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Topics in Heterocyclic Chemistry

Aims and Scope

The series Topics in Heterocyclic Chemistry presents critical reviews on present and future trends in the research of heterocyclic compounds. Overall the scope is to cover topics dealing with all areas within heterocyclic chemistry, both experimental and theoretical, of interest to the general heterocyclic chemistry community.

The series consists of topic related volumes edited by renowned editors with contributions of experts in the field. All chapters from Topics in Heterocyclic Chemistry are published OnlineFirst with an individual DOI. In references, Topics in Heterocyclic Chemistry is abbreviated as Top Heterocycl Chem and cited as a journal.

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László Somsák
Editor

Carbohydrate-spiro-heterocycles

With contributions by

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Preface

Spiro compounds that contain a bicyclic or tricyclic system to share a single atom between two rings represent an increasing class of molecules of both natural and synthetic origin. These compounds exhibit various biological activities and can be used in materials science applications due to, e.g. photochromism and hole transporting abilities. The unique and well-defined 3D structure of spiro derivatives makes them attractive targets in drug discovery, offering a deviation from the traditional aromatic/heterocyclic "flatland" chemistry. The conformational constraints resulting from the spiro structure lend rigidity to these molecules, and this may end up with a diminishing entropic penalty during binding to the biological targets. The spirocyclic constructs can also meet the needs of discovering new regions of chemical space and thereby facilitate uncovering new properties, biological effects as well as medical and other applications. In addition, these scaffolds may be advantageous in view of patentability as well. On the other hand, the construction of spirocycles especially in terms of regio- and stereoselectivities poses a highly provoking task to the preparative chemist. Due to the above important and interesting properties and the demanding synthetic challenges, the spiro compounds attract more and more attention both in academia and industry that is reflected in the appearance of five to six thousands of primary publications and patents per annum during the last decades. Furthermore, the utility of spirocyclic derivatives as commodities is demonstrated by marketed drugs, ophthalmic lenses and sunglasses, auxiliary compounds in stereoselective syntheses, electronic displays, optical data storage devices, etc. Several other utilizations towards, e.g. new medications, chemical biosensing, controlled release drug delivery, molecular switches and solar cells are in a developmental phase.

Carbohydrates are ubiquitous molecules in nature and participate in a vast number of biological interactions. Their conjugates, including all kinds of primary and secondary metabolic small molecules and also biomacromolecules, represent valuable tools for glycobiology research and also lead compounds for drug discovery. While monosaccharides per se appear as heterocycles, their natural conjugates frequently exhibit spiro(hetero)cyclic derivatives, in many cases of high therapeutic

relevance. Well-known carbohydrate-spiro-heterocycles are, e.g. the antifungal papulacandins, the antibiotic orthosomycins, the herbicidal hydantocidin, each of natural origin, and the synthetic tofogliflozin, the active ingredient of approved antidiabetic medications.

Monosaccharides with their multiple stereogenic centres and various intramolecular interactions involving the substituent groups on the sugar ring make the formation of spirocycles on such a skeleton even more challenging in controlling selectivities. Thus, the outcomes of a particular spirocyclization may well depend on the sugar moieties' stereochemical and conformational peculiarities resulting in different products or product ratios when the sugar is changed.

This book as a whole as well as its individual chapters intends to give an insight into the world of carbohydrate-spiro-heterocycles from various perspectives. In the introductory chapter, the cyclization methodologies to form a spiro-fused ring at the anomeric carbon of pyranoid sugars are categorized and a selection is presented by *Pommier* and *Vidal*, who also highlight some important biomedical applications of such compounds.

Specific methods of spiro ring formation are emphasized in the next chapters. *Pellegrini-Moïse* and *Richard* highlight 1,3-dipolar cycloadditions to form carbohydrate-derived spiro-isoxazolines and spiro-isoxazolidines and their transformations into other interesting compounds. *Martín* and *Suárez* have compiled a plethora of radical reactions to demonstrate their unique potential and versatility to achieve a wide range of spirocycles on both pyranoid and furanoid sugar units. The formation of spiroketals and related lactones based on unsaturated monosaccharide derivatives such as *endo*- and *exo*-glycals is surveyed by *Sridhar*. *Josse* and *Postel* summarize the uses of sugar-derived cyanohydrins and α-aminonitriles for the formation of spirocycles at ring positions of carbohydrates also involving biomedically outstanding derivatives.

Some important compound types are reviewed in the remaining chapters. The multifaceted chemistry of spirocyclic nucleosides is overviewed by *Soto*, *Rodríguez-Solla* and *Soengas* also pointing out their biological utility. *Yamamoto* presents the syntheses and uses of phthalane spiro-*C*-glycosidic compounds including papulacandins and tofogliflozin. Finally, a special and emerging type of glycomimetics, the spiro-iminosugars, is surveyed by *Hazelard*, *Hensienne*, *Behr* and *Compain*.

I greatly appreciate the meticulous work of the contributors, and I am also indebted to those colleagues from all over the world who voluntarily reviewed the manuscripts, thereby providing invaluable help in the editorial work.

Debrecen, Hungary László Somsák
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