



Transannular cyclizations of medium-ring amido alkenes: A computational study

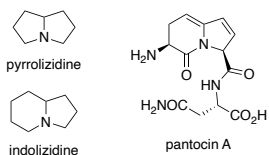
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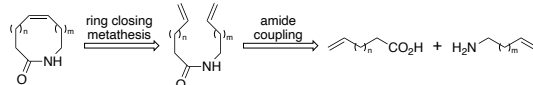
Heterocyclic synthesis & transannular cyclization

Fused heterocycles, such as pyrrolizidine and indolizidines are important intermediates for the synthesis of biologically active natural products, such as pantocin A. While a number of methods exists for their synthesis, transannular cyclization remains an underexplored strategy for transforming macrocyclic molecules into these fused bicyclic structures.

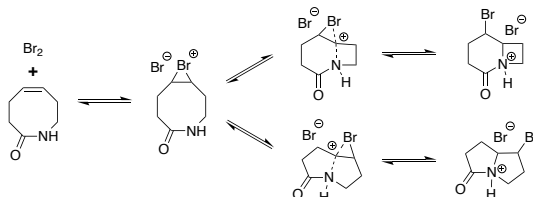


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Retrosynthetic rationale for amido alkene precursor



Potential cyclization pathways for bromonium ion



In order to better understand the factors governing regio- and stereoselectivity of this class of transannular cyclizations, a computational study was undertaken on a number of bromonium ions derived from medium ring amido alkenes.

General outline of the computational workflow

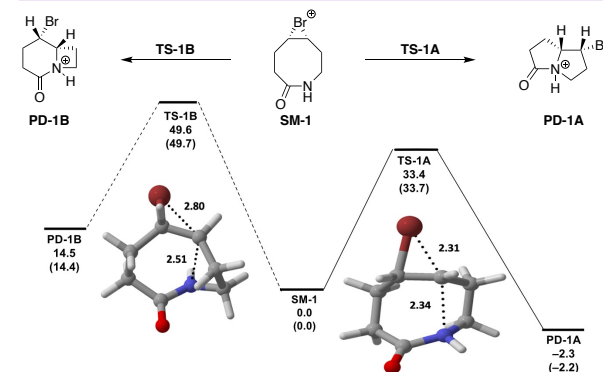
Spartan'18



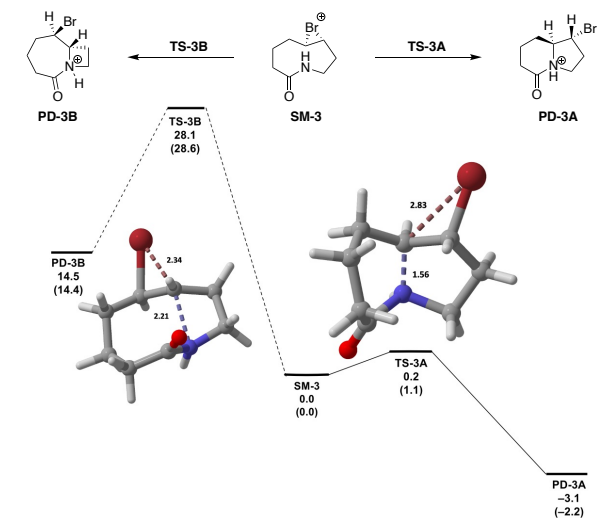
Gaussian16

Starting Material	Transition States	Products
<ul style="list-style-type: none">Run optimization and frequency calculationsDetermine lowest energy geometry & extract data	<ul style="list-style-type: none">Remove bond constraintsRun opt. & freq. calculationsDetermine lowest energy geometry & extract data	<ul style="list-style-type: none">Run optimization and frequency calculationsDetermine lowest energy geometry and extract data

Cyclization of *cis*-alkene derived bromonium ion SM-1



Cyclization of *trans*-alkene derived bromonium ion SM-3



Free energy diagrams from calculations carried out in Gaussian16 using B3LYP/6-31+G(d) as convergent, gas-phase calculations performed at 273 K. Free energies are given in kcal mol⁻¹. Interatomic distances given in Å.

Conclusions and Future Works

The thermodynamically and kinetically favored product for the 8- and 9-membered ring amido bromonium cyclizations were PD-1A and PD-3A. The higher energy of TS-1B and TS-3B are likely as a result of the strain associated with azetidine ring formation. Future efforts will be focused computationally modeling additional cyclizations, as well as investigating the synthesis of these bicyclic structures.

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