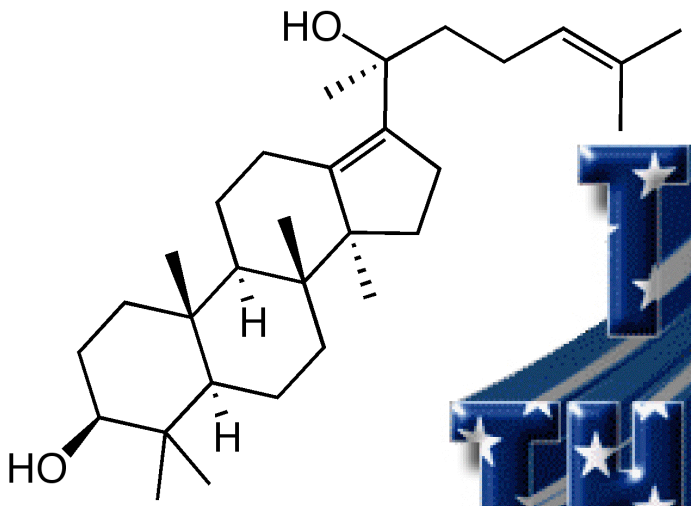
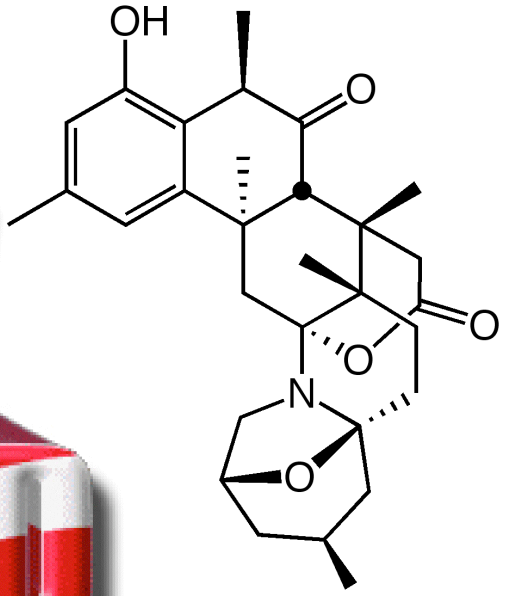
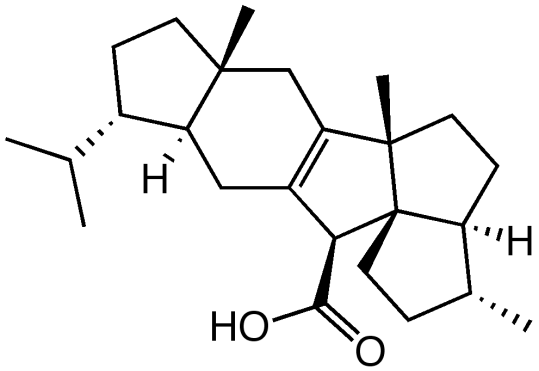




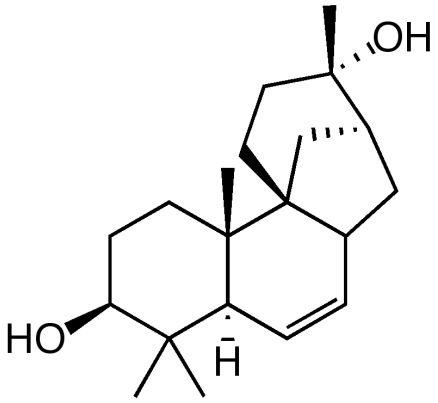
THE WAYS TO MAKE VICINAL QUAT CENTERS



Jenn Stockdill

Stoltz Group Meeting

05 December 2005



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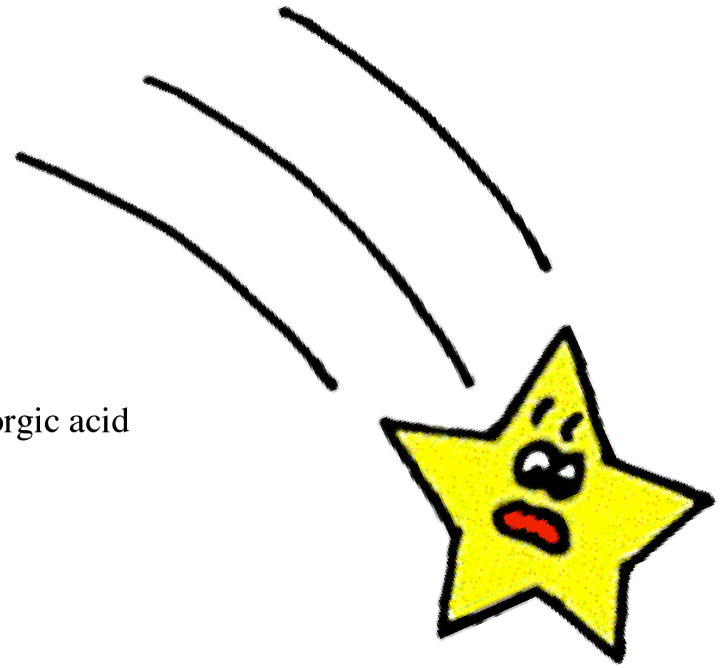

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A. Intramolecular Approaches

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B. Bimolecular Approaches

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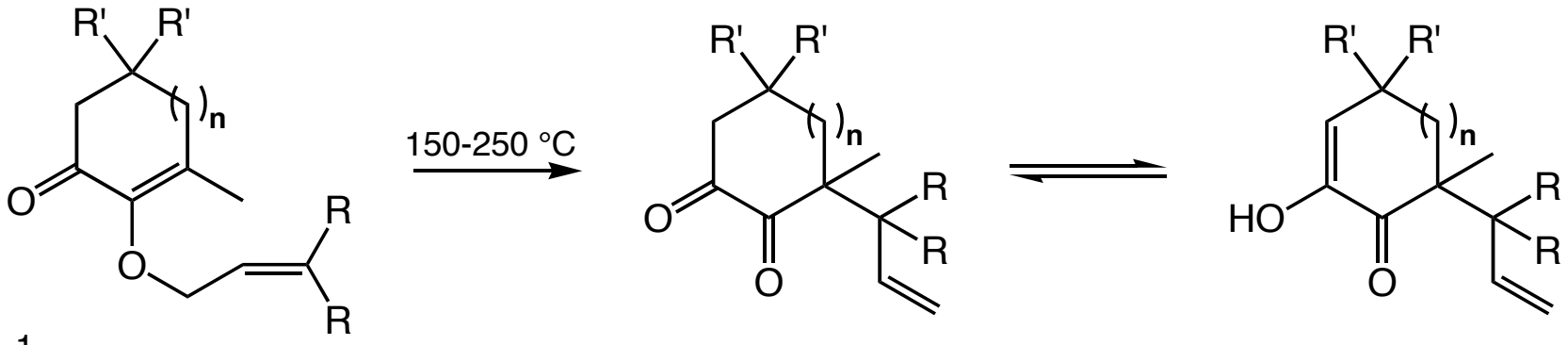
1995 - penitrem D
2002 - merrilactone A
2003 - (−)-idiospermuline

Claisen Variant to Accommodate VQCs

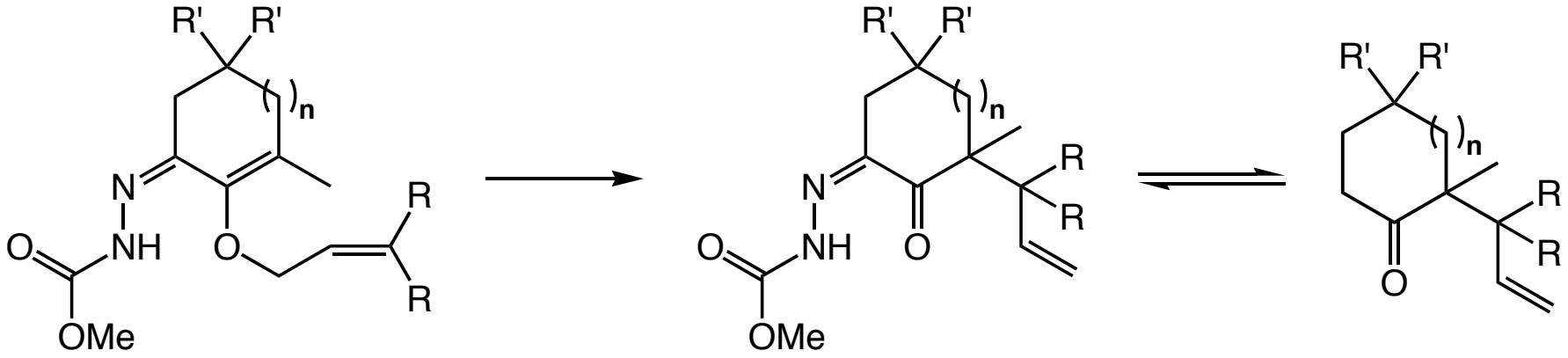
~Source Reaction: Cycloalkenyl Allyl Ether Claisen



n = 0, 1
R = H, Me
R' = H, Me

*Very slow; side reactions (deallylation or aromatization) are competitive at required temps.
*2 Carbonyl groups produced cannot always be distinguished easily in later chemistry.

~Modified Reaction: Carbomethoxyhydrazone derivative (and anionic version)

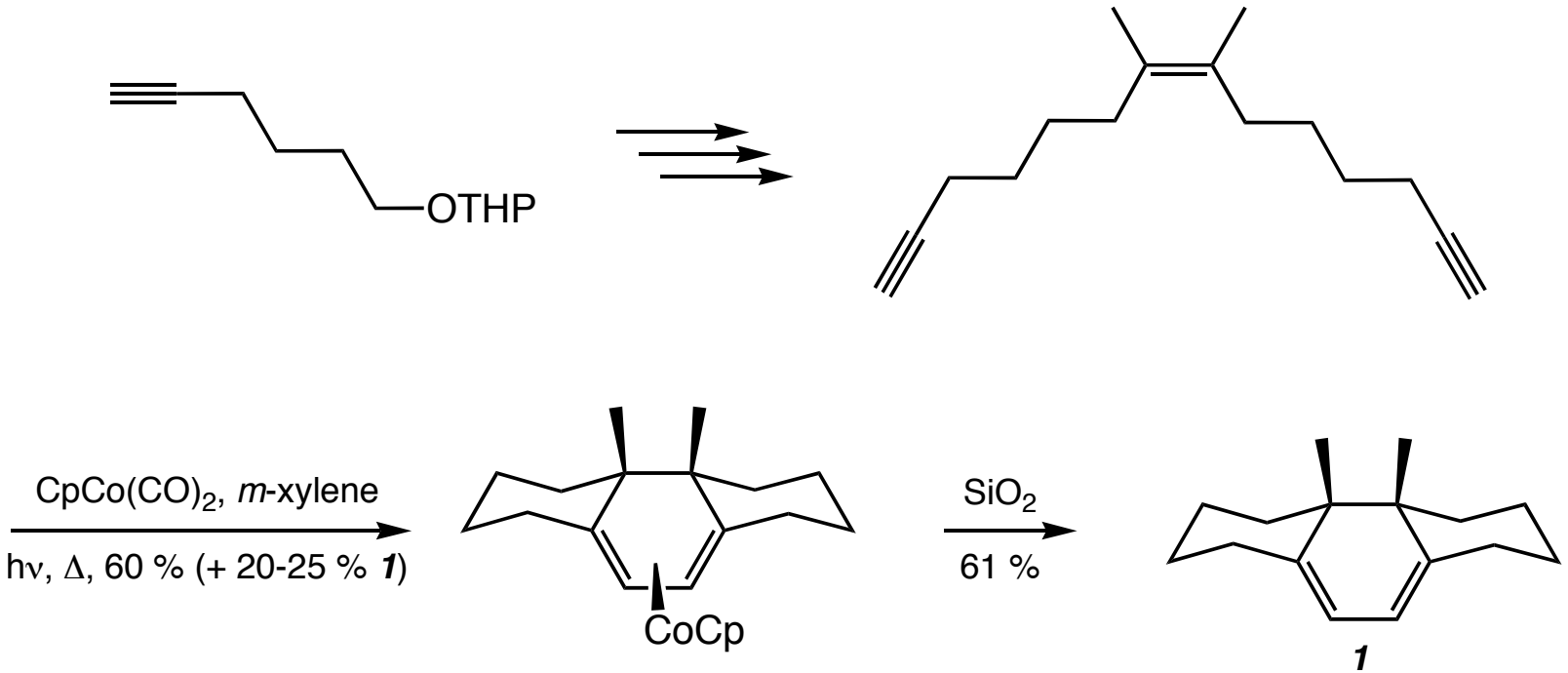


*6 to 31-fold rate increase for the hydrazone derivative, and a further 15 to 145-fold increase for the anionic version. This allows the reaction to be cooled to 66 °C. Na^+ vs. K^+ rates are not significantly different.
*Prenyl (R = Me) derivatives are slower, but not a huge difference. Complete allylic rearrangement is observed, verifying the [3,3]-sigmatropic nature of the transformation.
*For the hydrazone, $MeOH/H_2O$ is the best solvent system. For the anionic version, heating in aprotic solvents is best.

J. Org. Chem. **1983**, *48*, 3866-8.

Enediyne Cyclization

~A neat reaction, though not very general in its application.



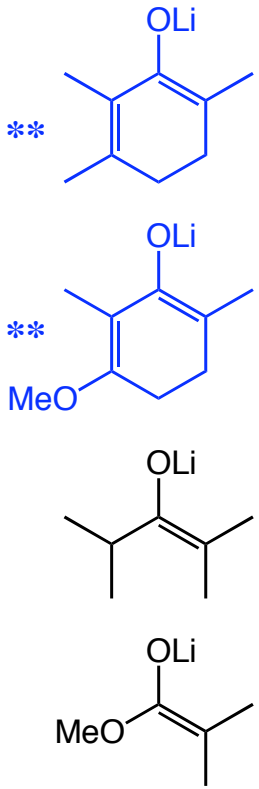
*Reaction works with 1-mono; 1,1- or 1,2-di; and 1,1,2-trisubstituted patterns as well.
*Proceeds with complete specificity relative to the starting olefin.

J. Org. Chem. **1984**, *49*, 5010-2.

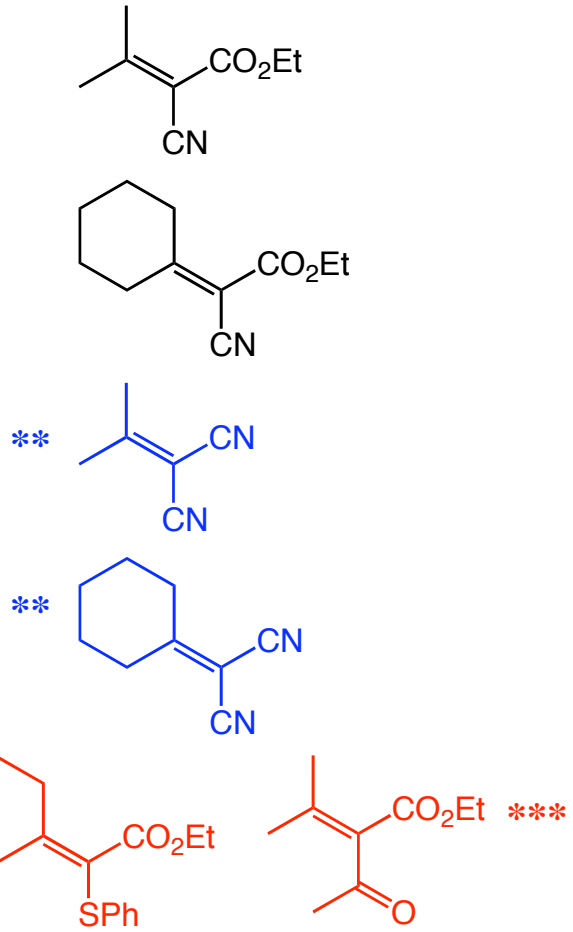
Michael Variant to Accommodate VQCs

~ "Electronic Compensation for Steric Congestion."

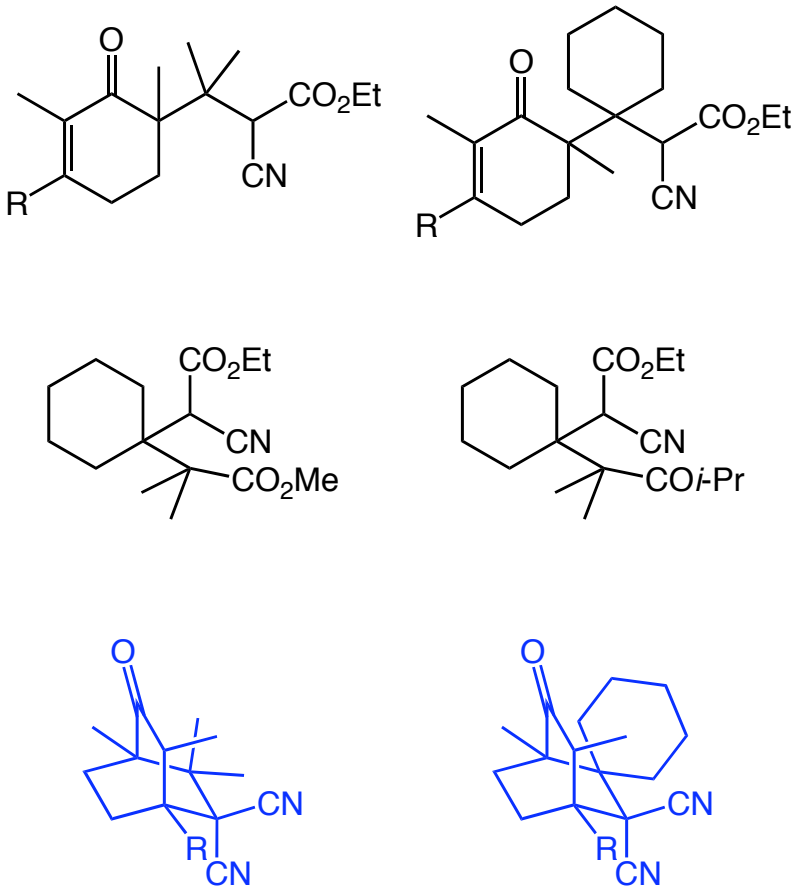
Enolates



Acceptors



Products

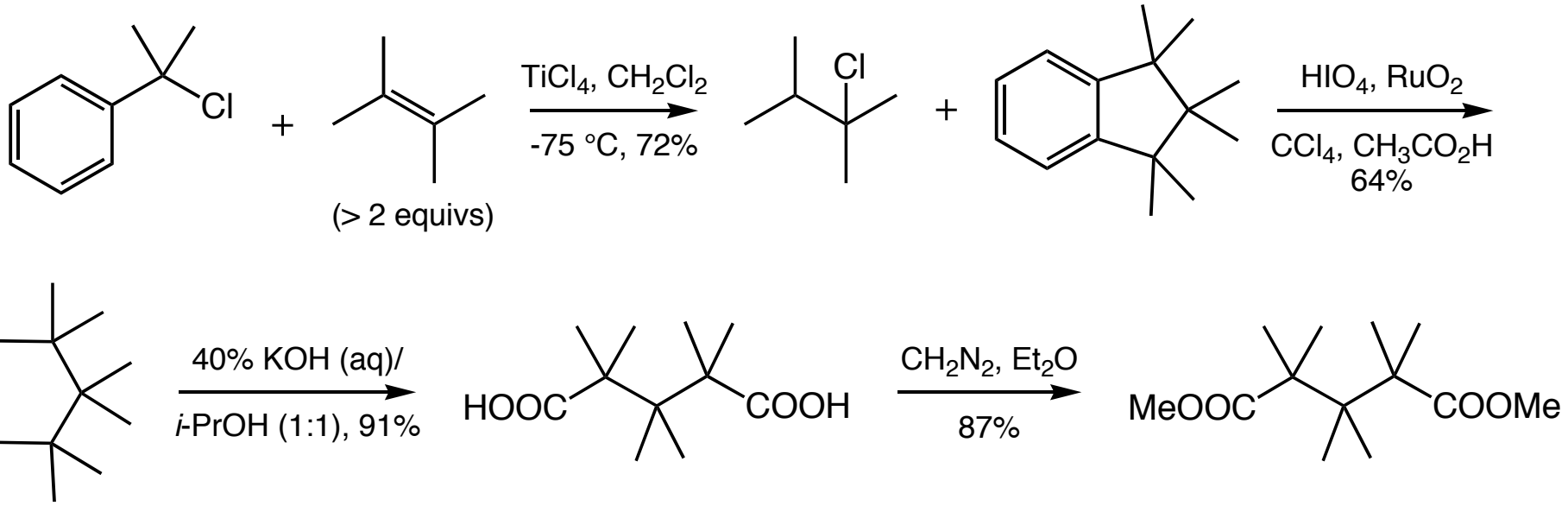


*Run in THF with LDA. Aprotic conditions for Michael rxns only possible in cases where product enolate is more stable than the initial enolate.
*Li^+ coordination may be accelerating cyanoester cases.
*Yields generally in 90s, except in cases of remote steric interference.
**Give double-Michael products with 4 contiguous QCs.
***Unreactive in VQC-forming reactions.

J. Org. Chem. **1986**, *51*, 5480-2.

Synthesis of Hexamethylglutaric Acid

~ Based on QC methodologies with formation of a tertiary carbocation followed by C-C bond formation. This approach generally fails for VQCs because the entropic and steric costs outweigh the energy gained by σ-bond formation.



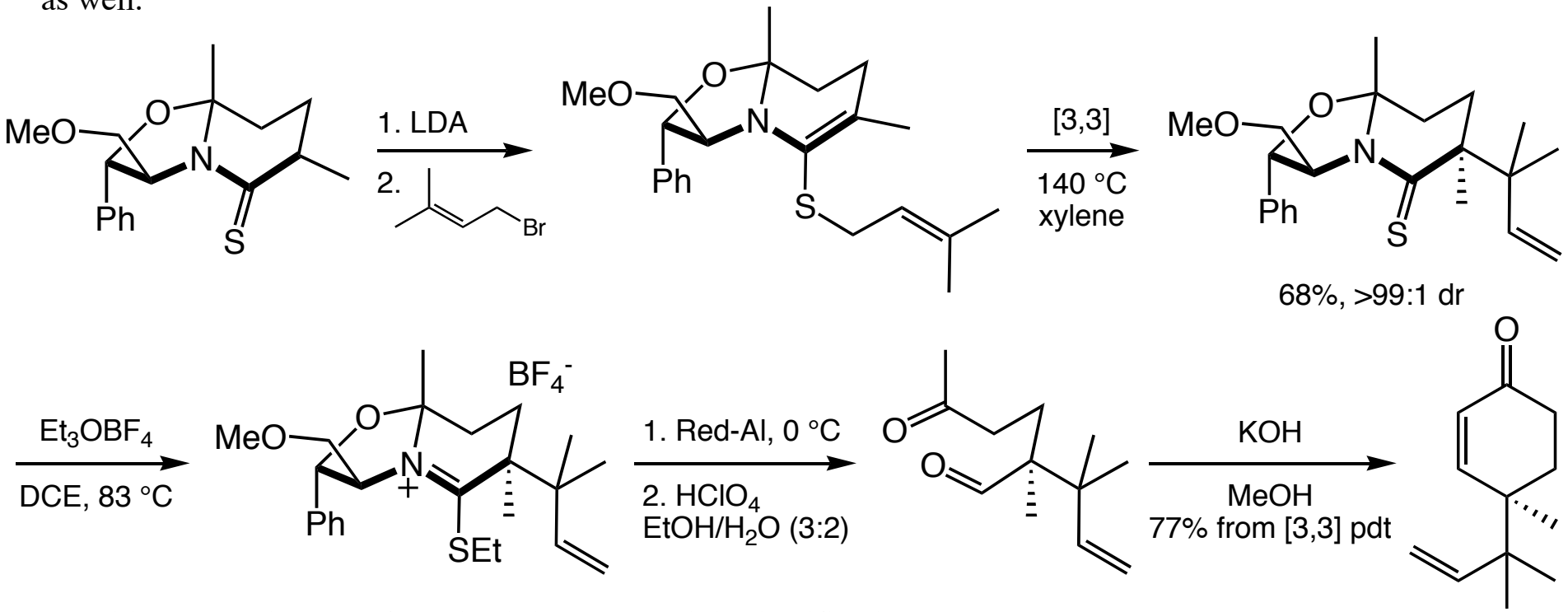
*This approach is successful in this case because the reverse reaction in step 1 is prevented by fixing the 2 fragments in a ring.

*The aromatic ring can be readily cleaved and the resulting anhydride opened to form a linear system.

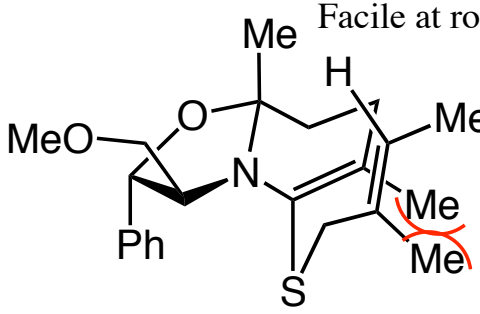
J. Org. Chem. **1988**, *53*, 4626-8.

Thio-Claisen Rearrangement

~Why the thio-Claisen? Because they couldn't make the correct O-allyl compound. Auxiliary provides selectivity as well.



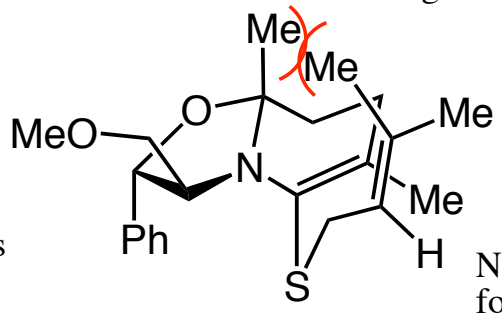
~Transition state diagrams for selectivity vs. reactivity justification:



Facile at room temperature.

Me/Me interaction lowers selectivity to 3:1 dr.

Need high temperature to overcome interaction.

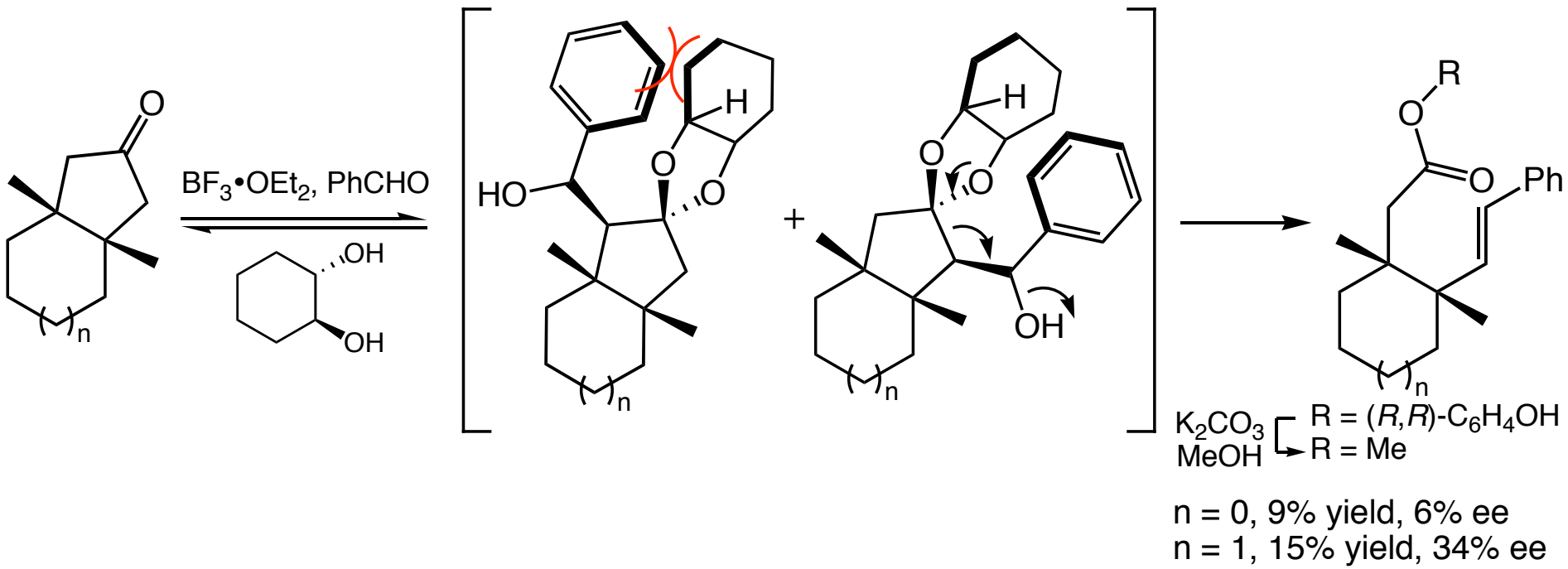


No Me/Me interaction, allowing for diastereoselectivity observed.

J. Am. Chem. Soc. **1994**, *116*, 2633-4.

"Desymmetrization" of Cyclic Ketones

~Ring cleavage reaction involving an intermolecular aldol and subsequent ketalization and fragmentation.



*Rxn without QCs gives 34% yield and 26% ee for the 5-membered ring case and 30% yield and 49% ee for the 6-membered ring case.

*The ees are probably better for the non-QC case because there is better facial bias for the Aldol step. It is difficult to determine by models whether the convex face is still more open when it has VQCs on it.

Tetrahedron **2004**, *60*, 2271-81.

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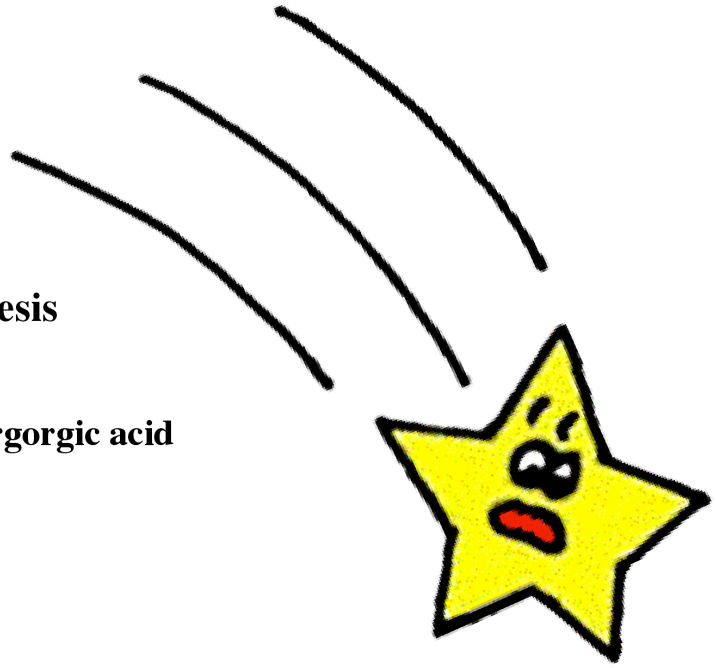

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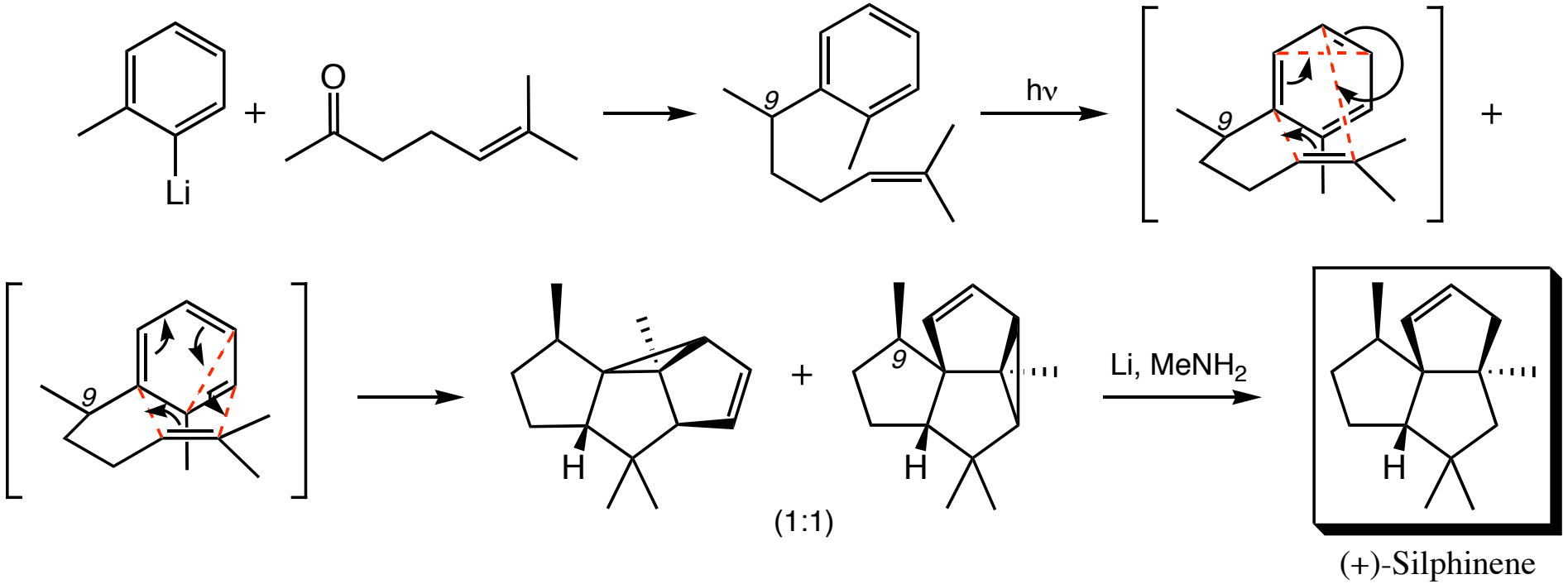
2003 - (–)-idiospermuline

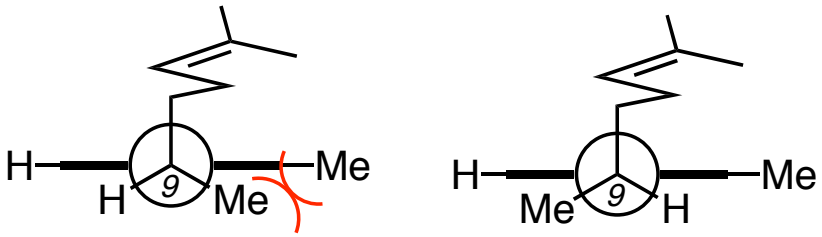
Arene-Alkyne Cycloadditions -- Total Synthesis of (+)-Silphinene

~ *Meta* reactivity pattern dictates resultant framework(s). Although a 1:1 mixture of isomers is observed, the total synthesis is only 3 steps, and multi-gram quantities of the natural product can be prepared in a few days.



(+)-Silphinene

*Mode of reactivity (*meta* vs. *ortho* or *para*) is controlled by the electronics of the arene and olefin.
*Regioselectivity is "controlled" by the donor alkyl groups on the olefin.
**Endo*/*exo* control results from strain (orbitals for *endo* TS do not easily overlap).
*C(9) stereocontrol:

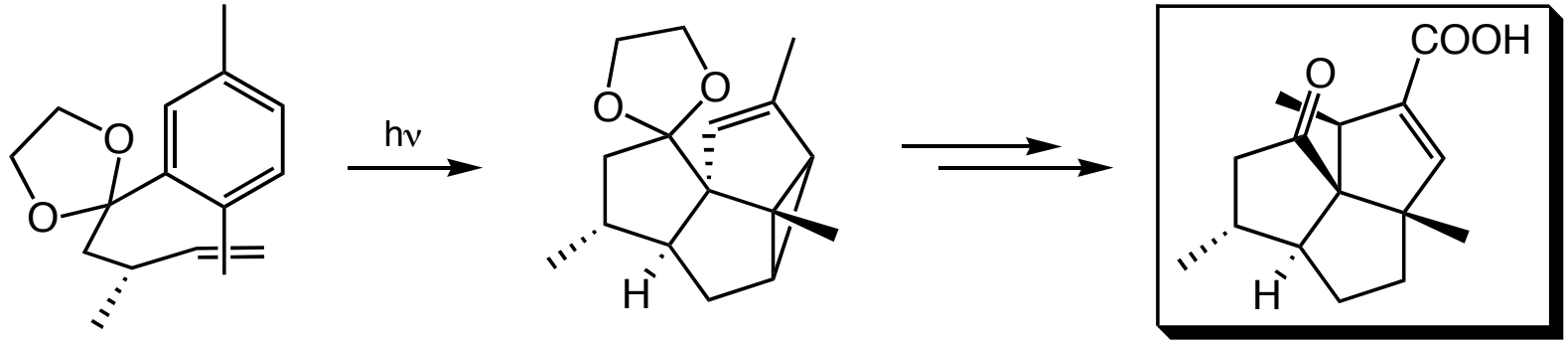


= aromatic ring (side view)

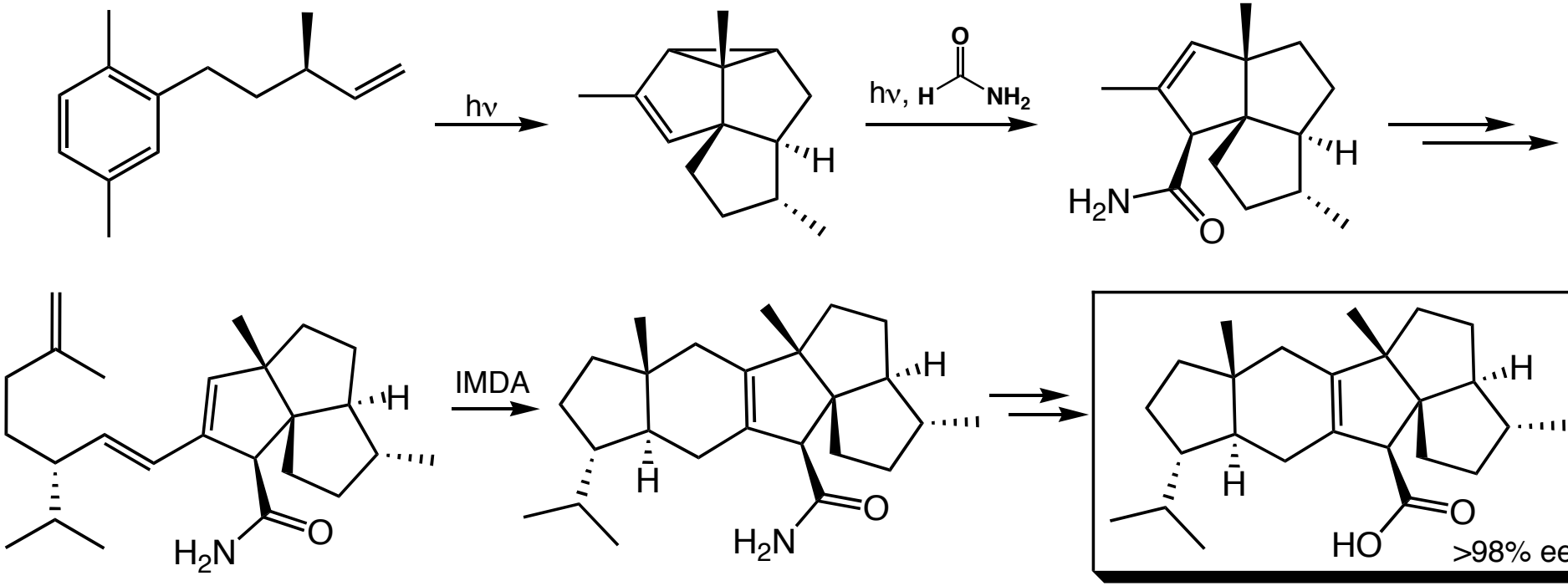
Wender, P.A. *Pure & Appl. Chem.* **1990**, *62*, 1597-1602.

Arene-Alkyne Cycloadd'ns -- (±)-Subergorgic Acid and (–)-Retigeranic Acid

~(±)-Subergorgic Acid Synthesis. Stereocontrol likely due to $A_{1,2}$-strain. Could potentially be made asymmetric with the use of a chiral ketal.

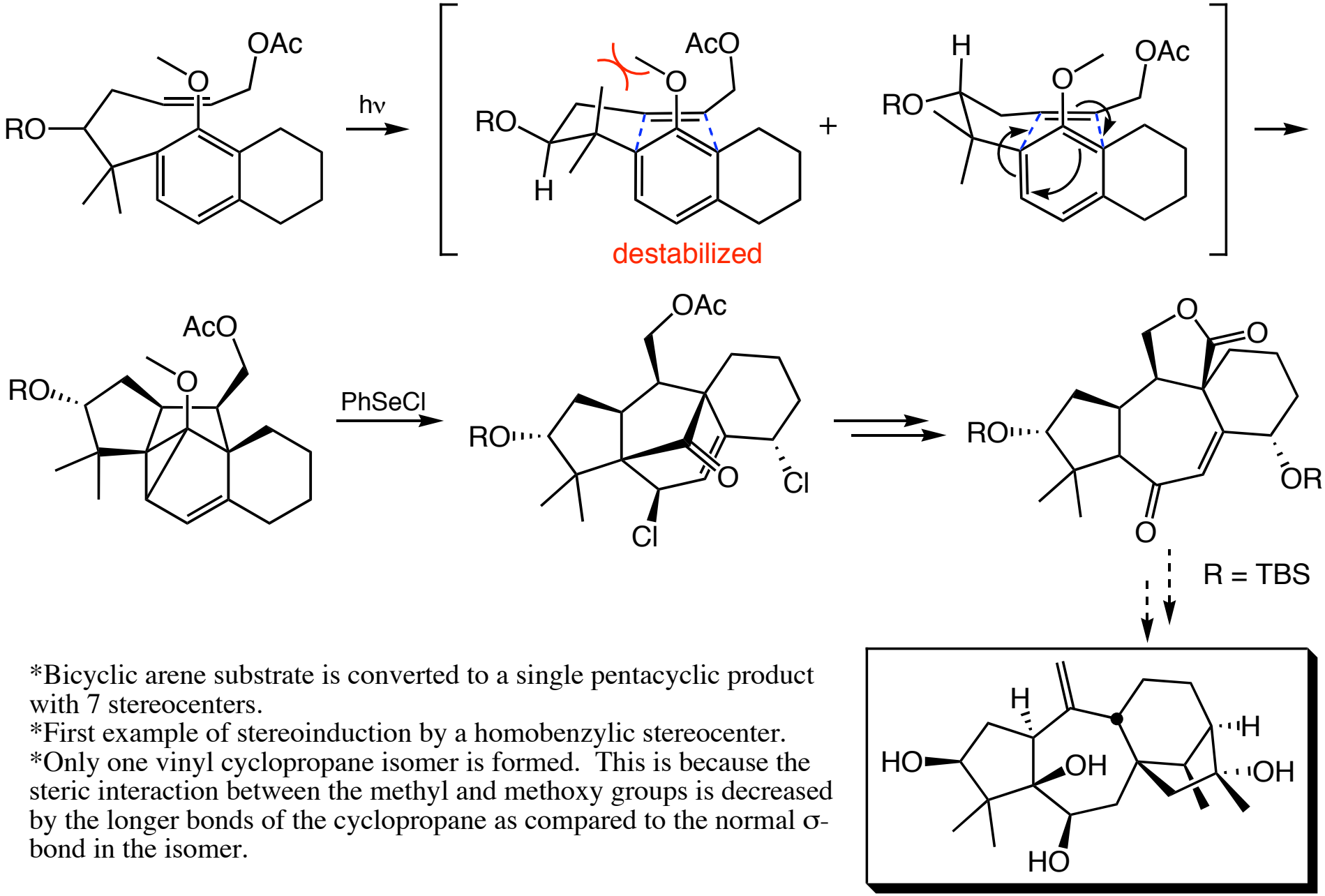


~(–)-Retigeranic Acid Synthesis: *meta*-photocycloaddition then IMDA.



Wender, P.A. *Pure & Appl. Chem.* **1990**, *62*, 1597-1602.

Arene-Alkyne Cycloadd'ns -- Towards the Synthesis of (±)-Grayanotoxin II

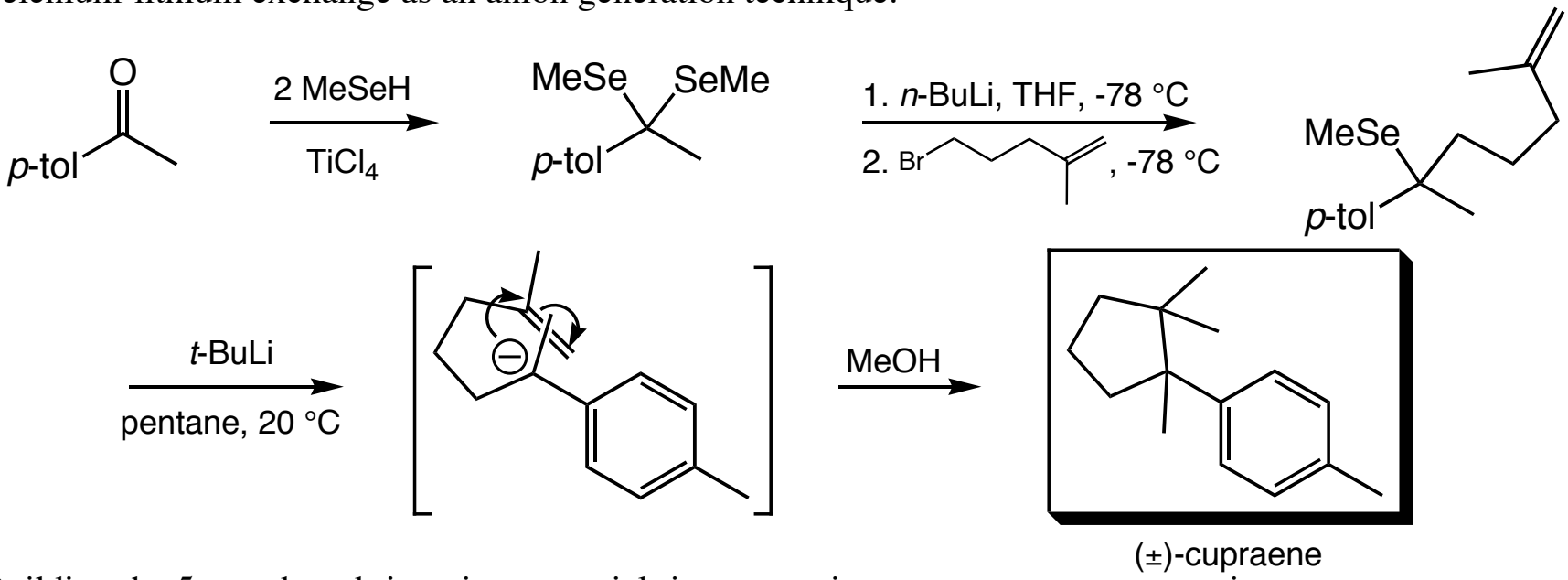


*Bicyclic arene substrate is converted to a single pentacyclic product with 7 stereocenters.
*First example of stereoinduction by a homobenzylic stereocenter.
*Only one vinyl cyclopropane isomer is formed. This is because the steric interaction between the methyl and methoxy groups is decreased by the longer bonds of the cyclopropane as compared to the normal σ-bond in the isomer.

Wender, P.A. *Pure & Appl. Chem.* **1990**, *62*, 1597-1602.

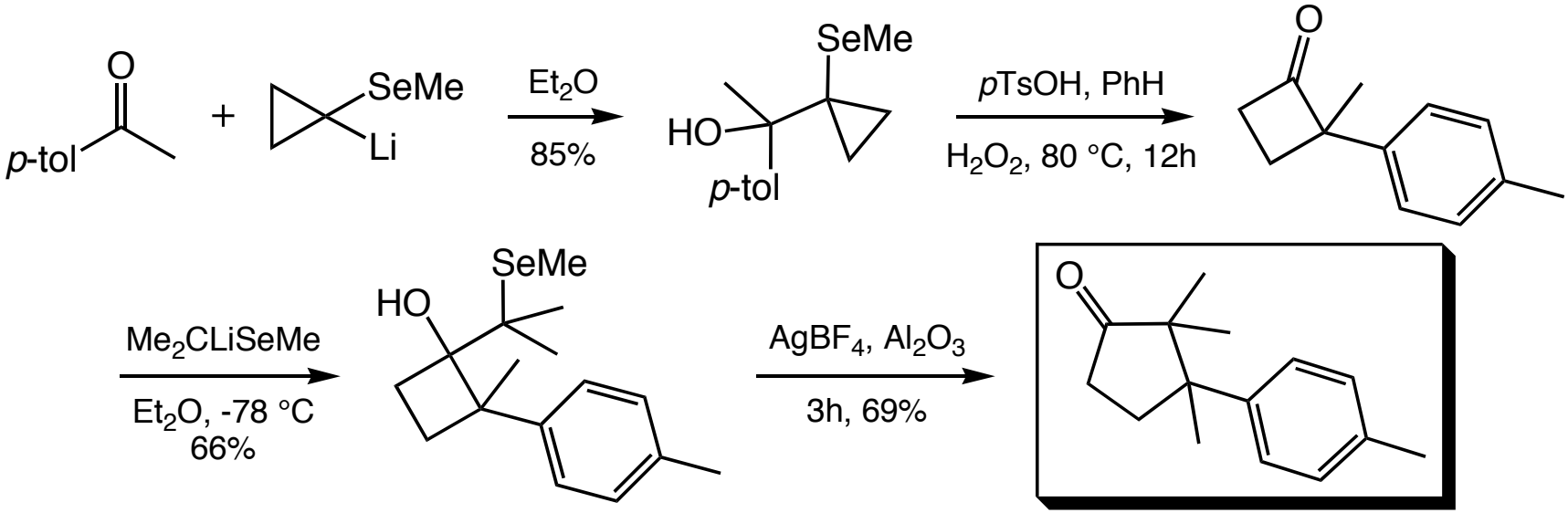
Total Synthesis of (±)-Cupraene and (±)-α-Cupraenone

~Selenium-lithium exchange as an anion generation technique.



(±)-cupraene

~Building the 5-membered ring via sequential ring expansions, one quat. center at a time.

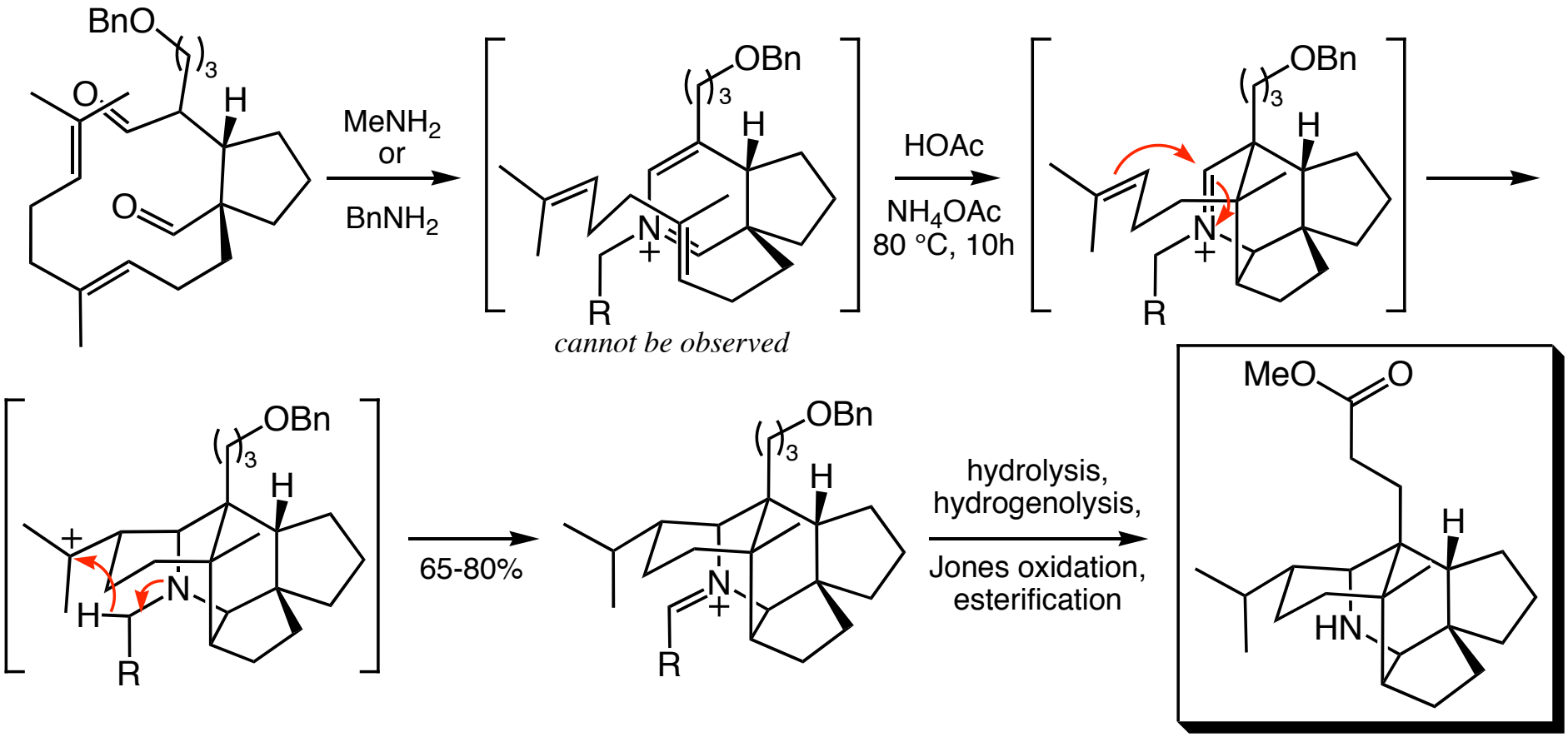


(±)-α-cupraenone

Studies in Natural Products Chemistry **1991**, *8*, 3-14.

Biomimetic Total Synthesis of Methyl Homosecodaphniphyllate

~Polycyclization of a squalene derivative is the key synthetic transformation.

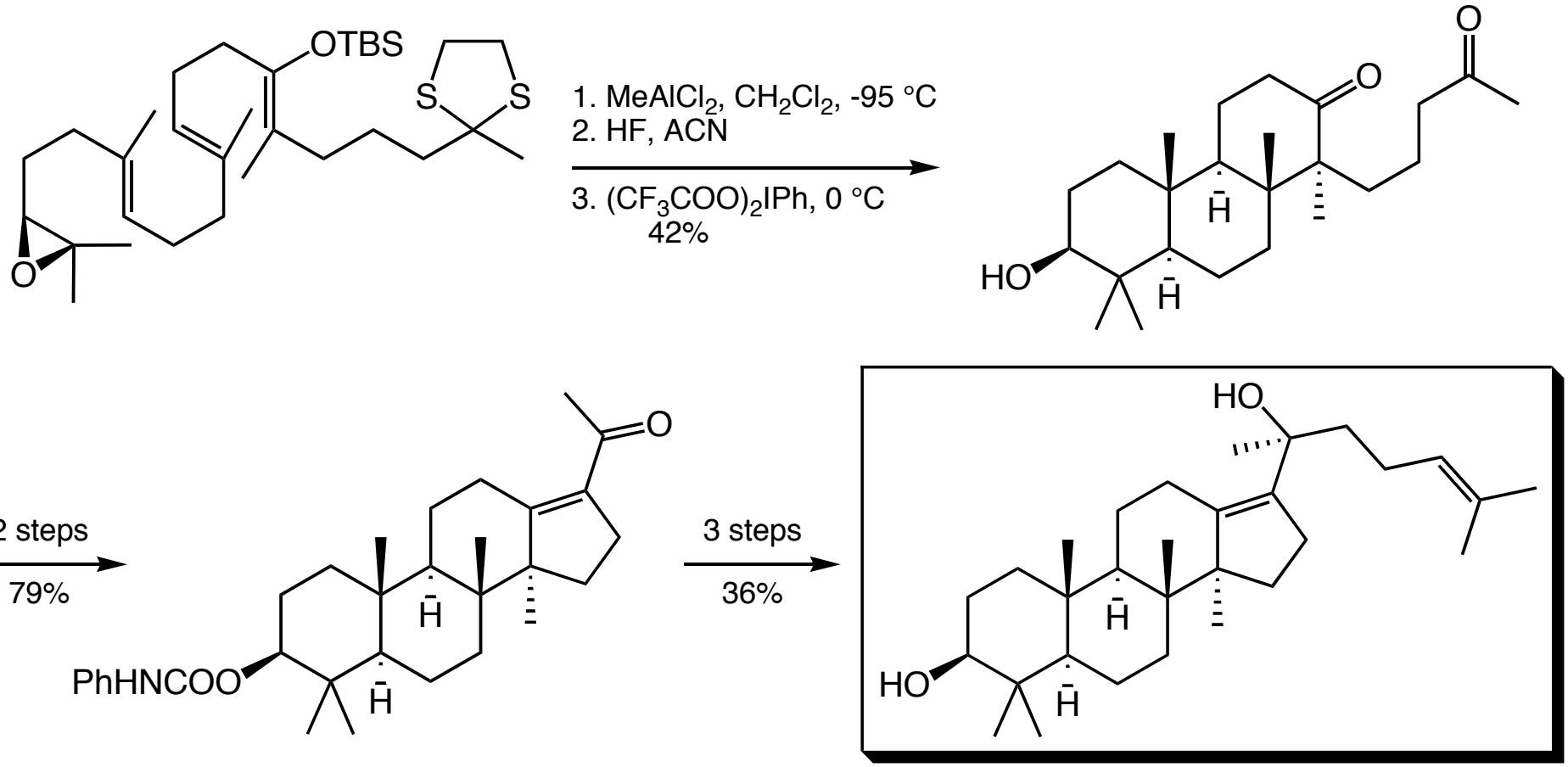


*VQCs set by *in-situ* intramolecular aza-DA, followed by acid-mediated cyclization to complete the core framework.
*Mild conditions lend credence to the biomimetic nature of the synthesis.

Overman, L.E. *Proc. Nat. Acad. Sci.* **2004**, *101*, 11943-8.
Heathcock, C.H. *J. Org. Chem.* **1992**, *57*, 2544-53.
For a similar strategy in secodaphniphylline, see: Heathcock, C.H. *J. Org. Chem.* **1990**, *55*, 5433-4.

Enantioselective Biomimetic Synthesis of Dammarenediol II

~Key step: cationic tricyclization of a triene epoxide

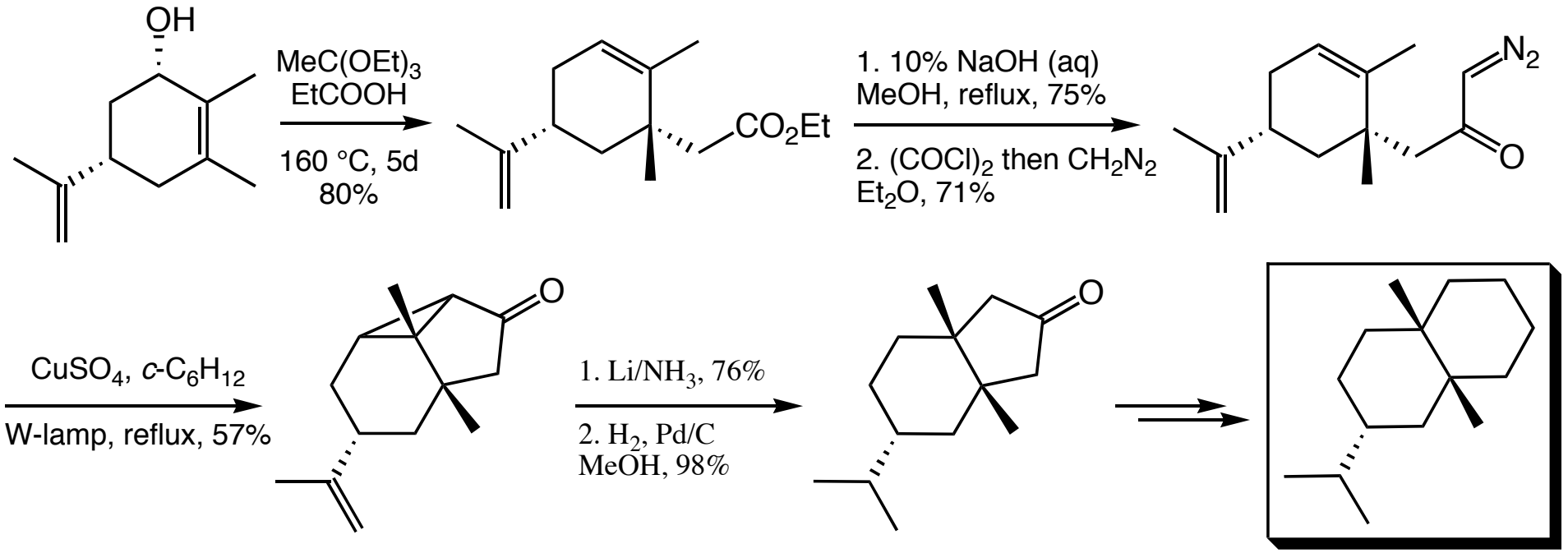


*Epoxide stereochemistry dictates the correct formation of the next 5 stereocenters, including the VQCs.
*Aldol cyclization forms the fused 5-membered ring and provides a handle with which to attach the homoprenyl group.

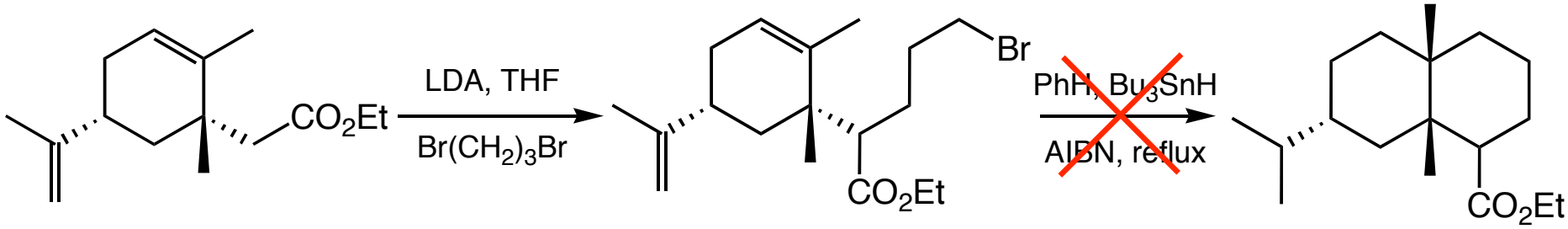
Overman, L.E. *Proc. Nat. Acad. Sci.* **2004**, *101*, 11943-8.
Corey, E.J. *J. Am. Chem. Soc.* **1996**, *118*, 8765-6.

Total Synthesis of (+)-Valerane

~Orthoester Claisen to set first QC, copper-carbene cyclopropanation to set second QC of the pair.



~First attempt to advance orthoester Claisen product was via radical cyclization.

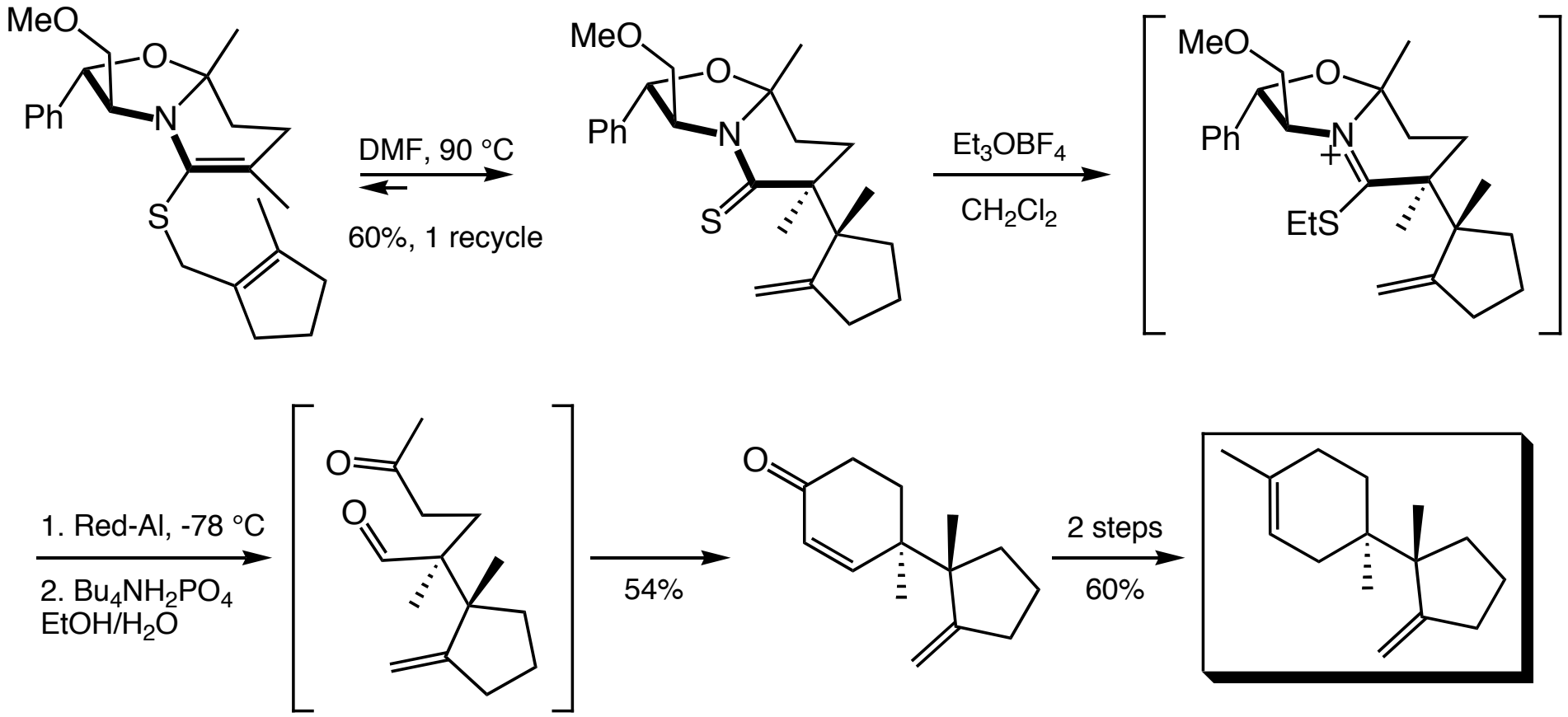


*Only des-bromo starting material was observed.

Srikrishna, A. *Tet. Lett.* **1996**, *37, 2863-4.*

Total Synthesis of (–)-Trichodiene

~Thio-Claisen rearrangement of a chiral bicyclic lactam sets VQCs at the ring junctions.

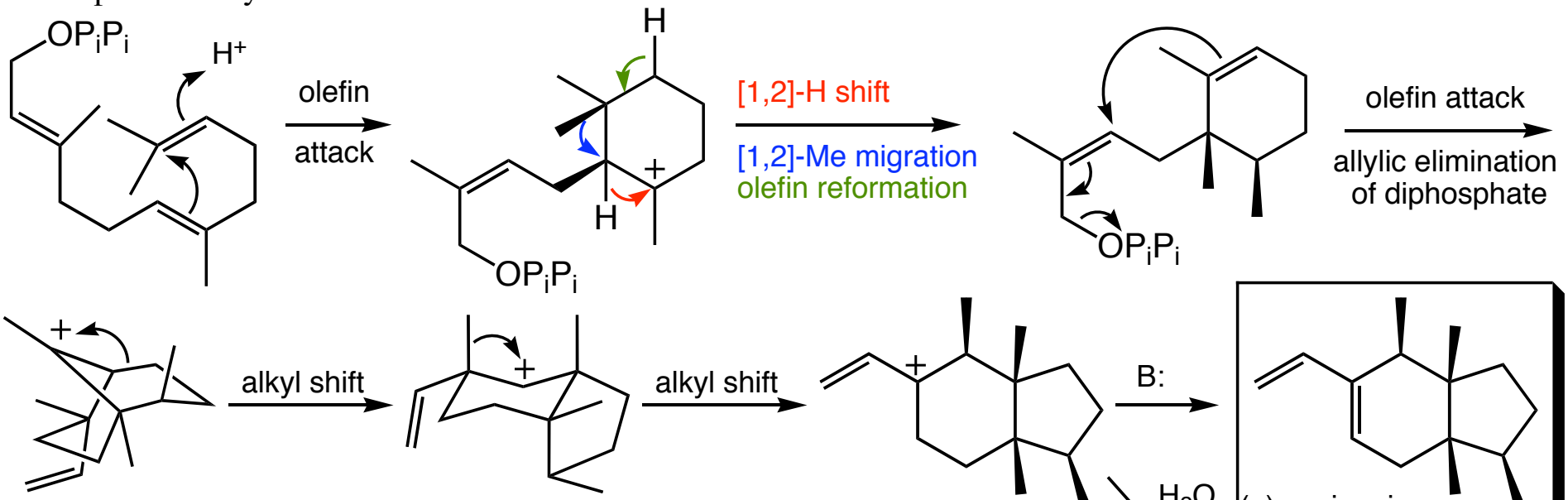


*Thiolactam is produced as a single diastereomer in the Claisen.
*Steric destabilization of the VQCs prevents complete conversion to product, producing an equilibrium mixture of 36:64 or about 1:1.8 (SM:Pdt). Reasonable quantities of material are obtained via recycling.

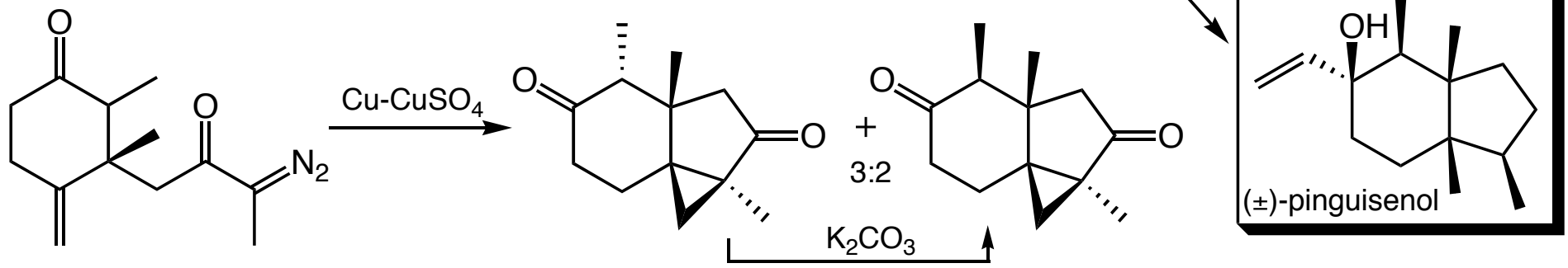
Overman, L.E. *Proc. Nat. Acad. Sci.* **2004**, *101*, 11943-8.
Meyers, A.I. *J. Am. Chem. Soc.* **1998**, *120*, 5453-7.

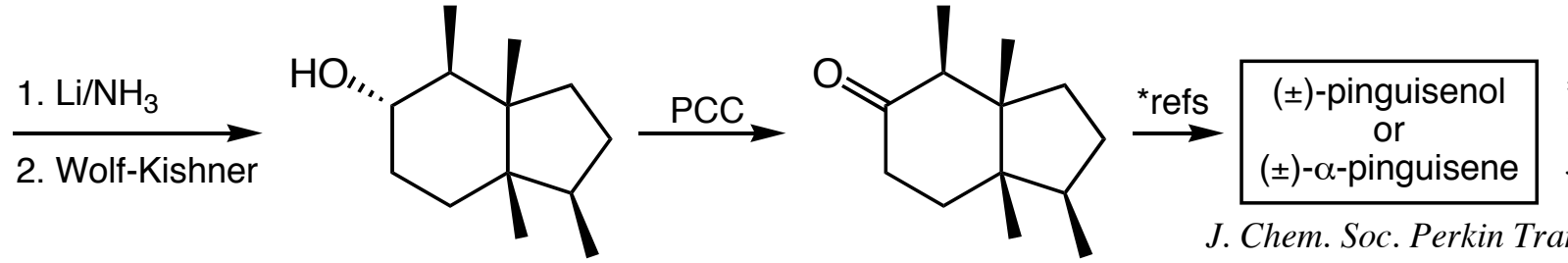
Formal Synthesis of (±)-α-Pinguisene and (±)-Pinguisenol

~Proposed Biosynthesis:



~Synthetic approach; VQCs formed via cyclopropanation and selective reduction.



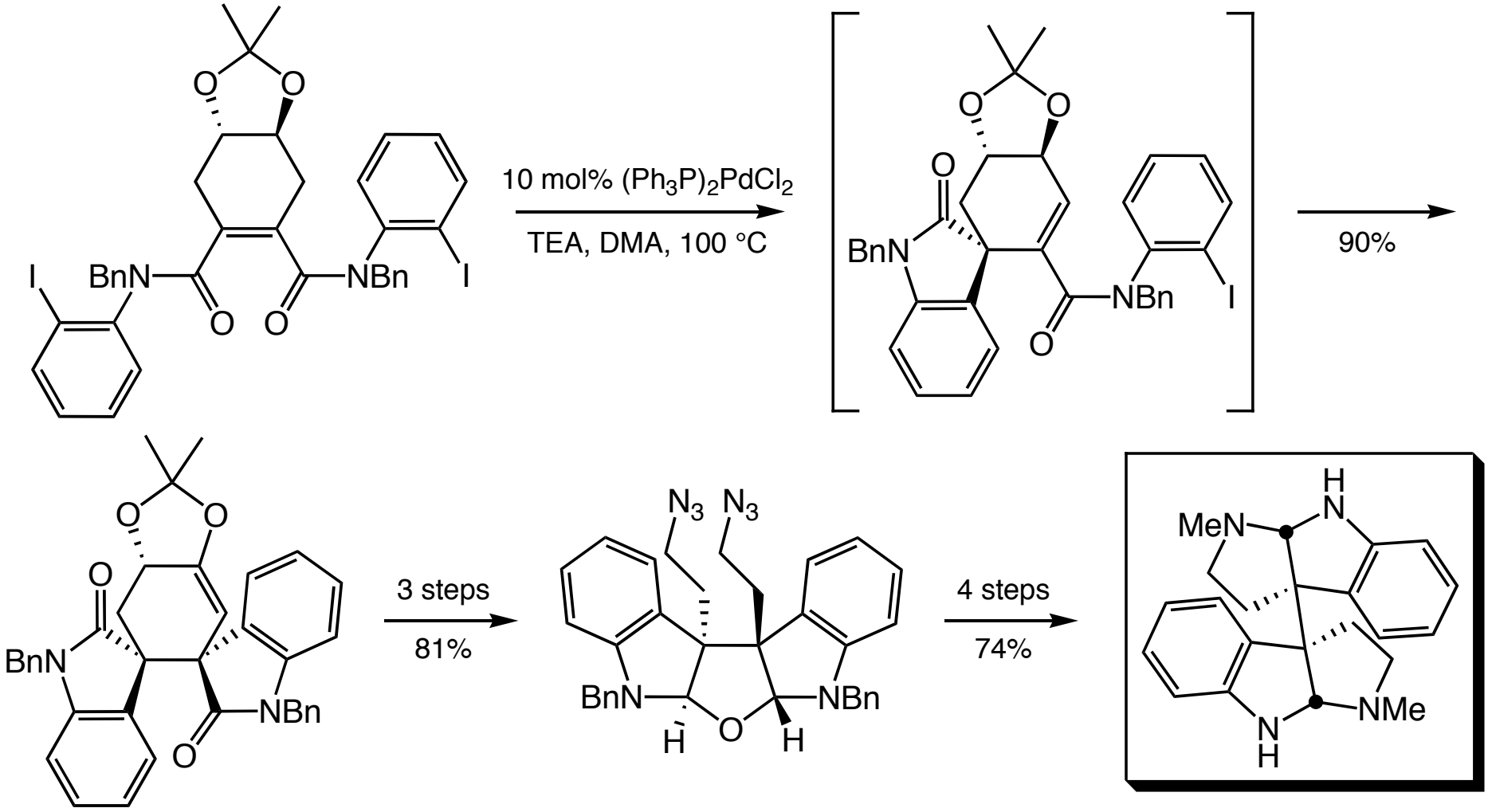


*TL **1995**, *36*, 4051.
*Tetahedron **1996**, *52*, 7475.

J. Chem. Soc. Perkin Trans. 1 **1999**, 1265-71.

Total Synthesis of (−)-Chimonanthine

~Diastereoselective intramolecular Heck cascade builds VQCs and sets their absolute stereochemistry.

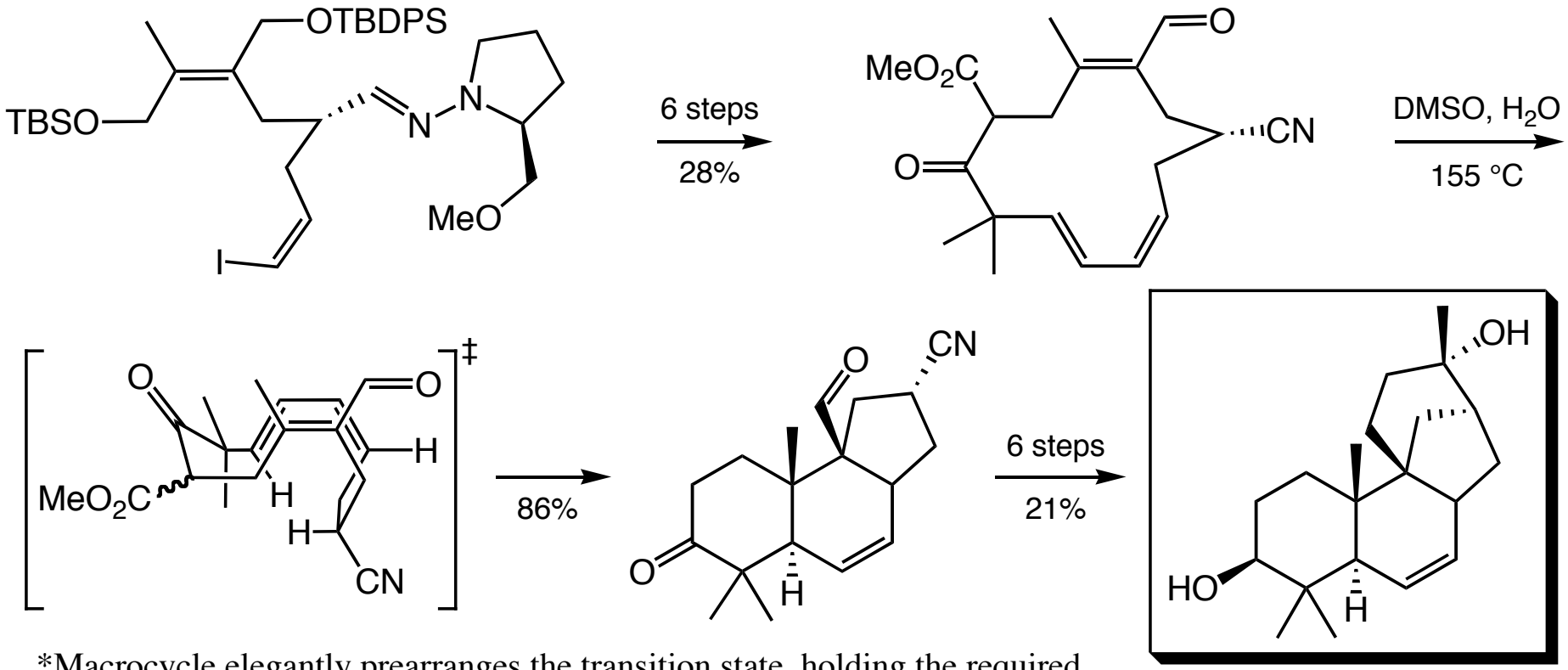


*A single enantiomer of the Heck cyclization cascade is formed, with its stereochemistry controlled by the configuration of the acetonide in the C_2-symmetric cyclization precursor.
*One of few examples of a catalytic reaction forming VQCs.

Overman, L.E. *Proc. Nat. Acad. Sci.* **2004**, *101*, 11943-8.
Overman, L.E. *J. Am. Chem. Soc.* **1999**, *121*, 7702-3.

Enantioselective Synthesis of (+)-Maritimol

~VQCs formed via transannular DA with concomitant decarboxylation.

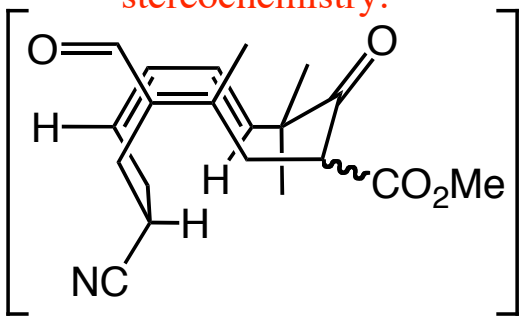


*Macrocycle elegantly prearranges the transition state, holding the required s-cis diene geometry and providing regiocontrol.

*Cyano stereocenter completely controls the formation of the desired product. Two *endo* transition states can be drawn, but in the disfavored TS, the CN protrudes into the macrocycle, causing steric problems.

*The transition state for epimeric cyano compound is pictured to the right, and would provide the enantiomeric product after decarboxylation.

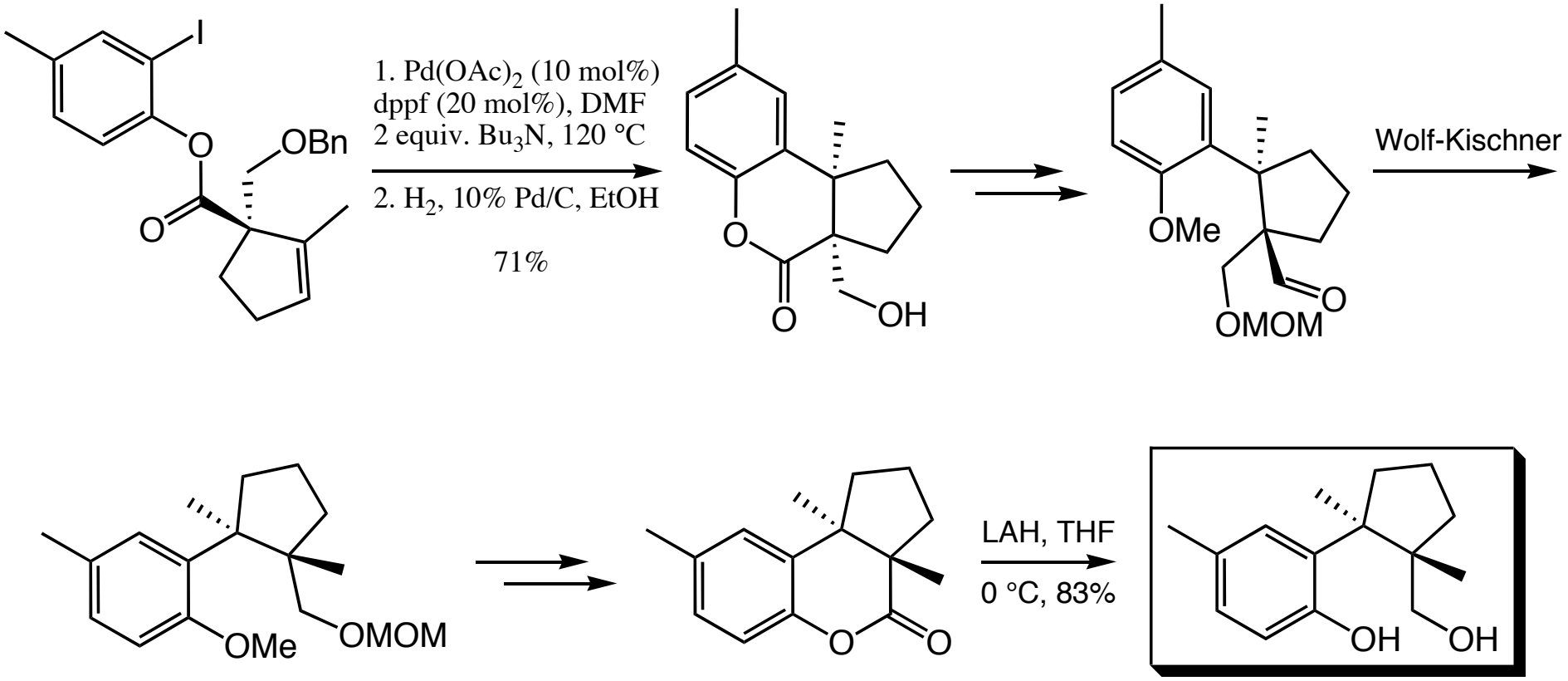
Transition state for opposite CN stereochemistry:



Overman, L.E. *Proc. Nat. Acad. Sci.* **2004**, *101*, 11943-8.
Deslongchamps, P. *J. Am. Chem. Soc.* **2000**, *122*, 4526-7.

Synthesis of 1,15-Dihydroxyherbertene

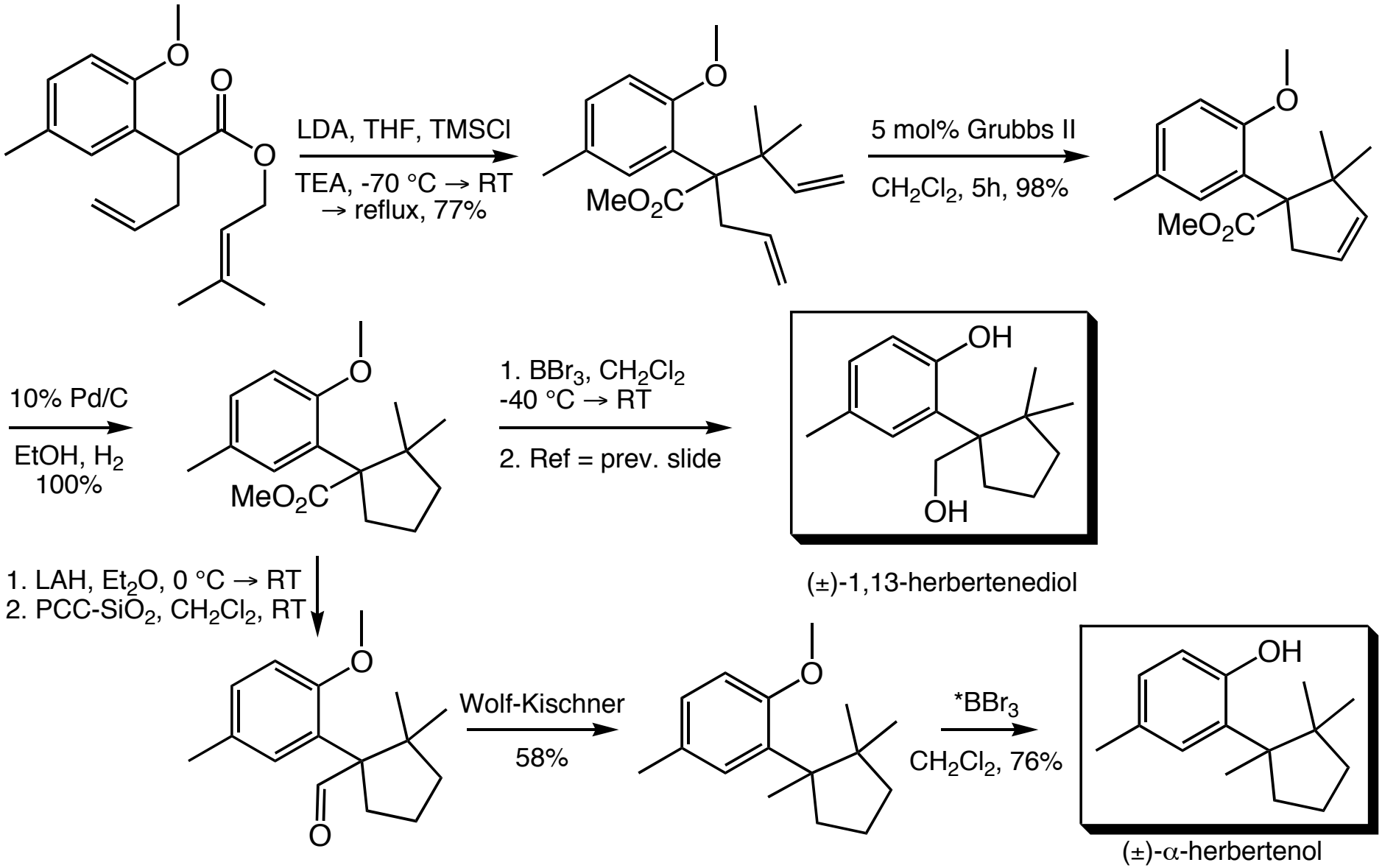
~Enolate alkylation sets first QC, intramolecular Heck adds the second.



Fukuyama, Y. *Tetrahedron* **2001**, *57*, 9299-9307.

Formal Syntheses of (±)-α-Herbertenol and (±)-1,13-Herbertenediol

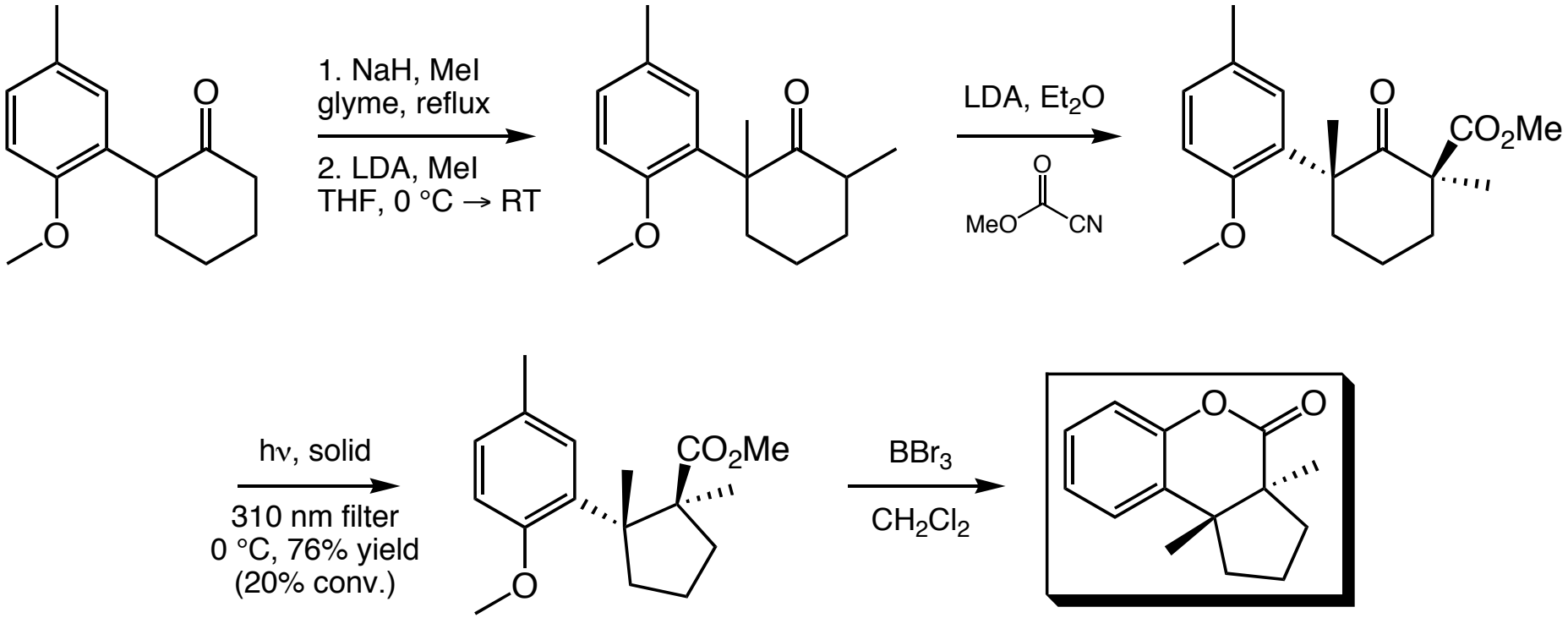
~VQCs formed via Claisen followed by metathesis to generate the 5-membered ring.



Srikrishna, A. *Tet. Lett.* **2003**, *44*, 1027-30. **Synlett* **2005**, *7*, 1173-5.

Synthesis of (±)-Herbertenolide

~VQCs formed via decarbonylation with retention of relative stereochemistry.



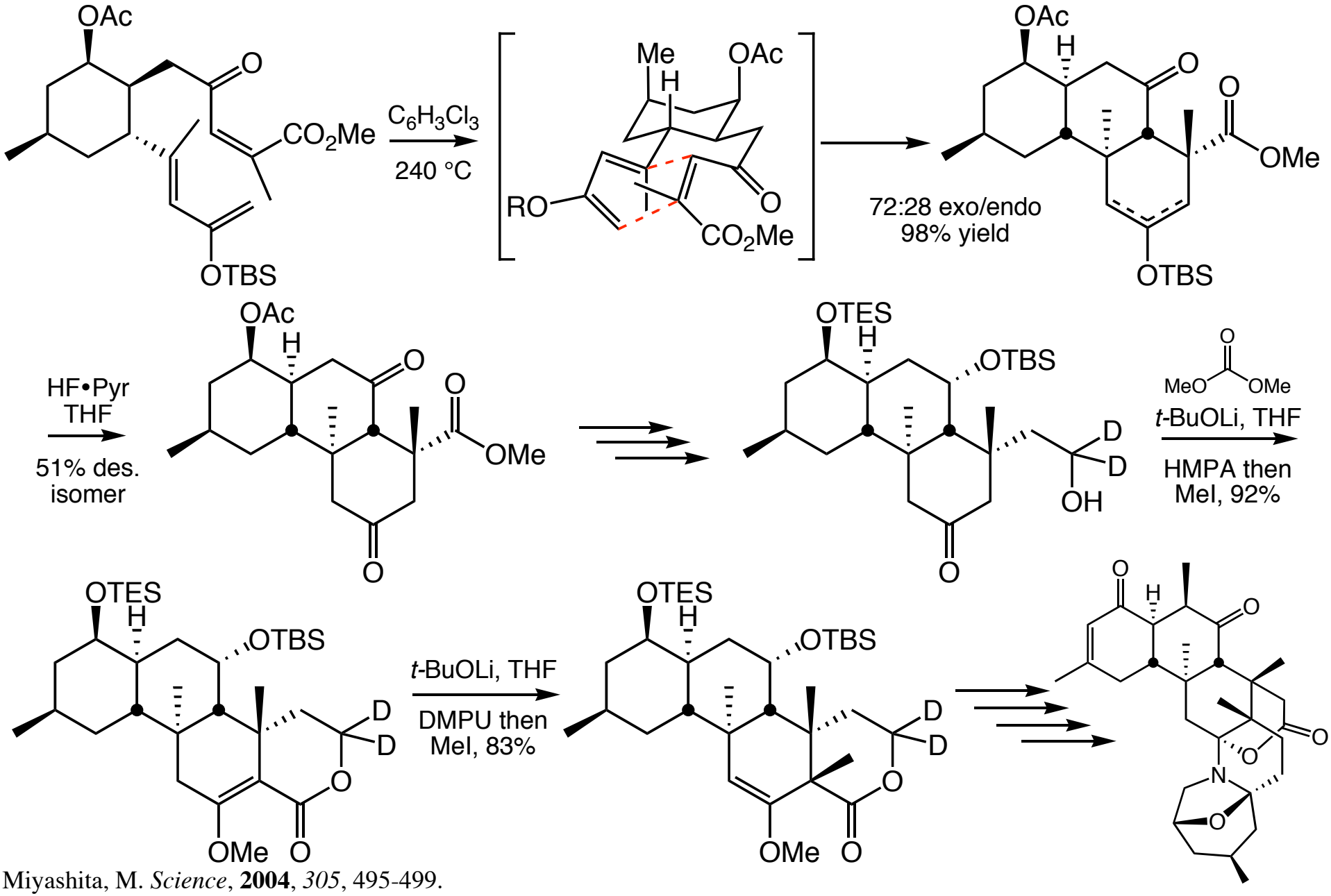
*Low conversion attributed to product melting after formation & causing soln phase side-product formation.

*High conversions should be attainable by the use of a different ester.

Garcia-Garibay, M.A. *Org. Lett.* **2004**, *6*, 645-7.

Total Synthesis of Norzoanthamine

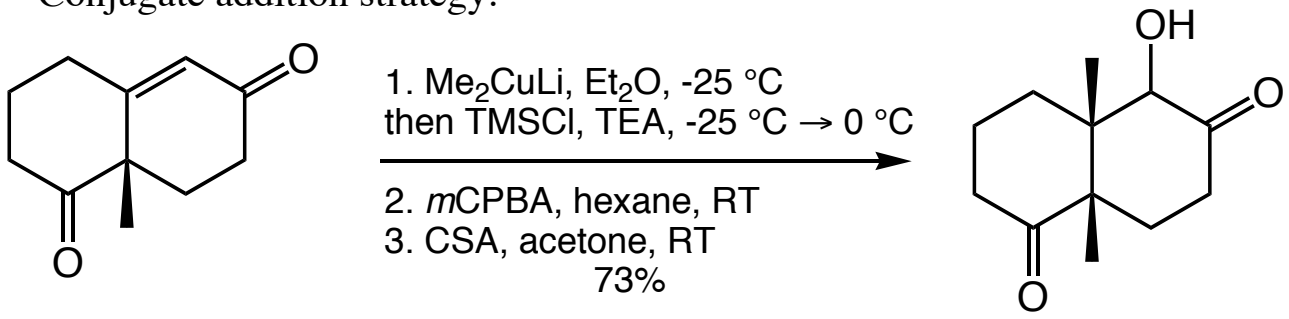
~First QC formed via IMDA, second one via enol ether methylation.



Miyashita, M. *Science*, **2004**, *305*, 495-499.

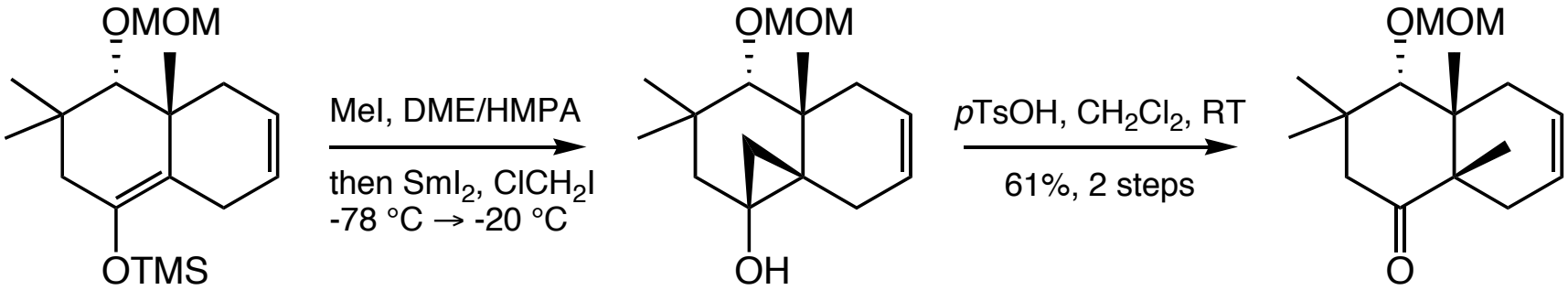
Norzoanthamine, Zoanthamine and Zoanthenol Attempts

~Conjugate addition strategy:



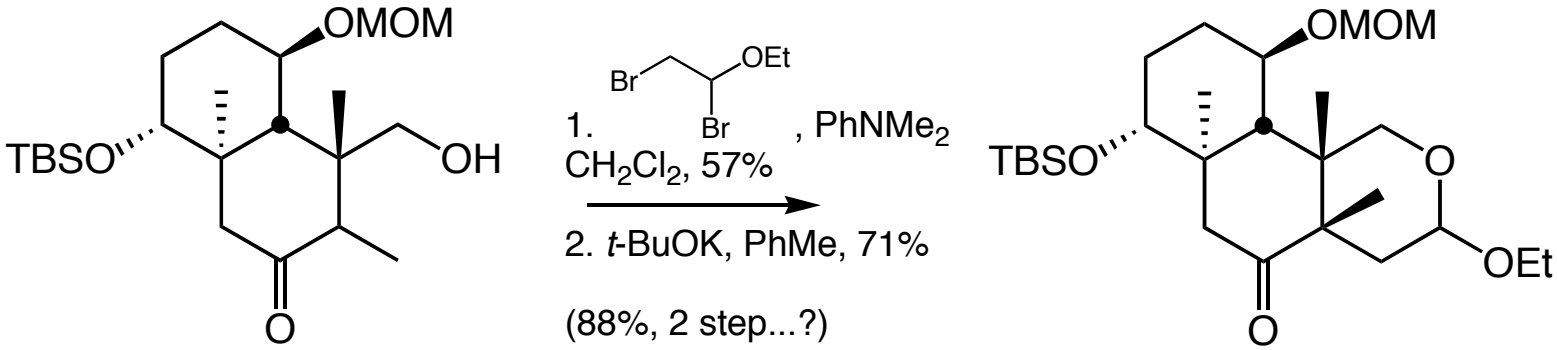
Kobayashi, S. *Tet. Lett.* **1998**, *39*, 6237-40.

~Simmons-Smith cyclopropanation:



Hirama, M. *Chem. Lett.* **1999**, 141-2.

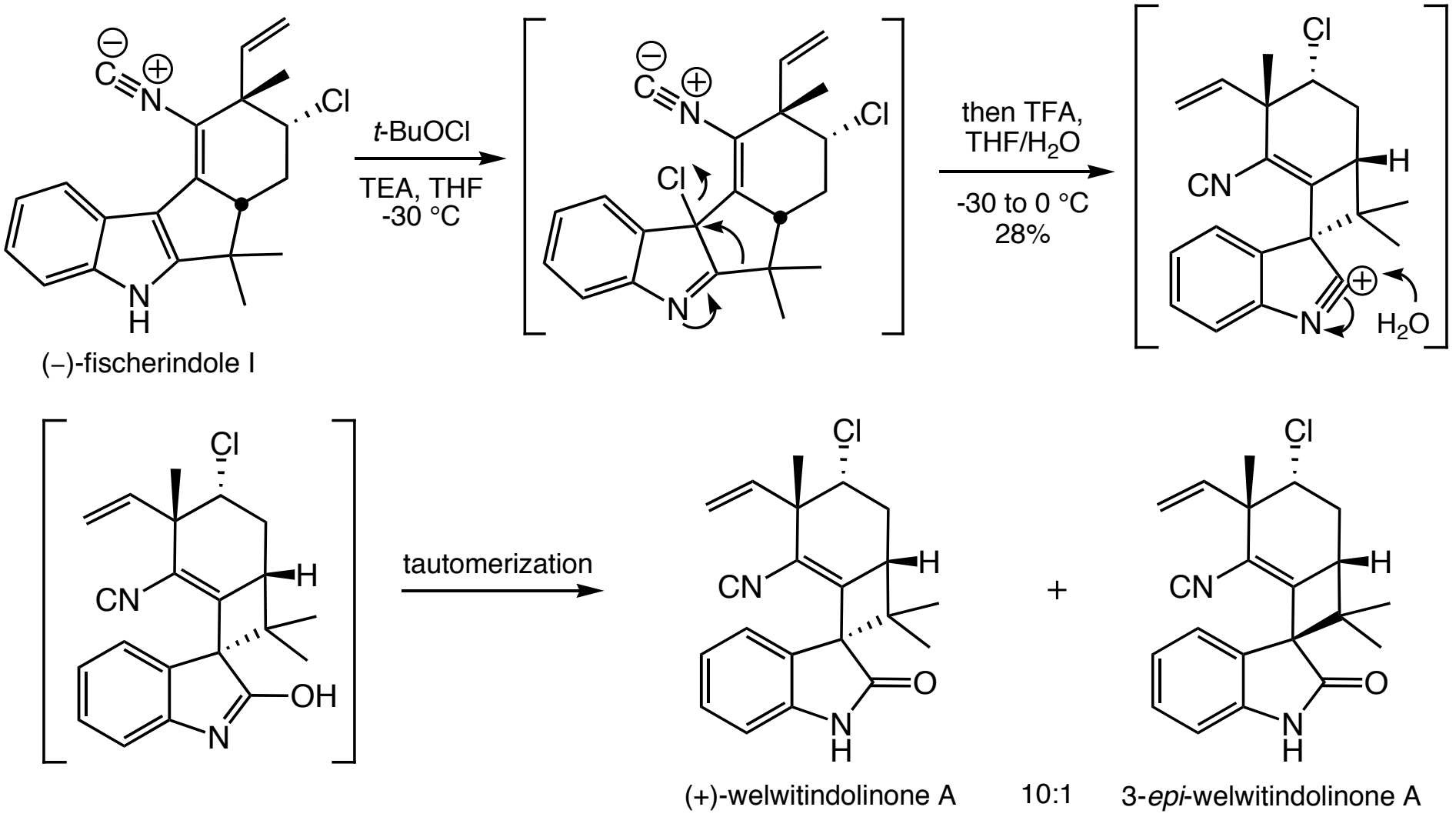
~Intramolecular alkylation:



Theodorakis, E. A. *Tet. Lett.* **2005**, *46*, 5281-5284.

Total Synthesis of (+)-Welwitindolinone A

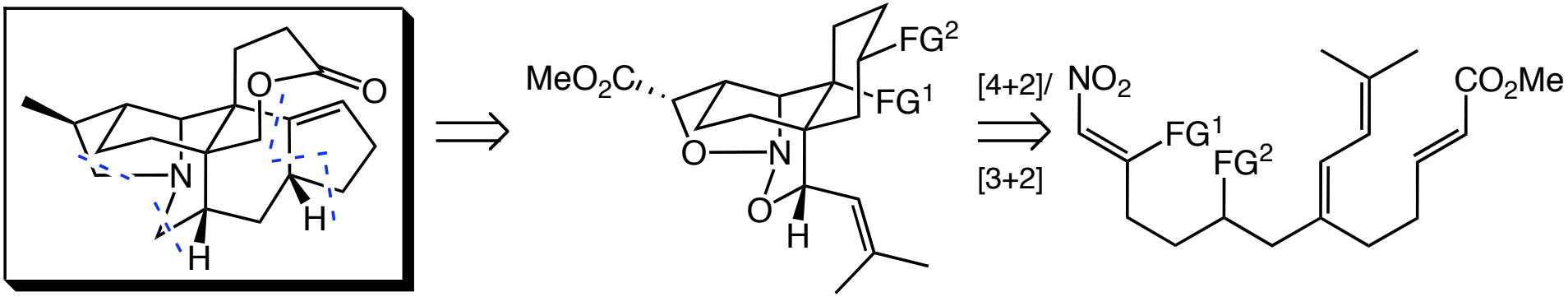
~Second QC formed via "exceedingly facile oxidative ring contraction."



Baran, P.S. *J. Am. Chem. Soc*. **2005**, *127*, 15394-6.

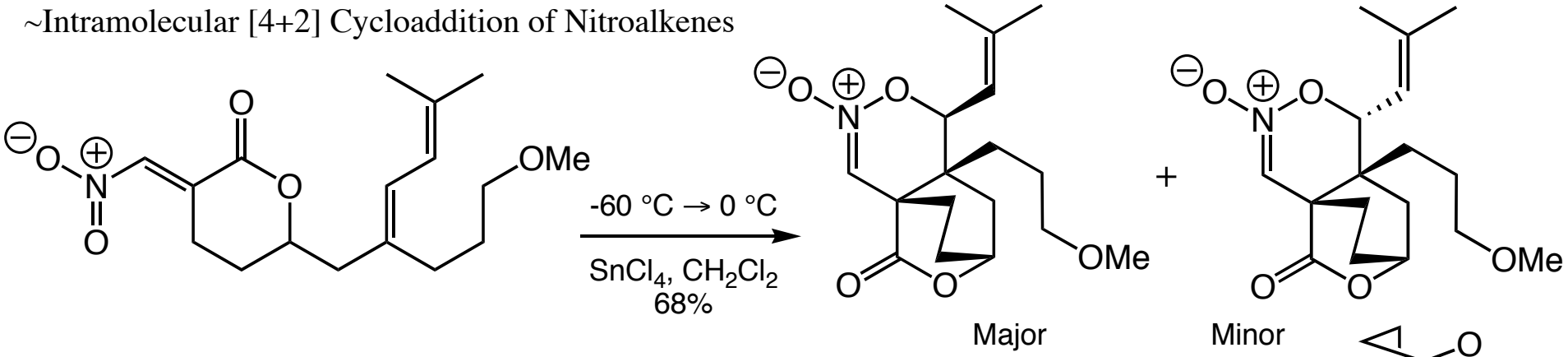
Towards the Total Synthesis of Daphnilactone B

~Retrosynthetic analysis

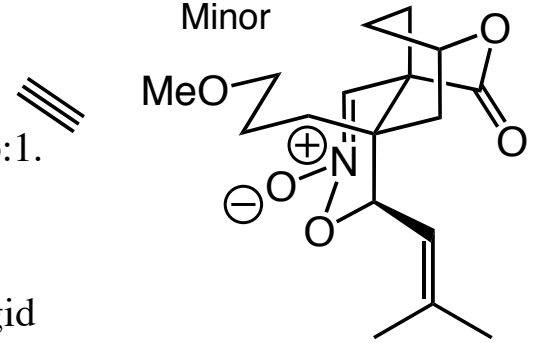


*FG^1 and FG^2 should maintain reactivity of nitroalkene as well as synthetic availability.
(FG^1=EWG, FG^2 contains O)

~Intramolecular [4+2] Cycloaddition of Nitroalkenes



Major Minor



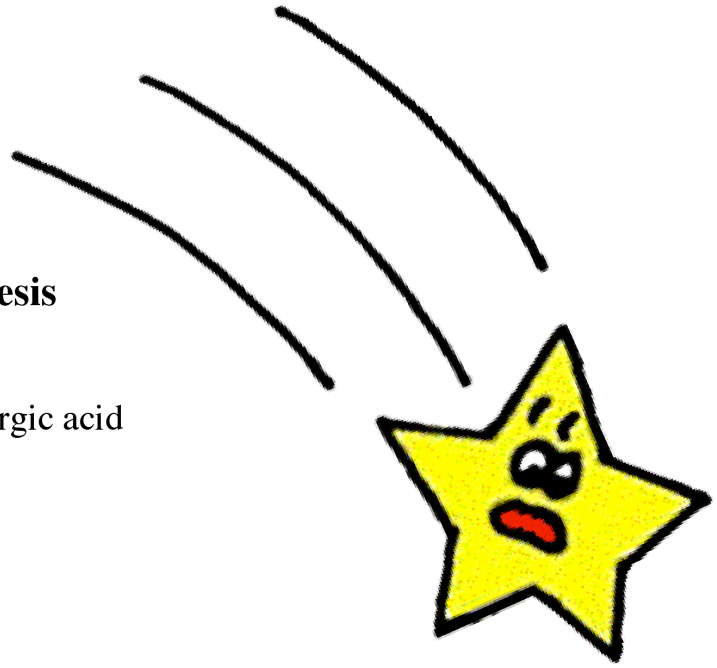
*Model [4+2] reaction occurs in up to 68% yield with dr varying from 1:1 to 6:1. Both were characterized by X-ray.
*Dipolarophile for [3+2] is not included in the model study for simplicity.
*At lower than -60 °C, side products were formed.
*Stereoselectivity at the VQCs is excellent. The lactone tether, providing a rigid backbone, is attributed with this accomplishment.

Denmark, S.E. *Org. Lett.* **2005**, *127*, 5617-20.

Outline

I. Vicinal Quaternary Centers in Methodology

1983 - O-allyl Claisen variant
1984 - intramolecular enediyne cyclization
1986 - Michael addition (2 EWGs)
1988 - hexamethylglutaric acid
1994 - thio-Claisen rearrangement
2004 - "desymmetrization" of cyclic ketones



II. Vicinal Quaternary Centers in Natural Products Synthesis

A. Intramolecular Approaches

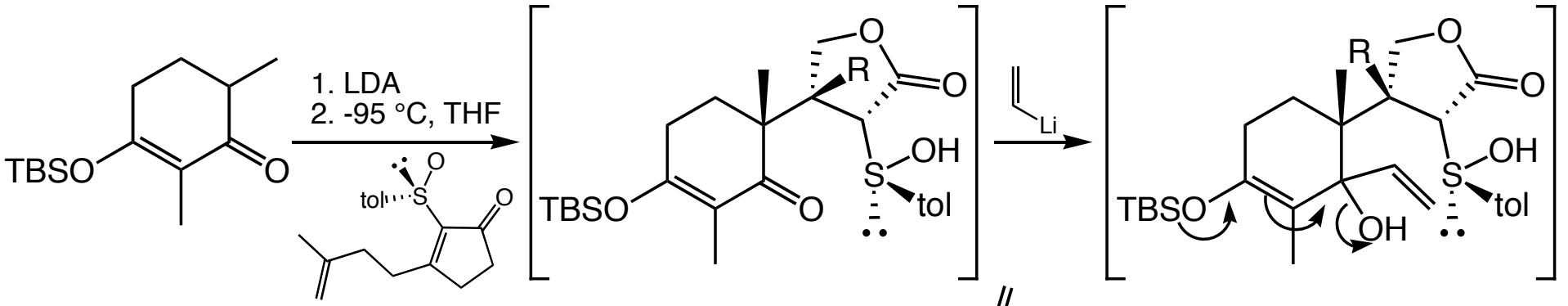
1990 - arene-alkene cycloadditions: (+)-silphinene, (±) subergorgic acid
(–)-retigeranic acid, (±)-grayanotoxin II
1990 - methyl secodaphniphyllate
1991 - α-cupraenone, cupraene
1996 - dammarenediol II, (+)-valerane
1998 - (–)-trichodiene
1999 - (±)-α-pinguisene, (±)-pinguisenol, (–)-chimonanthine
2000 - (+) maritimol
2001-4 - (±)-1,13- & 1,15-dihydroxyherbertene, (±)-herbertenolide, (±)-herbertenol
2004 - norzoanthamine & attempts
2005 - welwitinolinone A, daphnilactone B

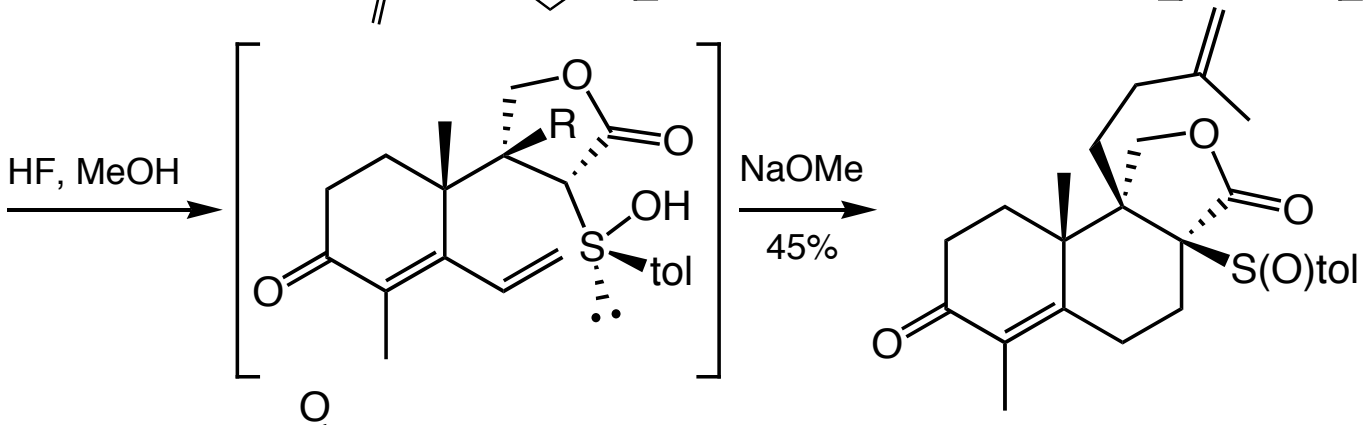
B. Bimolecular Approaches

1987 - aphidicolone
1995 - penitrem D
2002 - merrilactone A
2003 - (–)-idiospermuline

Synthesis of an Aphidicolone Derivative

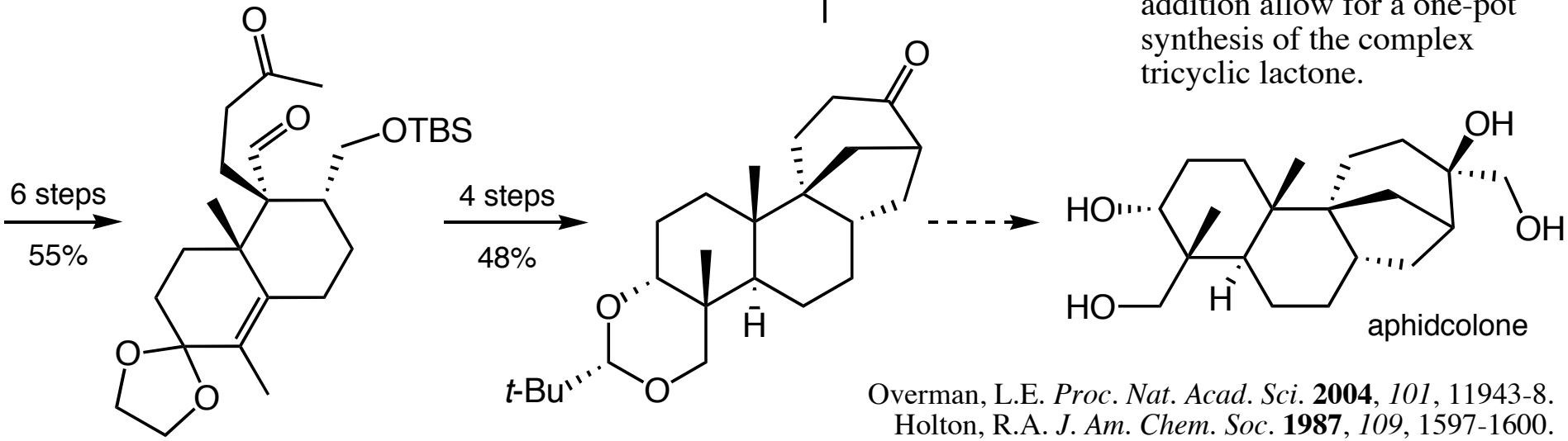
~Diastereoselective intermolecular Michael addition forms VQCs





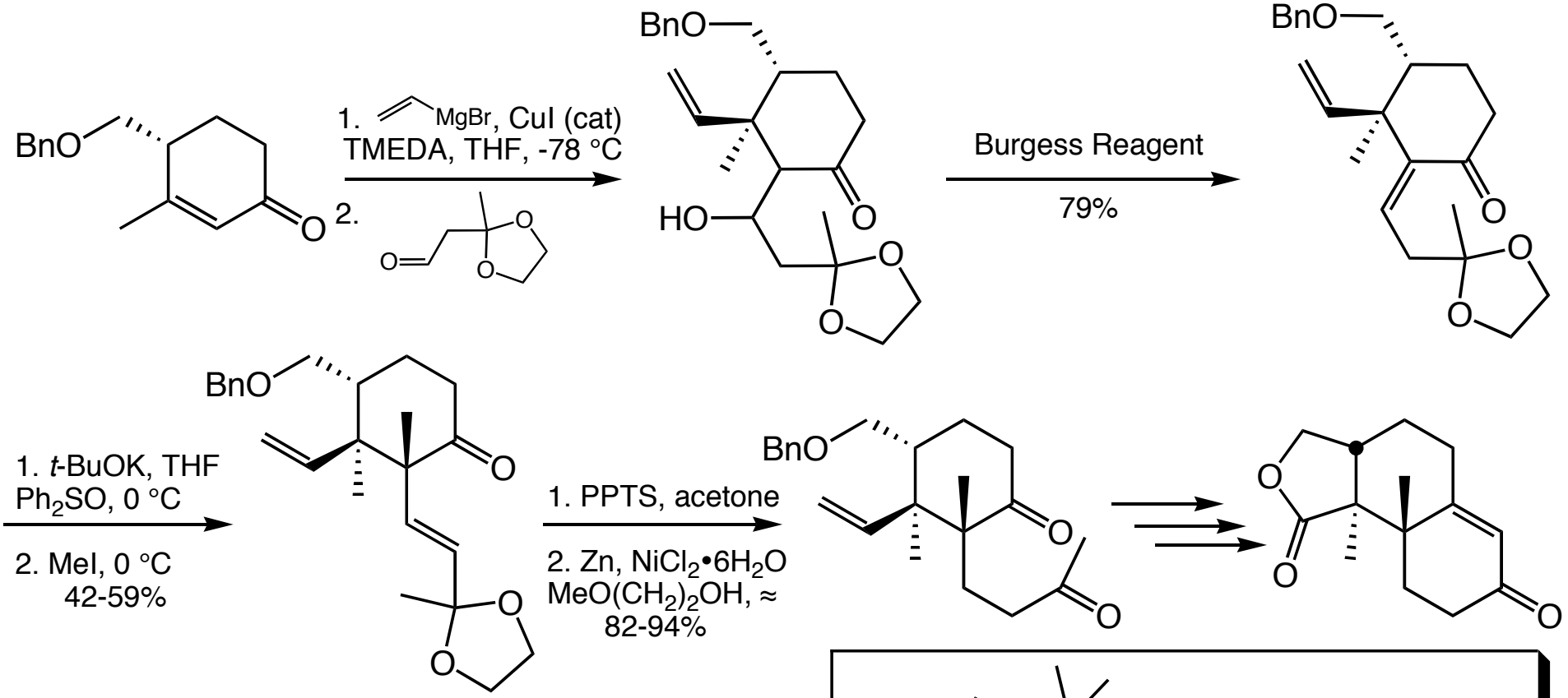
*Intermolecular Michael is organized by chelation between sulfinyl and enolate oxygen atoms. (7.4 : 1 dr)

*Subsequent *in situ* vinyl lithium addition, dehydration, and extended conjugate addition allow for a one-pot synthesis of the complex tricyclic lactone.



Overman, L.E. *Proc. Nat. Acad. Sci.* **2004**, *101*, 11943-8.
Holton, R.A. *J. Am. Chem. Soc.* **1987**, *109*, 1597-1600.

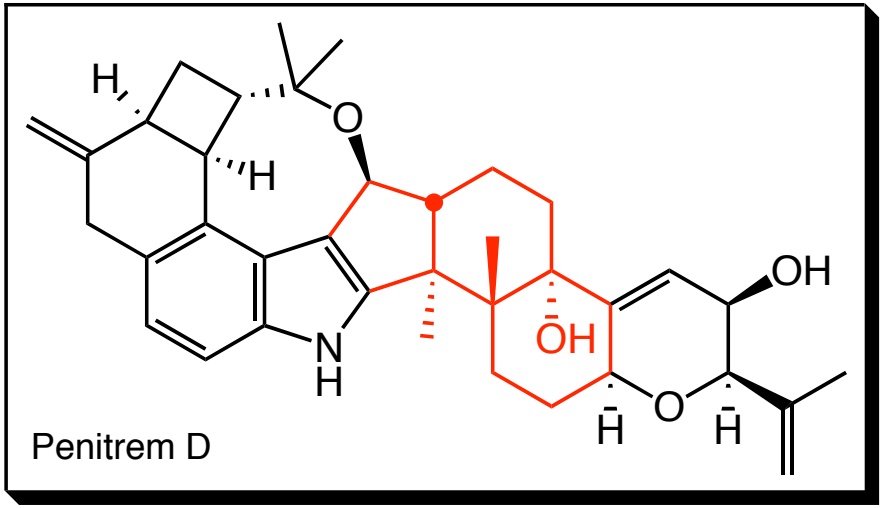
Synthesis of FGH-Ring Lactone Precursor towards Penitrem D



~Copper-catalyzed Grignard addition sets first QC, extended enolate formation with MeI trapping gives second one.

*Alcohol elimination gives a single olefin isomer, confirmed by NOE.

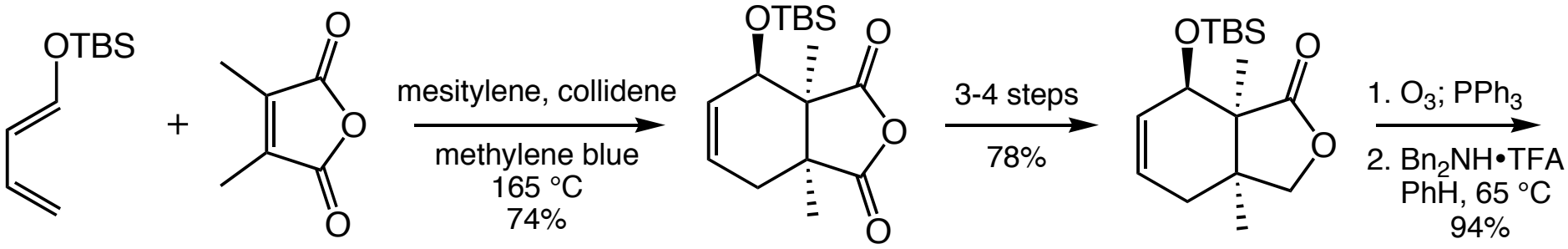
*Alkylation of the extended enolate occurs from the top face because in order for the vinyl and CH_2OBn groups to be pseudo equatorial, the methyl group is psuedo-axial and blocks the bottom face approach.

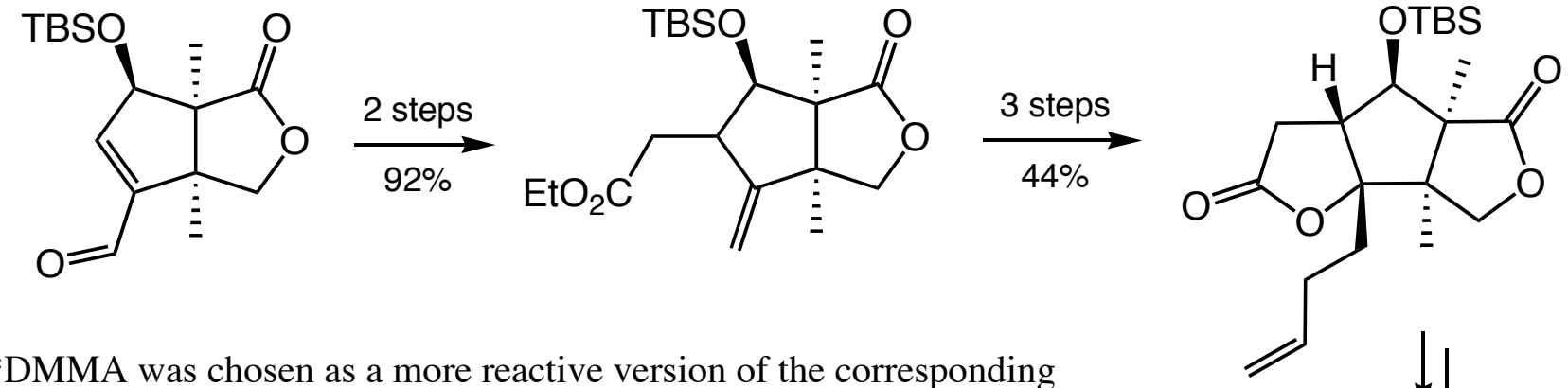


Smith, A.B. III *J. Org. Chem.* **1995**, *60*, 7837-48.

Total Synthesis of (±)-Merrilactone A

~Use of *endo* DA to install the VQCs at an early stage...like the first step.

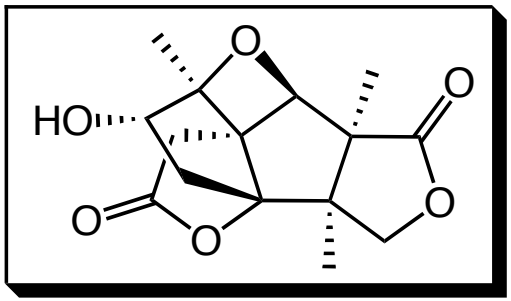




*DMMA was chosen as a more reactive version of the corresponding dimethyl butenolide dienophile. However, it is reactive only with the most reactive dienes, hence the conditions.

*Overall, the synthesis is completed in 20 steps and 10.7% yield

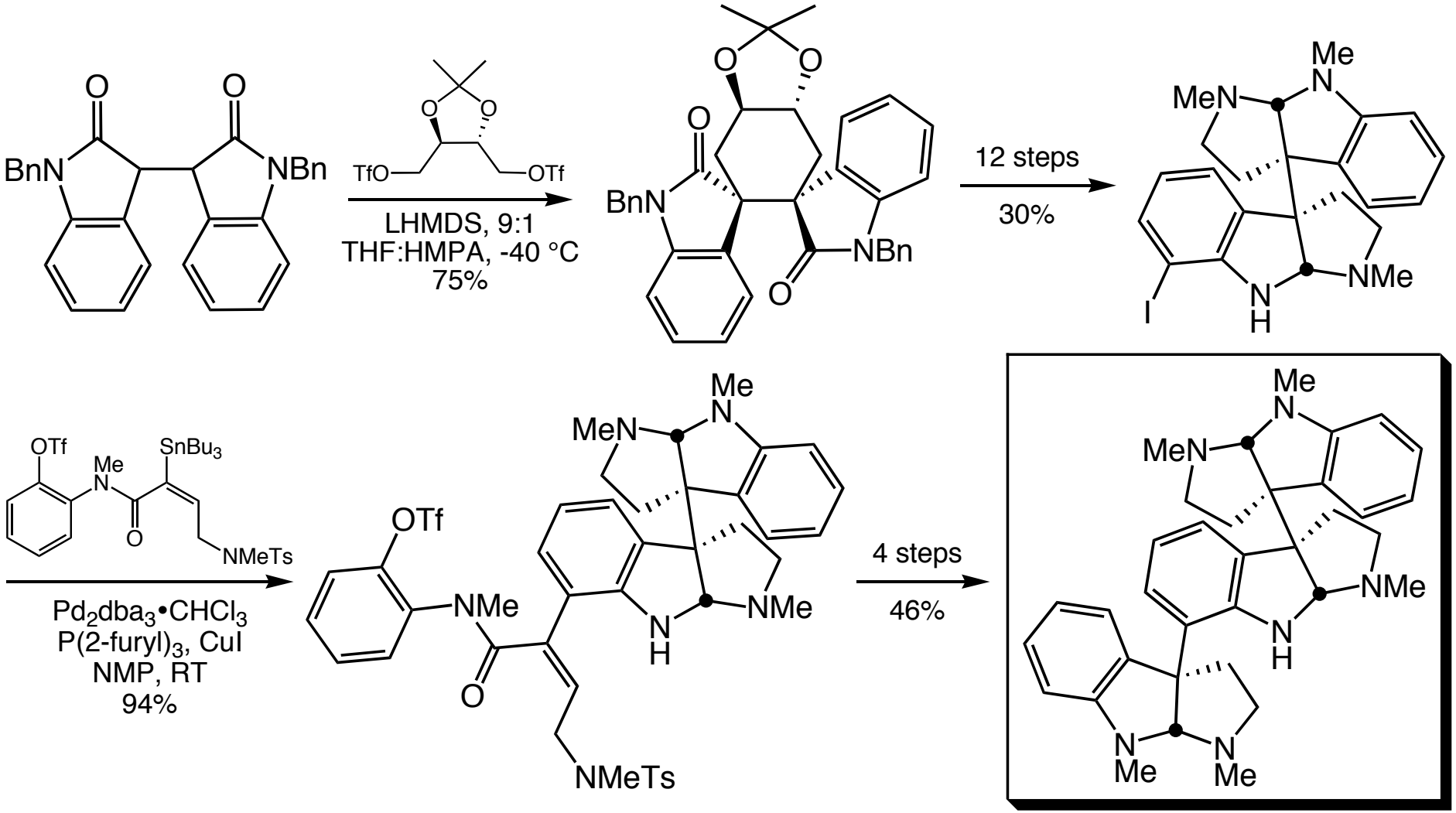
"The use of dimethylmaleic anhydride as a dienophile leading to the incorporation of two angular methyl groups has broad potential implications which warrant follow-up." ~Prof. Sam Danishefsky



Danishefsky, S.J. *J. Am. Chem. Soc.* **2002**, *124*, 2080-1.

Total Synthesis of (–)-Idiospermuline

~Dienolate dialkylation simultaneously forms both quaternary centers.



*Stereoselectivity in dialkylation step is determined by the tartrate-derived dielectrophile. The high yield acheived in this step is attributed to a high level of stereoselection in the first alkylation. It also requires that the second alkylation proceeds via a transition structure where the carbonyl and enolate oxygens are oriented away from each other. (Much like the DOAN in an Evans aldol orienting itself to minimize the dipole.)

Overman, L.E. *Proc. Nat. Acad. Sci.* **2004**, *101*, 11943-8.
Overman, L.E. *Angew. Chem. Int. Ed.* **2003**, *42*, 2525-8.

Conclusions

In the words of Larry Overman[1] (an amazing chemist[2]):

*To date, only one diastereoselective catalytic reaction has been developed for forming this structural unit (see chimonanthine slide), and no catalytic asymmetric transformation has been disclosed.

*...the extant chemistry for forming vicinal stereogenic quaternary carbons, although providing excellent solutions for the structures specifically addressed, will surely be found lacking when the target is even slightly different in structure.

*Until many additional new strategies and transformations are invented for constructing contiguous stereogenic centers in a stereocontrolled fashion, the chemical synthesis of this structural motif will remain a noteworthy challenge.

[1]Overman, L.E. *Proc. Nat. Acad. Sci.* **2004**, *101*, 11943-8.
[2]Meyer, M.E. *Larry Overman: Synthetic Highlights of an Amazing Chemist*. **December 2004.**
Supporting Info available on the web at http://stoltz.caltech.edu/clubs/category-lit.html