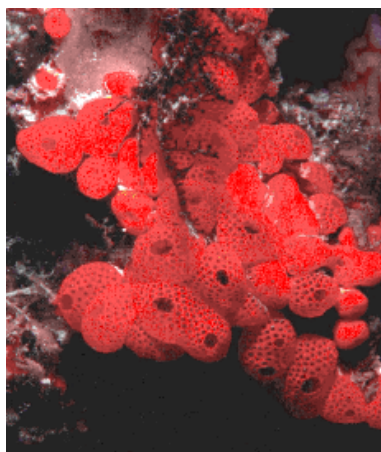


Harran's First total synthesis of Diazonamide A



Jing Li, Susan Jeong, Lothar Esser, and Patrick G. Harran*
Angew. Chem. Int. Ed. **2001**, 40, 4765-4769

Presented by
SRINIVASA RAO CHINTALA

Efforts toward the Total Synthesis of Diazonamide A

Total Syntheses



Nicolaou
"2002, 2003"



Harran
2003



David MacMillan



Fu



Vedejs

Contributions



Wood

Patrick G. Harran

- ❖ 1990: B.A. Skidmore College
- ❖ 1995: Ph.D. Yale University
- ❖ 1995 – 1997: Stanford University, NIH Postdoctoral Fellow
- ❖ 1997-2008: Associate professor, University of Texas Southwestern Medical Center
- ❖ 2008- Present: Professor, University of California, Los Angeles



The Origin of Diazonamide



✓ Isolated from the colonial ascidian *Diazona angulata*

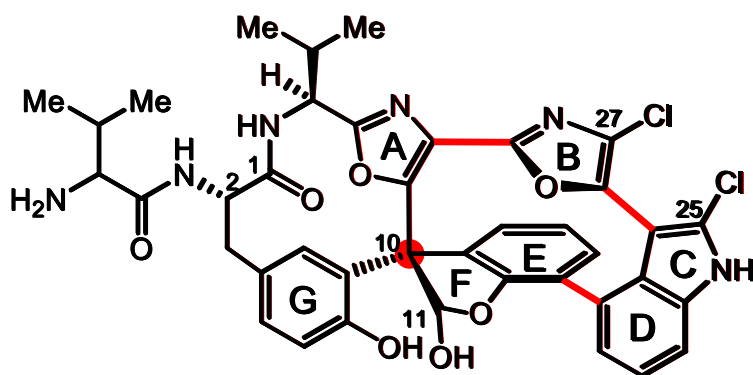
✓ Collected from the ceilings of caves along the northwest coast of Siquijor Island in the Philippines

Exhibits antimicrobial, cytotoxic, and antiviral activities



Why Is this Molecule So Interesting?

Over the years, many groups focused their efforts towards the synthesis of Diazonamide A. Only K. C. Nicolaou's and P. G. Harran's groups had been able to complete the total synthesis of the molecule.

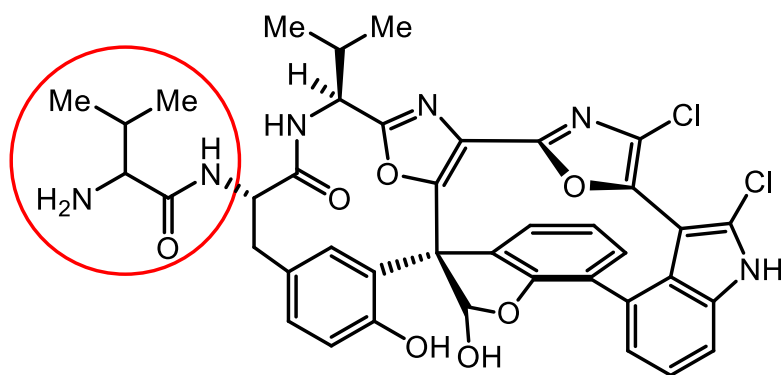


Initially proposed structure

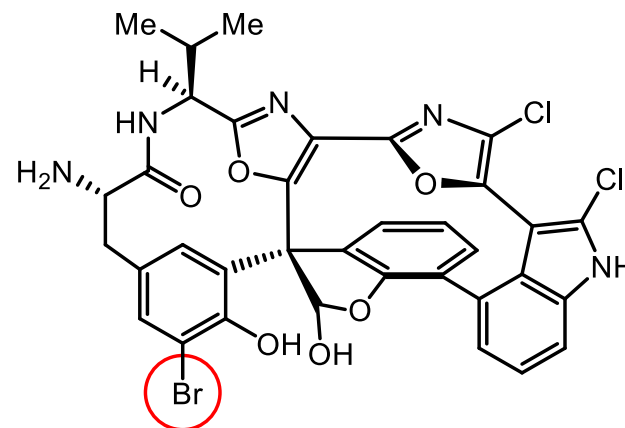
- ✓ Diazonamide A has a IC_{50} of 2-5 nM against 4 human cancer cell lines (Diazonamide A is more potent than Diazonamide B)
- ✓ Molecule is trapped as a single atropisomer because of its rigidity
- ✓ Macrolactam unit
- ✓ Macrocyclic Heterocyclic core
- ✓ Quaternary center at the center of the molecule

Structures of Diazonamide A and B

Structures determined by William Fenical (Scripps Institution of Oceanography)
And Jon Clardy (Cornell University) in 1991



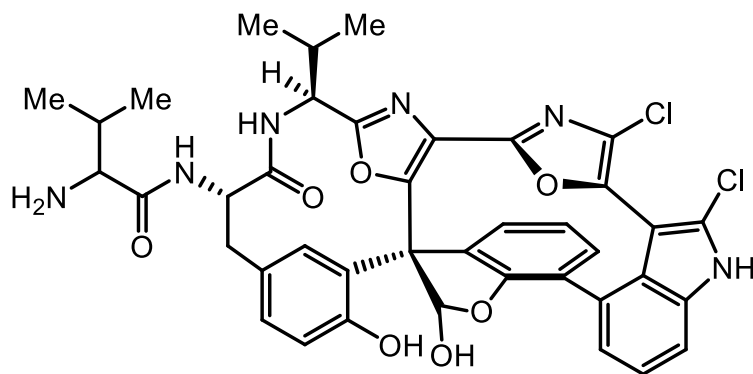
Diazonamide A



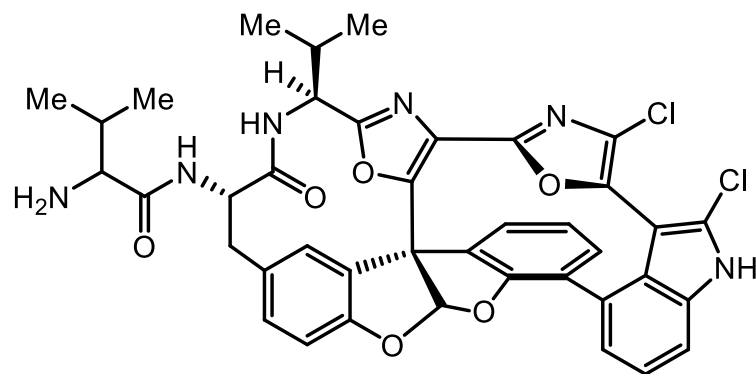
Diazonamide B

Diazonamide A Structure Revision

In 2001, P. G. Haran's group published the structure revision of Diazonamide



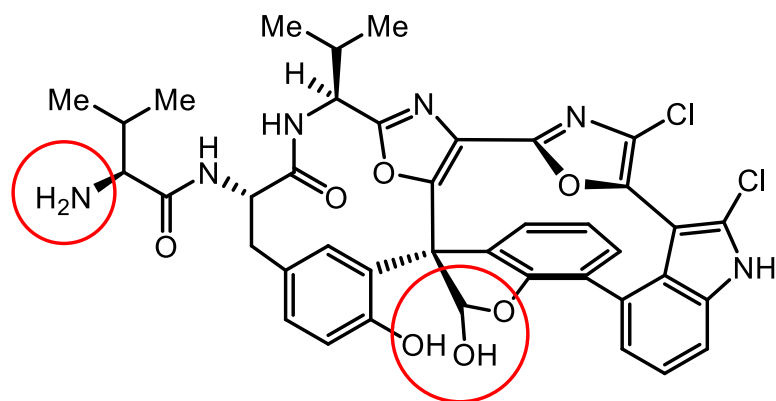
Originally proposed structure



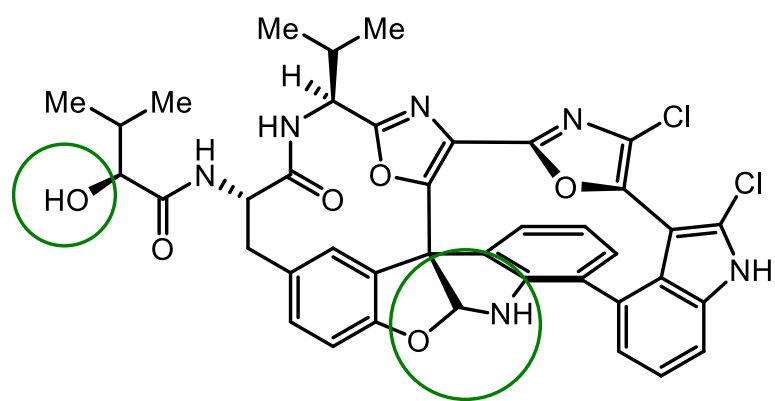
Dehydrated form

Mass spectroscopy and X-Ray appeared to coincide with the dehydrated form

Find the differences!



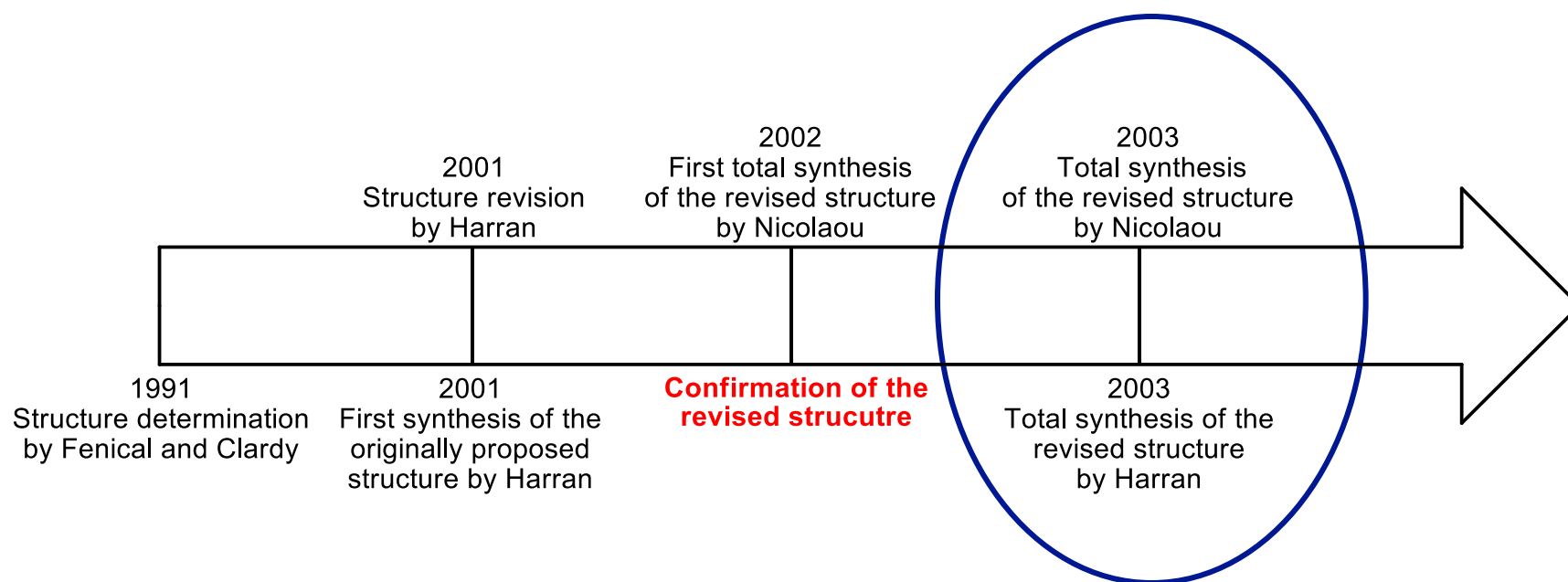
Original structure



Revised structure

**Later validated by
total synthesis**

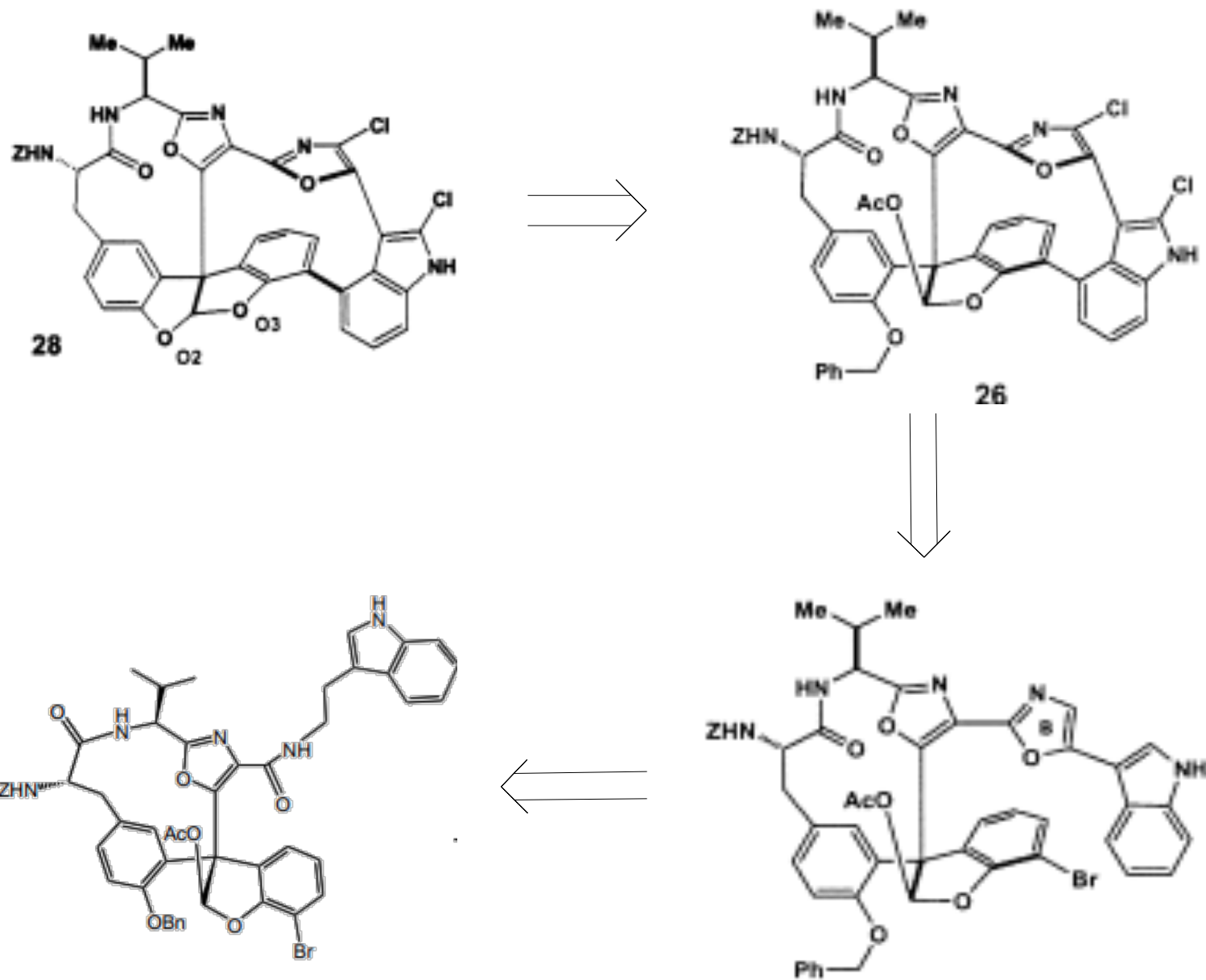
Diazonamide A Timeline Discovery

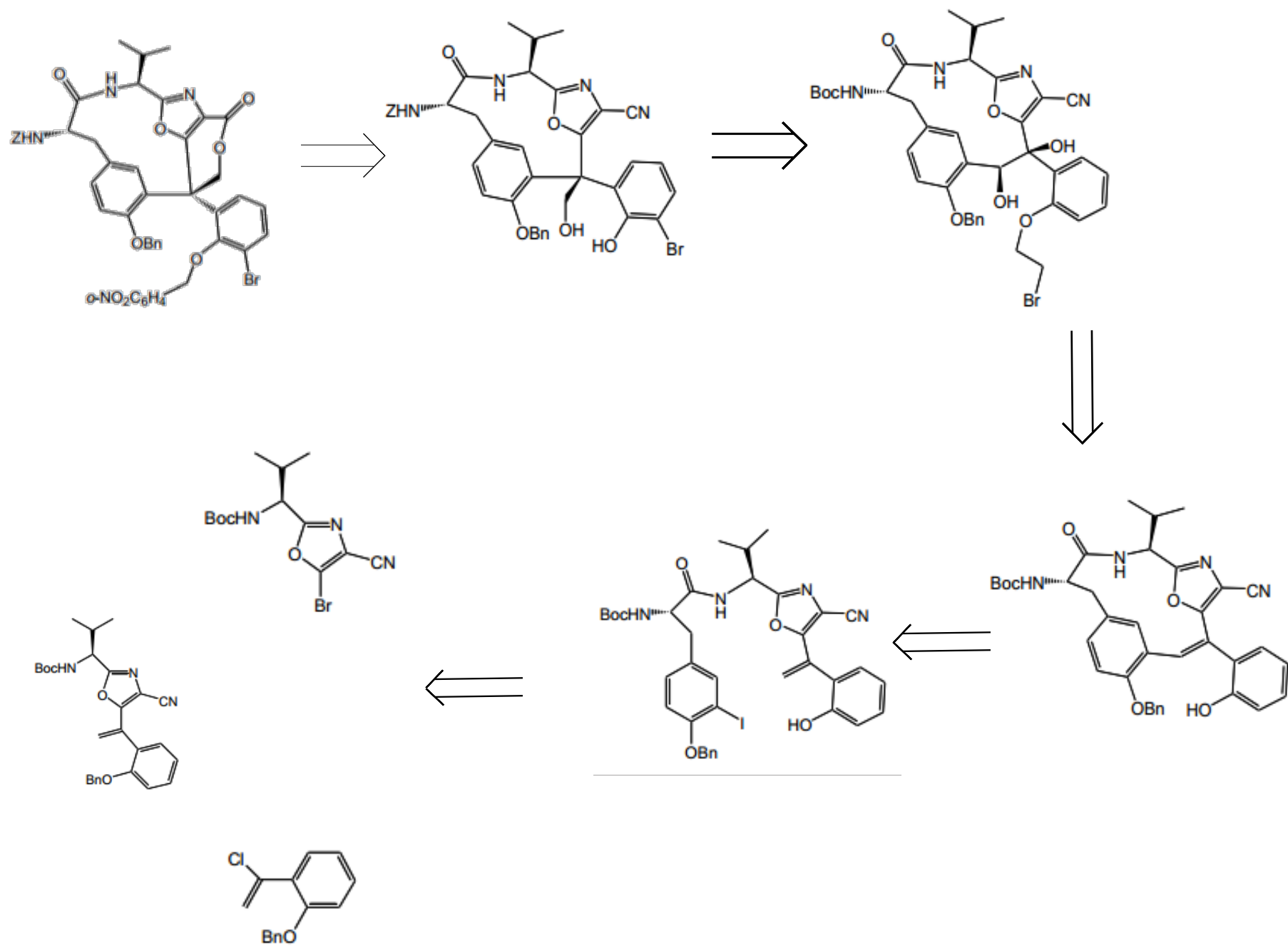


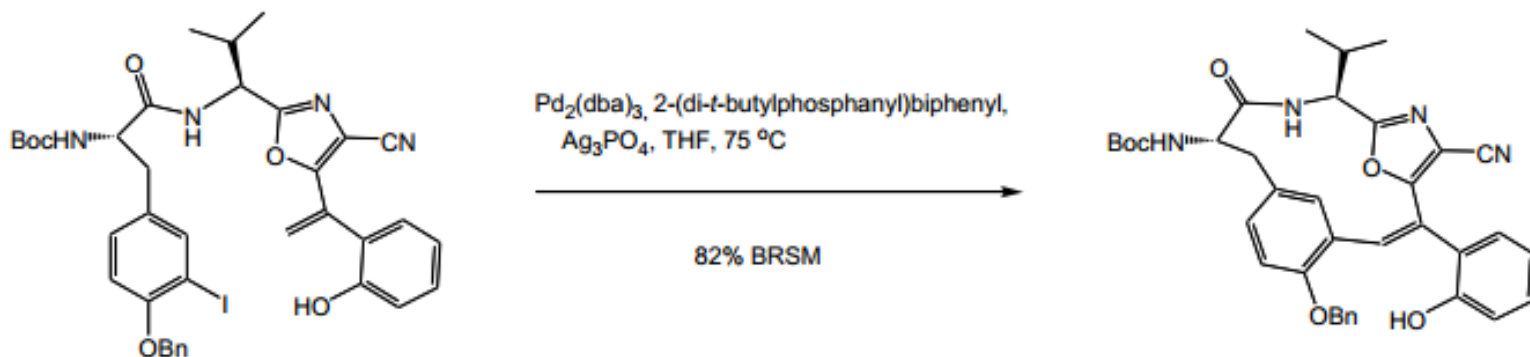
Fenical, W.; Clardy, J. *J. Am. Chem. Soc.* **1991**, 113, 2303
Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, 40, 4765
Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, 40, 4770
Nicolaou, K. C. *Angew. Chem., Int. Ed.* **2002**, 41, 3495

Nicolaou, K. C. *J. Am. Chem. Soc.* **2004**, 126, 12888
Nicolaou, K. C. *Angew. Chem., Int. Ed.* **2003**, 42, 1753
Nicolaou, K. C. *J. Am. Chem. Soc.* **2004**, 126, 12897
Harran, P. G. *Angew. Chem., Int. Ed.* **2003**, 42, 4961

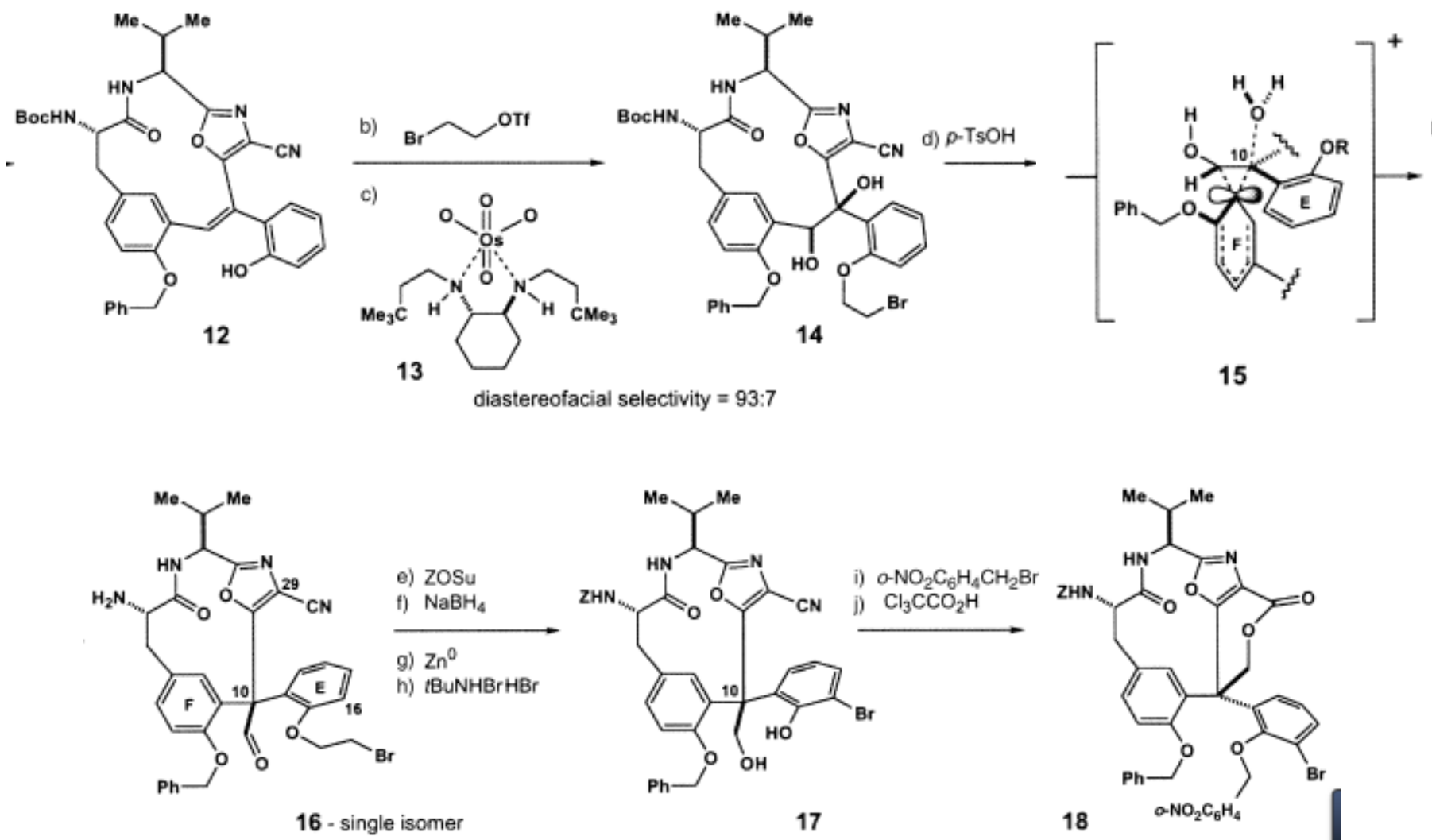
Retrosynthetic Analysis







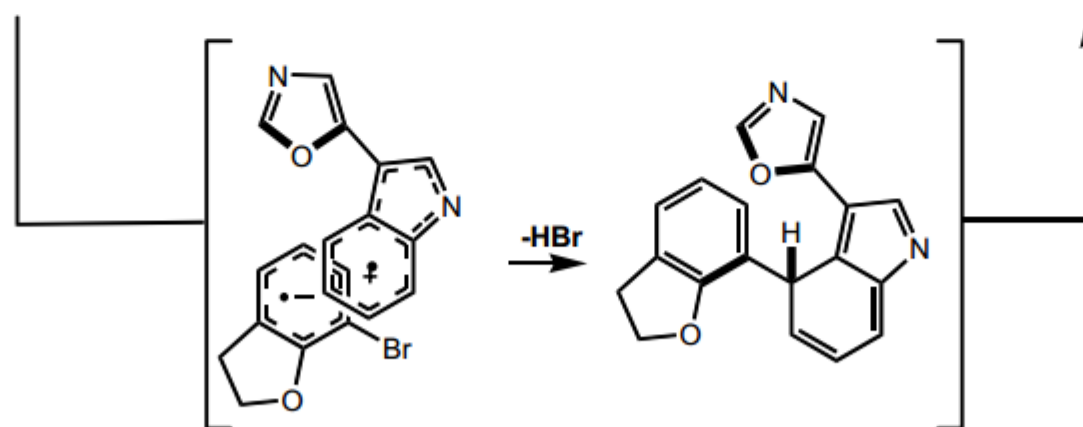
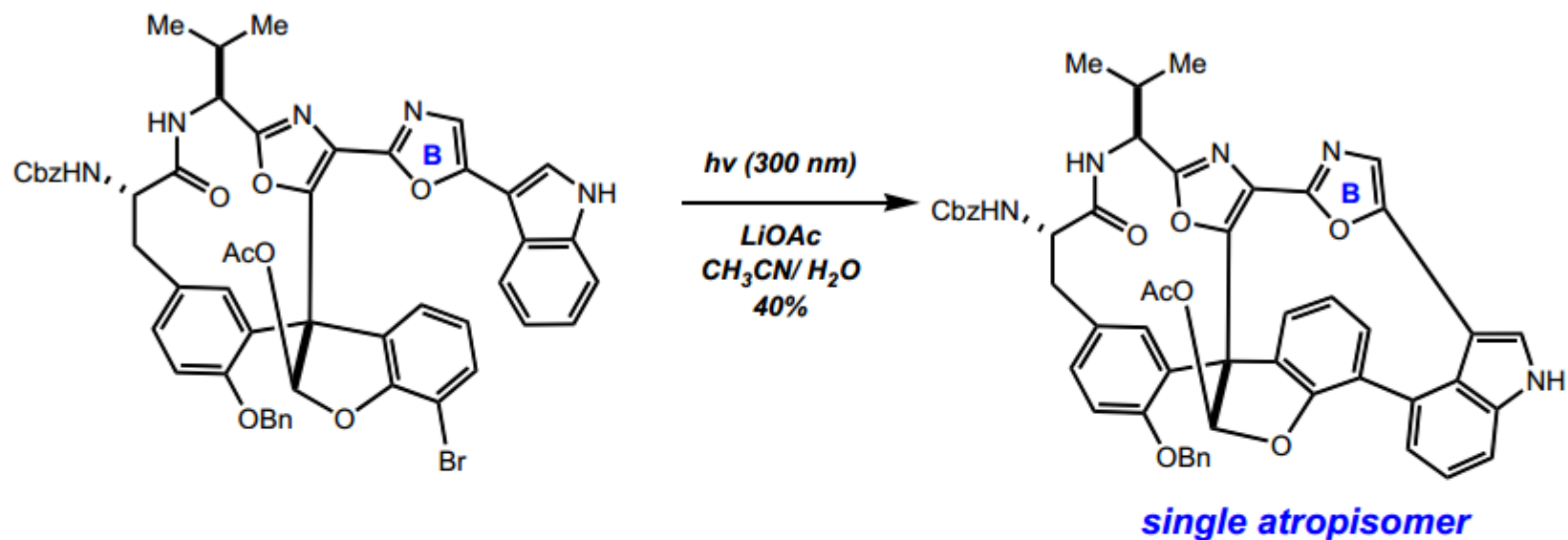
Harran's First Total Synthesis of Diazonamide A



Z= benzyloxycarbonyl; Su= N-succinimidyl

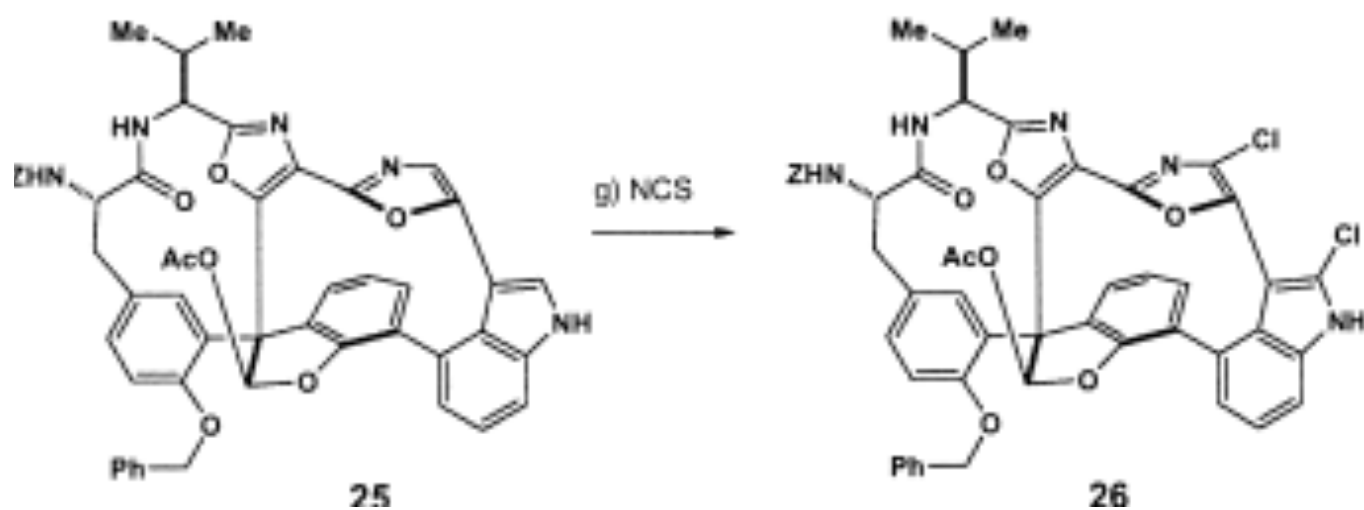


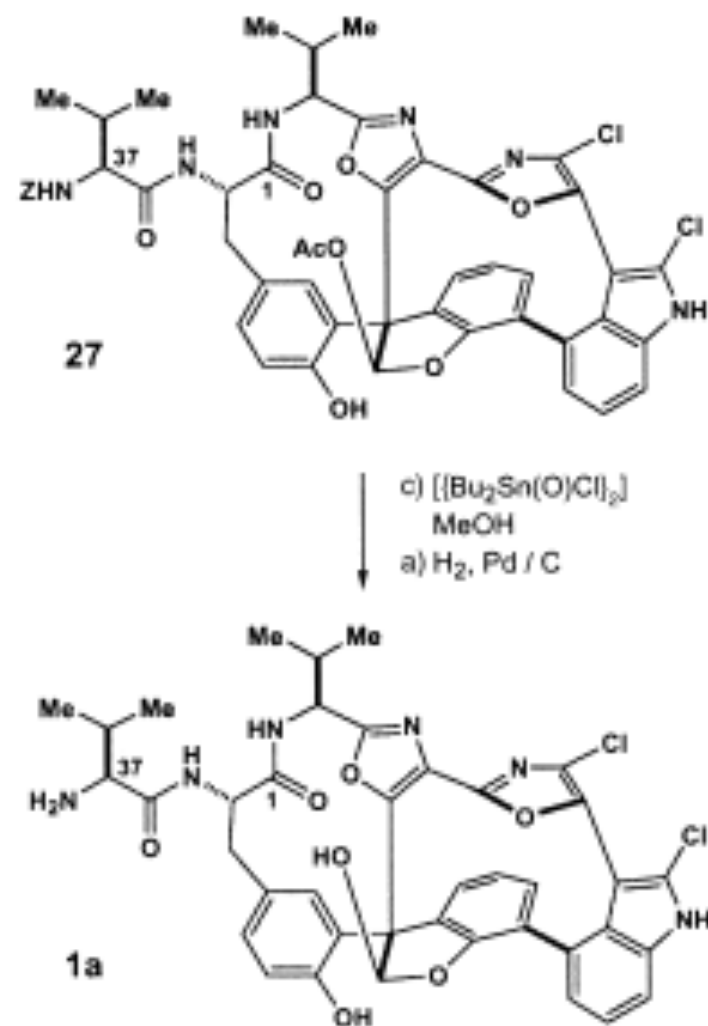
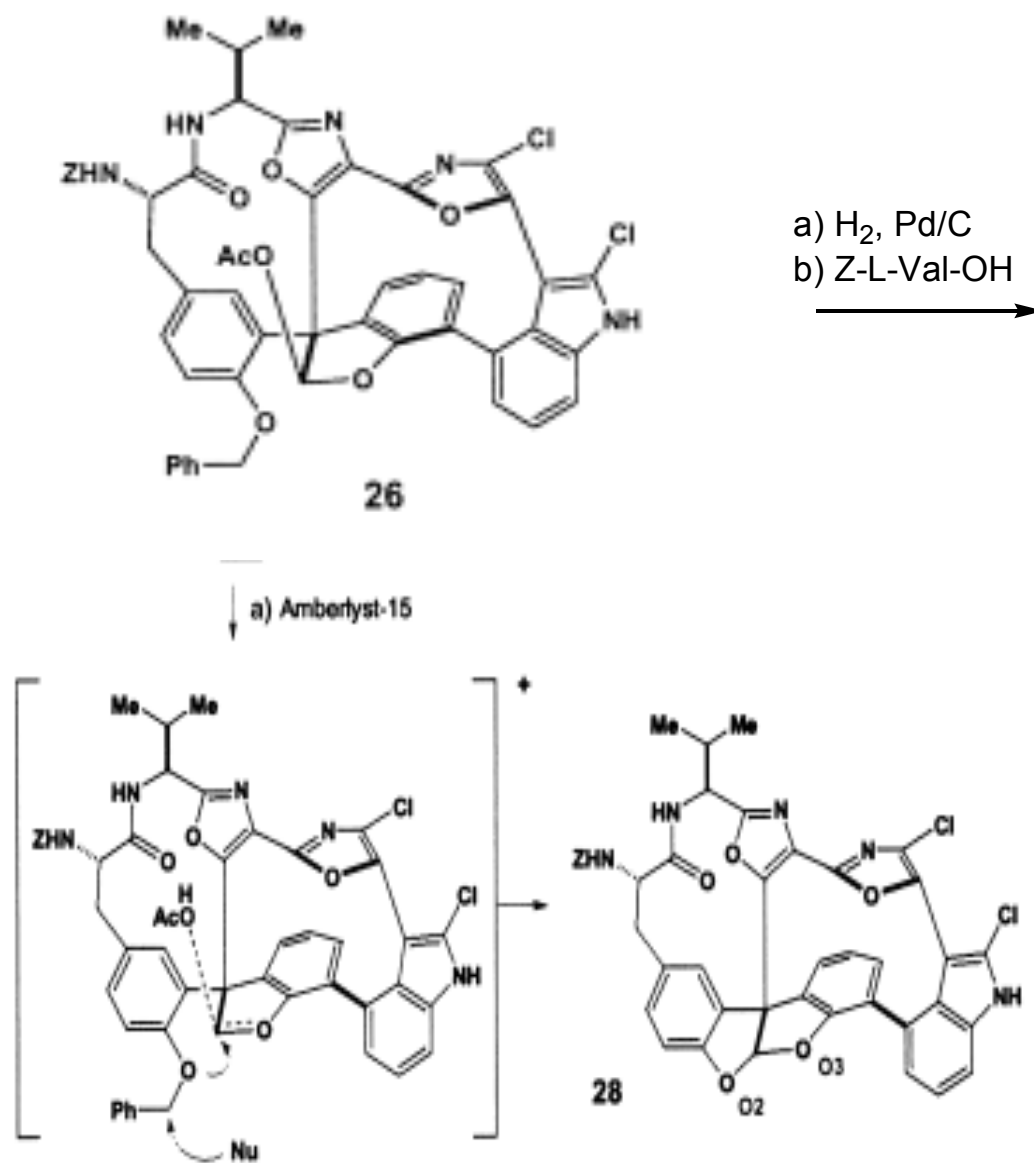
Witkop-type cyclization



Harran, P. G. *Angew. Chem. Int. Ed.* **2001**, 40, 4765
 Witkop, B. J. *Am. Chem. Soc.* **1966**, 88, 3941

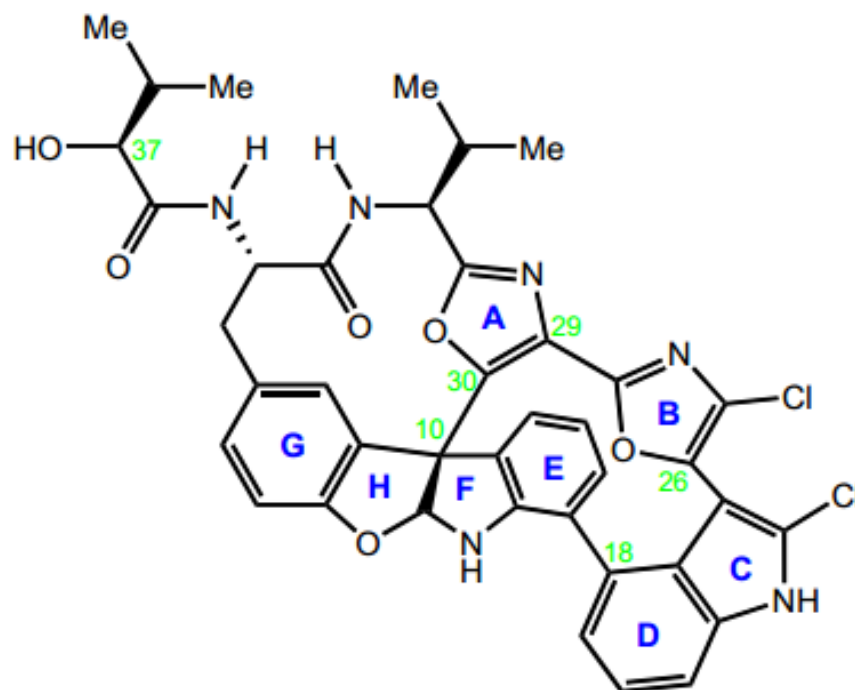
Harran's First Total Synthesis of Diazonamide A





Z-L-Val-OH= N-carbobenzyloxy-L-Valine

Summary



Harran
2001
23 steps
 $4.3 \times 10^{-4} \%$ overall yield

Nicolaou I
2002
24 steps
 $3.98 \times 10^{-4} \%$ overall yield

Nicolaou II
2003
31 steps
 $1.44 \times 10^{-4} \%$ overall yield

Harran
2003
19 steps
.01 % overall yield