Synthesis of quinine. Answers.

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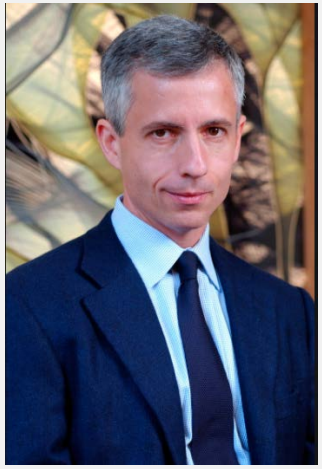
Photo : the main building of Moscow State University

Synthesis of quinine

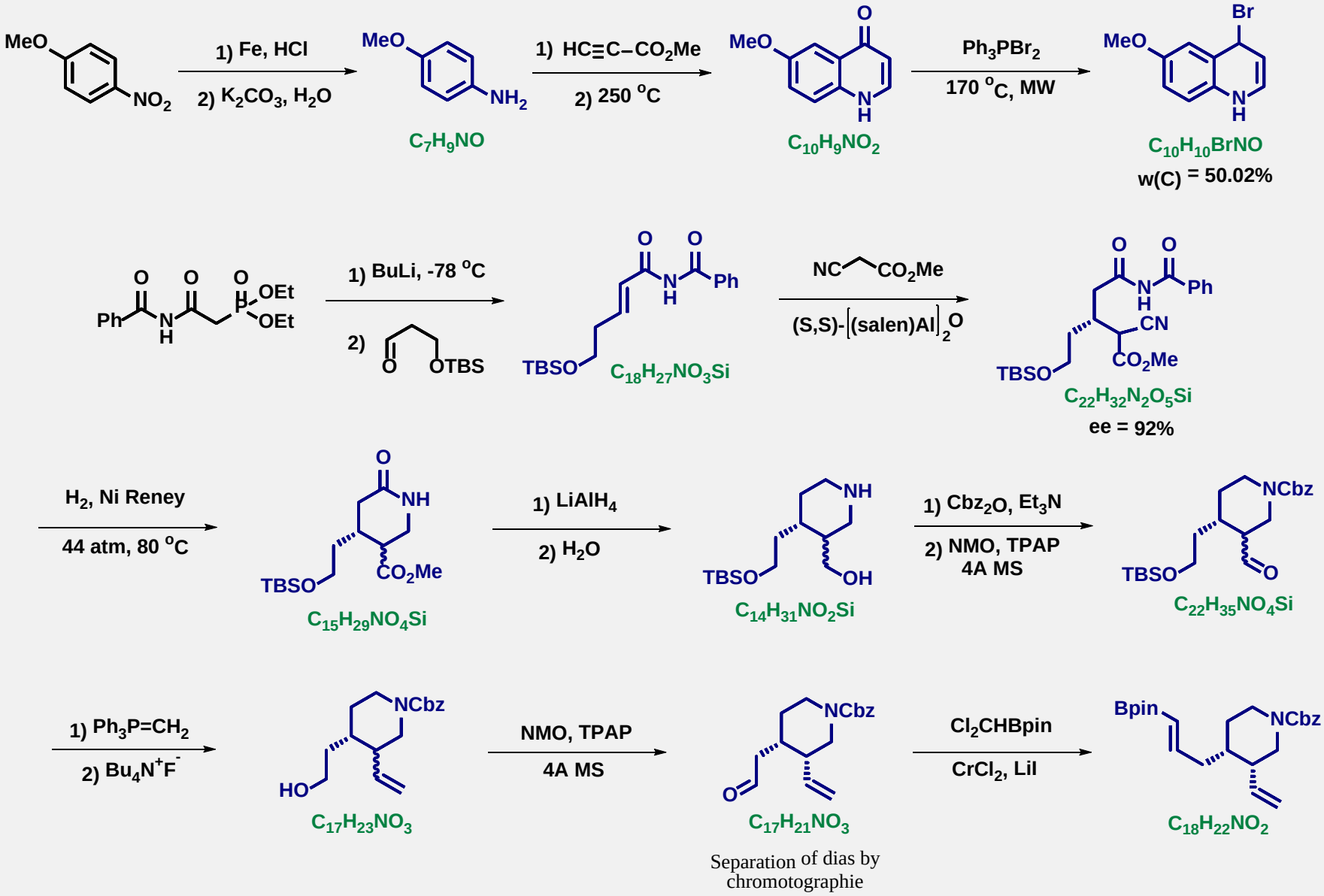
Outstanding organic chemist **Robert Burns Woodward** over 30 years has carried out about 20 complex syntheses of natural compounds such as quinine, cholesterol, cortisone, strychnine, lysergic acid, reserpine, chlorophyll, cephalosporin, and colchicine that previously seemed unrealizable. For his contribution in organic chemistry he was awarded the Nobel Prize in Chemistry in 1965. The goal of one of the first in a series of extremely complex and elegant syntheses he carried out was **quinine**, an alkaloid of the cinchona tree with a bitter taste. Quinine has antipyretic, analgesic, and antiarethmic properties and is still used in the treatment of malaria. Although the synthesis proved to be successful, it was too long and laborious to be applied on a practical scale. Later, **E. Jacobsen** and his co-workers were able to propose a much simpler enanteoselective synthesis of quinine using catalytic reactions.

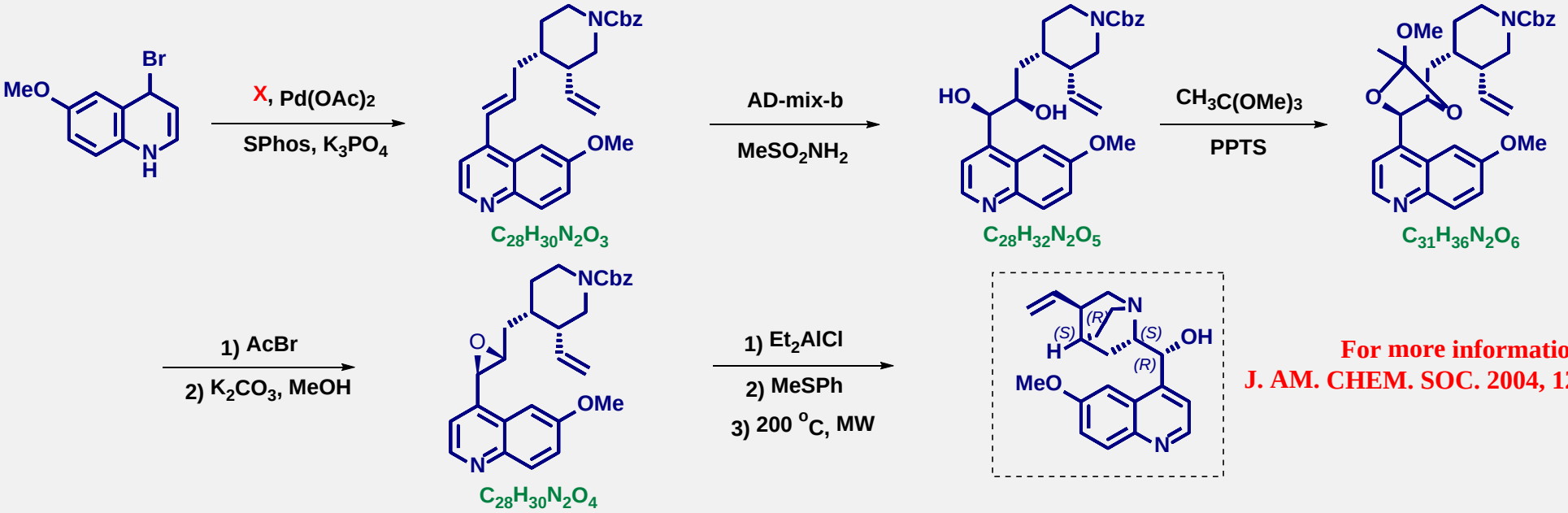
Robert Burns Woodward

April 10, 1917 – July 8, 1979



Steven E. Jacobsen


MeO
NO2
1) Fe, HCl
2) K2CO3, H2O
MeO
NH2
C7H9NO
1) HC≡C–CO2Me
2) 250 °C
O
MeO
N
H
C10H9NO2
Ph3PBr2
170 °C, MW
Br
MeO
N
H
C10H10BrNO
w(C) = 50.02%
O
O
O
OEt
Ph
N
H
OEt
1) BuLi, -78 °C
2)
O
OTBS
O
O
N
H
Ph
TBSO
C18H27NO3Si
NC
CO2Me
(S,S)-[(salen)Al]2O
O
O
N
H
Ph
CN
CO2Me
TBSO
C22H32N2O5Si
ee = 92%
H2, Ni Reney
44 atm, 80 °C
O
NH
TBSO
CO2Me
C15H29NO4Si
1) LiAlH4
2) H2O
NH
TBSO
OH
C14H31NO2Si
1) Cbz2O, Et3N
2) NMO, TPAP
4A MS
NCbz
TBSO
O
C22H35NO4Si
1) Ph3P=CH2
2) Bu4N+F-
NCbz
HO
C17H23NO3
NMO, TPAP
4A MS
NCbz
O
C17H21NO3
Separation of dias by chromotographie
Cl2CHBpin
CrCl2, LiI
Bpin
NCbz
C18H22NO2



For more information:
J. AM. CHEM. SOC. 2004, 126, 706-707

Compound	Brut formula	Compound	Brut formula	Compound	Brut formula	Compound	Brut formula
A	C_7H_9NO	E	$C_{22}H_{32}N_2O_5Si$	I	$C_{17}H_{23}NO_3$	L	$C_{28}H_{32}N_2O_5$
B	$C_{10}H_9NO_2$	F	$C_{15}H_{29}NO_4Si$	J	$C_{17}H_{21}NO_3$	M	$C_{31}H_{36}N_2O_6$
C	$C_{10}H_{10}BrNO$	G	$C_{14}H_{31}NO_2Si$	X	$C_{18}H_{22}NO_2$	N	$C_{28}H_{30}N_2O_4$
D	$C_{18}H_{27}NO_3Si$	H	$C_{22}H_{35}NO_4Si$	K	$C_{28}H_{30}N_2O_3$		

1. Write the scheme of transformations presented above, giving the structures of the substances **A-N** (it is not required to indicate the stereochemistry). Additionally, it is known that the molecular ion (MH^+) of **N** corresponds to a peak with m / z = 459.2285. The ^1H NMR spectrum of substance **B** contains the following signals: 11.8 (1H), 7.84 (1H), 7.52 (1H), 7.48 (1H), 7.27 (1H), 6.00 (1H), 3.82 (3H).

Interestingly, in its antiarethmic activity, **quinine** is significantly inferior to its stereoisomer **quinidine** and gives significantly more side effects. Therefore, of all the stereoisomers of **quinine**, it is **quinidine** that is currently used as an antiarethmic agent.

2. How many stereoisomers does **quinine** have in total? Determine the configuration of chiral centers in its molecule according to the (R, S) – nomenclature. **Answer: The quantity of diastereoisomeres can be calculated by equation: N = 2^n, where n is number of chiral centres in the molecule. N = 2^4 = 16 possible diastereosemeres for quinine. All chiral centres for quinine are shown in the structure above.**

3. Give the structural formula of **quinidine**, if it is known that the above scheme for the synthesis of **quinine** can be used to obtain **quinidine**, replacing the reagent AD-mix-β with AD-mix-α. These reagents differ in that they use different enantiomers as a chiral ligand. **Answer: The structure and the chiral centres of quinidine is shown below.**