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Introduction: Natural Product Synthesis

The synthesis of natural products plays such an important role in organic and biological chemistry that it is surprising that none of the previous 87 thematic issues of *Chemical Reviews* have been devoted to the subject. Since this is one of the oldest and most tradition-rich fields of chemistry, and the topic of innumerable monographs and compendia, it is difficult to offer any new or not oft-repeated general words of introduction. In the last half-century, many leading practitioners have paid elegant tribute to both the science and art of organic synthesis, and their works vividly illustrate why it is an enduring discipline that never goes out of style. Those on the outside looking in cannot help but to admire the incredibly complex structures that can be accessed with such exquisite precision. There is scarcely an organic chemist who does not hope to discover some procedure or reaction that would be useful to the field.

In this issue, a broad and internationally diverse spectrum of prominent experts showcase the vitality of natural product synthesis today. Their contributions furthermore illustrate the depth of the discipline, including underlying physical principles, design elements inspired by nature, and the molecular basis for biological activity. Importantly, around half of the drugs currently in clinical use are of natural product origin. The Editors are extremely grateful for the care and thought the authors have invested in this information- and idea-rich collection of 18 articles, which have been grouped as follows.

Natural products from marine sources, many with important types of biological properties, have yielded some of the most complex synthetic challenges in recent years. These are treated in several reviews, starting with two by Yeung and Paterson, and Nakata. The former covers marine macrolides such as the spongistatins, laucascandrolide A, and callipeltoside A. The latter deals with polycyclic ethers such as brevetoxin-B and gambierol. Other types of macrolides are discussed in the article by Kang and Lee. Their focus is on oxolane, oxane/oxene, and cyclic acetal or hemiketal macrodiolides that have been isolated from both microorganisms and marine sources. In the review by Inoue, specific strategies for constructing trans-fused polycyclic ethers—a motif that repeatedly recurs in marine natural products—are compared.

The article by Aho, Pihko, and Rissa focuses on the synthetic challenges associated with a functional assembly found in polyether antibiotics, marine natural products, and insect pheromones—non-anomeric spiroketals. The subtle interplay of stereoelectronic and conformational effects required to stabilize such structures is insightfully discussed. Hamada and Shioiri then detail syntheses of marine cyclic peptides and depsipeptides. These are characterized by unusual amino acids and exhibit unique conformational properties and biological activities. Clive, Yu, Wang, Yeh, and Kang describe the synthetic chemistry of halichlorine and the pinnaic acids, which are marine azaspirocycles that have attracted attention from many research groups.

Four articles are concerned with total syntheses of natural products with other types of functional group arrays. That by Miyashita and Imanishi deals with epoxyquinones, which are widely distributed in nature, are commonly highly functionalized, and exhibit antitumor, antibacterial, antifungal, and other biological activities. The review by Kang, Kang, Lee, and Buglass focuses on *tert*-alkylamino hydroxy carboxylic acids in which the *tert*-alkyl moiety is a stereocenter. The challenges associated with enantioselective syntheses are analyzed. Sunazuka and Ōmura report on total syntheses of microbe-derived α-pyrone meroterpenoids. These may serve as platforms for therapeutic drugs for hypercholestemia and Alzheimer's disease. Syntheses of dibenzocyclooctadiene lignans, all of which have axial chirality, are critiqued by Chang, Reiner, and Xie.

In the review by Welzel, the synthetic targets are grouped by function. Either they are acceptor substrates for the transglycosylases involved in biosyntheses of bacterial peptidoglycans that are responsible for cell integrity, or they interfere with the transglycosylation. Two articles then deal with specific natural products. That by Kuwajima and Tanino compares strategy and design in syntheses of ingenol that have been reported over the last two decades. Chen and Huang provide an analogous treatment of reserpine, ranging from Woodward's classical total synthesis in 1958 through the nine additional routes that have been reported to date. The target molecules in the treatise by Tatsuta and Hosokawa are also selected to illustrate strategy and design, and they

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come from the "big four" classes of antibiotics: macrolides, aminoglycolsides, β-lactams, and tetracyclines.

Two articles have a particularly strong connection to biosynthesis. That by Yoder and Johnston examines biomimetic polyolefin cyclizations to terpenes and steroids, and it includes heretofore unavailable material from Stork and Eschenmoser of considerable historical interest. Beaudry, Malerich, and Trauner highlight the increasing evidence for electrocyclic reactions in biosynthetic pathways and recount the growing number of biomimetic syntheses. Another pericyclic process, the intramolecular Diels−Alder reaction, sees extensive use in terpenoid, alkaloid, and polyketide syntheses, as detailed in the concluding review by Takao, Munakata, and Tadano.

It is by no means possible to adequately cover such a broad field in a thematic issue of only a few hundred pages, and there will undoubtedly be enthusiastic readers left wanting more. Fortunately, there is a partial solution. Other recent articles in *Chemical Reviews* dealing with natural product synthesis are cross-referenced to this one on the journal web site. Also, future installments can be anticipated in the course of upcoming regular issues.

In summary, this thematic issue provides an incisive and exciting glimpse into cutting-edge issues in the ever-evolving field of natural product synthesis. It admirably illustrates the key role that synthesis plays in advancing the frontiers of chemistry and allied disciplines, as well as the many challenges remaining for future generations of researchers.

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