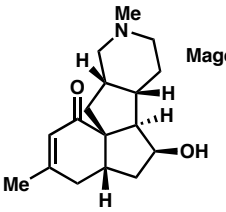
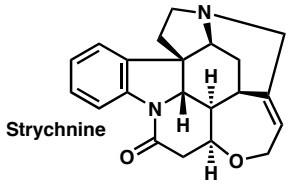
Larry Overman: Synthetic Highlights of an Amazing Chemist

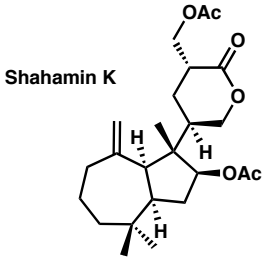


Magellanine

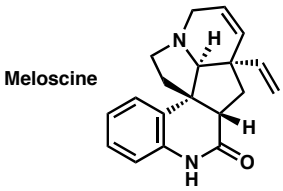
By Mike Meyer
Group Meeting
12/20/04
147 Noyes, 8pm



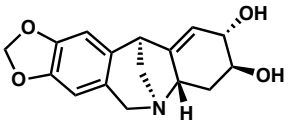
Strychnine



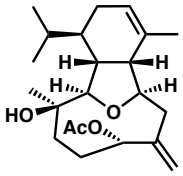
Shahamin K



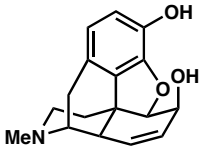
Meloscine



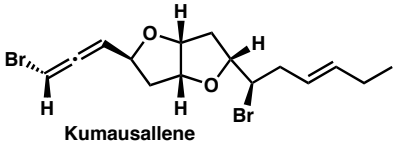
Pancracine



7-deacetoxyalcyonin Acetate



Morphine



Kumausallene

Introduction:

1. Introduction to Larry Overman

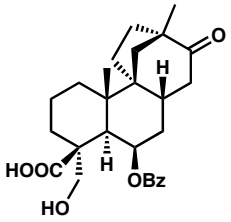
2. Targets Achieved by Prins-Pinacol Rearrangement
   a. (–)-Magellanine
   b. (+)-Shahamin K
   c. (–)-7-Deacetoxyalcyonin Acetate
   d. Briarellins E and F

3. Targets Achieved by an Aza-Cope-Mannich Rearrangement
   a. (±)-Meloscine
   b. (±)-*dl*-16-Methoxytabersonine
   c. (–)-Pancracine
   d. (–)-Strychnine

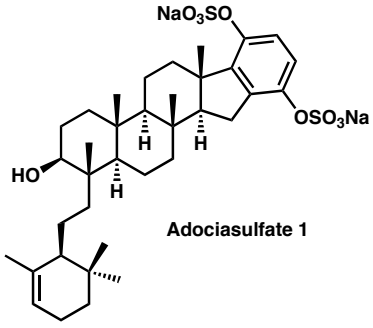
4. Targets Achieved via Asymmetric Heck Reaction
   a. (–)-Scopadulcic Acid A
   b. (–)-Chimonanthine
   c. (–)-Morphine

5. Misc. Targets achieved in the Overman Lab
   a. Adociasulfate 1
   b. (±)-Kumausallene

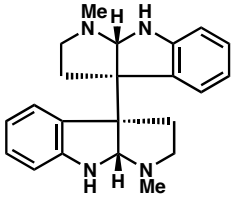
6. Conclusion



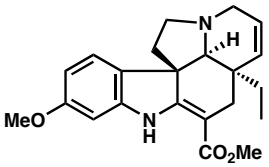
Scopadulcic Acid A



Adociasulfate 1



Chimonanthine



dl-16-Methoxytabersonine

Who is Larry E. Overman???

The Boy:

-Born in Chicago, Illinois, in 1943
-Raised in Hammond Indiana, an industrial town in which he worked in local steel mills during summers to pay for college

The Chemist:

-Obtained B.A. from Earlham College in 1965
-Received his Ph.D. from University of Wisconsin in 1969
-NIH postdoctoral fellowship with Prof. Ronald Breslow (Columbia)
-Began at UC Irvine in 1971
-Currently a Distinguished Professor of Chemistry
-Awards/Honors include: ACS Arthur C. Cope Award (2003), ACS Creative Work in Synthetic Organic Chemistry (1995), and much more...
-Lab has completed syntheses of over 80 complex natural products and close to 260 publications in major journals

Larry on chemistry:

"I had absolutely no interest in chemistry until I was inspired by a great teacher in college. What ultimately intrigued me was not only the idea of studying the natural world but also creating things that didn't exist before."[1]

"I hated chemistry in high school."[2]

"What my laboratory does is engineer and invent new chemical reactions that make structures that are by nature drug-like, and make them efficiently."[1]

Gilbert Stork on Larry:
"The remarkable fact is that essentially every one of [his] papers contains either novel methodology or the imaginative application of methodology, more often than not arising from Overman's own research, to highly original total syntheses."[2]

Dave Evans on Larry:
"[he is] one of those scientists who are changing the way organic chemists build molecules, ... [he has] encompassed both the synthesis of complex molecular targets and the development of highly innovative synthesis methodology, has elevated the capabilities of our discipline,"[2]

Currently:

Larry is editor-in-chief of *Organic Reactions*, an editor for *JACS, Org Lett,* and others. He consults for many pharmaceuticals, including Pfizer, Roche, Cytokinetics, and Chiron. He is married to wife Joanne, a high school chemistry teacher, and they have two children.

He is, of course, still at UC Irvine.

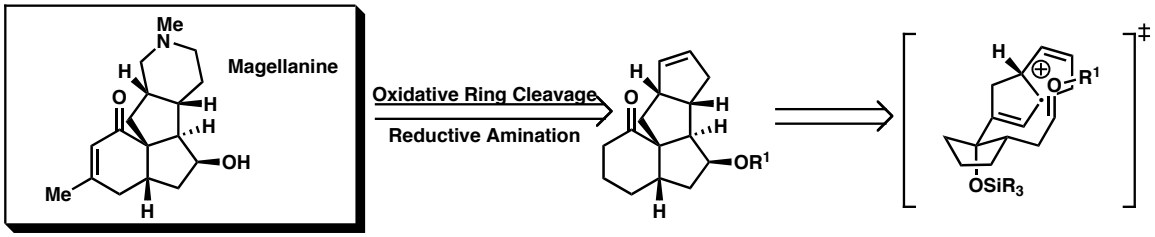
And most importantly, what about life outside of chemistry:

"I decided early on that there would be at least one day a week that I would not do anything related to work."

Larry enjoys free-diving and spear fishing in Australia, Mexico, and the southern California coast.[2]

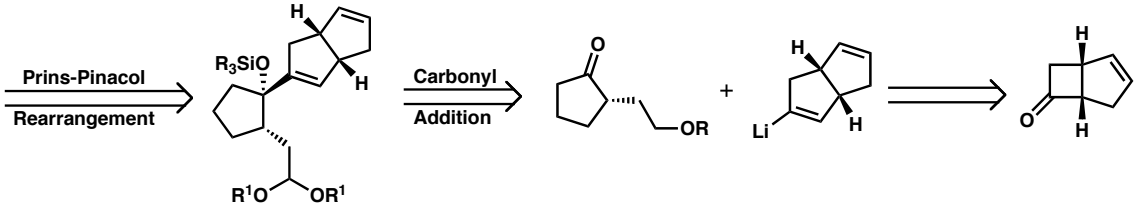
1. http://www.scienceblog.com/community/older/2003/C/2003436.html
2. http://pubs.acs.org/cen/awards/8106/8106awards.html

The Power of the Prins-Pinacol Rearrangement

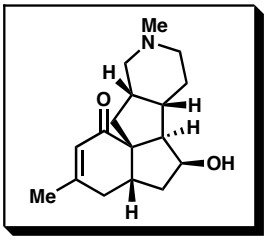


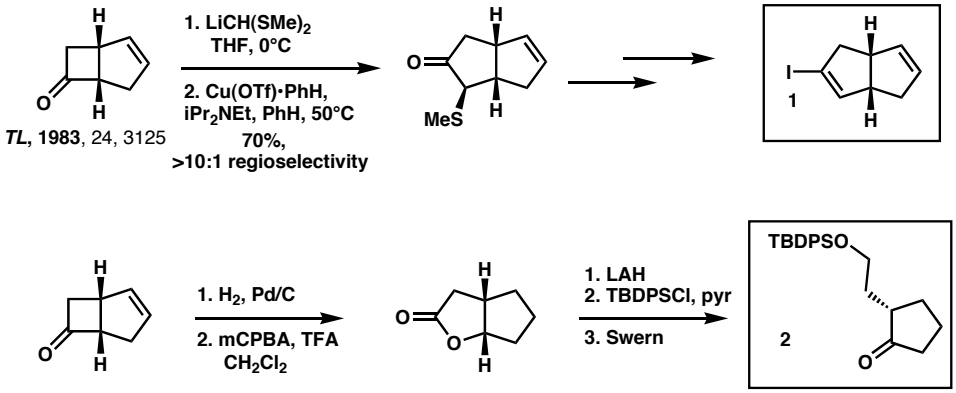
- isolated in moss, *Lycopodium magellanicum*
- member of the *Lycopodium* alkaloids
- tetracyclic framework; one quaternary center

J. Am. Chem. Soc. **1993,** *115*, 2992

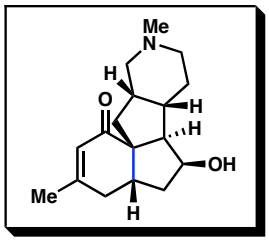


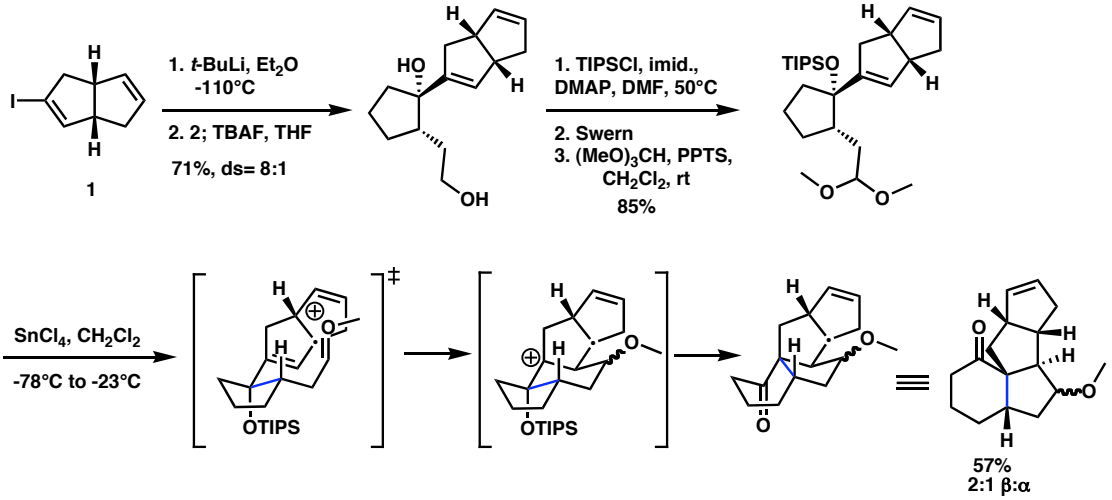
Total Synthesis of (–)-Magellanine



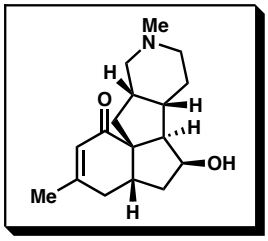


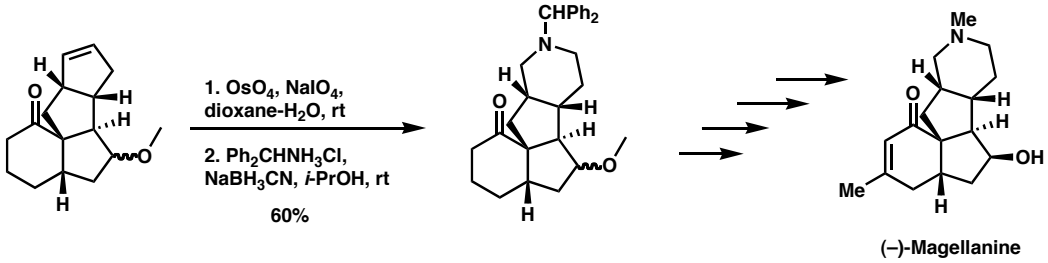
Total Synthesis of (–)-Magellanine: Prins-Pinacol Cyclization



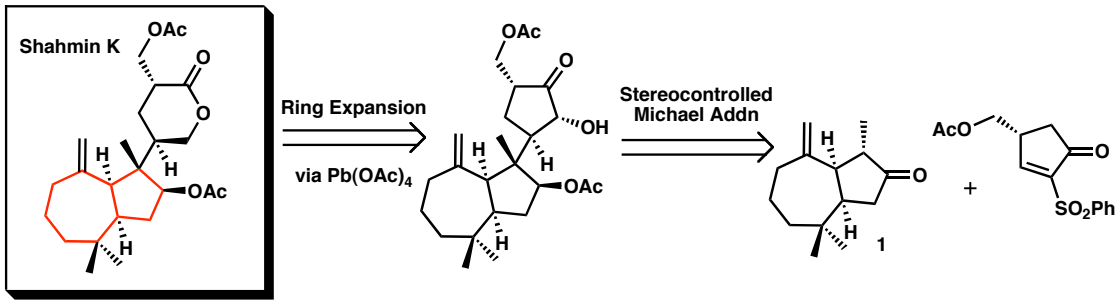


Total Synthesis of (–)-Magellanine: End Game



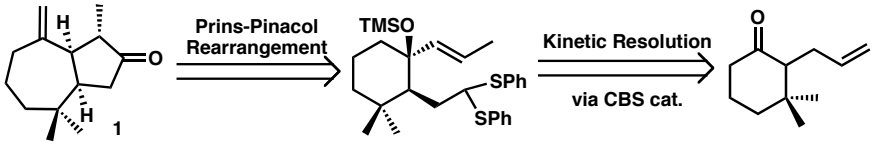


Total Synthesis of (+)-Shahamin K: Retrosynthetic Analysis

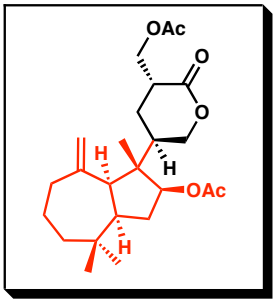


-isolated from Dorid nudibranches
-contains *cis*-hydroazulene (red)

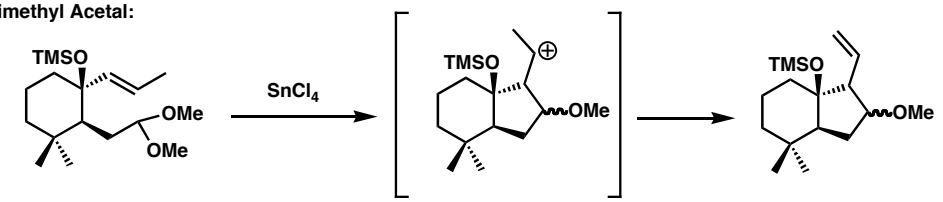
J. Am. Chem. Soc. **2001,** *123*, 4851



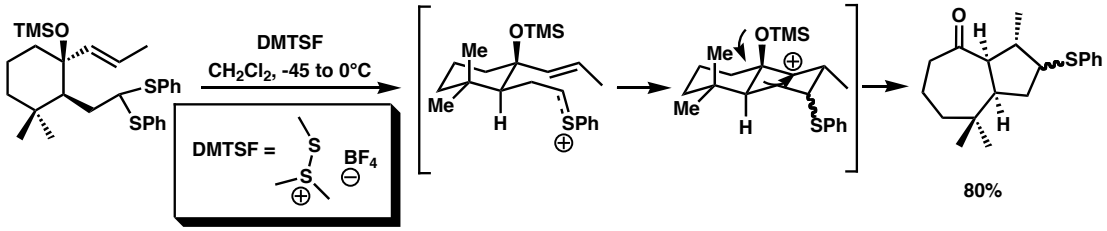
Total Synthesis of (+)-Shahamin K: Prins-Pinacol Cyclization



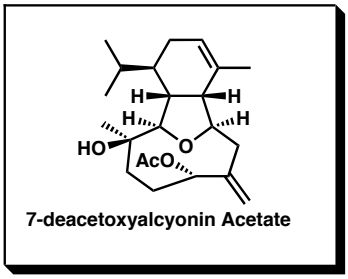
Dimethyl Acetal:

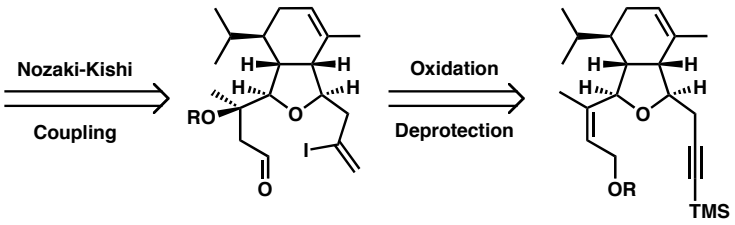


ThioPhenyl Acetal:



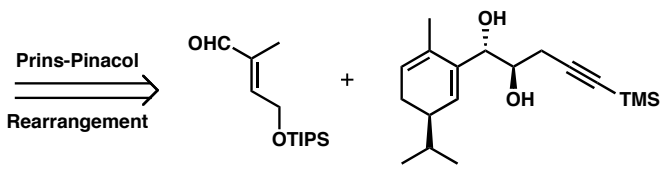
Total Synthesis of (–)-7-Deacetoxyalcyonin Acetate: Retrosynthetic Analysis

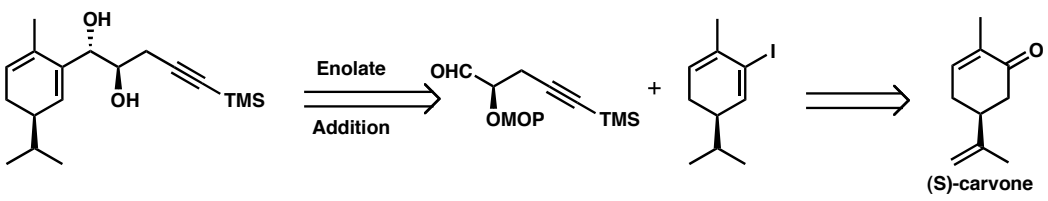




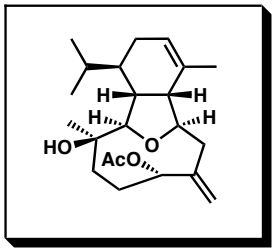
-isolated from soft coral
-class of Eunicellin diterpenes
-contains hydroisobenzofuran and oxonane ring

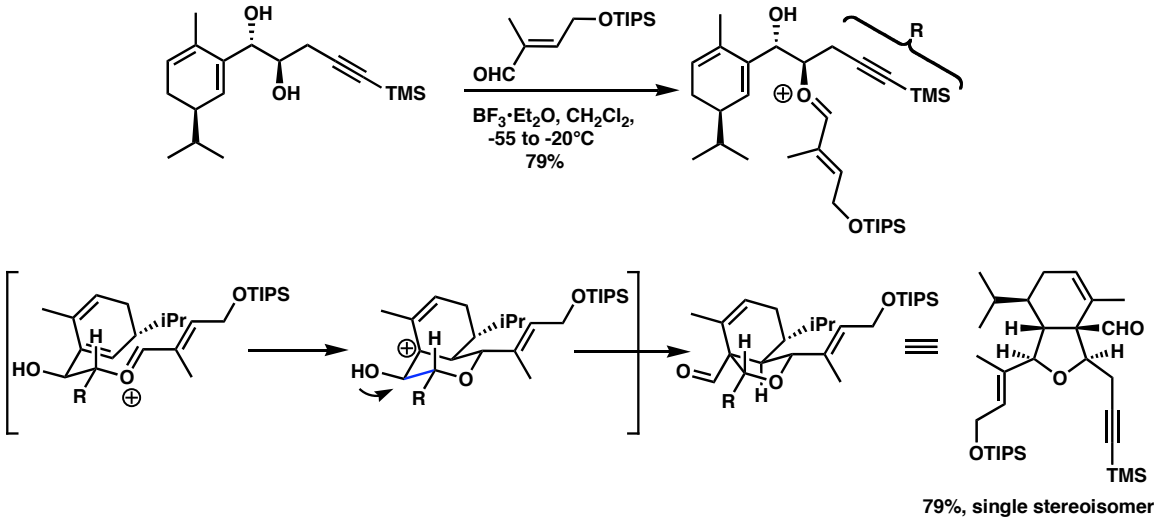
J. Am. Chem. Soc. **1995,** *117*, 10391
Improved: *Org. Lett.* **2000,** *2*, 2683



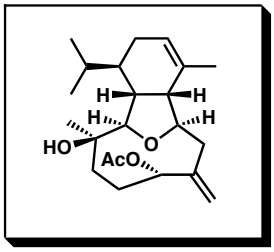


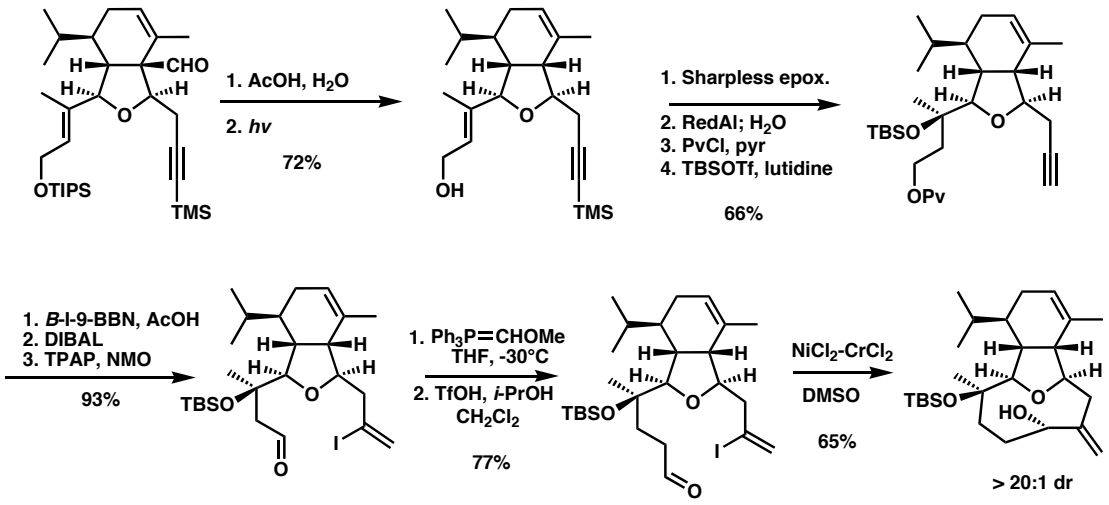
Total Synthesis of (–)-7-Deacetoxyalcyonin Acetate: Formation of the Hydroisobenzofuran System



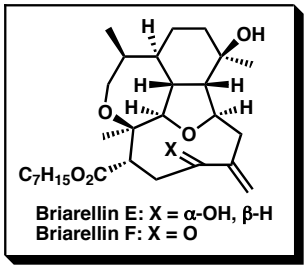


Total Synthesis of (–)-7-Deacetoxyalcyonin Acetate: Formation of the Oxonane Ring



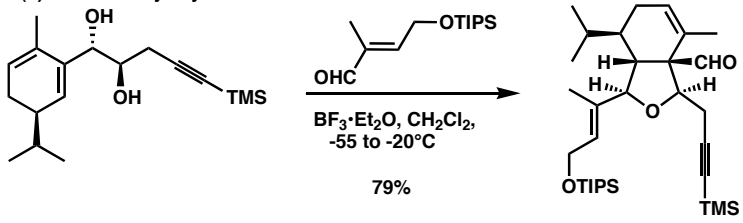


Briarellins E and F: A Similar Approach to Similar Molecules

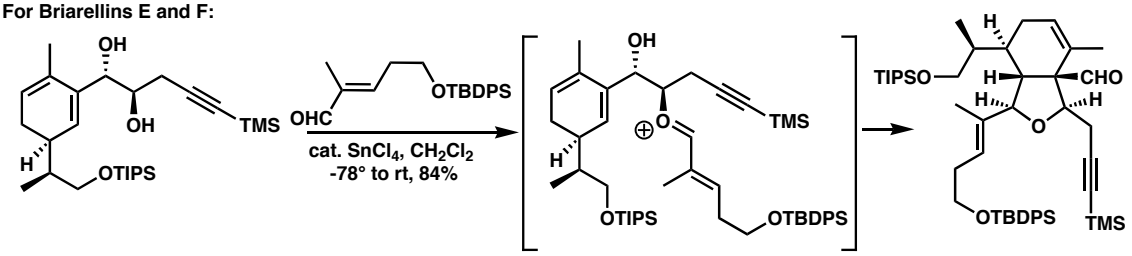


J. AM. Chem. Soc. **2003,** *125*, 6650

For (–)-7-Deacetoxyalcyonin:



For Briarellins E and F:



Introduction:

1. Introduction to Larry Overman

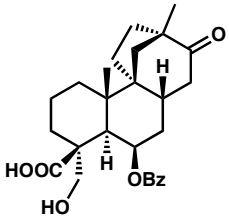
2. Targets Achieved by Prins-Pinacol Rearrangement
   a. (–)-Magellanine
   b. (+)-Shahamin K
   c. (–)-7-Deacetoxyalcyonin Acetate
   d. Briarellins E and F

3. Targets Achieved by an Aza-Cope-Mannich Rearrangement
   a. (±)-Meloscine
   b. (±)-*dl*-16-Methoxytabersonine
   c. (–)-Pancracine
   d. (–)-Strychnine

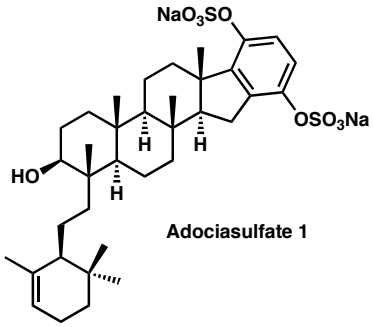
4. Targets Achieved via Asymmetric Heck Reaction
   a. (–)-Scopadulcic Acid A
   b. (–)-Chimonanthine
   c. (–)-Morphine

5. Misc. Targets achieved in the Overman Lab
   a. Adociasulfate 1
   b. (±)-Kumausallene

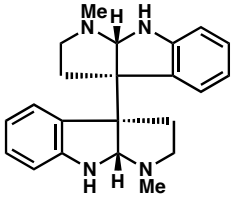
6. Conclusion



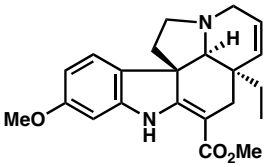
Scopadulcic A



Adociasulfate 1

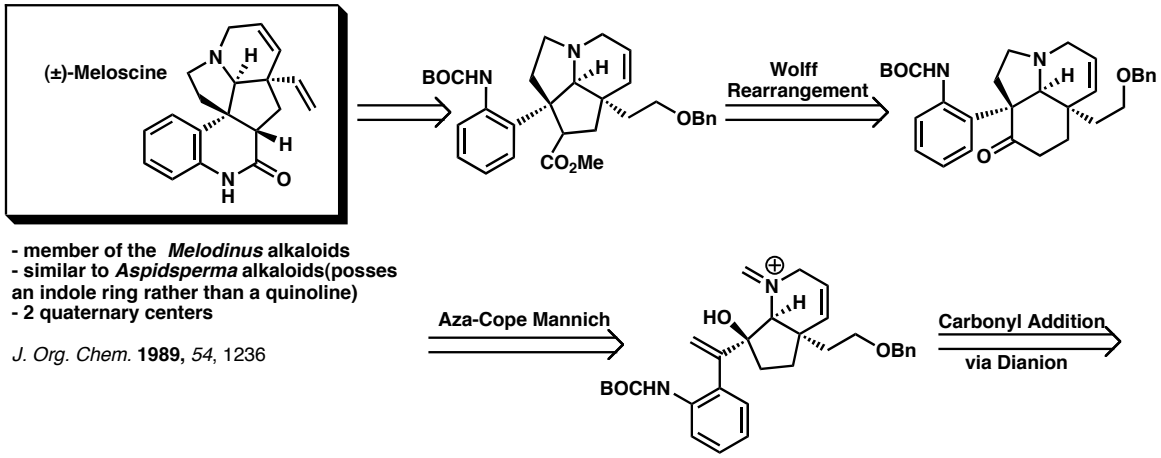


Chimonanthine

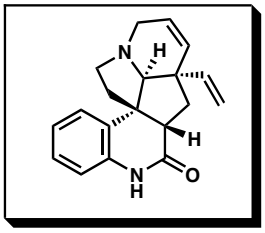


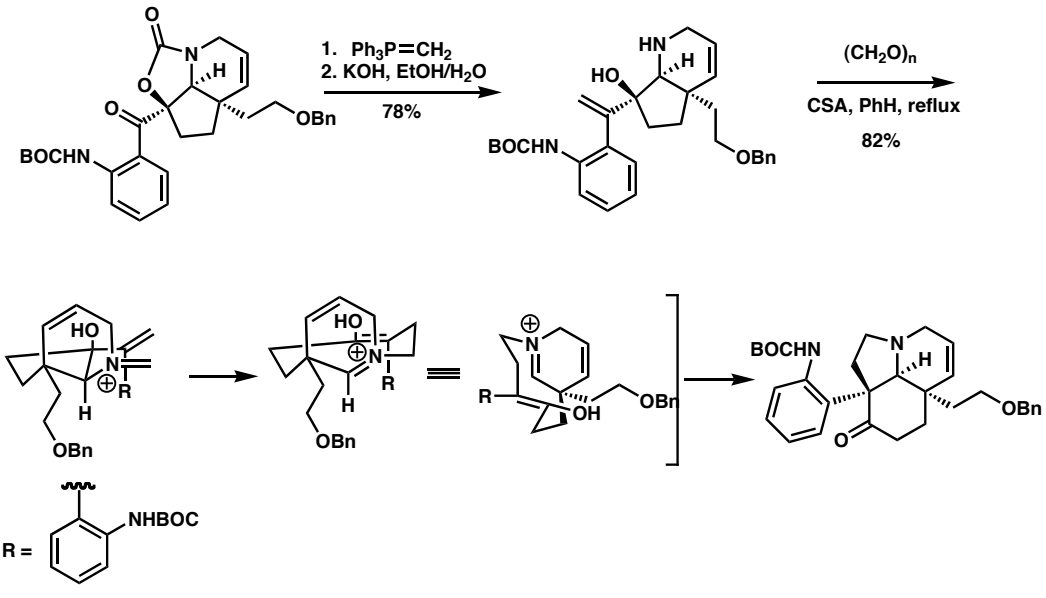
dl-16-Methoxytabersonine

Target: (±)-Meloscine, a Pentacyclic Alkaloid

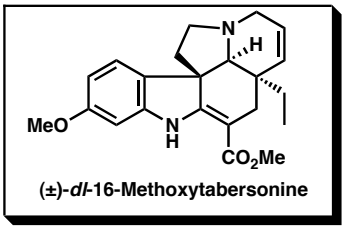


Key Transformations Towards (±)-Meloscine: Aza-Cope Mannich

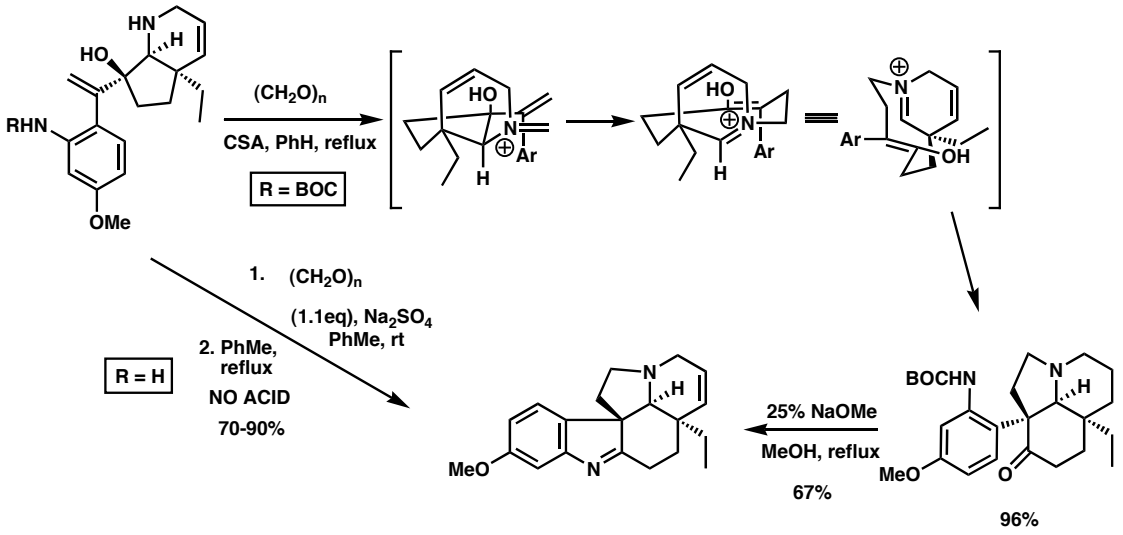




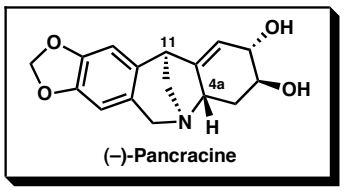
Part II: A Similar Approach to a Similar Molecule



(±)-*dl*-16-Methoxytabersonine



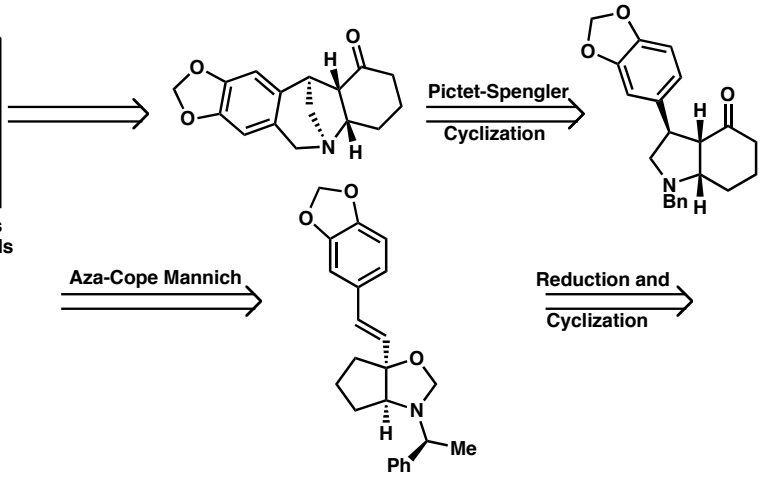
(–)-Pancracine: Another Alkaloid realized by the Aza-Cope Mannich Methodology

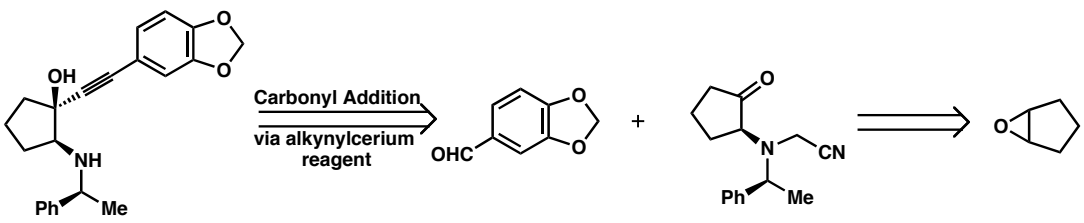


(–)-Pancracine

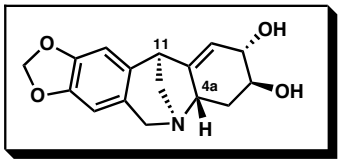
-isolated from various plant species
-member of *Amaryllidaceae* alkaloids
-pentacyclic structure

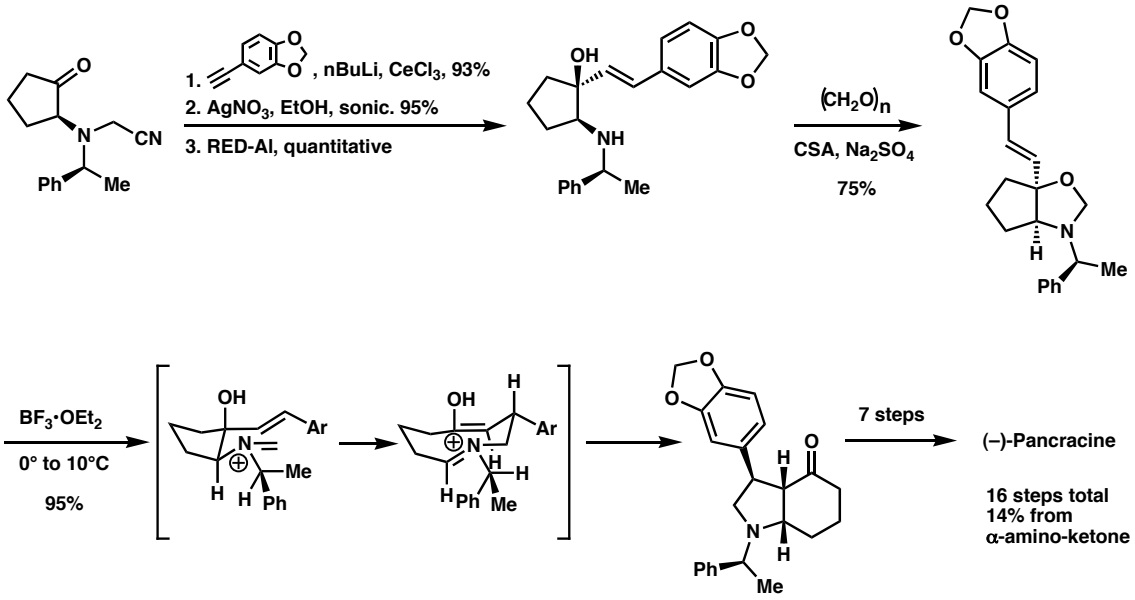
J. Org. Chem. **1993,** *58*, 4662



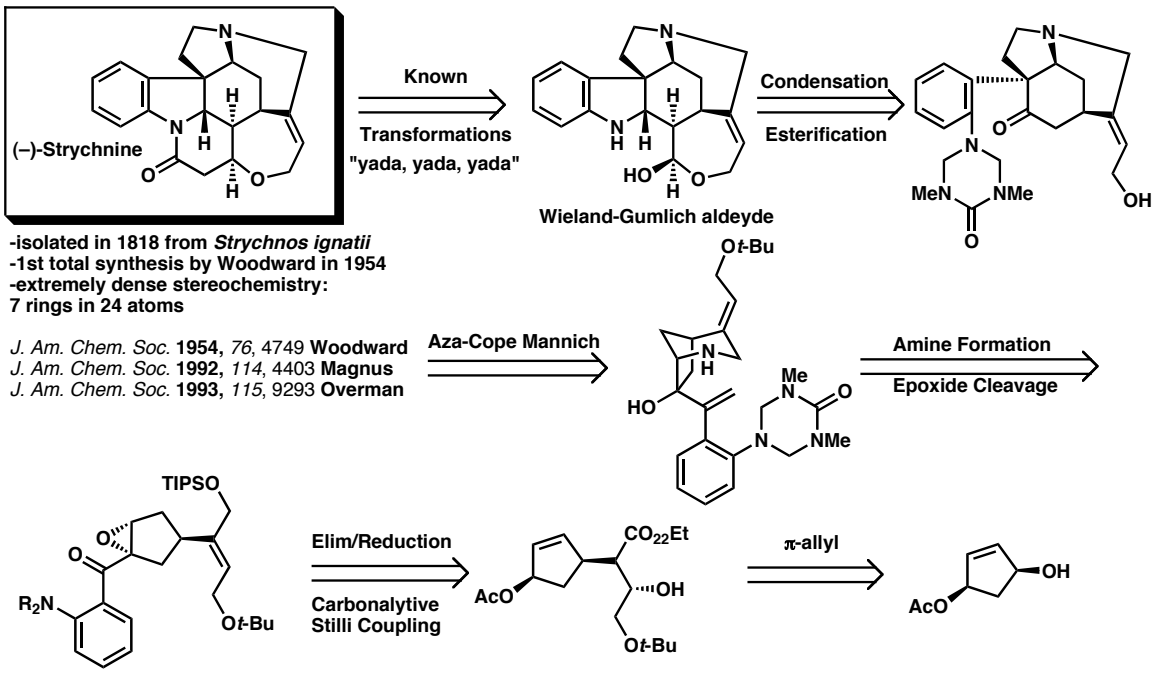


Key Steps Torwards the Total Synthesis of (–)-Pancracine

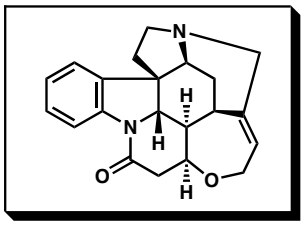


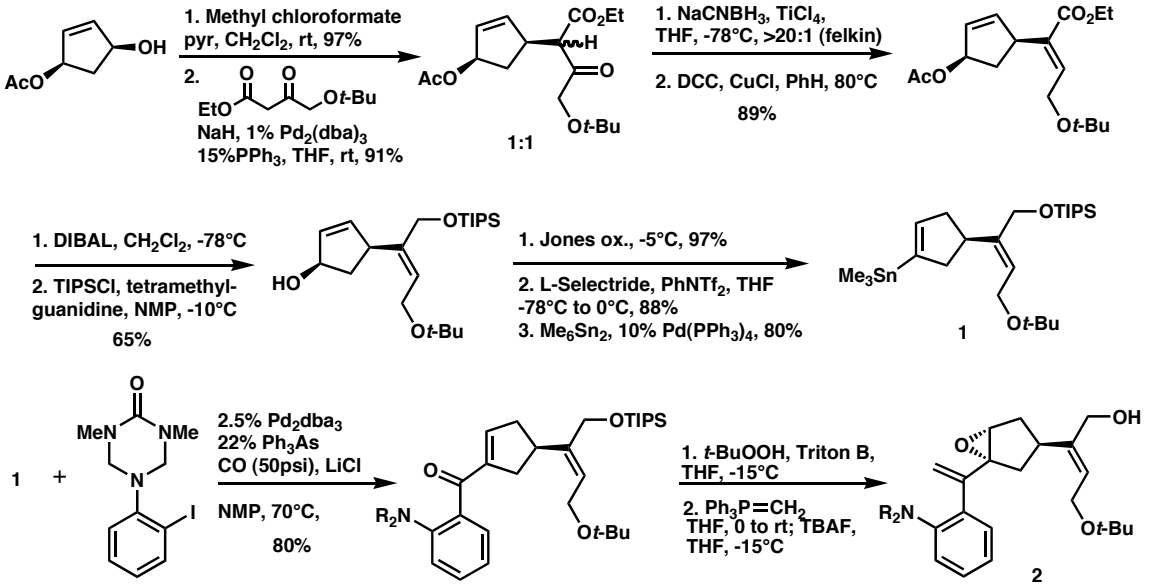


Last, but surely not least, all hail to (–)-Strychnine

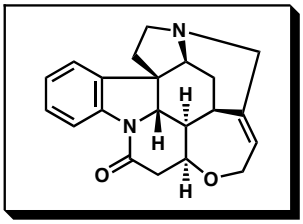


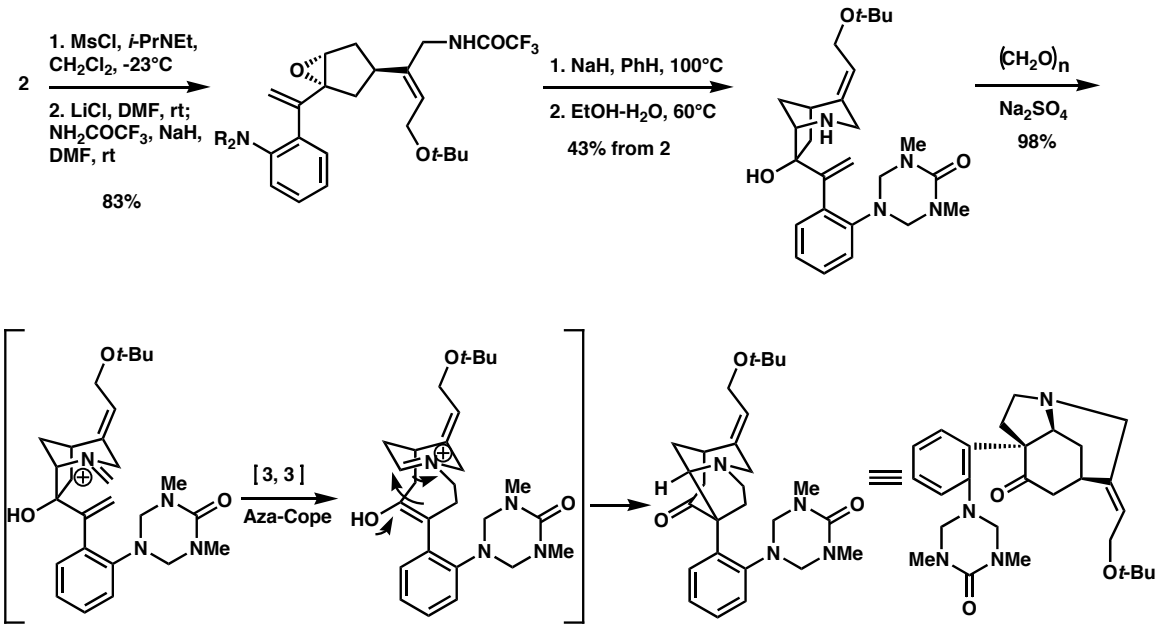
(–)-Strychnine: In the Forward Direction





(–)-Strychnine: In the Forward Direction (cont'd)





Introduction:

1. Introduction to Larry Overman

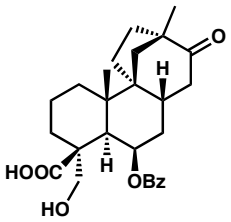
2. Targets Achieved by Prins-Pinacol Rearrangement
   a. (–)-Magellanine
   b. (+)-Shahamin K
   c. (–)-7-Deacetoxyalcyonin Acetate
   d. Briarellins E and F

3. Targets Achieved by an Aza-Cope-Mannich Rearrangement
   a. (±)-Meloscine
   b. (±)-*dl*-16-Methoxytabersonine
   c. (–)-Pancracine
   d. (–)-Strychnine

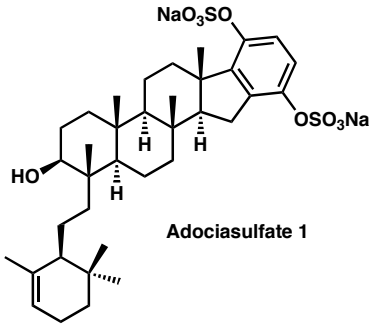
4. Targets Achieved via Asymmetric Heck Reaction
   a. (–)-Scopadulcic Acid A
   b. (–)-Chimonanthine
   c. (–)-Morphine

5. Misc. Targets achieved in the Overman Lab
   a. Adociasulfate 1
   b. (±)-Kumausallene

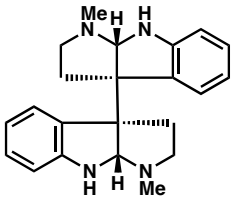
6. Conclusion



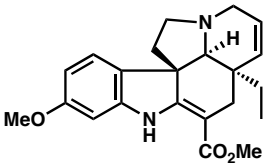
Scopadulcic A



Adociasulfate 1

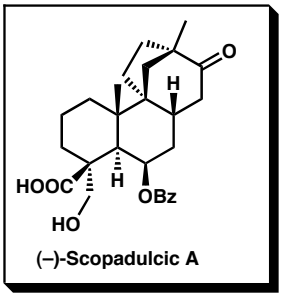


Chimonanthine



dl-16-Methoxytabersonine

Natural Products Arising from the Asymmetric Heck Reaction: Part I
(–)-Scopadulcic A

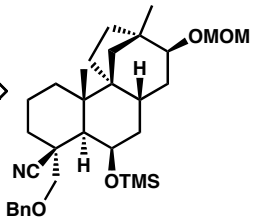


(–)-Scopadulcic A

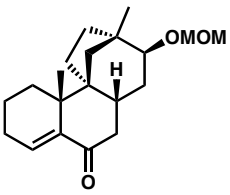
- isolated from *Scoparia dulcis L.* (herb)
- tetracyclic diterpene acid
- 4 quaternary centers

J. Am. Chem. Soc. **1999,** *121*, 5467

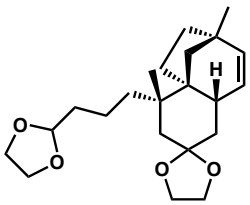
F.G.I.



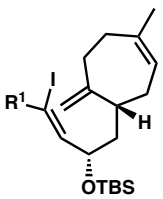
Asym. 1, 4 addn
Diastereoselective Reduction



Stereoselective Epoxide Cleavage
Acid catalyzed Aldol Condensation

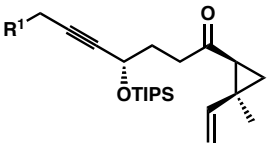


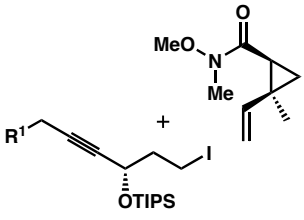
Heck Cascade



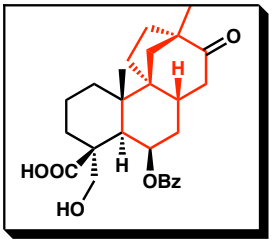
$R^1 = CH_2CH_2CH(OCH_2CH_2O)$

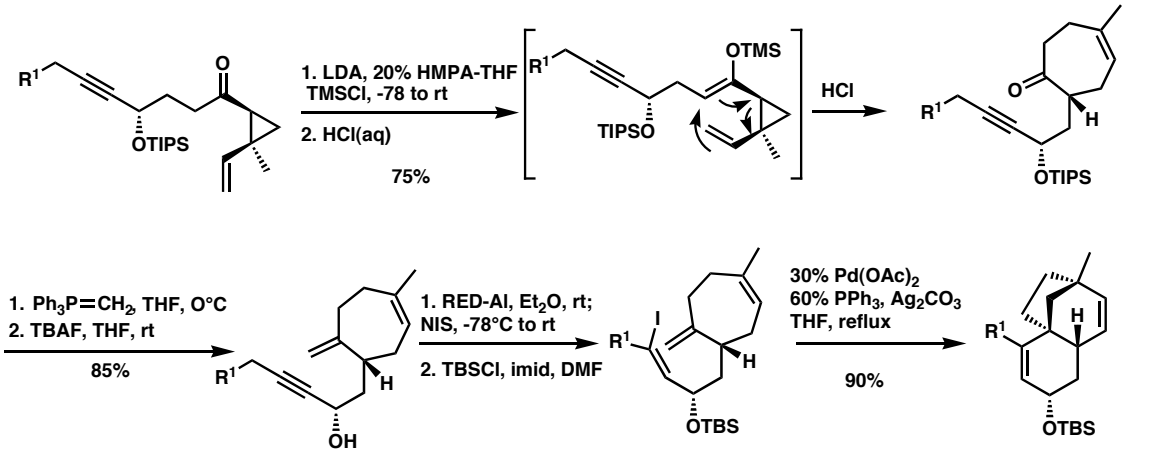
Divinylcyclopropane Rearrangement





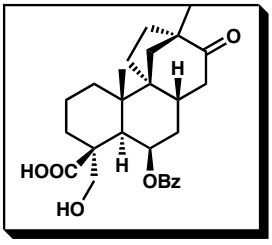
Rapid Ring Formation via Divinyl Cyclopropane Rearrangement and the Asymmetric Heck

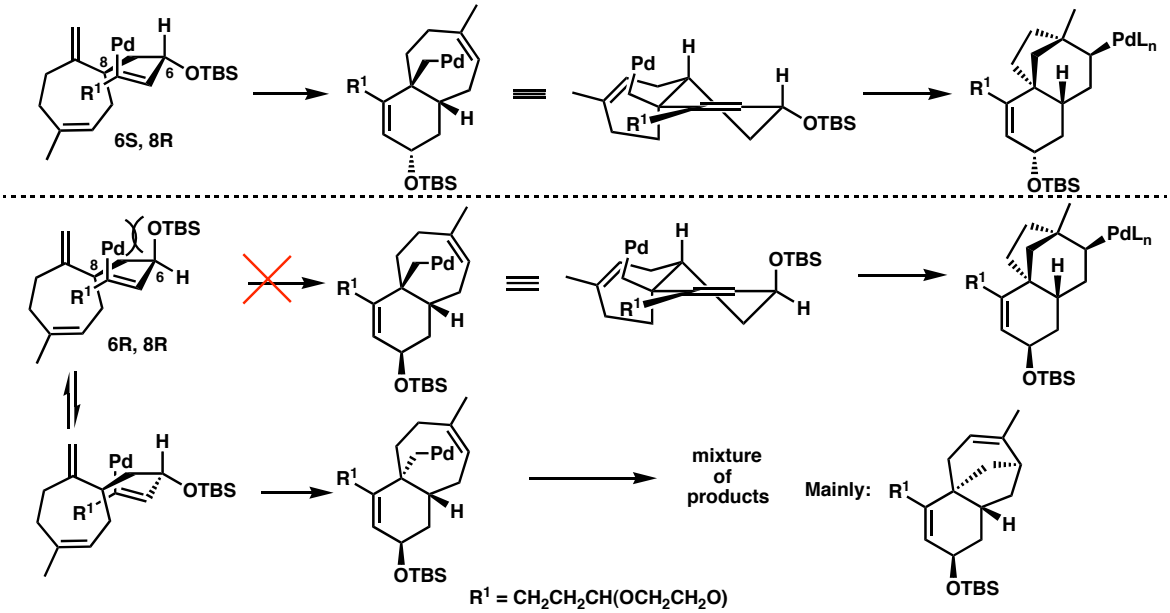




$R^1 = CH_2CH_2CH(OCH_2CH_2O)$

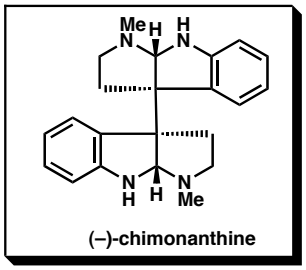
A Closer Insight into theAsymmetric Heck Cascade





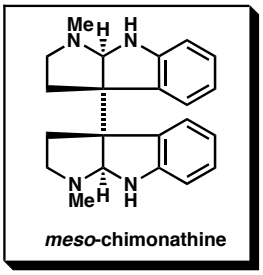
$R^1 = CH_2CH_2CH(OCH_2CH_2O)$

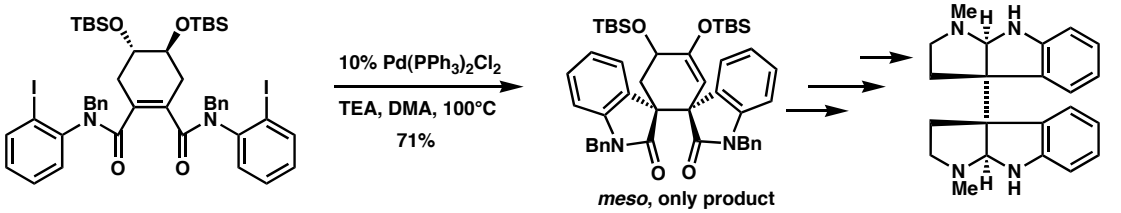
Formation of Vicinal Quaternary Carbon Centers using Intramolecular Heck Cascade

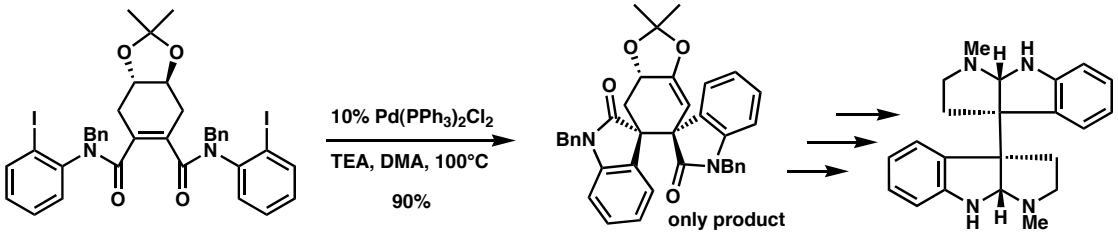


-isolated in dendrobatid frogs
-exsist as *meso*, and chiral C_2-symmetric molecules
-vicinal quaternary centers

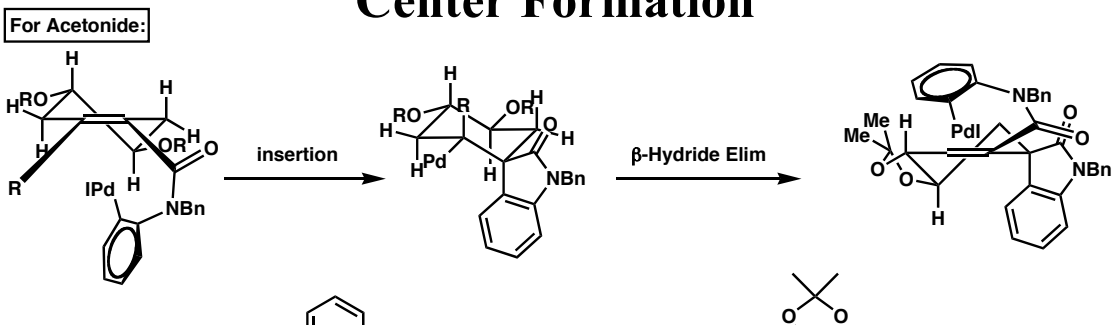
J. Am. Chem. Soc. **1999,** *121*, 7702

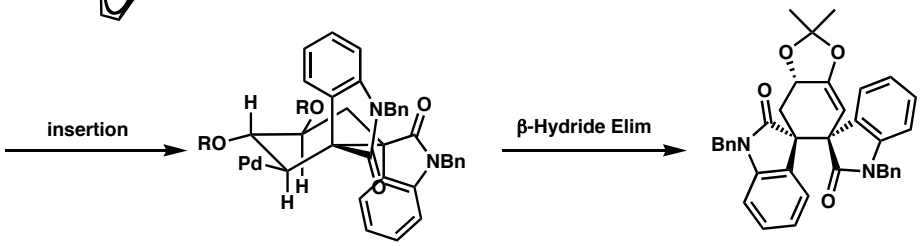


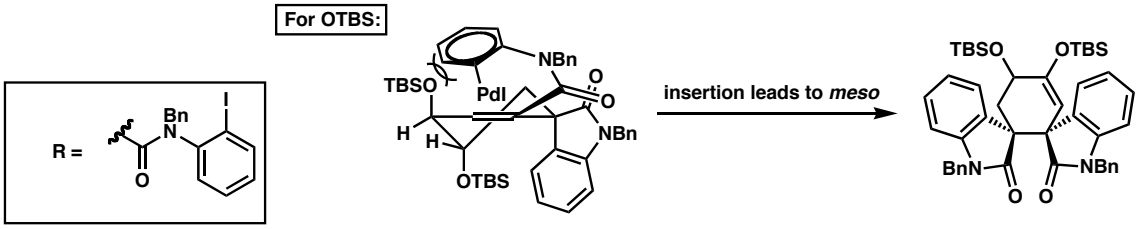




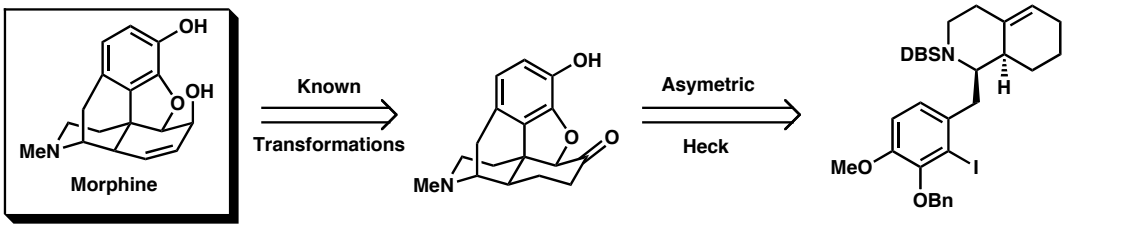
Meyer's Theory of Vicinal Quaternary Center Formation





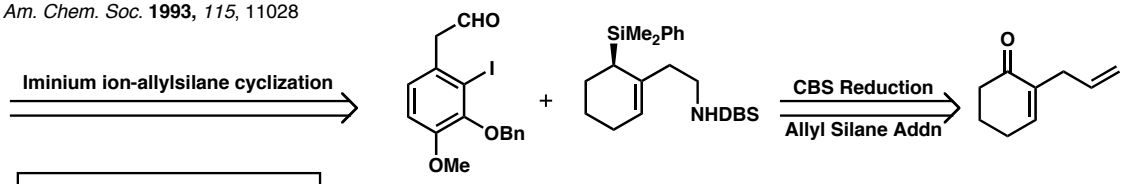


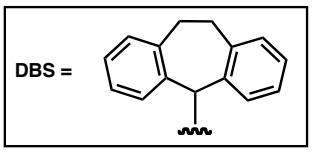
Asymmetric Synthesis of My favorite Analgesic: (–)-Morphine



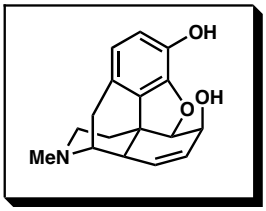
- found in opium containing plants
- opium receptor antagonists
- pentacyclic alkaloid
- one quaternary center

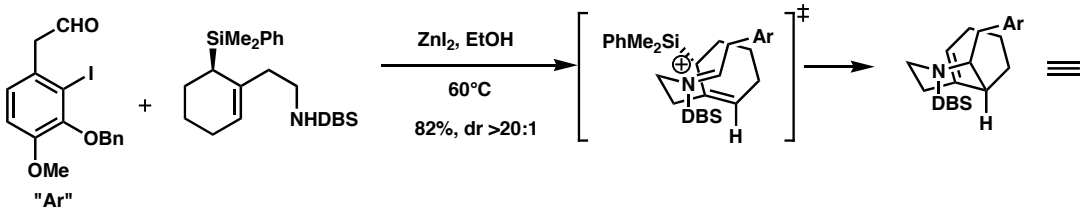
J. Am. Chem. Soc. **1993,** *115*, 11028

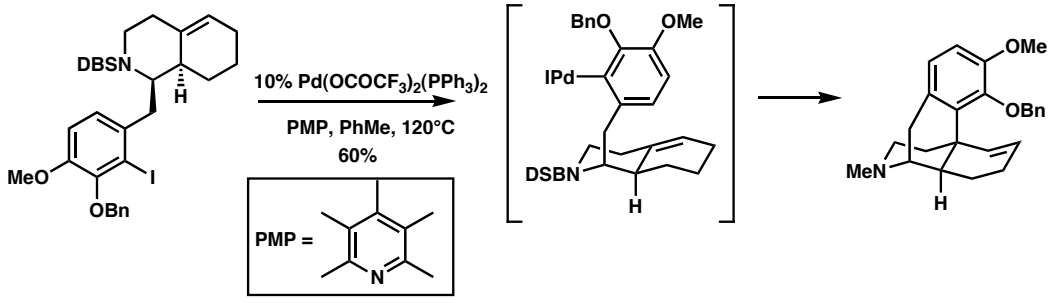




The Rapid Synthesis of the Morphine Core







Introduction:

1. Introduction to Larry Overman

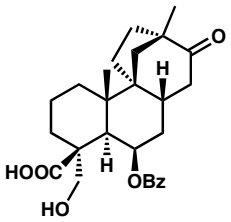
2. Targets Achieved by Prins-Pinacol Rearrangement
   a. (–)-Magellanine
   b. (+)-Shahamin K
   c. (–)-7-Deacetoxyalcyonin Acetate
   d. Briarellins E and F

3. Targets Achieved by an Aza-Cope-Mannich Rearrangement
   a. (±)-Meloscine
   b. (±)-*dl*-16-Methoxytabersonine
   c. (–)-Pancracine
   d. (–)-Strychnine

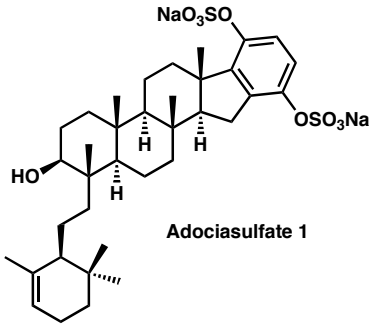
4. Targets Achieved via Asymmetric Heck Reaction
   a. (–)-Scopadulcic Acid A
   b. (–)-Chimonanthine
   c. (–)-Morphine

5. Misc. Targets achieved in the Overman Lab
   a. Adociasulfate 1
   b. (±)-Kumausallene

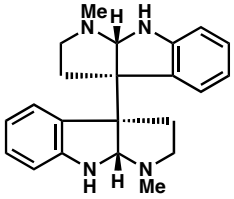
6. Conclusion



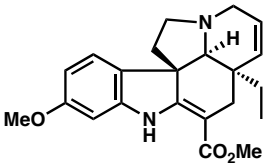
Scopadulcic A



Adociasulfate 1

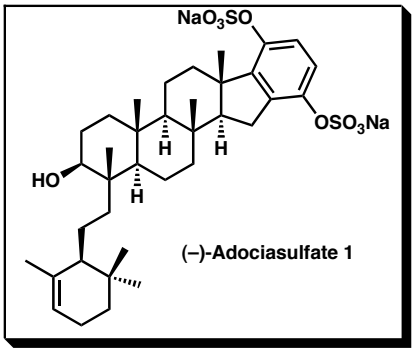


Chimonanthine



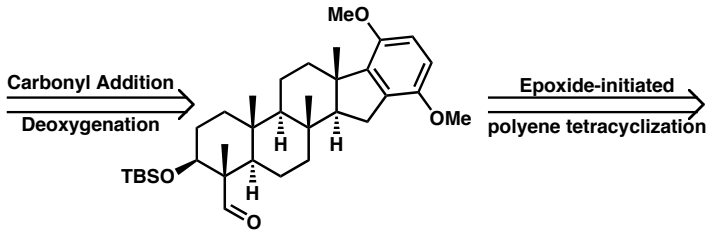
dl-16-Methoxytabersonine

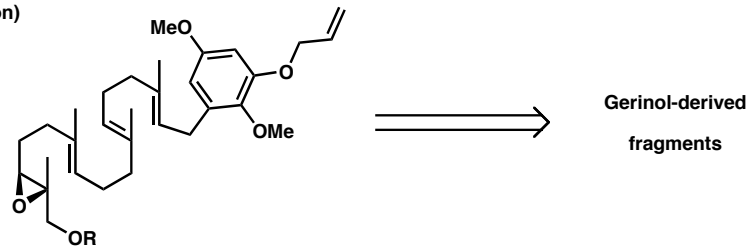
Retrosynthesis of (–)-Adociasulfate 1



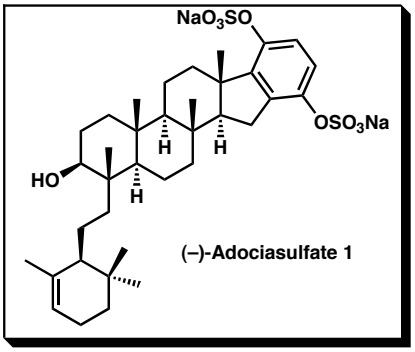
- isolated in sea sponges off of Australia
- kinesin inhibitors (slows cell division)
- proton pump inhibitors

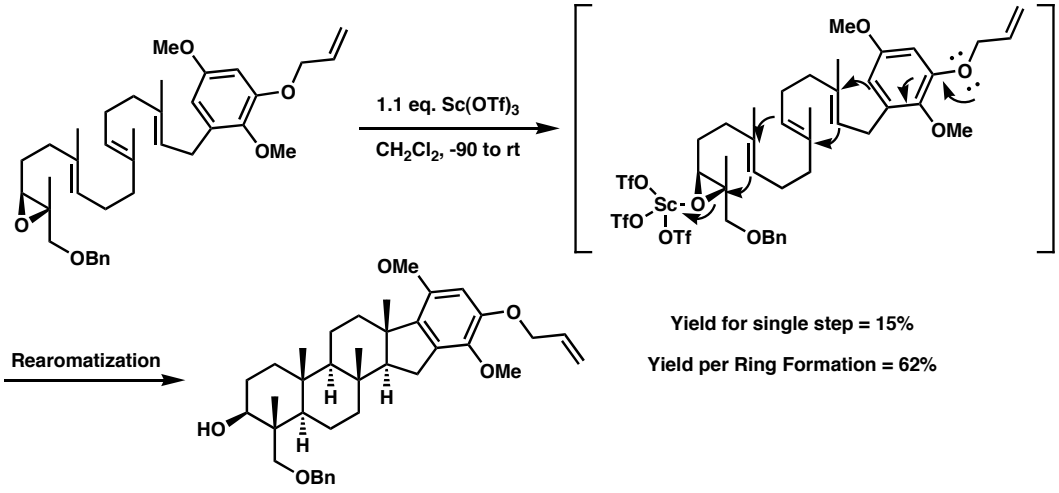
J. Am. Chem. Soc. **1999,** *121*, 12206





Epoxide-initiated polyene tetracyclization to Form the Pentacyclic system of (–)-Adociasulfate 1

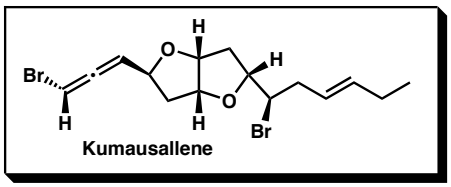




Yield for single step = 15%

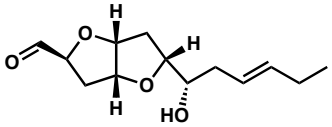
Yield per Ring Formation = 62%

Retrosynthesis of (±)-Kumausallene



Ti promoted acetylide addition

Sn2' addition to form allene

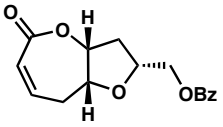


- isolated from red algae
- nonisoprenoid sesquiterpene
- family contains cis-dialkyltetrahydrofuran unit

J. Org. Chem. **1993,** *58*, 2468

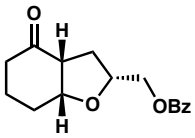
Tandem Methanolysis/cyclization

Sakurai Reaction

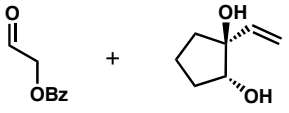


Baeyer-Villager

Oxidation

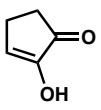


Prins-Pinacol Rearrangement

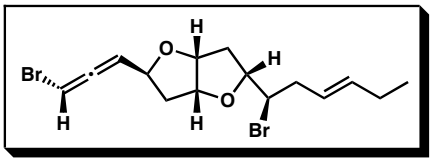


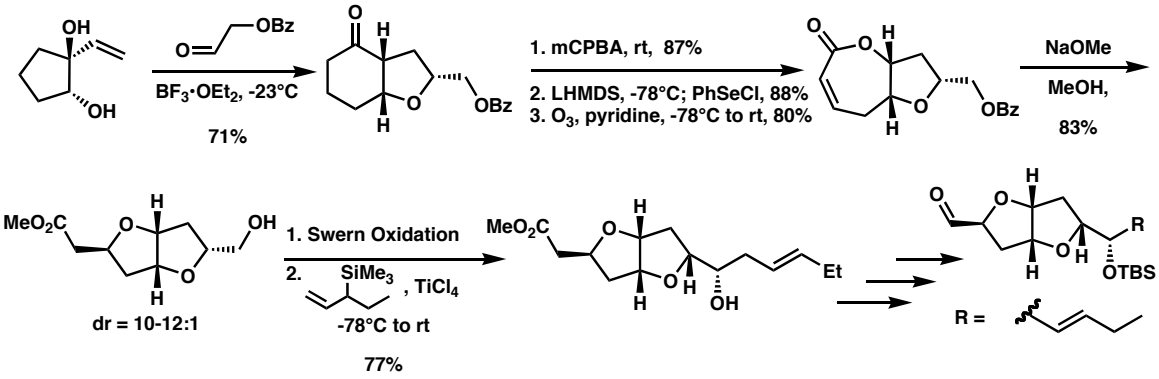
Grignard Addition

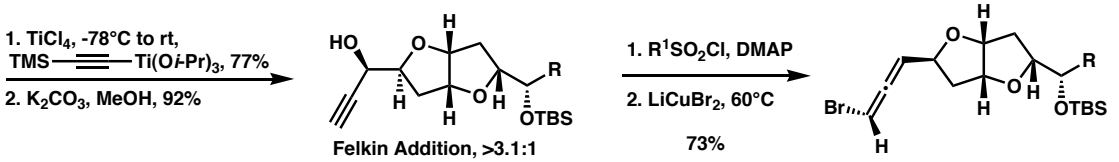
STAB Reduction



The Total Synthesis (most of it) of (±)-Kumausallene







R^1 = 2,4,6-triisopropylphenyl

To Conclude with Larry Overman

Goals of the Talk:

1. The power of the Prins-Pinacol Rearrangement to form highly substituted tetrahydrofurans with high stereo-control

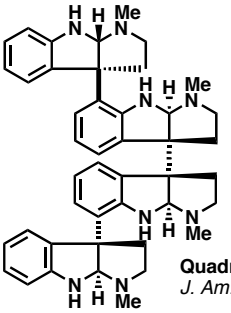
2. The power of the Aza-Cope Mannich to form highly substituted pyrrolidine rings and fused ring systems in a highly controlled manner

3. The power of the Heck Reaction to form isolated, and vicinal quaternary centers in an asymmetric manner

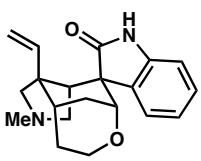
4. The amazing variety of natural products that have been synthesized by the latter methodologies, and more importantly, by a creative, thoughtful, and elegant mind of Larry Overman

Acknowledgements: There is one man to acknowledge: Larry Overman

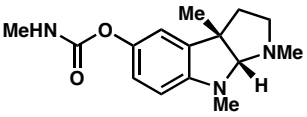
Other Molecules that are worth looking at:



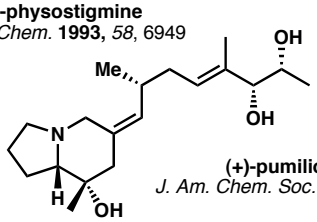
Quadrigemine C and Psycholeine
J. Am. Chem. Soc. **2002,** *124*, 9008



(±)-Gelsemine
ACIEE, **1999**, *38*, 2934



(–)-physostigmine
J. Org. Chem. **1993,** *58*, 6949



(+)-pumiliotoxin B
J. Am. Chem. Soc. **1984,** *106*, 4192