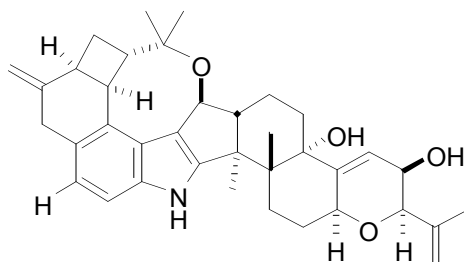


# Tremorgenic Indol Alkaloid (-)-Penitrem D

Matt Haley

5/24/2006



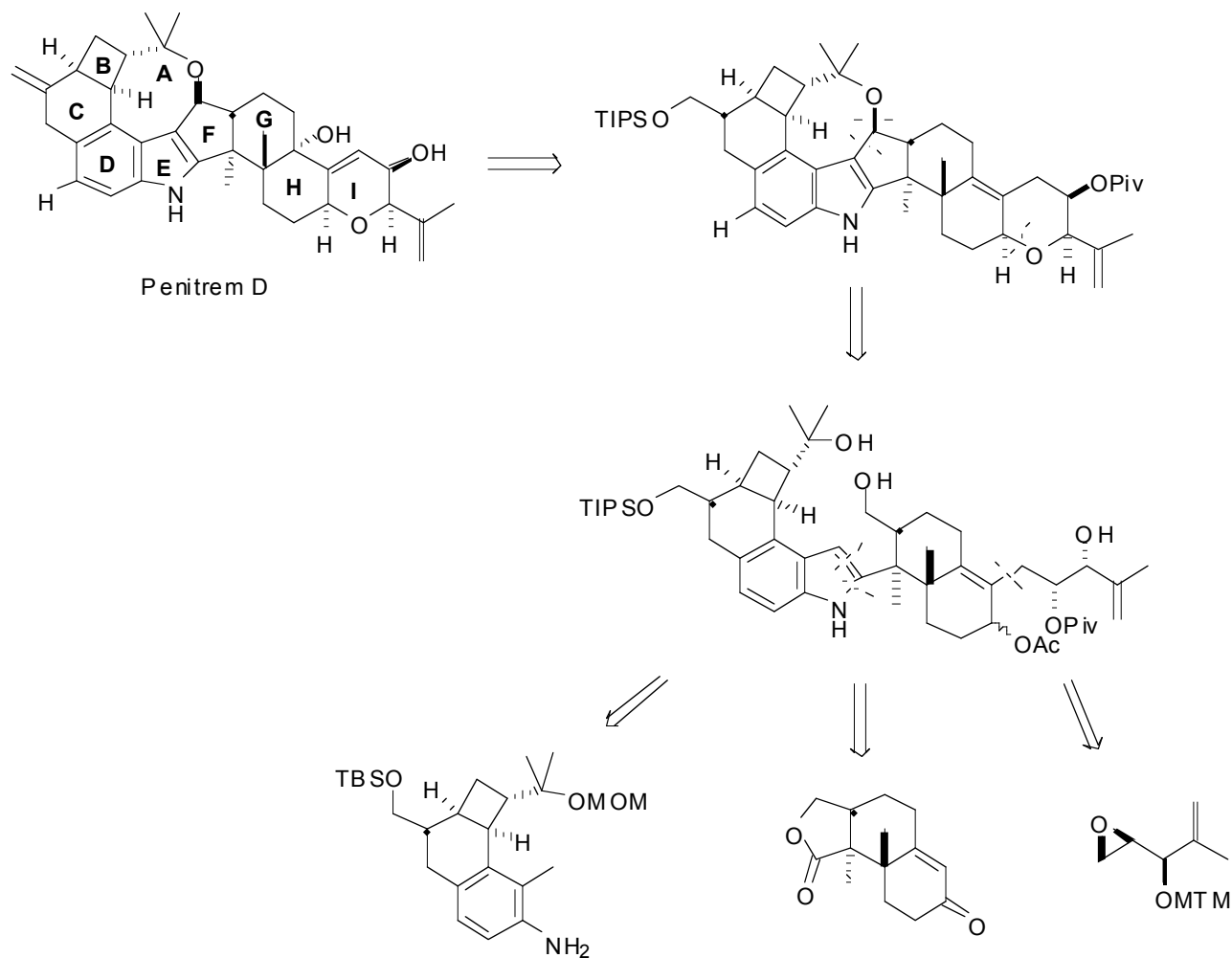
Penitrem D

- The first of the penitremes was isolated in 1968 by Wilson and co-workers<sup>1</sup>
- Produced by Ergot fungi
- Causes muscle tremors, limb weakness, ataxia, convulsions, and eventually death
- This fungi grows on grains and spoiling foods
- This same class of toxins is most likely the cause of the Salem witch trials
- (-)-Penitrem D is the only one in its family that has been synthesized<sup>2</sup>

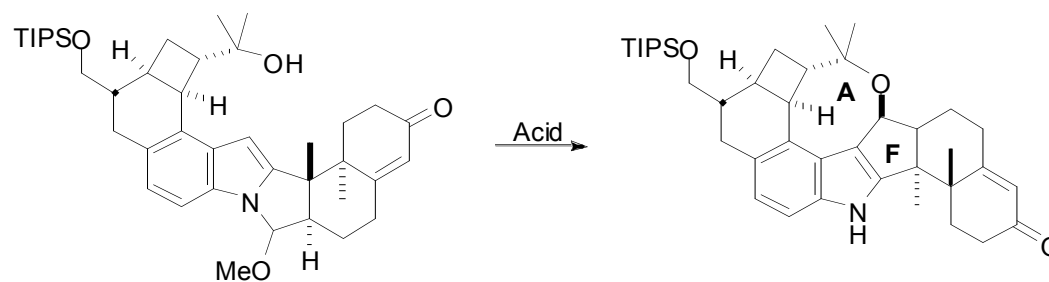
<sup>1</sup>Wilson, B. J.; Wilson, C. H.; Hayes, A. W. *Nature* **1968**, 220, 77

<sup>2</sup>Smith, A. B.; *et al.* *J. Am. Chem. Soc.* **2003**, 125, 8228

# Initial Retrosynthetic Analysis



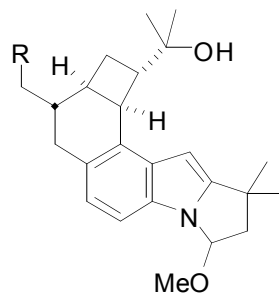
## Is Formation of A and F Rings in a Single Operation Feasible?



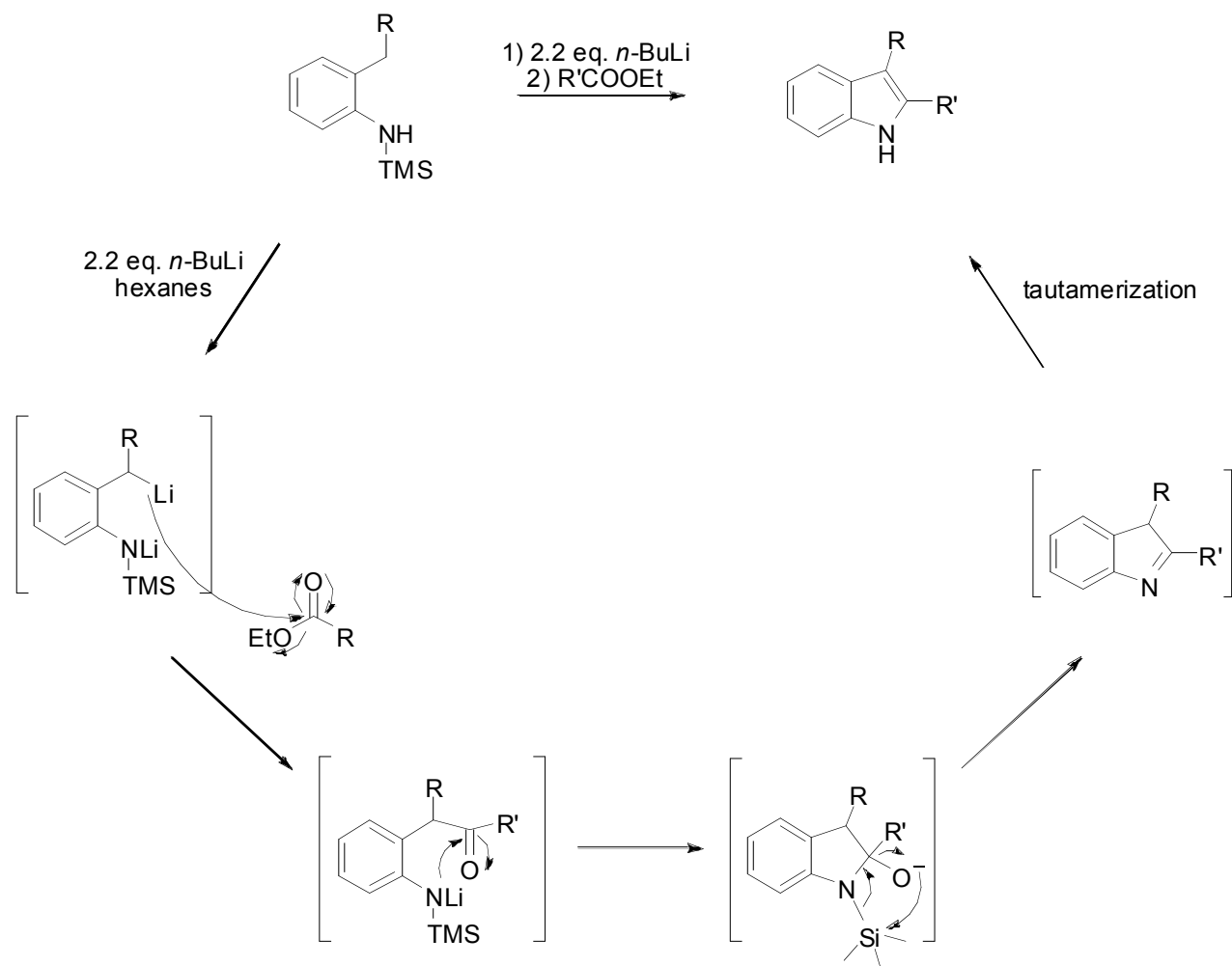
Construct a racemic model system



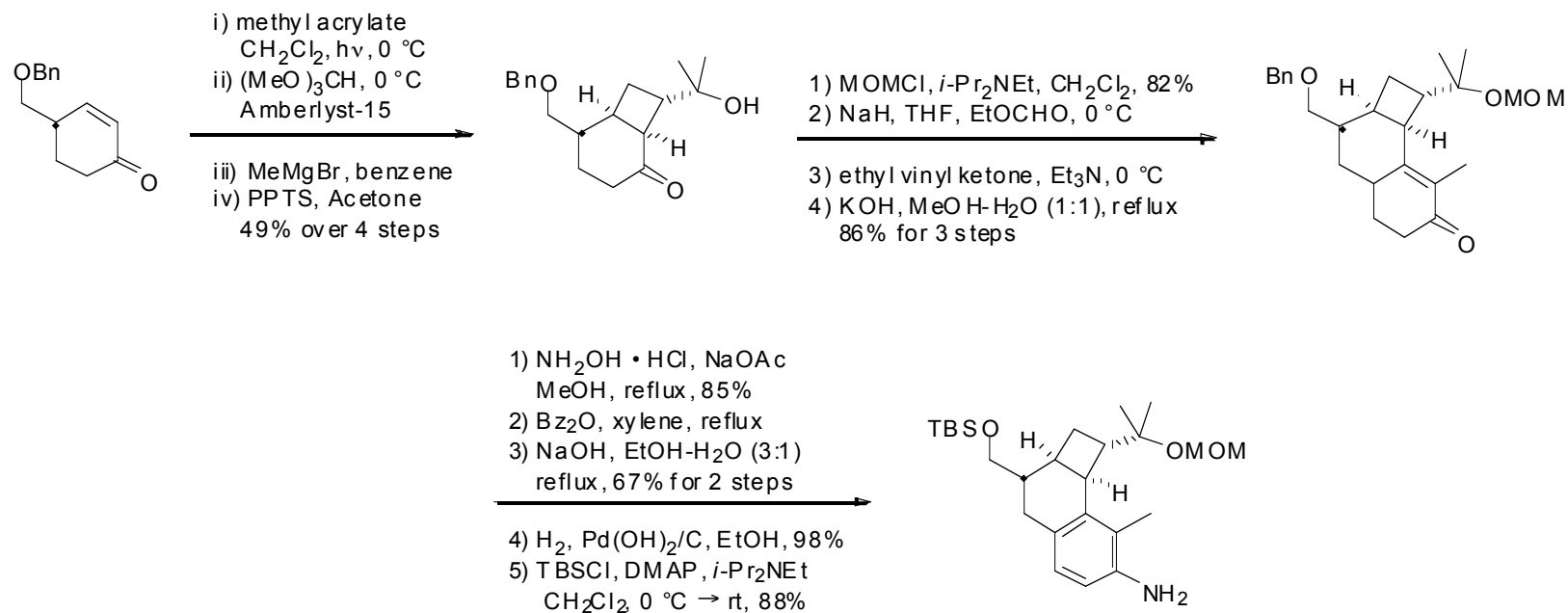
Construct complex indole intermediate



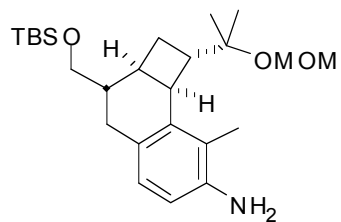
# Modified Madelung Indole Synthesis



## Construction of Model System



## Indole Formation

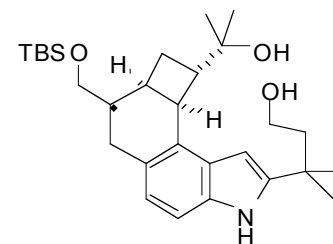


i) *n*-BuLi, TMSCl, Et<sub>2</sub>O, -78 °C → rt

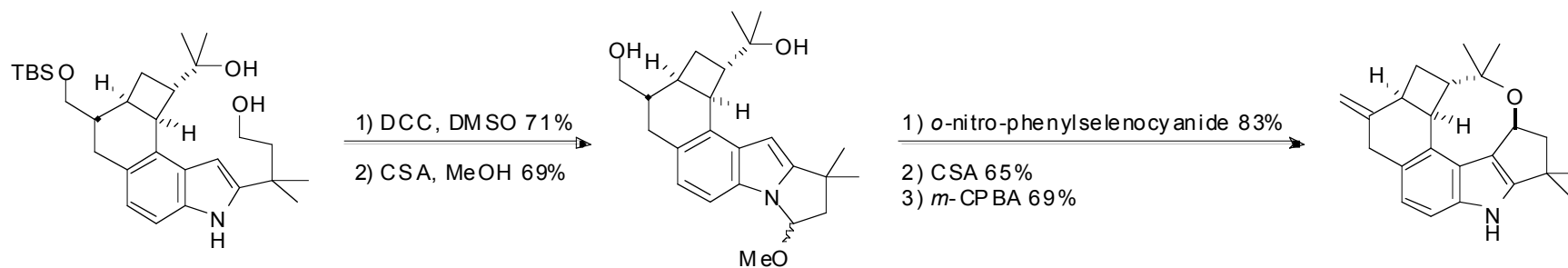
ii) *s*-BuLi, rt  
dimethylbutyrolactone  
20-30%

i) 2.5 eq. LDA, dimethylbutyrolactone  
THF, -78 °C → rt

ii) 4 eq. *n*-BuLi, THF, 0 °C → rt  
80%

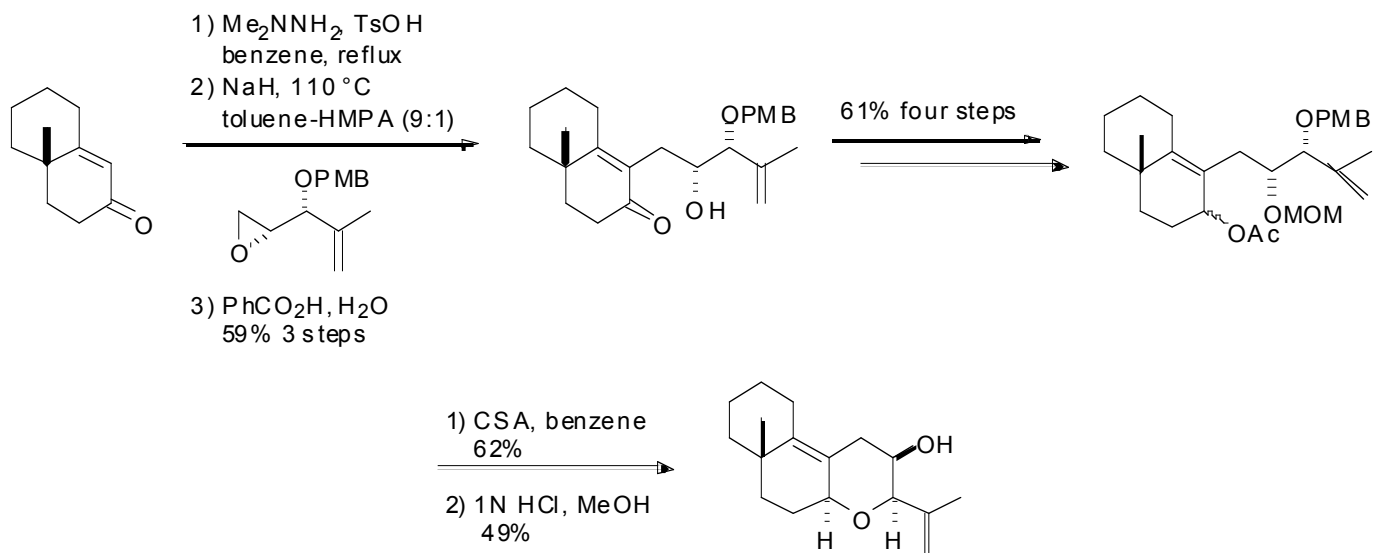
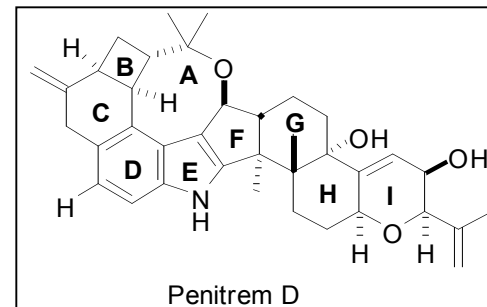


## A and F Ring Formation



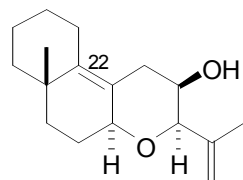
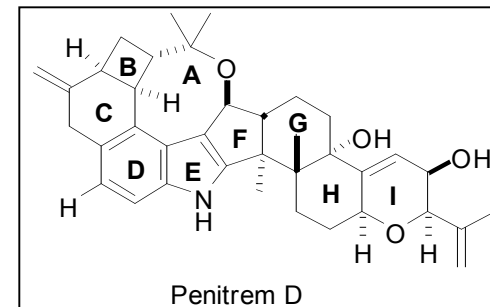
A and F ring formation in one step is feasible

# I Ring Formation Model System



correct stereochemistry achieved

## Installation of the C22 Hydroxyl Group

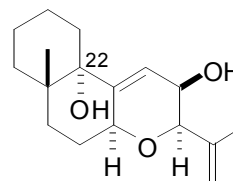


1)  $^1\text{O}_2$ , hv,  $\text{CHCl}_3$   
methylene blue

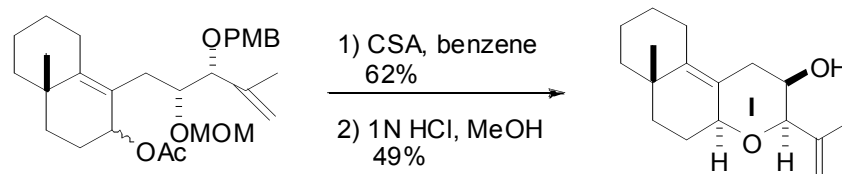
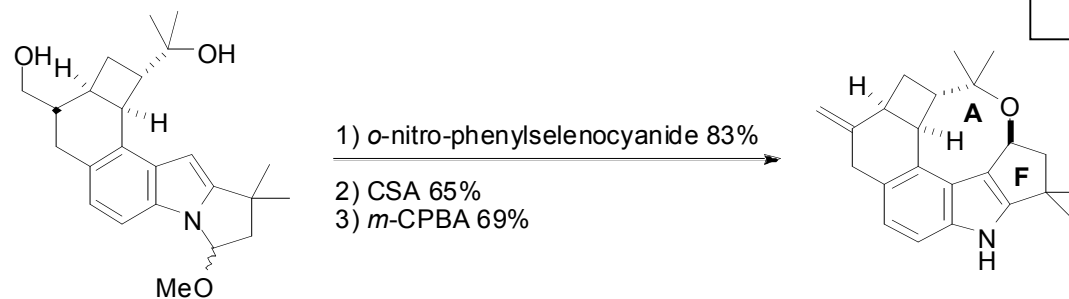
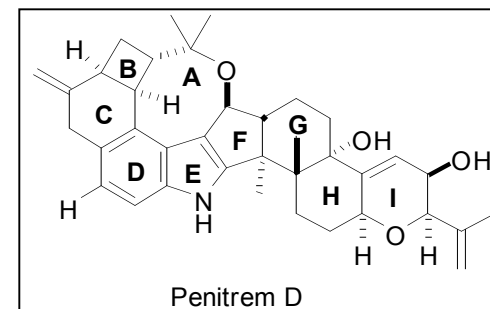
2)  $\text{NaBH}_4$ , MeOH  
54% 2 steps

$^1\text{O}_2$ , hv, py, 35 °C  
hematoporphyrin IX;

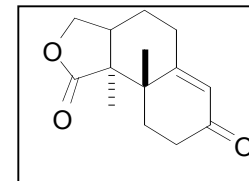
$\text{PPh}_3$ , 63%



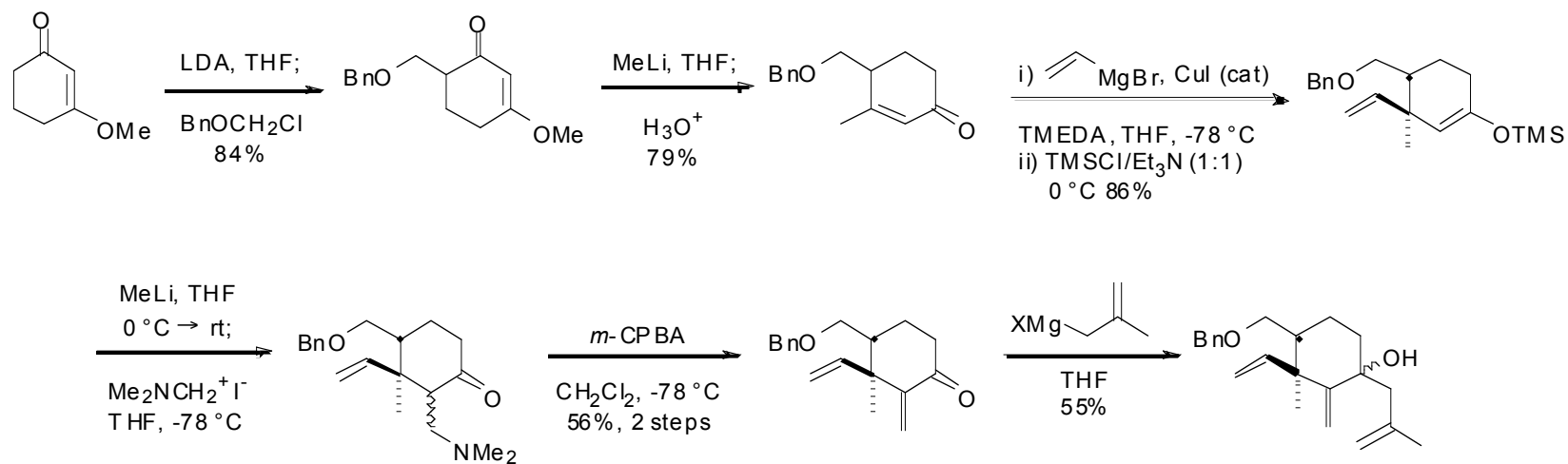
## Model Systems Summary



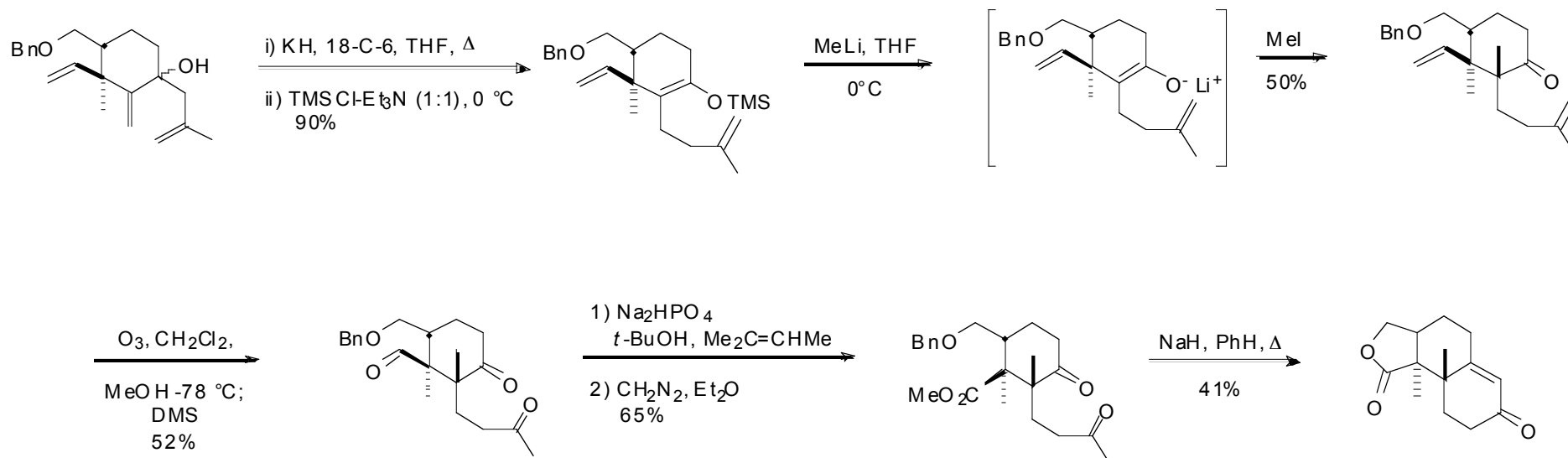
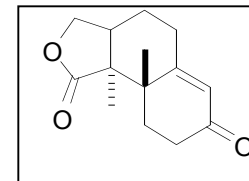
-Since the A and F rings cyclize under identical acidic conditions to I ring formation it was asserted that all three rings could be formed simultaneously



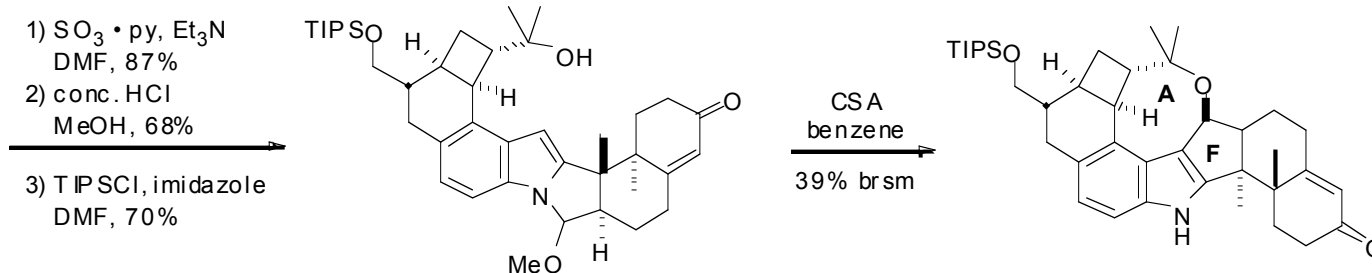
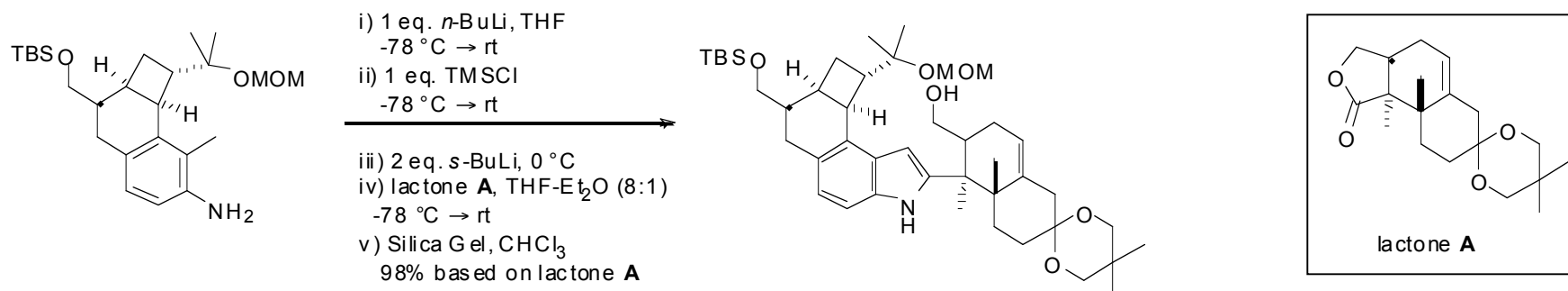
## Construction of G and H Ring Fragment



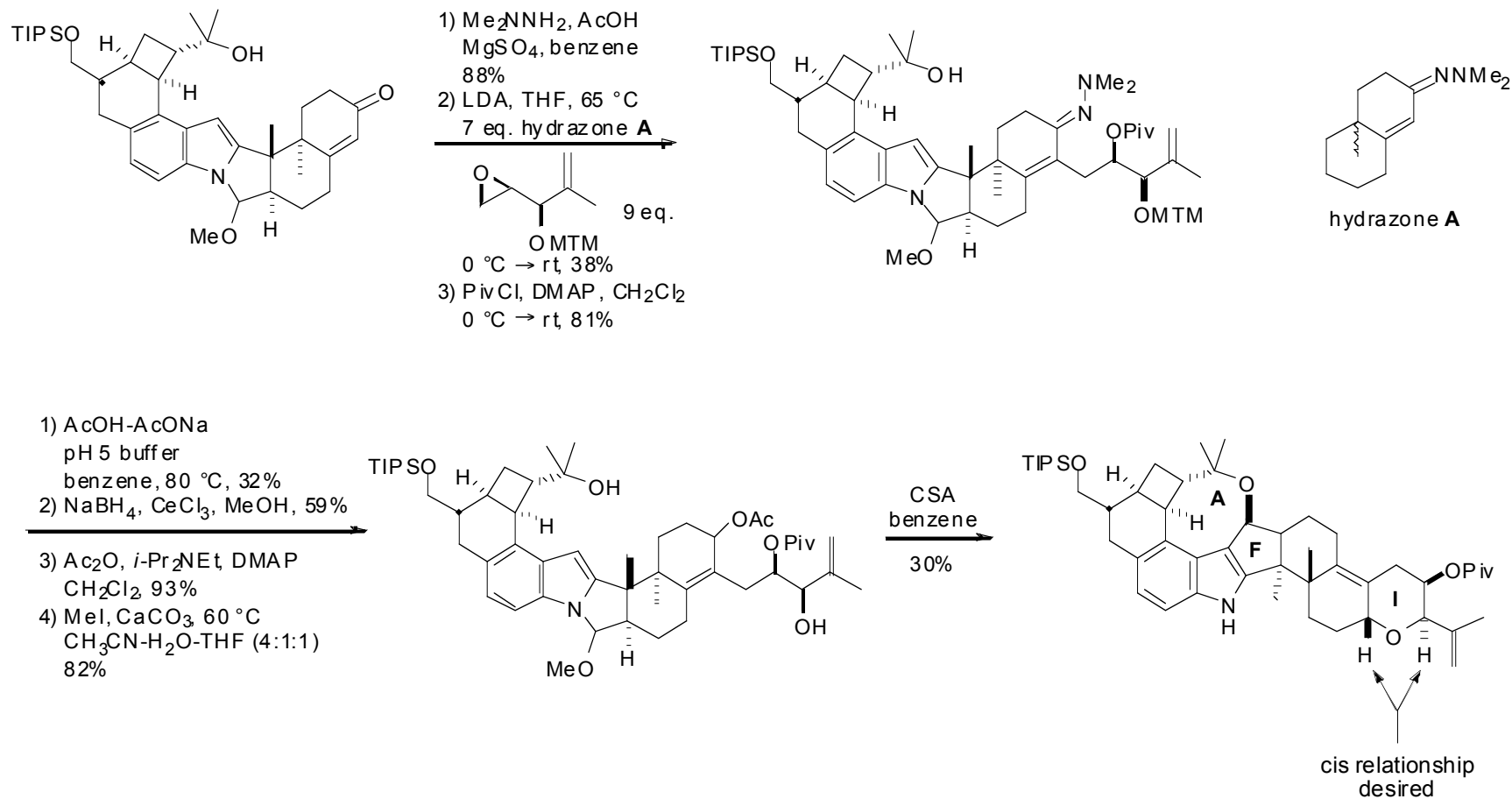
## Construction of G and H Ring Fragment (continued)



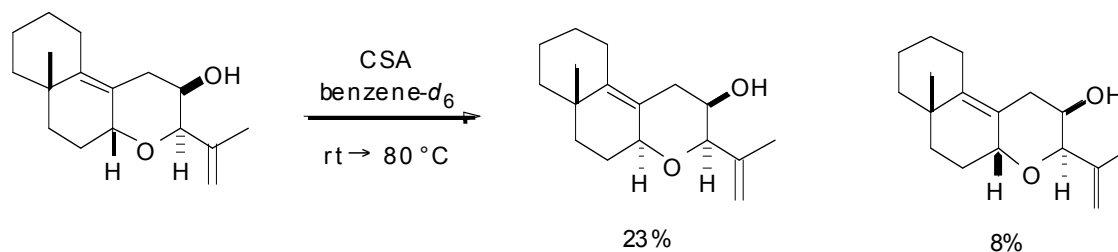
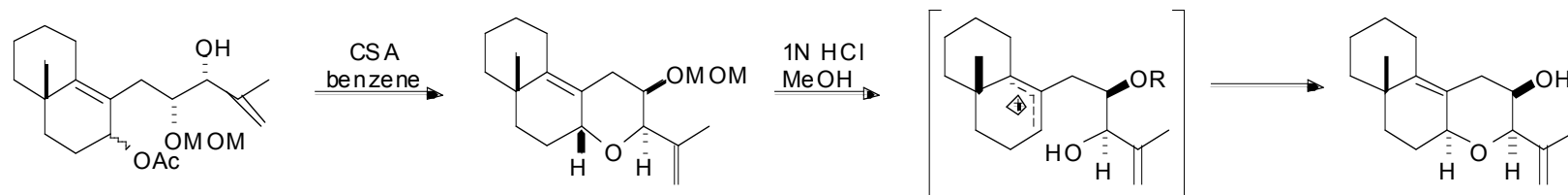
## Union of Western and Eastern Hemispheres



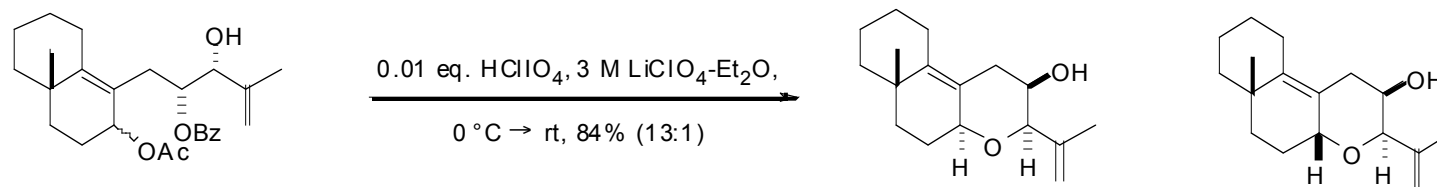
## Formation of A, F, and I Rings



## I Ring Model Study Revisited

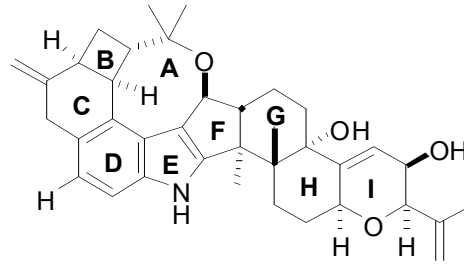


### New I Ring Formation Method:

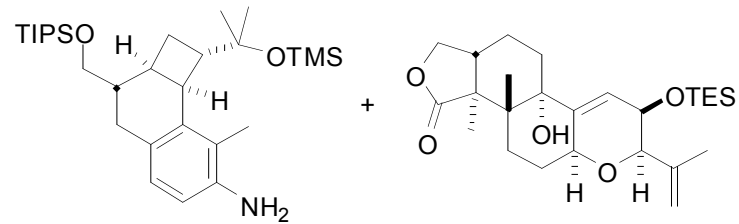
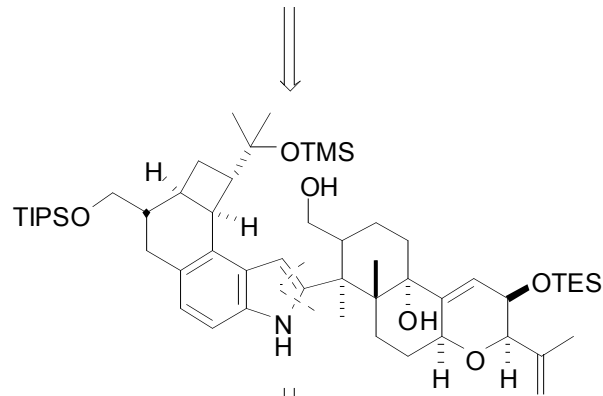


-conditions proved to be useful in forming the I ring  
 -were not useful in forming A and F rings

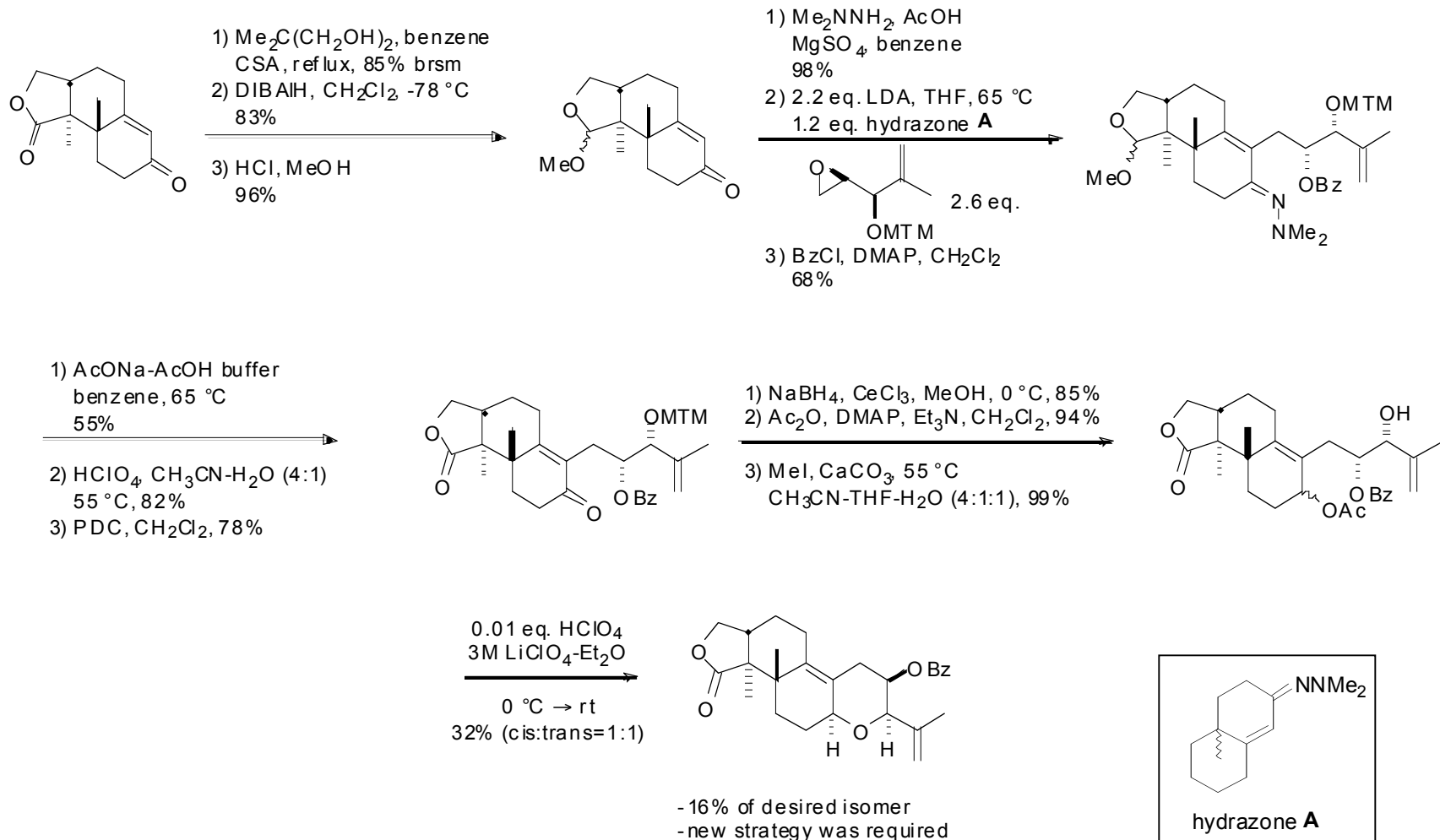
# Synthetic Strategy Revised



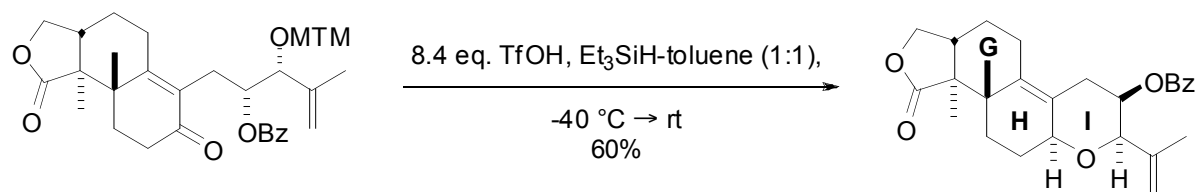
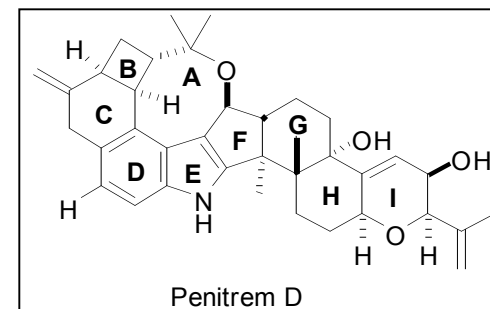
Penitrem D



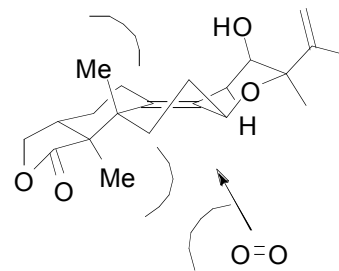
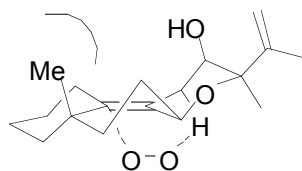
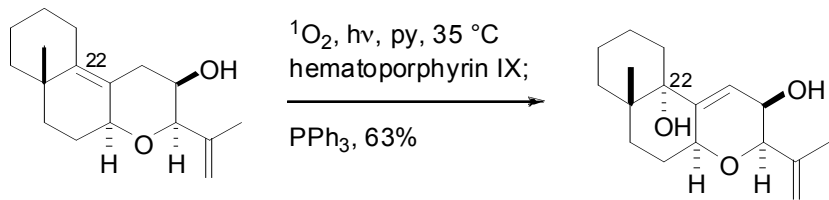
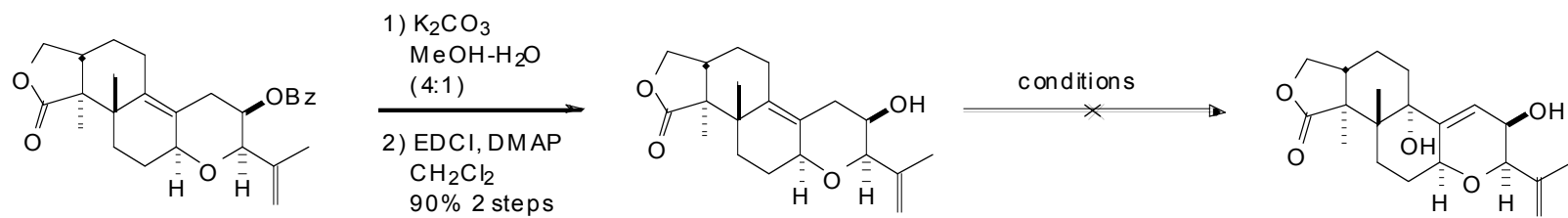
## Assembly of Eastern Hemisphere containing I Ring



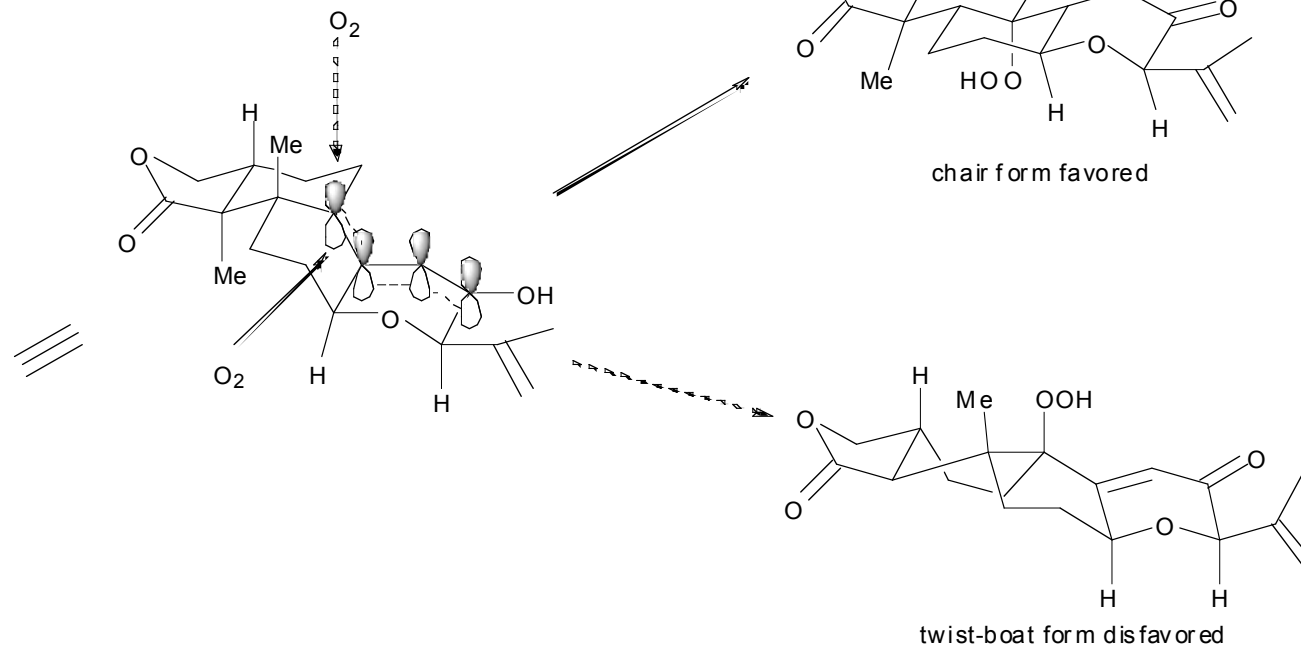
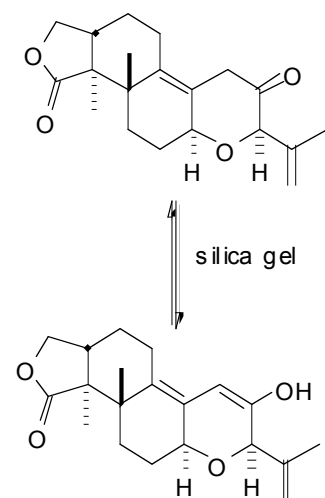
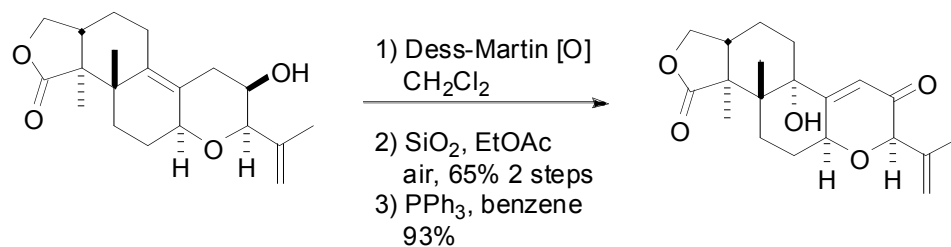
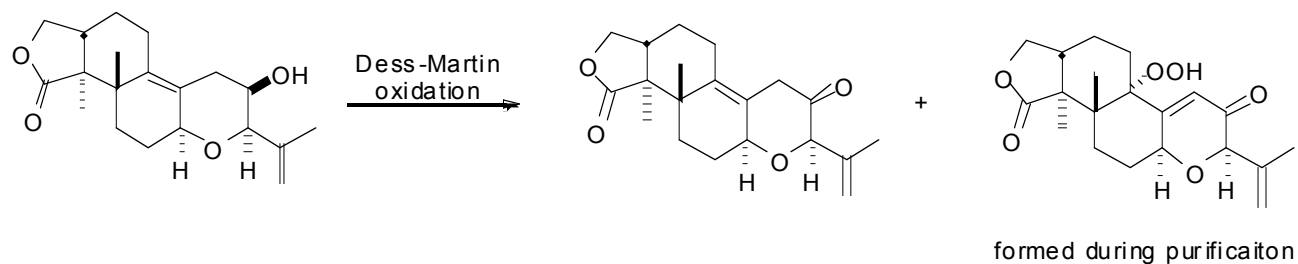
## A Viable Route to the Eastern Hemisphere



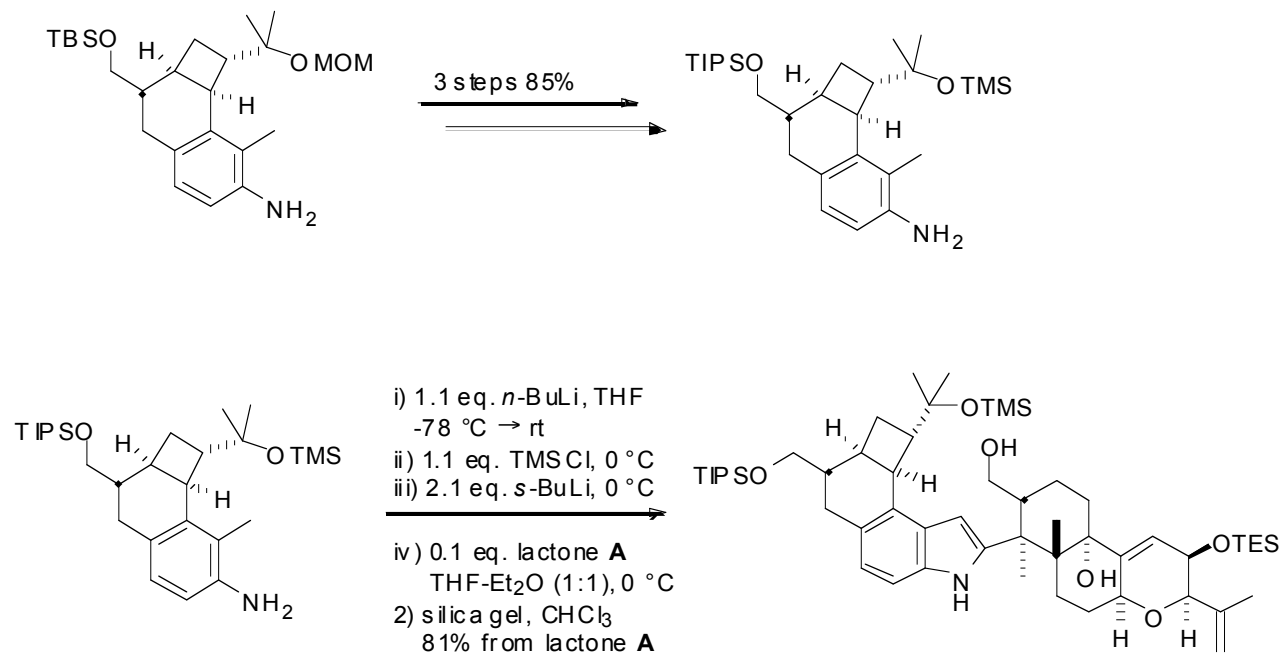
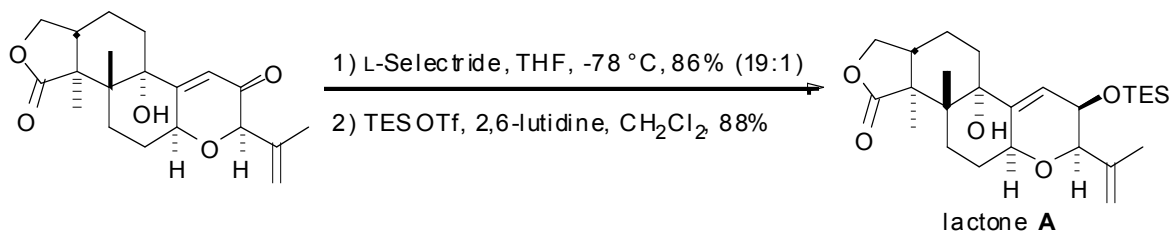
## Attempted Installation of C22 Hydroxyl Group



# Finally Something Goes Their Way



## Coupling the Eastern and Western Hemispheres



# Endgame

