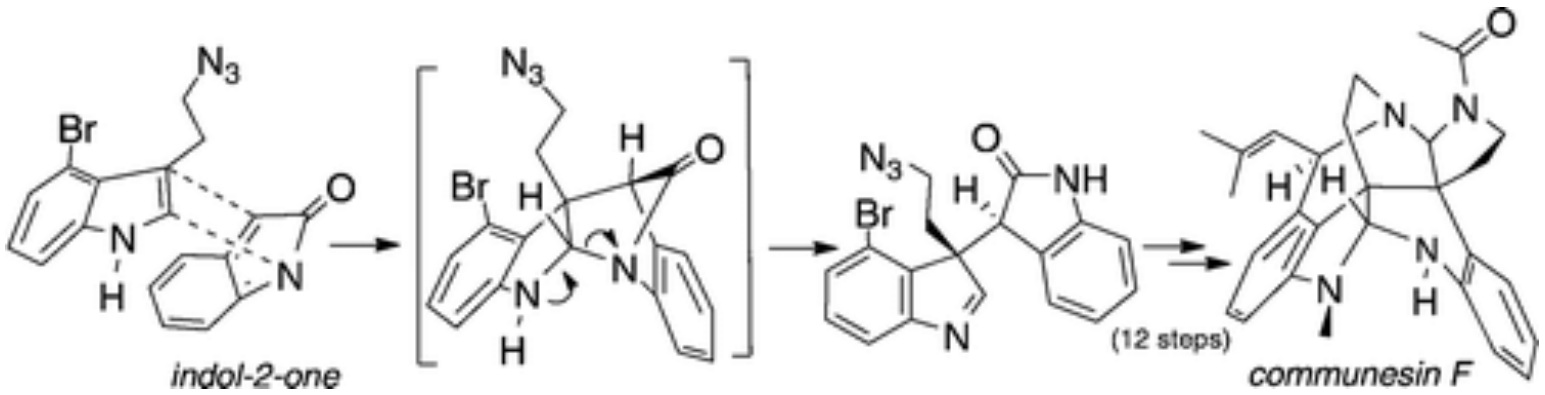
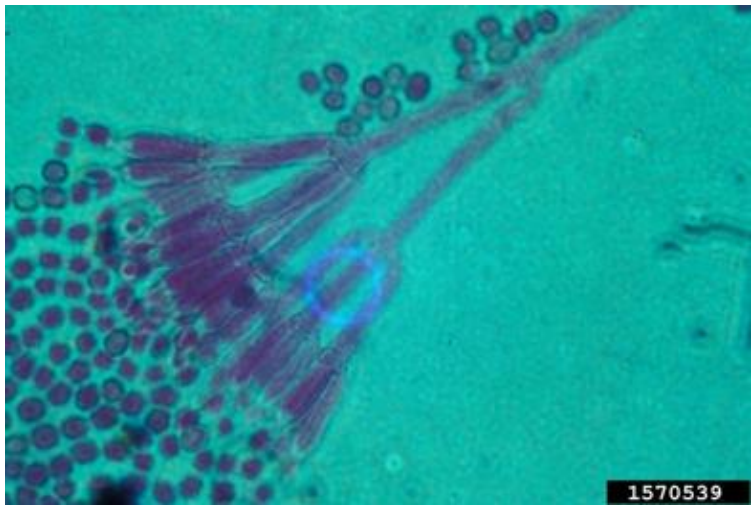
Total Synthesis of (±)-Communesin F via a Cycloaddition with Indol-2-one

Johannes Belmar and Raymond L. Funk. J. Am. Chem. Soc. 2012, 134, 16941−16943



Liming Cao
Wipf Group Current Literature
11/3/2012

Background



Penicillium Expansum

Enteromorpha Intestinalis

- Communesin A and B were isolated from *Penicillium sp*. stuck on the marine alga *Enteromorpha Intestinalis* in 1993 by Numata.

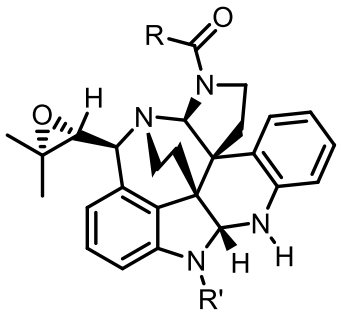
http://www.forestryimages.org/browse/detail.cfm?imgnum=1570539
http://nas.er.usgs.gov/XIMAGESERVERX/2009/20090611112410.jpg
Kerzaon, I., Pouchus, YF., Monteau, F. Le Bizec, B., Nourisson, MR., Biard, JF. and Grovel, O. *Rapid Commun. Mass Spectrom*. **2009**, *23*, 3928–3938
Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, 34, 2355

Background

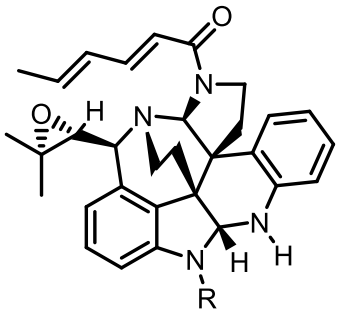
- Indole polycyclic alkaloids with:
  - Two contiguous quaternary centers at C 7 and C 8
  - Two aminal moieties

- Biological activity
  - Moderate activity against various leukemia cell lines
  - Antihelminthic acitivty
  - Insecticidal activity against silkworm

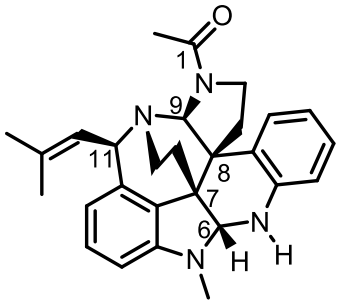
- Communesin B: microfilament disruption
  - Moderate cytotoxicity against cells:
    P-388 (ED50 = 0.88 mM)
    LoVo (MIC = 3.9 mM)
    KB (MIC = 8.8 mM)



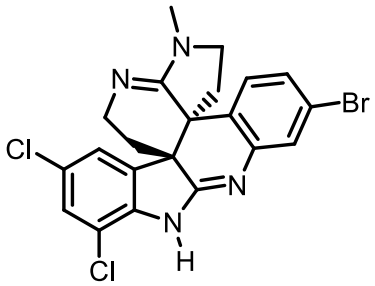
R = Me, R' = Me communesin A
R = Me, R' = H communasin E
R = Et, R' = Me communesin G
R = Pr, R' = Me communesin H



R = Me communesin B
R = H communesin C
R = CHO communesin D



communesin F

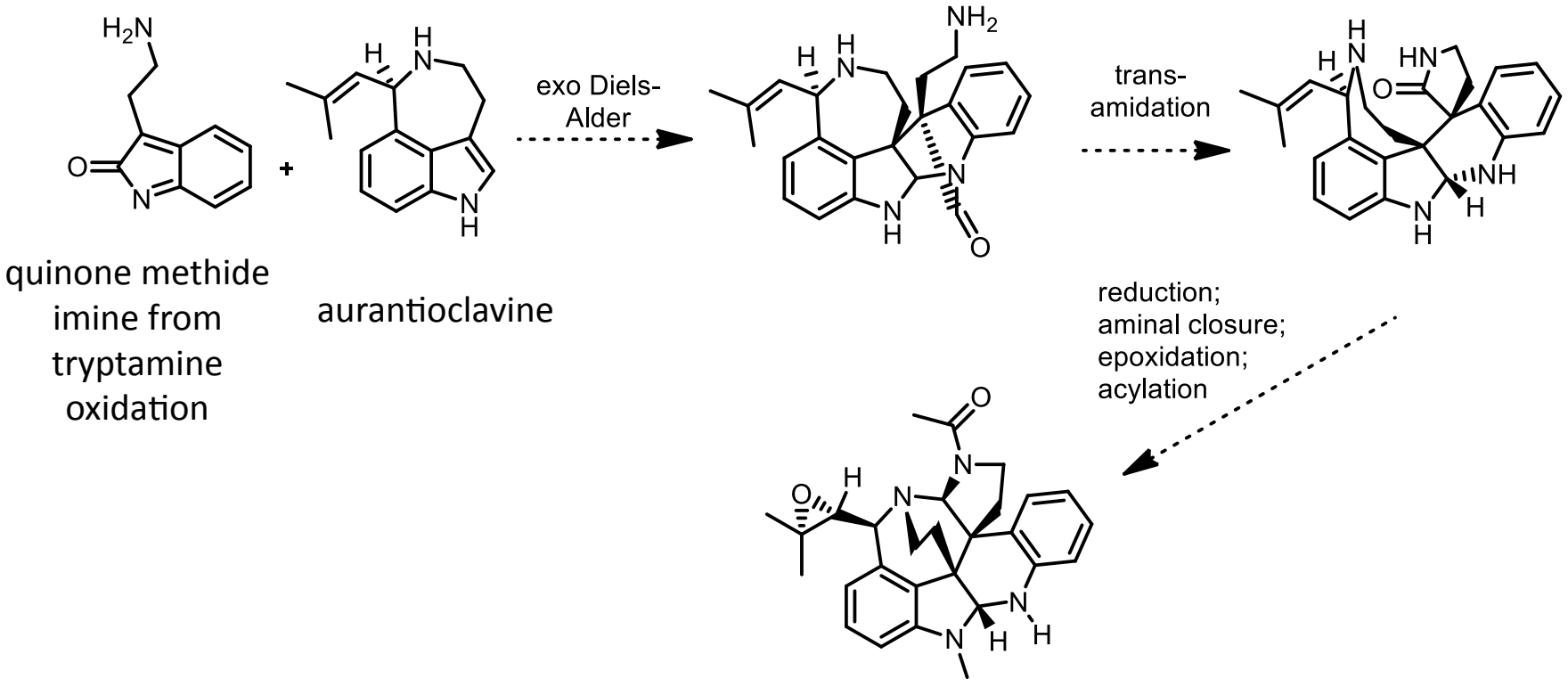


perophoramidine

Kerzaon, I.; *et al*. *Rapid Commun. Mass Spectrom*. **2009**, *23*, 3928–3938
Numata, A.; *et al. Tetrahedron Lett.* **1993**, *34,* 2355
Hayashi, H.; Matsumoto, H.; Akiyama, K. Biosci., *Biotechnol., Biochem*. **2004**, *68,* 753
Dalsgaard, P. W.; Blunt, J. W.; Munro, M. H. G.; Frisvad, J. C.; Christophersen, C. *J. Nat. Prod*. **2005**, *68*, 258
Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 5068

Proposed Biosynthetic Pathways

Stoltz and coworkers (2003):



quinone methide imine from tryptamine oxidation

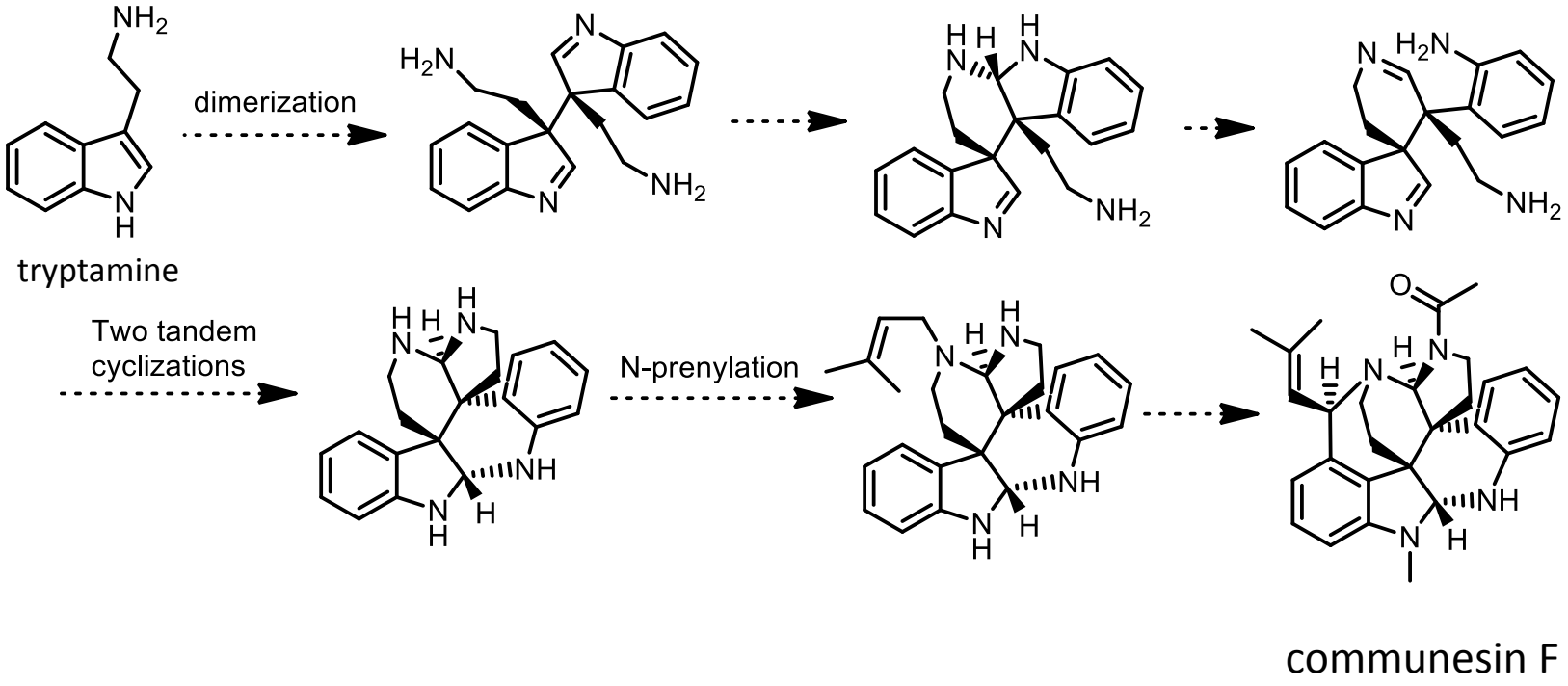
aurantioclavine

communesin A

May, J. A.; eidan, R. K.; Stoltz, B. *Tetrahedron Lett.* **2003,** *44*, 1203

Proposed Biosynthetic Pathways

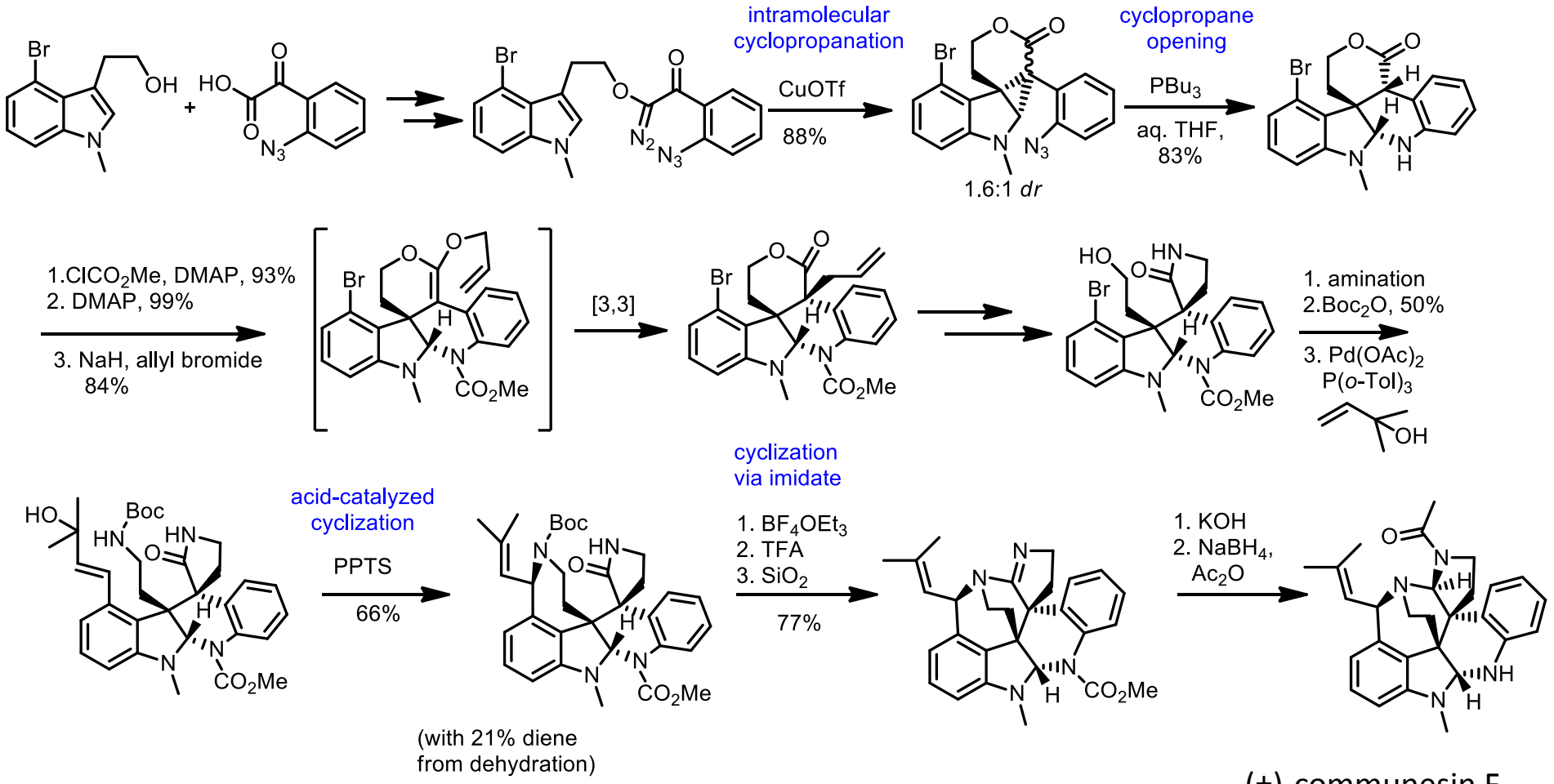
Mantle and coworkers (2006); Stoltz and coworkers (2006):



Wigley, L. J.; Mantle, P. G.; Perry, D. A. *Phytochemistry*, **2006**, *67*, 561.
May, J. A.; Stoltz, B. M. , **2006***, 62*, 5262

Previous Studies

Qin and coworkers (2007):

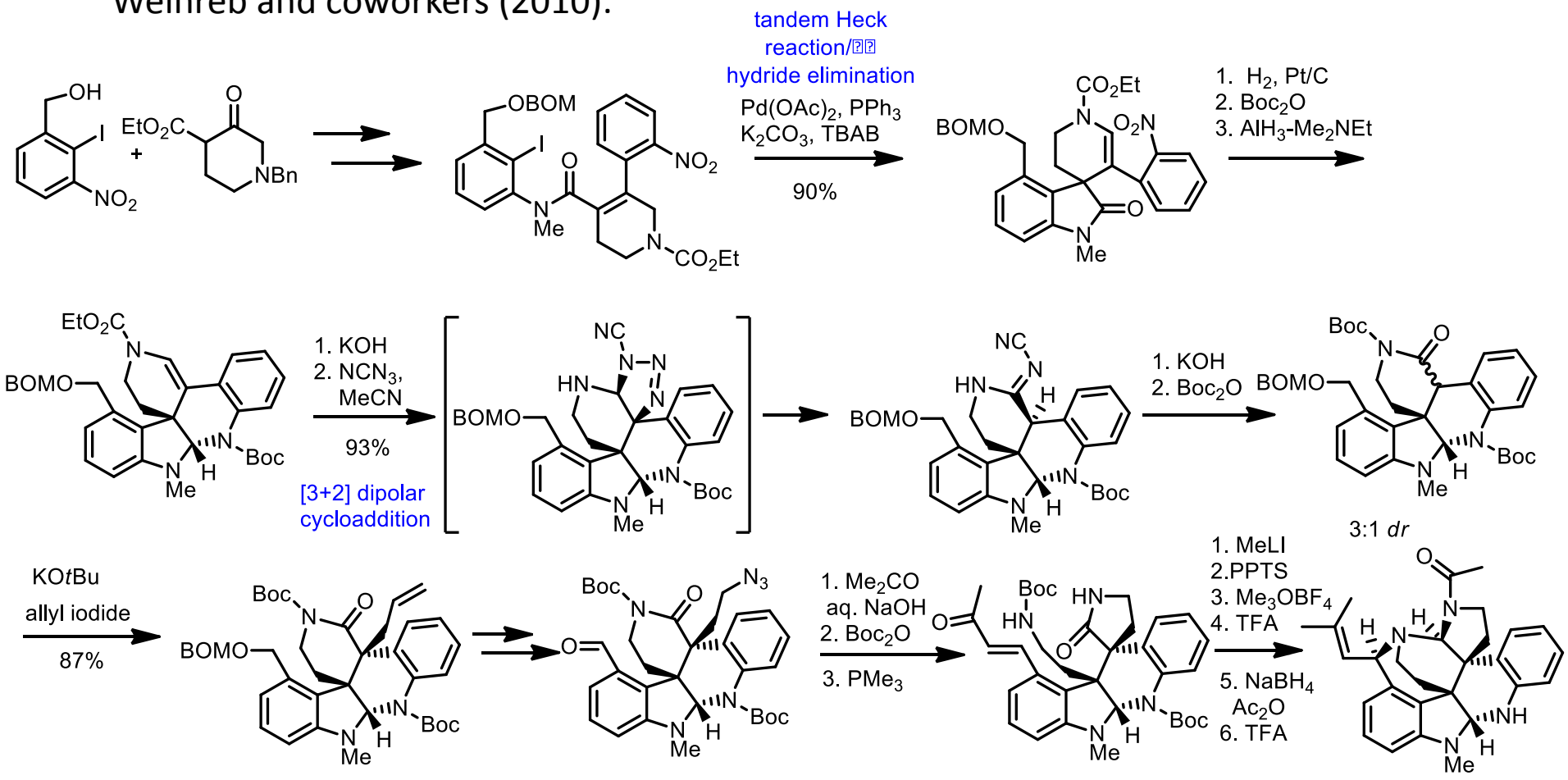


30 steps, 1.2% overall yield

Yang, J.; Wu, H. X.; Shen, L. Q.; Qin, Y. *J. Am. Chem. Soc*. **2007,** *129*, 13794

Previous Studies

Weinreb and coworkers (2010):



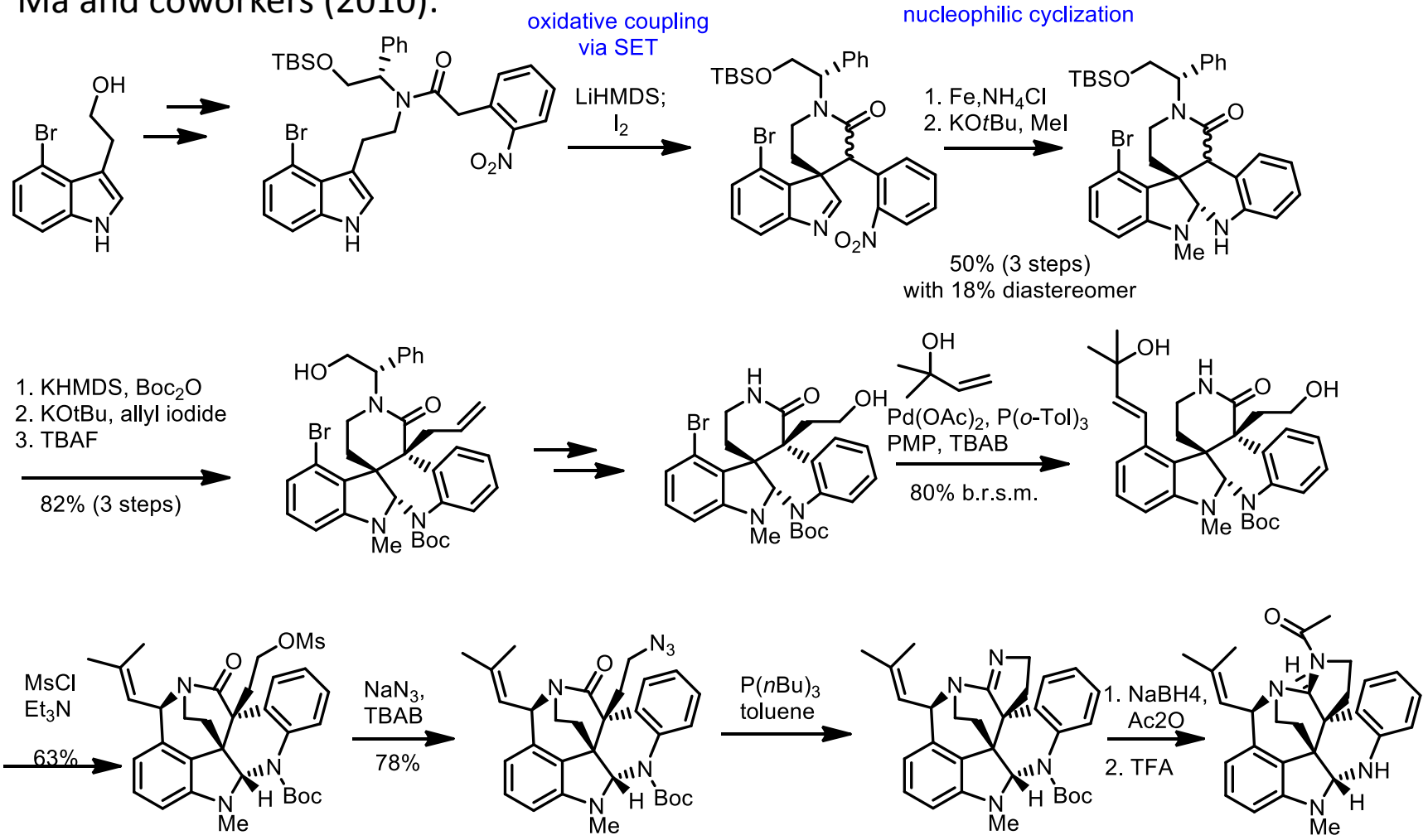
(±)-communesin F

31 steps, 0.9% overall yield

Liu, P.; Seo, J. H.; Weinreb, S. M. *Angew. Chem., Int. Ed.* **2010**, *49,* 2000

Previous Studies

Ma and coworkers (2010):



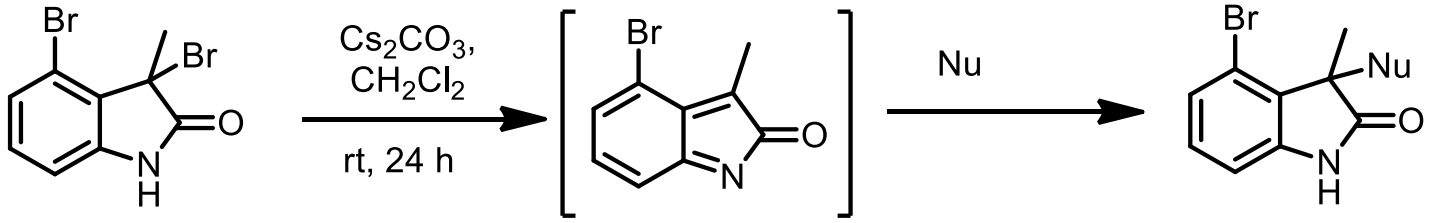
15 steps, 5.6% overall yield

(-)-communesin F

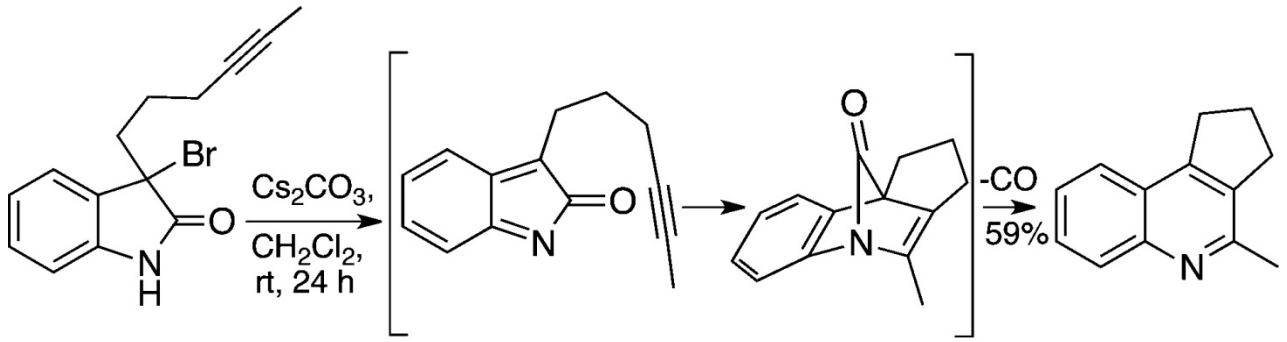
Zuo, Z. W.; Xie, W. Q.; Ma, D. W. *J. Am. Chem. Soc.* **2010**, *132*, 13226

Related Methodology

Methodology:
Indol-2-one from dehydrohalogenation of 3-alkyl-3-bromooxindoles



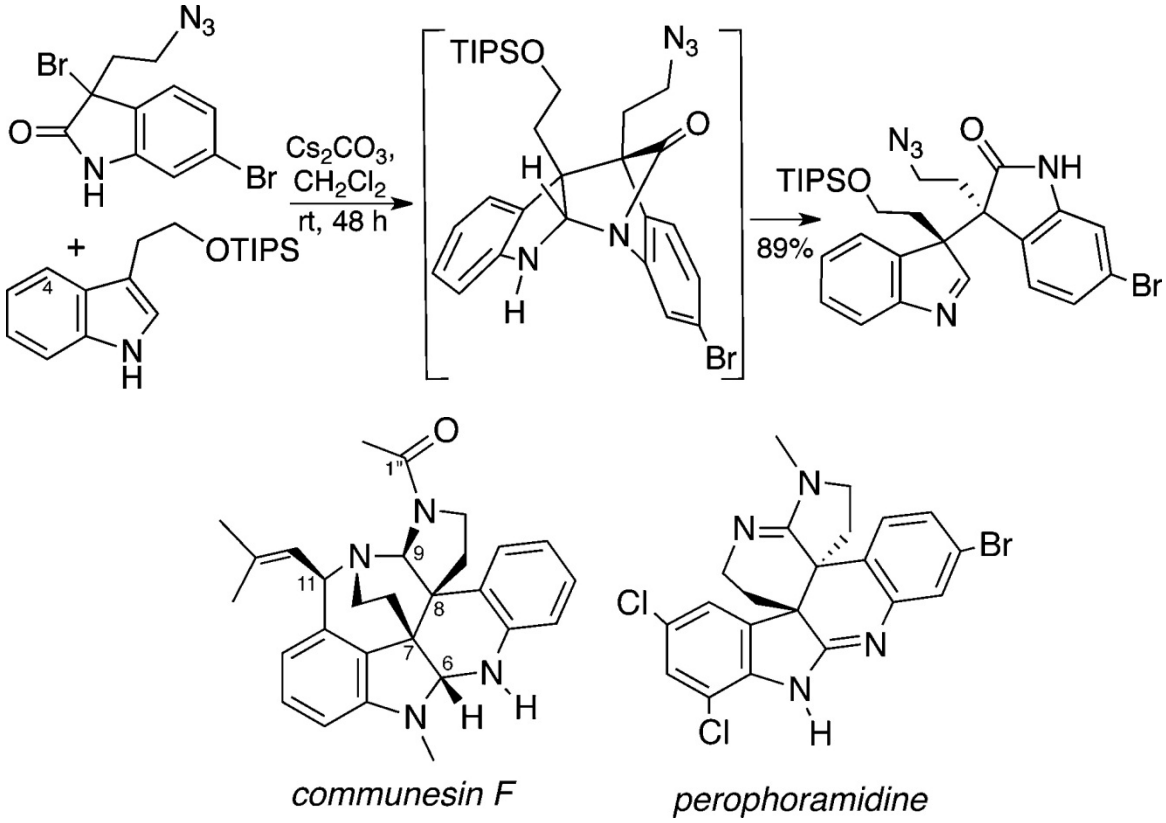
Evidence for an indol-2-one intermediate:



Fuchs, J. R.; Funk, R. L. *Org. Lett*. **2005**, *7*, 677
Funk, R. L.; Johannes, B. *J. Am. Chem. Soc.* **2012**, *134,* 16941

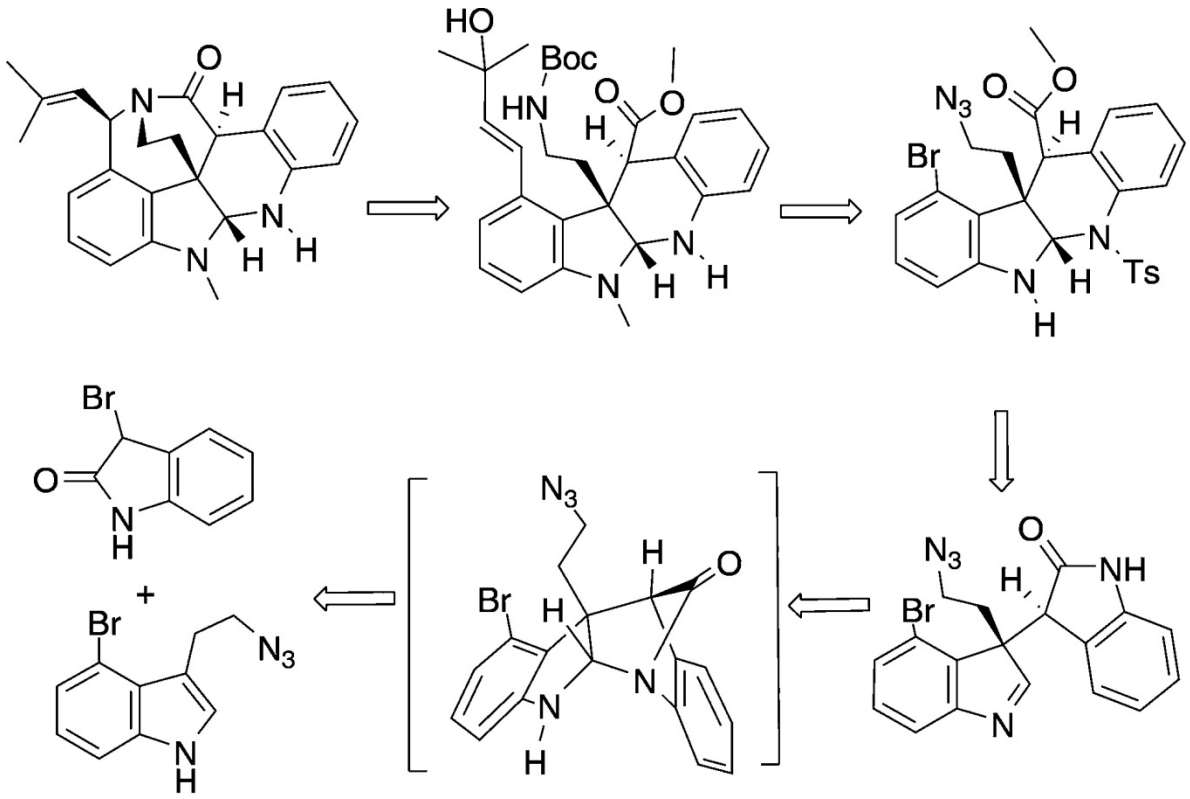
Title Paper

Perophoramidine: quick and stereoselective introduction of the vicinal quaternary centers



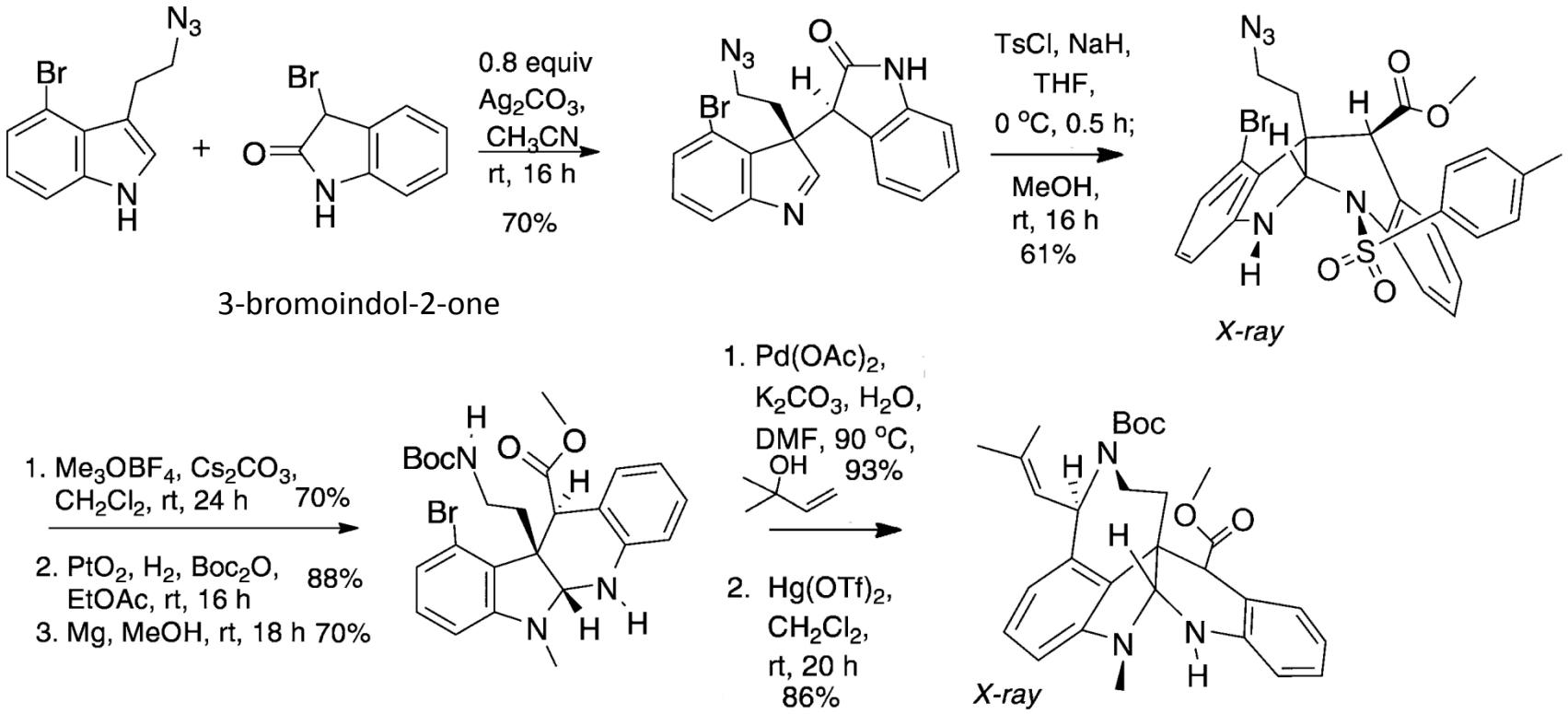
Fuchs, J. R.; Funk, R. L. *Org. Lett*. **2005**, *7*, 677
Funk, R. L.; Johannes, B. *J. Am. Chem. Soc.* **2012**, *134,* 16941
Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004,** *126*, 5068

Retrosynthetic Analysis



Funk, R. L.; Johannes, B. *J. Am. Chem. Soc.* **2012**, *134,* 16941

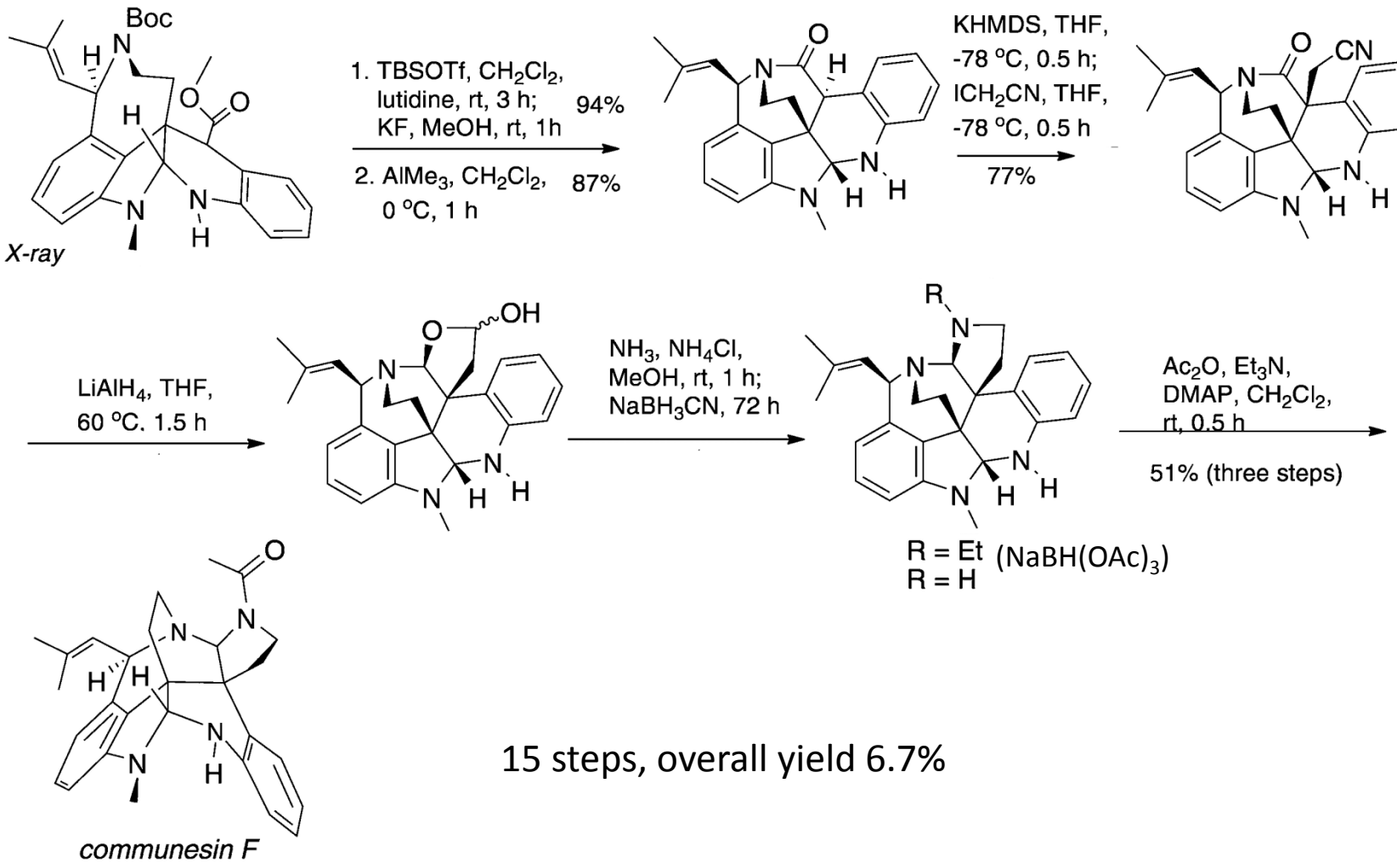
Title Paper



3-bromoindol-2-one

Funk, R. L.; Johannes, B. *J. Am. Chem. Soc.* **2012**, *134,* 16941

Title Paper



15 steps, overall yield 6.7%

Funk, R. L.; Johannes, B. *J. Am. Chem. Soc.* **2012**, *134,* 16941
Zuo, Z.; Ma, D. *Angew. Chem., Int. Ed.* **2011,** *50*, 12008

Conclusion

- A concise total synthesis of (±)-communesin F has been completed in 15 linear steps from 4-bromotryptophol in an overall yield of 6.7%.
- Highlights of this synthesis include:

1) A stereoselective cycloaddition with the *parent* indol-2-one;
2) An underutilized intramolecular mercuric triflate catalyzed cyclization of a carbamate with an allylic alcohol;
3) The preparation of a twisted, bridged lactam from an amino ester using trimethylaluminum.

- This total synthesis further documents the value of indol-2-one cycloadditions for the rapid construction of complex natural products that embody indolines bearing C(3) quaternary carbons.

Funk, R. L.; Johannes, B. *J. Am. Chem. Soc.* **2012**, *134,* 16941