Four Step Synthesis of the Antimalarial Cardamom Peroxide via an Oxygen Stitching Strategy

Xirui Hu and Thomas J. Maimone

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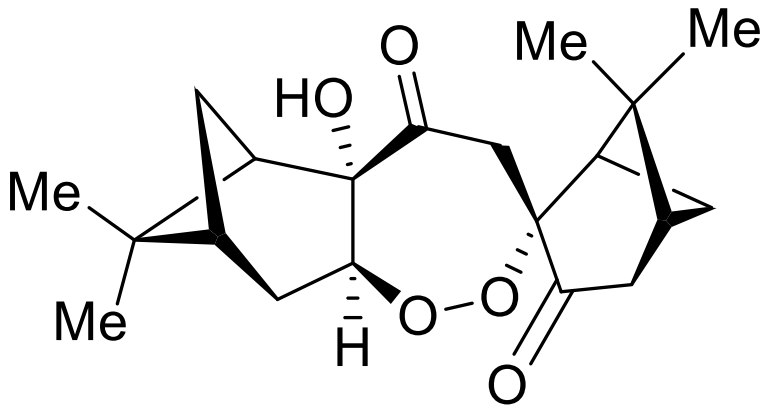
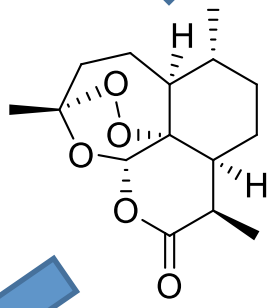


Nicholas Reed
Wipf Group Current Literature
April 12, 2014

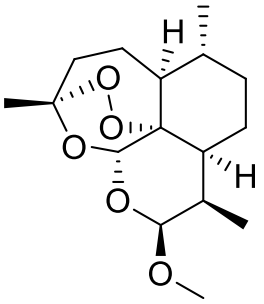
Malaria and Endoperoxides

- By the 1960s, Malaria had a resurgence
  - Mesquitos developed resistance to the insecticide DDT
  - Resistance to synthetic analogues of quinine
- Chinese government discovered that *Artemisis annua* had promising antimalarial properties
  - Led to isolation of artemisinin and development of better analogues via synthetic means
  - Has been the "front-line" treatment for malaria since
  - Artemisinin resistant malaria has begun to develop*
- Endoperoxide bridge is essential for activity
  - Build-up of free heme groups leads to breakdown of peroxide bridge
  - Resulting peroxy radical rearranges to carbon-centered radical (reductive scission vs. open peroxide models)

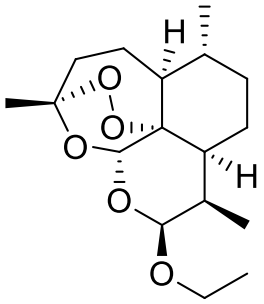
Artemisia annua
gobotany.newenglandwild.org



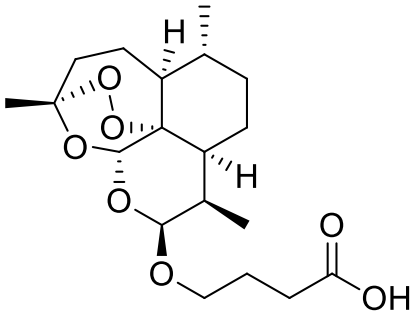
Artemisinin



Artemether



Arteether

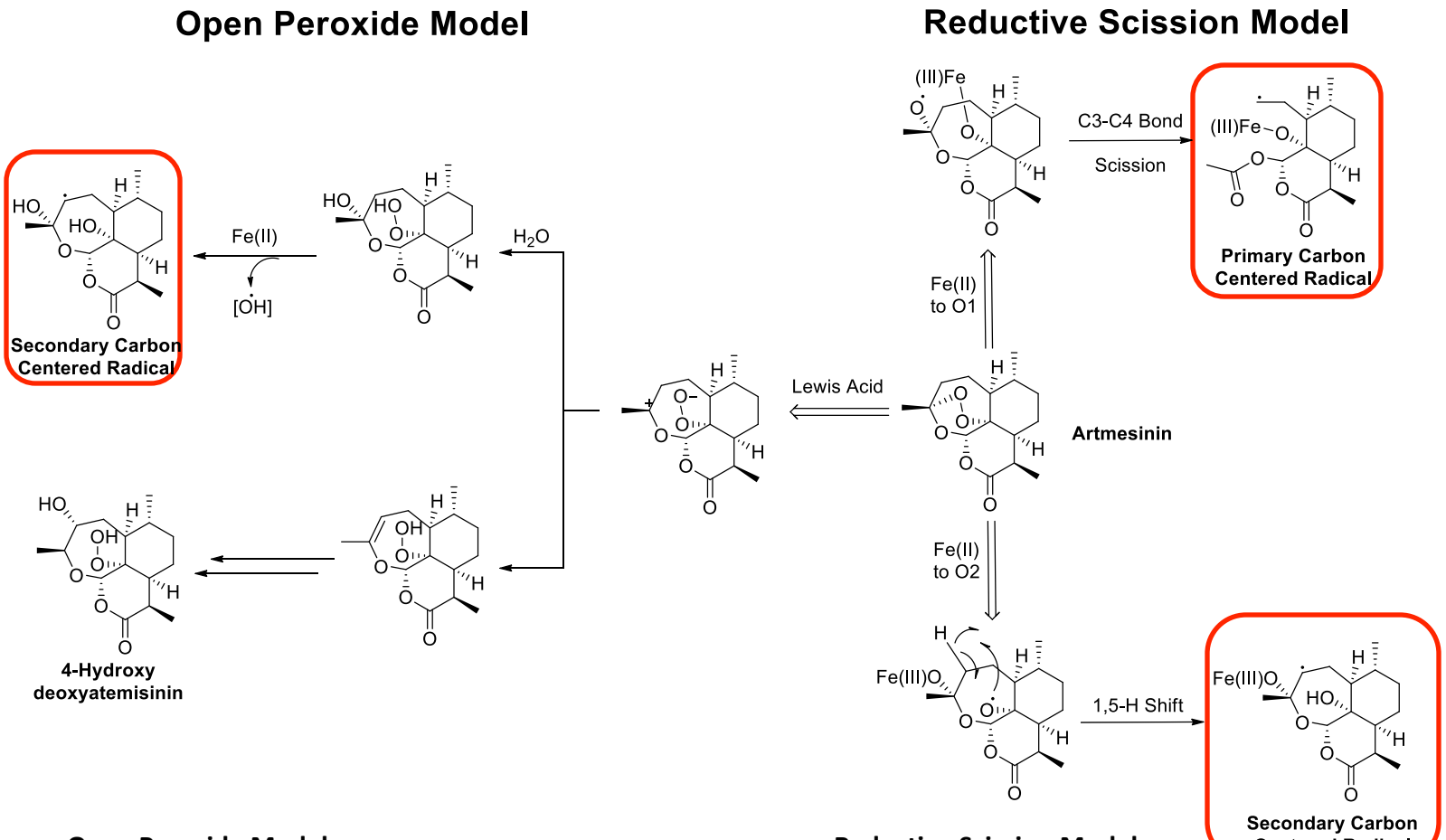


Artesunate

Molecules **2010**, *15*, 7603
Nat. Prod. Res.* **2004, *18*, 503
Drugs Future* **2005, *30*, 509

Presumed Mechanism of Action

- Analogous to mechanisms proposed for atemisinin

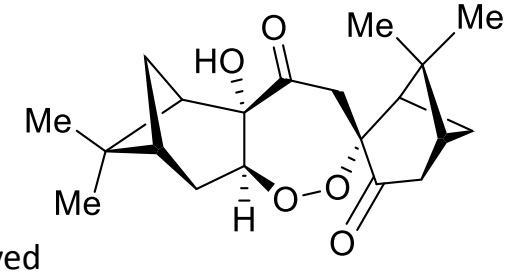


Open Peroxide Model:
ChemMedChem **2007**, *2*, 1480

Reductive Scission Model:
*J. Med. Chem.***1995,** *38*, 2273
J. Am. Chem. Soc. **1992**, *114*, 8328
Helv. Chim. Acta **1996**, *79*, 1475

Cardamom Peroxide

- Isolated from *Amomum krervanh* Pierre ("Round Siam Cardamom")
- Structure and relative stereochemistry determined primarily by NMR, IR, and X-ray diffraction experiments
  - Absolute stereochemistry unassigned but initially assumed to be derived from the same myrtenals that were also isolated



Cardamom Peroxide

- EC_{50} = 170 nm against *P. falciparum*
- Presumed mechanism of action involves activation by Fe(II) to cleave peroxide bridge and subsequent alkylation of malarial proteins


www.tcmfe.com

<u>Key Structural Features</u>

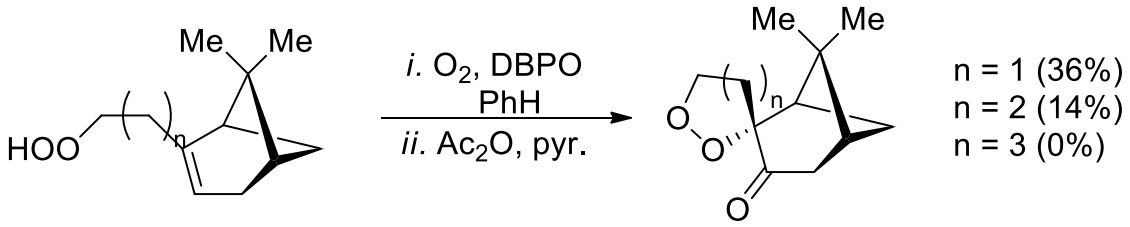
1,2-dioxepane motif

Semi-symmetric bipinane structure

Tetrahedron Lett. **1995**, *36*, 1821
Molecules **2010**, *15*, 1705

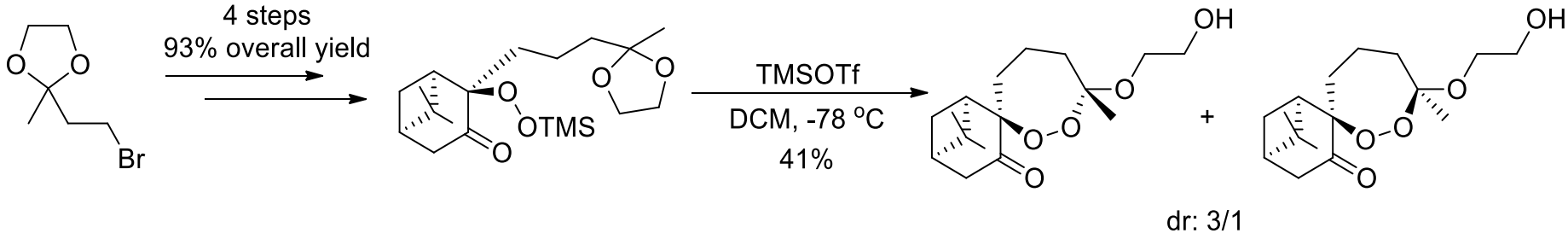
Previous Synthetic Work

- Unsuccessful radical cyclization to 7-membered endoperoxide



Tetrahedron Lett. **2002**, *43*, 6275

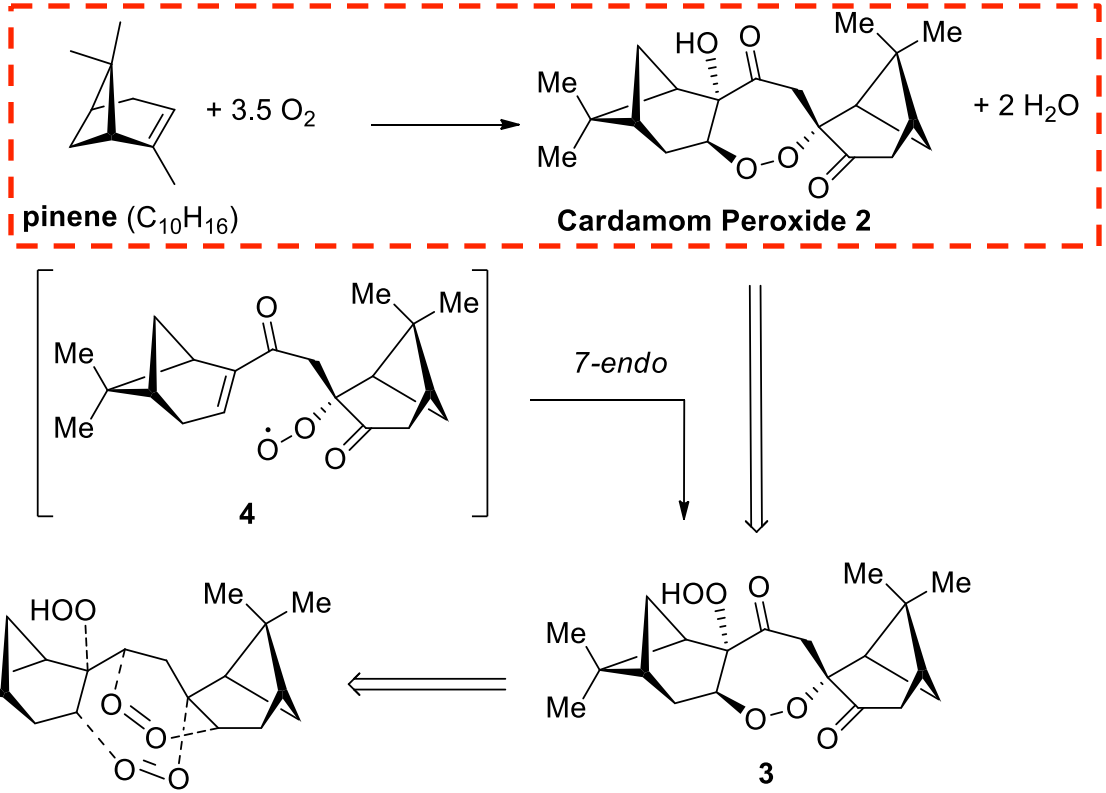
- Successful analog synthesis via silylperoxide cyclization onto a dioxolane



Bioorg. Med. Chem. **2003**, *11*, 3791

Analogs show roughly 10-fold decrease in potency
No synthesis of natural product to date!

Restrosynthesis



- Utilizes readily available pinene building blocks and molecular oxygen
- All stereochemical information comes from chiral pool (pinene skeleton)
- Challenges to overcome: 6-exo closure preference of peroxy radical, literature precedence, and chemo-, regio-, and stereochemical questions in cyclization

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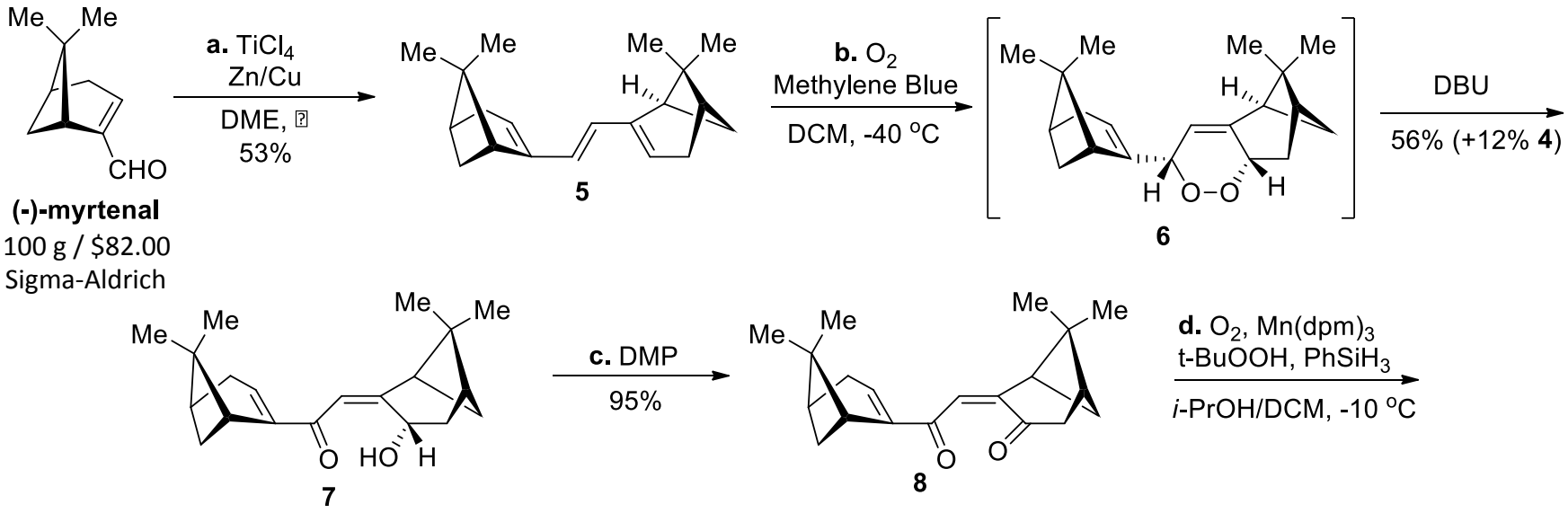
Tetrahedron Lett. **2002**, *43*, 6275

Four-Step Synthesis of (+)-Cardamom Peroxide



- McMurry Coupling
- [4+2] cycloaddition using singlet oxygen and Kornblum-DeLaMare Rearrangement
- Dess-Martin Oxidation

3 Steps

28% yield overall to penultimate compound

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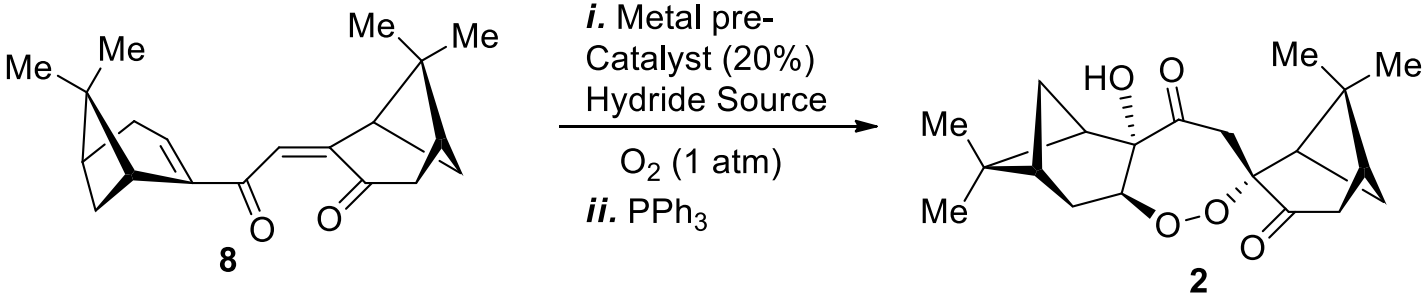

Entry	Conditions	Isolated Yield (%)[a]
1	$Fe_2(ox)_3 \cdot 6H_2O$ (5 equiv), $NaBH_4$ (6.4 eq), EtOH/H2O, 0 °C	0
2	$Fe^{II}(Pc)$, $NaBH_4$ (3 eq), EtOH, 0 °C	0
3	$Fe(acac)_3$, $PhSiH_3$ (2.5 eq), EtOH, 0 °C →rt	0
4	$Co(acac)_2$, $PhSiH_3$ (2.5 eq), DCM/*i*-PrOH, -10 °C →rt	6
5	$Mn(dpm)_3$, $PhSiH_3$ (2.5 eq), DCM/*i*-PrOH, -10 °C	34
6	$Mn(dpm)_3$, $PhSiH_3$ (2.5 eq), DCM/*i*-PrOH, -10 °C	41[b]
7	$Mn(dpm)_3$, $PhSiH_3$ (2.5 eq), *t*-BuOOH (1.5 eq), DCM/*i*-PrOH, -10 °C	52[b]

[a]Reaction performed on 0.1 mmol scale using 10 mol% of catalyst unless otherwise stated
[b]Phenylsilane added slowly over 12 h as a solution in DCM

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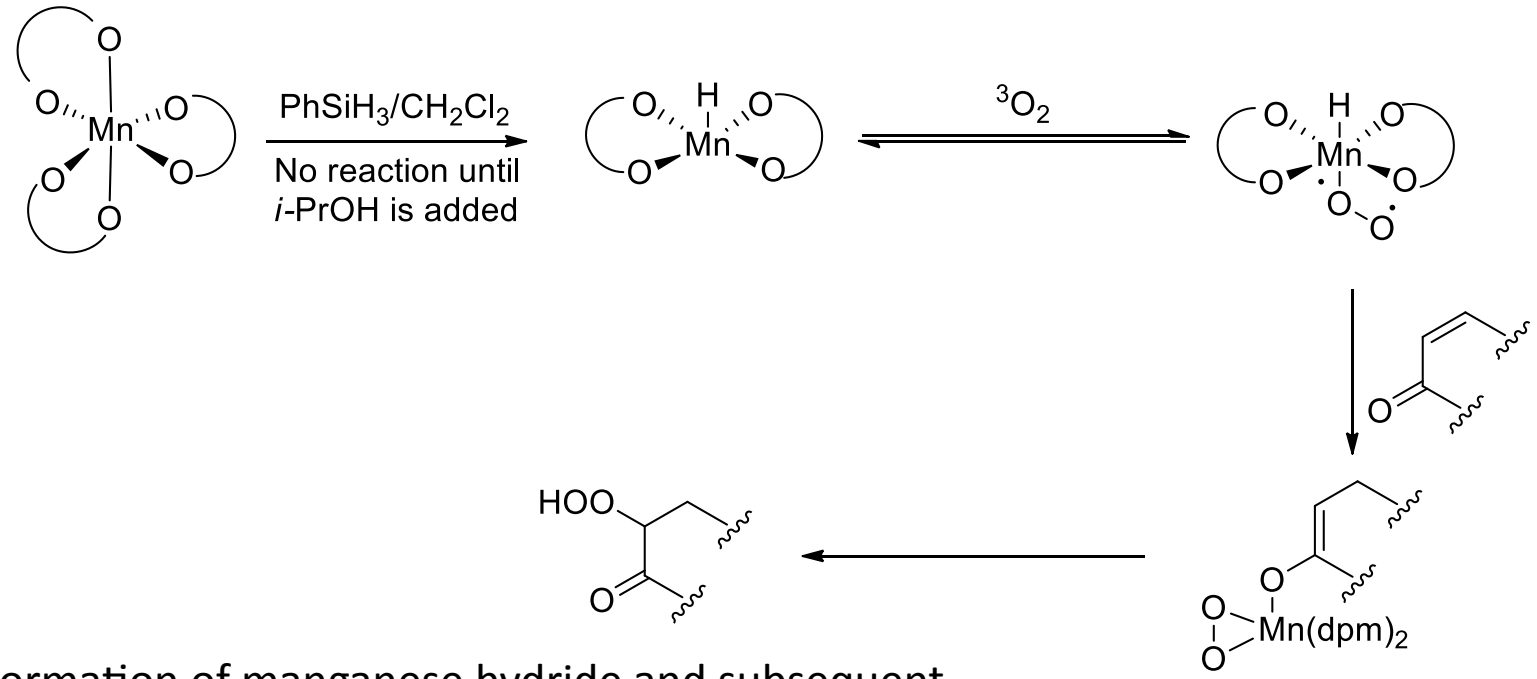
Four-Step Synthesis of (+)-Cardamom Peroxide

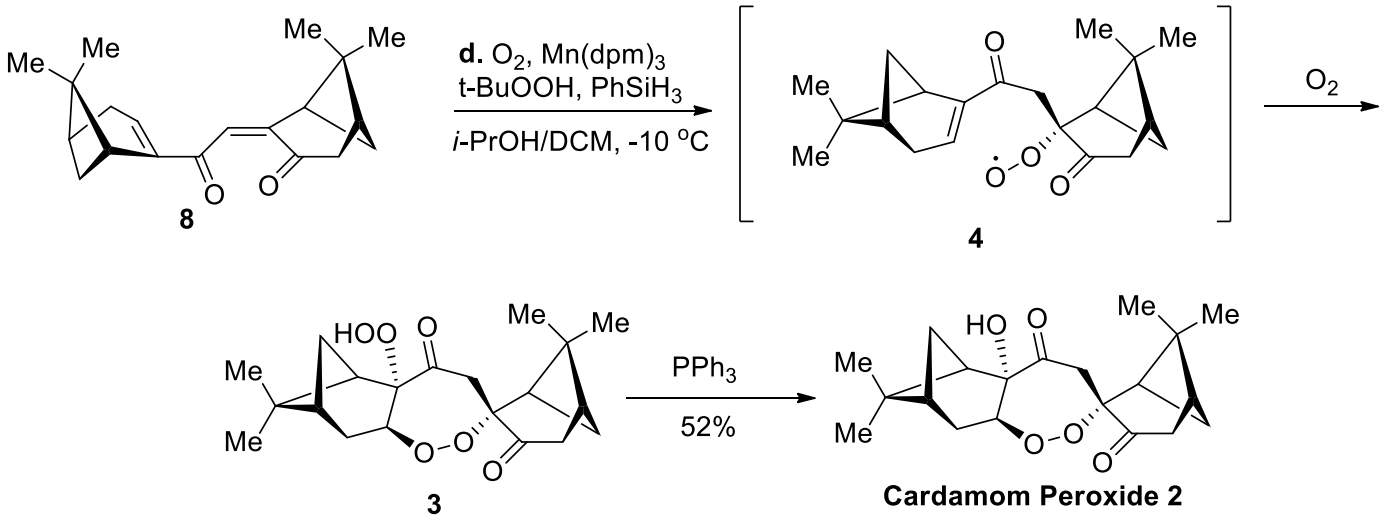


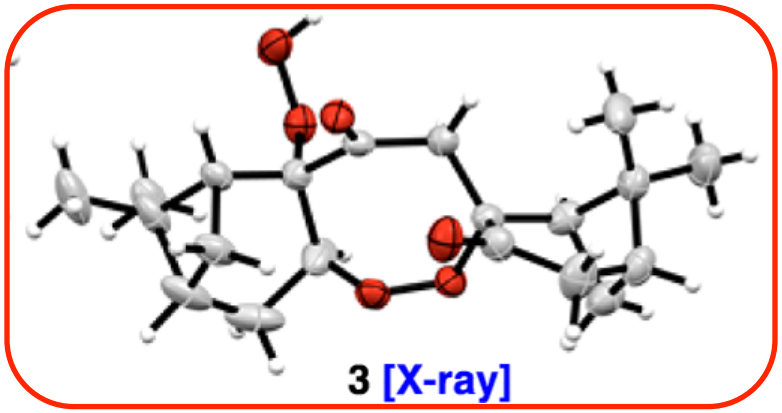
1. Formation of manganese hydride and subsequent complexation of triplet oxygen
2. Conjugate addition to form manganese peroxyenolate
3. Subsequent rearrangement to form peroxy ketone

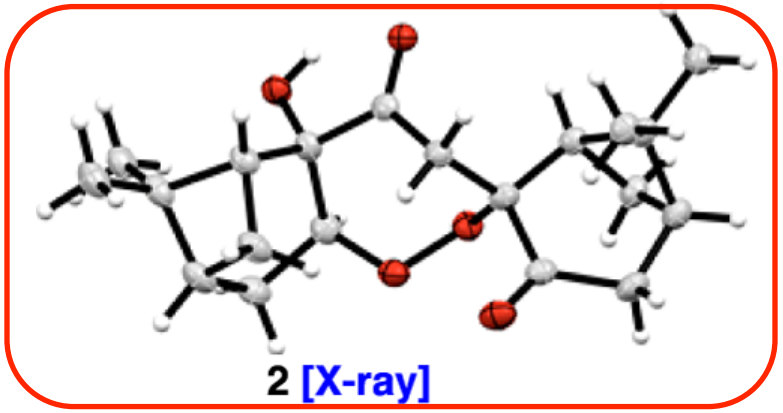
•Deuterium labeling experiments confirm irreversible addition of hydride by manganese
•Radical mechanism is also possible*

Tetrahedron Lett **2000**, *41*, 9725
Tetrahedron Lett **2000**, *41*, 9731

Four-Step Synthesis of (+)-Cardamom Peroxide







18% overall yield
4 steps from (-)-myrtenal

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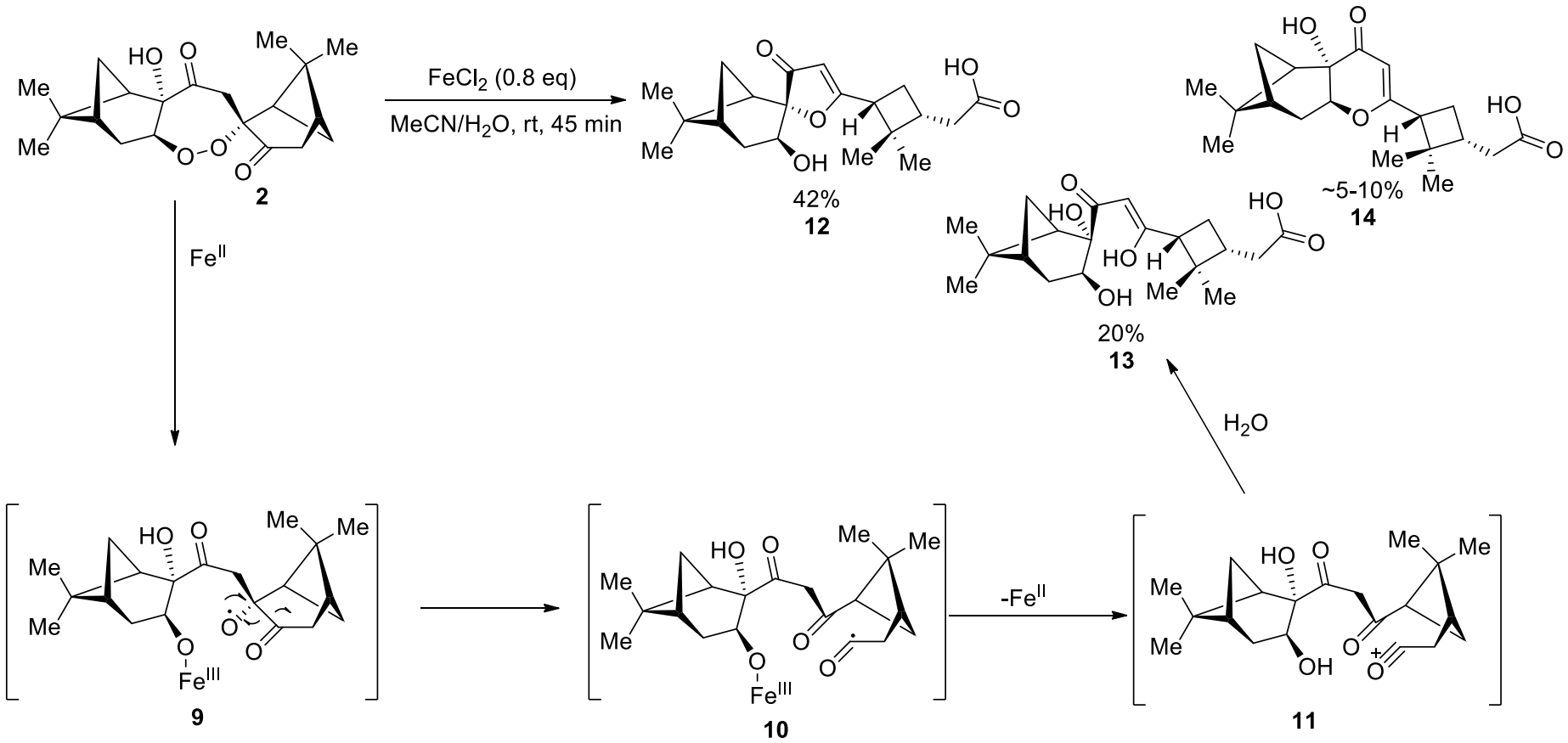
Reductive Cleavage with Fe(II)



- X-Ray confirmation of structures **12** and **14**

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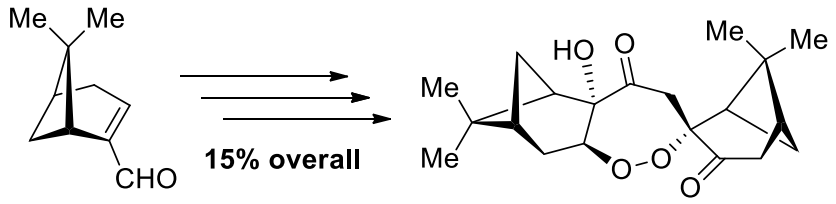
Conclusions

- 4 Step enantiospecific total synthesis of Cardamom Peroxide (15% overall yield)
  - Utilizes a Mn-catalyzed olefin hydroperoxidation



- Determined mode of reductive cleavage upon reaction with Fe(II)