

Total Synthesis of Strychnine



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CH-845 Course on Organic Synthesis



Strychnine & Brucine



Strychnine Tree (Nux Vomica) is native to India and Indian subcontinent

It is known as **Kuchla or Kajira in Hindi & Kanchiram/Ettirmaram in Tamil & Malayalam**

It is used as a remedy in **chronic dysentery**, paralytic and **neuralgic disorders**, **epilepsy**, **rheumatic arthritis**, and hydrophobia.

Green to orange fruit of this tree is the main **source of highly poisonous** and intensely bitter alkaloids **strychnine and brucine**

Review: *Chem. Rev.*, 2000, 100, 3455-3482.

Isolated from ***Strychnos nux-vomica*** in **1818**

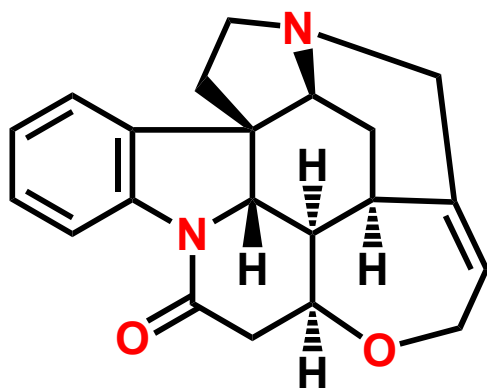
Elemental composition was established in **1838**

Dried seeds contain 1.5 % Strychnine by weight

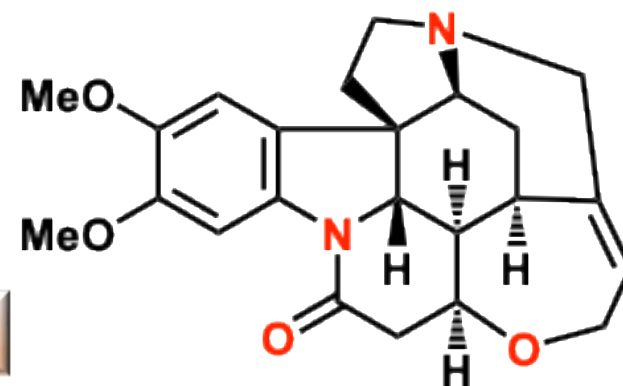
Dried blossoms contain 1.0 % Strychnine by weight

Consumption of 50 mg and above of Strychnine is **fatal**.

Discussed its usage in many novels or poetry for killing people



Strychnine



Brucine



Strychnine & Its Mention in Novels

Many novels mention the use of **Strychnine**: some as a cure for **insomnia** and some as a weapon **for murder**

Invisible man, The Sign of Four, Psycho, The Mysterious Affair at Styles, Mr. Mercedes, Practice of Pharmacy, Conan Doyle Detective, A Mussoorie Mystery are some of the novels where Strychnine was mentioned

Strychnine has been used in **Asia** mainly for controlling **pests** especially **rats**

Strychnine entered the European market **when ship trading became more popular**. All **ships have rats** and the sailors used **Strychnine as rodent controller** in merchant vessels

By late 1800, **500 tons** of **Strychnos seeds** have been imported in **London per year** to take care of rodents

Though it was difficult to get Strychnine from Pharmacy, it was available under the name '**Vermin Killer**'

Vermin Killer. mixture of **flour, soot, and strychnine**, to be applied to a **piece of bread or cheese** and left on the kitchen floor **overnight to kill rats and mice**



Misuse of Strychnine

Ignorant people started selling this **“Vermin Killer”** powder to more ignorant people, even if they had **murderous intent or suicidal thoughts**.

The use of **“Vermin Killer”** powder was then extended to kill **stray dogs and cats**.

One such purchaser was writer **“Henry N. Randolph”**. He bought this powder **to poison an annoying cat**. He labelled it as **“POISON”** and kept it near his **bed table** along with a bottle of **“QUININE”**. Unfortunately, in the **dark**, one night **he consumed Strychine** instead of **Quinine** and he was **found dead** after 4 hours

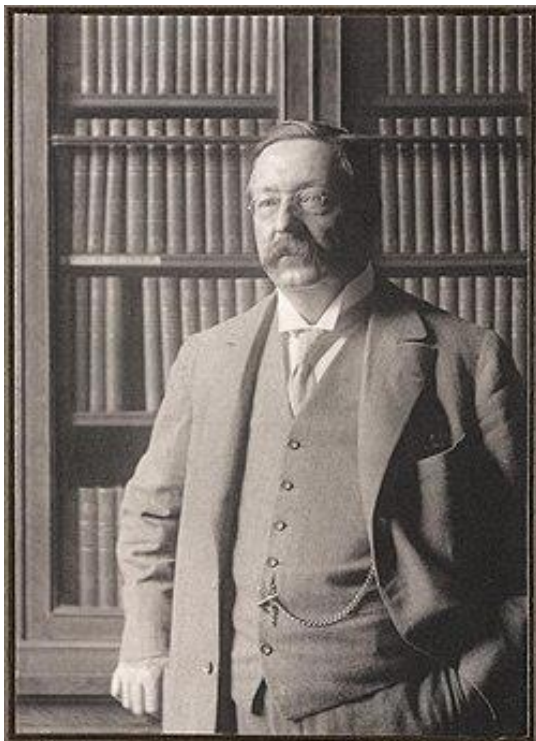
French Physicians during **Napolean era** assumed that if **quinine**, a **bitter powder** was **medically useful**, any other **white powder which is bitter** in nature should be **beneficial**.

William Palmer, a surgeon and apothecary who made a habit **of insuring members of his family**, and then **poisoning them with strychnine** to collect the **life insurance money**.

In the summer of 1911, two British female spiritualists arrived in Mussoorie and stayed at Savoy Hotel. One of the guests **was suspected to kill the other using Strychnine**



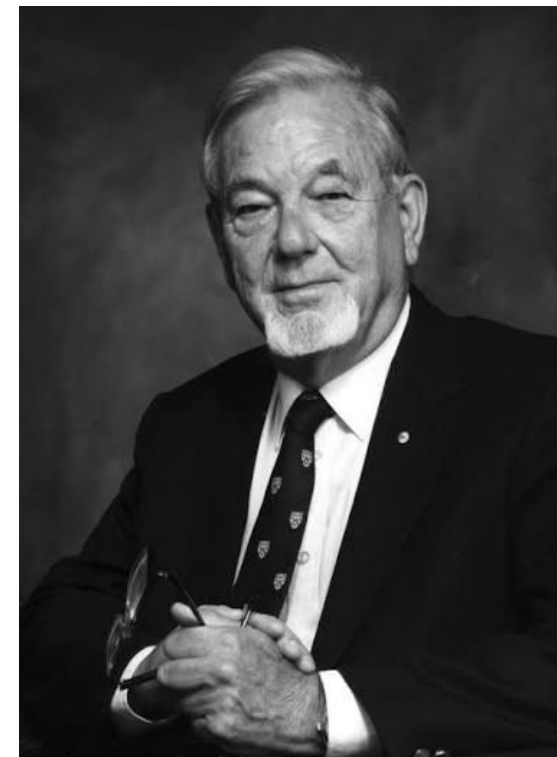
Perkin, Robinson & Birch



William Perkin Jr.



Sir Robert Robinson



Arthur J. Birch



Robinson & Strychnine

Robert Robinson began studying strychnine in **1910**

Worked with **William Henry Perkin**

Robinson published **47 papers** on strychnine

Many structural proposals were developed **over several decades**

January 14, 1946: Robinson proposed the **correct structure of Strychnine**

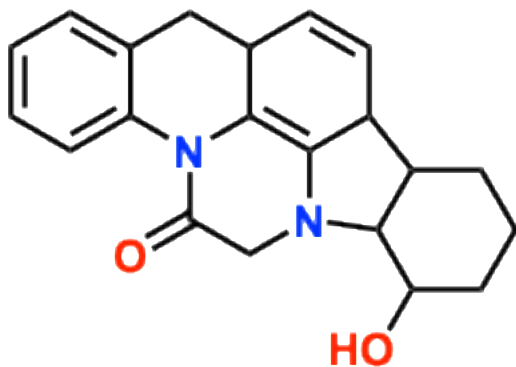
Published in **Experientia**

His proposal was based on accumulated **chemical evidence** and this became a major **milestone** in the strychnine story

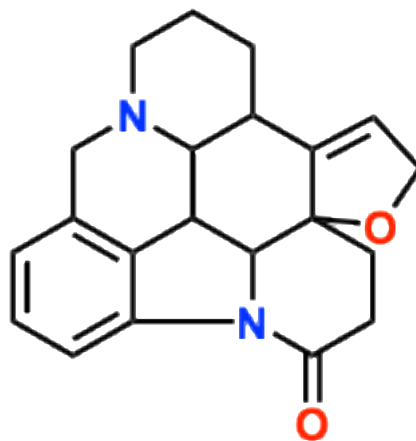




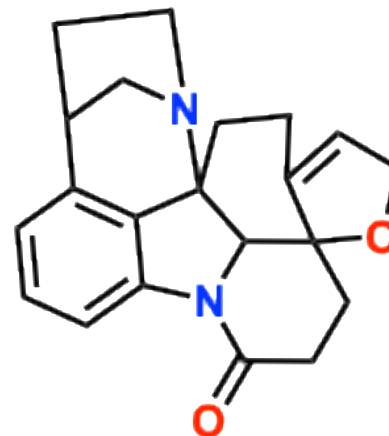
Robinson's Proposed Structures



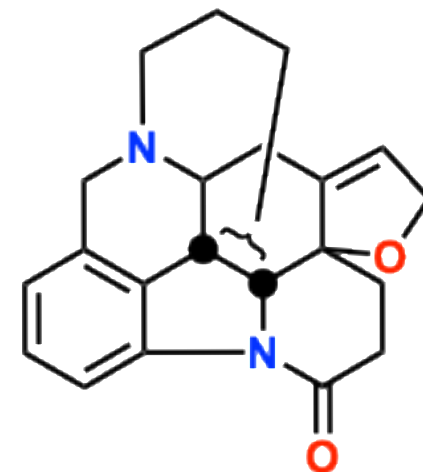
1910



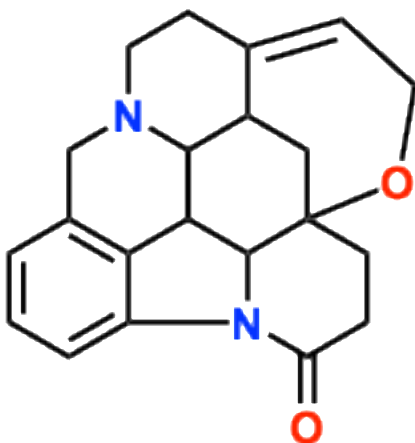
1928



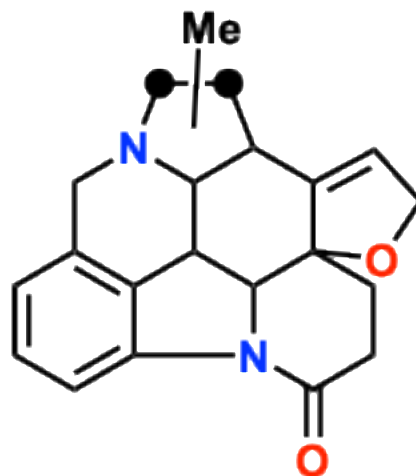
1928



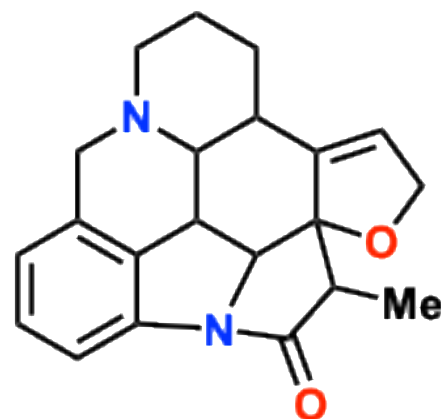
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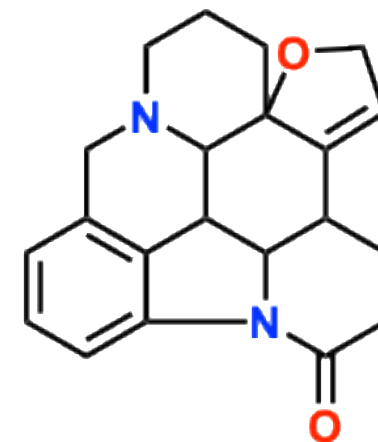
1928



1928



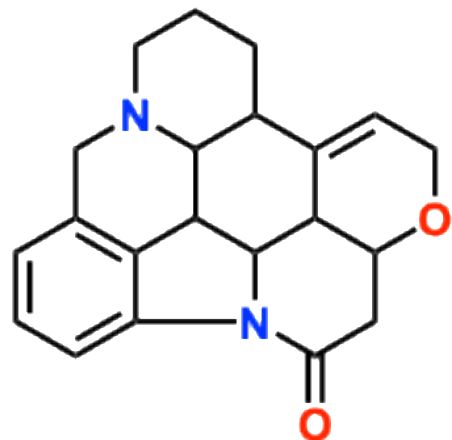
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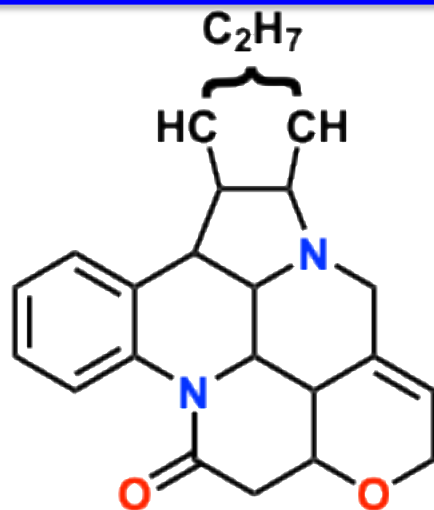
1928



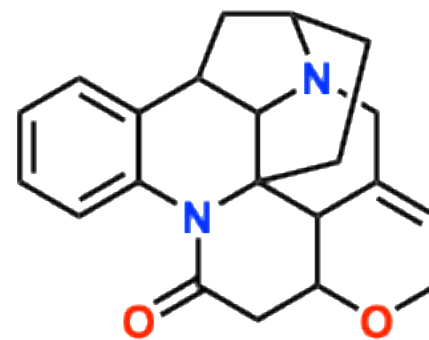
Robinson's Proposed Structures



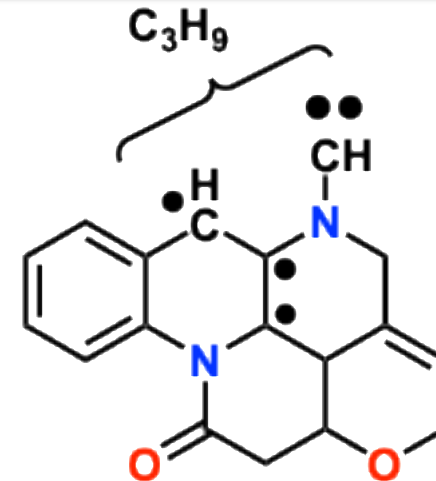
1928



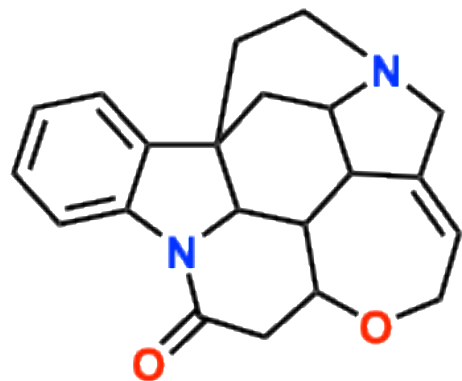
1930



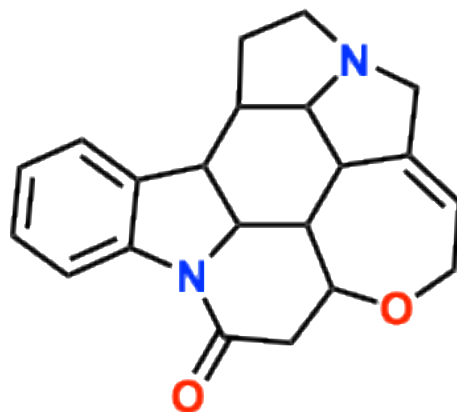
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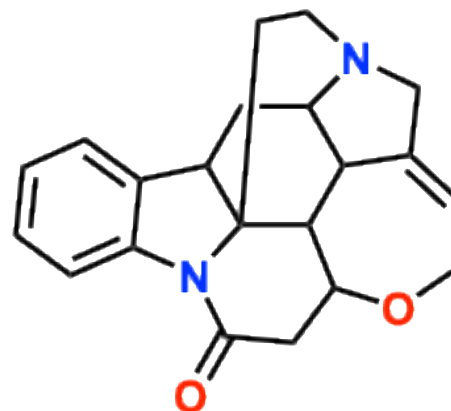
1932



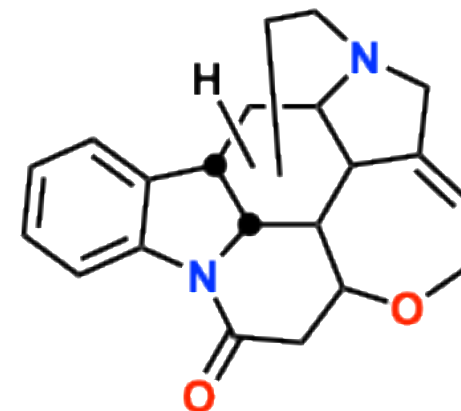
1932



1932



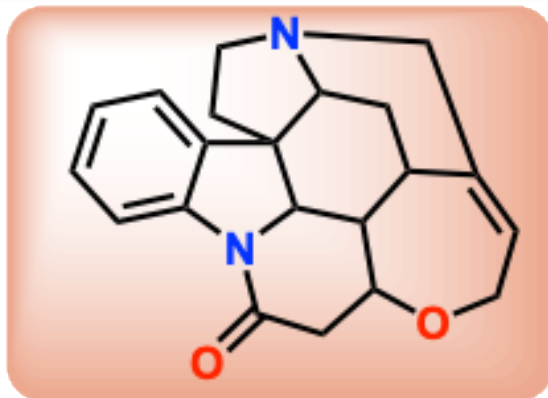
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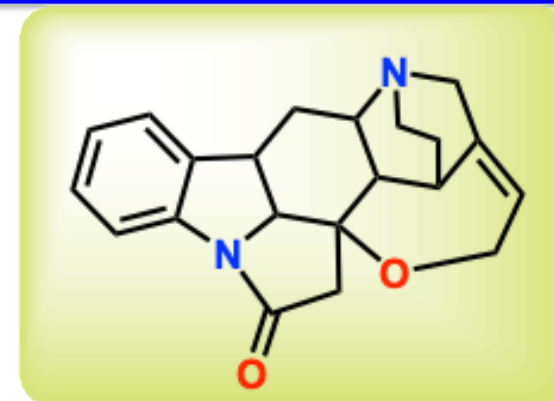
1936



Change of Mind



Robinson,
Submitted January
14, 1947



Robinson,
Submitted February
14, 1947

February 1947: Robinson abandoned his earlier correct structure (above left one)

Proposed a **different structure** (above right one)

His reasoning involved the **possible biosynthetic relationship** of strychnine

July 1947: He moved back toward his earlier structure



Woodward Enters the Story

R. B. Woodward **independently analyzed** the available evidence

Submitted a **JACS** paper on **July 28, 1947**

Assigned the **correct** structure

He **acknowledged** Robinson's earlier observations

Woodward presented **additional evidence** supporting the structure

Full paper submitted: **January 28, 1948**

Published in **JACS** in **June 1948**

Conclusion: **"The Structure for strychnine is established."**





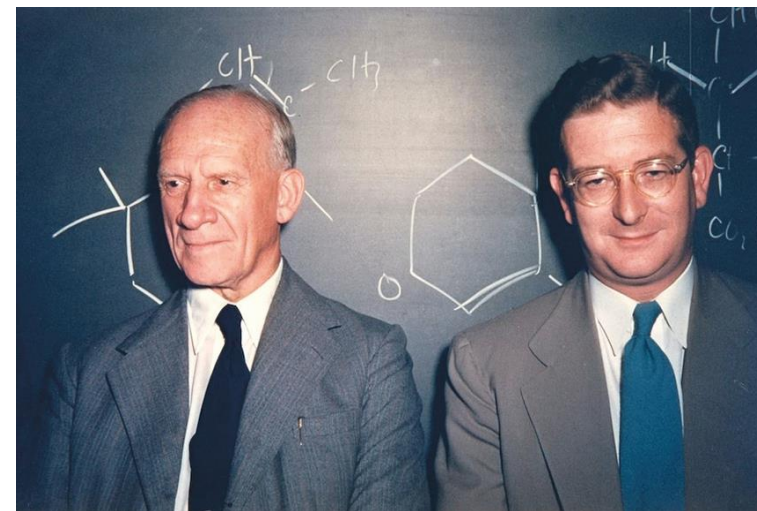
The Famous “Rubbish Formula”

Woodward showed the proposed structure to **Robinson**

Robinson reportedly **rejected** it strongly

Derek Barton later recalled **Robinson** saying: “That’s rubbish, absolutely rubbish!”

Woodward referred to it as the “**Rubbish formula**”





Lessons from Strychnine

Chemistry is not always a **straight line**

Scientists can propose a structure, **reject** it, **modify** it, and **return** to it

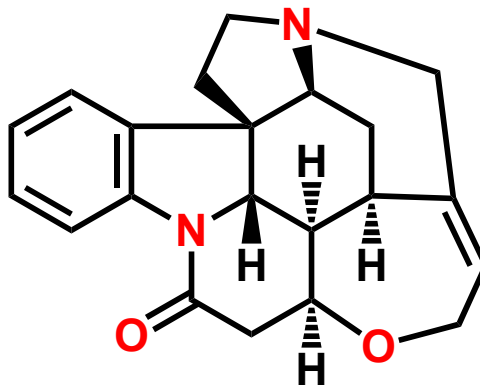
Experimental evidence is more important than simply being **confident**

Complex molecules can be solved **step-by-step**

A **wrong hypothesis** is not necessarily failure- it can be part of **scientific discovery**



Synthetic Challenges



Strychnine

7-Fused rings

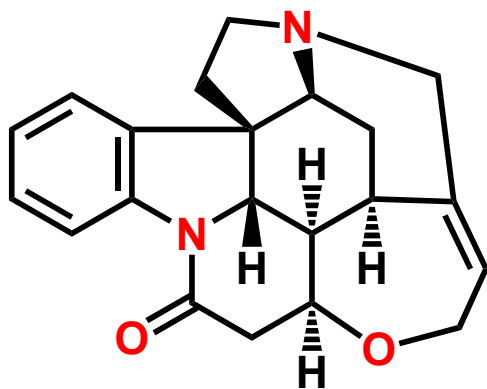
6-Stereocenters and out of which 5 are in one ring (contiguous)

Presence of a unique 7-membered ring

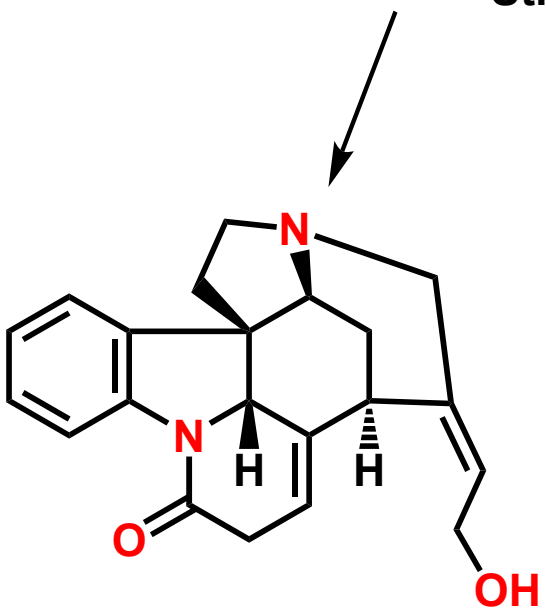
Presence of a unique spiro center

If we can't make Strychnine,
we will take it - R. B. Woodward

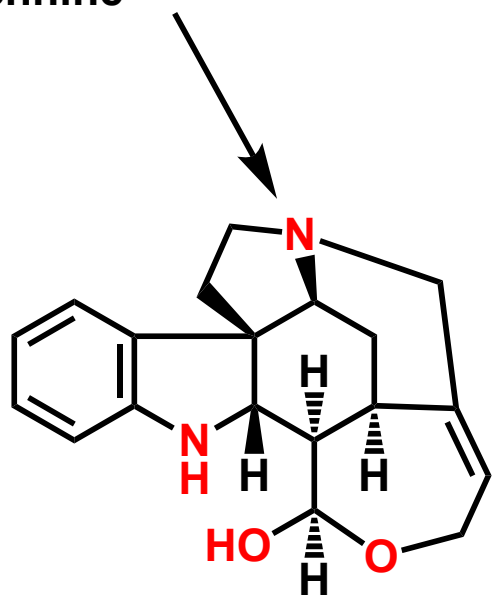
Degradation Products of Strychnine



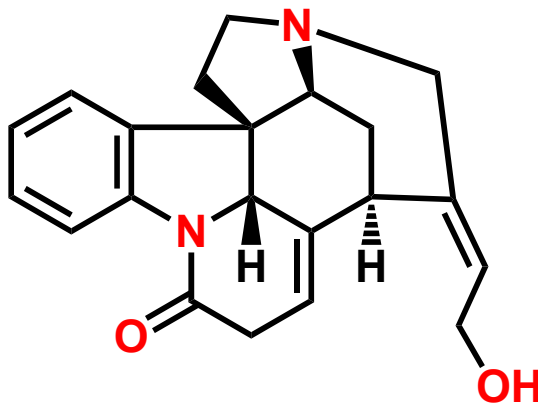
Strychnine



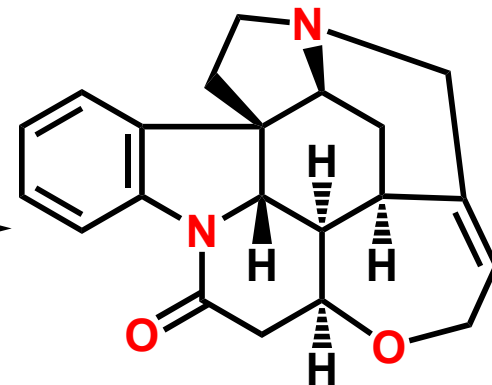
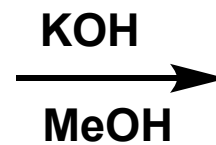
Isostrychnine



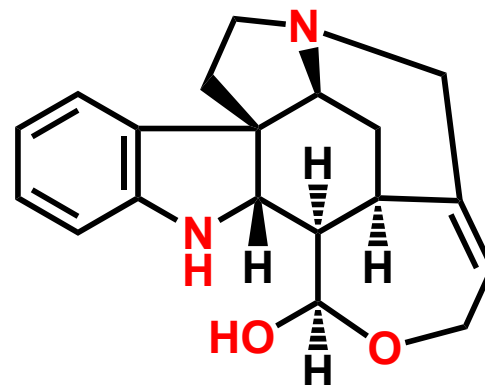
Wieland-Gumlich Aldehyde



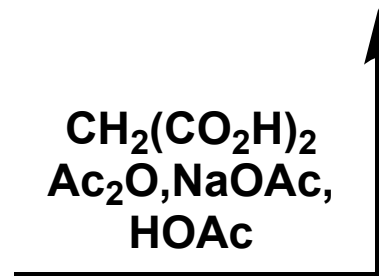
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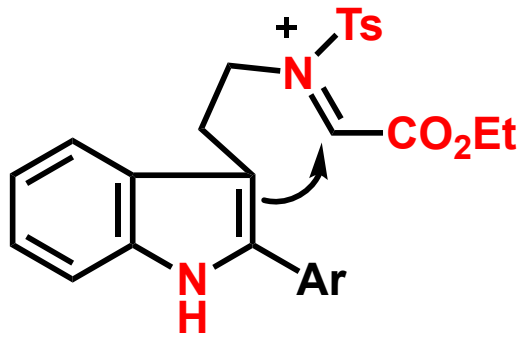
Strychnine



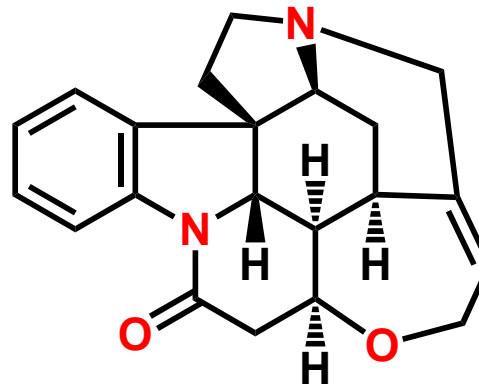
Wieland-Gumlich Aldehyde



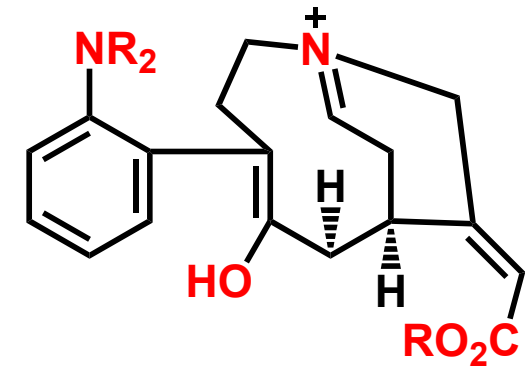
Key Disconnections of Strychnine



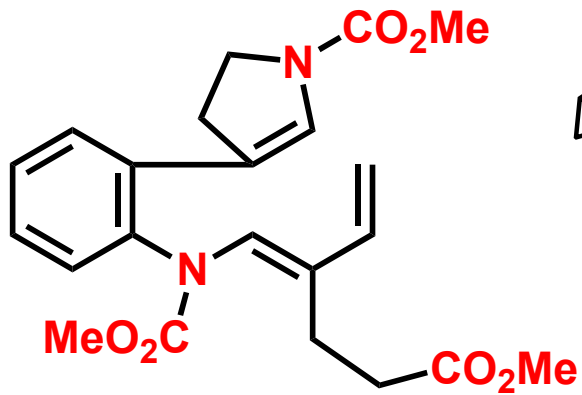
Woodward



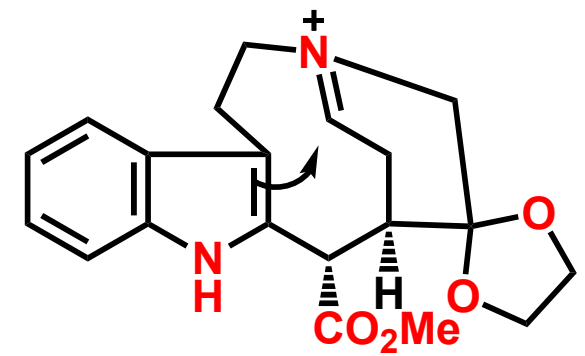
Strychnine



Overmann

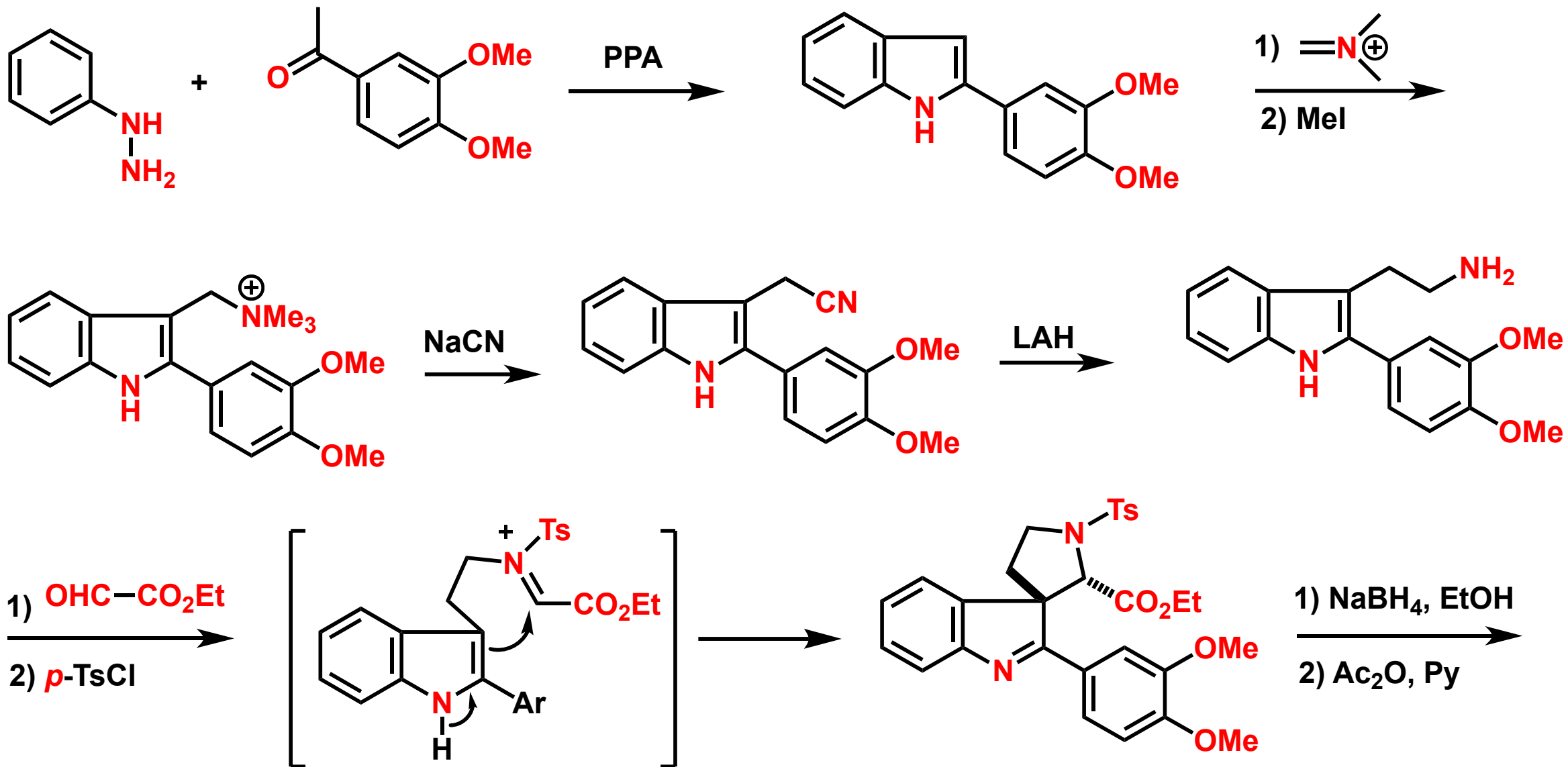


Rawal

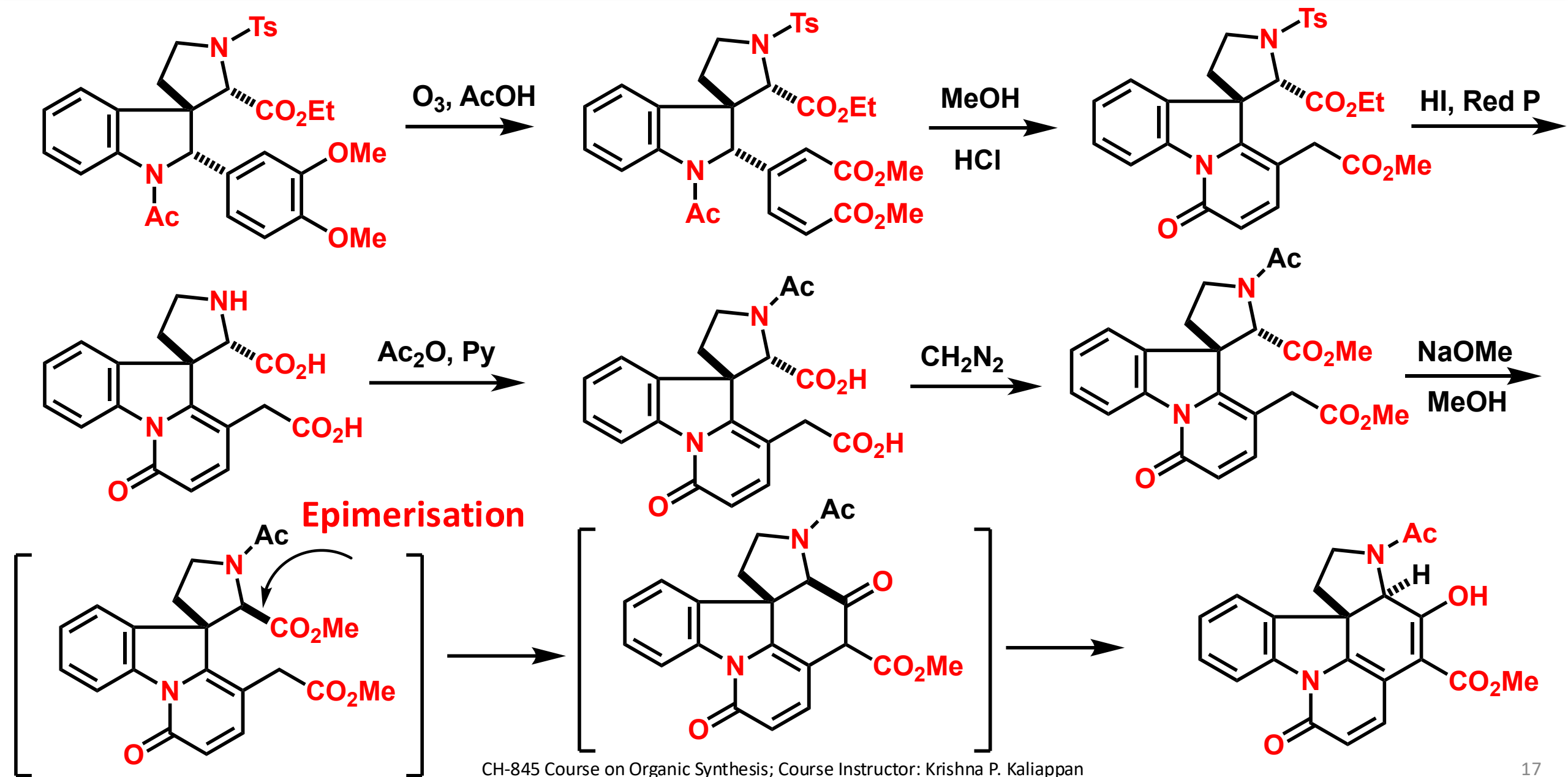


Magnus

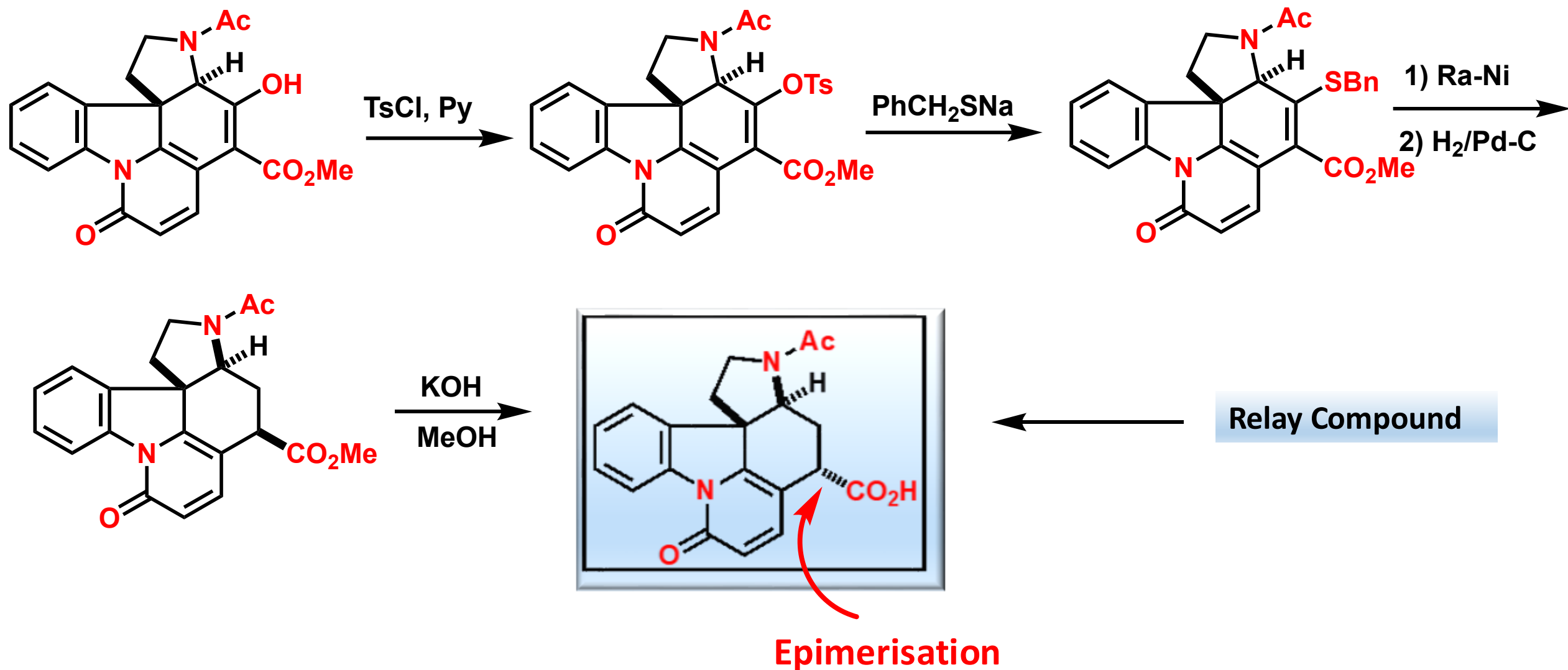
Woodward's Total Synthesis of Strychnine



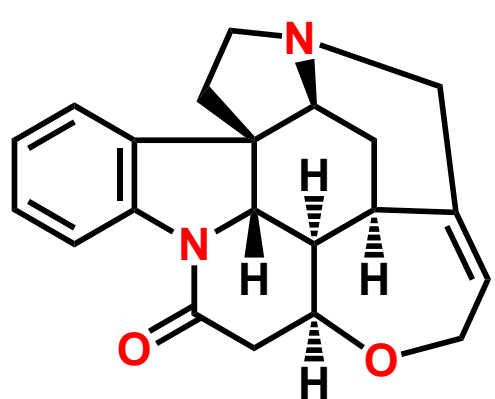
Woodward's Total Synthesis of Strychnine



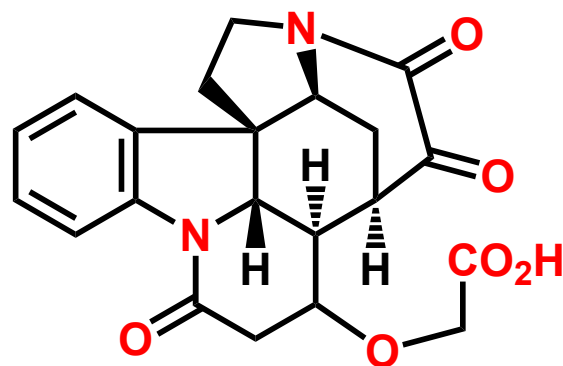
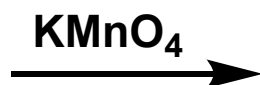
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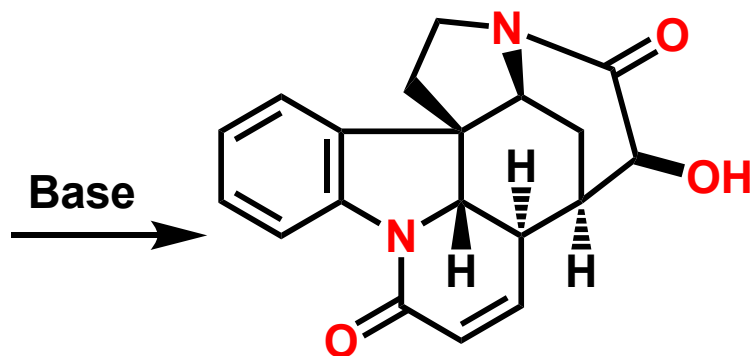
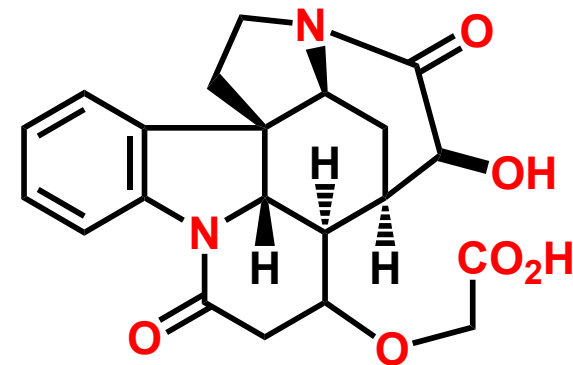
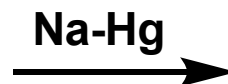
Woodward's Relay Approach



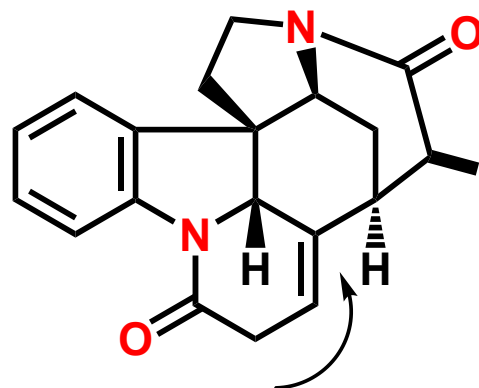
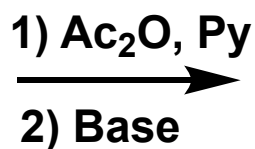
Strychnine



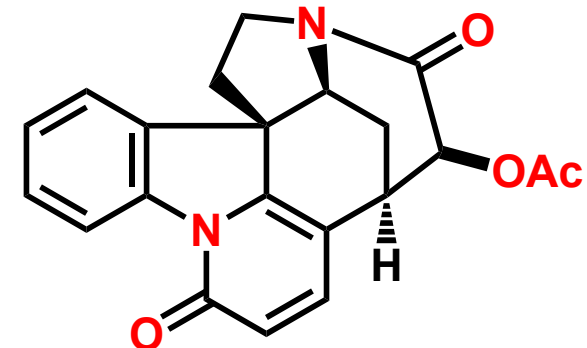
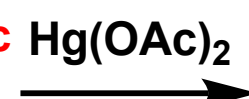
Strychninonic acid



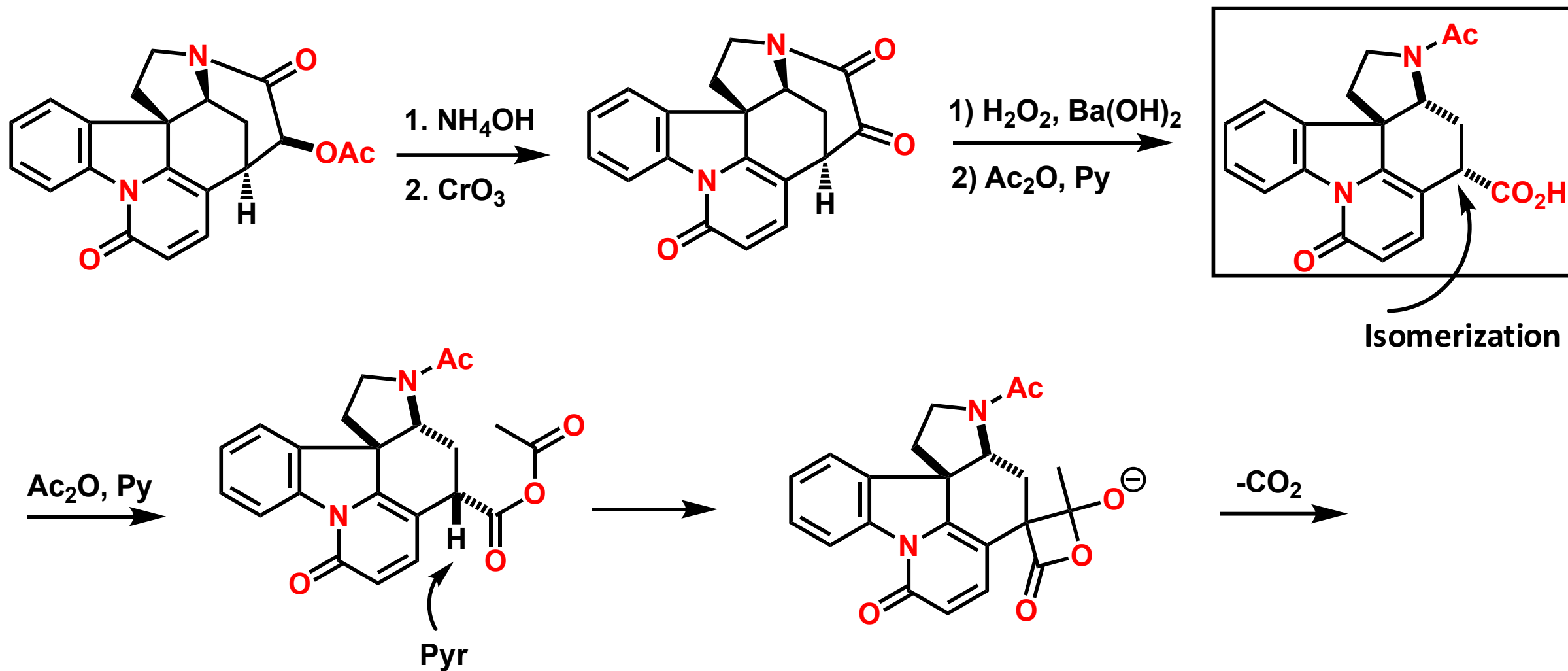
Strychninolone



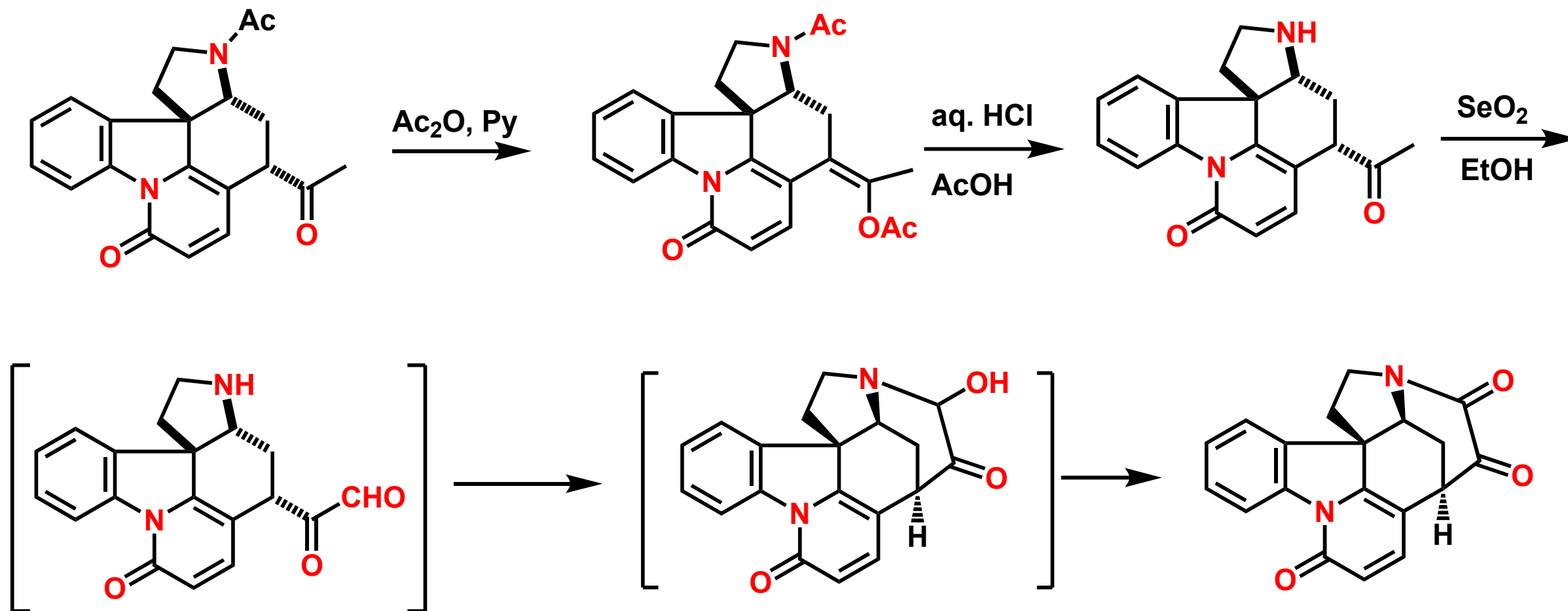
Isomerization

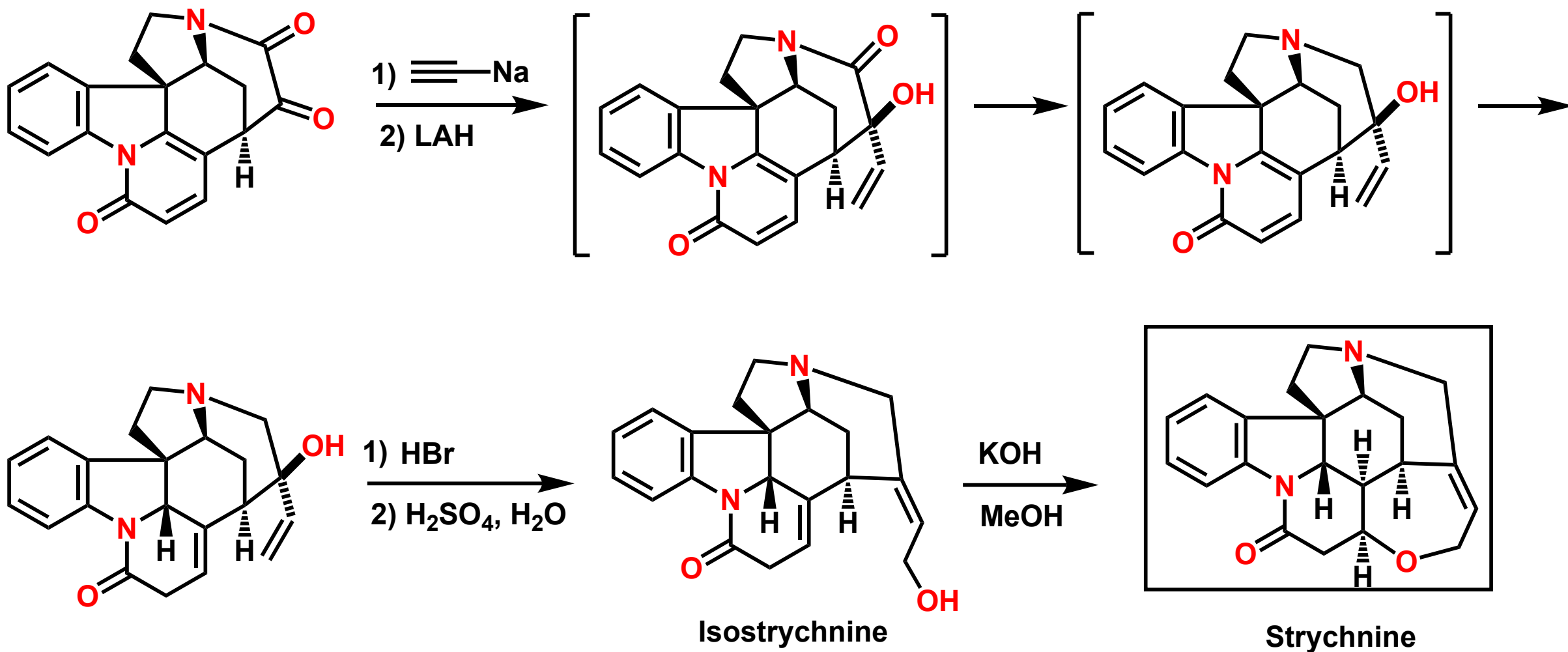


Woodward's Relay Approach

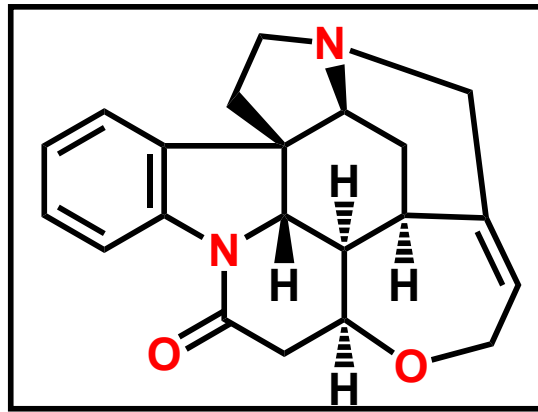


Woodward's Relay Approach

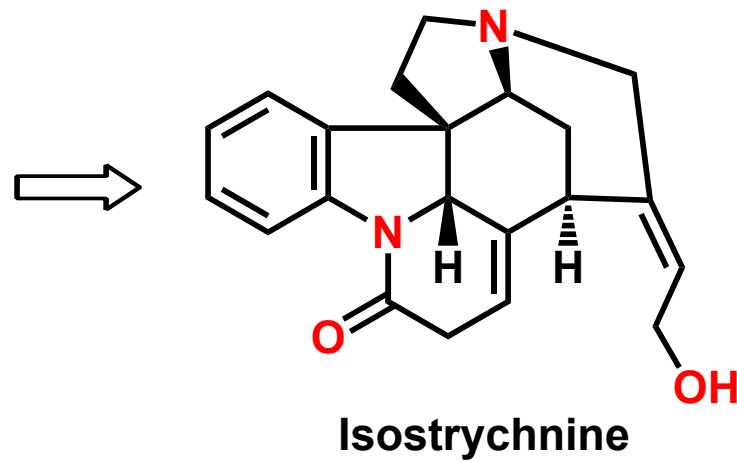




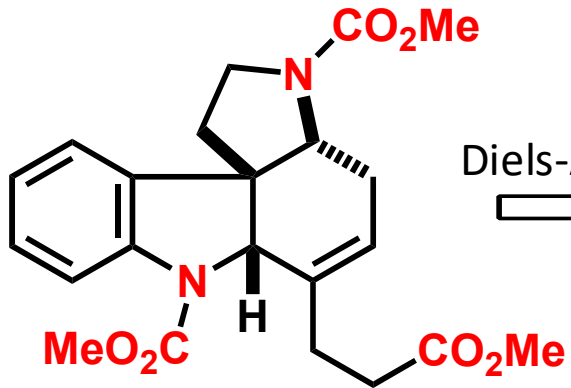
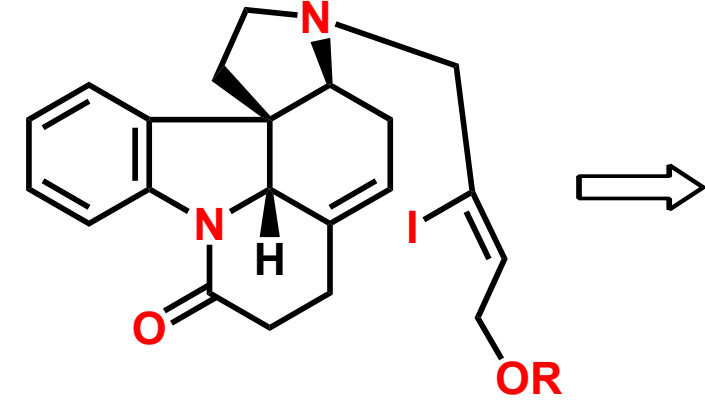
R. B. Woodward *et al.* *J. Am. Chem. Soc.*, 1954, 4749-4752.



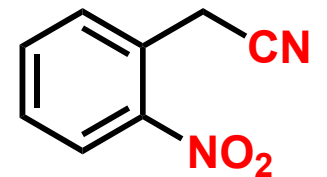
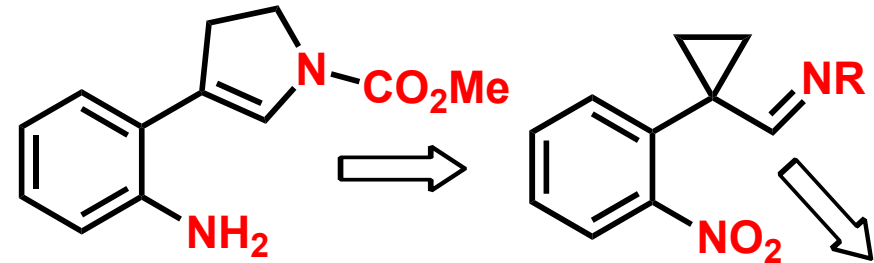
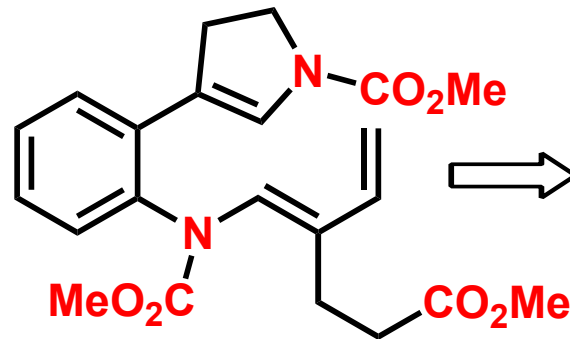
Strychnine



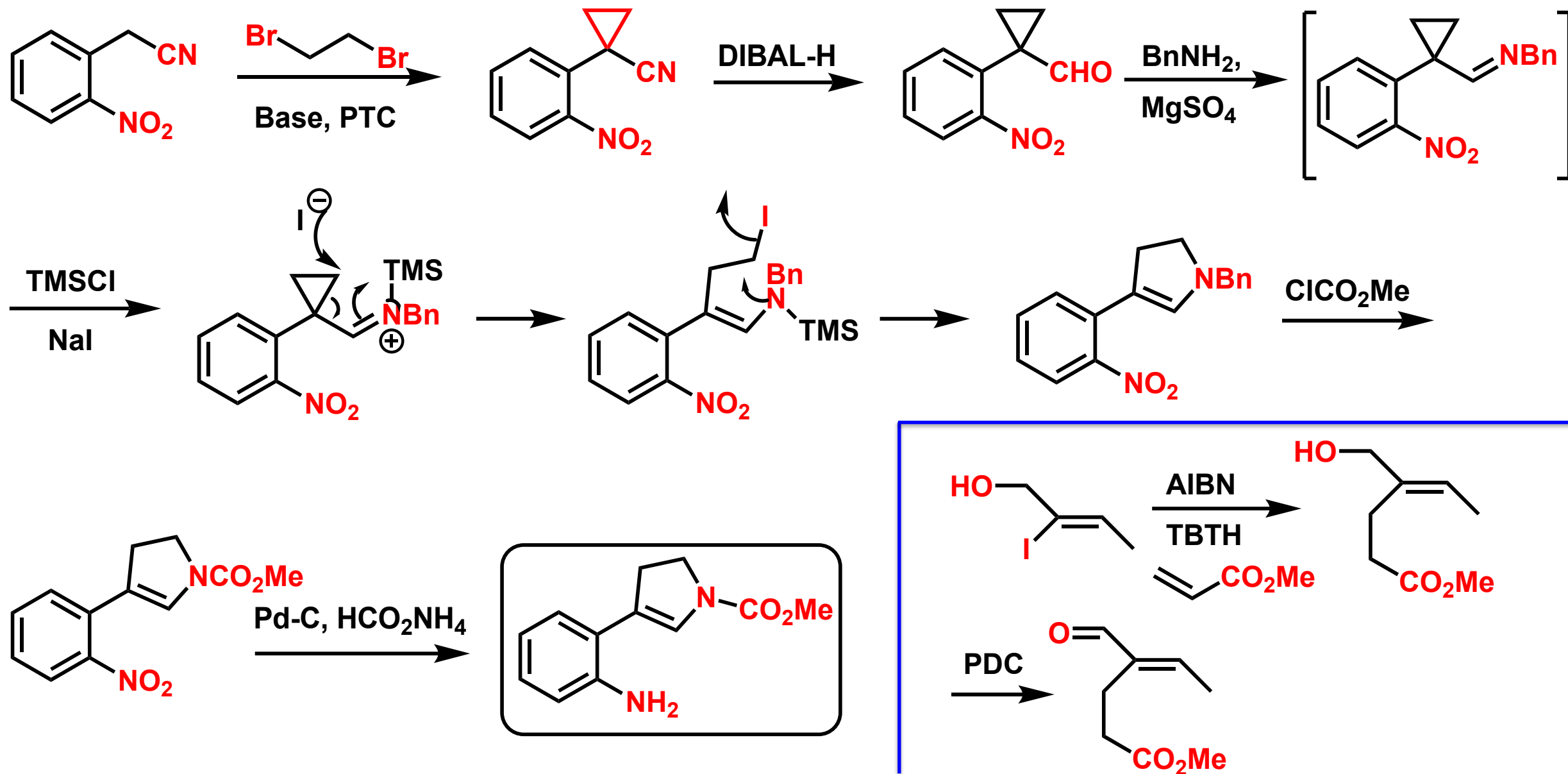
Heck

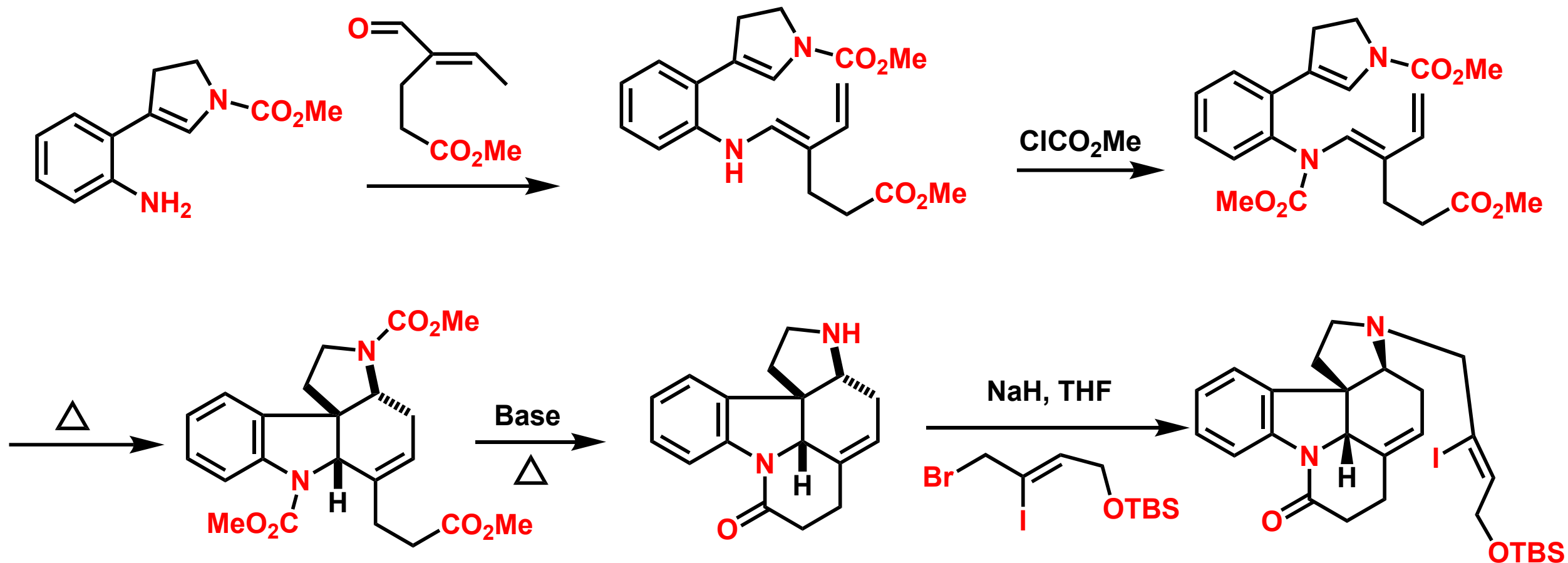


Diels-Alder



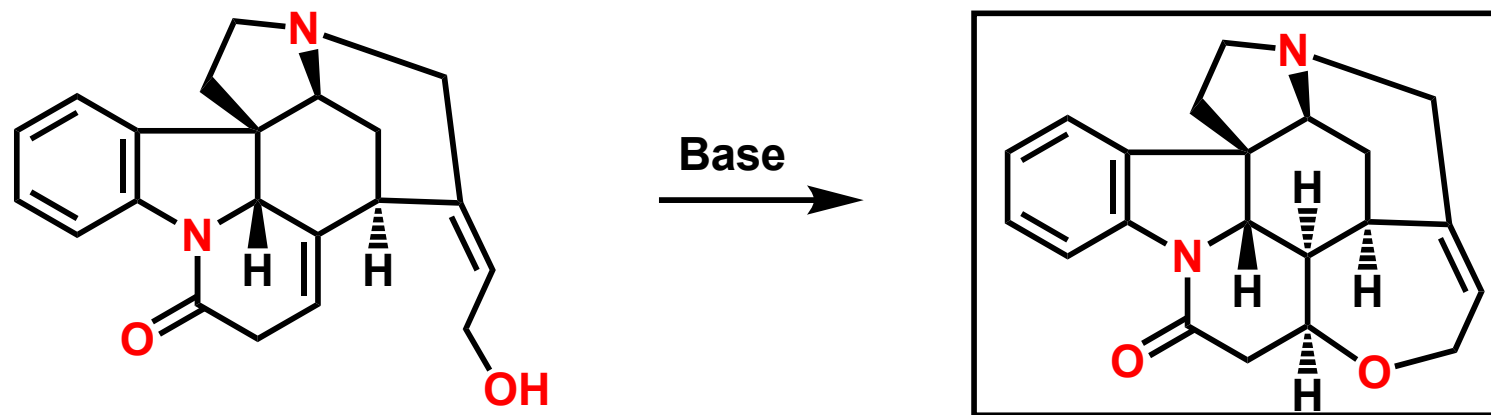
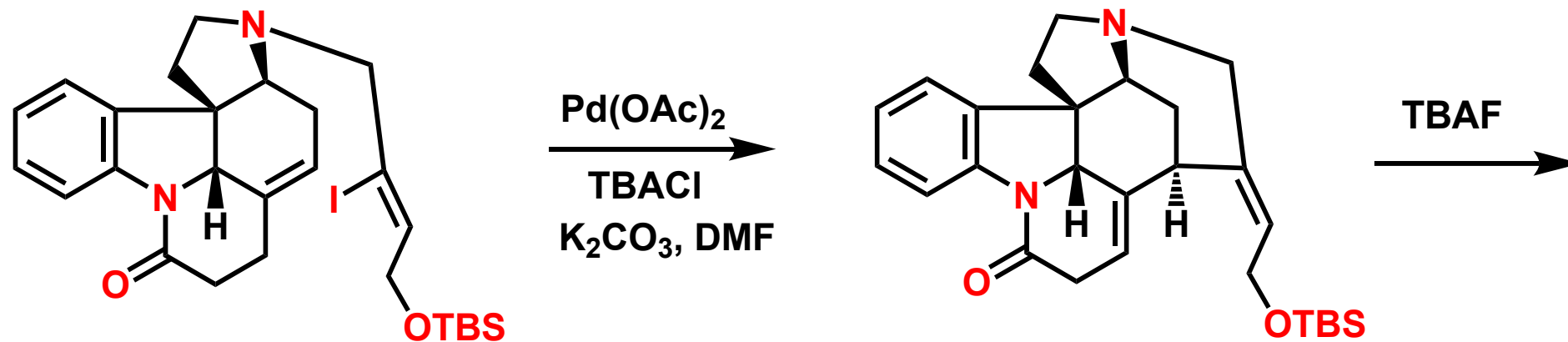
Rawal's Total Synthesis





Dieckmann cyclization

Rawal's Total Synthesis



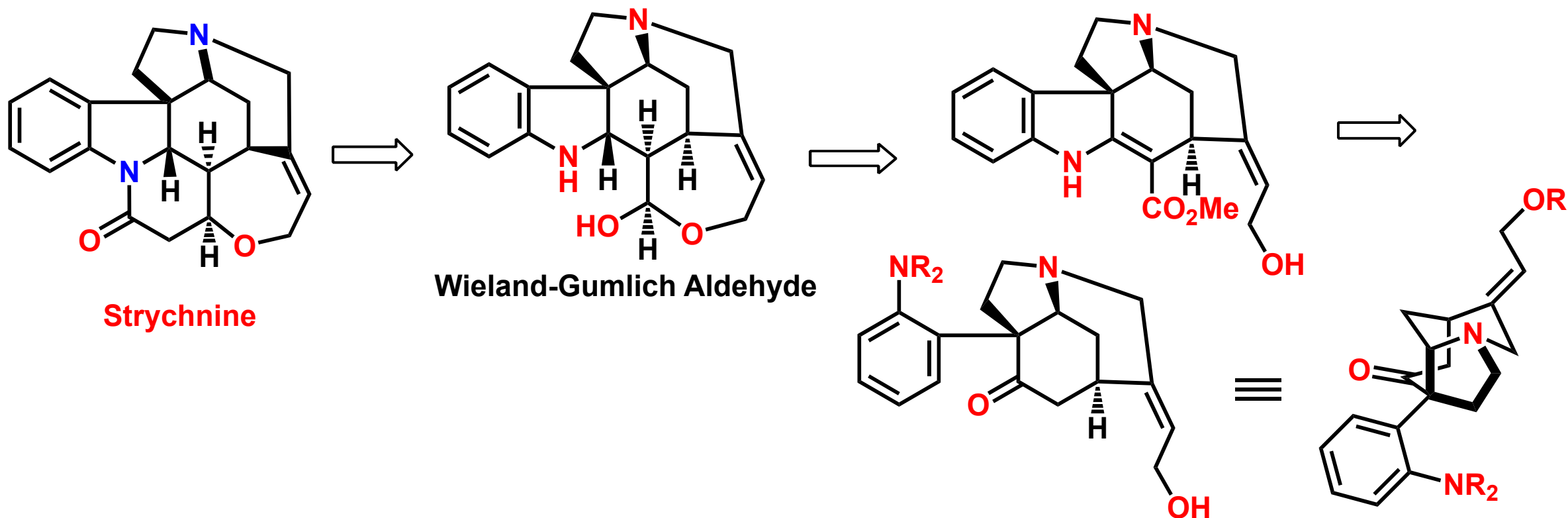
Isostrychnine

Strychnine

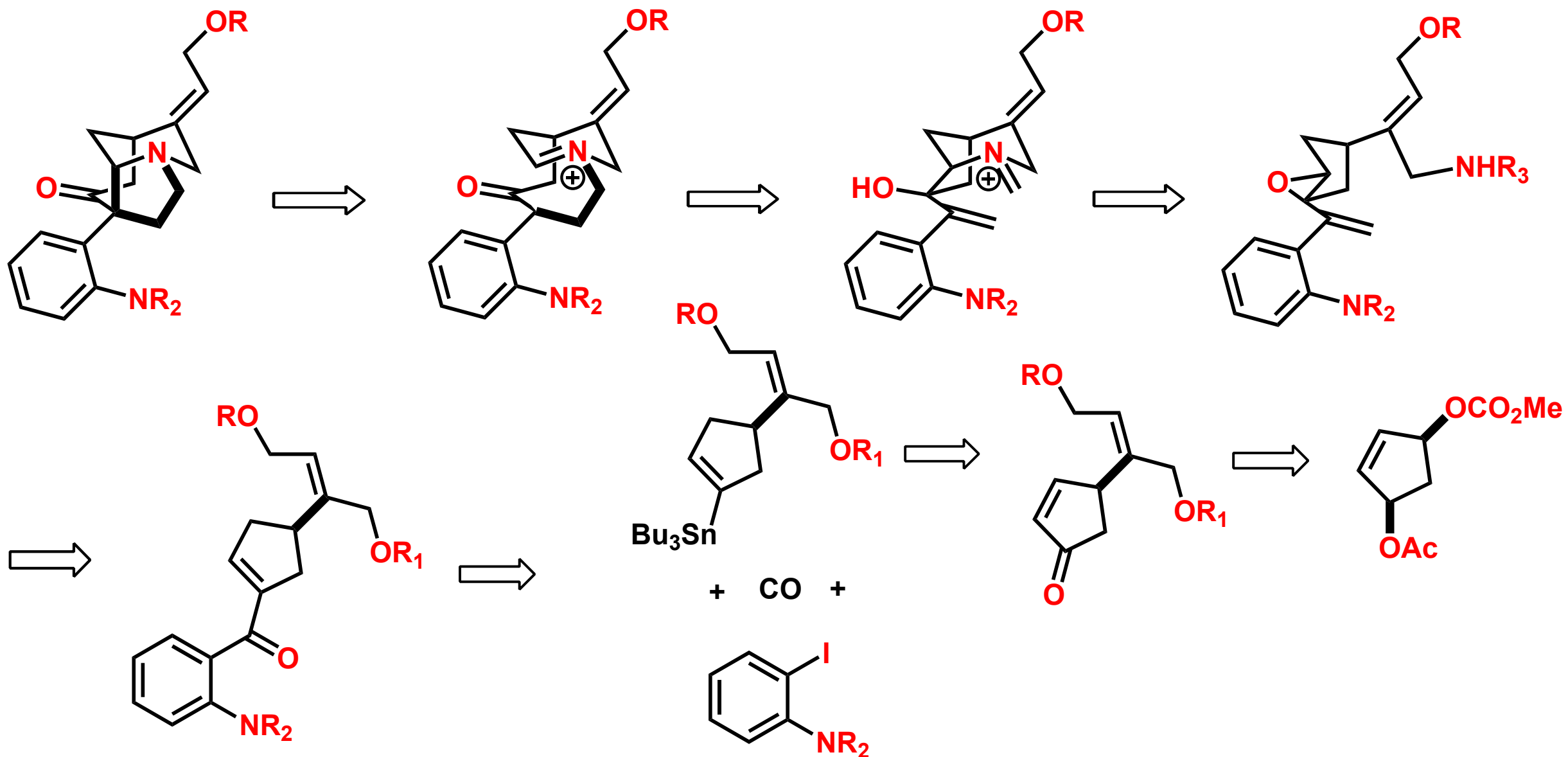
V. Rawal and co-workers. *J. Org. Chem.*, **1994**, *59*, 2685-86

Overman's Total Synthesis

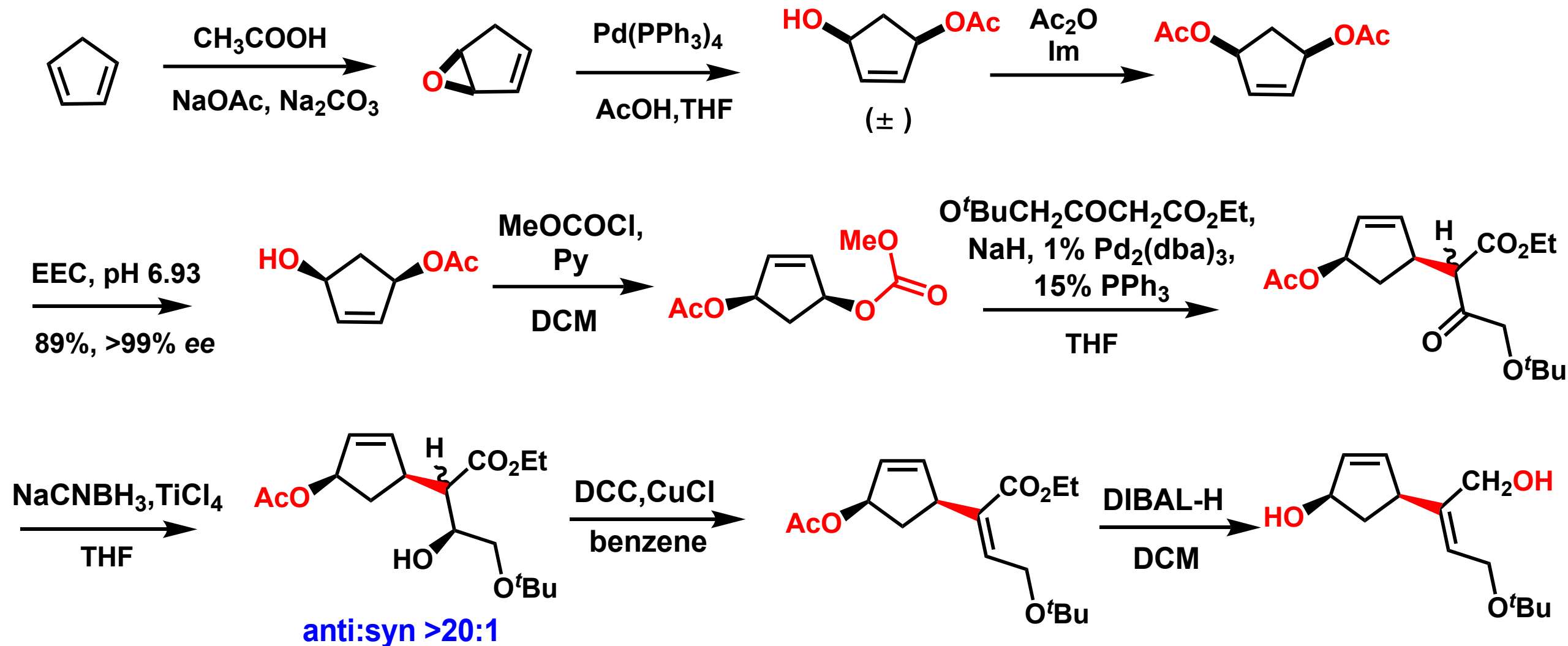
- First **asymmetric total synthesis** of (-)- strychnine
- This highly efficient total synthesis features the use of the cationic **aza-Cope-Mannich reaction** to assemble the pentacyclic strychnan core
- **20 step** total synthesis with **3% overall yield**

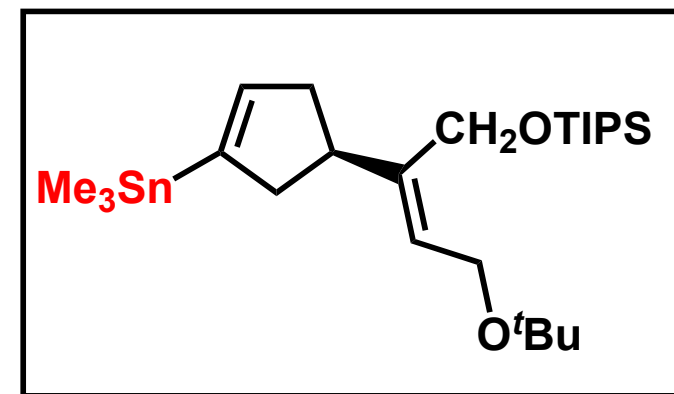
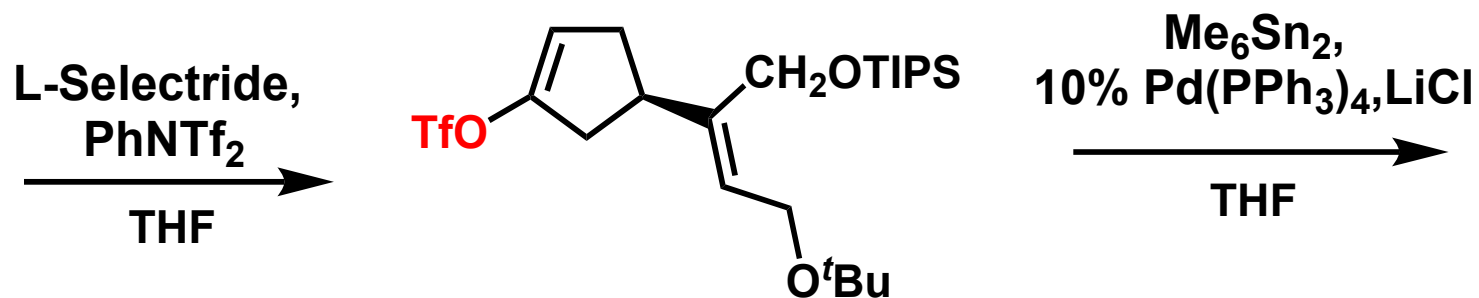
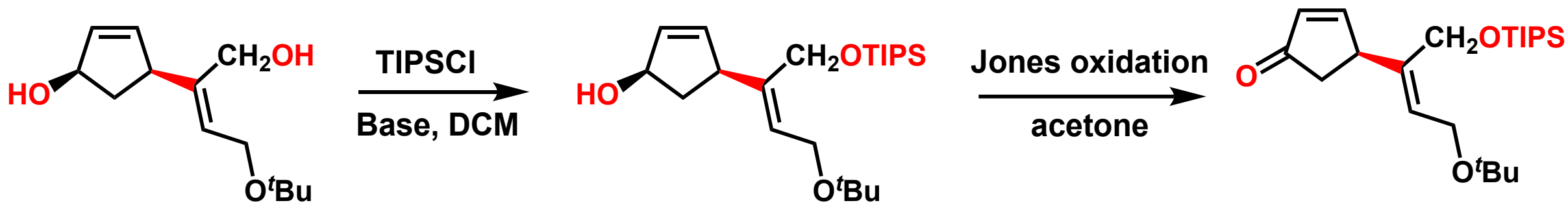


Overman's Total Synthesis



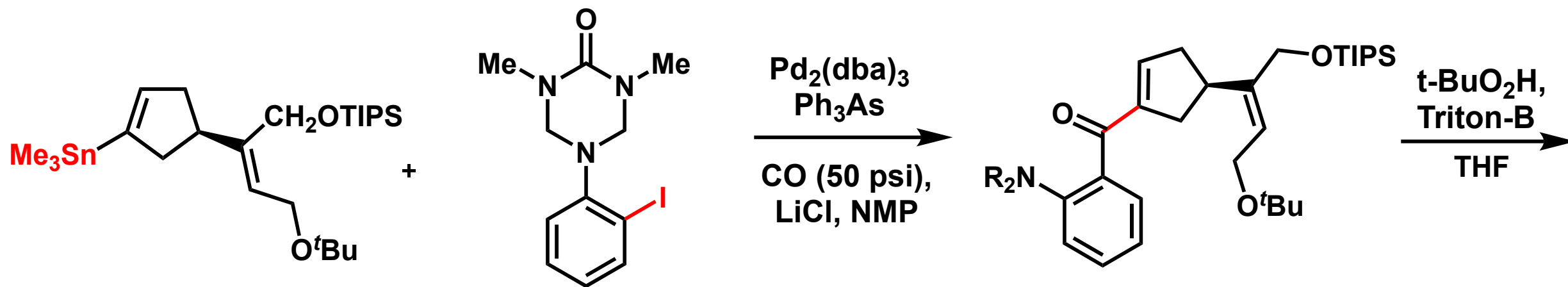
Overman's Total Synthesis



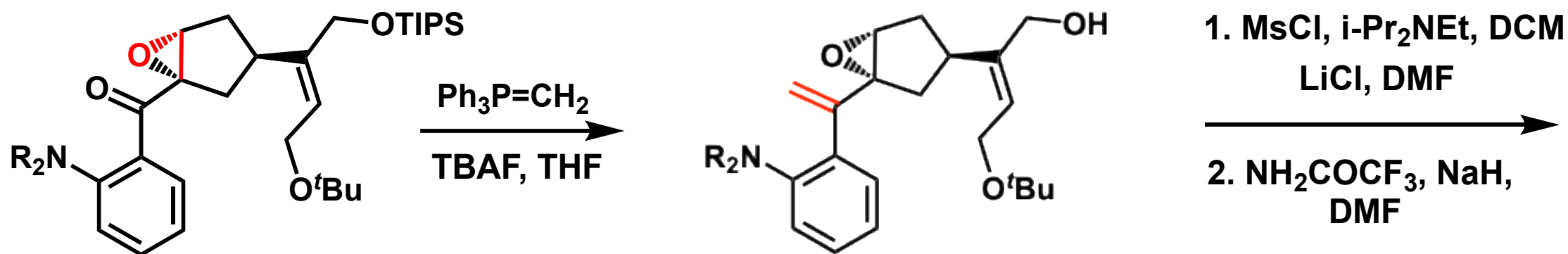


Fragment A

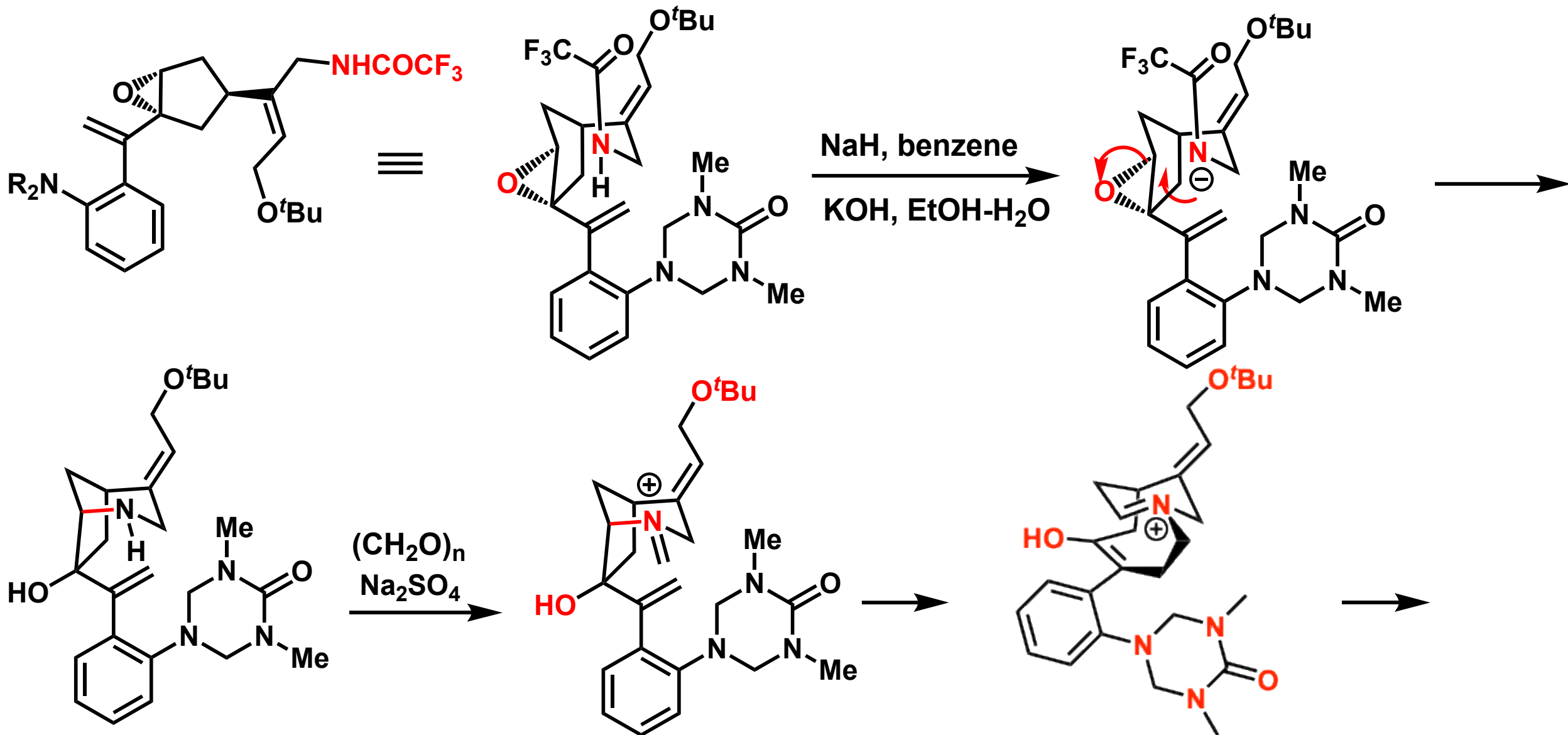
Overman's Total Synthesis



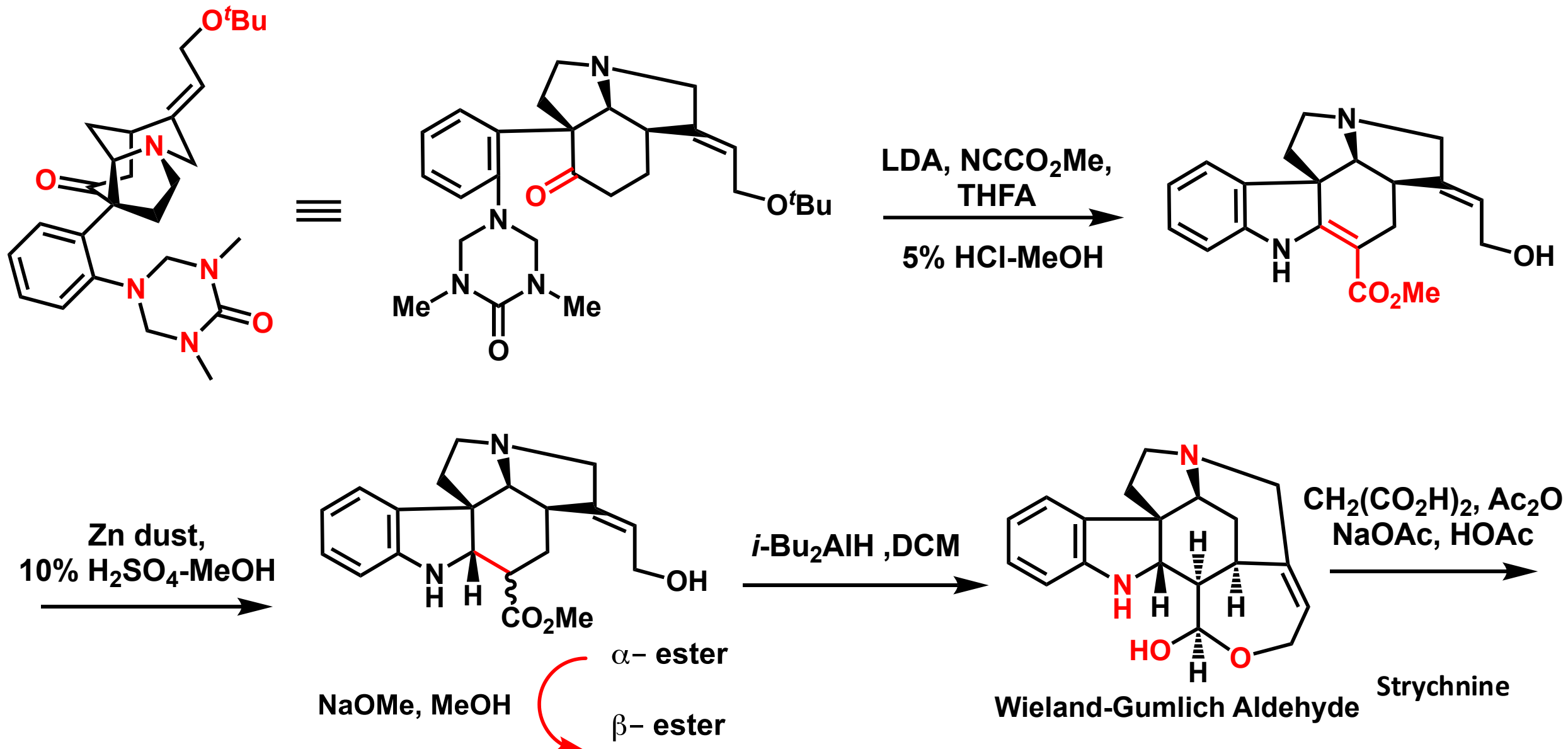
Fragment B



Overman's Total Synthesis

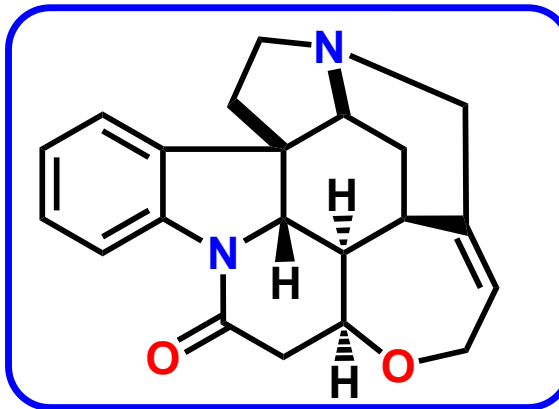


Overman's Total Synthesis





Kuehne's Synthesis of Strychnine



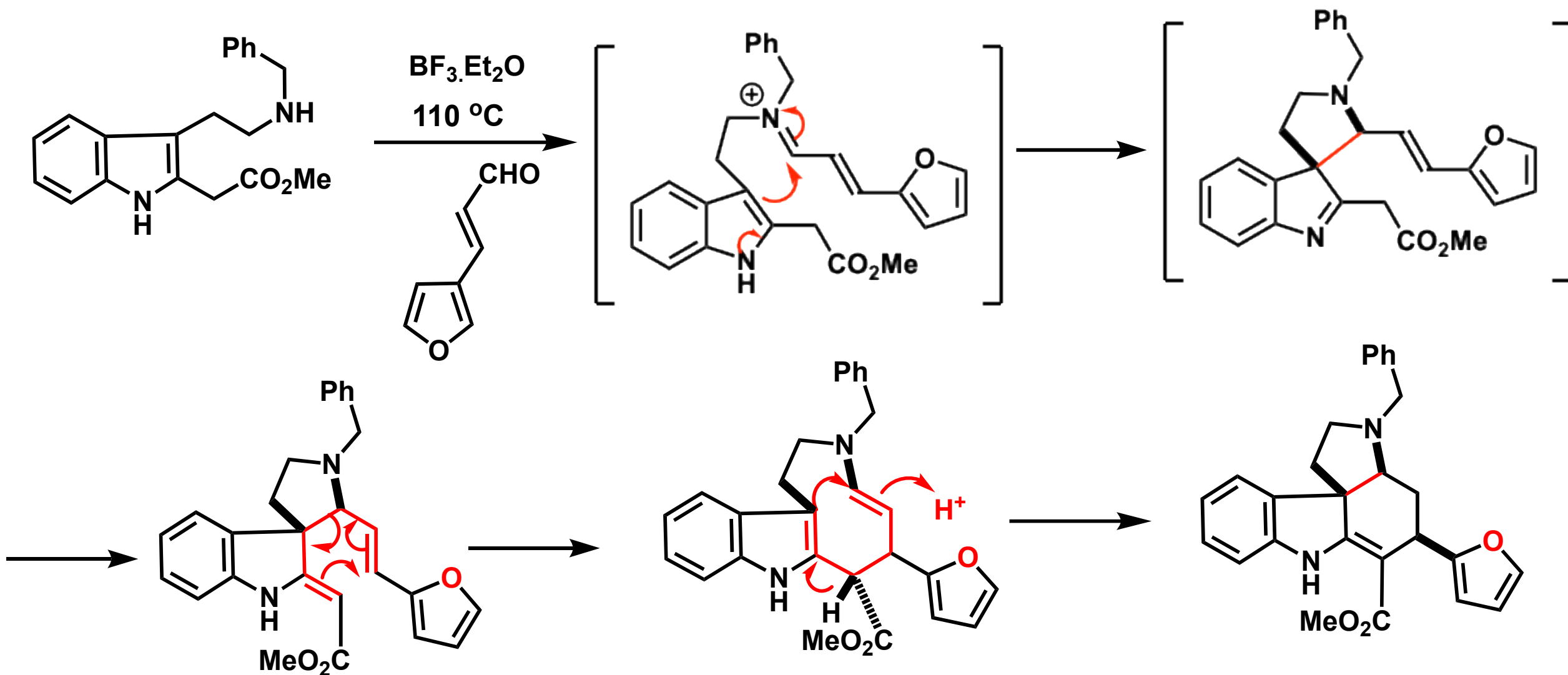
Strychnine

- This synthesis was based on new **tandem condensation**, **sigmatropic rearrangement**, and **cyclization sequence**
- **Racemic synthesis (14 steps)**
- This synthesis approach goes through **isostrychnine**

Kuehne, M. E.; *et al. J. Org. Chem.* **1993**, 58, 7490-7497



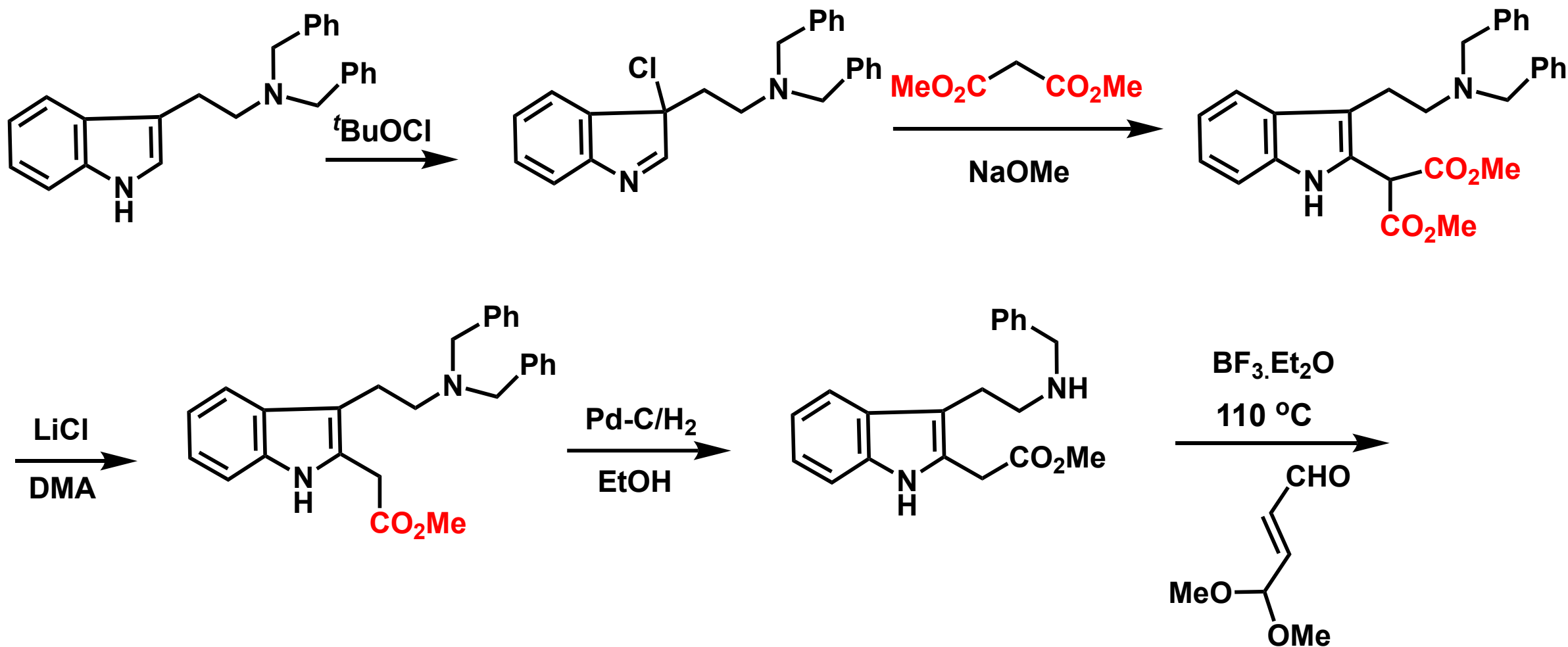
Synthetic Strategy Towards Strychnine



Kuehne, M. E.; Co-workers. *J. Org. Chem.* **1993**, *58*, 7482-7489



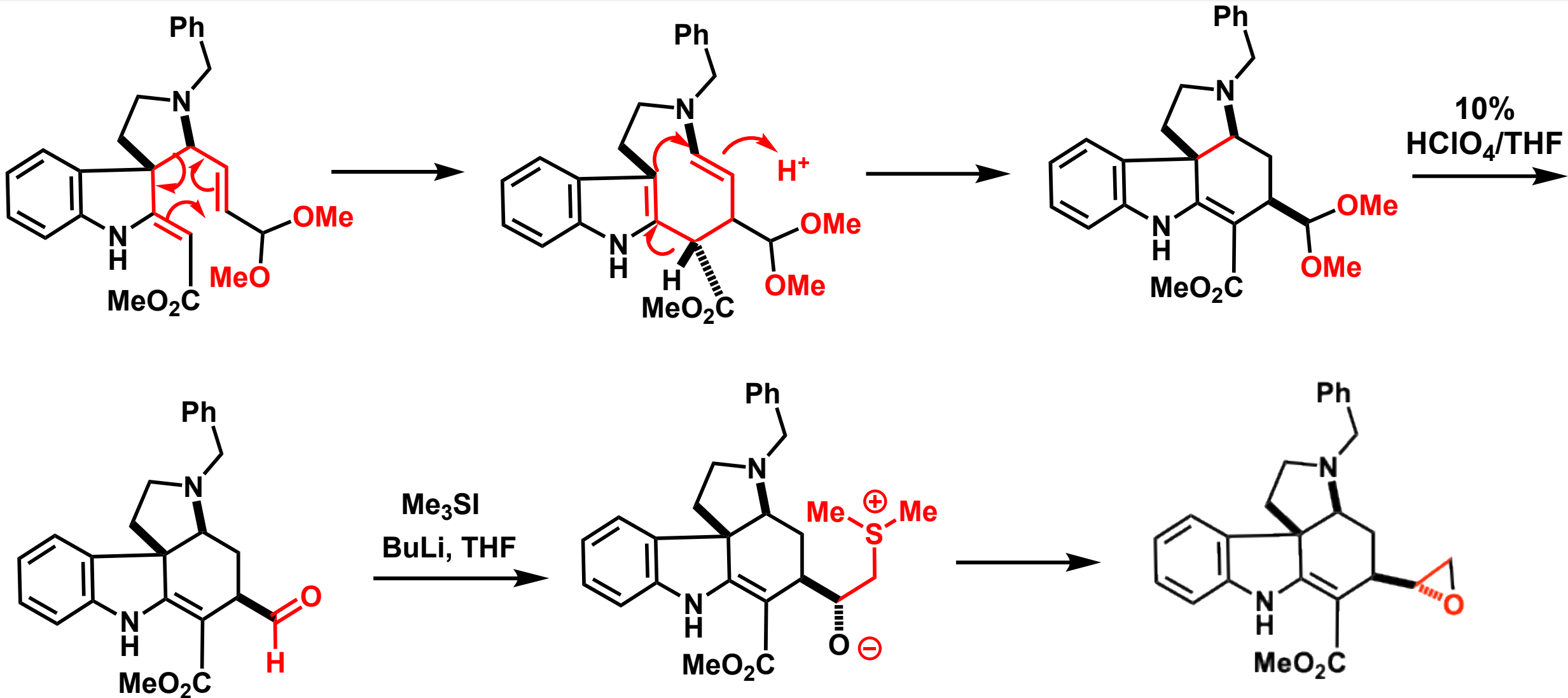
Synthetic Strategy Towards Strychnine



Kuehne, M. E.; Co-workers. *J. Org. Chem.* **1993**, *58*, 7482-7489

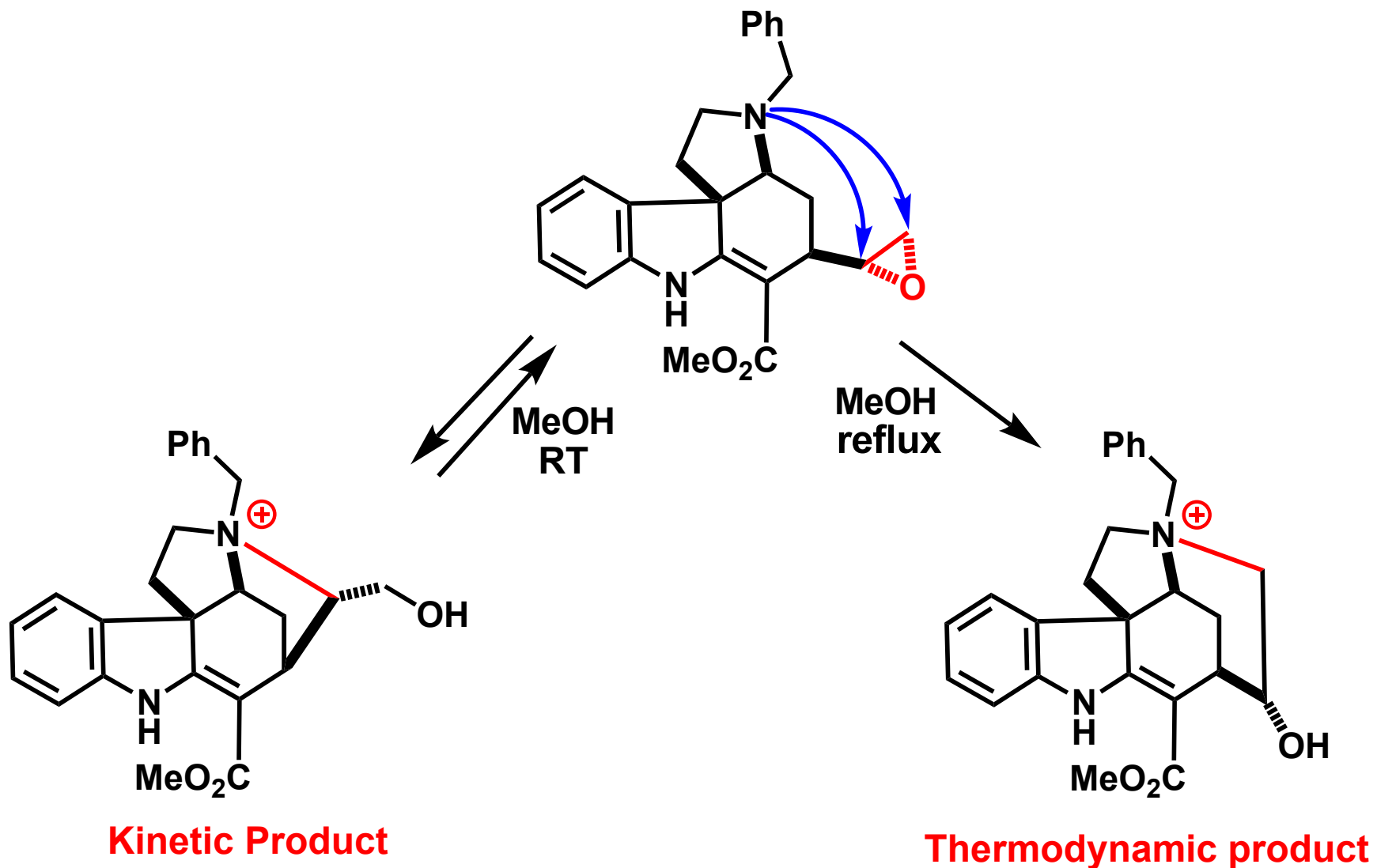


Synthetic Strategy Towards Strychnine



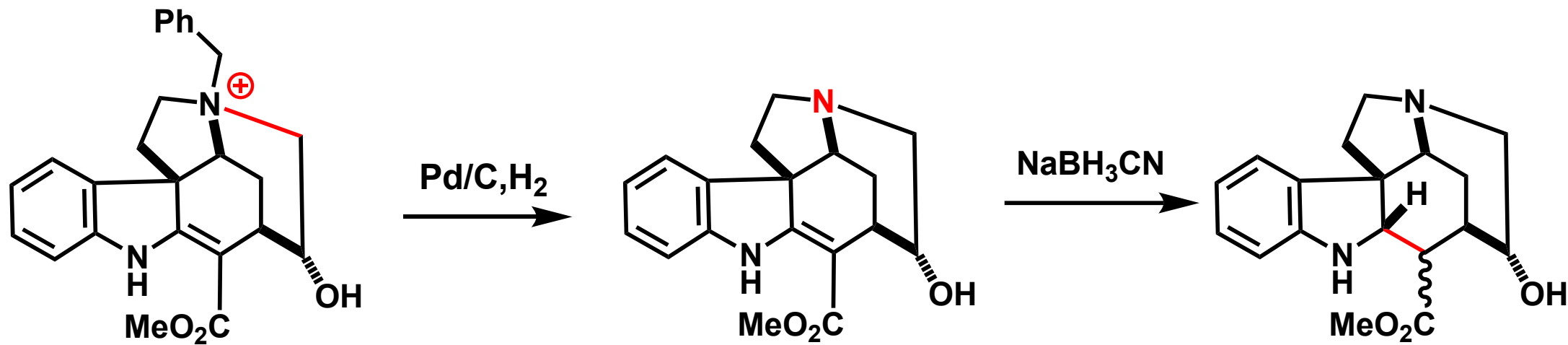


Synthesis of Pentacyclic Core

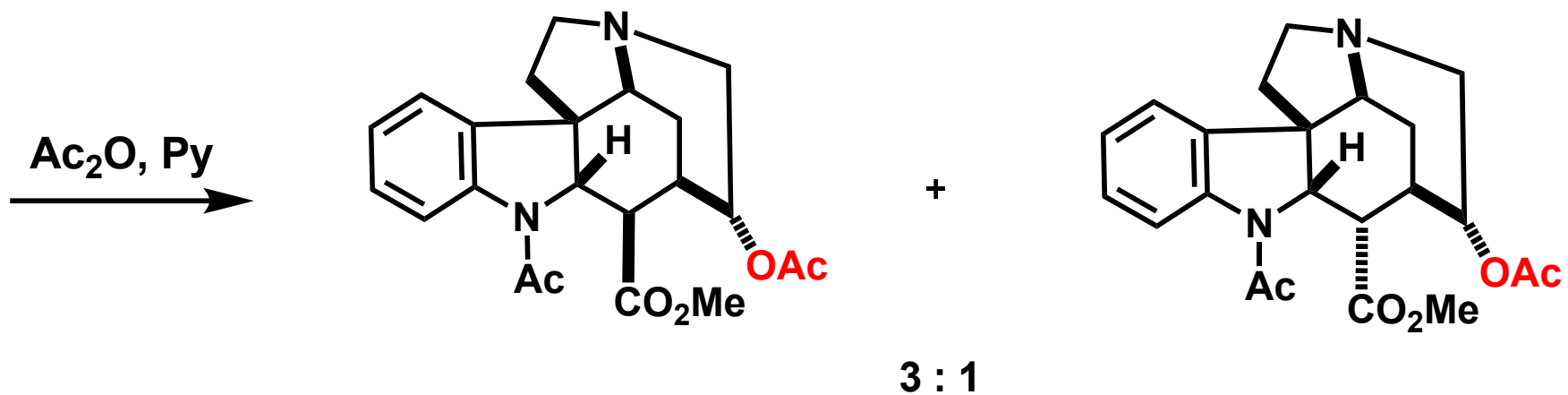




Synthesis of Pentacyclic Core

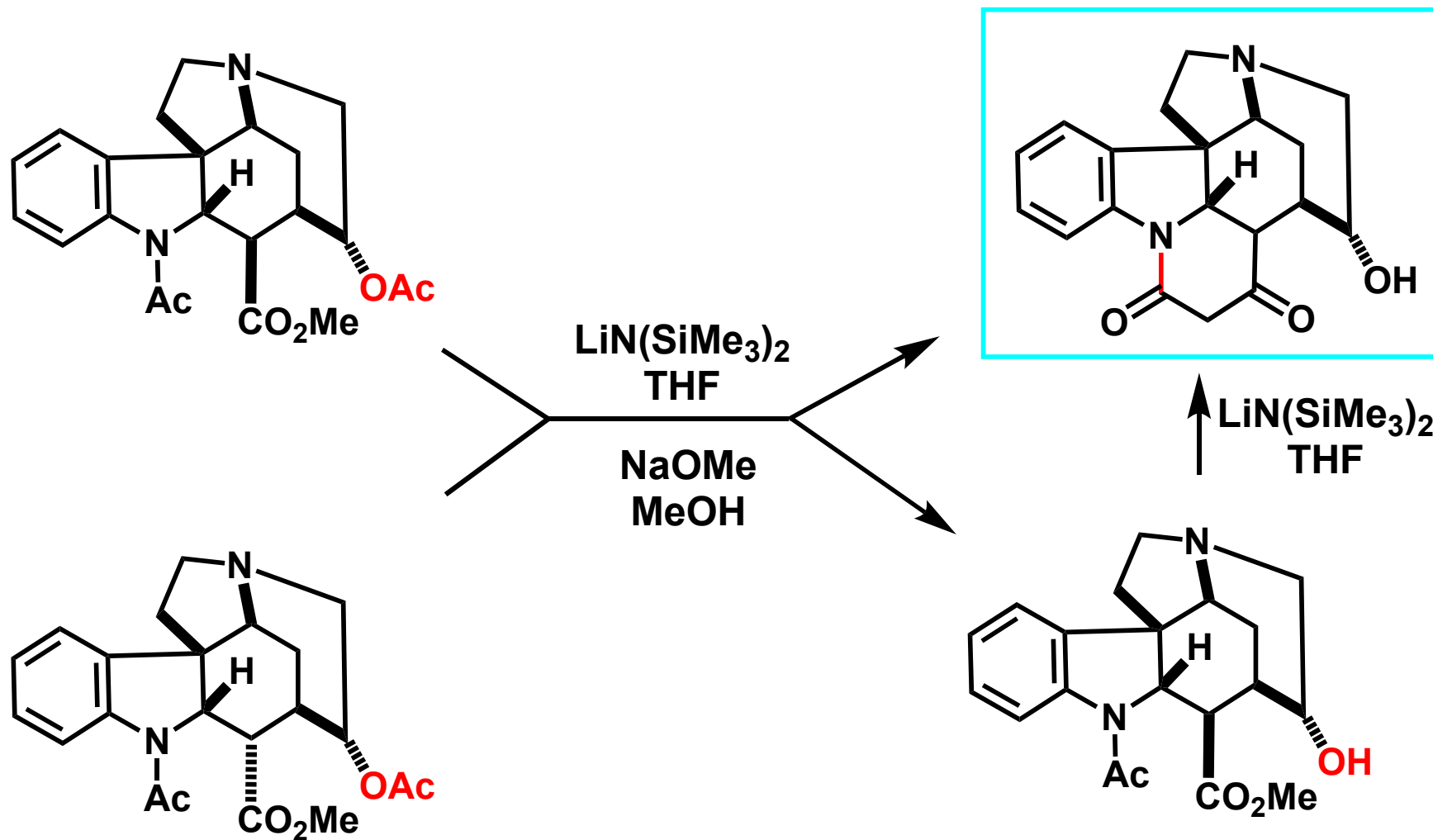


Thermodynamic product



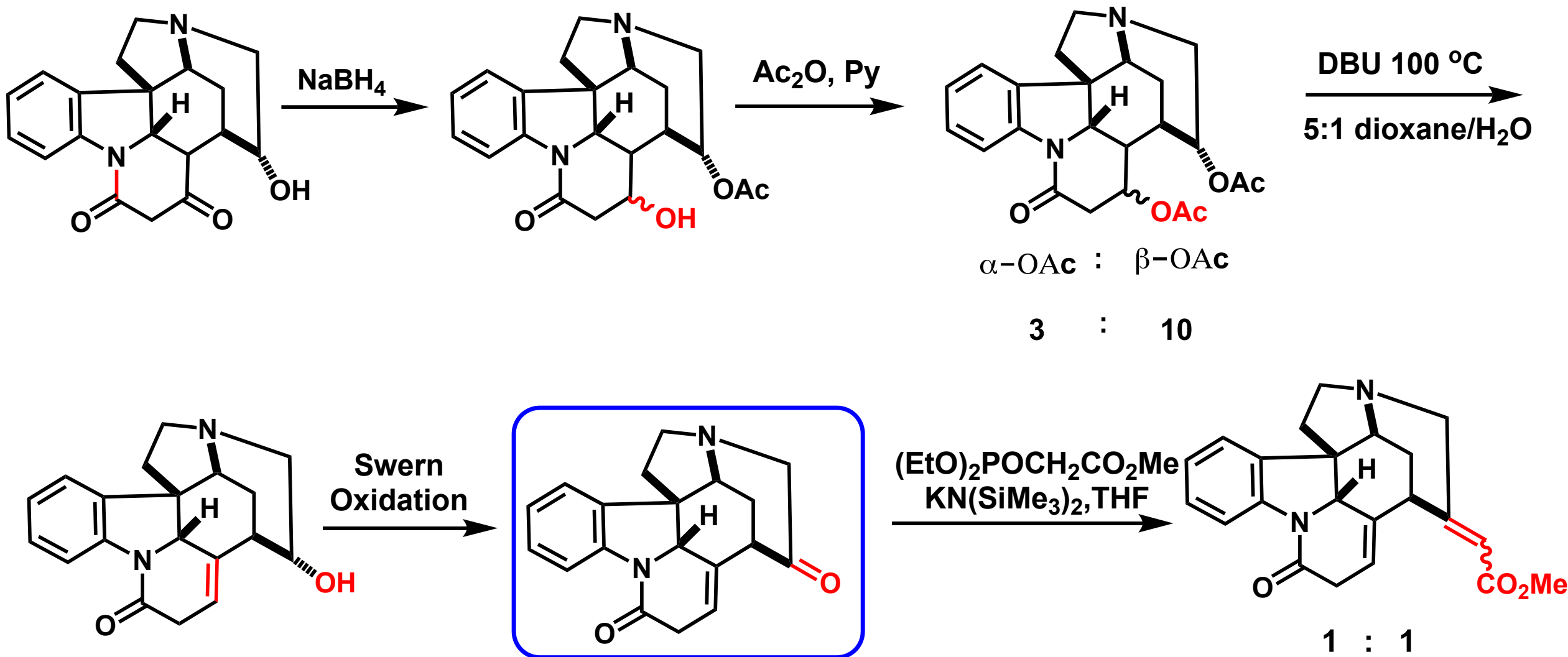


Forward Synthesis



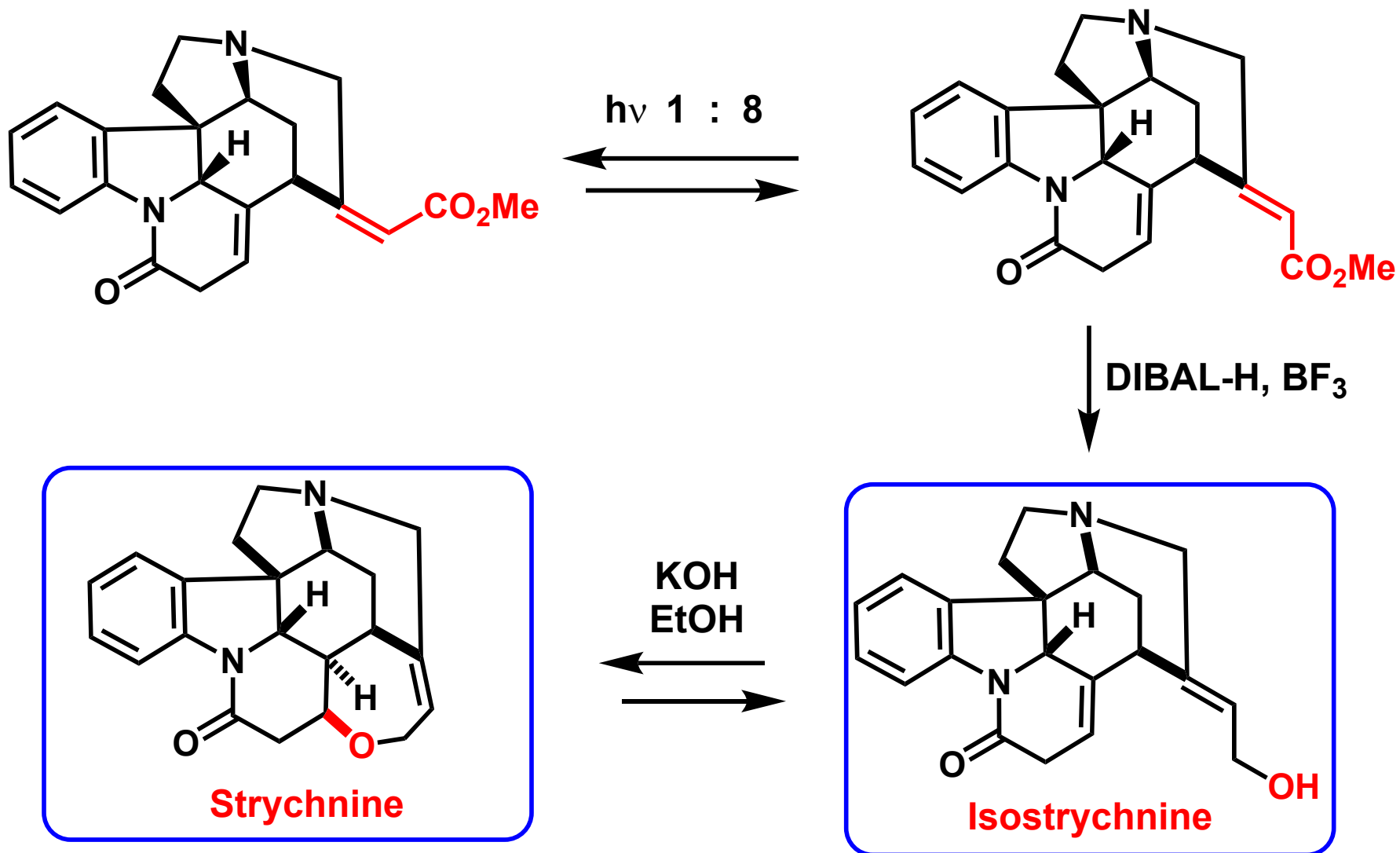


Forward Synthesis



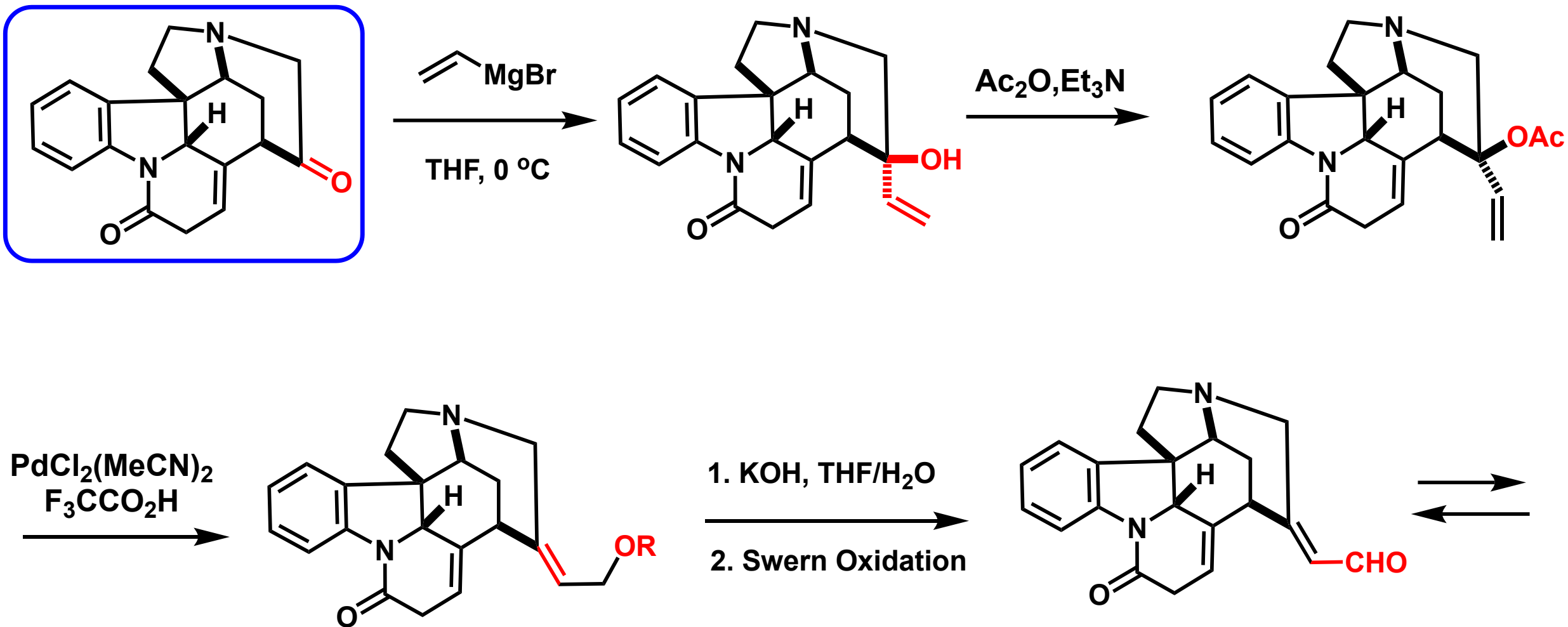


Completion of Synthesis of Strychnine





Vinyl Grignard Addition Route





Synthesis of Strychnine and Isostrychnine

