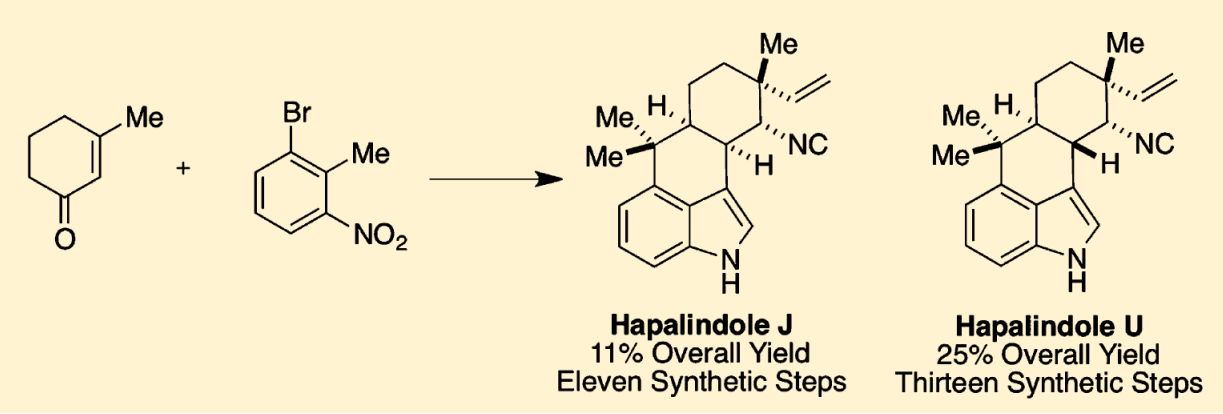
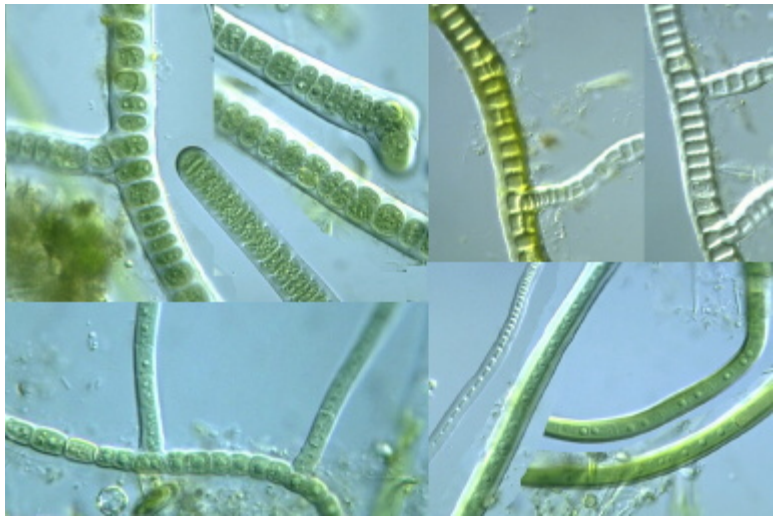
# Total Synthesis of Hapalindoles J and U




***Current Literature***
***Jie Xu***
***01.07.12***

Rafferty, R. J.; Williams, R. M. *J. Org. Chem.* ASAP

# Isolation



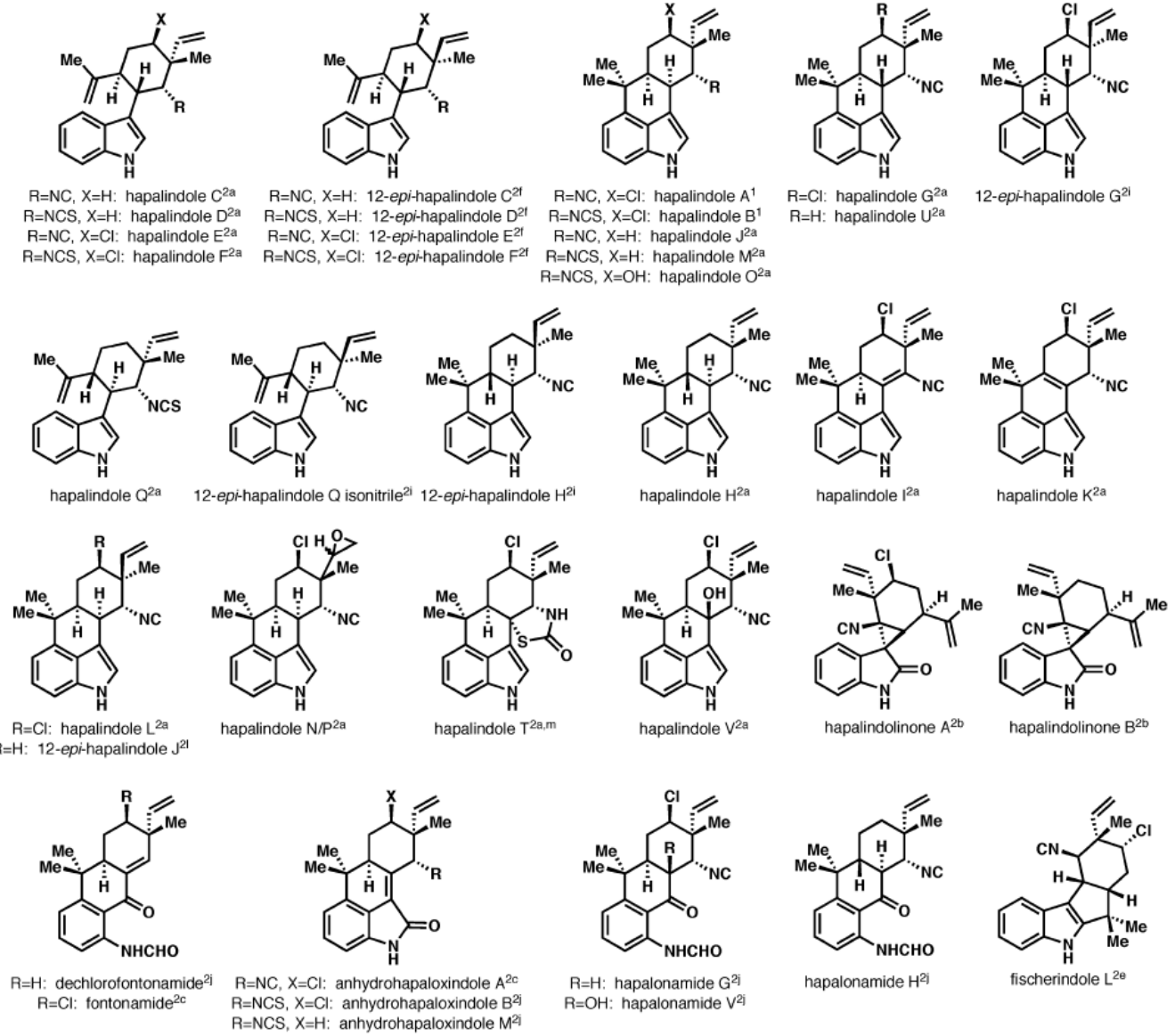
Stigonemataceae



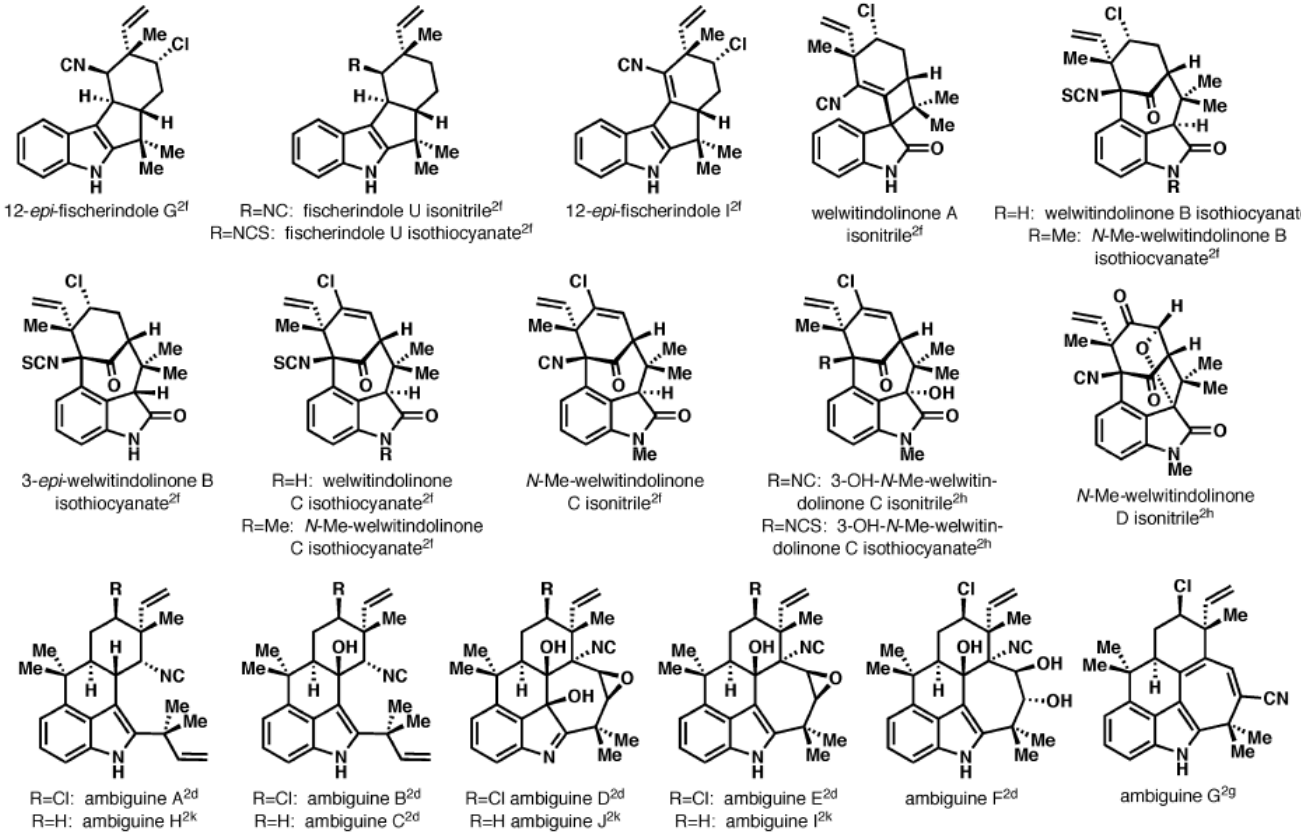
Marshall Islands

- ***The Stigonemataceae family of cyanobacteria has produced a class of over 60 indole natural products that form the basis of the hapalindole.***
- ***The hapalindoles were first isolated in 1984 by Moore and Patterson from a soil sample collected in Marshall Islands.***
- ***A broad range of bioactivities including antifungal, antibacterial, antimycotic and anticancer properties.***


Moore, R. E.; Cheuk, C.; Patterson, G. M. *J. Am. Chem. Soc.* **1984**, *106*, 6456.
Moore, R. E.; Cheuk, C.; Yang, X. Q.; Patterson, G. M. *J. Org. Chem.* **1987**, *52*, 1036.
Moore, R. E.; Cheuk, C.; Yang, X. Q.; Patterson, G. M. *J. Org. Chem.* **1987**, *52*, 3773.
http://www.worldatlas.com/webimage/countrys/oceania/mh.htm
http://protist.i.hosei.ac.jp/pdb/images/Prokaryotes/Cyanobacteria.html

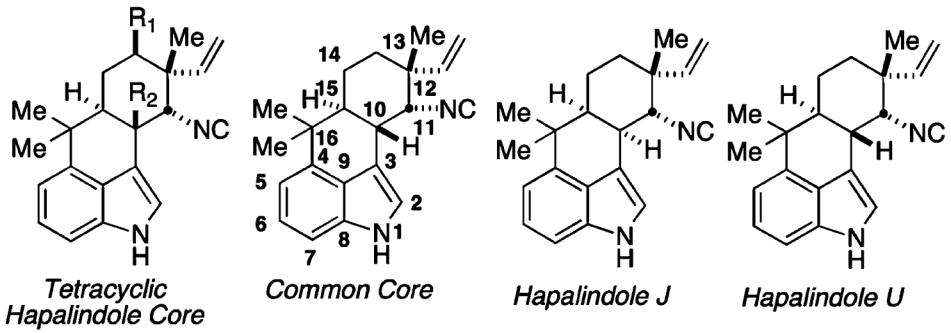


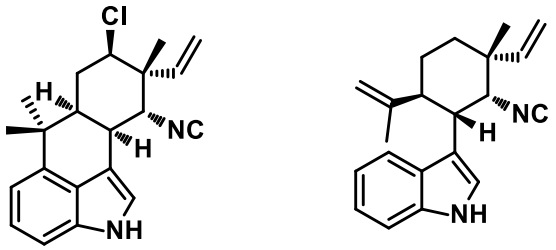

Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc*. **2008**, *130*, 17938.




Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc*. **2008**, *130*, 17938.

# Structure Feature



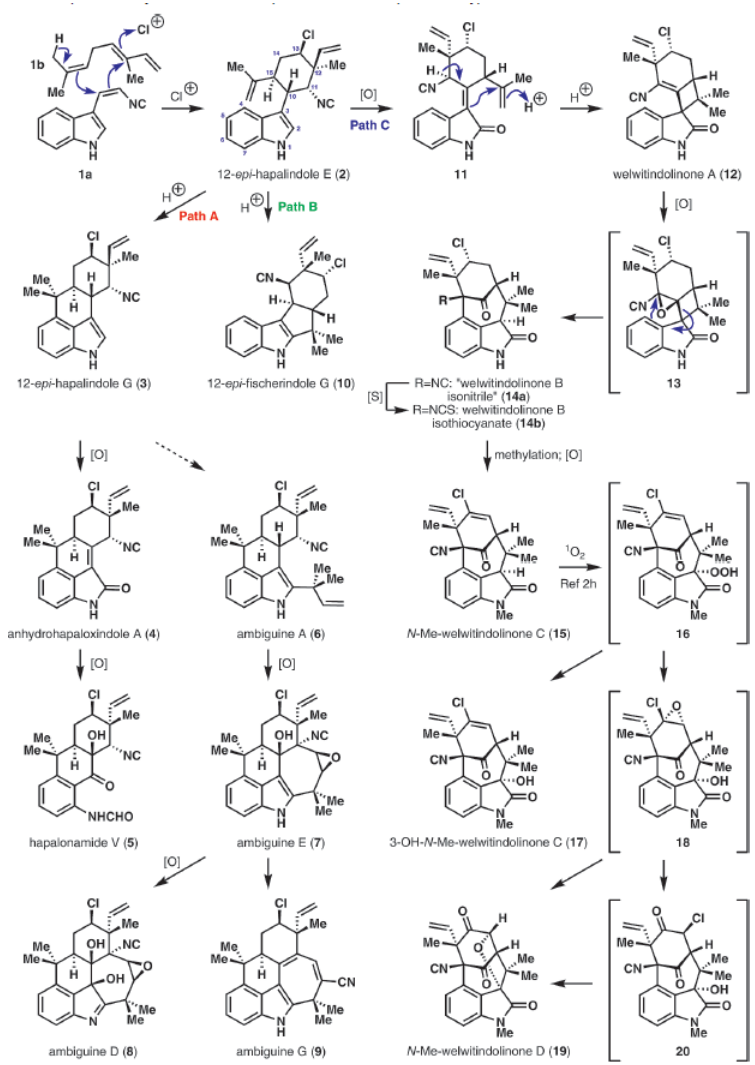



**Hapalindole A** **Hapalindole C**

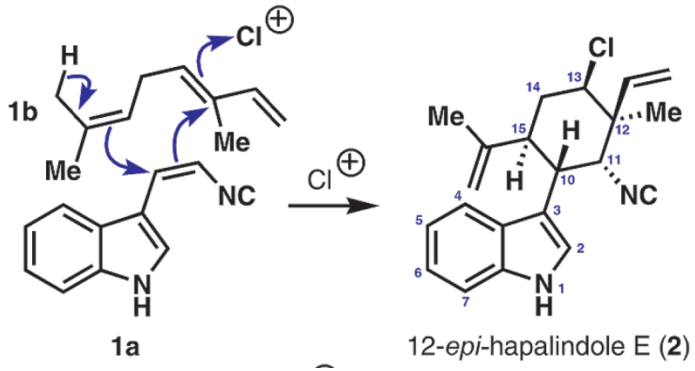
- ***Structure was determined by 1D and 2D NMR.***
- ***Tricyclic family and tetracyclic family***
- ***Indole heterocycle and monoterpene unit***

Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6331.

# Moore's Proposed Biosynthetic Relationships

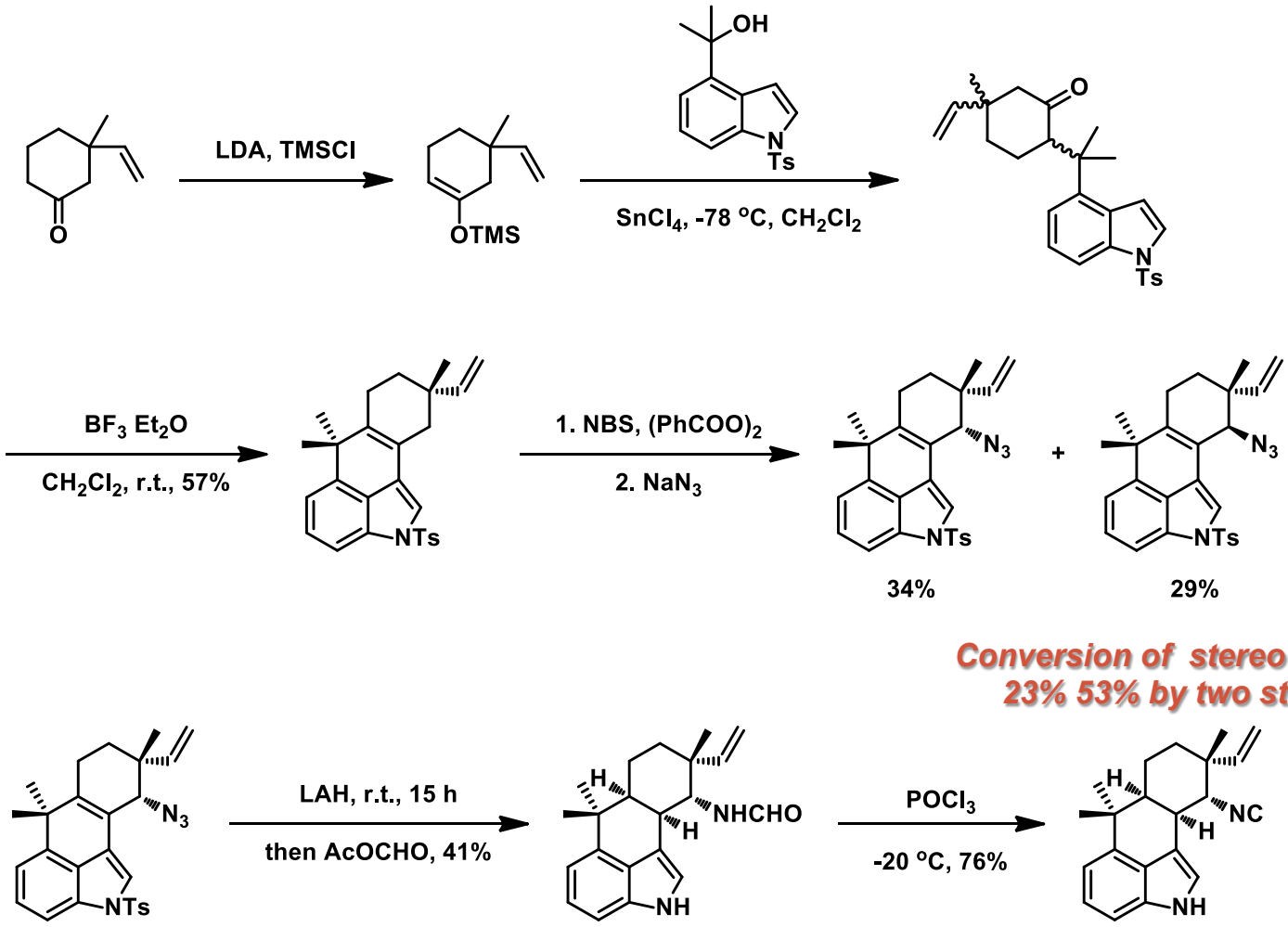



- ***Begins with the tryptophan derivative and terpene.***
- ***Enzymatically joined via chloronium-promoted polyolefin cyclization.***




Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 17938.

# Natsume's Synthesis of Hapalindole J



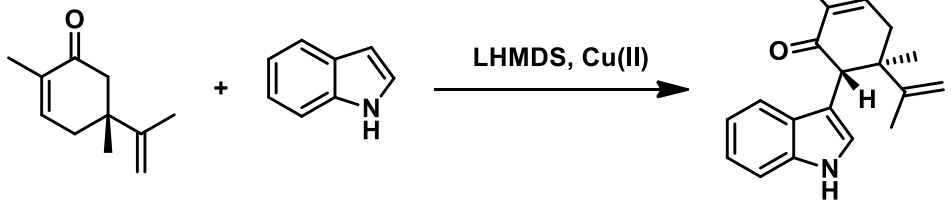

***Conversion of stereo center***
***23% 53% by two steps***

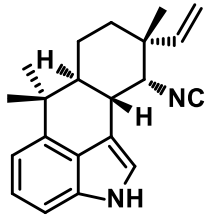
Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6331.

***20 steps, 0.2% yield***

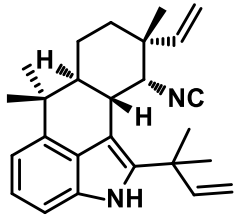
# Baran's Protecting Group Free Synthesis

## Oxidative Coupling of Indole



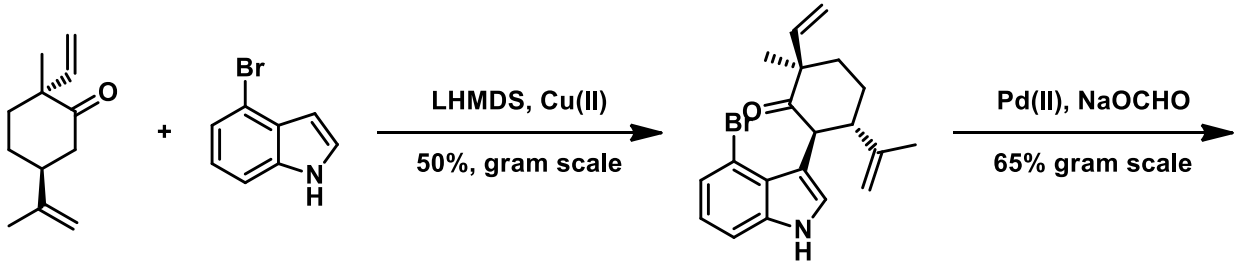



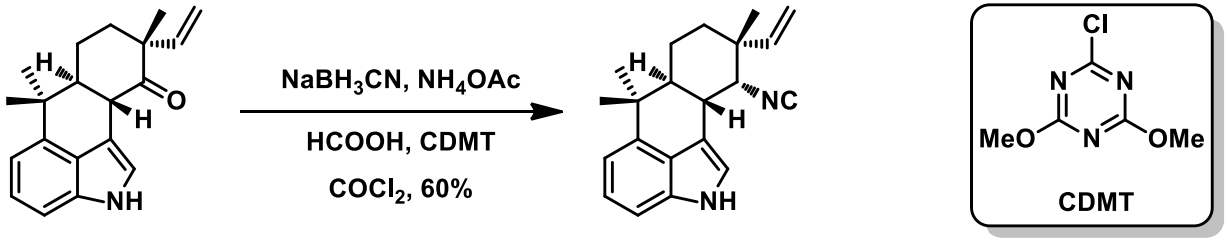
(-)-Hapalindole U



(+)-Ambiguine H

## Synthetic Route



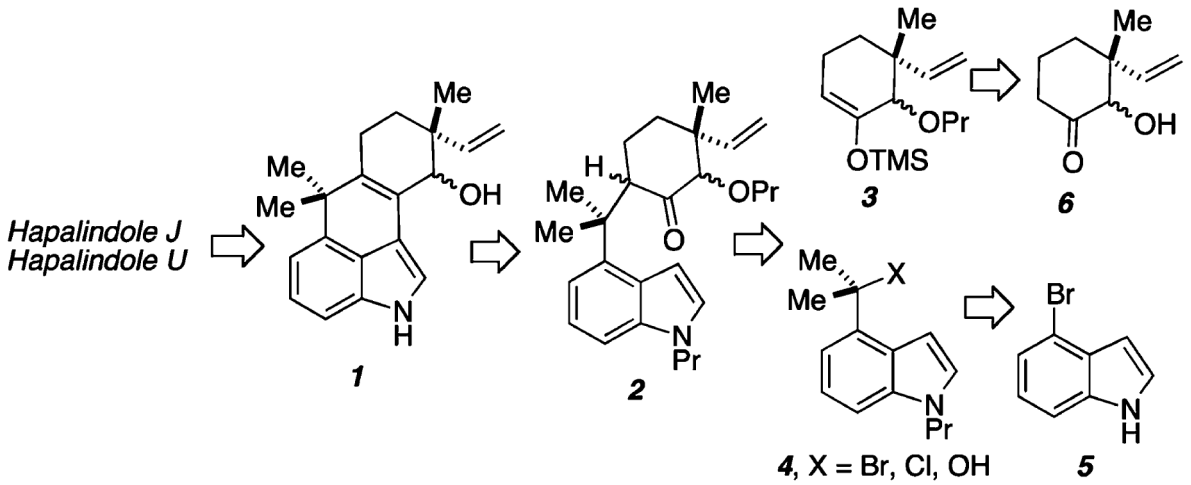




**9 steps 7% yield**
**Enantioselective Synthesis**

Baran, P. S.; Thomas J. Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404.

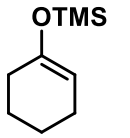
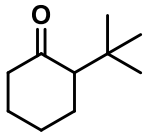
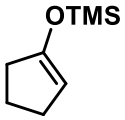
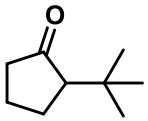
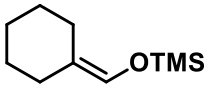
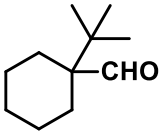
# Retrosynthetic Analysis



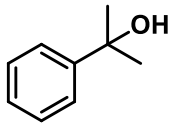
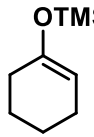
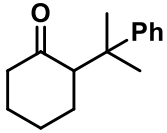
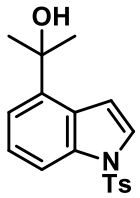
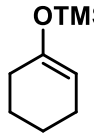
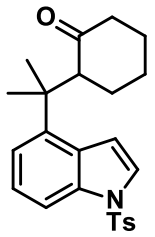
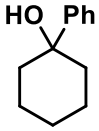
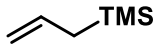
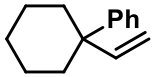

- ***Lewis Acid mediated coupling of silyl enol ether with alcohol***

# Preliminary Experiments

## $TiCl_4$

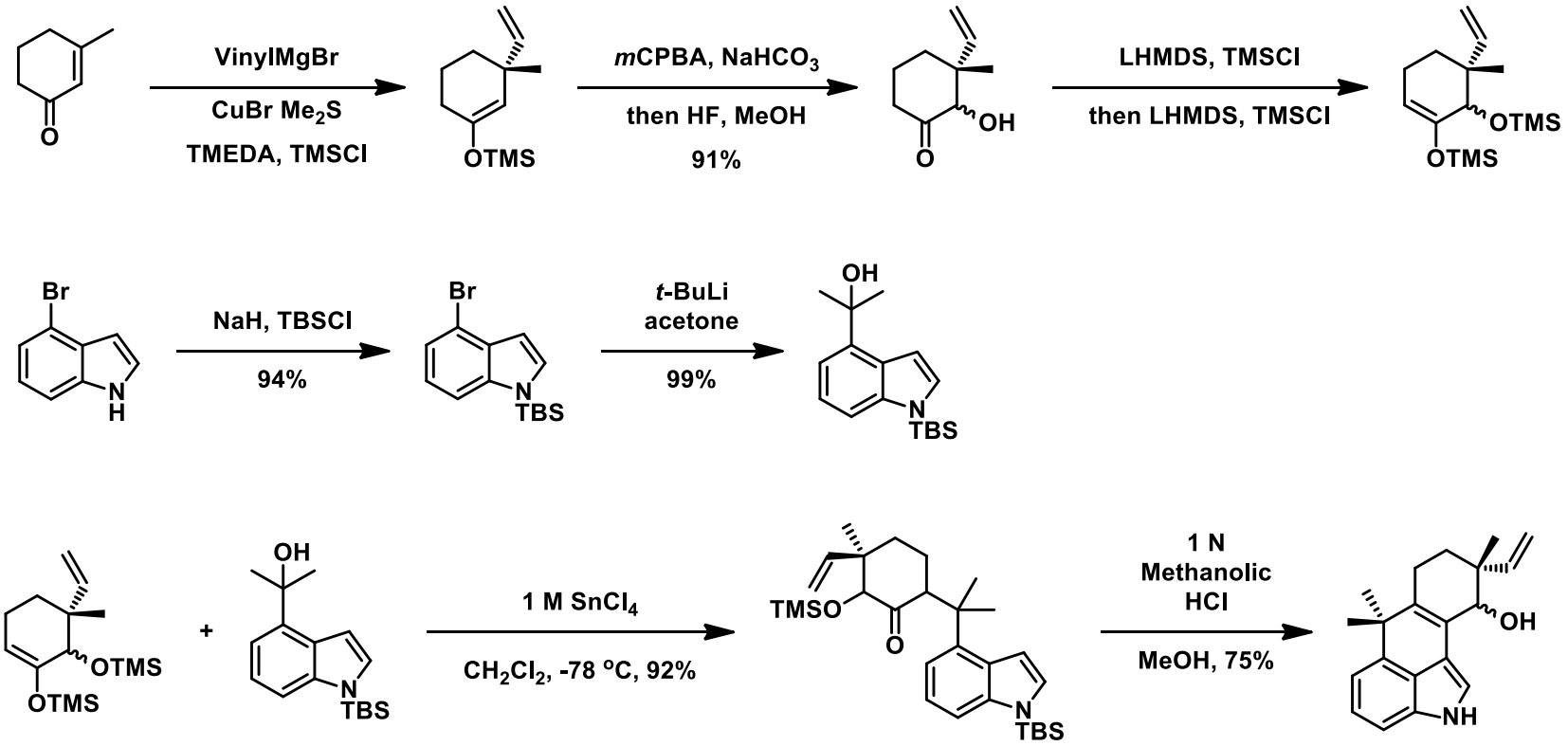
| Silyl Enol Ether | Product | Yield |
|---|---|---|
|  |  | 48% |
|  |  | 59% |
|  |  | 40% |

## $SnCl_4$

| Alcohol | Silyl Enol Ether | Product | Yield |
|---|---|---|---|
|  |  |  | 96% |
|  |  |  | 95% |
|  |  |  | 91% |

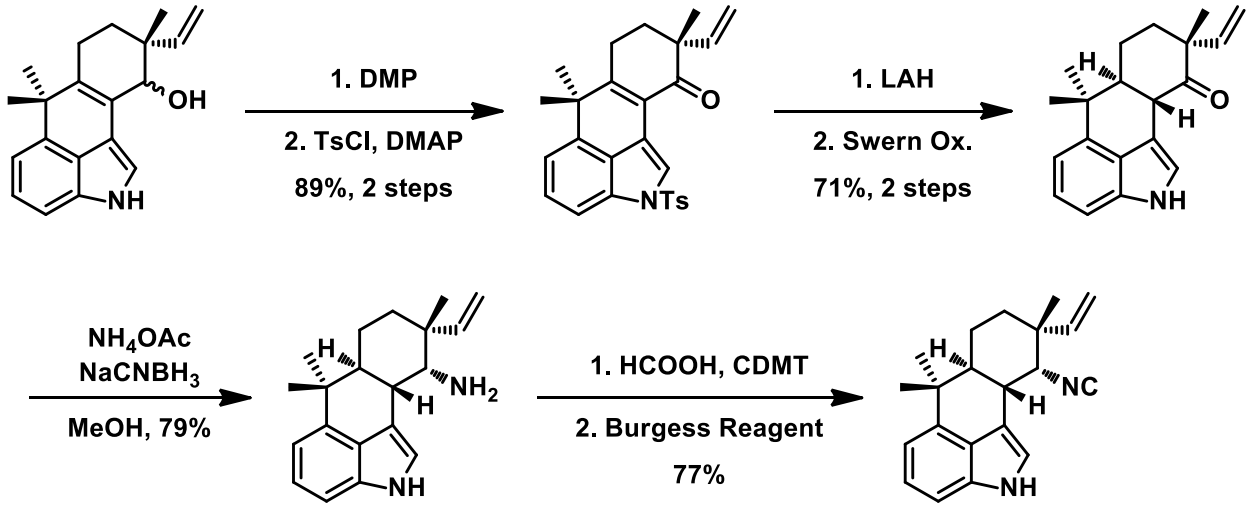
Chan, T. H.; Paterson, I.; Pinsonnault, J. *Tetrahedron Lett*. **1977**, 4183.
Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6331.

# Synthesis

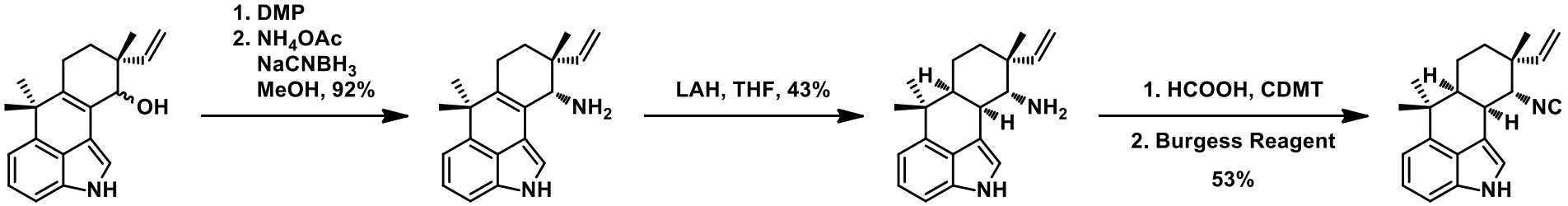

VinylMgBr
CuBr Me2S
TMEDA, TMSCl
OTMS
mCPBA, NaHCO3
then HF, MeOH
91%
OH
LHMDS, TMSCl
then LHMDS, TMSCl
OTMS
OTMS
Br
NaH, TBSCl
94%
Br
N
TBS
t-BuLi
acetone
99%
OH
N
TBS
OTMS
OTMS
+
OH
N
TBS
1 M SnCl4
CH2Cl2, -78 °C, 92%
TMSO
O
N
TBS
1 N
Methanolic
HCl
MeOH, 75%
OH
NH

# End Game

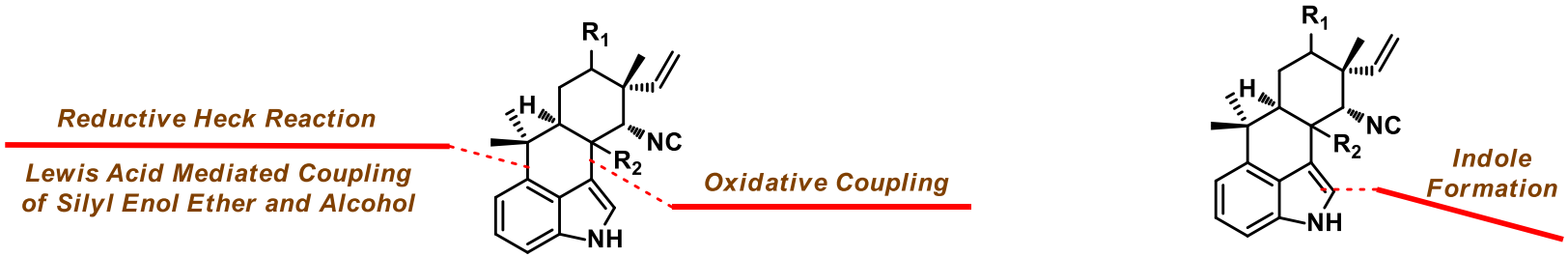
## Hapalindole U

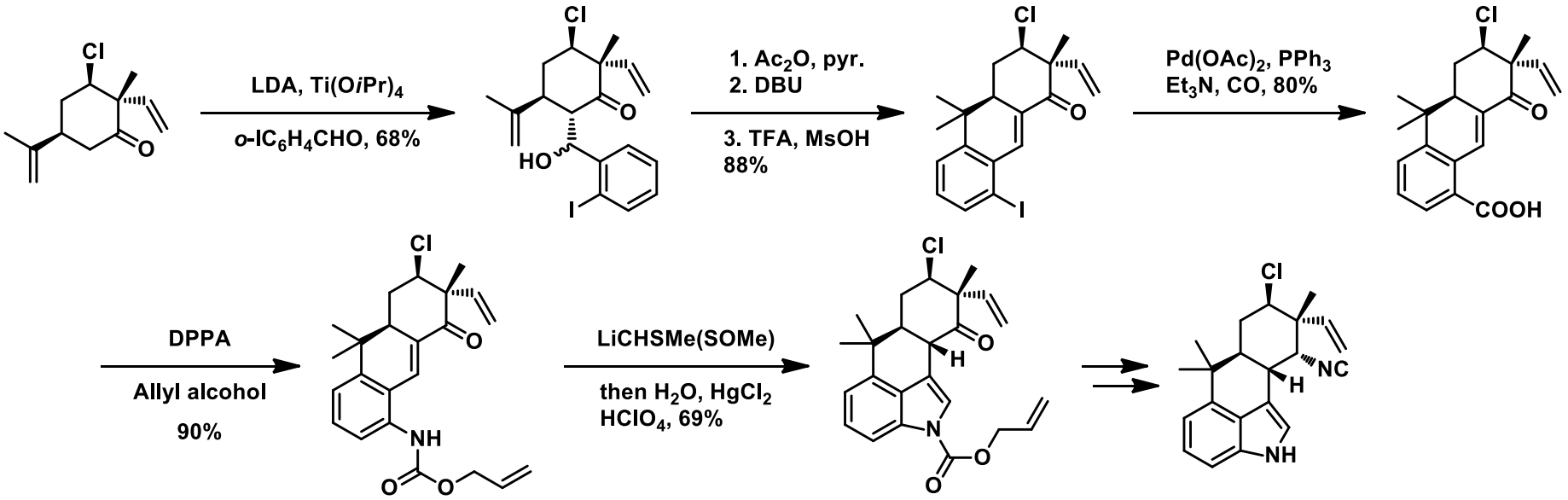



## Hapalindole J



# Outlook





Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6331.
Baran, P. S.; Thomas J. Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404.
Fukuyama, T.; Chen, X. *J. Am. Chem. Soc.* **1994**, *116*, 3125.

# Summary

- ***Total Synthesis of Hapalindole J and U***
- ***Same strategy, enhanced efficiency of accessing the functionalized tetracycle core.***

***Hapalindole U***

***Natsume 20 steps 0.2%***
***Baran 9 steps 7.5%***
***Williams 13 steps 25%***

***Hapalindole J***

***Six steps Shorter***
***22 fold high yielding***