

Preface

Ever since Emil Fischer established the stereochemical configuration of D-(+)-glucose at the end of the nineteenth century, carbohydrate chemistry has become an important branch of organic chemistry. Steady advances in carbohydrate synthetic and analytical methods have been made over the past hundred years. However, it is the past two decades that have seen remarkable new discoveries in the biology of carbohydrates and provided renewed impetus to the synthesis of complex glycoconjugates and pursuit of their medicinal and industrial applications. Glycobiology has emerged as an internationally recognized field of study and a potentially promising route to the discovery of novel medicines. Critical biological processes—including regulation of the growth and mobility of cells, immune responses, and reactions of cells to hormones and growth factors—all depend on carbohydrates. In addition, many viruses and bacteria use cell surface carbohydrates to get into cells and initiate infections.

The diversity of roles played by carbohydrates makes them exciting new targets for the development of novel treatments for cancer, infectious diseases, inflammation, and cardiovascular disorders. The spur in glycobiology research resulted in the appearance of several enormously successful carbohydrate-based drugs including but certainly not limited to heparin (an anticoagulant) and Relenza (an antiviral). Increasing numbers of organic chemists are venturing into the field of glycochemistry to bring in their own chemical expertise and to expand the area into a truly multidisciplinary field.

A major motivation among carbohydrate chemists is to develop tools for probing the biological functions of glycosylation. Genome sequencing projects present a vast repertoire of biosynthetic enzymes that may be targeted by selective carbohydrate-based drugs. Advances in automated oligosaccharide synthesis are highly significant as complex structures will soon be widely attainable and exploited in studies of biological phenomena. Their integration into complex assemblies (polymers, dendrimers, and liposomes) will provide cell surface mimics of unparalleled fidelity. Studies of glycobiology will benefit from the convergent application of chemical and biological techniques. Thus, in the past few years, glycochemistry has advanced from studies of chemical glycosylation reactions and synthesis of oligosaccharides to

chemo-enzymatic and solid-phase synthesis of glycoconjugates, carbohydrate combinatorial libraries, multivalent glycoconjugates, carbohydrate-peptide hybrids, and much more. It is the aim of this book to capture the essence of these latest developments and to provide a comprehensive review of modern glycochemistry in one collected volume. In recognition of the great potential applications of glycochemistry in the pharmaceutical and chemical industries, we solicited chapters that contain pertinent examples of the development of carbohydrate-based pharmaceuticals and commercial polymers. Each chapter is written by experts in their respective fields. Many are young scientists who have just begun research programs in carbohydrate chemistry. Although some chapters include relatively detailed experimental procedures for novel synthetic methodology, the book is intended to provide a reference framework for the latest developments in the field of glycochemistry.

Recent trends in glycochemistry are presented in three parts: synthesis, principles and applications. The first six chapters provide a comprehensive, up-to-date review on the chemical synthesis of complex carbohydrates for their potential use in biological systems. The following seven chapters reveal some fundamental principles that are used to design and exploit carbohydrates for their effects in biological settings. The remaining five chapters examine the applicability of enzymes towards the chemo-enzymatic synthesis and modification of carbohydrates and polysaccharides.

In Chapter 1, Peter Seeberger reflects on the promising strategies for the solid support synthesis of oligosaccharides and glycoconjugates. The chapter puts in focus the glycal assembly method and reveals protecting group strategies for carbohydrate components, synthesis of biologically important oligosaccharides, and selective glycosylation strategies.

Chapters 2 and 3 bring to light the potential of strategies for stereoselective glycosylation. David Gin examines a number of methodologies used in the glycosylation of 1-hydroxy donors and points out that in the direct dehydrative coupling with an appropriate dehydrating agent, the formation of undesired by-products of hemiacetal self-condensation can be minimized even when only a slight excess of the glycosyl acceptor components is employed. David Crich examines the glycosyl triflates as extremely reactive glycosyl donors. They are prepared from anomeric sulfoxides or thioglycosides upon activation with triflic anhydride or benzenesulfonyl triflate and provide access to the elusive β -mannopyranoside, which can be found in many biologically important oligomers.

Hydrolytic vulnerability of *O*-linked glycosides makes the *C*-glycosides attractive sugar mimics and stable drug candidates. Maarten Postema and Daniel Calimente (Chapter 4) report on the many methods for the preparation of both α - and β -*C*-glycosides that have been developed, as well as some new approaches currently in the literature. One of the key issues surrounding the synthesis of *C*-glycosides concerns the stereochemistry of the *C*-glycosidation step, which has seen a remarkable improvement over the years. As *C*-glycosides make their way to the forefront of carbohydrate synthesis, many mild conditions will be examined, and these sophisticated synthetic methods will facilitate their production.

Todd Lowary (Chapter 5) focuses on two major polysaccharides containing D-arabinofuranose, namely, arabinogalactan and lipoarabinomannan, in a quest to identify new antibiotics. These glycopolymers are found as important components of the cell wall of the *Actinomycete* family. Although there is now an understanding of the

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structure of mycobacterial arabinan, the biosynthetic pathway is yet to be understood. These investigations will depend critically on the access to synthetic oligosaccharides and their analogs, which are reviewed extensively.

In Chapter 6, Biao Yu and Yongzheng Hui discuss the relevance of saponins and their chemical synthesis. This important class of glycosidic steroids is found mainly in plants used as herbal medicines. However, a major issue surrounding the saponins is their ambiguous mechanism of action. The authors discuss two important strategies for the construction of saponins, each involving protective group manipulation and various glycosylation methodologies. Increasing interest in traditional herbal medicine and in "carbohydrate drugs" should bring further attention to this group of natural glycosides.

In Chapters 7–13, the focus shifts to the biochemistry of carbohydrates and the exploration of fundamental principles related to cell signaling and protein–carbohydrate interactions on a molecular level. Sialic acids are a class of nine-carbon monosaccharides found at the termini of oligosaccharides in many mammalian cellular systems. Randall Halcomb and Mark Chappell (Chapter 7) summarize the most current sialylation technology. Both chemical and enzymatic methodologies for coupling sialic acid to various carbohydrate moieties are examined while providing the reader with chemical detail that one requires to work in this field.

In Chapter 8, David Mann and Laura Kiessling explore a number of fundamental binding principles such as the energetics surrounding hydrogen bonding, metal chelation, hydrophobic effects, coulombic interactions, and the role of water in protein–carbohydrate interactions. The information provides a prelude to the concept of multivalency in understanding the principles, methodologies, and techniques used to increase an overall binding affinity between carbohydrates and proteins. One technique used to achieve multivalency revolves around linking carbohydrates to polymeric supports so as to increase the number of binding sites as well as obtain optimal distal properties for effective binding.

René Roy (Chapter 9), another pioneer in the application of multivalency effects in glycobiology, discusses some novel multivalent glycotools for biochemical investigations related to sialic acid. Roy describes methodology to produce sialyl-oligosaccharides, functionalized sialosides, sialoside clusters, *N*- and *O*-linked glycopeptides, amphiphilic calix[4]arene nanostructures, glycopolymers, and glycodendrimers. Hybrid dendrimer–polymer glycoclusters are also introduced as new and exciting complexes to show increased binding affinity.

In Chapters 10 and 11, Jalal Haddad and Shahriar Mobashery, Lakshmi Kotra, and Mei-Zheng Liu examine the diversity of aminoglycosides and their significant role as antibiotics. They reveal the specificity of aminoglycosides for binding to RNA constructs derived from the HIV–RRE and TAR RNA activator regions and examine the varying inhibitory effects of aminoglycans on different microorganisms. They also introduce methodologies in the synthesis of aminoglycoside antibiotics by examining the chemical strategies that have been developed.

In Chapter 12, Bryan Yeung, Pek Chong, and Peter Petillo survey the chemical preparation of the glycosaminoglycans, oligosaccharides of hyaluronan, chondroitin sulfate, dermatan sulfate, keratan sulfate, heparin, and heparan sulfate. Despite the biological importance of these ubiquitous carbohydrate polymers, there are few reports of the chemical syntheses of glycosaminoglycan (GAG) oligosaccharides. The multiple functionality of GAGs provides an excellent scaffold on which structure–

activity relationships can be studied, but their syntheses present an unparalleled challenge to the synthetic carbohydrate chemist. The authors recognize the difficulty in the construction of these highly functionalized carbohydrates and present newly developed protecting groups as well as glycosylation procedures to synthetically access GAG fragments.

In Chapter 13, Jacquelyn Gervay-Hague and Thomas Weathers, Jr., discuss some of the more recent chemistry behind pyranosyl sugar amino acids and the important role they play in biological systems. The authors make a complex group of carbohydrates seem relatively simple and interesting by addressing the important issues and illustrating them with clear, concise pictorial schemes. Included are the synthesis of C-aminoglycosides, protecting groups, the chemistry of glycosidic linkage, strategies for block synthesis, and the introduction of solid-phase synthesis of mixed sugar amino acid conjugates. The emphasis of this chapter is twofold: to describe the synthesis of aminoglycans oligomers and to examine the stable secondary structural characteristics of amido-linked oligomers.

Chapters 14–18 are meant to pioneer a chemo-enzymatic approach to the construction of carbohydrates. One of the underlying themes of this book is the exploitation of the complexity of carbohydrates and applying various methodologies to simplify their production. In Chapter 14, Xiangping Qian, Keiko Sujino, Monica Palcic, and Murray Ratcliffe discuss the potential of glycosyltransferases in oligosaccharide synthesis. The authors focus on the enzymes responsible for creating various glycosidic linkages and the sugar donor requirements for glycosyltransferases as well as giving some detailed information for applying this knowledge to large-scale carbohydrate synthesis.

Chapter 15, written by H. N. Cheng and Qu-Ming Gu, discusses the application of biotransformations to polysaccharides modification. Polysaccharides are natural materials ideally suited for enzymatic modifications. The chapter introduces lipase-catalyzed and β -galactosidase-catalyzed modifications of carbohydrate polymers.

Peter Andreana, Wei Zhang, and Peng George Wang (Chapter 16) take a close look at the α -gal epitope as a case study. This carbohydrate sequence is responsible for the hyperacute organ rejection associated with xenotransplantation. Efficient production of this carbohydrate epitope can lead to increased studies directed toward solving the xenotransplantation conundrum. The authors examine both chemical and enzymatic routes for synthesizing the epitope and present some important physical properties associated with binding of the carbohydrate to the protein (epitope-antibody interaction).

Bacterial glycosyltransferases, the topic of Chapter 17, by Przemyslaw Kowal, Xi Chen, and Peng George Wang, are enzymes responsible for the assembly of bacterial cell walls (e.g., succinoglycan) and lipopolysaccharides or polysaccharide structures attached to the lipids of the outer membrane of gram-negative bacterial cells. Lipopolysaccharides are at the forefront of bacterial interactions with the outside world. These structures have been found to be essential in processes ranging from root nodulation to human pathogenicity. Therefore studies on the corresponding glycosyltransferases are of great importance and interest. The authors mention an emerging technology using biosynthetic pathway engineering to produce carbohydrates on a large scale. We envision that such technology will be rapidly developed into commercial use.

Scarlett Goon and Carolyn Bertozzi close the book with a chapter discussing metabolic substrate engineering as a tool for glycobiology. In this approach, metabolic pathways are intercepted with unnatural monosaccharide substrates, leading to their incorporation into cell surface oligosaccharides. This provides an innovative method for studying the functions of the surface sugar structures. Modified substrates might also block biosynthetic enzymes, producing phenotypes similar to those induced by glycosyltransferase inhibitors. This chapter focuses on the flux of carbohydrate precursors and synthetic carbohydrate analogs through the metabolic pathways of the cell and the information that can be gained from investigating such processes.

This book is intended for graduate students and researchers in carbohydrate chemistry, biochemistry, medicinal chemistry, and glycobiology in both academic and industrial laboratories. We feel privileged to have attracted such a distinguished group of investigators and express our sincerest gratitude for their time and effort in making this endeavor a meaningful contribution.

*Peng George Wang
Carolyn R. Bertozzi*