Book Reviews

High Throughput Screening: The Discovery of Bioactive Substances. Edited by John P. Devlin (AART International, Inc.). Marcel Dekker: New York. xxiv + 673 pp. $165.00. ISBN 0-8247-0067-8.

High Throughput Screening is a timely and well-edited book in a rapidly developing field. The breadth of the book is at first startling; it ranges from discussions of the use of natural products and fermentation-derived brews as discovery resources through techniques, chemistries, automation, and robotics to end up with problems of data management. The handling of data is a critical process in terms of both what aspects are most usable and how the pertinent details may be retrieved at a later date in a field where even the shapes of the questions change rapidly. The area of bioinformatics, the use of genomic sequence data, in this search for bioactive substances was accorded little space. This is an area that is impinging on the whole field of high throughput screening (HTS) as the number of completed genome sequences begins to increase rapidly and the completion of the human genome now looms in the foreseeable future.

As Devlin emphasizes, HTS methodology has developed for the most part outside of academia. It is in the interest of the academic scientist to become familiar with this approach and how it is circumscribed in many ways by unsolved chemical problems. Basic research in many areas will be a continuing need. There are needs for solutions to critical analytical problems, for means to extend solid-phase techniques to widen venues by organic chemists, and for developments in other areas in the chemical sciences. These questions are addressed in this compendium.

Innovative applications promise results that will require a consummate knowledge of chemistry for deconvolution of vast libraries (10^3, 10^6, 10^9, ... compounds). Candidate ligands that must be effective at the nanomolar level must be screened at the micromolar level. But the medicinal chemist within a large and diverse HTS team effort must be given increasingly refined and predictive information in order to move forward. To do this effectively, "lead optimization" is needed; this is still a mixture of intuitive and rational approaches. While HTS can lead to syntheses of $>10^9$ compounds, generally only much smaller screens are amassed and organized. One team emphasized a chemical "Henry Ford" philosophy: Skip the production of compounds which were predicted to be difficult to synthesize. Such a philosophy brings us face-to-face with the basic need to develop shorter, robust synthetic routes so that compounds of great potential are not bypassed.

The above questions and many others are dealt with in an overall clear and provocative manner. Many practical details include commercial sources, guidelines for working with resources in other countries, prices of test materials, and details for techniques, instrumentation, and chemistry.

All in all, it should be a very good introduction to HTS for those who do not attend the frequent conferences and symposia on the subject. If you are going to read one book in this area, this one would suffice.

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Advances in Carbanion Chemistry, Vol. 2. Edited by Victor Snieckus (University of Waterloos). JAI: New York. 1996. vii + 272 pp. $109.50. ISBN 1-55938-548-0.

This is the second volume in the series Advances in Carbanion Chemistry edited by Victor Snieckus. This is an excellent monograph which contains five chapters written by experts in the field on mechanistic and synthetic aspects of carbanion chemistry.

The Wittig reaction is one of the most important and well-known organic reaction. The first chapter is a review written by Edwin Vedejs and Matthew Peterson on the mechanism of the Wittig reaction. This is an authoritative and critical review on the present status of the mechanism. The authors discuss in a chronological and logical fashion all the different mechanistic proposals which have been put forward for this important reaction. The writing is very lucid and organized and the authors have done a great job in presenting information that has accumulated over several decades.

The second chapter is a nice review on the synthesis and reactions of allyl metals written by Akira Yanagisawa and Hisashi Yamamoto. The preparation of various homogeneous allylic metals is presented and issues related to their stereochemical integrity are discussed. The review also contains synthetic applications of the allylic metals, especially their addition to acyl silanes. The chapter ends with a good discussion of the synthesis and reactions of allyl bariums discovered in Professor Yamamoto's laboratory.

In the third chapter, Tagliavini, Trombini, and Umani-Ronchi review synthetic aspects of zinc and boron enolates. The discussion is focused on the reaction of these enolates with carbonyl compounds. The review includes information on structure, preparation, and uses of these enolates in carbon−carbon bond formation. Stereoselective transformations of zinc and boron enolates using chiral substrates, chiral auxiliaries, and chiral ligands are presented. The use of zinc and boron enolates as reagents in the synthesis of complex targets are highlighted.

Photochemical reactions of carbanion intermediates can at times serve as useful alternatives to the traditional thermal reactions. In the fourth chapter David Budac and Peter Wan provide an overview of work carried out in the past two decades on the photochemistry, spectroscopic properties, and photochemical reactions of carbanions. The review highlights synthetic as well as mechanistic aspects and serves as a useful single source for obtaining information on these somewhat less frequently used branch of organic chemistry.

Information on the structure of carbanions can be very helpful in understanding their reactivity and also aid in designing experiments in the laboratory. In the fifth and final chapter Silvia Bradamante and Giorgio Pagani provide an excellent account on the structure and substituent effects in benzyl and heteroarylmethyl carbanions. Solid and solution state structure of carbanions is discussed in detail including the presentation of some NMR spectra. A useful compilation of benzylic hydrocarbon acidities is also included. The chapter ends with a discussion of the correlation between charge densities and carbon chemical shifts.

Overall, this is an excellent monograph which will be a valuable addition to chemistry libraries and to the personal libraries of practitioners of carbanion chemistry.

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The Alkaloids: Chemistry and Biology, Vol. 50. The Alkaloids: Chemistry and Pharmacology. Edited by Geoffrey A. Cordell (University of Illinois−Chicago). Academic Press: San Diego. 1998. xvi + 590 pp. $125.00. ISBN 0-12-469550-7.

This fiftieth volume of the long running series familiarly known as "Manske" continues the tradition of comprehensive excellence initiated by its founding editor, the late R. H. F. Manske, and begins with an engaging overview of the life of this outstanding alkaloid chemist by two of his colleagues, D. B. MacLean and V. Snieckus. The thirteen chapters which follow provide comprehensive reviews of specialized areas of alkaloid chemistry and biology.

The term biology in the subtitle of this volume presages a change in the series title to begin with Volume 51. The advances in understanding regarding the biochemical pathways of alkaloid synthesis, the molecular biology of these processes, and the application of this knowledge to commercial production of pharmaceutically important alkaloids are truly remarkable. Chapters by Gröger and Floss (Biochemistry of Ergot Alkaloids), Kutchan (Molecular Genetics of Plant Alkaloid Biosynthesis), and Verpoorte, Van der Heijden, and Memelink (Plant Biotechnology and the Production of Alkaloids) are illustrative.

The more traditional areas of alkaloid chemistry such as isolation, structure determination, and synthesis are not neglected. Contributions by Atta-ur-Rahman and Choudhary (Chemistry and Biology of Steroidal Alkaloids), Guggisberg and Hesse (Natural Polyamine Derivatives),

Ninomiya, Kiguchi, and Naito (Pseudodistomins), Saxton (Synthesis of the Aspidosperma Alkaloids), Szántay (Synthetic Studies in Alkaloid Chemistry), and Takamaya and Sakai (Monoterpenoid Indole Alkaloid Syntheses Utilizing Biomimetic Reactions) are up to date and authoritative.

The review by Daly (The Nature and Origin of Amphibian Alkaloids) is particularly timely in view of the recent report by Decker and coworkers (*Science*, **1998**, *279*, 77−81) of a powerful new non-opioid analgesic, ABT-594, a synthetic analog from Abbott Laboratories of the rare frog skin alkaloid epibatidine.

Additional reviews by Brossi (a former editor of the series) and Pei (Biological Activity of Unnatural Alkaloid Enantiomers), Wall and Wani (History and Future Prospects of Camptothecin and Taxol), and Waterman (Alkaloid Chemosystematics) round out the fiftieth volume of a series which has been so consistently useful to alkaloid scientists that it deserves to reach its centennial year.

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Advances in Asymmetric Synthesis, Vol. 2. Edited by Alfred Hassner (Bar-Ilan University). JAI Press: Greenwich. 1997. x + 314 pp. $128.50. ISBN 1-59938-797-1.

This book presents an extensive account of several current methods for the preparation of functionalized molecules with high levels of enantioselection. The reader is impressed by the seminal knowledge the respective contributors to this volume have on the subject matter and immediately recognizes them as distinguished researchers in the field of asymmetric synthesis. Volume 2 of this series focuses on the following: (i) the utility of chiral cyclopentadienes in Diels−Alder additions; (ii) the preparation of chiral amines via the stereoselective reactions of chiral 1,3-oxazolidines; (iii) the asymmetric synthesis of α,α-disubstituted β-ketone derivatives; (iv) the preparation of chiral ferrocene derivatives using chemical transformations as well as kinetic resolutions; (v) numerous methods for biocatalytic transformations and enzymatic resolutions. Each topic is discussed thoroughly in the sections following its introduction. Within each section, the relevant transition structures are clearly illustrated within the text to account for the observed levels of asymmetric induction. Each section is well organized with the key points highlighted at the end of the section using a bullet format for clarification. The conclusion of each chapter includes a brief summary which lists the important advances that have been made in the field as well as the future goals of the research. The authors do an especially nice job of emphasizing the limitations of a particular method as well as possible alternatives which provide higher levels of induction. A brief summary of the contents of the individual chapters in this volume follows.

Chapter 1 includes numerous applications of cyclopentadienes derived from the chiral pool in Diels−Alder reactions with symmetric and unsymmetric dienophiles. The chapter illustrates the synthetic concepts via numerous examples relative to the total synthesis of various natural products. Chapter 2 focuses on the preparation of several classes of chiral amines derived from naturally occurring α-amino acids. The primary focus of the chapter involves nucleophilic additions to 1,3-oxazolidines and the transformation of the oxazolidines to synthetically useful chiral amine synthons. Chapter 3 provides an extensive account of methods used to prepare chiral α,α-disubstituted β-ketone derivatives via chiral transition metal catalysts, chiral crown ether complexes, as well as by the addition of achiral electrophiles to chiral ester enolates. This chapter also provides an account of many types of alkylation and conjugate addition reactions to chiral β-enaminoesters. Chapter 4 focuses on the synthesis of chiral ferrocenes with lateral and planar chirality using both chemical and enzymatic methods. This chapter also includes a brief discussion on the application of ferrocenes in asymmetric catalytic reactions. Chapter 5 deals with biocatalytic systems that induce chirality using microorganisms and enzymes. The chapter also suggests models to account for the observed stereochemical outcome of some common enzymatic processes. Chapter 6 includes an overview of some nontraditional microbial transformations such as the hydrolysis of amides, nitriles, and glycosides as well as nitro group reductions, Baeyer−Villiger oxidations, and aldol bond constructions. As a whole, this text will be a useful reference source in the field of asymmetric synthesis for graduate students and professional chemists alike.

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Molecular Modeling: Basic Principles & Applications, Vol. 5. Methods & Principles in Medicinal Chemistry Series. By H.-D. Holtje (Heinrich-Heine-University) and G. Folkers (ETH Zurich). VCH: Weinheim. 1997. xii + 194 pp. DM198.00. ISBN 3-527-29384-1.

If the currently popular "Dummies" series of computer books were to publish a volume on molecular modeling this would be it. In the authors' own words "...this is a book to provide support for the beginner", and it fulfills that goal admirably. After a brief philosophical introduction to the concept of models in general, the book explores two broad categories: small molecules and protein modeling. Under the "small molecule" rubric the authors briefly describe, among other topics, data libraries, geometry optimization methods, conformational analysis, and quantum mechanical methods. Protein modeling includes an introduction to protein structure, discussions of knowledge-based modeling, sequence alignment, ligand-binding site interactions, as well several other common topics in the field. "Briefly" is the operative word. The topics are touched upon, as are their general advantages and pitfalls. Don't look for much depth. And do not look for the most current references. For the most part the literature cited seems to be at best from the early 1990s, with much of it considerably older. An interesting concept is the inclusion of a chapter-long "example" after both the small molecule and protein modeling sections. In the former case it is modeling of serotonin receptor ligands, and in the latter, modeling of antigen presentation by MHC class I. The text is enlivened by the inclusion of several color illustrations. However it is hard to imagine how a 1-year-old book on molecular modeling could fail to include any description at all of the immense resources available on the World Wide Web. The book would make an excellent text for an entry-level molecular modeling course, but with the caveat that the instructor must be prepared to build considerably on the themes presented.

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