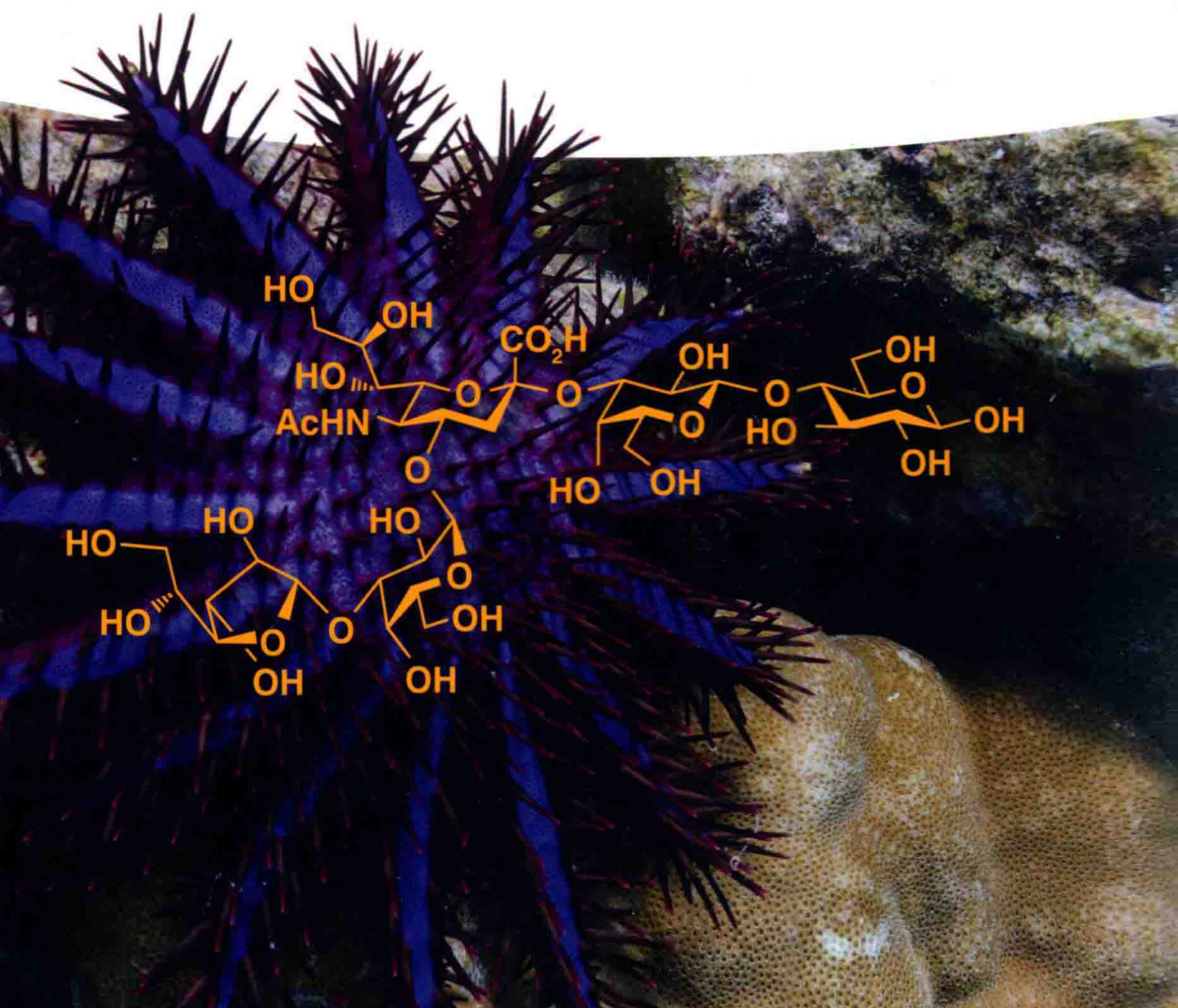


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Daniel B. Werz and Sébastien Vidal

Modern Synthetic Methods in Carbohydrate Chemistry

From Monosaccharides
to Complex Glycoconjugates

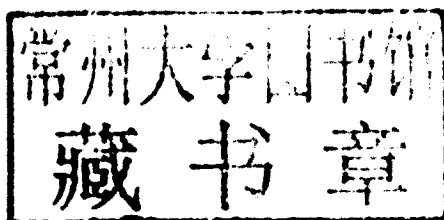
With a Foreword by David Crich



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Modern Synthetic Methods in Carbohydrate Chemistry

From Monosaccharides to Complex Glycoconjugates



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Foreword

The ever-expanding field of glycoscience is driven by the vast diversity of biological processes mediated by carbohydrates, their oligomers, and conjugates, thereby providing enormous opportunities for the use of carbohydrates and their derivatives as research tools and as therapeutic agents. The difficulties in isolating homogeneous glycoforms from nature in any significant quantity and the limitations of such methods to naturally occurring glycoforms underline the need for efficient and effective chemical synthesis of such molecules. The superficially simple mechanism of the glycosidation reaction masks what is, in reality, a very difficult problem and one that drives the need for innovative chemical solutions, which in turn is attracting an increasing number of bright young (and not so young) researchers to the area. Against this background, Sébastien Vidal and Daniel B. Werz have assembled in this book an outstanding collection of work of talented authors to give their individual perspectives on “Modern Synthetic Methods in Carbohydrate Chemistry,” be they at the level of “simple” monosaccharides or complex glycosides. As the title suggests, oligosaccharide synthesis and carbohydrate chemistry, in general, are but one facet of modern organic chemistry. This is richly brought out in the content of the book from which it is clear that many recent advances in glycochemistry and indeed glycoscience depend very heavily on the power and ingenuity of contemporary synthetic organic methodology.

The first chapter, an authoritative contribution by George O'Doherty from Northeastern University in Boston, sets the tone by drawing the reader's attention to the fact that monosaccharides and complex glycans are not necessarily best prepared from actual sugars and that modern synthetic chemistry in the form of *de novo* synthetic approaches has an important role to play. The second chapter continues the theme as Stéphane Vincent from the University of Namur reminds us of the importance of the aldohexoses and the need for their synthesis in terms of both biological probes and lipopolysaccharide (LPS) fragments. Mark Nitz from the University of Toronto then expounds on the protecting-group-free synthesis of glycoconjugates and in particular on the use of hydrazides and oxamine derivatives for the synthesis of *N*-glycosides, before Alphert Christina, Gijs van der Marel, and Jeroen Codée from the Leiden University laboratory describe the recent evolution of the stereocontrolled synthesis of the 1,2-*cis*-glycosidic linkages, thereby nicely

underlining the power of modern synthetic chemistry. Nikolay Nifantiev and his coauthors from the Zelinsky Institute of Organic Chemistry in Moscow continue with the theme of the stereocontrolled synthesis of the 1,2-*cis*-glycosides with particular emphasis on the role of participation by remote esters, a process for which the jury has yet to return a clear verdict. A chapter by Micha Fridman from Tel Aviv University then takes us into the realm of the aminoglycoside antibiotics and presents both useful chemistry and a perspective on novel applications of these compounds beyond their current use as antibacterials. Pierre-Alexandre Driguez at Sanofi in France takes us into the realm of complex oligosaccharide synthesis and tackles the vexing problems of the synthesis of heparin fragments, both natural and nonnatural, before Rajarshi Roychoudhury and Nicola Pohl from Indiana University set out the many advantages of light fluororous tag-assisted synthesis of oligosaccharides and the various strategies devised to date in order to take advantage of them. Samuel Guieu and Matthieu Sollogoub at the University of Aveiro and the Université Pierre and Marie Curie in Paris recount recent advances in cyclodextrin chemistry with an emphasis on selective functionalization methods, after which Anna Bernardi from the University of Milan takes up the theme of the design and synthesis of GM1 glycomimetics as cholera toxin ligands. This book continues with a chapter by Hiromune Ando and coworkers from Gifu University on recent advances in the synthesis of glycosphingolipids, from which much is to be learnt about the stereocontrolled synthesis of the once-difficult sialic acid glycosides. Finally, the volume closes with an important chapter from Daniel Varón Silva and his coauthors at the Max Planck Institute of Colloids and Interfaces in Berlin describing the need for, the many challenges in, and their numerous elegant solutions to, the synthesis of glycosylphosphatidylinositol (GPI) anchors and of GPI-anchored molecules.

The discerning reader will gain much from this volume not the least of which, hopefully, will be the recognition of the dynamic nature of the field of glycochemistry and of the many challenges still remaining. When viewed in the broader context, these many challenges are nothing more than problems in modern synthetic organic chemistry whose solution only awaits the arrival and ingenuity of fresh minds to the area.

Wayne State University
November 2013

David Crich

Preface

More than 100 years ago, pioneering achievements in carbohydrate chemistry were awarded the second Nobel Prize in Chemistry to Emil Fischer. Since that time this branch of organic chemistry has lost none of its fascination. The success story began with Fischer's brilliant logical deduction of the glucose structure (based on simple organic reactions performed with sugars) and was followed by basic glycosylation methods (such as the Fischer-Helferich or the Koenigs-Knorr procedures). Later, in 1937, another Nobel Prize was awarded for the investigation of disaccharides and vitamin C to Walter N. Haworth. After a long period of hibernation, carbohydrate chemistry has developed into an arsenal of highly sophisticated chemical methods, which have enabled the carbohydrate chemist to selectively build almost all of the possible glycosidic linkages. Since Nature has created an unbelievable variety of oligosaccharides and we can at least partially understand the biological significance of many of these structures today, it is very necessary to have a specialized chemical toolkit either to create mono- as well as oligosaccharides or to further modify any of these structures.

The present monograph comprises a fine selection of hot topics in carbohydrate chemistry that have found applications in biological studies and the preparation of complex natural glycans. The synthetic methodologies used for the preparation of these substrates have gathered modern skills from general organic chemistry to the more specific field of glycochemistry. Nevertheless, both organic chemistry and glycochemistry benefited from each other's experiences to push further the limits of the molecular architectures attainable.

In contrast to several other books dealing with carbohydrate chemistry, a collection of very recent synthetic developments in the field of carbohydrate chemistry are presented. Recent synthetic achievements including *de novo* synthesis of carbohydrates, highlights of cyclodextrin chemistry, synthesis of highly complex glycoconjugates such as glycosphingolipids and GPI anchors are treated, always with a strong focus on the synthetic aspects.

The idea for this book project came up at the European Young Investigators Workshop co-organized by us in April 2011 in Lyon (France). After this conference gathering young researchers in glycochemistry, we felt that putting together a book would help the scientific community to identify some key aspects of glycosciences

in order to address the next scientific challenges in the post-genomics and post-proteomics era. Glycomics are now the next leap for scientists and this book is intended to bring together techniques from synthetic organic and carbohydrate chemistry so that each domain would benefit from each other.

This book was the collective work of a number of glycochemists. Most importantly, we would like to thank all contributors whose time, efforts, and expertise have made this book a useful scientific resource for beginners and advanced researchers both in organic chemistry and glycochemistry. We are grateful to Drs. Elke Maase and Lesley Belfit at Wiley-VCH for their help and useful advices in preparing this book.

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