LATE-STAGE OLEFINATION IN PBD NATURAL PRODUCT TOTAL SYNTHESES

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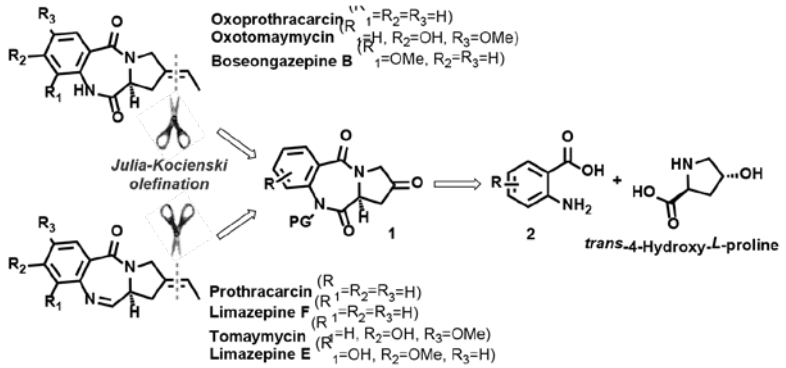
Pyrrolo[1,4]benzodiazepines (PBD) are a broad family of natural products possessing considerable anticancer activity owing to their ability to covalently bind to minor grove of DNA.[1] Several PBD members possess an *E*- configured C2 alkylidene group in the pyrrolidine ring, the configuration of which plays a crucial role in the cytotoxic properties of these compounds.[2] Although several total syntheses of these natural products have been published, a stereoselective introduction of the alkylidene substituent still possesses a considerable challenge. Within our preliminary studies,[3] we have shown that a late-stage olefination is a convenient approach to synthesize these natural products.

Herein we report our studies on the Julia – Kocienski olefination of PBD triones **1**, including the development of novel reagents, optimization of reaction conditions, and determining the olefination stereochemistry determining factors. The necessary triones **1** can be easily accessed starting from readily available *trans*-4-hydroxy-L-proline and the corresponding anthranilic acids **2**.



Scheme 1. *Retrosynthetic analysis of PBD natural products.*

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References:

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AZIDOAZOMETHINE-TETRAZOLE TAUTOMERISM IN PYRIDOPYRIMIDINES

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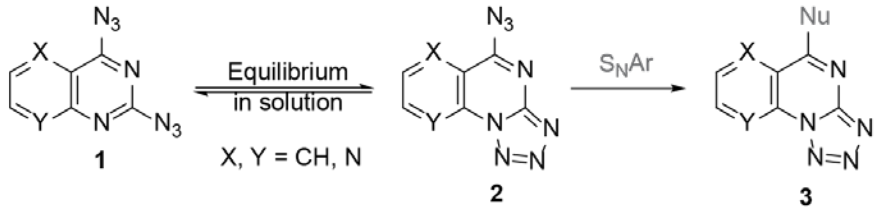
Heterocycles with azido-azomethine structural entity undergo dynamic azide tetrazole equilibrium in solution phase. The equilibrium can be shifted towards one or other tautomer by altering ambient conditions such as solvent polarity and temperature. Thus, azide tetrazole ring-chain tautomerism is known to influence S_NAr reactivity and regioselectivity.

We have synthesized a new class of tetrazolopyridopyrimidines **3** and characterized azidoazomethine-tetrazole tautomerism thereof. FT-IR and X ray analysis of **3** reveals tetrazole to be the major tautomeric form present in the solid state. Thermodynamic heats of tautomerization in solutions were calculated using variable temperature NMR and DFT.



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