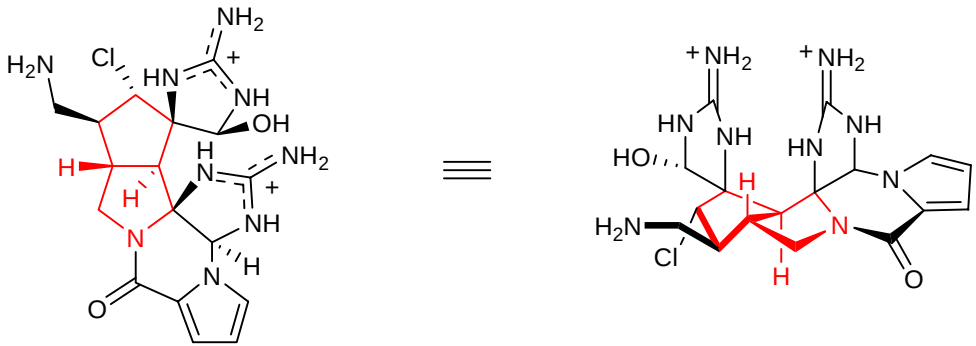
Total Synthesis of Palau'amine

Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem. Int. Ed.* **2009**, *early view*.



Chad Hopkins

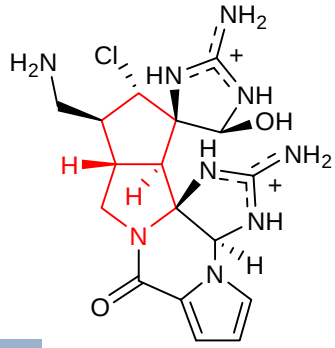
Wipf Group Literature Presentation

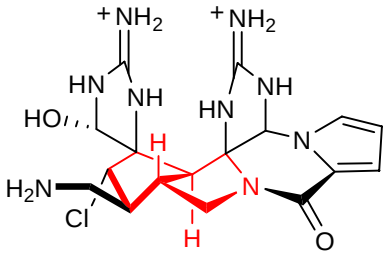
1-23-10

Isolation and Biological Activity

Stylotella aurantium

Meaning of Hawaiian word palau: *war club*





(revised structure)

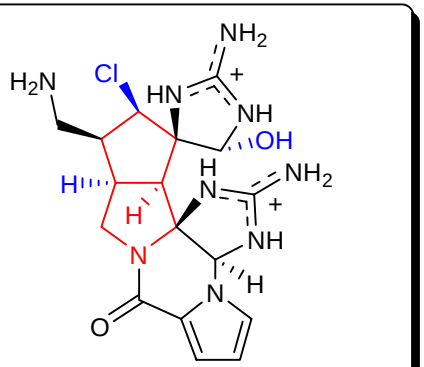
Chad Hopkins @ Wipf Group

- Isolated in 1993 from the sea sponge *Stylotella agminata* collected from the Western Caroline Islands in the Republic of Palau
- Low acute toxicity (LD_{50} 13mg/kg, mice)
- Significant immunosuppressive and antitumor activities (IC_{50}'s for P-388 and A-549 were 0.1 and 0.2 µg/mL, respectively)
- Displays antifungal and antibacterial activities
- Authors note that the dust from the sponge caused allergic reactions consisting of *severe* shortness of breath lasting for about 4 h and skin rashes.

Kinnel, R. B.; Gehrken, H.-P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376.

Kinnel, R. B.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281.

Synthetic Challenges



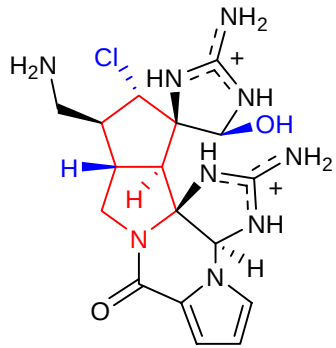
cis-5,5

A Formidable Opponent…..

Synthetic Publications: 34

PhD. Dissertations: 26

Total Synthesis: 1 (title paper)



trans-5,5

original structure

(incorrect)

revised structure

(correct)

- Unusually high nitrogen content (N/C ~ 1 : 2)
- Highly strained core with 8 contiguous stereocenters
- High polarity translates into difficulty in performing manipulations (solubility, purifications, etc.)
- pH stability (decomposes under basic conditions above pH 6.5)
- Absolute stereochemistry is unknown

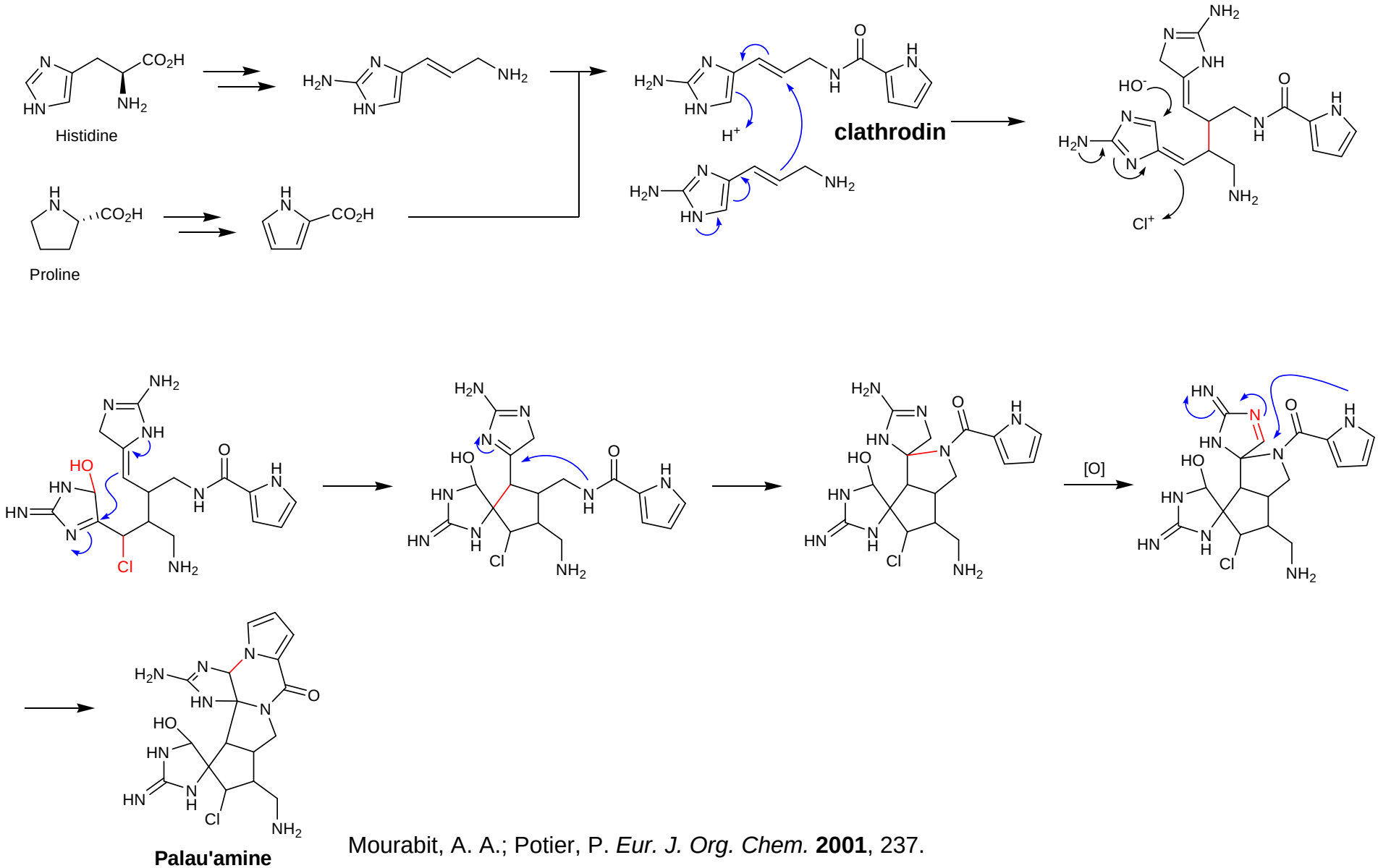
Structure revision:

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

Buchanan, M. S.; Carroll, A. R.; Quinn, R. J. *Tetrahedron Lett.* **2007**, *48*, 4573.

Kobayashi, H.; Kitamura, K.; Nagai, K.; Nakao, Y.; Fusetani, N.; van Soest, W. M.; Matsunaga, S. *Tetrahedron Lett.* **2007**, *48*, 2127.

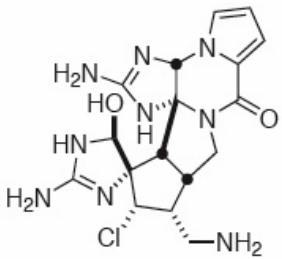
Hypothetical Biosynthesis



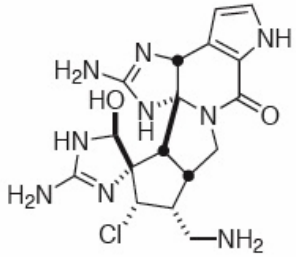
Mourabit, A. A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237.

Andrade, P.; Willoughby, R.; Pomponi, S. A.; Kerr, R. G. *Tetrahedron Lett.* **1999**, *40*, 4775.

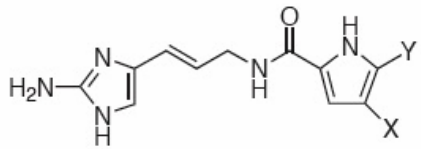
Oroidin-Derived Alkaloids



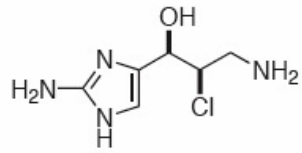
palau'amine (**1**)



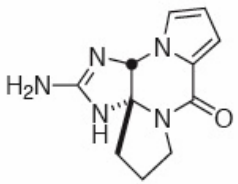
styloguanidine (**2**)



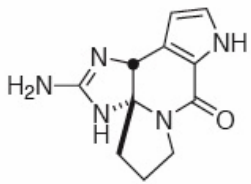
oroidin (X = Y = Br) (**3**)
hymendin (X = Br, Y = H) (**4**)
clathrodin (X = Y = H) (**5**)



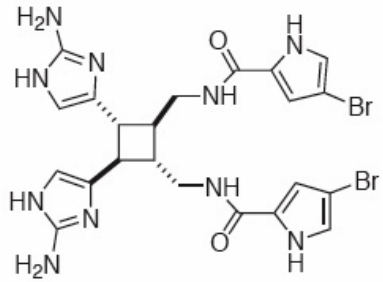
girolline (**6**)



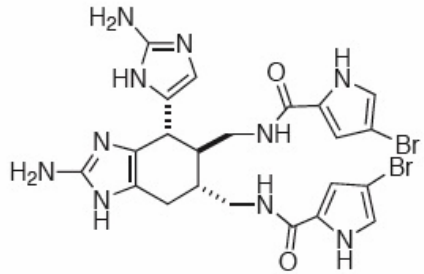
phakellin (**7**)



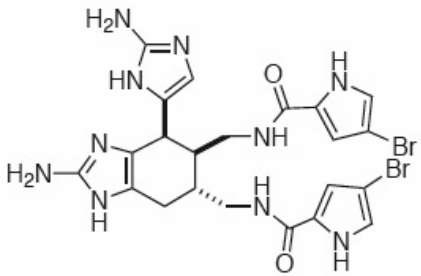
cantharelline (**8**)



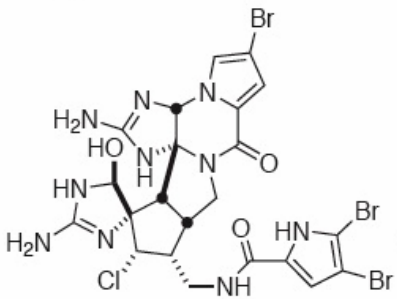
sceptrin (**9**)



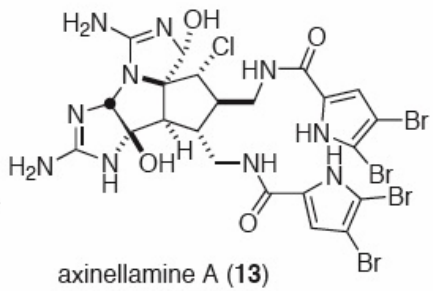
ageliferin (**10**)



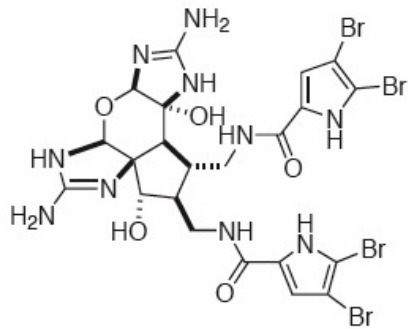
nagelamide E (**11**)



konbu'acidin A (**12**)



axinellamine A (**13**)



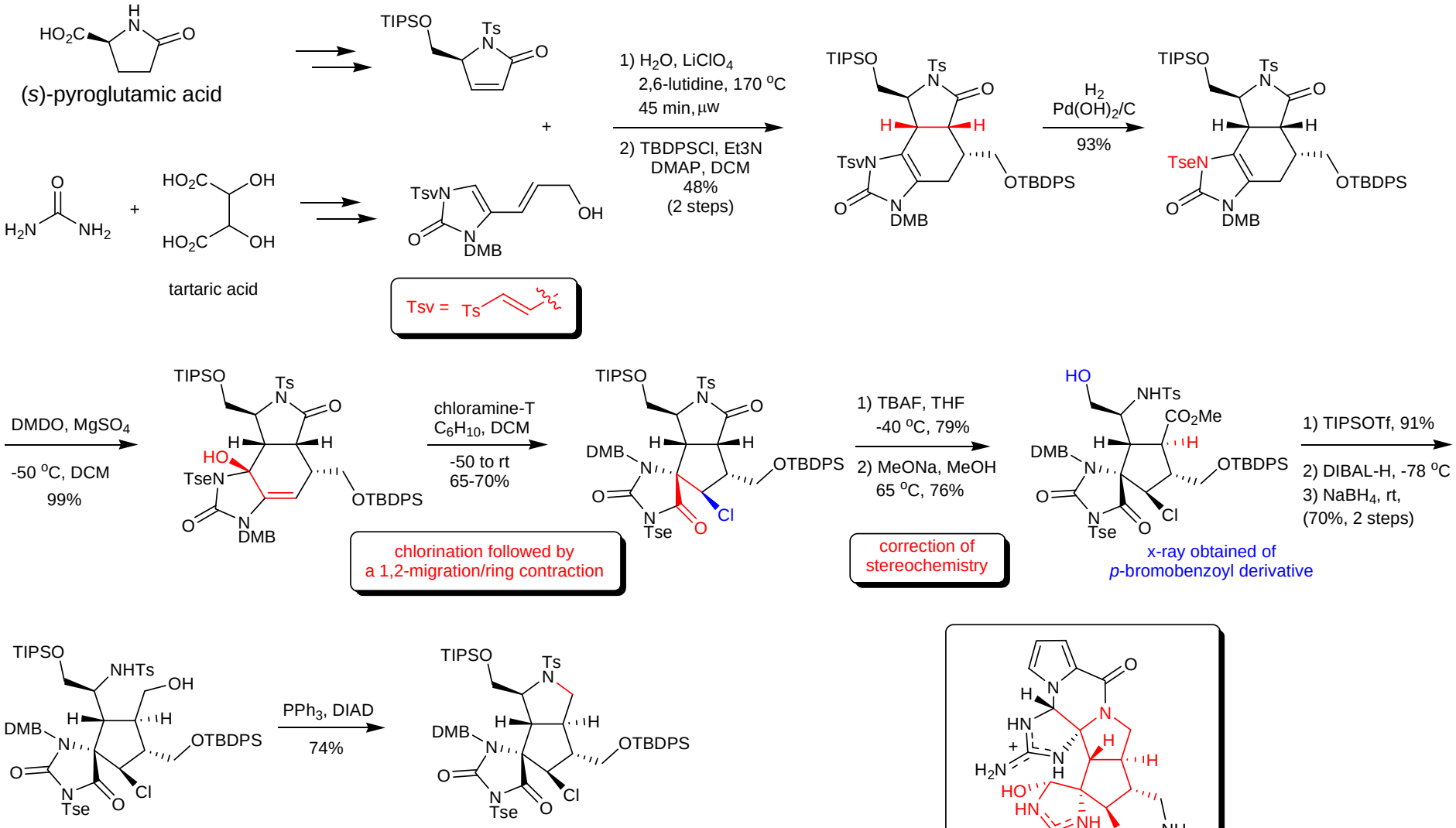
massadine (**14**)

Figure blatantly stolen from:

Du, H.; He, Y.; Sivappa, R.; Lovely, C. J. *Synlett* **2006**, 965.

Disclaimer: Relative stereochemistry unrevised

Highlights of Selected Previous Efforts Towards Palau'amine (Romo)



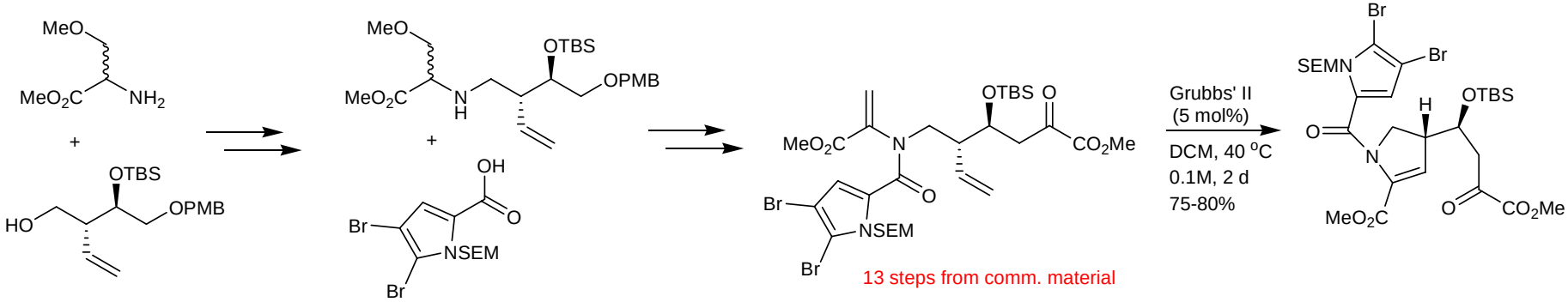
Dilley, A. S.; Romo, D. *Org. Lett.* **2001**, *3*, 1535.

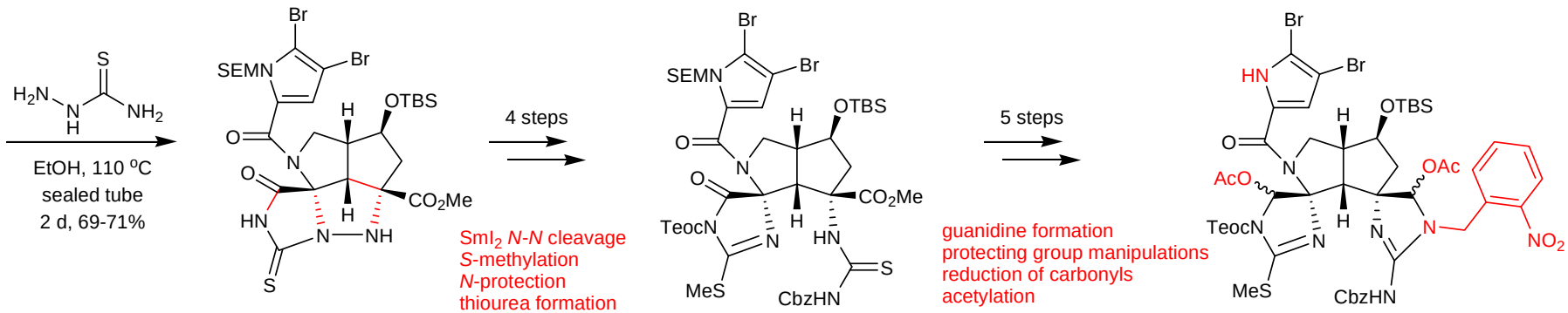
Dransfield, P. J.; Wang, S.; Dilley, A.; Romo, D. *Org. Lett.* **2005**, *7*, 1679.

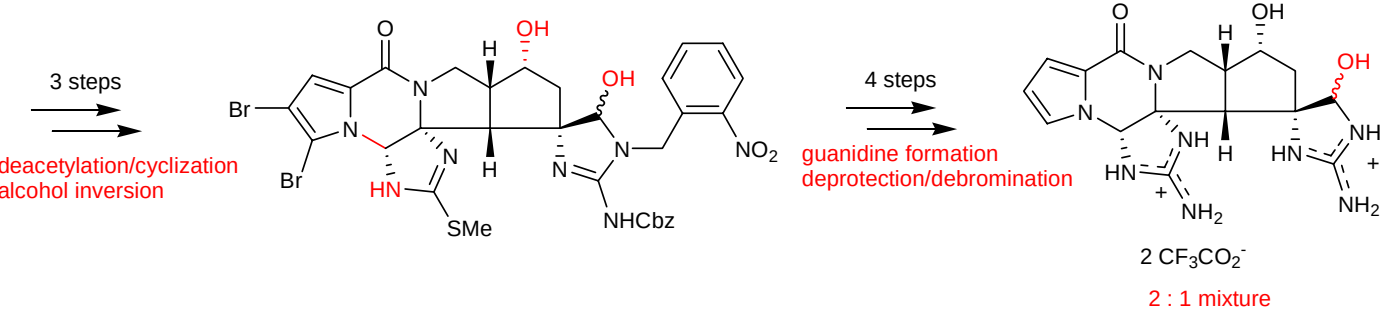
Wang, S.; Dilley, A. S.; Poullenec, K. G.; Romo, D. *Tetrahedron* **2006**, *62*, 7155.

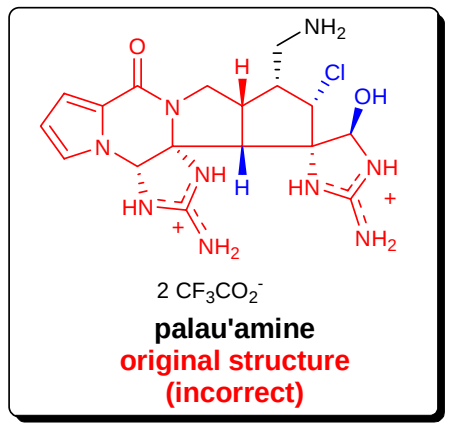
Dransfield, P. J.; Dilley, A. S.; Wang, S.; Romo, D. *Tetrahedron* **2006**, *62*, 5223; Zancanella, M. A.; Romo, D. *Org. Lett.* **2008**, *10*, 3685.

Highlights of Selected Previous Efforts Towards Palau'amine (Overman)





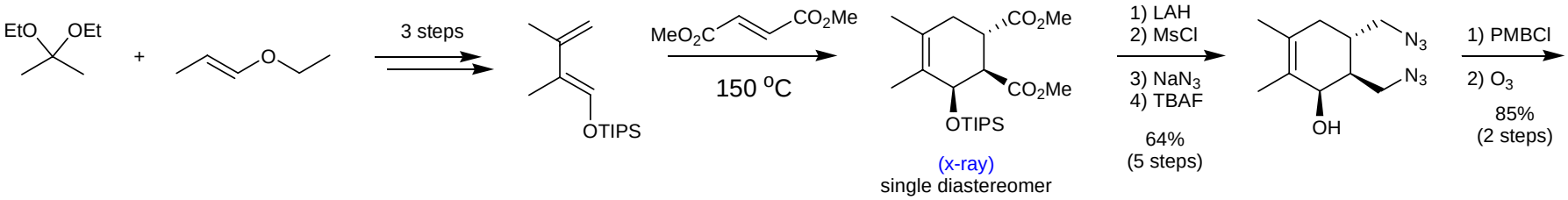


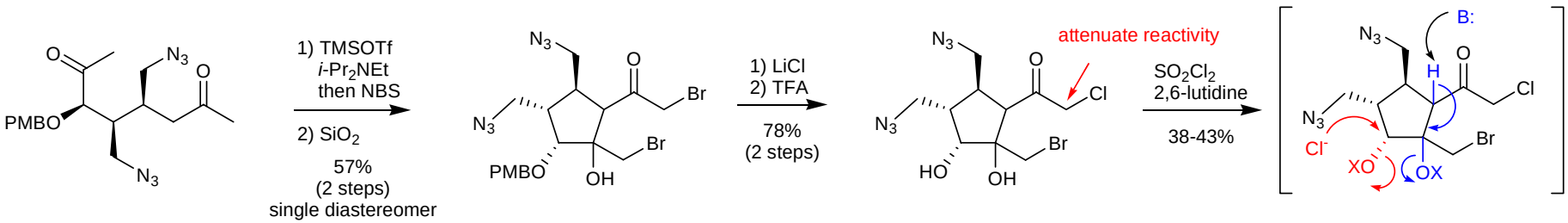


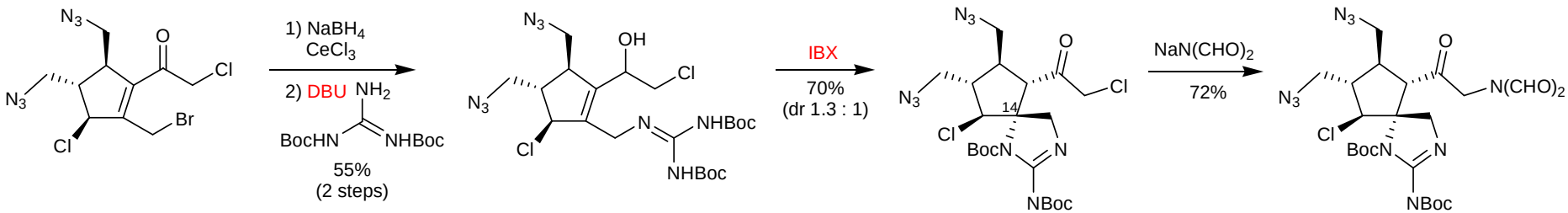
Katz, J. D.; Overman, L. E. *Tetrahedron* **2004**, *60*, 9559.

Lanman, B. A.; Overman, L. E.; Paulini, R.; White, N. S. *J. Am. Chem. Soc.* **2007**, *129*, 12896.

Synthesis of Functionalized Cyclopentane Core





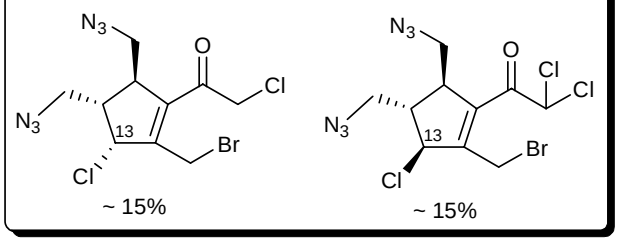


avoids intramolecular epoxidation and/or guanidine cyclization

other oxidation conditions afforded incorrect spirodiastereomer at C14

~ 2g prepared
19 steps, 1% overall

Chlorination Side Products

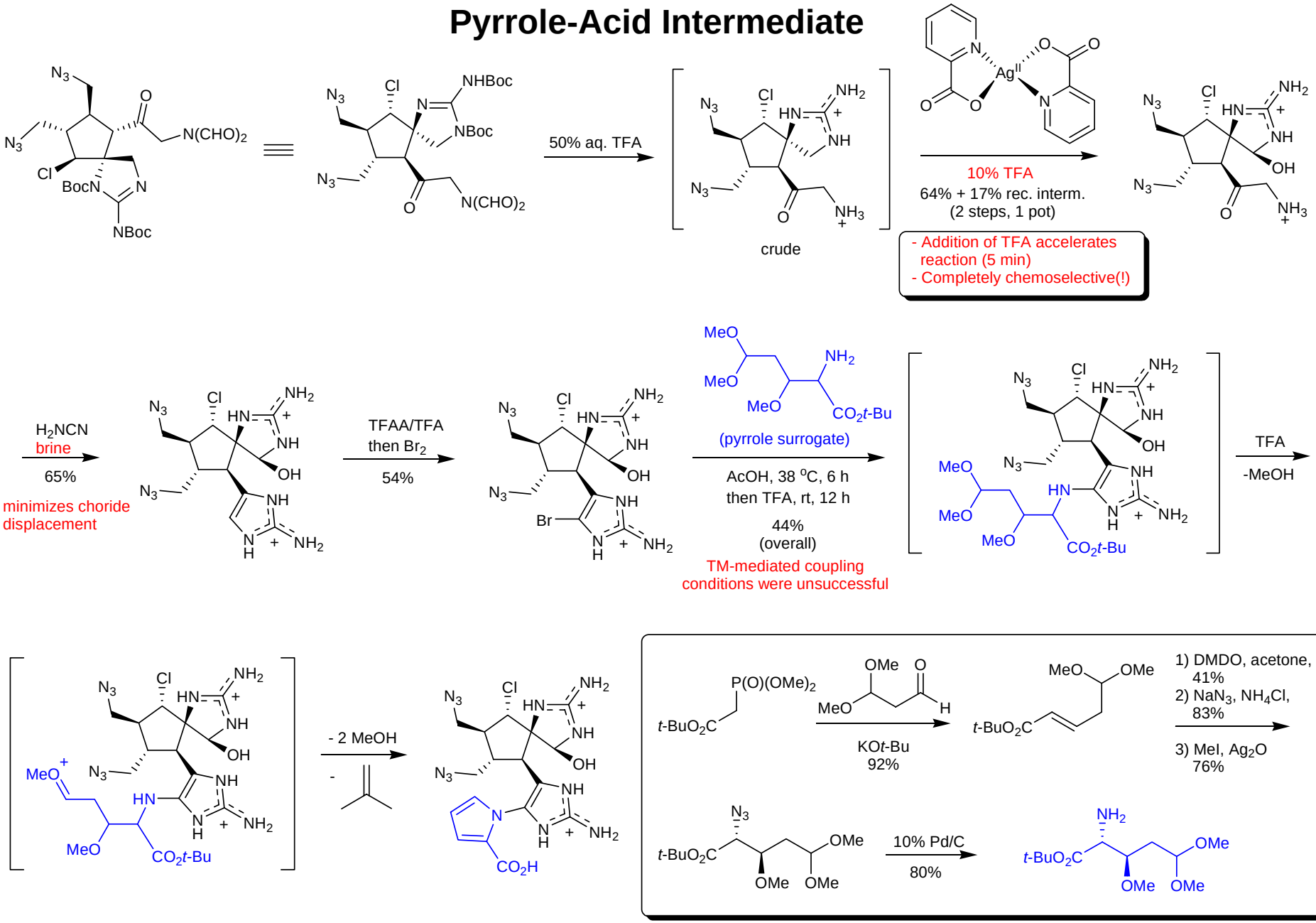


Gosselin, P.; Bourdy, C.; Mille, S.; Perrotin, A. *J. Org. Chem.* **1999**, *64*, 9557.

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

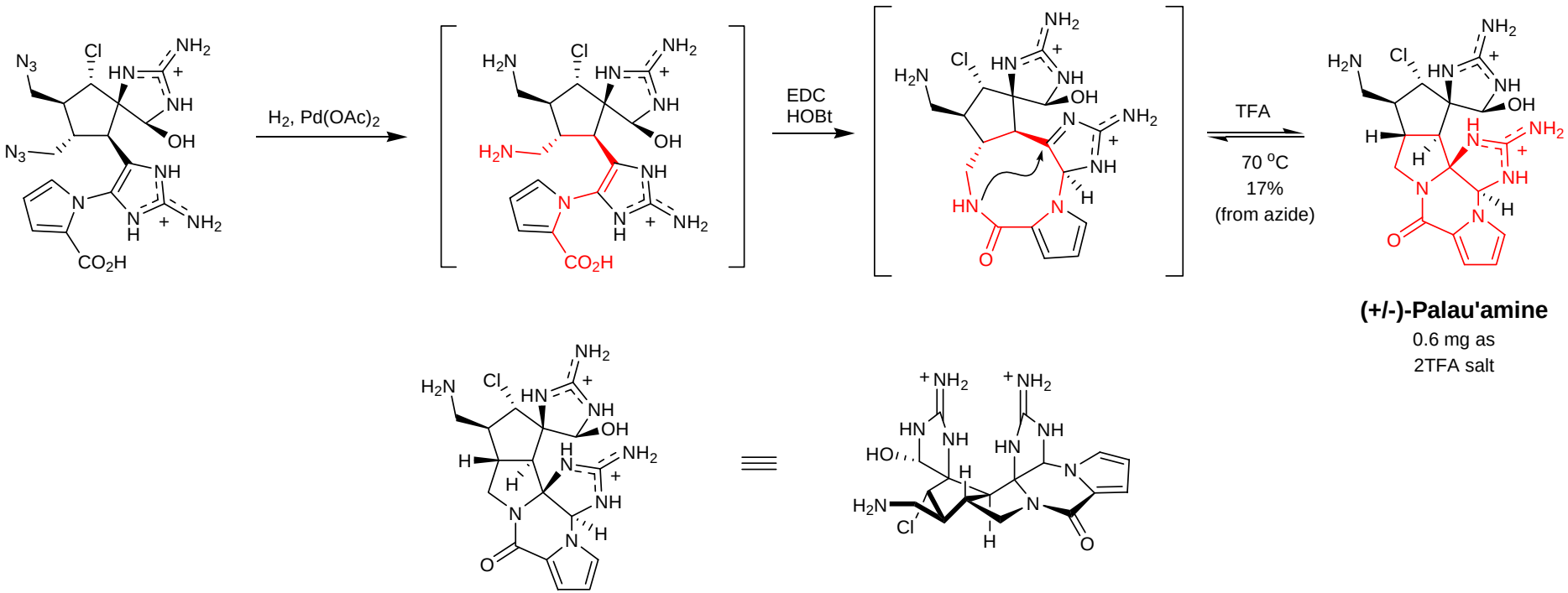
Su, S.; Seiple, I. B.; Young, I. S.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 16490.

Pyrrole-Acid Intermediate



Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem. Int. Ed.* **2009**, *Early View*.

Completion of Racemic Palau'amine



The following was taken from the SI:

- Attempted purification of intermediates (*in the above sequence*) led to a reduced yield of 'final product' due to their extreme polarity leading to difficulty in separation
- Purification of 'final product' had to be performed twice on two columns *(RP HPLC*) in 5-8 batches each

Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem. Int. Ed.* **2009**, *Early View*.

……what was the inspiration for the trans-annular cyclization?

Spectroscopic Comparison (^{1}H NMR)

Position	Natural (Quinn)[a]	Natural (Scheuer)[b]	Synthetic
3	6.89 (dd, 3.9, 1.6)	6.85 (dd, 3.9, 1.5)	6.89 (dd, 3.9, 1.5)
4	6.39 (dd, 3.9, 2.8)	6.35 (dd, 3.9, 2.8)	6.38 (dd, 3.9, 2.8)
5	7.03 (dd, 2.8, 1.6)	6.99 (dd, 2.8, 1.5)	7.02 (dd, 2.7, 1.6)
6	6.37 (s)	6.33 (s)	6.37 (s)
7 (N)			
8-NH_2			
9			
11	3.11 (d, 13.8)	3.08 (dd, 14.1)	3.11 (d, 14.1)
12	2.50 (m)	2.52 (dddd)	2.50 (m)
13	3.97 (dd, 10.2, 7.2)α	3.96 (dd, 10.4, 7.3)α	3.97 (dd, 10.4, 7.0)α
	3.31 (t, 10.2)β	3.28 (dd, 10.3, 10.4)β	3.31 (t, 10.2)β
17	4.34 (d, 7.8)	4.35 (d, 7.9)	4.35 (d, 7.8)
18	2.48 (m)	2.47 (dddd)	2.48 (m)
19	3.32 (dd, 13.2, 6.6)α	3.32 (dd, 13.2, 7.0)α	3.32 (dd, 13.3, 6.5)α
	3.27 (dd, 13.2, 6.6)β	3.24 (dd, 13.2, 7.0)β	3.26 (dd, 13.3, 6.5)β
20	5.98 (s)	5.96 (s)	5.98 (s)
20-OH			
21 (N)			
22-NH_2			
23 (N)			
24 (N)			

Buchanan, M. S.; Carroll, A. R.; Quinn, R. J. *Tetrahedron Lett.* **2007**, *48*, 4573.

Kinnel, R. B.; Gehrken, H.-P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376.

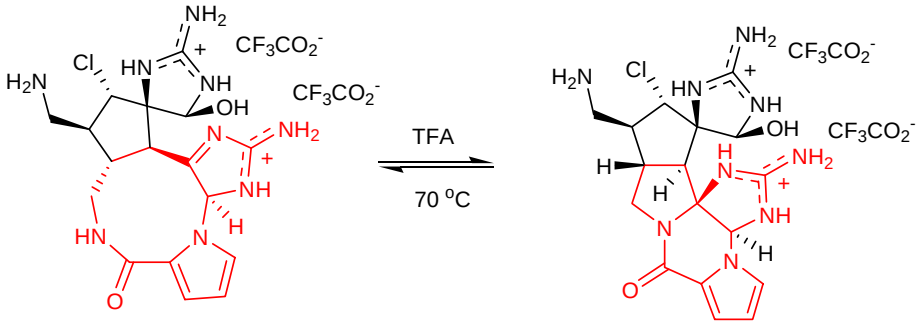
Spectroscopic Comparison (^{13}C NMR)

Position	Natural (Quinn)[a]	Natural (Scheuer)[b,c]	Synthetic
2	122.5	122.5	122.5
3	115.7	115.6	115.7
4	113.9	113.8	113.9
5	125.2	125.2	125.2
6	69.0	69.0	69.0
8	157.8	157.8[c] (159.6)[b]	157.8
10	80.7	80.8	80.8
11	56.3	56.3	56.3
12	41.8	41.8	41.9
13	46.0	46.1	46.1
15	159.5	159.5[c] (157.8)[b]	159.6
16	72.0	72.1	72.1
17	74.0	74.0	74.1
18	48.6	48.6	48.6
19	41.8	41.9	41.9
20	83.7	83.7	83.8
22	157.9	157.9	157.8

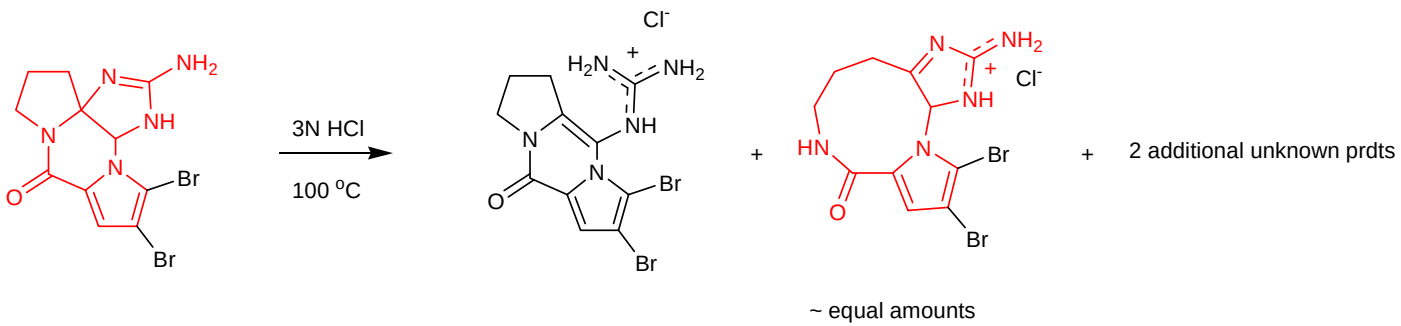
Buchanan, M. S.; Carroll, A. R.; Quinn, R. J. *Tetrahedron Lett.* **2007**, *48*, 4573.

Kinnel, R. B.; Gehrken, H.-P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376.

Inspiration for “Macro-Palau’amine”?



Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem. Int. Ed.* **2009**, *Early View*.



Sharma, G. M. *Drugs, Food, Sea, Myth, Reality [Intl. Symp. Proc.]* **1978**, 203.

Nakadai, M.; Harran, P. G. *Tetrahedron Lett.* **2006**, *47*, 3933.

“…exemplifies the innovative retrosynthetic analysis and mechanistic thinking that underpins the Baran group’s remarkable string of total synthesis…” - *C&EN*, **2010**, *88*(2), 5.

“…the macro-intermediate is just off the charts, and alone places Baran in rarified territory. It is not just non-obvious, it is totally counter intuitive on many levels…” – www.totalsynthetic.com, blogpost, Jan. 2, 2010.

Summary

- First synthesis of Palau'amine completed over 16 years after initial isolation
- Minimal protecting group operations
- Functionalized cyclopentane core prepared using strategic Diels-Alder, intramolecular aldol, and tandem oxidation/spirocyclization reactions
- Late stage chemoselective Ag(II)-picolinate oxidation installs key hemi-aminal
- Uncatalyzed coupling of pyrrole surrogate gives access to pyrrole acid intermediate
- Intriguing trans-annular cyclization establishes elusive *trans*-5,5 ring core and completes the synthesis
- According to Baran, an enantioselective, scalable variant is coming soon……please stay tuned.