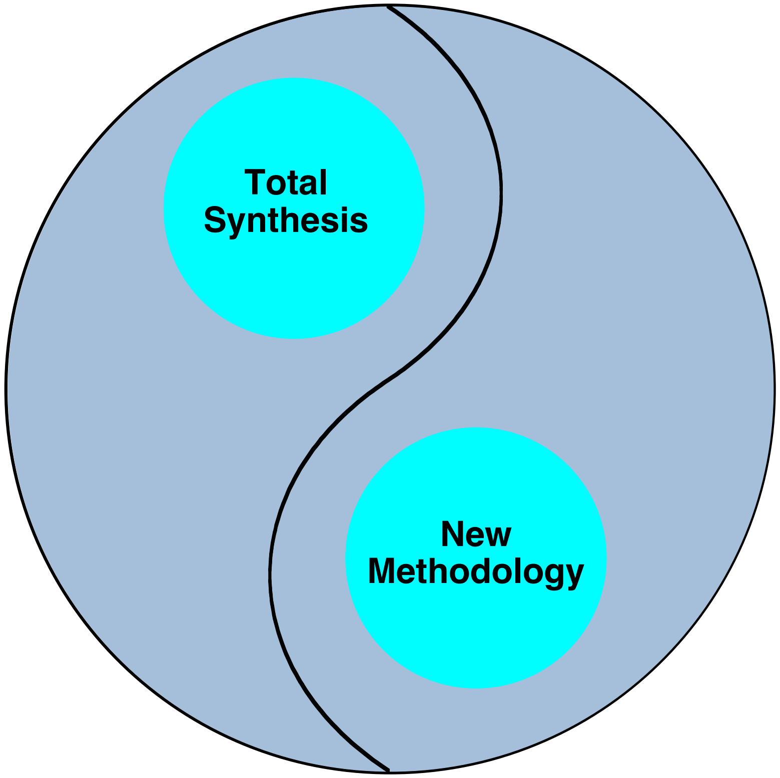
The Six Most Innovative Total Syntheses Known to Date



MacMillan Group Meeting
3-31-10
an opinion by
Anthony Casarez

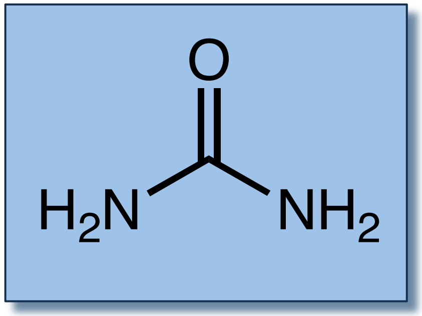
What Classifies as Innovative?

Innovation \i-nə-ˈvā-shən\ *n*:

1. The act of introducing something new.
2. A new idea, method, or device.

- Would introducing a new method in a total synthesis make it innovative? Yes but…
- Some innovations are considered to be more significant than others. How do we qualify these?
- In my view an innovation must dramatically change the landscape of our field or provide a method that is widely applicable.

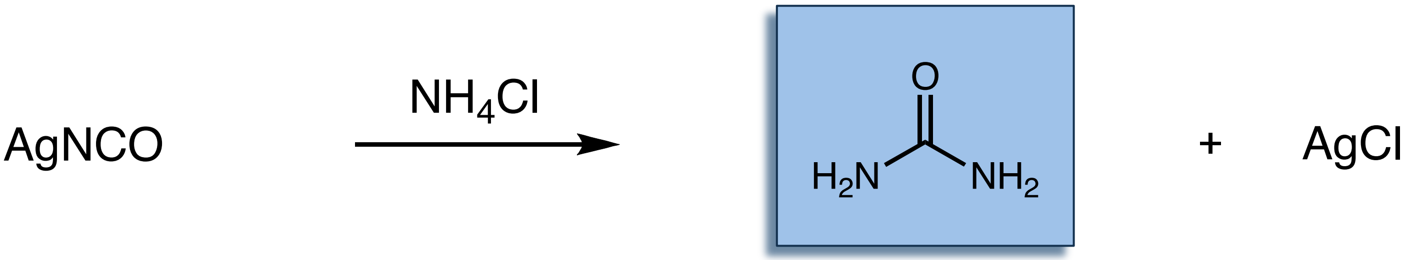
How Our Field was Born: UREA



- Isolated in 1773 from human urine (hence the name) by Hilaire M. Rouelle
- Intriguing to scientists who were eager to understand the mysteries of bodily functions .

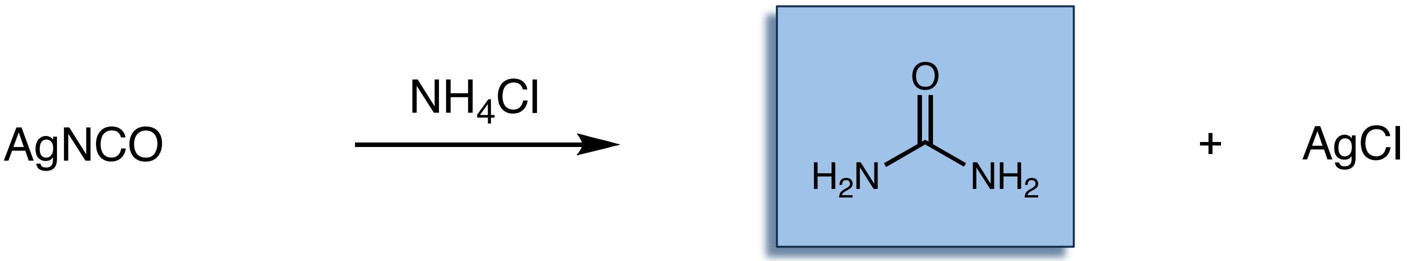
How Our Field was Born: UREA

- Friedrich Wöhler: 1800-1882; student of Jöns Jakob Berzelius.
- The synthesis of urea is known as the event that begot the field of synthetic organic chemistry.
- **“I cannot, so to say, hold my chemical water, and must tell you that I can make urea, without thereby needing to have kidneys, or anyhow, an animal, be it human or dog.”**
- Wöhler’s discovery should’ve refuted vitalism, the belief that organic molecules can only come from life which possesses a “vital force,” but the skeptics remained because he did not synthesize a C–C bond.



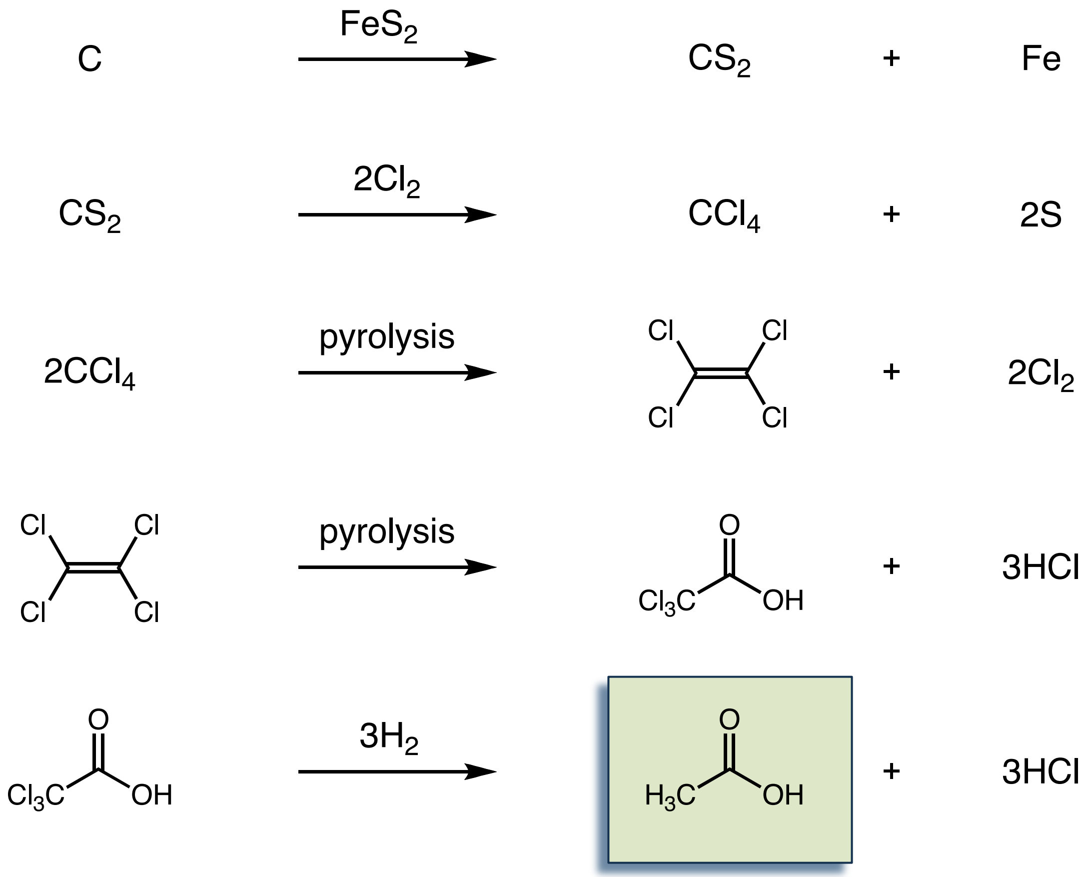
How Our Field was Born: UREA

- As if the birth of synthetic organic chemistry wasn't enough…
- Wöhler thought he was using AgOCN (silver cyanate) instead of AgNCO (silver isocyanate), both possessing the same formula as AgCNO (silver fulminate), studied by Justus von Liebig, but having different chemical properties.
- **This gave rise to the notion of isomerism.**



Convincing the Skeptics

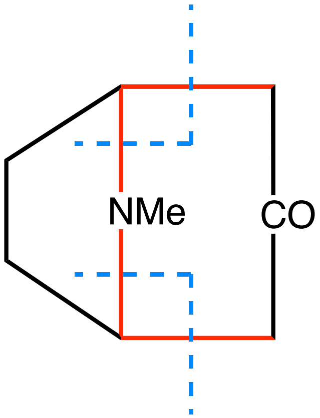
- 15 years later Hermann Kolbe silenced (most) skeptics by synthesizing acetic acid, literally from elements.



Retrosynthetic Application: Tropinone

Sir Robert Robinson

> "By the imaginary hydrolysis at the points indicated by the dotted lines, the substance may be resolved into succinaldehyde, methylamine, and acetone, and this observation suggested a line of attack of the problem which has resulted in a direct synthesis."
>
> –Sir Robert Robinson *J. Chem. Soc.* **1917**, 762.



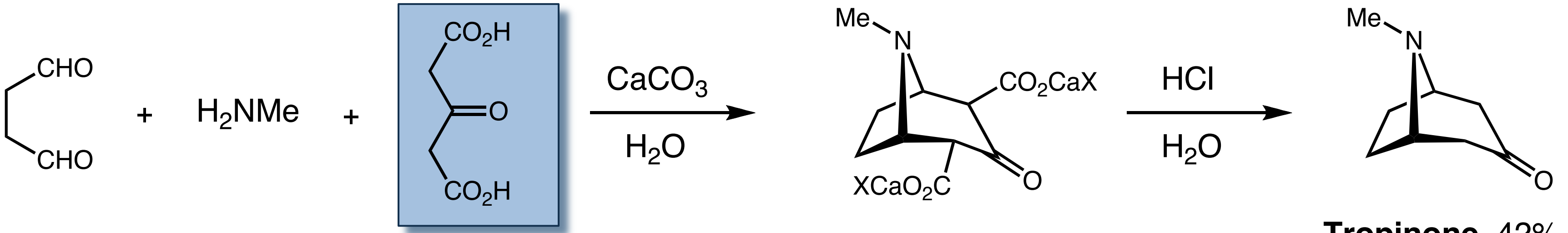
Tropinone

- Sir Robert's analysis was one of the simplest yet most powerful suggestions of its time. The fact that it worked was a testament to his intuition.

Retrosynthetic Application: Tropinone

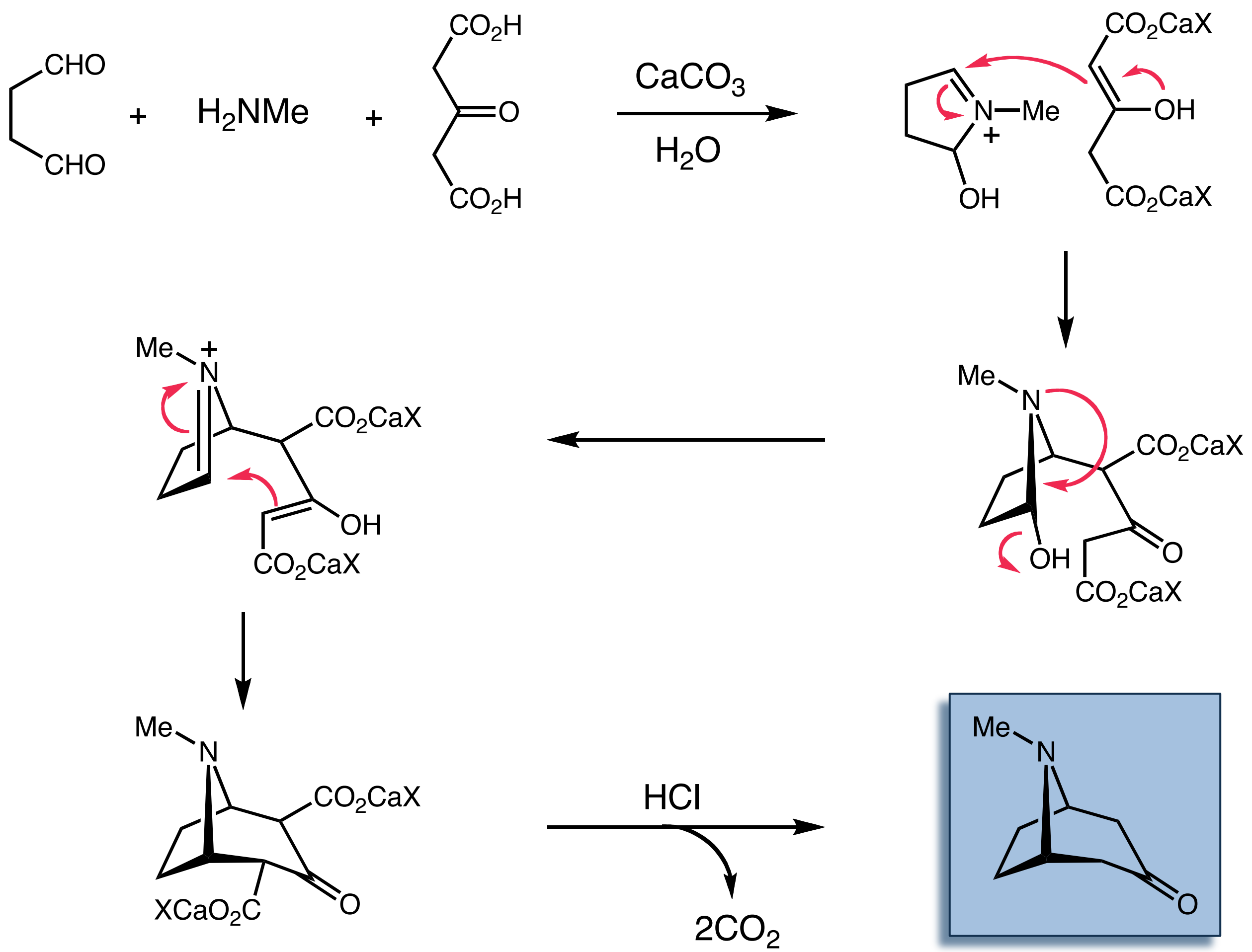
> "In Searching for a method of synthesis of any substance it is always convenient to be able to recognize the formation of traces of the desired product…tropinone is obtained in small yield by the condensation of succinaldehyde with acetone and methylamine in aqueous solution."
>
> –Sir Robert Robinson *J. Chem. Soc.* **1917**, 762-8.

- The forward synthesis only required a slight modification of starting materials.



Tropinone, 42%

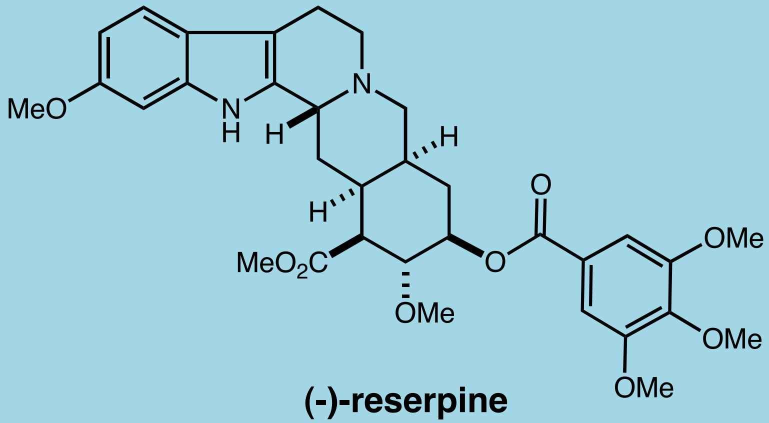
Tropinone: Mechanism



> “We have here a case where three rather simple molecules spontaneously unite into a complicated system, which earlier we could only build up step by step through a long series of reactions (13). **We may suppose that here Sir Robert has found the key to nature’s own way of working.**”
>
> –A. Fredga: Robinson’s Nobel presentation speech (1947).

Reserpine

R. B. Woodward

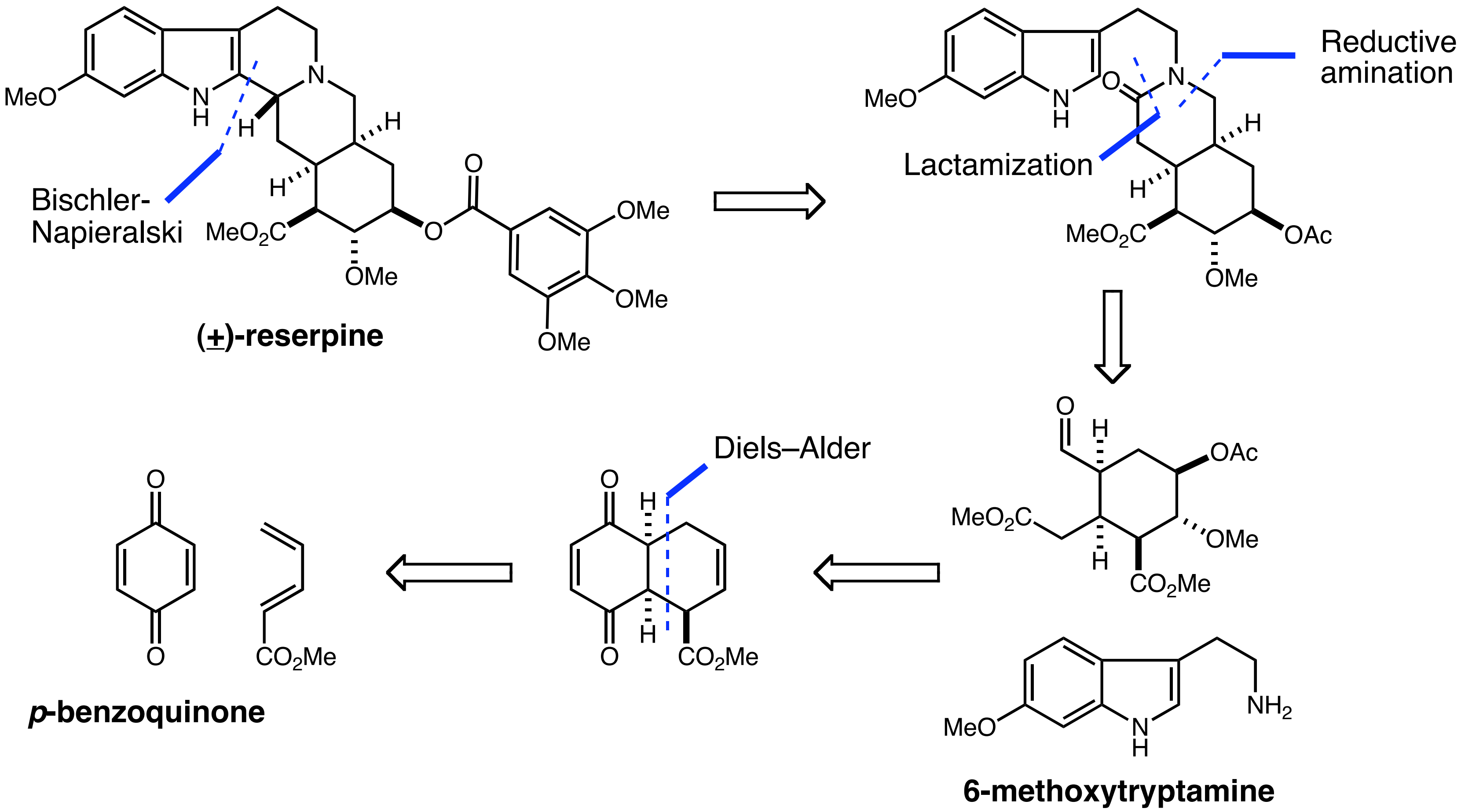


(-)-reserpine

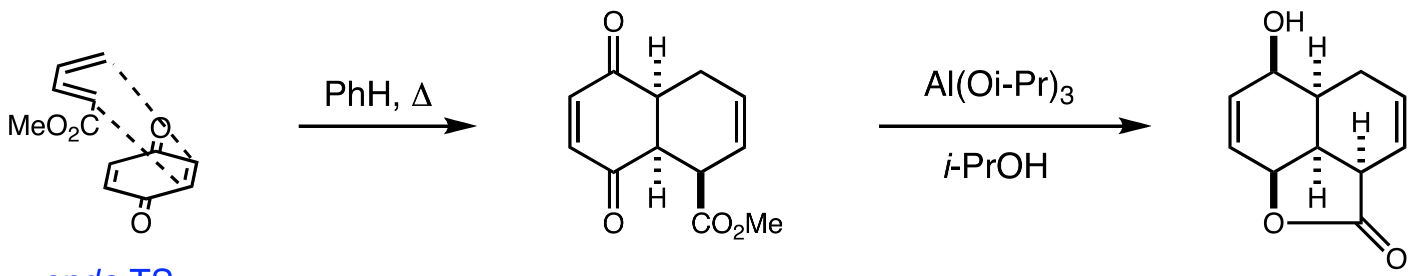
- Known as one of the hallmarks of synthetic manipulation by a master of the field.
- One of the greatest achievements of Woodward's career especially considering only IR and elemental analysis were used as guides.
- The dramatic conclusion taught chemists an invaluable lesson of thermodynamic engineering.

Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J; Kierstead, R. W. *J. Am. Chem. Soc.*, **1956**, *78*, 2023.

Reserpine: Retrosynthetic Analysis



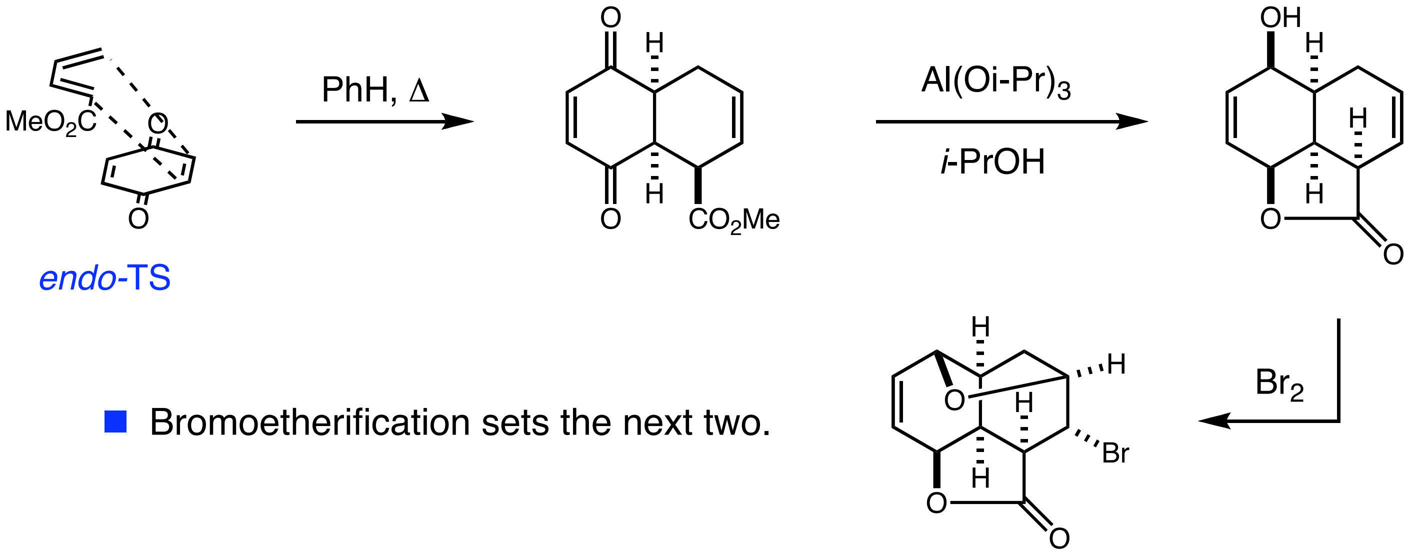
Reserpine



endo-TS

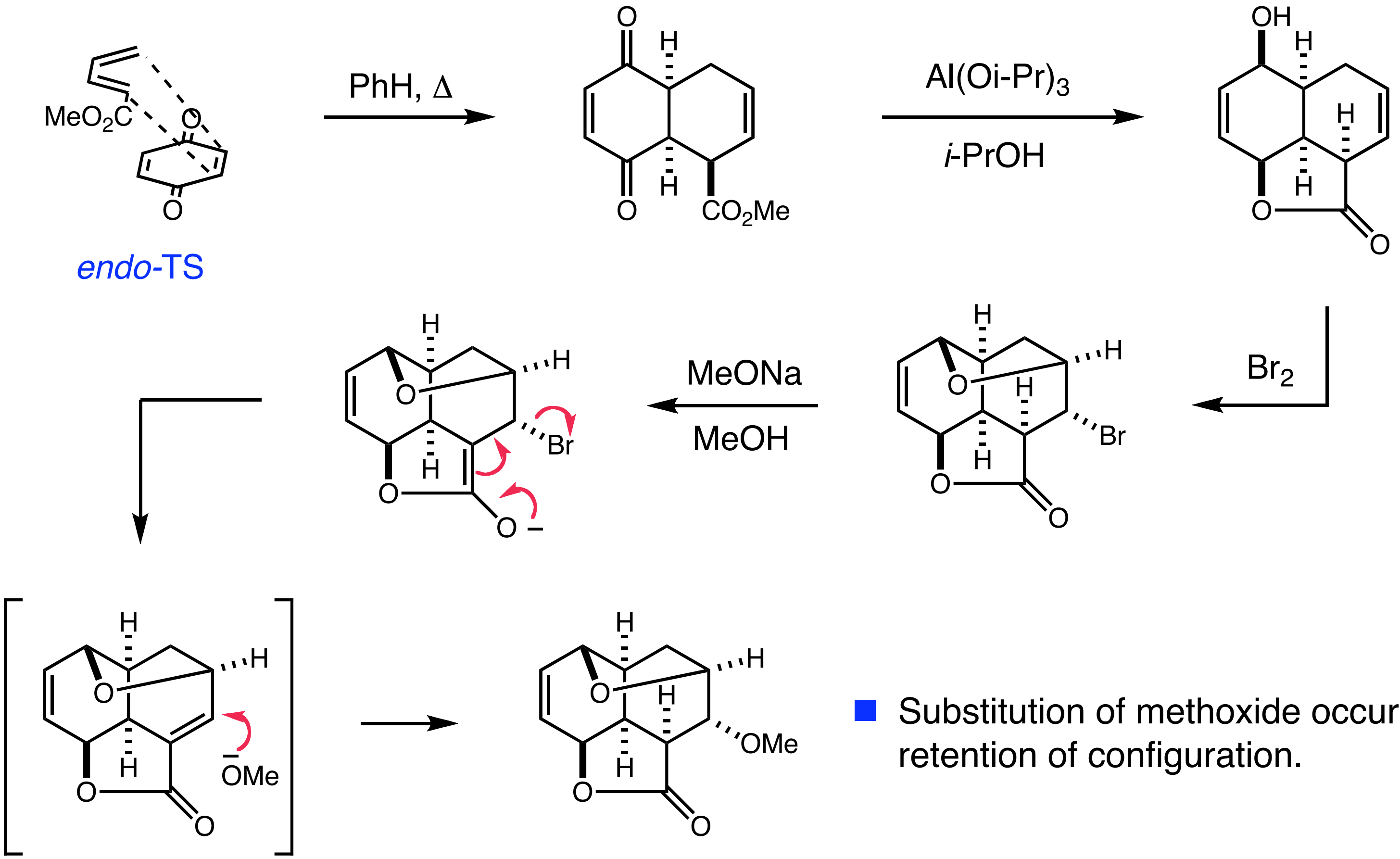
- A Diels–Alder sets the first three stereocenters
- Meerwein–Pondorff–Verley reduction creates the next two causing a spontaneous lactonization with the nearby ester.

Reserpine: Molecular Judo



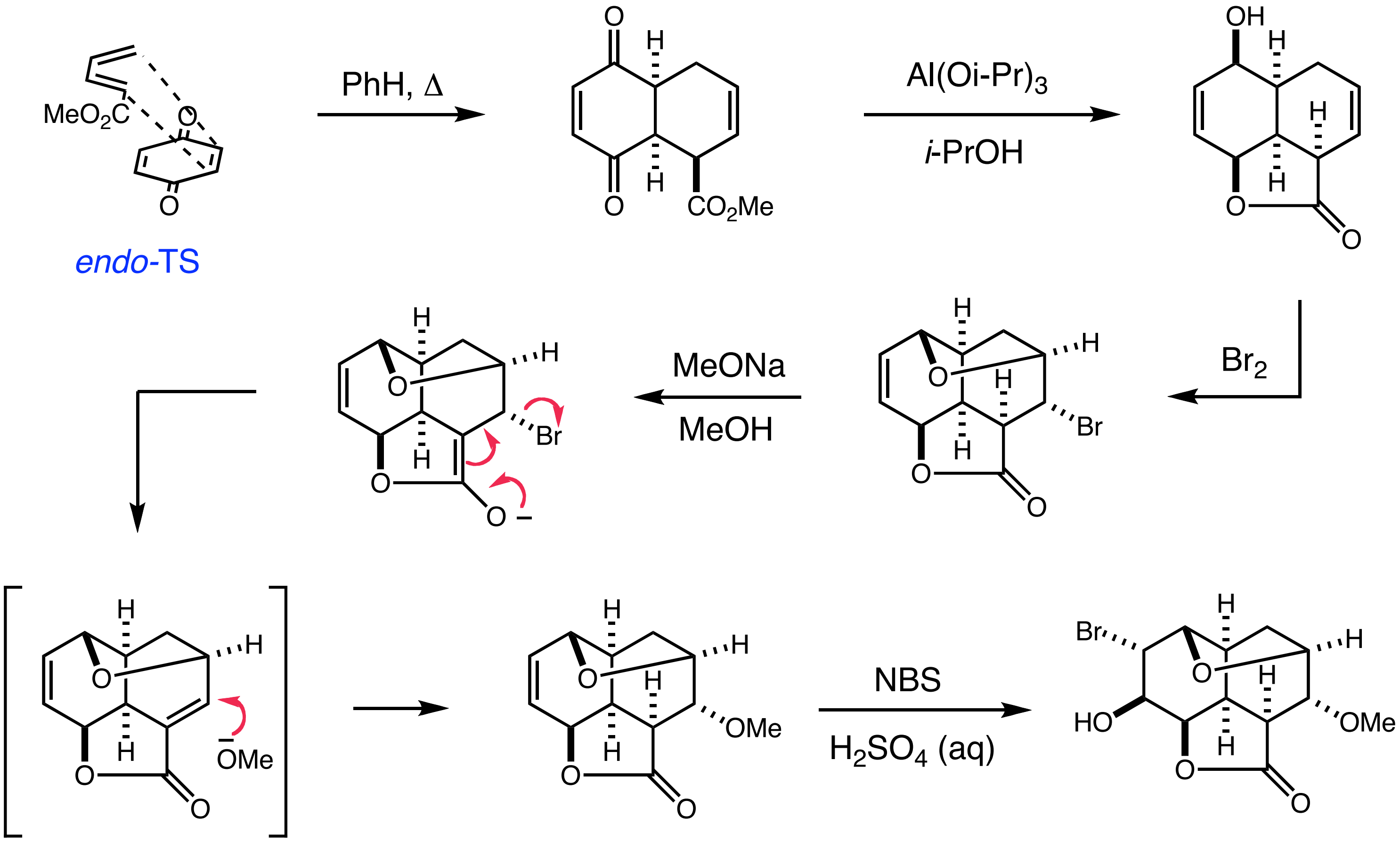
- Bromoetherification sets the next two.

Reserpine: Molecular Judo

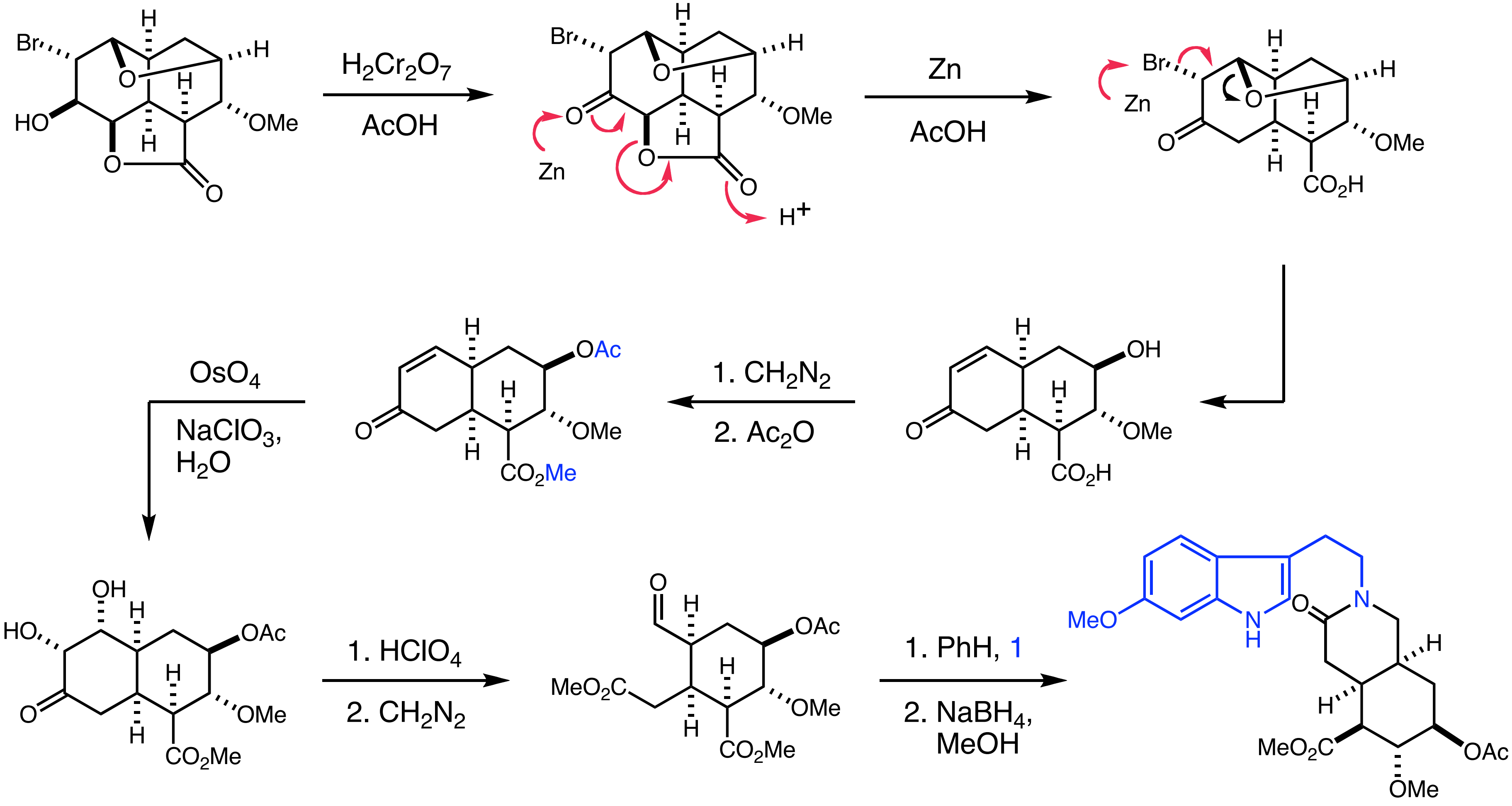


- Substitution of methoxide occurs with retention of configuration.

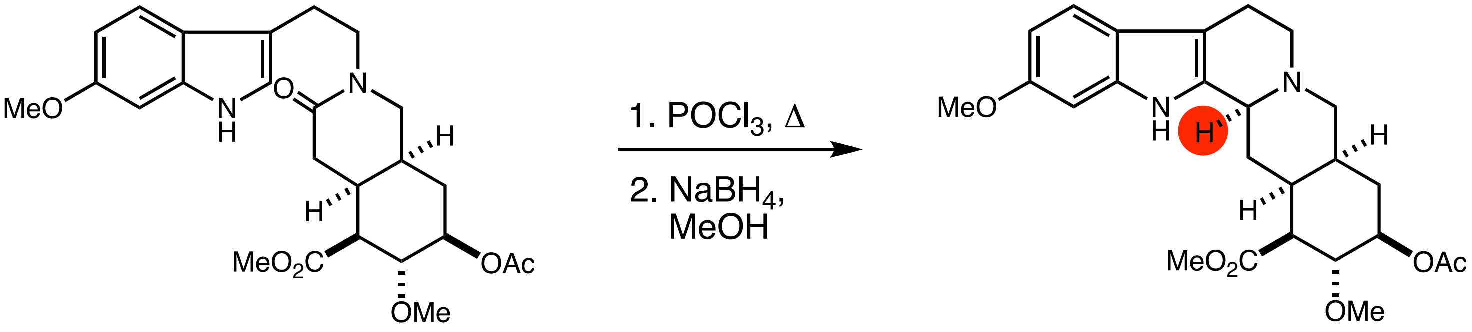
Reserpine: Molecular Judo



Reserpine


Br
HO
O
H
OMe
H₂Cr₂O₇
AcOH
Zn
H⁺
Zn
AcOH
CO₂H
OH
OAc
CO₂Me
1. CH₂N₂
2. Ac₂O
OsO₄
NaClO₃,
H₂O
1. HClO₄
2. CH₂N₂
MeO₂C
1. PhH, 1
2. NaBH₄,
MeOH
MeO
N
H

Reserpine



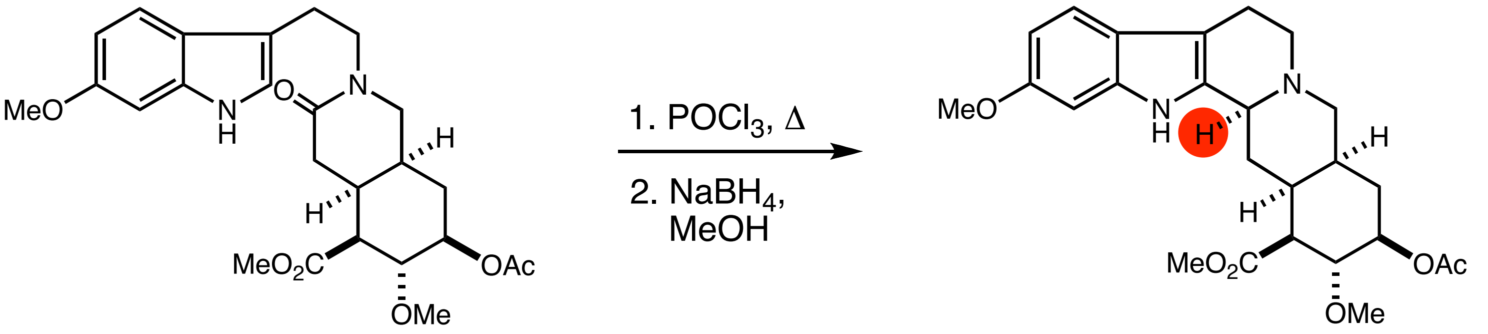
1. $POCl_3$, Δ

2. $NaBH_4$, MeOH

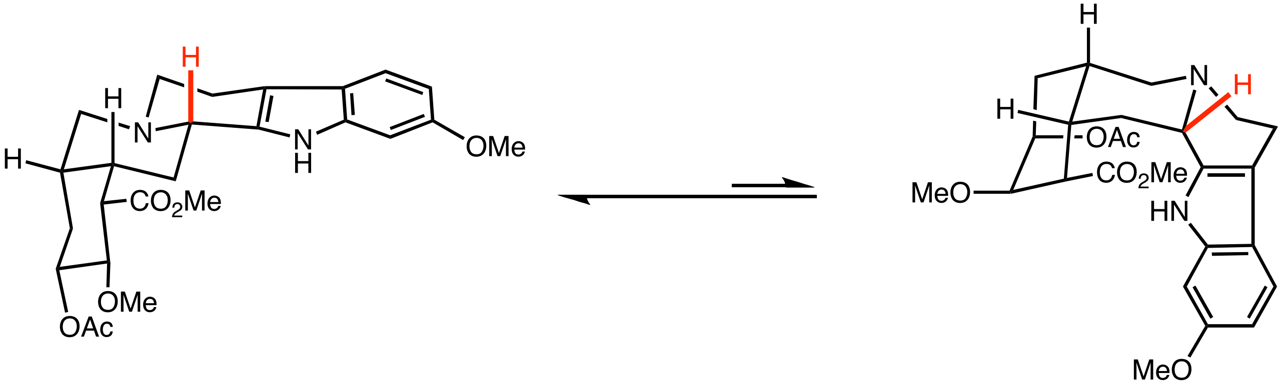
(±)-methyl-*O*-acetylisoreserpate

- Reduction of the iminium ion happens on the convex face providing the undesired epimer.

Reserpine

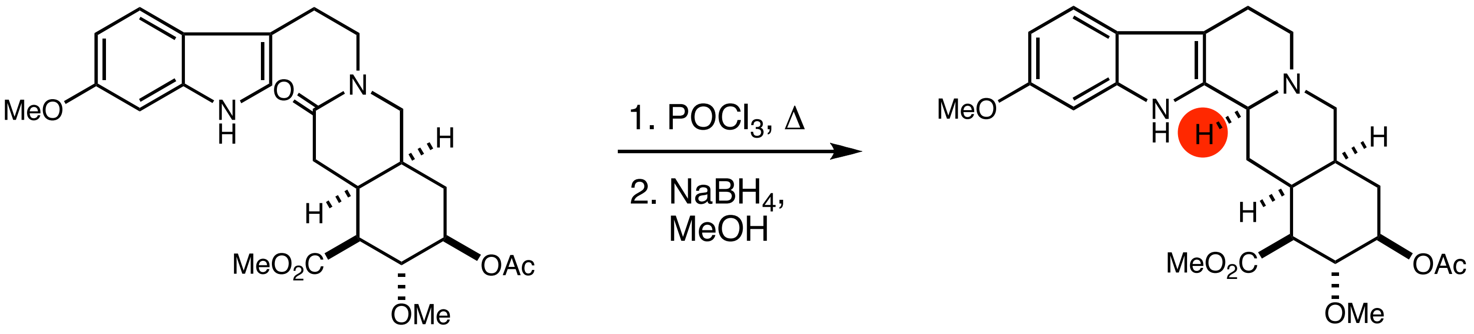


(±)-methyl-*O*-acetylisoreserpate

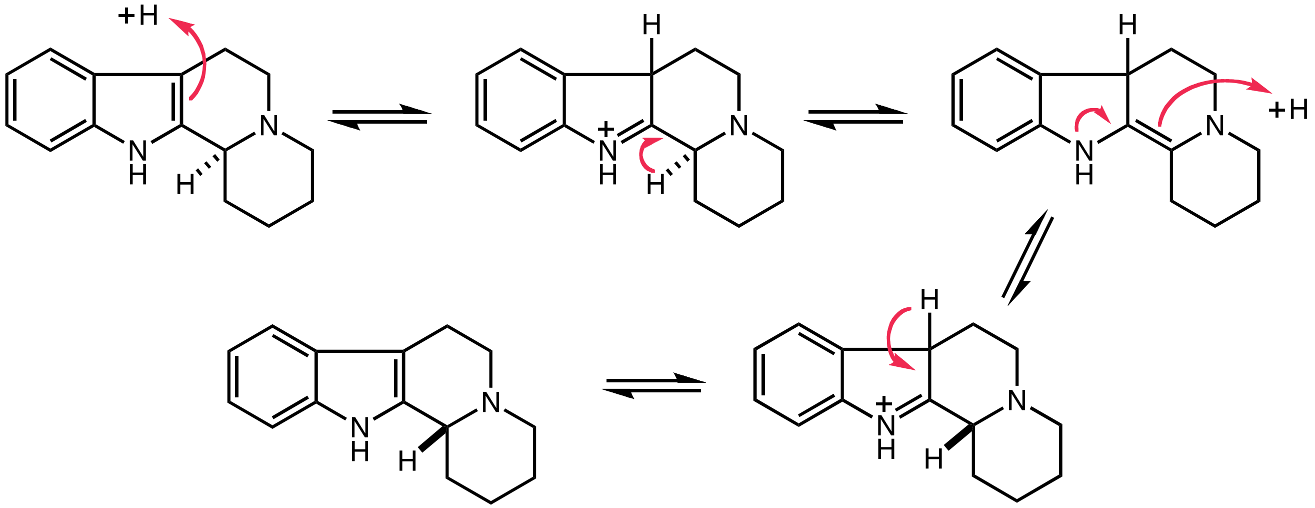


- Thermodynamics favors the wrong conformation for an acid catalyzed epimerization.

Reserpine

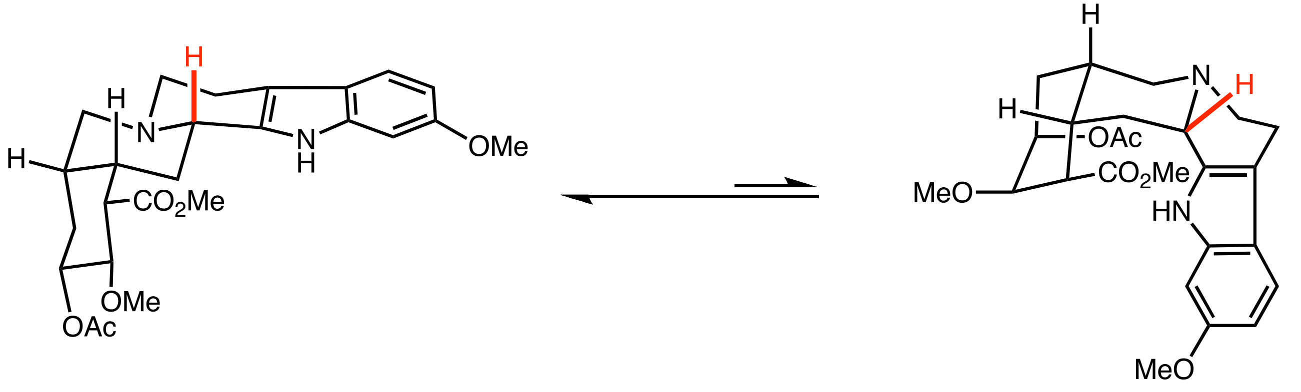


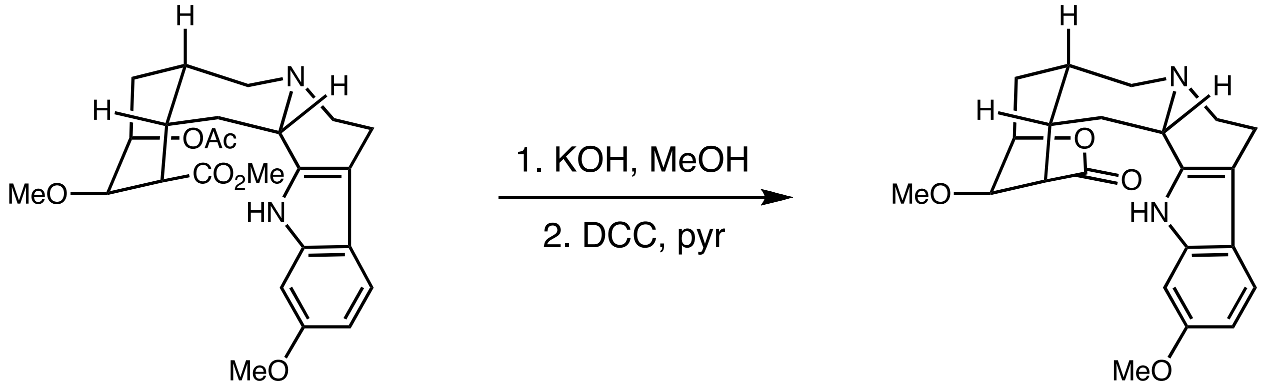
(±)-methyl-*O*-acetylisoreserpate



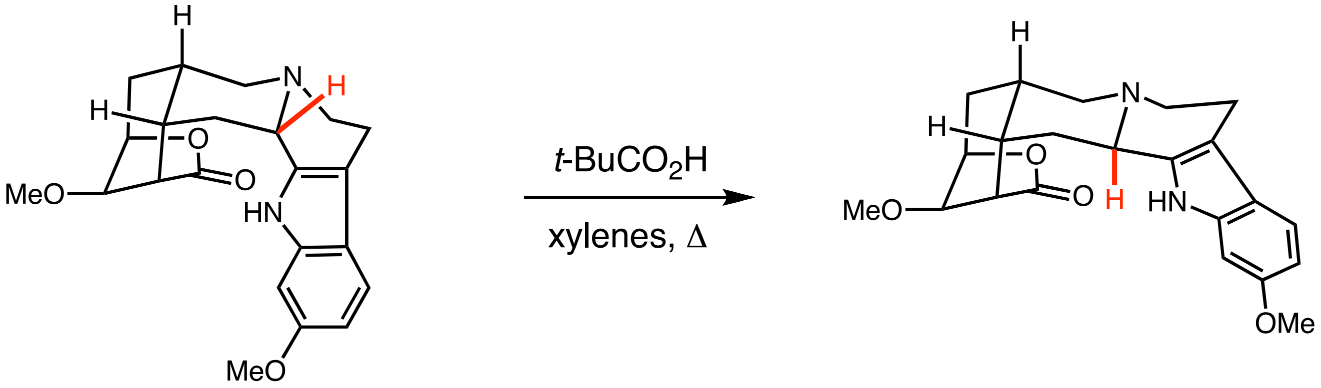
Reserpine: Molecular Judo

- Hydrolysis and lactone formation lock the molecule in the thermodynamically unfavorable conformation.



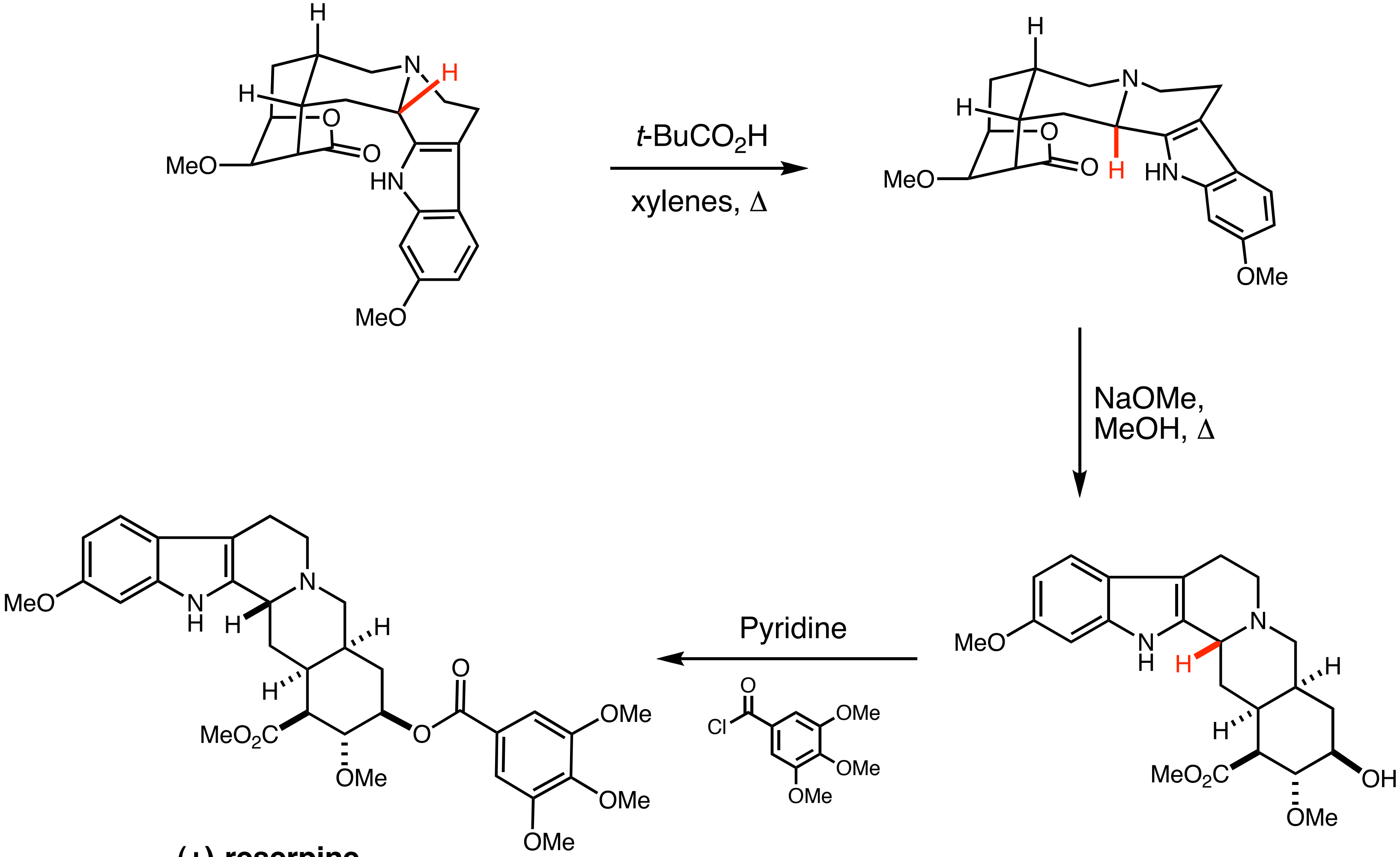


Reserpine: Molecular Judo



- Epimerization is now favored, correcting the stereochemistry

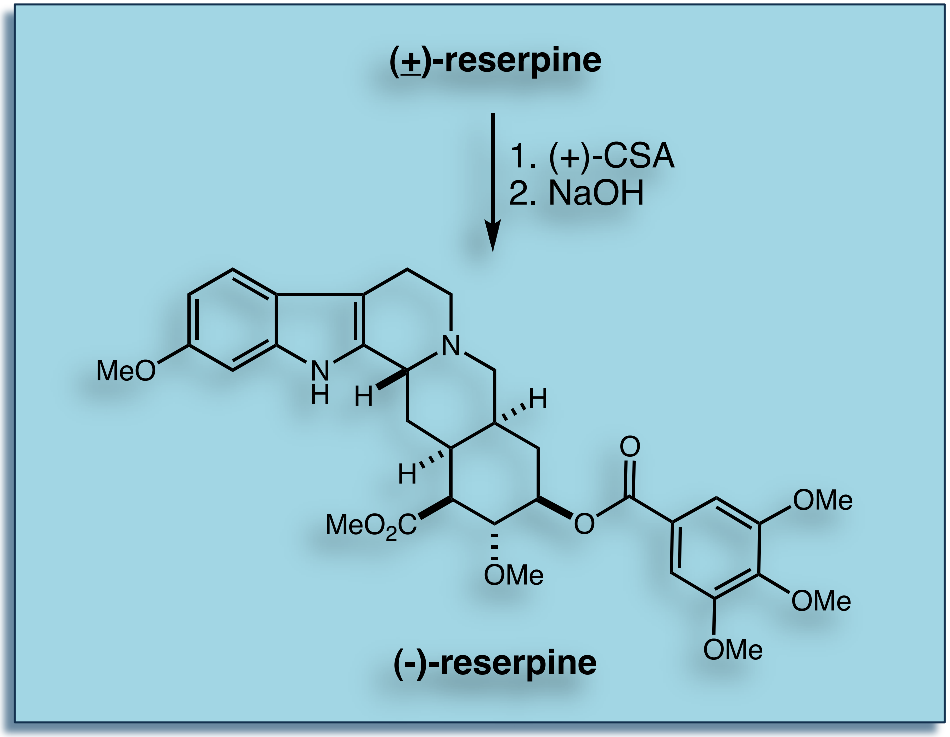
Reserpine



(±)-reserpine

Reserpine

Woodward: *Organic Ninja*



(±)-reserpine

1. (+)-CSA
2. NaOH

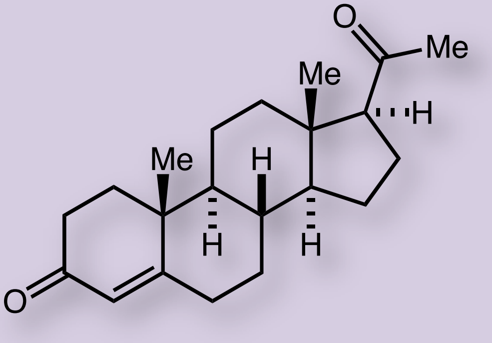
(-)-reserpine

- When defeated by both kinetics and thermodynamics, Woodward manipulated the system so that it worked in his favor.

  “It is sometimes said that you have demonstrated that nothing is impossible in organic synthesis. This is perhaps a slight exaggeration. You have, however, in a spectacular way expanded and enlarged the domain of the possible.”

  –A. Fredga: Woodward’s Nobel presentation speech (1965).

Progesterone



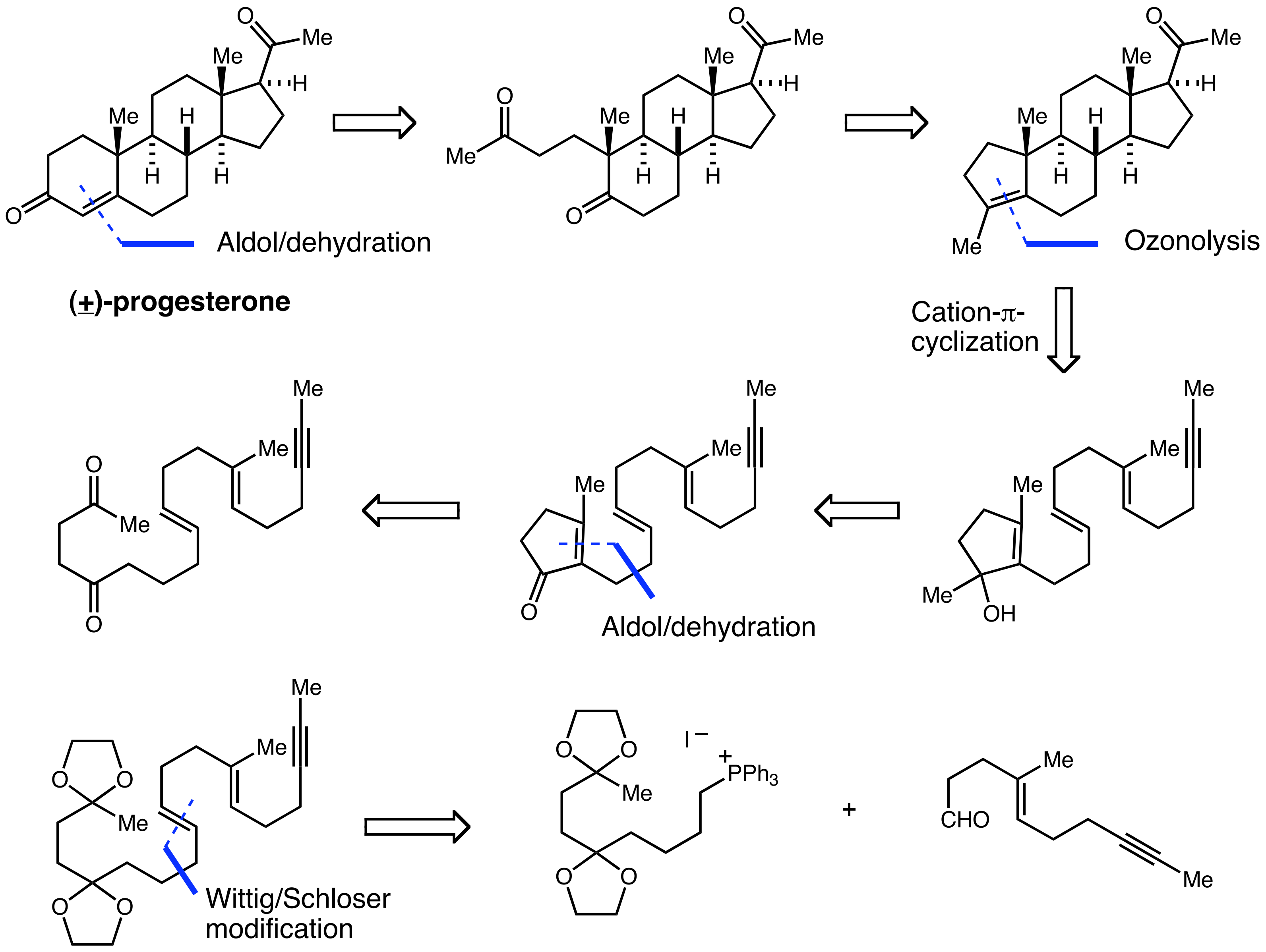
(±)-progesterone

W. S. Johnson

- A synthesis inspired by the polyene cyclization of squalene oxide to dammaradienol in the biosynthesis of lanosterol.
- Displayed a synthetically useful domino reaction and demostrated the utility of the Johnson–Claisen rearrangement.

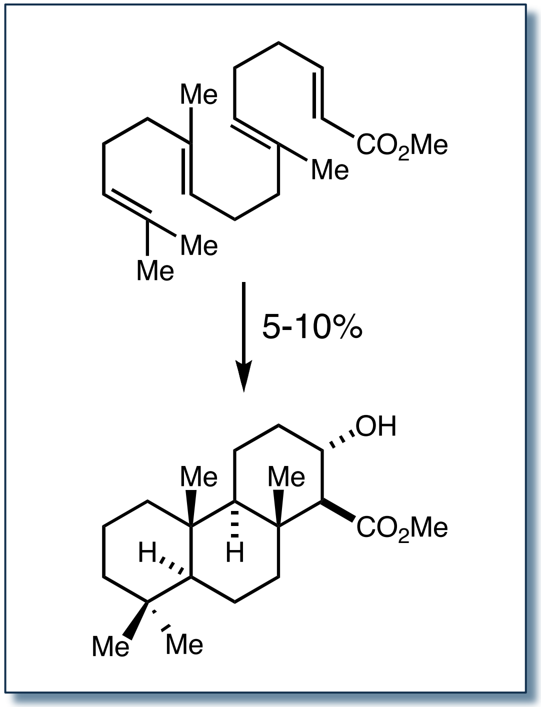
Johnson, W. S.; Gravestock, M. B.; McCarry, B. E. *J. Am. Chem. Soc.*, **1973**, *95*, 20, 6832.

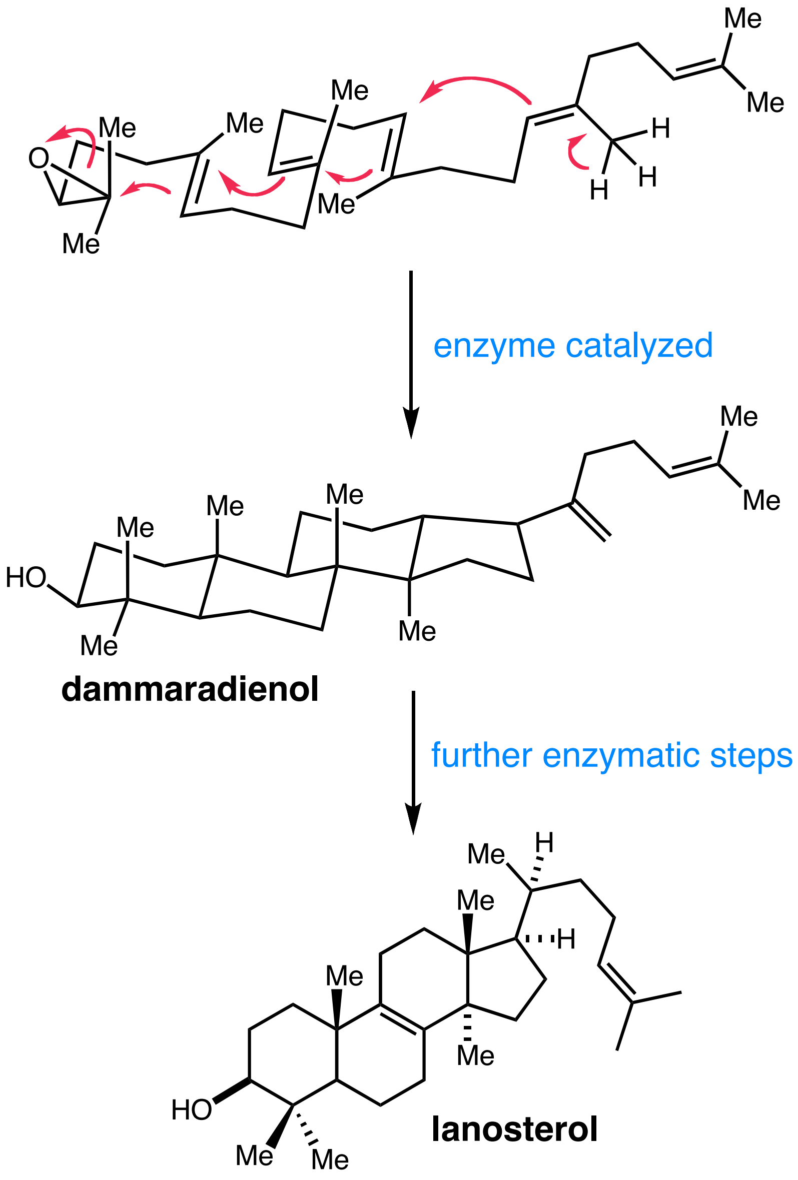
Progesterone: Retrosynthetic Analysis



Cyclization of Squalene Oxide

- Stork and Eschenmoser independently yet concomitantly proposed that the trans olefins in the substrate controlled stereoselectivity.
- Eschenmoser states: “It seems that with polyenes of this complexity (below), acid-catalyzed cyclization ceases to be a useful reaction from the preparative point of view.”





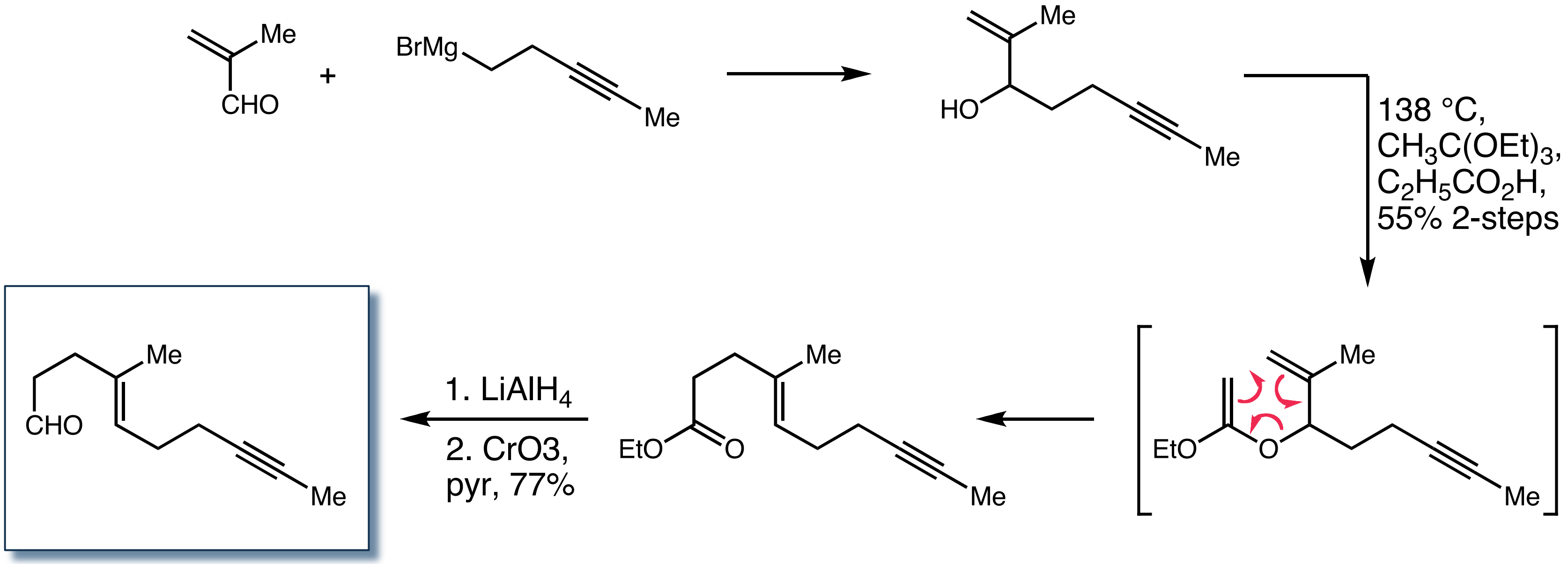
enzyme catalyzed

dammaradienol

further enzymatic steps

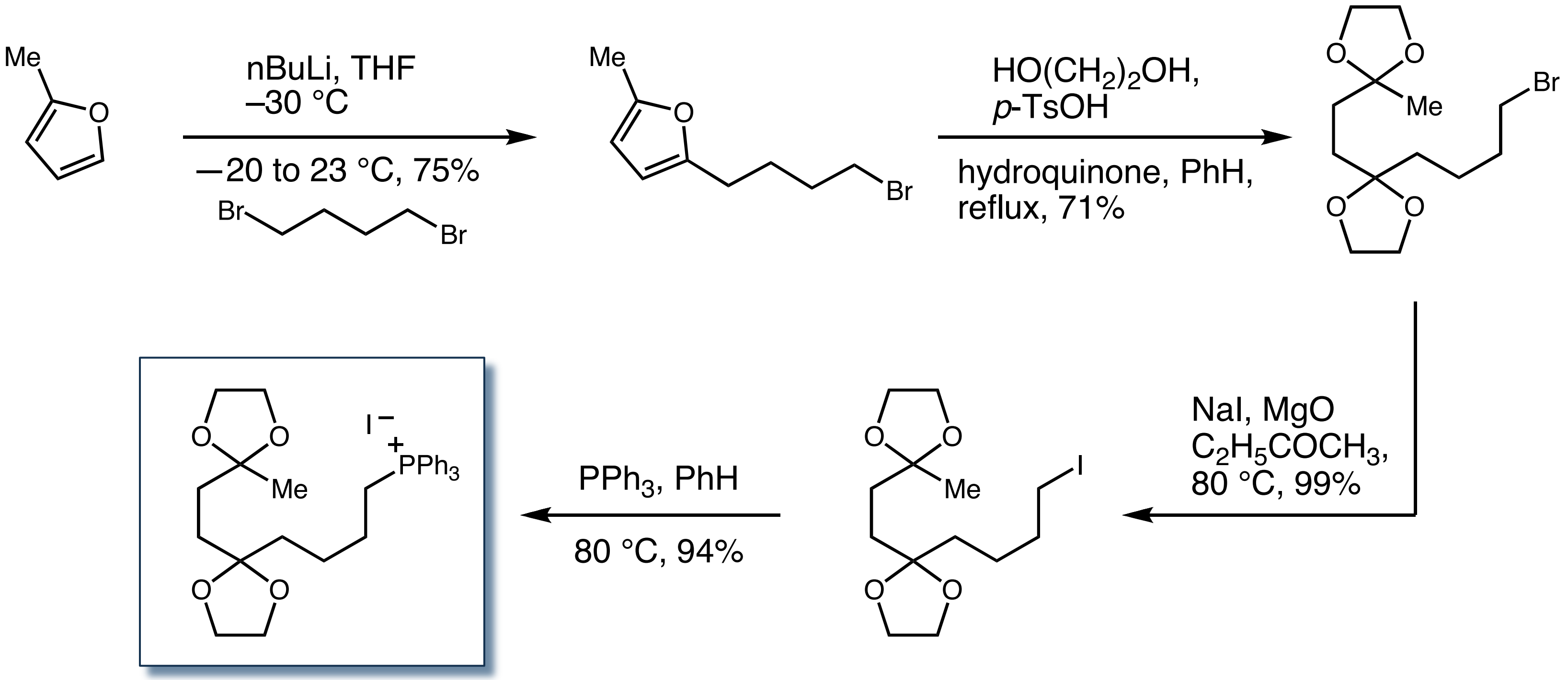
lanosterol

Progesterone: Right Half



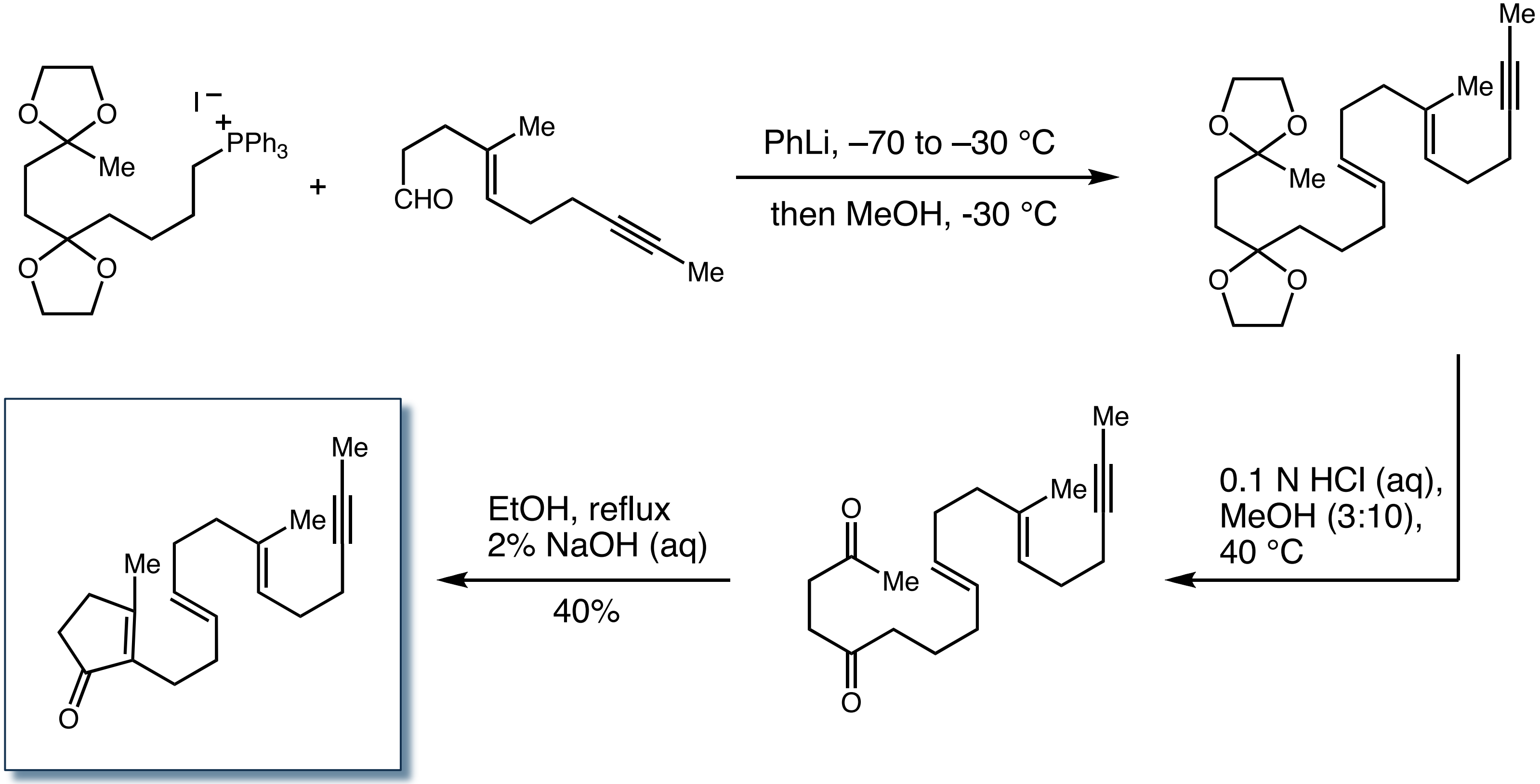
- Johnson–Claisen rearrangement sets the γ,δ-usaturation

Progesterone: Left Half



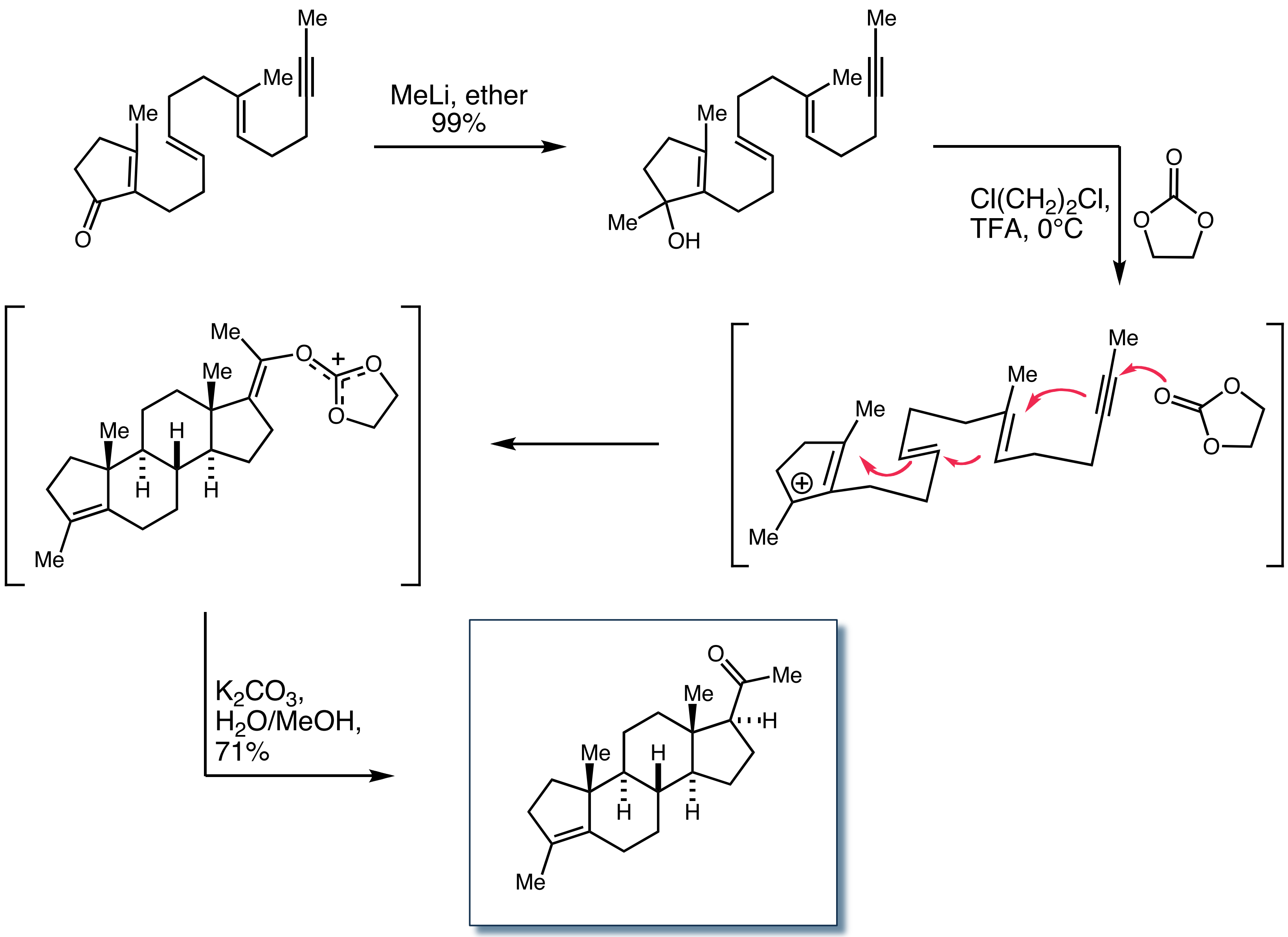
- Furan starting material installs the 1,4-diketo relationship.

Progesterone: Converging Two Halves

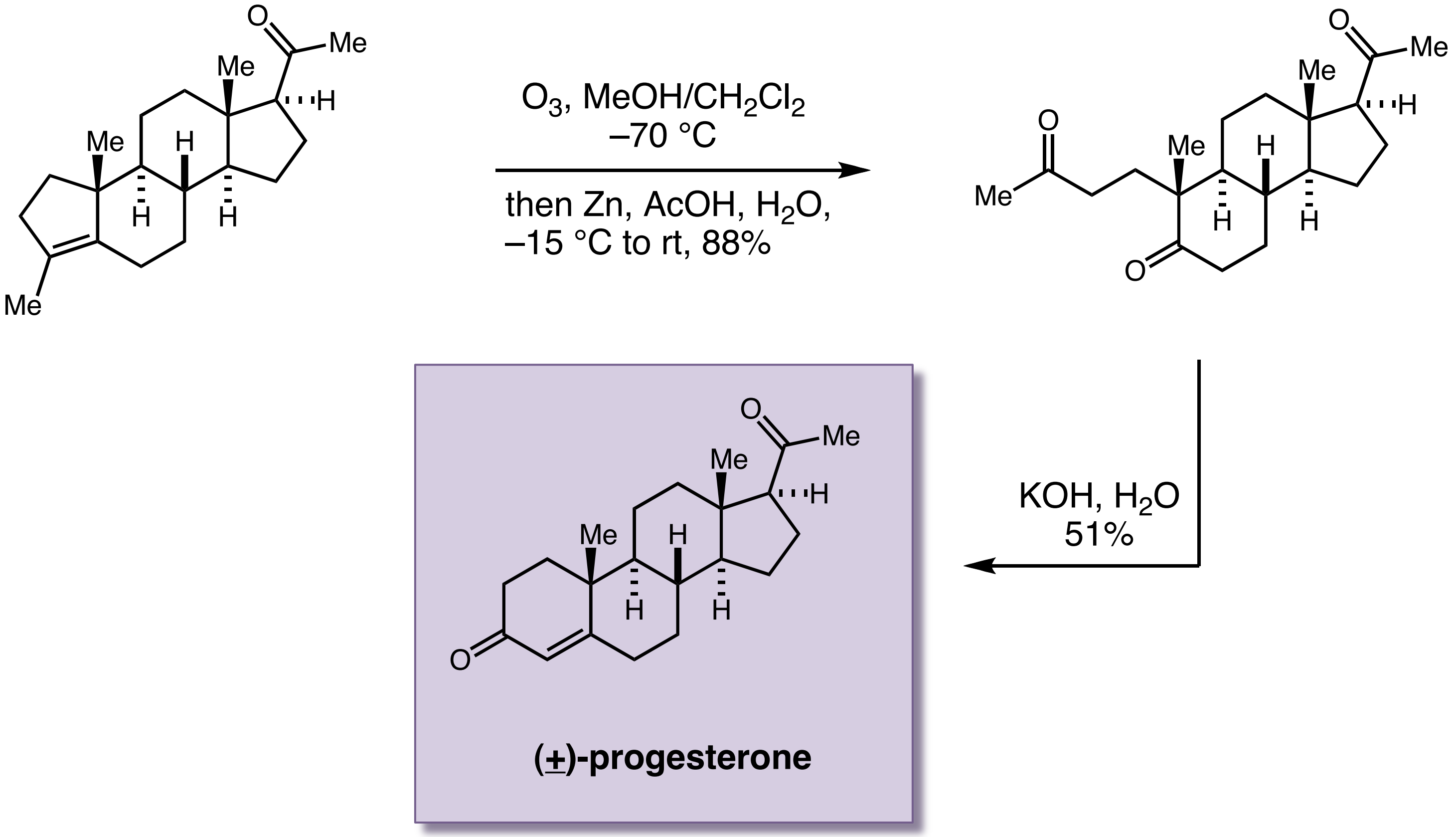


- Schlosser modification of the Wittig provides the requisite *E*-olefin.
- Deprotection and cyclization installs the final unsaturation.

Progesterone: Cation-π-Cylization

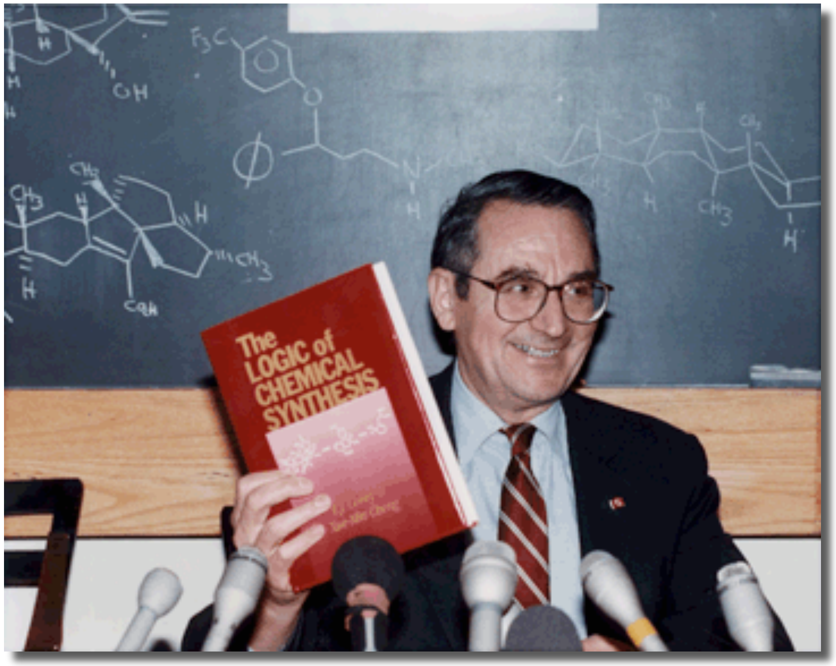


Progesterone

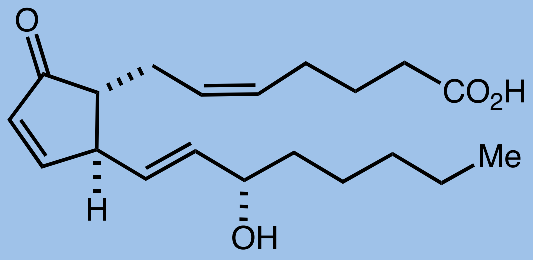


- Cation-π-cylization forges all six stereocenters in a tandem operation from the crude tertiary alcohol.
- Though biomimetic cation-π-cylizations had been previously demonstrated by Stork, Eschenmoser, and van Tamlen, this is the most elegant and highest yielding example applied to a total synthesis.

Prostaglandin A_2



Elias James Corey

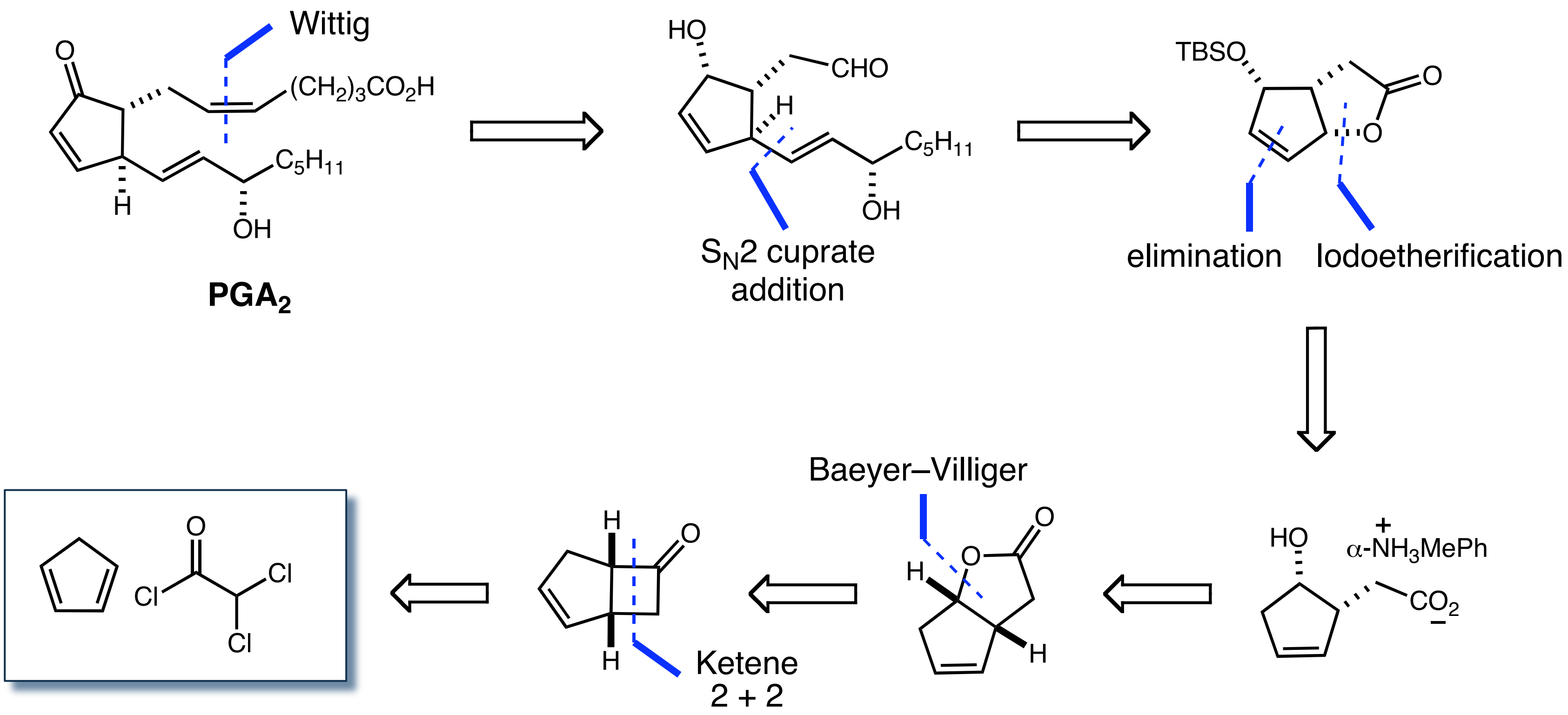


PGA_2

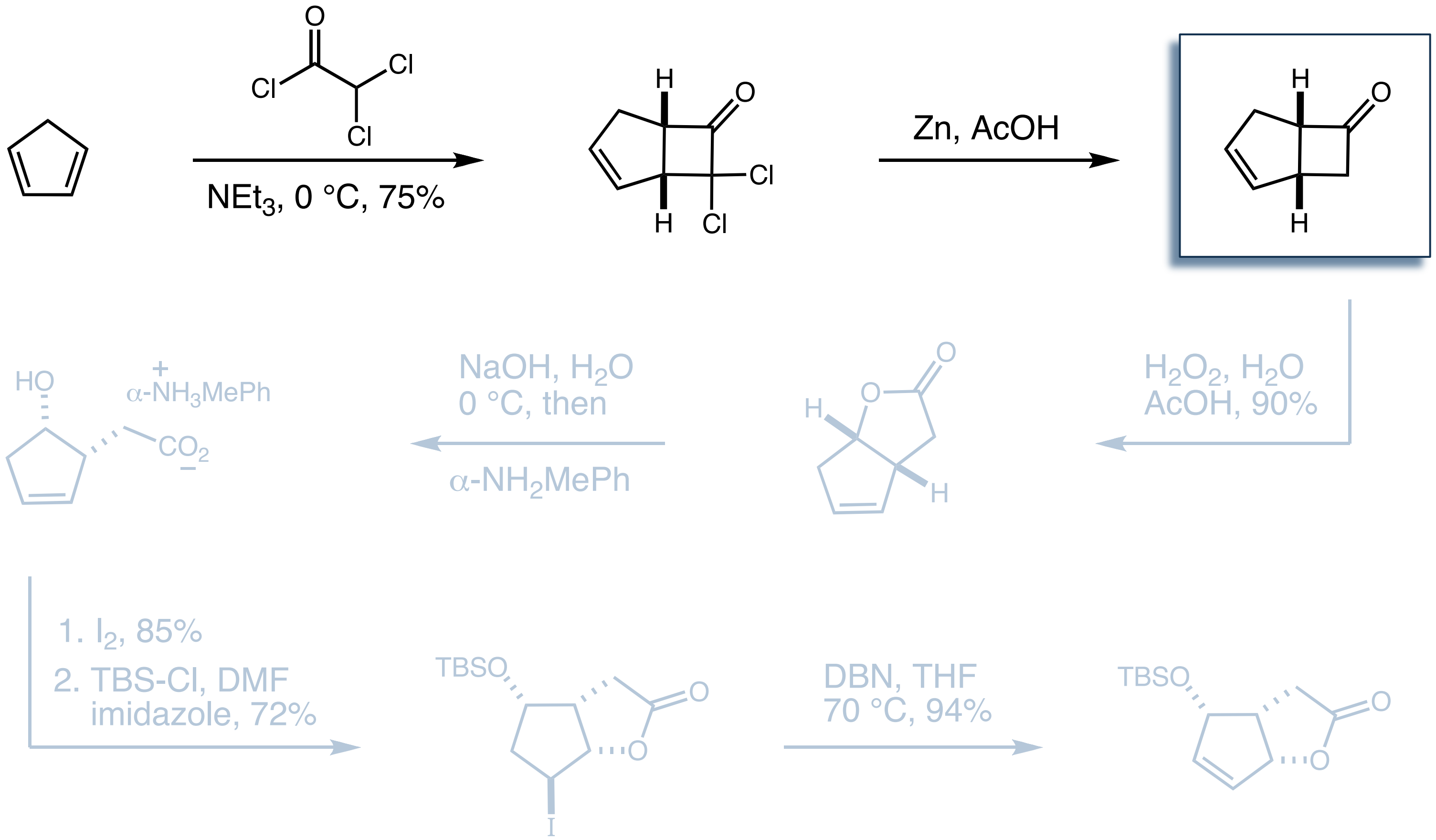
- The first example of a total synthesis using the TBS protecting group, which also directs a S_N2-selective organocuprate addition.
- Addition of a chiral organocuprate facilitates convergence within the synthesis.
- Introduction of the TBS protecting group has been one of the most enabling innovations of the 20th century.

Corey, E. J.; Mann, J. *J. Am. Chem. Soc.*, **1973**, *95*, 20, 6832.

Prostaglandin A_2: Retrosynthetic Analysis

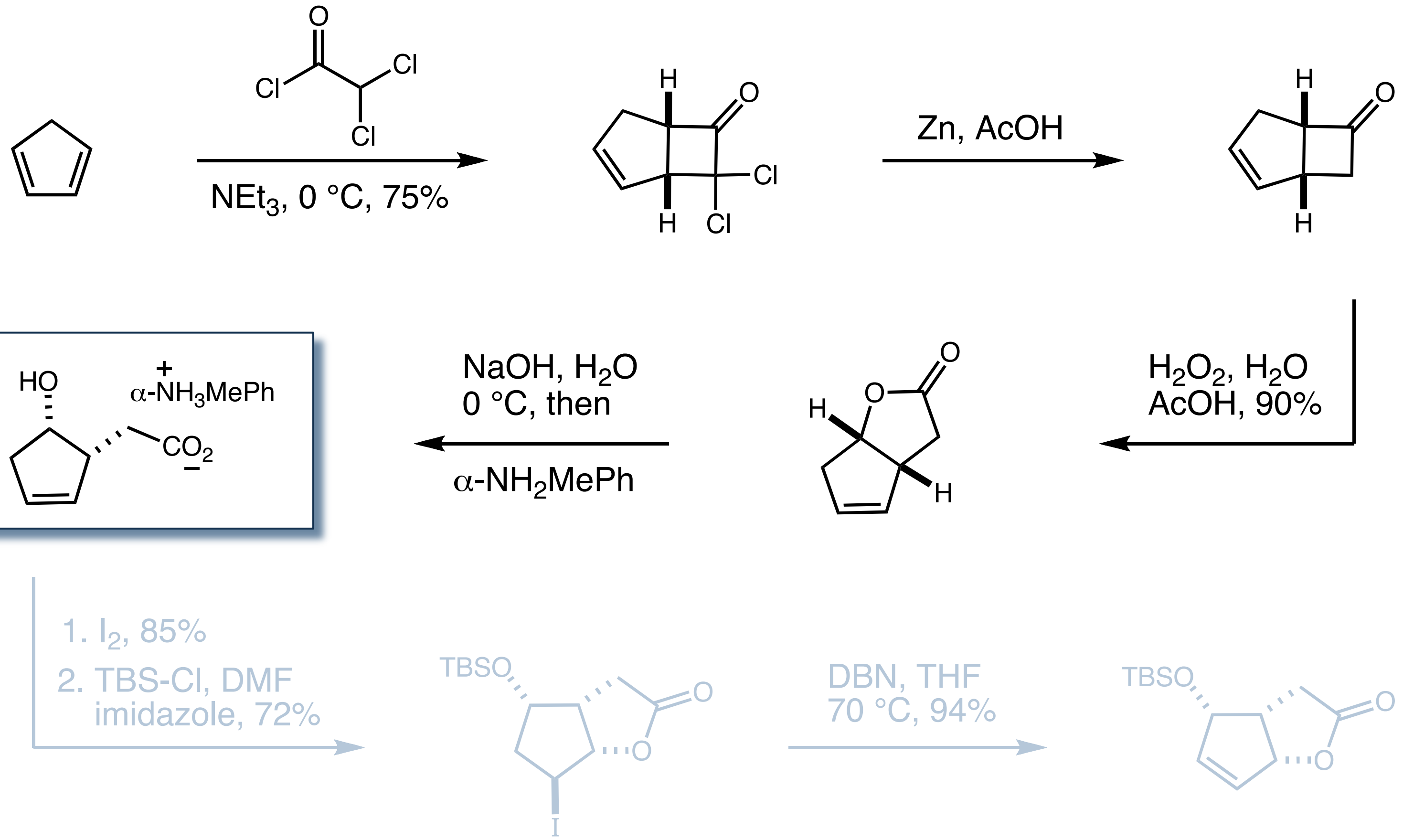


Prostaglandin A_2



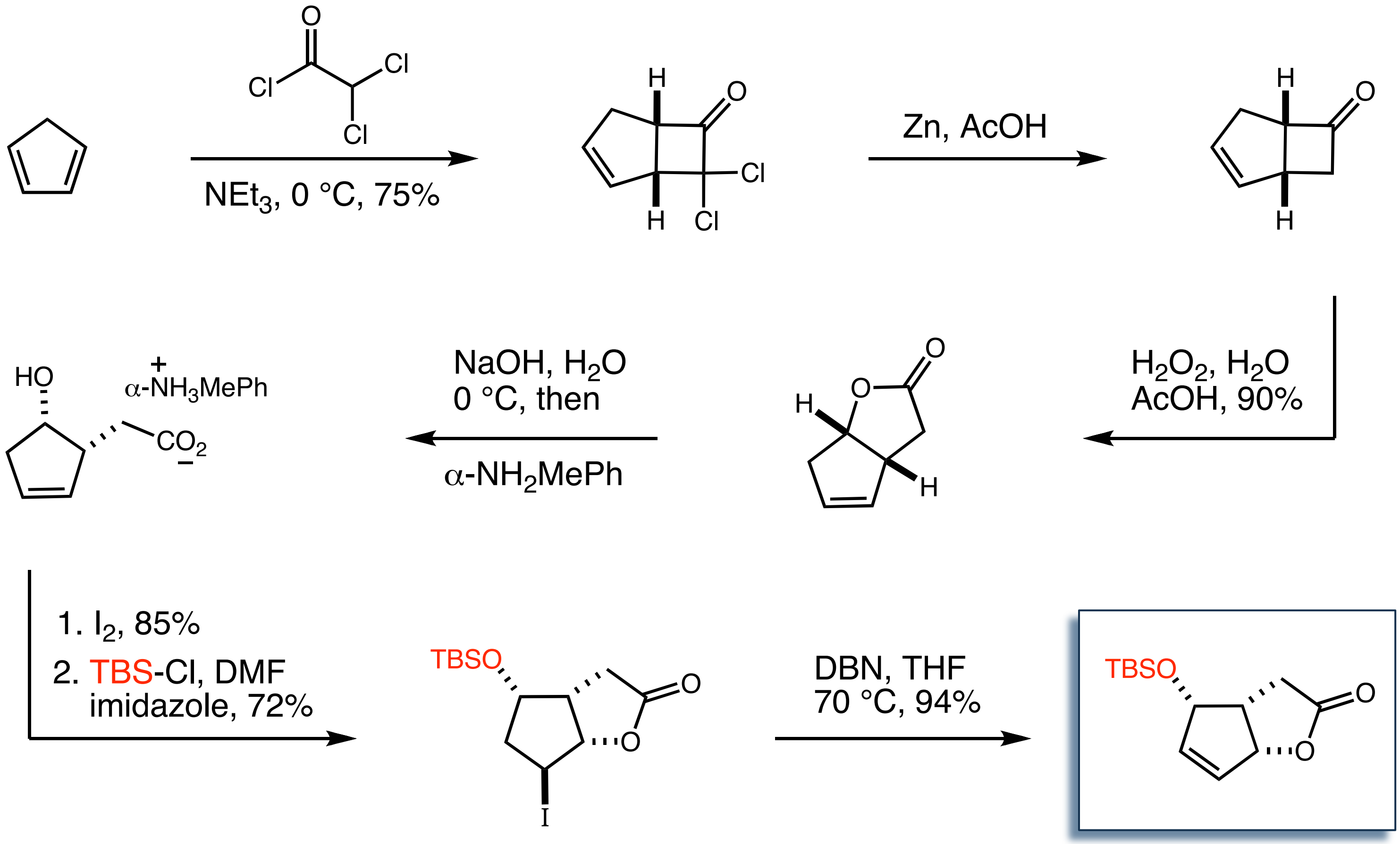
- Ketene 2 + 2 installs requisite lactone carbons.

Prostaglandin A_2



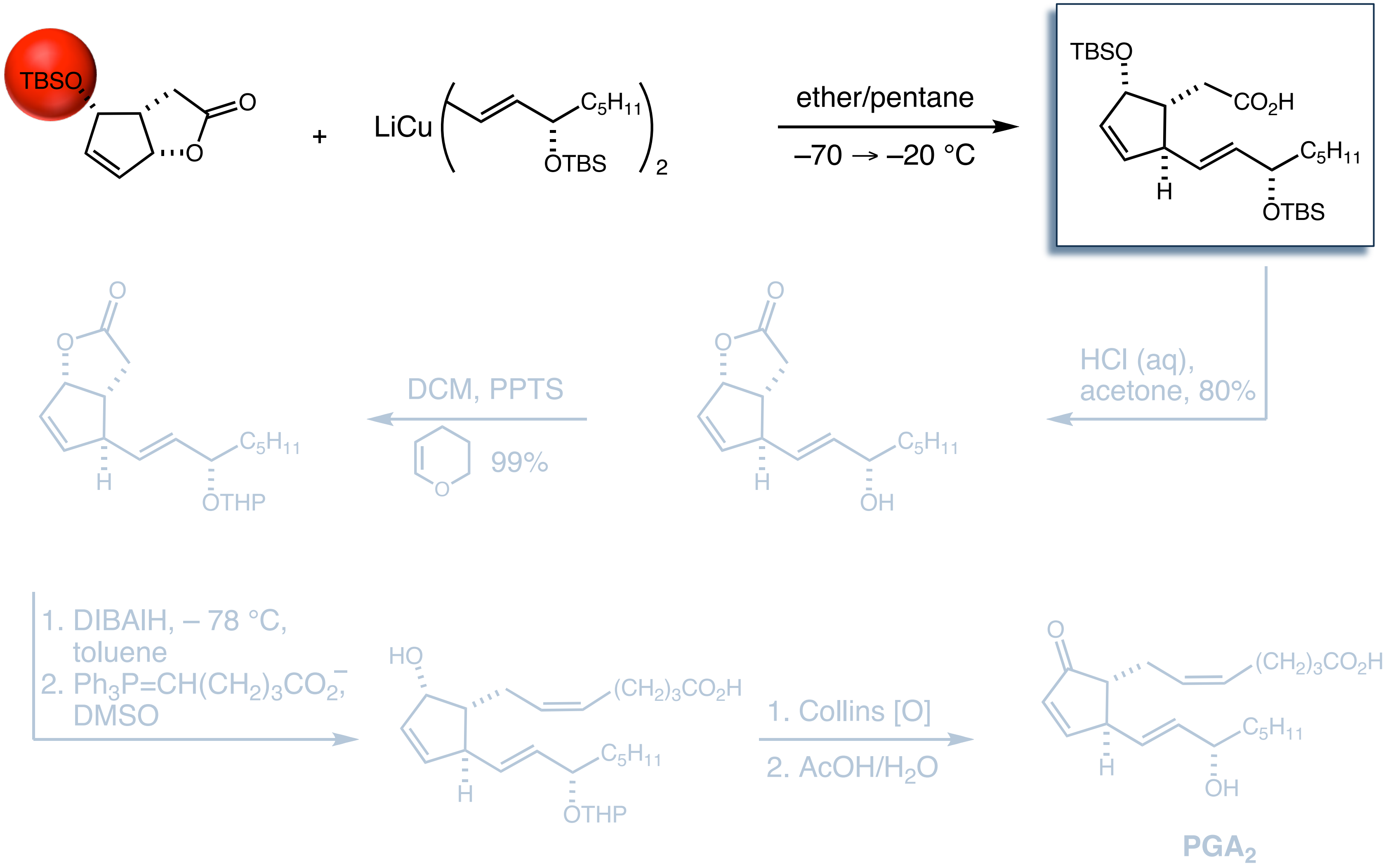
- Baeyer-Villiger oxidation followed by hydrolysis and resolution furnishes the enantioenriched hydroxy acid.

Prostaglandin A_2



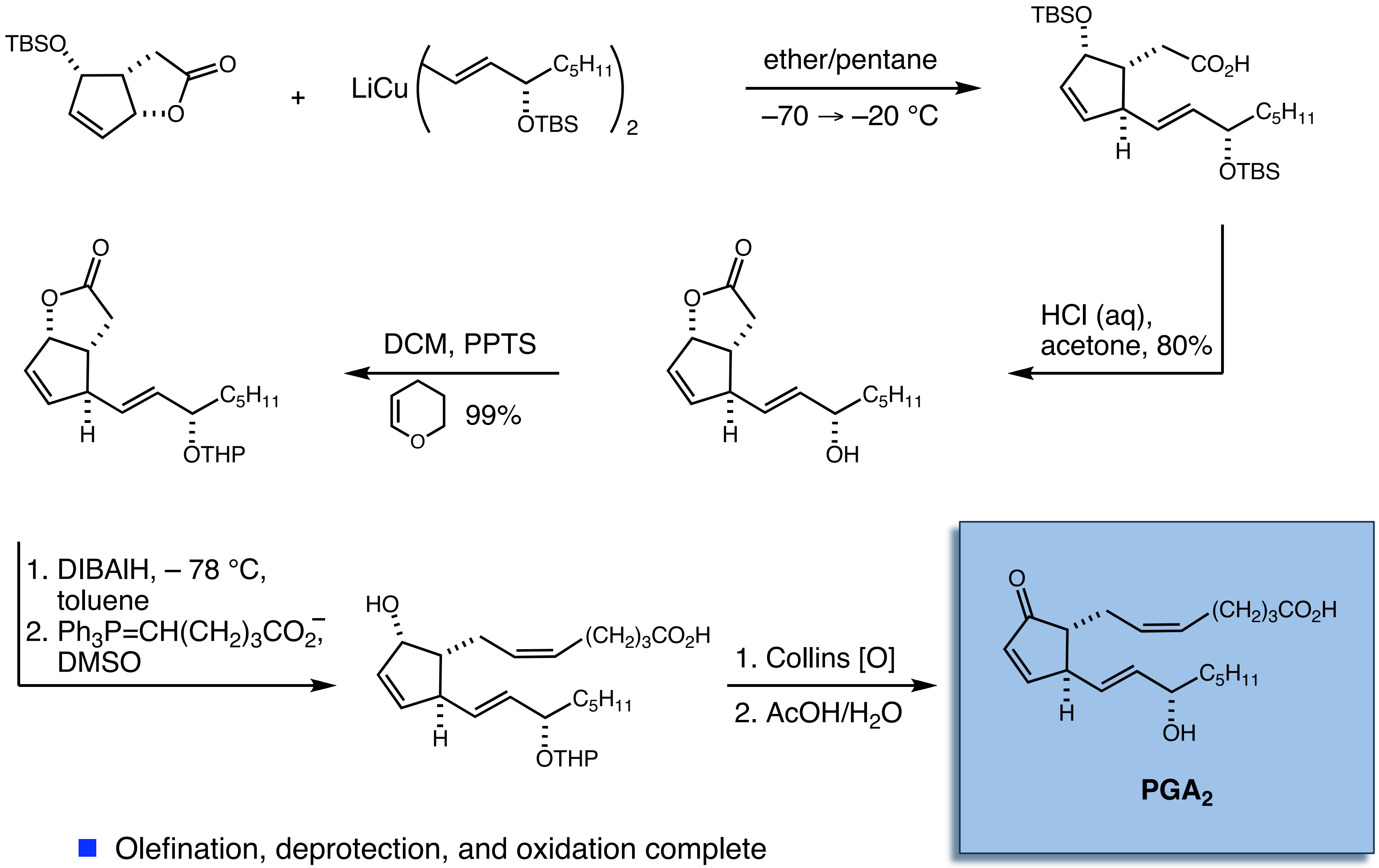
- Iodolactonization, TBS protection, and elimination provide the necessary precursor for cuprate addition.

Prostaglandin A_2



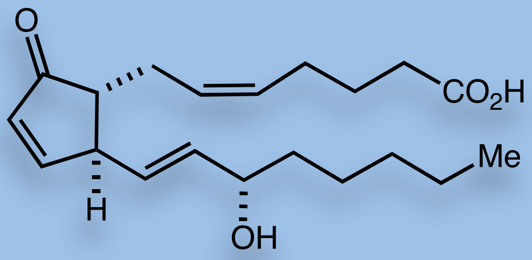
- Organicuprate addition happens in an S_N2 fashion over $S_N2´$ due to blocking from the –OTBS group.

Prostaglandin A_2



- Olefination, deprotection, and oxidation complete the synthesis of PGA_2

Prostaglandin A_2



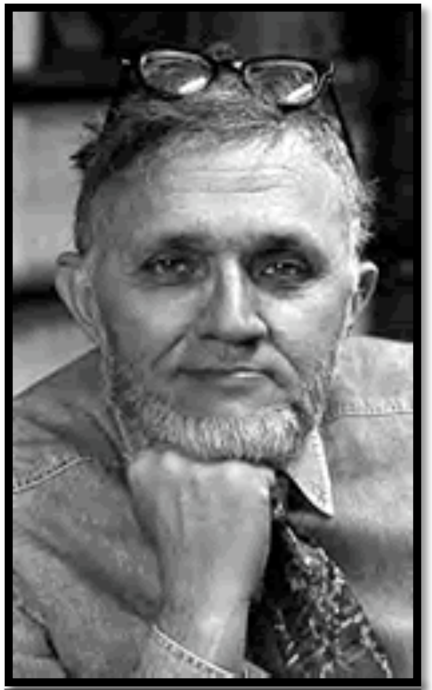
PGA_2

- TBS protecting group is one of the most widely used protecting groups in synthesis (43,200 web hits, original paper cited 2,256 times).

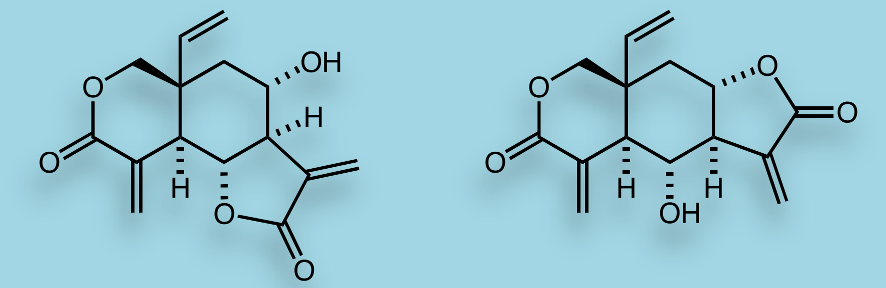
  “Corey's most important syntheses are concerned with prostaglandins and related compounds…No other chemist has developed such a comprehensive and varied assortment of methods, often showing the simplicity of genius, which have become commonplace in organic synthesis laboratories.

  –S. Gronowitz: Corey’s Nobel presentation speech (1990).

Vernolepin/Vernomenin



Samuel Danishefsky



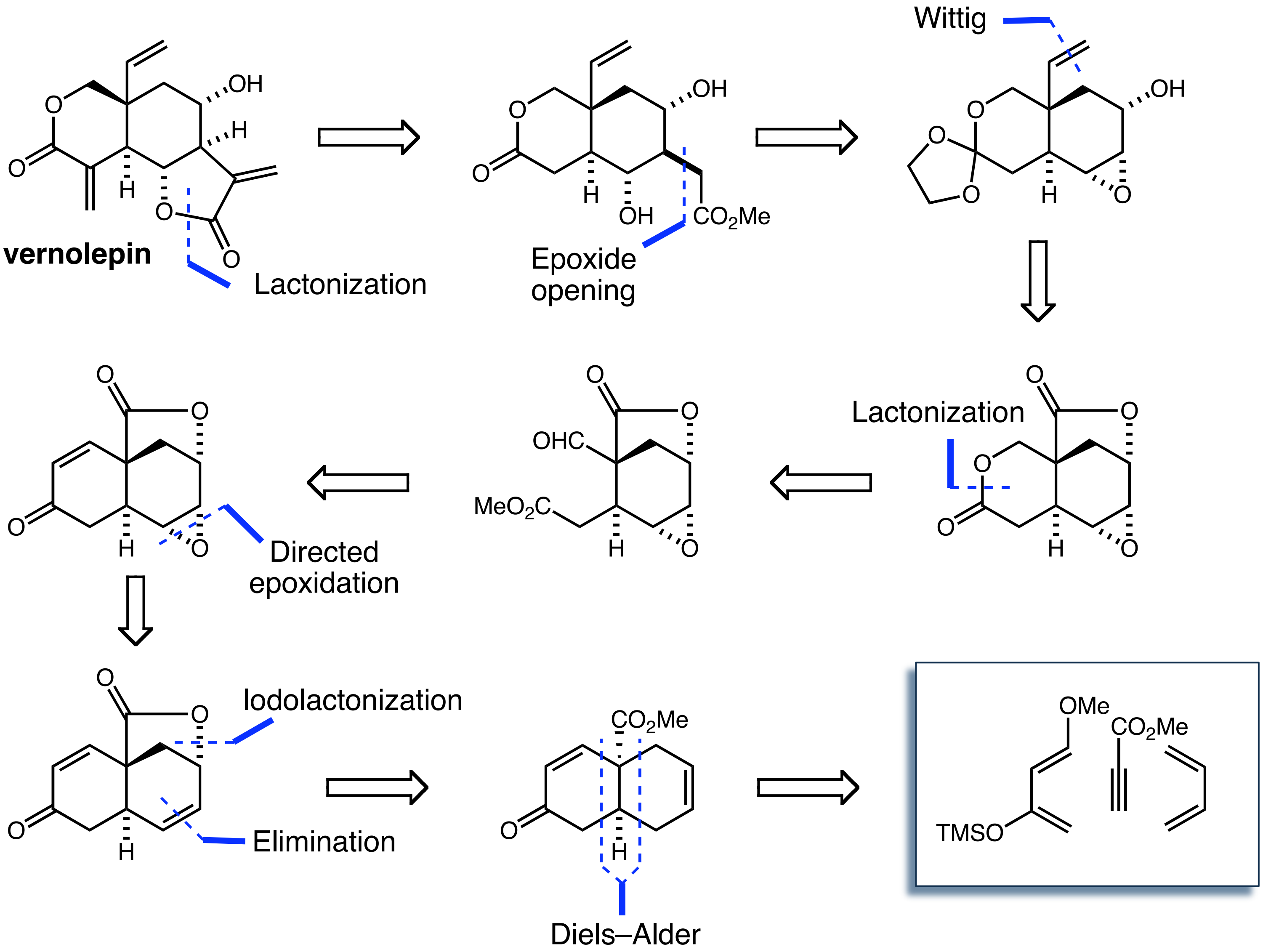
vernolepin

vernomenin

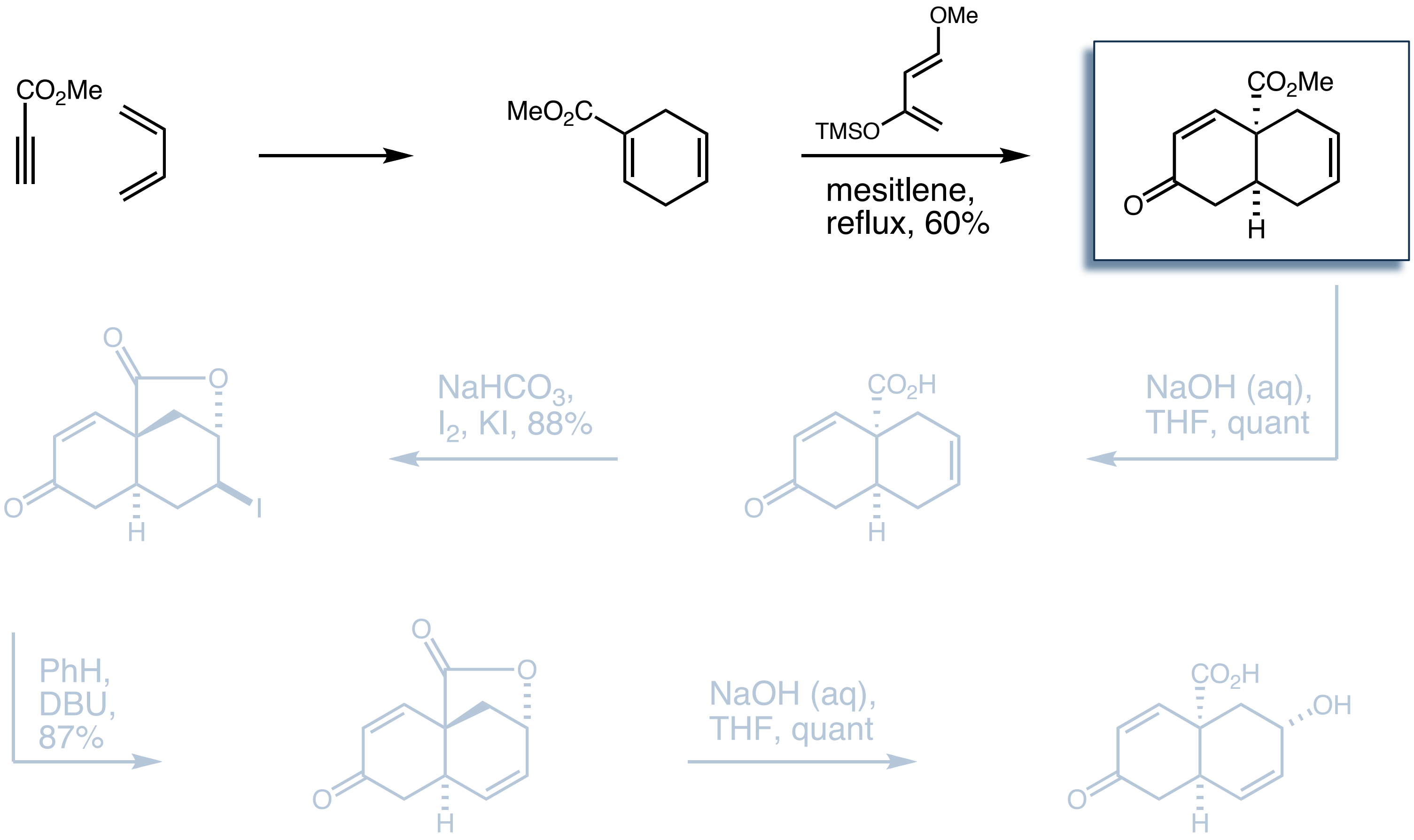
- First synthesis employing the synergistic diene: Danishefsky's diene (32,400 web hits, original paper cited 431 times).
- Brought this concept to the scientific community, inspiring additional contributions e.g. Rawal diene.

Danishefsky, S.; Schuda, P. F.; Kitahara, T.; Etheredge, S. J. *J. Am. Chem. Soc.*, **1977**, *99*, 18, 6066.

Vernolepin: Retrosynthetic Analysis

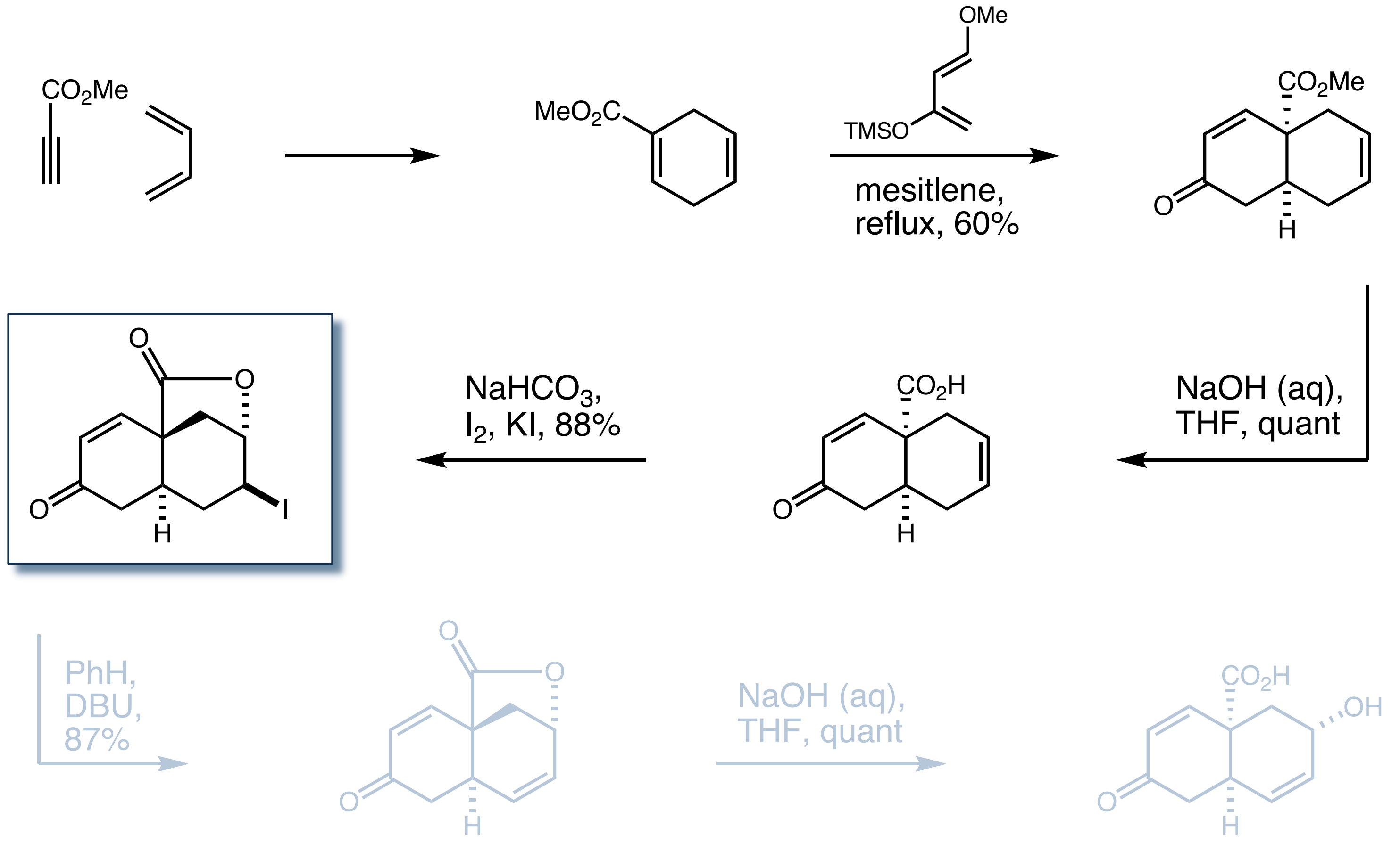


Vernolepin/Vernomenin



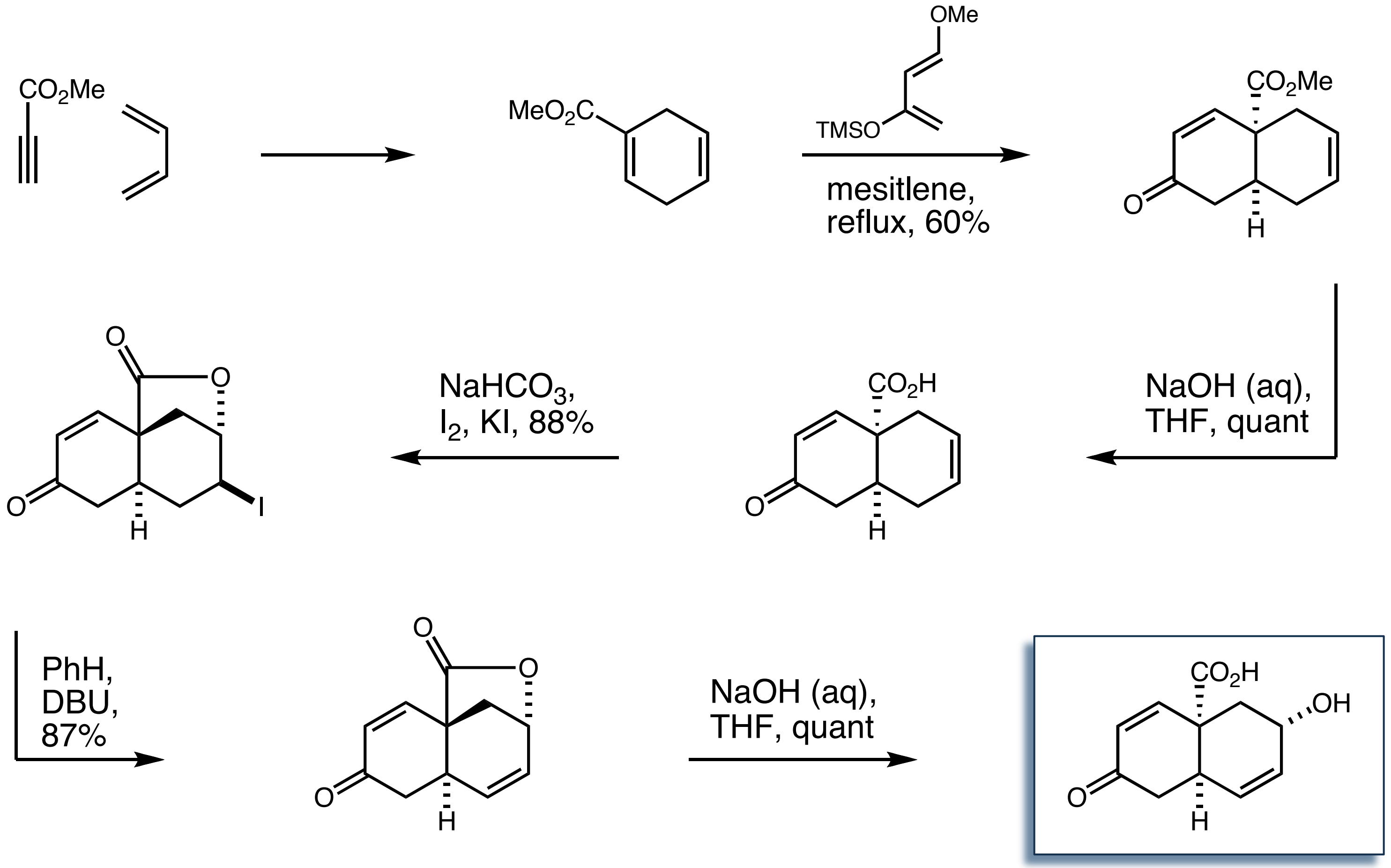
- Sequential Diels–Alders, the second utilizing Danishefsky's Diene, forge the quaternary decalone.

Vernolepin/Vernomenin



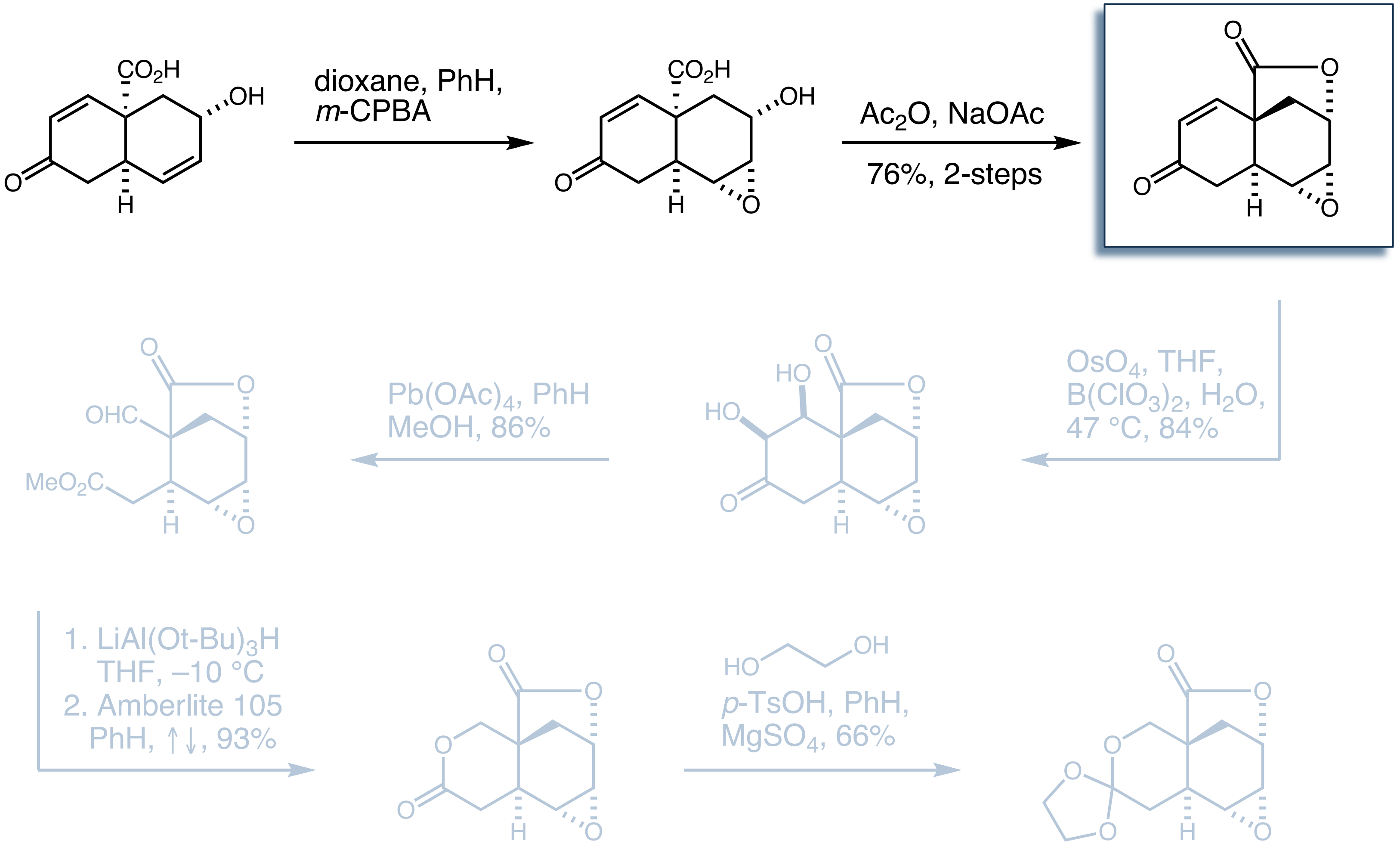
- Soponification followed by iodolactonization afford the tricyclic lactone.

Vernolepin/Vernomenin



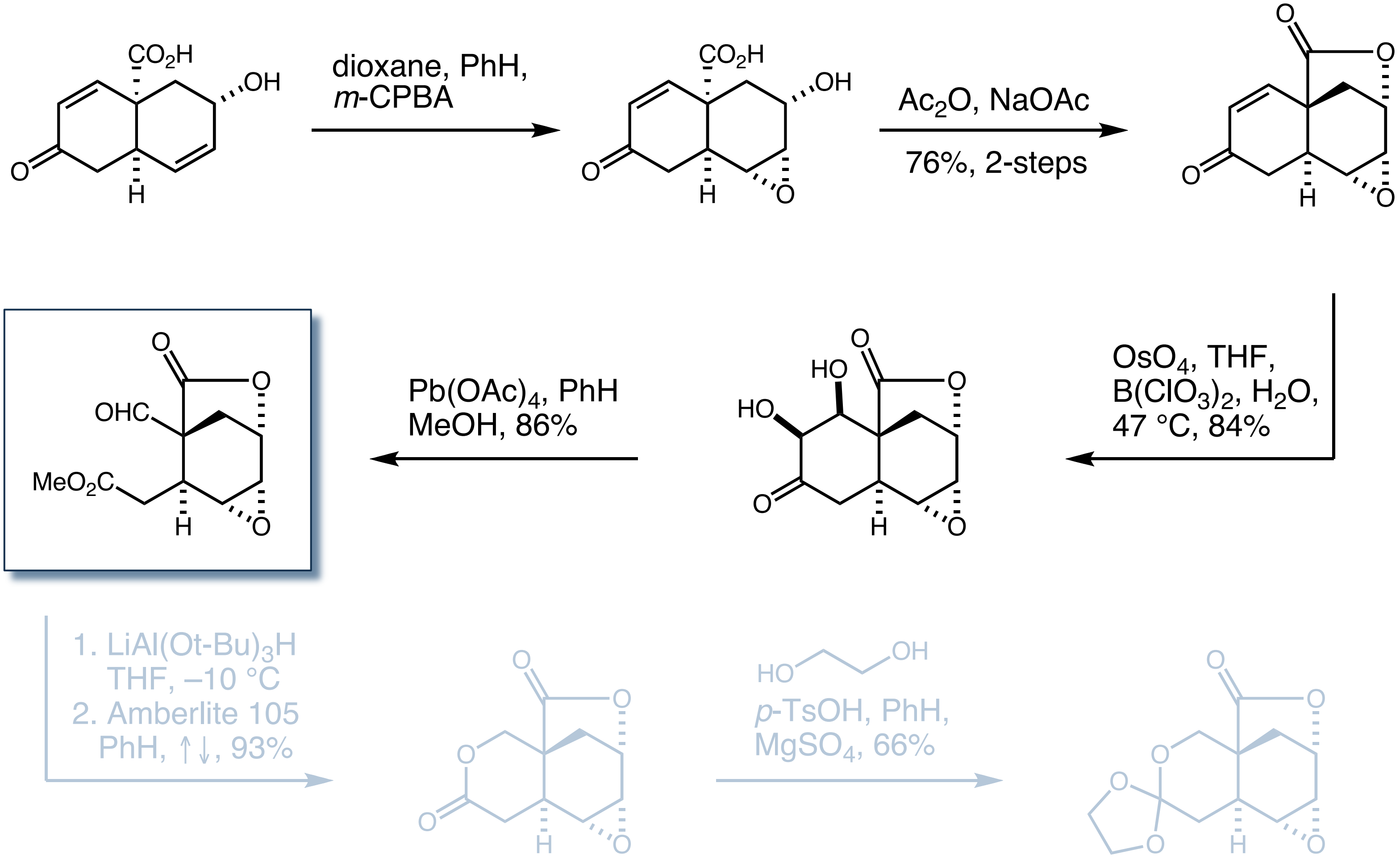
- E_2 Elimination and a second sponification provide the allylic alcohol necessary for epoxidation.

Vernolepin/Vernomenin



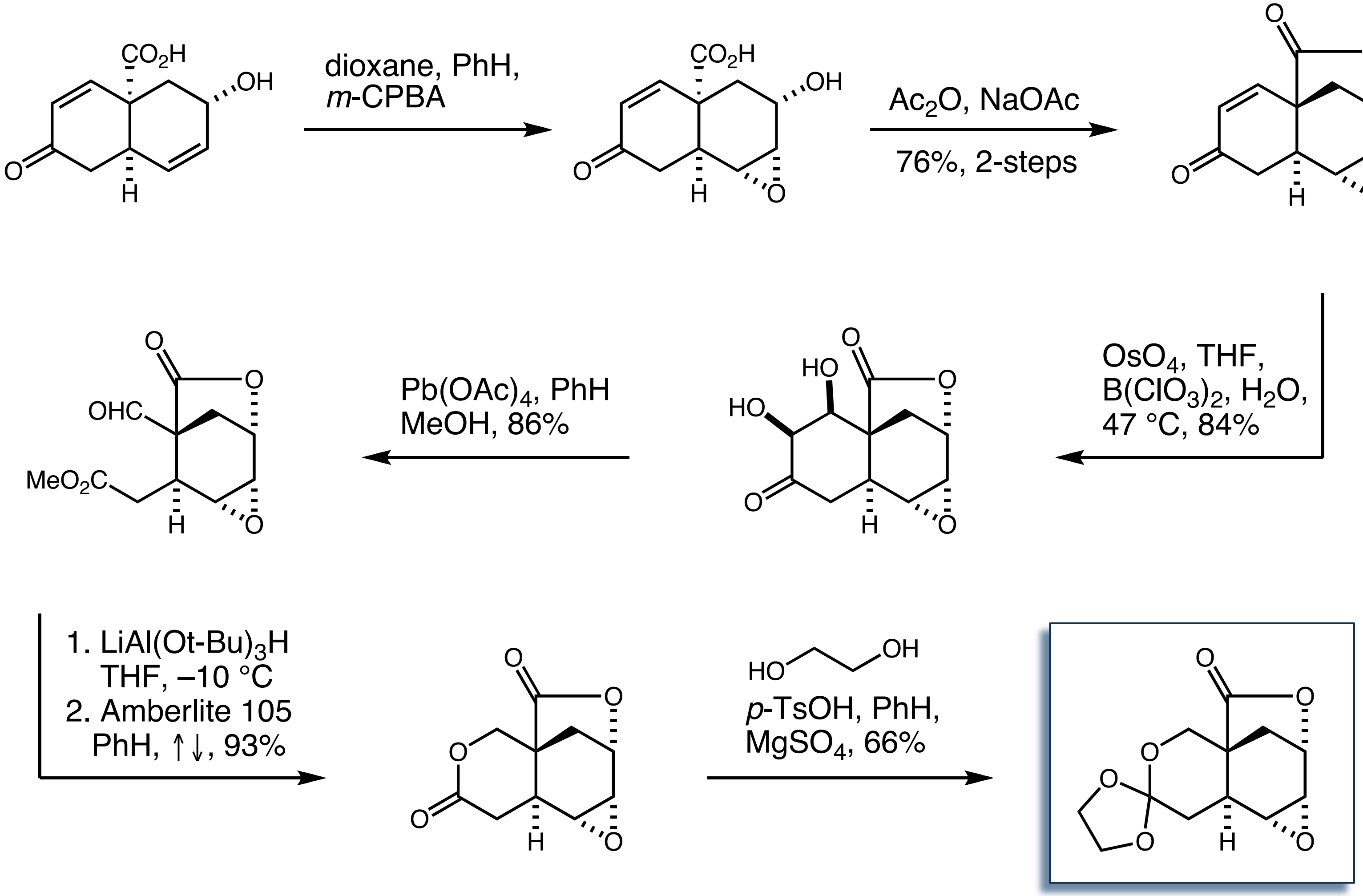
- Directed epoxidation installs the correct stereochemistry of the latent alcohol and esterification regenerates the lactone.

Vernolepin/Vernomenin



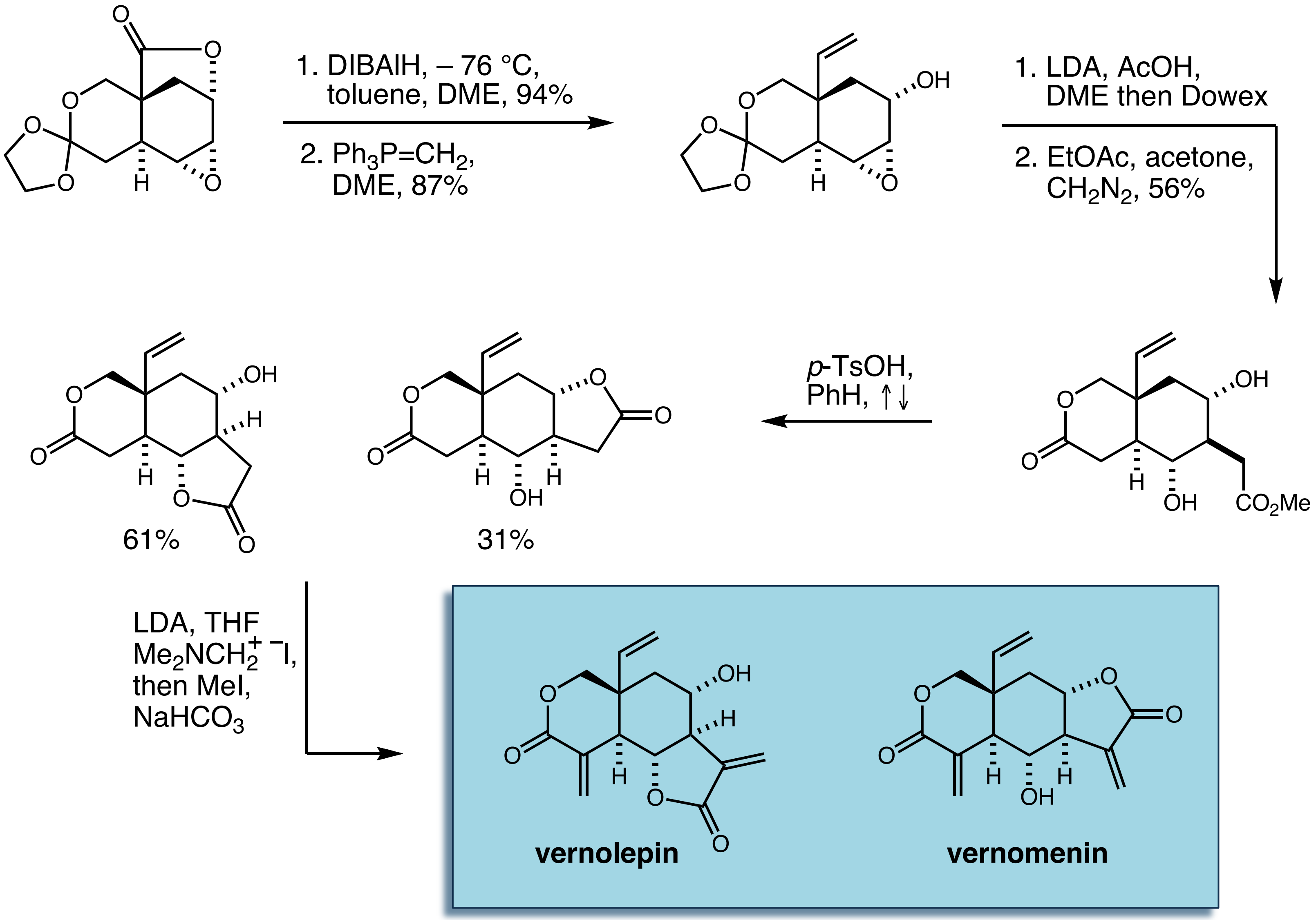
- Dihydroxylation followed by oxidative diol cleavage prepares the molecule for γ-lactone formation.

Vernolepin/Vernomenin

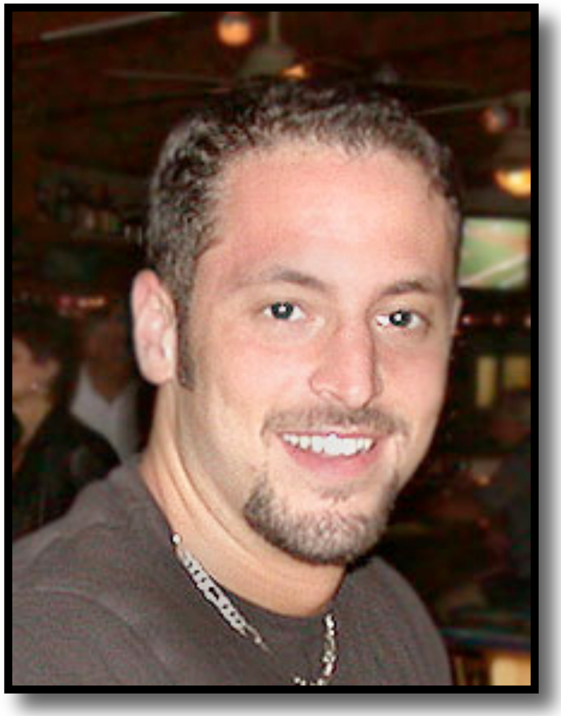


- Reduction and cyclization forge the γ-lactone functionality and surprising protection of this moiety via the orthoester happens under acetal forming conditions.

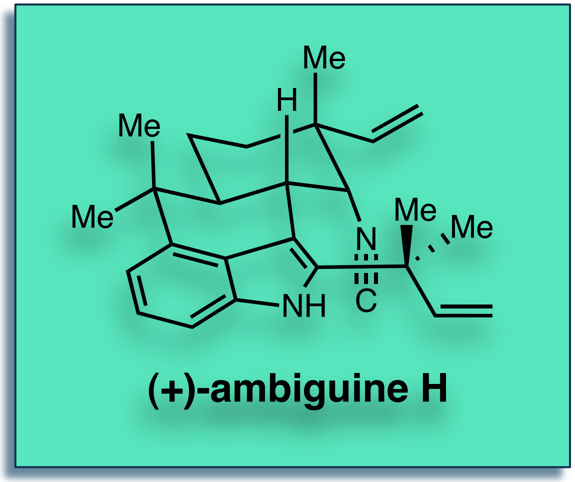
Vernolepin/Vernomenin



Ambigiune H



Phil S. Baran

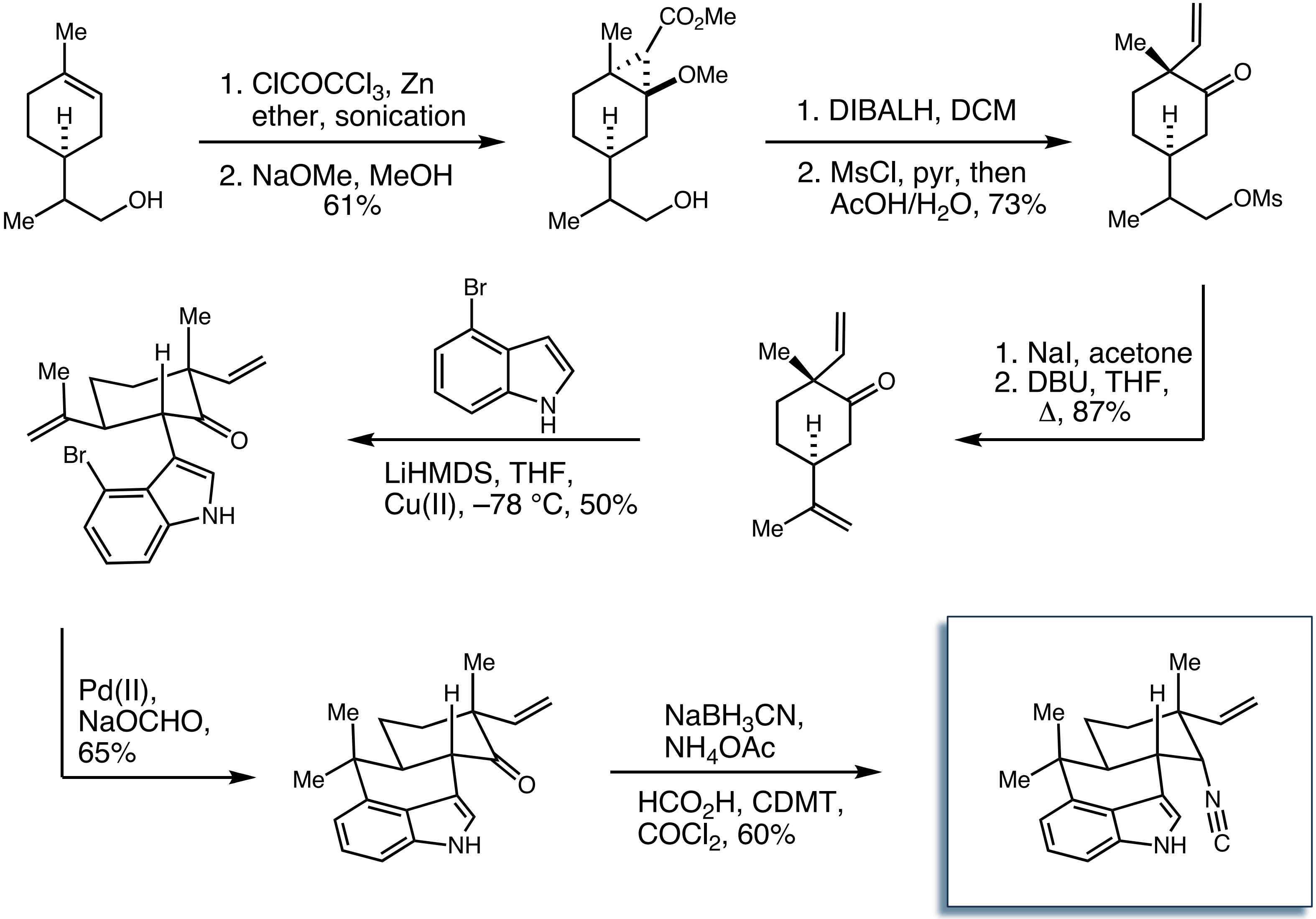


(+)-ambiguine H

- Reintroduced the notion of protecting group free (PGF) synthesis with the completion of (+)-hapalindole Q in 2004.
- Synthesized (+)-ambiguine H in 13 steps in a PGF manner. Provoked the chemical community to rethink its approach toward synthesis. Do we rely on protecting groups as a crutch?
- Have protecting groups ultimately held us back regarding step efficiency and more importantly development of new methodology?

Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature*, **2007**, *446*, 404.

Ambigiune H



1. $ClCOCCl_3$, Zn
ether, sonication
2. NaOMe, MeOH
61%

1. DIBALH, DCM
2. MsCl, pyr, then
$AcOH/H_2O$, 73%

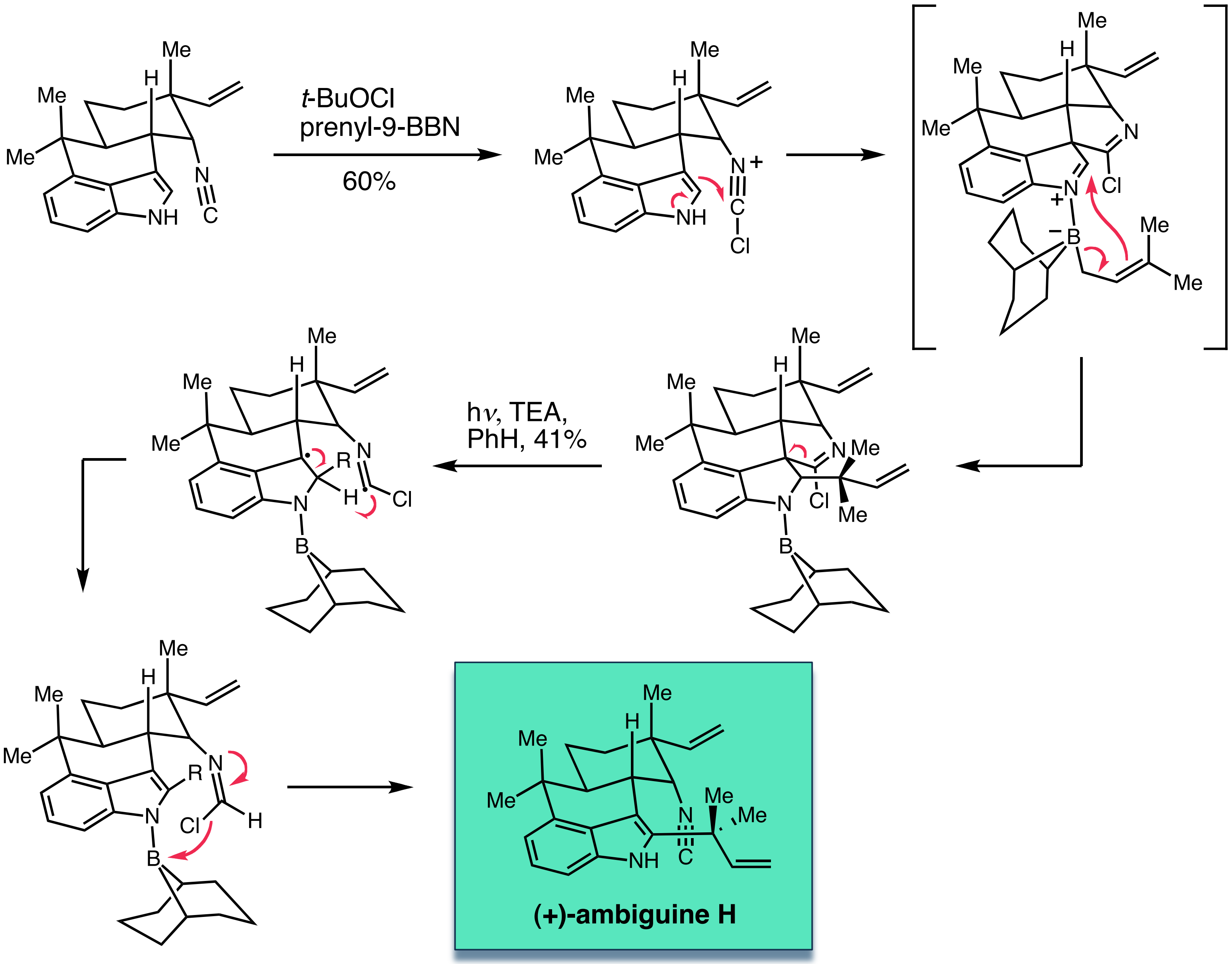
1. NaI, acetone
2. DBU, THF,
Δ, 87%

LiHMDS, THF,
Cu(II), –78 °C, 50%

Pd(II),
NaOCHO,
65%

$NaBH_3CN$,
NH_4OAc
HCO_2H, CDMT,
$COCl_2$, 60%

Ambigiune H



(+)-ambiguine H

Recap

- **Urea**: Gave birth to our field
- **Tropinone**: Demonstrated retrosynthetic analysis and was one of the first examples of a biomimetic synthesis.
- **Reserpine**: Illustrated the power of diasteroselective transformations and taught us a lesson about thermodynamic engineering.
- **Progesterone**: Exemplified how a bioinspired transformation can be applied in the lab efficiently and aslo the utility of the Johnson-Claisen.
- **PGA_2**: Gave us the TBS protecting group and demonstrated how it can be used to control reactivity.
- **Vernolepin**: Demonstrated the concept of the synergistic diene in the Diels–Alder reaction. Danishefsky's Diene has inspired other useful variations.
- **Ambigiune H**: Reminded us why we should strive to develop protecting group free syntheses. Presented an innovative example of said concept.