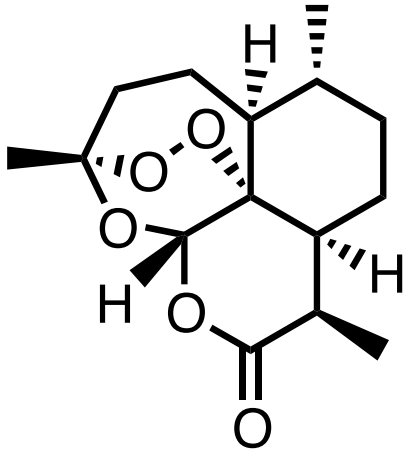
A Concise Synthesis of (+)-Artemisinin



Brandon Parks

Wipf Group Current Literature

October 6th, 2012

Qinghaosu (Artemisinin)

- Initially isolated in 1977 from *Artemisia annua* L. *Compositae* (Qinghao - Chinese herbal medicine)

- Currently the most effective treatment of malaria
  (ACT – artemisinin-based combination therapy)

- Estimated 225 million doses required per year

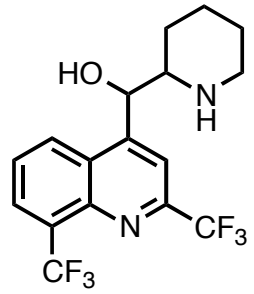
http://www.tcmwiki.com/wiki/qing-hao

Jing-Ming, L.; Mu-Yun, N.; Yu-Fen, F.; You-You, T.; Zhao-Hua, W.; Wei-Chan, C.; *Acta. Chim. Sinica*, **1979**, *37*, 129.
Zhou, W-S.; Xu, X-X.; *Acc. Chem. Res.*, **1994**, 27, 211.
World Health Organization. World Malaria Report 2010 (WHO. Geneva, **2010**).

Current Approaches and Modes of Action

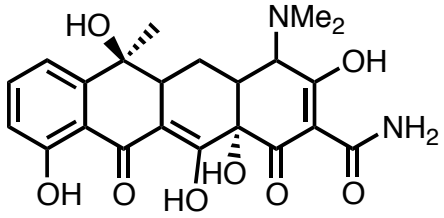
- Cytosol – Antifolates
  - Glycolysis, nucleotide biosynthesis

- Lysosomal Food Vacuole - Quinolines and Peroxides
  - Hematin interactions, free radical generation



mefloquine

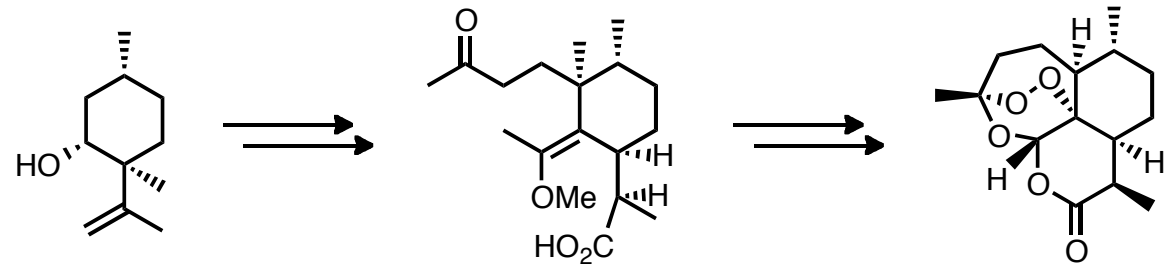
- Apicoplast – Antibiotics (tetracycline)
  - Plastid DNA replication and transcription
  - Type 2 fatty acid biosynthesis



tetracycline

Ridley, R. G.; *Nature*, **2002**, *415*, 686.

First Total Synthesis



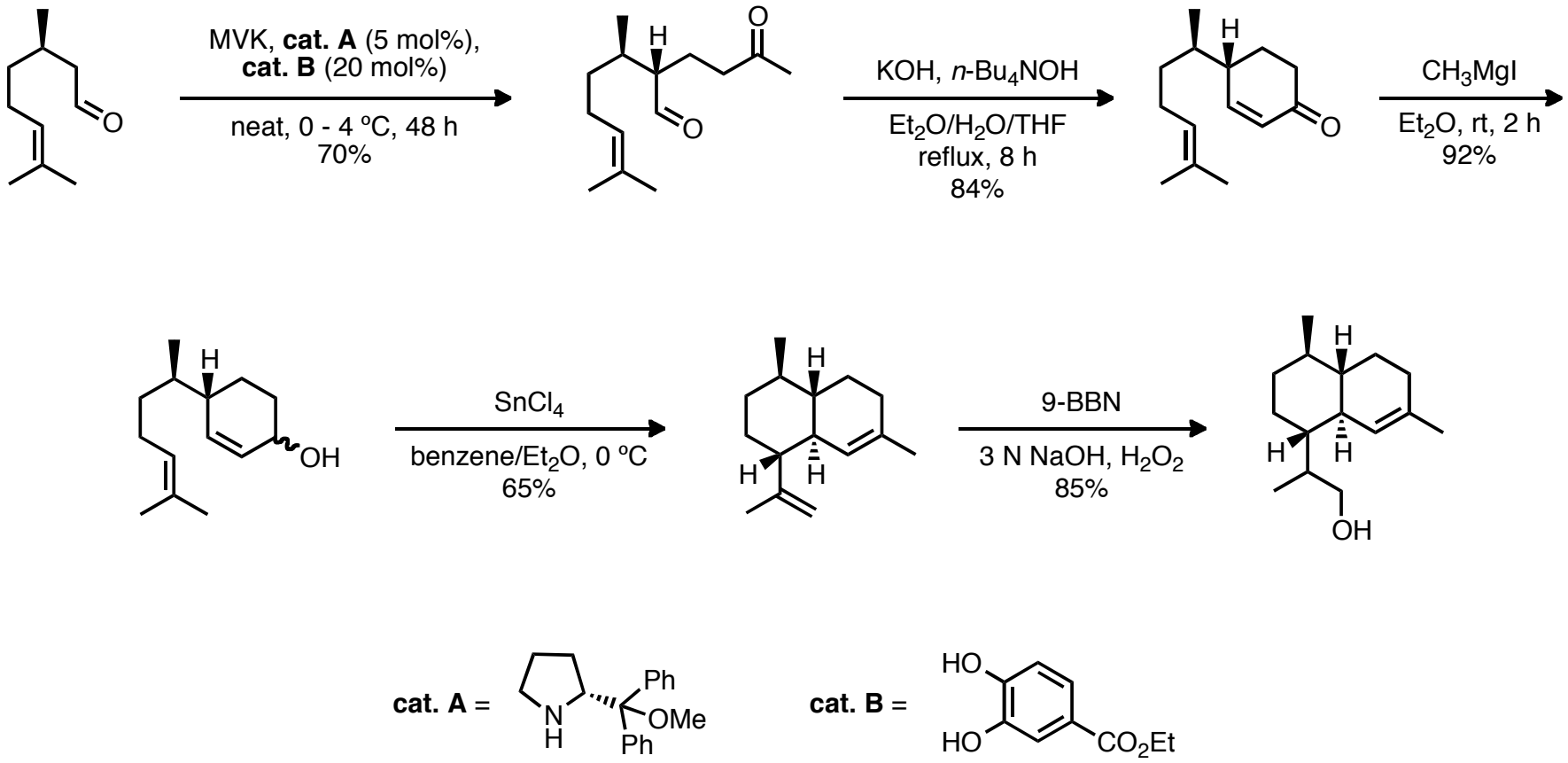
(-)-Isopulegol

- Utilized $^1O_2$ (methylene blue) for the introduction of the peroxide moiety

- 13 steps, 3% overall yield

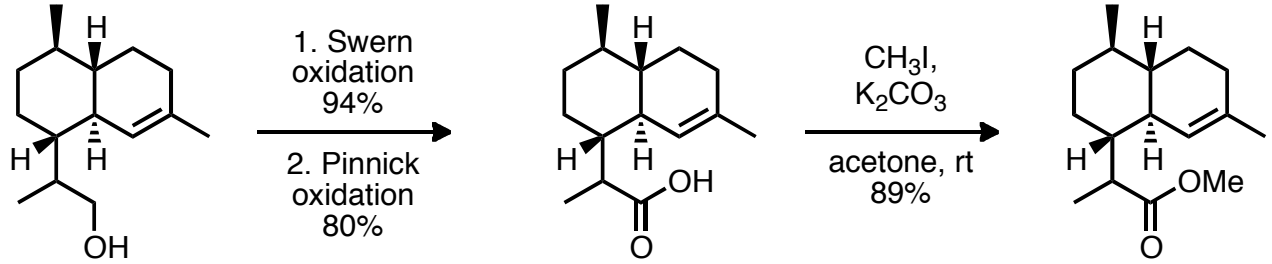
Schmid, G.; Hofheinz, W. *J. Am. Chem. Soc.*, **1983**, *105*, 624.

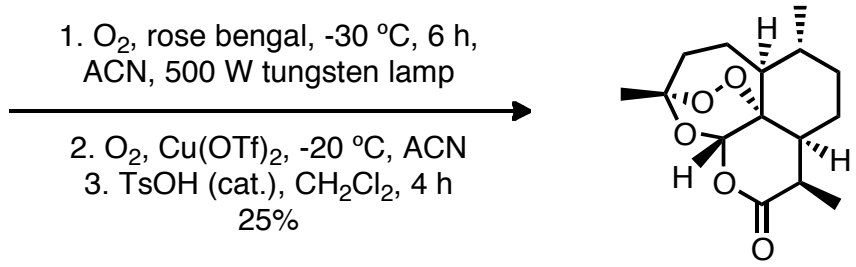
Recent Synthetic Strategy



Yadav, J.S.; Thirupathaiah, B.; Srihari, P. *Tetrahedron*, **2010**, *66*, 2005.

Oxidative Rearrangement

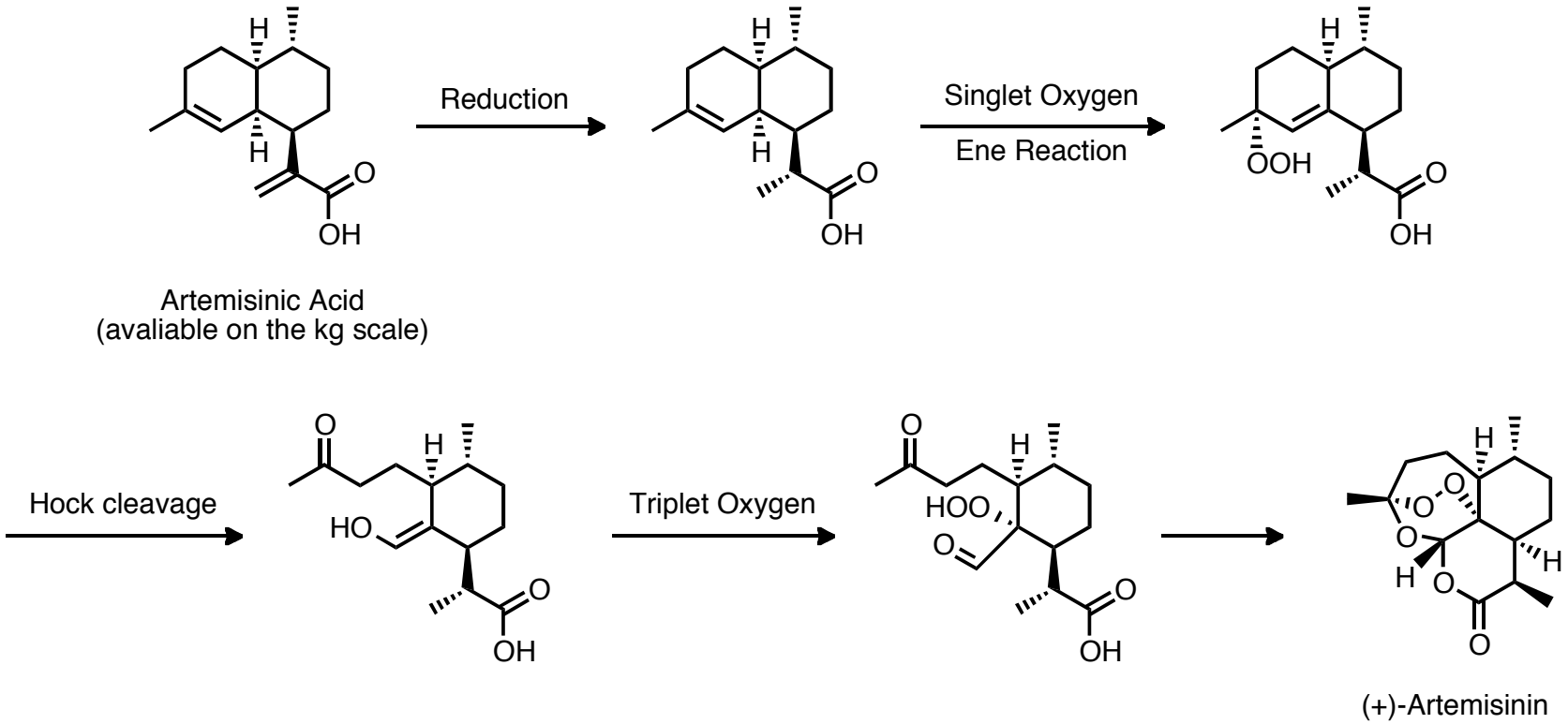




(+)-Artemisinin

- 11 steps, 5% overall yield
- Protecting group free-synthesis

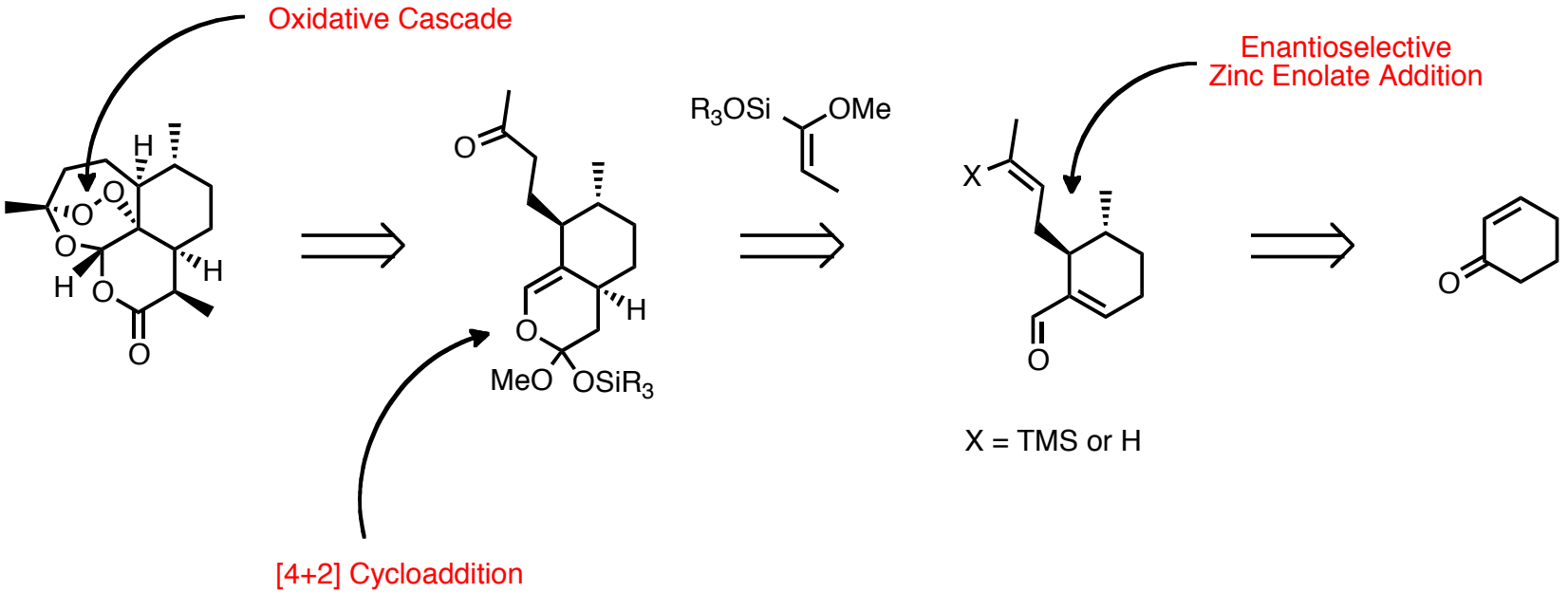
Continuous-Flow Synthesis



- Capable of producing 200 g per day…

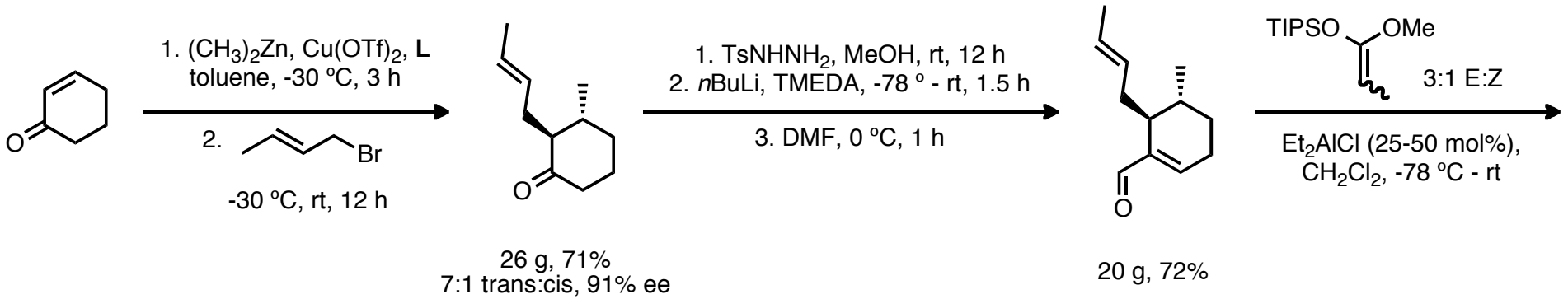
Lévesque, F.; Seeberger, P. H.; *Angew. Chem. Int. Ed.*, **2012**, *51*, 1706.

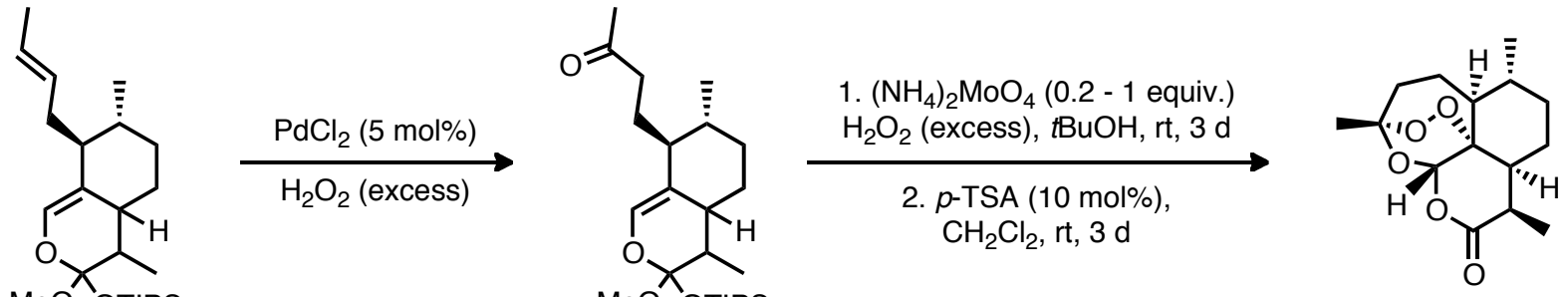
Synthetic Approach to (+)-Artemisinin



Zhu, C.; Cook, S.; *J. Am. Chem. Soc.*, **2012**, *134*, 13577.

Title Synthesis of (+)-Artemisinin





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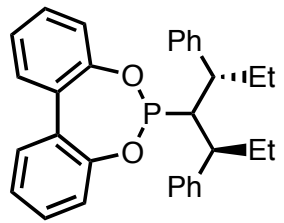

Conclusions

- Cost-efficient total synthesis of (+)-artemisinin was achieved
- Utilized enantioselective zinc enolate addition and an unconventional [4+2] cycloaddition
- Oxidative cascade could be optimized