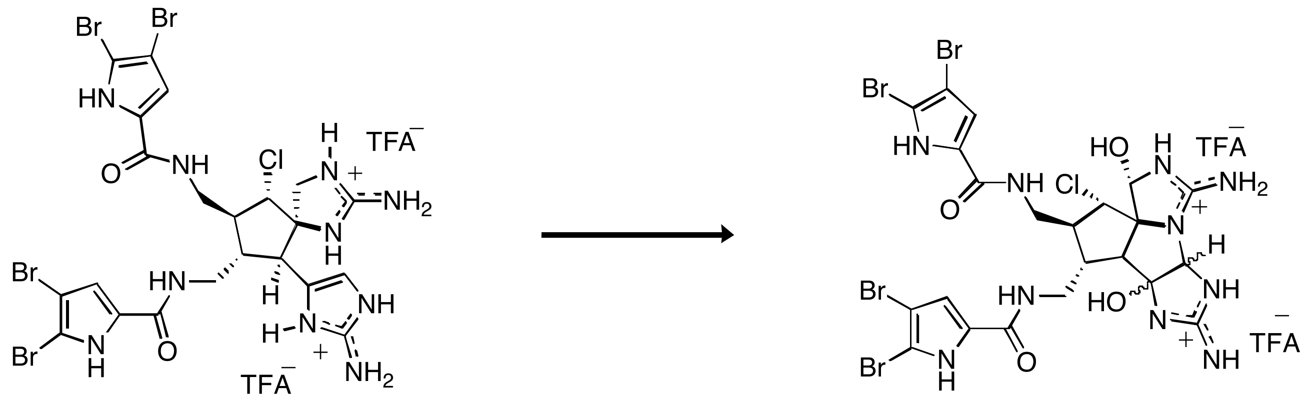
Baran Lab Syntheses of the Axinellamines:



Synthesis of 1,9-Dideoxy-pre-axinellamine:

Yamaguchi, J., Seiple, I. B., Young, I. S., O'Malley, D. P., Maue, M., Baran, P. S.;
ACIE, Early View DOI: 10.1002/anie.200705913

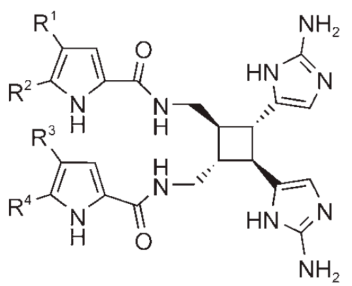
Total Synthesis of (±)-Axinellamines A and B:

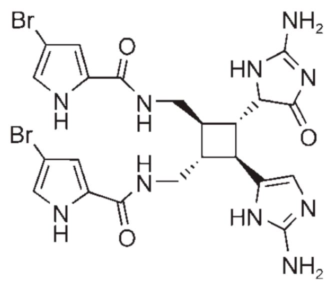
O'Malley, D. P., Yamaguchi, J., Young, J. S., Seiple, I. B., Baran, P.S.;
ACIE, Early View DOI: 10.1002/anie.200801138

Presented by: Melissa Sprachman
March 29, 2008

The Pyrrole-Imidazole Alkaloids

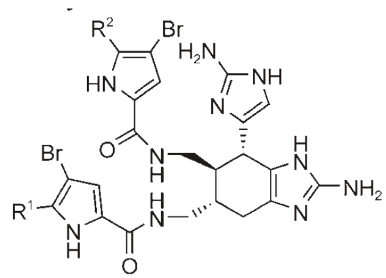
Mono-and Bicyclic Dimeric Pyrrole-Imidazole Alkaloids

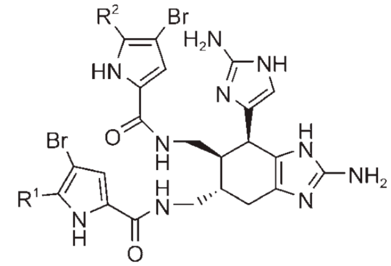




2: $R^1 = R^3 = Br$, $R^2 = R^4 = H$; sceptrin
3: $R^1 - R^4 = H$; debromosceptrin
4: $R^1 = Br$, $R^2 - R^4 = H$; monobromosceptrin
5: $R^1 - R^3 = Br$, $R^4 = H$; bromosceptrin
6: $R^1 - R^4 = Br$; dibromosceptrin

7: oxysceptrin

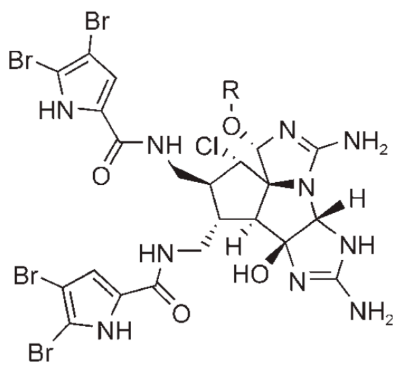




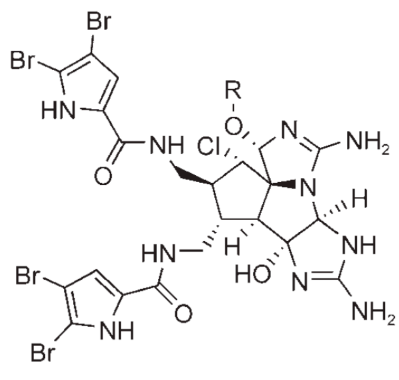
8: $R^1 = R^2 = H$; ageliferin
9: $R^1 = Br$, $R^2 = H$; bromoageliferin
10: $R^1 = R^2 = Br$; dibromoageliferin

11: $R^1 = R^2 = H$; nagelamide E
12: $R^1 = Br$, $R^2 = H$; nagelamide F
13: $R^1 = R^2 = Br$; nagelamide G

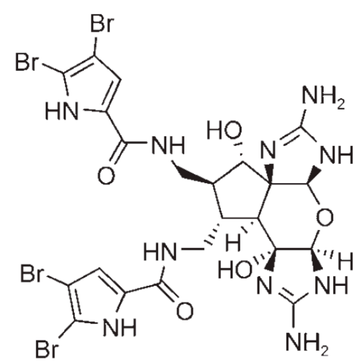
Tetracyclic Pyrrole-Imidazole Dimers



14: R = H; axinellamine A
15: R = Me; axinellamine C



16: R = H; axinellamine B
17: R = Me; axinellamine D

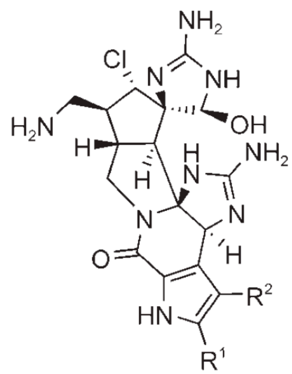


18: massadine

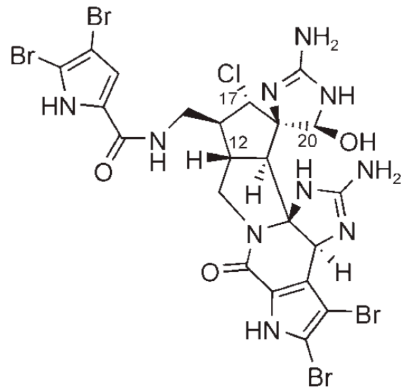
Copied from: Baran et al. *Angew. Chem. Int. Ed.* **2007**, *46,* 6586.

The Pyrrole-Imidazole Alkaloids (continued)

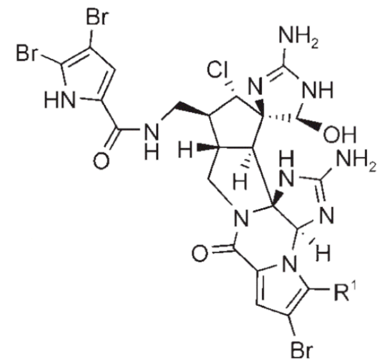
Hexacyclic Pyrrole-Imidazole Dimers



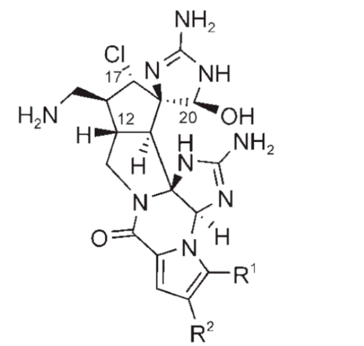
19: $R^1 = R^2 = H$; styloguanidine
20: $R^1 = H$, $R^2 = Br$; bromostyloguanidine
21: $R^1 = R^2 = Br$; dibromostyloguanidine



22: tetrabromostyloguanidine (carteramine A)

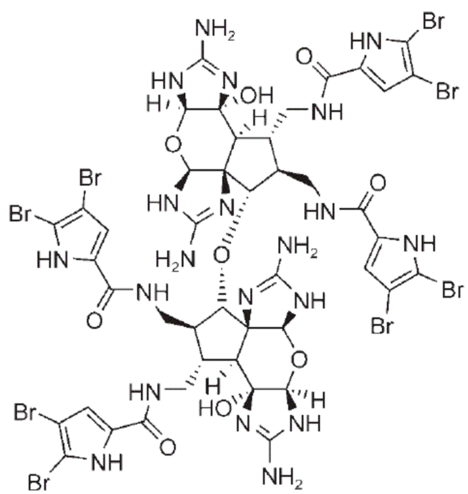


23: konbu'acidin A ($R^1 = H$)
24: konbu'acidin B ($R^1 = Br$)

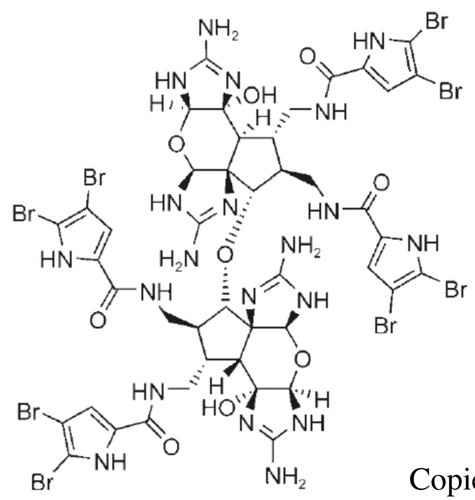


25: $R^1 = R^2 = H$; palau'amine
26: $R^1 = H$, $R^2 = Br$; bromopalau'amine
27: $R^1 = R^2 = Br$; dibromopalau'amine

Polycyclic Pyrrole-Imidazole Dimers



28: stylissadine A

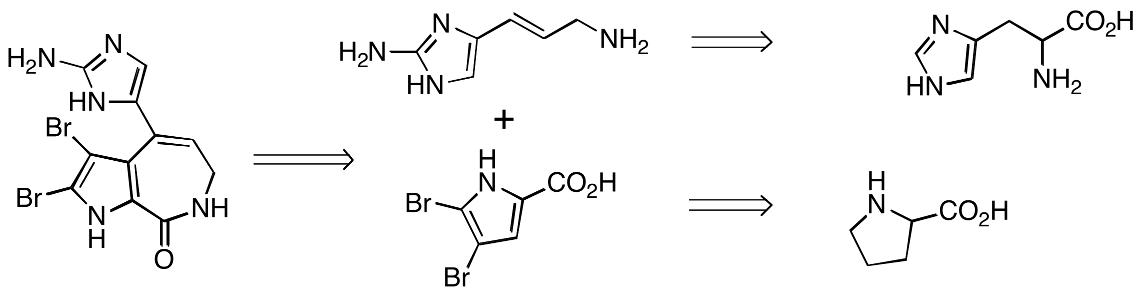


29: stylissadine B

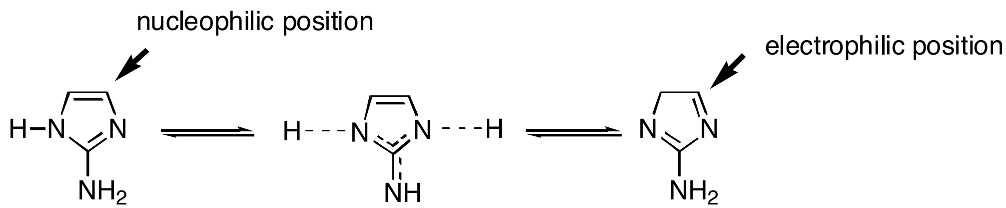
Copied from
Baran et al. *Angew*. *Chem*. *Int*. *Ed*. **2007**, *46,* 6586.

Biosynthetic Analyses and Features of Pyrrole-Imidazole Alkaloids

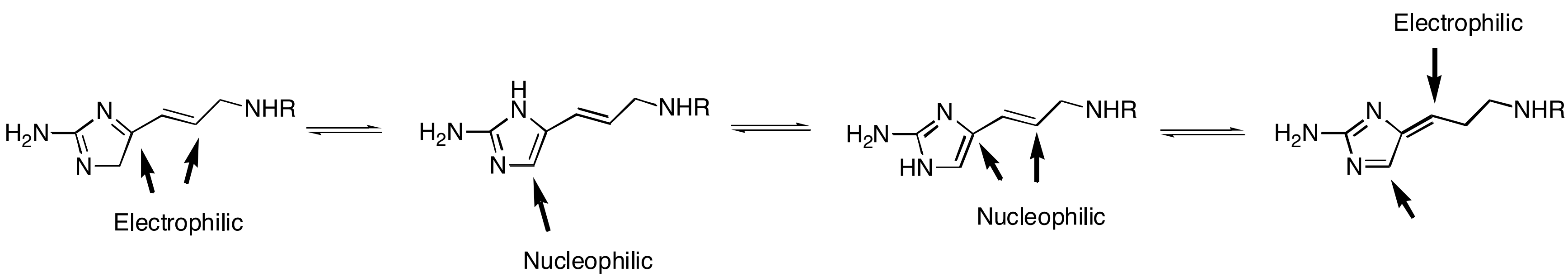
Feeding studies by Kerr and coworkers using a cell culture from *Teichaxinella morchalla* indicated that these amino acids are indeed precursors of odiline (a simple pyrrole-imidazole alkaloid).



The duel reactivity of the 2-aminoimidazole moiety helps to explain the molecular diversity in this group of alkaloids.

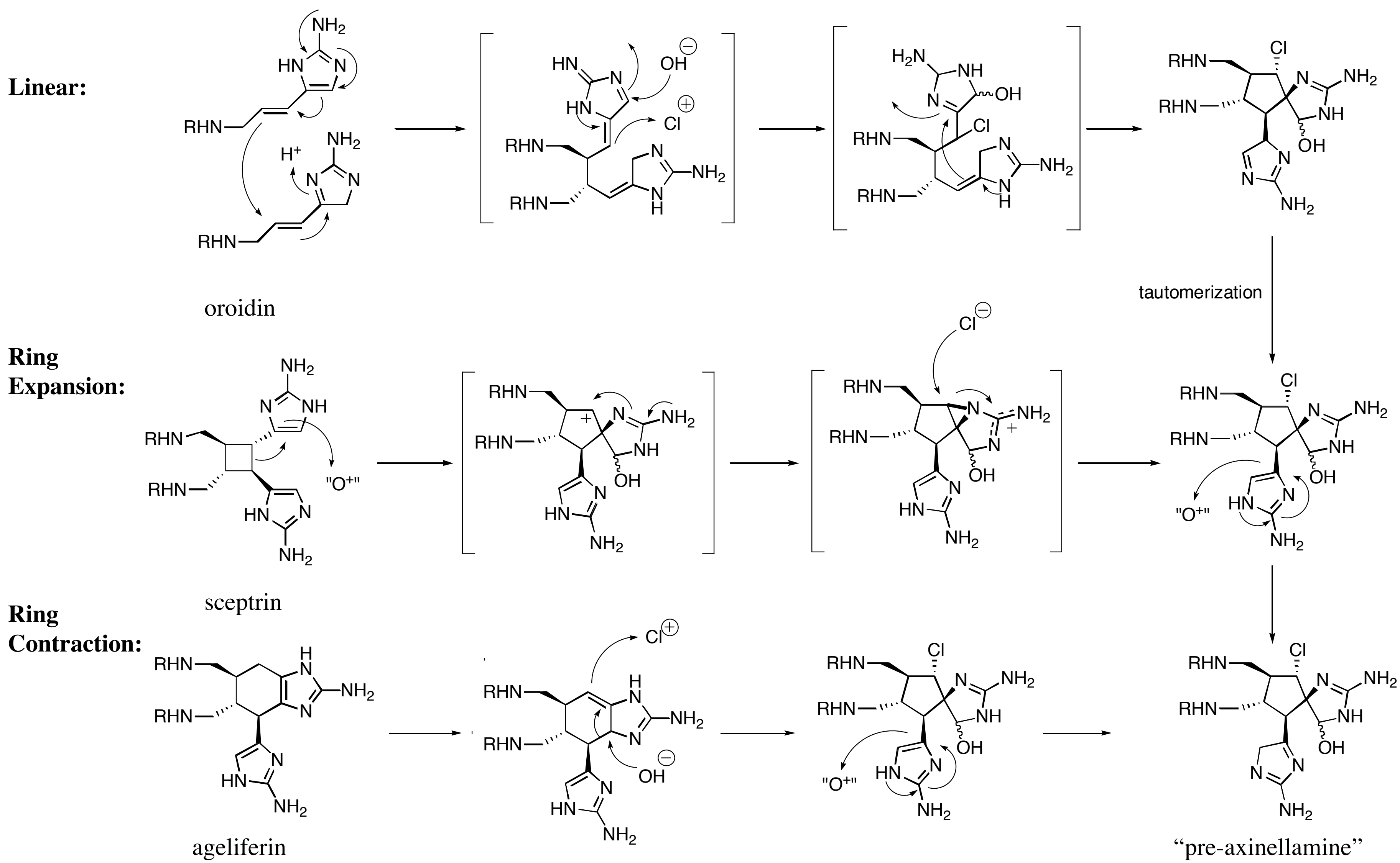


Tautomerism of the vinylogous 2-aminoimidazole also plays a key role in the metabolic route.



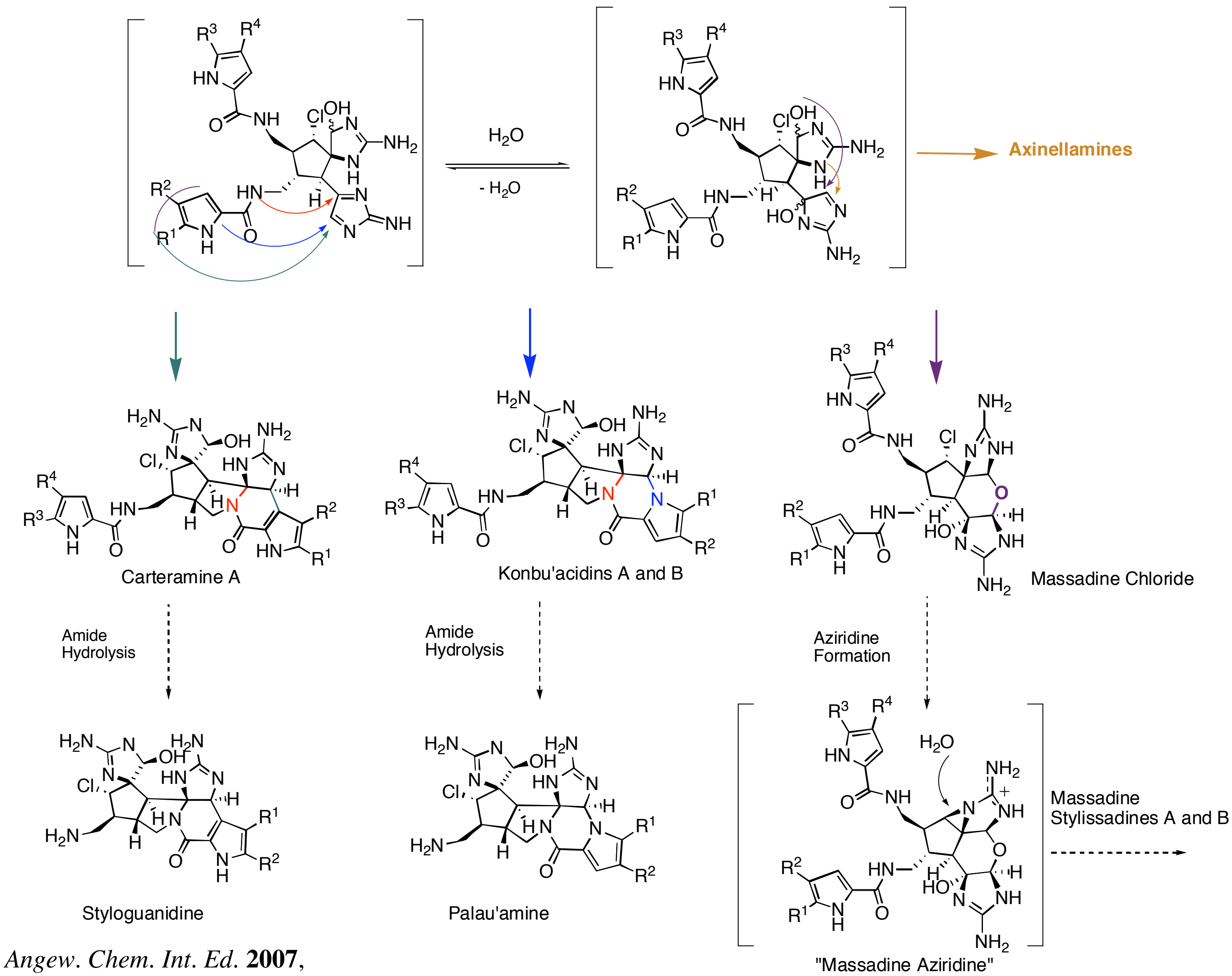
Mourabit et al. *Eur. J. Org. Chem.* **2001**, 237-243.

Baran's Proposed Biosynthesis of the Pre-Axinellamines



Baran et al. *Angew. Chem. Int. Ed.* **2007**, *46*, 6586-6594.

Baran's Proposed Biosynthesis of the Pyrrole-Imidazole Alkaloids

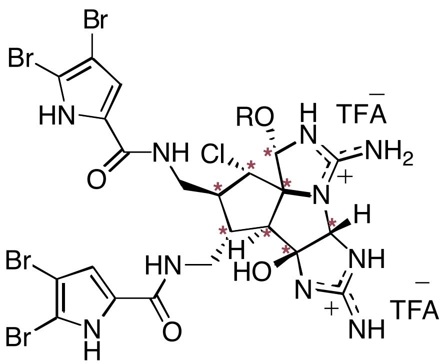


Baran et al. *Angew. Chem. Int. Ed.* **2007**, *46*, 6586-6594.

Isolation of Axinellamines

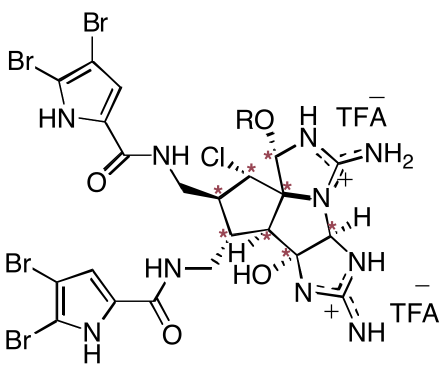
•Axinellamines A-D were isolated by Quinn and coworkers in 1999 from several species of marine sponge of genus *Axinella*.

•Axinellamines B-D show bactericidal activity against *Helicobacter pylori*; (MIC = 1000 μM)



R = H: Axinellamine A

R = Me: Axinellamine C



R = H: Axinellamine B

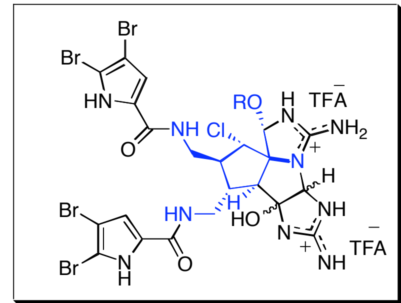
R = Me: Axinellamine D

Axinelle commune (Axinella polypoides)

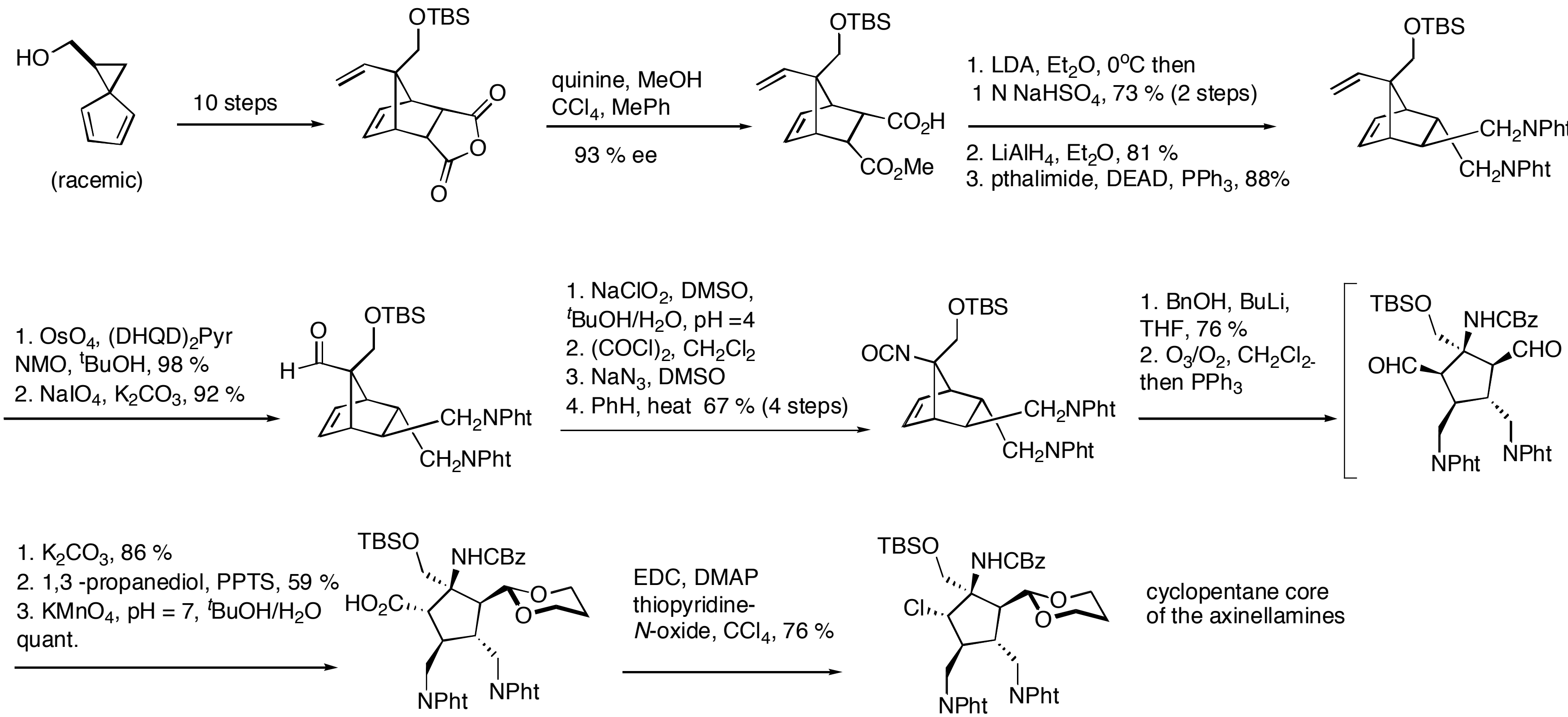
subaqua.web.cern.ch/.../3.jpg

Quinn et al. *J. Org. Chem.* **1999**, *64*, 731-735.

Synthetic Approaches to the Tetracyclic Core of the Axinellamines

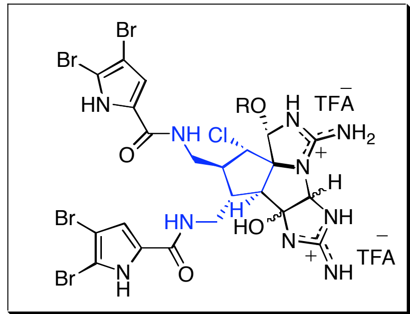


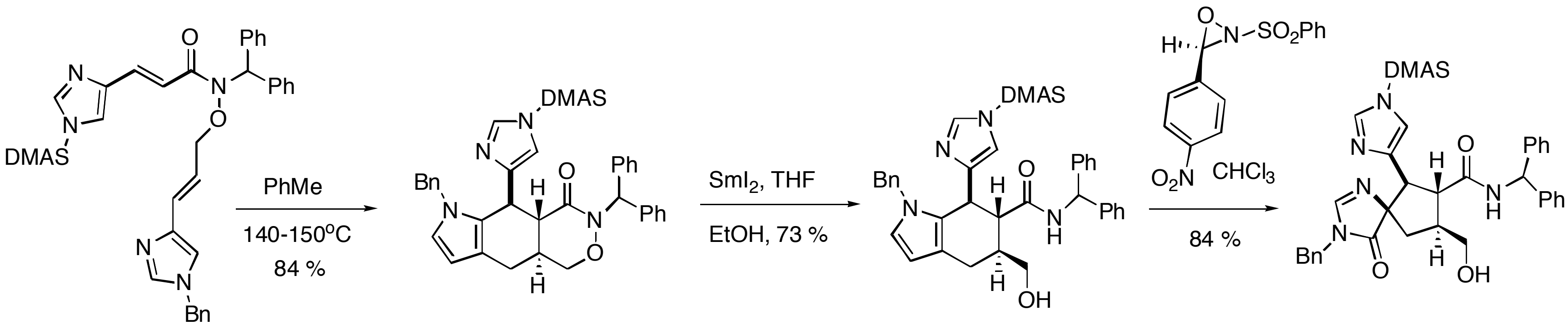
Carreira: Enantioselective synthesis of the core of the tetracycle:



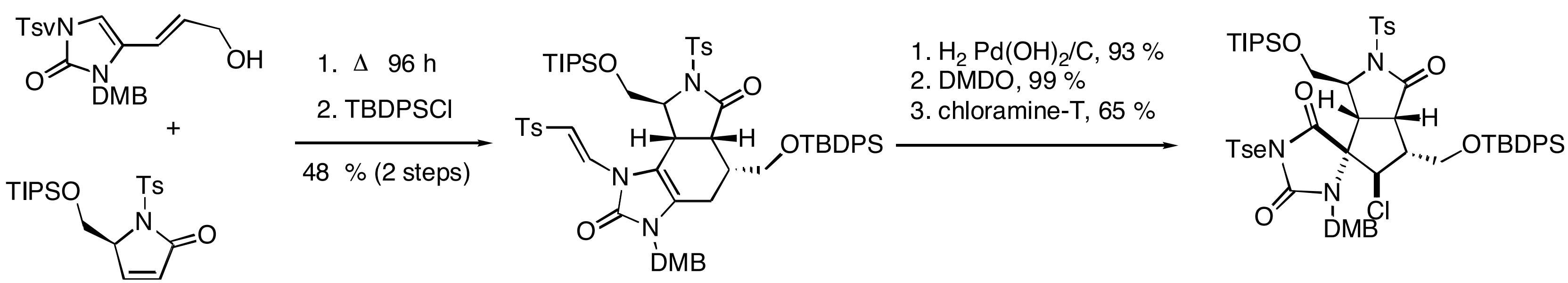
Carreira et al. *J. Am. Chem. Soc*. **2000**, *122*, 8793-8794.

Synthetic Approaches: Oxidative Ring Contraction



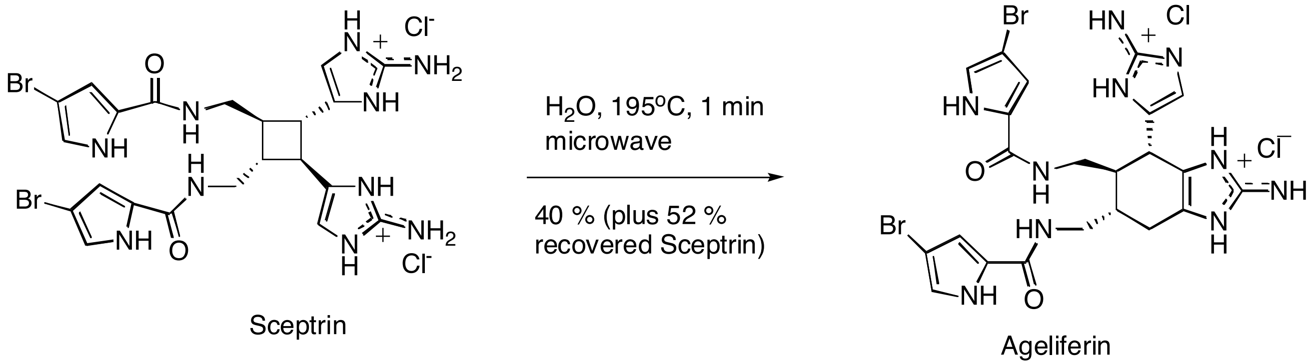


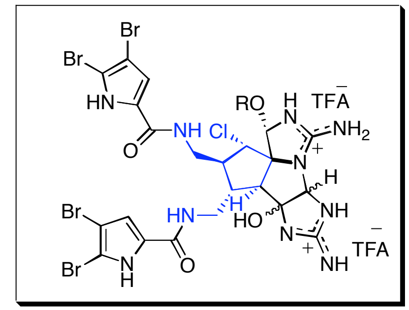
Lovely et al. *Org*. *Lett*. **2007**, *9*, 3861.



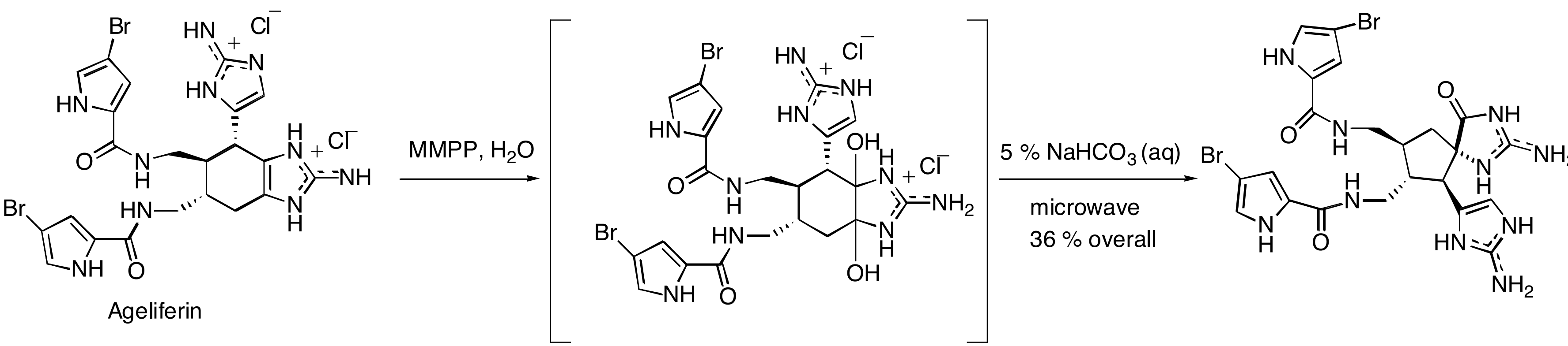
Romo et al. *Org*. *Lett*. **2005**, *7*, 1679.

Thermal Rearrangements within the Pyrrole Imidazole Alkaloids



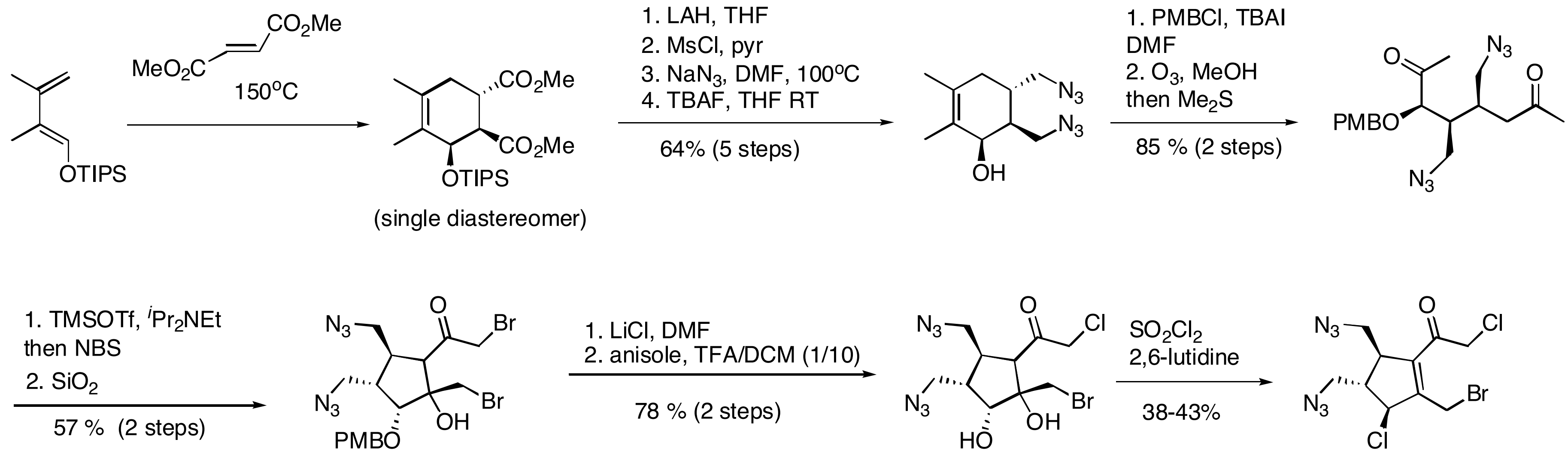


Baran et al. *Angew. Chem. Int. Ed.* **2004**, *43*, 2674.

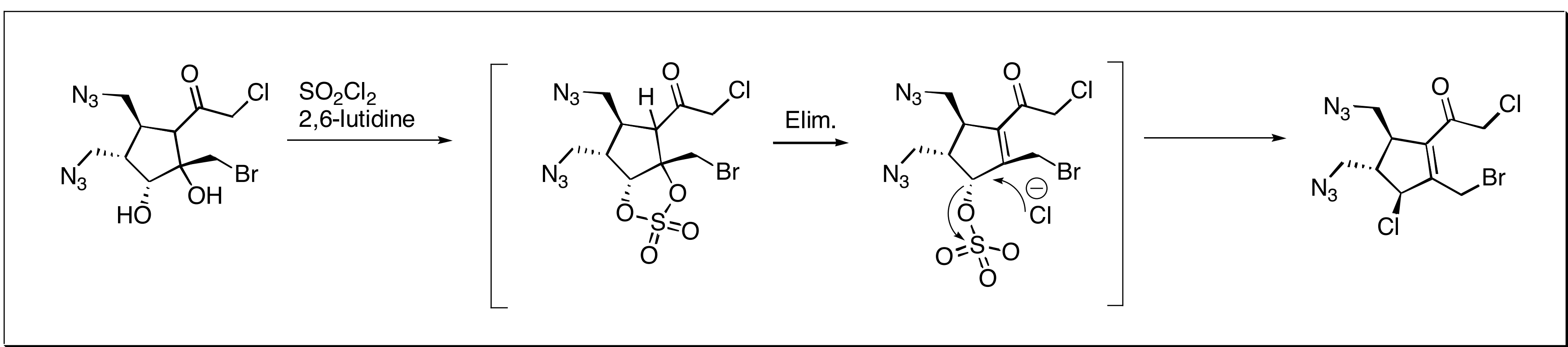


Baran et al. *J. Am. Chem. Soc.* **2007**, *129*, 4762.

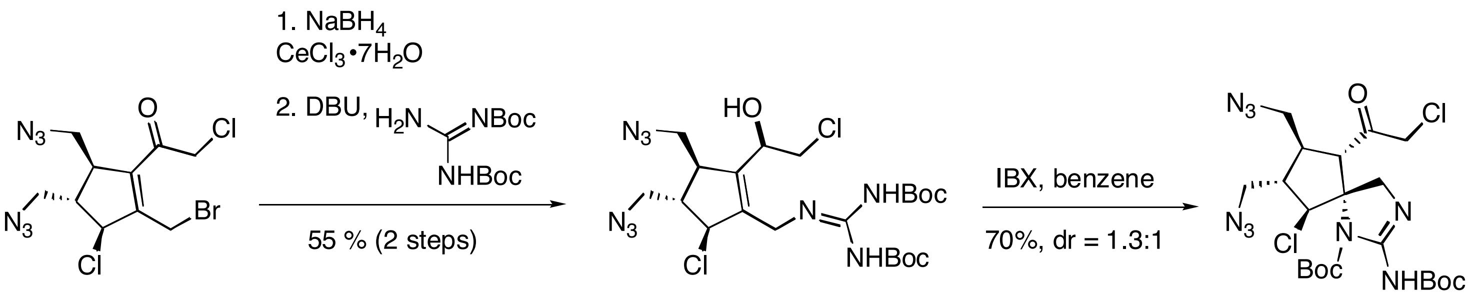
Synthesis of 1,9-Dideoxy-pre-axinellamine

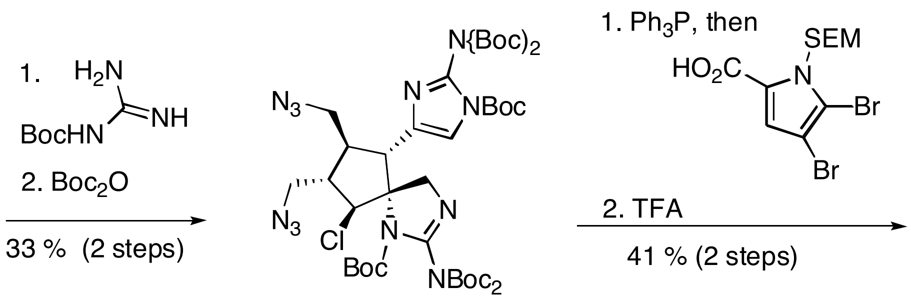


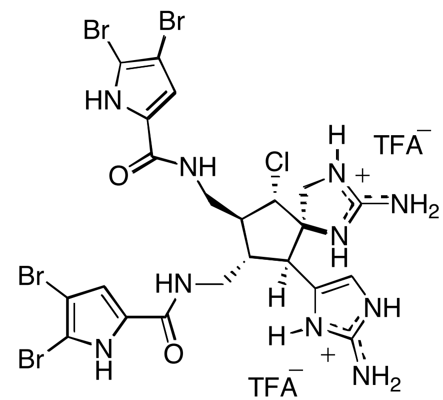
Key Intermediate



Synthesis of 1,9-Dideoxy-Pre-Axinellamine

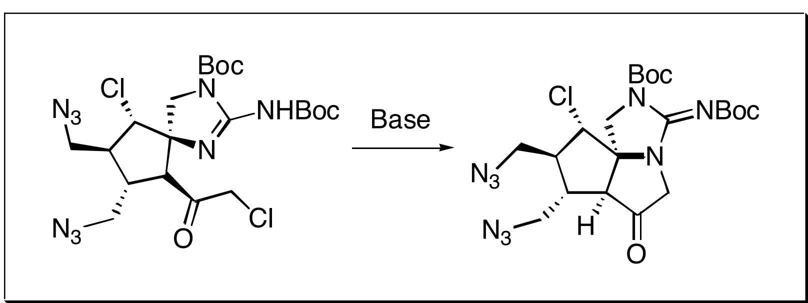






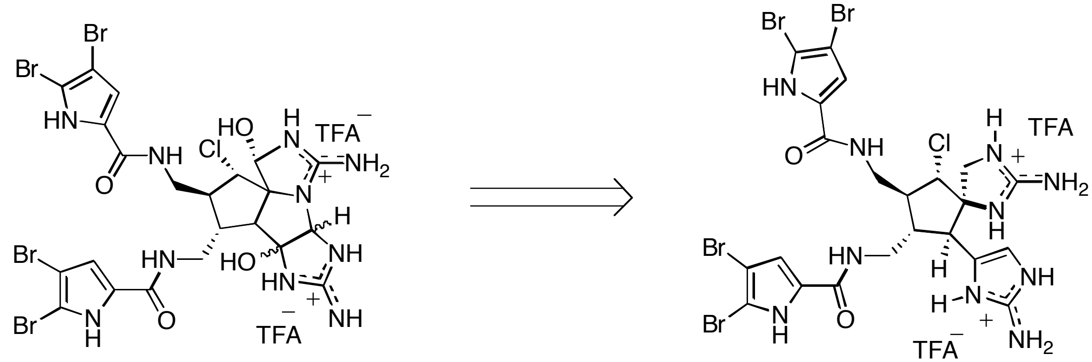
1,9-dideoxy-pre-axinellamine

Problem with Installation of the Final 2-Amino Imidazole:



Synthesis of Axinellamines A and B

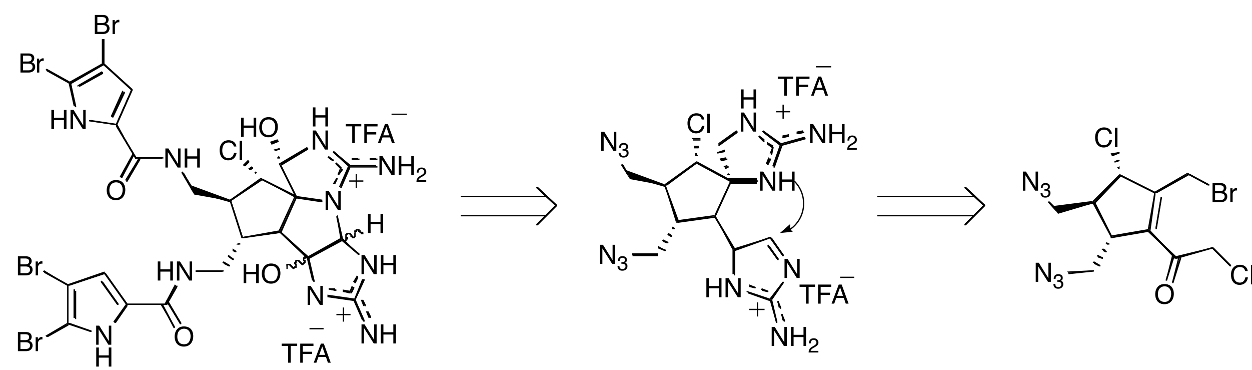
Strategy based on Baran's biosynthetic hypothesis:



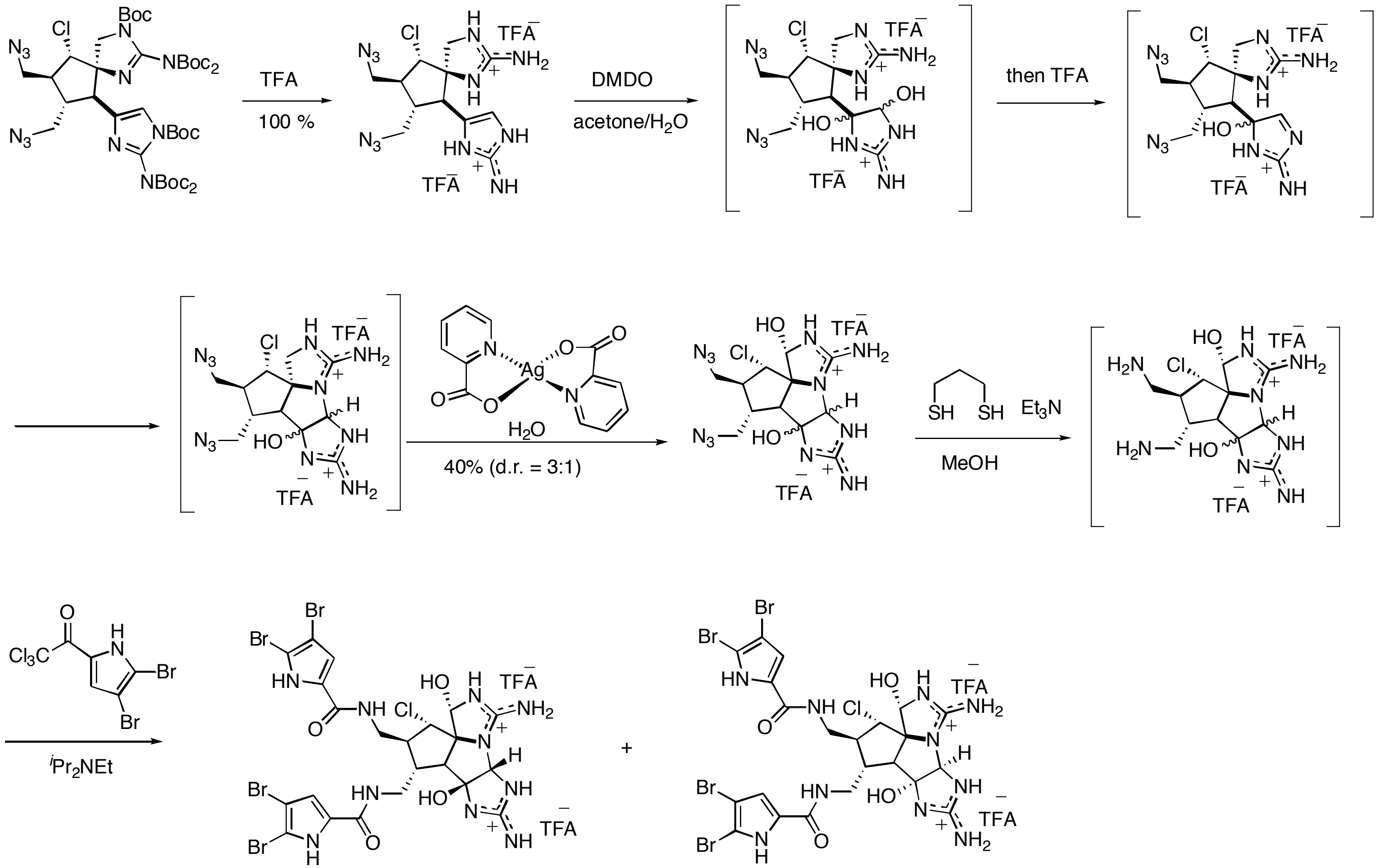
Axinellamine A (H, OH = β)
Axinellamine B (H, OH = α)

1,9-dideoxy-pre-axinellamine

Strategy used to avoid ring closures leading to other pyrrole-imidazole alkaloids:



Synthesis of Axinellamines A and B



Axinellamine A, 45 %

Axinellamine B, 24 %

Summary and Outlook

•Baran and coworkers have completed the racemic synthesis of Axinellamines A and B as well as the synthesis of the postulated species 1,9-dideoxy-pre-axinellamine. Both syntheses proceed through a highly functionalized cyclopentene intermediate which dictates the stereochemistry of the final product.

•Baran's synthesis is an achievement that marks the first synthesis of these marine natural products; however, several steps suffer from poor diastereoselectivities and low yields. .

•1,9-Dideoxy-pre-axinellamine was synthesized in 19 steps and 0.54 % overall yield (0.31 % based on the major diastereomer from the spirocyclization).

•Axinellamines A and B were synthesized in 23 steps and 0.24 % and 0.12 % overall yields, respectively.

•Perhaps we can expect to see syntheses of the pyrrole-imidazole alkaloids derived from 1,9-dideoxy-pre-axinellamine. Yet, cyclization selectivities may prove difficult to control in the laboratory setting.

•The challenge to complete an asymmetric synthesis remains to be solved.