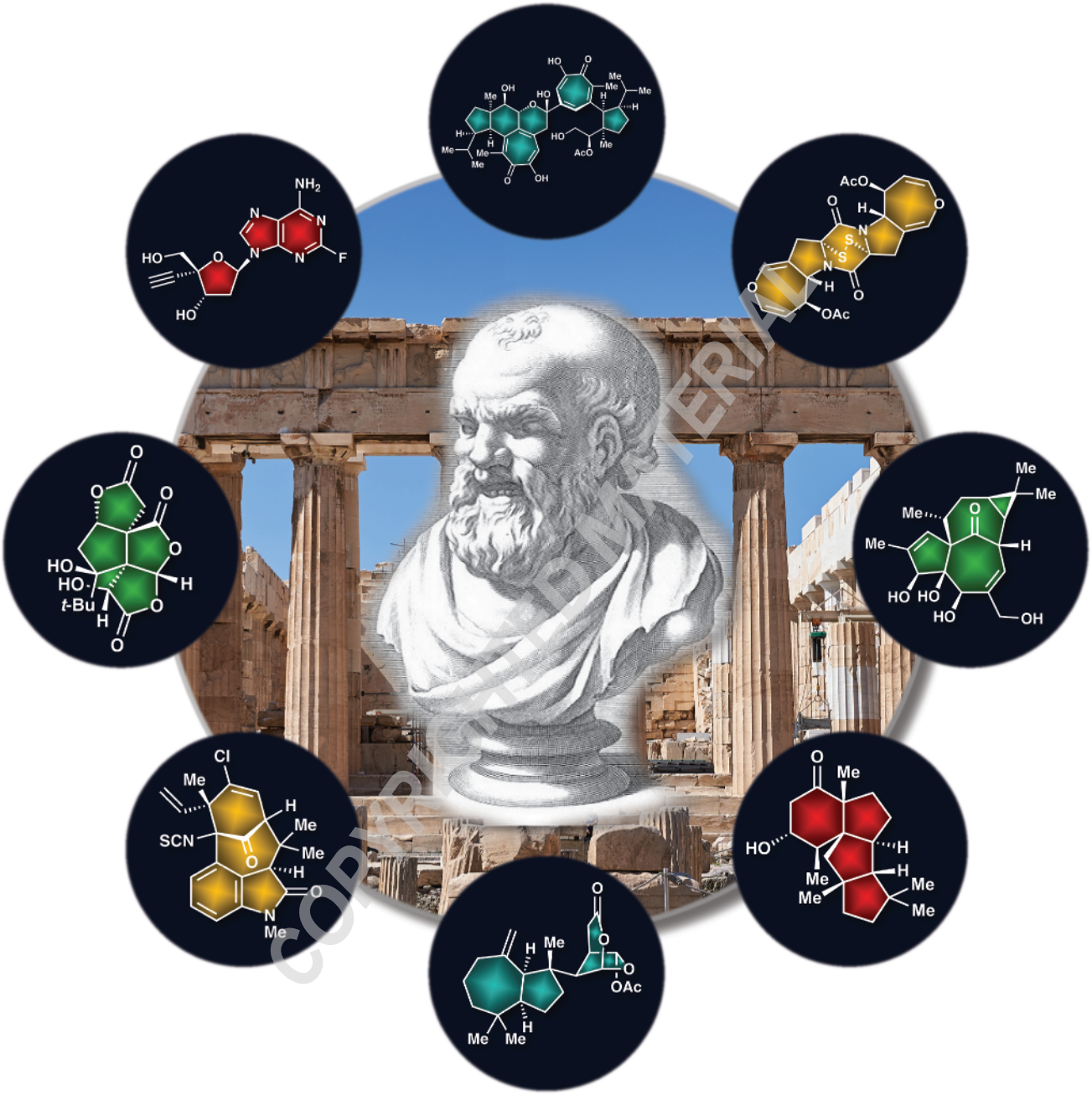

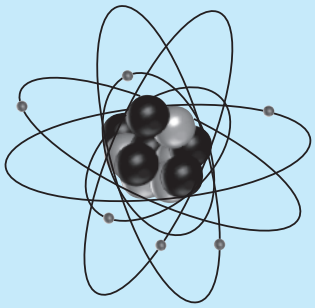

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Introduction: Total Synthesis Marching on with New Methods and Strategies and with Molecules for Biology and Medicine

With its power constantly increasing, the essence of total synthesis remains the same. What changes is its purpose. Originally, it was to confirm a proposed structure of a natural product, then it became a means to produce natural products in bulk as a means to fulfill a need for society. From here it turned into a practice to demonstrate intellect and elegance, along with an opportunity to discover and develop new synthetic methods, to test the applicability of newly discovered methods, and to fill voids where existing methods failed. The ability of biochemists and other chemists to isolate minute amounts of natural products and determine their structures created the need to render them readily available for biological investigations. This challenge was taken up by synthetic chemists in the last decades of the 20th century, who delivered, through total synthesis, not only the targeted scarce natural products but also their designed analogues for extensive biological studies. Today, total synthesis endeavours blend all these aspects of the art and science of this discipline with

Classics in Total Synthesis IV: New Targets, Strategies, Methods, First Edition.
K. C. Nicolaou, Ruocheng Yu, and Stephan Rigol.

constant new additions. In its modern paradigm, and with mission, total synthesis is gathering momentum as a harmonious endeavour aiming not only for its own advancement but also as a partner to biology and medicine in a systematic way. It has a profound impact on the sciences of chemistry, biology, and medicine, specifically interfacing and facilitating chemical biology, medicinal chemistry, and the drug discovery and development process in general.

Classics in Total Synthesis IV features a variety of total syntheses that have been published in the literature since 2009 and more. For comparison and perspective reasons, the total syntheses of natural products related to those covered herein are, in certain cases, included. And while the main focus of the book is still the art and science of total synthesis, aspects of new synthetic methods and analogue design, synthesis, and biological investigation are also discussed. The latter underscores the trends in the state of the art of the discipline and emphasizes its importance to the science of organic synthesis in general and its impact on biology and medicine. It is also interesting to note that total synthesis still retains, to this day, its role of structure confirmation or revision, despite the enormous progress in analytical techniques and instrumentation. Statistics based on past total synthesis endeavours originating from the Nicolaou group, which have delivered almost 200 naturally occurring molecules, show that 13% of them contributed, in one way or another, to some structural aspect of the molecule, whether absolute configuration, revision of at least one stereogenic center of the previously assigned structure, or even its total synthesis and prediction of its existence in Nature before it was discovered. These seemingly odd occurrences are still common. However, the errors should not be attributed to the heroes of isolation of natural products. Due to the scarcity of numerous naturally occurring compounds, their characterization is regularly conducted by investigating only minute amounts, which, understandably, sometimes results in inaccuracies concerning their structure. These investigators did not have the privilege of collecting sufficient quantities of their products from their rare sources, a fact denying them the full armamentarium of analytical techniques, including the optimum tool of X-ray crystallography.

1.1 Targets

Nature's molecules are of unimaginable variety, complexity, novelty, and biological activity. This is more impressive if one considers the limited collection of building blocks, reactions, enzymes, and conditions as compared to the vast number of building blocks, ever-growing number of synthetic methods, catalysts, and reaction conditions that synthetic organic chemists enjoy, and yet we still have to surpass Nature's power and beauty when it comes to biosynthesis and novelty of natural products' structures.

Figure 1 highlights a selected number of natural products featured in this book, *Classics IV*, and yet these molecules represent

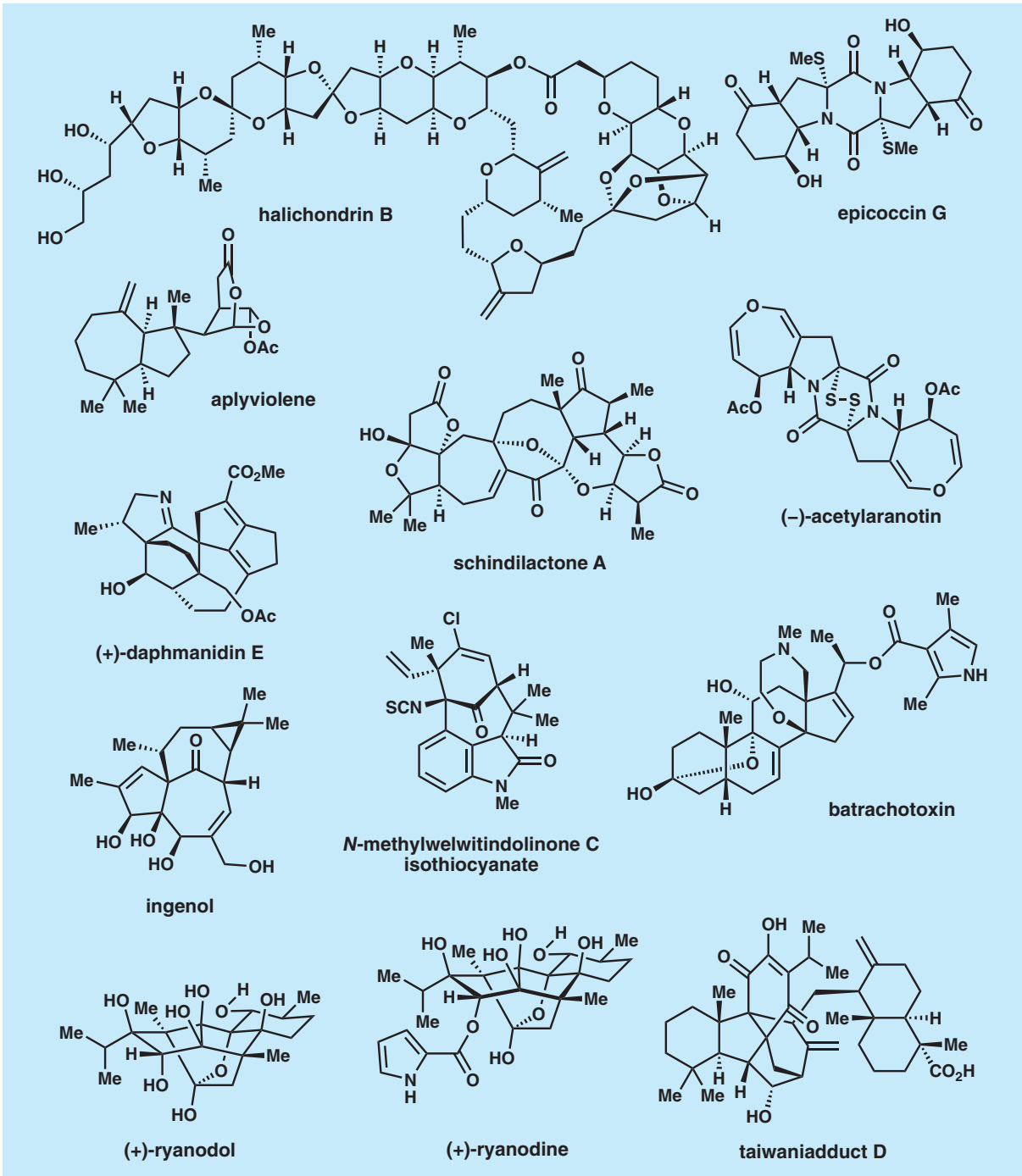


Figure 1. Molecular structures of selected natural products featured.

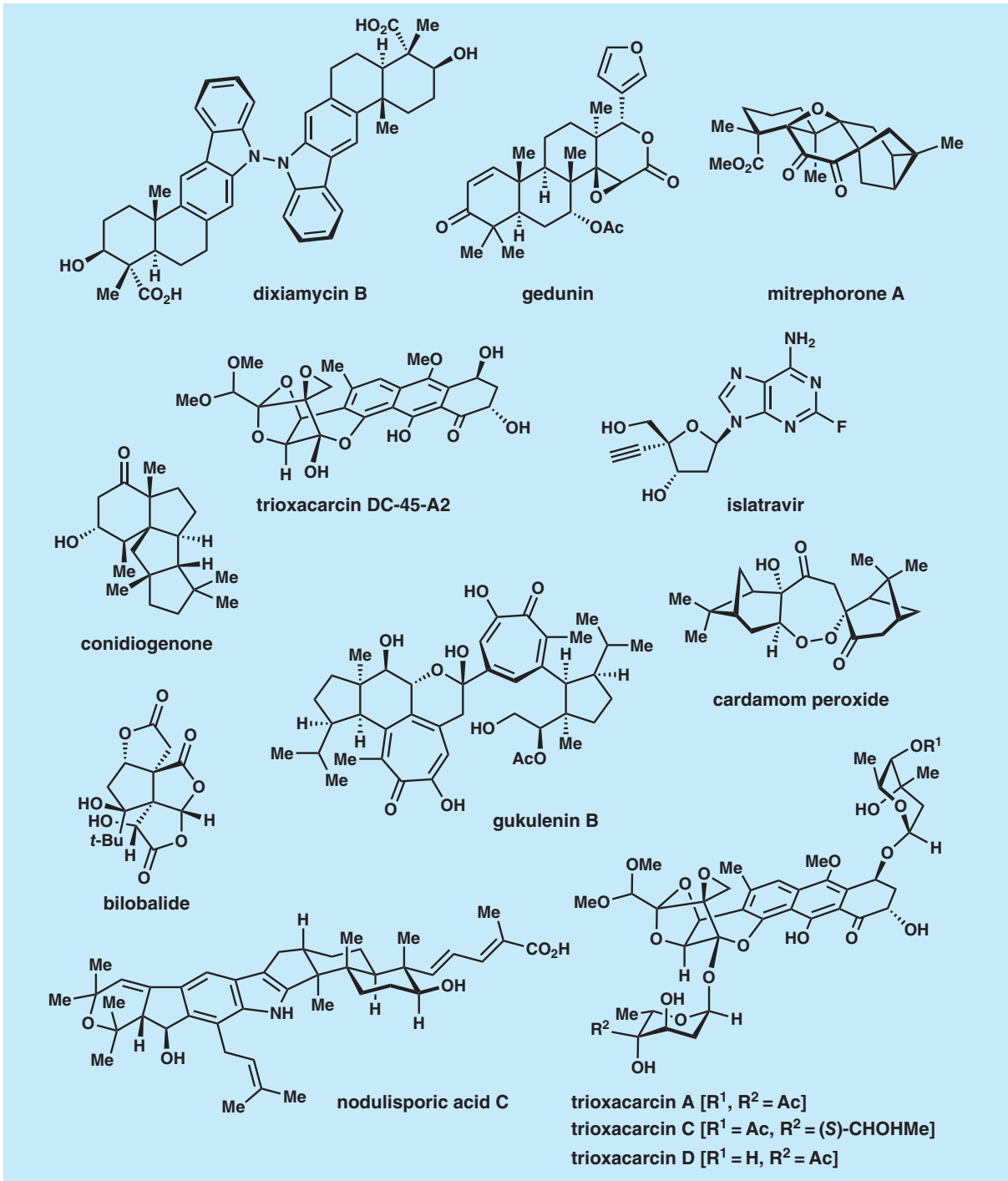


Figure 1. Molecular structures of selected natural products featured (continued).

the impressive richness of Nature in terms of molecular complexity and beauty, biological activity, and laboratory synthetic challenge. Behind these structures are hidden numerous golden opportunities for discovery, enrichment of the art and science of total synthesis in particular and organic synthesis in general, synergy studies with biology and medicine, and education and training of young practitioners of organic synthesis. The latter students will be equipped with knowledge, expertise, and inspiration to apply their skills for the benefit of science and society in the future.

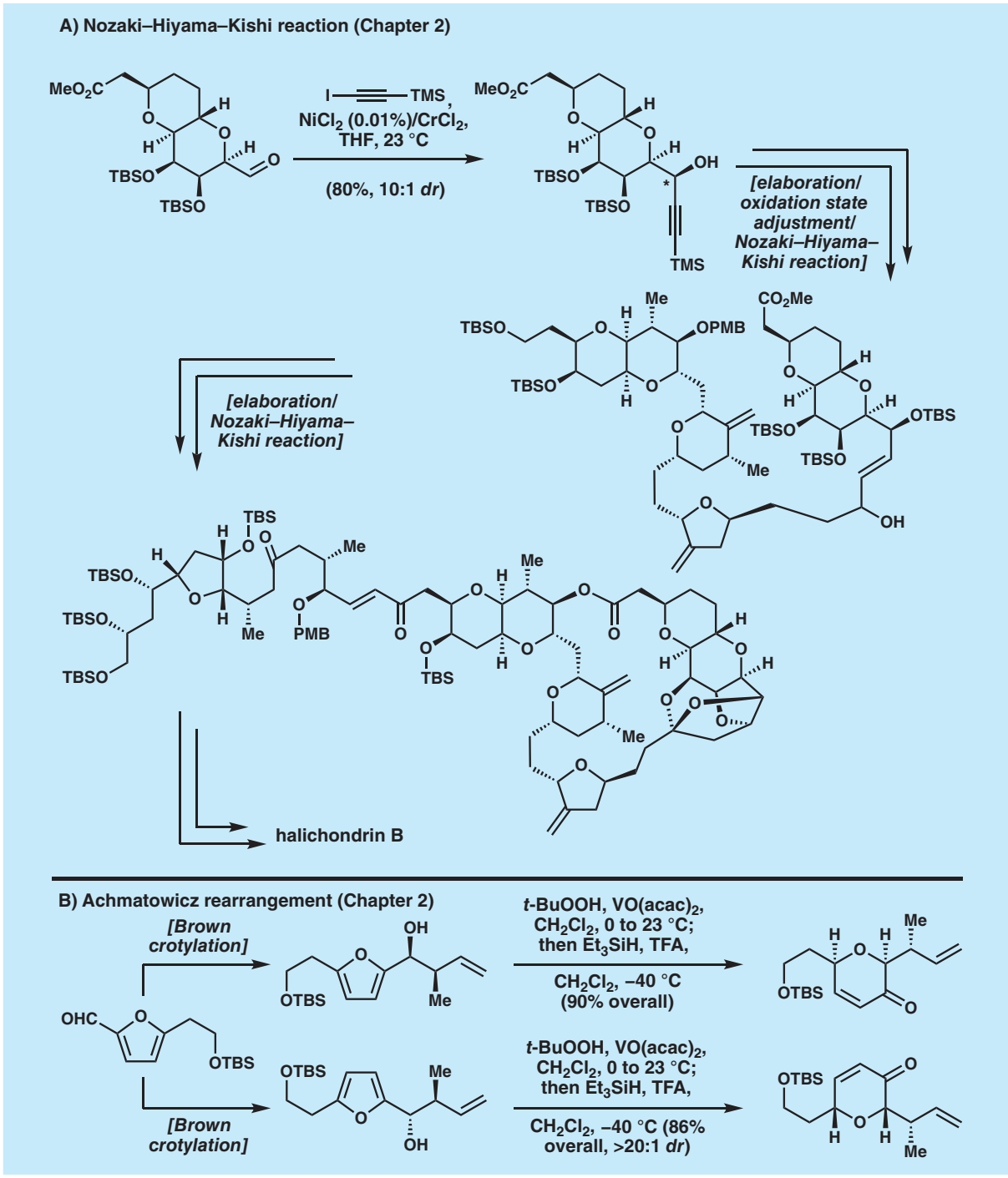
In going through the Chapters of this book, one can learn of the efforts of the pioneers to synthesize each naturally occurring molecule and, in many instances, their analogues for biological investigations. Although not all the time, in several cases, the path of the practitioner leads to drug candidates for clinical trials and beyond, thus enriching the repertoire of medicines for curing diseases, such as in the case of halichondrin B (Figure 1). In that case, the simpler analogue, eribulin, became an anticancer drug (brand name Halaven), available today from the Japanese company Eisai, for the treatment of patients suffering from breast cancer or liposarcoma. For sure, Nature holds further secrets waiting to be discovered and developed just as so many other discoveries were translated into therapies through design and chemical synthesis of natural products in the past. A number of such investigations will be mentioned in this book in addition to new synthetic methods and strategies for organic synthesis, constituting new advances in the field of total synthesis and its neighboring disciplines.

1.2 Methods and Strategies

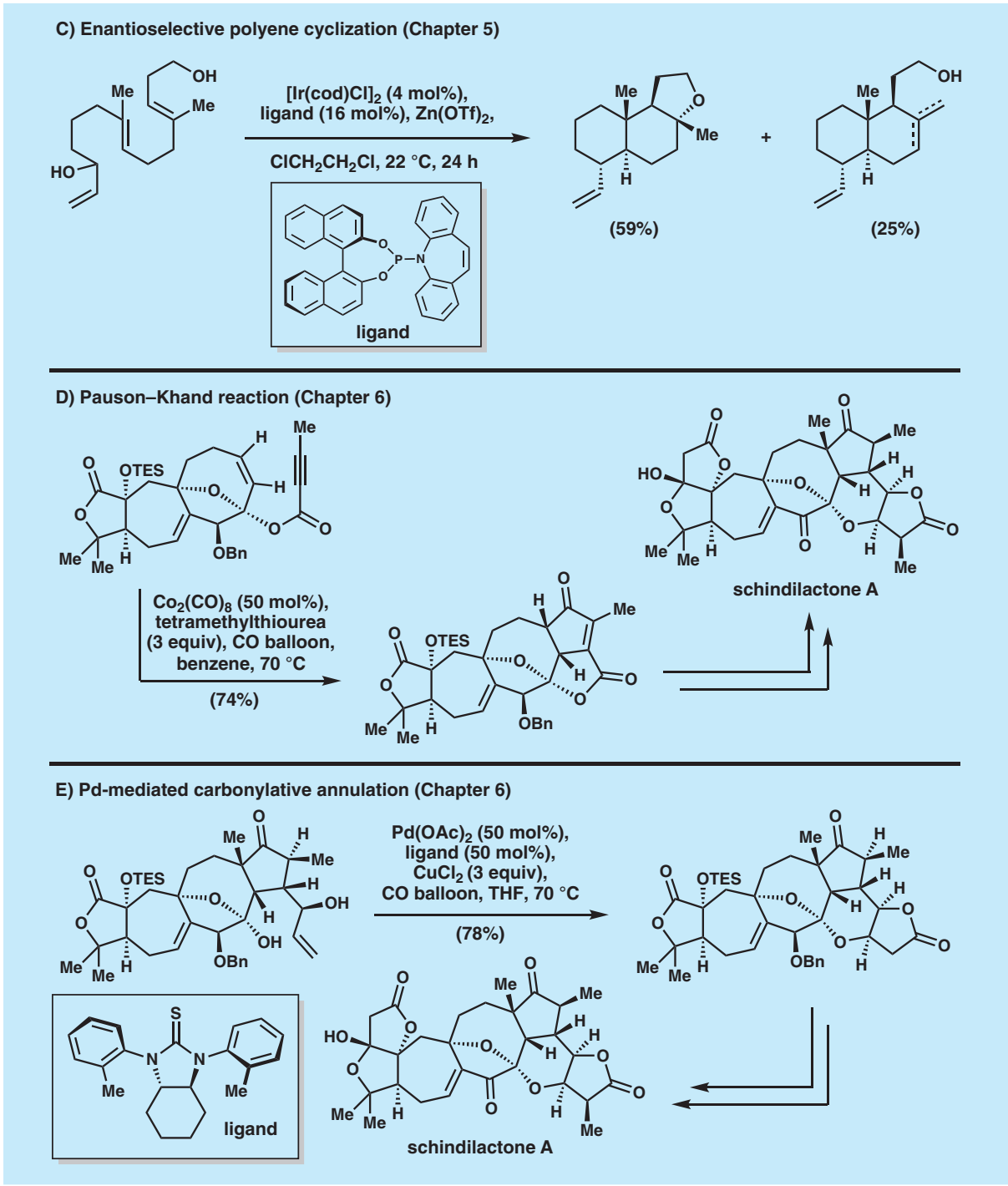
As organic synthesis advances, new methods become available for deployment and testing in total synthesis. Thus, in addition to the improvements of well-established methods and catalysts, totally new reactions and facilitators have appeared in the last few years, a number of which are included in some of the Chapters as updates in the field. Examples include C−H-activation/functionalization, photoredox catalysis, electrosynthesis, hydrogen atom transfer (HAT)-initiated radical reactions, and transformations catalyzed by engineered enzymes (integration of enzymatic reactions with traditional synthetic organic reactions within total synthesis strategies), among others. Scheme 1 highlights a number of such novel reactions and/or reagents or catalysts and their applications.

1.3 Classics in Total Synthesis IV

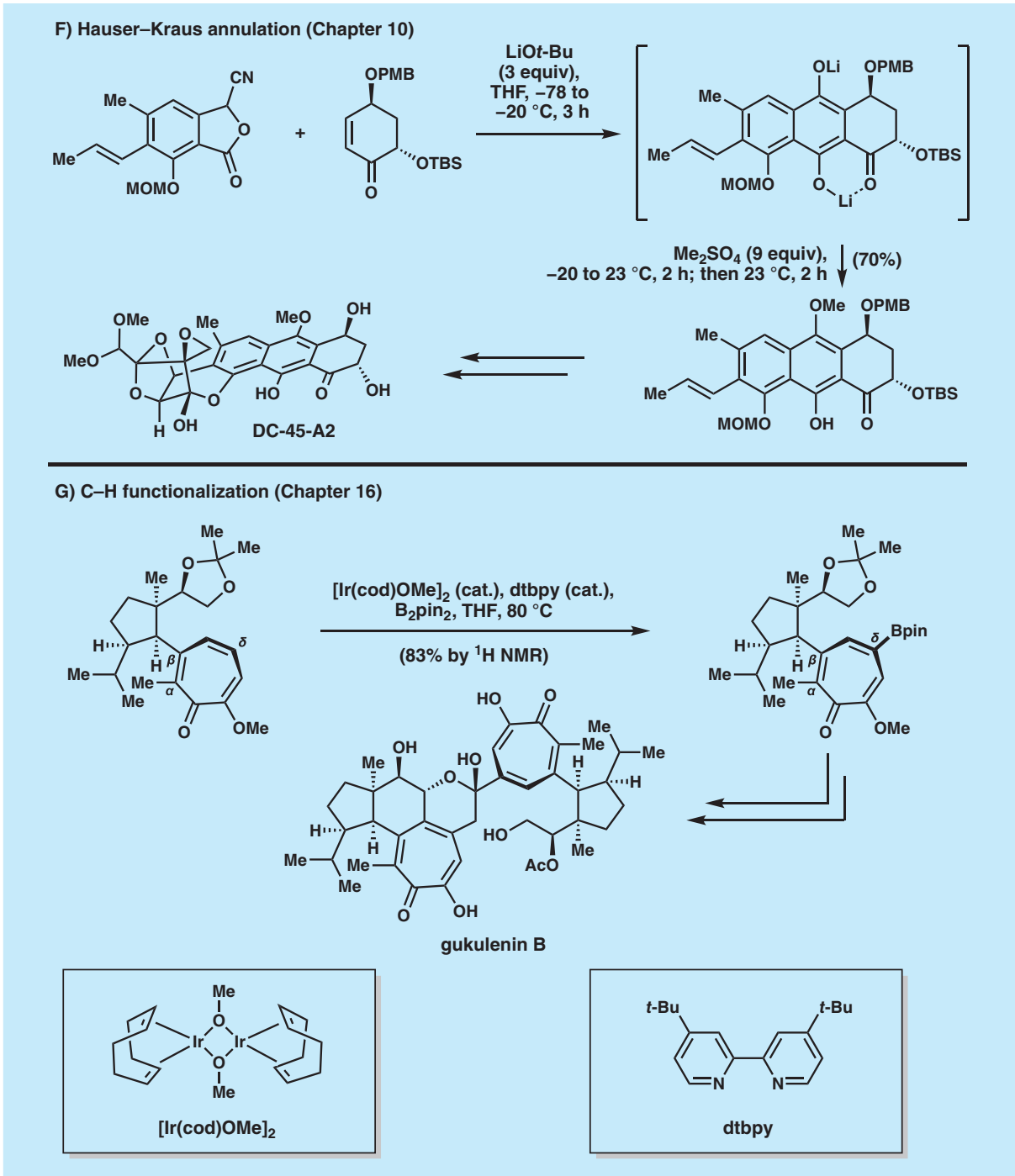
As a continuation of our series of *Classics in Total Synthesis*, we include in this edition a number of the latest endeavours in the field with appropriate references to older campaigns on the same or similar target molecules. We attempted to reflect as much diversity as



Scheme 1. Representative examples of selected methodologies featured.



Scheme 1. Representative examples of selected methodologies featured (continued).



Scheme 1. Representative examples of selected methodologies featured (continued).

possible, both with regard to the target molecules and the laboratories from where the works were published. Particular emphasis was placed on the latest trends in strategy and relevance of the work to translational aspects and applications to biology and medicine and other impacts of the work, including on the advancement of total synthesis for its own sake. We continued the inclusion of an artistic frontispiece that we introduced in *Classics in Total Synthesis III*. We hope and trust that the readers of this pedagogical book will find it enjoyable, inspirational, and rewarding. We congratulate all those faculty and students who contributed to the total synthesis achievements described in this volume, and we wish its readers all the best in their endeavours involving this special art and science of replicating the molecules of Nature, and others like them, in the laboratory. Needless to say, many more brilliant total syntheses were accomplished by other groups that, unfortunately, we could not accommodate in this volume. We apologize to the authors of those total syntheses and encourage students to study the related publications carefully to further enrich their knowledge and inspire them for continued advances in the field.