

Strategies in Synthetic Planning

Modern Stylistic Points in Retrosynthetic Analysis



"HIS PATH-PLANNING MAY BE
SUB-OPTIMAL, BUT IT'S GOT FLAIR."

Jen Alleva

MacMillan Group Meeting

January 8th 2014

Strategies in Synthetic Planning

Development and Conceptualization of Retrosynthetic Analysis

"By the end of this course I will be able to look at all of your retrosyntheses and know which one of you produced it. You will all develop your own unique and recognizable style over the next few months."

—Paul Reider, Graduate Synthesis



Common trend: Modern organic chemists have unique retrosynthetic strategies rendering their syntheses easily recognizable to the well-read practitioner of organic chemistry

Strategies in Synthetic Planning

Development and Conceptualization of Retrosynthetic Analysis

"Retrosynthetic analysis is a problem-solving technique for transforming the structure of a synthetic target (TGT) molecule to a sequence of progressively simpler structures along a pathway which ultimately leads to simple or commercially available starting materials for chemical synthesis."

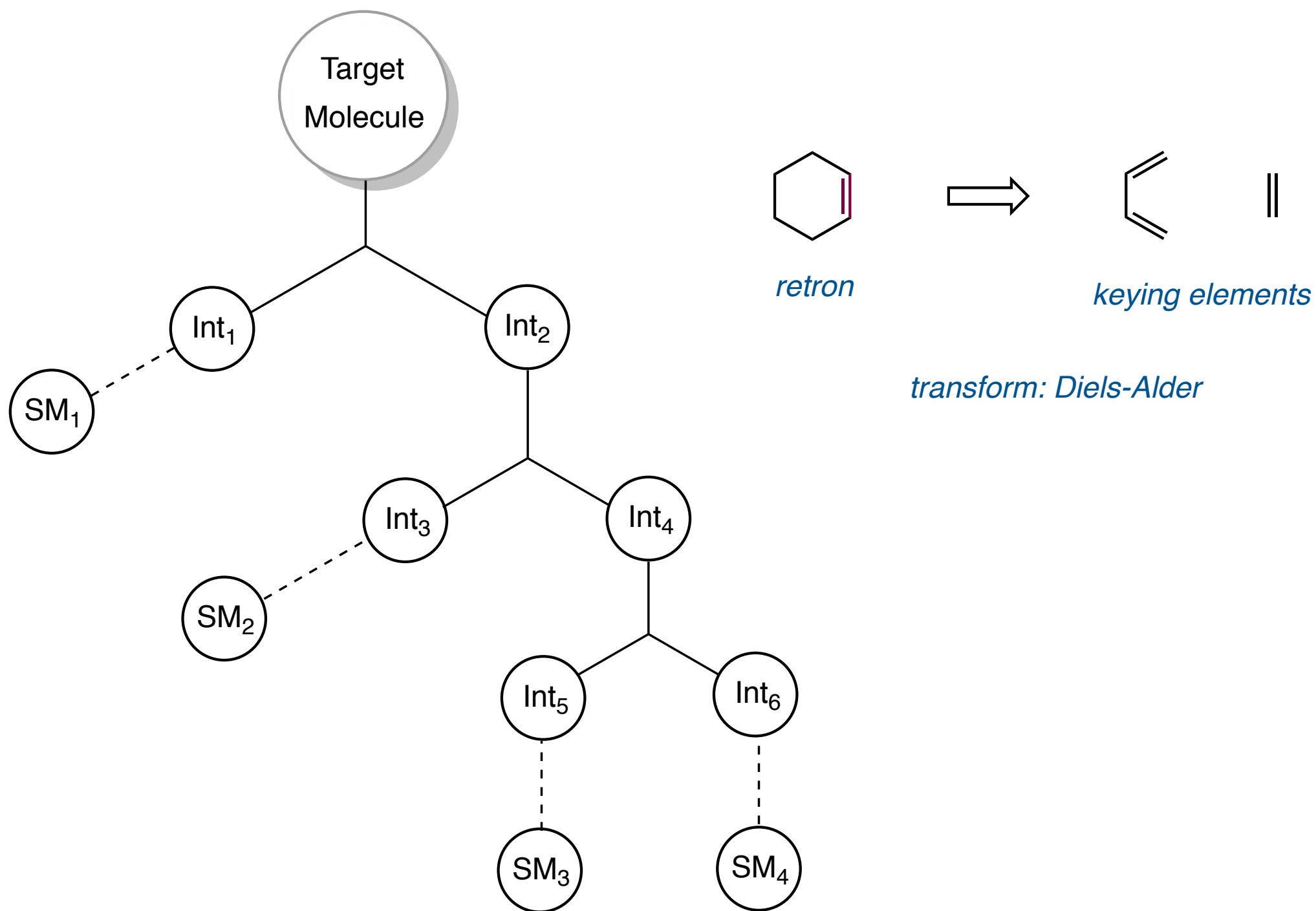
- E. J. Corey, Harvard University
 - MIT 1945–1950, John Sheehan
 - Appointed as Instructor at UIUC at age 22
 - Earned professorship at UIUC at age 27
 - Moved to Harvard in 1959
 - Nobel Prize in Chemistry 1990
 - Detailed retrosynthetic analysis and techniques



Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*, John Wiley & Sons, New York, 1995, pp 6.

Strategies in Synthetic Planning

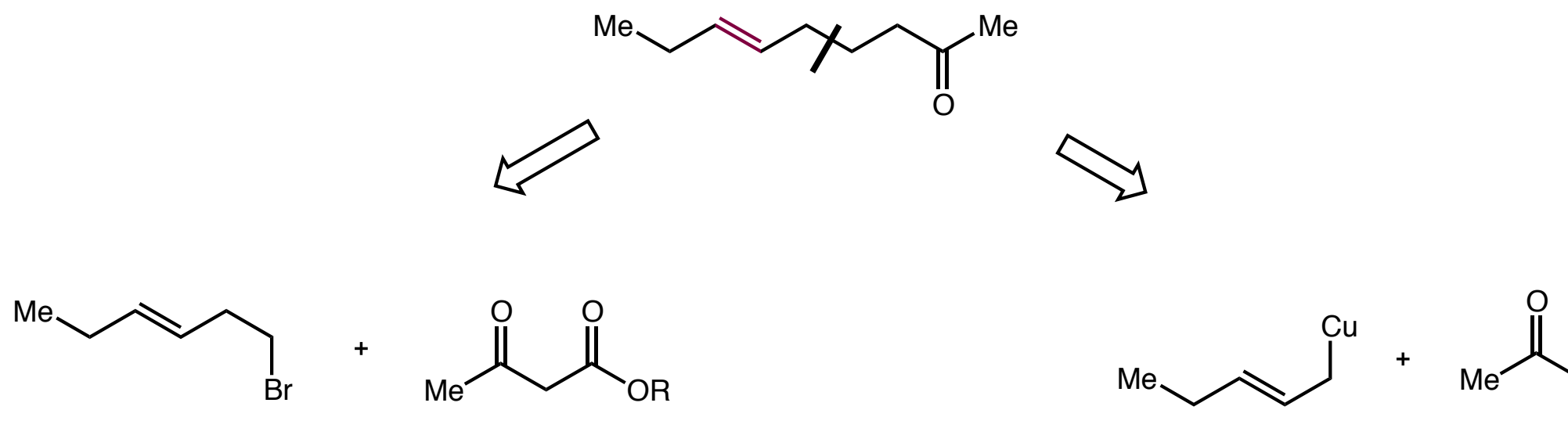
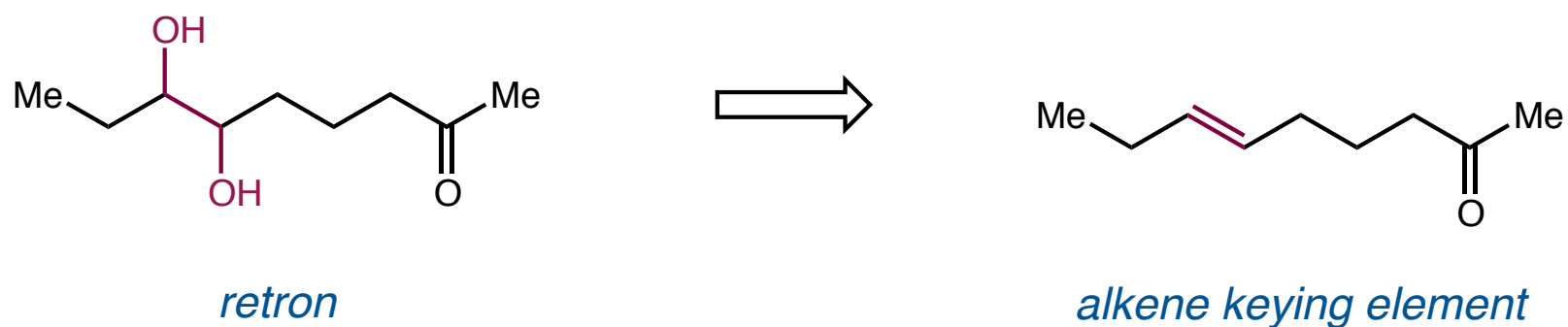
Development and Conceptualization of Retrosynthetic Analysis



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Strategies in Synthetic Planning

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Strategies in Synthetic Planning

decreasing complexity

The main goal of retrosynthetic analysis is to reduce the complexity of the target: [How?](#)

Strategies in Synthetic Planning

decreasing complexity

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1. The application of powerful transforms:

forming key bonds in the molecular skeleton (i.e. C–C bonds)

aldol, Diels-Alder, intramolecular alkylations, C–H activation, cross couplings

forging stereocenters through substrate control (modernly reagent control)

cascade reactions

Strategies in Synthetic Planning

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The main goal of retrosynthetic analysis is to reduce the complexity of the target: **How?**

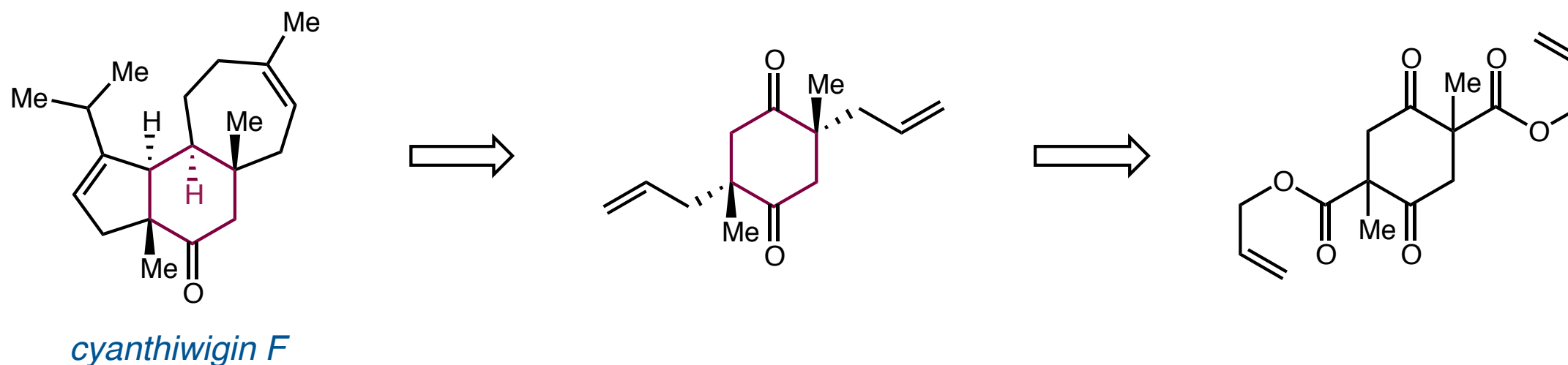
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skeletal rearrangements, transpositions, isomerization reactions, epimerizations

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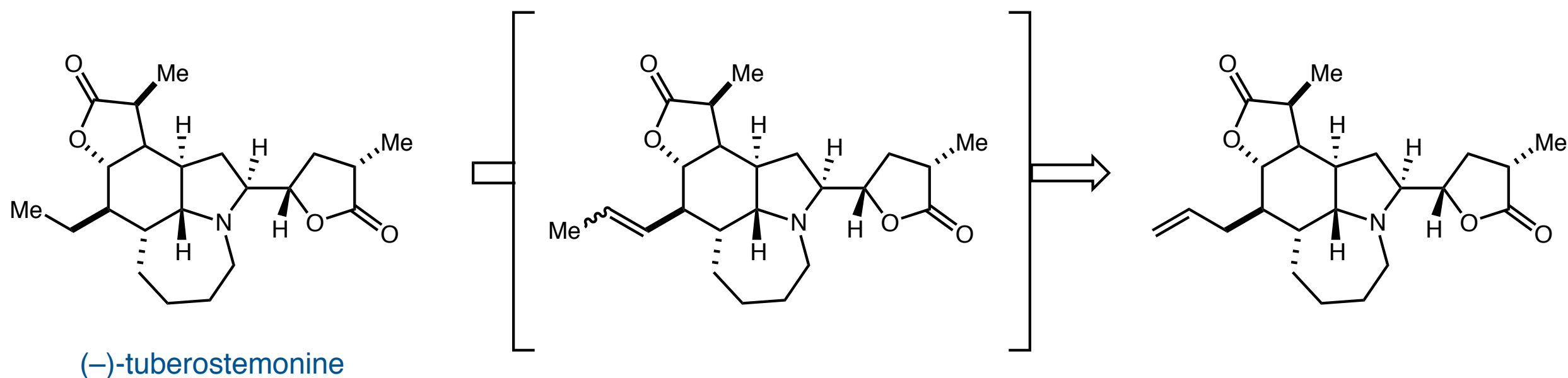
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protecting groups, masking groups, activating/deactivating groups, adding functional groups or bonds

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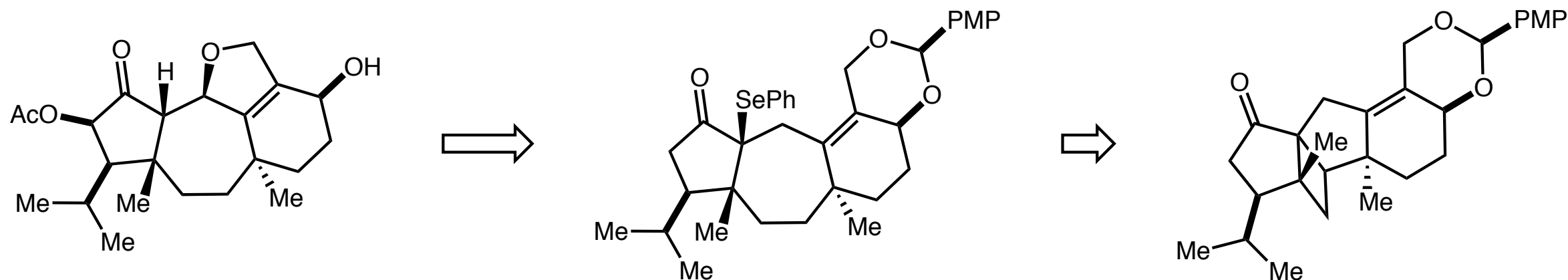
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guanacastepene E

Shipe, W. D.; Sorensen, E. J. *J. Am. Chem. Soc.*, **2006**, 128, 7025.

Strategies in Synthetic Planning

Classes of Retrosynthetic Disconnections

Transform-Based

look-ahead to powerfully simplifying
transform or tactic

i.e. the "Key Step"

Structure-Goal

directed at the structure of a potential
intermediate or SM

i.e. the branch point

Topological Strategies

strategic analysis of correlated
bond disconnections

i.e. rearrangements
and network analysis

Stereochemical Strategies

retrosynthetic strategy which clears stereocenters
with either mechanism or substrate control

most common in modern synthesis

Functional Group-Based Strategies

reduction in molecular complexity based on the
interchange, installation and removal of functional groups

"redox relay", directing groups, heterocycle formation

Strategies in Synthetic Planning

Acyclic Systems

What to disconnect and what to preserve

Strategies in Synthetic Planning

Acyclic Systems

What to disconnect and what to preserve

Disconnect

to make symmetrical fragments

C–X bonds (C–heteroatom, esters, amides, etc)

either E or Z double bonds

1–3 bonds away from functional groups

bonds that attach rings to chains (produce the largest fragment)

Preserve

building block groups (alkyl, aryl)

remote stereocenters (more than 3C is remote)

skeletal bonds proximal to remote stereocenters

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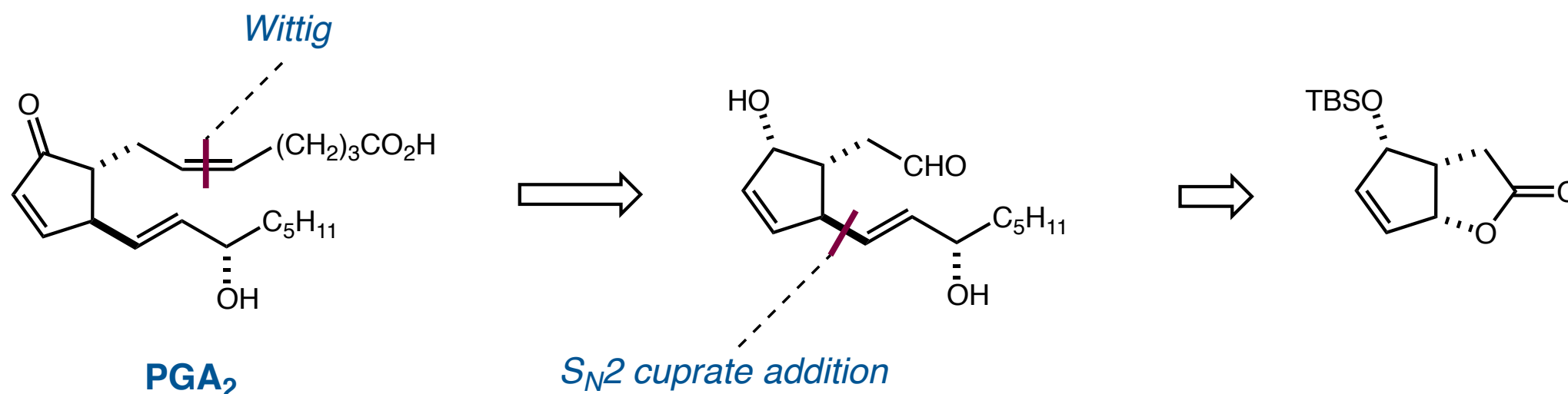
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Strategies in Synthetic Planning

Ring-Bonds in Isolated Rings

What to disconnect and what to preserve

Disconnect

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C–X bonds (C–heteroatom, esters, amides, etc)

easily formed rings (lactone, lactam, hemiacetal)

Strategies in Synthetic Planning

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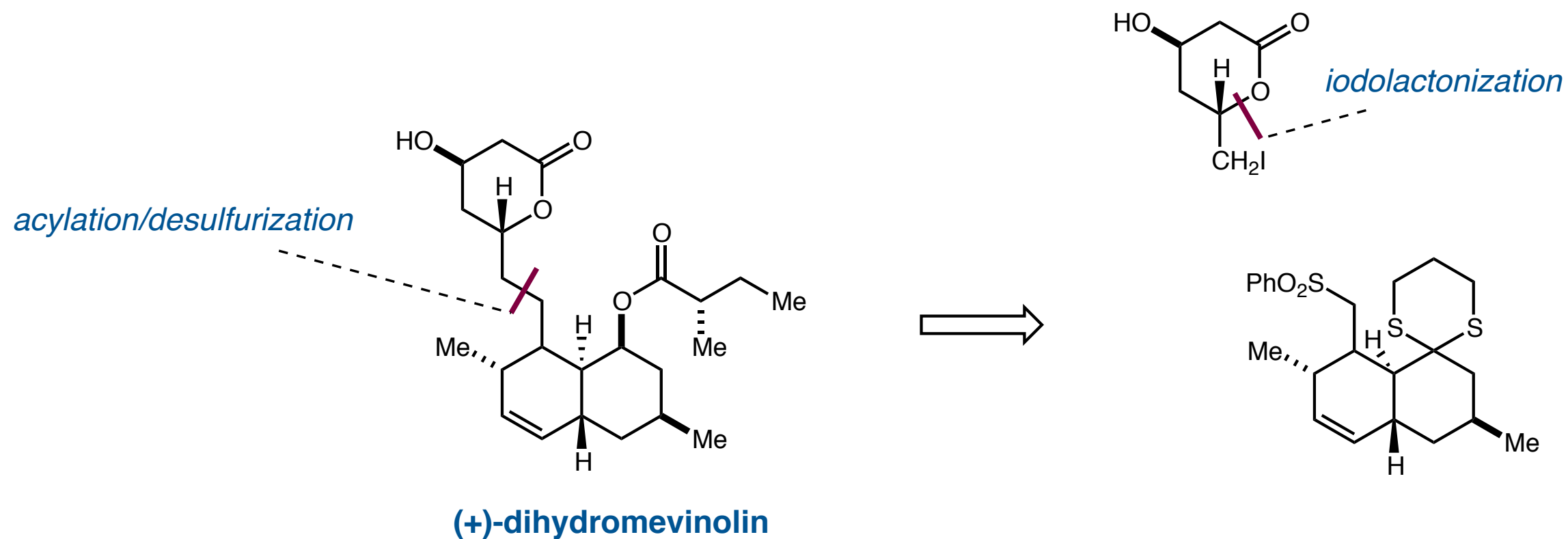
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Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*, John Wiley & Sons, New York, 1995, pp 38.

Strategies in Synthetic Planning

Disconnection of Fused Rings

What to disconnect and what to preserve

Disconnect

[2+1] and [2+2] retrons

cocyclic bonds (cycloaddition retrons)

heteratom containing rings (lactones, lactam, ketal)

fused rings with exendo bonds (cation- π -cyclizations)

Preserve

building block rings (aryl)

bonds that make ≥ 7 membered rings

skeletal bonds proximal to remote stereocenters

bonds that make stereocenters

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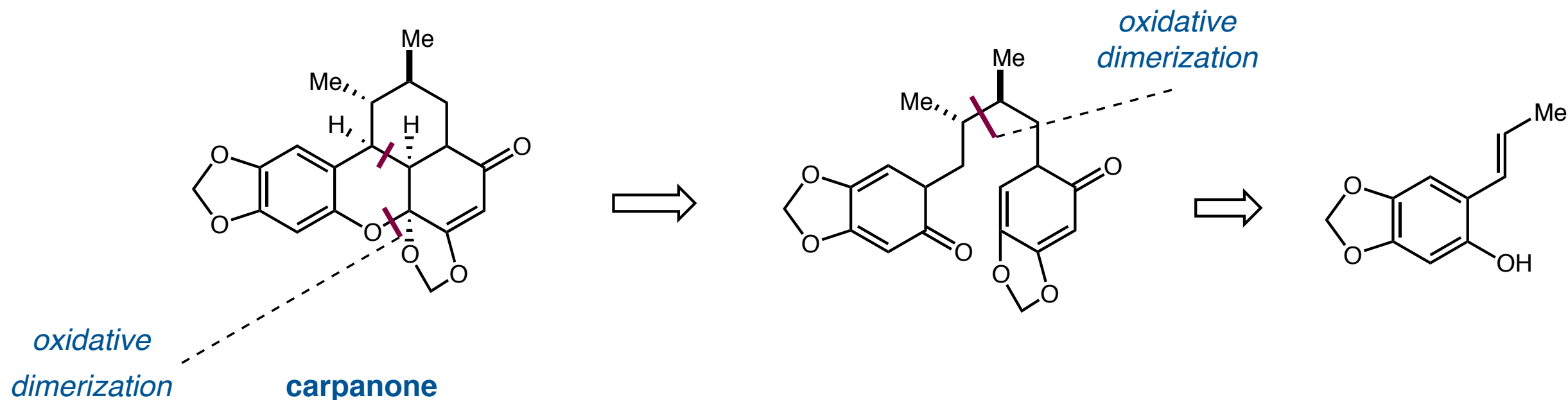
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Chapman, O. L.; Engel, M. R.; Springer, J. P.; Clardy, J. C. *J. Am. Chem. Soc.* **1971**, 93, 6696.
Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*, John Wiley & Sons, New York, 1995, pp 41.

Strategies in Synthetic Planning

Disconnection of Bridged Rings

What to disconnect and what to preserve

Disconnect

exendo bonds in 4–7 membered rings

C–heteratom bonds preferentially over C–C bonds

bonds that contain the most bridgehead atoms (network analysis)

Preserve

bridges that if disconnected yield ≥ 7 membered rings

bonds that would yield medium size rings

bonds that yield pendant chains

Strategies in Synthetic Planning

Disconnection of Bridged Rings

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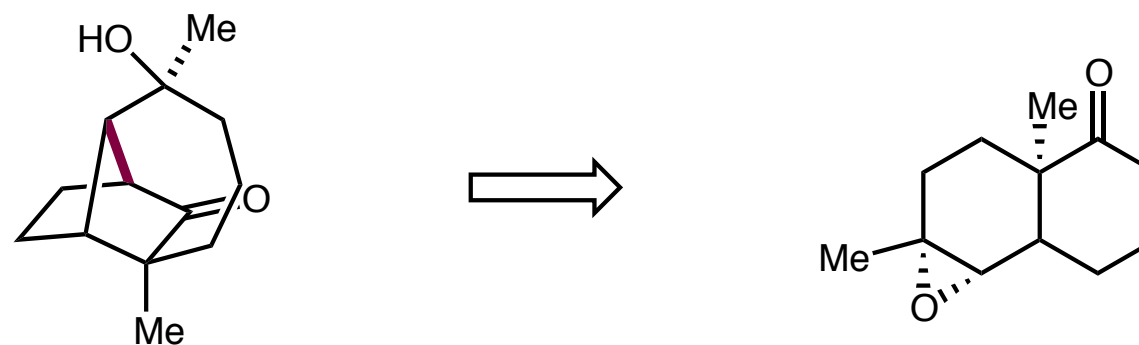
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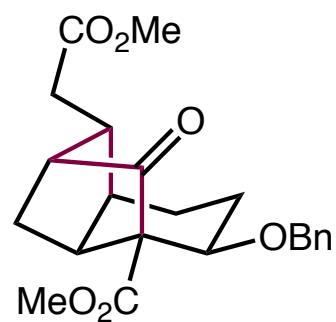
en route to longifolene

McMurry, J. E.; Isser, S. J. *J. Am. Chem. Soc.*, **1972**, *94*, 7132.

Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*, John Wiley & Sons, New York, 1995, pp 42.

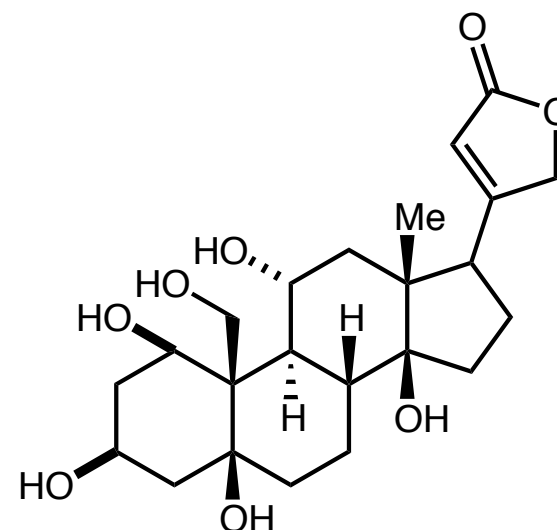
Applied Strategies in Retrosynthetic Analysis

Topological



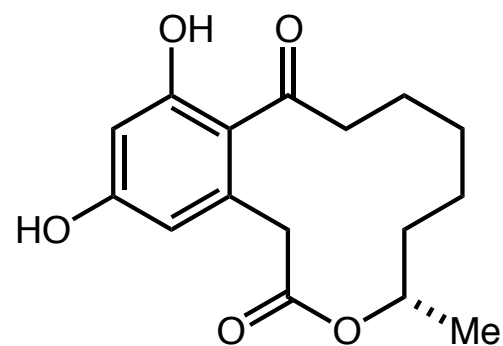
Phragmalin-type Limonoids
Sarpong Group, Berkeley

Functional Group-Based



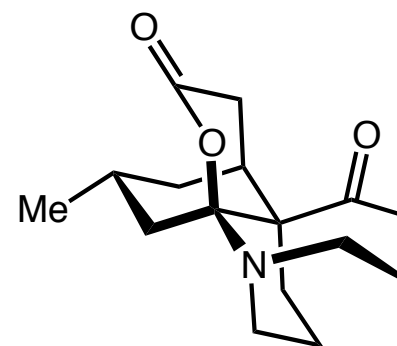
Ouabagenin
Baran Group, Scripps

Transform-Based



(-)-Curvularin
Stoltz Group, Caltech

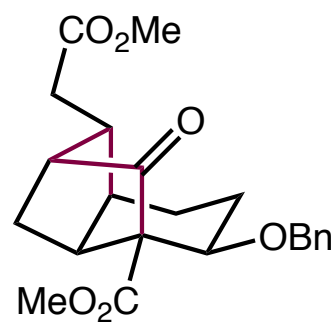
Structure-Goal



(-)-Lycojapodine A
Lei Group, Tianjin University

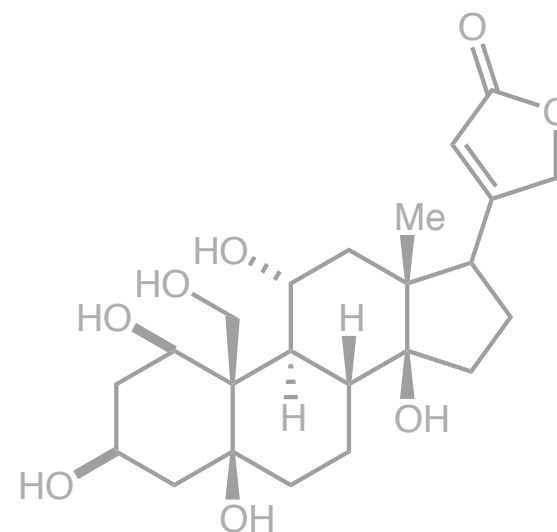
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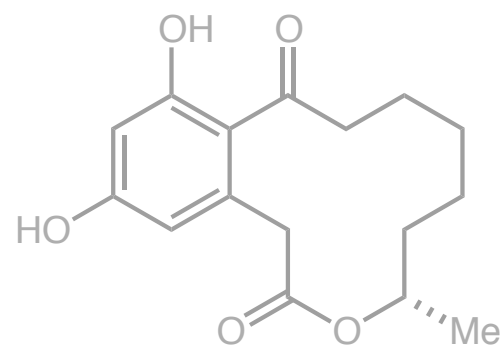
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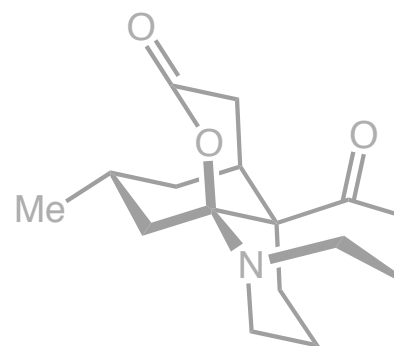
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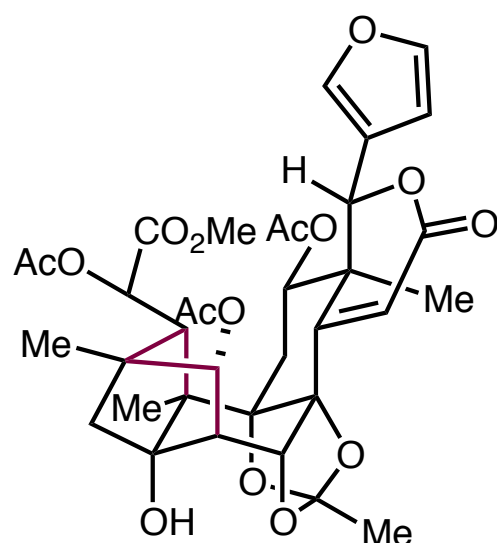
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Synthesis of the Framework of Phragmalin-Type Limonoids

Utilizing Network Analysis: a topological strategy



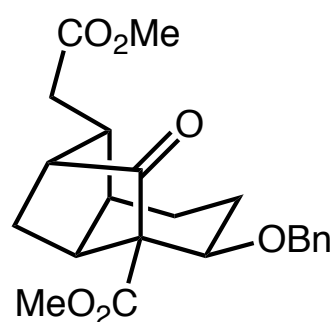
Xylococcinsin O

phragmalin-type limonoid

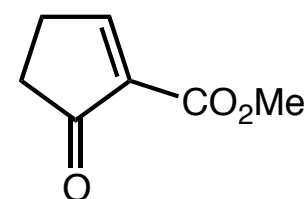
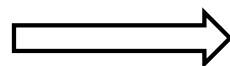
- potent anti-cancer, antibiotic, anti-inflammatory properties
- highly oxygenated triterpenoid
- key challenge is synthesis of the carbocyclic core



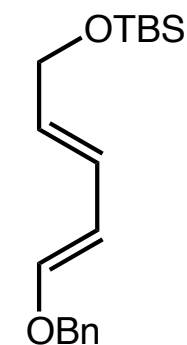
octahydro-1H-2,4-methanoindene core



6 steps



+



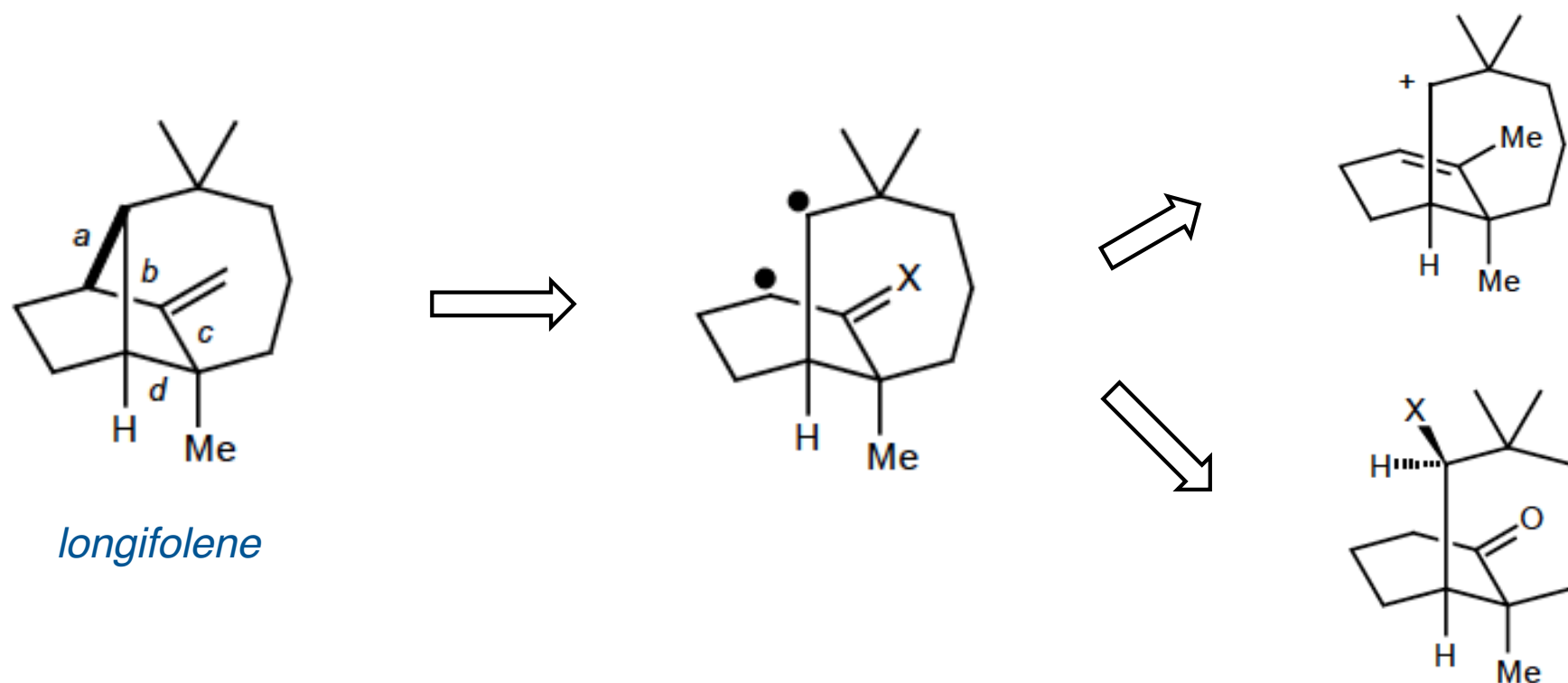
Lebold, T. M.; Gallego, G. M.; Marth, C. J.; Sarpong, R. *Org. Lett.*, **2012**, 8, 2110.

Synthesis of the Framework of Phragmalin-Type Limonoids

Utilizing Network Analysis: a topological strategy

Guiding Principles of Network Analysis

- in general: it is easier to synthesis fused rings that bridged systems
- identify the bonds that are made to the most bridged system
- retrosynthetic removal of these bonds will lead to the most simple keying element



Corey, E. J.; Ohno, M., Mitra, R. B.; Vatakancherry, P. A. *J. Am. Chem. Soc.* **1964**, *86*, 487.

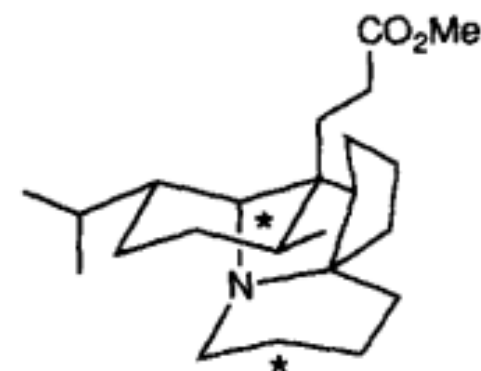
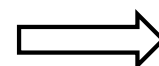
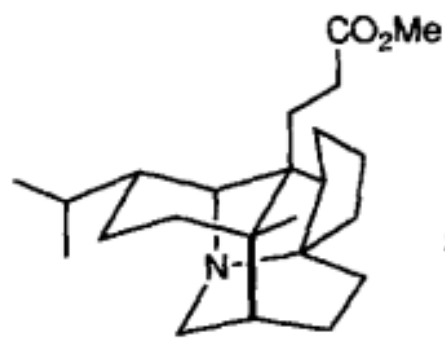
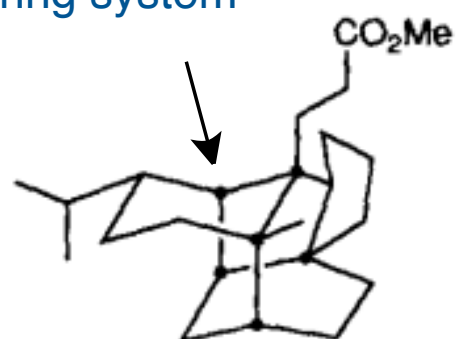
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most bridged
ring system

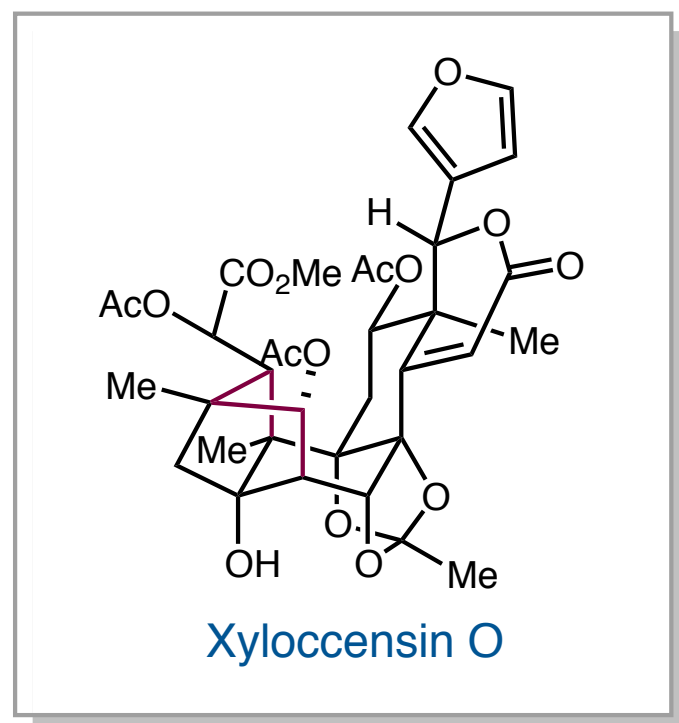


homodaphniphyllate framework

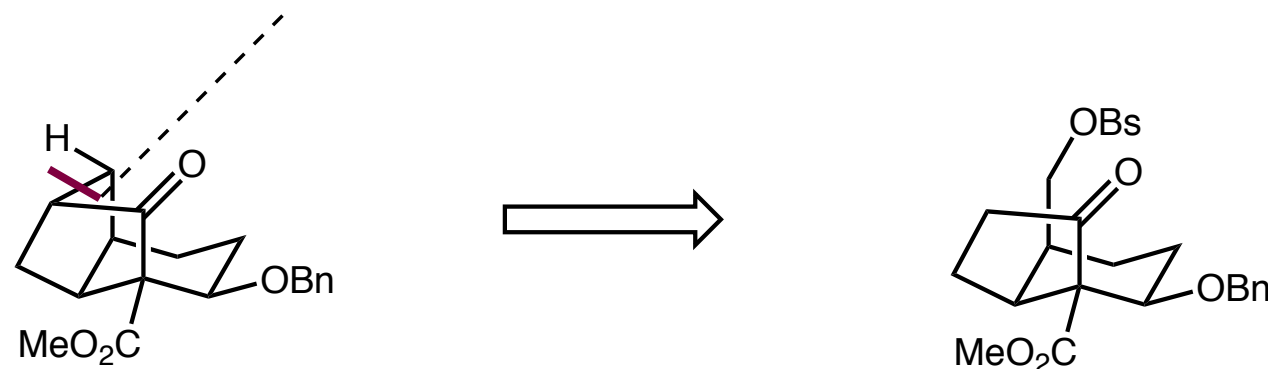
Heathcock, C. *Angew. Chem. Int. Ed.*, **1992**, 31, 665.

Synthesis of the Framework of Phragmalin-Type Limonoids

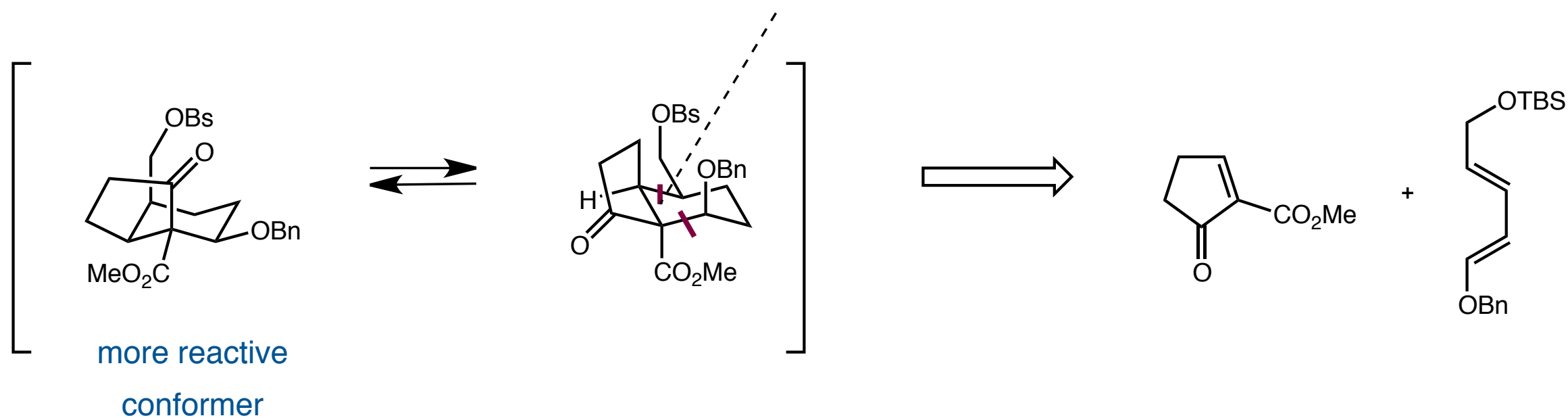
Retrosynthetic Analysis



intermolecular alkylation

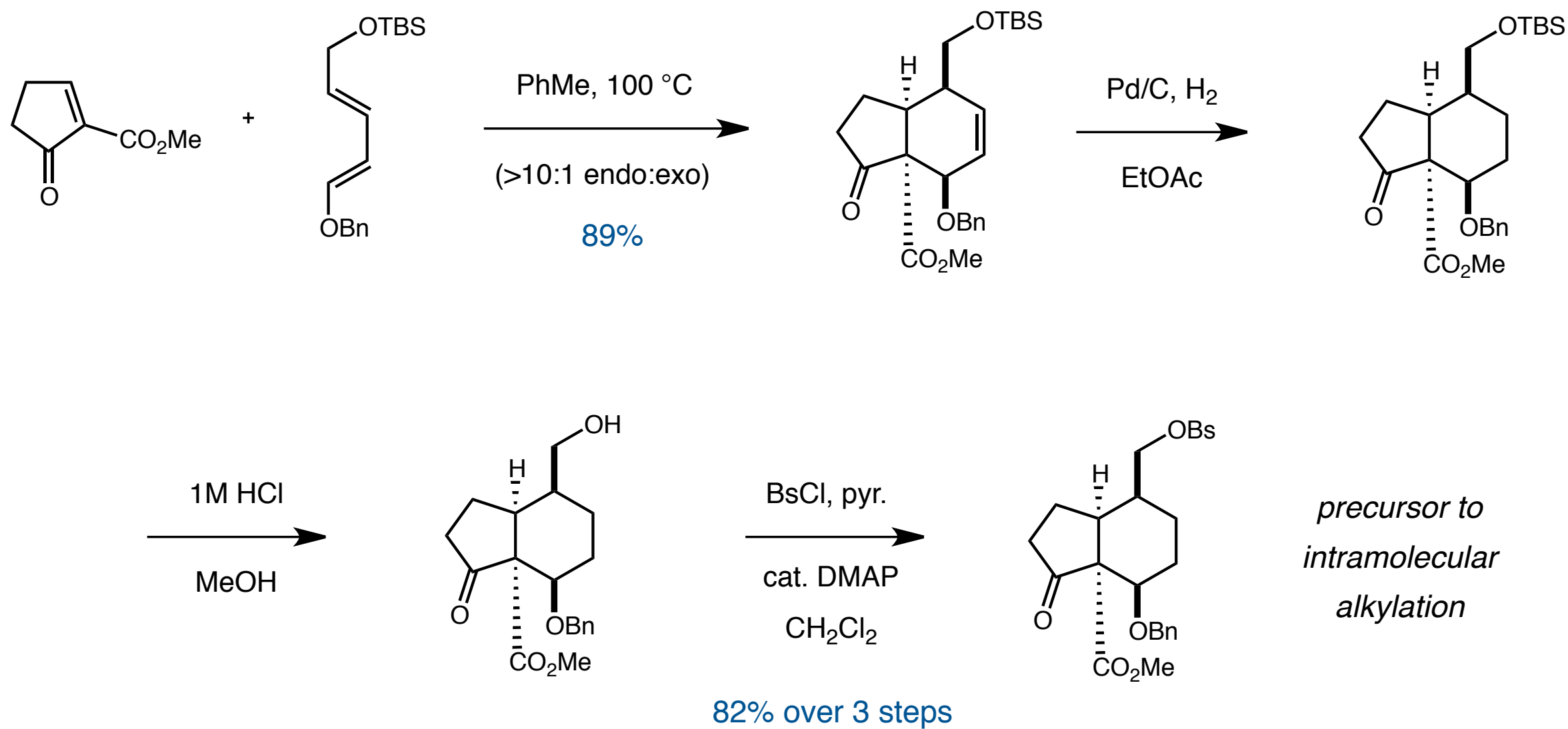


Diels-Alder



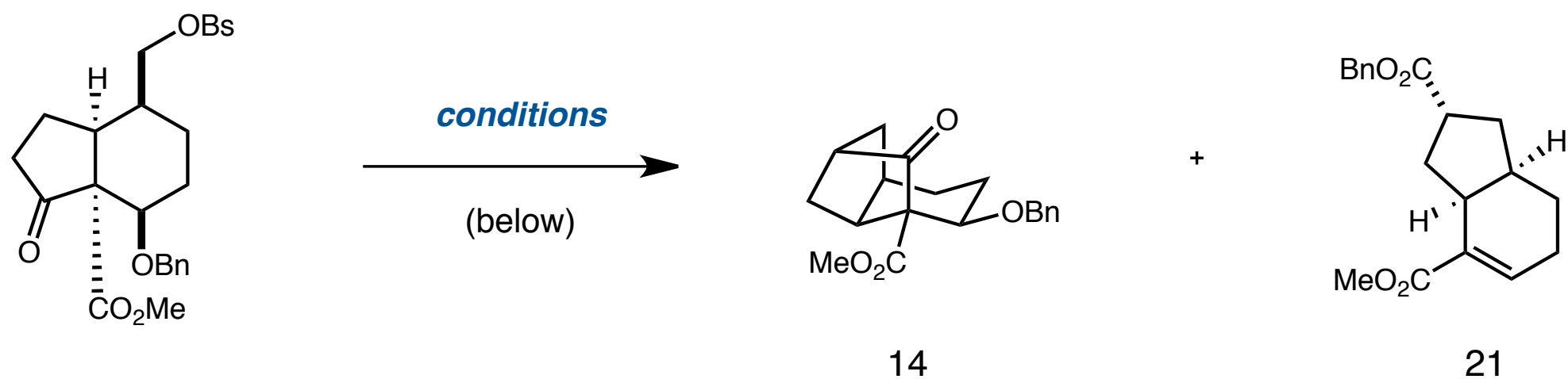
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Diels-Alder Approach



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Intramolecular Alkylation

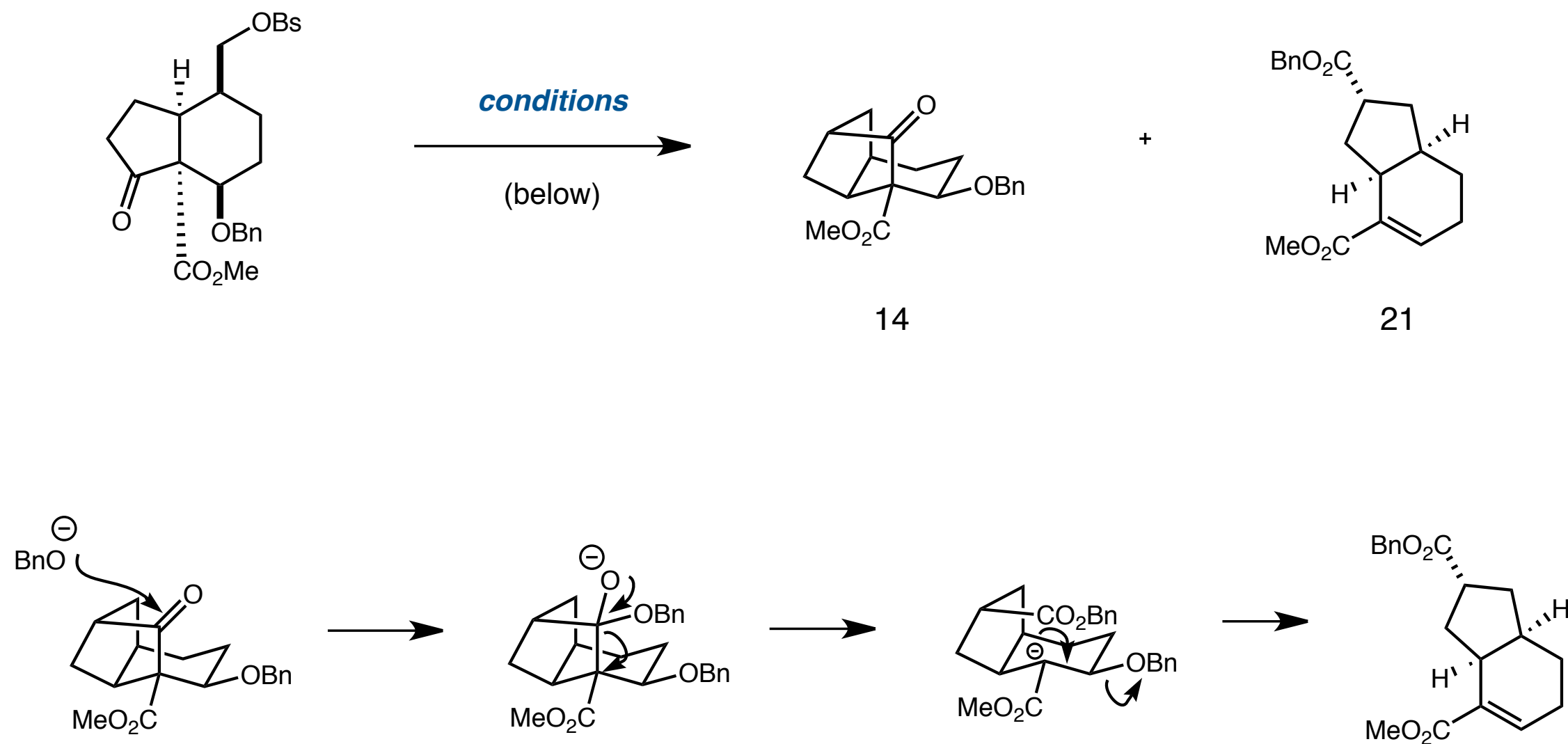


entry	conditions	result
1	KHMDS (2 equiv), THF, -78 °C to rt	decomposition
2	KHMDS (1.1 equiv), THF, -78 °C to rt	14 (38-84%)
3	KHMDS (1.1 equiv), TBAI (1 equiv) THF/NEt ₃ , -78 °C to rt	14 (74%)

Lebold, T. M.; Gallego, G. M.; Marth, C. J.; Sarpong, R. *Org. Lett.*, **2012**, 8, 2110.

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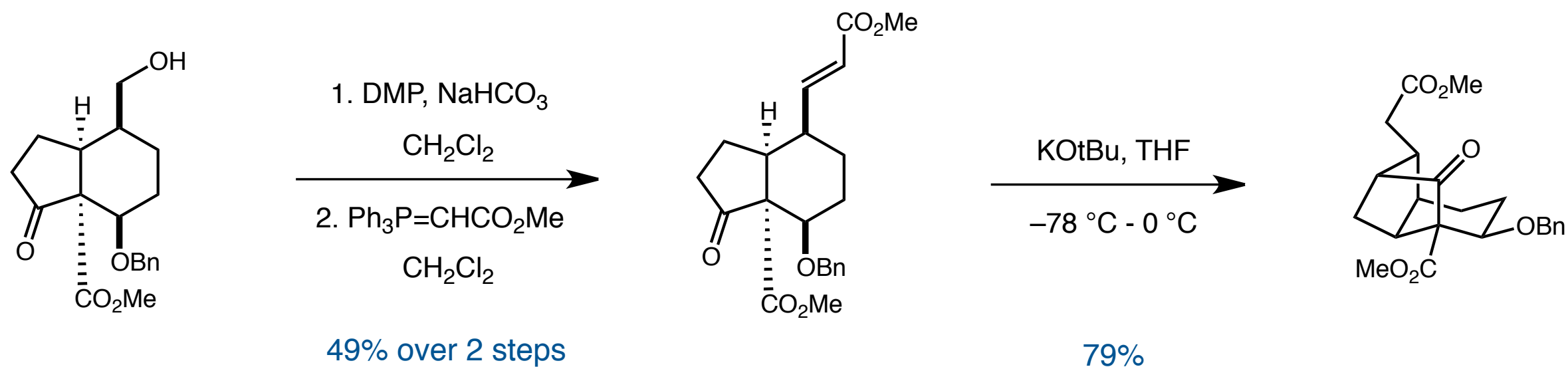
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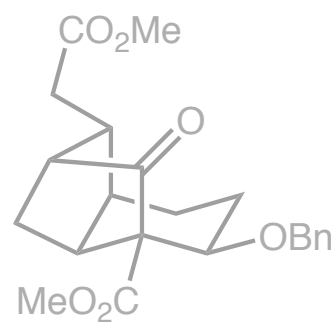
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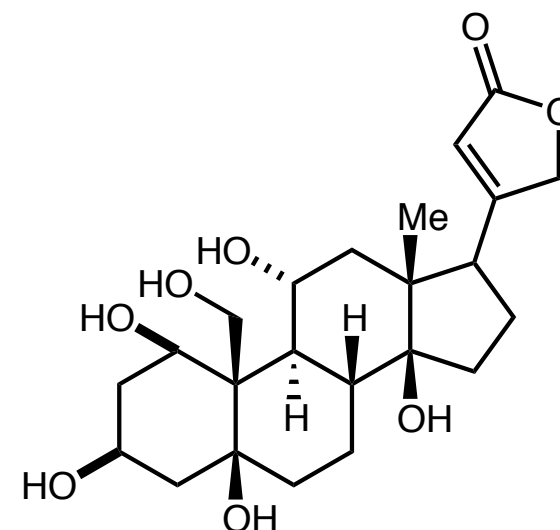
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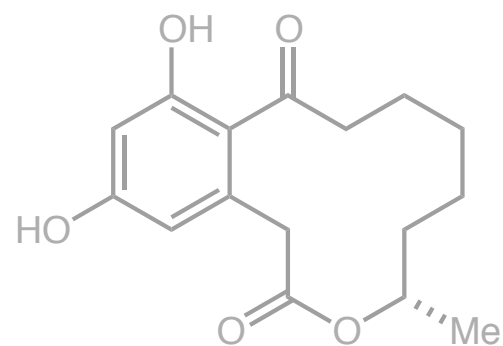
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Sarpong Group, Berkeley

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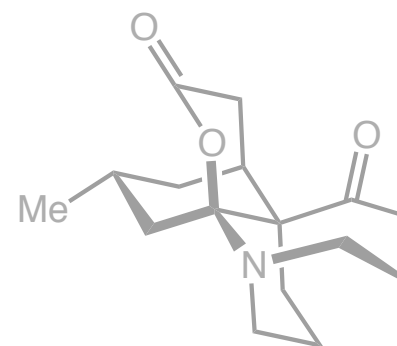
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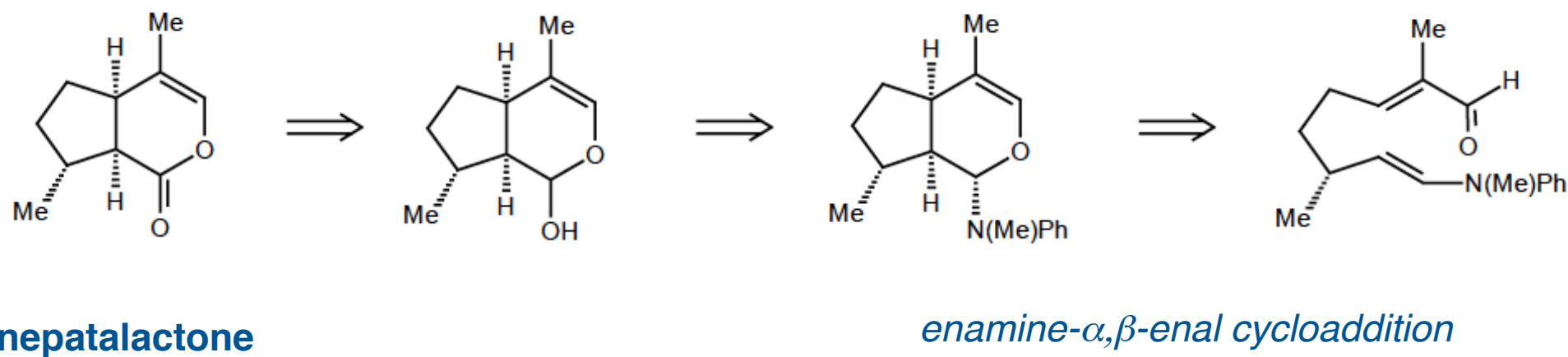
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Total Synthesis of Ouabagenin

a functional group-based approach

Key Features of a Functional Group-based Approach

- functional group in the target directly keys a disconnection
- functional group in the target is poised to assist in the installation of a key stereocenter
- often times installed and later removed in order to enable a key transform (overbred intermediate)
- may extend to modern photoredox radical chemistry, traceless directing groups, C–H activation



Clark, K. J.; Fray, G. I.; Jaeger, R. H.; Robinson, R. *Tetrahedron*, **1959**, 6, 217.

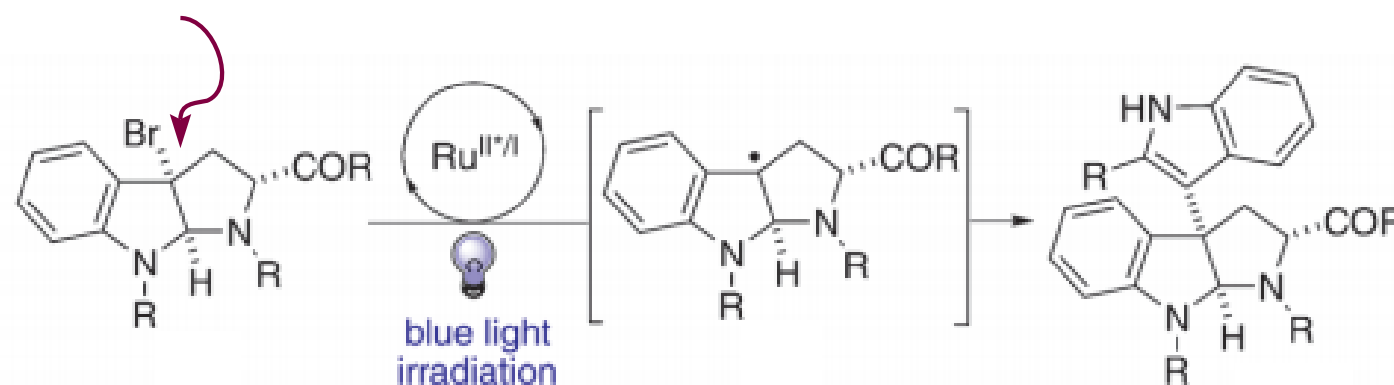
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functional group installed to assist key step



accessing
(+)-Gliocladin C

functional group
removed by photochemical
reduction

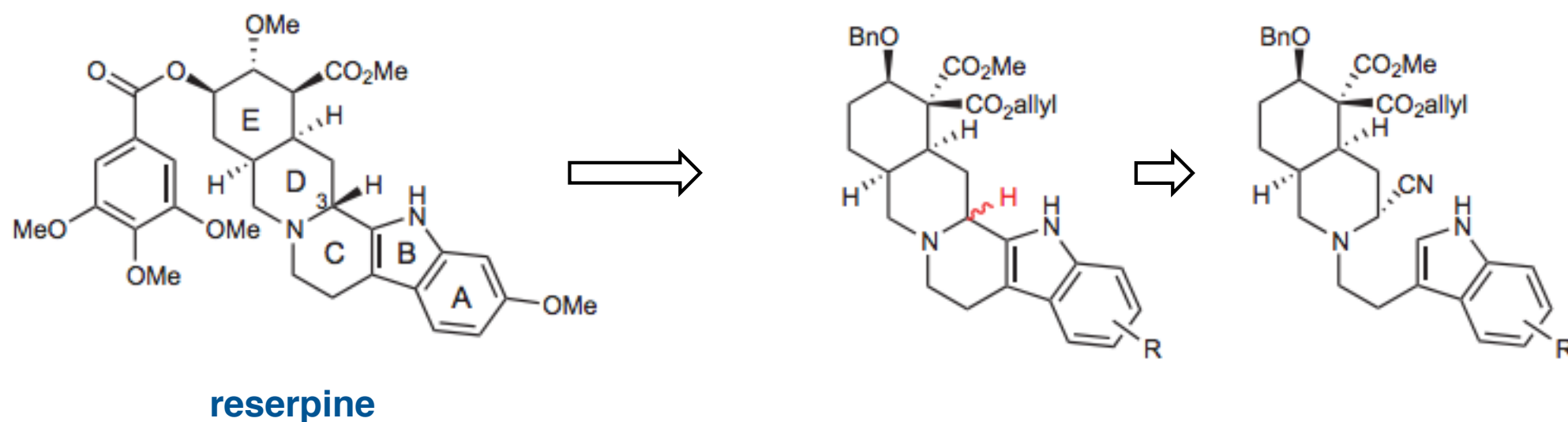
Furst, L.; Narayanam, J. M. R.; Stephenson, C. R. J. *Angew. Chem. Int. Ed.* **2011**, 50, 9655.

Total Synthesis of Ouabagenin

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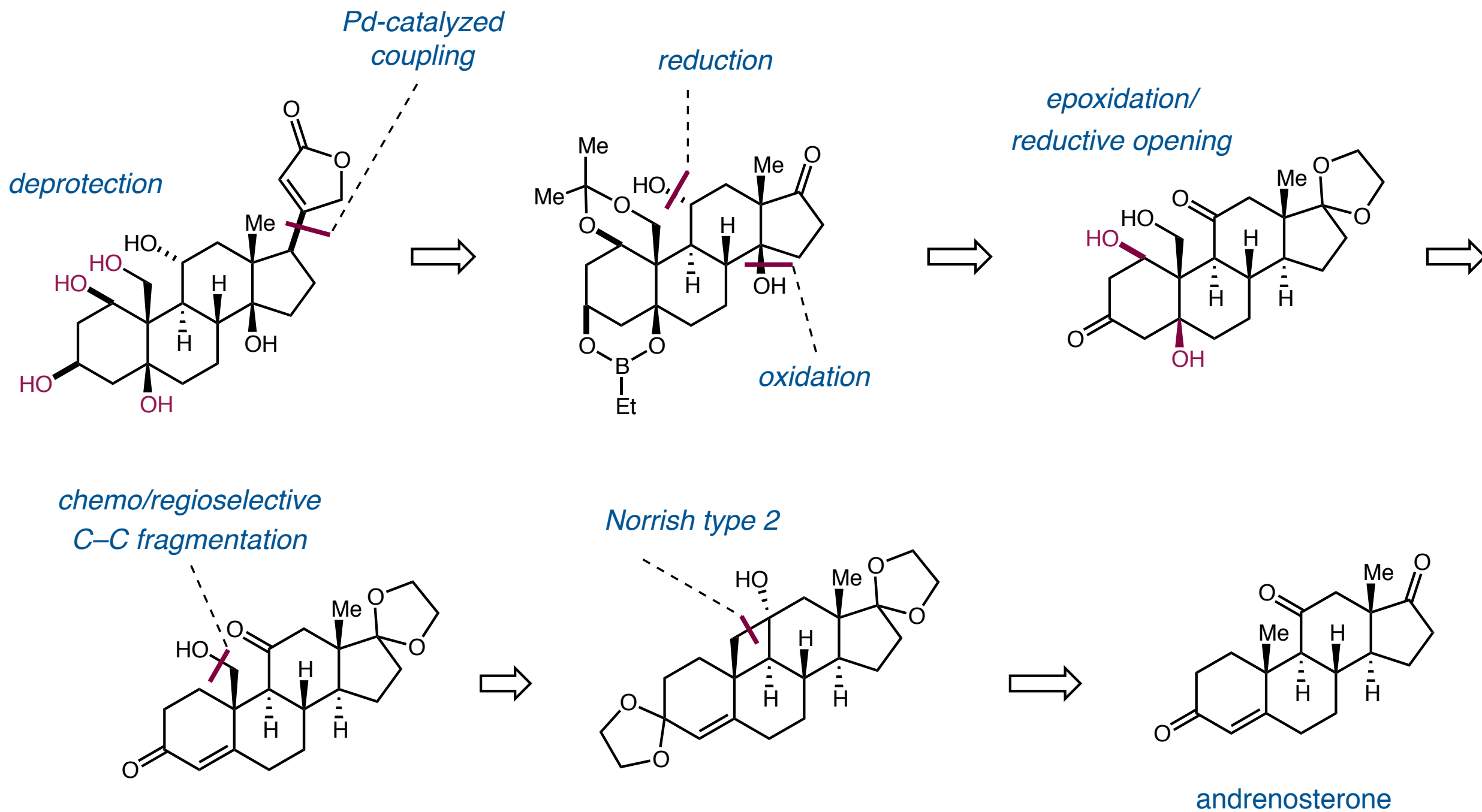
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LeBold, T. P.; Wood, J. L.; Deitch, J.; Lodewyk, M. W.; Tantillo, D. J.; Sarpong, R. *Nat. Chem.*, **2012**, 5, 126.

Total Synthesis of Ouabagenin

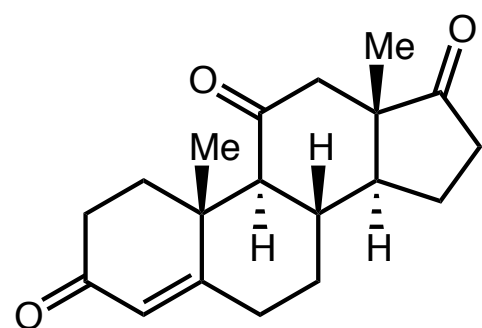
retrosynthetic analysis



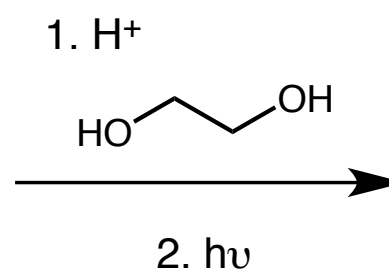
LeBold, T. P.; Wood, J. L.; Deitch, J.; Lodewyk, M. W.; Tantillo, D. J.; Sarpong, R. *Nat. Chem.*, **2012**, *5*, 126.

Total Synthesis of Ouabagenin

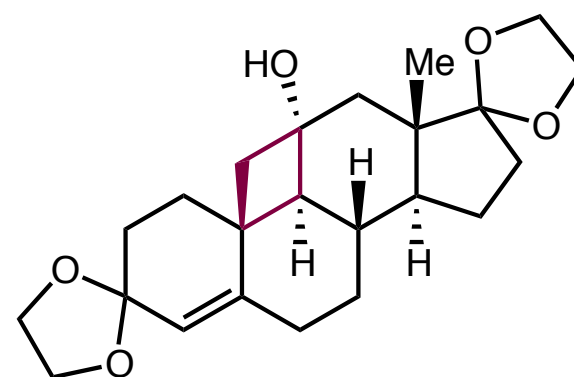
a functional group-based approach



adrenosterone



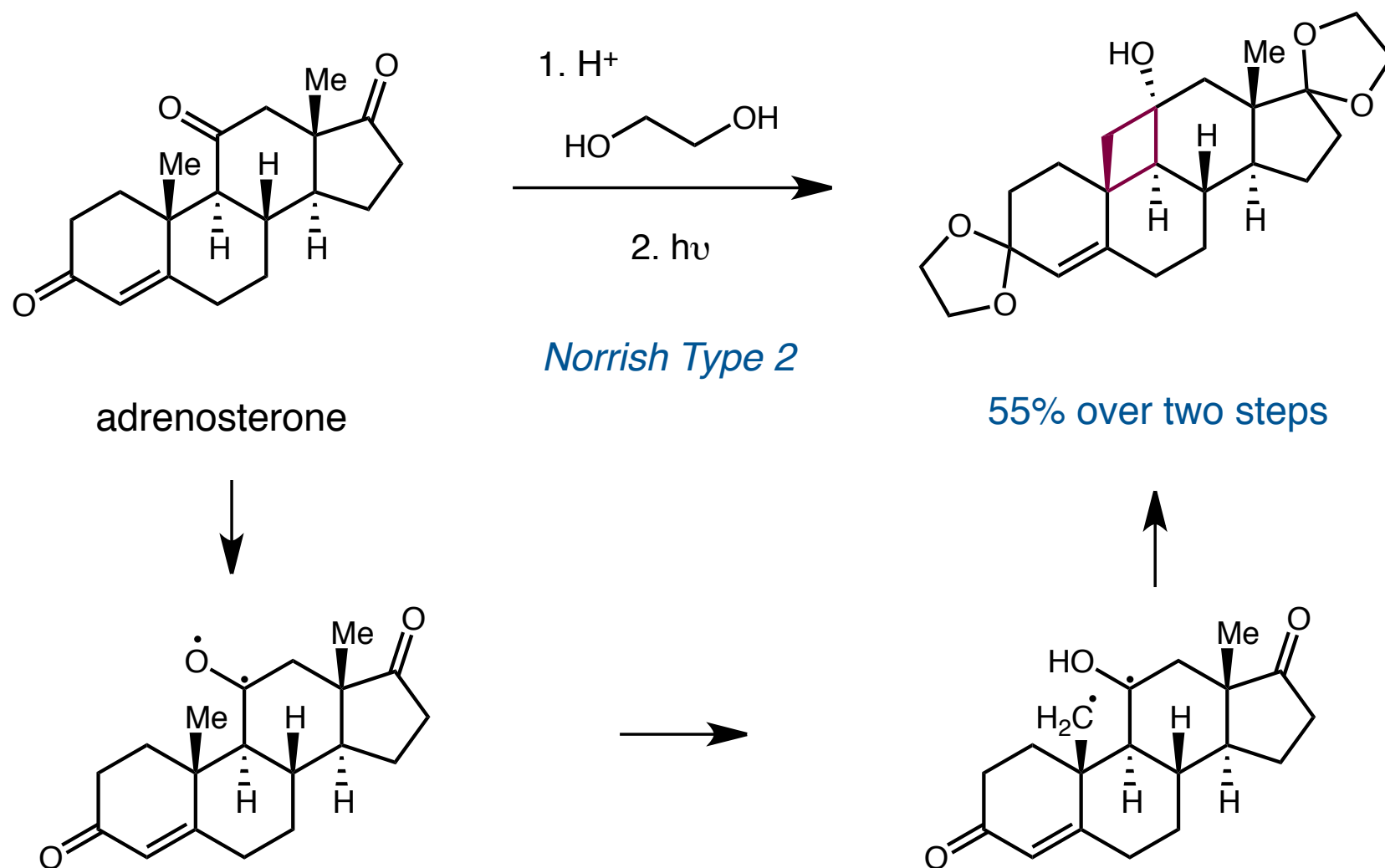
Norrish Type 2



55% over two steps

Total Synthesis of Ouabagenin

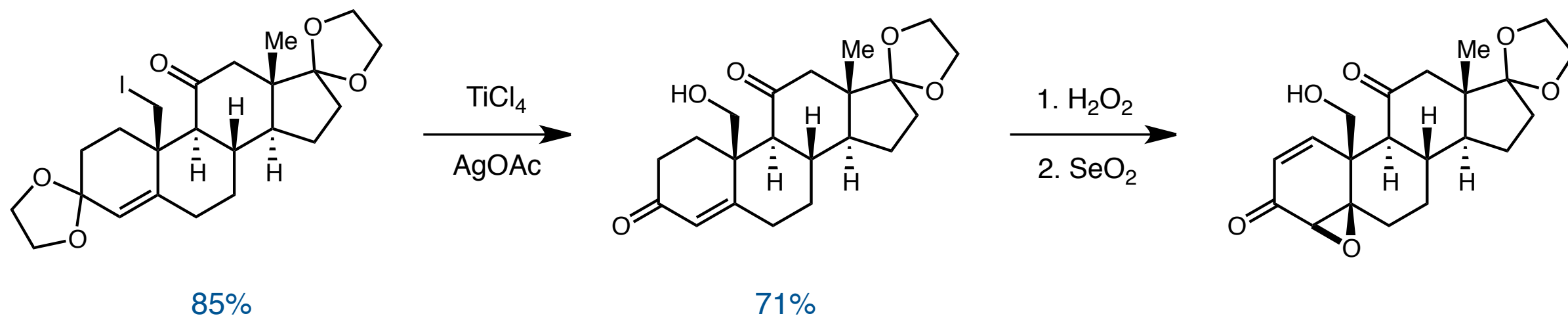
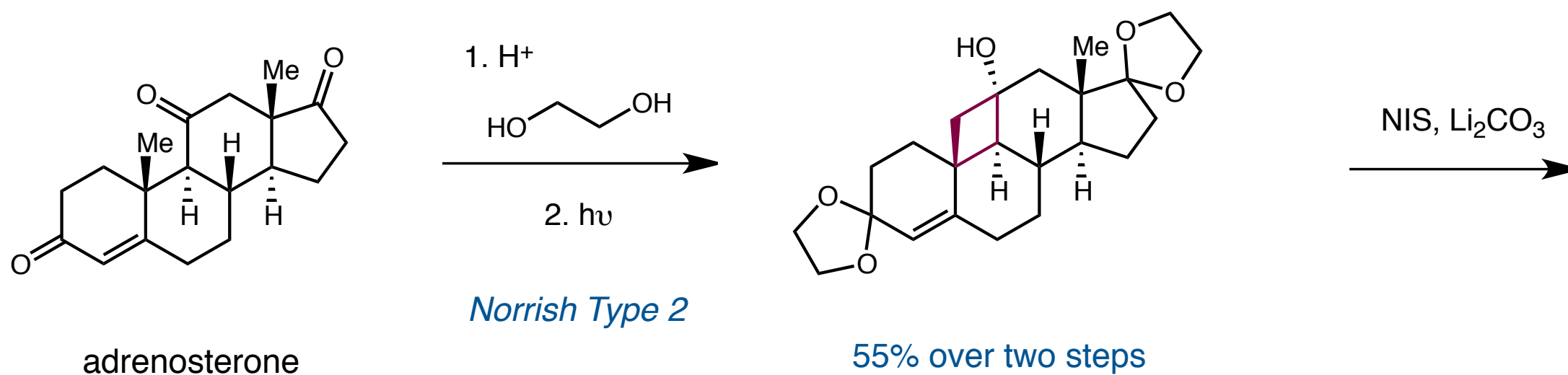
a functional group-based approach



Renata, H.; Zhou, Q.; Baran, P. S. *Science* **2013**, 339, 59.

Total Synthesis of Ouabagenin

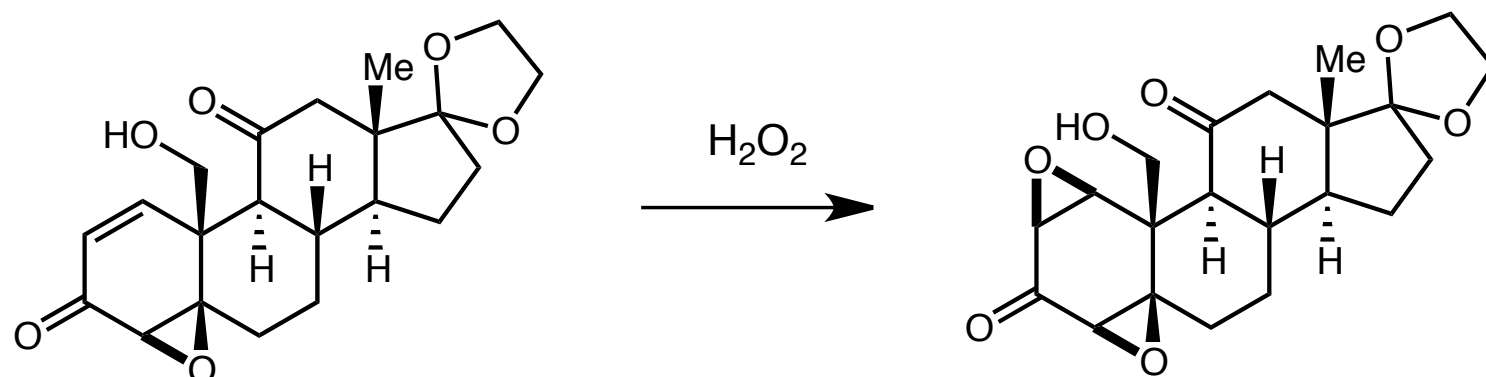
a functional group-based approach



Renata, H.; Zhou, Q.; Baran, P. S. *Science* **2013**, 339, 59.

Total Synthesis of Ouabagenin

a functional group-based approach

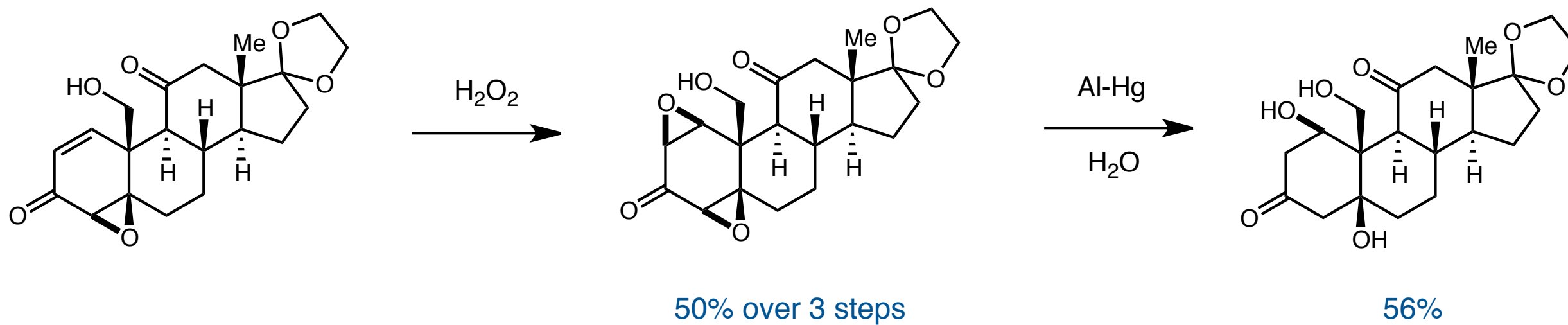


50% over 3 steps

Renata, H.; Zhou, Q.; Baran, P. S. *Science* **2013**, 339, 59.

Total Synthesis of Ouabagenin

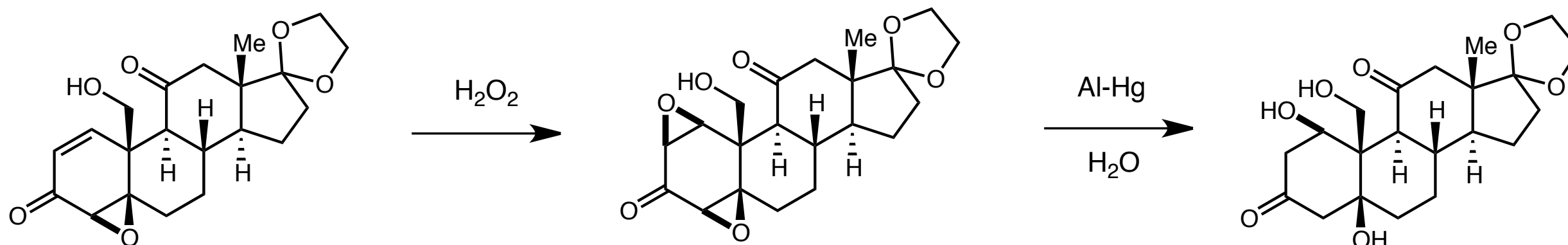
a functional group-based approach



Renata, H.; Zhou, Q.; Baran, P. S. *Science* **2013**, 339, 59.

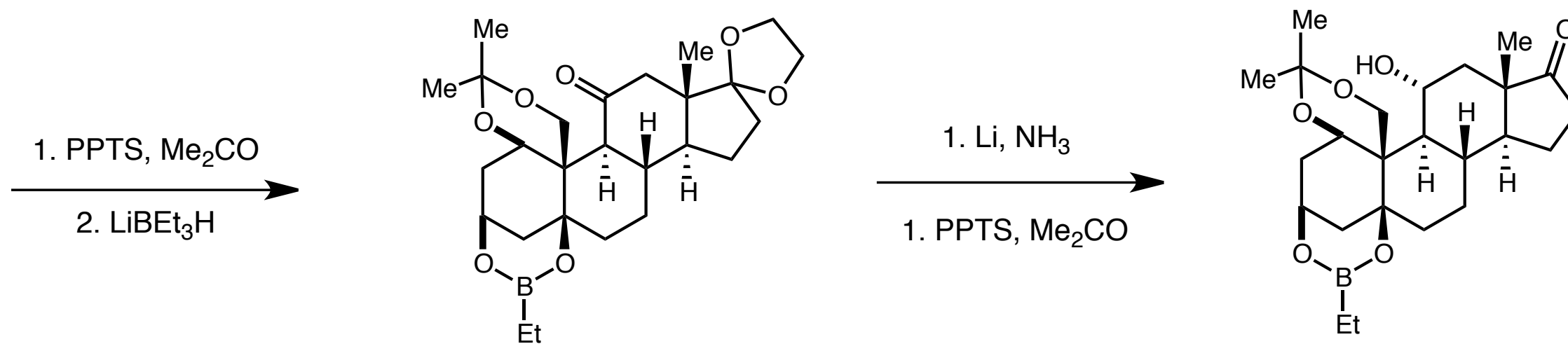
Total Synthesis of Ouabagenin

a functional group-based approach



50% over 3 steps

56%



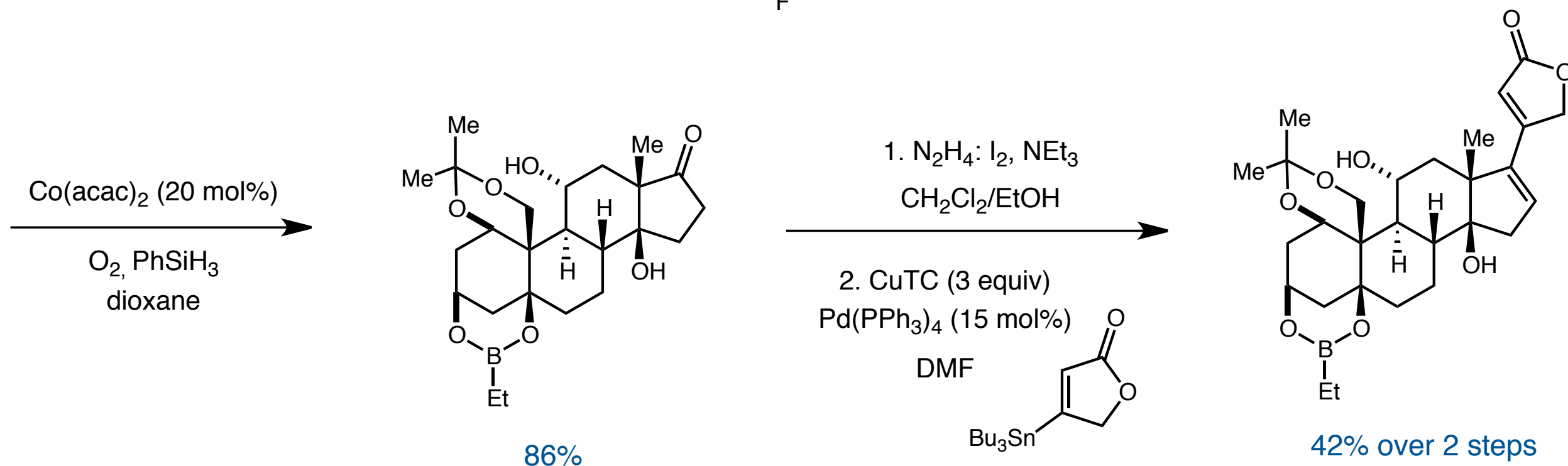
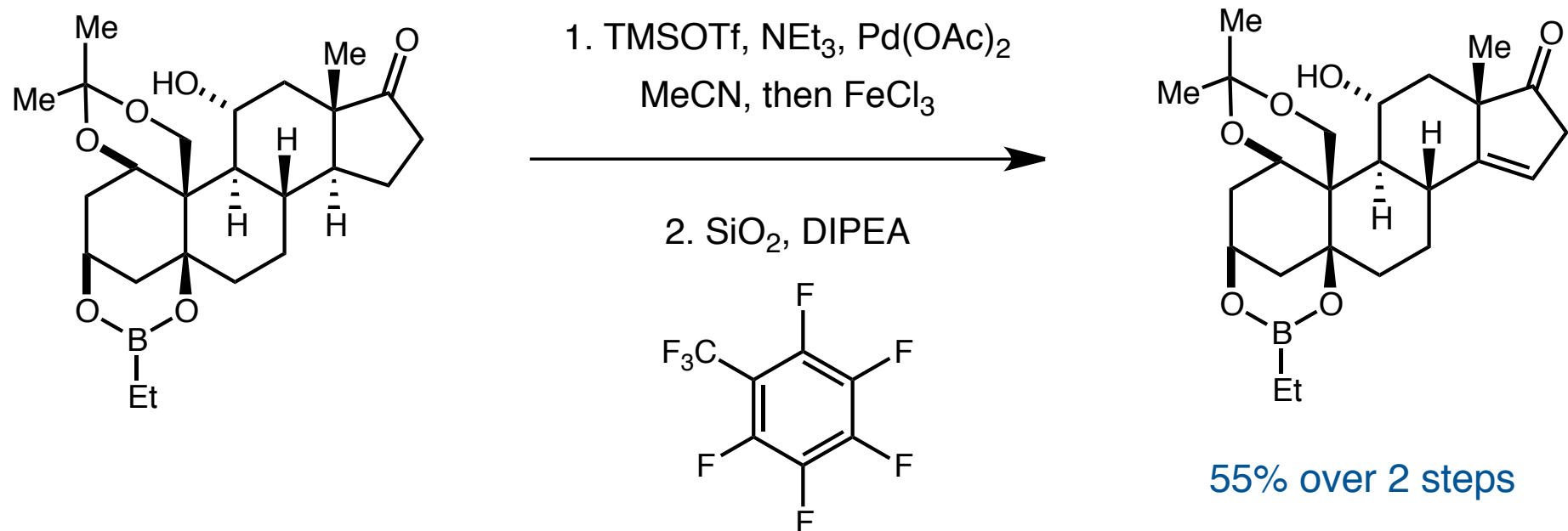
63% over 2 steps

69% over 2 steps

Renata, H.; Zhou, Q.; Baran, P. S. *Science* **2013**, 339, 59.

Total Synthesis of Ouabagenin

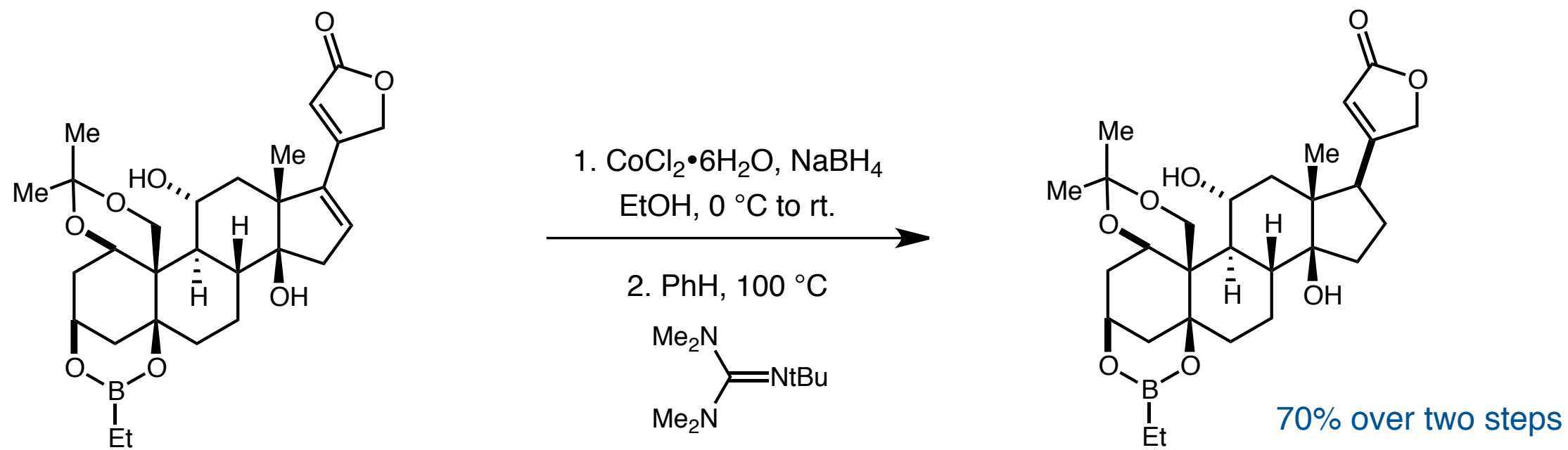
a functional group-based approach



Renata, H.; Zhou, Q.; Baran, P. S. *Science* **2013**, 339, 59.

Total Synthesis of Ouabagenin

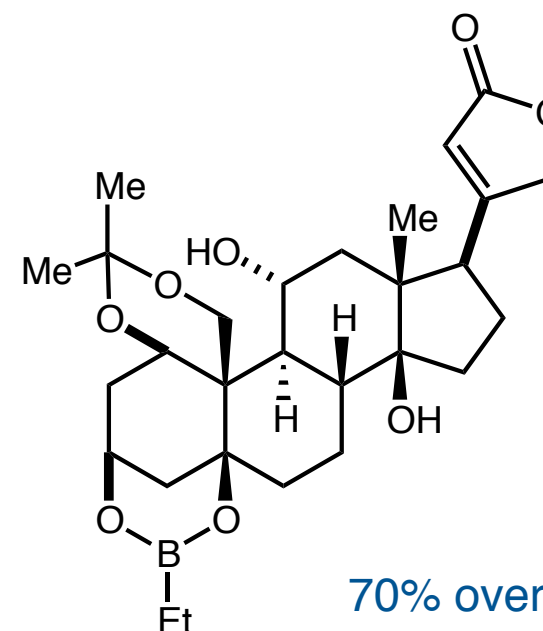
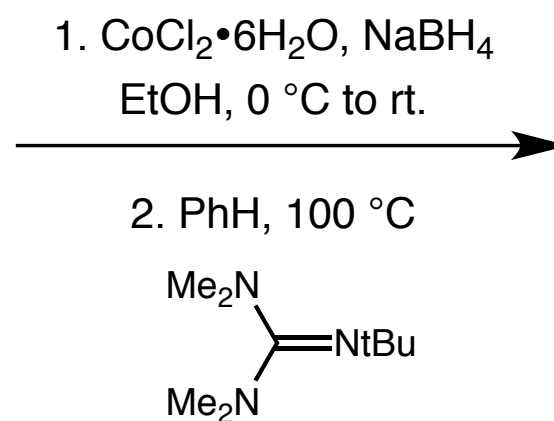
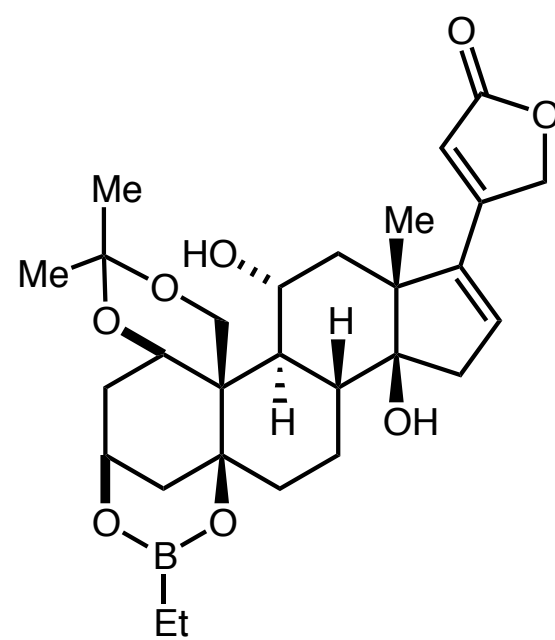
a functional group-based approach



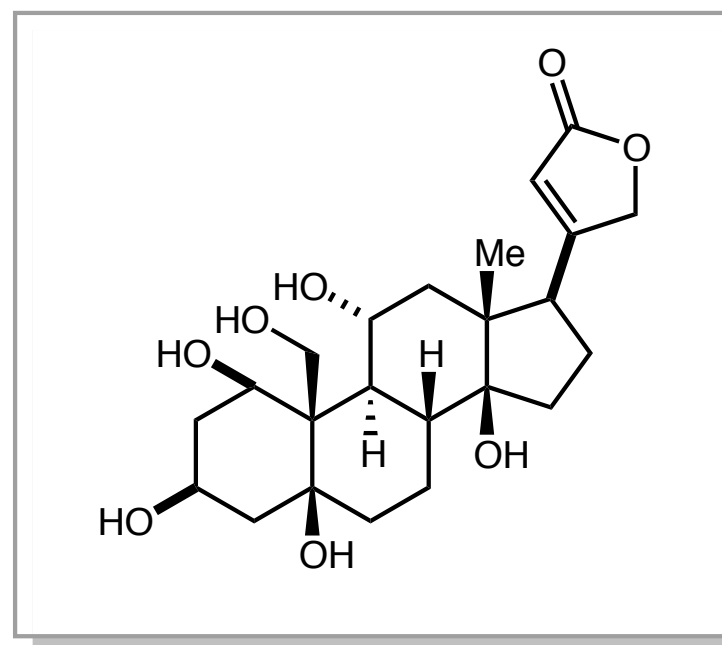
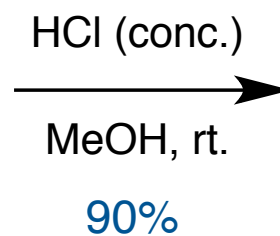
Renata, H.; Zhou, Q.; Baran, P. S. *Science* **2013**, 339, 59.

Total Synthesis of Ouabagenin

a functional group-based approach



70% over two steps

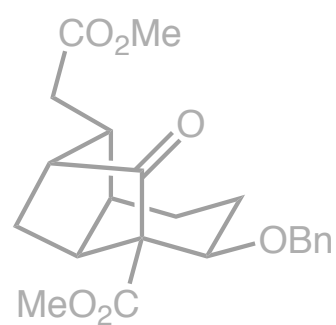


ouabagenin

20 steps from andrenosterone

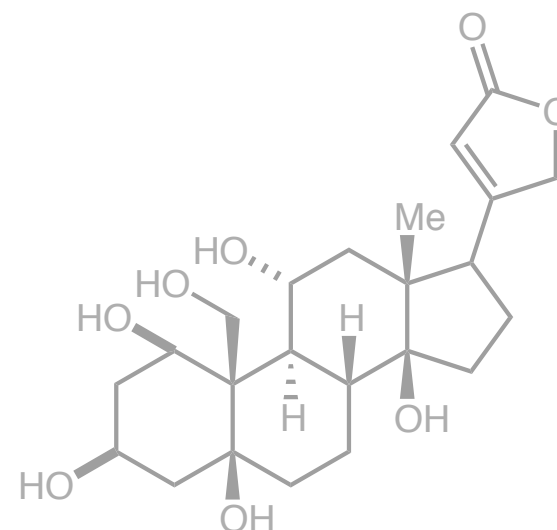
Applied Strategies in Retrosynthetic Analysis

Topological



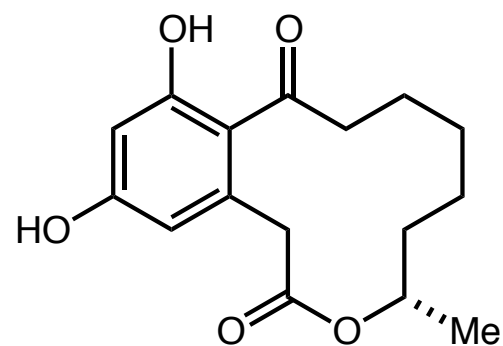
Phragmalin-type Limonoids
Sarpong Group, Berkeley

Functional Group-Based



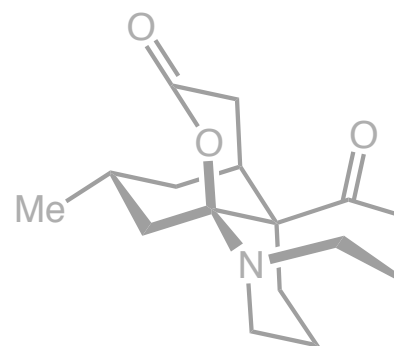
Ouabagenin
Baran Group, Scripps

Transform-Based



(-)-Curvularin
Stoltz Group, Caltech

Structure-Goal



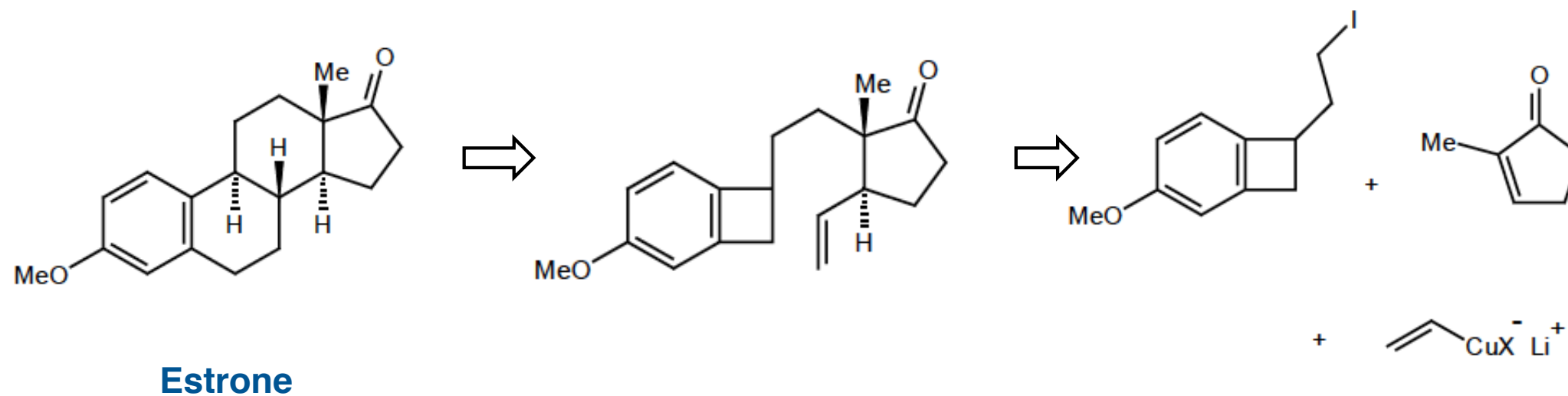
(-)-Lycojapodine A
Lei Group, Tianjin University

Total Synthesis of (–)-Curvularin

A Transform-Based Approach

Key Features of a Transform-Based Approach

- in general: the *late-stage* key-step
- look-ahead to apply a highly simplifying synthetic strategy
- often cascades, rearrangements, transformations which assemble multiple C–C bonds



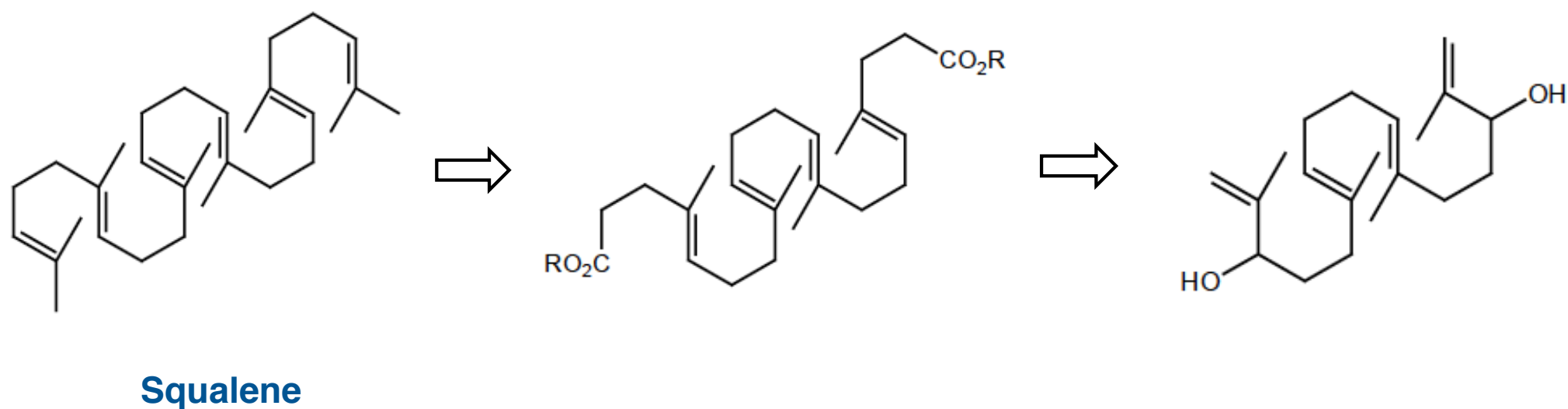
Corey, E. J.; Ohno, M.; Mitra, R. B.; Vatakancherry, P. A. *J. Am. Chem. Soc.* **1964**, 86, 487.

Total Synthesis of (–)-Curvularin

A Transform-Based Approach

Key Features of a Transform-Based Approach

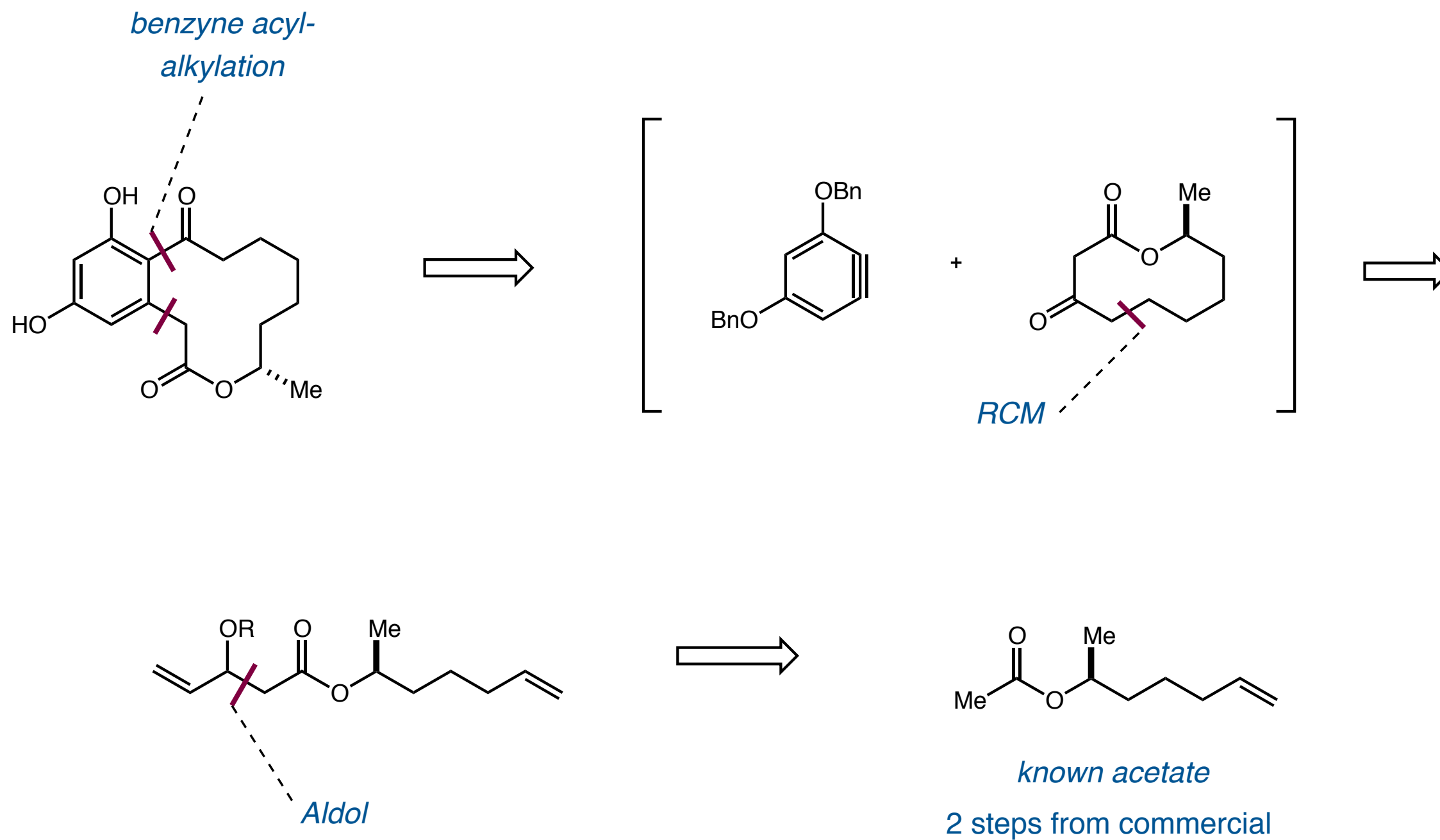
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Werthermann, L.; Johnson, W. S.; *Proc. Nat. Acad. Sci.*, **1970**, 67, 1465.

Total Synthesis of (–)-Curvularin

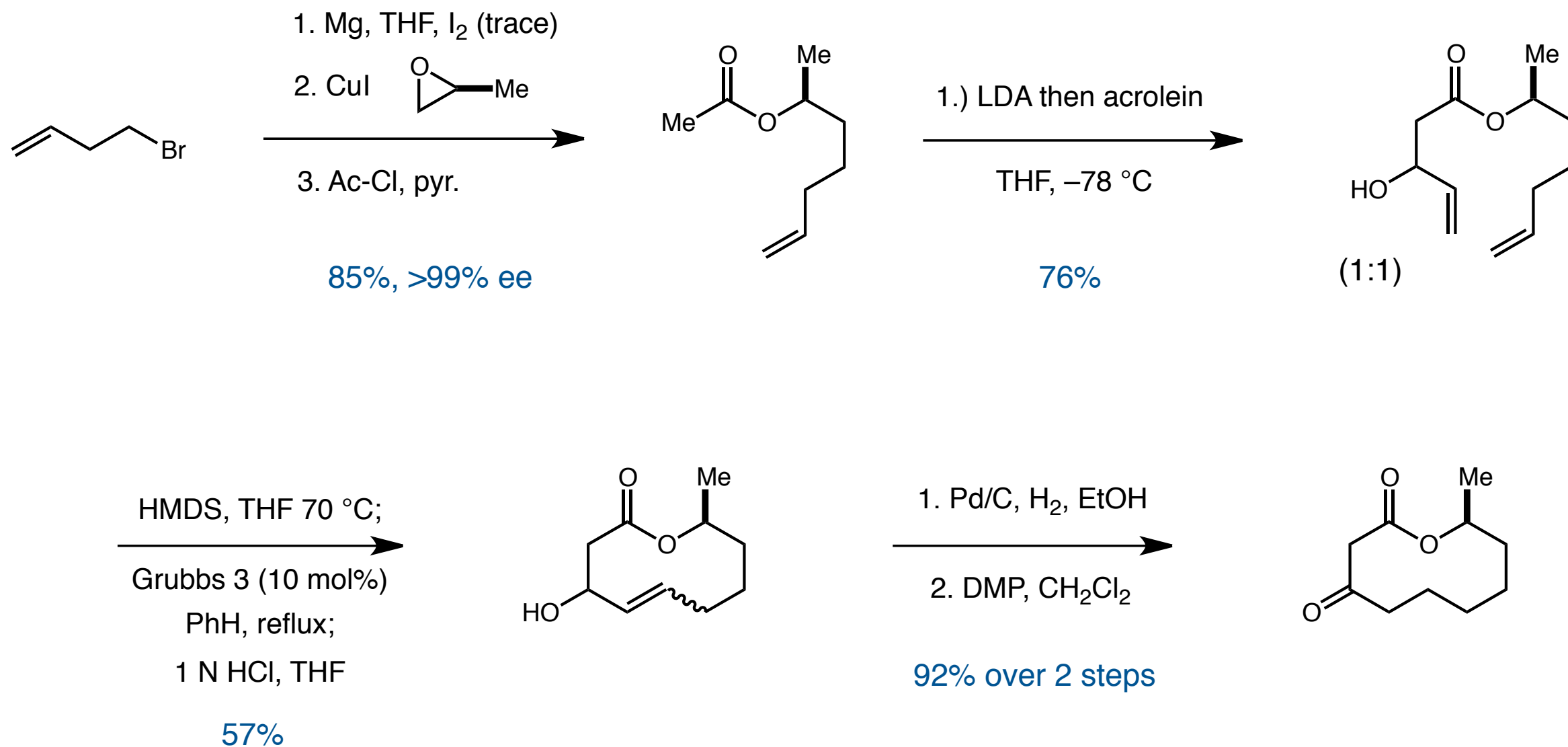
Retrosynthetic Analysis



Tadross, P. M.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.*, **2010**, 7, 1612.

Total Synthesis of (–)-Curvularin

preparation of the β -ketolactone

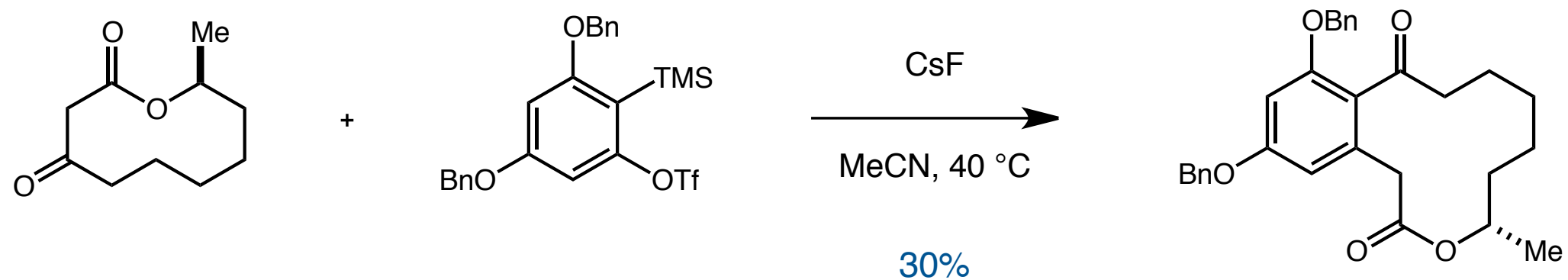


Lin, W.; Zercher, C. K.; *J. Org. Chem.*, **2007**, 72, 4390.

Tadross, P. M.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.*, **2010**, 7, 1612.

Total Synthesis of (–)-Curvularin

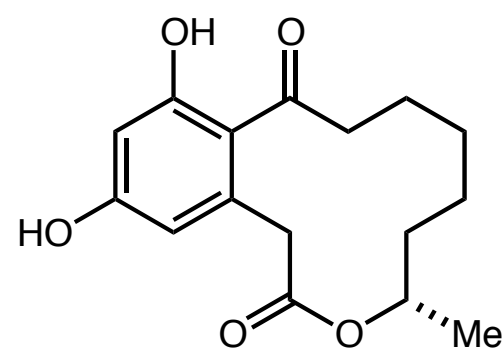
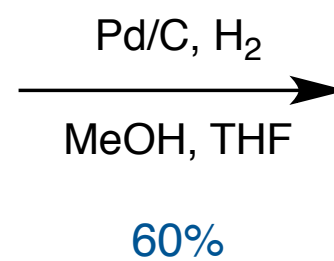
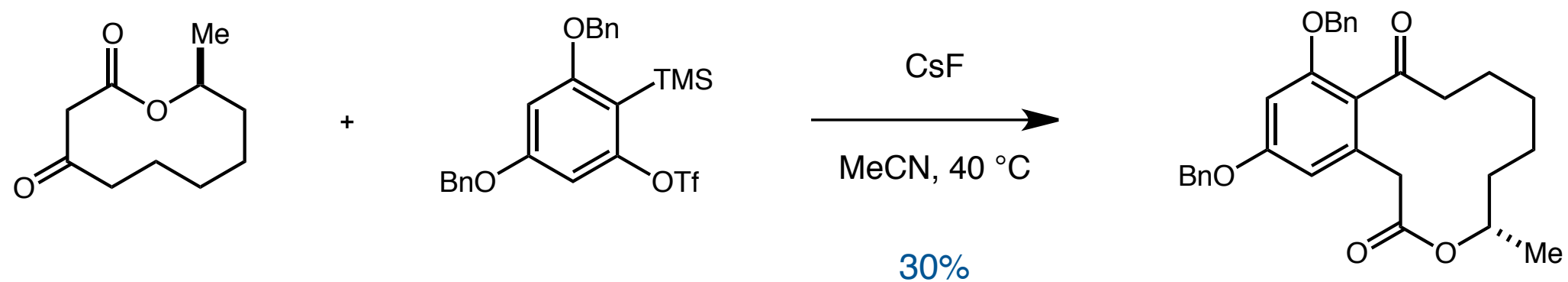
Key Step



Tadross, P. M.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.*, **2010**, 7, 1612.

Total Synthesis of (–)-Curvularin

Key Step

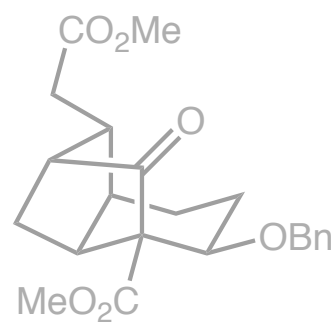


(–)-Curvularin

Tadross, P. M.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.*, **2010**, 7, 1612.

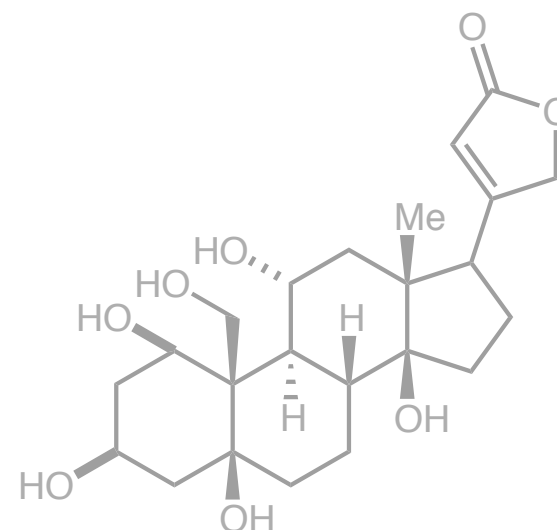
Applied Strategies in Retrosynthetic Analysis

Topological



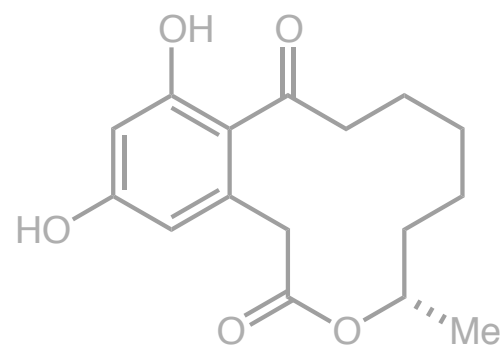
Phragmalin-type Limonoids
Sarpong Group, Berkeley

Functional Group-Based



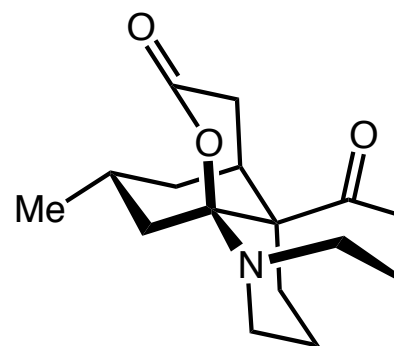
Ouabagenin
Baran Group, Scripps

Transform-Based



(-)-Curvularin
Stoltz Group, Caltech

Structure-Goal



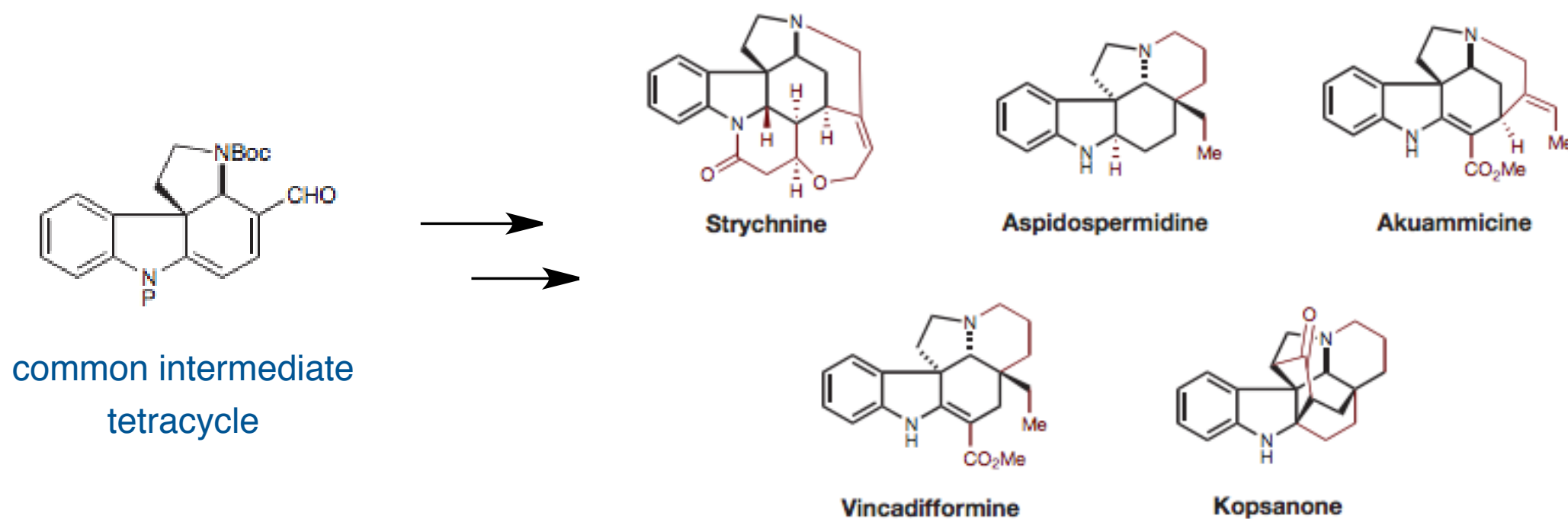
(-)-Lycojapodine A
Lei Group, Tianjin University

Total Synthesis of (–)-Lycojapodine A

A Structure-Goal Approach

Key Features of a Structure-Goal Approach

- Implemented when a large number of target structures are desired (collective synthesis)
- bulk of synthetic strategy relies on the synthesis of a highly simplifying intermediate
- allows the implementation of multiple retrosynthetic techniques



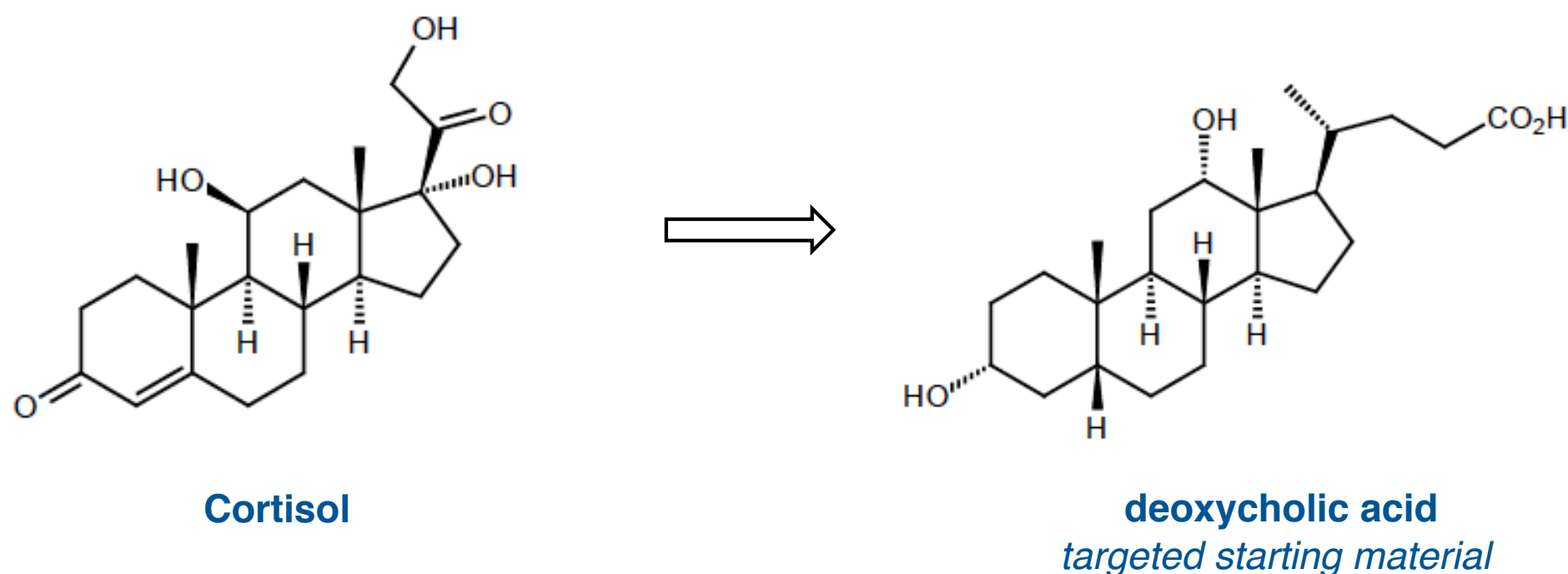
Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature*, **2011**, 475, 183.

Total Synthesis of (–)-Lycojapodine A

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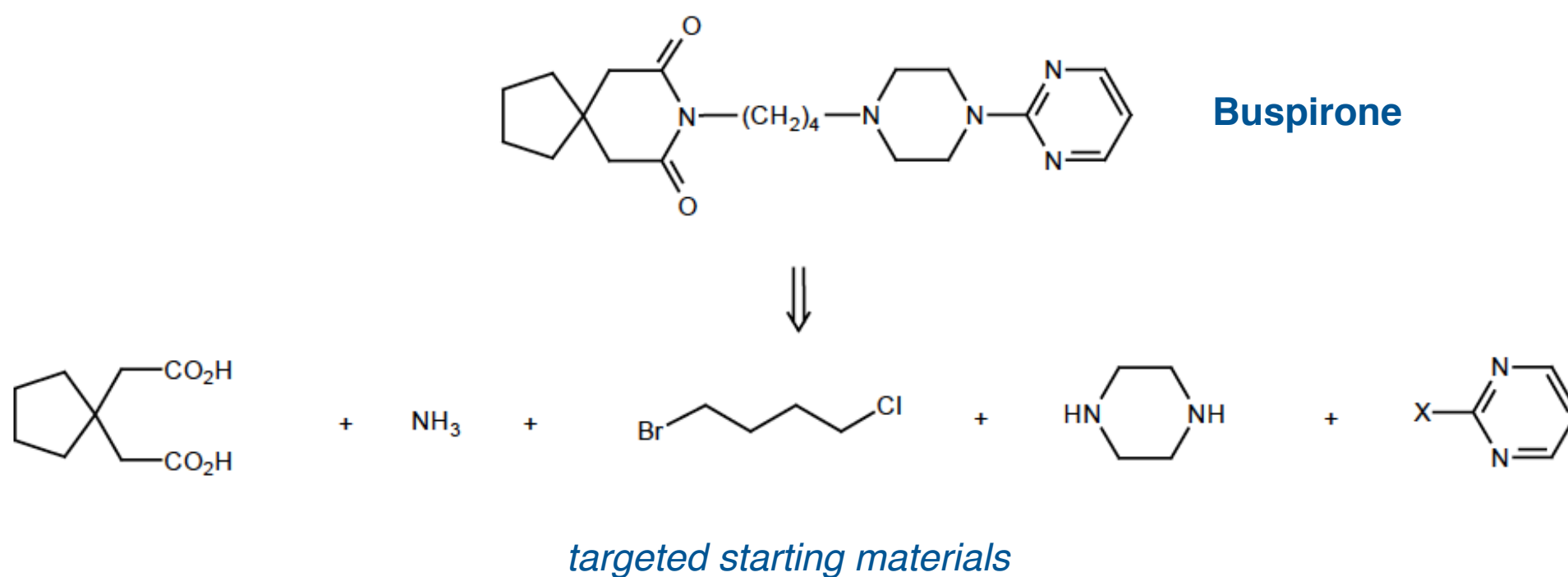
Fieser, L. F.; Fieser, M. *Steroids* Reinhold Publishing, New York, 1959. pp 645–659.

Total Synthesis of (–)-Lycojapodine A

A Structure-Goal Approach

Key Features of a Structure-Goal Approach

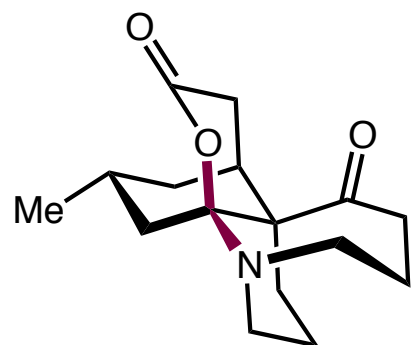
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Fieser, L. F.; Fieser, M. *Steroids* Reinhold Publishing, New York, 1959. pp 645–659.

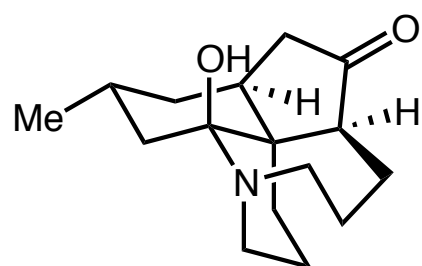
Total Synthesis of (–)-Lycojapodine A

A Structure-Goal Approach

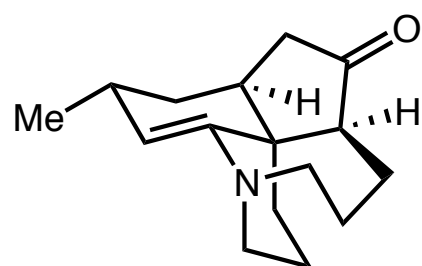


(–)-Lycojapodine A
fawcettimine-type alkaloid

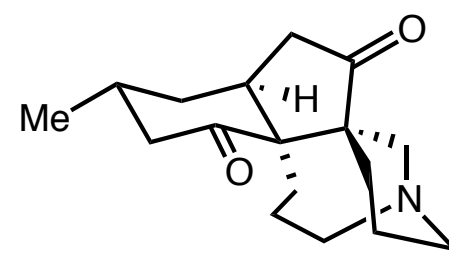
- more than 250 Lycopodium alkaloids have been characterized
- contains a unique 6/6/6/7 tetracyclic skeleton
- unprecedented carbinolamine lactone motif
- biosynthesis suggests that many natural products can be accessible through a common intermediate



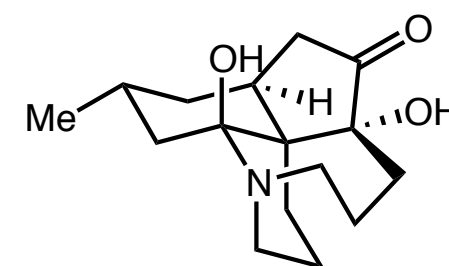
(+)-fawcettimine



(+)-fawcettidine



(+)-lycoflexine

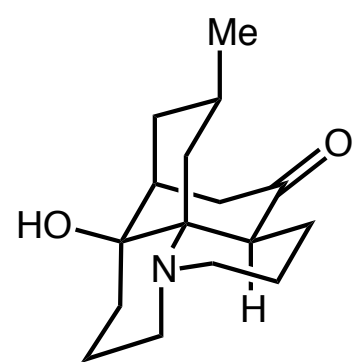


(+)-alopecuridine

Li, H.; Wang, X.; Hong, B.; Lei, X. *J. Org. Chem.*, **2013**, 78, 800.

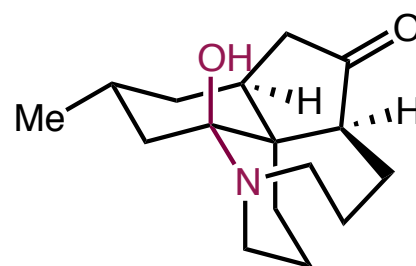
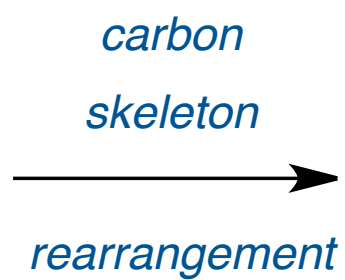
Total Synthesis of (–)-Lycojapodine A

simplified biogenesis



lycolidine

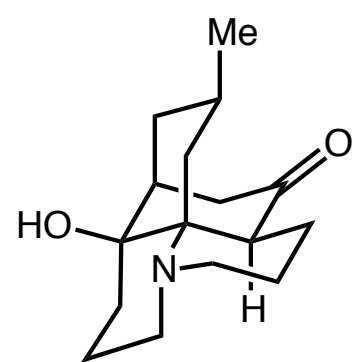
*biosynthetic common
intermediate*



(+)-fawcettimine

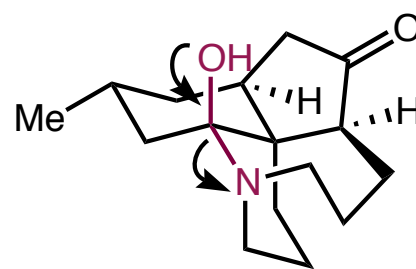
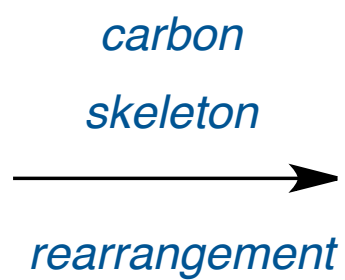
Total Synthesis of (–)-Lycojapodine A

simplified biogenesis

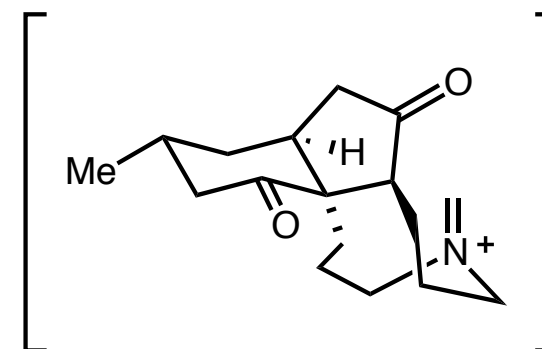
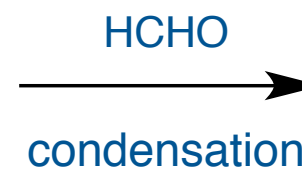


lycolidine

*biosynthetic common
intermediate*

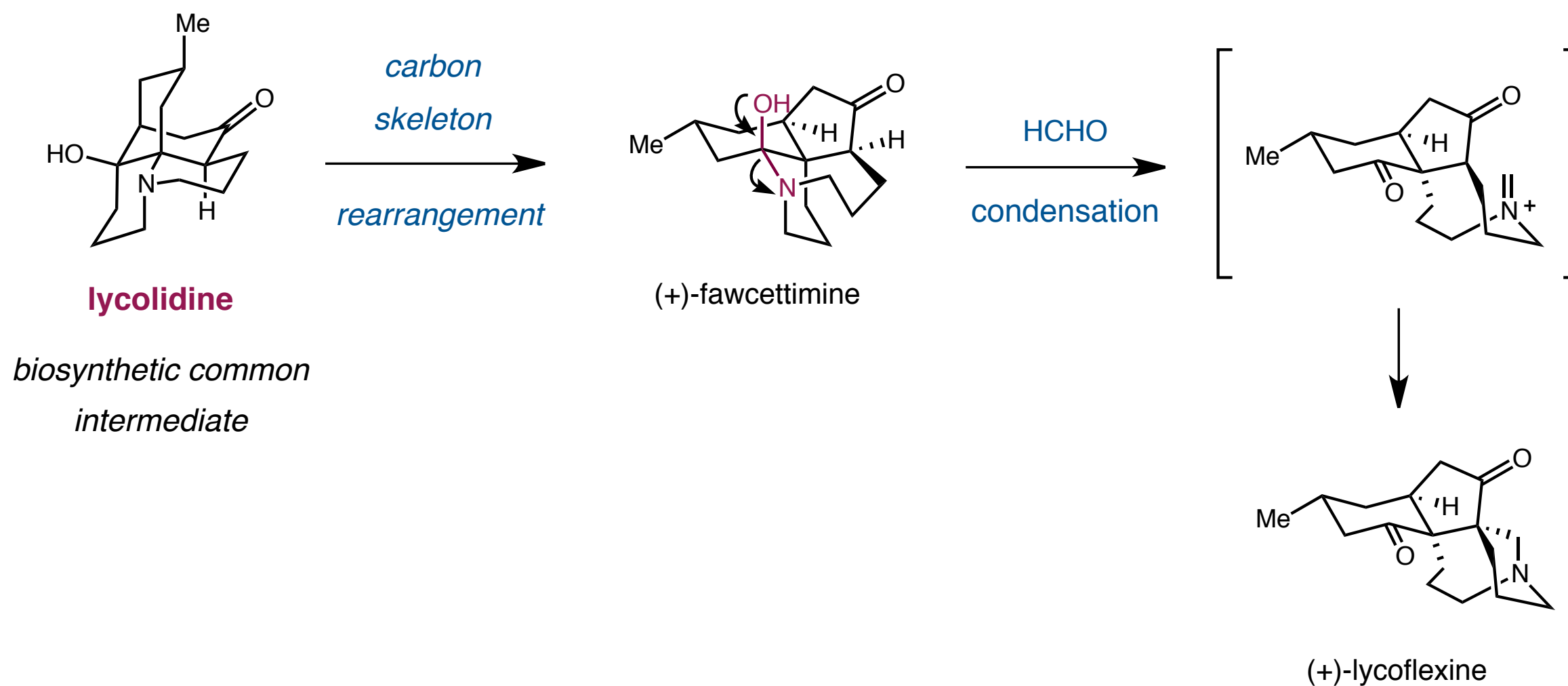


(+)-fawcettimine



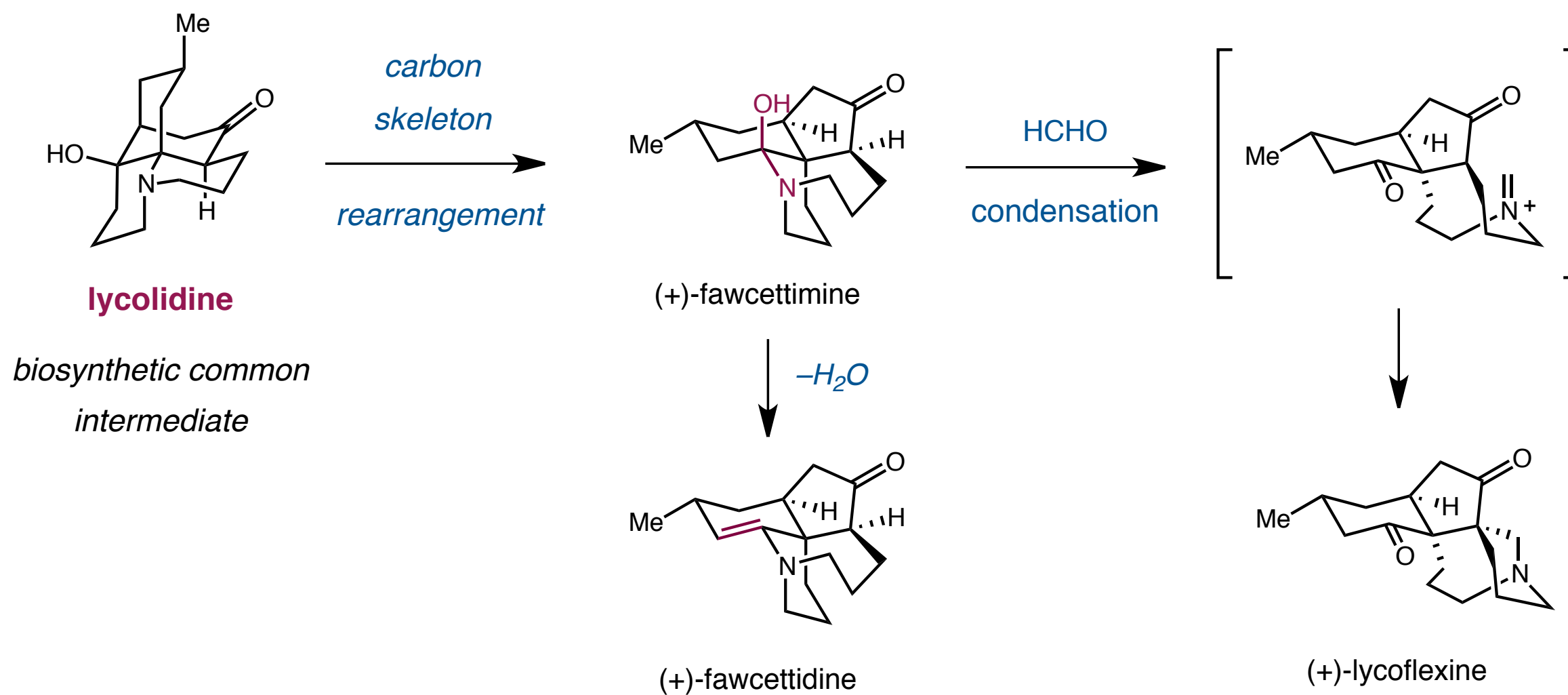
Total Synthesis of (–)-Lycojapodine A

simplified biogenesis



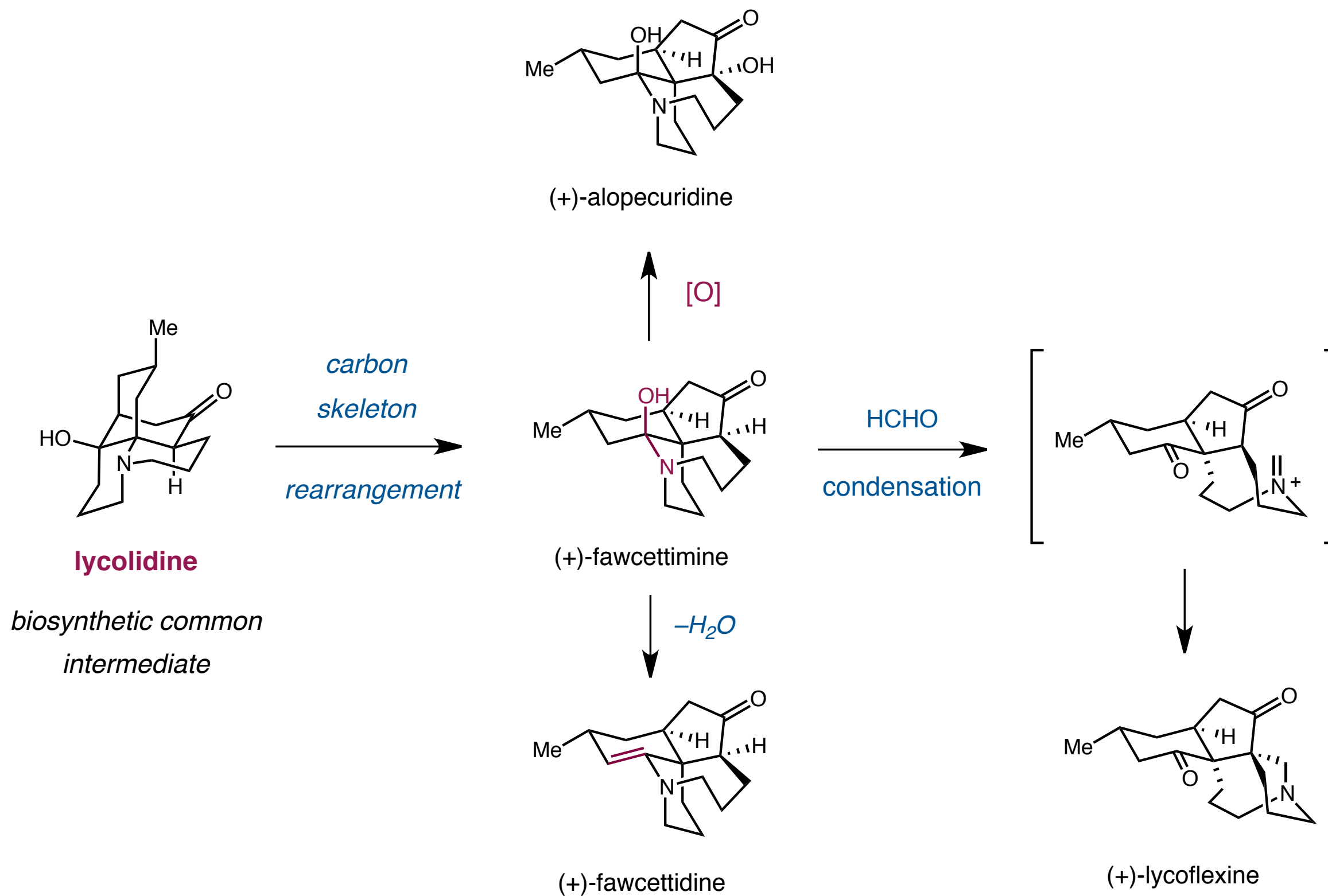
Total Synthesis of (–)-Lycojapodine A

simplified biogenesis



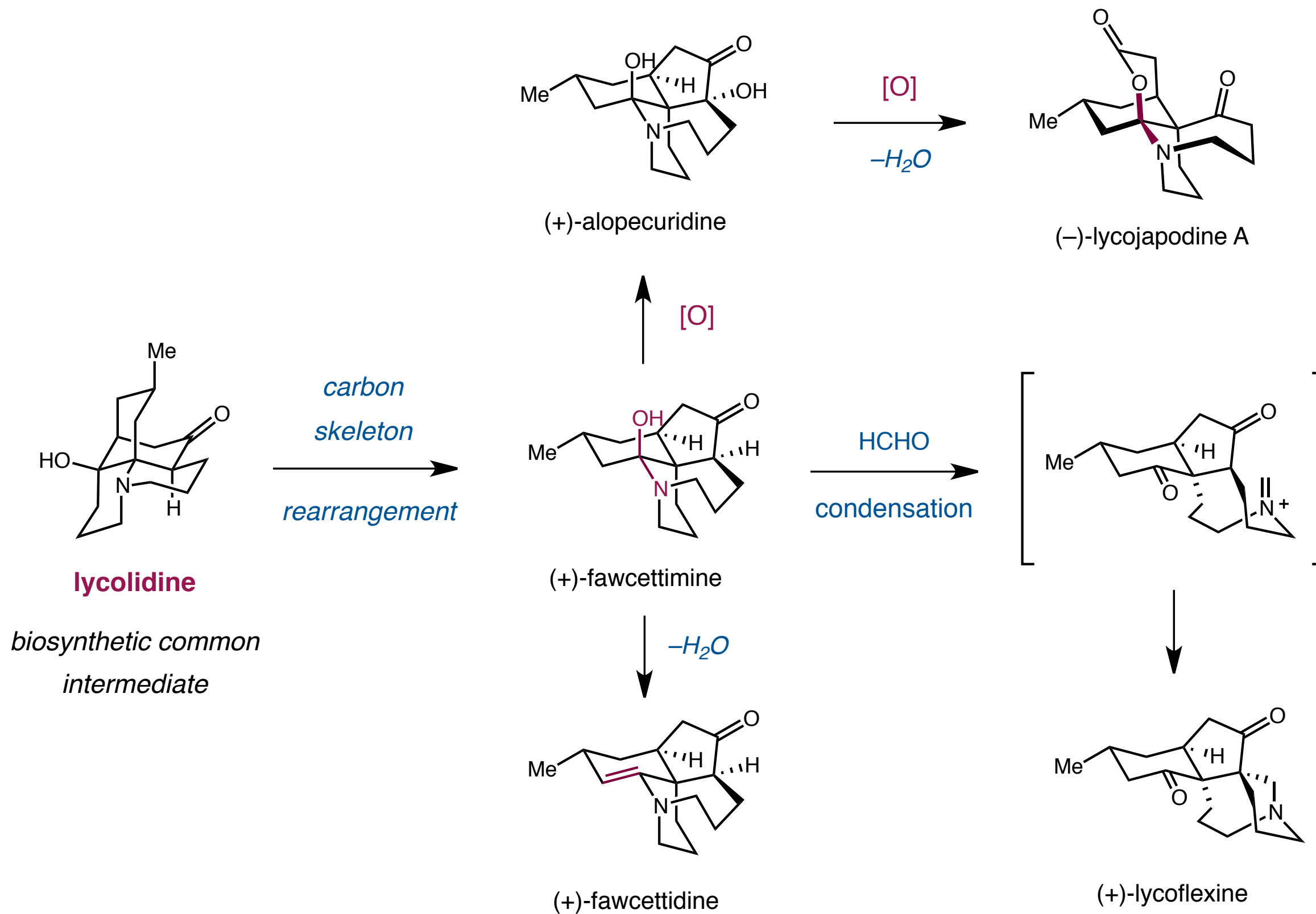
Total Synthesis of (-)-Lycojapodine A

simplified biogenesis



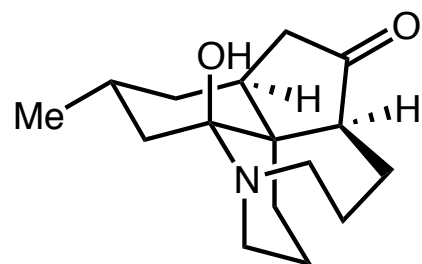
Total Synthesis of (–)-Lycojapodine A

simplified biogenesis

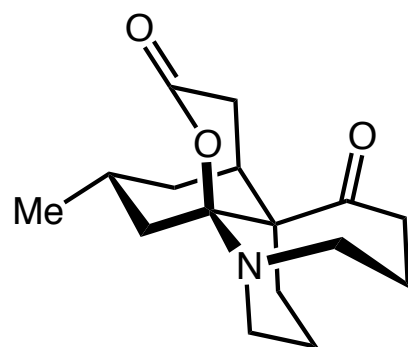


Total Synthesis of (–)-Lycojapodine A

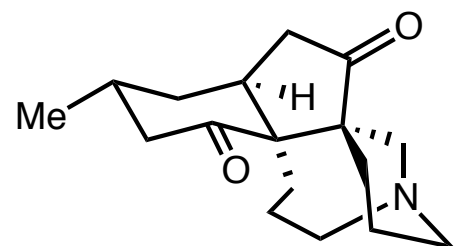
retrosynthetic analysis



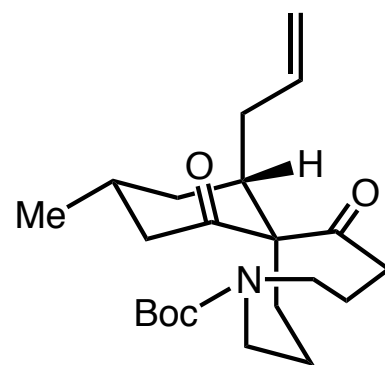
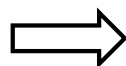
(+)-fawcettimine



(–)-Lycojapodine A



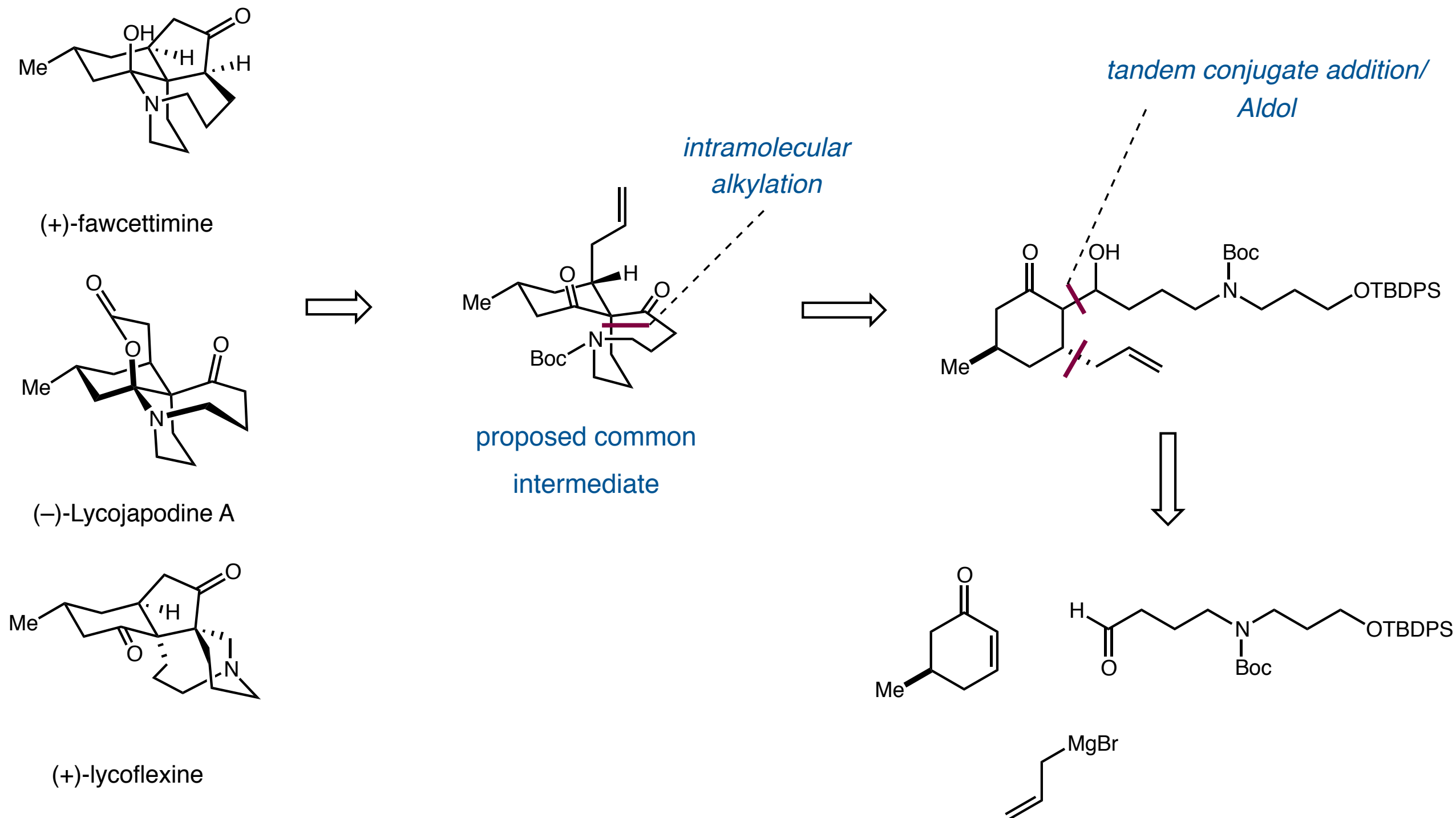
(+)-lycoflexine



proposed common
intermediate

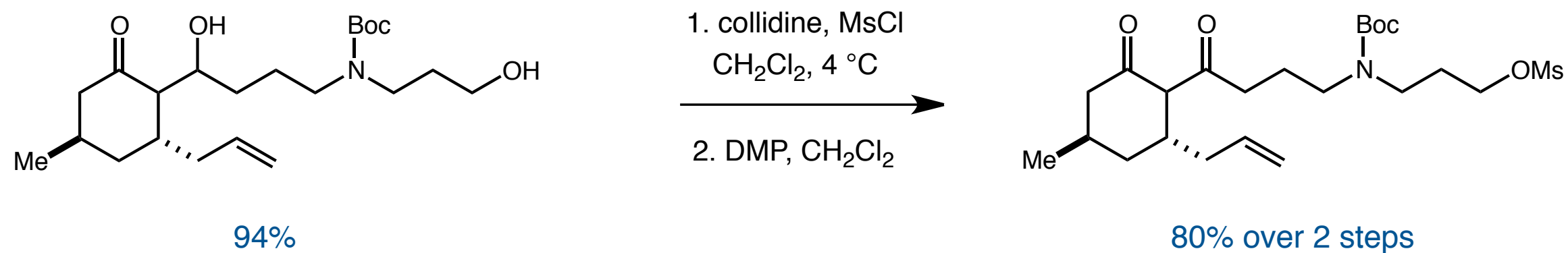
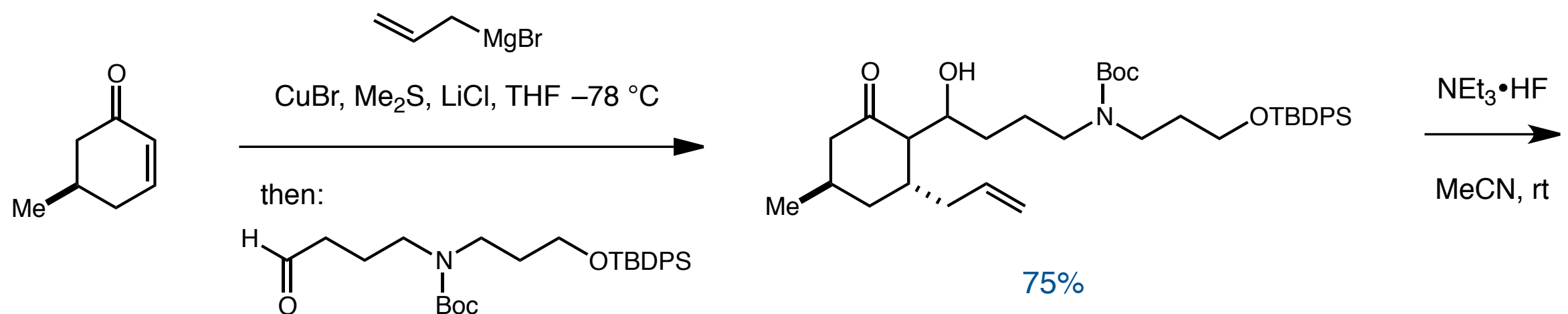
Total Synthesis of (–)-Lycojapodine A

retrosynthetic analysis



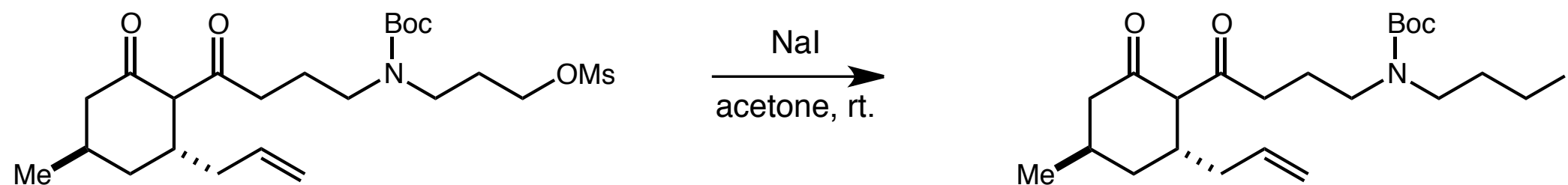
Total Synthesis of (–)-Lycojapodine A

preparing the common intermediate

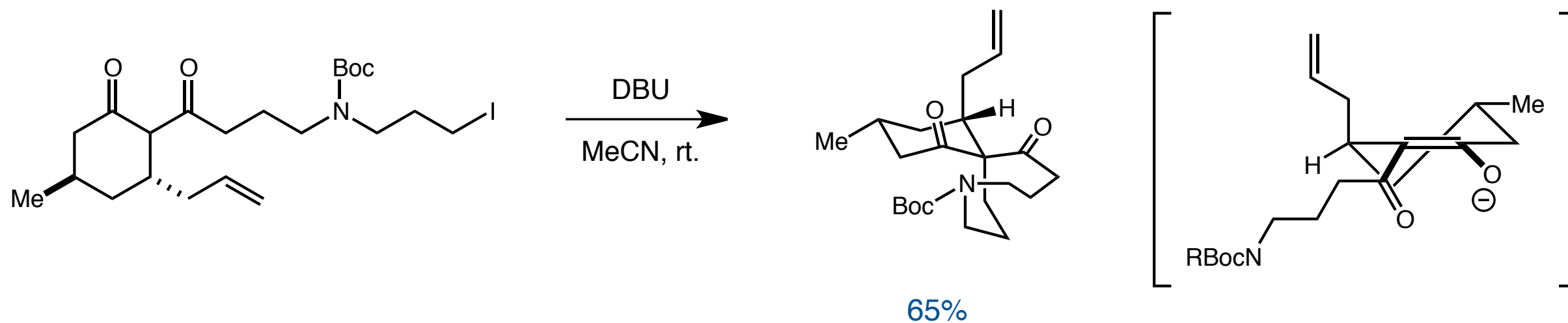


Total Synthesis of (–)-Lycojapodine A

preparing the common intermediate

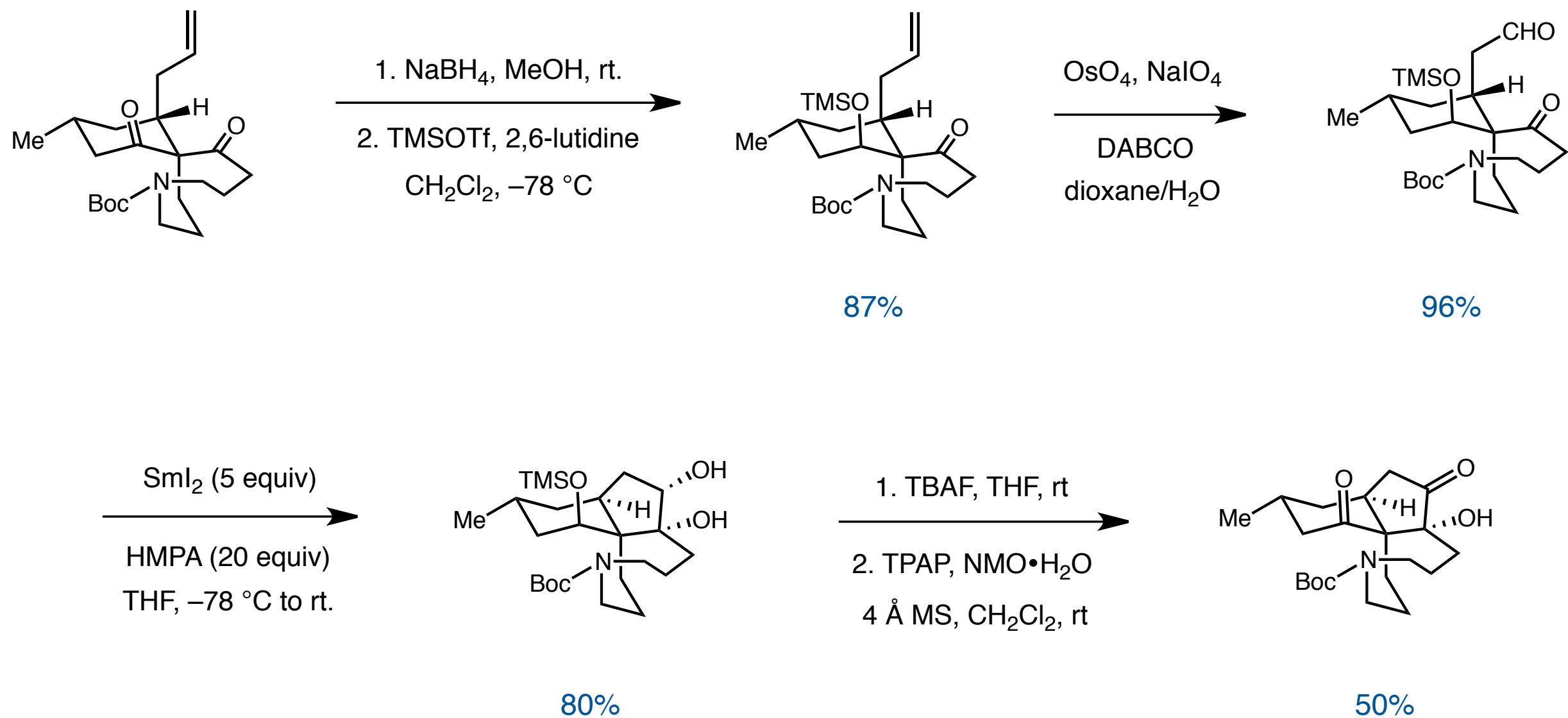


84%



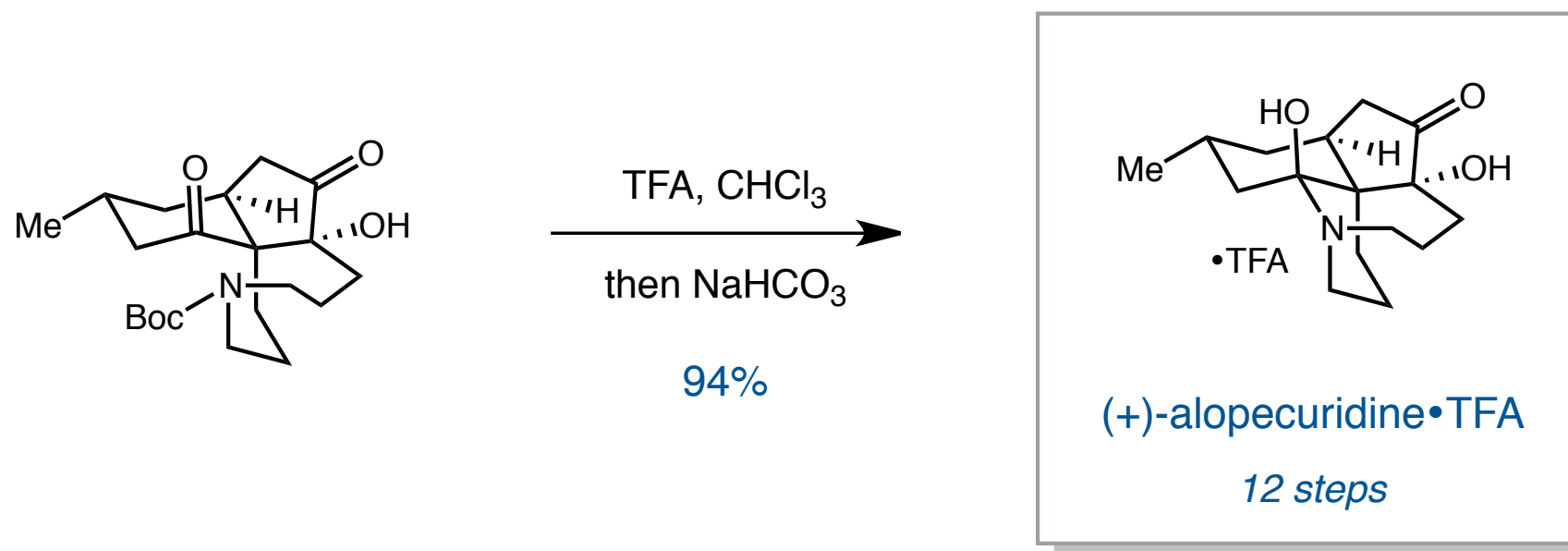
Total Synthesis of (–)-Lycojapodine A

synthesis of (+)-alopecuridine



Total Synthesis of (–)-Lycojapodine A

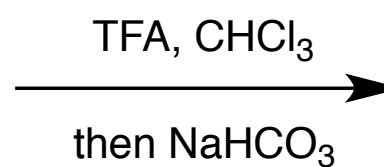
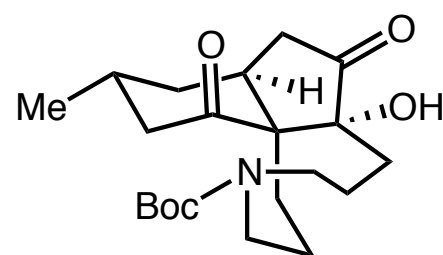
synthesis of (+)-alopecuridine and (–)-lycojapodine A



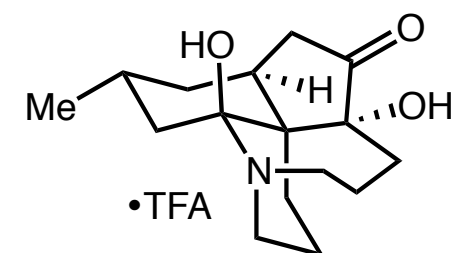
Li, H.; Wang, X.; Hong, B.; Lei, X. *J. Org. Chem.*, **2013**, 78, 800.

Total Synthesis of (–)-Lycojapodine A

synthesis of (+)-alopecuridine and (–)-lycojapodine A

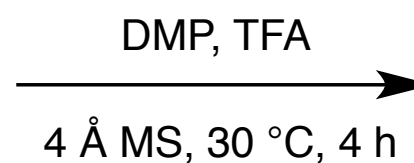
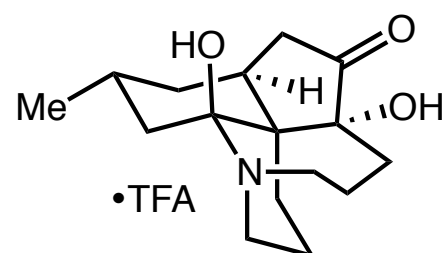


94%

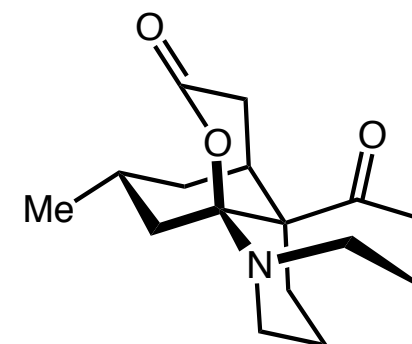


(+)-alopecuridine·TFA

12 steps



80%



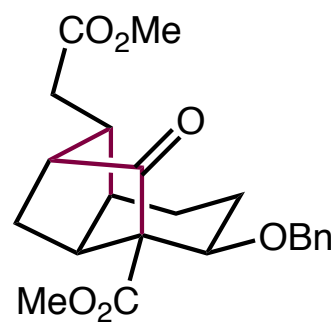
(–)-Lycojapodine A

13 steps

Li, H.; Wang, X.; Hong, B.; Lei, X. *J. Org. Chem.*, **2013**, 78, 800.

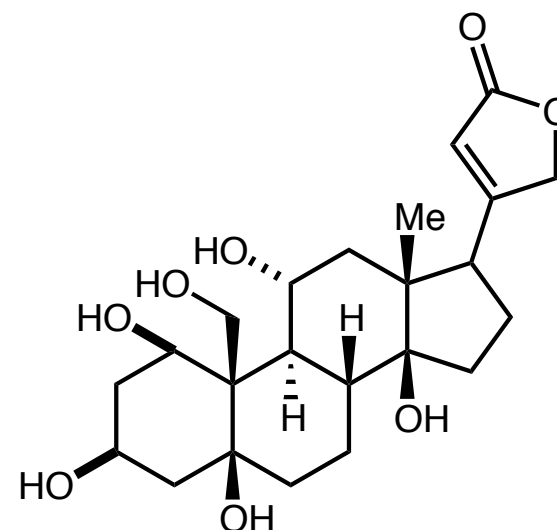
Applied Strategies in Retrosynthetic Analysis

Topological



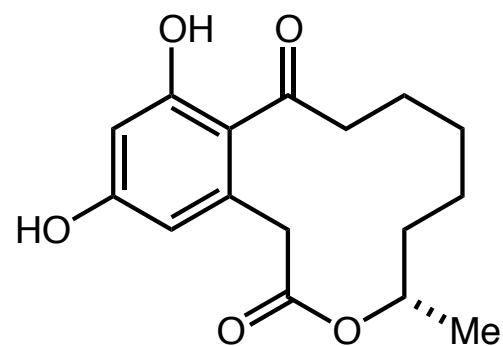
Phragmalin-type Limonoids
Sarpong Group, Berkeley

Functional Group-Based



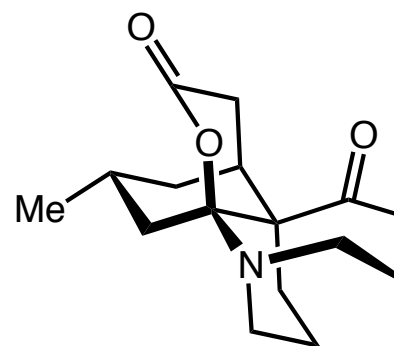
Ouabagenin
Baran Group, Scripps

Transform-Based



(-)-Curvularin
Stoltz Group, Caltech

Structure-Goal



(-)-Lycopodine A
Lei Group, Tianjin University