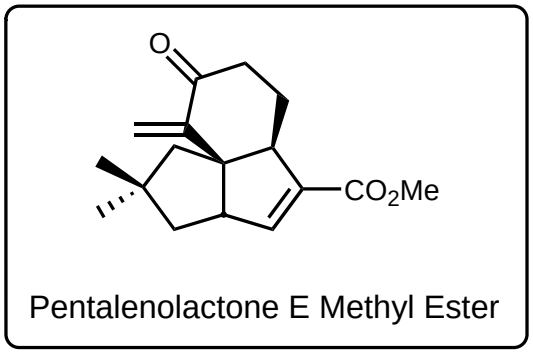
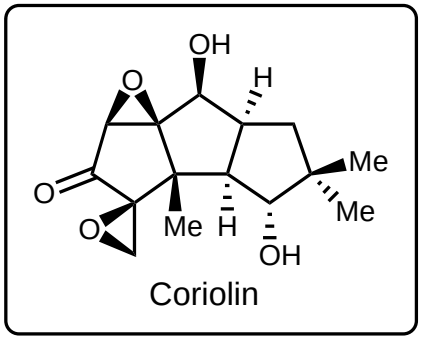
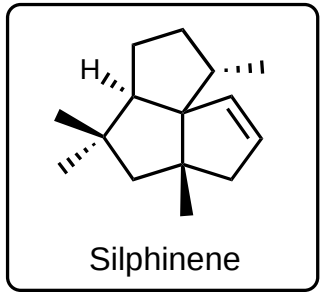
Highlights in Polyquinane Natural Product Synthesis



Pentalenolactone E Methyl Ester



Coriolin



Silphinene

Gretchen Peterson
Evans Group Afternoon Seminar
Feb. 5, 1999

Overview of Polyquinane Seminar

Leading References

Comprehensive coverage of syntheses and methodology

- early 1900's -1978: Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41
- 1979-1983: Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1
- 1984-1986: Paquette, L. A.; Doherty, A. M. *Recent Synthetic Developments in Polyquinane Chemistry*. Springer-Verlag: New York, 1987.
- 1986-1996: Mehta, G.; Srikrishna, A. *Chem Rev.* **1997**, *97*, 671

Methodology reviews

- Trost, B.M. *Chem Soc. Rev.* **1982**, *11*, 141
- Ramaiah, M. *Synthesis* **1984**, 529
- Hudlicky, T.; Price, J. D. *Chem. Rev.* **1989**, *89*, 1467
- Chanon, M.; Barone, R.; Baralotto, M.; Julliard, M.; Hendrickson, J. B. *Synthesis* **1998**, 1559

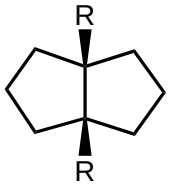
Overview of Seminar

Introduction
- Polyquinane Skeletal Motifs
- Biosynthetic Pathways

Representative Syntheses
- Diquinanes: Pentalenolactone E Methyl Ester
- Linear Triquinanes: Capnellene, Coriolin
- Angular Triquinanes: Siliphinene, Pentalenene
- Propellanes: Modhephene

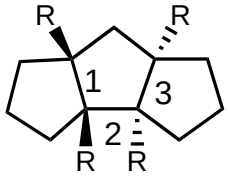
Polyquinane Nomenclature

Diquinanes



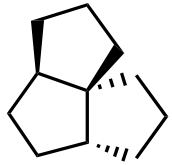
cis

Linear Triquinanes

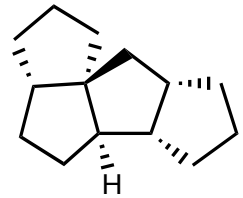


cis-anti-cis

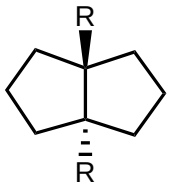
Angular Triquinaes



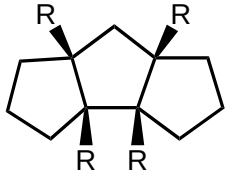
Tetraquinanes



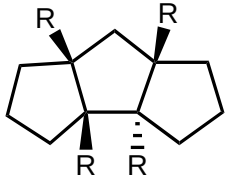
cis-anti-cis



trans



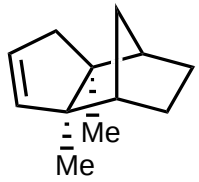
cis-syn-cis



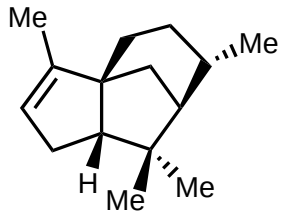
cis-anti-trans

• Highly strained ring systems which are not commonly found in polyquinane natural products

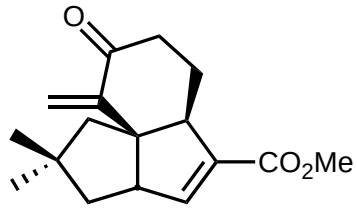
Polyquninane Structural Motifs: Diquinanes



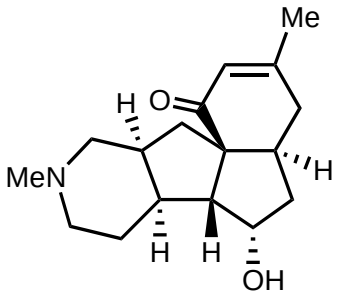
Albene



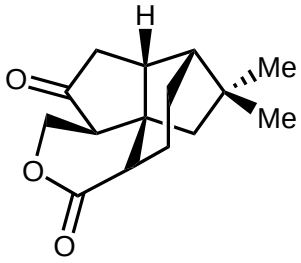
Cedrene



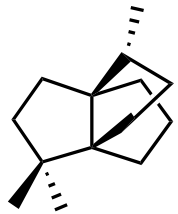
Pentalenolactone E Methyl Ester



Magellanine



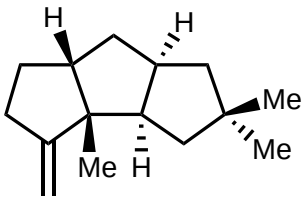
Quadrone



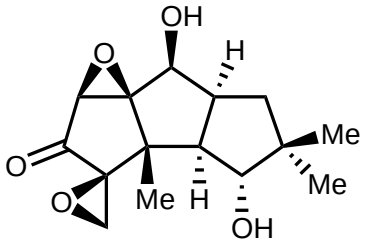
Modhephene

Polyquninane Structural Motifs: Higher Quinanes

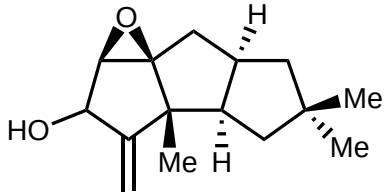
Linear Triquinanes



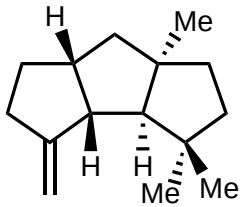
Hirsutene



Coriolin

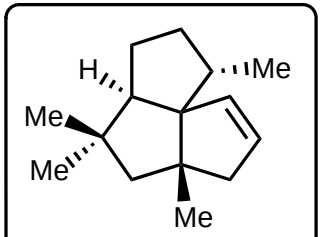


Hirsutic Acid-C

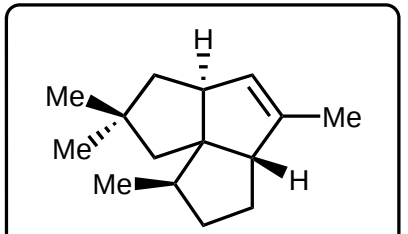


Capnellene

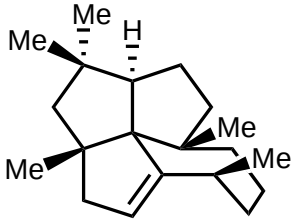
Angular Triquinanes



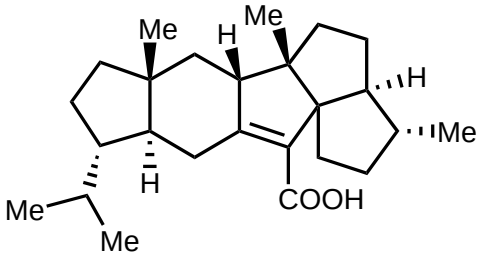
Silphinene



Pentalenene

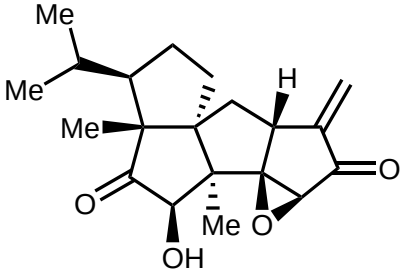


Laurenene



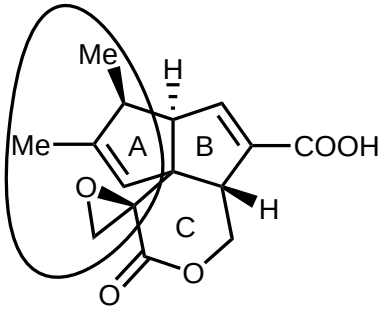
Retigeranic Acid

Tetraquinane

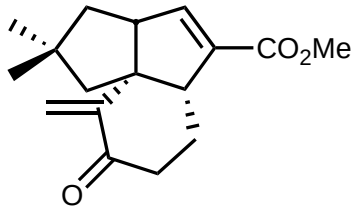


Crinipellin-B

Diquinanes: The Pentalenolactone Family



Pentalenolactone



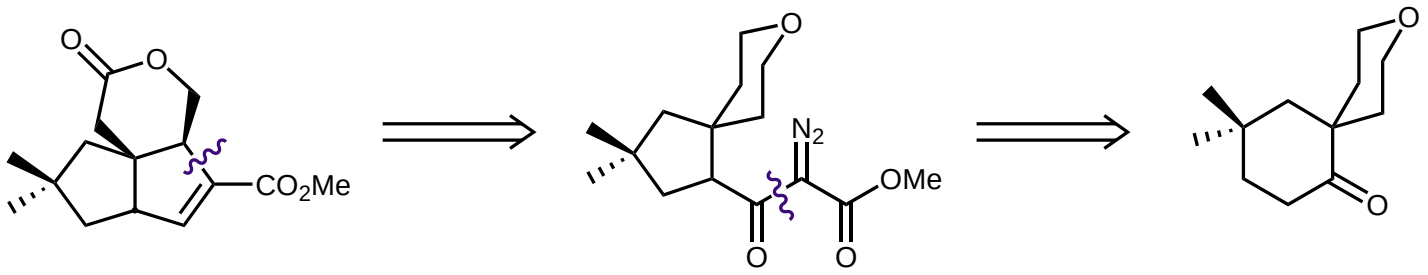
Pentalenolactone E Methyl Ester

• Pentalenolactones A, B, D, E, F, G, H, O, and P have been isolated and characterized from *Streptomyces* strains. They differ in placement of the methyl groups (gem-dimethyl vs. 1,2-stereochemistry) and unsaturation in ring A, and in having a methylene, epoxide or cyclopropyl group alpha to the lactone. Cane, D. E. et al. *J. Org. Chem.* **1992**, *57*, 845 and references therein.

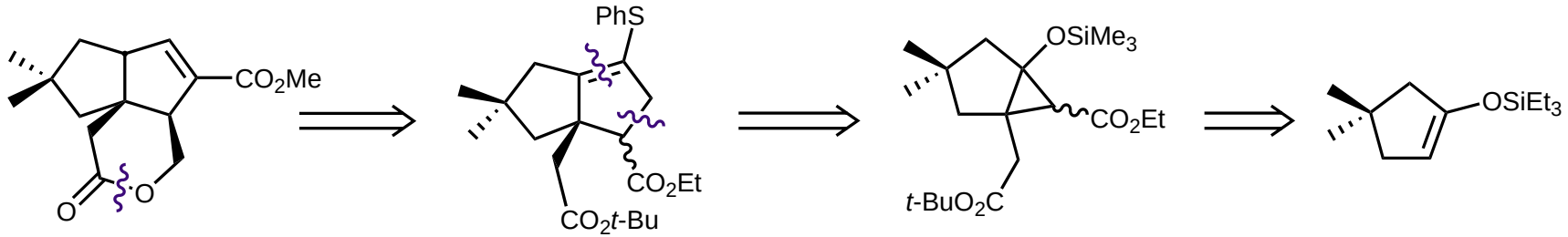
• Members of fhe pentalenolactone family have shown antibacterial, antiviral, and enzyme inhibitor properties. Cane D. E. et al. *Arch. Biochem. Biophys.* **1989**, *270*, 50 and references therein.

Retrosynthetic Analysis of (±)-Pentalenolactone E Methyl Ester

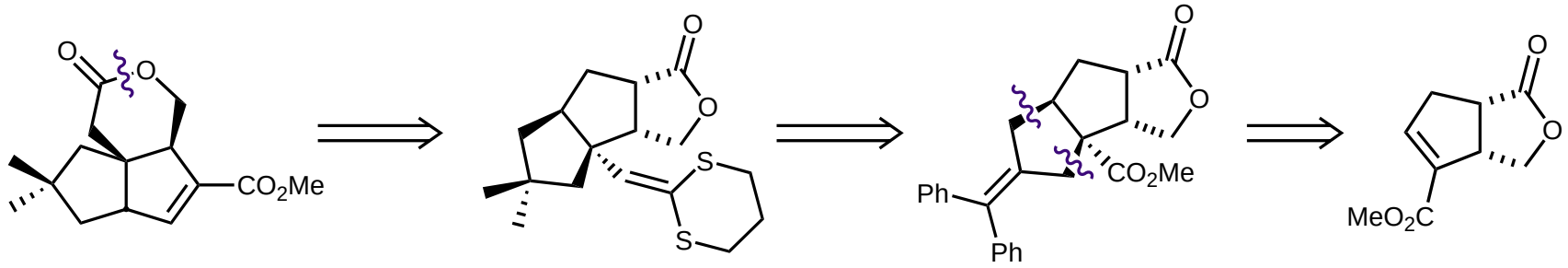
Taber: intramolecular C-H insertion



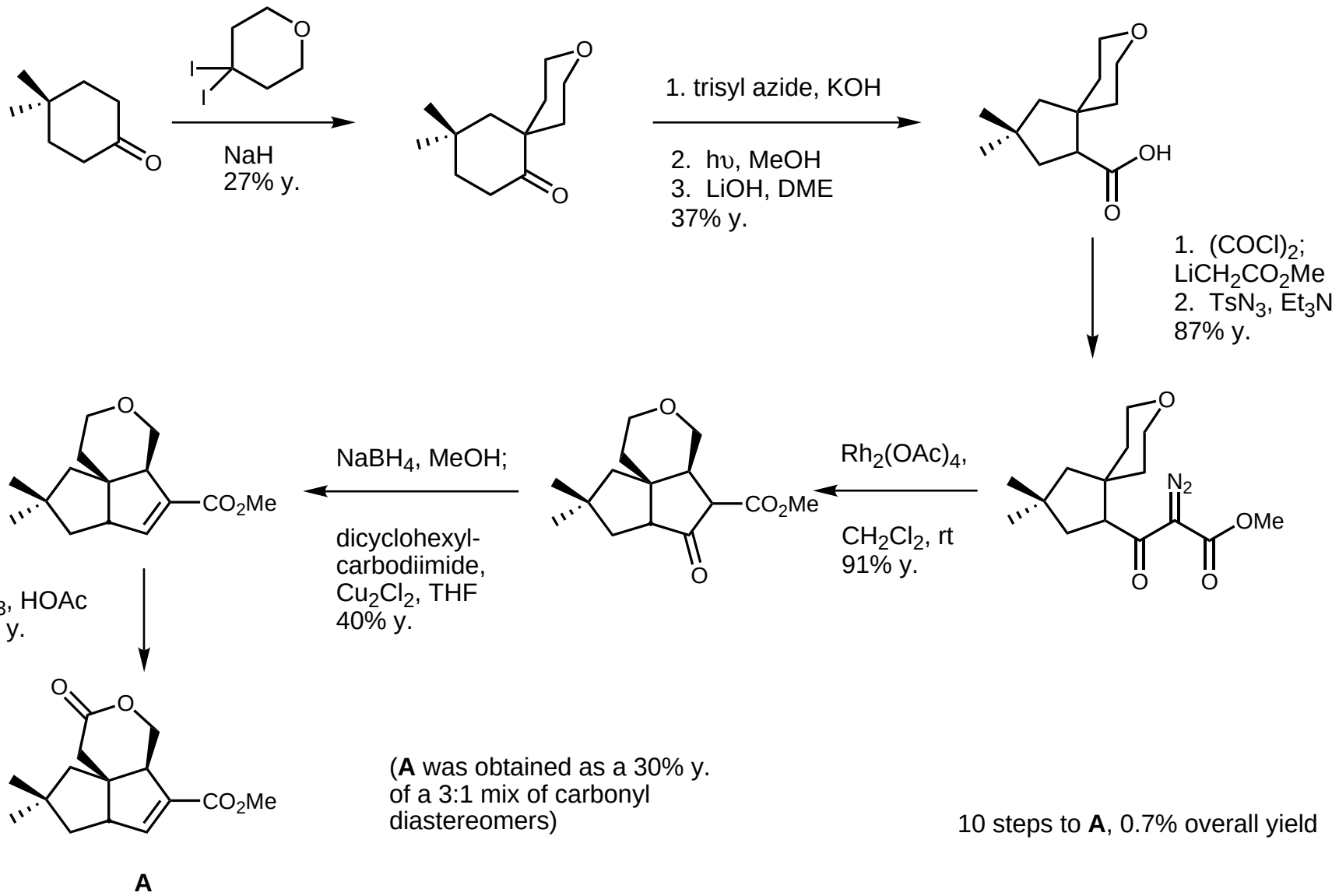
Marino: [3+2] annulation



Linder *et al.*: [3+2] annulation



(±)- Pentalenolactone E Methyl Ester: Intramolecular C-H Insertion



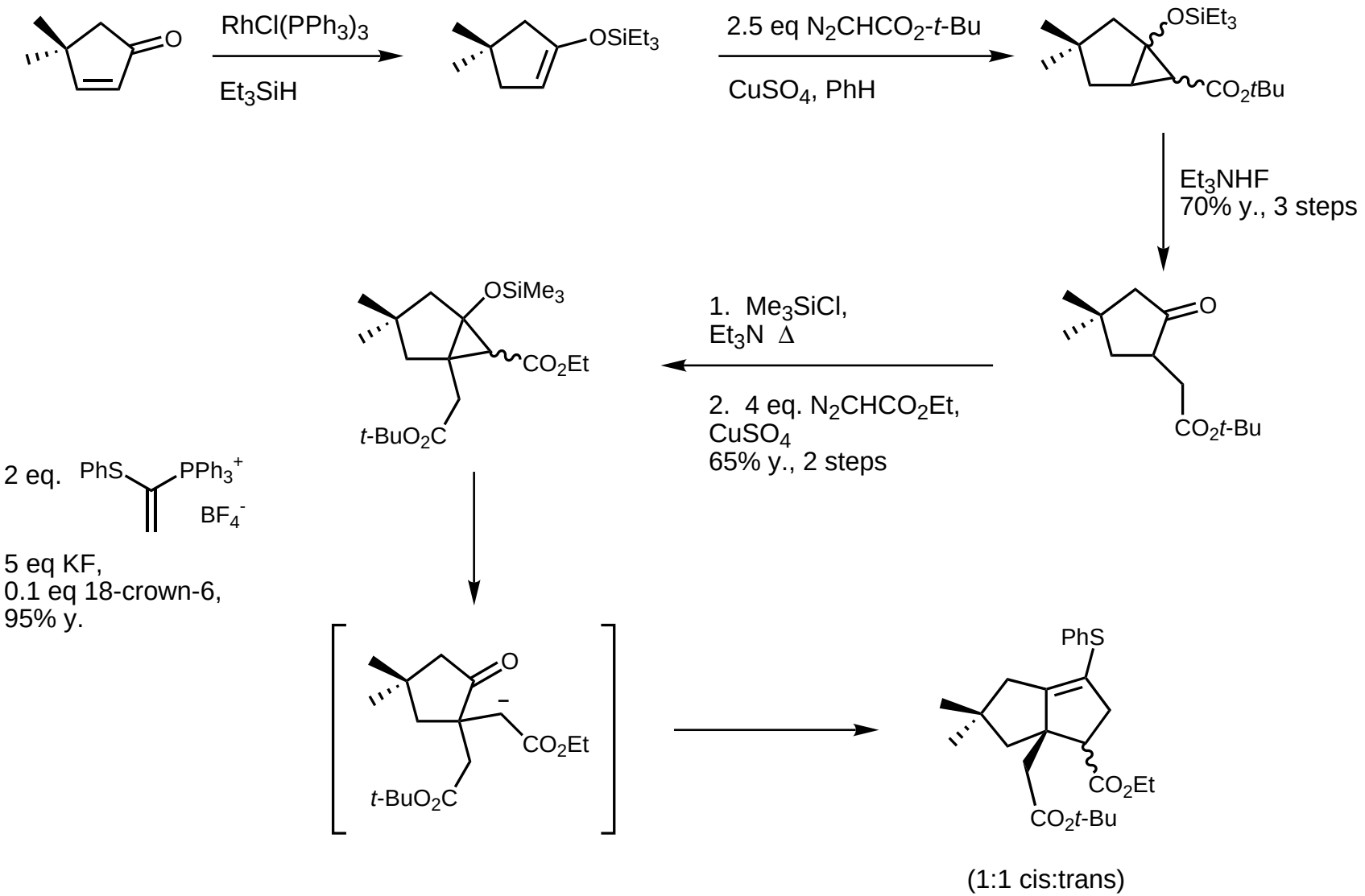
A

(**A** was obtained as a 30% y. of a 3:1 mix of carbonyl diastereomers)

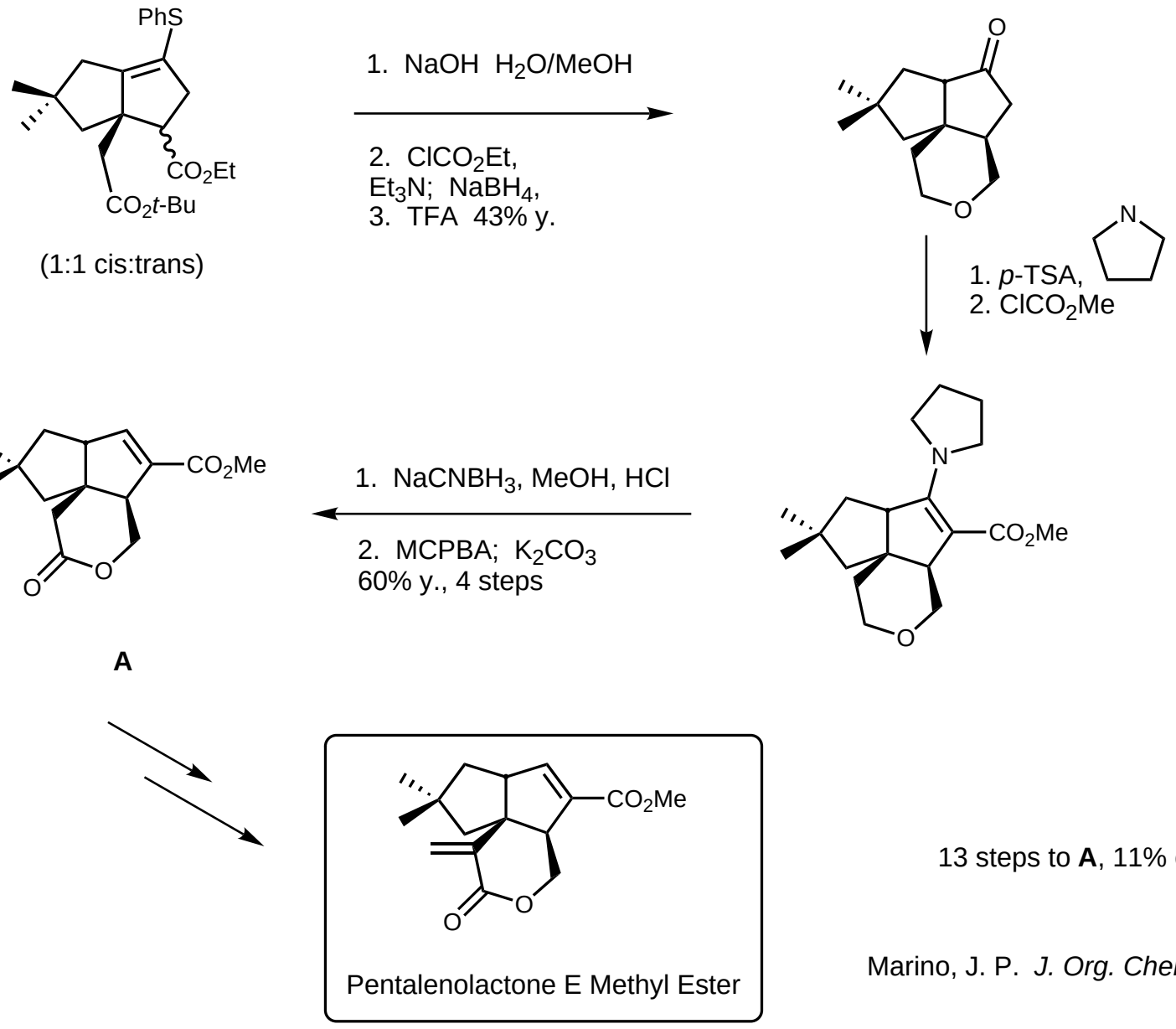
10 steps to **A**, 0.7% overall yield

Taber, D. F. *Tetrahedron* **1987**, *43*, 5677

(±)- Pentalenolactone E Methyl Ester: base-induced [3+2] annulation



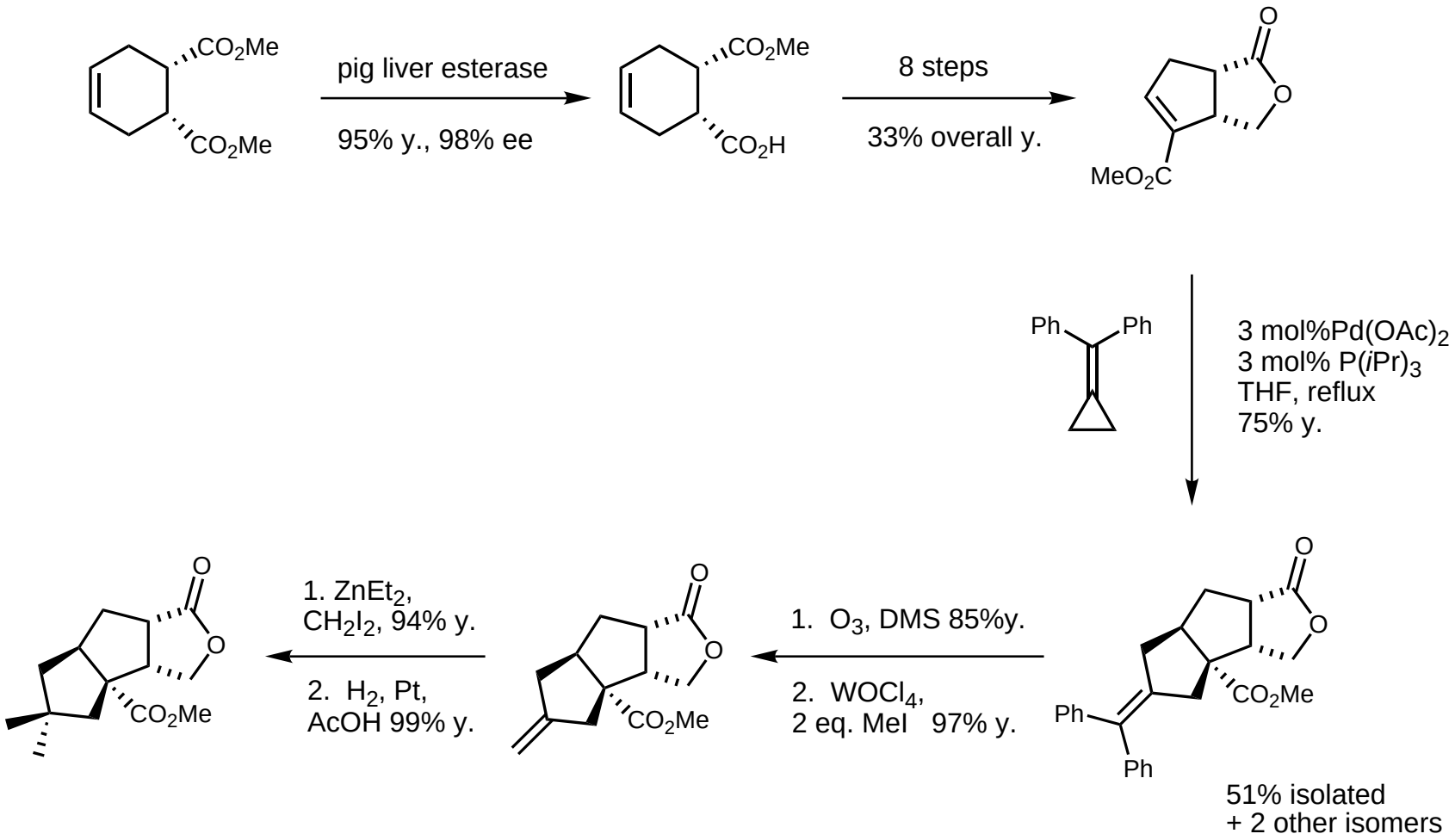
(±)- Pentalenolactone E Methyl Ester: base-induced [3+2] annulation



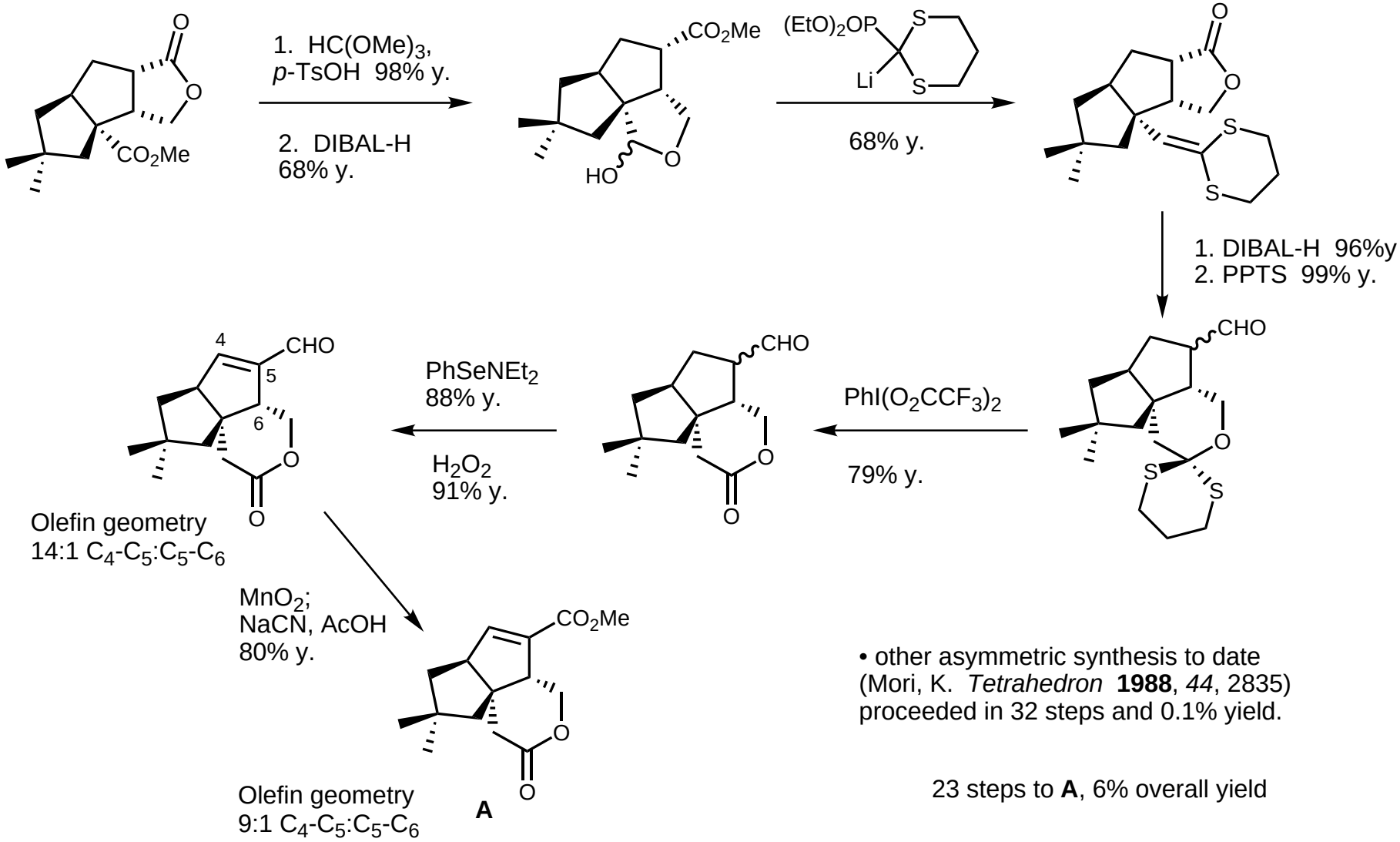
13 steps to **A**, 11% overall yield

Marino, J. P. *J. Org. Chem.* **1987**, *52*, 4140

(-) - Pentalenolactone E Methyl Ester: Pd-catalyzed [3+2] annulation



(-) - Pentalenolactone E Methyl Ester: Pd-catalyzed [3+2] annulation

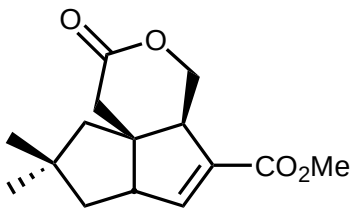


• other asymmetric synthesis to date (Mori, K. *Tetrahedron* **1988**, *44*, 2835) proceeded in 32 steps and 0.1% yield.

23 steps to **A**, 6% overall yield

Gais, H.-J.; Binger, P.; Linder, H. J. *Eur. J. Org. Chem.* **1998**, 257

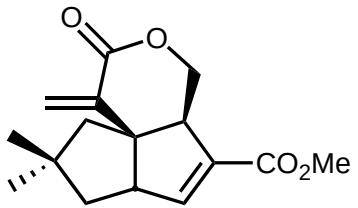
(±)- Pentalenolactone E Methyl Ester: Methylenation



A

1. $MeOMgOCO_2Me$

2. HCHO, Et_2NH, HOAc, NaOAc
27% y.



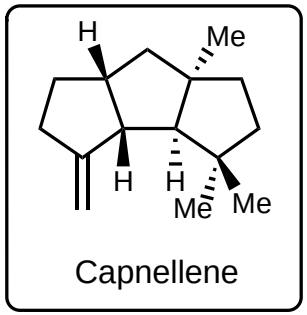
Pentalenolactone E Methyl Ester

• Use of Eschenmoser's salt in place of formalin/Et_2NH solution resulted in 40-50% yield in methylenation: Marino, J. P. *J. Org. Chem.* **1987**, *52*, 4140

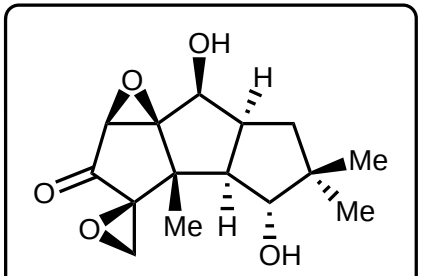
• On (-)-**A**, methylenation according to Paquette protocol proceeded in 73% yield: Mori, K. *Tetrahedron* **1988**, *44*, 2835

Paquette, L. A. *J. Am. Chem. Soc.* **1982**, *104*, 6646

Linear Triquinanes: Coriolin and Capnellene



Capnellene



Coriolin

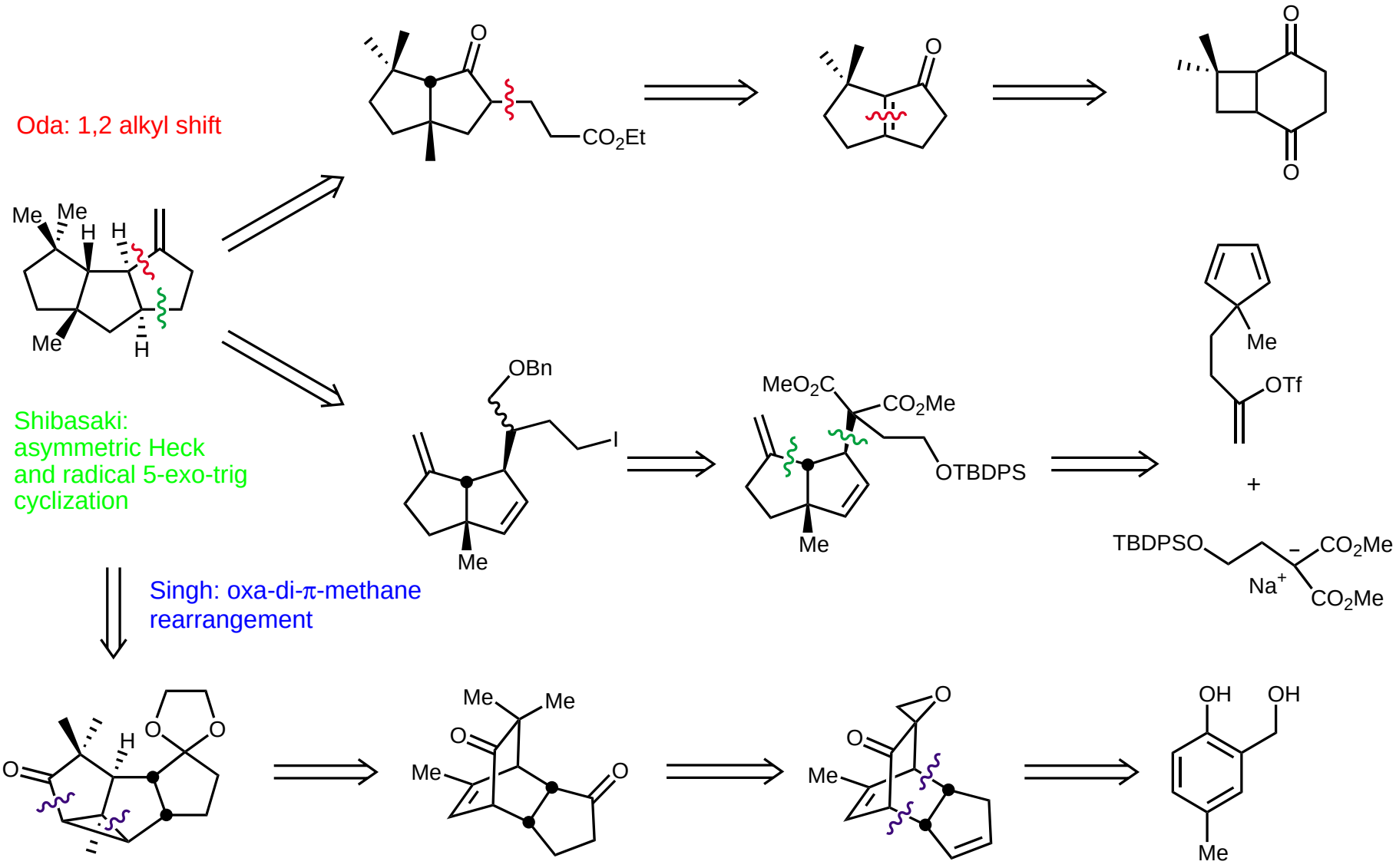
• Both Capnellene and Coriolin are members of the hirsutane structure class of linear triquinanes.

• Capnellene was isolated in 1978 from the soft coral *Capnella imbricata.* While not known precisely, capnellenes are thought to be chemical defense agents against microorganism and larval growth on the coral surface. Cierzsko, L. S.; Karns, T. K. B. in *Biology and Geology of Coral Reefs* vol. 3, Ed. Jones, A. and Endean, R. Academic Press: New York, Chap. 6, 1972.

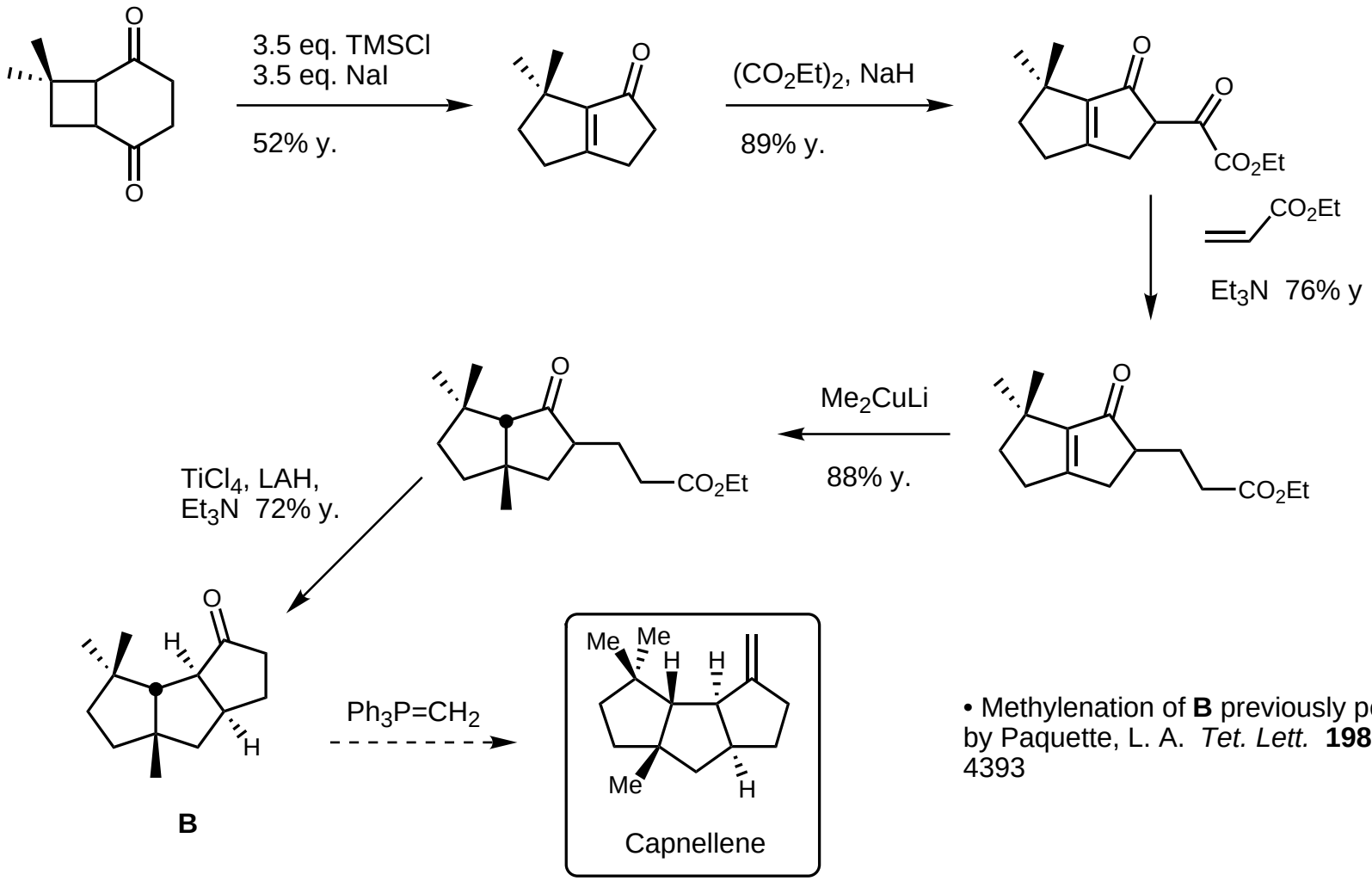
• Coriolin was first isolated from basidiomycete *Coriolus consors* in 1969, and has shown antibiotic and anti-tumor activity. Takeuchi, T. et al. *J. Antibiot.* **1969**, *22*, 215; **1971**, *24*, 631.

• Recent review on methods of creating linear triquinane skeleton: Singh, V.; Thomas, B. *Tetrahedron* **1998**, *54*, 3647.

Retrosynthetic Analysis of Capnellene



(±)-Capnellene: TMSI-based 1,2-alkyl shift

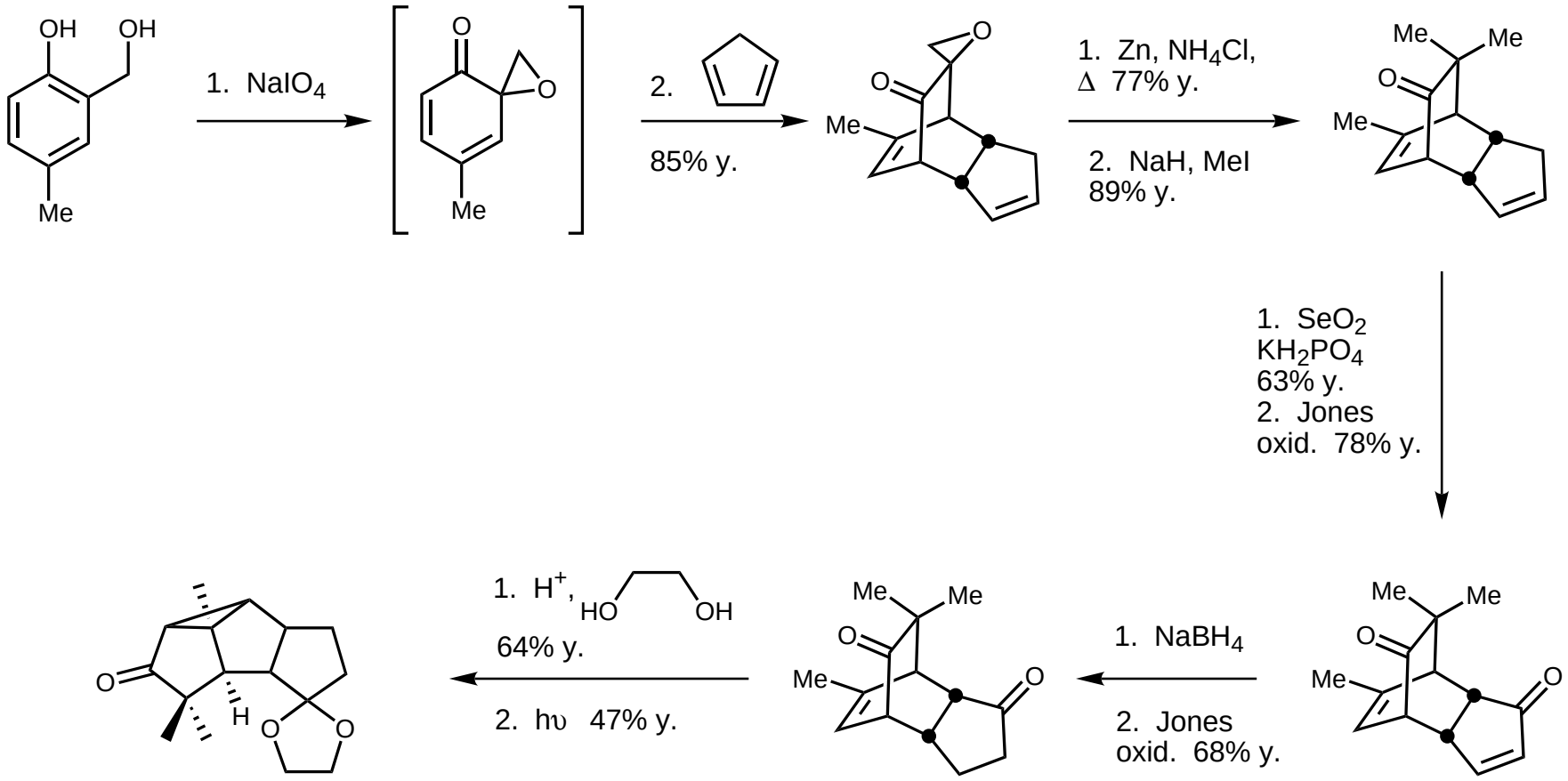


• Methylenation of **B** previously performed by Paquette, L. A. *Tet. Lett.* **1981**, *22*, 4393

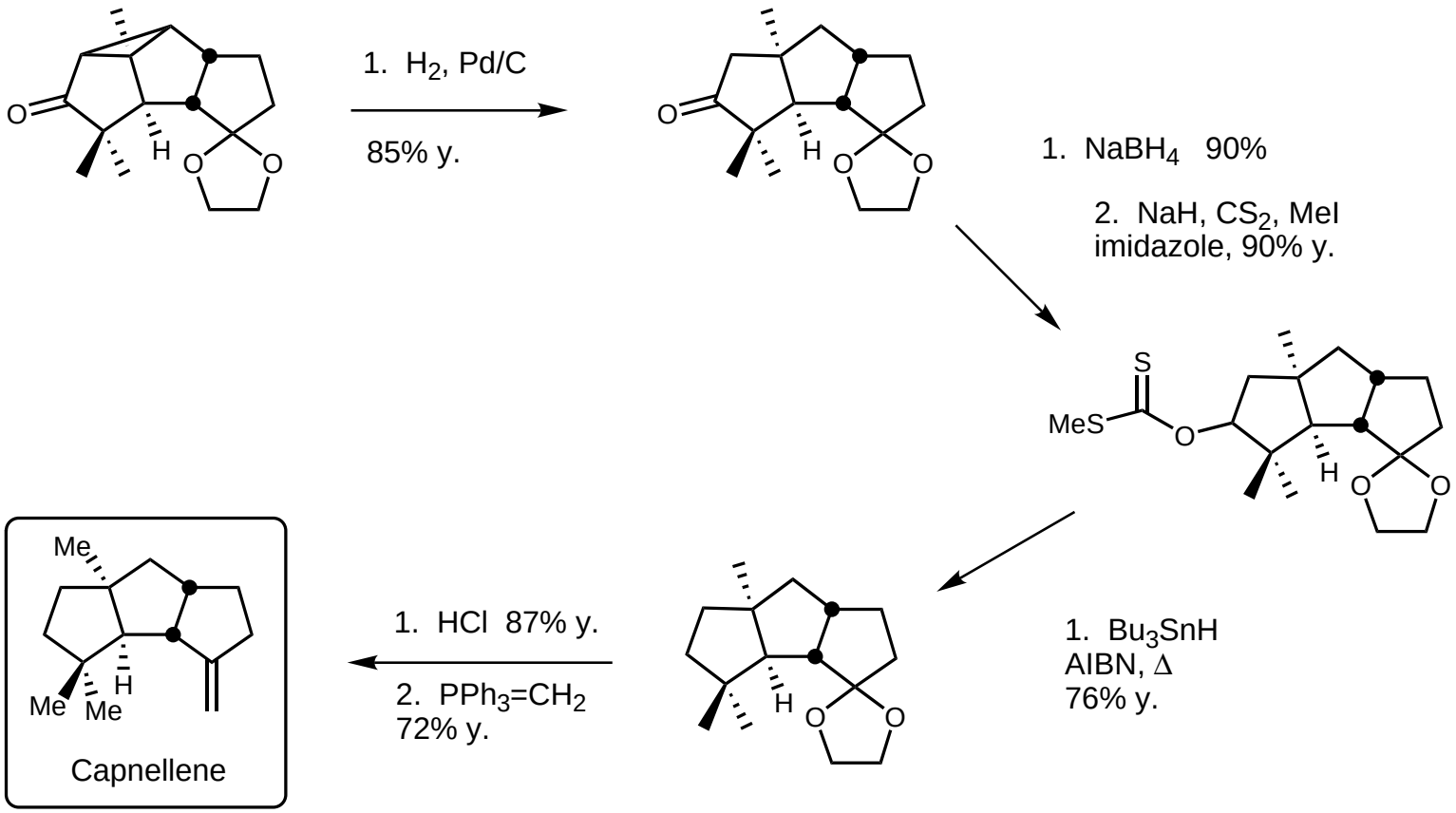
5 steps to **B**, 22% overall y.

Oda, M. *J. Chem. Soc. Chem. Commun.* **1987**, 1607

(±)-Capnellene: Oxa-Di-π-Rearrangement

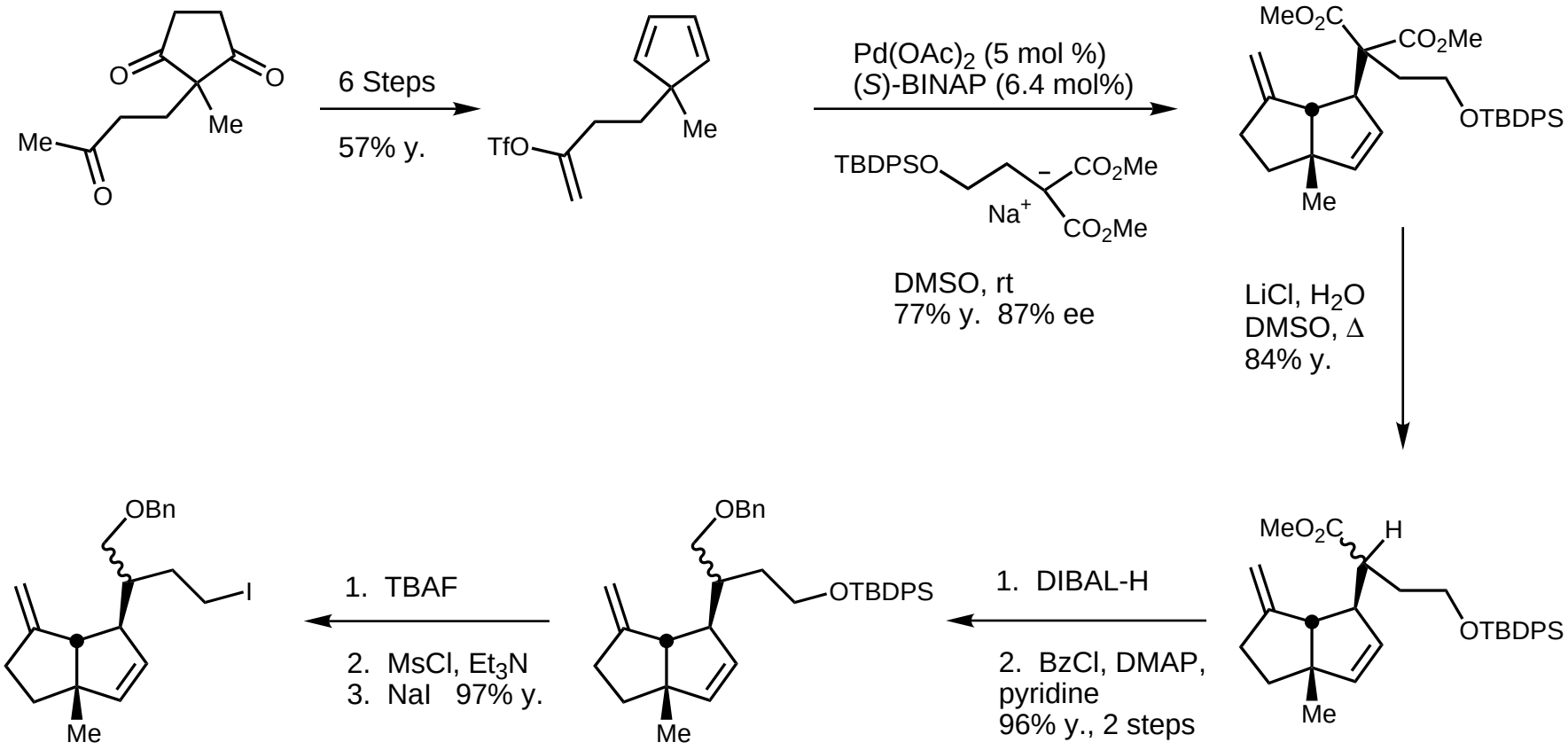


(±)-Capnellene: Oxa-Di-π-Rearrangement

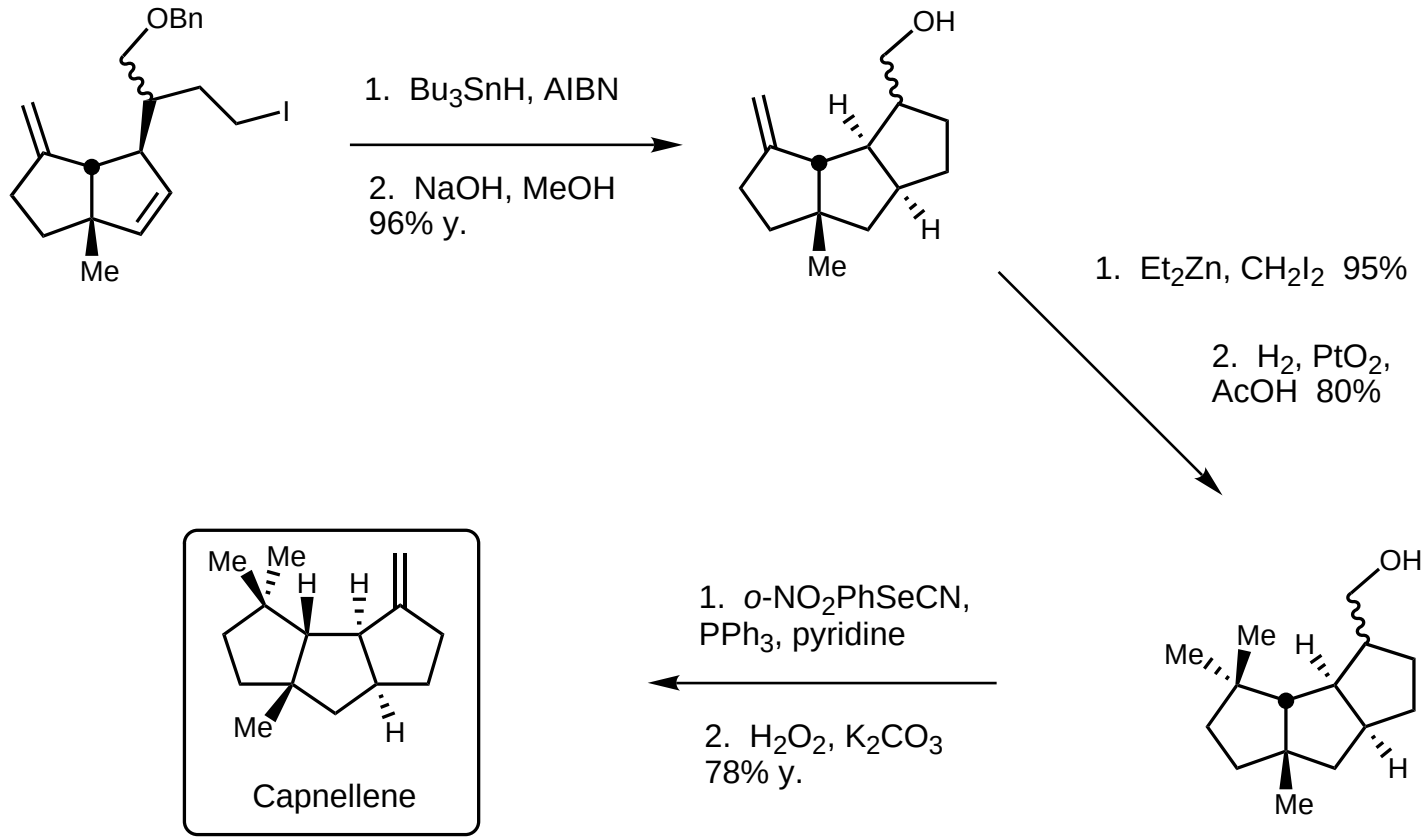


Singh, V. *J. Org. Chem.* **1998**, *63*, 4011

(-)-Capnellene: Annulation via Asymmetric Heck Reaction



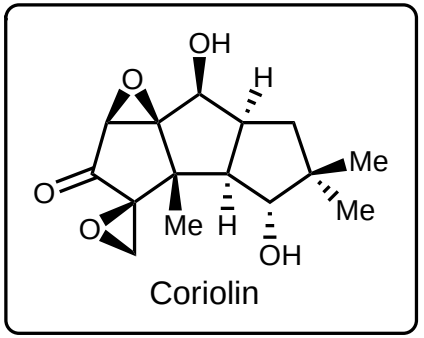
(-)-Capnellene: Annulation via Asymmetric Heck Reaction



20 steps, 20% overall yield

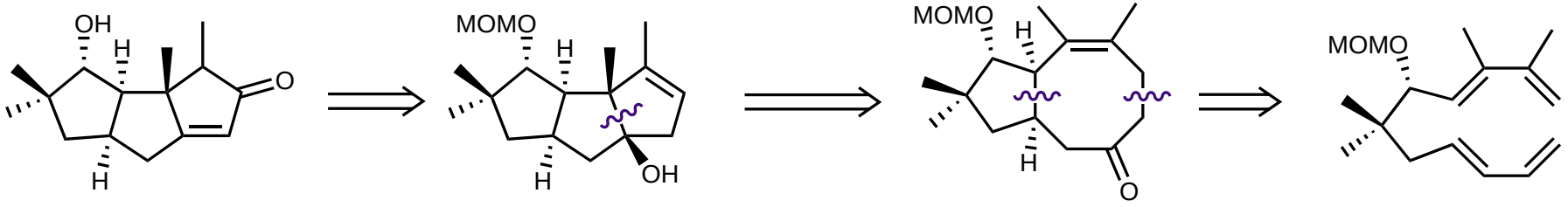
Shibasaki, M. *J. Am. Chem. Soc.* **1996**, *118*, 7108

Retrosynthetic Analysis of Coriolin



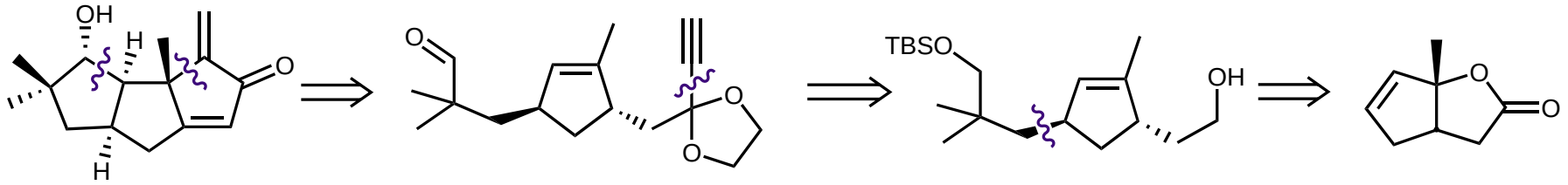
Coriolin

Wender: [4+4] Cycloaddition



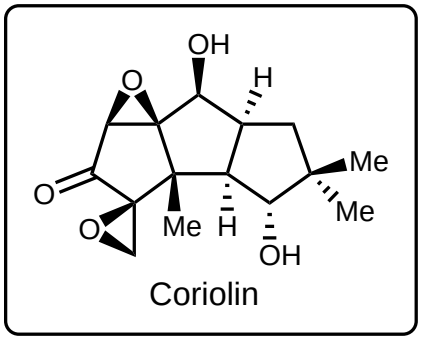
C

Curran: Tandem Radical Cyclization

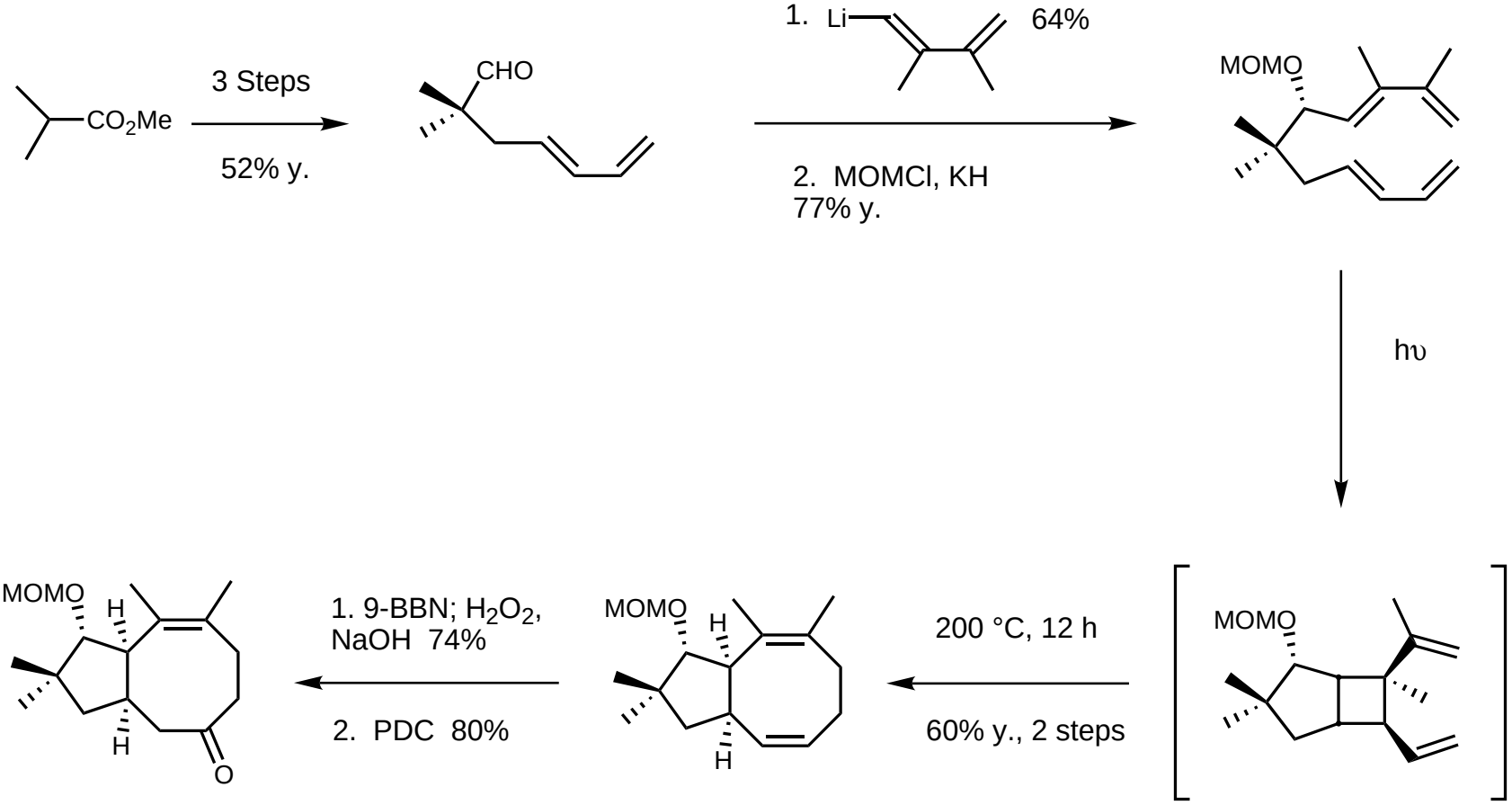


D

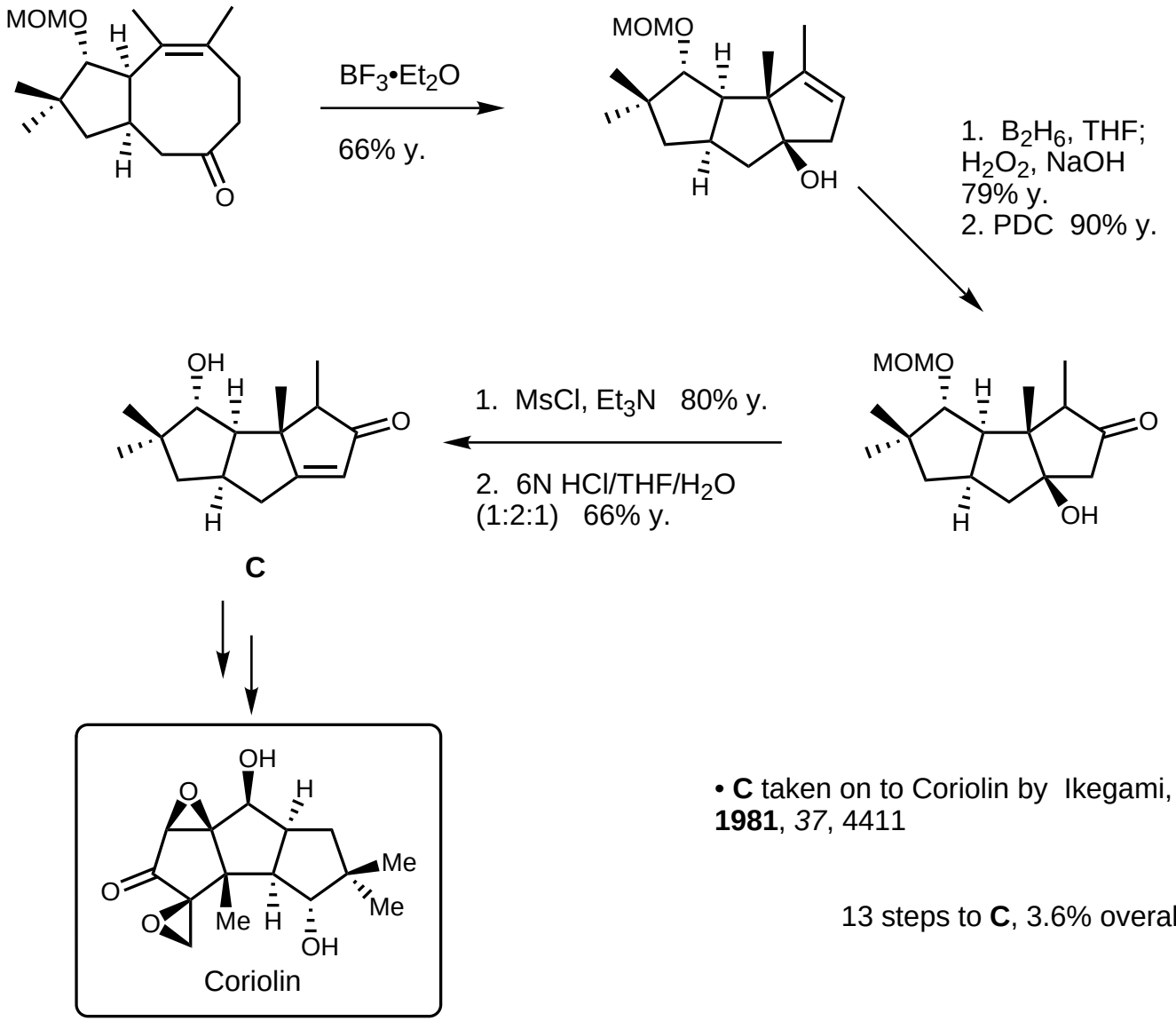
(±)-Coriolin: [4+4] cycloaddition



Coriolin



(±)-Coriolin: [4+4] cycloaddition

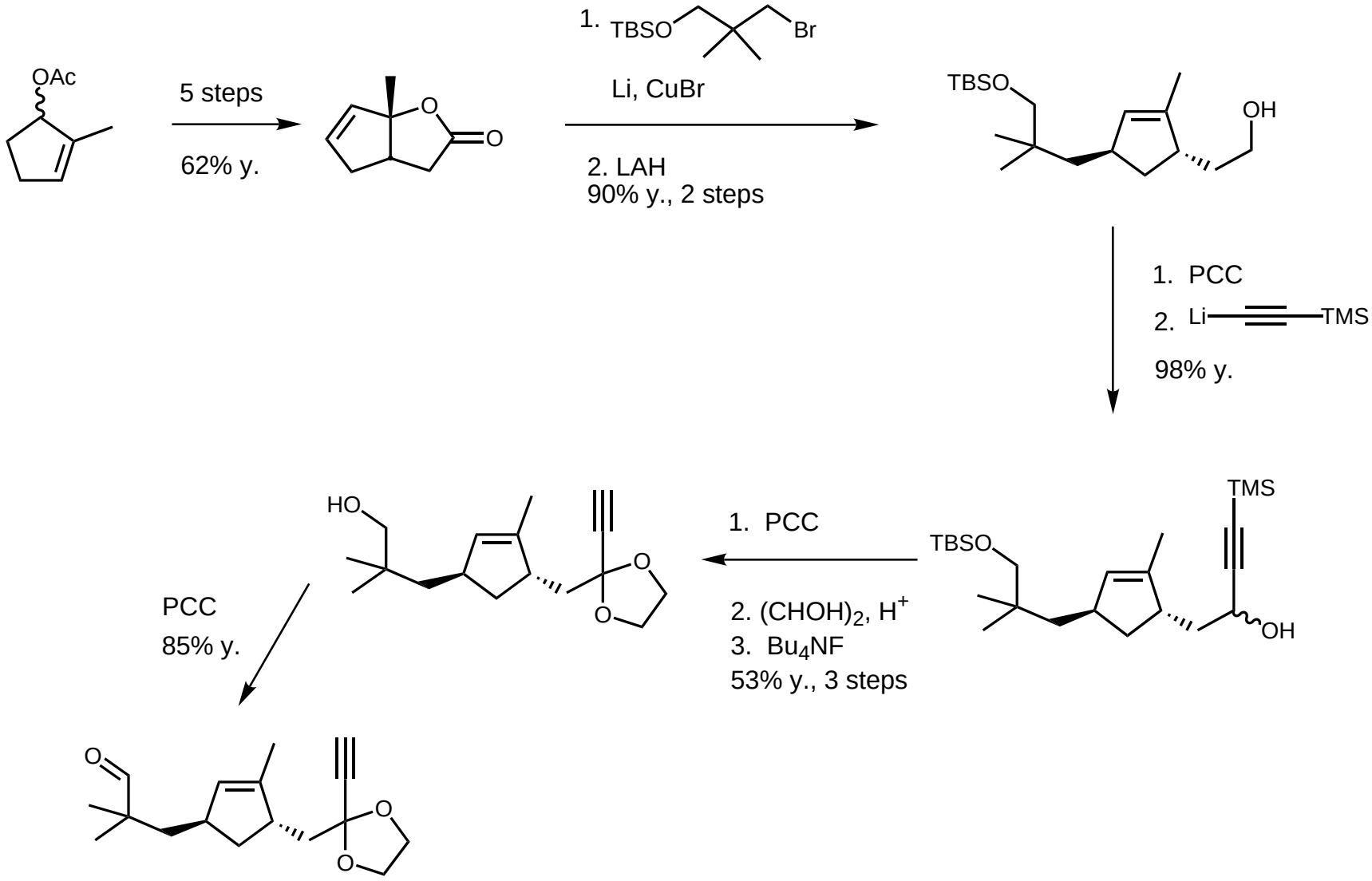


• **C** taken on to Coriolin by Ikegami, S. *Tetrahedron* **1981**, *37*, 4411

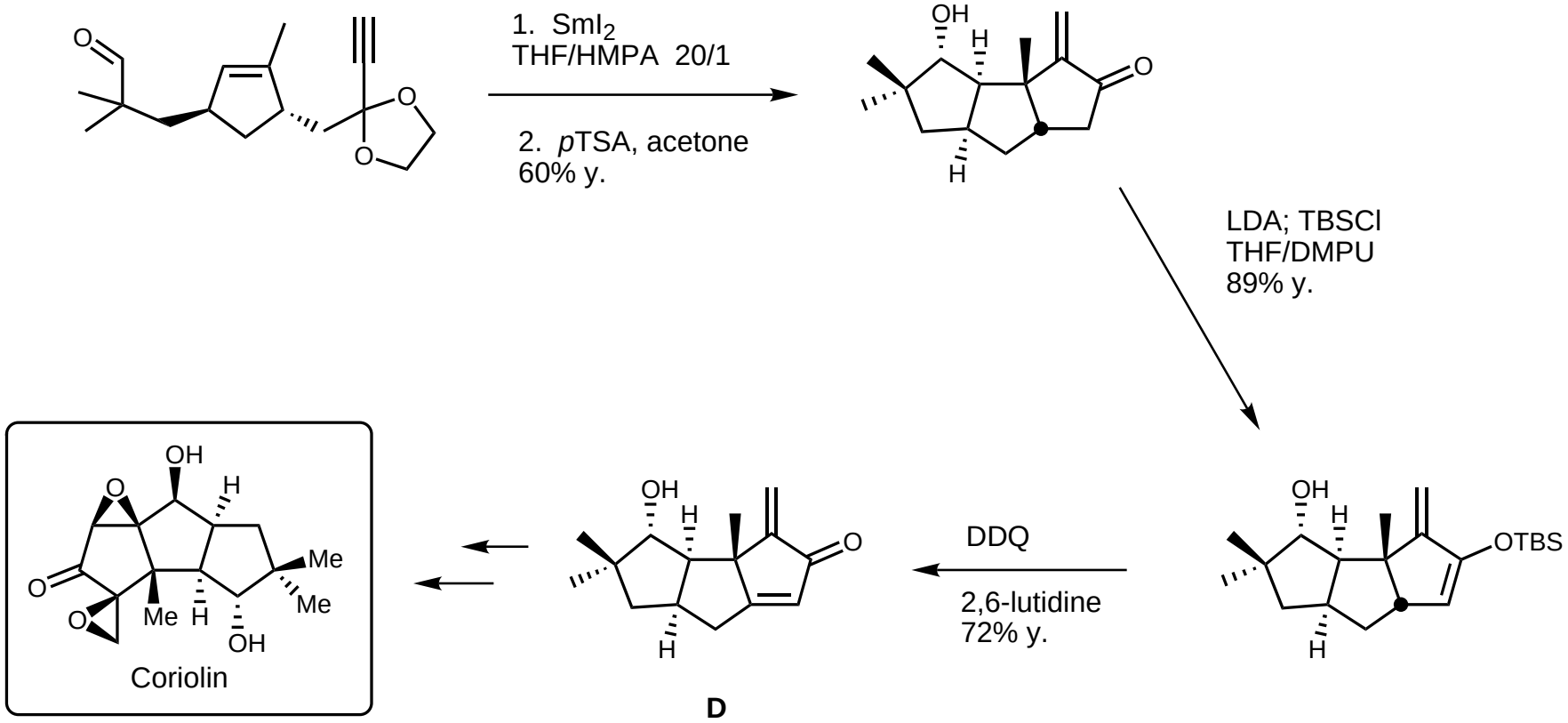
13 steps to **C**, 3.6% overall yield

Wender, P. A. *J. Am. Chem. Soc.* **1987**, *109*, 2523

(±)-Coriolin: Tandem Radical Cyclization



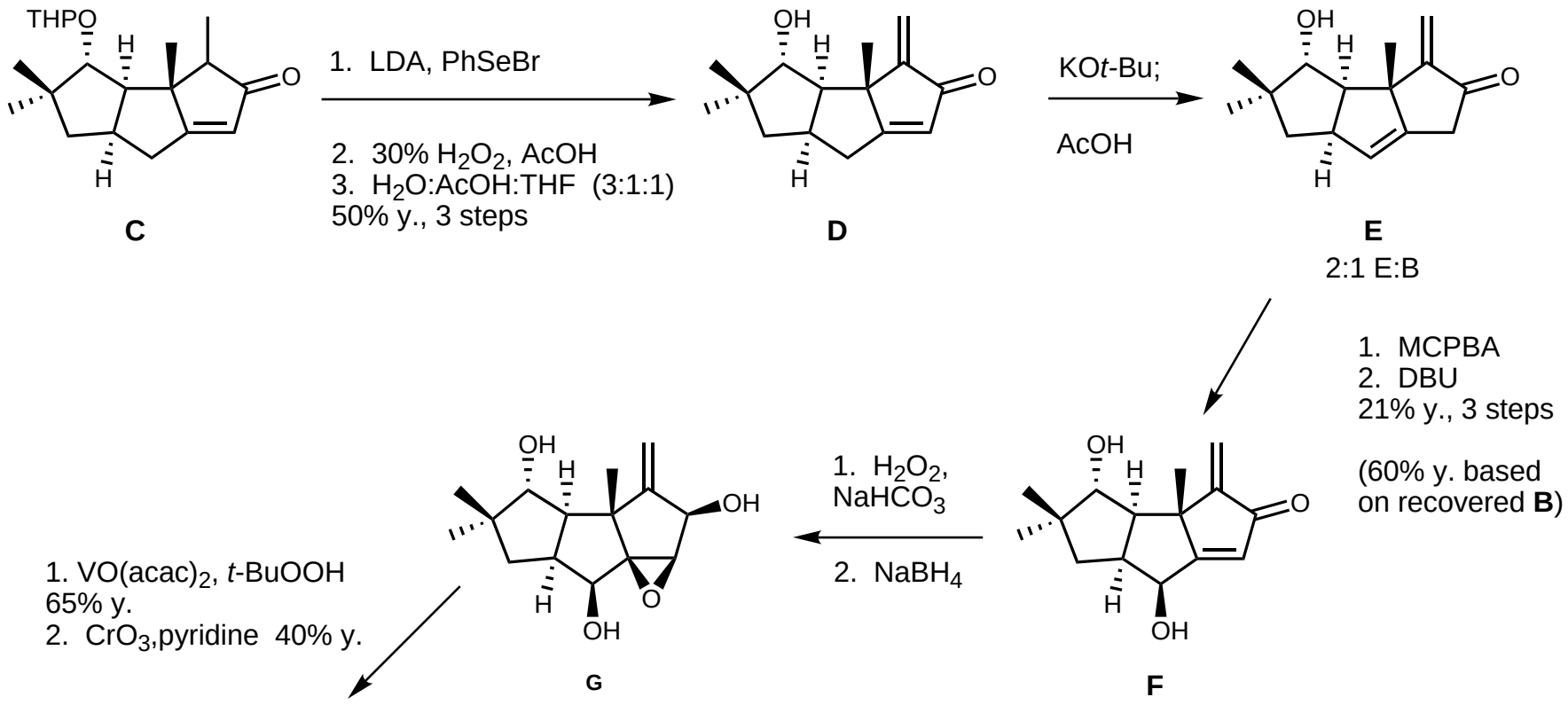
(±)-Coriolin: Tandem Radical Cyclization

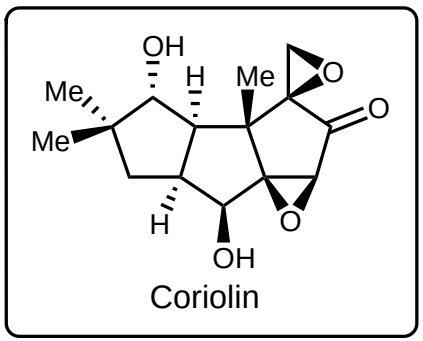


• **D** has been taken on to coriolin by Danishefsky, S. *J. Am. Chem. Soc.* **1981**, *103*, 3460

Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064

(±)-Coriolin: Final Oxygenation Strategies



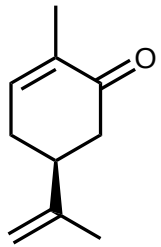


- Step **C** → **D** performed by Ikegami, S. *Tetrahedron* **1981**, *37*, 4411

- Step **D** → **G** performed by Danishefsky, S. *J. Am. Chem. Soc.* **1981**, *103*, 3460

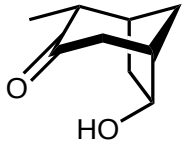
- Final CrO_3 oxidation performed by Umezawa, S. *J. Antibiot.* **1980**, *33*, 404

(±)-Coriolin: Tandem Radical Cyclization of Oxygenated Precursor



$Hg(OAc)_2$;

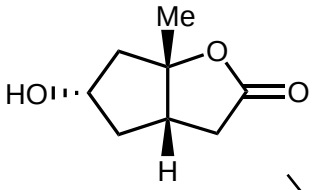
$NaBH_4$/MeOH
70% y.



1:1 endo:exo

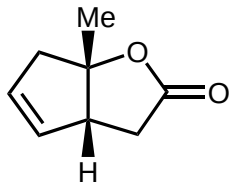
1. MCPBA
85% y.

2. K_2CO_3
98% y.



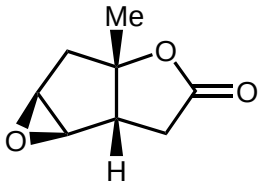
1. MsCl, Et_3N
quant.

2. pyridine
45% y.



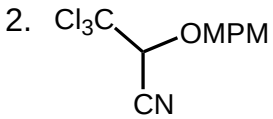
MCPBA

64% y. of
desired
epoxide

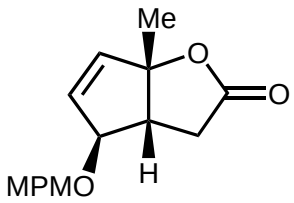


2:1 dr

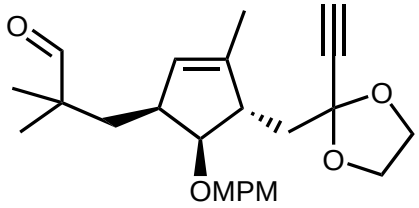
1. NaSePh;
H_2O_2 77% y.

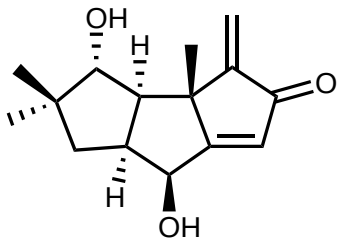
2. 

PPTS
91% y.



H





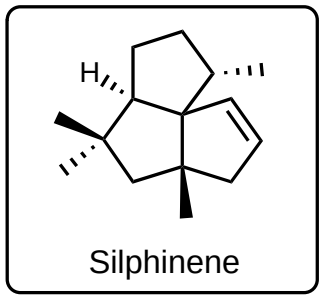
F

8 steps to **H**, 5.8% overall y.

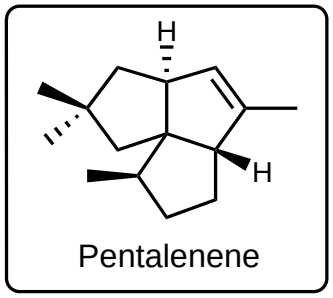
• Enantioselective synthesis of **H** allowed for elaboration to **F** via Curran's methodolgy

Weinges, K. *Liebig's Ann. Chem.* **1993**, 1133

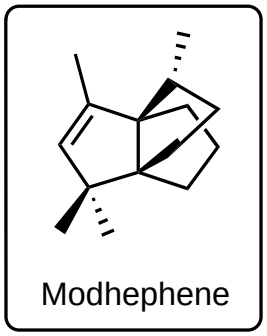
Angular Triquinanes: Silphinene and Pentalenene Propellanes: Modhephene



Silphinene



Pentalenene



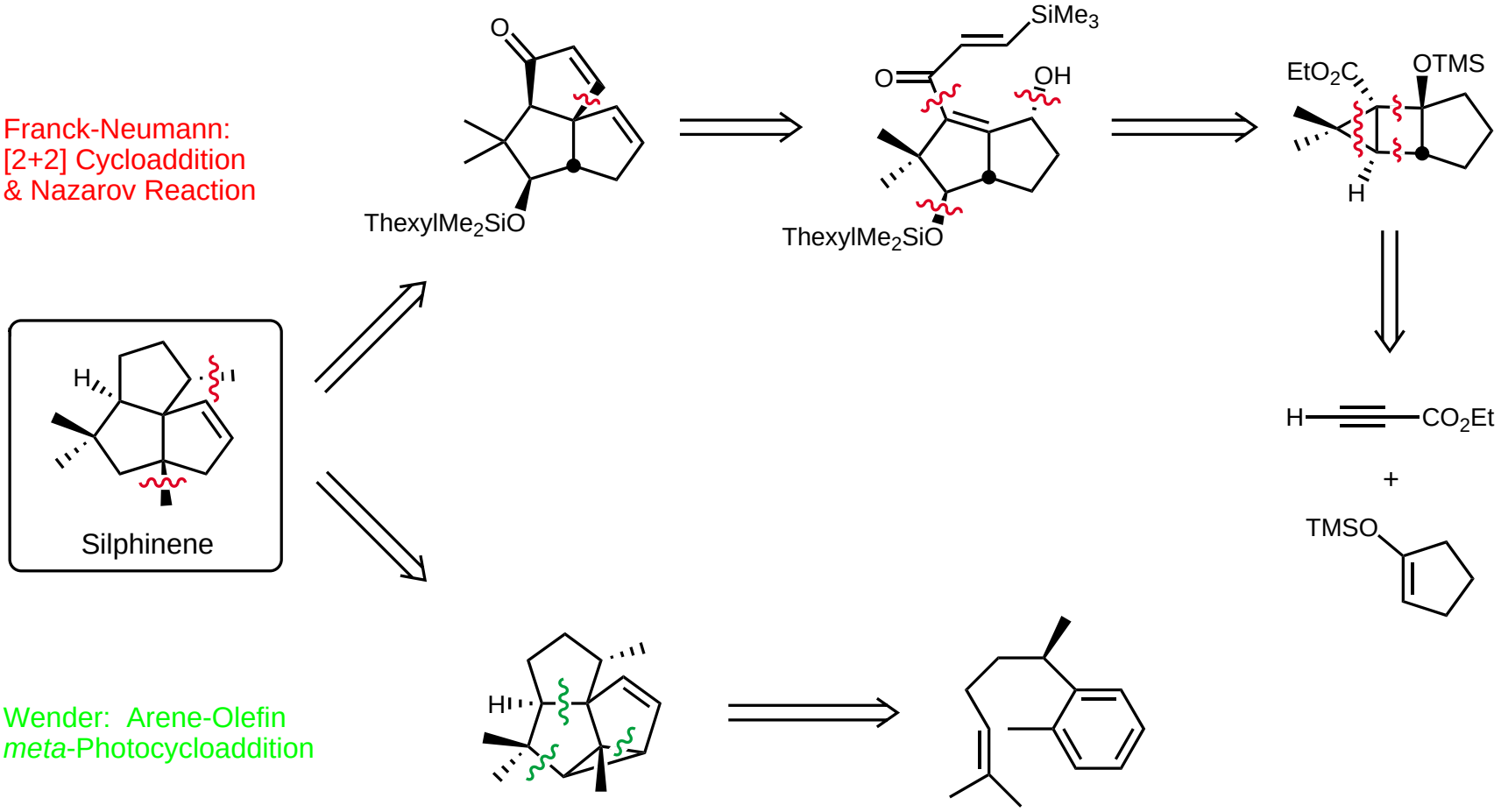
Modhephene

• Silphinene was isolated from the plant *Silphium perfoliatum* in 1980. Interest in its synthesis is derived mainly from the angular triquinane core; yet a recent report describes antifeedant activity against the Colorado potato beetle. Bohlman, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259. Mullen, C. A. *et al. J. Chem. Ecol.* **1997**, *23*, 1851.

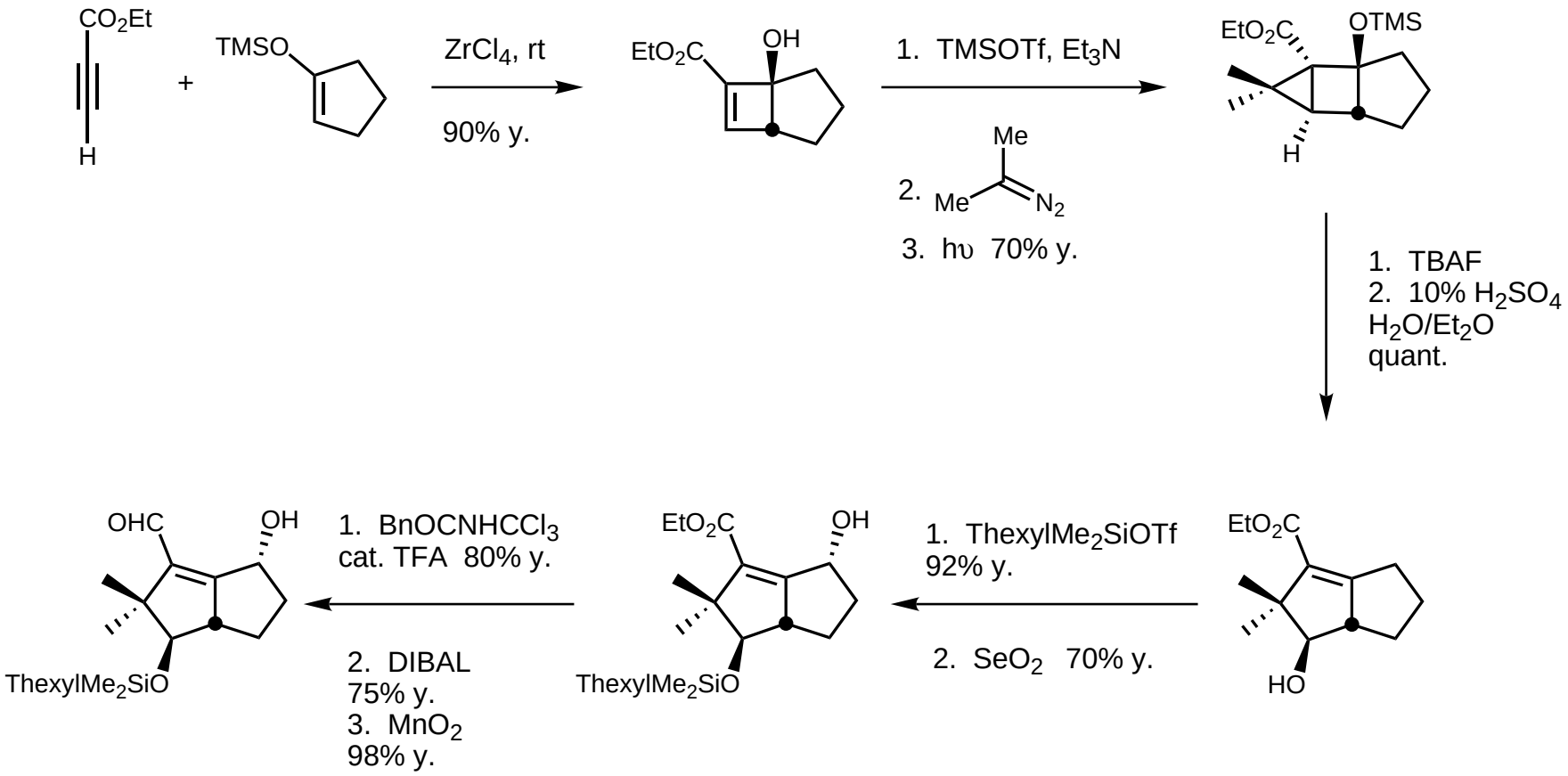
• Pentalenene, first isolated in 1980 from *Streptomyces griseochromongenes* by Seto and co-workers, has been shown to be the parent of the pentalenolactone family of antibiotics. Pentalenene synthase has been isolated and extensively studied to determine the biosynthtic origins of polyquinane natural products. Seto, H.; Yonehara, H. *J. Antibiot.* **1980**, *33*, 92. Cane, D. E. *et al. Bioorg. Chem.* **1984**, *12*, 312.

• Modhephene was isolated from the goldenrod plant *Isocoma wrightii* in 1978 and was the first natural product found to have the [3.3.3]-propellane skeleton. Zalkow, L. H. *et al. J. Chem. Soc. Chem. Commun.* **1978**, 420.

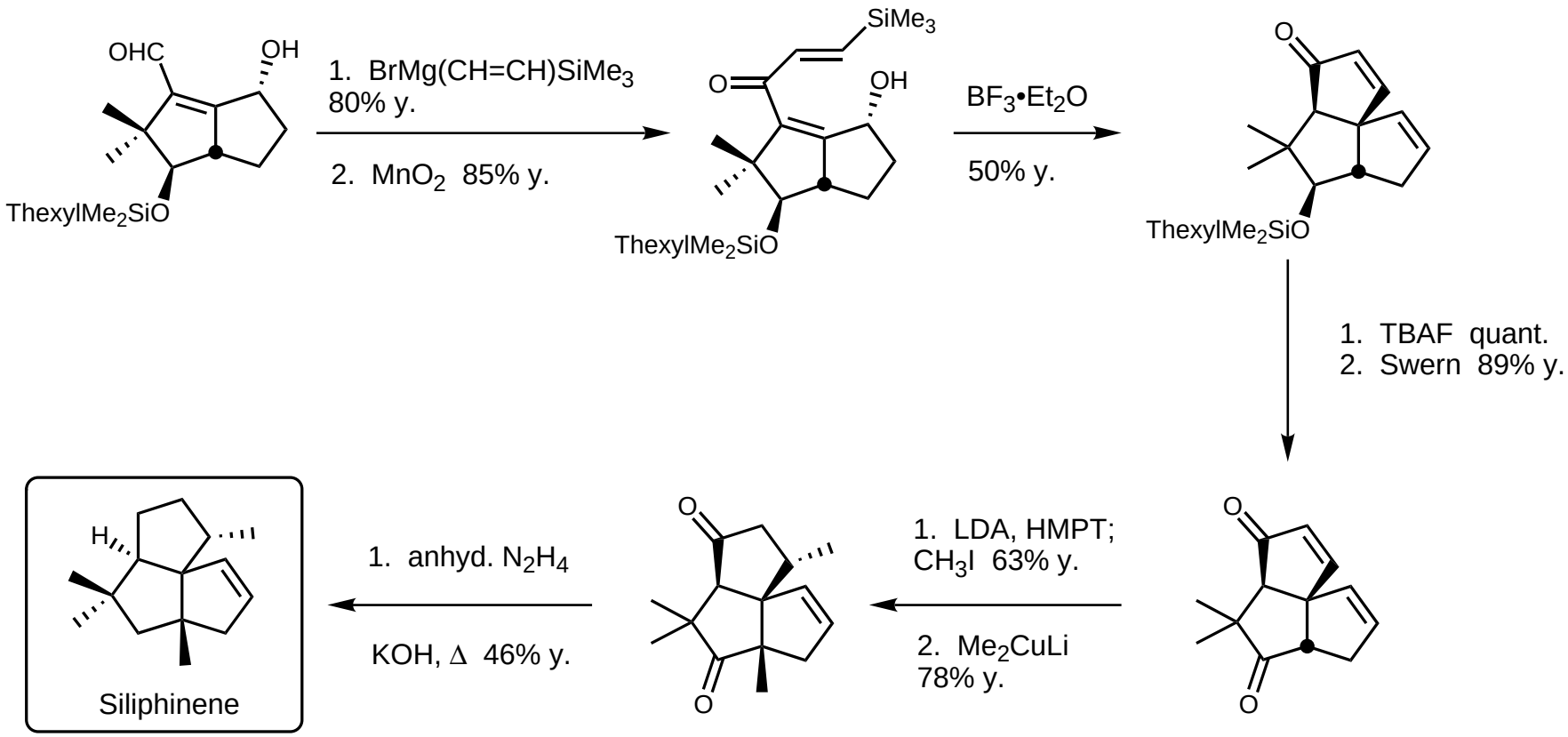
Silphinene: Retrosynthetic Analysis



(±)-Silphinene: [2+2] cycloaddition and Nazarov cyclization

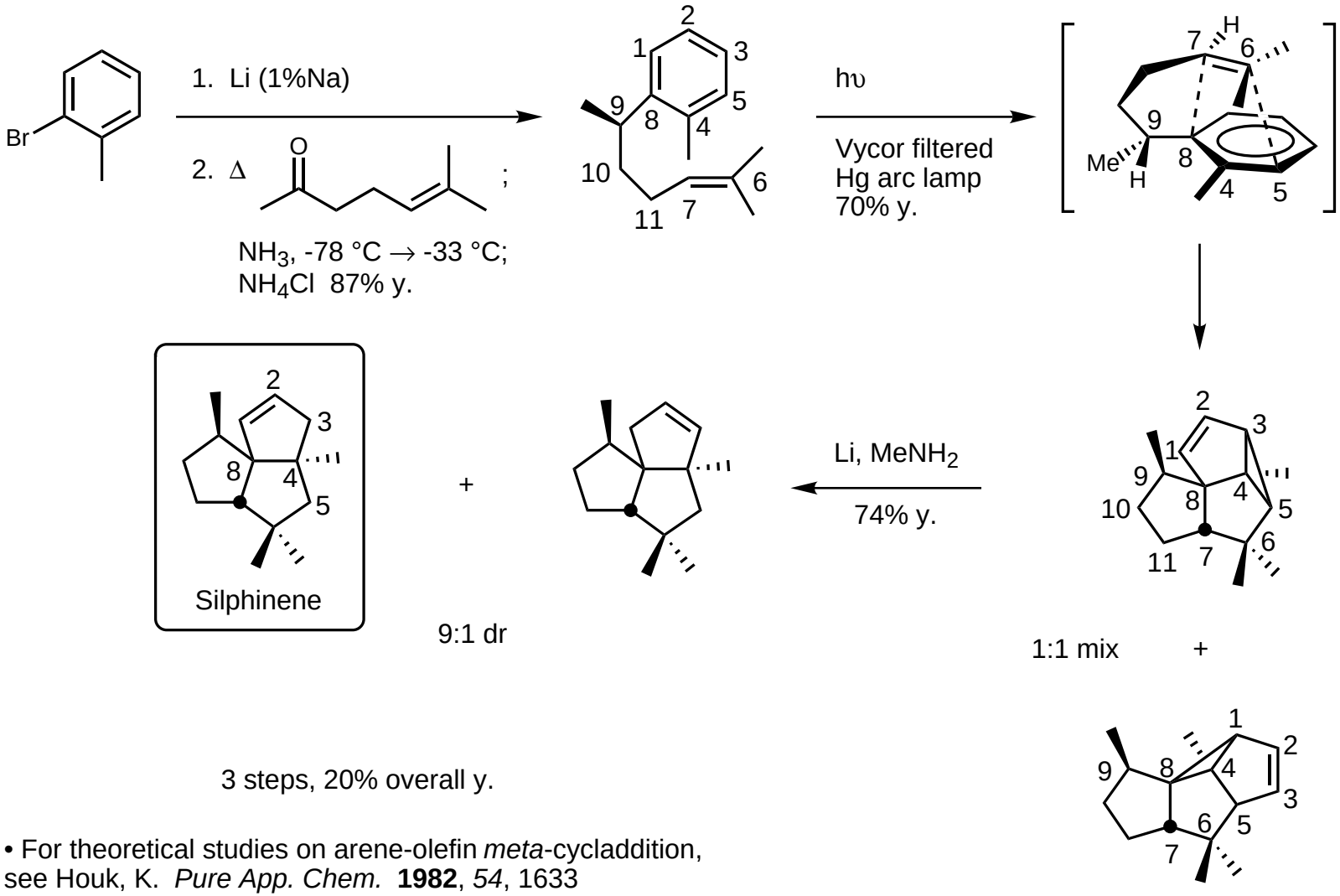


(±)-Silphinene: [2+2] cycloaddition and Nazarov cyclization



Franck-Neumann, M. *Tetrahedron* **1997**, *53*, 2103

(±)-Silphinene: Arene-Olefin *meta*-Cycloaddition

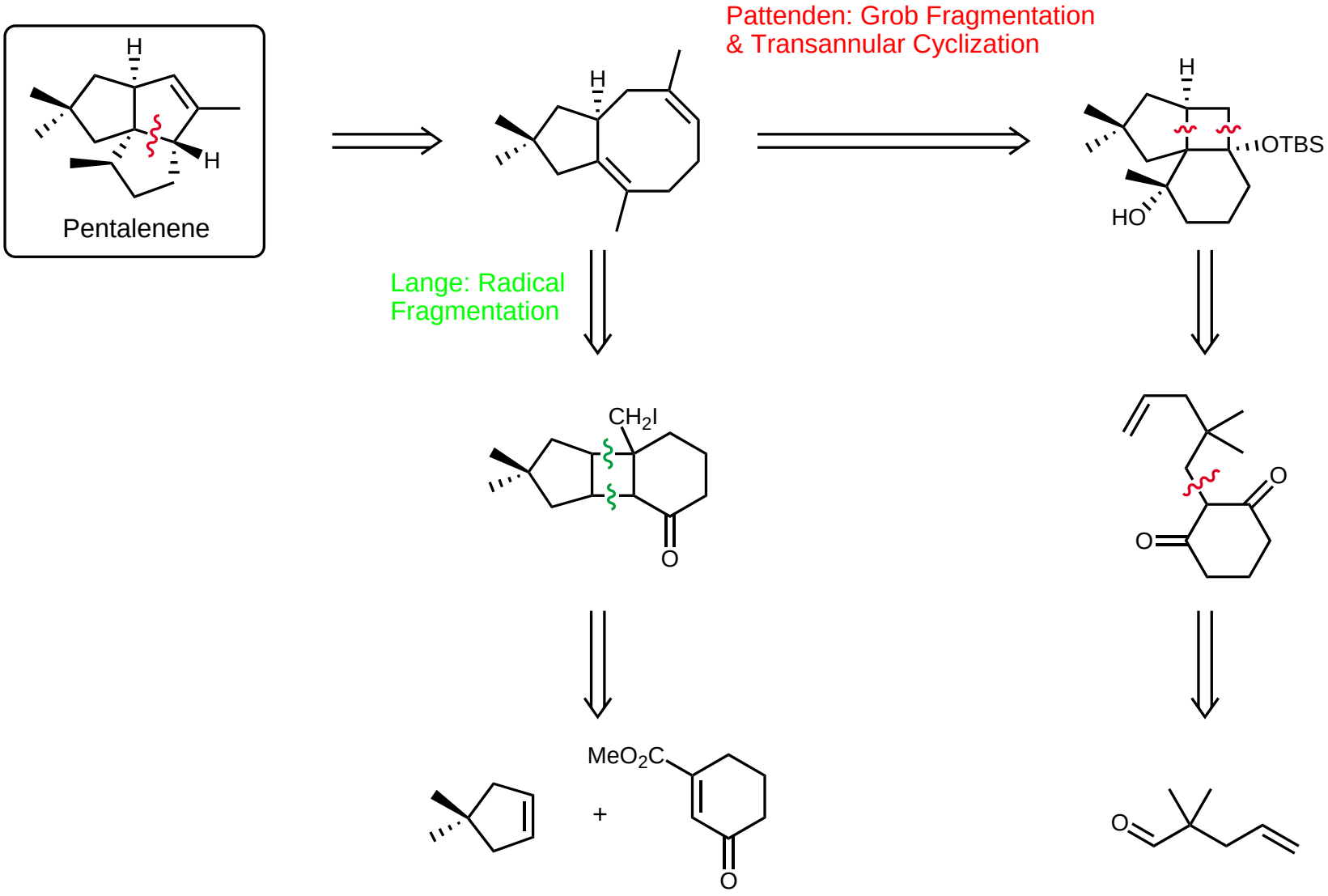


3 steps, 20% overall y.

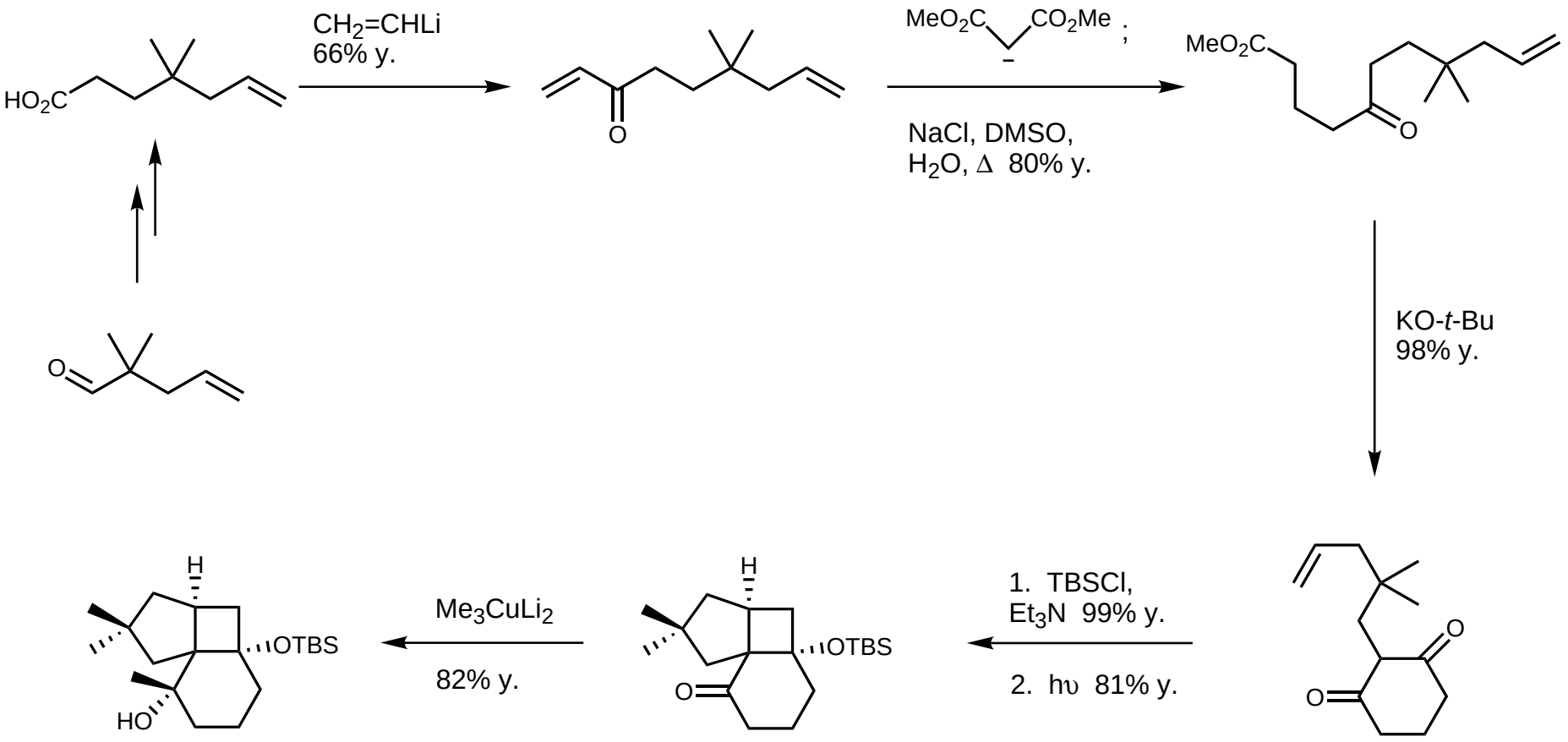
• For theoretical studies on arene-olefin *meta*-cycladdition, see Houk, K. *Pure App. Chem.* **1982**, *54*, 1633

Wender, P. A. *Tet. Lett.* **1985**, *26*, 2625

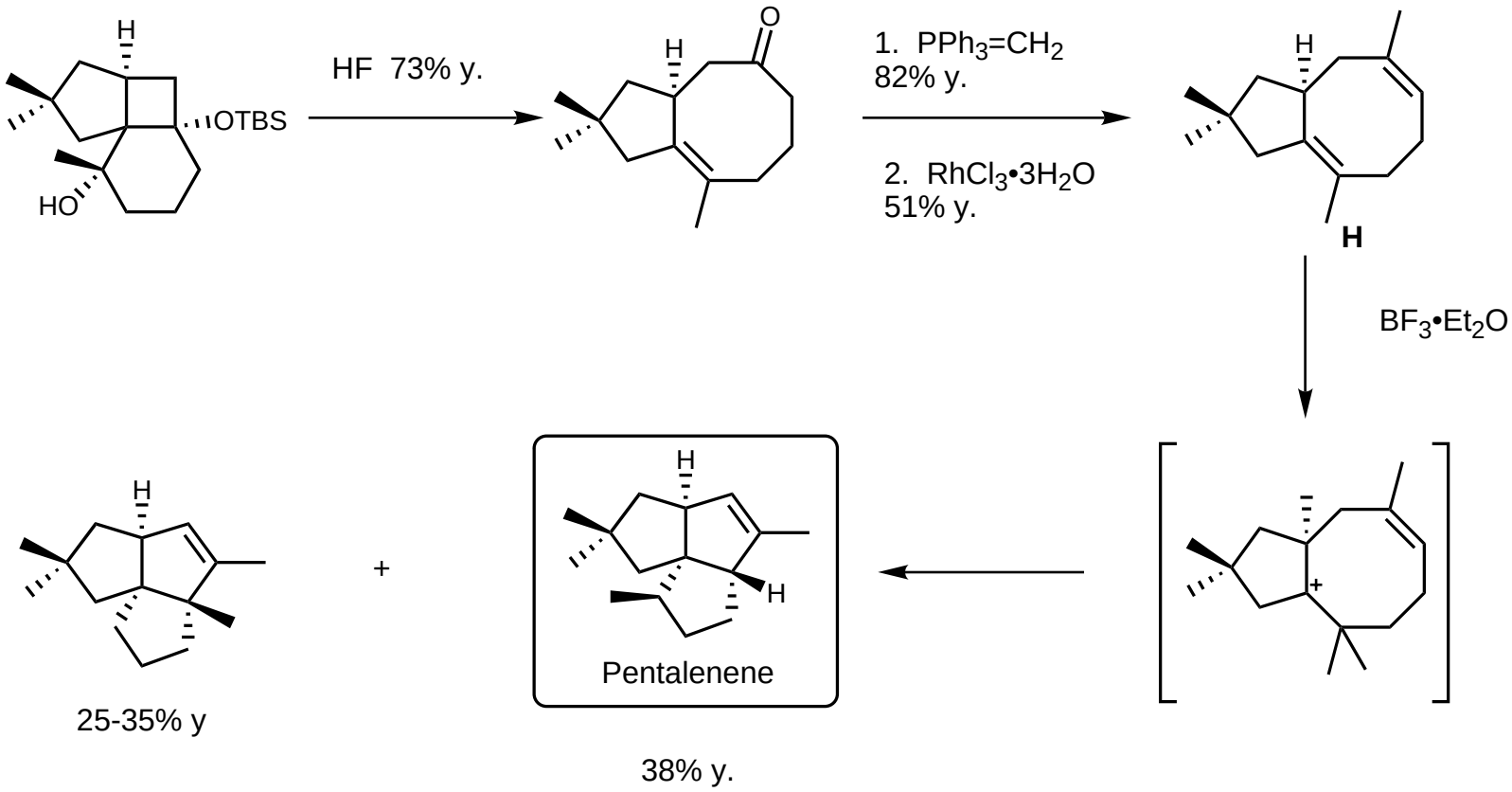
Pentalenene: Retrosynthetic Analysis



(±)-Pentalenene: Cationic Transannular Cyclization



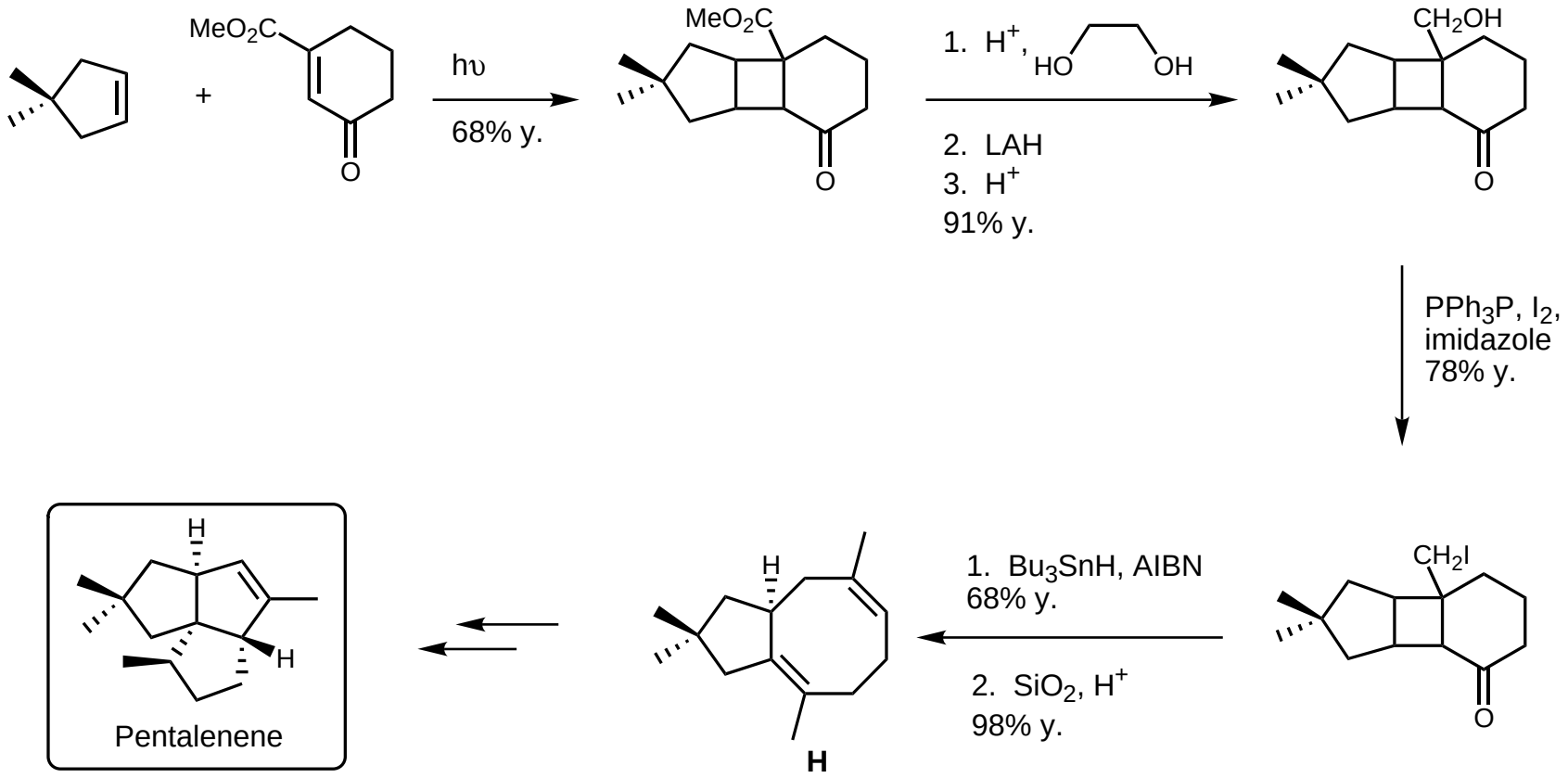
(±)-Pentalenene: Cationic Transannular Cyclization



11 steps, 4% overall yield

Pattenden, G. *Tetrahedron* **1987**, *43*, 5637

(±)-Pentalenene Precursor: Radical Fragmentation

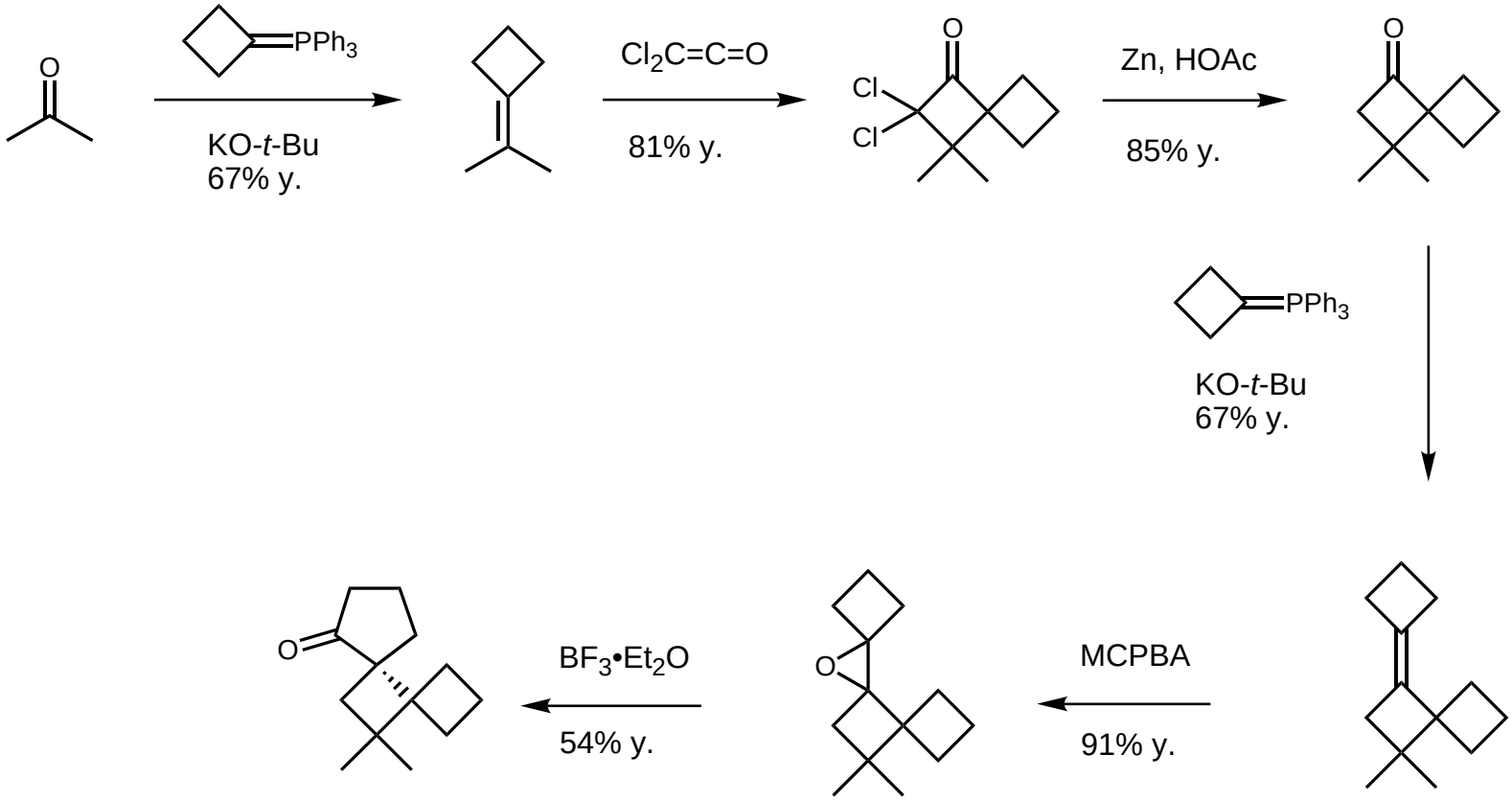


H

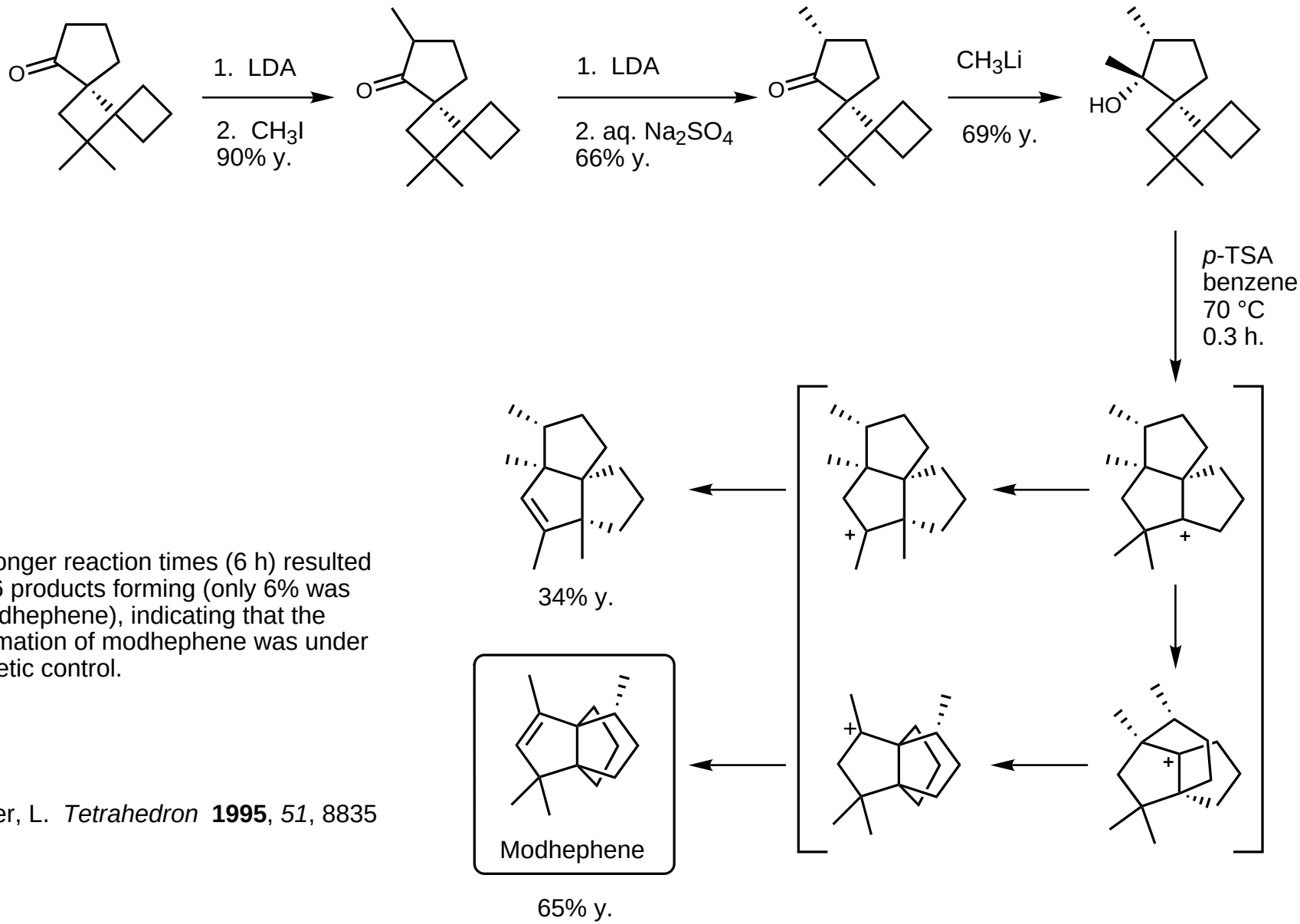
• For other syntheses of **H**, see Helquist, P. *Tet. Lett.* **1991**, *32*, 5753

Lange, G. L. *J. Org. Chem.* **1995**, *60*, 2183

(±)-Modhephene: Carbocation Rearrangements



(±)-Modhephene: Carbocation Rearrangements



• Longer reaction times (6 h) resulted in 6 products forming (only 6% was modhephene), indicating that the formation of modhephene was under kinetic control.

Fitjer, L. *Tetrahedron* **1995**, *51*, 8835