**Description for the general public**

Prostaglandins (PGs) 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, renal physiology, the cytoprotection of gastric mucosa, digestion and reproduction. They are also involved in many pathophysiological processes associated with inflammation and cancer. On the other hand, various members of the cyclopentenone PG family (cyPG), which are characterized by the presence of the α,β-unsaturated carbonyl moiety, exhibit anti-neoplastic, neoroprotective, anti-inflammatory and antiviral activities. 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 prostaglandins and their analogues are prepared by three main basic strategies. In the first one, the core cyclopentane bearing appropriate substituents is used as a precursor for further functionalization of α- and ω-chains. In the second strategy (a two-component coupling), a five- membered cyclic structure encompassing one of the two side chains is first synthesized and the second chain (either the α or the ω-chain) is introduced at a later stage. The third strategy (three-component coupling initiated and developed in Noyori's group), a one-pot procedure, involves a 1,4-addition of the ω-chain to the appropriate cyclopentenone, followed by *in situ* trapping with the required α-chain component as an electrophile. All these strategies are based mainly on such chiral substrates like Corey's lactone and its derivatives, 4-silyloxy- or 4-alkoxy derivatives of cyclopent-2-enone and 4,5-dihydroxycyclopent-2-enone acetonide. The syntheses of these cyclopentane and cyclopentene derivatives are often quite lengthy and based on the reagents which are expensive and/or hardly available.

As a result of our work carried out under the research program, focused on inventing and development of general methods for the synthesis of biologically active cyclopentanones and cyclopentenones using the heteroorganic reagents (phosphorus, sulfur), the diastereoisomers of camphor protected 3-[(dimethoxyphosphoryl)methyl]-4,5-dihydroxycyclopent-2-enone have been obtained. These chiral cyclopentenone building blocks are available in a two-step reaction sequence, which involves complete desymmetrization of *meso*-tartaric acid during the acid catalyzed reaction with (+)-camphor and methyl orthoformate and the transformation of the camphor protected dimethyl tartrate formed to a separable mixture of the diastereoisomeric acetals upon treatment with an α-phosphonate carbanion. The utility of these building blocks was demonstrated by the total synthesis of a series of optically active cross-conjugated cyclopentenones showing antitumor and neuroprotective effect and rosaprostol – a drug used to treat stomach ulcers. However the main disadvantage of application of these acetals as chiral building blocks is the difficulty in obtaining them in a diastereoisomerically pure form. Separation of these diastereoisomers is tedious and needs several times purification by column chromatography and crystallization. The use of these compounds involves some synthetic limitations resulting from the steric hindrance of the *cis*-diol moiety protecting group. To gain further flexibility in functionalization of the cyclopentenone ring and to overcome some limitations in the use of the diastereoisomers of camphor protected 3-[(dimethoxyphosphoryl)methyl]-4,5-dihydroxycyclopent-2-enone we decided to synthesize new chiral cyclopentenone building block i.e. 4,5-dihydroxy-2-(dimethoxyphosphoryl)cyclopent-2-enone acetonide **1**,whose synthesis based on the natural, cheap, chiral sugar reagent, will be elaborated as part of this project. The proposed synthesis of the mentioned compound may be carried on a few alternative pathways. The key steps of these approaches will involve formation of the five-membered ring by rhodium-catalyzed carbenoid cyclization of the corresponding α-diazo-β-ketophosphonate or by intramolecular alkylation of the appropriate derivative of β-ketophosphonate. Accomplishment of this research task will result in a broadening of the currently accessible chiral reagents pool and increase flexibility and freedom in planning the synthesis of prostanoids. The utility and applicability of this new block in the synthesis of prostaglandin analogues will be demonstrated by a new and short, three-component synthesis of NEPP11, whose promising anticancer activity has been recently discovered in our laboratory.

Our strategy assumes a three-component approach involving the coupling of the two side chains with starting reagent **1**. The ω-chain will be introduced by Michael addition of the corresponding lithium organocopper reagent. The presence of a phosphoryl moiety in our building block will allow us to install an appropriate α-chain by Horner olefination reaction. The combination of these two reactions will allow us to synthesize the corresponding 2,3-disubstituted cyclopentenone derivatives in a sequence of two reaction or as one-pot three-component coupling reaction (Michael addition/Horner olefination reaction). Transformation of the acetal group will be carried out by the reductive deacetalization, followed by dehydrogenation to the NEPP11. The new, step economy synthesis is modular and can be applied for the quick preparation of a library of cross-conjugated cyclopentenones which, in turn, will enable extensive studies on the structure-activity relationship in this class of compounds.