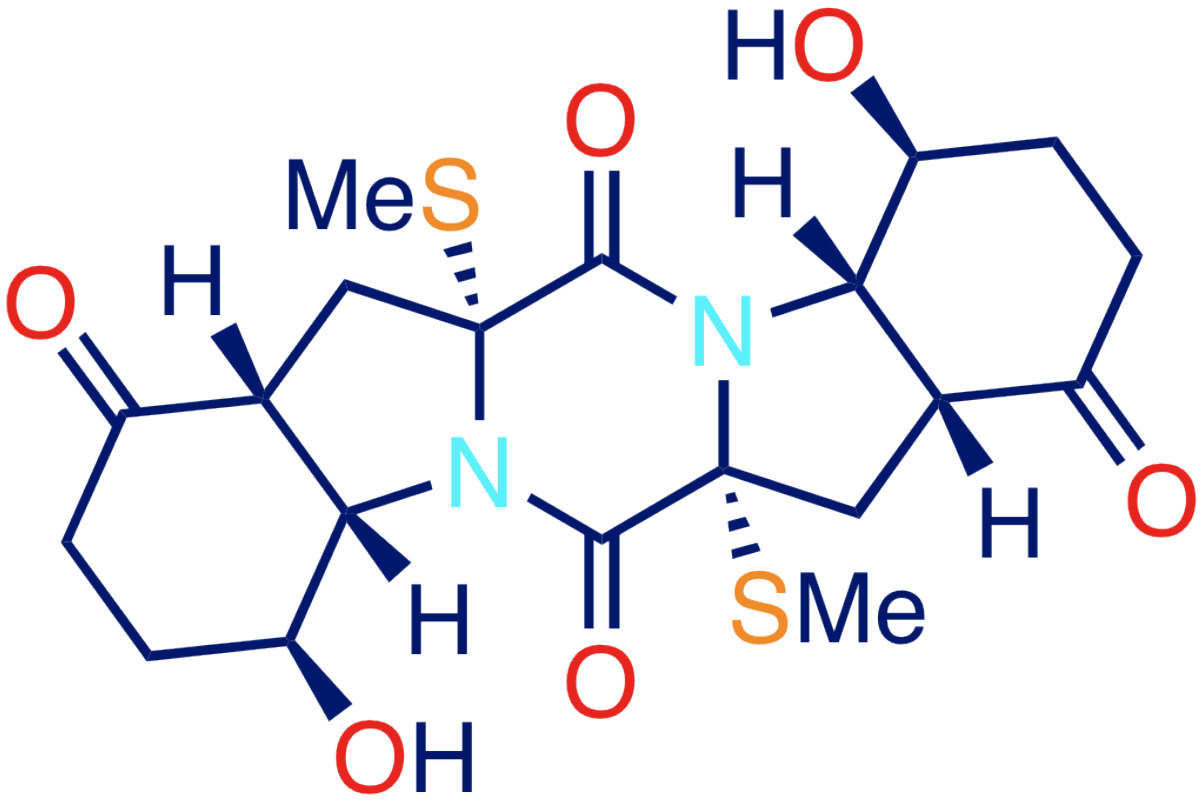
Total Synthesis of Epicoccin G

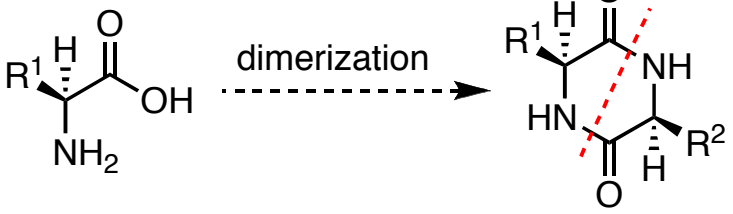
K. C. Nicoalou, Sotirios Totokotsopoulos, Denis Giguère,
Ya-Ping Sun, and David Sarlah

JACS. ASAP. May 6, 2011
DOI: 10.102/ja2032635

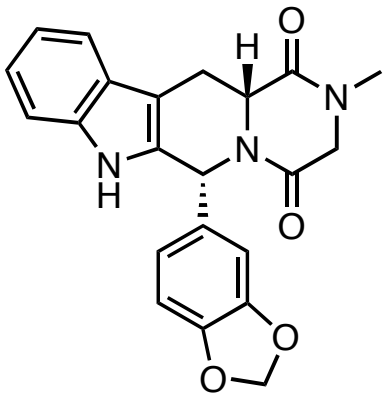


Christopher Rosenker
Wipf Group - Current Literature
May 21, 2011

Biological activities and clinical use of diketopiperazines



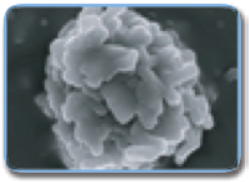
Biosynthetically derived by the dimerization of amino acids

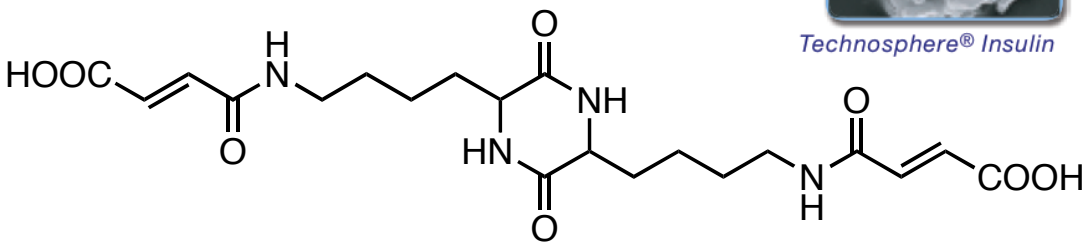


Cialis (Tadalafil)
Ranked 61st in 2009 ($1.6 billion)
treatment of erectile dysfunction
(phosphodiesterase 5 inhibitor)

124 DKP's have been isolated from marine sources up to 2008. A subclass includes dithio substitution.

Exhibit interesting bioactivities including:
- plant-growth promotion
- antimicrobial activity
- quorum-sensing signaling (used by groups of organisms to coordinate behavior)
- antitumor activity
- antiviral activity
- inhibition against aflatoxin production


Technosphere® Insulin

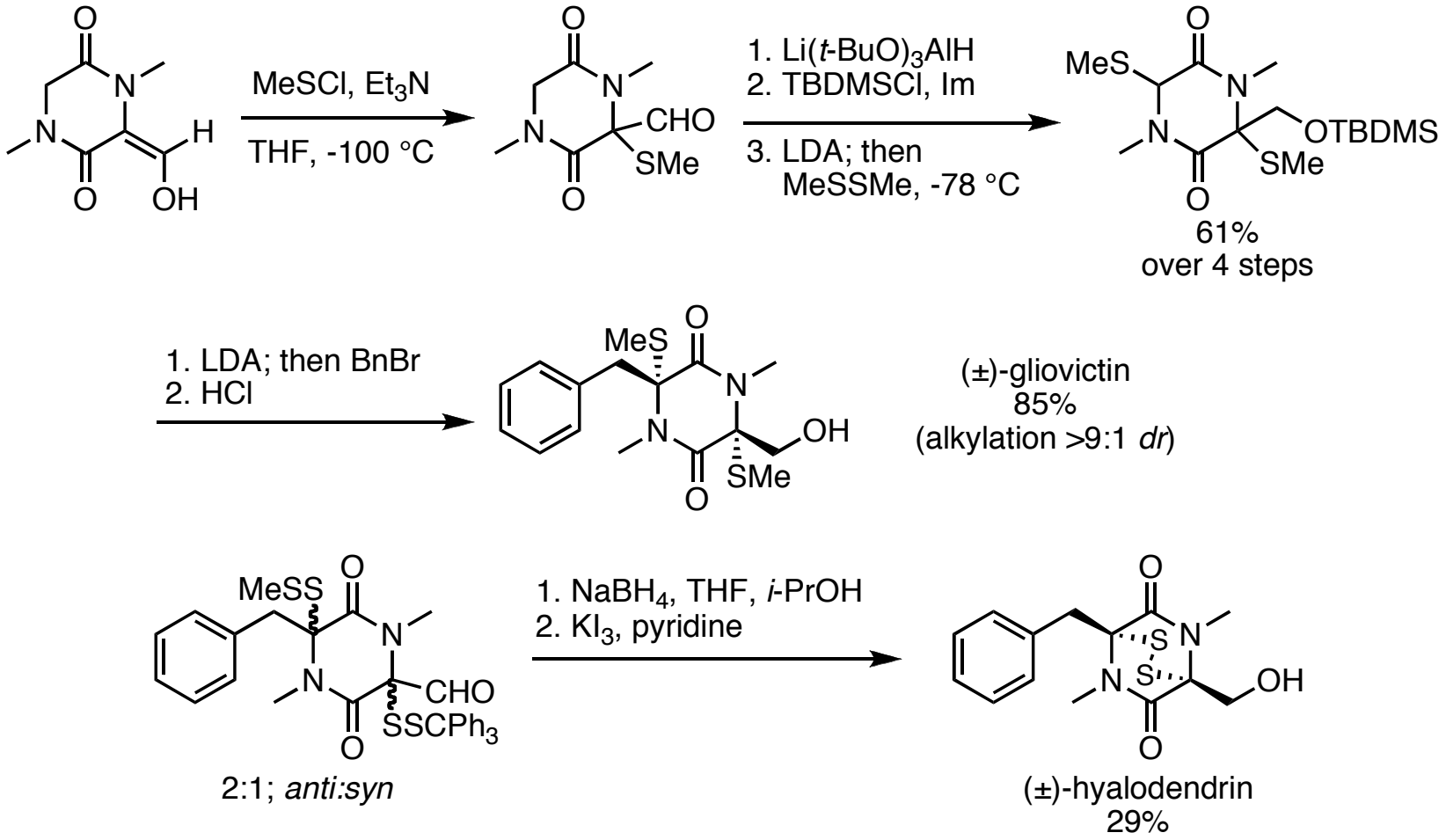


Technosphere® technology
Part of formulation for inhaled insulin marketed by MannKind

Huang, R.; Zhou, X.; Xu, T.; Yang, X.; Liu, Y. *Chem. Biodivers.* **2010**. *7*. 2809.
Martins, M. B.; Carvalho, I. *Tetrahedron* **2007**. *63*. 9923.
Mack, D. J.;Brichacek, M.; Plichta, A.; Njardrson J. T. "Top 200 Pharmaceutical Products by Worldwide Sales in 2009" http://cbc.arizona.edu/njardarson/group/sites/default/files/Top200PharmaceuticalProductsByWorldwideSalesin2009.pdf
Image from http://www.mannkindcorp.com/Collateral/Documents/English-US/101LR-TechnosphereTechTeaser-01.19.11.pdf

Synthesis of diketopiperazine natural products

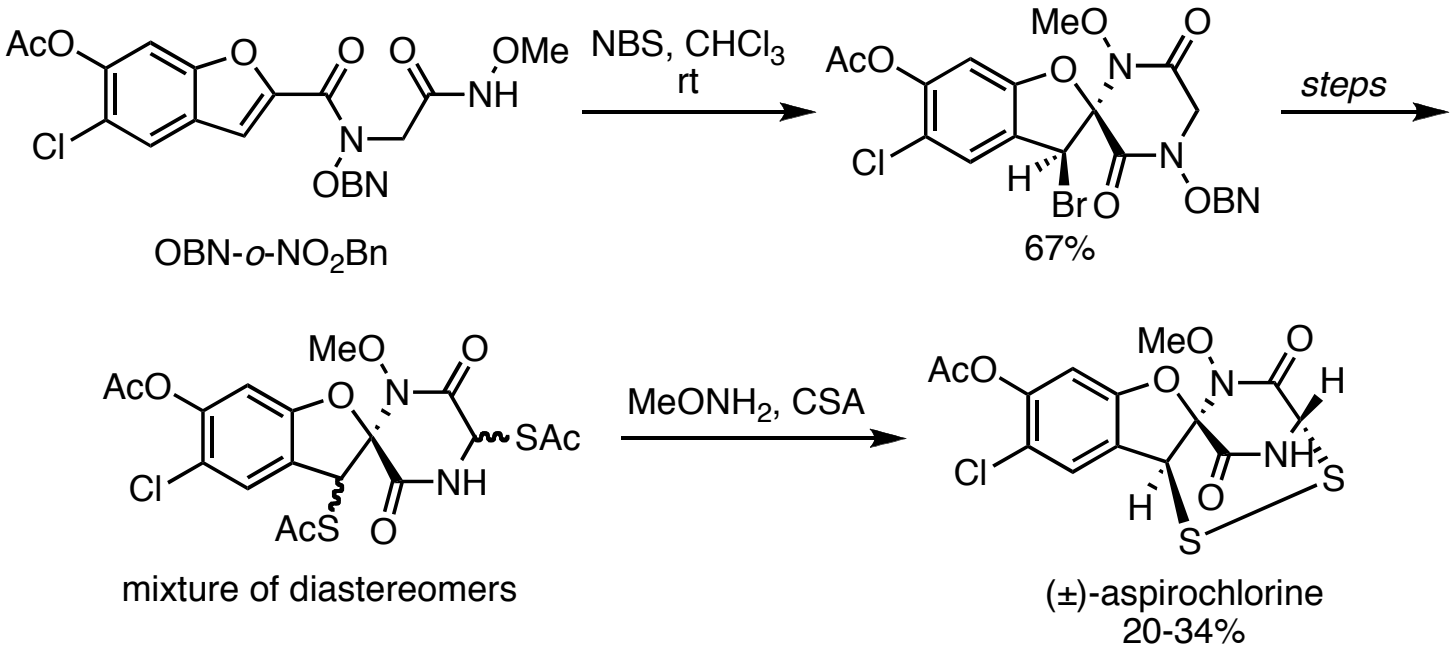
Rastetter and Williams: Sulfenylation strategy and epidithiodiketopiperazine formation during the synthesis of (±)-gliovictin and (±)-hyalodendrin.



Williams, R. M.; Rastetter, W. H. *J. Org. Chem.* **1980**. *45*. 2625.

Synthesis of diketopiperazine natural products

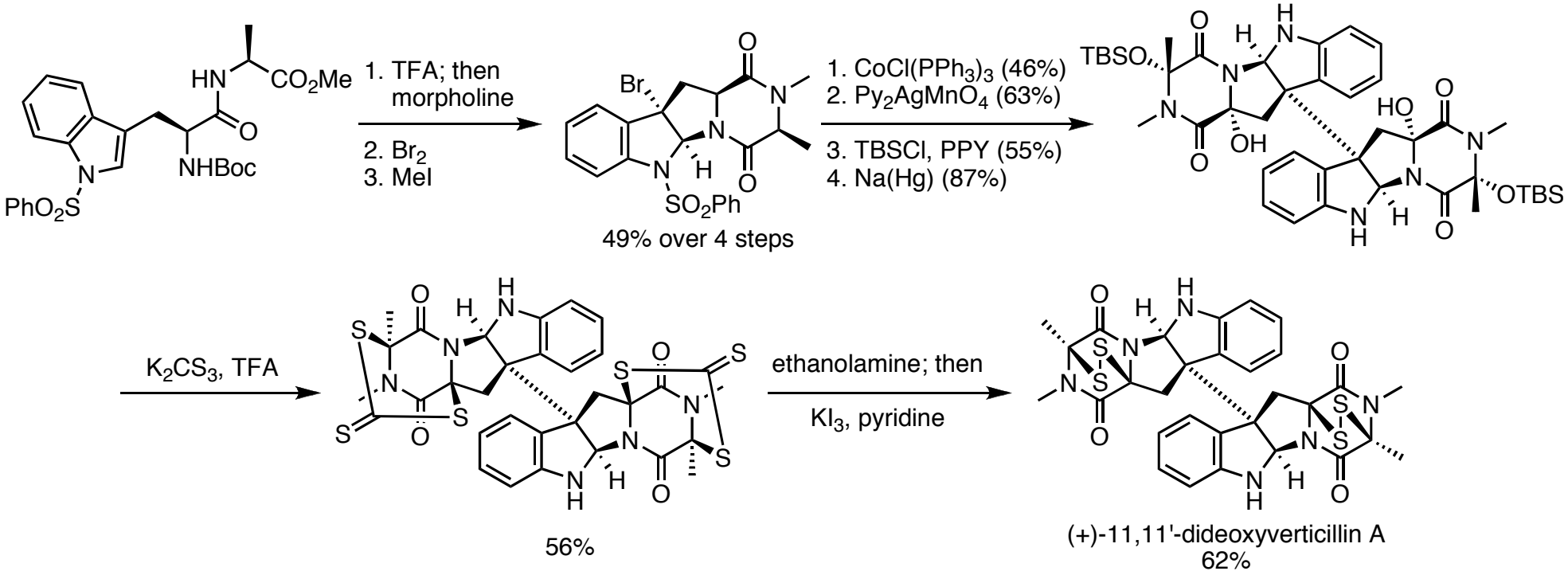
Williams and Miknis: Interesting diketopiperazine formation strategy and disulfide formation for the synthesis of (±)-aspirochlorine.



Miknis, G. F.; Williams, R. M. *J. Am. Chem. Soc.* **1993**. *115*. 536.

Synthesis of diketopiperazine natural products

Movassaghi and co-workers: Biosynthetically inspired approach to (+)-11,11'-dideoxyverticillin A

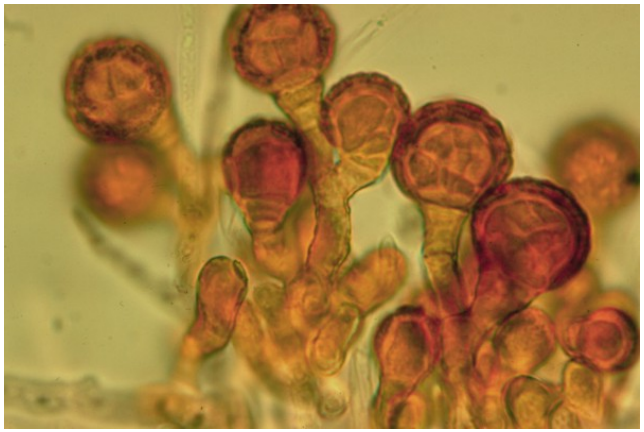


First total synthesis of dimeric epidithiodiketopiperazine alkaloid

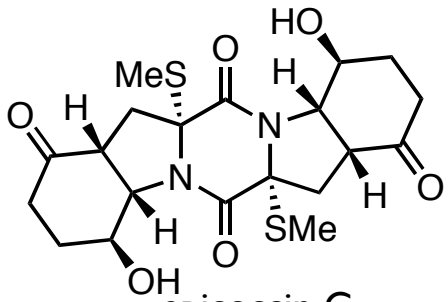
Kim, J.; Ashenhurst, J. A.; Movassaghi, M. *Science* **2009**. *324*. 238.

Epicoccin G isolation and structural assignment

Isolated by two groups from *epicoccum nigrum* (endophytic fungus) in China

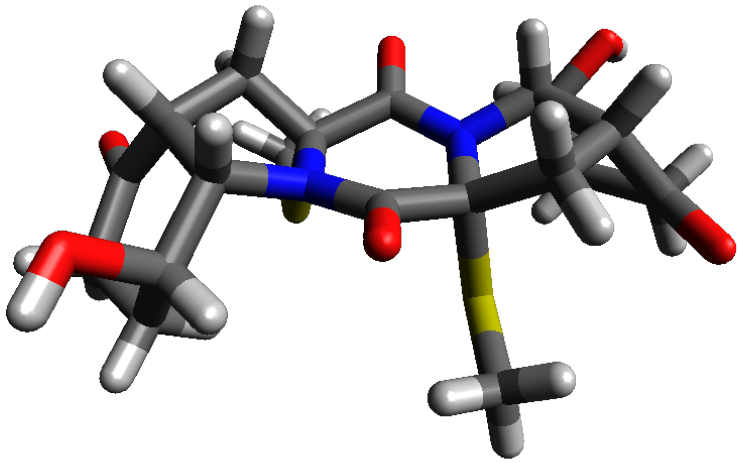


33 g of crude extract provided 91 mg of epicoccin G



epicoccin G

X-ray structure of epicoccin G



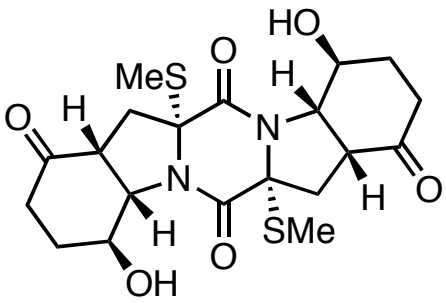
Structure and relative stereochemistry was determined by HRMS, ^{1}H, ^{13}C, and 2-D NMR; absolute configuration determined by Mosher ester analysis and single crystal X-ray crystallography

Groups report identical characterization data except for $[\alpha]_D$ of +69.0 (c = 0.17, MeOH) and -141.5 (c = 0.1, MeOH)

Reported as epicoccin G and *ent*-epicoccin G but had the same structure

Guo, H.; Sun, B.; Gao, H.; Chen, X.; Liu, S.; Yao, X.; Liu, X.; Che, Y. *J. Nat. Prod.* **2009**. *72*. 2115.
Wang, J.; Ding, G.; Fang, L.; Dai, J.; Yu, S.; Wang, Y.; Chen, X.; Ma, S.; Qu, J.; Xu, S.; Du, D. *J. Nat. Prod.* **2010**. *73*. 1240.
Image copied from http://website.nbm-mnb.ca/mycologywebpages/NaturalHistoryOfFungi/Hyphomycetes.html

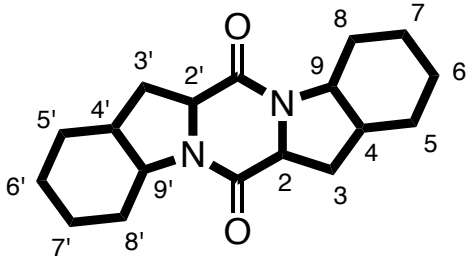
Selected dithiodiketopiperazines

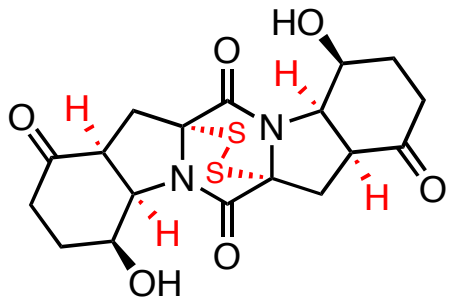


epicoccin G

Epicoccum nigrum (endophytic fugus)

anti-HIV IC_{50}: 13.5 μM (C8166 cells)

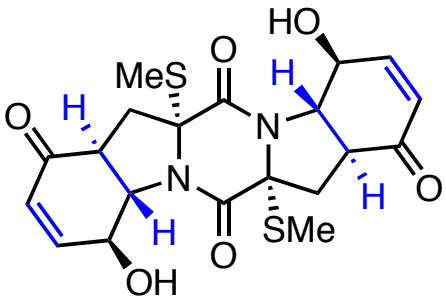




rostratin B

Exserohilum rostratum (marine-derived fungus)

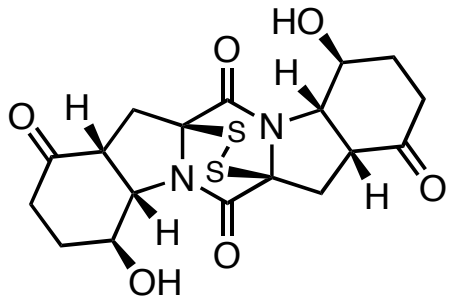
human colon carcinoma IC_{50}: 1.9 μM (HTC-116)



exserohilone

Exserohilum holmii (endophytic fungus)

suspected antibactrial and antifungal activity

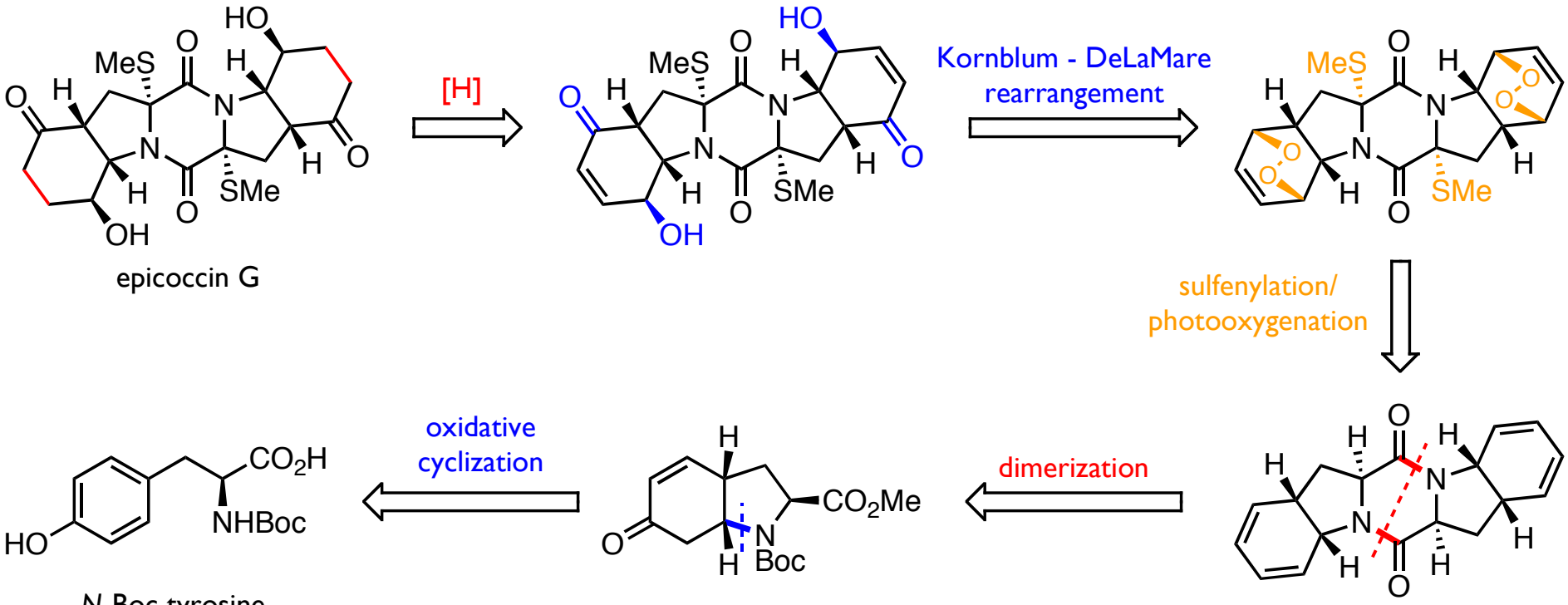


8,8'-*epi-ent*-rostratin B

SciFinder: Substructure search of 6-5-6-5-6 diketopiperazine core gives 40 structures
8 references (6 isolation papers, 2 synthetic methodologies)

Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun, Y.; Sarlah, D. *J. Am. Chem. Soc.* **2011**, DOI: 10.1021/ja203263

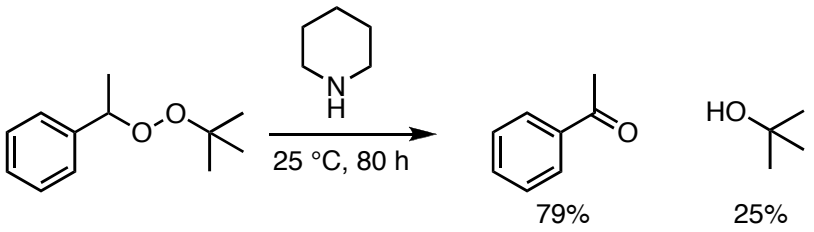
Retrosynthetic analysis of epicoccin G



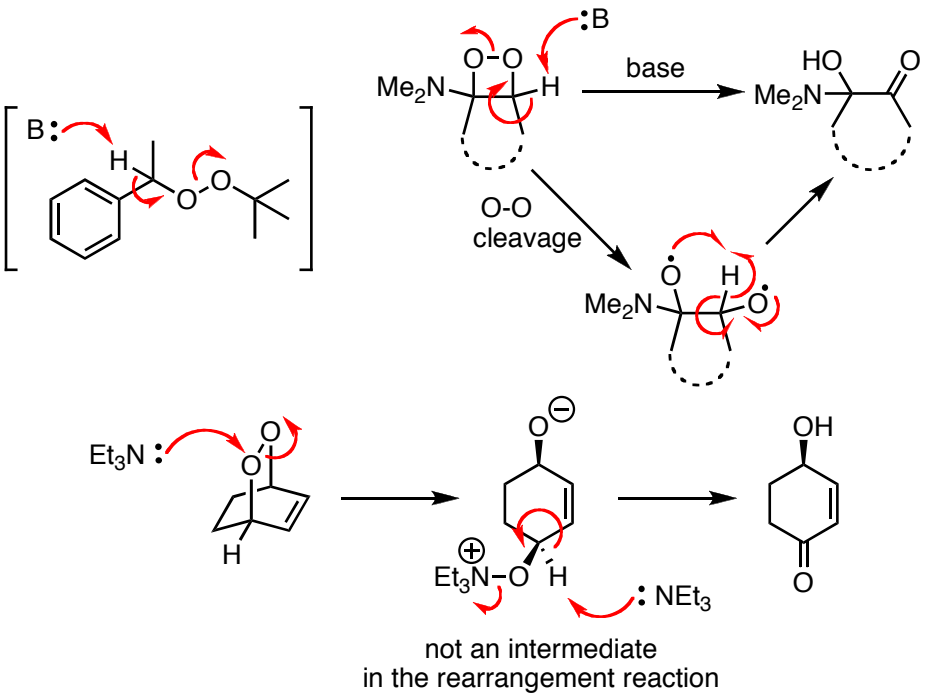
Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun, Y.; Sarlah, D. *J. Am. Chem. Soc.* **2011**, DOI: 10.1021/ja2032635

Kornblum-DeLaMare rearrangement

"The base catalyzed decompostion of a dialkyl peroxide"
Journal of the American Chemical Society, **1951**
Nathan Kornblum and Harold E. DeLaMare (Purdue University)

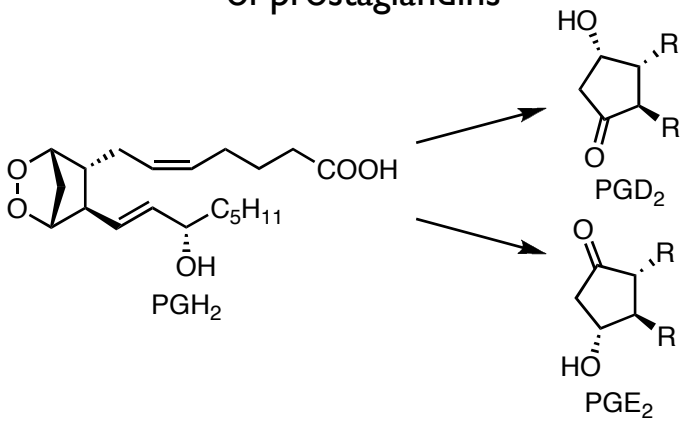


Mechanistic considerations

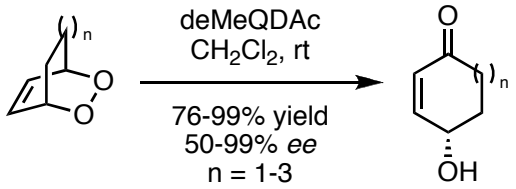


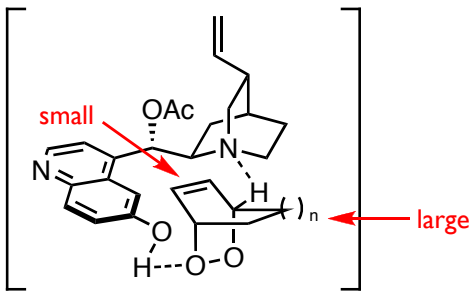
not an intermediate
in the rearrangement reaction

Important key step in the biosynthesis of prostaglandins



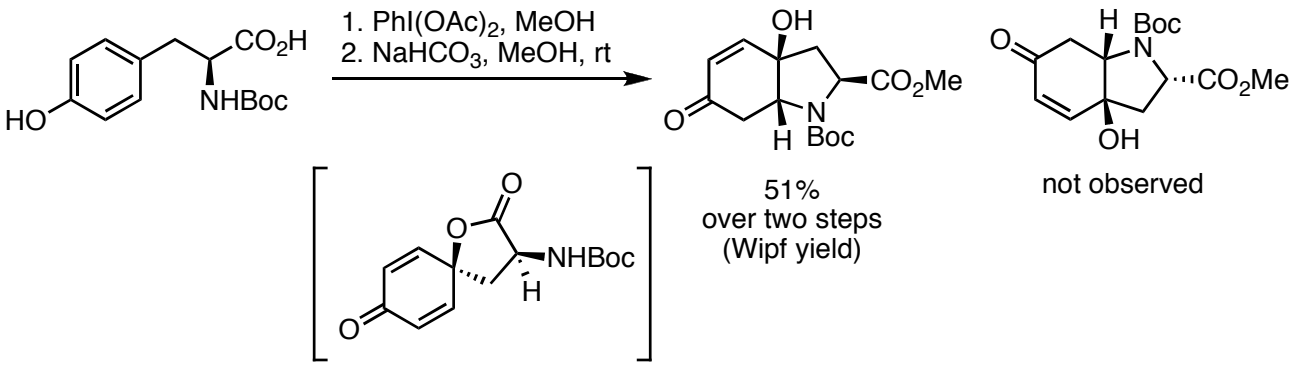
First enantioselective Kornblum-DeLaMare rearrangement utilized *Meso*-endoperoxides and chiral cinchona alkaloids



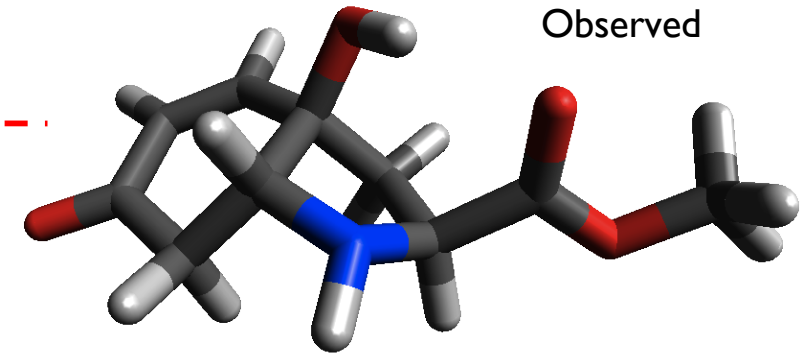


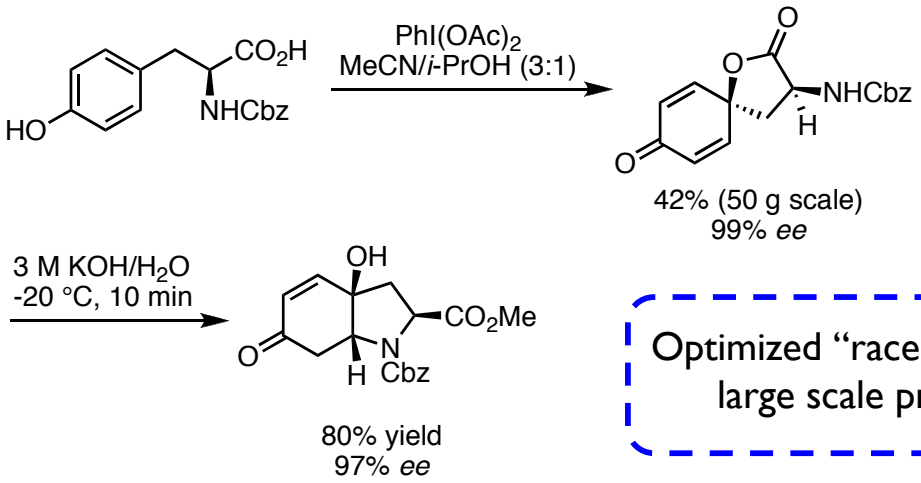
Kornblum, N.; DeLaMare, H. E. *J. Am. Chem. Soc.* **1951**. *73*. 880.
Frimer, A. A. *Chem. Rev.* **1979**. *79*. 359.
Kelly, D. R.; Bansal, H.; Morgan, J. J. G. *Tetrahedron Let.* **2007**. *43*. 9331.
Staben, S. T.; Linghu, X.; Toste, F. D. *J. Am. Chem. Soc.* **2006**. *128*. 12658.

Oxidative cyclization of tyrosine

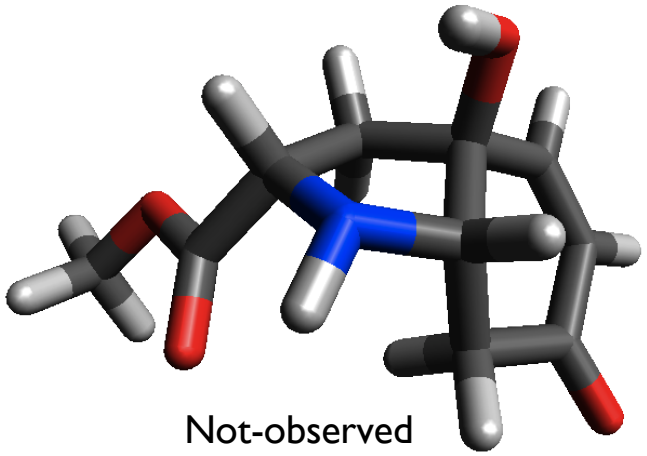


~1 kcal/mol difference in energy;
Only one cyclization product observed;
Intramolecular hydrogen bonding may account for selectivity



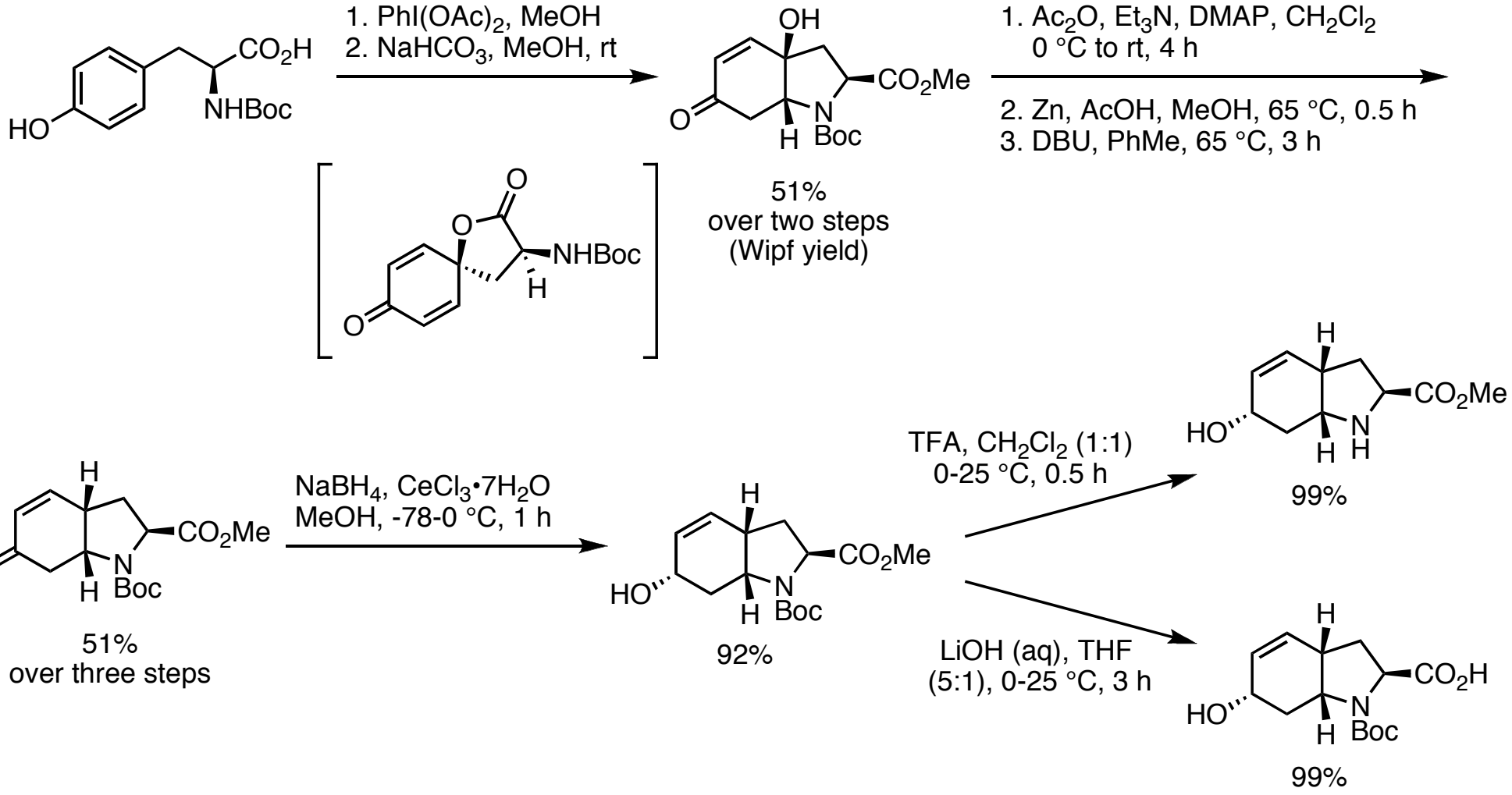


Optimized "racemization free" large scale preparation



Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**. 33, 5477.
Pierce, J. G.; Kasi, D.; Fushimi, M.; Cuzzupe, A.; Wipf, P. *J. Org. Chem.* **2008**. 73. 7807.
Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun, Y.; Sarlah, D. *J. Am. Chem. Soc.* **2011**, DOI: 10.1021/ja2032635
Avogadro: an open-source molecular builder and visualization tool. Version 1.03. http://avogadro.openmolecules.net/

Synthesis of epicoccin G



Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun, Y.; Sarlah, D. *J. Am. Chem. Soc.* **2011**, DOI: 10.1021/ja2032635
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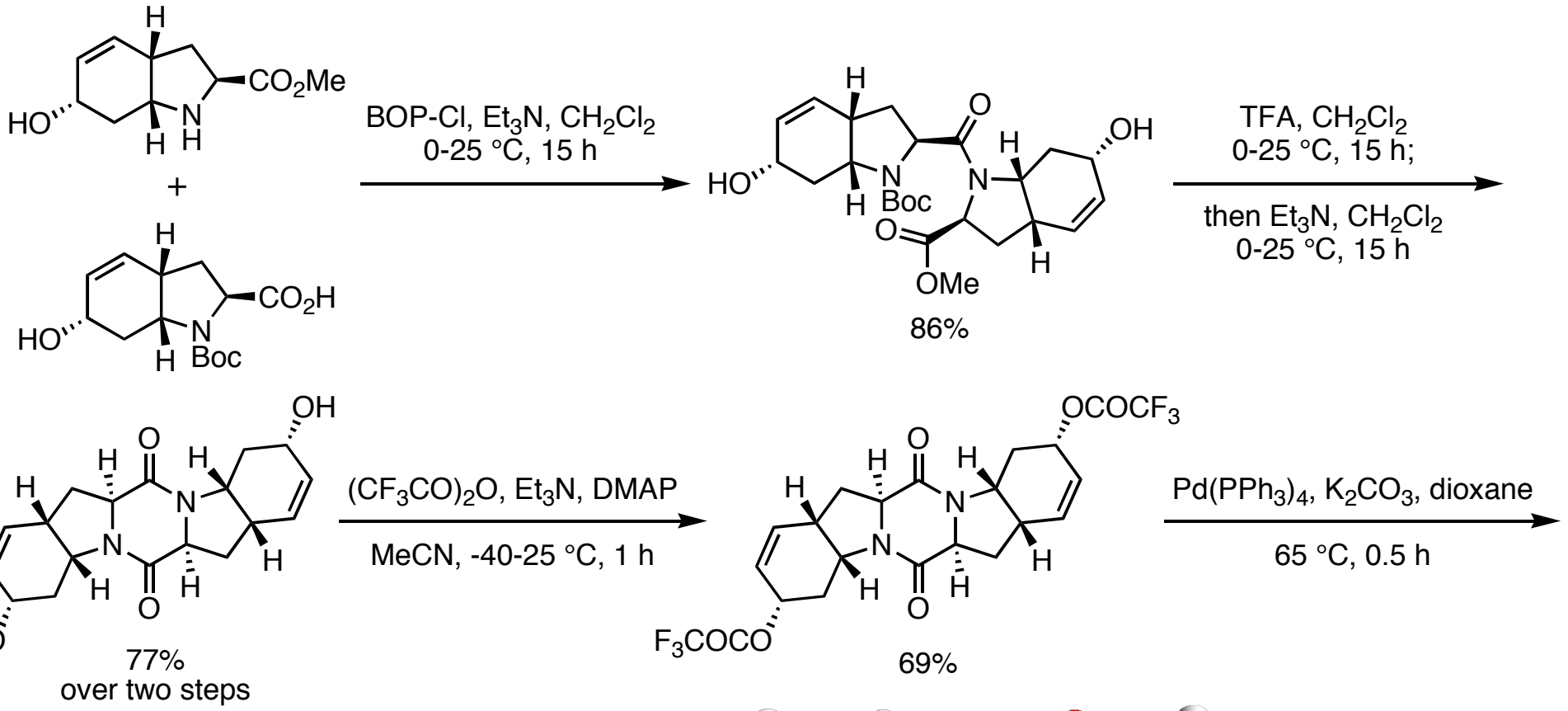

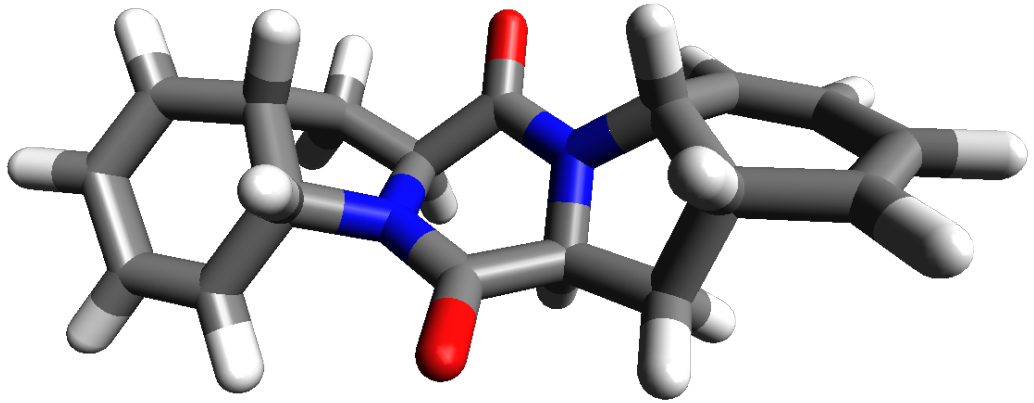

Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun, Y.; Sarlah, D. *J. Am. Chem. Soc.* **2011**, DOI: 10.1021/ja2032635

Avogadro: an open-source molecular builder and visualization tool. Version 1.03. http://avogadro.openmolecules.net/

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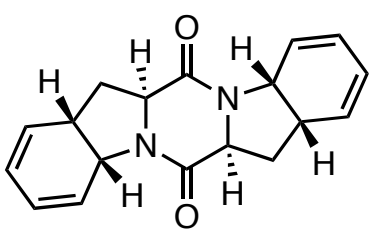
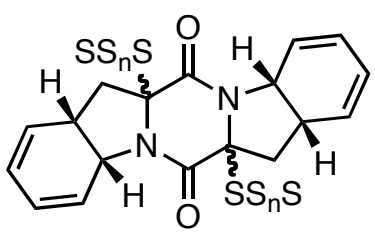


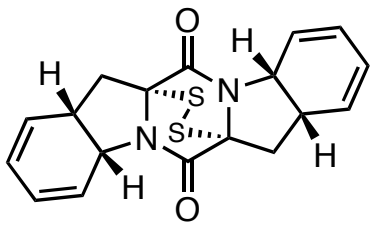
A

S_8, NaHMDS, THF, 25 °C
1 min; then **A,** 1 min; then
NaHMDS, 25 °C, 0.5 h



n = 0-6

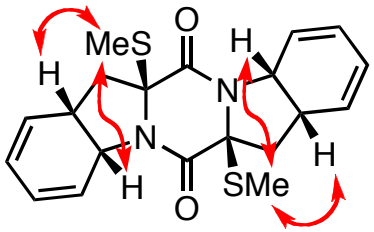
$NaBH_4$, THF:MeOH (1:1)
0-25 °C, 0.75 h; then aq KI_3
25 °C, 10 min



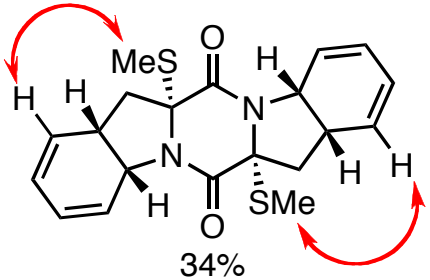
32% and
23% 2,2'-*epi*
(from **A**)

$NaBH_4$, THF:MeOH (1:1)
0-25 °C, 0.75 h; then MeI
25 °C, 15 h (65%)

$NaBH_4$, THF:MeOH (1:1)
0-25 °C, 0.75 h; then MeI
25 °C, 15 h

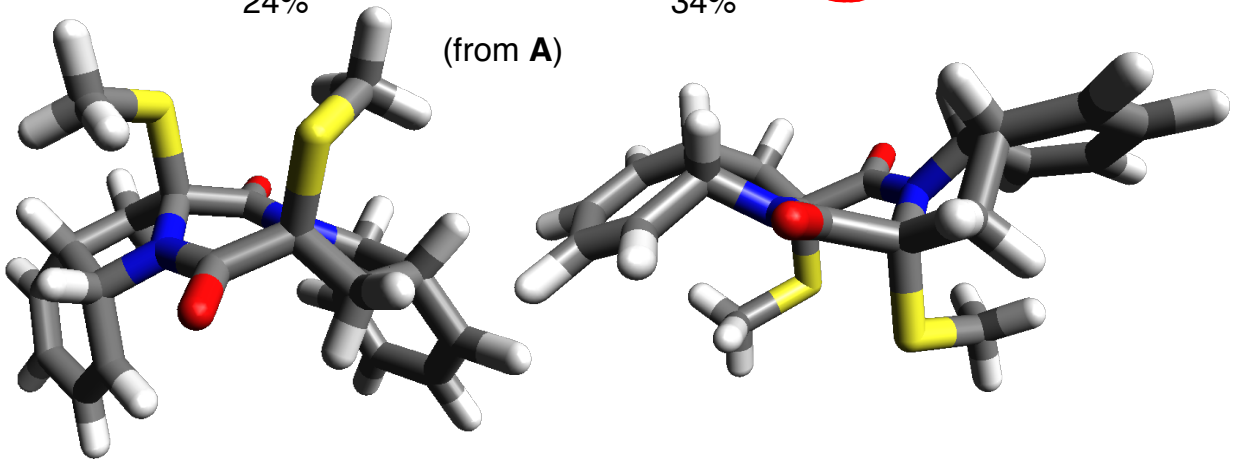


24%



34%

(from **A**)



no trans sulfenylation observed;
suggesting intramolecular delivery

Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun, Y.; Sarlah, D. *J. Am. Chem. Soc.* **2011**, DOI: 10.1021/ja2032635
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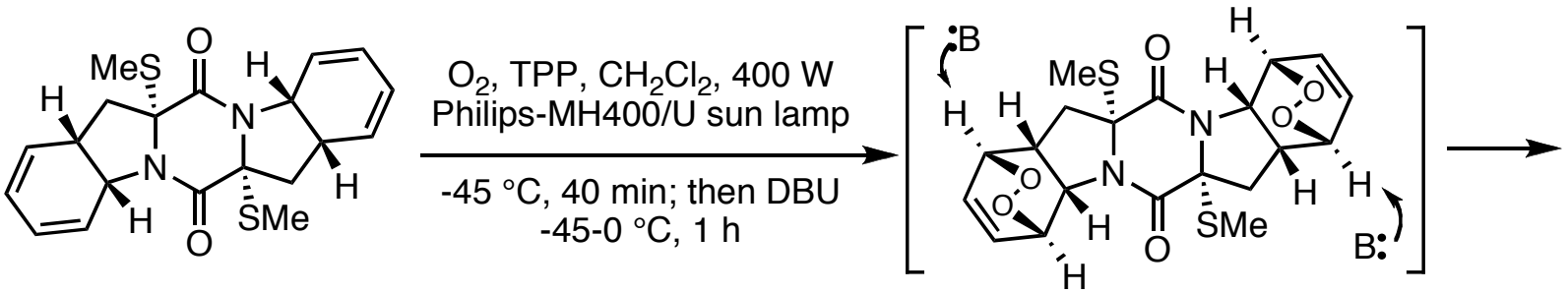
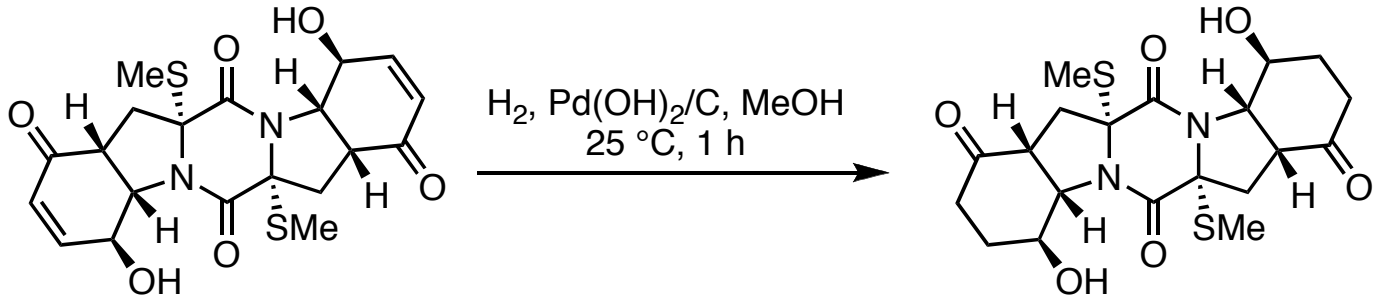


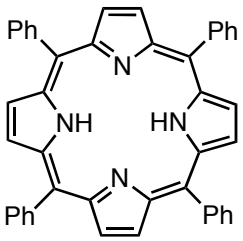


52%

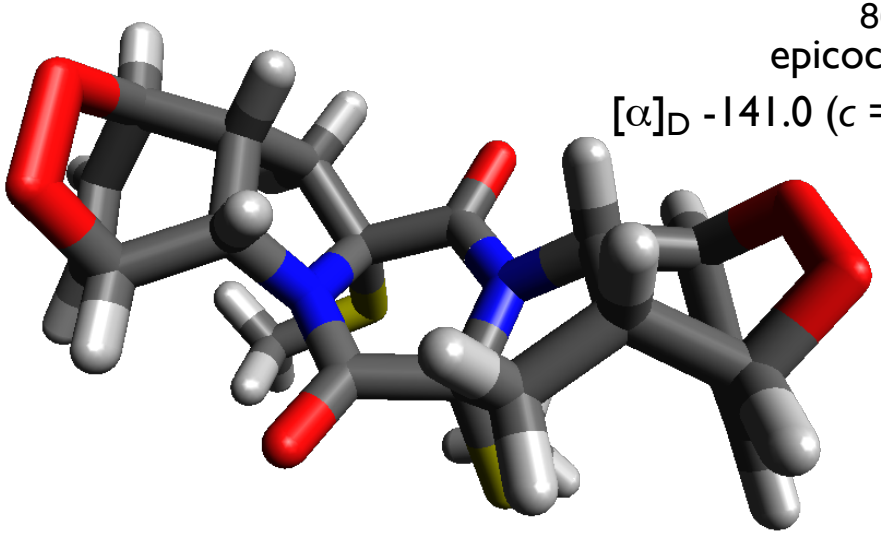
86%

epicoccin G

$[\alpha]_D$ -141.0 (*c* = 0.10, MeOH)



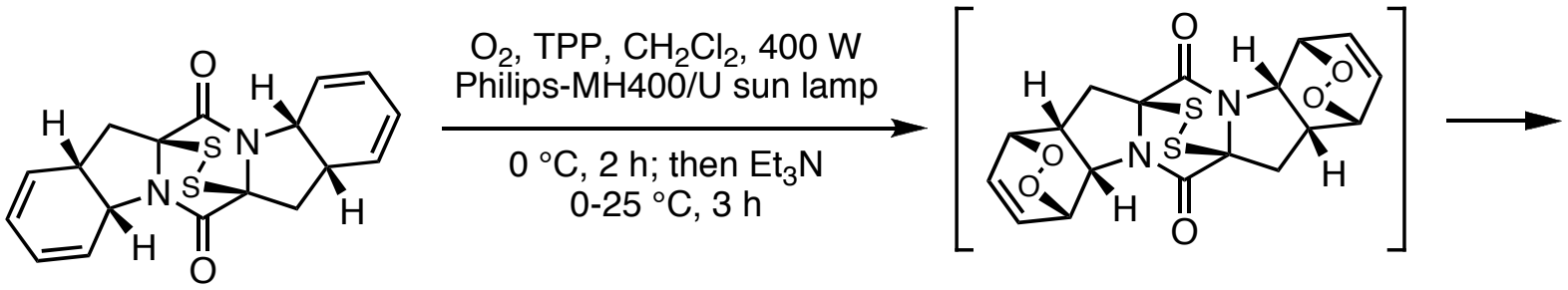
TPP

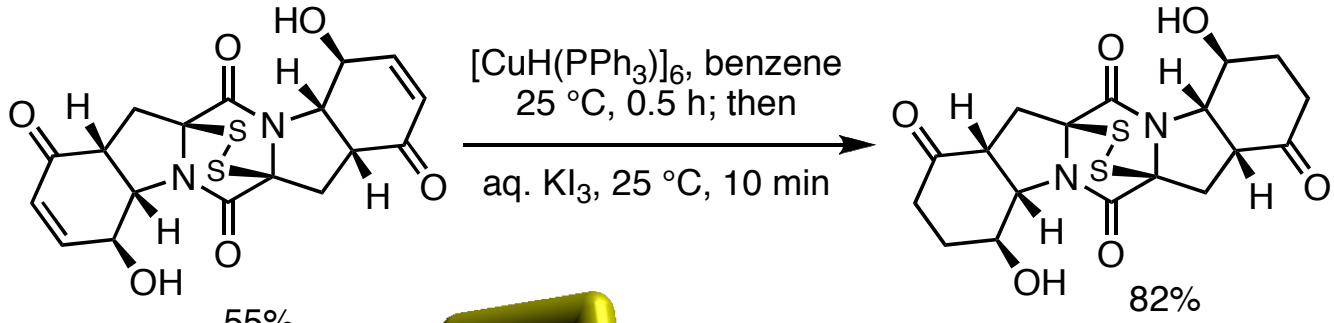


Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun, Y.; Sarlah, D. *J. Am. Chem. Soc.* **2011**, DOI: 10.1021/ja2032635

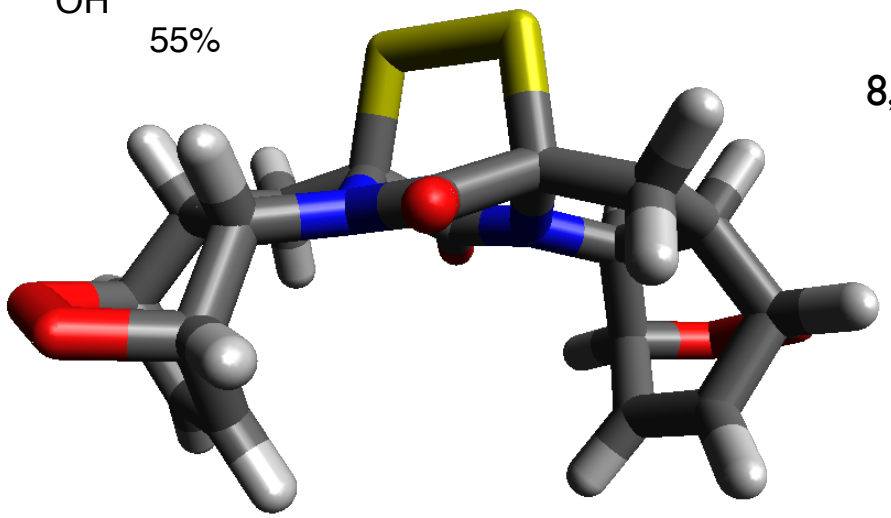
Avogadro: an open-source molecular builder and visualization tool. Version 1.03. http://avogadro.openmolecules.net/

Synthesis of 8,8'-*epi*-*ent*-rostratin B





8,8'-*epi*-*ent*-rostratin B



Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun, Y.; Sarlah, D. *J. Am. Chem. Soc.* **2011**, DOI: 10.1021/ja2032635
Avogadro: an open-source molecular builder and visualization tool. Version 1.03. http://avogadro.openmolecules.net/

Conclusions

- Key steps include:
  - Oxidative cyclization of tyrosine for starting material synthesis
  - Two-directional, intramolecular sulfenylation
  - Photooxygenation - Kornblum-DeLaMare rearrangement
- Synthesis of Epicoccin G in 18 steps from *N*-Boc tyrosine (longest linear sequence) with a 2.9% yield (from Wipf indoline).
- Synthesis of 8,8'-*epi*-*ent*-rostratin B in 19 steps from *N*-Boc tyrosine (longest linear sequence) with a 2.0% yield (from Wipf indoline).