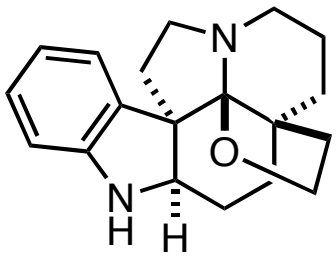
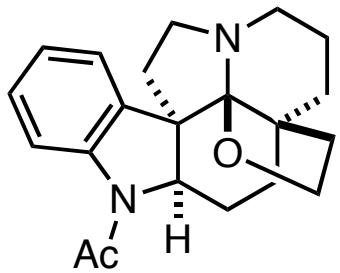
# Total Synthesis of (+)-Fendleridine and (+)-1-Acetylaspidoalbidine

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



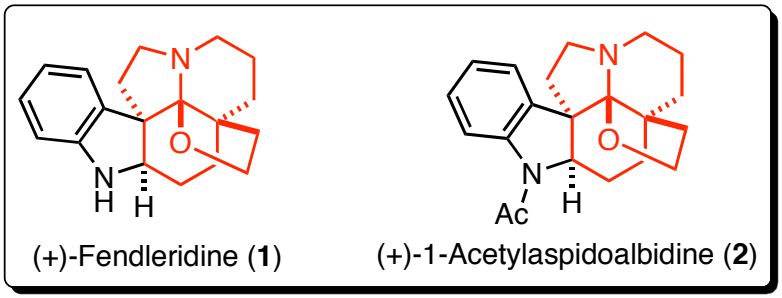

(+)-Fendleridine

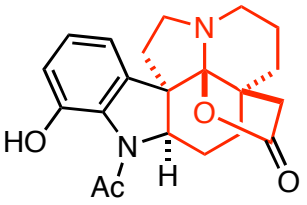


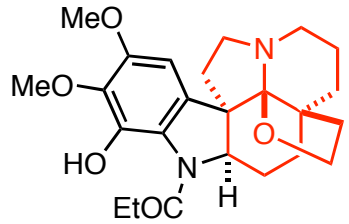

(+)-1-Acetylaspidoalbidine

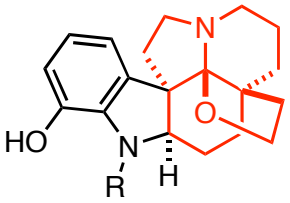
Kara George
Current Literature
March 6, 2010

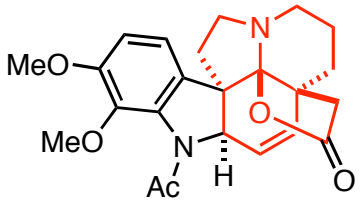
# Isolation, Structural Features, & Previous Syntheses



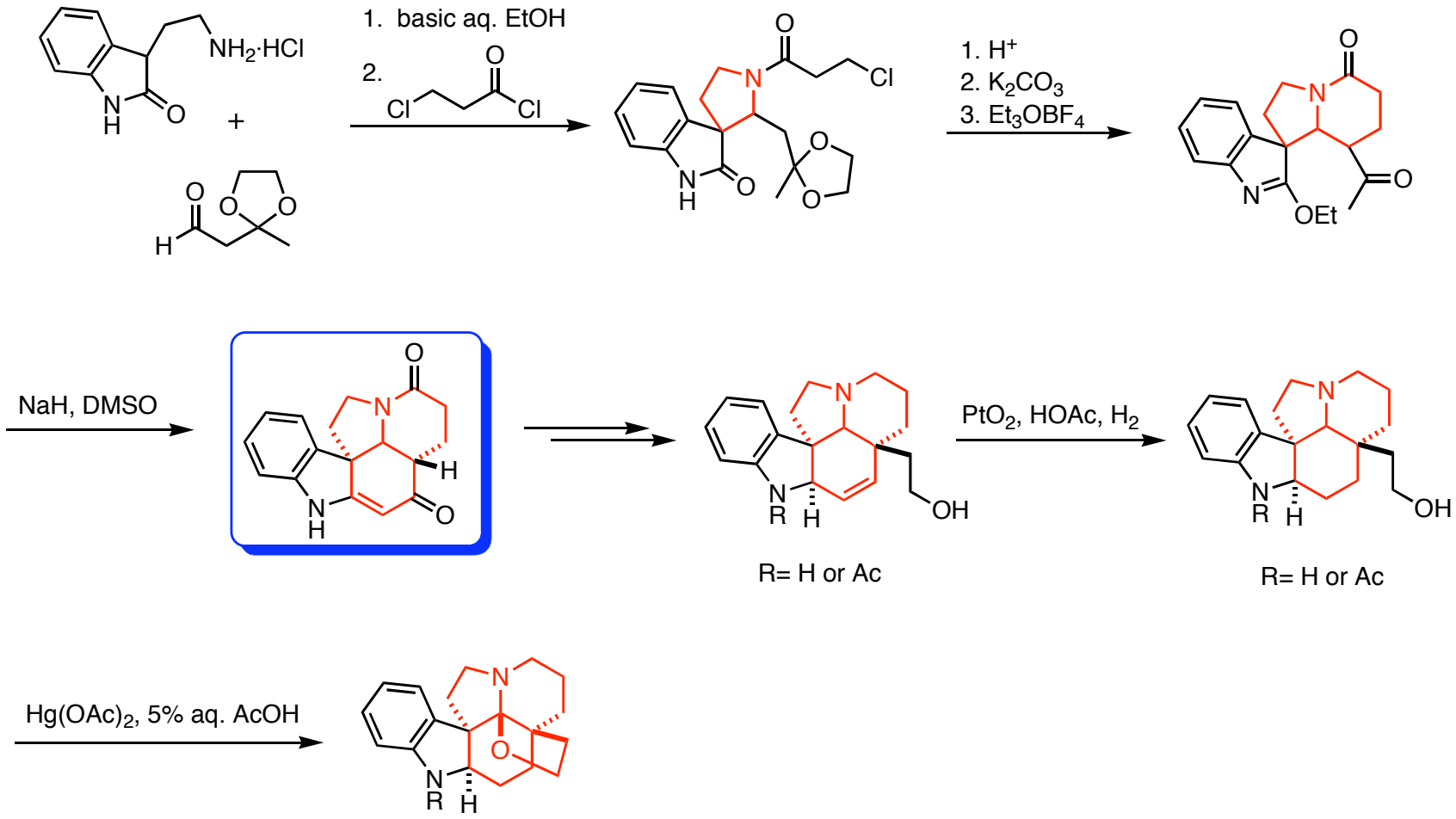




- Parent members of the aspidoalbine family of alkaloids
- Fendleridine (**1**) was first isolated in 1964 from the Venezuelan tree *Aspidosperma fendleri* WOODSON by Burnell and co-workers
- Only one total synthesis of **1** reported by Ban and co-workers in 1976
- 1-Acetylaspidoalbidine (**2**) was first isolated in 1963 from *Vallesia dichotoma* RUIZ et PAV in Peru
- Ban reported the first total synthesis of **2** in 1975 and an improved formal synthesis in 1987
- A formal synthesis of **2** was disclosed by Overman in 1991

Burnell, R. H.; Medina, J. D.; Ayer, W. A. *Can. J. Chem.* **1966**, *44*, 28.
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.

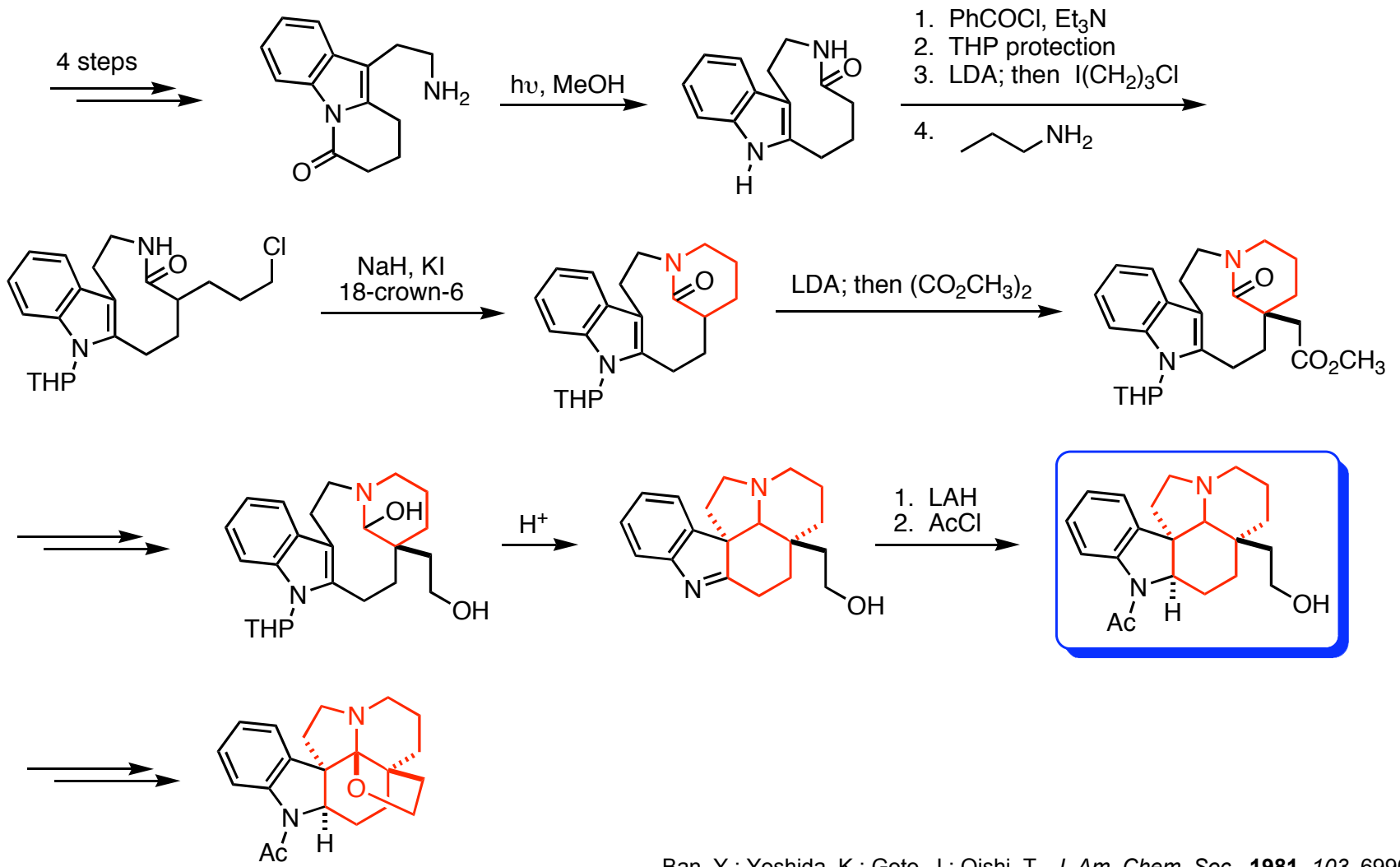
# First Total Synthesis of (±)-Fendleridine and (±)-1-Acetylaspidoalbidine




(±)-Fendleridine (R=H)
(±)-1-Acetylaspidoalbidine (R= Ac)


Oishi, T.; Nagai, M.; Ban, Y. *Tetrahedron Lett.* **1968**, 491.
Ban, Y.; Ohnuma, T.; Seki, K.; Oishi, T. *Tetrahedron Lett.* **1975**, 727.
Honma, Y.; Ohnuma, T.; Ban, Y. *Heterocycles* **1976**, *5*, 47.

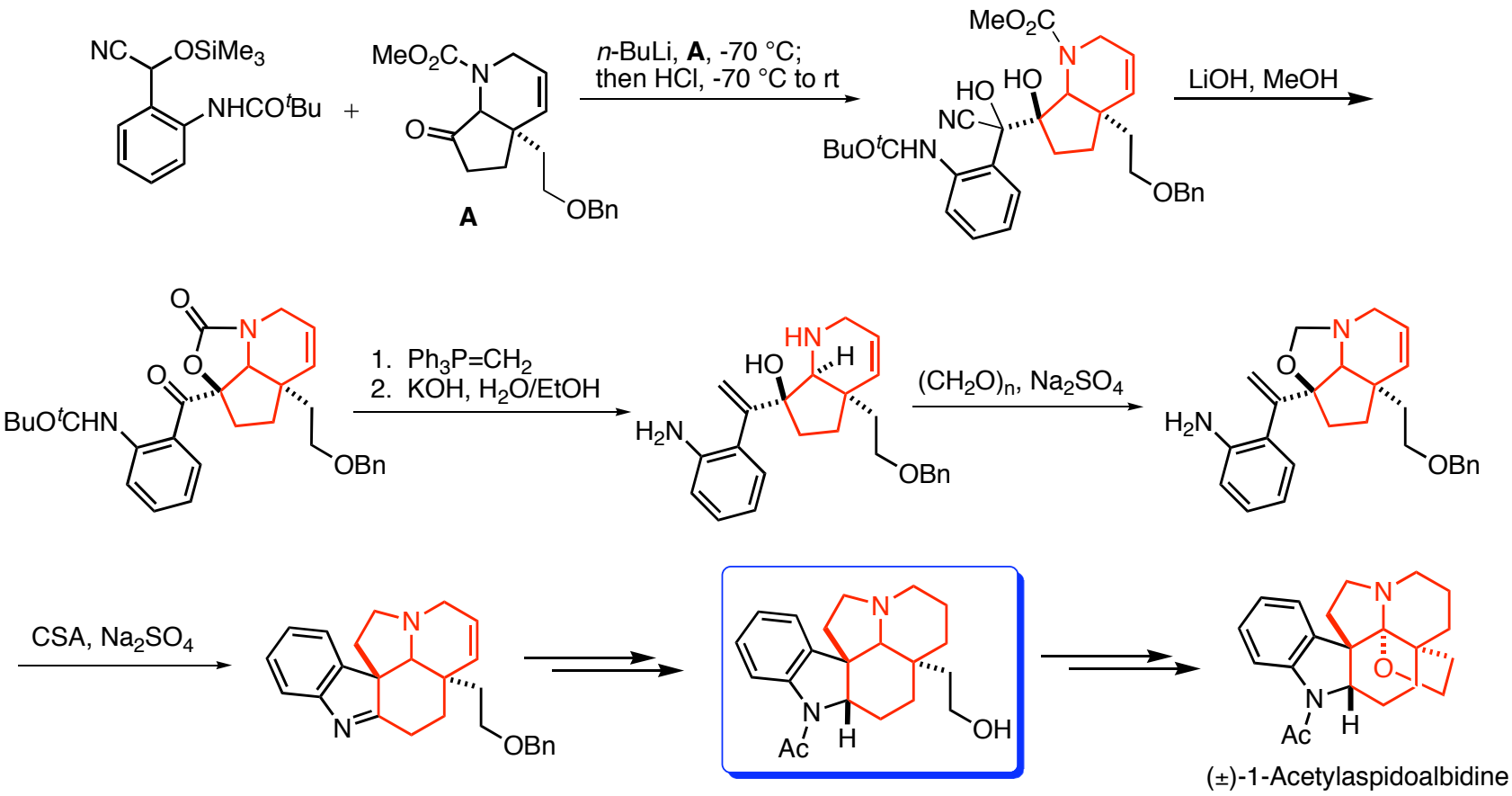
# Improved Formal Synthesis of (±)-1-Acetylaspidoalbidine by Ban and co-workers




(±)-1-Acetylaspidoalbidine

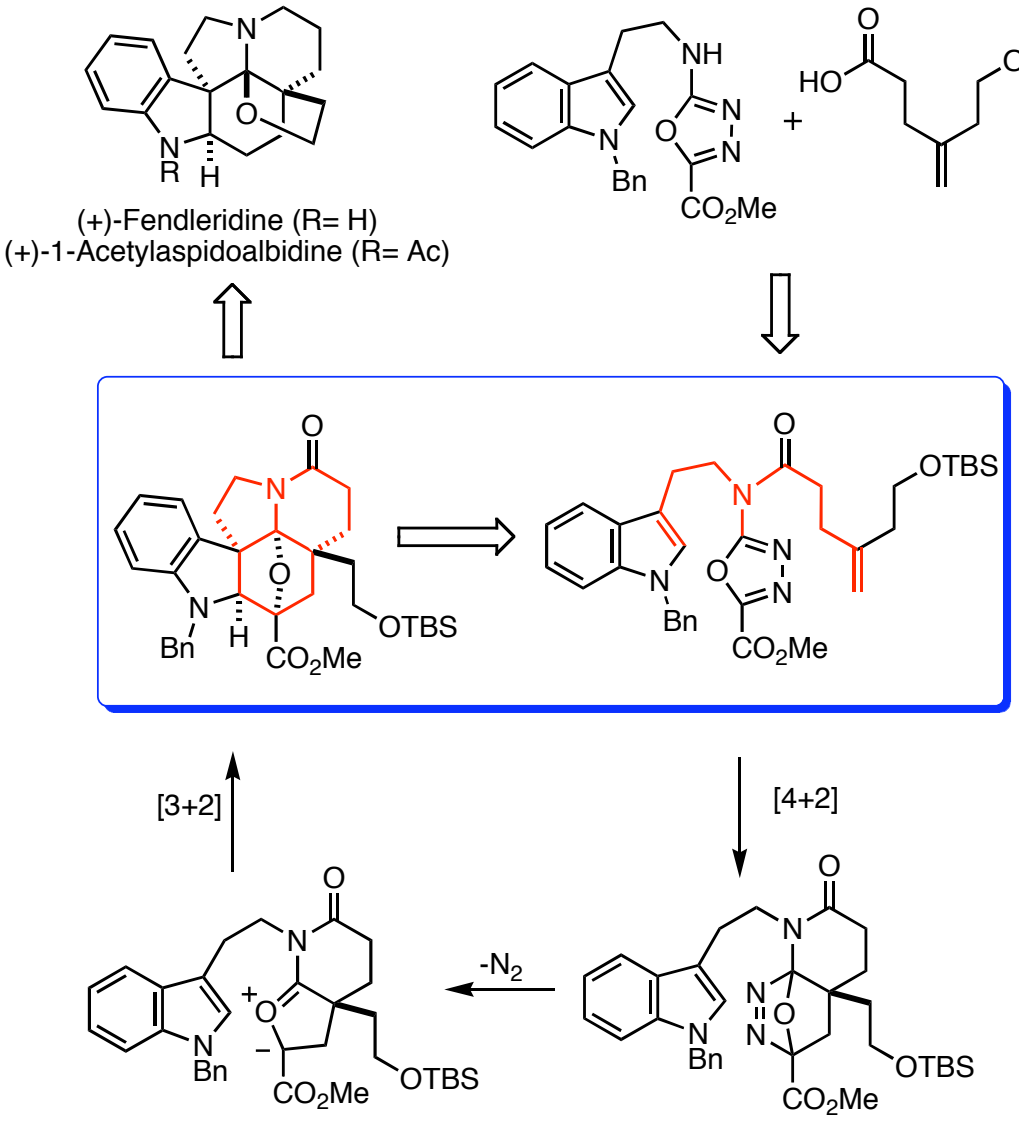

Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, *103*, 6990.
Yoshida, K.; Sakuma, Y.; Ban, Y. *Heterocycles* **1987**, *25*, 47.

# Formal Synthesis of (±)-1-Acetylaspidoalbidine by Overman and co-workers




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

# Title Paper: Tandem [4+2]/[3+2] Cycloaddition Cascade

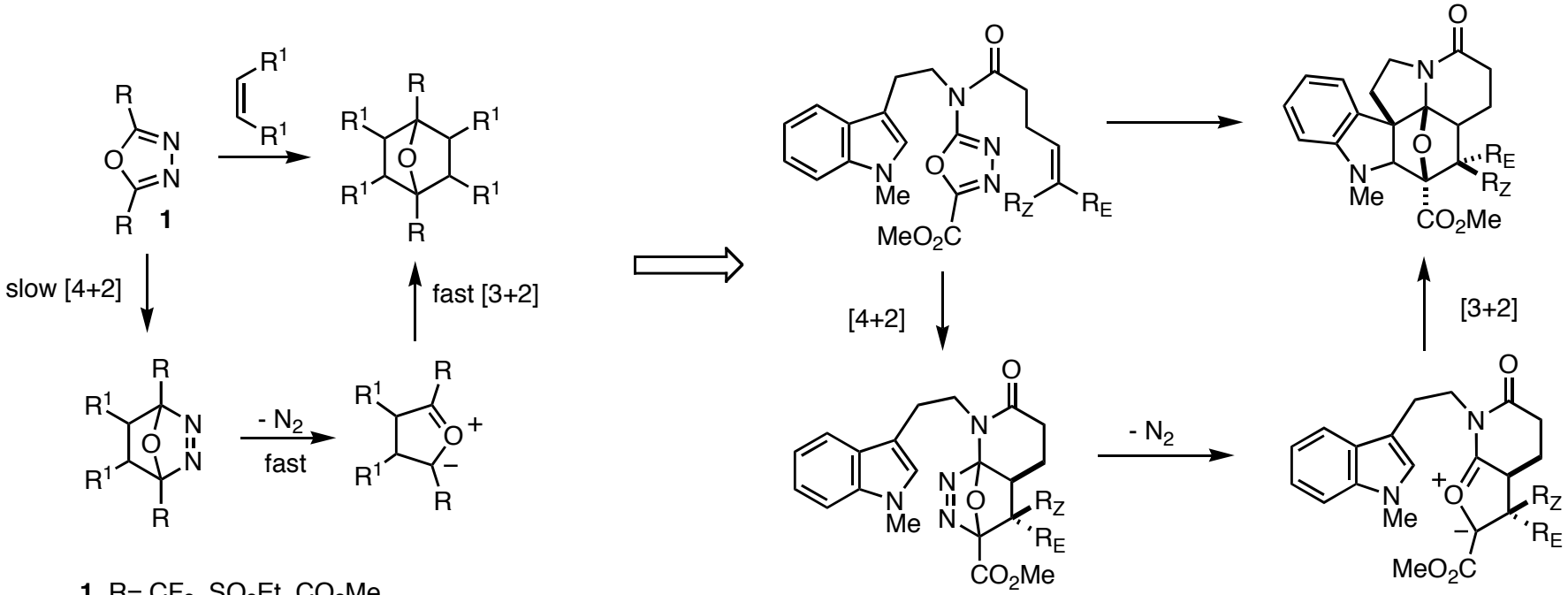


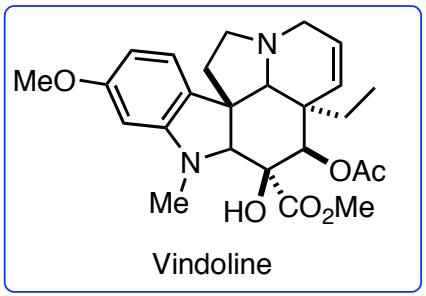

Tandem [4+2]/[3+2] cycloaddition cascade:

- 4 C-C bonds
- 3 rings
- 5 stereogenic centers

# Tandem Intramolecular Diels-Alder/1,3-Dipolar Cycloaddition Reactions of 1,3,4 Oxadiazoles

- Previously reported cycloaddition reactions of electron-deficient and symmetrical 1,3,4-oxadiazoles by Vasilíev, Sauer, Seitz, and Warrener:




Vindoline


Warrener, R. N. *Eur. J. Org. Chem.* **2000**, 3363.
Thalhammer, F.; Wallfahrer, U.; Sauer, J. *Tetrahedron Lett.* **1988**, *29*, 3231.
Vasiliev, N. V.; Lyashenko, Y. E.; Patalakha, A. E.; Sokolski, G. A. *J. Fluorine Chem.* **1993**, *65*, 227.
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.
Wilkie, G. D.; Elliott, G. I.; Blagg, B. S. J.; Wolkenberg, S. E.; Soenen, D. R.; Miller, M. M.; Pollack, S.; Boger, D. L. *J. Am. Chem. Soc.* **2002**, *124*, 11292.

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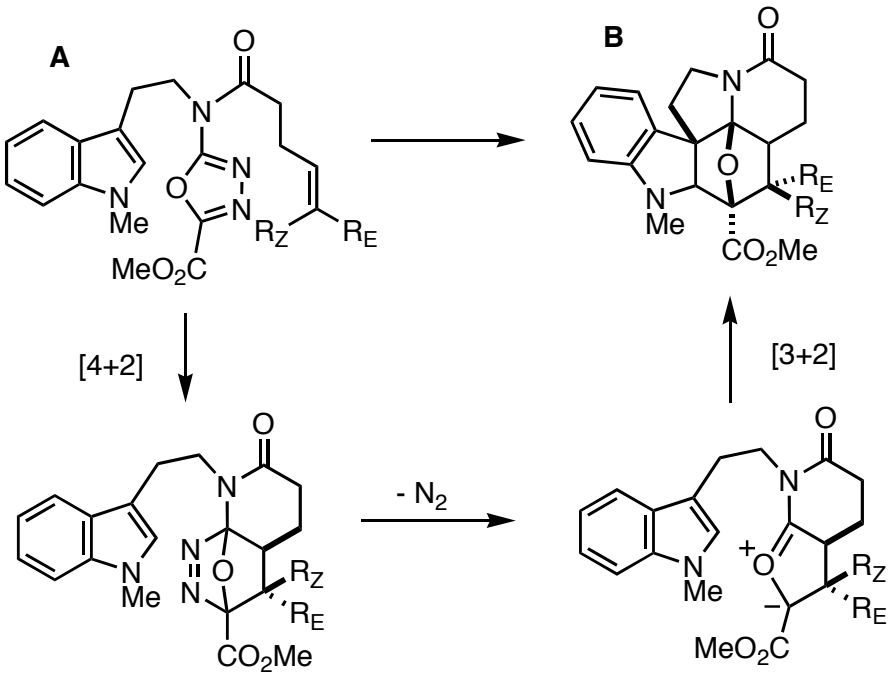
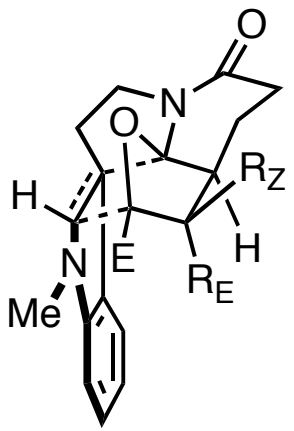



| | | |
|---|---|---|
| **1a**, R=H | *o*-$Cl_2C_6H_4$, 180 °C, 3 h | 87% **1b** |
| (*E*)- **2a**, $R_E$ = Me | *o*-$Cl_2C_6H_4$, 180 °C, 24 h | 65% **2b** |
| (*E*)- **3a**, $R_E$ = OBn | TIPB, 230 °C, 19 h | 88% **3b** |
| (*Z*)- **4a**, $R_Z$ = OBn | TIPB, 230 °C, 38 h | 41% **4b** |



- Single diastereomer with relative stereochemistry set by:
  (1) dienophile geometry
  (2) Exclusive indole endo [3+2] cycloaddition sterically directed to the $\alpha$-face of the 1,3-dipole
- Forms: 3 rings
  4 C-C bonds
  6 stereocenters
  4 quaternary centers


Ishikawa, H.; Elliott, G. I.; Velcicky, J.; Choi, Y.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 10596.
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.
Wilkie, G. D.; Elliott, G. I.; Blagg, B. S. J.; Wolkenberg, S. E.; Soenen, D. R.; Miller, M. M.; Pollack, S.; Boger, D. L. *J. Am. Chem. Soc.* **2002**, *124*, 11292.

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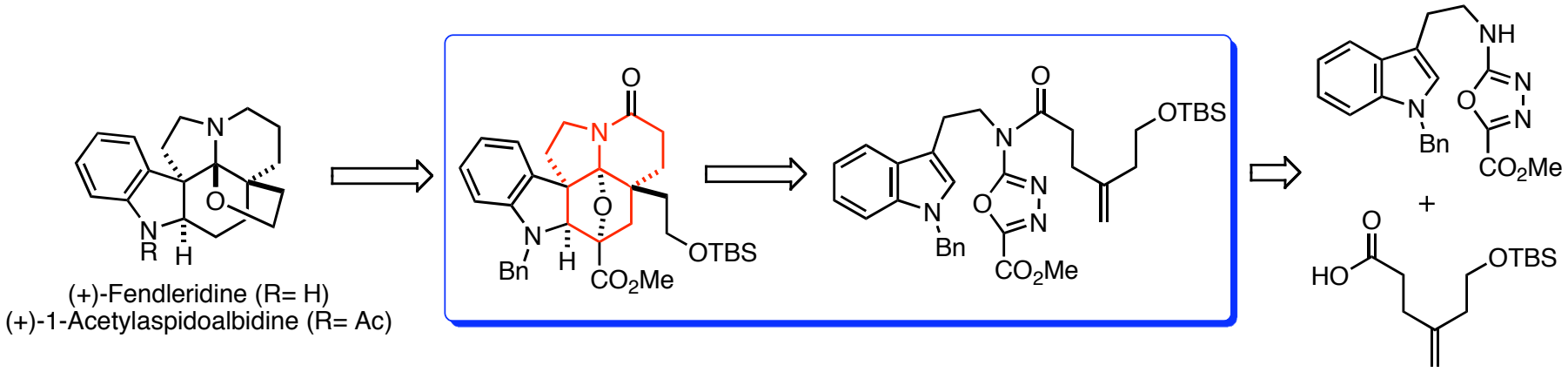


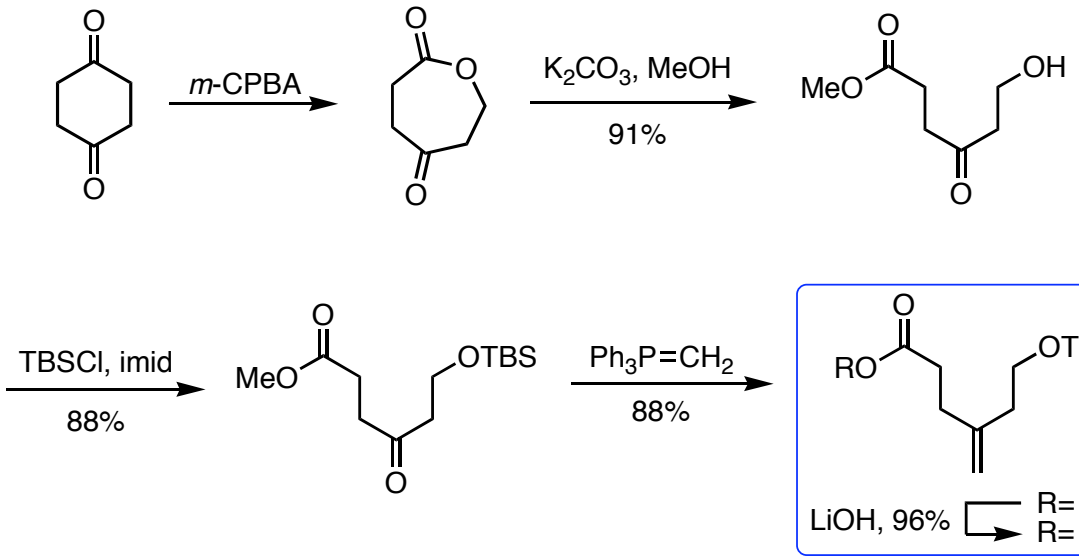

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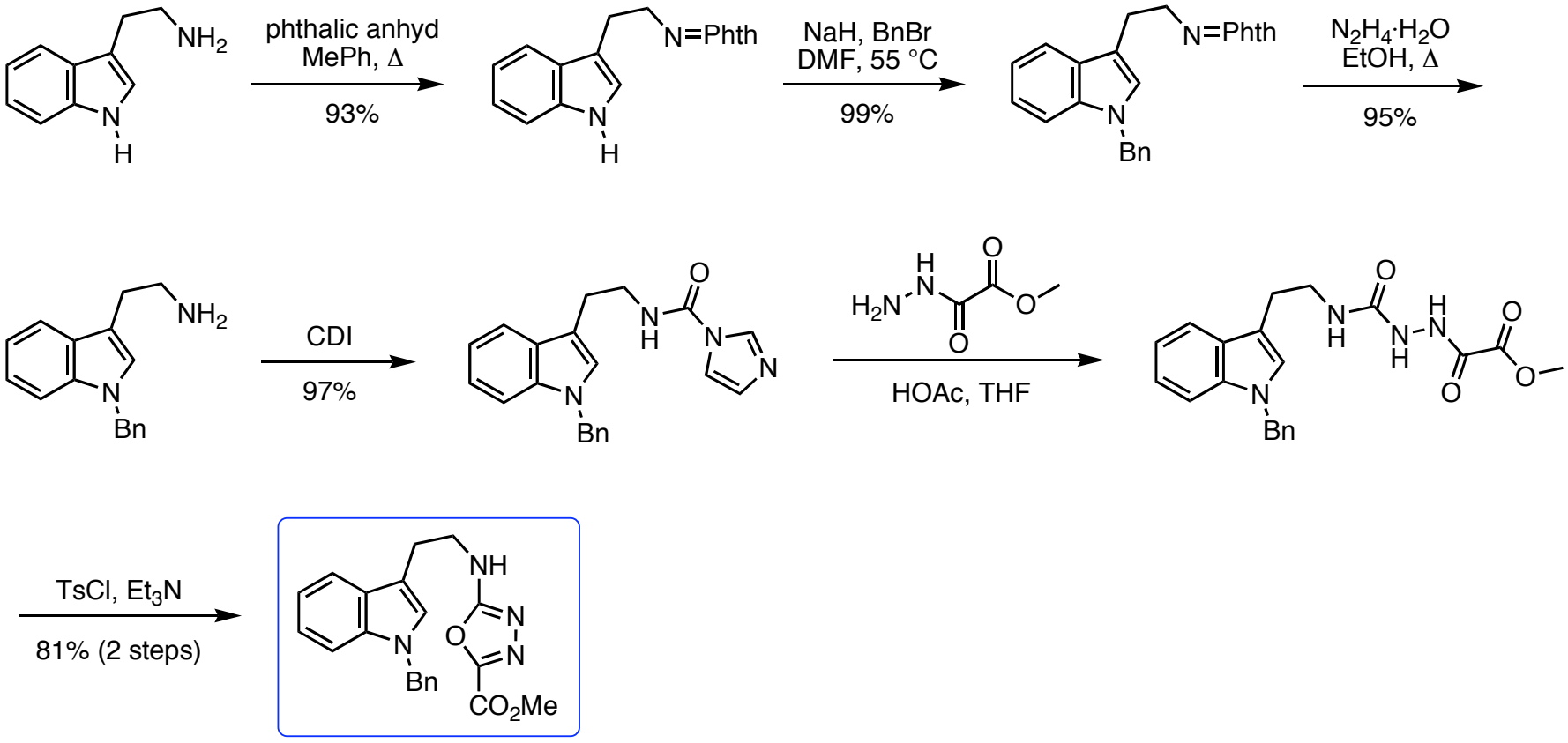

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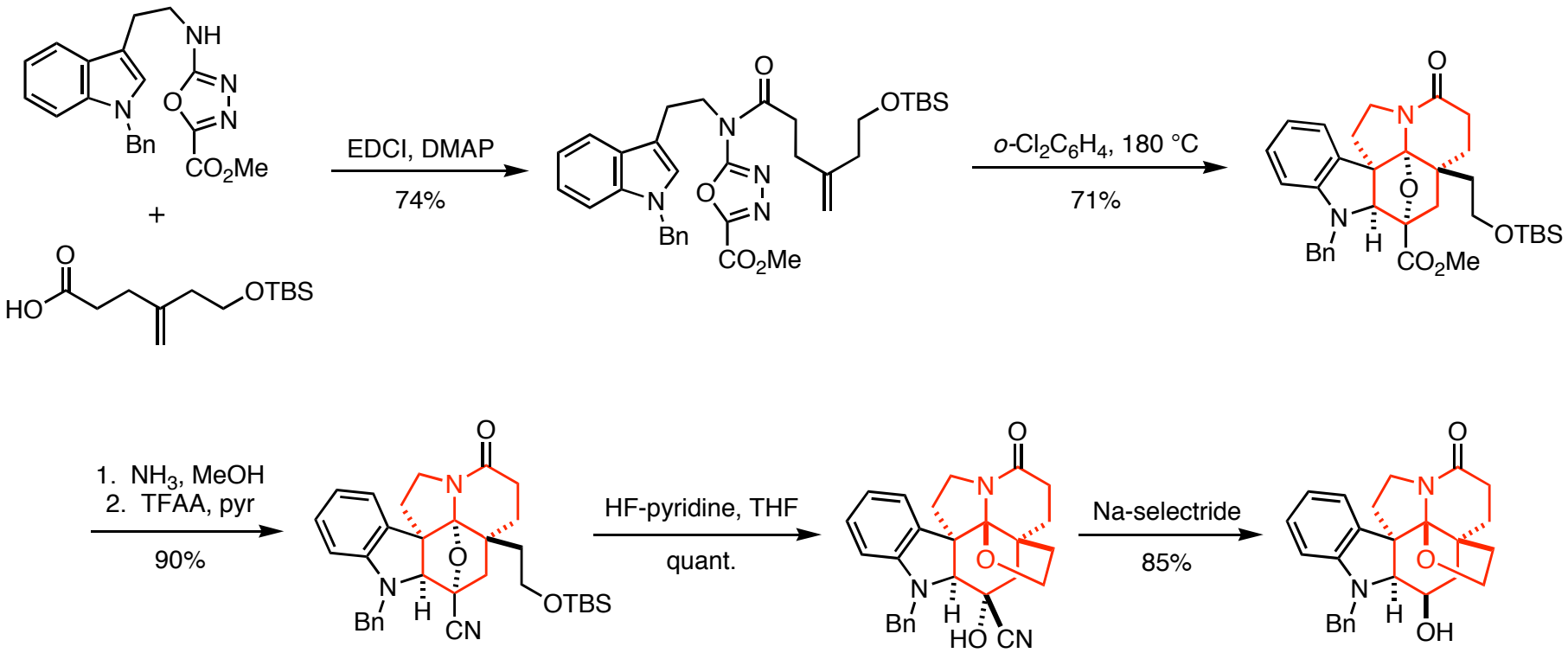

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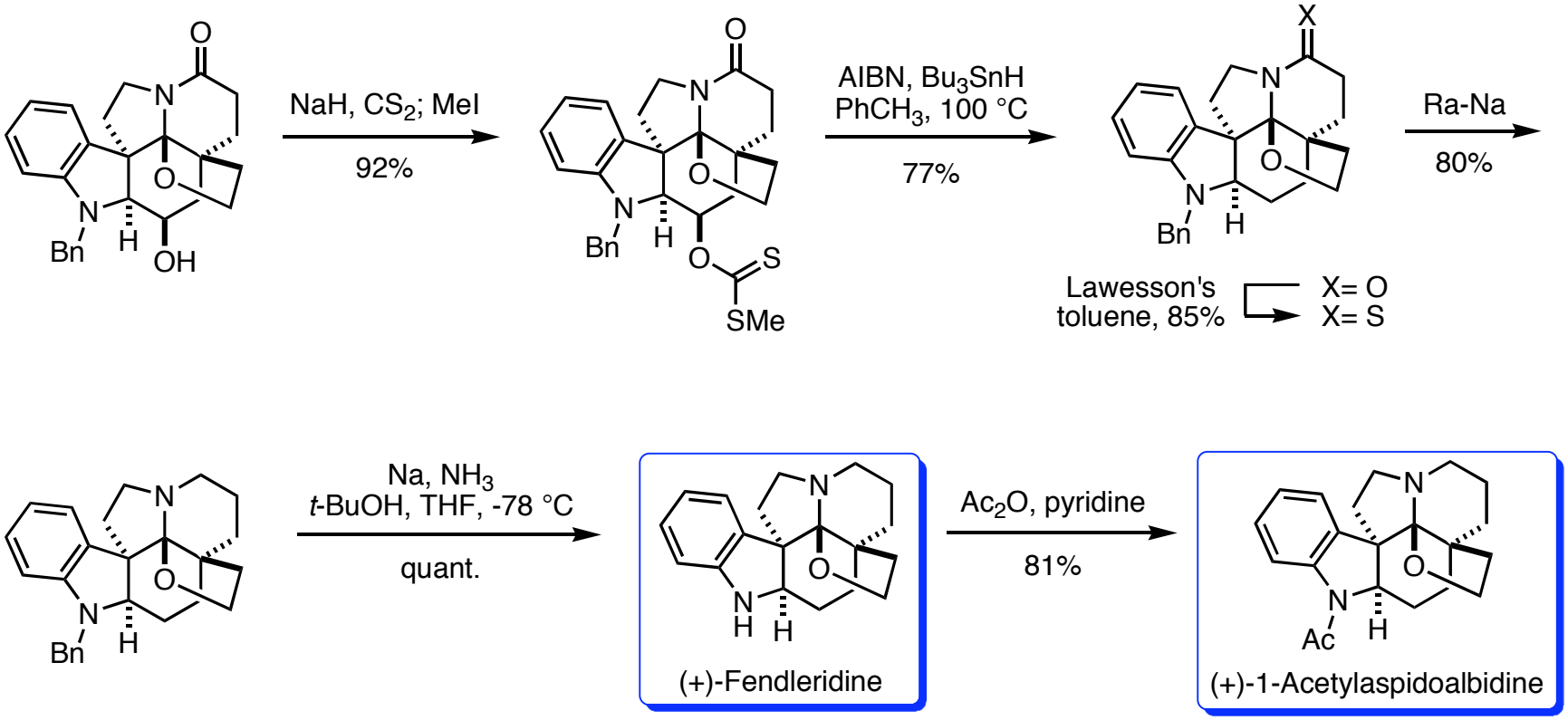

# Conclusions & Future Directions

- Total synthesis of (+)-fendleridine and (+)-1-acetylaspidoalbindine was achieved
- The pentacyclic core and all necessary stereochemistry of the natural products are assembled in one step via intramolecular [4+2]/[3+2] cycloaddition cascade
- Tandem [4+2]/[3+2] cycloaddition cascade reaction can be applied to a variety of natural products containing a similar pentacyclic ring core
- Extension of this methodology to alternative tethering and/or transannular cycloadditions provides access to other interesting ring systems