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Carlos A. Guerrero† and Erik J. Sorensen*

Frick Laboratory, Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States

ejs@princeton.edu

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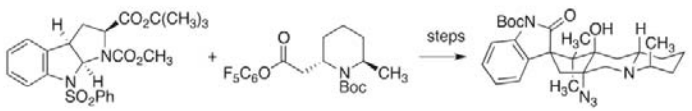
ABSTRACT



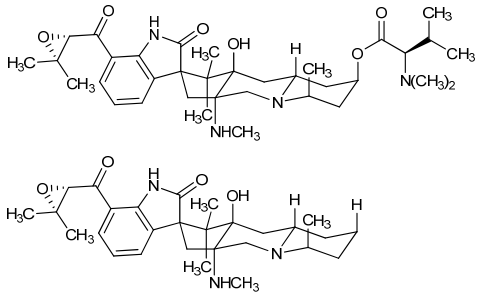
Benjamin R. Eyer
Wipf Group- Current Literture
November 26, 2011

Isolation and Structural Determination

- Isolated from *Penicillium citrinum* (strain N059) separated from the marine red alga, *Actinotrichia fragilis* collected at Hedo Cape, Okinawa Island
  - Citrinadin A: Novel pentacyclic spiroindolinone alkaloid with an *N*,*N*-dimethylvaline residue and an α,ß-epoxy carbonyl unit
  - Citrinadin B: 14-des(*N*,*N*-dimethyl)valyloxy congener of Citrinadin A
- Structural Determination and Confirmation of Absolute Stereochemistry
  - Pentacyclic core
    - Confirmed by 2D-NMR of Citrinadin A & B
    - Comparison of Citrinadins to the ECD of known spiroxiindole alkaloids
  - Absolute configuration of epoxide ring
    - Assigned as *S* by comparison to the VCD of 2*S*- and 2*R*-2,3-epoxy-3,3-dimethyl-1-phenylpropan-1-one

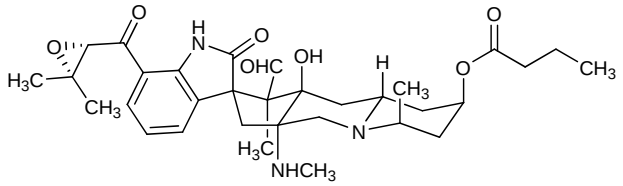
http://microfungi.truman.edu/gallery/Anamorphic/Penicillium/Penicillium-citrinum-heads-4b-100x.jpg

http://www.oceanlink.info/biodiversity/seaweeds/redalgae.jpeg

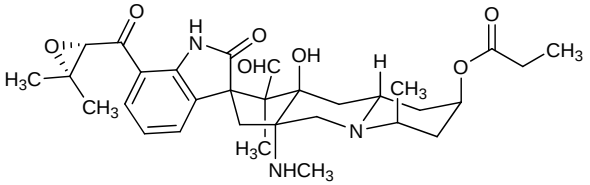


Mugishima, T.; Tsuda, M.; Kasai, Y.; Ishiyama, H.; Fukushi, E.; Kawabata, J.; Watanabe, M.; Akao, K.; Kobayashi, J. *J. Org. Chem.* **2005**, 70, 9430–9435.
Tsuda, M.; Kasai, Y.; Komatsu, K.; Sone, T.; Tanaka, M.; Mikami, Y; Kobayashi, J. *Org. Lett.* **2004**, 6, 3087.

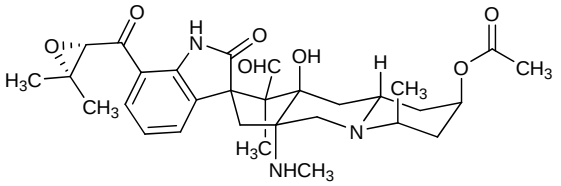
Biological Activity



PF1270A



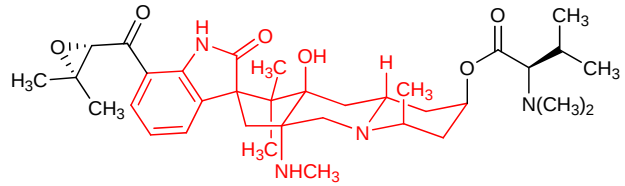
PF1270B



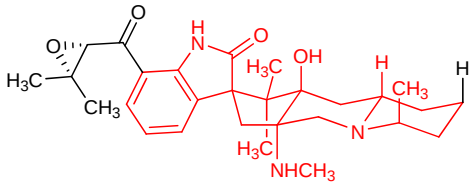
PF1270C

- Isolated from *Penicillium waksmanii* (strain PF1270)
- Histamine H3 receptor (H3R) ligands
  - Rat H3R: *Ki*=0.058, 0.17, 0.19 μM
  - Human H3R: *Ki*=0.047, 0.12, 0.22 μM
  - EC_{50}=0.12, 0.15, 0.20 μM
- Potential Therapeutic Applications: diabetes, obesity, ADHD, depression, epilepsy, and sleep disorder

Kushida, N.; et al.. *J. Antiobiot.* **2007**, 60, 667.
Eur. Pat. Appl. 1612273, 2004.; U.S. Patent 7,501,431, March 10, 2009.

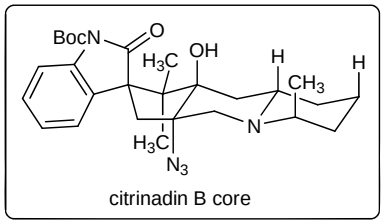


citrinadin A



citrinadin B

- Murine leukemia L1210 cells (IC_{50}=6.2 μg/mL)
- Human epidermoid carcinoma KB cells (IC_{50}=10 μg/mL)

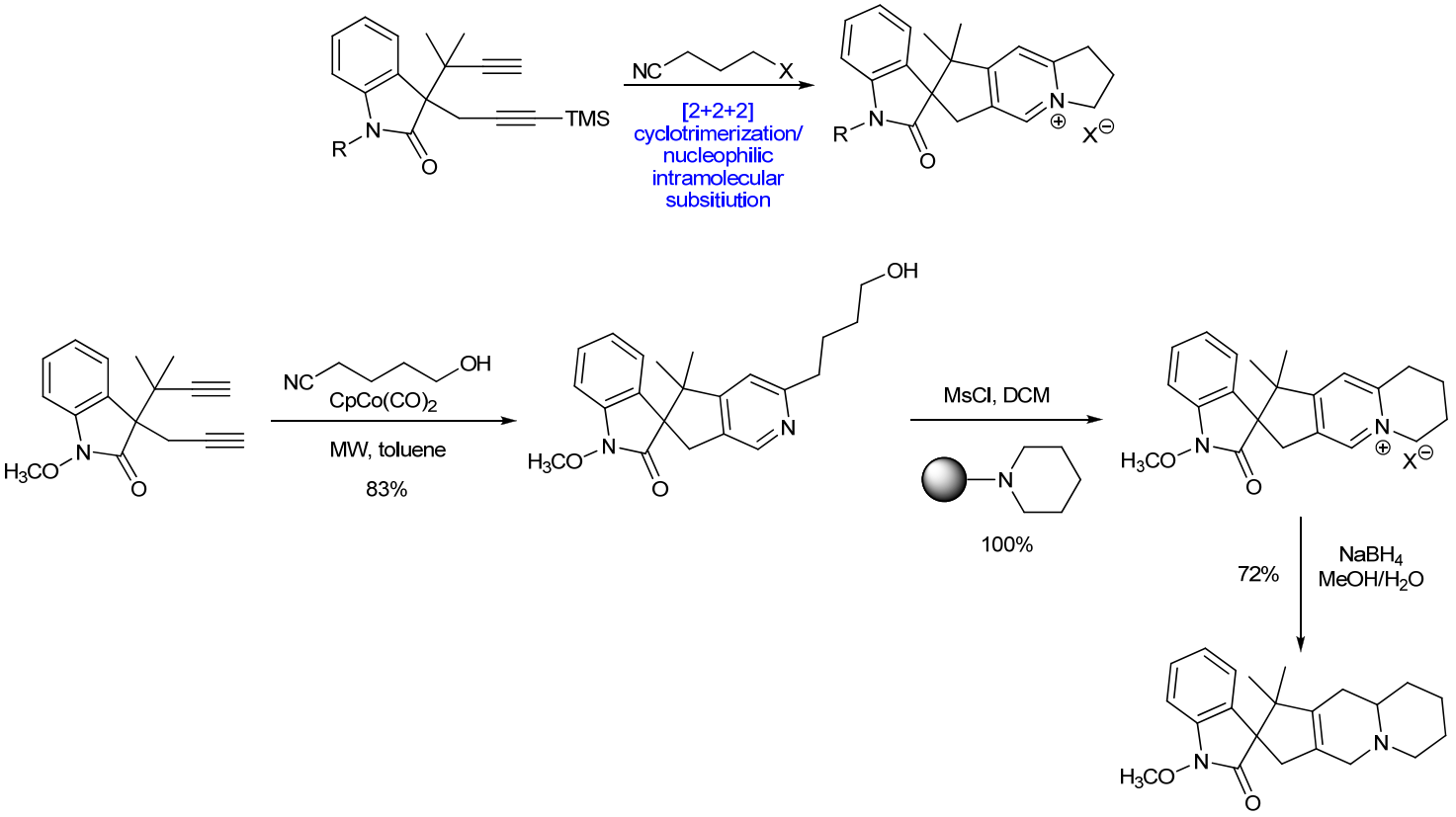


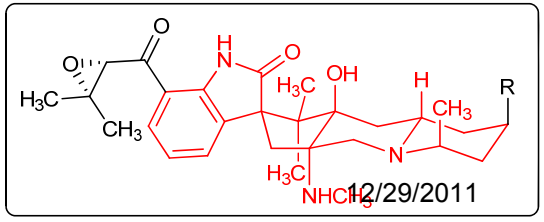
citrinadin B core

- Murine leukemia L1210 cells
  - Modest cytotoxicity
  - IC_{50}=10 μg/mL

Mugishima, T.; Tsuda, M.; Kasai, Y.; Ishikawa, H.; Fukushi, E.; Kawabata, J.; Watanabe, M.; Akao, J.; Kobayashi, J. *J. Org. Chem.* **2005**, 70, 9430–9435.
Tsuda, M.; Kasai, Y.; Komatsu, K.; Sone, T.; Tanaka, M.; Mikami, Y; Kobayashi, J. *Org. Lett.* **2004**, 6, 3087.

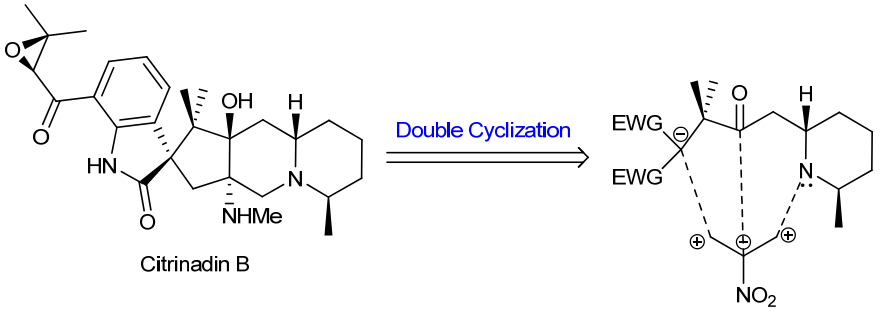
Recent Attempts at Core from Other Groups

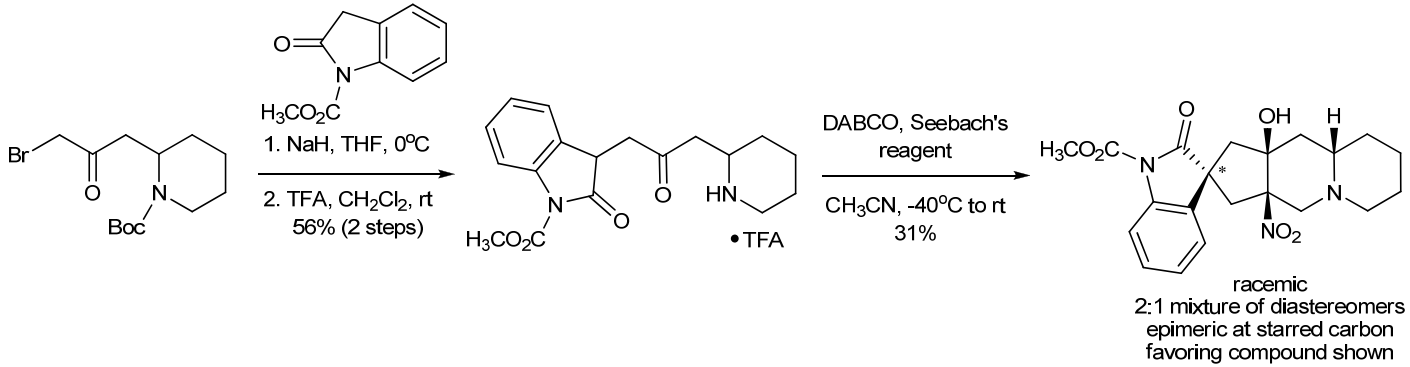




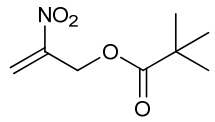
McIver, A. L.; Deiters, A. *Org. Lett.* **2010**, *6*, 1288.

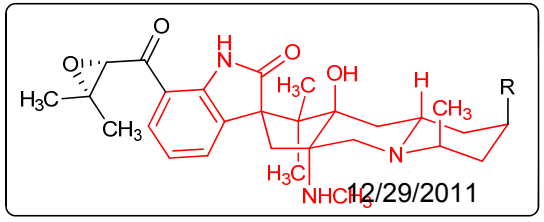
Recent Attempts at Core from Sorensen Group





Unable to isomerize the cis ring fusion to trans by retro-Henry/Henry process under basic conditions





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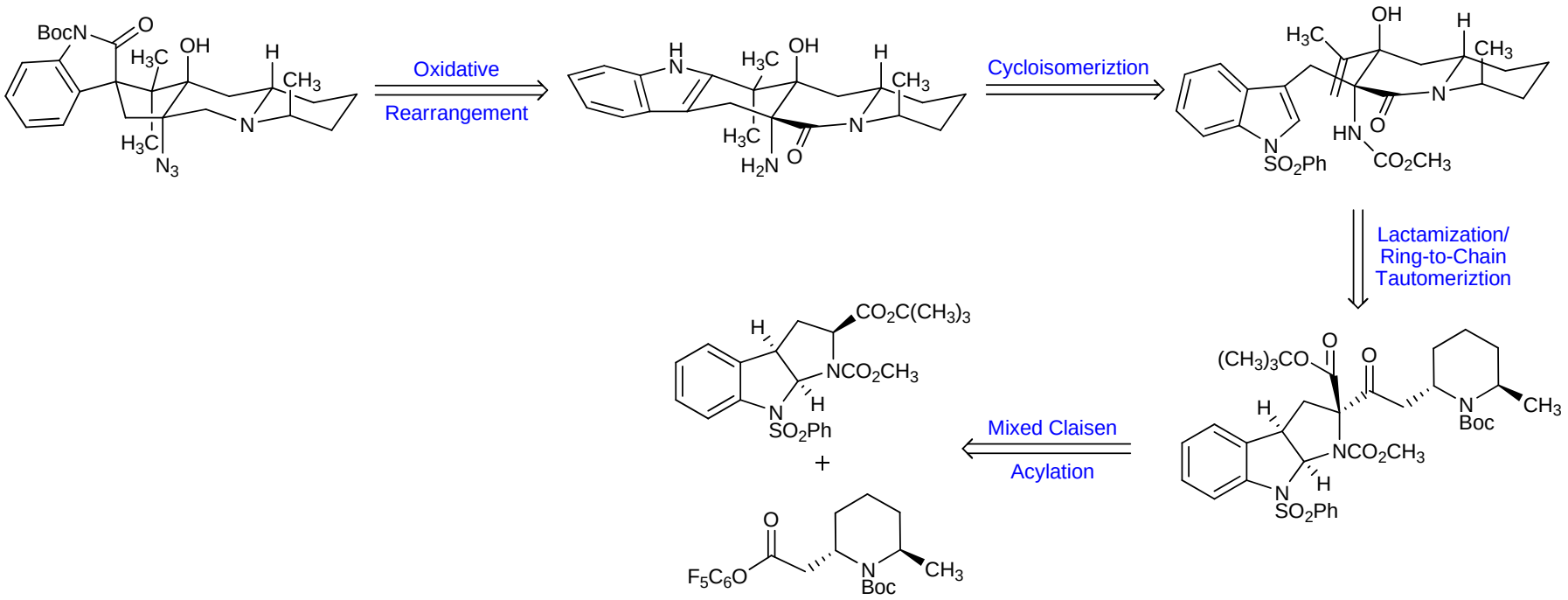
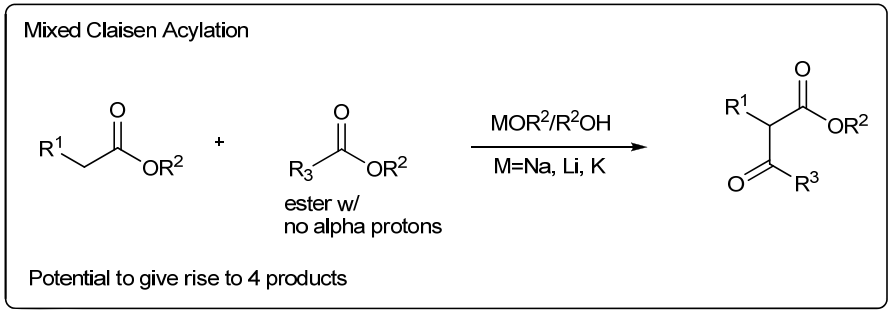
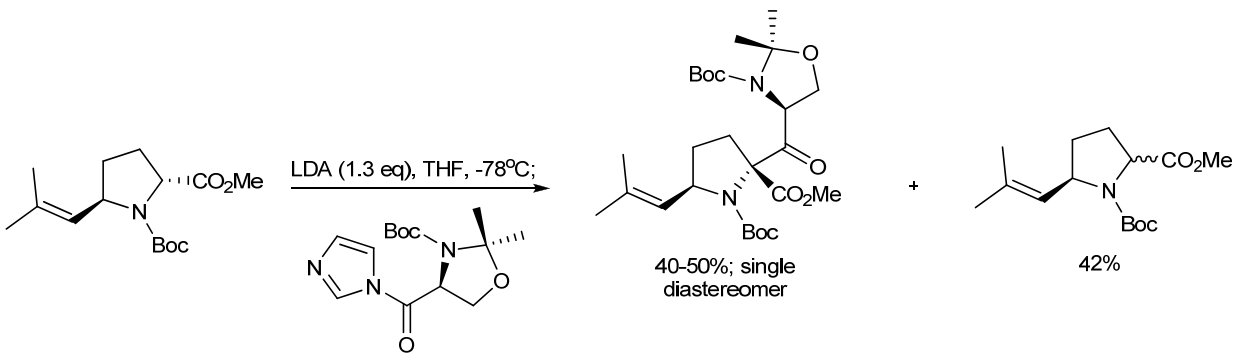
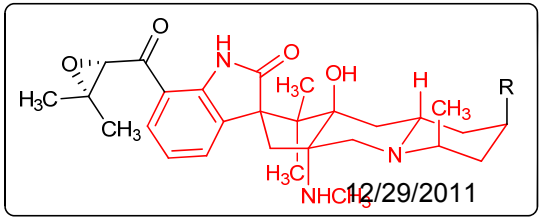
Title Paper: Retrosynthetic Analysis



Designed Mixed Claisen Acylation

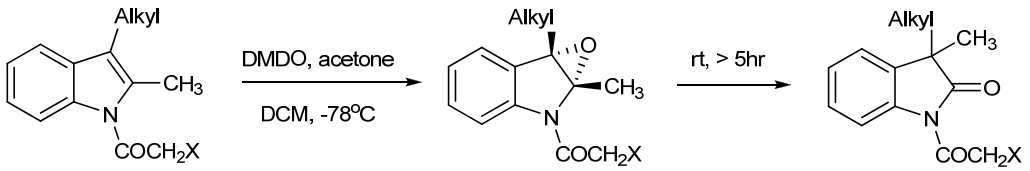






Vaswani, R. G.; Chamberlin, A. R. J. *Org. Chem.* **2008**, 73, 1661.

Oxidative Ring Closure Strategy



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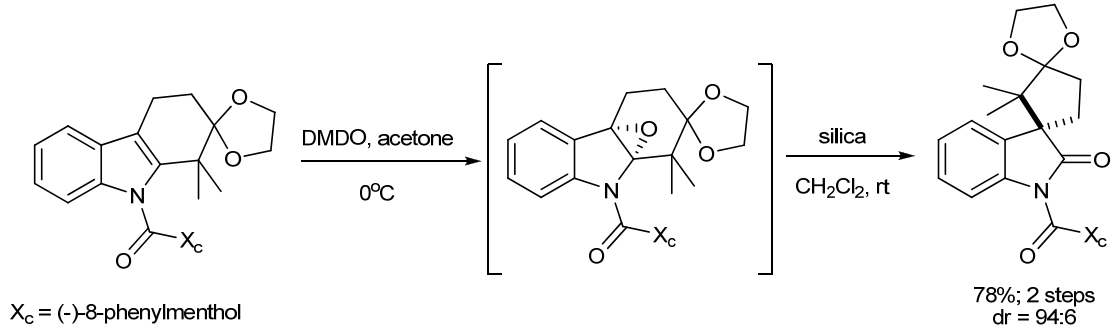
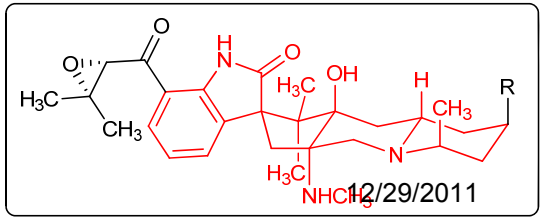
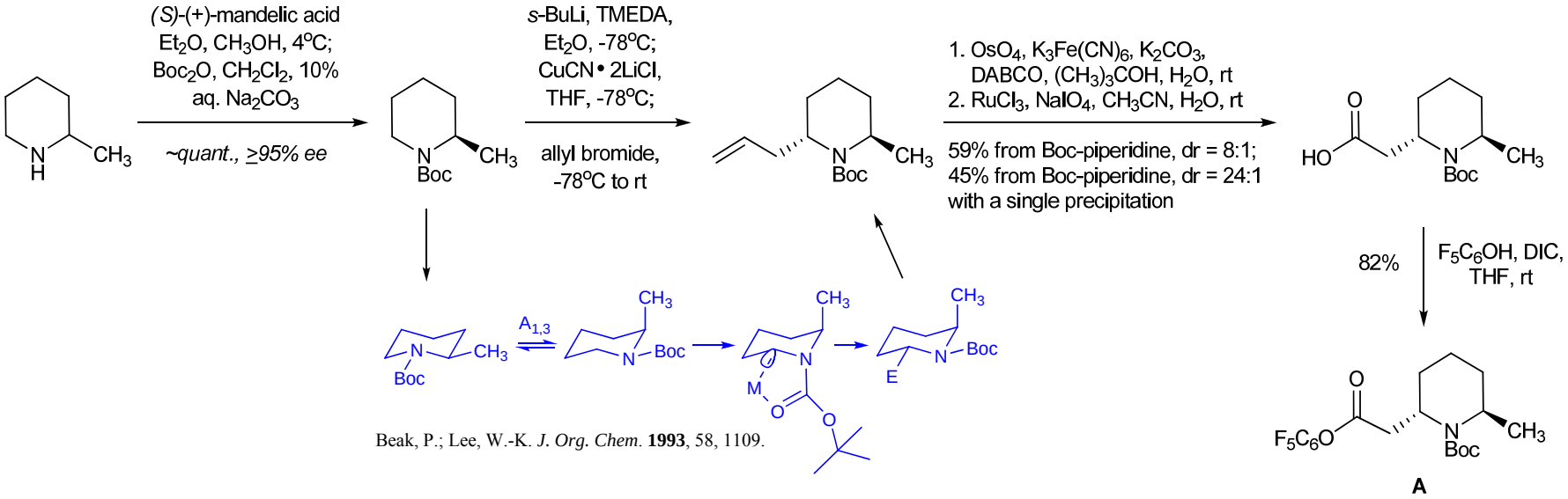


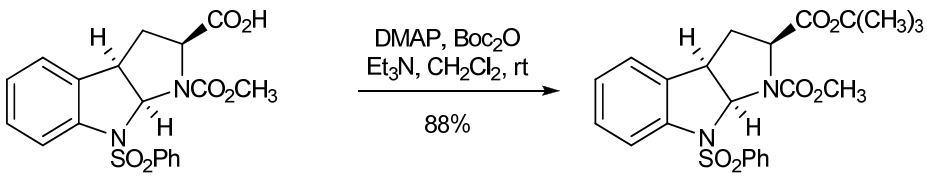
Xc = (-)-8-phenylmenthol

Pettersson, M.; Knueppel, D.; Martin, S. F. *Org. Lett.* **2007**, 9, 4623.

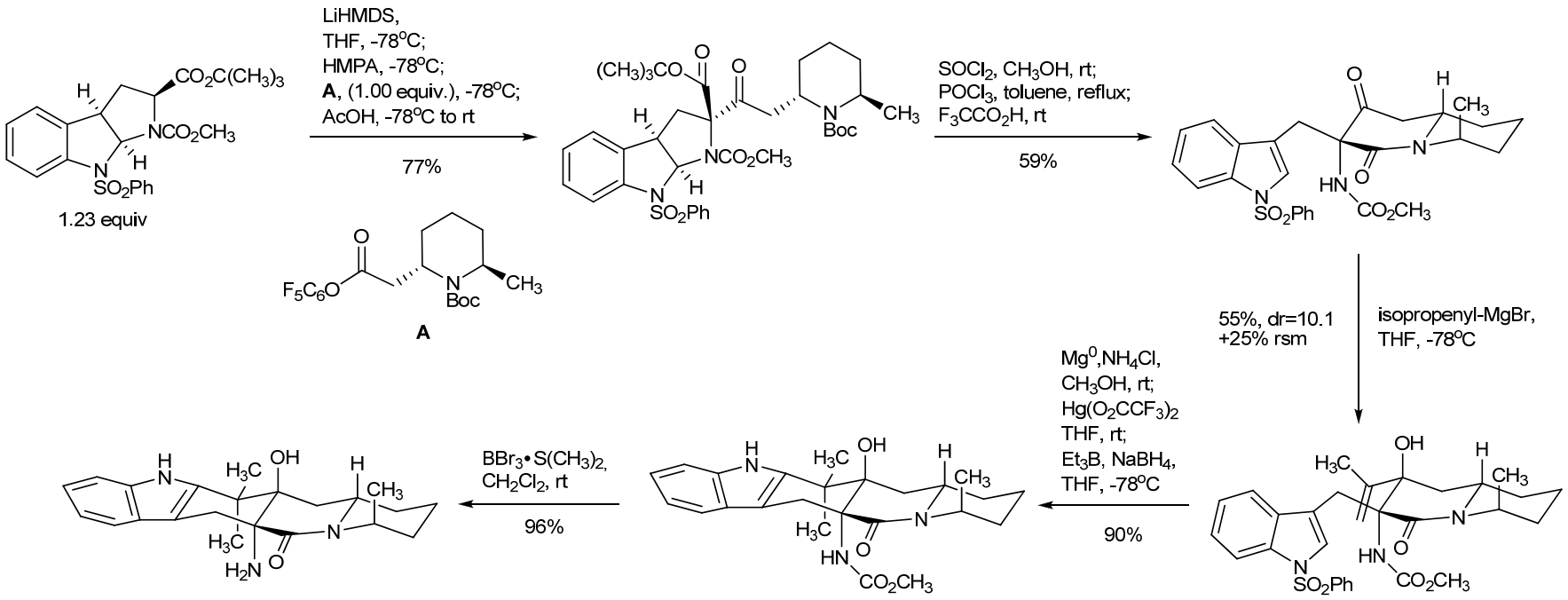


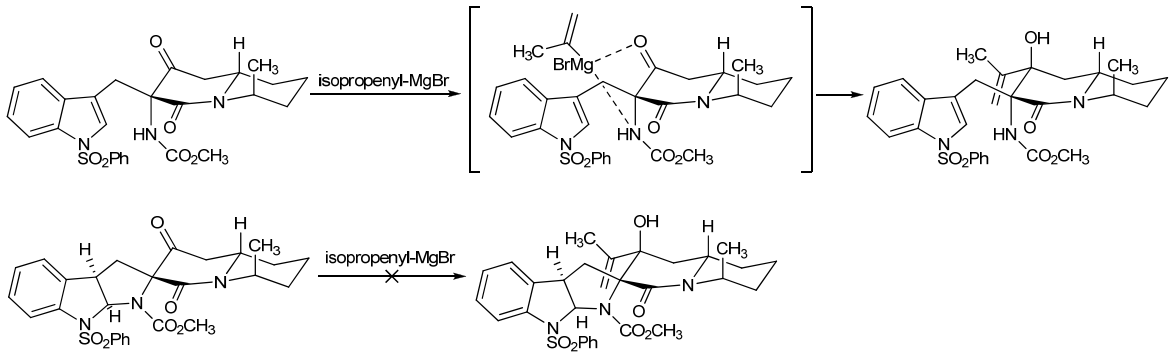
Title Paper: Synthesis of Piperidine and L-tryptophan fragments



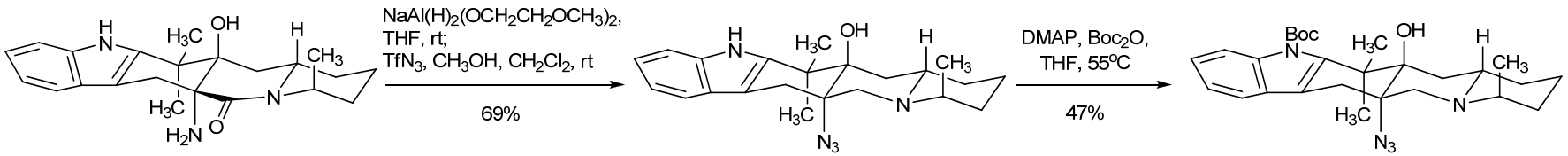


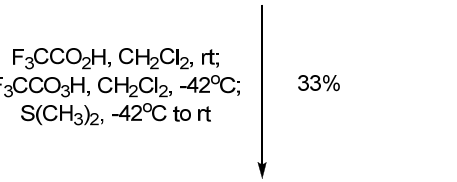
Title Paper: Synthesis of Core Ring Architecture



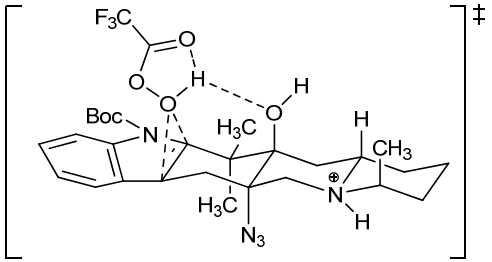


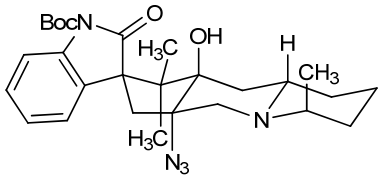
Title Paper: Completion of the Citrinadin Core Architecture



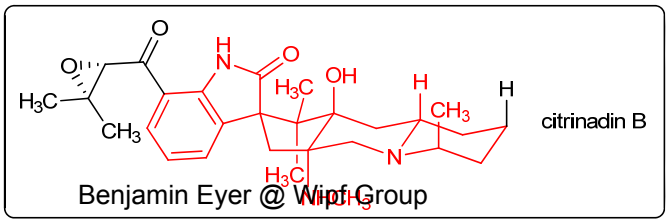


Proposed TS for Oxidative Rearrangement:





citrinadin B core



citrinadin B

Conclusions

- Transfer of chirality from starting material L-tryptophan
- An efficient and selective mixed Claisen acylation
- Lactamization/Chain-to-Ring tautomerization and Cycloisomerization
- Oxidative rearrangement to furnish core
- Brief and operationally simple route that addresses the remaining problems of stereocontrol in citrinadin B core