# Total Synthesis of Natural Products
# CH438

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**Teaching Assitant:**

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***Lecture Time: Thursday 15:00-17:00***
***Lecture Room: BCH 1103***

***Exercise(s): …***

# Outline

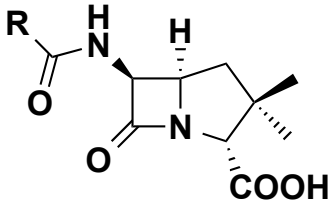
- **Introduction**

- **Classical examples (Longifolene, Reserpine, Strychinine…)**

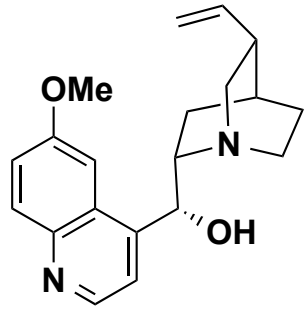
- **Syngernism between strategy and total synthesis**

  **Domino, multicomponent reaction**
  **Oxidative coupling, Pattern Recognition**
  **Hiden Symmetry, C-H Functionalization**
  **Asymmetric organocatalysis**
  **……**

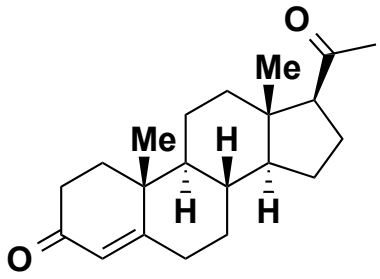
# Why Natural Products: Source of Drugs, Structural diversity and Complexity



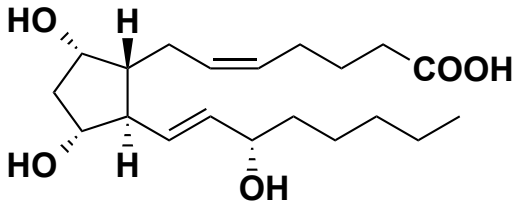
Penicillin



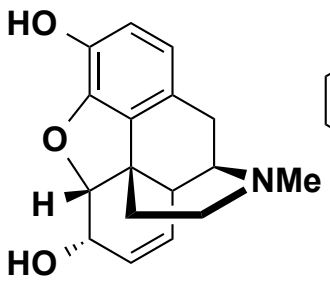
Quinine



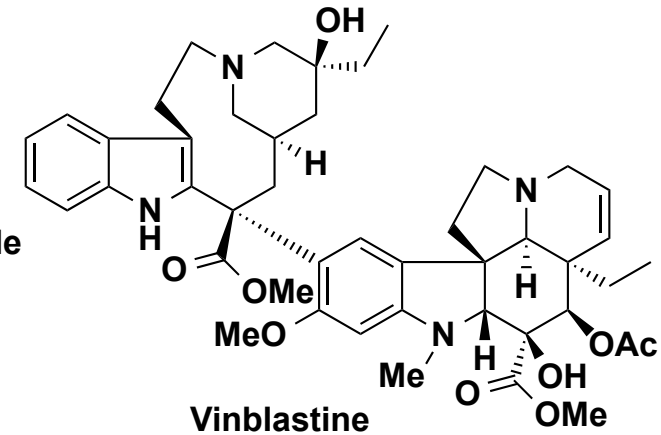
Progesterone



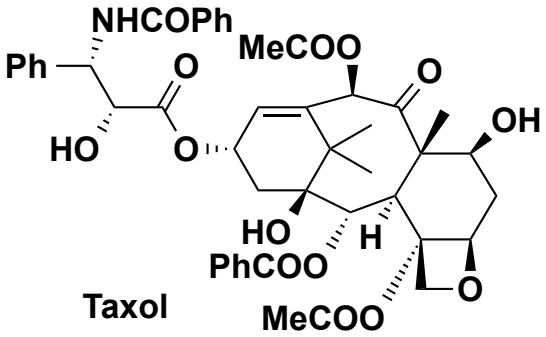
PGF2a



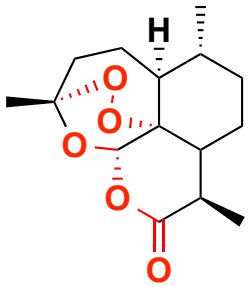
Morphine



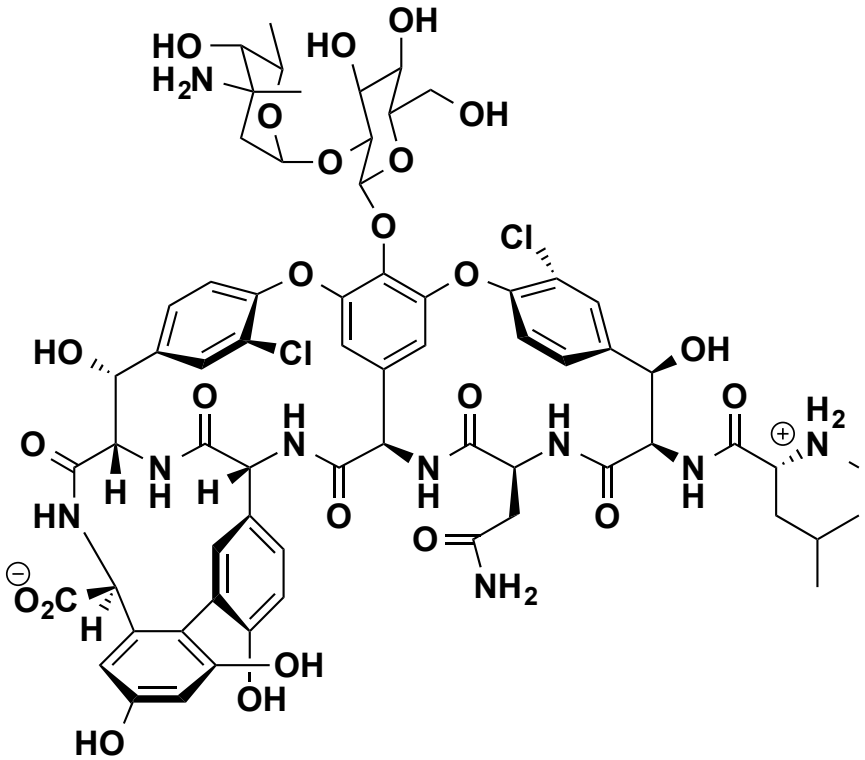
Vinblastine



Taxol



Artemisinine



Vancomycine

# What is Total Synthesis ?

# Total Synthesis: Why, What's for, What's after

# Terms

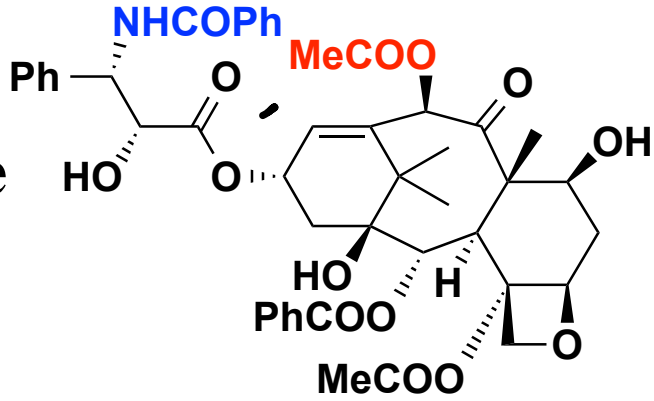
**Total Synthesis: The production of a molecule from commercially or readily available chemicals through a series of chemical transformations.**
***Not limited to Natural Product***

**Formal total synthesis: the chemical synthesis of an advanced intermediate that has already been transformed into the desired target.**

# Terms

**Partial synthesis or semisynthesis:**

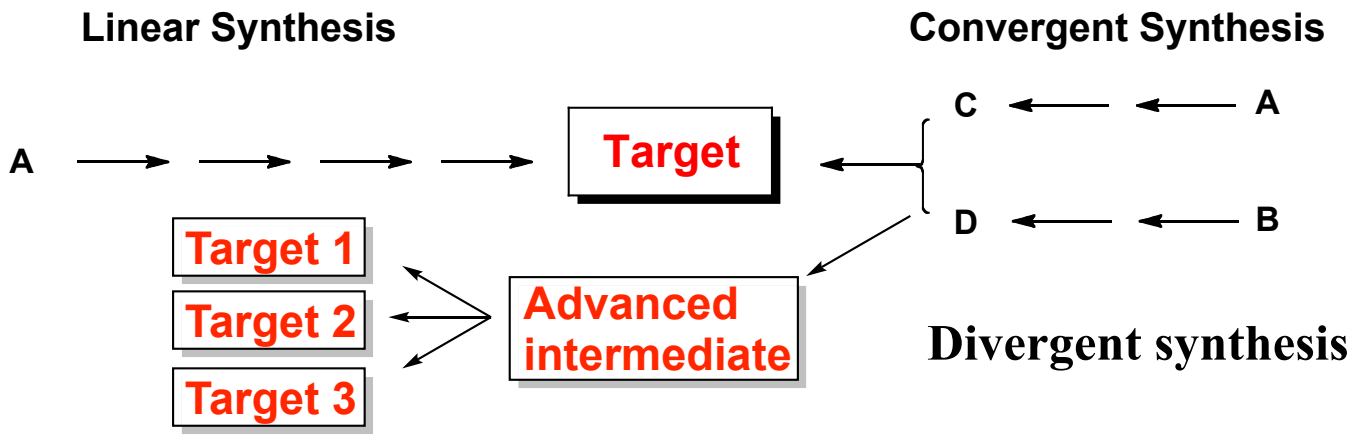
**Designates the synthesis of a given molecule from an advanced precursor related to it.**




**Relay Synthesis: defines the process in which an advanced synthetic intermediate is readily accessible by degradation of the target molecule.**

# Total Synthesis

**The production of a molecule from commercially or readily available chemicals through a series of chemical transformations**
**Not limited to natural products**




**Target-oriented Synthesis**
**Methodology-oriented Synthesis**
**Divergent Synthesis (Unified Strategy)**

**To be the first**
**or**
**To be the best**

# Total Synthesis: To be the First *vs* To be the Best

**The race to be the first to get there is still real**

**The philosophy of being the first wasn't necessary prolific to the fundamental discoveries along the way.**

**The imperative of being the first to cross the line is somehow down-regulated nowadays.**

**To be the best:**

**A relative term that is difficult to quantify, evolves constantly.**

**Key to Synthesis:**

**a) Selection of target**
**(structure, bioactivity, physical property)**

**b) *Synthetic strategy***

**c) New reaction, new reactivity**

# Total Synthesis: Why


**Why did you want to climb Mount Everest?**
**George Mallory (Mountaineer): "Because it's there"**

**R. B. Woodward: "Because nobody else could do it"**

**A Paradigm shift: "*Can we make everything*" became "*How well can we make everything*" or "*Can we impact science (society) on the way making molecules*"**

**Climbing Mount Everest:** **Became accessible to non-professionals**

**Mostly *follow the same pathway***

**Total synthesis:** **Reserved only to skilled synthetic chemists**

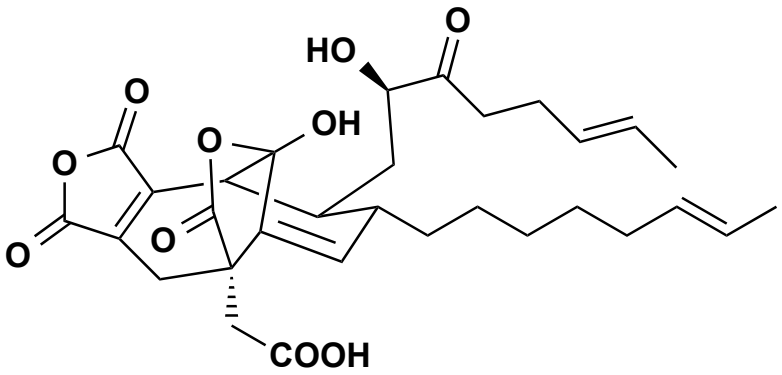
**Need constantly to *find new routes* to cross the line**

# Total Synthesis: Why, What's for, What's after

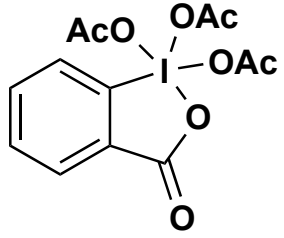
# Total Synthesis: For the discovery of new reactions

***Many new synthetic processes have been discovered as a result of a perceived need in connection with specific problems involving novel or complicated structures and a deliberate search for suitable methodology***

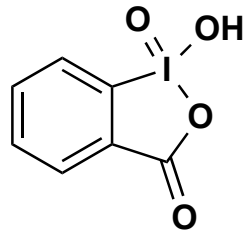
**E. J. Corey (*From "Classic in Total Synthesis II" Nicolaou, KC, Snyder, SA)***




**CP-225917, phomoidride A**
**Squalene synthase inhibitor**




**Dess-Martin periodinane (DMP)**




**2-iodoxybenzoic acid (IBX)**

**On the way to the total synthesis of CP molecules, a series of new reactions have been discovered based on the well-known oxidants, DMP and IBX. For a review, see:**

Nicolaou, K. C.; Baran, P. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 2678

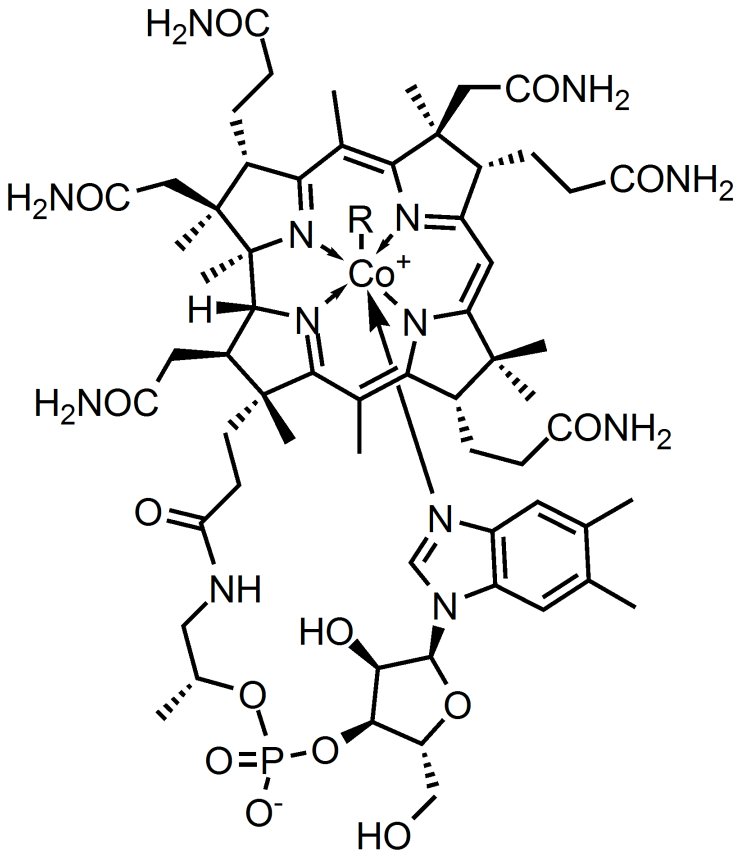
# Total Synthesis: For Serendipity…

***Most of the chemical reactions are discovered, not invented…***

***Even the "simplest" transformation may fail to go as expected in a complex molecular settings. Observation of an unexpected reaction pathway may lead to the development of a new reaction.***

***Something unexpected is bound to happen when you're dealing with the synthesis of a complex natural product.***

# Total Synthesis: For the discovery of new fundamental principles in organic chemistry




R = 5'-deoxyadenosyl, Me, OH, CN

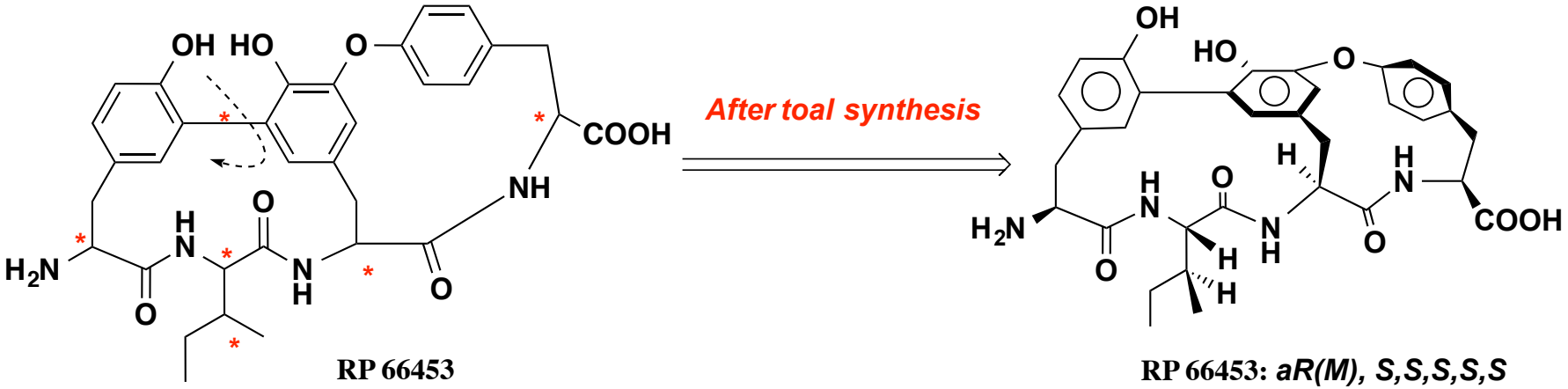
**Total synthesis of vitamin B12**
**By Woodward and Eschenmoser**

⇓

**Woodward-Hoffman rules**

# Total Synthesis: For the Structural Determination

## *Less prominant nowadays, but still valide*

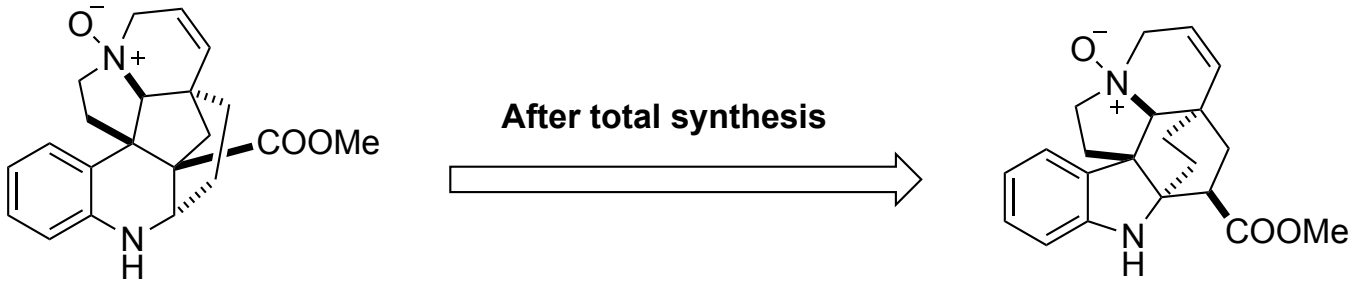



RP 66453

RP 66453: ***aR(M), S,S,S,S,S***

***5 stereocenters, 1 axial chirality***

Bois-Choussy, M.; Cristau, P.; Zhu, J. *Angew. Chem. Int. Ed*. **2003**, *42*, 4238-4241.

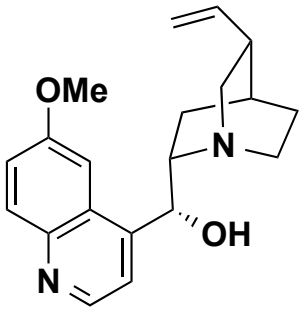



**melognine (reported structure)**

**melodinine L**

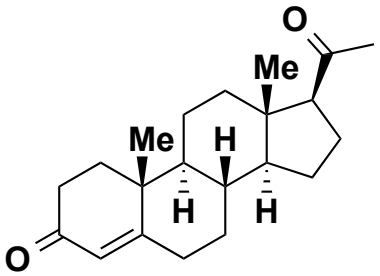
Yokoshima, S. *J. Am. Chem. Soc*. **2024**, *146*, 9526.

# Total Synthesis: Impact Science and Society



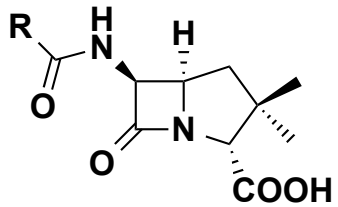

Quinine

**From eariler part of 20th century**
**Chemistry of heteroaromatics, quinoline, pyridine**
**Organocatalysts**
**Drug: New synthetic antimalaria agents**




Progesterone

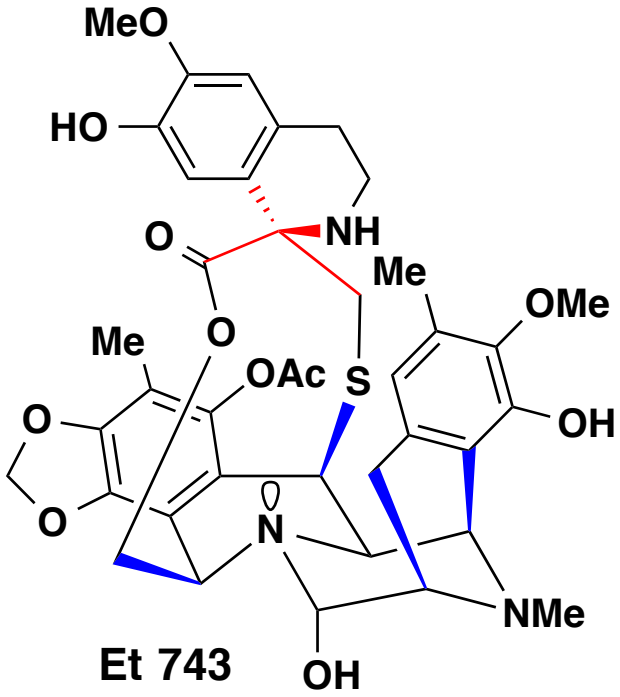
**From 1930's onward**
**Conformational analysis**
**Synthetic strategies**
**Drug: Birth control pill**




Penicillin

**From 1950's**
**β-lactam chemistry**
**Carbodiimide: Revolutionized peptide chemistry**
**Drug: New synthetic Antibiotics**

# Total Synthesis: Impact Society by Solving Supply Issue




Et 743

**Isolation: From Caribbean Sea squirt *Ecteinascidia Turbinate***

**Structural determination: 1990**

**Antitumor activities: 10-100 times more active than Taxol, Camptothecin...**

**Marketing Authorization: 2007**

**Mode of Action:**

- **DNA-Alkylator**
- **Protein interaction…**
- **Disrupting Protein-DNA interaction**

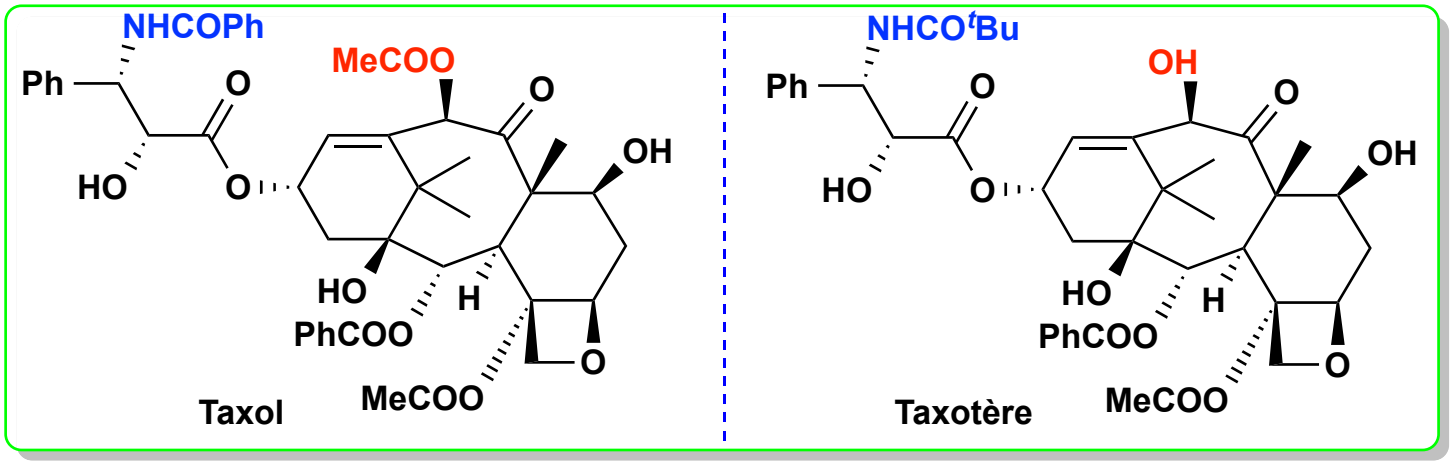
**Isolation yield: $10^{-5}$%**

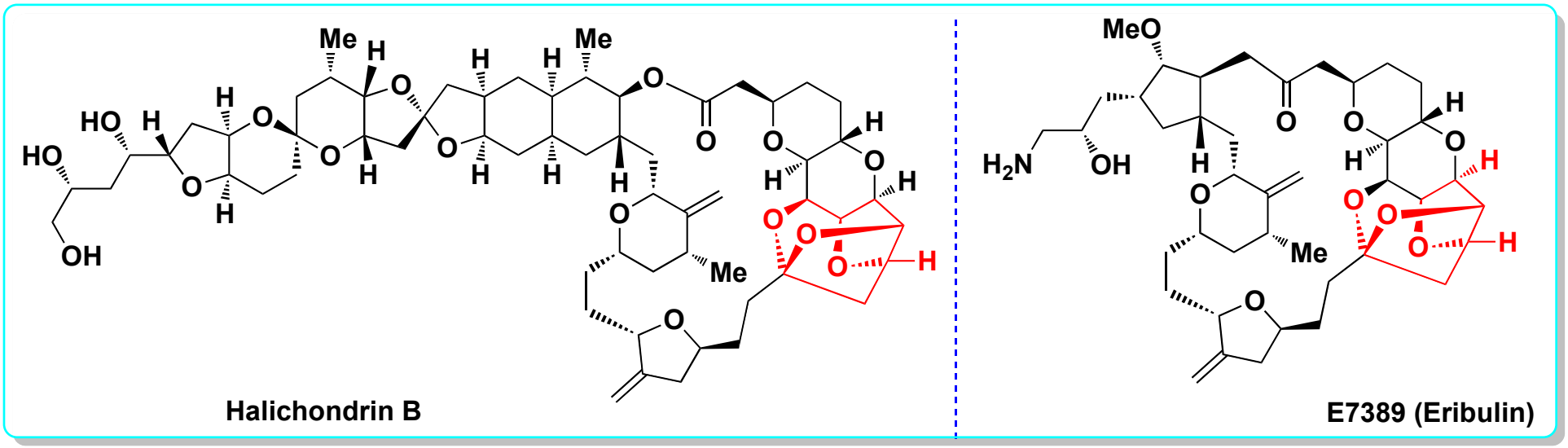
**Acquaculture: feasible but too expensive**

***SYNTHESIS is the only solution***

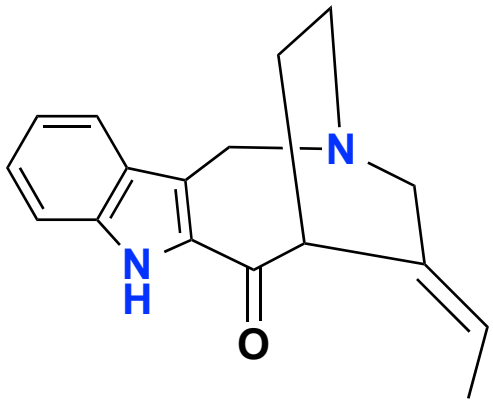
For a review: Cuevas, C. *Nat. Prod. Rep*. **2009**, *26*, 322-337.

# Total Synthesis: Developing (Creating) New Natural Product-Based Drugs



# Total Synthesis: To deepen and Broaden biological studies of a given natural product




Conolidine

**Thanks to a total synthesis program, conolidine has been identified to be a potent non-opioid analgesic for tonic and persistent pain.**
**Micalizio, G. C. *Nat. Chem*. 2011, *3*, 449-453.**

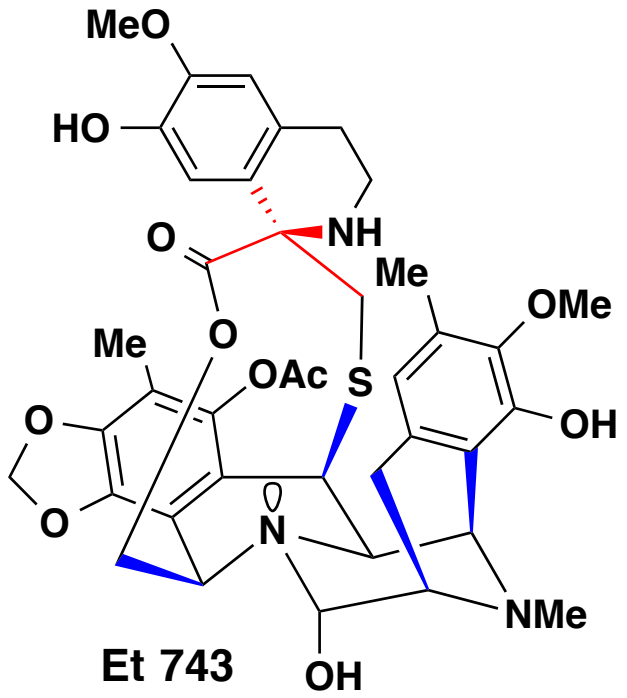
# Total Synthesis: A superb learning and creating process

***"The drug companies love to hire total synthesis people. They figure (correctly) that dealing with the adversity of that work is good training for drug discovery, where most things don't work, either…"***

***For the intellectual challenge and sheer excitement of the endeavor***

# Total Synthesis:

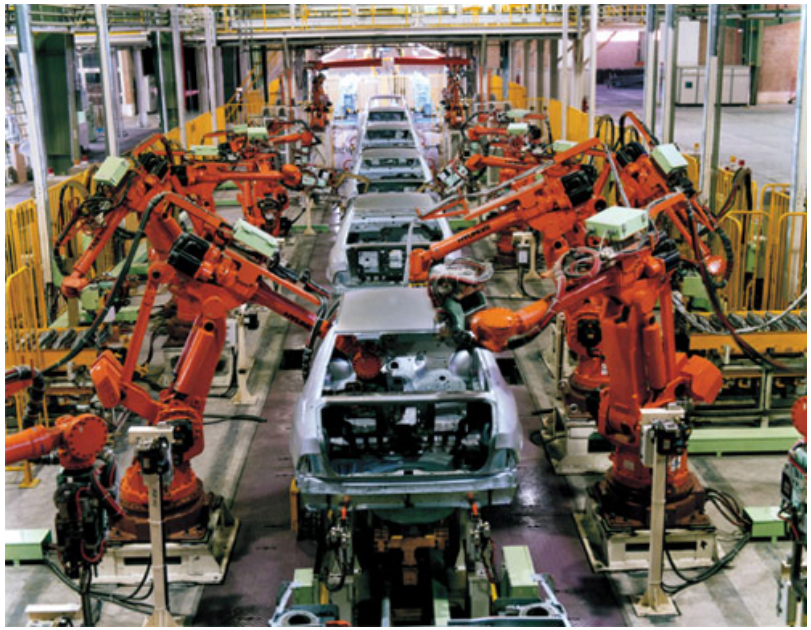
## Science Behind Art
## or
## Art Behind Science




Et 743

**Yes, but the truth is** $\Longrightarrow$

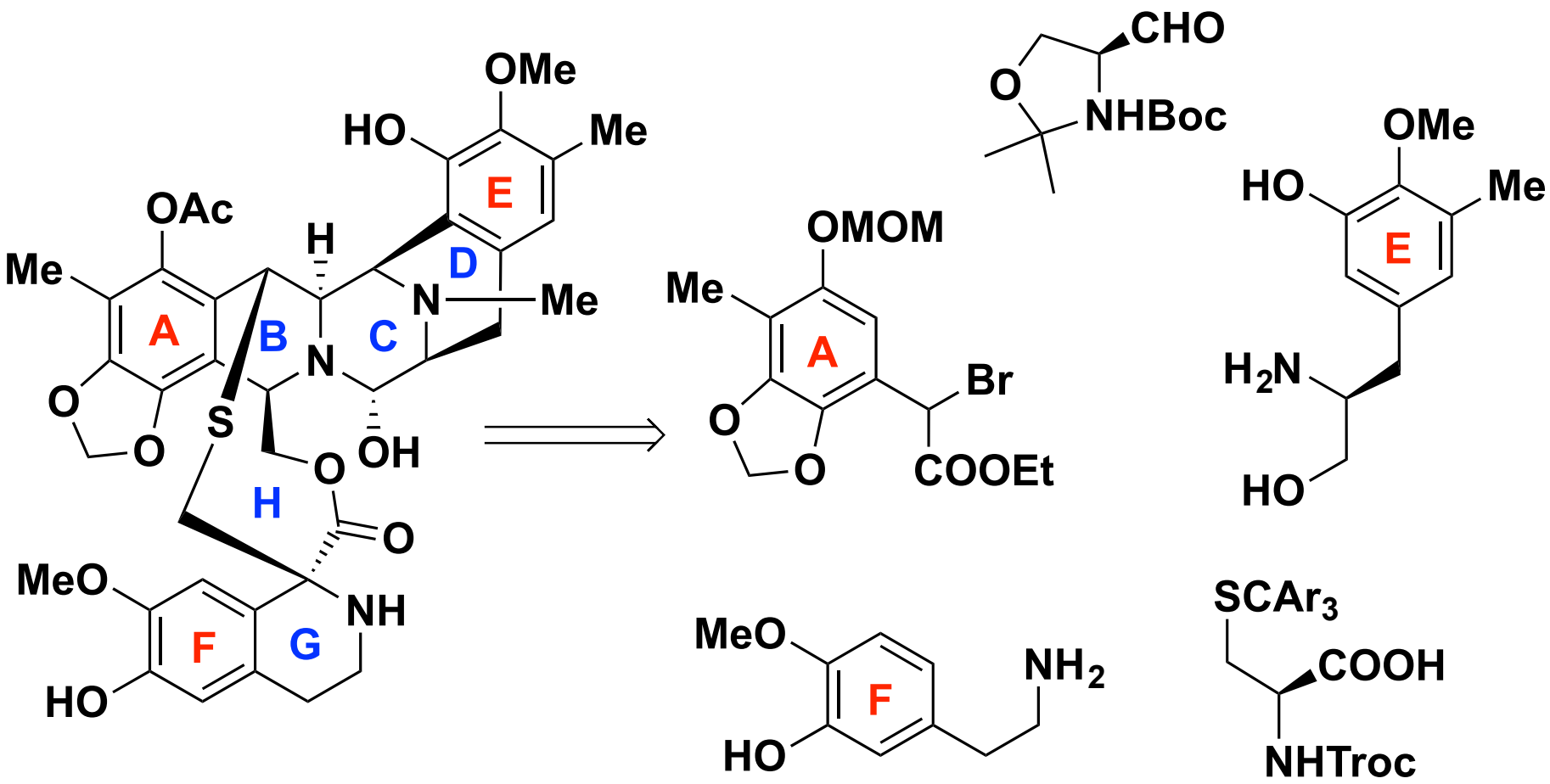
# Total Synthesis: How



**Taj Mahal**

Alper, J. *Science* **1994**, *264*, 1399-1401.

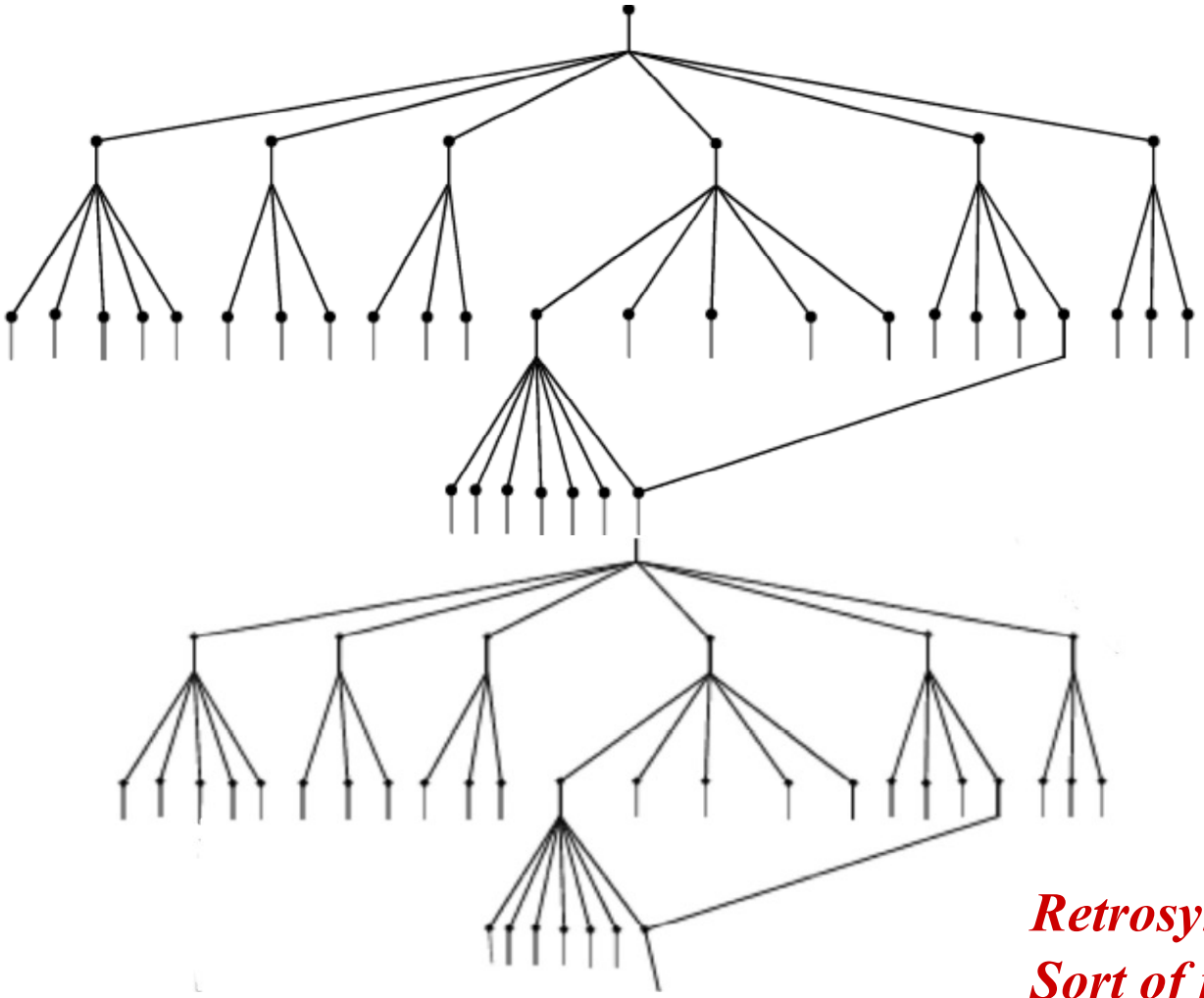
# Total Synthesis: How




J. Chen, X. Chen, M. Bois-Choussy, J. Zhu, *J. Am. Chem. Soc*. **2006**, *128*, 87.

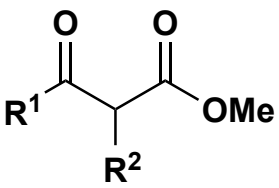
# Logic of Total Synthesis—Retro Synthetic Analysis

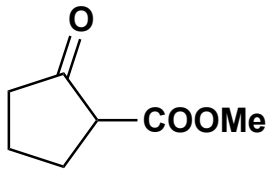
**Reducing the molecular complexity by disconnecting the Chemical bond(s)**

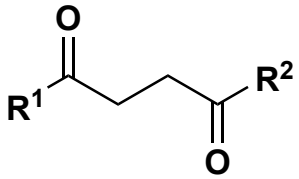


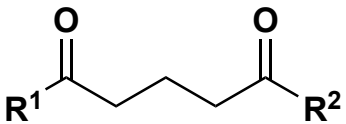

***Retrosynthesis:***
***Sort of pattern recognition***

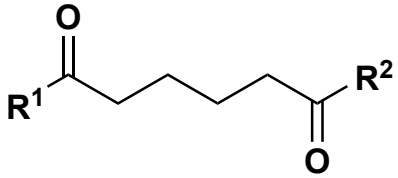
# Basic Structure Motifs: Simple exemples

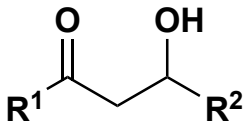


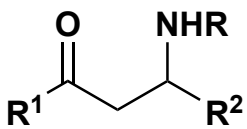



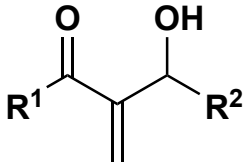



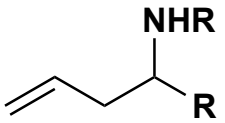



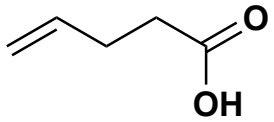



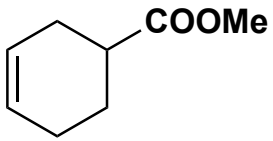



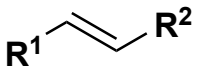



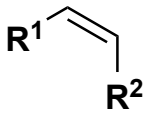



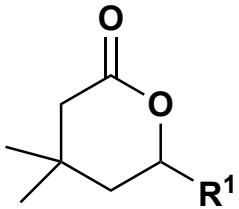



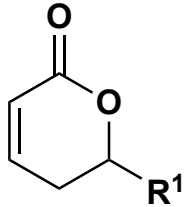



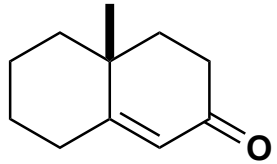



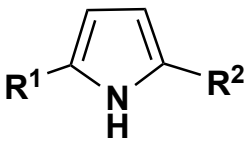



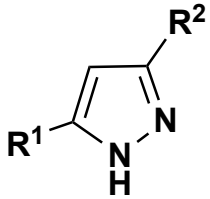



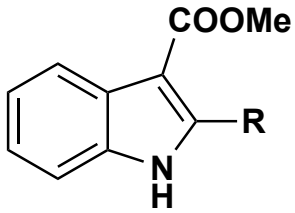



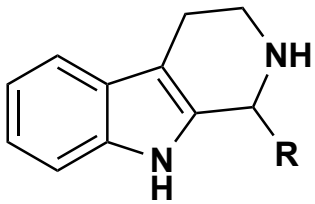



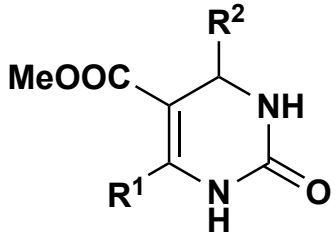



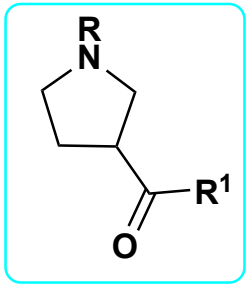



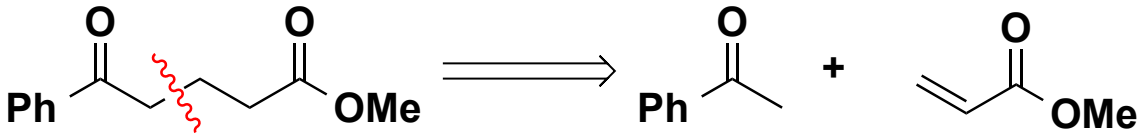



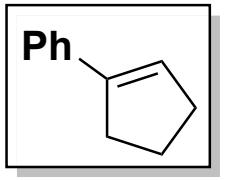



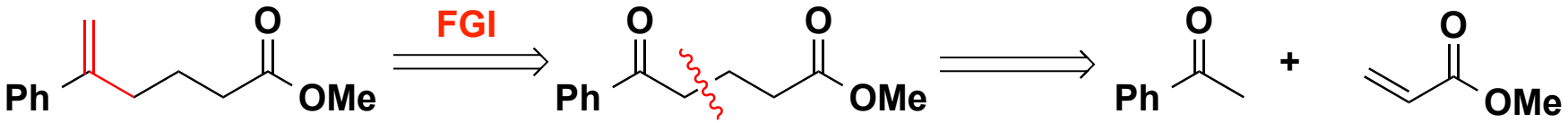
# Retro-Synthetic Analysis: Approaches

1. **Direct structure simplification**




2. **Fonctional Group Interchange (FGI) Transforms which bring about essentially no change in molecular complexity but allow the subsequent application of simplifying transforms:**

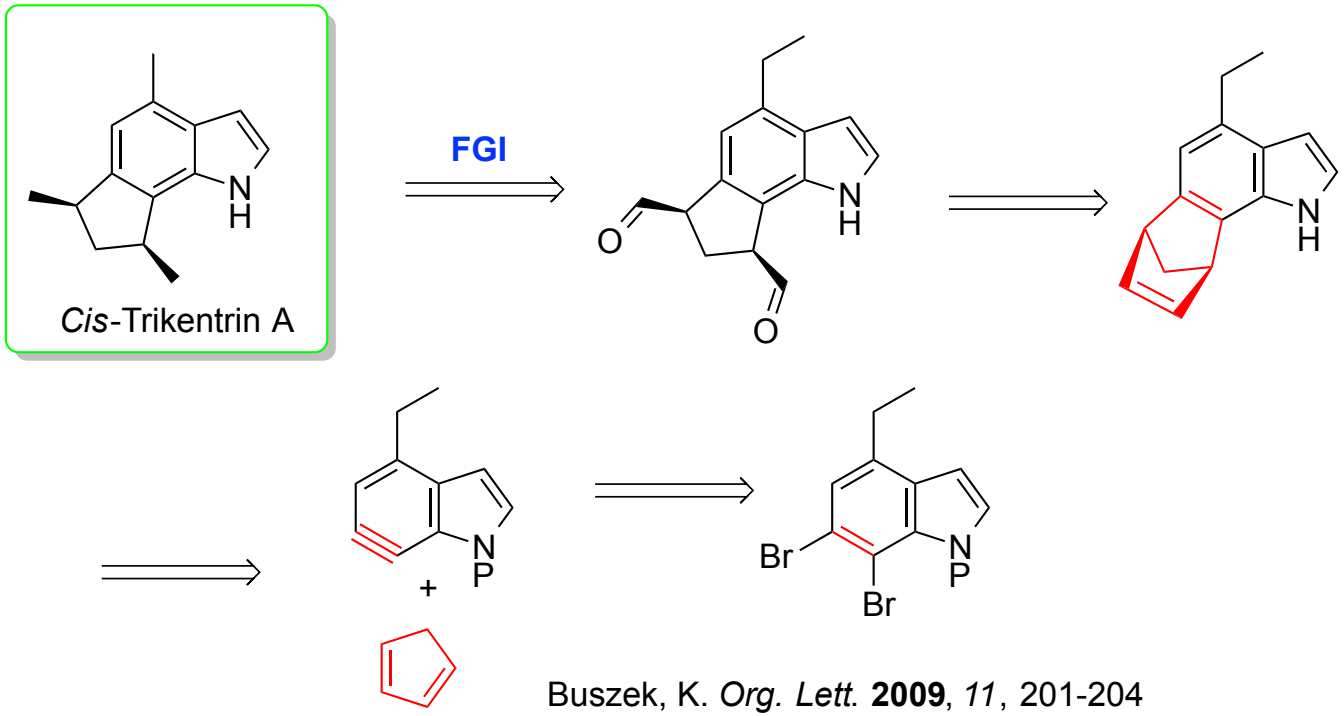



3. **Opposite to 1, increasing structure complexity includes addition of rings, functional groups (FGA), or stereocenters etc (Pattern recognition).**

# Retro-Synthetic Analysis: Approaches

**Increasing structure complexity includes addition of rings, functional groups (FGA), or stereocenters etc (Pattern recognition).**


FGI = Functional Group Interchange




*Cis*-Trikentrin A

Buszek, K. *Org. Lett.* **2009**, *11*, 201-204

# Total Synthesis: Evolution of Criteria

**Selectivity (Chemo-, Diastereo-, Enantioselectivity)**
**Convergency, Divergency, Overall yields** } **"High"**

**Economy**

**Atom-Economy, Step-Economy, Redox-Economy**

**Free**

**Protective group-Free, Redox-Free**

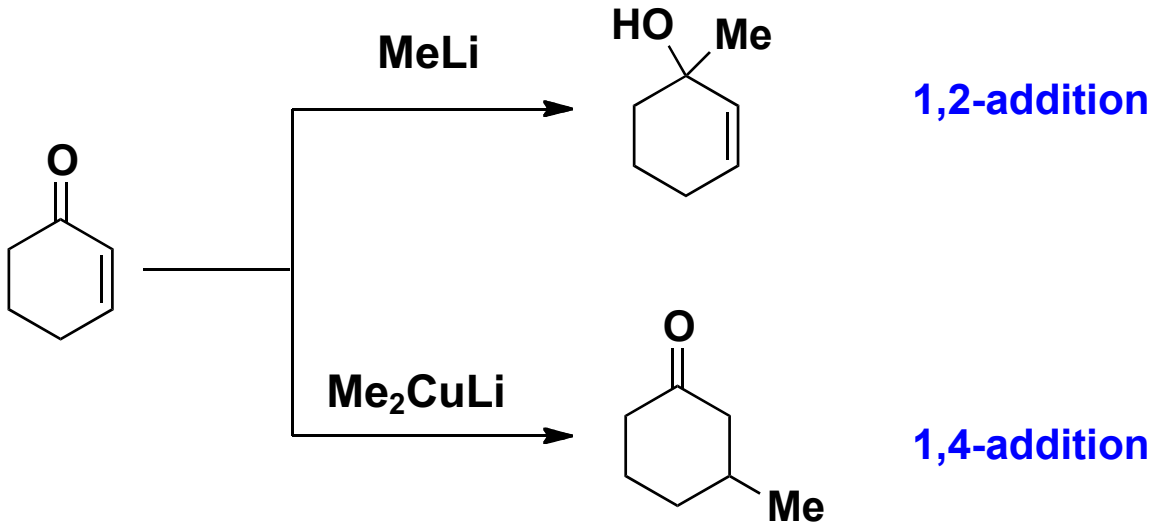
**Hendrickson's definition of ideal synthesis : " ...creates a complex molecule...in a sequence of only construction reactions involving no intermediary refunctionalizations, and leading directly to the target, not only its skeleton but also its correctly placed functionality."**
Hendrickson, J. B. *J. Am. Chem. Soc*. **1975**, *97*, 5784.

***Total synthesis: Be short, selective and high yielding***

# Chemo-, Regio-, and Stereo-selectivity

## Chemo-selectivity

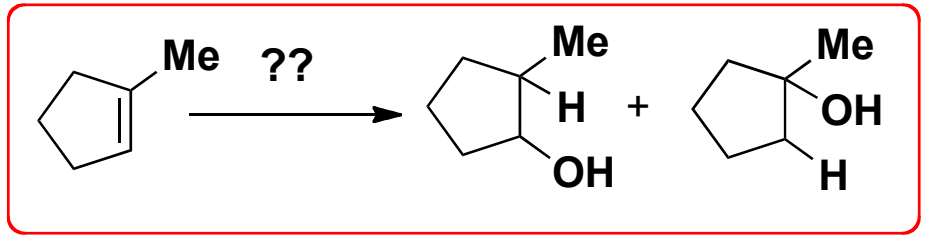
**The preferential reaction of a given reagent with one of two or more functional groups**



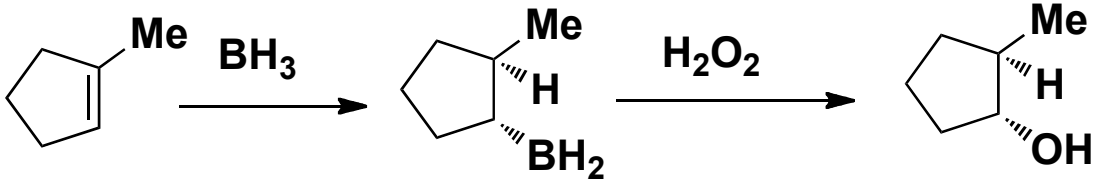
# Chemo-, Regio-, and Stereo-selectivity

## Regioselectivity

**The directional preference of breaking or making a chemical bond**

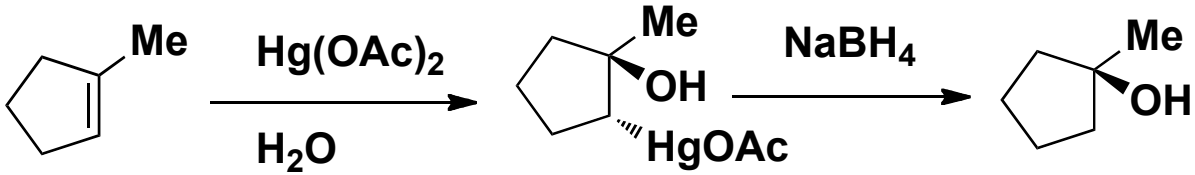



### Hydroboration




*Syn-addition* *Retention of Stereochemistry*

### Oxymercuration/Reduction

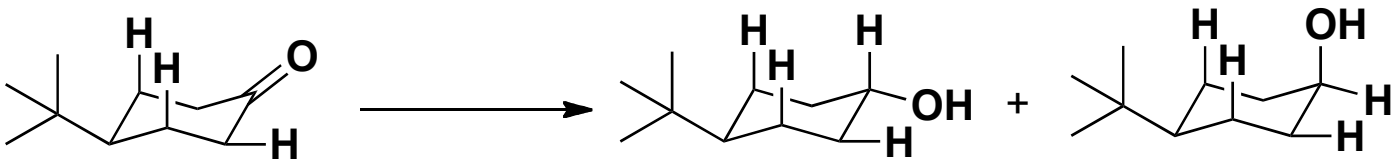



*Anti-addition*

# Chemo-, Regio-, and Stereo-selectivity

## Stereoselectivity

**The preferential formation of one stereoisomer over another (diastereo-, enantio-selectivity)**

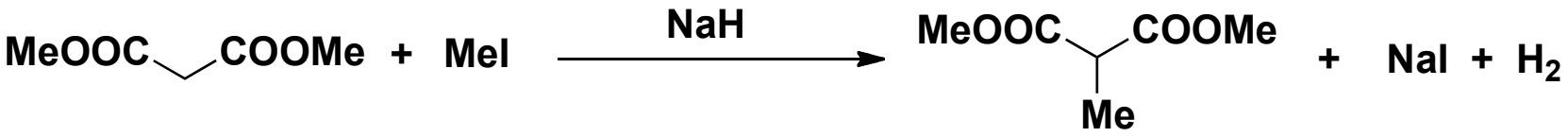



| | | |
|---|---|---|
| LAH | 90 | 10 |
| LiB(*i*-Bu)$_3$H | 3.5 | 96.5 |

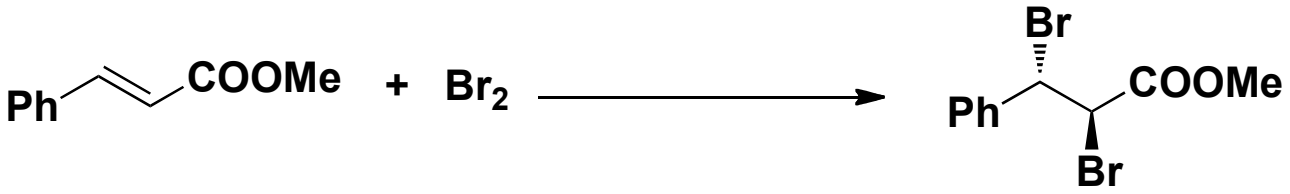
# Atom-Economy

$$\text{Atom-economy\%} = \frac{\text{Mass of Products}}{\text{Mass of Starting Matrerials}} \times 100$$

*Minimizing waste at the Molecular level*




Y: 100%
But not atom-economic




Y: 100%
atom-economic

**Good: Addition, (cyclo)isomerizations, Pericyclic reactions using catalytic amount of reagent if needed. Ideal: « Mix and Go »**

**Bad: Substitution reaction, using stoichiometric reagents**

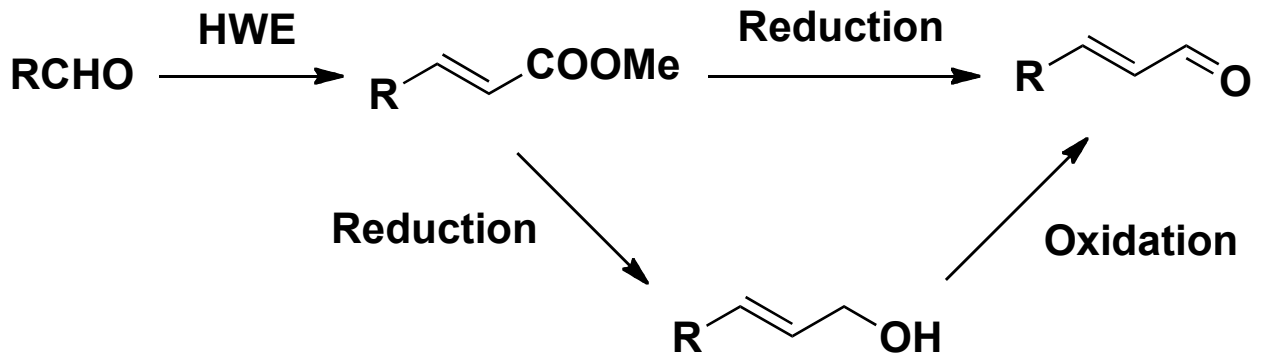
# Redox-Economy

* Reducing the number of nonstrategic or corrective Oxidation and Reduction steps
* Isohypsic = A synthesis sequence that is devoid of redox steps

**Nonstrategic or corrective Redox reactions:**

- increasing the length of synthesis (bad in step economy)
- increasing the waster production
- generally difficult to scale up in industrial settings

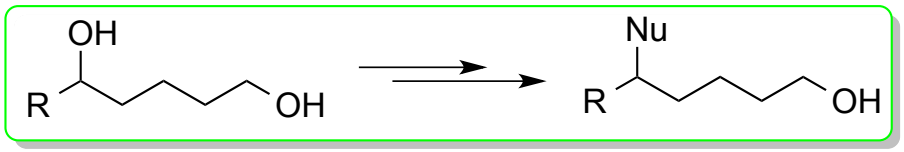
**A sequence of low redox-economy (nevertheless "synthetically efficient")**




Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew Chem. Int . Ed.* **2009**, *48*, 2854-2867.

# Protecting-Group-Free Synthesis

**Many creative synthesis would most likely be impossible without the Assistance of protective groups (PGs). The choice of PGs is part of the Synthesis Art.**
***Orthogonality*** **of PGs is a key issue that one has to consider in planning a synthesis**



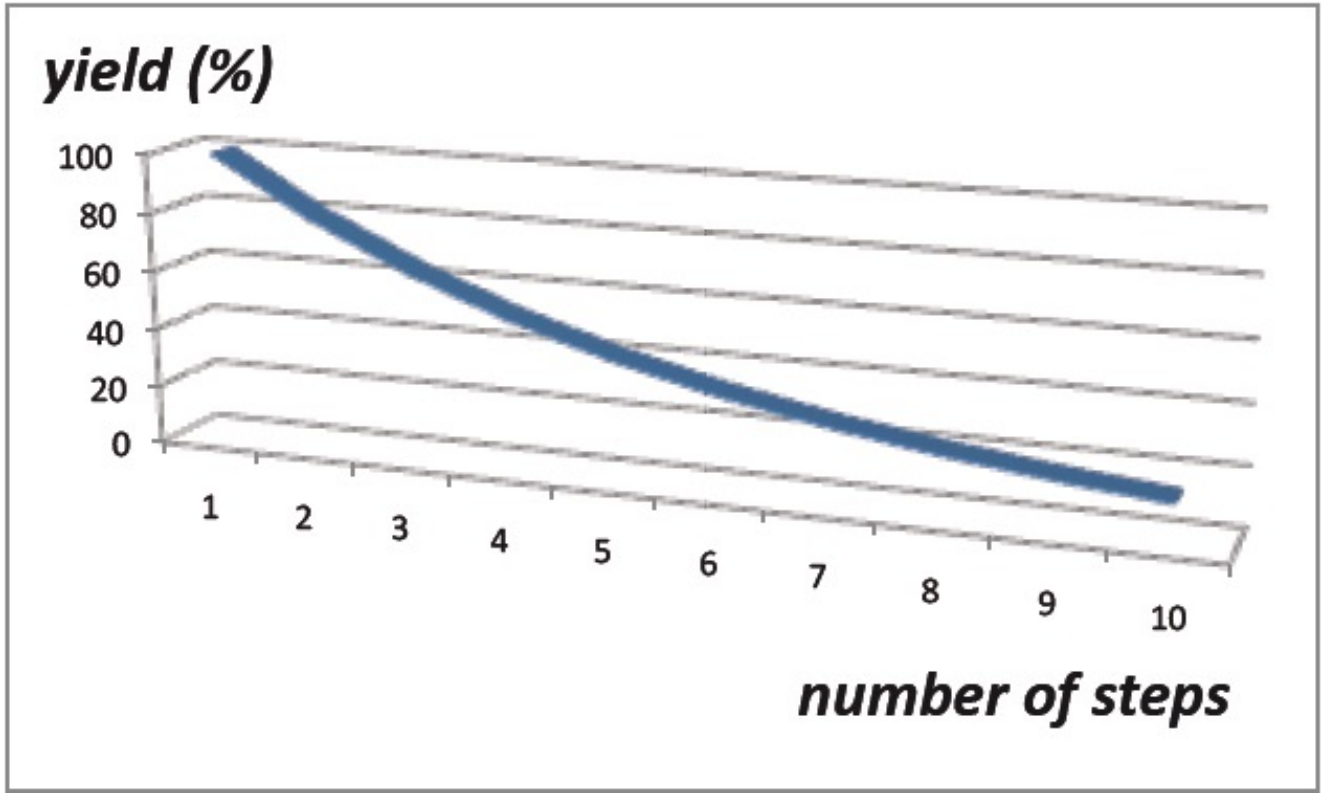

***However using PGs in a synthesis*:**

- **Add at least two steps (bad *step economy* and increasing waste production)**
- **Atoms corresponding to the protecting group is lost (bad *atom economy*)**
- **Could kill a synthesis due to difficulties in removing PGs (worst case but not rare).**

**The major challengs (in chemistry) are the construction of molecules without using protecting group chemistry and the ability to put molecules together in Fast and efficient ways (R. H. Grubbs, Nobel laureate 2005)**

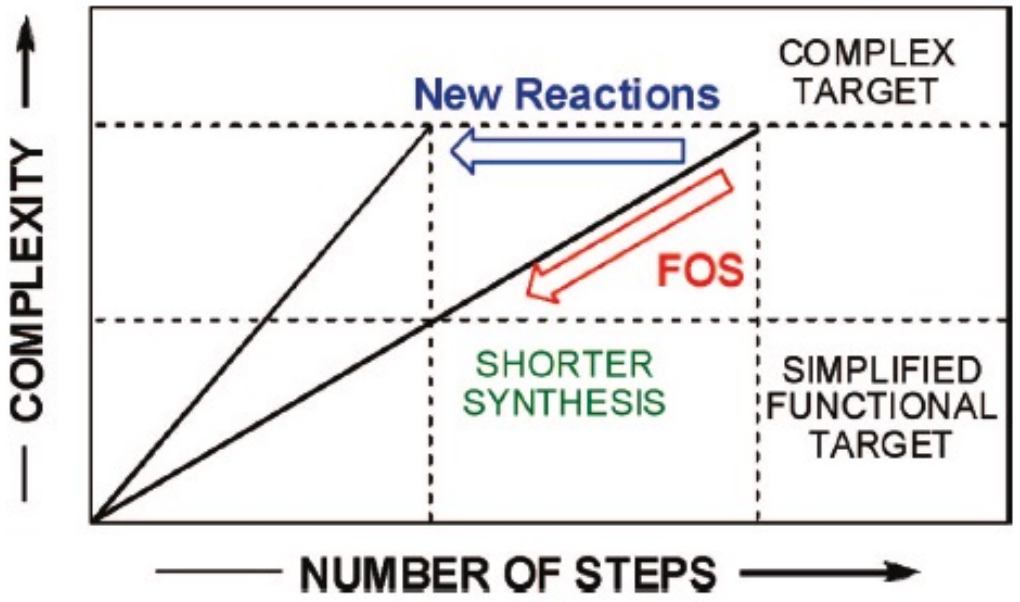
Young, I. S.; Baran, P. S. *Nature Chem*. **2009**, *1*, 193-205.

# Convergency, Divergency, Overall Yield



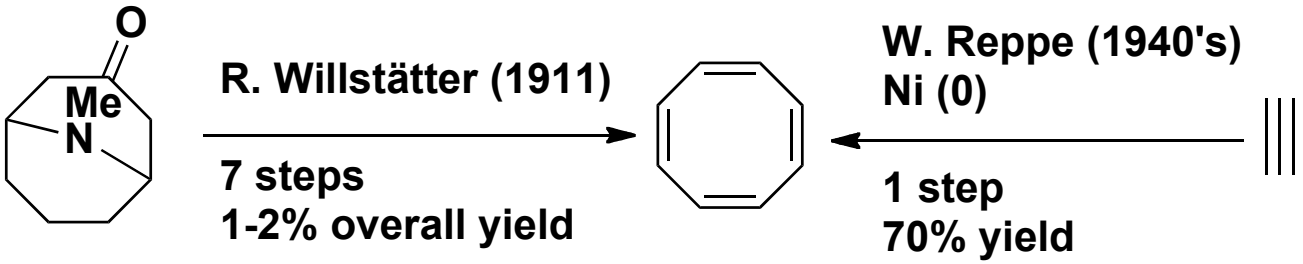

**Assuming each step proceeds in 80% yield, one will Lose abut 90% of his materials after a 10-step synthesis**

# Step-Economy



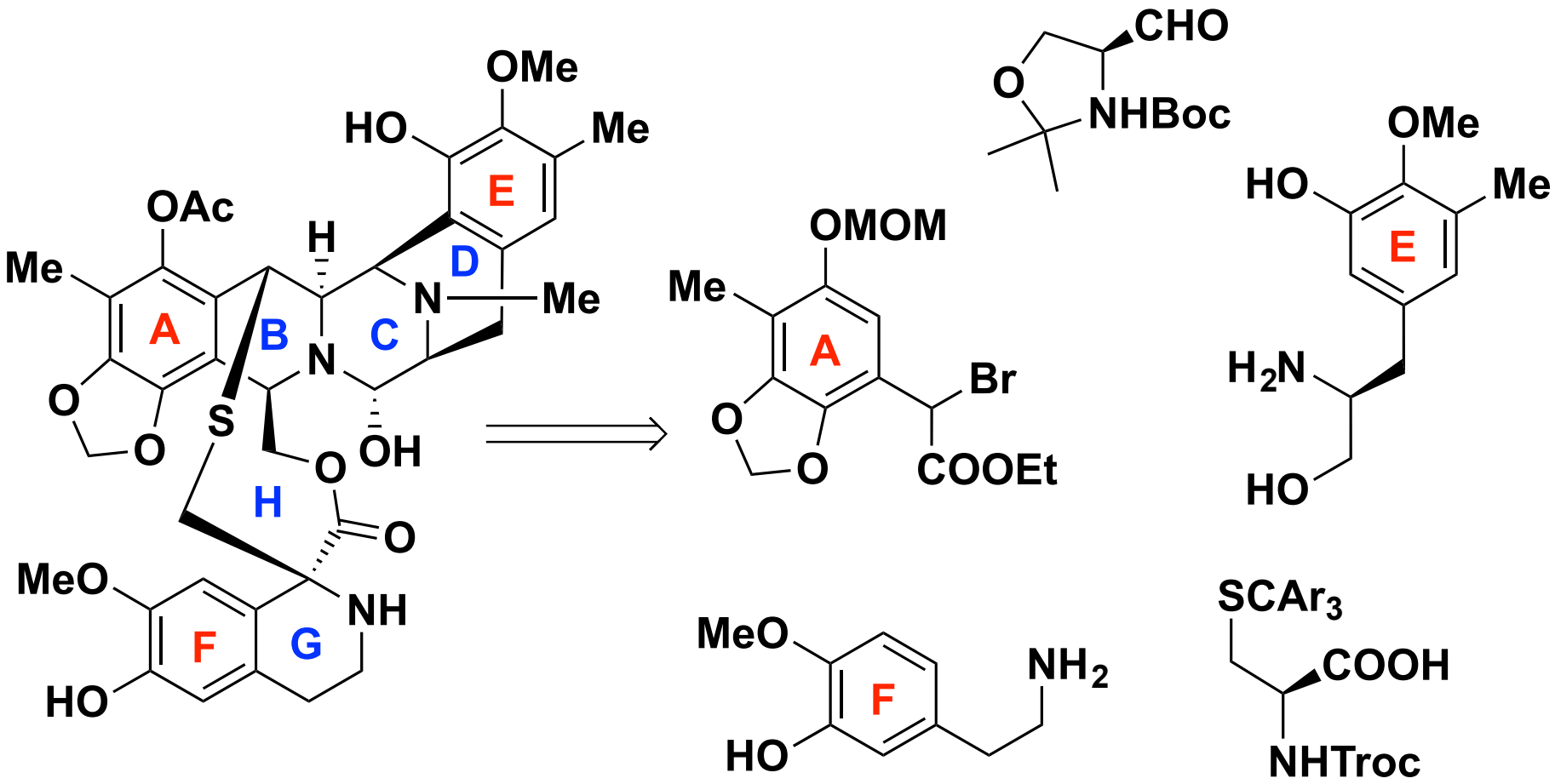

**Increasing Time, Cost efficiency; Reducing Waste production**

***Need New Reactions, New Synthetic strategies, Tactics***




Wender, P. A. *et al. Acc Chem. Res*. **2008**, *41*, 40-49.

# Retrosynthetic Analysis: Any Guideline




J. Chen, X. Chen, M. Bois-Choussy, J. Zhu, *J. Am. Chem. Soc*. **2006**, *128*, 87.

# "Guidelines for Retrosynthetic Analysis"

- **NO universal algorithum for synthesis design (machine learning re-populized recently)**
- **NO universal reactions (well, some are very reliable)**
- **Targets are too diverse**

***Nevertheless some good practices could be helpful***

- **Careful background check including biosynthesis pathway, degradation studies, what has been done, especially what has failed to be productive.**
- **Draw the targets in as many ways as possible**
- **Get a feeling for the three-dimensional structure**
- **Cleave the easy-forming bonds (e.g. C-X bonds), maximize convergency**
- **Looking for hidden symmetry**
- **Looking for multiple-bond forming processes (Dominio and Multicomponent reactions)**
- **Identify the thermodyamic sink**
- **Apply the atom-, redox-economy and protecting-group-free principle.**
- **Pattern recognition: identification of reactivity pattern within the target (moving backward could be rewarding in retrosynthesis)**

***When the retrosynthetic analysis converges with a feasible starting material, a synthesis plan is at hand.***

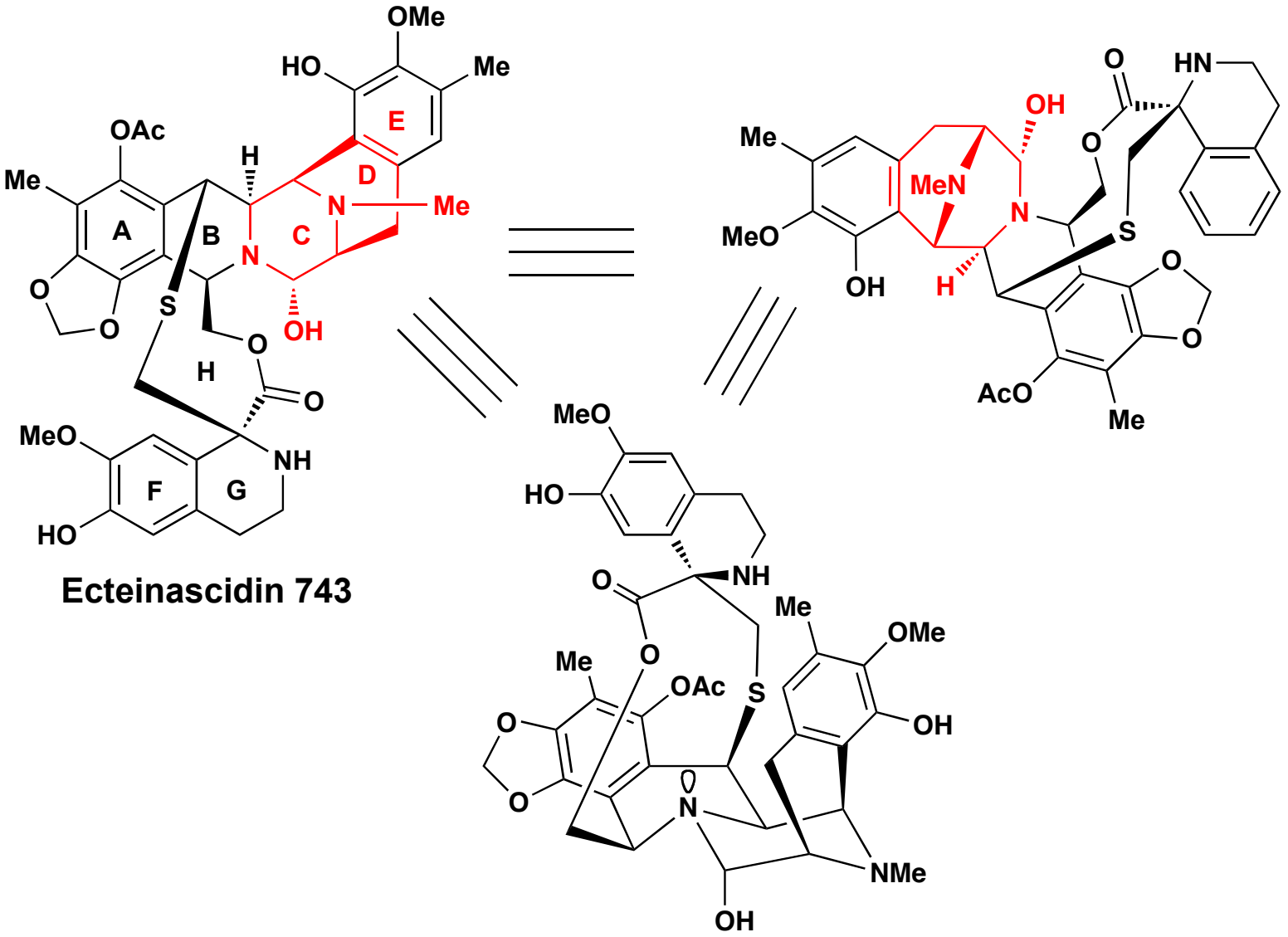
**"To study without thinking is futile, To think without studying is dangerous"**

**---Confucius**

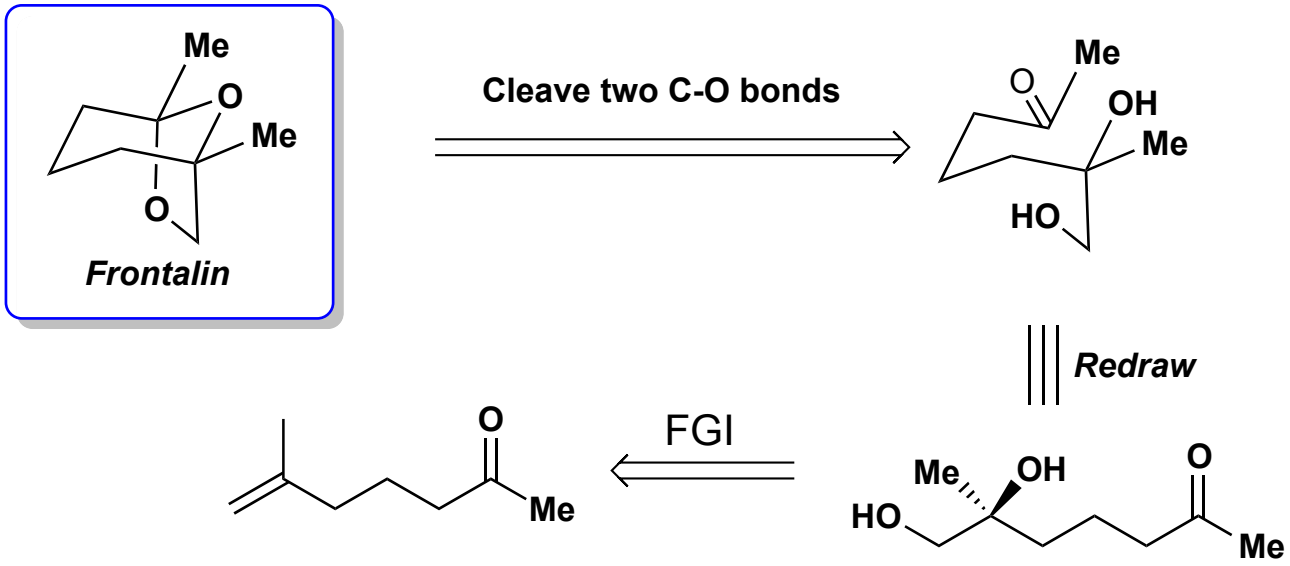
**"If you want to be creative, then you will have to get used to spending most of your time not being creative, to being becalmed on the ocean of scientific knowledge"**

**---Steven Weinberg**

# Draw the target in as many ways as possible: Different drawings gave different impression and possibly different bond disconnection

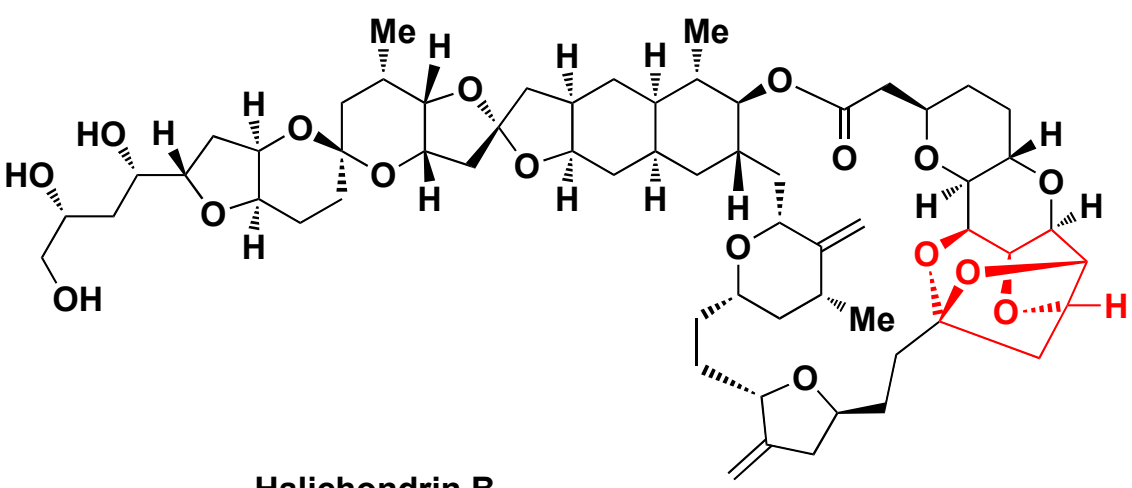


# Cleave the easy-forming bond to simplify the target

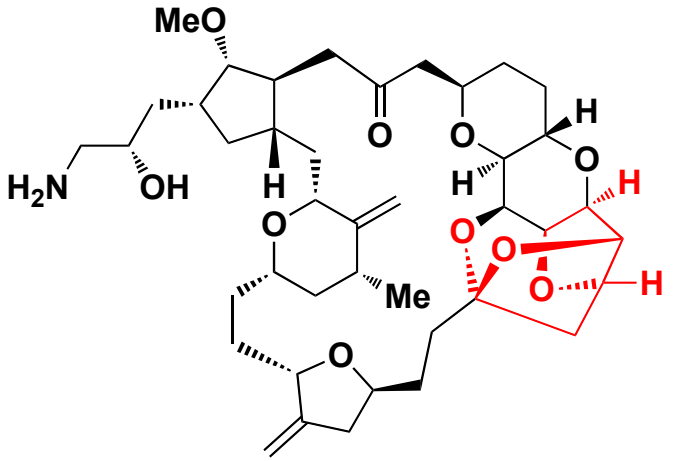



J. A. Turpin; L. O. Weige; *Tetrahedron Lett.* **1992**, *33,* 6563.

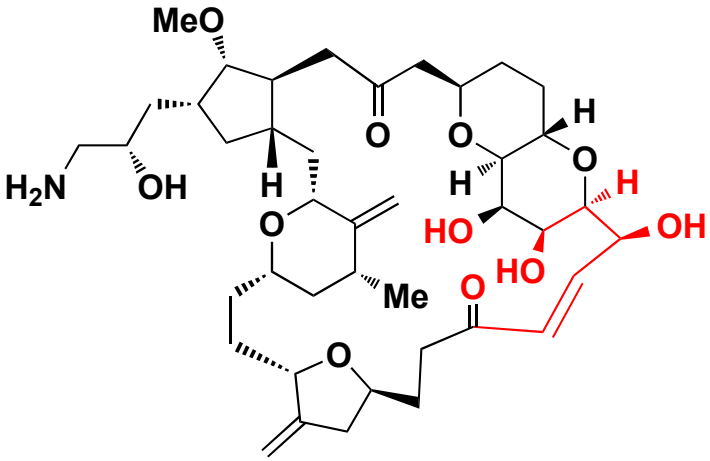
# Cleave the easy-forming bond to simplify the target

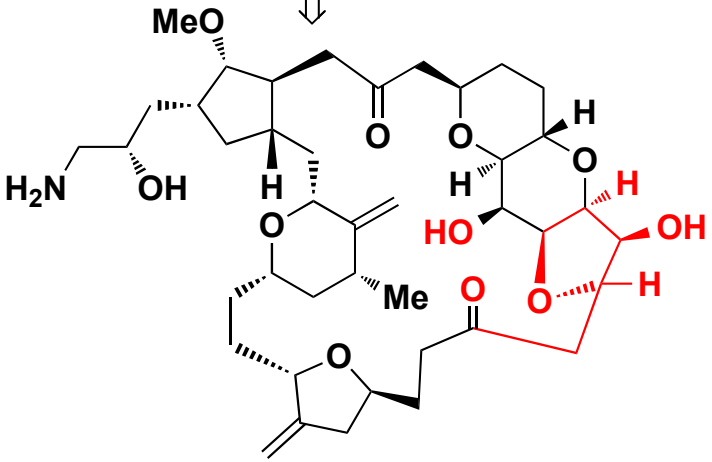


Halichondrin B



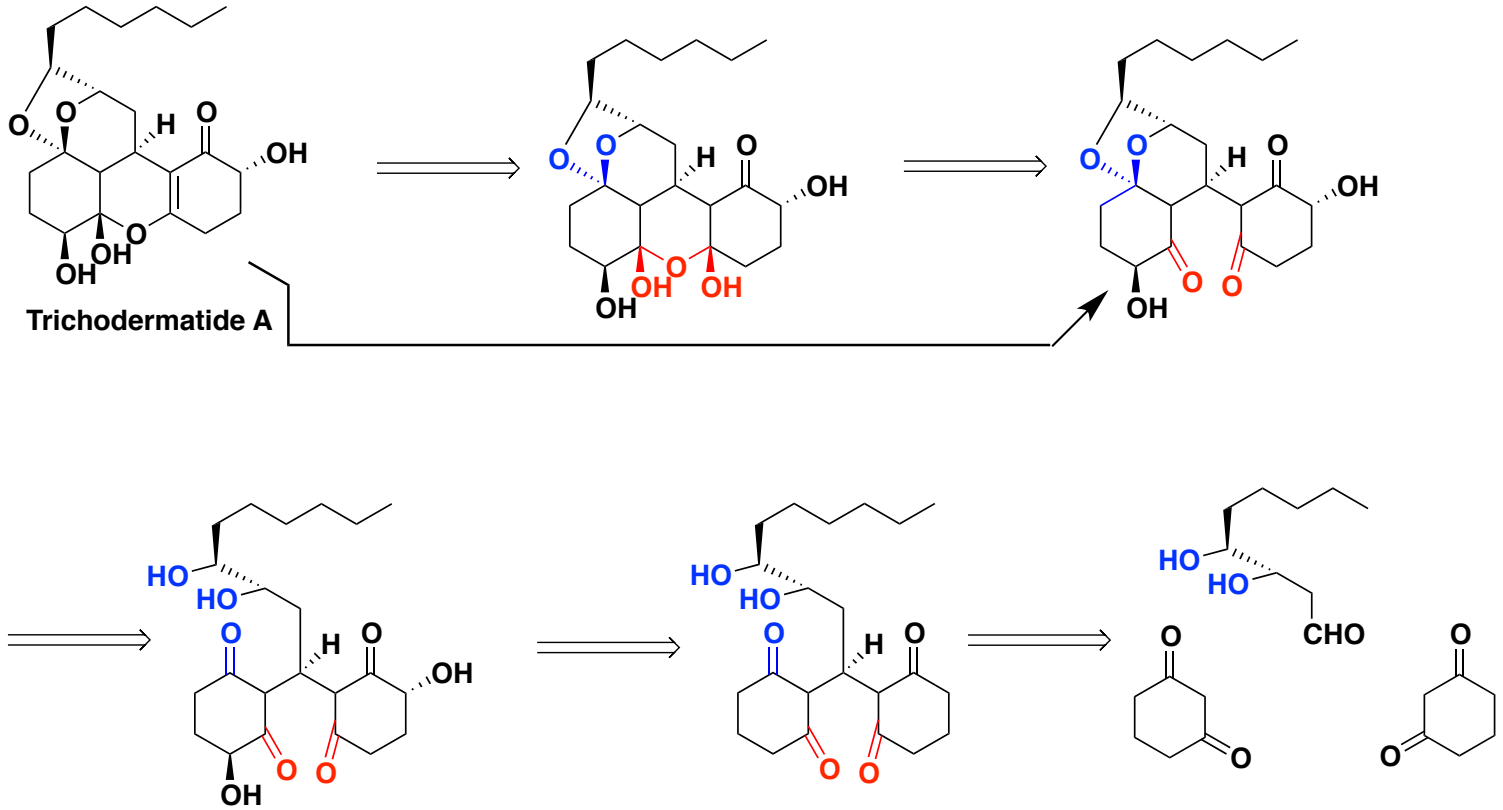
E7389 (Eribulin)





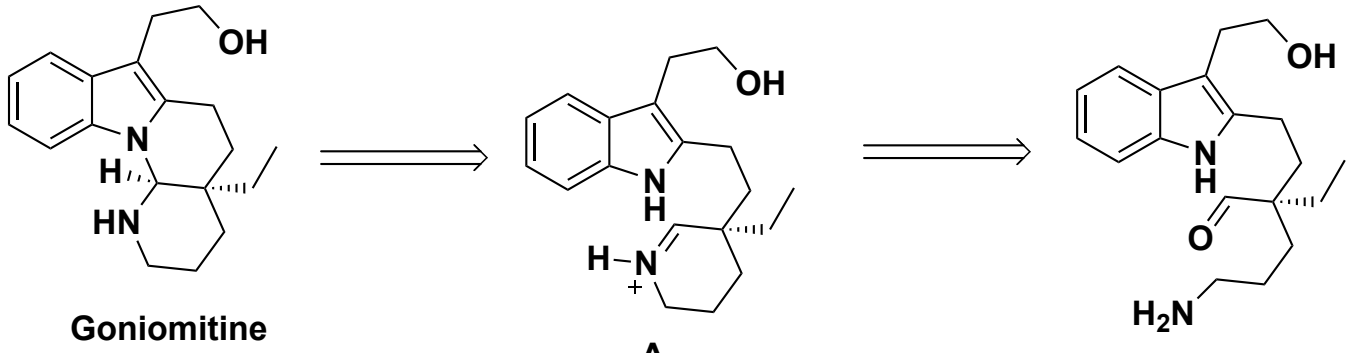
D.-S. Kim, C.-G. Dong, J. T. Kim, H. Guo, J. Huang, P. S. Tiseni, Y. Kishi,
*J. Am. Chem. Soc.* **2009**, *131*, 15636-15641.

# Cleave the Easiest Bond and Find the Hidden Symmetry



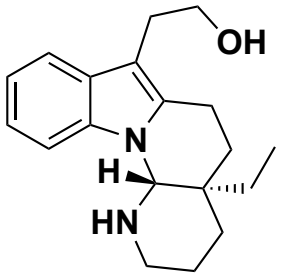

Hiroya, K. *Angew. Chem. Int. Ed.* 2013. 52, 3646-3649.

# Identifiy the Thermodynamic Sink: Favorable Case




Goniomitine

A




*epi*-Goniomitine

**Kinetic selectivity**: Cyclization of A will give goniomitine as a major product

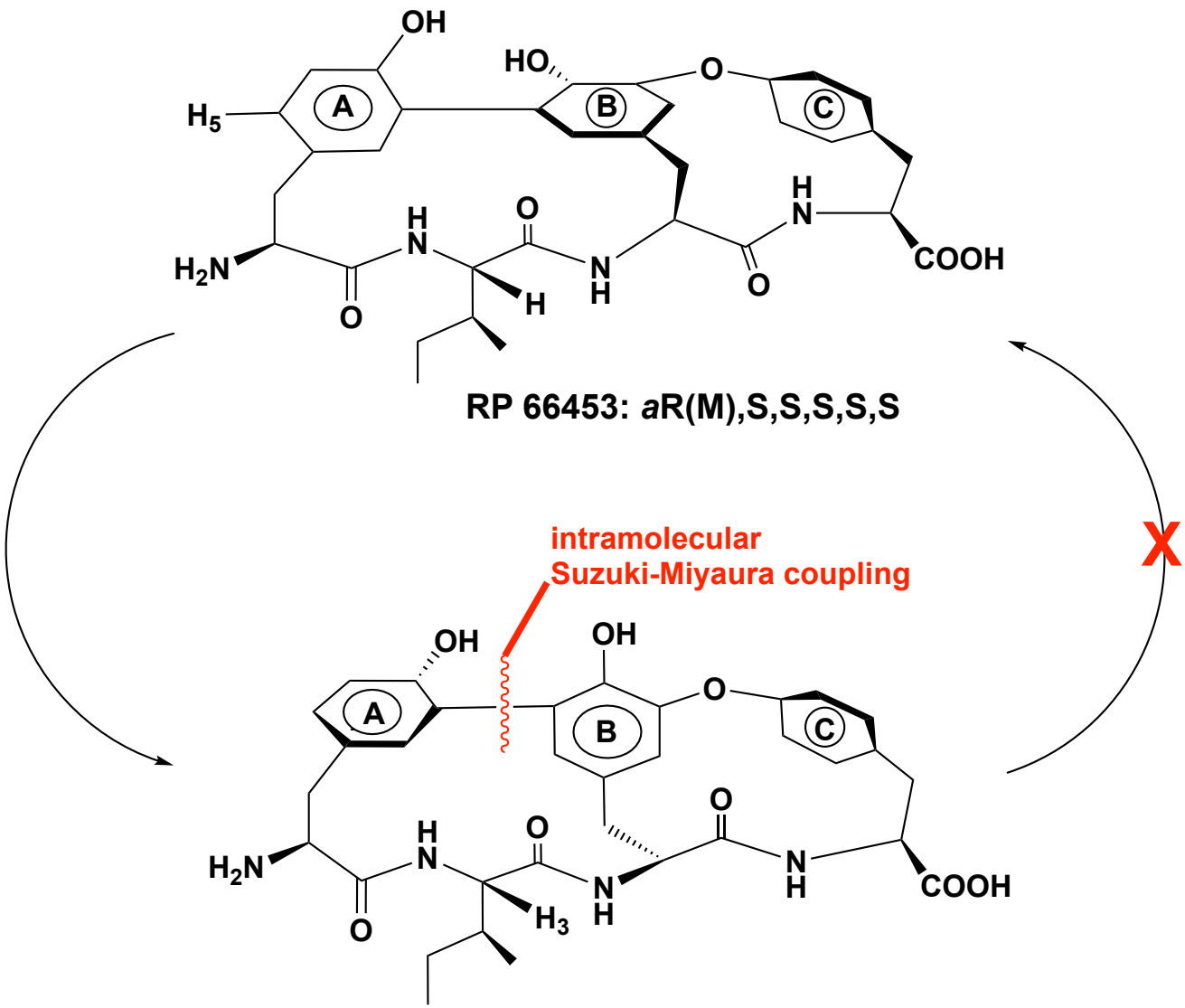
**Thermodynamic selectivity**: Goniomitine is thermodynamically more stable than its epimer

**Conclusion**: a favorable case for chemists…

Takano, S. *J. Chem. Soc. Chem. Commun*. **1991**, 462.

***But: in many case, a thermodynamic sink is difficult to identify though it many very often be one of the reasons that failed your synthesis plan.***

# Thermodynamic Sink: Unfavorable Case



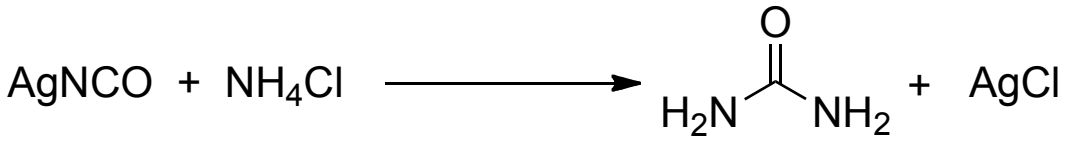
# "Wrong", yet still popular terminologies

| "Wrong" | "Correct" |
|---|---|
| **Asymmetric synthesis** | **Enantioselective synthesis**<br>**Diastereoselective synthesis** |
| **Chiral center** | **Stereocenter** |
| **Chiral HPLC** | **Enantioselective HPLC** |
| **Chiral column** | **Enantioselective column** |
| **Optical purity** | **Enantiomeric excess** |

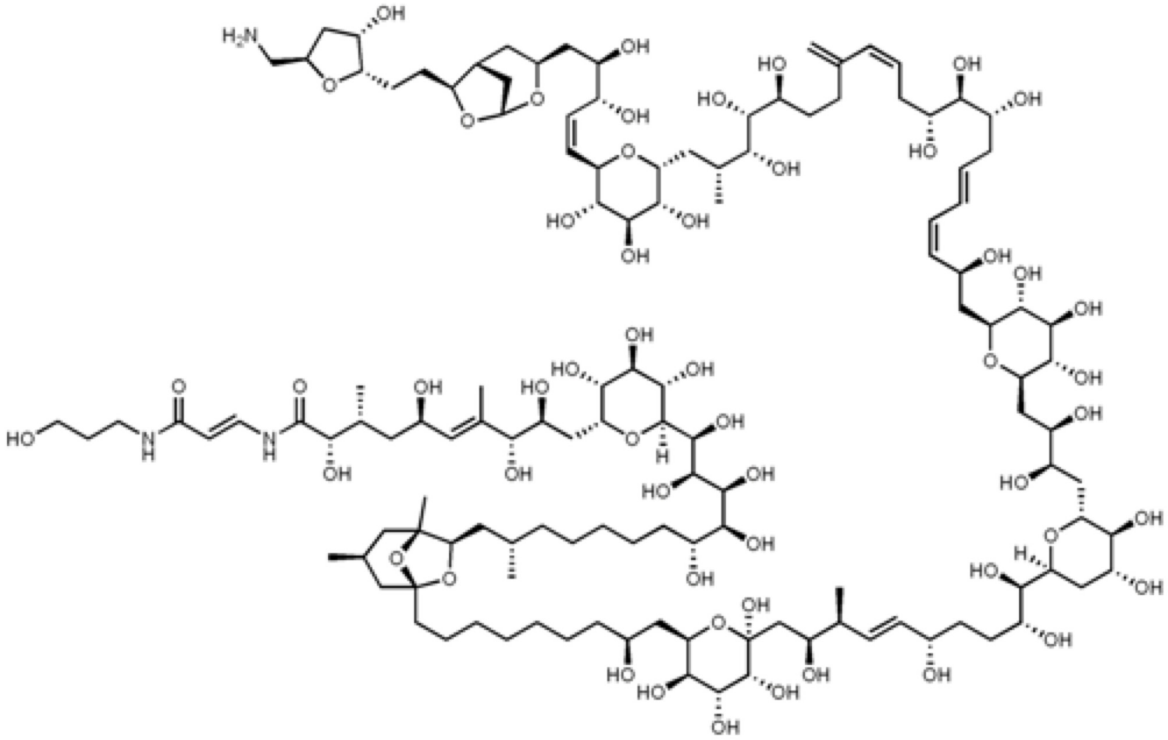
a) Mislow, K, Siegel, J. *J. Am. Chem. Soc*. **1984**,*106*, 3319-3328.
b) Eliel, E. L.: http://www.uottawa.ca/publications/interscientia/inter.4/eliel/eliel.html

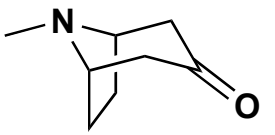
# Total Synthesis: Where we stand

**Urea Synthesis by Friedrich Wöhler (1828)**

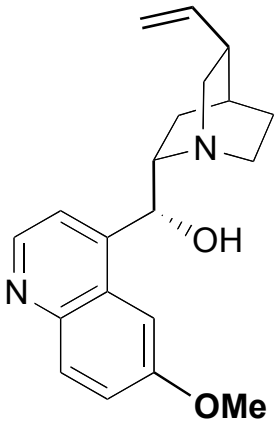



**Palytoxin Synthesis by Y. Kishi (JACS, 1994, *116*, 11205)**






**Tropinone**
**Robinson 1917**




**Quinine**
**Woodward 1940's**

$C_{129}H_{223}N_3O_{54}$, **64 Chiral centre, $2^{64}$ enantiomers possible**

***The question is not "Can we make it?" but "How well can we make everything" or "Can we impact science (society) on the way making molecules"***

# Total Synthesis: Where We Stand

**New Reaction**

**New Strategy**

**Short and Simple**

***The shorter the distance, the stronger the punch can be***

**By Bruce Lee**

# Total Synthesis: Molecular Complexity of Target

**Size**

**Topology**

**Stereochemistry**

**Functionality**

**Appendage**

# Reference books

**Basic:**

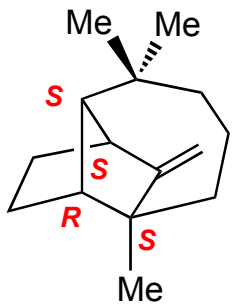
**"Organic Synthesis, The Disconnection Approach"**
**and "Workbook for Organic Synthesis, The Disconnection Approach"**
**by Warren, S.; Wyatt, P., 2nd Ed. Wiley 2008**

**Advanced:**

**"The Logoic of Chemical Synthesis"**
**by Corey, E. J.; Cheng, X-M. Wiley and Son 1989**
**" Classics in Total Synthesis: Targets, Strategies, Methods", Wiley**
**by Nicolaou, K. C. Sorensen, E. J., Wiley VCH 1996**
**" Classics in Total Synthesis II: Targets, Strategies, Methods", Wiley**
**by Nicolaou, K. C. Snyder, S., Wiley VCH 2003**
**" Classics in Total Synthesis III"**
**by Nicolaou, K. C.; Chen, J. S., Wiley VCH 2011**

**And more importantly: *Original publications of each total synthesis***

# Longifolene



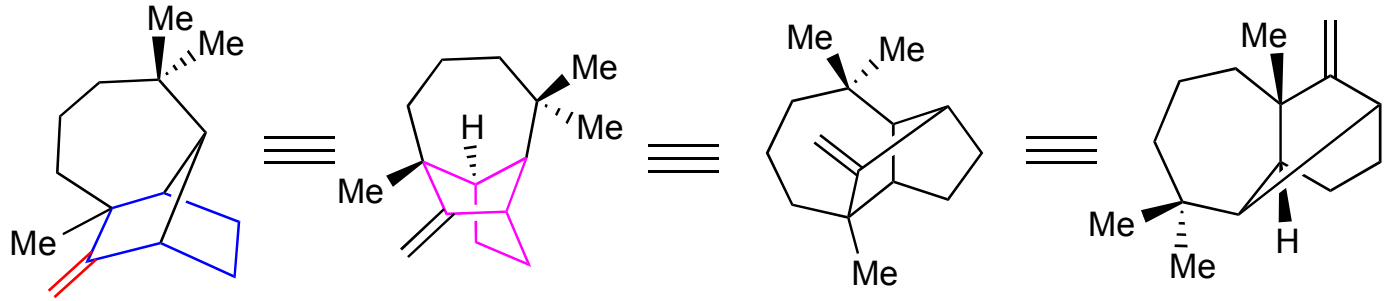

(+)-Longifolene

**Isolation: G. Ourisson, *Bull. Soc. Chim. Fr.*, 1955, 895 from " *pinus logifolia*", a *sesquiterpene***

**Used as fragrance**

**(-)-logifolene also exit in Nature from Fungi and liverworts**

***Formular of terpenes: $(C_5H_8)_m$***
***m = 2, monoterpene***
***m = 3 sesquiterpene***
***m = 4 diterpene***
***m = 5 triterpene***



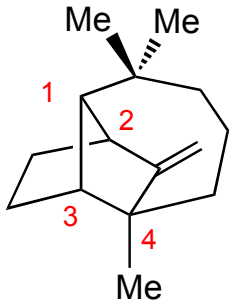

**Bridged ring system is reinforced** **Fused ring system is evidenced**

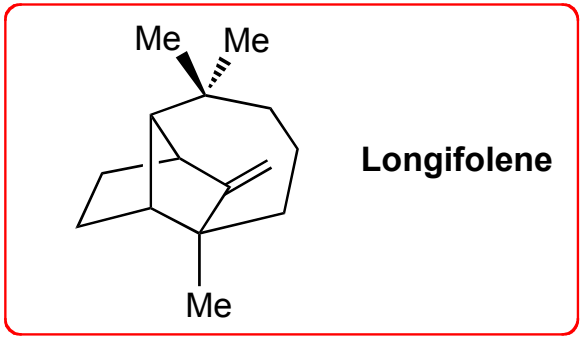
**Using Molecular Models!!!**

***Corey's 1961 synthesis of longifolene « officially » introduced the principles of retrosynthetic analysis!***

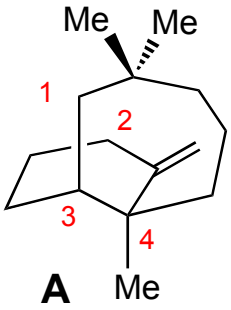
# Longifolene—Corey 1961

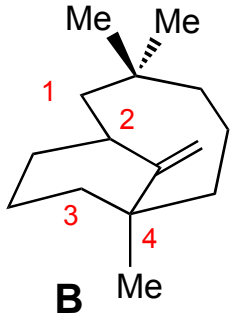
**Step 1:**
Number the bridge atom

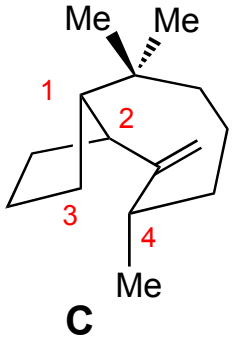


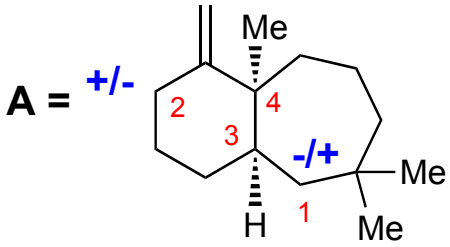

**Step 2:** Disconnect the chemical bond between the bridge atoms

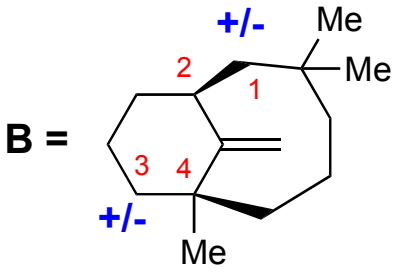


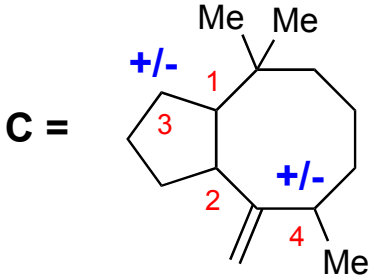




**Step 3:** Redraw the synthons to make them more familiar to you

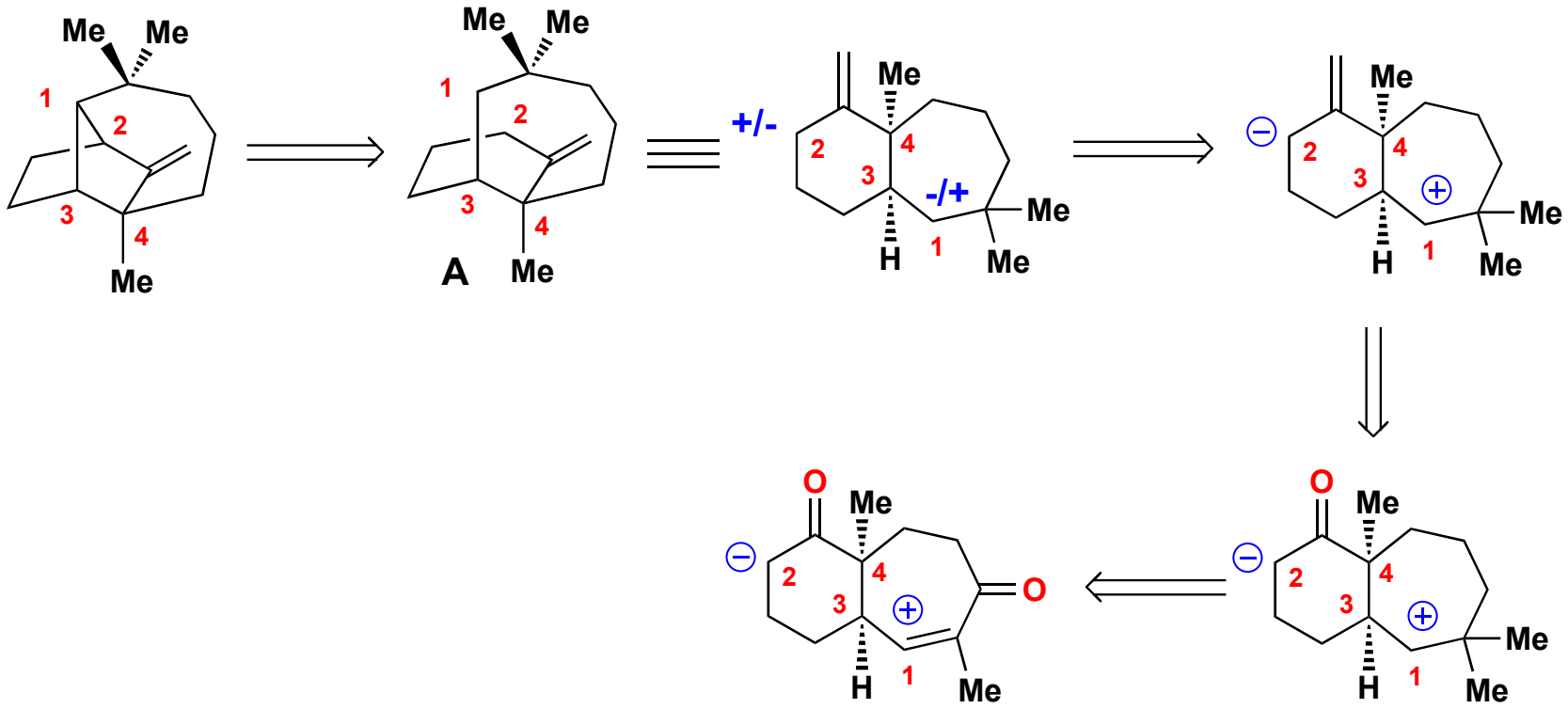


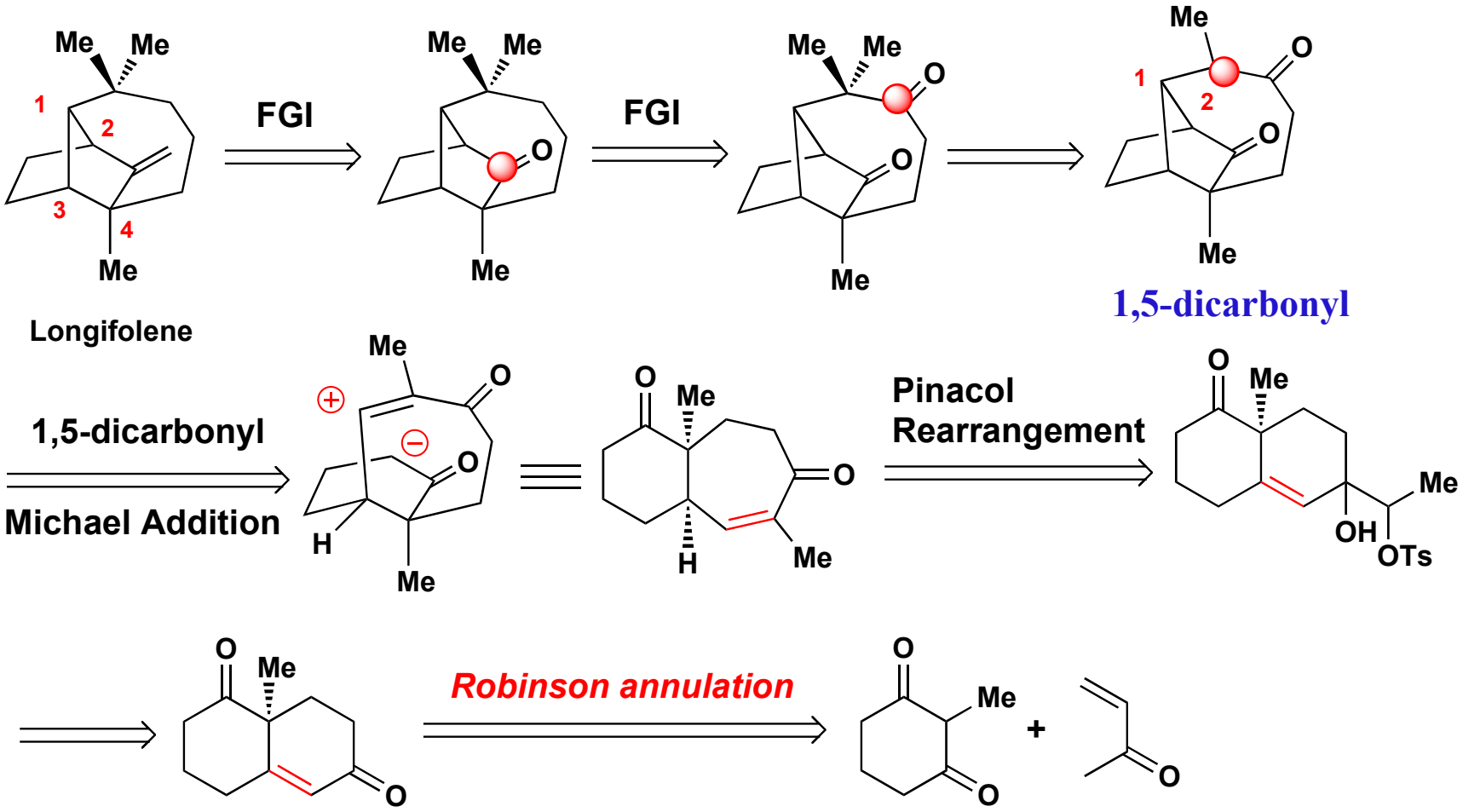




**8-membered ring, acces difficult**

# Longifolene—Corey 1961



# Longifolene—Corey 1961




**Wieland-Miescher ketone**

Wieland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 2215.

Corey, E. J. et al *J. Am. Chem. Soc*. **1961**, *83*, 1251-1231; **1964**, *86*, 478-485.

Rev on Wieland-Miescher Ketone: Bradshaw, B.; Bonjoch, J. *Synlett* **2012**, *23*, 337-356.

# Reactions Needed to Know

**Robinson Annulation (Michael/aldol cascade)**

**Wittig reaction**

**Michael addition: For the synthesis of 1,5-dicarbonyls**

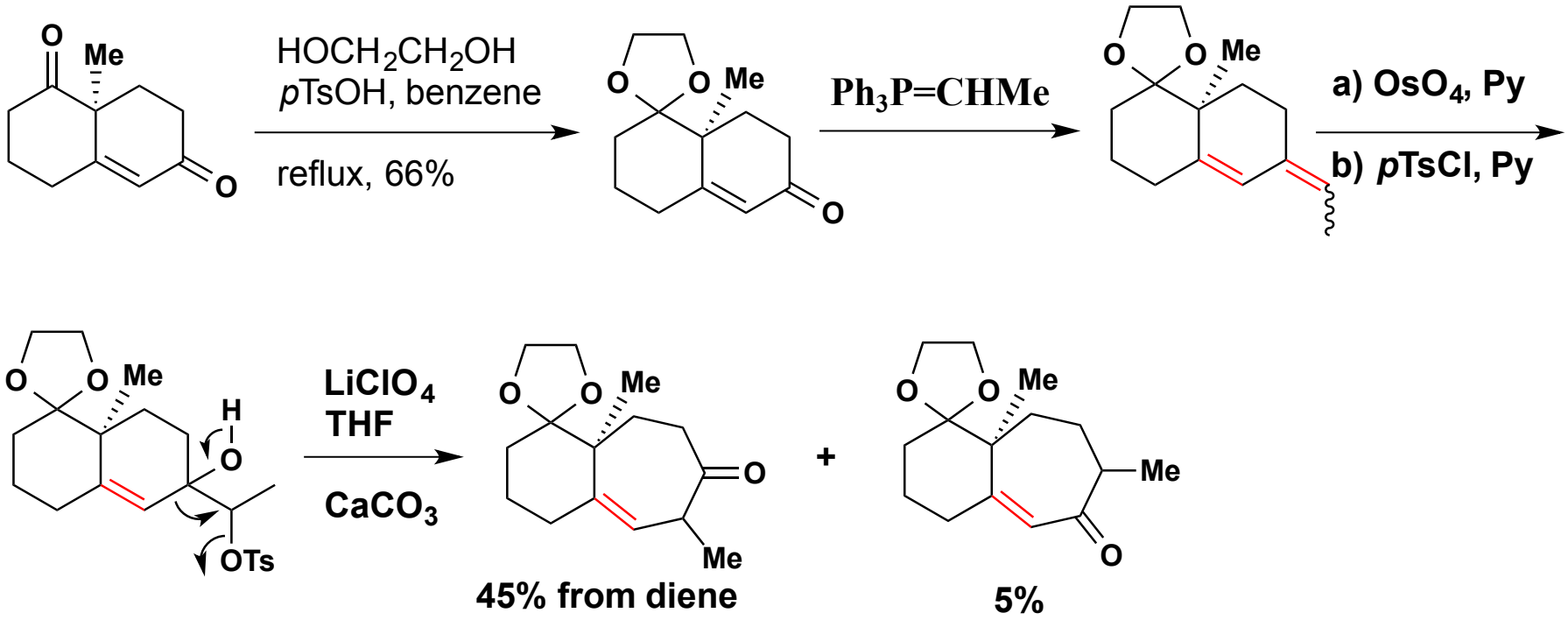
**Dihydroxylation of Alkene with $OsO_4$**

**Pinacol Rearrangement: Chemo- and Regio-selectivities**

**Enolate Alkylation: Regioselectivity**

**Reactivity of Carbonyl Group**

# Longifolene—Corey 1961



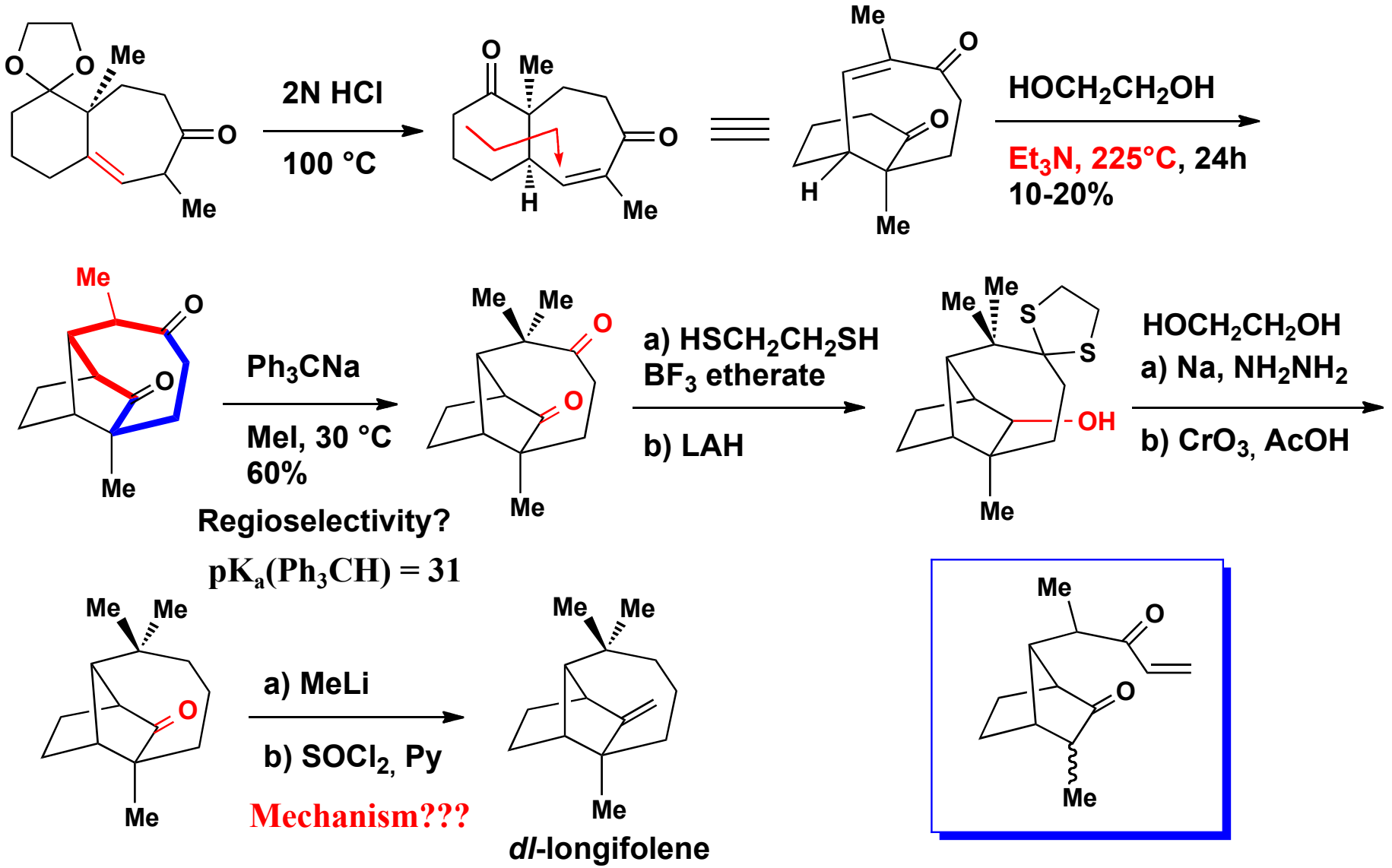

*** Regio-selective dihydroxylation of diene**

*** Pinacol rearrangement:**

**a) migration aptitude: vinyl *vs* $Csp_3$ carbon**

**b) solvolysis of tosylsulfonate vs tertiary allylic alcohol**

# Longifolene—Corey 1961




Corey, E. J. et al *J. Am. Chem. Soc*. **1961**, *83*, 1251-1253; **1964**, *86*, 478-485.

# Summary of the Synthesis: Reactions and Tactics

**Robinson Annulation (Michael/aldol cascade)**
**Wittig reaction**
**Michael addition: For the synthesis of 1,5-dicarbonyls**
**Dihydroxylation of Alkene with $OsO_4$**
**Pinacol Rearrangement: Chemo- and Regio-selectivities**
**Enolate Alkylation: Regioselectivity**

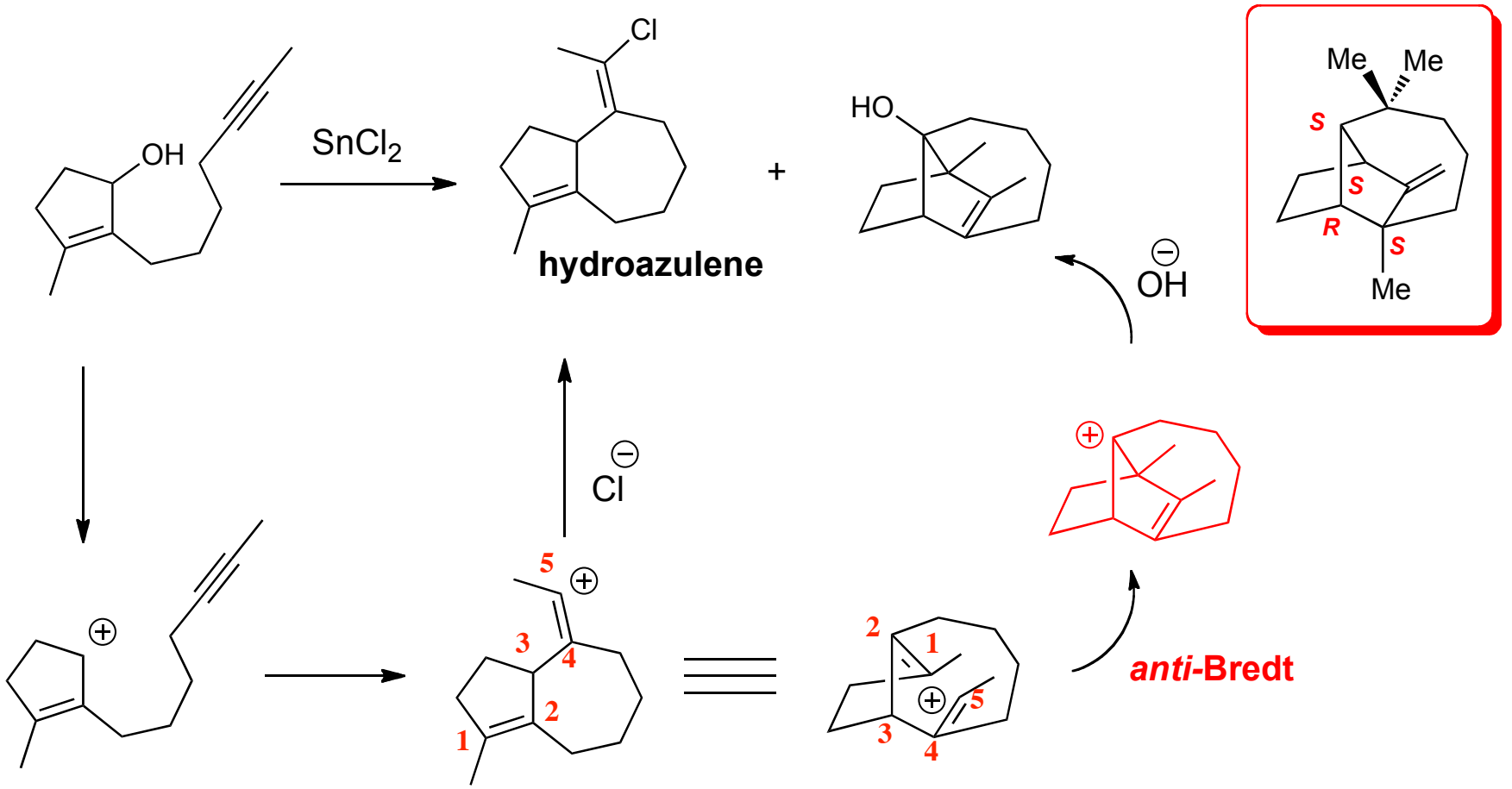
**Protective group: Heavily used**
**Protection of Carbonyl: Acetal, thioacetal**

**How the 7-membered ring was synthesized?**

**Ring expansion via pinacol rearrangement (Strategic)**

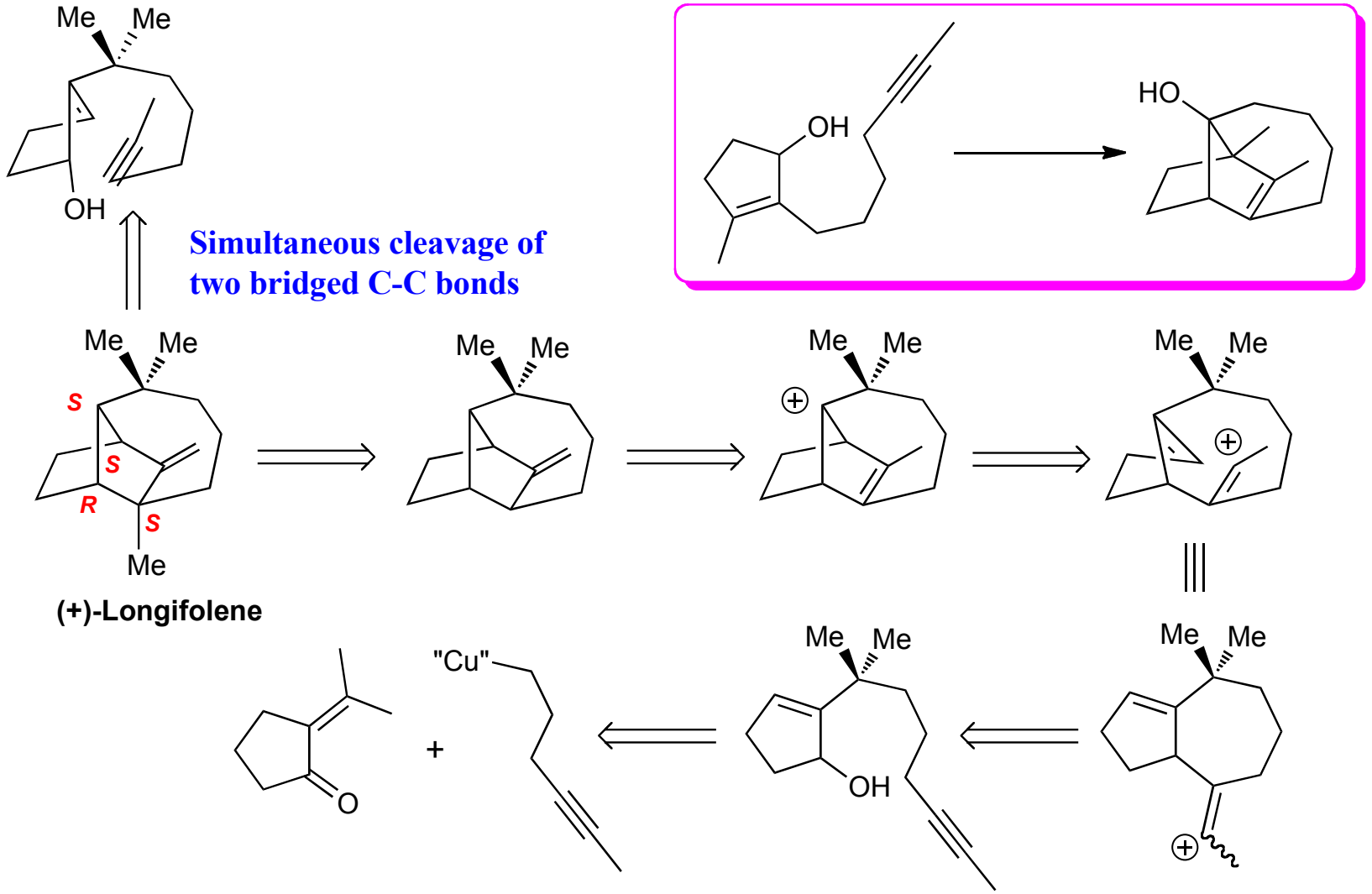
# Longifolene (Johnson 1975): Unexpected Results

**From hydroazulene to longifolene**




Johnson, W. S. et al *J. Am. Chem. Soc*. **1975**, *97*, 4777-4779.

# Longifolene—Johnson 1975




Johnson, W. S. et al *J. Am. Chem. Soc*. **1975**, *97*, 4777-4779

# Reactions Needed to Know

**Organocuprate: 1,4-addition to enone**

**Cationic cyclizations: Alkenes and alkynes are π-nuclophiles**

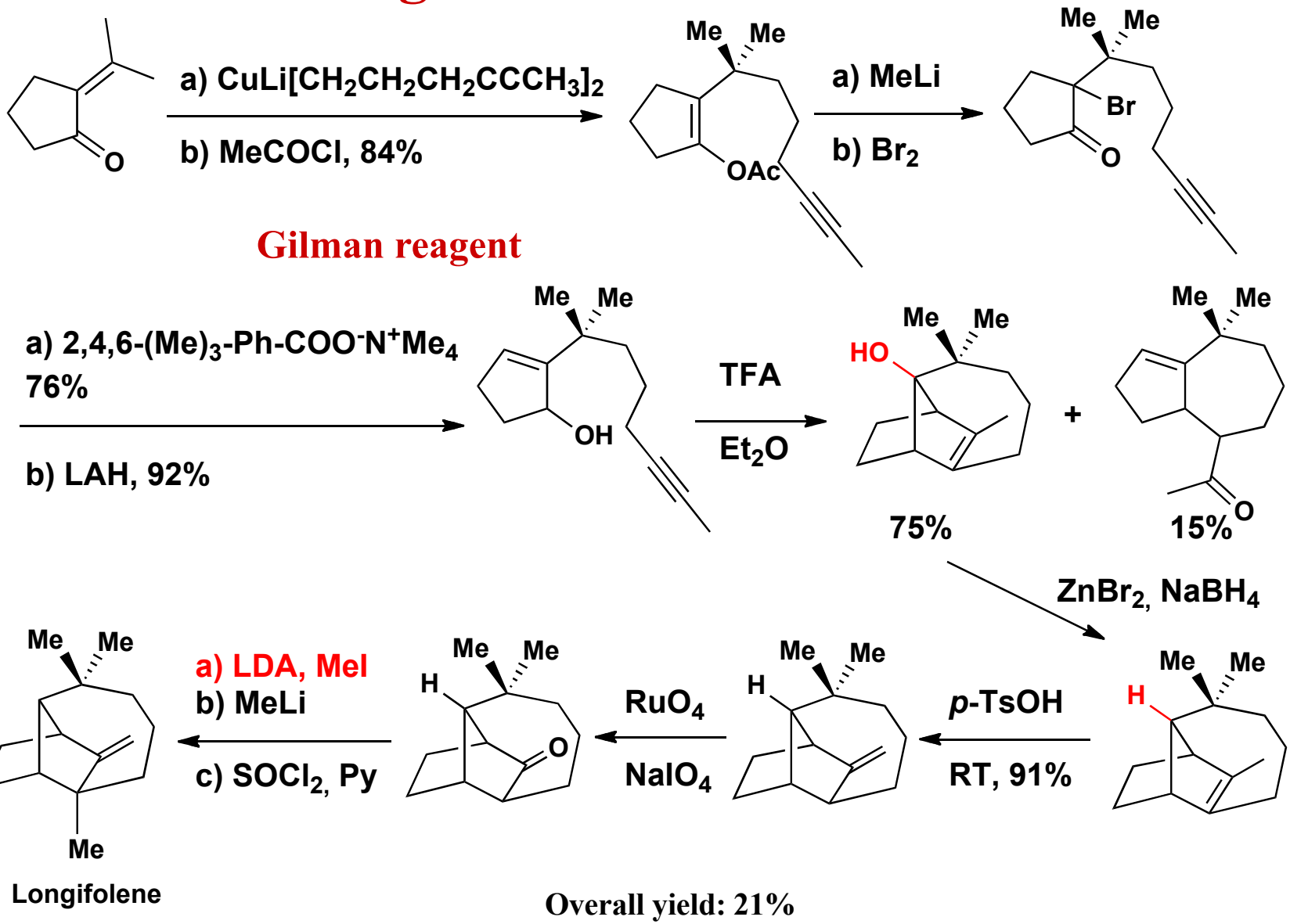
**Oxidation of ketone to enone: Control of regioselectivity**

**Dihydroxylation of alkenes with $RuO_4$/$NaIO_4$**

**Non-Classic carbocation**

**Bredt Rule, Anti-Bredt**

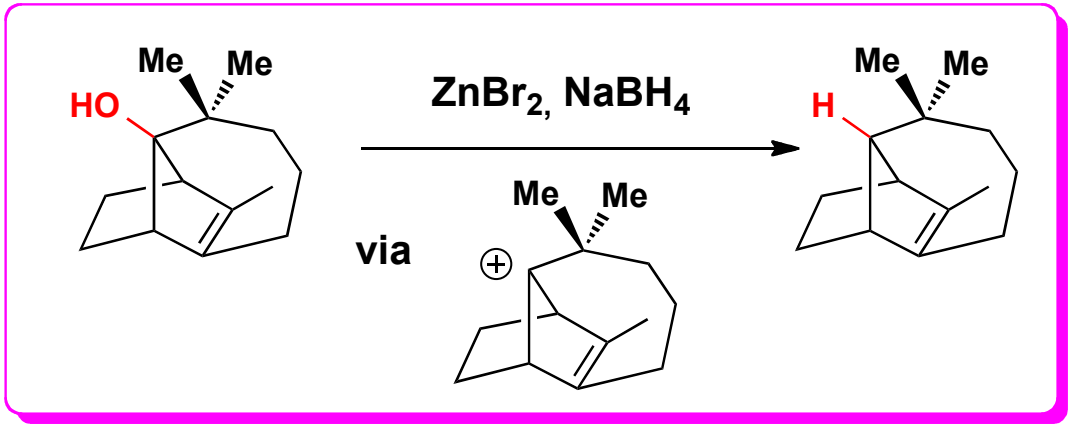
# Longifolene—Johnson 1975

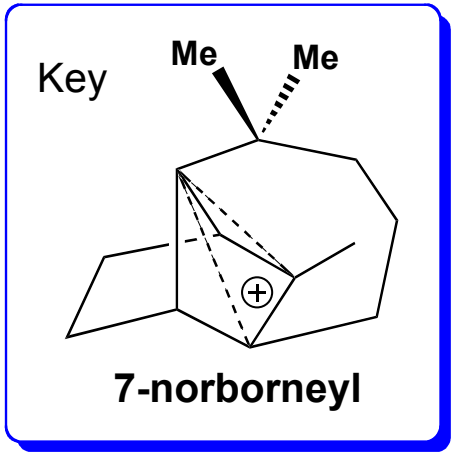


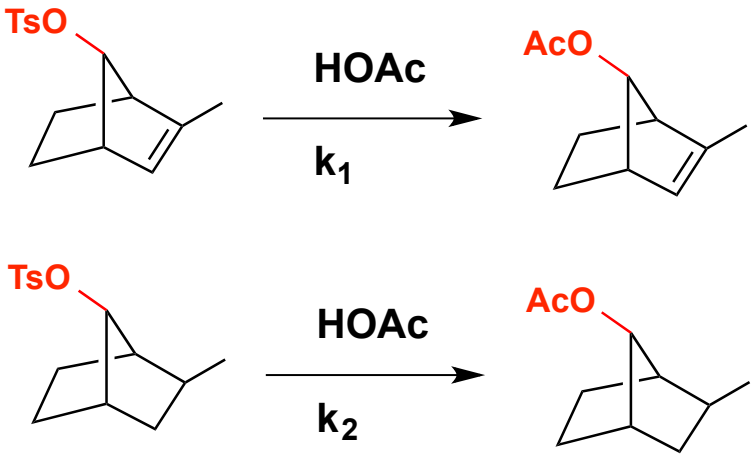

**Overall yield: 21%**

Johnson, W. S. et al *J. Am. Chem. Soc*. **1975**, *97*, 4777-4779

# Non-Classical Carbocation




$k_1/k_2 > 10^{11}$

***anti* 7-TsO-Norbornene solvolysis occurs with complet retention of stereochemistry**


Weinstein, S. *J. Am. Chem. Soc*. **1956**, *78*, 592; **1963**, *85*, 2324-2326.
Brown, H. C. *J. Am. Chem. Soc*. **1963**, *85*, 2324.

Computational studies on Johnson's synthesis: Tantillo, D. J. *J. Org. Chem*. **2005**, *70*, 5139-43.

# Summary of the Synthesis: Reactions and Tactics

**Organocuprate: 1,4-addition to enone**

**Cationic cyclizations: Alkenes and alkynes are π-nuclophiles**

**Oxidation of ketone to enone: Control of regioselectivity**

**Dihydroxylation of alkenes with $RuO_4$/$NaIO_4$**

**Non-Classic carbocation**

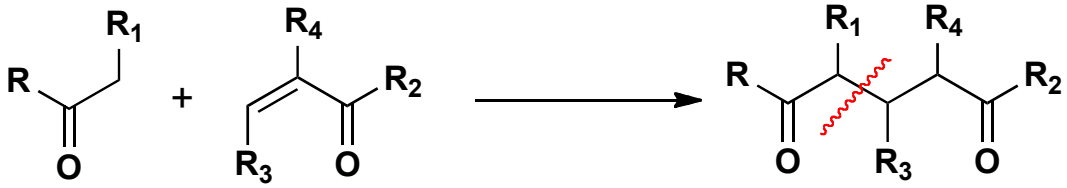
**How to cleave a C=C double bond?**

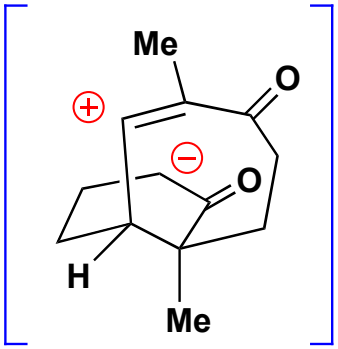
a) **Ozonolysis**

b) **Dihydroxylation followed by oxidative cleavage of the resulting 1,2-diol**

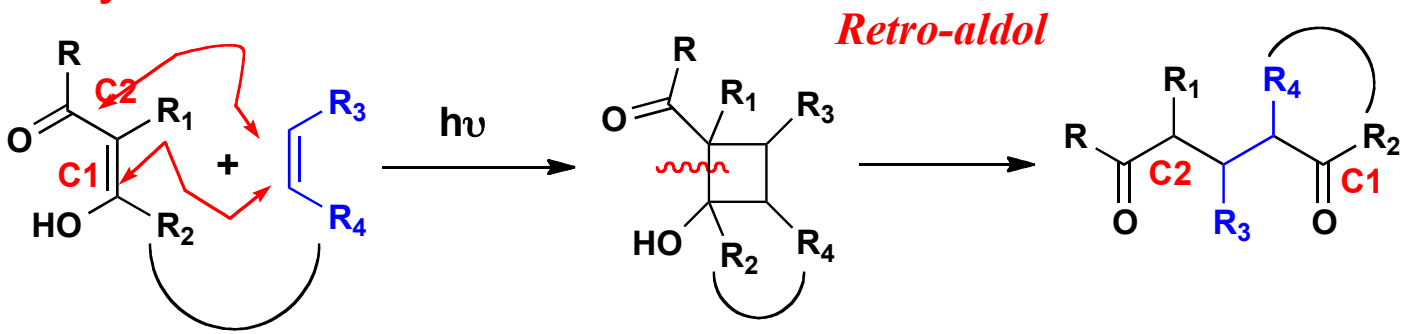
# Synthesis of 1,5-Dicarbonyl Compounds

## Micheal Addition



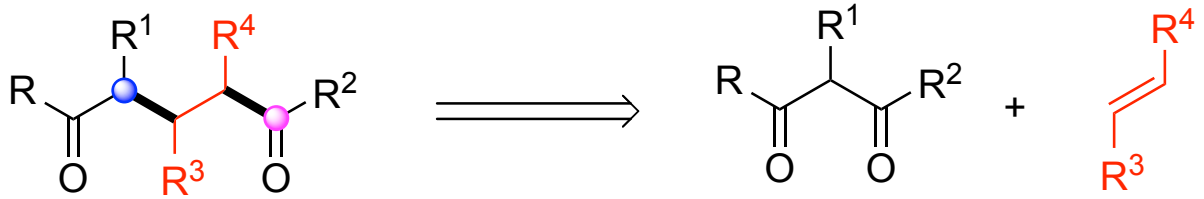

## De Mayo reaction



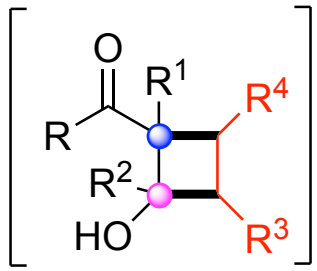

**Olefin inserted into the C1-C2 bond of the enol ether**

P. de Mayo, *Acc. Chem. Res.*, **1971**, *4*, 41;
W. Oppolzer, *Acc. Chem. Res.*, **1982, *15*,** 135

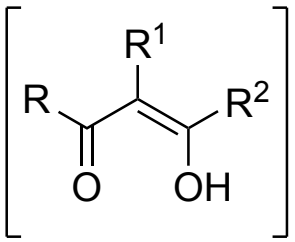
# Synthesis of 1,5-dicarbonyls by De Mayo Reaction

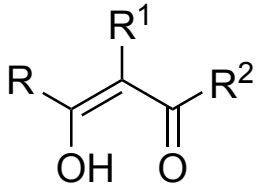



via




via

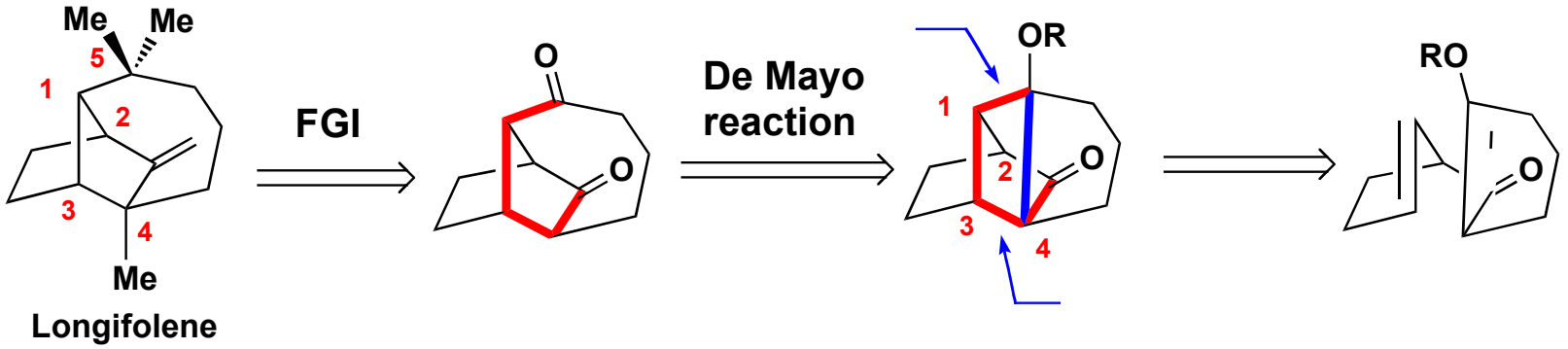



**Will give another regioisomer**

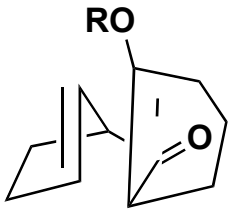
P. de Mayo, *Acc. Chem. Res.*, **1971**, *4*, 41;
W. Oppolzer, *Acc. Chem. Res.*, **1982, *15*,** 135

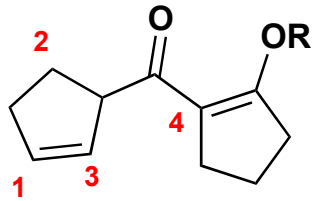
# Longifolene—Oppolzer 1978




**Simultaneous cleavage of C1-C5 and C3-C4**
**C3-C4 is certainly not the "classic strategic bond"**

***"Pattern recognition"***

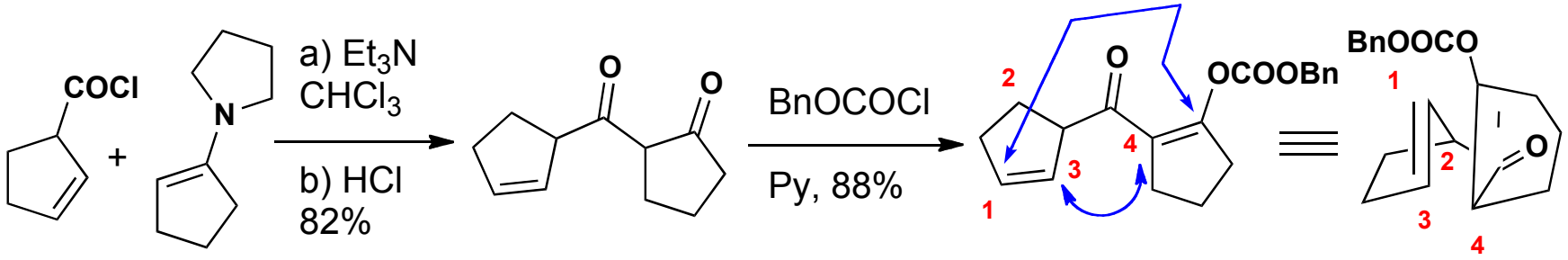


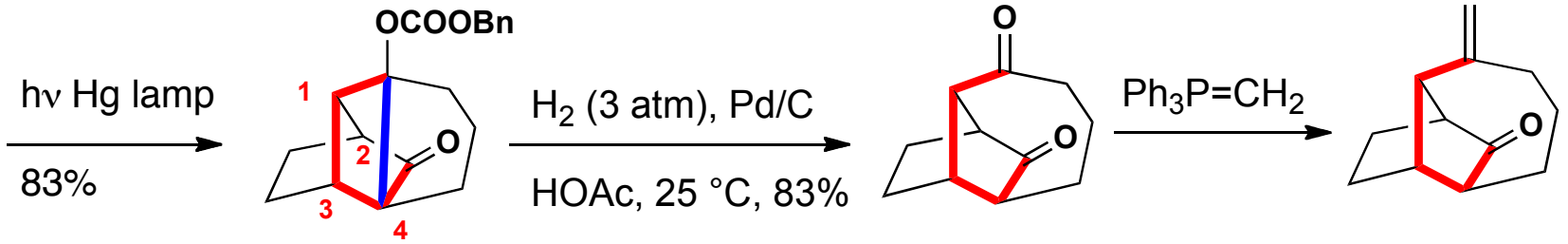

## *High level strategic design*

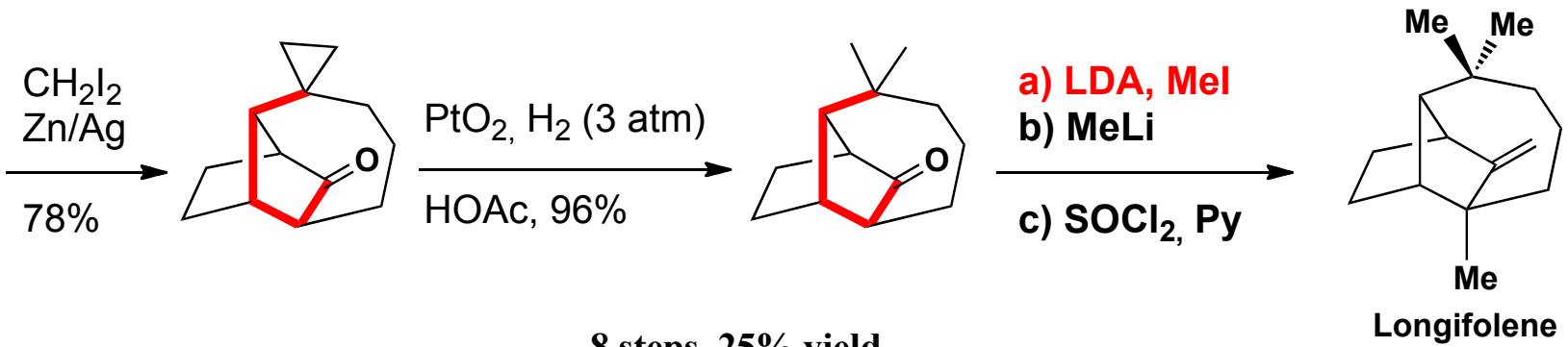
**"Pattern recognition", termed by Danishefsky, seeks to discover an exploitable substructural motif around which to organize the thought process and then the synthesis. The most fascinating cases arise when the target itself must actually be modified leading to a more complex compound before a staple pattern is revealed.** M. Wilson, S. J. Danishefsky, *J. Org. Chem*. **2007**, *72*, 4293-4305.

# Longifolene—Oppolzer 1978




***Acylation of enolate, potential problem?***




**8 steps, 25% yield.**


Oppolzer, W.; Godel, T. *J. Am. Chem. Soc*. **1978**, *100*, 2583-2584.

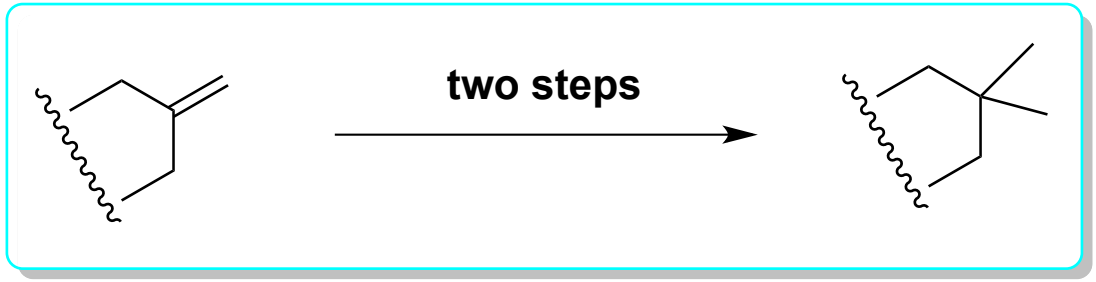
# Summary of the Synthesis: Reactions and Tactics

**Stork enamine acylation: Synthesis of 1,3-dicarbonyls**

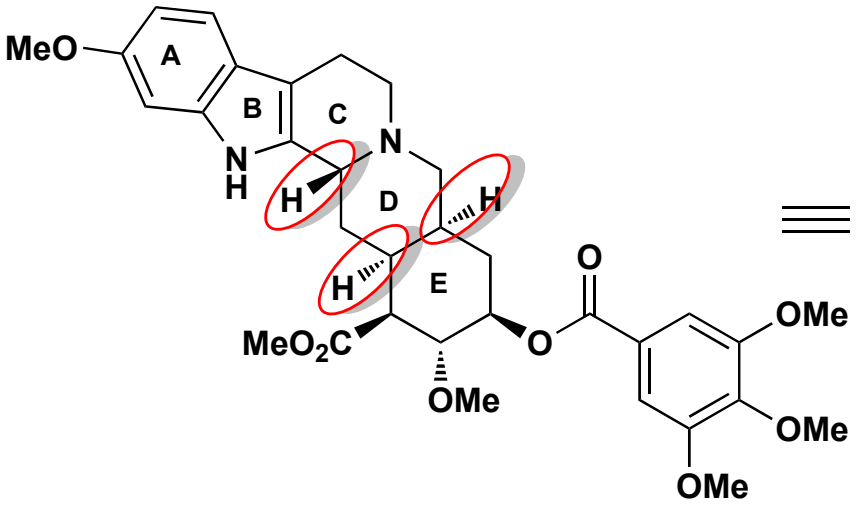
**De Mayo reaction: [2+2] cycloaddition/retro-aldol for the Synthesis of 1,5-dicarbonyls**

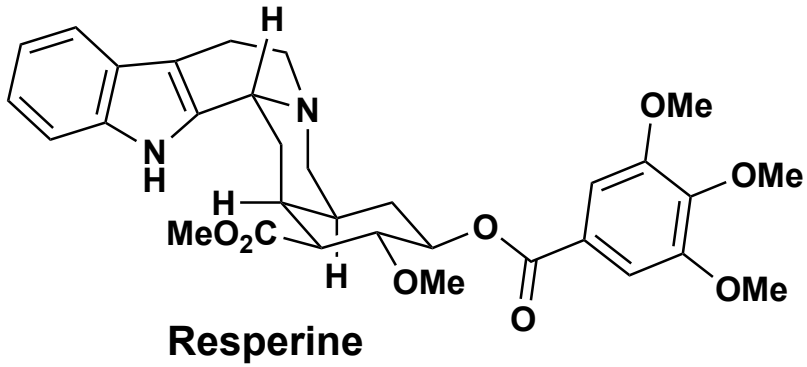
**Simmons-Smith cyclopropanation**

**How to realize the following transformation**



# Reserpine




Resperine

**Isolation: 1952,**

**Structural determination: Plane structure 1953**

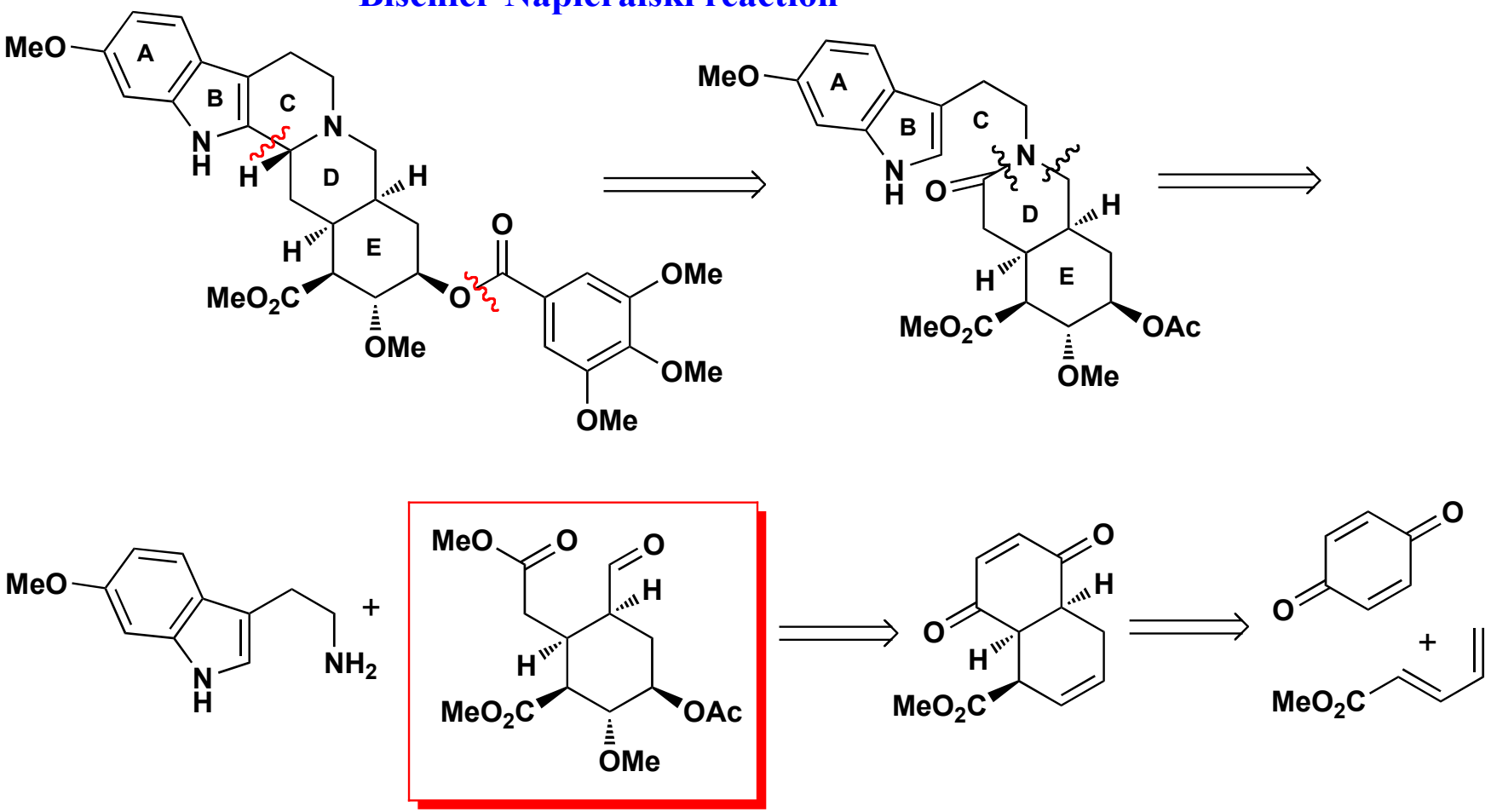
**Stereochemistry: 1955**

**Bioactivities: Used for the tratement of hypertensive, nervous and mental disorder, discontinued due to side-effects including Depression.**

**First total synthesis by Woodward 1956**

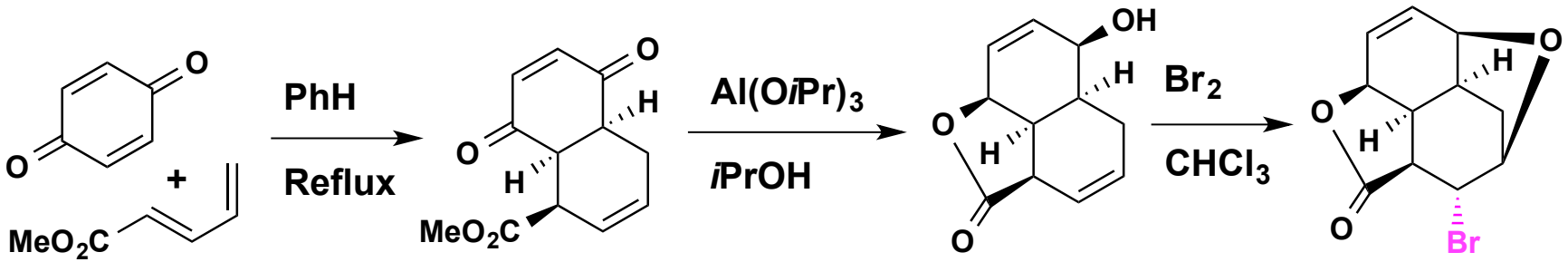
# Reserpine-Woodward

**Bischler-Napieralski reaction**

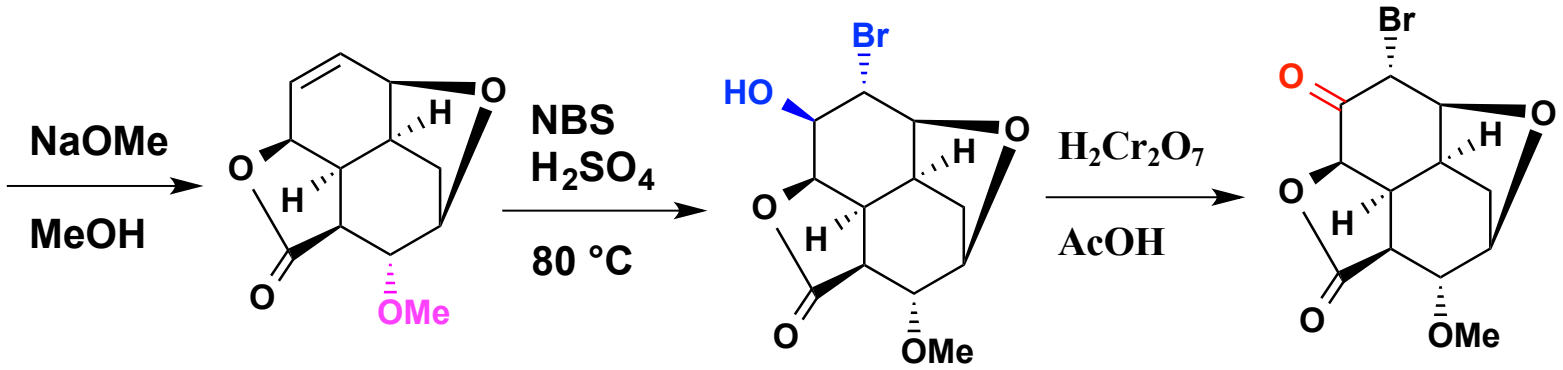



R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, R. W. Kierstead, *J. Am. Chem. Soc*. **1956**, *78*, 2023-2025.

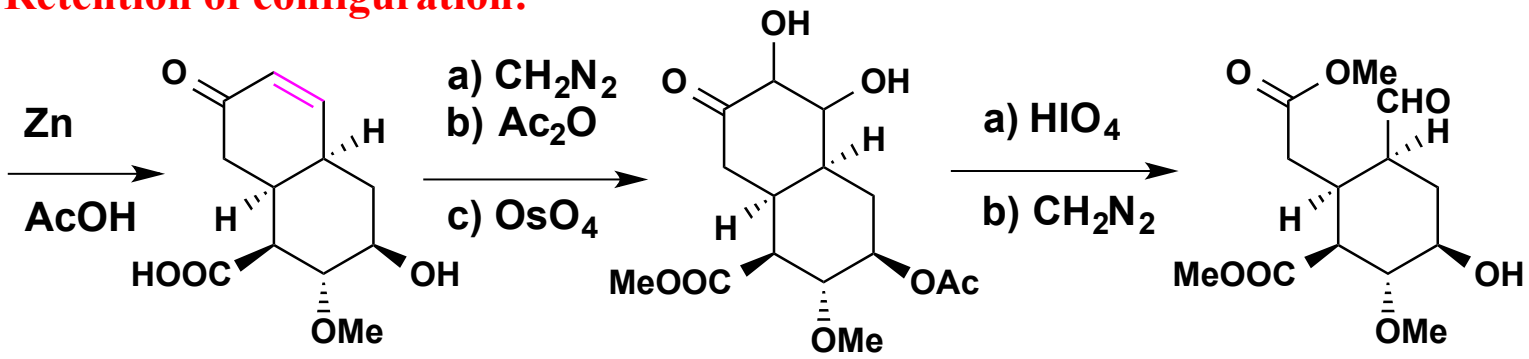
# Reserpine-Woodward




Meerwein-Ponndorf-Verley



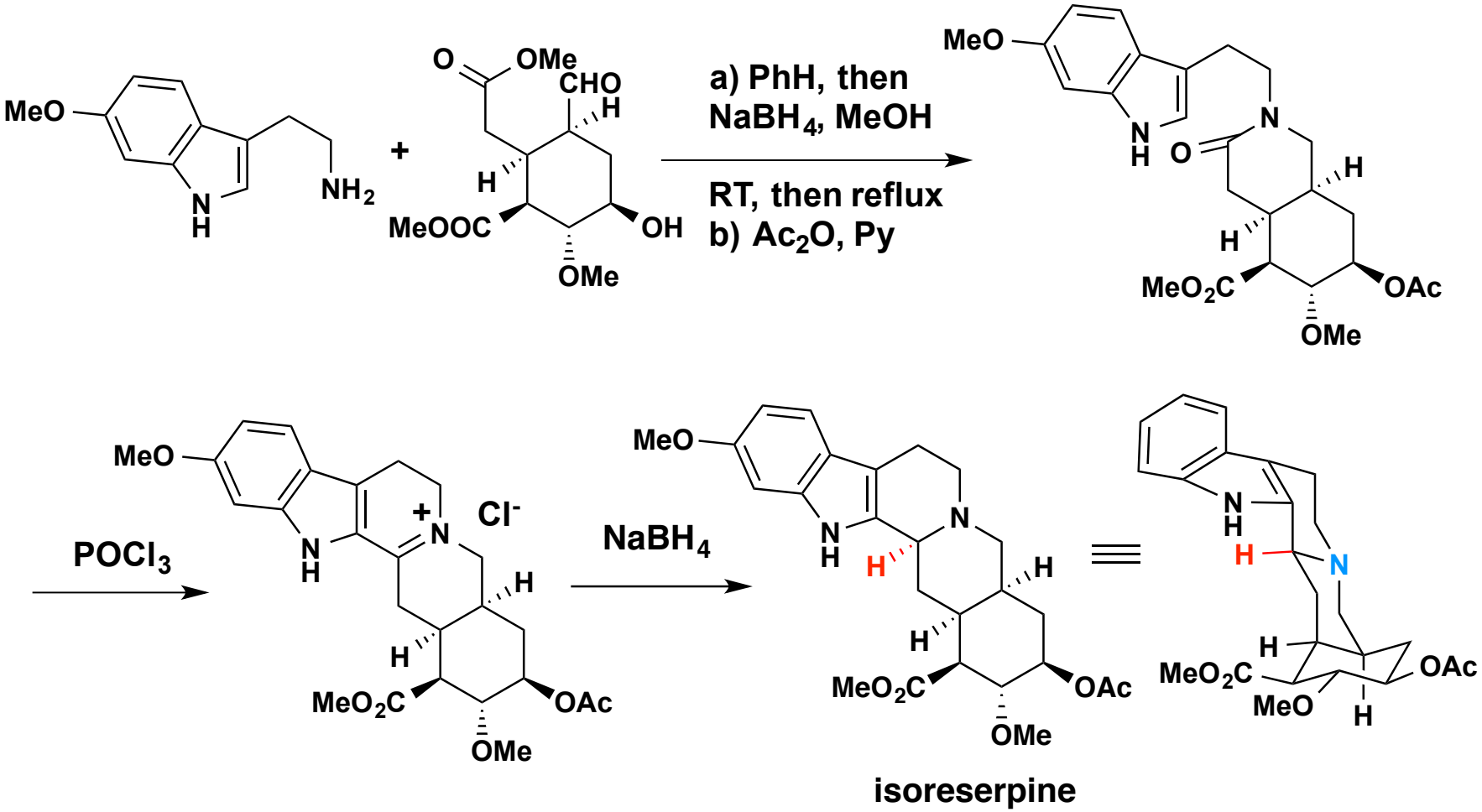

**Retention of configuration!**




***Control of relative stereochemistry: "A Cyclic trick"***

R. B. Woodward, *J. Am. Chem. Soc*. **1956**, *78*, 2023-2025 and *Tetrahedron* **1958**, *2*, 1-57.

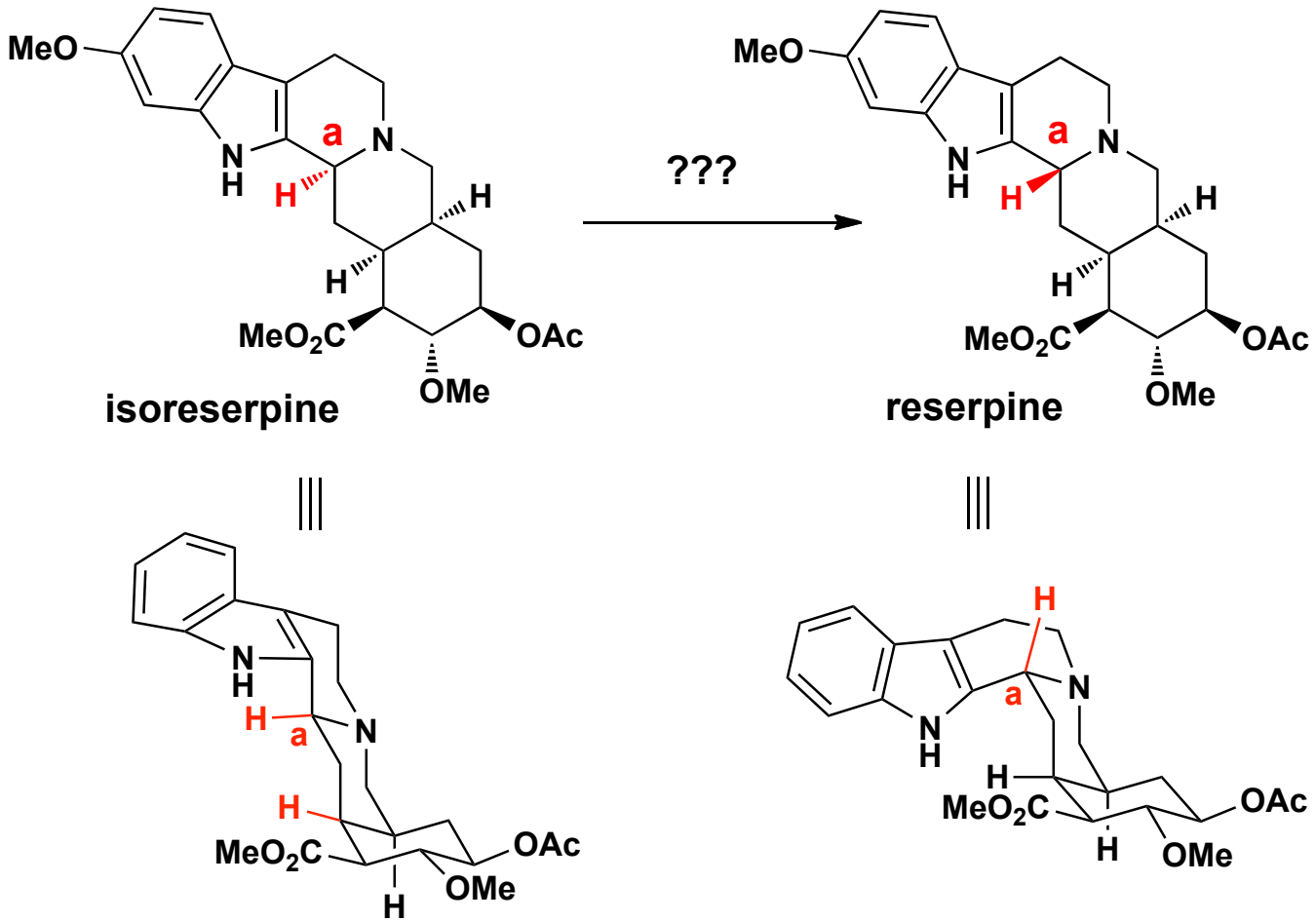
# Reserpine-Woodward




***Hydride attacks on the convex face affording the epimer of natural product***


R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, R. W. Kierstead, *J. Am. Chem. Soc*. **1956**, *78*, 2023-2025.
*Tetrahedron* **1958**, *2*, 1-57.

# Reserpine-Woodward

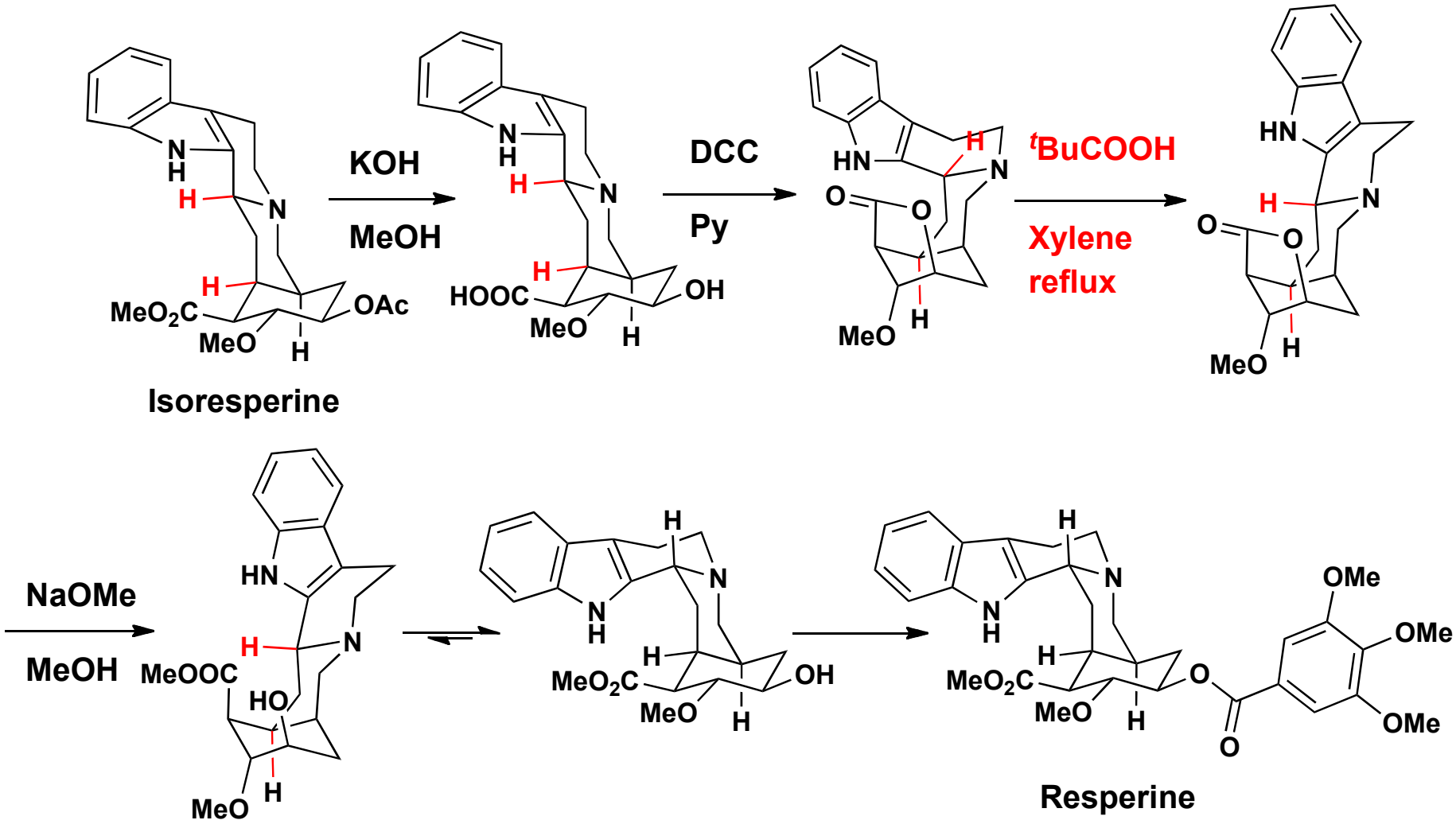



**Isomerization:** Mechanistically possible However, $C_a$ of isoreserpine is configurationally quite stable and is kinetically and thermodynamically favored

**Solution:** Change the conformation of isoreserpine!!!

**Conformational analysis: Barton, D. H. R. *Experientia* 1950, 316-320.**

# Reserpine-Woodward

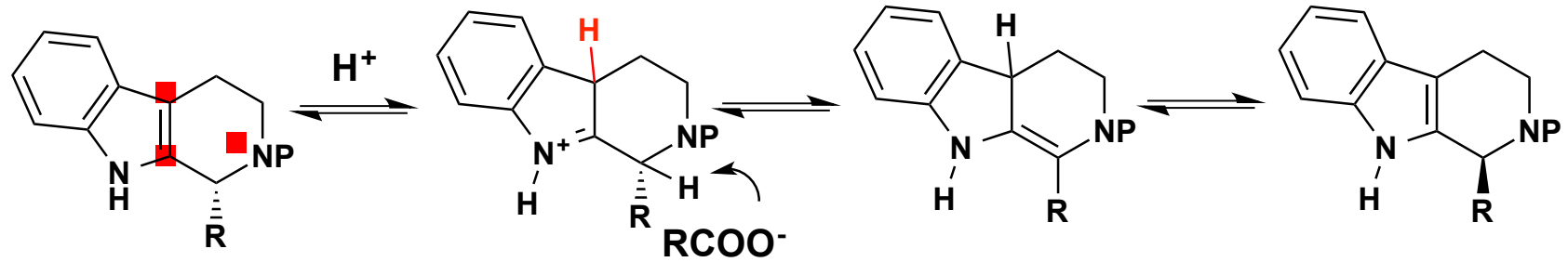



R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, R. W. Kierstead, *J. Am. Chem. Soc*. **1956**, *78*, 2023-2025.
*Tetrahedron* **1958**, *2*, 1-57.

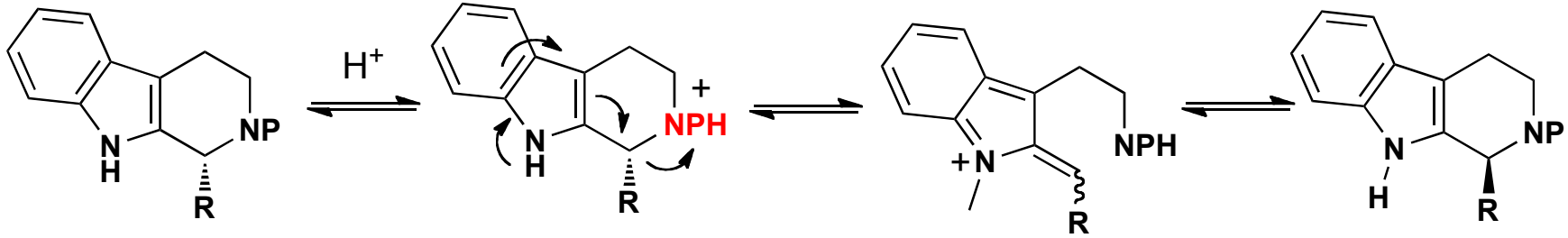
# Reserpine-Woodward

## Possible Mechanism of Epimerization of Carbazole

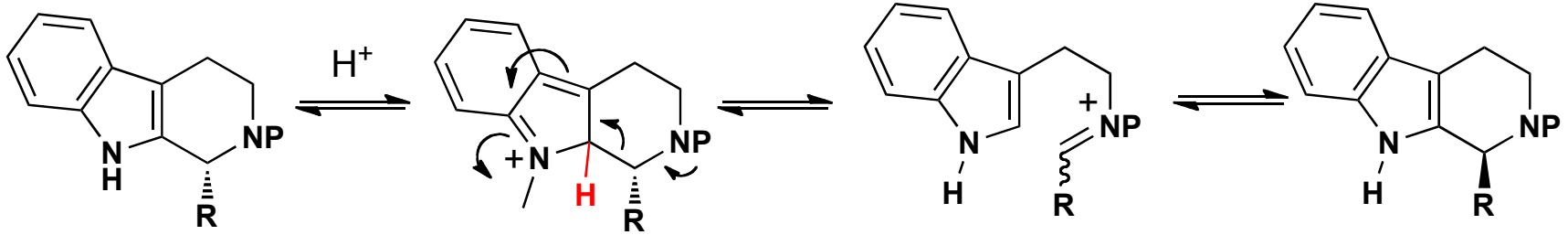
**Mechanism 1**




**Mechanism 2**



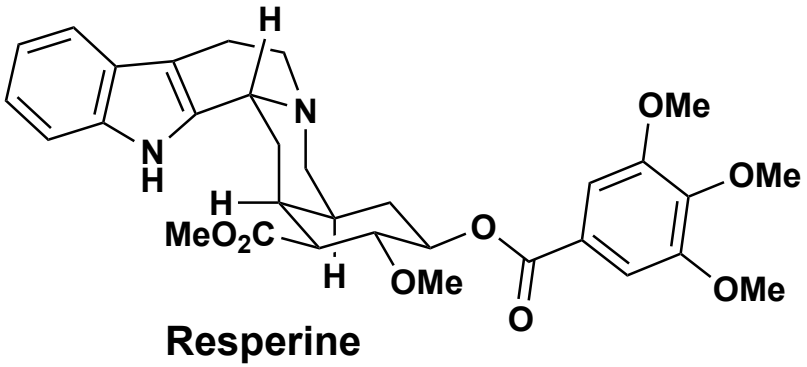

**Mechanism 3**



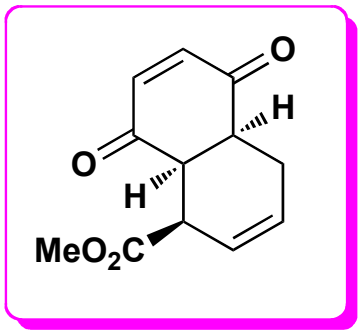



*Which mechanism is the most probable one*

# Reserpine-Woodward




Resperine




**Considered as one of Woodward's greatest contributions to synthesis**

- **Using Diels-Alder to generate *cis*-fused bicyclic ring system.**
- **Conceptulized the use of cis-fused bicyclic ring system as stereocontrol element.**
- **Pioneering conformational analysis in total synthesis**

R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, R. W. Kierstead, *J. Am. Chem. Soc*. **1956**, *78*, 2023-2025.
*Tetrahedron* **1958**, *2*, 1-57.

For a recent total synthesis, see: R. Sarpong, *Nat. Chem*. **2013**, *5*, 126-131.
***Home work: Read this paper and understand the design principle***

# Summary of the Synthesis: Reactions and Tactics

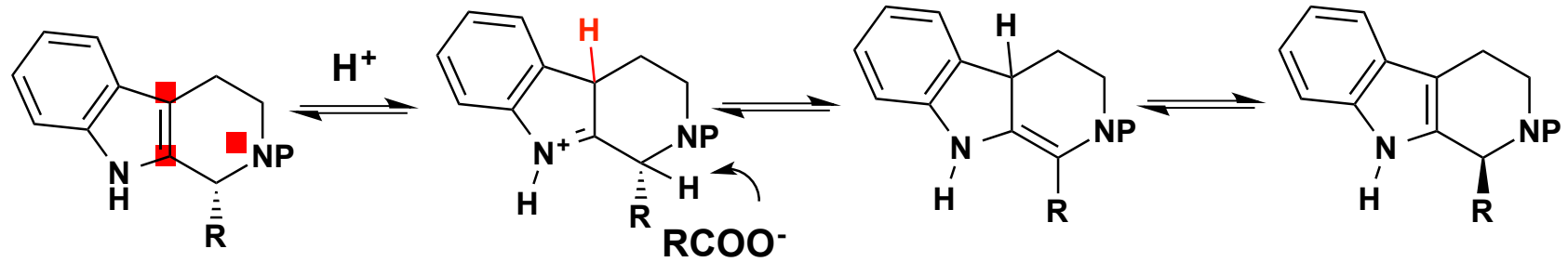
**Diels-Alder cycloaddition**
**Meerwein-Ponndorf-Verley (MPV) reaction**
**Bromoetherification**
**Beta-Elimination**
**Dihydroxylation of alkene/cleavage of diol**
**Bischler-Napiralski reaction**

**Cyclic trick to control the relative stereochemistry**
**Conformation analysis solve the stereochemical problem**

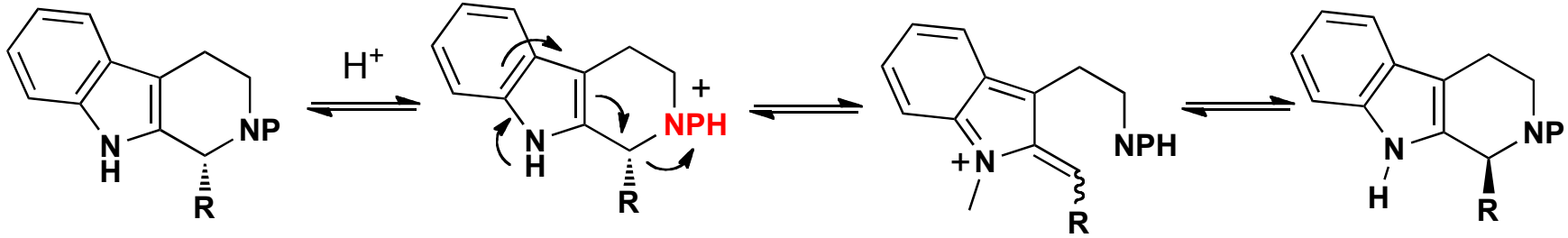
# Reserpine-Woodward

## Possible Mechanism of Epimerization of Carbazole

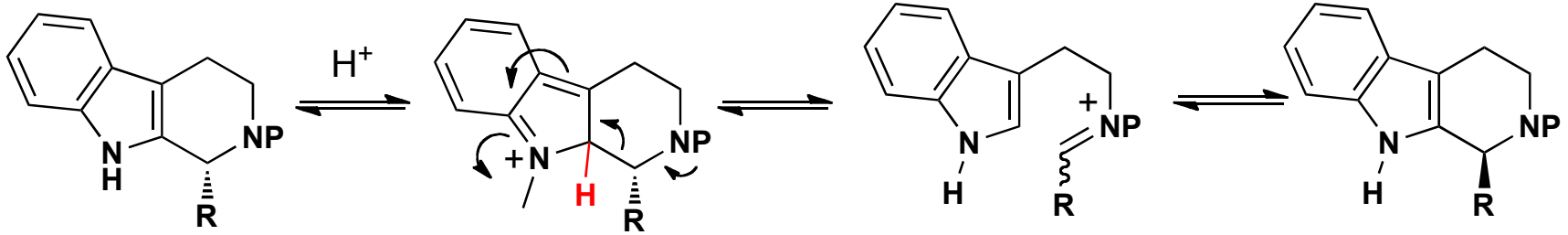
**Mechanism 1**




**Mechanism 2**



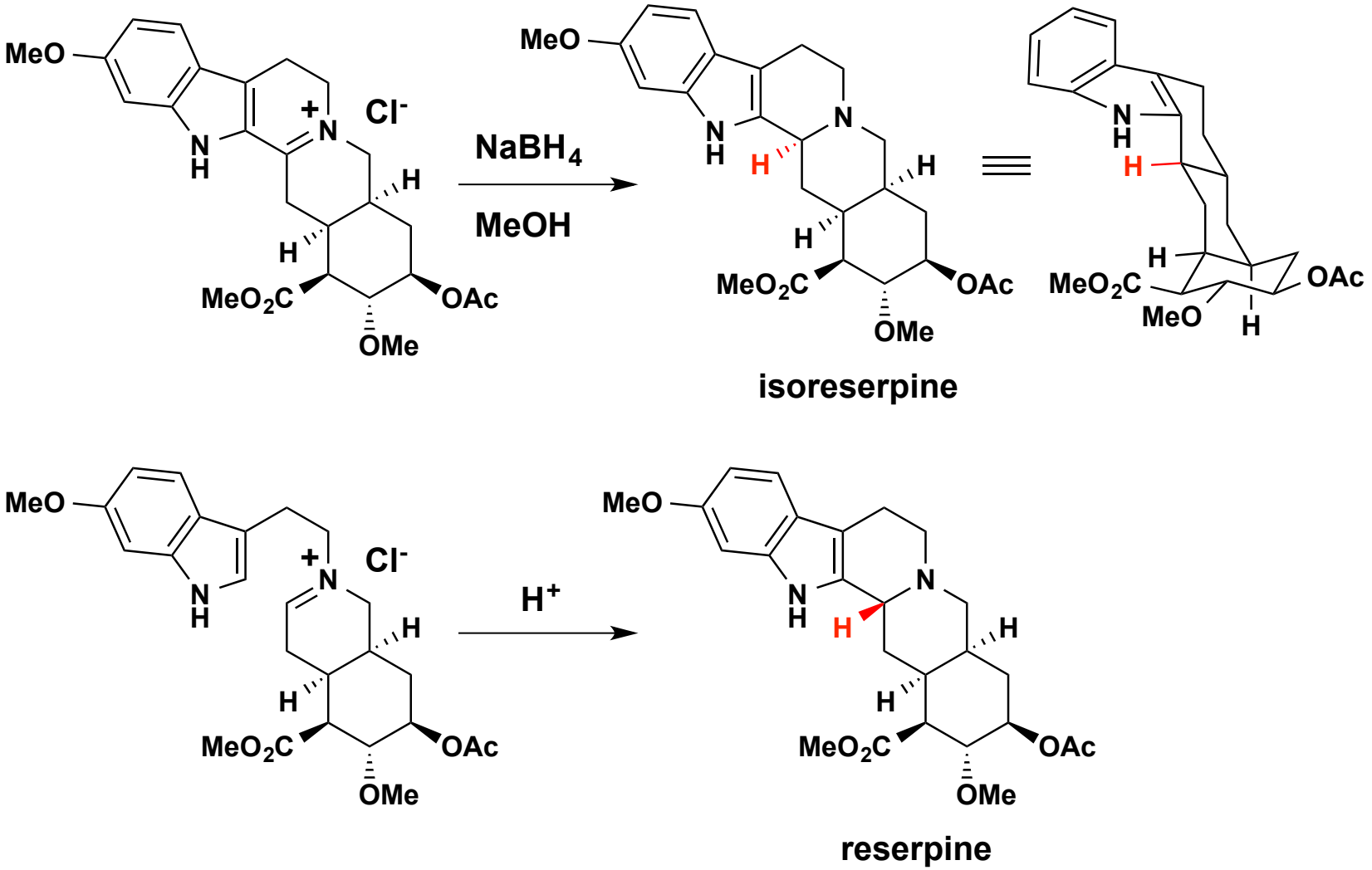

**Mechanism 3**





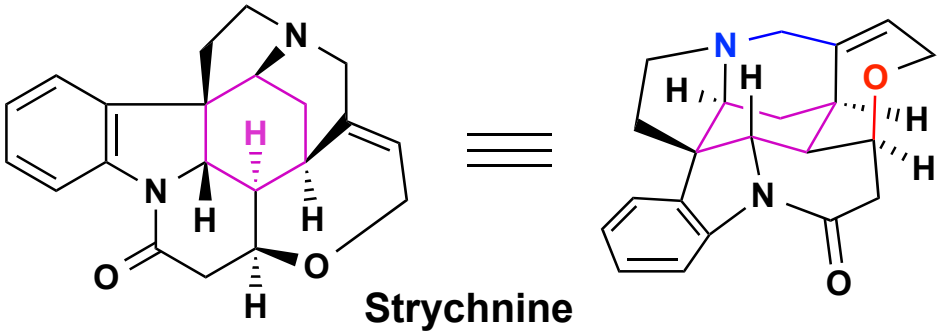

*Which mechanism is the most probable one*

# Reserpine Synthesis through Pictet-Spengler Reaction




For a recent total synthesis, see: R. Sarpong, *Nat. Chem*. **2013**, *5*, 126-131.

# Strychnine



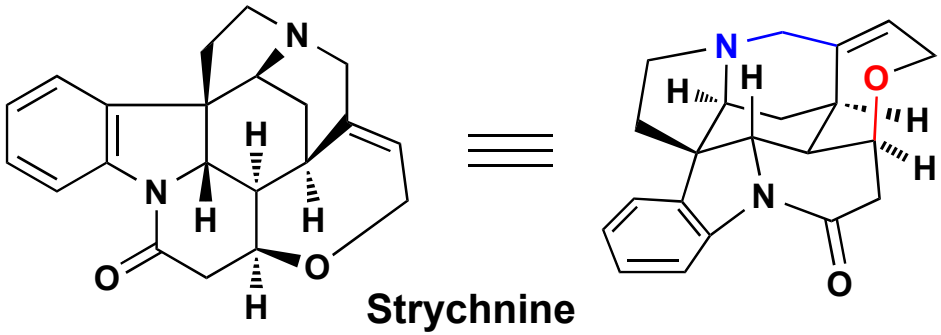

**Strychnine**

**1818**: Isolated by Pelletier & Caventou, *Ann. Chim. Phys*. **1818**, *8*, 323.
**1838**: Molecular formule determined by Regnault, *Ann*. **1838**, *26*, 35.
**1946**: Structure determined by Robinson, *Nature* **1946**, 157, 438.
and in **1947** by Woodward, *J. Am. Chem. Soc*. **1948**, *70*, 2107-2115.
**1950:** Relative stereochemistry determined by X-ray analysis
Robertson & Beevers, *Nature* **1950**, *165*, 690-691.
Bijvoet *et al. Acta Crystallogr.* **1951**, *4*, 275-280.
**1956**: Absolute configuration defined by X-ray crystal by Peerdeman,
*Acta Crystallogr*. **1956**, *9*, 824.
**1963**: Absolute configuration confirmed by chemical methods by Schmid
*Helv. Chim. Acta*. **1963**, *46*, 1212-1231.
Strong poision (≈ 50 mg is lethal for an adult human).

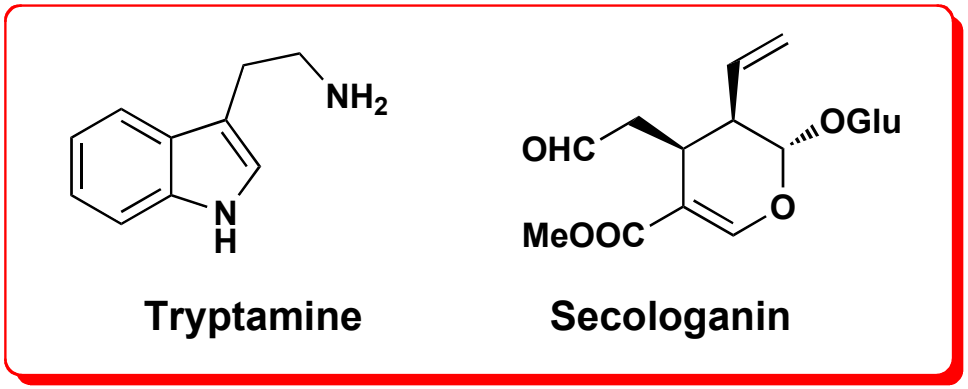
***Between the isolation and structure elucidation, Sir Robert Robinson's group alone published over 250 communications on the subject. Hermann Leuchs contributed another 125 papers.***

Review, see: Bonjoch, J.; D. Solé, *Chem. Rev.* **2000**, *100*, 3455-3482.
Mori, M. Heterocycles **2010**, *81*, 259-292.

# Strychnine

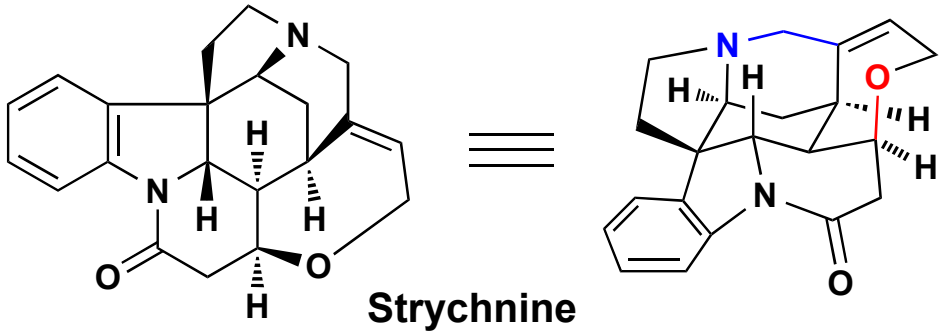



**Molecular formule: $C_{21}H_{22}N_2O_2$**
**24 skeletal atoms, 7 Rings, 6 Contiguous stereocentres, 5 in the cyclohexane ring.**
**A monoterpenoid indole alkaloid biogenetically derived from tryptamine and secologanin**




Biosynthesis of monoterpenoid indole alkaloids: T. M. Kutchan, *Phytochem*. **1993**, *32*, 493-506.
S. E. O' Connor, J. J. Maresh, *Nat. Prod. Rep*. **2006**, *23*, 532-547

# Total Synthesis of Strychnine




**Strychnine**

**R. B. Woodward** - Harvard University (**1954**) **28 steps**

**38 years**

**Philip Magnus** - University of Texas (**1992**)
**Gilbert Stork** - Columbia University (**1992**)
**Larry E. Overman** - University of California, Irvine (**1993**)
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**Viresh H. Rawal** - The Ohio State University (**1994**) **14 Steps**
**Josep Bonjoch & Joan Bosch** - University of Barcelona (**1999**)
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**Miwako Mori** - Hokkaido University (**2002**)
**Masakatsu Shibasaki** - University of Tokyo (**2002**)
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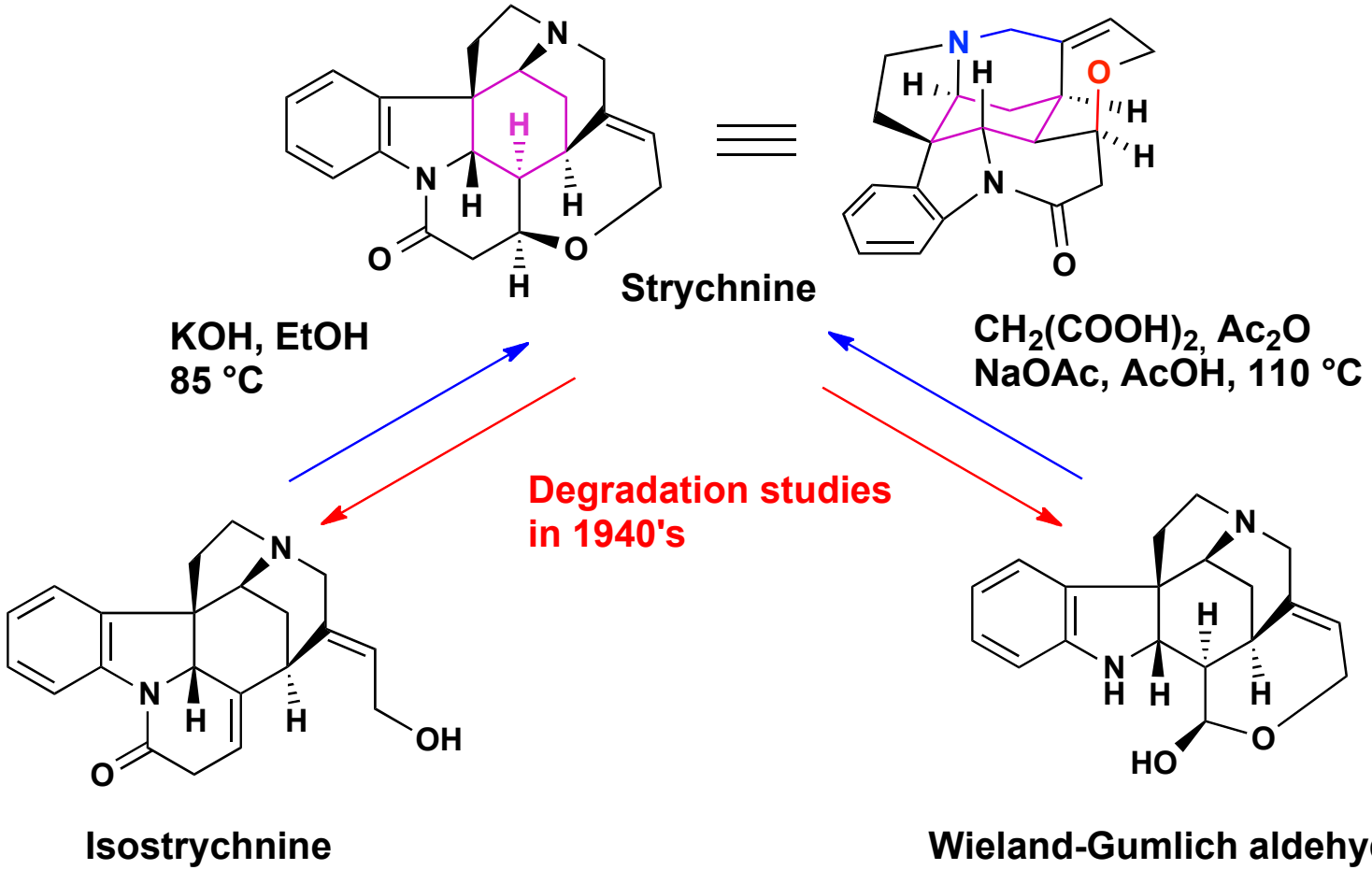
**Rodrigo, B. Andrada,** Temple University **(2010)**
**Hans-Ulrich, Reissig,** Freie University Berlin **(2010)**
**Christopher, D. Vanderwal,** University of california, Irvine **(2011)** **6 Steps**

Recent rev: Overman, L. E. *Angew. Chem. Int. Ed.* **2012**, 51, 4288-4311.

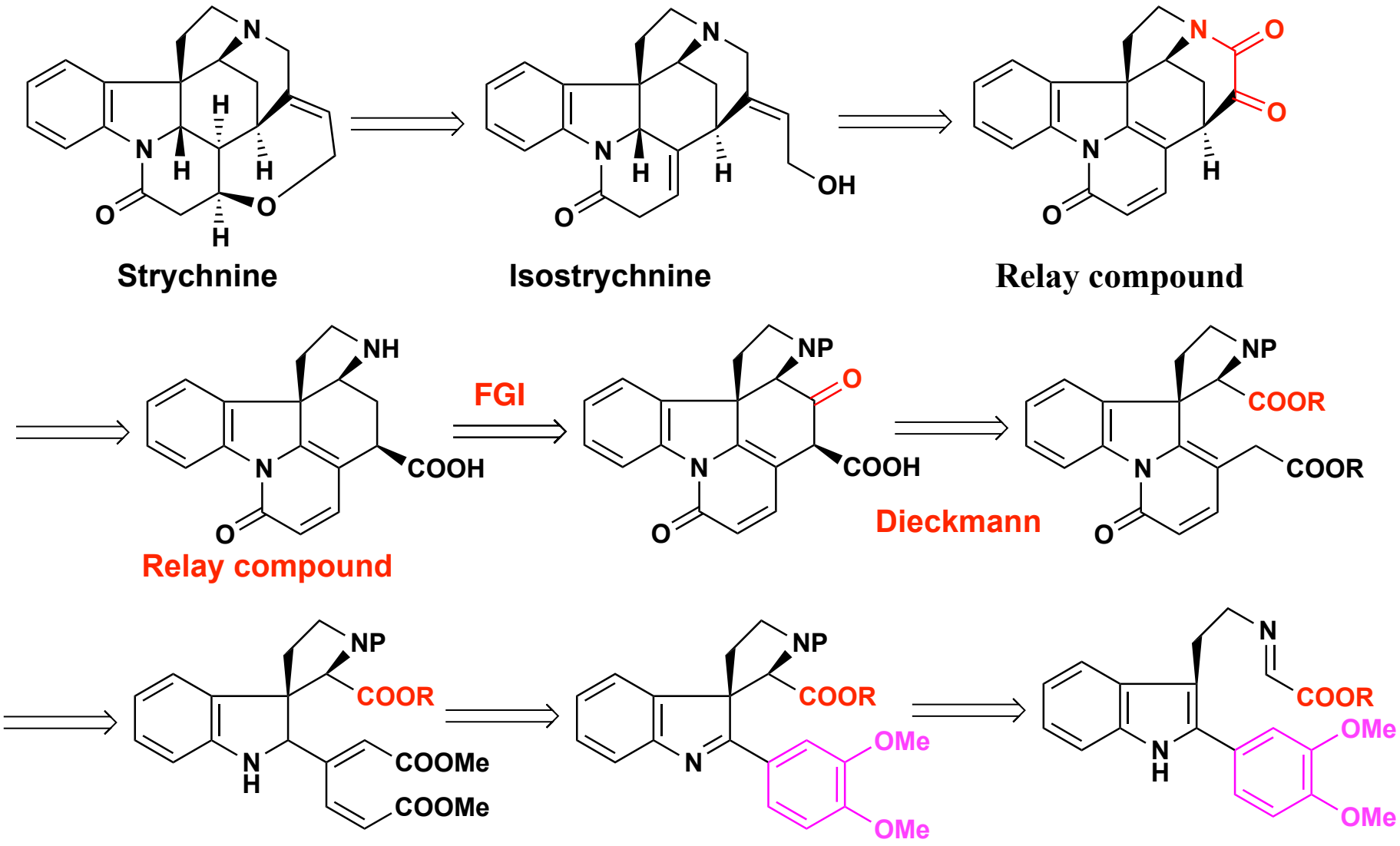
# Strychnine: Key background




In 1970's, both Isostrychnine and Wieland-Gumlich aldehyde were found in Nature.

**Heinrich Wieland: Nobel Prize in 1927.**

# Woodward's Total Synthesis of Strychnine: *A Relay Synthesis*




One of the key strategic considerations: **Relay Synthesis**

Woodward, R. B. *J. Am. Chem. Soc*. **1954**, *76*, 4749-4751; *Tetrahedon* **1963**, *19*, 247-288.

# Reactions Needed to Know

**Fischer indole synthesis**

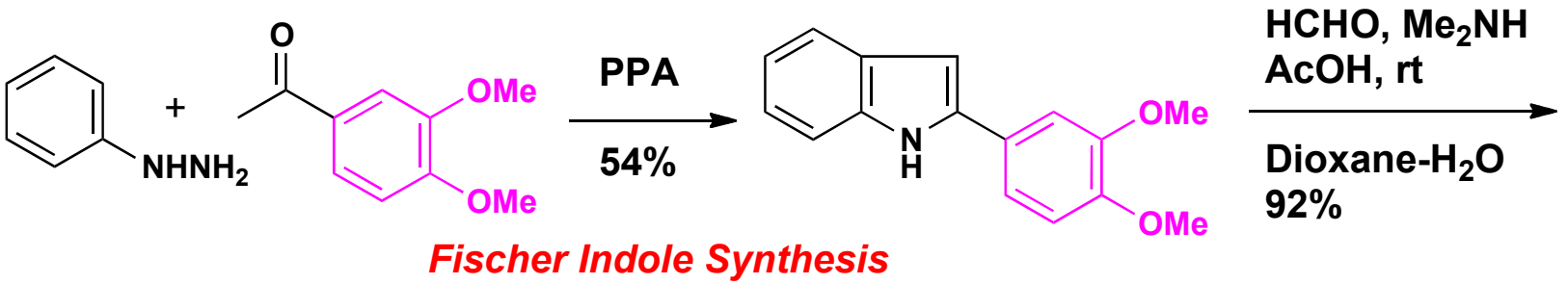
**Dieckman condensation**

**Pictet-Spengler reaction and Interrupted Pictet-Spengler reaction**

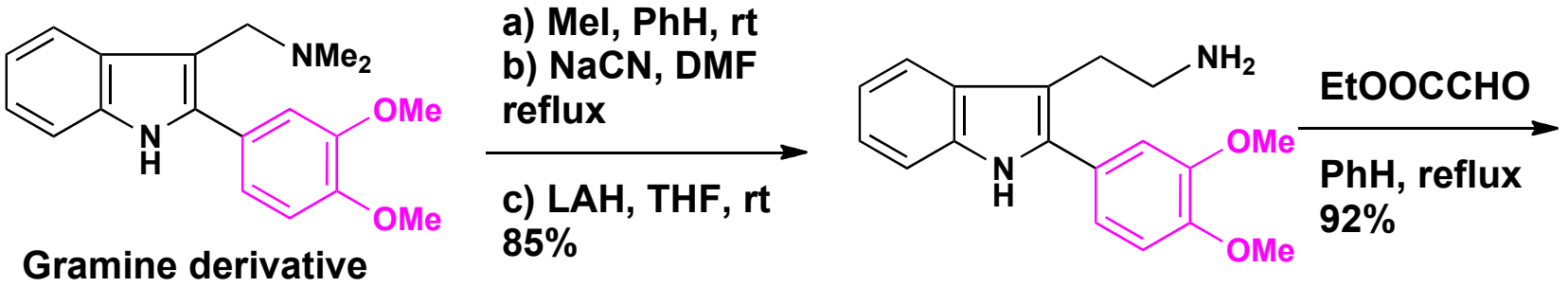
**Azalacton formation**

**Alpha-hydroxylation of ketone ($SeO_2$, Ene reaction/2,3-σ rearrangement)**

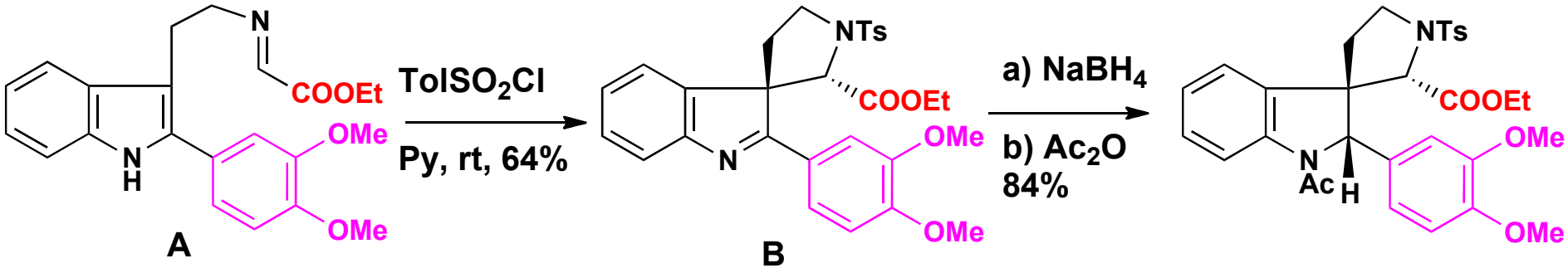
# Woodward's Total Synthesis of Strychnine




*Fischer Indole Synthesis*

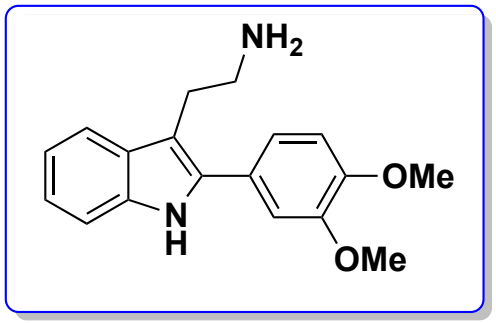



Gramine derivative

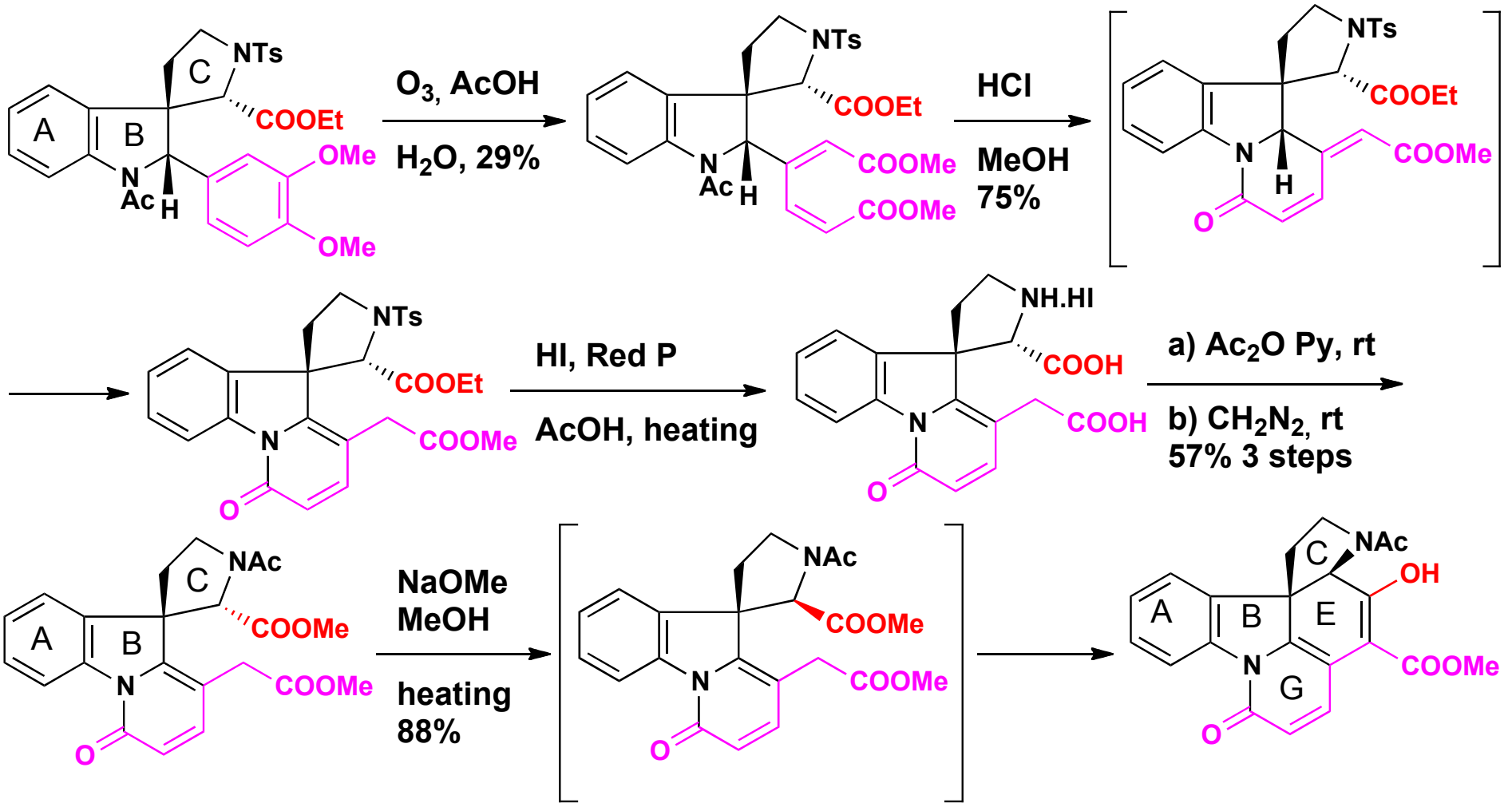



**The C-2 position of Indole is blcoked by the aromatic ring. Only spiroindolene was produced in the Pictet-Spengler reaction (*Interrupted Pictet-Spengler reaction*).**

# Alternative Syntheses of 2,3-Disubstitutes Indoles

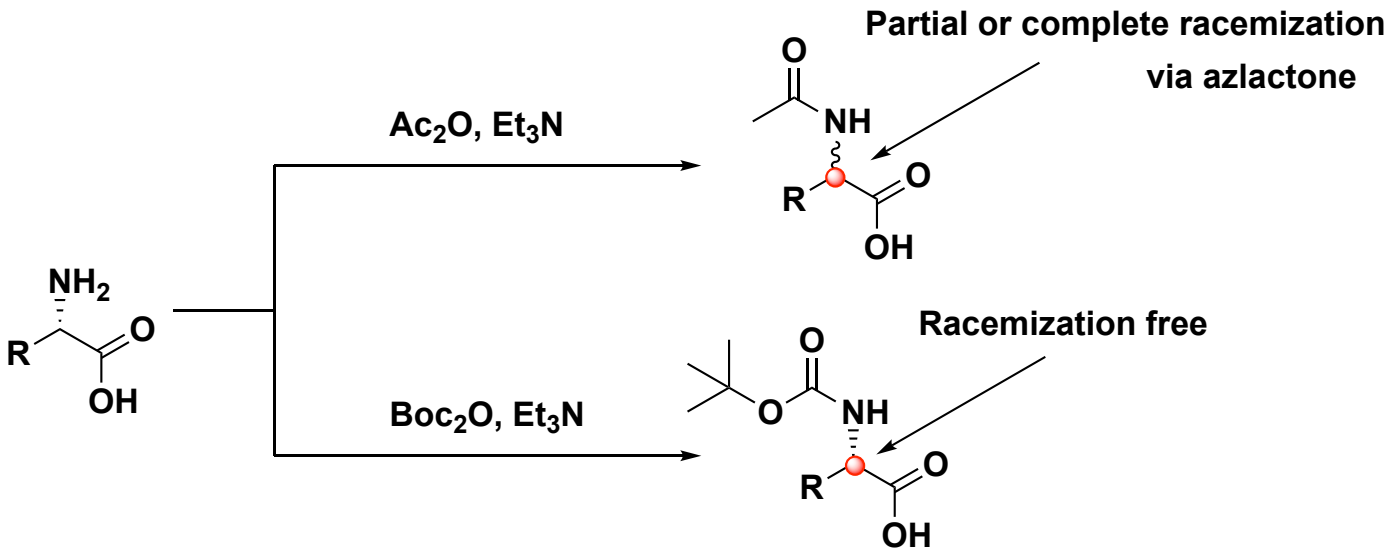


# Woodward's Total Synthesis of Strychnine

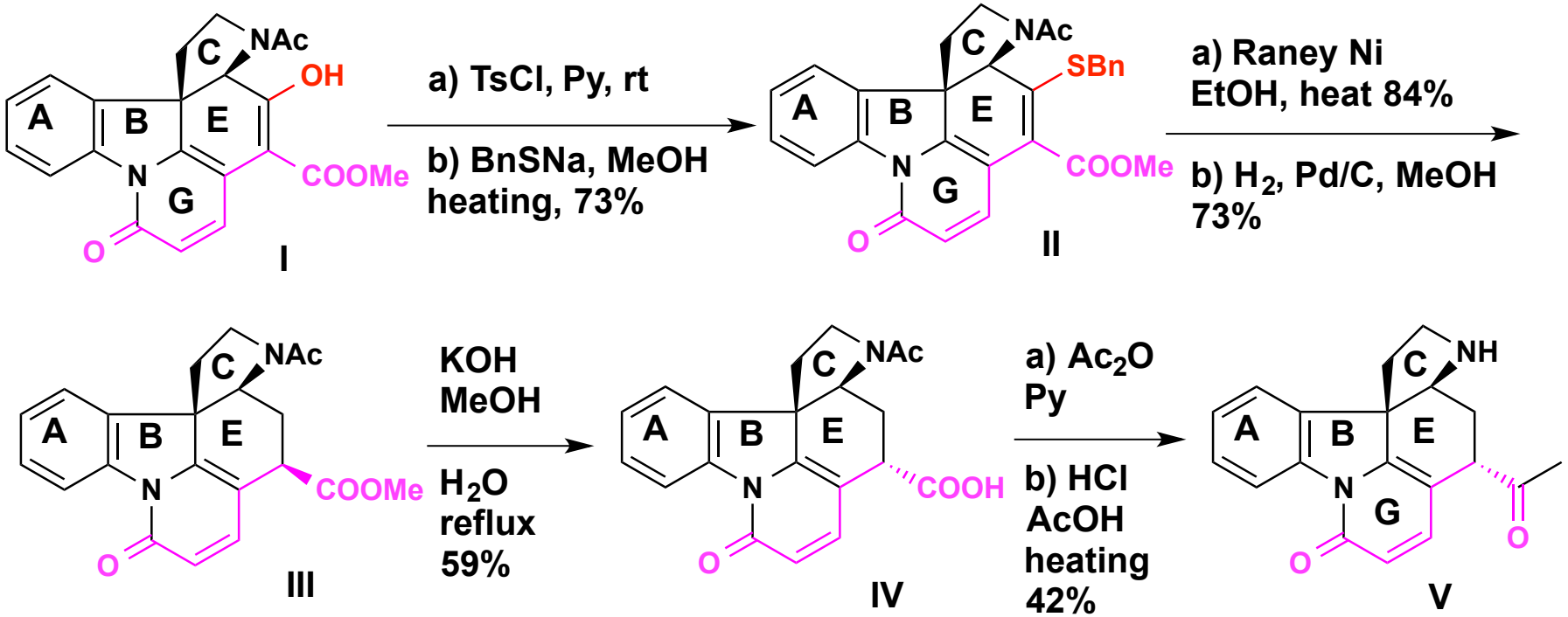


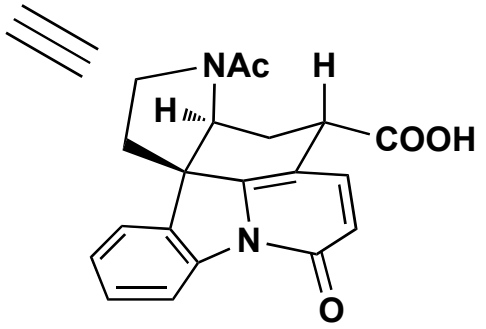

* Conversion of NTs to NAc at the C-ring is required to avoid the decomposition.
* Epimerization at the C- ring is required before Dieckman condensation (draw the conformer)
* The original aromatic ring became integral part of the G, E rings (beauty of the design, based on author's biosynthesis hypothesis, thought late it was proved to be wrong).

# Avoiding Acetylation of Free α-Aminoacid



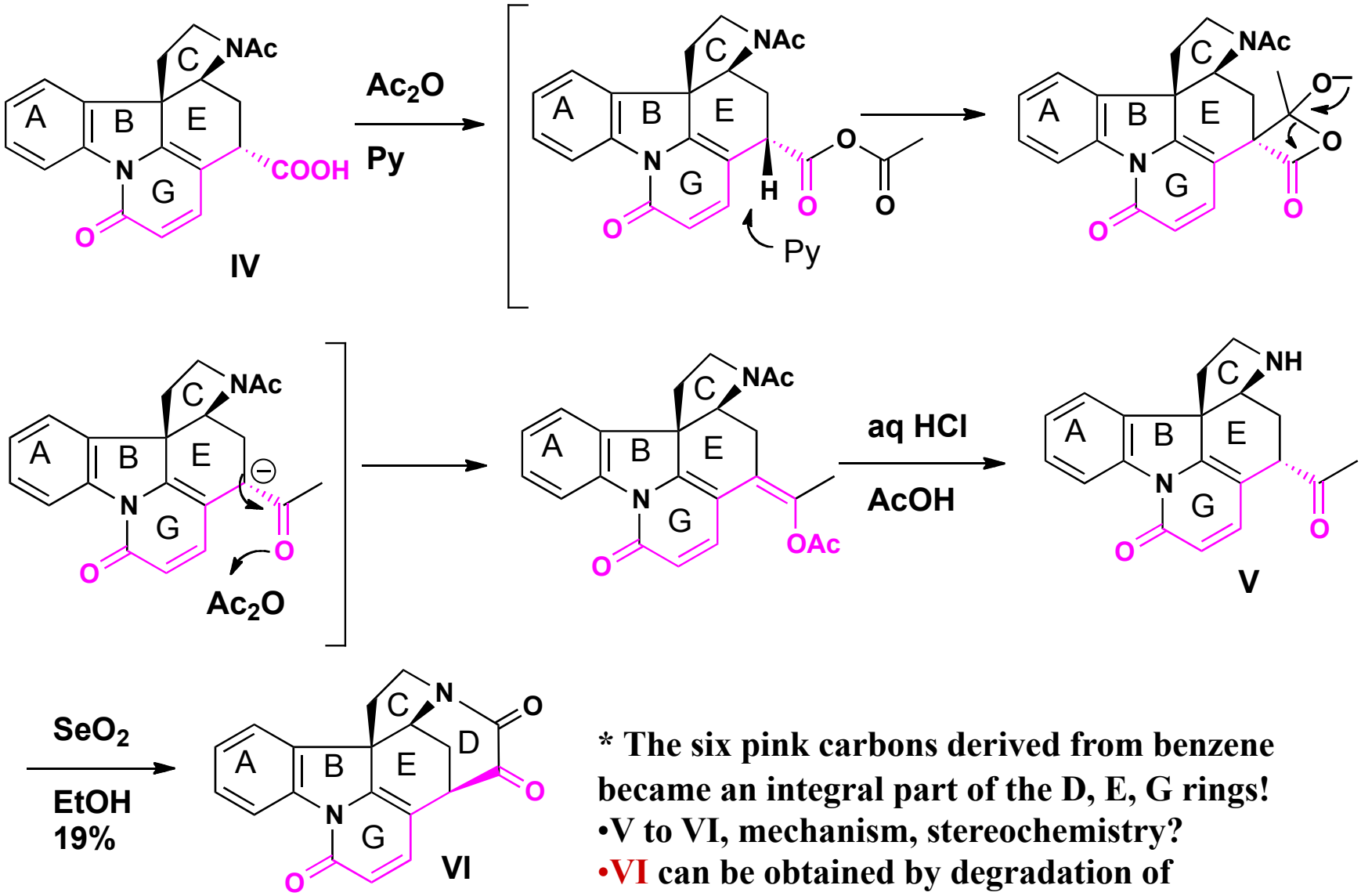
# Woodward's Total Synthesis of Strychnine




* I to II, addition-elimination.
* III: Kinetic product
• IV: Thermadynamically more stable product
  Can be obtained by degradation, 1st relay intermediate
• IV to V: Mechanism

# Woodward's Total Synthesis of Strychnine

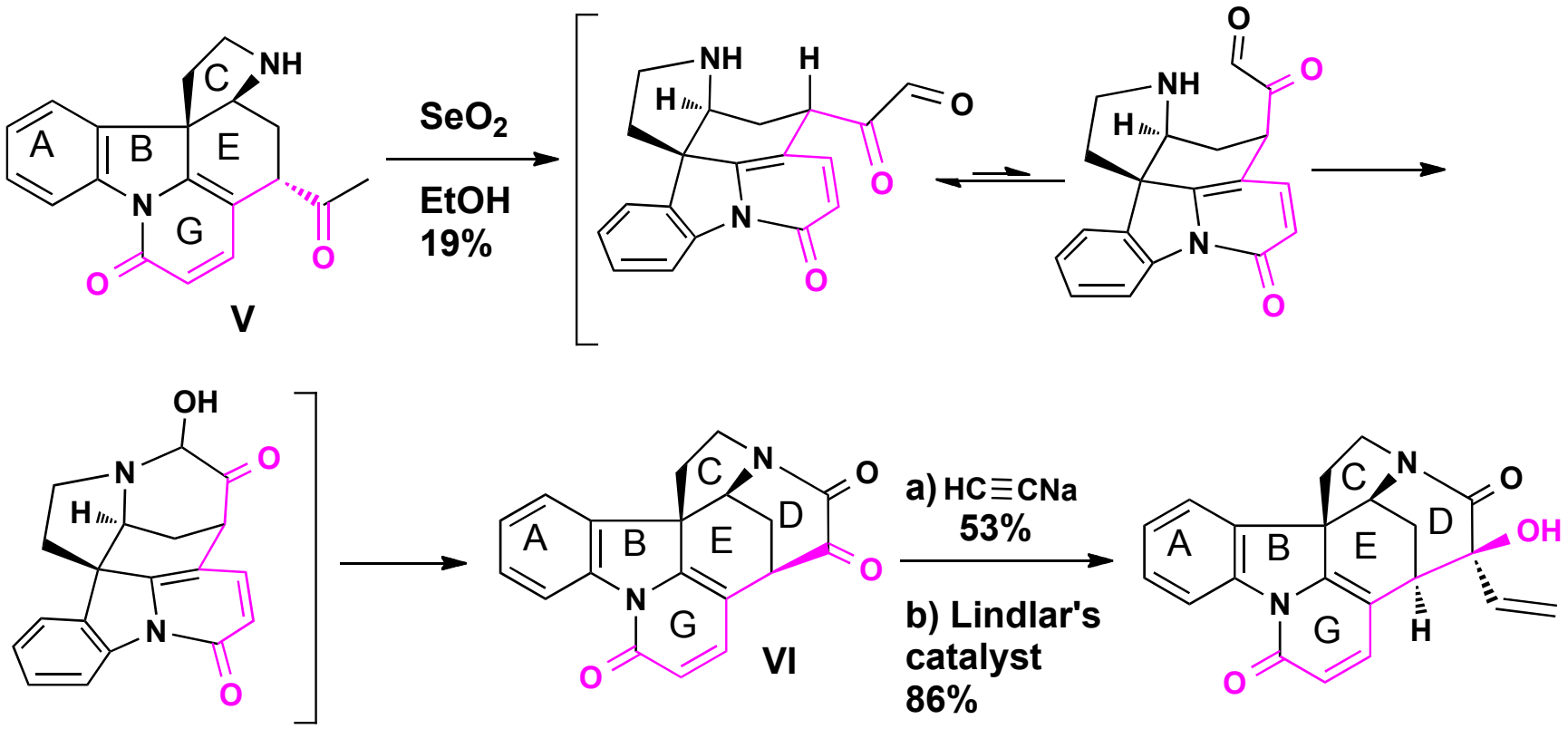



*** The six pink carbons derived from benzene became an integral part of the D, E, G rings!**

**•V to VI, mechanism, stereochemistry?**

**•VI can be obtained by degradation of strychnine (8 steps), 2nd relay intermediate**

# Woodward's Total Synthesis of Strychnine



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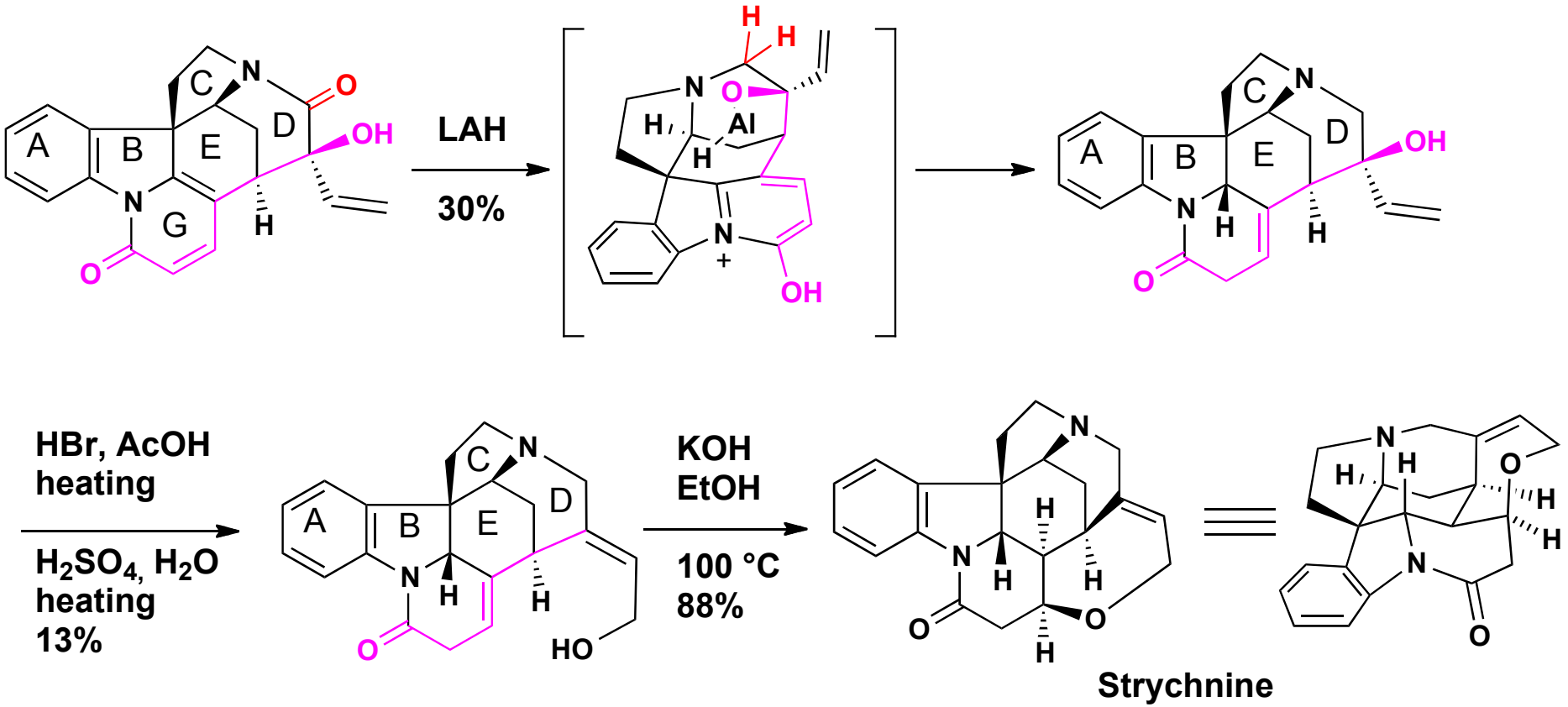
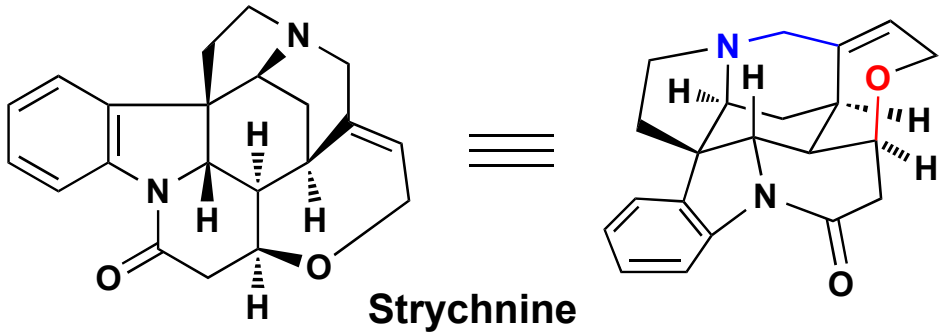



*Neighboring group-directed Diastereoselective reduction*

Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749-4751; *Tetrahedron* **1963**, *19*, 247-288.

# Woodward's Total Synthesis of Strychnine




Strychnine

"For its molecular size it is the most complex substance known."
Robert Robinson (1952)

**Key points**

**a) Using simple reagents available at that time.**

**b) A classic example of relay synthesis**

**28 Steps, 0.00006% overall yield, using relay intermediates**

**Truly spectacular, remained as one of the most significant landmarks in total synthesis.**

**Commercially available at 273 dollar/Kg (2011)**


Review, see:

Bonjoch, J.; D. Solé, *Chem. Rev.* **2000**, *100*, 3455-3482.

Mori, M. *Heterocycles* **2010**, *81*, 259-292.

Overman, L. E. *Angew. Chem. Int. Ed*. **2012**, 51, 4288-4311.

# Summary of Woodward's Synthesis: Reactions and Tactics

**Fischer indole synthesis**

**Dieckman condensation**

**Pictet-Spengler reaction and Interrupted Pictet-Spengler reaction**

**Azalacton formation**

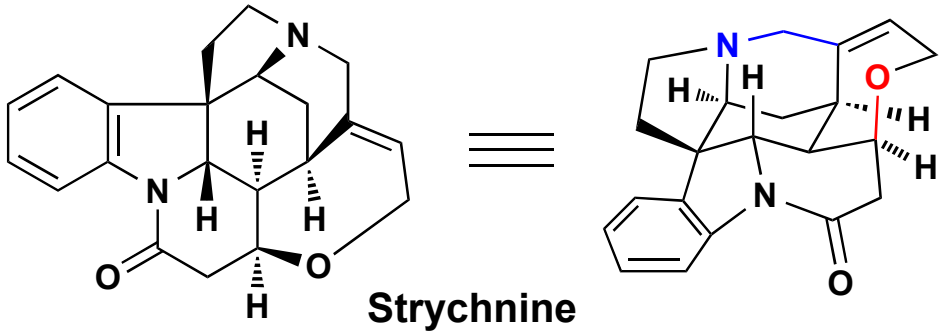
**Alpha-hydroxylation of ketone ($SeO_2$, Ene reaction/2,3-σ rearrangement)**

***Key Features:***

***Stepwise construction of ring system***

***Neighboring group-directed Diastereoselective reduction***

# Total Synthesis of Strychnine



Strychnine

**R. B. Woodward** - Harvard University (**1954**) **28 steps**

**38 years**

**Philip Magnus** - University of Texas (**1992**)
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**Viresh H. Rawal** - The Ohio State University (**1994**) **14 Steps**
**Josep Bonjoch & Joan Bosch** - University of Barcelona (**1999**)
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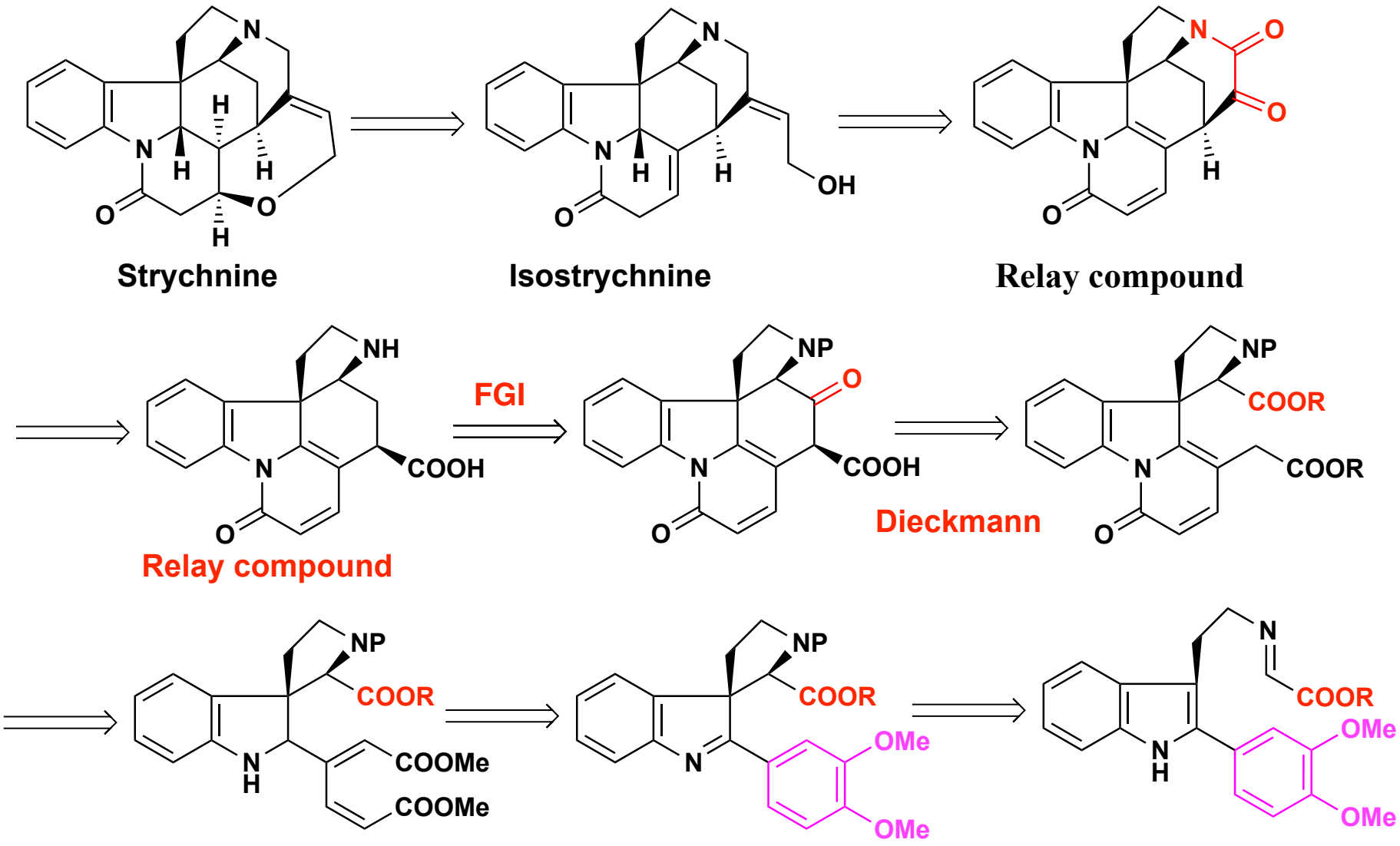
**Christopher, D. Vanderwal,** University of california, Irvine **(2011)** **6 Steps**

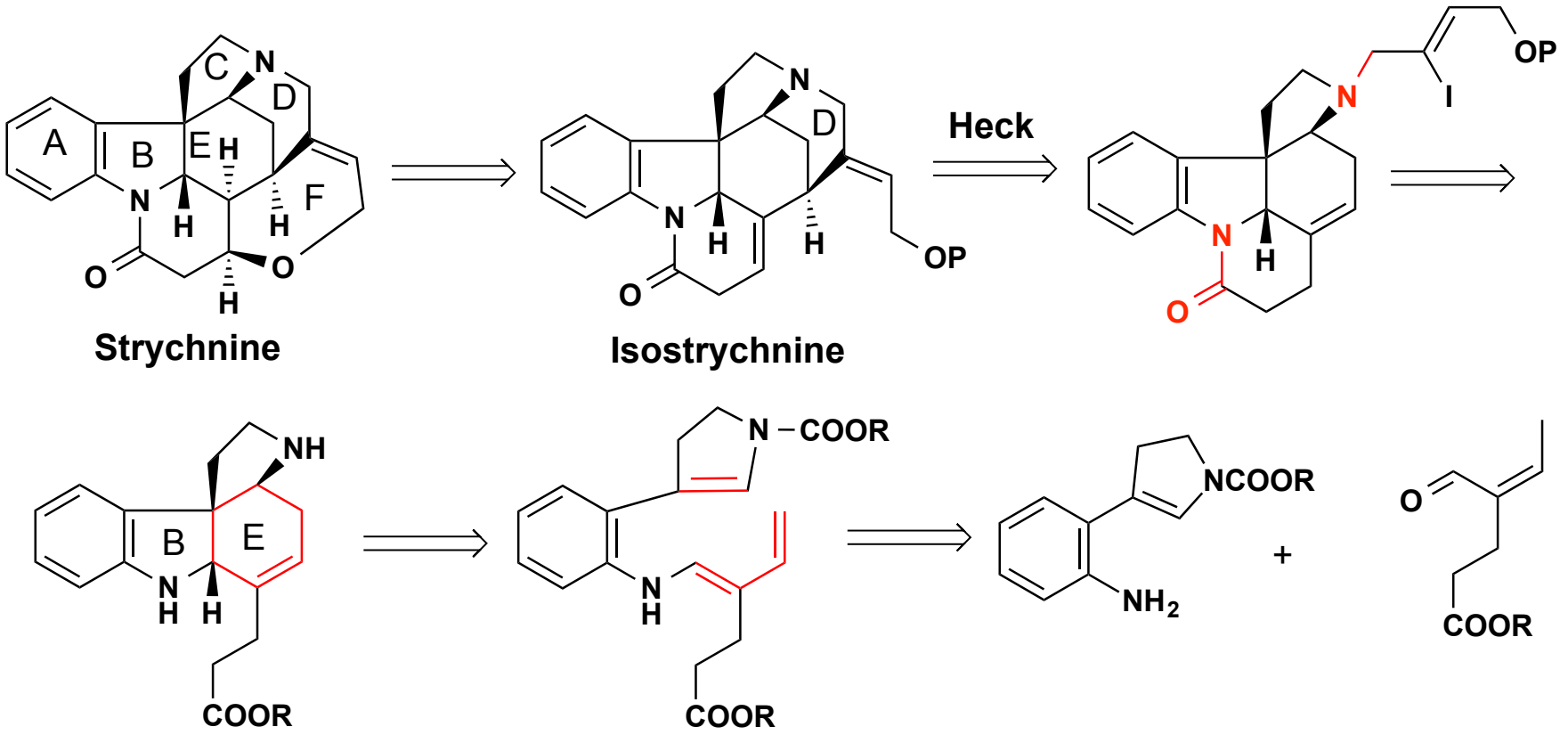
# Woodward's Total Synthesis of Strychnine: *A Relay Synthesis*




One of the key strategic considerations: **Relay Synthesis**

Woodward, R. B. *J. Am. Chem. Soc*. **1954**, *76*, 4749-4751; *Tetrahedon* **1963**, *19*, 247-288.

# Rawal's Total Synthesis of Strychnine




**Key disconnections**

*** Isostrychnine as a late stage intermediate**

*** Intramolecular Heck reaction for the construction of D-ring**

*** Intramolecular Diels-Alder cycloaddition for the simultaneous construciton of B and E ring**

Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685-2686.

# Reactions Needed to Know

**Cyclopropane to cyclopentene rearrangement**

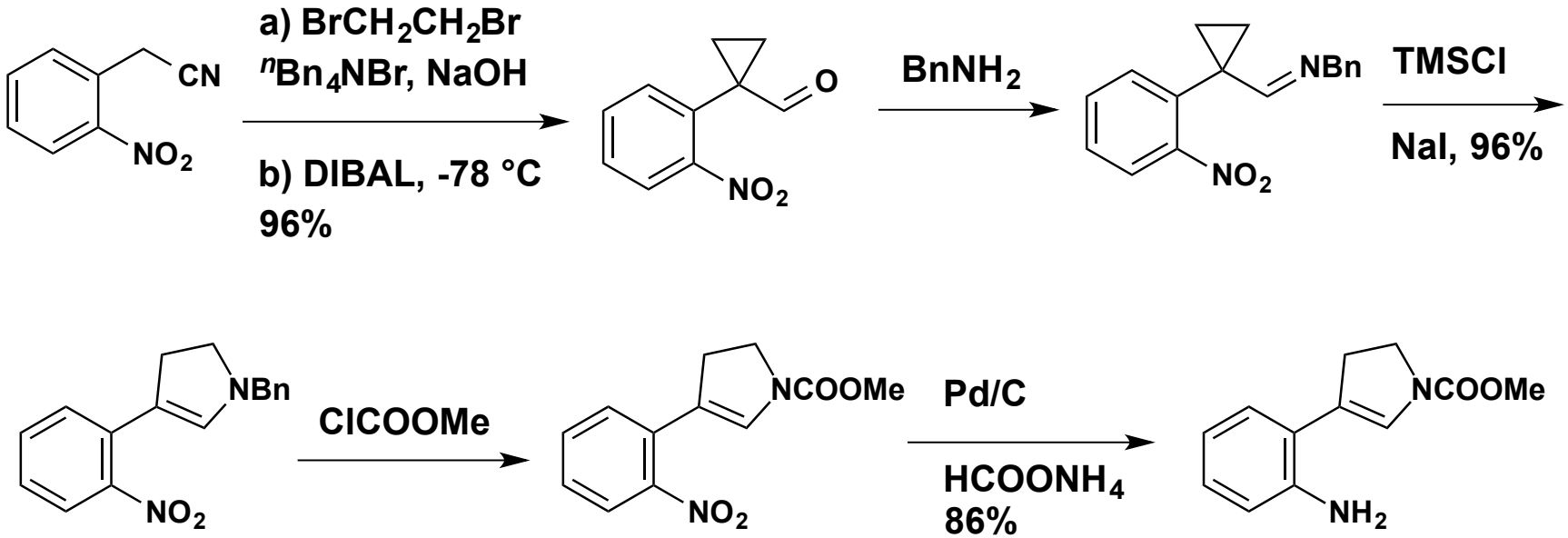
**Cyclopropylimine to pyrrole rearrangement**

**Von Braun Reaction**

**Diels-Alder reaction**

**Heck reaction**

# Rawal's Total Synthesis of Strychnine

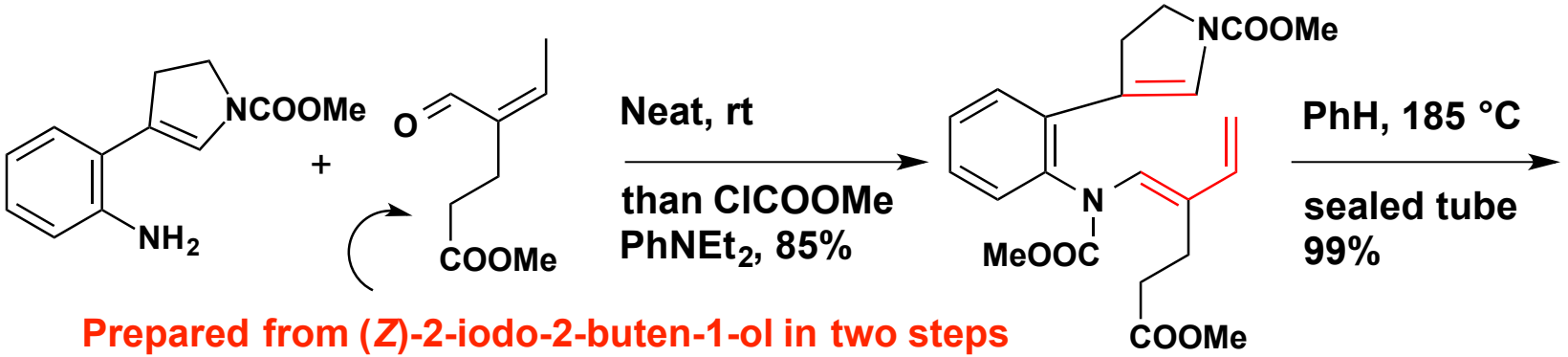



**Von Braun Reaction**

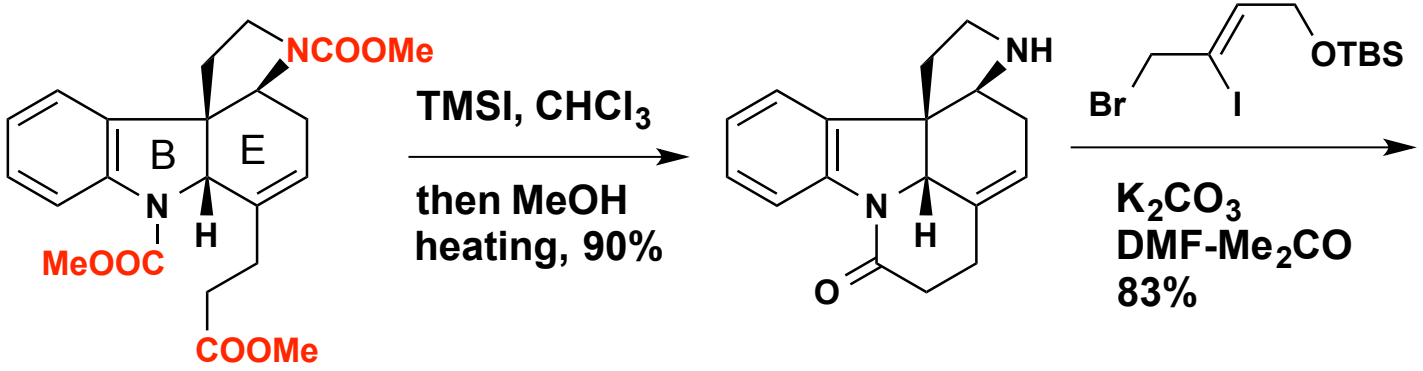
**Mechanism of:**
**Cyclopropyliminium ion rearrangement**
**Von Braun reaction**

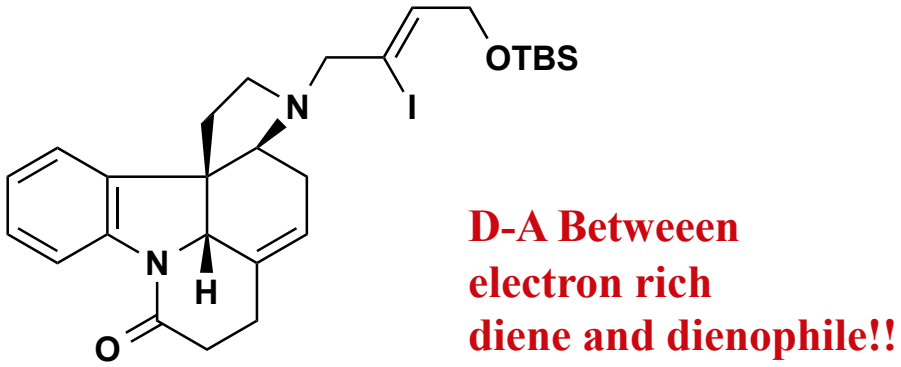
Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685-2686.

# Rawal's Total Synthesis of Strychnine

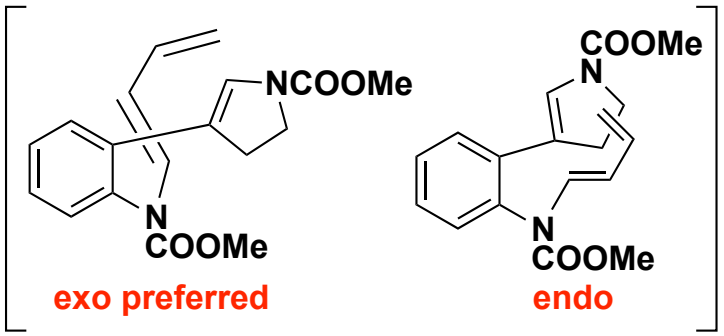



Prepared from (*Z*)-2-iodo-2-buten-1-ol in two steps



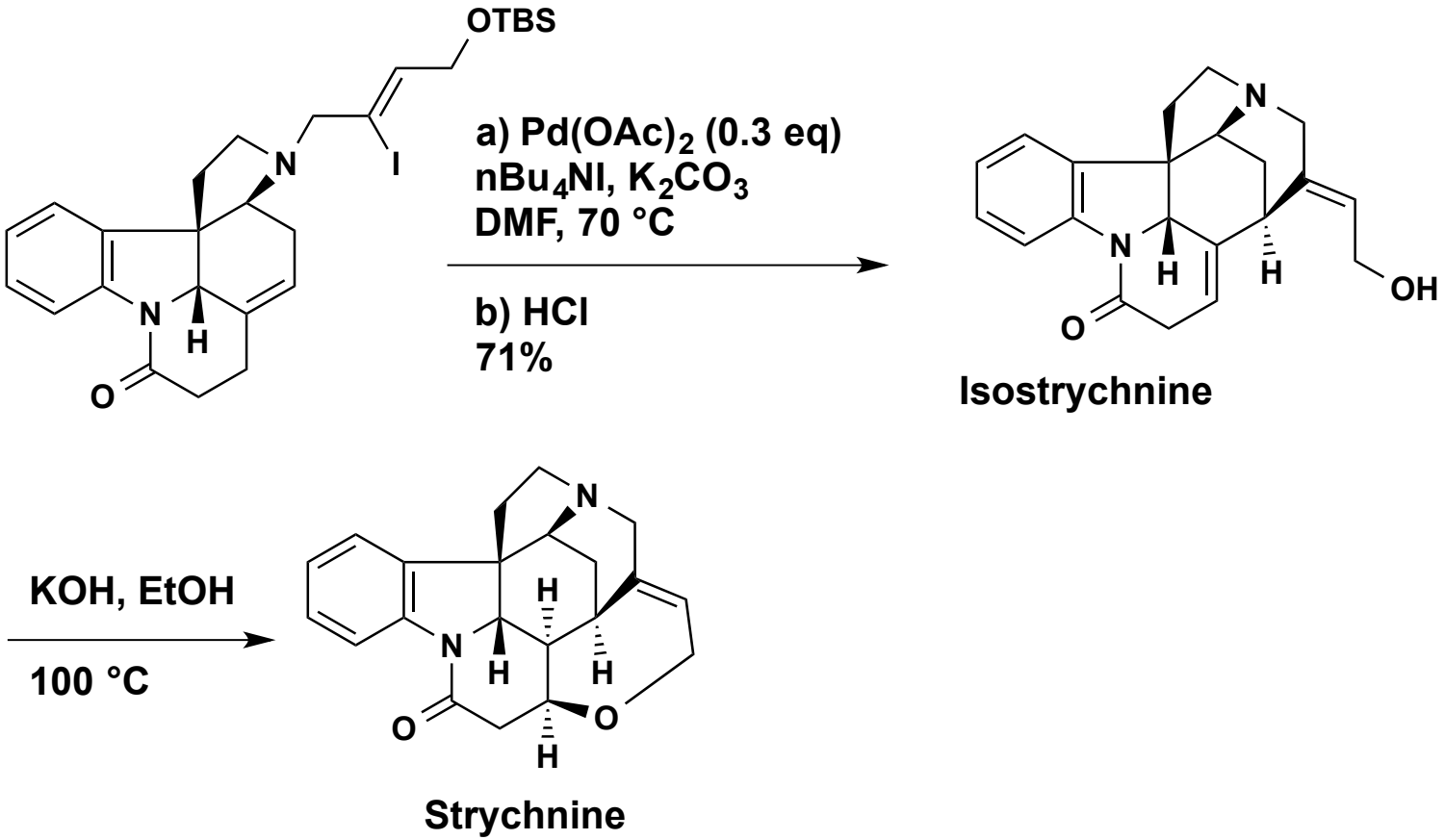




**D-A Betweeen electron rich diene and dienophile!!**




Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685-2686.

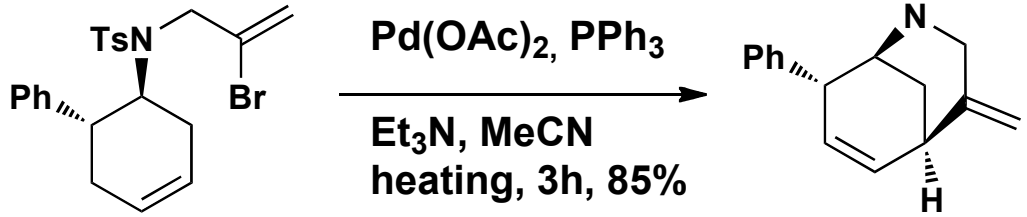
# Rawal's Total Synthesis of Strychnine



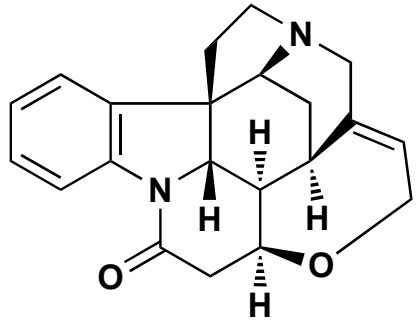

**Heck reaction**: Heck, R. F. *Org. React*. **1982**, *27*, 345.
Jeffery's conditions: *Tetrahedron Lett*. **1985**, *26*, 2667.

Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685-2686.
See also: Rawal et al. *J. Am. Chem. Soc*. **1993**, *115*, 3030-3031.

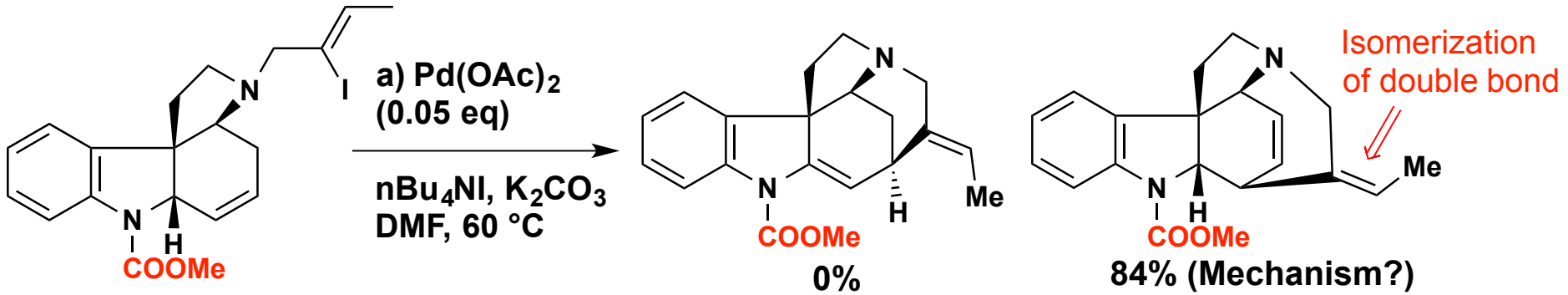
# Rawal's Model Studies: Influence of Protective Group

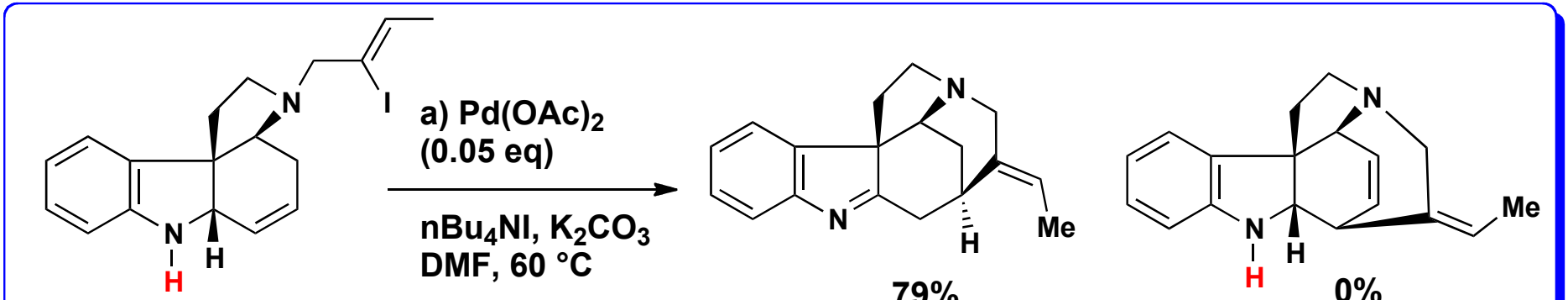



Rawal, V. H. *Tetrahedron Lett.* **1991,** *32,* 1695-98.



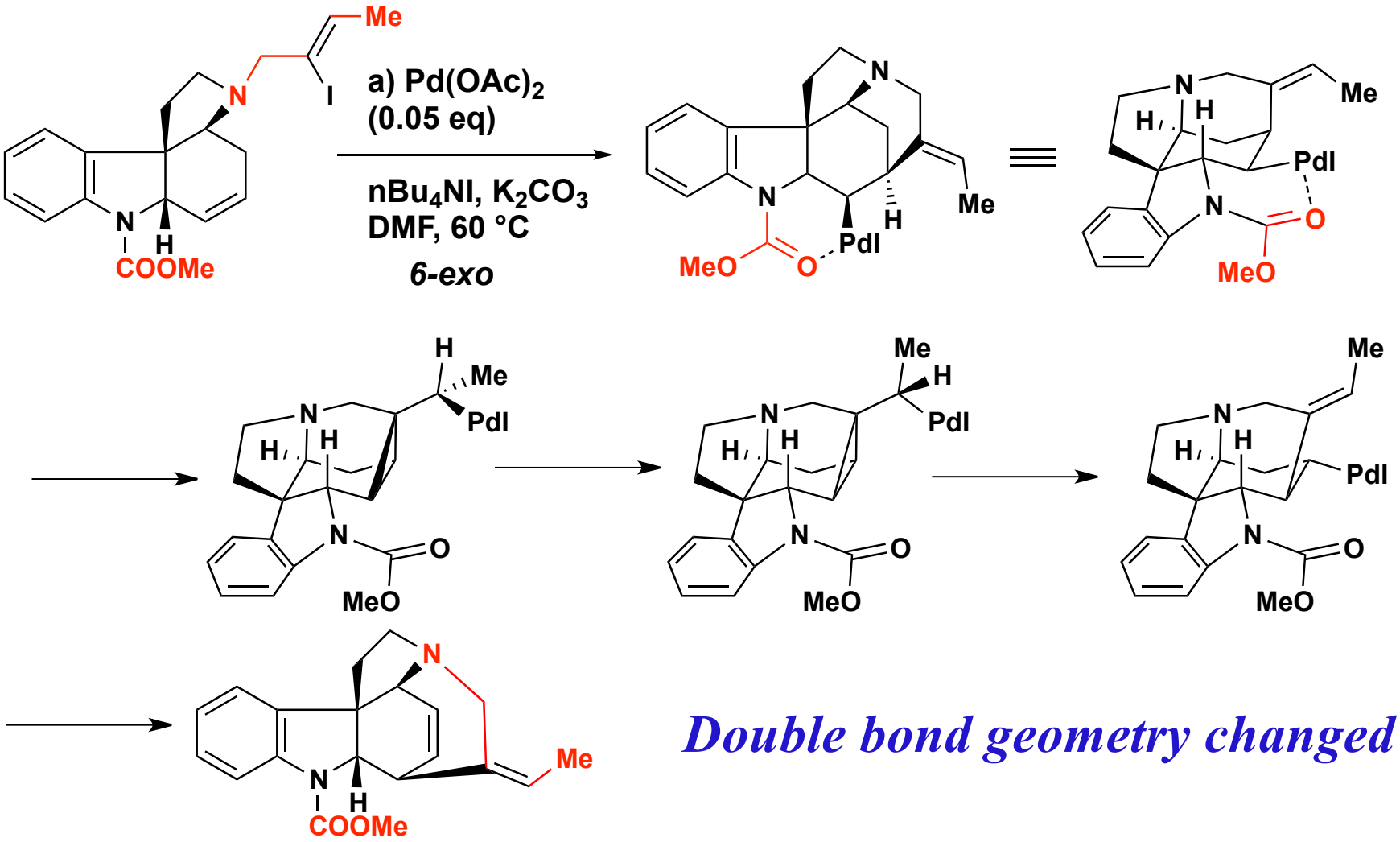

**Strychnine**




Rawal, V. H. *J. Org. Chem.* **1993,** *58,* 5583-5584.

# Formation of "Formal 7-*endo*" Product: Mechansim




***Double bond geometry changed***

Rawal, V. H. *J. Org. Chem.* **1993,** *58,* 5583-5584.

# Summary of Rawal's Synthesis: Reactions and Tactics

**Cyclopropane to cyclopentene rearrangement**

**Cyclopropylimine to pyrrole rearrangement**

**Von Braun Reaction**

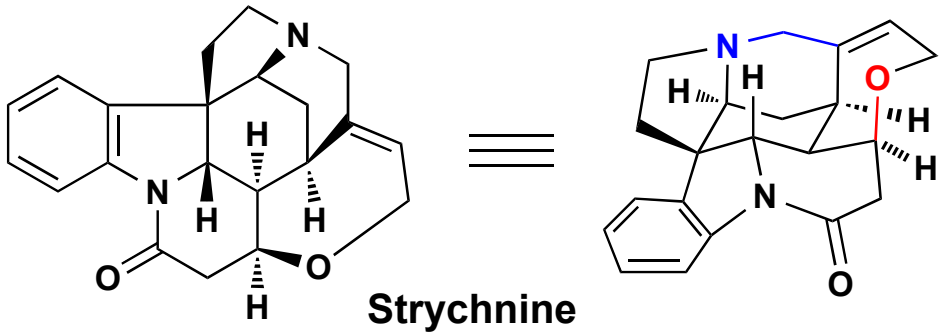
**Diels-Alder reaction**

**Heck reaction**

**Key Features:**

**Intramolecular Diels-Alder reaction for the rapid construction of tetracyclic ring system.**

# Strychnine: Key background

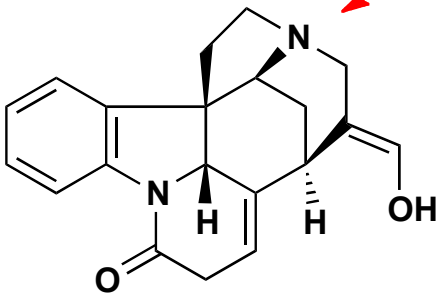


Strychnine

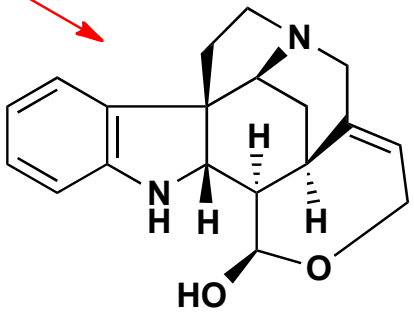
KOH, EtOH
85 °C

$CH_2(COOH)_2$, $Ac_2O$
NaOAc, AcOH, 110 °C

Degradation studies
in 1940's

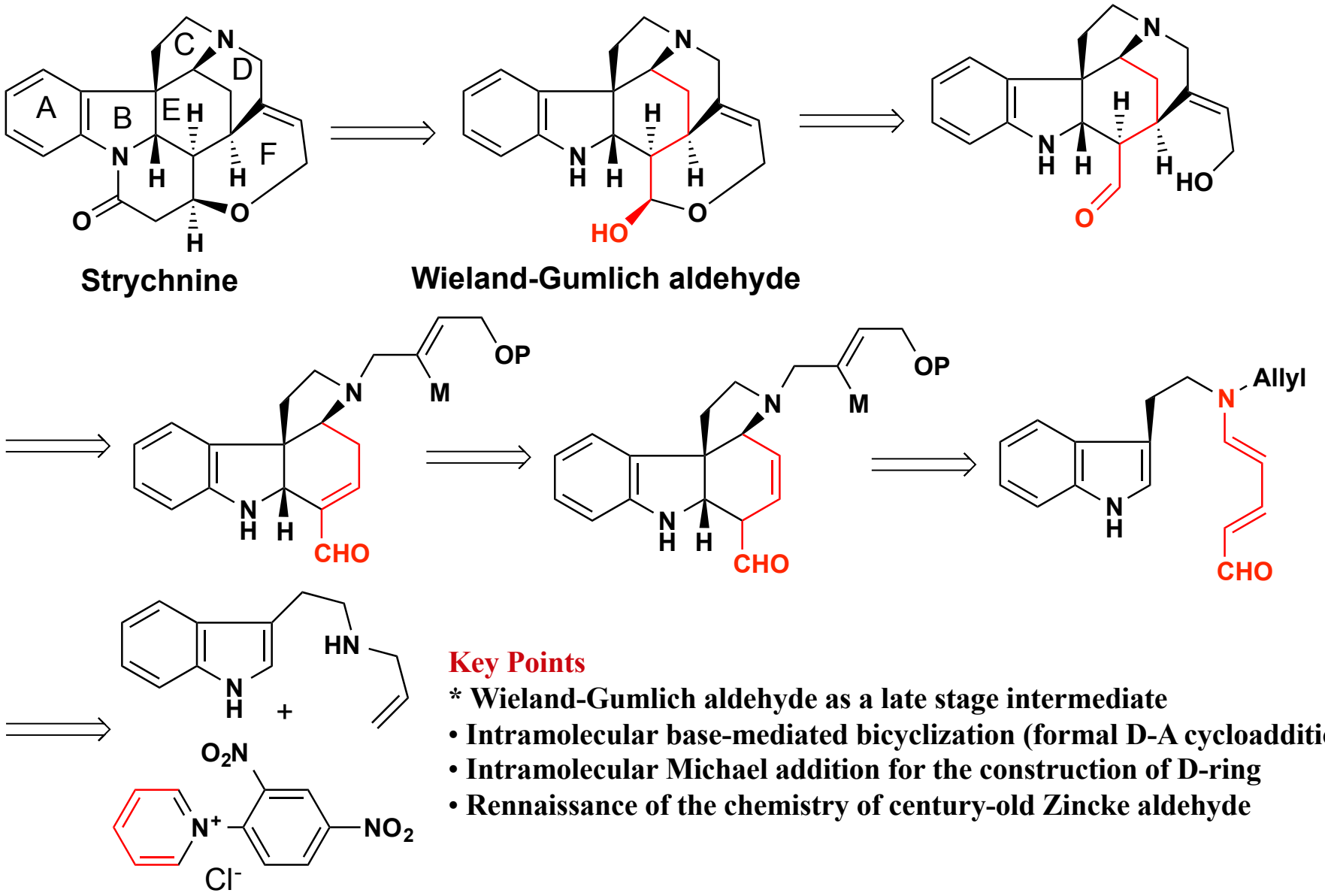


Isostrychnine



Wieland-Gumlich aldehyde

# Vanderwal's Total Synthesis of Strychnine-Retro




Strychnine

Wieland-Gumlich aldehyde

**Key Points**

*** Wieland-Gumlich aldehyde as a late stage intermediate**

**• Intramolecular base-mediated bicyclization (formal D-A cycloaddition)**

**• Intramolecular Michael addition for the construction of D-ring**

**• Rennaissance of the chemistry of century-old Zincke aldehyde**


Martin, D. B. C.; Vandewal, C. D. *Chem. Sci.* **2011**,*2,* 649-651. *J. Am. Chem. Soc*. **2009**, *131*, 3472-3473.

Full account: *J. Org. Chem.* **2012**, *77*, 17-46.

# Reactions Needed to Know

**Zincke aldehyde**

**N-Deallylation**

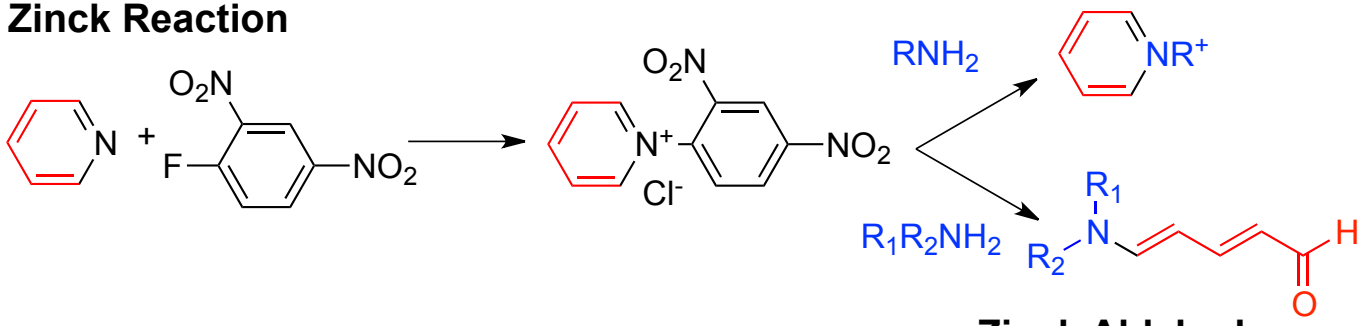
**Diels-Alder reaction**

**Brook rearrangement**

**Michael addition**

# Zincke Reaction and Zincke's Aldehyde

**Zinck Reaction**




**Zinck Aldehyde**

**Mechanism: Initiated by nucleophilic addition of amine to the C-2 of pyridinium followed by ring opening ...**

**Discovered by Zincke in 1904**

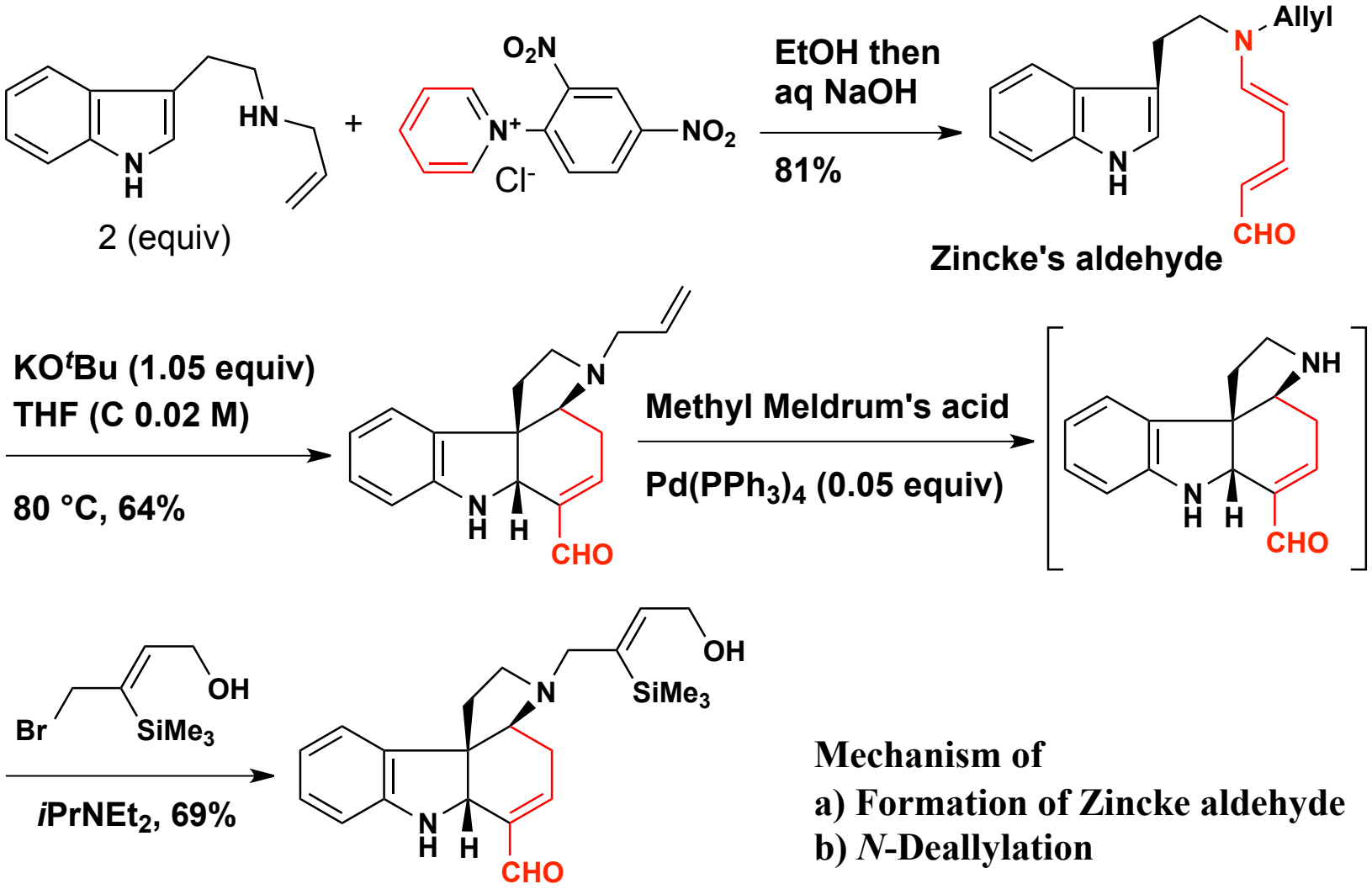
**Re-discovered in 2006 with wrong structure**

F. M. Menger, *Angew. Chem. Int. Ed*. **2007,** *46,* 5889 – 5891 (VIP)

I. Yamaguchi, *Org. Lett*. 2006, *8*, 4279 – 4281.

Correspondance : M. Christl, *Angew. Chem. Int. Ed*. **2007,** 46, 9152-9153.

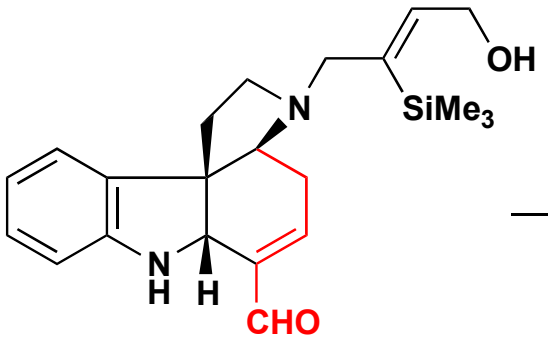
# Vanderwal's Total Synthesis of Strychnine





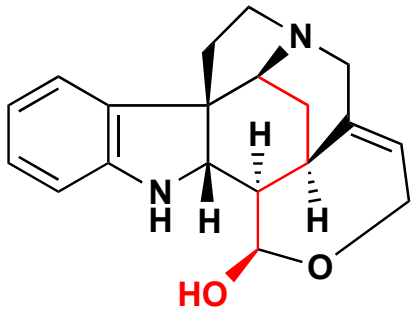
Martin, D. B. C.; Vandewal, C. D. *Chem. Sci.* **2011**, *2,* 649-651. *J. Am. Chem. Soc*. **2009**, *131*, 3472-3473.
Full account: *J. Org. Chem.* **2012**, *77*, 17-46.
Cycloaddition: Stepwise mechanism: Vandewal, C. D.; Houk, K. N. *Chem. Sci.* **2012**, *3,* DOI: 10.1039/c2sc01072k

# Vanderwal's Total Synthesis of Strychnine




NaHMDS, NMP
then $CuBr.SMe_2$

0° to 65 °C
5-10%

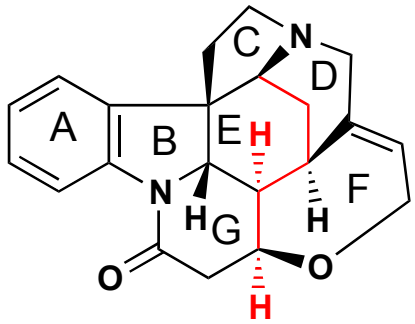



Wieland-Gumlich aldehyde

*via:*
*Brook rearrangement*
*Conjugate addition*

$CH_2(COOH)_2$, $Ac_2O$
NaOAc, AcOH

60-80%




Strychnine

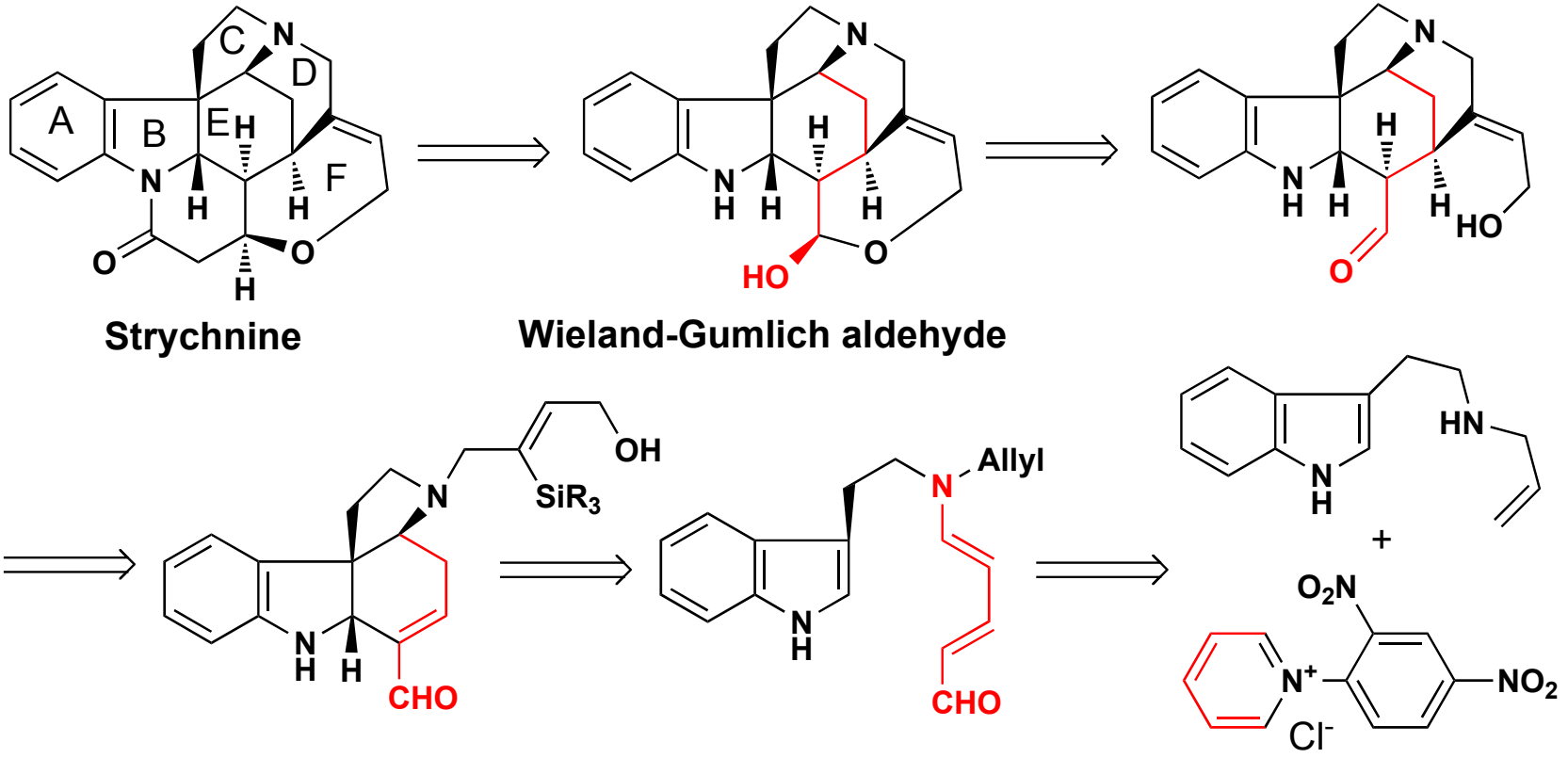
*5 carbon derived from pyridine were engaged in the formation of C, D, E, F, G ring*

**Has anybody ever imagined that strychnine can be synthesized in only 6 steps!!**


Martin, D. B. C.; Vandewal, C. D. *Chem. Sci.* **2011**, *2,* 649-651. *J. Am. Chem. Soc*. **2009**, *131*, 3472-3473.
Full account: *J. Org. Chem.* **2012**, *77*, 17-46.

1,4 $C_{sp2}$-to-O Silyl Migration, see: Takeda, T., *J. Org. Chem*. **2002**, **67**, 8450-8456.

# Vanderwal's Total Synthesis of Strychnine-Retro




Strychnine

Wieland-Gumlich aldehyde

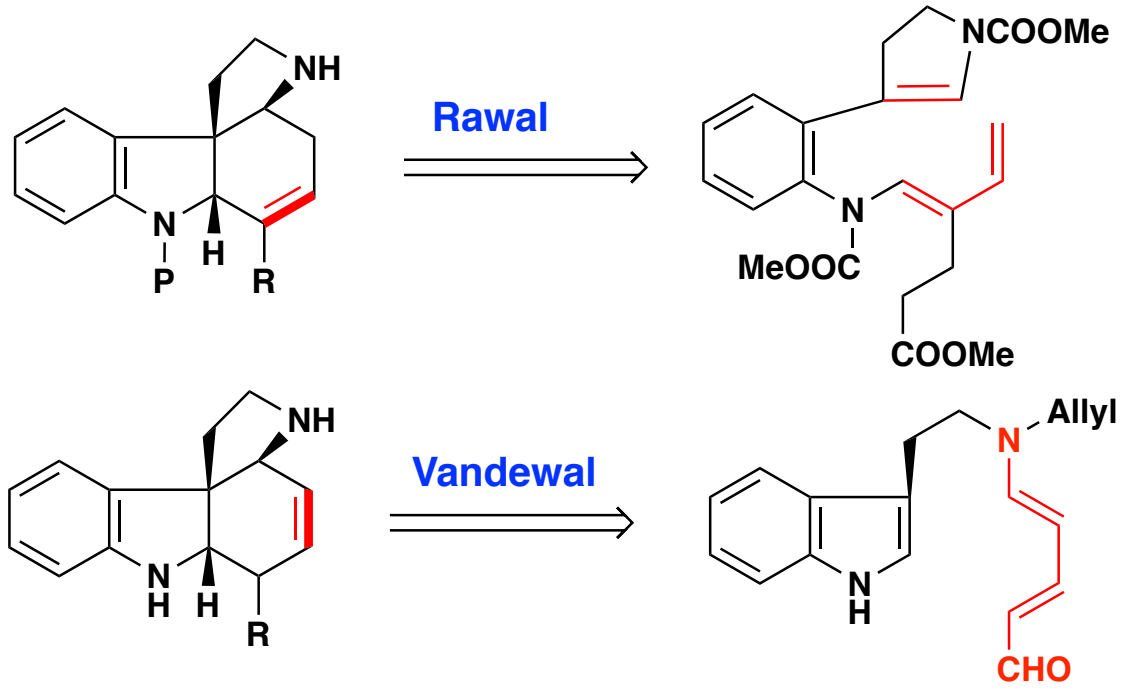
**Formation of tetracycle: an Anion-Induced Biscyclization:**
**Not concerted, but a Domino Michael addition/Mannich sequence**


Martin, D. B. C.; Vandewal, C. D. *Chem. Sci.* **2011**, *2,* 649-651. *J. Am. Chem. Soc*. **2009**, *131*, 3472-3473.
Full account: *J. Org. Chem.* **2012**, *77*, 17-46.
Review: Overman, L. E. ACIE, **2012**, 10.1002/anie.201107385

# Summary of Vanderwall's Synthesis: Reactions and Tactics

1) Zincke aldehyde
2) N-Deallylation
3) Diels-Alder reaction
4) Brook-rearrangement
5) Michael addition

**Key Feature:** Intramolecular Diels-Alder reaction for the rapid construction of tetracyclic ring system.



# Strychnine Synthesis

| | Functional group manipulation | Protective Group | Redox Process | Multiple bond forming process |
|---|---|---|---|---|
| Woodward (1954) | +++++ | +++++ | ++++++ | + |
| Rawal (1994) | + | ++ | ++ | +++ |
| Vanderwal (2011) | - | + | - | +++++ |