MSc Beata Łukasik

Centre of Molecular and Macromolecular Studies Polish Academy of Sciences in Lodz

Sienkiewicza 112 90-363 Lodz

„Synthesis of new chiral building blocks and their application in the synthesis of cyclopentanoids”

Prostanoids are part of a family of naturally occurring biologically active lipid mediators derived from the oxidation of polyunsaturated twenty-carbon fatty acids. These labile, highly potent molecules, regulate a broad range of physiological processes in animals and humans, including blood circulation, the contraction and relaxation of smooth muscle tissue, inflammatory and pain mediation, digestion and reproduction. However, the utility of natural prostaglandins in medicine is limited because of their low chemical stability, fast metabolism and side effects. Synthetic analogs of prostaglandins are selective and simultaneously the range of their therapeutic applications is very wide (anti-inflammatory activity, antiviral, antitumor, antiulcer). The complex structures of prostaglandins together with their broad spectrum of biological activity have stimulated the development of new methods for their synthesis for over 40 years. Currently, the dominant strategies in the synthesis of this type of prostaglandins are based mainly on the use of chiral building blocks such as the Corey’s lactone, optically active 4-silyloxy- or 4-alkoxy substituted cyclopenten-2-enone and acetonide 4,5-dihydroxycyclopent-2-enone. Current synthetic methods of these cyclopentane and cyclopentene derivatives often involve enantiomer separation or the use of reagents which are expensive and/or difficult to prepare. These limitations show that there is still a need for the development and evaluation of new versatile chiral building blocks and new synthetic methods.

The subject of my PhD thesis was the development of efficient methods of synthesis of new optically active building blocks and demonstration of their utility in the synthesis of bioactive compounds.

In the first part I reported the total synthesis of enantiomerically pure stereoisomers of rosaprostol, an antiulcer drug. At the end of the last century, racemic rosaprostol became an interesting target of biological and synthetic studies. As a result, various synthetic approaches to this compound have been reported, including two of them developed by our group. Recently, inspired by the trend in pharmaceutical sciences and industry to replace racemic by enantiomeric drugs (so-called “chiral shift”) and as part of our research program on the

synthesis and study of the stereostructure–bioactivity relationship in biologically active compounds I synthesized enantiomerically pure stereoisomers of rosaprostol starting from camphor protected 3-[(dimethoxyphosphoryl)-methyl]-4,5-dihydroxy-cyclopent-2-enones-a building block prepared earlier in our laboratory. The key steps involved a fully diastereoselective hydrogenation of the endocyclic carbon-carbon double bond in the cyclopentenone ring controlled by a chiral diol moiety and the conversion of obtained compound into a new cyclopentenone with a transposed olefinic bond.

The integral part of my work was the synthesis of both enantiomers of 4,5-dihydroxy-3-(formyl)cyclopent-2-enone acetonide. The synthesis of both enantiomers of acetonide was accomplished in five steps starting from *meso*-tartaric acid. The key steps involved cyclization of dimethyl 2,2-dimethyl-1,3-dioxo-4,5-dicarboxylate upon treatment with lithium salt of dimethyl methanephosphonate, followed by the Horner-Wadsworth-Emmons reaction of the phosphonate formed with D-(*R*)-glyceraldehyde acetonide and fully regioselective ozonolysis of the exocyclic carbon-carbon double bond of separated diastereoisomeric dienones. The determination of their absolute configuration by two methods: by theoretical calculations of their chiroptical properties (optical rotation and electronic circular dichroism) and by X-ray structure determination of phenylhydrazone obtained from the dextrorotatory enantiomer of this compound. The utility of 4,5-dihydroxy-3-(formyl)cyclopent-2-enone acetonide was demonstrated in the synthesis of both enantiomers of Neplanocin A.

In continuation of my research program aimed at the invention and elaboration of general methods for the synthesis of bioactive cyclopentenones and cyclopentanones using phosphorus reagents was development of method for the synthesis of 4,5-dihydroxy-2-(dimethoxyphosphoryl)cyclopent-2-enone acetonide- a new chiral building block in the synthesis of cross-conjugated cyclopentanoids. My approach to the synthesis of this compound involved ring closure in a rhodium-catalyzed carbenoid cyclization of the corresponding α-diazo-β-ketophosphonate. The lactone, which was easily available via a two-step reaction sequence has been converted into the appropriate Weinreb amide upon treatment with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of trimethylaluminium followed by the protection of the hydroxyl group in the hydroxyamide formed. In the next step, its reaction with anion generated from dimethyl methanephosphonate furnished β-ketophosphonate, which has been subsequently converted into α-diazo-β-ketophosphonate in the diazotransfer reaction with tosyl azide. Finally, rhodium-catalyzed carbenoid cyclization of the diazo-compound followed by thermal elimination of *tert*-butyldimethylsilanol from cyclopentane derivative formed gave the final product.