Off To a Great Start:

First Syntheses by Three Untenured Synthetic Organic Chemists

Joseph M. Ready
Assistant Professor (2003)
University of Texas Southwestern Medical Center
Postdoctoral Research: John L. Wood (Yale)
PhD: Eric N. Jacobsen (Harvard)

Andrew J. Phillips
Assistant Professor (2002)
University of Colorado Boulder
Postdoctoral Research: Peter Wipf (Pittsburgh)
PhD: University of Cantebery (New Zealand)

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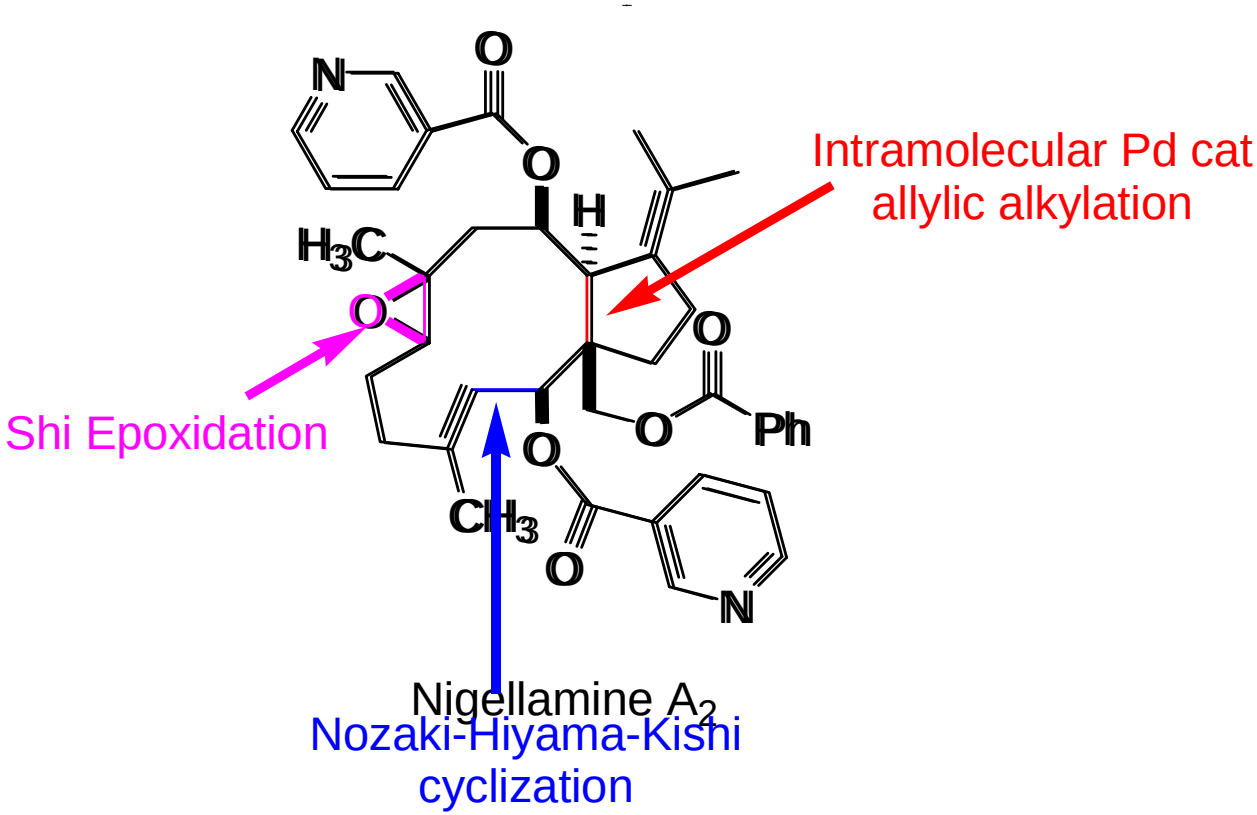
Assistant Professor (2003)
MIT
Postdoctoral Research: Eric N. Jacobsen (Harvard)
PhD: Andrew Meyers (Harvard)

Enantioselective Total Synthesis of (+) and (-)-Nigellamine A_2

J. Am. Chem. Soc. **2006**, *128*, 7428-7429

Bian, J.; VanWingerden, M.; Ready, J. M.

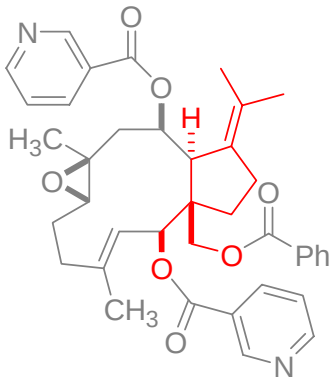


Review of dolabellane diterpenes: Rodriguez, A. D.; Gonzalez, E.; Ramirez, C. *Tetrahedron* **1998**, *54*, 11683

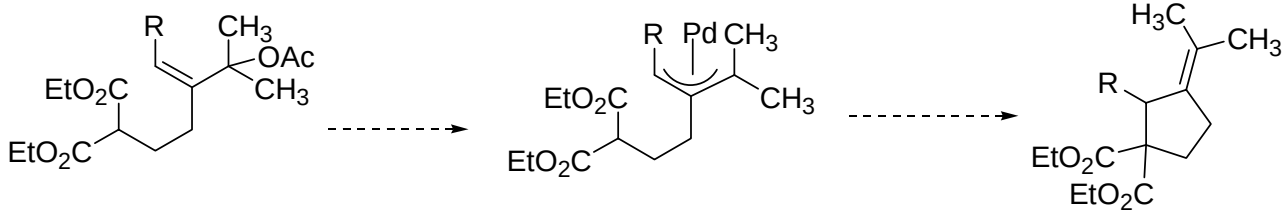
Isolated: From *Nigella sativa* (black cumin); Yoshikawa, M.; et al. *Org. Lett.* **2004**, *6*, 869

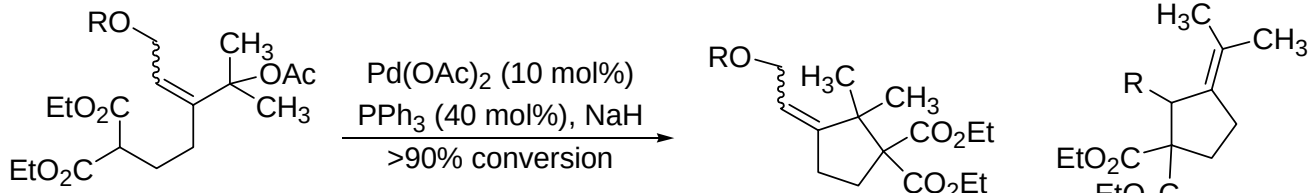
Biological Activity: Potent lipid metabolism-promoting activity

Development of Pd(π-allyl) Cyclization to Form Tetrasubstituted Olefins



Initial Attempts

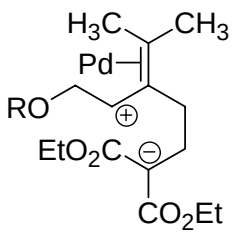




R= H, MOM, TBS, Bn, CH_2SCH_3

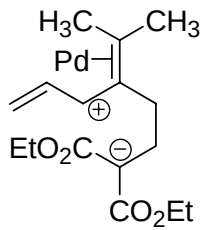
NOT Observed

Reasoned that the problem was due to the electronics of the OR group



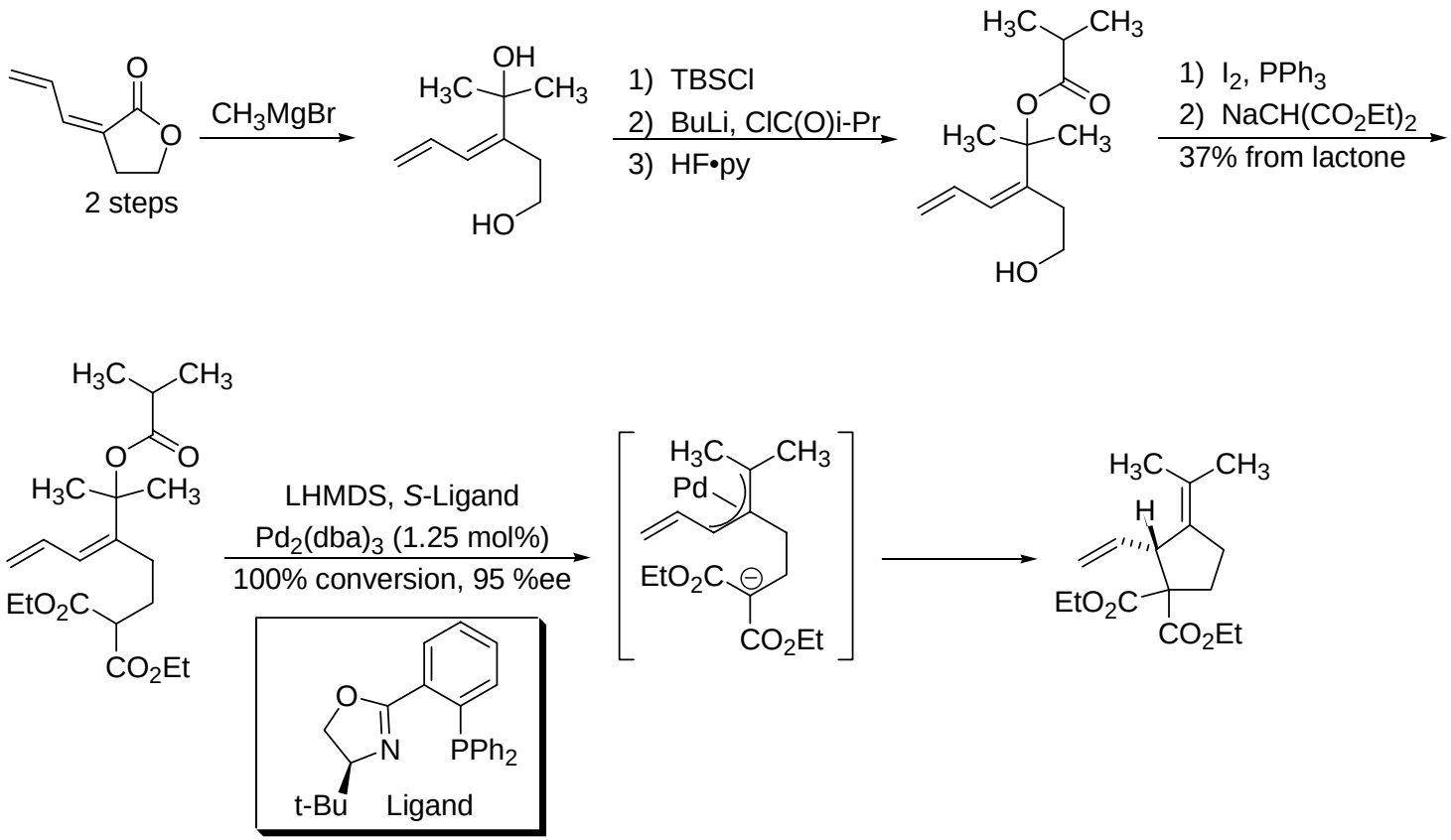
Destabilized

Solution was to change from CH_2OR to a vinyl group



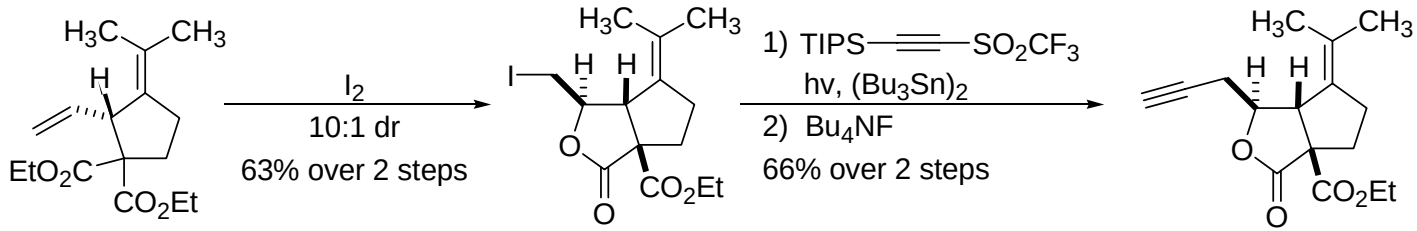
Stabilized

Application of Pd(π-allyl) Cyclization to Nigellamine A_2

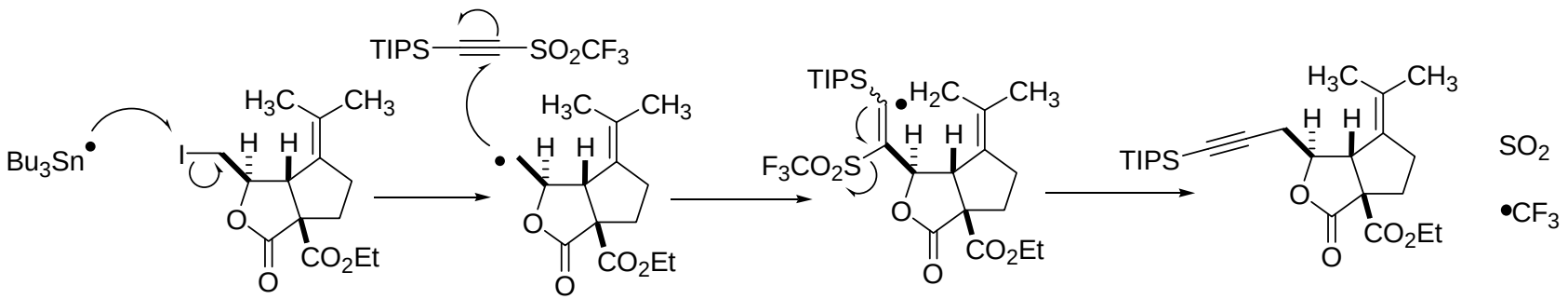


Phosphinooxazoline Ligand: Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149

Elaboration of Cyclopenane Core

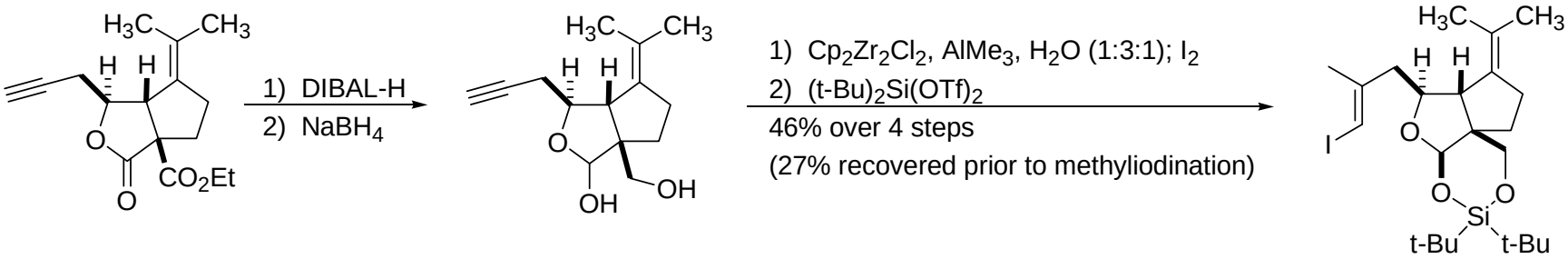


Proposed Mechansim for Radical Alkynylation

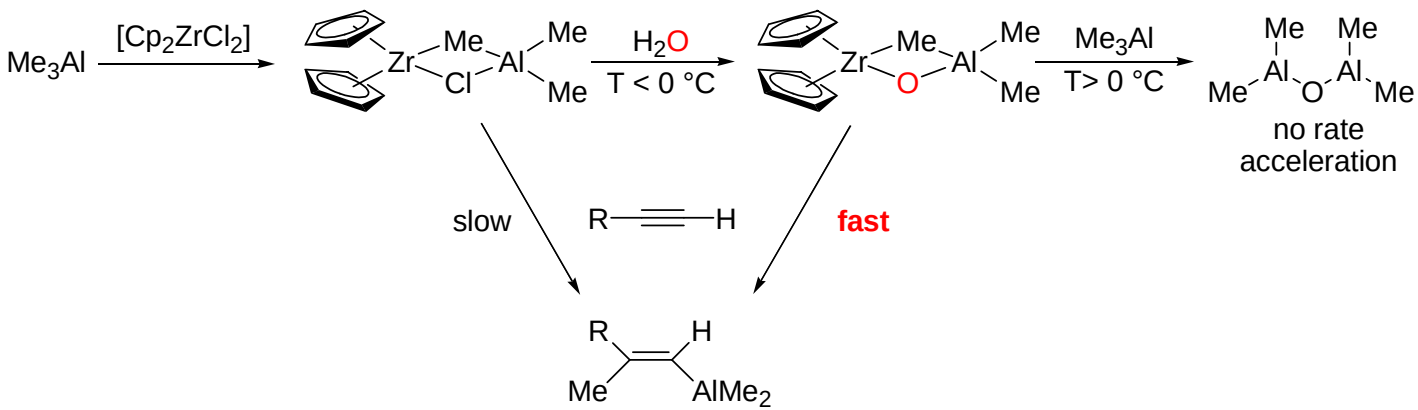


Radical Alkynylation: Xiang, J.; Fuchs, P. L. *Tetrahedron Lett.* **1998**, *39*, 8597.

Water-Accelerated Methyliodination of Alkyne

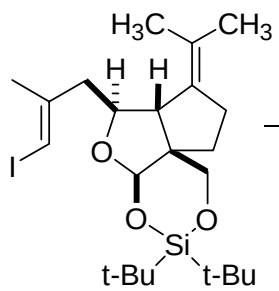


Proposed Rationale for Water Acceleration

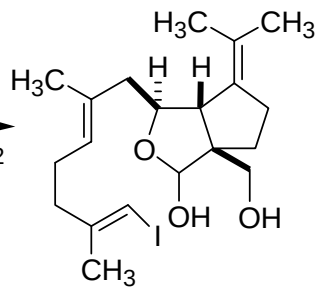


Water Accelerated Methyliodination: Wipf, P; Lim, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068

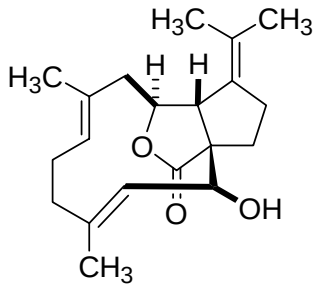
Completion of the Synthesis of *ent*-Nigellamine A_2



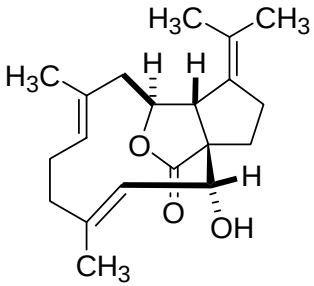
1) $PdCl_2(dppf)$ (cat)
TMS—≡—ZnBr
2) Bu_4NF
3) Cp_2ZrCl_2, Al_3Me, H_2O; I_2
63% over 3 steps



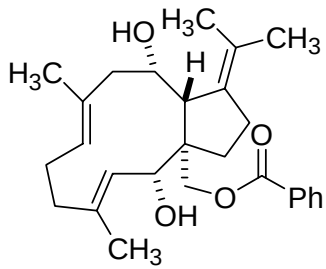
1) PCC (50%)
2) $CrCl_2$, $Ni(acac)_2$ (cat)
sonication
73% yield, d.r. >10:1



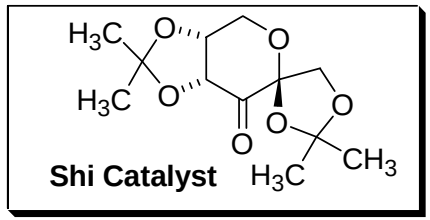
1) Dess Martin
2) $LiAlH(i\text{-}Bu)_2t\text{-}Bu$
82% over 2 steps



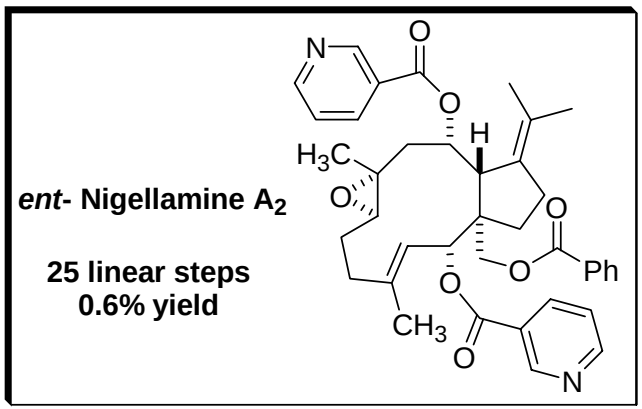
1) $LiAlH_4$
2) PhCOCl
51% over 2 steps



1) Shi catalyst, oxone
(7:1 chemoselectivity)
2) Nicotinic acid, DCC, DMAP
51% over 2 steps



Shi Catalyst



***ent*- Nigellamine A_2**

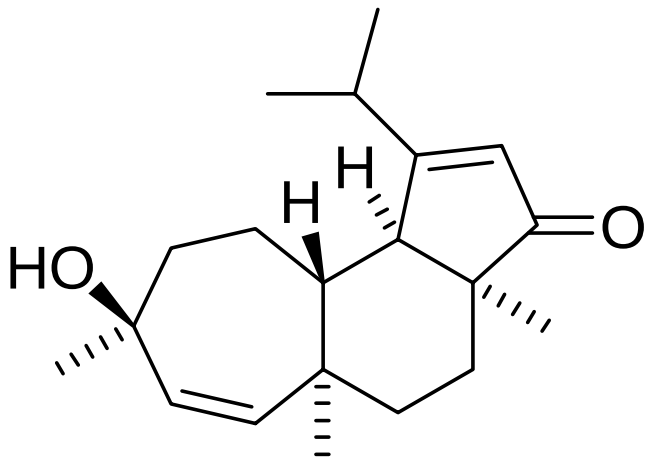
25 linear steps
0.6% yield

Shi Epoxidation: Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488; Wang, Z. -X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 3099.
$LiAlH(iBu)_2tBu$: Trost, B. M.; Nichimura, Y.; Yammamoto, K.; McElvain, S. S. *J. Am. Chem. Soc.* **1979**, *101*, 1328.

Total Synthesis of (+)-Cyanthiwigin U

J. Am. Chem. Soc. **2005**, *127*, 5334.

Pfeiffer, M. W. B.; Phillips, A. J.

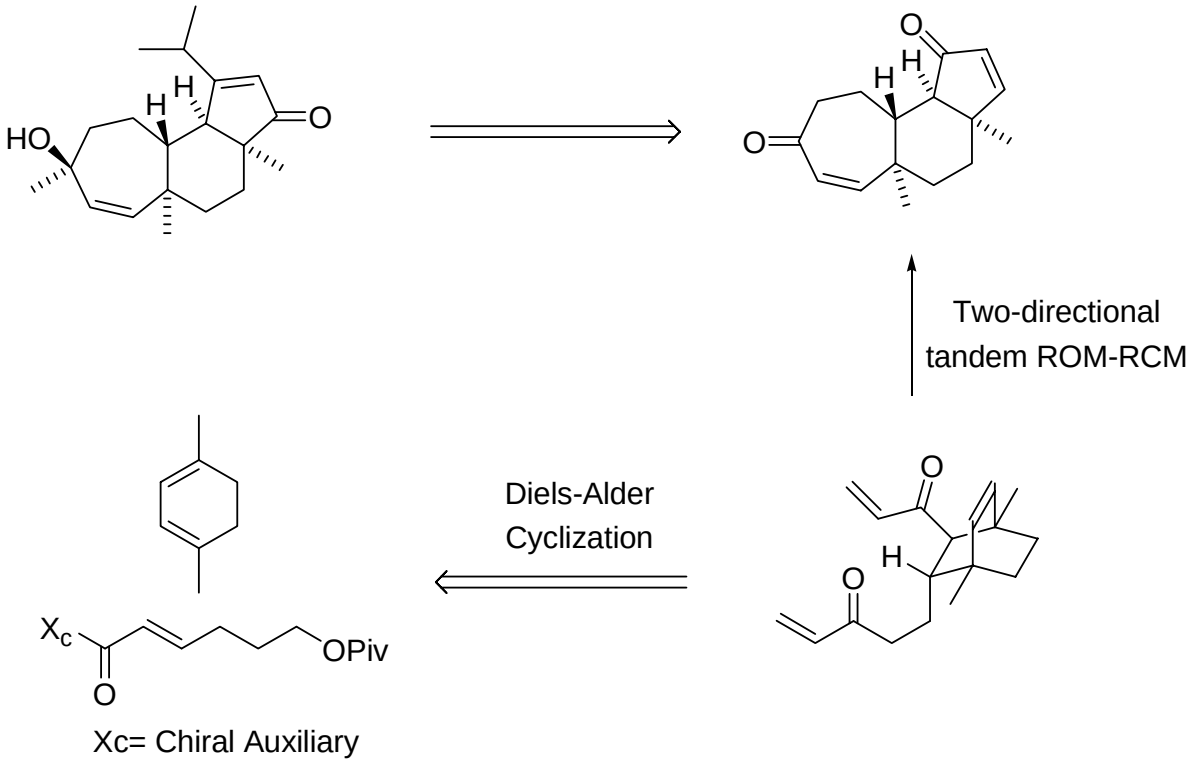


(+)-Cyanthiwigin U

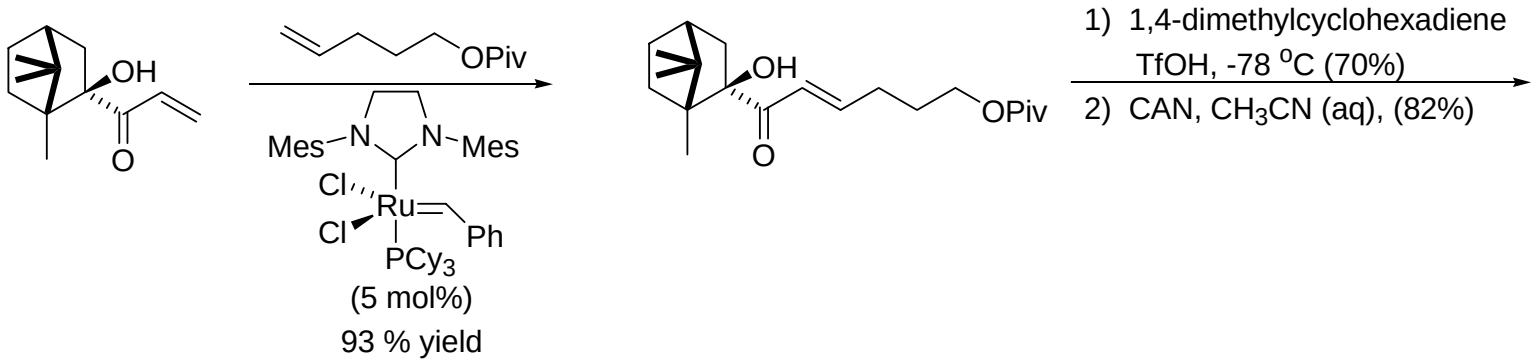
Isolated: Jamaican sponge *Myrmedioderma styx;* Hamann, M. T. et al *Tetrahedron*, **2002**, *58*, 7809

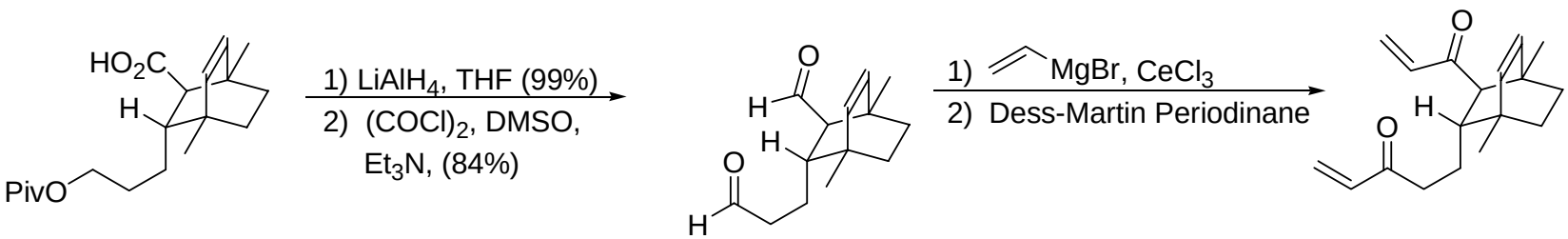
No biological activity (but many structurally related compounds are active against various cancer cell line, as well as viruses such as HIV-1 and hepatitis B)

Retrosynthetic Analysis of Cyanthiwigin U



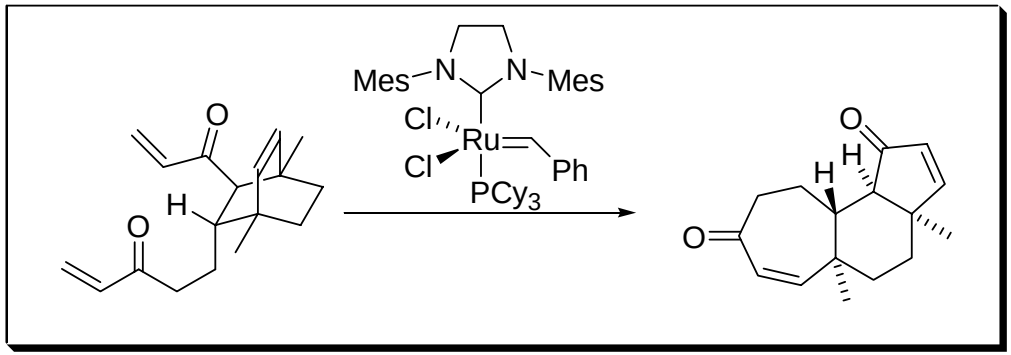
Synthesis of ROM/RCM Precursor

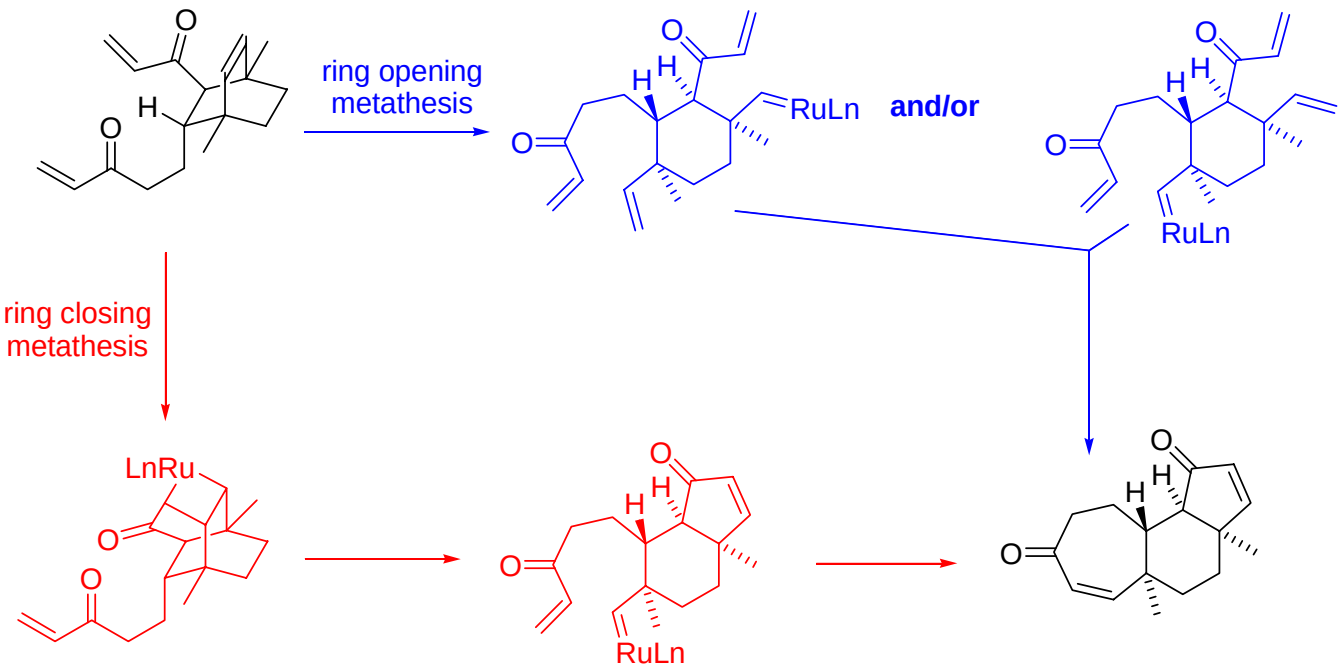




Palomo Chiral Auxiliary:
Palomo, C.; Oiarbide, M.; Garcia, J. M.; Gonzalez, A.; Lecumberri, A.; Linden, A. *J. Am. Chem. Soc.* **2002**, *124*, 10288

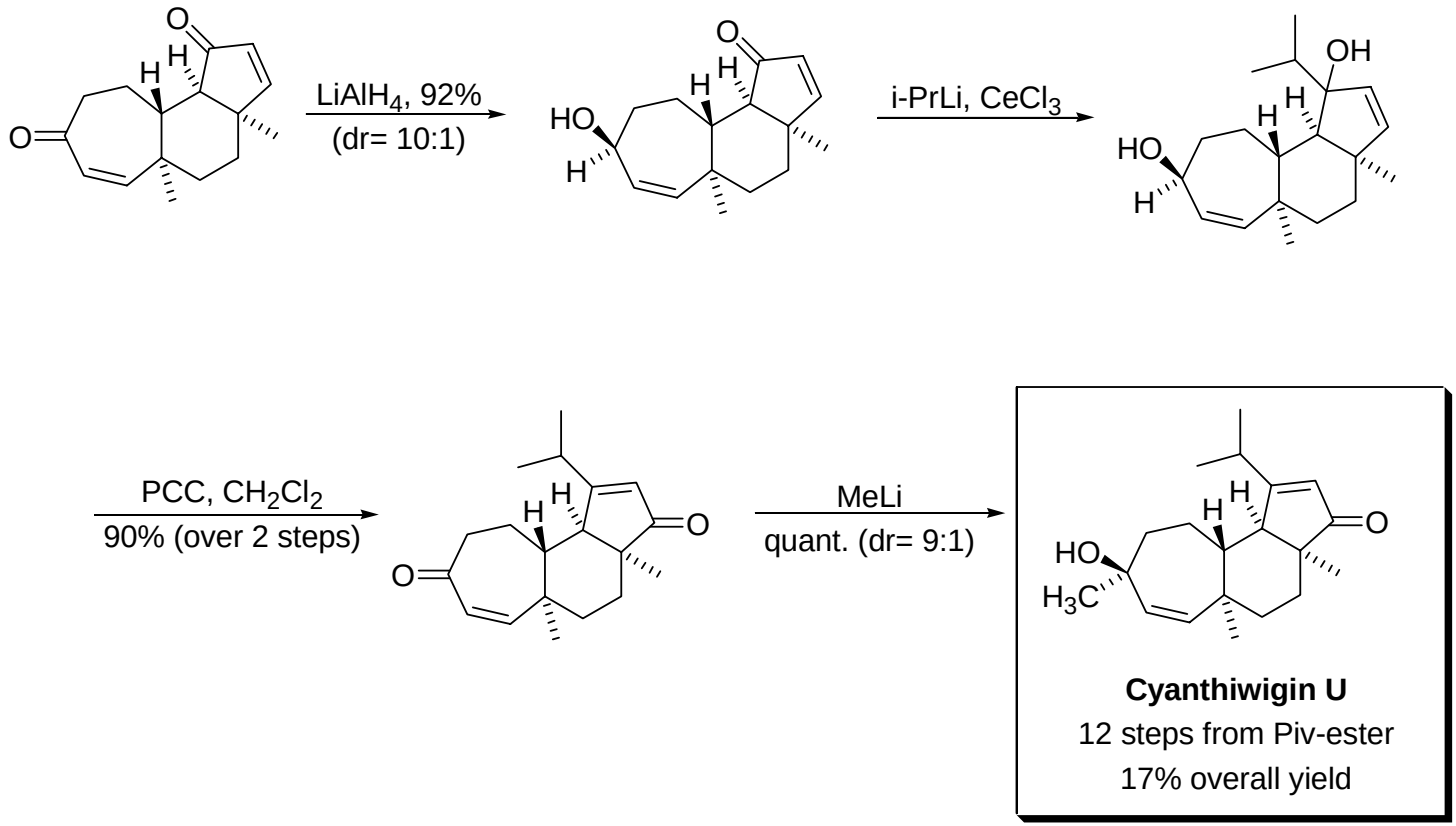
ROM/RCM to Form Desired Tricycle





Previous work by Phillips: Minger, T. L.; Phillips, A. J. *Tetrahedron Lett.* **2002**, *43*, 5357.
First example of ROM-RCM stradegy in total synthesis: Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 855.

Completion of the Total Synthesis of Cyanthiwigin U

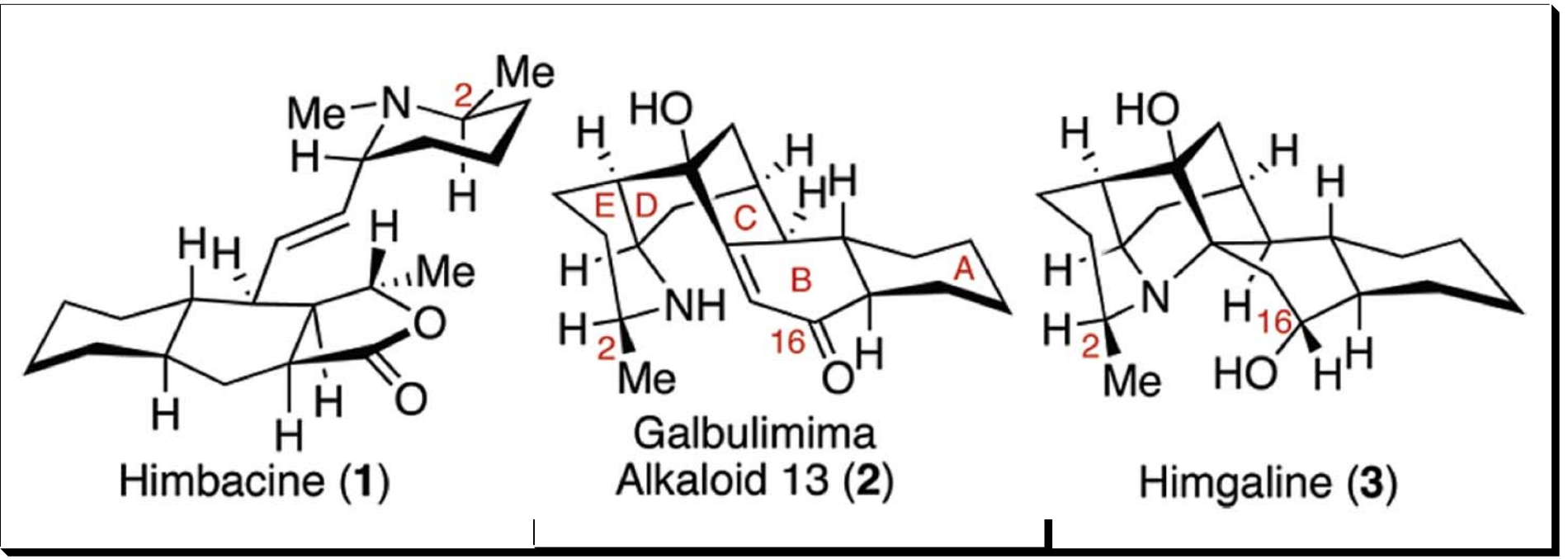


Dauben oxidation: Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.

Total Synthesis and Absolute Stereochemical Assignment of (+) and (-)-Galbulimia Alkaloid 13

J. Am. Chem. Soc. **2006**, *128*, 8126.

Movassaghi, M.; Hunt, D. K.; Tjandra, M.

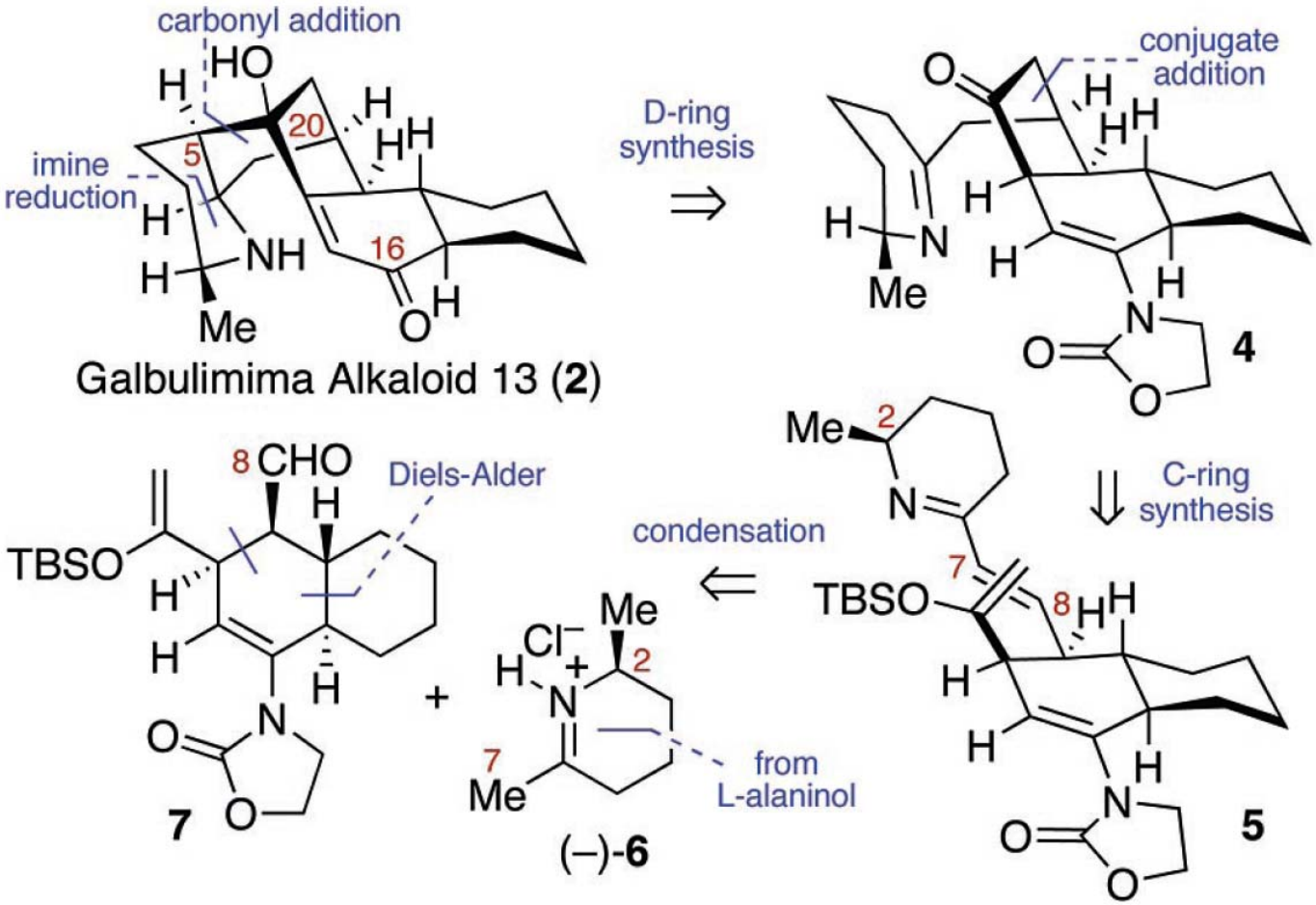


Isolated from the bark of *Galbulimima belgraveana*: Taylor, W. C. et al. *Aust. J. Chem.* **1967**, *20*, 1705

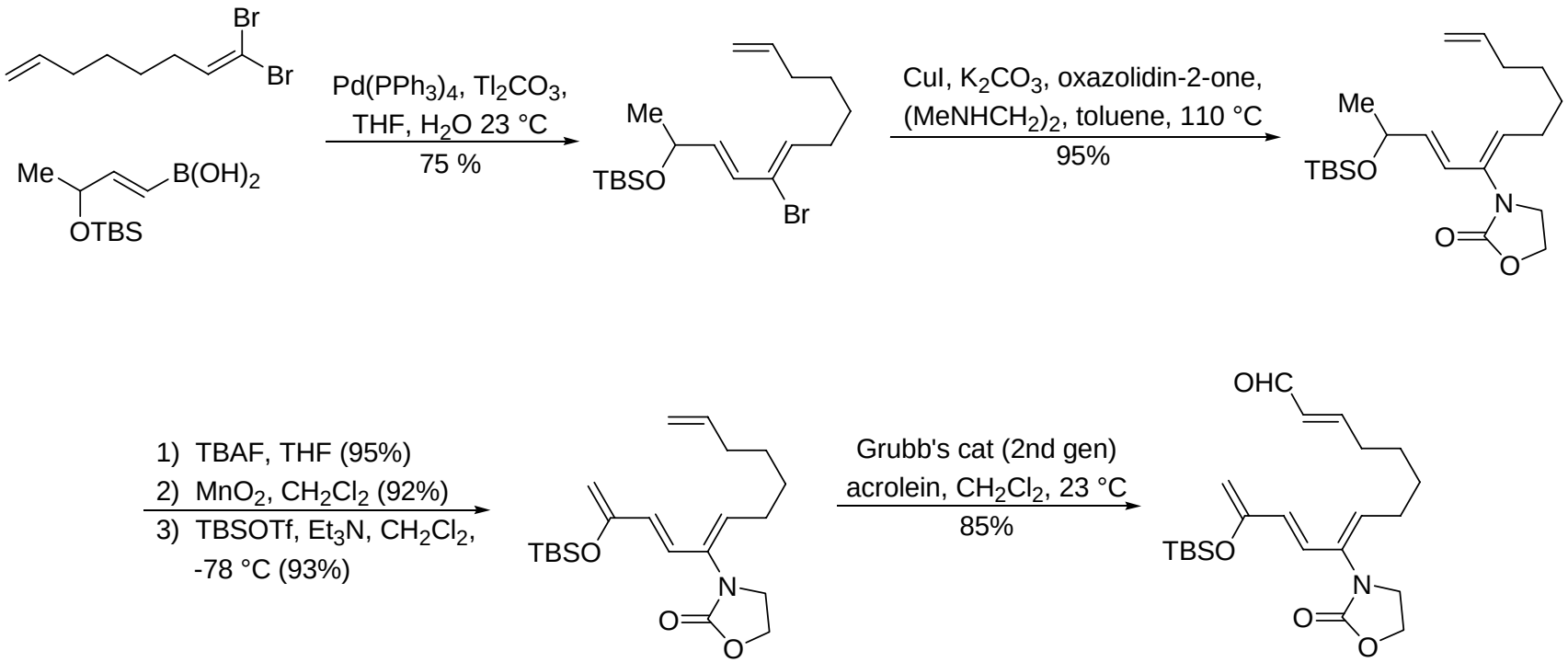
Biological Activity: Galbulimima Alkaloid 13 has not been tested but Himacine is a potential treatment for Alzheimer's disease McKinney, M. et al. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 797; **1995**, *5*, 61.

Previous synthesis of (+/-) Galbulimima Alkaloid 13: Mander, L. N.; McLachlan, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 2400.

Retrosynthetic Analysis of Galbulimima Alkaloid 13

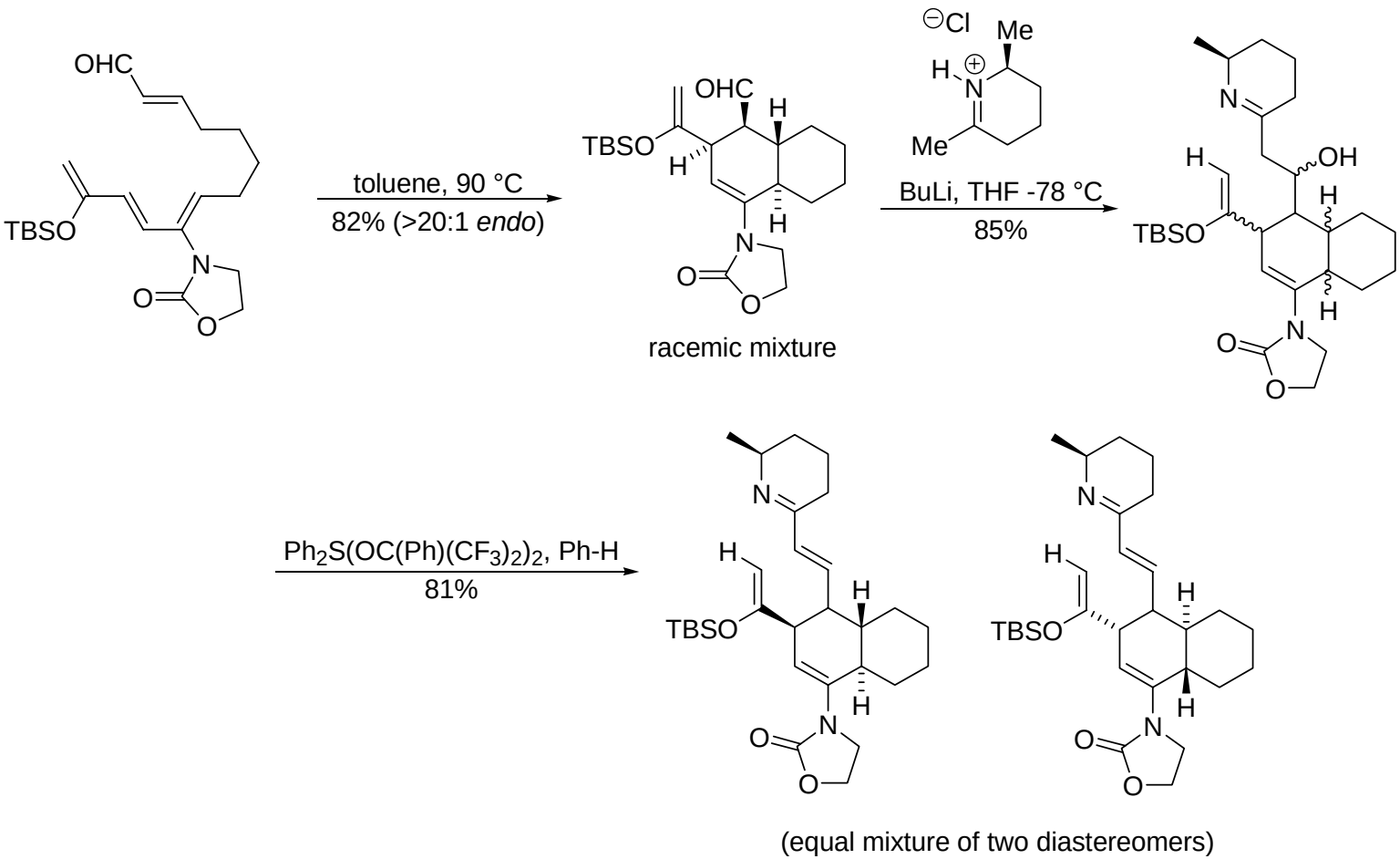


Synthesis of Diels Alder Precursor



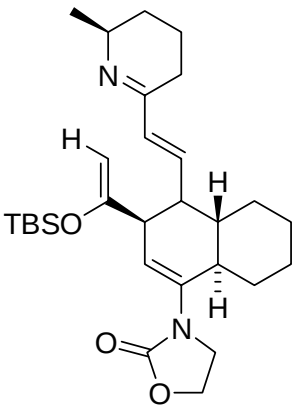
Use of Tl_2CO_3: Hoshino, Y.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3008.
Copper Catalyzed amidation: Jiang, L.; Fob, G. E.; Klapars, A.; Buchwald, S. *Org Lett.* **2003**, *5*, 3667.

Synthesis of Radical Cyclization Precursor



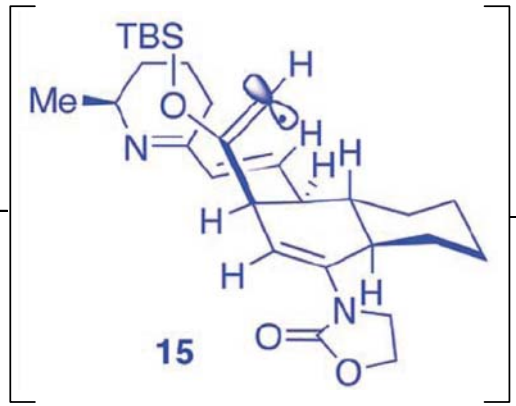
Martin sulfurane: Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327.

Cyclizations to form Galbulimima Alkaloid 13 Core

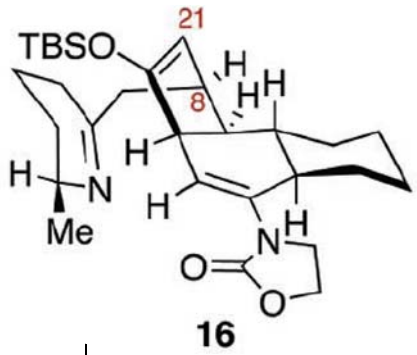


(+ diastereomer)

1) NBS, $NaHCO_3$, THF 0 °C
2) Bu_3SnH, AIBN Ph-H, 60 °C
55% yield

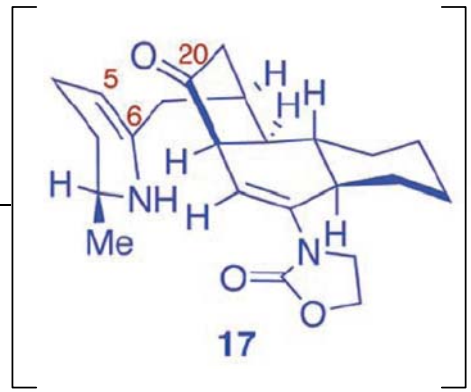


15

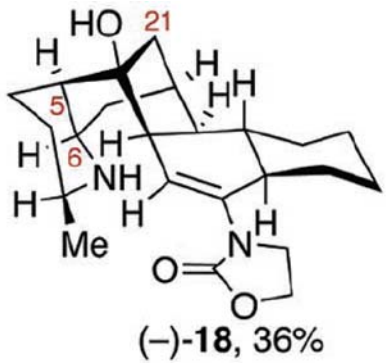


16

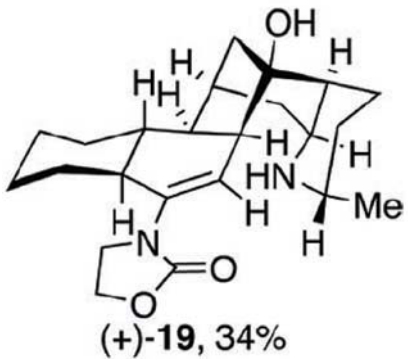
1) $Et_3N{\bullet}(HF)_3$, THF
2) $NaBH_4$, EtOH, 0 °C
70% yield



17



(–)-18, 36%

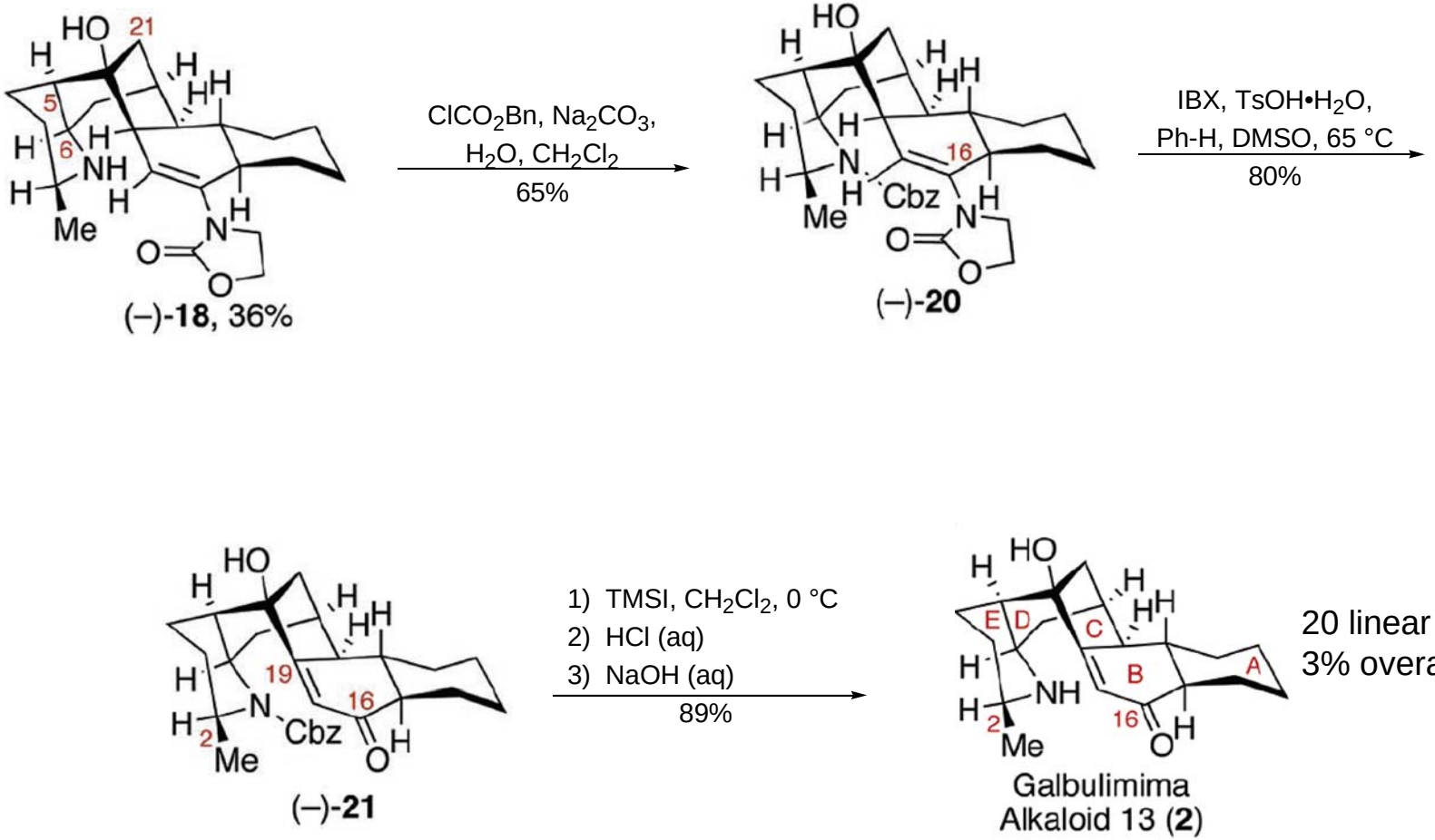


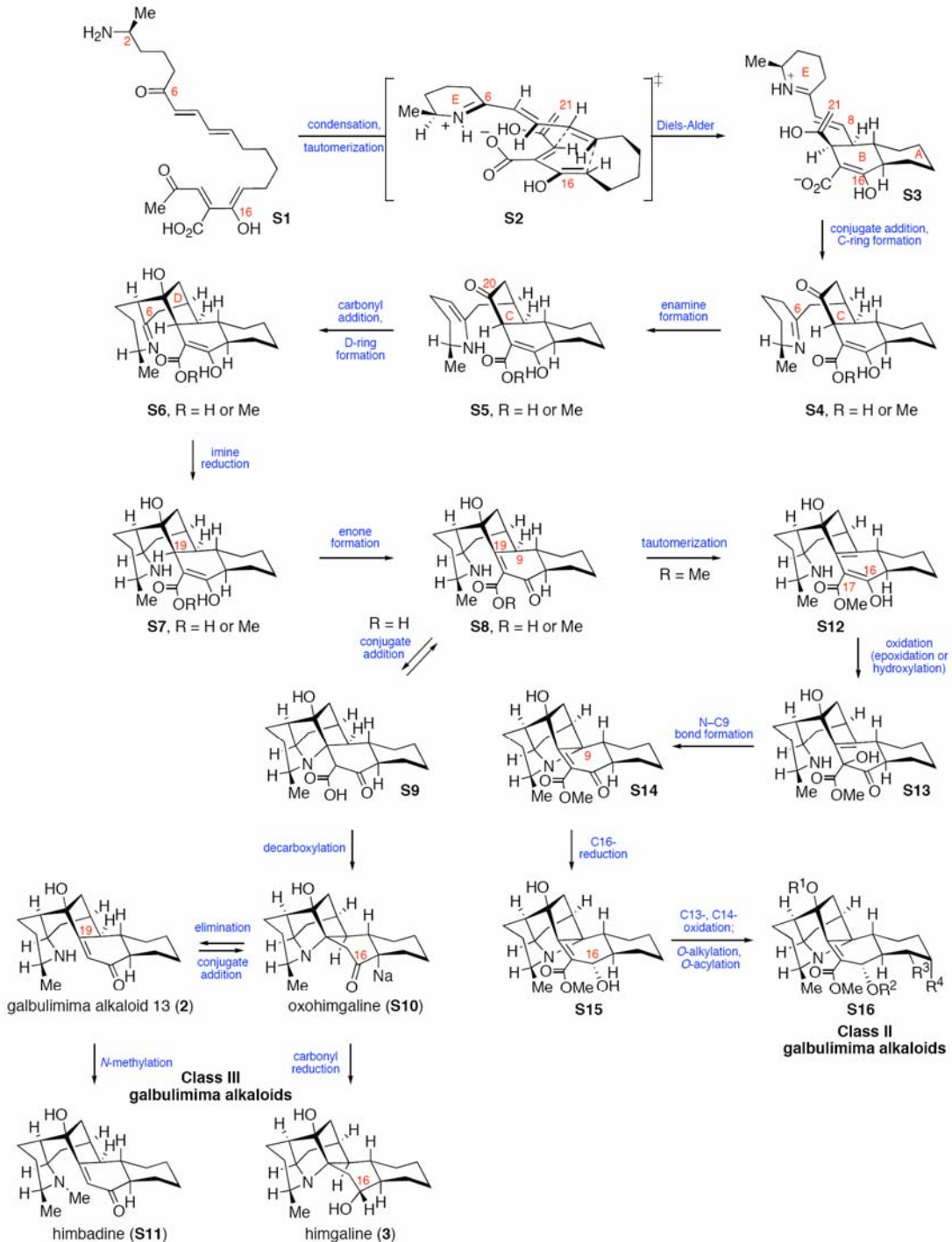
(+)-19, 34%

(product of diastereomer not shown)

First example of vinyl radical cyclizations: Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321.

Completion of the Total Synthesis of Glabulimima Alkaloid 13




S1
condensation, tautomerization
S2
Diels-Alder
S3
conjugate addition, C-ring formation
S4, R = H or Me
enamine formation
S5, R = H or Me
carbonyl addition, D-ring formation
S6, R = H or Me
imine reduction
S7, R = H or Me
enone formation
S8, R = H or Me
tautomerization
R = Me
S12
oxidation (epoxidation or hydroxylation)
S13
N–C9 bond formation
S14
R = H
conjugate addition
S9
decarboxylation
C16-reduction
galbulimima alkaloid 13 (2)
elimination
conjugate addition
oxohimgaline (S10)
S15
C13-, C14-oxidation; O-alkylation, O-acylation
S16
Class II galbulimima alkaloids
N-methylation
carbonyl reduction
Class III galbulimima alkaloids
himbadine (S11)
himgaline (3)