A COMBINED EXPERIMENTAL AND THEORETICAL INVESTIGATION OF THE STEREOSELECTIVITY IN THE SYNTHESIS OF AZAHETEROCYCLIC PHOSPHONATES

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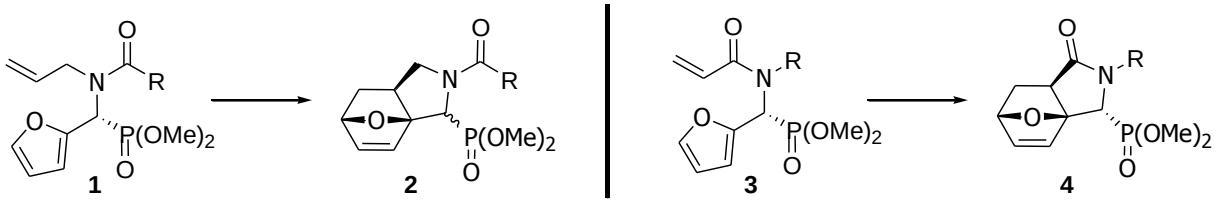
Since the discovery of the biological activity of aminoalkylphosphonates, e.g. as enzyme inhibitors, many researchers have focused their attention on conformationally constrained azaheterocyclic phosphonates. Stereocontrol is of major interest during the synthesis of these products. Therefore our research group has developed a new route towards tricyclic phosphono pyrrolidines using an intramolecular Diels-Alder reaction with furans (IMDAF), as given in the scheme. We wanted to reveal the stereoselectivity of these IMDAF-reactions experimentally and computationally. This would enable us to direct the reaction to one isomer and gives an idea of the influence of the position of the carbonyl group on the stereoselectivity.



Difference NOE, 2-dimensional NMR-data and an X-ray analysis of adducts **2** revealed that the cycloaddition occurred *exo*, but the phosphonate substituent on the tether had an *exo*- or *endo*-orientation. A thermodynamic preference for the minor isomer with an *endo*-substituent was observed experimentally. DFT calculations confirmed this and linked it with a larger steric hindrance of the bulky tether substituents in the *exo*-isomer. The same computational methods predicted that the single isomer formed starting from aminophosphonate **3** was the *endo*-isomer. A relation with the J_{HP} coupling constant was found. Furthermore, a computational study at the post Hartree-Fock level could reproduce the kinetic preference for the *exo*-isomer of adduct **2**, while the presence of the carbonyl function in the tether results in the *endo*-isomer only.

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