Massachusetts Institute of Technology

Organic Chemistry 5.511

October 31, 2007
Prof. Rick L. Danheiser

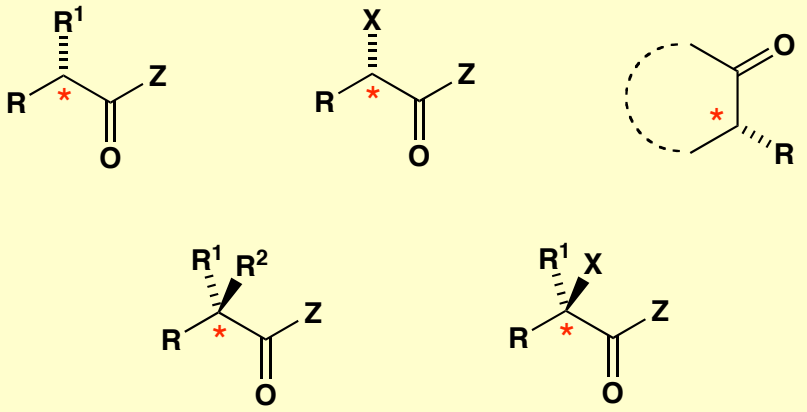
Lecture 9

Unit 3

Stereocontrolled Alkylation

and Related Electrophilic Substitution Strategies

Key Retrons



Outline of Unit

I. Intrinsic Stereochemistry

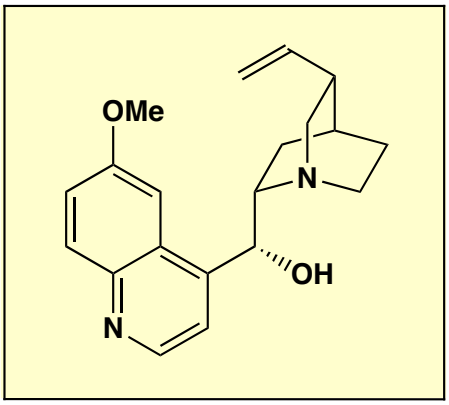
II. Substrate Control: Asymmetric Induction by Molecular Framework

III. Substrate Control: Asymmetric Induction by Chiral Auxiliaries

IV. Reagent Control Strategies: Chiral Electrophiles

V. Catalytic Methods

Case Study **Quinine**

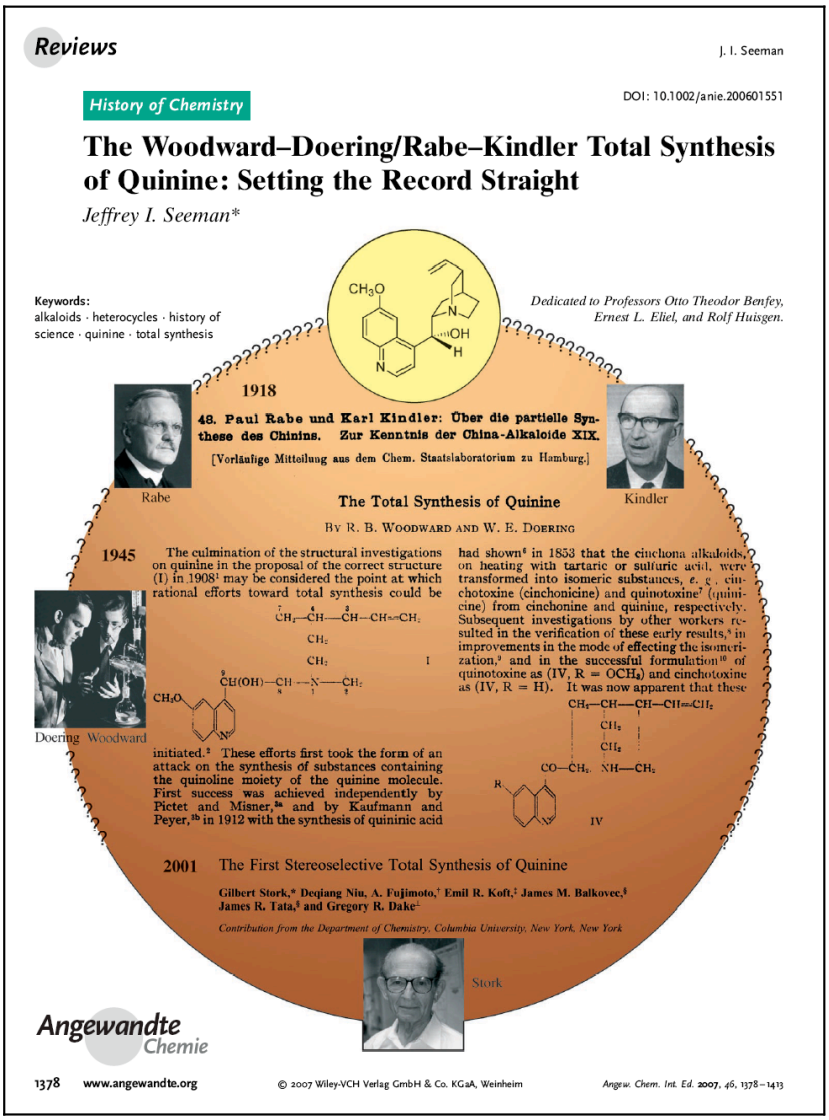


"Two 27-year-old chemists, Robert Burns Woodward and William von Eggers Doering announced last month that they had made quinine by a laboratory process from synthetic chemicals derived from coal tar. This is the first time quinine has been produced outside the life processes of the tropical Cinchona tree ... Although responsible war agencies have not yet decided on its necessity, the Woodward–Doering synthesis does open the possibility of mass production of quinine ... "[48] (from *Life* magazine; included in the article were photographs of crystals of "synthetic quinotoxine" and "quinine ... in actual crystals.")

"a notable peace victory ... of great benefit to mankind ... a victory for science ... "[56] (from the Virginia *Gazette*, Alexandria)

"a promise of life and health for millions now suffering and dying from malaria"[57] (from the Philadelphia *Inquirer*)

"one of the greatest scientific achievements of our time"[59] (from the Kentucky *Messenger*, Owensboro)



Reviews

J. I. Seeman

History of Chemistry

DOI: 10.1002/anie.200601551

The Woodward–Doering/Rabe–Kindler Total Synthesis of Quinine: Setting the Record Straight

*Jeffrey I. Seeman**

Keywords:
alkaloids · heterocycles · history of science · quinine · total synthesis

Dedicated to Professors Otto Theodor Benfey, Ernest L. Eliel, and Rolf Huisgen.

1918

48. Paul Rabe und Karl Kindler: Über die partielle Synthese des Chinins. Zur Kenntnis der China-Alkaloide XIX.

[Vorläufige Mitteilung aus dem Chem. Staatslaboratorium zu Hamburg.]

Rabe

Kindler

The Total Synthesis of Quinine

By R. B. Woodward and W. E. Doering

1945

The culmination of the structural investigations on quinine in the proposal of the correct structure (I) in 1908[1] may be considered the point at which rational efforts toward total synthesis could be

had shown[6] in 1853 that the cinchona alkaloids, on heating with tartaric or sulfuric acid, were transformed into isomeric substances, *e. g.*, cinchotoxine (cinchonicine) and quinotoxine[7] (quinicine) from cinchonine and quinine, respectively. Subsequent investigations by other workers resulted in the verification of these early results,[8] in improvements in the mode of effecting the isomerization,[9] and in the successful formulation[10] of quinotoxine as (IV, R = OCH_3) and cinchotoxine as (IV, R = H). It was now apparent that these

Doering Woodward

initiated.[2] These efforts first took the form of an attack on the synthesis of substances containing the quinoline moiety of the quinine molecule. First success was achieved independently by Pictet and Misner,[3a] and by Kaufmann and Peyer,[3b] in 1912 with the synthesis of quininic acid

IV

2001 The First Stereoselective Total Synthesis of Quinine

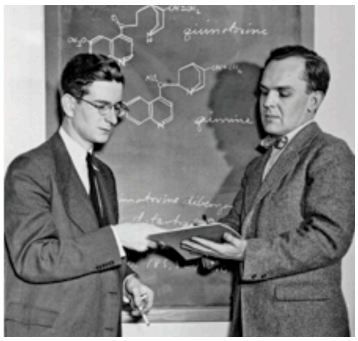
Gilbert Stork,* Deqiang Niu, A. Fujimoto,† Emil R. Koft,‡ James M. Balkovec,§ James R. Tata,§ and Gregory R. Dake‖

Contribution from the Department of Chemistry, Columbia University, New York, New York

Stork

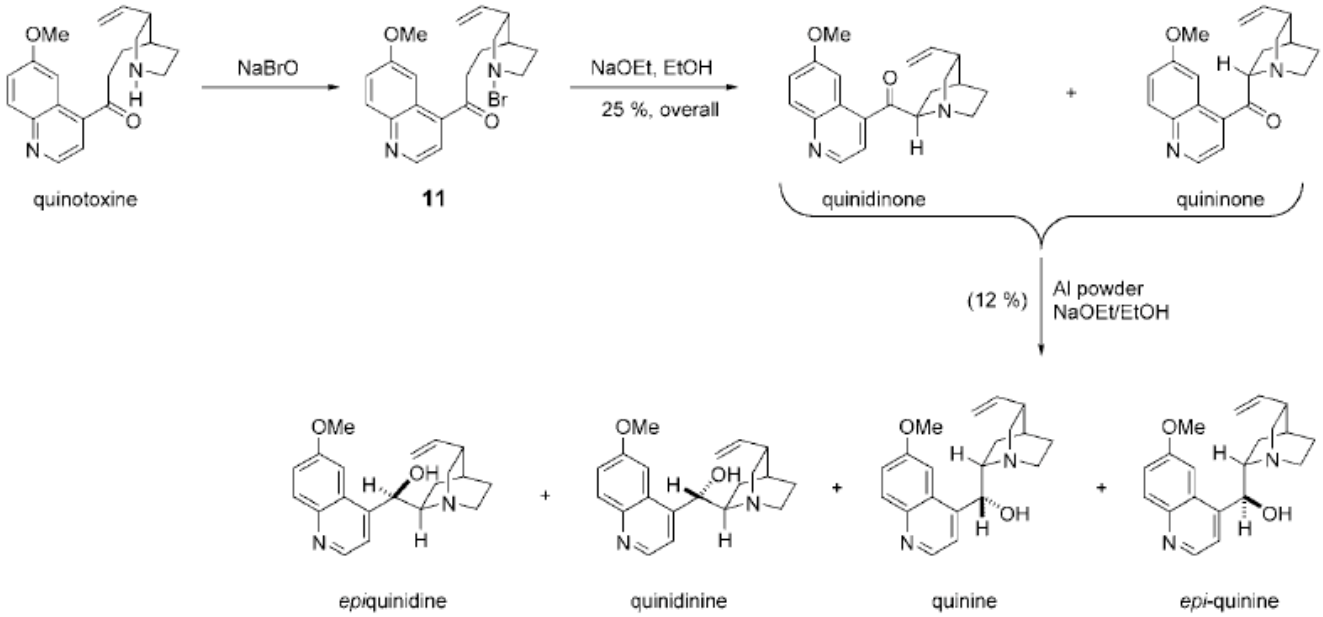
Angewandte Chemie

1378 www.angewandte.org © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim *Angew. Chem. Int. Ed.* **2007**, *46*, 1378–1413



Woodward and Doering
1944

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



Scheme 5. Apparent course of synthesis of quinine developed by Rabe and Kindler in 1918.

Reported conversion of quinotoxine (prepared by acid degradation of quinine) to quinine reported by Rabe and Kindler in 1918

Gilbert Stork
(1921 -)

1944

2007

J. Am. Chem. Soc. **2001,** *123,* 3239−3242

The First Stereoselective Total Synthesis of Quinine

Gilbert Stork,* Deqiang Niu, A. Fujimoto,† Emil R. Koft,‡ James M. Balkovec,§ James R. Tata,§ and Gregory R. Dake⊥

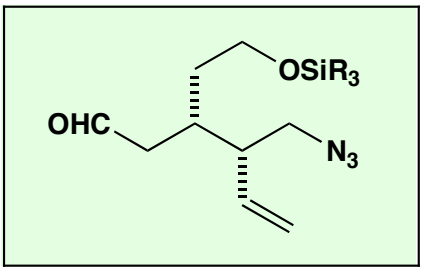
Contribution from the Department of Chemistry, Columbia University, New York, New York 10027

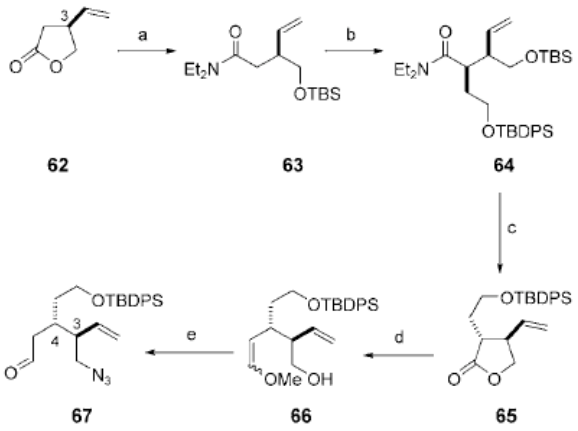
"An inexperienced observer of a great performance might leave with a view that there are no new steps. But one schooled in the field will see the exquisite choreography, the remarkable timing, the efficiency of execution, and the economy of movement - and leave inspired."

Paul Wender in C&EN (May 7, 2001, page 56) commenting on Stork's synthesis of quinine

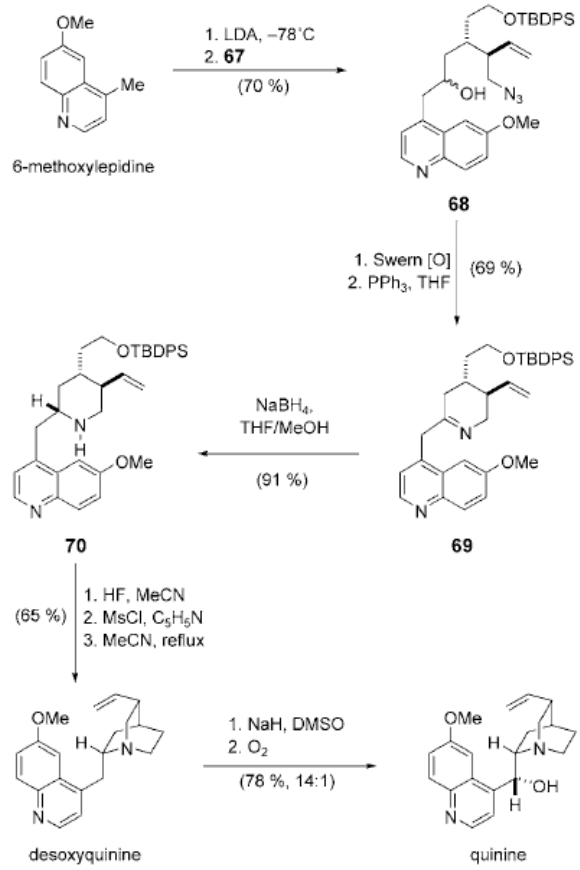
Case Study

"The first Stereoselective Synthesis of Quinine"
G. Stork et al. *J. Am. Chem. Soc.* **2001**, *123*, 3239





Scheme 20. Synthesis of quinine by Stork et al. by chemical manipulation of Taniguchi's lactone. Reagents and conditions: a) 1. Et_2NAlMe_2; 2. TBSCl, imidazole (79%); b) 1. LDA, −78°C; 2. $ICH_2CH_2OTBDPS$ (79%, 20:1); c) 1. PPTS, EtOH; 2. xylene (93%), d) 1. DIBAL-H; 2. $Ph_3PCH(OMe)$ (93%); e) 1. $(PhO)_2P(O)N_3$; PPh_3, DEAD; 2. 5N HCl (74%). DEAD = diethylazodicarboxylate, PPTS = pyridinium *p*-toluenesulfonate, TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl.



Scheme 21. Synthesis of quinine by Stork et al.: The final steps.