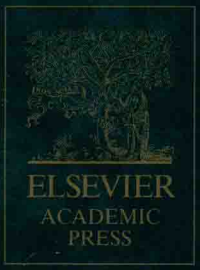

ADVANCES IN CARBOHYDRATE CHEMISTRY AND BIOCHEMISTRY

58

Advances in Carbohydrate Chemistry and Biochemistry

Editor
DEREK HORTON
The American University
Washington, DC

Volume 58

ELSEVIER
ACADEMIC
PRESS

Amsterdam – Boston – Heidelberg – London – New York – Oxford
Paris – San Diego – San Francisco – Singapore – Sydney – Tokyo

ELSEVIER B.V.
Sara Burgerhartstraat 25
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1000 AE Amsterdam
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San Diego
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The Boulevard
Langford Lane, Kidlington
Oxford OX5 1GB
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84 Theobalds Road
London
WC1X 8RR
UK

First edition 2003

Library of Congress Cataloging in Publication Data
A catalog record is available from the Library of Congress.

British Library Cataloguing in Publication Data
A catalogue record is available from the British Library.

ISBN: 0 12 227258 0

♾ The paper used in this publication meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper).
Printed and bound in Great Britain by MPG Books Ltd, Bodmin, Cornwall.

Advances in
Carbohydrate Chemistry and Biochemistry

Volume 58

PREFACE

This 58th volume of *Advances* continues the sustained theme of definitive articles written by leaders in the field, providing comprehensive coverage of mature fields or selective treatment of evolving areas. In contrast to the strong emphasis on glycoconjugates and biological aspects in the preceding Volume 57, the contents of the present issue reflect mainly structural and synthetic aspects of simpler sugars.

Methodology for glycosidic coupling continues to pose challenges for the synthetic chemist, and the synthesis of defined oligosaccharide sequences remains a problem requiring great skill and experimental versatility. In contrast to the effective and widely available automated procedures based on solid-support technology for synthesis of oligopeptides and oligonucleotides, comparable procedures in the carbohydrate field have been lacking, on account of the complexities of linkage position, anomeric orientation, and protecting-group manipulation. Among the investigators addressing this problem, Seeberger (Cambridge, Massachusetts) and his coworkers Plante and Palmacci have made significant strides in developing the functional solid-phase automated synthesizer presented here. It provides practical feasibility for synthesis of selected oligosaccharide sequences, although further research to permit general application for other linkage patterns clearly remains necessary.

Although sugar derivatives containing unsaturated functionality were introduced back in Emil Fischer's time, and the rather inappropriate name "glycal" became a term that persists to this day, much of their chemistry remained confusing until the advent of NMR spectroscopy. Early surveys in Volumes 7 and 9 of this series, by Freudenberg and Blair respectively, were followed notably by Ferrier's landmark article in Volume 20, which demonstrated the exceptional versatility of unsaturated sugars in synthesis. Ferrier augmented his article soon afterwards, in Volume 24. The innovative leadership of Ferrier in this area of synthesis has become legendary, and here he and his colleague Hoberg (Lower Hutt, New Zealand) revisit the subject of unsaturated sugars in a definitive treatment from the current viewpoint.

A comprehensive survey of all classes of internal anhydrides of sugars is provided in this volume by Černý (Prague), encompassing cyclic sugars bridged by three-, four-, and five-membered oxygenated rings. Many such derivatives offer important potential in synthesis. Earlier articles in this series, especially those by Peat in Volume 2 and by Černý and Stanék in Volume 34, still provide useful background and older detail on these derivatives, as does the 1972 survey by Guthrie in Volume 1A of "The Carbohydrates, Chemistry and Biochemistry," edited by Pigman and Horton (Academic Press).

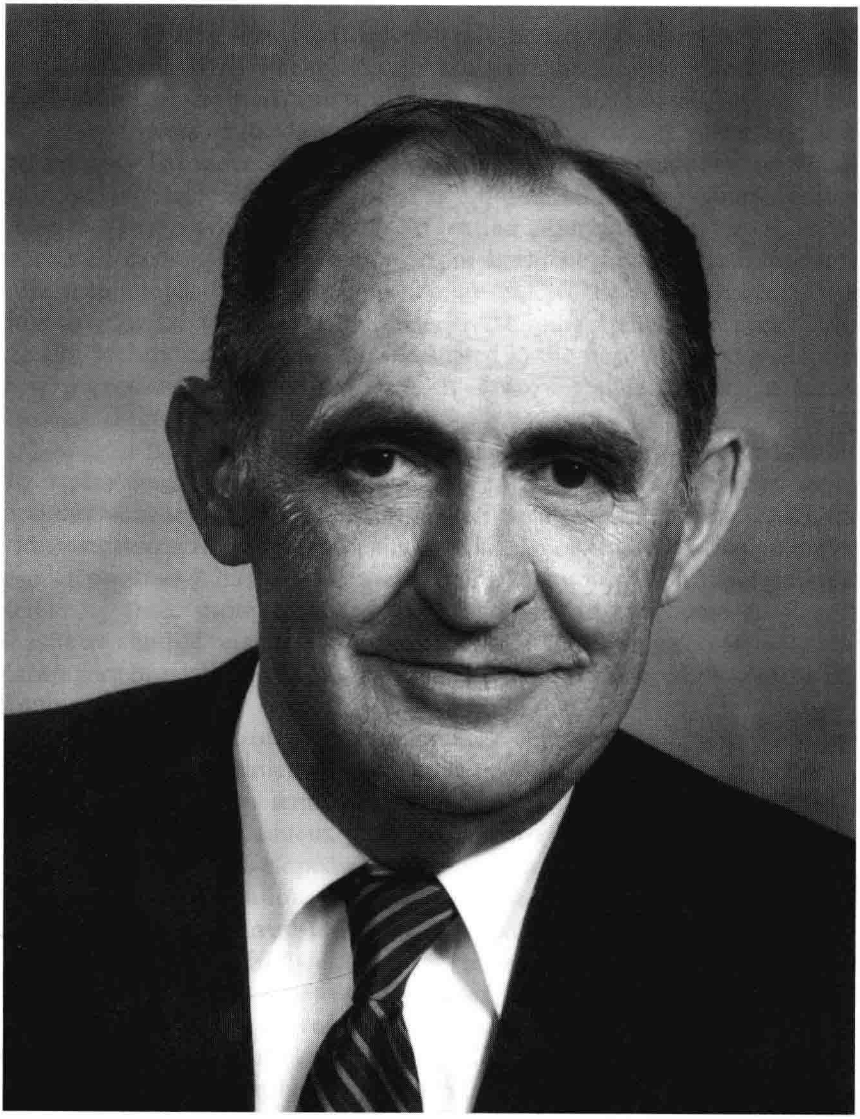
Two related chapters, contributed by de Lederkremer and Marino, and by Varela, both from Buenos Aires, deal with the processes and products of oxidation of carbohydrates, and offer extensive updating of the 1980 article by Green on acids and other oxidation products of sugars, and the one by Theander on oxidative and degradative reactions of sugars and polysaccharides, both published in Volume 1B of the Pigman–Horton treatise. These two articles from Argentina offer broad coverage of all aspects of carbohydrate oxidation, from both the fundamental view and from technological considerations. As an aid to the reader, titles of the cited articles are included in the extensive bibliographic references. Titles are also incorporated in the references cited in the Ferrier–Hoberg chapter. It is proposed to incorporate such titles on a standard basis in future volumes in this series.

The great biological significance of the sialic acids, nine-carbon 5-amino sugars, has long been recognized, and Schauer provided a definitive survey of their chemistry and biochemistry in Volume 40. Much more recently, the wide occurrence in microorganisms of related nonulosonic acids aminated also at position 7 has been demonstrated. Major work on these diamino sugars by three groups has led to the collaborative chapter by Knirel, Shashkov, and Tvetskov (Moscow), Jansson (Huddinge, Sweden), and Zähringer (Borstel, Germany) featured here as the last contribution to this volume.

The life and work of one of the greatest carbohydrate scientists of our time, Raymond U. Lemieux, is recalled here in a sensitive account by Bundle (Edmonton). During a remarkably productive career extending over more than half a century, Lemieux pioneered the application of NMR spectroscopy in chemistry, developed rational approaches for glycosidic coupling, made major contributions to our understanding of three-dimensional carbohydrate structures and protein binding, and made important contributions in the biomedical area. His own articles in these *Advances* include the chemistry of streptomycin in Volume 3, the mechanisms of replacement reactions in Volume 9, and in Volume 50 a consideration of Emil Fischer's "lock and key" concept of enzyme specificity.

With this present volume we welcome Peter H. Seeberger and Yuriy Knirel to the Board of Advisors.

Washington, DC DEREK HORTON
August 2003



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RAYMOND URGEL LEMIEUX

1920–2000

Raymond Urgel Lemieux, the seventh child of a pioneer homesteader, was born on June 16th 1920, in the small prairie community of Lac La Biche, two hundred kilometers northeast of Edmonton, Alberta. His mother died when he was only seven years of age and he was raised by his older sister, Alice. Raymond's father was an itinerant carpenter normally employed in the foothills of Alberta throughout the "dirty thirties" in the so-called coal branch. Consequently, he saw relatively little of his father, who nevertheless was dedicated to the welfare of his large family, a fact that left its mark with his son. The family moved from Lac La Biche to Edmonton, where in Lemieux's words "they lived in a basically Irish–French–Ukrainian ghetto, where the main challenge was to avoid associations that could lead to reform school." Although he did well in school, Lemieux had a passion for hockey and played in the Edmonton Junior Hockey League, but this experience, coupled with his slight physique, convinced him that he lacked the bulk to be truly successful in the sport. At this time his sister Annette met, and later married, a graduate student in physics, John Convey, who showed great interest in Raymond's high school studies and encouraged him to consider attending the University of Alberta. Supported in large part during his first year by tuition fees paid by his sister, Lemieux began his University education in the fall of 1939.

One of his major considerations in choosing to study chemistry was that the University employed a number of second year honours chemistry students as teaching assistants, an appointment he secured by virtue of leading his class in his freshman courses. This income ($18 per month) was of crucial importance to his finances. In order to remain at University during this period, he had to volunteer for active duty, and throughout his undergraduate years he was heavily involved in the Officer's Training Corps. However, due to his involvement with research, he was never called up. At the suggestion of his favorite professor, Rubin Sandin, Lemieux worked with Jack Morrison on detonators. This work did not amount to much,

0065-2318/03 $35.00

and in the Spring of 1943, after graduating, he stayed on with Morrison to investigate what happened to coconut charcoal when it was activated for use in gas masks.

Later that same year Lemieux left Edmonton for Montreal, a three-day train trip, and McGill University, where he registered for graduate studies with Clifford Purves, at the Pulp and Paper Research Institute of Canada. Research at McGill continued to be related to the war effort, first on oxycellulose and then on nitrocelluloses. Although he found the work to be not particularly engaging, the exposure to Purves and discussions with him kindled Lemieux's interest in stereochemistry, and cemented his decision to seek a career in research, primarily in the general area of carbohydrate chemistry. It was here in Purves' office, smoking hand-rolled cigarettes, that he became completely entranced by stereochemistry and fascinated by the structure and synthesis of sucrose, a topic to which he would later return, with considerable effect, on more than one occasion.

By 1946 he had completed his studies for his doctoral dissertation, and the possibility of postdoctoral studies attracted him. The discovery that the antibiotic streptomycin was a carbohydrate was of great interest, not least because ten years earlier his younger brother Gerard had died of a streptococcal infection. When he discovered that research on streptomycin was being pursued in the laboratory of Melville Wolfrom, Lemieux sought Purves' opinion as to whether he should apply for postdoctoral studies at Columbus, Ohio. The postdoctoral position he ultimately secured there was sponsored by Bristol Laboratories, an association that set the stage of a 25-year long research relationship between the young chemist and the pharmaceutical company. As important as this was, the move to Ohio held far greater significance, since it was at Ohio State University that Raymond Lemieux met Virginia McConaghie, who was studying for her Ph.D. degree in high-resolution infrared spectroscopy. They were married in New York City in 1948, and over the ensuing years they raised five daughters and one son, initially in Saskatoon, then Ottawa, and finally home to Edmonton. Referring to his family as one of his proudest accomplishments, he also acknowledged in his autobiography the dominant role of Jeanne (Mrs. Lemieux). Like many brilliant and driven scientists, his work made excessive demands on him and his family. Notwithstanding all these pressures he was proud to observe the considerable and diverse academic and professional achievements of all six children.

It was in the famous carbohydrate group at Ohio State University that Lemieux became involved in the structural elucidation of streptomycin. He also became fascinated by the configurational correlation of sugars and amino acids, and realized that he could address this unresolved question by

combining recent results from the Wolfrom group on the synthesis of peracetylated D-glucosamine diethyl dithioacetal with the Raney nickel desulfurizations he was then conducting. Reduction of the dithioacetal followed by periodate oxidation provided a route to L-alanine and hence its correlation to the relative configuration of D-glyceraldehyde. This work served as a milestone in stereochemistry by linking the stereochemical notation for these two important classes of molecules. Many years later Lemieux used D-glucose in a related fashion to synthesize one enantiomer of 1-deuterioethanol. This was one of the first examples of the use of a carbohydrate to provide a specific asymmetric center of known chirality in the synthesis of an unrelated molecule.

In 1947 Raymond Lemieux became Assistant Professor at the University of Saskatchewan, and two years later he joined the National Research Council's Prairie Regional Laboratory, also in Saskatchewan. During this period he attracted considerable public and scientific attention with the first rational synthesis of sucrose. In fact there was a brief dip in the commodities market for cane sugar when the news of his synthetic achievement broke and before the modest scale and yield of the reaction were properly appreciated. Two reactions involving oxidative cleavage of double bonds by sodium periodate and potassium permanganate, and periodate–osmium tetraoxide were also published at this time and bear his name, the Lemieux–von Rudloff, and the Lemieux–Johnson reactions. During this, his first academic appointment, he began his studies and life-long interest in the chemistry of the anomeric center. Observations on neighboring-group participation, anomerizations, and preferential reactions of certain anomers set the stage for the synthesis of sucrose. The recognition accompanying this achievement lead to an invitation to participate in the 5th Summer Seminar on the Chemistry of Natural Products at the University of New Brunswick in 1953. His lecture entitled "Reactions at the Anomeric Center of Acetylated Sugar Derivatives" in front of such luminaries of the period as R. B. Woodward, and D. H. R. Barton, gave Lemieux his first taste of contact with the leaders of the field, and also convinced him that he could hold his own in this company. It was obvious that the methods available at the time for determination of the stereochemistry at the anomeric center were certainly laborious and left a great deal of uncertainty. It was clear to him that there were special effects in play when it came to the conformational preference of certain pyranose derivatives, such that large substituents at C-1 of the pyranose ring did not occupy the expected equatorial position, but rather the axial orientation. In 1953, however, there was no way to obtain direct evidence for the preferred conformations of such molecules in solution. The solution to this problem lay just around the corner and coincided with his move to Ottawa in 1954.

The then president of the National Research Council, E. W. R. Steacie, had strongly urged the young Lemieux to consider a move to Ottawa to help recruit faculty to the Department of Chemistry at the University of Ottawa and develop an "atmosphere of research." Such were the hierarchical and paternalistic attitudes of the time, that one would have been ill advised to swim against such strong currents. Raymond Lemieux became Professor and Chairman of the Department of Chemistry at the University of Ottawa in 1954, and served as the Vice-Dean of the Faculty of Pure and Applied Science. During his tenure, he not only designed and supervised the building of a new chemistry department but, through his energy and perceptive staff appointments he established a flourishing research environment.

It was in Ottawa at the National Research Council that Lemieux first heard a presentation on NMR. He immediately began to speculate on the steric effects that might influence the chemical shifts of the protons of the pyranose ring. After approaching W. G. Schneider and H. J. Bernstein, Lemieux learned that if he provided manpower to assist in recording the spectra (a considerable task at that time) he would be able to study the NMR of the sugar acetates. With Rudolf Kullnig, a graduate student in Lemieux's group, and under the guidance of Harold Bernstein (NRC), the first NMR spectra of these compounds were obtained at 40 MHz. The work provided the long-sought definitive assessment of the preferred conformations of the sugar acetates in solution. Expansion of the approach led to the first application of ^{1}H NMR spectroscopy for the establishment of relative configurations of chiral centers in organic compounds, and thus the foundation of the Karplus relationship. It is interesting to note that this work was presented in the Karl Folkers Lectures at the University of Illinois in 1958, prior to publication. In attendance, and much impressed, was Martin Karplus, whose yet to be published theoretical work strongly aided in establishing this correlation as one of organic chemistry's most potent stereochemical probes. Karplus later wrote "Just as I finished the work on vicinal coupling constants, I heard a lecture by R. U. Lemieux on the conformations of acetylated sugars. I do not remember why I went to the talk because it was on organic chemistry. Lemieux reported results for vicinal coupling constants and noted that there appeared to be dihedral angle dependence, although the details of the behavior were not clear. However, it was evident that these experimental results confirmed the theory even before it was published." In the same year Lemieux discovered the anomeric effect, now recognized as a fundamental stereoelectronic phenomenon and one that governs the outcome of many organic reactions.

In 1961 Lemieux received an offer of a Professorship from the University of Alberta. Burdened with administrative duties and barely able to find time

for writing up his most successful work in Ottawa, this offer was too good to refuse. Discoveries of large conventional oil deposits had swelled the provincial coffers and the province was preparing to flex its newfound wealth through judicious investment in its main University. With carte blanche to build a strong Department of Chemistry, the recruitment of a young star was a cornerstone in the University's strategy. And so Lemieux returned to the University of Alberta Chemistry Department, where he maintained an active research program well into the 1990s. From 1966 to 1973, he was Chairman of the Division of Organic Chemistry and, aided by his influence and stature, the department grew to become one of the largest and foremost research centers for chemistry in North America.

His Alberta research group of the early 1960s undoubtedly represented one of the high points of his career. Several truly outstanding Ph.D. students during the period 1961–73 helped him establish an undisputed reputation as a world leader in his field. Key advances in the chemistry of orthoesters, glycals, and their nitrosyl chloride adducts, with Richard Morgan, Bert Fraser-Reid, and T. L. (Nag) Nagabushan, represented major breakthroughs during this period. Against this backdrop of new synthetic chemistry, and an increasing understanding of the anomeric effects, the exploitation of ^{1}H NMR spectroscopy to solve conformational and configurational questions was proceeding swiftly. The determination of the opposite relative signs of geminal and vicinal coupling constants in the proton magnetic resonance spectra of saturated organic molecules was made in 1961, followed in 1963 by the determination of the absolute configuration of dextrorotatory l-deuterioethanol, and in 1965 by the proposition of the reverse anomeric effect. Work on the NMR spectra of acetylated sugars continued, together with key developments in the use of NMR to determine the anomeric configurations of sugars and glycosides in D_2O solution. During the same period several postdoctoral fellows and students were engaged in the study of conformational equilibria in solution, using both NMR and chiroptical approaches. Such work added to the appreciation of the importance of the anomeric effect in dictating not only the anomeric preference of electronegative substituents but also the conformation of glycosides (exo-anomeric effect).

With the increasingly sophisticated understanding of reactions at the anomeric center, and the capability to contemplate synthetic targets that few others could consider in the late 1960s, attention turned to the selection of challenging targets. At this time circumstantial evidence was accumulating that complex oligosaccharides, whose structures were just then being solved, were critically involved in phenomena as diverse as cell–cell recognition and development, and control of glycoprotein biosynthesis and transport. It became apparent that the oligosaccharide chains of glycoproteins and

glycolipids could no longer be ignored, as these structures, in fact, carry messages essential for the control of many crucial cellular functions. The study of these new phenomena was critically hampered by the enormous difficulties encountered in trying to obtain even milligram quantities of structurally well-characterized carbohydrates. The most direct solution was to synthesize the required complex oligosaccharides, but this had not been attempted because of the difficulties involved.

At that time the synthesis of a disaccharide was considered a major undertaking, and preparation of the more elaborate oligosaccharides must have appeared as an unrealistic project. The successful completion of such a program required, at a minimum, the development of new glycosylation methods, especially for the synthesis of the α-glycosidic linkage, and the development of new methods for the structural analysis of both protected oligosaccharide intermediates and of the final synthetic products.

Largely as the result of research in his group during the 1960s, these essential methodologies for the stereospecific formation of the glycosidic linkage came to a climax in the early 1970s. For the first time, the synthesis of oligosaccharides of sufficient complexity that they would parallel the bioactivity of the naturally occurring structures could be accomplished. These new synthetic reactions included the oximino–chloride glycosylation method for the preparation of α-linked 2-amino-2-deoxyglycosides and the phthalimido glycosylation procedure for the preparation of β-linked 2-amino-2-deoxyglycosides. Most importantly, the development of the halide-ion glycosylation reaction permitted the synthesis of the hitherto elusive α-glycosidic linkage. These achievements resulted in four 1975 publications on the synthesis of the trisaccharide antigenic determinants for both the group B and Lewis-a human blood types, and opened the way for a host of other laboratories to join in the effort.

It is fair to say that Lemieux did not enjoy the process of manuscript preparation, and his breakthroughs in the rational synthesis of oligosaccharides appeared in several remarkable bursts of back-to-back publications. Thus the reaction of oximino chlorides and related papers appeared in the Canadian Journal of Chemistry as four consecutive publications in 1968, followed by eight consecutive publications in 1973. This extensive body of work would not have been achieved without the drive and commitment of Lemieux's close collaborator T. L. Nagabushan, who played a major role in helping Lemieux run his group during the period from the mid 1960s to 1973. An even more remarkable burst of publications followed in 1975 with the appearance of four papers in the Journal of the American Chemical Society announcing: the halide method, the first syntheses of the human blood group determinants, the use of a tether to