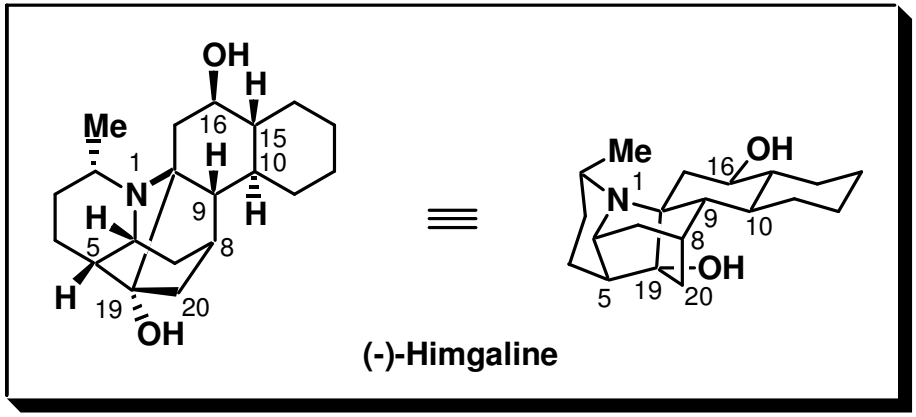
# Total Synthesis of (-)-Himgaline

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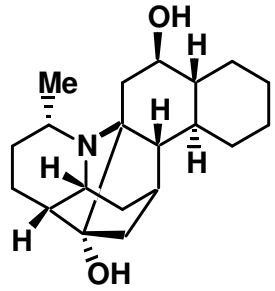
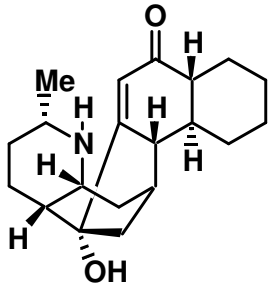
9-30-06 Literature Presentation
Wipf Group

# Structurally Complex Alkaloids Isolated from the Tree, *Galbulimima belgraveana*

A Few Representative Examples from the 28 Novel Structures Isolated

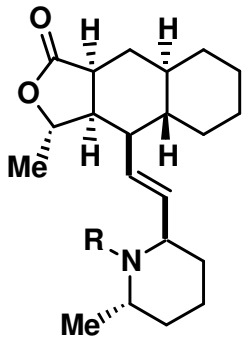



**(-)-Himgaline**

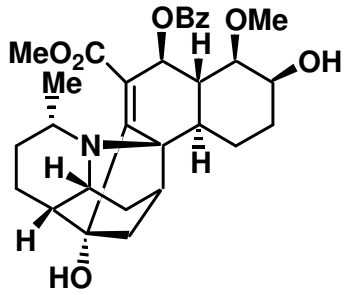



**GB 13**

Structure elucidation was conducted utilizing exhaustive degradation studies




**R = Me Himbacine**
**R = H Himbaline**

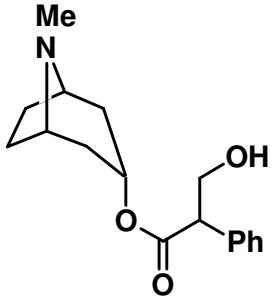



**Himandridine**

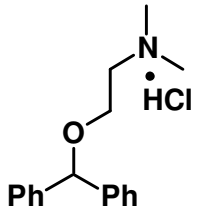
Mander, L. N.; Prager, R. H.; Rasmussen, M.; Ritchie, E.; Taylor, W. C. *Aus. J. Chem.* **1967,** *20,* 1705.

# Is this Merely a Challenge for Synthetic Chemists?
## *Or is there also Therapeutic Value?*

## Some Muscarinic Antagonists




**Atropine**
Dilate pupils

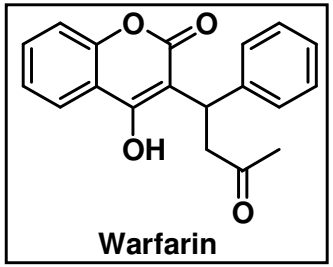



**Benadryl**
**(Pfizer)**
Allergies

## Some Antithrombotic Agents (aka anticoagulants)

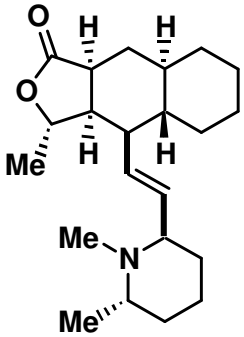
Thrombosis is the formation of clots within blood vessels or veins

**Heparin** – A glycosaminoglycan




**Warfarin**

•Some anticoagulants suffer from low efficacy and oral bioavailability




**Himbacine**

•Himbacine is a potent inhibitor of the muscarinic receptor M2 by ceasing the release of acetylcholine and may serve as a potential lead for Alzheimer's therapy

•Muscarinic receptors are present in the CNS and play various roles including cognitive thinking and memory

•Himbacine also demonstrates potential antithrombotic activity

# Why are Anticoagulant/Antithrombotic Agents Important?

## Some Thrombotic Diseases

•Deep venous thrombosis (DVT) – formation of a clot in a deep vein (typically in the legs which causes discomfort and may become more severe if embolism occurs)

•Renal vein thrombosis – leads to reduction in drainage of the kidney (can affect urination)

•Atherosclerosis – disease regarding hardening of arteries (underlying cause of strokes and heart attacks)

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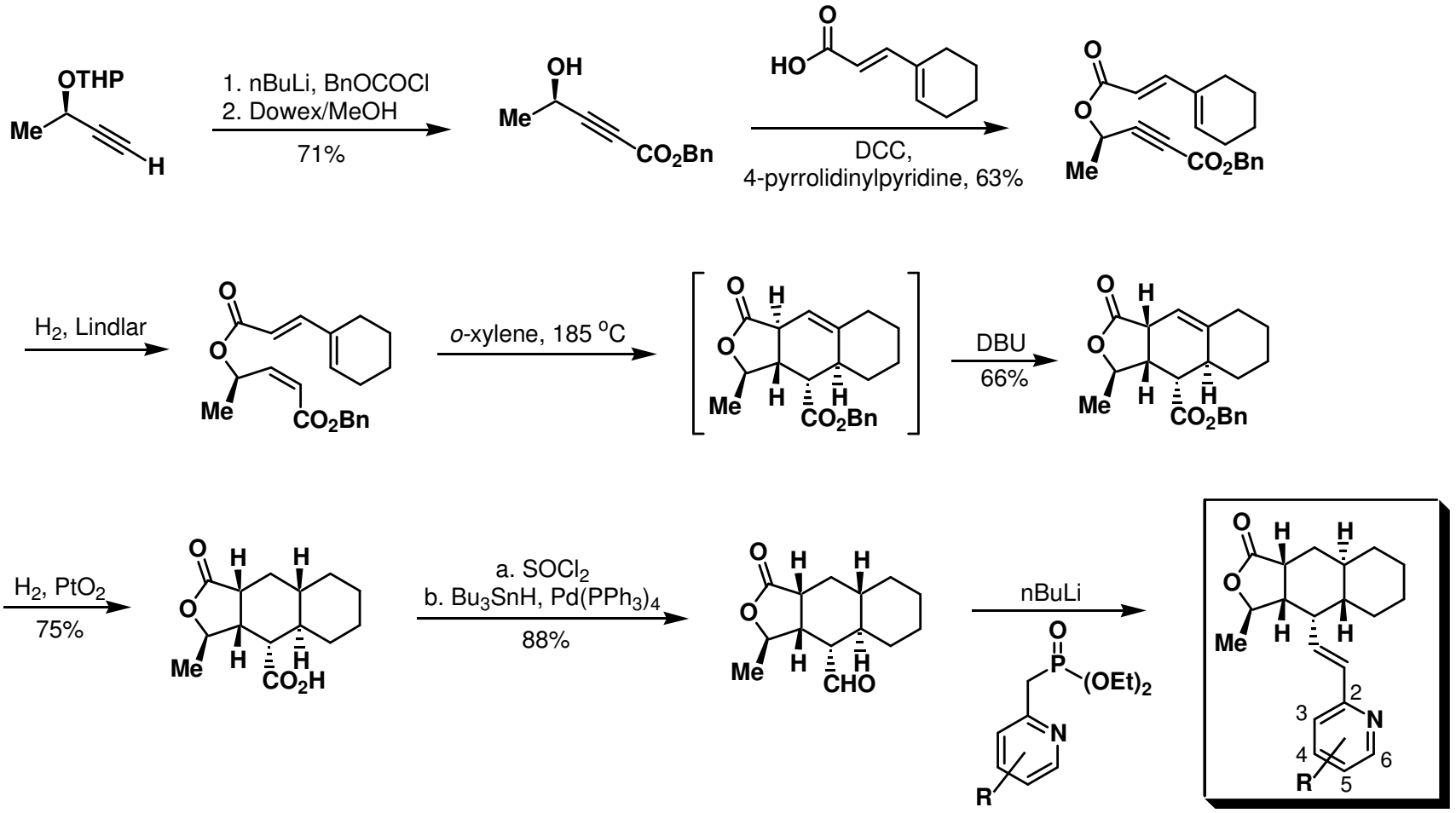
•According to NIH, about 2 million people get DVT and 60,000 die from pulmonary embolism per year

•Diseases caused by atherosclerosis are the leading cause of illness and death in the US (NIH)

http://www.health-news-and-information.com/3lourdesnet/libv/h16.shtml
http://www.nhlbi.nih.gov/health/dci/Diseases/Atherosclerosis/Atherosclerosis_WhatIs.html

# Development of Orally Active Antithrombotic Agents
## *Synthesis of Himbacine Analogues*




Chackalamannil, S.; et. al. *J. Med. Chem.* **2005,** *48,* 5884.

# Pharmacological Profile of Himbacine Analogues

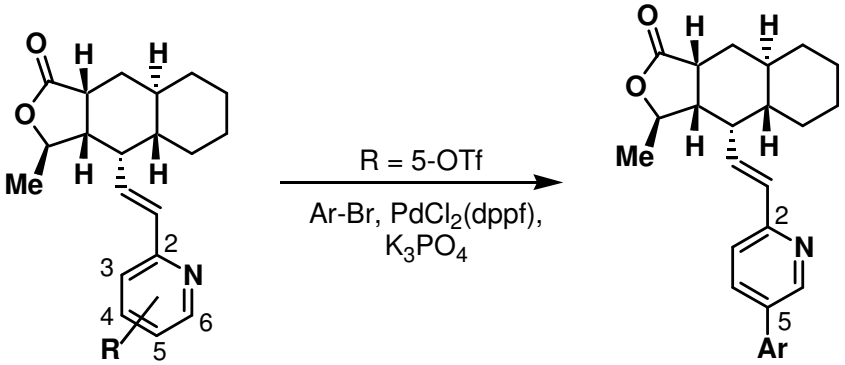



**Table 1.** SAR of Non-Aryl Substituted Pyridine Derivatives (Compound Type A)

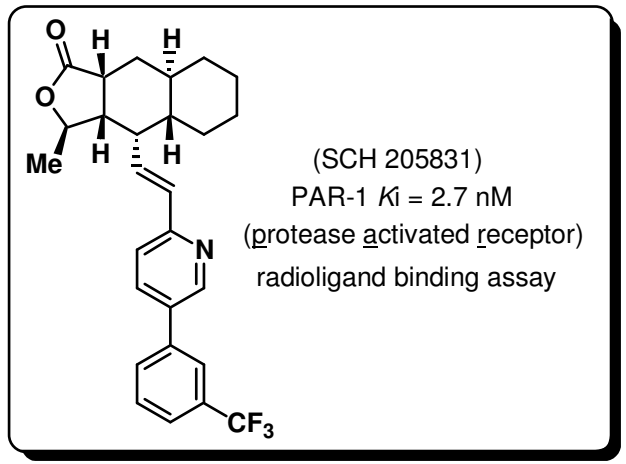
| compd | R | $IC_{50}$ (nM)[a] | compd | R | $IC_{50}$ (nM)[a] |
|---|---|---|---|---|---|
| (±)-**12** | 6-$CH_3$ | 300 | (±)-**25** | 6-*cy*-Pr | 210 |
| (±)-**14** | H | 4000 | (±)-**26** | 6-$NHCH_3$ | 1250 |
| (±)-**15** | 3-$CH_3$ | >5000 | (±)-**27** | 6-$CH_2OH$ | 1500 |
| (±)-**16** | 4-$CH_3$ | 2100 | (±)-**28** | 6-$CH_2OCH_3$ | 850 |
| (±)-**17** | 5-$CH_3$ | 1100 | (±)-**29** | 6-$CH_2Ph$ | 900 |
| (±)-**18** | 6-Et | 85 | (±)-**30** | 6-$OCH_3$ | inactive |
| (±)-**19** | 6-vinyl | 150 | (±)-**31** | 6-Ph | inactive |
| (±)-**20** | 6-*n*-Pr | 250 | (±)-**32** | 5-Bn | 3681 |
| (±)-**21** | 6-*n*-Bu | 143 | (±)-**33** | 5-$OCH_3$ | 325 |
| (±)-**22** | 6-*n*-hex | 3500 | (±)-**34** | 5-OBn | 19 |
| (±)-**23** | 6-*i*-Pr | 725 | (+)-**35** | 5-Ph | 27 |
| (±)-**24** | 6-*i*-Bu | 550 | | | |

[a] PAR-1 binding assay ligand: [$^3$H]haTRAP, 10 nM ($K_d$ = 15 nM).[30]

**Table 2.** SAR of 5-Aryl Substituted Pyridine Derivatives (Compound Type B)

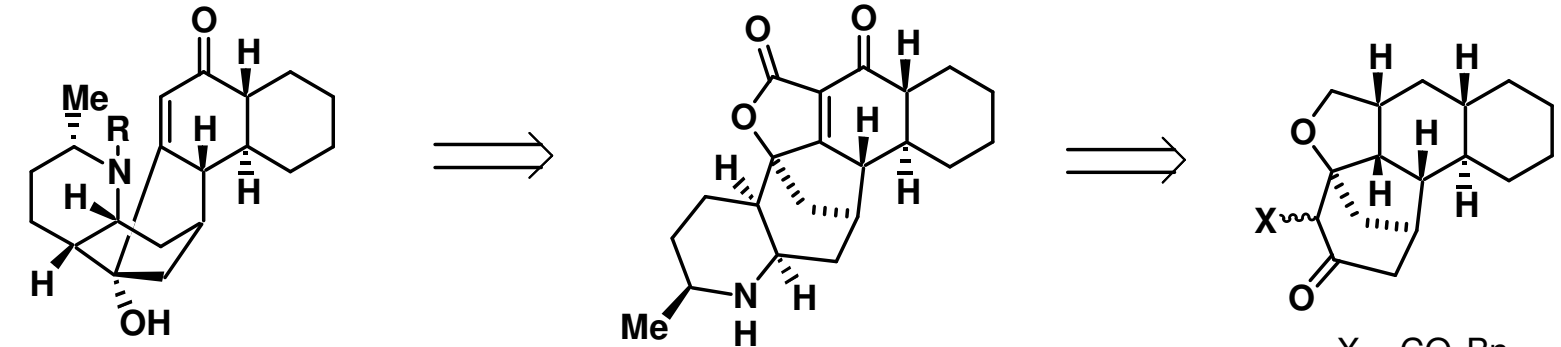
| compd | Ar | $IC_{50}$ (nM)[a] | rat PK[b] AUC, $C_{max}$ |
|---|---|---|---|
| (+)-**35** | Ph | 27 | 917, 453 |
| (±)-**36** | (*p*-$CH_3$)-phenyl | 325 | ND |
| (±)-**37** | (*p*-$OCH_3$)-phenyl | 204 | ND |
| (±)-**38** | (*p*-F)-phenyl | 467 | ND |
| (±)-**39** | (*p*-Cl)-phenyl | 1000 | ND |
| (±)-**40** | (*p*-$CF_3$)-phenyl | >300 | ND |
| (+)-**41** | (*o*-$CH_3$)-phenyl | 14 | 2805, 1222 |
| (+)-**42** | (*o*-$CF_3$)-phenyl | 46 | 2350, 1004 |
| (+)-**43** | (*o*-$CO_2Et$)-phenyl | 44 | ND |
| (+)-**44** | (*o*-$OCH_3$)-phenyl | 11 | 413, 419 |
| (+)-**45** | (*o*-F)-phenyl | 22 | 2467, 1077 |
| (+)-**46** | (*o*-Cl)-phenyl | 26 | 4285, 1785 |
| (+)-**47** | (*m*-F)-phenyl | 35 | 3553, 1516 |
| (+)-**48** | (*m*-Cl)-phenyl | 10 | 4112, 1457 |
| (+)-**49** | (*m*-Br)-phenyl | 25 | ND |
| (+)-**50** | (*m*-CN)-phenyl | 25 | ND |
| (+)-**51** | (*m*-$CH_3$)-phenyl | 13 | 331, 380 |
| (+)-**52** | (*m*-*i*Pr)-phenyl | 19 | 258, 289 |
| (+)-**53** | (*m*-$OCH_3$)-phenyl | 28 | 12, 20 |
| (+)-**54** | (*m*-$SO_2NH_2$)-phenyl | 100 | ND |
| (+)-**55** | (*m*-$CF_3$)-phenyl | 11 | 6116, 2300 |

[a] PAR-1 binding assay ligand: [$^3$H]haTRAP, 10 nM ($K_d$ = 15 nM).[30] [b] Compounds were dosed in 20% HPBCD. AUC measurements are given in nM·h and $C_{max}$ in nM.



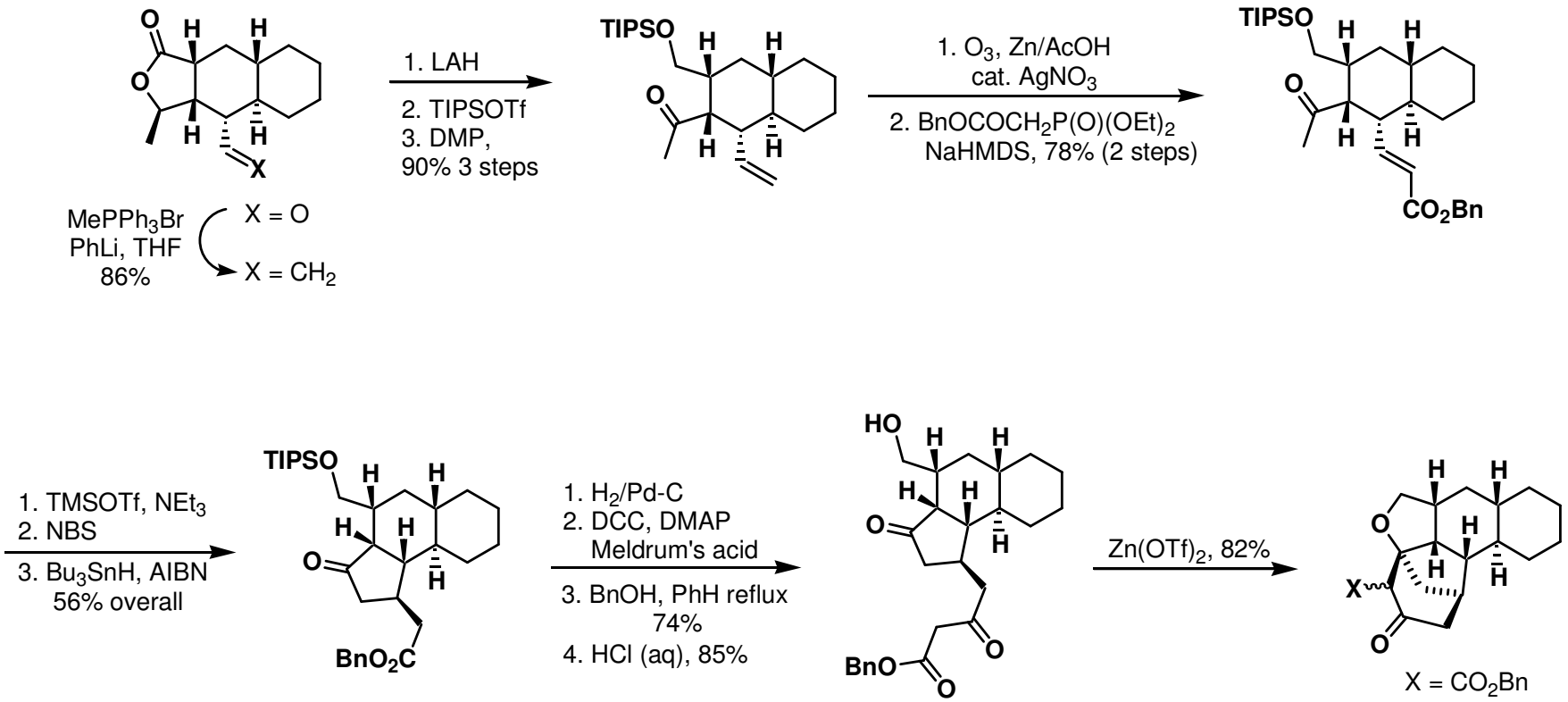

PAR's are activated by thrombin (a coagulation protein) upon cleavage of the N-terminus of the receptor causing a cascade of events leading to thrombosis or clotting

# Total Synthesis of (-)-Himgaline
## *Retrosynthetic Analysis*

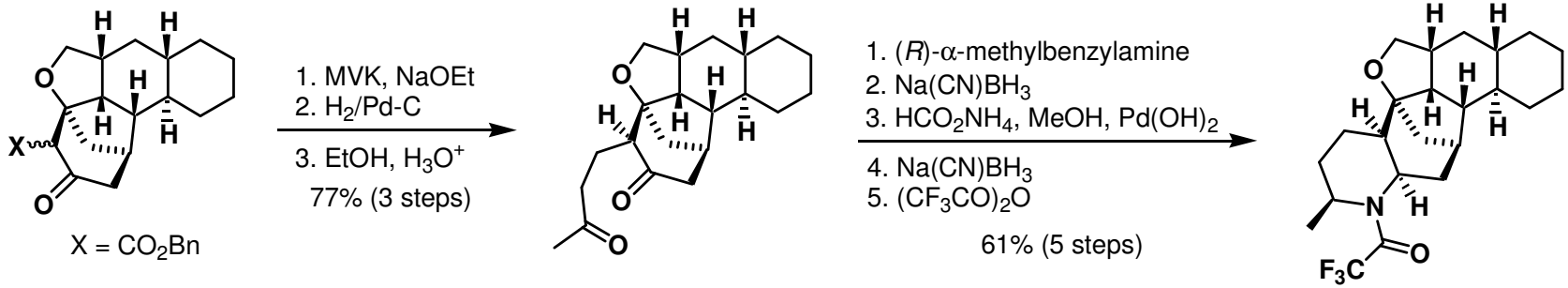


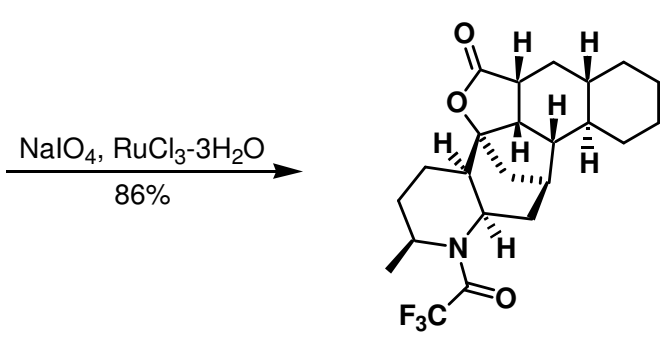

•The pharmacological properties of (-)-himgaline and GB 13 are currently unexplored

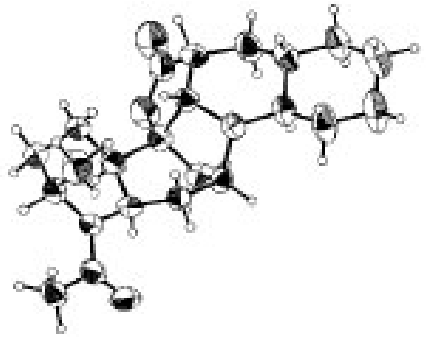
# Construction of the Pentacyclic Core



# Elaboration of the Complex Pentacyclic Structure
## *Formation of the Crucial Piperidine Moiety*



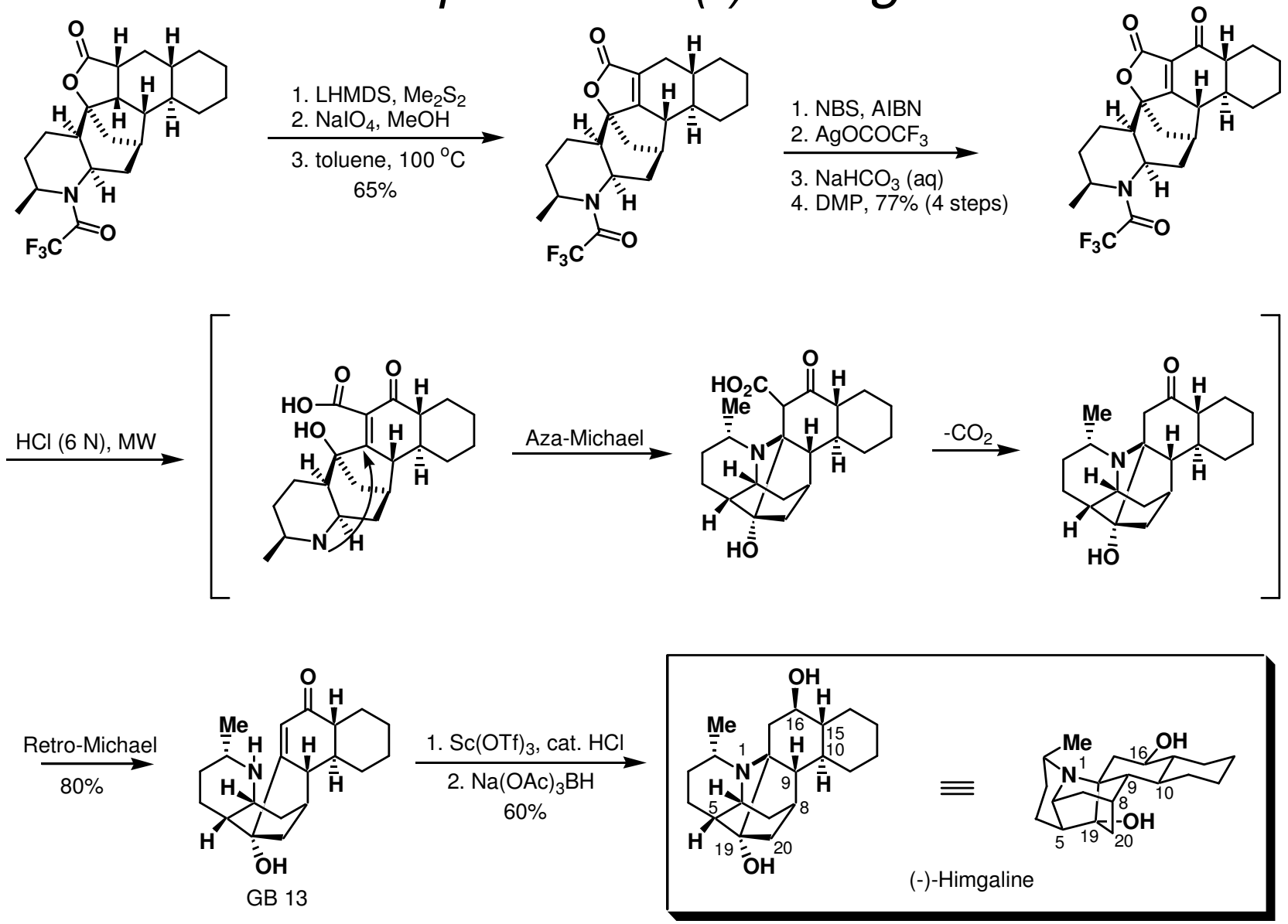



Crystal structure of *N*-acetyl compound

# A Series of "Fortunate" Events

## *Completion of (-)-Himgaline*



# Summary

•Total synthesis of (-)-himgaline is the first to be reported

-Highlighted by an intramolecular Aza-Michael/decarboxylation/retro-Michael cascade

•(-)-Himgaline and GB 13 represent a class of molecules that warrant biological studies to determine their potential biological activity

•Himbacine analogue (SCH 205831) is currently the most potent orally active PAR-1 antagonist

•The development of chemotherapies toward Alzheimer's and thrombotic diseases continues to remain a high priority among the pharmaceutical and biotechnology sectors