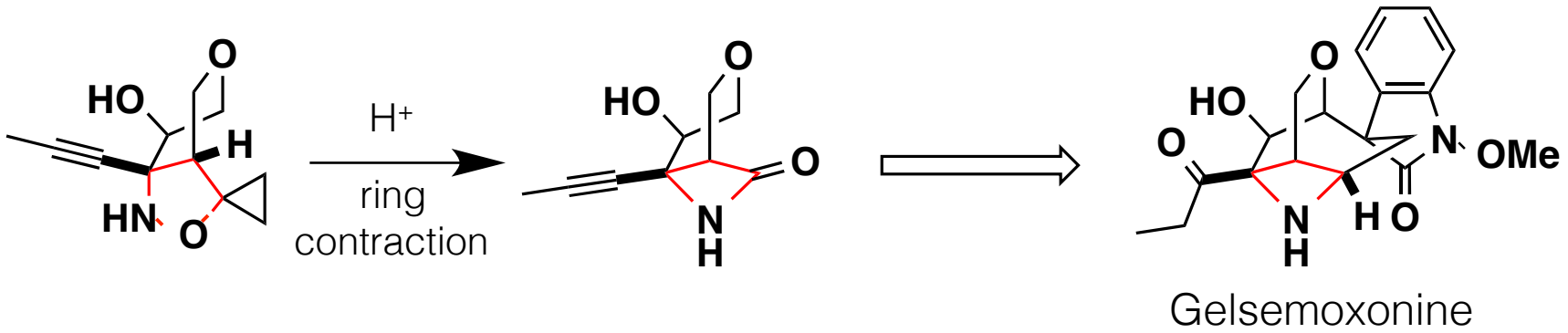
Total Synthesis of Gelsemoxonine through a Spirocyclopropane Isoxazolidine Ring Contraction

Stefan Diethelm and Erick M. Carreira

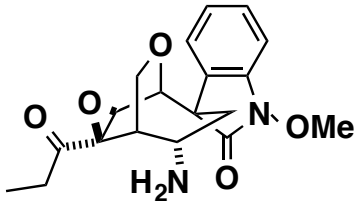


Gelsemoxonine

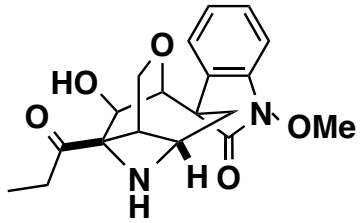
Evan Carder
Wipf Group Current Literature
July 25, 2015

[1] *J. Am. Chem. Soc.* **2015**, 137, 6084.
[2] *J. Am. Chem. Soc.* **2013**, 135, 8500.

Gelsemoxonine



Gelsemoxonine
(reported by Lin *et. al.*)[1]

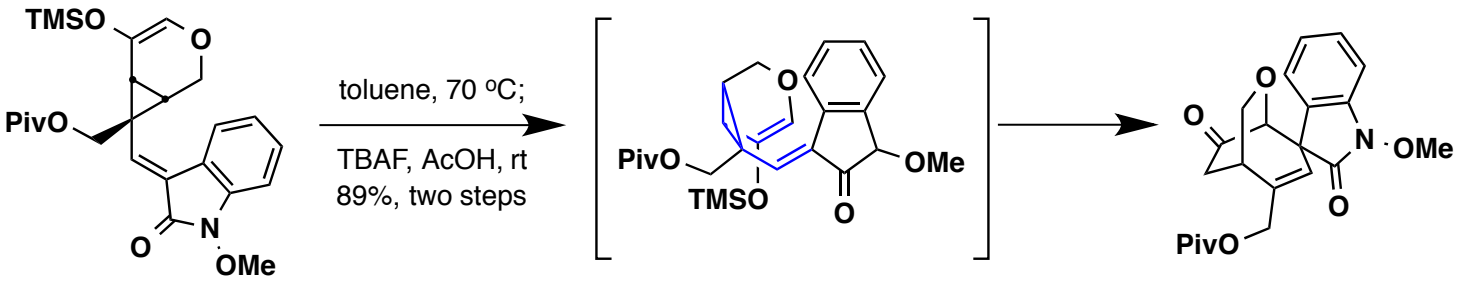


Gelsemoxonine
(revised by Aimi *et. al.*)[2]

- A member of the *Gelsemium* alkaloid family
- Isolated from the leaves of *Gelsemium elegans* found in China and Japan
- Employed as an analgesic, antispasmodic, and treatment of ulcers
- Features an intricate polycyclic framework with two quaternary centers, spiro-fused N-methoxy oxindole ring, and a highly substituted azetidine ring

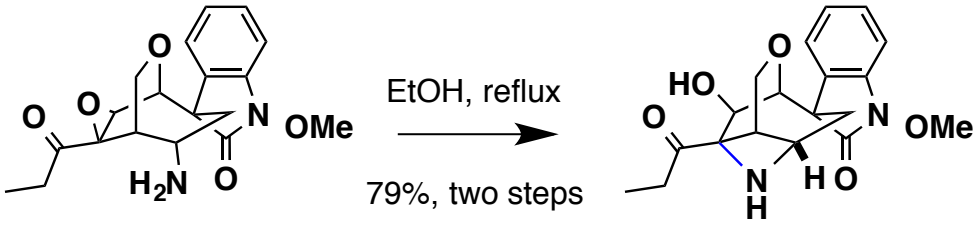
[1] *Phytochemistry* **1991**, 30, 1311. [2] Org. Lett. **2003**, 5, 2075. [3] Proc. Japan Acad., Ser. B **1998**, 74, 159.

Previous Synthesis



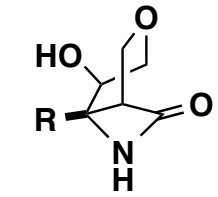
- First synthesis of Gelsemoxonine was conducted by the Fukuyama group
- 26 linear steps; 2.2% overall yield
- Key step: constructed the quaternary center of the spiro-indoline through a divinylcyclopropane-cyclopentadiene rearrangement

Final step:



J. Am. Chem. Soc. **2011**, 133, 17634.

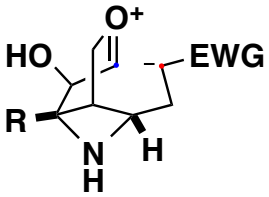
Current Synthetic Strategy



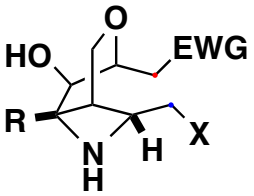
advanced intermediate

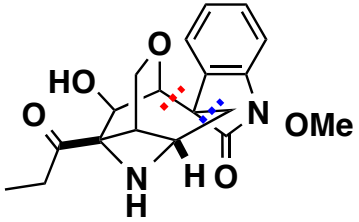
Synthetic Strategy

Path A



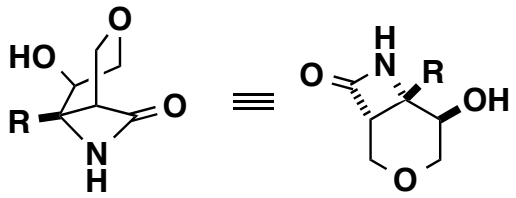
Path B





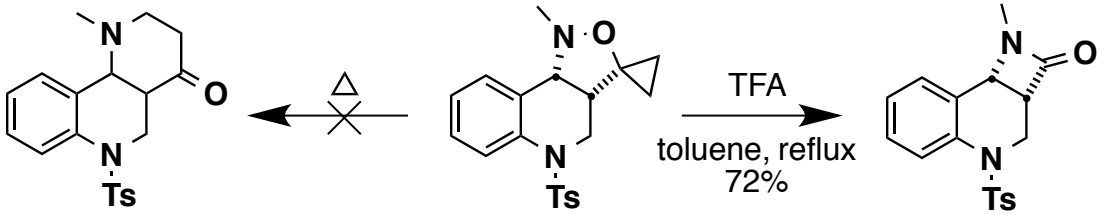
Gelsemoxonine

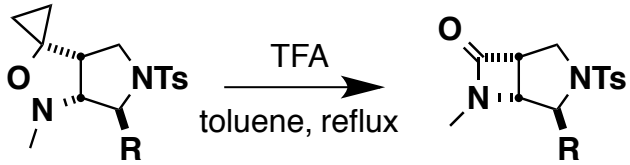
Cis-Fused Beta-Lactam



advanced intermediate

5-spirocyclopropane isoxazolidines ring contraction

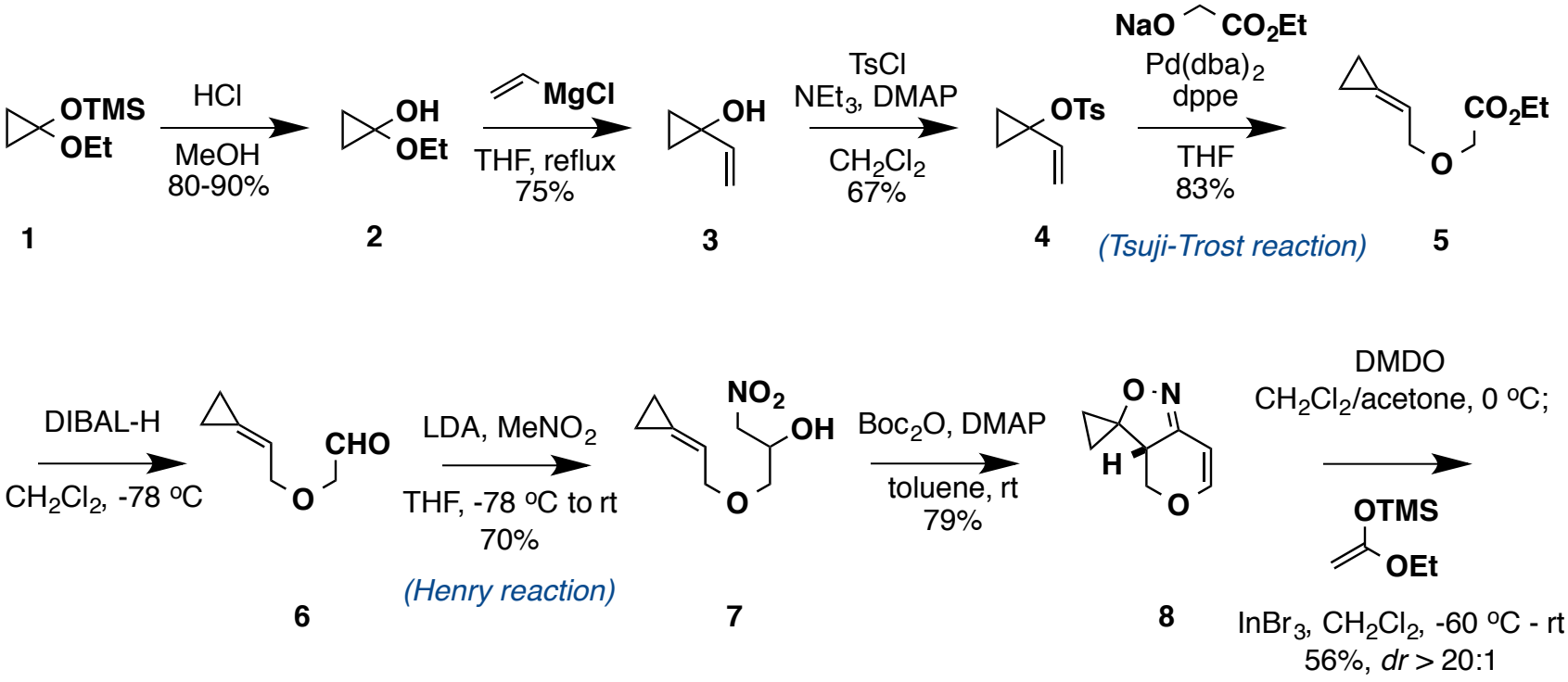




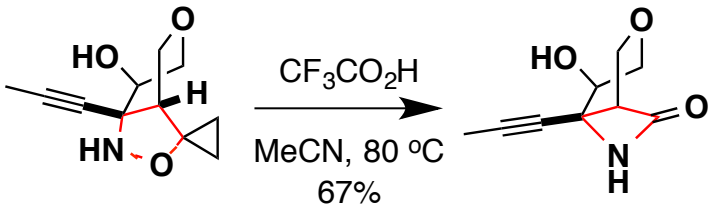
R = Me, 60%
R = i-Pr, 63%
R = 3-indoyl-CH_2, 57%

J. Am. Chem. Soc. **2000**, 122, 8075.

Synthesis Toward an Advance Intermediate



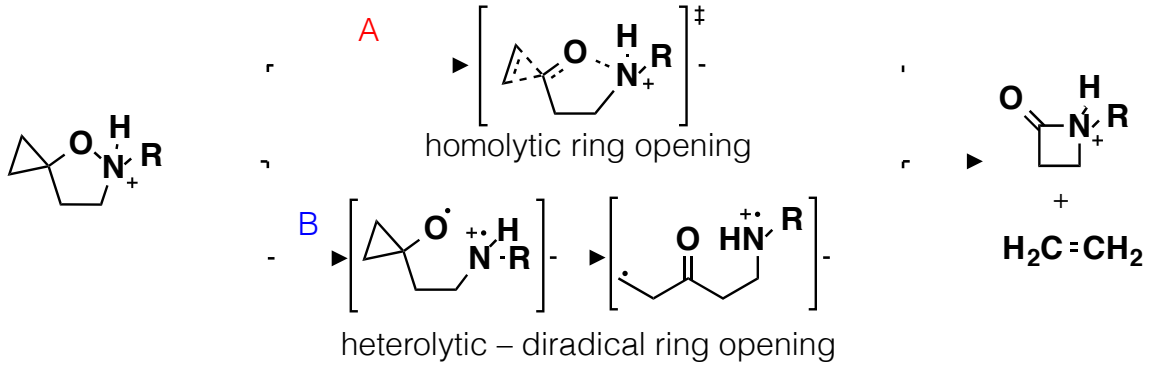
Spirocyclopropane Isoxazolidine Ring Contraction

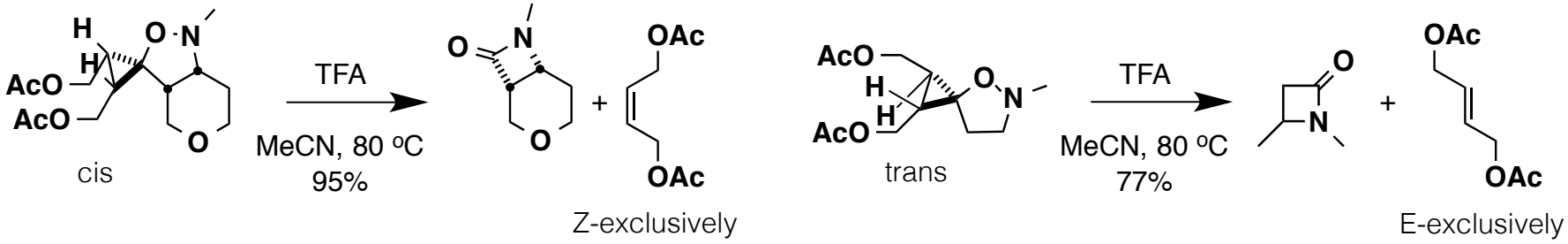


10 **11**

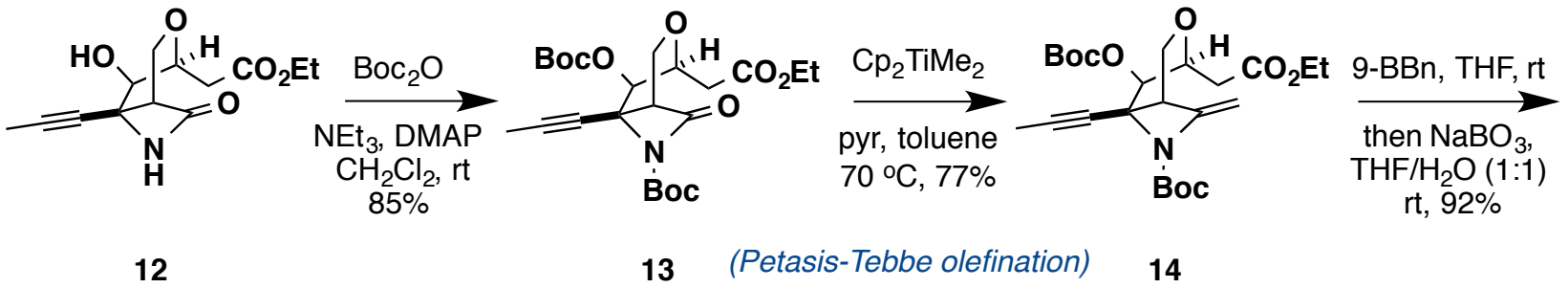
Mechanistic hypothesis:

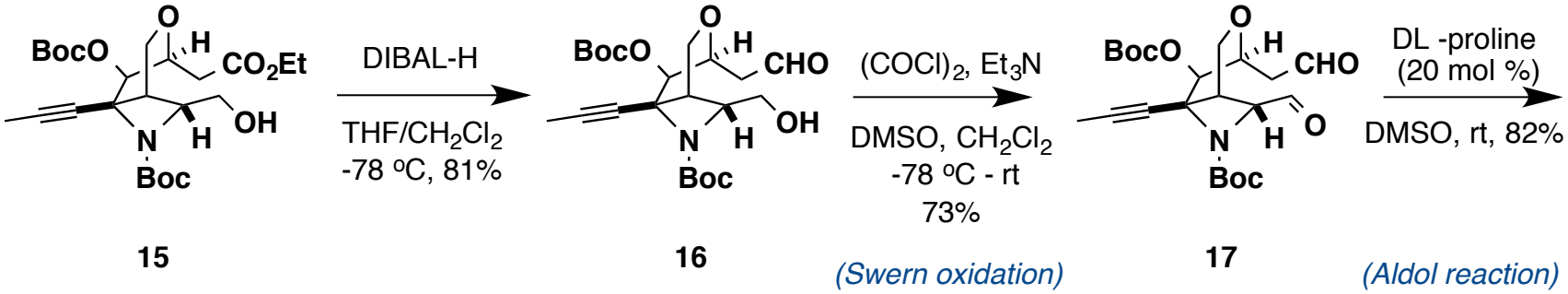
Org. Lett. **2014**, 16, 960.

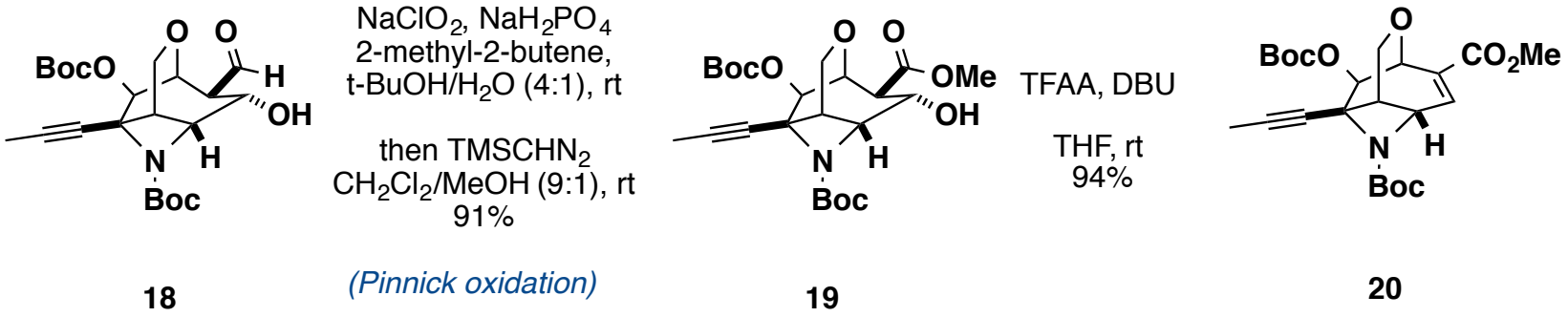




Completion of Gelsemoxonine



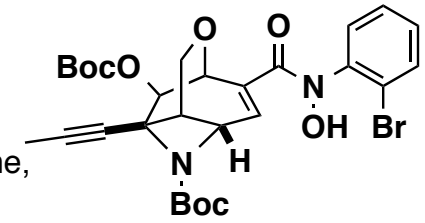




Completion of Gelsemoxonine

$(COCl)_2$, DMF (cat.)
CH_2Cl_2, rt;

N-(2-bromophenyl)hydroxylamine,
$NaHCO_3$, Et_2O/CH_2Cl_2 (3:1)
0 °C, 58% (two steps)

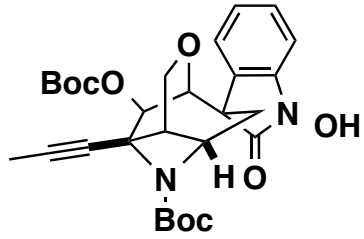


21

$PdCl_2(MeCN)_2$ (10 mol %)

1,2,2,6,6-pentamethylpiperidine
HCO_2H, DMF, 60 °C
72% (dr > 20:1)

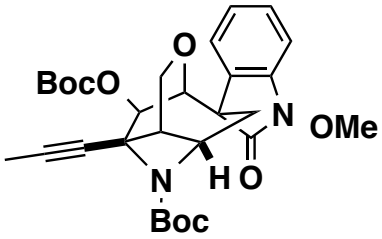
(Reductive Heck cyclization)



22

NaH, MeI

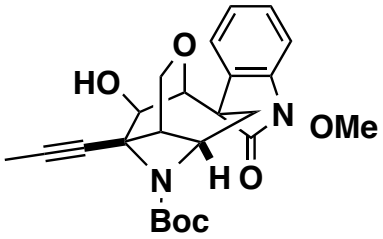
DMF, 0 °C - rt
92%



23

K_2CO_3

MeOH, 50 °C
87%

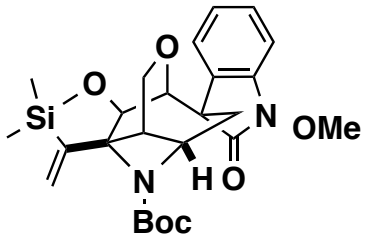


24

$(Me_2SiH)_2NH$, 50 °C;

$[RuCl_2(C_6H_6)]_2$ (20 mol %)
CH_2Cl_2, rt
58%

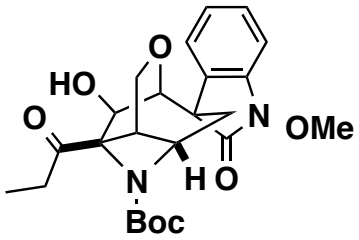
(directed hydrosilation)



25

KHF_2, Ac_2O

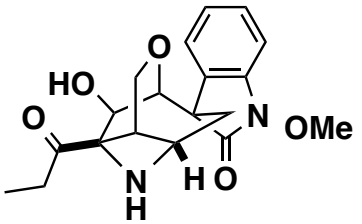
H_2O_2, DMF
65%



26

3 M HCl

EtOAc, 0 °C
97%



Gelsemoxonine

Conclusions

Major accomplishments

- Employed a spirocyclopropane oxazolidine ring contraction to furnish a polycyclic beta-lactam in a complex molecule synthesis.
- Extended the scope of this reaction by highlighting broad functional group tolerance - starting molecule contained an alcohol, alkyne, ether, and ester functionality.
- Performed a diastereoselective reductive Heck cyclization in the construction of the oxindole ring.