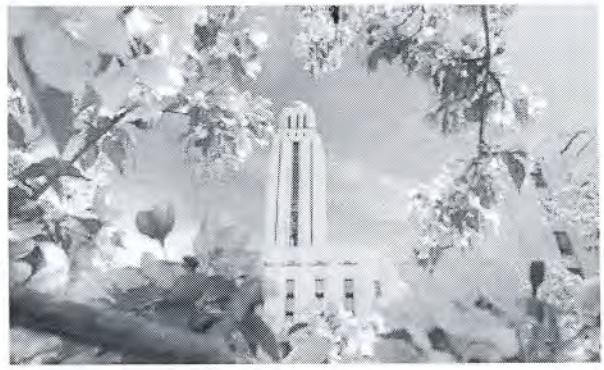
"Incentives for New Methodology through Natural Product Synthesis"

Stephen Hanessian
University of Montreal



IASOC
ISCHIA ADVANCED SCHOOL OF ORGANIC CHEMISTRY

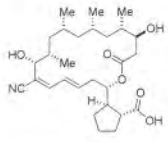
Ischia Porto
September 18-23, 2004

LIVING THROUGH A TOTAL SYNTHESIS

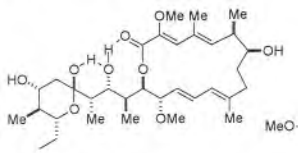
A. Choice of target molecule
B. Perceptive powers and seeing through the mind's eye
C. Emergence of a strategy
D. Generation of a synthesis plan

E. Execution
F. Endurance
G. Contribution to science
H. Recognition
I. Lasting value

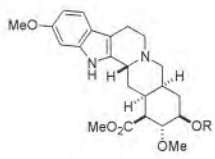
- Relevance
- Heuristics, open-eyed serendipity, and personal bias
- Individual prowess, creativity
- Attention to detail, possible fixation (beware!)
- Efficiency, practicality
- What price synthesis?
- New concepts, reactions, reagents, etc.
- Fame, fortune, legacy
- Coworker training



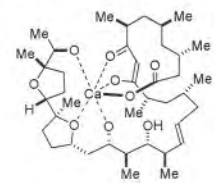
Borreledin
(2003)



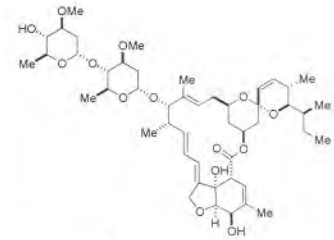
Bafilomycin A_1
(2001)



Reserpine
(1997)



Ionomycin Ca salt
(1990)



Avermectin B_{1a}
(1986)

SYNTHESIS PLANNING AND KEY-STEP METHODOLOGIES

Totally new methods
(Archimedes approach)

Known methods
(Nike approach)

New Methods
(Kekulé approach)

Improved, known methods
(Avis approach)

In-house methods
(Sinatra approach)

REAL LIFE SCENARIOS

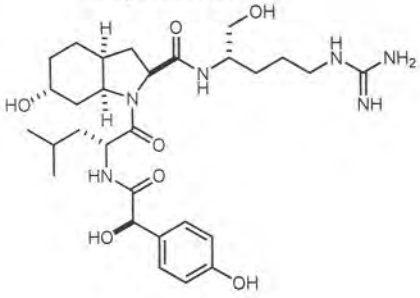
- Synthesis completed; constants match… All's well. ☺
- Synthesis completed; constants do *not* match… All's *not* well. ☹
- Synthesis completed; natural product structure/stereochemistry needs revision! … All's well that ends well. ☺ ☺ ☺
- Synthesis almost completed; problems with last steps…Maybe serious. ☹
- Synthesis strategy changed… Optimism is a necessity. ☺
- Synthesis abandoned, deferred, or forgotten… ☹ ☹ ☹

- First Synthesis
  - Second Synthesis
    - Third Synthesis
      - N^{th} Synthesis?

Bioactive Compounds Produced by Cyanobacteria

- Isolated from the blue-green algae *Microcystis aeruginosa*
- Thrombin and trypsin inhibitors

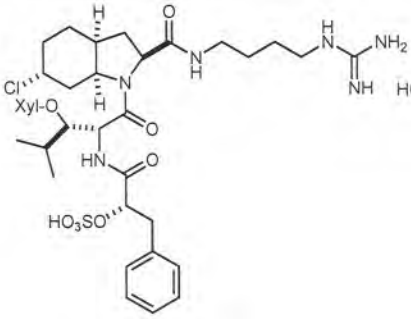
Aeruginosin 298-A



Trypsin IC_{50} 1.0 μM
Thrombin IC_{50} 0.5 μM

Microcystis aeruginosa

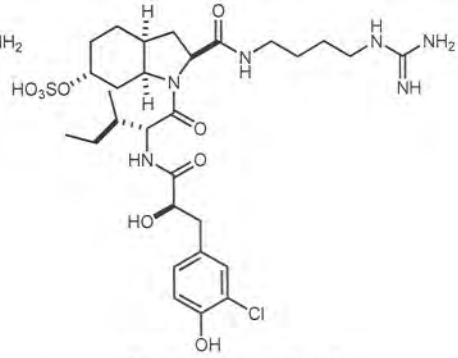
Aeruginosin 205-A



Trypsin IC_{50} 0.07 μM
Thrombin IC_{50} 0.1 μM

Oscillatoria agardhii

Aeruginosin 98A

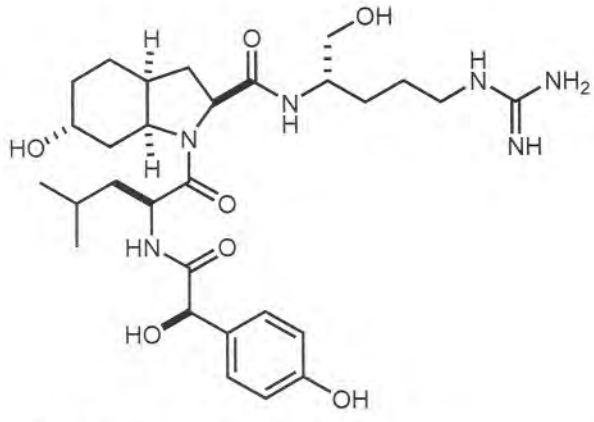


Trypsin IC_{50} 0.6 μM
Thrombin IC_{50} 7.0 μM

Microcystis aeruginosa

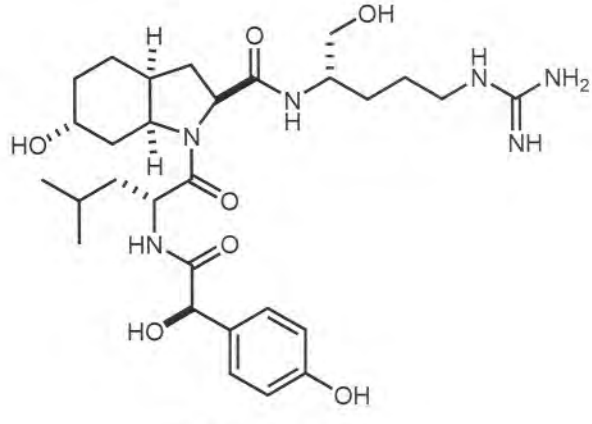
Reviews: Leusch, H. *et al Curr. Med. Chem.* **2002**, *9*, 179.
Murakami, M *et al Tetrahedron* **1999**, *55*, 10971
Namikoshi, M.; Rinehart, K.L. *J. Indust. Microbiol.* **1996**, *17*, 373.

Aeruginosin 298-A: Configurational Revision Through Total Syntheses



From X-ray complex with thrombin

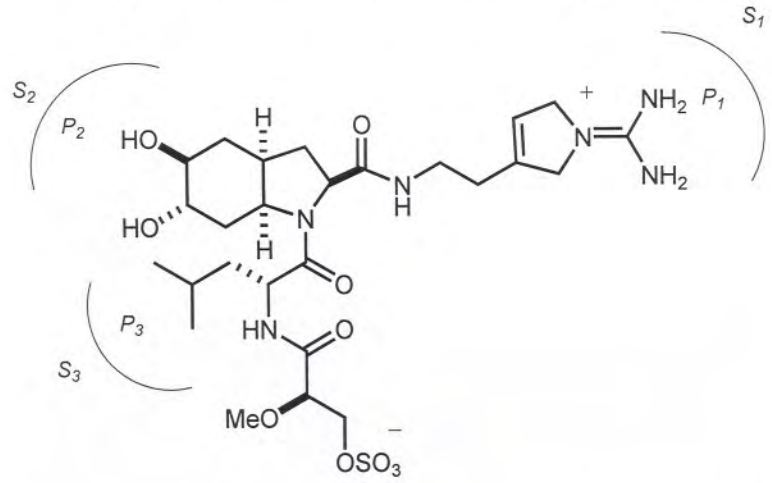
Tulinsky, A. *et al J. Am. Chem. Soc.* **1998**, *120*, 597.



From synthesis

Bonjoch, J. *et al J. Am. Chem. Soc.* **2000**, *122*, 11248.
Bonjoch, J. *et al Chem. Eur. J.* **2001**, *7*, 3446.
Wipf, P. *et al Org. Lett.* **2000**, *2*, 4213.

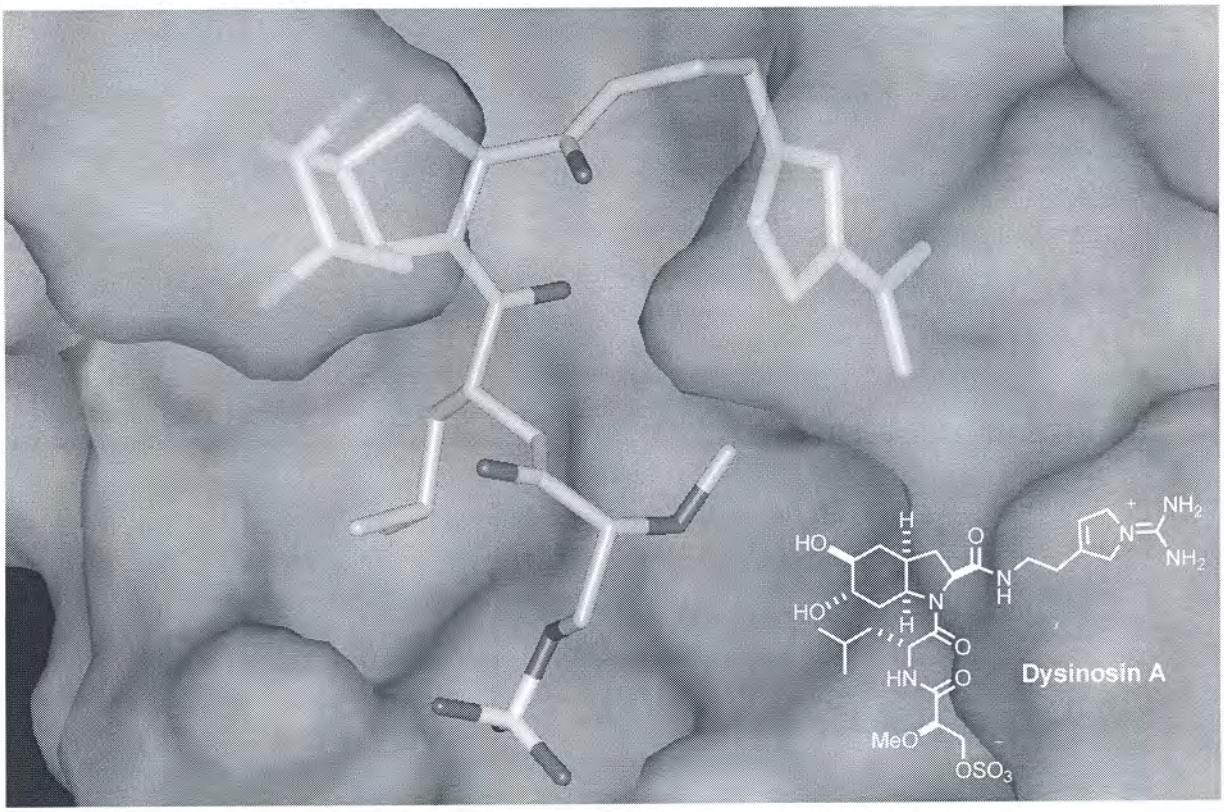
Dysinosin A: A New Aeruginosin



- Isolated from a new genus and species of sponge of the family Dysidea sp, Lizard Island, North Queensland, Australia
- Potent inhibitor of blood coagulation cascade Factor VIIa (Ki = 108 nM)
- Inhibitor of serine protease thrombin (Ki = 432 nM)
- Structure determined by 1H, 13C NMR
- Absolute stereochemistry from an X-ray co-crystal structure with thrombin

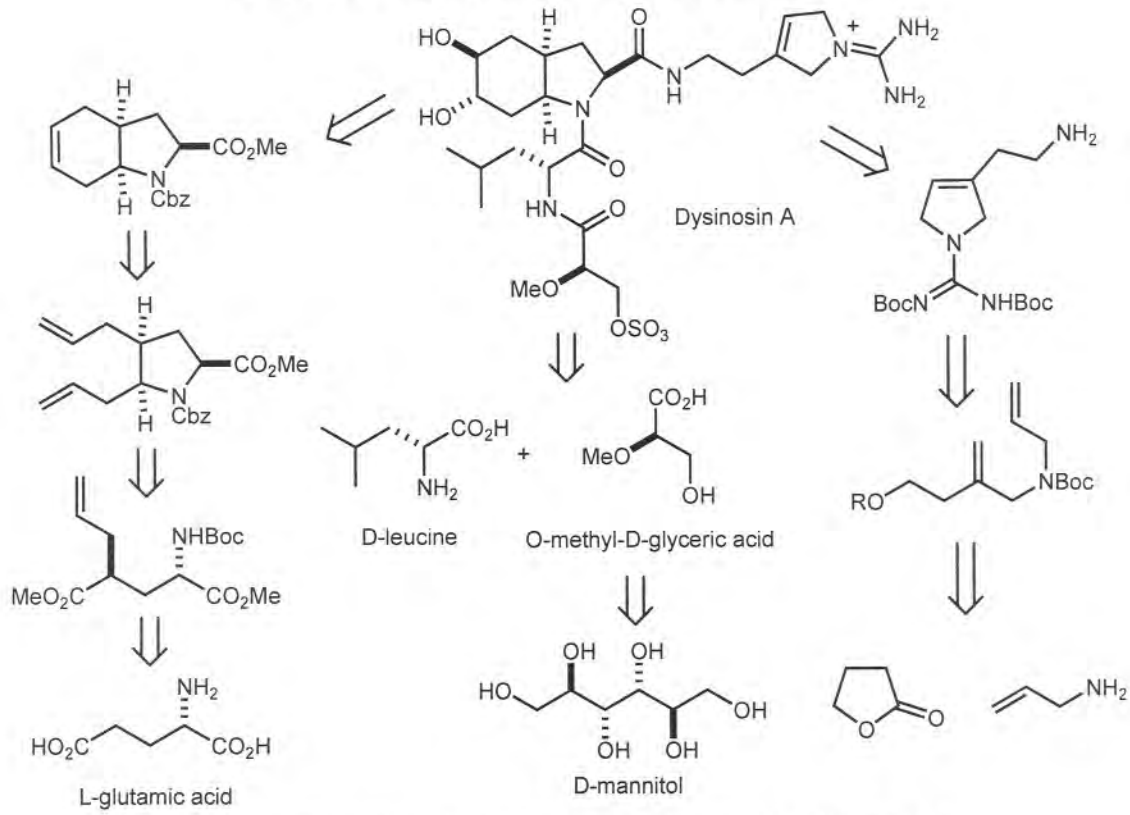
Carroll, A. R.; Pierens, G.; Fechner, G.; Almeida Leone, P.; Ngo, A.; Simpson, M.; Hooper, J. A.; Bostrom, S.-L.; Musil, D.; Quinn, R. J.; J. Am. Chem. Soc. 2002,124, 13340. AstraZeneca R&D Griffith University, Brisbane, Australia.

X-ray Co-crystal Structure of Dysinosin A with Thrombin



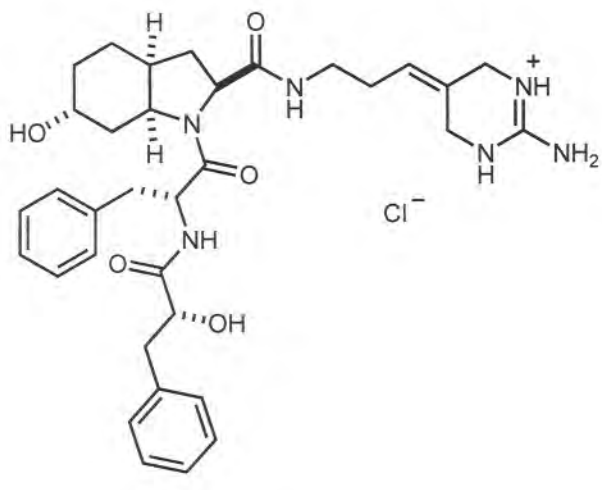
Carroll, A.-R.; Quinn, R. *et al. J. Am. Chem. Soc.* **2002**,*124*, 13340

Disconnections of Dysinosin A



Hanessian, S. *et al J. Am. Chem. Soc.* **2002**, *124*, 13342

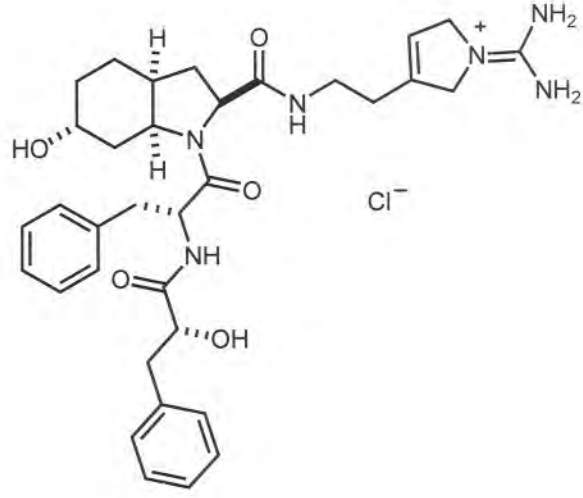
New Aeruginosins from *Oscillatoria agardhii*



Presumed Oscillarin

Boehringer Mannheim

WO 96/11941



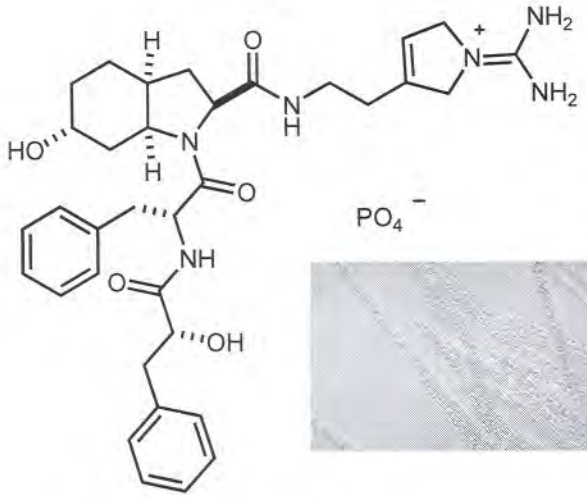
Oscillarin (D-Pla-D-Phe-L-Choi-Adc)

Boehringer Mannheim

WO 97/21725; U.S. 2002/0026034

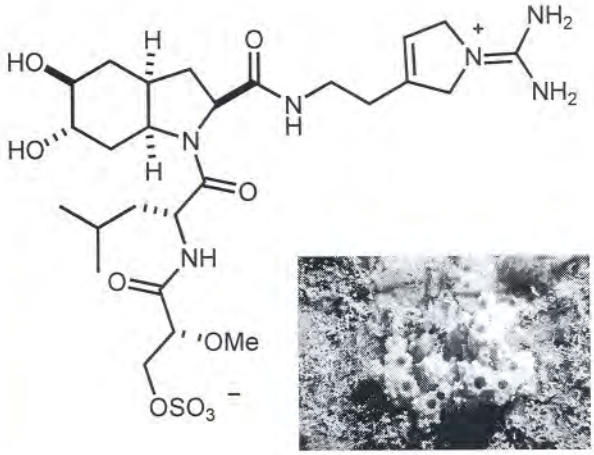
Oceans Apart…

Oscillarin



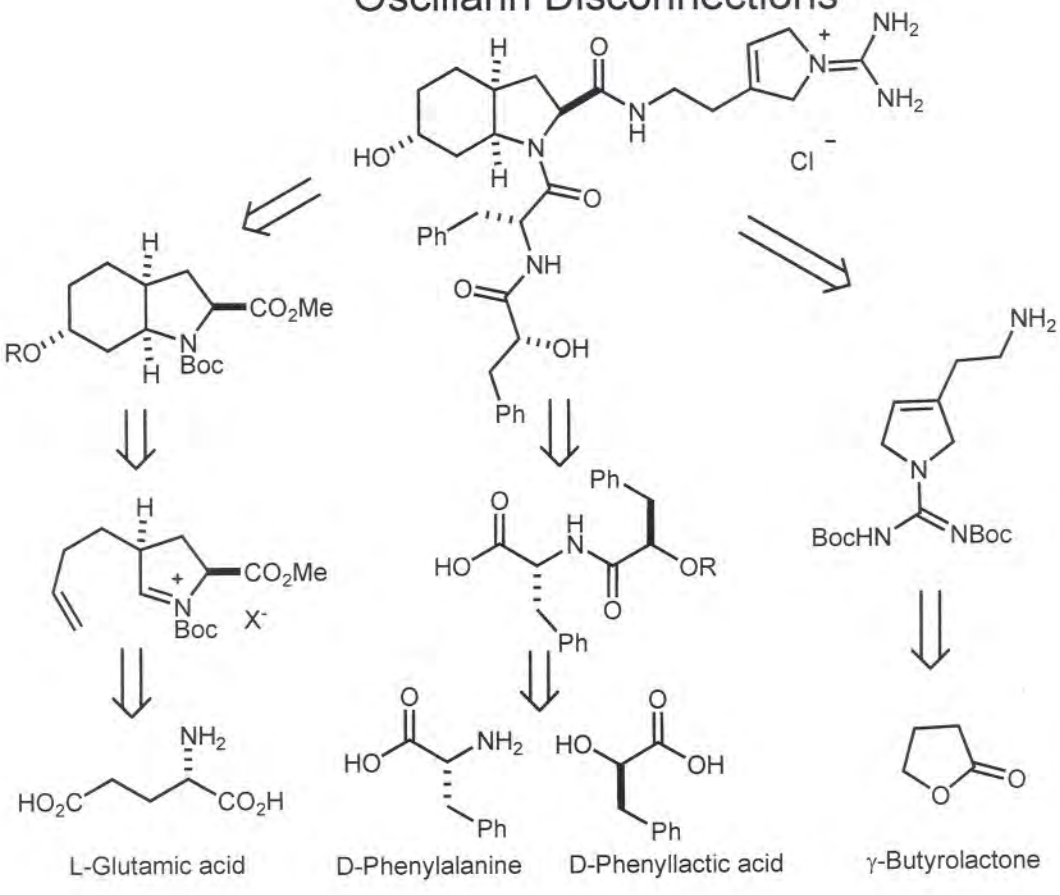
- Isolated from the marine algae *Oscillatoria agardhii*
- Algae culture (strain B3.82) from the University of Göttingen, Germany
- Co-crystal with trypsin

Dysinosin A

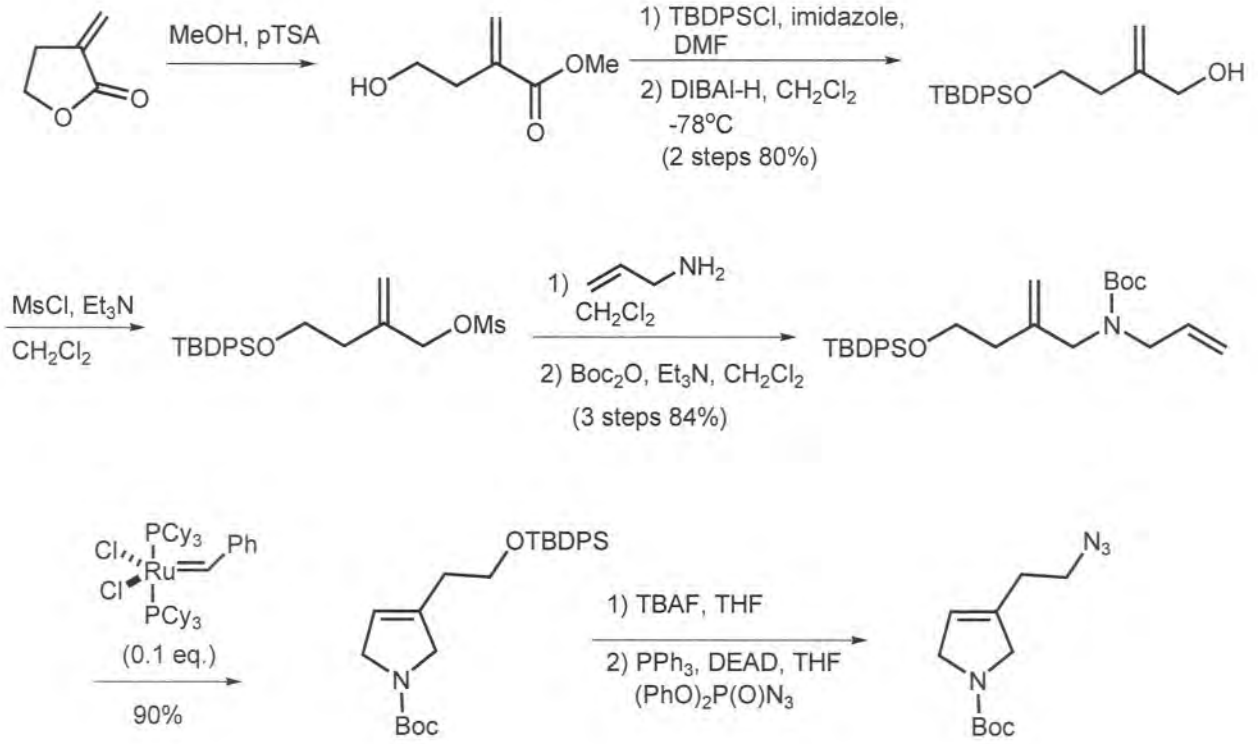


- Isolated from a marine sponge of the family *Dysidea sp.*
- Lizard Island, Australia

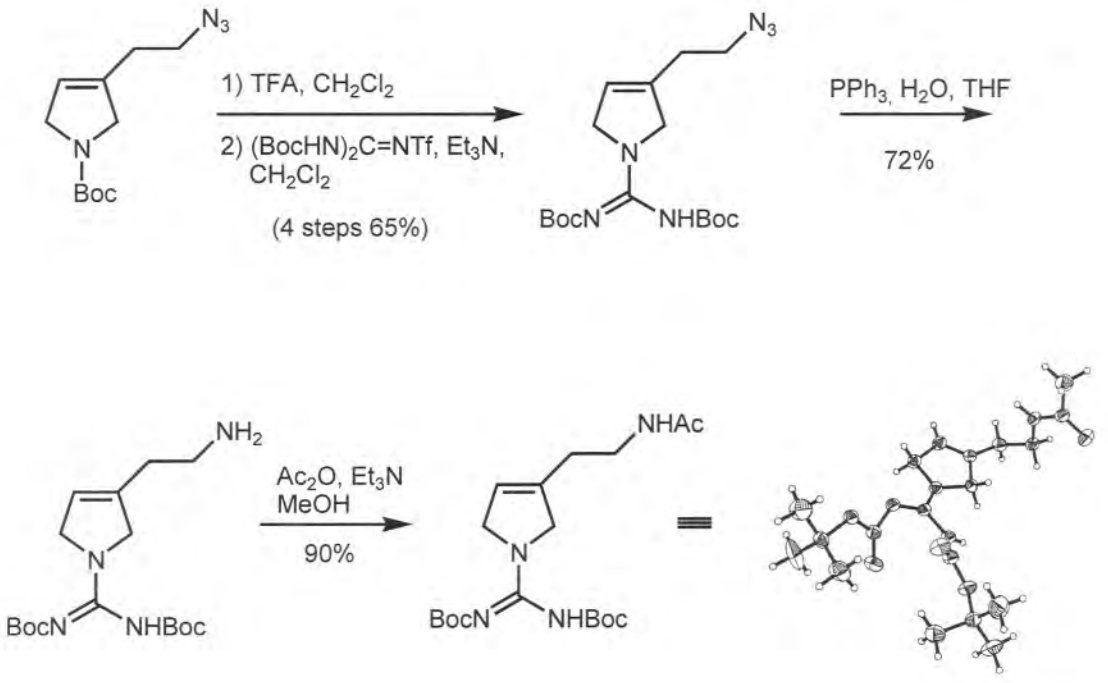
Oscillarin Disconnections



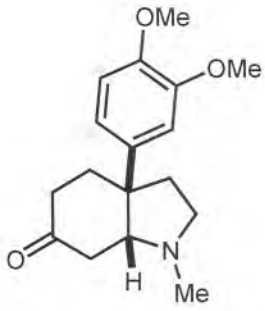
The Δ-3-Pyrroline Ring



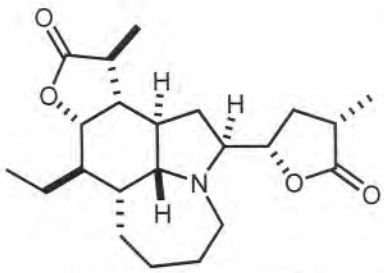
The Δ-3-Pyrroline Ring



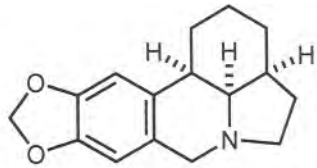
Octahydroindoles and Perhydroquinolines in Natural Products



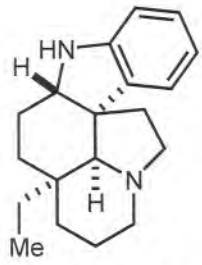
Sceletium alkaloids
mesembrine



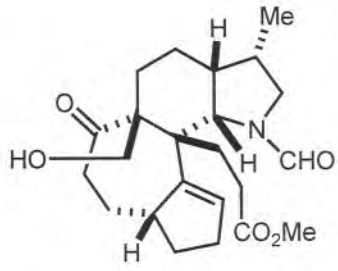
Stemona alkaloids
tuberostemonine



Amaryllidaceae alkaloids
γ-lycorane

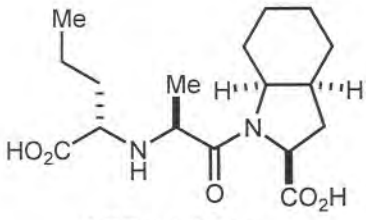


Aspidosperma alkaloids
aspidospermidine

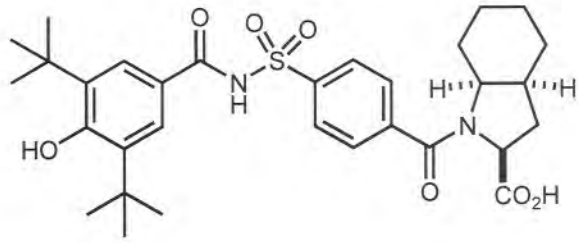


Daphniphyllum alkaloids
daphniglaucin C

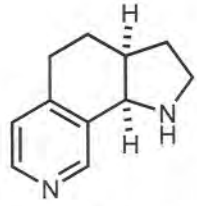
Medicinal Chemistry



ACE inhibitors
perindoprilat



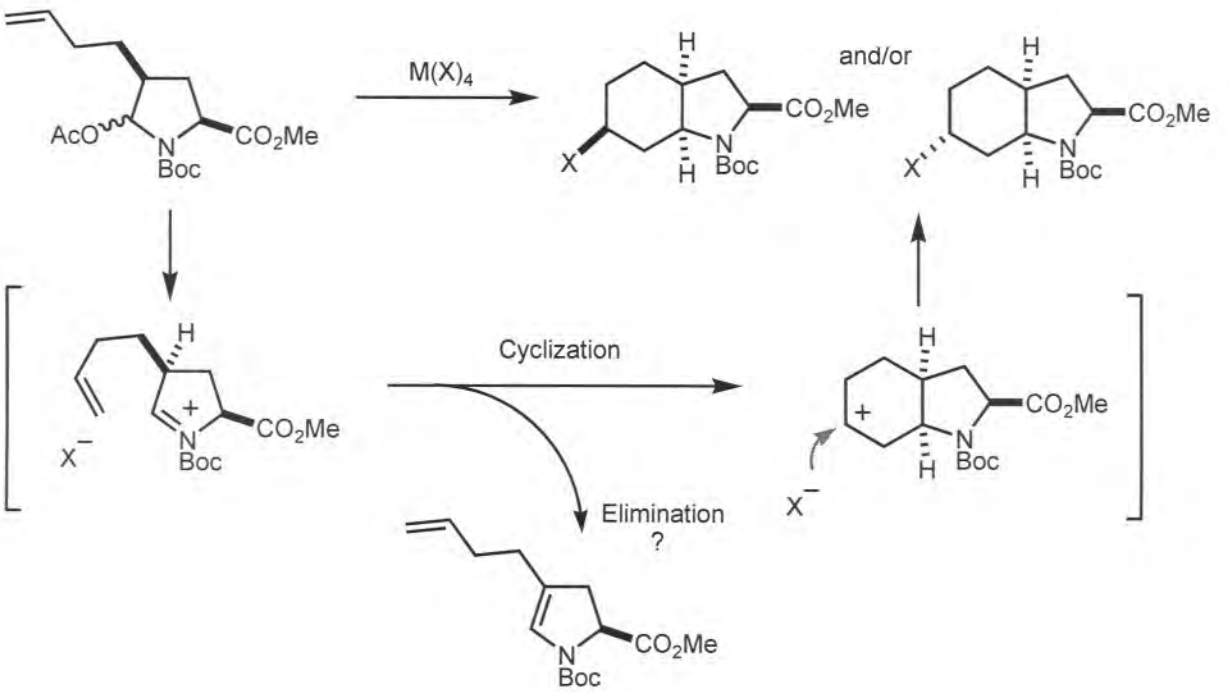
Elastase inhibitors



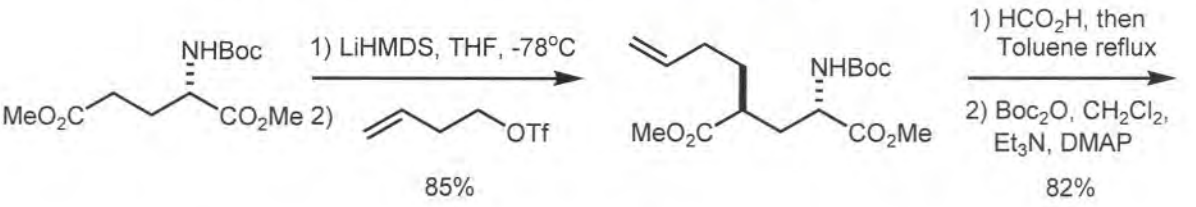
Nicotine analogues

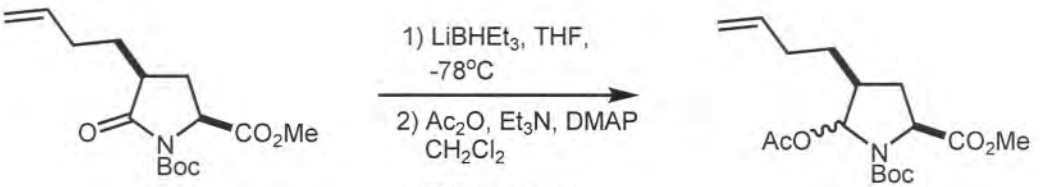
Azonia-Prins Type Synthesis of Octahydroindole 2-Carboxylic Acids

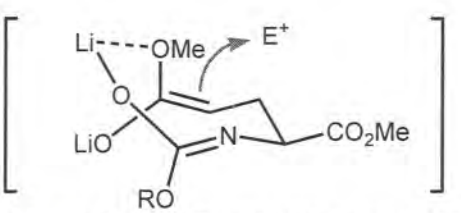
A Proposal:



Preparation of the Hemiaminal Precursor

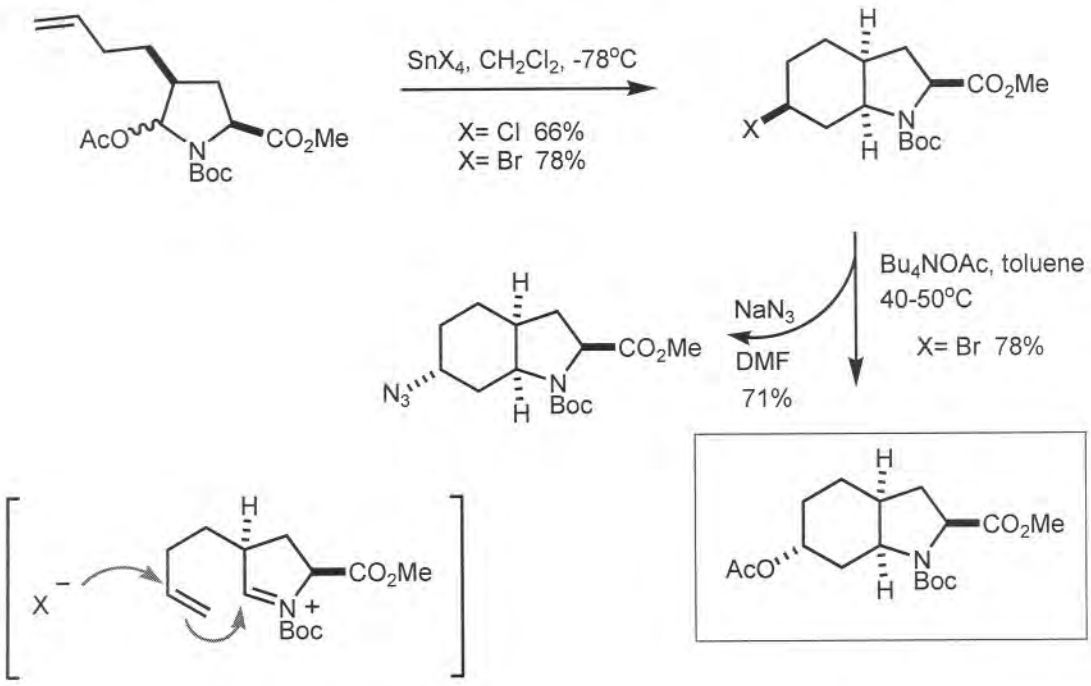






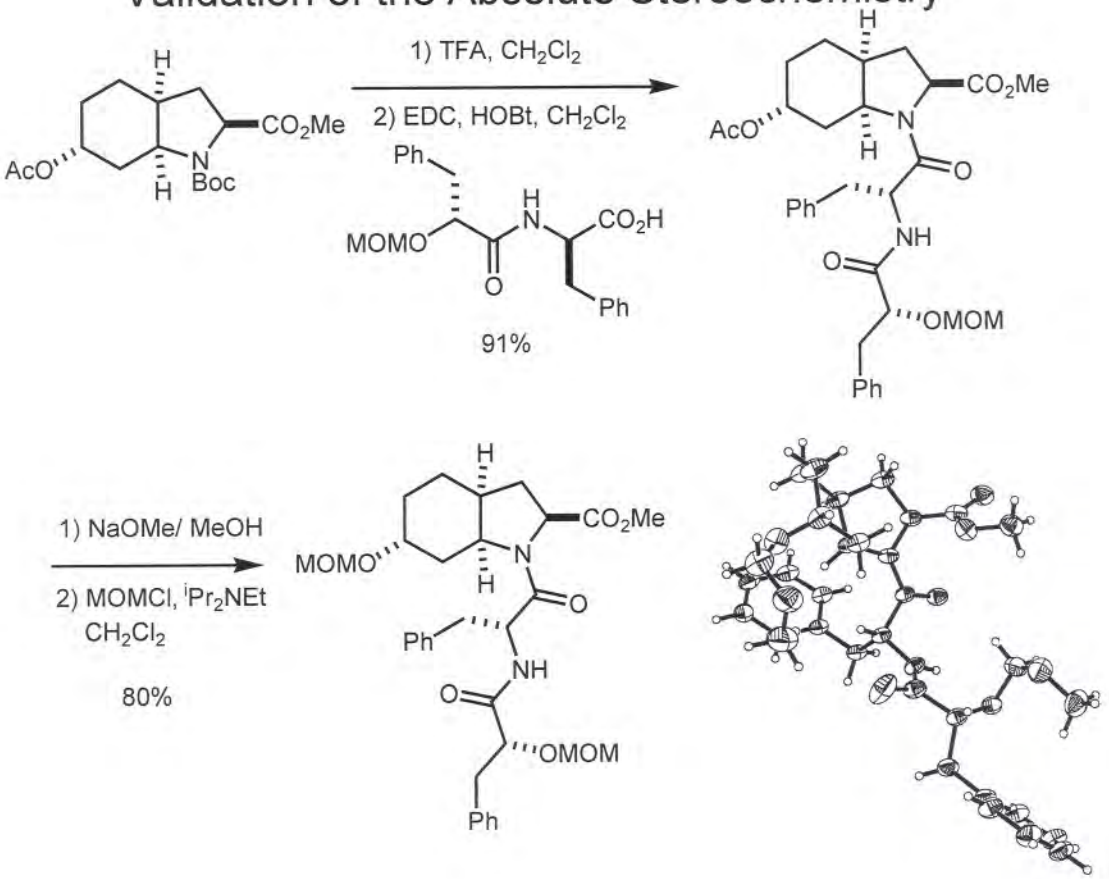
Hanessian, S.; Margarita, R. *Tetrahedron Lett.* **1998**, *39*, 5887

The L-Choi Moiety

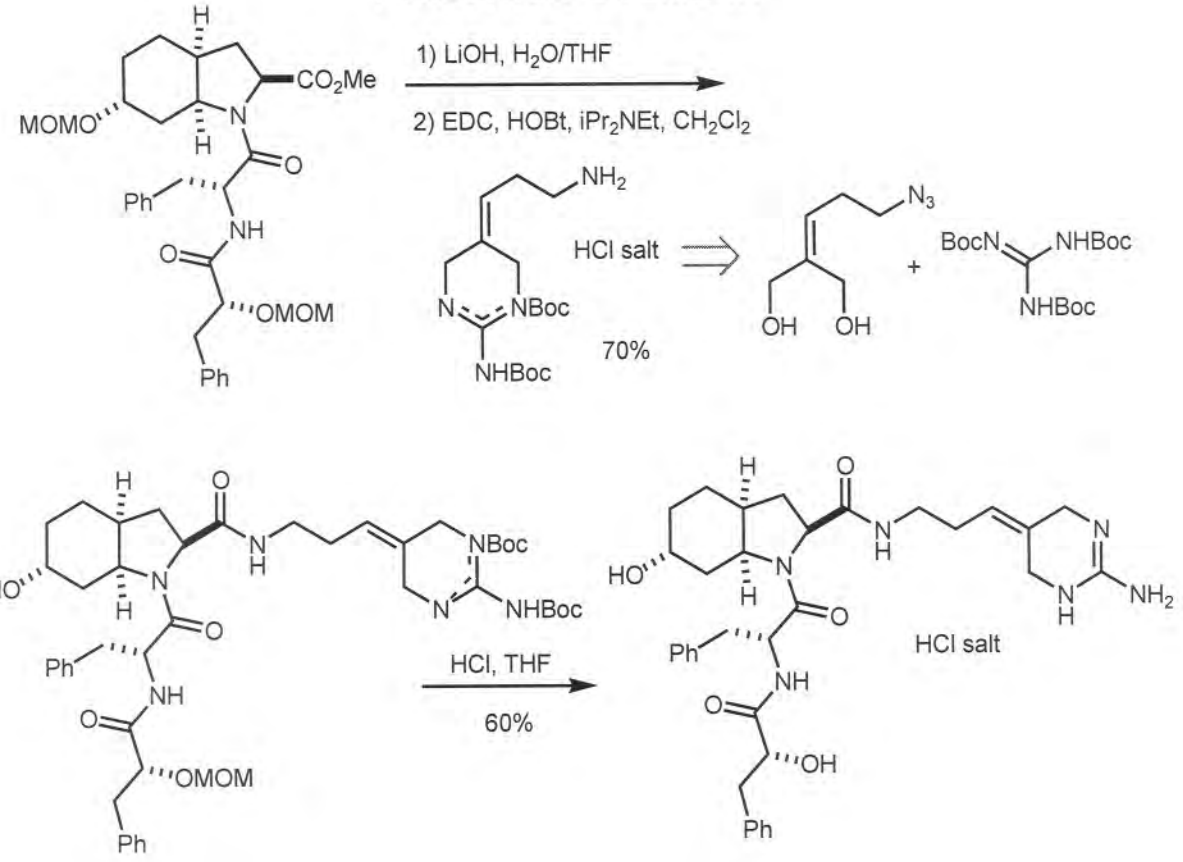


9 steps from L-glutamic acid (36% overall yield)

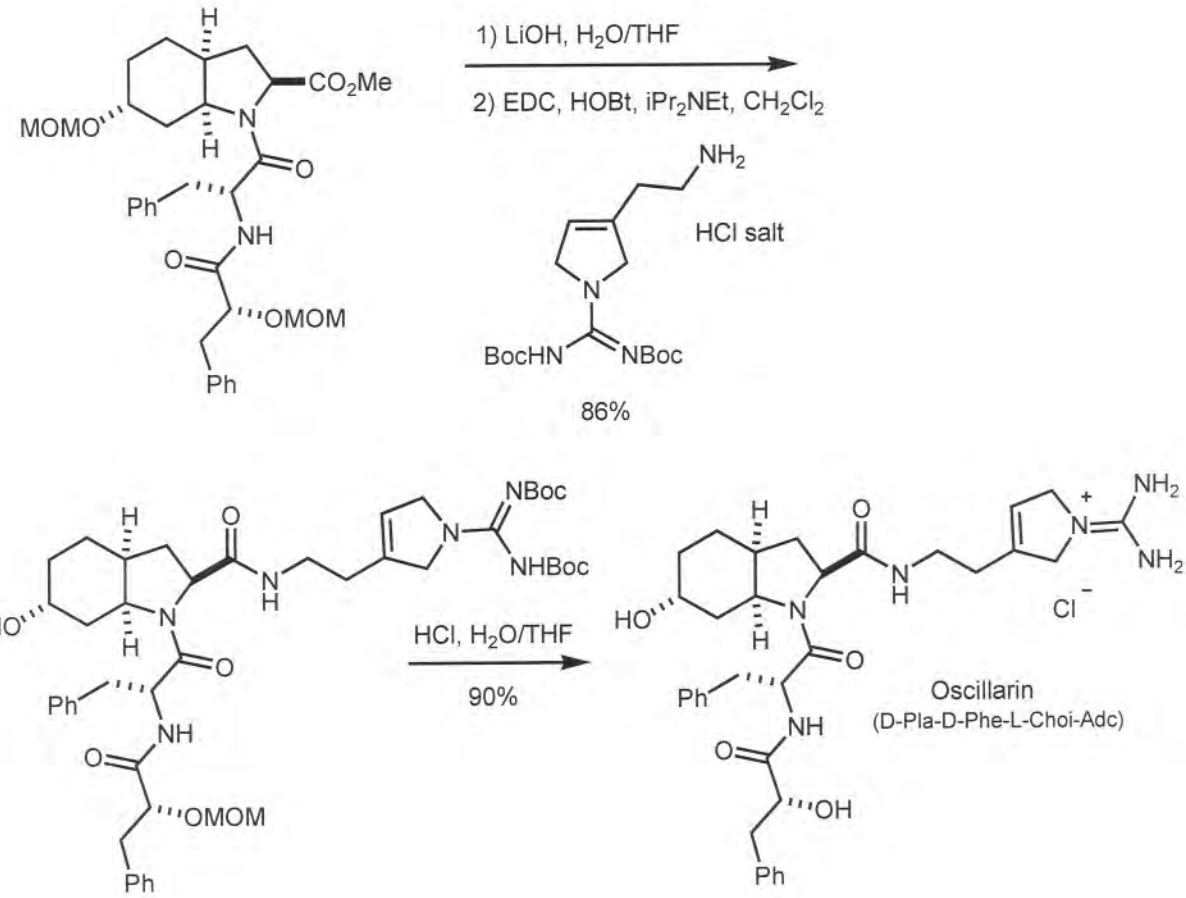
Validation of the Absolute Stereochemistry

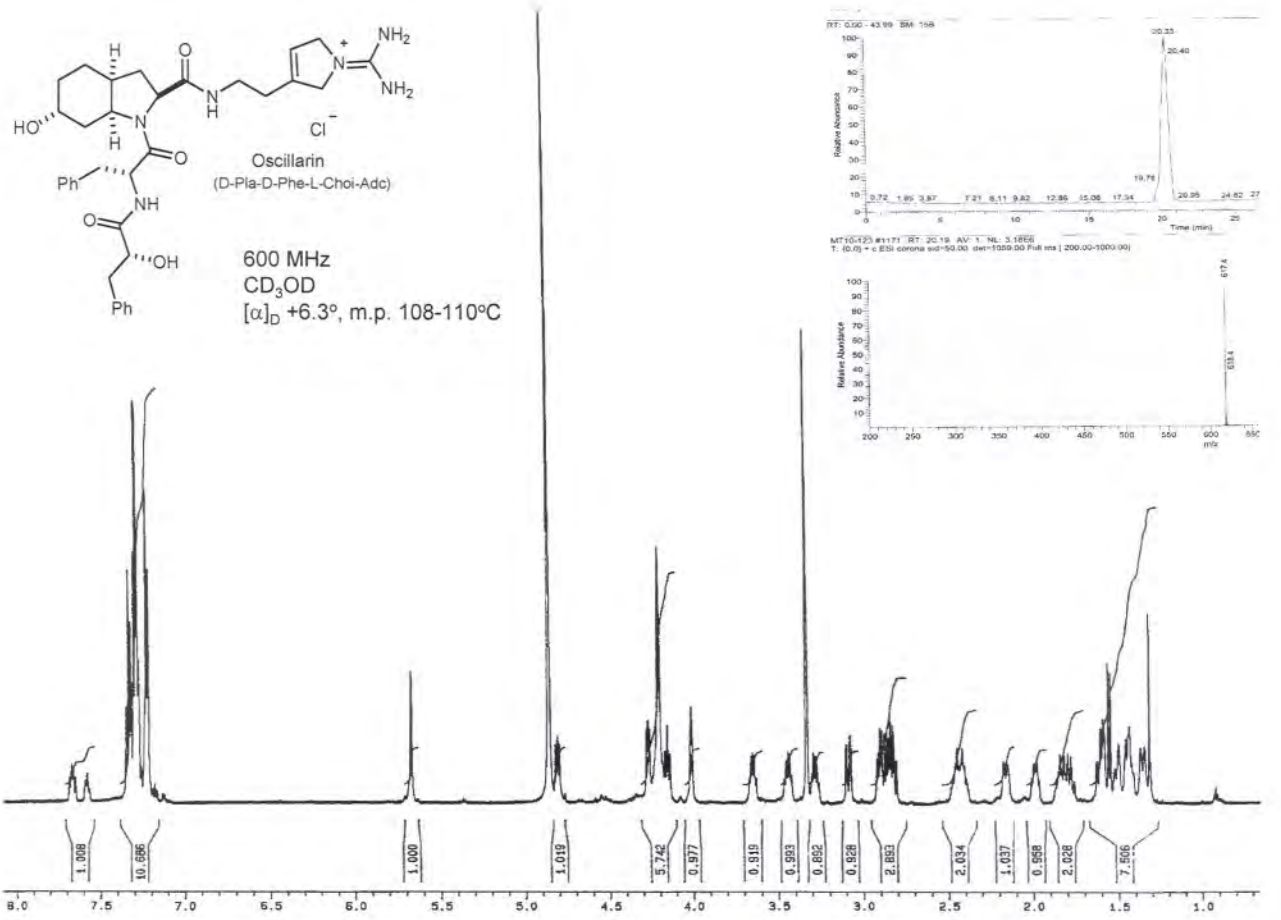


Presumed Oscillarin

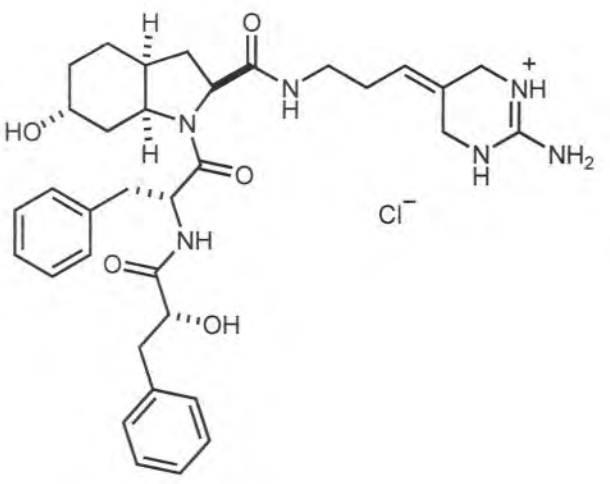


The *Real* Target



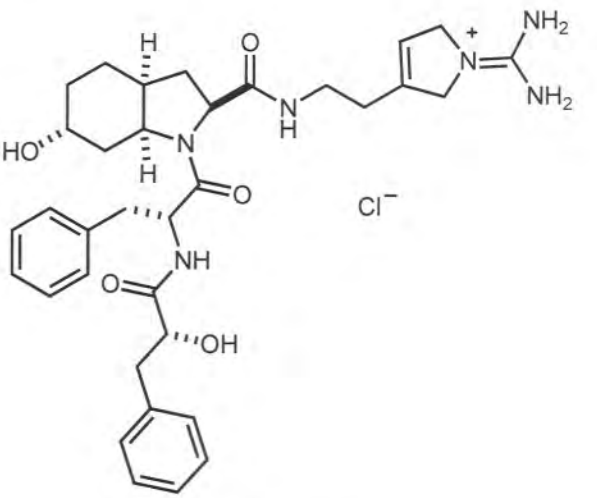


Biological Activity



Synthetic Presumed Oscillarin

IC_{50} thrombin > 44 μM



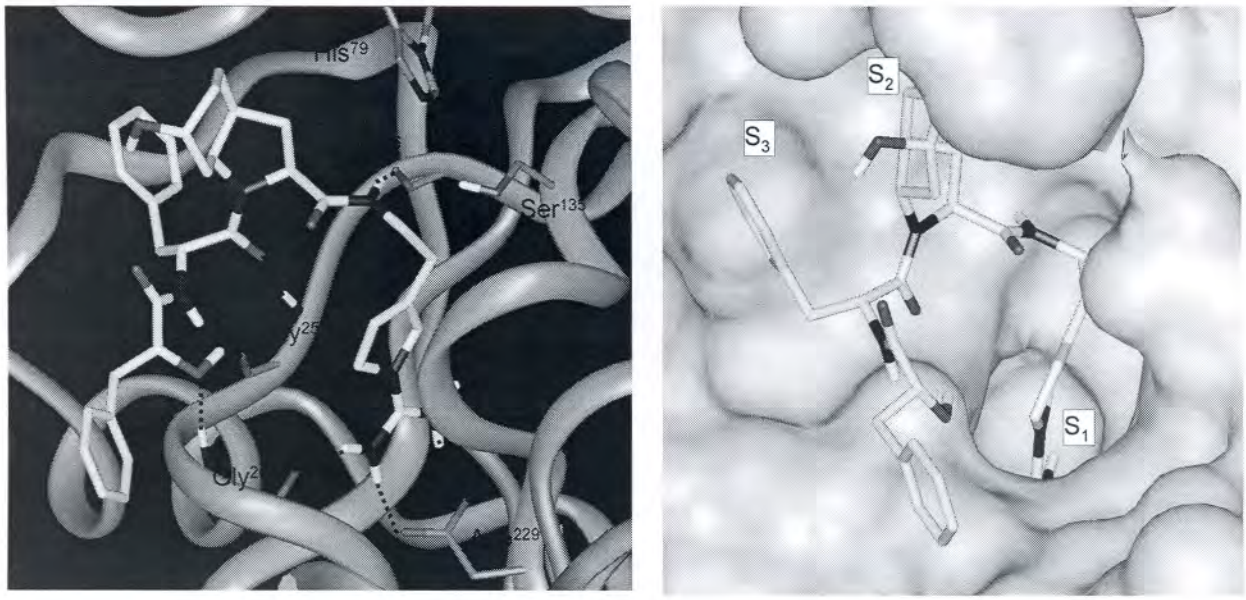
Synthetic Oscillarin

IC_{50} thrombin = 28 nM

Courtesy: AstraZeneca, Mölndal, Sweden

Hanessian, S.; Tremblay, M.; Petersen, J. F. W. *J. Am. Chem. Soc.* **2004**, *126*, 6064

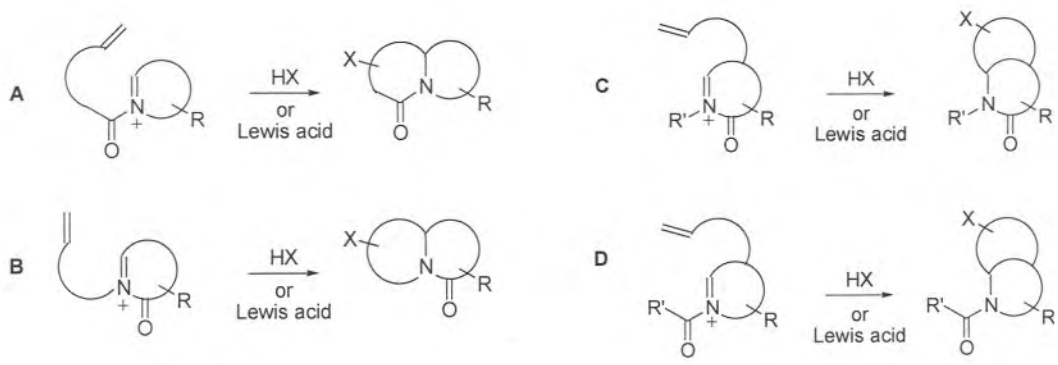
X-ray Co-crystal Structure of Oscillarin with Thrombin



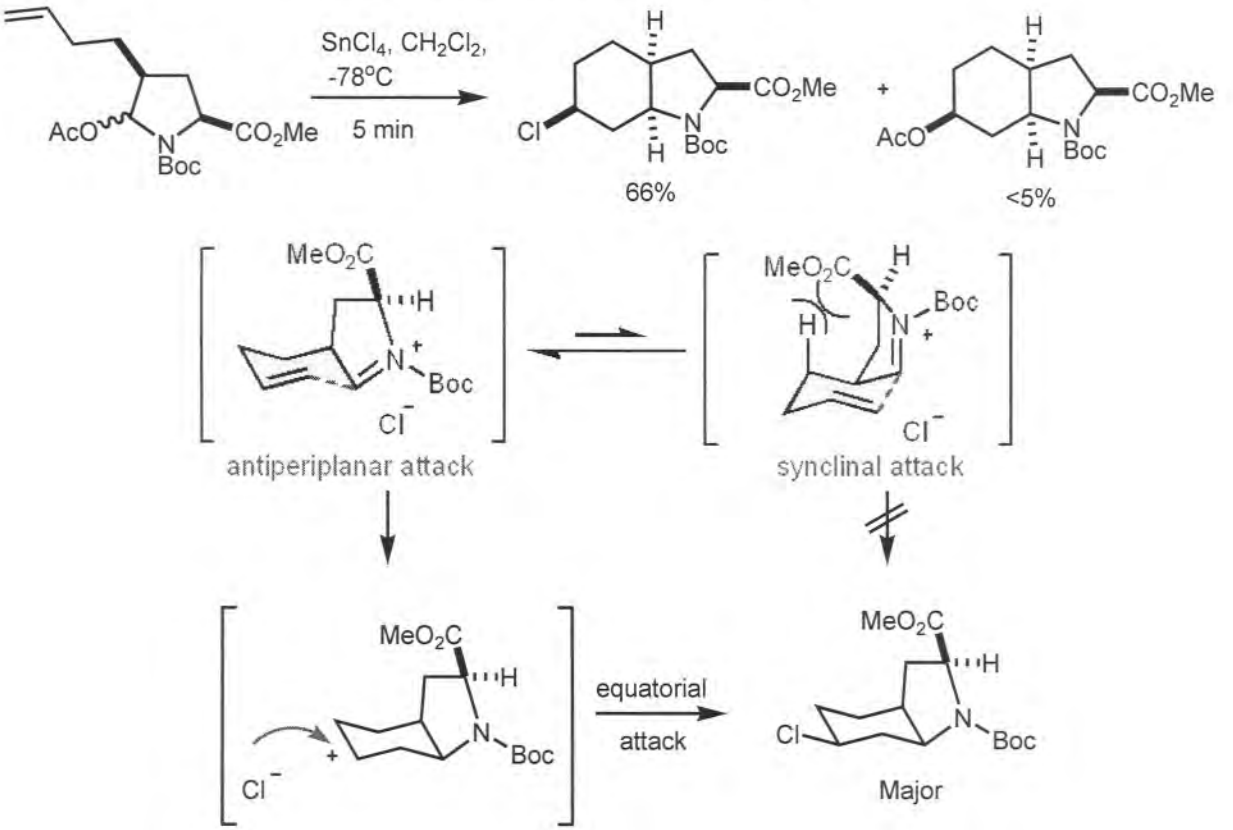
Courtesy: J.F.W. Petersen, AstraZeneca Structural Chemistry Laboratory, Mölndal, Sweden

LEADING REVIEWS ON N-ACYLIMINIUM ION CHEMISTRY

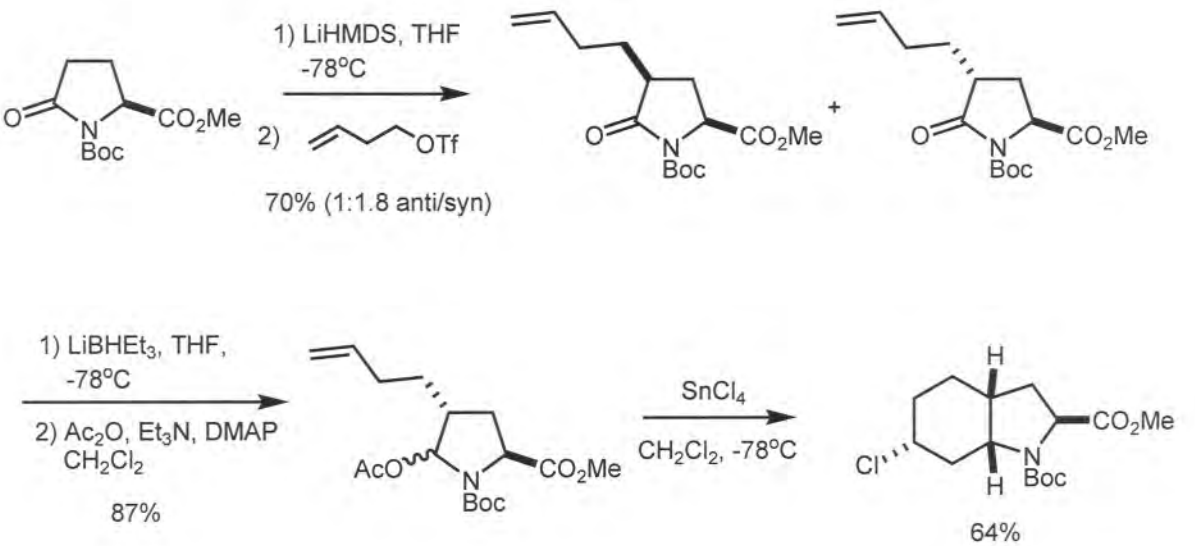
- B.E. Maryanoff, H.-C. Zhang, J. H. Cohen, I.J. Turchi, C.A. Maryanoff, *Chem. Rev.* **2004**, *104, 1431.*
- J. Royer, M. Bonin, J. Micouin, *Chem. Rev.* **2004**, *104,* 2311.
- W. N. Speckamp, M. J. Moolenaar, *Tetrahedron* **2000**, *56*, 3817.
- H. Hiemstra, W. N. Speckamp In *Comprehensive Organic Synthesis*, M. B. Trost, I. Fleming, C. H. Heathcock, Pergamon: New York, 1991, 2, 1047.
- W. N. Speckamp, H. Hiemstra, *Tetrahedron* **1985**, *41*, 4367.
- W. N. Speckamp, *Rec. Trav. Chim. Pays-Bas* **1981**, *100*, 345.



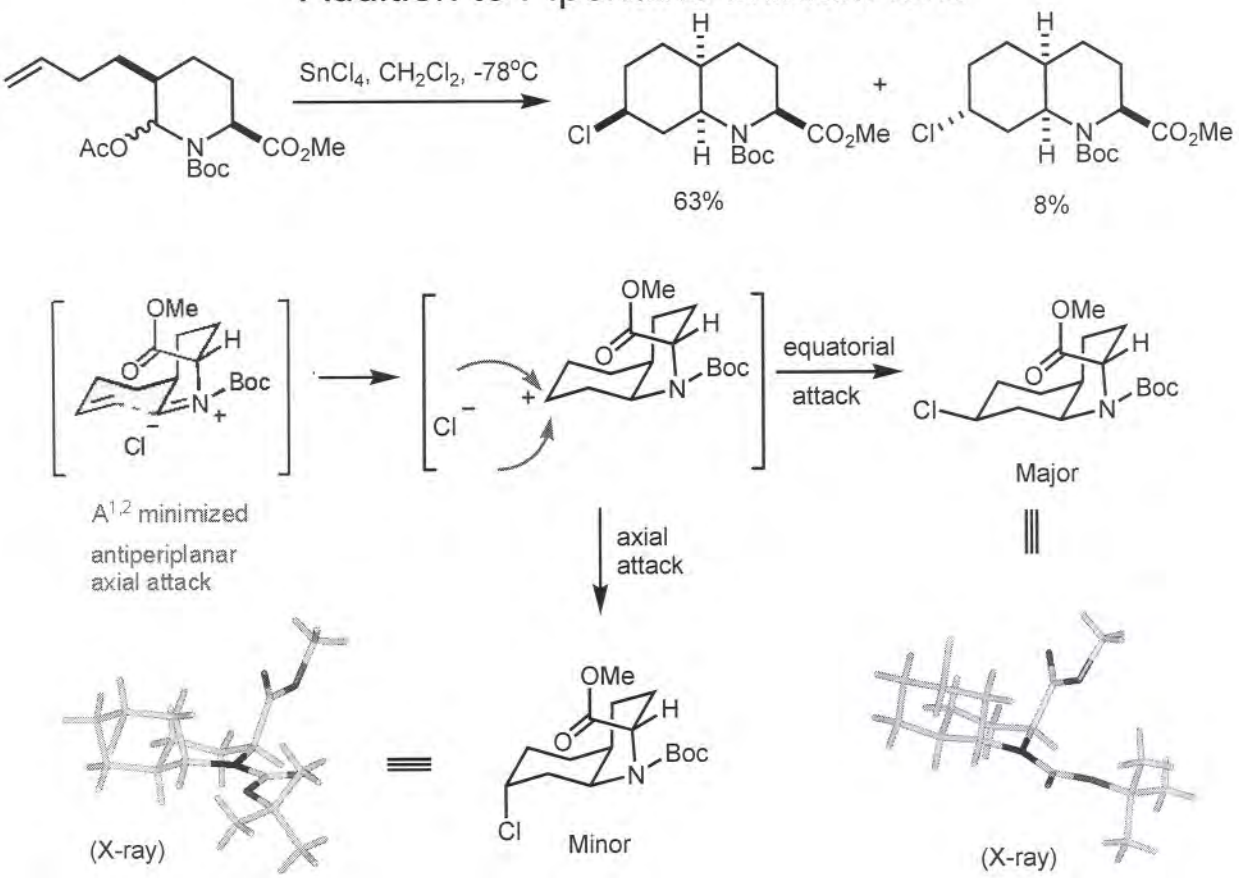
Mechanistic Considerations



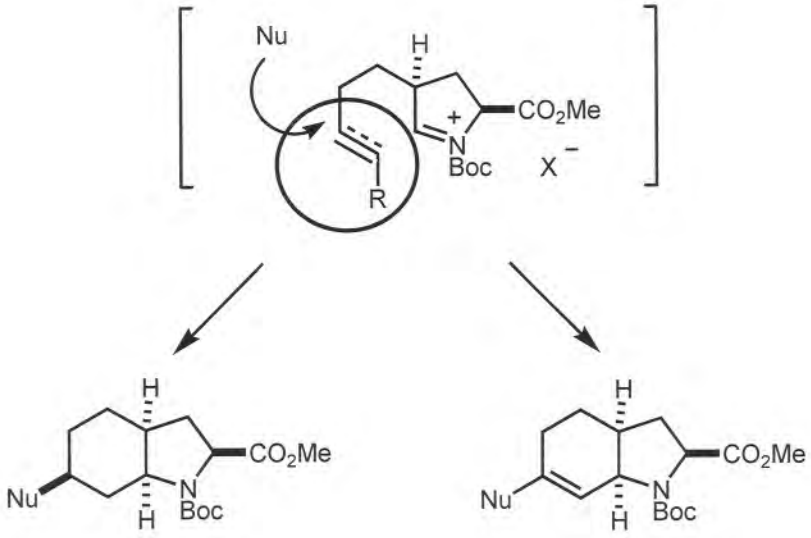
Azonia-Prins Cyclization of the *anti*-Isomer



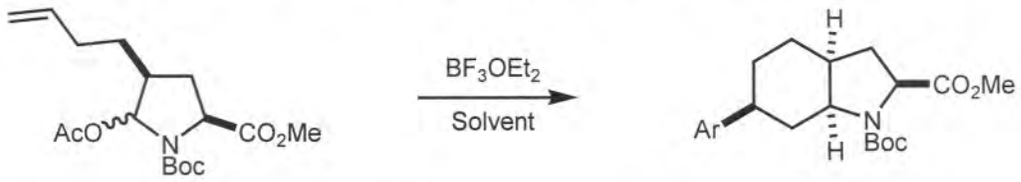
Addition to Piperidine Iminium ions

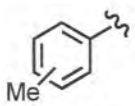
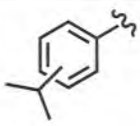
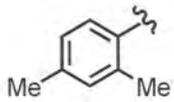
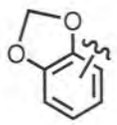
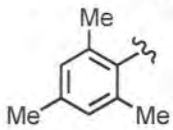
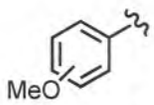
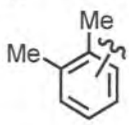
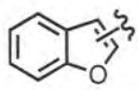


Functionalization of Non-activated Terminal Alkenes and Alkynes



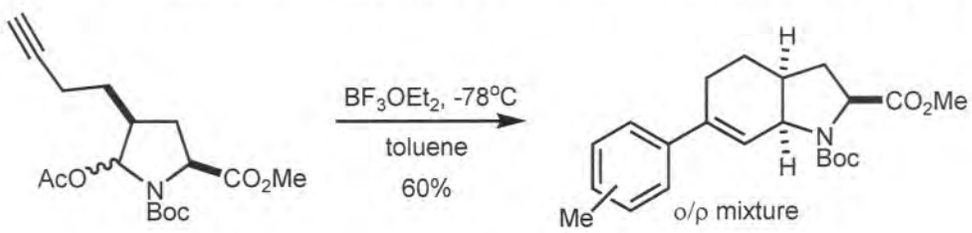
Tandem Azonia-Prins / Friedel-Crafts Cyclization

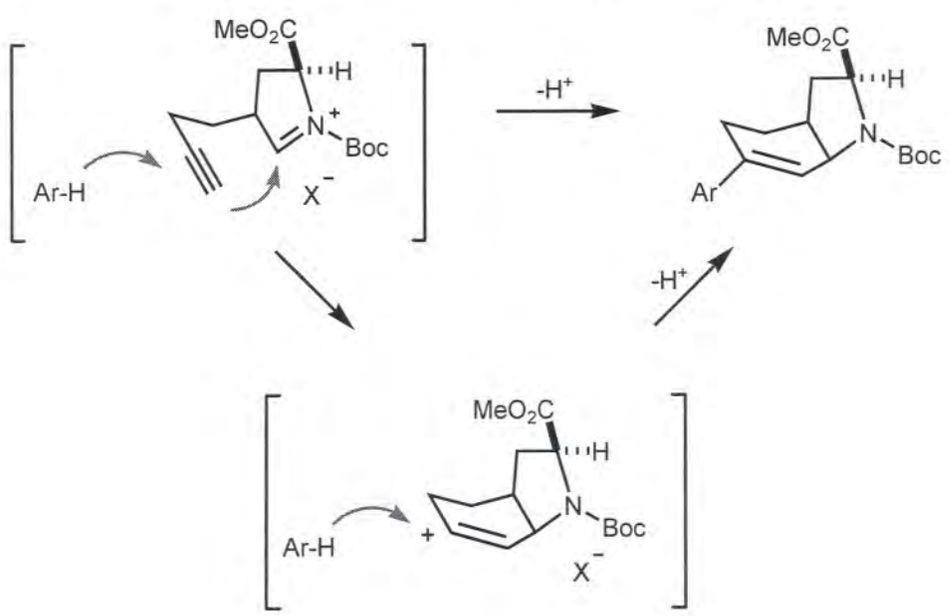


Ar-H	Temperature	Yield	Ar-H	Temperature	Yield
	-78°C	77%[a]		-78°C	70%[a]
	-45°C	64%		-15°C	58%[a]
	-40°C	78%		-35°C	69%[a]
	-20°C	67%[a]		-25°C	50%[b]

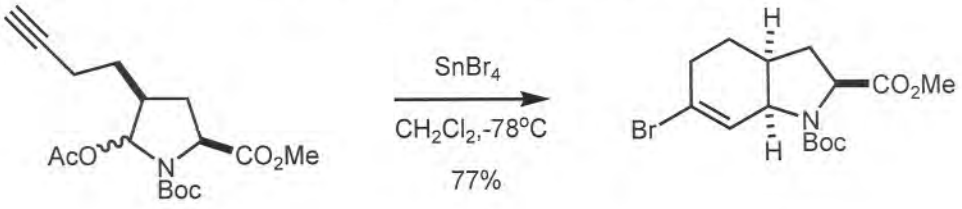
a) mixture of o/p isomers. b) mixture of regioisomers.

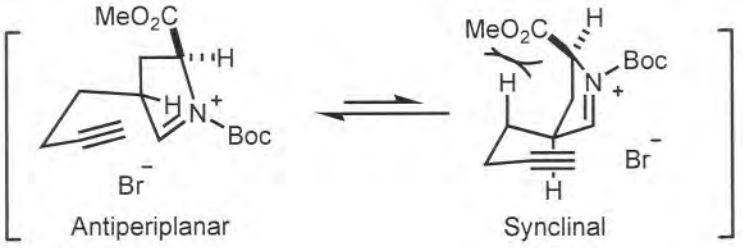
Terminal Yne Tandem Azonia-Prins / Friedel-Crafts Cyclization

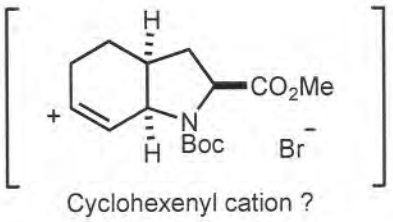




Halocyclization of Terminal Alkynes

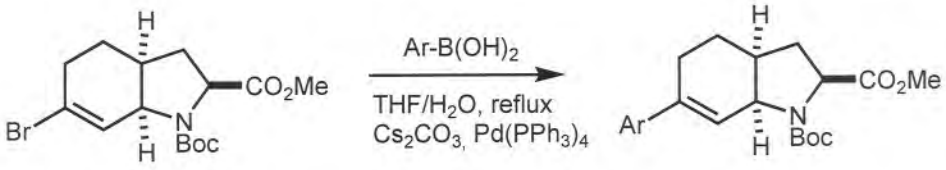


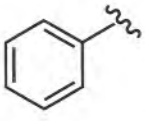
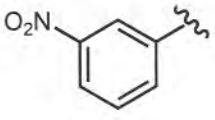
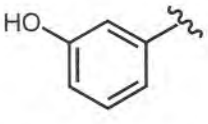
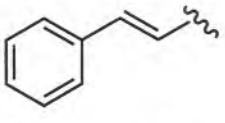
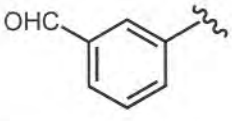
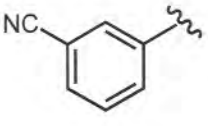




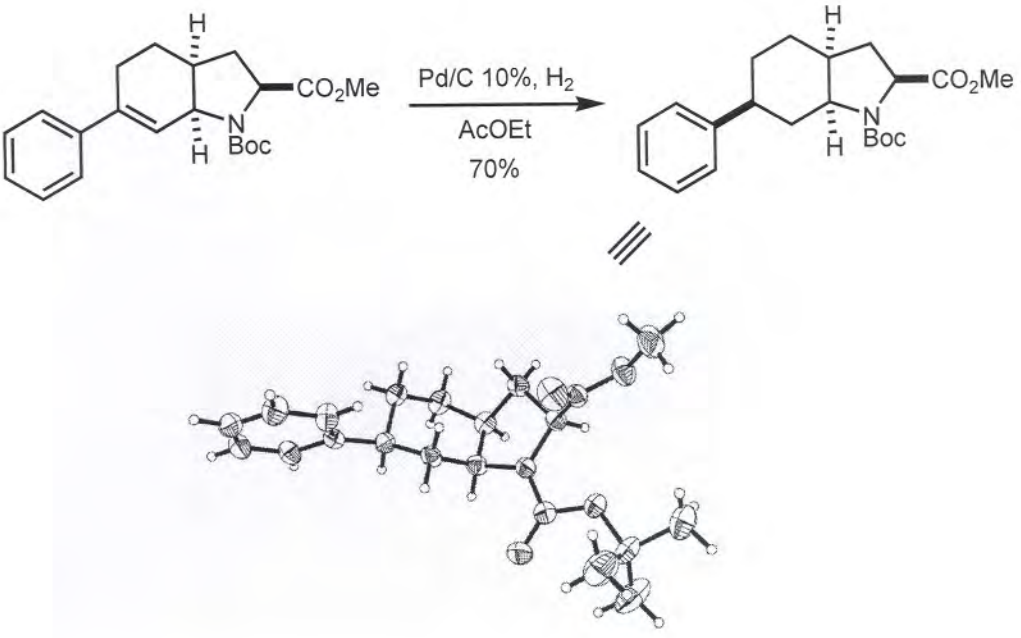
Cyclohexenyl cation ?

Suzuki Cross-Coupling

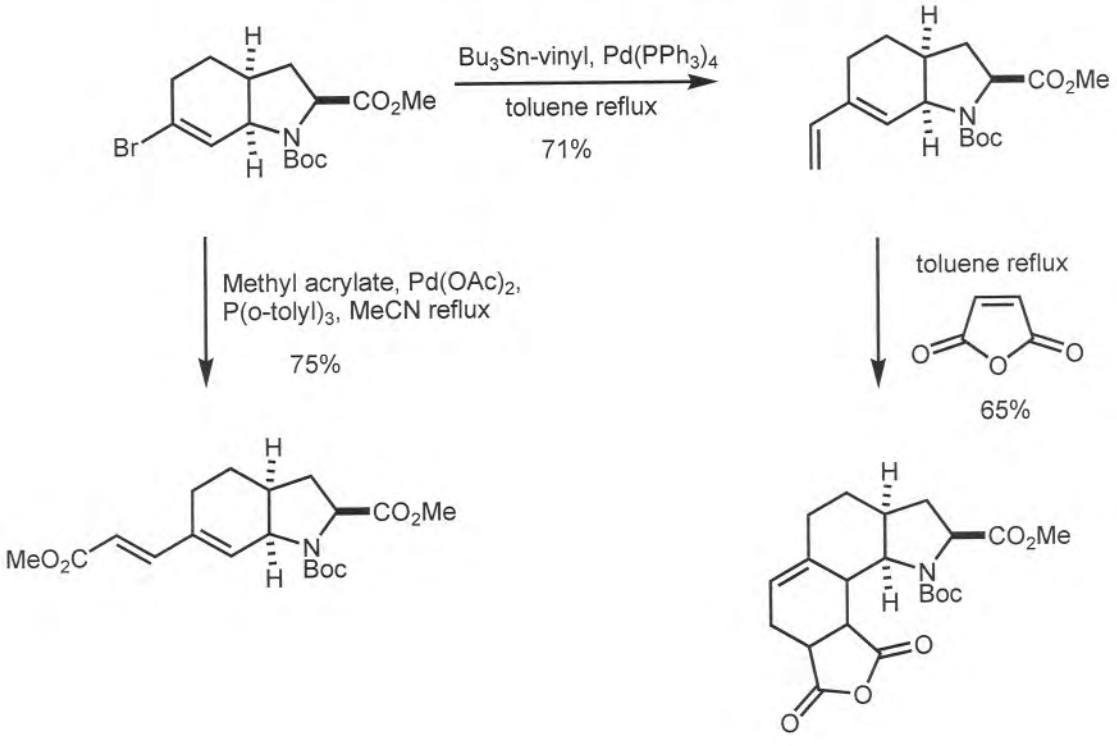


Ar-H	Yield	Ar-H	Yield
	84%		73%
	85%		81%
	70%		78%

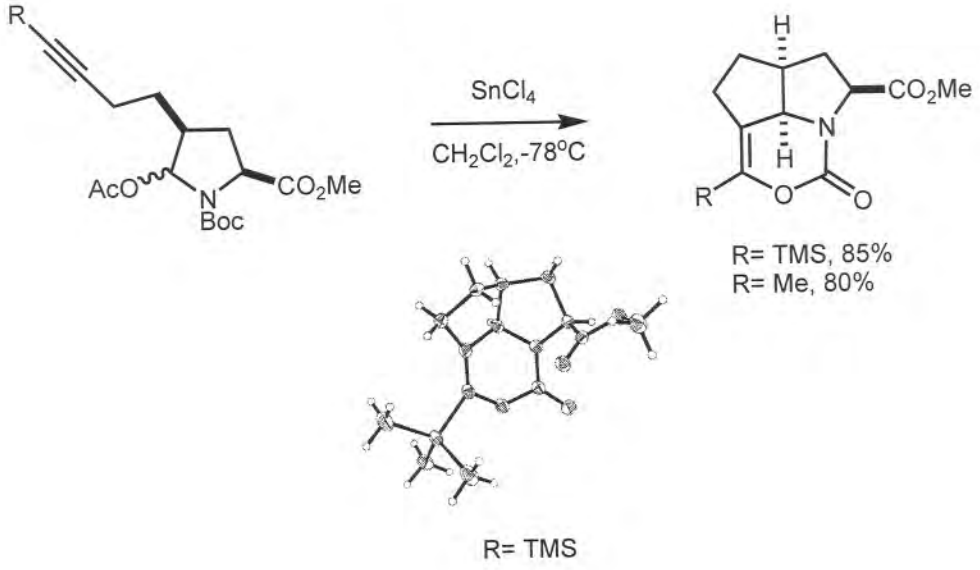
(6-*S*)-Phenyl Octahydroindole-2-carboxylic acid



Stille, Heck and Diels-Alder Reactions

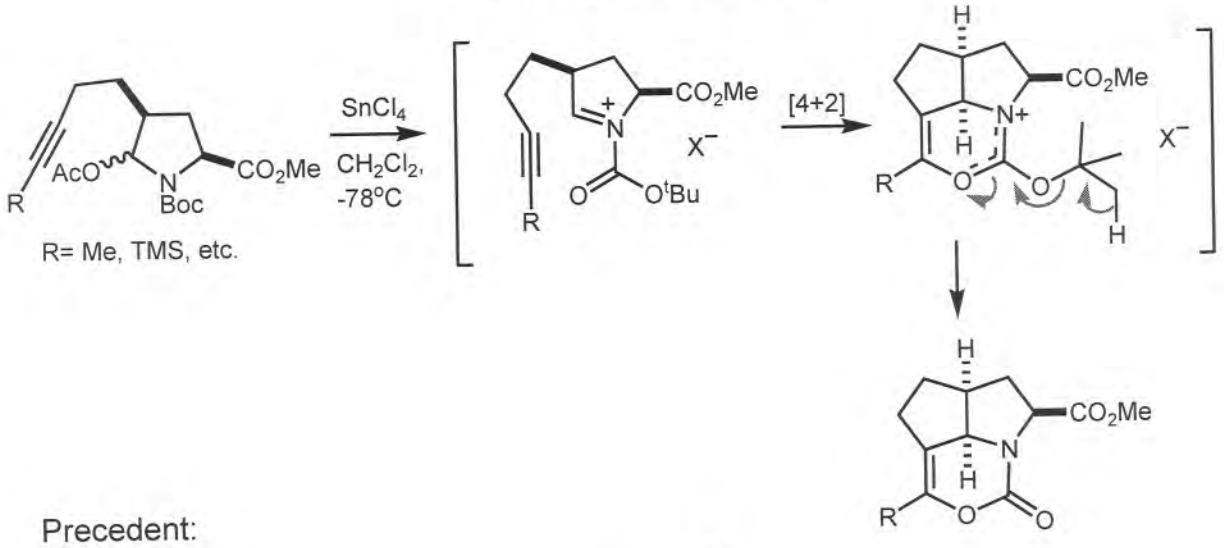


Substituted Terminal Alkynes –A New Twist
Tricyclic Dihydrooxazinones

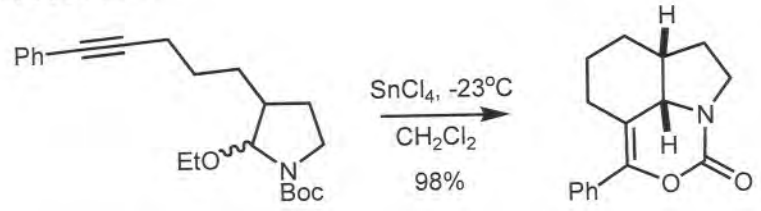


R= TMS

Possible Mechanism

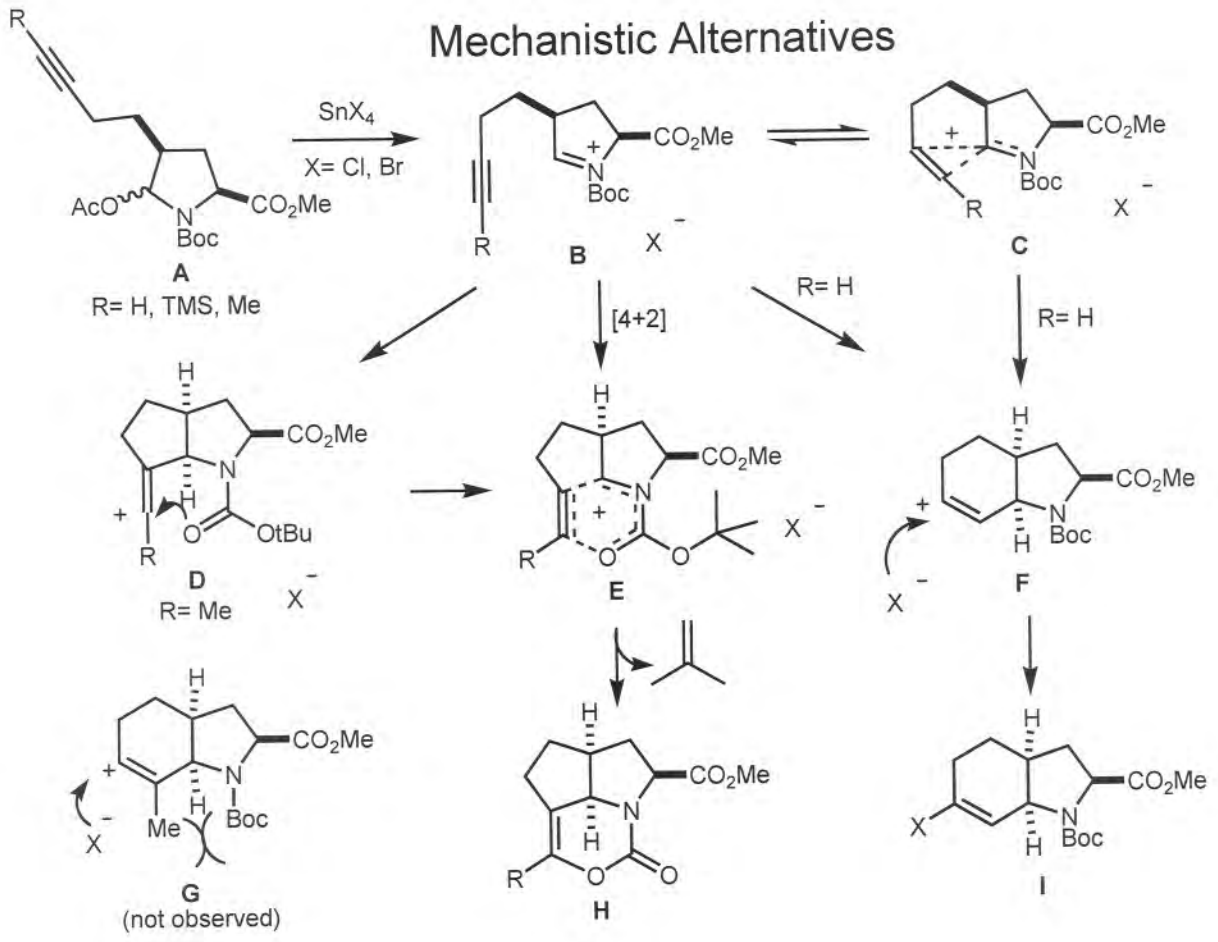


Precedent:

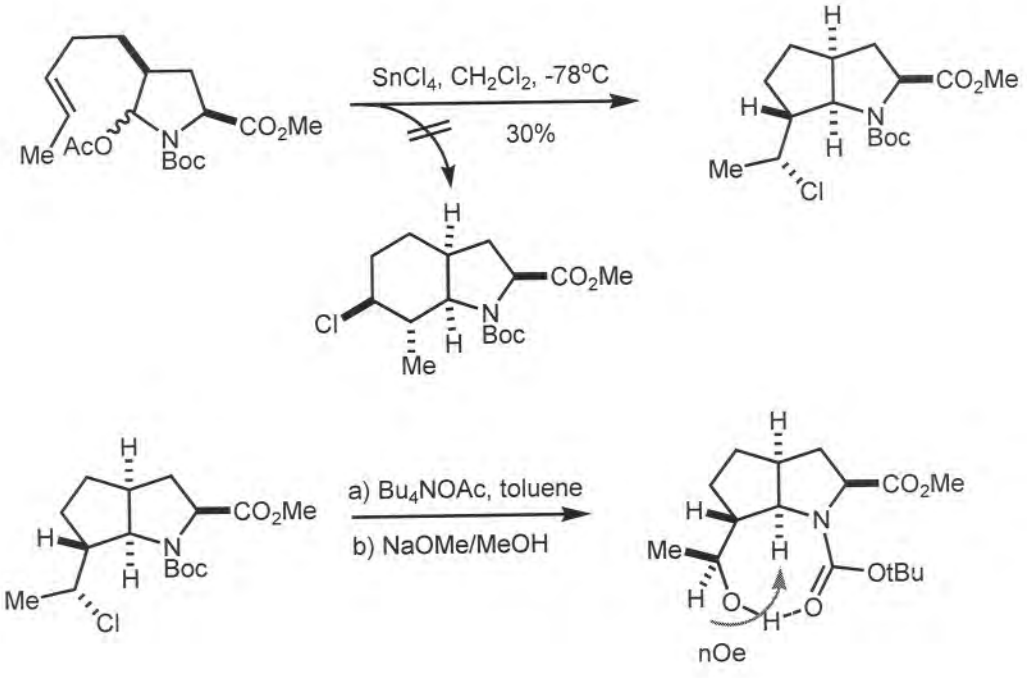


Fisher, M. J.; Overman, L.E. *J. Org. Chem.* **1990**, *55*, 1447.

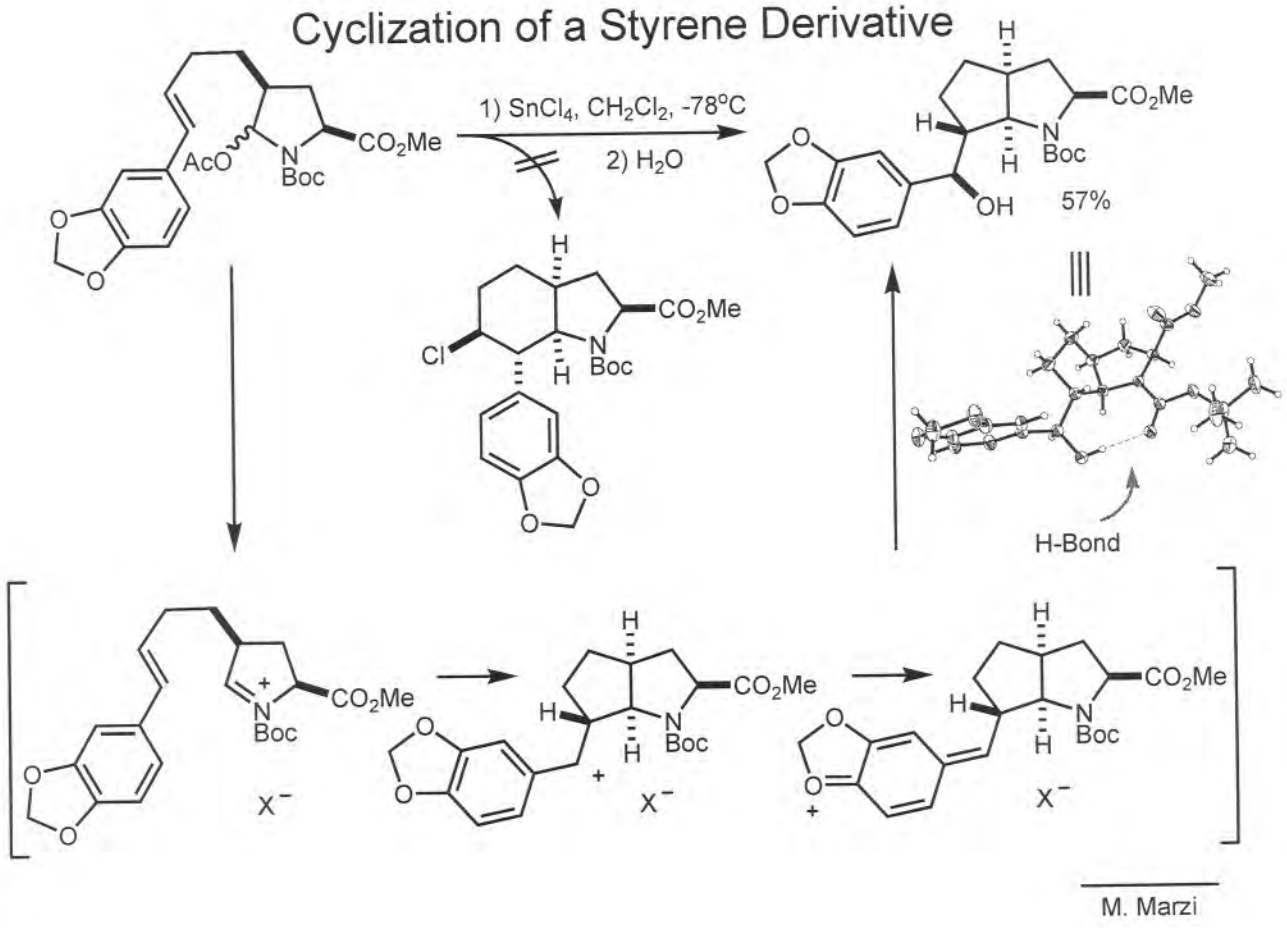
Mechanistic Alternatives



Cyclization of a Substituted Alkene

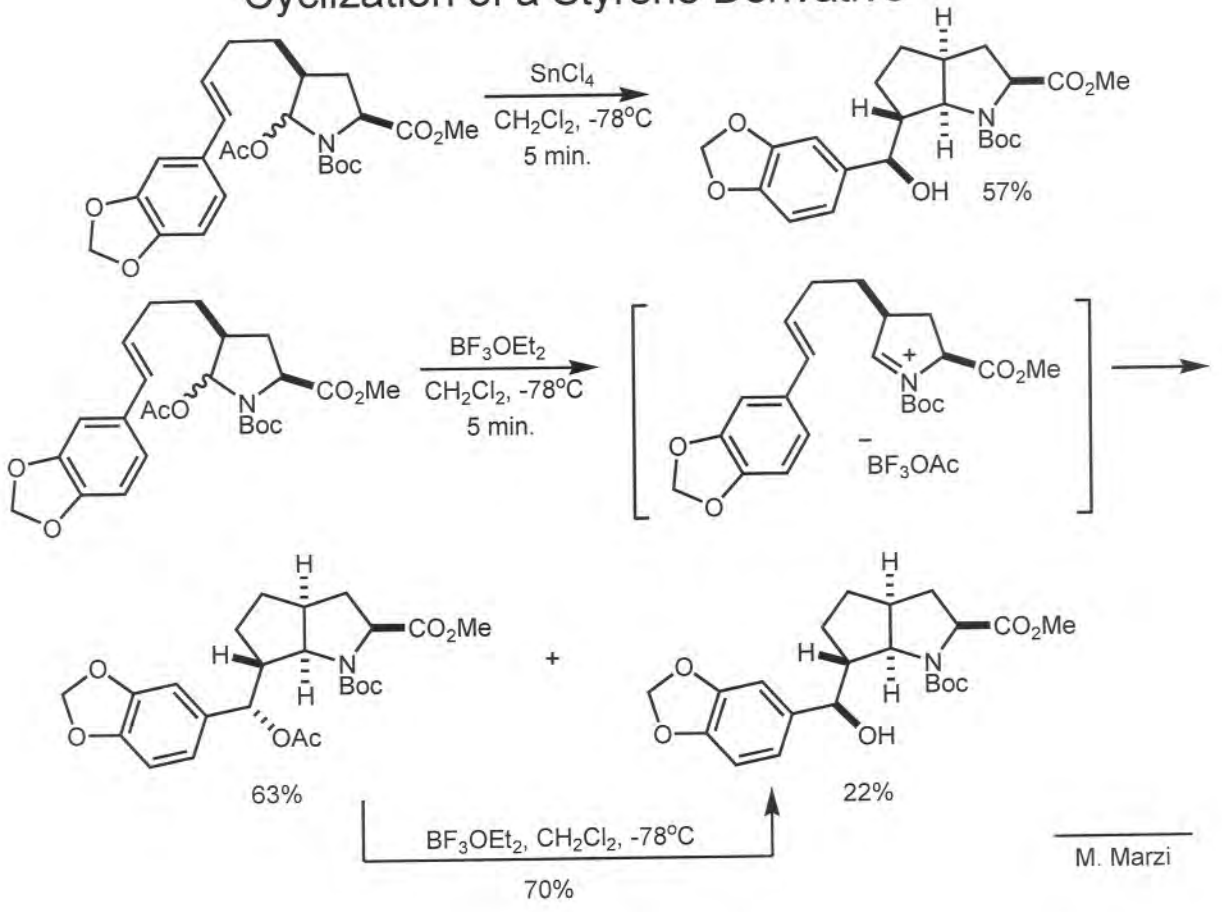


Cyclization of a Styrene Derivative



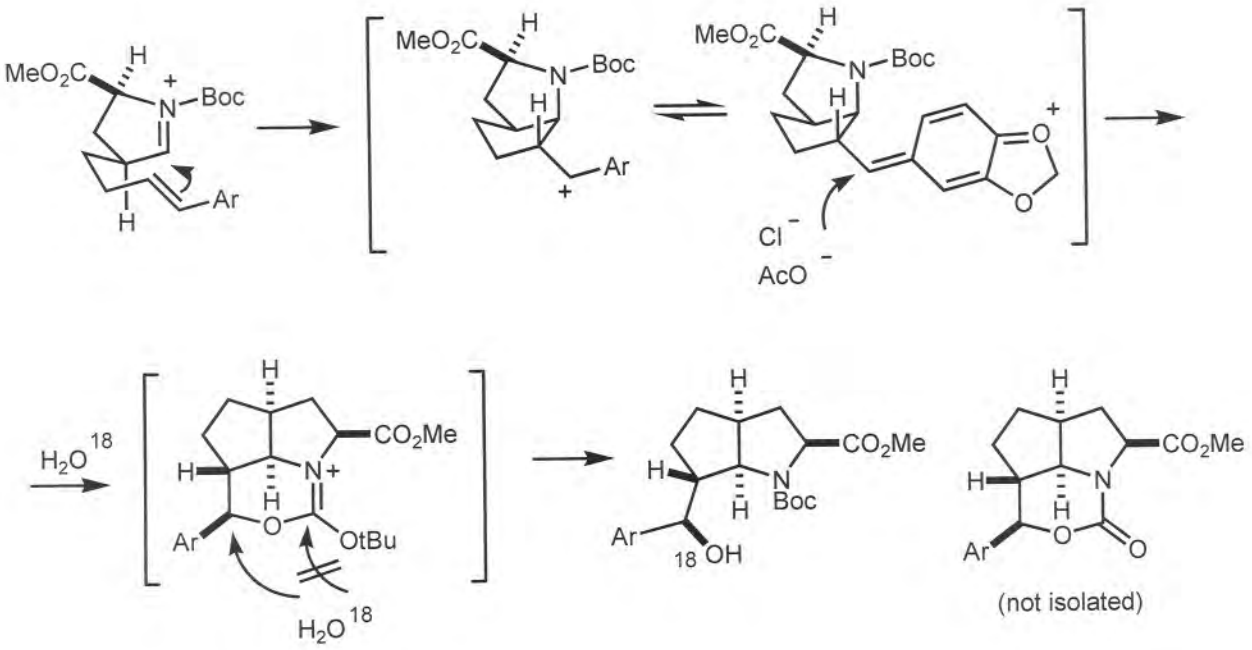
M. Marzi

Cyclization of a Styrene Derivative

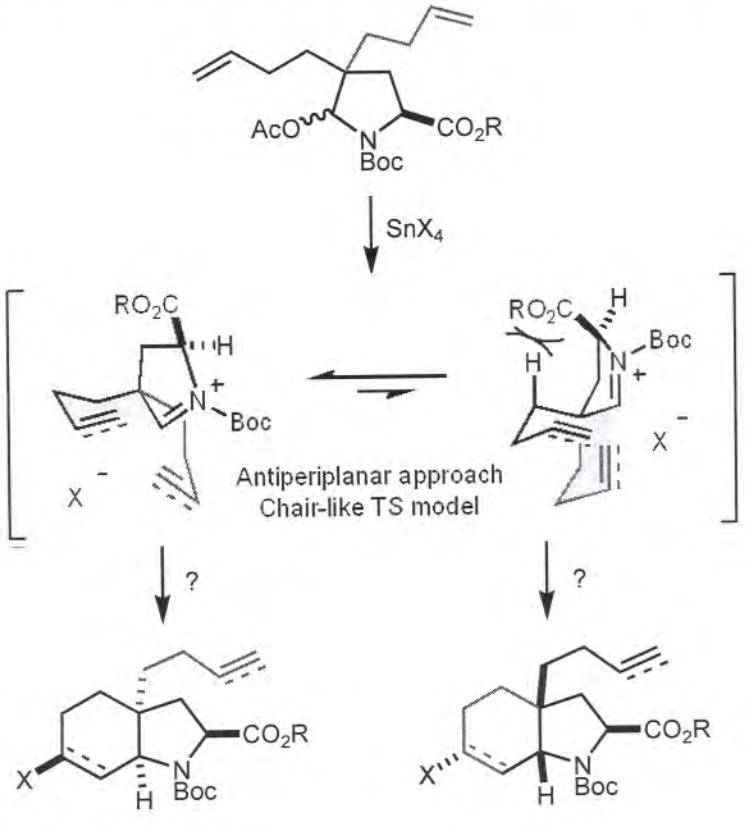


M. Marzi

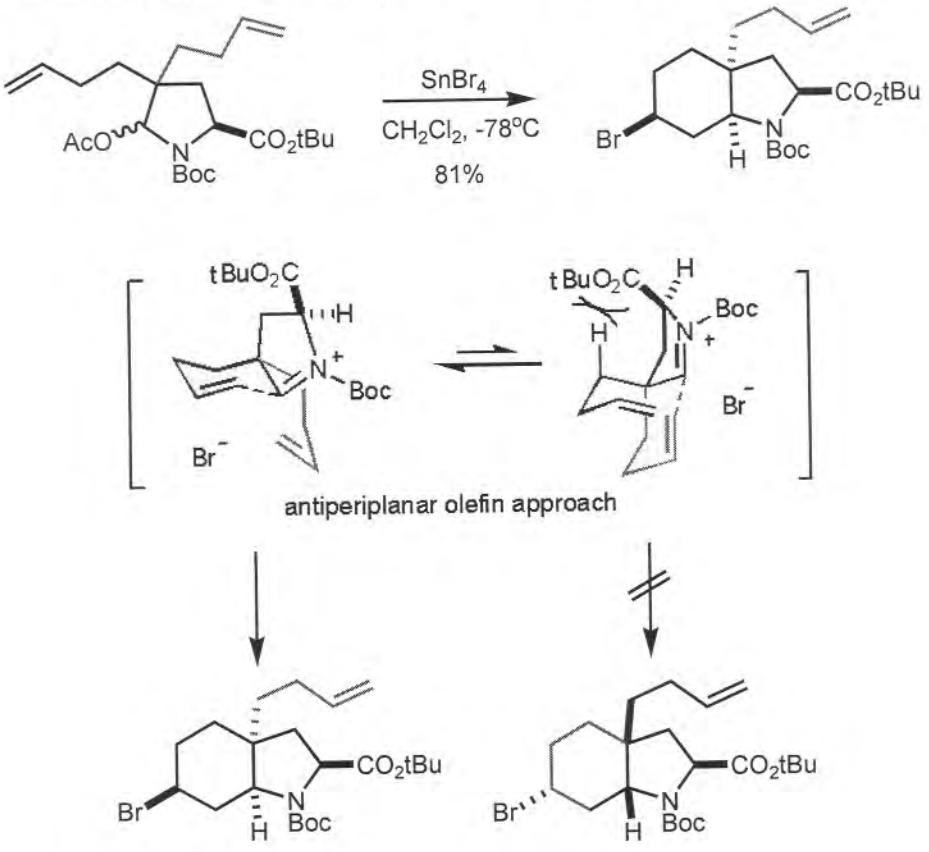
H_2O^{18} Experiment



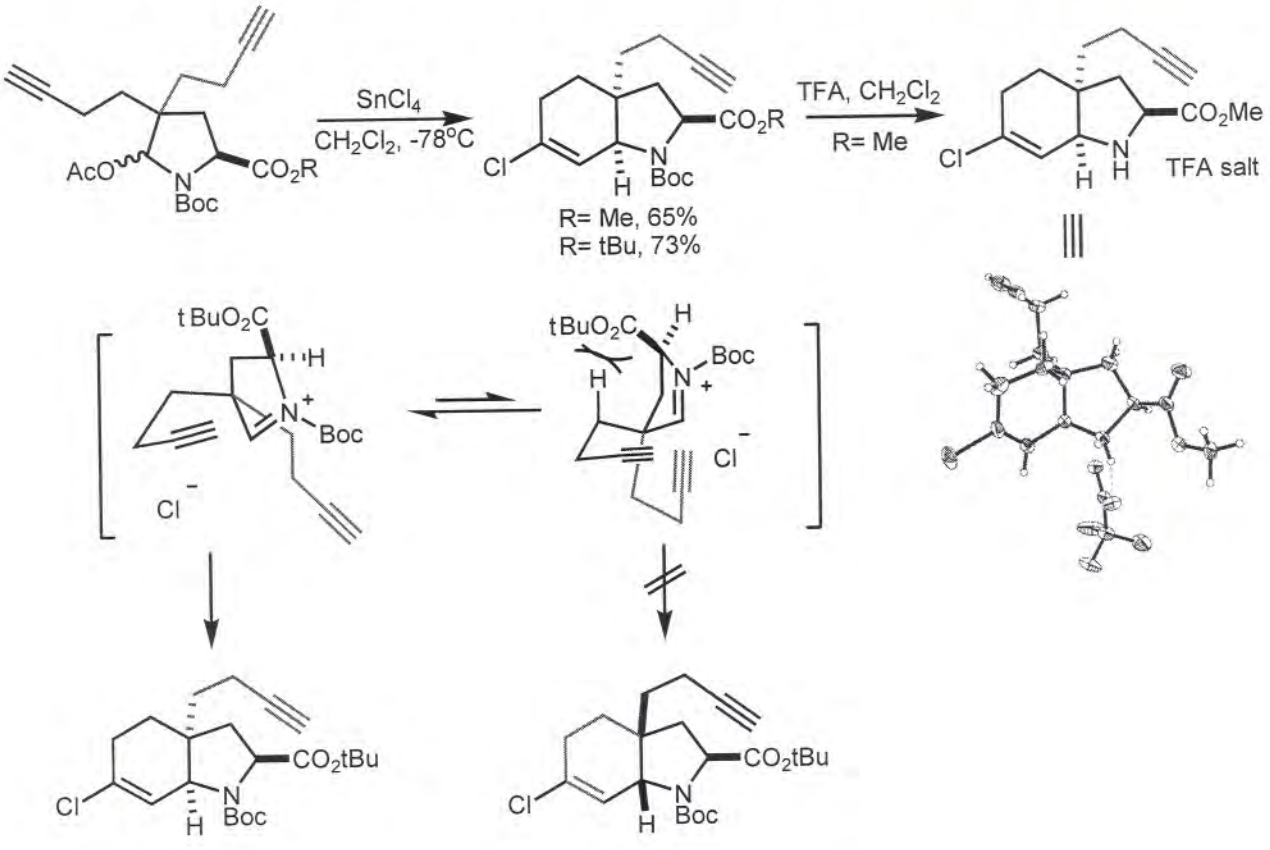
Stereoelectronic, Steric and Allylic Strain Effects



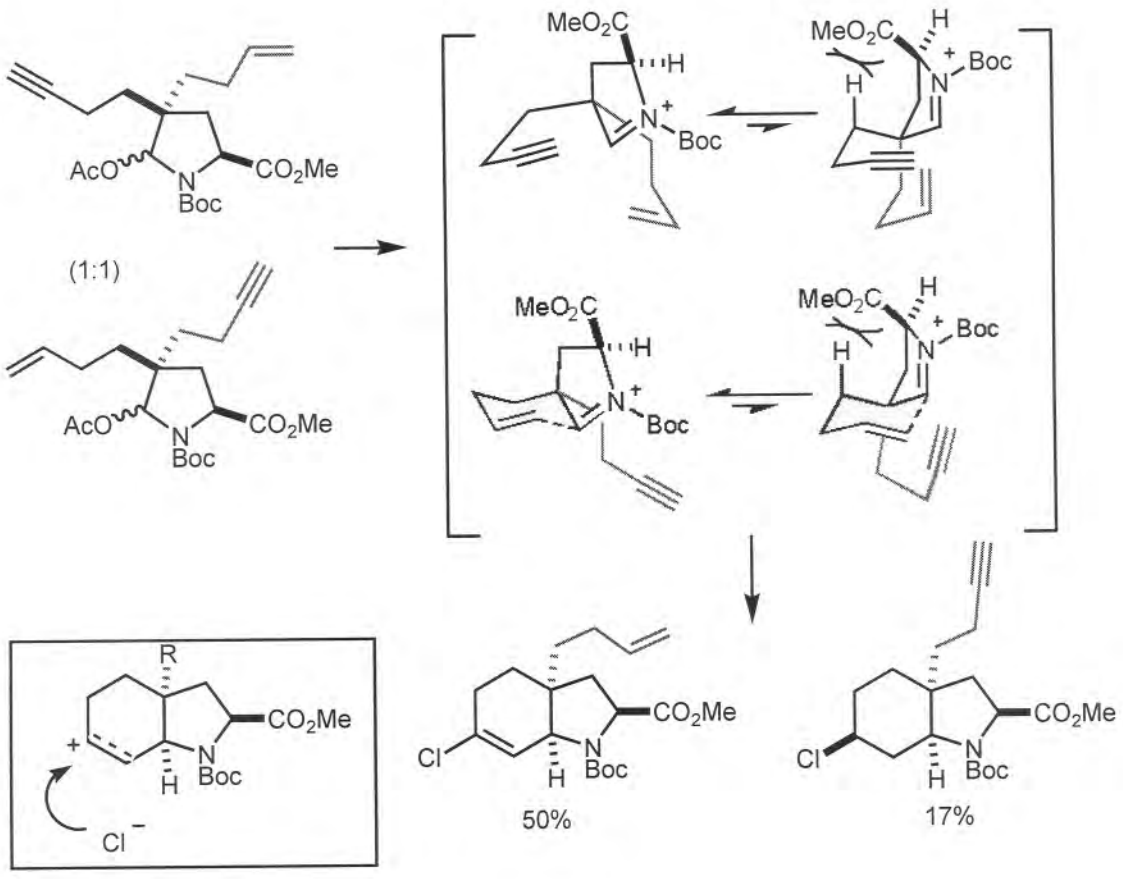
Stereodifferentiation of Diastereotopic Olefins



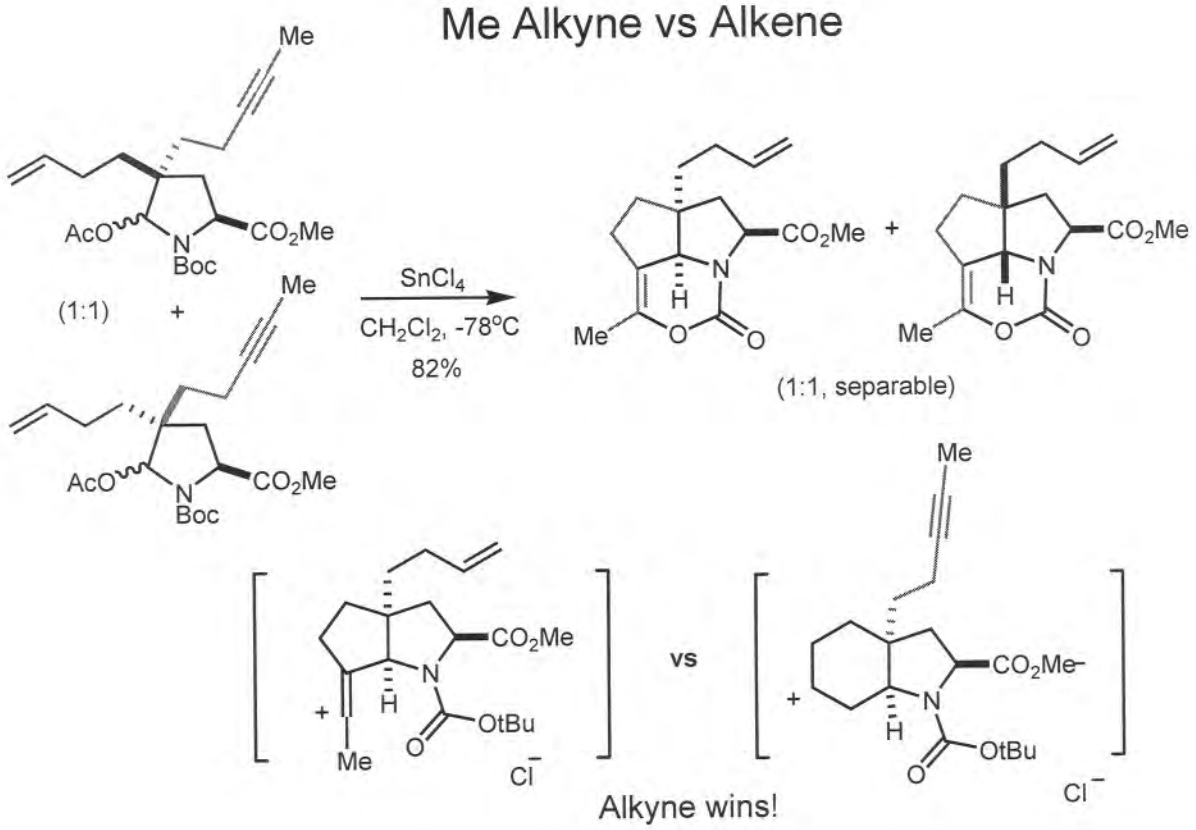
Stereodifferentiation of Diastereotopic Terminal Alkynes

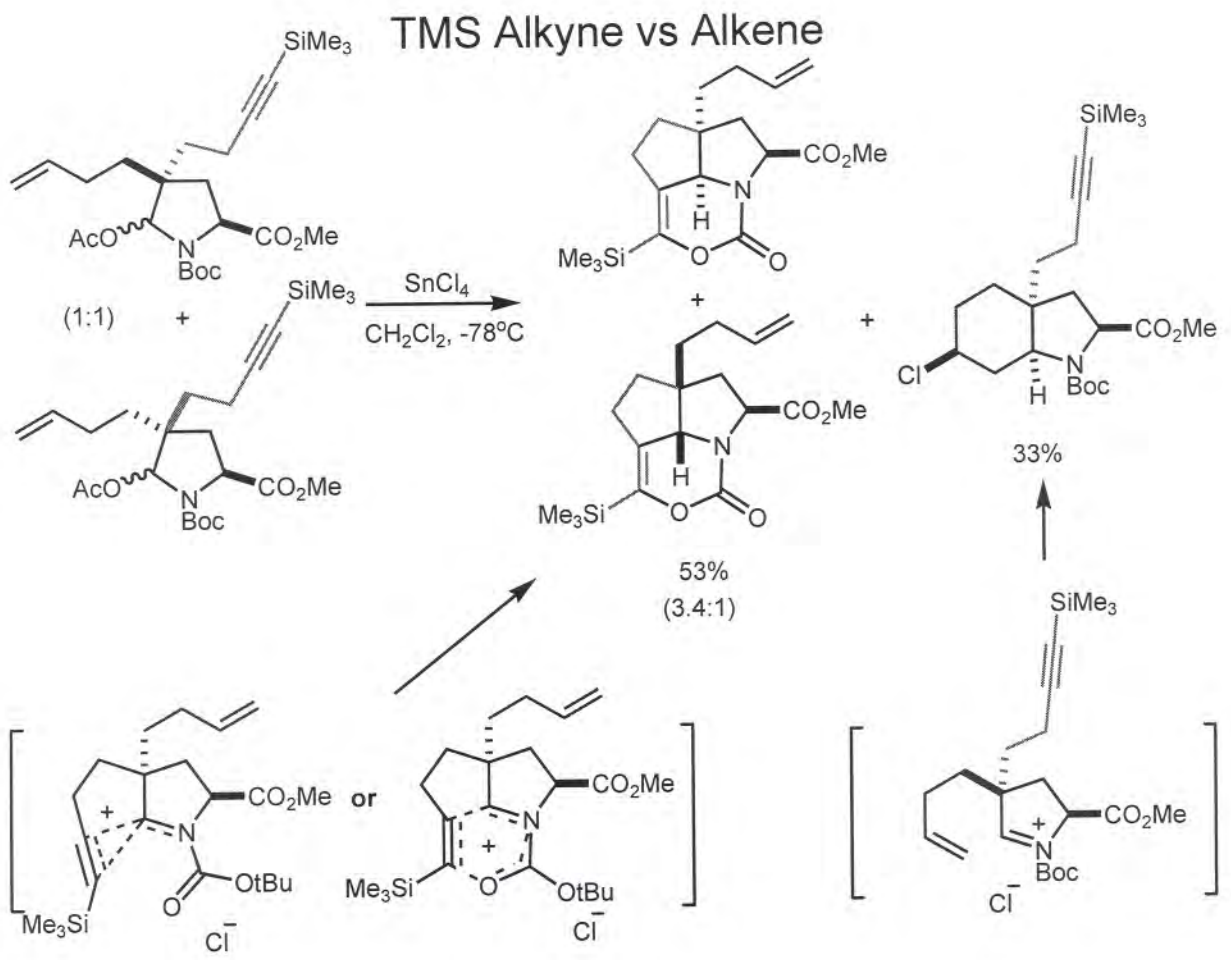


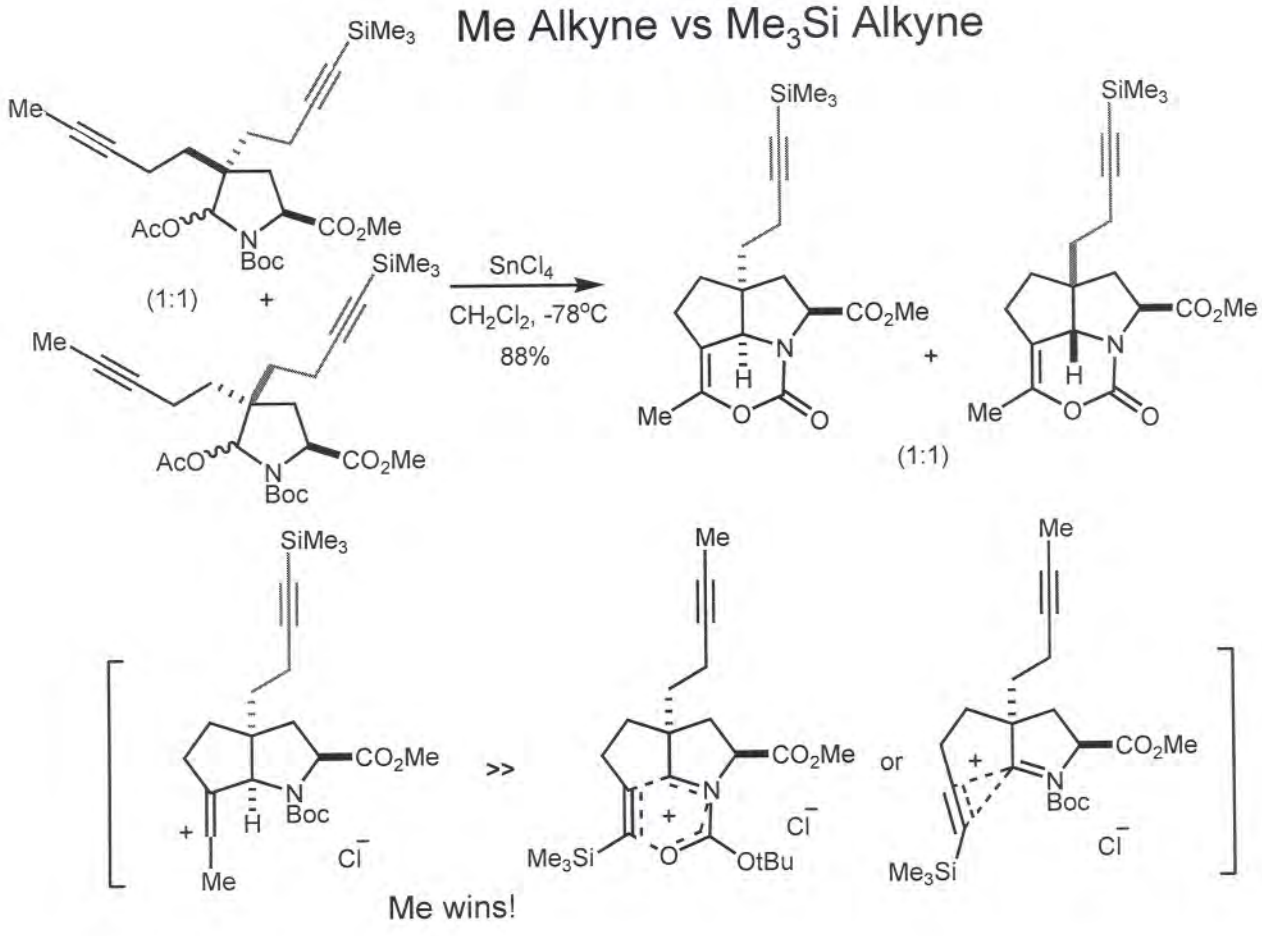
Alkyne vs Alkene



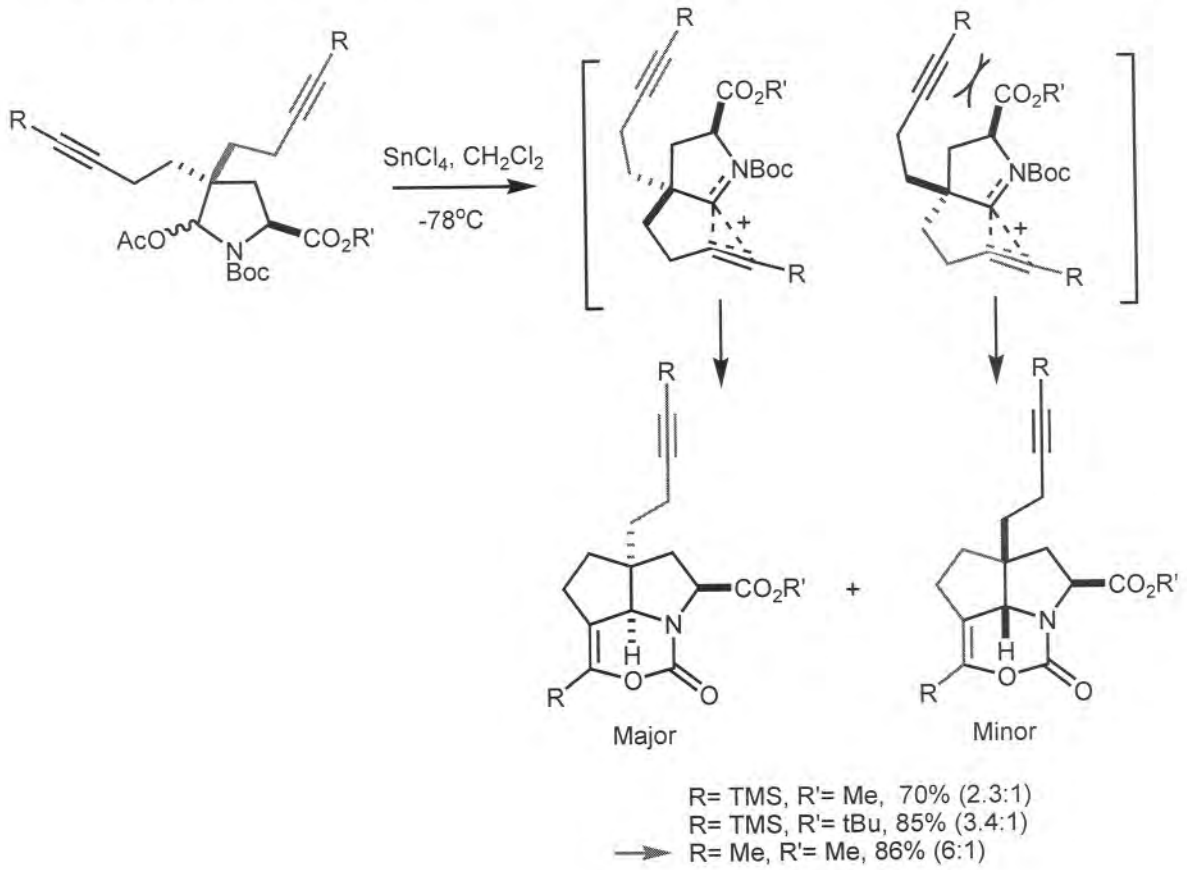
Me Alkyne vs Alkene



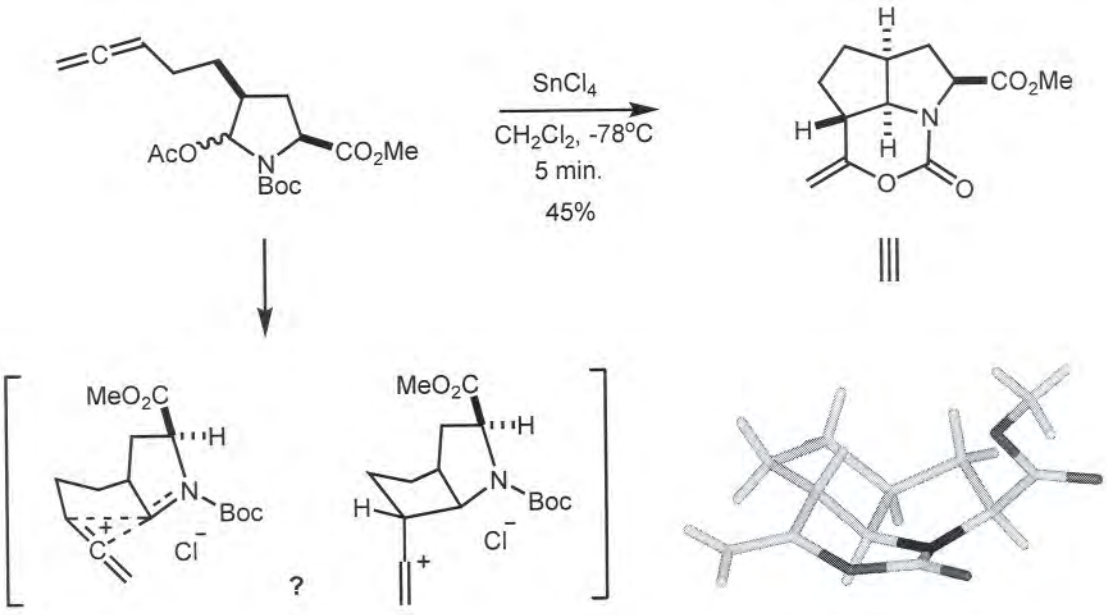

TMS Alkyne vs Alkene
SiMe3
AcO
N
Boc
CO2Me
(1:1)
+
SnCl4
CH2Cl2, -78°C
Me3Si
H
O
53%
(3.4:1)
Cl
33%
or
OtBu
Cl−


Me Alkyne vs Me3Si Alkyne
SiMe3
Me
AcO
N
Boc
CO2Me
(1:1)
+
SnCl4
CH2Cl2, -78°C
88%
(1:1)
or
>>
Me wins!

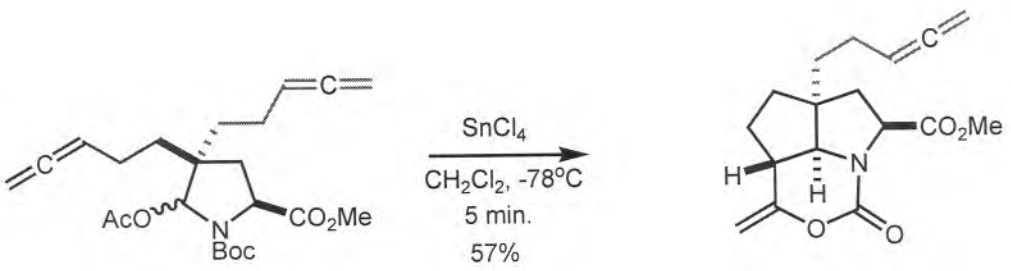
Stereodifferentiation of Diastereotopic Substituted Alkynes



Allene Tether !



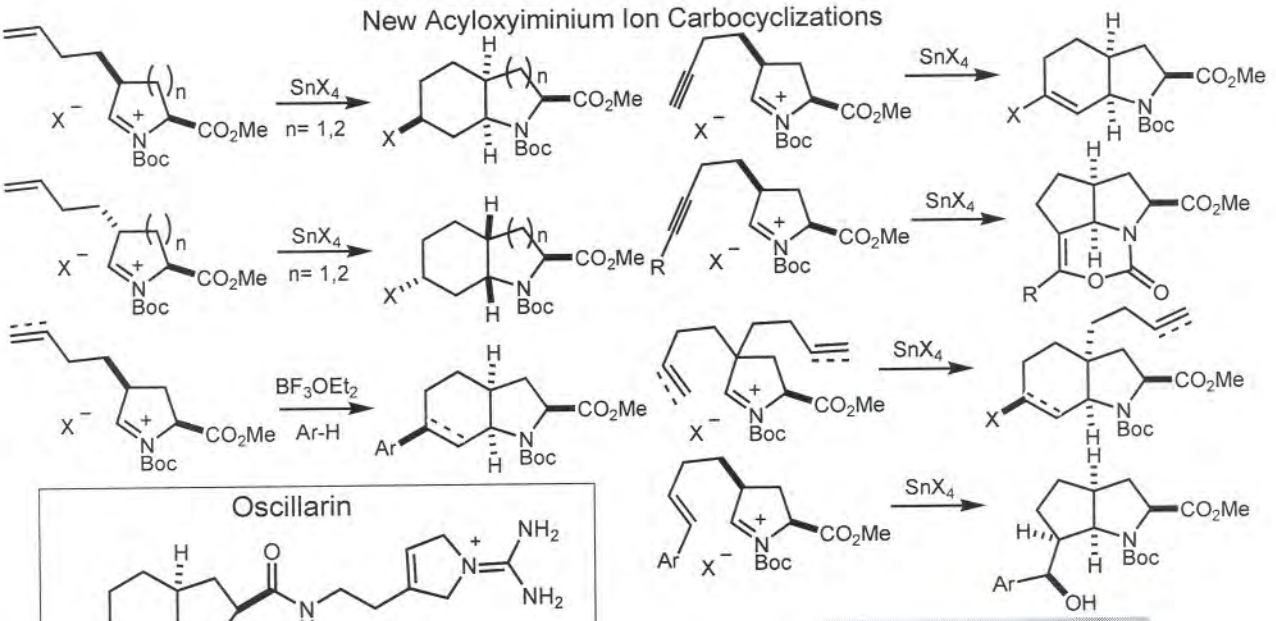
Stereodifferentiation of Diastereotopic Allenes



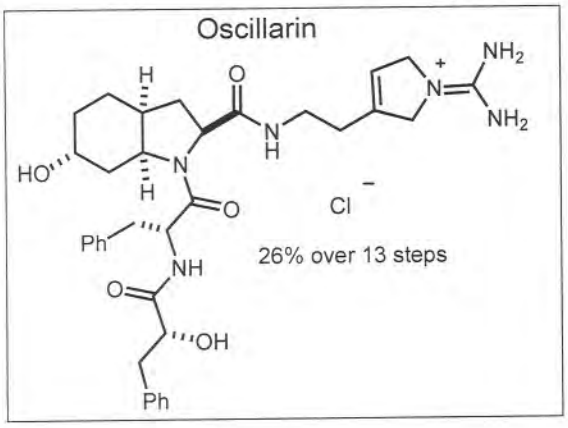
J. Del Valle

Contribution to the Field

New Acyloxyiminium Ion Carbocyclizations



Oscillarin



Martin Tremblay