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BOOK REVIEWS

Handbook on Syntheses of Amino Acids: General Routes for the Syntheses of Amino Acids. By Mark Blaskovich (Mimetica, Milton, Australia). Oxford University Press (developed and distributed in partnership by the American Chemical Society): New York. 2010. xviii + 1306 pp. $175.00. ISBN 978-0-84-127219-4.

In this treatise, Blaskovich sets out to cover the most important developments in amino acid chemistry "in the last 150 years." This is a rather daunting task, and clearly some editorial license needed to be exercised to pare this down so that such coverage might be captured in one, albeit voluminous, monograph. The classic work in this area is *Synthesis of Optically Active* α*-Amino Acids* (Pergamon, 1989) by Williams, and although this book was exceptionally well constructed and written, it is now two decades old and, thus, in need of a supplement.

Although not a replacement for Williams's book, this handbook basically covers the literature through about 2006 and, thereby, fills a significant portion of the gap between the two volumes. Thematically, Blaskovich seeks to cover broader synthetic space and dedicates a significant amount of it to the synthesis of racemic amino acids. As he points out, it may be more practical and/or economical, in some cases, to resolve the racemate rather than engage in stereoselective synthesis. Indeed, this will likely be a useful reference for the process chemist, given its focus on amino acids, particularly those that must be produced on large scale and in enantio-enriched form. The author also provides extensive discussion of resolution, chromatographic separation, and stereoanalytical methods.

Chapter 1 is well written and provides a satisfying overview of the field, from the basics of the 20 traditional proteinogenic amino acids to the fascinating, more recent discoveries of the "21st and 22nd amino acids", L-selenocysteine and L-pyrrolysine. The author discusses some of the medicinal chemistry of natural and unnatural amino acids and even ventures into the modern biology and biochemistry of neuroactive amino acids, such as D-serine. In this way, he successfully conveys the excitement of the field, which encompasses important aspects of synthetic, medicinal, and biological chemistry.

In terms of organization, the Table of Contents is masterfully done and helps the reader enormously to navigate this dense work. The same cannot be said for the indices. Although this work is similar in feel and style to March's *Advanced Organic Chemistry*, it would have benefited greatly from the sort of multiple indices that March employed. Blaskovich does provide a reasonably good keyword index, but there are no indices for either authors or transformations, which is perhaps the most useful cataloguing feature of the March book in its many editions. This reader strongly encourages the author to add these features to this volume in any future editions.

Not surprisingly, the bulk of the conceptually more innovative chemistry featured in this book begins with a discussion of the "golden days" of asymmetric amino acid synthesis with the likes of Schöllkopf in the 1970s and early 1980s and the major advances of Seebach and Williams in the 1980s. This was also the period in which side-chain "elaboration" chemistry flourished and continued to be developed into the 1990s. Blaskovich transitions from the 1990s to the current century by shifting focus from native α-amino acid targets to the engineering of new secondary structures based upon β-, γ-, and ω-amino acids.

Highlights of the book are the illustrative introductory schematics, delineating multifarious synthetic solutions to key synthetic problems. Some of my favorites include tables of commonly encountered noncoded amino acids; schemes of chiral glycine equivalents; tables of Jackson's serine-derived organozinc- and organocopper-based chemistry; and the schemes of cyclic β-amino acids, bicyclic β-amino acids, and peptide-coupling reagents.

On the other hand, many pages in this volume are dedicated to tabular summaries of specific chemistries, which, though useful, are often unwieldy; e.g., Table 11.2 is over 85 pages! The methodological components cannot be extracted from such tables by the reader without substantial effort. Although the author states at the outset that the book is not meant to give the reader a synthetic route to a specific target amino acid of interest, this reader found many of these tables best suited for this purpose. In other words, it is generally easier for the reader to scan these tables for structures than for chemistry.

Chapters 9 and 10, in which Blaskovich describes side-chain elaboration approaches from optically active amino acids other than L-serine (9) and L-serine (10), are innovative in their organization and very attractive. Here one finds a set of useful methods of the chiron ilk, emanating from a natural amino acid, but molding the side-chain or the carbonyl functionality typically to generate novel nonproteinogenic amino acids. One thinks reflexively of the Garner aldehyde in this vein, but Blaskovich goes far beyond this in Chapter 10, where he discusses other very useful serine-based chirons, several of these featuring "Umpolung," with anionic-carbon reactivity. These include the Sibi ylide, the dianionic serinol developed by Taylor, and the β-Cu and β-Zn reagents developed by Jackson. This is a very useful collection of reagents, which, relative to the Garner system, appear to be underappreciated and underused in the community. This encyclopedic work may help to bring this chemistry to the benchtop, if placed in the proper hands.

Chapter 9 continues the "elaboration" theme but is reserved for all things nonserine and, thus in my view, should follow rather than precede Chapter 10. I think that this flow would be optimal, because serine itself is really the standard-bearer for elaboration chemistry, as described above. Here, the author wisely covers the aspartate, glutamate, and pyroglutamate frameworks, etc. that possess side-chain active methylene positions and can be selectively alkylated under properly engineered conditions. The author nicely builds up from foundational work in this area in the late 1970s and early 1980s from some of the most storied players in the field, including Rappoport, Seebach, Danishefsky, and Baldwin.

In addition to these chiral reagent-based approaches, Blaskovich also includes some examples of catalytic chirality in the assembly of amino acids, although this is not a major

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focus of the book. Perhaps most importantly, the area of chiral phase-transfer catalyst-based formal chiral glycine alkylation is presented and given appropriate focus, from the pioneering work of O'Donnell, based on the cinchona alkaloids, to the more recent, complementary systems of Maruoka, based upon binaphthyl ammonium salts.

Perhaps the most timely and noteworthy section of this work is the extensive coverage of synthetic methods toward β-, γ-, and ω-amino acid synthesis in Chapter 11. This section is almost a "book within a book," numbering almost 300 pages, and provides a comprehensive discussion of the methodology directed at these emerging classes of peptidomimetic-building blocks. Given the striking success of the groups of Gellman and Seebach in building well-defined secondary structures based upon these "extended" amino acid motifs, this adds an important contemporary element to this work.

All in all, this will be a useful reference work, particularly for the peptide and medicinal chemistry communities. Though a voluminous work, the well-organized and detailed Table of Contents will allow the reader to home in on the class of amino acid that he or she seeks and expeditiously capture the range of reaction modality available to access these targets. As such, active practitioners of the art of peptide or peptidomimetic construct design, synthesis, and study will likely benefit from having this volume on a nearby shelf.

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Ionic Liquid Applications: Pharmaceuticals, Therapeutics, and Biotechnology. Edited by Sanjay V. Malhotra (National Cancer Institute at Frederick, MD). American Chemical Society (distributed by Oxford University Press): Washington, DC. 2010. x + 226 pp. $150. ISBN 978-0-8412-2547-3.

This book presents some of the papers given at a symposium of the same title at the 236th National Meeting of the American Chemical Society sponsored by the Organic Division in Philadelphia in August, 2008. Some of the topics covered include a historical perspective on ionic liquids as pharmaceutical salts; ionic liquids as solvents for the synthesis, separation, and analysis of pharmaceuticals; the preparation of biomaterials using ionic liquids for biomedical applications; analysis of the toxicology of ionic liquids; the application of ionic liquids in biotechnology; and many more. There are 16 chapters as well as both author and subject indices at the end of the book.

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Macromolecular Crystallization and Crystal Perfection. IUCr Monographs on Crystallography, 24. By Naomi E. Chayen (Imperial College, London, U.K.), John R. Helliwell (University of Manchester, U.K.), and Edward H. Snell (Hauptman-Woodward Medical Research Institute, Buffalo, USA). Oxford University Press: Oxford, New York. 2010. xii + 222 pp. $125. ISBN 978-0-19-921325-2.

Biological macromolecules are the machinery of life. To understand the fundamental mechanisms of the processes in living organisms that are enabled and regulated by proteins and nucleic acids, data on the atomic structure of the biological macromolecules are needed. The main method for macromolecular structure determination is X-ray crystallography; it accounts for the characterization of approximately 87% of all protein structures. The majority of other determinations are carried out by nuclear magnetic resonance spectroscopy. Of course, X-ray crystallography relies on the availability of high-quality protein crystals, and herein lies a major problem.

Proteins and nucleic acids are notoriously recalcitrant to crystallization: in several recent massive efforts at protein structure determination, only 12% of the purified protein samples led to structures, the main obstacle being the unavailability of crystals suitable for structure determination. This poor crystallizability severely limits the known macromolecular structures, and perhaps more consequentially, it introduces a bias in the conclusions based on the known structures about the many more numerous, unknown structures.

A recent conjecture links the recalcitrance of proteins and nucleic acids to crystallization to the necessary resistance of proteins to aggregating in the crowded cytosol. Hence, protein crystals are typically grown in environments far removed from those in which the proteins perform their physiological functions: i.e., within pH values that vary from 2 to 11, in electrolyte concentrations that reach several molar, and in the presence of polymers and small organic molecules whose concentrations may reach 25%. There may be a few proteins that would form crystals in a random combination of additives and concentrations, but the overwhelming majority of proteins would likely require a unique combination of pH, buffer, salt, additive type and concentration, and other parameters to induce crystallization. Thus, the main problem facing structural biologists is how to find this unique combination.

The book by Chayen, Helliwell, and Snell is written from the viewpoints of practicing protein crystallographers. They present a streamlined and logical summary of the sequence of procedures that a crystallographer needs to follow to obtain the structure of a protein of interest. After a brief introduction to the theory of crystallization and a review of the common methods for protein crystallization, the authors address the main method for searching for conditions of crystallization: screening. Particularly appealing is their focus on new developments: automation and the use of robots for crystallization, analysis of large sets of data, and computerized sample imaging and monitoring. The authors then discuss how to optimize the conditions for crystallization if the initial screening is successful and the strategies to employ if the screening fails to yield crystals at all tested conditions. The peculiarities of the large class of membrane proteins, of which structural knowledge lags far behind that of soluble proteins, are also highlighted. In all cases, the state of the art of the respective methods and techniques is addressed. The discussion greatly benefits from the authors' practical experience as protein crystallographers who have important structures under their belts.

The correlation between crystal perfection and the diffraction data is then examined at length and in depth. Descriptions of short-range molecular order and long-range order in the crystal, twinning, and other diffraction disorders are followed by discussions of radiation damage, cryo-cooling and dehydration, and optimization of the diffraction geometry. The book concludes with coverage of nontraditional techniques for diffraction and a brief but fascinating review of a future that may lead us to the use of X-ray lasers and determination of structures of noncrystalline samples.

There is one conspicuous question that is not addressed in the book, i.e., "Can current approaches to protein crystallography ensure that knowledge of protein structures will increase near-exponentially, as it has from its inception to 2005?" A brief look at the database for protein structures indicates that a plateau in the rate of protein structure determination was reached in 2007 at about 7000 structures per year. Progress in this field in the past 10 years has been underwritten by massive investment from agencies of several governments worldwide, which is unlikely to extend into the future. The viewpoint that the current structures represent "low-lying fruit" and that the determination of new structures will be an uphill journey is widely spread. If one is to accept this viewpoint, the relevant questions become "How do we improve the chances of crystallographic structure determination, short of the X-ray laser?" and "Do we address the fundamentals of macromolecular crystallization—a direction boldly abandoned in the past several years—or do we stay with the methods that have taken us thus far?" The macromolecular crystallography community will be facing these questions in the immediate future.

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Cellulose Solvents: For Analysis, Shaping and Chemical Modification. Edited by Tim F. Liebert, Thomas J. Heinze (both at Friedrich Schiller University of Jena, Germany), and Kevin J. Edgar (Virginia Tech, Blacksburg, VA, USA). American Chemical Society (distributed by Oxford University Press): Washington, DC. 2010. xii + 408 pp. $175. ISBN 978-0-8412-0006-7.

This book evolved from a symposium entitled "Cellulose Solvents" held at the 235th National Meeting of the American Chemical Society in New Orleans, LA in April, 2008. There are 20 chapters, which are grouped under the following headings: Approaches for the Dissolution of Cellulose; Interaction of Solvents with Cellulose; and Modifications of Cellulose Using Solvents. A subject and an author index complete the book.

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