

# Radical Cyclization via Samarium(ii) Iodide for the Synthesis of Rugulovasine A

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Central to the synthesis of Rugulovasine A is the formation of an Uhle's ketone derivative. This step was accomplished by Zhang and coworkers via a Reformatsky reaction in which *t*-BuLi facilitates a halogen replacement and the resulting intermediate undergoes cyclization via an attack on the carbonyl carbon of the carboxylic ester. The  $\pi$ -bond is then reformed and the methoxide is ejected, producing a ketone on the newly formed six member ring.

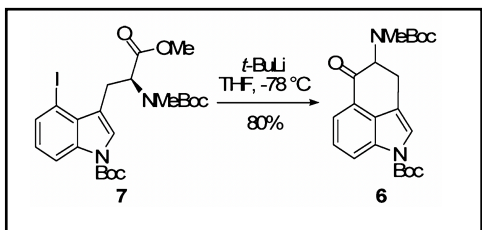


Fig 1: *t*-BuLi promoted radical cyclization.

Yu-An Zhang, Qiang Liu, Chao Wang, and Yanxing Jia  
Total Synthesis of Rugulovasine A  
Organic Letters 2013 15 (14), 3662-3665  
DOI: 10.1021/ol401541t

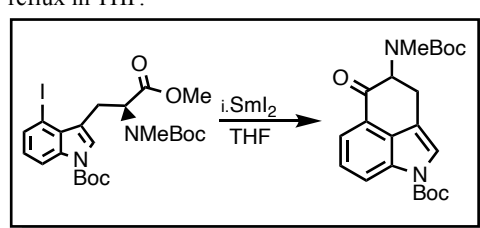


Fig 3: Proposed SmI<sub>2</sub> promoted radical cyclization

Yang S, Xi Y, Zhu R, Wang L, Chen J, Yang Z.  
Asymmetric total syntheses of ansamacrolactams  
(+)-Q-1047H-A-A and (+)-Q-1047H-R-A.  
Org Lett. 2013 Feb 15;15(4):812-5.  
doi: 10.1021/ol400038h. Epub 2013 Jan 31. PMID: 23368957.

This SmI<sub>2</sub> induced ring closure appears to be an excellent candidate for implementation into the Rugulovasine A synthesis due to the similarity of reaction conditions. Precursors in both syntheses contain protecting groups which are left undisturbed during the reaction due to the selectivity of SmI<sub>2</sub> for halogens. Additionally, both reactions utilize THF as the solvent. The most significant difference between the reactions is that the total synthesis uses a carboxylic ester precursor, while the replacement reaction was used on an aldehyde (which could result in the formation of the hemiacetal, and is thus why the choice of a simple acidic protonation was made).

Single Electron Transfer (SET) will also occur in the SmI<sub>2</sub> reaction, which causes radical generation. This phenomena should not result in significant mechanistic differences, as the same nucleophilic attack is expected to occur.

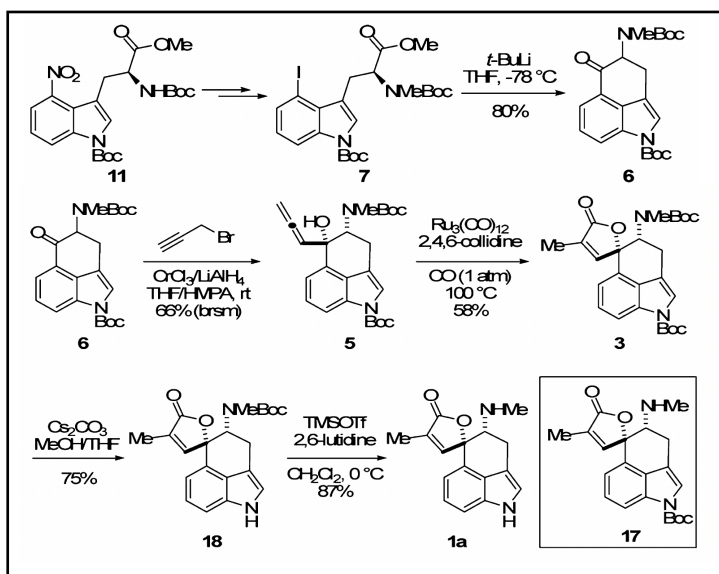


Fig 2: Total synthesis of Rugulovasine A (Compound 17)

While the use of SmI<sub>2</sub> is likely to produce a ketone, the potential exists for the formation of a secondary hemiacetal. In the case of this reaction, a simple protonation through the addition of acid (such as a mixture of H<sub>2</sub>O and H<sub>2</sub>SO<sub>4</sub>) would result in the ejection of the methoxide and formation of a ketone.

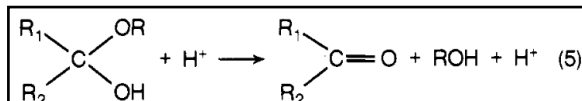


Fig 4: Secondary hemiacetal to ketone conversion in presence of acid.

E. H. Cordes and H. G. Bull  
Mechanism and catalysis for hydrolysis of acetals, ketals, and ortho esters  
Chemical Reviews 1974 74 (5), 581-603  
DOI: 10.1021/cr60291a004

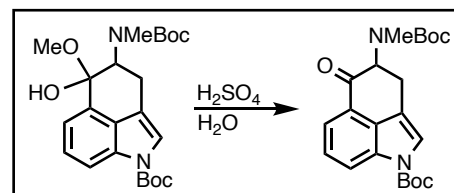


Fig 5: Proposed reduction of hemiacetal to Uhle's ketone derivative.

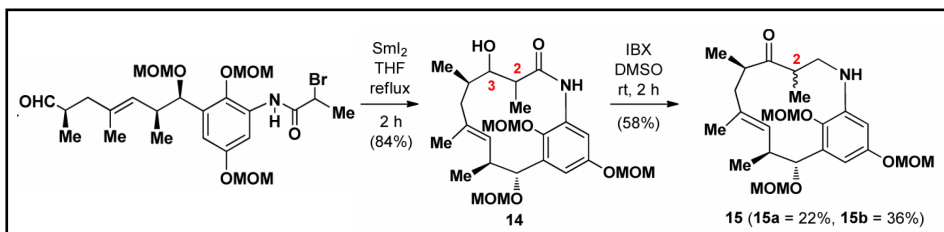


Fig 6: Zhang and coworkers' SmI<sub>2</sub> induced cyclization and subsequent conversion to a ketone.