

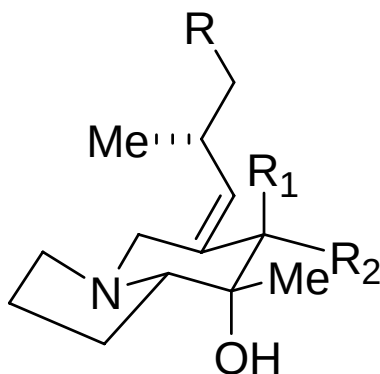
Pumiliotoxin A and Allopumiliotoxin Alkaloids

Pharmacologically Active Natural Products, New Synthetic Methods and Strategies

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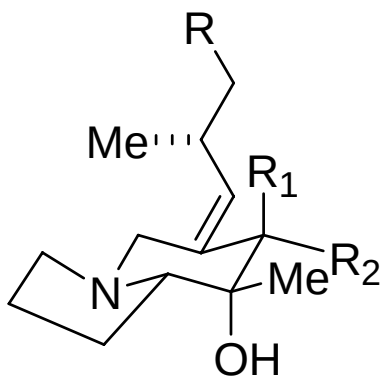


1. The Pumiliotoxin A and Allopumiliotoxin Alkaloids
2. Total Synthesis of Pumiliotoxin A Alkaloids using Iminium Ion – Vinylsilane Cyclizations
 - Retrosynthetic Analysis and Strategy
 - Total Synthesis of (+)-Pumiliotoxin 251D
 - Total Synthesis of (+)-Pumiliotoxin B
3. Total Synthesis of Pumilotoxin A and Allopumiliotoxin Alkaloids using Iodine-Promoted Iminium Ion – Alkyne Cyclizations
 - Retrosynthetic Analysis and Strategy
 - Efficient Total Synthesis of Pumiliotoxins A and B
 - Total Synthesis of Allopumiliotoxin 339A
 - A Simplified Procedure for Preparing Pumiliotoxin 251D Analogs
4. Alternative Strategies for Pumiliotoxin A and Allopumiliotoxin Synthesis
5. Conclusions

1. The Pumiliotoxin A and Allopumiliotoxin Alkaloids



- Isolated from skin extracts of frogs of the family Dendrobatidae and also in amphibians
- Substances that presumably serve a defensive role
- The Pumiliotoxin A and Allopumiliotoxin Alkaloids are a group of about 40 heterocycles having the general structure
- Not produced by biosynthesis – no alkaloids are found in captive raised frogs
- Alkaloids are accumulated by food
- up to 200 μg total alkaloids / 100 mg skin extract



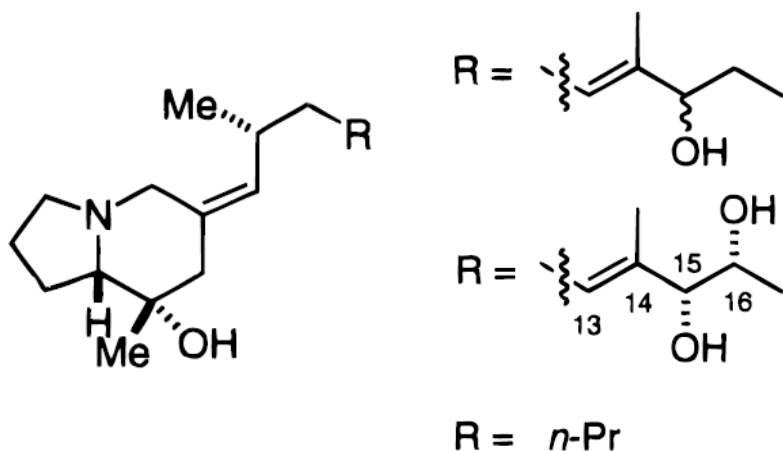
1. The Pumiliotoxin A and Allopumiliotoxin Alkaloids



Pumiliotoxins A & B were first isolated from the Panamanian poison frog *Dendrobates pumilio* in 1967



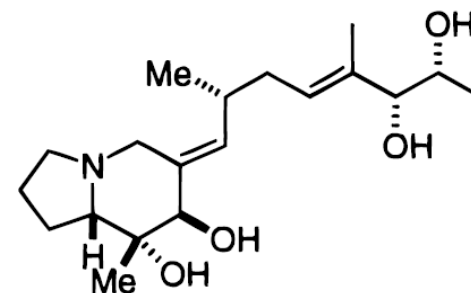
Pumiliotoxin 251D was isolated in 1980 from the Ecuadorian poison frog *Dendrobates tricolor*



1. The Pumiliotoxin A and Allopumiliotoxin Alkaloids



- Structure remained obscure until 1980
- X-ray analysis of Pumiliotoxin 251D established the structure & absolute configuration
- The defining structural element of the Pumiliotoxin A family is the **(Z)-6-alkylideneindolizidine** ring system
- Allopumiliotoxins are hydroxyl congeners of the Pumiliotoxin A class and possess a vicinal diol group in the indolizidine ring
- Pumiliotoxin B and congeners enhance Na influx by binding to a unique modulatory site on the voltage-dependent Na channel
→ **cardiotonic & myotonic activity**



(+)-allopumiliotoxin 339A

Daly, J.W. et al., *Science (Washington, D.C.)* **1967**, 156, 970.
Daly, J.W. et al., *J. Am. Chem. Soc.* **1980**, 102, 830.
Daly, J.W. et al., *Mol. Pharmacol.* **1992**, 42, 1104.
Daly, J.W. et al., *J. Med. Chem.* **1985**, 28, 482

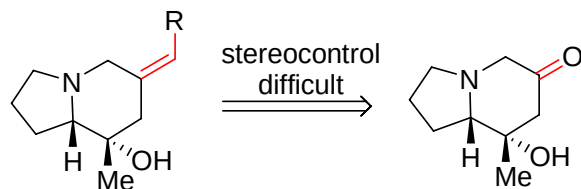
Daly, J.W. et al., *J. Med. Chem.* **1988**, 31, 477.
Daly, J.W. et al., *Biochem. Pharmacol.* **1990**, 40, 315.
Overman, L.E. et al., *Abstracts International Union of Physiological Sciences*,
Vancouver, Canada, July 1986.

2.A. Total Synthesis of Pumiliotoxin A Alkaloids using Iminium Ion – Vinylsilane Cyclizations

Retrosynthetic Analysis and Strategy



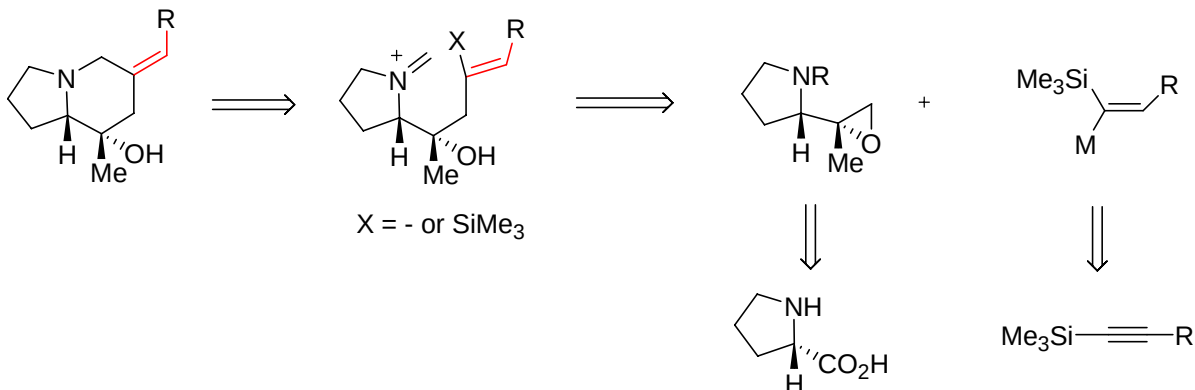
(Z) – Alkylidene side chain presents particular problems, since stereocontrolled synthesis of exocyclic alkenes is particularly challenging



- Possibility of (Z)-side chain via Wittig-type rct are dim
- Fundamental disconnection is the cleavage of a bond β to nitrogen in alkaloid retrosynthetic analysis
- retro-Mannich disconnection of alkylideneindolizidine generates a zwitterionic synthon

2.A. Total Synthesis of Pumiliotoxin A Alkaloids using Iminium Ion – Vinylsilane Cyclizations

Retrosynthetic Analysis and Strategy



- (Z)-Vinylsilane are viable equivalents since they react with electrophiles under retention of alkene stereochemistry
- Vinylsilane as Mannich component was daring, since no example of intramolecular rcts with electrophiles were extant at that time
- Also the rct of Iminium Ions with Vinylsilanes was unknown – because of the weakly nucleophilic character and the moderate reactivity of simple Iminium electrophiles
- The Iminium Ion – Vinylsilane approach was verified in 1981 in the first total synthesis of (+)-Pumiliotoxin 251D

Koenig, K.E. et al., *J. Am. Chem. Soc.* **1973**, 95, 3416.

Colvin, E.W. *Silicon Reagents in Organic Synthesis*; Academic: London, 1988.

Overman, L.E. et al., *Chem. Rev.* **1986**, 86, 857.

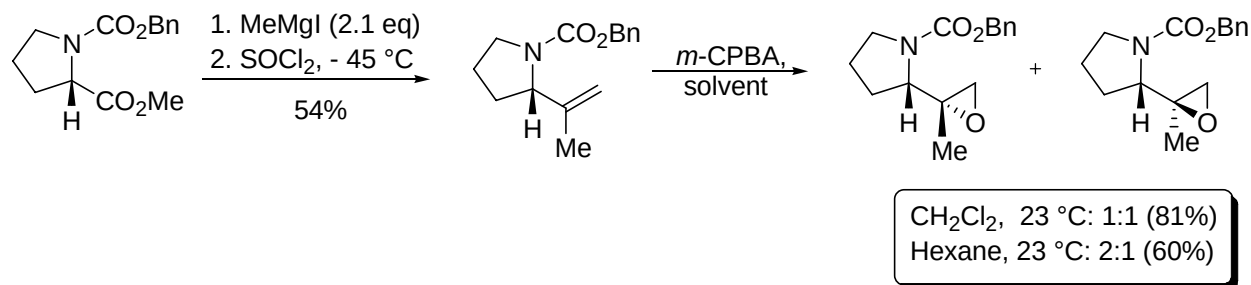
Overman, L.E. et al., In *Comprehensive Organic Synthesis*; Trost, B.M., Fleming, I., Heathcock, C.H., Eds.; Pergamon: Oxford, 1991; Vol. 2, Chapter 4.4

Overman, L.E. et al., *J. Am. Chem. Soc.* **1981**, 103, 1851.

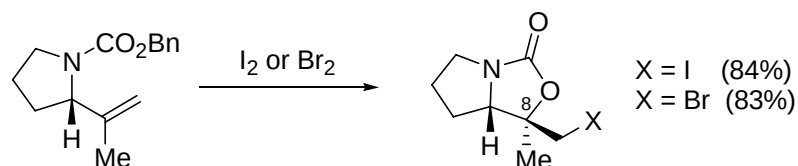


2.B. Total Synthesis of (+)-Pumiliotoxin 251D

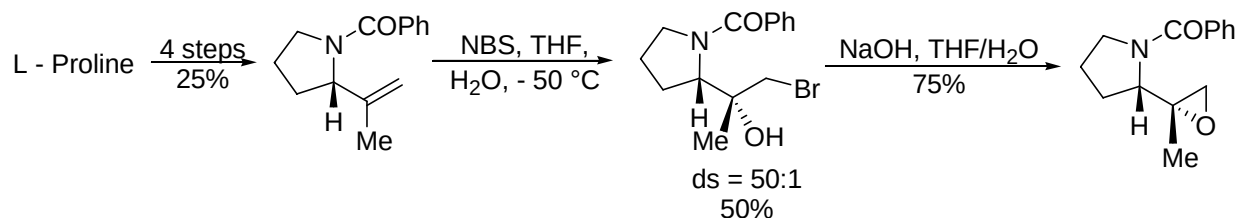
Nonstereoselective route to Pyrrolidine epoxide:



Stereocontrolled Synthesis of the Pyrrolidine epoxide fragment:

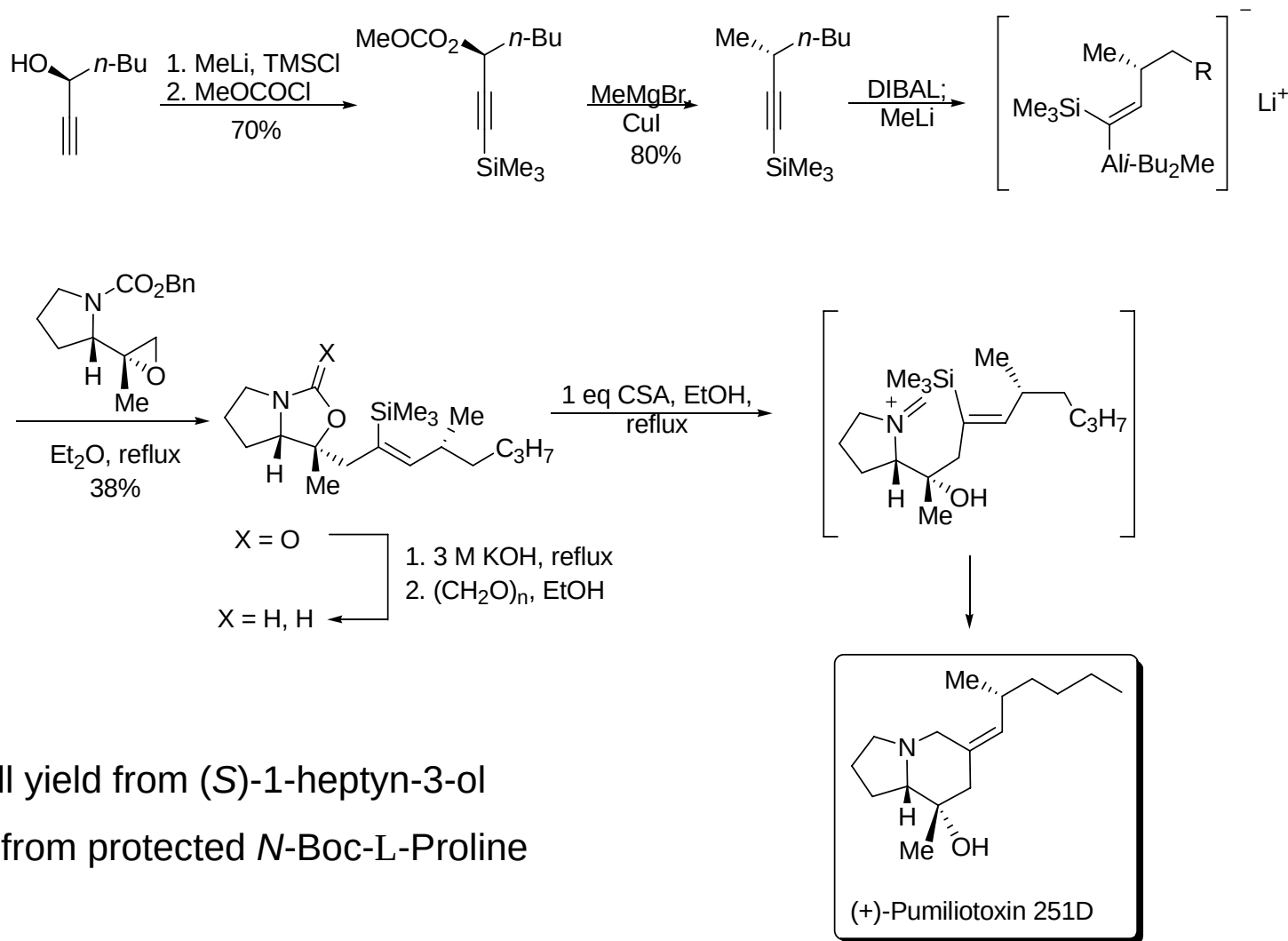


Development of a Stereoselective Synthesis of epoxide amides:



2.B. Total Synthesis of (+)-Pumiliotoxin 251D

Preparation of the side chain & Completion of Pumiliotoxin 251D



13% overall yield from (S)-1-heptyn-3-ol

4.7% yield from protected N-Boc-L-Proline

Midland, M.M. et al., *J. Am. Chem. Soc.* **1980**, 102, 867.

Pirkel, W.H. et al., *J. Org. Chem.* **1977**, 42, 1839.

Rinaldi, P.L. et al., *J. Org. Chem.* **1980**, 45, 4348.

Pirkel, W.H. et al., *J. Org. Chem.* **1977**, 42, 2781.

Macdonald, T.L. et al., *J. Org. Chem.* **1980**, 45, 4740.

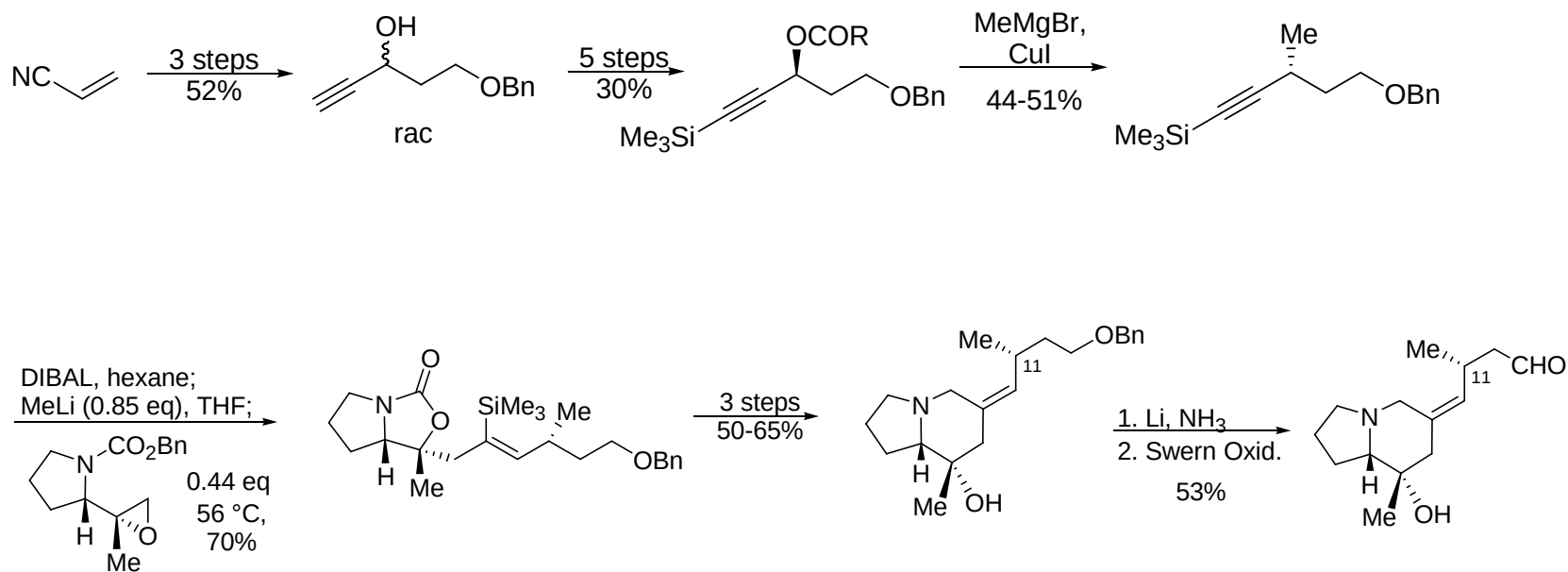
Eisch, J.J. et al., *J. Org. Chem.* **1971**, 36, 3520.

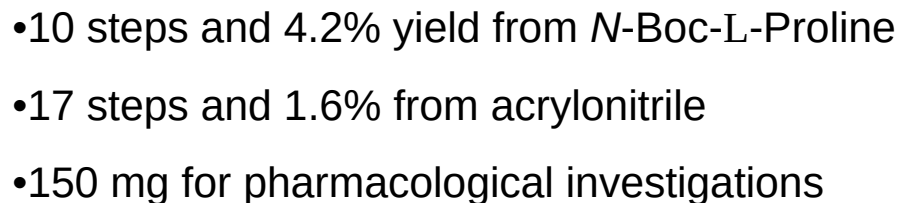
Eisch, J.J. et al., *J. Org. Chem.* **1976**, 41, 2214.

2.C. Total Synthesis of (+)-Pumiliotoxin B



Preparation of the side chain & of the alkylideneindolizidine aldehyde:



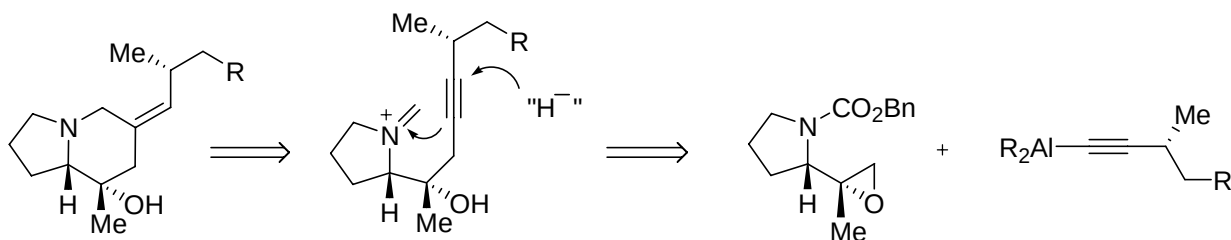


3. Total Synthesis of Pumilotoxin A and Allopumiliotoxin Alkaloids Using Iodine-Promoted Iminium Ion – Alkyne Cyclizations

3.A. Retrosynthetic Analysis and Strategy



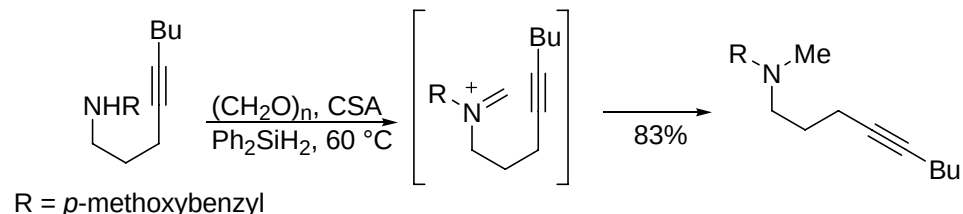
- Drawback of the strategy is the coupling of the vinylsilane side chain & the pyrrolidine epoxide fragment
- This step requires special optimization for each side chain nucleophile
- often low yielding
- **New Strategy:** Z stereochemistry of the alkylidene side chain evolves from the stereoelectronic preference for electrophile – nucleophile pairs to add to alkynes in an antarafacial fashion



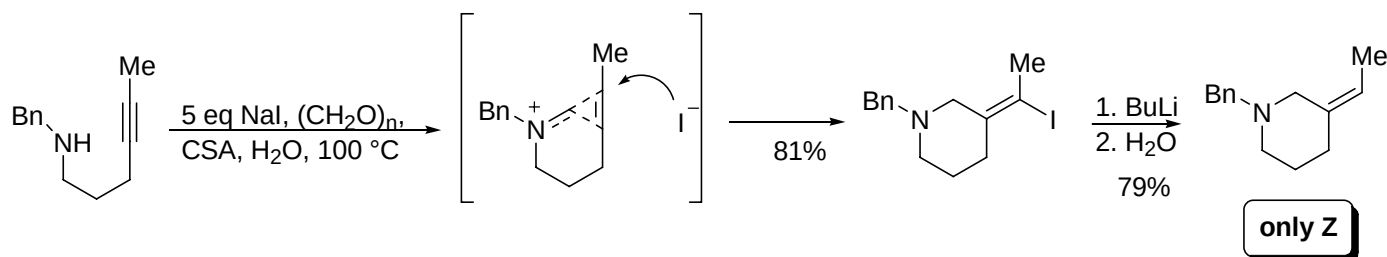
3.A. Retrosynthetic Analysis and Strategy



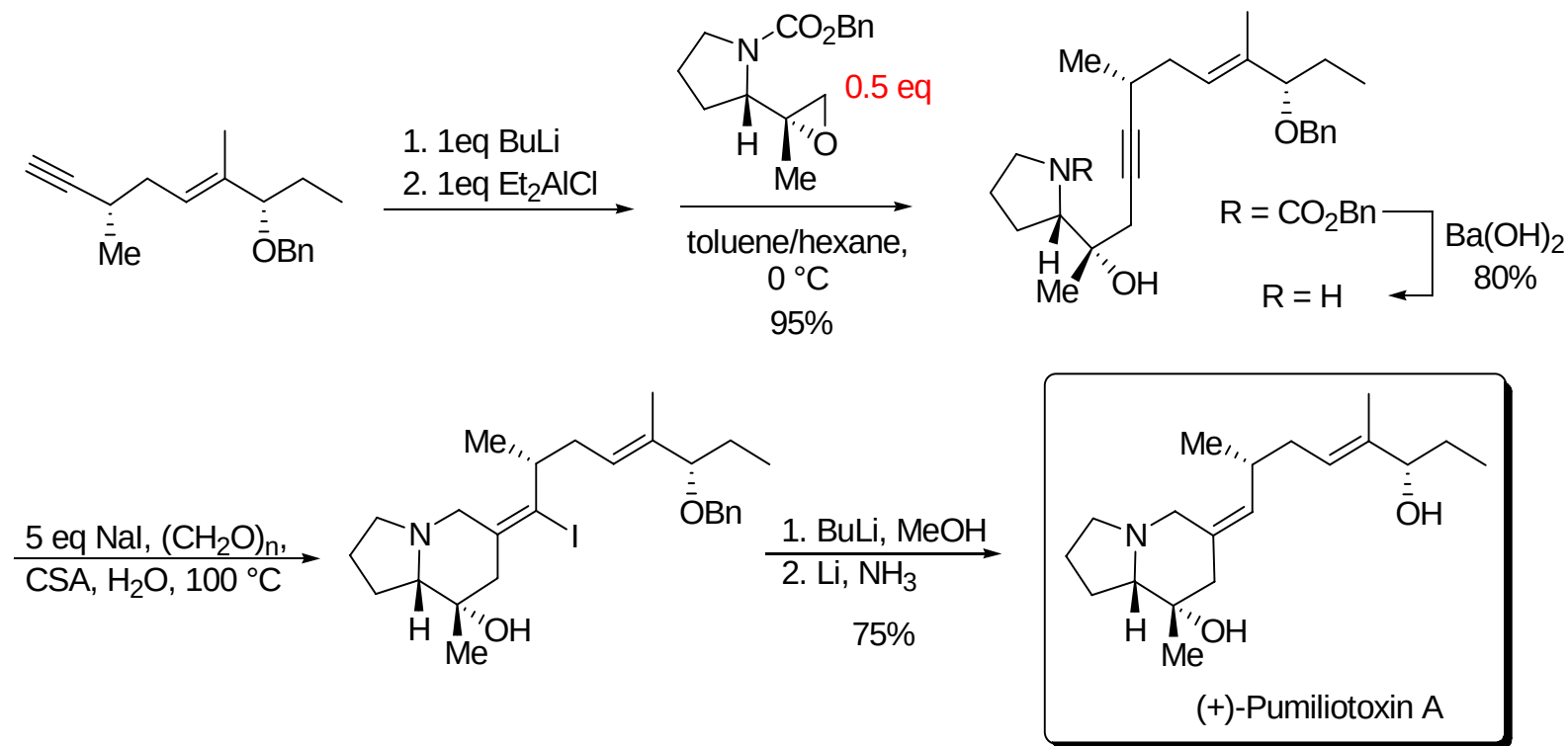
- Examination of Mannich cyclizations of 4-alkynylamines in the presence of reducing agents such as silicon hydrides:



- Mannich cyclizations of alkynes are possible in the presence of external nucleophiles:



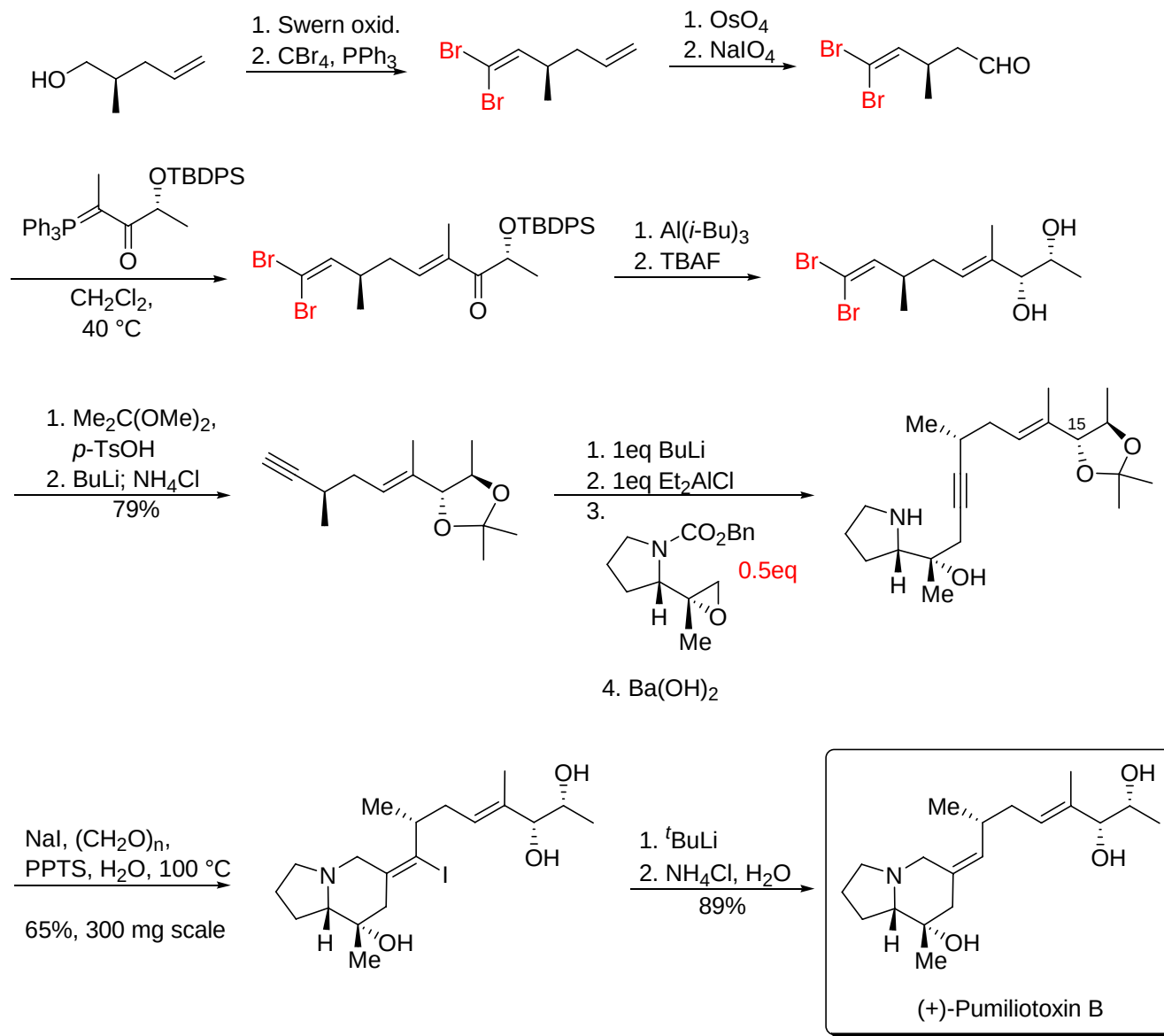
3.B. Efficient Total Synthesis of Pumiliotoxins A and B



The synthesis proceeded in:

- 13 steps and 14.4% overall yield from (S)-2-methyl-1-penten-3-ol
- 8 steps and 8.8% overall yield from *N*-Boc-L-proline

3.B. Efficient Total Synthesis of Pumiliotoxins A and B



• 500 mg had been prepared in a short time

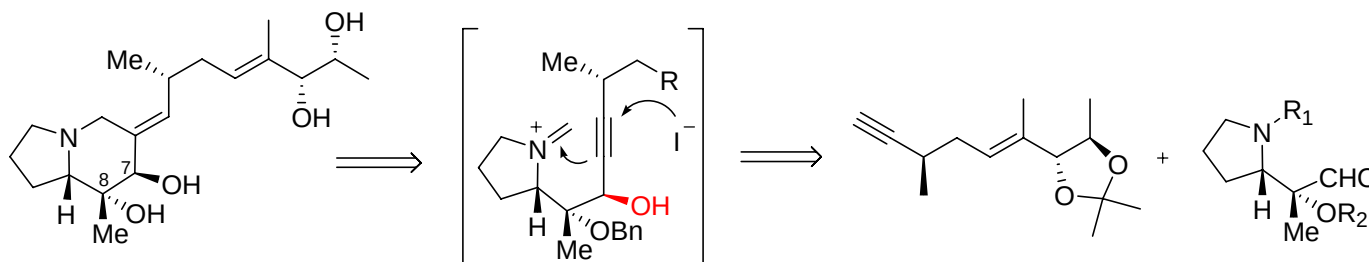
• Overall yield from *N*-Boc-L-proline: 8%

• From (4*S*,5*R*)-4-methyl-5-phenyl-2-oxazolidinone: 10%

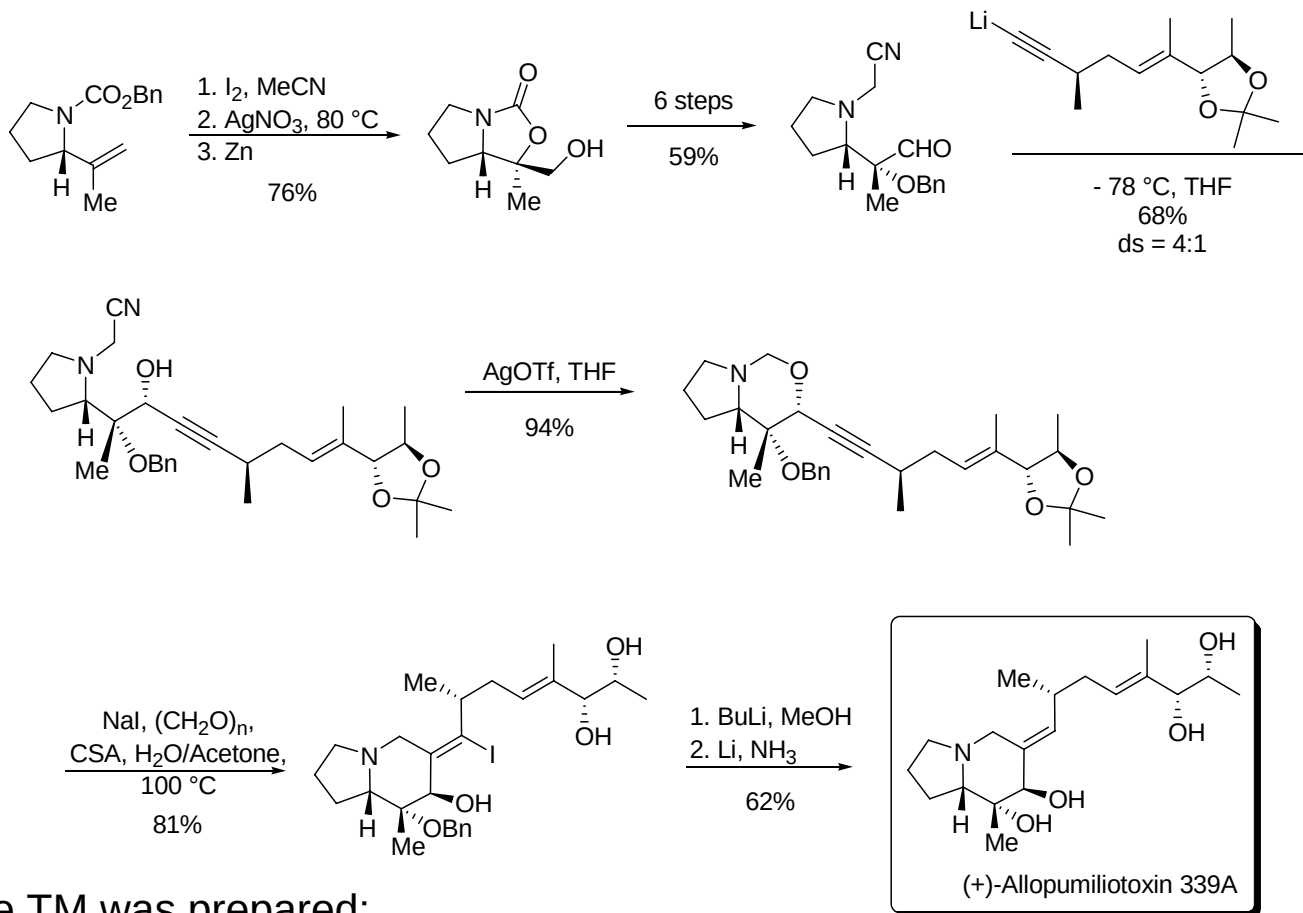
3.C. Total Synthesis of Allopumiliotoxin 339A



- extremely scarce in nature
- chemical synthesis required to fully define the structure
- Allopumiliotoxins containing a β -oriented C(7) hydroxyl group
- examined was the viability of the **iodine-promoted iminium ion – alkyne cyclization** with a substrate that contains a potentially **labile & inductively deactivating** C(7) propargylic hydroxyl group
- to obtain the desired *R* stereochemistry PG's are chosen to favor chelate – organization by C(8) alkoxy substituent in the condensation step



3.C. Total Synthesis of Allopumiliotoxin 339A



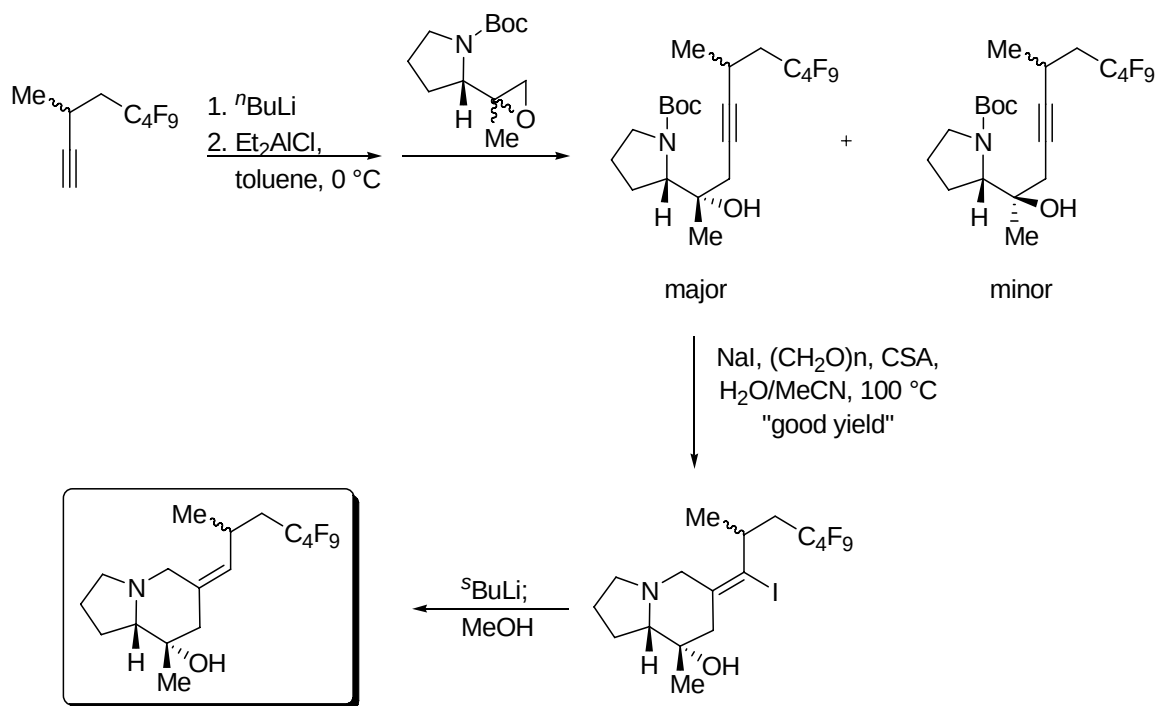
Enantiopure TM was prepared:

- 16 steps and 7.5% yield from *N*-Boc-L-proline
- 16 steps and 6% yield from enantiopure oxazolidine precursor

3.D. A Simplified Procedure for Preparing Pumiliotoxin 251D Analogs



- Synthesis employing mixture of epoxides
- direct cyclization of Boc-protected amino alcohol to iodoalkylideneindolizidine
- Synthesis by DowElanco (joint venture between DowChemical & Eli Lilly, 1989)

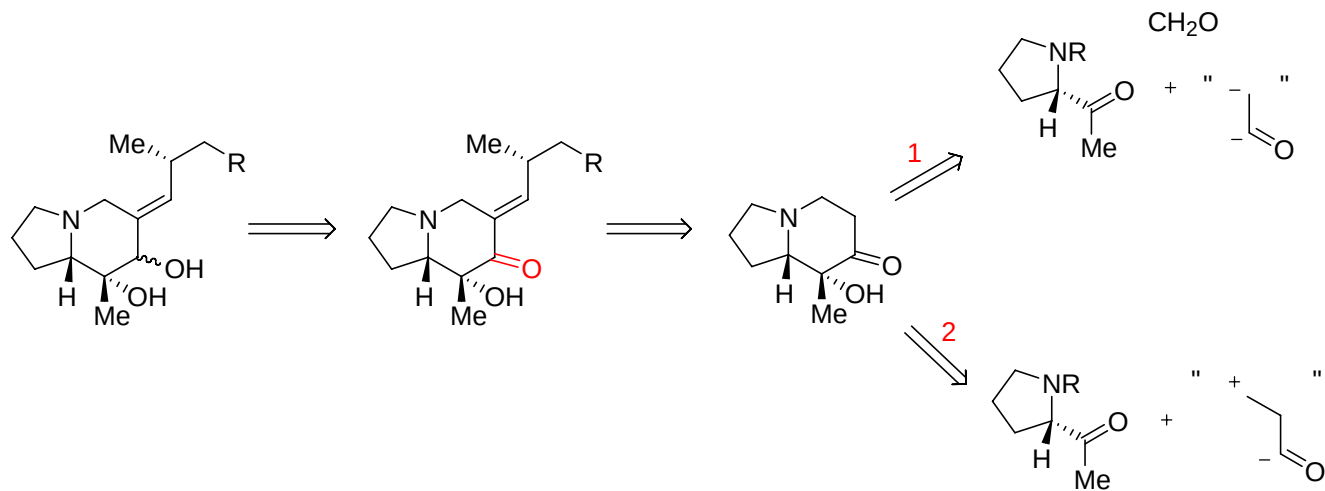


4. Alternative Strategies for Pumiliotoxin A and Allopumiliotoxin Synthesis



- **Aldol attachment** of the alkylidene side chain for Allopumiliotoxins 267A & 339B
 - Synthesis of Allopumilitoxin 339B using **Pd(0) catalysis**
 - Synthesis of Allopumiliotoxins 267A & 339A using **Nozaki-Hiyama-Kishi cyclization**
-

4.1. Aldol attachment of the alkylidene side chain Retro synthetic plan

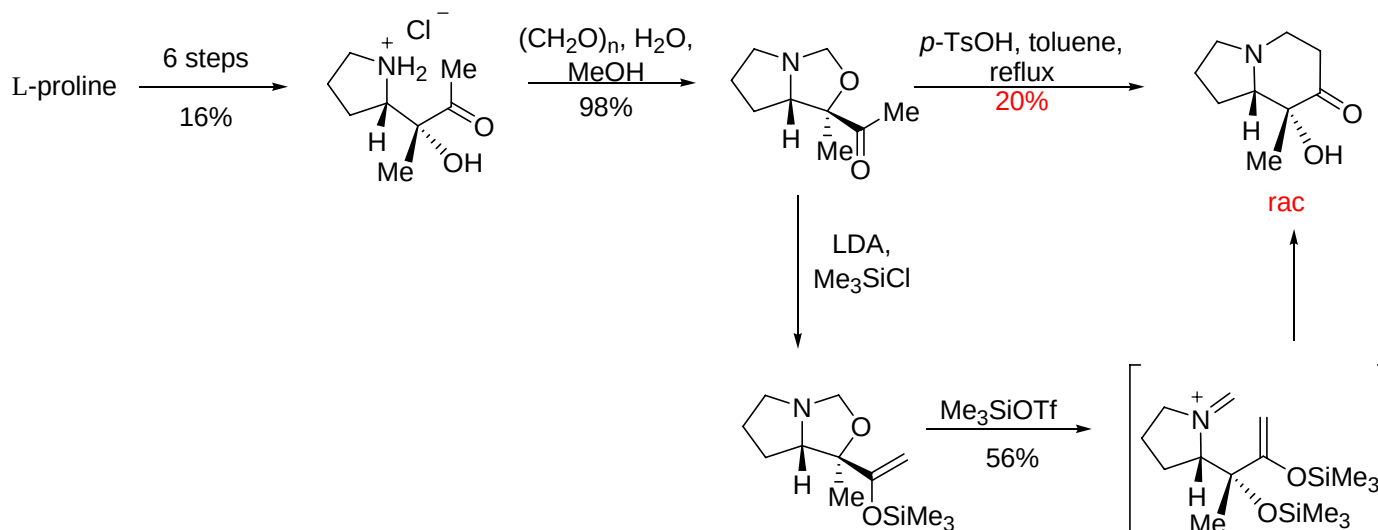


1. Addition of a 2 carbon acyl anion equivalent to a protected 2-acetylpyrrolidine followed by Mannich ring closure
2. Addition of a 3 carbon nucleophile and elaboration of the piperidine ring by *N*-alkylation

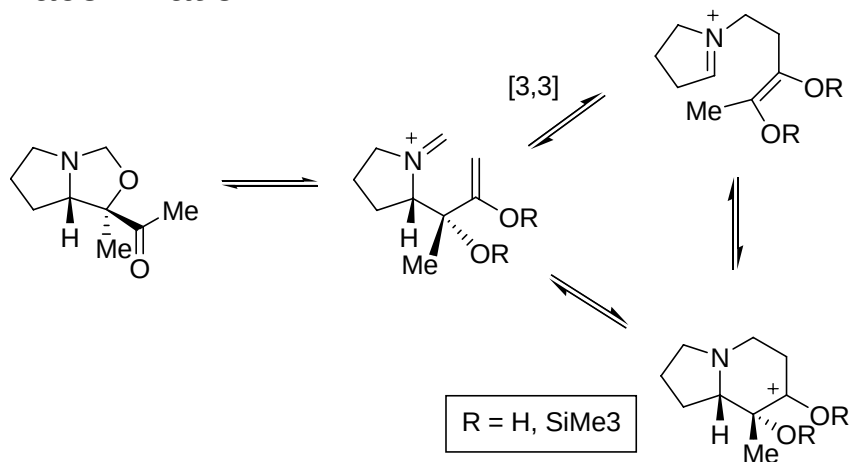
4.1 Total synthesis of Allopumiliotoxin 267A & 339B



Synthesis of indolizidinone:



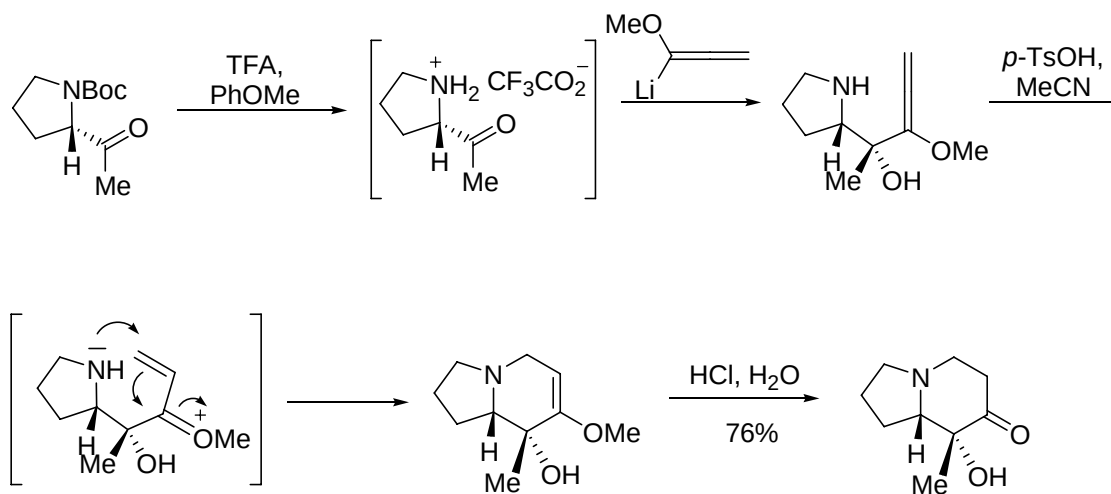
Rationalization of racemization:



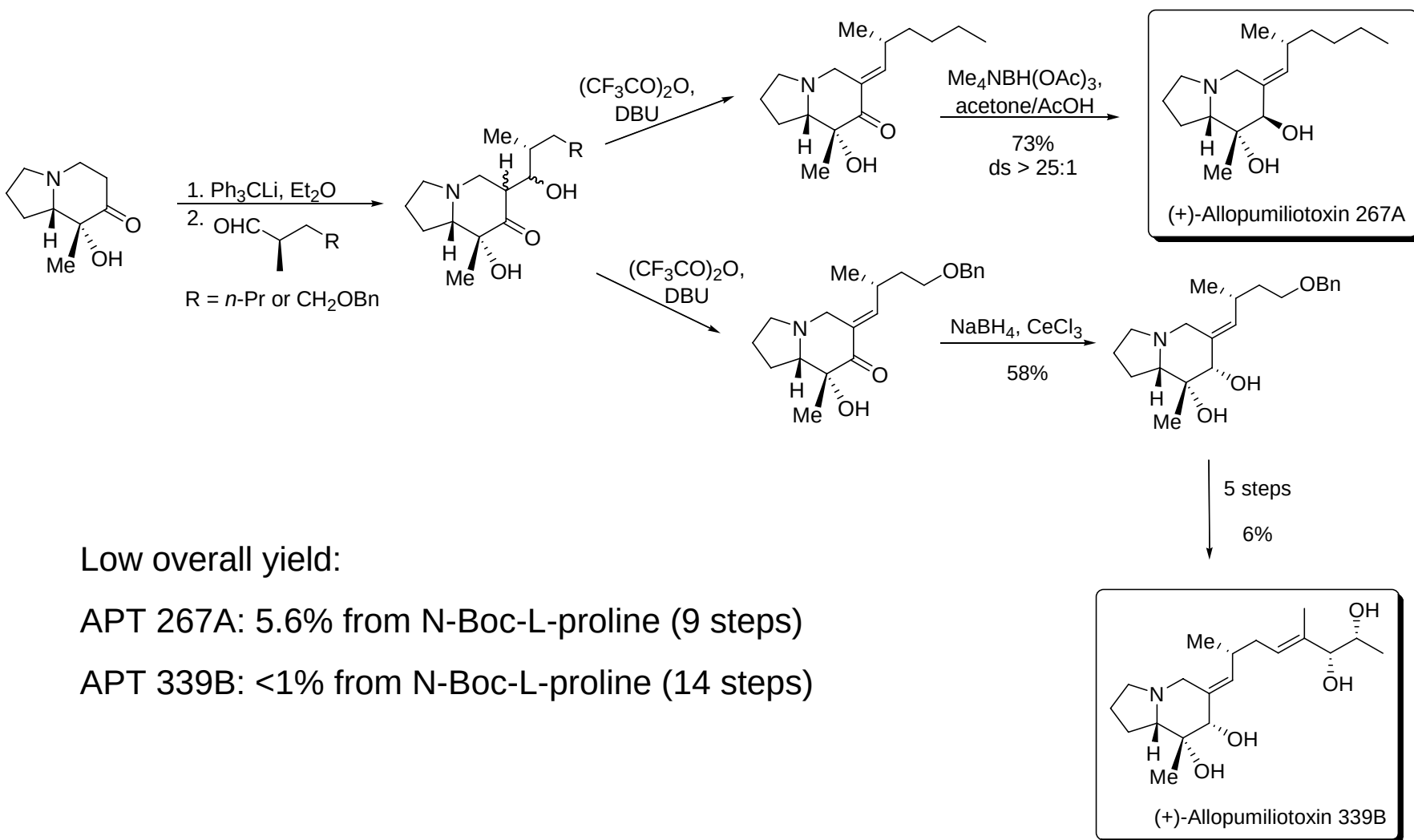
4.1. Total synthesis of Allopumiliotoxin 267A & 339B



Successful synthesis of the core:



4.1 Total synthesis of Allopumiliotoxin 267A & 339B



Low overall yield:

APT 267A: 5.6% from N-Boc-L-proline (9 steps)

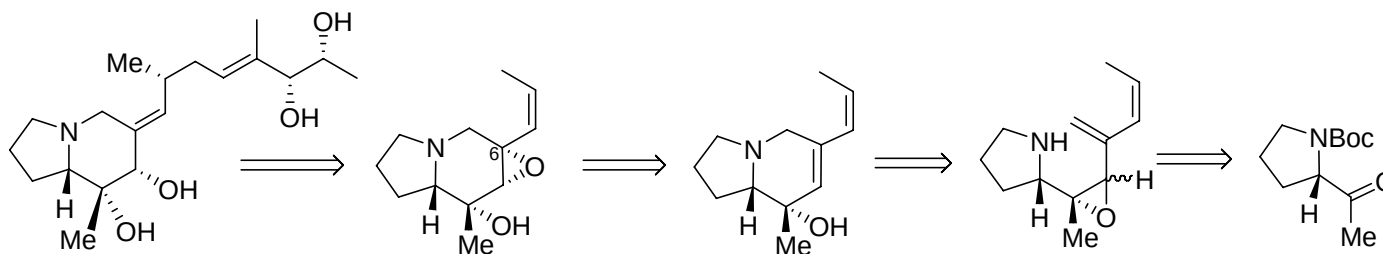
APT 339B: <1% from N-Boc-L-proline (14 steps)

4.2. Synthesis of Allopumilitoxin 339B using Pd(0) catalysis

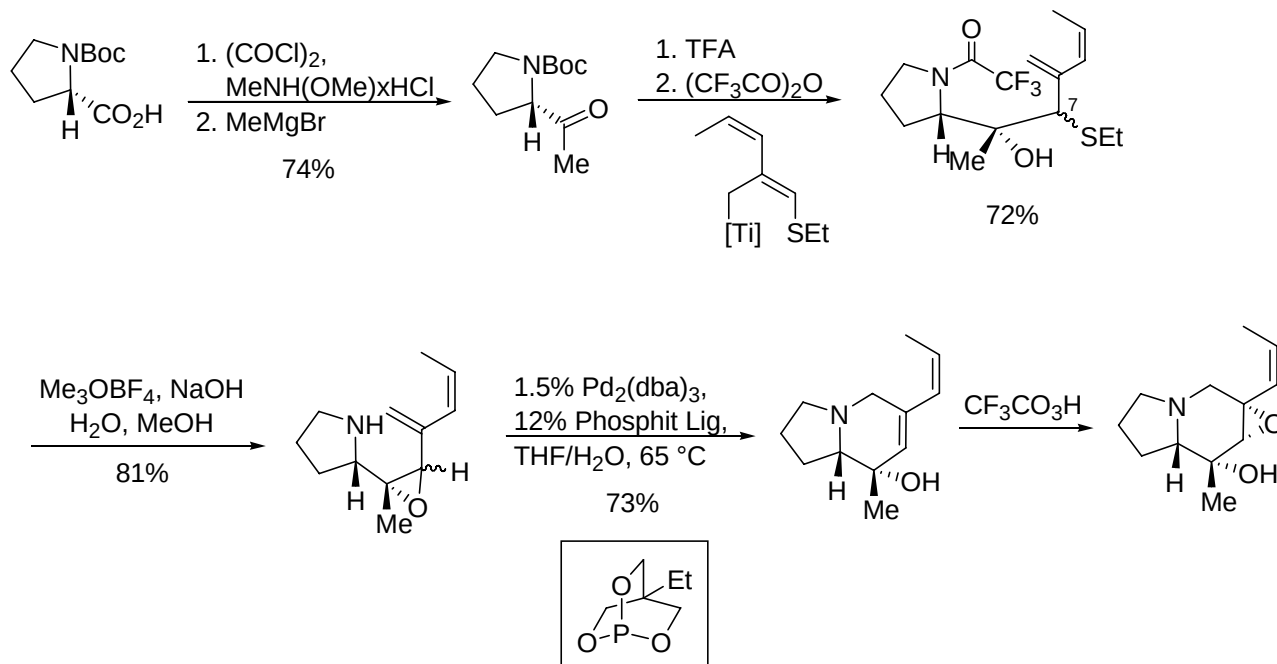
Retrosynthesis & strategy



- Pd(0) mediated cyclization of vinyl epoxide as key step
- 1st example of a Pd(0)-mediated **6-endo** cyclization
- control of both the C(11) stereochemistry & the alkylidene geometry through intermolecular Pd(0)-mediated allylic alkylation

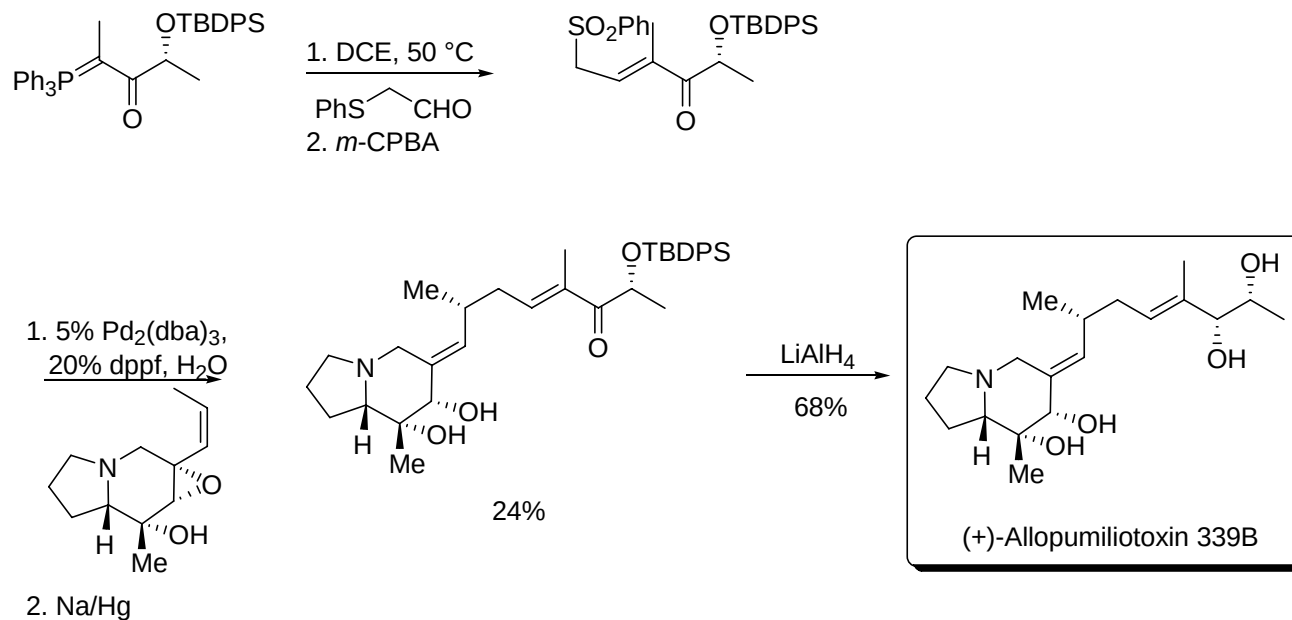


4.2. Synthesis of Allopumilitoxin 339B using Pd(0) catalysis



4.2. Synthesis of Allopumilotoxin 339B using Pd(0) catalysis

Completion of the synthesis



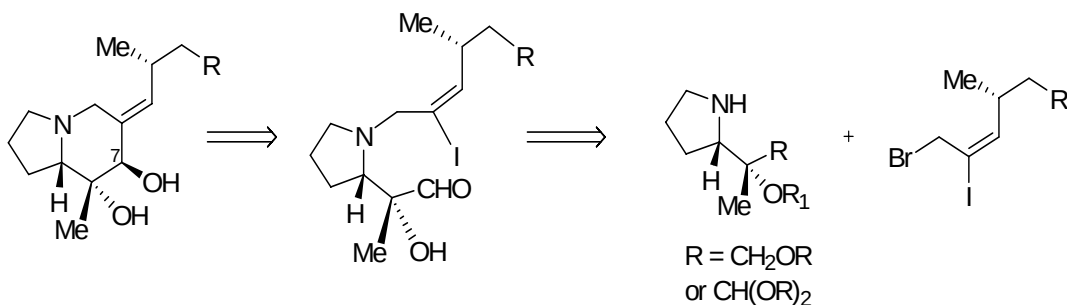
Mission accomplished in:

- only 11 steps from *N*-Boc-L-proline, but <3% yield !
- Due to the low yielding of the bimolecular π -allylpalladium alkylation step

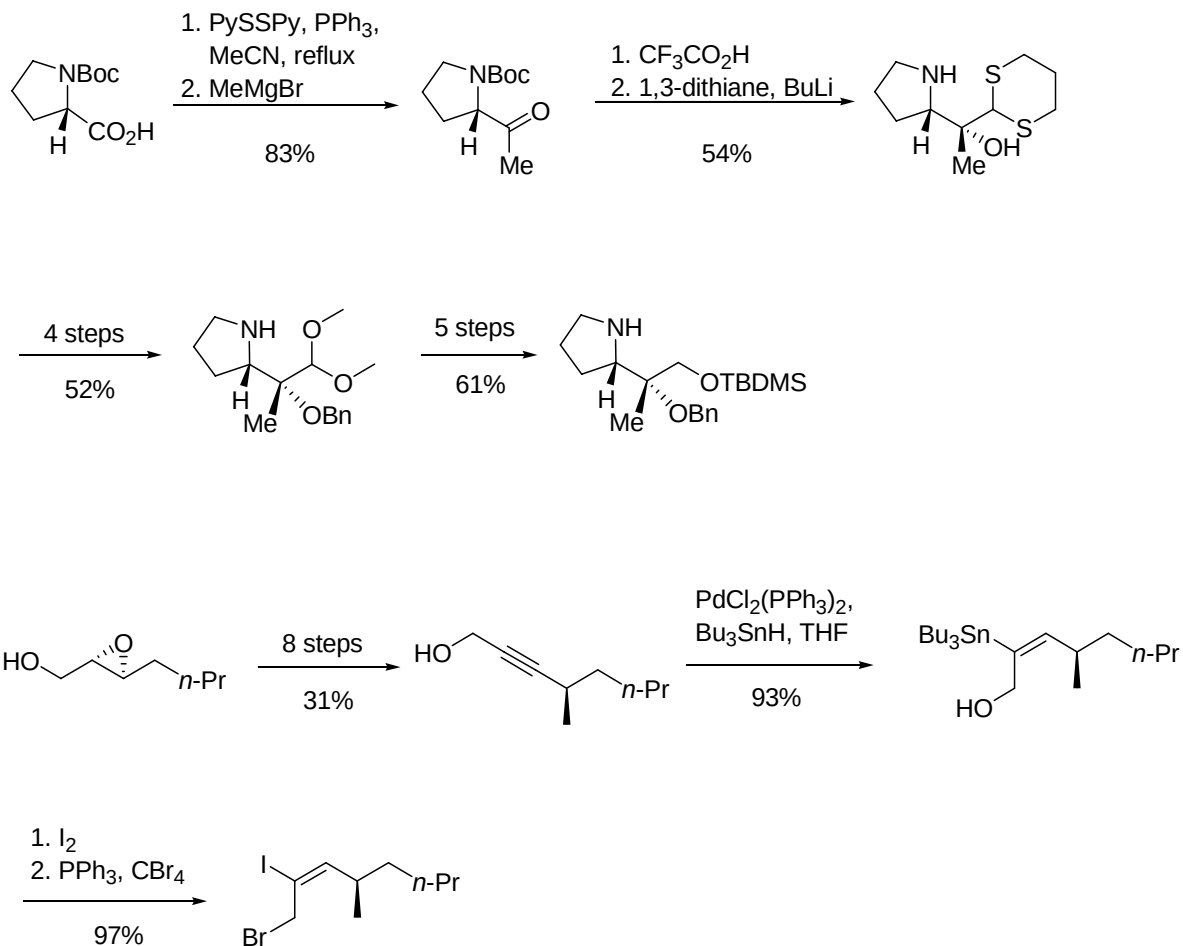
4.3. Synthesis of Allopumiliotoxins 267A using Nozaki-Hiyama-Kishi cyclization



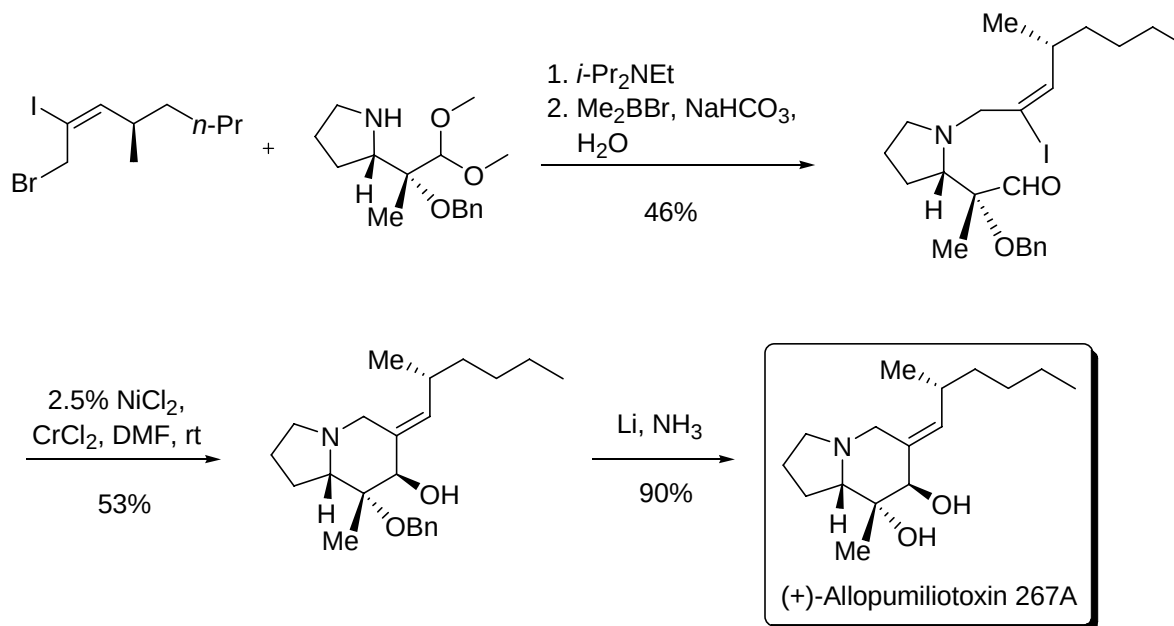
- NHK cyclization generates:
 - indolizidine core
 - (*E*)-alkylidene side chain
 - establishes stereochemistry at C(7)
-
- Retrosynthetic analysis:



4.3. Preparation of the pyrrolidine ring & of the side chain for (+)-Allopumiliotoxin 267A



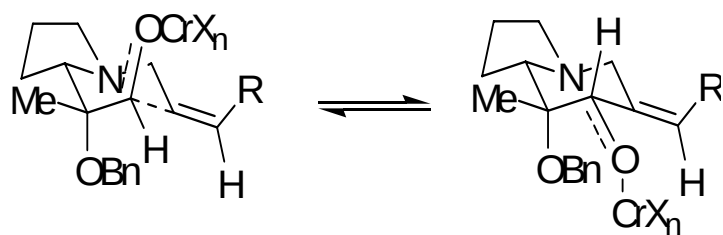
4.3. Coupling of the fragments & chromium – nickel – mediated cyclization



Overall yield:

- 5.1% (12 steps) from *N*-Boc-L-proline
- 6.2% (15 steps) from epoxy alcohol

4.3. Explanation of stereoselection at C(7)



5. Conclusions



- a number of innovative syntheses have been developed
- syntheses played an important role in defining the full stereostructure of these amphibian alkaloids
- iminium ion – vinylsilane & iminium ion – alkyne cyclization routes are sufficiently efficient that 50 – 500 mg of the natural toxins & gram quantities of the simpler congeners can be prepared
- numerous analogs have contributed substantially to defining structure-activity relationships
- no really new strategies had been developed in the last few years



Thank You !!

