A Concise Synthesis of (+)-Artemisinin


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Research:
- Total synthesis of molecules with biological activity in oncology, anti-infectives, neurological disorders and Third World Ailments
- Catalysis: Wide range, focus on “green catalysis” e.g. iron
Currently, the most effective treatment against Malaria-causing *Plasmodium* parasites is an artemisinin-based combination therapy.

Malaria affects over 200 million people each year, around one million dies.

Artemisinin is currently obtained by extraction or semi-synthesis, but too expensive.

Previous total-syntheses start from expensive terpene-based materials.

*World Malaria Report 2011; World Health Organization, Geneva, 2011*
La-Roche synthesis

Jennings-White synthesis

Retrosynthetic plan

4 -> 5

5a: X = TMS
5b: X = H

6 -> artemisinin (1)
Forward synthesis I

1) (CH$_3$)$_2$Zn (1.0 equiv)  
Cu(OTf)$_2$ (1 mol %)  
L$^*$ (2 mol %)  

2) \(\text{Br}\)  

1) TsNHNH$_2$  
2) nBuLi (4 equiv)  
3) DMF  
as Jennings-White

7g = 71% yield; 9:1 trans:cis  
26g = 61% yield; 7:1 trans:cis, 91% ee

4.6g = 77% yield  
20g = 72% yield
Mechanism of cyclohexanone functionalization

The yield was improved from 26% to 80% by switching to toluene, bringing zinc-enolates back in the game

Forward synthesis II

- Unusual [4+2] reaction for the installation of the lactone ring

\[
\text{TIPSO}_2\text{OCH}_3 \xrightarrow{3:1 \text{ E:Z}} \text{Et}_2\text{AlCl} \xrightarrow{0.25-0.5 \text{ equiv}} \]

1.8g = 95% yield; 6/2/1/1 dr
47g = >98% yield; 10/4/1/1 dr

"2 of 3 centers are irrelevant for the synthesis"
The center with the proton is probably fully controlled

\[
\xrightarrow{\text{PdCl}_2 (5 \text{ mol } \%), \text{H}_2\text{O}_2 (\text{excess})} \]

9.4g = 61% yield
(31% ethyl ketone)
Mechanism of the [4+2] - I

- Looks like a simple [4+2] mechanism, what could go wrong?
Mechanism of the [4+2] - II

- Possible side reactions

- [4+2]
- Mukaiyama Aldol
- Mukaiyama Michael
- [2+2]
Forward synthesis III

- The usual steps to complete the molecule

1. \((\text{NH}_4)_2\text{MoO}_4\) (0.2-1 equiv)
2. \(\text{H}_2\text{O}_2\) (excess)
3. t-BuOH, RT, 3 d

29% yield after crystallization

2H\(_2\)O\(_2\) + MoO\(_4^{2-}\) \(\rightarrow\) 2H\(_2\)O + \(^{1}\text{O}_2\)

Mechanism/ Intermediates in the oxidation

None of the three papers mentioned could determine the nature of the intermediate, oxidated compounds.

Strategy overview
The conclusion

- The synthesis solves the problem of expensive starting materials.
- The synthesis is somewhat shorter (less steps) than the previous ones.
- Key steps: Zinc enolate alkylation, [4+2] annulation and high-yielding oxidation of internal olefin.
The conclusion

- The synthesis does not solve the problem of the late peroxide formation with bad selectivity (all the syntheses have only 30-40% yield for the last steps)

- The last two steps take 3 days each

- The paper provides little information about the stereochemistry of some intermediates and the mechanism of the last steps