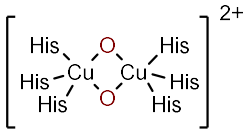
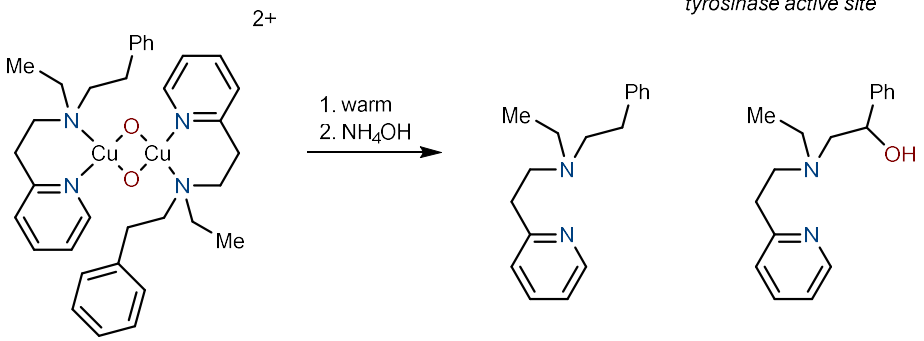
Baran's Modified Schönecker Oxidation

Background

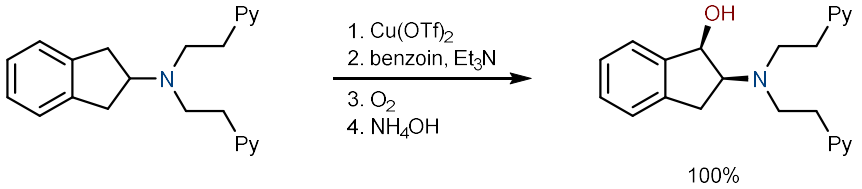
- Bis(μ-oxo)dicopper complexes oxidize phenols like tyrosine and dopamine in biological systems
- Involved in the biosynthesis of melanin



tyrosinase active site



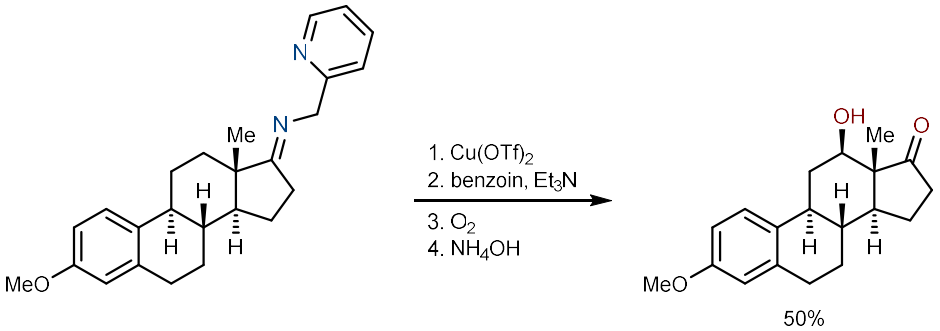
Moro-oka, Y. *Chem. Rev.* **1994**, *94*, 737. https://doi.org/10.1021/cr00027a010
Que, L.; Tolman, W. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 1114. https://doi.org/10.1002/1521-3773(20020402)41:7<1114::AID-ANIE1114>3.0.CO;2-6



100%

Reglier, M. *Eur. J. Inorg. Chem.* **1998**, *9*, 1297. https://doi.org/10.1002/(SICI)1099-0682(199809)1998:9<1297::AID-EJIC1297>3.0.CO;2-M

Schönecker's Original Conditions

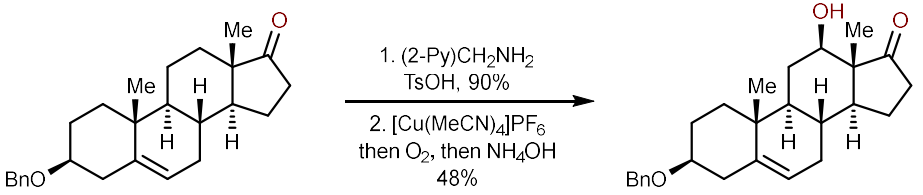


50%

Schönecker, B. *Angew. Chem. Int. Ed.* **2003**, *42*, 3240. https://doi.org/10.1002/anie.200250815

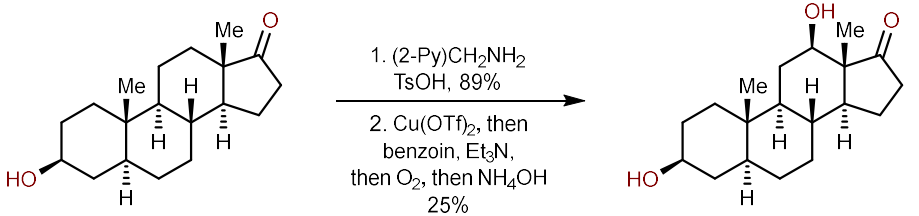
Applications in Total Synthesis

- **Cyclopamine** (Giannis, 2009)



Giannis, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 7911. https://doi.org/10.1002/anie.200902520

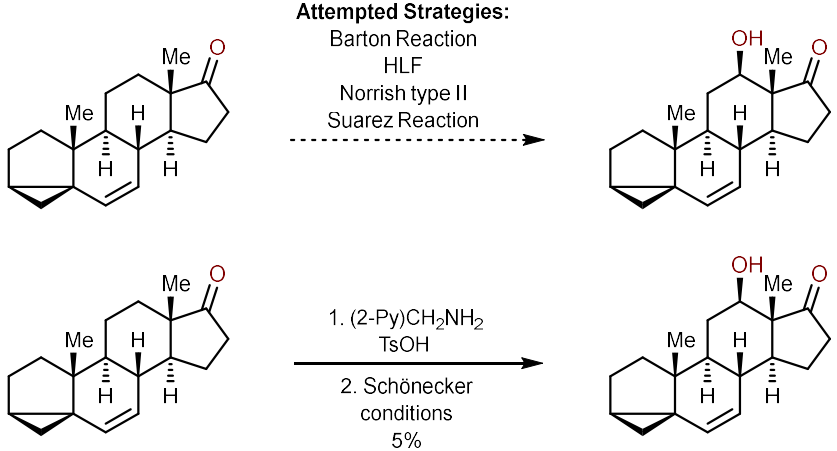
- **(+)-Cephalostatin 1** (Shair, 2010)



Shair, M. *J. Am. Chem. Soc.* **2010**, *132*, 275. https://doi.org/10.1021/ja906996c

Baran's Involvement

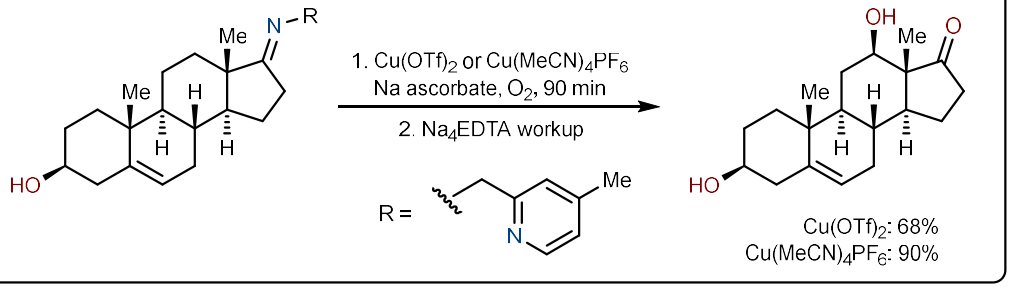
- An intermediate in Baran's synthesis of pregnane-containing natural products proved difficult to oxidize at C12

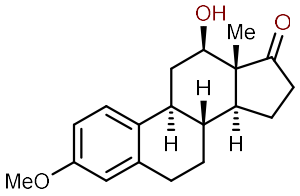


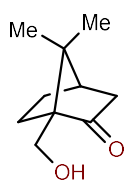
Baran, P. *J. Am. Chem. Soc.* **2015**, *137*, 13776. https://doi.org/10.1021/jacs.5b09463

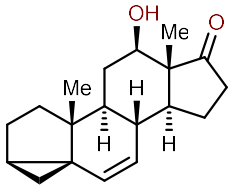
Baran's Modified Schönecker Oxidation

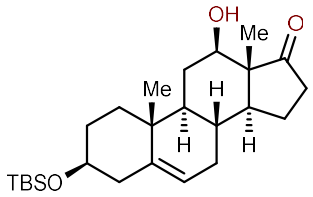
The Baran Modification

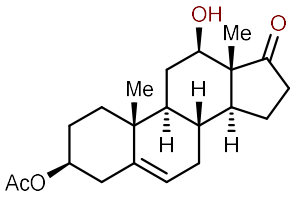


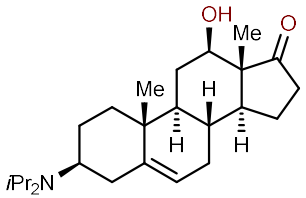


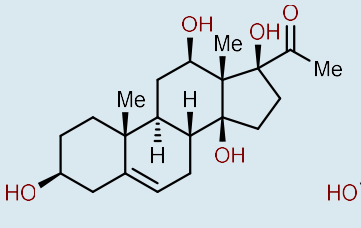


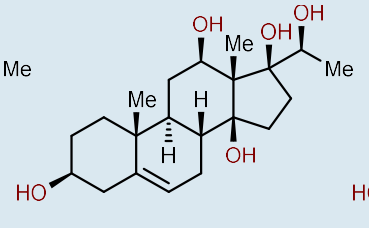


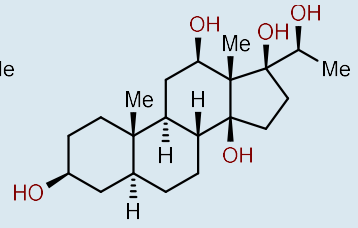







pergularin

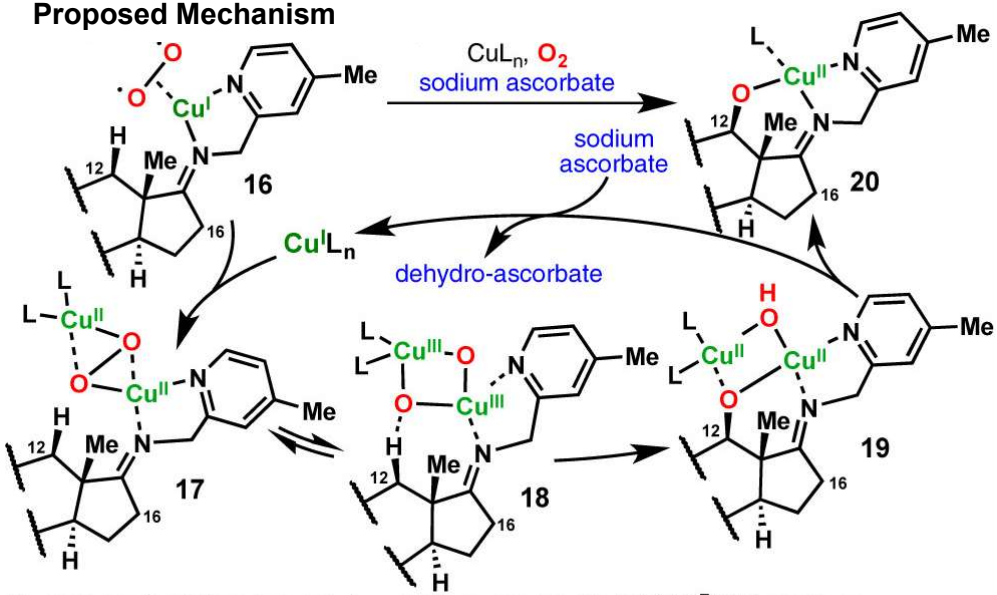

utendin


tomentogenin

Baran, P. *J. Am. Chem. Soc.* **2015**, *137*, 13776. https://doi.org/10.1021/jacs.5b09463

Mechanistic Studies: Baran

Proposed Mechanism



Current mechanistic proposal: **L = sodium ascorbate, MeCN, $^-$OTf, acetone**
Schönecker's mechanistic proposal: **L = DHEA imine, MeCN, $^-$OTf, acetone**

Supporting Observations

Substoichiometric NMR Experiments

- 0.5 equiv. $Cu(OTf)_2$ and 1.5 equiv. sodium ascorbate lead to no conversion after 1 h
- Additional 0.25 equiv. $Cu(OTf)_2$ led to 12% oxidation at 2 h
- Additional 0.5 equiv. $Cu(OTf)_2$ and 1.0 equiv. sodium ascorbate led to minor increase in conversion

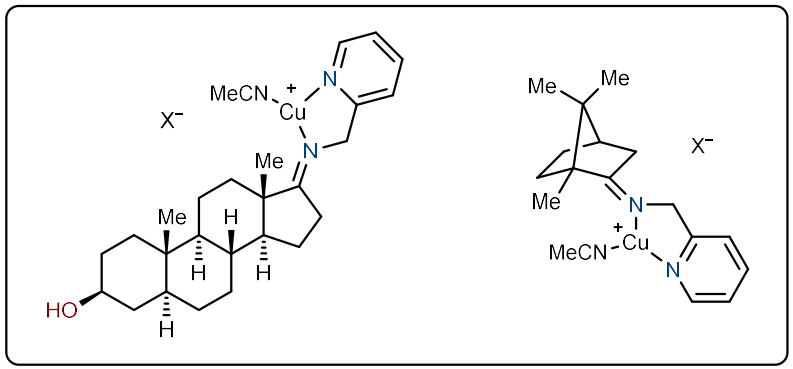
Superstoichiometric NMR Experiments

- In contrast, 1.05 equiv. $Cu(OTf)_2$ and 1.5 equiv. sodium ascorbate gave 50% conversion in just 30 min
- Additional 0.75 equiv. sodium ascorbate gave full conversion in 3.5 h

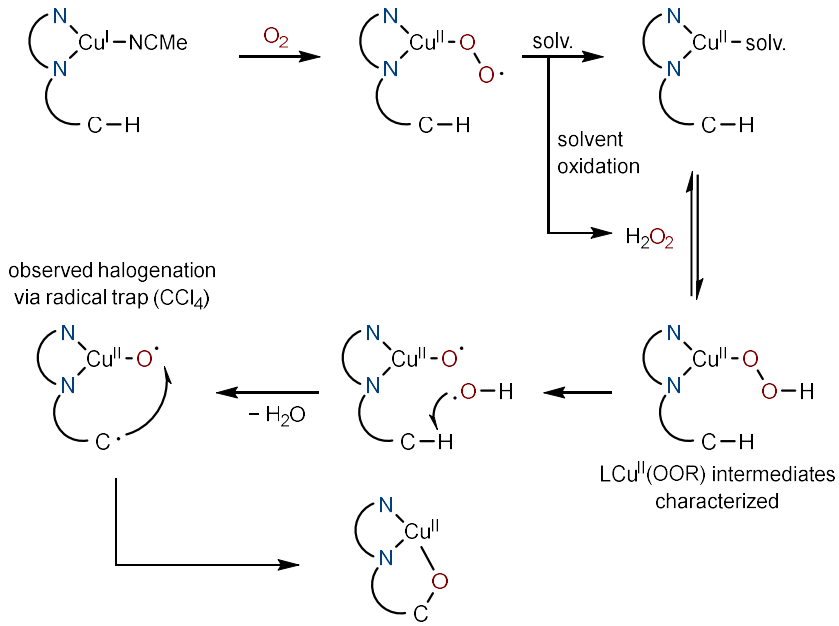
Baran, P. *J. Am. Chem. Soc.* **2015**, *137*, 13776. https://doi.org/10.1021/jacs.5b09463

Baran's Modified Schönecker Oxidation

Mechanistic Studies: Baran and Garcia-Bosch



- Elusive copper complexes characterized, subject to in-depth kinetic and spectroscopic studies

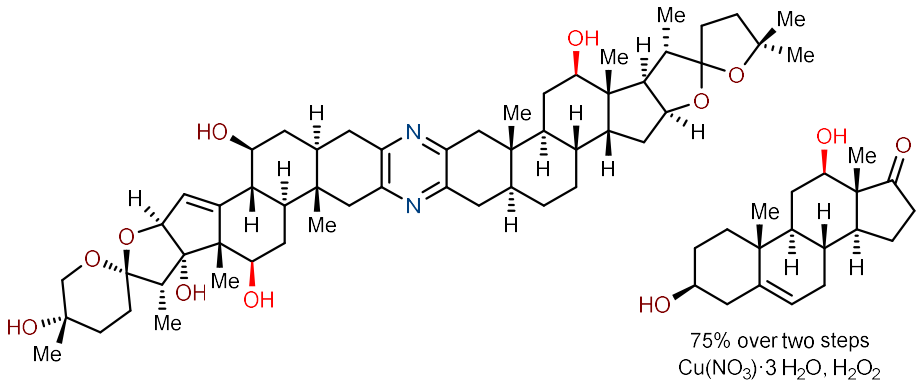


- New conditions: $Cu(NO_3)\cdot 3\,H_2O$, H_2O_2
- Improvements include use of H_2O_2 as oxidant instead of O_2
- No external reductant required
- Shorter reaction times, lower temperatures

Baran, P.; Garcia-Bosch, I. *J. Org. Chem.* **2017**, *82*, 7887. https://doi.org/10.1021/acs.joc.7b01069

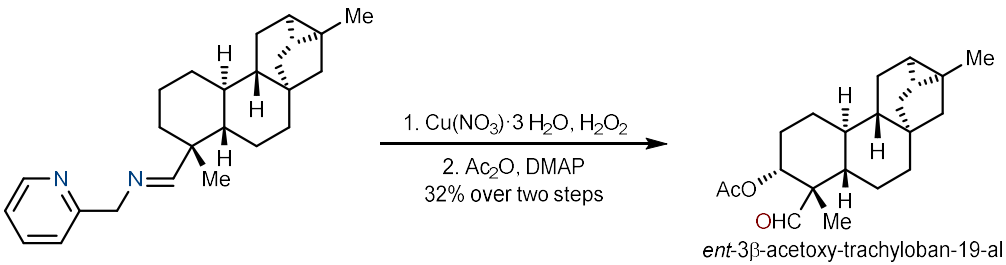
Applications in Total Synthesis

- **Ritterazine B** (Reisman, 2021)



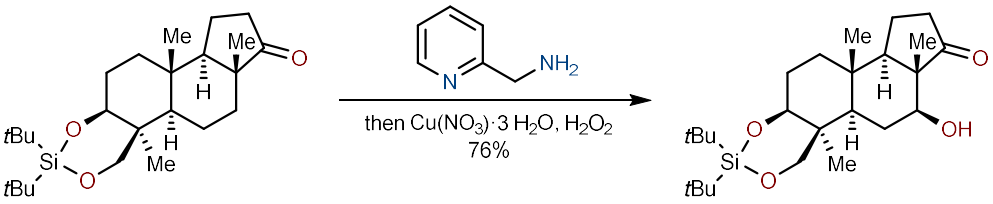
Reisman, S. *J. Am. Chem. Soc.* **2021**, *143*, 4187. https://doi.org/10.1021/jacs.1c01372

- ***ent*-Trachylobanes** (Magauer, 2021)



Magauer, T. *Angew. Chem. Int. Ed.* **2021**, ASAP. https://doi.org/10.1002/anie.202113829

- **Phainanoid A** (Dong, 2021)



Dong, G. *J. Am. Chem. Soc.* **2021**, *143*, 19311. https://doi.org/10.1021/jacs.1c11117