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Solvent Effect in Diastereoselective Intramolecular Diels-Alder Reactions

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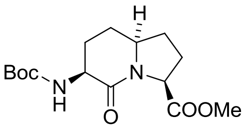
ABSTRACT

In the process of improving the synthesis of a novel class of chiral drug scaffolds, first reported in 2010, we observed that the stereochemical outcome of the key chemical transformation appeared to be correlated to the solvophobicity of the reaction medium. Our mechanistic investigations by NMR monitoring of the reaction confirmed the proposed acylation/intermolecular cycloaddition sequence. The computational studies using DFT methods next predicted *exo/endo* stereoselectivity (4.3:1 in $CHCl_3$, 1.6:1 in H_2O) in agreement with the experimental results (3.3:1 in $CHCl_3$, 1:1 in H_2O). The observed stereoselectivity was related to the different level of asynchronicity of the diastereomeric transition states. This leads to different solvent stabilization of the cycloaddition transition state of one diastereomer more than the other.

1. Introduction

Scaffold hopping, the replacement of a bioactive molecule's core by a structure of similar geometry and/or properties, is an efficient strategy for lead optimization in medicinal chemistry.[1] This strategy is obviously limited by the number and diversity of available scaffolds. The design and synthesis of molecular scaffolds[2] and peptidomimetics[3] has been an active field over the last decades and led to the development of novel structures with novel biological activity profiles.[4-6]

More specifically, bicyclic scaffolds are of particular interest as they allow to rigidify the compound to afford a more selective binding to the target. For instance, the Lubell and Hruby groups have reported **1** and **2** as dipeptide mimetics[7,8] while Lesma and co-workers reported **3**,[9] and we reported **4**. These and other bicyclic scaffolds have successfully been incorporated into a number of active molecules such as prolyl oligopeptidase inhibitors (**5**),[10] Smac mimetics (**6**),[11] and prostaglandin F2α receptor antagonists (**7**)[12] (Figure 1). In 2010, we reported our preliminary results leading to the preparation of a rigid Ala-Val dipeptide mimic **4** using what we proposed to be a tandem amide formation/intramolecular Diels-Alder reaction (IMDA).[13] Throughout the course of the optimization of its synthesis, a solvent effect was observed. Although this phenomenon was previously reported,[14,15] no definite explanation as to why it arises has been reported. In the meantime, the stereoselectivity of the IMDA reaction of systems similar to ours has been studied computationally,[16] but again, the solvent effect was not part of the study. We report herein experimental and computational details on the solvent effect of the tandem acylation/IMDA.



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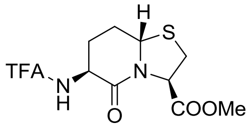

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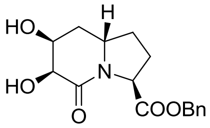

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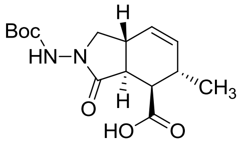

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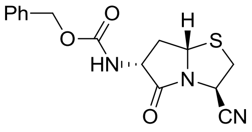

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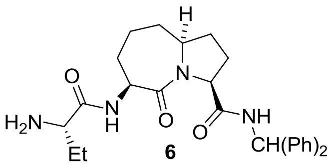

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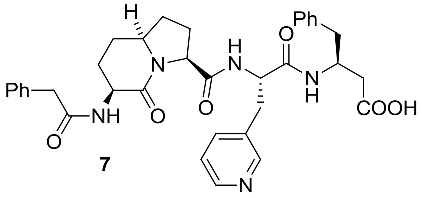

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