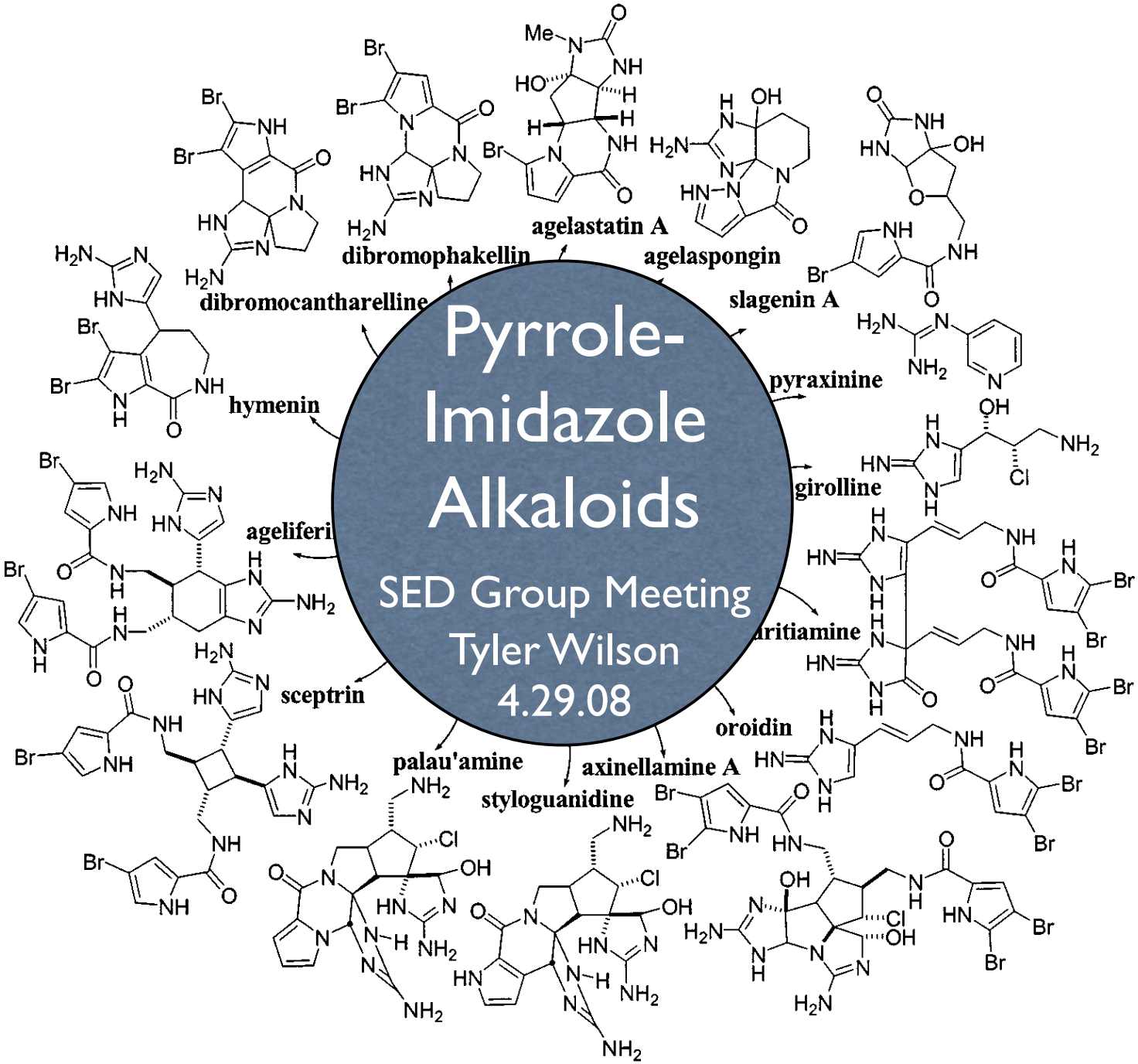
Pyrrole-Imidazole Alkaloids

SED Group Meeting
Tyler Wilson
4.29.08



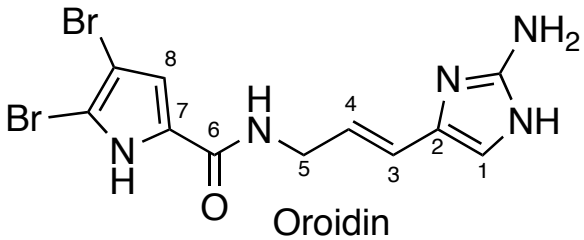
Outline

- Introduction
- Structure
  - -Revisions by characterization of new family members
  - -Overman synthesis
- Baran synthesis of Sceptrin and Ageliferin
  - -Biosynthetic implications
- Synthesis of Axinellamine
  - -Synthesis of core by Carreira
  - -First reported synthesis by Baran

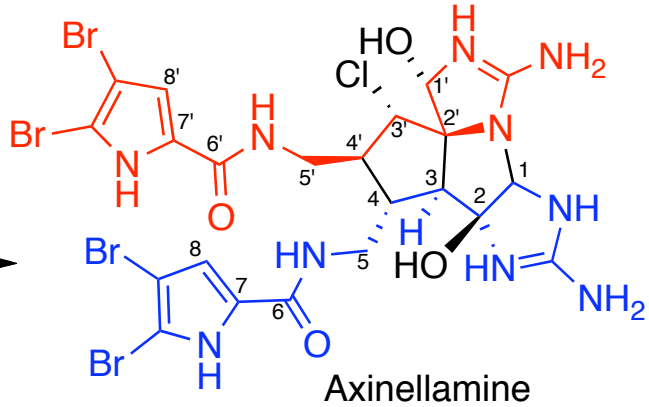
Initial Isolation of Alkaloids

- Isolated from marine sponges (Phylum Porifera)

- Oroidin
  - >First member of the family to be isolated (1971)
  - >Major fish feeding deterrent agent of sponges
  - >Isolation of more complex alkaloids followed



Oroidin

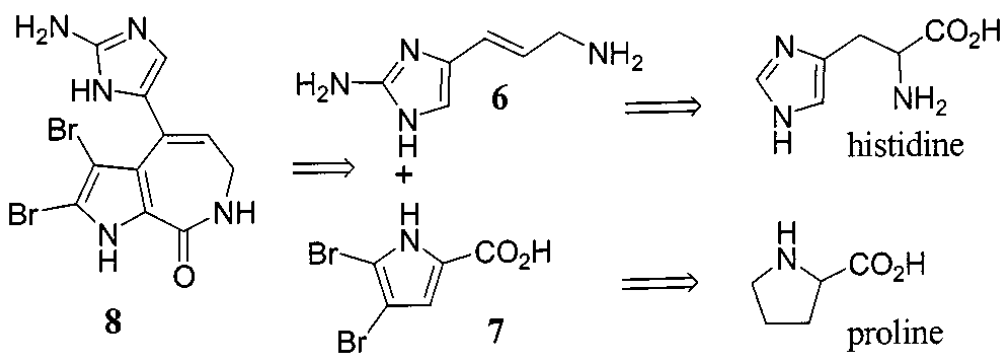


Axinellamine

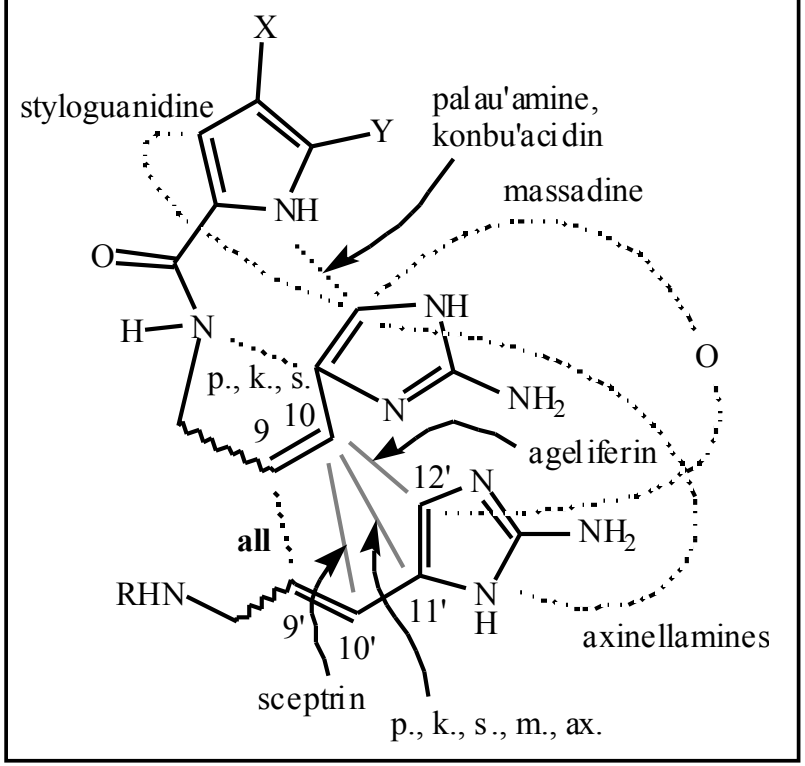
Relating All Members to Oroidin Core

- All members of the family can be mapped back to oroidin
- Incredible amount of molecular complexity arises from this simple core
- Biosynthetic pathway is not known

> Feeding studies are complicated by difficulty in culturing marine sponges
> Single study by Kerr



Road map to pyrrole-imidazole alkaloids

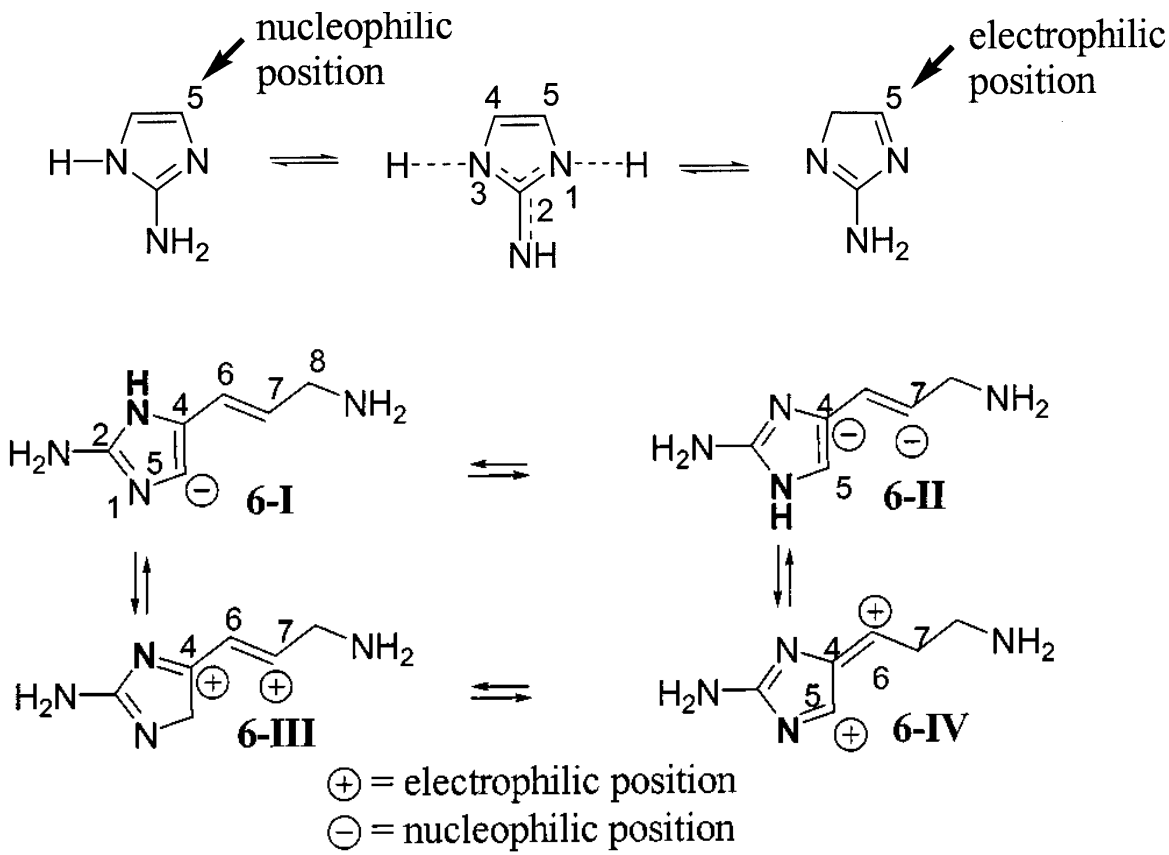


Jacquot, D. E. N.; Lindel, T. Curr. Org. Chem. 2005, 9, 1551-1565

Biosynthetic Hypothesis

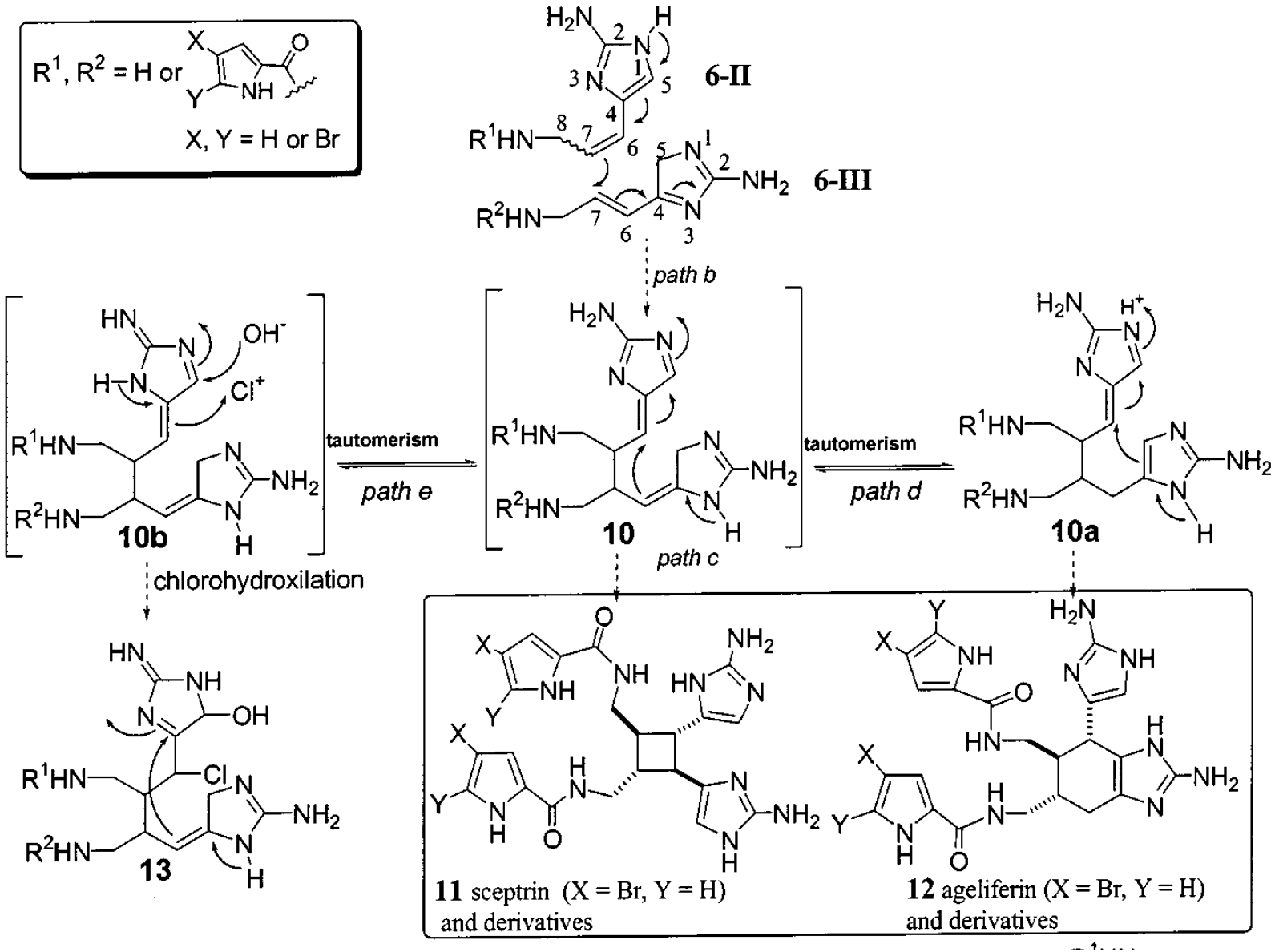
- How can such complexity arise from a simple building block

- Proposal by Mourabit and co-workers takes advantage of ambivalent reactivity inherent to oroidin core



Mourabit, A. A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237-243

Biosynthetic Hypothesis



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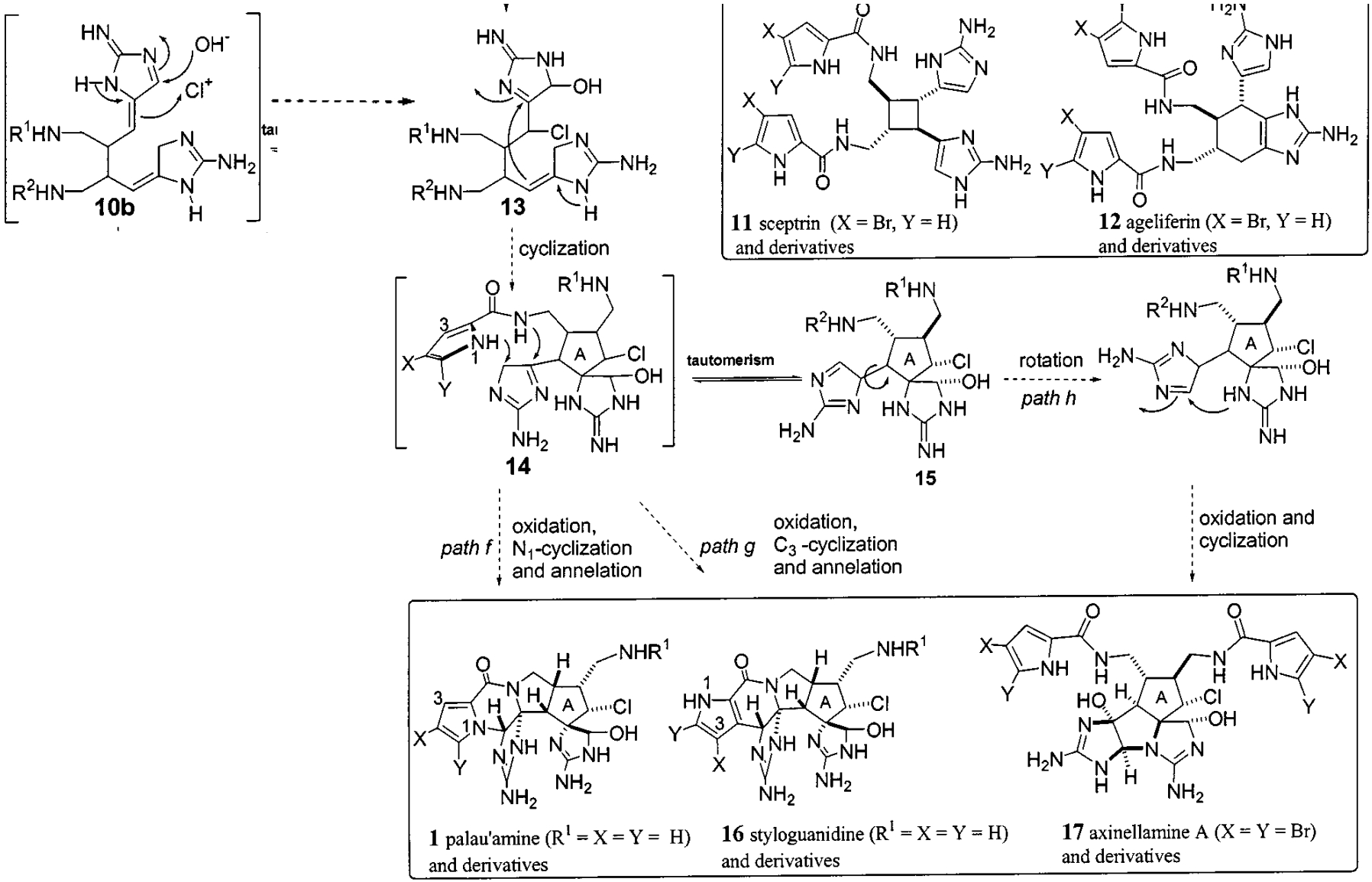
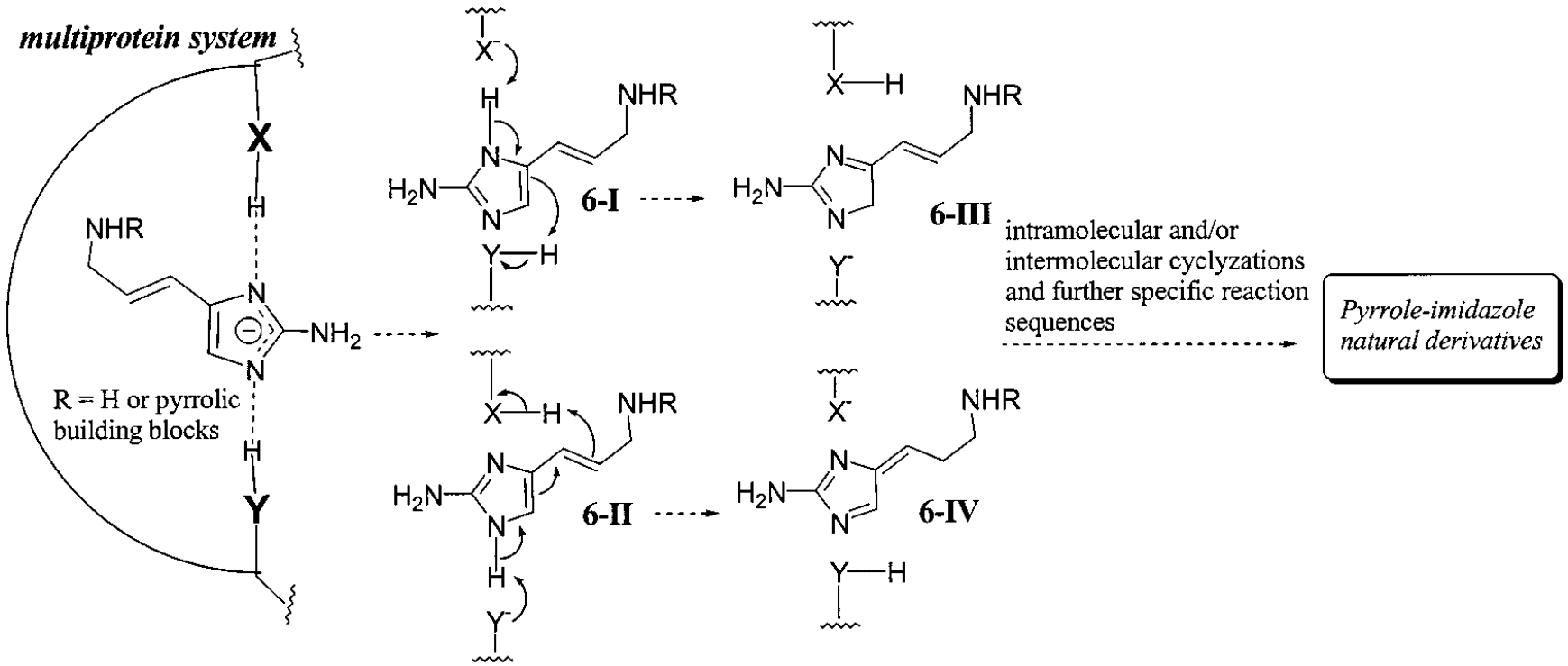
Biosynthetic Hypothesis



Mourabit, A. A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237-243

Biosynthetic Hypothesis

- Potential role of enzymes
  > Controlling tautomeric forms by position of specific amino acid side chains



Mourabit, A. A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237-243

Synthesis of Pyrrole-Imidazole Alkaloids

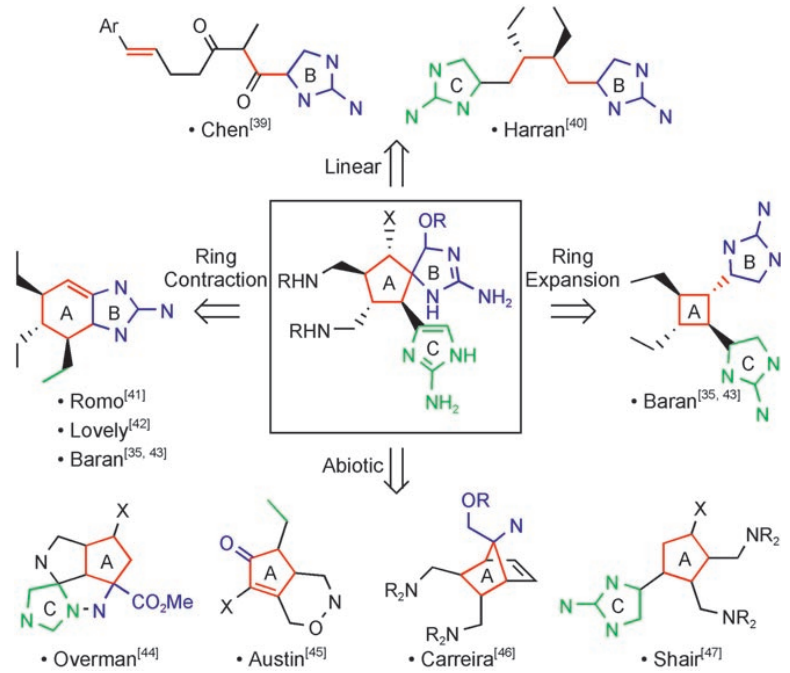
- Simple biosynthetic pathways have been proposed

- Different story for synthesis in the laboratory

Mode	Isolated Compounds	Publ. on Total Synthesis
sceptrin	9	0
ageliferin	10	0[b]
axinellamine	4	0
palau'amine	4	0
styloguanidine	3	0
partial structures	18	9
total	93	40

Lindel, T. *Synthesis*, **2003**, 1753

Core strategies:

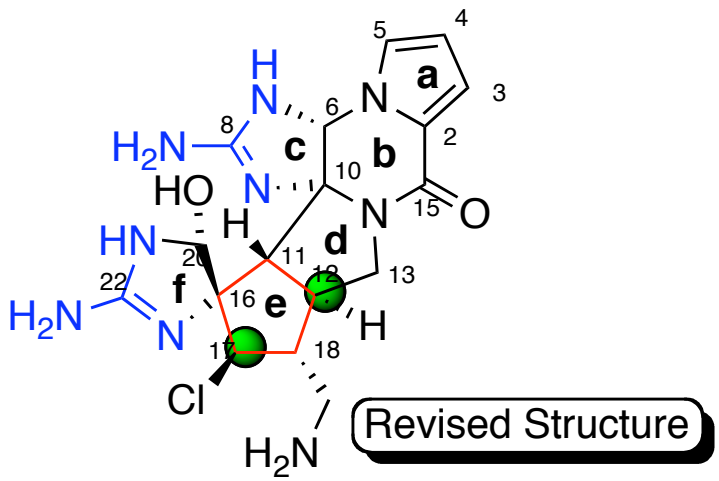


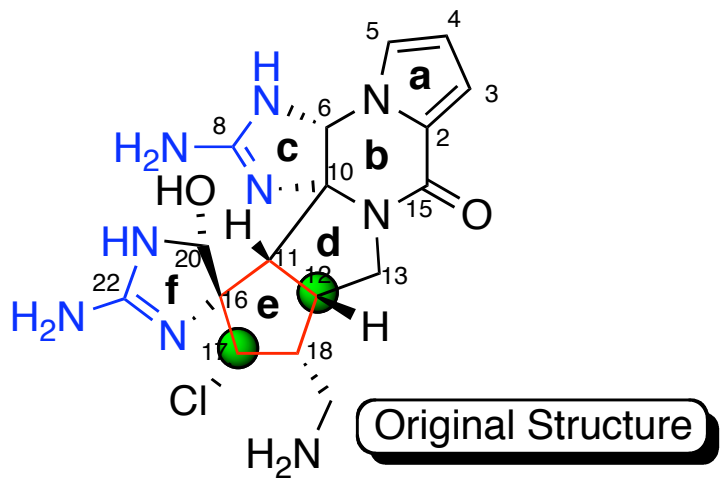
Angew. Chem. Int. Ed. **2007**, *46*, 6586

- Since 2003 review by Lindel
  - > Baran published syntheses of sceptrin (2004), ageliferin (2004) and axinellamine (2008)
  - > Birman published on sceptrin (2004)

- Palua'amine and styloguanidine remain despite numerous reports on core strategies

Palau'amine Structure and Features





Structural Features

- Strained *trans*-azabicyclo[3.3.0] octane fragment
- 6 rings
- Bis-guanidines, including spirocyclic guanidine
- Fully substituted stereogenic cyclopentane core
- 8 contiguous stereogenic carbons
- Low C/N ratio (1.9)
- Absolute stereochemistry is unknown

Palau'amine Elucidation of Cis-Sturucture

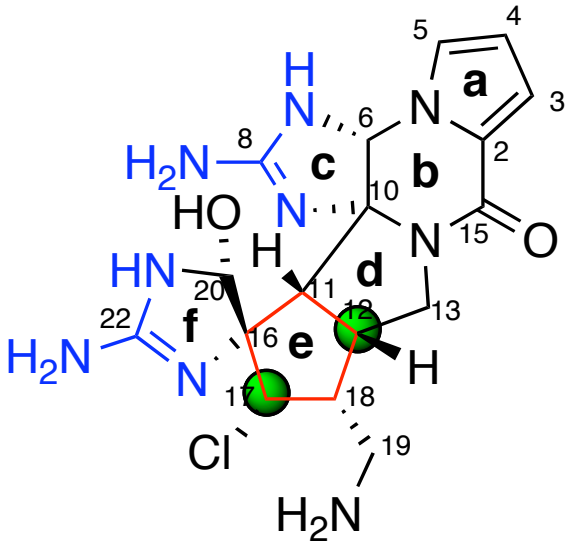


Table I. ^{1}H and ^{13}C NMR Data for Palau'amine (1) in D_2O

carbon	^{13}C, ppm[a]	multiplicity	^{1}H, ppm[b]	multiplicity
2	122.5	s		
3	115.6	d	6.85	dd, J = 3.9, 1.5
4	113.8	d	6.35	dd, J = 3.9, 2.8
5	125.2	d	6.99	dd, J = 2.8, 1.5
6	69.0	d	6.33	s
8	159.5	s		
10	80.8	s		
11	56.3	d	3.08	d, J = 14.1
12	41.8	d	2.52	dddd
13	46.1	t	3.96	dd, J = 7.3, 10.4
			3.28	dd, J = 10.3, 10.4
15	157.8	s		
16	72.1	s		
17	74.0	d	4.35	d, J = 7.9
18	48.6	d	2.47	dddd
19	41.9	t	3.32	dd, J = 13.2, 7.0
			3.24	dd, J = 13.2, 7.0
20	83.7	d	5.96	s
22	157.9	s		

MS Data:

- HRFABMS: found 420.166 calc. for $C_{17}H_{22}ClN_9O_2$ [MH+]
-Isotopic cluster indicates one Cl

IR Data:

O-H (3350), N-H(3350), guanidine hydrochloride (1700), and amide (1658)

NMR Data:

-Strong ROESY and NOE for H11/H6
-ROESY correlation for H17/H12, H17/H19, and a weak correlation for H17/H11

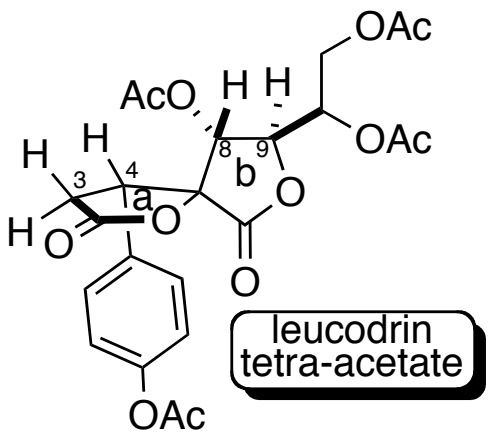
Relative stereochemistry:

Cis-fusion of rings **d**/**e** assigned by coupling constant of H11 (J = 14.1 Hz)

"This coupling constant seems large, but comparable values are observed in similarly rigid, spiroannulated five-membered rings. See, for example: Lowry, J. B.; Riggs, N. V. *Tetrahedron Lett.* **1964**, 2911-2914."

Kinnel, R. B.; Gehrken, H. P.; Scherer, P. J.; *J. Am. Chem. Soc.* **1993**, 3376-3377

Palau'amine Elucidation of Cis-Structure



Assignment	Spectral type	Tetra-acetate of compound (I)
Aromatic protons	A_2B_2	$\tau_A \sim 2{\cdot}8$ ‡ $\tau_B \sim 2{\cdot}6$
Lactone ring A CH–CH_2	ABC	τ_A 5·80, $^3J_{AB}$ 12·4 τ_B 6·72, $^3J_{AC}$ 7·8 τ_C7·13, $^2J_{BC}$ −17·2
Lactone ring B CH–CH	AB	τ_A 4·18, $^3J_{AB}$ 8·3 τ_B 6·23

- What assumptions may have been made in assigning 12.4 Hz as a cis-coupling cst in leucodrin?

  Fact: (x-ray):
  -Lactone ring B: J_{AB} = 8.3 Hz (trans)
  Assumption:
  -Lactone ring A: J_{AC} = 7.8 Hz
  is similar in magnitude to *trans* coupling cst. in ring B and therefore must also be *trans.* This leaves J_{AB} = 12.4 as cis coupling constant.
  -$J_{11,12}$ = 14.1 Hz in Palau'amine (cis?)

- Alternatively,

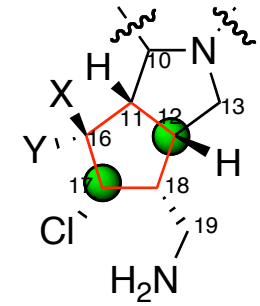
  "On this basis we assign the methylene proton exhibiting the larger vicinal coupling (B) to the proton trans to the methine proton A."

  From:
  Perold, G.W.; Pachler, G.R. *J. Chem. Soc. C,* **1966**, 1918-1923

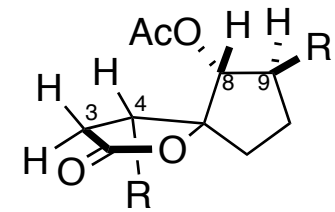
Palau'amine Elucidation of Cis-Structure

- Leucrodrine is a poor model for palau'amine
  - Structural features
  - 2 Hz difference in relative *J*-values

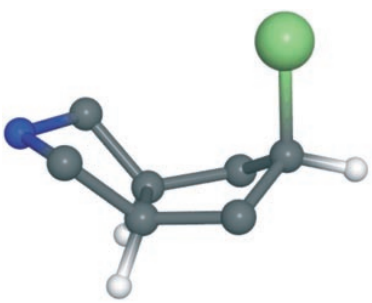
- Other plausable reasons for adopting cis structure
  - Thermodynamics:
    > Cis is energetically favored by as much as 27.3 kcal/mole (DFT B3 LYP, 6-31G(d) basis-set)
  - Trans-fused azabicyclo[3.3.0]octanes are rare, but not unknown

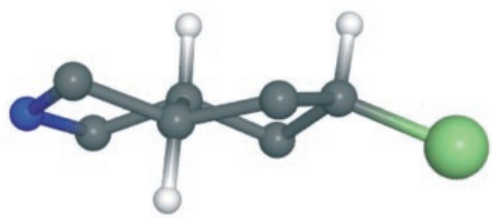


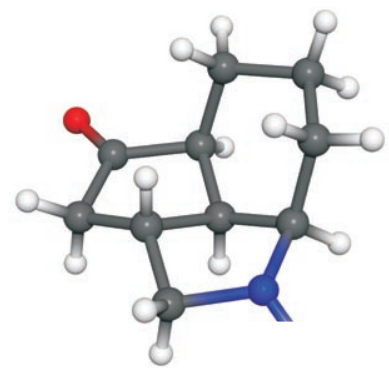
Azabicyclo[3.3.0]octane



Spirocyclic bis-lactone


cis-azabicyclo core

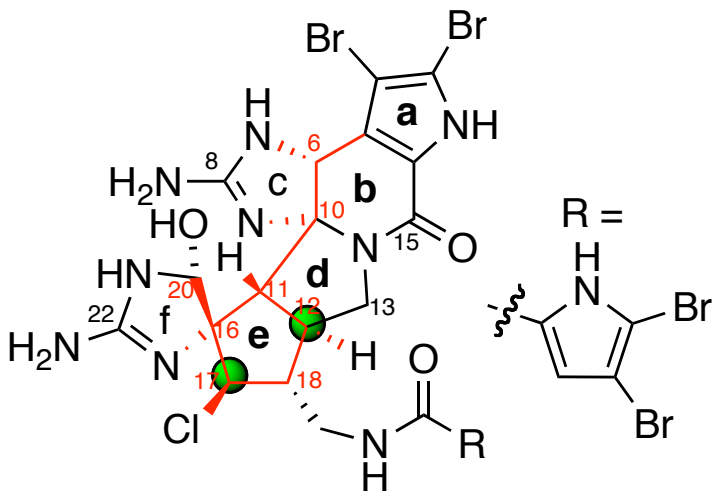

trans-azabicyclo core


azatricyclo[6.2.1.0] undecanone

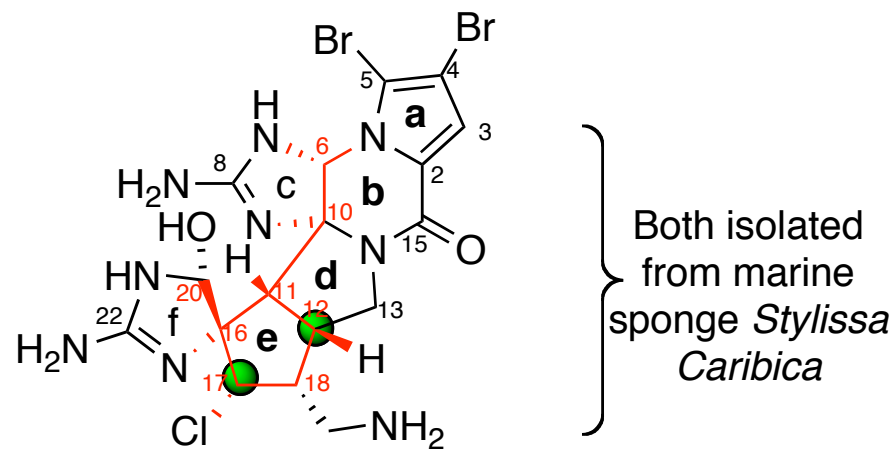
Kock, M; Grube, A.; Seiple, I. B. Baran, P. S. *Angew. Chem. Int. Ed*, **2007**, *47*, 6586-6594

Structural Revision of Palau'amine

- Isolation/characterization of two new family members



tetrabromostyloguanidine (**2**)
(revised structure)



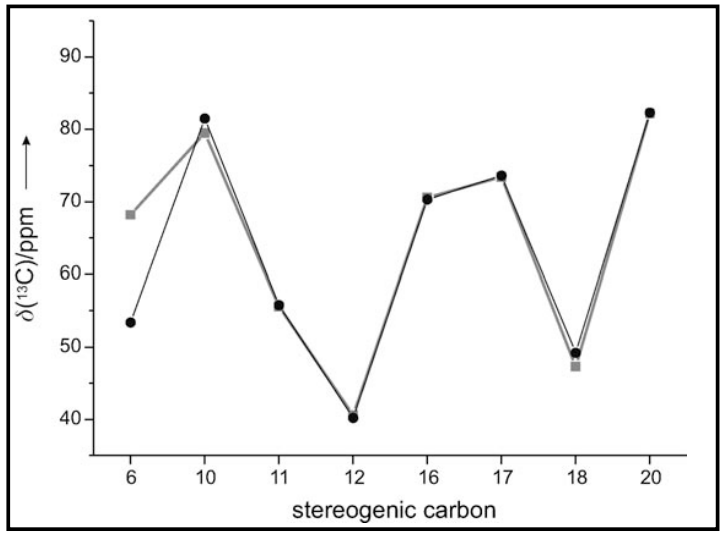
dibromopalau'amine (**1a**)
(original structure)

Both isolated from marine sponge *Stylissa Caribica*

- Differ structurally by disposition of pyyrole

- ROESY of **2** showed a weak signal for H11/H17 and strong signal for H12/H17

- Comparison of ^{13}C data suggests an identical relative configuration



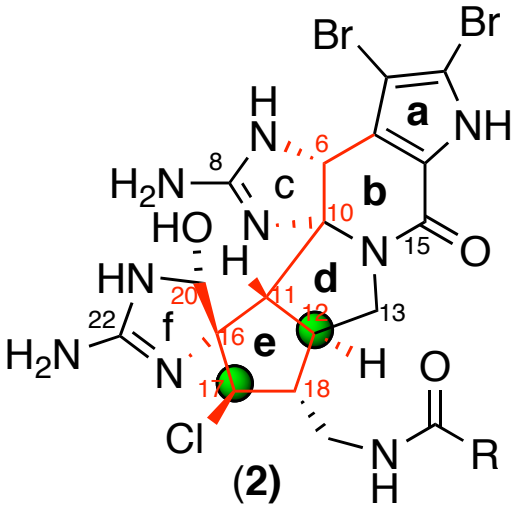
Grube, A.; Kock, M; *Angew. Chem. Int. Ed*, **2007**, *46*, 2320-2324

Structural Revision of Palau'amine

- Calculated interproton distances via quantitative ROESY Exp.

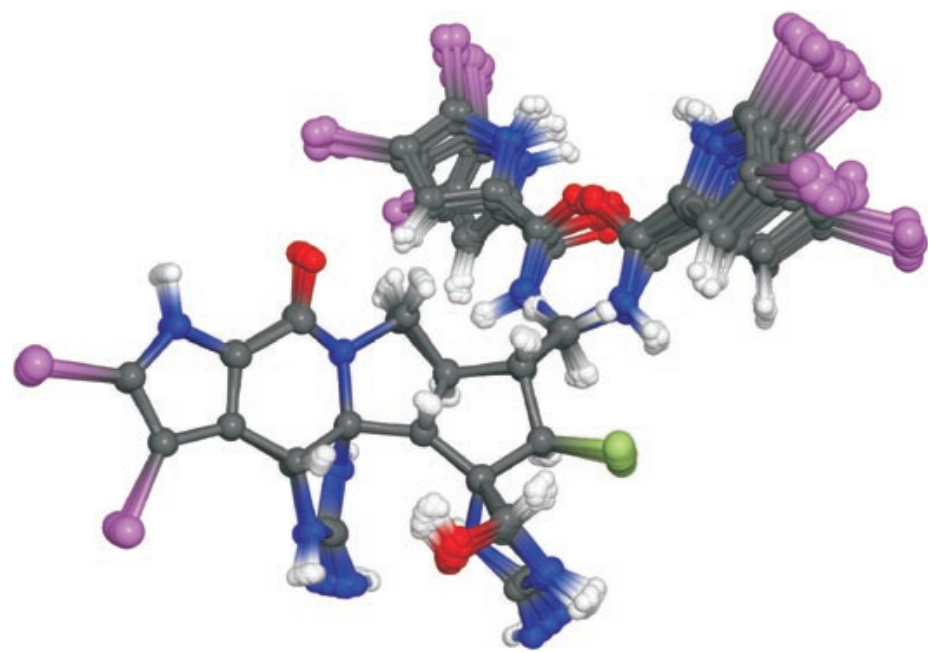
- Used fc-rDG/DDD with 27 interproton distances (no restraint on H11/H12) to calculate relative configuration.

fc = floating chirality
r = NOE-derived distance restraint
DG = distance geometry
DDG = Distance-bounds-driven-dynamics



-8 stereocenters = 256 stereoisomers
-set C6 and thus maximum is 128
-Computation generated 5 of the 128

67 superimposed structures of best fit using fc-rDG/DDD all show same relative configuration as **2**

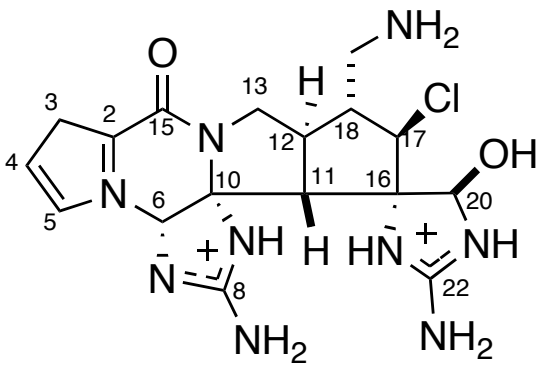


Grube, A.; Kock, M; *Angew. Chem. Int. Ed*, **2007**, *46*, 2320-2324

Structural Revision of Palau'amine

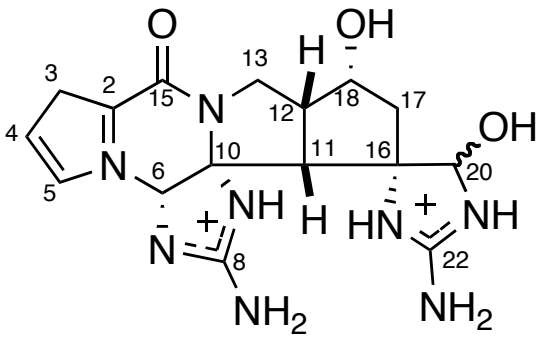
- Evidence for revised structure via chemical synthesis
- Overman and co-workers previously report nice route to cis-fused core
- Lemons into lemonade appoach

  > Prepare cis-fused derivative
  > Compare NMR of synthetic and natural material



Palau'amine **1**
(revised structure)

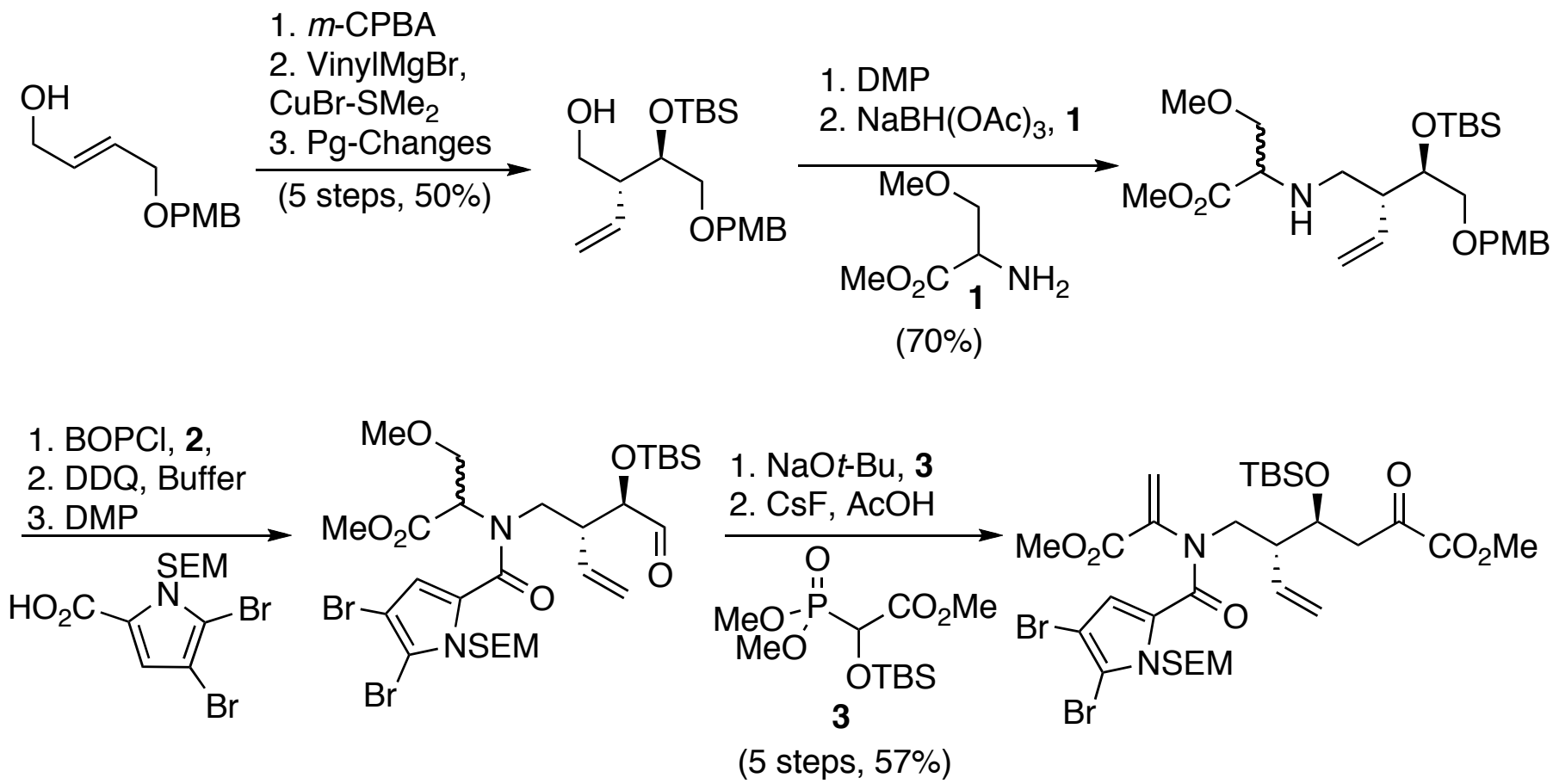
Vs.



Overman Model Compounds
3: C-20 β–OH
4: C-20 α–OH

Structural Revision: Overman Synthesis

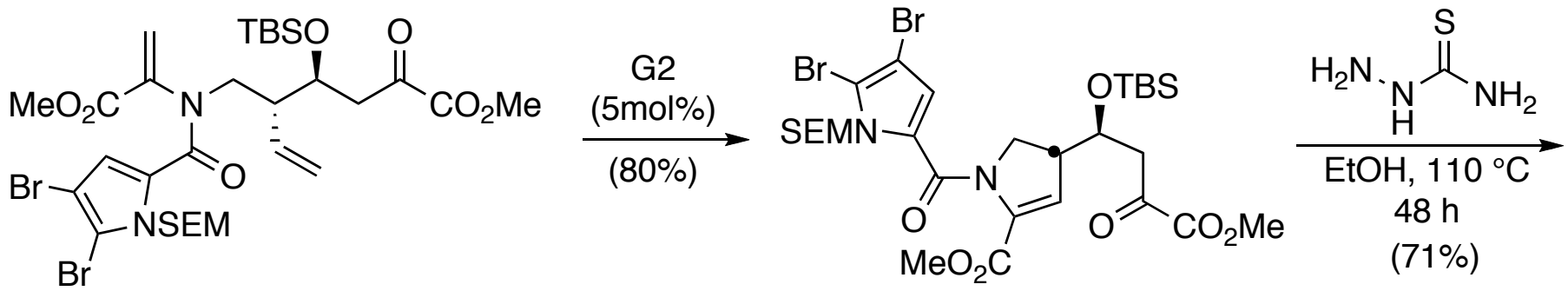
- Synthesis of precursor



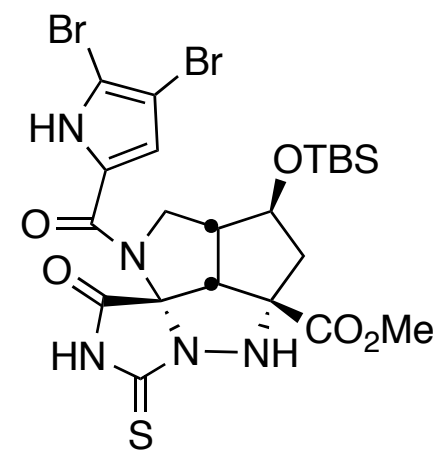
Katz, J. D.; Overman, L. E. *Tetrahedron*, **2004**, *60*, 9559-9568

Structural Revision: Overman Synthesis

- Creating the 3-azabicyclo[3.3.0] core



Draw a mechanism for the formation of the observed product



Katz, J. D.; Overman, L. E. *Tetrahedron*, **2004**, *60*, 9559-9568

Structural Revision: Overman Synthesis

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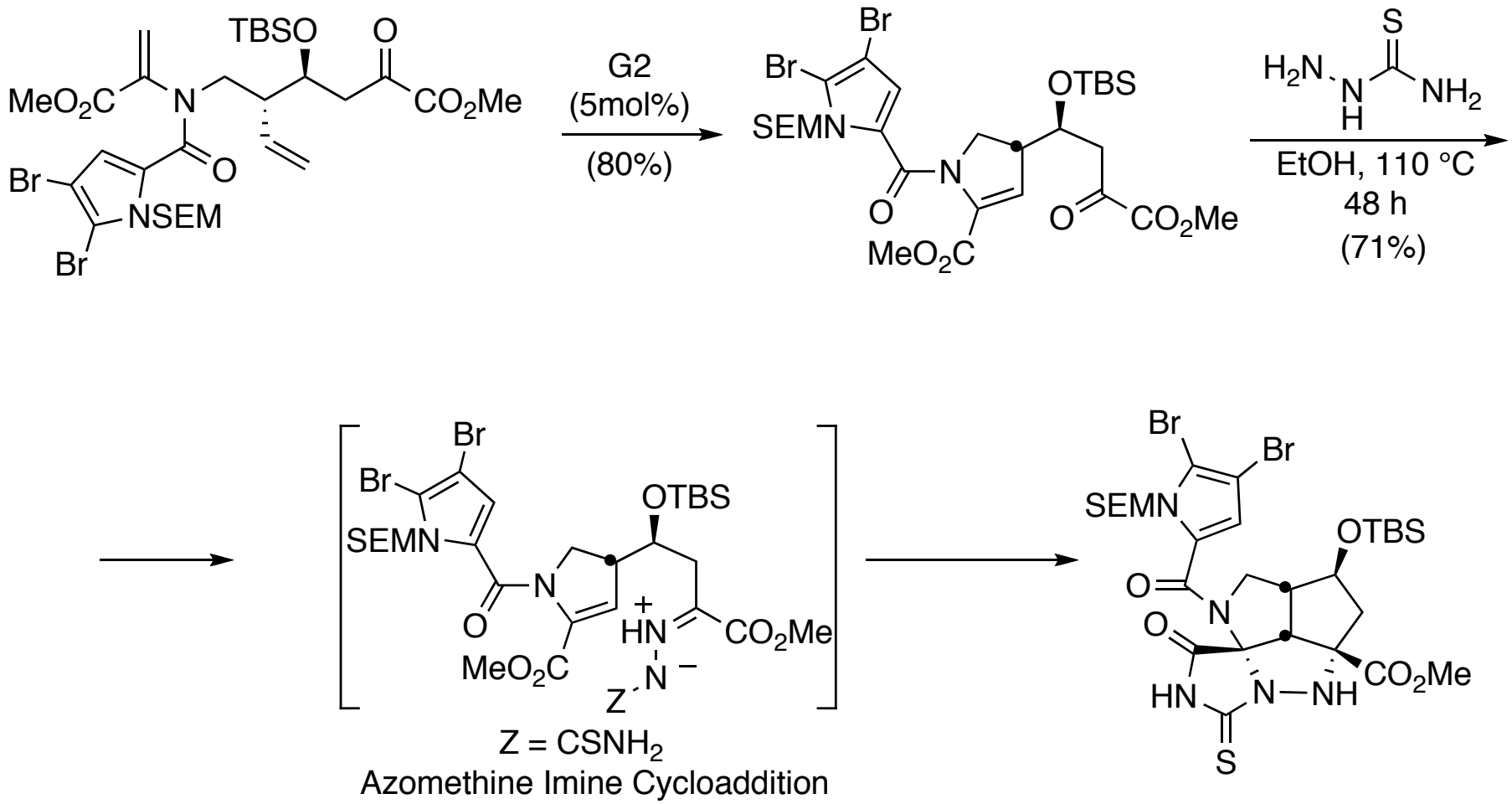

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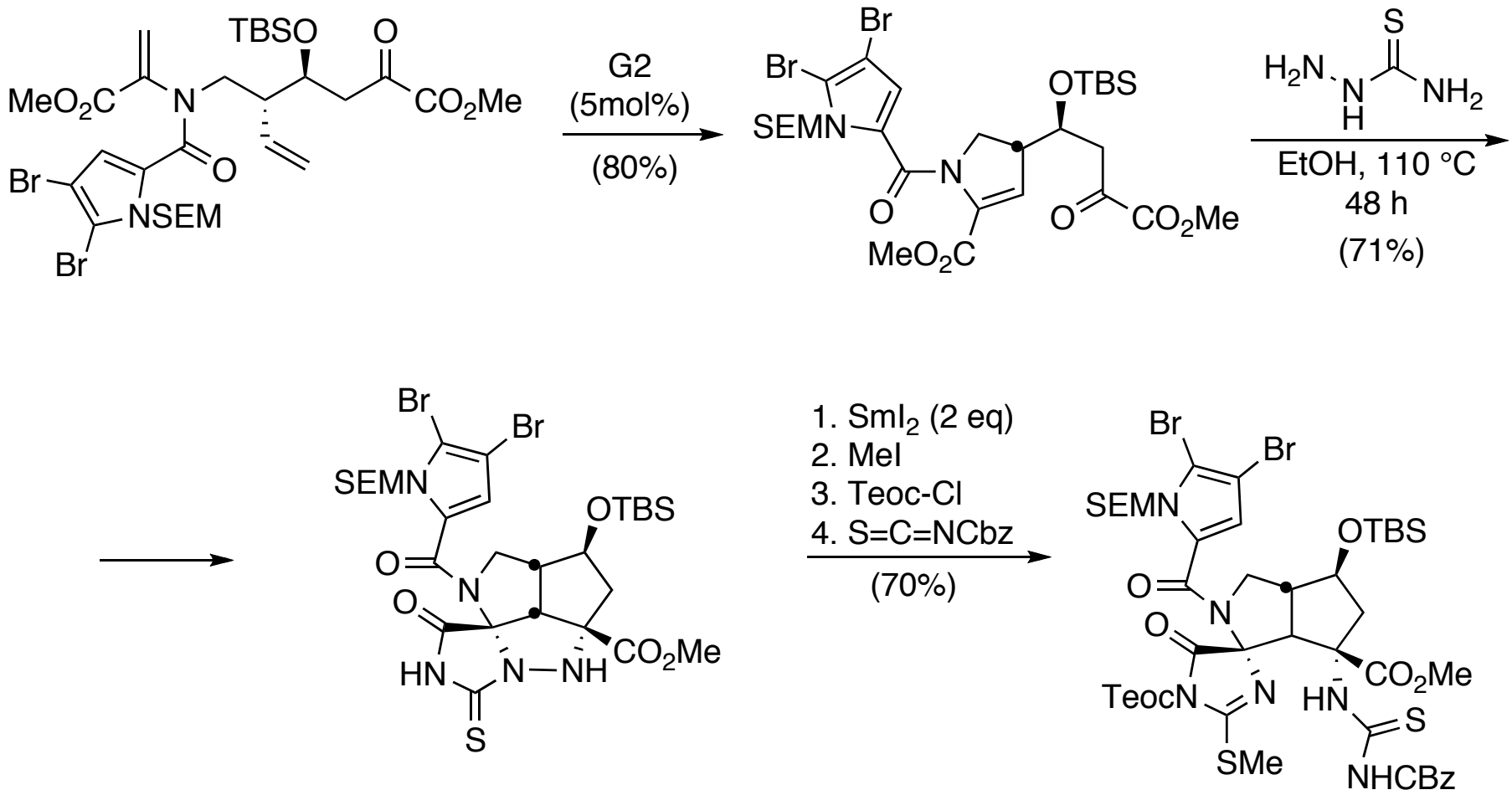
Structural Revision: Overman Synthesis

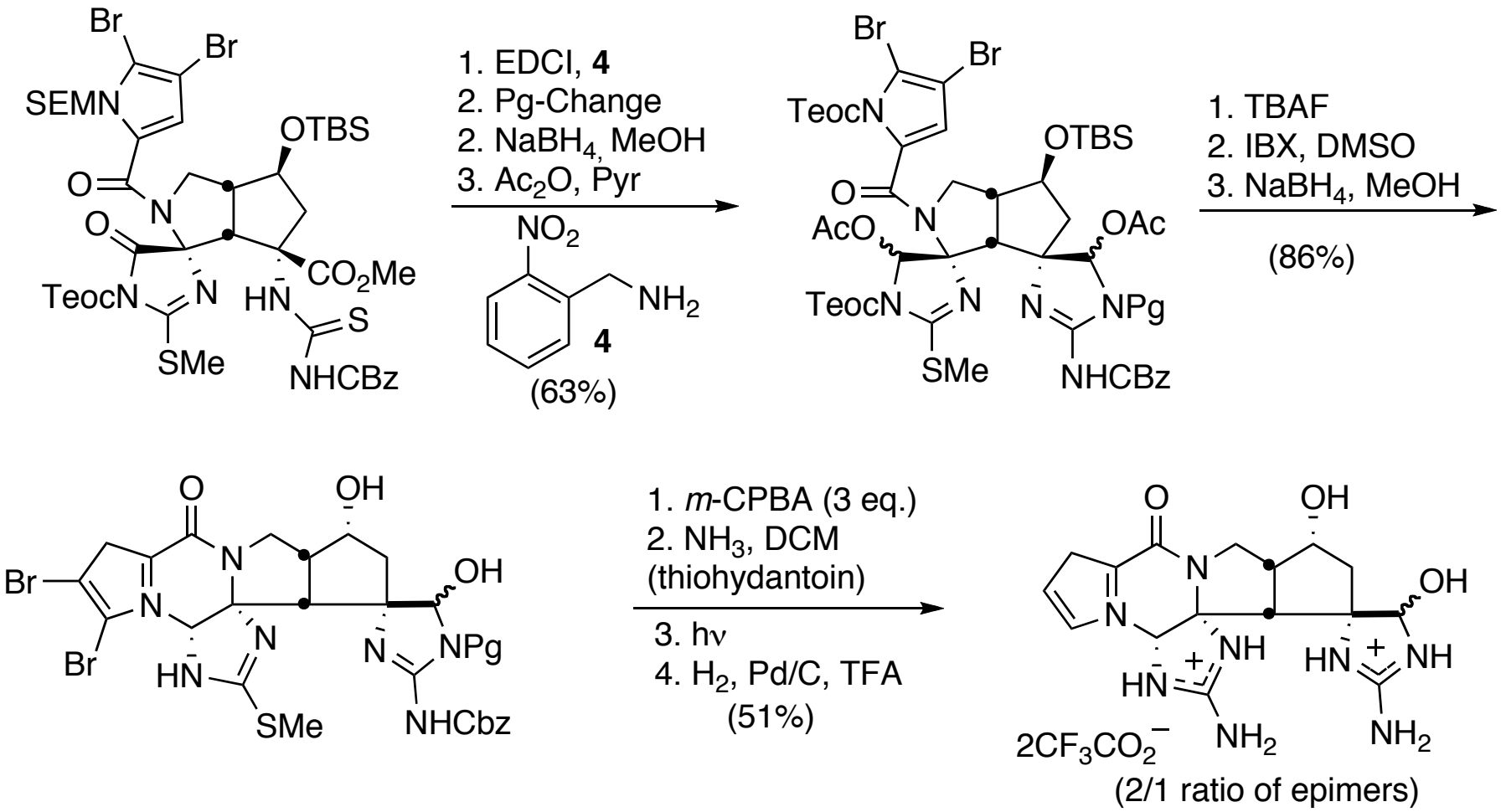
- Creating the 3-azabicyclo[3.3.0] core



Katz, J. D.; Overman, L. E. *J. Am. Chem. Soc.*, **2007**, *129*, 12896-12900

Structural Revision: Overman Synthesis

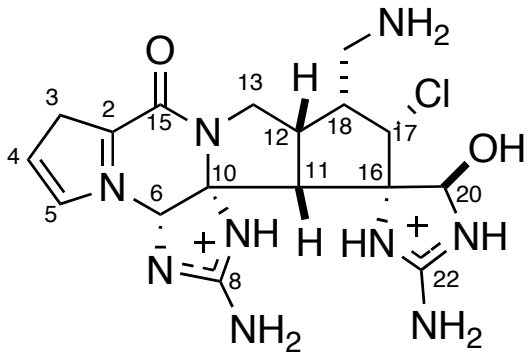
- Building in piperdine and bis-guanidines



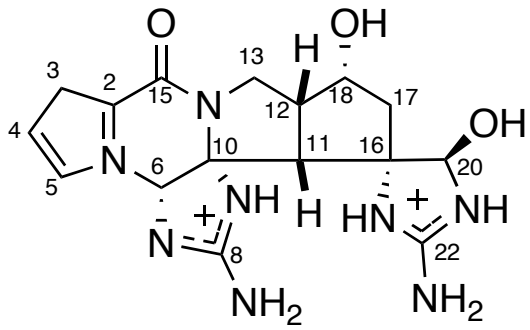
Katz, J. D.; Overman, L. E. *J. Am. Chem. Soc.*, **2007**, *129*, 12896-12900

Structural Revision: Overman Synthesis

- Results of spectroscopic comparison

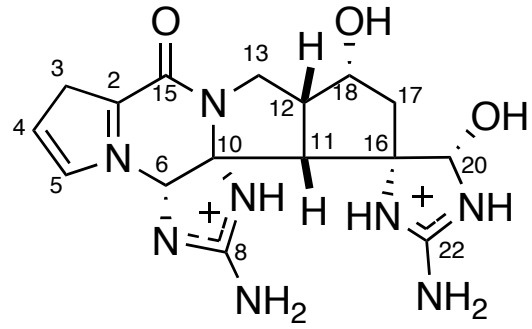


Palau'amine **1**
(original structure)
$J_{11,12}$ =14 Hz



3: C-20 β–OH

$J_{11,12}$ = 12.0 Hz



4: C-20 α–OH

$J_{11,12}$ = 10 Hz

- Largest J-value is still 2 Hz lower than palau'amine
- <u>NOE Correlation:</u>
  > **3/4** show strong correlation for H11/H12 (NOE correlation not mentioned in isolation)
- Chemical synthesis also supports revised structure

Interproton Distance:

protons	**3**[b]	**3**[c]	**4**[b]	**4**[c]	**1**[c]	*trans*–**3**[c,d]	*trans*–**4**[c,d]
11/12	221	221	228	224	226	304	304
11/13β	335	342	334	343	407	268	267
11/18	n.o.	405	n.o.	407	327	253	258
11/20	270	317	208	221	311	322	264
12/18	249	240	227	240	221	305	305
13α/18	313	299	292	297	381	346	345
13β/18	n.o.	349	n.o.	348	359	251	249

b: experimentally determined from NOE
c: calculated distances from computational modeling

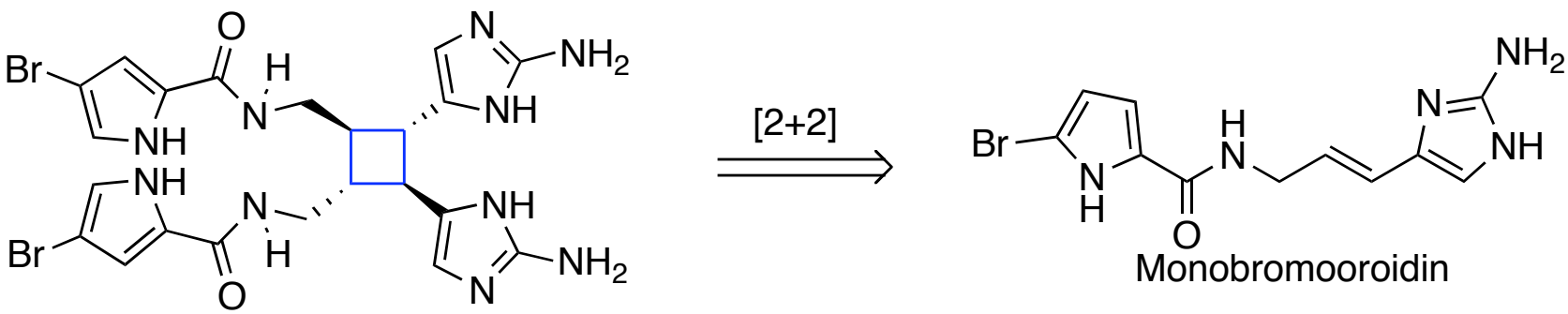
Katz, J. D.; Overman, L. E. *J. Am. Chem. Soc.*, **2007**, *129*, 12896-12900

Outline

- Introduction
- Structure
  - -Revisions by characterization of new family members
  - -Overman synthesis
- Baran synthesis of Sceptrin and Ageliferin
  - -Biosynthetic implications
- Synthesis of Axinellamine
  - -Synthesis of core by Carreira
  - -First reported synthesis by Baran

Synthesis of Sceptrin

- First isolated and characterized by Faulkner in 1981
- Formally could arise from a [2+2] of monobromooroidin
- Isolated at ocean depths where photochemistry is unlikely

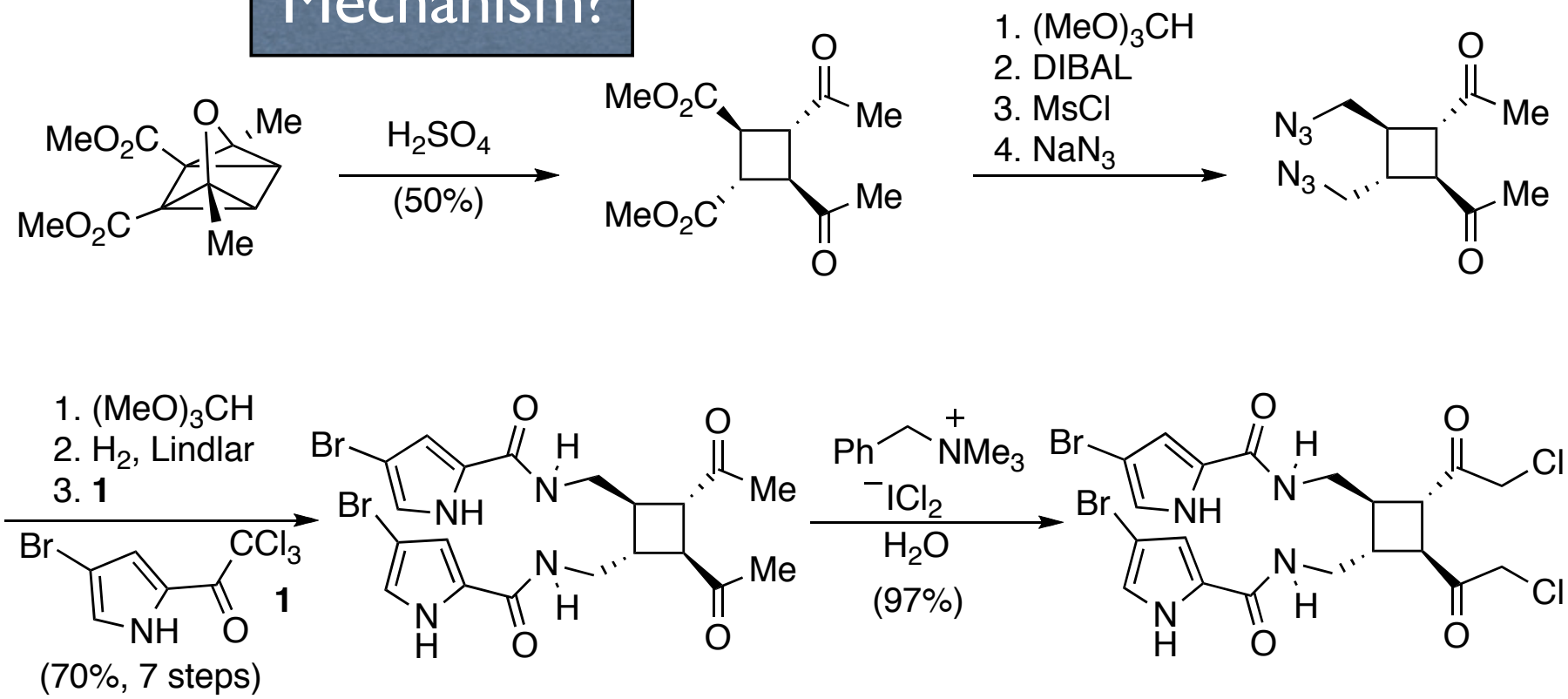


Sceptrin

Monobromooroidin

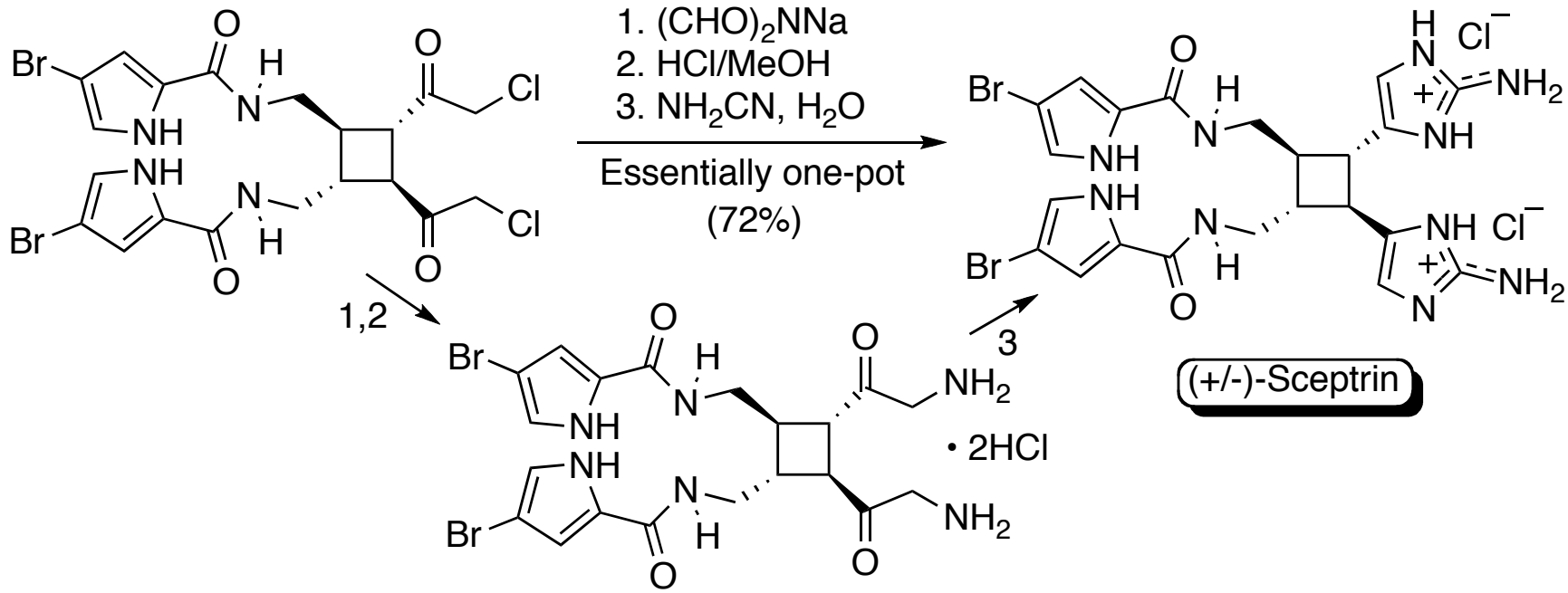
Baran Synthesis of (+/-)-Sceptrin

Mechanism?



Baran, P. S.; Zografos, L.; O'Malley, D. P.; *J. Am. Chem. Soc.*, **2004**, *126*, 3726-3727

Baran Synthesis of (+/-)-Sceptrin

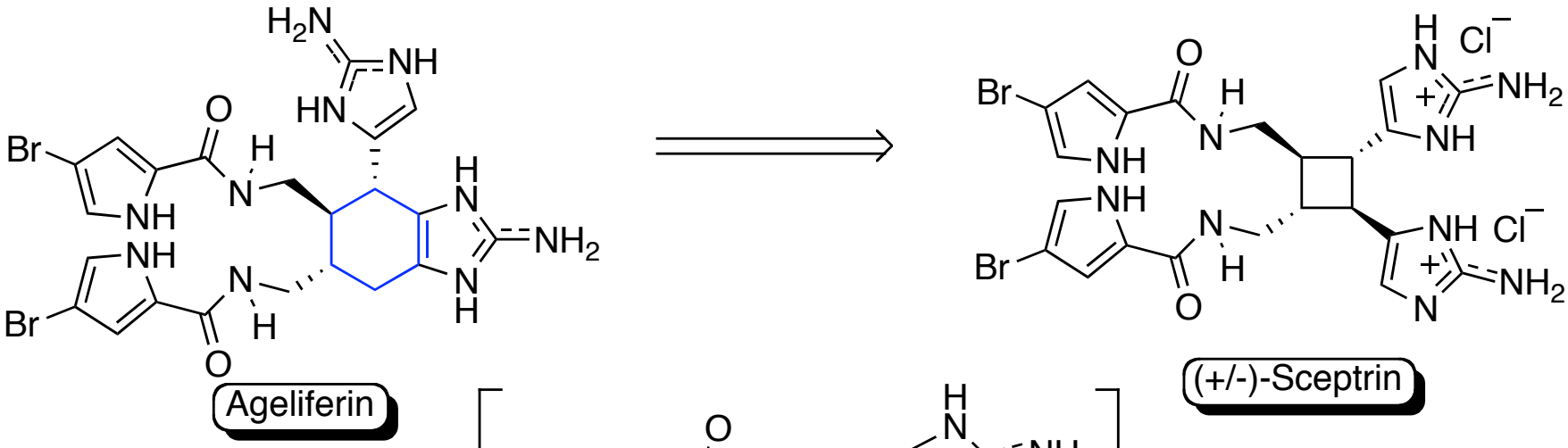


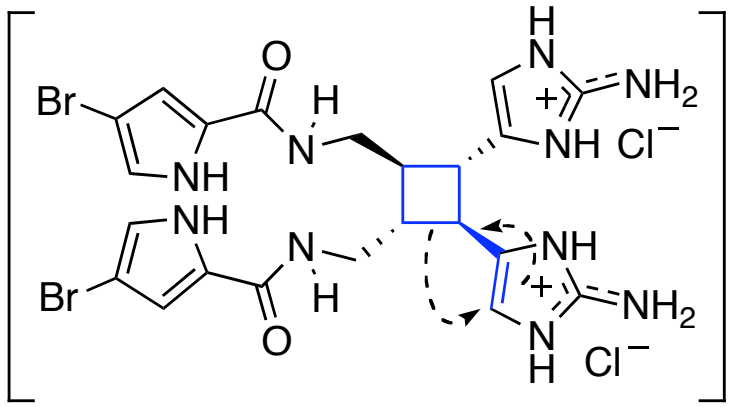
- 1st Reported synthesis of Sceptrin
- No chromatography, 24% yield from DMAD
- Later that year a second synthesis was reported by Birman which utilized a [2+2] photocycloaddition (see Birman, V. B.; Jiang, X-T. *Org. Lett*. **2004**, *6*, 2369-2371

Baran, P. S.; Zografos, L.; O'Malley, D. P.; *J. Am. Chem. Soc.*, **2004**, *126*, 3726-3727

Sceptrin Relation to Ageliferin

- Can Ageliferin be obtained from Sceptrin?

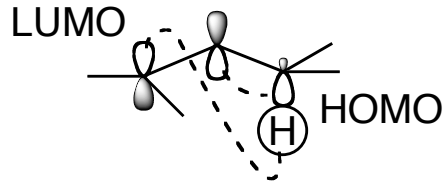




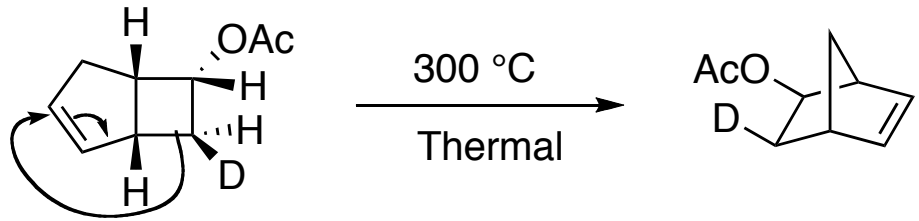
Vinyl Cyclobutane Rearragnement

FMO-Analysis for [1,3]-Rearrangents

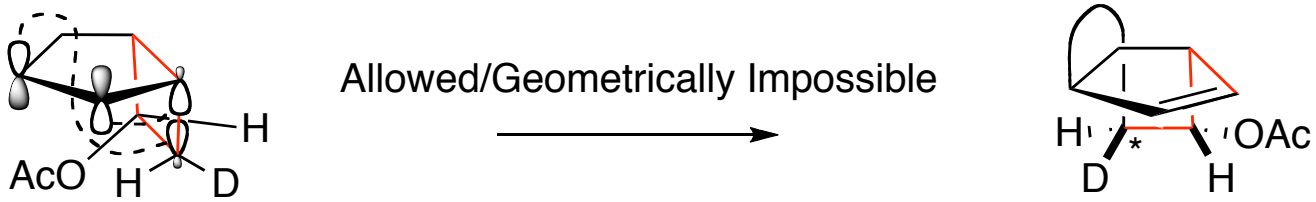
Antrafacial allowed for thermal [1,3]-hydride shift, but very rare



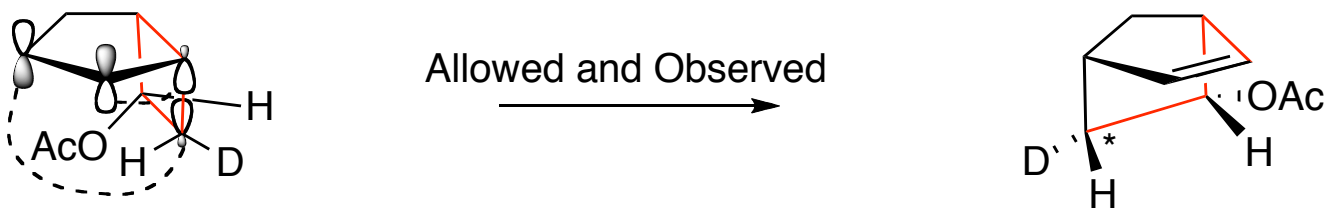
Rearragements of vinyl-cyclobutenes



Antarafacial migration with retention (C*)



Suprafacial migation with inversion (C*)

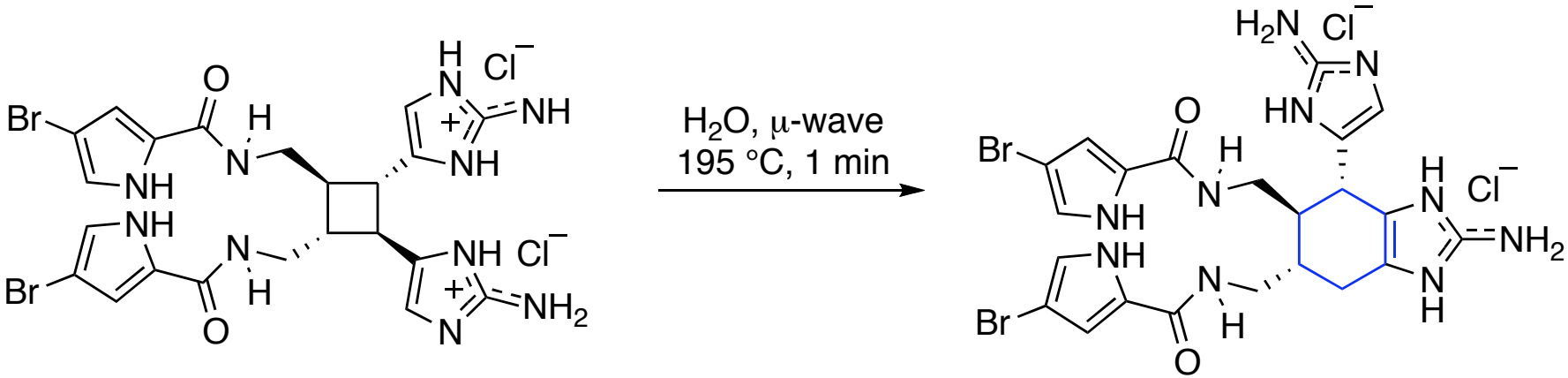


-Not likely with hydrogen because p-orbitals are too high in energy

I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, John Wiley & Sons, New York, 1978

Synthesis of Ageliferin

- Experimental Test



(+/-)-Sceptrin
52 % recovered

Ageliferin
40% yield

- First synthesis of Ageliferin

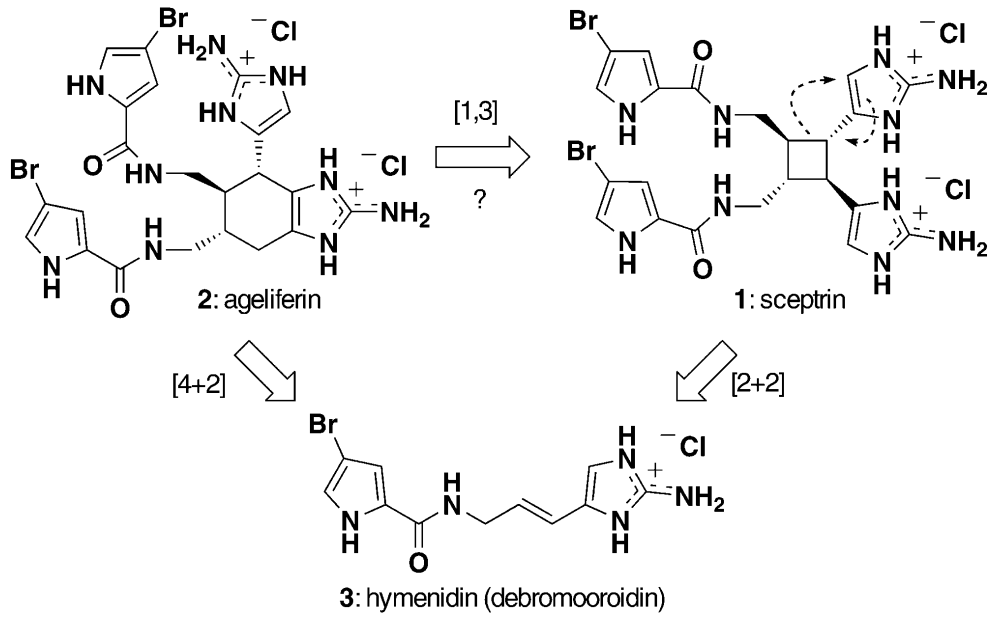
- Observe retention of configuration at migrating carbon suggests radical pathway (also, computational study w/Houk)

- What implications does this have on biosynthesis

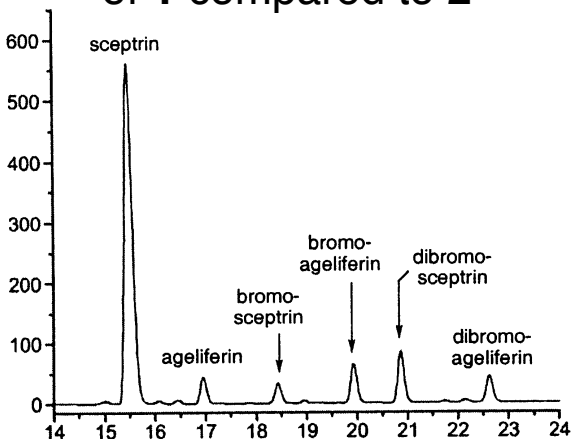
Baran, P. S. O'Malley, D. P.; Zografos, A. L..; *Angew. Chem. Int. Ed.*, **2004**, *43*, 2674-2677

Baran's Biosynthetic Hypothesis

(1) Baran and co-worker's proposes that sceptrin is the biosynthetic precursor of ageliferin via [1,3]-rearrangement
(2) Previous hypothesis proposes ageliferin is derived from debromrooroidin via a [4+2]



<u>Thermodynamic Argument of Baran and co-workers:</u>
Proposal (2) is not consistent w/isolation abundance of **1** compared to **2**



- Harsh conditions needed, could an enzyme overcome high activation barrier?
- Biological systems do not always give thermodynamic product (e.g. trans-azabicyclo[3.3.0]cyclooctane of Palau'amine)

Baran, P. S. O'Malley, D. P.; Zografos, A. L..; *Angew. Chem. Int. Ed.*, **2004**, *43*, 2674-2677

Outline

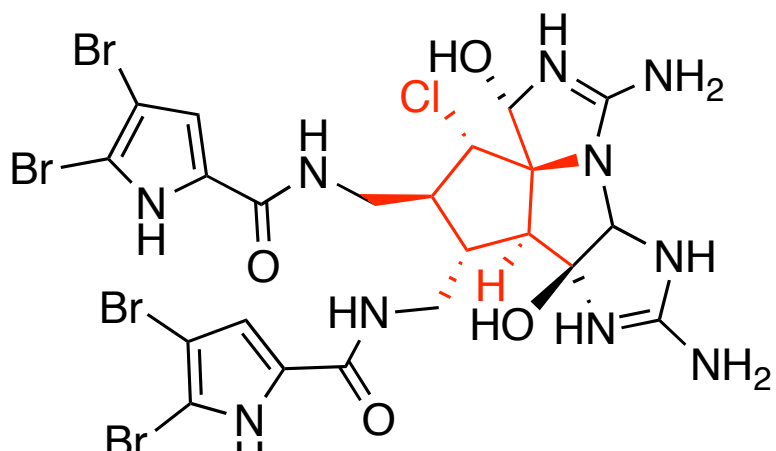
- Introduction
- Structure
  - -Revisions by characterization of new family members
  - -Overman synthesis
- Baran synthesis of Sceptrin and Ageliferin
  - -Biosynthetic implications
- Synthesis of Axinellamine
  - -Synthesis of core by Carreira (2000)
  - -First reported synthesis by Baran (2008)

Synthesis of Axenellamine

- 1st isolated and characterized in 1999
- Tetracycle with 8 contiguous stereocenters
- Major challenges

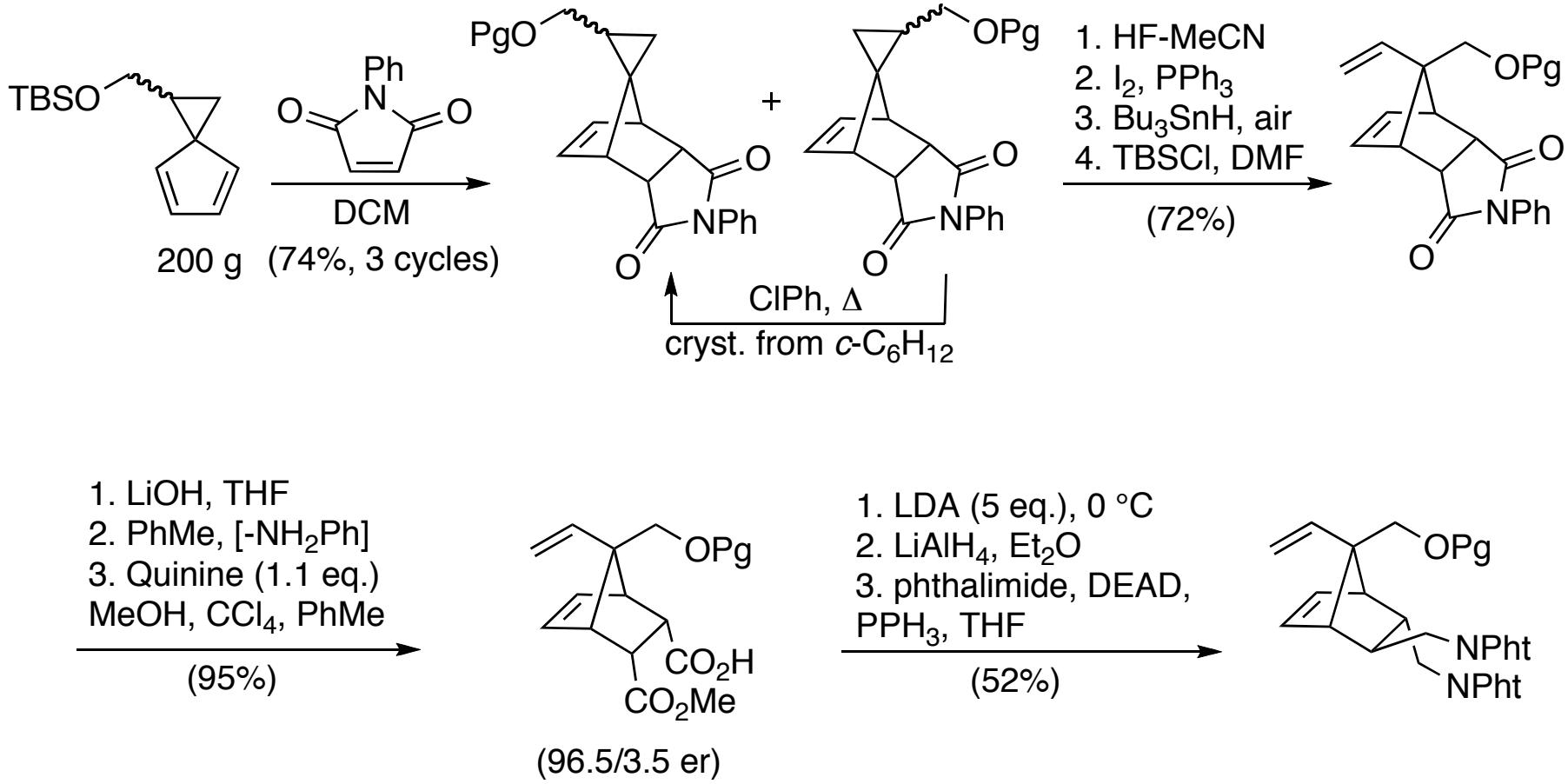
  > Accessing the fully substituted cyclopentane core

  > Introduction of correct oxidation around periphery



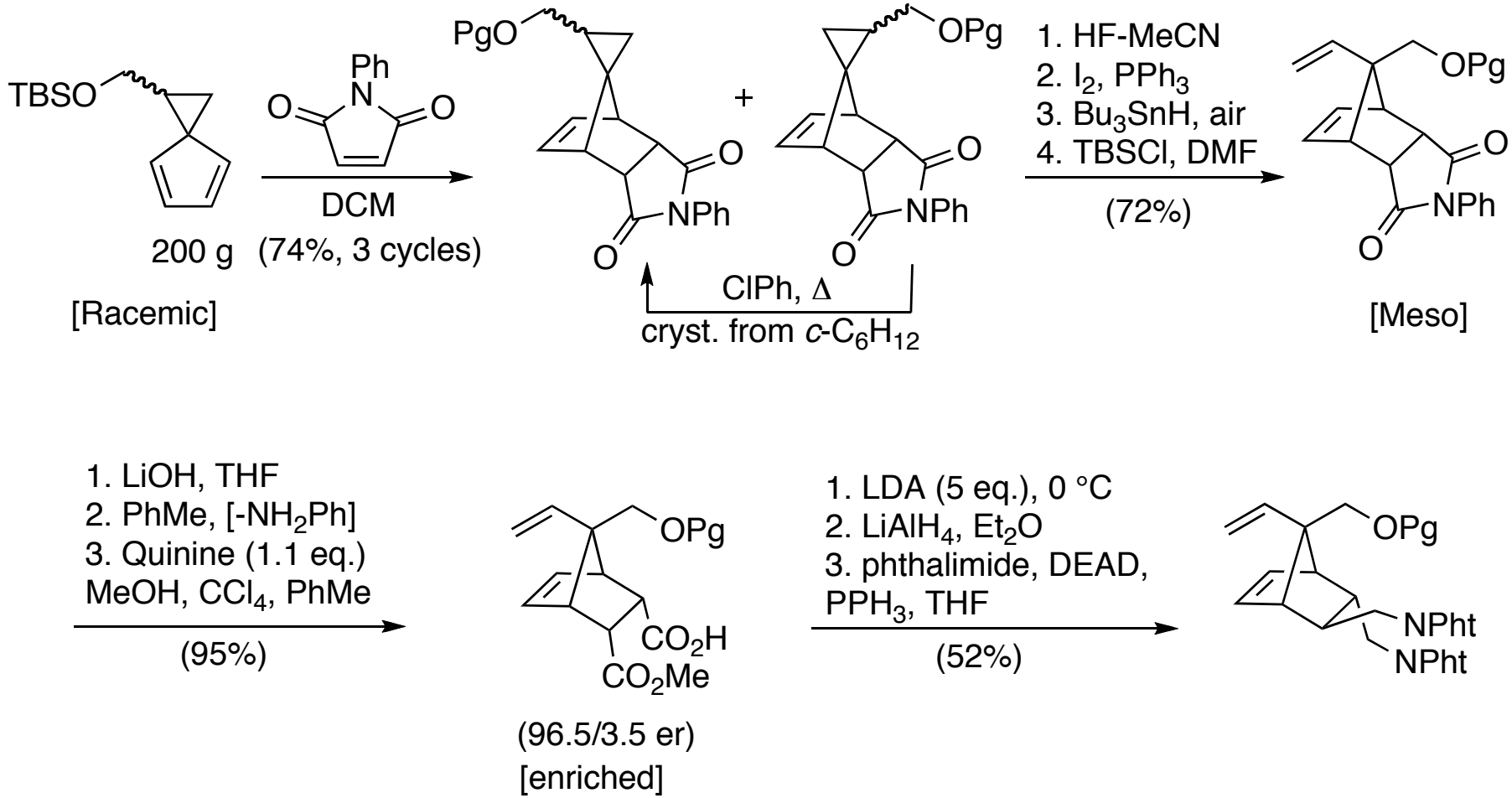
Axinellamine

Carreira Synthesis of Axinellamine Core



Ledford, B. E.; Carreira, E. M.; *J. Am. Chem. Soc.* **2000**, *117*, 11811-11812

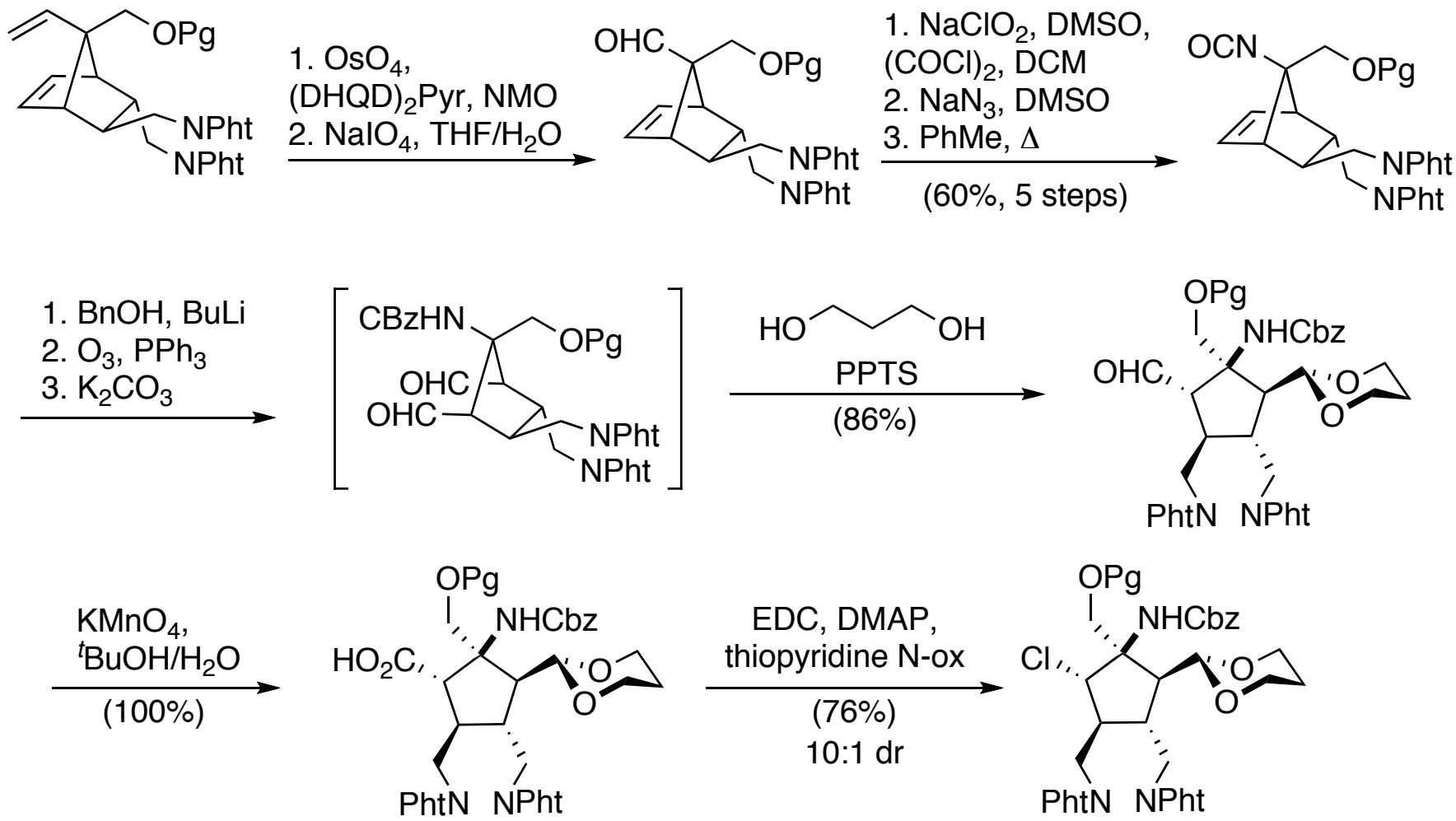
Carreira Synthesis of Axinellamine Core



- Racemic -> Meso -> Desymmetrization

Ledford, B. E.; Carreira, E. M.; *J. Am. Chem. Soc.* **2000**, *117*, 11811-11812

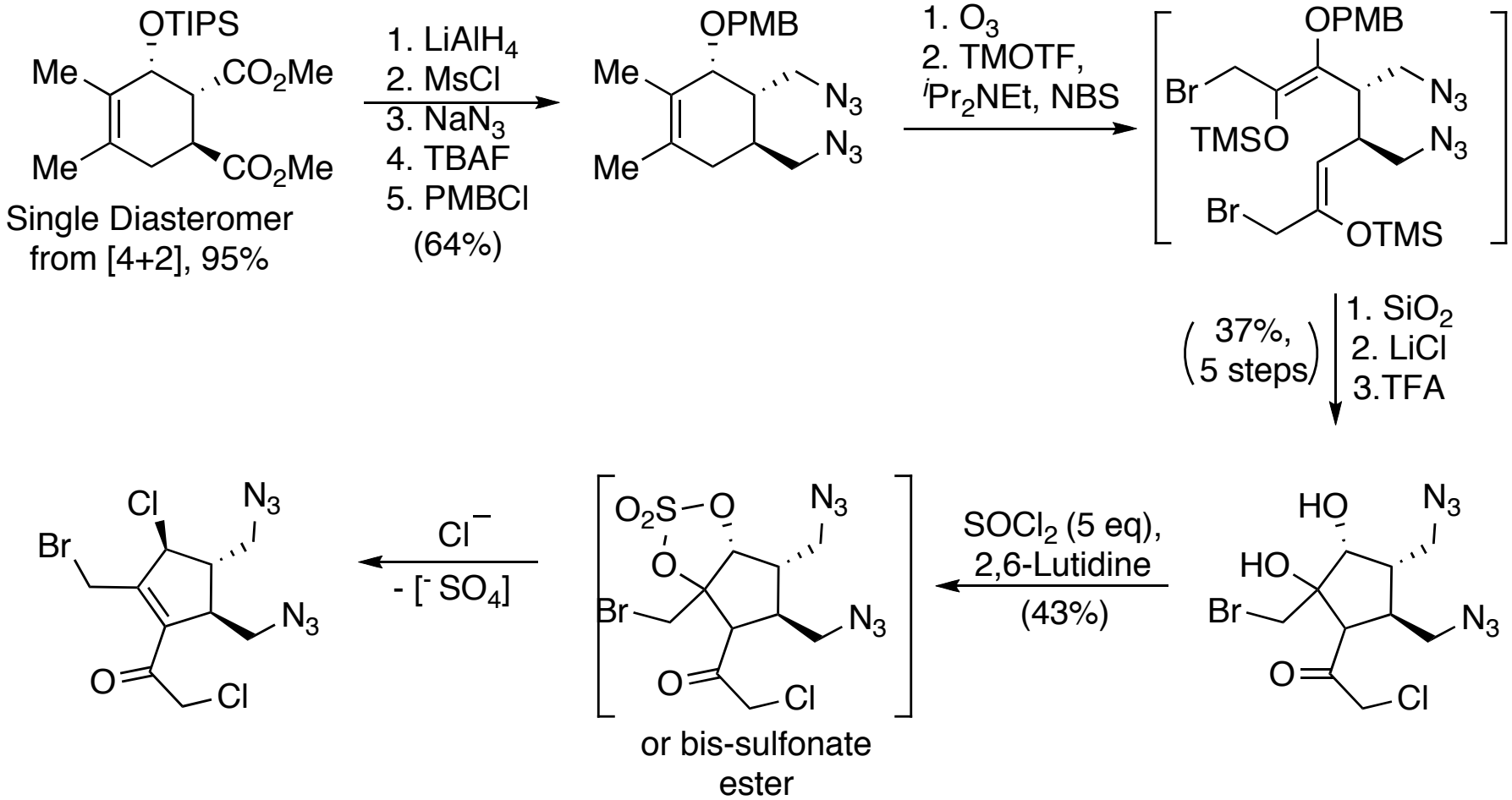
Carreira Synthesis of Axinellamine Core



Ledford, B. E.; Carreira, E. M.; *J. Am. Chem. Soc.* **2000**, *117*, 11811-11812

Baran Synthesis of (+/-)-Axinellamine

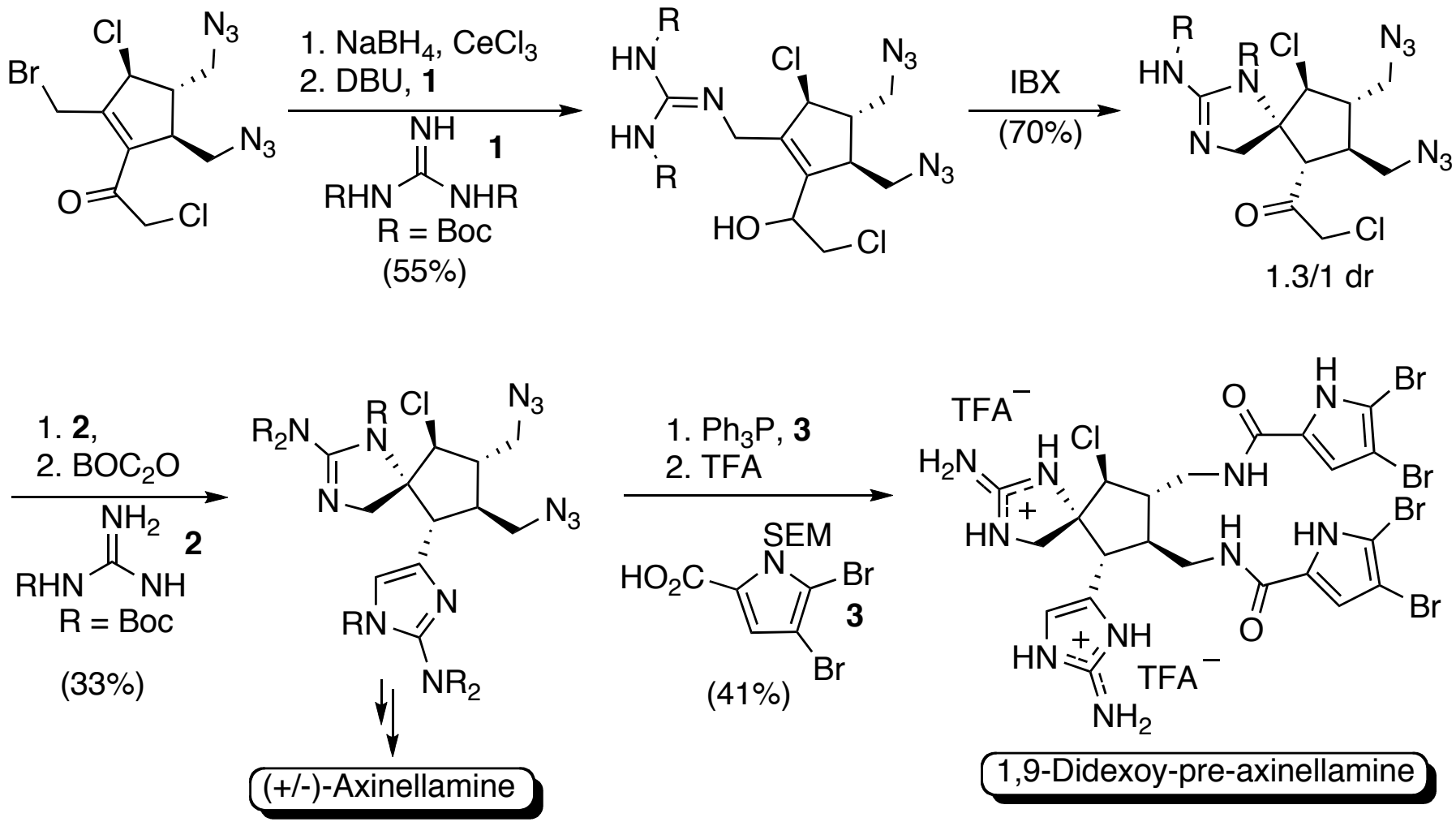
- Synthesis of cyclopentane core



Yamaguchi, J. Seiple, I. B. Young, I. S.; O'Malley, D. P.; Maue, M.; Baran, P. S. *Angew. Chem. Int. Ed.* **2008**, *47*,3578-3580

Baran Synthesis of (+/-)-Axinellamine

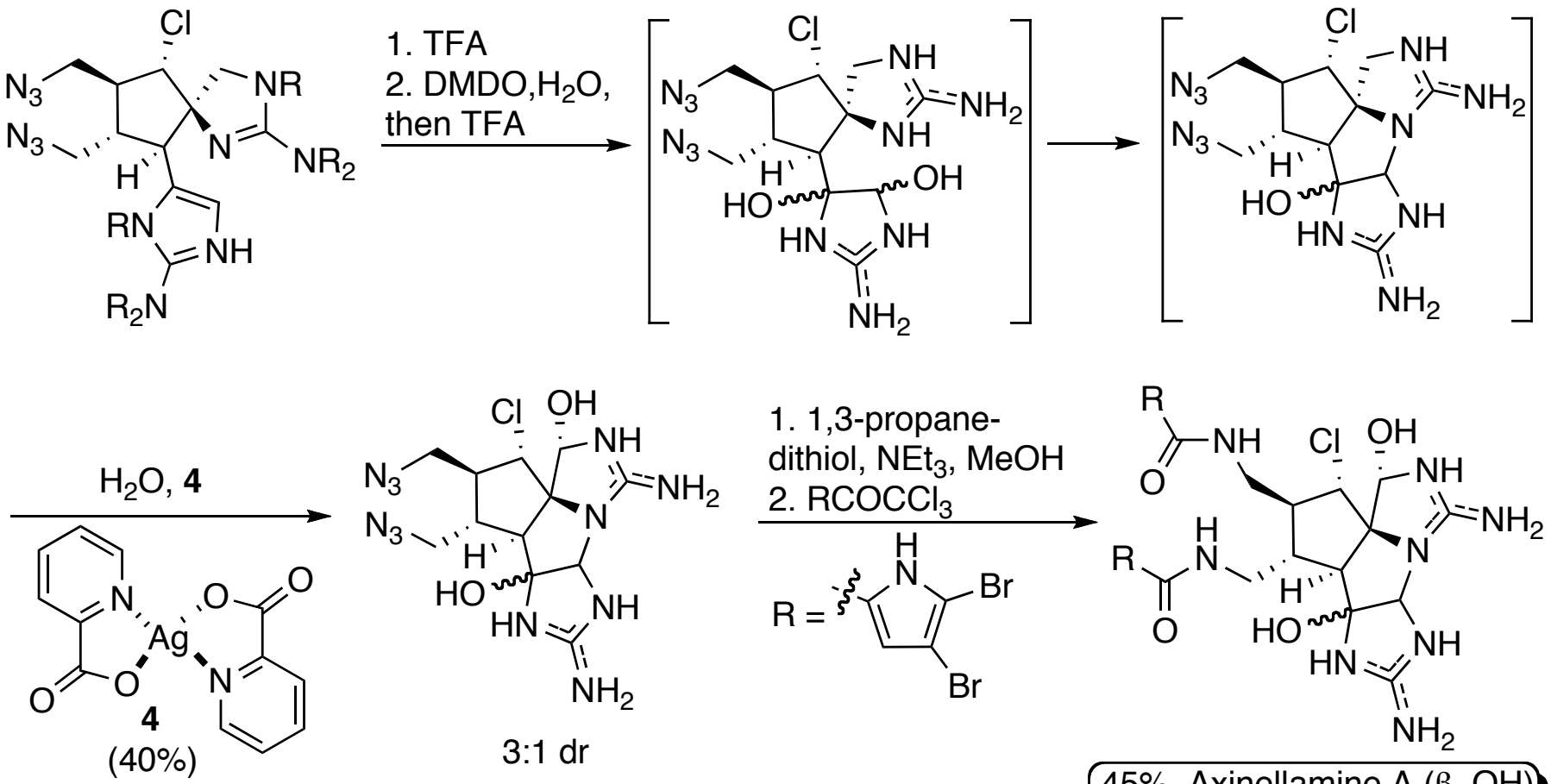
- Installation of bis-guanidines



Yamaguchi, J. Seiple, I. B. Young, I. S.; O'Malley, D. P.; Maue, M.; Baran, P. S. *Angew. Chem. Int. Ed.* **2008**, *47*,3578-3580

Baran Synthesis of (+/-)-Axinellamine

- Completion of Synthesis

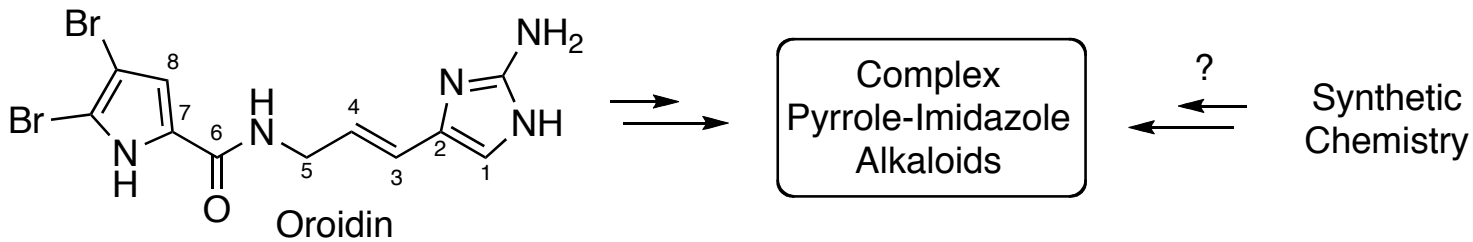


- Overall yield is 0.004 %
- Most complicated pyrrole-imidazole alkaloid synthesized to date

O'Malley, D. P; Yamaguchi, J;. Young, I. S.; Seiple, I. S.; Baran, P. S. *Angew. Chem. Int. Ed.* **2008**, *47*,3581-3583

Conclusions

• Nature has designed a simple building block able to access extremely complex architectures



• Important lessons to be learned from biosynthesis in regards to future synthetic efforts

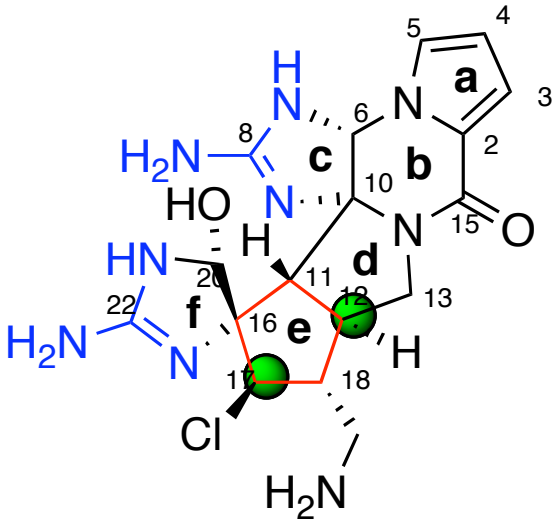
• Structure elucidation of palau'amine

> Large structural implications for switching configuration at C12

> Original isolation and characterization was very close (cis may have originally been favored b/c trans is so strained)

> Always double check the data

> Will this pave the road to new syntheses?



References

- Reviews on Pyrrole-Imidazole Alkaloids including Palau'amine:

  Kock, M; Grube, A.; Seiple, I. B. Baran, P. S. *Angew. Chem. Int. Ed*, **2007**, *47*, 6586-6594

  Jacquot, D. E. N.; Lindel, T. *Curr. Org. Chem*. **2005**, 9, 1551-1565

  Lindel, T. *Synthesis*, **2003**, 1753

  Mourabit, A. A.; Potier, P. *Eur. J. Org. Chem*. **2001**, 237-243

- Isolation, Structure Determination and Revisions of Palau'amine:

  Katz, J. D.; Overman, L. E. *J. Am. Chem. Soc.*, **2007**, *129*, 12896-12900

  Grube, A.; Kock, M; *Angew. Chem. Int. Ed*, **2007**, *46*, 2320-2324

  Kinnel, R. B.; Gehrken, H. P.; Scherer, P. J.; *J. Am. Chem. Soc.* **1993**, 3376-3377

- Total Synthesis of Sceptrin and Ageliferin:

  Baran, P. S.; Zografos, L.; O'Malley, D. P.; *J. Am. Chem. Soc.*, **2004**, *126*, 3726-3727

  Baran, P. S. O'Malley, D. P.; Zografos, A. L..; *Angew. Chem. Int. Ed.*, **2004**, *43*, 2674-2677

  Birman, V. B.; Jiang, X-T. *Org. Lett.* **2004**, *6*, 2369-2371

- Core Synthesis and Total Synthesis of Axinellamine:

  Baran, P. S. et. al. *Angew. Chem. Int. Ed.* **2008**, *47*,3578-3580

  Baran, P. S. et. al. *Angew. Chem. Int. Ed.* **2008**, *47*,3581-3583

  Ledford, B. E.; Carreira, E. M.; *J. Am. Chem. Soc.* **2000**, *117*, 11811-11812

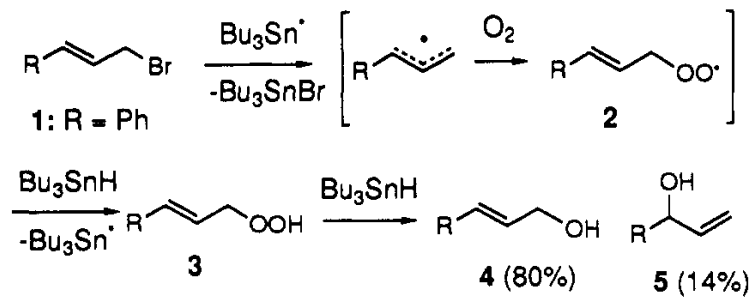
- Group Exercises:

  Nelson, S. F.; Calabrese, J. C. *J. Am. Chem. Soc.* **1973**, *95*, 8385-8388

  Overman, L. E. et. al. *J. Org. Chem.* **2002**, *67*, 7880-7883

Backup Slides: Nakamura chemistry

Scheme I



Scheme II

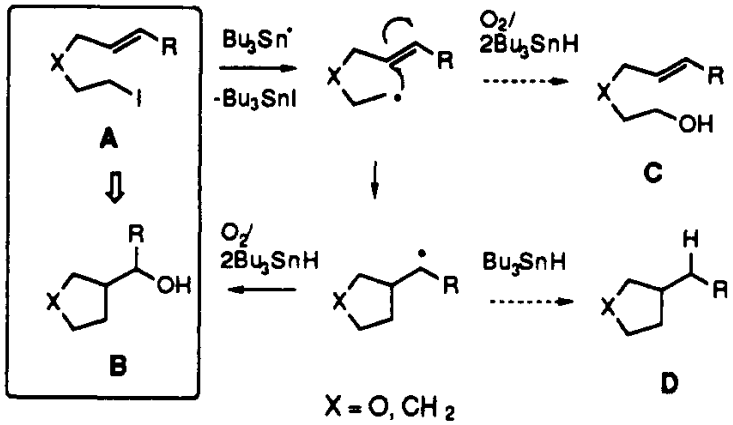
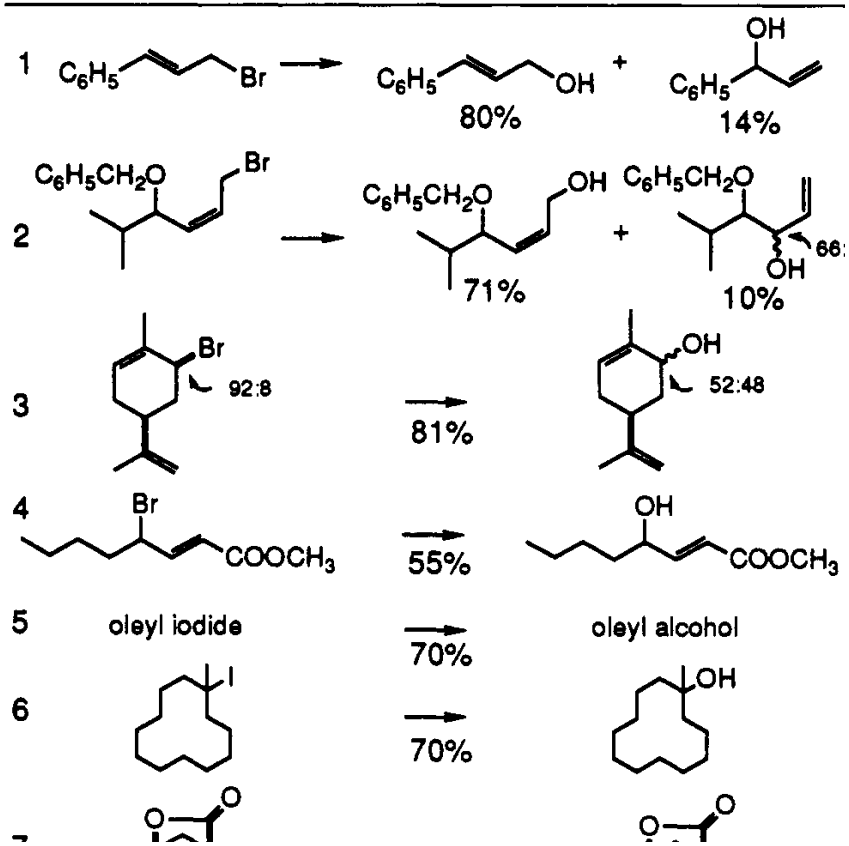


Table I. Reductive Oxygenation of Organic Halides[a]



Nakuamura E. et. al. *J. Am. Chem. Soc.* **1991**, *113*, 8980