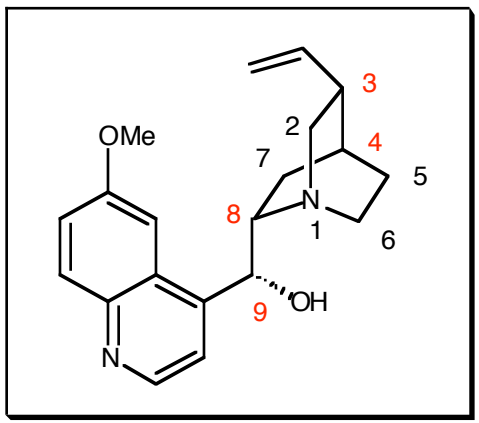
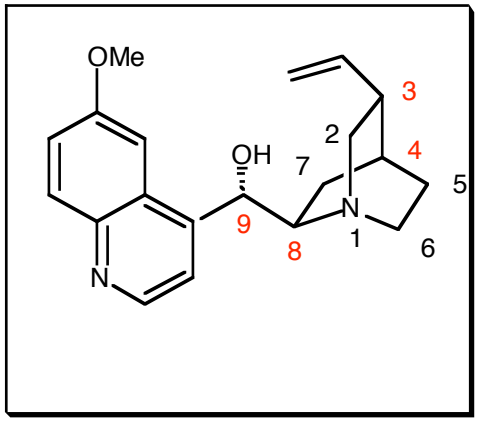
Catalytic Asymmetric Total Syntheses of Quinine and Quinidine



Quinine



Quinidine

Zhensheng Ding

January 22 2004

Chinese New Year Day

1. Jacobsen, E., N. *J. Am. Chem. Soc.* **2004**, ASAP

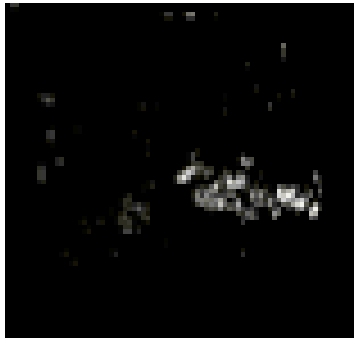
2. Stork, G.; Niu, D. *J. Am. Chem. Soc.* **2001**, 123, 3239

3. Nicolaou, K., C. *Classics in Total Synthesis II: More Targets, Strategies, Methods*, Wiley-VCH: Weinheim, Germany, **2003**, Ch. 15

Quinine : The Anti-Malaria Drug

1630

Quina bark administered to the Countess of Chinchon

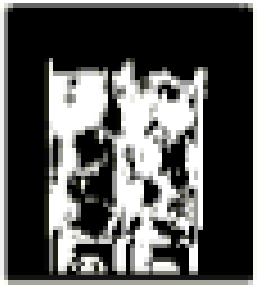


1679

Robert Talbot used 'Jesuit's Powder' to cure King Charles II

1850

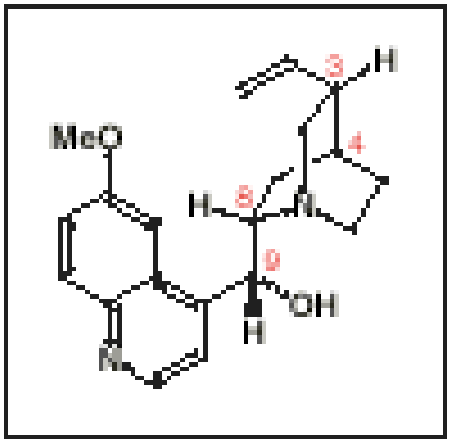
The G&T's of the Raj – a necessity before a pleasure



1897

Sir Ronald Ross deduced that the malaria parasite is spread by mosquitoes

Quinine : Early Investigations



1

1820 : P. J. Pelletier and J. B. Caventou identified Quinine as the active ingredient of Cinchona.

Ann. Chim. Phys. 1820, *15*, 291 and 337

1852 : Initial stereochemical investigations undertaken by L. Pasteur, identifying Quinine as *laevo*-rotatory.

Compt. Rend. 1853, *37*, 110

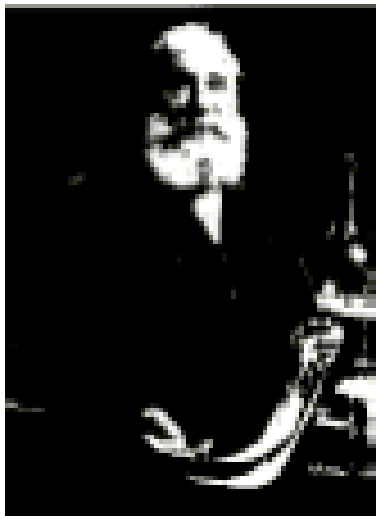
1854 : A. Strecker established the empirical formula of Quinine as $C_{20}H_{24}N_2O_2$. Later confirmed by Zd. Skraup.

Ann. 1854, *91*, 155

1907 : The correct connectivity of the atoms was established – largely through the work of P. Rabe.

Ann. 1907, *40*, 3655

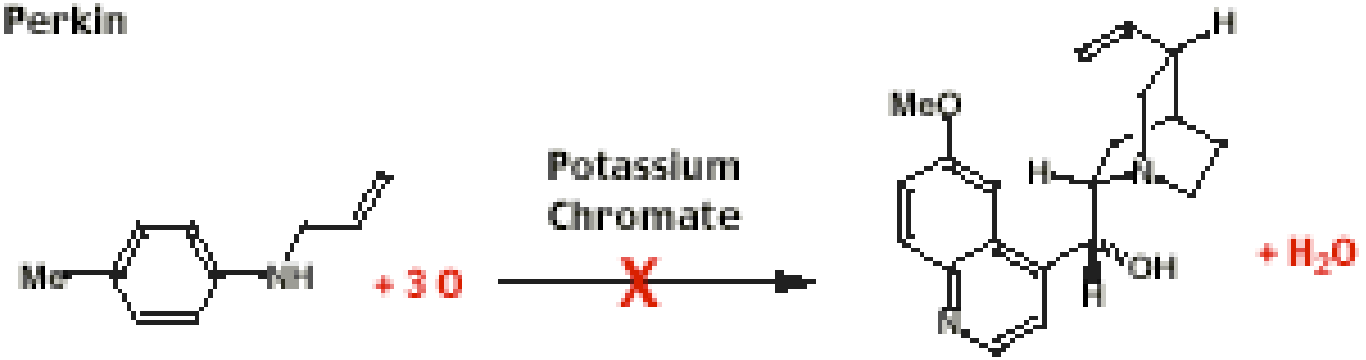
Quinine : First Attempted Synthesis



Sir William H. Perkin

"... it is obvious that *napthalidine*, 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."

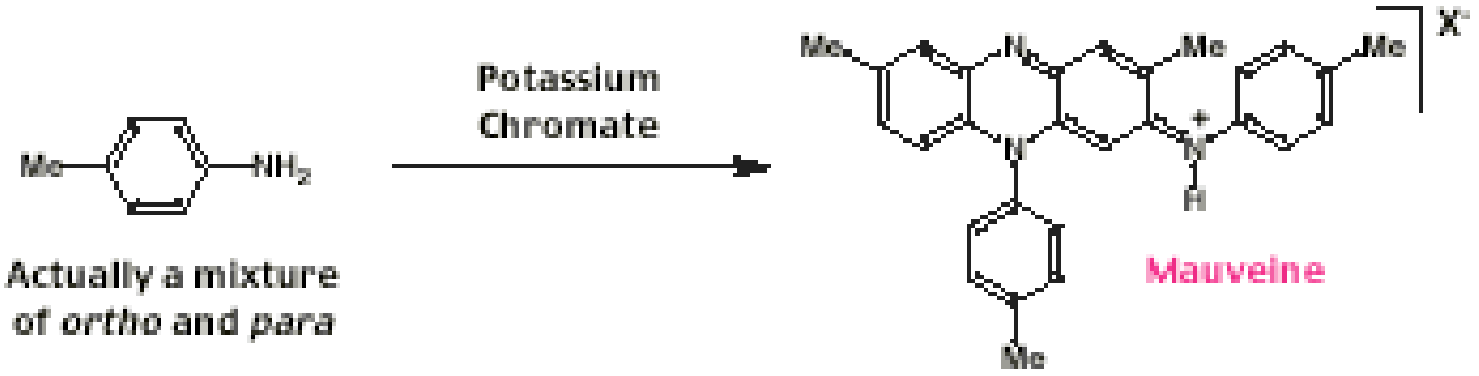
A. W. Hofmann, *Report of the Royal College of Chemistry*, 1849



$C_{10}H_{13}N$

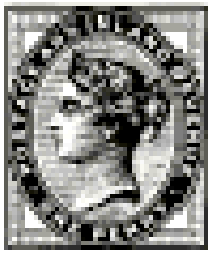
$C_{20}H_{24}N_2O_2$

Sir William H. Perkin : Easter, 1856



Actually a mixture
of *ortho* and *para*

Mauveine



Penny Red

1857 : A dye factory set up to produce Mauveine, located just south of the Black Horse public House, in Greenford, West London. The Pub is still there.

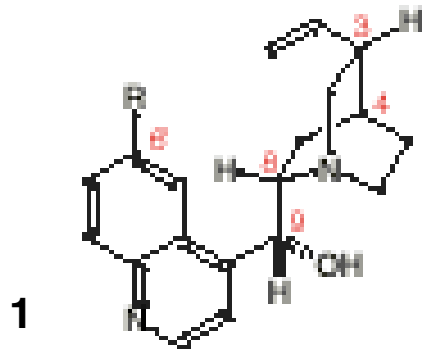
1862 : At the Royal Exhibition, Queen Victoria made an appearance in a silk gown dyed with mauveine

1865 : The Perkin Process is patented and the 'Aniline Dye Industry' goes on to spawn many of the world's major pharmaceutical companies including BASF, Hoechst, Ciba-Geigy and ICI

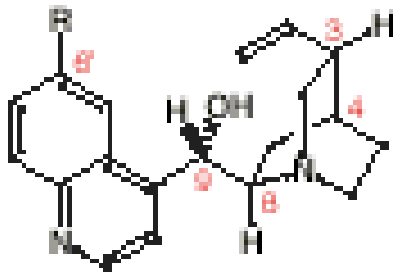
Account presented in Hofmann Memorial Lecture
J. Chem. Soc. 1896, *69*, 596

Corrected Mauveine Structure
J. Chem. Soc., Perkin Trans. 1, 1994, 5

Quinine : The Issue of Stereochemistry



1



2

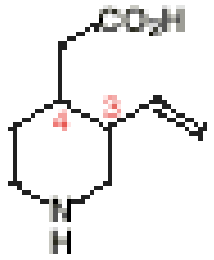
		α_D
R = H	Cinchonidine	−111
R = OMe	Quinine	−158

		α_D
R = H	Cinchonine	+224
R = OMe	Quinidine	+254

All 4 Compounds

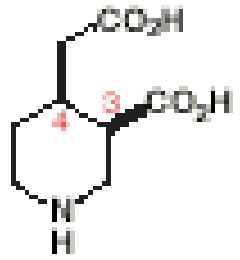
Destructive Fusion

Caustic Potash

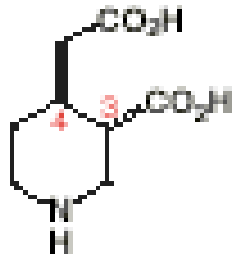


Meroquinene

Oxidation



β-Cincholoiponic Acid



α-Cincholoiponic Acid

The Alkaloids, R. H. F. Manske, Ed; Academic Press, NY, 1953, Vol. 3, Chap. 16, p. 25

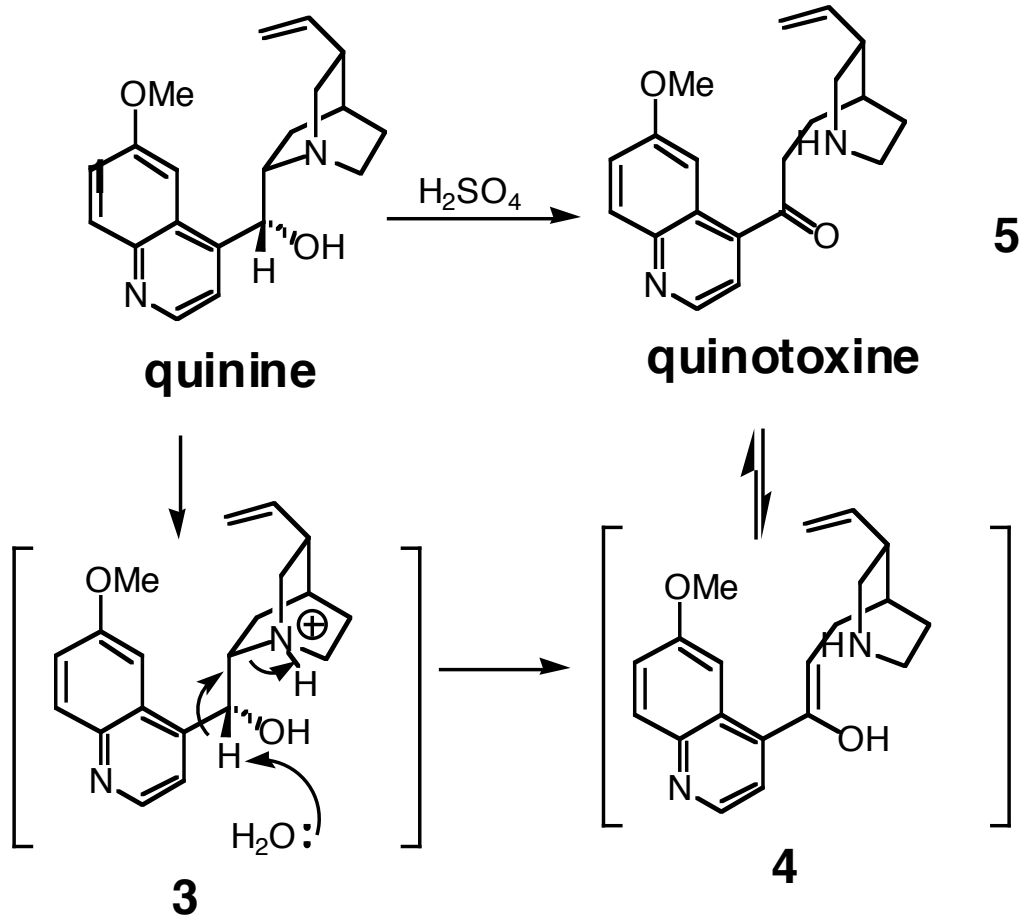
Pasteur's Degradation Reaction of Quinine

Louis Pasteur

(1822 - 1895)

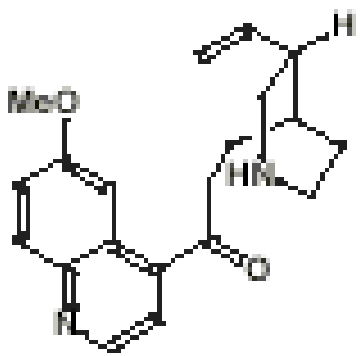
Chance favors only the prepared mind.

—Louis Pasteur



Classics in Total Synthesis II, Wiley-VCH,Germany, 2003, Ch. 15

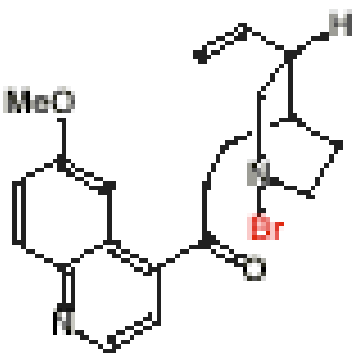
Quinine : 1918, the 'Rabe' Synthesis



Quinotoxin

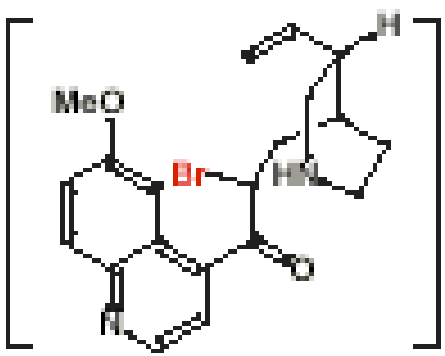
5

HOBr



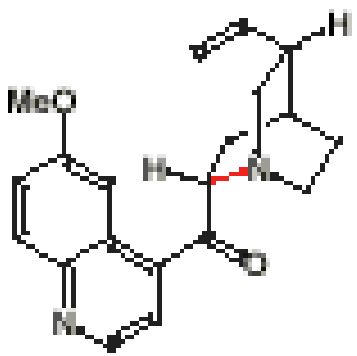
6

NaOEt



7

25%
2 steps



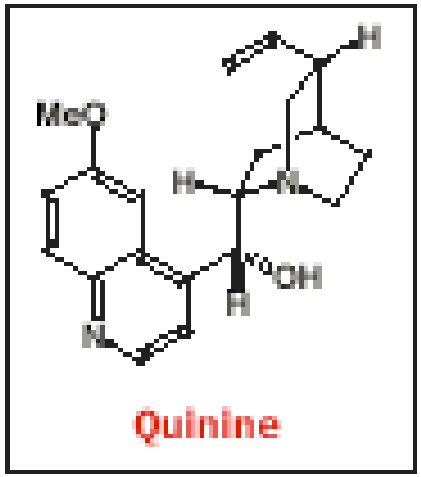
Quininone

8

Al Powder

EtOH/NaOEt

12%

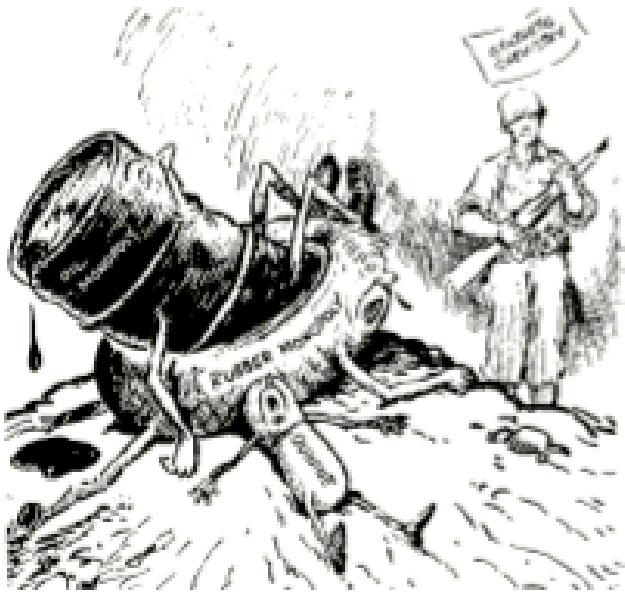


Quinine

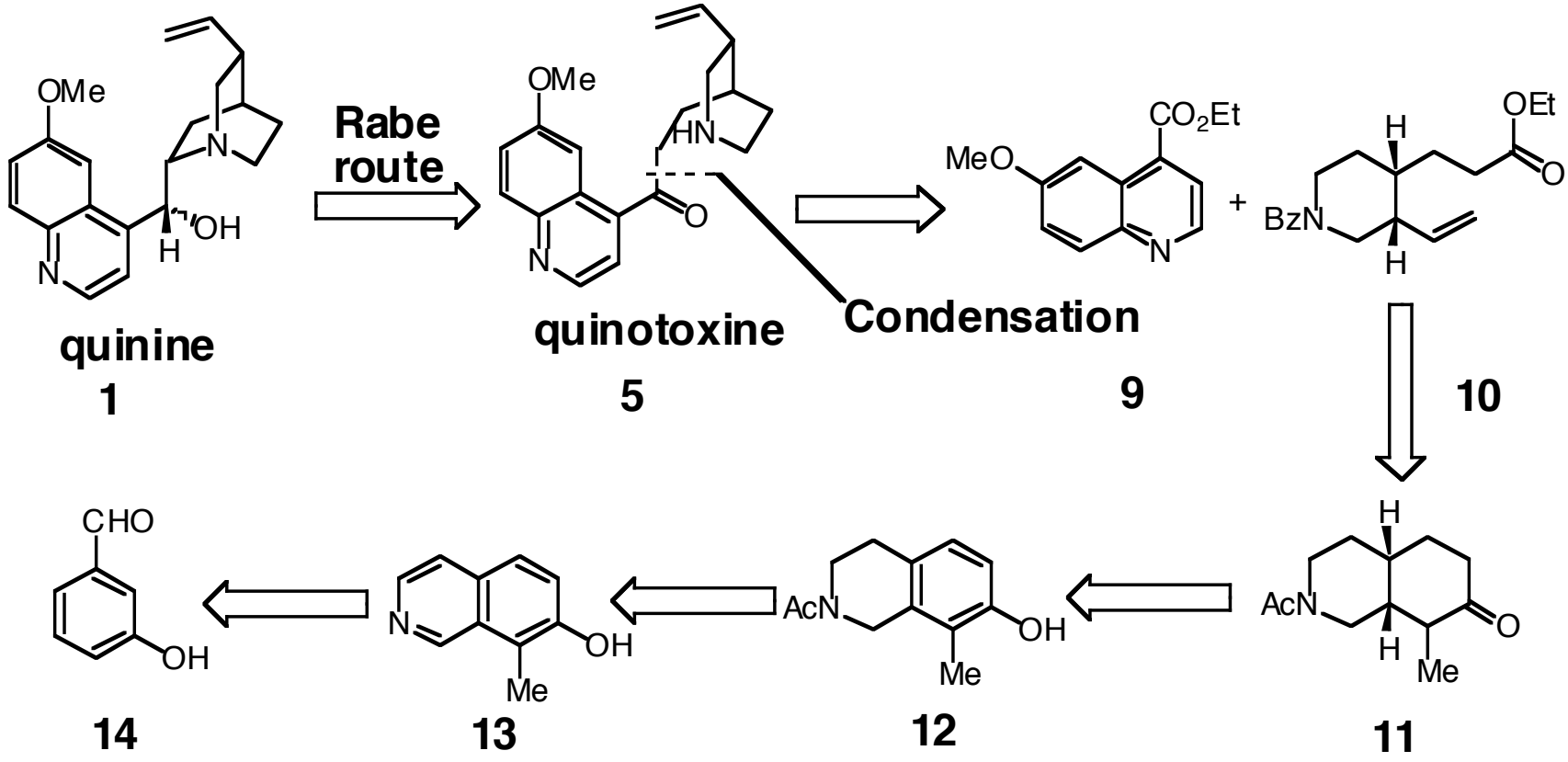
1

P. Rabe, *Chem. Ber.* 1918, *51*, 466
P. Rabe, *Chem. Ber.* 1911, *44*, 2088

Formal Synthesis of Quinine By Woodward and Doering

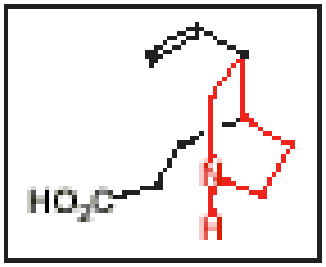


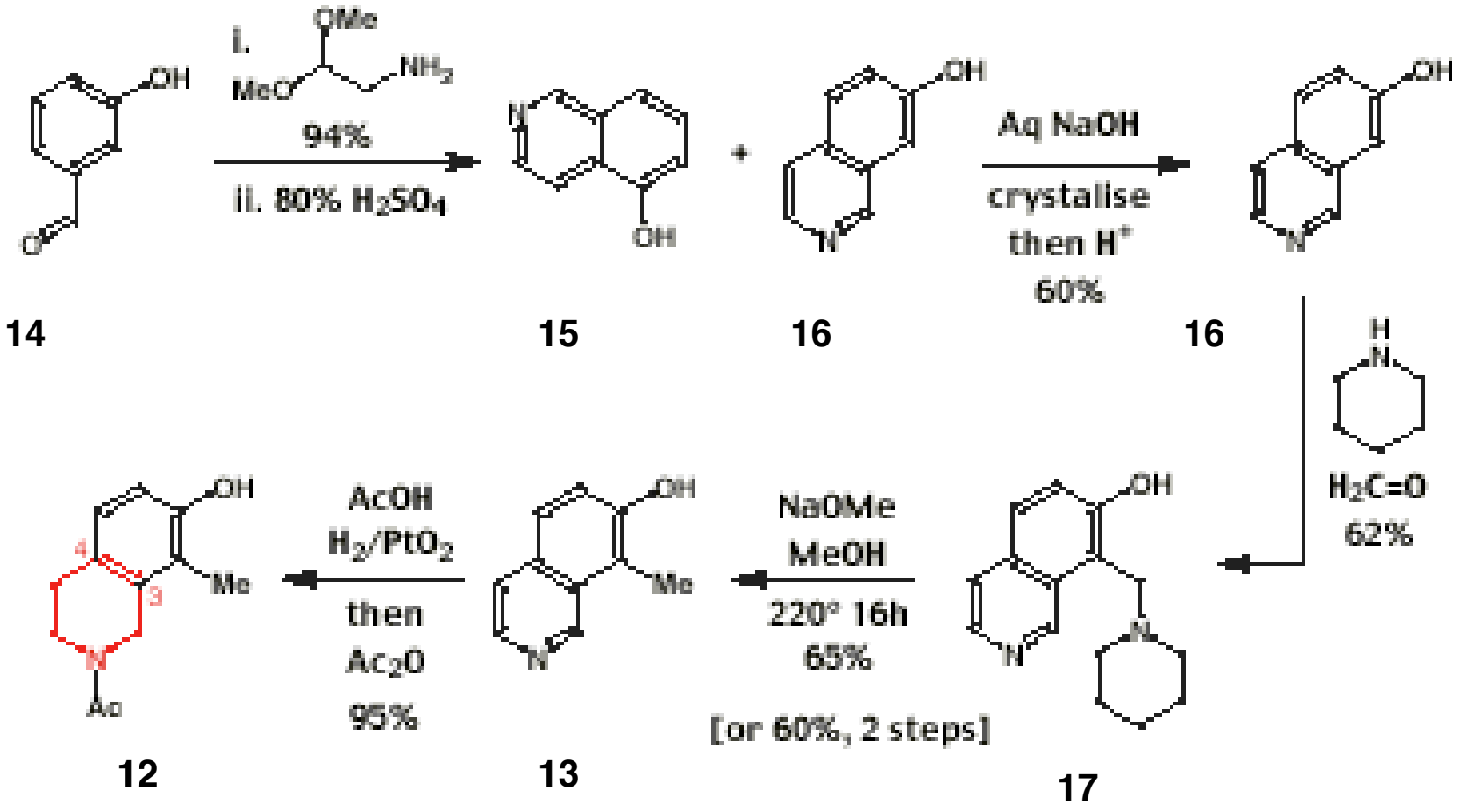
Woodward/Doering' Retrosynthetic Analysis and Strategy



J. Am. Chem. Soc. 1945, 67, 860
J. Am. Chem. Soc. 1944, 66, 849

Woodward : Synthesis of Homomeroquinene

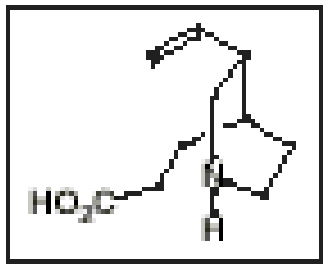


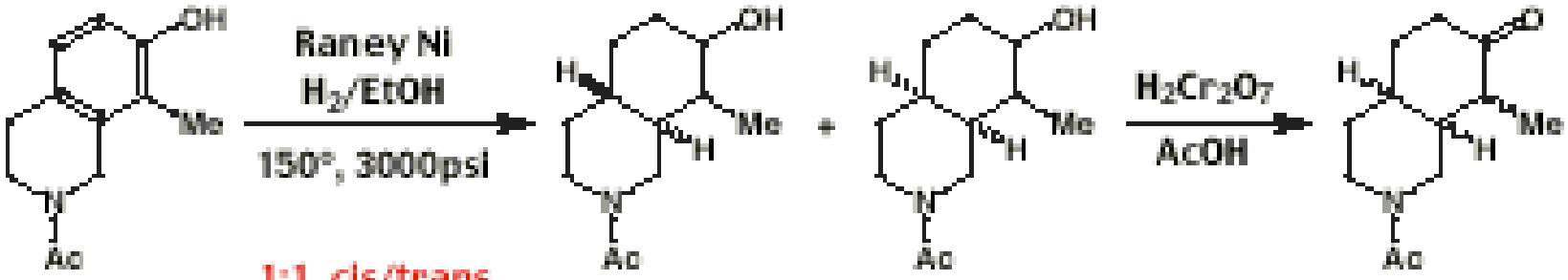


14 15 16 16 12 13 17

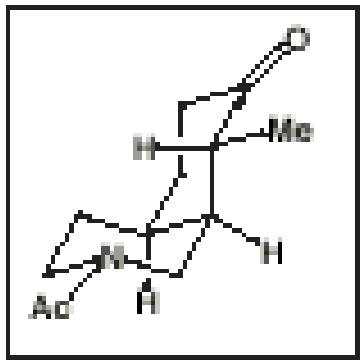
J. Am. Chem. Soc. 1944, *66*, 849
J. Am. Chem. Soc. 1945, *67*, 860

Woodward : Synthesis of Homomeroquinene

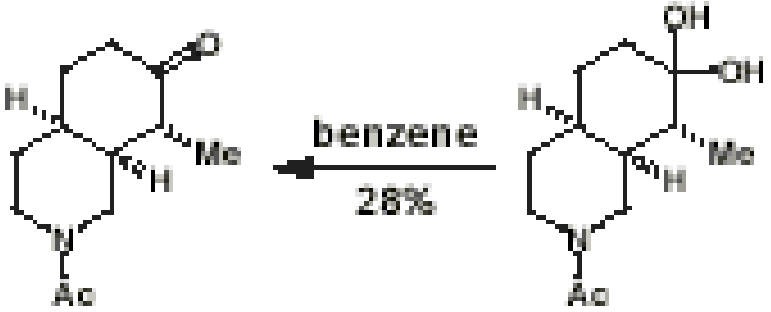




12



"...the system would assume, by facile inter-conversion through the enol, whatever configuration was most stable."

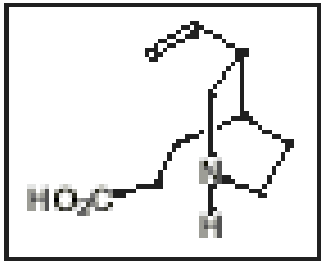


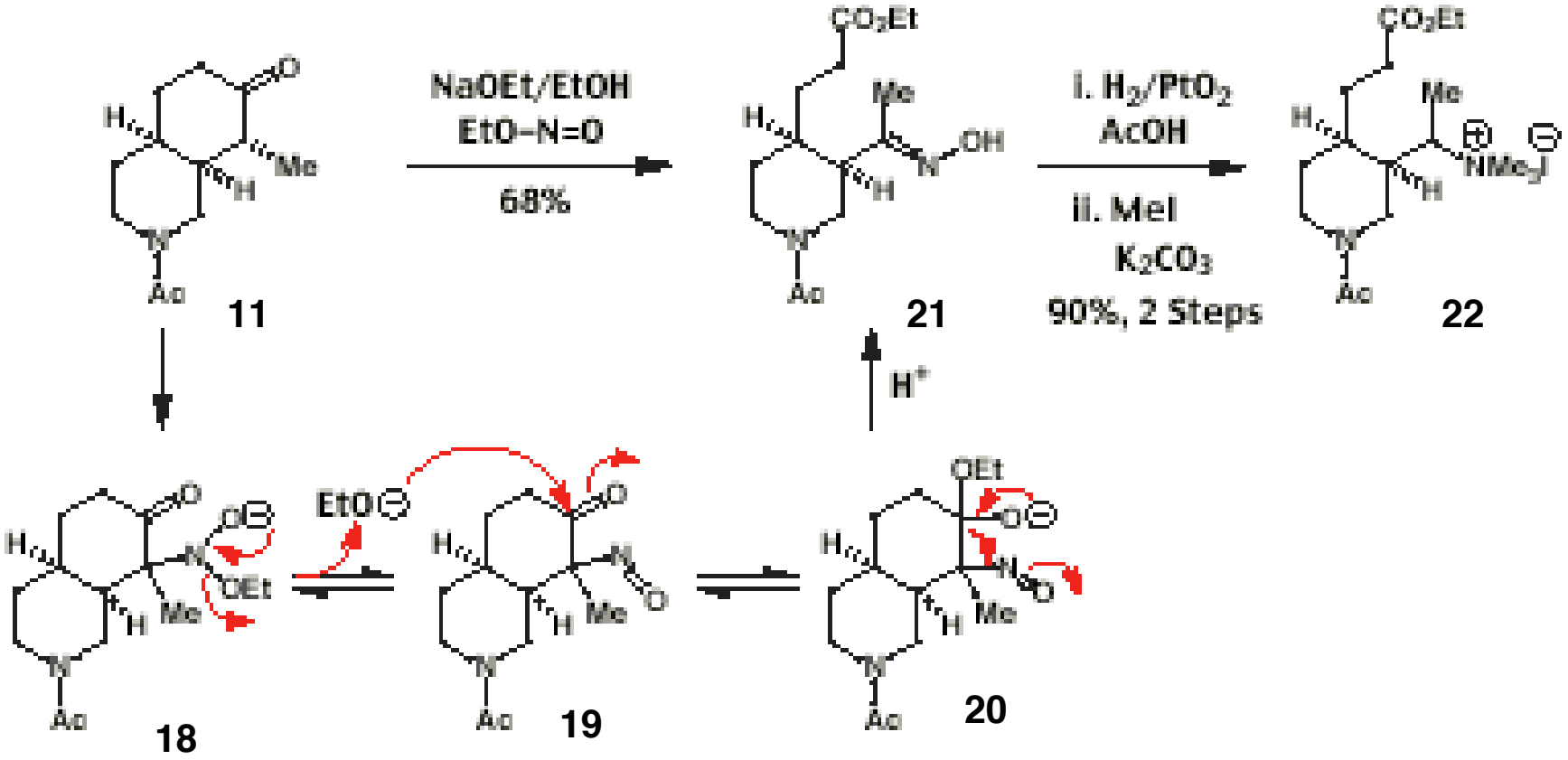
11

crystalline

J. Am. Chem. Soc. 1945, *67*, 860

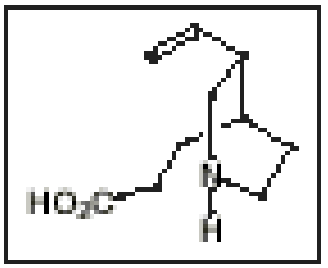
Woodward : Synthesis of Homomeroquinene

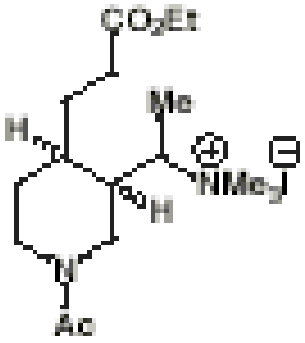




J. Am. Chem. Soc. 1945, *67*, 860

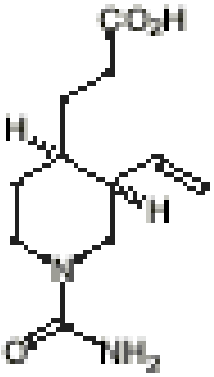
Woodward : Synthesis of Homomeroquinene





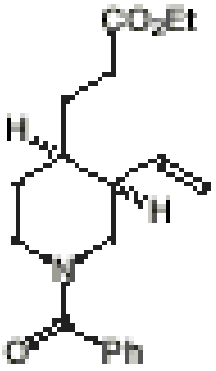
22

c. NaOH, 180°
then KCNO
40%
from oxime



23

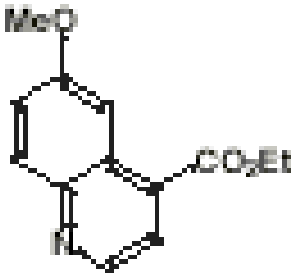
dil. HCl/EtOH
then PhCOCl, K_2CO_3
96%



10

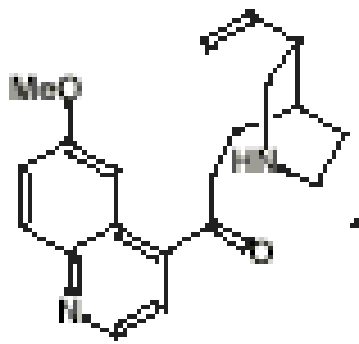
Prelog

i. NaOEt
fusion
ii. 6N HCl
50%



Rabe

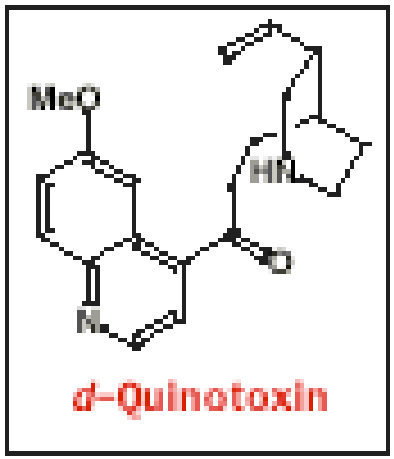
9



5 *racemic* Quinotoxin

1.4g

dibenzoyl
d-tartrate



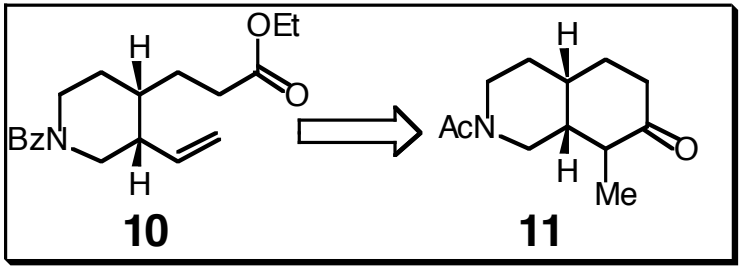
d-Quinotoxin

30 mg after
4 recrystalisations

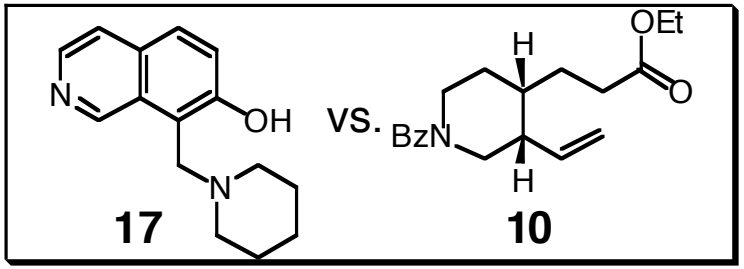
J. Am. Chem. Soc. 1945, *67*, 860

What we can learn from Woodward's Synthesis

1. The formation, modification, and eventual cleavage of carbon frameworks in cyclic settings to generate acyclic stereochemical elements

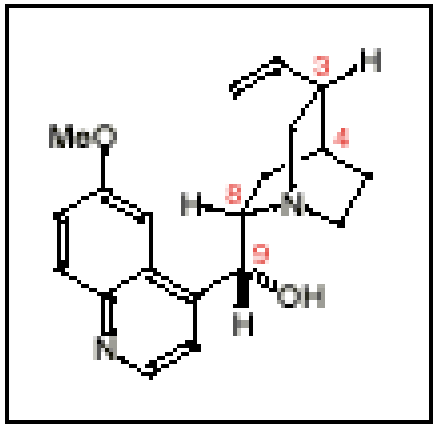


2. Rapid construction of the carbon framework in the target molecule



3. The application of nitrite ester cleavage protocol can prevent epimerization, directly afford the requisite ester side chain, and make it easy to make double bond

Summary of Quinine Syntheses



Date	Group	Steps	Yield	Reality	Key Step	
1918	Rabe	3[a]	3%	C8/9 All 4	1:1	Original C8–N disconnection
1944	Woodward	23	0.075%[b]	C8/9 All 4	1:1	Non-selective hydrogenation
1970	Uskokovic	14	5%	C8 1:1	C9 5:1	Vinyl quinoline; C9 O_2 oxidation
1970	Gates	15[c]	3%[c]	C8 1:1	C9 5:1	Wittig reagent from meroquinine
1974	Taylor	13[c]	2%[c]	C8 1:1	C9 5:1	Quinoline derived phosphorane
1978	Uskokovic	15	5%	C8 1:1	C9 High	Amino-chloroepoxide cyclisation
1978	Uskokovic	17	1%	C8 1:1	C9 High	Via quinuclidine electrophile

a : Starts from Quinotoxin

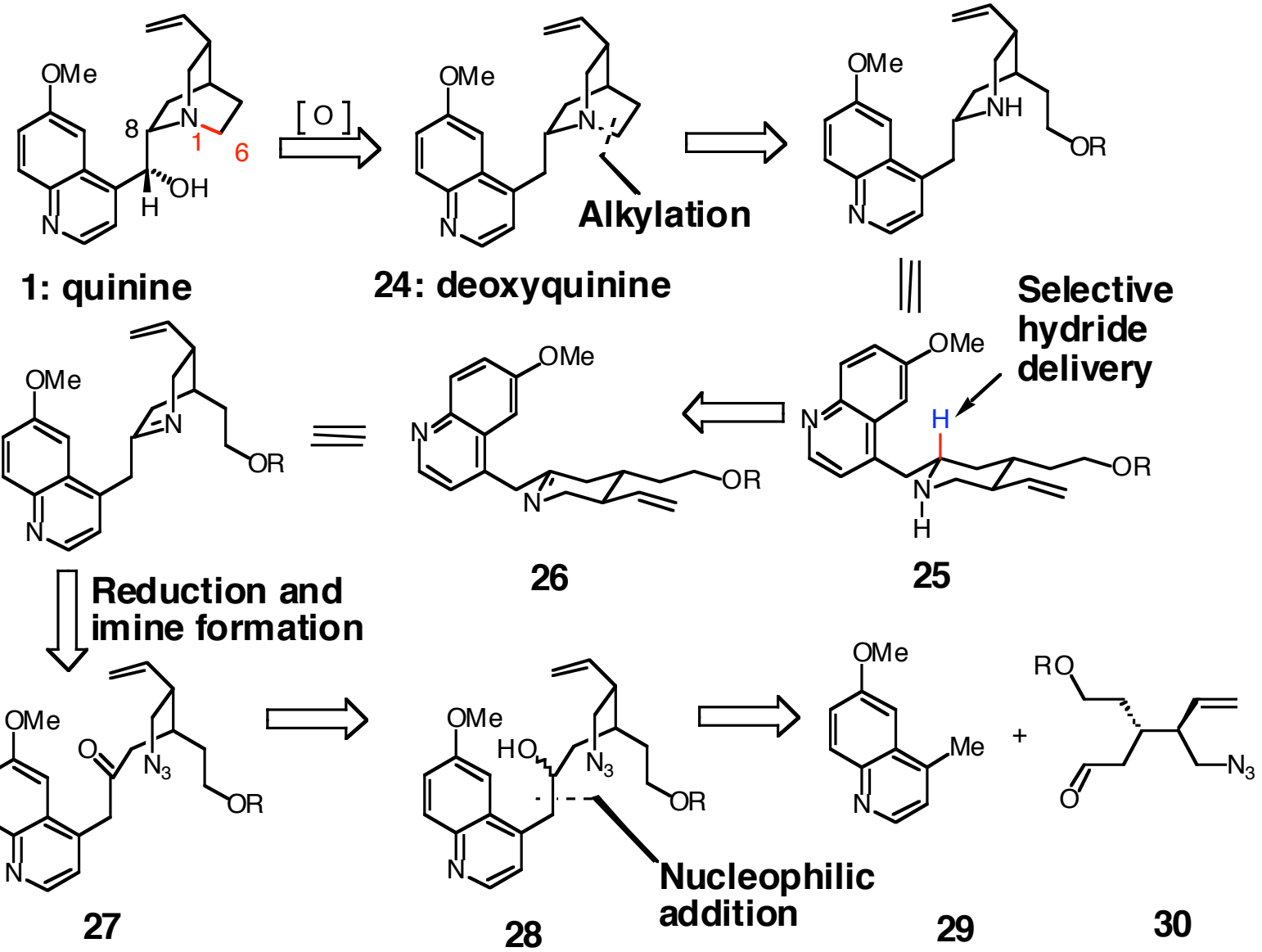
b : Uses Rabe results to complete a formal synthesis

c : Incorporated Uskokovic steps and yields for meroquinine

The First Stereoselective Total Synthesis of Quinine By Stork

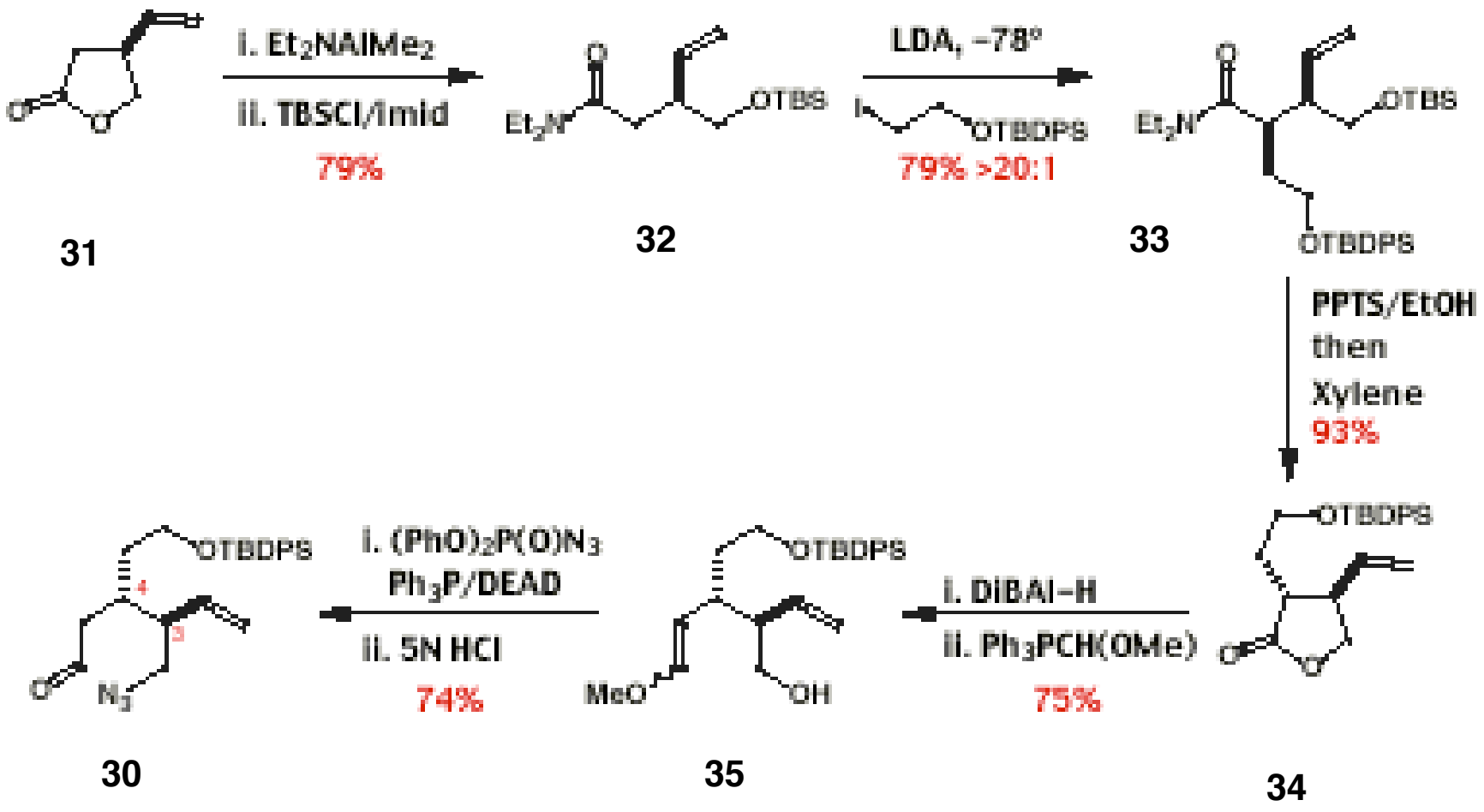
Gilbert Stork (Emeritus)
Department of Chemistry
Columbia University
Box 3118, Havemeyer Hall
New York, NY 10027
(212) 854-2178
gjs8@columbia.edu

Stork's Retrosynthetic Analysis and Strategy



J. Am. Chem. Soc. 2001, 123, 3239

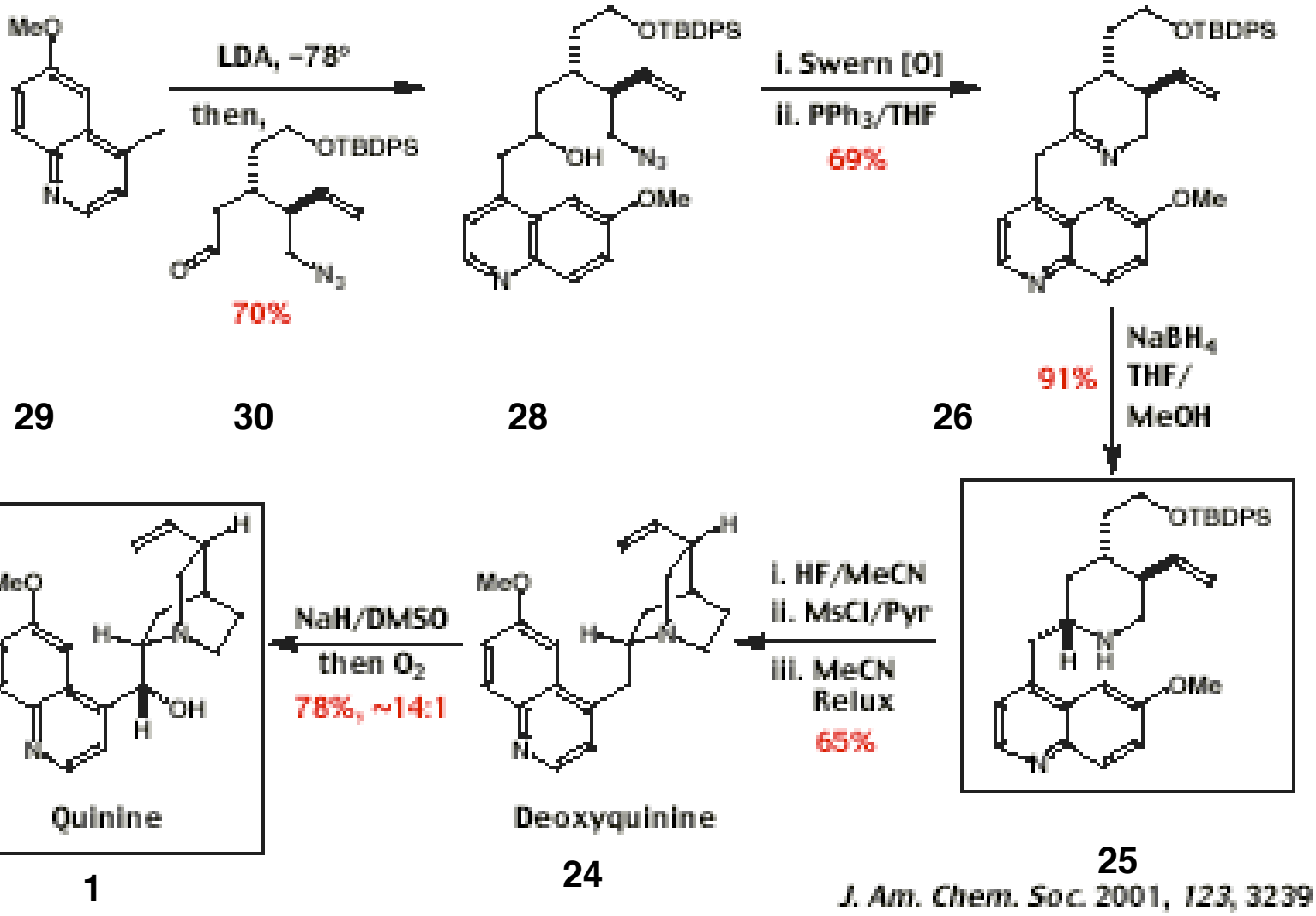
Stork : Quinine Synthesis



31 32 33 34 35 30

J. Am. Chem. Soc. 2001, *123*, 3239

Stork : Quinine Synthesis

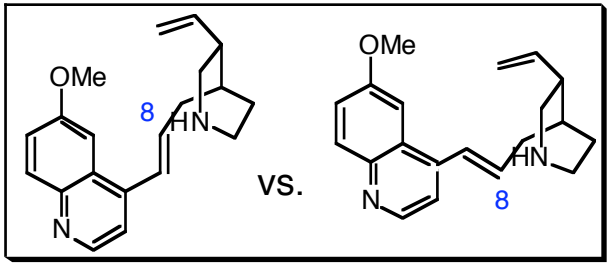


29 30 28 26 25 1 24

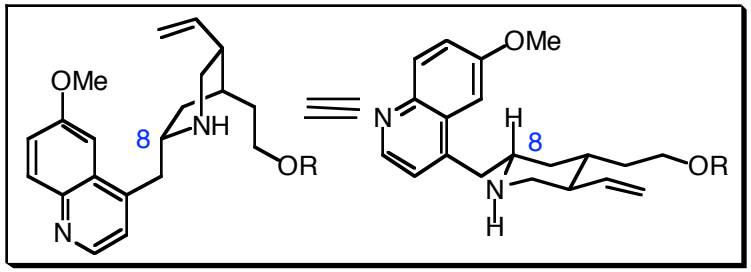
J. Am. Chem. Soc. 2001, *123*, 3239

What we can learn from Stork's Synthesis

1. Conformational analysis shows that the two pseudo-chair forms of the synthetic precursor are of similar energy, and makes the C-8 non-stereoselective.



2. Follow the words of wisdom by Robert Ireland: "All too often the most convenient way to draw a molecule on paper belies the most efficient synthetic approach." This helps to construct the C-8 stereocenter.



3. Install C-9 stereocenter by oxygenation which utilize the steric bulk of the bridgehead nitrogen in the quinuclidine ring.

Catalytic Asymmetric Synthesis of Quinine and Quinidine By Jacobsen

Eric N. Jacobsen
Sheldon Emery Professor of Chemistry

Harvard University
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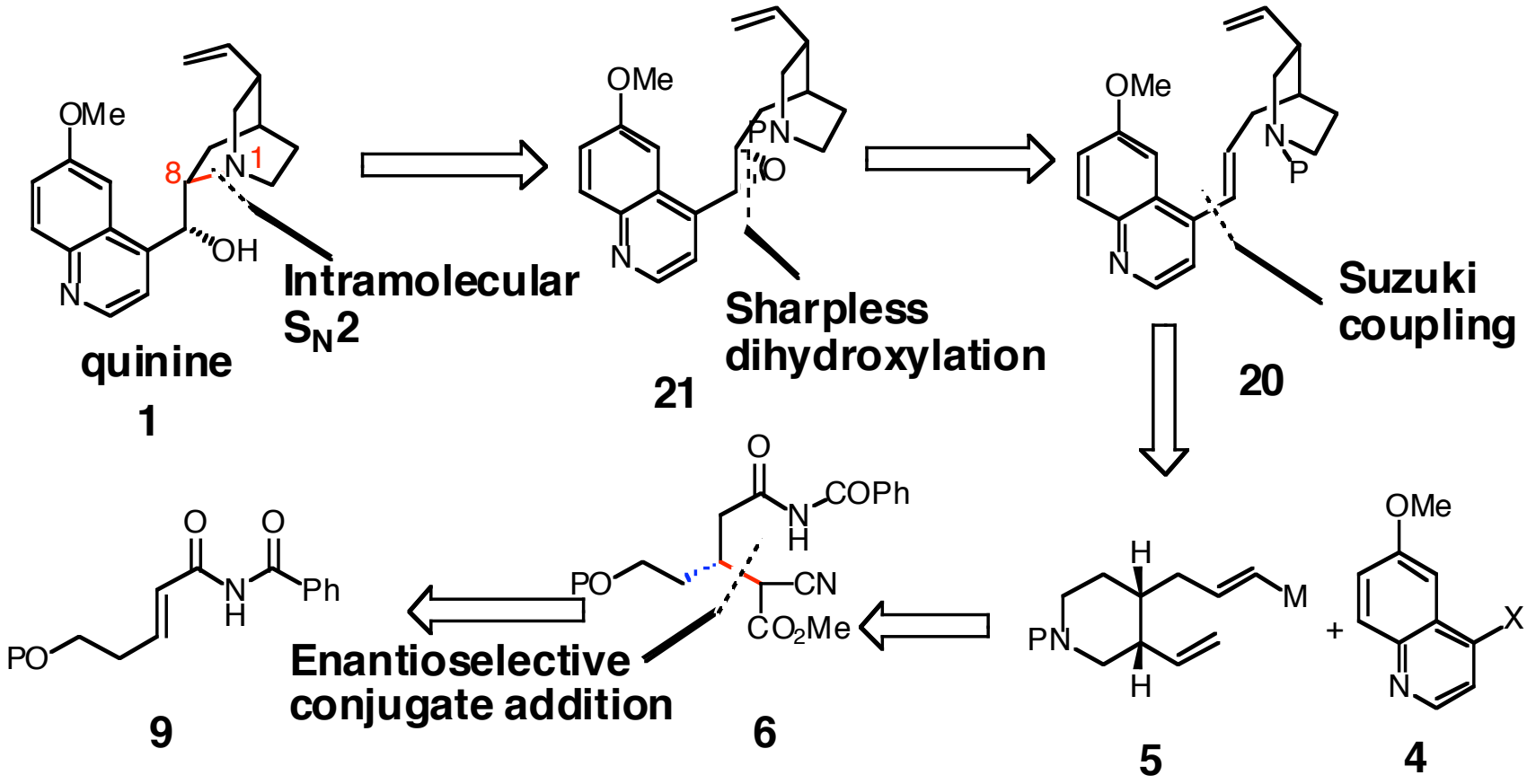
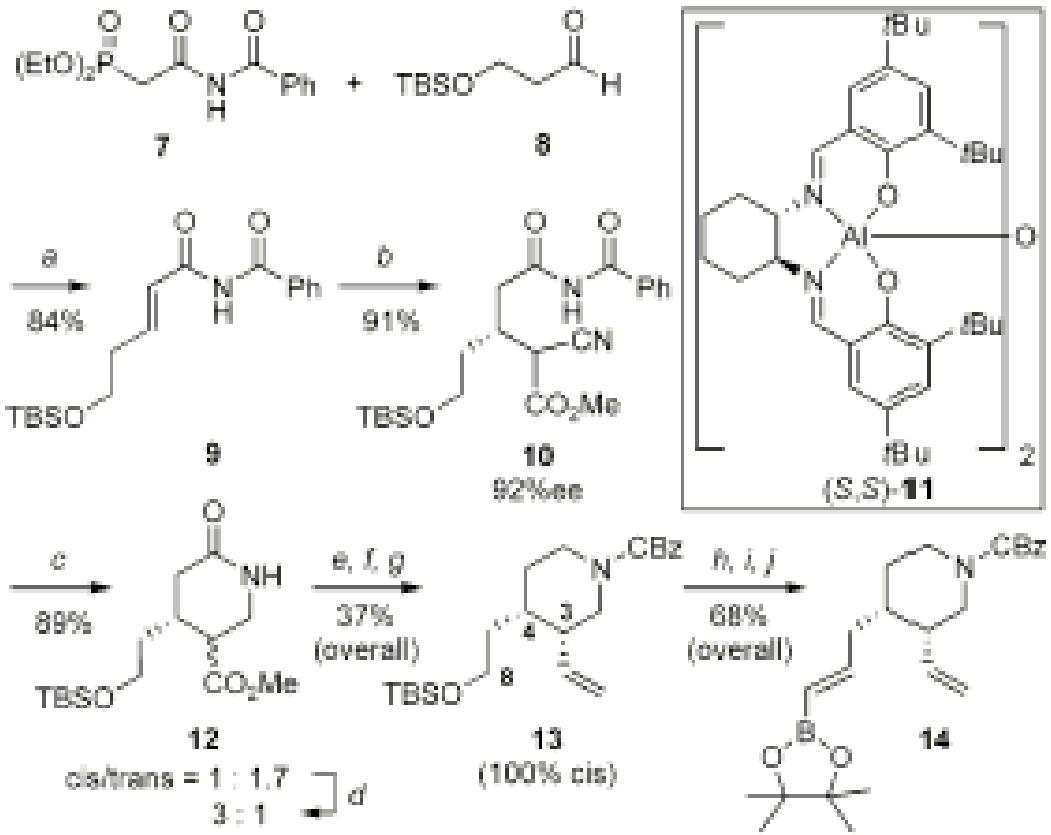
Yesterday Once More: N1-C8 Disconnection
Jacobsen's Retrosynthetic Analysis and Strategy



J. Am. Chem. Soc. 2004, ASAP

Jacobsen's Total Synthesis of Quinine



[a] Conditions: (a) *n*-BuLi, THF, −78 °C to 0 °C, >50:1 *E*/*Z*; (b) methyl cyanoacetate, (*S*,*S*)-**11** (5 mol %), *t*-BuOH, C_6H_{12}, rt; (c) Raney Ni, H_2, tol/MeOH (3:1), 650 psi, 80 °C, 12 h, 89%; (d) i. LDA, THF, −78 °C; ii. H_2O/THF (5%), −78 °C; (e) i. LAH, THF; ii. CBz_2O, TEA, CH_2Cl_2, 51%, separation of diastereomers by flash chromatography; (f) TPAP, NMO, CH_2Cl_2; (g) methyltriphenylphosphonium bromide, KO*t*Bu, THF, 0 °C, 73% (two steps); (h) TBAF, THF; (i) TPAP, NMO, CH_2Cl_2, 86% (two steps); (j) Cl_2CHB(pinacolate) (**15**), $CrCl_2$, LiI, THF, >20:1 *E*/*Z*, 79%.

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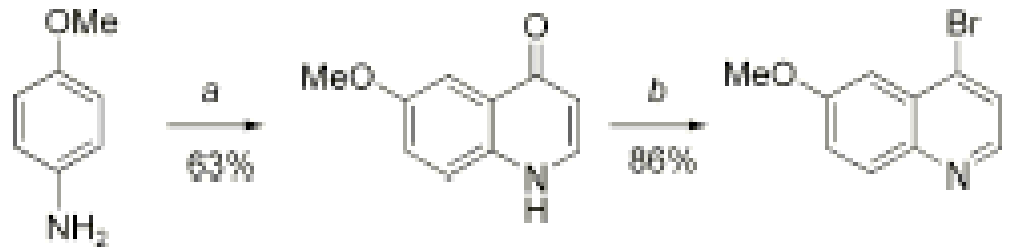
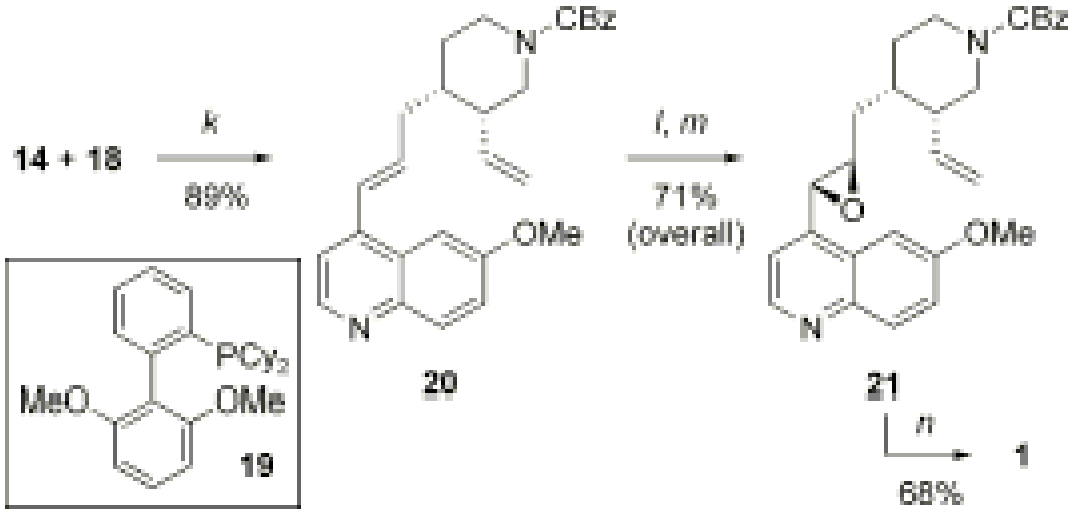
Jacobsen's Total Synthesis of Quinine



16 17 18

[a] Conditions: (a) i. ethyl propiolate, MeOH, rt, 12 h; ii. Dowtherm A, 250 °C, 30 min; (b) Ph_3PBr_2, CH_3CN, microwave, 170 °C, 15 min.



[a] Conditions: (k) $Pd(OAc)_2$, **19** (2.5 mol %), $K_3PO_4 \cdot H_2O$, THF, 16 h, rt, >20:1 *E*/*Z*, 89%; (l) ADmix-β, $CH_3SO_2NH_2$, *t*BuOH, H_2O, 0 °C, >96:4 dr, 88%; (m) i. trimethylorthoacetate, PPTS (cat), CH_2Cl_2; ii. acetyl bromide, CH_2Cl_2; iii. K_2CO_3, MeOH, 81%; (n) Et_2AlCl, thioanisole, 0 °C to rt, then microwave, 200 °C, 20 min, 68%.

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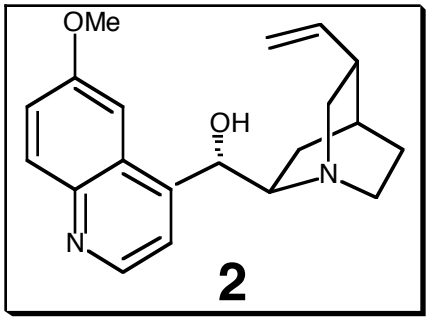
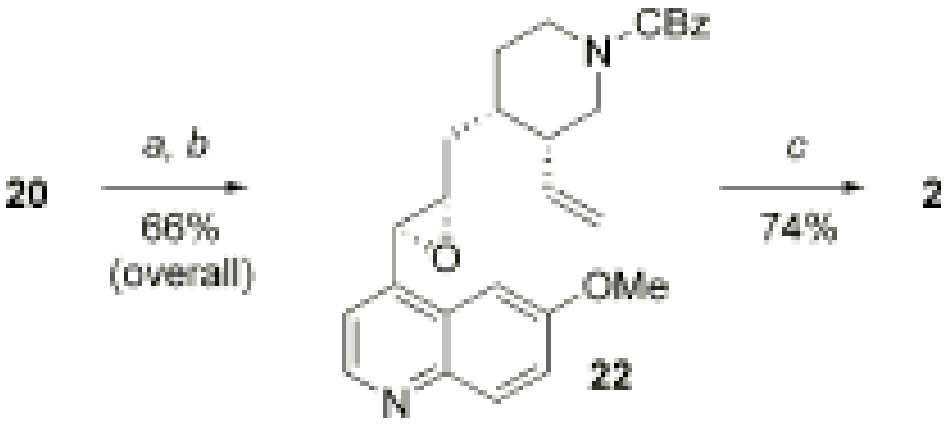
Jacobsen's Total Synthesis of Quinidine





[a] Conditions: (a) ADmix-α, $CH_3SO_2NH_2$, *t*BuOH, H_2O, 0 °C, 86%; (b) i. trimethylorthoacetate, PPTS (cat), CH_2Cl_2; ii. acetyl bromide, CH_2Cl_2; iii. K_2CO_3, MeOH, 77%; (c) i. Et_2AlCl, thioanisole, 0 °C to rt, then microwave, 200 °C, 20 min, 74%.

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What we can learn from Jacobsen's Synthesis

1. Application of recently developed (salen)Al-Catalyzed conjugate addition of methyl cyanoacetate to construct C4 stereocenter efficiently.

2. C8 & C9 chiral center can be formed by Sharpless dihydroxylation with high dr.

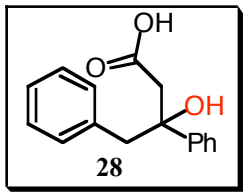
3. Yes, disconnection of N1-C8 bond provides a way to asymmetric total synthesis of quinine

Comparison of the Two Steroselective Total Synthesis of Quinine

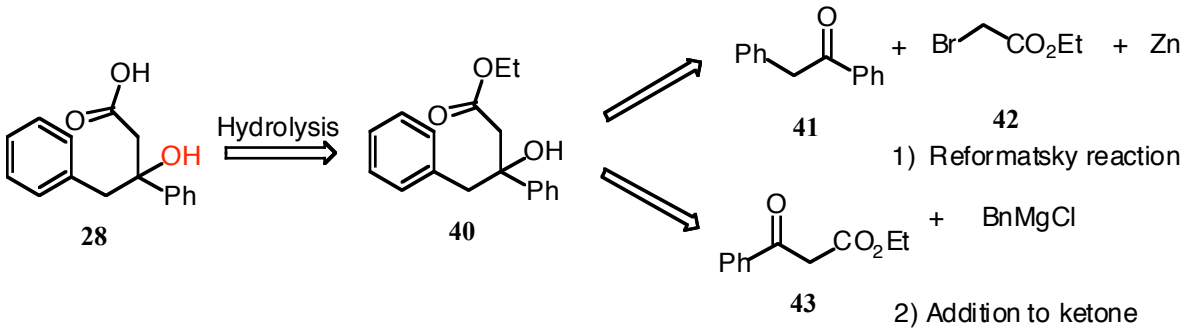
Date	Group	Step	Yield	Reality	Key Step
2001	Stork	16	7%	Stereoselective	C8 High Stereospecific reduction set C8
2004	Jacobsen	16	5%	Catalytic, Asymmetric	C4, C8 and C9 High, Sharpless dihydroxylation

Thank you and questions?

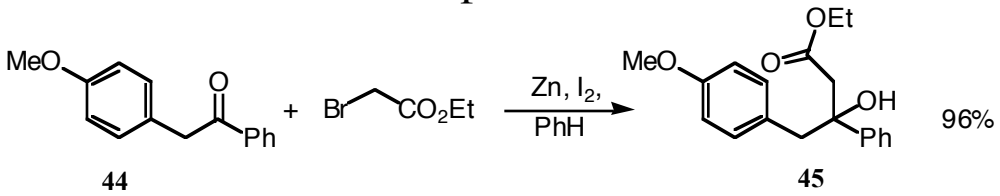
Method IV to intermediate **20**



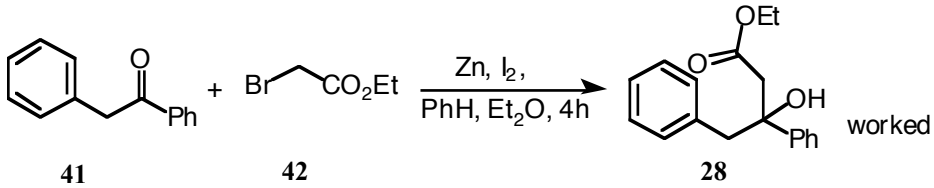
- Synthesis of **20** from b-hydroxyester



- Successful examples:

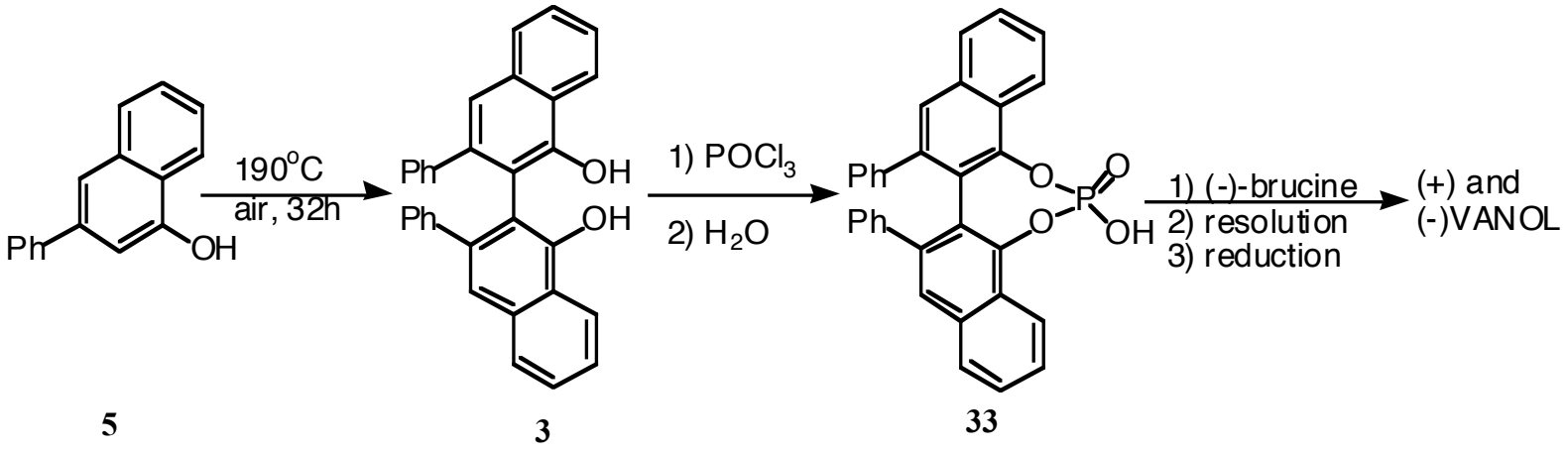


- Can this condition be used for my compound?



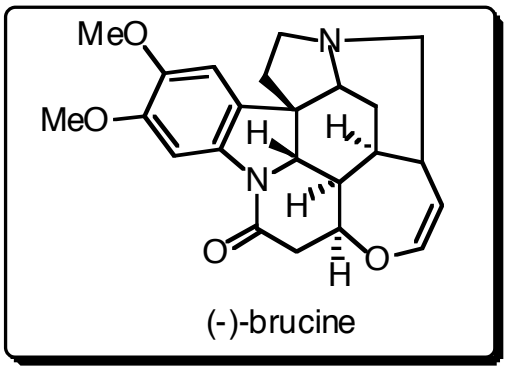
Park, O. S, Jang, B. S. *Archives of Phar.Research*, **1995,** 18, 277

Future Work: Synthesis of VANOL and Resolution



5 **3** **33**

Key point: monomer **5** must be pure for oxidative coupling



(-)-brucine

Bao, J.; Wulff, W. D. et al *J. Am. Chem. Soc.*, **1996,** *118*, 3392

Conclusions

1) A new synthetic approach of VANOL was studied. This new method provides a cheap, efficient way for large scale synthesis of VANOL ligand.

2) Conditions for Michael addition, hydrolysis and Friedel-Crafts reaction were optimized.

3) Michael addition was scaled up successfully in high yields. More work is needed to scale up Friedel-Crafts reactions.

4) Dehydrogenation reaction was studied and optimization of the conditions is in progress.

5) Some new methods have been briefly discussed.

Thank you!