USE OF RING-CLOSING METATHESIS TO FORM *TRANS*-FUSED MACROCYCLIC BIS(HYDANTOINS): SYNTHESIS AND THEORY

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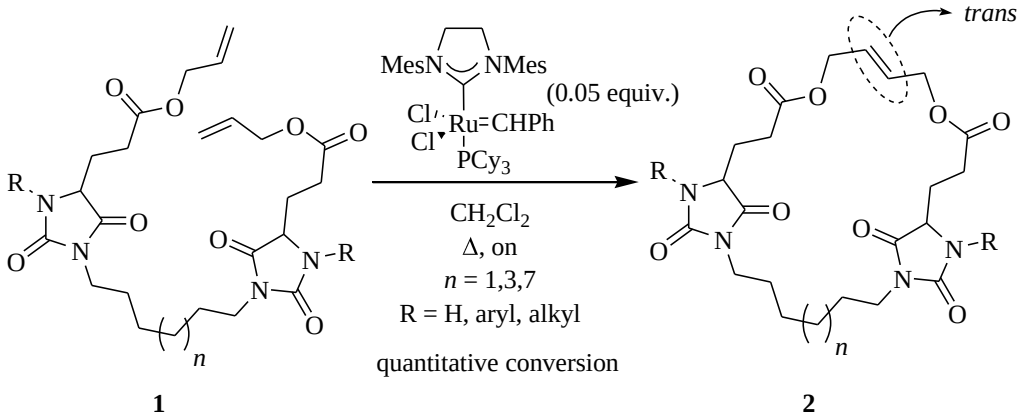

The hydantoin, or imidazolidine-2,4-dione, nucleus is a privileged structure with a broad range of biological activities and applications in human medicine and agriculture. Several *N*(3),*N'*(3)-polymethylenebis(hydantoins) have been evaluated as hexamethylenebis(acetamide) (HMBA) analogues. HMBA is a compound that induces cancer cells to differentiate to a less malignant phenotype, which provides an attractive area for the development of new anticancer drugs as it is not primarily based on cytotoxity.

An efficient and straightforward approach towards *N*(3),*N'*(3)-polymethylenebis(hydantoins) was developed using the pyroglutamate hydantoin rearrangement.[1] In this reaction an *N*-carbamoylated pyroglutamate undergoes a double ring transformation with formation of a hydantoin. These compounds **1** were subsequently ring-closed using second-generation Grubbs' catalyst to form 24- to 30-membered heterocycles **2**. This RCM could be performed after alkylation of the hydantoin at the 3-position or on the free lactam, meaning that the amide did not inhibit the catalyst.

It was proven that only the *trans*-isomers were formed using HSQC experiments with inverse detection.[2] Usually RCM results in a mixture of *trans*- and *cis*-isomers, but in this case only *trans*-isomers were formed. As the allylic positions are not densely functionalized, this was thought to be caused by the ability of the second-generation Grubbs' catalyst to isomerize the initial product under the reaction conditions, thereby progressively enriching the mixture in the thermodynamically favoured *trans*-isomer.

In order to obtain more insight into the selectivity pattern, theoretical calculations were performed on this system. Techniques able to scan for various conformers of the heterocycles were applied. Due to the large amount of atoms involved a molecular dynamics approach at elevated temperature was chosen. Theoretical and experimental findings are confronted with each other.

[1] a) Dieltiens, N.; Claeys, D.D.; Zhdankin, V.V.; Nemykin, V.N.; Allaert, B.; Verpoort, F.; Stevens, C.V. *Eur. J.Org.Chem.* **2006**, 2649; b) Dieltiens, N.; Claeys, D.D.; Stevens, C.V. *J. Org. Chem.* **2006**, *71*, 3863.
[2] Claeys, D.D.; Dieltiens, N.; Stevens, C.V. *Eur. J.Org.Chem.* **2008**, 171.
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