

## Professor Rosa M. de Lederkremer A Tribute



The chemistry and biochemistry of carbohydrates has been, and still is, an intensive area of research in Argentina. The biochemical aspects of carbohydrates were studied by Leloir, who was awarded the Nobel Prize in Chemistry (1970) for his discovery of sugar nucleotides and their role in the biosynthesis of saccharides. The pioneering work of Venancio Deulofeu is also well recognized. In the second quarter of the 20th century, he began an investigation on the chemistry of sugars, a field that was virgin in Latin America. These investigations were flourishing at the time Rosa Muchnik obtained her degree in Chemistry from the University of Buenos Aires (1954). However, at the outset, she was not a sugar chemist. At that time, the unstable political situation in the country had a serious impact on academic life at the University. For unjustifiable political reasons, Dr. Deulofeu was stripped of his professorship in 1952. Therefore, Rosa started her Ph. D. studies in the area of microbiology under the guidance of Professors A. Ferramola and O. Peso. She received her Ph. D. degree in 1956, and then returned to her preferred discipline, the study of organic chemistry. The academic climate improved and Dr. Deulofeu returned to the University of Buenos Aires as Professor of Organic Chemistry and Director of the Department of Biological Chemistry at the School of Exact and Natural Sciences (FCEN). Rosa obtained a position as assistant instructor of chemistry from this institution and Professor Deferrari introduced her to the field of carbohydrates. Years later she referred to that time as “the beginning of sweet investigations after a bitter period”.

In fact, her first work was not too sweet. Dr. Deferrari was studying the ammonolysis of acylated hexoses, and he wanted to extend the study to heptoses. Therefore, Rosa was appointed to conduct a Kiliani synthesis of heptoses starting from hexoses. She still remembers how afraid she was of using the large volumes of hydrogen cyanide required for the synthesis.

In 1955 Rosa married Jehoszua M. Lederkremer, her former classmate during their undergraduate studies in chemistry. Therefore, even in her first publication in *J. Org. Chem.* she appeared as Rosa M. de Lederkremer, as we have always known her. In 1957 their first son, Gerardo, was born. He was five years old when RML was awarded an external fellowship from

the National Research Council of Argentina (CONICET) to carry out postdoctoral studies in the USA. The family moved to Columbus, Ohio and she joined the research group of Professor M. L. Wolfrom, at The Ohio State University. She spent three years working in the famous “sugar alley”, where I also worked twenty years later. Thin-layer chromatography (TLC) was then a rather new analytical technique, and RML had gained some experience in Buenos Aires working with Professor Deferrari on TLC of acyl derivatives of sugars. As a continuation of this work at OSU, she succeeded in the separation and quantification of free sugars by TLC on microcrystalline cellulose.

At the same time many reactions of carbohydrates were studied. For example the oxidation of methyl  $\beta$ -D-cellobioside by alkaline hypochlorite was examined as a model for the oxidation of cellulose. The formation of acetals by reaction of vinyl ethers with glycosides and their removal under weak acid conditions, was also investigated and thus Dr. Lederkremer regarded her stay in USA as very successful, from both professional and personal points of view.

RML returned to Buenos Aires in 1965 and joined the Department of Organic Chemistry (FCEN-UBA) as an Instructor of Chemistry first, and a couple of years later, as Assistant Professor. She was the first woman to reach the latter position in the Department and she started to organize her own research group with Alicia Fernández Cirelli as her first graduate student. The subject of her investigation was the structure of polysaccharides isolated from the fungus *Cyttaria harioti*. This fungus is a parasite of trees that grow in the Patagonian Andes and is responsible for the development of nodules (tumors) in the trees. Some species of the fungus had been employed by native people to prepare an alcoholic beverage by fermentation which suggested a high content of sugars. As expected, glucans were isolated and purified, and their structures elucidated. Alicia finished her thesis in 1972, and this work was awarded the Enrique Herrero Ducloux prize from the Argentine Chemical Society. The beginning of this thesis was almost coincident with the birth of Miguel, Dr. Lederkremer's second son and by the time of the defense Javier, the third son, was born.

The early seventies found RML working on synthetic aspects of sugars. In 1971, she and her second Ph. D. student, Marta Litter, published a paper on the formation of an unsaturated lactone derivative on prolonged benzylation of D-galactonolactone. The interesting  $\beta$ -elimination in aldonolactones reported there initiated a new line of research in which many students (including myself) were subsequently involved. The reaction constitutes a key step in the synthesis of 3-deoxy sugars, prepared by the sequence of  $\beta$ -elimination followed by catalytic hydrogenation.

In spite of her success as an independent researcher, RML decided to move to Brazil with her family in 1974. Her husband had been appointed by private industry to organize a research and development laboratory in Sao Paulo. But probably the main reason was that the political situation in Argentina had deteriorated again and became chaotic by the middle of the year. Once installed in Sao Paulo, RML contacted Professor Walter Colli at the State University of Sao Paulo and they started a cooperative project that lasted for more than 20 years. Dr. Lederkremer became involved in the glycobiology of *Trypanosoma cruzi*, the agent of Chagas disease, an endemic illness that affects hundreds of thousands of people in tropical regions of South and

Central America. A glycoconjugate of the membrane of *T. cruzi* was isolated and purified. It turned out to be a lipopeptidophosphoglycan (LPPG) having the structure of glycoinositolphosphoceramide. These studies led to several publications in highly reputable journals.

After two years in Brazil the family decided, fortunately, to return to Argentina. I met RML in 1977, shortly after her return to Argentina, and I joined a team that was supervised by her and Fernández Cirelli. I remember her great enthusiasm for chemistry, and her friendly approach accompanied by a sense of strong but fair leadership. She was an excellent supervisor to her students and both friendly and helpful to her associates and acquaintances. I was extremely fortunate in having her first as supervisor and then in becoming her coworker, colleague and friend. I therefore feel highly honored to contribute an article dedicated to her in an Arkivoc issue.

I started my doctoral studies a few months after Luis F. Sala and both of us were involved in the  $\beta$ -elimination reactions. He studied the oxidative degradation of 3-deoxy-aldonolactones by Ce(IV), as a route to 2-deoxysugars, and I employed the unsaturated lactone derived from L-rhamnono-1,5-lactone as a precursor to the naturally occurring ascarylose (a component of the lipopolysaccharide from a Gram negative bacteria). Other doctoral students namely Marcos Sznajdman, Lucio Jeroncic, Cecile du Mortier, Carla Marino and Carola Gallo subsequently worked on related projects. Similarly, Noemí Waksman, Alicia Couto, Liliana Casal, José Groisman, Claudio Wolfenson, Maria Isabel Ramirez, Carlos Lima, Laura Bertello, María Laura Uhrig and Rosalía Agustí participated in research on the structure of polysaccharides and glycoconjugates of plants and microorganisms. To date RML has supervised nineteen doctoral theses, and five more are currently in progress. Many of her former students continue as Professors of National Universities, and others occupy important positions in private industry in Argentina and abroad.

The research activities of RML resulted in 181 publications in international journals, and 234 communications in meetings and symposia. She has delivered lectures in universities and research centers in Argentina, Brazil, the United States and Israel. These investigations have been supported by regular grants from national funding agencies such as CONICET, UBA, the Secretary of Science and Technology (SECYT) and the National Agency for Promotion of Science and Technology (ANPCYT). Grants were also received from international organizations such as UNESCO (annually from 1979 to 1983) and the World Health Organization (1985-1987, 1988-1990, 1992, and 1993-1995).

Nowadays, as Emeritus Professor of the University of Buenos Aires she is still actively working on the structure of polysaccharides and glycoconjugates of fungi and trypanosomatids, particularly glycosylphosphatidylinositol protein anchors. She is also involved in the design of chemotherapeutic agents targeted to enzymes specific for microbial pathogens, but absent in mammalian cells. These include the trans-sialidase of *Trypanosoma cruzi*, and the galactofuranosyltransferases and D-galactofuranosidases that are responsible for the biosynthesis and processing of galactofuranose. The synthesis and evaluation of substrates and inhibitors of

those enzymes, is another subject of study.

RML is a Research Member of CONICET; she started as Assistant Researcher and today occupies the highest position of Superior Researcher. She has been invoked frequently to integrate evaluation committees from universities and research centers. She was founder and Director (1995-2000) of the Center for Research in Carbohydrates (CIHIDECAR), a CONICET Institute. She was in charge of the Direction of the Department of Organic Chemistry, FCEN-UBA (1995-1997) and re-elected for a second period (1997-1999). She was a Member of the Editorial Board of "*Carbohydrate Research*" (1980-1984) and also Director of the journal "*Anales de la Asociación Química Argentina*" (1989-1994). Currently she acts as a Member of the Committee for the designation of Emeritus Professors from the UBA (2004).

The scientific reputation of RML has been acknowledged through a number of awards. In 1983, she received the Konex Foundation Award to the most representative of personalities in Science and Technology (discipline Organic Chemistry). In 1983 and 1988 LALCEC (Argentine League against Cancer) gave her an award for collaborative works on antitumor activities of a polysaccharide from the fungus *Cyttaria johowii*. She was nominated Corresponding Member of the Brazilian Academy of Sciences (1987), and distinguished in 1990 with the Enrique Herrero Ducloux Award from the National Academy of Exact and Natural Sciences in recognition of research activities performed in the triennium 1986-88. She also received the Venancio Deulofeu Award of the Argentine Chemical Society in 2000 and in 2004 and the Bernardo Houssay National Award in Exact and Natural Sciences from the Ministry of Education, Science and Technology.

In the name of all the researchers that participate in this special issue, I should like to congratulate Professor Rosa M. de Lederkremer for her outstanding contributions to chemistry.

### **Selected publications of Rosa M. de Lederkremer**

1. Ledekremer, R. M.; Litter, M. I. The formation of an unsaturated lactone derivative on benzylation of D-galactonolactone. *Carbohydr. Res.* **1971**, *20*, 442.
2. Lederkremer, R. M.; Alves, M. J. M.; Fonseca, G. C.; Colli, W. A lipopeptidophosphoglycan from *Trypanosoma cruzi* (epimastigota). Isolation, purification and carbohydrate composition. *Biochim. Biophys. Acta* **1976**, *444*, 85.
3. Varela, O.; Fernandez, Cirelli, A.; Lederkremer, R. M. Synthesis of 3,6- dideoxy-L-arabino-hexose (ascarylose). *Carbohydr. Res.* **1979**, *70*, 27.
4. Lederkremer, R. M.; Casal, O. L.; Alves, M. J. M.; Colli, W. Evidence for the presence of D-galactofuranose in the lipopeptidophosphoglycan from *Trypanosoma cruzi*. *FEBS Lett.* **1980**, *116*, 25.
5. Lederkremer, R. M.; Couto, A.; Rumi, L. S.; Chasseing, N. A. Purification of the polysaccharide from *Cyttaria johowii* and studies on its antitumor activity. *Carbohydr. Res.* **1983**, *113*, 331.

6. Varela, O.; Cicero, D.; Lederkremer, R. M. A convenient synthesis of 4-thio-D-galactofuranose. *J. Org. Chem.* **1989**, *54*, 1884.
7. Du Mortier, C.; Varela, O.; Lederkremer, R. M. A new approach to the synthesis of disaccharides having a furanose as the reducing unit. *Carbohydr. Res.* **1989**, *189*, 79.
8. Marino, C.; Varela, O.; Lederkremer, R. M. Synthesis of galactofuranose disaccharides of biological significance. *Carbohydr. Res.* **1989**, *190*, 65.
9. Lederkremer, R. M.; Lima, C.; Ramirez, M. I.; Ferguson, M. A. J.; Homans, S. W.; Thomas-Oates J. Complete structure of the glycan of lipopeptidophosphoglycan from *Trypanosoma cruzi* epimastigotes. *J. Biol. Chem.* **1991**, *266*, 23670.
10. Lederkremer, R. M.; Lima, C. E.; Ramirez, M. I.; Gonçalvez, M. F.; Colli, W. Hexadecylpalmitoylglycerol or ceramide is linked to similar glycoposphoinositol anchor like structures in *Trypanosoma cruzi*. *Eur. J. Biochem.* **1993**, *218*, 929.
11. Lederkremer, R. M.; Nahmad, V.; Varela, O. Synthesis of  $\alpha$ -D-galactofuranosyl phosphate. *J. Org. Chem.* **1994**, *59*, 690.
12. Bertello, L. E.; Gonçalvez, M. I.; Colli, W.; Lederkremer, R. M. Structural analysis of inositolphospholipids from *Trypanosoma cruzi* epimastigote forms. *Biochemical J.* **1995**, *310*, 255.
13. Lederkremer, R. M.; Colli, W. Galactofuranose-containing glycoconjugates in trypanosomatids. *Glycobiology* **1995**, *5*, 547.
14. Gallo-Rodriguez, C.; Varela, O.; Lederkremer, R. M. First synthesis of  $\beta$ -D-Galf(1-4)GlcNAc, a structural unit *O*-glycosidically attached in glycoproteins of *Trypanosoma cruzi*. *J. Org. Chem.* **1996**, *61*, 1886.
15. Di Nardo, C.; Jeroncic, L. O.; Lederkremer, R. M.; Varela, O. A carbohydrate approach to the enantioselective synthesis of 1,3-polyols. *J. Org. Chem.* **1996**, *61*, 4007.
16. Bertello, L. E.; Andrews, N. W.; Lederkremer, R. M. Developmentally regulated expression of ceramide in *Trypanosoma cruzi*. *Mol. Biochem. Parasitol.* **1996**, *79*, 142.
17. Gallo-Rodriguez, C.; Varela, O.; Lederkremer, R. M. One-pot synthesis of Gal $\beta$ 1-4(Gal $\beta$ 1-6)GlcNAc, a "core" trisaccharide linked *O*-glycosidically in glycoproteins of *Trypanosoma cruzi*. *Carbohydr. Res.* **1998**, *305*, 163.
18. Marino, C.; Mariño, K.; Miletto, L.; Manso Alves, M. J.; Colli, W.; Lederkremer, R. M. 1-Thio-  $\beta$ -D-galactofuranosides. Synthesis and evaluation as  $\beta$ -D-galactofuranosidase inhibitors *Glycobiology* **1998**, *8*, 901.
19. Gallo-Rodriguez, C.; Gandolfi, L.; Lederkremer, R. M. Synthesis of  $\beta$ -D-Galf-(1-3)-D-GlcNAc by the trichloroacetamide method and of  $\beta$ -D-Galf-(1-6)-D-GlcNAc by SnCl<sub>4</sub>-promoted glycosylation. *Org. Lett.* **1999**, *1*, 245.
20. Miletto, L.C.; Marino, C.; Mariño, K.; Lederkremer, R.M.; Colli, W.; Alves, M.J.M. Immobilized 4-aminophenyl 1-thio- $\beta$ -D-galactofuranoside as a matrix for affinity purification of  $\beta$ -D-galactofuranosidase. *Carbohydr. Res.* **1999**, *320*, 176.
21. Bertello, L.E.; Alves, M.J.M.; Colli, W.; Lederkremer, R. M. Evidence for phospholipases from *Trypanosoma cruzi* active on phosphatidylinositol and inositolphosphoceramide.

- Biochem. J.* **2000**, 345, 77.
22. Salto, M.L.; Gallo-Rodriguez, C.; Lima, C.; Lederkremer, R.M. Separation of Gal $\beta$ 1-XGlcNAc and Gal $\beta$ 1-XGlcNAc (X=3,4 and 6) as the alditols by high-pH anion exchange chromatography and thin layer chromatography: characterization of mucins from *Trypanosoma cruzi*. *Anal. Biochem.* **2000**, 279, 79.
  23. Salto, M. L.; Furuya, T.; Moreno, S.; Docampo, R.; Lederkremer R. M. The phosphatidylinositol-phospholipase C from *Trypanosoma cruzi* is active on inositolphosphoceramide. *Mol. Biochem. Parasitol.* **2002**, 119, 131.
  24. Mariño, K.; Marino, C.; Lederkremer, R. M. Specific tritium labeling of  $\beta$ -D-galactofuranosides at the 6-position. A tool for  $\beta$ -D-galactofuranosidase detection. *Anal. Biochem.* **2002**, 301, 325.
  25. Gandolfi-Donadio, L.; Gallo-Rodríguez, C.; Lederkremer, R. M. Synthesis of  $\alpha$ -D-Galp-(1-3)- $\beta$ -D-Galf-(1-3)-D-Man, a terminal trisaccharide of *Leishmania* type-2 glycoinositolphospholipids. *J. Org. Chem.* **2002**, 67, 4430.
  26. Mariño, K.; Lima, C.; Maldonado, S.; Marino, C.; Lederkremer, R. M. Influence of exo  $\beta$ -D-galactofuranosidase inhibitors in cultures of *Penicillium fellutanum* and modifications in hyphal cell structure. *Carbohydr. Res.* **2002**, 337, 891.
  27. Gallo-Rodriguez, C.; Gil Libarona, M. A.; Mendoza, V.; Lederkremer, R. M. Synthesis of  $\beta$ -D-Galp-(1-3)- $\beta$ -D-Galp-(1-6)-[ $\beta$ -D-Galf-(1-4)]-D-GlcNAc, a tetrasaccharide component of mucins of *Trypanosoma cruzi*. *Tetrahedron* **2002**, 58, 9373.
  28. Chioconi, A.; Marino, C.; Otal, E.; Lederkremer, R. M. Photoinduced electron transfer and chemical  $\alpha$ -deoxygenation of D-galactono-1,4-lactone. Synthesis of 2-deoxy-D-lyxohexofuranosides. *Carbohydr. Res.* **2002**, 337, 2119.
  29. Salto, M. L.; Bertello, L. E.; Vieira, M.; Docampo, R.; Moreno, S. N. J.; Lederkremer, R. M. Formation and remodeling of inositolphosphoceramide during differentiation of *Trypanosoma cruzi* from trypomastigote to amastigote. *Eukaryot. Cell* **2003**, 2, 756.
  30. Gandolfi-Donadio, L.; Gallo-Rodriguez, C.; Lederkremer, R.M. Syntheses of  $\beta$ -D-Galf-(1-6)- $\beta$ -D-Galf-(1-5)-D-Galf and  $\beta$ -D-Galf-(1-5)- $\beta$ -D-Galf-(1-6)-D-Galf, trisaccharide units in the galactan of *Mycobacterium tuberculosis*. *J. Org. Chem.* **2003**, 68, 6928.
  31. Bertello, L.E.; Alves, M.J.M.; Colli, W.; Lederkremer, R.M. Inositolphosphoceramide is not a substrate for the first steps in the biosynthesis of glycoinositolphospholipids in *Trypanosoma cruzi*. *Mol. Biochem. Parasitol* **2004**, 133, 71.
  32. Agusti, R.; Paris, G.; Ratier, L.; Frasch, A.C.C.; Lederkremer, R.M. Lactose derivatives are inhibitors of *Trypanosoma cruzi* trans-sialidase toward conventional substrates *in vitro* and *in vivo*. *Glycobiology* **2004**, 14, 659.
  33. Agusti, R.; Mendoza, V.M.; Gallo-Rodriguez, C.; Lederkremer, R. M. Selective sialylation of 2,3-di-O-( $\beta$ -D-galactopyranosyl)-D-galactose catalyzed by *Trypanosoma cruzi* trans-sialidase. *Tetrahedron: Asymmetry* **2005**, 16, 541.

## Books and book chapters

1. Lederkremer, R. M.; Varela, O. *Hidratos de carbono*. Monografía OEA, 1998, Número 32, p144.
2. Synthetic reactions of aldonolactones. Lederkremer, R. M.; Varela, O. *Adv. Carbohydr. Chem. Biochem.* 1994; Vol. 50, pp 125-209.
3. Acids and other oxidation products. Lederkremer, R.M.; Marino, C. *Adv. Carbohydr. Chem. Biochem.* 2003; Vol. 58, pp 199-306.
4. Occurrence, properties and preparation of naturally occurring monosaccharides (including 6-deoxysugars). Lederkremer R.M. & Gallo-Rodriguez, C. *Adv. Carbohydr. Chem. Biochem.* 2004, Vol. 59, pp 9-67

Oscar Varela  
CIHIDECAR-CONICET  
Departamento de Química Orgánica  
Facultad de Ciencias Exactas y Naturales  
Universidad de Buenos Aires  
Pabellón 2, Ciudad Universitaria  
C1428EHA-Buenos Aires  
Argentina  
E-mail: [varela@qo.fcen.uba.ar](mailto:varela@qo.fcen.uba.ar)