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

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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 peroxo radical rearranges to carbon-centered radical (reductive scission vs. open peroxide models)

*Artemisia annua*  
gobotany.newenglandwild.org

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

Reductive Scission Model:

J. Med. Chem. 1995, 38, 2273
J. Am. Chem. Soc. 1992, 114, 8328

Open Peroxide Model:

ChemMedChem 2007, 2, 1480
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
- 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

**Key Structural Features**
- 1,2-dioxepane motif
- Semi-symmetric bipinane structure

*Molecules* **2010**, *15*, 1705

www.tcmfe.com
Previous Synthetic Work

- Unsuccessful radical cyclization to 7-membered endoperoxide

\[ \text{HOOC} \rightarrow \text{PhH} \rightarrow \text{Ac}_2\text{O, pyr.} \]

\[ n = 1 \ (36\%) \]
\[ n = 2 \ (14\%) \]
\[ n = 3 \ (0\%) \]


- Successful analog synthesis via silylperoxide cyclization onto a dioxolane

\[ \text{Br} \rightarrow \text{OTMS} \rightarrow \text{DCM, -78 °C} \]

\[ 41\% \]

\[ \text{dr: 3/1} \]

*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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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 (%)**<sup>a</sup>  
---|---|---  
1 | Fe<sub>2</sub>(ox)<sub>3</sub>·6H<sub>2</sub>O (5 equiv), NaBH<sub>4</sub> (6.4 eq), EtOH/H2O, 0 °C | 0  
2 | Fe<sup>II</sup>(Pc), NaBH<sub>4</sub> (3 eq), EtOH, 0 °C | 0  
3 | Fe(acac)<sub>3</sub>, PhSiH<sub>3</sub> (2.5 eq), EtOH, 0 °C → rt | 0  
4 | Co(acac)<sub>2</sub>, PhSiH<sub>3</sub> (2.5 eq), DCM/i-PrOH, -10 °C → rt | 6  
5 | Mn(dpm)<sub>3</sub>, PhSiH<sub>3</sub> (2.5 eq), DCM/i-PrOH, -10 °C | 34  
6 | Mn(dpm)<sub>3</sub>, PhSiH<sub>3</sub> (2.5 eq), DCM/i-PrOH, -10 °C | 41<sup>b</sup>  
7 | Mn(dpm)<sub>3</sub>, PhSiH<sub>3</sub> (2.5 eq), t-BuOOH (1.5 eq), DCM/i-PrOH, -10 °C | 52<sup>b</sup>

<sup>a</sup>Reaction performed on 0.1 mmol scale using 10 mol% of catalyst unless otherwise stated  
<sup>b</sup>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

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Reductive Cleavage with Fe(II)

\[
\text{FeCl}_2 (0.8 \text{ eq}) \quad \text{MeCN/H}_2\text{O, rt, 45 min}
\]

• 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)