Bredt's Rule and Strategies Towards Anti-Bredt Natural Products

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Shenvi Lab Group Meeting 04/20/2024

What to expect

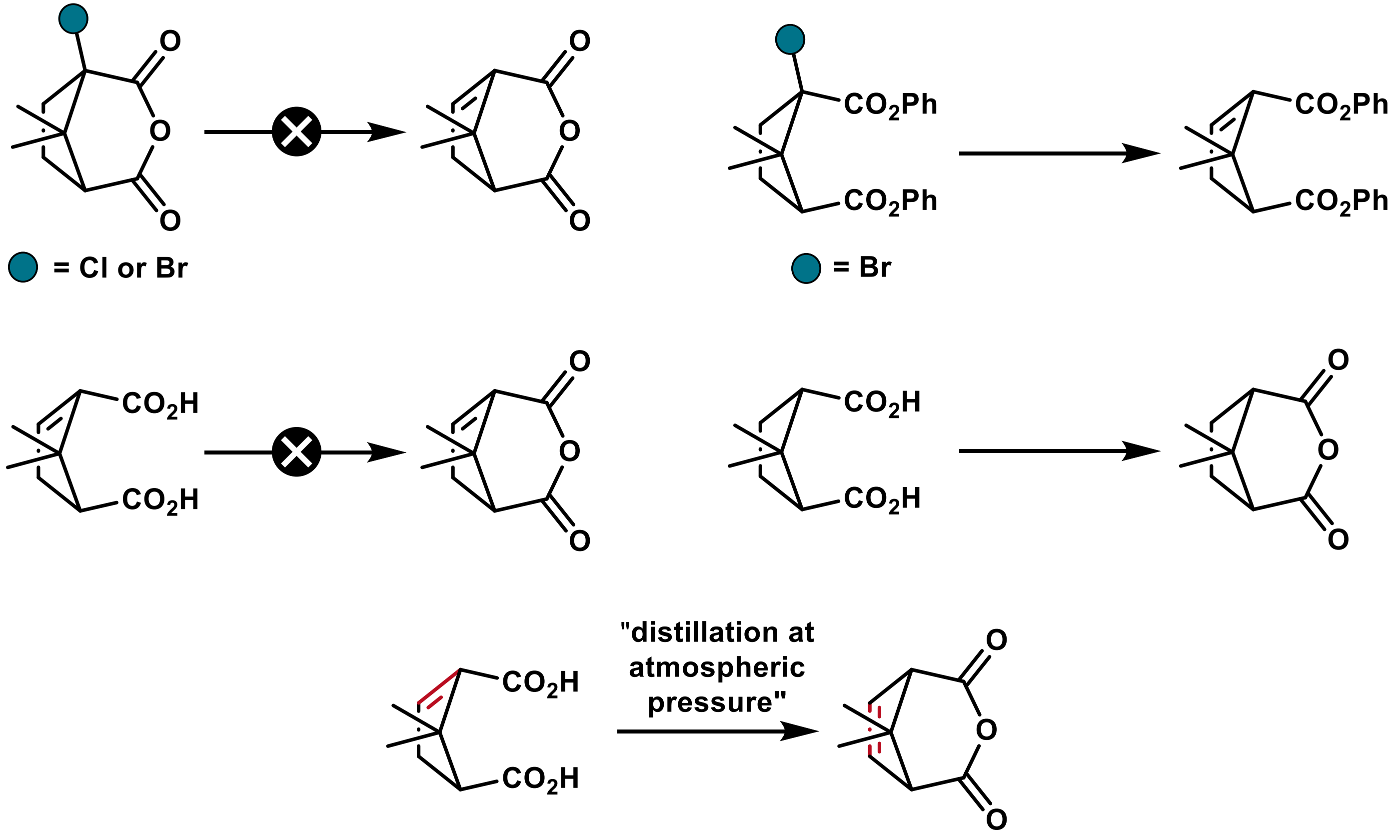
- Part 1: What is Bredt's rule?
  - What is an "anti-Bredt" olefin?
  - Predictors of bridgehead olefin isolability
- Part 2: Key strategies for the synthesis of bridgehead olefins
  - Case studies of relevant syntheses
- Not meant to be an in-depth treatment of each synthesis, nor a rigorous interrogation of Bredt's rule

Bredt's Rule

Originally formulated around

Camphane & Pinane Derivatives

Bredt's early studies on camphane derivatives:



"On the basis of our conceptions of the positions of atoms in space, in the systems of the pinane and camphane series, as well as similarly constituted compounds, a carbon double bond cannot occur at bridgehead positions* A *and* B *of the carbon bridge."
-A 'typical statement of the rule', J. Bredt, 1924

Fawcett, F.S. *Chem. Rev.* 1950, 46(2), 219-274
Bredt, J., *Liebigs. Ann. Chem*. 1924, 437(1), 1-13

A point on nomenclature

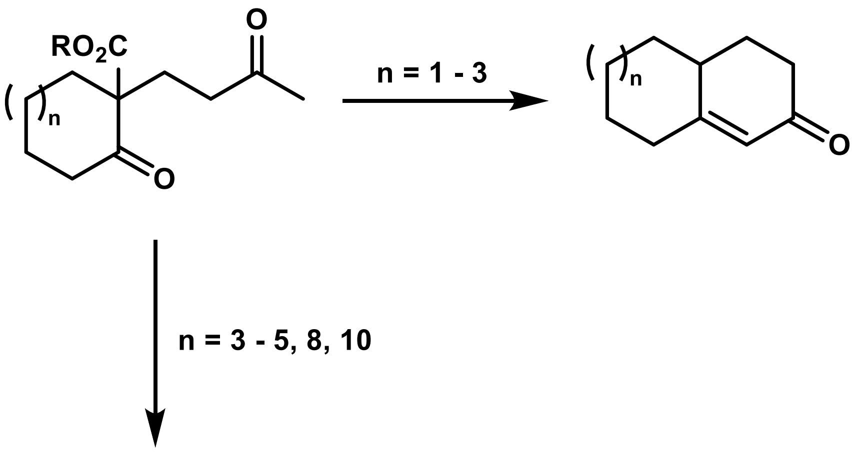
"Since Bredt clearly did not intend that the rule should apply to larger ring systems, it seems inappropriate to regard the existence of bridgehead double bonds in such systems as violations."
- Wiseman and Pletcher, JACS 1969

"The term 'anti-Bredt' infers that a compound is unstable, and in the context of natural products, too unstable to be isolated. Therefore, by definition, it could be argued that most, if not all, isolated bridged bicyclic natural products containing a bridgehead olefin cannot be labeled anti-Bredt."
- Craig Williams, ACIE 2014

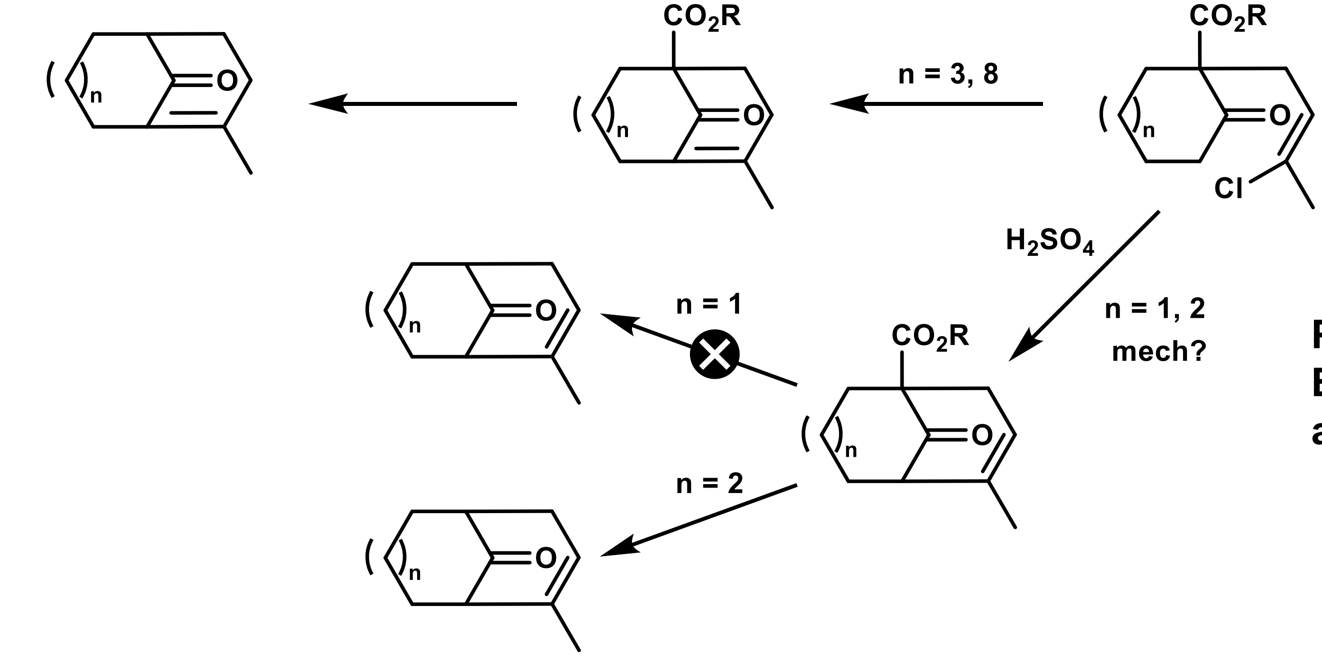
For the purposes of this group meeting, "Anti-Bredt olefin" and "bridgehead olefin" will be used interchangeably

Wiseman J.R. *JACS,* 1970, 92(4), 956-962
Krenske, E.H. *ACIE*, 2015, 54(36), 10608-10612

The First Systematic Study: [n.3.1] systems, Prelog



"These experiments permit some definition of the limits of Bredt's rule... it is therefore clear that a double bond may lie at the bridgehead of a bicyclic system if the ring only be large enough."
- Prelog, J. Chem. Soc. 1949

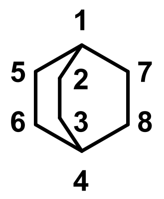


Prelog concludes: "The limit of applicability of Bredt's rule lies between the systems with a 7- and an 8- membered ring."

Prelog, V. *J. Chem. Soc.* 1950, 420-428
Dauben, W.G. *JACS*, 1960, 82, 16, 4245-4248

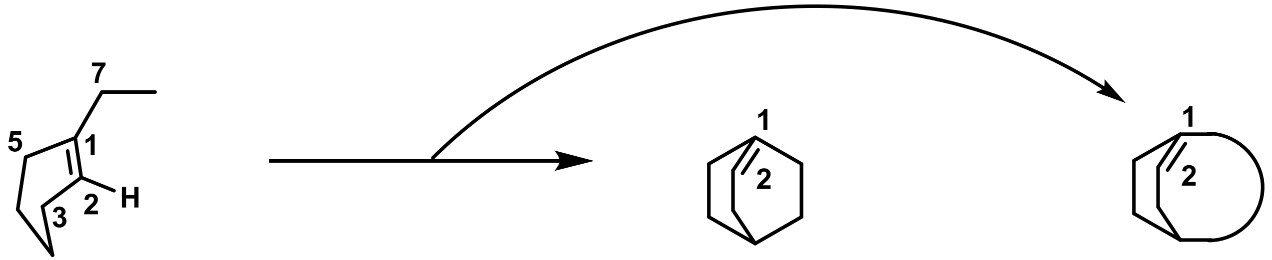
Predicting Bridgehead Olefin Stability

Fawcett's review and "S-number":
Based on reviewing literature through the 1950s and considerations of ball-and-peg models



bicyclo[2.2.2]octane

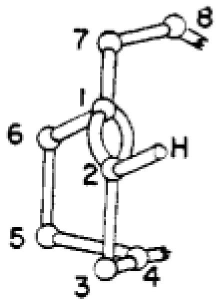
C-7 and C-8 bridge easily accomodated in saturated system



C-1, 2, 3, 5, 7 prefer to be in plane

Forming the C-7,8 bridge requires strong distortion of bond angles and places C-5 and C-7 on the "same side" of the plane defined by the double bond

In ball & peg model, bridgehead olefins can be made strainlessly when for [x.y.z], *S* = x+y+z = 11



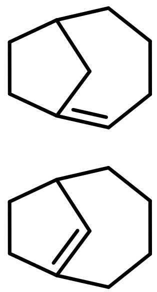
Based on further modeling, Fawcett's generalization is as follows:
S >= 9 and MAYBE S = 8 are isolable
S = 7 is observable but not isolable
S = 6 can be a reactive intermediate

Fawcett, F.S. *Chem. Rev.* 1950, 46(2), 219-274

Fawcett, F.S. *Chem. Rev.* 1950, 46(2), 219-274
Kobrich, G. *ACIE*, 1973, 12(6), 464-473
Wiseman J.R. *JACS*, 1970, 92(4), 956-962

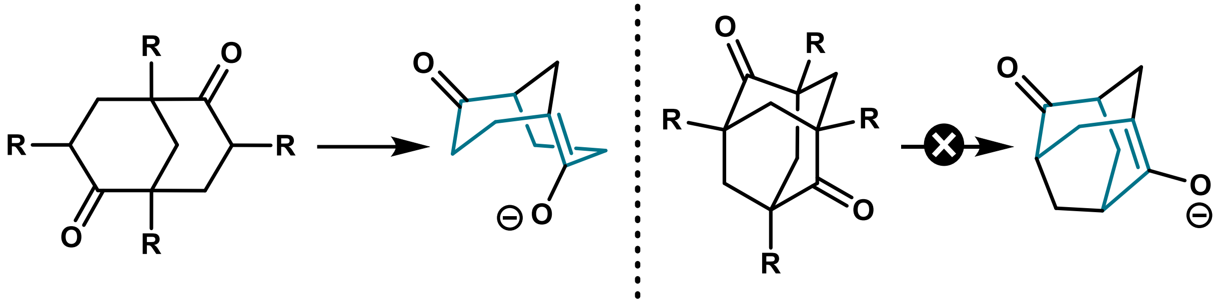
Predicting Bridgehead Olefin Stability

Limitation to the *S* value:
Known now to be flawed, and does not account for which ring the olefin is endocyclic to.



Consider the S = 7 case: which is more stable?

Williams and Pletcher:
Isolable bridgehead olefins are contained in *trans*-cycloalkane units with at least 8 carbon atoms.



R = CO_2H

Köbrich's Expansion of the *S* value (1973):

Rule A: For homologs with different *S* value, the ring strain varies inversely with *S*.

Rule B: For a given *S*, the ring strain varies inversely with the size of the larger of the two rings with respect to which the bridgehead double bond is *endocyclic*.

Rule C: For a given bicyclic ring skeleton, the ring strain varies inversely with the size of the bridge containing the bridgehead double bond.

However, there are now known experimental or computed violations of each of these rules...

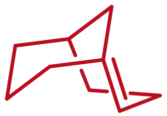
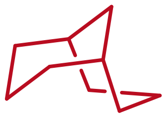
Predicting Bridgehead Olefin Stability

Schleyer's Calculational Study:

From Lesko and Turner, 1968: Strain energy of a bridgehead olefin is derived from extra strain associated with the double bond and the strain associated with the carbon skeleton.

In other words, bridgehead olefin stability can be related to strain imposed by the olefin.

Schleyer defines a new term:
Olefinic Strain (OS) = Strain Energy of Olefin - Strain Energy of Parent Alkane

Example: Olefinic Strain = Energy of  **- Energy of** 

Computationally (force field, molecular mechanics) assessed ~30 different compounds, with some comparison to experimental heats of formation.

Comparison of OS values with experimental behavior yields (in kcals/mol):

isolable bridgehead olefins: OS =< 17

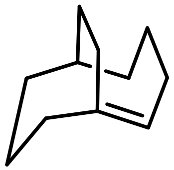
observable bridgehead olefins: 17 =< OS =< 21

unstable bridgehead olefins: OS >= 21

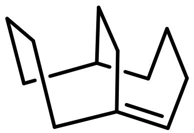
Maier, W.F., *JACS,* 1981, 103(8), 1891-1900
McEwen, A.B. *JACS*, 1986, 108(14), 3951-3960
Lesko, P.M. *JACS,* 1968, 90(24), 6888-6889

An interesting phenomenon: hyperstability

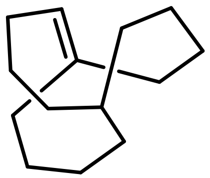
Schleyer's calculations: some bridgehead olefins exhibited negative OS values; bridgehead olefin more stable than parent compound?



bicyclo[4.3.2]undecene
OS: -5.4 kcal/mol

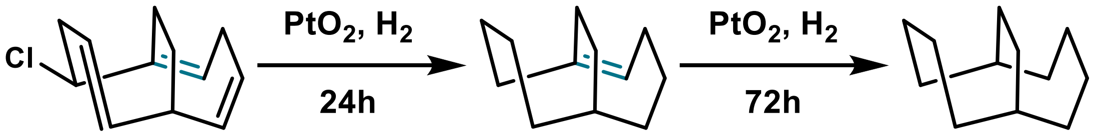


bicyclo[4.4.2]dodecene
OS: -13.0 kcal/mol

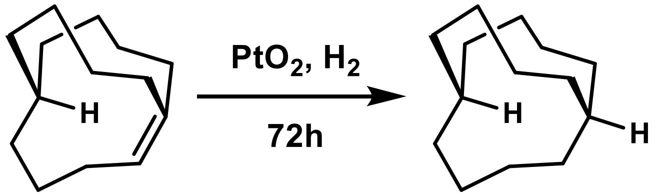


bicyclo[4.4.4]tetradecene
OS: -14.1 kcal/mol

Follow up studies by a number of chemists provided experimental support for a "hyperstability" effect in bridgehead olefins (Schleyer, de Meijere, McMurry, Hopf, and others)



3x longer reaction time!



"catalytic hydrogenation proceeded slowly"

Kukuk, H. *ACIE*, 1982, 21(4), 306
Maier, W.F., *JACS,* 1981, 103(8), 1891-1900
McMurry, *JACS,* 1984, 106(21), 6450-6451
McEwen, A.B. *JACS*, 1986, 108(14), 3951-3960

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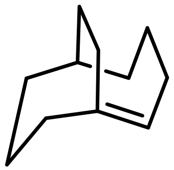

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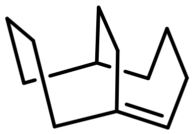

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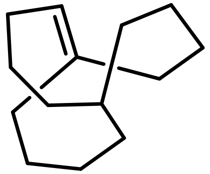

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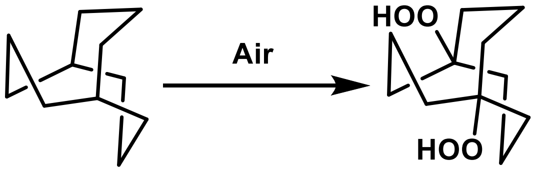
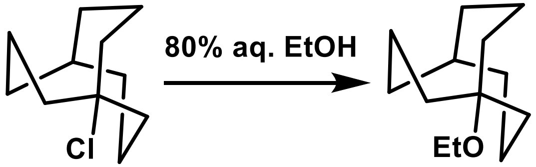
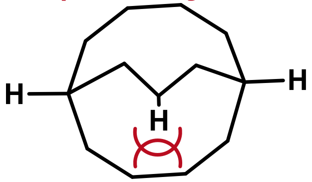


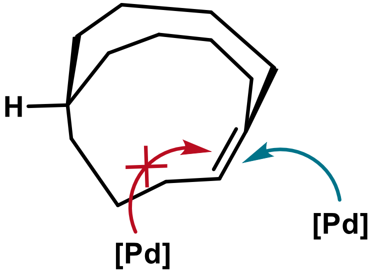


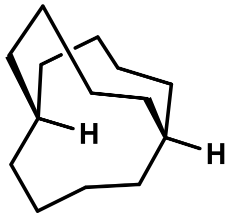
***ca.* x10^4 more reactive than tBuCl in same solvent**

medium ring bridgehead bond angles prefer to planarize
(as they are larger than the ideal sp^3 bond angle (~115 in example)



"out, out" isomer less stable in larger bridged medium sized rings

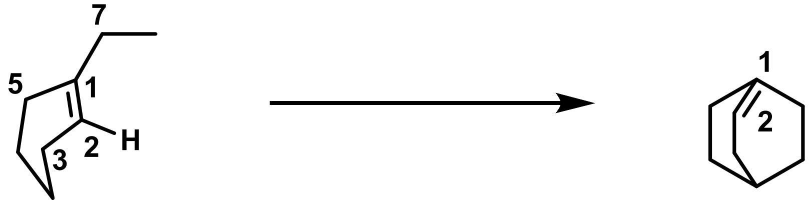




wider C-C bond angles for "in, out" isomer (but still need to consider preference for planarity)

Parker, W. *JACS,* 1974, 96(22), 7121-7122
Hilderbrandt, R.L., *JACS*, 1973, 95(26), 8598-8605
Pawar, D.M., *JOC*, 2007, 72(1), 25-29
Alder, R.W. *Acc. Chem. Res.* 1983, 16(9), 321-327

Basis of Bredt's Rule: Bridgehead olefins cause strain structure due to geometrical constraints



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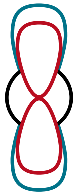
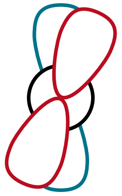


Normal olefin



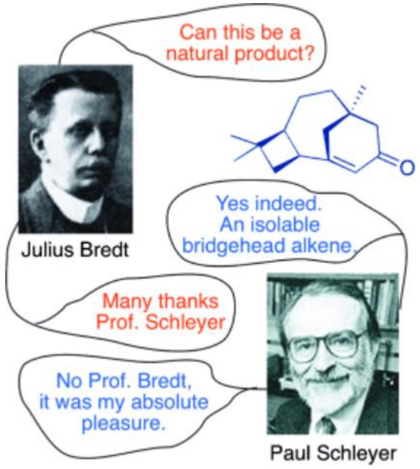
Bridgehead olefin

Multiple predictors exist in the literature, but many have exceptions.
Schleyer's olefinic strain force field calculation based metrics so far hold true
(and have been examined against isolated natural products)

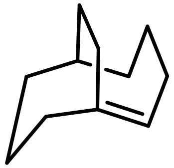
isolable bridgehead olefins: OS =< 17

observable bridgehead olefins: 17 =< OS =< 21

unstable bridgehead olefins: OS >= 21



Bridgehead olefins can exhibit hyperstability in larger rings



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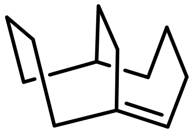

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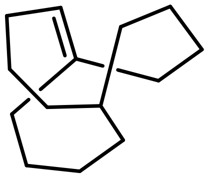
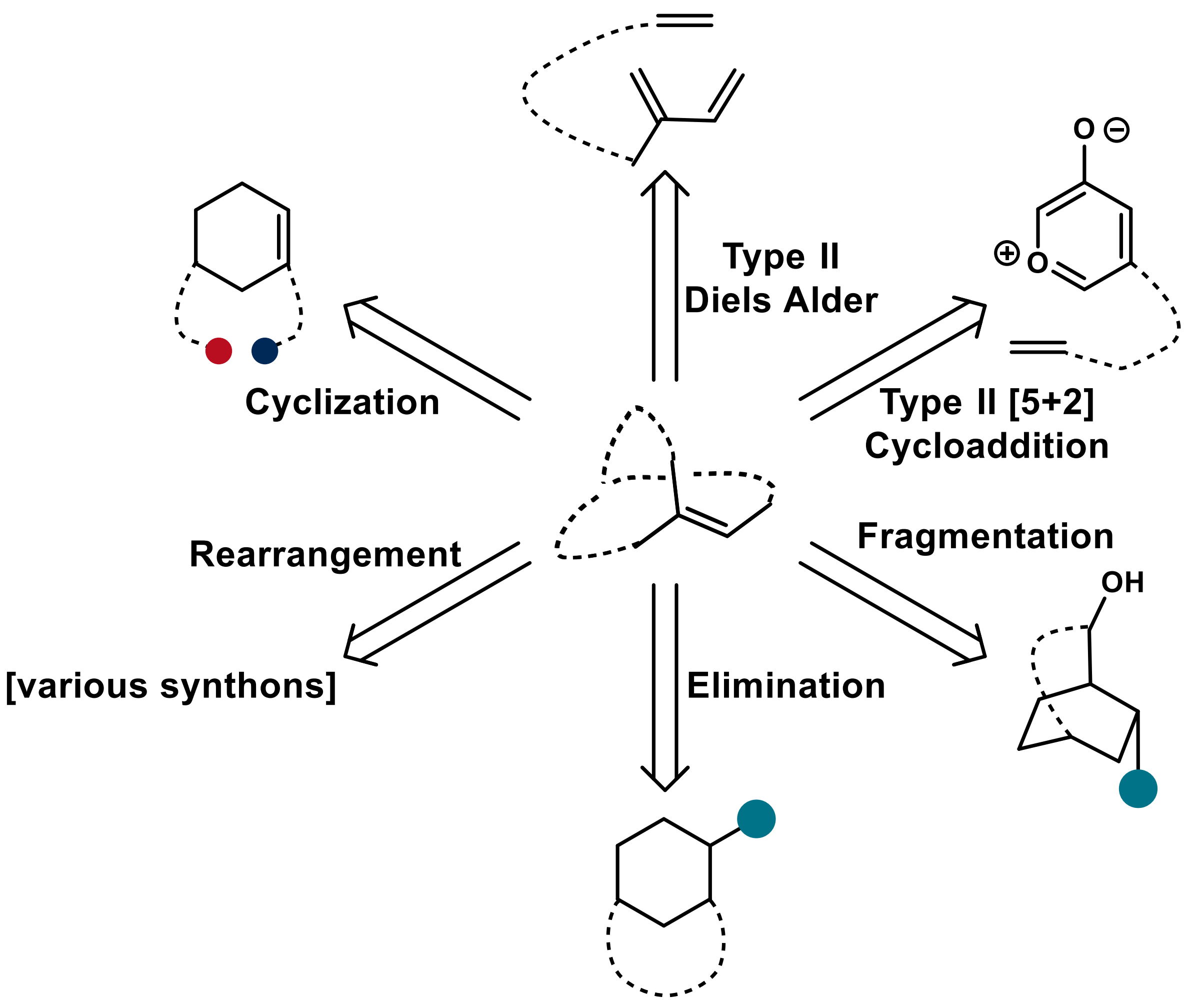


bicyclo[4.4.4]tetradecene
OS: -14.1 kcal/mol

Contrary to my own undergrad education, many bridgehead olefins are in fact quite stable

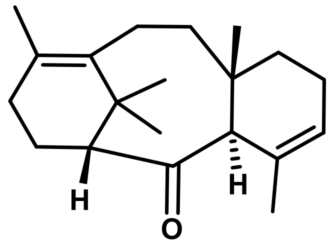
Part 2: Synthetic Strategies

A challenging motif



Key review: Liu, J. *Chem*, 2020, 6, 579-615

Type II Diels-Alder: Taxanes (Baran)



Taxadienone

Mendoza, A. *Nat. Chem.*, 2012, 4, 21-25

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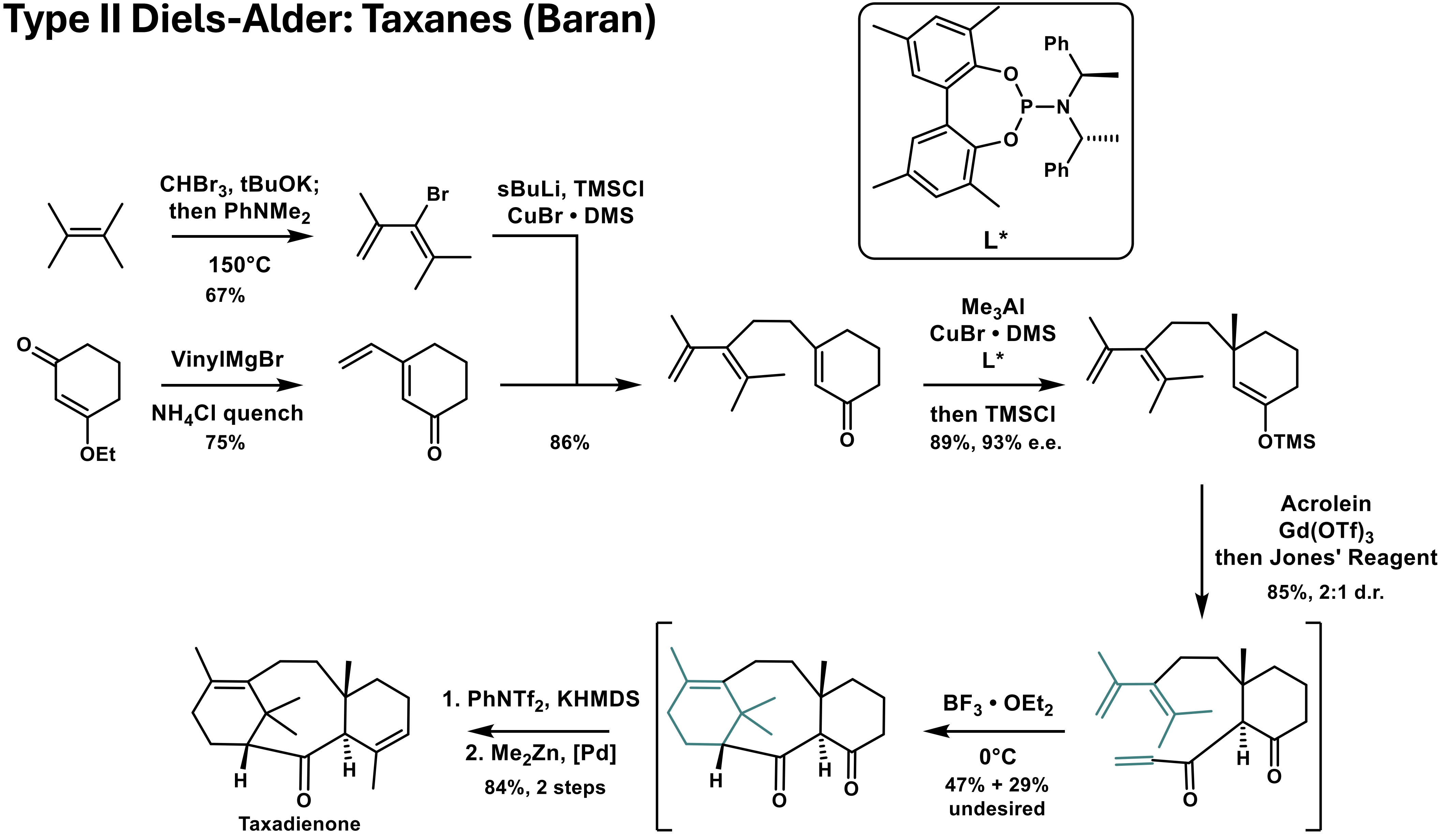
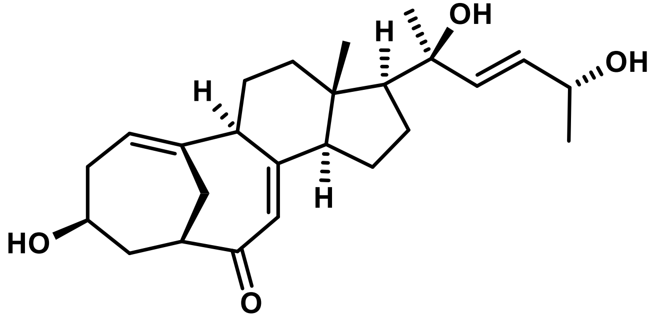


Mendoza, A. *Nat. Chem.*, 2012, 4, 21-25

Type II [5+2] Cycloaddition: Cyclocitronol (Li)



Cyclocitrinol

Liu, J. *JACS*, 2018, 140(16), 5365-5369

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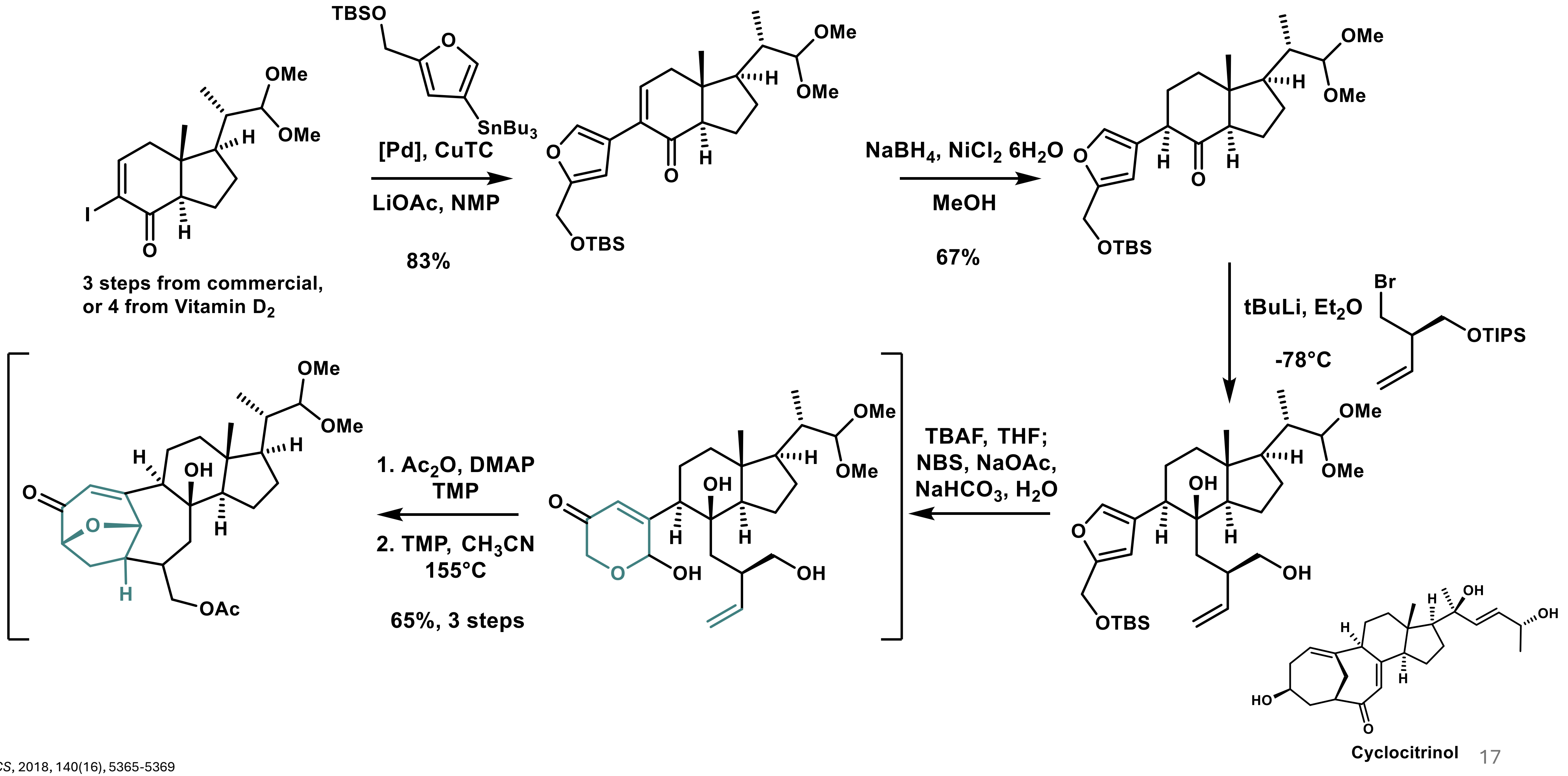

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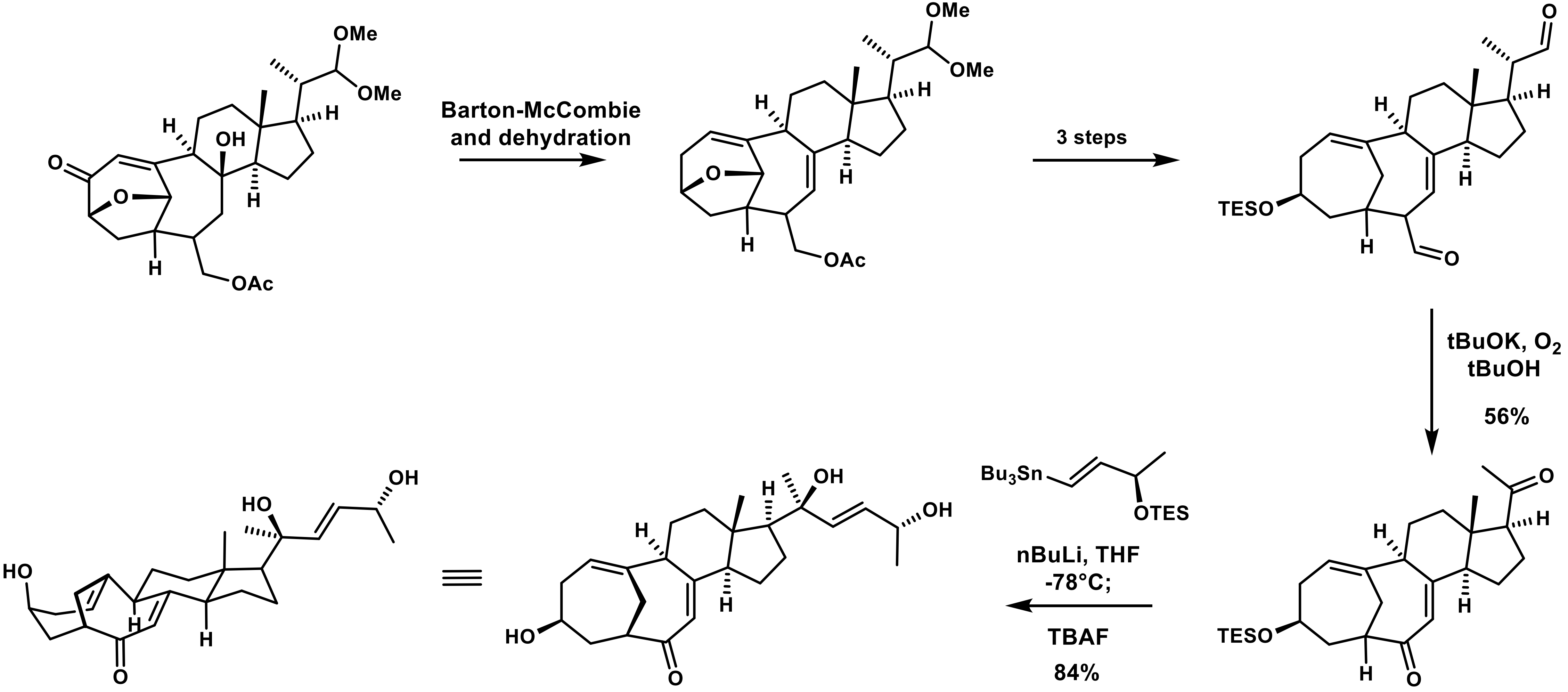
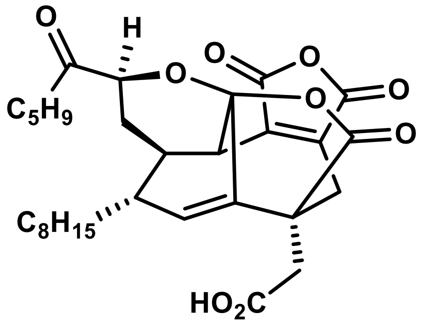


Cyclocitrinol

Liu, J. *JACS*, 2018, 140(16), 5365-5369

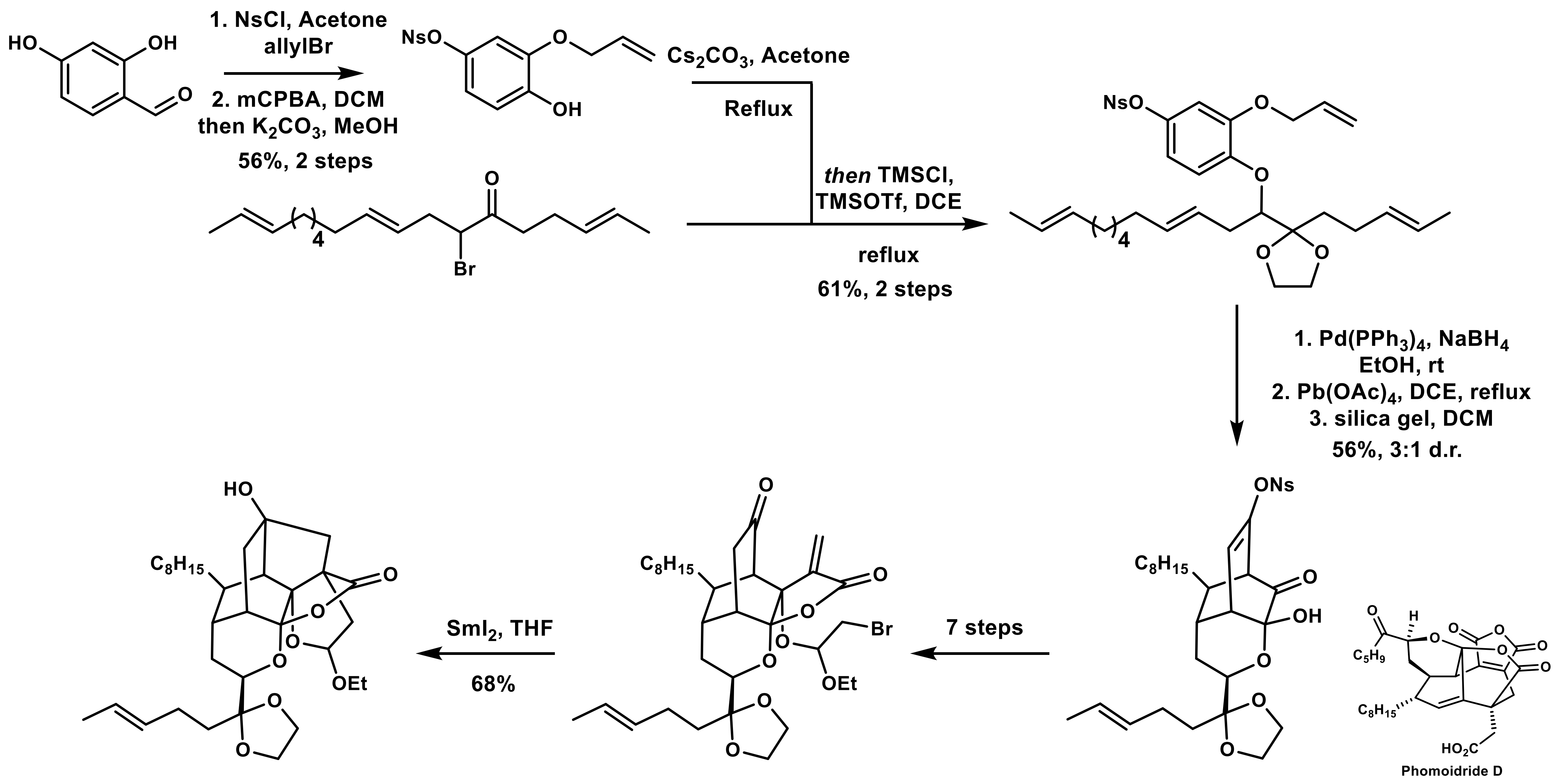
Fragmentation: Phomoidride D (Wood)



Phomoidride D

Leung, J.C., *ACIE*, 2017, 57(7), 1991-1994

Fragmentation: Phomoidride D (Wood)



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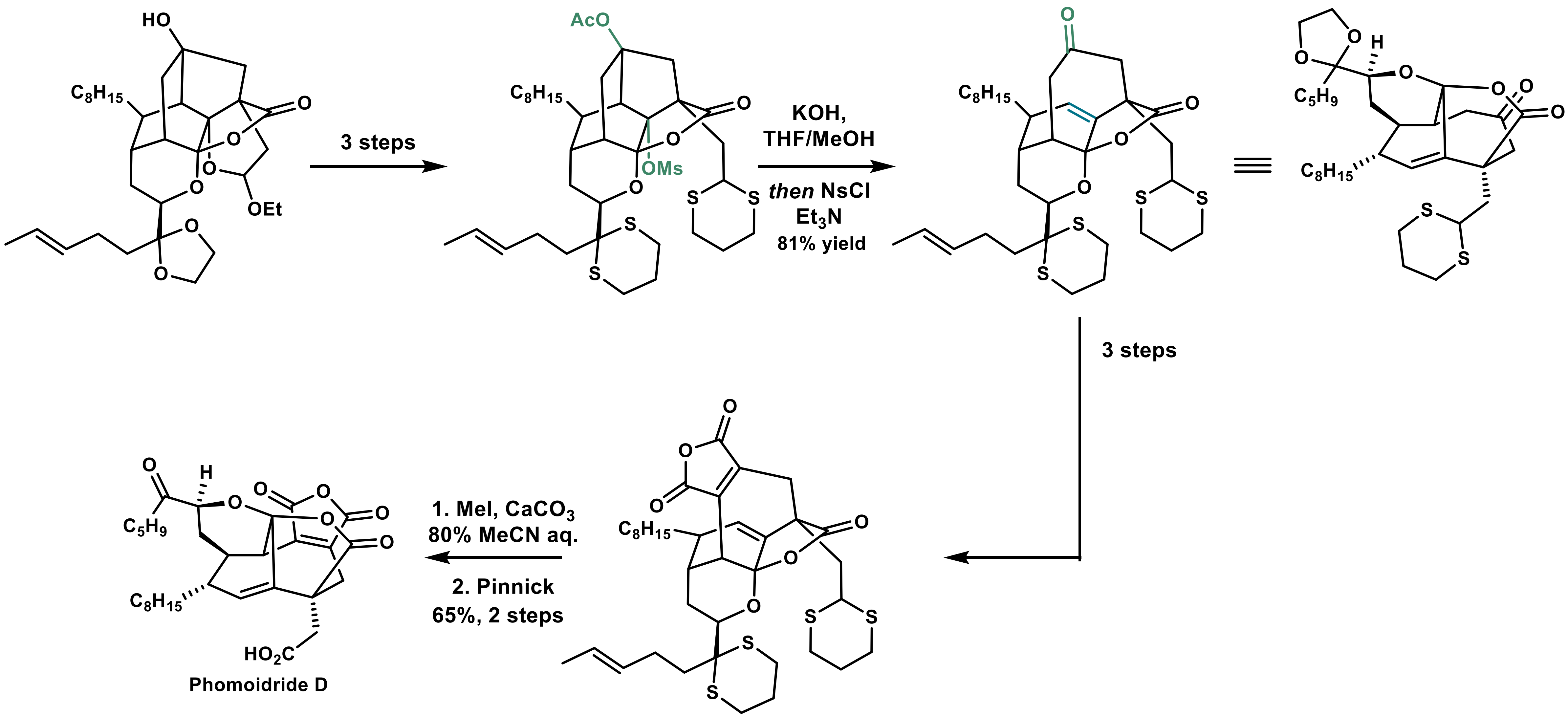
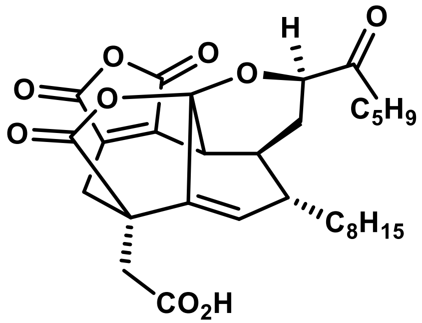


Leung, J.C., *ACIE*, 2017, 57(7), 1991-1994

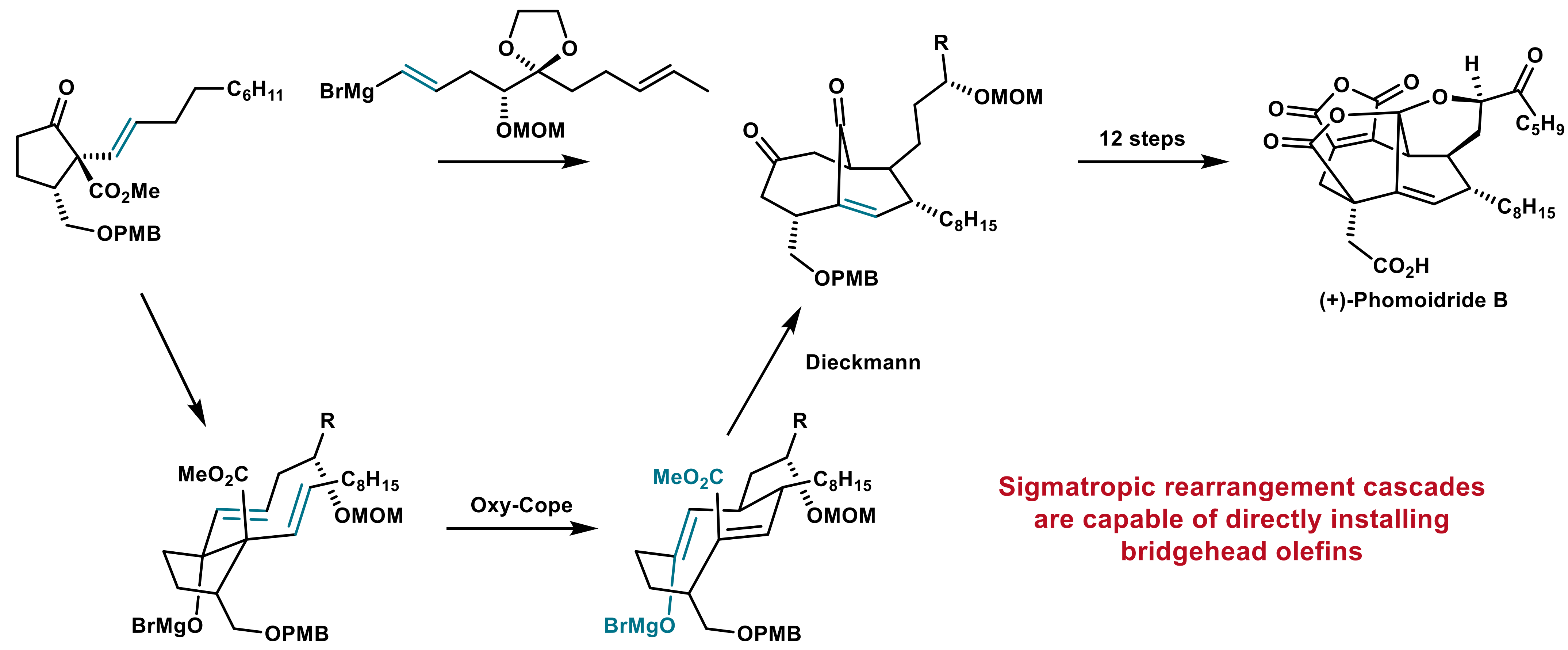
Rearrangement: (+)-Phomoidride B (Shair)



(+)-Phomoidride B

Chen. C. *JACS*, 2000, 122(30), 7424-7425

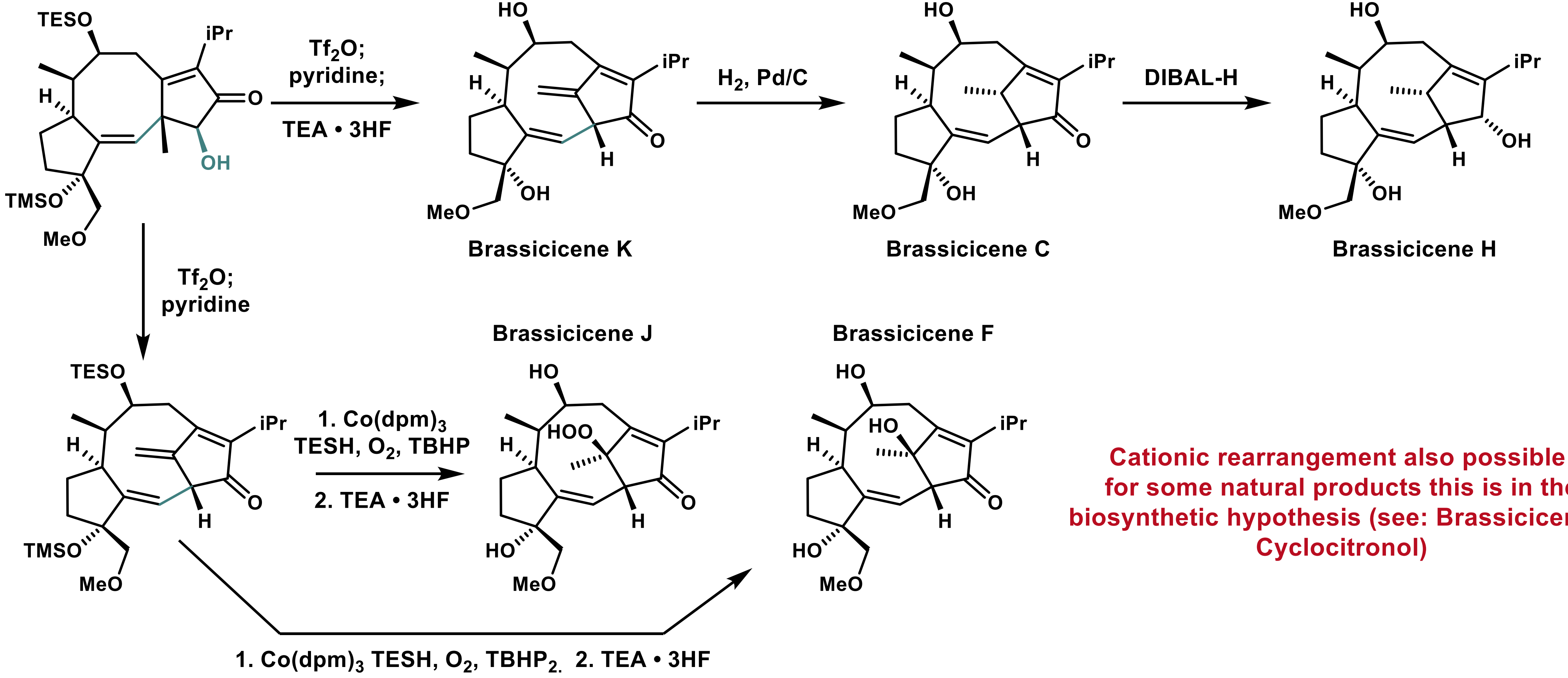
Rearrangement: (+)-Phomoidride B (Shair)



Sigmatropic rearrangement cascades are capable of directly installing bridgehead olefins

Chen. C. *JACS*, 2000, 122(30), 7424-7425

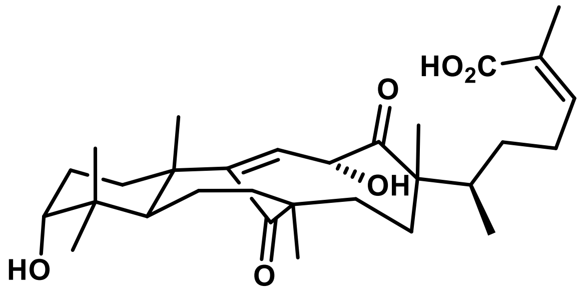
Rearrangement: Brassicicenes (Renata)



Cationic rearrangement also possible; for some natural products this is in the biosynthetic hypothesis (see: Brassicicenes, Cyclocitronol)

Jiang, Y. *ChemRxiv*, 2023: 10.26434/chemrxiv-2023-gfh8l

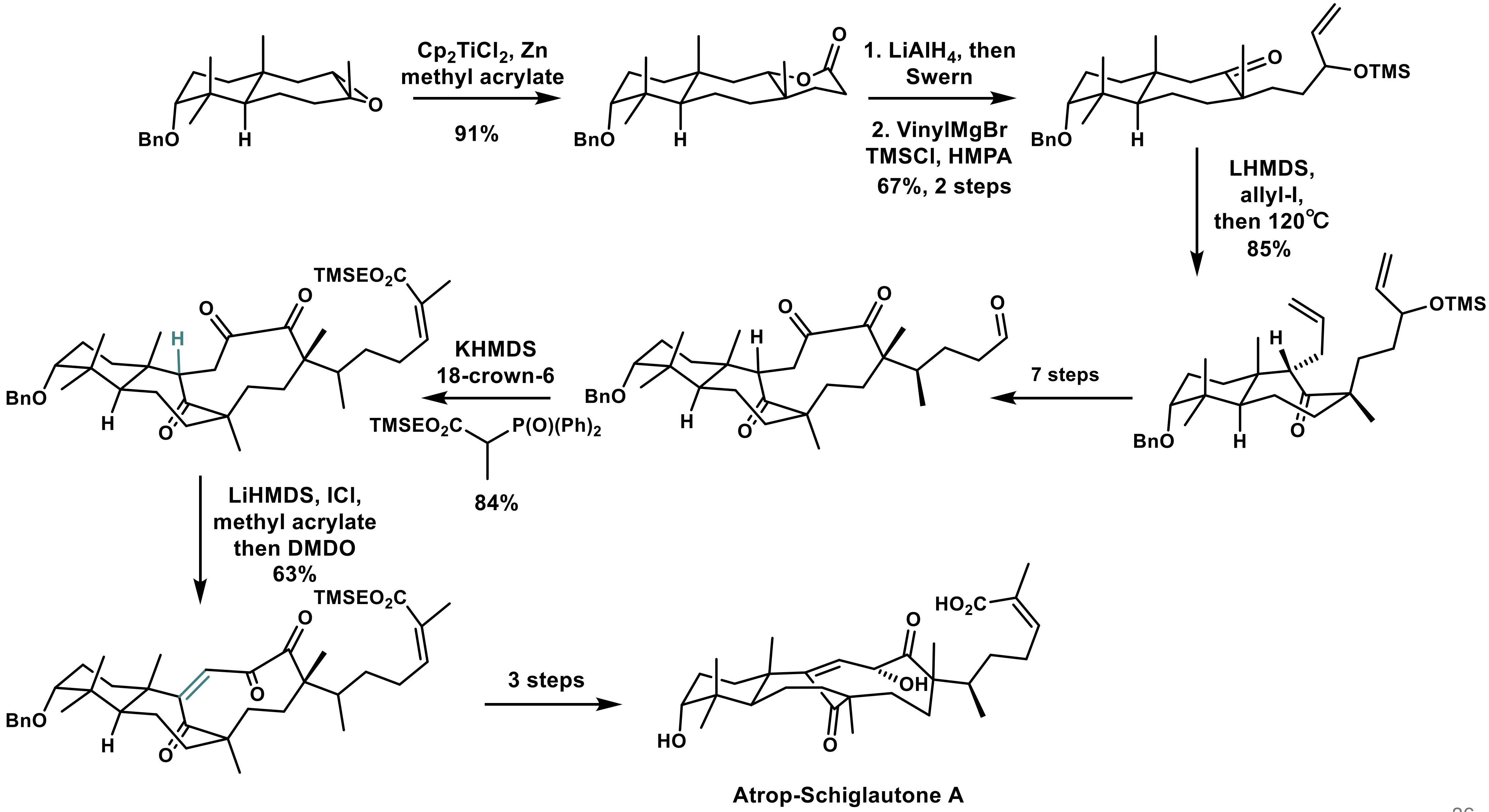
Elimination: Schiglautone A Atropisomer (Ding)



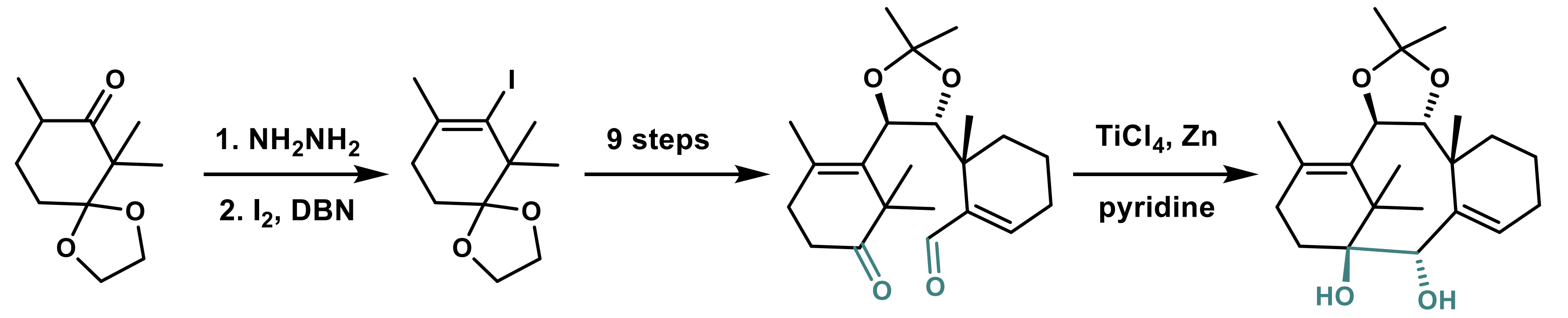
Atrop-Schiglautone A

Ma, B. *ACIE*, 2018, 57(47), 15567-15571

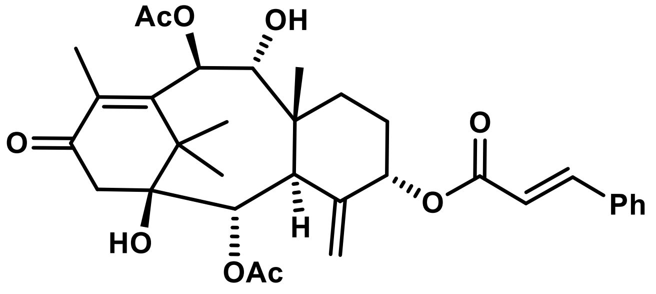
Elimination: Schiglautone A Atropisomer (Ding)



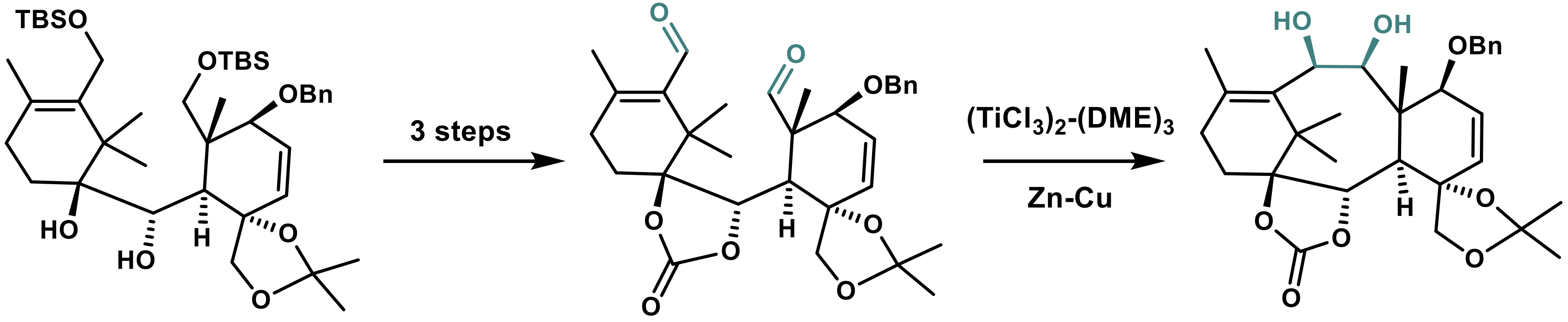
Cyclization (Quick Examples): Taxanes (Inoue, Nicolaou)



en route towards:



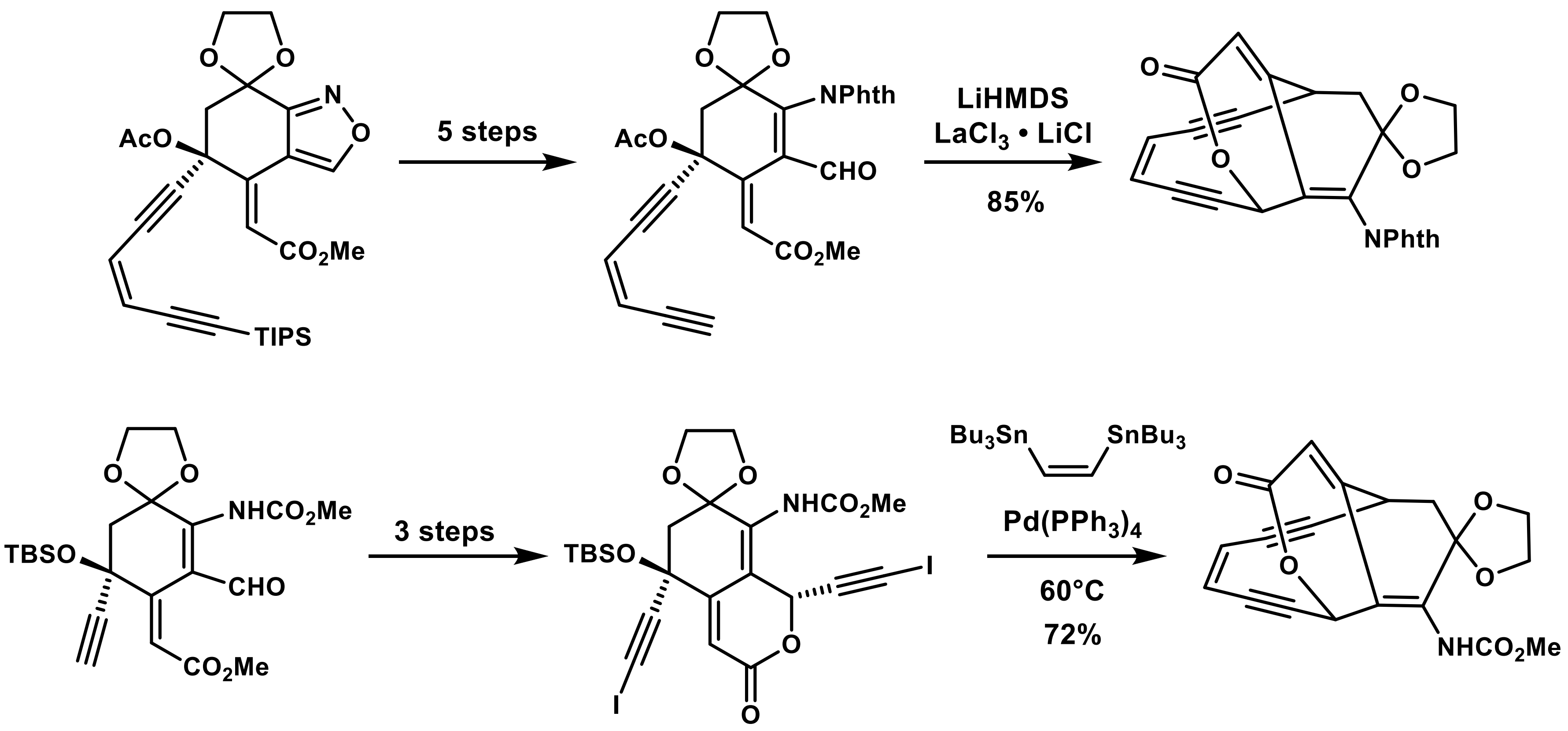
1-hydroxytaxinine



en route towards taxol

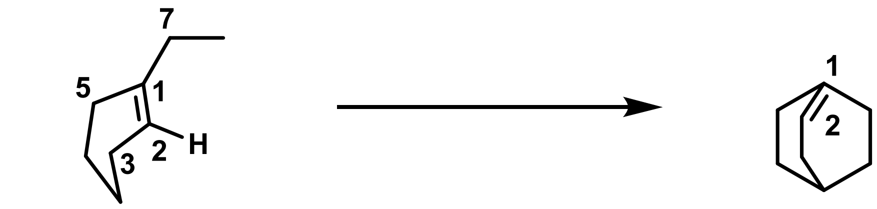
Imamura, Y. *ACIE*, 2019, 58(35), 12159-12163
Nicolaou, K.C. *Nature,* 1994, 367, 630-634

Cyclization (Quick Examples): Calicheamicinone (Nicolaou, Clive)



Nicolaou, K.C. *JACS,* 1992, 114(25), 10082-10084
Clive, D.L., *JACS,* 1996, 118(20), 4904-4905

Basis of Bredt's Rule: Bridgehead olefins cause strain structure due to geometrical constraints



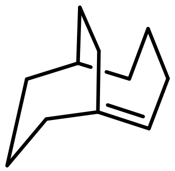
C-1, 2, 3, 5, 7 prefer to be in plane

Forming the C-7,8 bridge requires strong distortion of bond angles and places C-5 and C-7 on the "same side" of the plane defined by the double bond

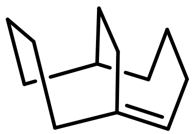
However, when ring sizes are large enough bridgehead olefins can be stable and isolable

The space of natural products is an example of this

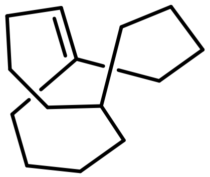
Not only this, but it is possible for bridgehead olefins to be "hyperstable"



bicyclo[4.3.2]undecene
OS: -5.4 kcal/mol

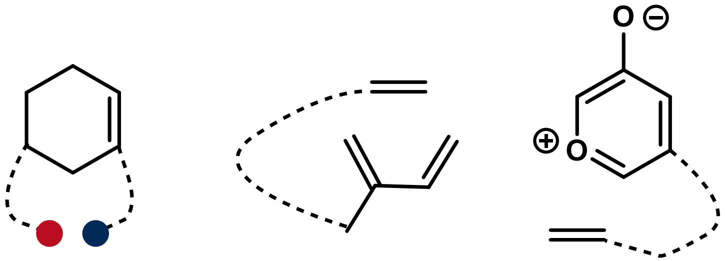


bicyclo[4.4.2]dodecene
OS: -13.0 kcal/mol

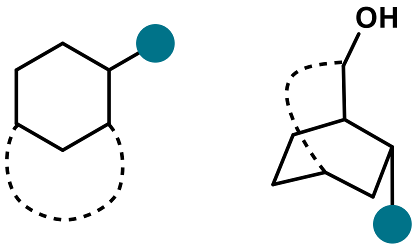


bicyclo[4.4.4]tetradecene
OS: -14.1 kcal/mol

In the context of natural product synthesis... it seems no special strategies are required to access bridgehead olefins



Cyclization (radical, nucleophilic, [M] cat. (not discussed here)) and cycloaddition among the most common strategies.



● = Leaving Group

Typical methods for forming or manipulating olefins, such as rearrangements, elimination, or fragmentation are also feasible and powerful tools