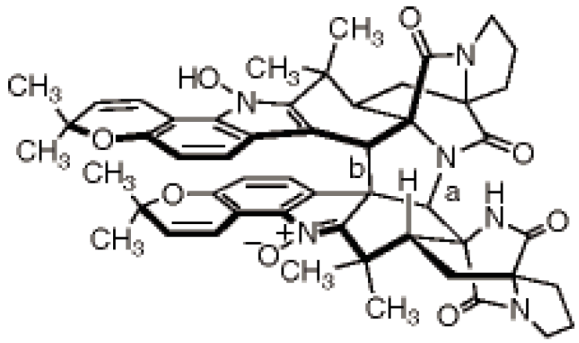
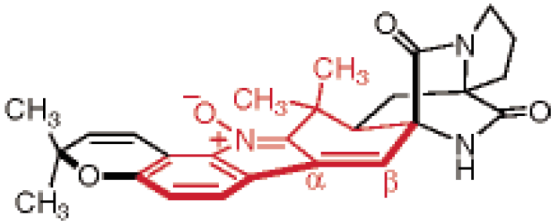
Enantioselective Synthesis of Stephacidin B



Stephacidin B

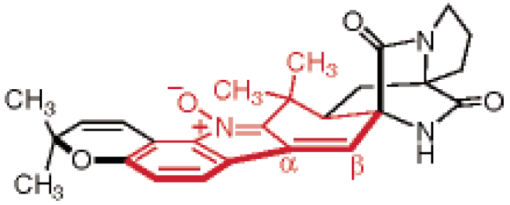


Avrainvillamide

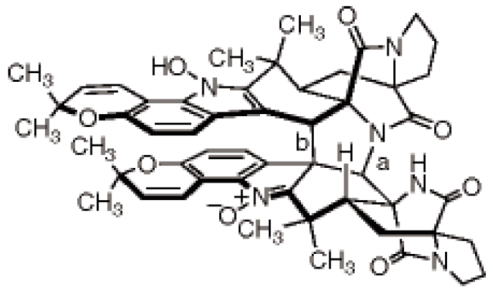
Herzon, B. S; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 5342

Department of Chemistry and Chemical Biology

Harvard University



Avrainvillamide **1**



Stephacidin B **2**

- Isolated from a culture media from various strains of *Aspergillus ochraceus*
- Stephacidin B exhibits selective, *in vitro*, cytotoxic activity against various human tumor cell lines

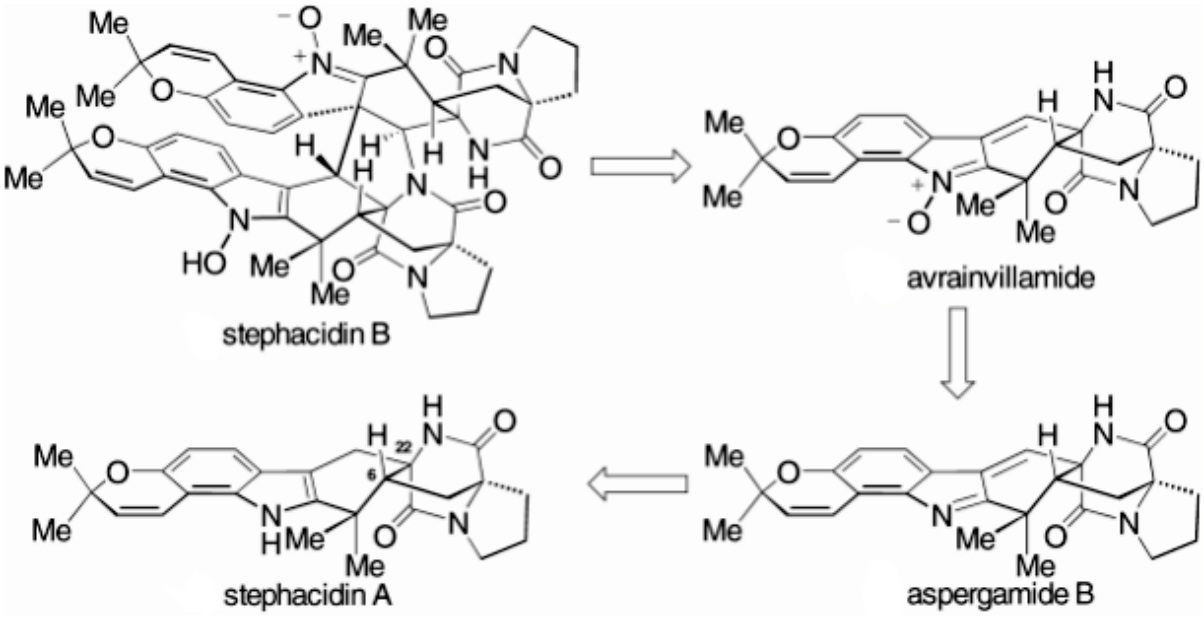
Table 1: In Vitro Cytotoxicity of **1** and **2** (IC_{50} in μM)

cell line	histotype	characteristic	**1** (IC_{50})	**2** (IC_{50})
PC3	prostate	testosterone-independent	2.10	0.37
LNCaP	prostate	testosterone-sensitive	1.00	0.06
A2780	ovarian	parental	4.00	0.33
A2780/DDP	ovarian	mutp53/bcl2+	6.80	0.43
A2780/Tax	ovarian	taxol-resistant	3.60	0.26
HCT116	colon	parental	2.10	0.46
HCT116/mdr+	colon	overexpress mdr+	6.70	0.46
HCT116/topo	colon	resistant to etoposide	13.10	0.42
MCF-7	breast	estradiol-sensitive	4.20	0.27
SKBR3	breast	estradiol-independent	2.15	0.32
LX-1	lung	sensitive	4.22	0.38

- Bioactivity is not mediated by p53, mdr, bcl2, tubulin, or topoisomerase II, which suggest a novel mechanism of action
- N-hydroxyindoles and indole nitrones are rarely isolated from natural sources

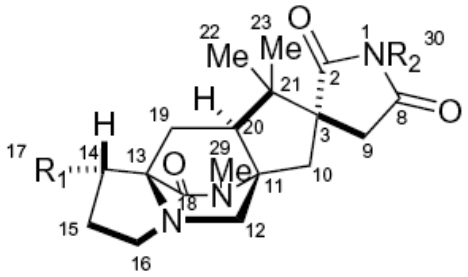
Qian-Cutrone, J.; Huang, S.; Vyas,D.; Fairchild, C.; Menendez, A,; Krampitz, K. D.; Daltiero, R.; Klohr, S. E.Shu, Y. *J. Am. Chem.Soc.* **2002**, *124*, 14556. b) Somei, M. *Adv. Hetocycl. Chem.* **2002**, *82*, 101.
c) Von Nussbaum, F.; *Angew. Chem. Int. Ed.* **2003**, *42*, 3068

Stephacidins and their proposed biogenetic relationship

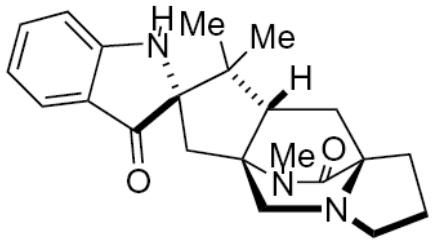


Baran, P.S.; Guerrero, C. A.; Ambhaikar, N.B.; Hafensteiner, B.D.
Angew. Chem. Int. Ed. **2004**, *44*, 606

- Other syntheses of bicyclo[2.2.2] indole alkaloids



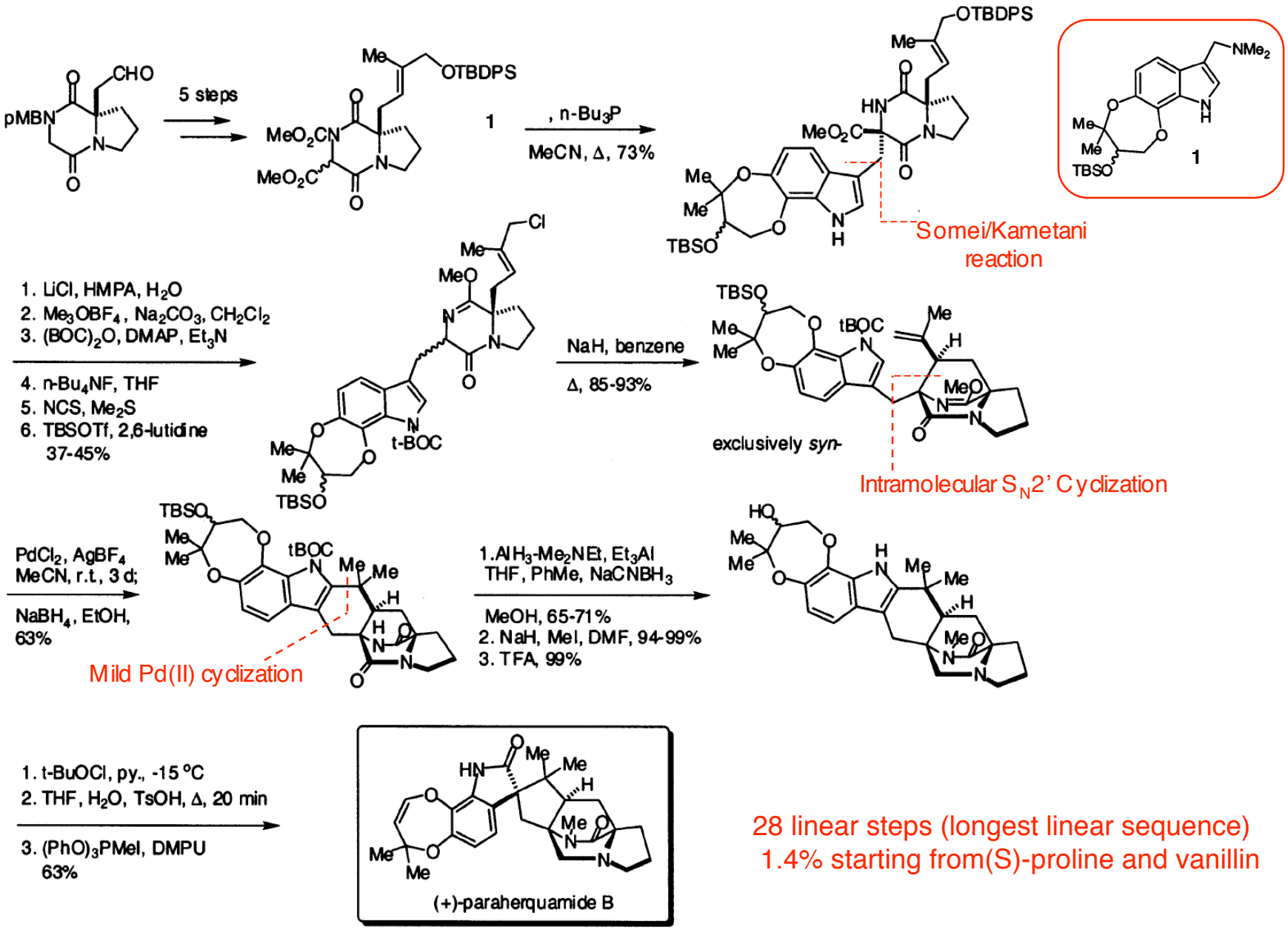
asperparaline A, R_1 = Me, R_2 = Me
(aspergillimide)
asperparaline B, R_1 = Me, R_2 = H
asperparaline C, R_1 = H, R_2 = Me



brevianamide A

Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127-139
and references therein.

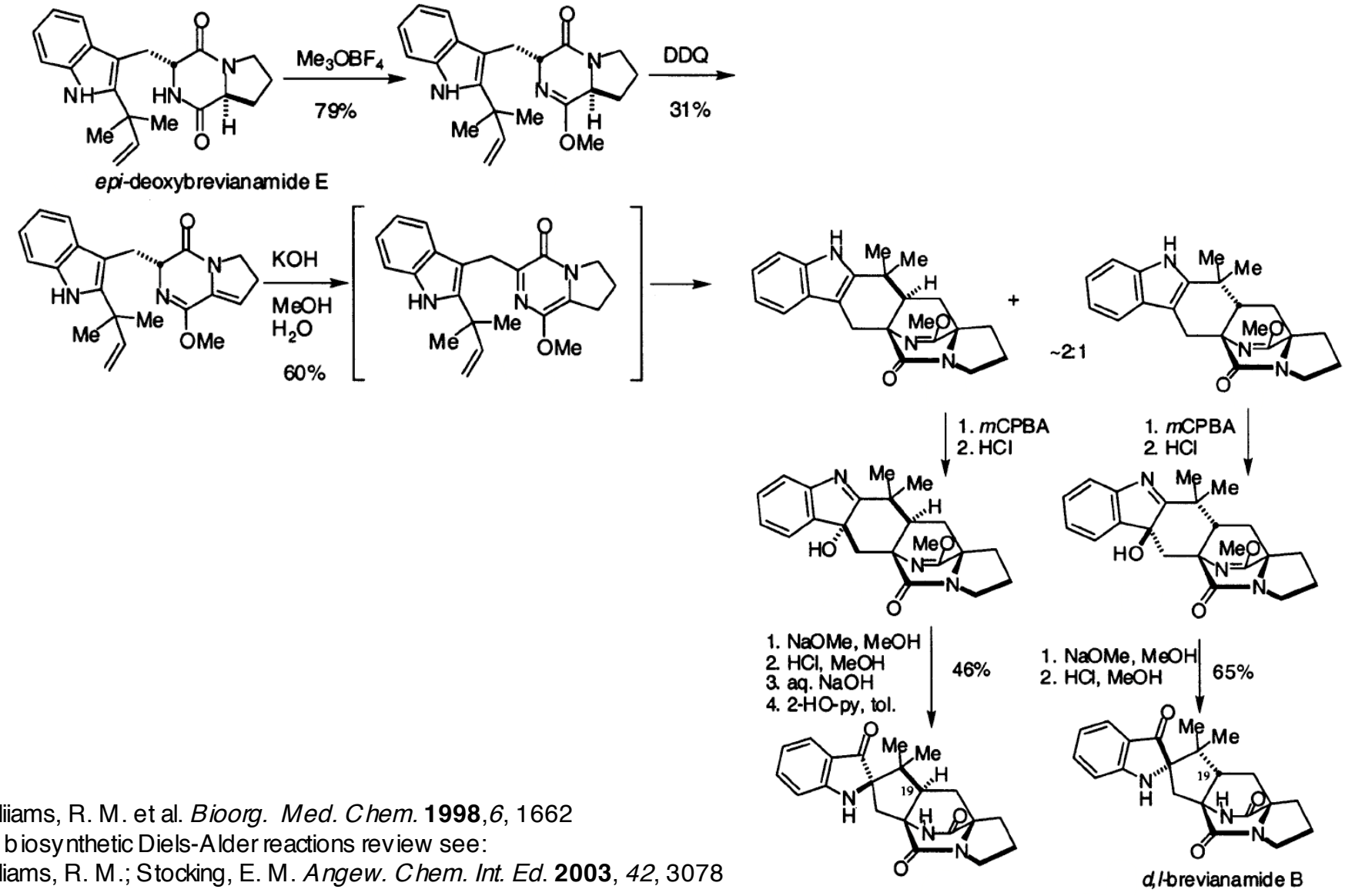
Total Asymmetric Synthesis of (+)-Paraherquamide B



28 linear steps (longest linear sequence)
1.4% starting from(S)-proline and vanillin

Cushing, T. D.; Sanz-Cervera, J. F.; Williiams, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 5579

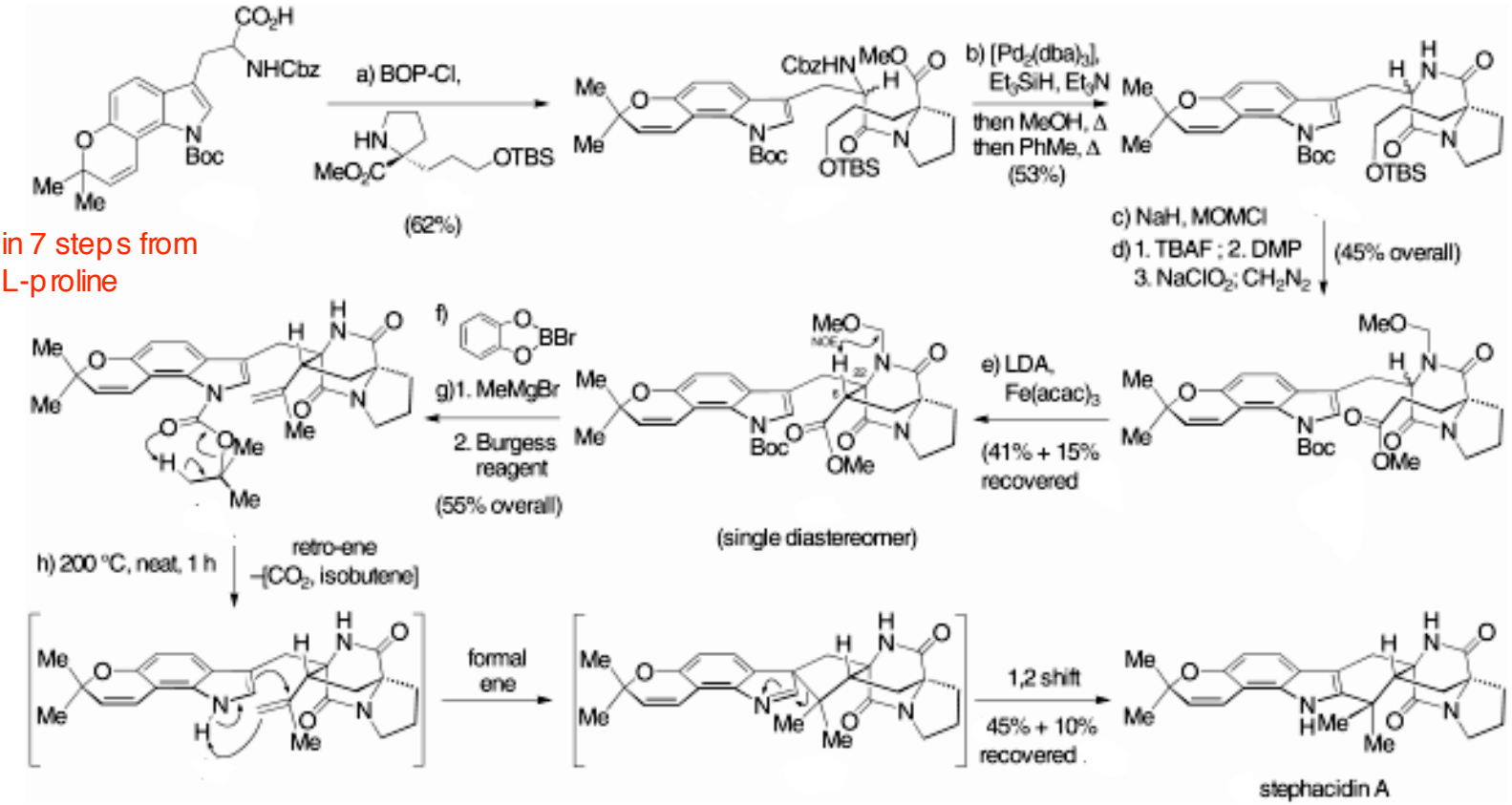
Biomimetic Total Synthesis of Racemic Brevianamide B



Williams, R. M. et al. *Bioorg. Med. Chem.* **1998**,*6*, 1662
For biosynthetic Diels-Alder reactions review see:
Williams, R. M.; Stocking, E. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 3078

Enantioselective Total synthesis of Stephacidin A

Made in 7 steps from L-proline

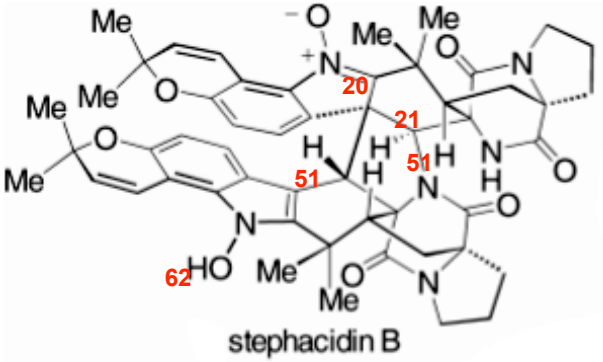


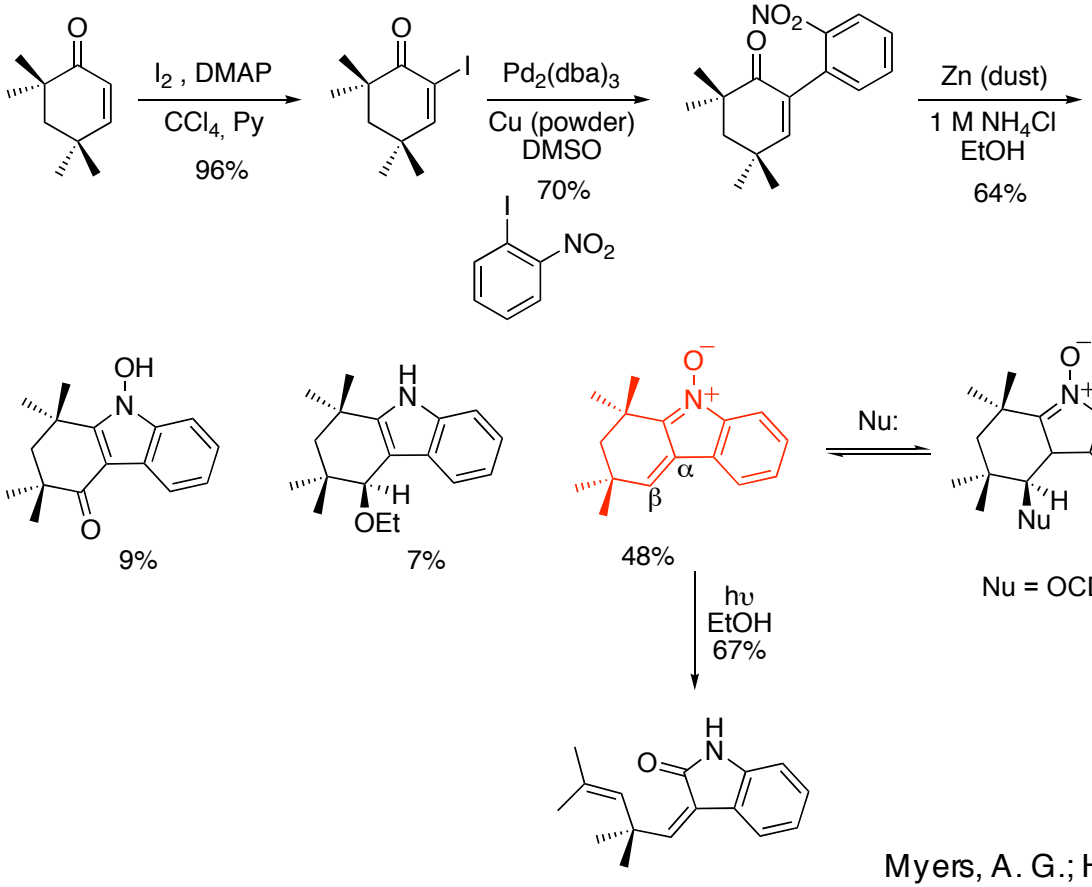
- Construction of the bicyclo[2.2.2] core via metal-mediated oxidative coupling
- Deprotection/annulation cascade to stitch the last ring
- 15 linear steps, 0.8 % from pyroglutamate and L-proline

Baran, P.S.; Guerrero, C. A.; Ambhaikar, N.B.; Hafensteiner, B.D. *Angew. Chem. Int. Ed.* **2004**, *44*, 606

Synthesis and Reactivity of the 3-Alkylidene-3H-indole 1-Oxide Function of Avrainvillamide (A novel Michael Acceptor)

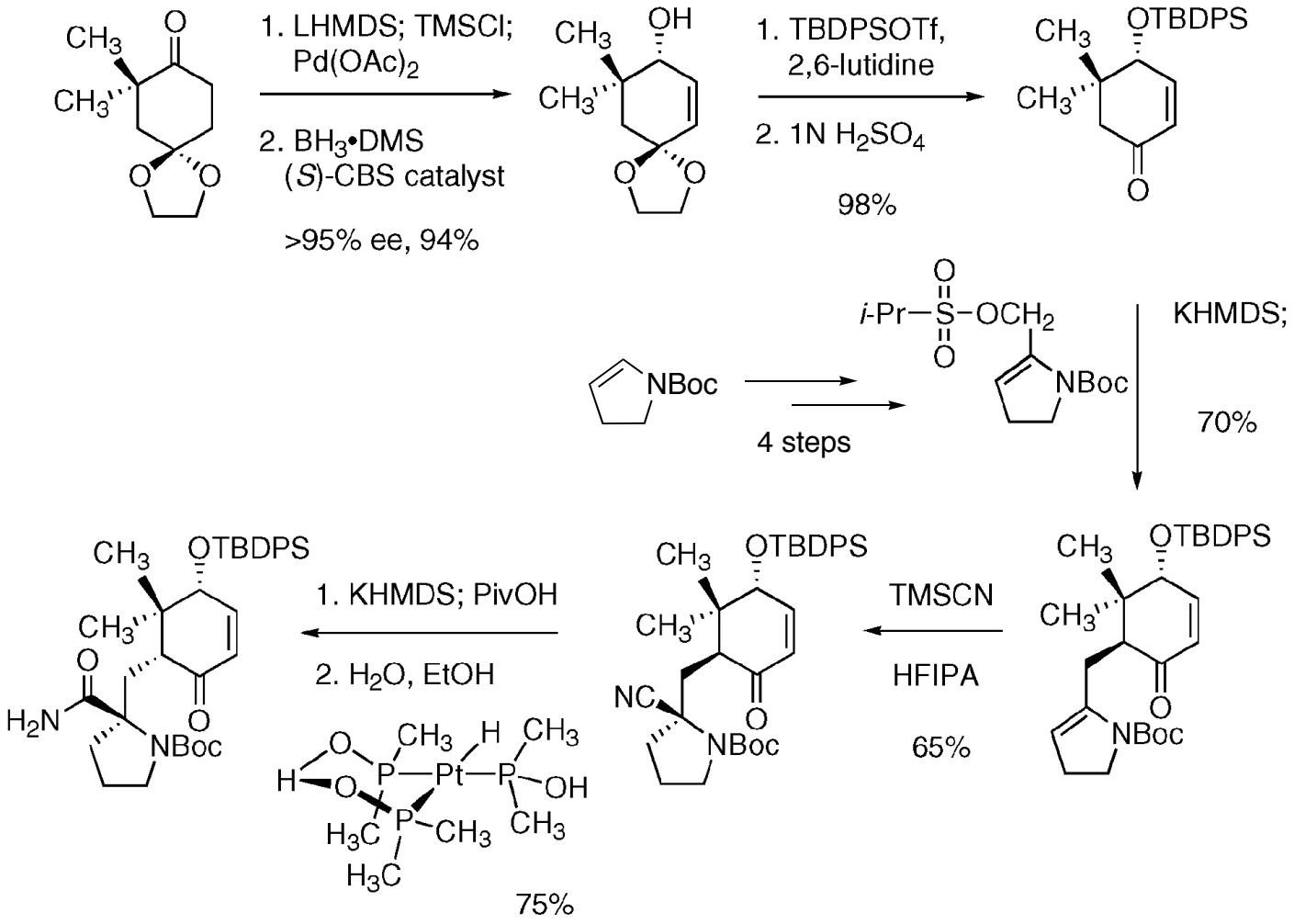
- BMS group proposed dimerization might be initiated at α–C
- Model compound (in red) underwent reversible addition of oxygen- and sulfur-based nucleophiles to the β carbon



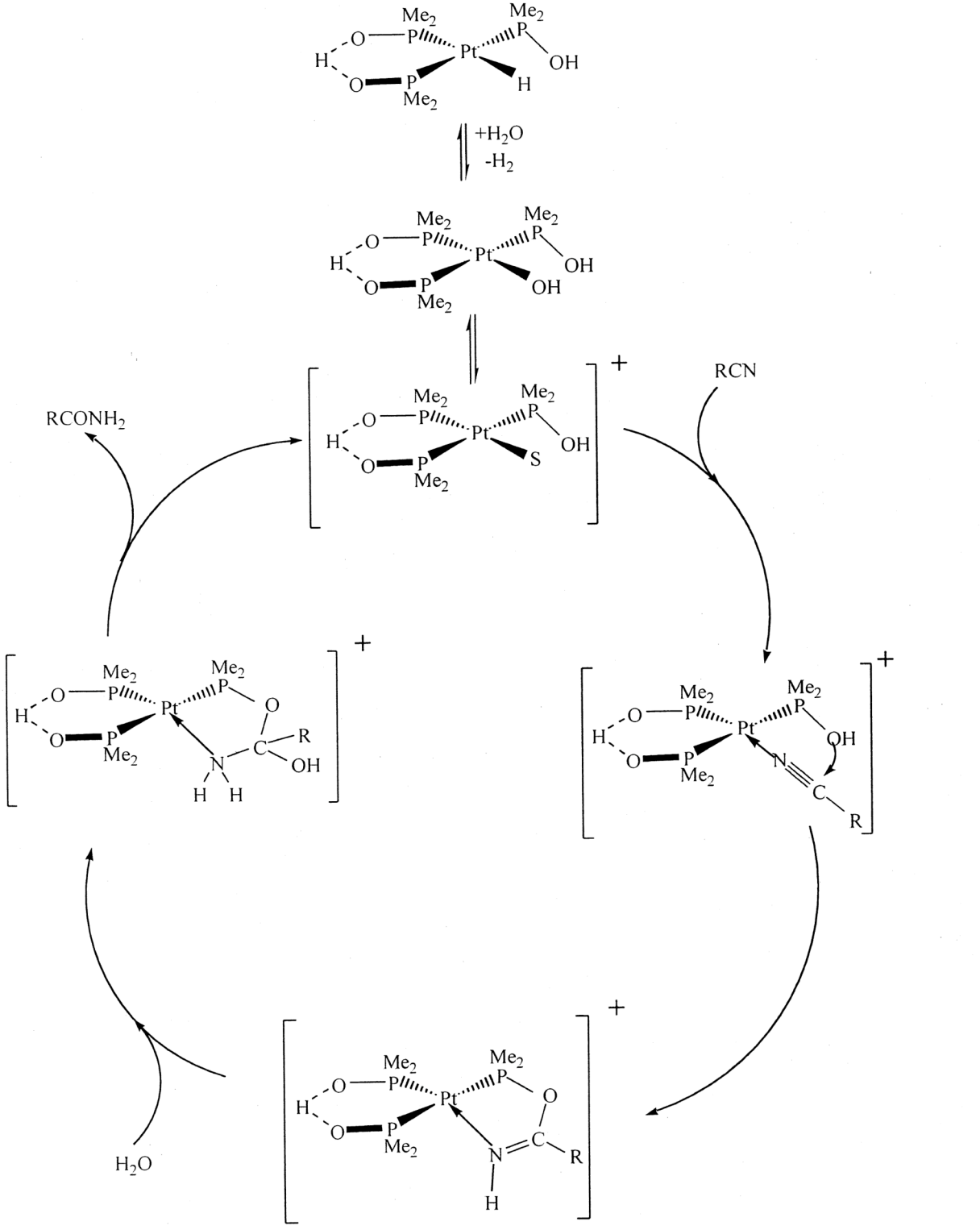


Myers, A. G.; Herzon, S. B. *J. Am. Chem. Soc.* **2003**, *125*, 12080

Enantioselective Synthesis of Stephacidin B

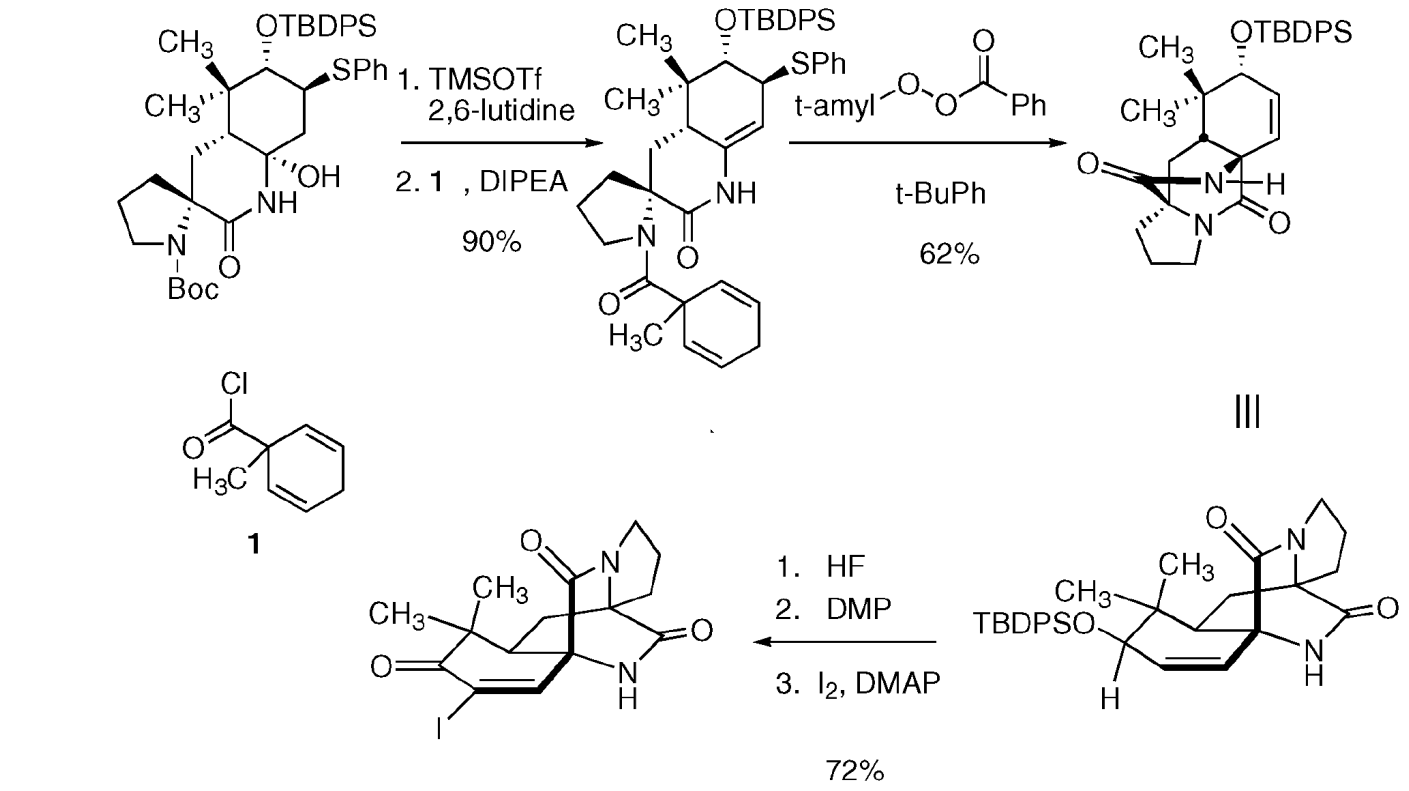


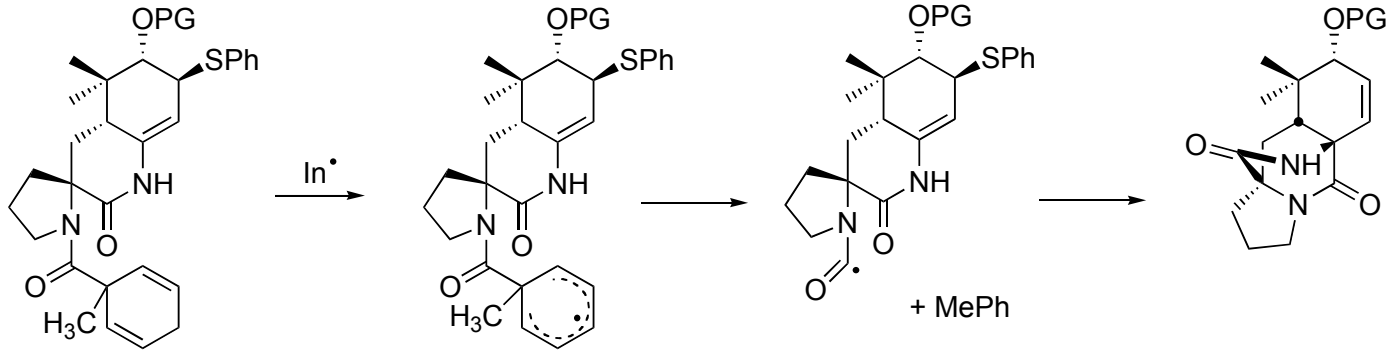
Myers, A. G.; Herzon, S. B. *J. Am. Chem. Soc.* **2005**, *127*, 5342



Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett.* **1995**, *36*, 8657.
J. Mol. Catal. **2000**, *160*,2499

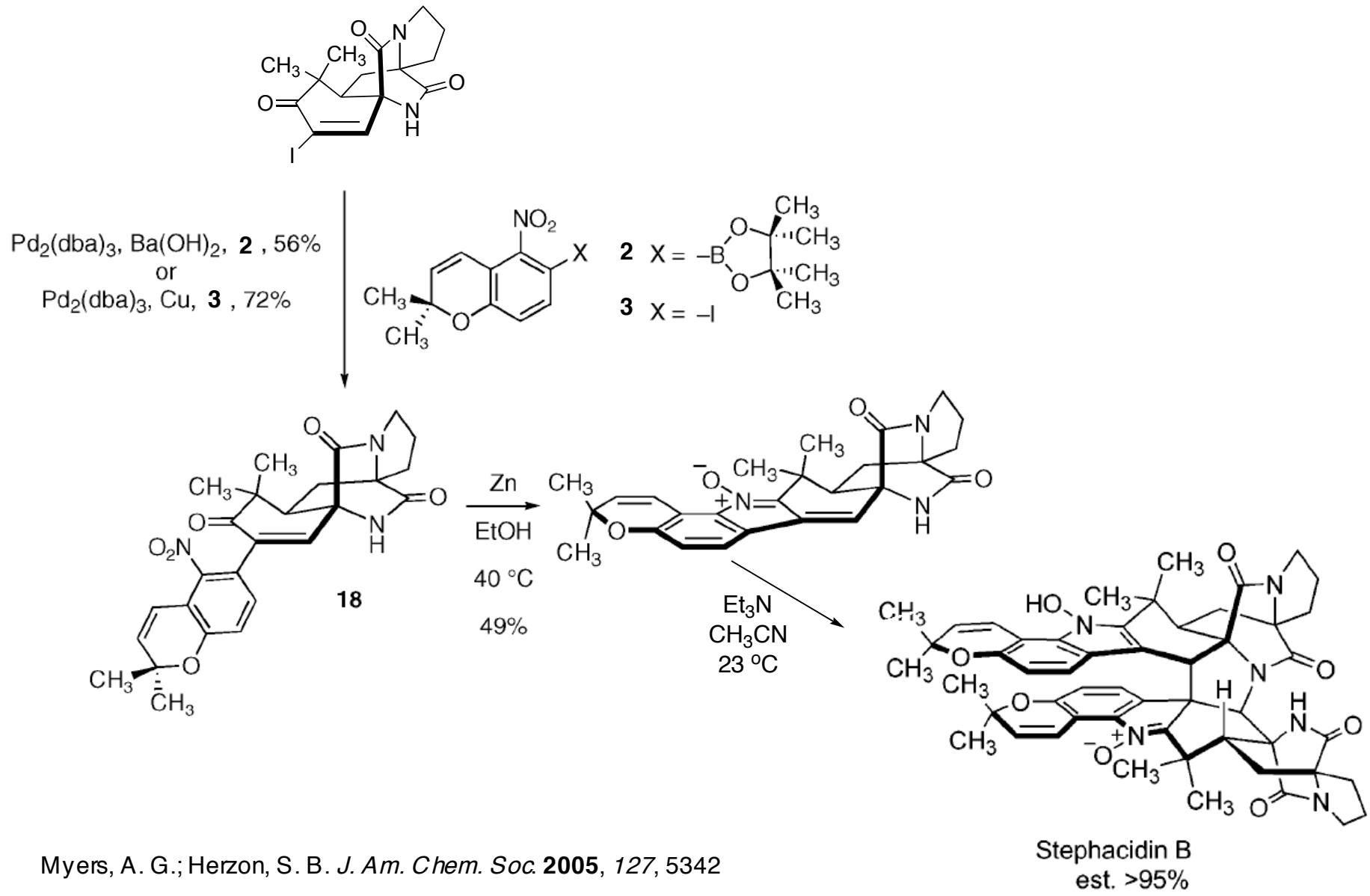
Enantioselective Synthesis of Stephacidin B



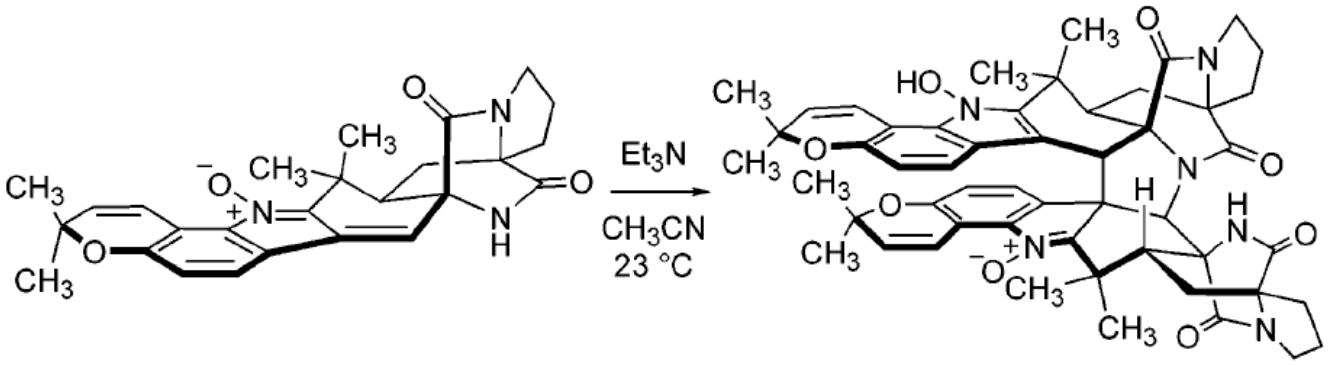


Jackson, L. V.; Walton, J. C. *Chem. Commun.* **2000**, 2327. Bella, A.F.; Jackson, L. V.; Walton, J. C. *Org. Biomol. Chem.* **2004**, *2*, 421

Enantioselective Synthesis of Stephacidin B



Myers, A. G.; Herzon, S. B. *J. Am. Chem. Soc.* **2005**, *127*, 5342



Stephacidin B
est. >95%

Summary

- 17 steps (longest linear sequence), 25 steps total, 4.2% overall yield.
- 1.7mg of Avrainvillamide was prepared in the final step of the experimental section.
- Highlights of the synthesis included a Strecker-like addition to N-Boc enamine, neutral platinum catalyzed reduction of nitrile to amide, and bicyclo[2.2.2] core formation by an acyl radical precursor.
- Spectroscopic data still lacks correspondence with authentic sample.
- Preliminary studies conclude that Avrainvillamide and Stephacidin B interconvert readily in solution.
- A new mechanism for the dimerization of Avrainvillamide to form Stephacidin B has been proposed.