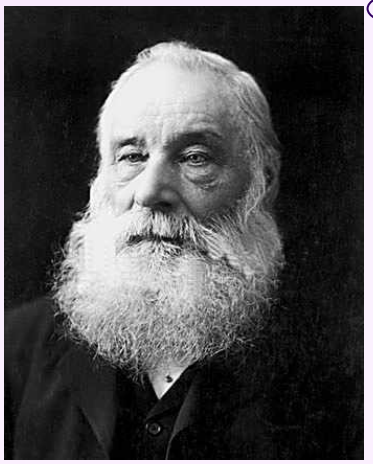
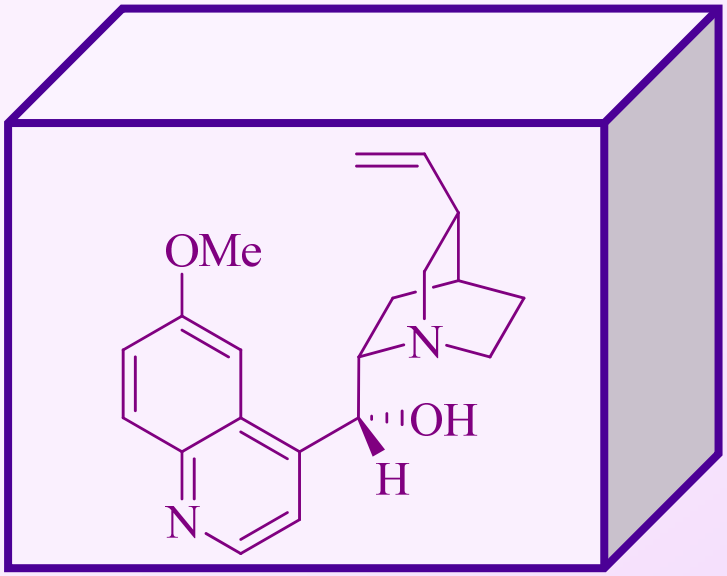
Quinine?
An Old and
Long Quest !





Literature Presentation, JM, April, 1st, 2010

Plan

Introduction

- ✓ Malaria a current life-threatening disease
- ✓ Brief Historic of the discovery of Quinine and its structure

Syntheses

- ✓ The well-known Easter story of Perkin Sr.
- ✓The three important steps provided by Rabe and Kindler
- ✓ Woodward and Doering: The first formal synthesis of Quinine
- ✓ Mastering the C8-N strategy: Works supervised by Uskoković
- ✓ Mastering another strategy: the C2-N by Stork
- ✓ Return to the C8-N strategy: Jacobsen and Kobayashi
- ✓ Rabe rest in peace

Conclusion

Malaria

« *The most significant disease for world civilization over the past three millenia* »

Caused by different species of the parasite *Plasmodium*

Transferred to another person by the females of *Anopheles mosquitoes*

Most conspicuous symptom: fever

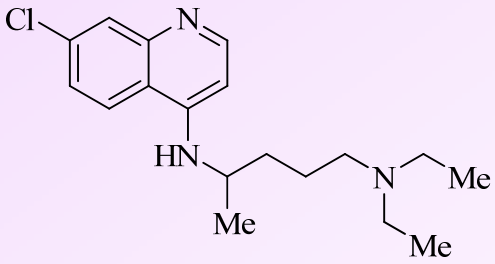
- Patients can recover but weakened (listless and anemic)
- A fatal form of Malaria caused by *Plasmodium Falciparum*

Clots in the brain

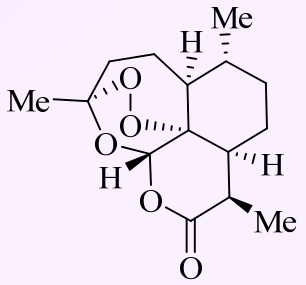
Today: - Between 300 and 500 million of new cases worldwide each year
- Between 1.5 and 2.7 million deaths caused

Kaufman, T. S.; Ruveda, E. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 854-885

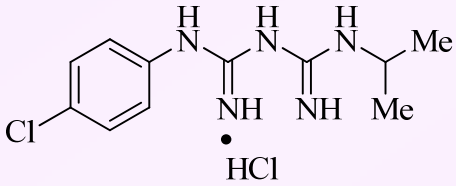
Examples of Anti-Malarial Drugs



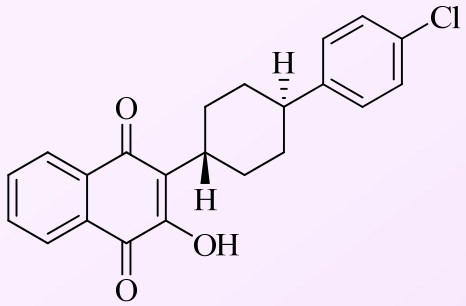
Chloroquine
(marketed under a variety of names)



Artemisin
(Natural product, used in Chinese medicine called qinghaosu)

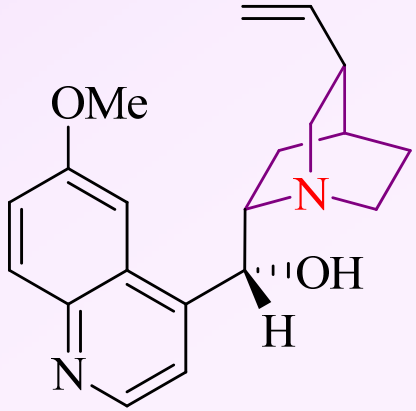


Proguanil hydrochloride



Atovaquone

Combination (Malarone®)



300-500 tons per annum

produced commercially

by extraction from cinchona barks

40% (Pharmaceutical)

60% (Food)

History of discovery of Quinine and its structure

1500 ~ • Malaria brought by the Europeans to America

• Remedy found by the Incas, despite their relative inexperience with this disease

Extracts from the bark of the cinchona trees (rain forests covering the eastern flank of the Andes mountains)

Cinchona officinalis

• Remedy brought back to Europe (role of the Jesuites at Rome)

1677 • Bark introduced in the London Pharmacopeia

1681 • Universally accepted as an antimalarial drug

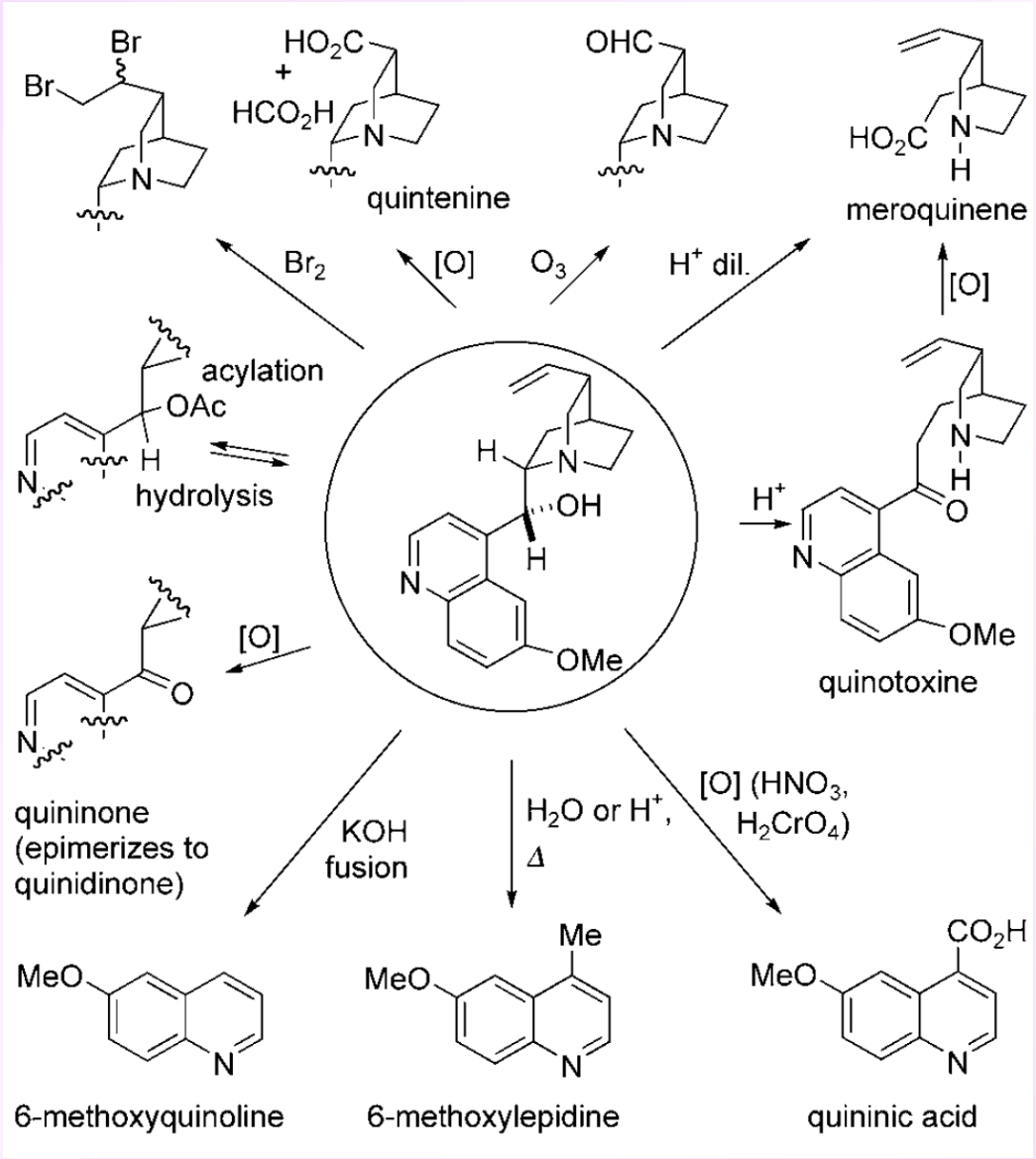
1820 ~ **Pierre Joseph Pelletier** and **Joseph Bienaimé Caventou** isolated quinine from cinchona bark.

It allowed:
- to show that quinine was the active compound against malaria
- to administrate accurate doses of medicine for patients
- the first extraction factory of quinine in Paris

1849 ~ **Adolf Strecker** identified the correct formula for quinine:

$C_{20}H_{24}N_2O_2$

1850-1908 Since then, several laboratories carried out experiments to understand the connectivity and identify the different functionnal groups

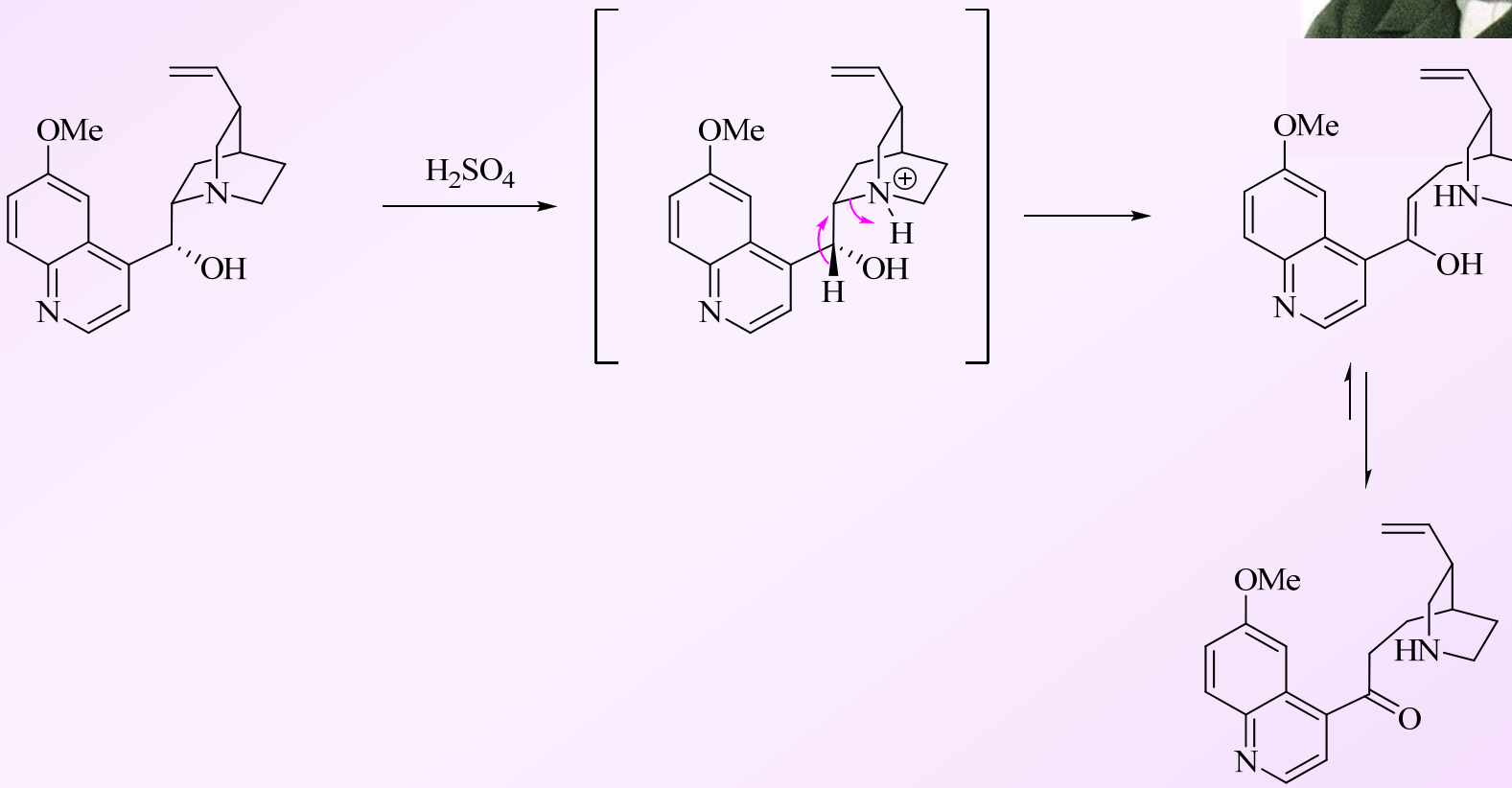

Br
Br
N
HO2C
+
HCO2H
N
quintenine
OHC
N
HO2C
N
H
meroquinene
Br2
[O]
O3
H+ dil.
[O]
acylation
OAc
H
N
hydrolysis
H
N
OH
H
N
OMe
H+
N
H
O
N
OMe
quinotoxine
[O]
O
N
quininone
(epimerizes to
quinidinone)
KOH
fusion
H2O or H+,
Δ
[O] (HNO3,
H2CrO4)
MeO
N
6-methoxyquinoline
Me
MeO
N
6-methoxylepidine
CO2H
MeO
N
quininic acid

The discovery of an important intermediate by Pasteur

1853

• During his works on tartaric acid, Pasteur searched for chiral amines for resolution of the salts of this acid.

• In this context, he tried:



Quinotoxine

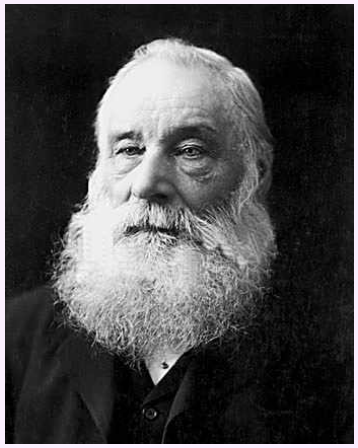
First Attempt for the Synthesis: William Henry Perkin, Sr.

1854 ~ **August Wilhelm von Hoffman**:

"… it is obvious that naphthalidine [now α-naphthylamine], differing only by the elements of two equivalents of water might pass [into quinine] simply by an assumption of water. We cannot of course, expect to induce the water to enter merely by placing it in contact, but a happy experiment may attain this end by the discovery of an appropriate metamorphic process …".[37]

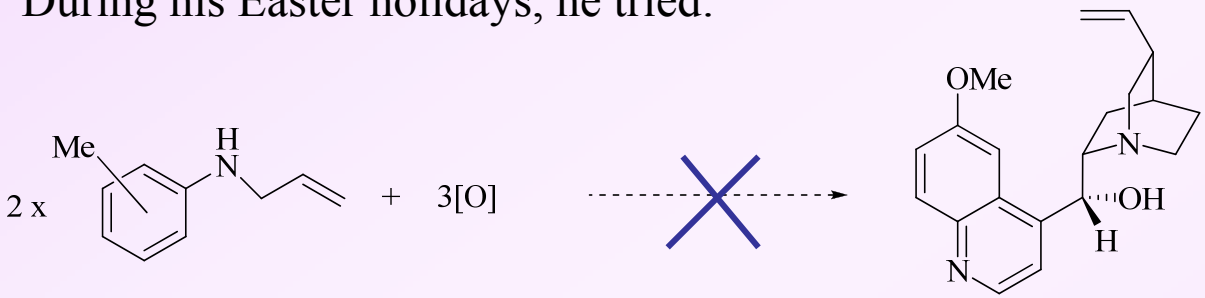
$$2 \times (C_{10}H_9N) + 2\ H_2O \ = \ C_{20}H_{22}N_2O_2$$

1856 ~ **Perkin, Sr.** following his mentor arithmetical idea considered:



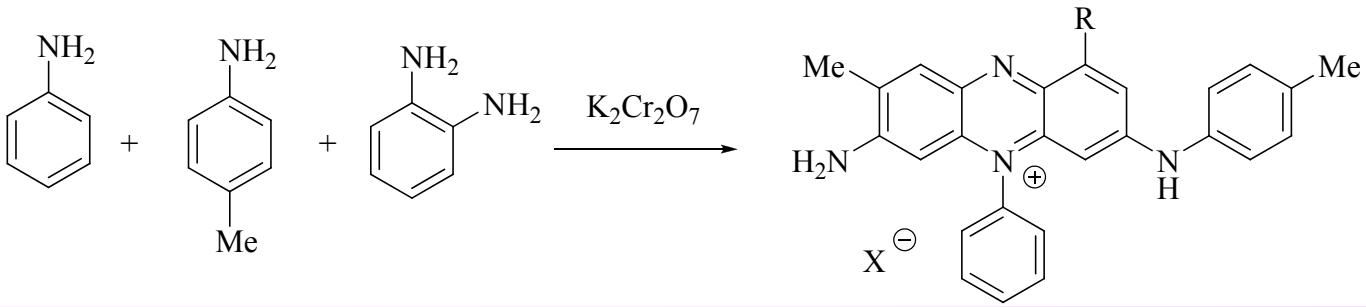
$$2 \times (C_{10}H_{13}N) + 3\,[O] \;=\; C_{20}H_{24}N_2O_2 - H_2O$$

~ During his Easter holidays, he tried:



N-allyltoluidine :
coal tar product

~ Finally, he discovered:



Mauveine: a typical purple dye

The three important steps provided by Rabe and Kindler

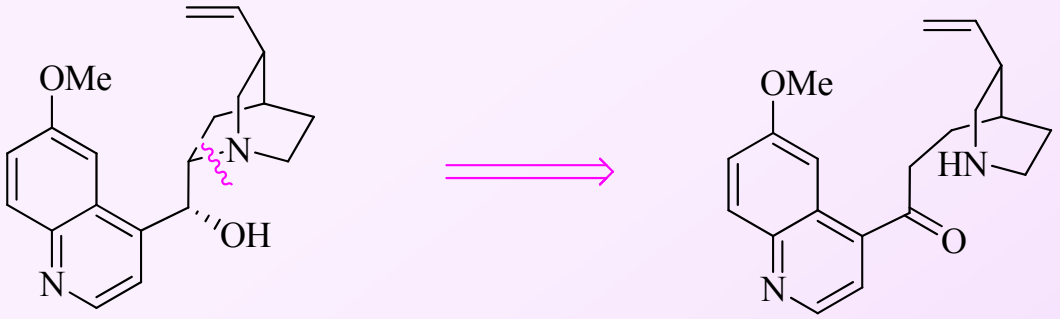
1908 ~ Connectivity of Quinine established by Paul Rabe

He began to consider the possibility of a synthesis of the alkaloid

Quite challenging!

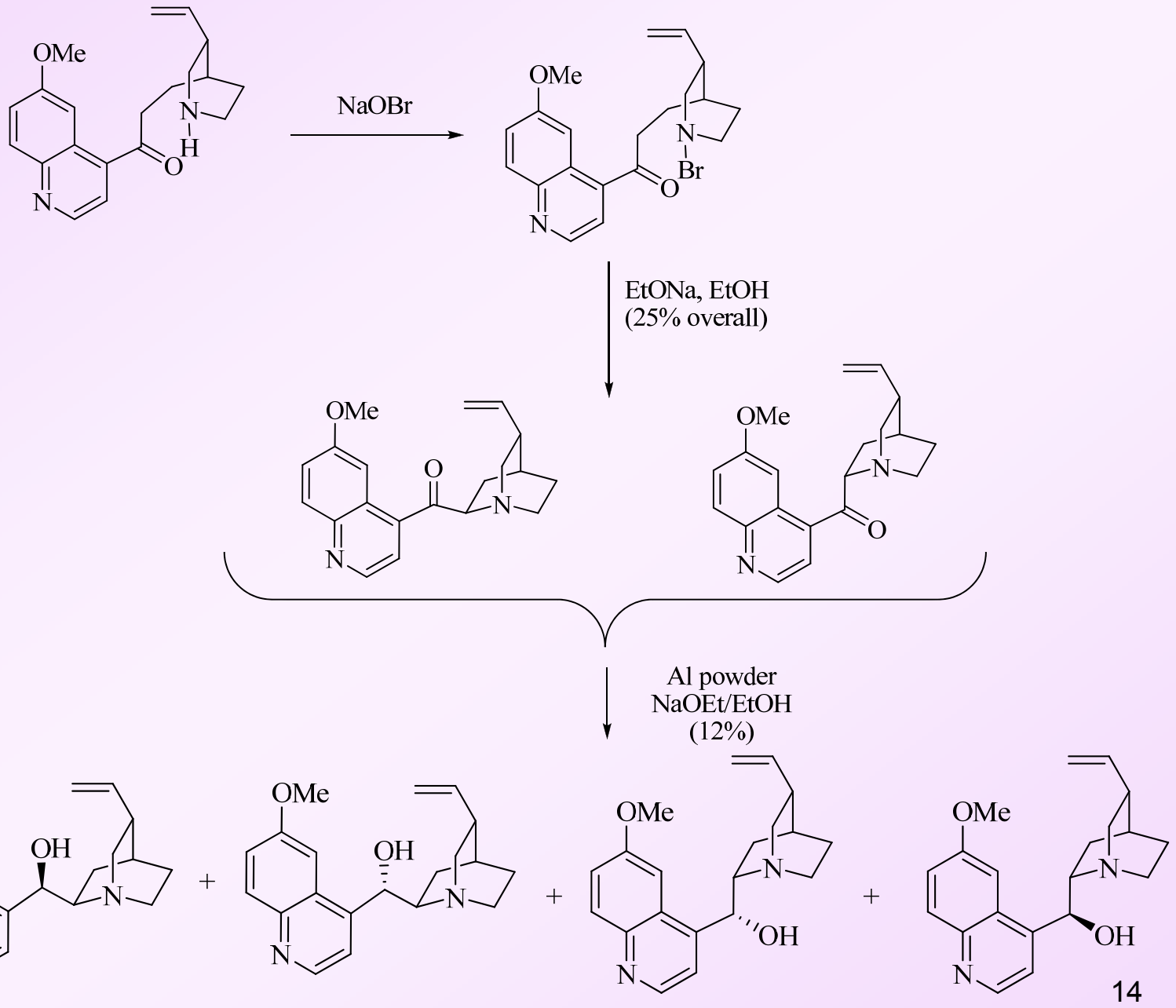
16 stereoisomers possible (4 stereocenters)

He chose to try to reconstruct quinine from quinotoxine



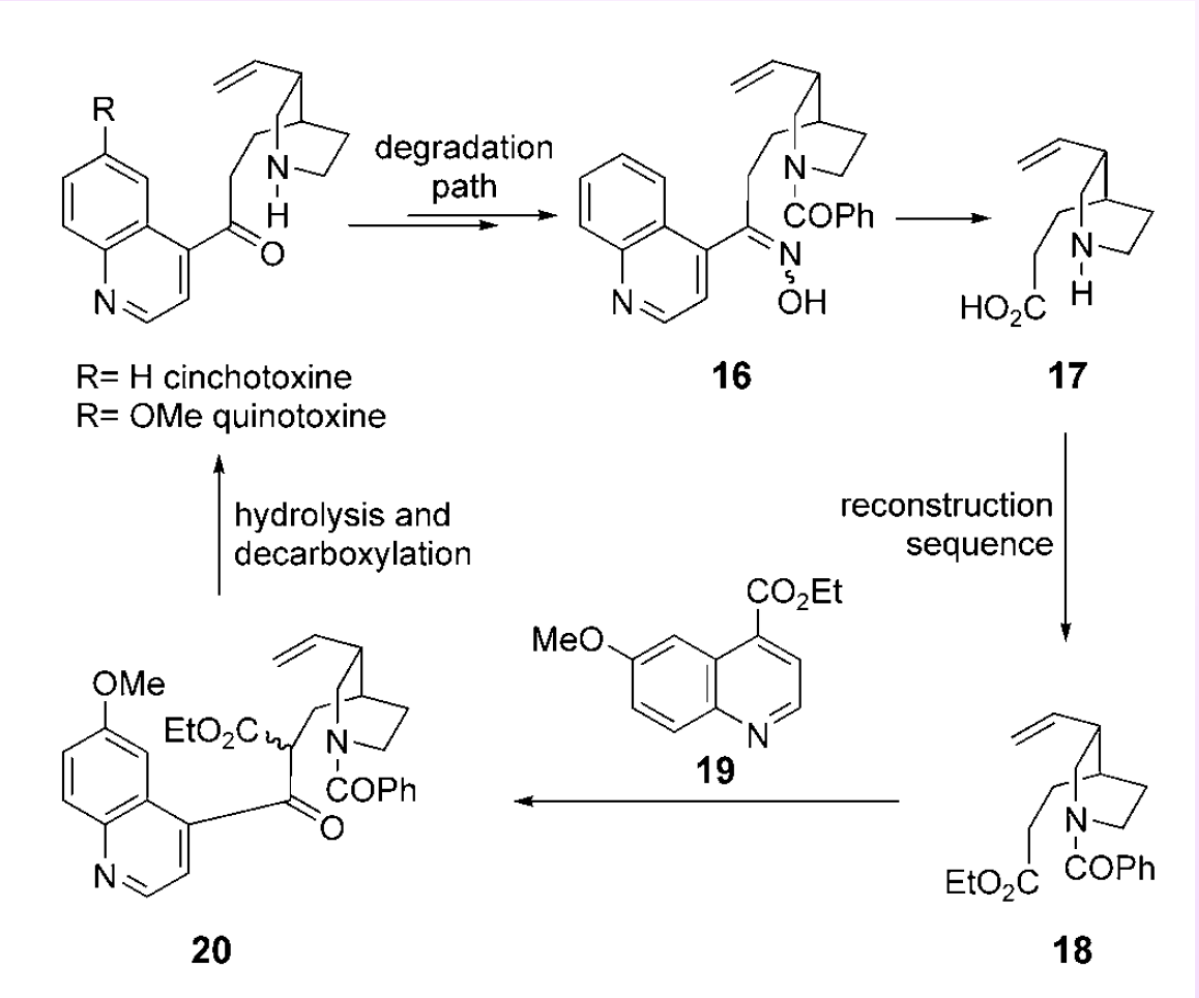
The three important steps provided by Rabe and Kindler

1918



Epi-quinidine **Quinidine** **Quinine** **Epi-quinine**

Prelog's degradation and reconstitution of Quinotoxine



Homomeroquinene

Woodward and Doering: The first formal synthesis of Quinine

Doering

1966 ACS award
for Creative Work
in Synthetic Organic Chemistry
(Most known his research
in physical organic chemistry)

Woodward

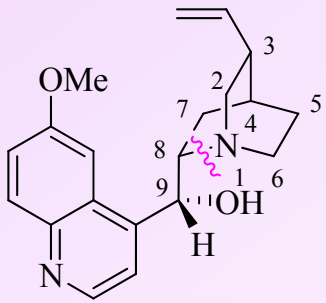
1965 Nobel Prize for Chemistry
for « *his outstanding achievements in the art of organic chemistry* »

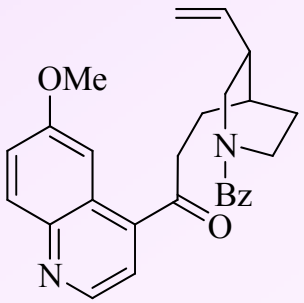
Total Syntheses
cholesterol, cortisone (1952),
strychnine (1954),
colchicine (1965)
cephalosphorin (1966)

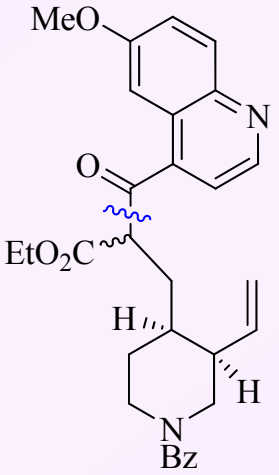
1944: Context of the synthesis: the Second World War

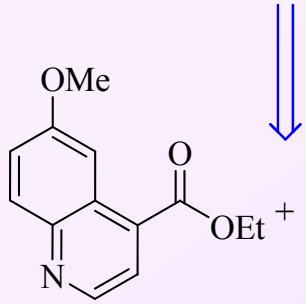
Seeman, J. I. *Angew. Chem. Int. Ed.* **2007**, *46*, 1378-1413

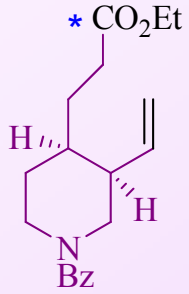
Woodward's Strategy: Access to (±)-Homomeroquinene

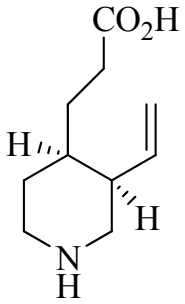




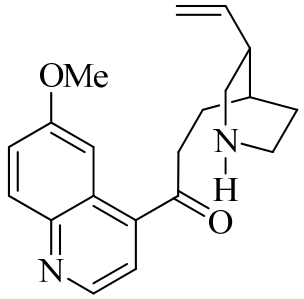




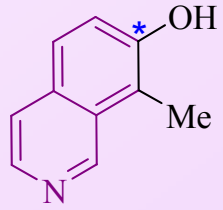




Homomeroquinene

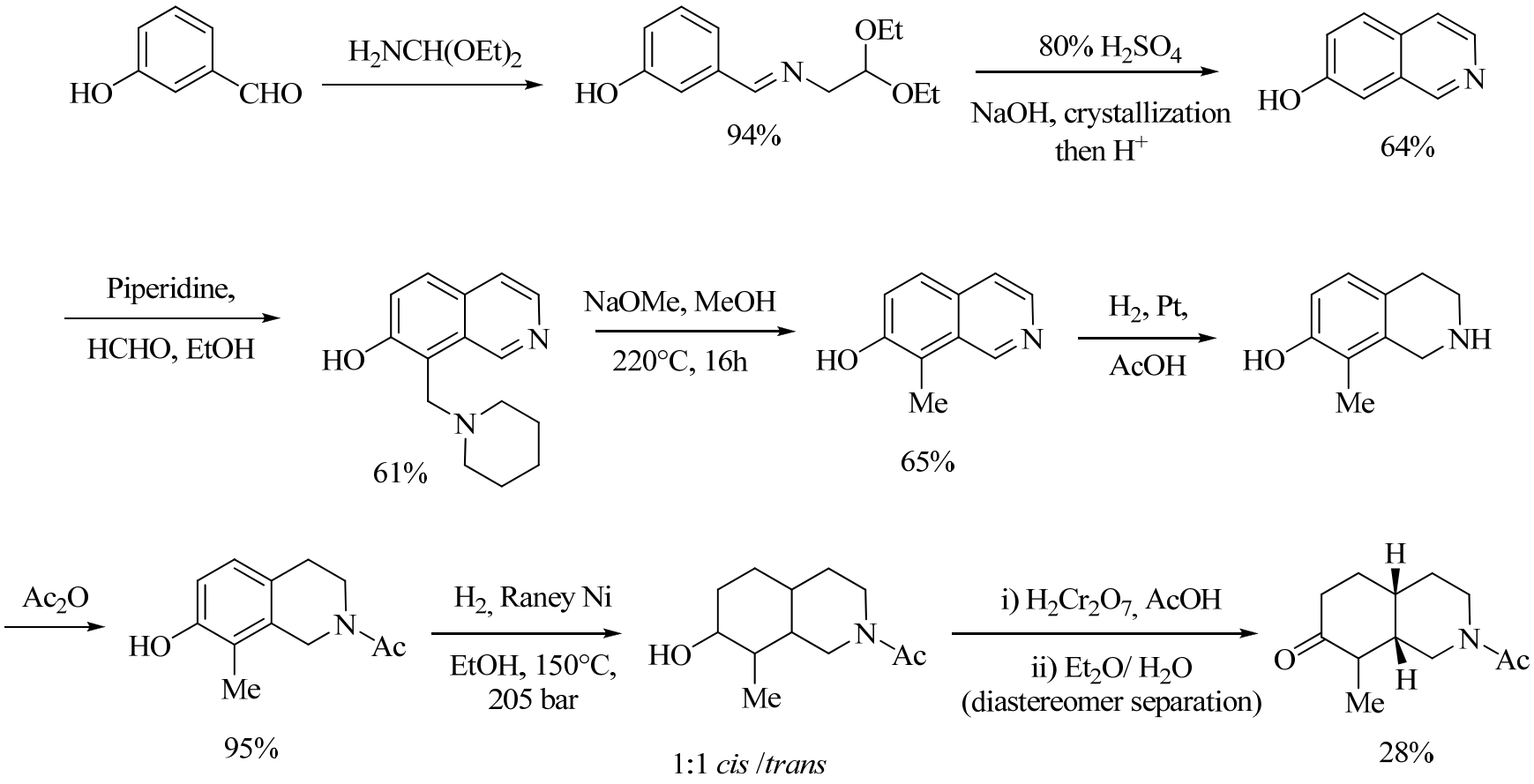


Quinotoxine

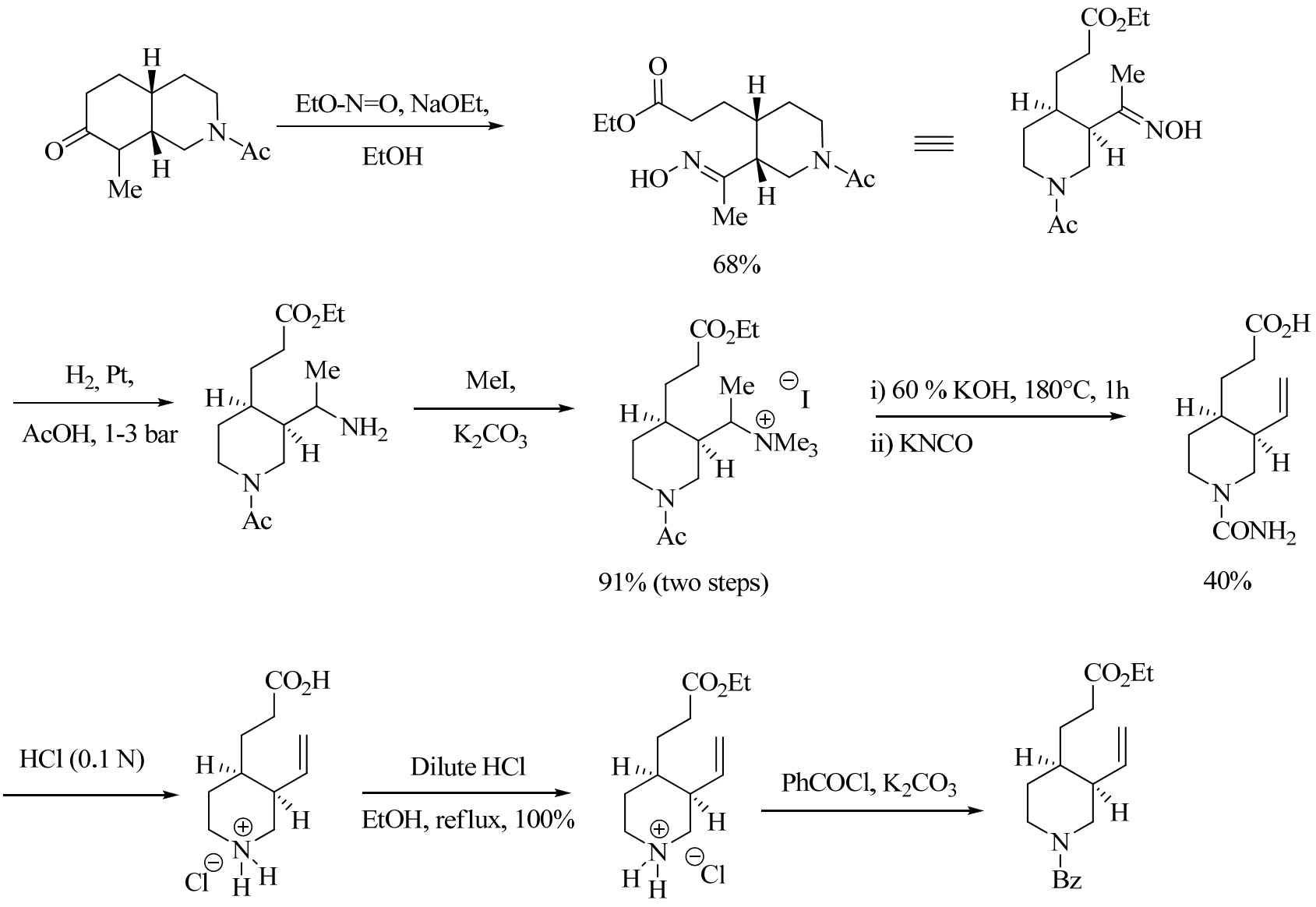


Woodward, R. B.; Doering W. E. *J. Am. Chem. Soc.* **1944**, *67*, 860-874

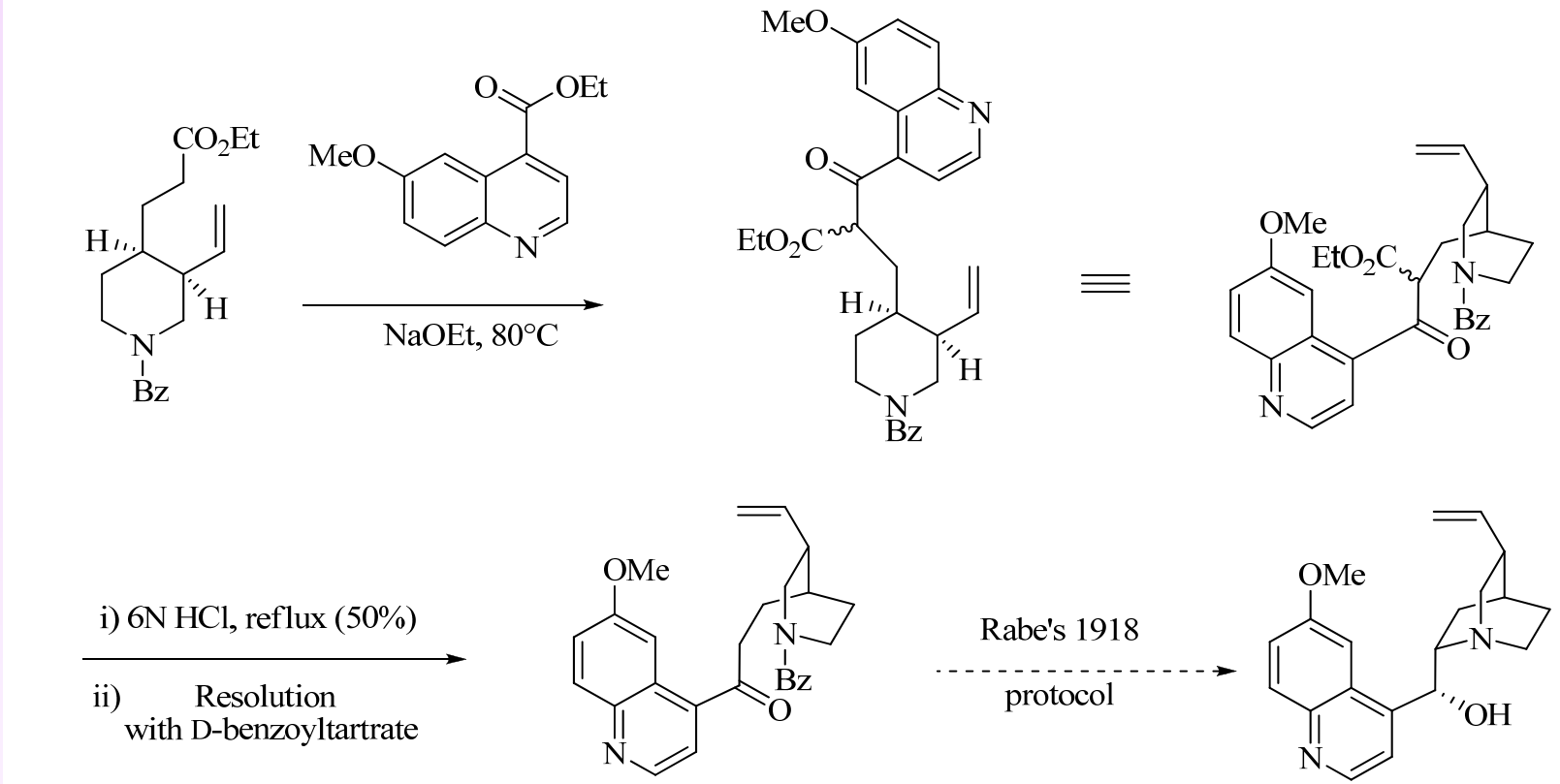
Woodward and Doering: The first total synthesis of (±)-Homomeroquinene



Woodward and Doering:
The first total synthesis of (±)-Homomeroquinene



Woodward and Doering:
The first total synthesis of (±)-Homomeroquinene



First entry to synthetic quinine
(considering Rabe's protocol repeatable)

They obtained 30 mg of synthetic *D*-quinotoxine

In view of the established conversion of quinotoxine to quinine,[12] with the synthesis of quinotoxine the total synthesis of quinine was complete.

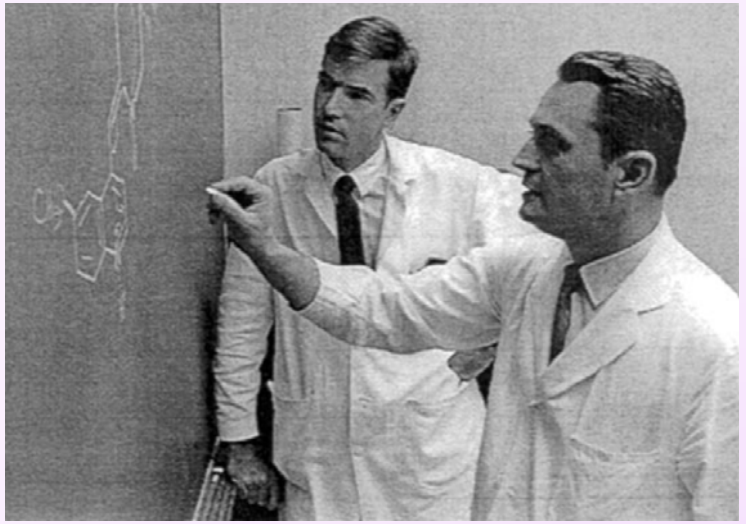
Mastering the C8-N strategy: Works supervised by Uskokovic

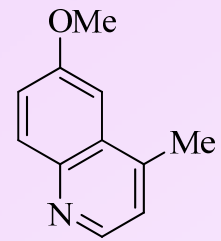
1970

Researchers of the laboratories Hoffman-LaRoche
under the leadership of Milan R. Ukoskovic
Concentrated their efforts to mastering the C-8 N approach

Disclosed
a total synthesis of quinine
(close to a stereoselective one)

Series of total syntheses
based on the same approach

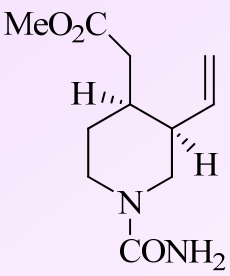


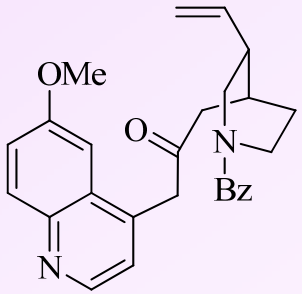


6-methoxylepidine

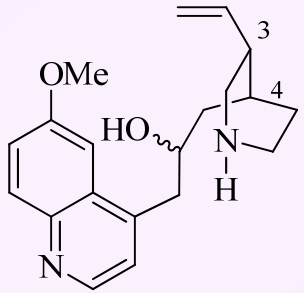
1) LDA, -78°C

2)





DIBAL-H

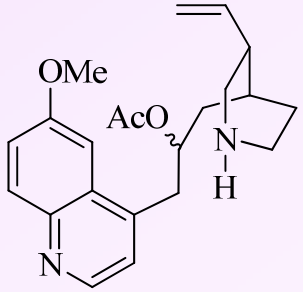


85%

Resolved with
benzoyl D-tartaric acid

$BF_3.Et_2O$

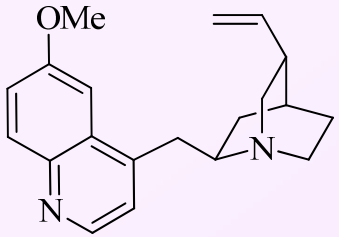
AcOH



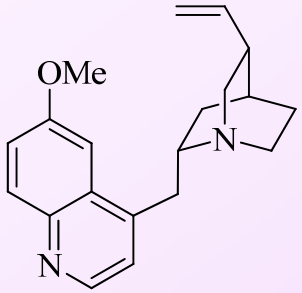
96%

NaOAc,

AcOH/benzene



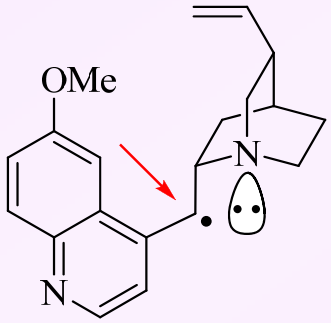
+



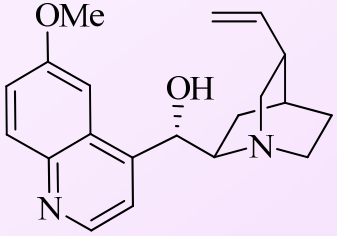
79%

57 : 43

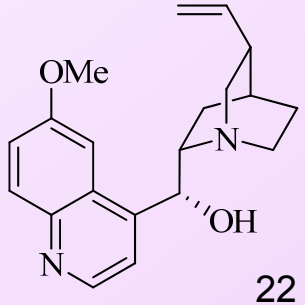
t-BuOK, $^1O_2$,
t-BuOH, DMSO
(40%)



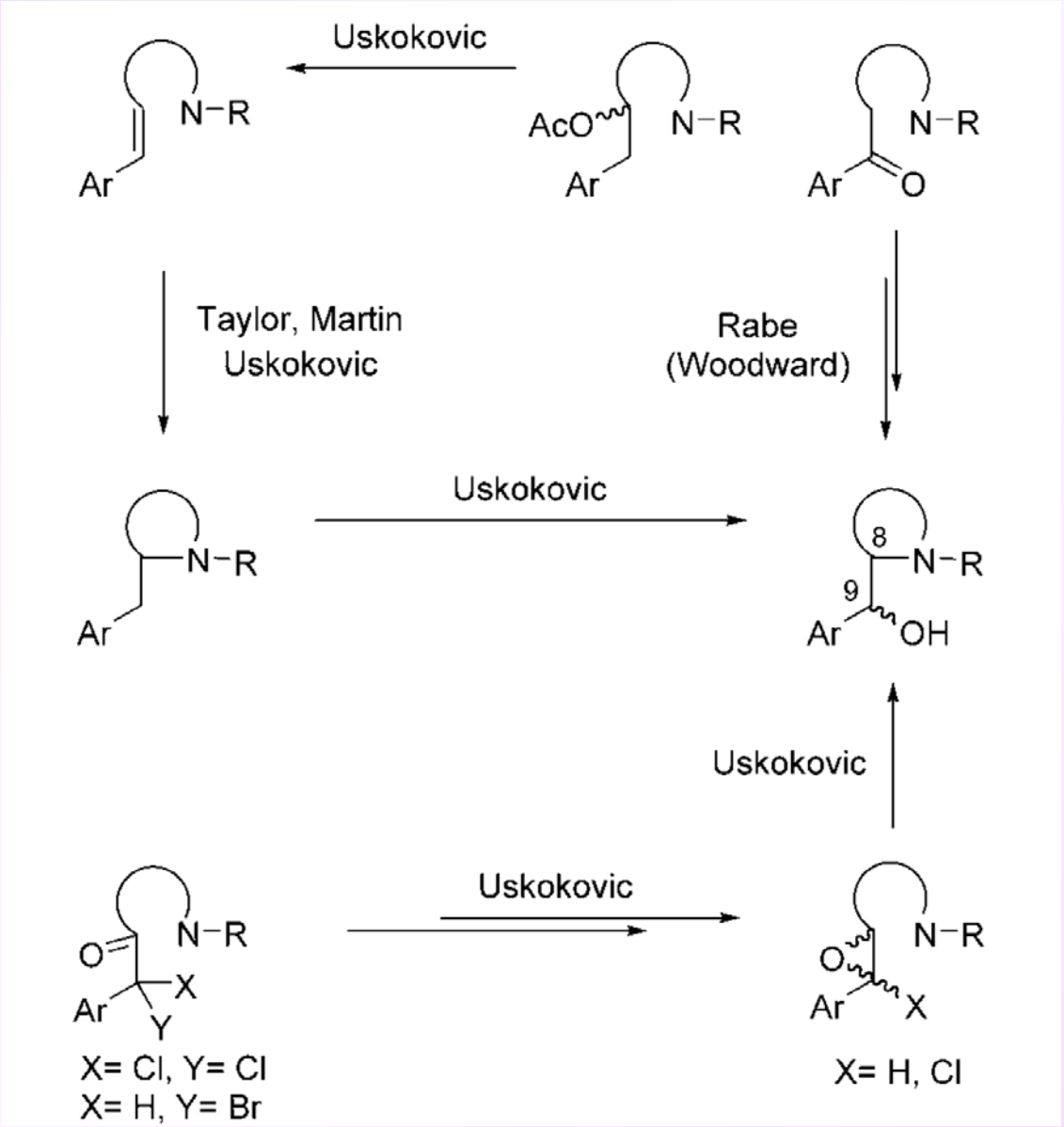
Autooxidation with oxygen catalyzed by *t*-BuOH
Stereoselectivity (5:1)
Quinidine/Quine (1:1)



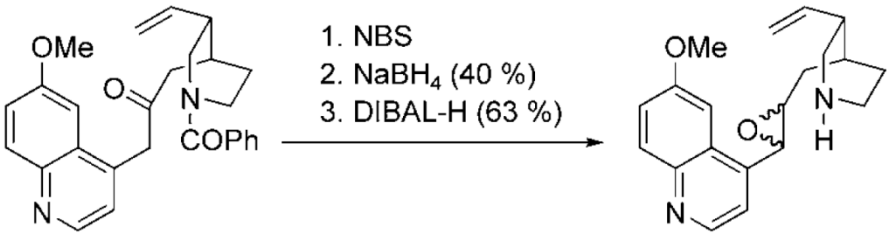
Quinidine



Quinine

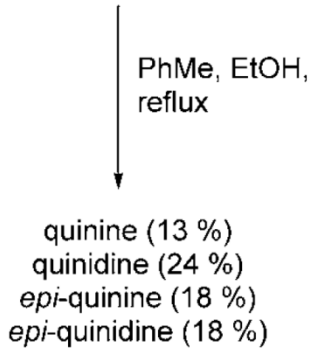


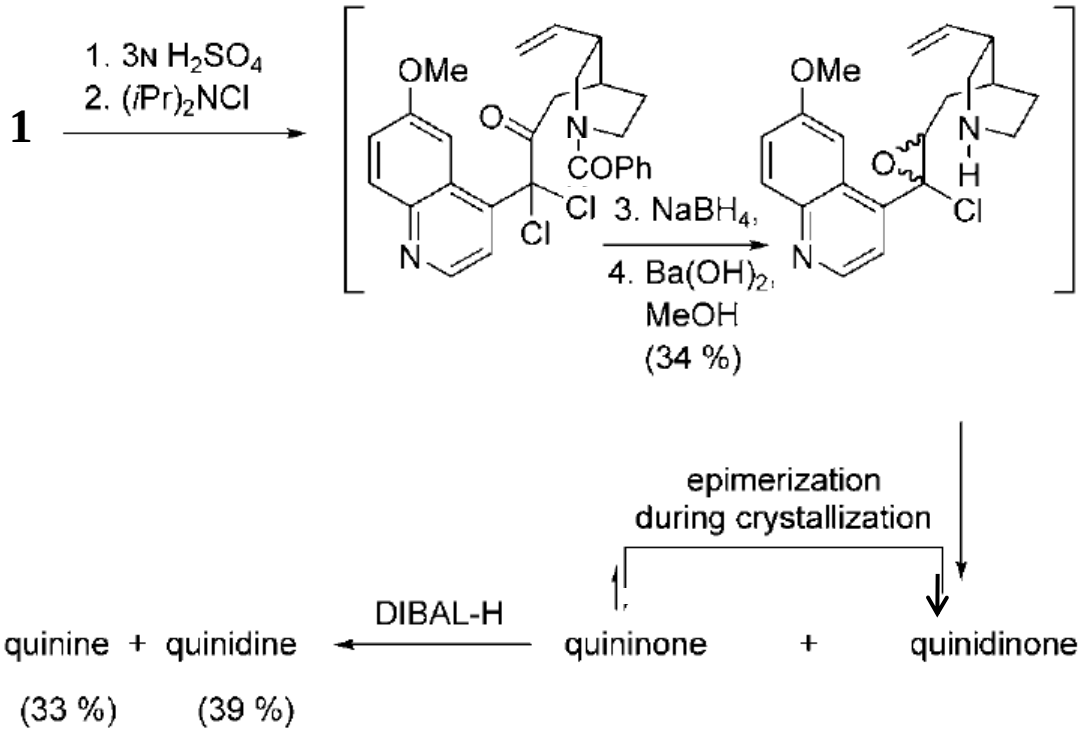
Different strategies for the C8-N closing



Key Ketone
1

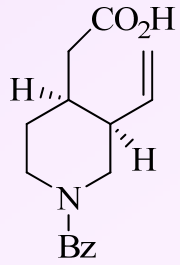
Other strategies used by Ukoskovic *et al.*



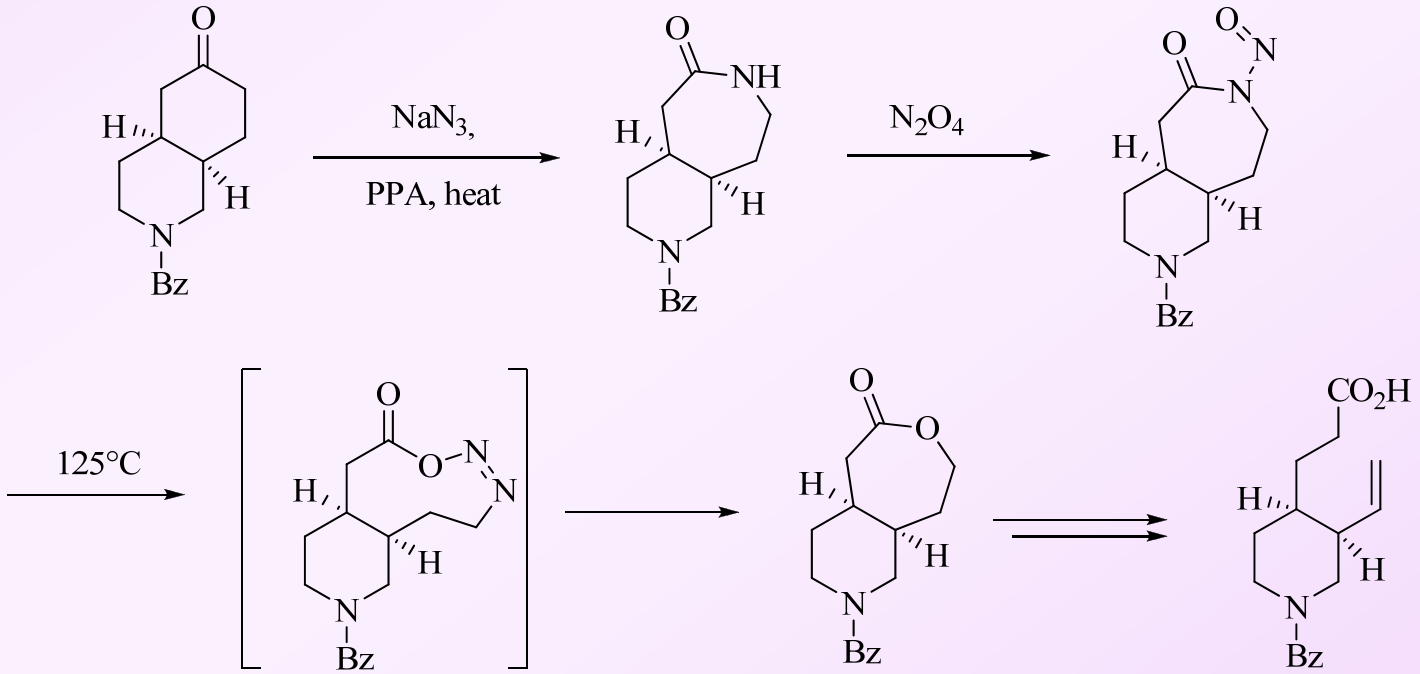


_N_-benzoylmeroquinene derivative used in these last 70's synthesis:

pure enantiomer form obtained by degradation of quinidinone



A Synthesis proposed by Uskokovic in the first synthesis of 1970:



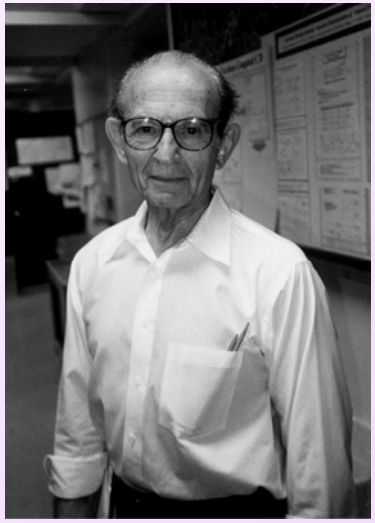
First Totally Stereocontrolled Synthesis of (-)-Quinine: Gilbert Stork

"The Woodward–Doering synthesis of homomeroquinene (*cis*-3-vinyl-4-piperidinepropionic acid referred to above) deserves our admiration, not because of its putative relationship to Rabe's work, but for its own sake. It is beautiful and inspiring … the inspired

G. Stork, 1944

- His doubt: **Did the three last steps of the Woodward-Doering synthesis really work ?**

1946 ~ First Works of Stork on the synthesis of quinine:
Stereoselective synthesis of a dihydromeroquinene derivative

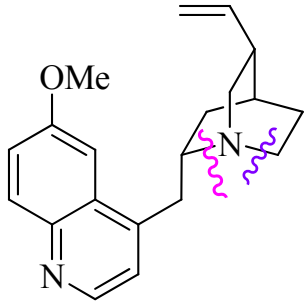


G. Stork, 1996

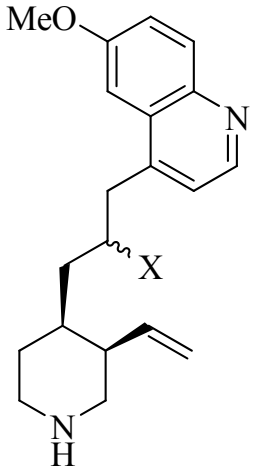
Possible Strategies for the Formation of the Bicyclic Pattern of Quinidine

2001

Deoxyquinine

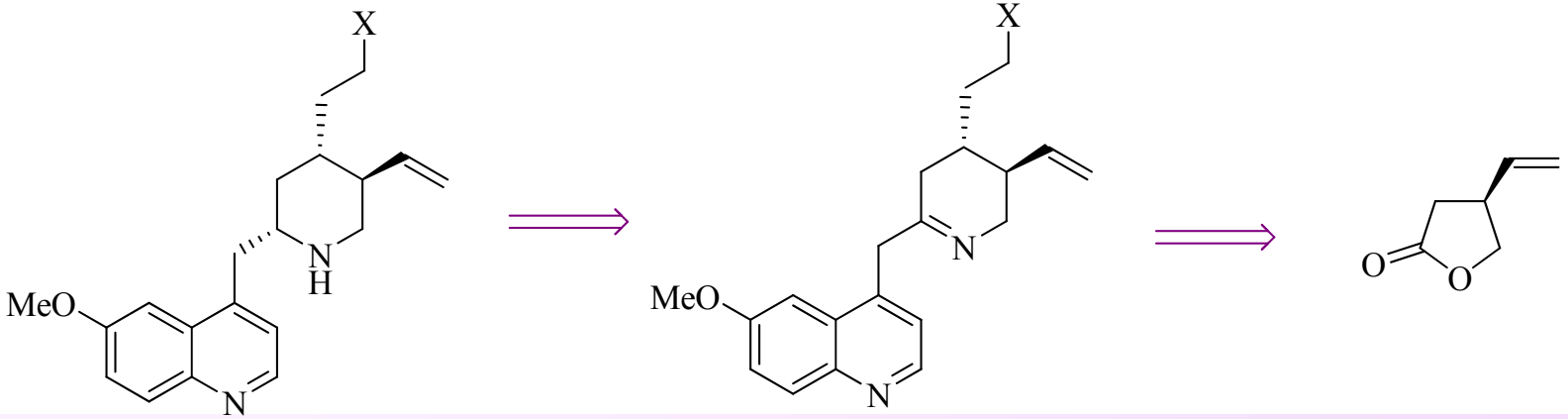


a)



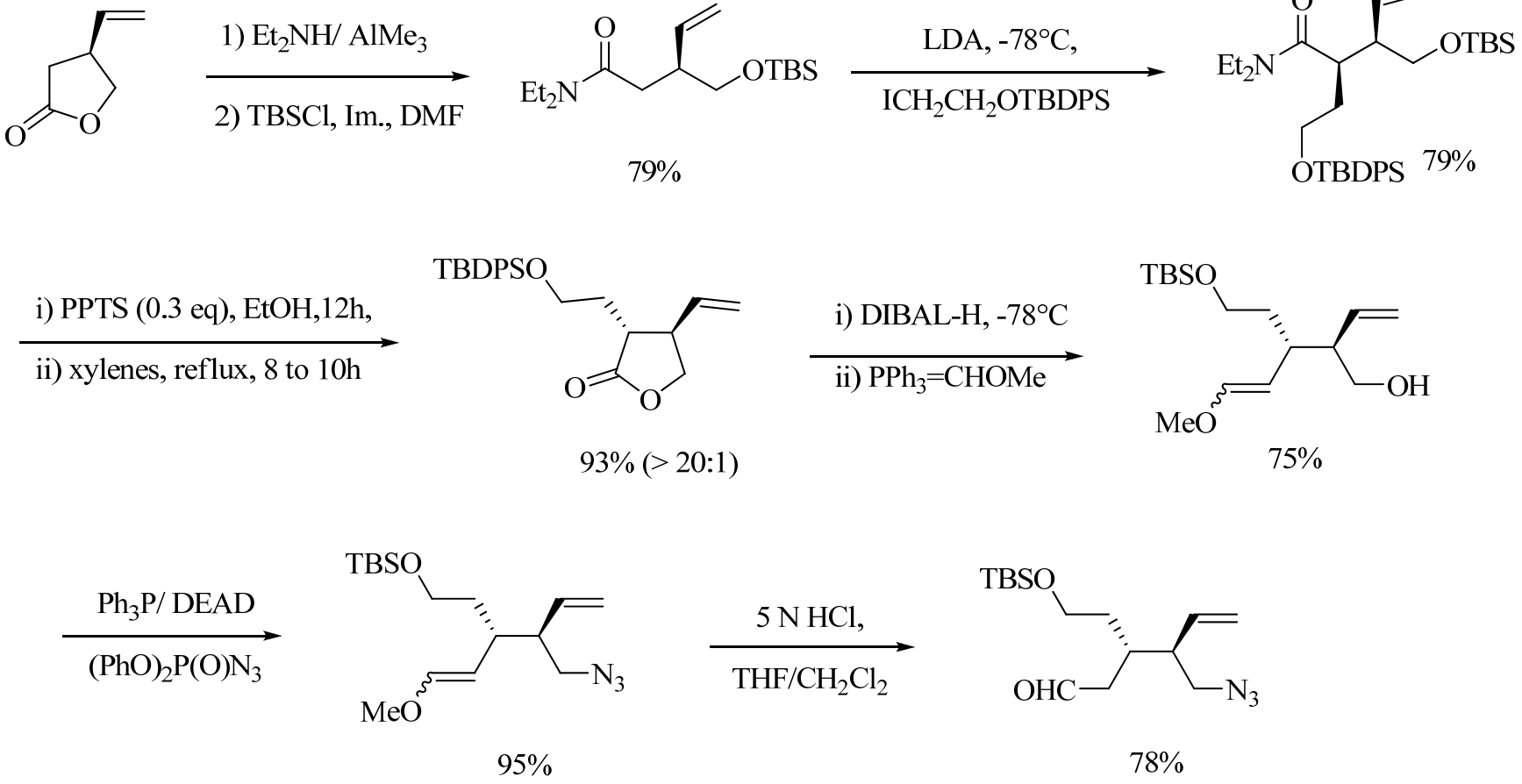
b)

a) Classical C8-N approach
b) Stork's approach

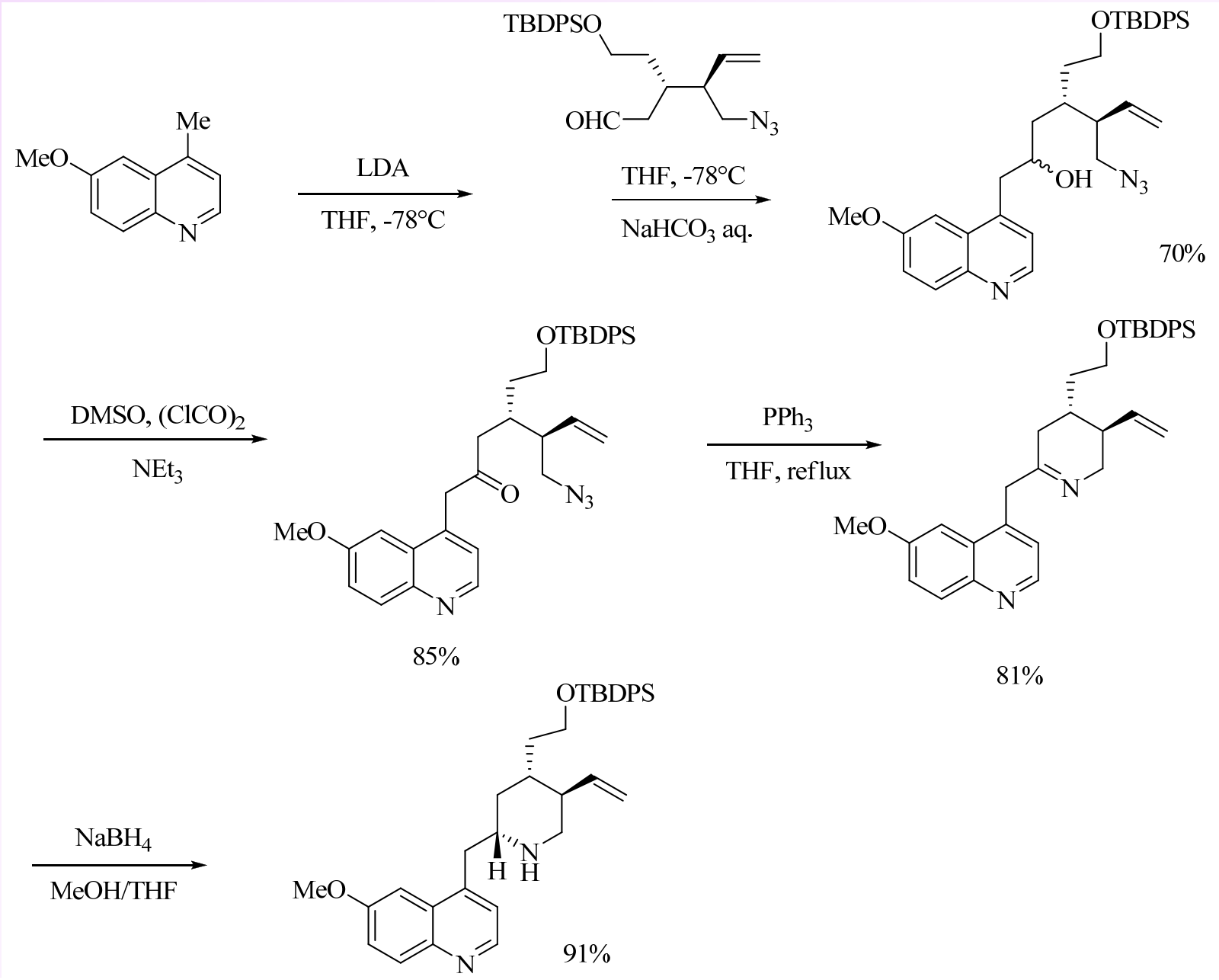


Stork, G. *et al. J. Am. Chem. Soc.* **2001**, *123*, 3239-3242

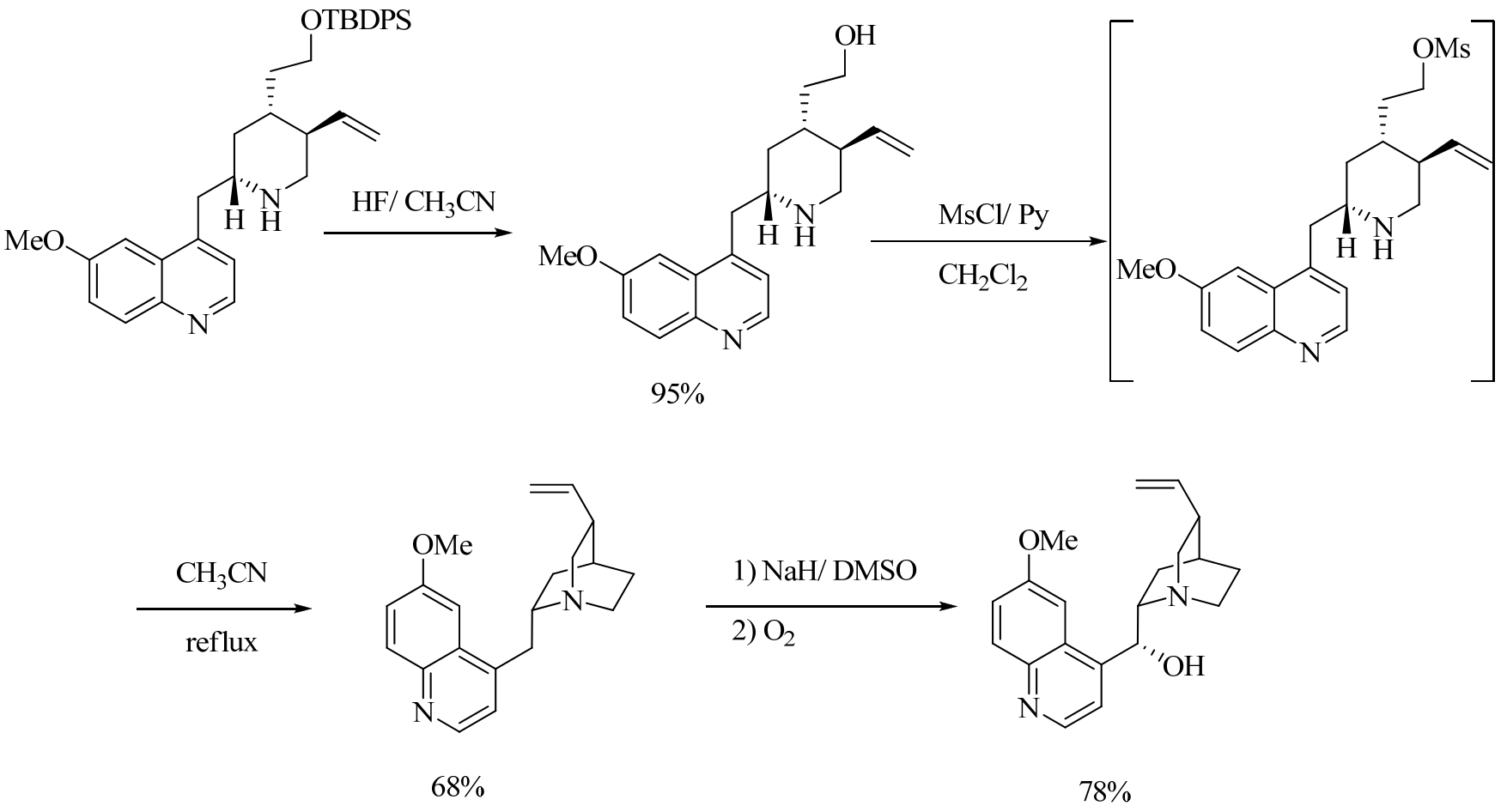
Synthesis of the trisubstituted tetrahydropyridine



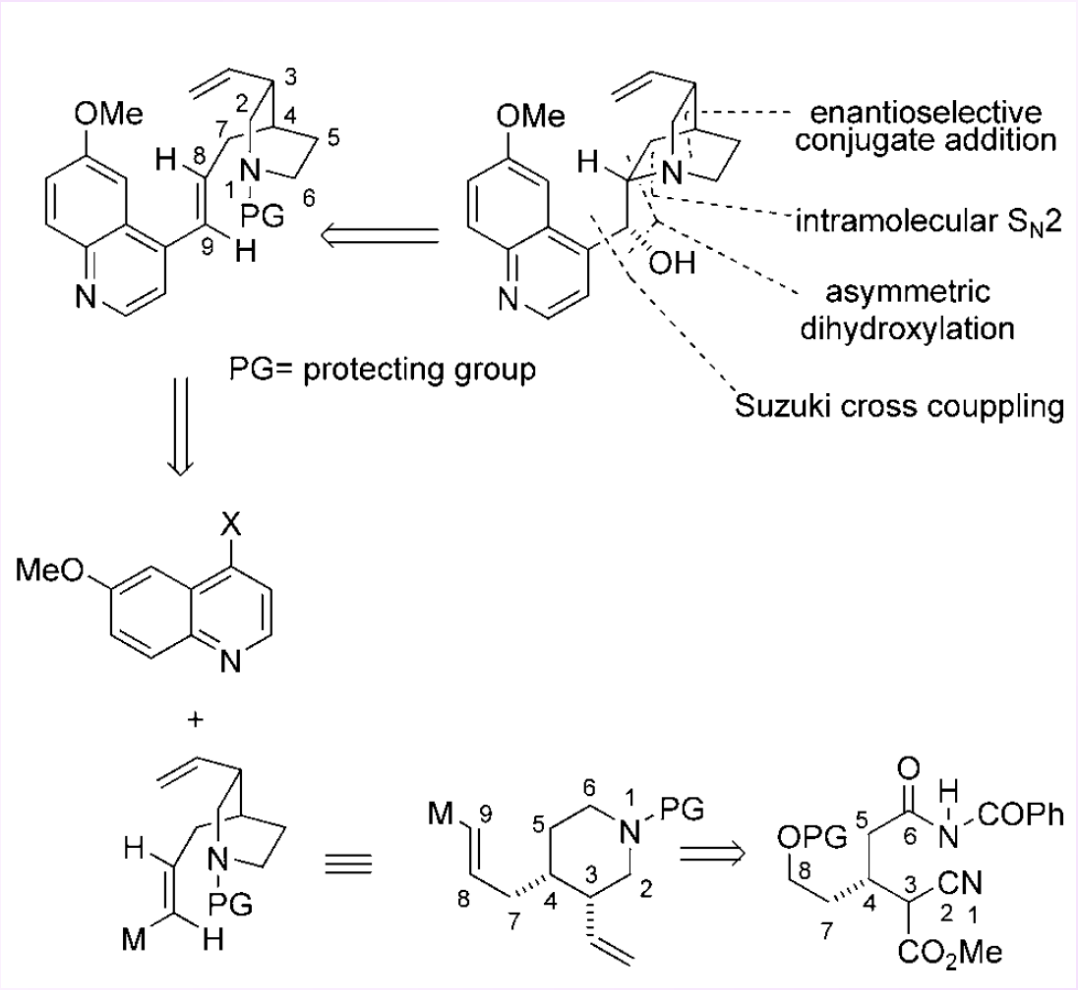
Synthesis of the trisubstituted tetrahydropyridine



Access to Deoxyquinine and Quinine

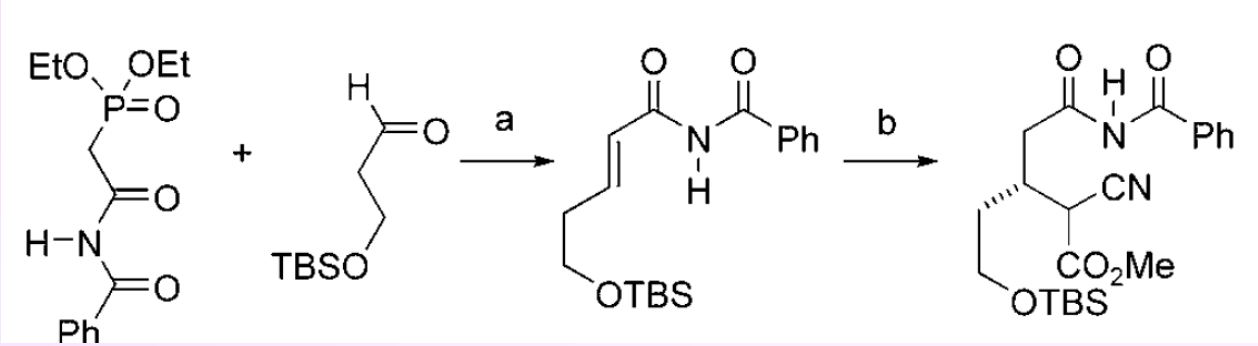


2004 ~ Jacobsen's retrosynthesis



Key Step: Modern and stereocontrolled version of the aminoepoxide cyclisation conceptually established by Uskokovic

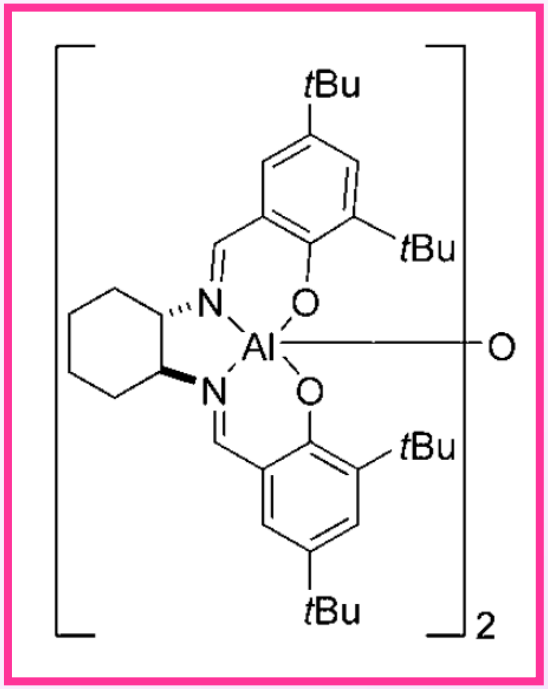
Jacobsen, E. N. *et al. J. Am. Chem. Soc.* **2004**, *126*, 706

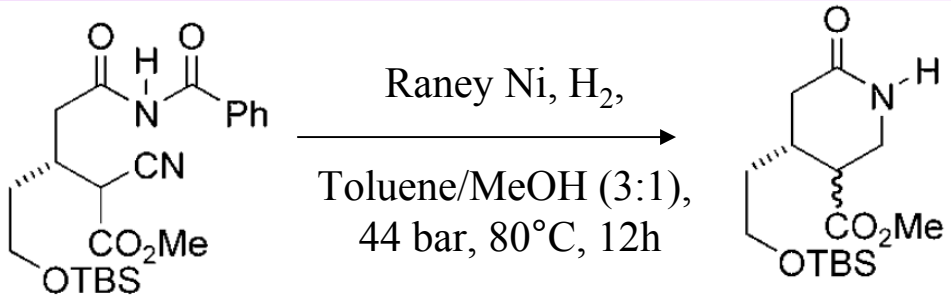


84% (E/Z>50:1) **91%**

a) *n*-BuLi, THF, -78°C-0°C

b) $NCCH_2CO_2Me$, (S,S)-Complex Al-Salen (5 mol%), *t*-BuOH, Cyclohexane, rt



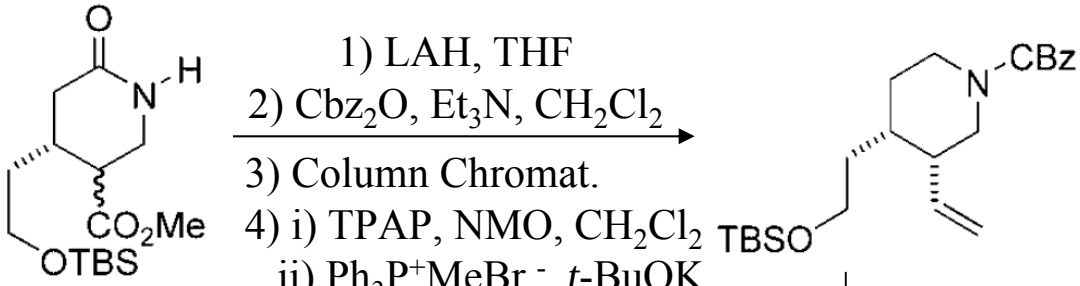


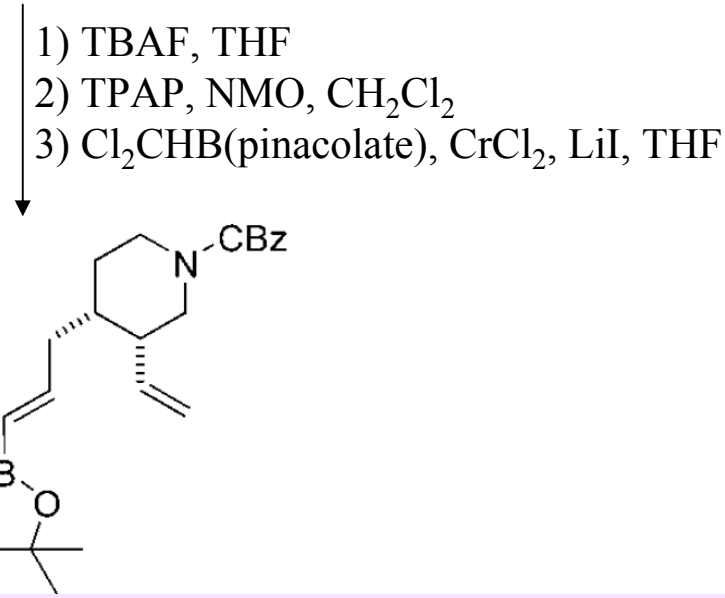
89%

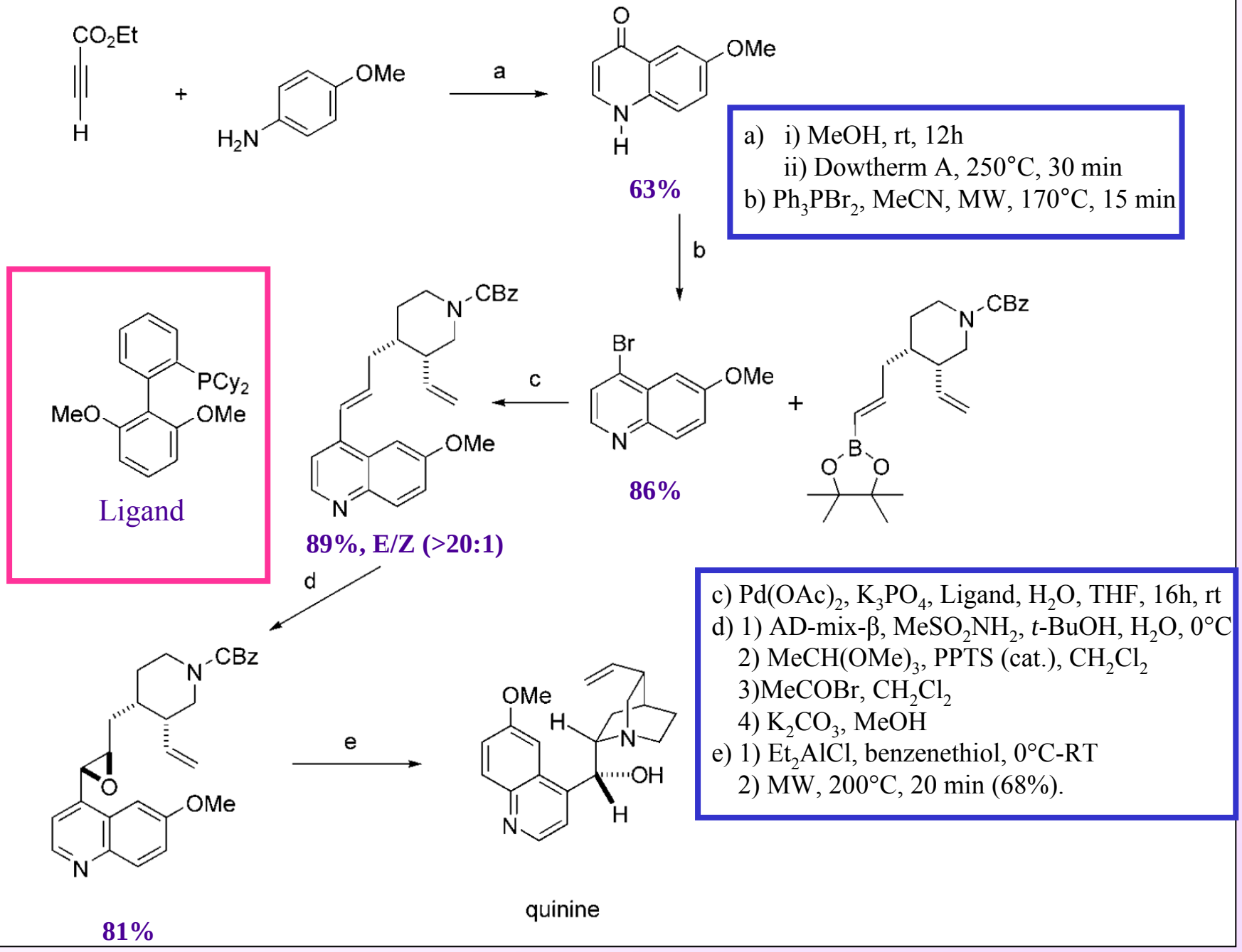
Cis/trans 1:1.7

i) LDA, THF, -78°C
ii) 5% H_2O/ THF, -78°C

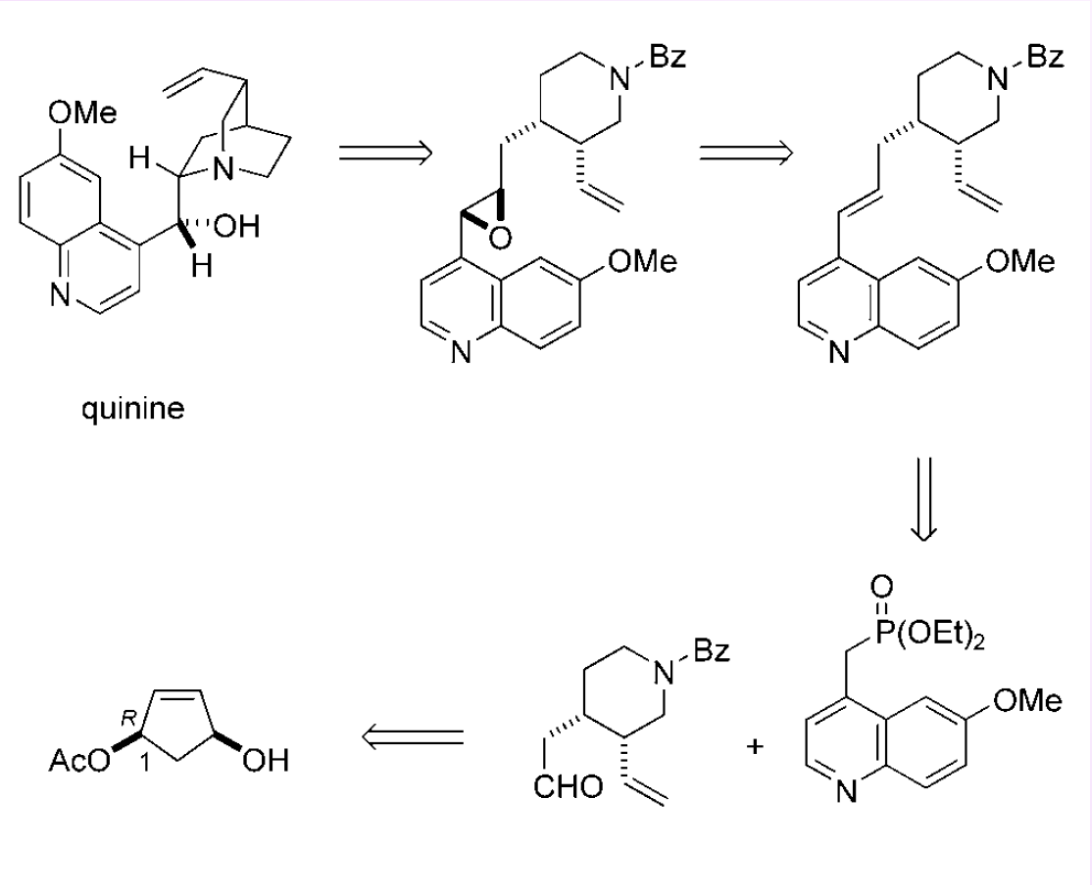
Cis/trans 3:1






CO2Et
H
+
H2N
OMe
a
O
N
H
OMe
63%
a) i) MeOH, rt, 12h
ii) Dowtherm A, 250°C, 30 min
b) Ph3PBr2, MeCN, MW, 170°C, 15 min
b
Br
N
OMe
86%
+
N
CBz
B
O
O
c
N
CBz
OMe
N
89%, E/Z (>20:1)
PCy2
MeO
OMe
Ligand
d
N
CBz
O
OMe
N
81%
e
OMe
H
N
OH
H
N
quinine
c) Pd(OAc)2, K3PO4, Ligand, H2O, THF, 16h, rt
d) 1) AD-mix-β, MeSO2NH2, t-BuOH, H2O, 0°C
2) MeCH(OMe)3, PPTS (cat.), CH2Cl2
3)MeCOBr, CH2Cl2
4) K2CO3, MeOH
e) 1) Et2AlCl, benzenethiol, 0°C-RT
2) MW, 200°C, 20 min (68%).

2004 ~ Kobayashi's retrosynthesis

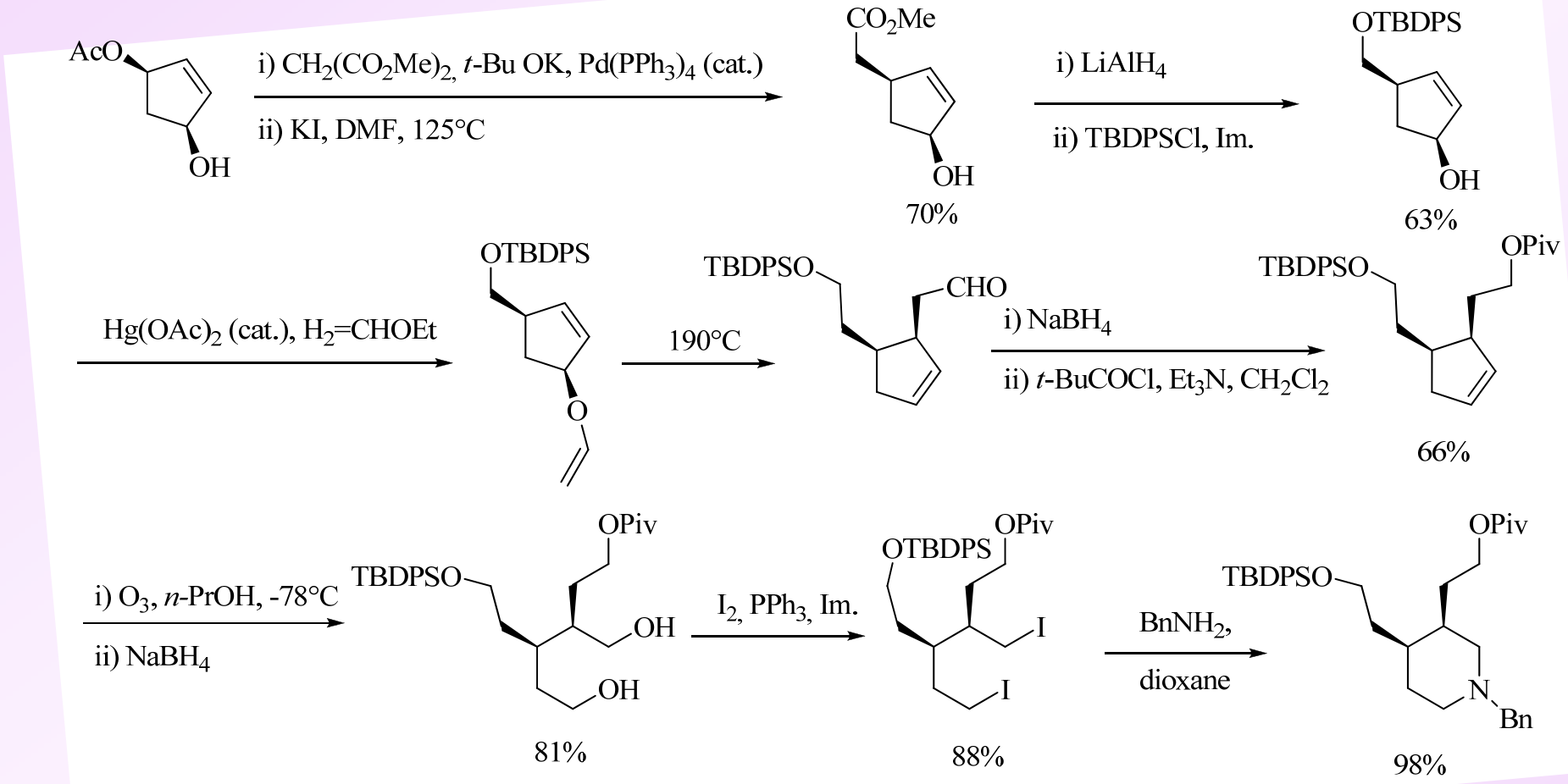


- Based on previous experience accumulated by Ukoskovic, Taylor and Martin and Jacobsen
- **Special Features:** Highly stereocontrolled synthesis of the meroquinene moiety
  One of the key steps: Wittig Horner olefination
  Starting material readily available

Kobayashi, Y. *et al. Tetrahedron Lett.* **2004**, *45*, 3783

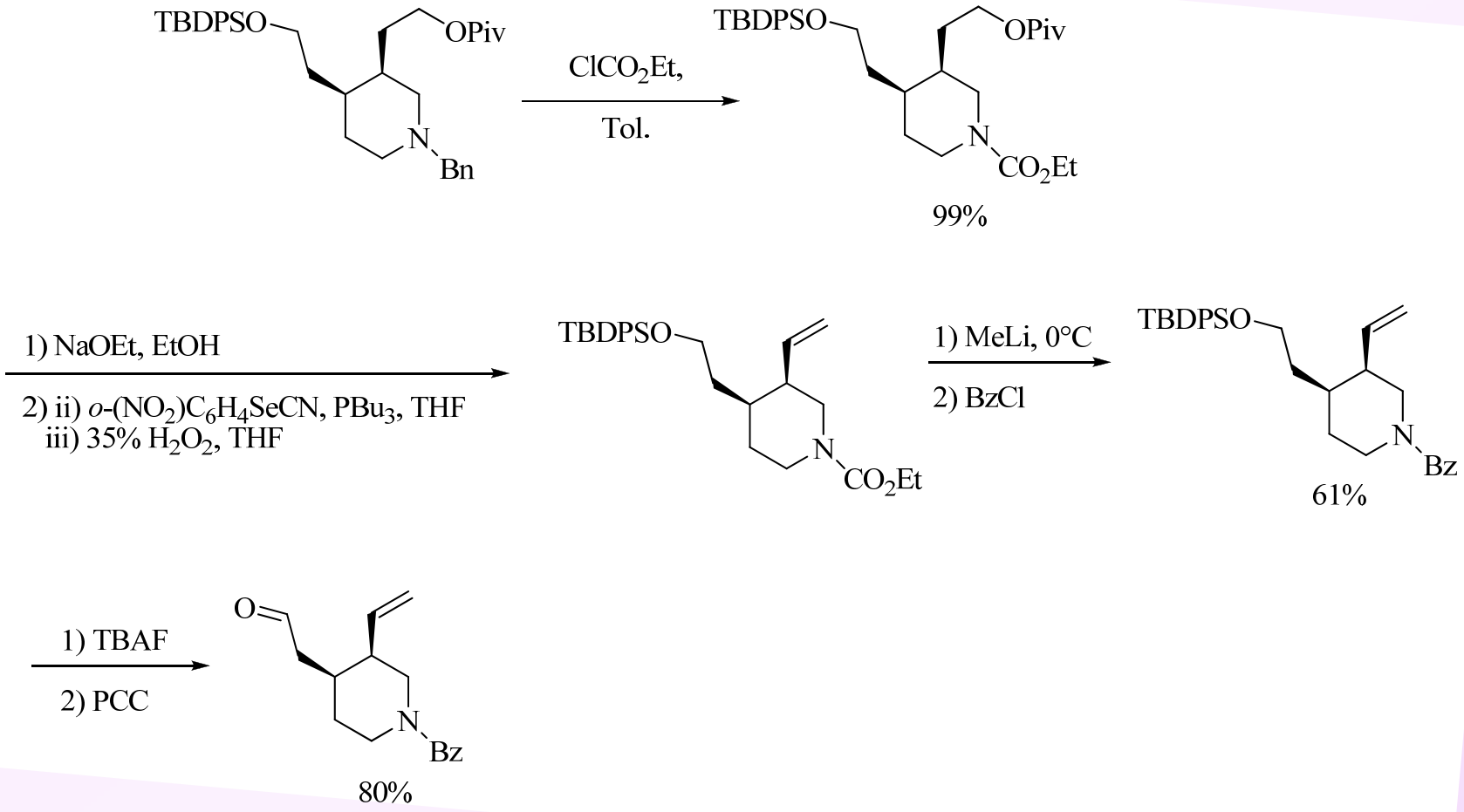
2004 ~ Kobayashi's synthesis:

Elaboration of the pepiridine moeity

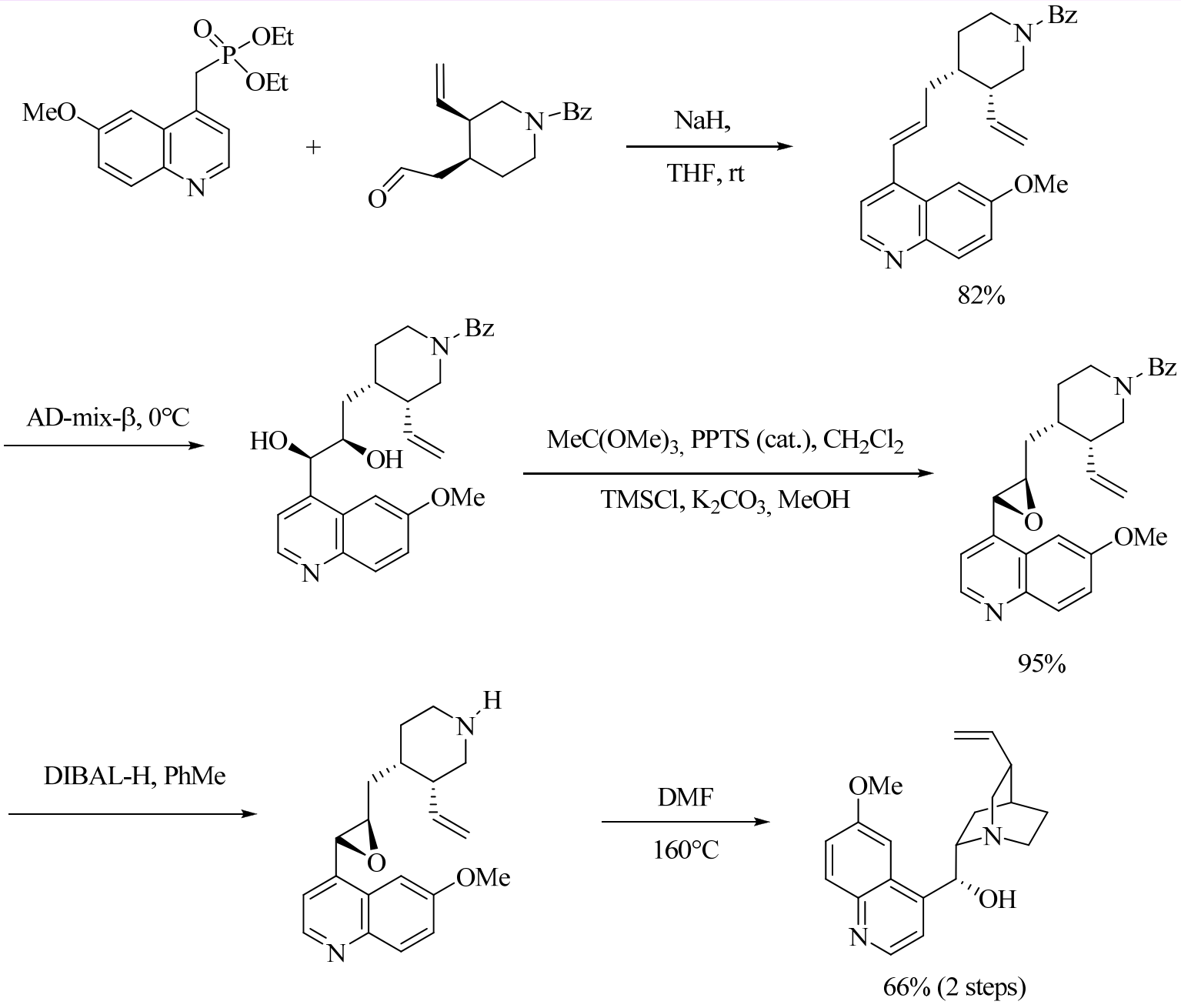


Kobayashi, Y. *et al. Tetrahedron Lett.* **2004**, *45*, 3783

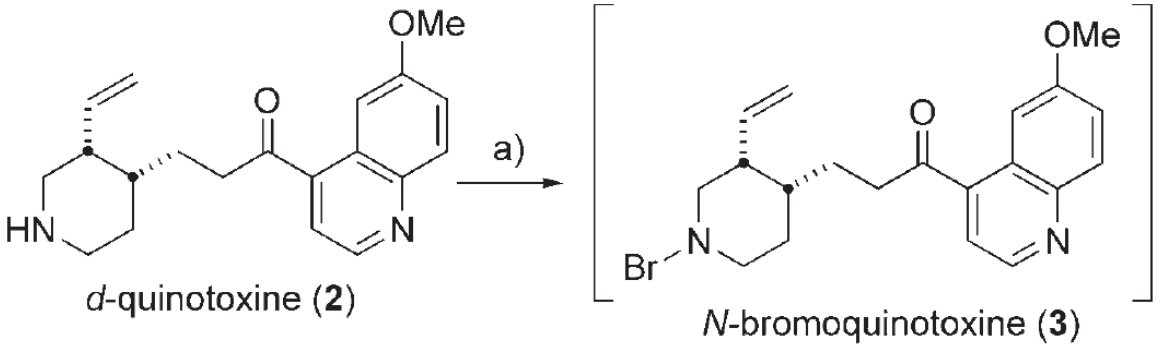
Kobayashi's synthesis: Elaboration of the pepiridine moeity

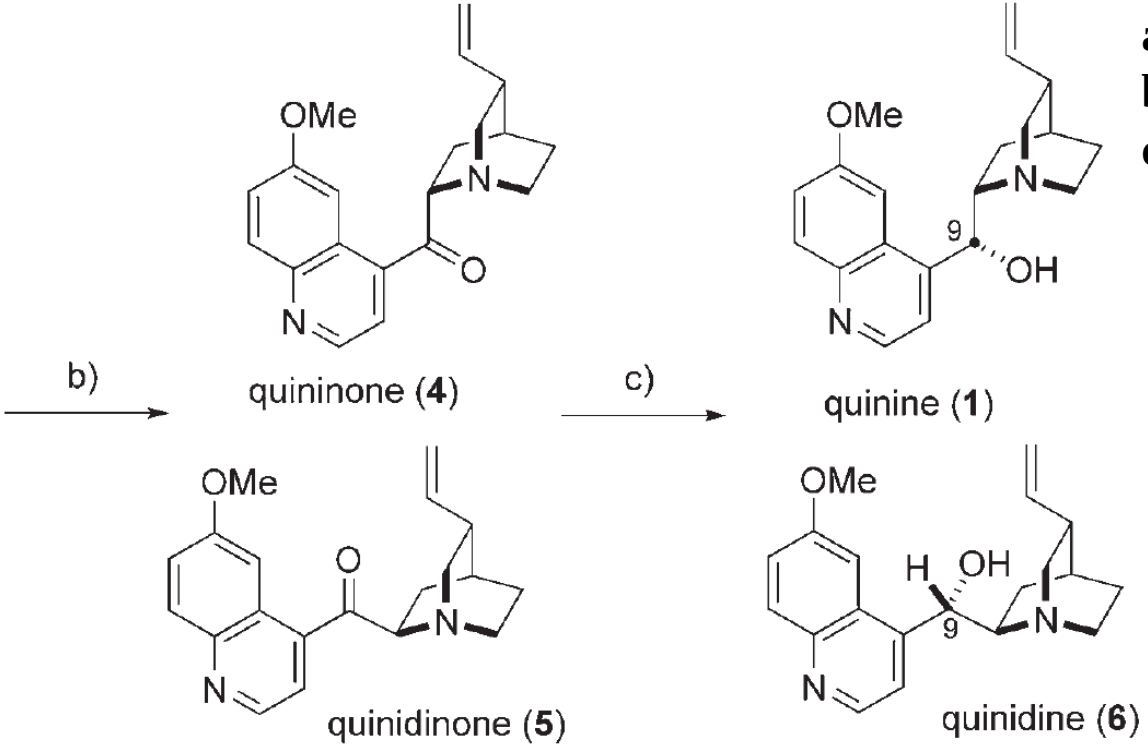


Kobayashi's synthesis: Attachments of the aryl moiety to the piperidine core



The reproduction of the three important steps provided by Rabe and Kindler





a) NaOBr, 55% of crude pdt
b) EtONa, EtOH, 88% crude pdt
c) Al powder, NaOEt/EtOH
5% as the tartrate salt

Entry	Reducing conditions	T [°C]	Yield of isolated quinine/quinidine	Yield of quinine[f]
1[a]	DIBAL-H benzene	20	72%	33%
2[b]	$NaBH_4$, EtOH	0	11%	4%
3	Al powder (new)[c] NaOEt, EtOH	reflux	trace	trace
4	Al powder (new)[d] NaOEt, EtOH	reflux	30% (1.1:1)	16%
5	Al powder + Al_2O_3 NaOEt, EtOH	reflux	26% (1.1:1)	14%
6	Al powder (aerated)[c] NaOEt, EtOH	reflux	24% (1.1:1)	13%
7	Al powder MeOH, NaOMe	reflux	8% (1.2:1)	4%
8	Al powder (sonication) NaOEt, EtOH	reflux	22% (1.1:1)	12%
9	Al powder, Na(O*i*Pr), *i*PrOH	reflux	32% (1:1.2)	15%
10	$Al(OiPr)_3$, *i*PrOH	reflux	28%	16%
11	$LiAlH_4$, ether	−78	45%	trace
12	$LiAlH_4$, ether	0	59%	trace
13	$LiAlH_4$, ether	20	56%	trace
14	$LiAlH_4$, ether[e]	0	40% (1:1.5)	16%

[a] Experiment from Ref. [11]. [b] General reaction conditions here. [c] Bottle #1. [d] Bottle #2. [e] After epimerization. [f] Calculated based on ^1H NMR spectra.

Conclusion

A fascinating and long quest:

-For the discovery of the structure

-For the development of the different syntheses