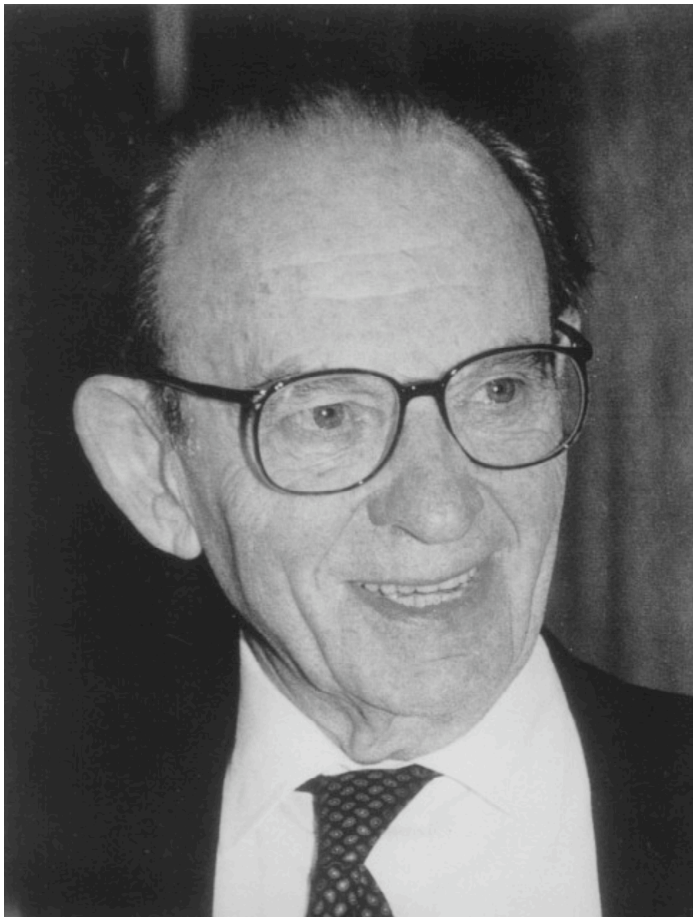


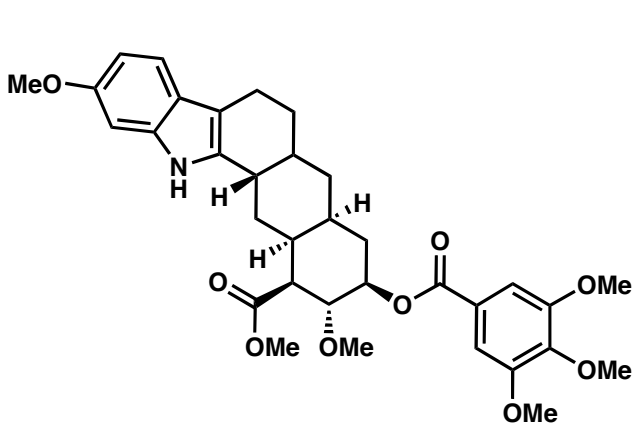
Gilbert Stork:

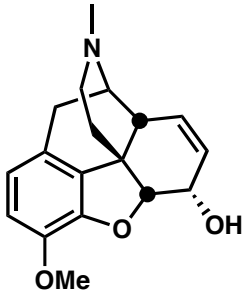
Explorations into Position Selectivity and Stereocontrol, a Synthetic Renaissance

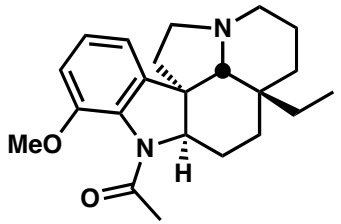
Jenn Stockdill

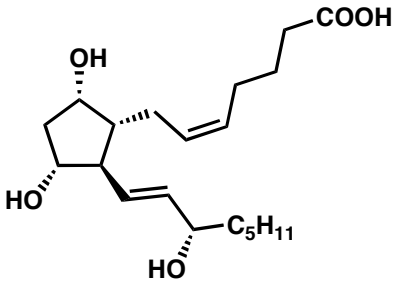
29 January 2007

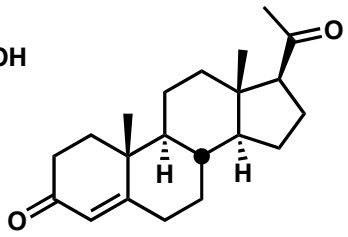
A Stoltz Group Literature Presentation

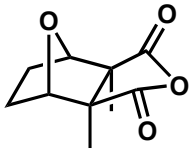


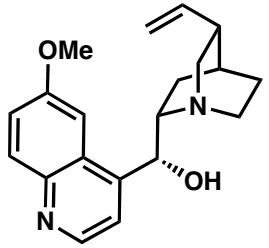












~Gilbert Stork~

- **Born: 31 December 1921 in Brussels, Belgium**
- **Secondary education in France (Paris and Nice)**
- **Moved to the United States in 1939**
- **B.S. at University of Florida in 1942**
- **Ph.D. at University of Wisconsin in 1945**
- **Harvard: 1946-1948 (Instructor) and 1948-1953 (Assistant Professor)**
- **Columbia University: 1953-1955 (Associate Professor), 1955-1967 (Professor), 1967-1993 (Eugene Higgins Professor), 1993-present (Eugene Higgins Professor Emeritus)**

1957 Award in Pure Chemistry, American Chemical Society
1959 Guggenheim Foundation Fellow
1961 D.Sc. (honorary), Lawrence University
1961 Baekeland Medal, North Jersey Section, ACS
1962 Harrison Howe Award
1966 Edward Curtis Franklin Memorial Award, Stanford University
1967 Award for Creative Work in Synthetic Organic Chemistry, ACS
1971 Gold Medal, Synthetic Organic Chemical Manuufacturers Association
1973 Nebraska Award
1978 Roussel Prize, Paris
1979 D.Sc. (honorary), Université Pierre et Marie Curie
1980 Nichols Medal, New York Section, ACS
1982 Edgar Fahs Smith Award, Philadelphia Section, ACS
1982 Willard Gibbs Medal, Chicago Section, ACS
1982 Award in Chemical Sciences, National Academy of Sciences
1982 D.Sc. (honorary), University of Rochester
1983 National Medal of Science
1983 Pauling Award
1985 Tetrahedron Prize
1986 Remsen Award, Maryland Section, ACS
1986 Cliff S. Hamilton Award, Nebraska
1987 Monie A. Ferst Award and Medal, Georgia Tech
1988 D.Sc. (honorary), Emory University
1991 Roger Adams Award
1992 George Kenner Award, Liverpool
1992 Robert Robinson Lectureship Award, U. K.
1992 D.Sc. (honorary), Columbia University
1993 Robert A. Welch Award
1996 Wolf Prize, Israel
1997 D.Sc. (honorary), University of Wisconsin

"Not many people have had a greater impact on modern organic chemistry than Gilbert Stork. His original and profound intellectual style strongly influence the way organic chemists now think about synthesis. In particular, the invention of a new reagent to solve a specific problem in total synthesis, and the inclusion of stereospecificity in a synthetic design are Stork trademarks."

From: http://www.chemistry.msu.edu/Portraits/PortraitsHH_Detail.asp?HH_LName=Stork

Outline

- ♦ **Stereochemistry of polyene cyclizations**
  - **Application to cyclopropyl ketones**
  - **Bicyclo[2.2.1]heptanes**

- ♦ **Enamine alkylation & acylation of ketones and aldehydes**
  - **Aspidospermine**
  - **Byssochlamic acid**
  - **Yohimbine alkaloids**

- ♦ **Regiospecific formation and trapping of enolates**
  - ◊ **via Addition of 2 e^- and 1H^+ to an enone**
    - **Lupeol**
    - ***dl*-D-Homotestosterone and *dl*-progesterone**
    - **Adrenosterone**
  - ◊ **Conjugate addition of an organometallic reagent to an enone**
    - **Lycopodine**
    - **Prostaglandin $F_{2\alpha}$**

- ♦ **Regiospecific deprotonation & trapping with saturated ketones**
  - **β-Vetivone**

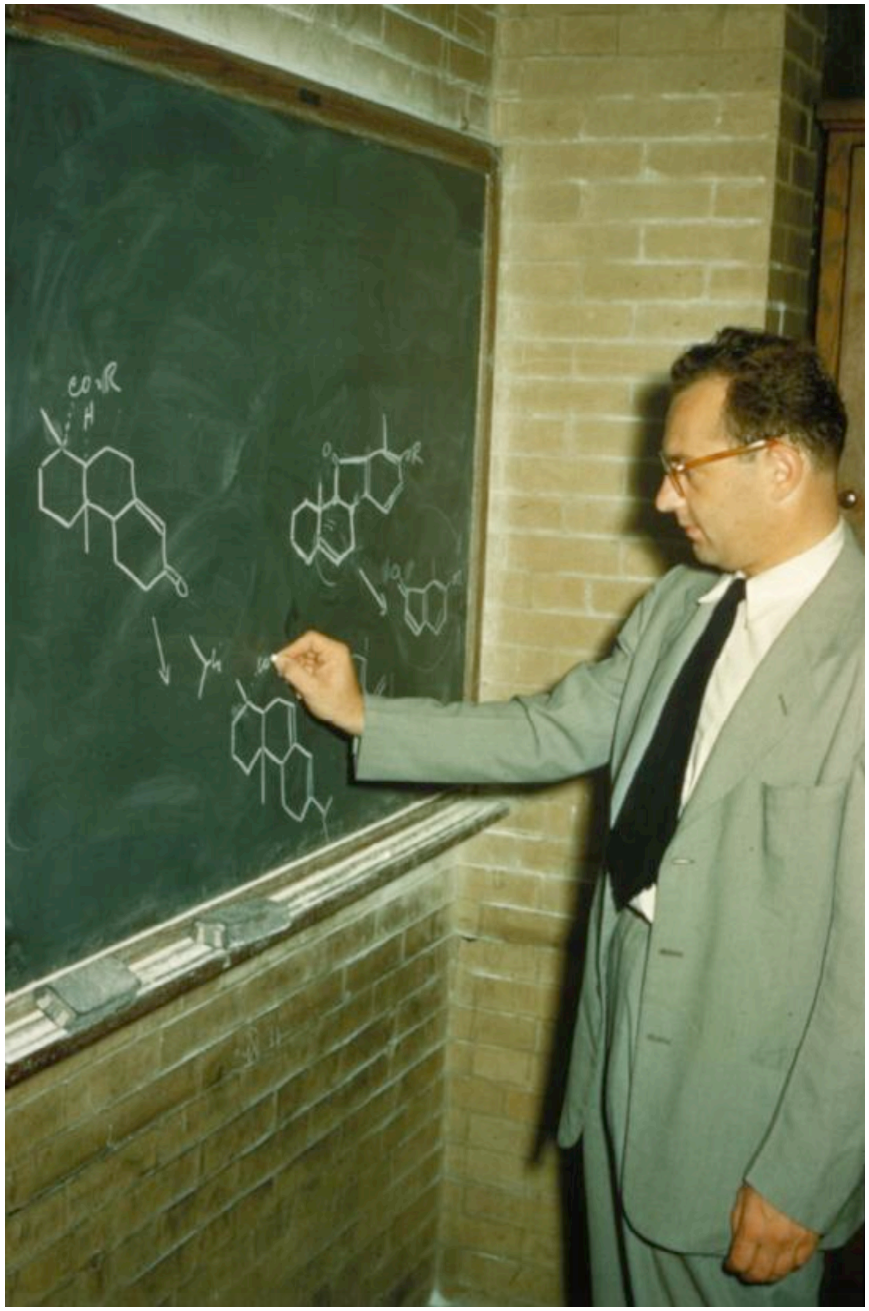
- ♦ **Cyano-epoxide and allylic-epoxide carbocyclizations**
  - **Histrionicotoxin**

- ♦ **Cyclization of alkynyl ketones**
  - **Gibberellic acid**

- ♦ **Protected cyanohydrins as acyl carbanion equivalents**
  - **Taxol**
  - **Prostaglandin $F_{2\alpha}$**

- ♦ **Vinyl radical cyclization**
  - ***rac*-Patchouli alcohol**
  - **(+)-Digitoxigenin**

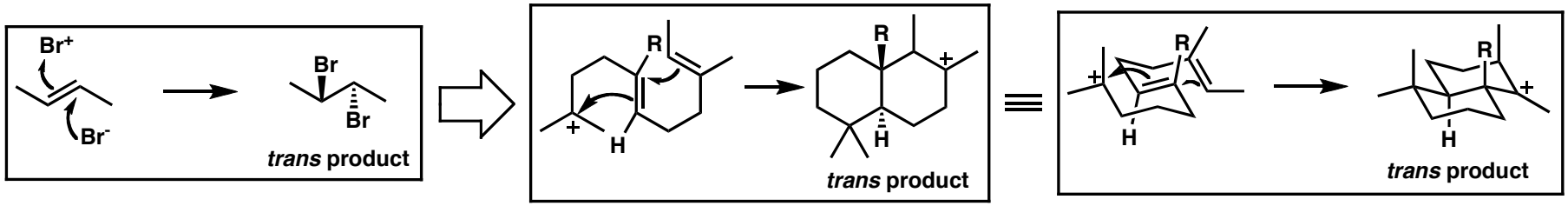
- ♦ **Radical cyclization to form a temporary ring**
  - ◊ **Mixed acetal linkage**
    - **12a-deoxytetracycline**
    - **Calcitriol**
  - ◊ **Temporary silicon connection**



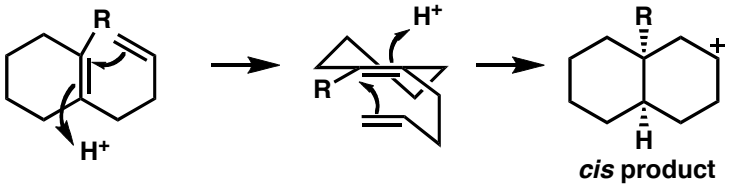
Key Review: *Medicinal Research Reviews* **1999**, *19*, 370-387.

Polyene Cyclizations

- **The idea: a cationic olefic cyclization should proceed analogously to the dibromination of an olefin.**

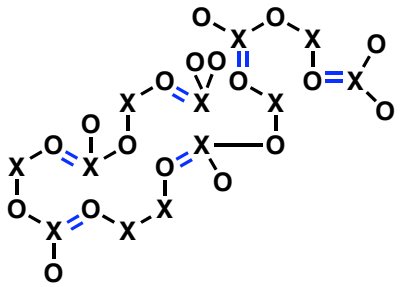


- **Note: When the precursor to the cationic cyclization contains a 6-membered ring, the product will have a *cis*-fused ring junction.**

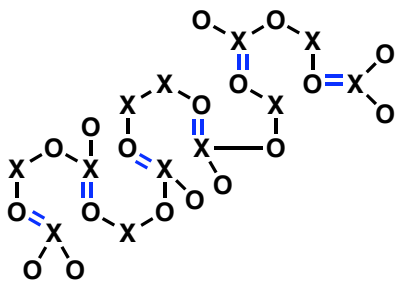


- **Harvard Colloquium March 14, 1950: Stork suggests a *concerted* polyene cyclization as the mechanism for steroid formation in natural triterpene steroids based on their *trans-anti-trans* ring junctions.**

- *JACS* **1953**, *75*, 2023: **Woodward proposes this idea as the mechanism for squalene cyclization to for cholesterol (below)**
- *JACS* **1955**, *77*, 5068: **Stork's Propsal of synthetic routes to Lupeol, Lanosterol, and Cholesterol**
- **Stork, ACS Meeting, San Diego, CA March 2005: "The sincerest form of flattery?"**



A



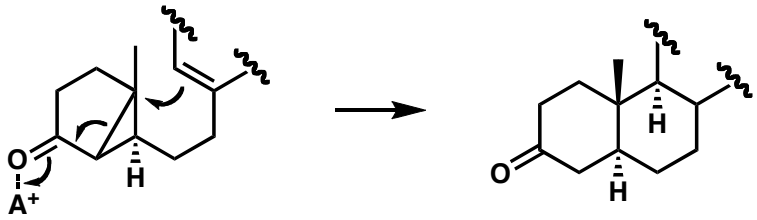
B

"We now wish to propose the alternative mechanism shown in Fig. 1B, as a more likely one to be involved in this transformation."

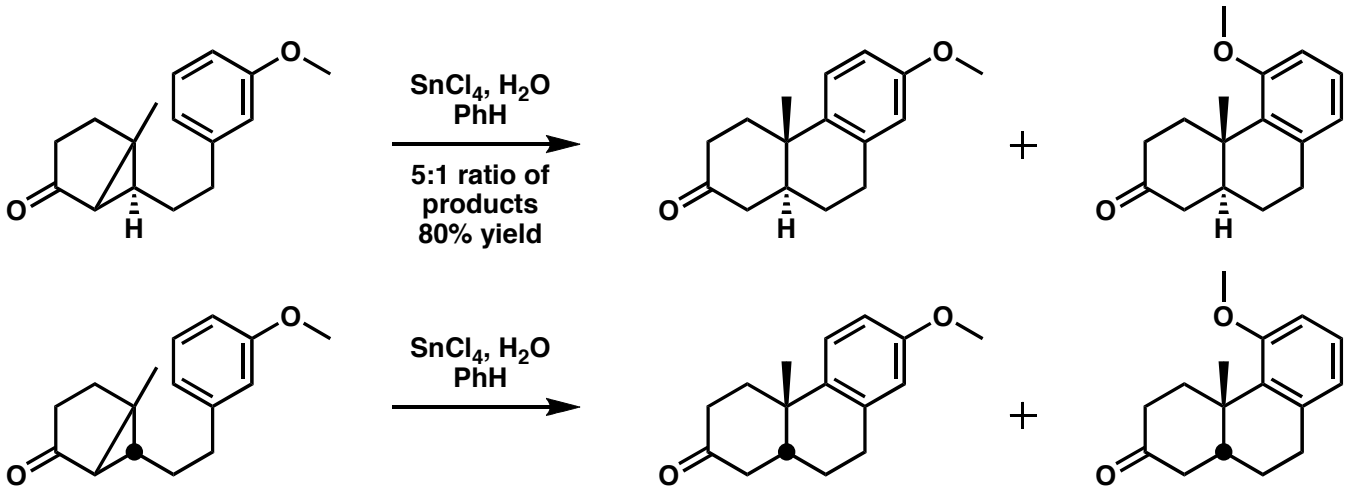
~R.B. Woodward and Konrad Bloch

Acyl Cyclopropanes in Cationic Cyclizations

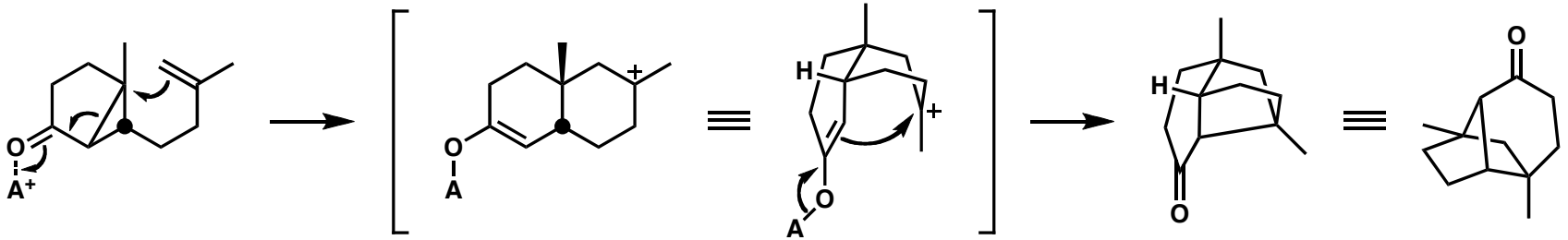
- **C(3)-keto groups in steroid systems could be synthesized directly and the ring junction formed stereoselectively.**
  (*JACS* 1969, *91*, 2371)
  For acyl cyclopropane synthesis, see: Stork *JACS* 1961, *83*, 4678.



- **Cyclopropyl cleavage was determined to be *concerted* with bond formation by stereochemical studies (*JACS* 1969, *91*, 2373)**



- **Synthesis of bicyclo[2.2.1]heptanes (*JACS* 1969, *91*, 2407):**

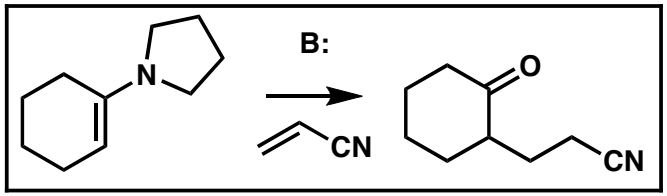


Enamine Alkylation and Acylation

Key Features:

- **Allows alkylation in presence of unsubstituted α-methylenes, giving acess to mono-alkylated products**
- **Allows alkylation with electrophilic olefins, including Michael acceptors**
- **Alkylation of α-monosubstituted ketones gives further alkylation at the α' position**
- **Alkyl halide electrophiles must be particularly active**

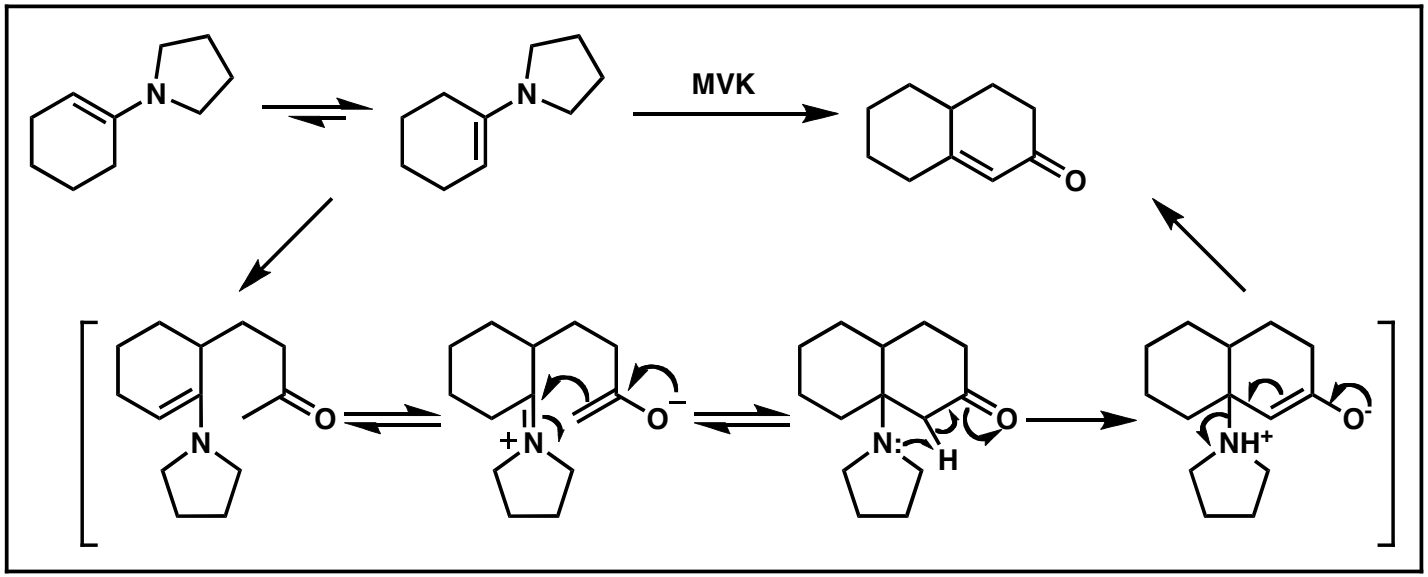
(*JACS* 1954, *76*, 2029, *JACS* **1956**, *78*, 5128, **and** *JACS* **1963**, *85*, 207**)**



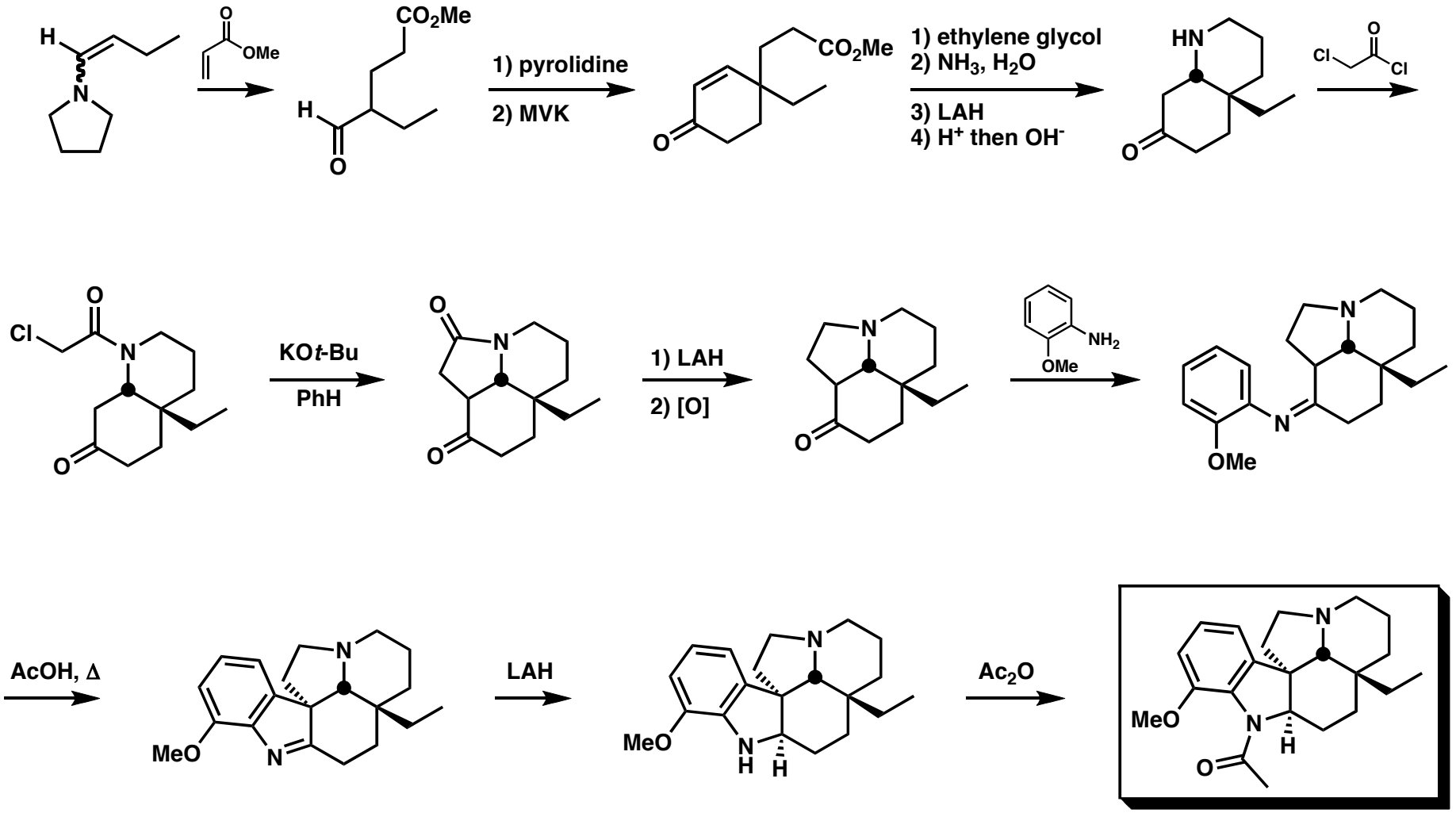
Later, the *Metalloenamine Alkylation* was developed...features:

- **Works with unreactive alkyl halides**
- **Allows mono-alkylation**
- **Can use Grignards or LDA and an electrophile**
- **works with *N,N*-dimethylhydrazones as well (further developed by Corey & Enders)**

(*JACS* **1963**, *85*, 2178 **and** *JACS* **1971**, *93*, 5938**)**

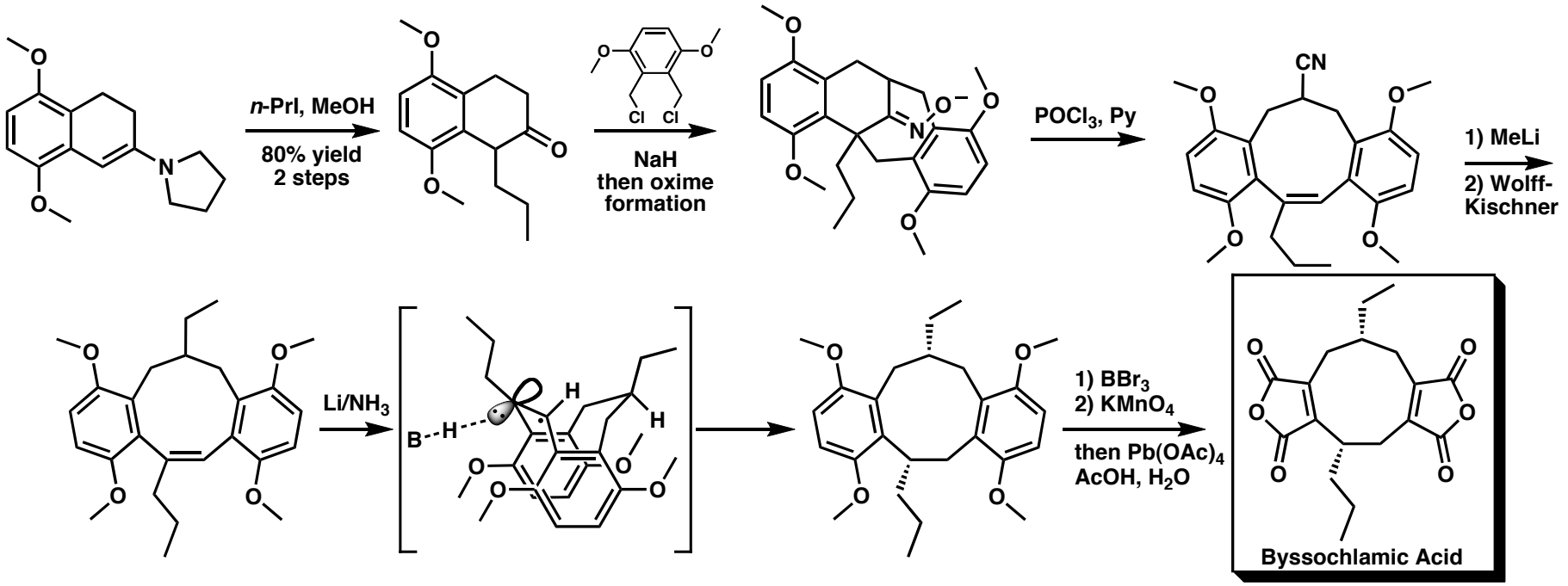


Total Synthesis of Aspidospermine

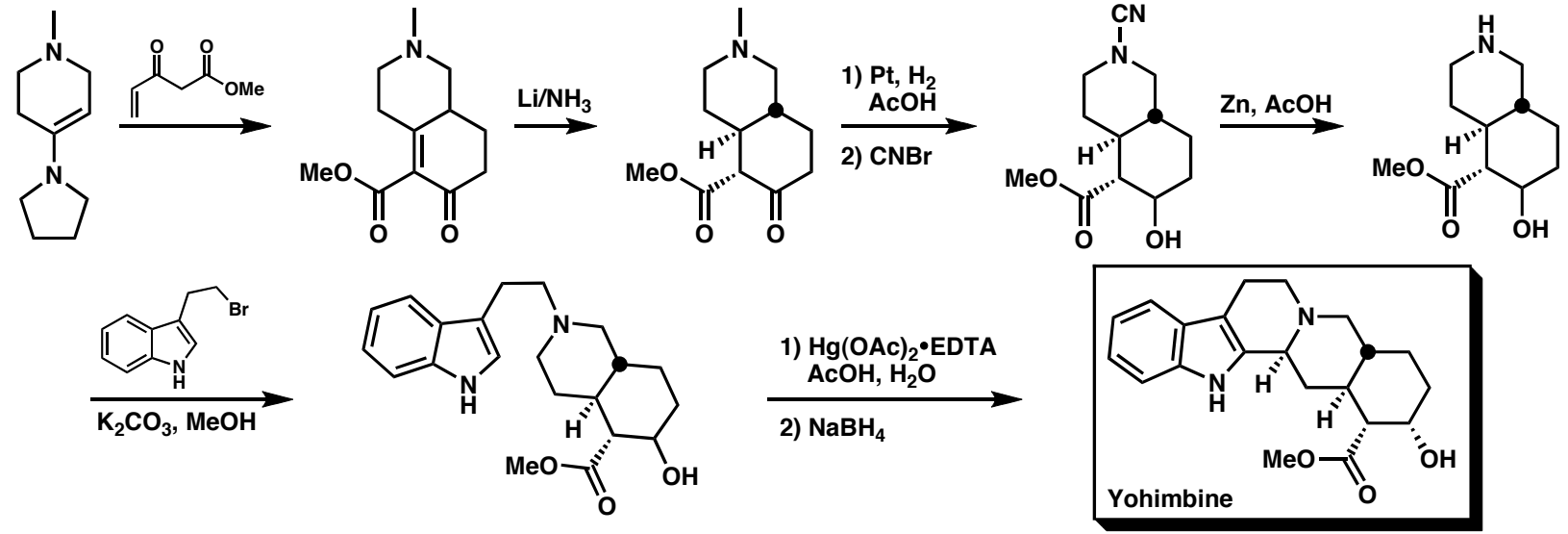


JACS **1963**, *85*, 2872

Byssochlamic Acid and Yohimbine



JACS **1972**, *94*, 4735

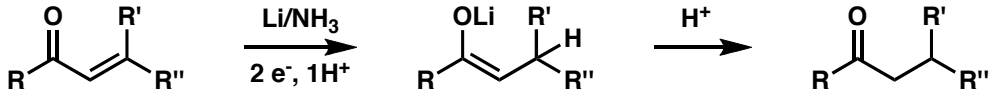


JACS **1972**, *94*, 5109

Regiospecific Formation/Trapping of Enolates

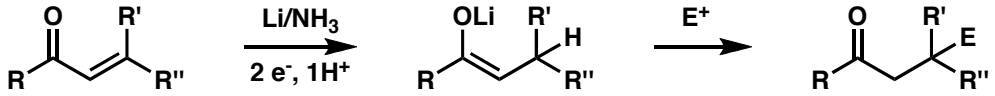
Adding $2e^-$ and $1H^+$ to an Enolate

- **Regiospecific alkylation was a big problem, and it often required blocking the undesired site.**
- **Metal/ammonia reduction of an α,β–unsaturated keton proceeds through an intermediate enolate, which is formed regiospecifically!**

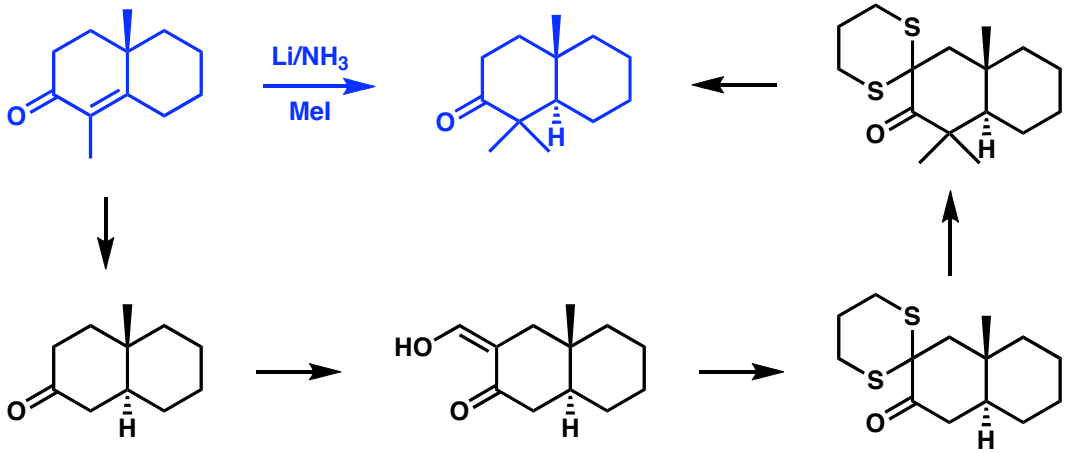


- **If it is a Li enolate, alkylation is faster than protonation.**

JACS **1961**, *83*, 2965



- **This is a good way to save steps:**

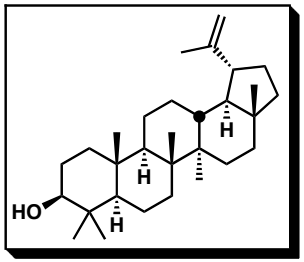


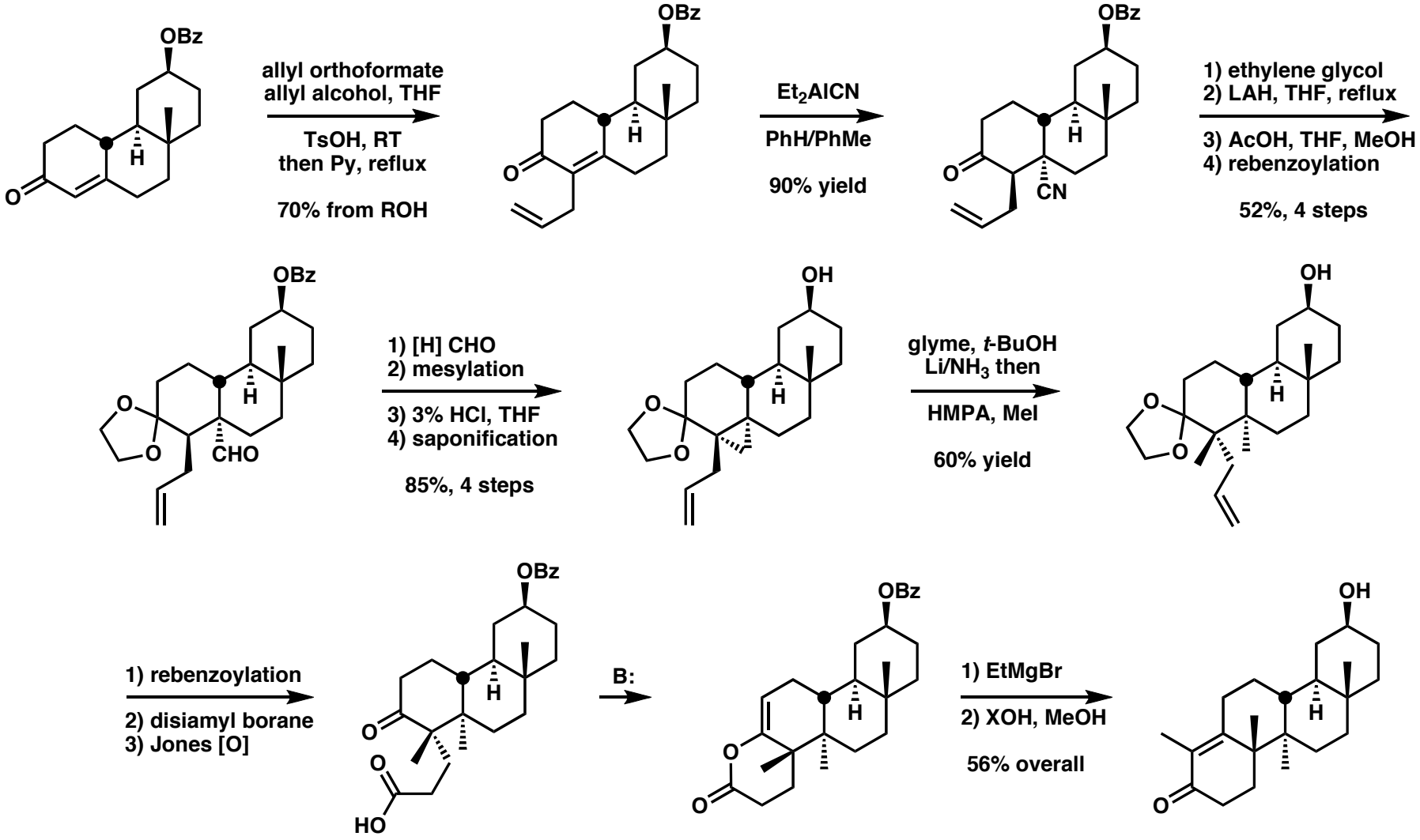
JACS **1965**, *87*, 275

- **Also a good technique for reductive alkylation of enediones, useful in the synthesis of corticosteroids.** *JACS* **1980**,*102*, 1218 **and** *JACS* **1980**,*102*, 1219

- **Examples in total synthesis (that I don't have time to discuss): *dl*-D-homotestosterone and *dl*-progesterone (***JACS* **1967**, *89*, 5464**) and Adrenosterone (***JACS* **1982**,*104*, 3767**).**

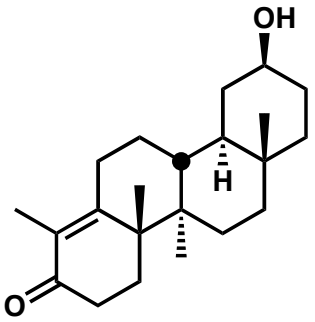
Total Synthesis of Lupeol





JACS **1971**, *93*, 4945

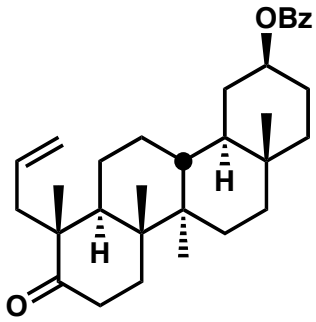
Total Synthesis of Lupeol



1) Li/NH_3
allyl bromide

2) rebenzoylation

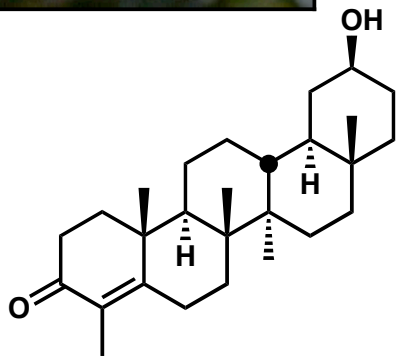
80%, 2 steps



1) ethylene glycol
2) disiamyl borane
3) Jones [O]

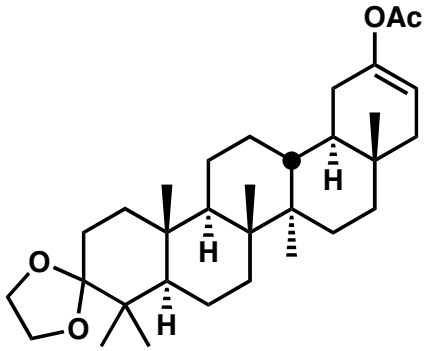
4) EtMgBr
5) XOH, MeOH

50% overall



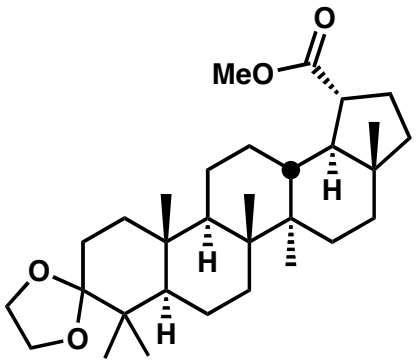
1) Li/NH_3, MeI
2) ethylene glycol

3) [O]
4) $NaHMDS$, Ac_2O



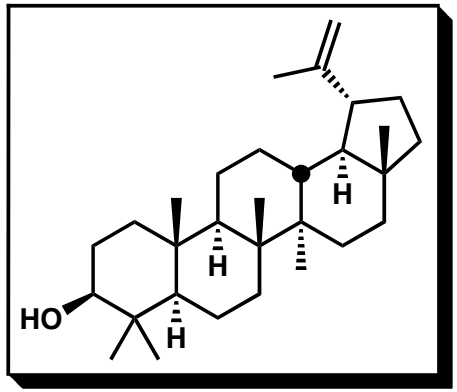
1) O_3, $NaBH_4$
NaOH
2) AcOH

3) CH_2N_2
4) TsCl
5) NaHMDS, PhH



1) MeLi, dioxane
2) $POCl_3$, Py

3) deketalization
4) $NaBH_4$



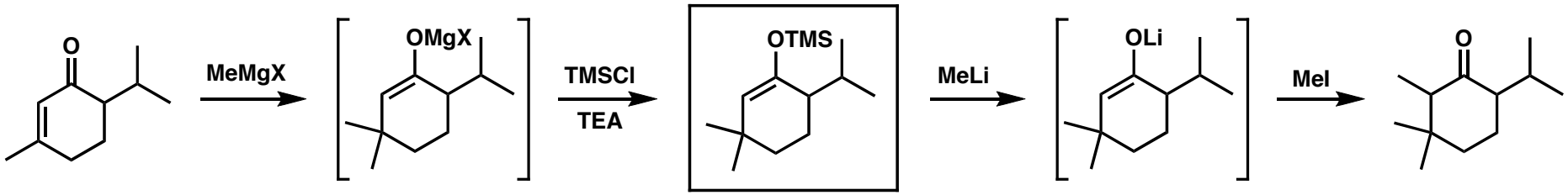
JACS **1971**, *93*, 4945

Regiospecific Formation/Trapping of Enolates

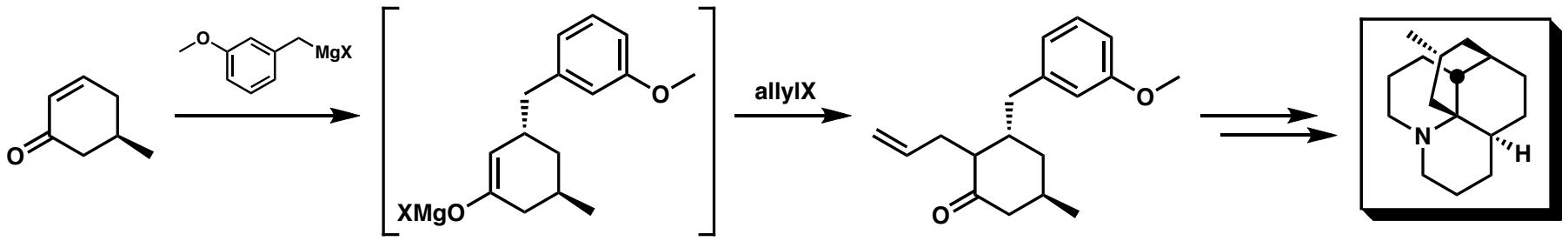
Conjugate Addition of an Organometallic Reagent into an Enolate

- **Another alternative developed to avoid blocking groups, this time allowing effective β-alkylation by conjugate addition.** *JACS* **1968**, *90*, 4462 **and** *JACS* **1968**, *90*, 4464

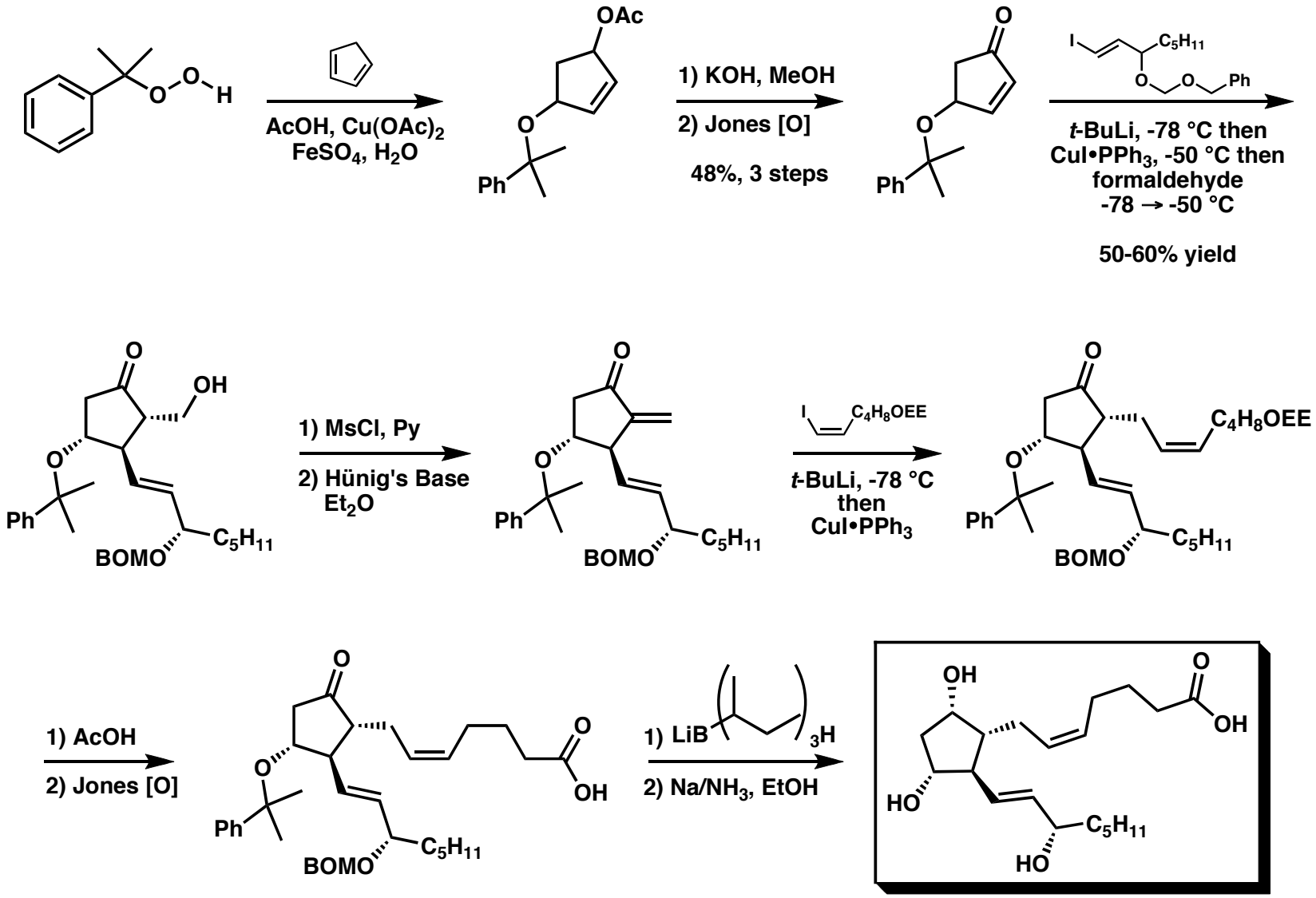
- **Trapping the enolate as a silyl enol ether was key to the general applicability of this method, allowing addition of the trapped enolates to α,β-unsaturated systems.**



- **From the total synthesis of Lycopodine (***Pure Appl. Chem.* **1968**, *17*, 383**):**



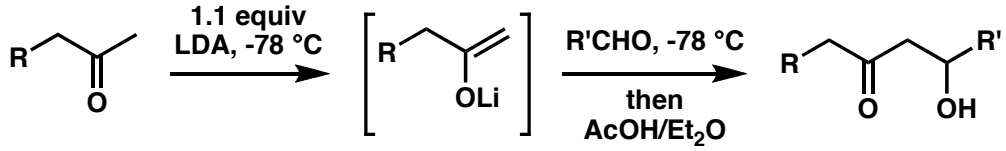
Total Synthesis of Prostaglandin F2α



JACS **1975**, *97*, 6260

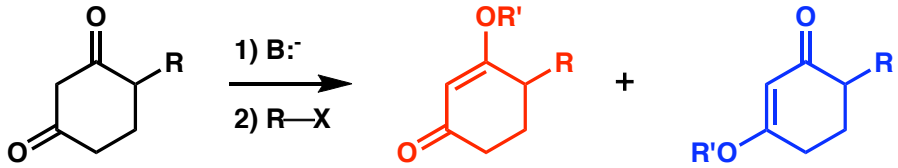
Regiospecific Deprotonation-Trapping with Saturated Carbonyls

- **Key finding thus far: Lithium enolates are special!**
- **Eventually discovered that even kinetic enolates capable of undergoing qeuilibration to the thermodynamic enolate retain their regiochemical fidelity.**
- **For methyl ketone enolates, this development made *inter*molecular aldol reactions possible by trapping with an aldehyde.** *JACS* **1974**, *39*, 3459.



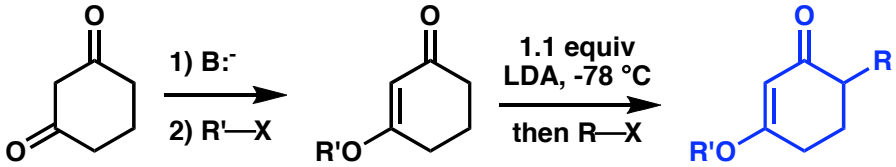
- **A very useful and well-known application of the regiospecific deprotonation: alkylation of β-alkoxy enones (Stork-Danheiser!)** *JOC* **1973**, *38*, 1775

Previously:

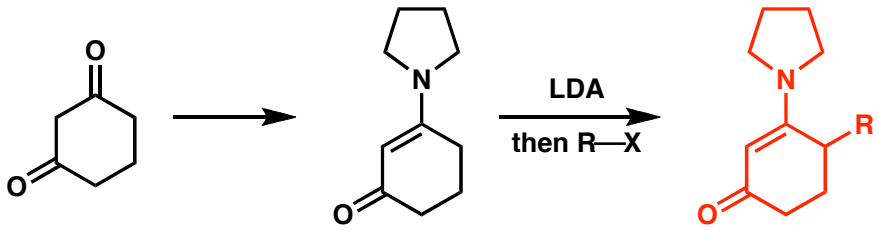


Mixture of products!

Solution: A kinetic lithium enolate

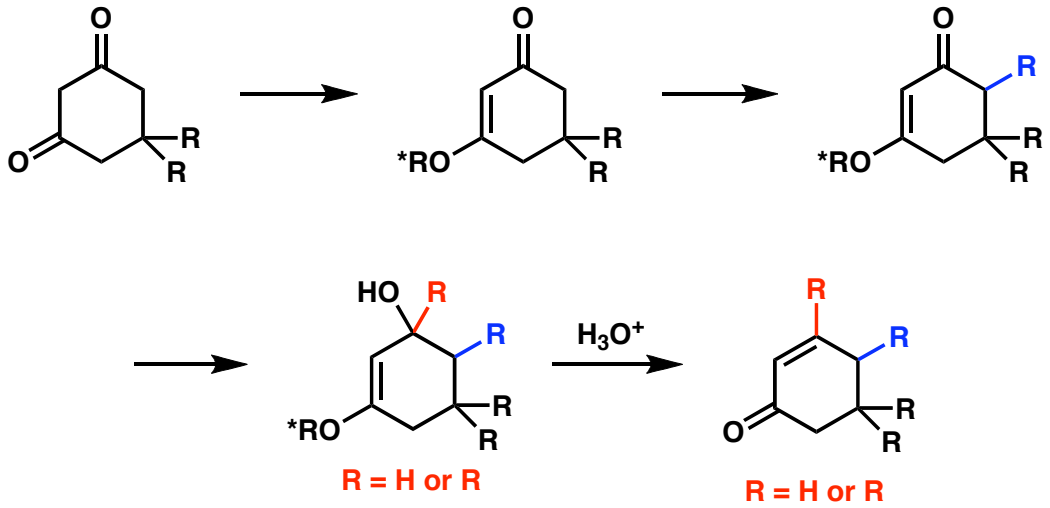


AND the other product is still available through enamine alkylation chemistry!

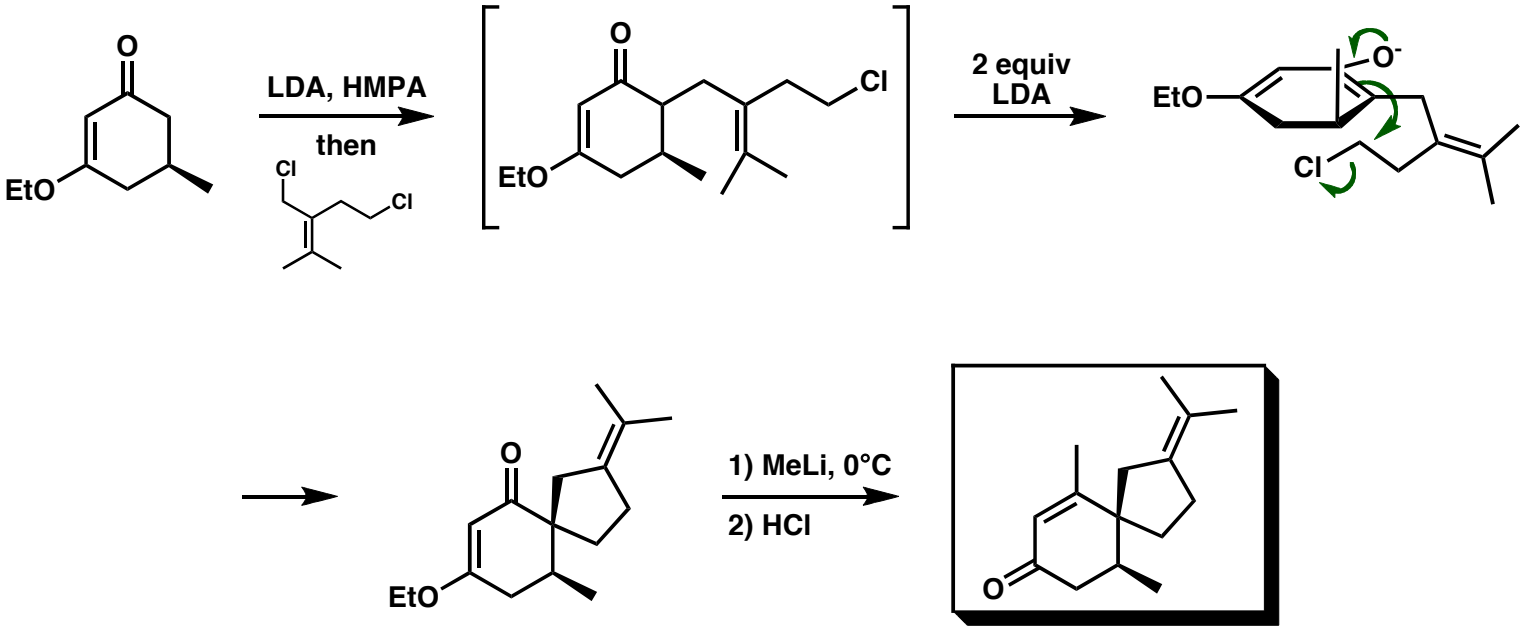


Poly-Alkylations and Synthesis of β-Vetivone

- **In Stork-Danheiser chemistry followed by dehydration, the conjugated enone is always formed, no matter how stable the β,γ-isomer is.**



- **Total synthesis of β-vetivone.** *JACS* **1973**, *95*, 3414



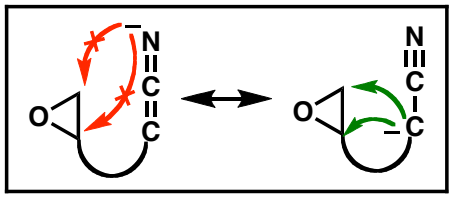
Cyano-Epoxide Cyclizations

- **Key: The α anion of a nitrile is unusually effective in opening even tetrasubstituted epoxides in a position- and stereo-controlled and predictable manner.**

- **Nitrile features (*JACS* 1974, *96*, 5268):**

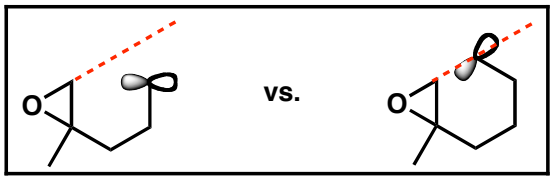
1) High nucleophilicity as a result of the low acidity of the α-methylene.

2) Displacement by the anion delocalized on the heteroatom is geometrically impossible for normal ring sizes.

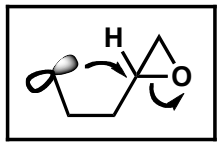


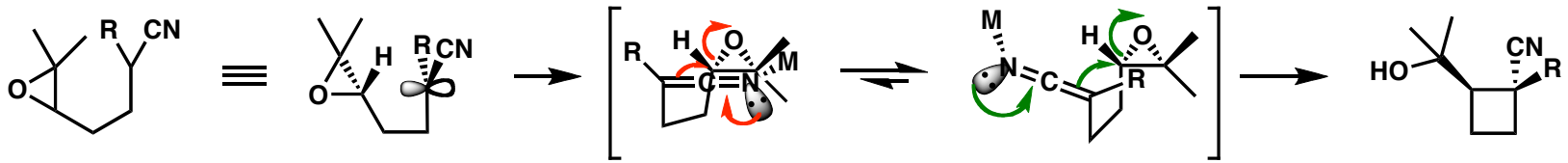
- **Enolates either do not cyclize or give the *O*-alkylated product.**

- **If the cyclization is an *endo* S_N2-type epoxide opening, the 6-membered ring forms *faster* than the corresponding 5-membered ring system would because no distortion is needed to acheive the necessary angle of approach. *JOC* 1974, *96*, 5270**



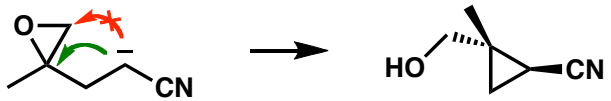
- **The 4-membered ring is similarly well-poised, but for an *exo* cyclization. It proceeds stereospecifically to the *trans* product.**





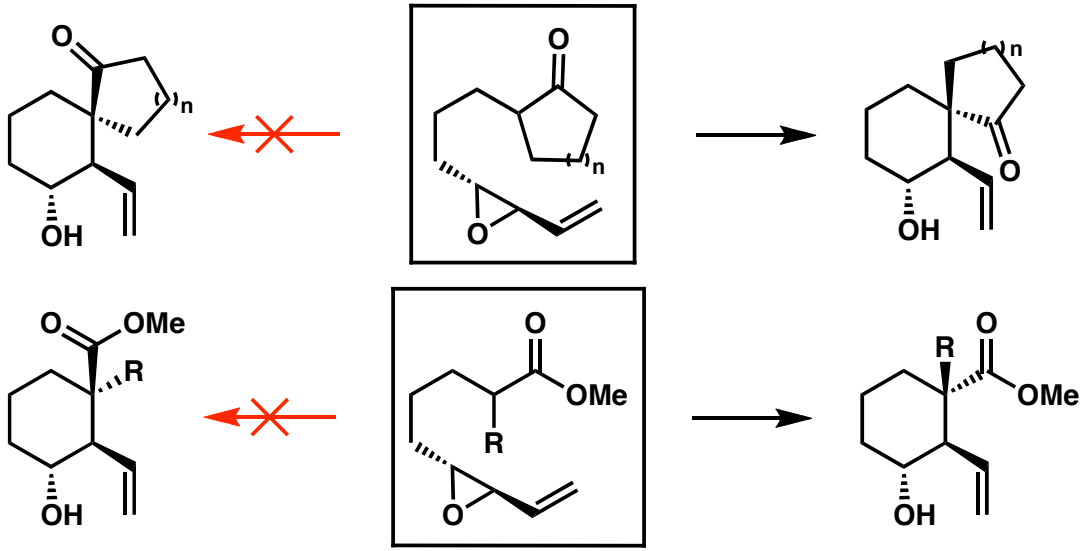
***The effective steric hinderance of a cyano anion is larger than a normal alkyl group.**

- **Given an equal degree of substitution on either side of the epoxide, the smaller ring (*exo* product) will always form.**
- **A cyclopropane ring will always form in preference to a cyclobutane ring, regardless of the substitution on the epoxide.**

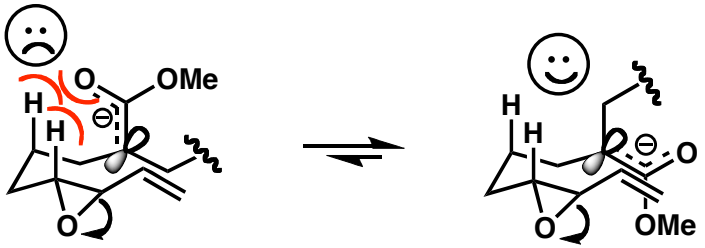


Allylic Epoxide Cyclizations

- **Ketone enolates can be used in conjunction with *trans*-substituted allylic epoxides to form cyclized products.**
- **This is particularly useful if you want to make a 6-membered ring out of an equally substituted epoxide.**
- **The cyclizations proceed analogously when a disubstituted ethynyl group is used in place of the olefin. (*JACS* 1990, *112*, 1661)**



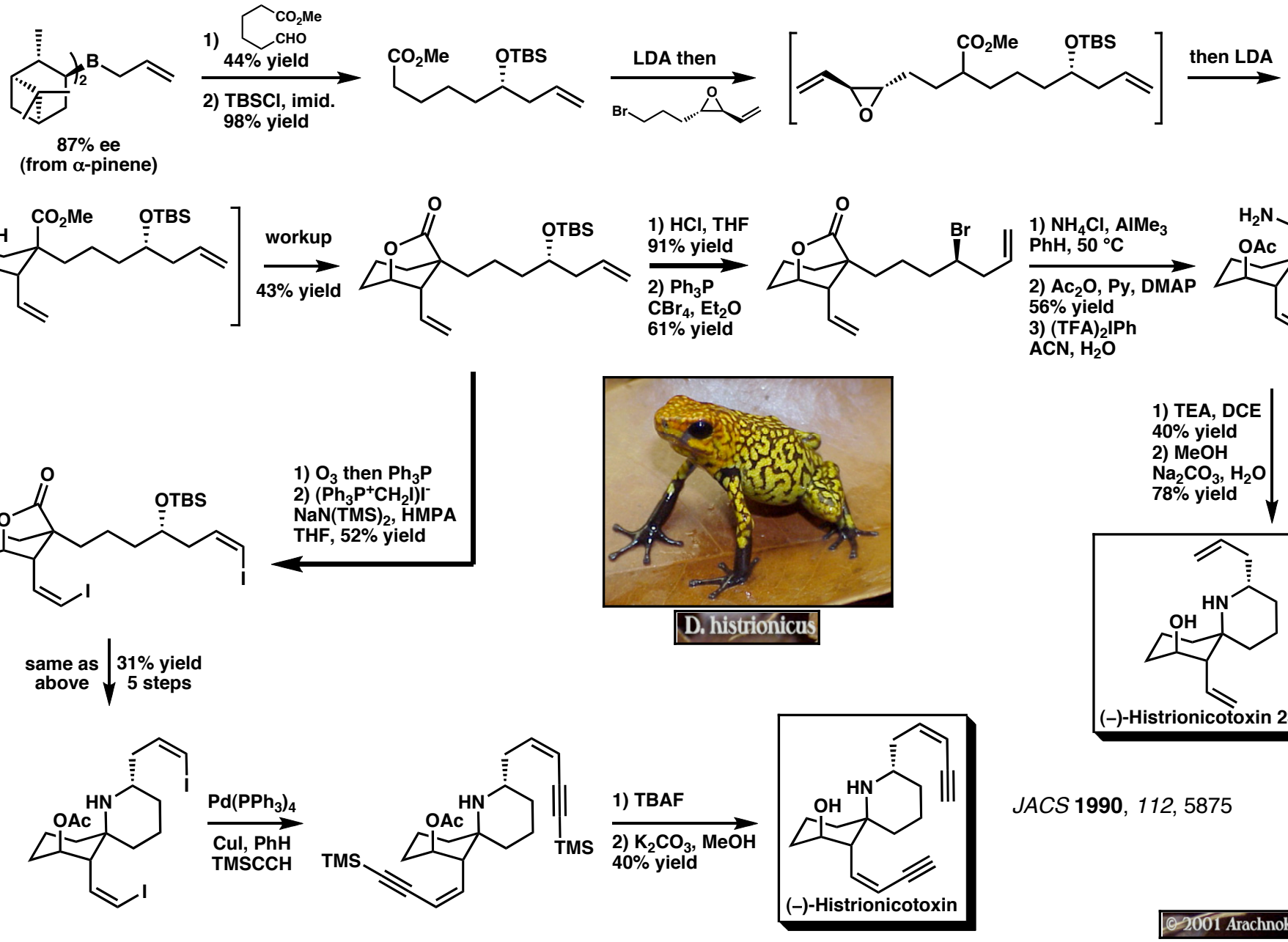
- **Stereochemical Interpretation:**



axial enolate **equatorial enolate**

In both cases, the carbanion orbital is perpendicular to the plane of the carboxylate, so all orbitals are correctly alligned.

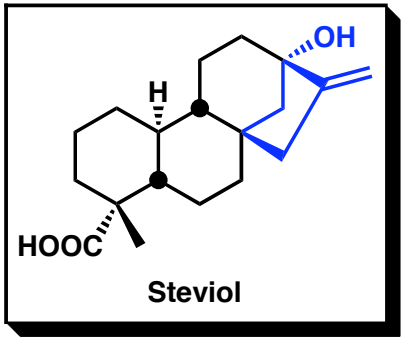
Total Syntheses of (–)-Histrionicotoxin and (–)-Histrionicotoxin 235A



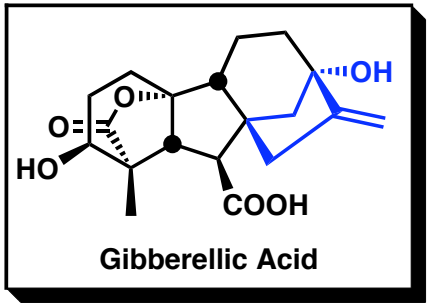
JACS **1990**, *112*, 5875

Cyclization of Alkynyl Ketones

- **Inspiration for this work came from natural products such as Steviol and Gibberellic Acid.**

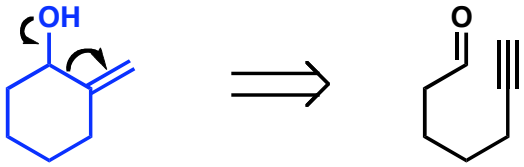


Steviol

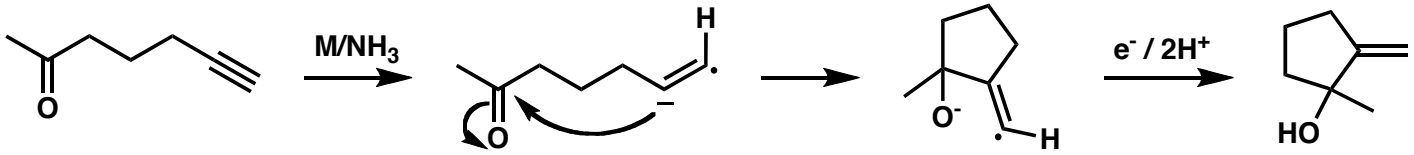


Gibberellic Acid

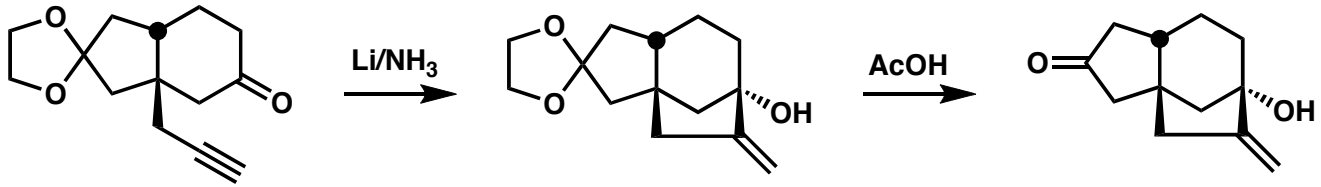
- **A retrosynthetic analysis reveals the synthon:**



- **Stork reveals the method!**



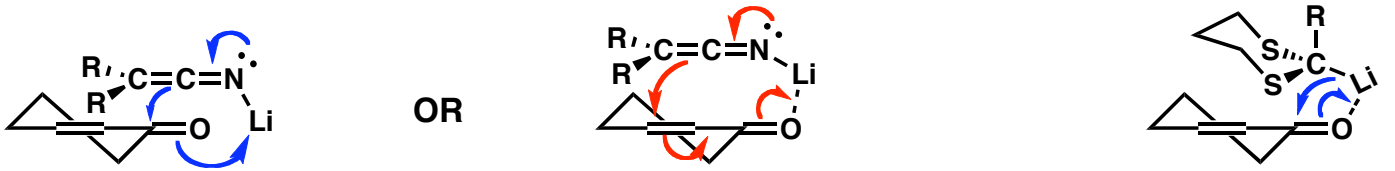
- **Toward Giberellic Acid:**



JACS **1965**, *87*, 1148**,** *JACS* **1979**, *101*, 7107**, and** *JACS* **1979**, *101*, 7109

Protected Cyanohydrins as Acyl Carbanion Equivalents

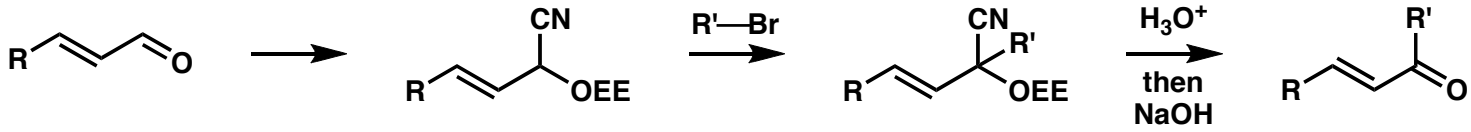
- **Protected cyanohydrins undergo conjugate addition to enone systems. A common acyl carbanion equivalent, the dithiane, generally undergoes 1,2-addition (*JACS* 1971, *93*, 5286 and *JACS* 1974, *96*, 5272):**



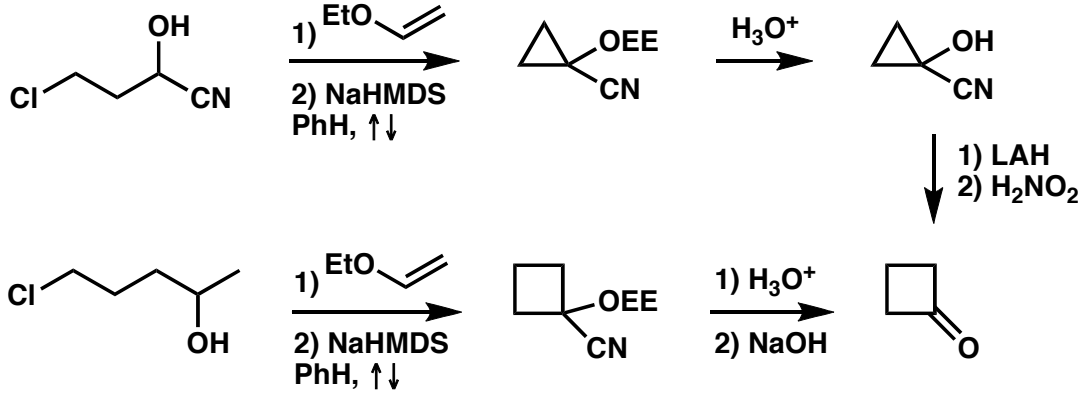
1,2-addition* 1,4-addition* 1,2-addition ONLY

*NOTE: Steric hinderance in the R groups or near the carbonyl of the enone lead to more 1,4-addition.

- **α,β-Unsaturated aldehydes can be made into α,β-unsaturated ketones:**

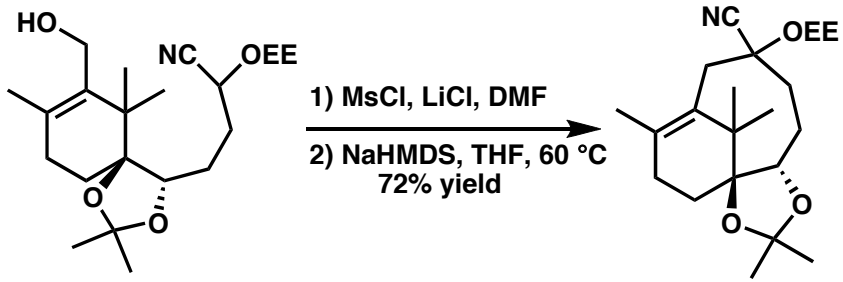


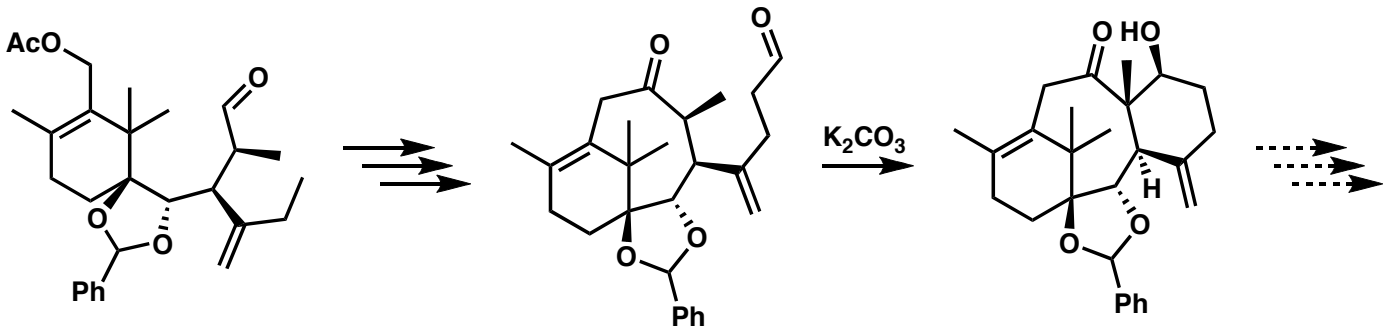
- **Protected cyanohydrins are useful for small ring synthesis (*TL* 1975, 389):**



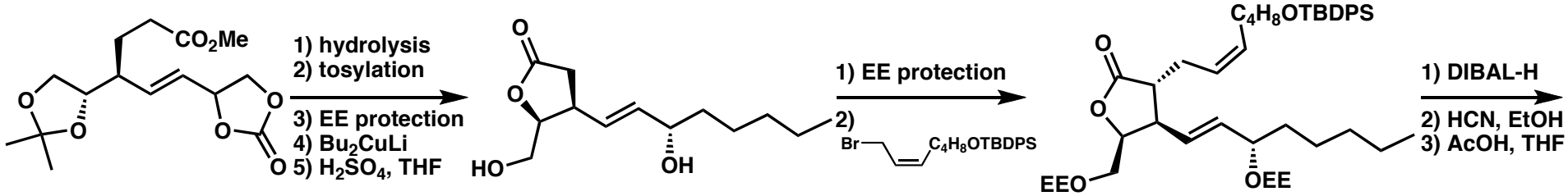
Application to the ABC Rings of Taxol and to Prostaglandin F2α

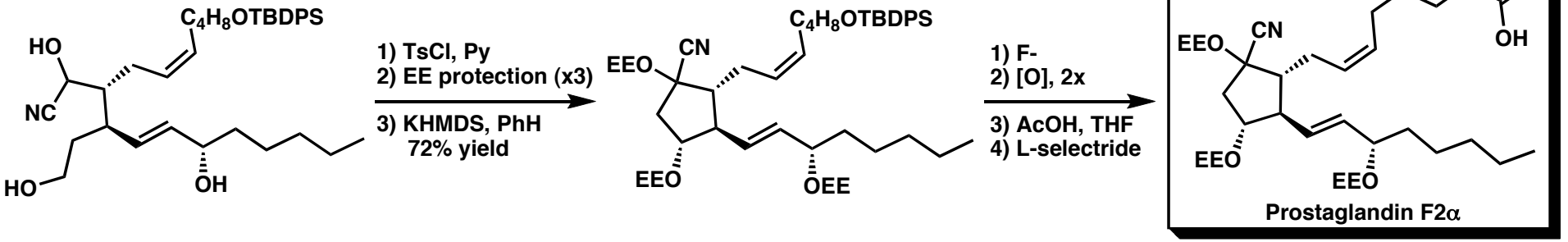
• **Model System:**
(*TL* **1997**,*38*, 7471)





JACS **1998**,*120*, 1337

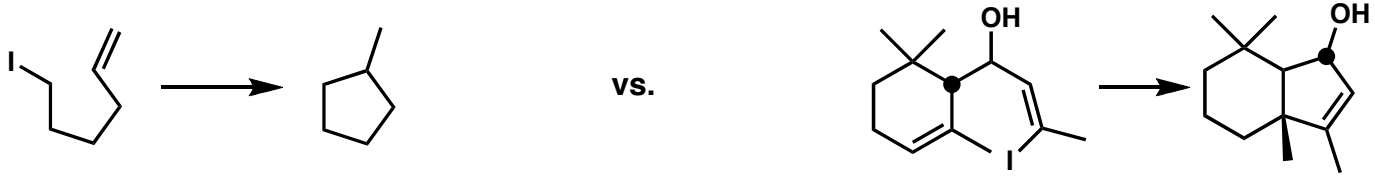




JACS **1978**, *100*, 8272

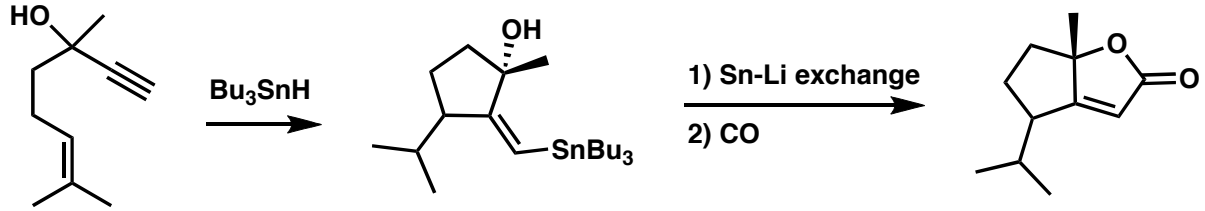
The Vinyl Radical Cyclization

- **Goal: To build rings with a predictably placed olefin, which could be used as a functional group handle, unlike the alkyl radical cyclization, which results in a saturated ring. (*JACS* 1982, *104*, 2321)**

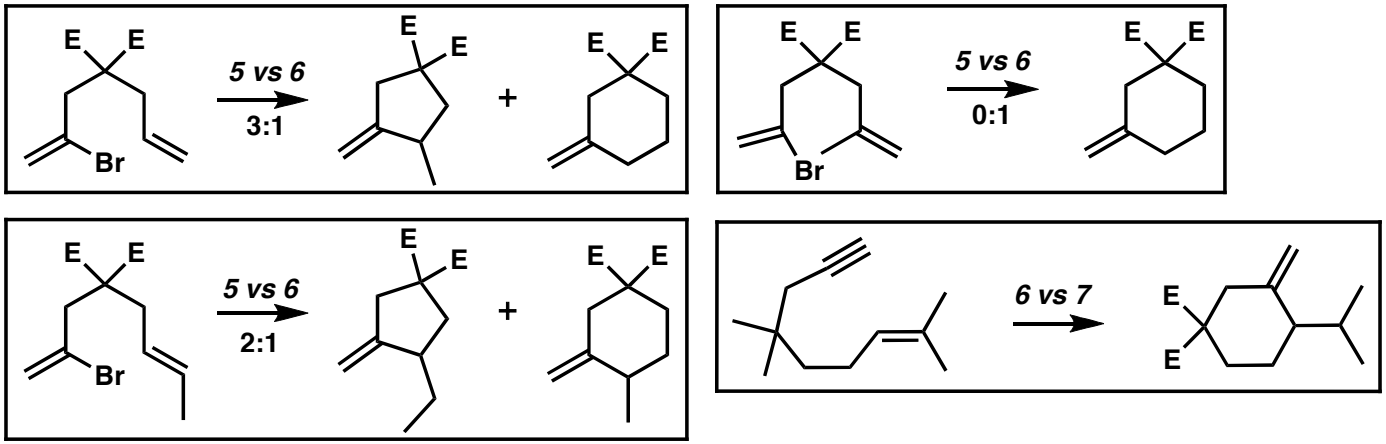


Other Advantages:

- **Smaller steric hinderance than even an alkyl radical.**
- **More reactive than an alkyl radical.**
- **Earlier transition state may decrease the effect of sterics even further.**
- **Can be generated from vinyl halides (generated by alkylation with a substituent containing a vinyl halide, Corey reductive halogenation of ethynyl carbinols, or addition of HBr to a terminal acetylene) or by addition of Bu_3SnH across an alkyne. (*JACS* 1987, *109*, 2829)**
  The vinyl stannane product can be reduced to an olefin or further manipulated.

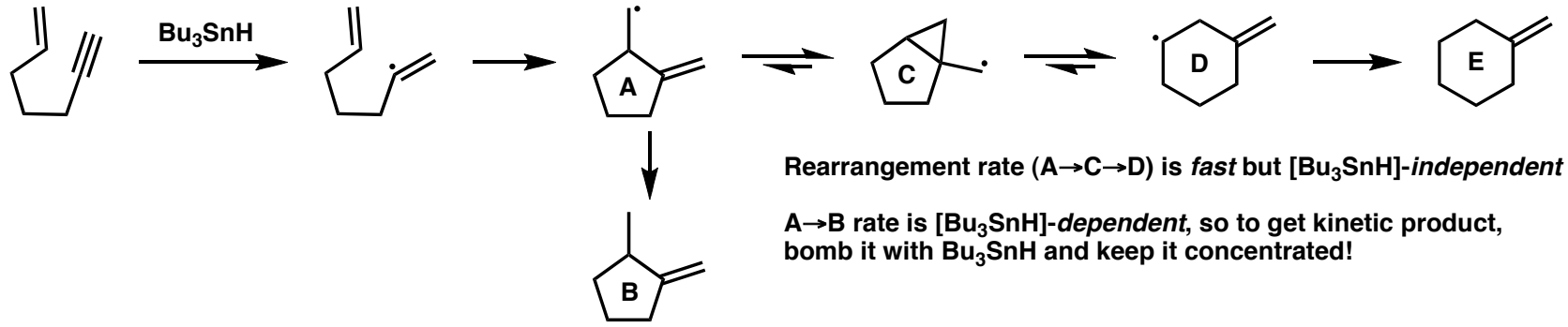


- **Kinetics vs. Thermodynamics... similar to ratios observed for alkyl radical cyclizations.**



The Vinyl Radical Cyclization

- **The product ratio is a bit more tunable in the case of vinyl stannane-derived radicals.**
  (*JACS* 1987, *109*, 2829 and *TL* 1986, *27*, 4529)

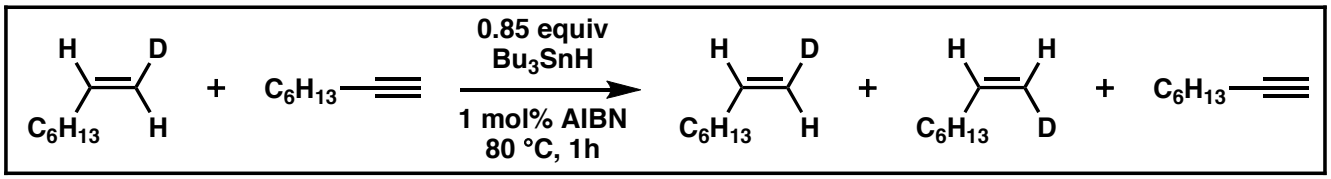


Rearrangement rate (A→C→D) is *fast* but [Bu_3SnH]-*independent*

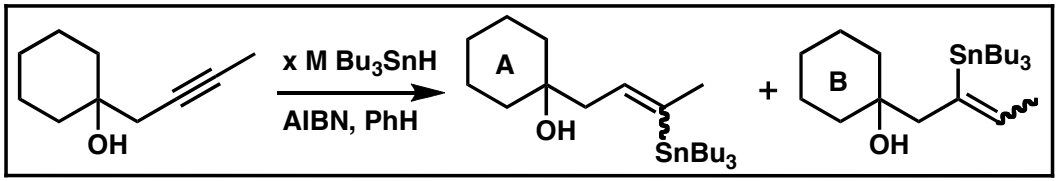
A→B rate is [Bu_3SnH]-*dependent*, so to get kinetic product, bomb it with Bu_3SnH and keep it concentrated!

- **The selectivity for cyclization of the vinyl radical onto the olefin vs. the cyclization of an alkyl radical onto the alkyne is somewhat surprising and has important implications. (Stannyl radical addition to the olefin is reversible.)**

"Enyne cyclizations are successful because cyclization is faster, and reversal slower, for vinyl radicals than for their alkyl counterparts, so that the whole cyclization pathway is via the adduct of the stannyl radical to the acetylene rather than to the olefin."

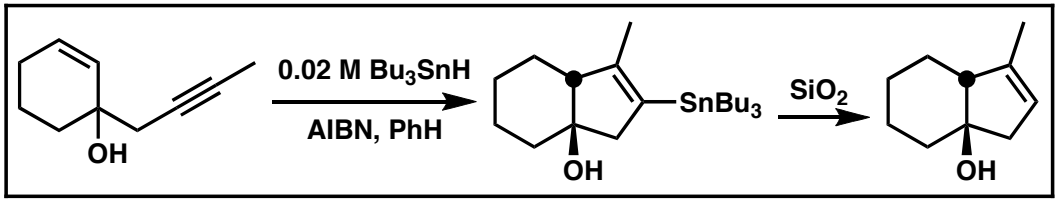


- **The regioselectivity of stannyl radical formation and subsequent cyclization implies that its addition to the *triple* bond is *also* reversible!**



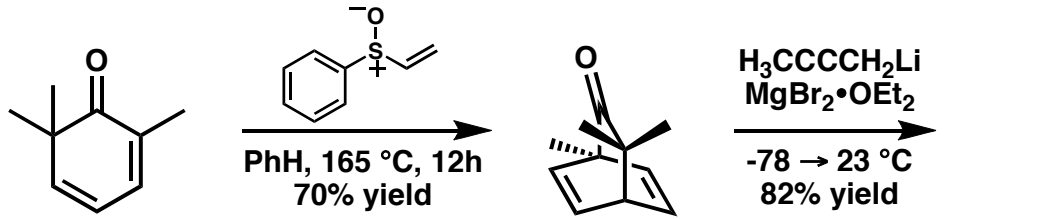
For x = 0.02 M Bu_3SnH (normal conditions), *no* product is observed.

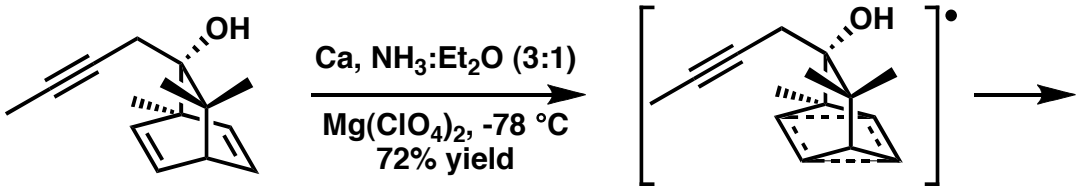
For x = 0.77 M Bu_3SnH, a 1.2:1 ratio of A:B is observed in addition to some SM.

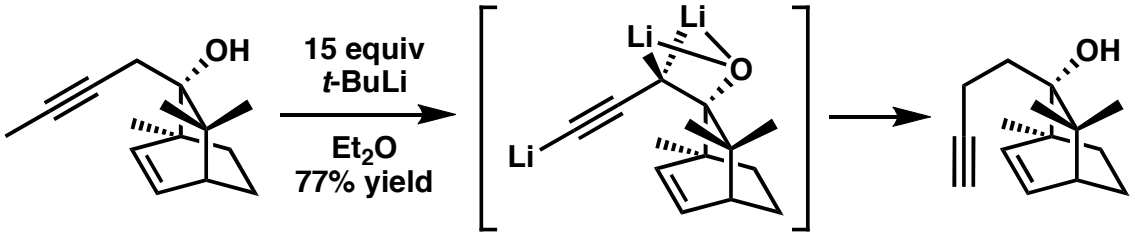


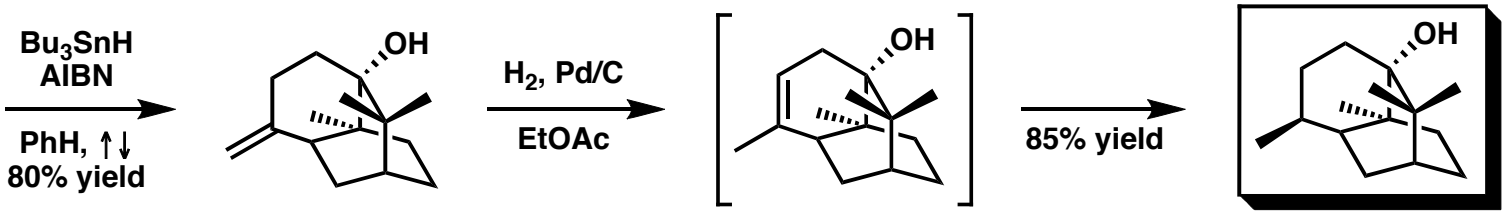
Reactivity is now observed at *low* tin concentrations, thus confirming that the *reversibility* of the stannyl radical radical addition to the triple bond leads to the preferential formation of the more rapidly formed ring (here 5 vs. 4).

Total Synthesis of Patchouli Alcohol



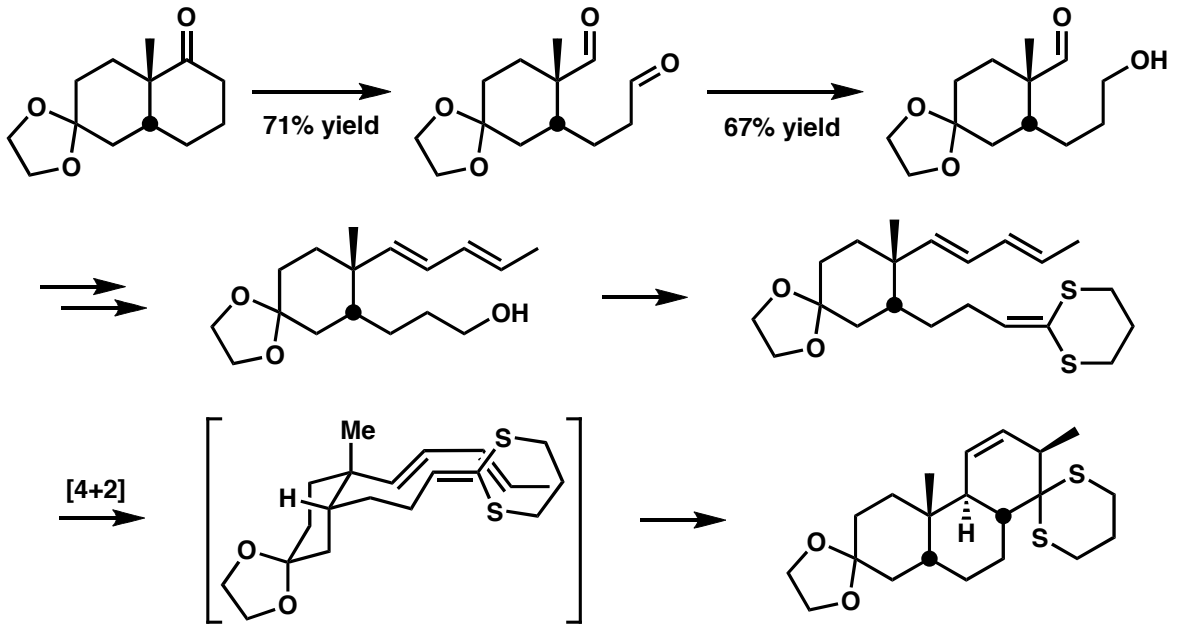


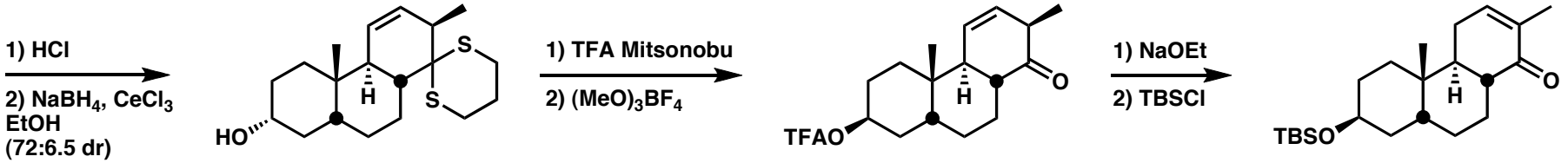


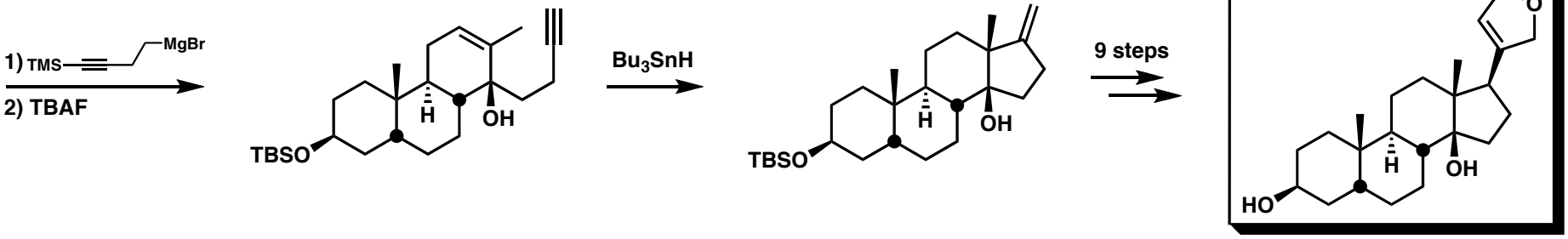


TL **1995**,*36*, 7607

Total Synthesis of (+)-Digitoxigenin



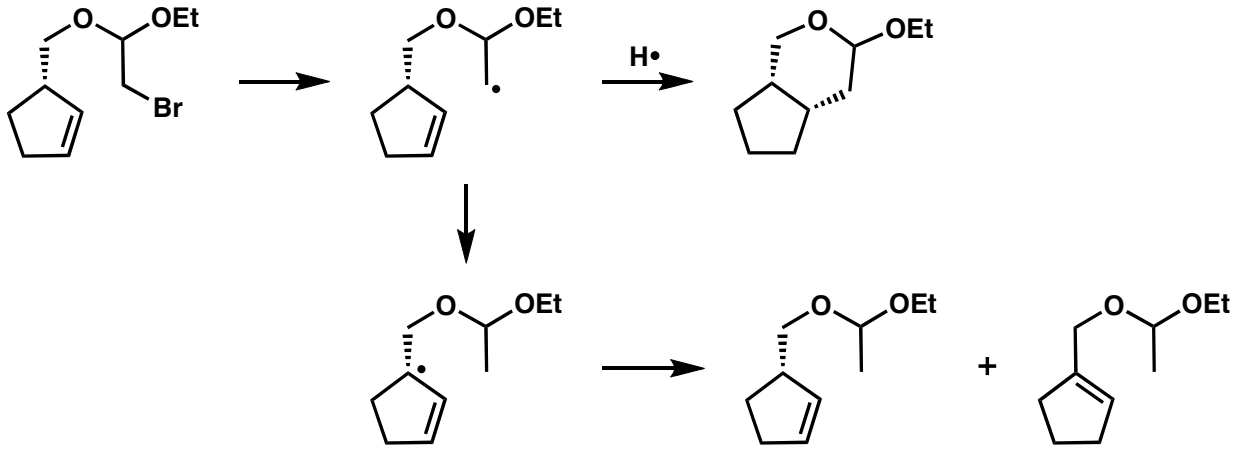




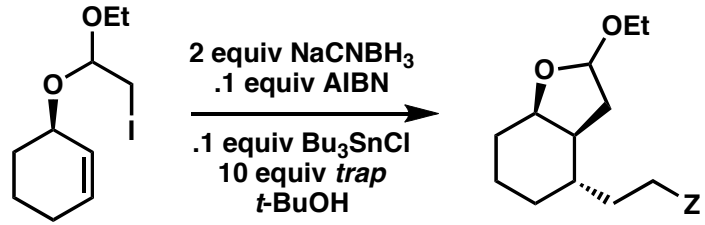
JACS **1996**, *118*, 10660

Position and Stereochemical Control by Radical Cyclization to Form a Temporary Ring ~ Mixed Acetal Linkages

- **Goal: Take advantage of the position selectivity and stereochemical fidelity of the previously developed radical cyclizations, but allow the ring to be disassembled after the relevant stereocenters are set.**
  JACS, **1983**, *105*, 3741 **and** *JACS*, **1985**, *107*, 500



- **Trapping with an electrophile enables multiple new stereocenters to be set during the cyclization.**
  JACS, **1986**, *108*, 303

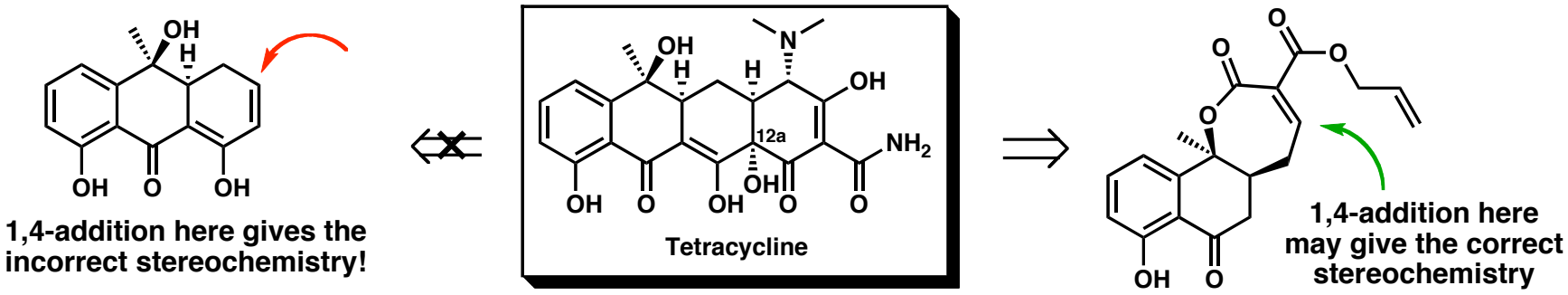


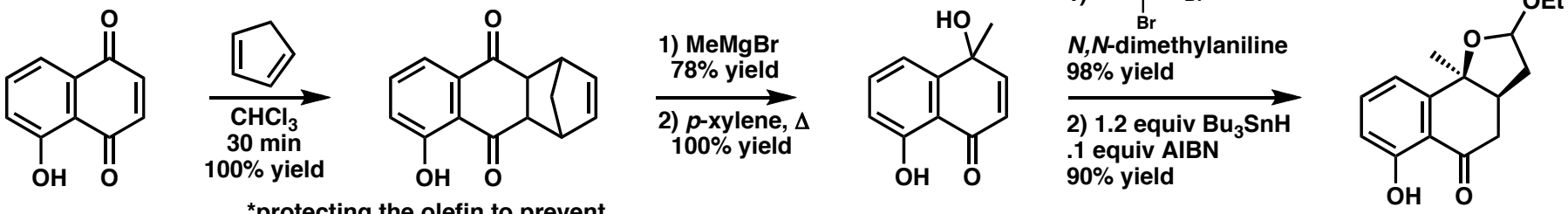
Z = CN, CO_2Me, COEt, $PO(OEt)_2$, SO_2Me, SO_2Ph

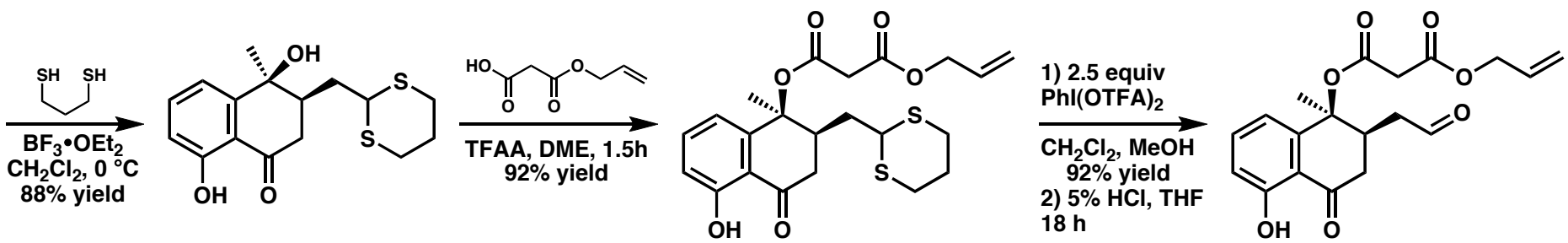
- **Mini-Review: Radical Cyclization in the Control of Regio- and Stereochemistry.** *Bull. Chem. Soc. Jpn.* **1988**, *61*, 149-154.

- **Synthetic Applications:**
  Prostaglandin F2α *JACS*, **1986**, *108*, 6384.
  Reserpine *JACS*, **2005**, *127*, 16255.

Total Synthesis of 12a-Deoxytetracycline

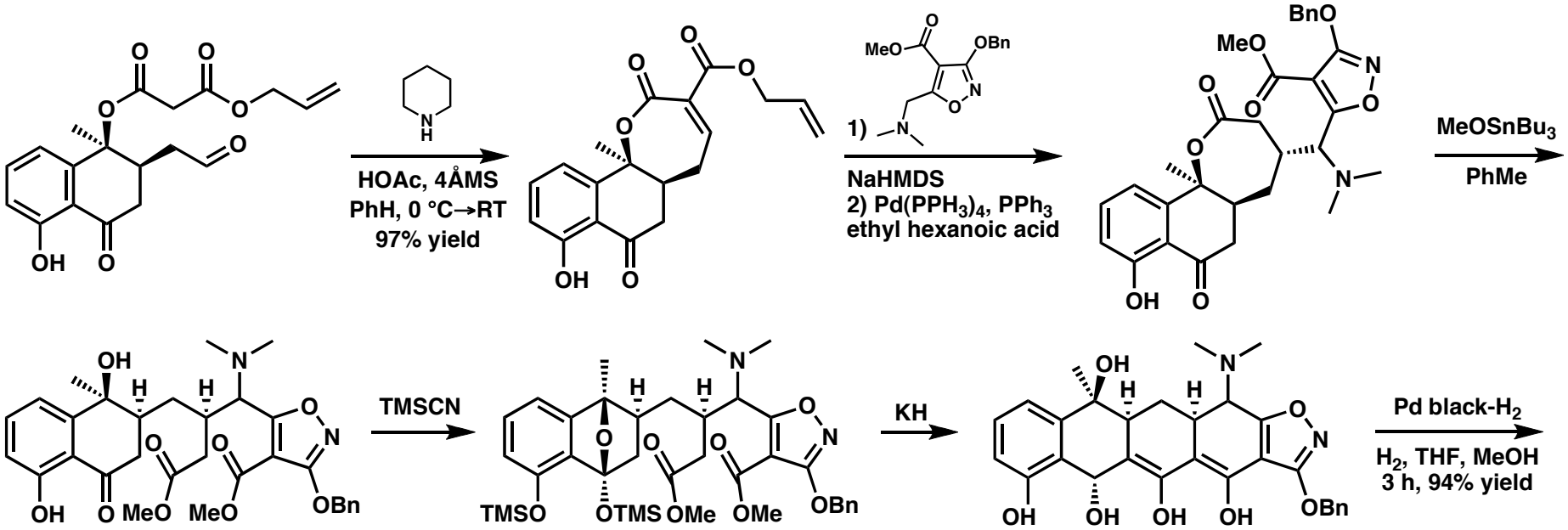


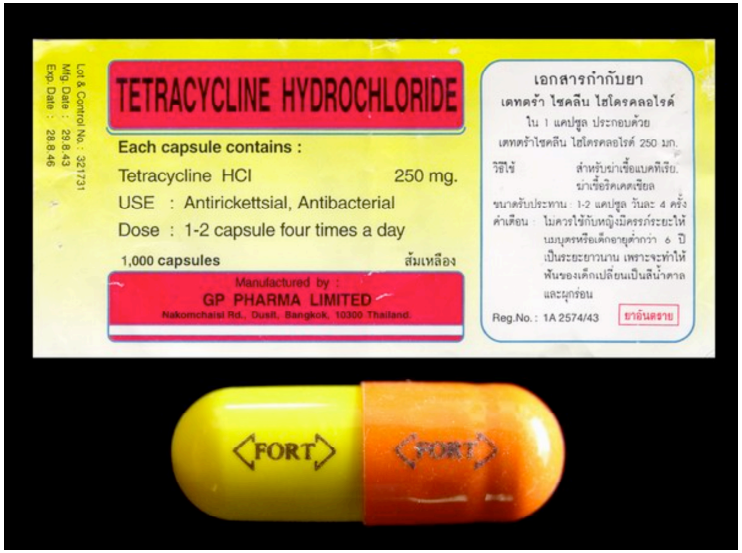


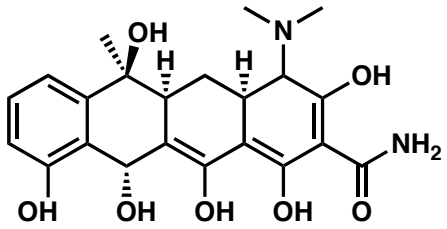


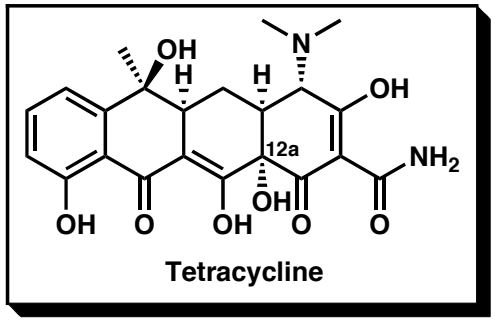
JACS, **1996**, *118*, 5304

Total Synthesis of 12a-Deoxytetracycline





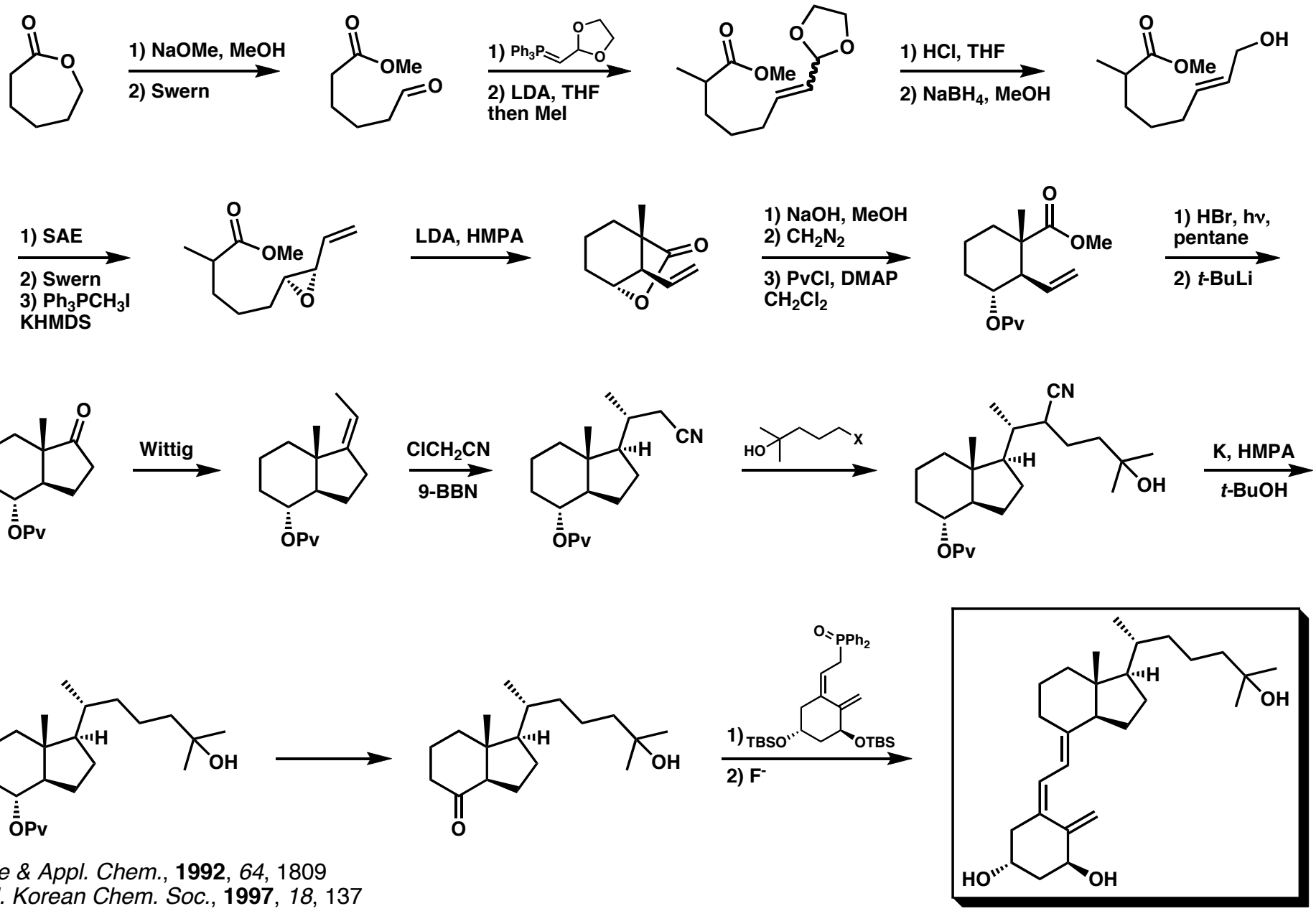




"Methods have been claimed for the stereospecific 12a-oxidation of 2. We are not aware, however, that a reproducible method for the oxidation of 2 to 1 is available."

JACS, **1996**, *118*, 5304

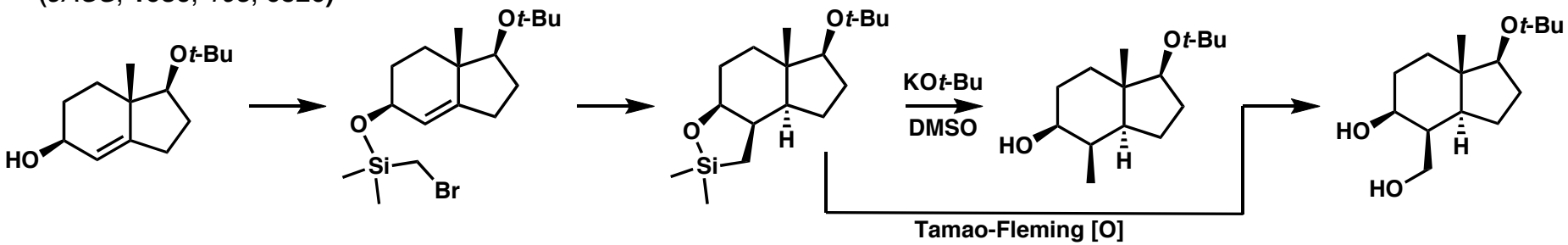
Total Synthesis of Calcitriol



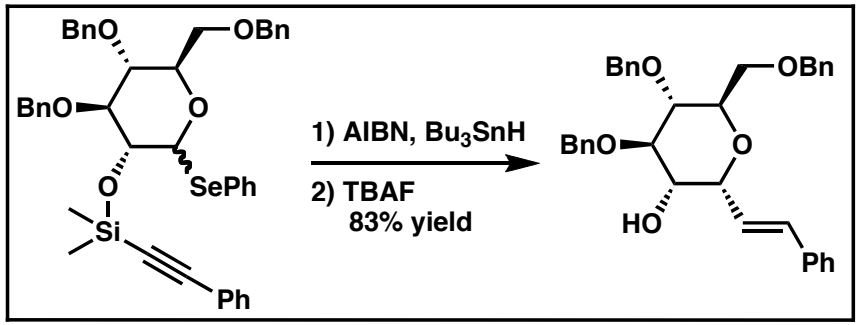
Pure & Appl. Chem., **1992**, *64*, 1809
Bull. Korean Chem. Soc., **1997**, *18*, 137
Aust. J. Chem., **1992**, *45*, 275

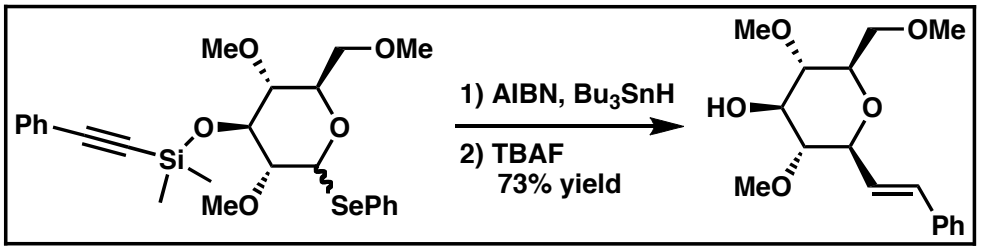
Position and Stereochemical Control by Radical Cyclization to Form a Temporary Ring ~ Temporary Silicon Connection

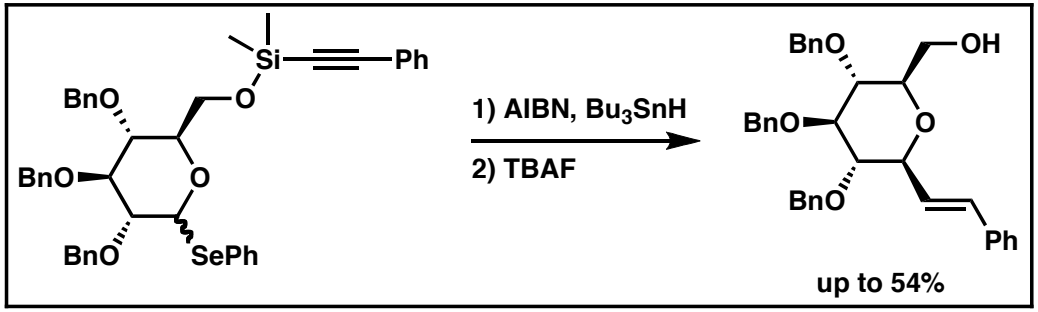
- **Same Goal: (Take advantage of the position selectivity and stereochemical fidelity of the previously developed radical cyclizations, but allow the ring to be disassembled after the relevant stereocenters are set.)**
  (*JACS*, 1986, *108*, 6826)



- **Allows stereocontrol to be acheived at the anomeric center of a sugar.** (*JACS*, **1991**, *113*, 7054)



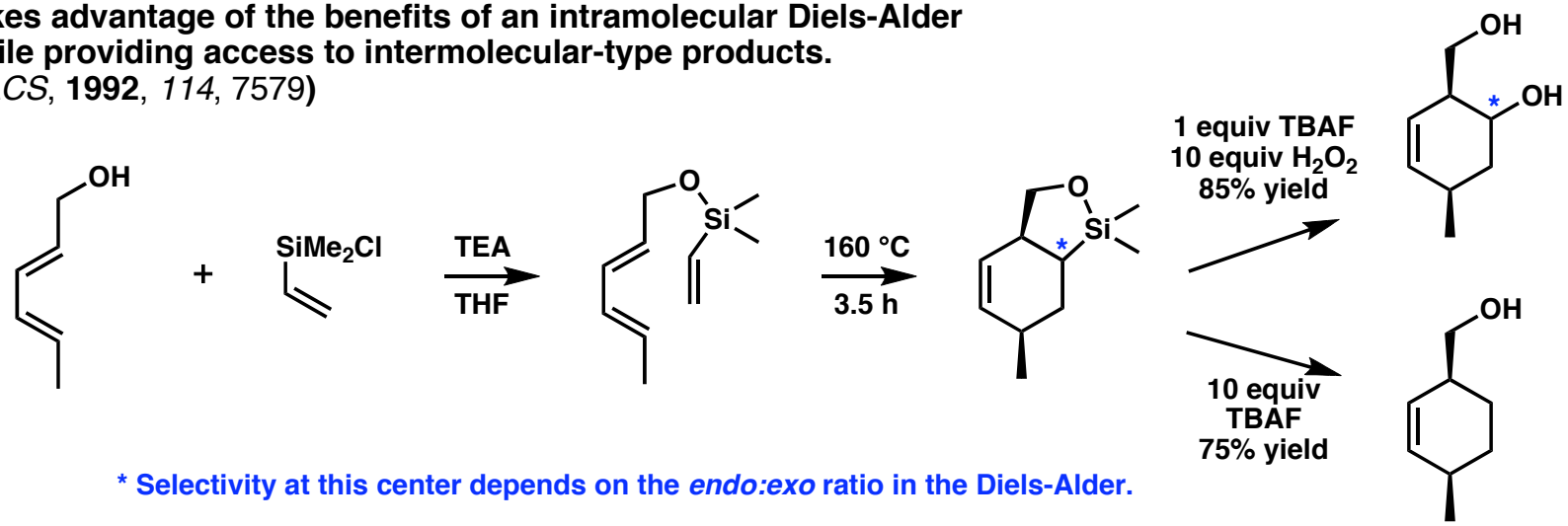




- **See also: Synthesis of β-mannopyranosides**
  JACS **1996**, *118*, 247.

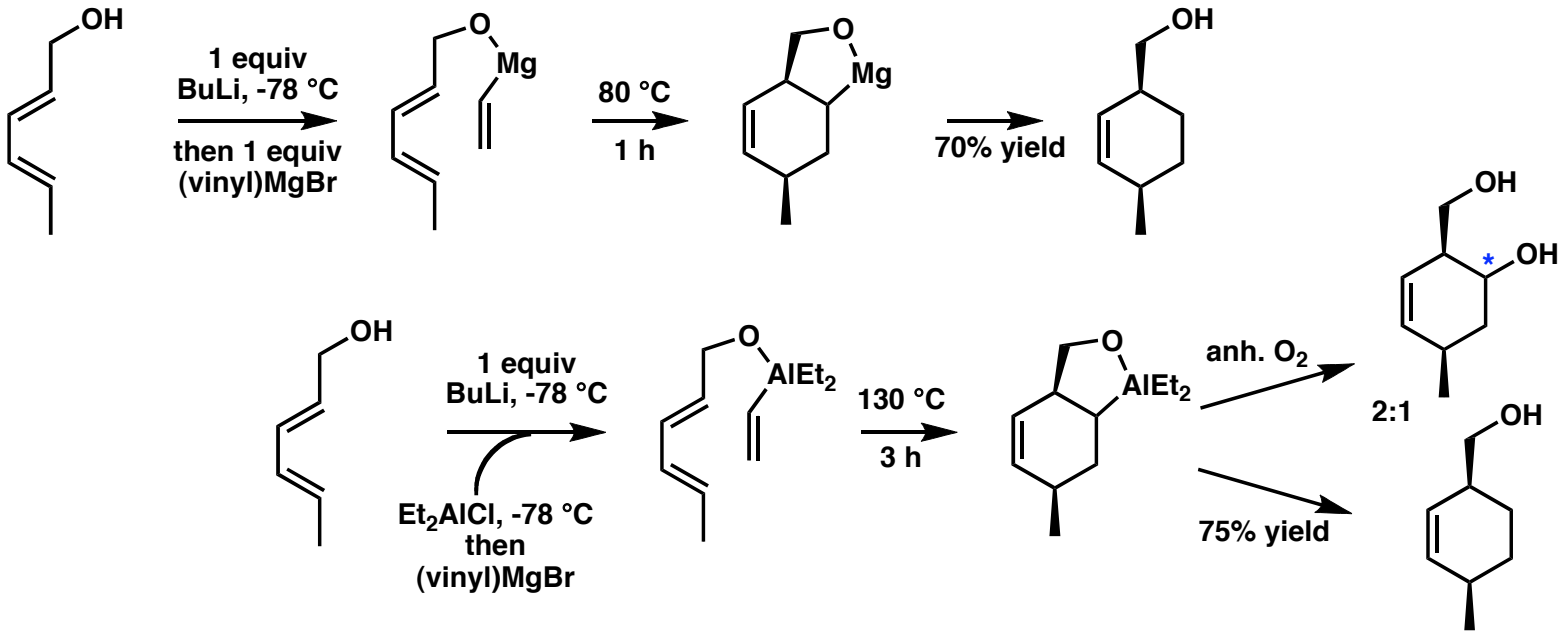
Temporary Silicon Connection in the Diels-Alder Reaction

- **Takes advantage of the benefits of an intramolecular Diels-Alder while providing access to intermolecular-type products.** (*JACS*, **1992**, *114*, 7579)



* Selectivity at this center depends on the *endo:exo* ratio in the Diels-Alder.

- **This transformation can also be effected with a temporary Mg/Al connection.** (*JACS*, **1995**, *117*, 6595)




Stork is AWESOME!
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