attracting a lively interest in research laboratories around the world today, the reasons for practicing it vary. A synthetic chemist may wish to exploit the opportunity that a challenging molecular architecture presents for the discovery and invention of new synthetic strategies and methods to be used in a wider range of applications. Another practitioner may wish to produce a scarce, but biologically intriguing, natural product in larger quantities for further extensive biological investigations and/or medicinal applications. And, to the extent that a natural substance of some potential application can be synthesized in the laboratory, or the chemical plant, in a more cost-effective process than the one entailing its extraction from nature, its use becomes economically more feasible and desirable. Yet another synthetic chemist may be interested in applying his or her skills and developed synthetic technologies to tweak the structure of a natural product for the purposes of enhancing its potency or improving its selectivity and physical and chemical properties. Such endeavors often lead to superior pharmacological properties than those possessed by the natural products themselves in terms of efficacy and safety. And, as surprising as this may sound these days, the chemical synthesis of a natural product still provides the absolute proof of the assigned structure, for the recent literature abounds with revisions of structures of natural products whose originally isolated minute quantities complicated their characterization. Finally, there are those who will proudly and bravely proclaim that they enter total synthesis campaigns for the intellectual challenge and sheer excitement of the endeavor. Such synthetic odysseys, like Odysseus' journey to Ithaca from Troy, provide wonderful opportunities for discoveries and inventions and ideal arenas to educate and train young practitioners of the art of synthesis. The fundamental and ubiquitous nature of this art in so many disciplines, including biology, and the drug discovery and development process underscore the importance of both advancing the field for its own sake and educating new generations of synthetic chemists.

Given the centrality and importance of the field of natural product synthesis as articulated above, it is not surprising that endeavors in total synthesis continue to lure some of the most talented organic chemists of our times as they did in generations past. To be sure, this field will continue to excite, enable, and reward as we move forward in the 21st century, because a myriad of intriguing molecules from nature still remains to be discovered. And, when they are, they will hopefully stimulate new campaigns that will inevitably lead to further sharpening of the enabling tool of chemical synthesis as we strive to mimic nature in its elegance and efficiency.

The impressive collection of Perspectives and research articles in this issue of PNAS demonstrates both the power and value of natural product synthesis as outlined above. Because of the importance of natural products in chemistry, biology, and medicine, the theme of natural product synthesis seems most appropriate for highlighting in a multidisciplinary journal such as PNAS.

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*Natural Product Synthesis is one in a continuing series of Special Features. Themes of previous features have included: Supramolecular Chemistry; Sustainable Development; and, most recently, Asymmetric Catalysis. Scheduled for future issues are Chemical Theory and Computations; Long-Range Electron Transfer; and Molecular Electronics. One objective of these Special Features is to enhance the journal's ongoing initiative to expand its coverage of the physical and social sciences. PNAS continues to encourage and welcome contributions of research articles in all areas of the natural and social sciences, as well as mathematics.

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