Catalytic Asymmetric Total Syntheses of Quinine and Quinidine

Zhensheng Ding

January 22 2004
Chinese New Year Day

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

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


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

*Compt. Rend.* 1853, 37, 110

1854: A. Strecker established the empirical formula of Quinine as C_{20}H_{24}N_{2}O_{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

"... 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

Sir William H. Perkin

\[
\begin{align*}
\text{Me} & \quad \text{NH} \\
C_{10}H_{13}N & \quad + 3O \\
\xrightarrow{\text{Potassium Chromate}} & \\
C_{20}H_{24}N_{2}O_{2} & \quad + H_{2}O
\end{align*}
\]
Sir William H. Perkin: Easter, 1856

Actually a mixture of ortho and para

Potassium Chromate

Mauveine

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-Gelgy and ICI.

Account presented in Hofmann Memorial Lecture
J. Chem. Soc. 1896, 69, 596
Corrected Mauveine Structure
Quinine: The Issue of Stereochemistry

\[
\begin{align*}
\text{R} & = \text{H} \quad \text{Cinchonidine} \quad \alpha_D = -111 \\
\text{R} & = \text{OMe} \quad \text{Quinine} \quad \alpha_D = -158 \\
\text{R} & = \text{H} \quad \text{Cinchonine} \quad \alpha_D = +224 \\
\text{R} & = \text{OMe} \quad \text{Quinidine} \quad \alpha_D = +254
\end{align*}
\]

All 4 Compounds

- Destructive Fusion
- Caustic Potash

Meroquinene

Oxidation

\(\beta\)-Cinchololiponic Acid
\(\alpha\)-Cinchololiponic Acid

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

Quinine

Quinonone

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

\[ \text{quinine} \xrightarrow{\text{Rabe route}} \text{quinotoxine} \xrightarrow{\text{Condensation}} \text{9} \]

\[ \text{14} \xleftarrow{\text{13}} \text{12} \xleftarrow{\text{11}} \]

\[ \text{J. Am. Chem. Soc. 1945, 67, 860} \]
\[ \text{J. Am. Chem. Soc. 1944, 66, 849} \]
Woodward: Synthesis of Homomeroquinene

\[ \text{14} \xrightarrow{\text{MeO-CO-NH$_2$, 94\%}} \text{15} \xrightarrow{\text{ii. 80\% H$_2$SO$_4$}} \text{16} \xrightarrow{\text{Aq NaOH, crystallise then H$^+$, 60\%}} \text{17} \]

\[ \text{12} \xrightarrow{\text{AcOH, H$_2$/PtO$_2$, then Ac$_2$O, 95\%}} \text{13} \xrightarrow{\text{NaOMe, MeOH, 220$^\circ$C 16h, 65\%}} \text{17} \]

\[ \text{17} \xrightarrow{\text{H$_2$C=O, 62\%}} \]

*J. Am. Chem. Soc.* 1944, 66, 849
Woodward: Synthesis of Homomeroquinone

12

Raney Ni
H₂/EtOH
150°, 3000 psi

1:1, cis/trans
crystalline

H₂Cr₂O₇
AcOH

Et₂O
H₂O

benzene
28%
crystalline

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

J. Am. Chem. Soc. 1945, 67, 860
Woodward: Synthesis of Homomeroquinene

11

[Chemical reactions and structures]

J. Am. Chem. Soc. 1945, 67, 860
Woodward: Synthesis of Homomeroquinene

\[ \text{Prelog} \]

\[ \text{d-Quinotoxin} \]

30 mg after 4 recrystallisations

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

![Chemical structure](image1)

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

![Chemical structure](image2)

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

<table>
<thead>
<tr>
<th>Date</th>
<th>Group</th>
<th>Steps</th>
<th>Yield</th>
<th>Reality</th>
<th>Key Step</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918</td>
<td>Rabe</td>
<td>3(^a)</td>
<td>3%</td>
<td>C8/9 All 4</td>
<td>1:1 Original C8–N disconnection</td>
</tr>
<tr>
<td>1944</td>
<td>Woodward</td>
<td>23</td>
<td>0.075% (^b)</td>
<td>C8/9 All 4</td>
<td>1:1 Non-selective hydrogenation</td>
</tr>
<tr>
<td>1970</td>
<td>Uskokovic</td>
<td>14</td>
<td>5%</td>
<td>C8 1:1</td>
<td>C9 5:1 Vinyl quinoline; C9 O₂ oxidation</td>
</tr>
<tr>
<td>1970</td>
<td>Gates</td>
<td>15(^c)</td>
<td>3%(^c)</td>
<td>C8 1:1</td>
<td>C9 5:1 Wittig reagent from meroquinine</td>
</tr>
<tr>
<td>1974</td>
<td>Taylor</td>
<td>13(^c)</td>
<td>2%(^c)</td>
<td>C8 1:1</td>
<td>C9 5:1 Quinoline derived phosphorane</td>
</tr>
<tr>
<td>1978</td>
<td>Uskokovic</td>
<td>15</td>
<td>5%</td>
<td>C8 1:1</td>
<td>C9 High Amino–chloroepoxide cyclisation</td>
</tr>
<tr>
<td>1978</td>
<td>Uskokovic</td>
<td>17</td>
<td>1%</td>
<td>C8 1:1</td>
<td>C9 High Via quinuclidine electrophile</td>
</tr>
</tbody>
</table>

\(^a\): 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

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New York, NY 10027
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Stork’s Retrosynthetic Analysis and Strategy

1: quinine

[O] →

24: deoxyquinine

Alkylation

Selective hydride delivery

Reduction and imine formation

26

25

27

28

Nucleophilic addition

J. Am. Chem. Soc. 2001, 123, 3239
Stork: Quinine Synthesis

31

\[ \text{Et}_2\text{NAIMe}_2 \]
\[ \text{TBSCI/imid} \]
\[ \text{79\%} \]

32

\[ \text{LDA, -78°} \]
\[ \text{79\% >20:1} \]

33

\[ \text{PPTS/EtOH then Xylene 93\%} \]

30

\[ \text{i. (PhO)}_2\text{P(O)}_\text{N}_3 \]
\[ \text{Ph}_3\text{P/DEAD} \]
\[ \text{ii. 5N HCl} \]
\[ \text{74\%} \]

34

\[ \text{i. DIBAI-H} \]
\[ \text{ii. Ph}_3\text{PCH(OMe)} \]

35

\[ \text{MeO} \]
\[ \text{OH} \]
\[ \text{75\%} \]

J. Am. Chem. Soc. 2001, 123, 3239
Stork: Quinine Synthesis

29

LDA, $-78^\circ$
then, OTBDPS

70%

30

28

i. Swern [O]
ii. PPh$_3$/THF
69%

26

NaBH$_4$
THF/MeOH
91%

25

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

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Sheldon Emery Professor of Chemistry

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Department of Chemistry, 12 Oxford Street
Cambridge, MA 02138
(617) 496-3690 (Assistant)
Yesterday Once More: N1-C8 Disconnection
Jacobsen’s Retrosynthetic Analysis and Strategy

1. Intramolecular $S_n\text{2}$
2. Sharpless dihydroxylation
3. Suzuki coupling

Enantioselective conjugate addition

J. Am. Chem. Soc. 2004, ASAP
Jacobsen’s Total Synthesis of Quinine

$\text{O} \text{H} \text{N} \text{P(O)(OEt)$_2$} \text{Ph} + \text{TBSO} \text{Ph} \text{CH}_2 \text{CO}_2 \text{Me}$

1. $a \rightarrow \text{CO}_2 \text{Me} \text{N} \text{H} \text{Ph} \text{C}_{\text{cis}} \text{trans} = 1:1.7$ (yield: $84\%$)
2. $b \rightarrow \text{Ph} \text{CN} \text{H} \text{N} \text{Ph} \text{CO}_2 \text{Me}$ (yield: $91\%$)
3. $c \rightarrow \text{Ph} \text{CO}_2 \text{Me}$ (yield: $89\%$)
4. $e, f, g \rightarrow \text{Ph} \text{CO}_2 \text{Me}$ (overall yield: $37\%$)
5. $h, i, j \rightarrow \text{Ph} \text{CO}_2 \text{Me}$ (overall yield: $68\%$)

$^a$ Conditions: (a) $n$-BuLi, THF, $-78^\circ\text{C}$ to $0^\circ\text{C}$, $>50:1$ $E/Z$; (b) methyl cyanoacetate, $(S, S)$-11 (5 mol %), $t$-BuOH, C$_6$H$_{12}$, rt; (c) Raney Ni, H$_2$, tol/MeOH (3:1), 650 psi, 80 $^\circ\text{C}$, 12 h, 89%; (d) i. LDA, THF, $-78^\circ\text{C}$; ii. H$_2$O/THF (5%), $-78^\circ\text{C}$; (e) i. LAH, THF; ii. CB$_2$O, TEA, CH$_2$Cl$_2$, 51%, separation of diastereomers by flash chromatography; (f) TPAP, NMO, CH$_2$Cl$_2$; (g) methyltriphenylphosphonium bromide, KO$_2$Bu, THF, 0 $^\circ\text{C}$, 73% (two steps); (h) TBAF, THF; (i) TPAP, NMO, CH$_2$Cl$_2$, 86% (two steps); (j) Cl$_2$CHB(pinacolate) (15), CrCl$_2$, LiI, THF, >20:1 $E/Z$, 79%.

Jacobsen’s Total Synthesis of Quinine

\[ \text{Conditions: (a) i. ethyl propiolate, MeOH, rt, 12 h; ii. Dowtherm A, 250 \degree C, 30 min; (b) Ph}_3\text{PBr}_2, \text{CH}_3\text{CN, microwave, 170 \degree C, 15 min.} \]

\[ \text{Conditions: (k) Pd(OAc)}_2, 19 (2.5 \text{ mol \%}), \text{K}_3\text{PO}_4\cdot\text{H}_2\text{O, THF, 16 h, rt, } >20:1 \text{ E/Z, 89\%; (l) ADmix-} \beta, \text{CH}_3\text{SO}_2\text{NH}_2, \text{tBuOH, H}_2\text{O, 0 \degree C, } >96:4 \text{ dr, 88\%; (m) i. trimethylorthoacetate, PPTS (cat), CH}_2\text{Cl}_2; \text{ii. acetyl bromide, CH}_2\text{Cl}_2; \text{iii. K}_2\text{CO}_3, \text{MeOH, 81\%; (n) Et}_2\text{AlCl, thioanisole, 0 \degree C to rt, then microwave, 200 \degree C, 20 min, 68\%.} \]
Jacobsen’s Total Synthesis of Quinidine

\[ \text{Conditions: (a) ADmix-} \alpha, \text{ CH}_3\text{SO}_2\text{NH}_2, \text{ tBuOH, H}_2\text{O, 0 }^\circ\text{C, 86%;}\]

\[\text{(b) i. trimethylorthoacetate, PPTS (cat), CH}_2\text{Cl}_2; \text{ ii. acetyl bromide, CH}_2\text{Cl}_2;\]

\[\text{iii. K}_2\text{CO}_3, \text{ MeOH, 77%; (c) i. Et}_2\text{AlCl, thioanisole, 0 }^\circ\text{C to rt, then microwave, 200 }^\circ\text{C, 20 min, 74%.}\]
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

<table>
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<th>Step</th>
<th>Yield</th>
<th>Reality</th>
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</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Stork</td>
<td>16</td>
<td>7%</td>
<td>Stereoselective</td>
<td>C8 High Stereospecific reduction set C8</td>
</tr>
<tr>
<td>2004</td>
<td>Jacobsen</td>
<td>16</td>
<td>5%</td>
<td>Catalytic, Asymmetric</td>
<td>C4, C8 and C9 High, Sharpless dihydroxylation</td>
</tr>
</tbody>
</table>
Method IV to intermediate 20

- Synthesis of 20 from b-hydroxyester

\[
\text{Hydrolysis} \quad \xrightarrow{\text{Reformatsky reaction}} \quad \text{Addition to ketone}
\]

- Successful examples:

\[
\text{MeO} + \text{BrCO}_2\text{Et} \quad \xrightarrow{\text{Zn, I}_2, \text{PhH}} \quad \text{MeO} + \text{EtO} \quad 96\%
\]

- Can this condition be used for my compound?

\[
\text{EtO} + \text{BrCO}_2\text{Et} \quad \xrightarrow{\text{Zn, I}_2, \text{PhH, Et}_2\text{O}, 4h} \quad \text{worked}
\]

Future Work: Synthesis of VANOL and Resolution

Key point: monomer 5 must be pure for oxidative coupling

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!