

Literature Report V

Total Synthesis of Pentacyclic (-)-Ambiguine P Using Sequential Indole Functionalizations

Reporter: Xin-Wei Wang

Checker: Chang-Bin Yu

Date: 2019-3-4

Baran, P. S. *et al. Nature* **2007**, 446, 404.

Sarpong, R. *et al. J. Am. Chem. Soc.* **2019**, 141, 2233.

CV of Professor Sarpong, R.



Sarpong, R.

Background:

- ❑ **1991-1995** B.S. in Macalester College;
- ❑ **1995-2000** Ph.D. in Princeton University;
- ❑ **2000-2004** Postdoctoral Fellow, Caltech;
- ❑ **2004-Now** University of California, Berkeley.

Research:

Organic and Organometallic Chemistry: Total synthesis of biologically active and architecturally complex natural products as a platform for the development of new synthetic methods and strategies.

Contents

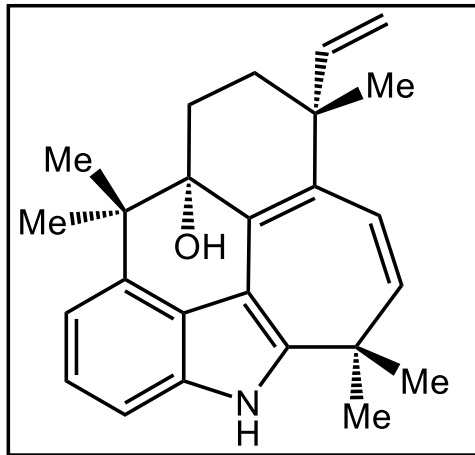
1 Introduction

2 Total Synthesis of (+)-Ambiguine H

3 Total Synthesis of (-)-Ambiguine P

4 Summary

Introduction



(-)-Ambiguine P

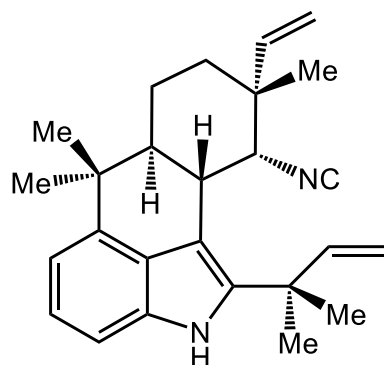


cyanobacterium

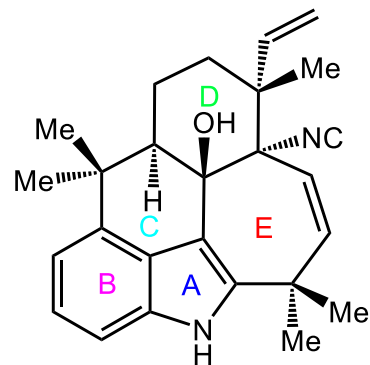
- It was identified from the cultured cyanobacterium *Fischerella ambigua* in 2010;
- It possessed fused pentacyclic;
- Ambiguine congeners exert a broad spectrum of biological activities, including antibacterial and antimycotic activity.

Orjala, J. *et al. Phytochemistry* **2010**, 71, 2116.

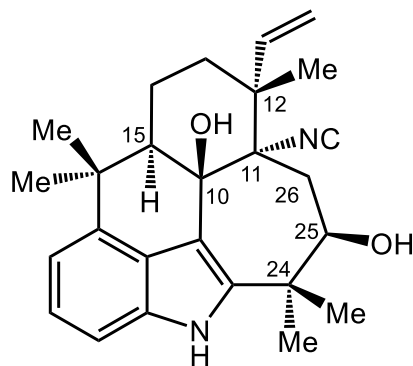
Introduction



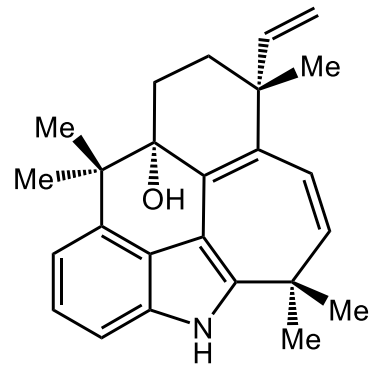
Ambiguine H (1)



Ambiguine L (2)



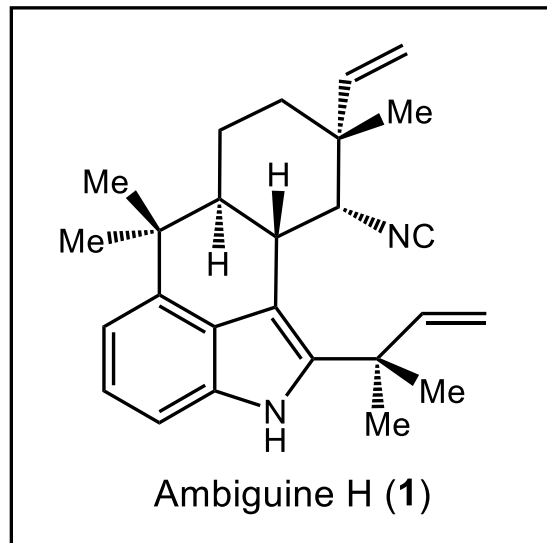
Ambiguine N (3)



Ambiguine P (4)

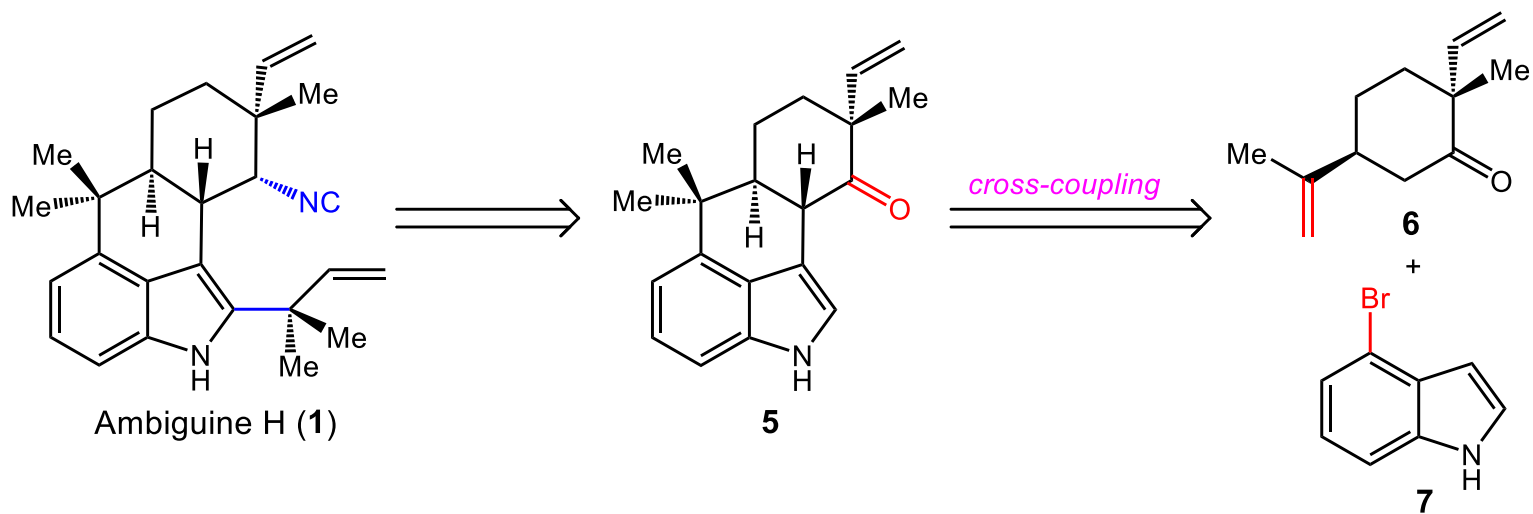
Baran, P. S. *et al. Nature* **2007**, 446, 404.
Sarpong, R. *et al. J. Am. Chem. Soc.* **2019**, 141, 2233.

Total Synthesis of (+)-Ambiguine H

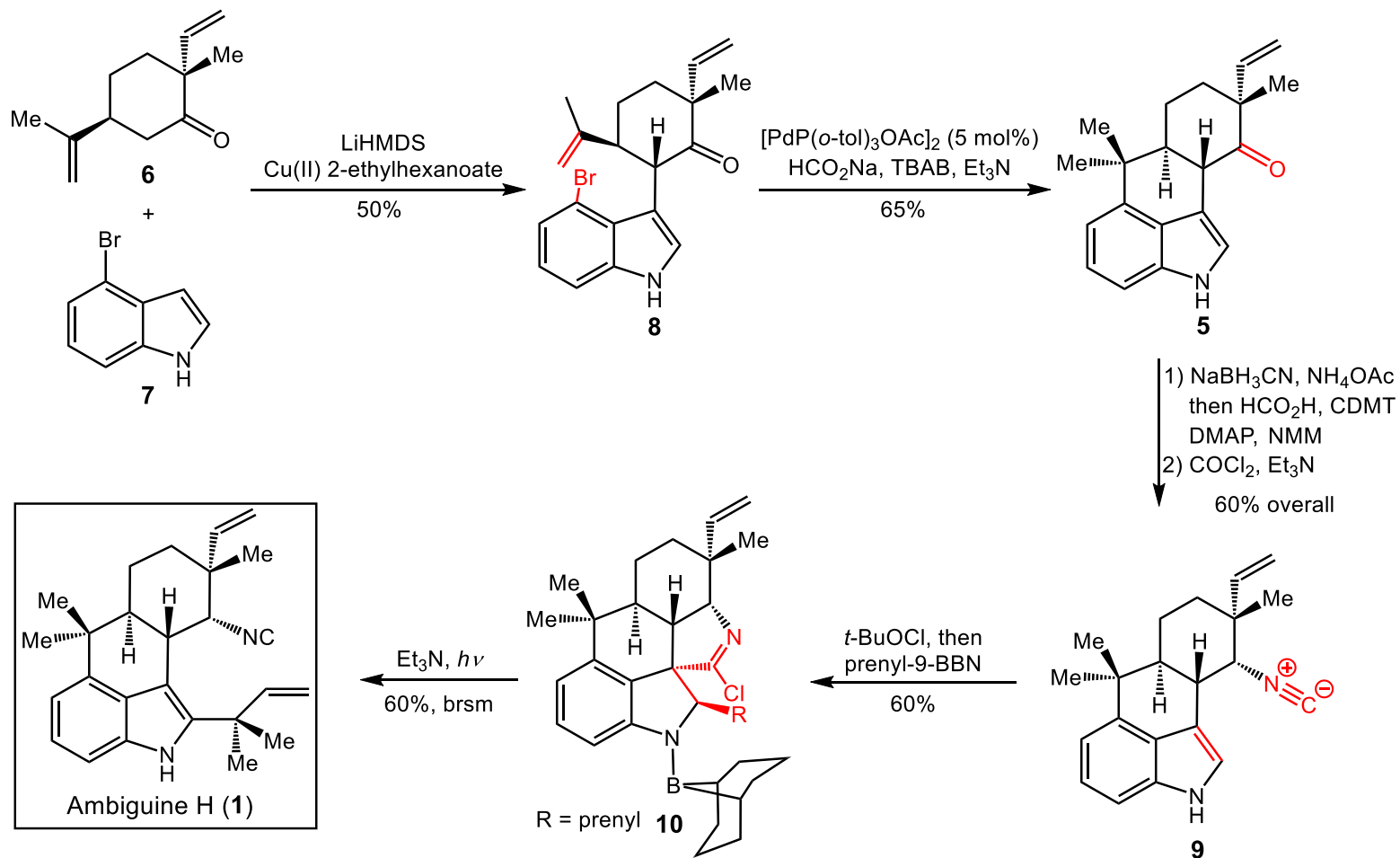


Baran, P. S. *et al. Nature* **2007**, 446, 404.

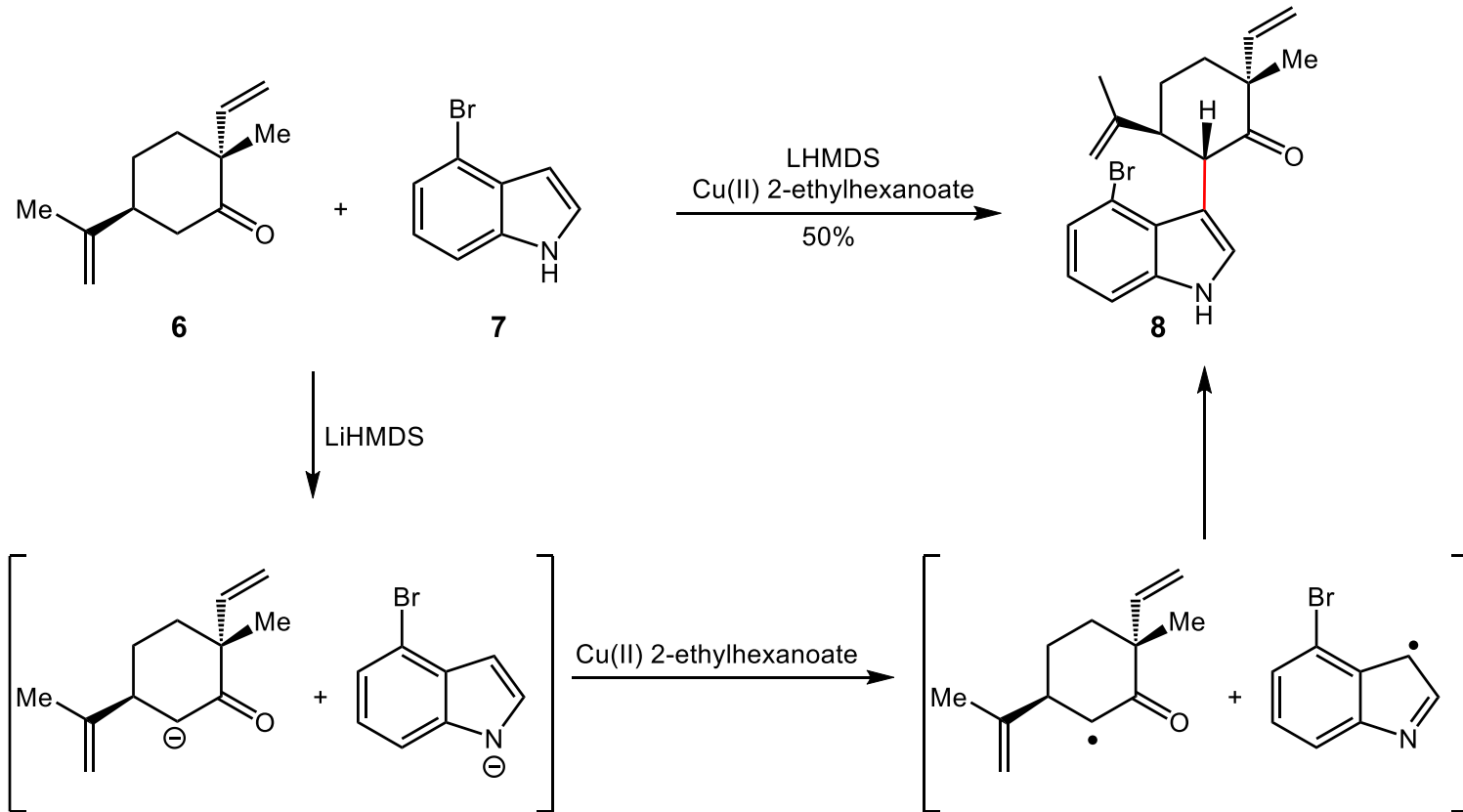
Retrosynthetic Analysis of Ambiguine H



Synthesis of Ambiguine H

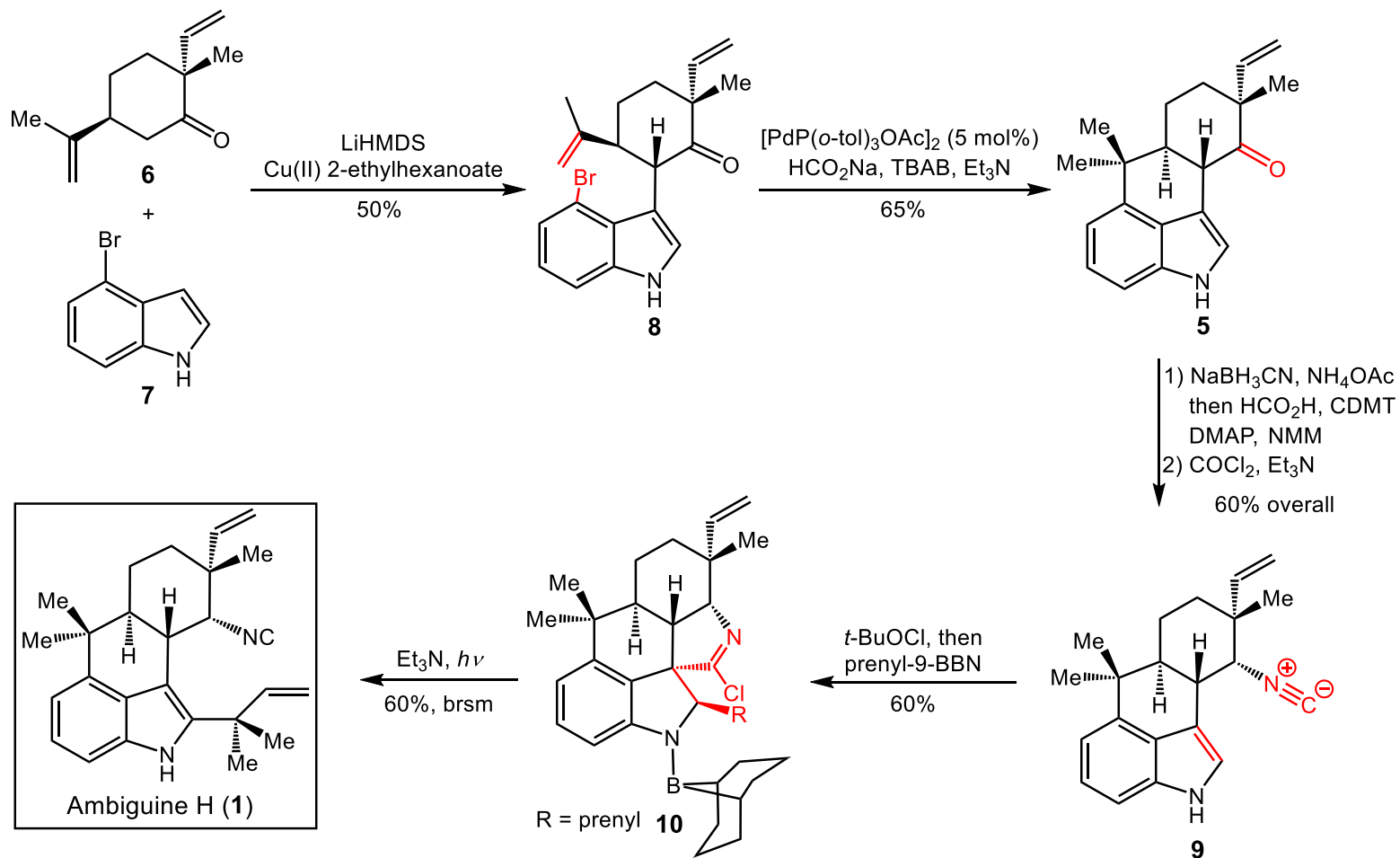


Coupling of Indoles with Carbonyl Compounds

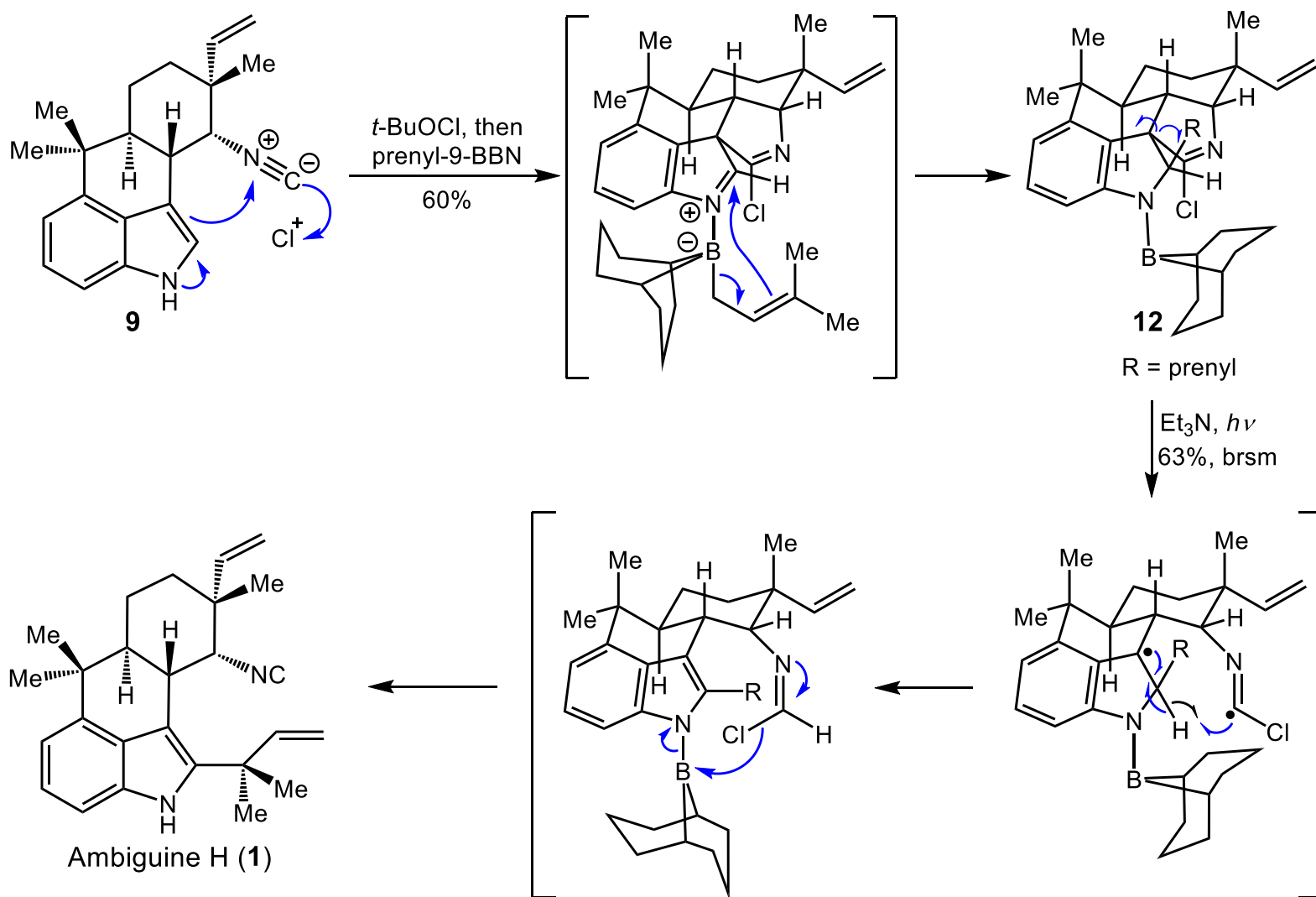


Baran, P. S. *et al. J. Am. Chem. Soc.* **2004**, 126, 7450.

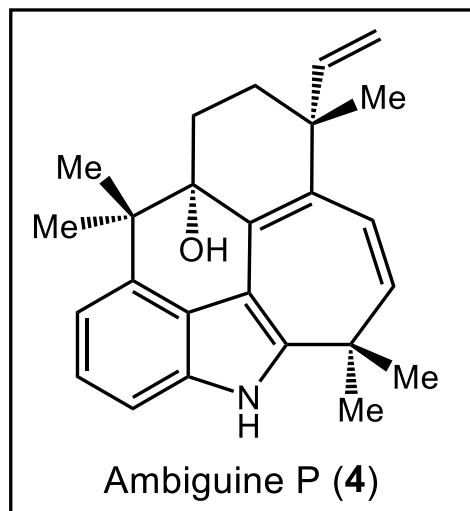
Synthesis of Ambiguine H



Possible Mechanism for the Tandem Sequence

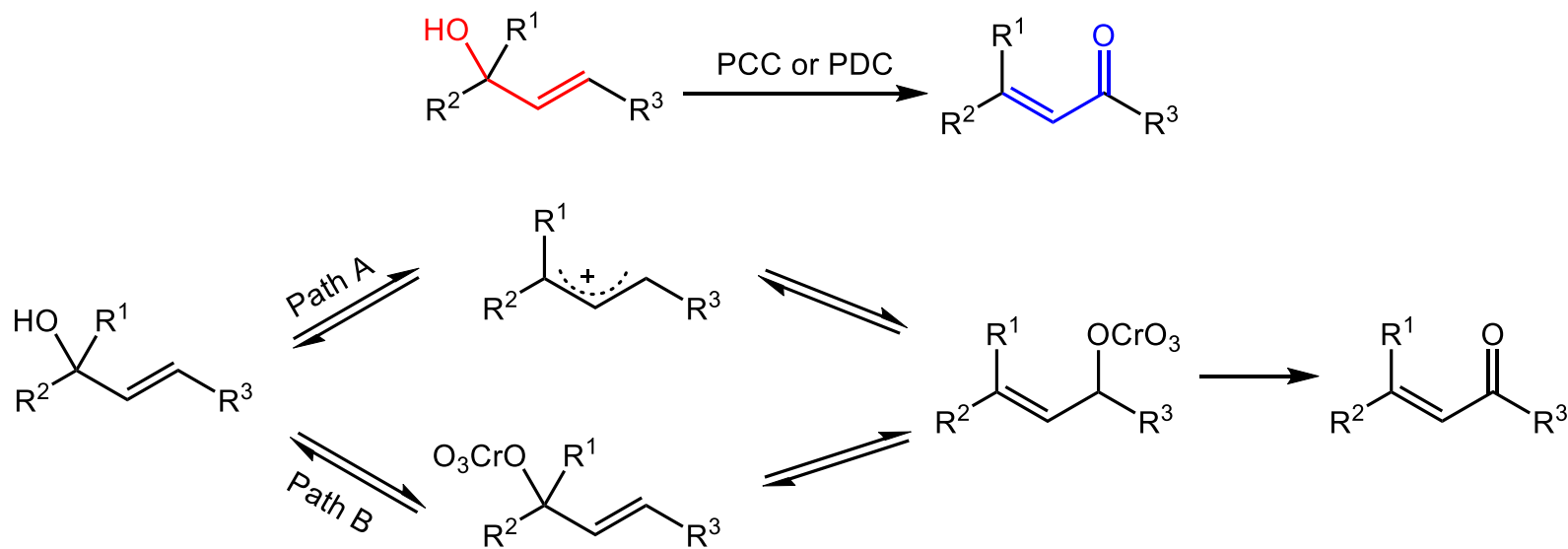


Total Synthesis of (-)-Ambiguine P



Sarpong, R. *et al.* *J. Am. Chem. Soc.* **2019**, *141*, 2233.

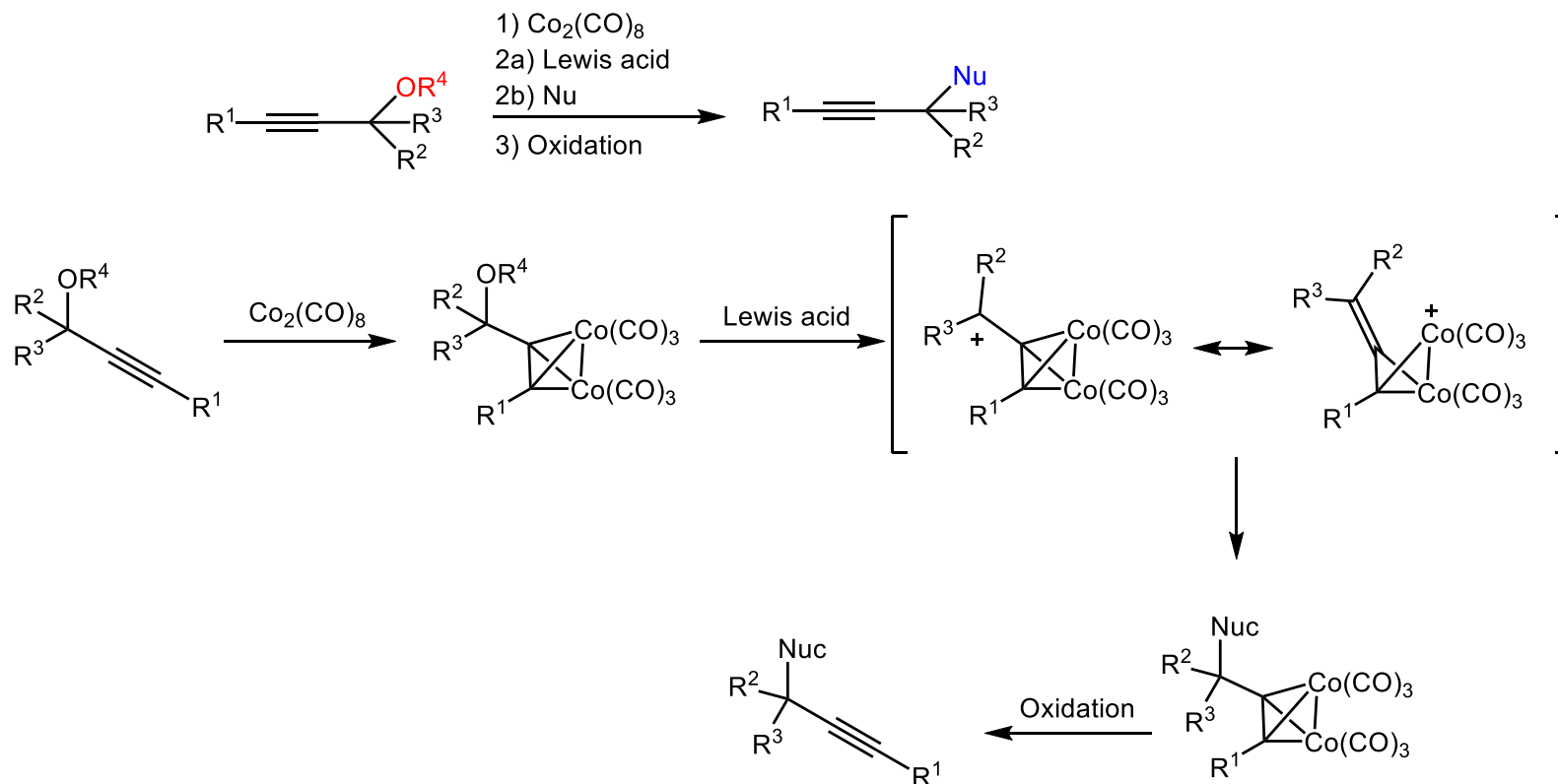
Babler–Dauben Oxidative Transposition



PCC: Pyridinium Chlorochromate
PDC: Pyridinium Dichromate

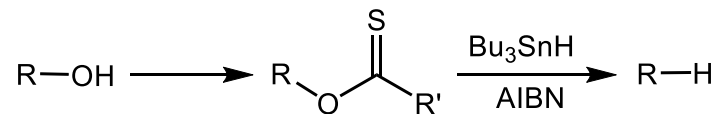
Dauben, W. G. *et al. J. Org. Chem.* **1977**, *42*, 682.

Nicholas Reaction

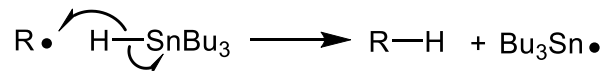
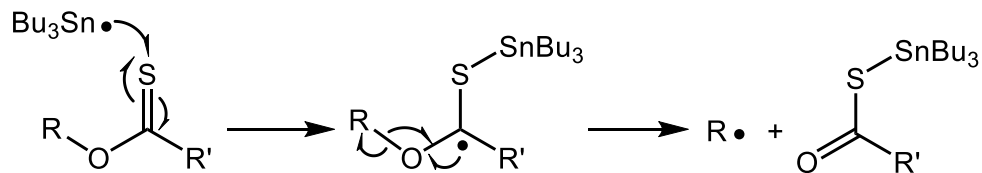
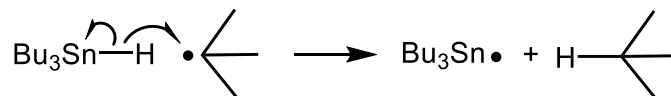
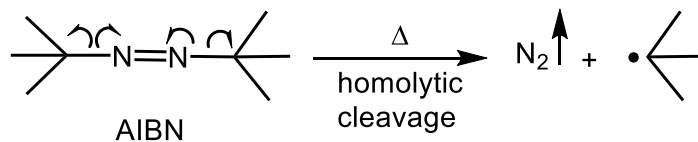


From Wikipedia

Barton-McCombie Deoxygenation

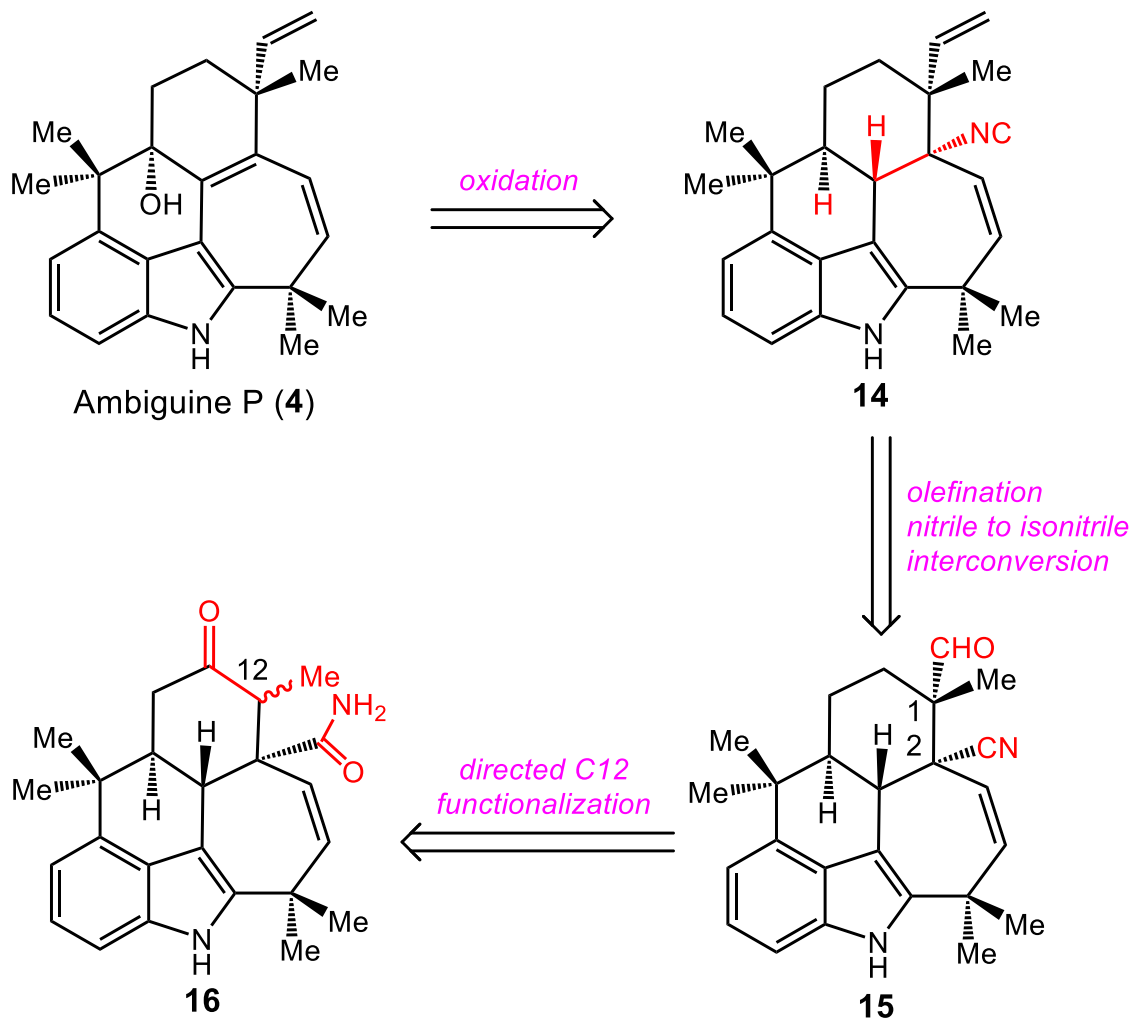


R = Alkyl R' = H, CH₃, SCH₃, OCH₃
Ph, Bn, Imidazolyl

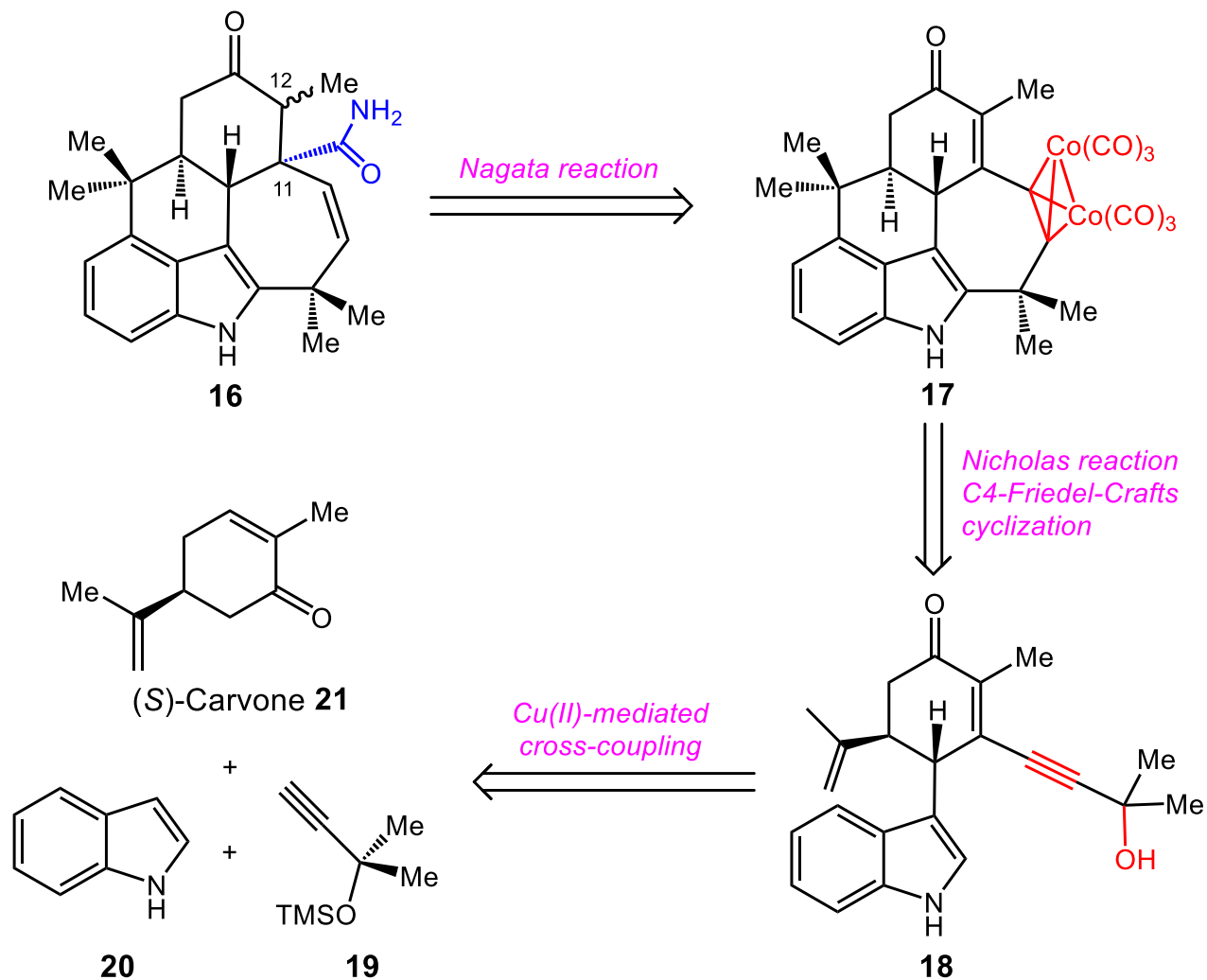


From Name Reactions

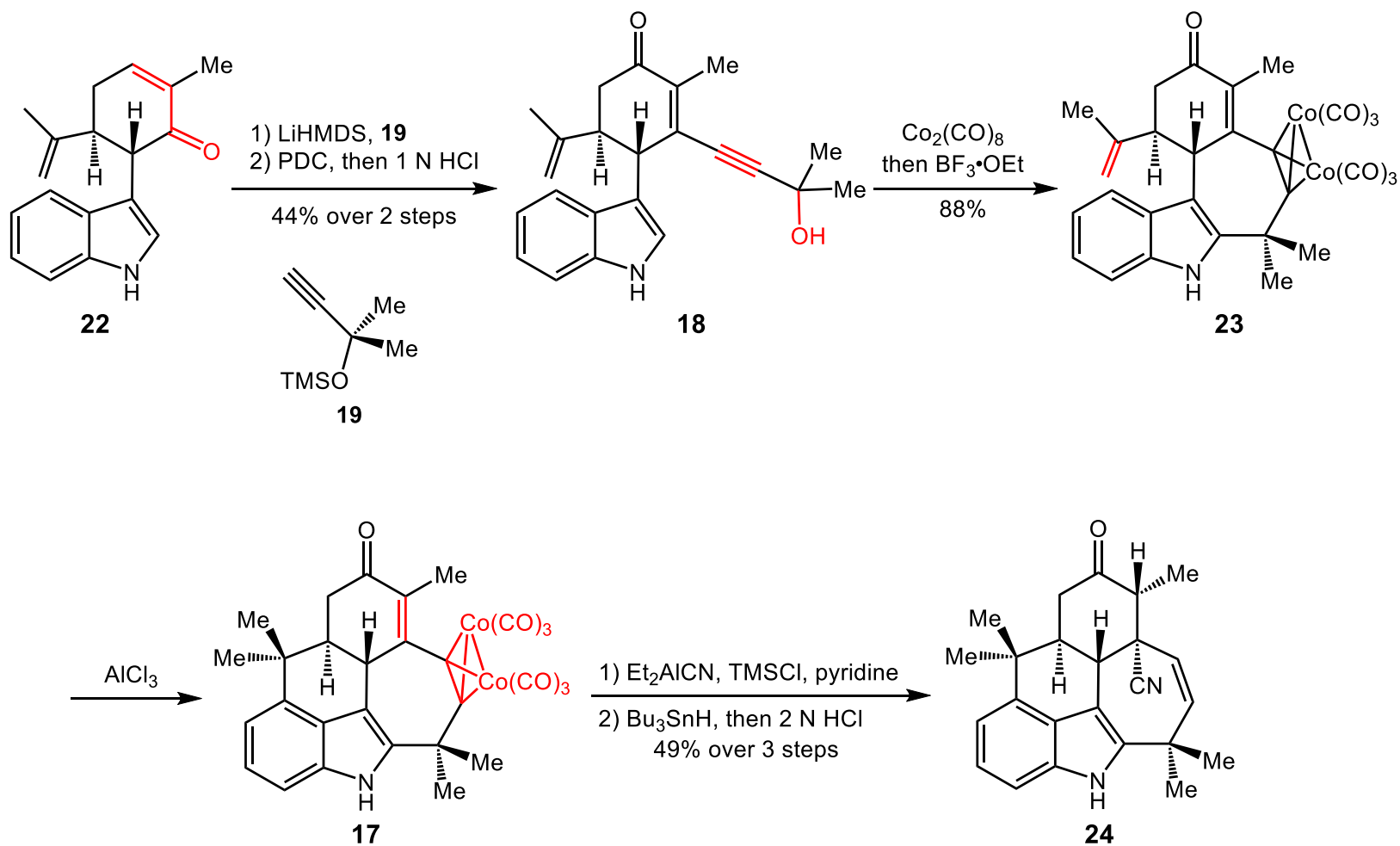
Retrosynthetic Analysis



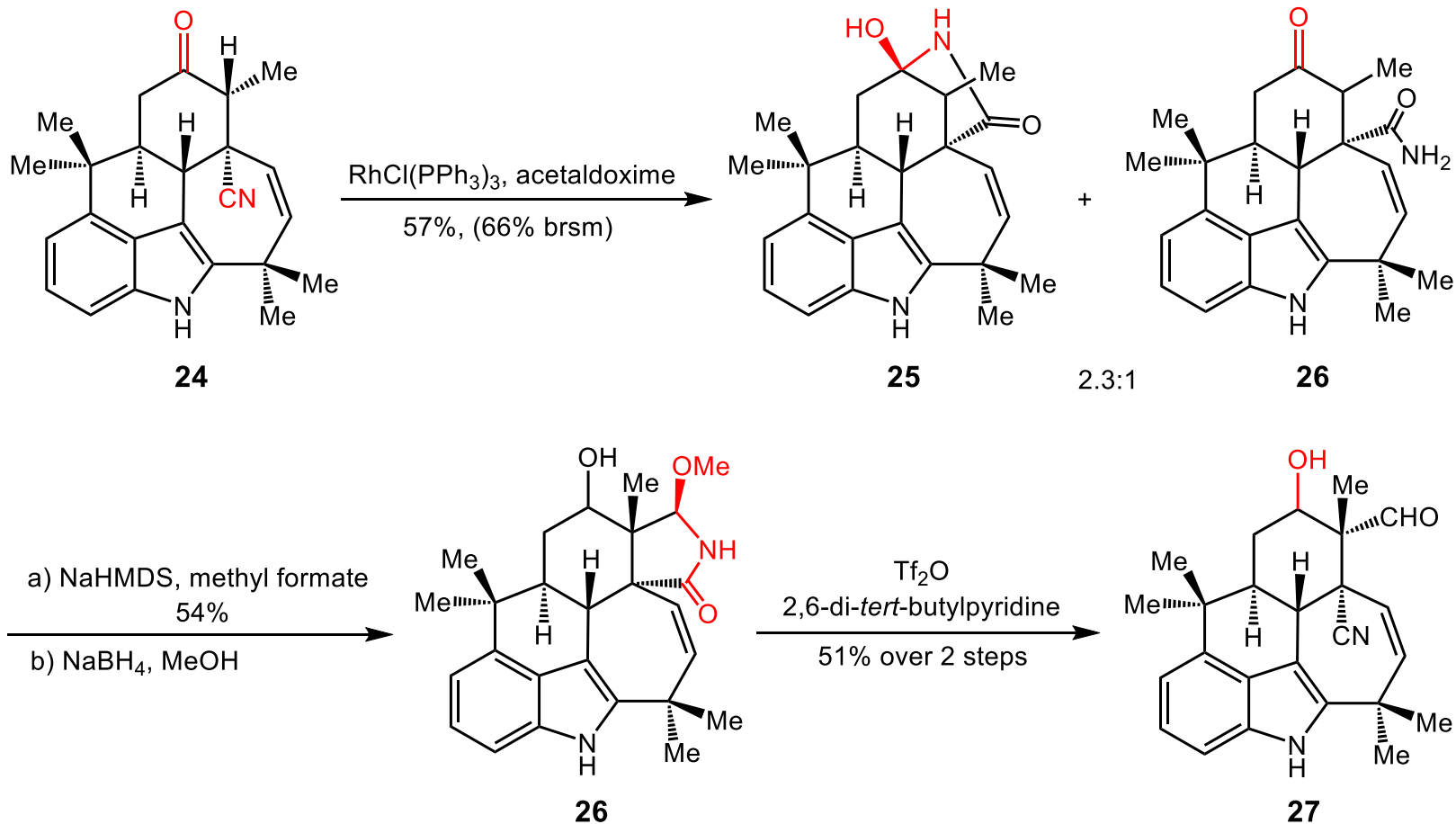
Retrosynthetic Analysis



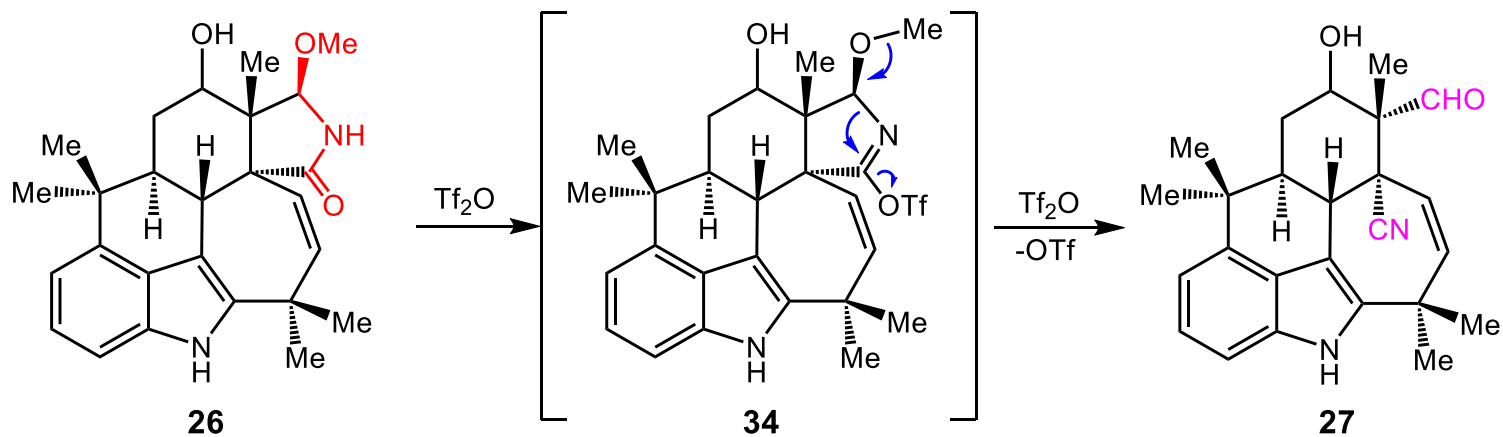
Construction of the Pentacyclic Core



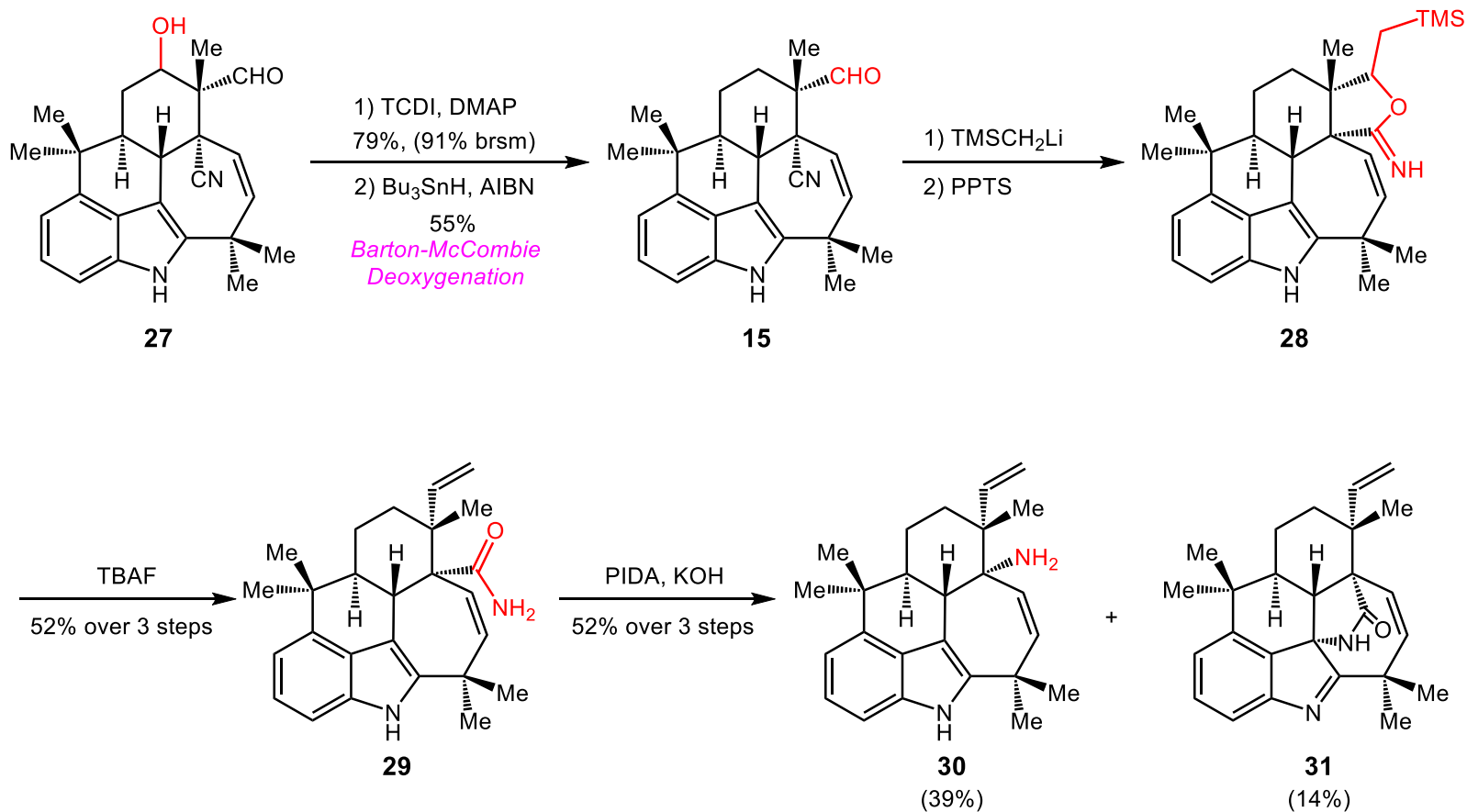
Synthesis of Compound 27



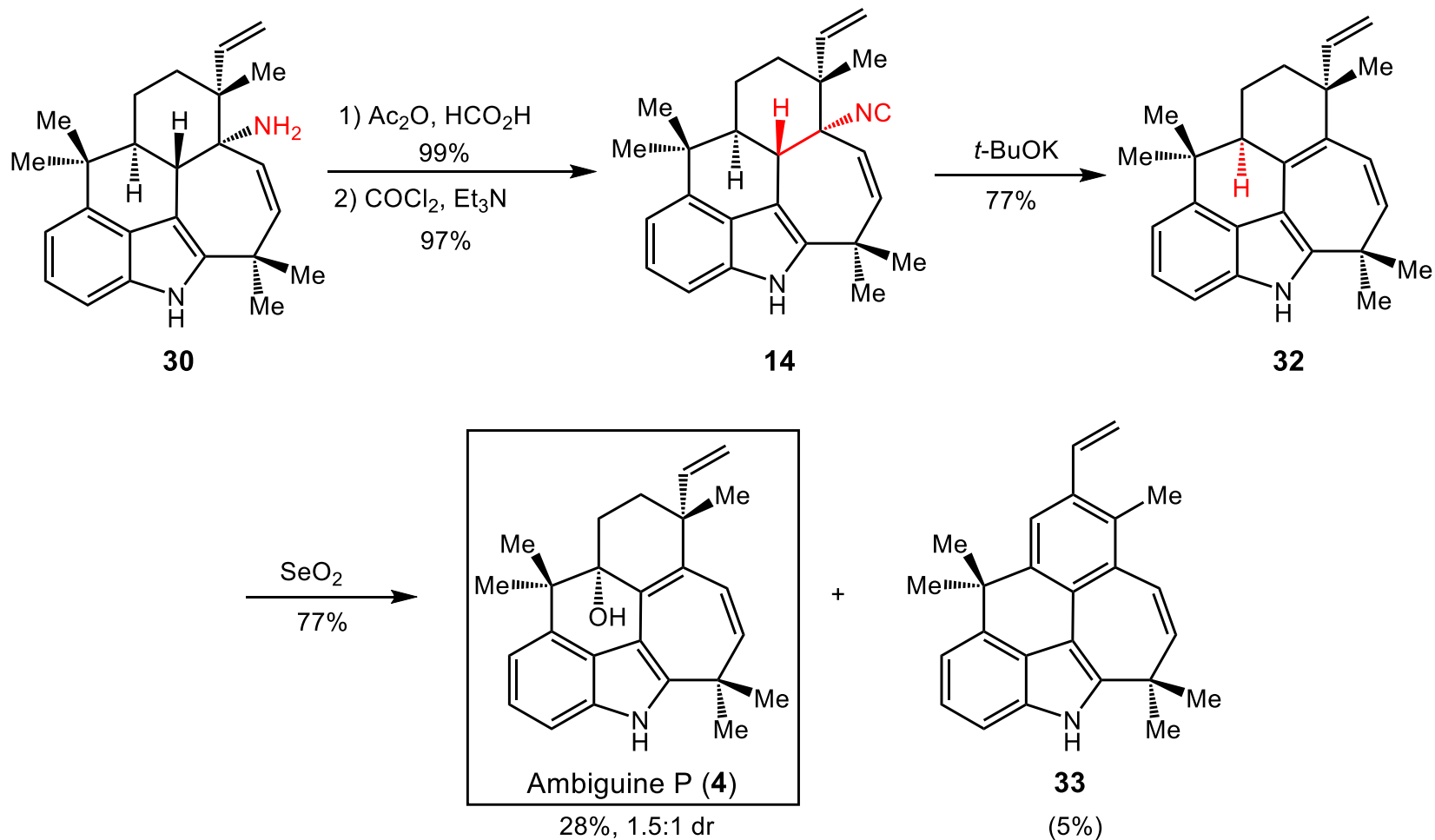
Possible Transformation Process



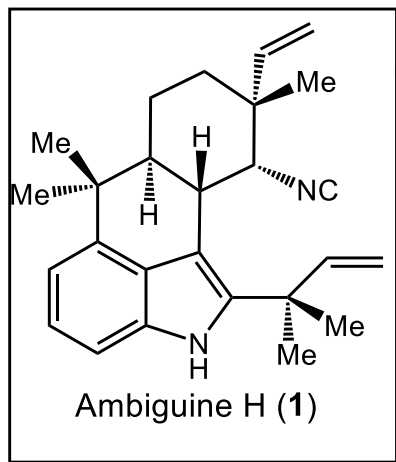
Synthesis of Compound 30



Synthesis of (-)-Ambiguine P

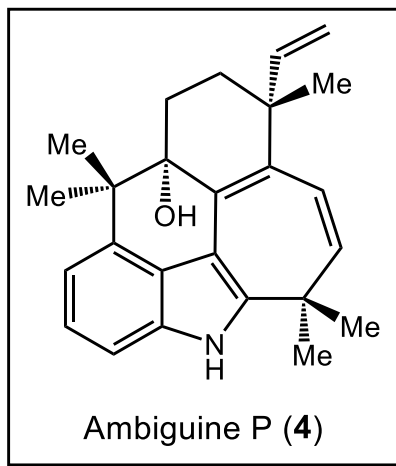


Summary



- The first total synthesis;
- 7 steps, 7.4 % overall yield;
- Palladium-mediated annulation;
- C2 C-C forming by tandem sequence.

Baran, P. S. *et al. Nature* **2007**, 446, 404.



- The first total synthesis;
- 20 steps, 0.033% overall yield;
- Nicholas reaction to alkylate at C2;
- An amide-directed functionalization at C12.

Sarpong, R. *et al. J. Am. Chem. Soc.* **2019**, 141, 2233.

The First Paragraph

The ambiguline natural products, are a subset of a larger family of indole secondary metabolites known as the hapalindoles. With the exception of four ambigulines, which are tetracyclic, the ambigulines possess a fused pentacyclic scaffold featuring a characteristic seven-membered ring moiety. Since the first reported isolation of ambiguline congeners in 1992, there have been continued efforts aimed at their total synthesis given their intriguing structures. In addition, some members of the hapalindole family, exert a broad spectrum of biological activities. Therefore, there has also been interest in exploring the function of the ambigulines in a biological context. While preliminary bioactivity studies on the ambigulines have been conducted, comprehensive studies have yet to be undertaken.

The First Paragraph

It is our anticipation that structurally related derivatives of the ambiguines, which may be accessed en route to their chemical preparation, may also possess interesting activity. As such, a total synthesis of the pentacyclic ambiguines could unveil their biological potential as well as set the stage for an understanding of their biosynthesis, especially the poorly understood late-stage oxidations of the fused seven-membered ring.

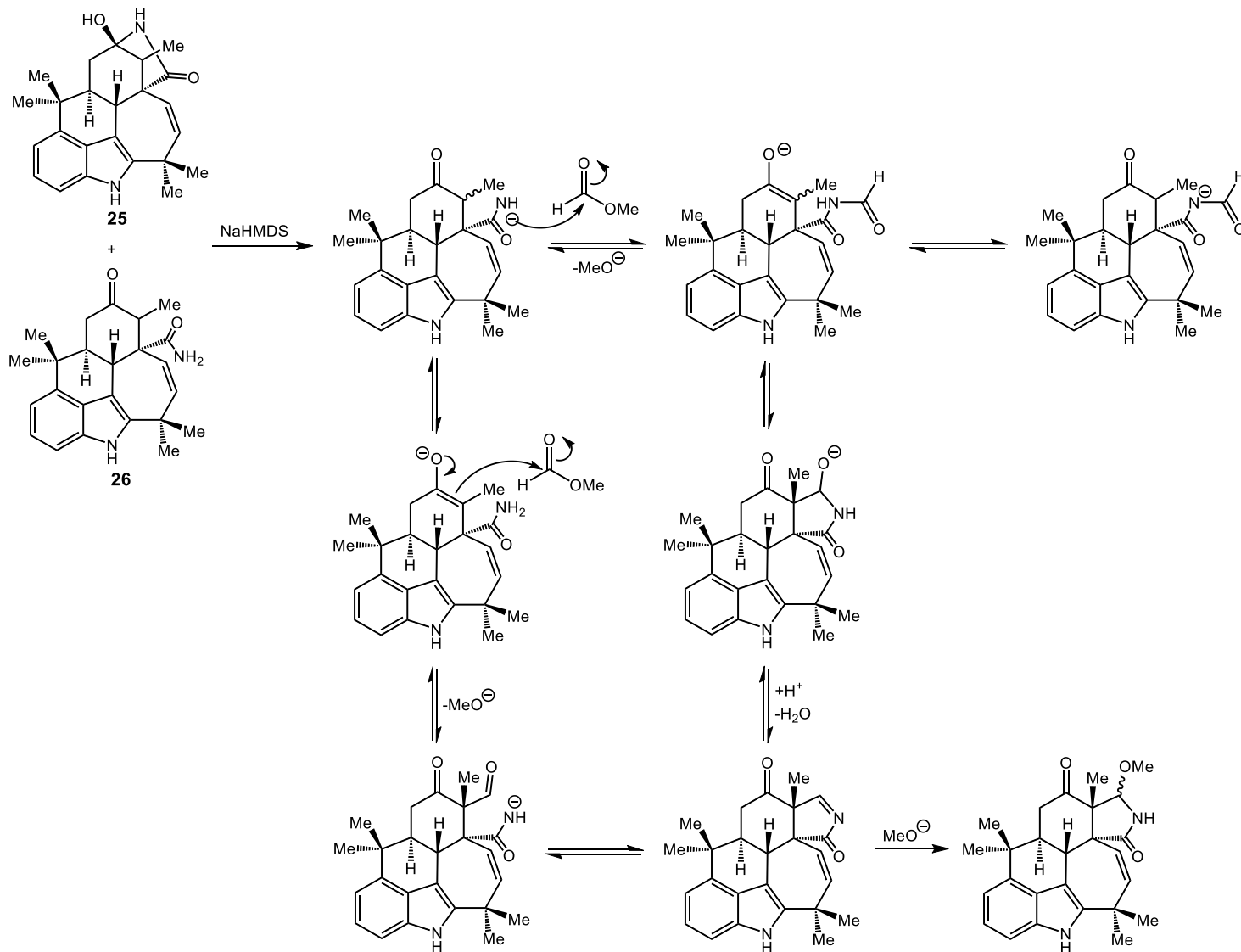
The Last Paragraph

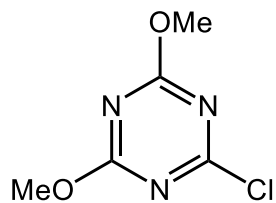
In summary, the first total synthesis of a pentacyclic ambiguine has been achieved in 20 steps from C3-functionalized indole, which is readily available in multigram quantities in a single step from commercial materials. Overall, our approach to the pentacyclic ambiguines highlights rapid construction of the pentacyclic skeleton through sequential alkylative functionalizations of indole using robust C-C bond-forming reactions as well as a novel application of an amide group to accomplish a stereoselective C12 functionalization. With ready access to pentacyclic isonitrile, current efforts are being directed toward its late-stage derivatization to access other pentacyclic members of the ambiguine family that retain the isonitrile group.

Acknowledgement

***Thanks
for your attention***

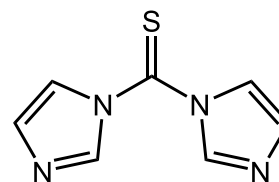
Possible mechanism For C12 functionalization





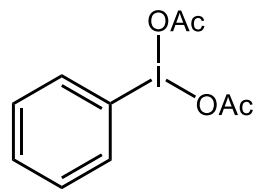
CDMF

2-chloro-4,6-dimethoxy-1,3,5-triazine



TCDI

1,1'-Thiocarbonyldiimidazole



PIDA