Synthesis of Complex Polycyclic Scaffolds Incorporating α-Amino Esters

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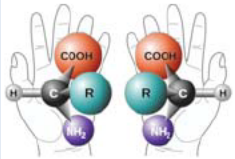
Abstract

In order to keep up with the high demand for biologically active molecules, chemists devised several synthetic strategies to access novel chemical spaces. The two main strategies to construct new scaffolds are to revisit underexploited or forgotten reactions or to devise new transformations. We are exploring a unique and underexploited reaction, the Himbert–Henn cycloaddition, to produce complex molecular scaffolds in a single step (strategy 1).[1] In a second novel approach, we are modifying the Hantzsch 4-component reaction (4CR) by incorporating an α-amino ester residue to construct new molecules (strategy 2).[2] Both of these reactions have great potential to synthesize novel and chiral molecules from proteinogenic α-amino esters. These unprecedented and complex polycyclic molecules have potential application in medicinal chemistry and natural product synthesis. 4-aza-podophyllotoxins obtained by the Hantzsch-4CR have been proven to be potent as anti-leukemia, anti-colon cancer, and vascular disrupting agents (with nanomolar activity).

Introduction

Objective: Building chiral complex polycyclic scaffolds incorporating α-amino esters that are applicable to a wide variety of substrates in an efficient manner.

Enantiomers



Chiral molecules possess one or more stereocenters which are extremely important in all recognition and activation processes of biological machinery; α-amino acids, glycosides, and nucleotides are the main types of chiral building blocks used by nature to create chiral architectures.

Strategy 1

- Himbert–Henn cycloaddition is a modification of the Diels–Alder reaction that specifically enables the dearomatization of arenes.[3] No chiral version of this reaction exists. We intend to utilize this underexplored reaction to create chiral scaffolds containing an α-amino ester residue.

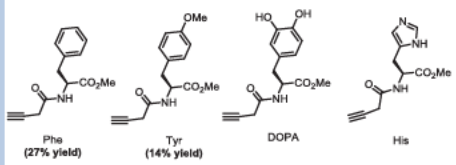
Strategy 2

- 4-aza-podophyllotoxins were previously prepared using a 3-component reaction (3CR) developed by Husson. Due to the important biological activity of these compounds, we proposed a second generation synthesis involving a novel 4CR to develop an asymmetric synthesis of 4-aza-podophyllotoxin derivatives.[4]

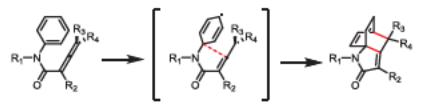
Strategy 1: Himbert–Henn Cycloaddition

a. Synthesis of the chrial precursors

b. Chrial precursors with various substituents ("R" groups)



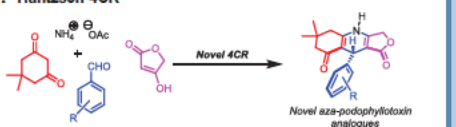
c. Proposed mechanism for the Himbert–Henn cycloaddition



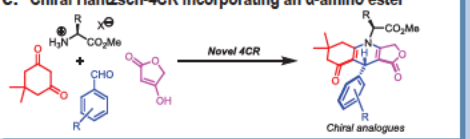
Strategy 2: Multicomponent Reaction

a. Husson-3CR

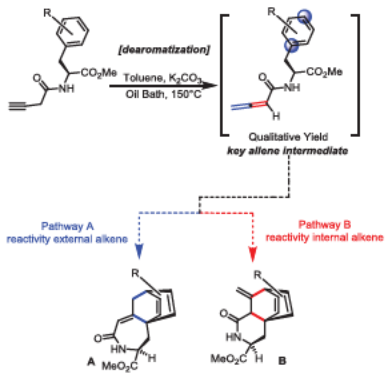
b. Hantzsch-4CR



c. Chiral Hantzsch-4CR incorporating an α-amino ester

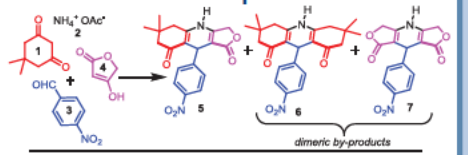


Himbert–Henn Cycloaddition Unreactive Allene Intermediate



- Himbert–Henn cycloaddition: alkyne was smoothly converted to allene intermediate, but no further cyclization was observed yet.
- Several allenes containing α-amino esters will be further tested to attempt the synthesis of both ring systems (A & B) in order to obtain new molecules with potentially important biological activity.

Hantzsch Multicomponent Reaction



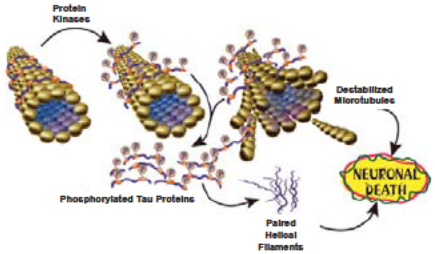
Entry	Additives	Solvent, Time, Temp	% Conv	% Yield (5)
1	–[c]	2 h, RT	3 (8%); 5 (39%); 6 (25%); 7 (27%)	27%
2	CAN (5 mol%)	EtOH 25 min, RT	3 (11%); 5 (54%); 6 (0%); 7 (18%)	40%
3	I_2 (30 mol%)	EtOH 3 h, RT	3 (8%); 5 (26%); 6 (15%); 7 (23%)	11%
4	$Yb(OTf)_3$ (10 mol%)	ACN 4 h, RT	3 (4%); 5 (24%); 6 (0%); 7 (12%)	14%
5	$Sc(OTf)_3$ (10 mol%)	ACN 4 h, RT	3 (6%); 5 (38%); 6 (25%); 7 (15%)	33%
6	montmorillonite (750 mg)	EtOH 18 h, RT	3 (5%); 5 (51%); 6 (20%); 7 (16%)	50%
7	$Ru(BPy)_3Cl_2$ (1 mol%)	ACN 3 h, RT	3 (0%); 5 (34%); 6 (14%); 7 (53%)	n.d.
8	–	EtOH 18 h, RT	3 (0%); 5 (52%); 6 (17%); 7 (31%)	40%

- 4-multicomponent reaction: desired product 5 was obtained in 50% yield and two dimeric by-products were characterized for the first time (Table above).
- The best reaction conditions for the challenging Hantzsch-4CR were found using clay (entry 6).
- We are now working on α-amino ester incorporation for a diastereoselective-4CR to create chiral molecules with biological activity against Tau aggregation.

Discussion & Future Directions

- Although the Himbert–Henn cycloaddition reaction did not successfully undergo the cycloaddition yet, the allene intermediate was isolated. Photochemistry and other approaches can alter the reaction pathway to favor the desired cycloaddition reaction towards **A** and **B**.[5]
- The Hantzsch-4CR was successfully completed using an achiral model reaction. Currently, the incorporation of chiral α-amino esters into the axa-podophyllotoxin scaffolds is under investigation.
- The long term goal is to synthesize a library of chiral and novel aza-podophyllotoxin analogues which we believe could be selective and potent inhibitors of Tau aggregation.[6]
- Hyperphosphorylation of Tau leads to massive detachment, which in turn reduces the stability of microtubules in neurons. Neurodegenerative disorders such as Alzheimer's disease (AD) and other tauopathies are characterized by the accumulation of protein aggregates such as Tau.

Hyperphosphorylation of the Tau protein



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