Enantioselective Total Synthesis of (-)-Acetylaranotin, a Dihydrooxepine Epidithiodiketopiperazine

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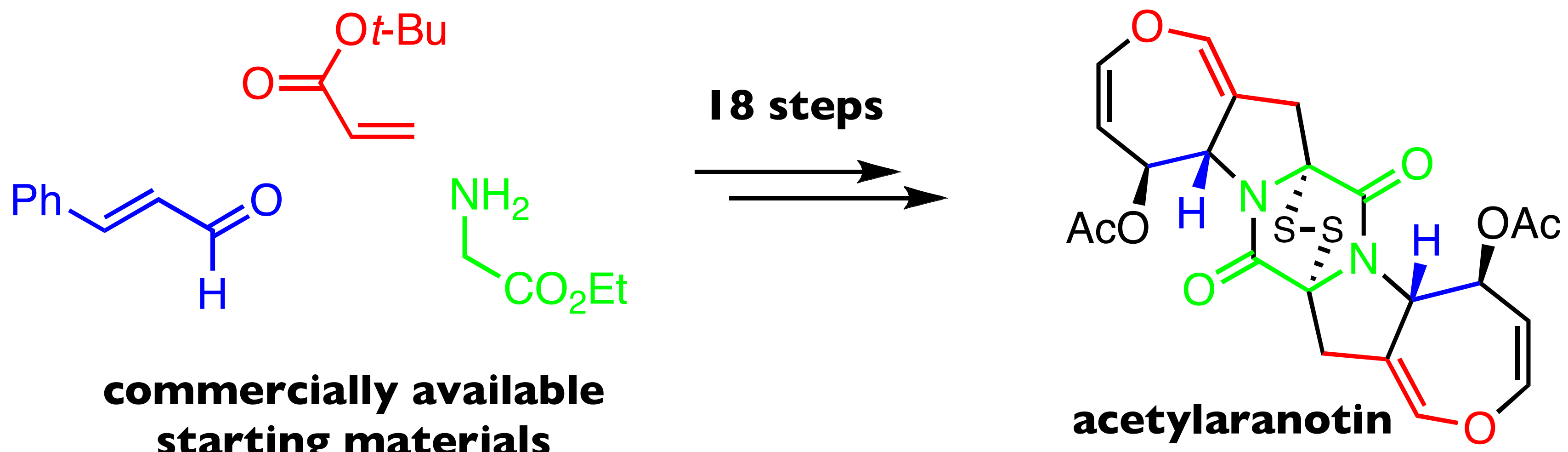


commercially available starting materials

acetylaranotin

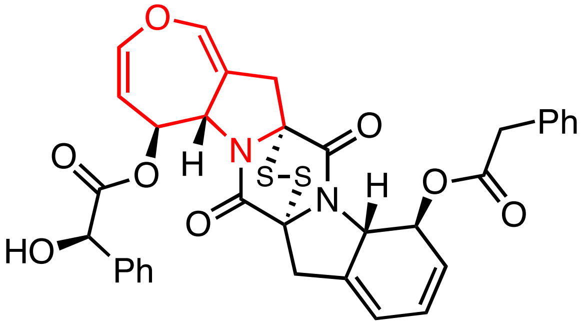
Christopher Rosenker
Wipf Group - Current Literature
November 12, 2011

Epidithiodiketopiperazine natural products

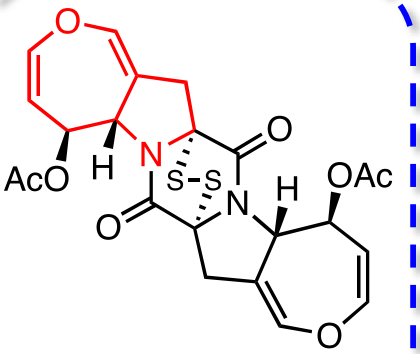
Epidithiokiketopiperazines (ETP) are a broad collection of fungal metabolites that contain at least 14 different core structures.

- •Biosynthetically arise by the joining of two amino acids which are further functionalized via oxidative pathways
- •Subset contains a 7-membered dihydrooxepine ring

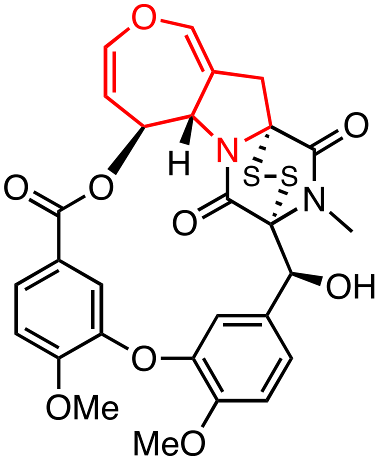
Biological activity of dihydrooxepine containing ETPs include inhibition of viral RNA polymerase and antiproliferative/apoptotic activity against human cancer cells.



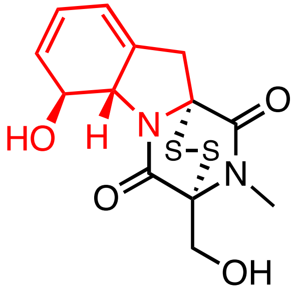
(–)-emethallicin A



(–)-acetylaranotin



(+)-MPC1001B

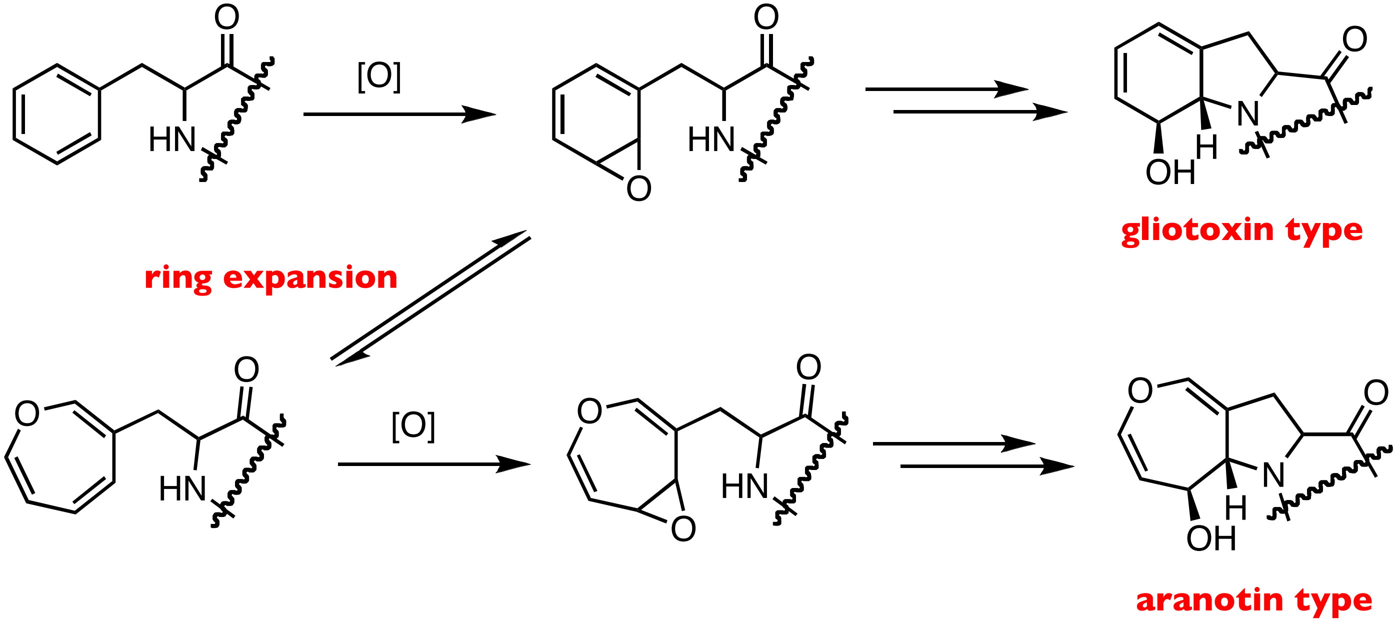


(–)-gliotoxin

Gardiner, D. M.; Waring, P.; Howlett, B. J. *Microbiology* **2005**, *151*, 1021.
Codelli, J. A.; Puchlopek, A. L. A.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, DOI: 10.1021/ja209354e.

Biosynthetic proposal of gliotoxin and aranotin type natural products

The biosynthesis of gliotoxin and aranotin type natural products is hypothesized to occur via an epoxidized benzene ring.

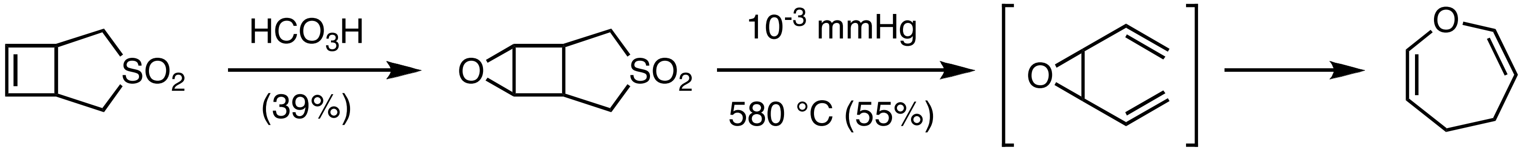


Neuss, N.; Boeck, L. D.; Brannon, D. R.; Cline, J. C.; DeLong, D. C.; Gorman, M.; Huckstep, L. L.; Lively, D. H.; Mabe, J.; Marsh, M. M.; Molloy, B. B.; Nagarajan, R.; Nelson, J. D.; Stark, W. M. *Antimicrob. Agents Chemother.* **1968**, 213.

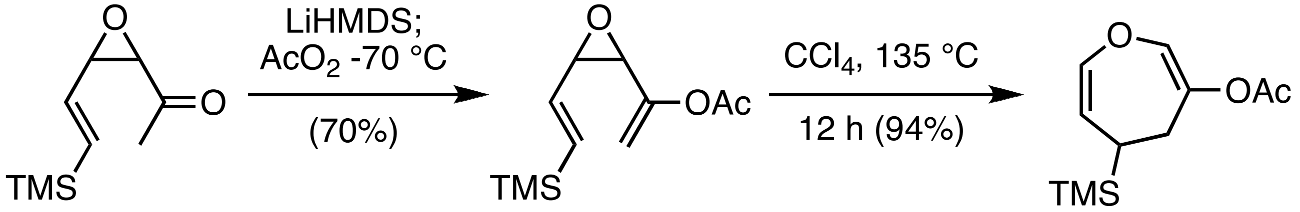
Gardiner, D. M.; Waring, P.; Howlett, B. J. *Microbiology* **2005**, *151*, 1021.

Synthetic Methodologies to from Oxepines

Cadogan, Gosney & Co-workers: Cope rearrangement using a highly strained epoxycyclobutane.



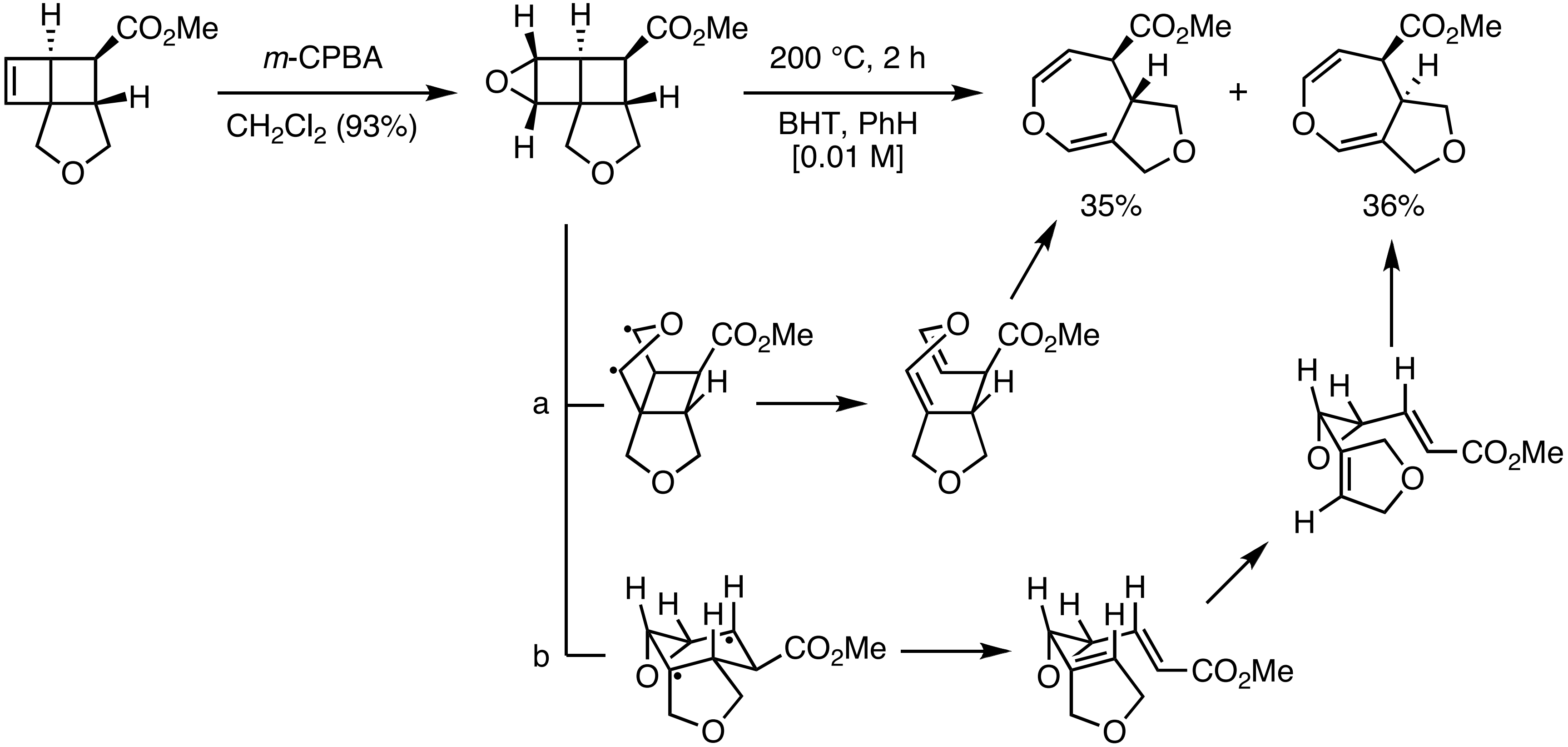
White & Co-workers: Cope rearrangement of *cis*-divinyl epoxide.



Aitken, R. A.; Cadogan, J. I. G.; Gosney, I.; Hamill, B. J.; McLaughlin, L. M. *J. Chem. Soc.; Chem. Comm.* **1982**, 1164.
Clark, D. L.; Chou, W.-N.; White, J. B. *J. Org. Chem.* **1990**, *55*, 3975.

Synthetic Methodologies to from Oxepines

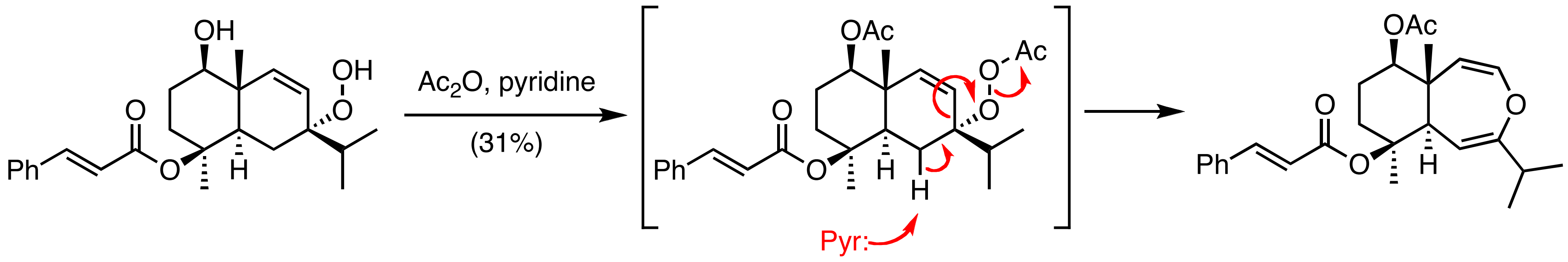
Snapper & Leyhane: Thermal fragmentation of highly strained epoxides provides functionalized oxepines.



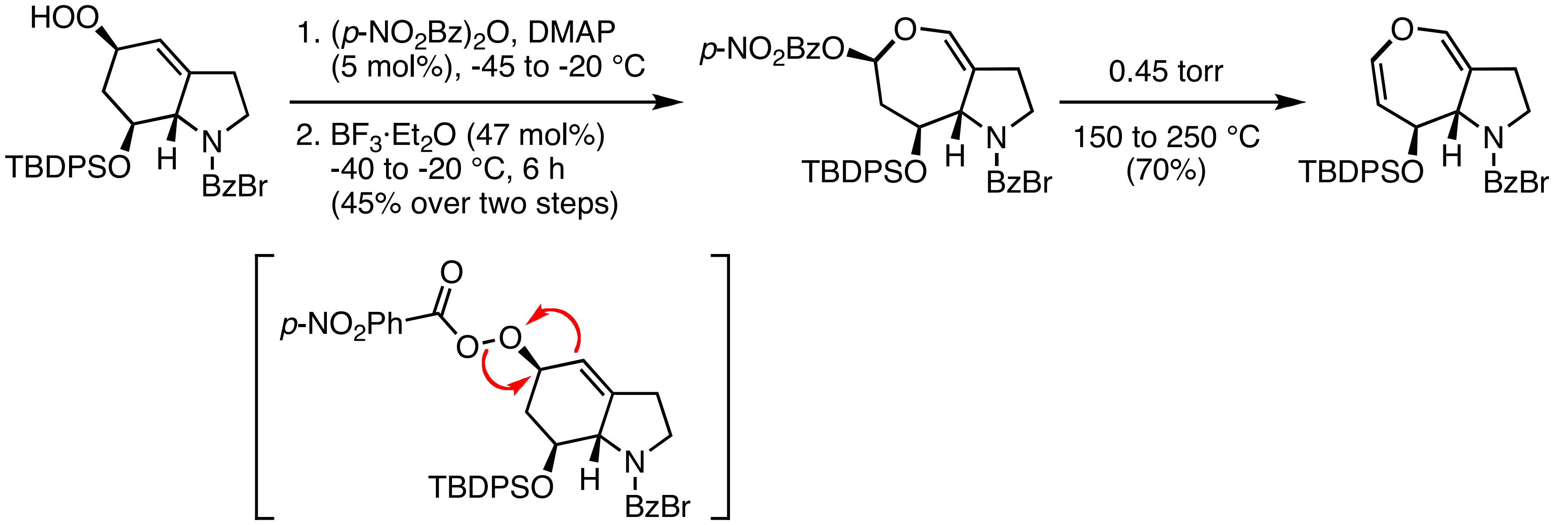
Leyhane, A. J.; Snapper, M. L. *Org. Lett.* **2006**, *8*, 5183.

Synthetic Methodologies to from Oxepines

Vargas & Co-workers: Isolated oxepine during structural elucidation of sesquiterpene hydroperoxide.



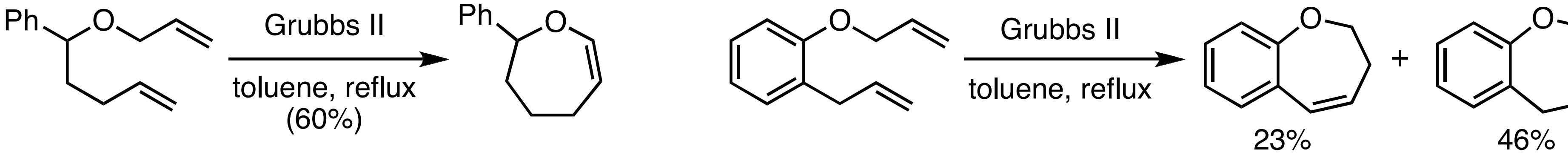
Kishi & Goodman: Criegee rearrangement of allylic hydroperoxides to form an Aranotin type precursor.



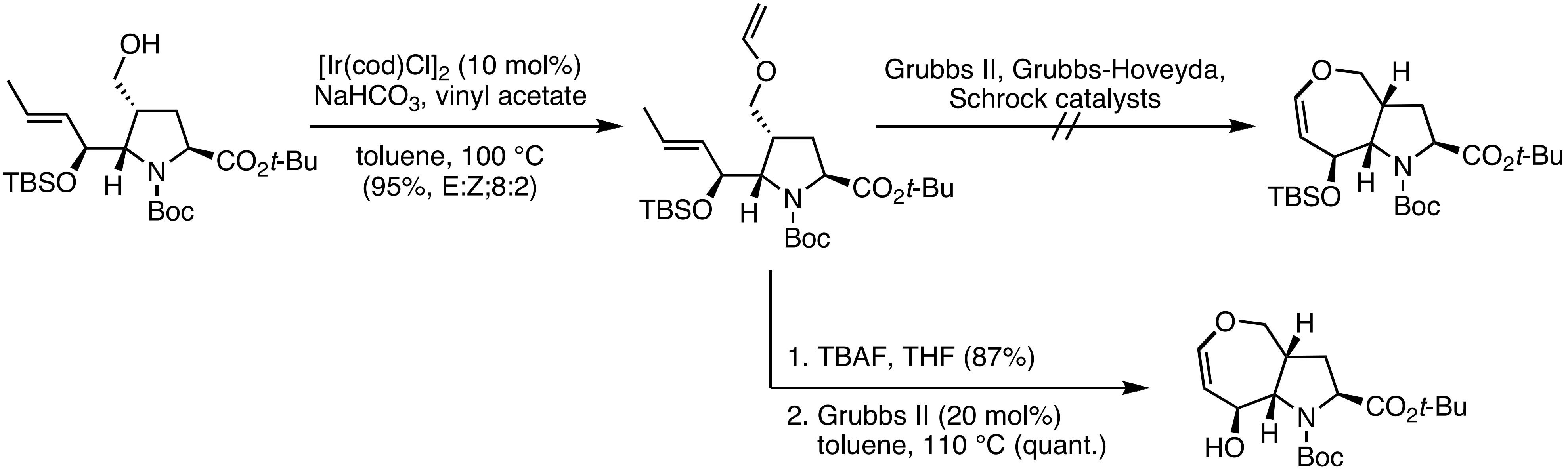
Lu, T.; Vargas, D.; Fischer, N. H. *Phytochemistry* **1993**, *34*, 737.
Goodman, R.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9392.
Goodman, R. M. Ph.D. Thesis, Harvard University, May 1998.

Synthetic Methodologies to from Oxepines

Fustero & Co-workers: Tandem RCM-olefin isomerization methodology.



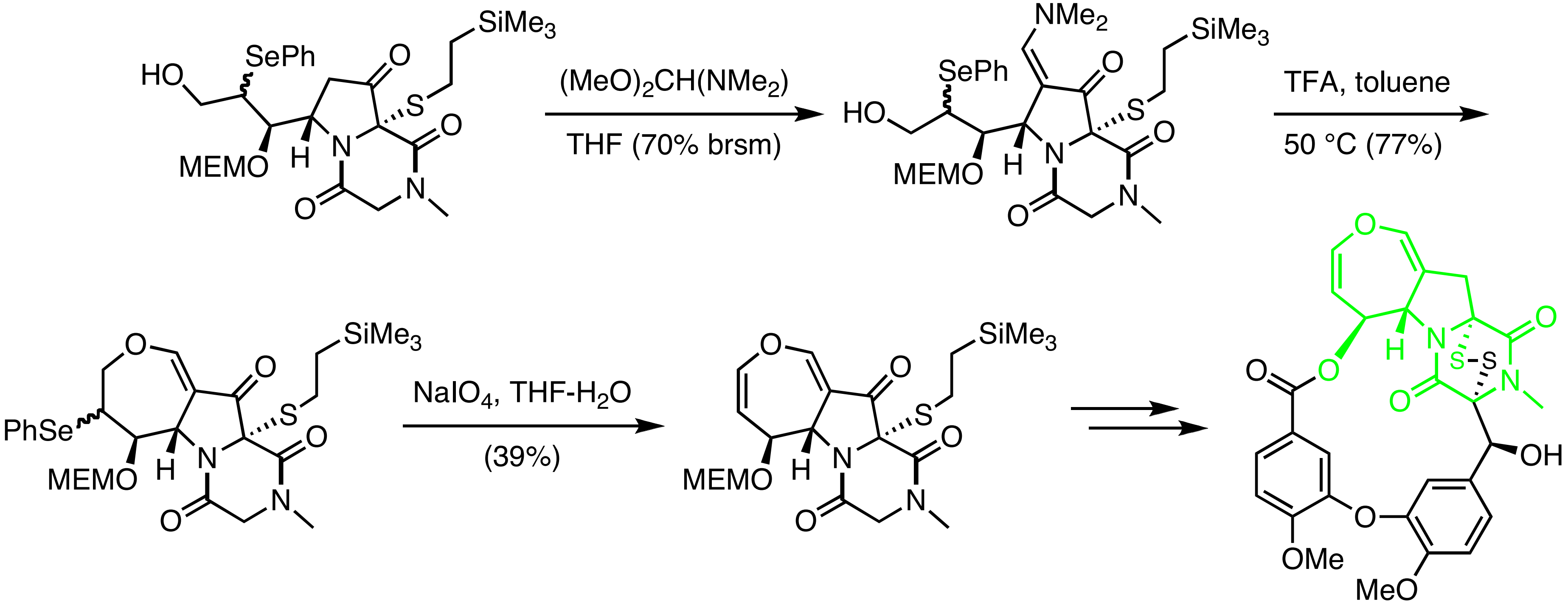
Bräse & Co-workers: Enol-ether RCM on an unprotected allylic alcohol.



Fustero, S.; Sáchez-Roselló, M.; Jiménez, D.; Sanz-Cervera, J. F.; del Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 2706.
Gross, U.; Nieger, M.; Bräse, S. *Chem.-Eur. J.* **2010**, *16*, 11624.

Synthetic Methodologies to from Oxepines

Clive & Peng: Acid-induced cyclicization of pendant alcohol onto a vinylogous amide.



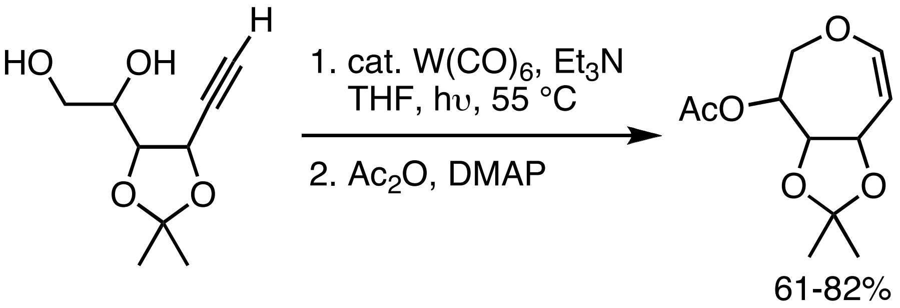
(+)-MPC1001B

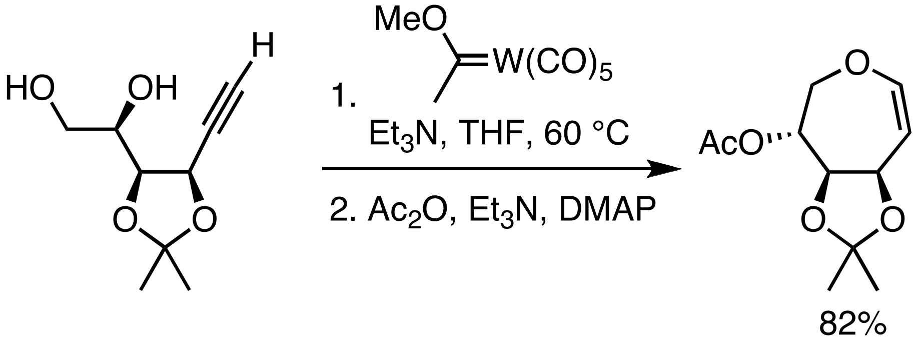
Peng, J.; Clive, D. L. J. *Org. Lett.* **2007**, *9*, 2939.
Peng, J.; Clive, D. L. J. *J. Org. Chem.* **2009**, *74*, 513.

Synthetic Methodologies to from Oxepines

McDonald & Co-workers

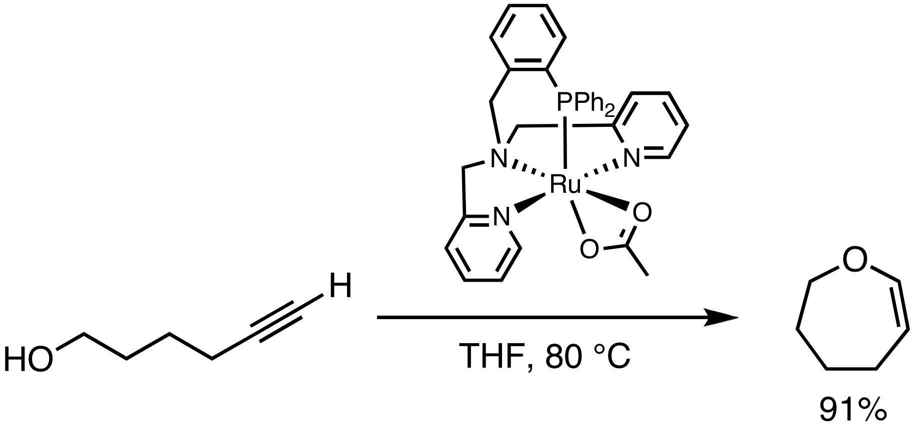
W-cat cycloisomerization





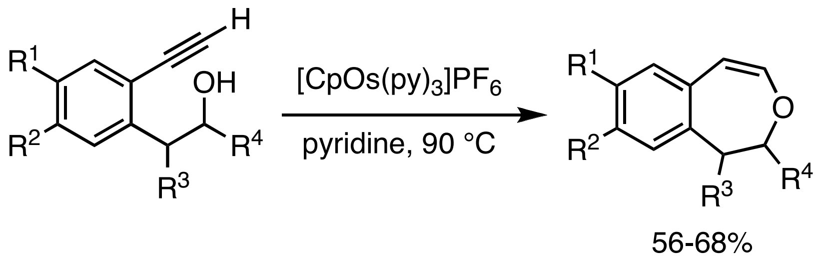
Jia & Co-workers

Ru-cat cylcoisomerization



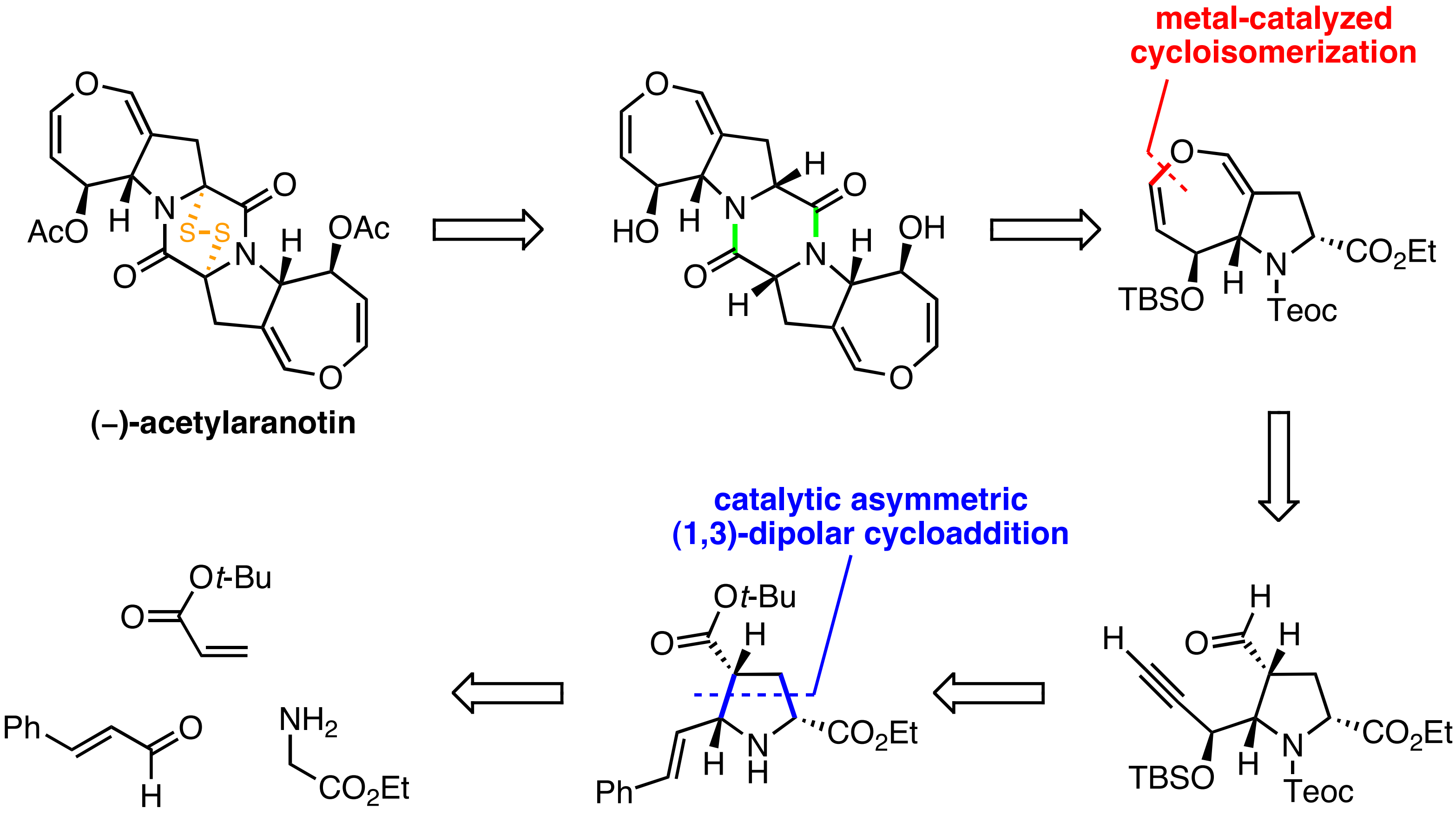
Esteruelas, Saá & Co-workers

Os-cat cylcoisomerization



Alcázar, E.; Pletcher, J. M.; McDonald, F. E. *Org. Lett.* **2004**, *6*, 3877.
Koo, B.; McDonald, F. E. *Org. Lett.* **2007**, *9*, 1737.
Liu, P. N.; Su, F. H.; Wen, T. B.; Sung, H. H. Y.; Williams, I. D.; Jia, G. *Chem.-Eur. J.* **2010**, *16*, 7889.
Varela-Fernández, A.; García-Yebra, C.; Varela, J. A.; Esteruelas, M. A.; Saá, C. *Angew. Chem. Int., Ed.* **2010**, *49*, 4278.

Reisman Group Retrosynthetic Analysis



(–)-acetylaranotin

metal-catalyzed cycloisomerization

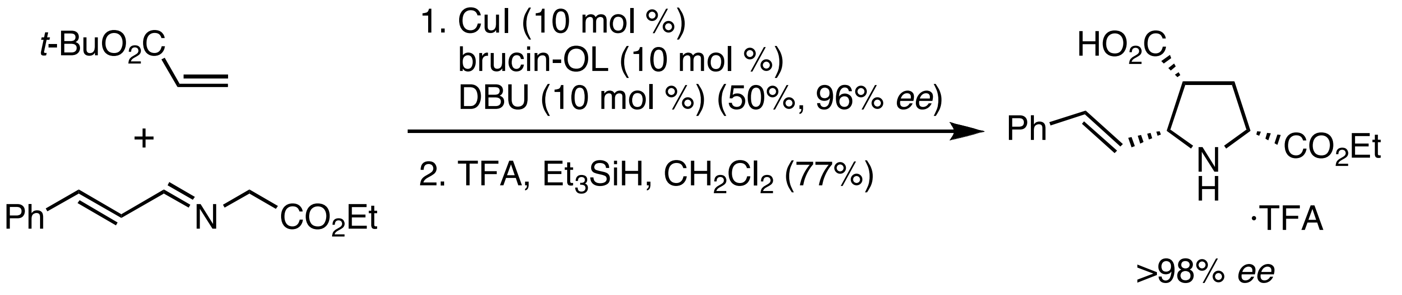
catalytic asymmetric (1,3)-dipolar cycloaddition

commercially available starting materials

(-)-acetylaranotin was isolated over 40 years ago and had not yet been synthesized

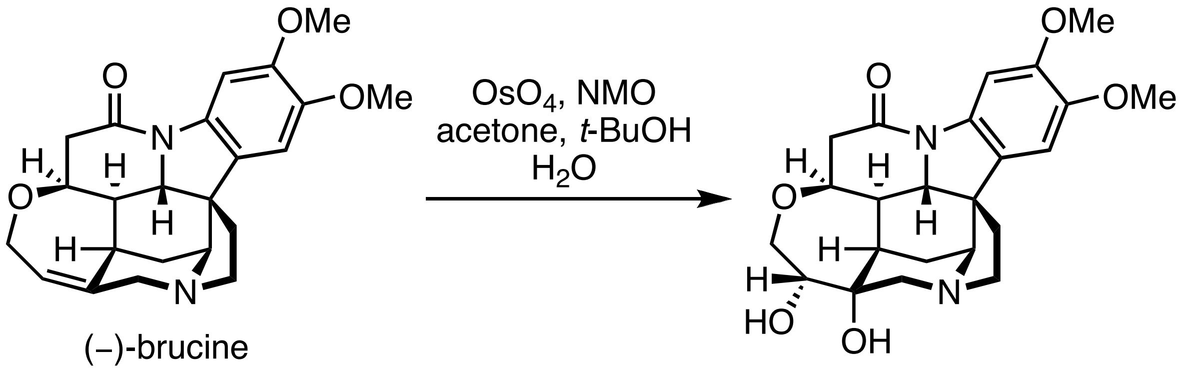
Codelli, J. A.; Puchlopek, A. L. A.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, DOI: 10.1021/ja209354e.

Catalytic asymmetric (1,3)-dipolar cycloaddition



1. CuI (10 mol %) brucin-OL (10 mol %) DBU (10 mol %) (50%, 96% *ee*)
2. TFA, Et_3SiH, CH_2Cl_2 (77%)

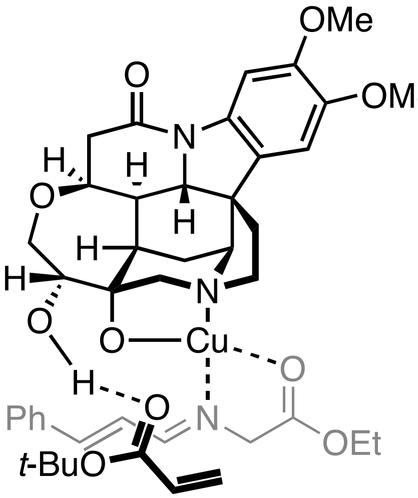
>98% *ee*



OsO_4, NMO acetone, t-BuOH H_2O

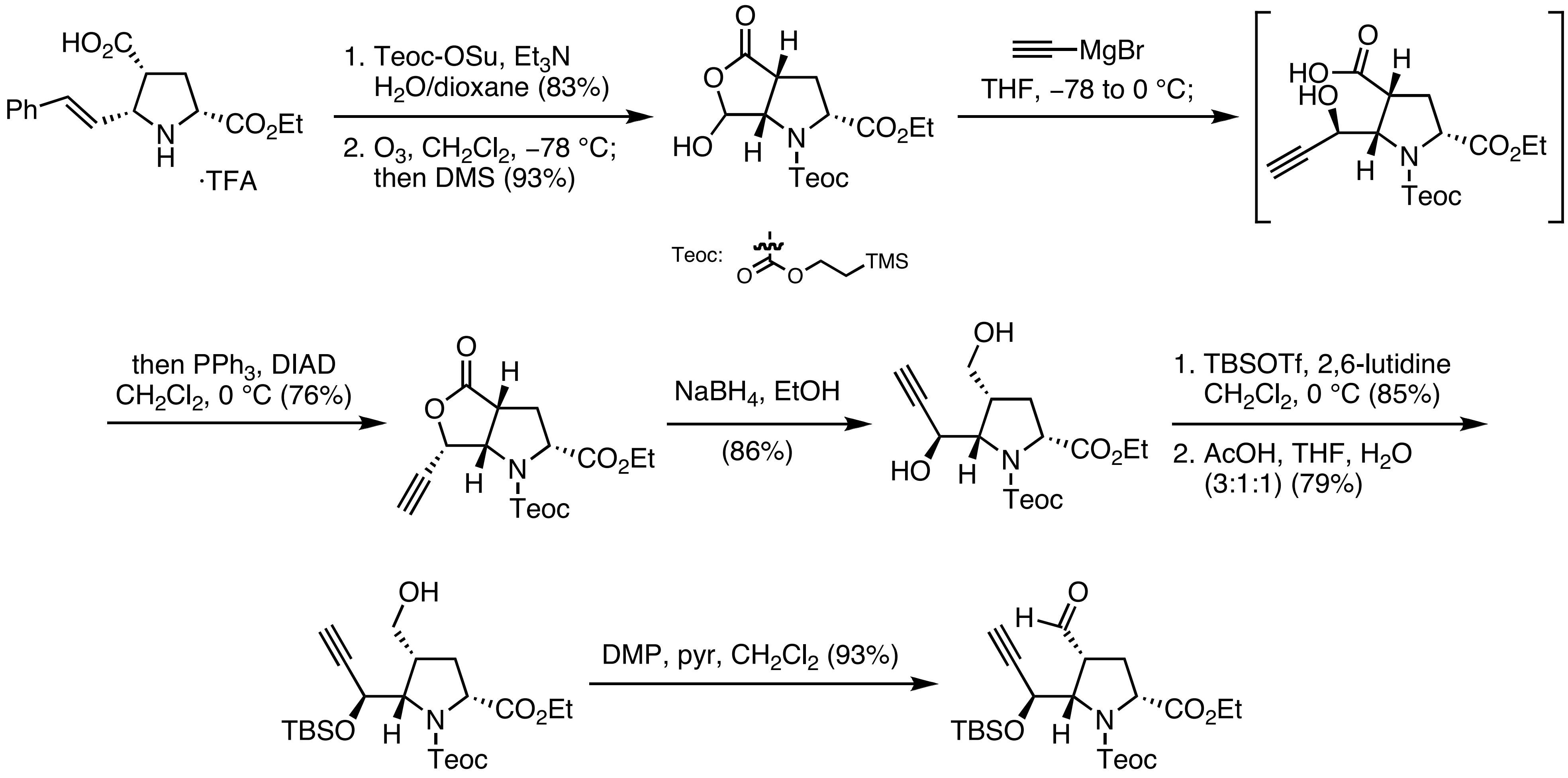
(–)-brucine
$3.34/g (Aldrich)

95%
brucin-OL



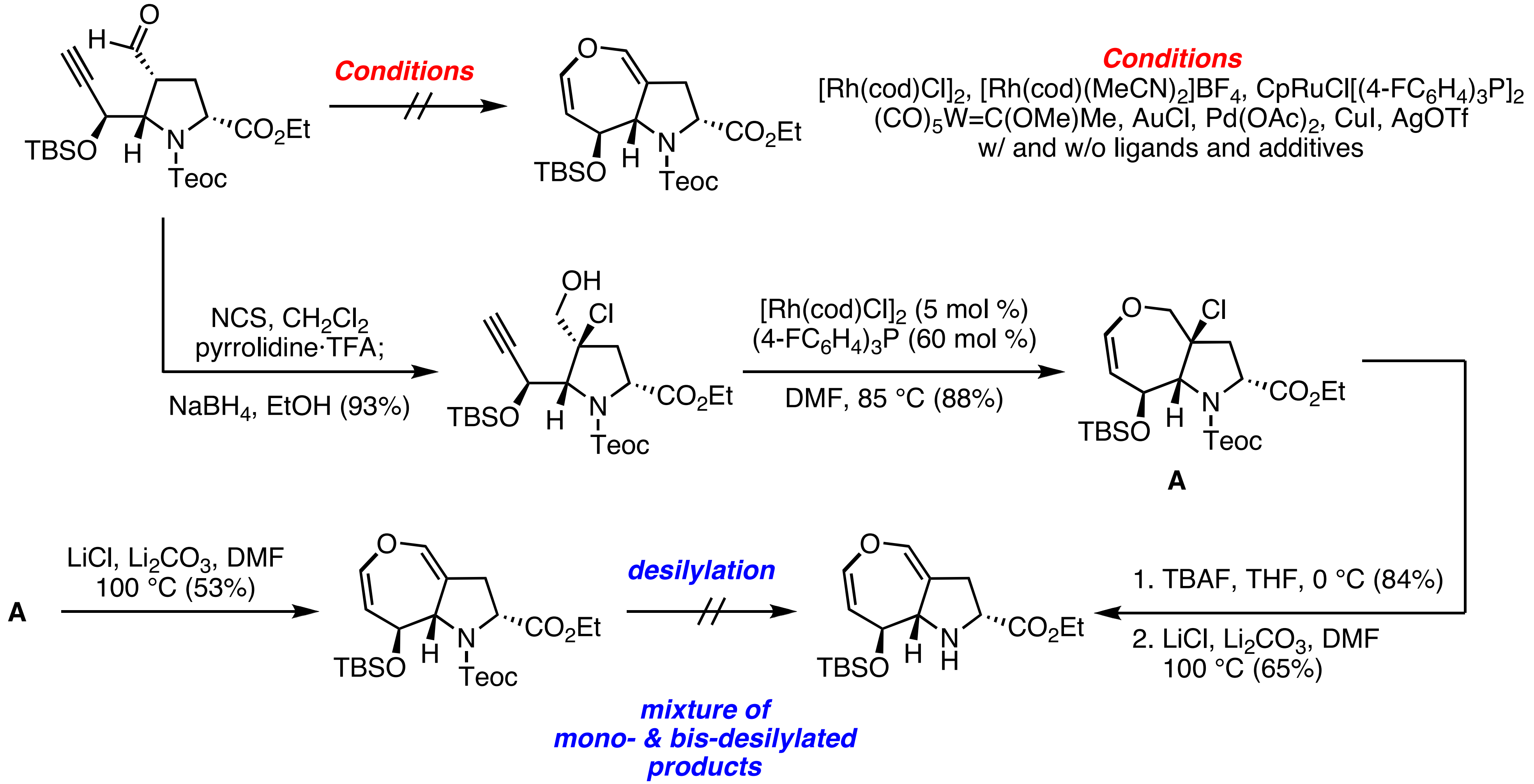
Codelli, J. A.; Puchlopek, A. L. A.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, DOI: 10.1021/ja209354e.
Kim, H. Y.; Shih, H.-J.; Knabe, W. E.; Oh, K. *Angew. Chem., Int. Ed..* **2009**, *48*, 7420.

Synthesis of Acetylaranotin



Codelli, J. A.; Puchlopek, A. L. A.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, DOI: 10.1021/ja209354e.

Synthesis of Acetylaranotin: dihydrooxepine formation



Conditions

$[Rh(cod)Cl]_2$, $[Rh(cod)(MeCN)_2]BF_4$, $CpRuCl[(4\text{-}FC_6H_4)_3P]_2$
$(CO)_5W{=}C(OMe)Me$, AuCl, $Pd(OAc)_2$, CuI, AgOTf
w/ and w/o ligands and additives

NCS, CH_2Cl_2
pyrrolidine·TFA;
$NaBH_4$, EtOH (93%)

$[Rh(cod)Cl]_2$ (5 mol %)
$(4\text{-}FC_6H_4)_3P$ (60 mol %)
DMF, 85 °C (88%)

A

LiCl, Li_2CO_3, DMF
100 °C (53%)

desilylation

mixture of
mono- & bis-desilylated
products

1. TBAF, THF, 0 °C (84%)
2. LiCl, Li_2CO_3, DMF
100 °C (65%)

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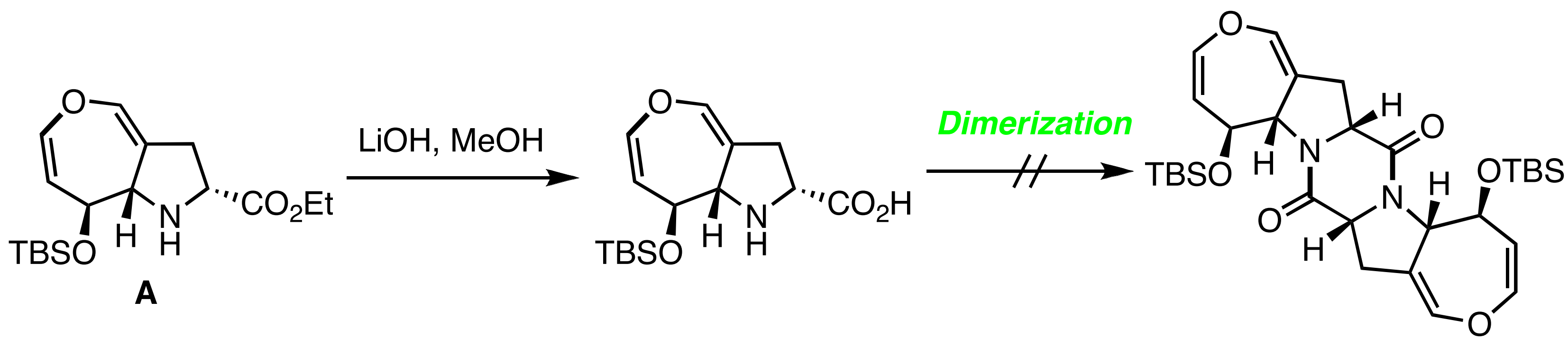
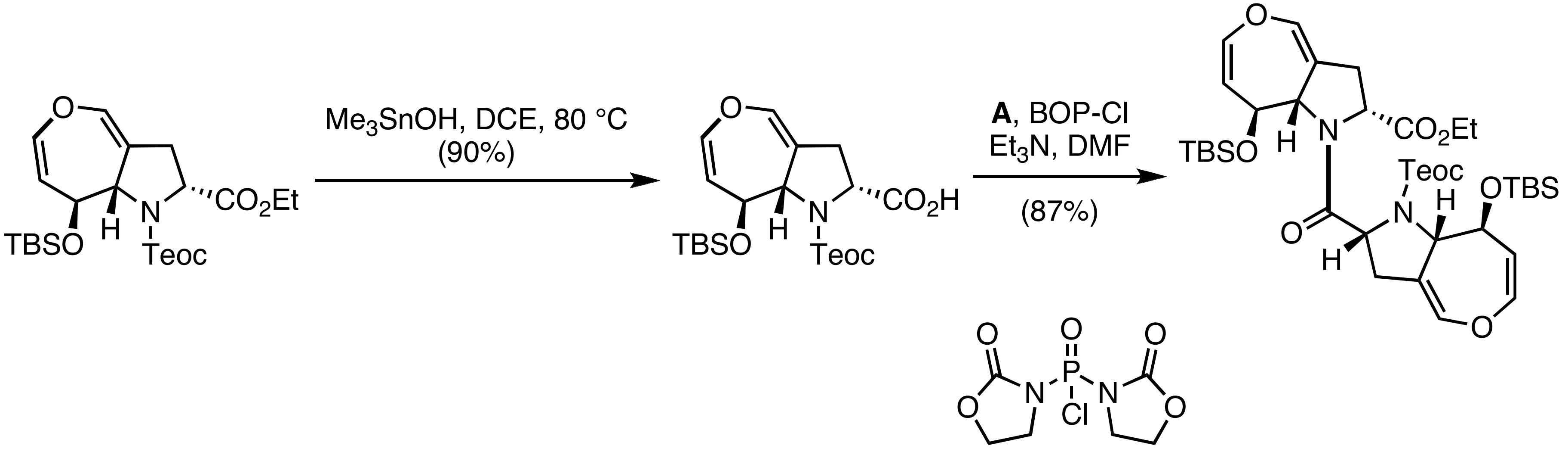
Synthesis of Acetylaranotin

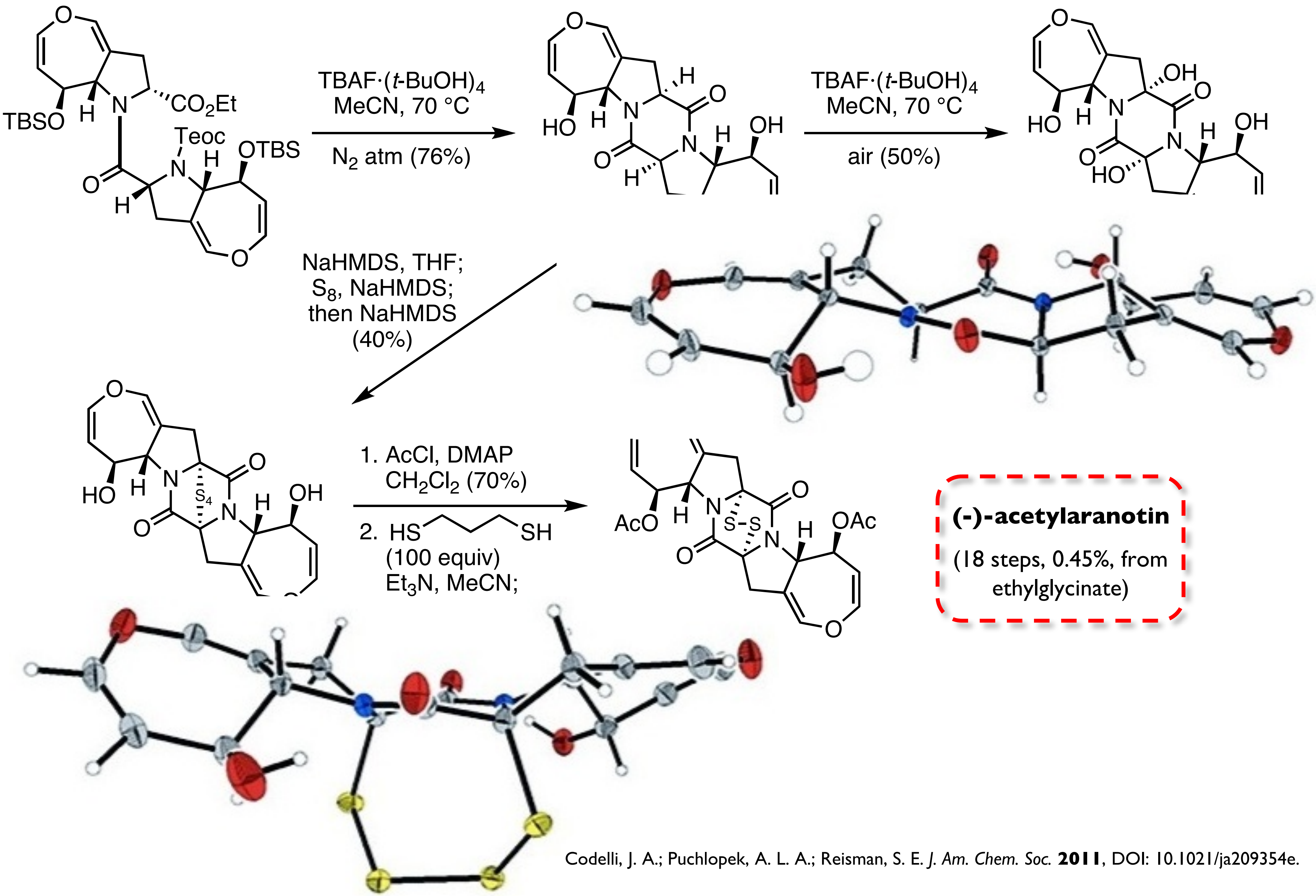




BOP-Cl

Codelli, J. A.; Puchlopek, A. L. A.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, DOI: 10.1021/ja209354e.

Synthesis of Acetylaranotin



TBAF·(*t*-BuOH)$_4$
MeCN, 70 °C
N_2 atm (76%)

TBAF·(*t*-BuOH)$_4$
MeCN, 70 °C
air (50%)

NaHMDS, THF;
S_8, NaHMDS;
then NaHMDS
(40%)

1. AcCl, DMAP
CH_2Cl_2 (70%)
2. HS∕∖∕SH
(100 equiv)
Et_3N, MeCN;

(-)-acetylaranotin
(18 steps, 0.45%, from ethylglycinate)

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Conclusion

- Completed the first total synthesis of (-)-acetylaranotin in 18 steps (~0.45 % yield)
- Synthetic highlights include:
  - Rhodium-catalyzed cycloisomerization/chloride elimination to provide dihydrooxepine
  - Azomethine ylide (1,3)-dipolar cycloaddition gave stereoselective access to functionalized pyrrolidine
  - Complete retention of steroechemistry during epitetrathiodiketo-piperazine formation