Total Synthesis of (+)-Fendleridine (Aspidoalbidine) and (+)-1-Acetylaspidoalbidine

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Literature Presentation

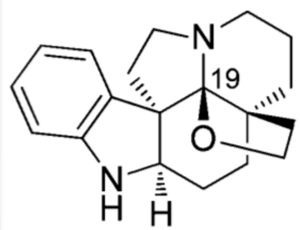
Nilanjana Majumdar

09/24/10

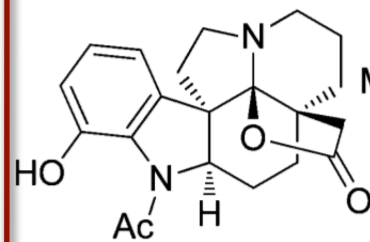
Introduction

Aspidoalbine family of alkaloids

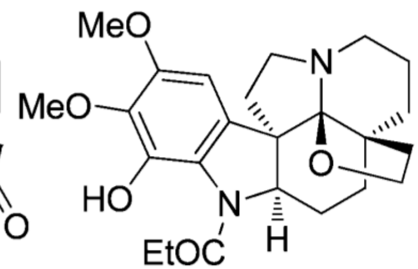
Parent members



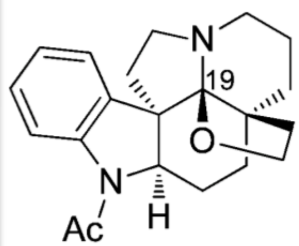
1, (+)-Fendleridine



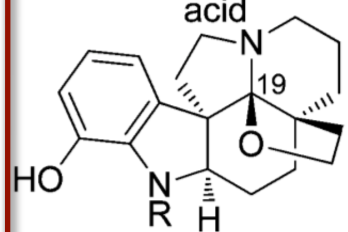
Aspidospermidin-21-oic acid



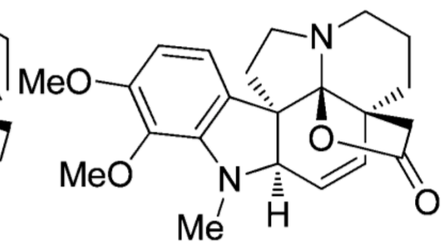
Aspidoalbine



2, (+)-1-Acetyl-aspidoalbidine



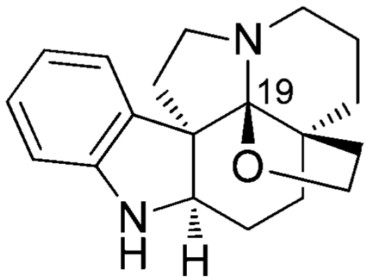
Haplocidine (R = H)
Haplocin (R = COEt)



(–)-Aspidophytine

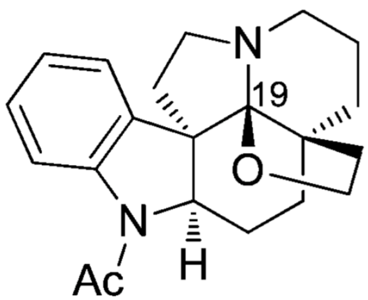
Unique Feature: Oxidized C19 *N, O*-ketal embedded in the characteristic *Aspidosperma* alkaloid pentacyclic ring system

Introduction



1, (+)-Fendleridine

- First isolated in 1964 from the Venezuelan tree *Aspidosperma fendleri* Woodson by Burnell
- Only total synthesis in 1976 by Ban and co-workers



2, (+)-1-Acetyl-aspidoalbidine

- First isolated in 1963 from *Vallesia dichotoma* Ruiz et PAV in Peru by Djerassi
- First total synthesis in 1975 by Ban and co-workers
- Improved formal synthesis by Ban in 1987
- Formal synthesis in 1991 by Overman

Honma, Y.; Ohnuma, T.; Ban, Y. *Heterocycles* **1976**, *5,* 47

Ban, Y.; Ohnuma, T.; Seki, K.; Oishi, T. *Tetrahedron Lett.* **1975**, *16,* 727

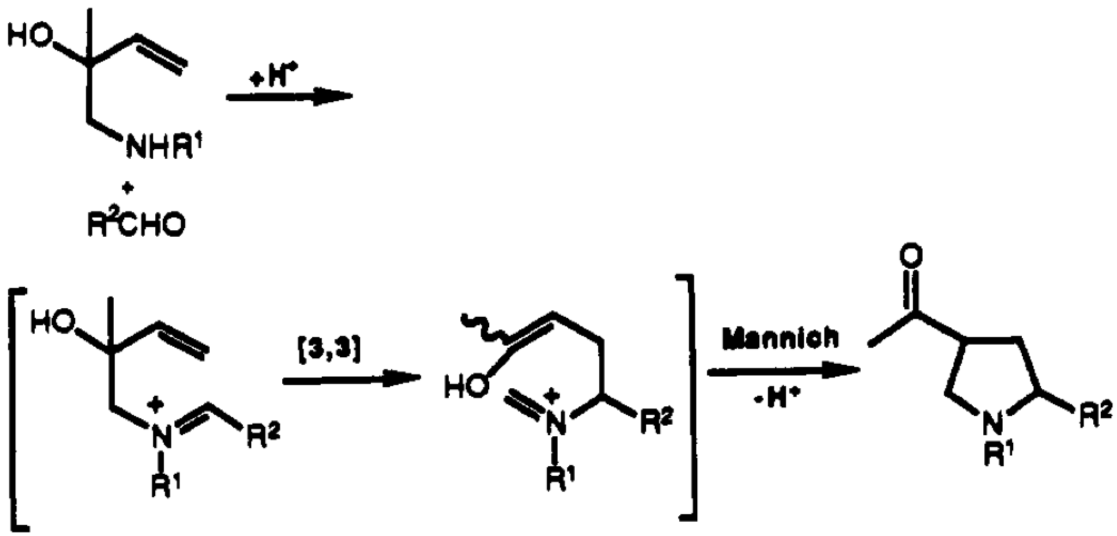
Yoshido, K.; Sakuma, Y.; Ban, Y. *Heterocycles* **1987**, *25,* 47

Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113,* 2598

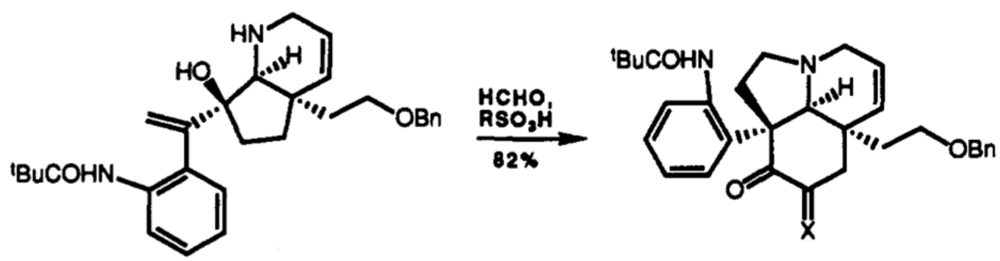
Outline

- Overman's Synthesis
- Boger Synthesis

Overman Strategy: Aza-Cope-Mannich Reaction

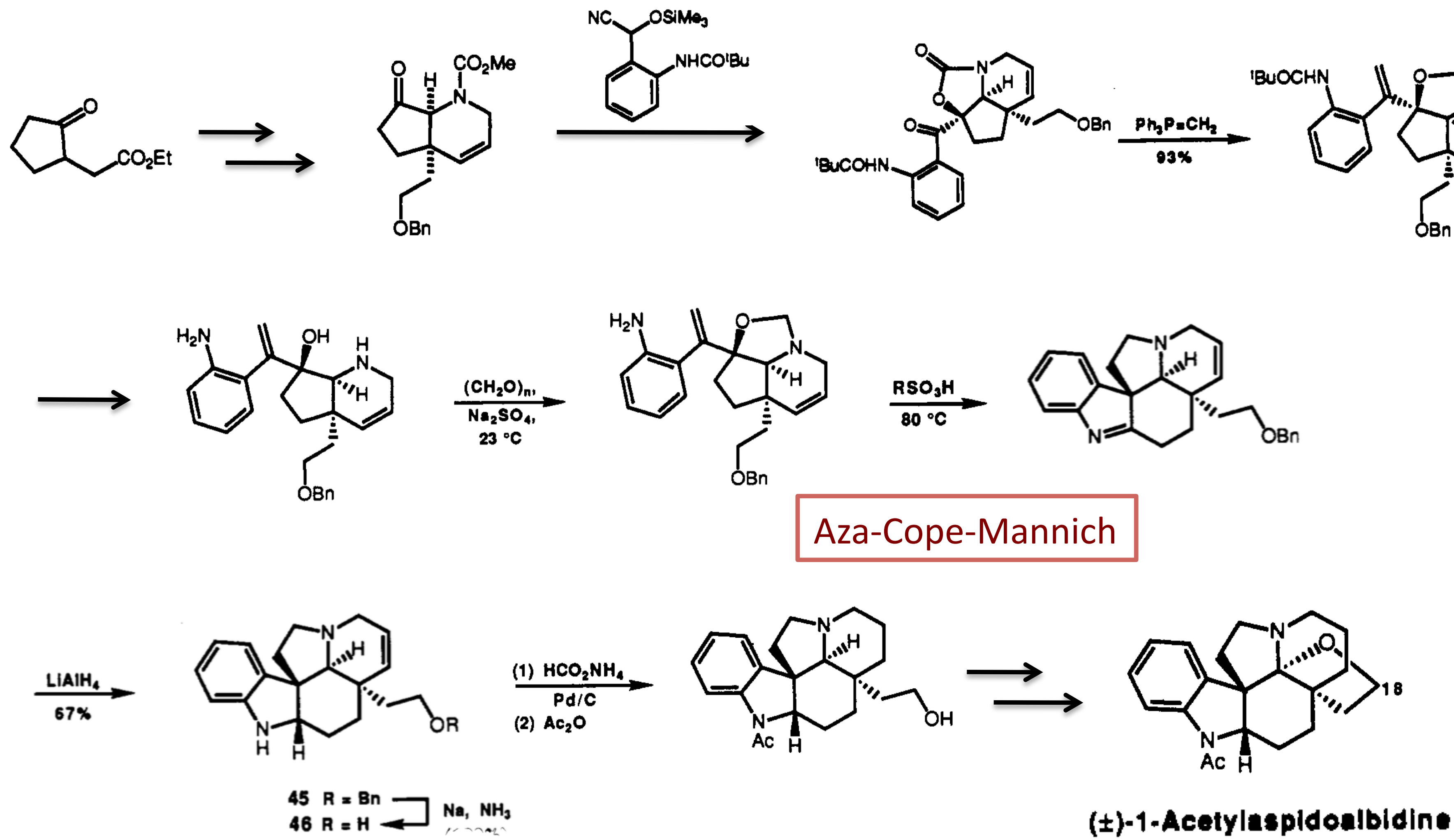


Application in synthesis:



Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598

Overman's Total Synthesis of Acetylaspidoalbidine



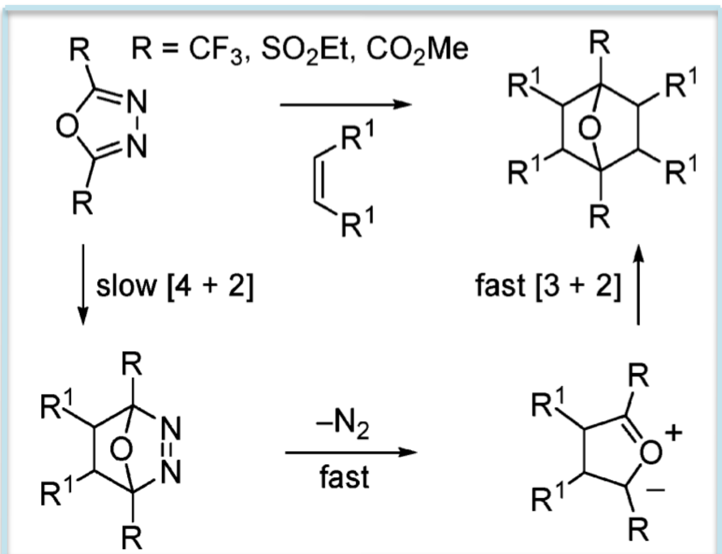
Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598

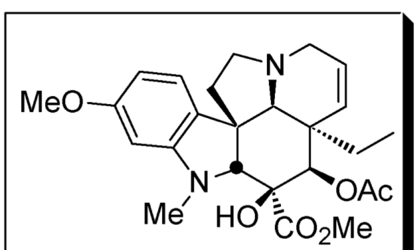
Outline

- Overman's Synthesis
- Boger Synthesis

1,3,4-Oxazole Cycloaddition Cascade

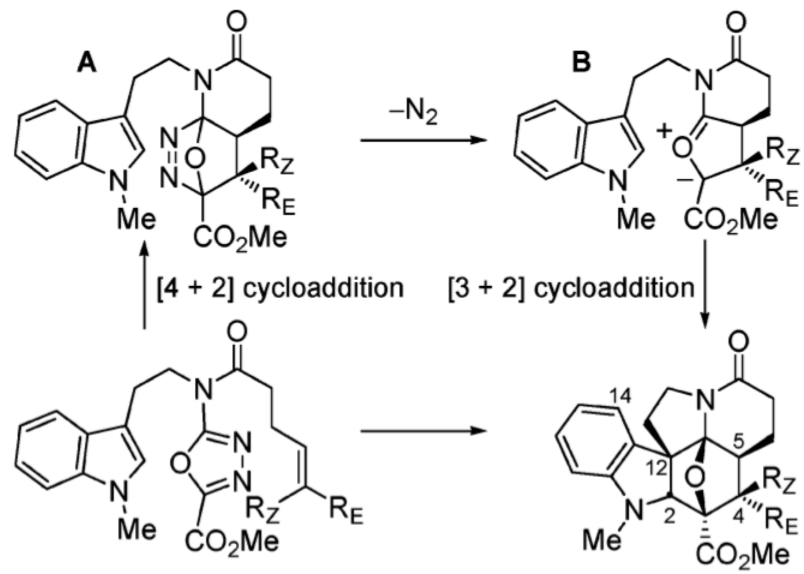
Studies by Vasiliev, Sauer, Seitz and Werner:





Vindoline

Application by Boger:



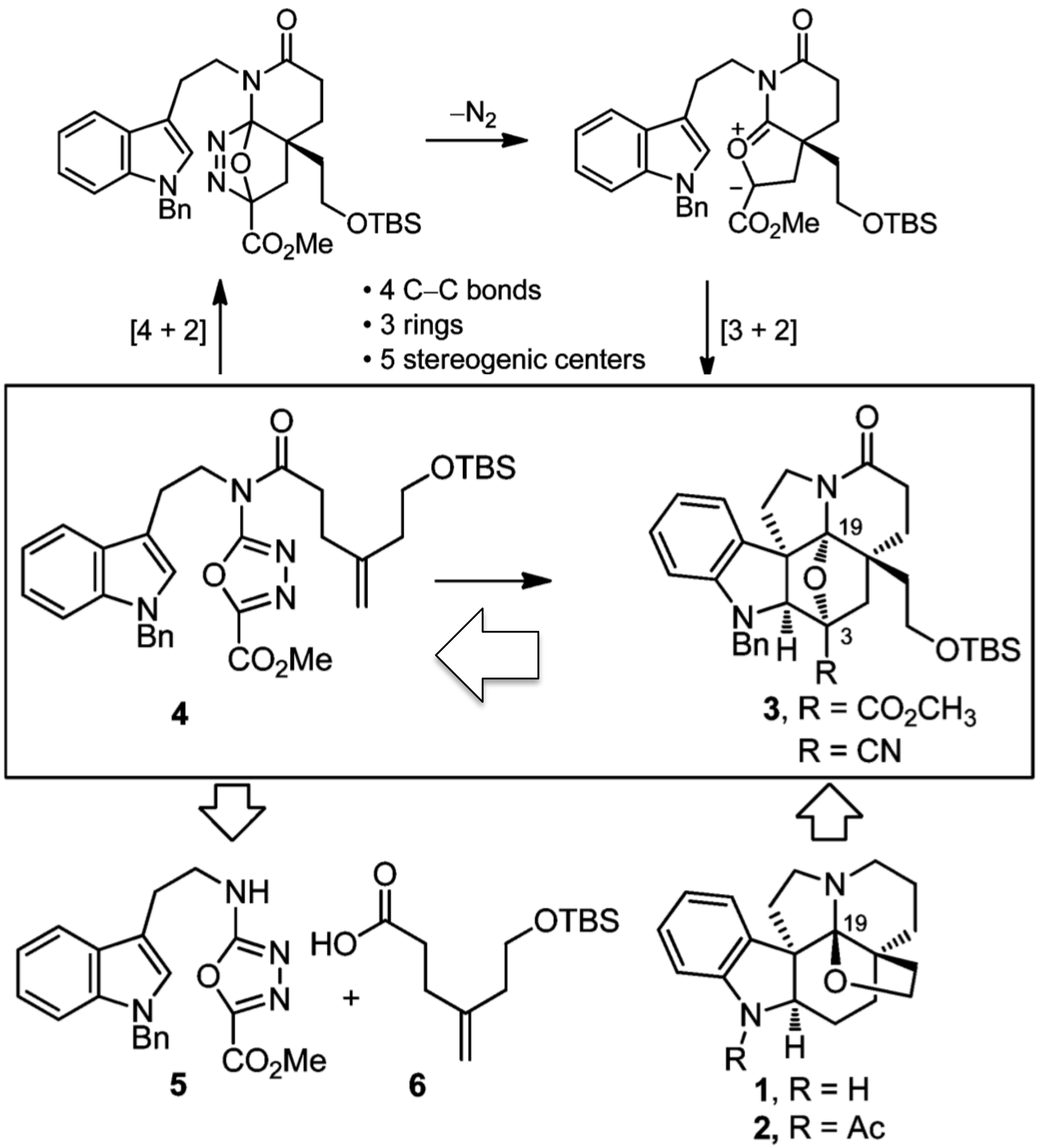
1a, R = H	*o*-$Cl_2C_6H_4$, 180 °C, 3 h	87% **1b**
(*E*)-**2a**, R = Me	*o*-$Cl_2C_6H_4$, 180 °C, 6 h	65% **2b**
(*Z*)-**3a**, R = Me	*o*-$Cl_2C_6H_4$, 180 °C, 6 h	65% **3b**
(*E*)-**4a**, R = CH_2OTBS	*o*-$Cl_2C_6H_4$, 180 °C, 24 h	86% **4b**
(*E*)-**5a**, R = Ph	*o*-$Cl_2C_6H_4$, 175 °C, 14 h	61% **5b**

Stereochemistry is defined by:

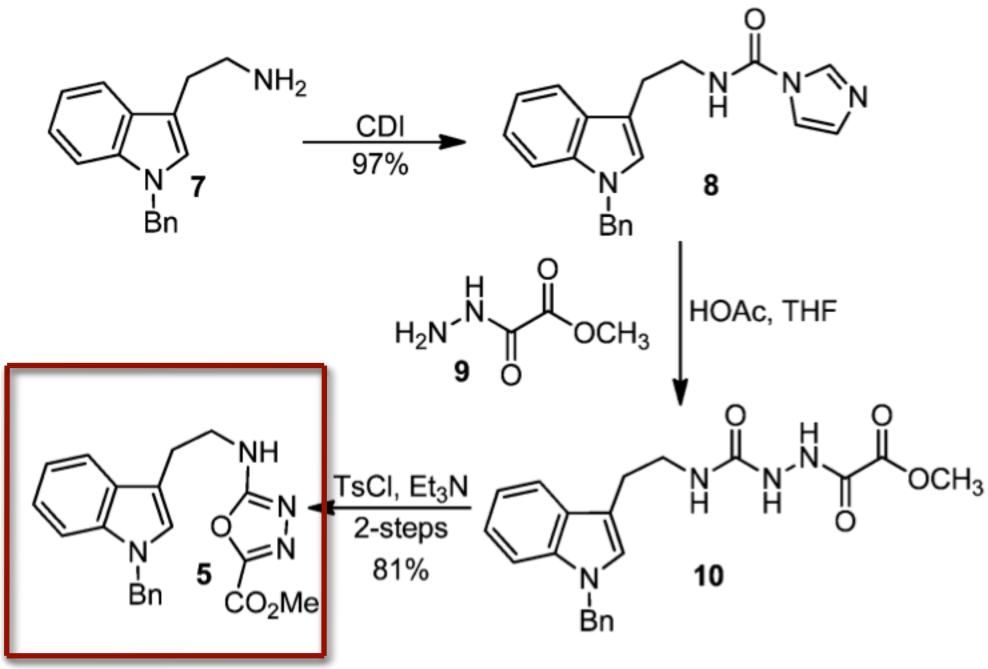
- Dienophile and dipolarophile geometry
- Indole endo [3+2] cycloaddition

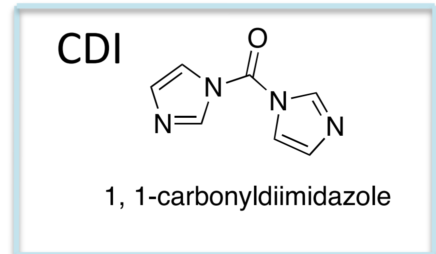
Elliot, G. I.; Fuchs, J. R.; Blagg, B. S. J.; Ishikawa, H.; Tao, H.; Yuan, Z.-Q.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 10589

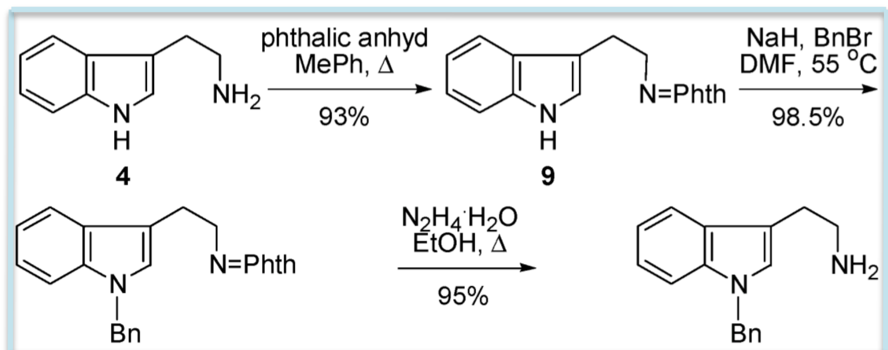
Key Cycloaddition Cascade and Retrosynthesis

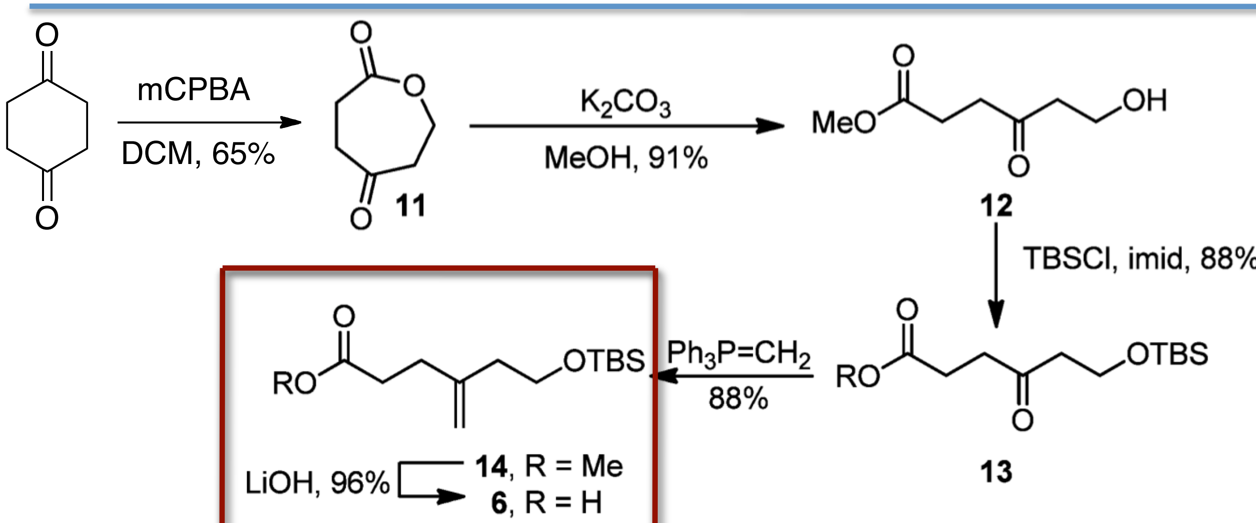


Synthesis of Intermediate 5 and 6







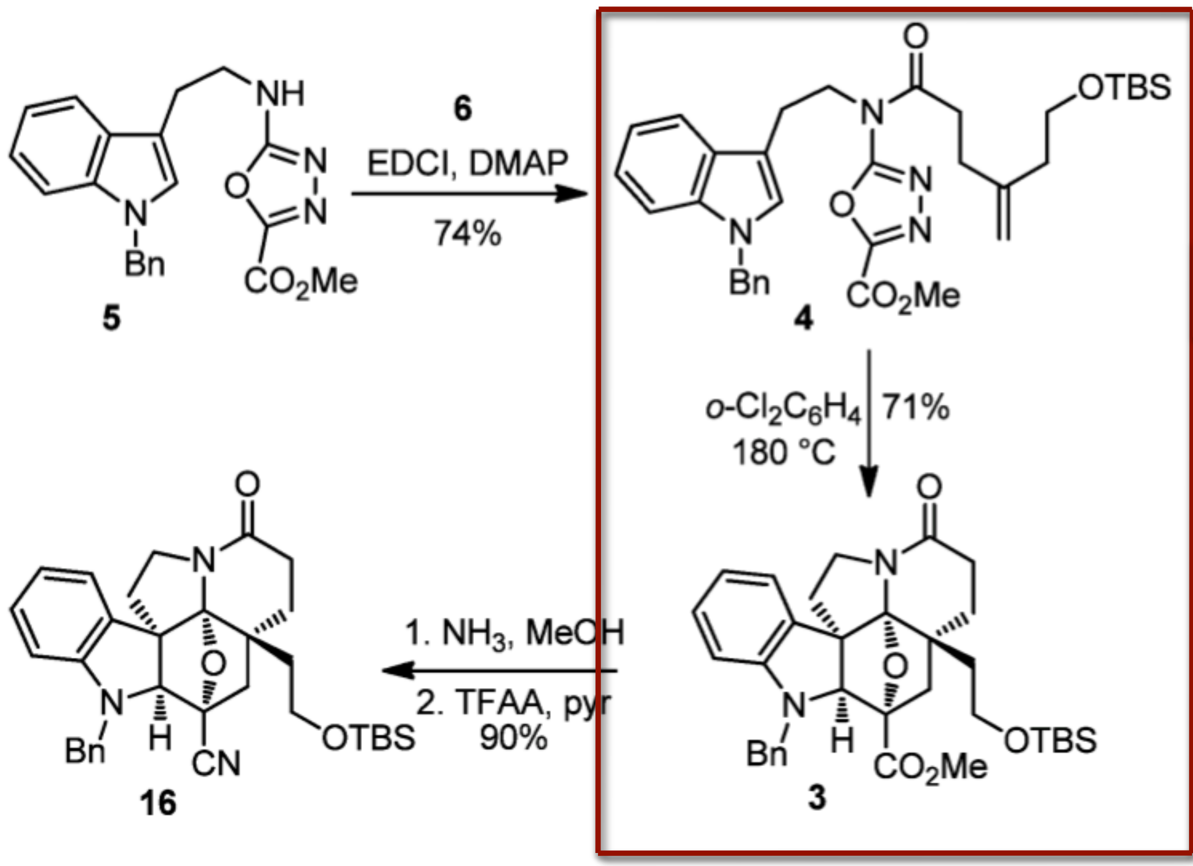


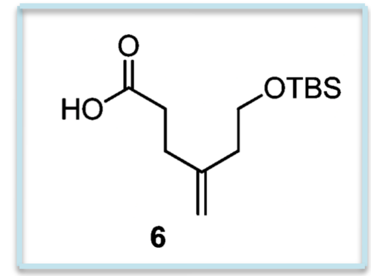
Luo, S.; Fu, X.; Fang, F.; Zhuang, Z.; Xiong, W.; Jia, X.; Zhai, H. *Org. Lett.* **2006**, *8*, 115

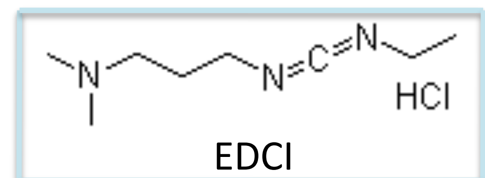
Van der Ende, A. E.; Kravitz, E. J.; Harth, E. *J. Am. Chem. Soc.* **2008,** *130*, 8706

Campbell, E. L.; Zuhl, A. M.; Liu, C. M.; Boger, D. L. *J. Am. Chem. Soc.* **2010,** *132*, 3009

[4+2]/[3+2] Cycloaddition Cascade







- Four C–C bonds
- Three rings
- Five relative stereogenic centers including C19 *N, O*-ketal
- Complete natural product skeleton in single step
- Single diastereomer

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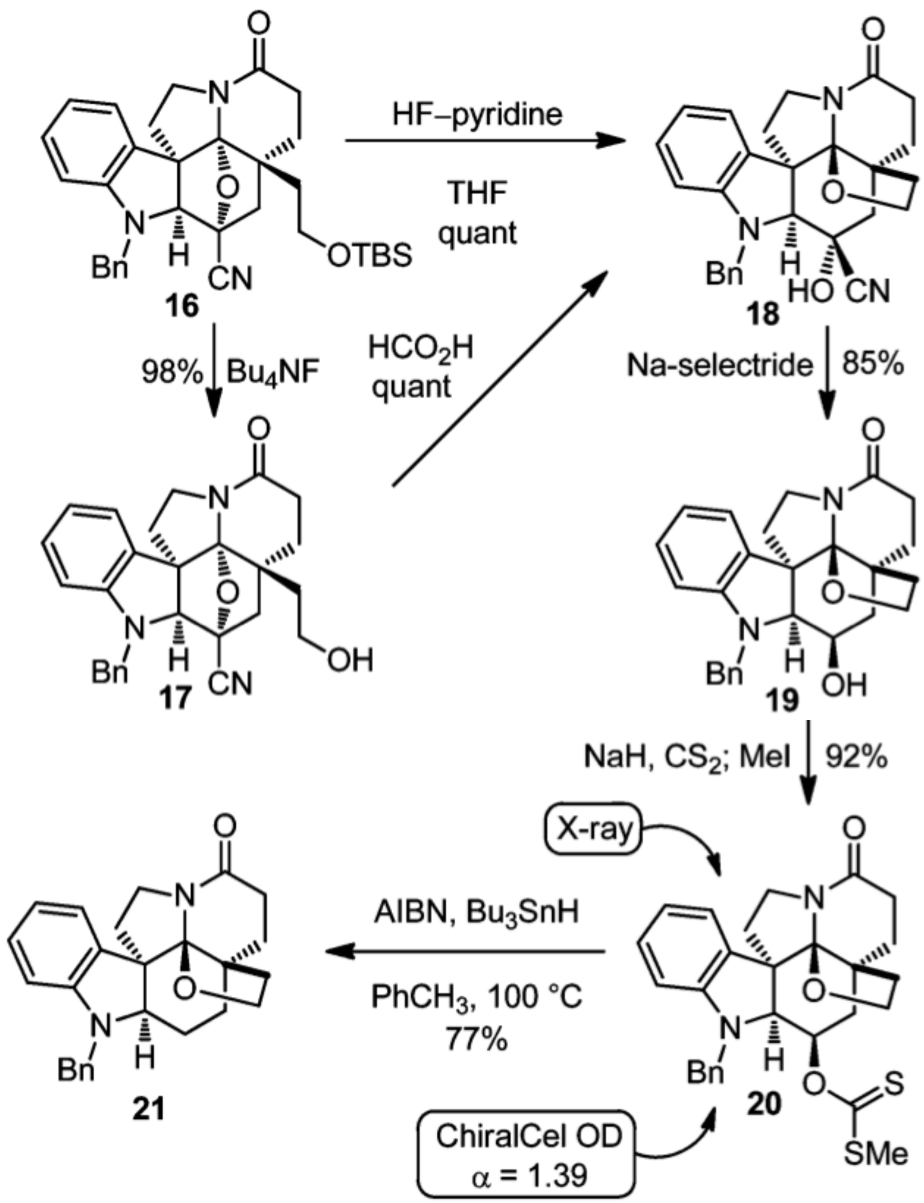
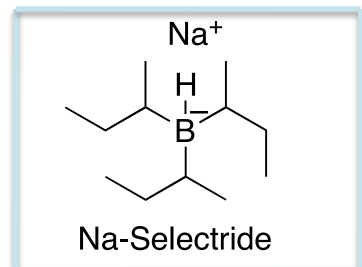
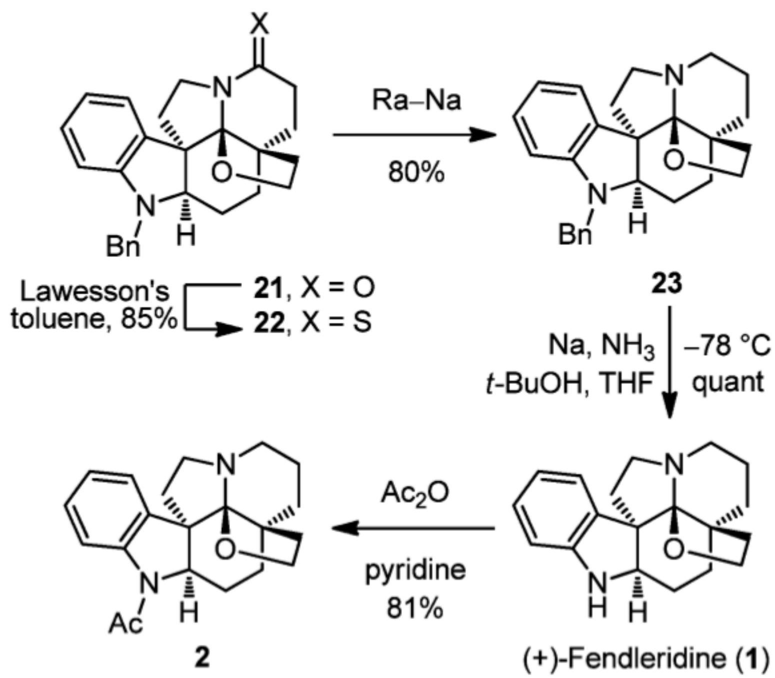
Introduction of THF ring





Final Step of the Synthesis

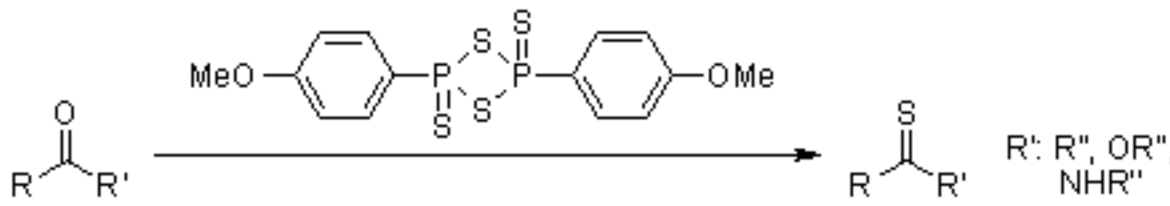


In conclusion:

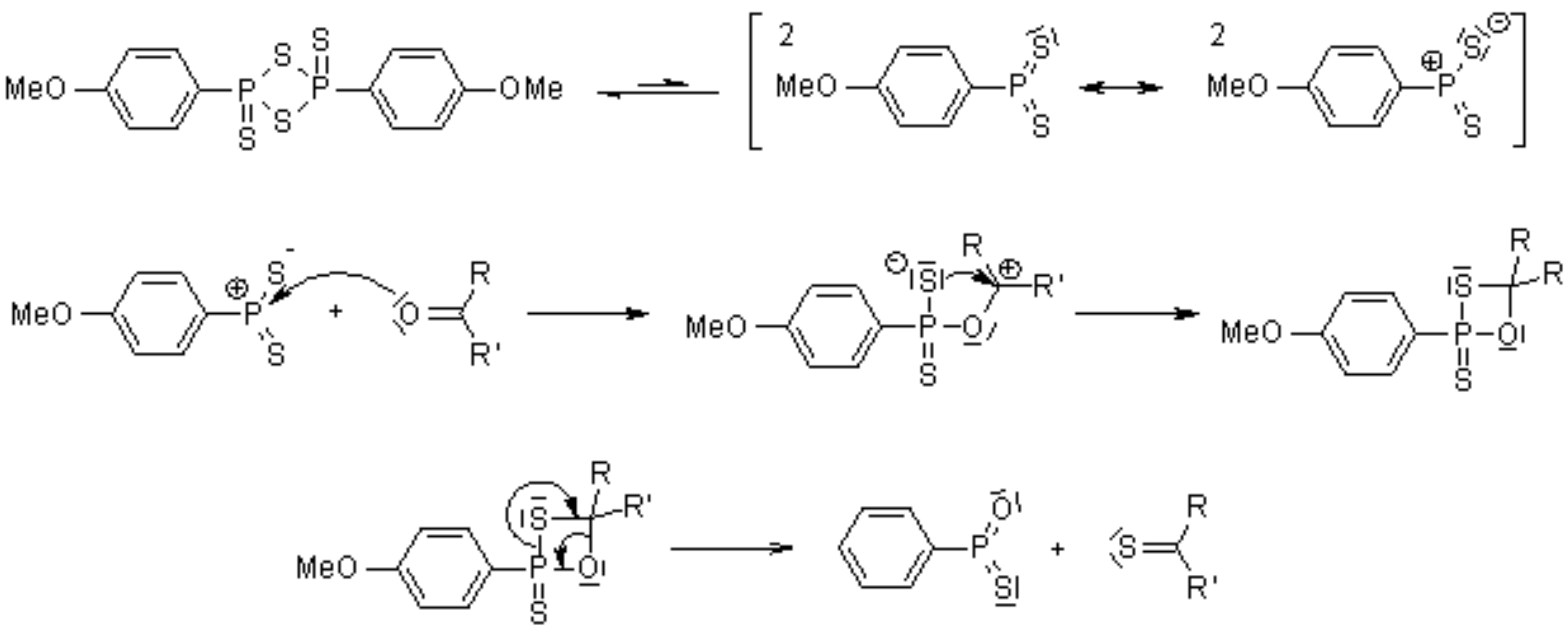
- Powerful intramolecular [4+2]/[3+2] cycloaddition cascade of 1,3,4-oxadiazole
- In one step:
  1. Pentacyclic skeleton and all the stereochemistry
  2. Three rings
  3. Four C–C bonds
  4. Five stereogenic centers
  5. Three contiguous quaternary centers
- Final THF bridge installation in one step

Lawesson's Reagent

Reaction:



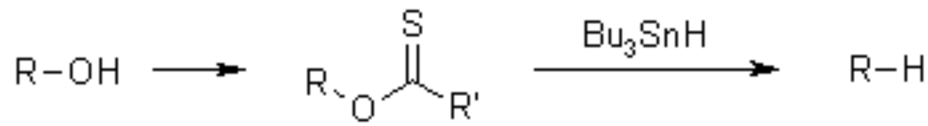
Mechanism:



http://www.organic-chemistry.org/namedreactions/lawessons-reagent.shtm

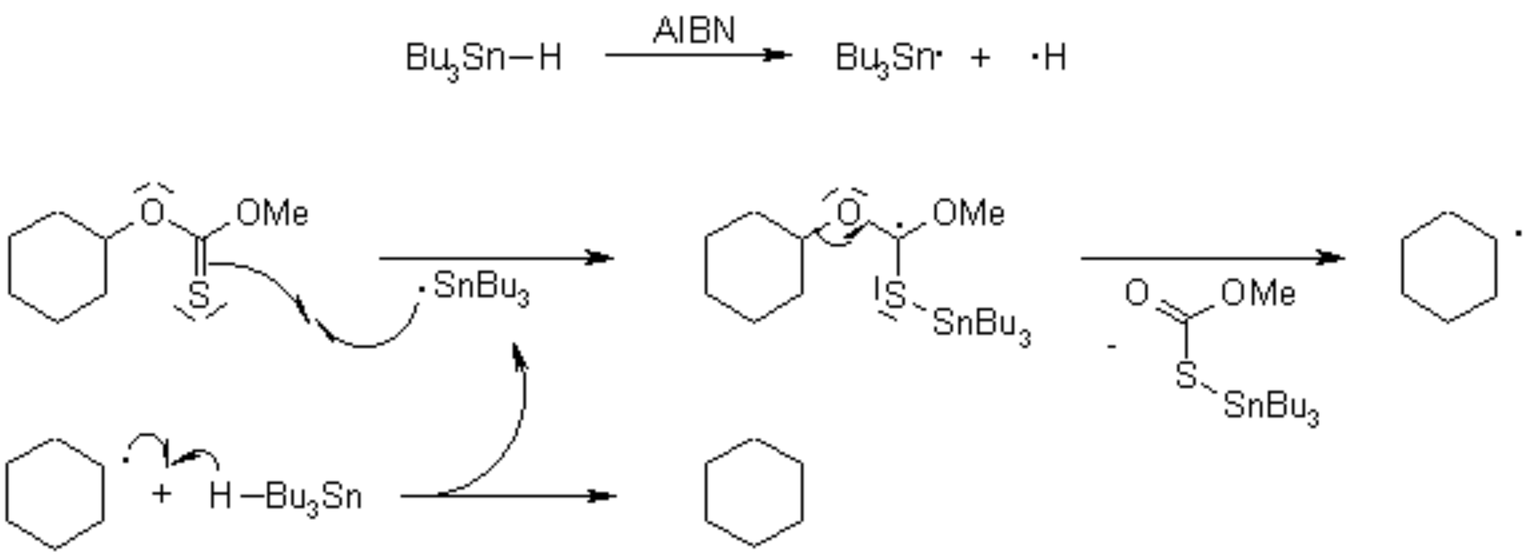
Barton McCombie Reaction

Reaction:



R = Alkyl, R' = H, CH_3, SCH_3, OCH_3 Ph, OPh, Imidazolyl

Mechanism:



http://www.organic-chemistry.org/namedreactions/barton-mccombie-reaction.shtm