ABSTRAKT:

Within the framework of this thesis, a large series of 5-(acyloxymethyl)-3-aryl-5,6-dihydro-2*H*-pyran-2-ones was prepared and their cytostatic activity investigated. The key steps in the preparation of the compounds were alkylation of esters of substituted phenylacetic acids with 2-iodomethyl-5,5-dimethyl-1,3-dioxane, followed by cyclization to furnish a saturated lactone into which a double bond was introduced in the next step. Some of the target compounds displayed interesting cytostatic activity (IC_{50} < 10 μmol/L) against a panel of standard cell lines including both leukemic cells and those derived from solid tumours. The activity against colorectal carcinoma HT29 cell line, which is otherwise resistant against the standard combination of cytostatic agents used in the treatment of these tumours is especially remarkable. In the next part, the development of the synthesis of the 5-alkylidene analogues of these compounds, which are also analogous to bioactive natural products, such as the gelastatins and CR377, is described. Successful strategy is based on the use of 2-iodo allylic alcohols as the starting materials, which are converted into the target 3-substituted-5-alkylidene pentenolides via an array of Pd-catalyzed reactions, including Sonogashira coupling with methyl propiolate, stereoselective hydrostannation, cyclization into 5-alkylidene-2-tributylstannyl-5,6-dihydro-2*H*-pyran-2-ones and the Stille coupling of these compounds with various alkenyl-, aryl- and heteroaryl iodides. The target compounds exhibited selective cytostatic activity (IC_{50} < 10 μmol/L) against leukemic cells CCRF-CEM and human cervix carcinoma HeLa S3 cells.