Total Synthesis of Natural Products
CH438

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Lecture time: Tuesday 8h15-10 am
Lecture Room: ELG116

Exercise(s): …

Outline

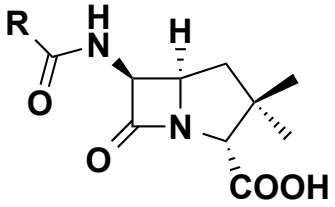
- **Introduction**

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

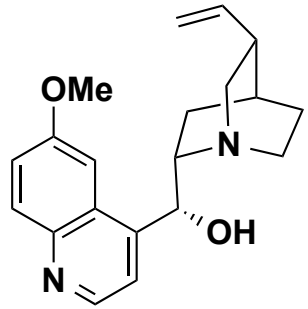
- **Syngernism between strategy and total synthesis**

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

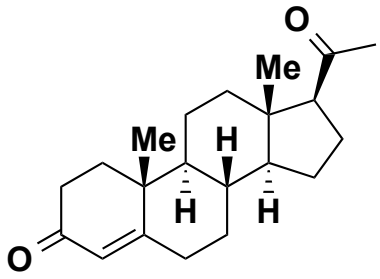
Why Natural Products: Source of Drugs, Structural diversity and Complexity



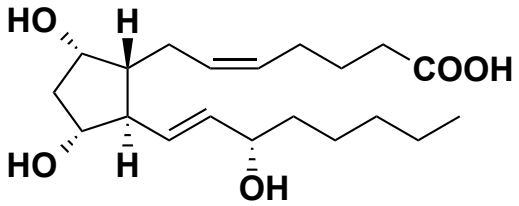
Penicillin



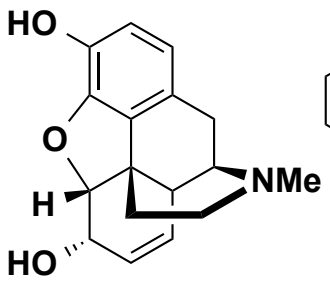
Quinine



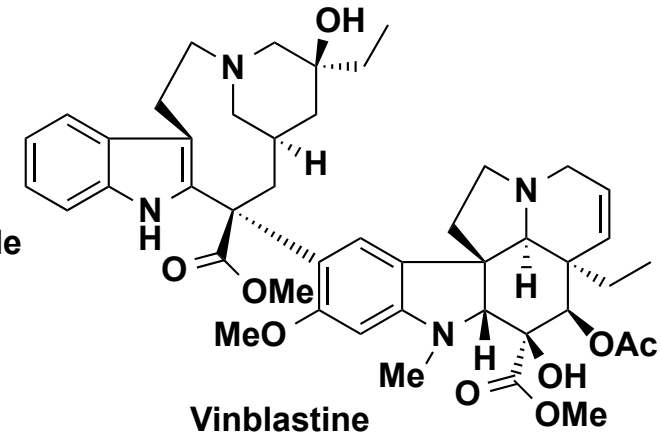
Progesterone



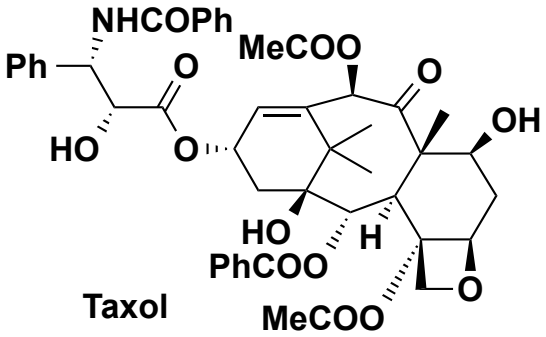
PGF2a



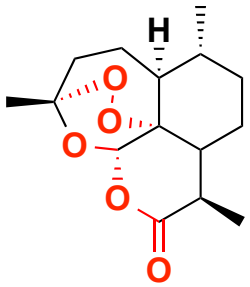
Morphine



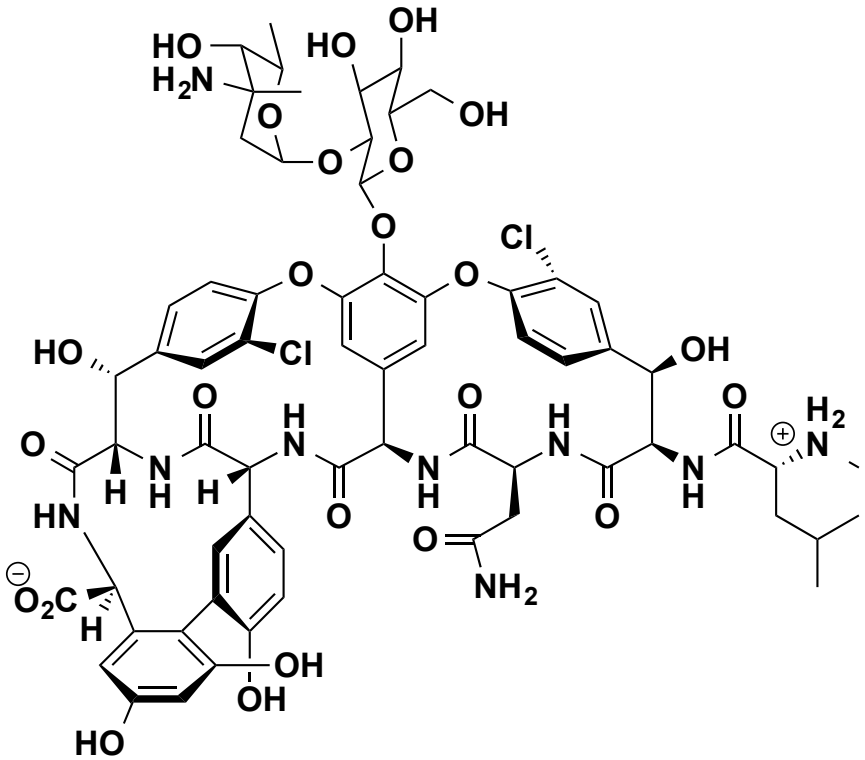
Vinblastine



Taxol



Artemisinine



Vancomycine

What is Total Synthesis ?

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

Terms

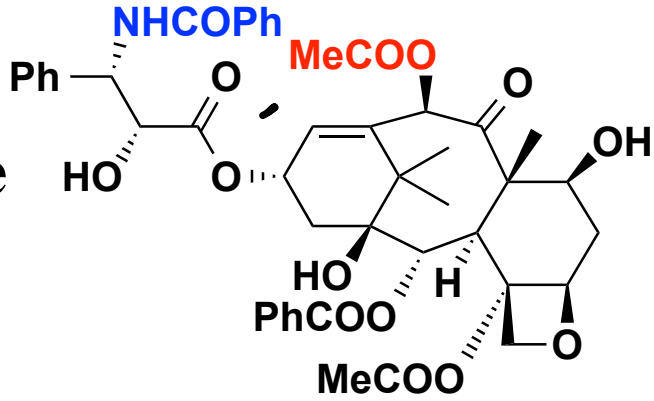
Total Synthesis: The production of a molecule from commercially or readily available chemicals through a series of chemical transformations.
Not limited to Natural Product

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

Terms

Partial synthesis or semisynthesis:

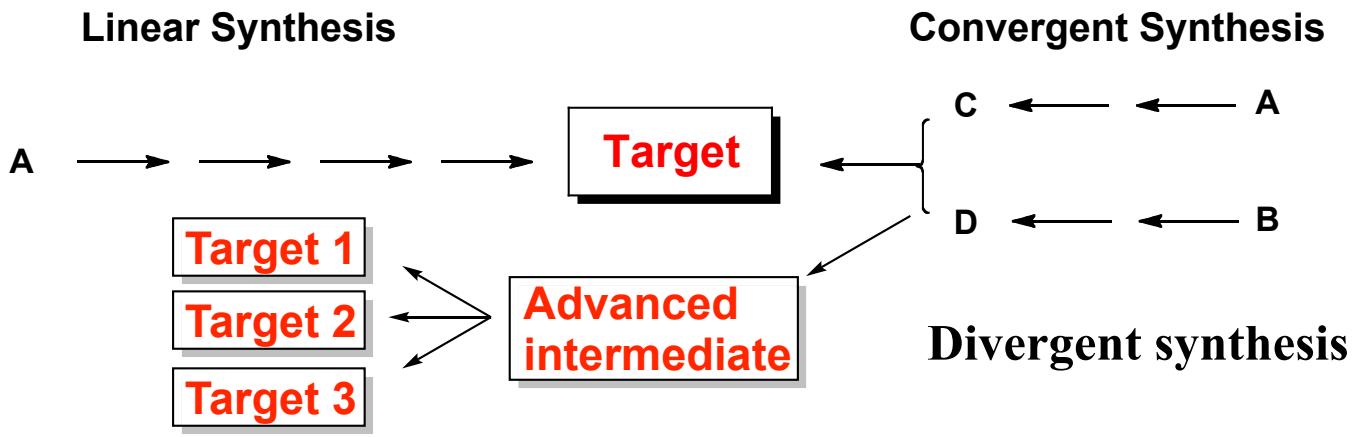
Designates the synthesis of a given molecule from an advanced precursor related to it.



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**

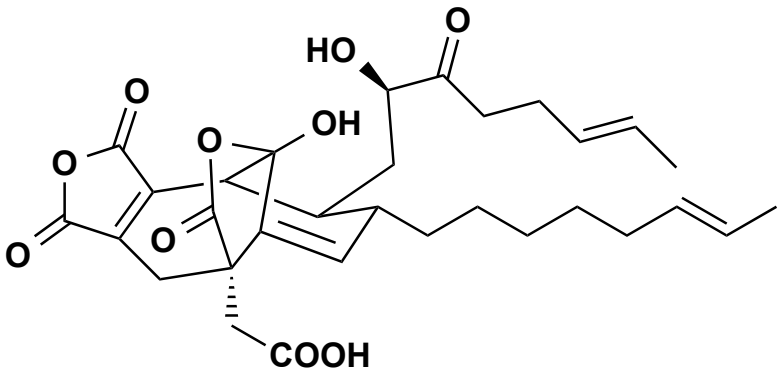
Need constantly to *find new routes* to cross the line

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

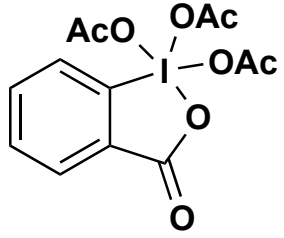
Total Synthesis: For the discovery of new reactions

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

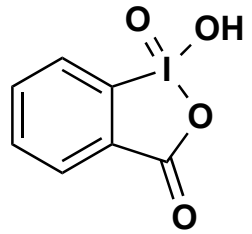
E. J. Corey (*From "Classic in Total Synthesis II" Nicolaou, KC, Snyder, SA)*



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

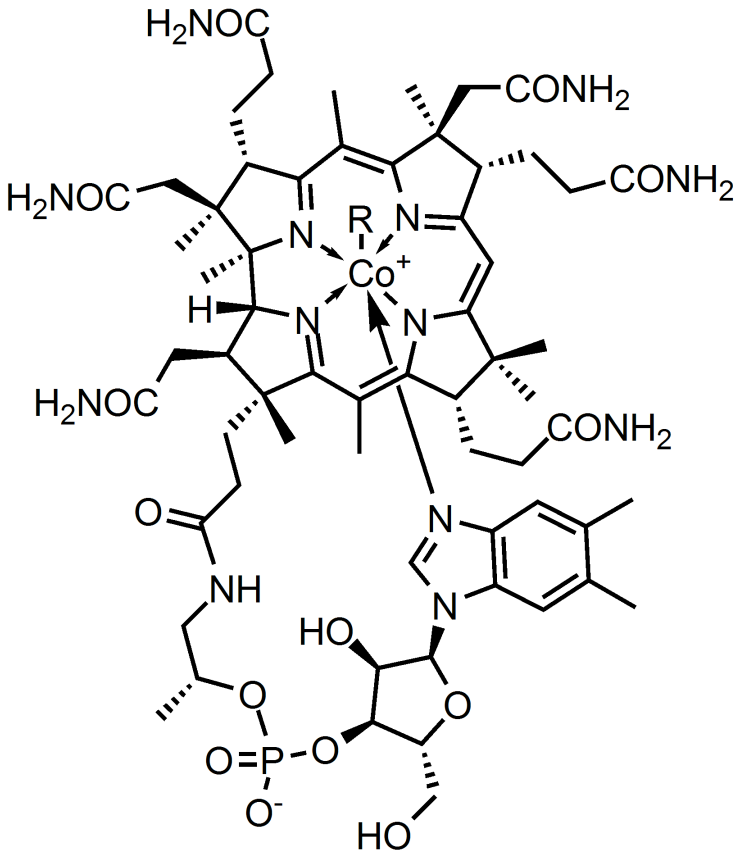
Total Synthesis: For Serendipity…

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

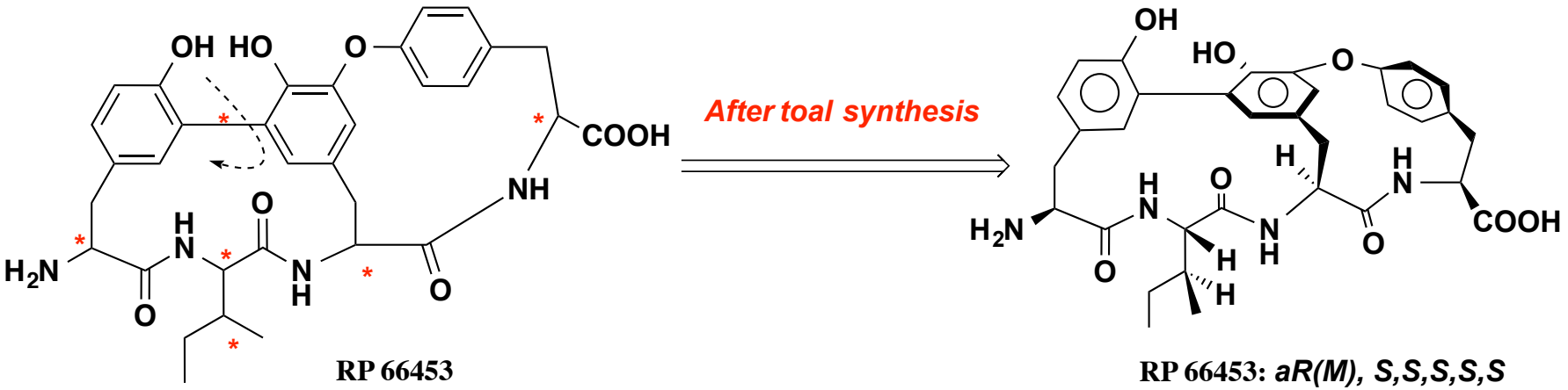
Total synthesis of vitamin B12
By Woodward and Eschenmoser

⇓

Woodward-Hoffman rules

Total Synthesis: For the Structural Determination

Less prominant nowadays, but still valide



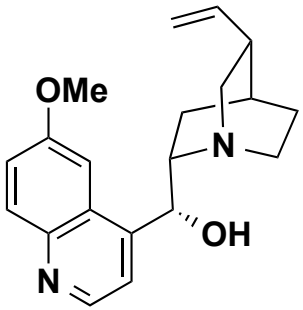
RP 66453

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

5 stereocenters
1 axial chirality

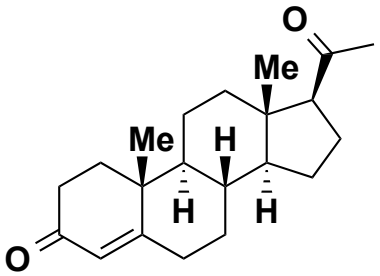
Bois-Choussy, M.; Cristau, P.; Zhu, J. *Angew. Chem. Int. Ed*. **2003**, *42*, 4238-4241.

Total Synthesis: Impact Science and Society



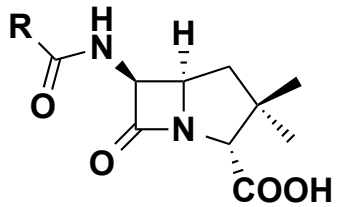
Quinine

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



Progesterone

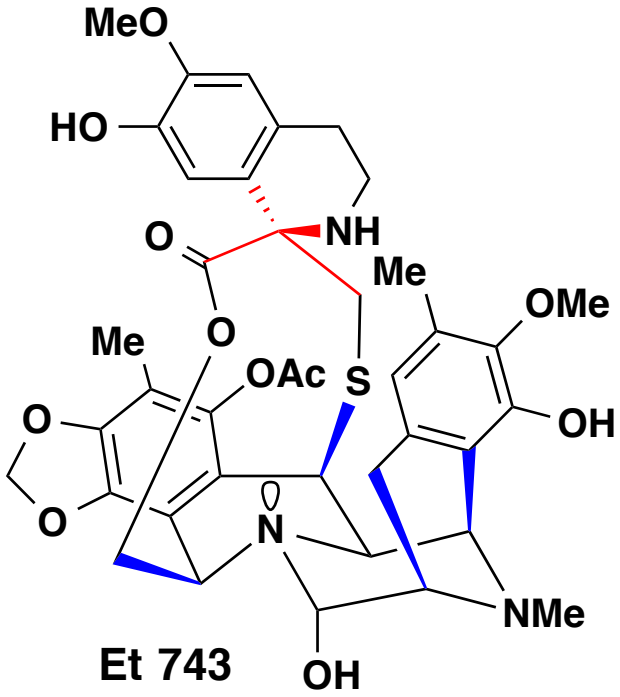
From 1930's onward
Conformational analysis
Synthetic strategies
Drug: Birth control pill



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**

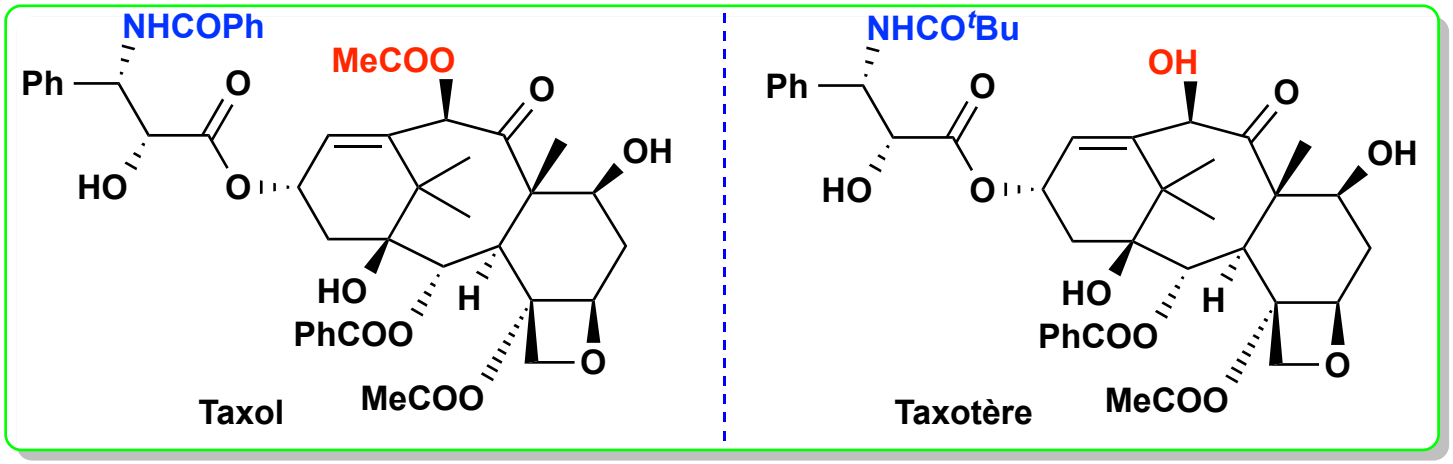
Isolation yield: 10^{-5}%

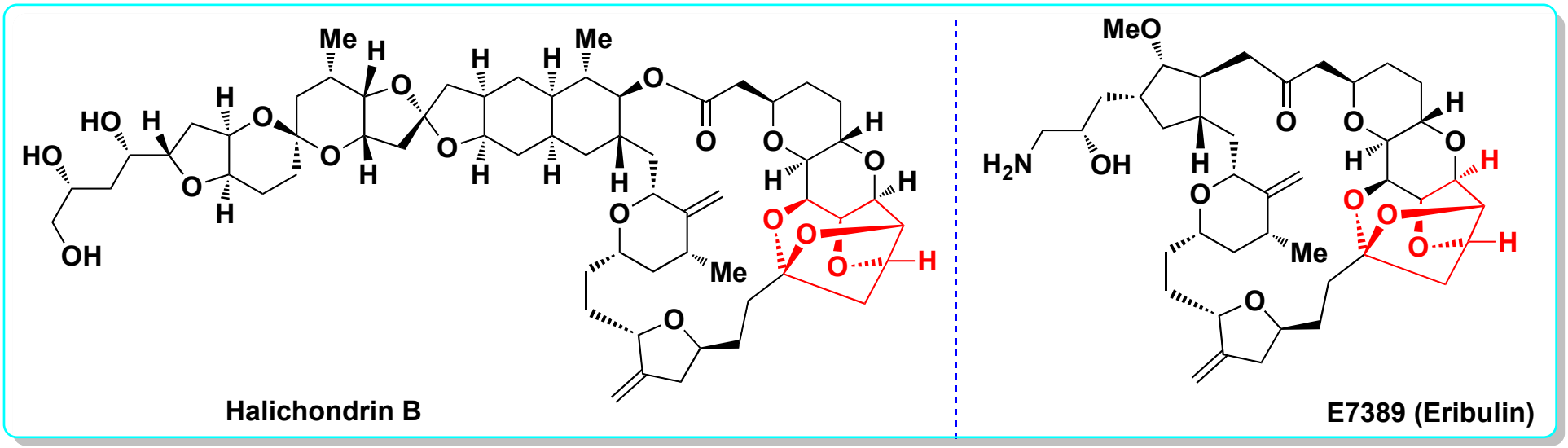
Acquaculture: feasible but too expensive

SYNTHESIS is the only solution

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

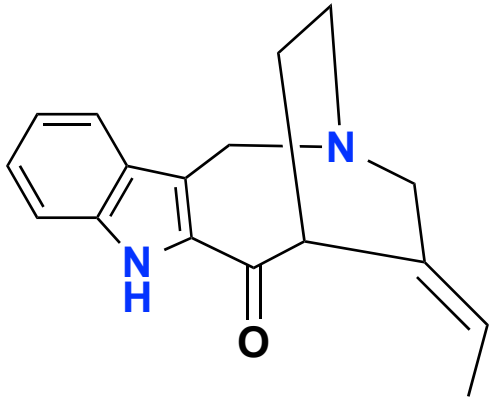
Total Synthesis: Developing (Creating) New Natural Product-Based Drugs





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

A recent example



Conolidine

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

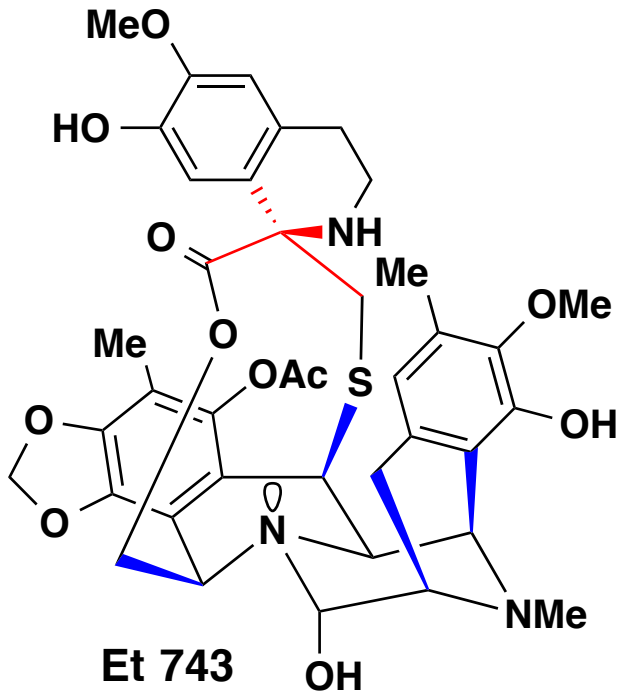
Total Synthesis: A superb learning and creating process

"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:

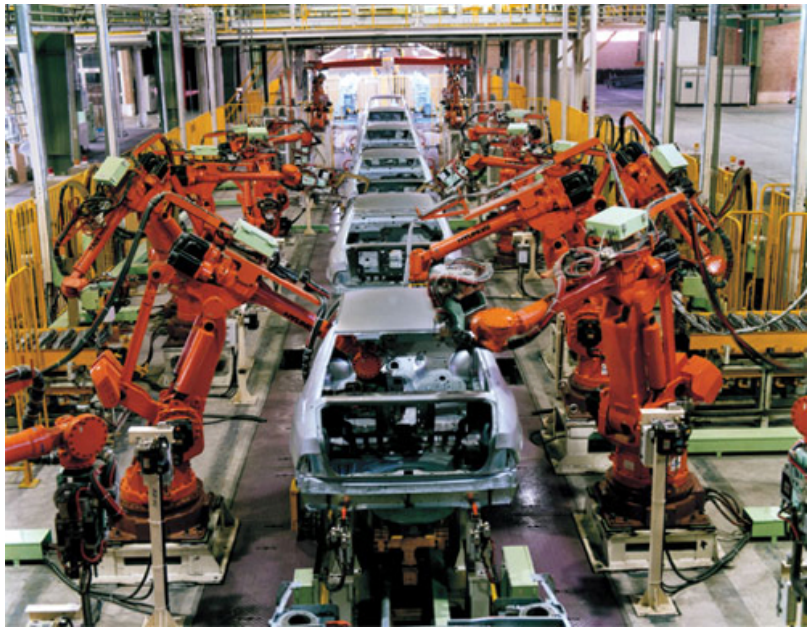
Science Behind Art
or
Art Behind Science



Et 743

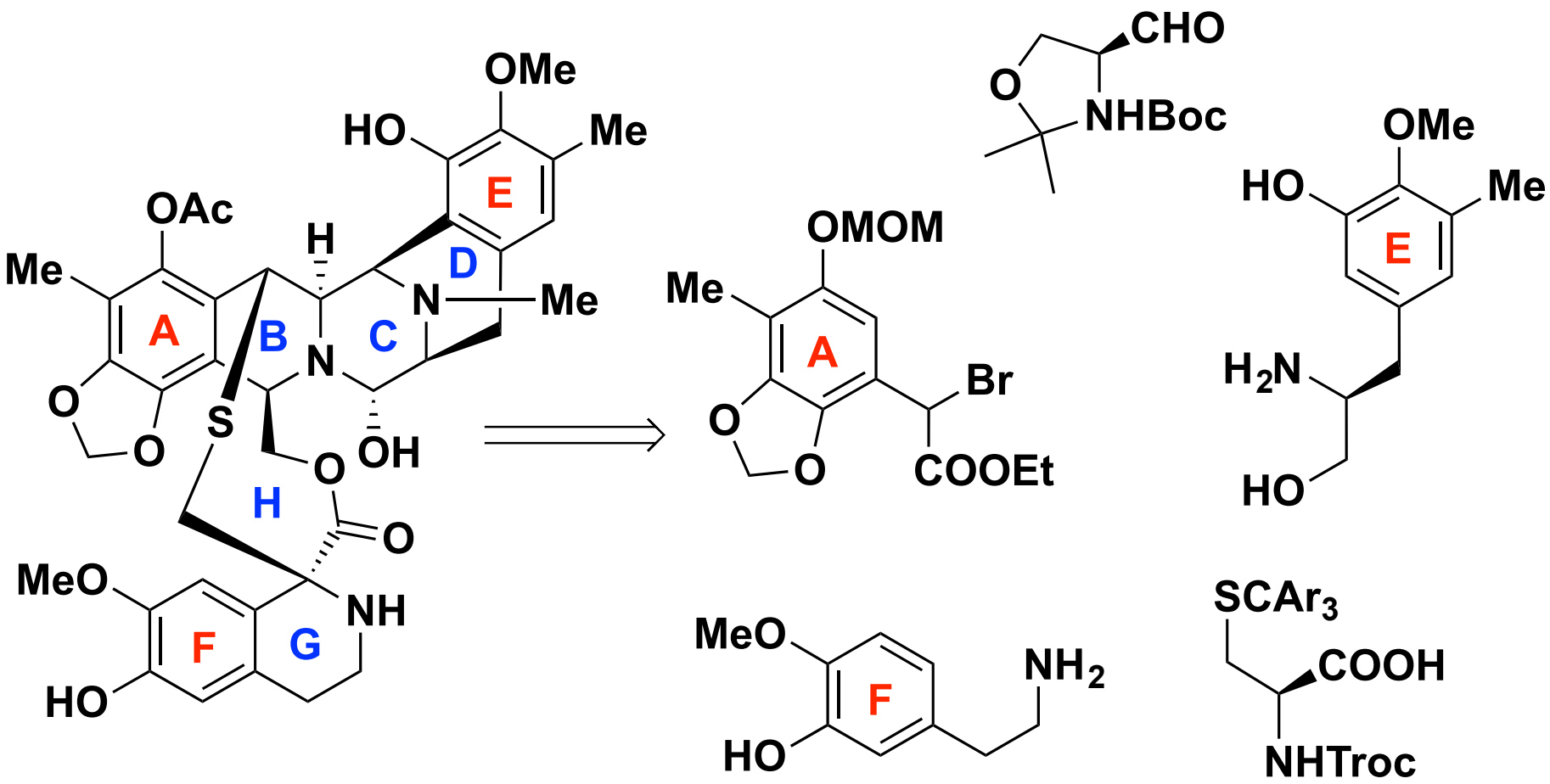
Yes, but the truth is $\Longrightarrow$

Total Synthesis: How



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

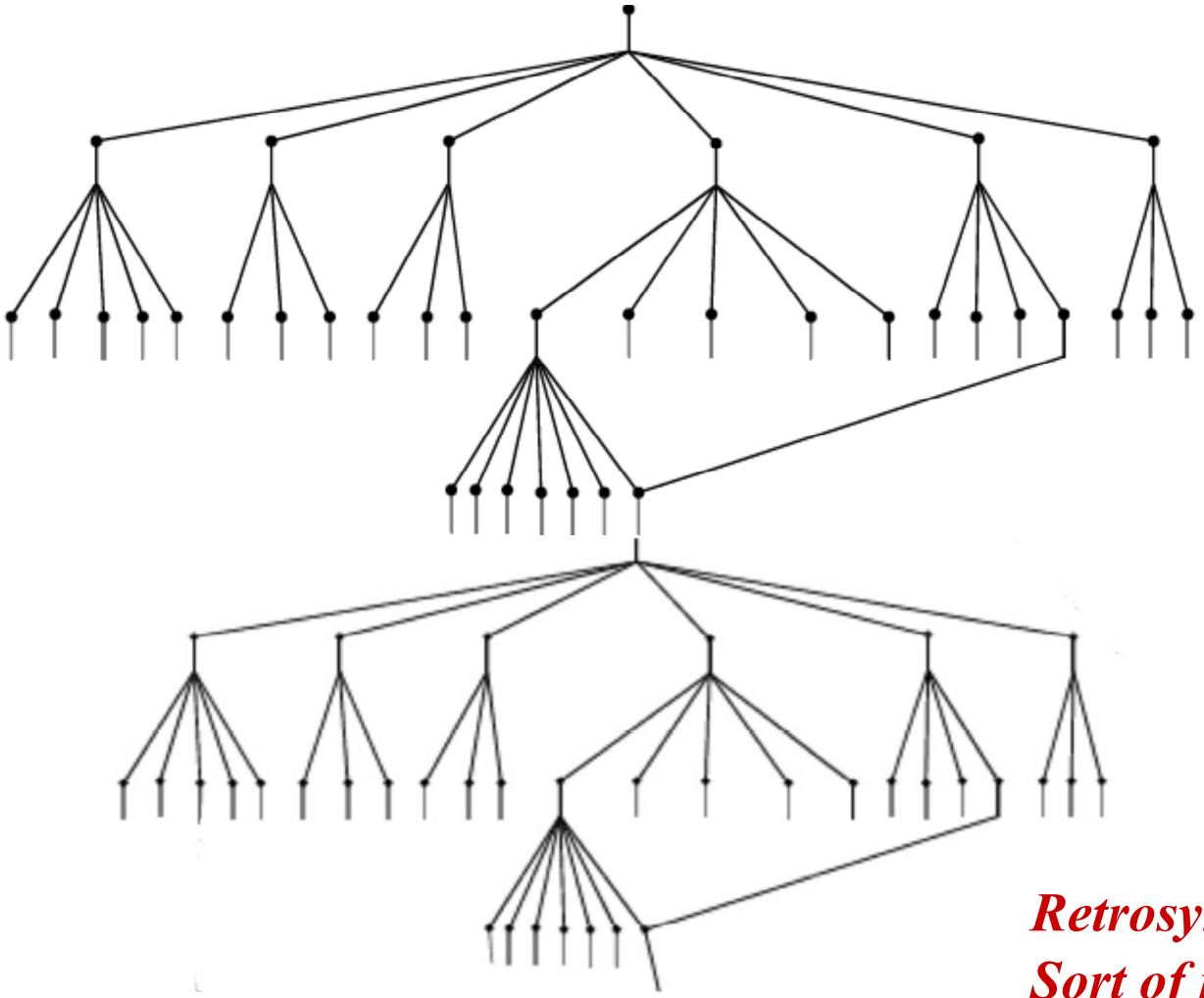
Total Synthesis: How



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

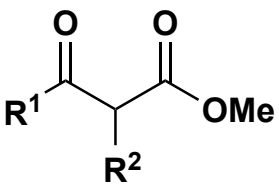
Logic of Total Synthesis—Retro Synthetic Analysis

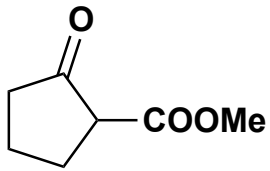
Reducing the molecular complexity by disconnecting the Chemical bond(s)

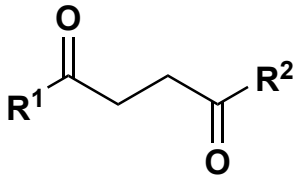


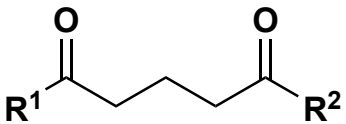
Retrosynthesis:
Sort of pattern recognition

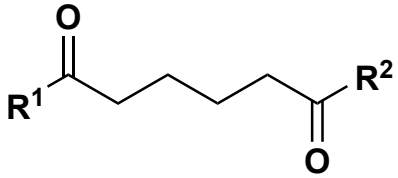
Basic Structure Motifs: Simple exemples

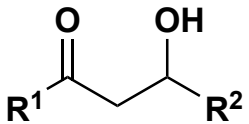


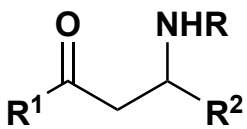


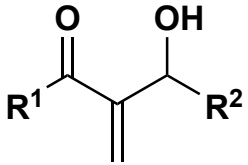


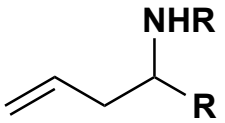


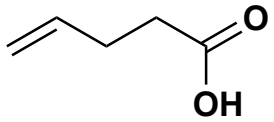


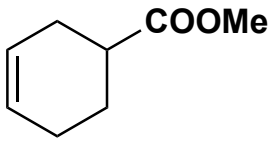


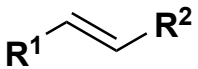


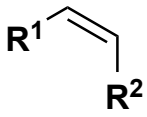


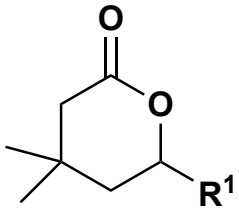


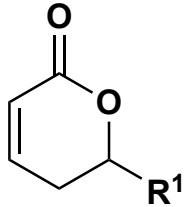


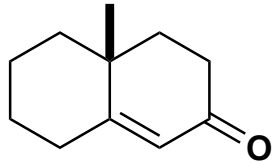


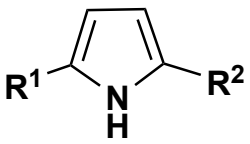


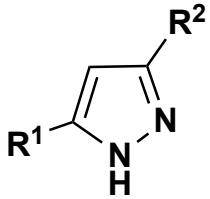


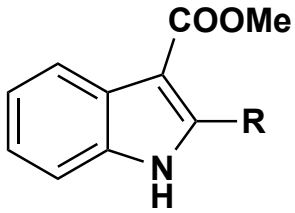


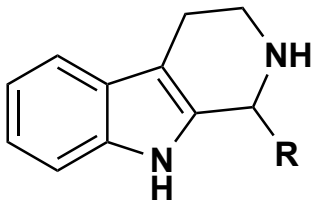


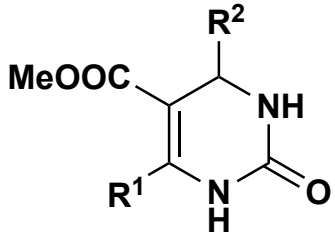


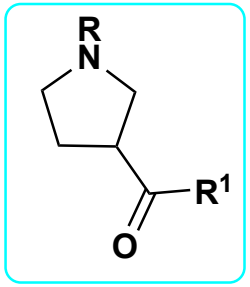






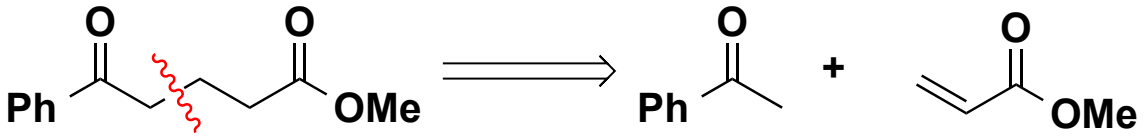


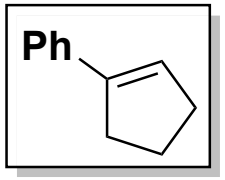




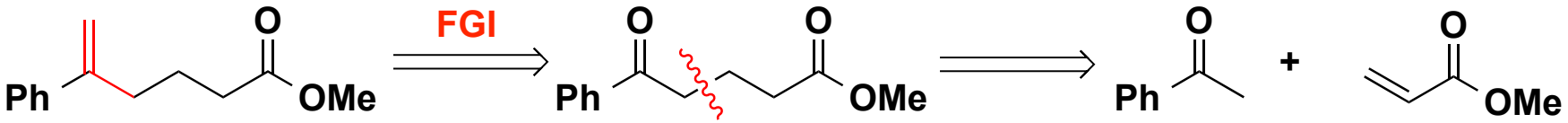
Retro-Synthetic Analysis: Approaches

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:**

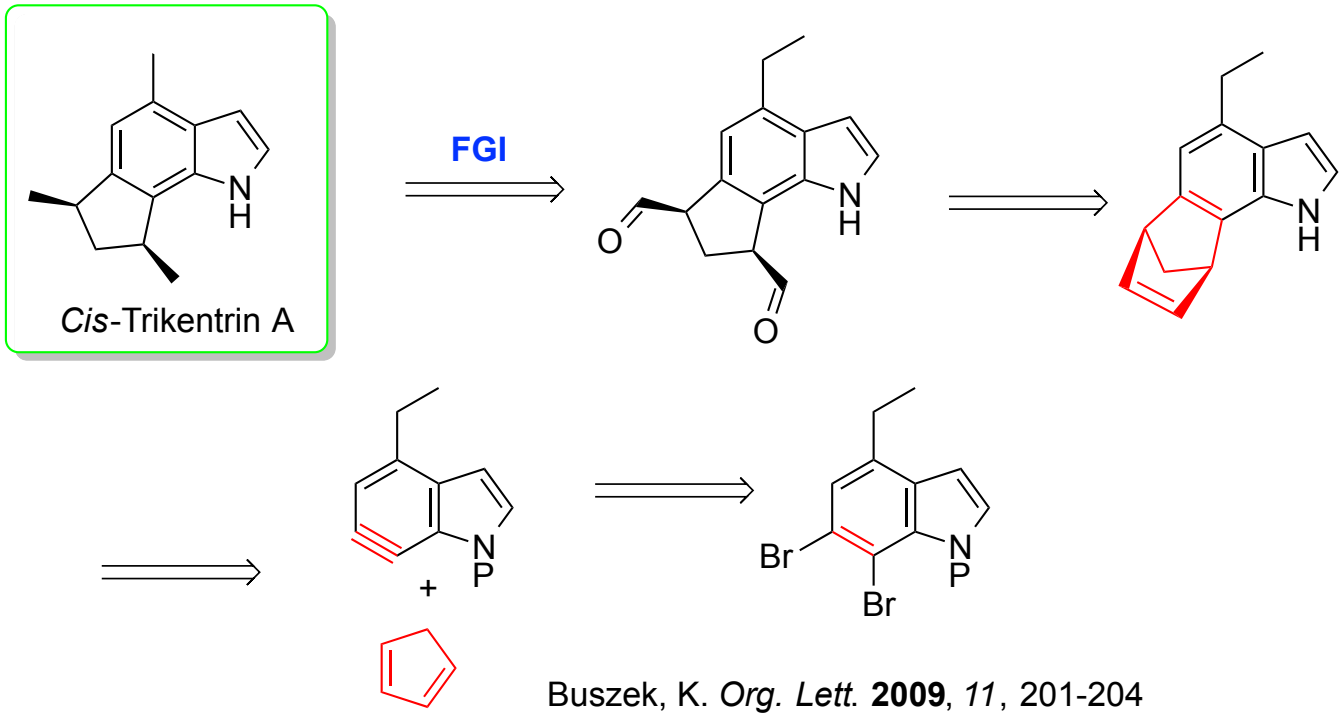


3. **Opposite to 1, increasing structure complexity includes addition of rings, functional groups (FGA), or stereocenters etc (Pattern recognition).**

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

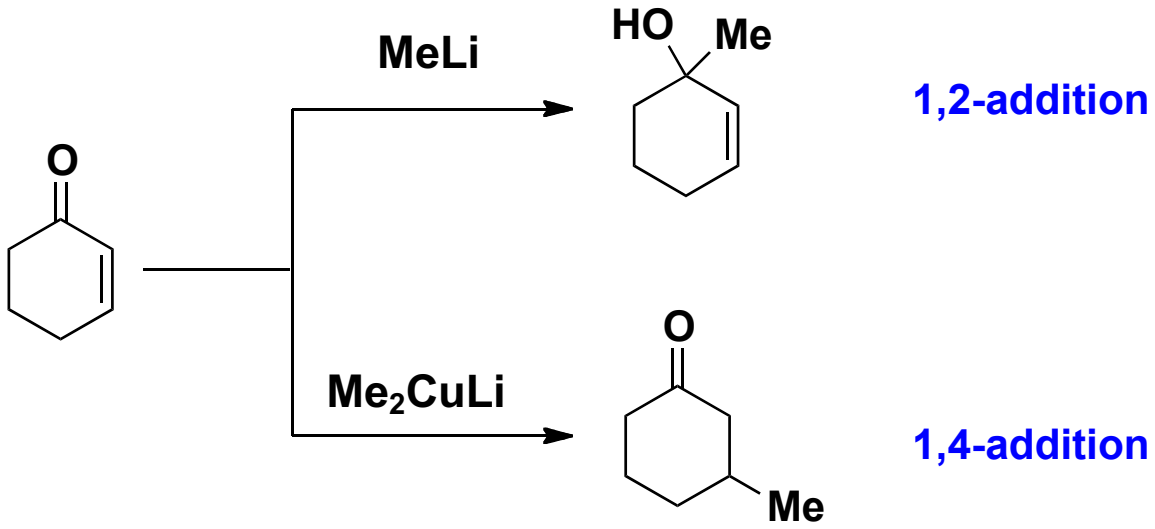
Hendrickson's definition of ideal synthesis : " ...creates a complex molecule...in a sequence of only construction reactions involving no intermediary refunctionalizations, and leading directly to the target, not only its skeleton but also its correctly placed functionality."
Hendrickson, J. B. *J. Am.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

Total synthesis: Be short, selective and high yielding

Chemo-, Regio-, and Stereo-selectivity

Chemo-selectivity

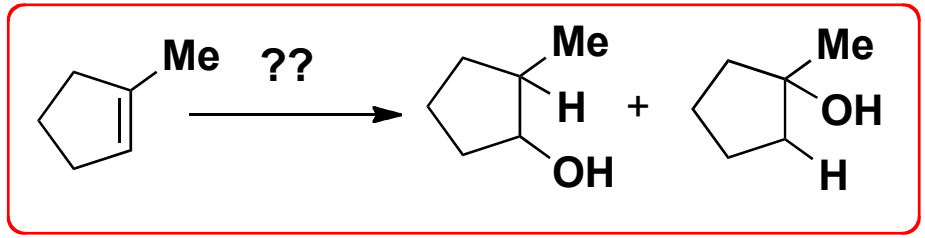
The preferential reaction of a given reagent with one of two or more functional groups



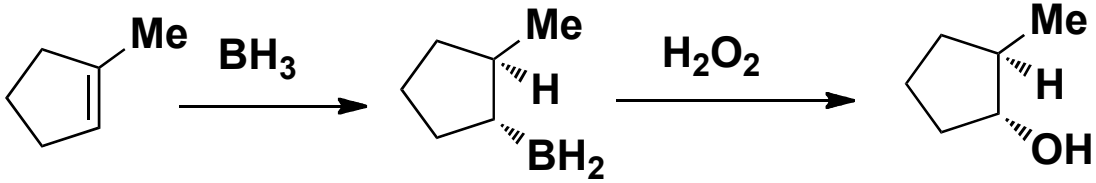
Chemo-, Regio-, and Stereo-selectivity

Regioselectivity

The directional preference of breaking or making a chemical bond

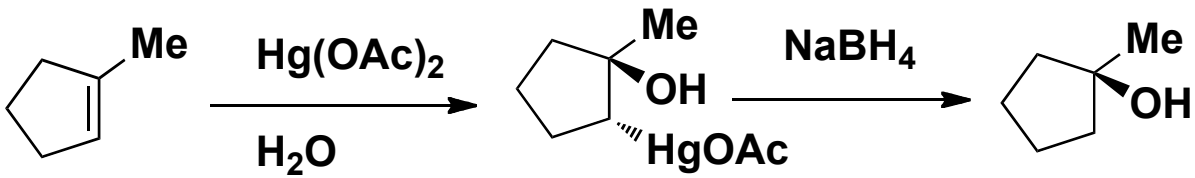


Hydroboration



Syn-addition *Retention of Stereochemistry*

Oxymercuration/Reduction

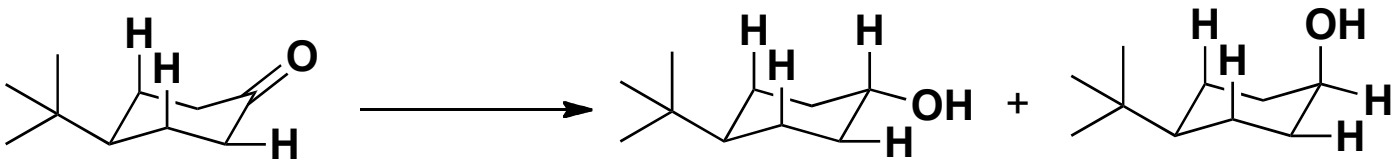


Anti-addition

Chemo-, Regio-, and Stereo-selectivity

Stereoselectivity

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

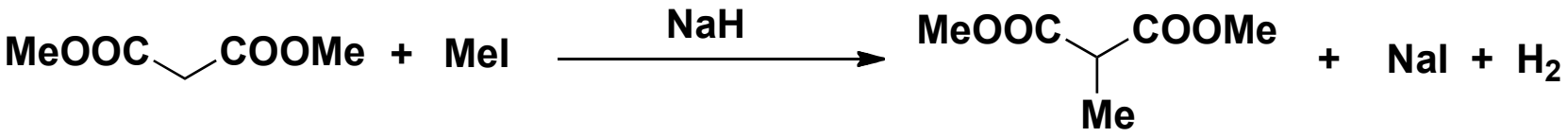


LAH	90	10
LiB(*i*-Bu)$_3$H	3.5	96.5

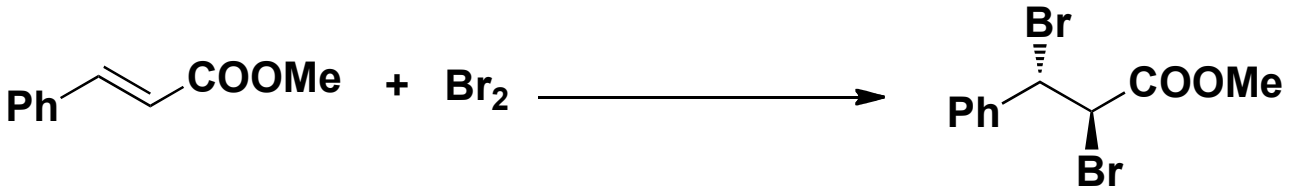
Atom-Economy

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

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

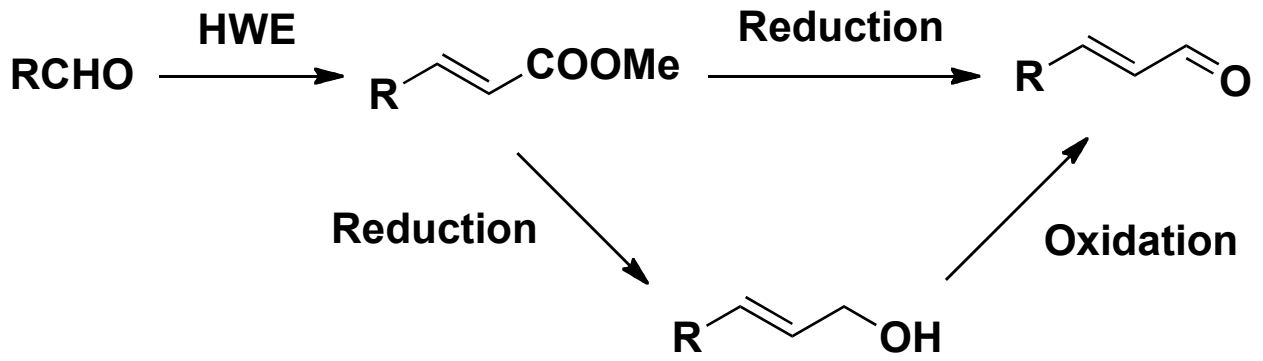
Redox-Economy

* 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

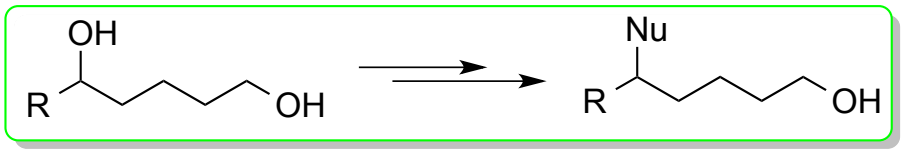
A sequence of low redox-economy (nevertheless "synthetically efficient")



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**



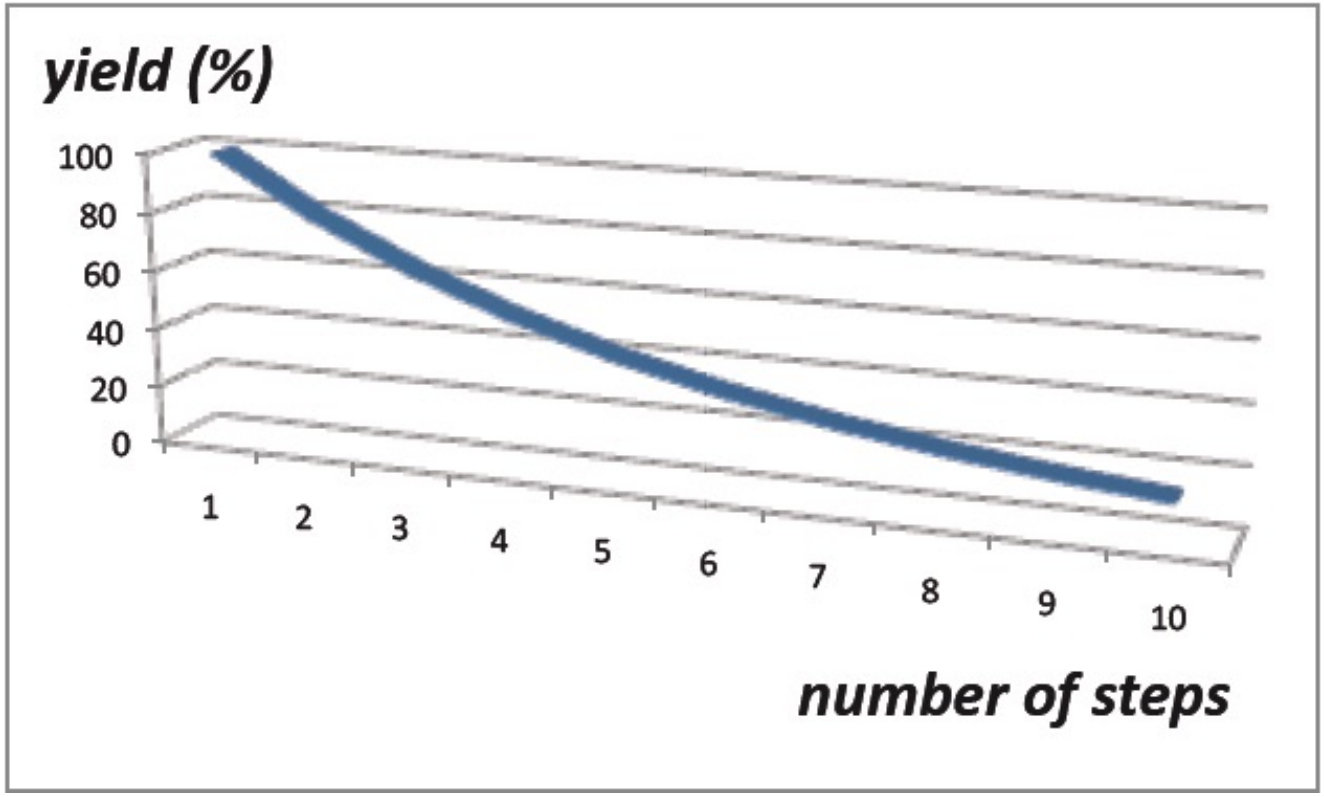
***However using PGs in a synthesis*:**

- **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)

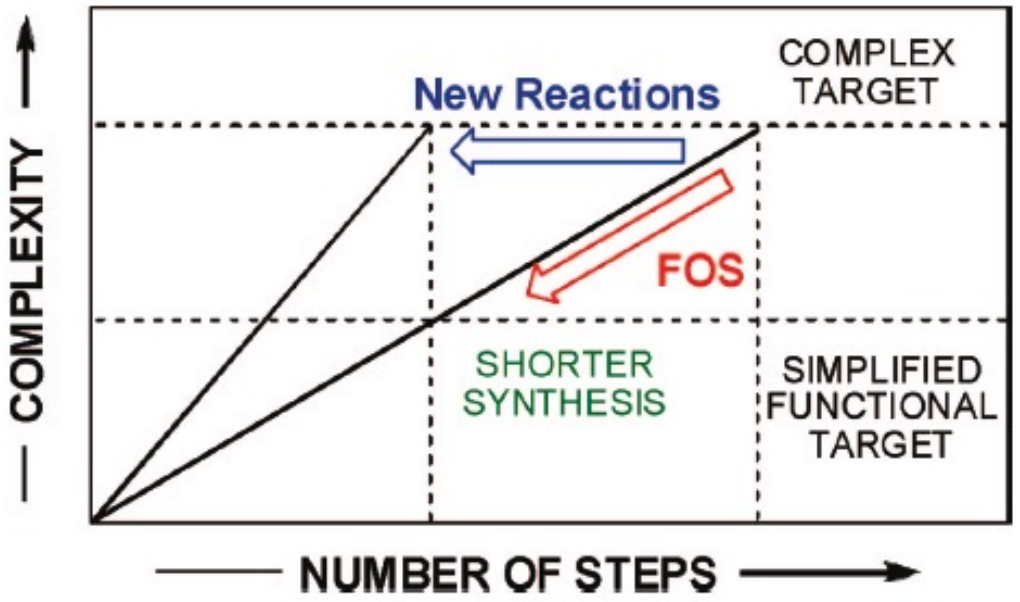
Young, I. S.; Baran, P. S. *Nature Chem*. **2009**, *1*, 193-205.

Convergency, Divergency, Overall Yield



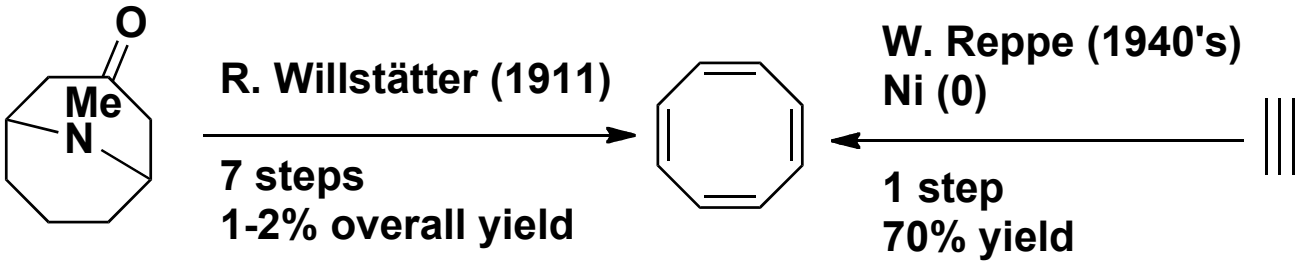
Assuming each step proceeds in 80% yield, one will Lose abut 90% of his materials after a 10-step synthesis

Step-Economy



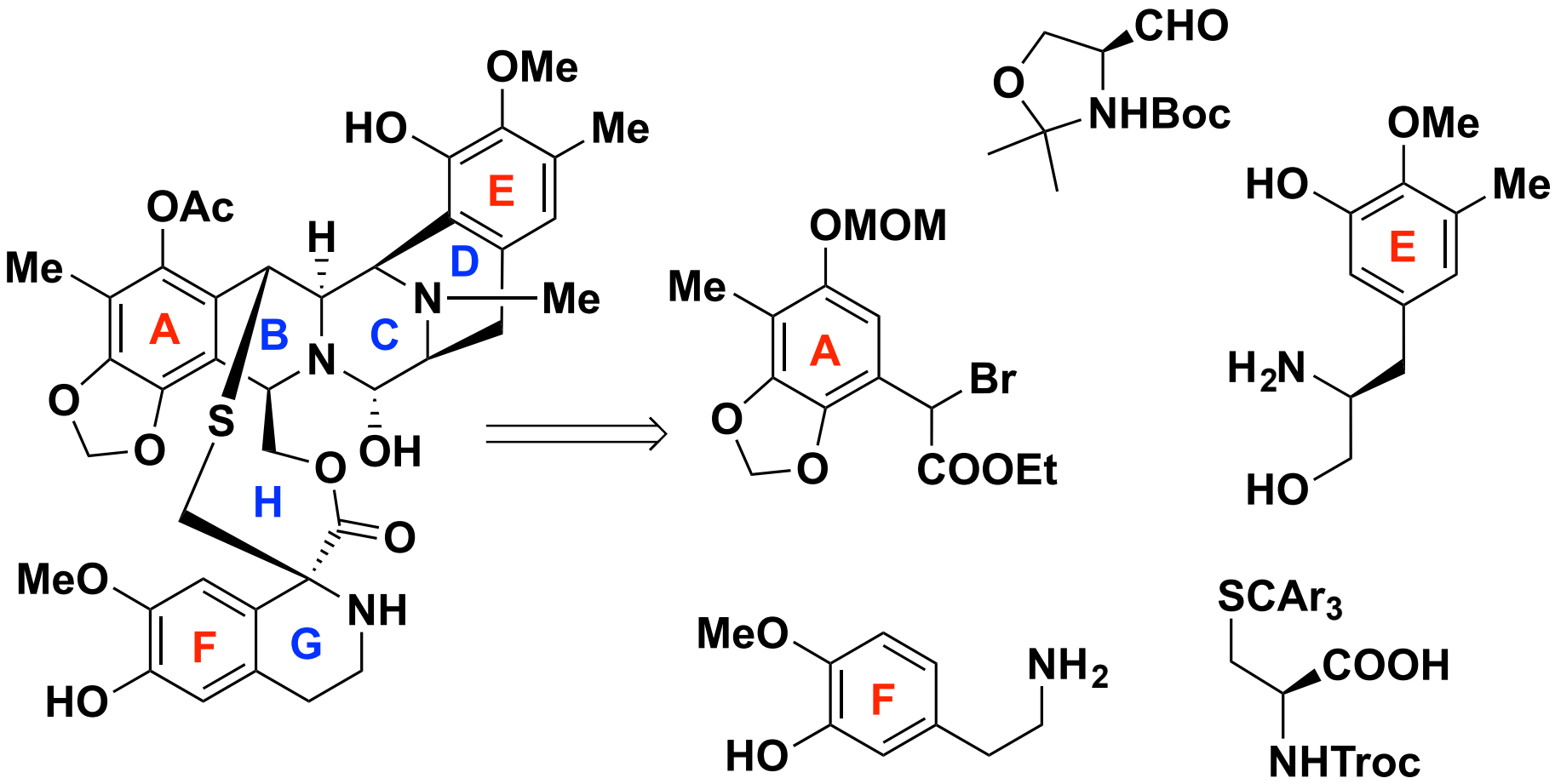
Increasing Time, Cost efficiency; Reducing Waste production

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 synthetic 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.

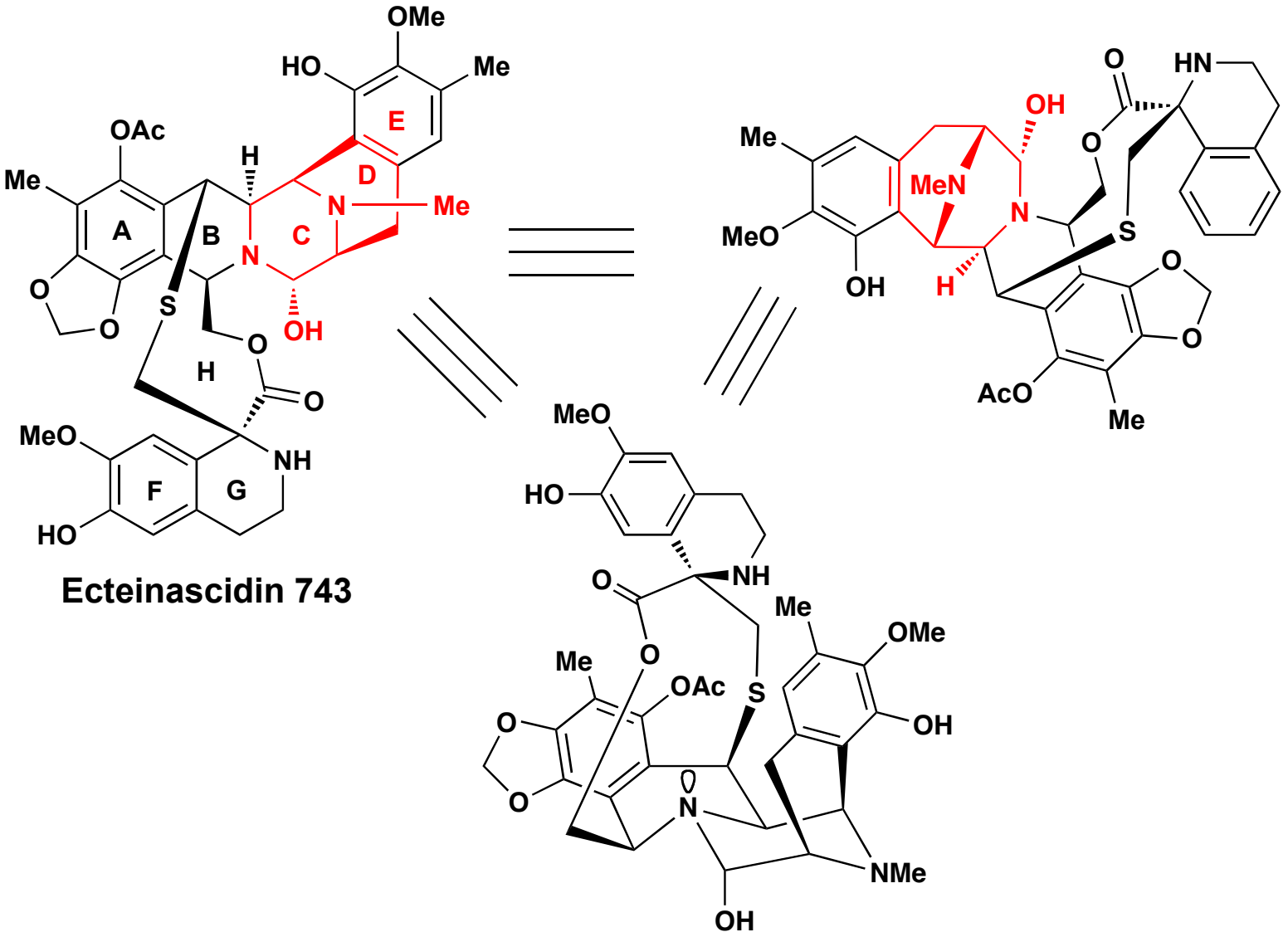
"To study without thinking is futile, To think without studying is dangerous"

---Confucius

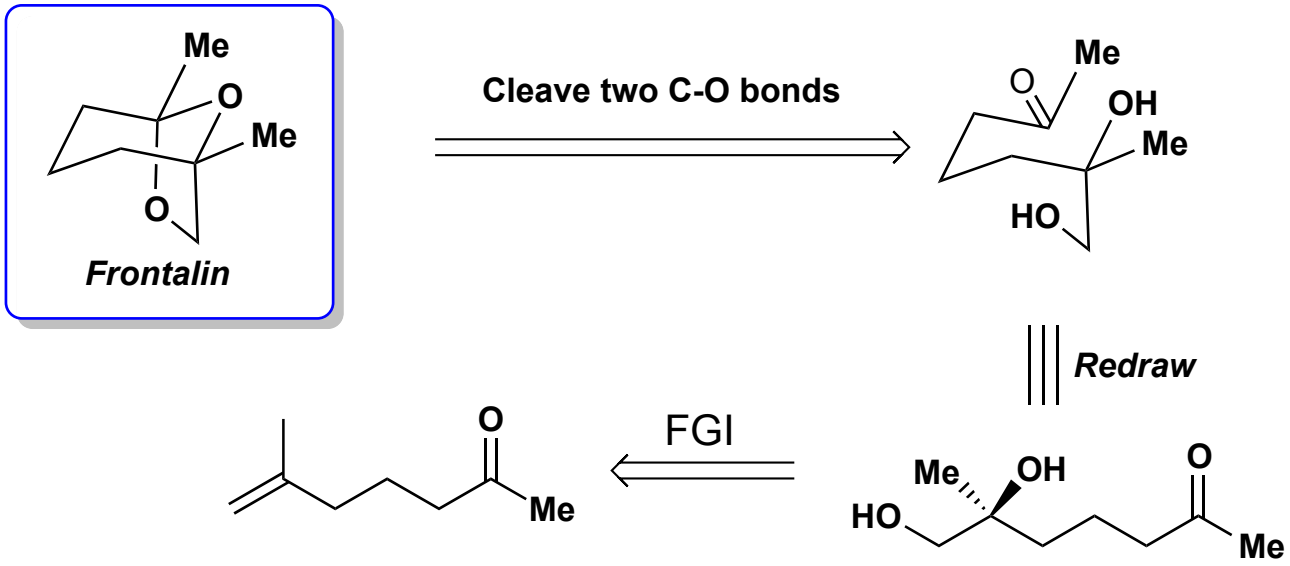
"If you want to be creative, then you will have to get used to spending most of your time not being creative, to being becalmed on the ocean of scientific knowledge"

---Steven Weinberg

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

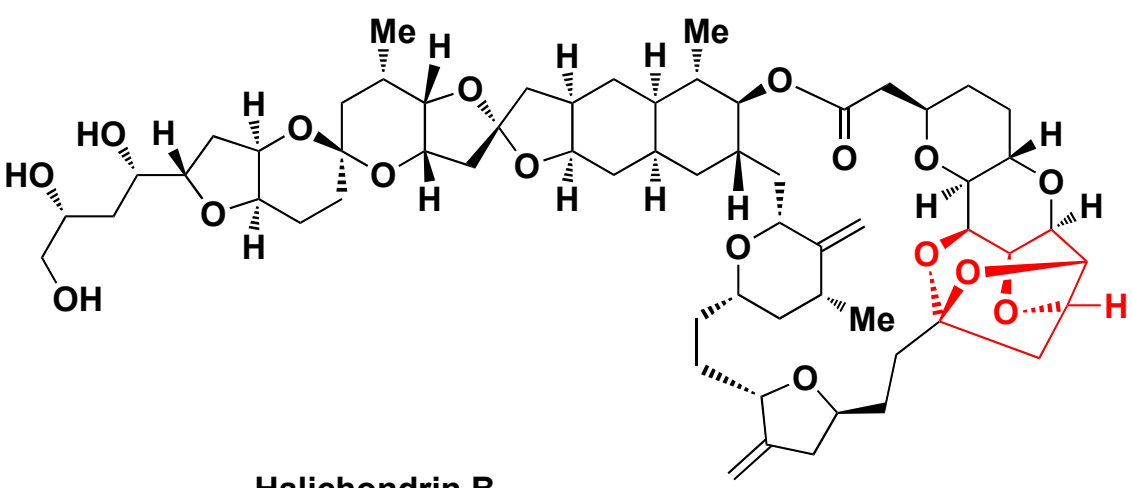


Cleave the easy-forming bond to simplify the target

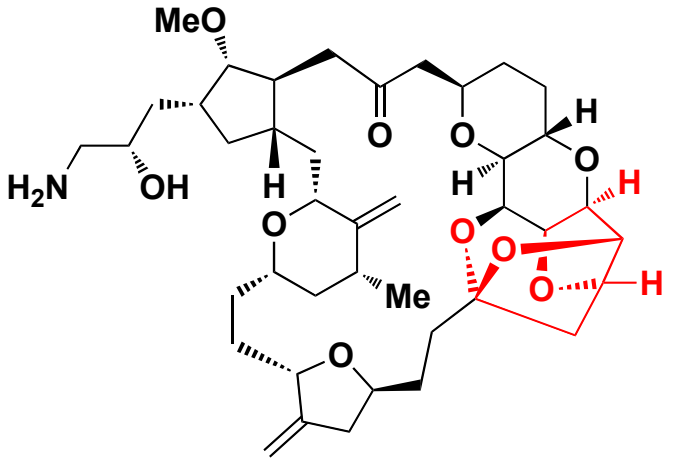


J. A. Turpin; L. O. Weige; *Tetrahedron Lett.* **1992**, *33,* 6563.

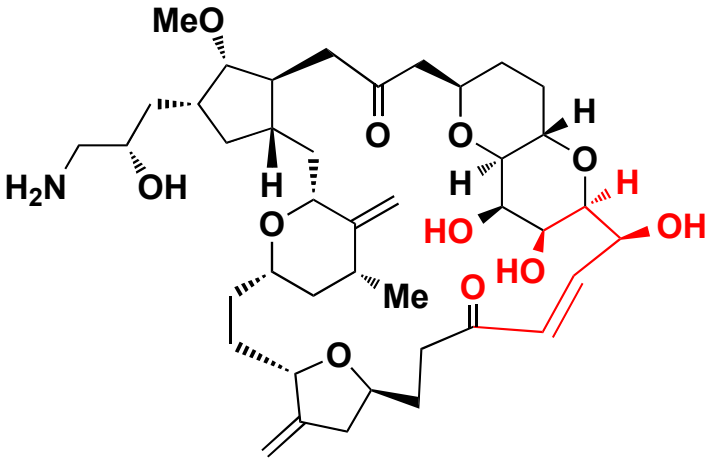
Cleave the easy-forming bond to simplify the target

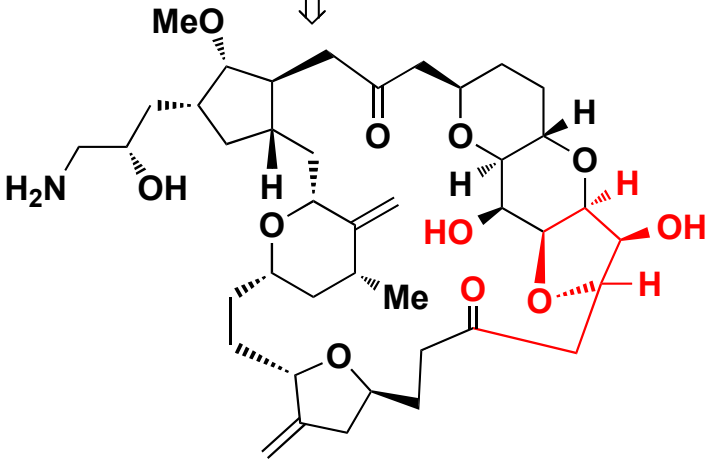


Halichondrin B



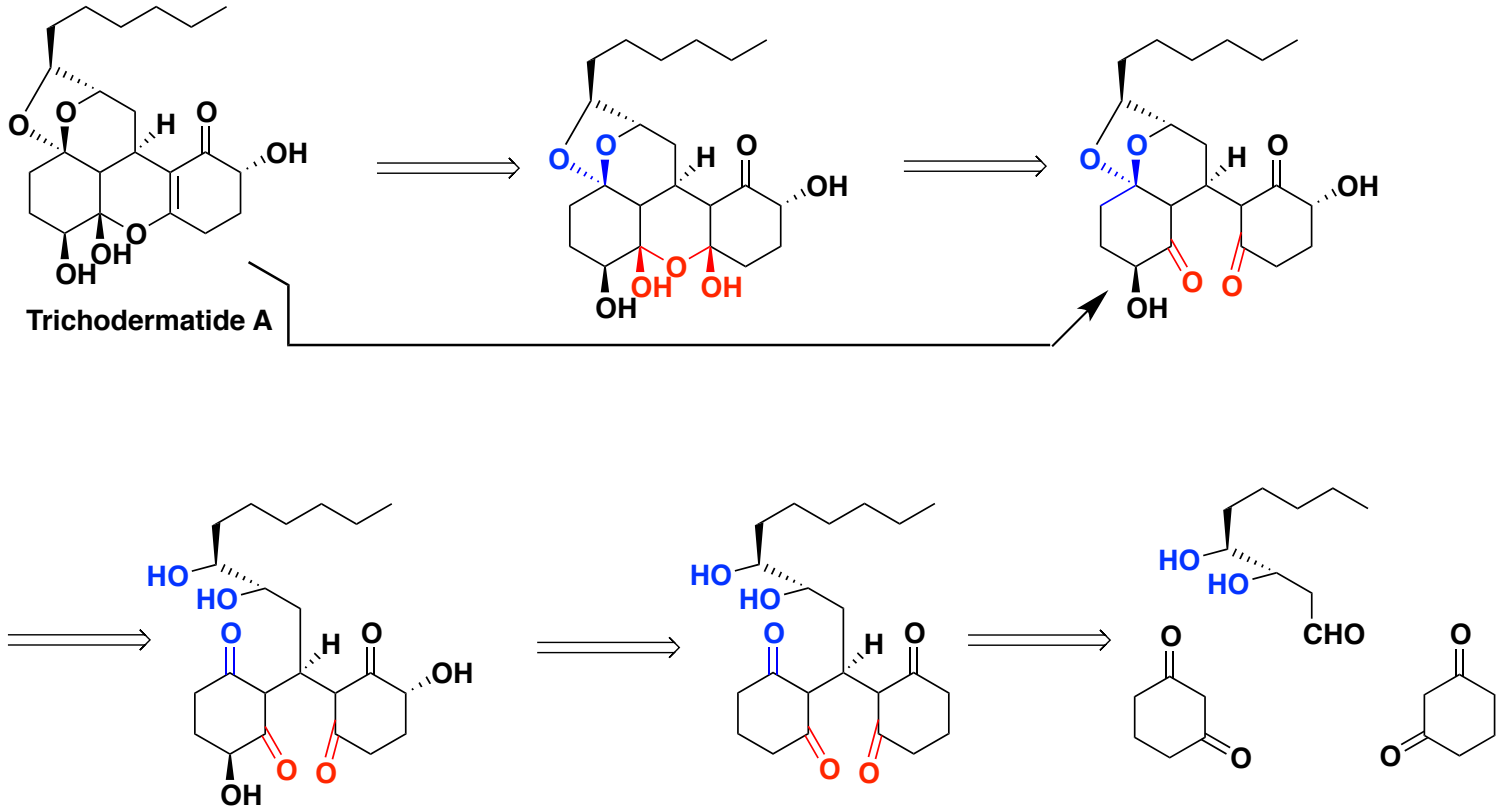
E7389 (Eribulin)





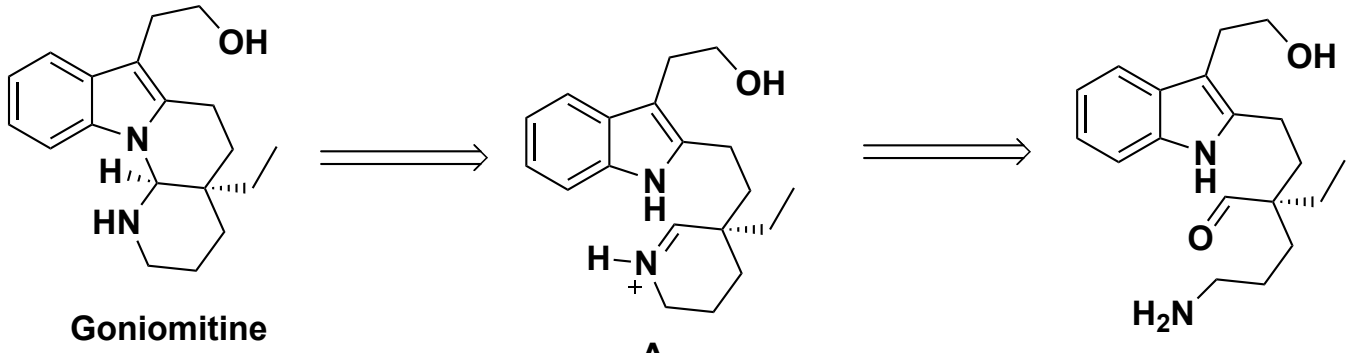
D.-S. Kim, C.-G. Dong, J. T. Kim, H. Guo, J. Huang, P. S. Tiseni, Y. Kishi,
J. Am. Chem. Soc. **2009**, *131*, 15636-15641.

Cleave the Easiest Bond and Find the Hidden Symmetry



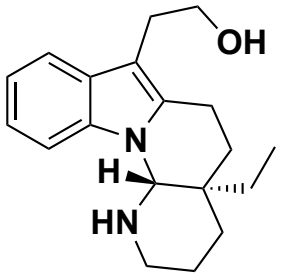
Hiroya, K. *Angew. Chem. Int. Ed.* 2013. 52, 3646-3649.

Identifiy the Thermodynamic Sink: Favorable Case



Goniomitine

A



epi-Goniomitine

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

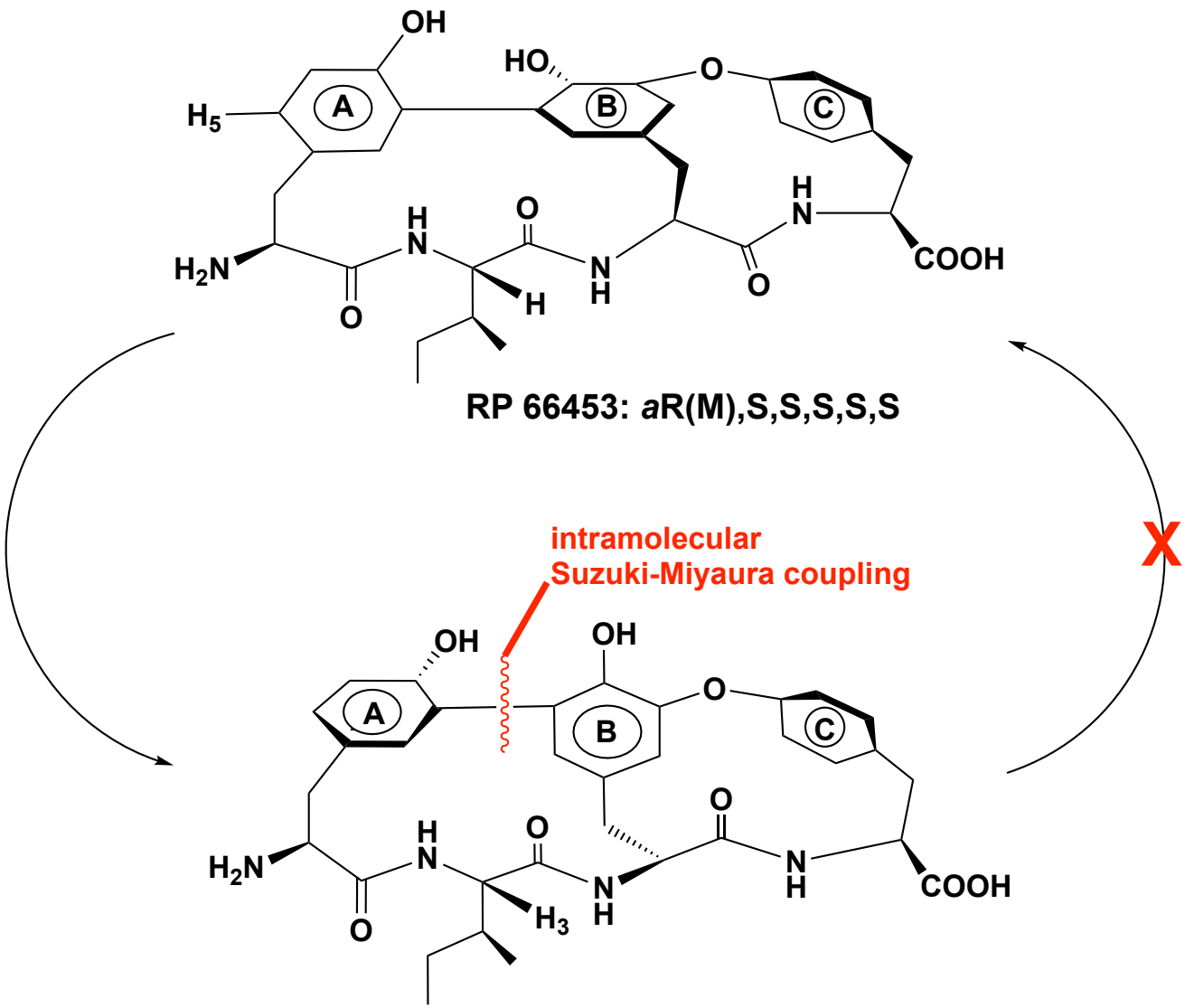
Thermodynamic selectivity: Goniomitine is thermodynamically more stable than its epimer

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



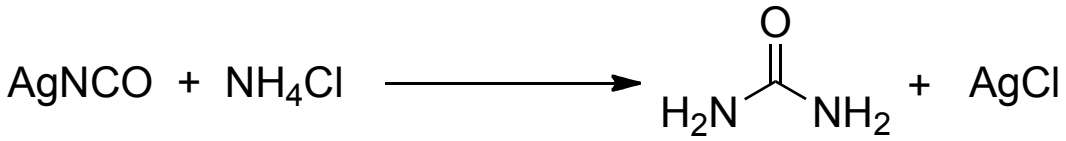
"Wrong", yet still popular terminologies

"Wrong"	"Correct"
Asymmetric synthesis	**Enantioselective synthesis** **Diastereoselective synthesis**
Chiral center	**Stereocenter**
Chiral HPLC	**Enantioselective HPLC**
Chiral column	**Enantioselective column**
Optical purity	**Enantiomeric excess**

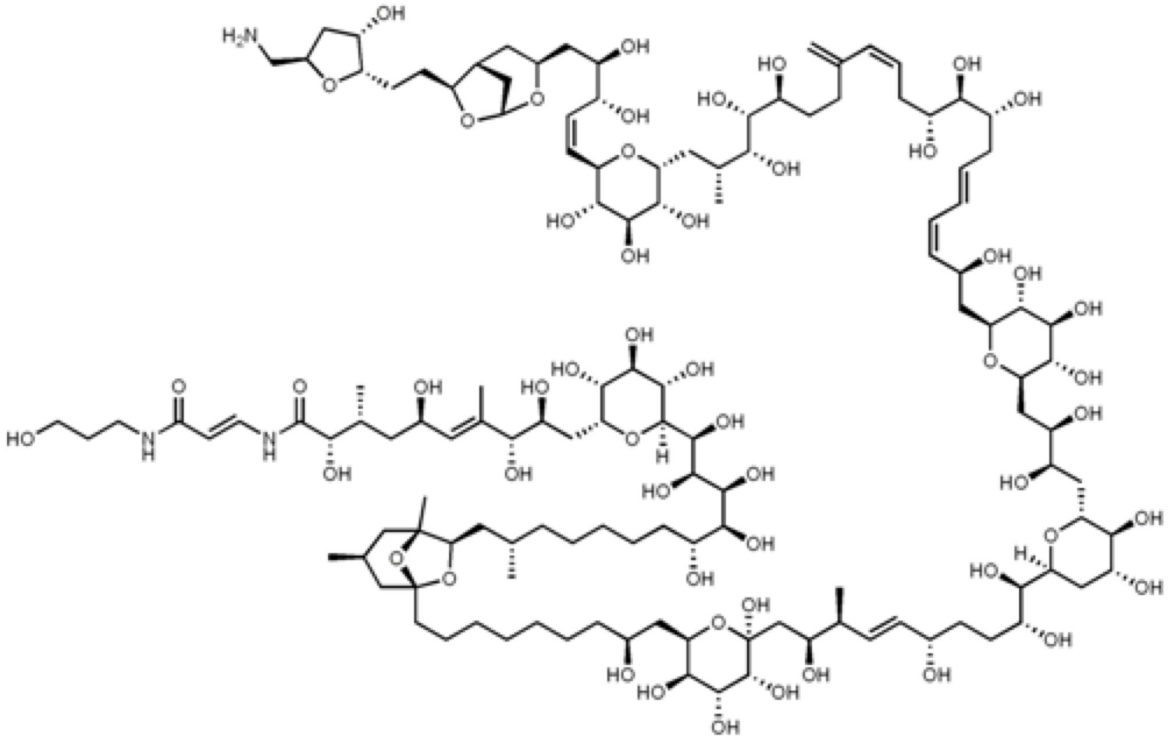
a) Mislow, K, Siegel, J. *J. Am. Chem. Soc*. **1984**,*106*, 3319-3328.
b) Eliel, E. L.: http://www.uottawa.ca/publications/interscientia/inter.4/eliel/eliel.html

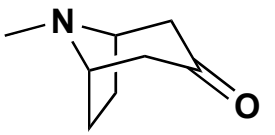
Total Synthesis: Where we stand

Urea Synthesis by Friedrich Wöhler (1828)

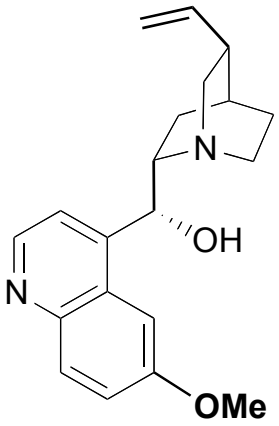


Palytoxin Synthesis by Y. Kishi (JACS, 1994, *116*, 11205)





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:

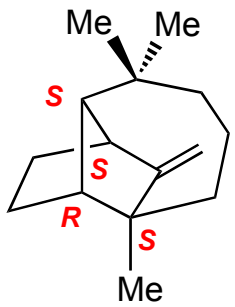
"Organic Synthesis, The Disconnection Approach"
and "Workbook for Organic Synthesis, The Disconnection Approach"
by Warren, S.; Wyatt, P., 2nd Ed. Wiley 2008

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



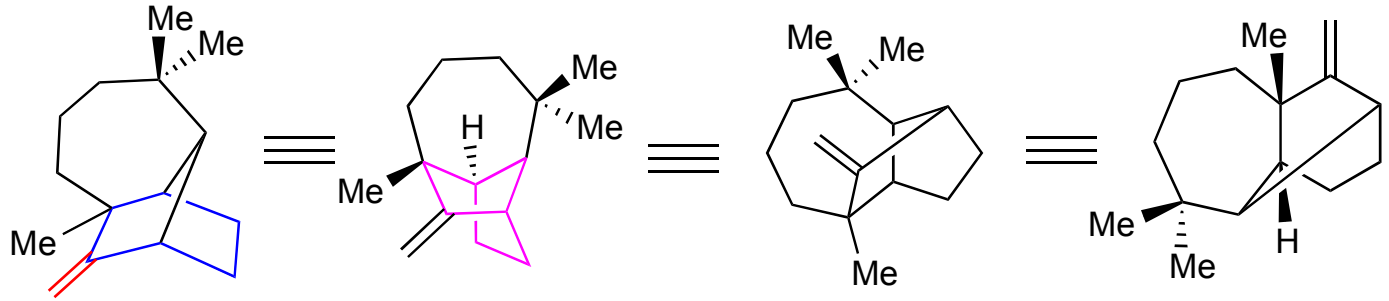
(+)-Longifolene

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



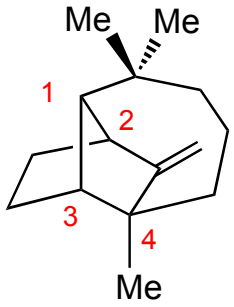
Bridged ring system is reinforced **Fused ring system is evidenced**

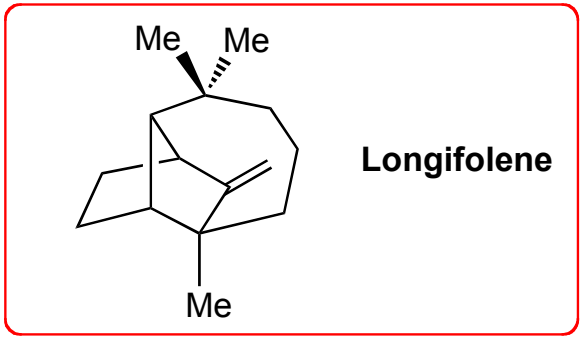
Using Molecular Models!!!

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

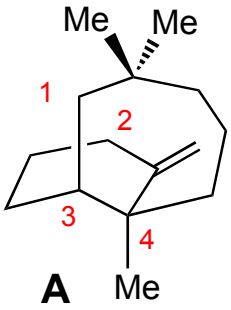
Longifolene—Corey 1961

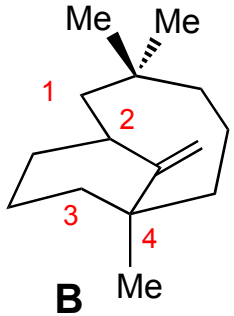
Step 1:
Number the bridge atom

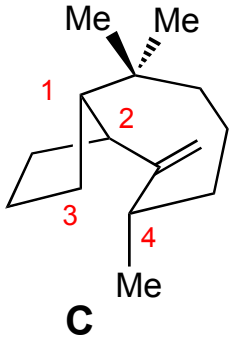




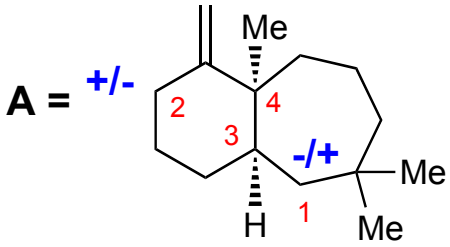
Step 2: Disconnect the chemical bond between the bridge atoms

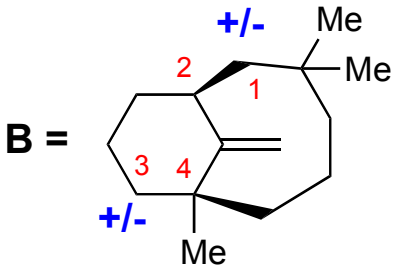


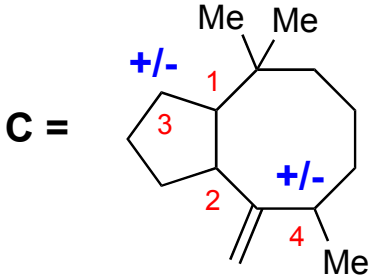




Step 3: Redraw the synthons to make them more familiar to you

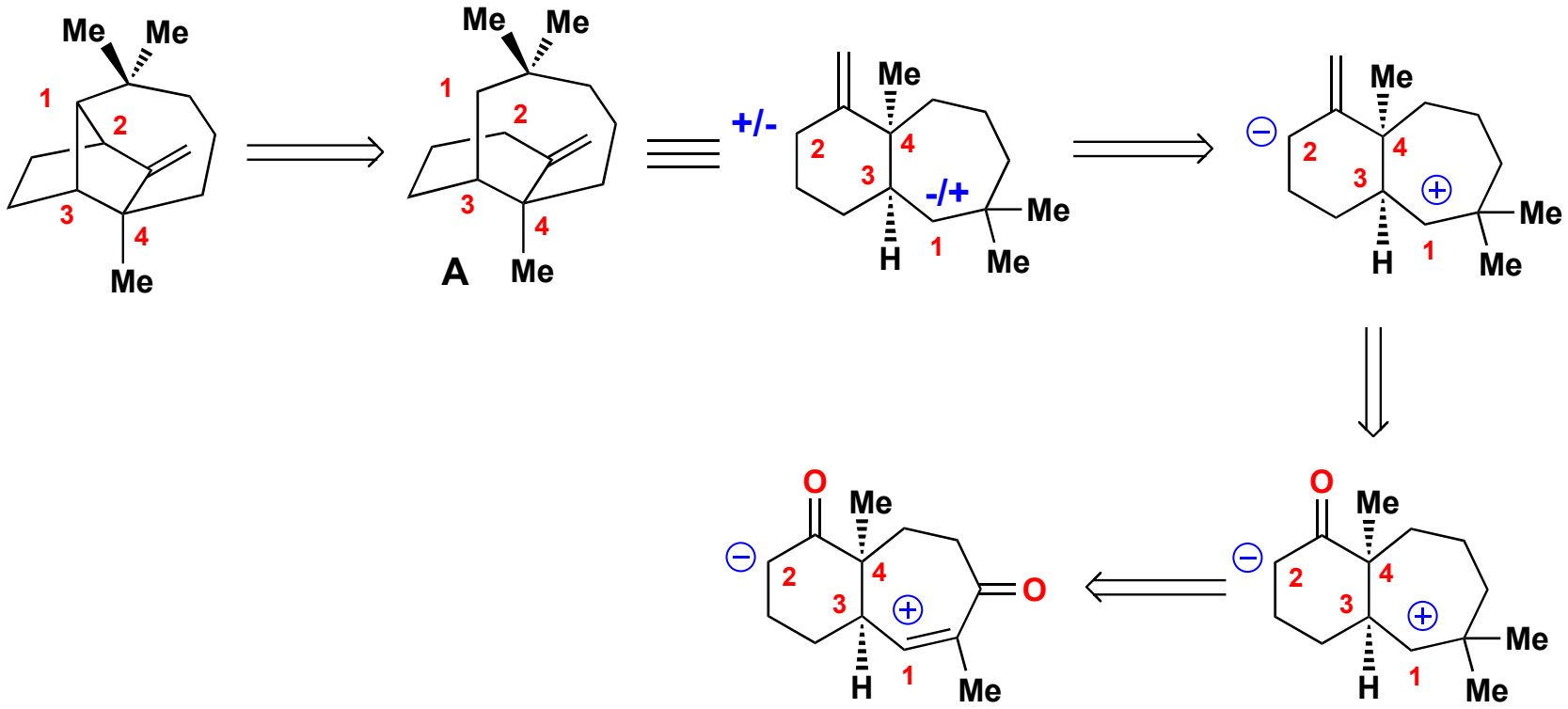




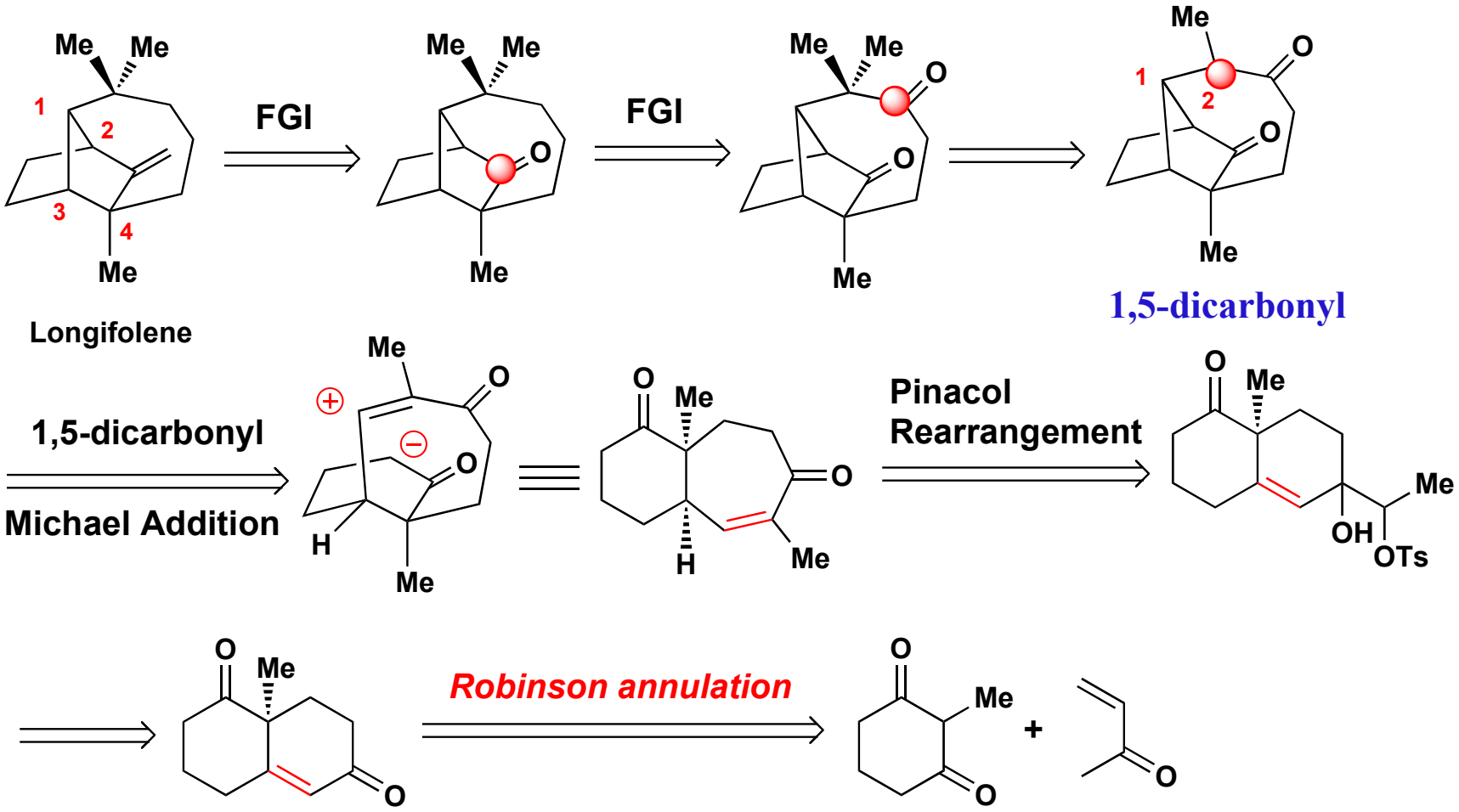


8-membered ring, acces difficult

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

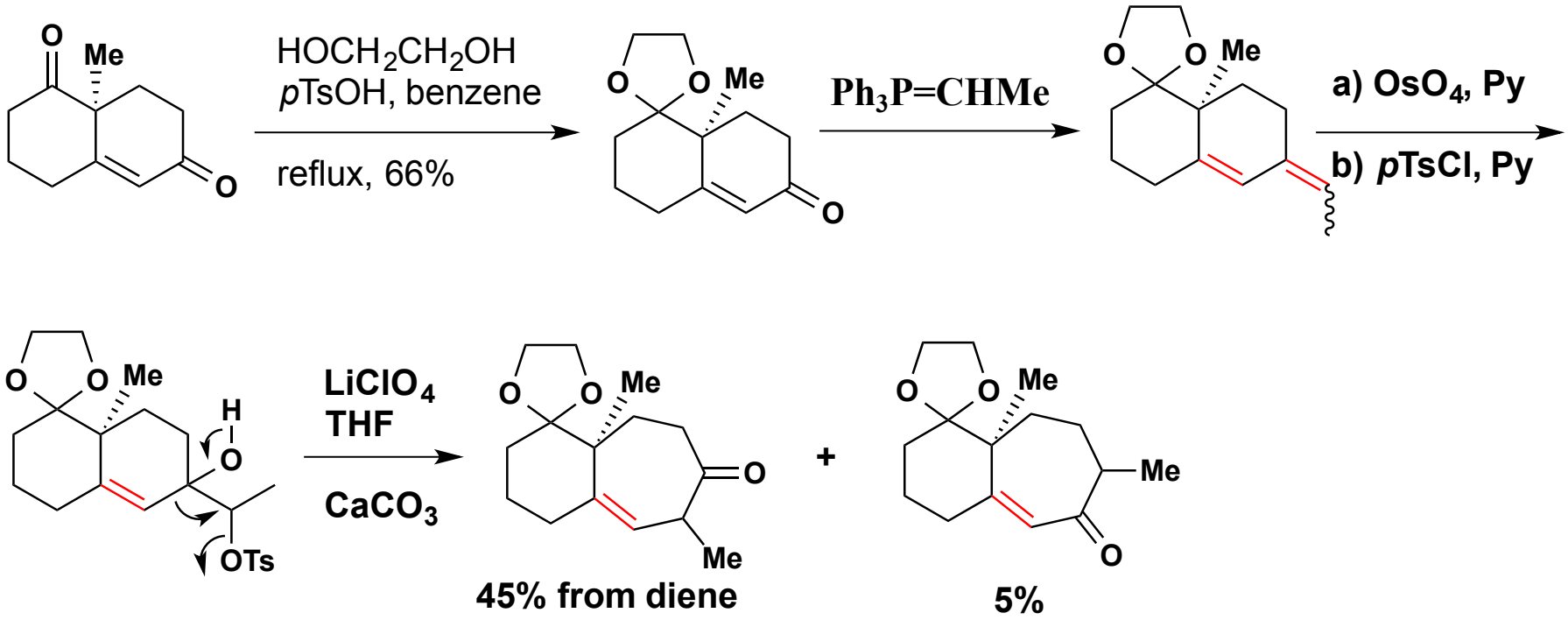
Dihydroxylation of Alkene with OsO_4

Pinacol Rearrangement: Chemo- and Regio-selectivities

Enolate Alkylation: Regioselectivity

Reactivity of Carbonyl Group

Longifolene—Corey 1961



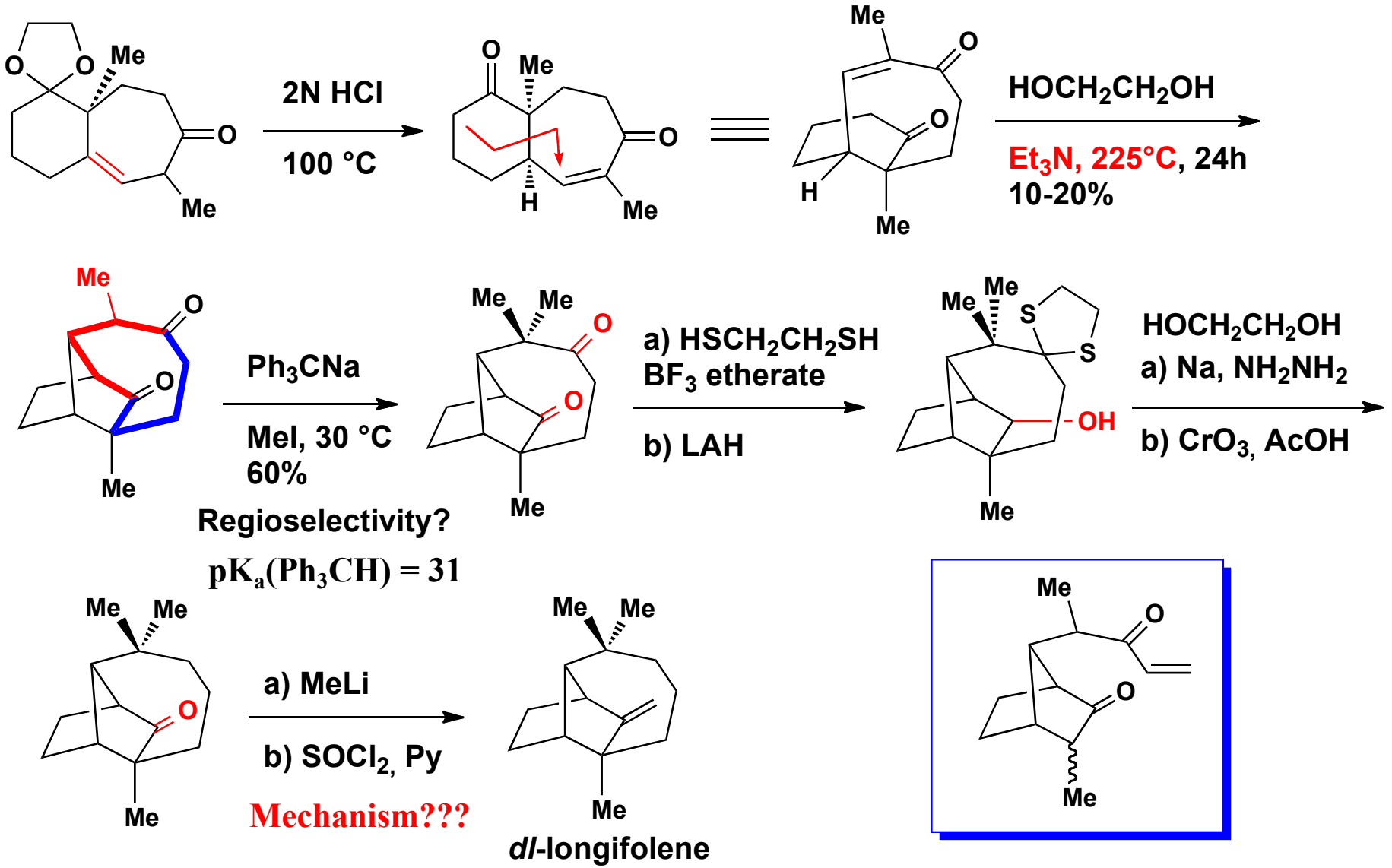
*** Regio-selective dihydroxylation of diene**

*** 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

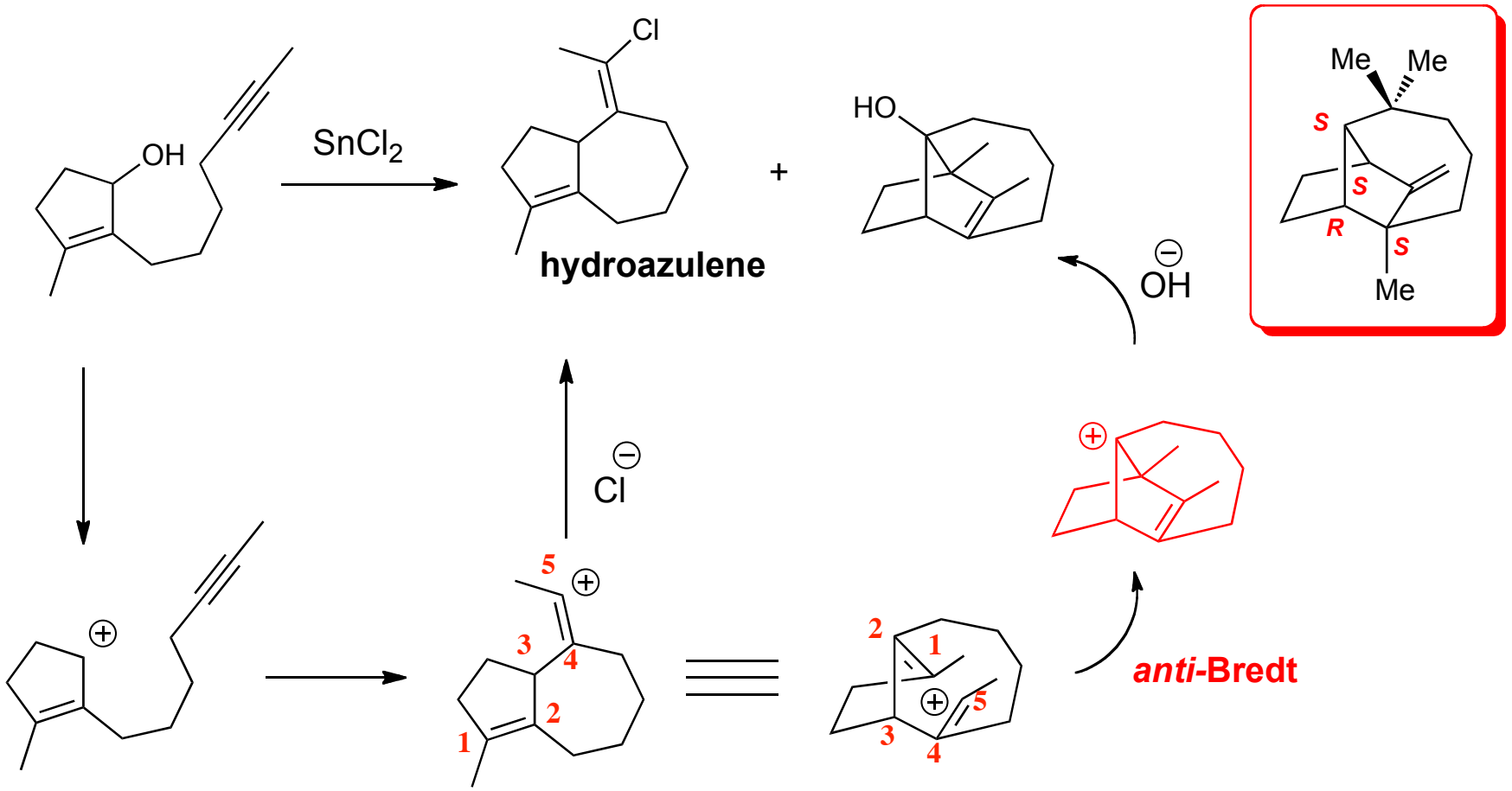
Protective group: Heavily used
Protection of Carbonyl: Acetal, thioacetal

How the 7-membered ring was synthesized?

Ring expansion via pinacol rearrangement (Strategic)

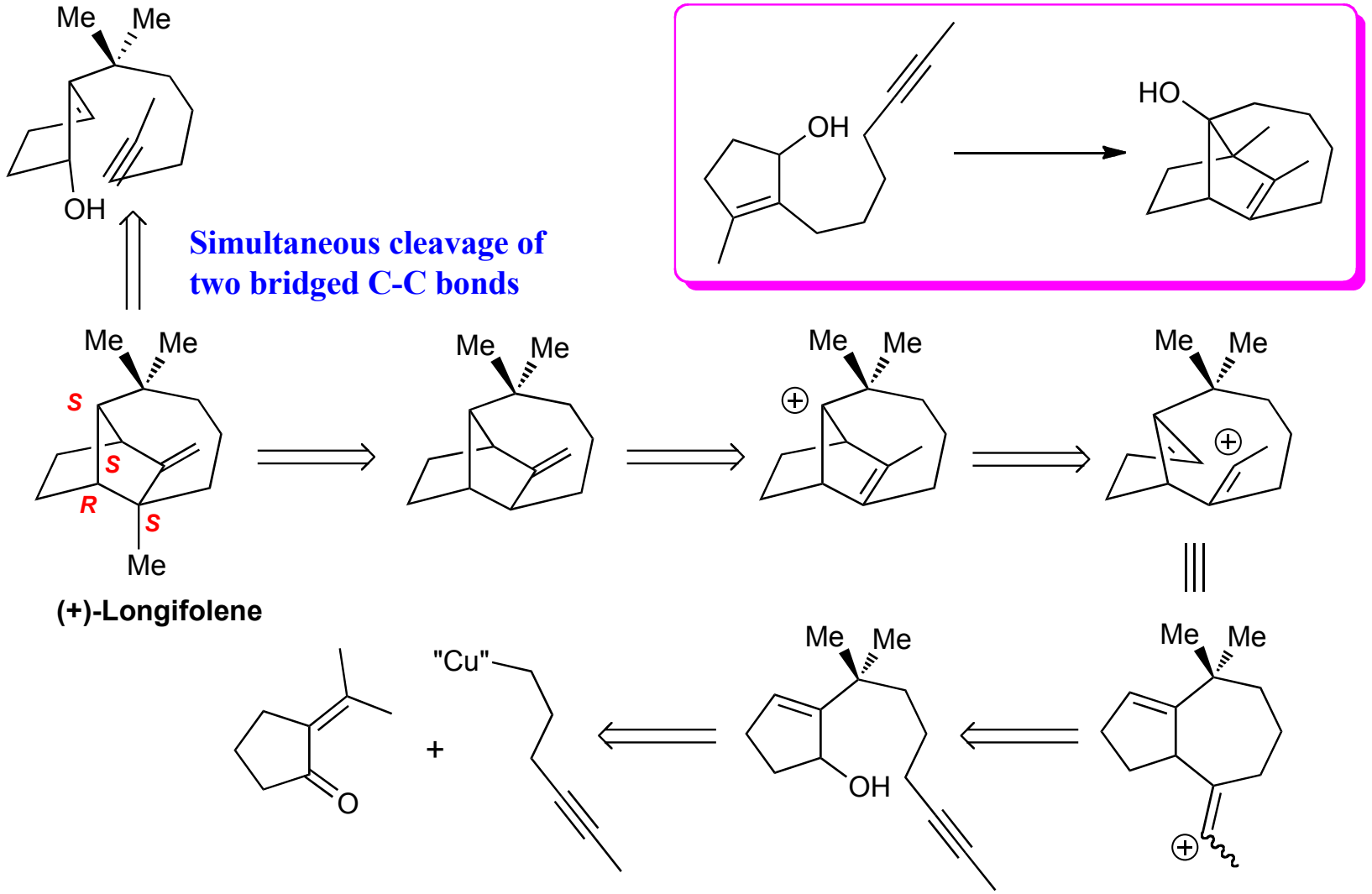
Longifolene (Johnson 1975): Unexpected results

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

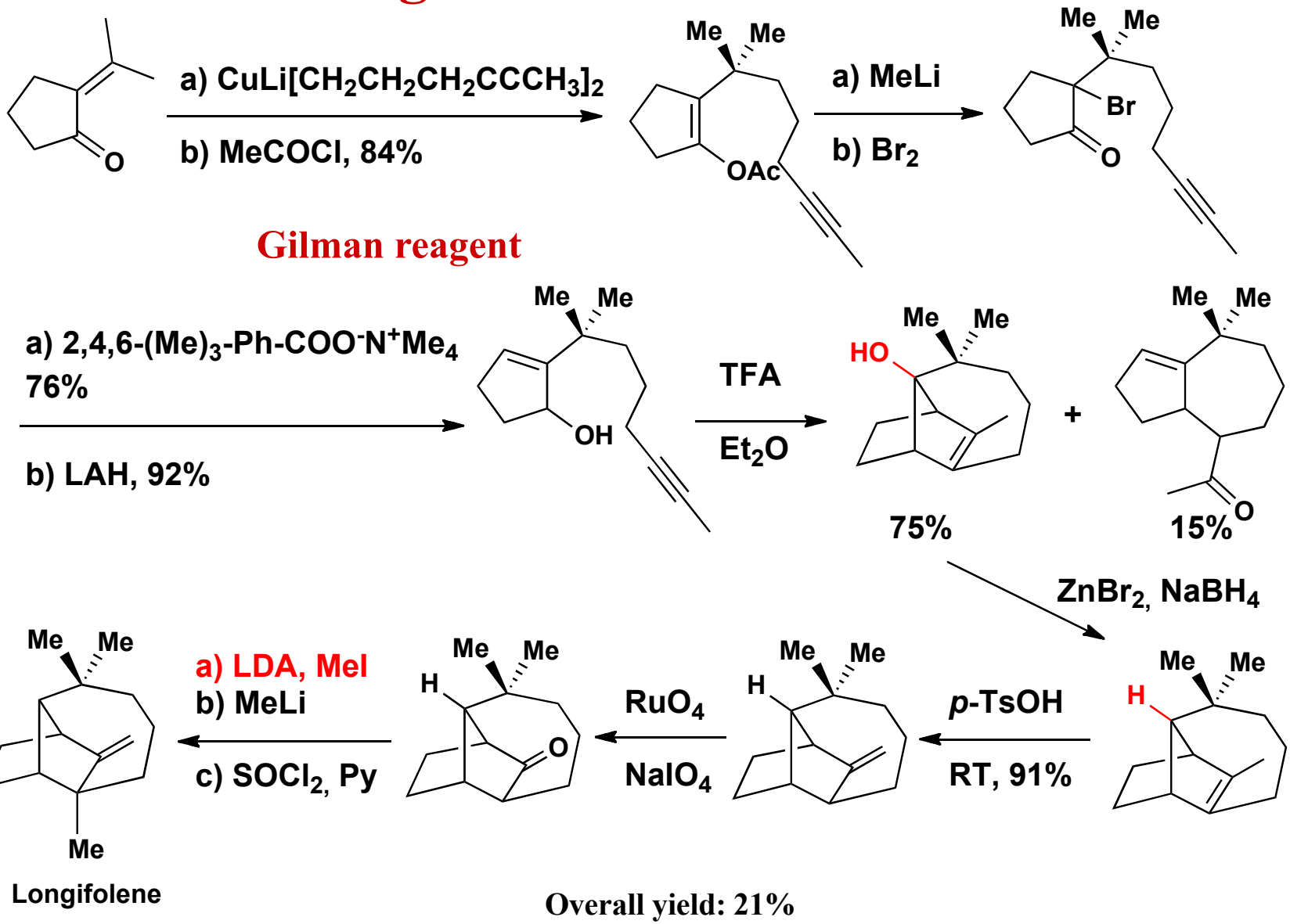
Oxidation of ketone to enone: Control of regioselectivity

Dihydroxylation of alkenes with RuO_4/$NaIO_4$

Non-Classic carbocation

Bredt Rule, Anti-Bredt

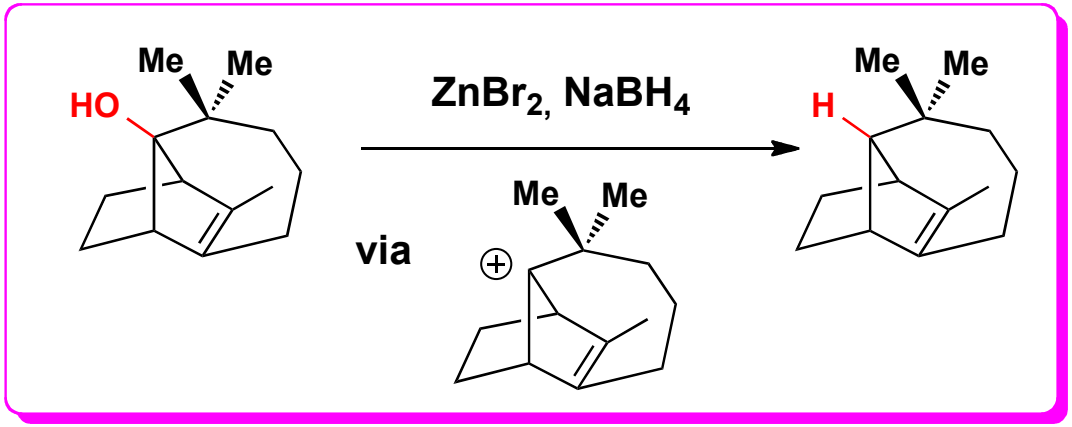
Longifolene—Johnson 1975

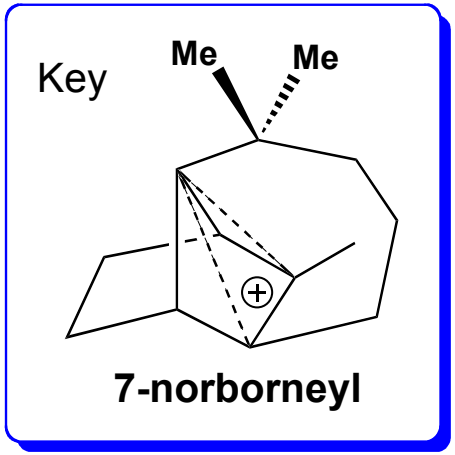


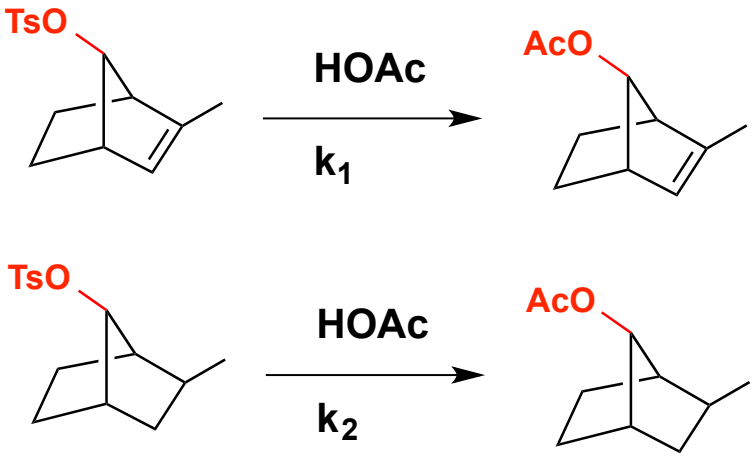
Overall yield: 21%

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

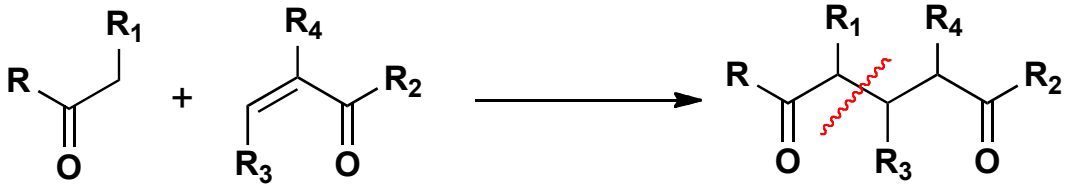
How to cleave a C=C double bond?

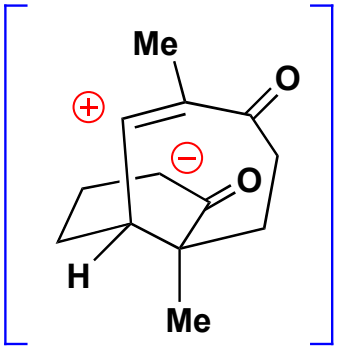
a) **Ozonolysis**

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

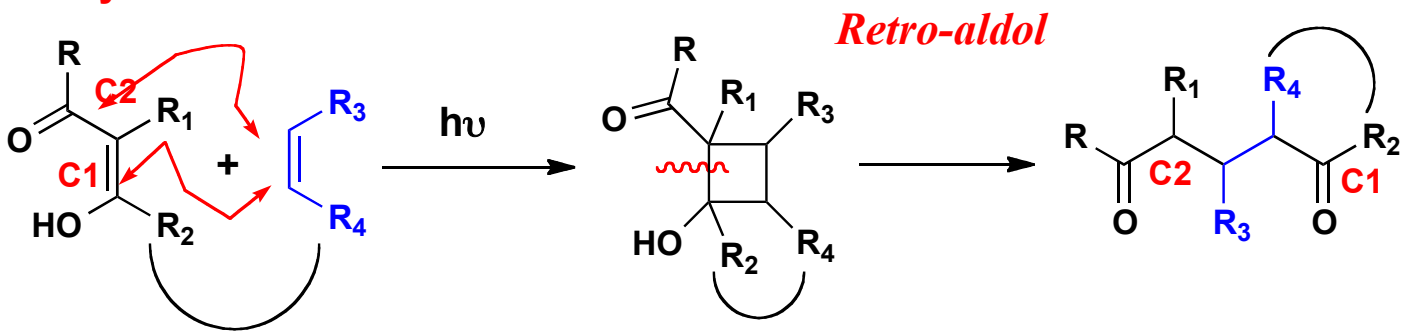
Synthesis of 1,5-dicarbonyl compounds

Micheal Addition





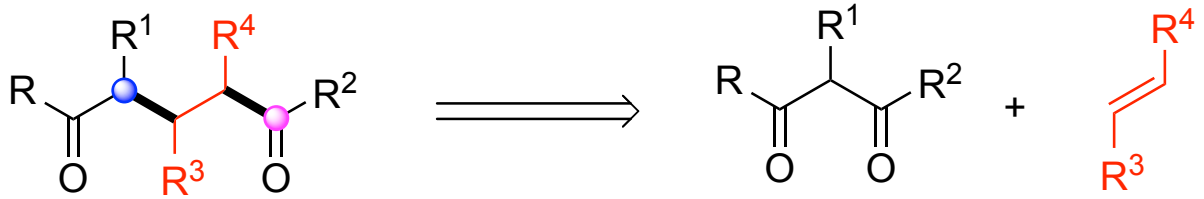
De Mayo reaction



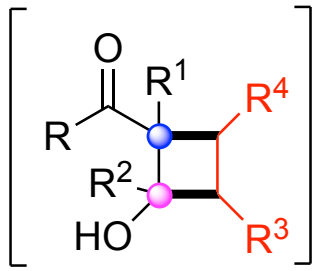
Olefin inserted into the C1-C2 bond of the enol ether

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

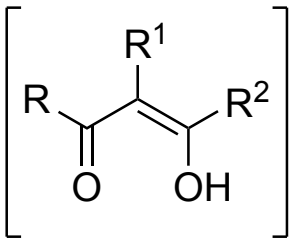
Synthesis of 1,5-dicarbonyls by De Mayo Reaction

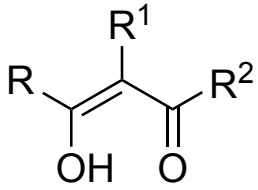


via



via

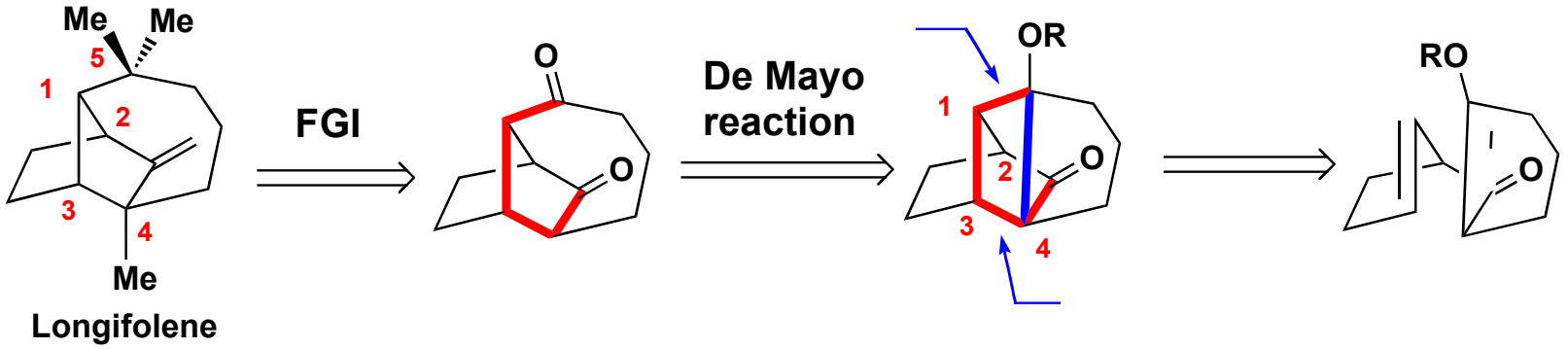




Will give another regioisomer

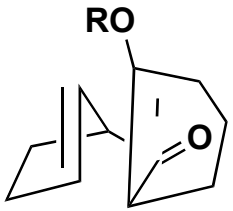
P. de Mayo, *Acc. Chem. Res.*, **1971**, *4*, 41;
W. Oppolzer, *Acc. Chem. Res.*, **1982, *15*,** 135

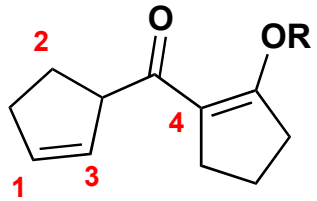
Longifolene—Oppolzer 1978



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

"Pattern recognition"

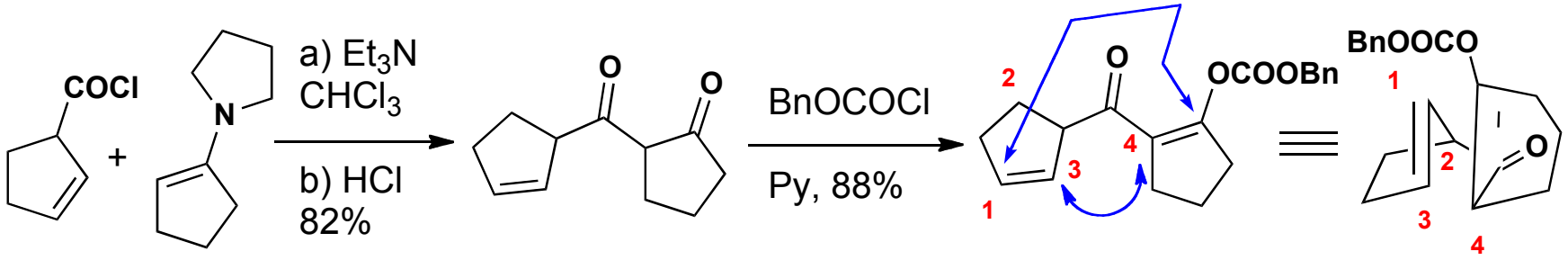




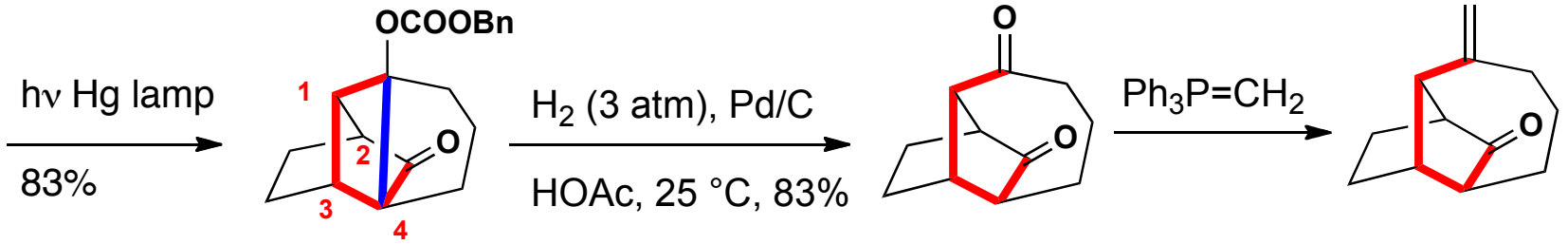
High level strategic design

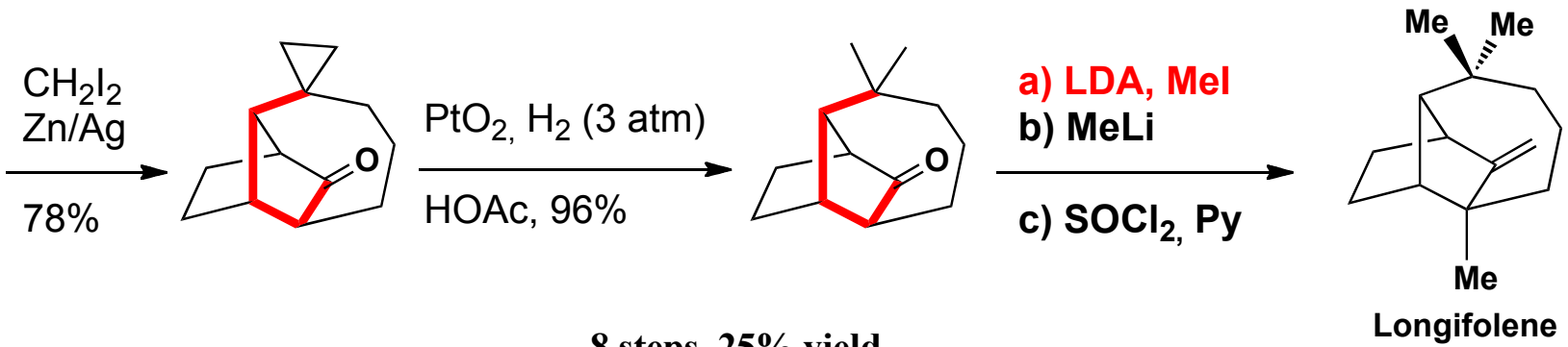
"Pattern recognition", termed by Danishefsky, seeks to discover an exploitable substructural motif around which to organize the thought process and then the synthesis. The most fascinating cases arise when the target itself must actually be modified leading to a more complex compound before a staple 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.

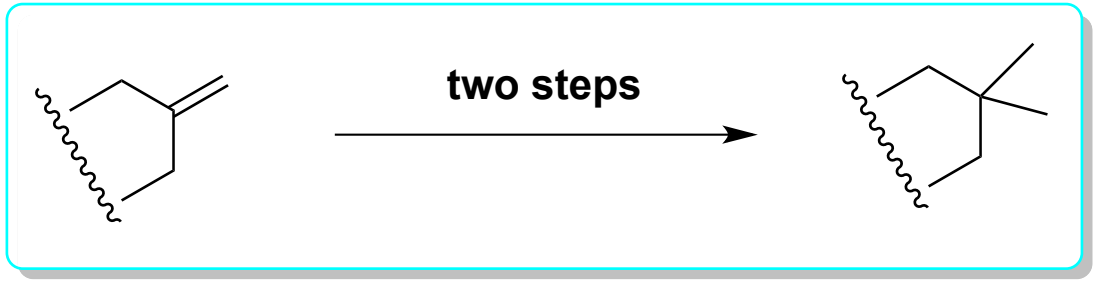
Summary of the Synthesis: Reactions and Tactics

Stork enamine acylation: Synthesis of 1,3-dicarbonyls

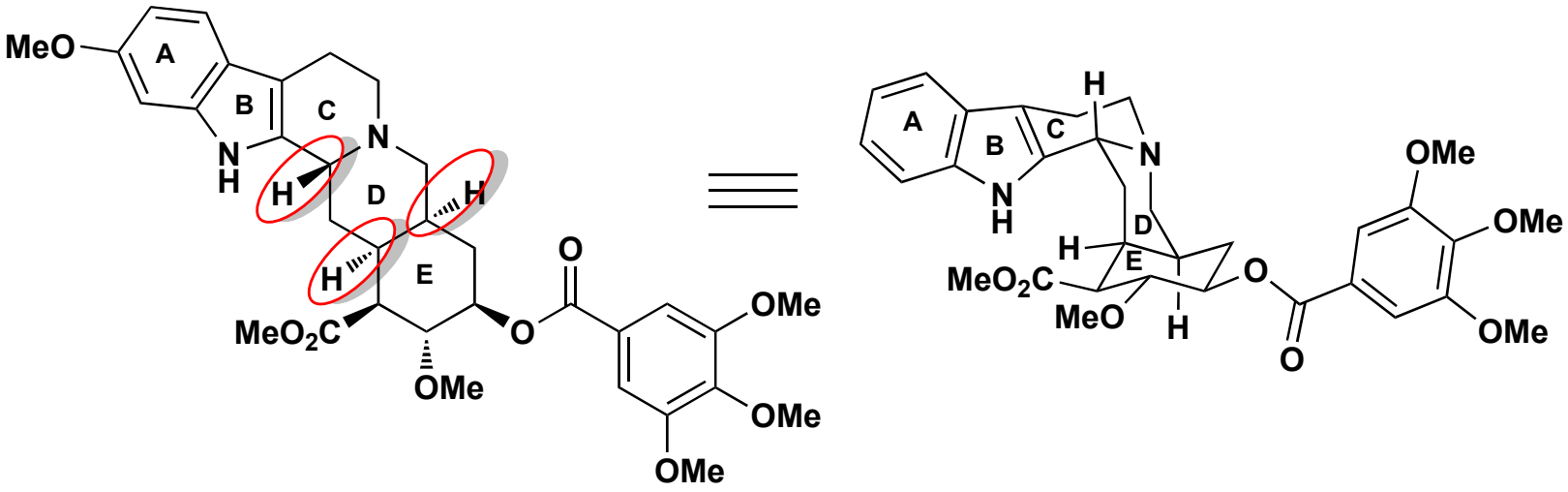
De Mayo reaction: [2+2] cycloaddition/retro-aldol for the Synthesis of 1,5-dicarbonyls

Simmons-Smith cyclopropanation

How to realize the following transformation



Reserpine



Isolation: 1952,

Structural determination: Plane structure 1953

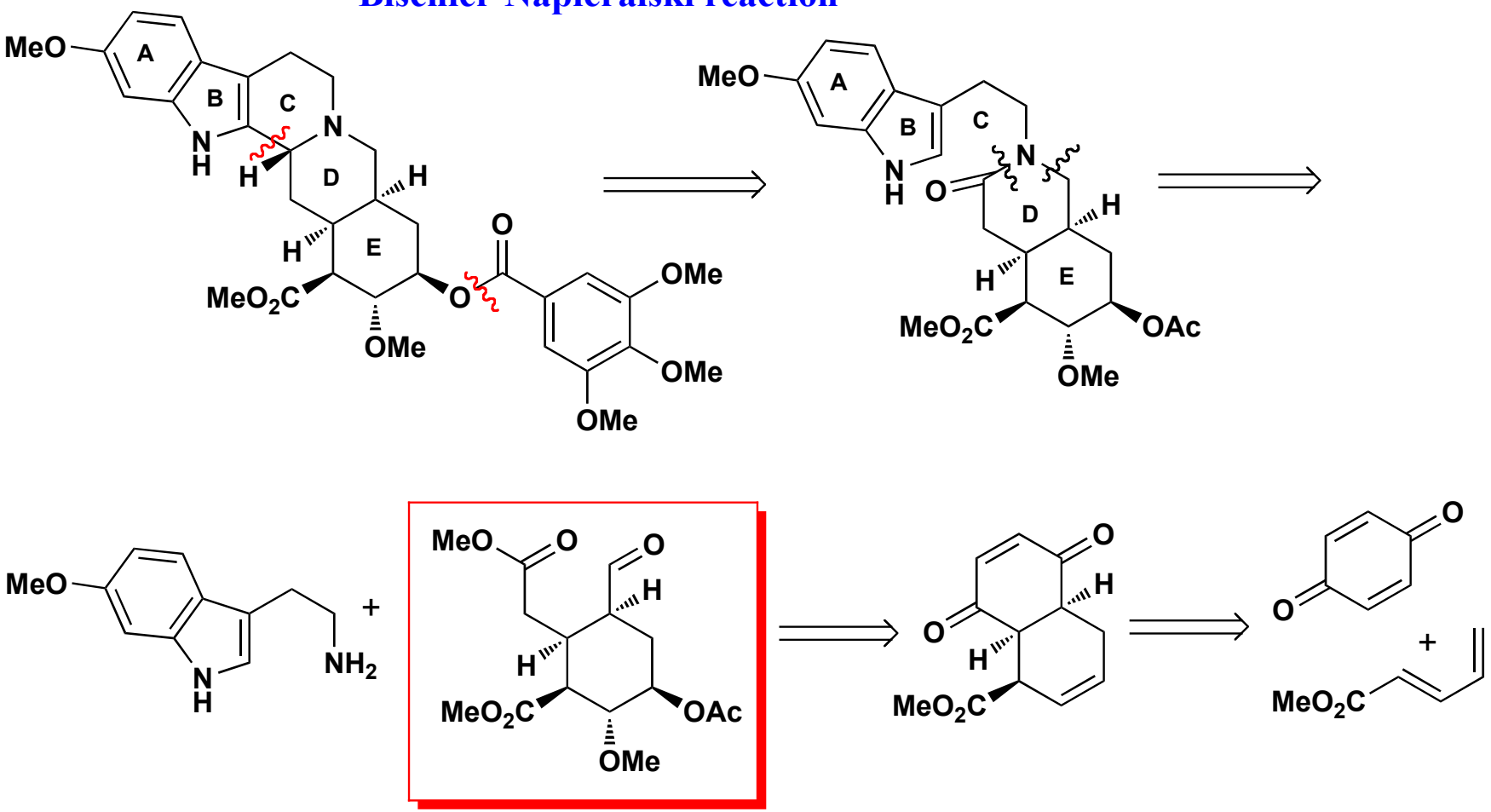
Stereochemistry: 1955

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

First total synthesis by Woodward 1956

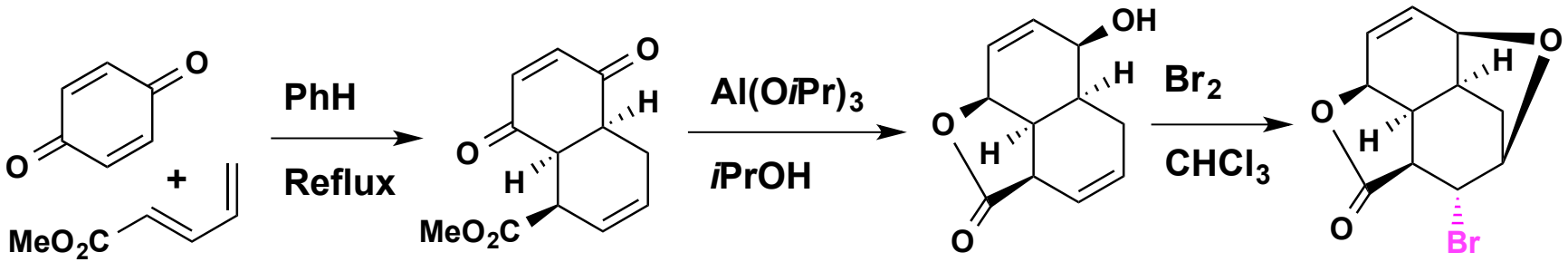
Reserpine-Woodward

Bischler-Napieralski reaction

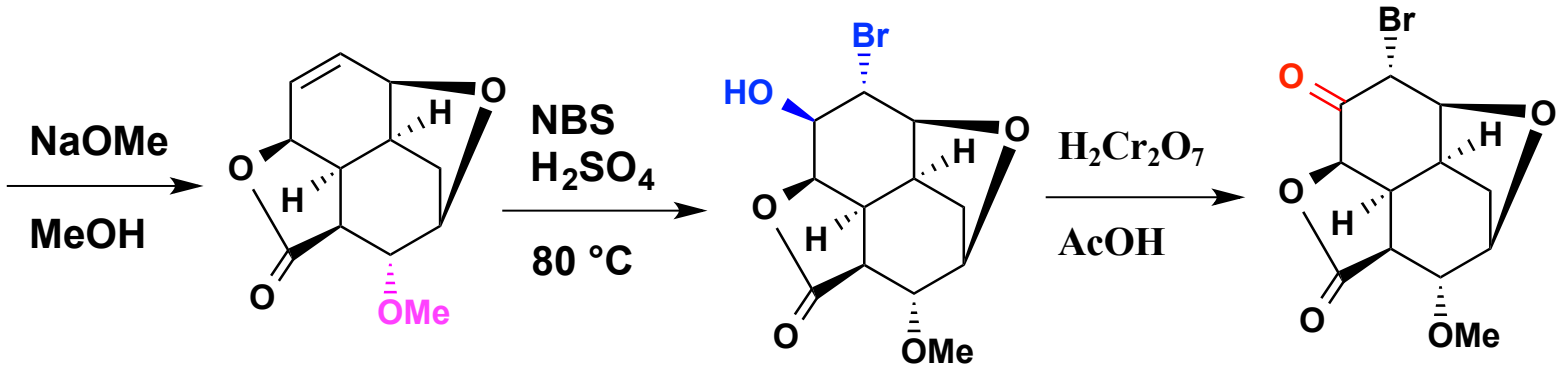


R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, R. W. Kierstead, *J. Am. Chem. Soc*. **1956**, *78*, 2023-2025.

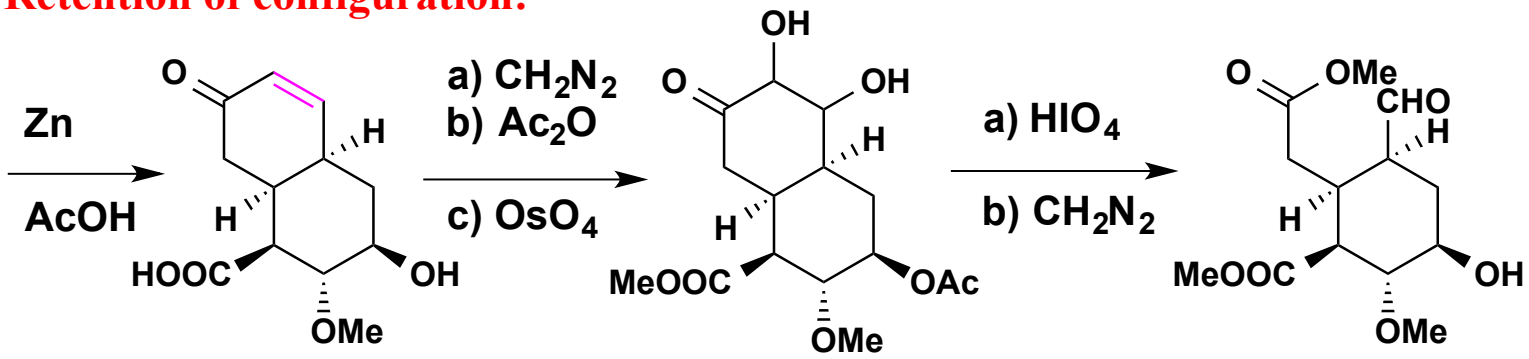
Reserpine-Woodward



Meerwein-Ponndorf-Verley



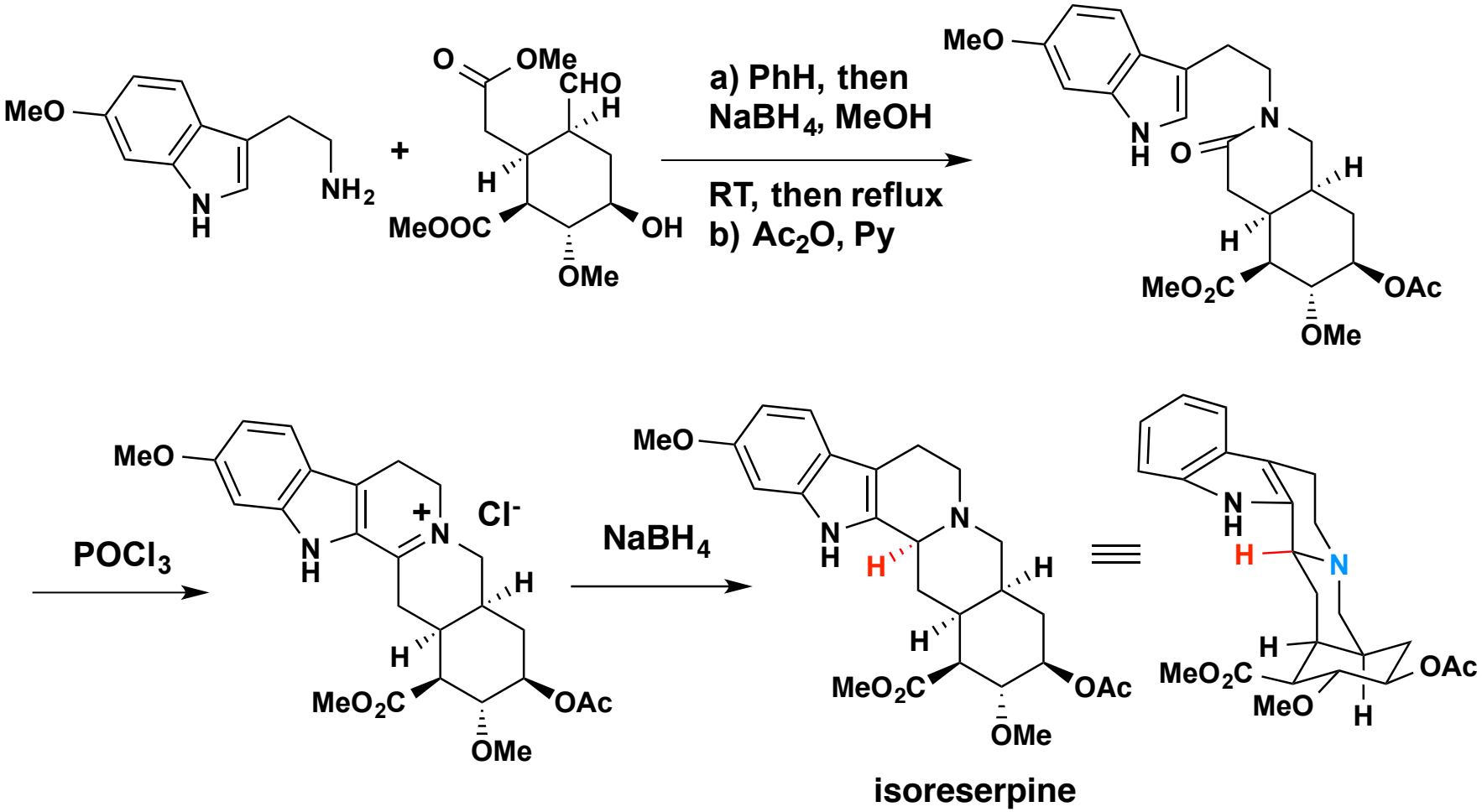
Retention of configuration!



Control of relative stereochemistry: "A Cyclic trick"

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

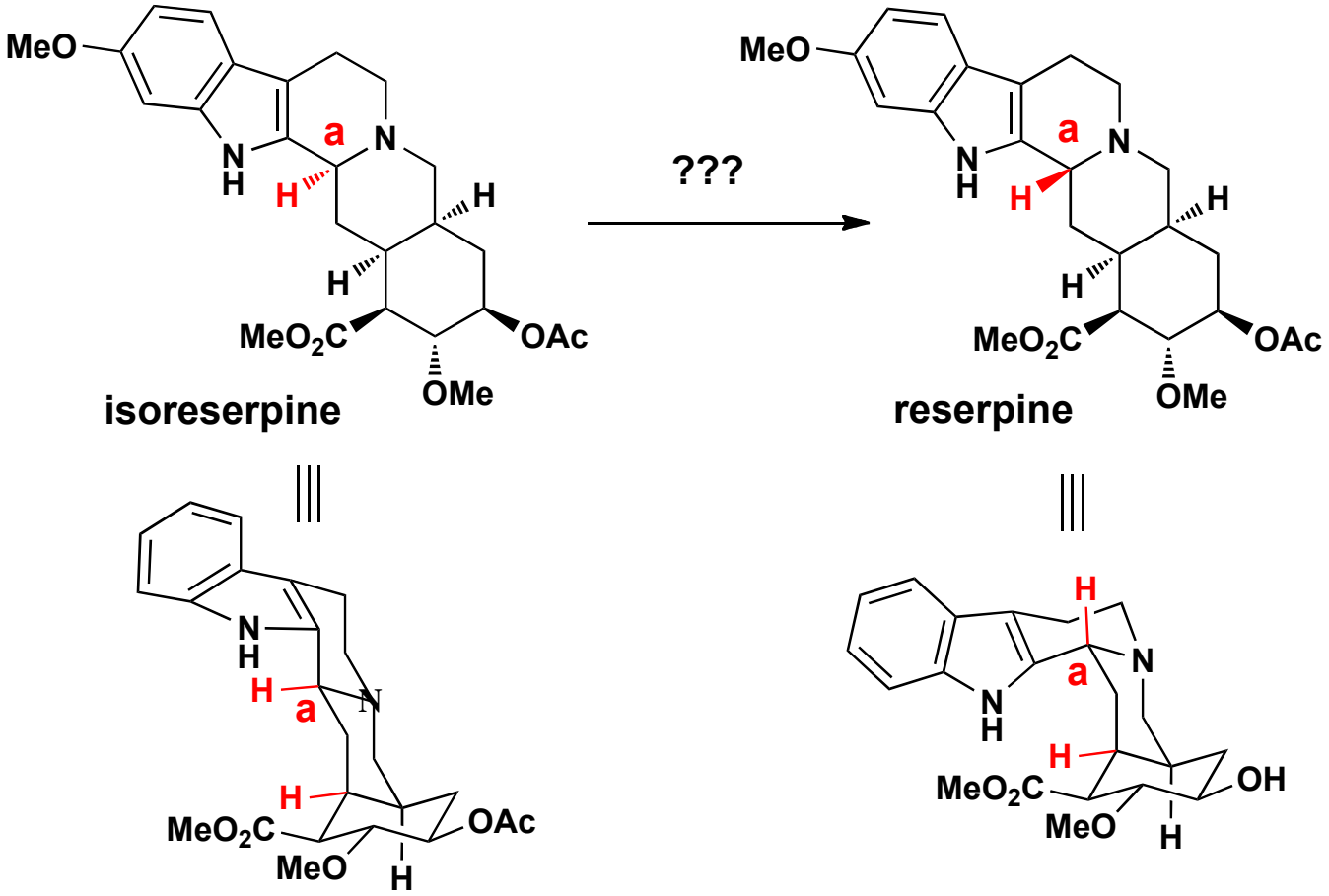
Reserpine-Woodward



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

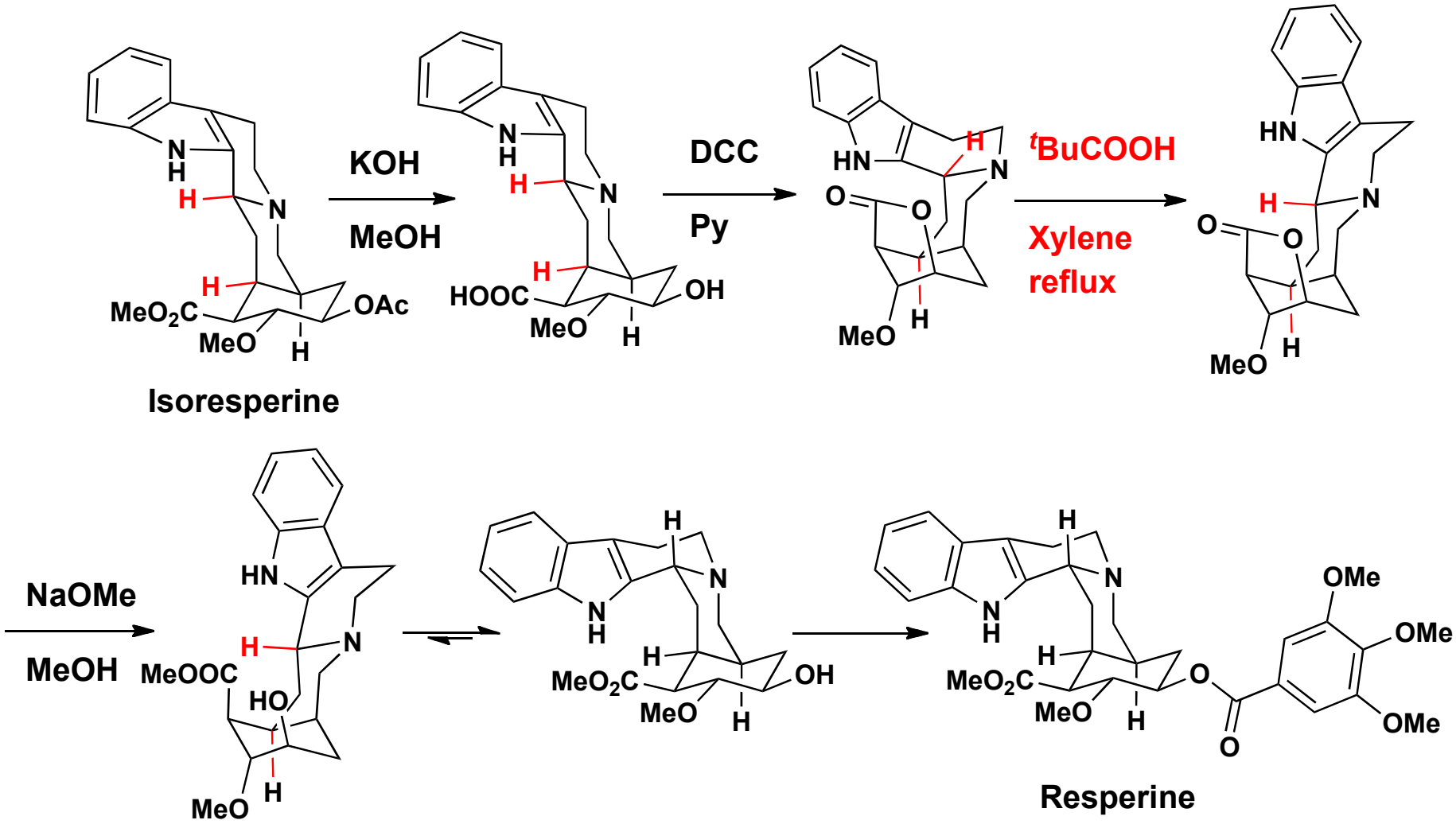


Isomerization: Mechanistically possible However, C_a of isoreserpine is configurationally quite stable and is kinetically and thermodynamically favored

Solution: Change the conformation of isoreserpine!!!

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

Reserpine-Woodward

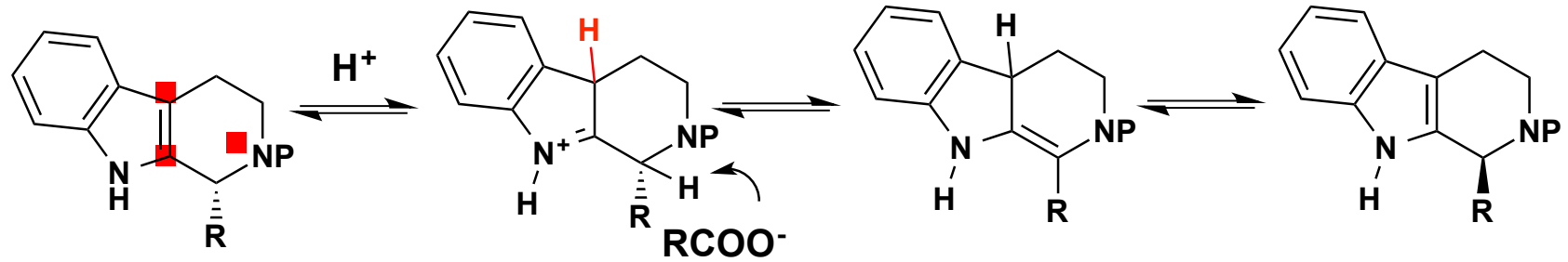


R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, R. W. Kierstead, *J. Am. Chem. Soc*. **1956**, *78*, 2023-2025.
Tetrahedron **1958**, *2*, 1-57.

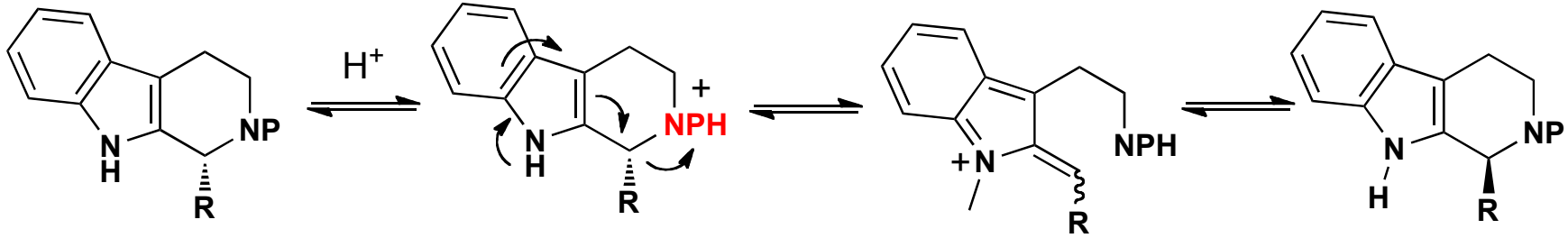
Reserpine-Woodward

Possible Mechanism of Epimerization of Carbazole

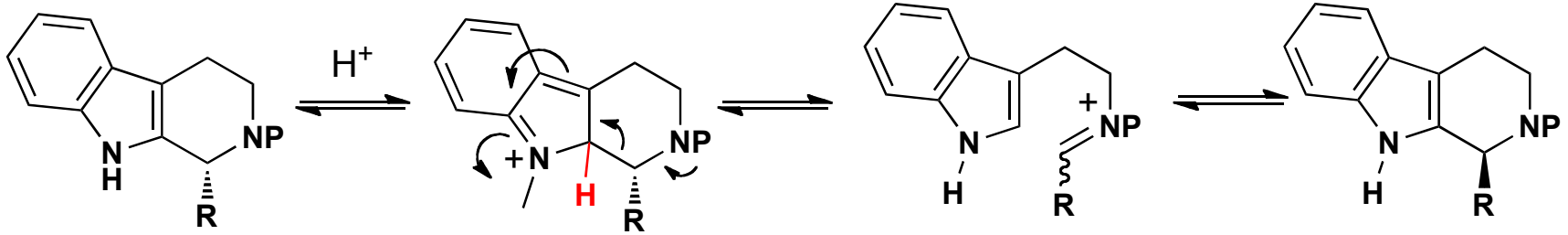
Mechanism 1



Mechanism 2

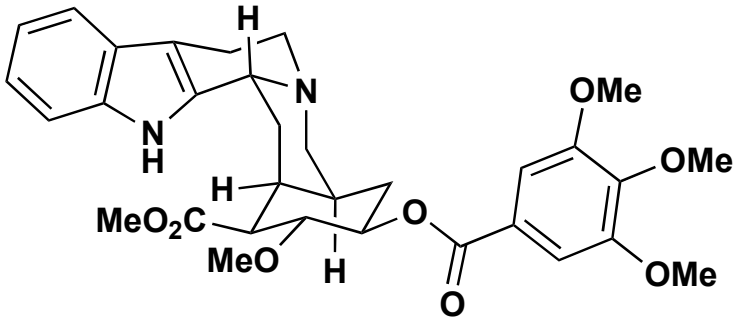


Mechanism 3

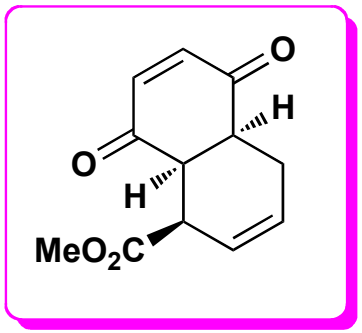


Which mechanism is the most probable one

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

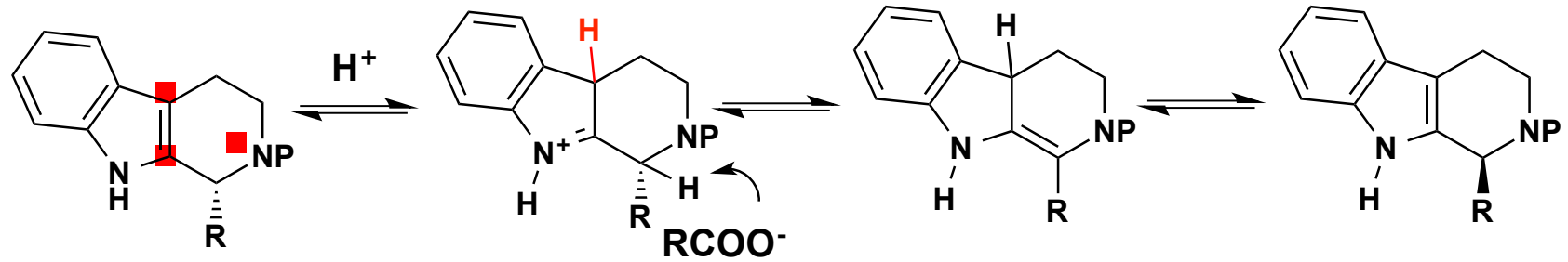
Diels-Alder cycloaddition
Meerwein-Ponndorf-Verley (MPV) reaction
Bromoetherification
Beta-Elimination
Dihydroxylation of alkene/cleavage of diol
Bischler-Napiralski reaction

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

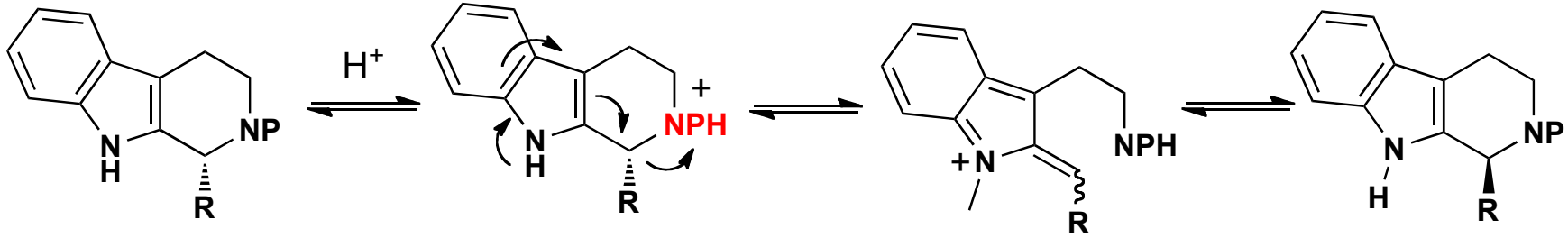
Reserpine-Woodward

Possible Mechanism of Epimerization of Carbazole

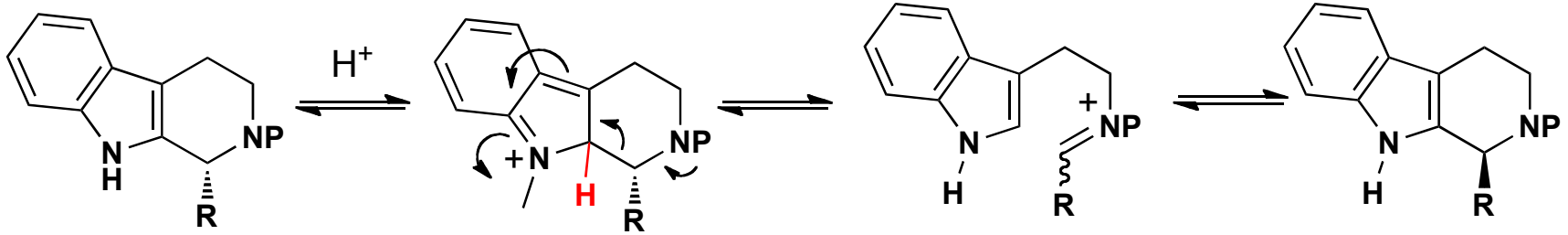
Mechanism 1



Mechanism 2

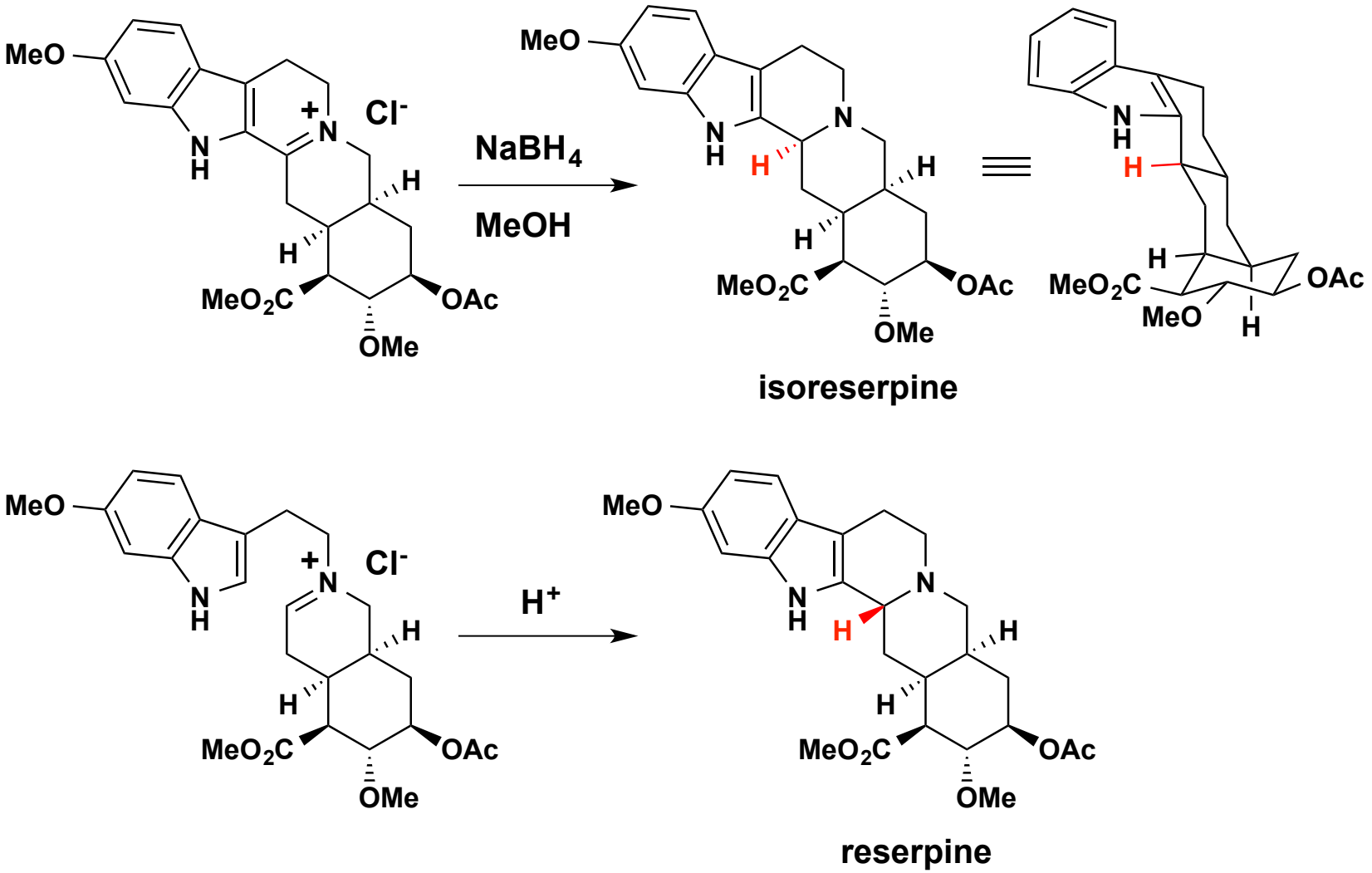


Mechanism 3



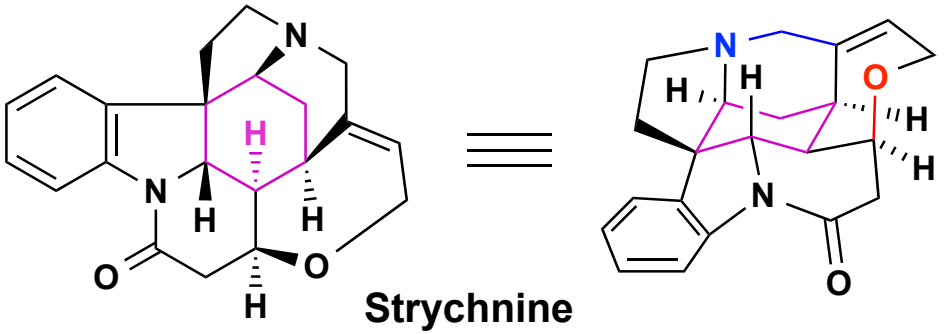
Which mechanism is the most probable one

Reserpine Synthesis-Variation



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

Strychnine



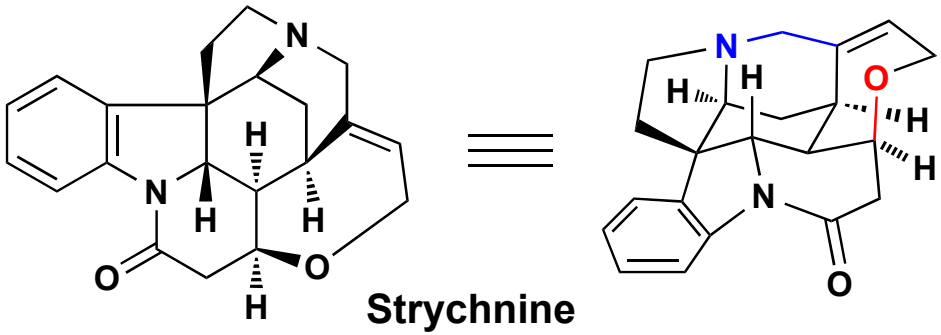
Strychnine

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).

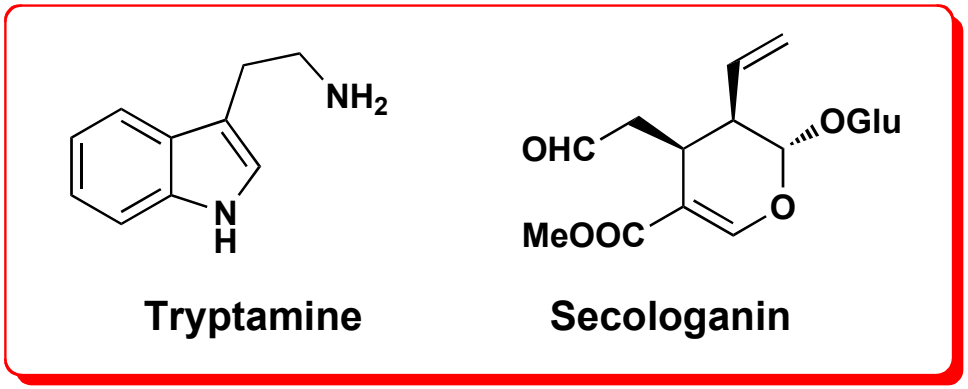
Between the isolation and structure elucidation, Sir Robert Robinson's group alone published over 250 communications on the subject. Hermann Leuchs contributed another 125 papers.

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

Strychnine

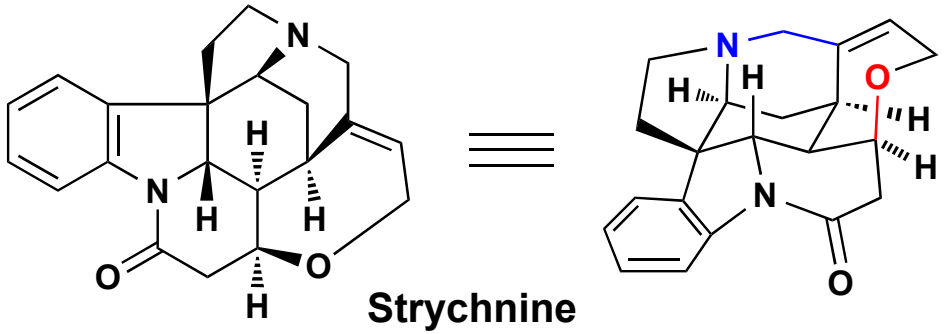


Molecular formule: $C_{21}H_{22}N_2O_2$
24 skeletal atoms, 7 Rings, 6 Contiguous stereocentres, 5 in the cyclohexane ring.
A monoterpenoid indole alkaloid biogenetically derived from tryptamine and secologanin



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**
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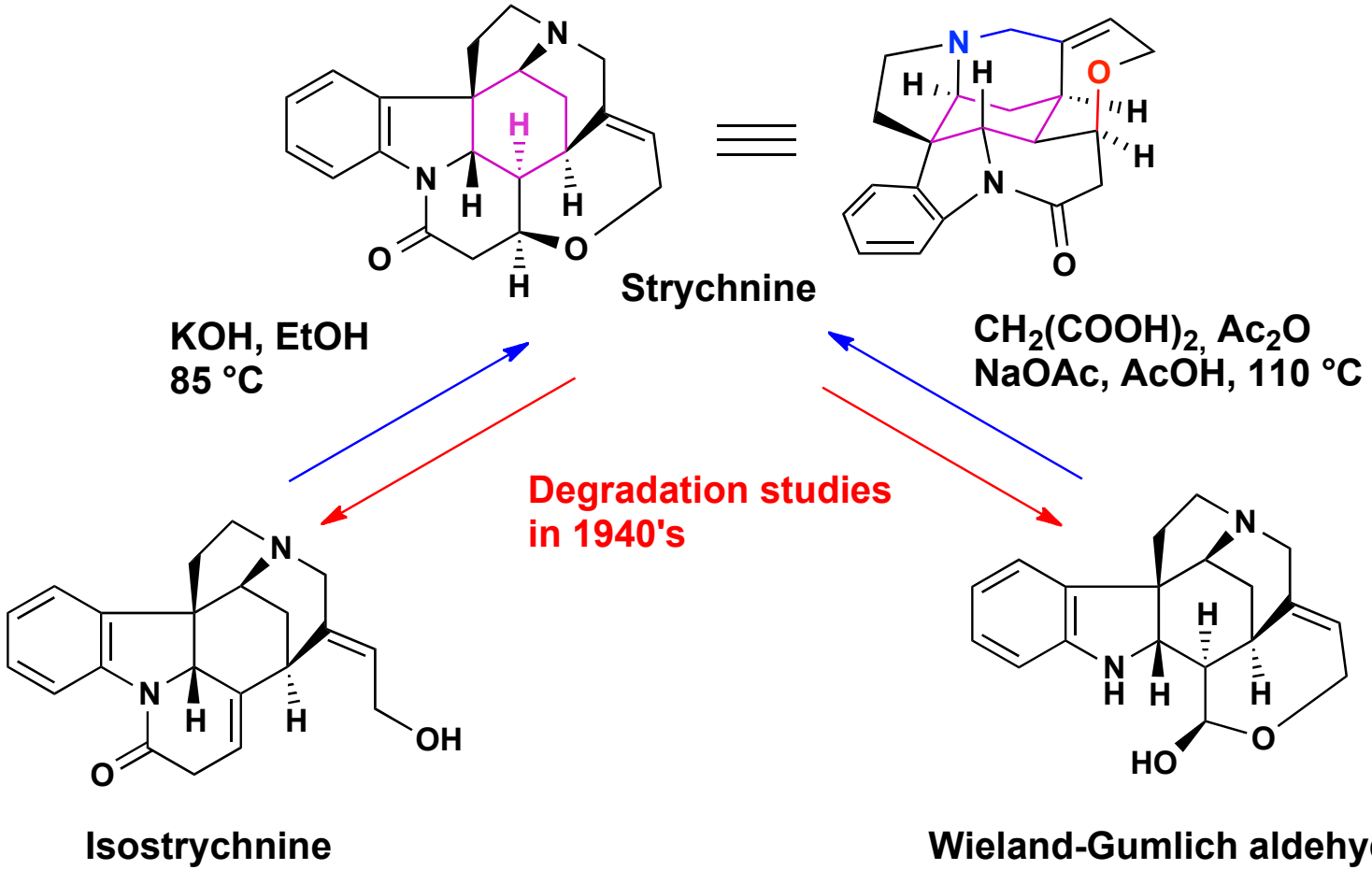
Graham J. Bodwell - Memorial University of Newfoundland (**2002**)
Miwako Mori - Hokkaido University (**2002**)
Masakatsu Shibasaki - University of Tokyo (**2002**)
Tohru Fukuyama - University of Tokyo (**2004**)
Albert Padwa - Emory University (**2007**)
Rodrigo, B. Andrada, Temple University **(2010)**
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.

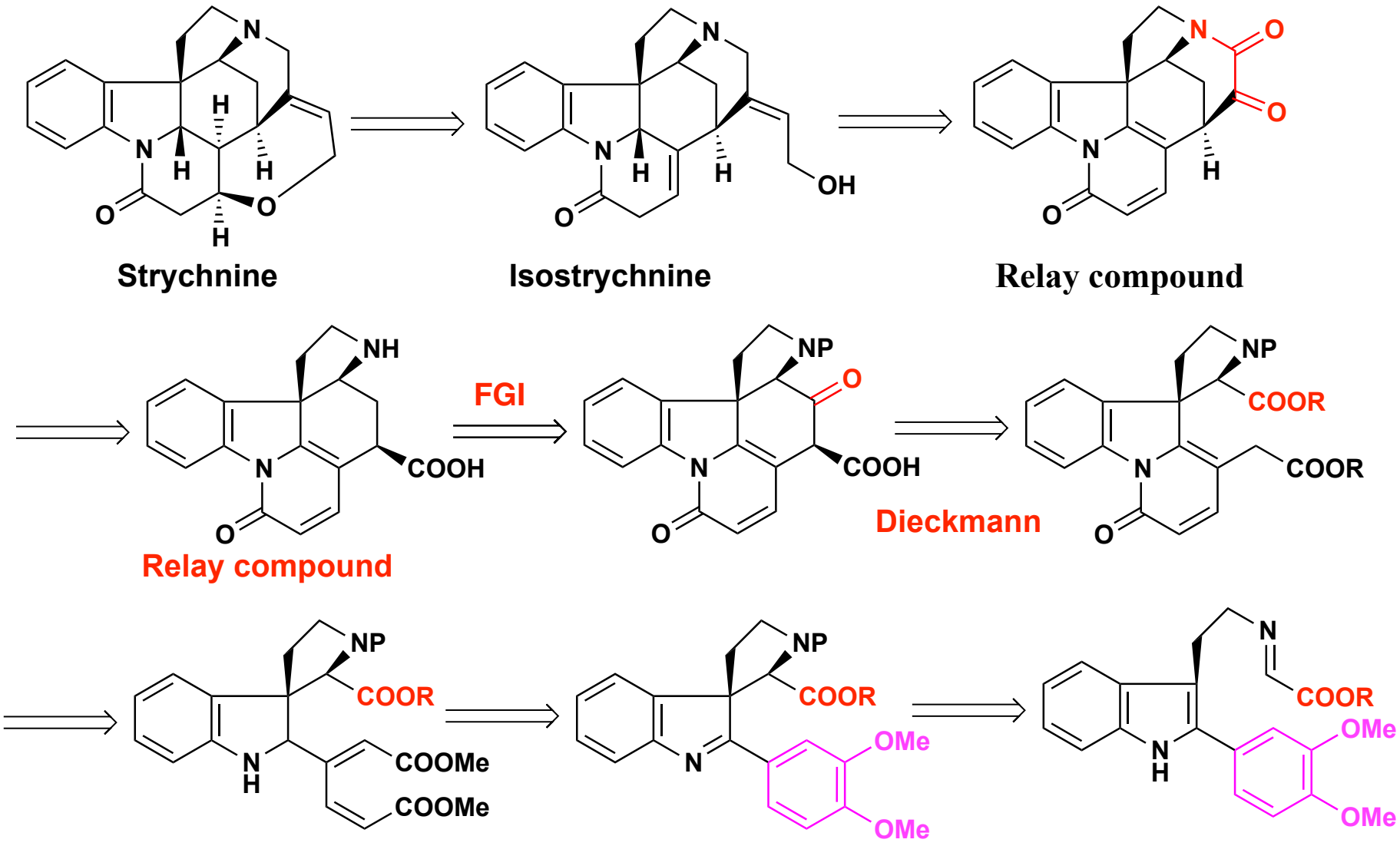
Strychnine: Key background



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

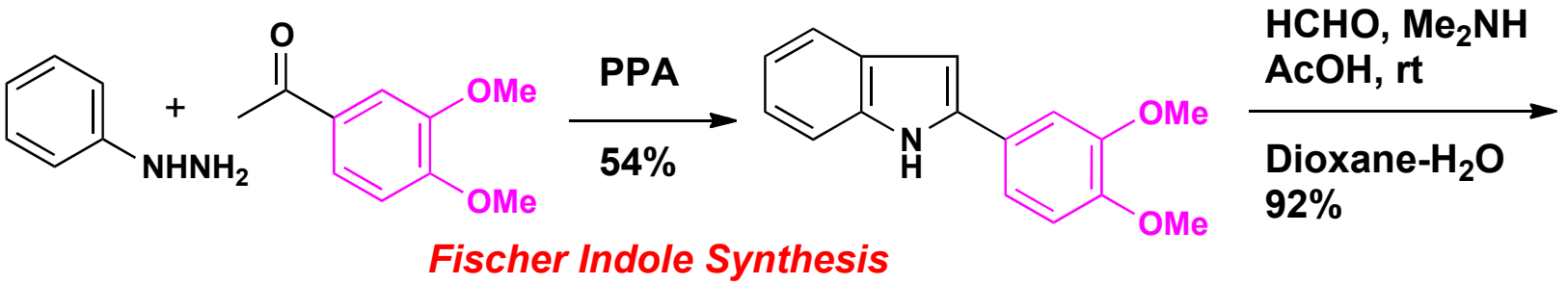
Dieckman condensation

Pictet-Spengler reaction and Interrupted Pictet-Spengler reaction

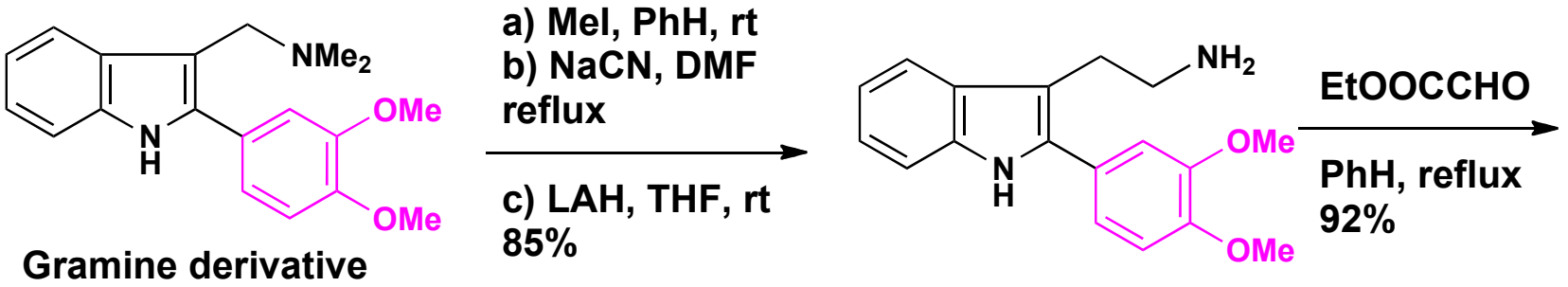
Azalacton formation

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

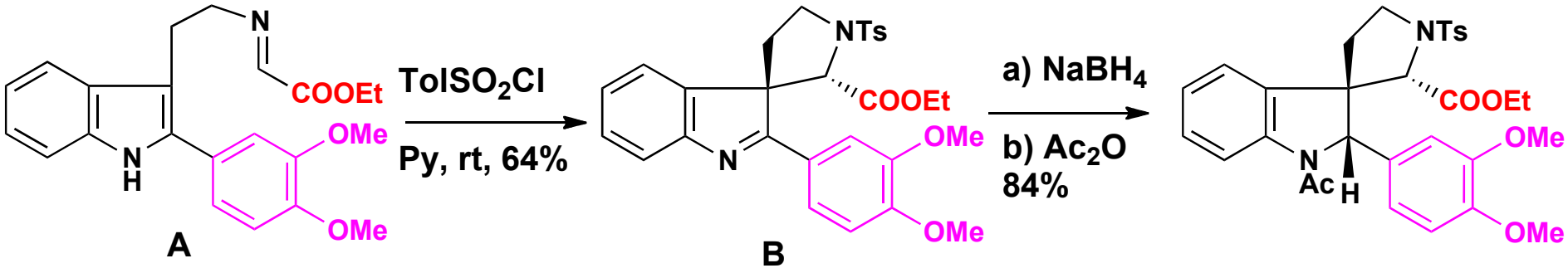
Woodward's Total Synthesis of Strychnine



Fischer Indole Synthesis

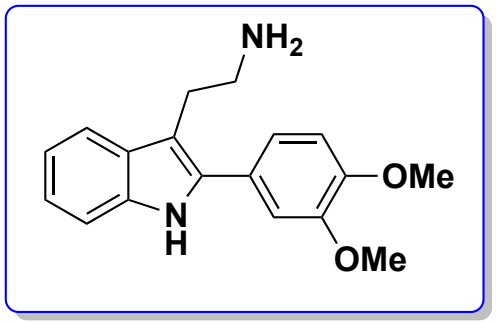


Gramine derivative

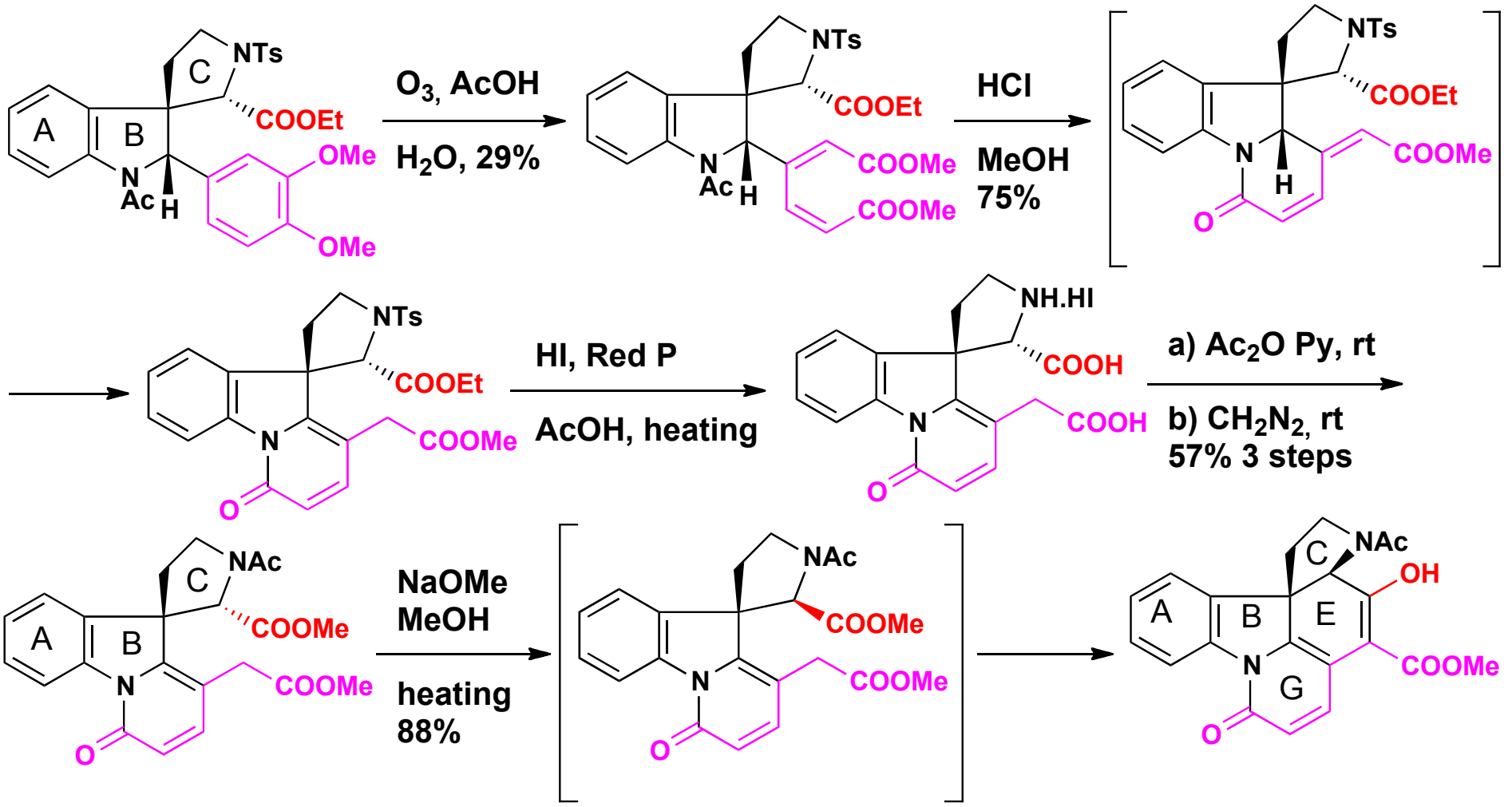


The C-2 position of Indole is blcoked by the aromatic ring. Only spiroindolene was produced in the Pictet-Spengler reaction (*Interrupted Pictet-Spengler reaction*).

Alternative Syntheses of 2,3-Disubstitutes Indoles

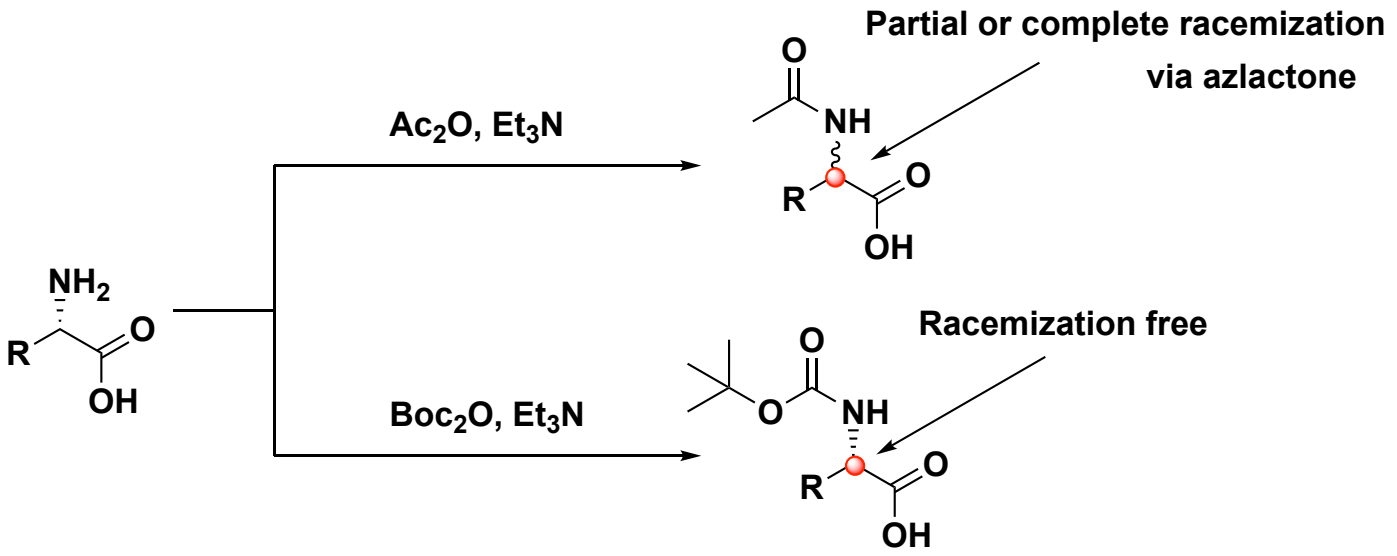


Woodward's Total Synthesis of Strychnine

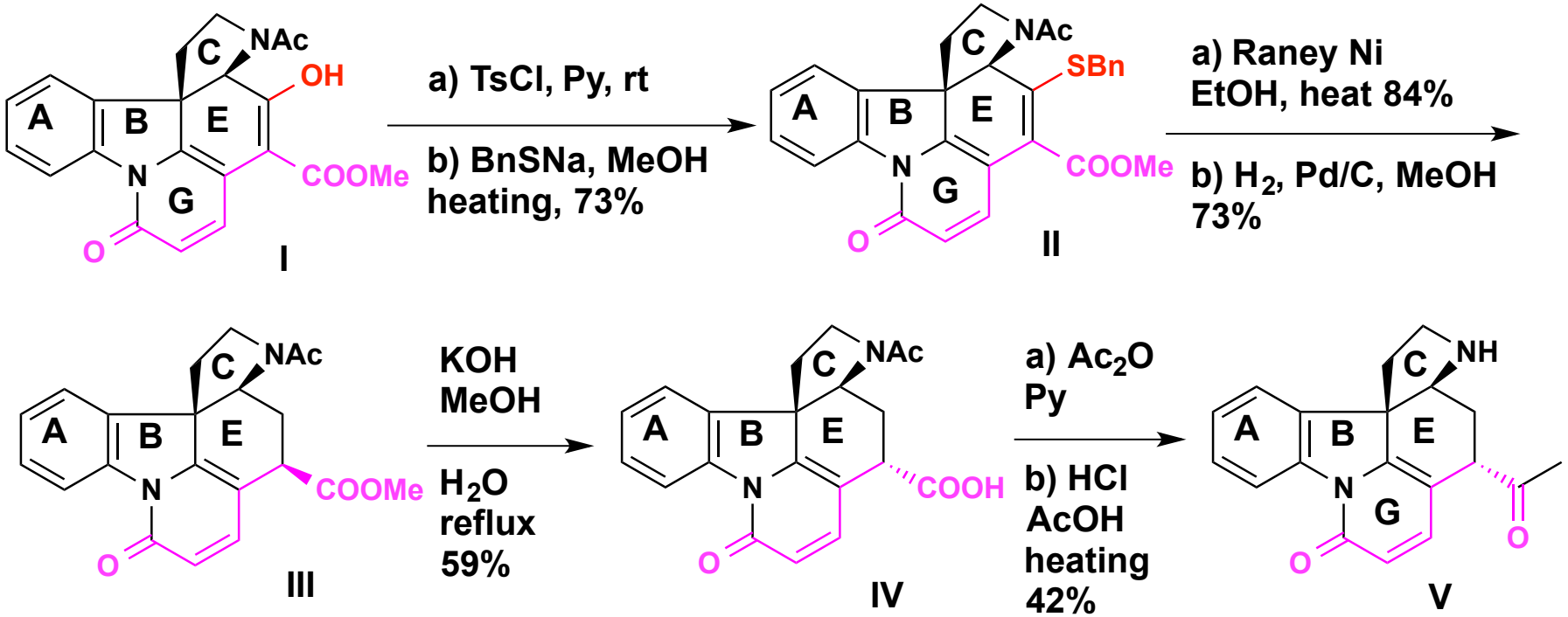


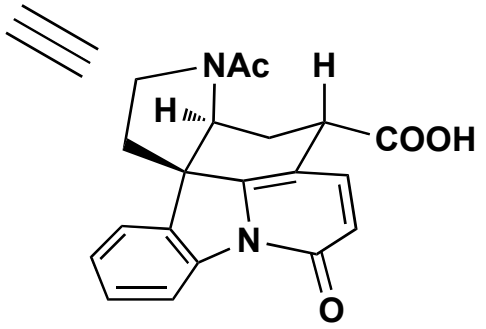
* Conversion of NTs to NAc at the C-ring is required to avoid the decomposition.
* Epimerization at the C- ring is required before Dieckman condensation (draw the conformer)
* The original aromatic ring became integral part of the G, E rings (beauty of the design, based on author's biosynthesis hypothesis,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

Avoiding Actelytion of Free α-Aminoacid



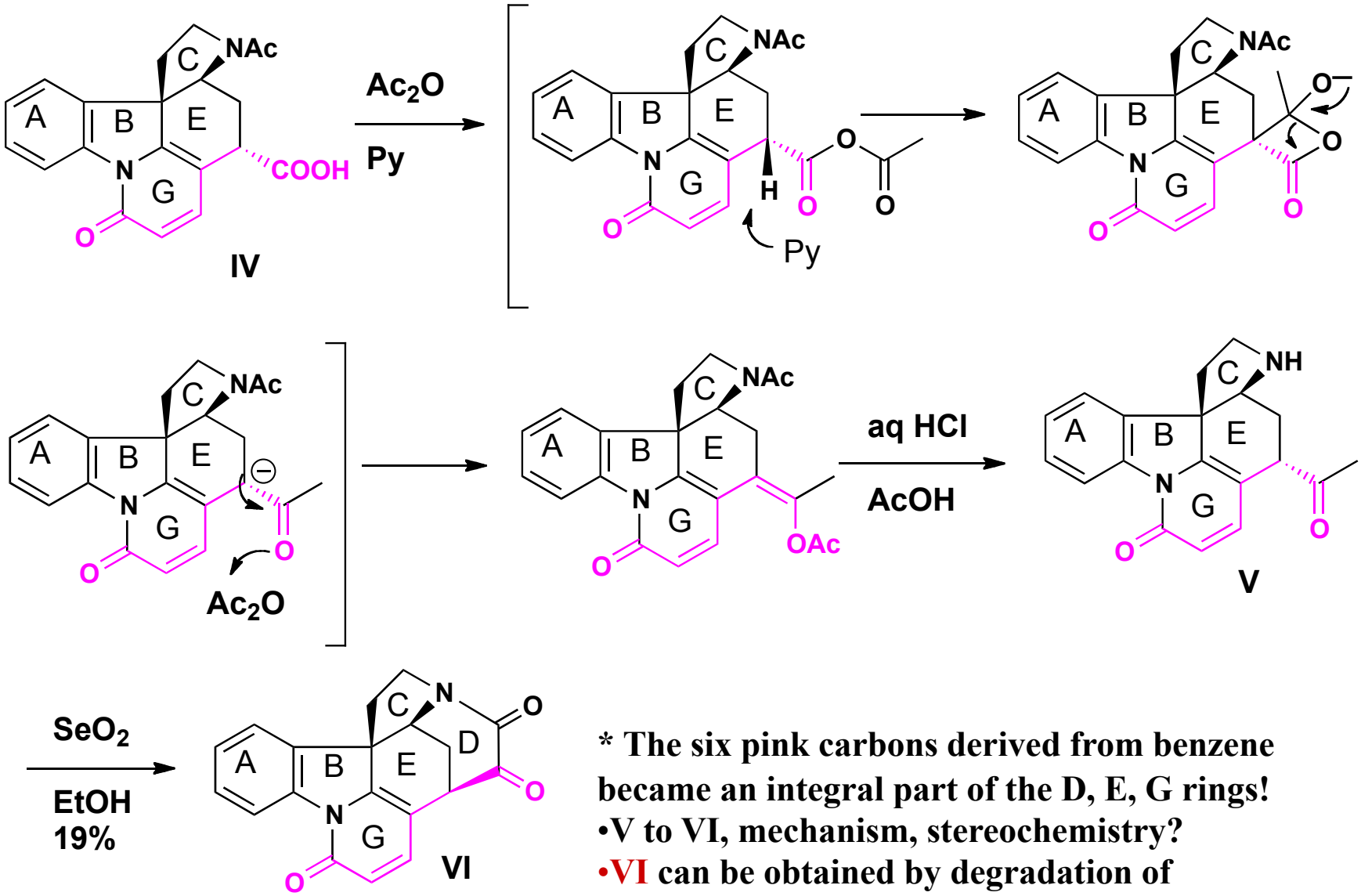
Woodward's Total Synthesis of Strychnine





* 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

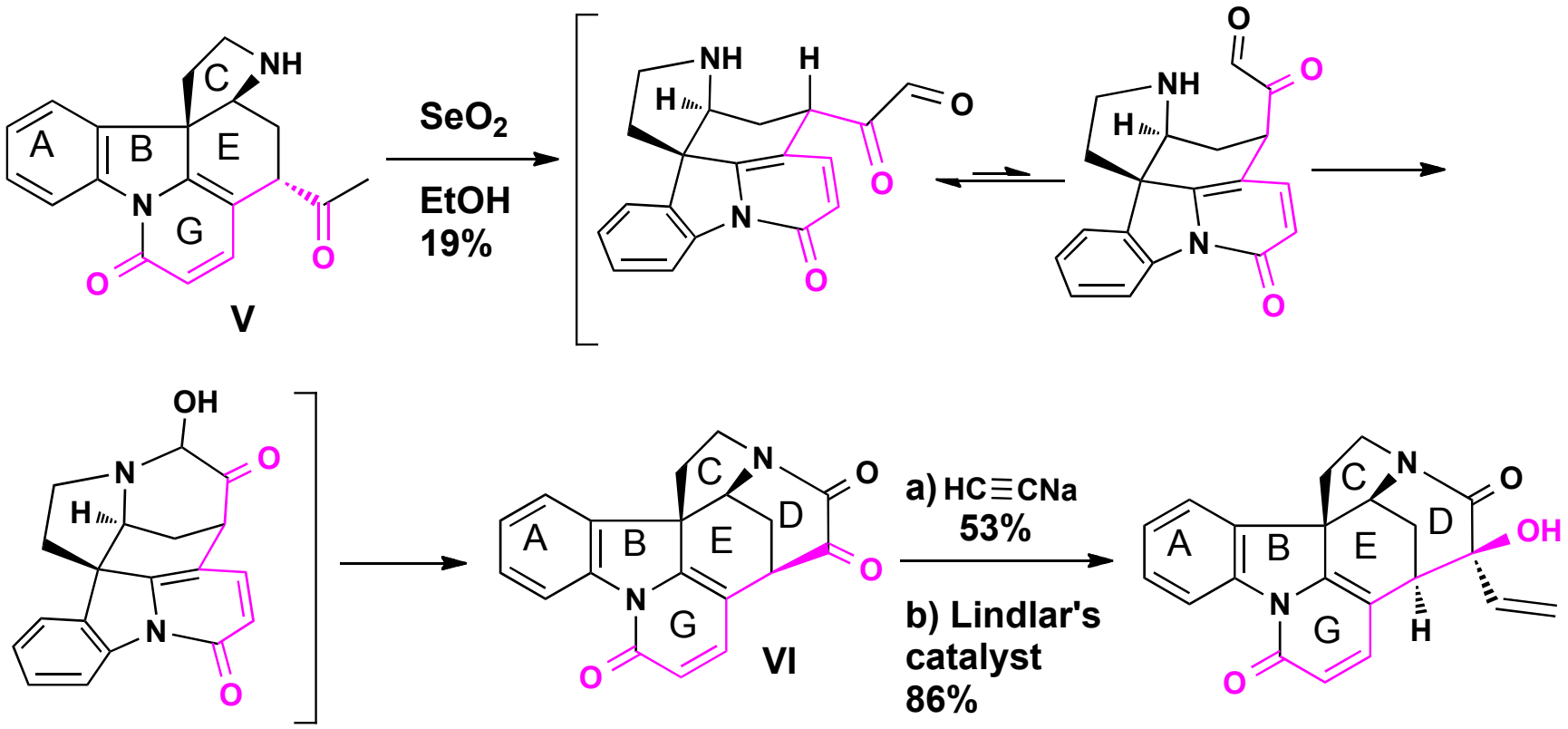


*** The six pink carbons derived from benzene became an integral part of the D, E, G rings!**

•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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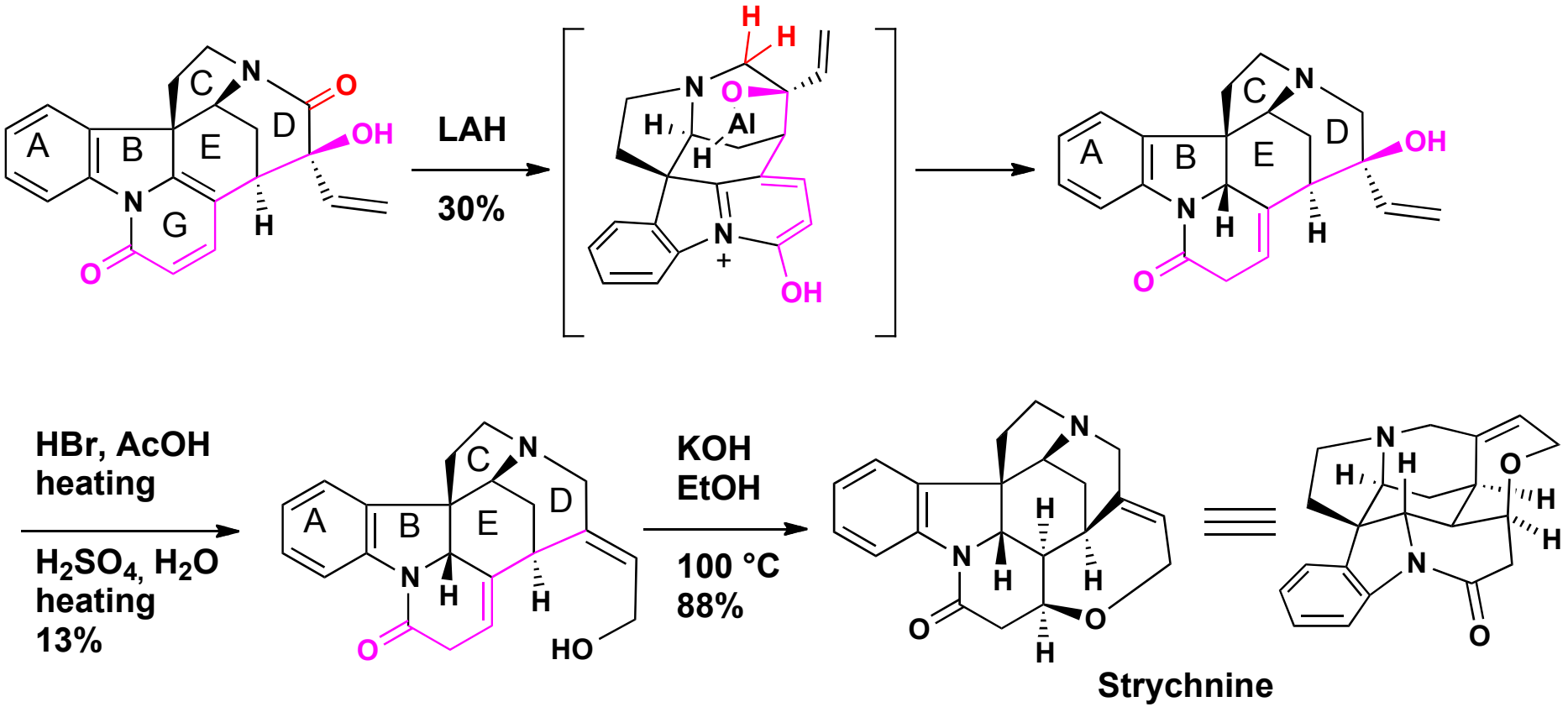
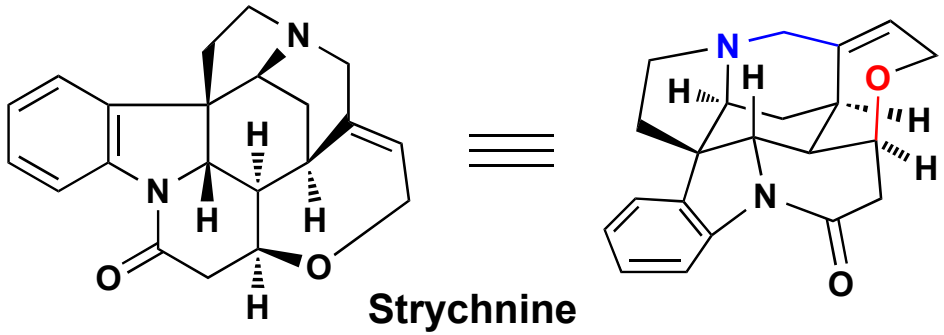


Neighboring group-directed Diastereoselective reduction

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

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

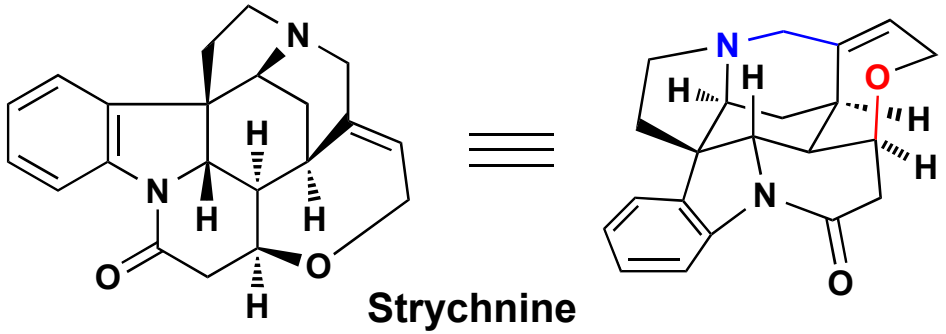
Alpha-hydroxylation of ketone (SeO_2, Ene reaction/2,3-σ rearrangement)

Key Features:

Stepwise construction of ring system

Neighboring group-directed Diastereoselective reduction

Total Synthesis of Strychnine



Strychnine

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Rodrigo, B. Andrada, Temple University **(2010)**
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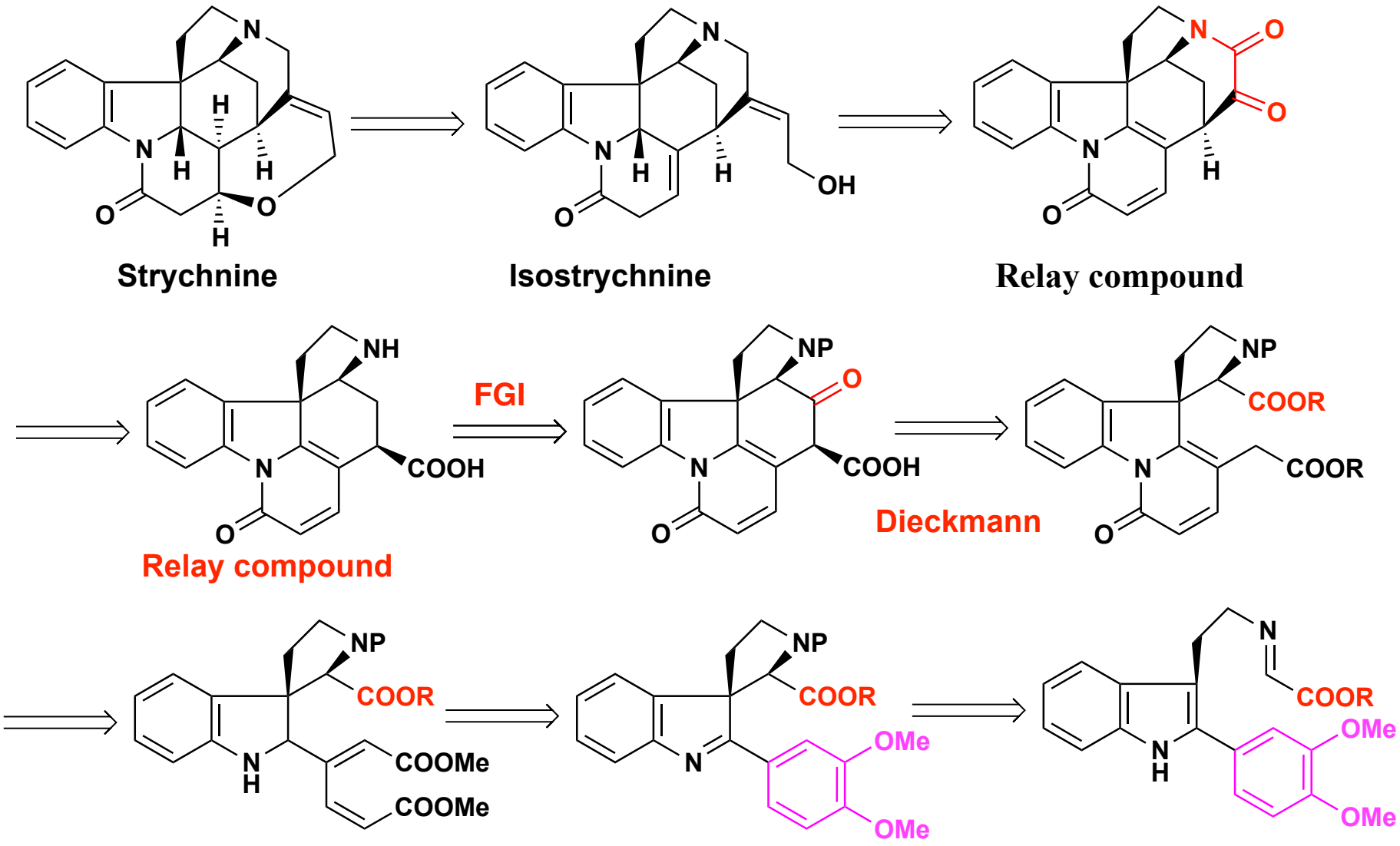
Christopher, D. Vanderwal, University of california, Irvine **(2011)** **6 Steps**

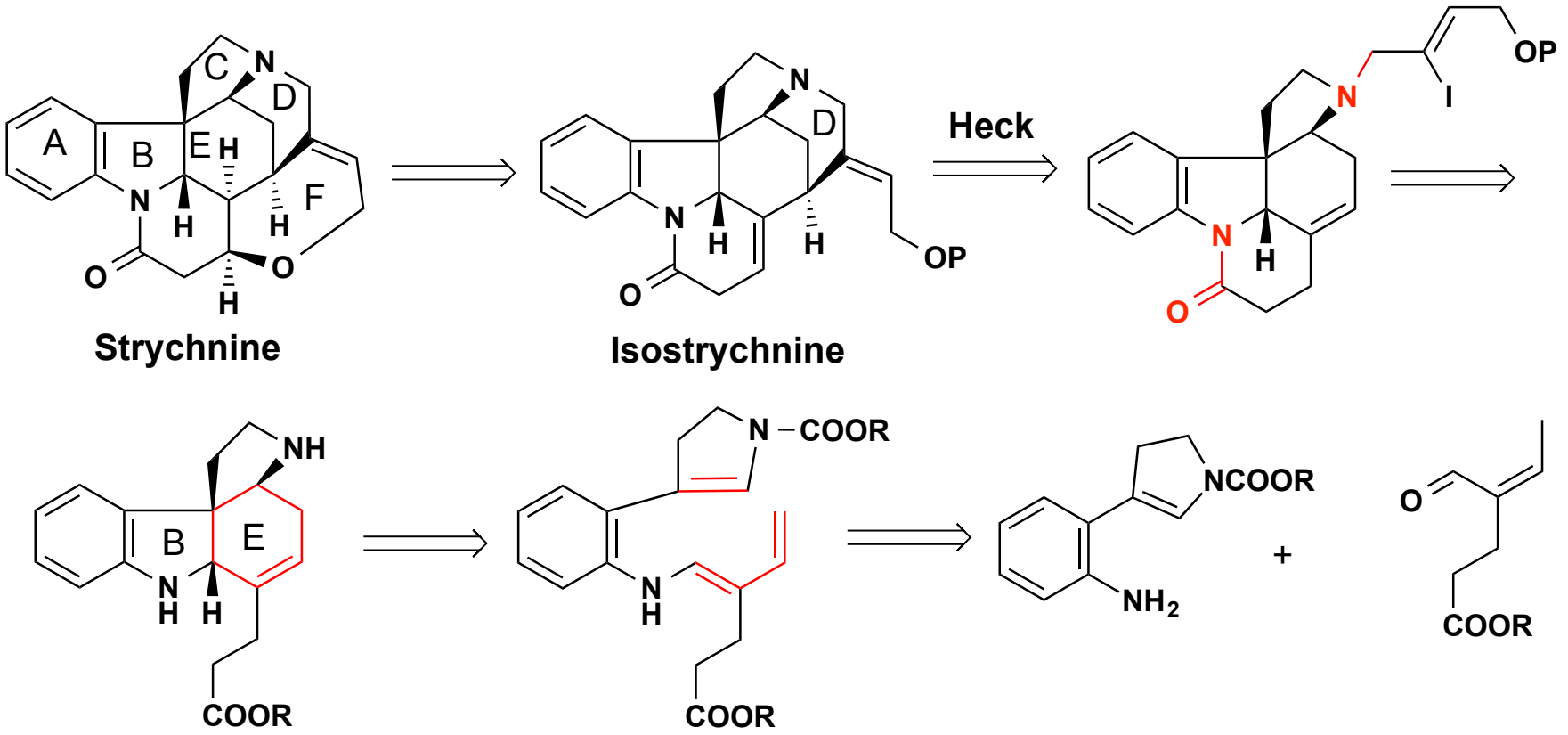
Woodward's Total Synthesis of Strychnine: *A Relay Synthesis*



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 Kown

Cyclopropane to cyclopentene rearrangement

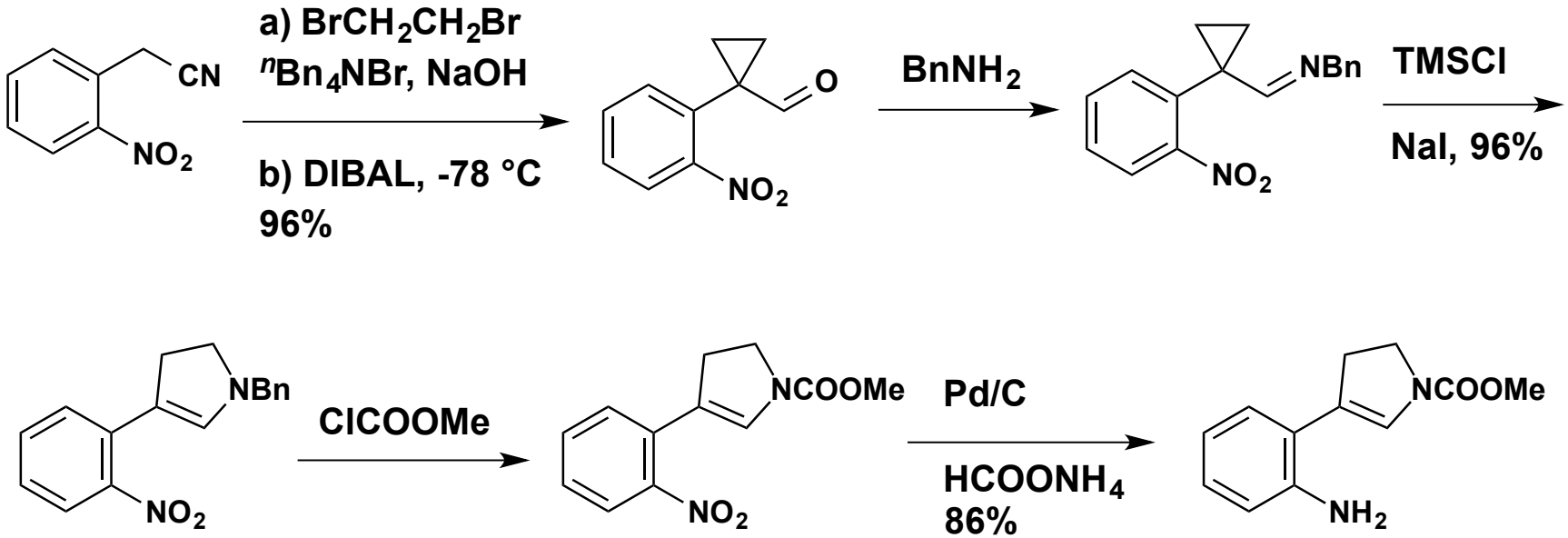
Cyclopropylimine to pyrrole rearrangement

Von Braun Reaction

Diels-Alder reaction

Heck reaction

Rawal's Total Synthesis of Strychnine

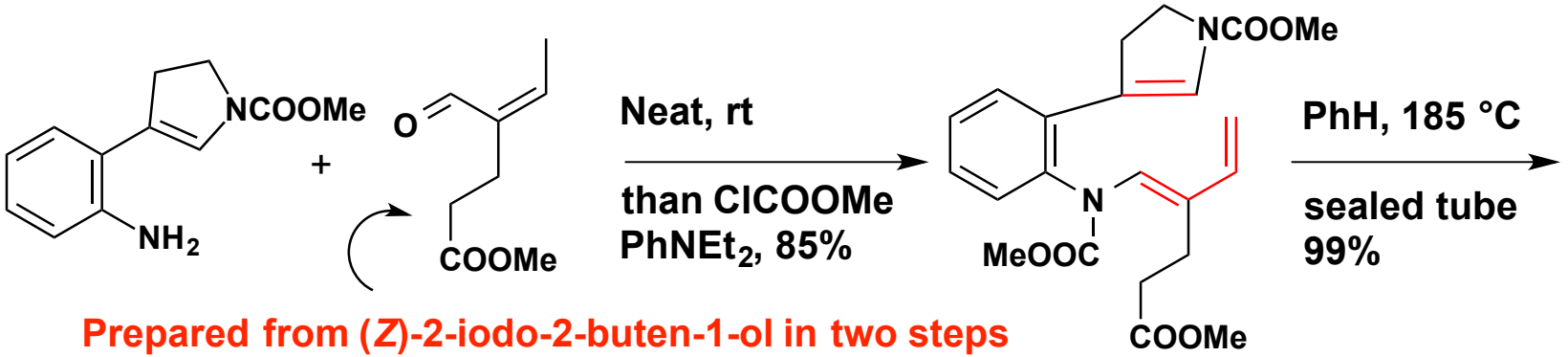


Von Braun Reaction

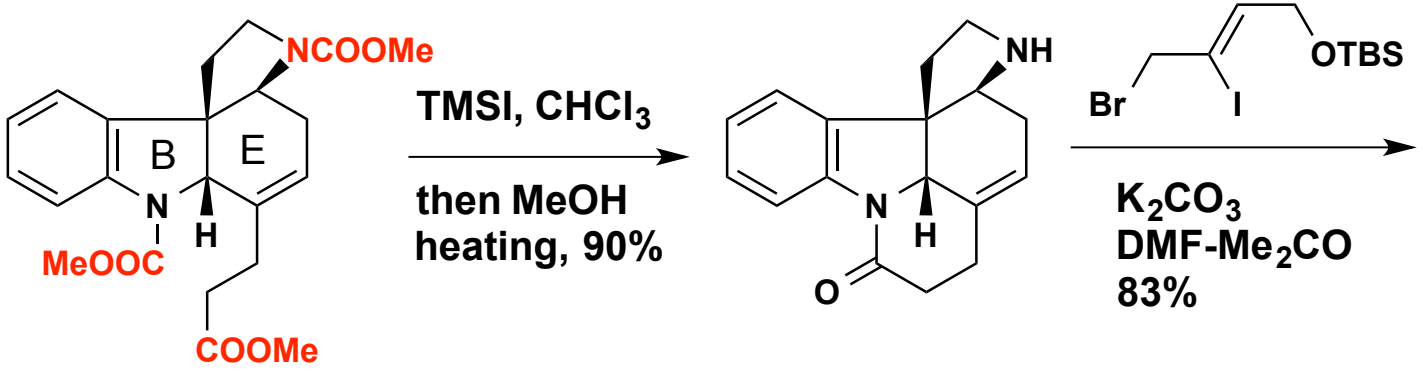
Mechanism of:
Cyclopropyliminium ion rearrangement
Von Braun reaction

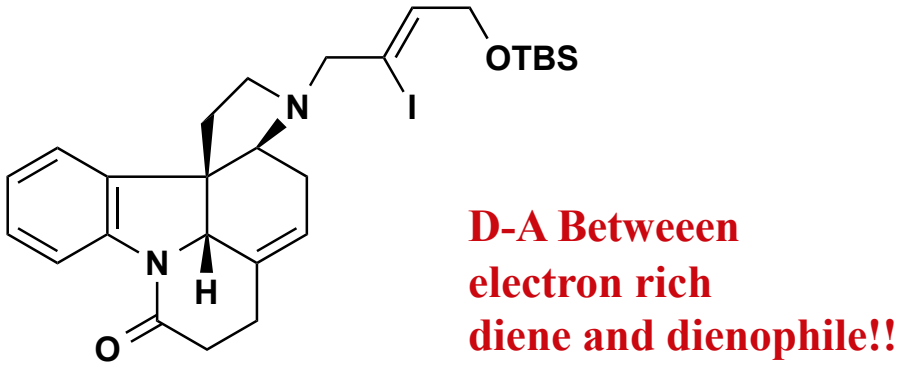
Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685-2686.

Rawal's Total Synthesis of Strychnine

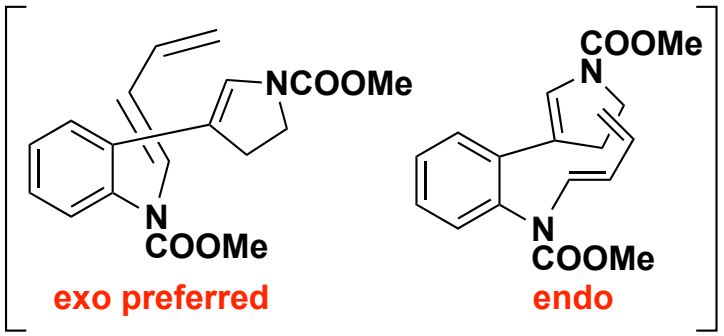


Prepared from (*Z*)-2-iodo-2-buten-1-ol in two steps





D-A Betweeen electron rich diene and dienophile!!



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

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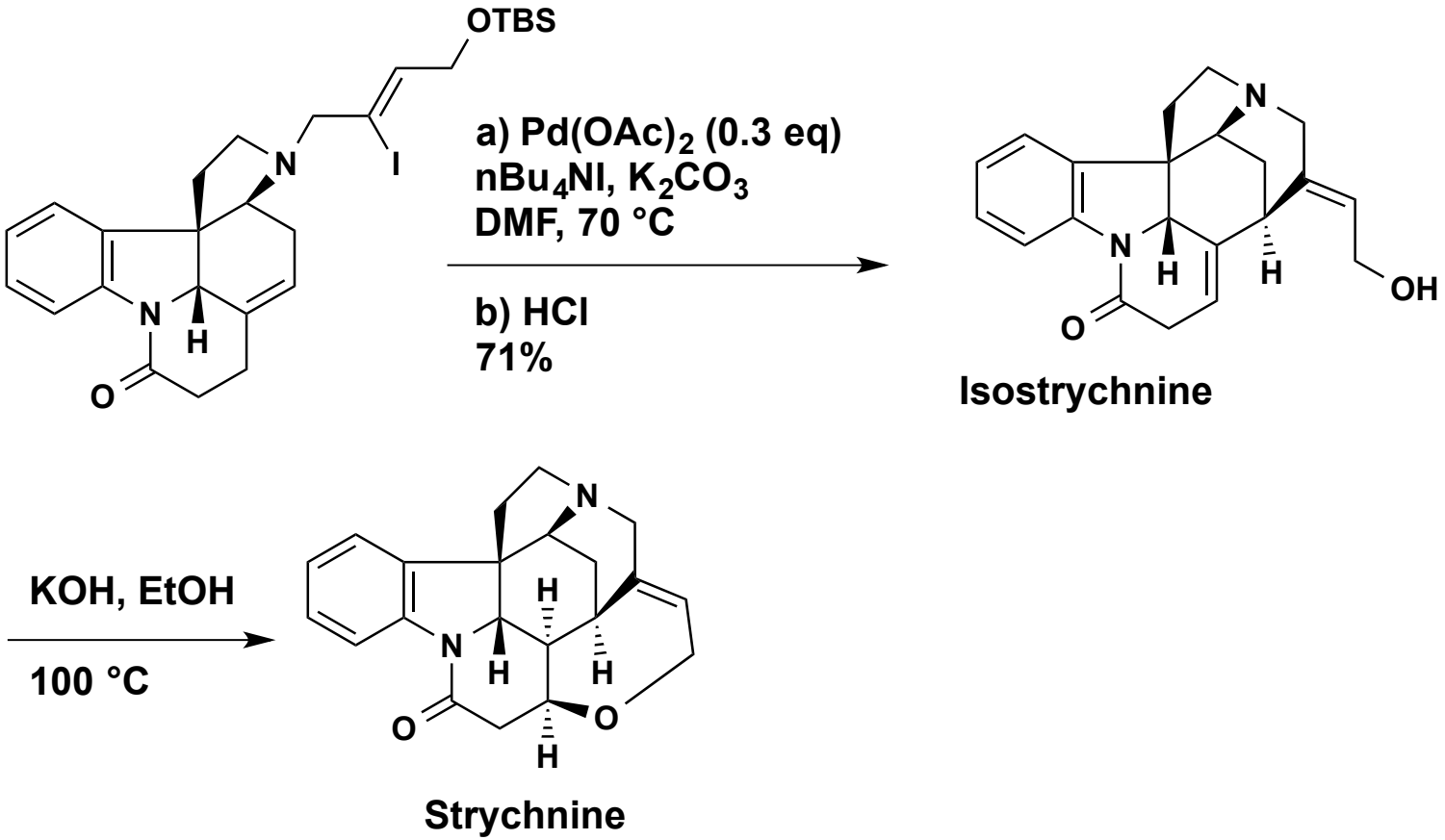
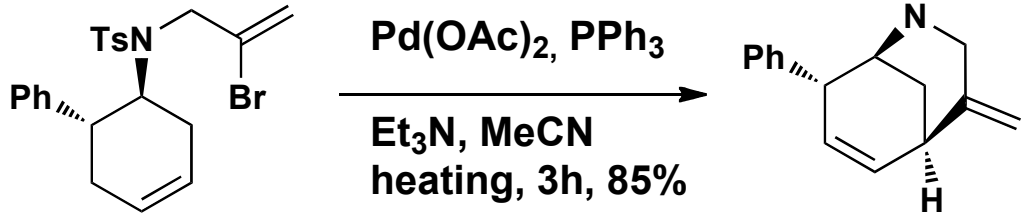


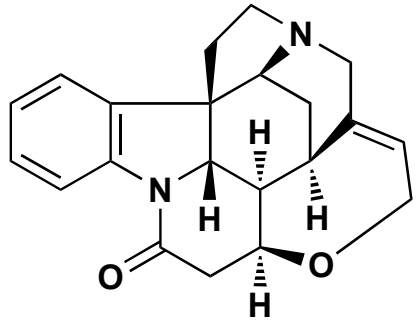
Heck reaction: Heck, R. F. *Org. React*. **1982**, *27*, 345.
Jeffery's conditions: *Tetrahedron Lett*. **1985**, *26*, 2667.

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.

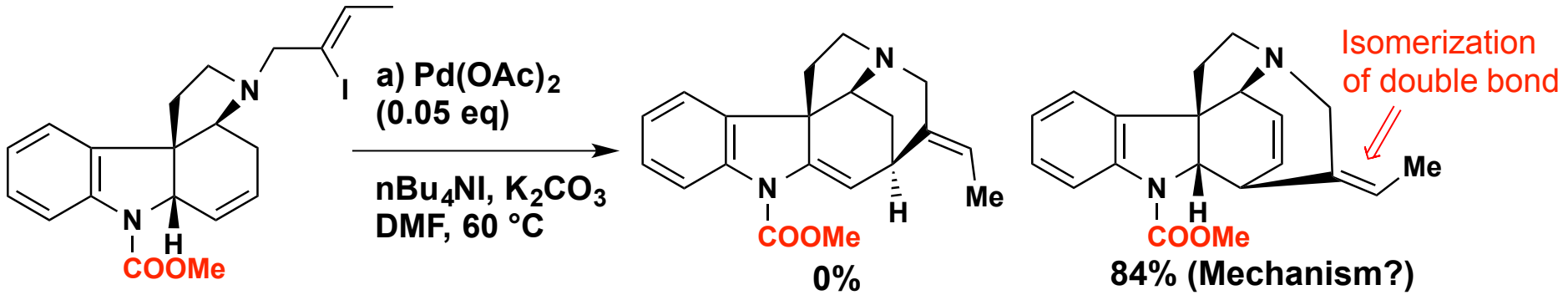
Rawal's Model Studies: Influence of Protective Group

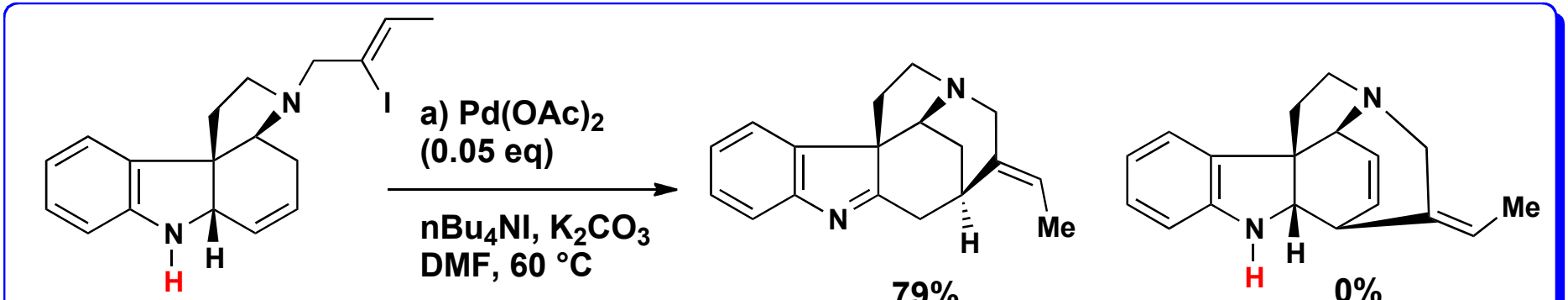


Rawal, V. H. *Tetrahedron Lett.* **1991,** *32,* 1695-98.



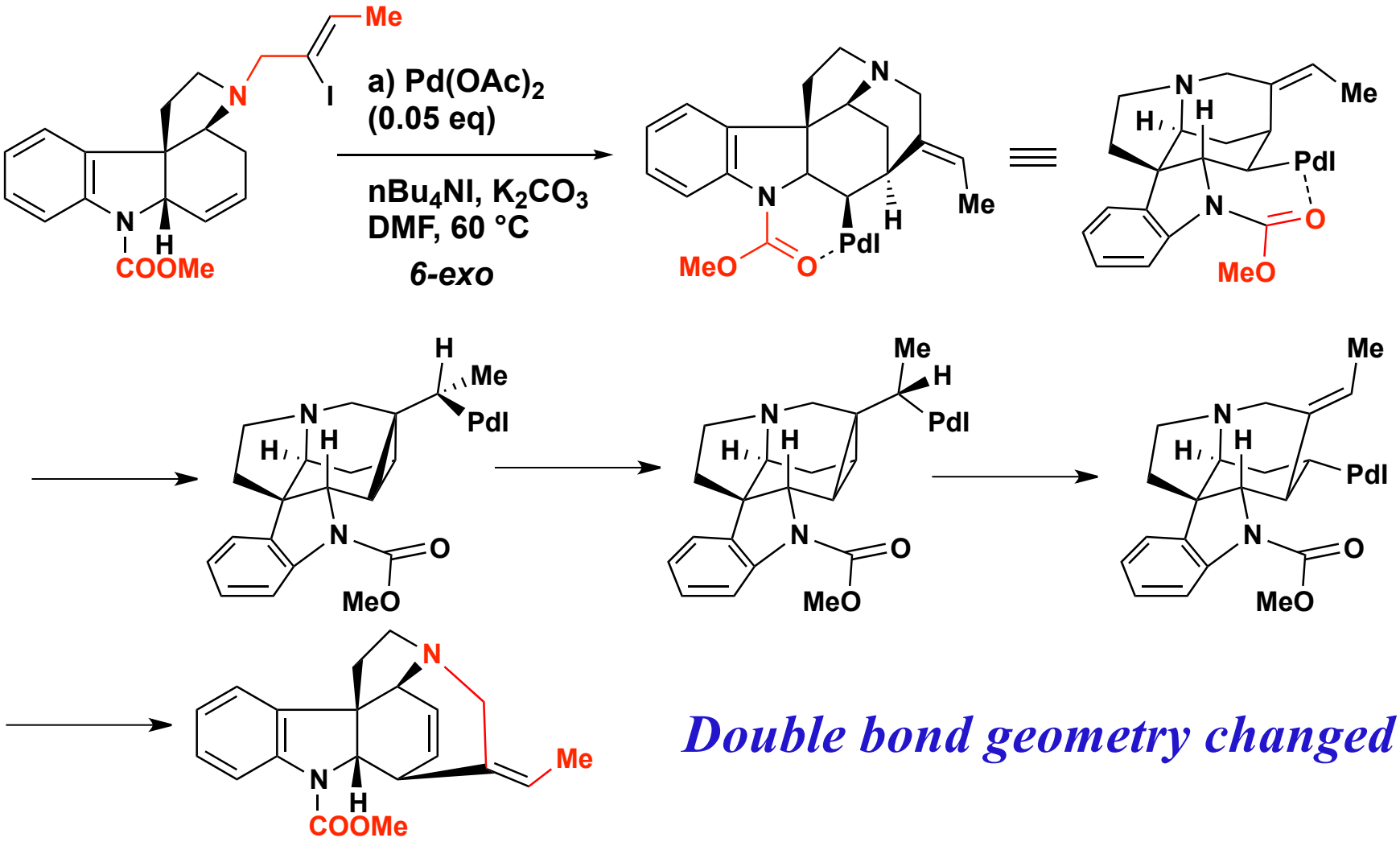
Strychnine





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

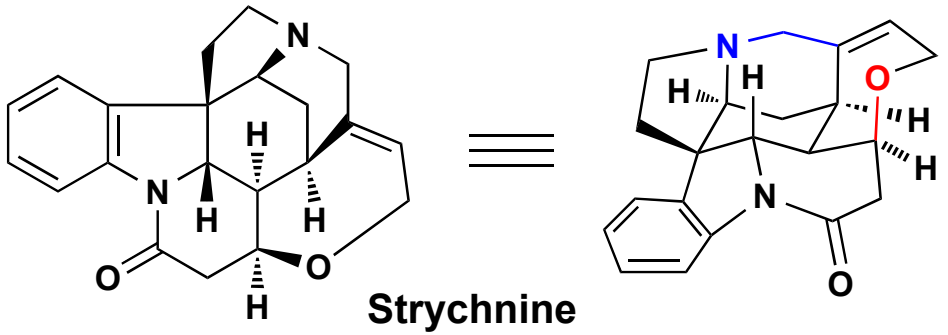
Diels-Alder reaction

Heck reaction

Key Features:

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

Strychnine: Key background

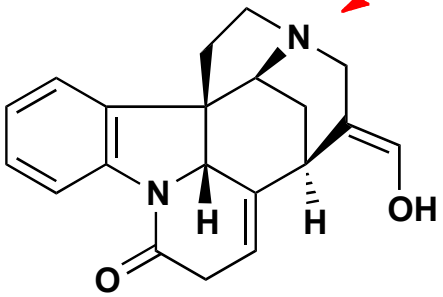


Strychnine

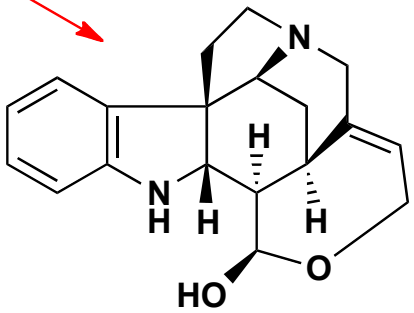
KOH, EtOH
85 °C

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

Degradation studies
in 1940's

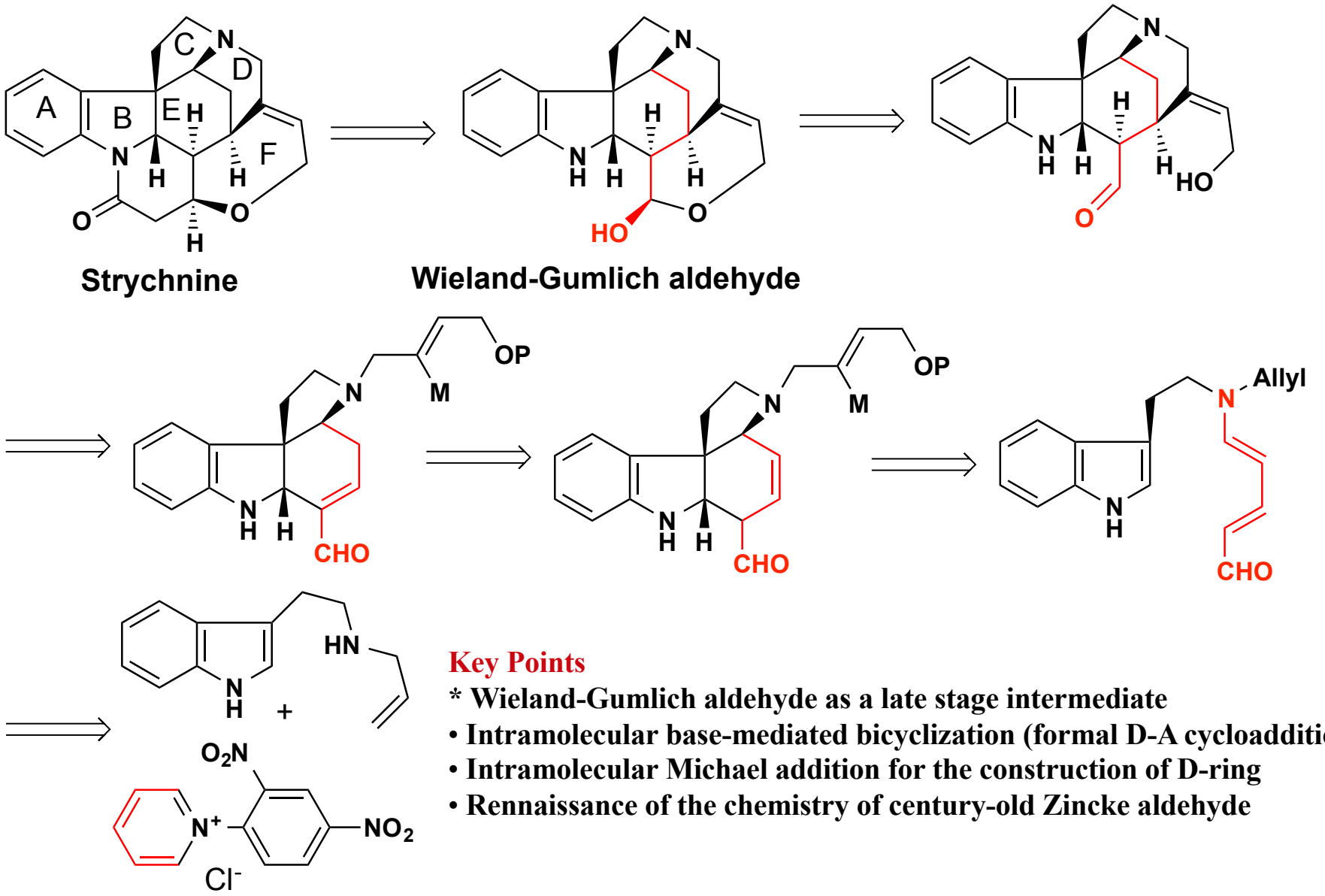


Isostrychnine



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

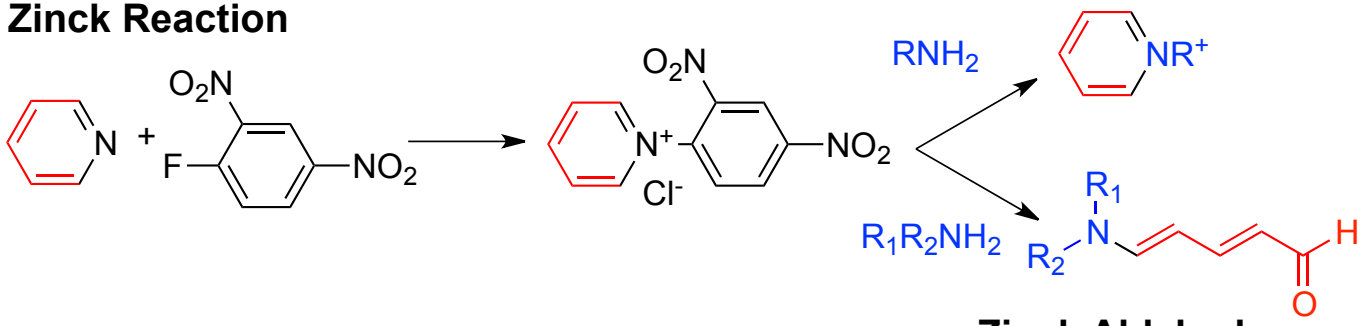
Diels-Alder reaction

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

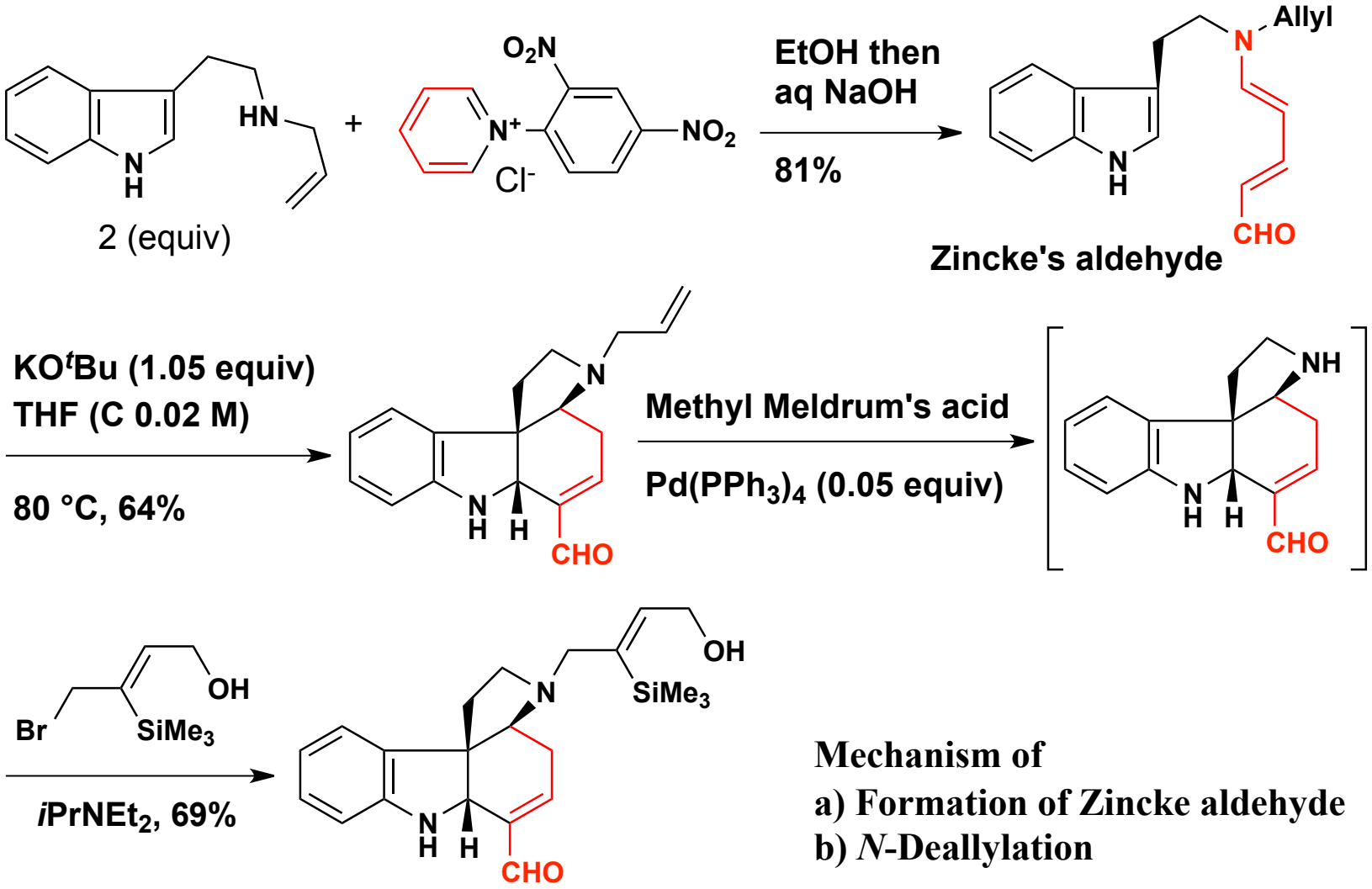
Re-discovered in 2006 with wrong structure

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



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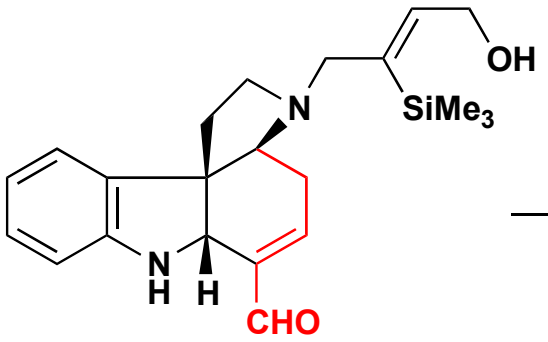
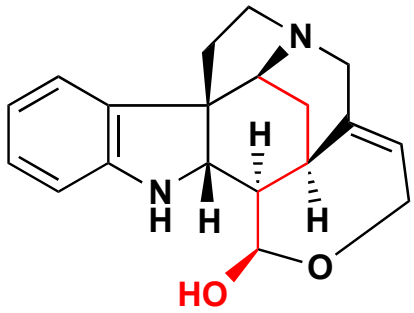
Full account: *J. Org. Chem.* **2012**, *77*, 17-46.
Cycloaddition: Stepwise mechanism: Vandewal, C. D.; Houk, K. N. *Chem. Sci.* **2012**, *3,* DOI: 10.1039/c2sc01072k

Vanderwal's Total Synthesis of Strychnine



NaHMDS, NMP
then $CuBr.SMe_2$

0° to 65 °C
5-10%

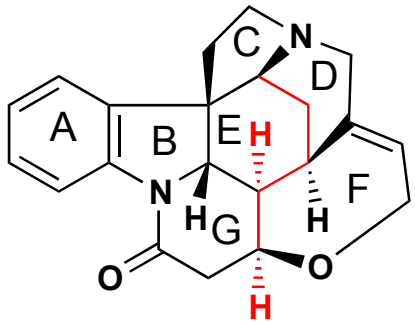


Wieland-Gumlich aldehyde

via:
Brook rearrangement
Conjugate addition

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

60-80%



Strychnine

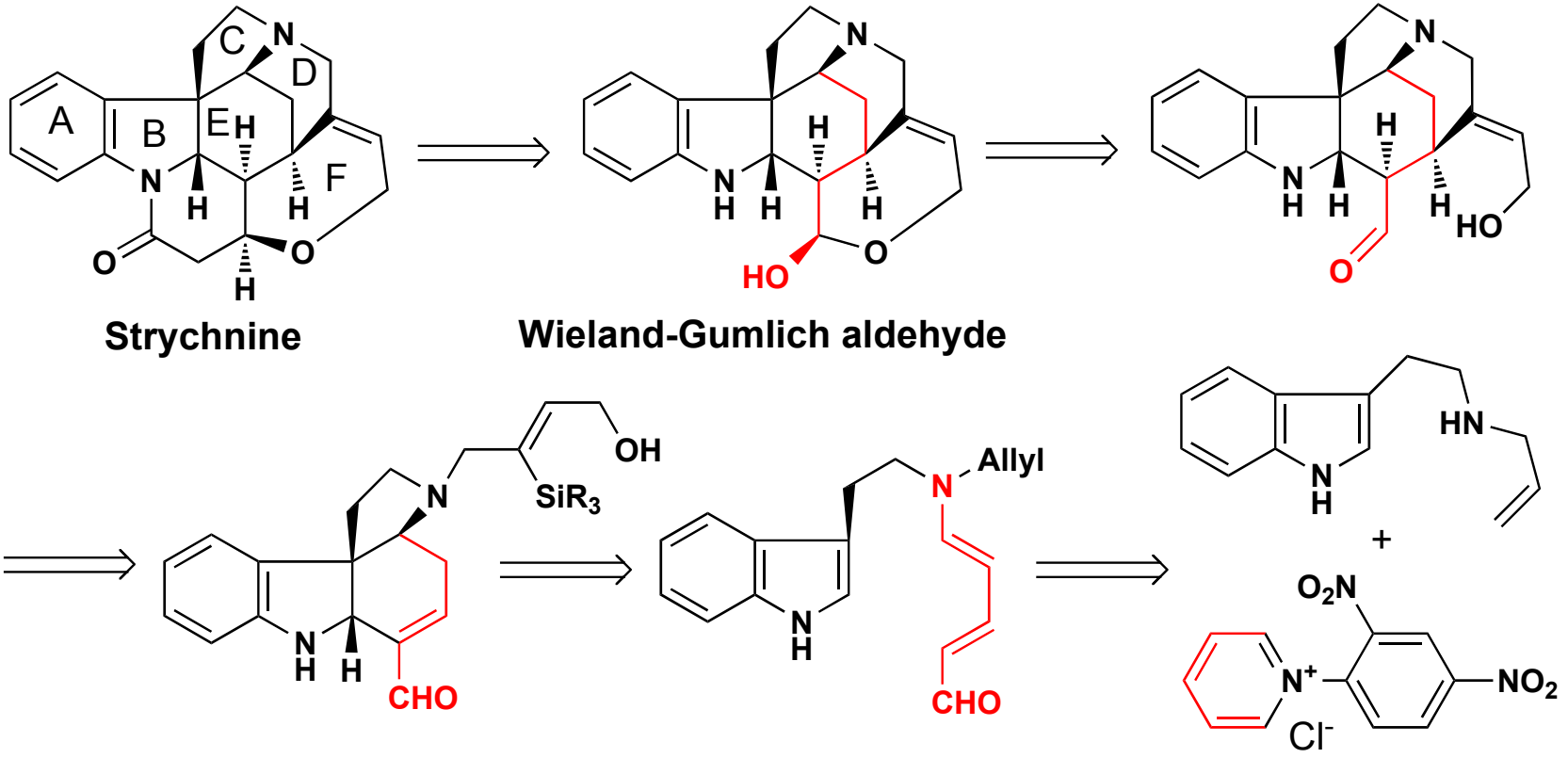
5 carbon derived from pyridine were engaged in the formation of C, D, E, F, G ring

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

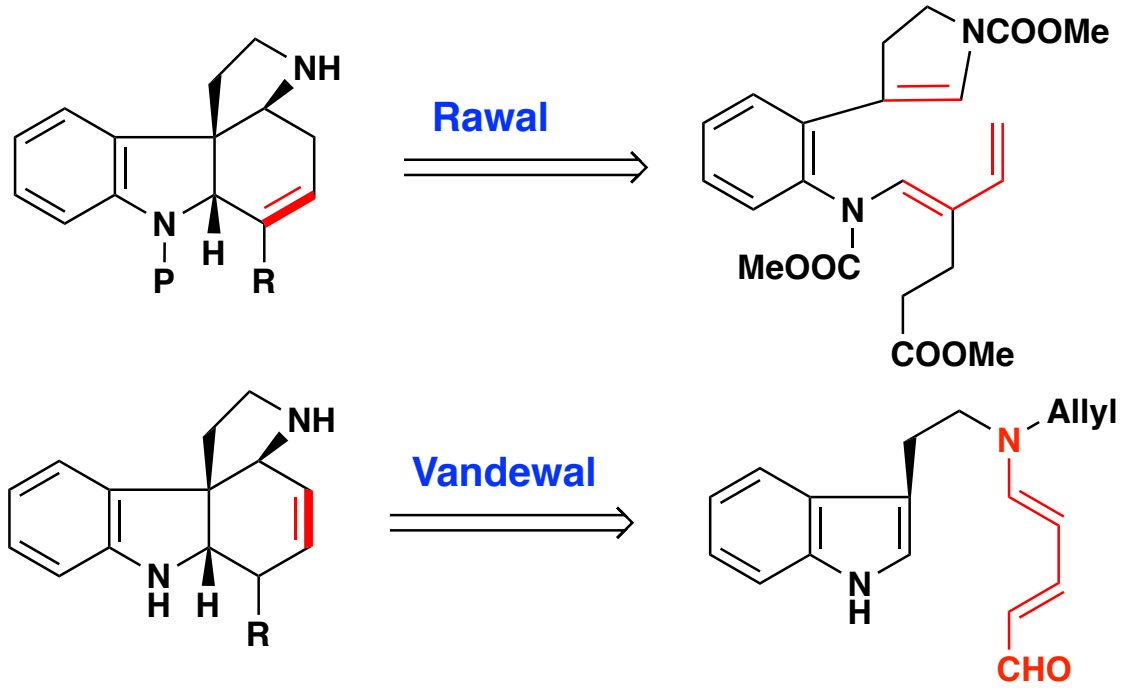
Formation of tetracycle: an Anion-Induced Biscyclization:
Not concerted, but a Domino Michael addition/Mannich sequence

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)	-	+	-	+++++