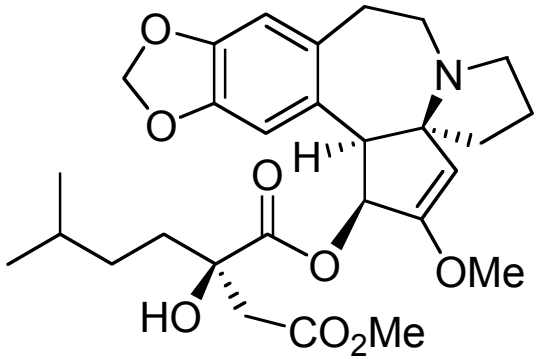
Strain Release Rearrangement of *N*-Vinyl-2-Aziridines. Total Synthesis of the Anti-Leukemia Alkaloid (-)-Deoxyharringtonine

J.D.Eckelbarger, J.T.Wilmot, D.Y.Gin

J.A.C.S. ASAP



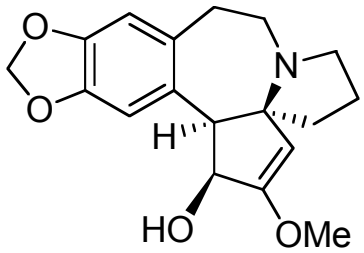
Deoxyharringtonine

Outline:

- Introduction
- Synthetic History
- *N*-Vinyl-Aziridine Rearrangement
- Current Synthesis
- Conclusion

Introduction

- Cephalotaxus esters
  - Occur in 8 species of genus *Cephalotaxus* evergreen plum yews
    - Located in Southeastern Asian
  - Several family members target P388 and L1210 leukemia cells with IC_{50} values in the ng/mL range
    - Inhibit protein biosynthesis
- Cephalotaxine
  - Most abundant parent member of the harringtonine alkaloid family
  - Weak biological activity
  - Isolated in 1963 and structure definitively proven through X-ray crystallography in 1974 (*J.O.C.* **1963**, *28*, 1445 and *J.O.C.* **1974**, *39*, 1269)



cephalotaxine

J. Am. Chem. Soc.; **1999**; *121*; 10264

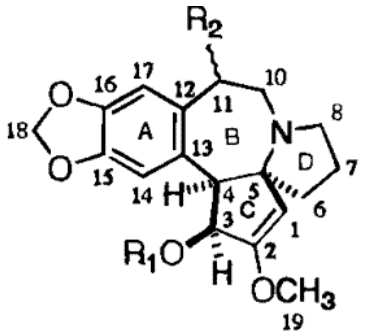
Biologically Active Esters

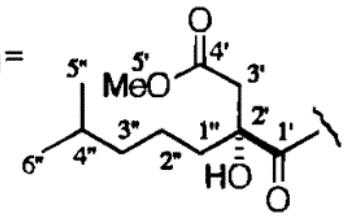
- *Group1*
  - 0.024-0.056 μg/ml against P-388
- *Group 2*
  - 0.17-0.38 μg/ml
- L1210 IC50 (μg/ml)
  - Harringtonine: 2.0
  - Deoxyharringtonine: 0.0082
  - Isoharringtonine: 0.14

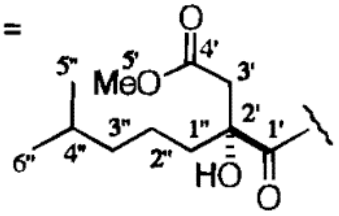
(*Tetrahedron*, **2000**, *56*, 2929)

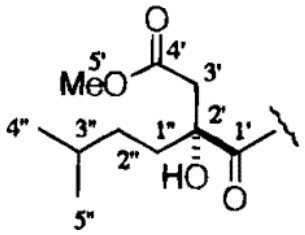
Group1

(*J. Nat. Prod.*, **59**, 1192, 1996)



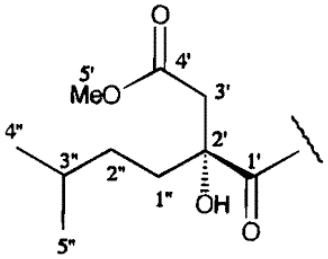
1 R_1=  R_2 = α-OH

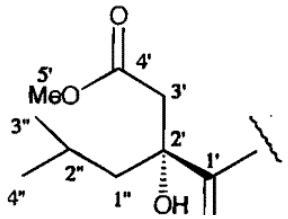
2 R_1=  R_2 = β-OH

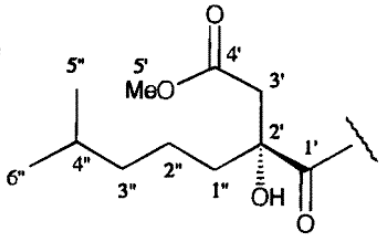
3 R_1=  R_2 = β-OH

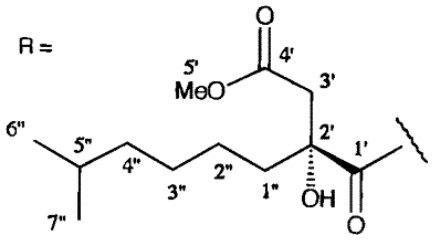
Group 2, R_2=H

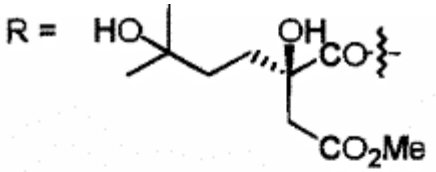
(*J. Nat. Prod.*, **59**, 965, 1996)

R = 

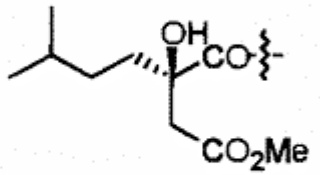
R = 

R = 

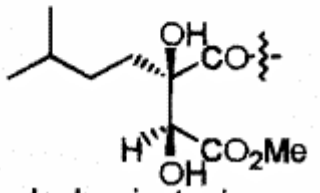
R = 

R = 

Harringtonine



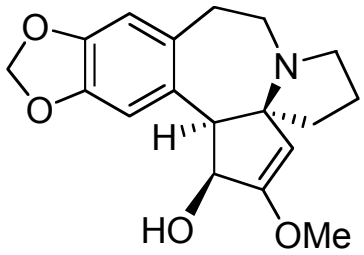
Deoxyharringtonine



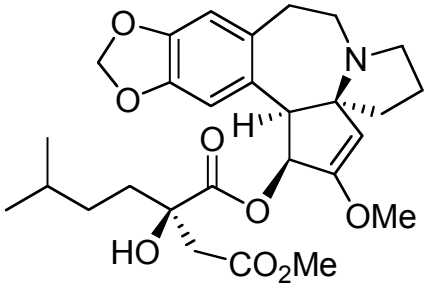
Isoharringtonine

Synthetic History

- Most of the syntheses have targeted cephalotaxine
  - Over 20 syntheses of this target
  - First racemic synthesis by Weinreb (*JACS*, **1972**, *94*, 7172)
- Deoxyharringtonine
  - Difficult to acylate alcohol
  - Several syntheses of related cephalotaxine esters present in literature
    - Harringtonine (*J.O.C*, **1978**, *43*, 4762)
    - Homoharringtonine (*JOC*, **1983**, *48*, 5321)



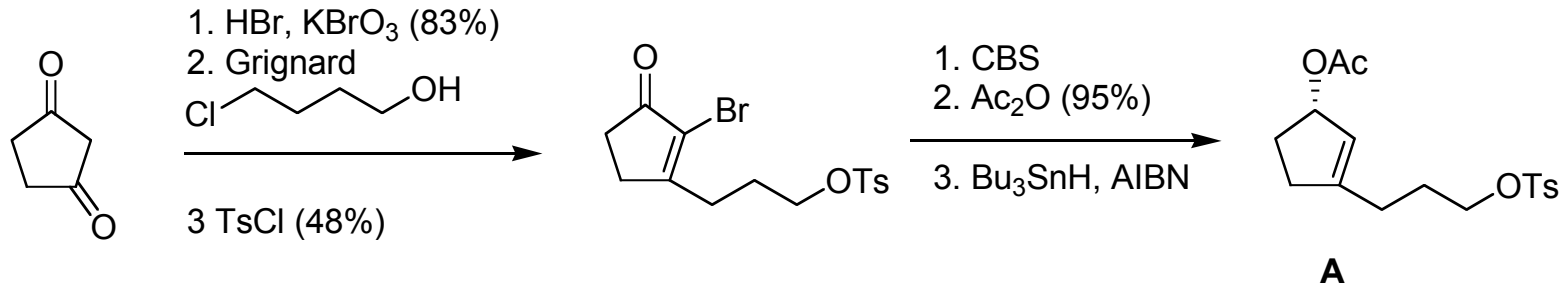
cephalotaxine

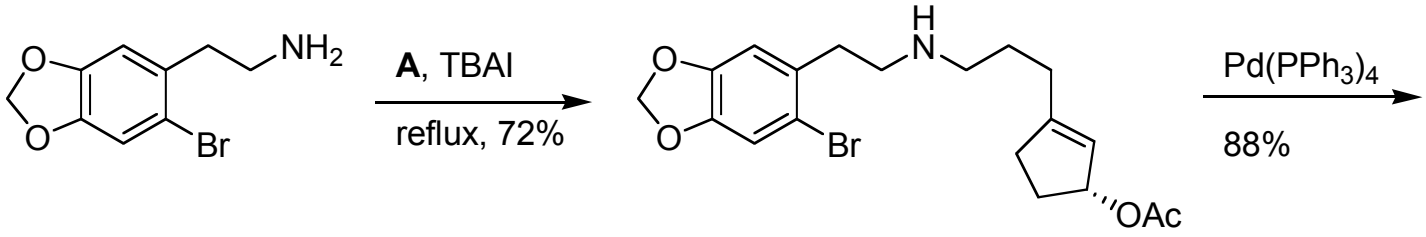


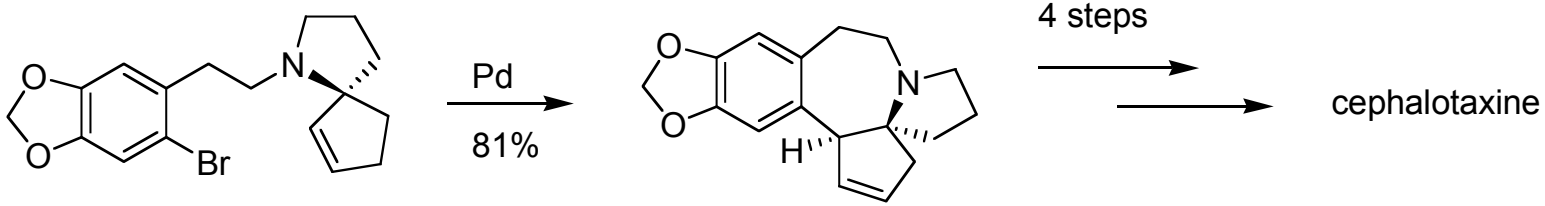
Deoxyharringtonine

Synthetic History (cont)

- Tietze (*JACS*, **1999**, *121*, 10264)

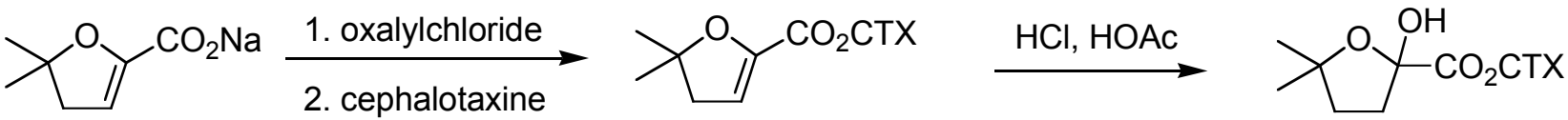




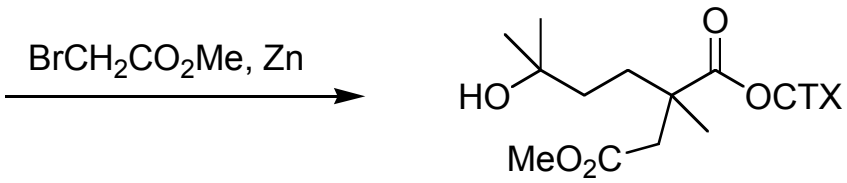


Cephalotaxine Acylation

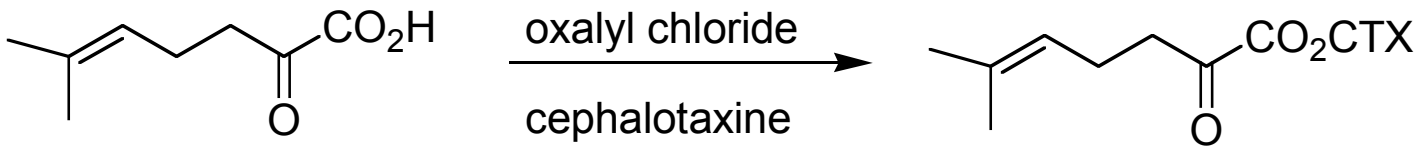
- Mikoajczak (*JOC*, **1978**, *43*, 4762)



CTX = cephalotaxine core

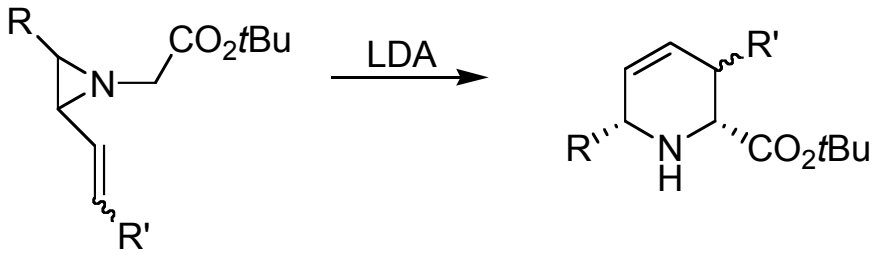


- Hudlicky (*JOC*, **1983**, *48*, 5321)

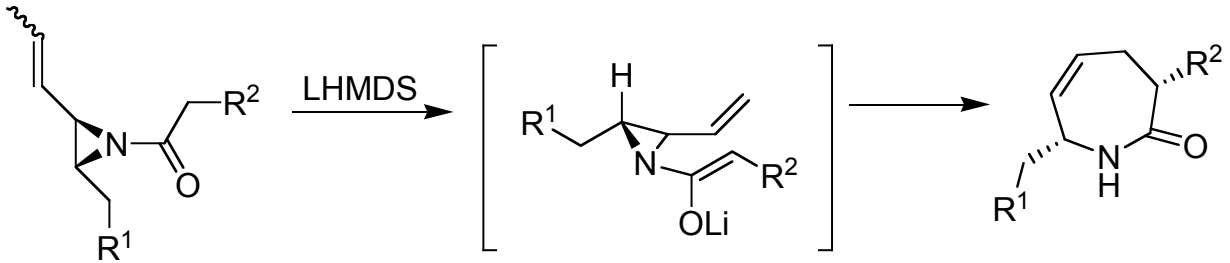


N-Vinyl-Aziridine Rearrangement

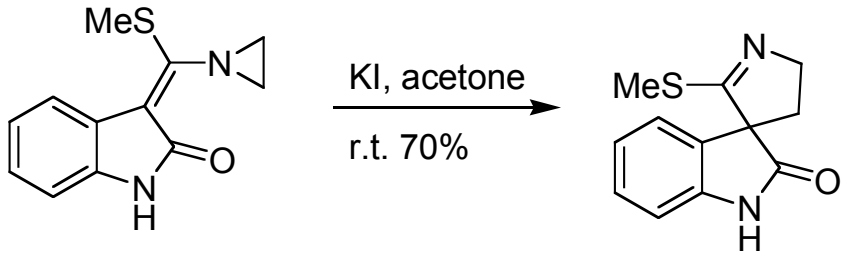
- Aza[2,3]-Wittig (Samfai, *J.O.C.* **1996**, *61*, 8148)



- Aza[3,3]-Claisen Rearrangement (Samfai, *JACS*, **1997**,*119*, 8385)

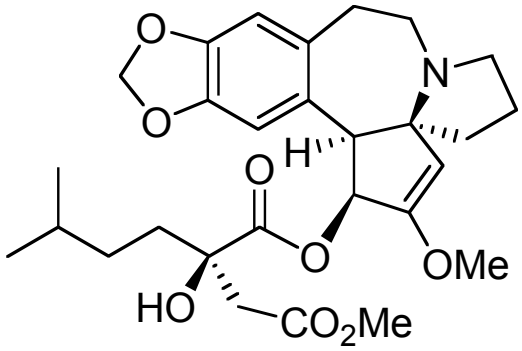


- Spirocycle Synthesis (*Org.Lett*, **2001**, *3*, 4193)

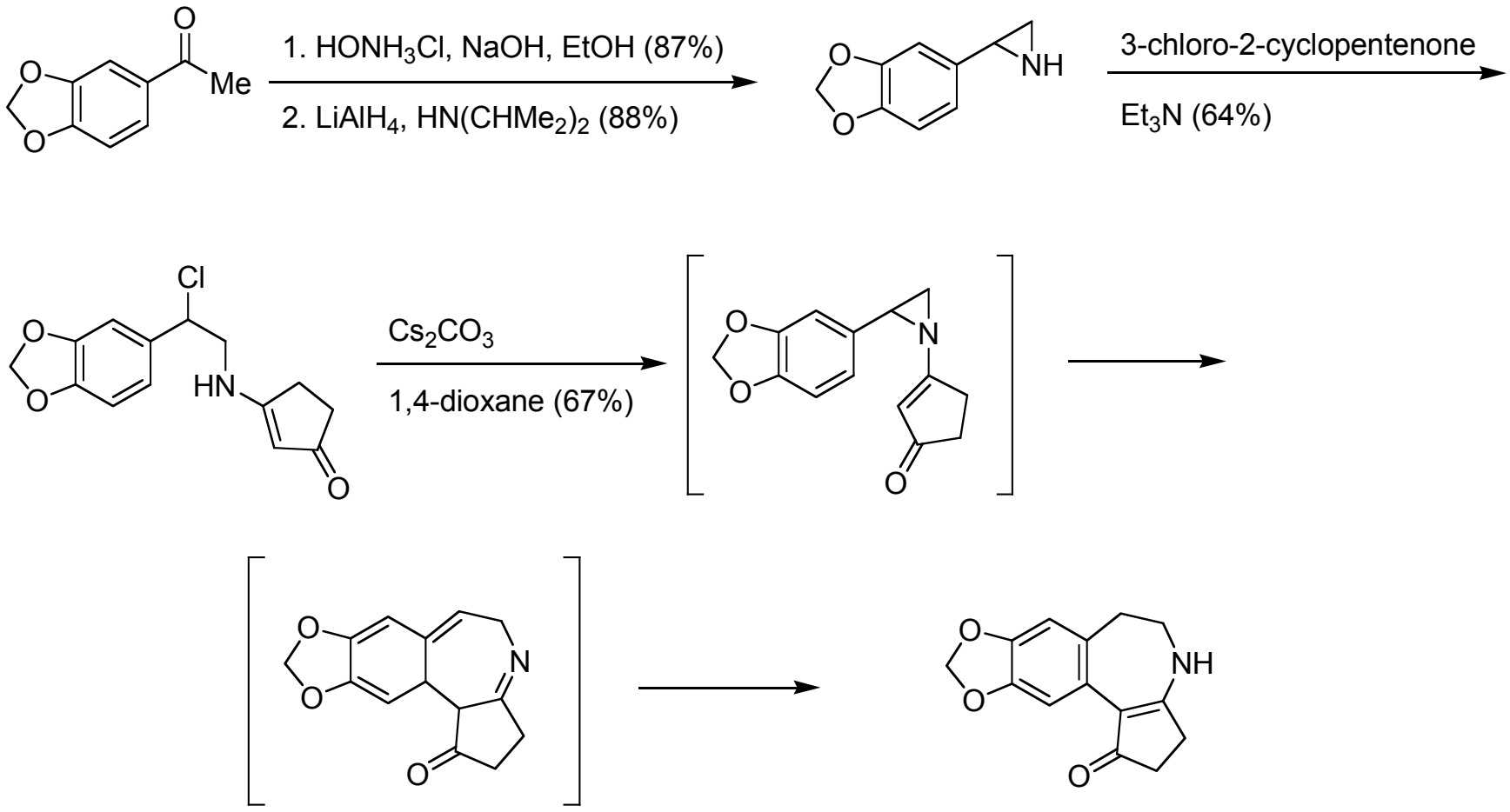


Title Paper:

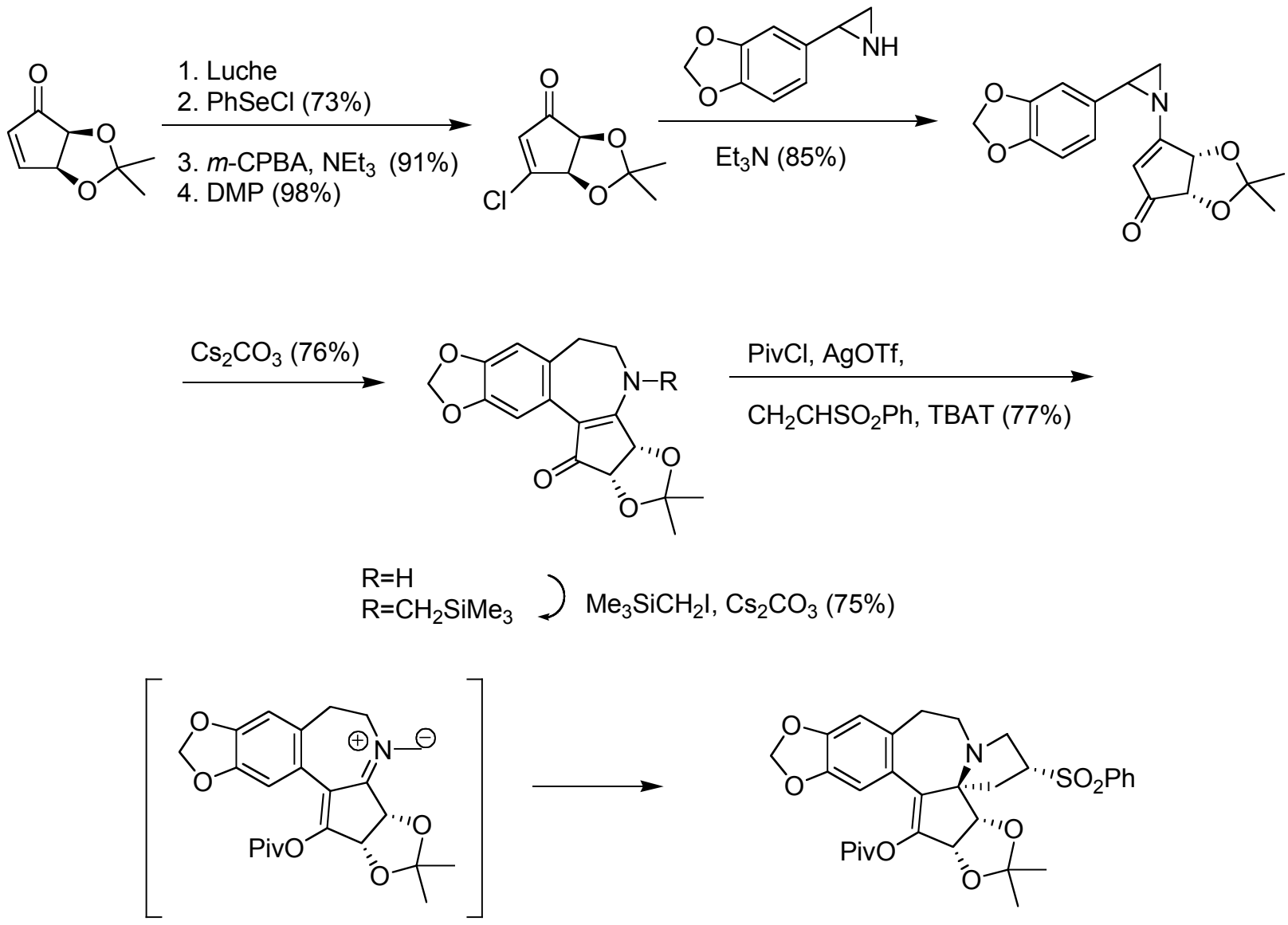
- [3,3] rearrangements demonstrated for [1]benzazepine systems in the literature. No examples of [3]benzazepine formation via an *N*-vinyl aziridine.
- No reported enantioselective total syntheses of deoxyharringtonine



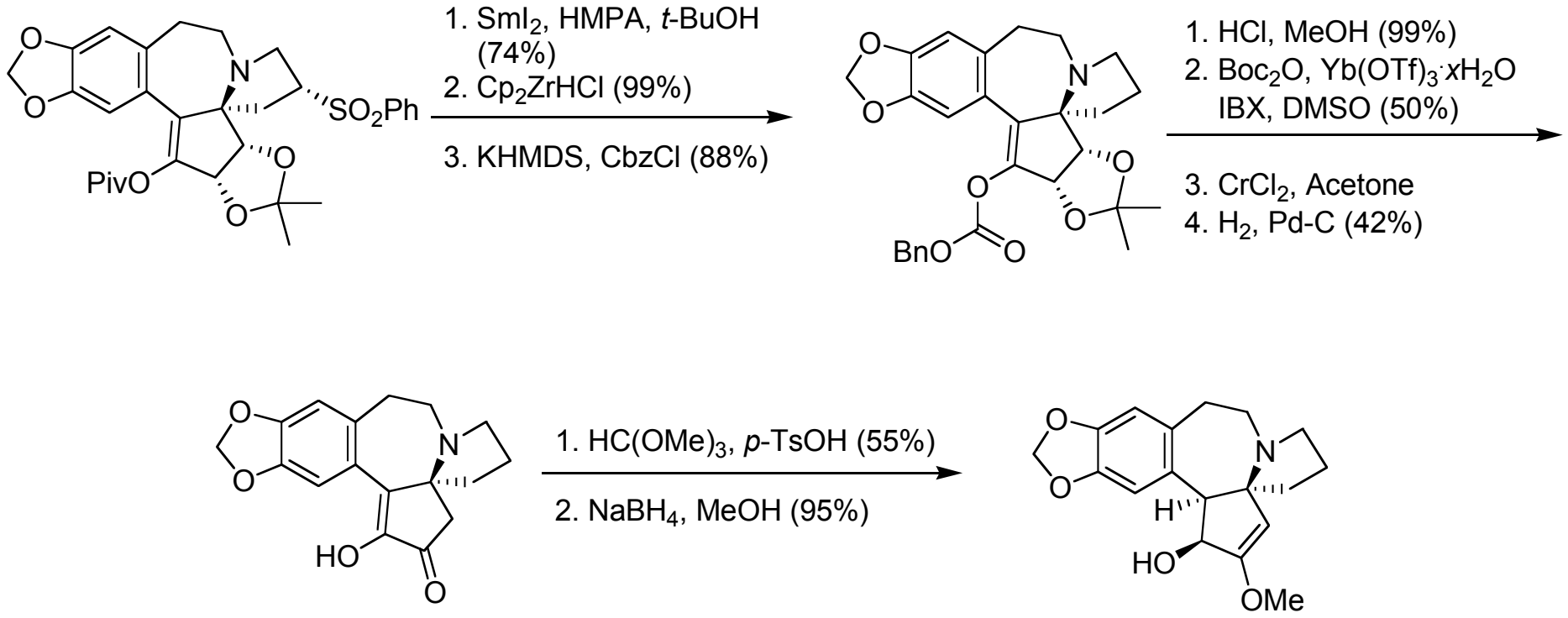
Model Study


O
O
O
Me
1. HONH3Cl, NaOH, EtOH (87%)
2. LiAlH4, HN(CHMe2)2 (88%)
O
O
NH
3-chloro-2-cyclopentenone
Et3N (64%)
Cl
O
O
HN
O
Cs2CO3
1,4-dioxane (67%)
O
O
N
O
O
O
N
O
O
NH
O

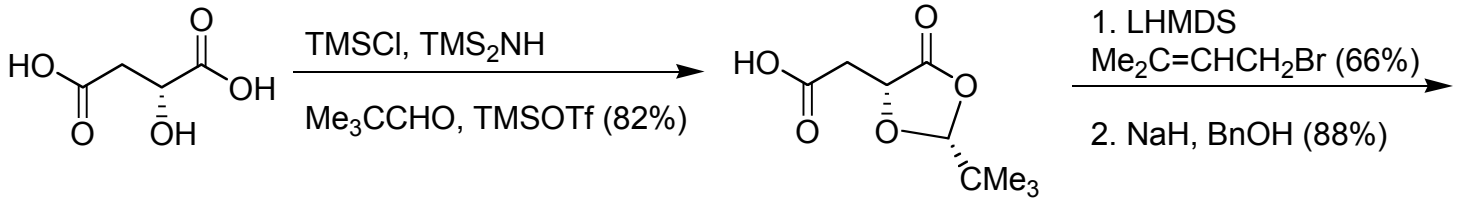
Deoxyharringtonine Synthesis

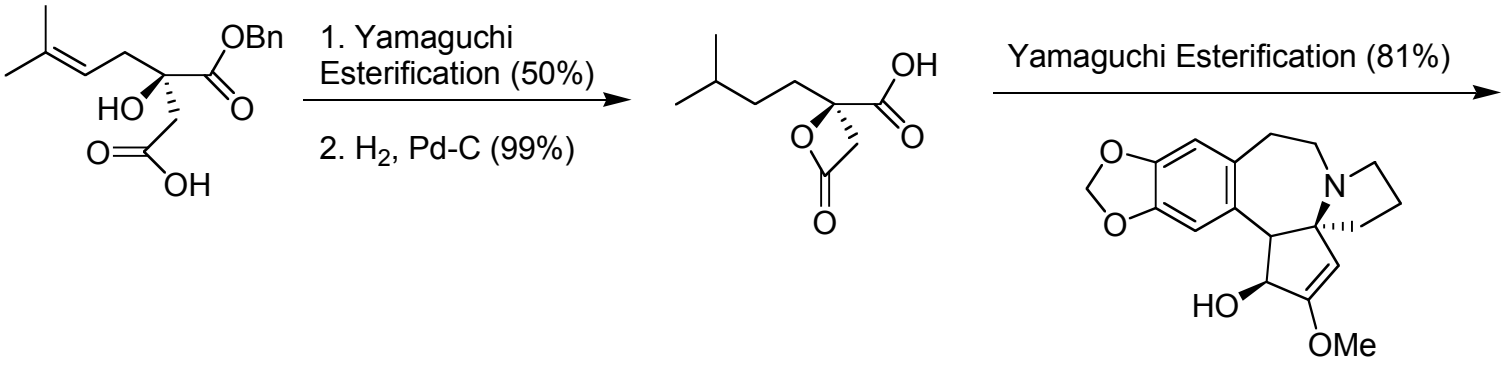


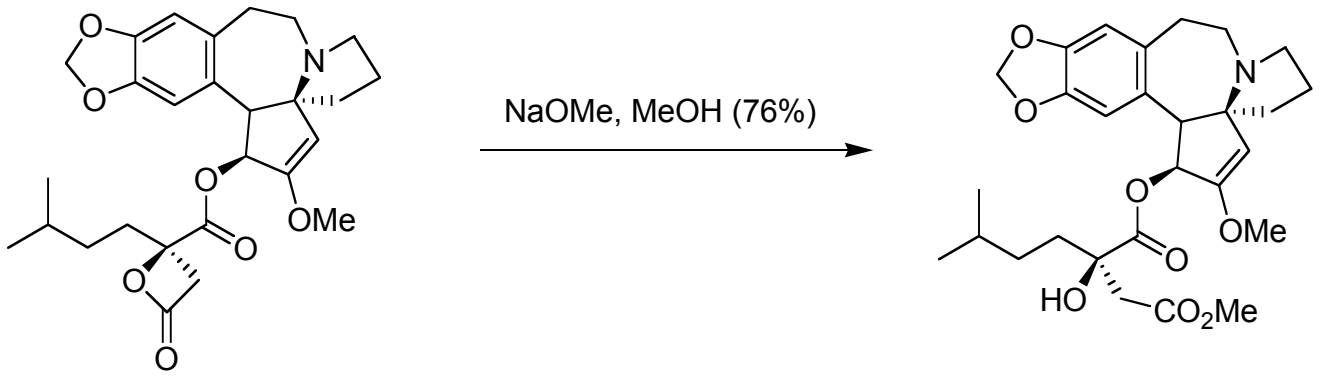
Deoxyharringtonine (cont)



Deoxyharringtonine-final







Deoxyharringtonine

Conclusion

- The total synthesis of deoxyharringtonine was accomplished in 28 steps and 0.19% overall yield from known starting materials. The longest linear sequence was 19 steps
- The first demonstration of a [3,3]-rearrangement of *N*-vinyl aziridines to form a [3]benzazepine system was demonstrated
- An acylation protocol was developed that could potentially be applied to the synthesis of other cephalotaxine esters or analogues