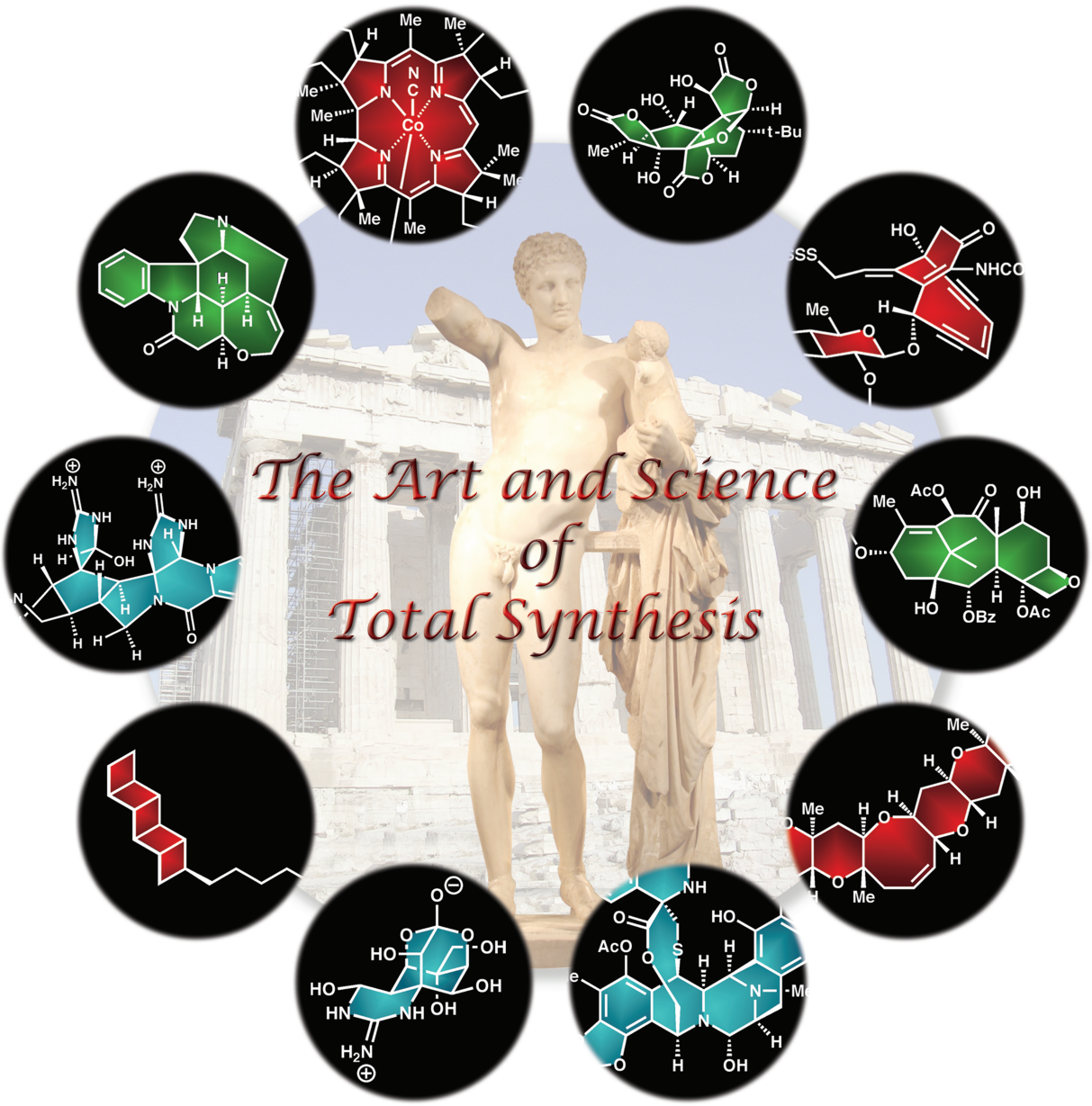
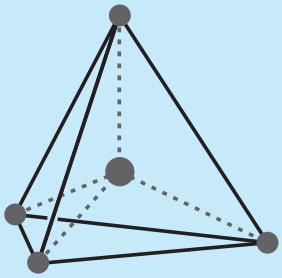

The Art and Science
of
Total Synthesis



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Introduction: The Advancing Field of Total Synthesis

Creativity and problem-solving ability are arguably the two most important traits of successful people in all endeavors. Developing these skills in young students is, therefore, of utmost importance for their success, and is critical to the continued advancement of science and technology. Total synthesis presents to its practitioners many challenging problems in search of creative solutions. Therefore, the discipline is useful not only for advancing the chemical and biological sciences by rendering bioactive molecules readily available, but also for training and preparing young scientists to be competitive in an increasingly demanding and globalized environment.

The success of *Classics in Total Synthesis I* and *II* as educational tools is reflected in their broad acceptance by students and educators alike. It is especially satisfying and rewarding to read about imaginative synthetic approaches from young assistant professors who, as students, were inspired by these books. Much has happened within the field since the publication of *Classics II* in 2003. New young players have appeared on the scene, and novel ideas and concepts have transformed the landscape of the discipline. This is clearly reflected in the fact that 15 of the 25 chapters to follow in this volume feature molecules from twenty-four principal investigators who do not appear in either *Classic I* or *II*. *Classics in Total Synthesis III* was penned with the motivation and intention of continuing to inspire young students. It also serves as an update on the state of the art in total synthesis and as a reference book for synthetic organic chemists.

1.1 Targets

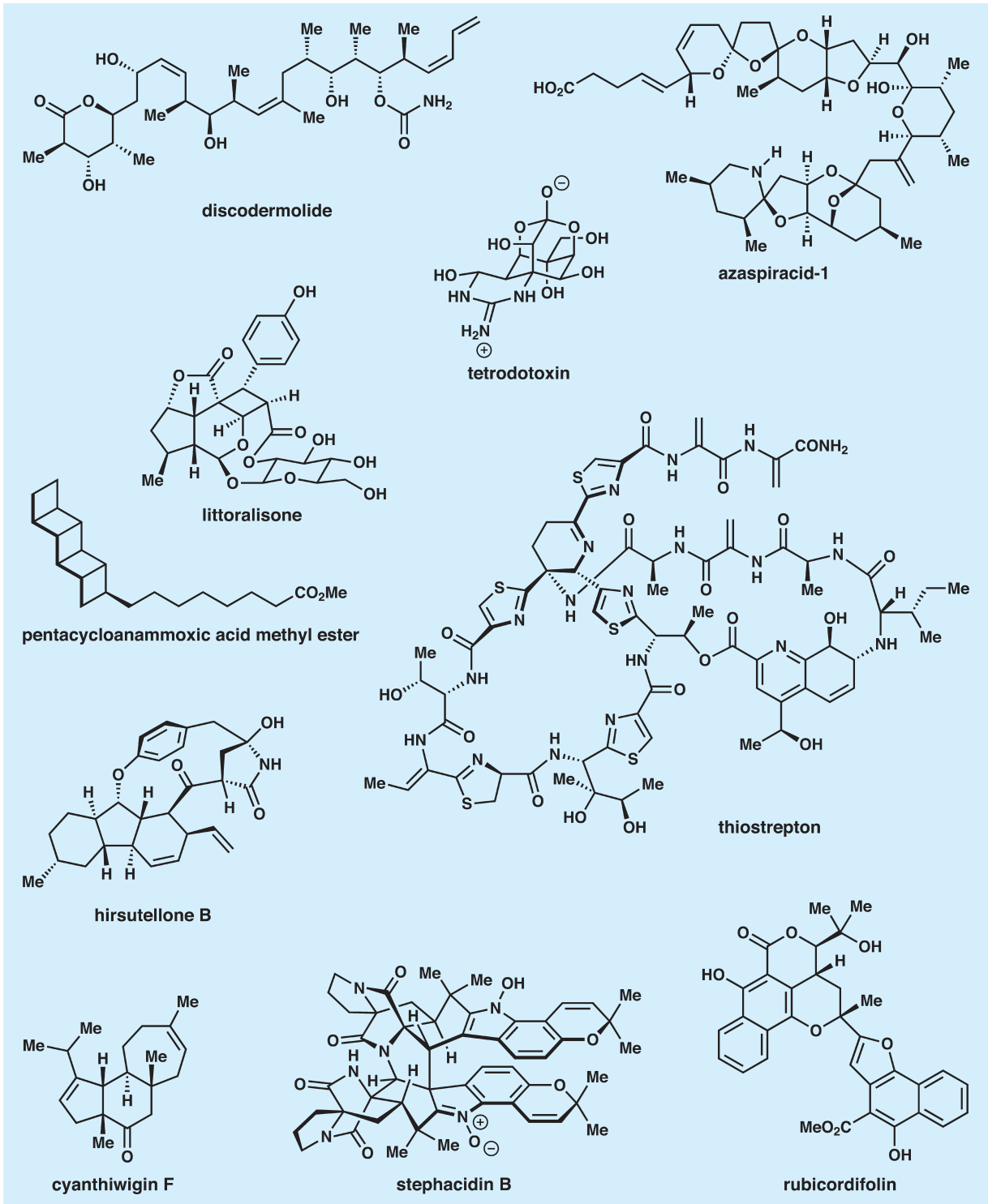
Nature employs a limited arsenal of building blocks and reactions to construct secondary metabolites that possess significant variations in both structure and function. Synthetic organic chemists continue to be challenged and inspired by nature, with its seemingly limitless variety of molecular architectures. As shown in Scheme 1, *Classics III* features a diverse array of targets selected from several major structural classes (e.g., polyketides, terpenes, alkaloids, polypeptides, and lipids). The featured molecules vary dramatically in size, containing anywhere from 11 to 72 carbon atoms, and the carbon skeletons are decorated with between 1 and 42 heteroatoms. One molecular target, tetrodotoxin, possesses as many heteroatoms (eight oxygens, three nitrogens) as it does carbons. The resulting structures are assembled into 0 to 15 rings, ranging from epoxides (3-membered) to large macrocycles (up to 27-membered). The target molecules also include anywhere from 2 to 20 stereocenters; one of the natural products, azadirachtin, contains 16 contiguous stereogenic centers.

As eye-opening as these metrics are, they fail to convey the unique structural properties of some of the featured natural products. For example, chlorosulfolipid cytotoxin contains six chlorine atoms, while pentacycloanammoxic acid methyl ester possesses an unprecedented array of five fused cyclobutane rings. A few molecules, such as 11,11′-dideoxyverticillin and stephacidin B, have unusual heteroatom–heteroatom bonds (S–S and N–O, respectively). Yet others, such as the nine-membered ring enediynes kedarcidin chromophore and maduropeptin chromophore, are fleeting species that have limited half-lives under ambient conditions. On occasion, the full appeal of a synthetic target is not evident until after the synthesis has been completed, and such is the case with molecules that ultimately require structural revision. One particularly intriguing example, abyssomicin C, has an unusual, naturally occurring atropisomer (i.e., *atrop*-abyssomicin C) first identified through its total synthesis.

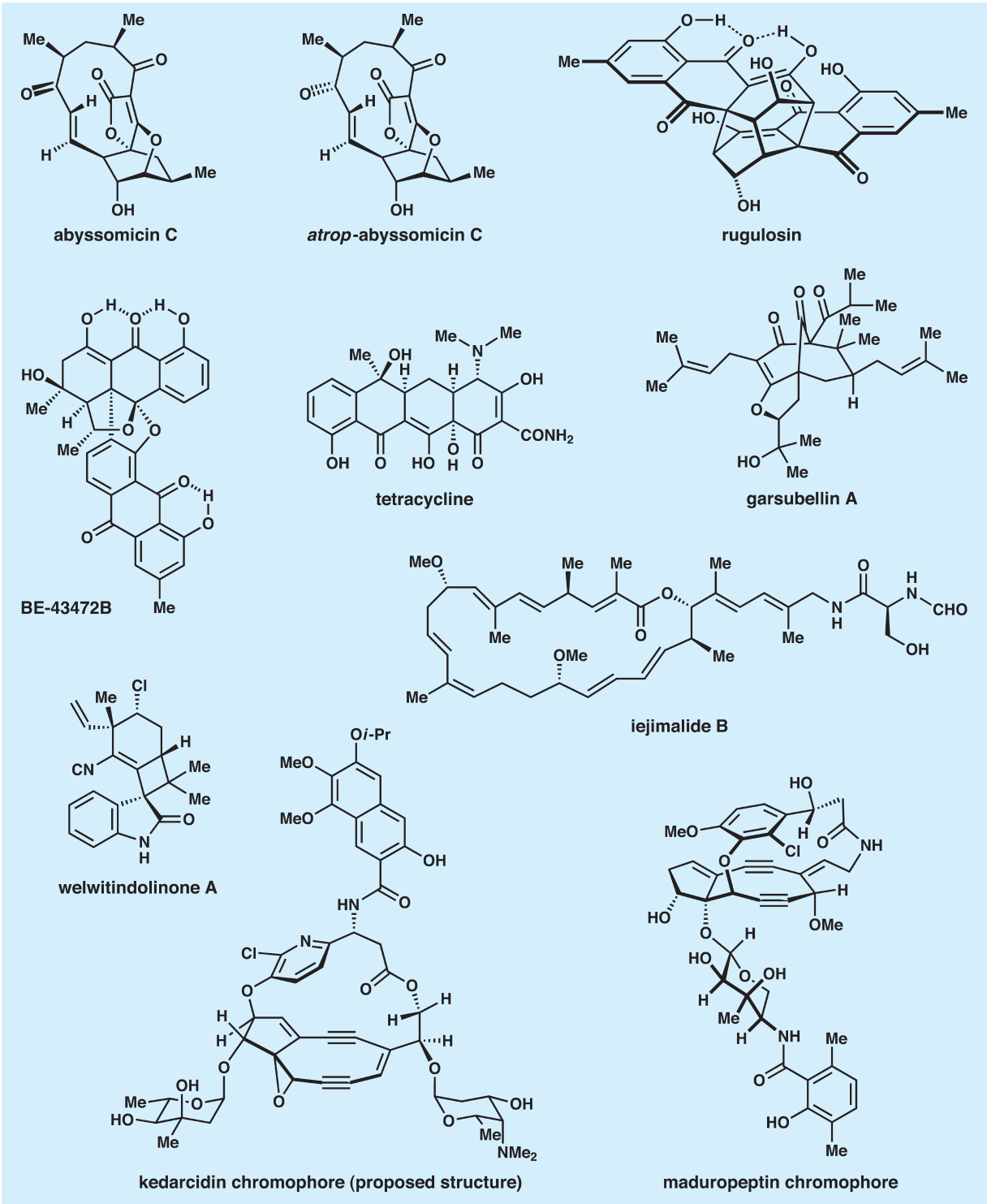
Although most of this book is devoted to the synthesis of natural product targets, selected aspects of the history, biosynthesis, function, and medical use (or potential use) of these and related molecules are also highlighted. In many cases, this background information reveals opportunities for total synthesis to drive key advances in research on the target molecules.

1.2 Strategies and Methods

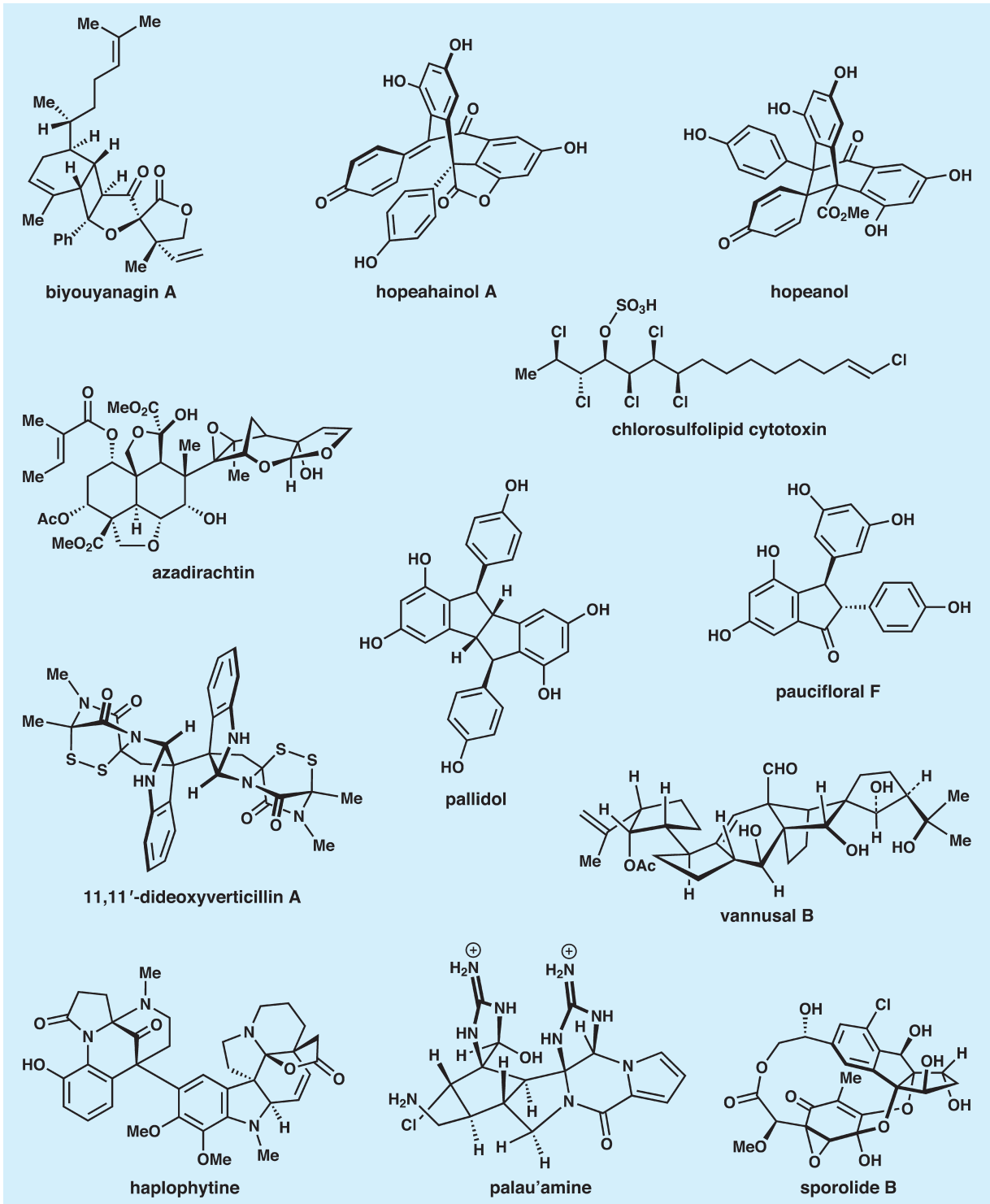
Strategies for the total synthesis of natural products are as varied as the architectures of the target molecules themselves. In several cases, more than one approach for the construction of the molecule is featured, in order to highlight different successful strategies for



Scheme 1. Molecular structures of selected natural products featured.



Scheme 1. Molecular structures of selected natural products featured (continued).



Scheme 1. Molecular structures of selected natural products featured (continued).

accessing the same structural motifs. The development and selection of synthetic strategies is intimately linked to the availability of enabling reactions. This book continues in the *Classics* tradition of providing brief overviews of key methodologies associated with the featured structure types and/or synthetic strategies. Selected examples of these methods are shown in Scheme 2. In the years since the writing of *Classics II*, multiple reaction types, loosely grouped into the categories of C–H functionalization (see Scheme 2a) and asymmetric organocatalysis (see Scheme 2c), have become quite popular. As we shall see, both C–H functionalization and organocatalysis comprise multiple distinct and complementary reaction types with origins that can be traced back decades. In view of the breadth of these fascinating topics, only a brief overview is possible in the allotted space. However, it is hoped that the selected examples will whet the reader's appetite to find out more about these promising reaction classes.

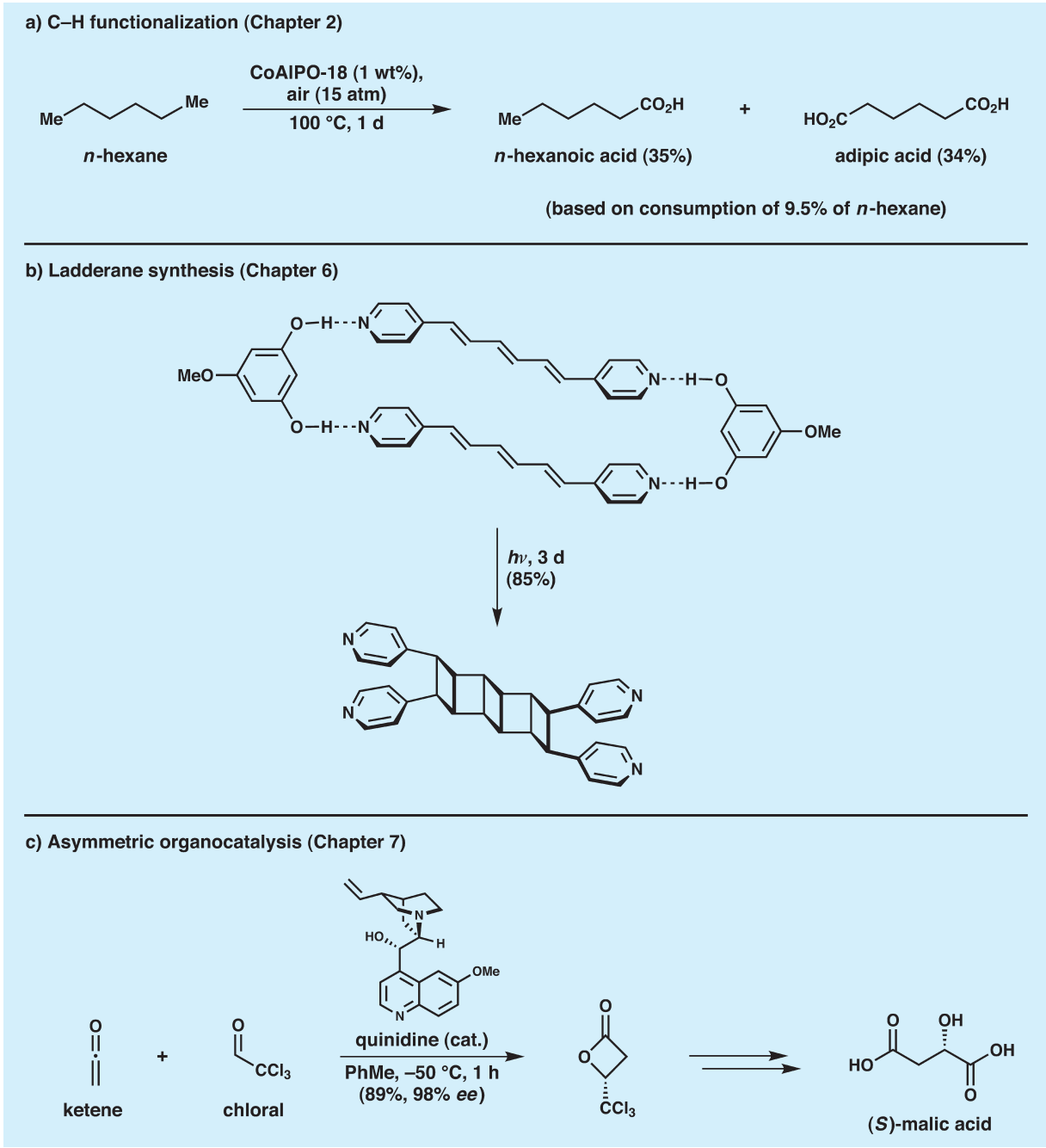
Other reactions, including the singlet oxygen ene reaction (see Scheme 2d), the [2+2] photocycloaddition (see Scheme 2e), the *o*-quinone Diels–Alder (see Scheme 2g), the [2+2+2] cycloaddition (see Scheme 2h), and the SmI_2-mediated ketyl–olefin cyclization (see Scheme 2i) also are discussed in the context of syntheses that employ these transformations. Furthermore, although the featured syntheses do not employ a cascade ladderane synthesis (see Scheme 2b) or an asymmetric halogenation reaction (see Scheme 2f), these reaction types are covered, since they represent promising approaches toward some of the featured targets and other related molecules.

The inclusion of the above methodologies does not imply that older reactions are obsolete. Indeed, familiar and time-honored reactions such as the Diels–Alder cycloaddition feature prominently in several syntheses. The state of the art in synthesis is an amalgamation of both new and old techniques. The prudent chemist will consider all options available before selecting those that appear to be the most advantageous.

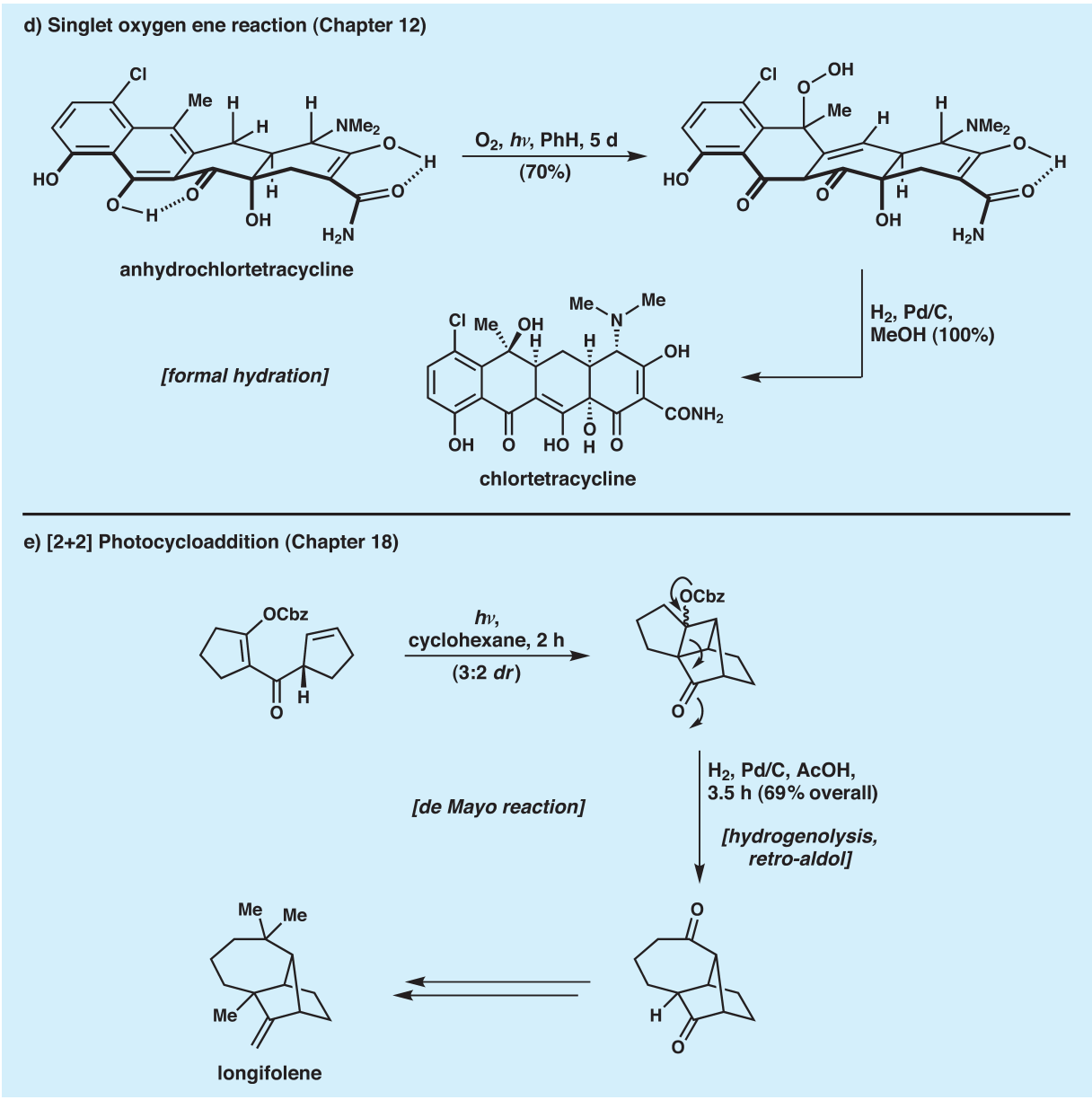
To young students who are not as familiar with the essence and beauty of synthesis, we offer the following inspirational quotes:

> *"The domain in which chemical synthesis exercises its creative power is vaster than that of nature itself".*[1]
>
> Mercelin Berthelot

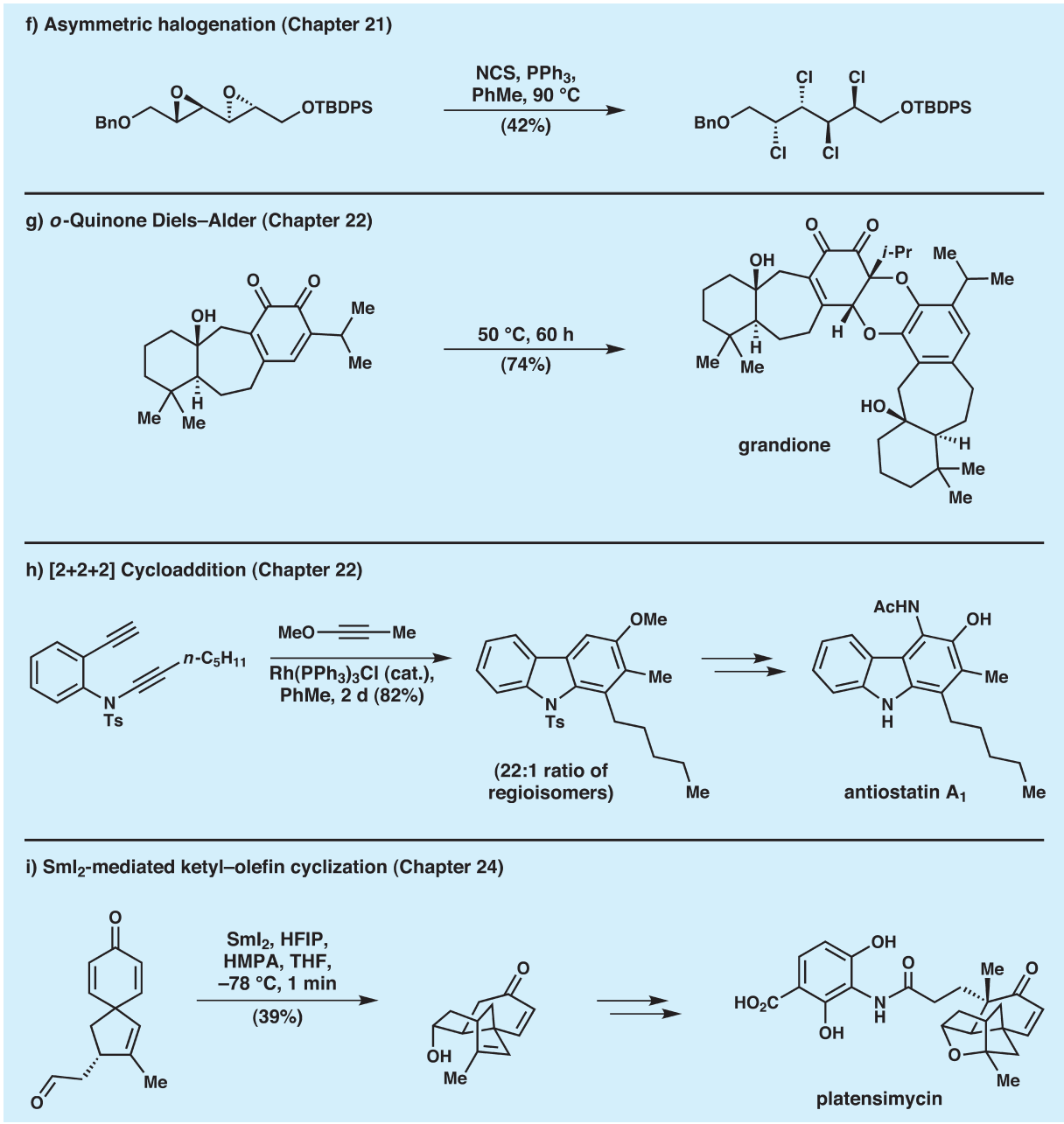
> *"The gift of original melody, as it is called, is rare and precious. But no melody could possibly speak to us except a combination of perfectly well known elements. The only originality is in their assimilation and reproduction".*[2]
>
> John Pentland Mahaffy



Scheme 2. Representative examples of selected methodologies featured.



Scheme 2. Representative examples of selected methodologies featured (continued).



Scheme 2. Representative examples of selected methodologies featured (continued).

1.3 Classics in Total Synthesis III

The following chapters in this book primarily feature total syntheses completed since the writing of *Classics II* in 2003. Unfortunately, space does not allow for all noteworthy total syntheses to be included; consequently, the final selection of molecules and approaches reflects a desire to encompass a broad range of structural classes and synthetic strategies. The framework of each chapter should be familiar to readers of previous volumes in the *Classics* series, but with two notable changes. For improved clarity, in those chapters where more than one total synthesis is featured, the retrosynthetic analysis for a particular approach is now followed immediately by a discussion of the synthetic campaign. We also have taken the liberty of incorporating an artistic frontispiece at the beginning of each chapter.

The following 25 chapters feature 42 total syntheses and 10 methodology highlights. We truly have enjoyed writing about the diverse and stimulating array of topics contained within *Classics III*. It is our sincere hope that the reader will find the contents to be equally enjoyable, instructive, and inspirational.

References

1. *Chemically Speaking, A Dictionary of Quotations*, (Eds.: C. C. Gaither, A. E. Cavazos-Gaither), IOP Publishing, Philadelphia, **2002** p. 583.
2. J. P. Mahaffy, *What Have the Greeks Done for Modern Civilisation*, G. P. Putnam's Sons, New York, **1910**, p. 10.