Book Reviews

Combinatorial Synthesis of Natural Product-Based Libraries. Edited by Armen M. Boldi. CRC Press, Taylor & Francis Group, Boca Raton, FL. 2006. xii + 347 pp. 18 × 26 cm. ISBN 0-8493-4000-4. $198.95.

This book is the second of a forthcoming series of monographs in molecular diversity and combinatorial chemistry, high-throughput discovery, and associated technologies. The first monograph, "Combinatorial and High-Throughput Discovery and Optimization of Catalysts and Materials", was published in July 2006. These two monographs complement each other very nicely. The one reviewed here concentrates more on the strategies of combining natural-product-derived templates with recent developments in diversity-oriented synthesis as a way of generating structural diversity on pools of scaffolds that have proven to be biologically relevant by the forces of evolution. This book is not a simple textbook, and the reader is expected to have a solid foundation in mechanistic and synthetic organic chemistry to reap its benefits. Details on the selection of resins, linkers, and loading and cleavage procedures are sparse in some chapters, and the reader must consult the references for details. The book can be an excellent companion for an advanced course in organic synthesis and is a first-rate source of information for a synthetic medicinal chemist to learn about different planning strategies.

The book encompasses 11 chapters written by 25 authors from academic and industrial laboratories in the U.S., Europe, and Japan. Because the authors of each chapter present their reasons why natural products are a rich source of discovery leads, there is a bit of redundancy and repetition of concepts at the beginning of each chapter.

A. M. Boldi and D. R. Dragoli (Chapter 1) present a graphical dictionary of natural products and compare it to recently approved drugs to bring home the point that natural-product-derived drugs are indeed well represented in that category. Specific examples of solid-phase syntheses of prostaglandins, vancomycin, and benzopyran-derived libraries are included.

After a brief history of natural products and drug discovery since the 19th century, A. Ganesan (Chapter 2) discusses two parallel universes divided in chemical space between purely synthetic compounds and natural products. Continued testing of natural products is encouraged as a source of unexpected solutions. This effort combined with the identification of biosynthetic gene clusters by molecular biology will allow the expression of these genes in heterologous organisms to discover new, hybrid platforms. The chapter ends with combinatorial chemistry efforts applied to tetrahydro-β-carbolines and pyrazinoquinazolinediones, two privileged scaffolds of interest to the author.

F. L. Stahura, and J. Bajorath (Chapter 3) deal with computational analysis of natural molecules and strategies for the design of natural-product-based libraries. This is the shortest chapter of the book. This is not surprising because, compared to other areas of chemicoinformatics and molecular design, the study of natural products using computational means is still a fairly underdeveloped field. Nevertheless, the use of specific mathematical descriptors for natural products and synthetic molecules, virtual screening methods using complex natural products, similarity searching, and docking calculations has allowed the identification of compounds with similar activities that are more synthetically accessible.

S. D. Dong and D. C. Myles (Chapter 4) devoted the entire chapter to the process of engineering structural diversity in polyketides (PKs) and nonribosomal peptides (NRP) achieved by manipulating the biological machinery responsible for the biosynthesis of these classes of compounds. The processivity in the assembly of repetitive units by modular arrays in PK synthetases is key to generating structural diversity within these scaffolds. Various genetic engineering techniques of mixing and matching appropriate subunits are described. This is a highly specialized field that sometimes is complicated by the poor productivity of engineered strains.

P. Eckard, U. Abel, H.-F. Rasser, W. Simon, B. Sontag, and F. G. Hansske (Chapter 5) discuss the advantages and disadvantages of generating adequate amounts of scaffolds by fermentation methods, semisynthetic approaches from easily available natural precursors, direct isolation from plants or marine organisms, and total synthesis. The success of these approaches based on betulinic acid, fredericamycin A, borrelidin, and irumamycin are highlighted. Using the ability of microorganisms to degrade or modify these scaffolds is also an attractive possibility discussed in this chapter.

S. V. Ley, I. R. Baxendale, and R. M. Myers (Chapter 6) provide an excellent account on the use of polymer-supported reagents, scavengers, and catch-and-release techniques for the synthesis of natural products. This approach provides access to specific scaffolds and can be extended to the generation of chemical libraries. Supported reagents, featured in all of the steps, lead to pure products following simple filtration methods. Many examples in the alkaloid area, including syntheses of oxomaritidine and epimaritidine, norarmepavine, epibatidine, nornicotine and nicotine, and plicamine provide a strong support for this technique.

A. M. Boldi (Chapter 7) introduces the reader to a number of recently approved small-molecule carbohydrate-based and carbohydrate mimetic drugs, including the new antiviral agent oseltamivir (Tamiflu). Carbohydrates are described as privileged platforms to display functional groups in a controlled three-dimensional fashion to help map a pharmacophoric space or as sources of more complex structures generated from simple carbohydrates that, following esterification with acyl groups containing terminal olefins, can, for example, generate large and medium size bicyclic rings by ring-closing metathesis. These processes can be used for the construction of lead discovery libraries containing tricyclic systems and the ubiquitous spirocyclic templates common to many natural products.

M. J. Sofia (Chapter 8) describes processes of searching for novel antibiotic activity using natural product templates and discusses some aspects of SAR in detail. Two antibiotics, moenomycin (Flavomycin) and anisomycin, were highlighted. A structurally simpler moenomycin disaccharide degradation product attached on a solid support served as a source of 1300 discrete disaccharide analogues, some of which demonstrated antibacterial activity not observed in moenomycin itself. A solid-phase combinatorial method also yielded novel anisomycin analogues with useful antifungal activity.

M. C. Pirrung, Z. Li, and H. Liu (Chapter 9) contrast the approach of decorating a natural product template with substituents around its perimeter versus the more difficult assembly of natural-product-based core structures. The "combinatorialization" of natural products requires the selection of targets that

are inherently modular, which is illustrated with asterriquinone and illudin libraries. This chapter is very strong in synthetic methodology and provides useful recommendations for the retrosynthetic planning of libraries.

T. Doi and T. Takahashi (Chapter 10) report on the use templates, such as 11-hydroxyvitamin D, to generate molecular diversity through the combination of various modular fragments. The use of a traceless sulfonate linker is highlighted for the synthesis of libraries where the chemistry of the final diversity step concomitantly cleaves the product off the solid support. The chapter ends with the design of combinatorial strategies for highly modular systems consisting of macrosphelides and cyclic depsipeptides.

P. M. Abreu, P. S. Branco, and S. Matthew (Chapter 11) wrote the longest chapter of the book. It is a tour de force of discoveries made using combinatorial natural-product-based libraries. The chapter discusses strategies utilized for carbohydrates, fatty acids, polyketides, peptides, terpenoids, steroids, alkaloids, flavonoid, and other natural products. Although the reader has to refer to the cited references for details, the chapter succeeds in discussing the strength of the combinatorial approach achieved by dissecting the target templates into accessible fragments.

This book is priced at $198.95, and it is a worthwhile investment for any one seriously interested in the field or planning to get involved. It has an adequate seven-page index, and each chapter has ample and up-to-date references.

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Greene's Protective Groups in Organic Synthesis. Fourth Edition. By Peter G. M. Wuts and Theodora W. Greene. John Wiley & Sons, Inc., Hoboken, NJ. 2006. xvii + 1082 pp. 16 × 24 cm. ISBN 0-471-69754-0. $94.95.

This book represents the fourth edition of a classic reference for the identification, incorporation, removal, and appropriate use of protecting groups for reactive moieties in organic chemical synthesis. Previous editions have been the mainstay of synthetic organic and medicinal chemists. This edition has been significantly updated from its predecessor and includes several developments since 1998. In particular, the fourth edition includes (1) the addition of new protecting groups including fluorous moieties, (2) new methods for the incorporation and removal of protecting groups, especially when selectivity issues have been identified in the primary literature, (3) additional details with respect to unexpected side reactions, (4) a novel selectivity chart with respect to the deprotection of specific silyl ethers in the presence of other silyl structural variants, and (5) over 3000 additional literature references, complete through the end of 2005.

The current edition is preceded by a complete list of abbreviations and then is divided into 10 chapters. The first chapter highlights the eloquent use of multiple protecting group schemes employed during the classical and elegant synthesis of two important natural products, himistatin and palytoxin carboxylic acid. The next eight chapters are devoted to the protection and subsequent removal of individual reactive groups (e.g., hydroxyls (including 1,2- and 1,3-diols), phenols, and catechols, carbonyls, carboxyls, thiols, aminos, alkynes, and phosphates) that are suitably subdivided with respect to specific protecting group subtypes. To expedite access, up-to-date experimental conditions are referenced in the primary literature for each of the specific protecting group sections rather than as a group at the end of the overall chapter. The 10th chapter contains compatibility tables that represent a highly useful quick reference guide providing an evaluation of the relative reactivity of individual protecting groups with respect to conditions that are normally encountered during a typical organic synthetic scheme (e.g., aqueous (acidic and basic), nonaqueous basic, nucleophilic, electrophilic, organometallic, catalytic, acidic, basic, neutral or hydride reductive, oxidative, radical, and thermal). It can be assumed that this chapter will be the most utilized by chemists for the initial evaluation of synthetic strategies for the preparation of target molecules. These tables have represented a highlight of previous volumes and, likewise, of the current edition. It should be noted that the new table on silyl ethers is not a standard compatibility table but rather provides information on the selective deprotection of individual silyl protecting groups in the presence of other silyl variants. Unlike the other tables, specific literature references are provided. Finally, the authors have provided a complete and well-organized 30-page index.

In order to demonstrate the comprehensiveness of the present edition, Chapter 5 on the protection of the carboxyl group will be used as an illustration. This chapter is divided into two major protection strategies: esters and amides or hydrazides. As far as ester protecting groups are concerned, this section is subdivided into nine different subgroups in which more than 120 specific esters are described, discussed, and referenced. As an example, for the methyl ester the authors provide 18 methods for its incorporation with 25 primary literature references and 32 methods for the regeneration of the parent carboxyl group with 42 primary literature references.

Overall, this book represents an important and complete reference source with respect to the selection of appropriate protecting groups for specific reactive moieties to be utilized during an organic synthetic scheme, along with strategies for their removal. In all cases, appropriate and current references are provided to experimental details in the primary literature. This publication represents the most up-to-date compilation available. Therefore, this updated edition should be an integral part of all institutional libraries; however, it is also highly recommended that individuals routinely involved in synthetic organic and medicinal chemistry maintain their own copy, since experience has shown that circulating copies are notoriously difficult to locate. This expanded fourth edition is very reasonably priced considering its overall breadth and utility to the research chemist and in fact is less expensive than its predecessor.

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Chemistry and Medicines. An Introductory Text. By J. R. Hanson. The Royal Society of Chemistry, Cambridge, U.K. 2006. x + 156 pp. 16 × 24 cm. ISBN 0-85404-645-3. £27.50.

The aim of this slim book, as described in its preface, is to "provide a brief introduction to medicinal chemistry for final year chemistry and biochemistry undergraduates and for chemistry postgraduates." The text is "based on short lecture courses" given to such students at the University of Sussex. Moreover, as "many chemists are employed by the pharmaceutical industry in the design and synthesis of new drugs ... it is hoped that this book will provide a broad short introduction ... for chemists starting work in these areas." The volume comprises seven chapters, each beginning with a list of four to six performance aims together with a brief discussion. Topics in medicinal chemistry that follow include an introduction to the field, general principles, neurotransmitter agents, central nervous system compounds, hormone medicines, anti-infectives, and cancer chemotherapeutics. A list of books for further reading, a glossary, and a useful index are also provided.

In a brief orientation in the science of medicinal chemistry and drug discovery, surely it is crucial to discuss and illustrate clearly its central tenet: the structural basis for pharmacological specificity, already postulated more than 100 years ago in the "magic bullet" and "lock and key" theories of Paul Ehrlich and Emil Fischer. Yet only a brief and inadequate consideration (pp 39−40) regarding drug−target interactions, no illustrations at all for enzyme−inhibitor complexes, and egregiously erroneous diagrams for G-protein-coupled receptors (p 46) and a membrane channel (p 22) are provided to help the reader understand the terse, highly condensed presentation. There are errors in the text as well. In showing the sequence of activities in drug development, the author places the identification of candidate drugs and large-scale synthesis prior to ADME (absorption, distribution, metabolism, and excretion) and toxicity studies (p 7), whereas the results of at least some of such studies are required to select the candidate drug(s). Later, the author states that "the gall bladder produces bile acids from cholesterol" (p 101), when in fact the conversion takes place in the liver.

Individuals and institutions considering purchase of this expensive book (40¢ per page) may also wish to examine two excellent, recent alternatives that authoritatively consider the same general area in greater detail at reasonable cost: (1) Silverman, R. B. *Chemistry of Drug Design and Drug Action*, 2nd ed.; Academic Press: New York, 2004; (2) Nogrady, T.; Weaver, D. *Medicinal Chemistry. A Molecular and Biochemical Approach*, 3rd ed.; Oxford University Press: New York, 2005.

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