A Concise Synthesis of (+)-Artemisinin

Brandon Parks
Wipf Group Current Literature
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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


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

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

First Total Synthesis

- Utilized $^{1}\text{O}_2$ (methylene blue) for the introduction of the peroxide moiety

- 13 steps, 3% overall yield

Recent Synthetic Strategy

MVK, **cat. A** (5 mol%), **cat. B** (20 mol%) neat, 0 - 4 ºC, 48 h 70%

KOH, n-Bu₄NOH Et₂O/H₂O/THF reflux, 8 h 84%

CH₃Mgl Et₂O, rt, 2 h 92%

SnCl₄ benzene/Et₂O, 0 ºC 65%

9-BBN 3 N NaOH, H₂O₂ 85%

**cat. A =** [structure image]  
**cat. B =** [structure image]  

Oxidative Rearrangement

1. Swern oxidation 94%
2. Pinnick oxidation 80%

1. O₂, rose bengal, -30 °C, 6 h, ACN, 500 W tungsten lamp
2. O₂, Cu(OTf)₂, -20 °C, ACN
3. TsOH (cat.), CH₂Cl₂, 4 h 25%

(+)-Artemisinin

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

Artemisinic Acid (available on the kg scale)

- Capable of producing 200 g per day…

Synthetic Approach to (+)-Artemisinin

Title Synthesis of (+)-Artemisinin

1. (CH₃)₂Zn, Cu(OTf)₂, L
toluene, -30 °C, 3 h
2. Br
-30 °C, rt, 12 h

26 g, 71%
7:1 trans:cis, 91% ee

1. TsNHNH₂, MeOH, rt, 12 h
2. nBuLi, TMEDA, -78 ° - rt, 1.5 h
3. DMF, 0 °C, 1 h

20 g, 72%

1. (NH₄)₂MoO₄ (0.2 - 1 equiv.)
H₂O₂ (excess), tBuOH, rt, 3 d
2. p-TSA (10 mol%),
CH₂Cl₂, rt, 3 d

9.4 g, 61%

(+)-Artemisinin
1.26 g, 29%,
9 steps, 9% overall yield
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