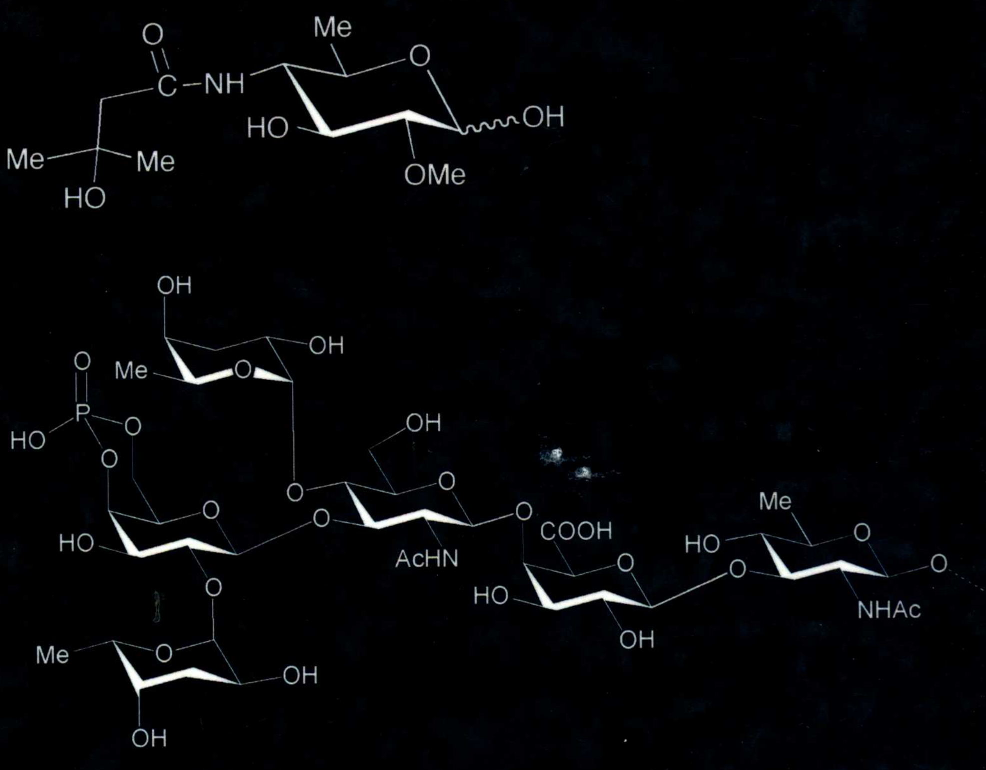
# Carbohydrate Chemistry

## Proven Synthetic Methods

Volume 1




Editor-in-Chief Pavol Kováč

CRC Press
Taylor & Francis Group

Carbohydrate Chemistry | Proven Synthetic Methods Series

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Edited by
Pavol Kováč



CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742



Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number: 978-1-4398-6689-4 (Hardback)



**Library of Congress Cataloging-in-Publication Data**

Carbohydrate chemistry : proven synthetic methods / edited by Pavol Kovac.
p. cm.
ISBN 978-1-4398-6689-4 (hardcover : alk. paper)
1. Carbohydrates--Synthesis. I. Kovác, Pavol, 1938- II. Title.

QD322.S95C37 2011
547'.27--dc22 2011010495

# Carbohydrate Chemistry

## Proven Synthetic Methods

Volume 1

**Carbohydrate Chemistry: Proven Synthetic Methods**

**Series Editor: Pavol Kováč**

*National Institutes of Health, Bethesda, Maryland, USA*

***Carbohydrate Chemistry: Proven Synthetic Methods, Volume 1***, by Pavol Kováč

*This series is dedicated to Sir John W. Cornforth, the 1975 Nobel Prize winner in chemistry, who was the first to publicly criticize the unfortunate trend in chemical synthesis, which he described as "pouring a large volume of unpurified sewage into the chemical literature."*[1]

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# Foreword

In long-established carbohydrate laboratories around the world there are to be found dog-eared and tattered, but precious, copies of early volumes of the "Methods in Carbohydrate Chemistry" series dating from the 1960s, which were edited by Whistler and Wolfrom. These volumes constitute a trove of valuable proven procedures for the synthesis of sugars and their derivatives and methods for their analysis. Most of the articles were written by the original investigators and include enough practical detail to enable a competent technician, rather than an experienced researcher, to repeat them.

Unfortunately the "Methods" series has long been out of print and is not accessible online. Consequently, investigators in the numerous new laboratories now focusing on carbohydrates can thank Paul Kováč for his initiative in launching a new series—*Carbohydrate Chemistry: Proven Synthetic Methods*. This promises to revive the concept of the "Methods" series and make it accessible to today's greatly expanded community of researchers working in the field of carbohydrate chemistry. Selecting from a broad international pool of respected contributors, this first volume features a wide range of general synthetic methods, together with procedures for particular useful intermediates, written with careful attention to reproducible experimental detail.

Research on carbohydrates was once the province of a handful of determined investigators bold enough to work in a "difficult" field of multifunctional compounds that often gave unpredictable results and afforded complex mixtures presenting formidable challenges in separation. The eventual characterization of pure products employed the classical criteria of combustion analysis, recrystallization to constant melting point, specific optical rotation, and later the revolutionary tool of NMR spectroscopy.

Nowadays, recognition of the great significance of carbohydrates in a multitude of important applications has led to a veritable explosion of research effort throughout the world, and with it a vast increase in the number of research reports in the literature. Target structures of great complexity have been attained by improved synthetic methods, coupled with advanced separation methodology and powerful spectroscopic tools.

However, along with this augmentation of the literature record there has been a regrettable trend toward the suppression of much experimental detail and a decrease in the quality of characterization of new compounds. Authors frequently resort to "preliminary communications" to stake a claim, but fail to follow up with publication of satisfactory experimental detail. Even when experimental procedures are recorded, many authors fail to provide sufficient information to permit another investigator to repeat the procedure, and frequently omit such traditional criteria of identity as elemental analysis, crystallinity, chiroptical data, and proof of homogeneity, to the point that the veracity of many claimed new structures may be called into question.

Such periodicals as *Organic Syntheses* and *Biochemical Preparations* have earned high respect because of their policy of inviting volunteer "checkers" to repeat submitted procedures in the laboratory and subsequently share coauthorship of the article. This practice, although difficult in today's grant-driven and targeted research, has nevertheless been adopted by Dr. Kováč in this series. Users of this and subsequent volumes can therefore take confidence in the reliability of the selected procedures. Authors of stature in the field attest to the validity of their contributions. The efforts of the independent checkers serve to verify that the methods are reproducible and that sufficient detail is given to the procedures and the thorough characterization of the products and intermediates described.

It is to be hoped that this series will provide a significant contribution to ongoing research with its trustworthy collection of procedures. It should help in preventing much wasteful hit-or-miss experimentation aimed at repeating the synthesis of compounds claimed in the literature, but offered with unjustifiably inflated yields and woefully inadequate characterization or procedural detail.

Dr. Kováč is to be commended upon his initiative to help today's researchers with reliable experimental access to key structures and synthetic methodology, and it is to be hoped that other investigators will be encouraged to submit new procedures and to serve as independent checkers.

**Derek Horton**
*Emeritus Professor of Chemistry*
*Ohio State University*

# Foreword

The rapid and dynamic growth in the area of glycosciences has been based on modern techniques provided by genetics, enzymology, and advanced analytic instrumentation as well as on the key expertise and methodology developed by carbohydrate chemists, thereby linking organic chemistry with medicinal chemistry and glycobiology. The experience that has accumulated over the past years, however, has not always been fully transmitted to younger glycoscientists, and the general annotation of the field is seen as a rather challenging part of natural product chemistry. The inherent difficulties of carbohydrate chemistry, which are related to the presence of many stereogenic centers, multiple conformations, the need for stereoselective and high-yielding transformations of the anomeric center, a well-conceived choice of protecting groups, and elaborated analytical techniques, have further labeled the field for "dedicated experts only."

The novel series, *Carbohydrate Chemistry: Proven Synthetic Methods*, edited by Paul Kováč, aims at bridging this gap between potential newcomers and experienced glycochemists by providing a compendium of preparatively useful procedures that have been checked by independent research groups elsewhere. Thus, the main concept of this series follows other successful precedents in the field of general organic synthesis. The compilation of protocols covers both common and important analytical and synthetic methods as well as illustrates the synthesis of selected carbohydrate intermediates with general utility. The major focus is devoted to the proper practice of state-of-the-art preparative procedures, including the detailed description of the starting materials used, reaction setup, and work-up and isolation of products followed by identification and proof of purity of the final material (nota bene: regrettably, this requirement is not always fulfilled in many of the papers published nowadays). In addition, general information regarding convenience of operation and comments on safety issues have been addressed, where appropriate. Versatile and practically useful methods that have not received long-lasting recognition or that are difficult to access from their primary sources have also been revitalized and brought forward to the attention of the reader.

The reliability and reproducibility of the methods contained in this collection have been carefully established and will thus be highly valued and appreciated by the scientific community, in particular by postdoctoral staff as well as PhD students with less "hands-on" experience.

A series of this type has long been overdue, and Volume 1 should be followed by many future volumes in due course of time. One can safely expect that this series will receive a warm reception from organic chemists, biochemists, and glycoscientists and will be consulted many times during daily experimental benchwork.

**Paul Kosma**

# Foreword

In setting up my initial research group at the University of Waterloo, one of my first purchases was Volumes I and II of "Methods in Carbohydrate Chemistry." Unsaturated sugars were central to our research plans, and triacetyl glucal was to be our starting material. The compound was either not commercially available or was beyond our economic means, so it had to be prepared. The literature procedure was brief and somewhat dense, but fortunately, the authors' version in "Methods" was highly detailed and user-friendly. Indeed, the "Methods" procedure was so reliable that Mark Yunker, our undergraduate intern, was able to mass-produce triacetyl glucal by using a plastic garbage pail as his reaction vessel. In order to efficiently stir the large amount of zinc required, he borrowed a stirrer from the university's swimming pool, facilitated by the fact that he was on the water polo team.

Today's carbohydrate literature with its myriad experiments in organic synthesis biology, biochemistry, etc., presents even more formidable obstacles. For this reason, the advent of the first volume of *Carbohydrate Chemistry: Proven Synthetic Methods* is timely, and these volumes will be seen as equivalent to *Organic Syntheses*. Now that glycoscience is attaining well-deserved prominence, a ready compilation that gives easy access to user-friendly methods not only for synthesis but also for biochemistry and biology will be welcome.

Dr. Kováč is to be warmly congratulated for his vision in championing this new series.

**Bert Fraser-Reid**

# Introduction

The idea to start the *Carbohydrate Chemistry: Proven Synthetic Methods* series was conceived after many discussions with colleagues at conferences, symposia, and also privately, when the conversation almost invariably ended with joint complaints about "a lot of junk in the synthetic literature." What we primarily meant was that results of many papers on synthetic methods published recently could not be reproduced because of lack of data presented or inflated yields. In some publications, inclusion of data had been so carefully avoided that one could easily write such papers even without doing any work in the laboratory. Another pile of "junk" in the chemical literature is formed by a large number of new synthetic compounds that have not been properly characterized. The 1975 Nobel Prize winner in chemistry, Sir John Cornforth, obviously had not much regard for such substances when he referred to them very appropriately as "unpurified sewage."[1] Encouraged by Sir John, I had first written my commentaries[2,3] and later tried to find a sponsor for the publication of a series in preparative carbohydrate chemistry that would be similar to what already existed in general organic chemistry, and where the reproducibility of every protocol would be ensured by results of an independent "checker." My thanks are due to CRC Press/Taylor & Francis and, in particular, to Hilary Rowe (acquisition editor) and Jennifer Ahringer (project coordinator), who were instrumental in launching this series.

Reproducibility of synthetic work has always been of concern to chemists, and irreproducibility, which was recently eloquently criticized,[4] has become a serious problem. The days are long gone when authors included in their publications parallel preparative experiments to document reproducibility of their work (e.g., Ref. [5]) and when journals would publish such papers. Fierce competition for priority and funding often leads to hasty publication of synthetic work without optimizing reaction conditions and/or without proper characterization of products. It also often results in including in papers on synthesis unproven, unreliable experimental protocols. Responsibility for publishing manuscripts that describe such work lies mainly with editors of journals because it is the editors who have the final say as to what does and what does not get published. This state of affairs with publishing synthetic chemistry is alarming knowing that Guidelines for Authors, which most journals make available to authors, state clearly the strict requirements for acceptance of papers for publication. Among those, many journals that publish synthetic chemistry require that proof of purity be provided by correct analytical figures obtained by combustion analysis. That notwithstanding, editors often do not adhere to those requirements and routinely accept manuscripts that would not pass criteria of what once used to be considered acceptable standards. Those criteria are not something that may be arbitrarily changed. What is pure is pure, and what is not is not. Sadly, the current norm seems to be HRMS figures, which provide no clues about the purity and which even the clumsiest chemist can readily obtain. Authors and editors alike seem to have forgotten that it used to go without saying that reports of syntheses of new, simple, stable compounds had to either include combustion analysis figures as the criterion of purity or, in preliminary communications, a statement to that effect. With the ever-increasing number of individuals involved in organic synthesis, as well as with the exploding number of journals available for publication of synthetic work, it is virtually impossible to sort out laboratories or individuals whose work is reliable. With that in mind, I have ventured to start a series for publication of selected preparative procedures whose reliability has been verified by independent checkers. I have done so in the hope that a compilation of methods that have been checked would be of great value to the present and future generations of carbohydrate chemists, as has been the case with a revered, independent, now apparently defunct previous series in the field of carbohydrate chemistry.

I realize that by what I said above and what follows I may be stepping on some toes. If this sounds like I am trying to shake up the establishment a little, then this writing fulfilled its purpose, and I am doing this in the hope that the field of synthetic organic chemistry will benefit from it. The good work of contributors to the first volume of *Proven Synthetic Methods* and this Introduction is supposed to be a wake-up call to the community of synthetic organic chemists, which will have to police itself, lest the misguided, prevailing trend of executing and publishing organic chemistry might continue.

Now, when a group of dedicated carbohydrate chemists had put extra effort into making a volume of reliable synthetic protocols available to their peers, I was disturbed to see that the editor in chief of a major organic chemistry journal, which has been referred to as a "high-impact journal," has informed the potential contributors that his journal has softened its requirements for accepting papers for publication. One can surmise from the tone of the announcement that the editor was actually proud to make it known that as part of "ongoing efforts to streamline the publication process for authors," the journal has "made a significant change to the purity requirements for manuscripts submitted in 2009." While in the past the journal "required that the purity of all tested compounds should be not less than 98% and that documentation be provided as evidence of purity," the journal's revised policy requires that "tested compounds, whether synthesized or purchased, should possess a purity of not less than 95%." And as if the above were not shocking enough, the information continued as follows: "No documentation for purity is required in the manuscript." It is incredible that this can come from a journal that is highly relevant to the life sciences, where purity and proper characterization of chemicals is particularly important when such substances are used as probes or as drugs, lest the effect of more potent minor impurity might be misinterpreted as that of the major component.

Even in the prevailing "publish or perish" atmosphere, it is hard to understand the obsession of authors with the desire to have their work published in the so-called high-impact journals when, judging by any standard, *what* is published is more important than *where*. The flaws of the system that grants the impact status to journals are obvious and well documented, as a simple Google search can quickly reveal. To all those examples found on Google of how the impact factor can be manipulated to go up without a valid reason, one could readily suggest another one: Soften the requirements for quality of work to be acceptable for publication. The impact factor is, essentially, calculated as a ratio of the number of citations over the number of papers published during a two-year period. It can be reasonably assumed that when the number of papers published—good or bad—increases, so does the number of citations. Taking that into consideration, lowering the stick that some journals use to categorize submissions as acceptable or not acceptable for publication becomes now quite understandable, although not condonable. The best proof of inadequacy of the concept of high-impact journals is the high impact of journals that publish review articles. The value of review articles is indisputable, but it is the *authors* who deserve the credit, since it is their work that made the high impact on science and not the *journals* that publish such articles. Journals that publish review articles get a disproportional number of citations and, consequently, readily win the status of high-impact factor journals mainly because readers take shortcuts and seek information in review articles instead of searching for it primarily in the original publications. It is actually the authors of valuable work and not the journals who should be given the high-impact factors. Should we respect Emil Fisher and Albert Einstein for their accomplishments and ideas that changed the world or glorify journals that published their work? The answer to this question should be a no-brainer. However, it is neither possible nor necessary to assign a numerical impact factor to authors. We cannot objectively rank authors either by number of papers or citations. Doing the former would encourage fragmentation of results, and if we were to do the latter, anybody could collect a lot of citations by publishing an idea that would be later proven wrong. The only objective method of evaluating the quality of any scientist's work would be the one based on discussions his or her peers have during coffee breaks at scientific meetings. It is there that conferees freely voice among themselves appreciations, or lack thereof, of the work of their colleagues. In this context, I cannot but express sadness over the nothing but profit-driven mushrooming of scientific journals. Just look how many more "Letters," "Natures," "Trends," and the like have been created during the last decade or two. Or should we, perhaps, cheer because that is supposed to reflect the ever-increasing volume of good science produced by the new generation of scientists? Hardly. Instead of contributing to the advancement of science, publishers of these offshoot journals have, in fact, done a great service to Parkinson, by confirming the validity of his law of scientific publishing: "The progress of science varies inversely with the number of scientific journals published," which is no longer funny.

In this high-impact-journal mania, it should not, perhaps, be surprising to see some unscrupulous editors prey on potentially gullible contributors for their new journals, which came into existence for no other than economical reasons. I can only guess how it resonated with hundreds of colleagues who received the same invitation to contribute as I did, but the following e-mail from the editor of a new journal came to me as a shock (I shall be kind here, and not name the editor or the journal): "WX Publishing recently announced the online publication of the first issue of YZ Publication, a new high-impact, peer-reviewed journal for the rapid publication of research in the XY Field." Reading this highly misleading, pathetic advertising is analogous to a "We are #1"-type desperate sales pitch by a used-car dealer. I could not resist and responded to the sender with a query: "Could you please explain how has it been determined that YZ Publication is a new *high-impact* journal when only one issue has been published?" I did not expect any answer because if I had been the sender of that note, I would have felt embarrassed and rather not responded.

However, there came a reply, and it addressed the issue in the following way: "At WZ Publishing, our aim when launching new journals is for them to be amongst the leading and highest-impact publications in the field. Our inclusion of the term 'high-impact' reflects our belief that amongst the articles published in the first issue and beyond will be work which the MN community will see as high-quality and thought-provoking." Well, I wish the new journal the impact they hope for. Nevertheless, as long as the scientific community requires that the content of a paper published in a respectable journal be based on solid scientific evidence supported by data and not *belief*, the same standards should be required of and maintained by the publishers and the editors. Just because one *believes* that one is a bird does not mean one actually can fly, and one should be careful or one may get hurt. Examples of the same go back to ancient mythology.

Volume 1 of *Carbohydrate Chemistry*: *Proven Synthetic Methods* is organized a little differently than similar, existing series. The most important part of each topic is, of course, the experimental protocol. In *Proven Synthetic Methods*, it often contains more experimental details and data than is normally found in full papers or communications on synthesis. In addition to numerical data, copies of 1D NMR spectra of compounds prepared are also included. These are presented at the end of each contribution to give readers an idea about the purity they can expect of the products described.

In addition to those I mentioned above, I should like to thank all authors who contributed to this volume, which made it possible to get this series started. My undiminished thanks are also due to all those who have acted as checkers, accepting thereby a great part of the responsibility for the reproducibility of protocols contained in this volume. The work of Dr. Amélia Pilar Rauter, who has proofread the carbohydrate nomenclature with the aid of Bernardo Herold and Gerry Moss, is hereby gratefully acknowledged.

It is commendable, and I highly appreciate it, that many contributors to this volume belong to the new generation of young carbohydrate chemists. This volume could have been even more valuable if many more laboratories known for producing credible work had participated, and I trust that they will do so when the future volumes of *Proven Synthetic Methods* will be in preparation.

**Pavol Kováč**
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