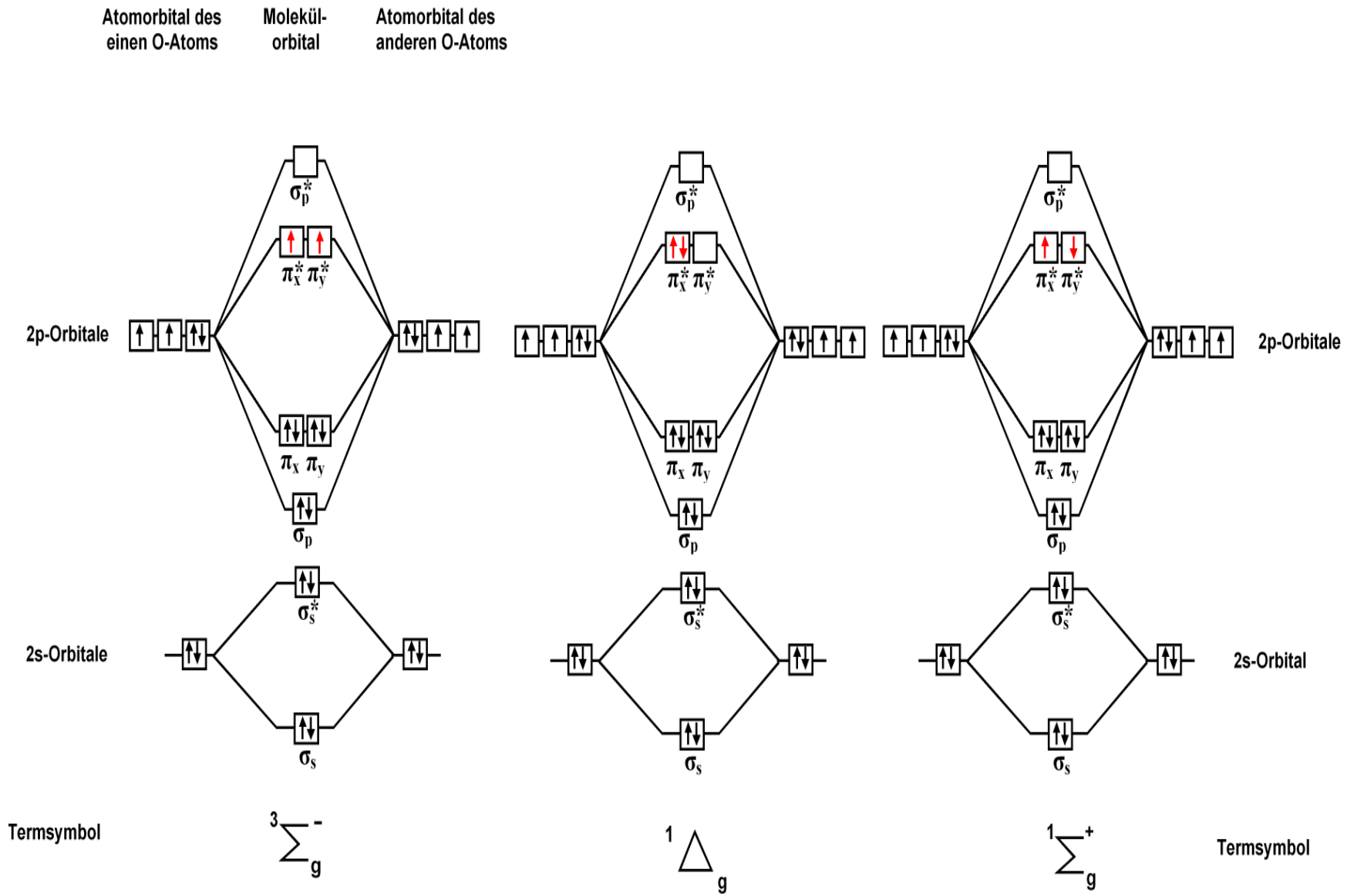
Singlet Oxygen Problem Set

Simon Lang

Friday Sept 7 2012

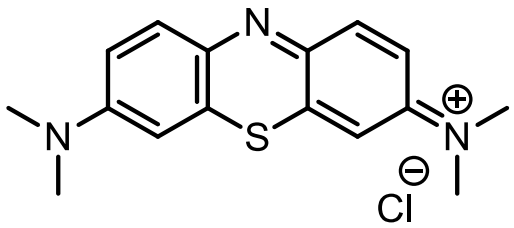

Atomorbital des einen O-Atoms
Molekül-orbital
Atomorbital des anderen O-Atoms
2p-Orbitale
2s-Orbitale
Termsymbol
σ_p^*
$\pi_x^* \pi_y^*$
$\pi_x \pi_y$
σ_p
σ_s^*
σ_s
$^3\Sigma_g^-$
$^1\Delta_g$
$^1\Sigma_g^+$
2p-Orbitale
2s-Orbital
Termsymbol
Triplett-Sauerstoff (stabil)
Singulett-Sauerstoff (kurzlebig, reaktiv)

General Properties

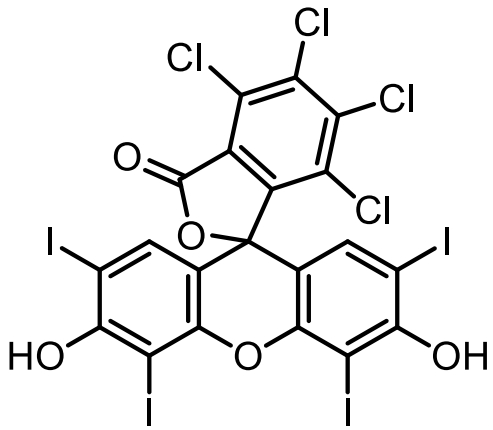
- Singlet oxygen is 22 kcal above the ground state
- The lifetime of singlet oxygen in solvents:
  - Carbon tetrachloride (59 ms)
  - Benzene (30 μs)
  - Water (3.5 μs)
  - Deuterium oxide (65 μs)

$$\text{Dye} + h\nu \longrightarrow \text{Dye}^*$$

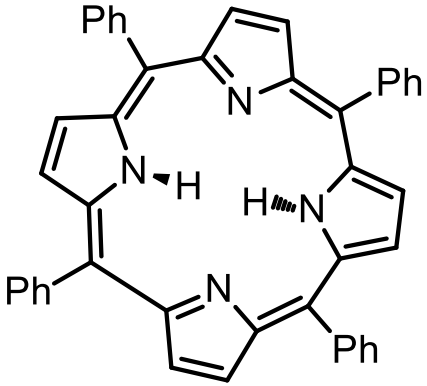
$$\text{Dye}^* + {}^3O_2 \longrightarrow \text{Dye} + {}^1O_2$$



Methylene blue



Rose Bengal

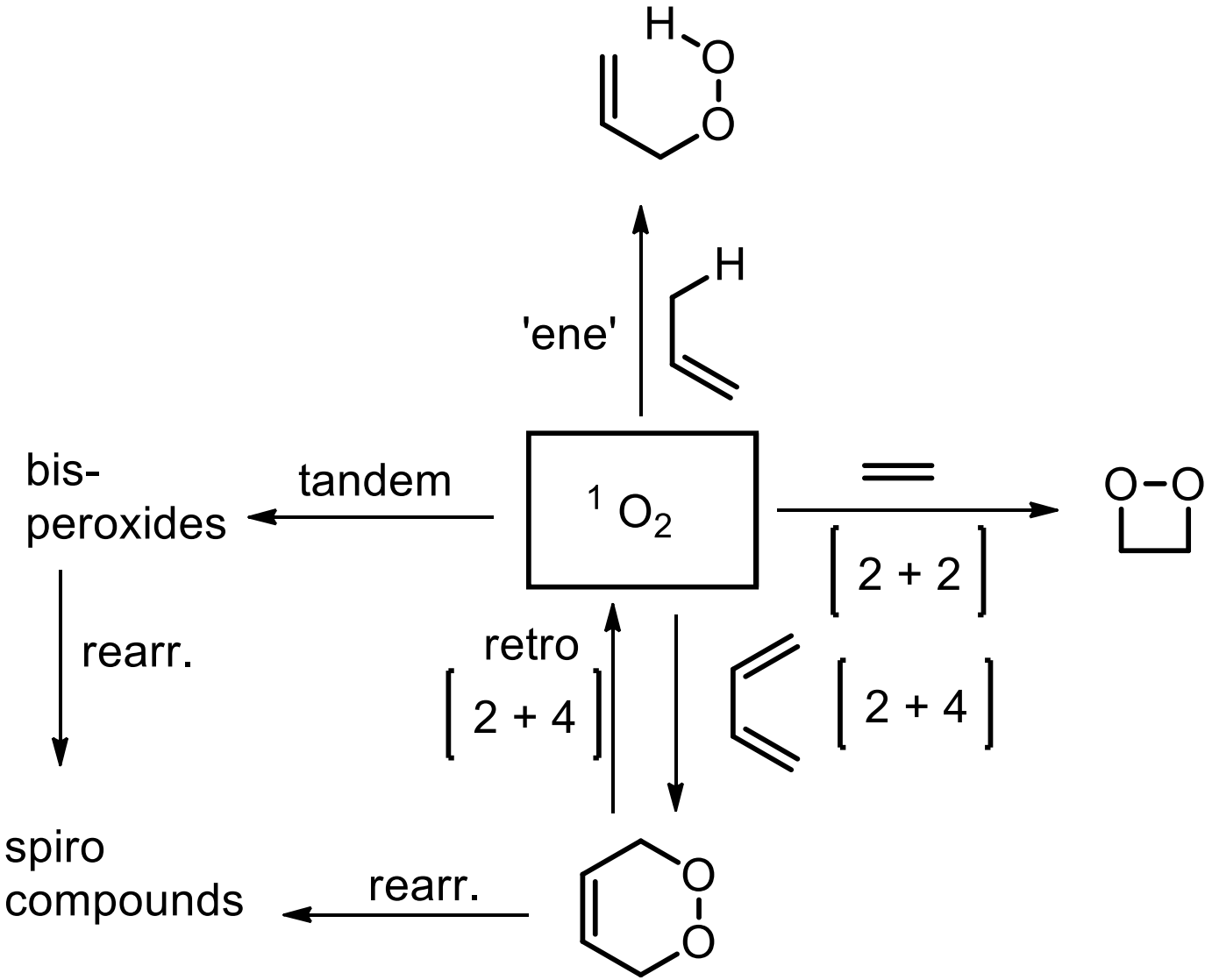


Tetraphenylporphyrin

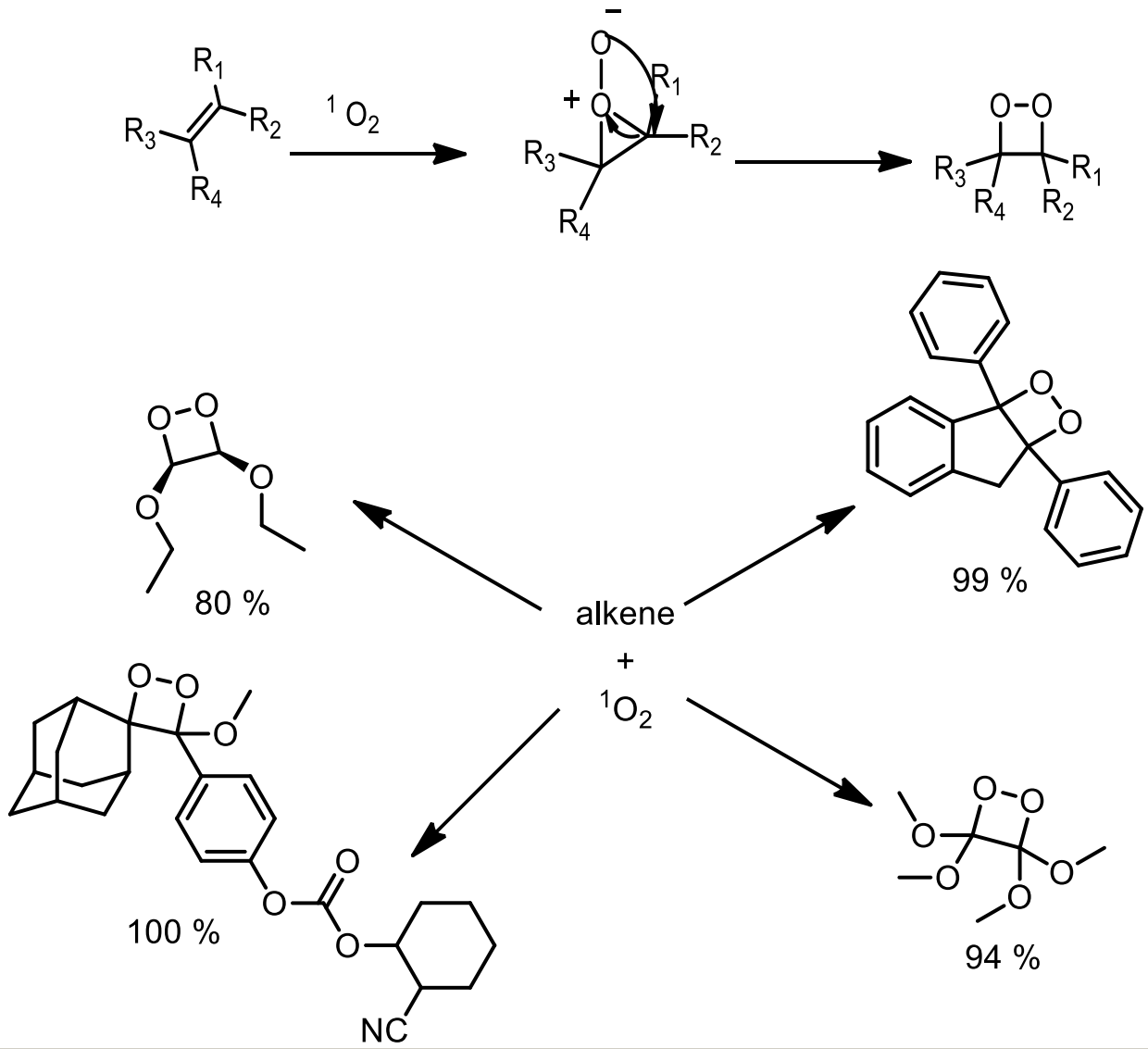
sensitizers

Biomimetic synthesis

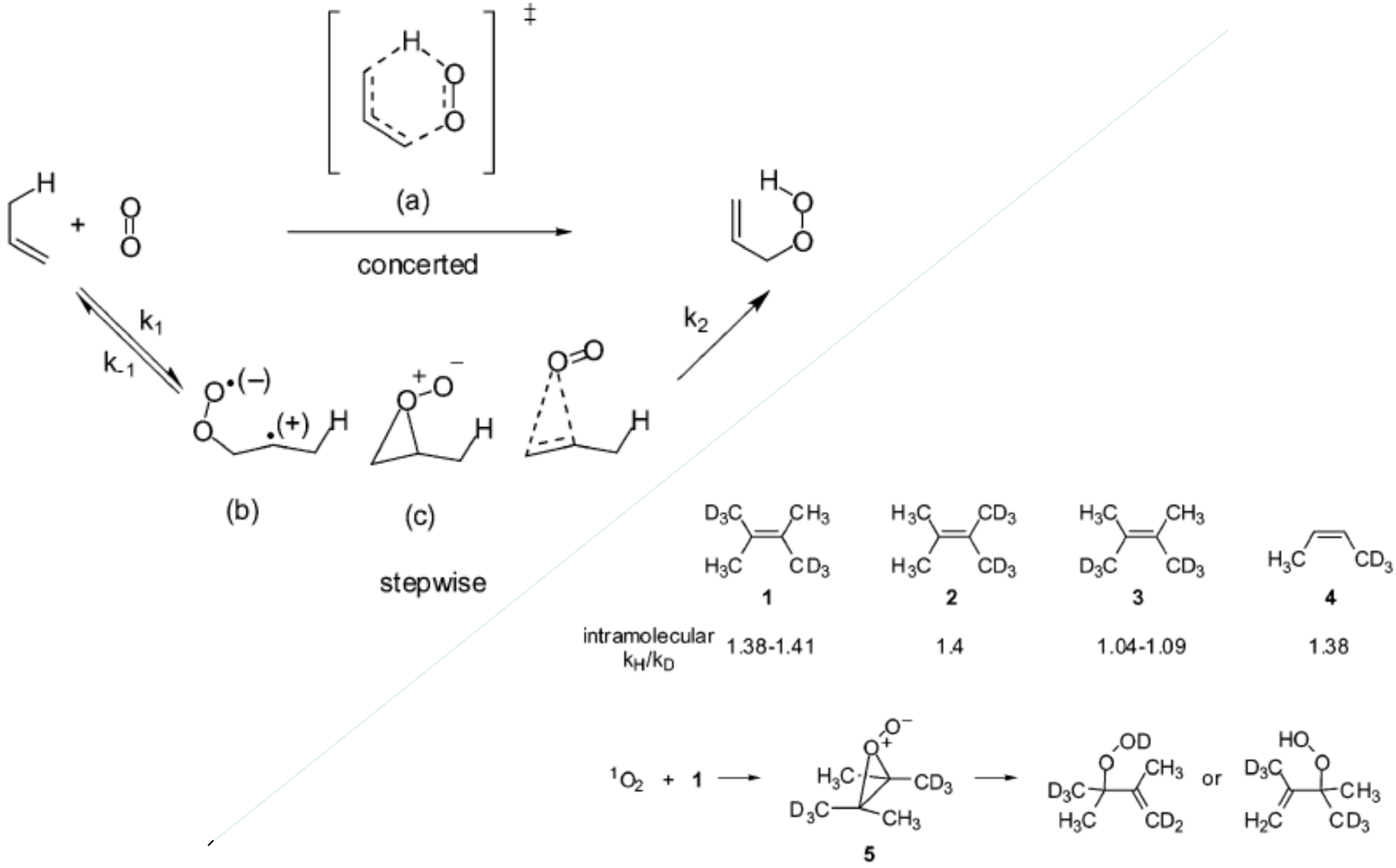
- Four criteria
  - Presence of natural sunlight
  - Proliferation of photosensitizes (tannins, porphyrins, chlorophyll)
  - Molecular dioxygen
  - Abundance of oxidizable substrates


H
O
O
'ene'
H
bis-
peroxides
tandem
$^1O_2$
O–O
2 + 2
rearr.
retro
2 + 4
2 + 4
spiro
compounds
rearr.
O
O

[2+2] Cycloadditions



‘Ene’ reaction



cis effect

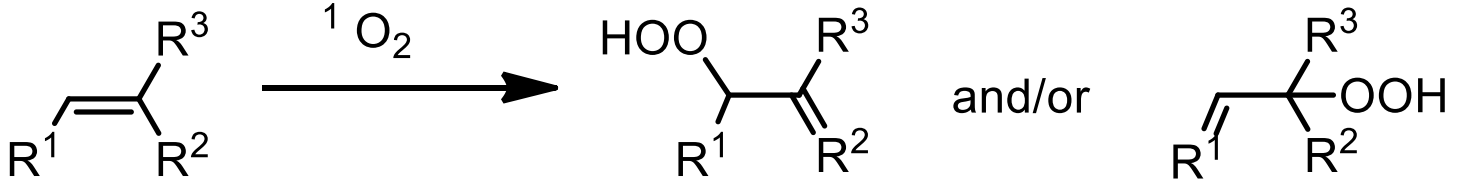
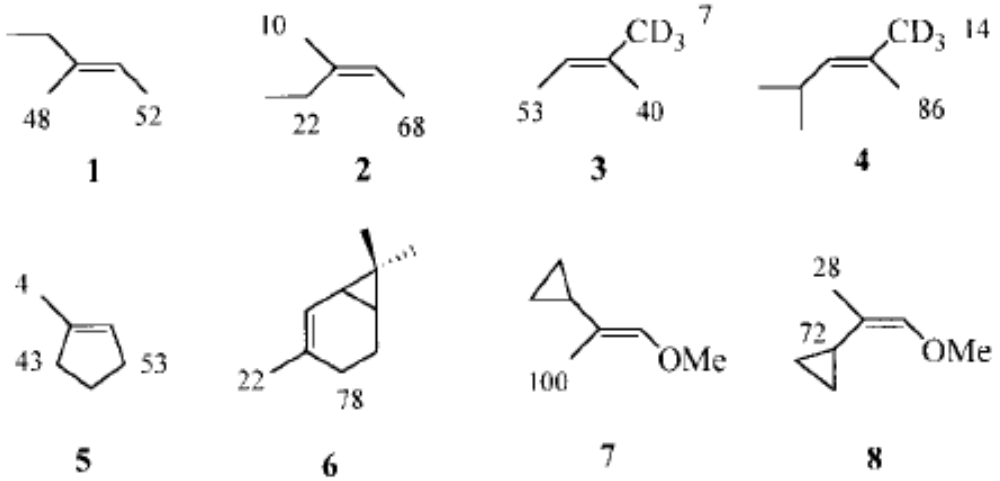
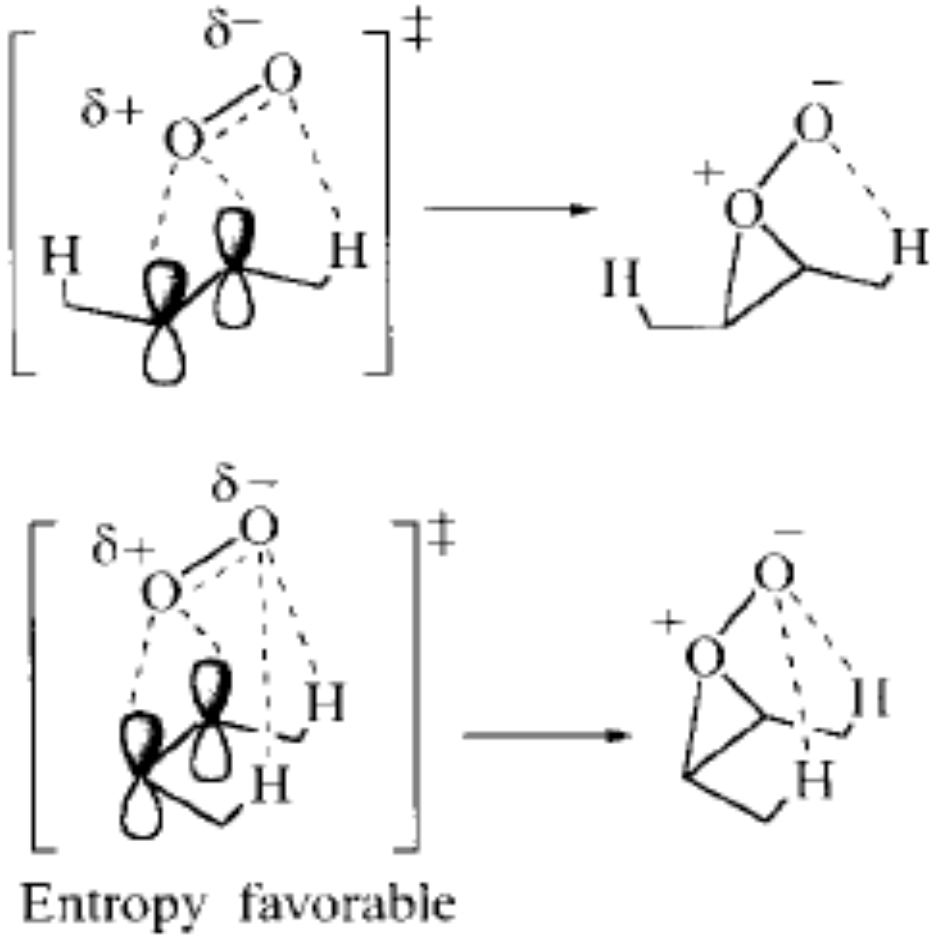
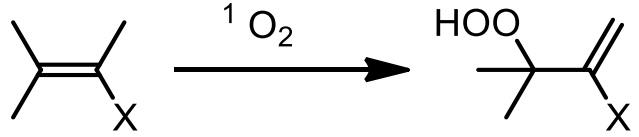


Table 1. Numbers indicate percentage of double bond formation in the ene adducts



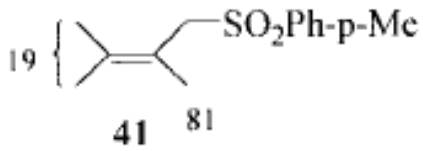

δ−
δ+
O
O
H
H
‡
O
+
O
H
H
δ−
δ+
O
O
H
H
‡
O
+
O
H
H
Entropy favorable

geminal effect

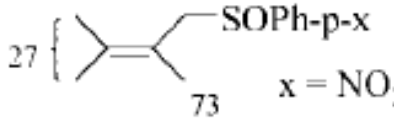


[X = C(O)R, CO_2R, CN, SO_2R, Ph, etc.]

Table 8. Numbers indicate percentage of double bond formation in the ene adducts

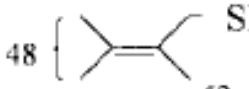


41

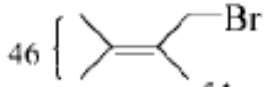


x = NO_2, H, Me, MeO

42



43 x = Me, NO_2

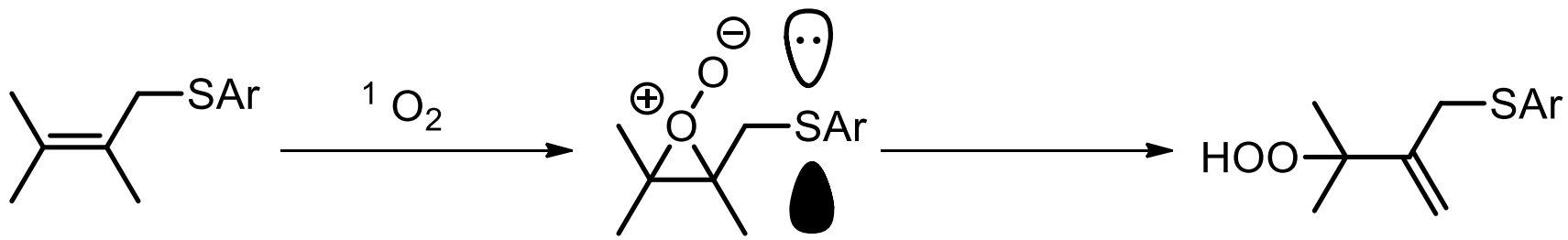


44

THE UNIVERSITY OF KANSAS

Explanation 1

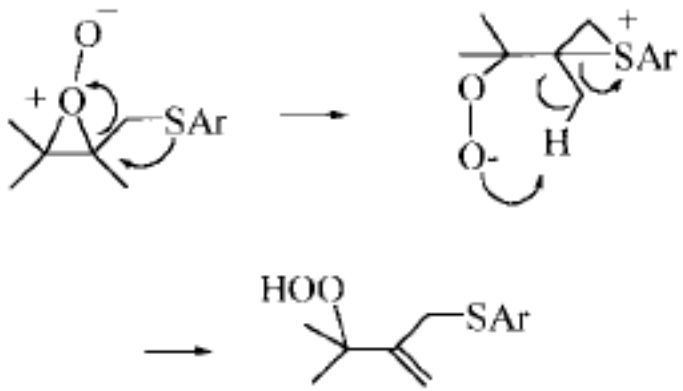
- Electronic repulsion between heteroatom and negatively charged oxygen of perepoxide.

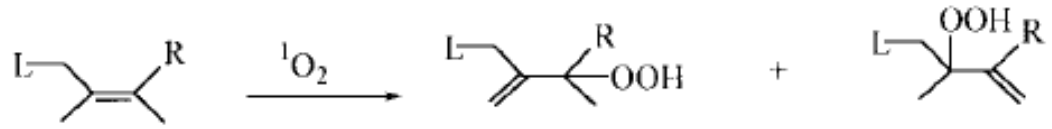


M. Stratakis, M. Orfanopoulos,
Tetrahedron **2000**, 1595

Explanation 2

- Anchimeric assistance leads to regioselective perepoxide opening

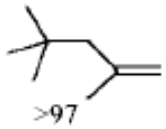




L = large alkyl substituent
R = H, Me

major product

minor product



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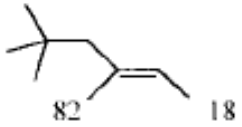

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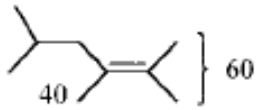

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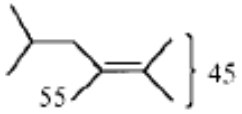

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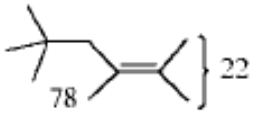

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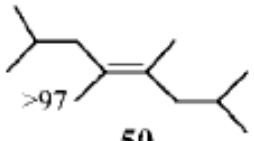

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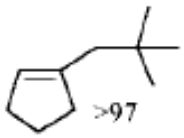

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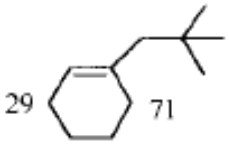

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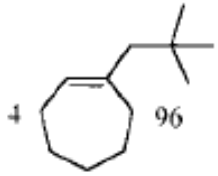

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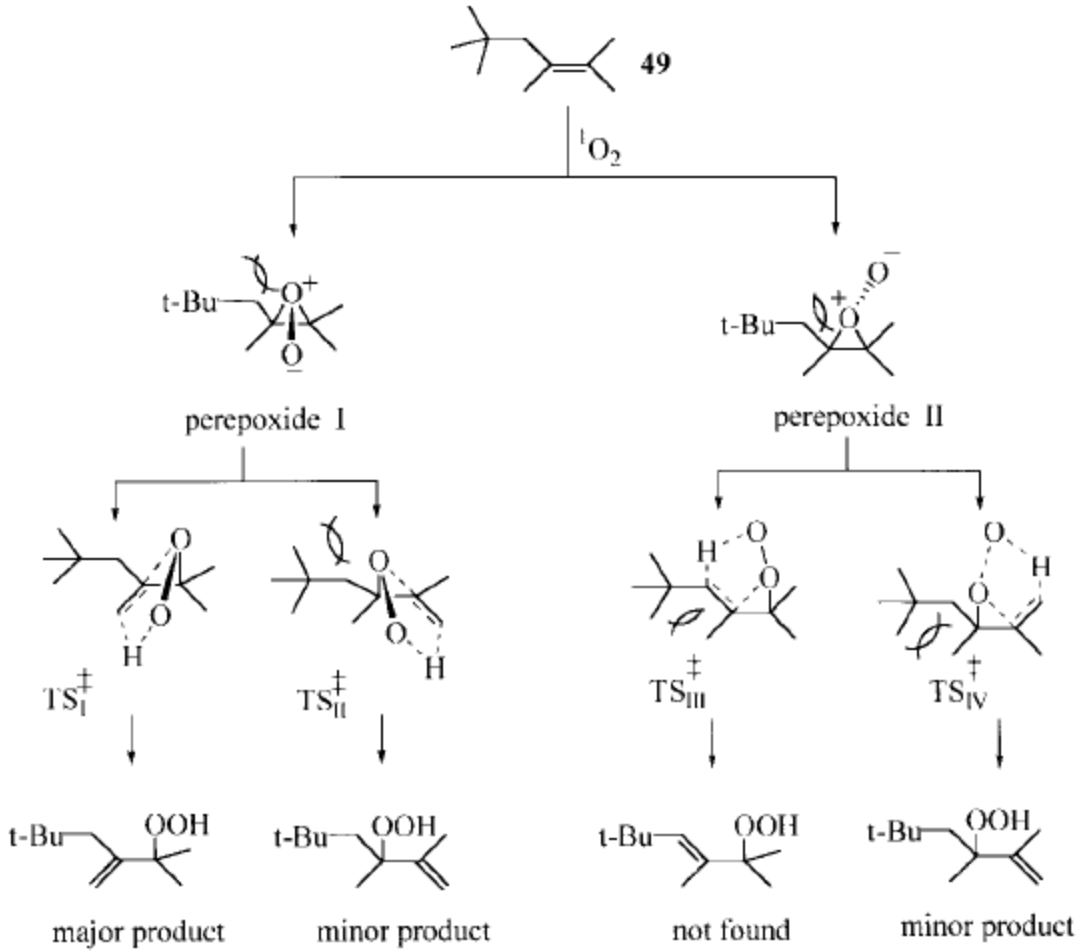
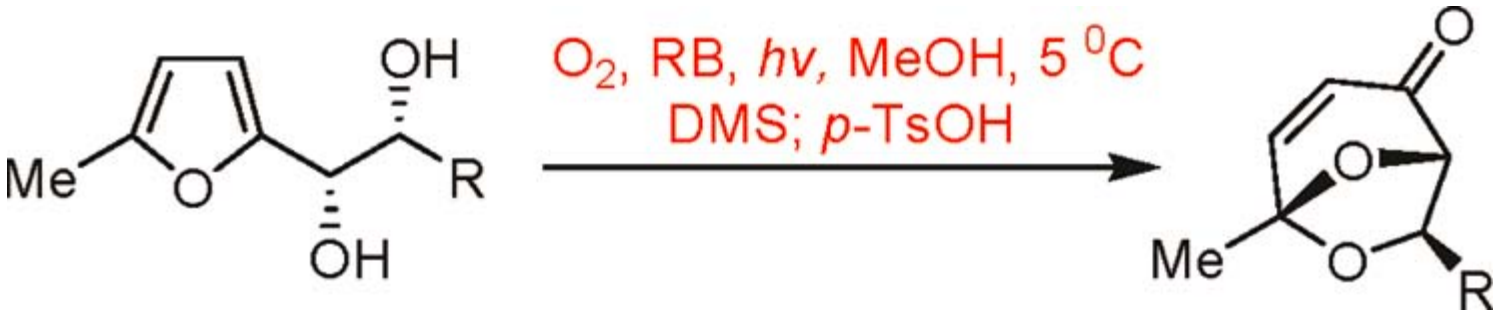
Explanation 3

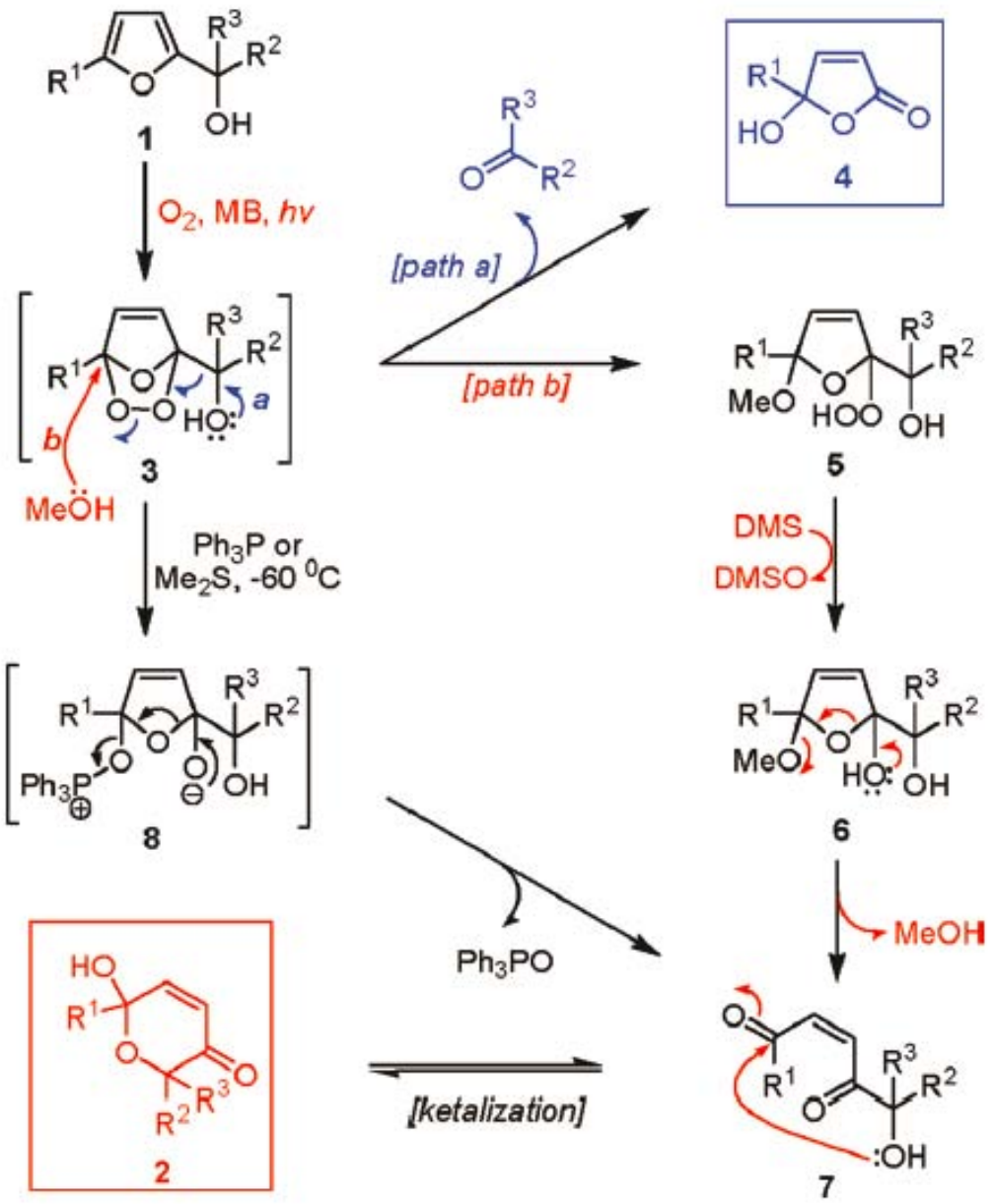
M. Stratakis, M. Orfanopoulos / Tetrahedron 56 (2000) 1595–1615

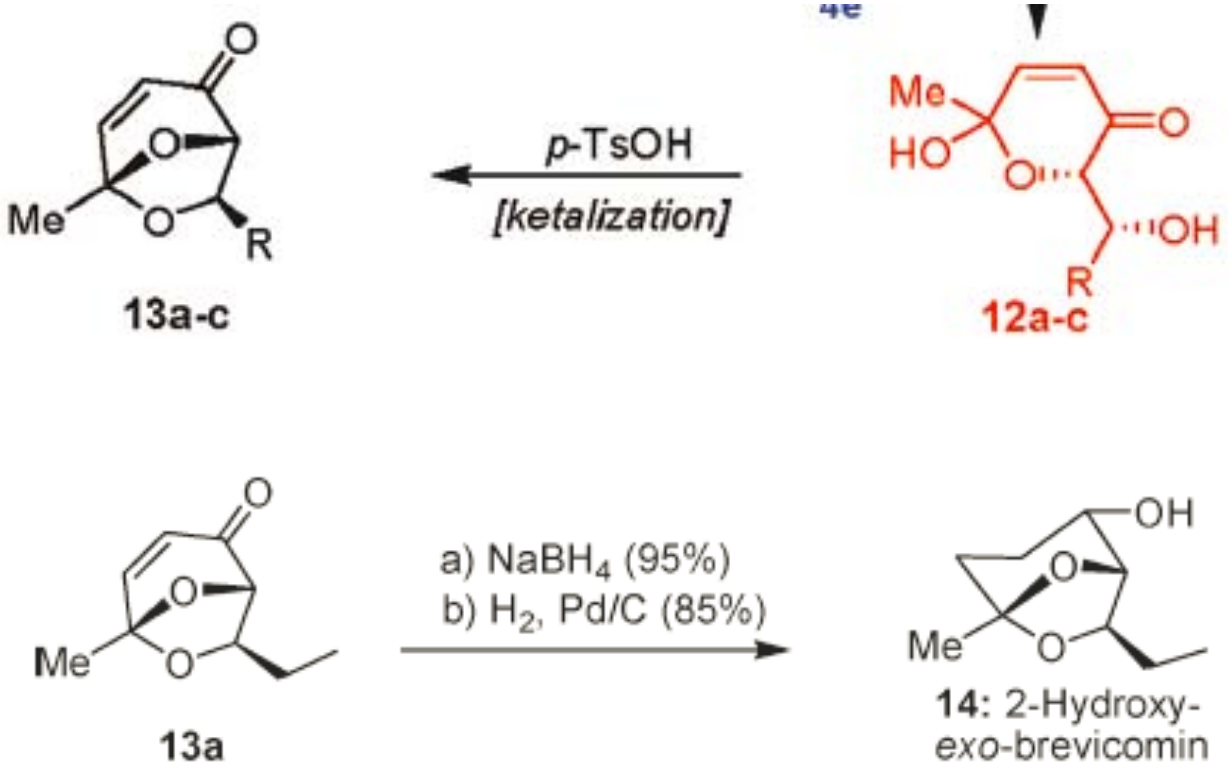




- Rearrangement name?
- Mechanism?

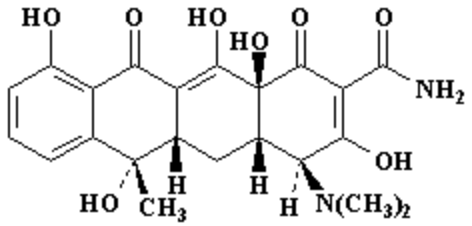
- Georgios Vassilikogiannakis
- University of Crete


1
O_2, MB, *hv*
3
MeOH
Ph_3P or
Me_2S, -60 ^{0}C
8
Ph_3PO
2
[ketalization]
[path a]
[path b]
4
5
DMS
DMSO
6
MeOH
7


Me
O
O
R
13a-c
p-TsOH
[ketalization]
Me
HO
O
O
OH
R
12a-c
Me
O
O
13a
a) NaBH4 (95%)
b) H2, Pd/C (85%)
OH
O
Me
O
14: 2-Hydroxy-
exo-brevicomin

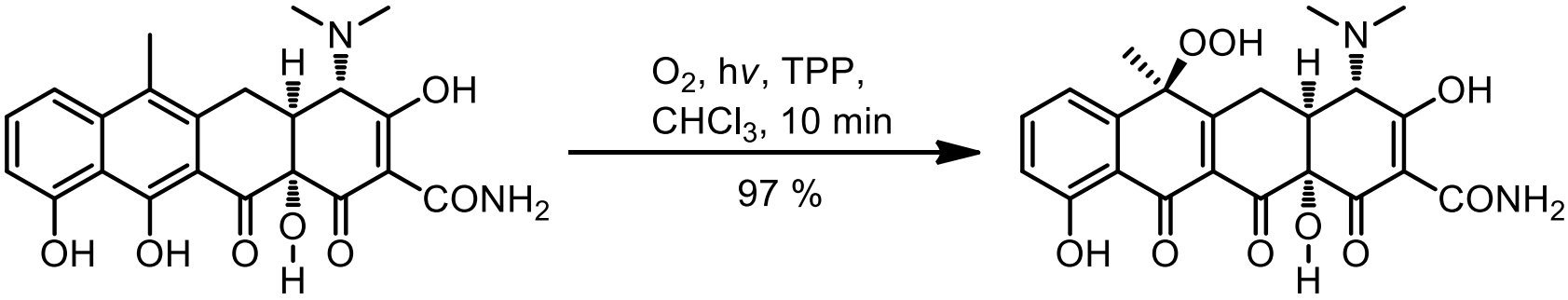
Tetracycline

Tetracycline
$C_{22}H_{24}N_4O_8$

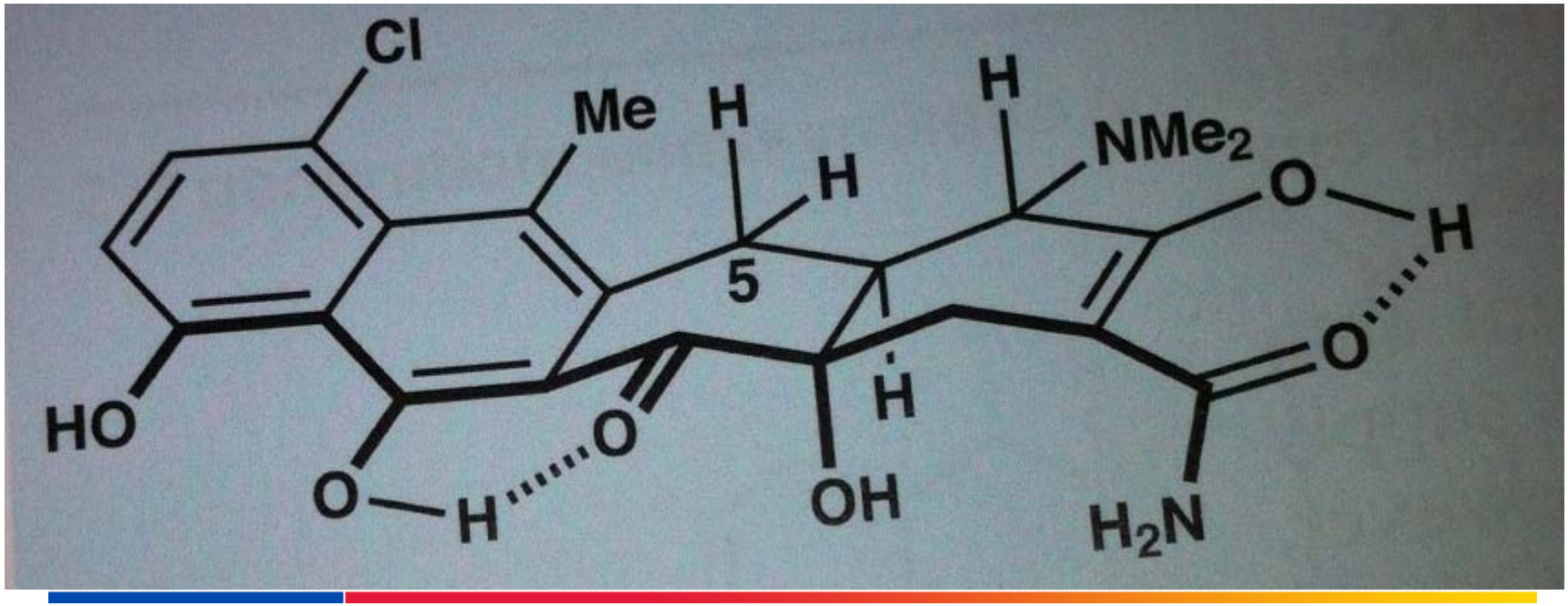


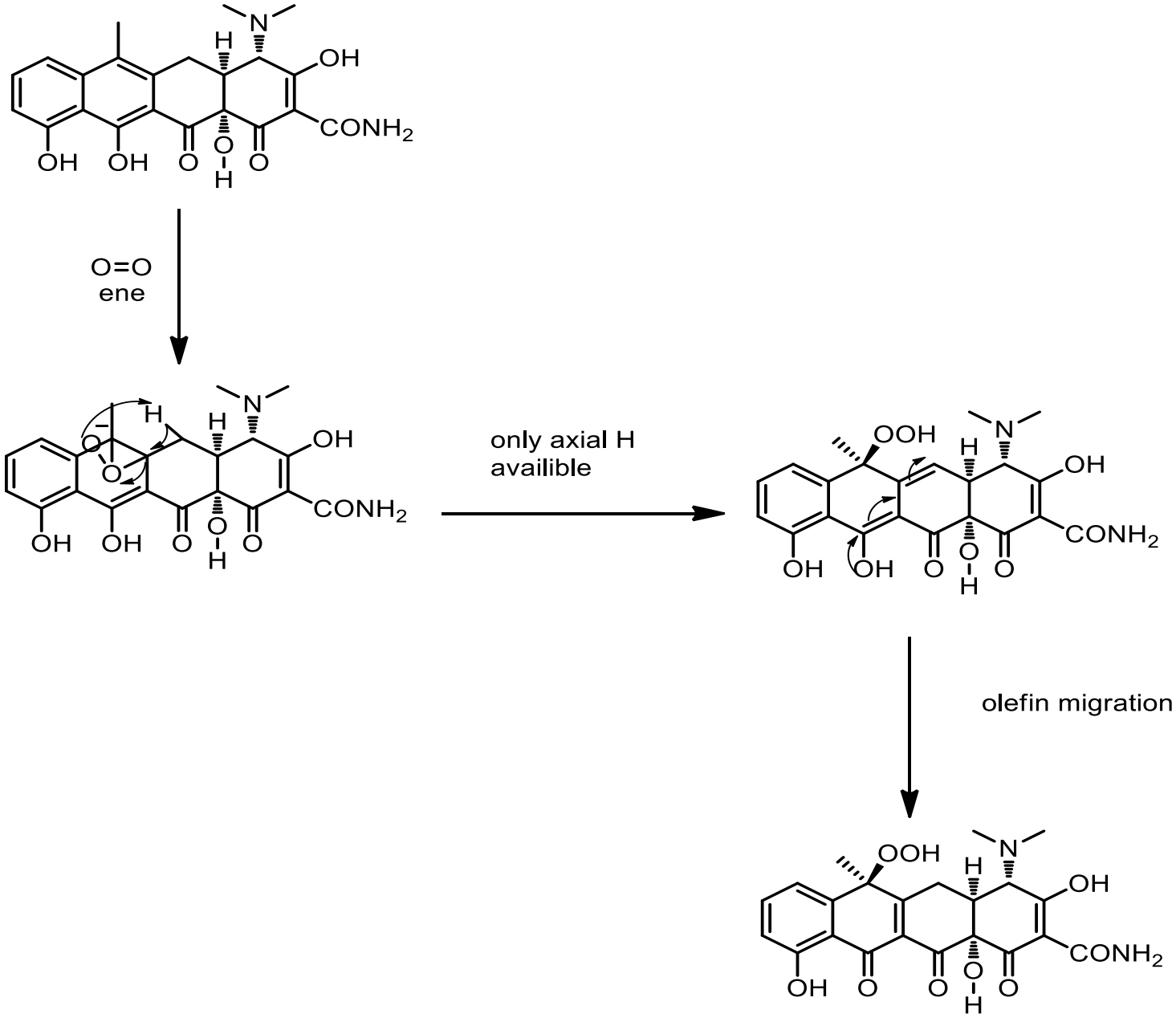
- Inhibit bacterial protein synthesis by reversibly blinding to ribosomal subunit which inhibits tRNA.

- Global market for tetracycline and derivs. ~ 5000 metric tons.

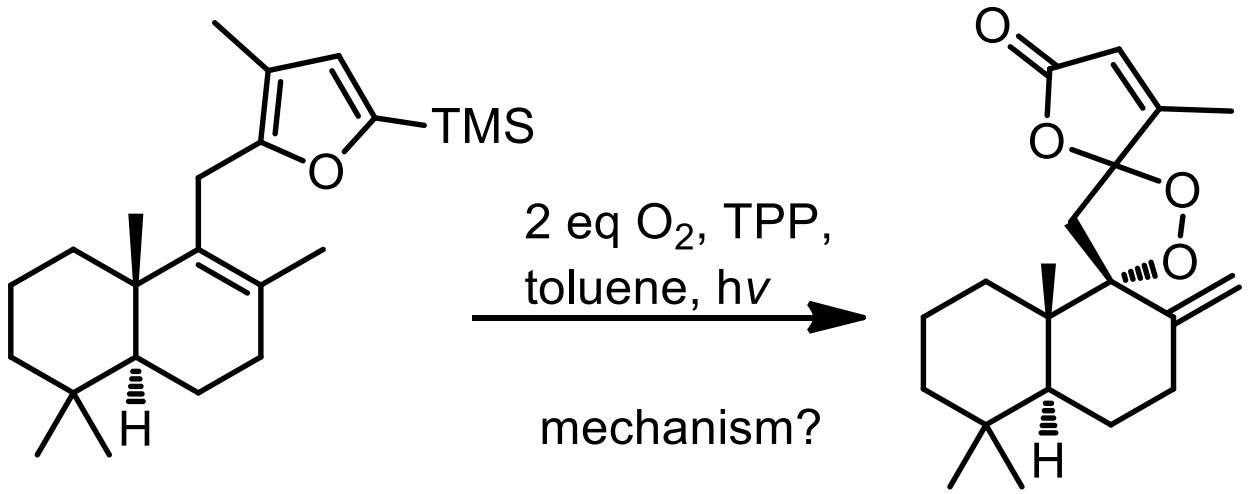


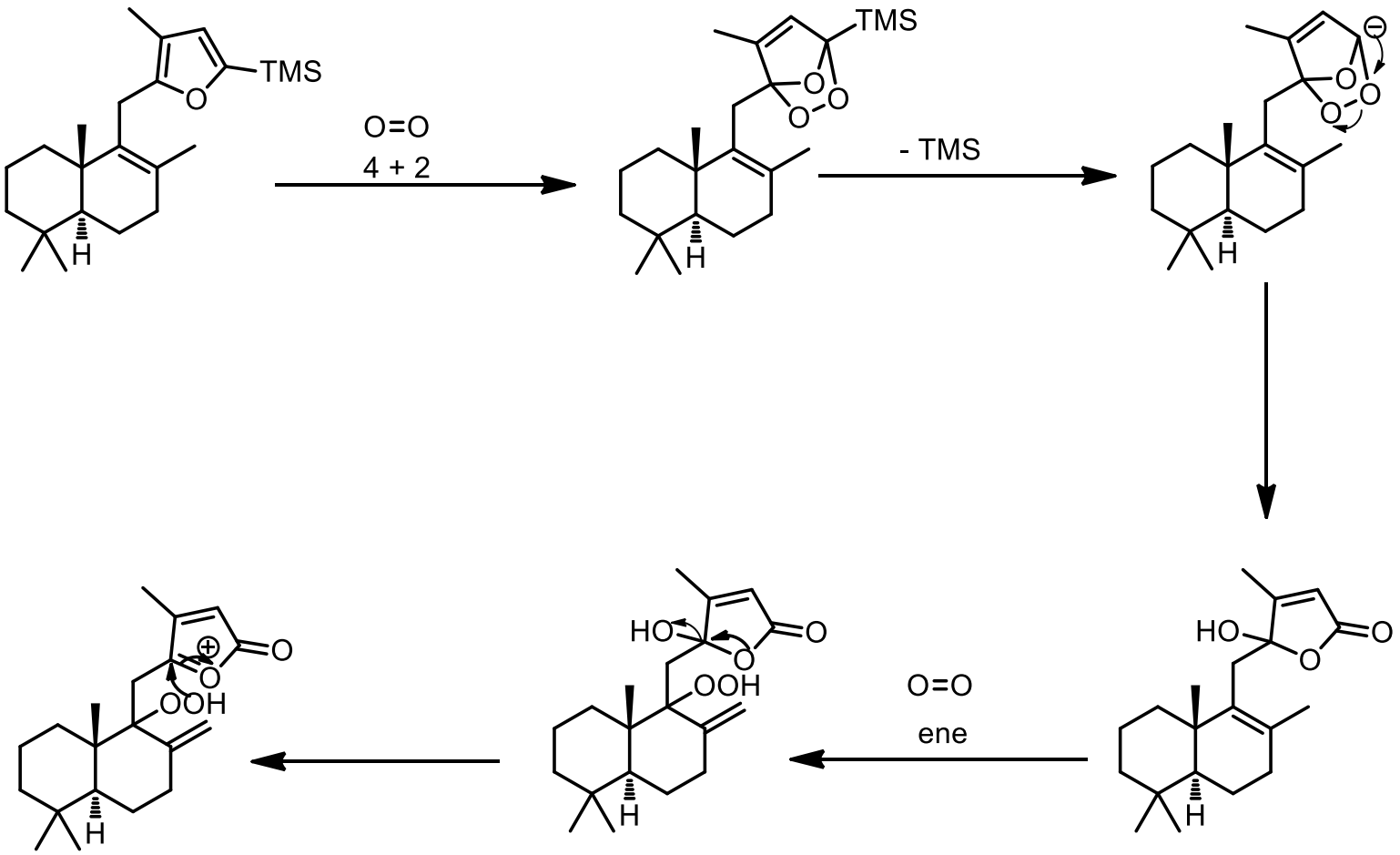
mechanism that accounts for stereoselectivity?



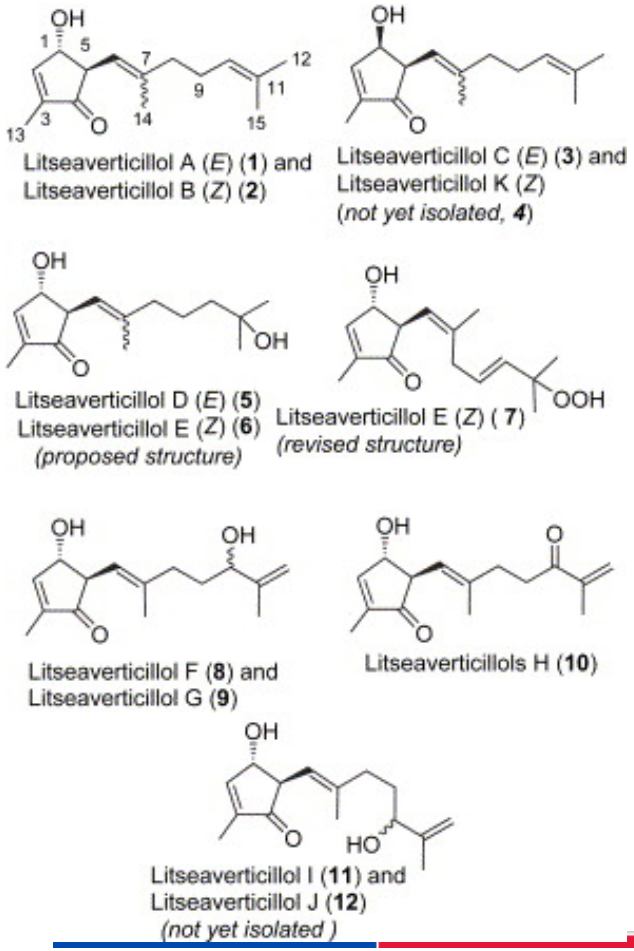

O=O
ene
only axial H
availible
olefin migration

(+)-Premnalane A studies




TMS
O
H
O=O
4 + 2
TMS
O
O
O
H
- TMS
O
O
O
H
HO
O
O
H
O=O
ene
HO
O
OOH
H
O
O
OOH
H

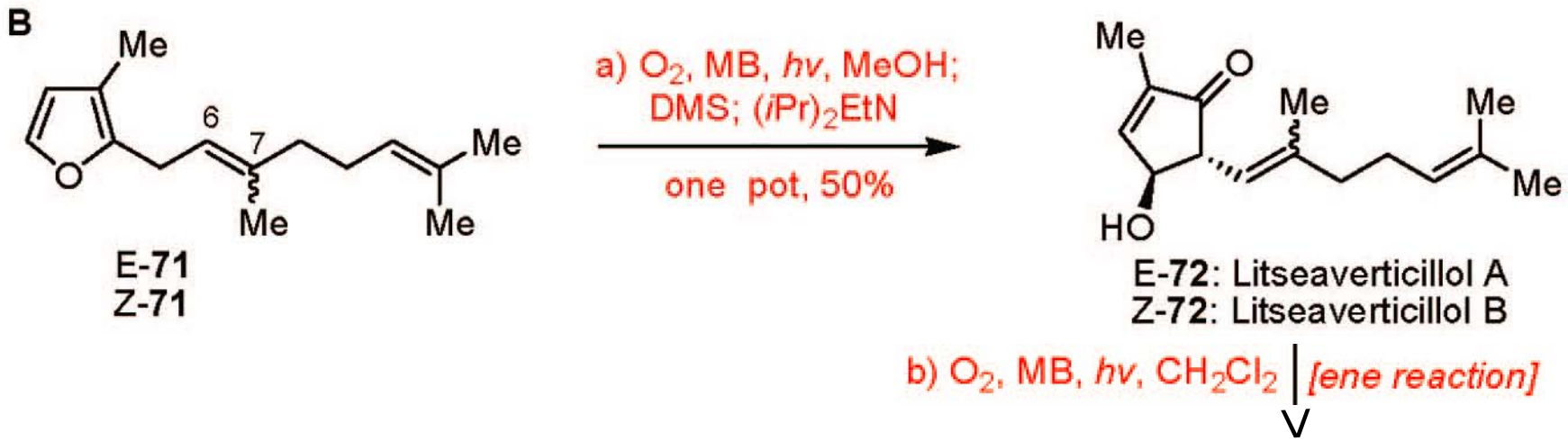
Litseaverticillols A-G, I,J

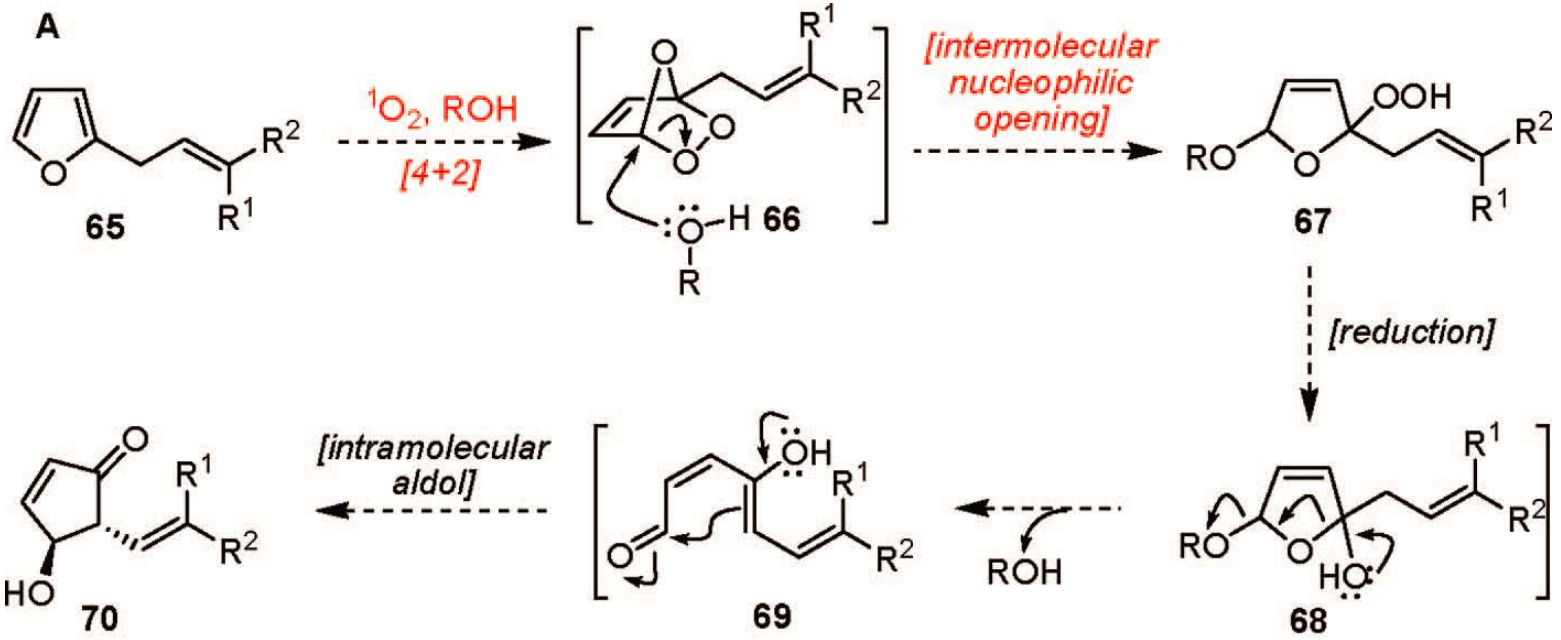


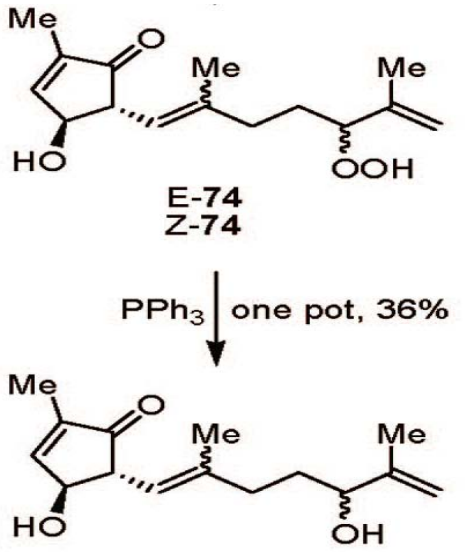
- Active against HIV-1 replication in HOG.R5 cells
- Selective antiviral selectivity does not affect growth of host cell

Tetrahedron **2007** 2613

Biomimetic synthesis from naturally occuring furan

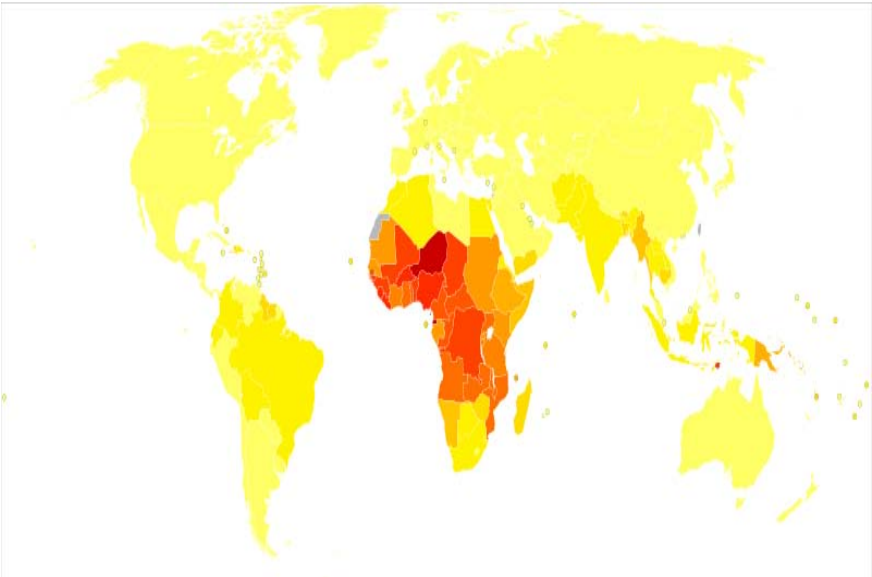


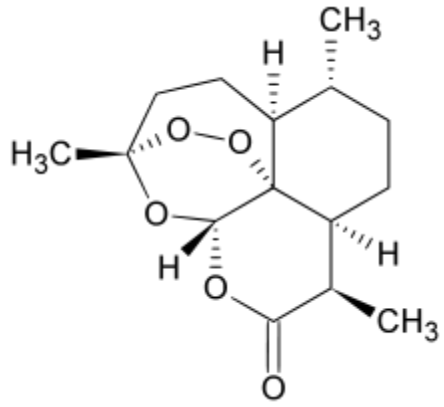




Acc. Chem. Res. **2008** 1008

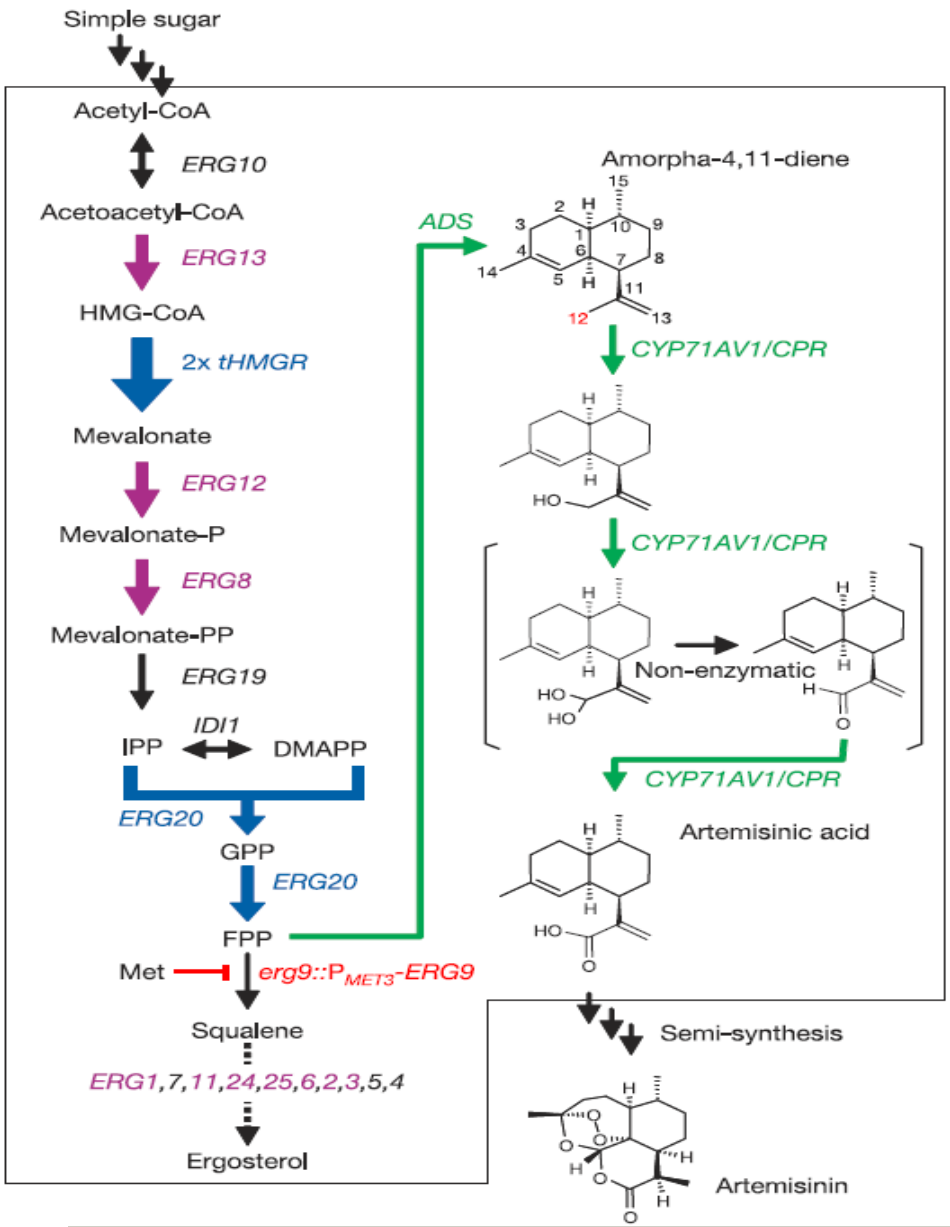
Malaria





- Kills 1,000,000 people a year (bad)
- Most potent inhibitor (Artemisinin) total synthesis too expensive for widespread use (bad)
- Limited supply of sweet wormwood plants cultivated for drug extraction raises cost of drug (bad)

Angew. Chem. Int. Ed. **2012**, 1706



- Engineer yeast to produce artemisinic acid faster and for less money than raising plants
- Environmentally friendly, easy purification, no plants.

Angewandte Communications

Anti-Malaria Drugs

DOI: 10.1002/anie.201107446

Continuous-Flow Synthesis of the Anti-Malaria Drug Artemisinin**

*François Lévesque and Peter H. Seeberger**

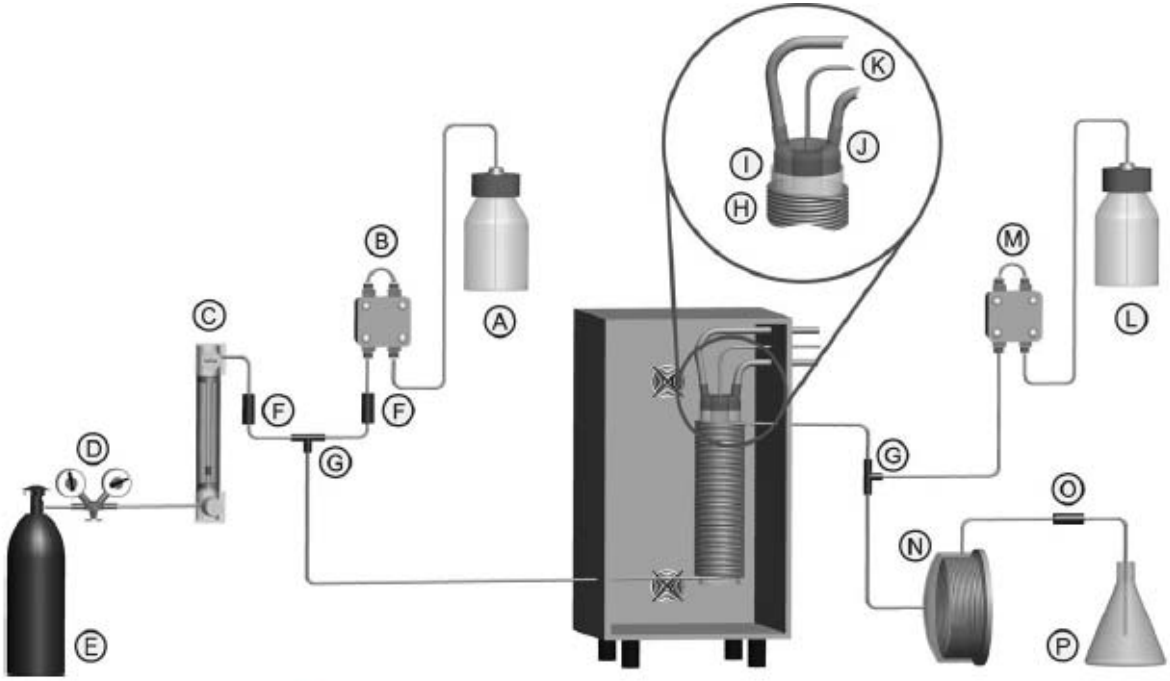
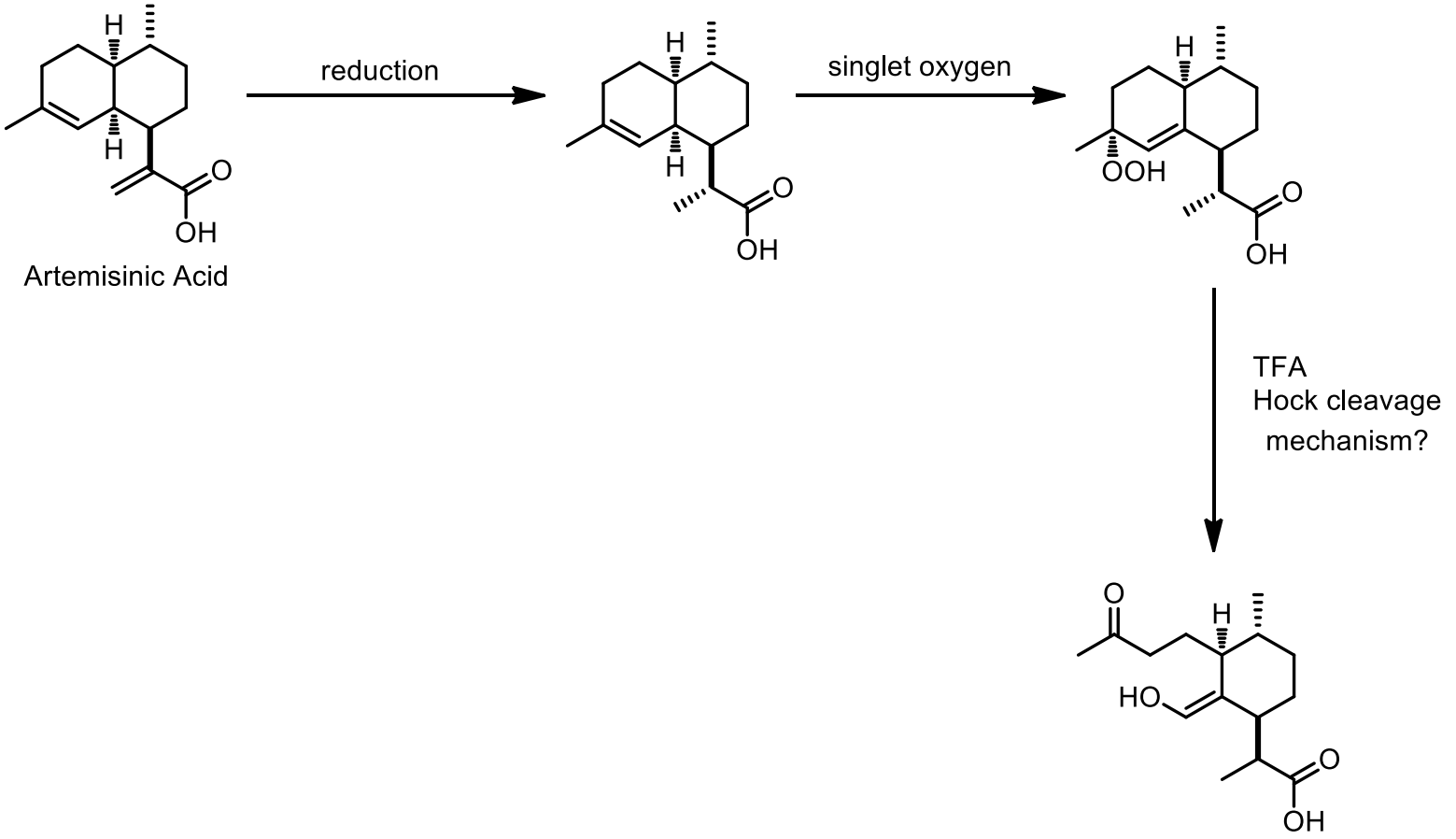
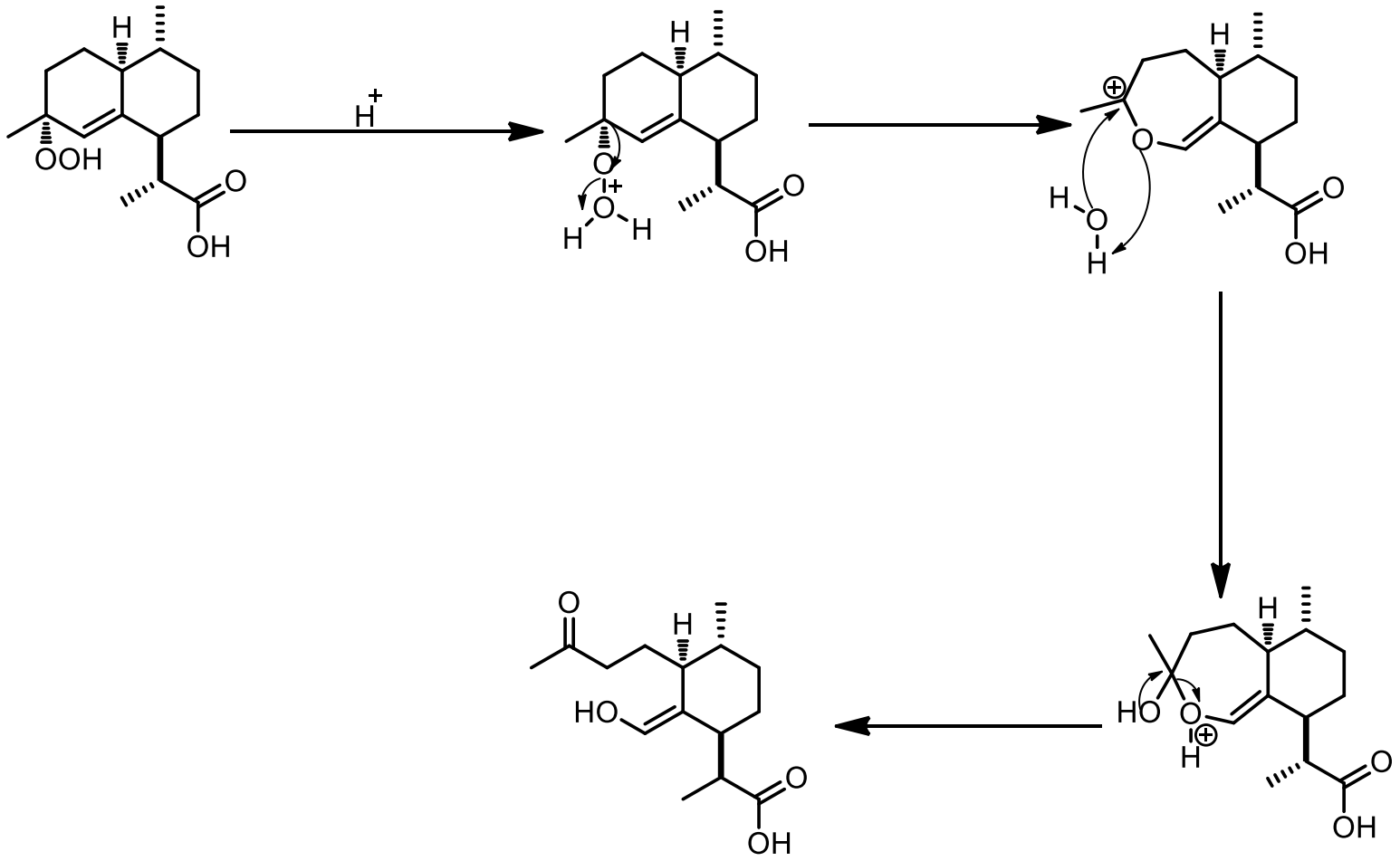


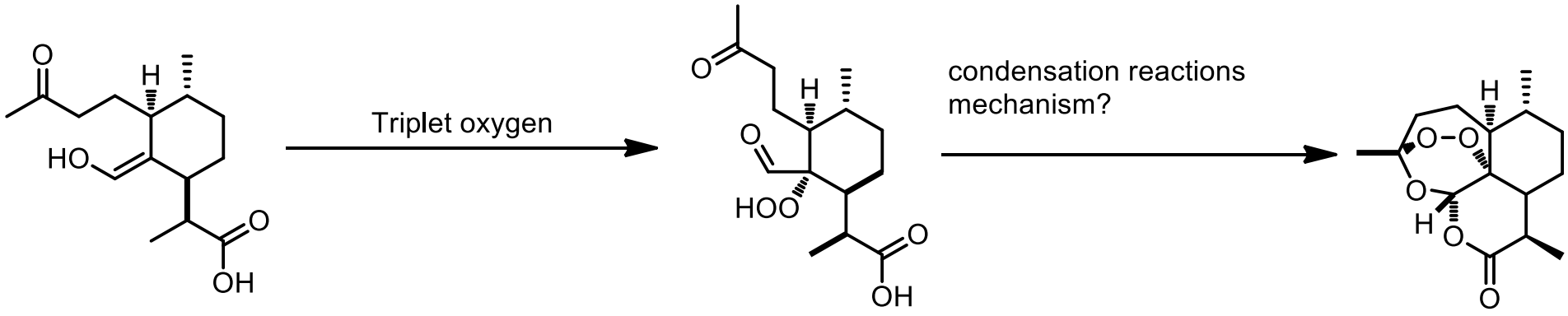
Figure 1. Continuous flow set-up for the conversion of dihydroartesiminic acid (**2**) into artemisinin (**6**). See text for details.

Setup produces ~ 200 g of artemisinin/day

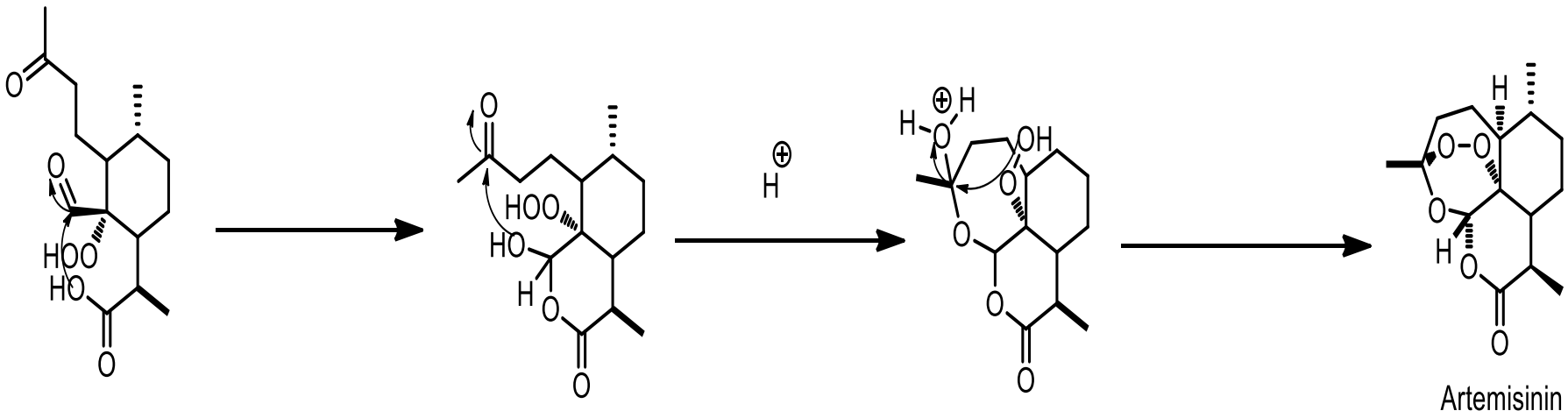
1500 reactors would meet the global demand for low cost artemisinin


H
H
O
OH
Artemisinic Acid
reduction
H
H
O
OH
singlet oxygen
H
OOH
O
OH
TFA
Hock cleavage
mechanism?
O
H
HO
O
OH


H
OOH
O
OH
H+
H
O
H
O
H
H
O
OH
H
O
H
H
O
OH
H
HO
O
H
O
OH
O
H
HO
O
OH



Artemisinin


Artemisinin