

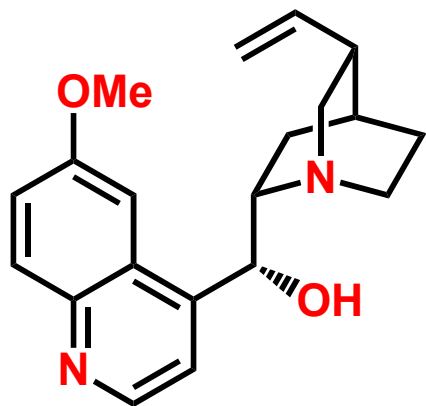
Total Synthesis of Quinine



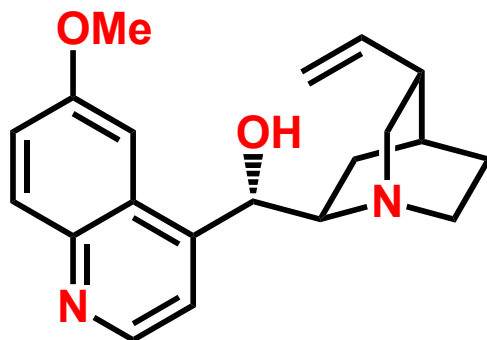
Krishna P Kaliappan
Professor of Chemistry, IIT Bombay

CH-845 Course on Organic Synthesis

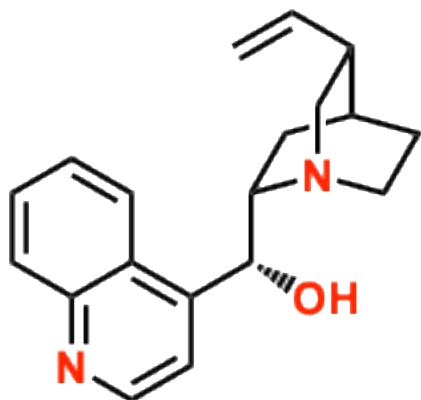
Discovery of Quinine



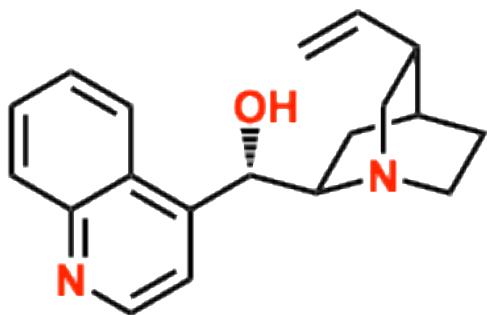
Quinine



Quinidine



Cinchonidine



Cinchonine

Cinchona alkaloids are found in the bark of **Cinchona** and **Remijia** species, which are evergreen trees originally part of the high forest in the eastern slopes of the **Ande** mountains from **Venezuela** to **Bolivia**.

Natives called them as *quina-quina* (bark of barks)

They used the **bark** for the treatment of fever long before the Spanish arrived.

Spanish Viceroy's wife in **Peru** was miraculously cured from **malaria** by the extracts from **Cinchona** bark

This observation has brought **bark** of **Cinchona** trees to **Europe**, especially to **Rome** which was considered as the **Malaria** capital.



Quinine



Quinine was **first used** in the form of extracts to **treat malaria** officially in Rome **in 1631**.

Quinine was **isolated and named in 1820** by French researchers **Pierre Joseph Pelletier** and **Joseph Bienaime caventou**.

British succeeded in Cinchona plantations in **Sri Lanka and India**

Dutch succeeded the same in **Java and Indonesia**, which later became the main hub for exporting quinine.

Quinine acts as an antipyretic, antimalarial, analgesic, anti-inflammatory agent.

Native of **Peru and Bolivia** but cultivated mainly in **Java**

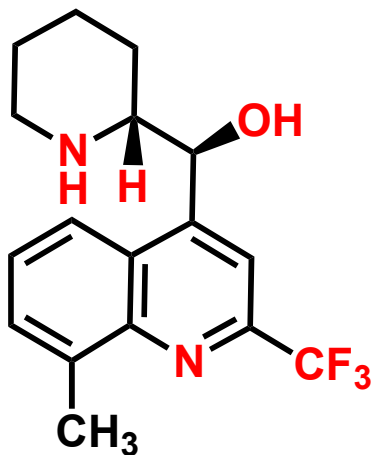
Cultivated bark contains **7-10% of alkaloid**, of which **70% is quinine**.

US imports **~70 tons of quinine annually**.

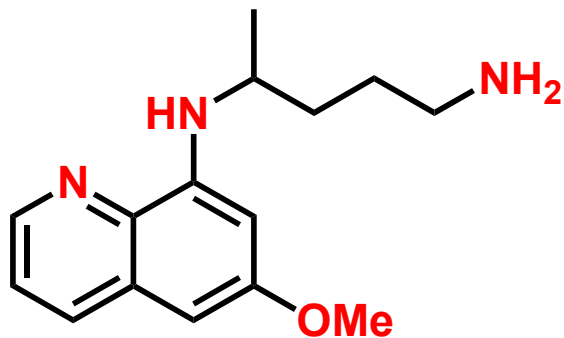
The cost of **quinidine** is 5 g - \$35

The **chemical synthesis of quinine** was one of the most active areas in organic chemistry in **19th and 20th centuries**

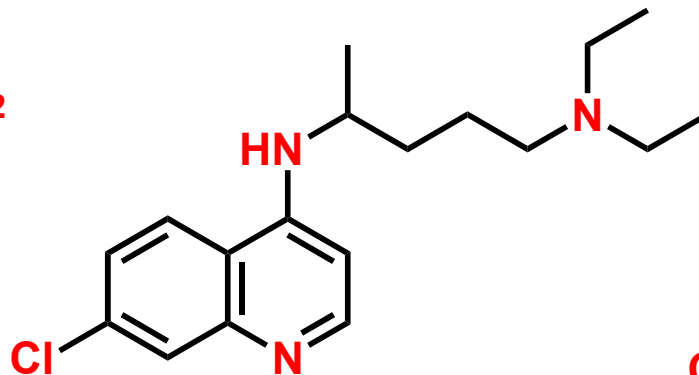
In **1950**, 'French Society of Pharmacy' even **announced a prize money of 4000 Francs** to the person who successfully make **synthetic quinine**



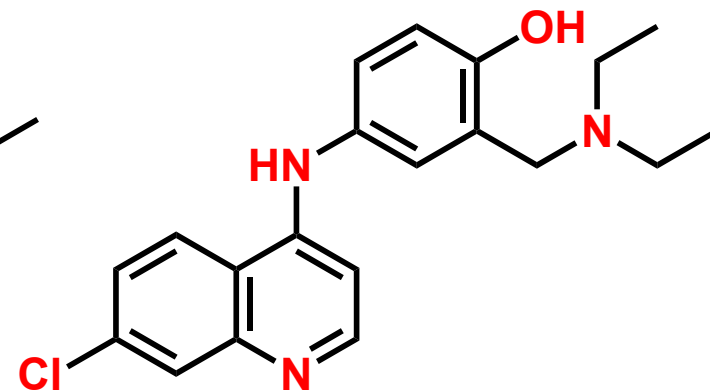
Mefloquine



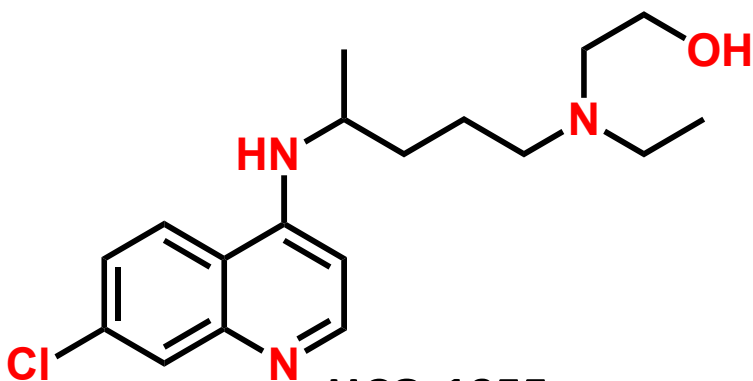
Primaquine



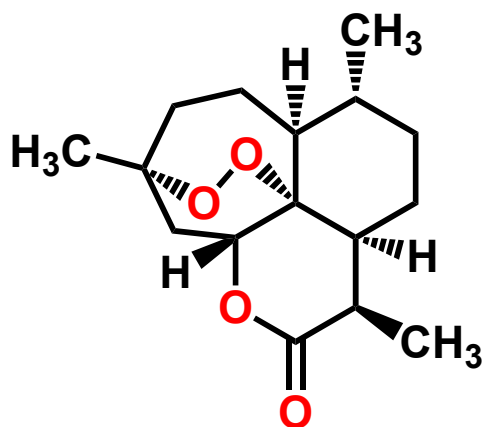
Chloroquine -1947



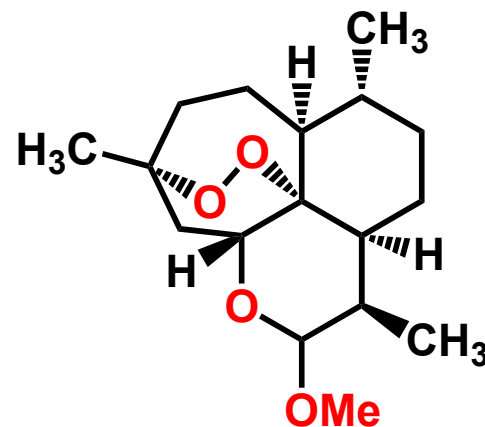
Amodiaquine-1948



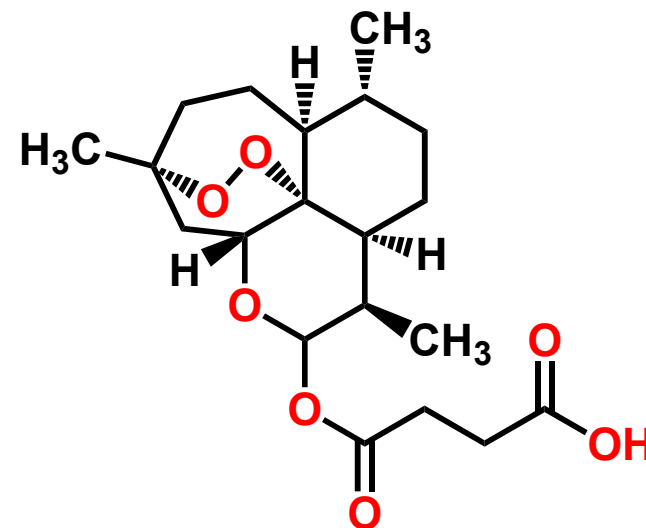
HCQ-1955



Artemisinin



Artemether



Artesunate

Structure of Quinine was reported by Paul Rabe in 1907

First partial synthesis was reported by Paul Rabe in 1918

Another partial synthesis was reported by Prelog in 1943

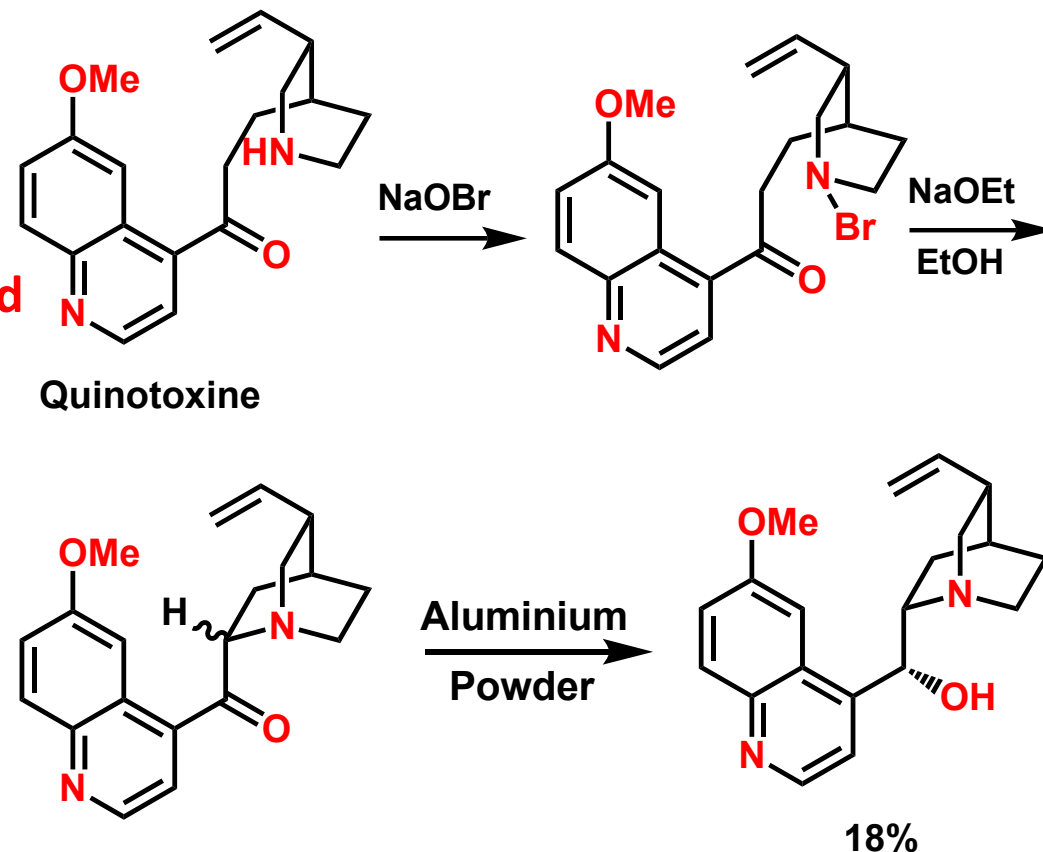
First formal total synthesis of quinine was reported by Woodward in 1944

First stereoselective total synthesis was reported by Stork in 2001

Syntheses of Quinine and Quinidine were reported by Jacobsen

Williams reported and confirmed the total synthesis of quinine in 2010

Rabe's Synthesis of Quinine



P. Rabe. K. Kindler *Ber. Deutsch. Chem. Ges.* **1918**, 51, 466-467

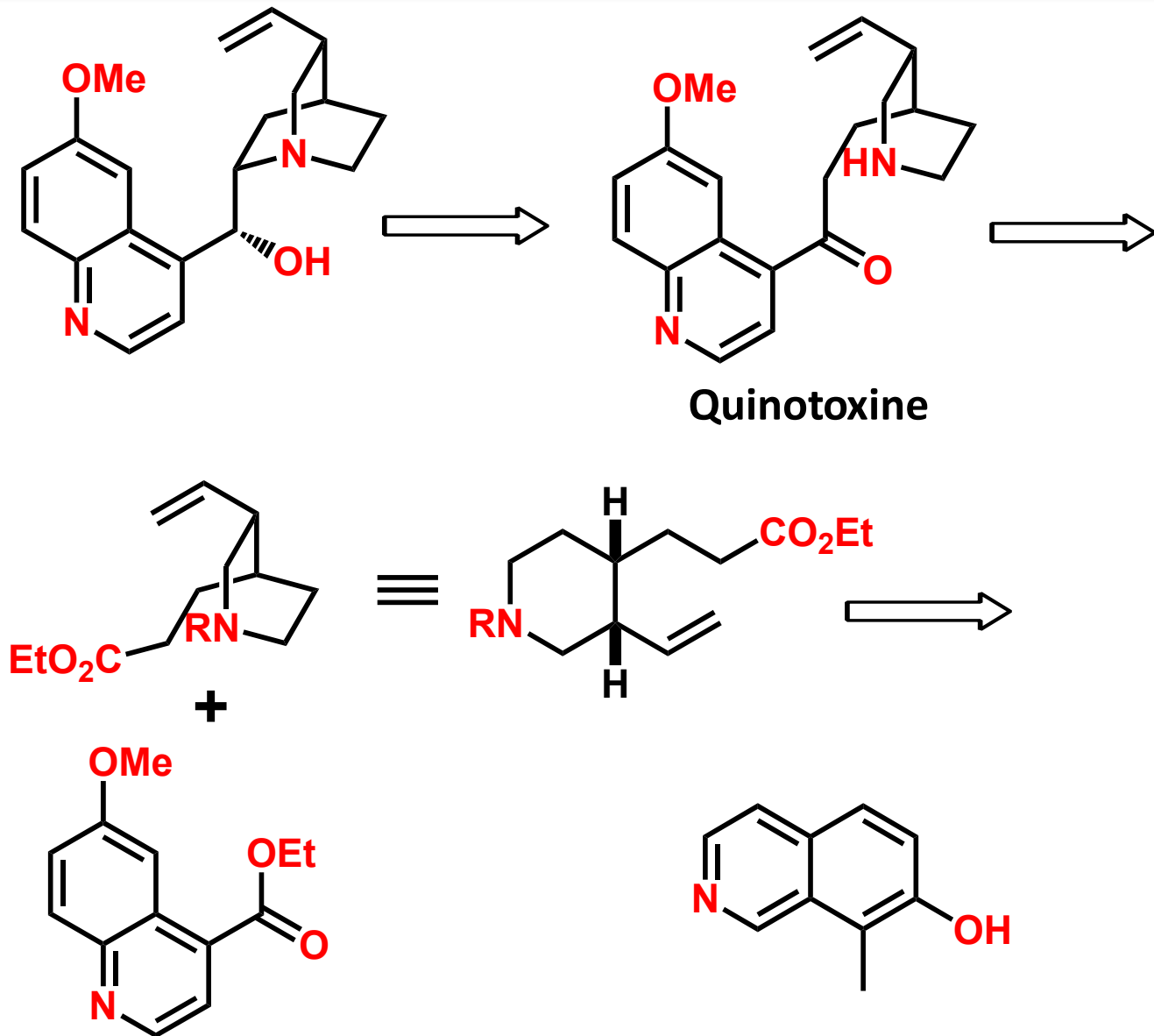
Background

During the **world war II**, thousands of soldiers died due to **scarcity of quinine**.

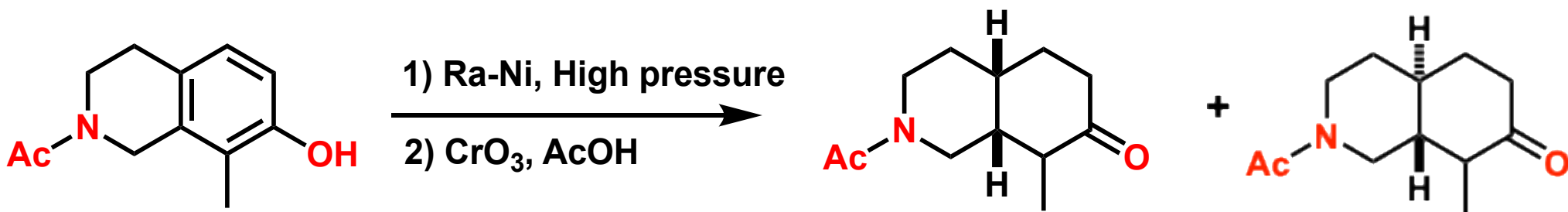
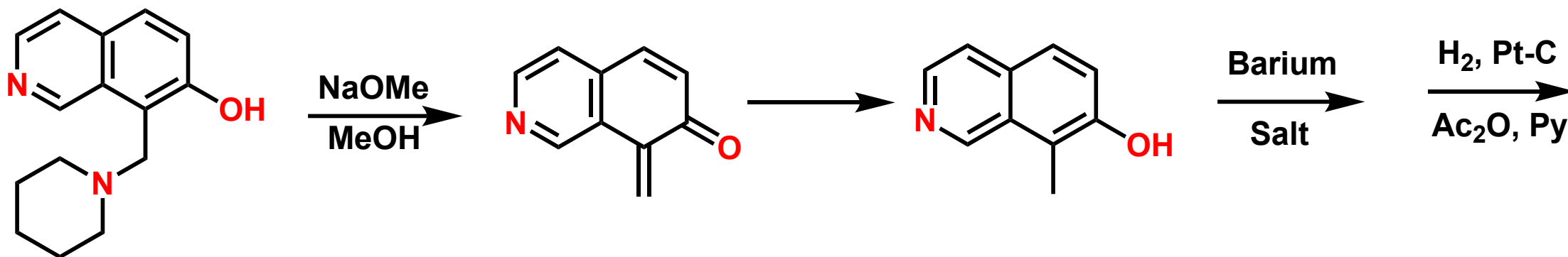
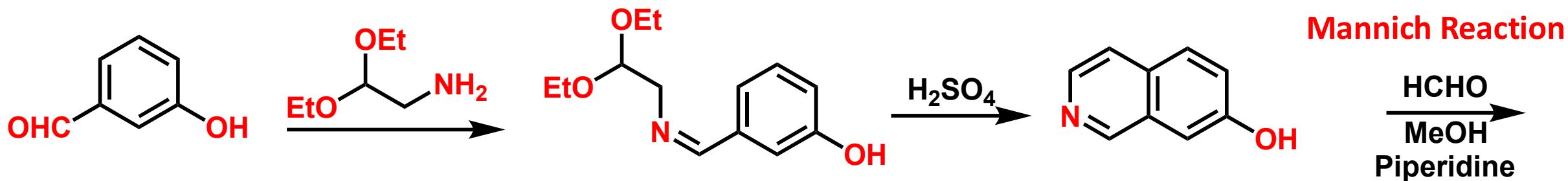
Polaroid company dependent on **quinine** as light sensitizer

Woodward was a consultant to **Polaroid**

The owner of **polaroid** agreed to fund **Woodward's** synthesis project on **quinine**

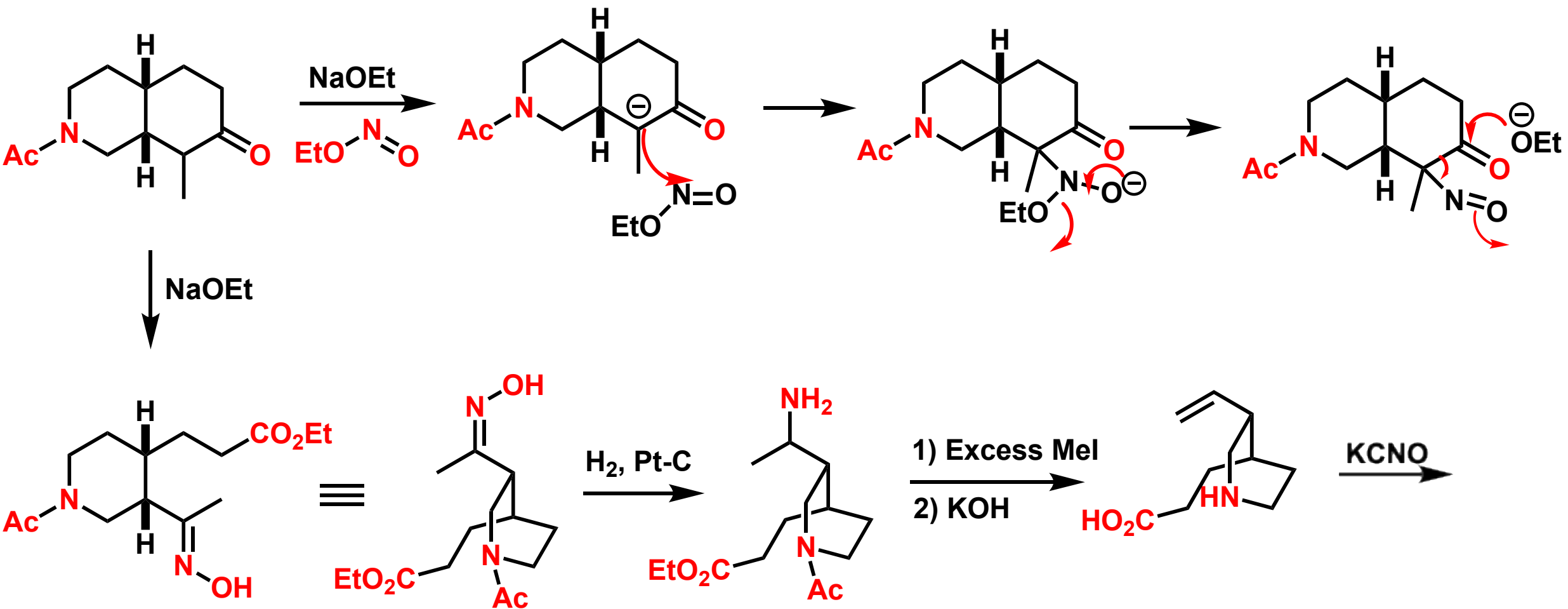


Total Synthesis of Quinine

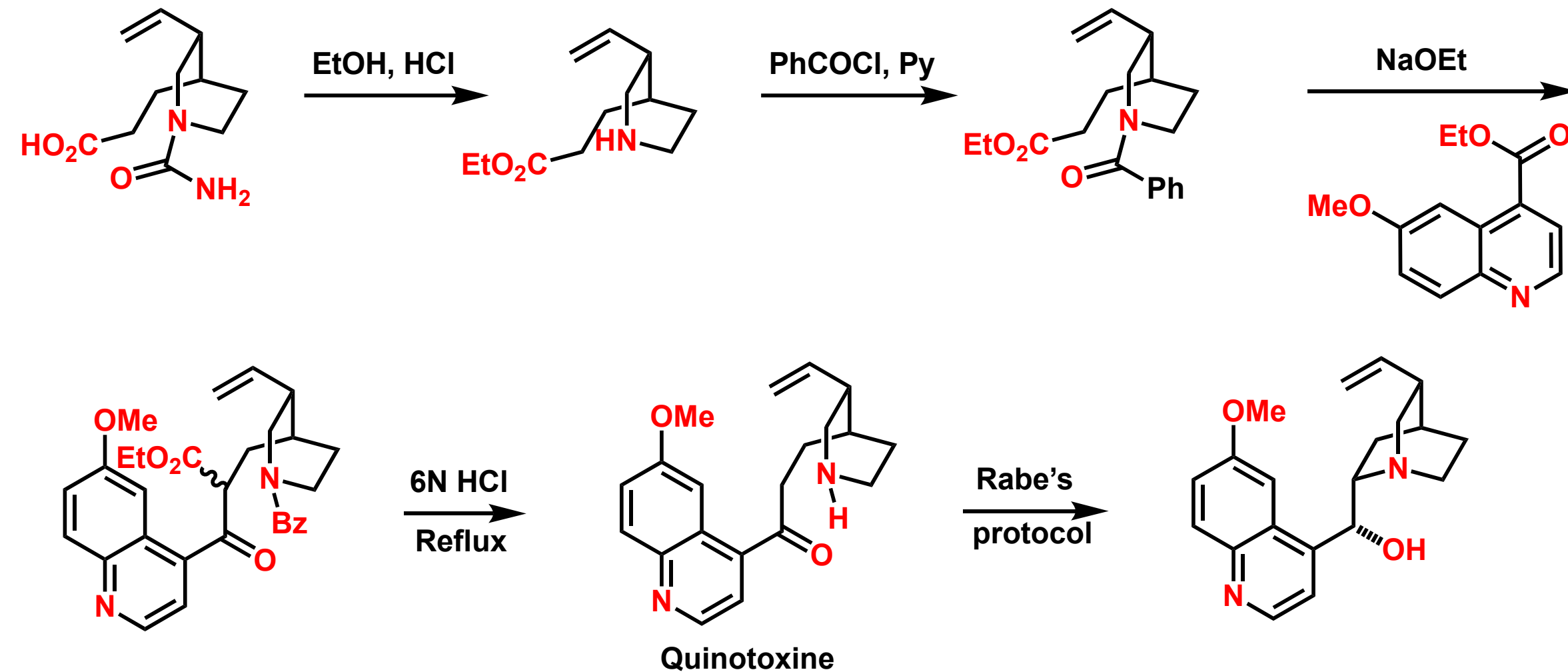


Crystalline

Woodwards's Synthesis

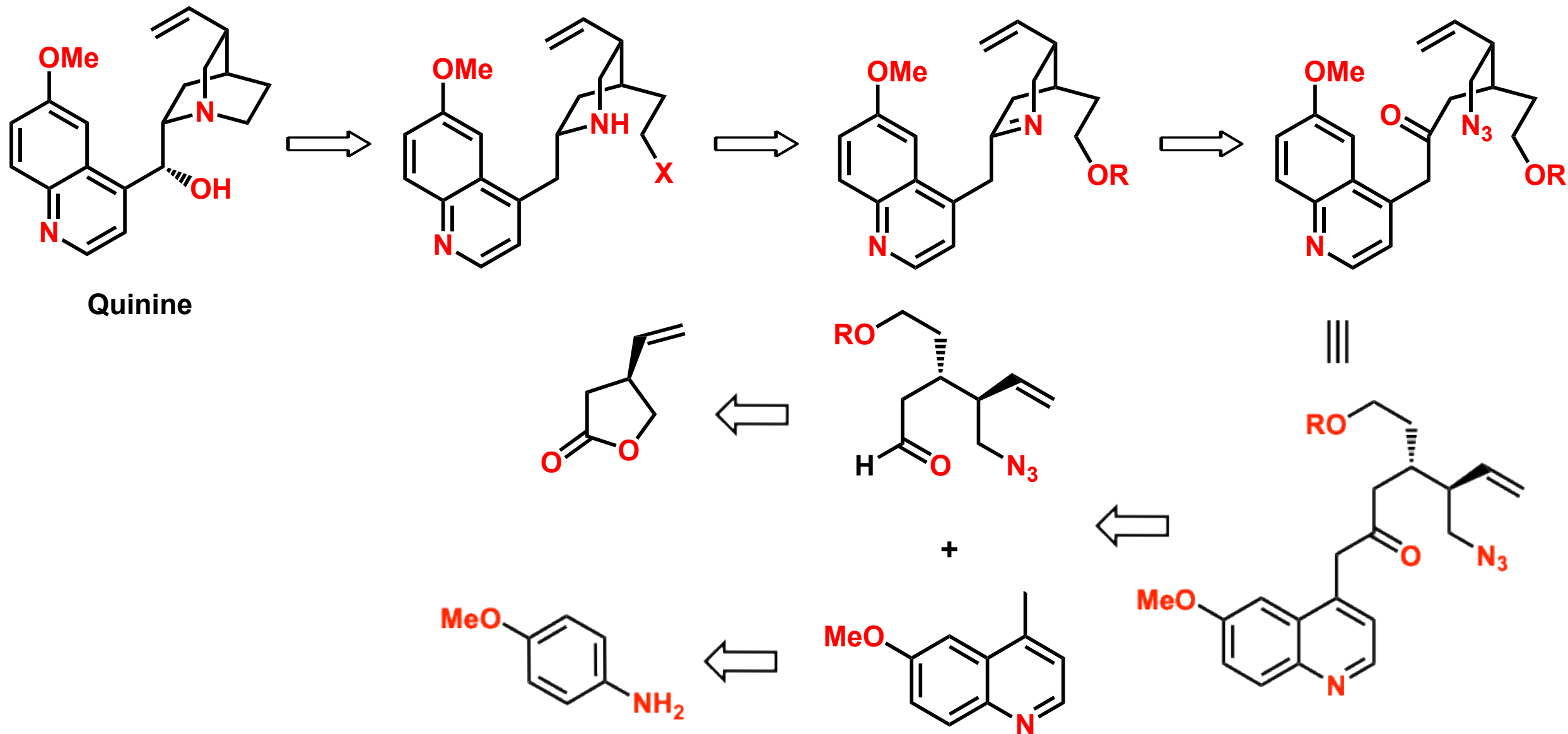


Woodward's Formal Synthesis of Quinine

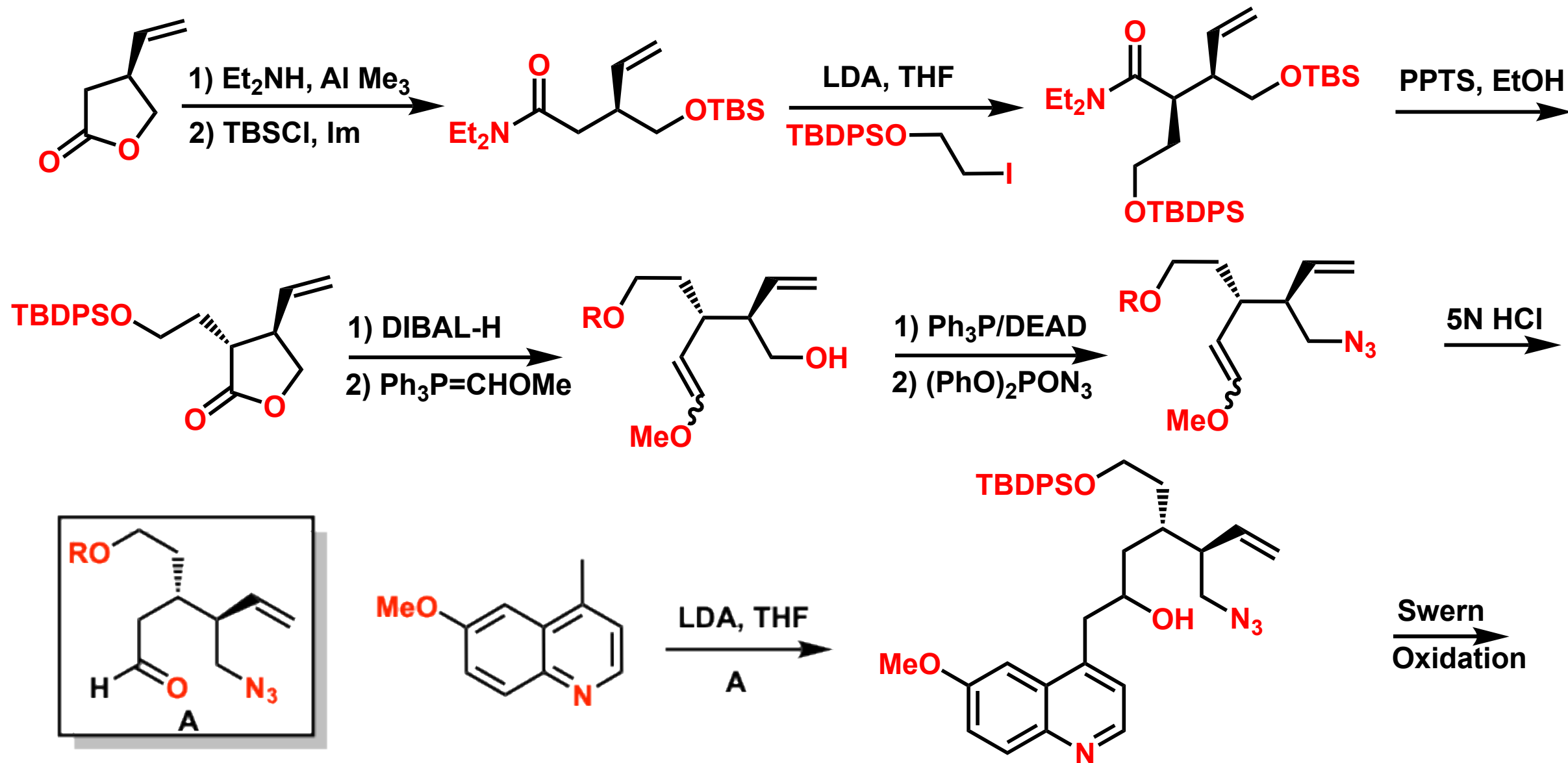


Woodward R. B.; Doering W. E. *J. Am. Chem. Soc.* **1945**, 67, 860-874.

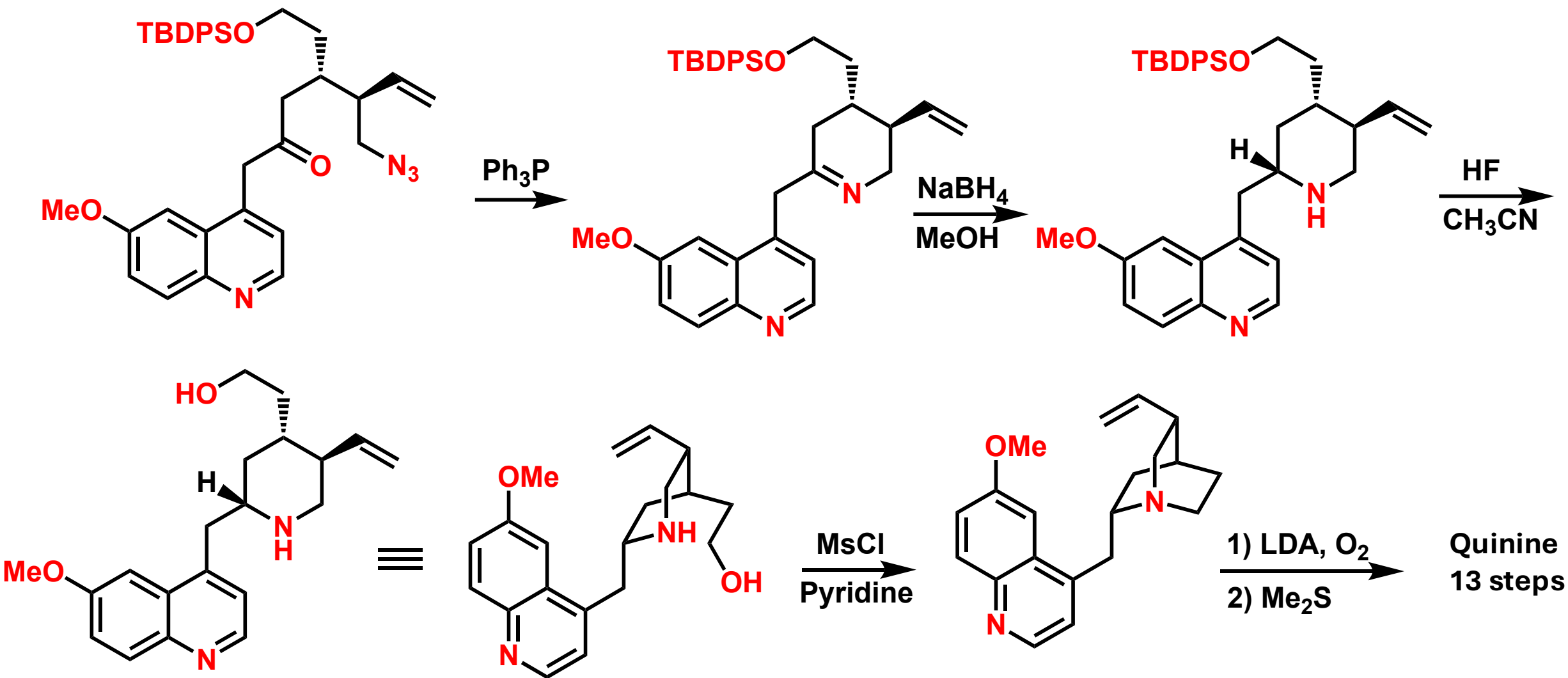
Stork's Asymmetric Synthesis of Quinine



Stork's Total Synthesis of Quinine



Stork's Total Synthesis of Quinine

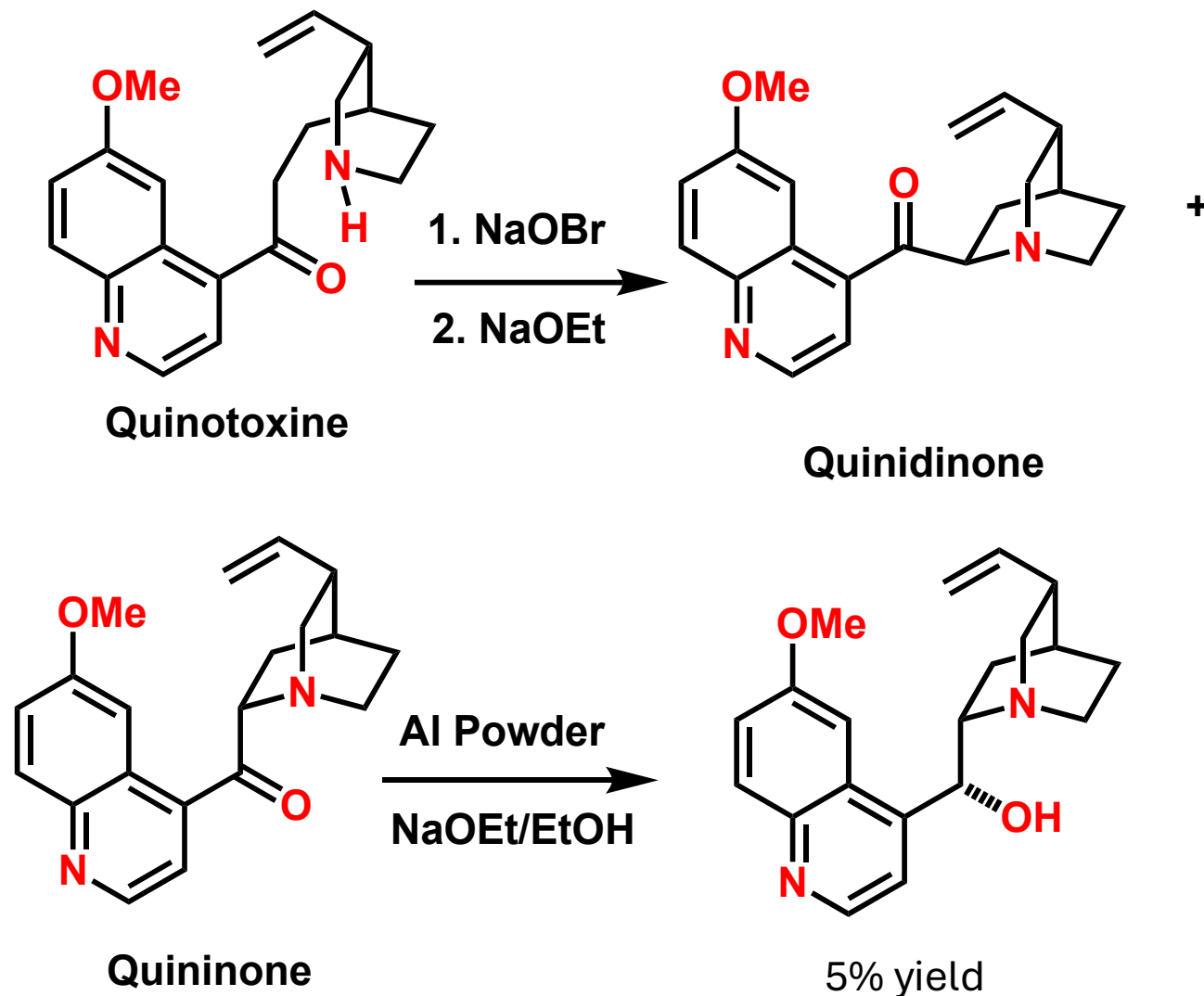
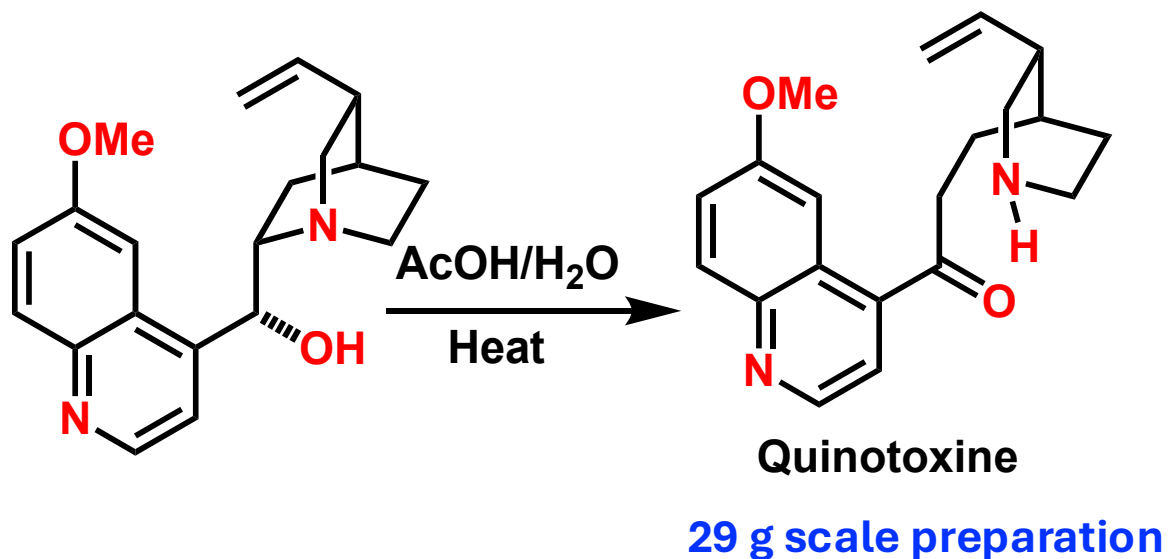


Stork, G.; Niu, D.; Fujimoto, R. A.; Koft, E.; R.; Balkovec, J. M.; Tata, J. R.; Dake G. R. *J. Am. Chem. Soc.* **2001**, *123*, 3239-3242.

Controversy about Woodward's Synthesis and Setting the Record Straight

As Rabe did not publish the full experimental details of the conversion of quinotoxine to quinine, **Gilbert Stork** had his reservation on the total synthesis of quinine reported by Woodward.

Robert Williams' group from Colorado University repeated the Rabe's conversion of quinotoxine to quinine and confirmed that Woodward's formal total synthesis of quinine is indeed valid



Smith A. C.; Williams R. M. *Angew. Chem. Int. Ed.* **2008**, 47, 1736-1740.