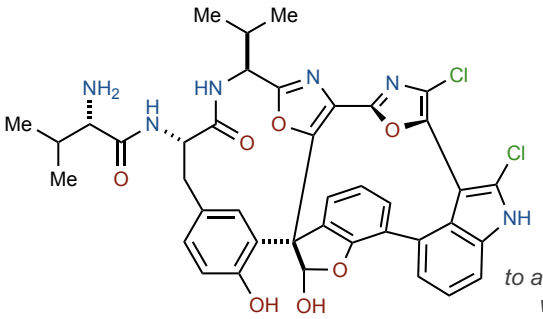
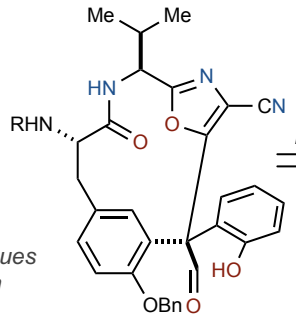
Diazonamide A (Harran, 2003)

- IC_{50} < 15 ng/mL (HCT-166)
- Unknown mechanism
- Low isolation yield
- Highly unsaturated halogenated cyclic peptide containing *Tyr*, *Trp*, *Val*
- Potential atropoisomers



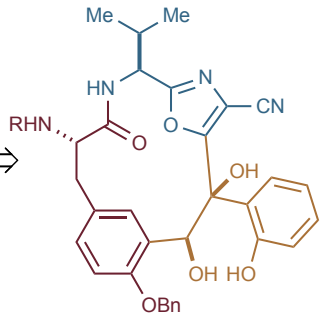
diazonamide A

Aryl-Coupling

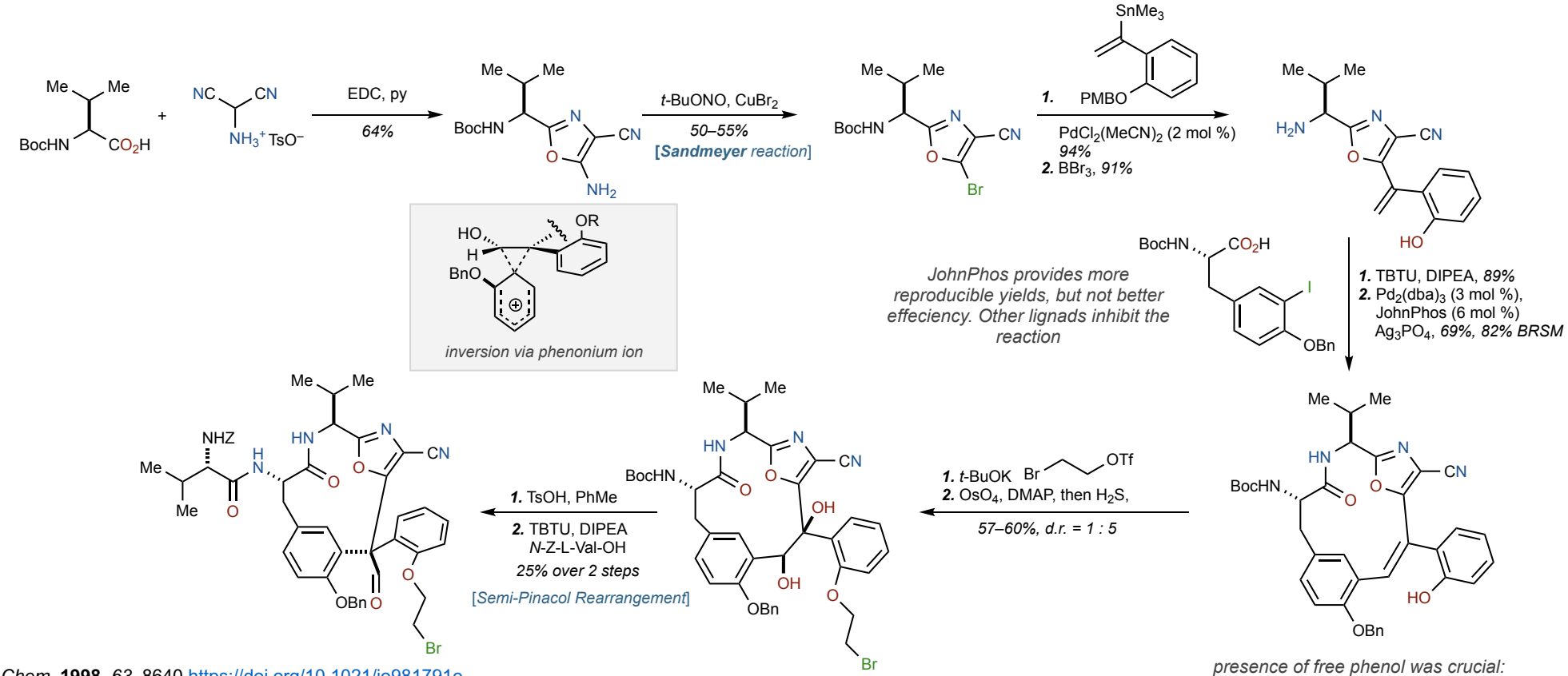


to avoid complicating issues with atropoisomerism

Ring-Contraction



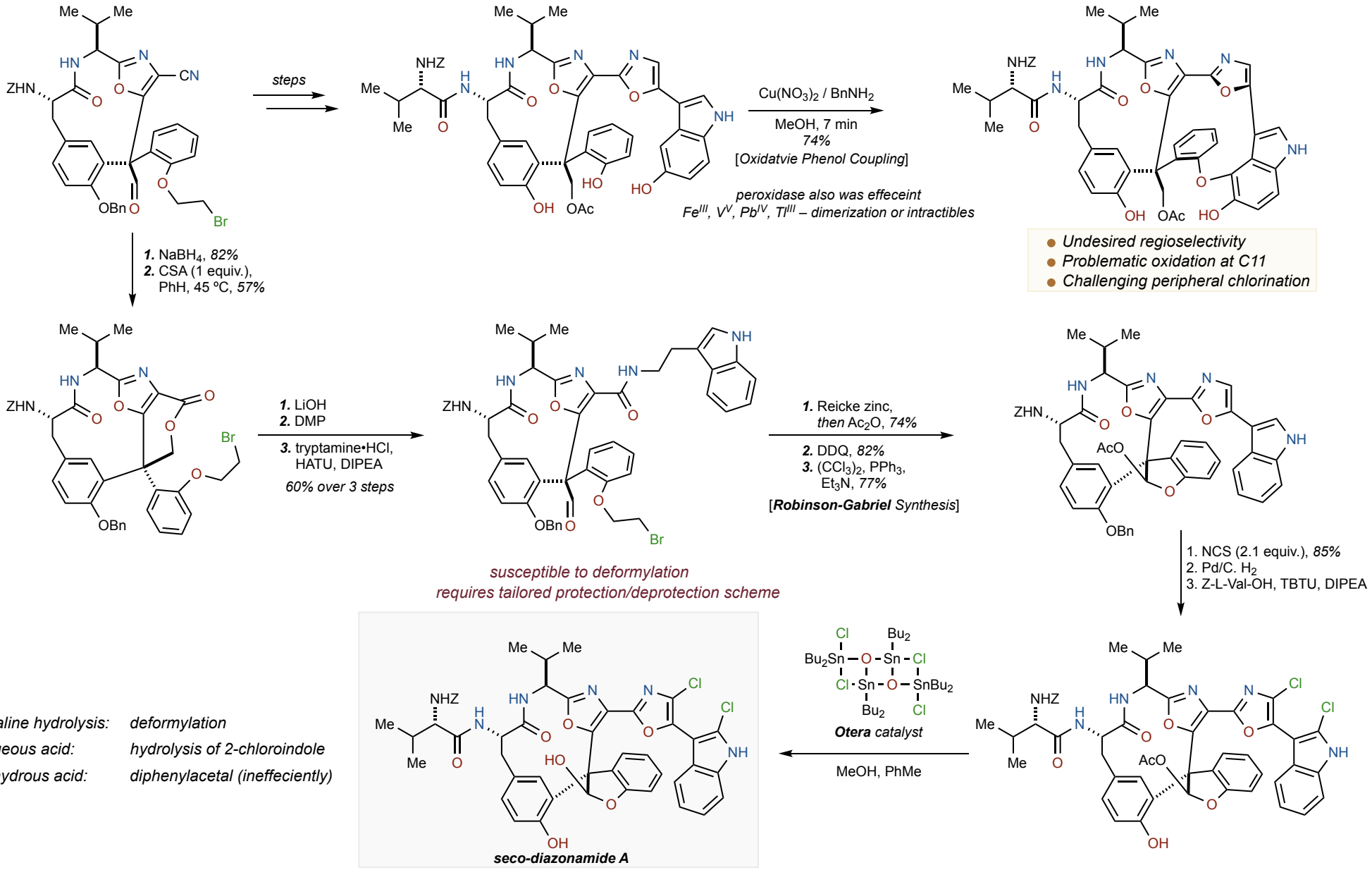
Isolaition: Fenical W. *J. Am. Chem. Soc.* **1991**, *113*, 2303
https://doi.org/10.1021/ja00006a060



J. Org. Chem. **1998**, *63*, 8640 https://doi.org/10.1021/jo981791e
Angew. Chem. Int. Ed. **2000**, *39*, 937 https://doi.org/10.1002/(SICI)1521-3773(20000303)39:5<937::AID-ANIE937>3.0.CO;2-A

Diazonamide A (Harran, 2003)

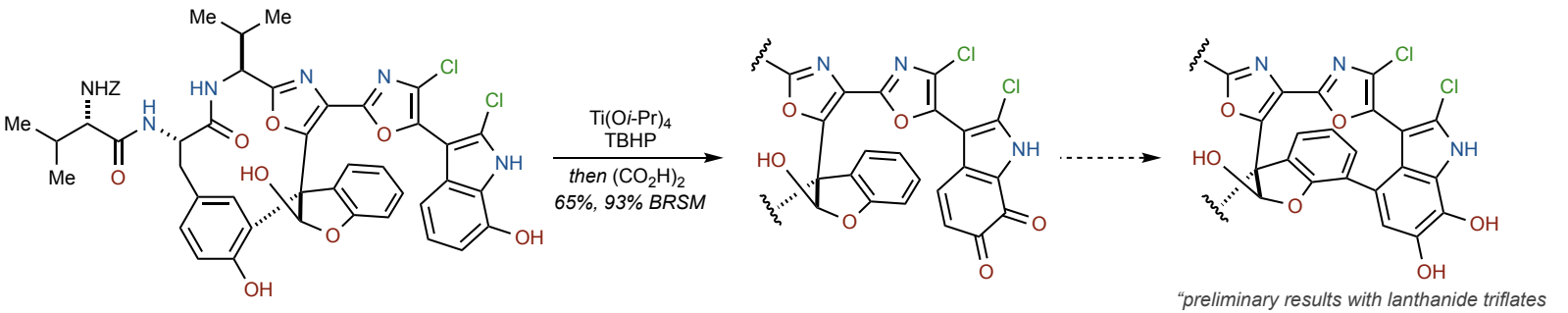
Angew. Chem. Int. Ed. **2001**, *40*, 2682 https://doi.org/10.1002/1521-3773(20010716)40:14<2682::AID-ANIE2682>3.0.CO;2-R



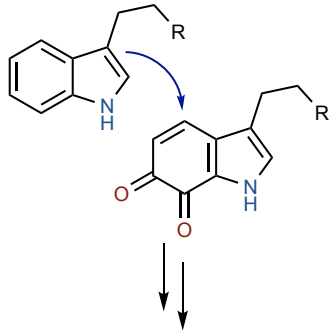
- *alkaline hydrolysis:* *deformylation*
- *aqueous acid:* *hydrolysis of 2-chloroindole*
- *unhydrous acid:* *diphenylacetal (ineffeciently)*

Diazonamide A (Harran, 2003)

Two-electron Oxidation Approach



Analogous Process in Biosynthesis

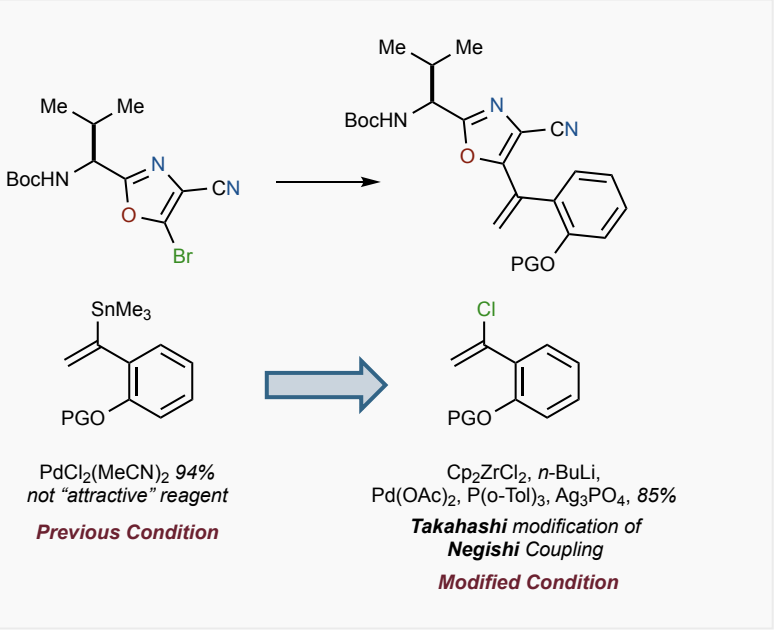


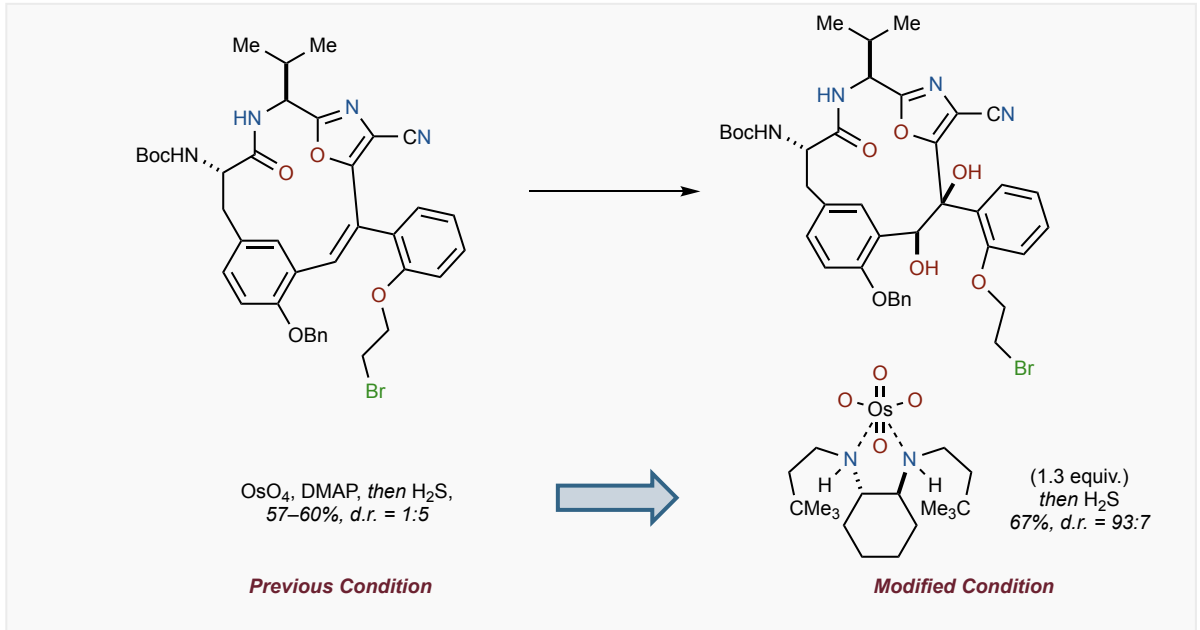
Tryptophan Tryptophylquinone Prosttetic Cofactor

Angew. Chem. Int. Ed. **2001**, *40*, 4765
https://doi.org/10.1002/1521-3773(20011217)40:24<4765::AID-ANIE4765>3.0.CO;2-1

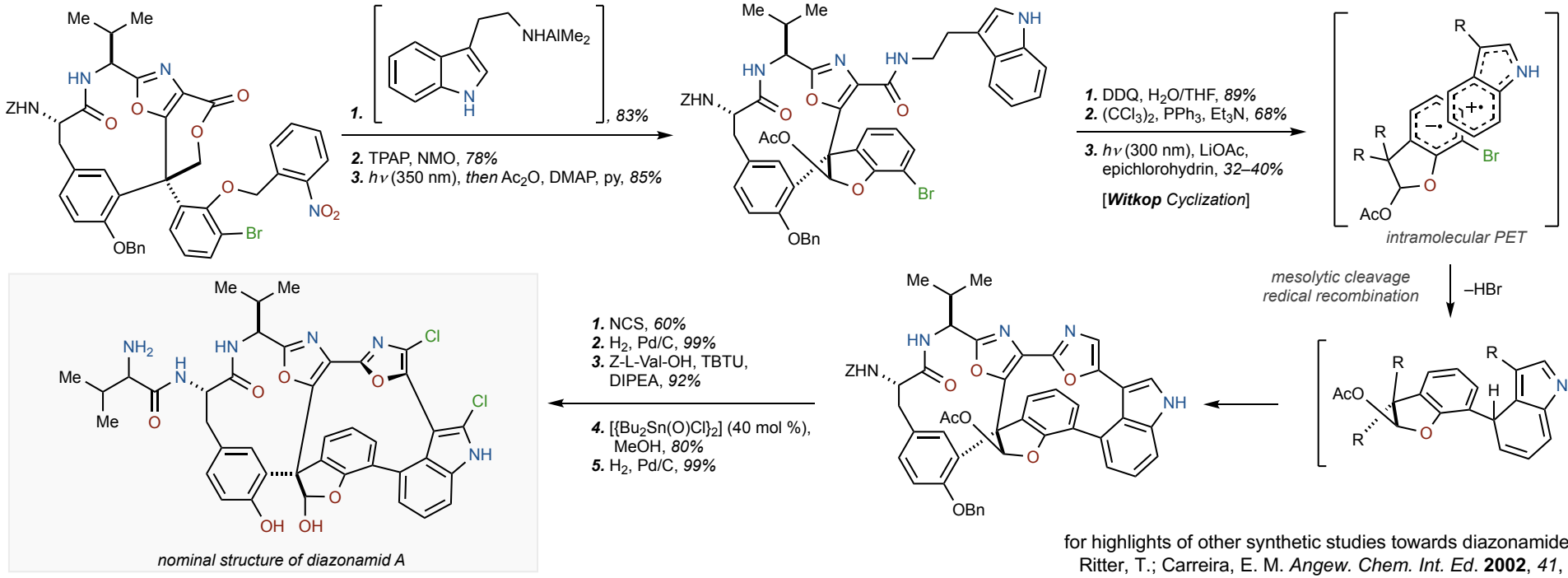
Angew. Chem. Int. Ed. **2001**, *40*, 4770
https://doi.org/10.1002/1521-3773(20011217)40:24<4770::AID-ANIE4770>3.0.CO;2-T

Advancements in the Synthetic Route



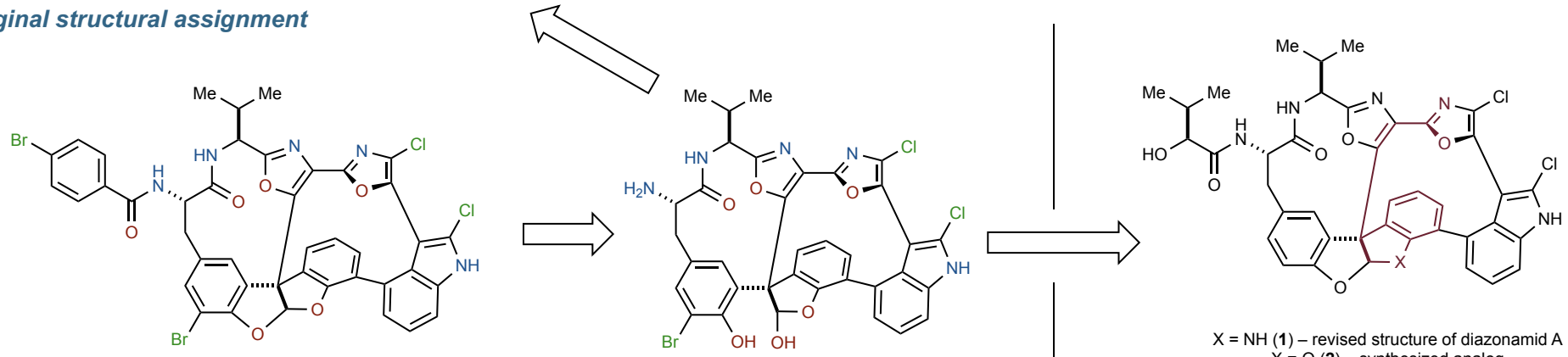


Diazonamide A (Harran, 2003)



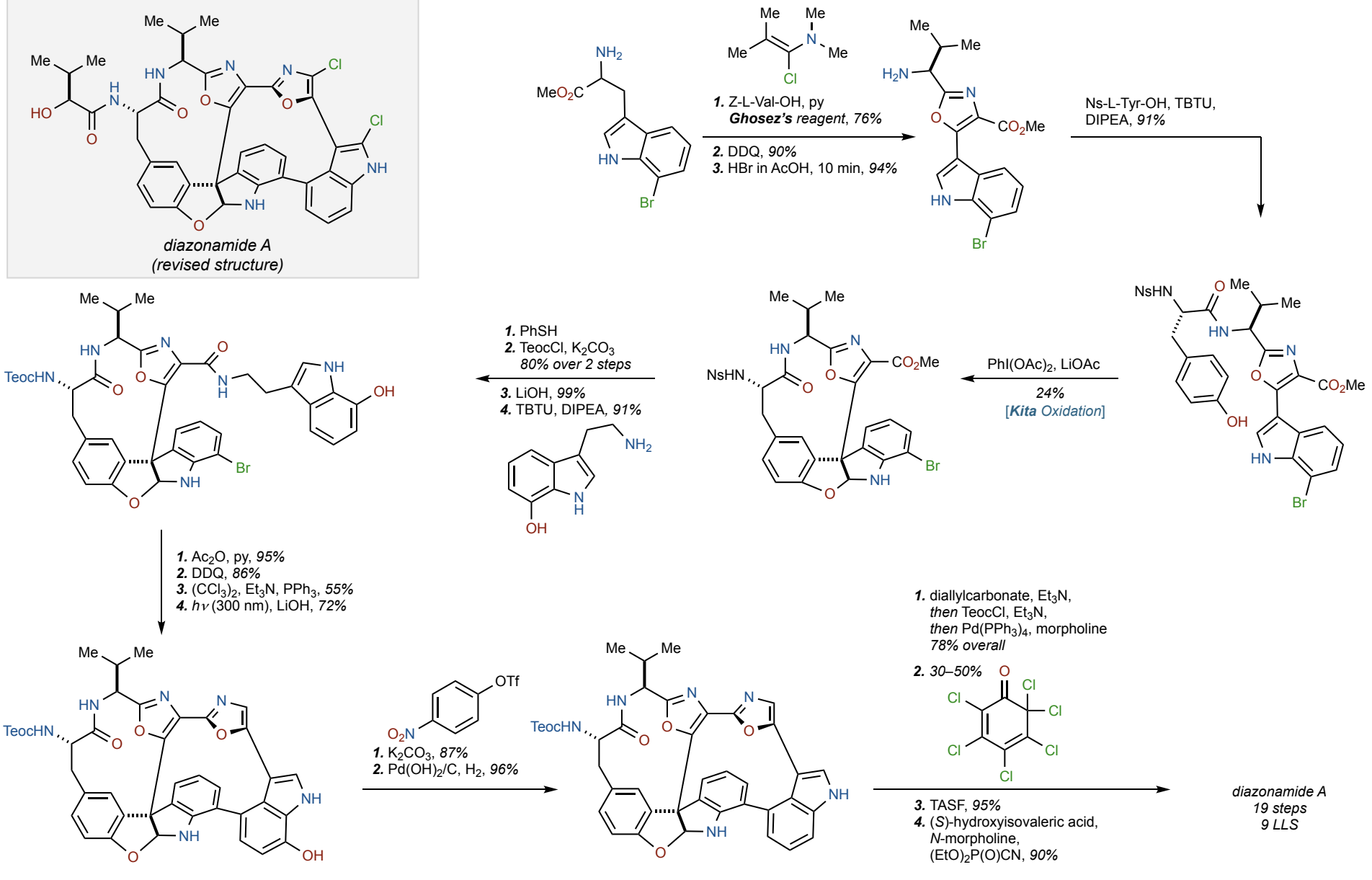
for highlights of other synthetic studies towards diazonamide see:
Ritter, T.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2002**, *41*, 2489
https://doi.org/10.1002/1521-3773(20020715)41:14<2489::AID-ANIE2489>3.0.CO;2-V

Original structural assignment



Diazonamide A (Harran, 2003)

Angew. Chem. Int. Ed. **2003**, *42*, 4961 https://doi.org/10.1002/anie.200352577



Diazonamide A (Harran, 2003)

Tubulin-binding toxins are clinically effective as cancer chemotherapy:

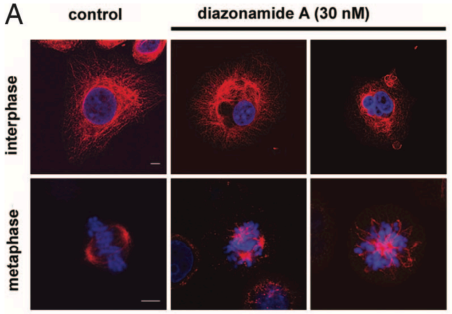
- Vinca alkaloids
- Colchicine
- Paclitaxel

Despite the diverse array of spindle proteins, only tubulin-binding agents are currently in clinical use

Drawbacks:
Microtubule poisons disturb nonmitotic functions of the cytoskeleton in both replicating cells and differentiated nondividing cells

Side-effects:

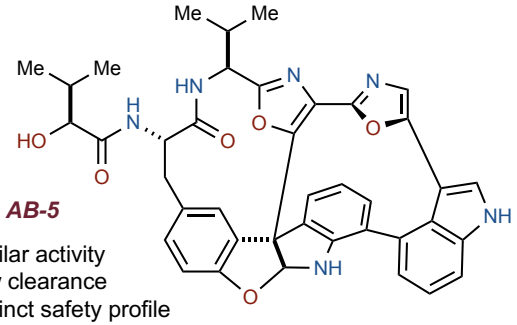
- chemotherapy-induced peripheral neuropathy
- bone marrow suppression
- hypersensitivity reactions
- dose-limiting toxicity



PNAS **2007**, *104*, 2068 https://doi.org/10.1073/pnas.0610832104
PNAS **2007**, *104*, 2074 https://doi.org/10.1073/pnas.0611340104

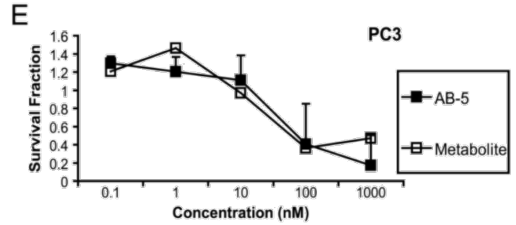
Observations of Diazonamide A Function:

1. Antimitotic activity. G2/M phase growth arrest
2. Multinucleation phenotype
3. NCI's COMPARE display similarity with vinblastin
4. No detection of complex with tubulin or microtubules *in vitro* using biotinylated or radiolabeled congeners. However, efficient induction of spindle abnormalities during mitosis



AB-5

- Similar activity
- Low clearance
- Distinct safety profile
- Outperformed Paclitaxel and vinblastin sulfate in toxicological testing

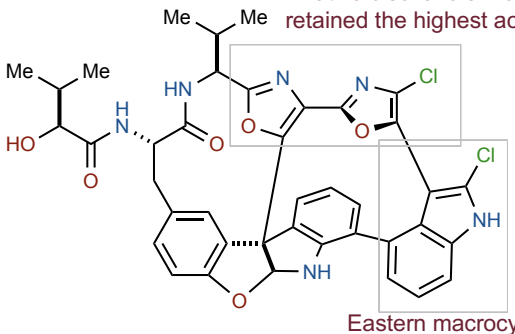


Diazon Pharmaceuticals

SAR-studies

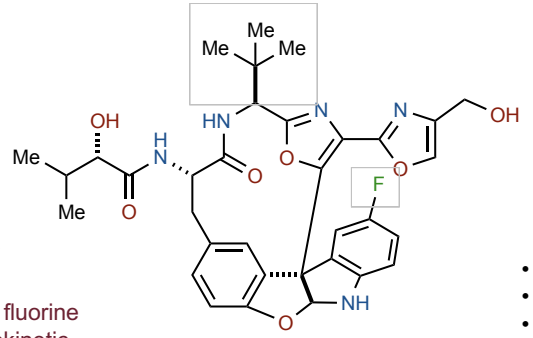
Hundreds of analogues tested

Native bisoxazole moiety retained the highest activity



Eastern macrocycle and the ansa-bridged indole moiety are not necessary for activity

Tert-butyl group and fluorine improved pharmacokinetic profile

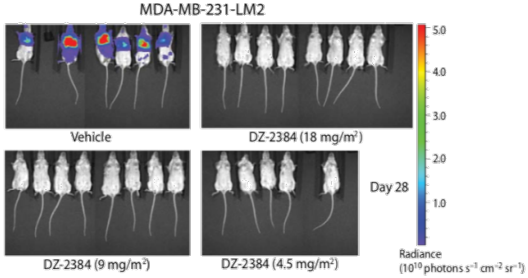


DZ-2384

Tested disease models:

1. Metastatic breast cancer
2. Acute lymphocytic leukemia
3. Pancreatic adenocarcinoma
4. Colon cancer

lacks neurotoxicity at effective doses

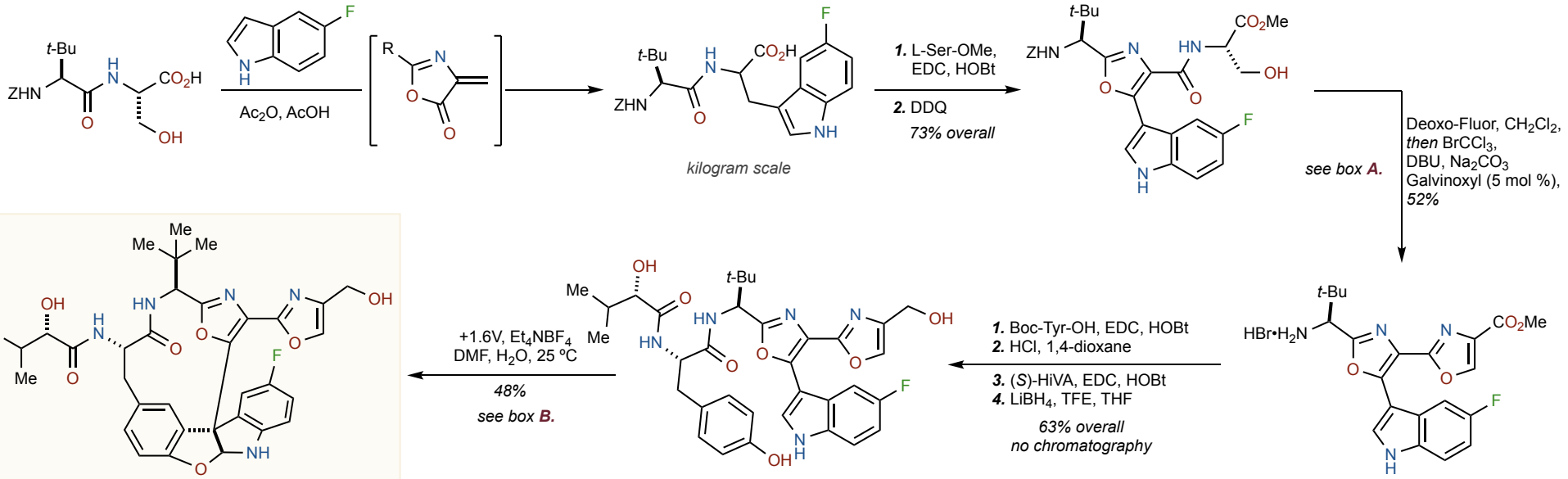


- Competitive binding to tubilin with vinorelbine
- Binding to vinca alkaloid site
- Mild effect on interphase and mitotic microtubule networks
- Pronounced straightening in the curvature and pitch of microtubule protofilaments upon formation of DZ- 2384−tubulin complexes

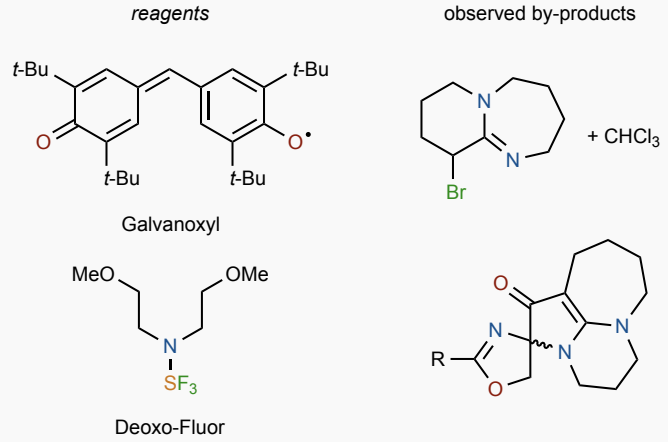
Sci, Transl. Med. **2016**, *8*, 365ra159 https://doi.org/10.1126/scitranslmed.aag1093

Diazonamide A (Harran, 2003)

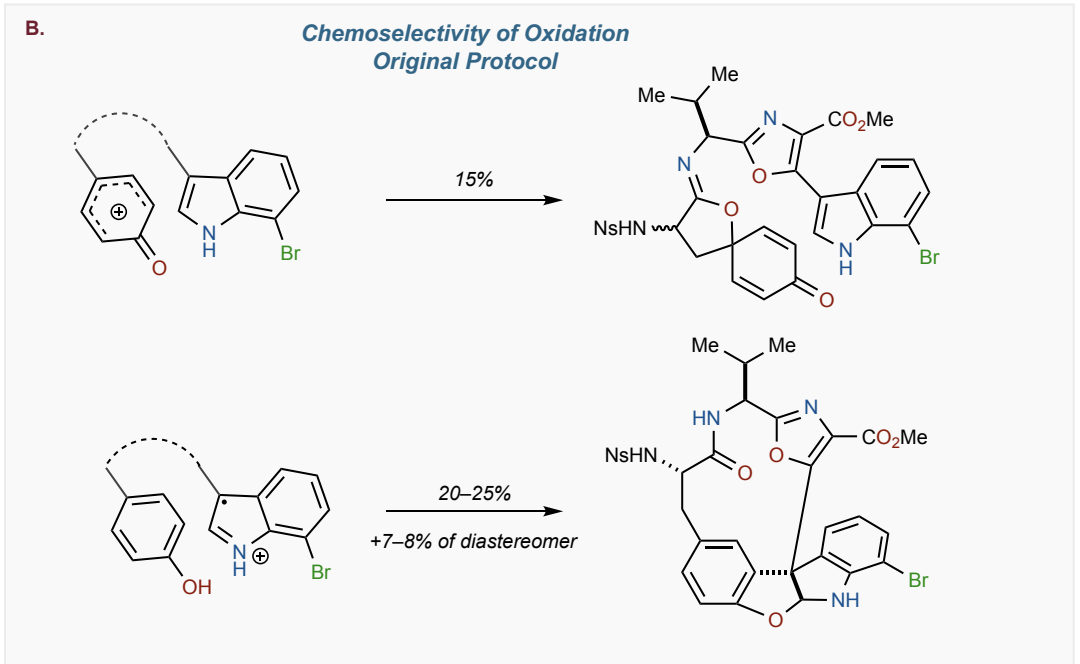
Angew. Chem. Int. Ed. **2015**, *54*, 4818 https://doi.org/10.1002/anie.201411663



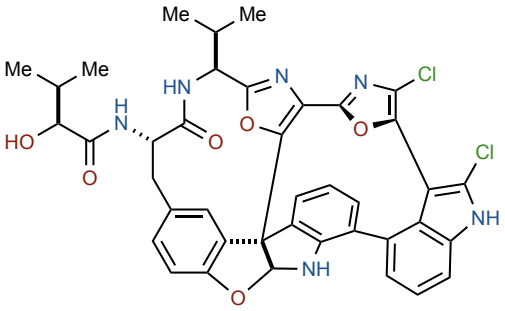
A.



B.



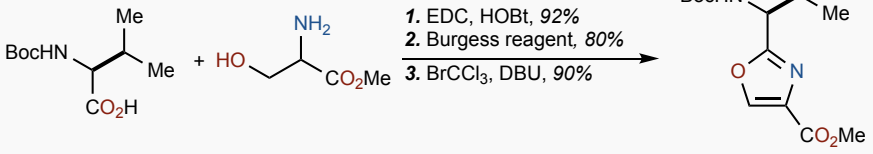
Diazonamide A (Nicolaou, 2002)



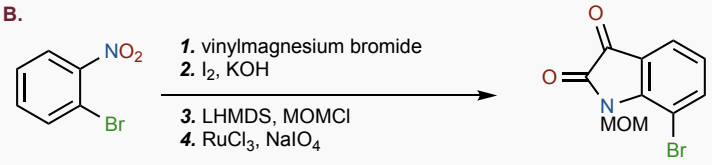
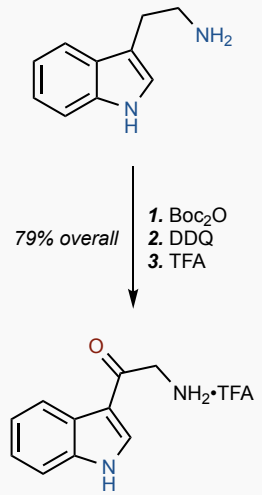
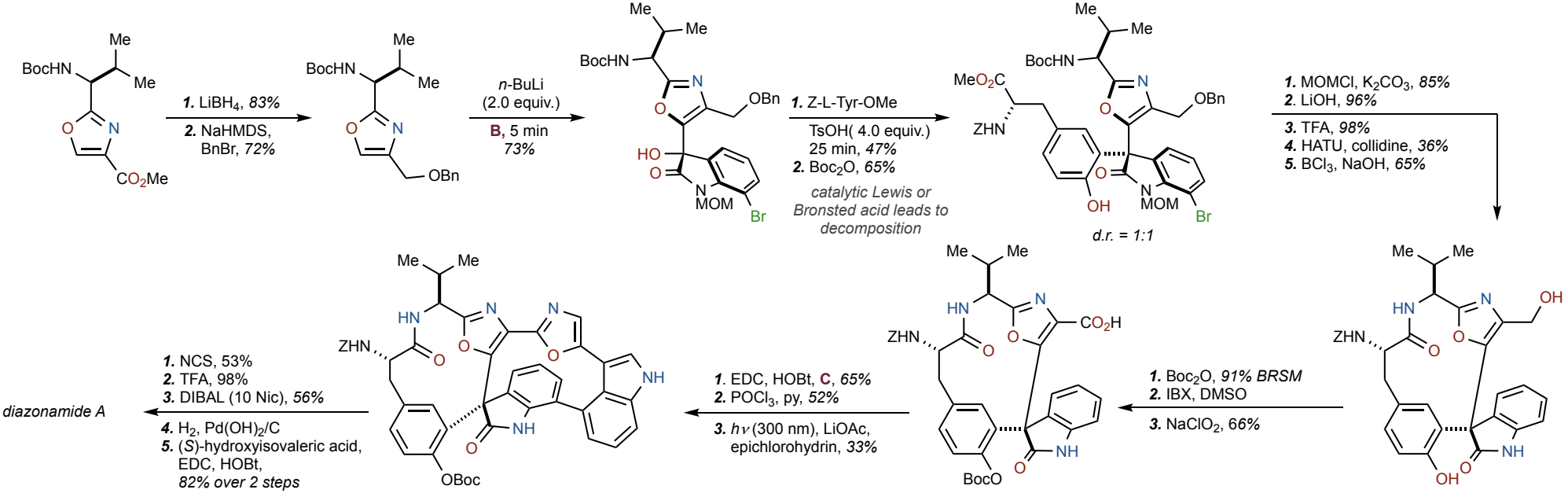
Angew. Chem. Int. Ed. **2002**, *41*, 3495
J. Am. Chem. Soc. **2004**, *126*, 10162
J. Am. Chem. Soc. **2004**, *126*, 10174
J. Am. Chem. Soc. **2004**, *126*, 12888

Synthesis of Fragments

A.



B.



C.