

Topic Review:

Semipinacol Rearrangement in Natural Product Synthesis

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Bern, 27.04.2012

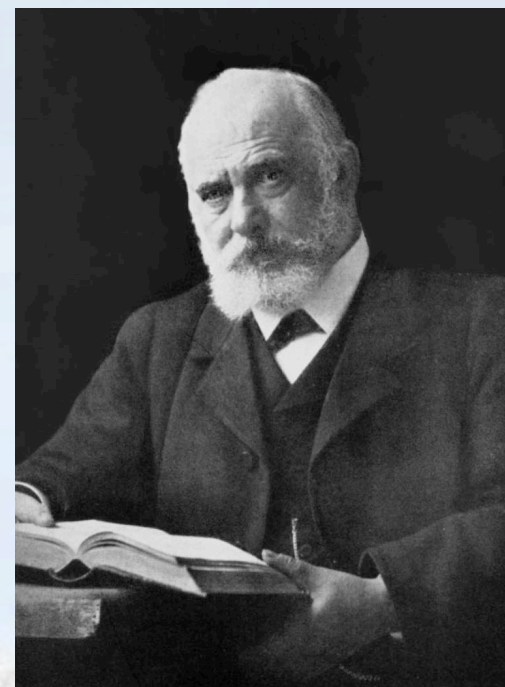
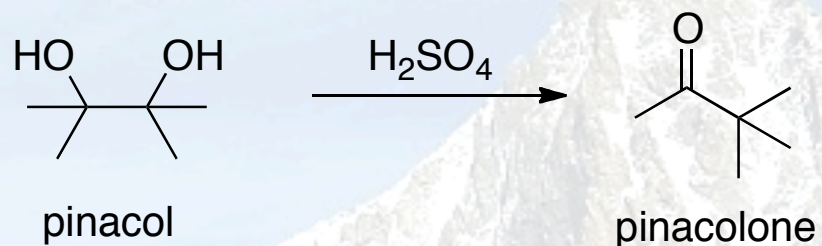
Overview

1. Introduction – History
2. Rearrangement of 2-heterosubstituted alcohols (Type I)
3. Rearrangement of allylic alcohols (Type II)
4. Rearrangement of epoxides (Type III)
5. Rearrangement of α -hydroxy ketones and imines (Type IV)
6. Biosynthesis and Biomimetic Synthesis involving semipinacol rearrangement
7. Recent Example
8. Summary

1. Introduction - History

Classical Pinacol Rearrangement:

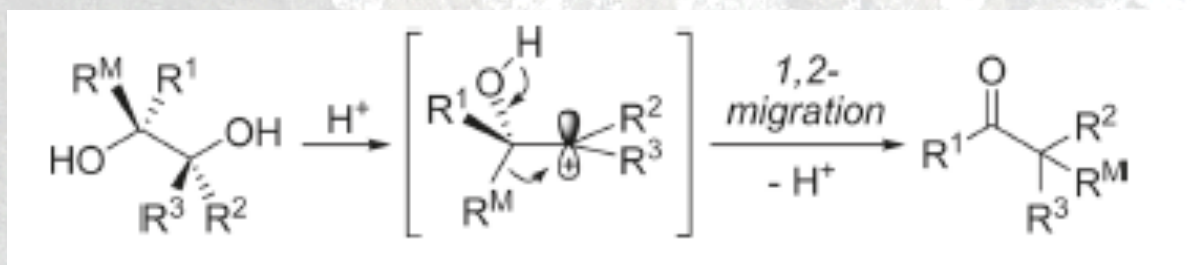
Fittig 1860:



Wilhelm Rudolph Fittig
1835 - 1910

Disadvantages:

- poor regio- and diastereoselectivity
- unpredictable side reactions



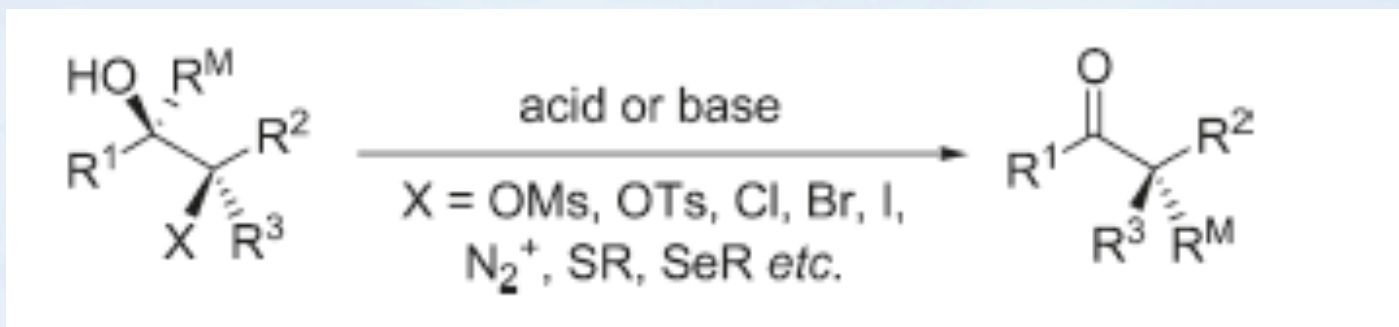
Semipinacol rearrangement – definition:

- common reactive species: electrophilic carbon center (including but not limited to carbocations) is vicinal to an oxygen-containing carbon
- 1,2-migration of a C-C or C-H bond to terminate the process generating a carbonyl group



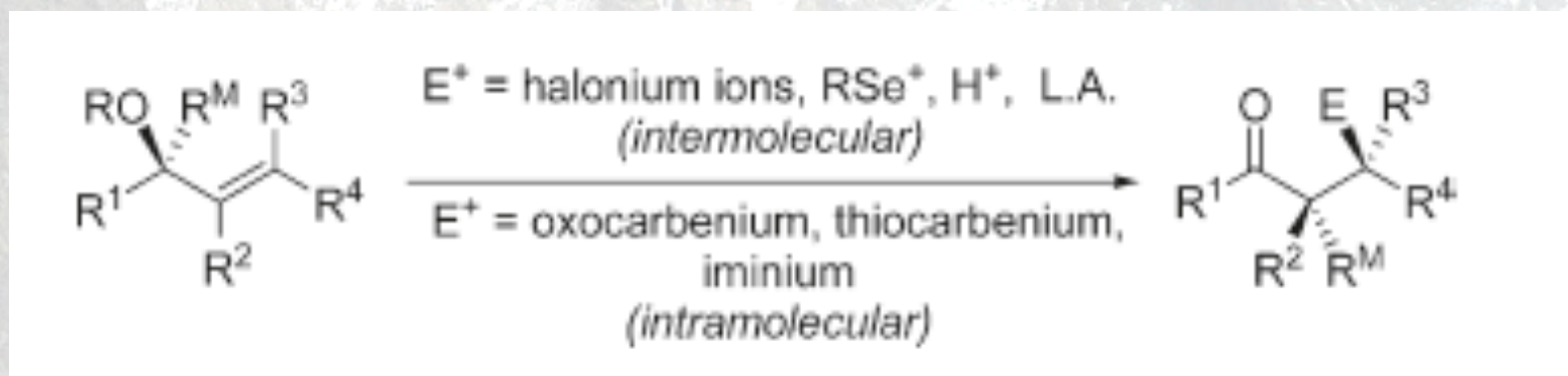
Semipinacol Rearrangement – 4 different types

Type I: rearrangement of 2-heterosubstituted alcohols and their derivatives



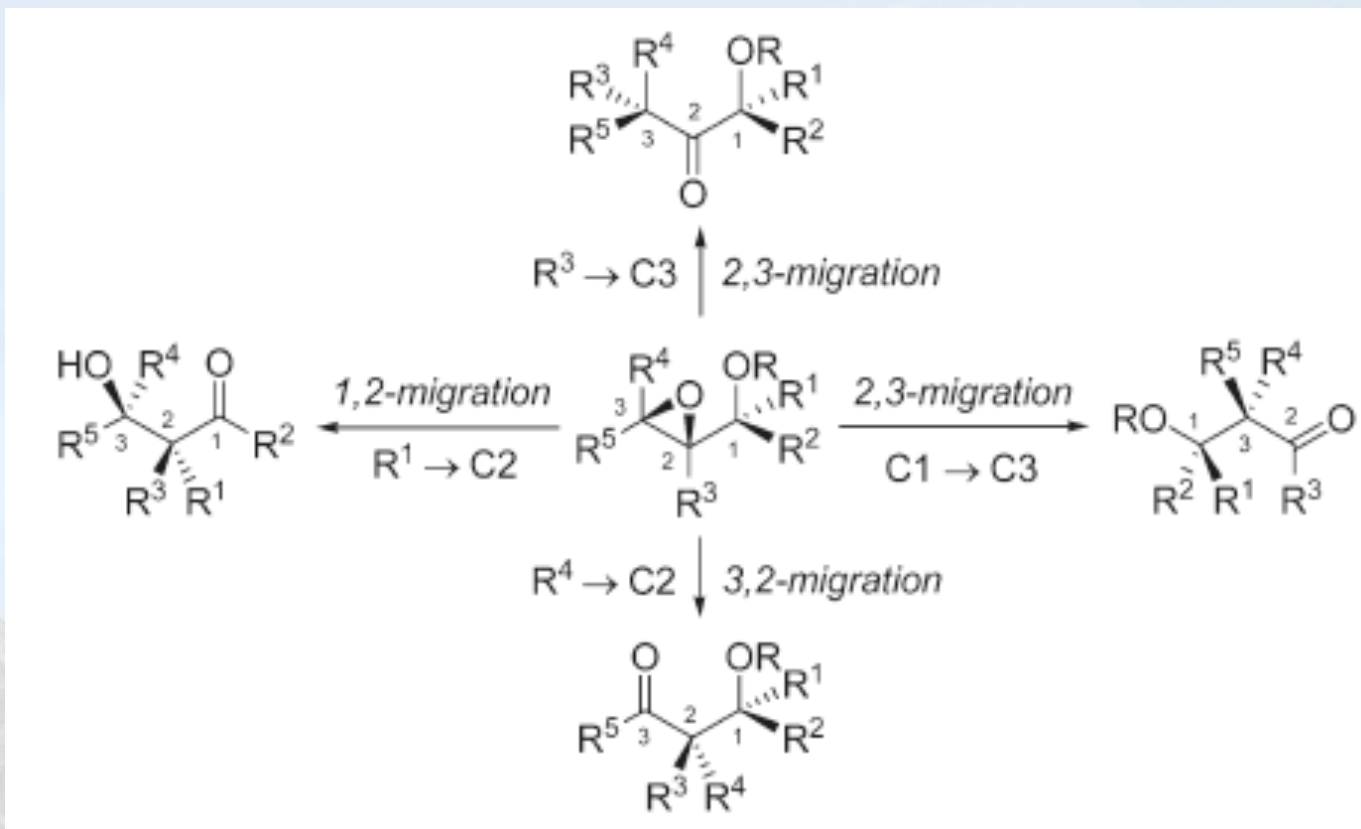
rearrangement is facilitated by the loss of the leaving group

Type II: rearrangements of allylic alcohols and their derivatives



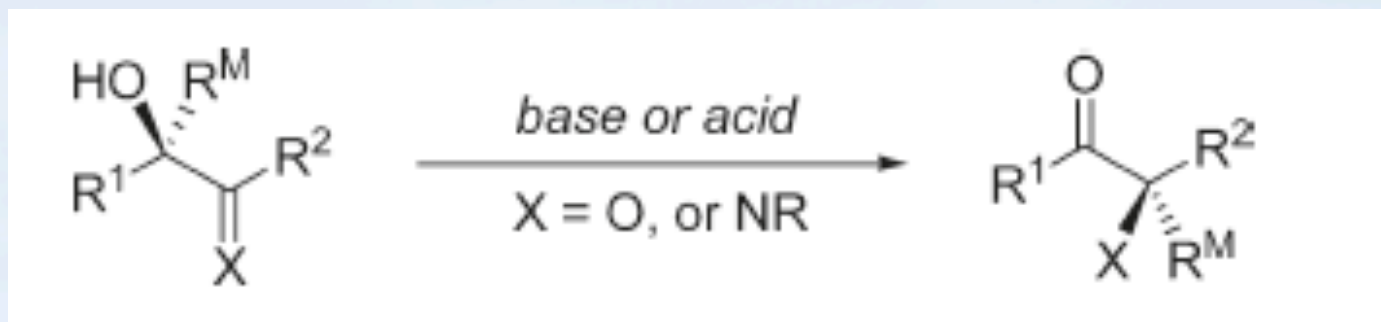
addition of an electrophile to a C=C bond (intramolecular with oxocarbenium is also known as the Prins-Pinacol Rearrangement)

Type III: rearrangements of epoxides – mainly focused on 2,3-epoxy alcohols



migration depends on the structural feature of the substrate and the reaction conditions

Type IV: rearrangements of tertiary α -hydroxy ketones or imines (also known as acyloin rearrangement or α -ketol rearrangement)



Advantages of the semipinacol compare to the pinacol rearrangement:

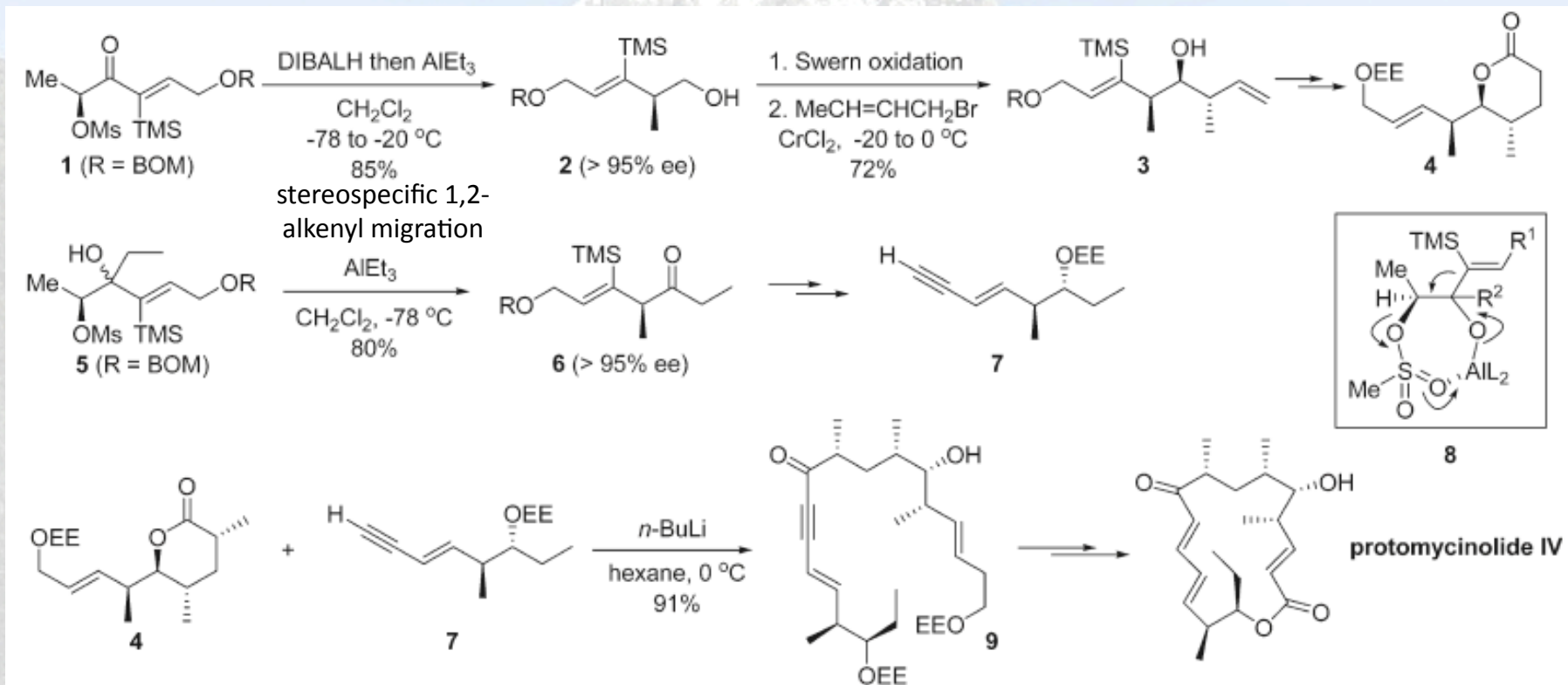
- not restricted to 1,2-diols
- compatible with a variety of reaction conditions
- no problem of regioselectivity
- migratory aptitude of substituents is also often controlled by stereoelectronic effect (migratory group must be antiperiplanar to the leaving group)
- key part of tandem reactions

2. Rearrangement of 2-heterosubstituted alcohols (Type I)

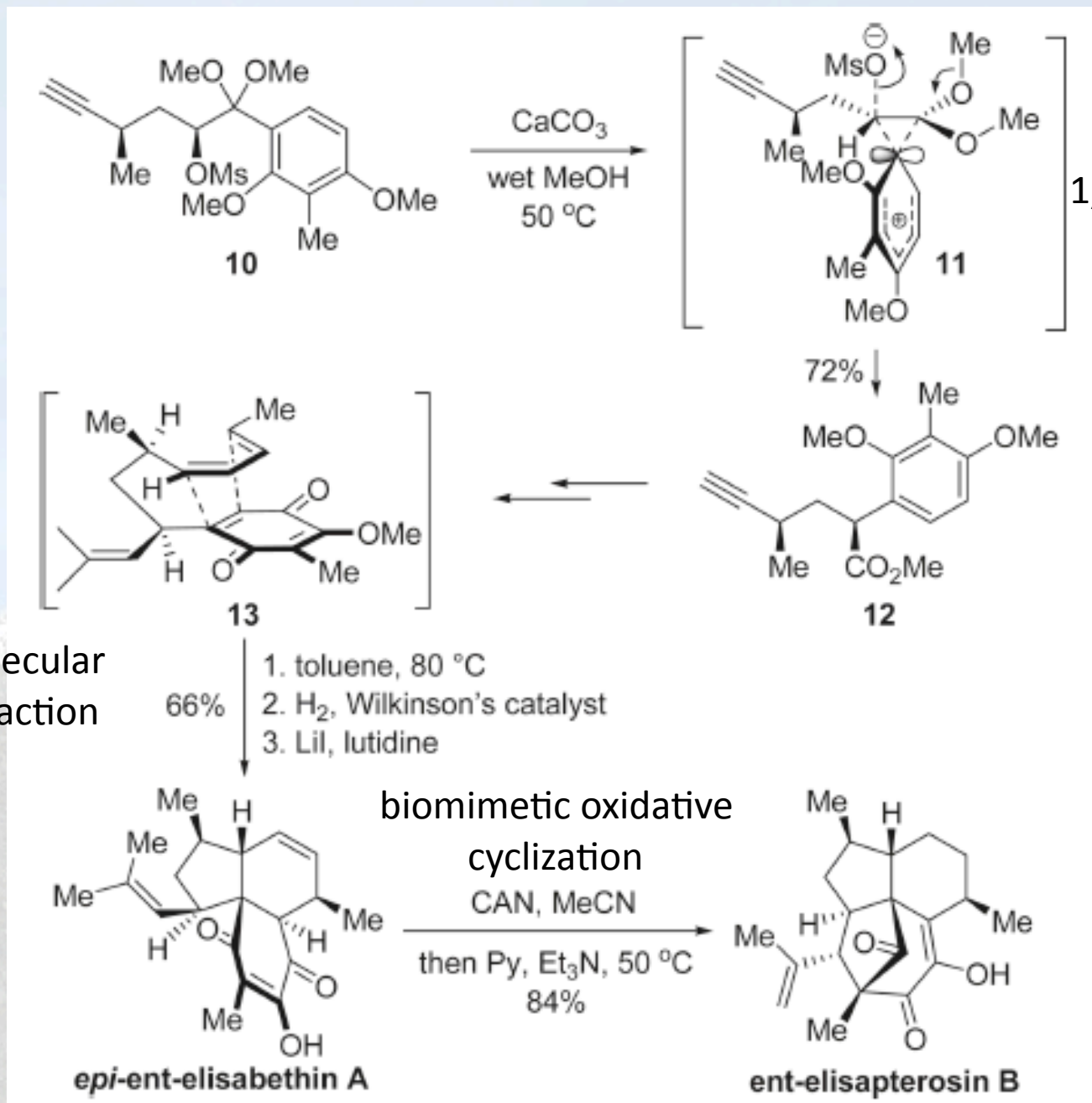
2.1 Sulfonates as Leaving Group

- Reproducibly efficient in both cyclic and acyclic systems
- Lewis acid and base can promote the 1,2-migration with loss of OMs or OTs

Tsuchihashi's Total Synthesis of Protomycinolide IV:



Rawa's Total Synthesis of Ent-elisapterosin B:



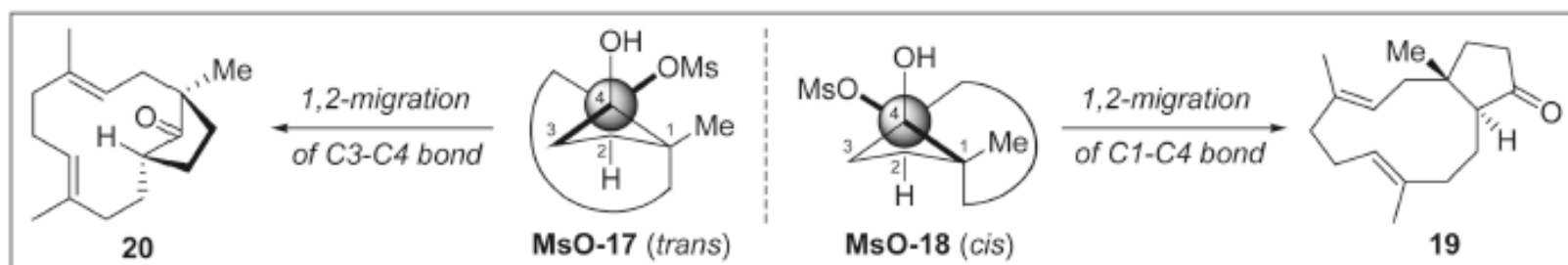
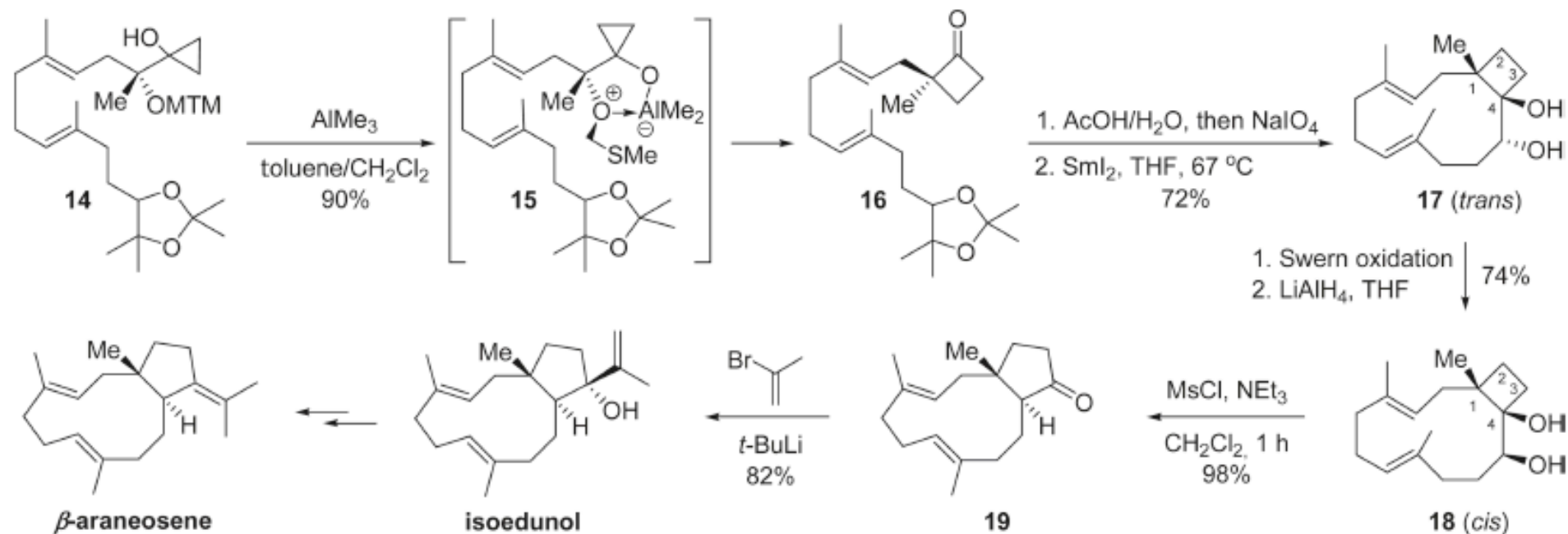
stereospecific
1,2-aryl migration

endo-intramolecular
Diels-Alder reaction

biomimetic oxidative
cyclization

Corey's Total Syntheses of Isoedunol and β -Araneosane:

sequential ring expansion to construct the trans-fused 5,11-membered ring system

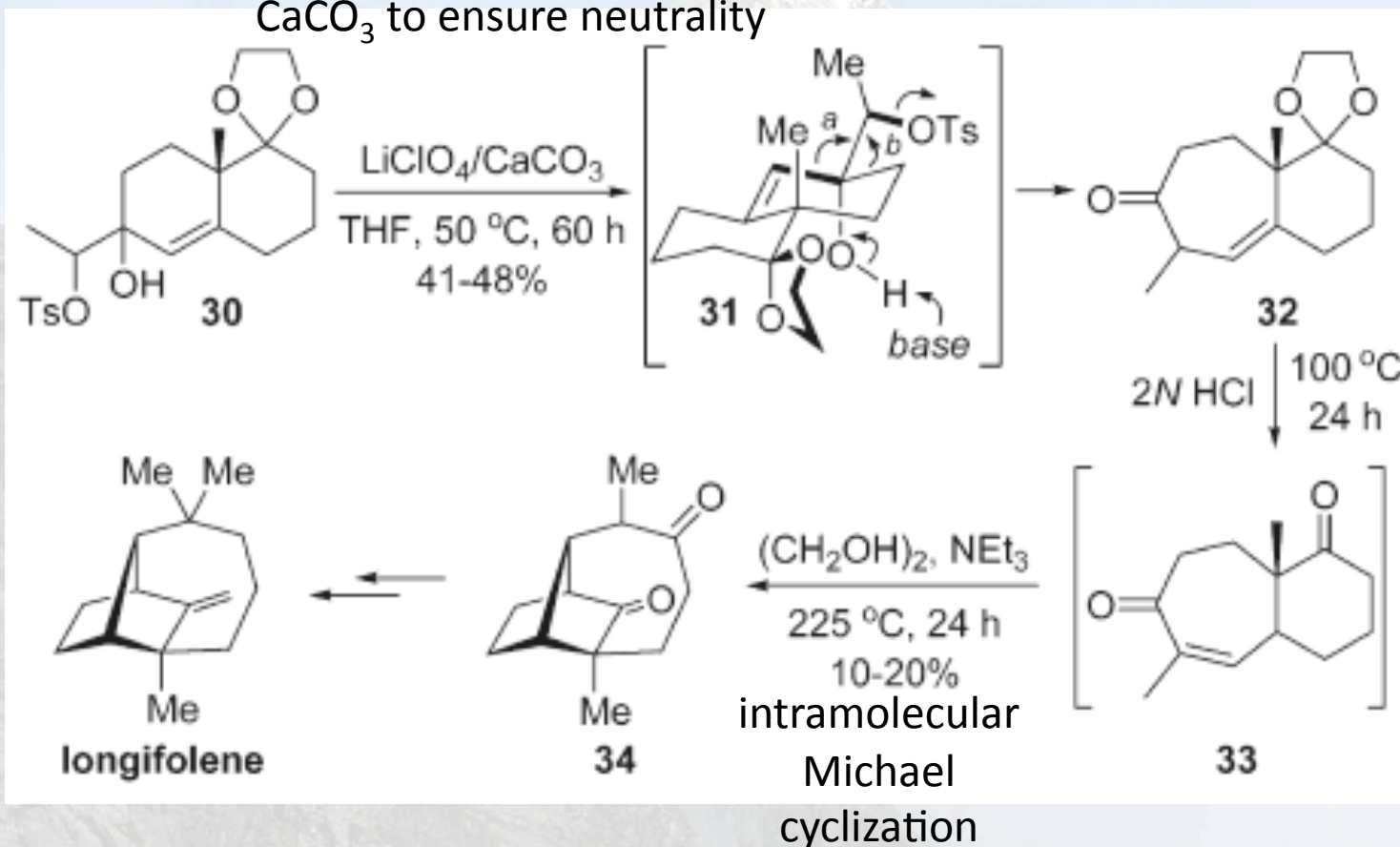


conformational rigidity imposed by the 12-membered ring orients different C-C bonds antiperiplanar to the secondary C-O bond in **MsO-17 (trans)** and **MsO-18 (cis)**

Corey's Total Synthesis of Longifolene:

solvolytic ring expansion

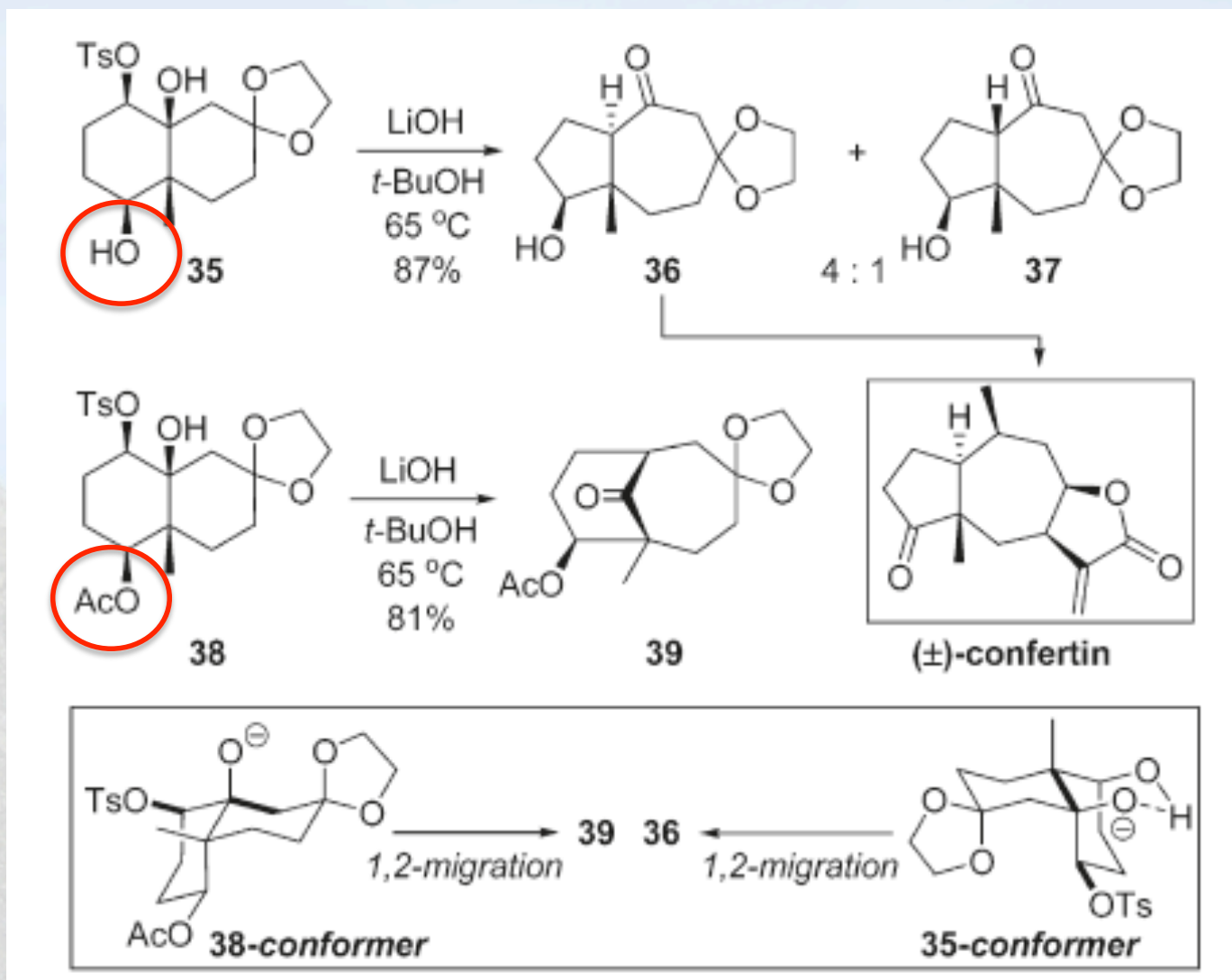
LiClO₄ at saturation to facilitate
ionization of Ts
CaCO₃ to ensure neutrality



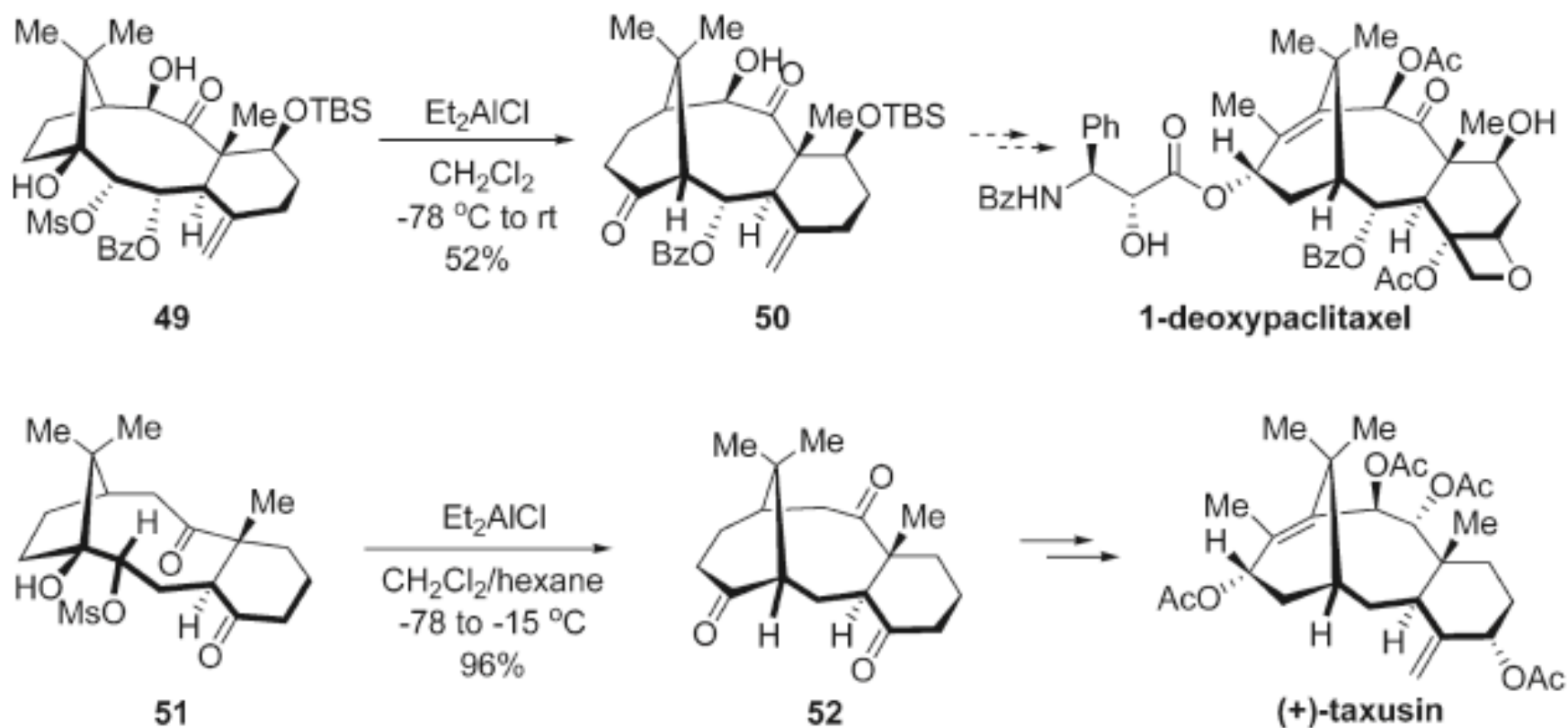
more favorable 1,2-
migration of vinyl
group (a) than alkyl
migration (b)

Heathcock's Total Synthesis of (±)-Confertin:

different conformer because of hydrogen bonding => different 1,2-migration



Paquette's Total Synthesis of (+)-Taxusin and Synthesis of an Advanced Precursor of 1-Deoxytaxusin:

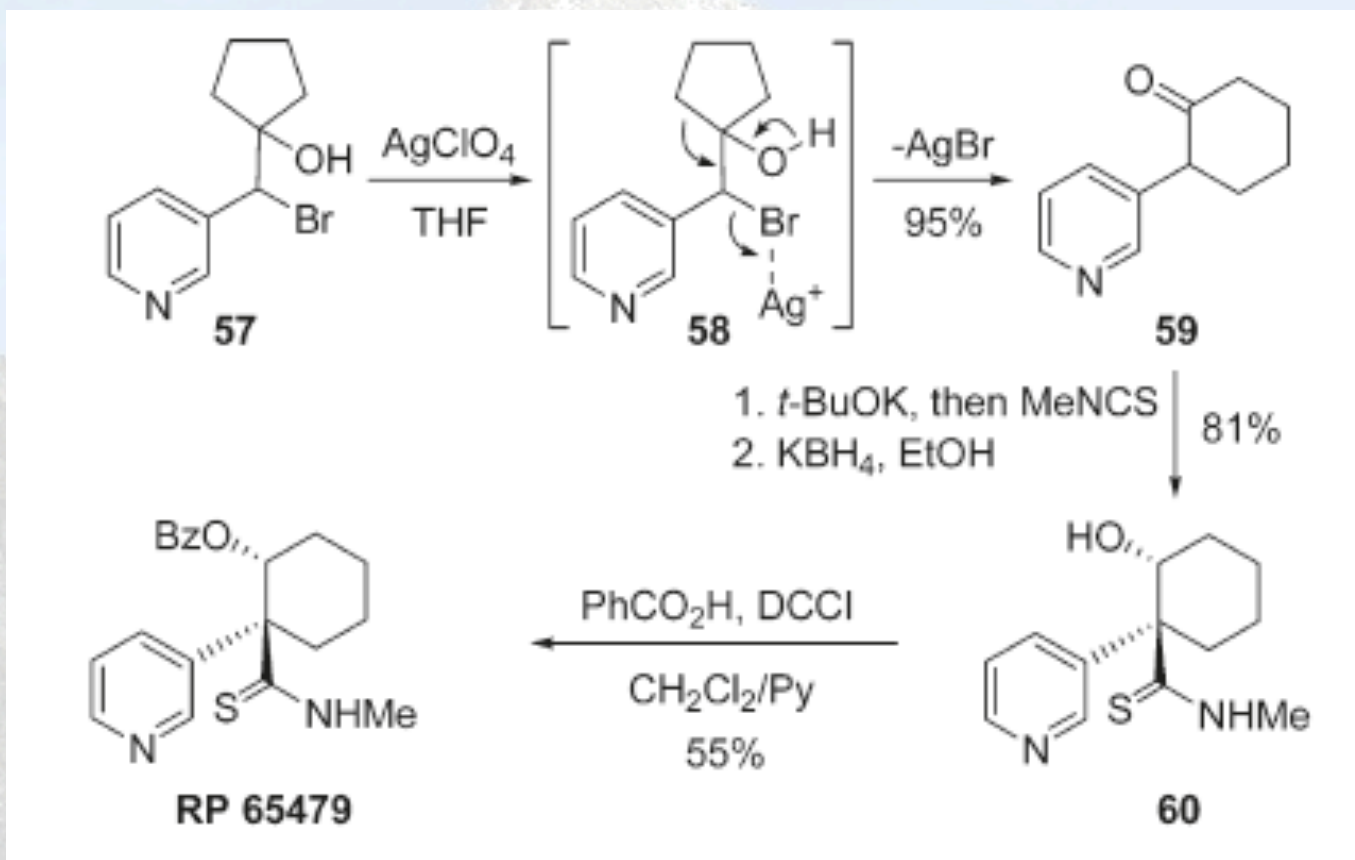


antiperiplanar alignment of the α -oriented OMs Leaving group and the vicinal bond in the bridge \Rightarrow stereospecific 1,2-migration of the bridge

2.1 Halides as Leaving Group

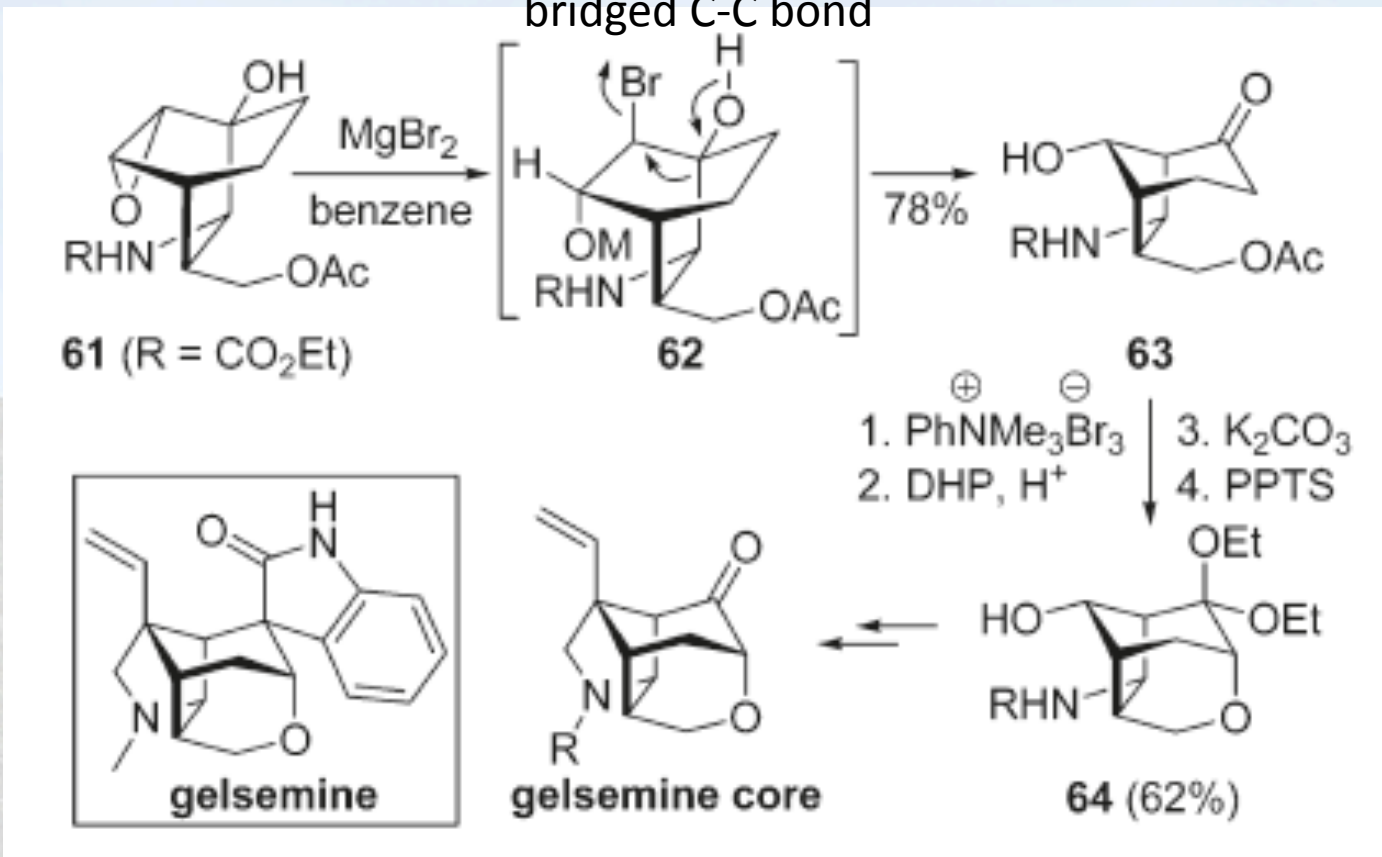
- halohydrins rearrange under either basic conditions or in the presence of various silver salts
- halohydrins rearrange with loss of halogen and formation of carbonyl group

Hart's Total Synthesis of RP 65479:



Fleming's Approach to Gelsemine:

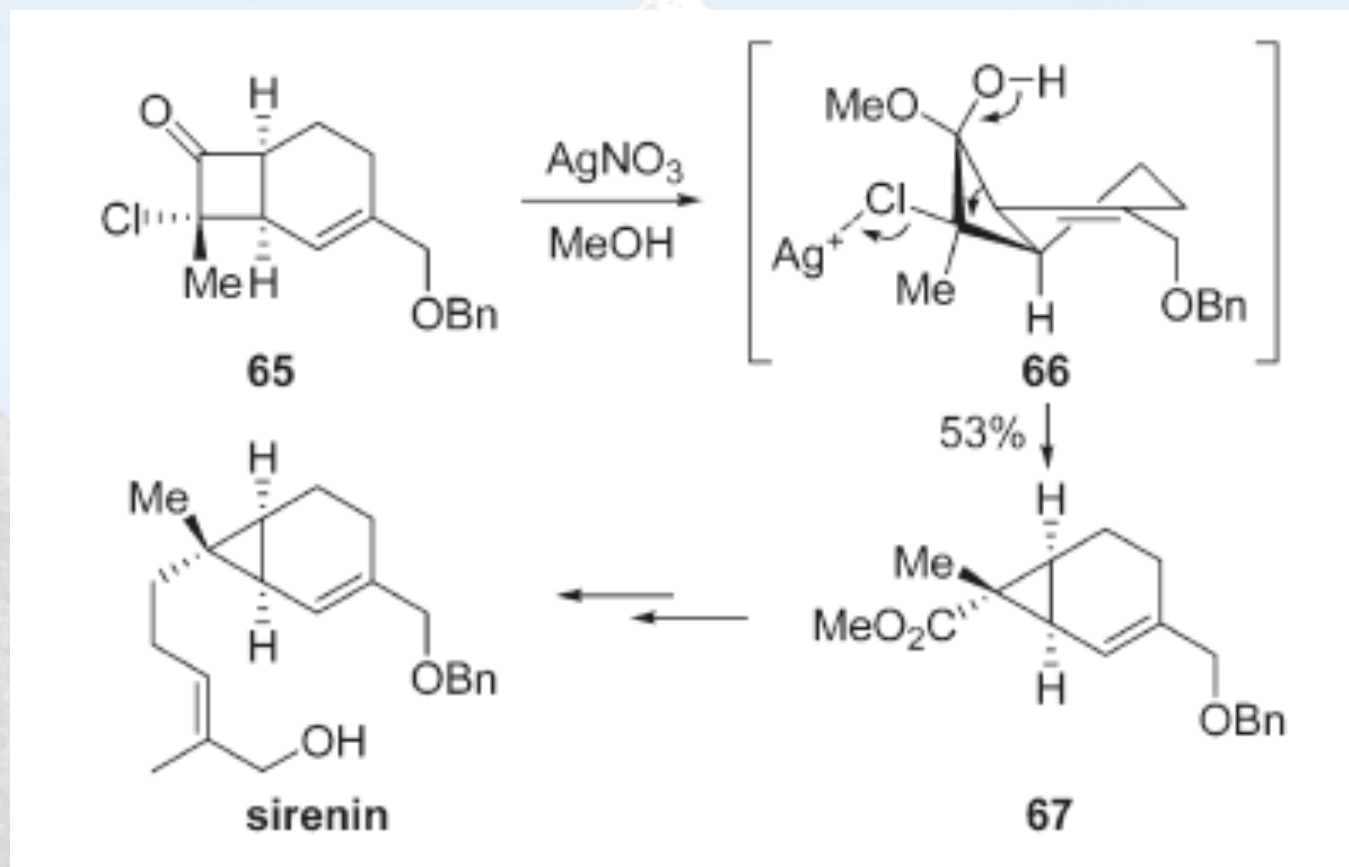
stereospecific 1,2-
migration of the
bridged C-C bond



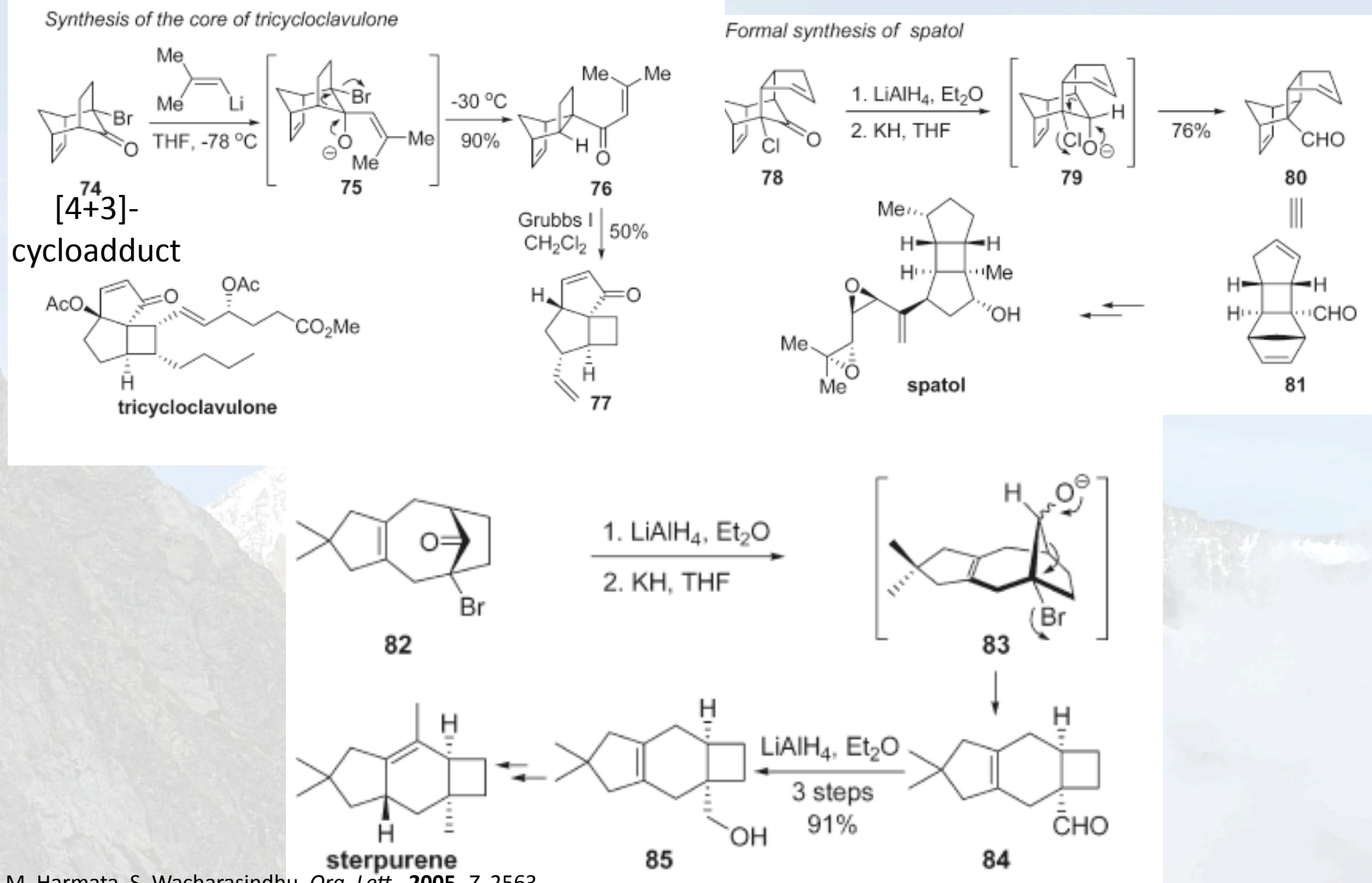
subsequent
intramolecular S_N2
substitution

Harding's Total Synthesis of (±)-Sirenin:

access to highly substituted cyclopropane moiety by ring contraction



Harmata's [4+3]-Cycloaddition/Quasi-Favorskii Process in Natural Product Synthesis:



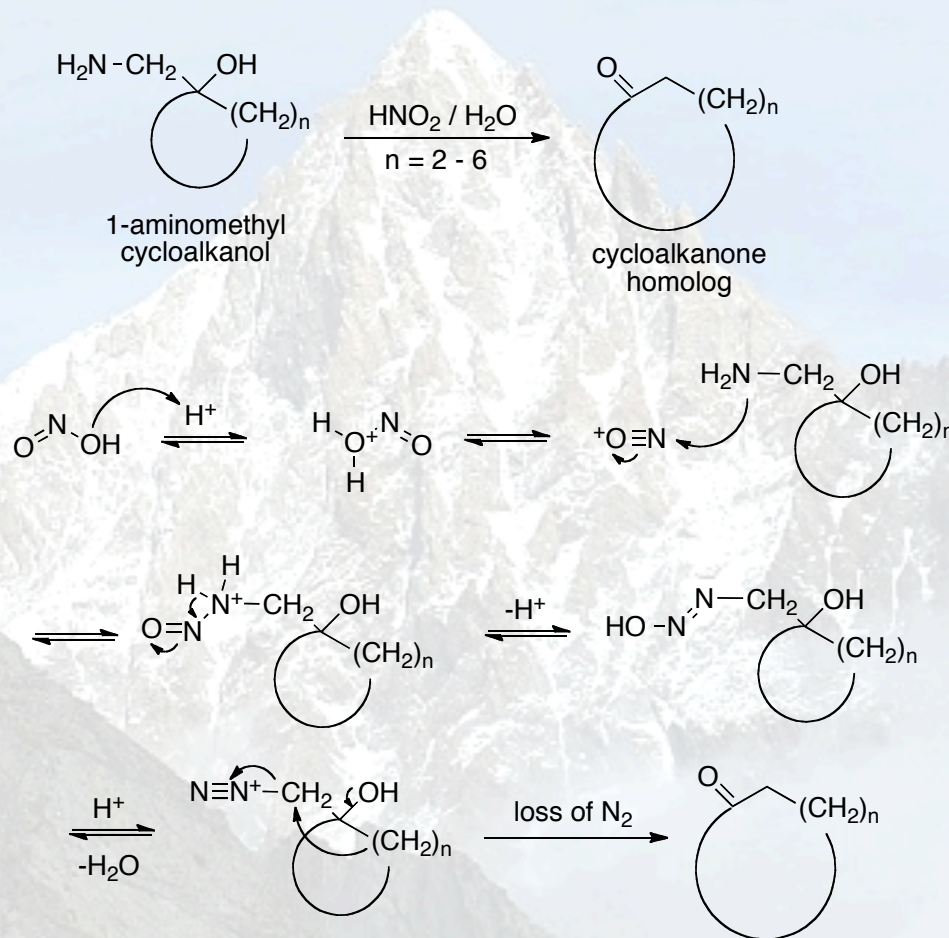
M. Harmata, S. Wacharasindhu, *Org. Lett.*, **2005**, *7*, 2563.

M. Harmata, P. Rashatasakhon, *Org. Lett.*, **2001**, *3*, 2533.

M. Harmata, G. J. Bohnert, *Org. Lett.*, **2003**, *5*, 59.

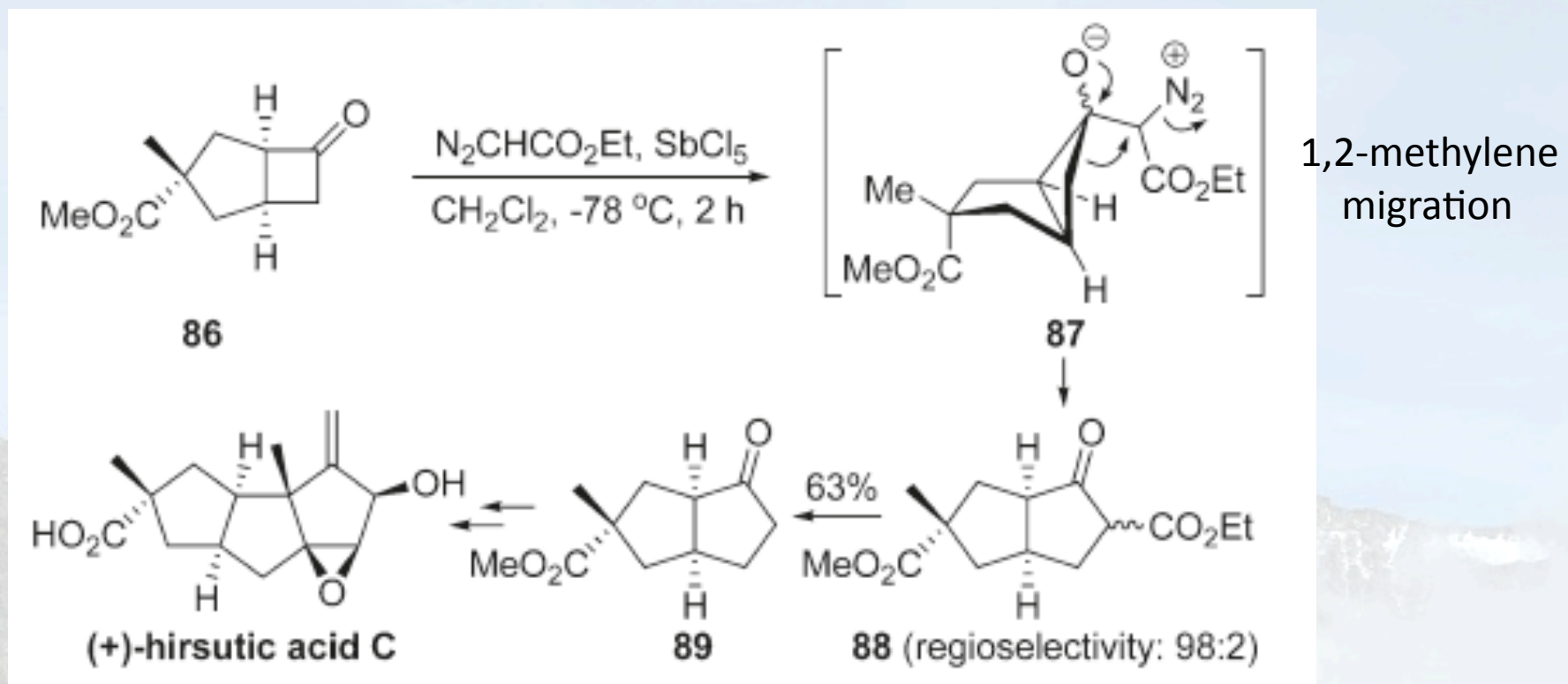
2.3 N₂ as Leaving Group

- diazotation of 1,2-amino alcohols by nitrous acid or direct addition of diazoalkane to ketones can lead to efficient ketone homologation (also known as Tiffenau-Demjanov rearrangement)



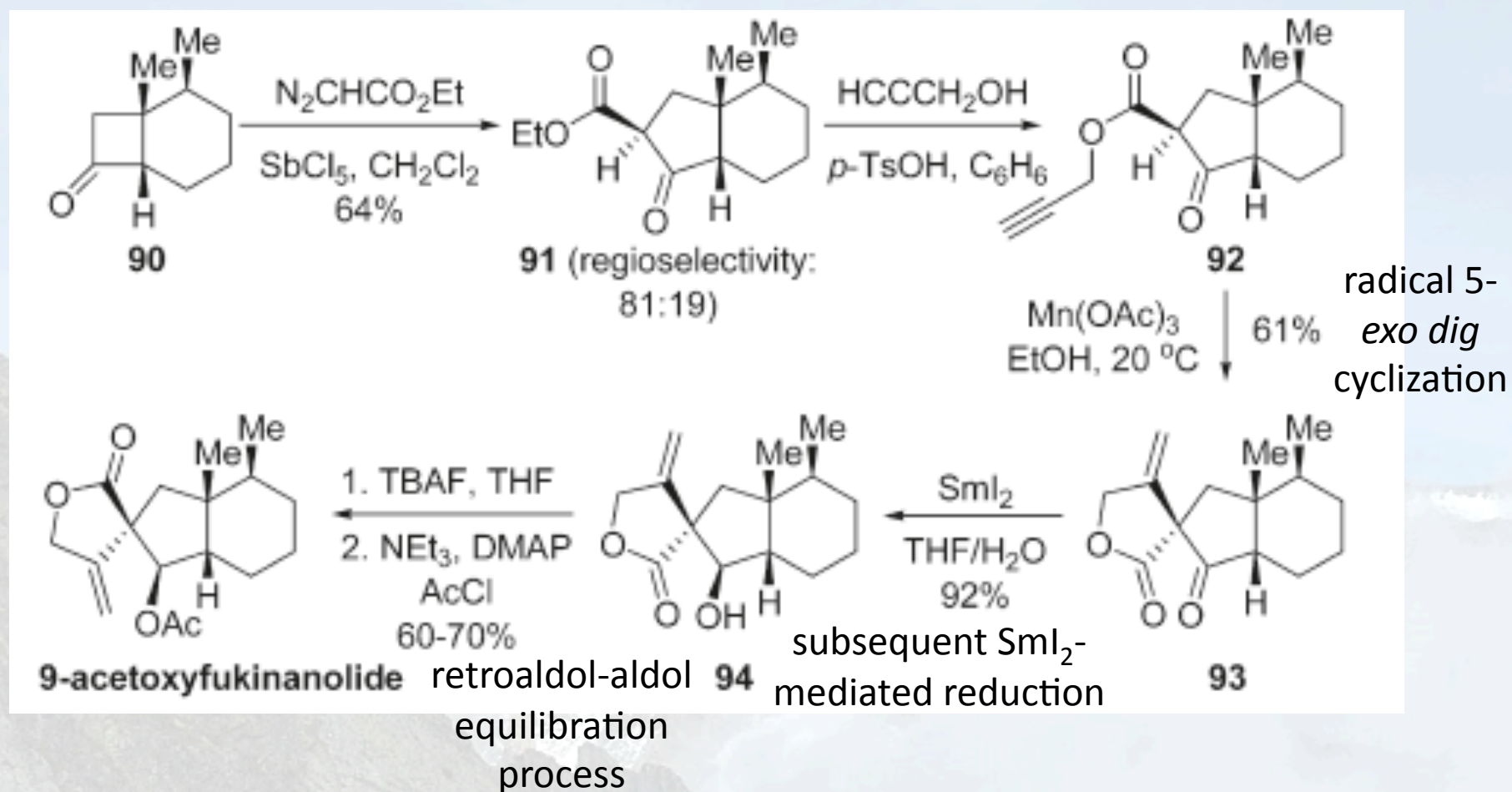
- migration of the less-substituted group usually preferred

Greene's Total Synthesis of (+)-Hirsutic Acid C:



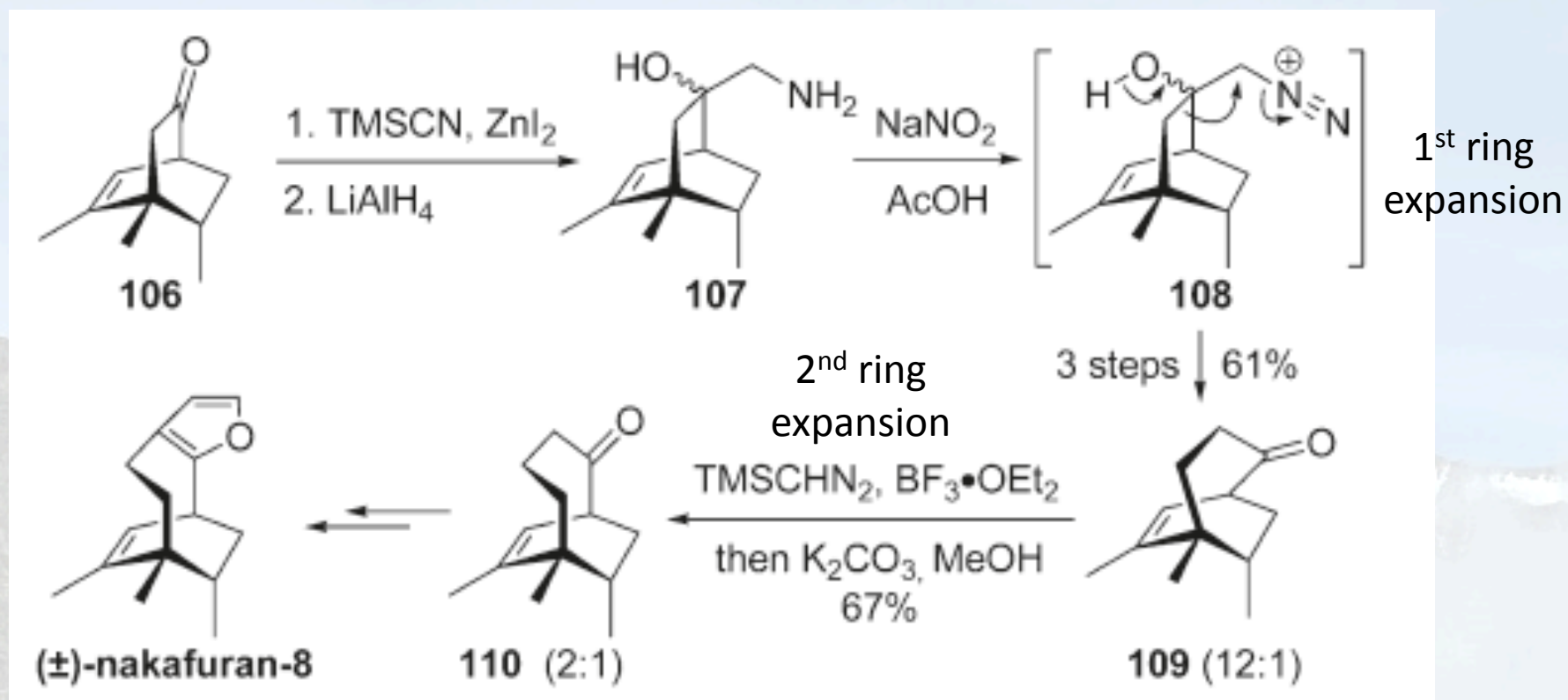
Deprés and Greene's Total Synthesis of 9-Acetyoxyfukinanolide:

interesting spiro- γ -butyrolactone hydrindane structure



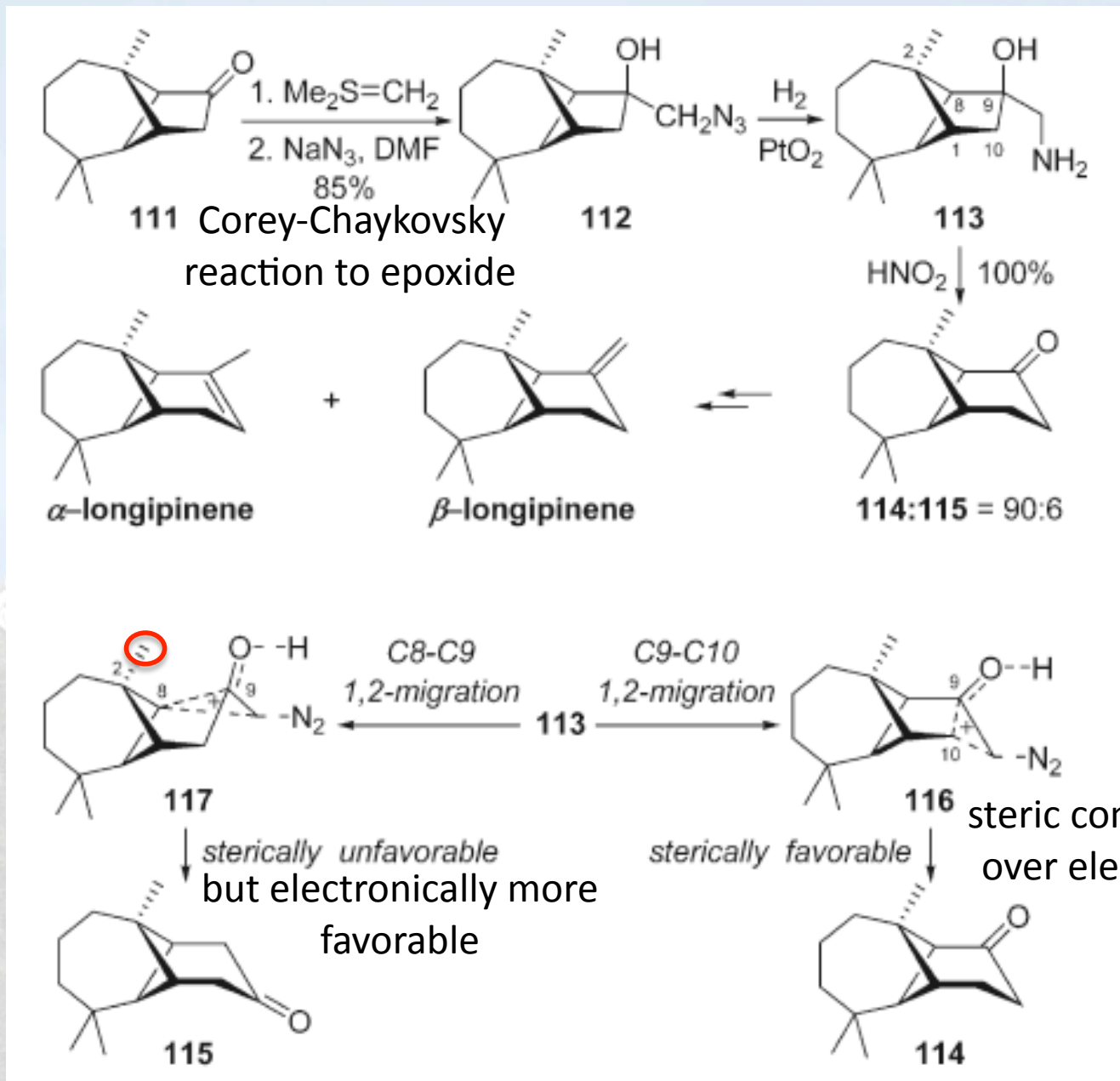
Uyehara and Yamamoto's Total Synthesis of (±)-Nakafuran-8:

bridged or highly strained polycyclic systems:



in both ring expansions the methylene group was the predominant migration group

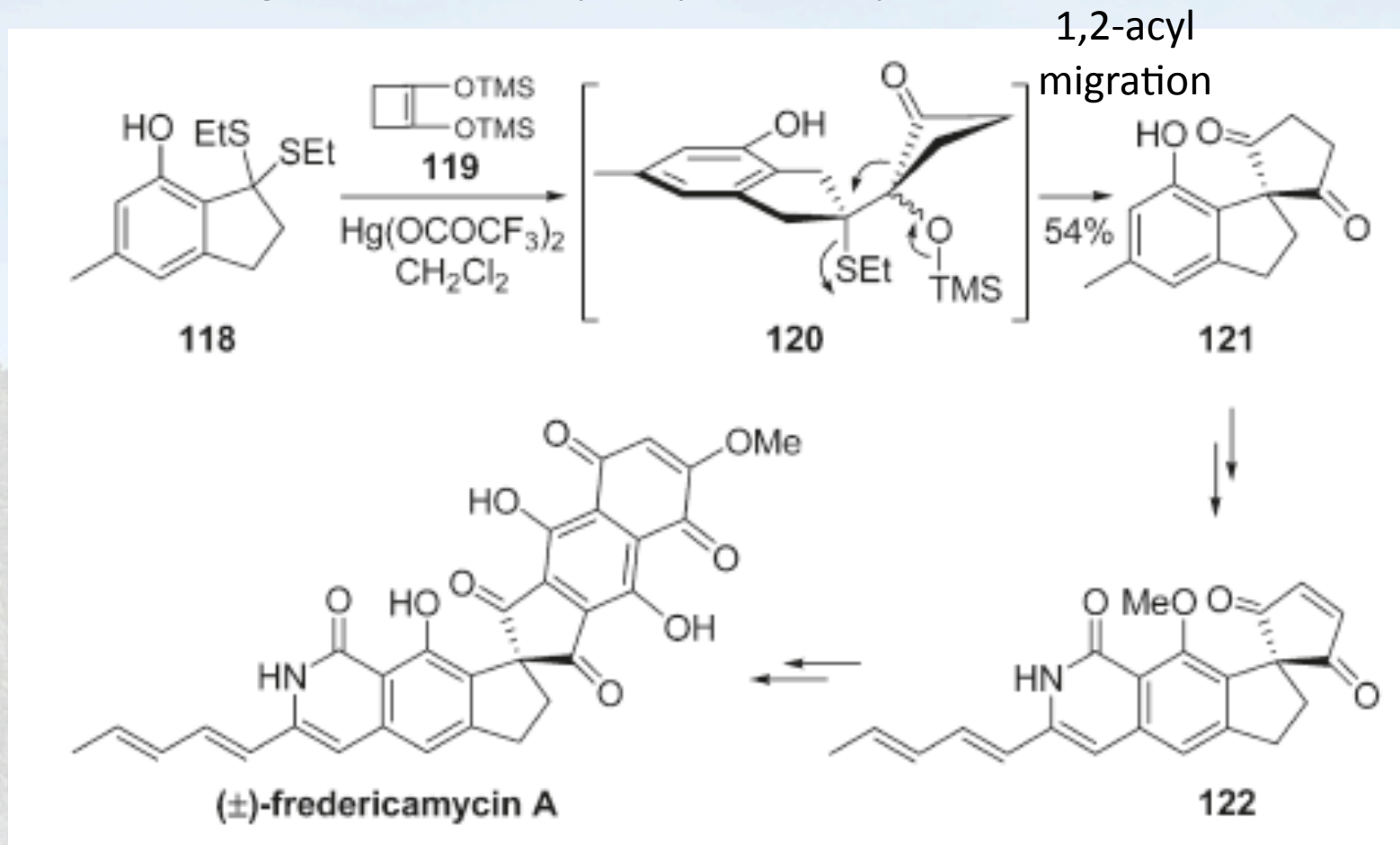
Yoshikoshi's Total Synthesis of Longipinenes:



2.3 Thiolates and Selenolates as Leaving Group

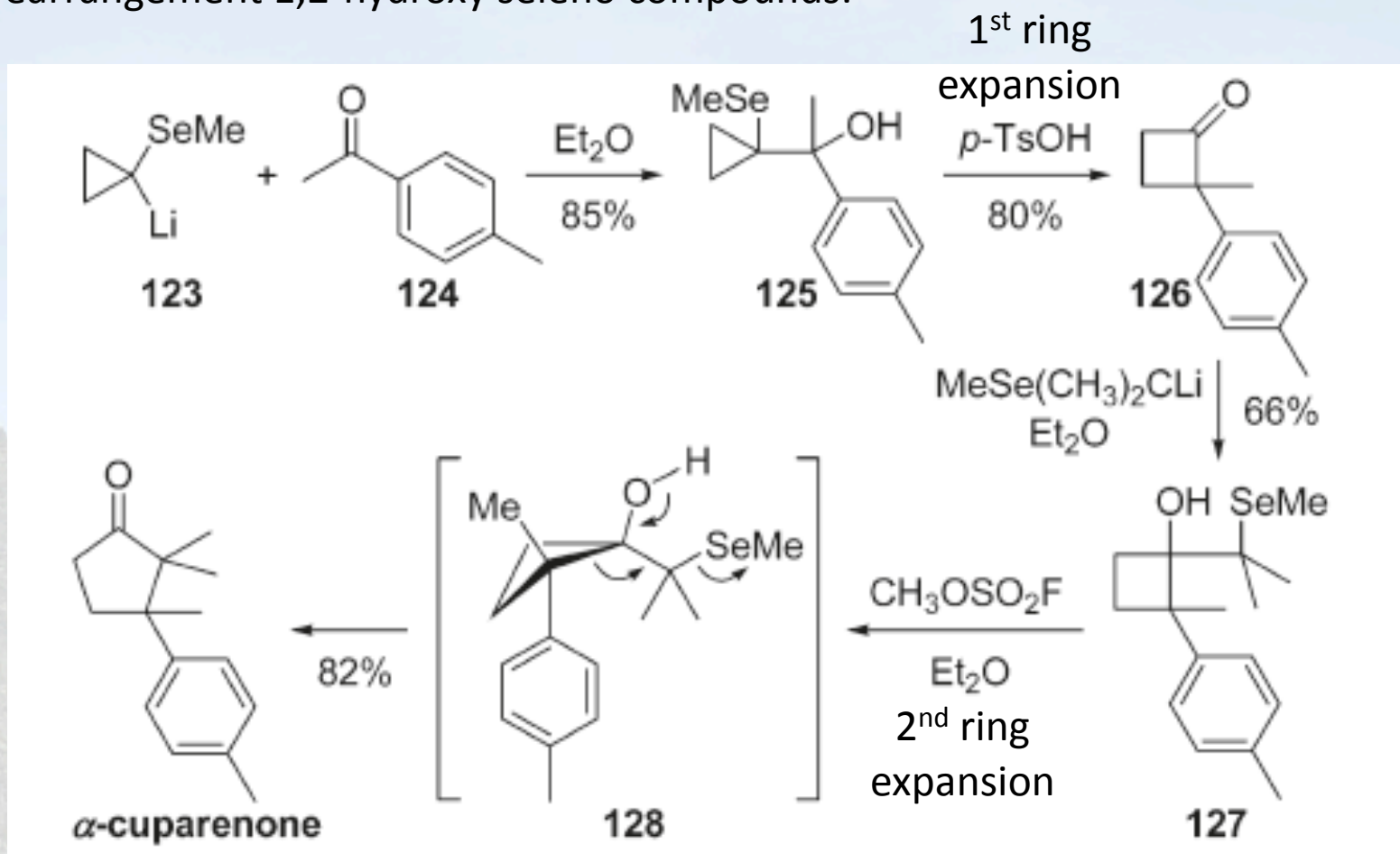
Bach's Total Synthesis of (±)-Fredericamycin A:

rearrangement of a 1,2 hydroxy thiol compound



Krief's Total Synthesis of α -Cuparenone:

rearrangement 1,2-hydroxy seleno compounds:

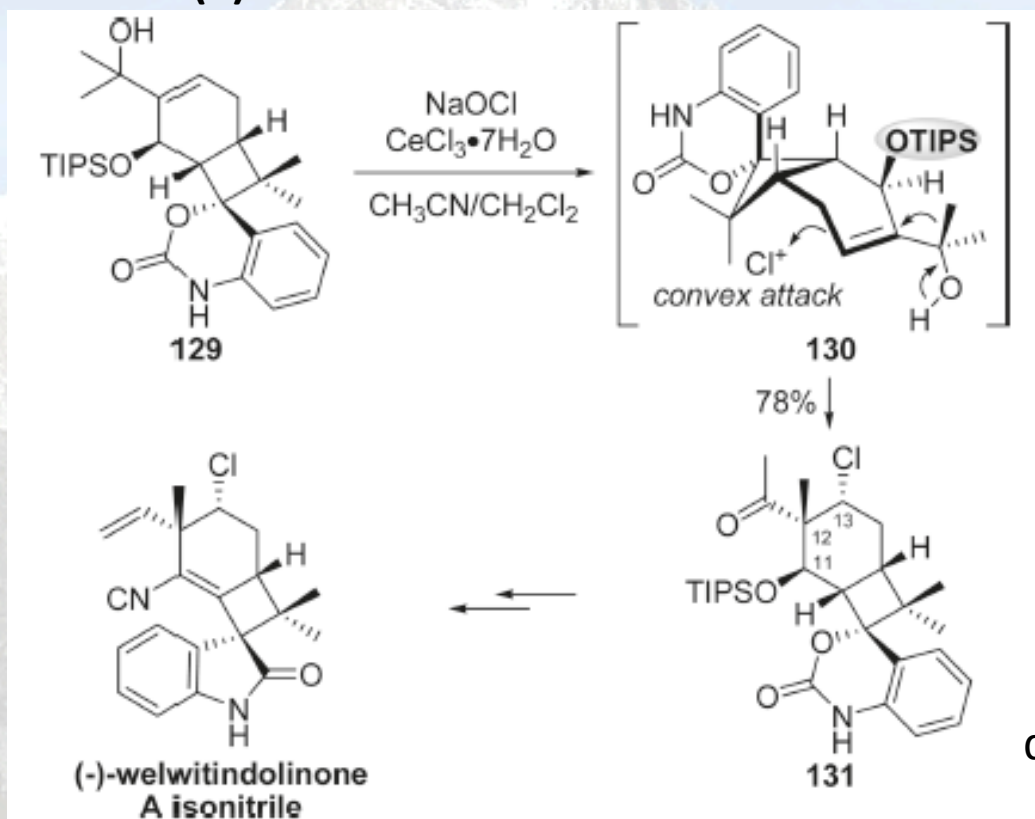


3. Rearrangement of allylic alcohols (Type II)

3.1 Induced by Halonium Ions

Halonium ions are highly electrophilic species that can induce semipinacol rearrangement of various allylic alcohols and their derivatives to give synthetically useful β -halo carbonyl compounds

Wood's Total Synthesis of (-)-Welwitindolinone A Isonitrile:

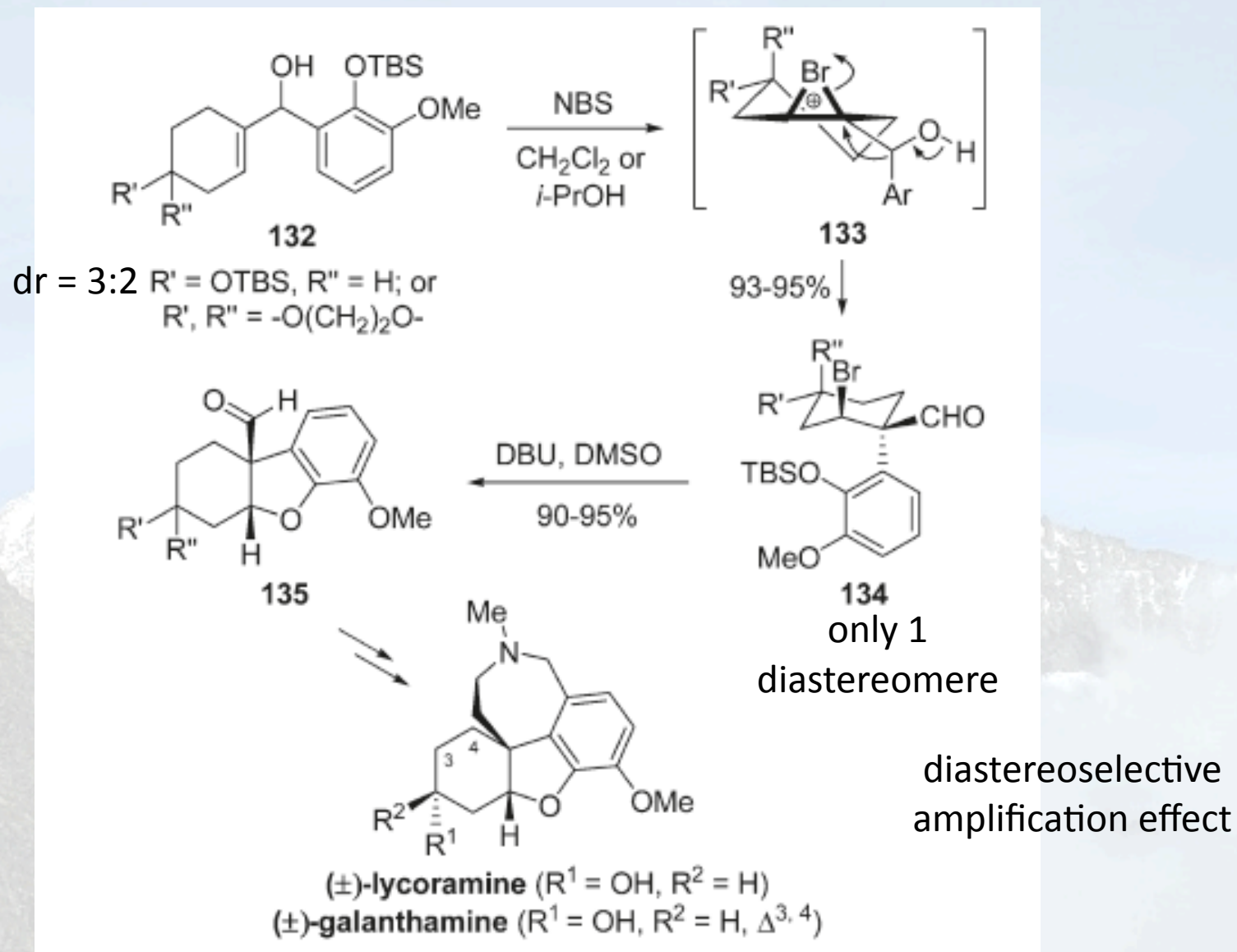


1,2-methyl migration anti to chloronium ion

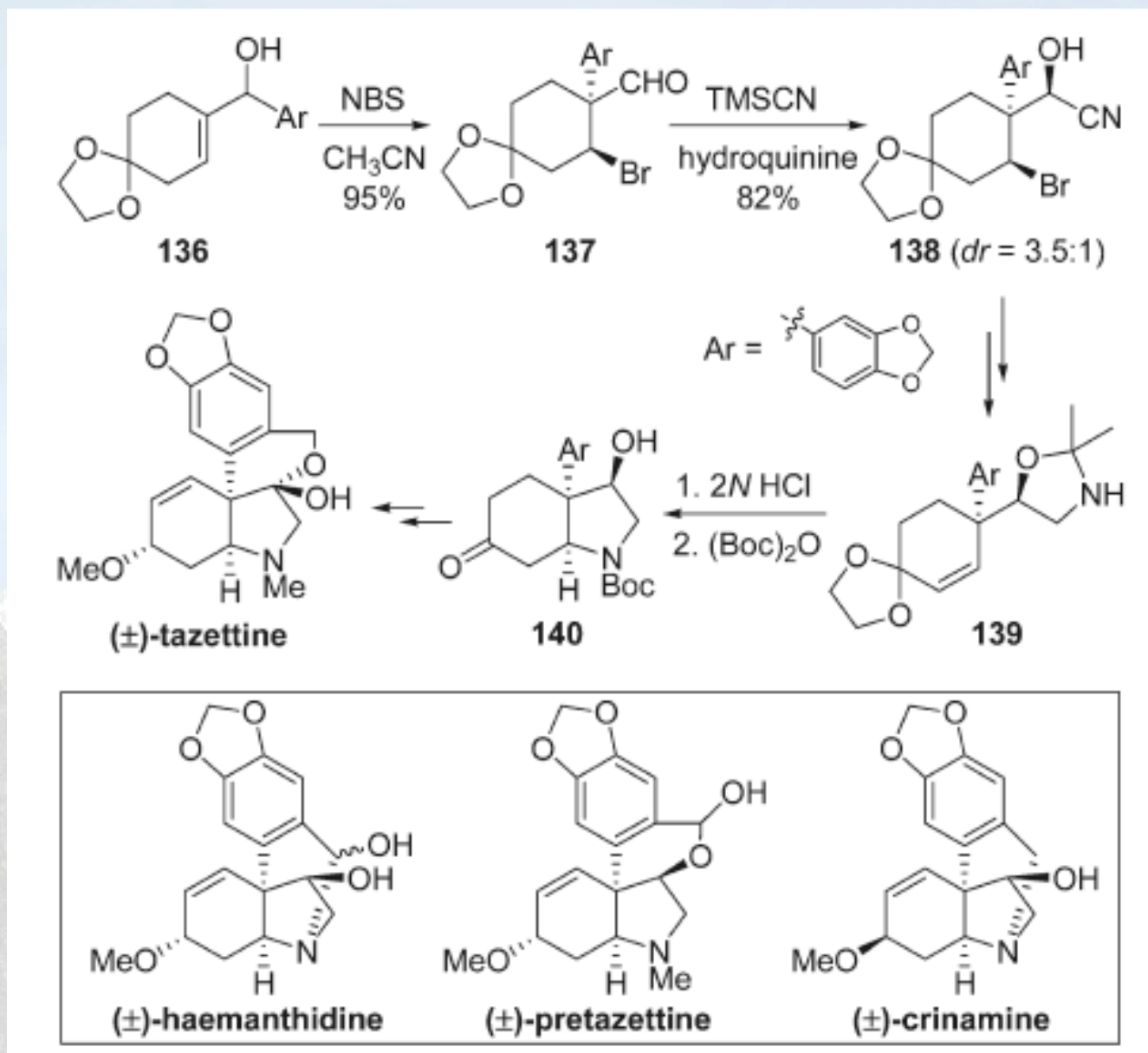
introduction of a quaternary center and neopentyl chlorine diastereoselectively

Tu's Total Syntheses of (±)-Lycoramine and (±)-Galanthamine:

NBS-induced rearrangement/desilylation/cyclization process



Tu's Total Syntheses of (±)-Tazettine, (±)-Haemanthidine, (±)-Pretazettine, and (±)-Crimamine:

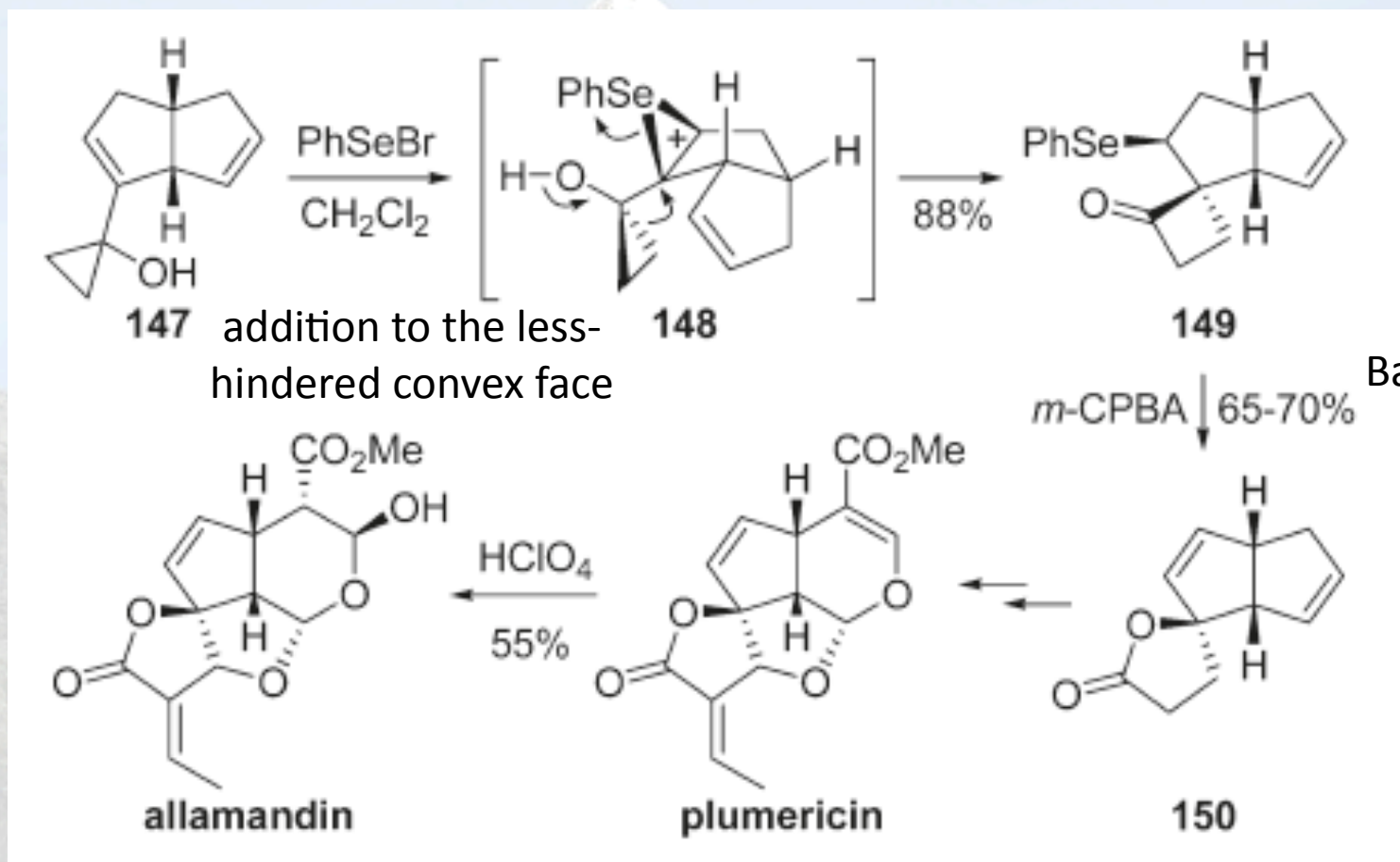


intramolecular
Michael
addition

3.2 Induced by Selenium Ion

similar electrophilicity as halonium ions

Trost's Total Synthesis of Plumericin and Allamandin:



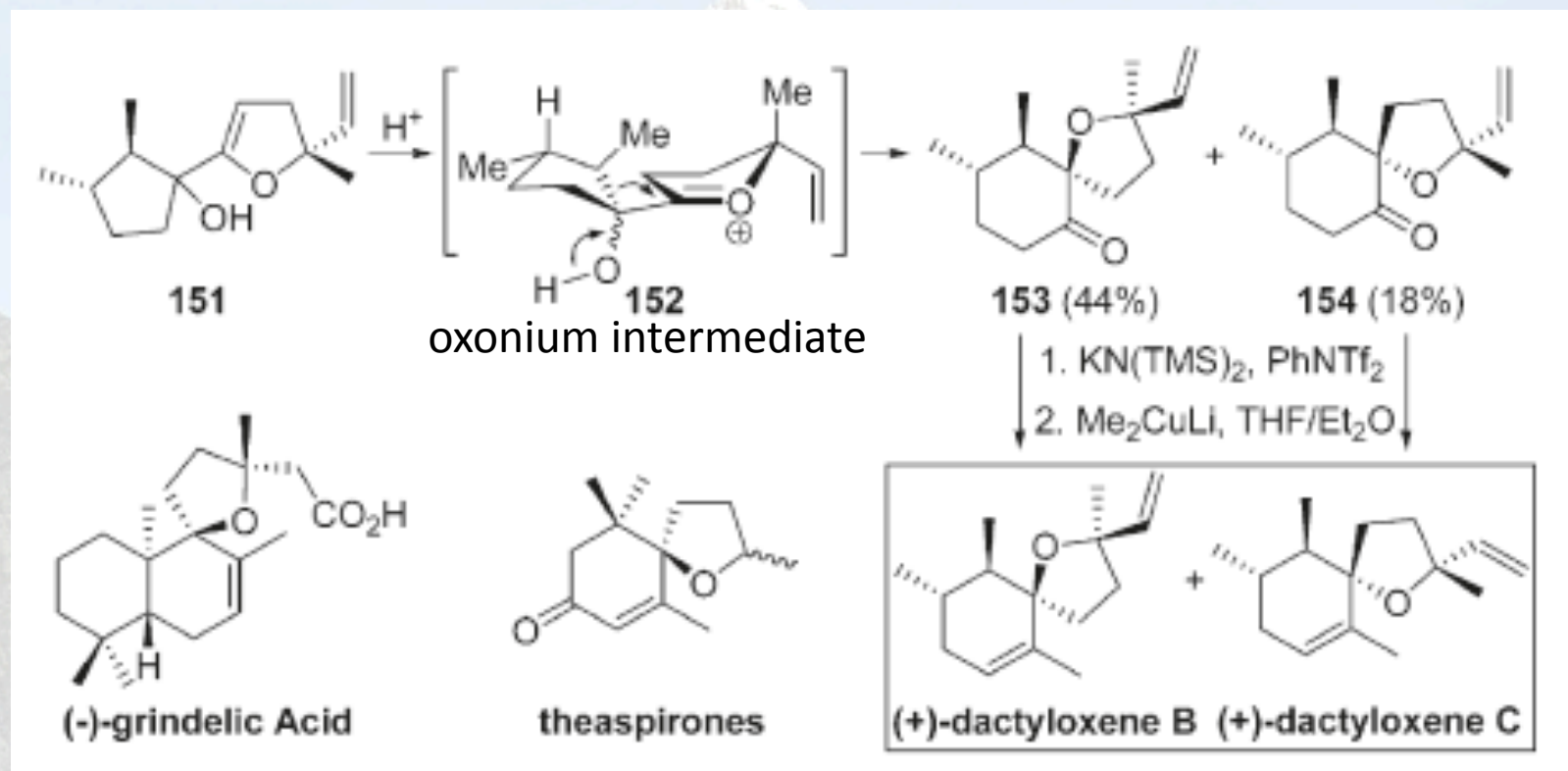
B. M. Trost, M. K. T. Mao, J. M. Balkovec, P. Buhlmyer, *J. Am. Chem. Soc.*, **1986**, *108*, 4965.

B. M. Trost, J. M. Balkovec, M. K. T. Mao, *J. Am. Chem. Soc.*, **1986**, *108*, 4974.

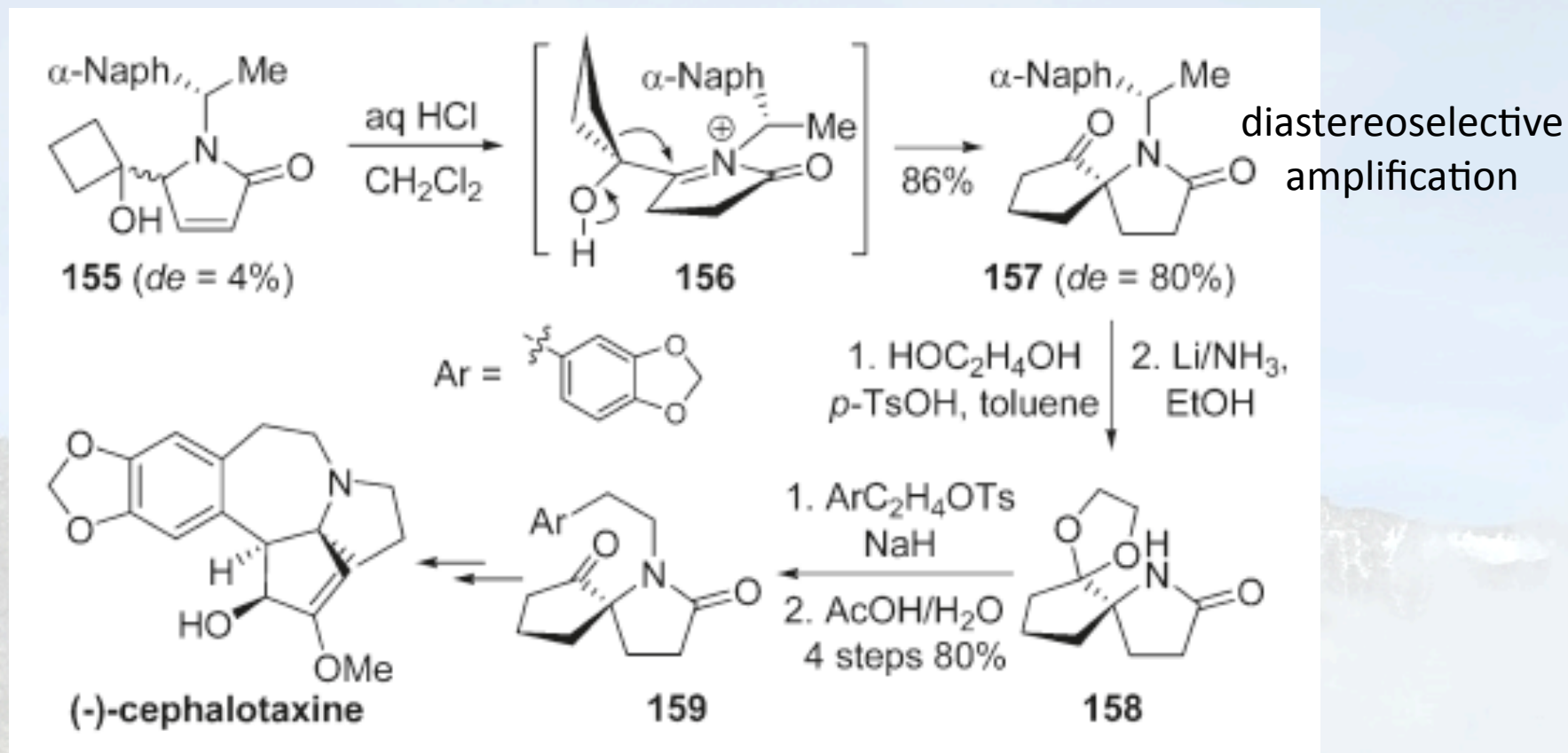
3.3 Induced by Brønsted Acids

Paquette's Total Synthesis of (+)-Dactyloxene B and C:

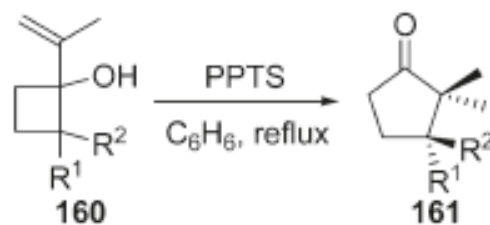
rearrangement of vinyl ether-derived tertiary allylic alcohols



Royer's Total Synthesis of (-)-Cephalotaxine:

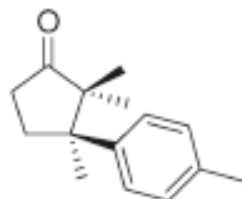


Pira's Total Syntheses of (\pm)- α -Cuparone and Its Analogues:

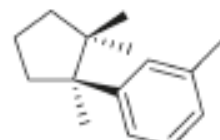


selective 1,2-migration of the more-substituted alkyl group

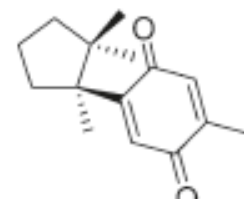
| entry | R ¹ | R ² | yield | natural product |
|-------|----------------|--|--------|----------------------|
| 1 | Me | -C ₆ H ₄ -4-Me- | 76% | 162 |
| 2 | Me | -C ₆ H ₄ -3-Me- | 70% | 163 |
| 3 | Me | -C ₆ H ₂ -2-OMe-4-Me-5-OMe | 91-94% | 164, 165, 166 |
| 4 | Me | -C ₆ H ₂ -2-OMe-4-Me | 91-94% | 167 |



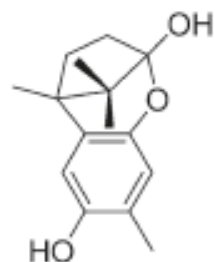
(\pm)- α -cuparenone **162**



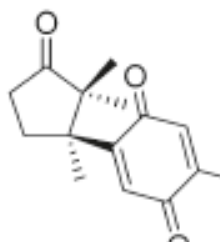
(\pm)-herbertene **163**



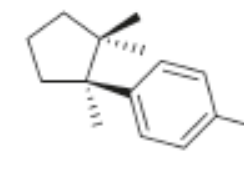
(\pm)-cuparene-1,4-quinone **164**



(\pm)-enokipodins A **165**



(\pm)-enokipodins B **166**

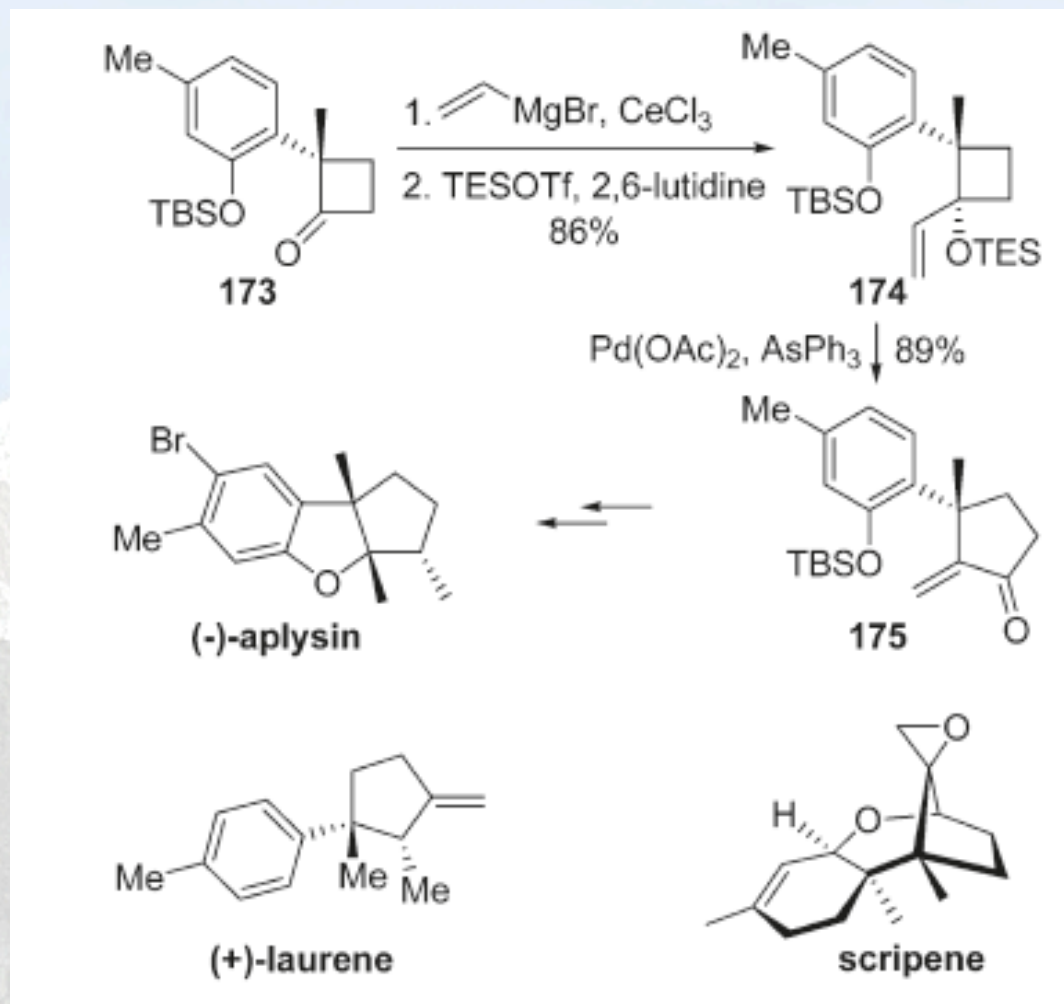


(\pm)-cuparene **167**

3.4 Induced by Lewis Acid

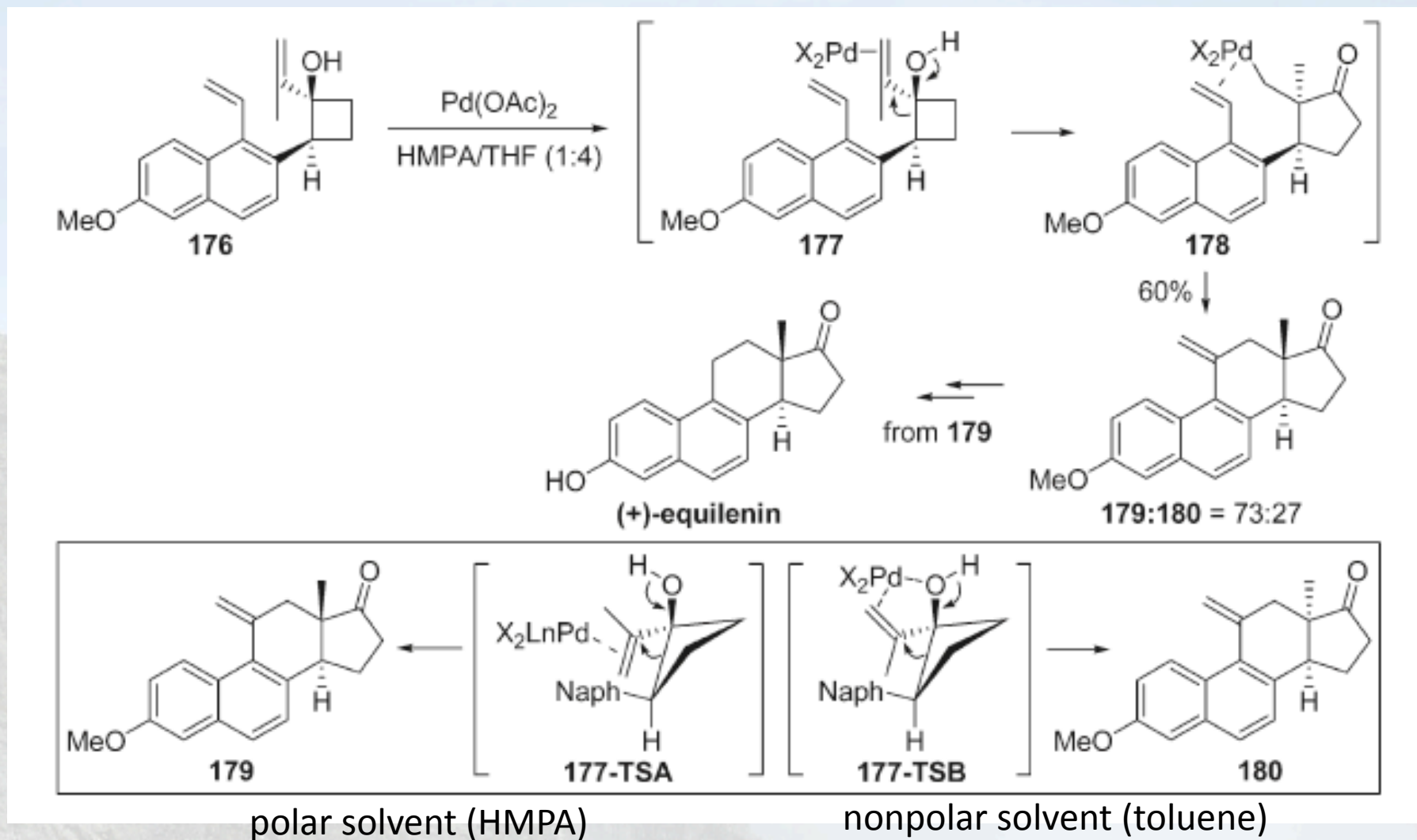
such as $\text{BF}_3 \cdot \text{OEt}_2$, $\text{Hg}(\text{OCOCF}_3)$ and $\text{Pd}(\text{II})$ catalysts by activating the $\text{C}=\text{C}$ bond

Nemoto and Fukumoto's Total Synthesis of (-)-Aplysin:



Nemoto and Ihara's Asymmetric Total Synthesis of (+)-Equilenin:

tandem Pd(II)-promoted ring-expansion/intramolecular-insertion process

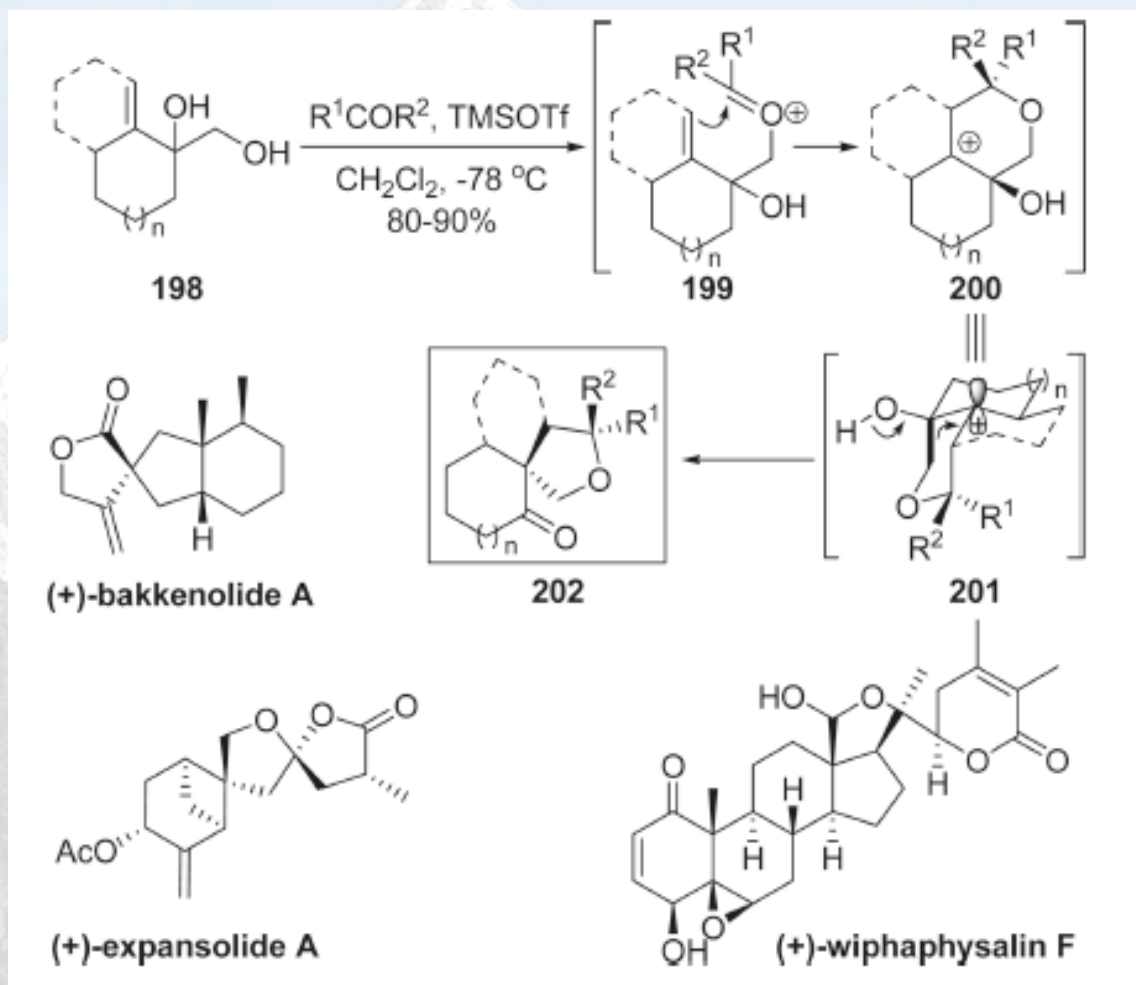


3.4 Prins-Pinacol rearrangement

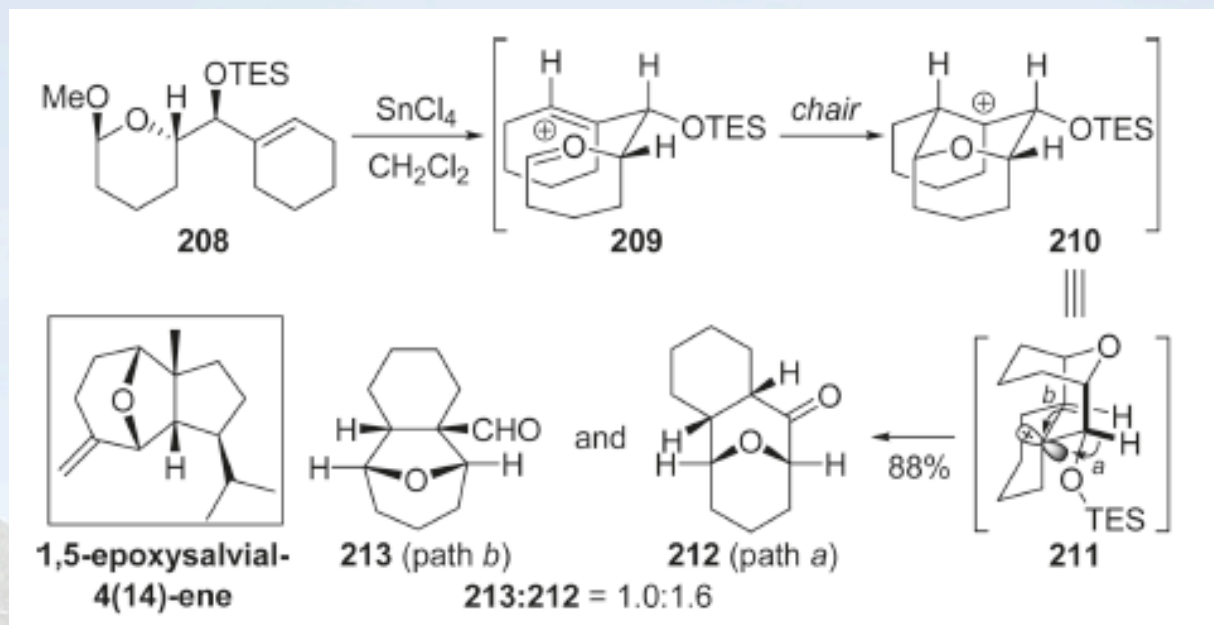
rearrangement involves a final Prins reaction followed in tandem by a pinacol-like (or semipinacol) rearrangement (Overman's group)

Min and Cho's Stereocontrolled Synthesis of Spiro Oxabicycles via Prins-Pinacol Annulation:

method for synthesis of spirooxacyclic compounds:

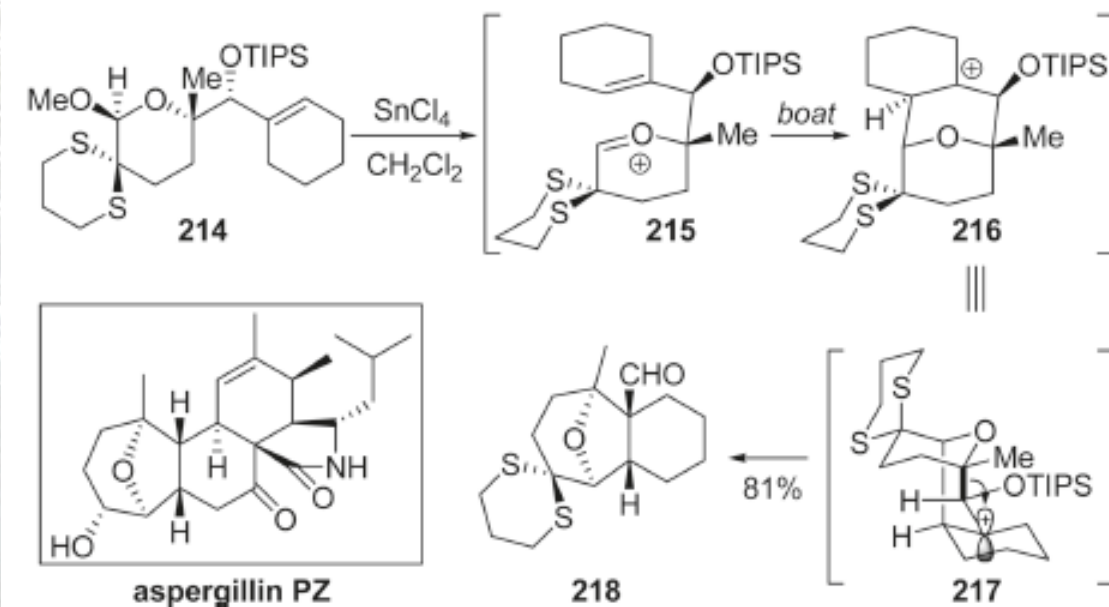


Overman's Stereocontrolled Construction of Either Stereoisomer of 12-Oxatricyclo-[6.3.1.0]-dodecanes:



a: 1,2-migration of C-H bond
b: 1,2-migration of C-C bond

idea: tuning the substrate to control the stereochemistry of the transition state between chair and boat conformations during the Prins cyclization

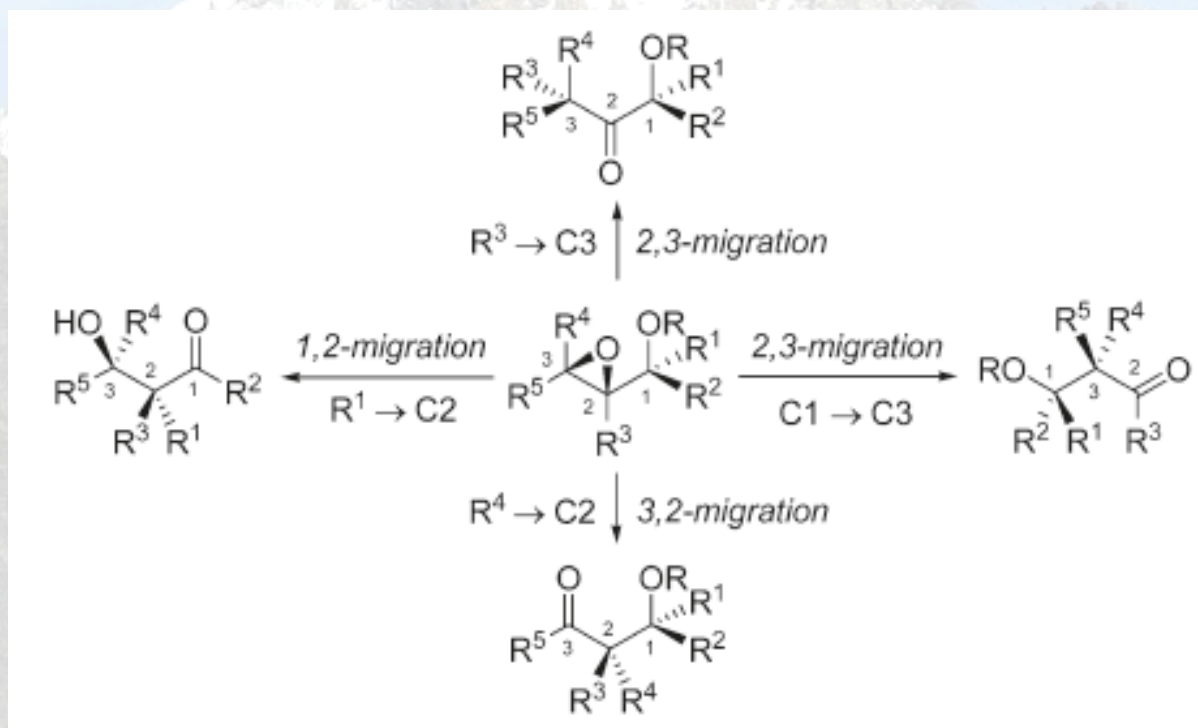


4. Rearrangement of epoxides (Type III)

4.1 2,3-Epoxy Alcohols and the Derivatives

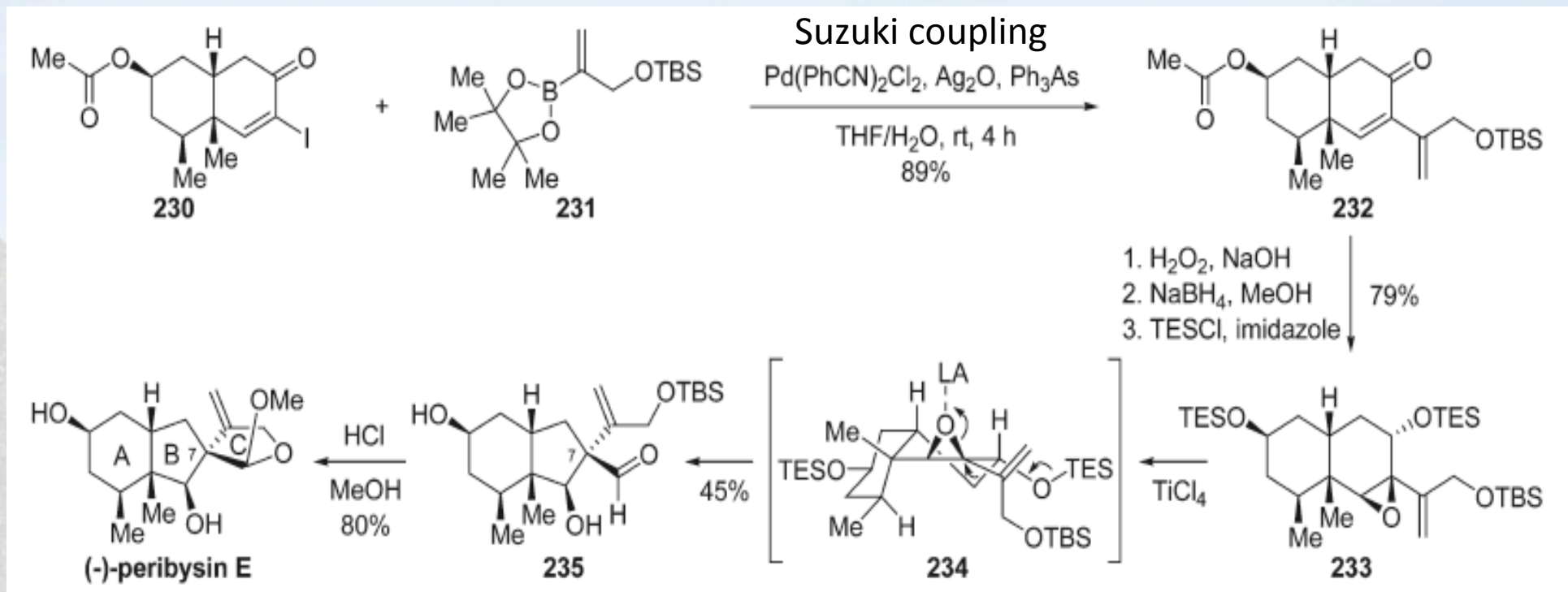
advantages:

- variety of Lewis acids can be used (also in catalytic amount)
- migrating group generally attacks anti to the epoxide
- reaction can generate various aldol-type products diastereoselectively or enantioselectively if antipure 2,3 epoxy alcohols are used (easily prepared via Sharpless asymmetric epoxidation)
- resulting carbonyl can serve as reactive site to support tandem reactions



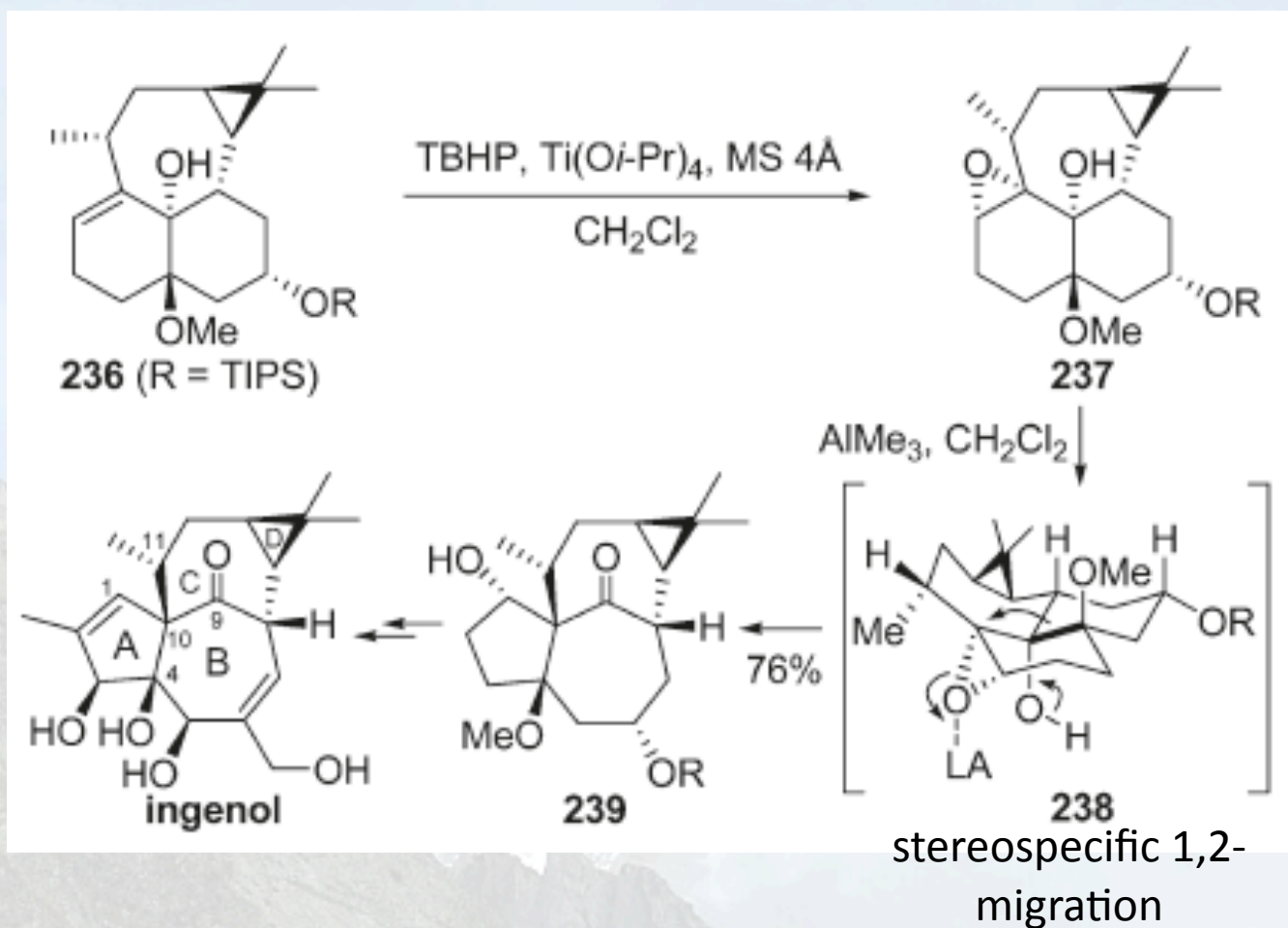
1,2-migration

Danishefsky's Total Synthesis of (-)-Peribysin E:



Tanino and Kuwajima's Total Synthesis of Ingenol:

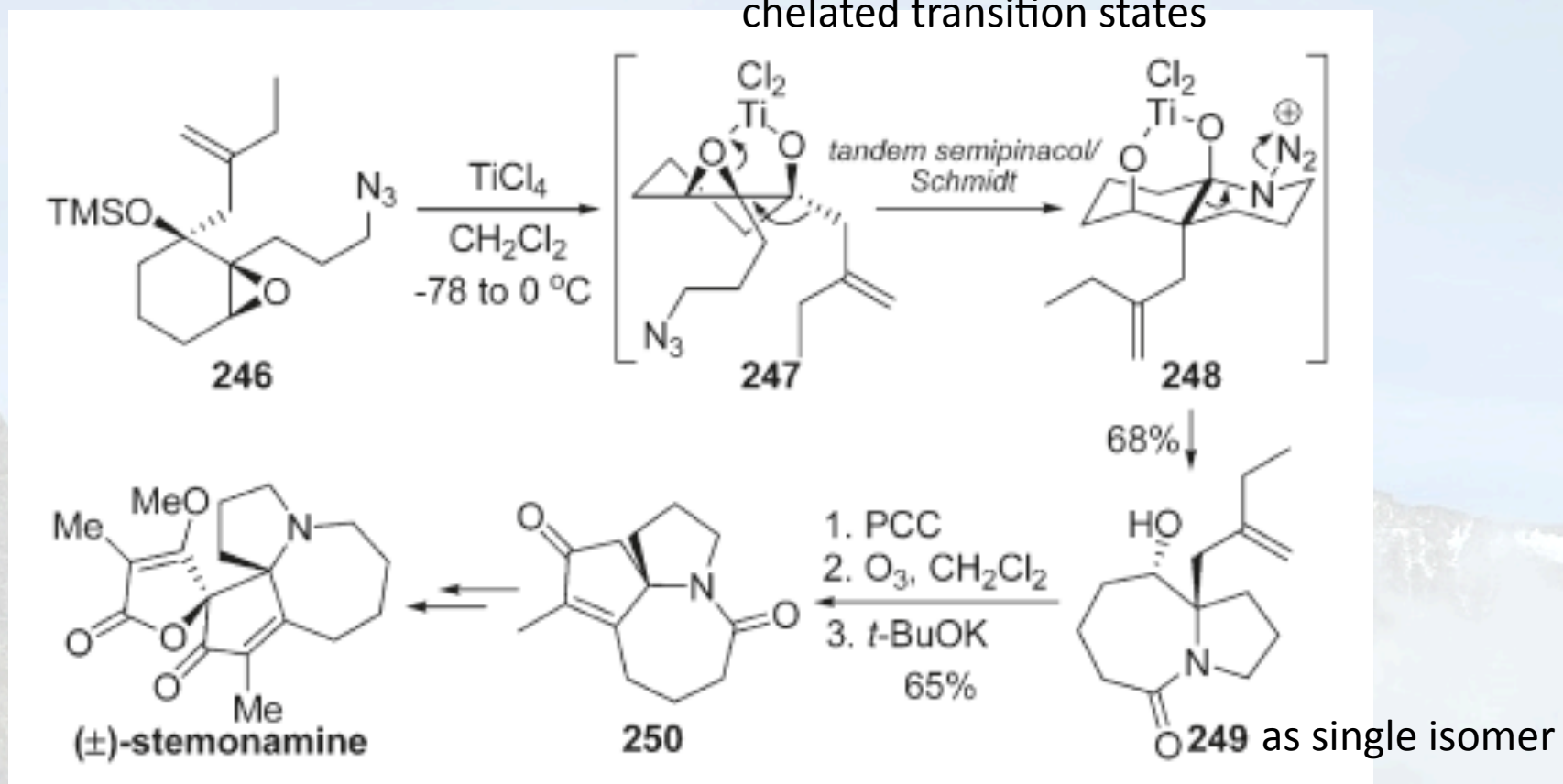
interesting highly strained „inside-outside“ trans intrabridge-head



Tu's Total Synthesis of (\pm)-Stemonamine:

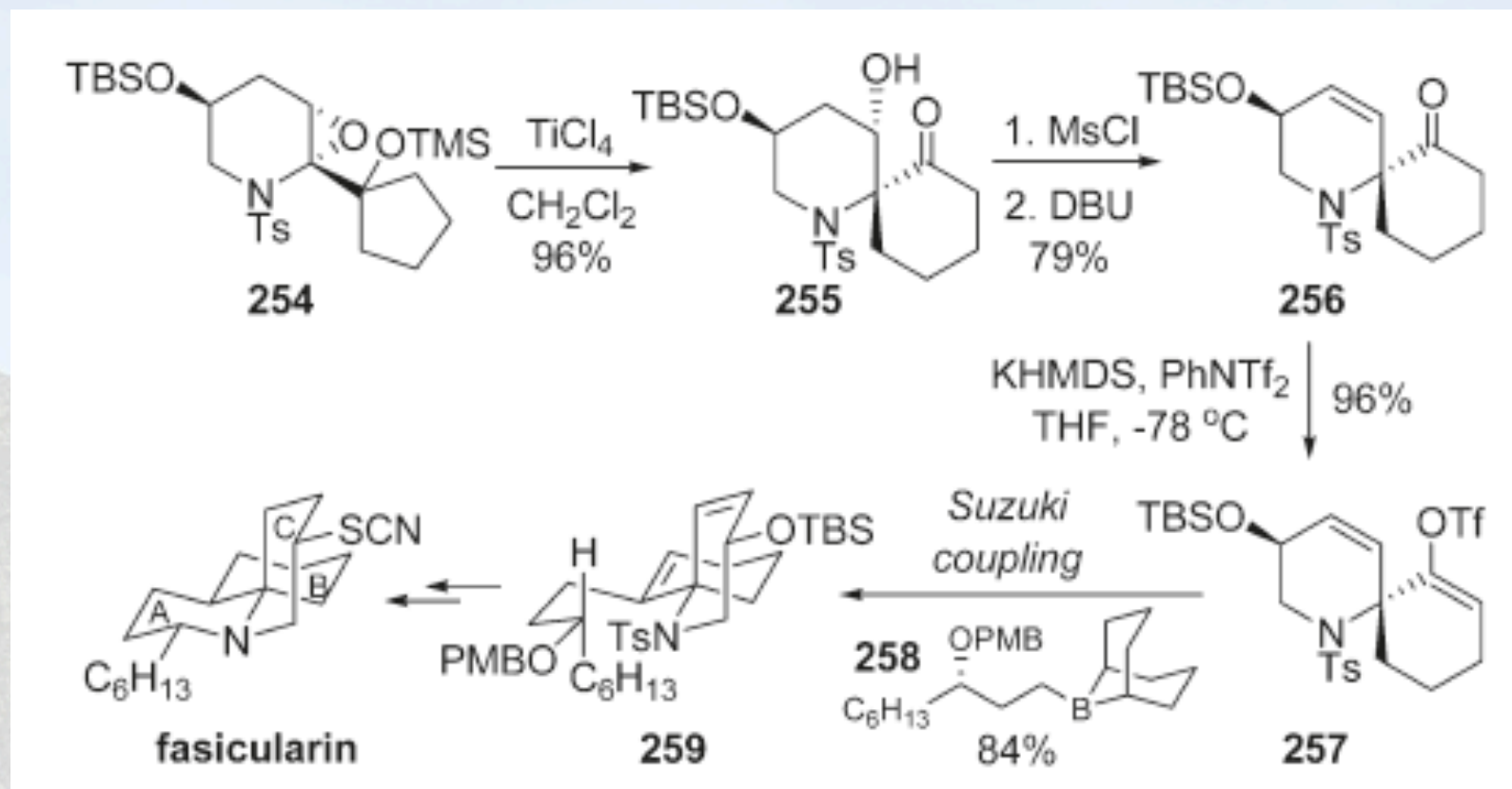
tandem semipinacol/Schmidt reaction

chelated transition states



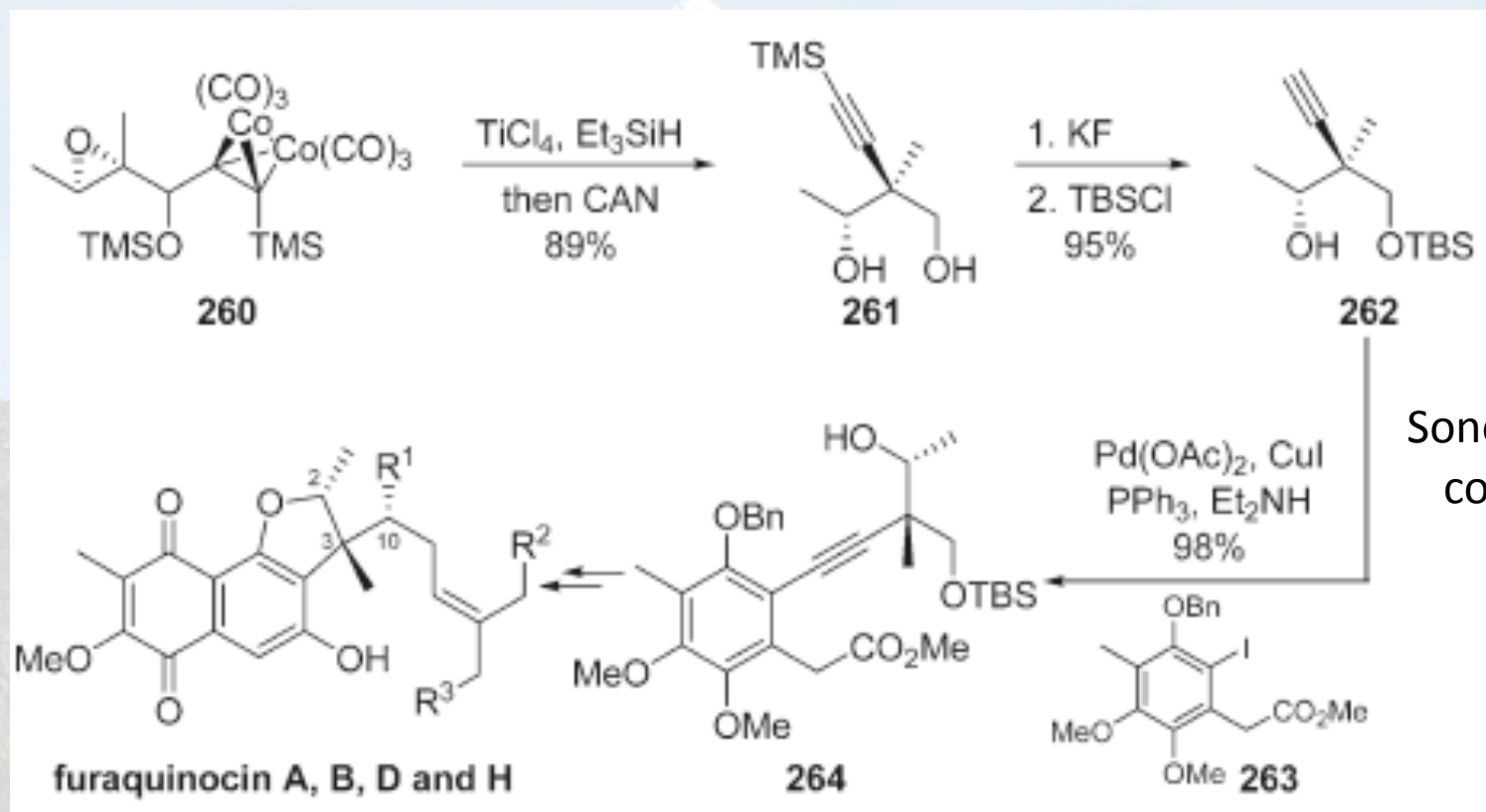
Dake's Formal Total Synthesis of Fascicularin:

method to construct aza-spirocyclic skeleton



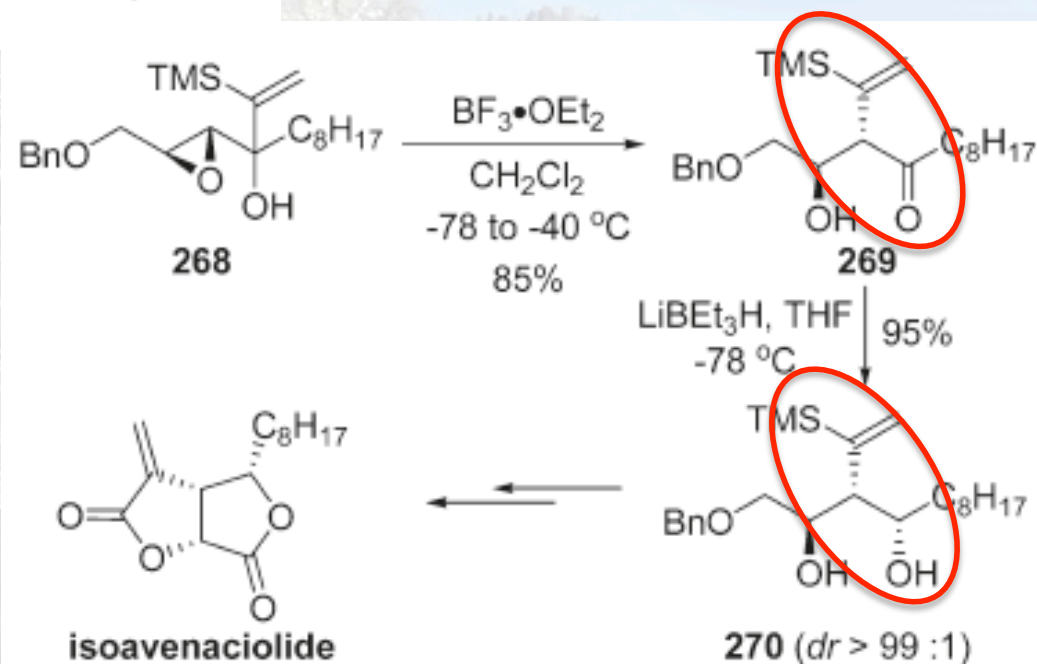
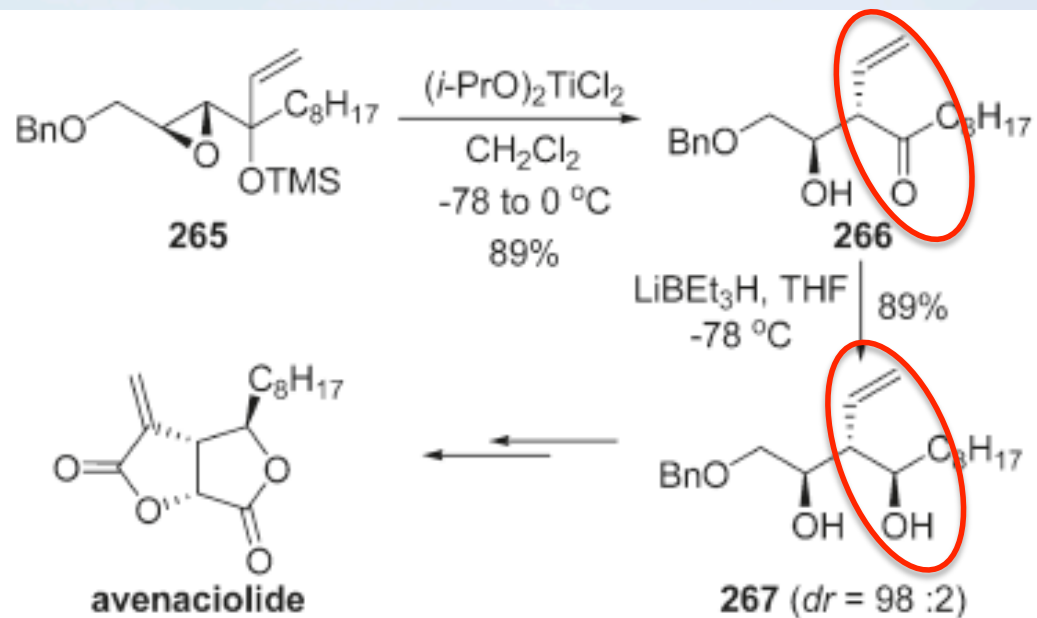
Suzuki's Total Syntheses of Furaquinocins A, B, D, and H:

acyclic 2,3-epoxy silyl ether containing a Co-complexed alkynyl group
=> introduction of quaternary center stereoselectively



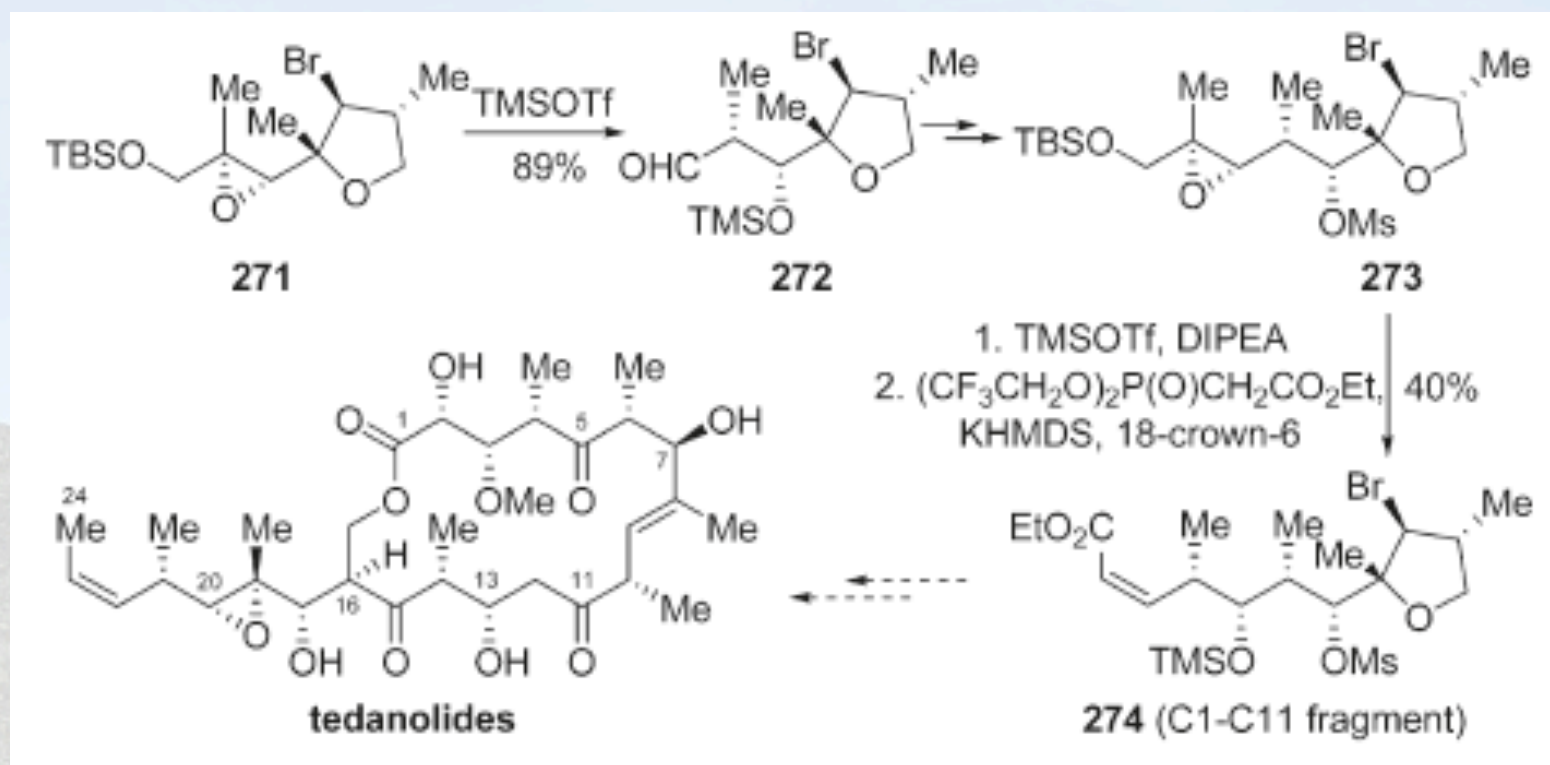
Sonogashira
coupling

Tsuchihashi and Suzuki's Total Syntheses of Avenciolide and Isoavenciolide:



Jung's Synthesis of the C1-C11 Subunit of Tedanolides:

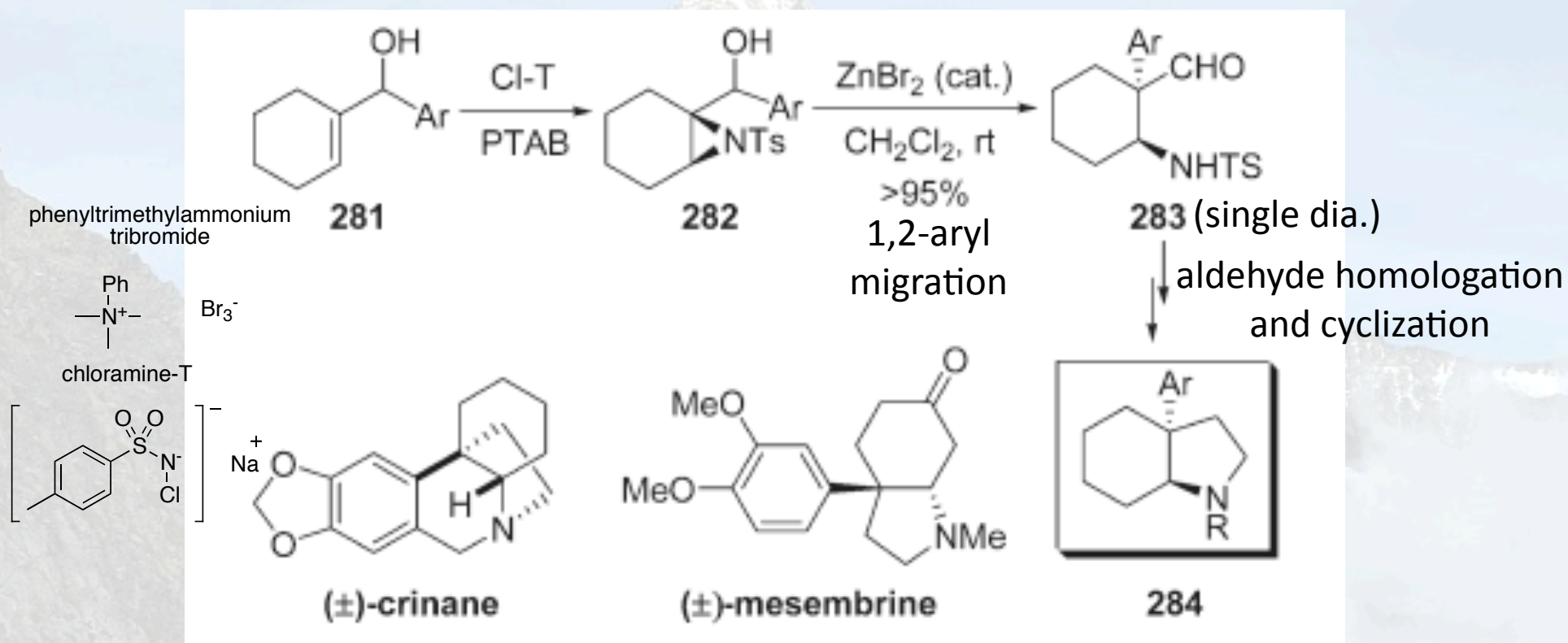
useful „nonaldol aldol“ process based on acyclic 2,3-epoxy silyl ethers



unusual 1,2-migration of C-H bond

Tu's Total Syntheses of (±)-Crinane and (±)-Mesembrine:

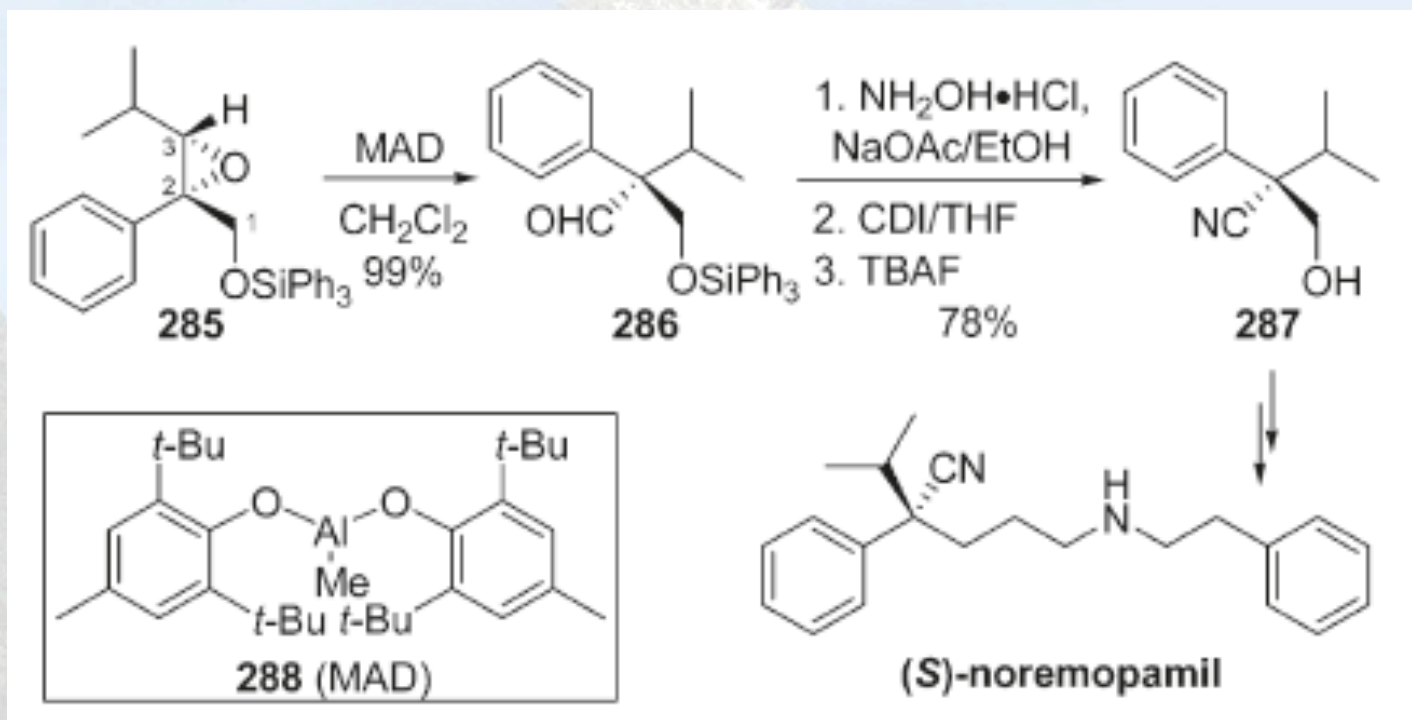
2,3-aziridino alcohols can also undergo Lewis acid-catalyzed semipinacol rearrangement => α -quaternary, β -amino carbonyl compounds



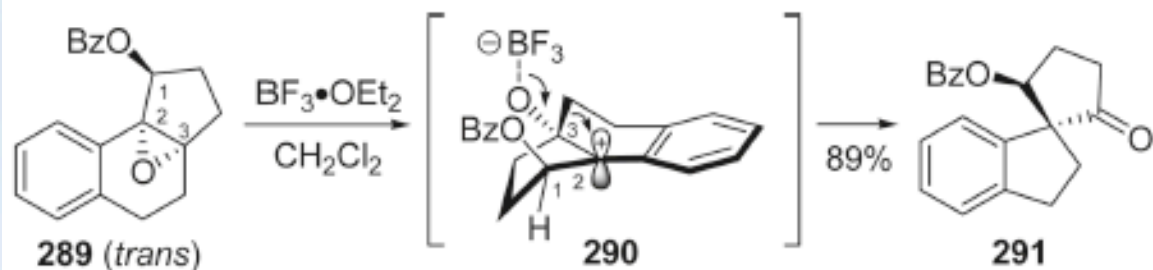
3,2-migration

in some special cases 3,2-migration instead of 1,2-migration occurs during the rearrangement

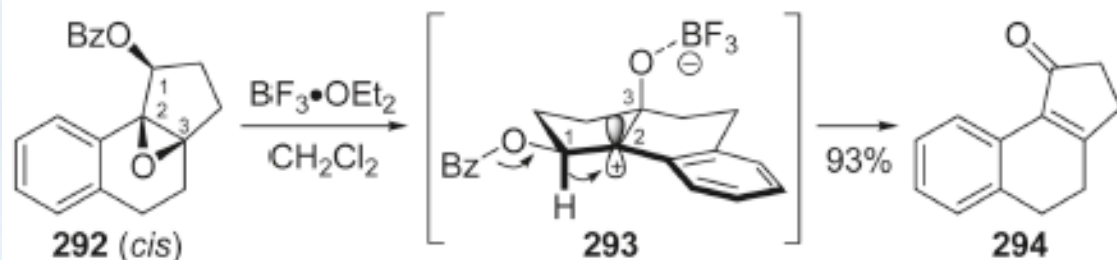
Kimura's Total Synthesis of (S)-Noremopamil:



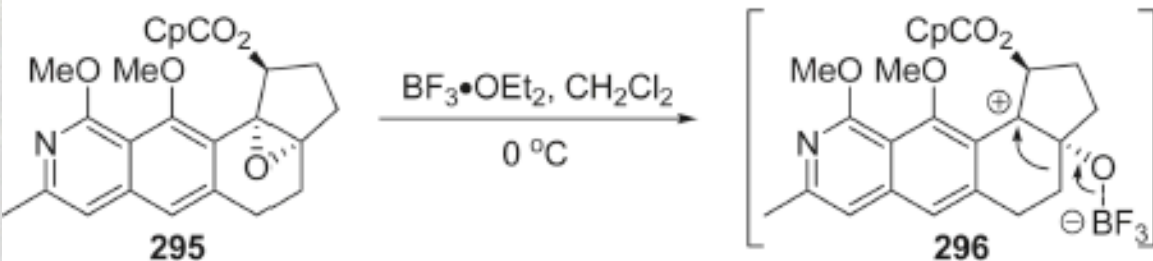
Kita's Total Synthesis of Fredericamycin A:



3,2-migration of C-C bond

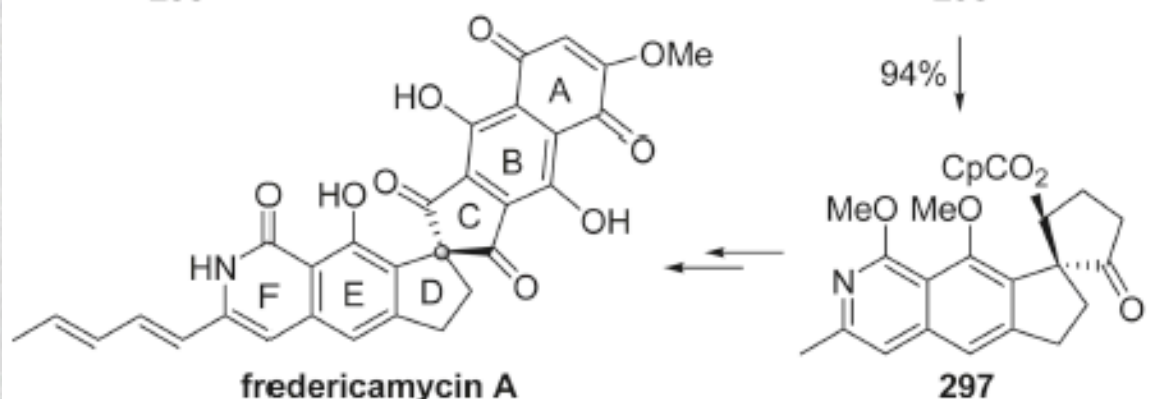


1,2-migration of C-H bond



reason:

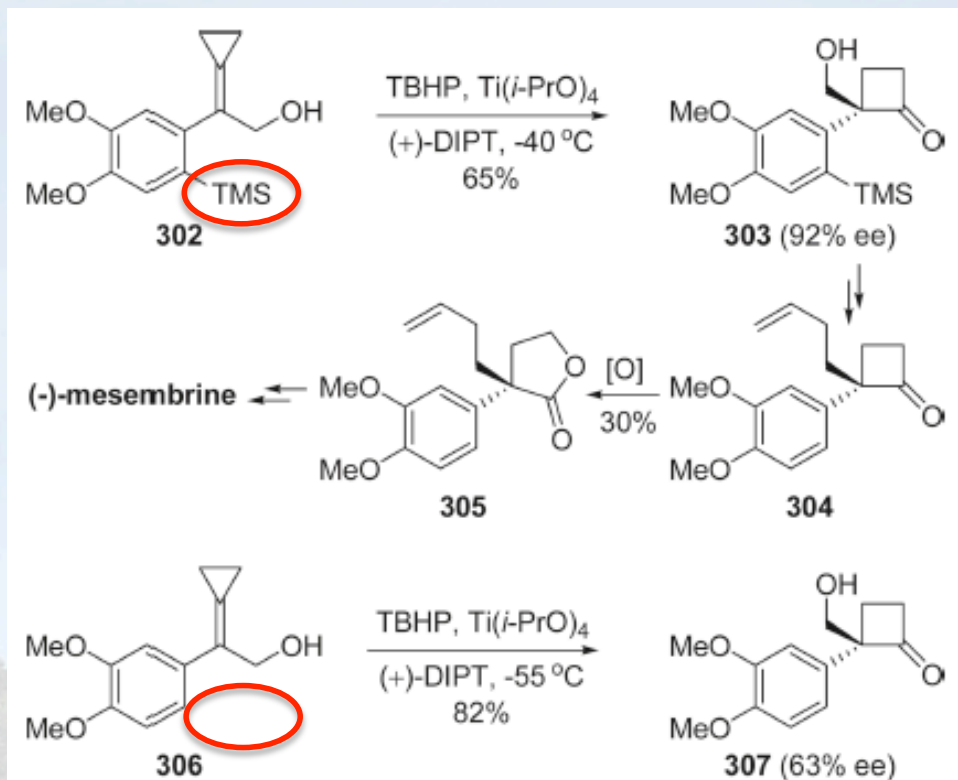
- regioselective epoxide opening to give the more stable benzylic carbocation
- in **290**: C-C bond antiperiplanar to empty vicinal *p* orbital => such situation does not exist for **293** => alternative 1,2-migration of C-H bond adjacent to benzoyl group



Y. Kita, K. Higuchi, Y. Yoshida, K. Iio, S. Kitagaki, S. Akai, H. Fujioka, *Angew. Chem., Int. Ed.*, **1999**, 38, 683.

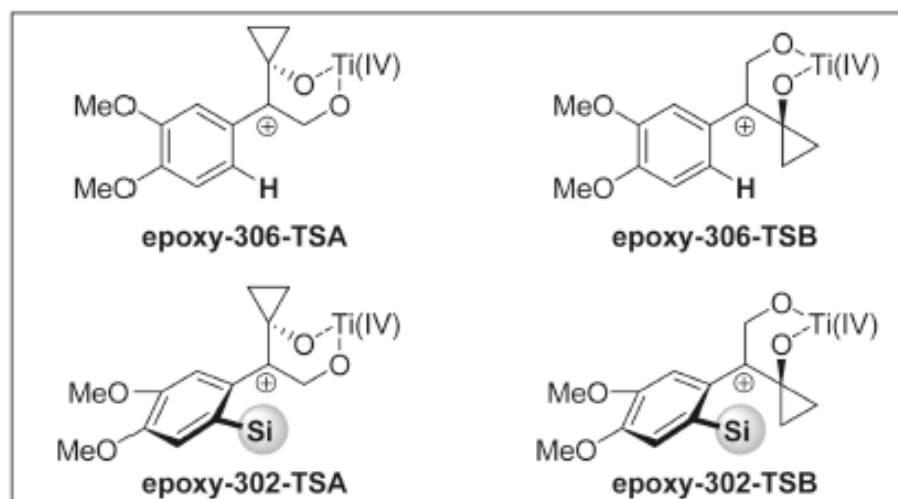
Y. Kita, K. Higuchi, Y. Yoshida, K. Iio, S. Kitagaki, K. Ueda, S. Akai, H. Fujioka, *J. Am. Chem. Soc.*, **2001**, 123, 3214.

Nemoto and Fukumoto's Total Synthesis of (-)-Mesembrine:



classical conditions for SAE =>
good ee but lower yield

classical conditions for SAE =>
good yield but lower ee

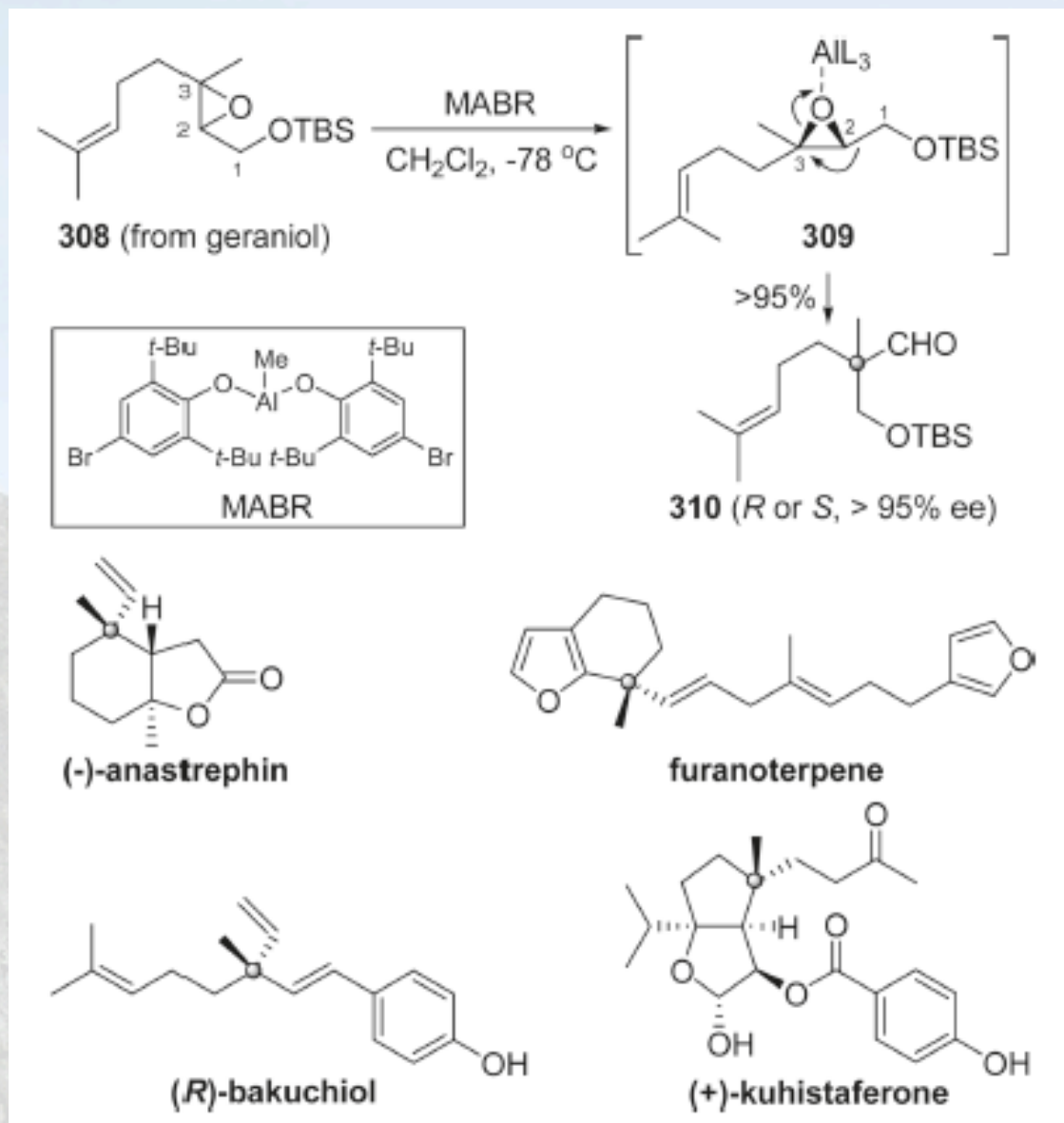


benzylic carbocation stabilized by overlap
with phenyl group => high reactivity of
306 => epimerization possible

steric hindrance between TMS and
hydroxyl methyl and cyclopropyl group
=> phenyl no longer coplanar to
carbocation center => lack of stabilization
=> reduction of reactivity => preventing
epimerization

2,3-migration

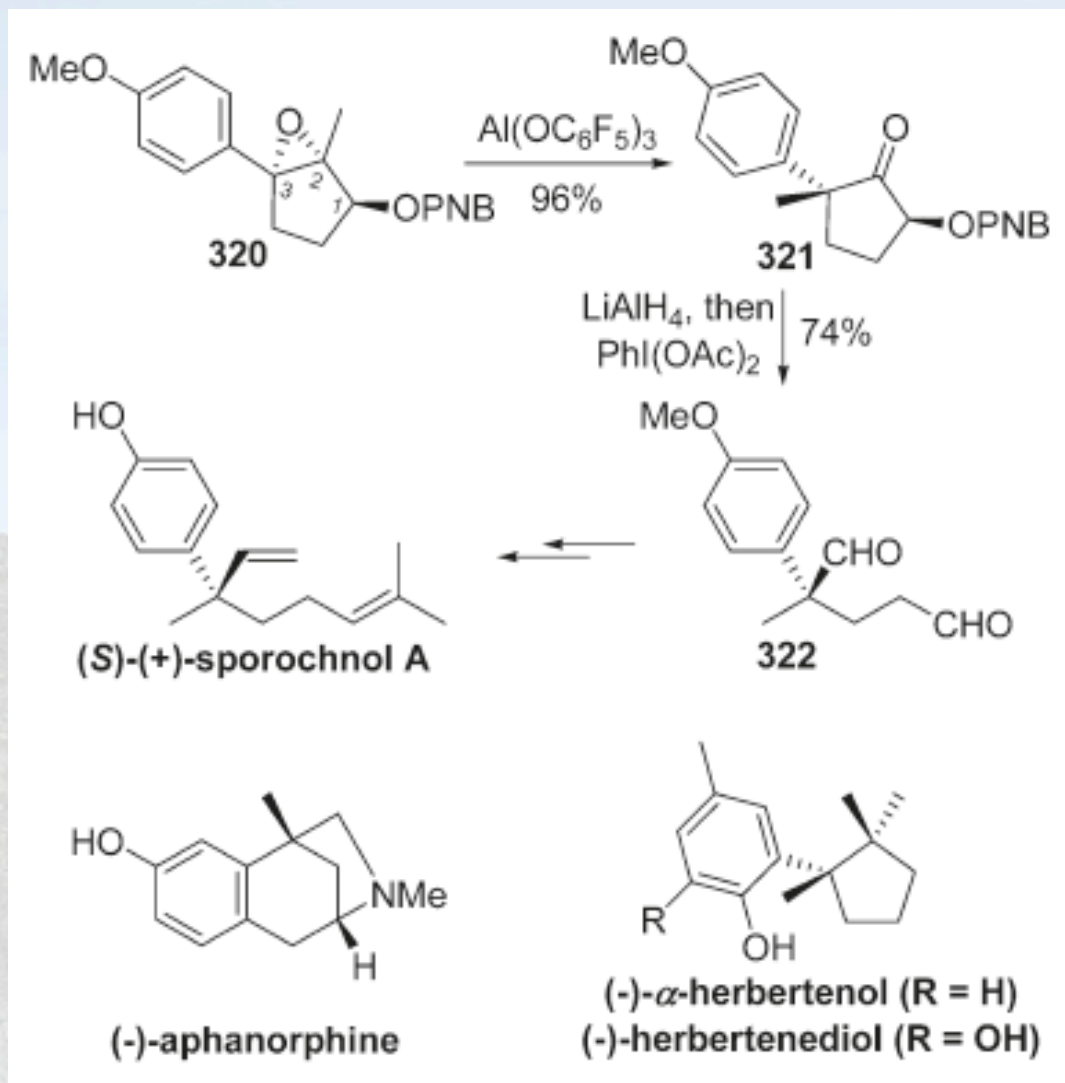
Yamamoto's Semipinacol Rearrangements of 2,3-Epoxy Silyl Ethers Promoted by MABR:



Generally:

- two substituents or cation-stabilizing group at C3
- selective opening at C3 => 2,3-migration
- bulky ligand on catalyst crucial for rearrangement:
 - 1) repulsion between ligand and siloxymethyl moiety facilitates alkyl migration
 - 2) bulky ligand inhibits siloxymethyl moiety interaction with cation

Kita's Total Syntheses of (S)-(+)-Sporochnol A, (-)-Aphanorphine, (-)- α -Herbertenol, and (-)-Herbertenediol:



regioselective C3-cleavage of oxirane ring \Rightarrow 2,3-migration of methyl group

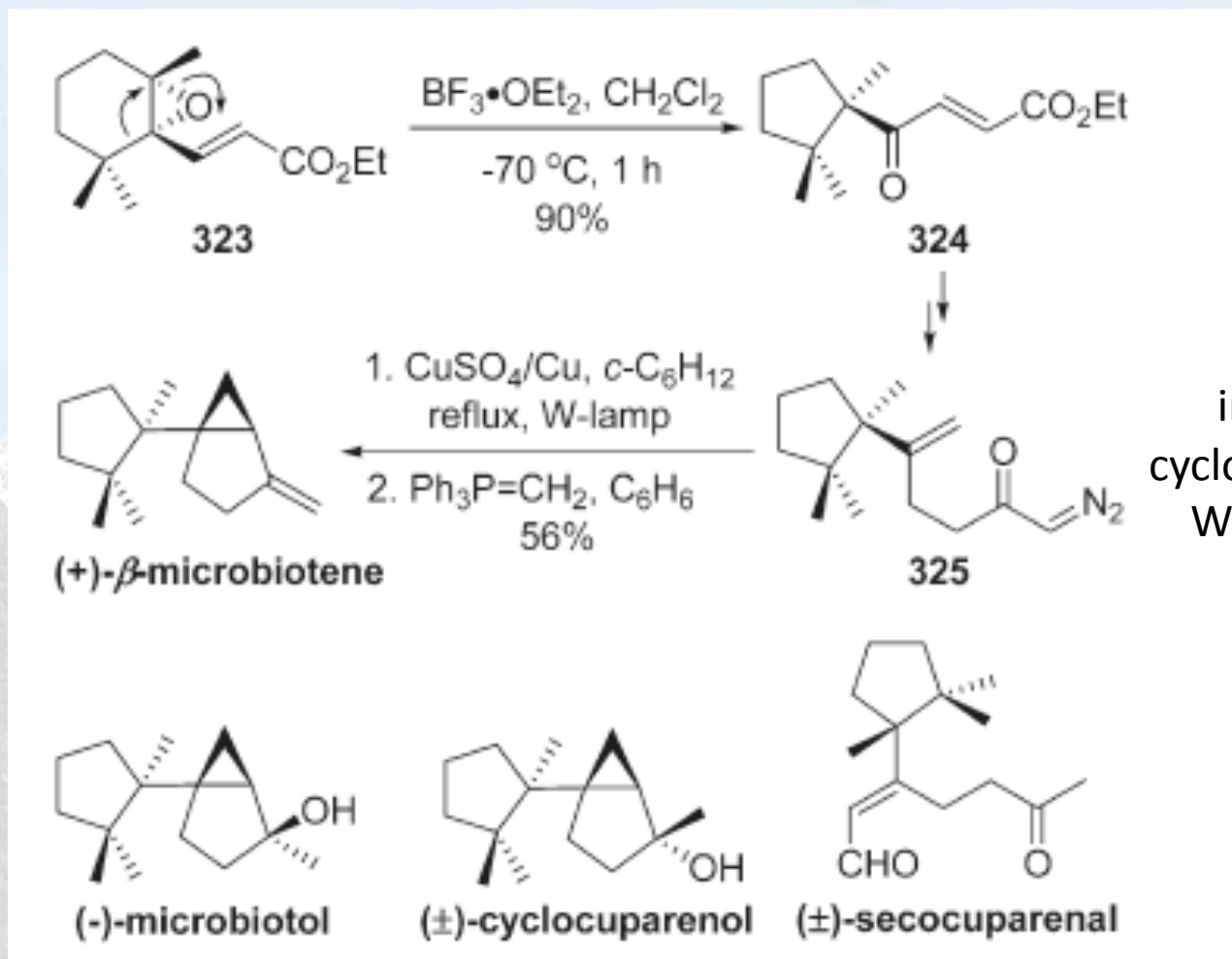
Reasons for regioselectivity:

- electron-withdrawing nature of acyloxy alkyl group
- stabilizing ability of the electron-rich aryl group

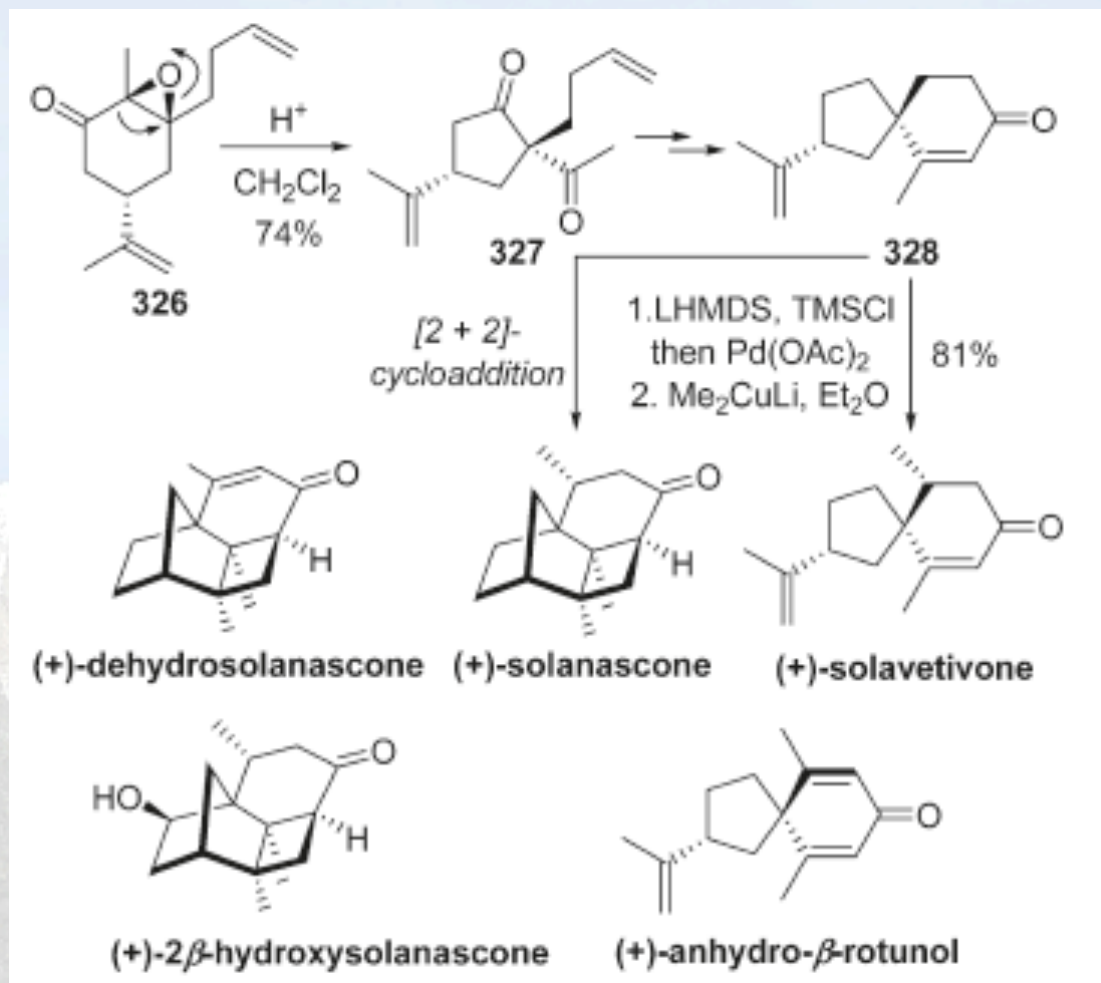
4.2 Simple Epoxides and 2,3-Epoxy Ketones

Srikrishna's Total Syntheses of (-)-Microbiotol and (+)- β -Microbiotene:

semipinacol rearrangement of tetrasubstituted cyclic epoxides with one electron-withdrawing substituent



Srikrishna's Total Syntheses of (+)-Solavetivone and (+)-Solanascon:

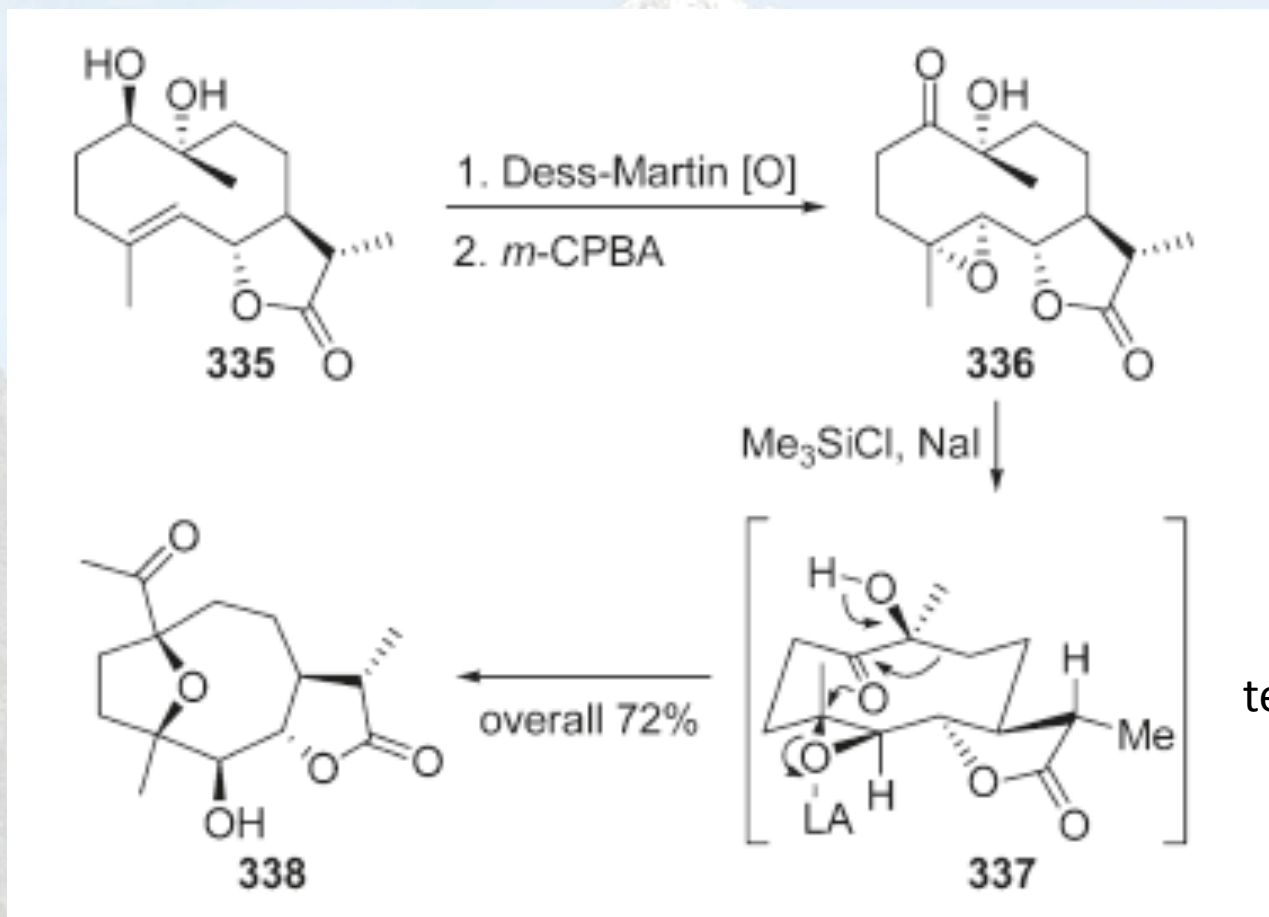


A. Srikrishna, S. S. V. Ramasastry, *Tet. Lett.*, **2005**, 46, 7373.

A. Srikrishna, S. S. V. Ramasastry, *Tet. Lett.*, **2006**, 47, 335.

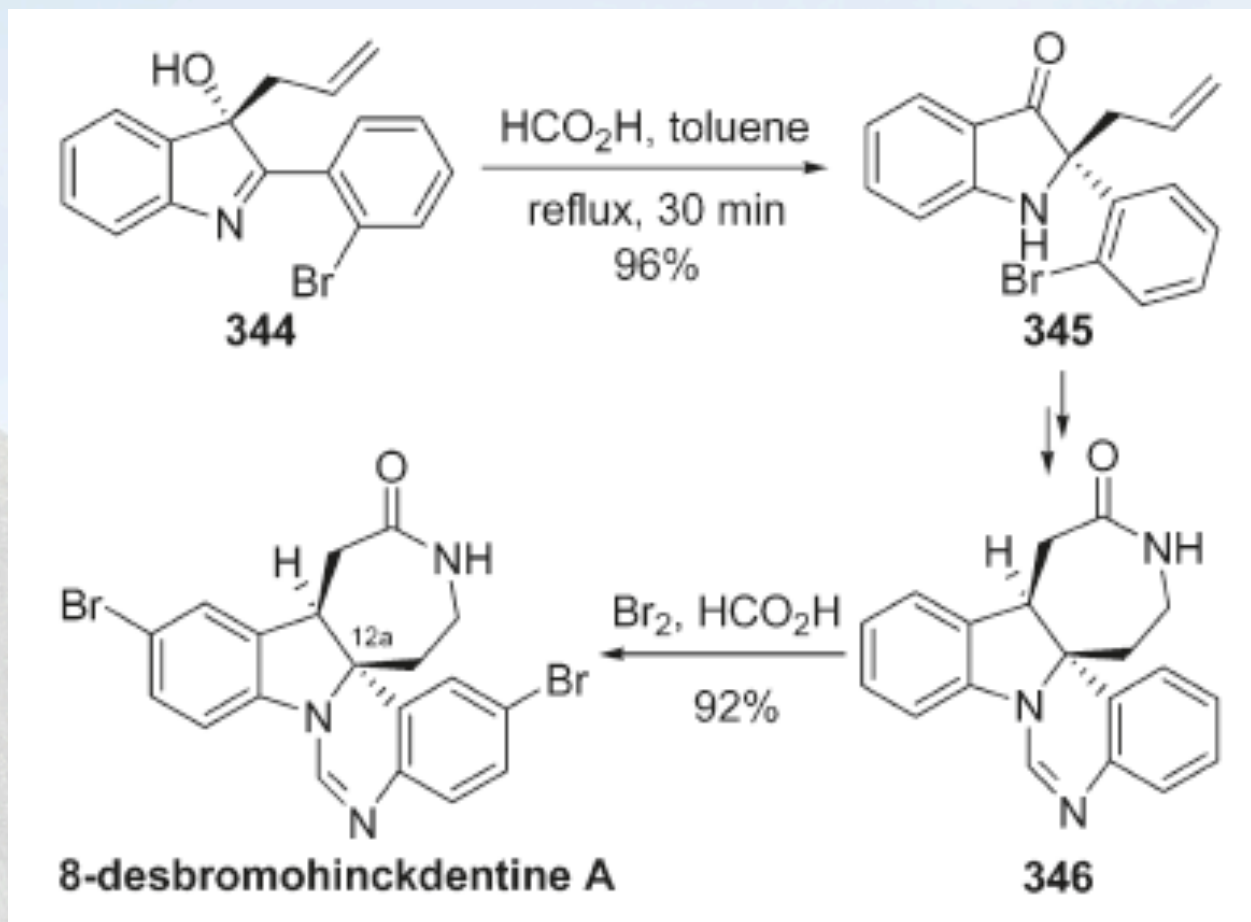
5. Rearrangement of α -Hydroxy Ketones and Imines (Type IV)

Oltra's Tandem Transannular Cyclization and Ring-Contraction Process Towards Oxygen-Bridged Terpenoids:



rearrangement of α -tertiary hydroxy ketone moiety

McWhorter's Synthesis of 8-Desbromohinckdentine A:



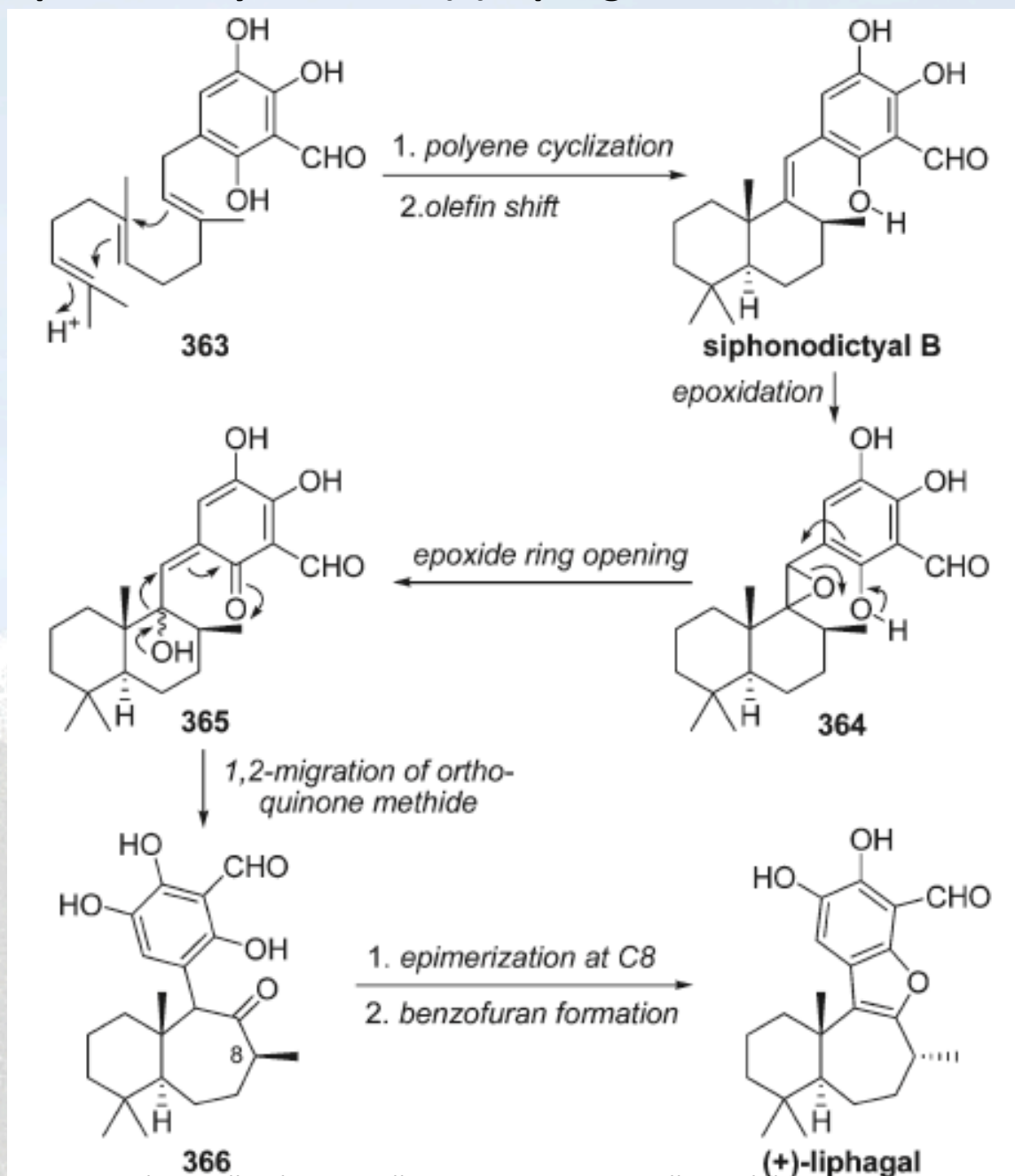
stereospecific 1,2-migration
of allyl group => key C12
quaternary carbon



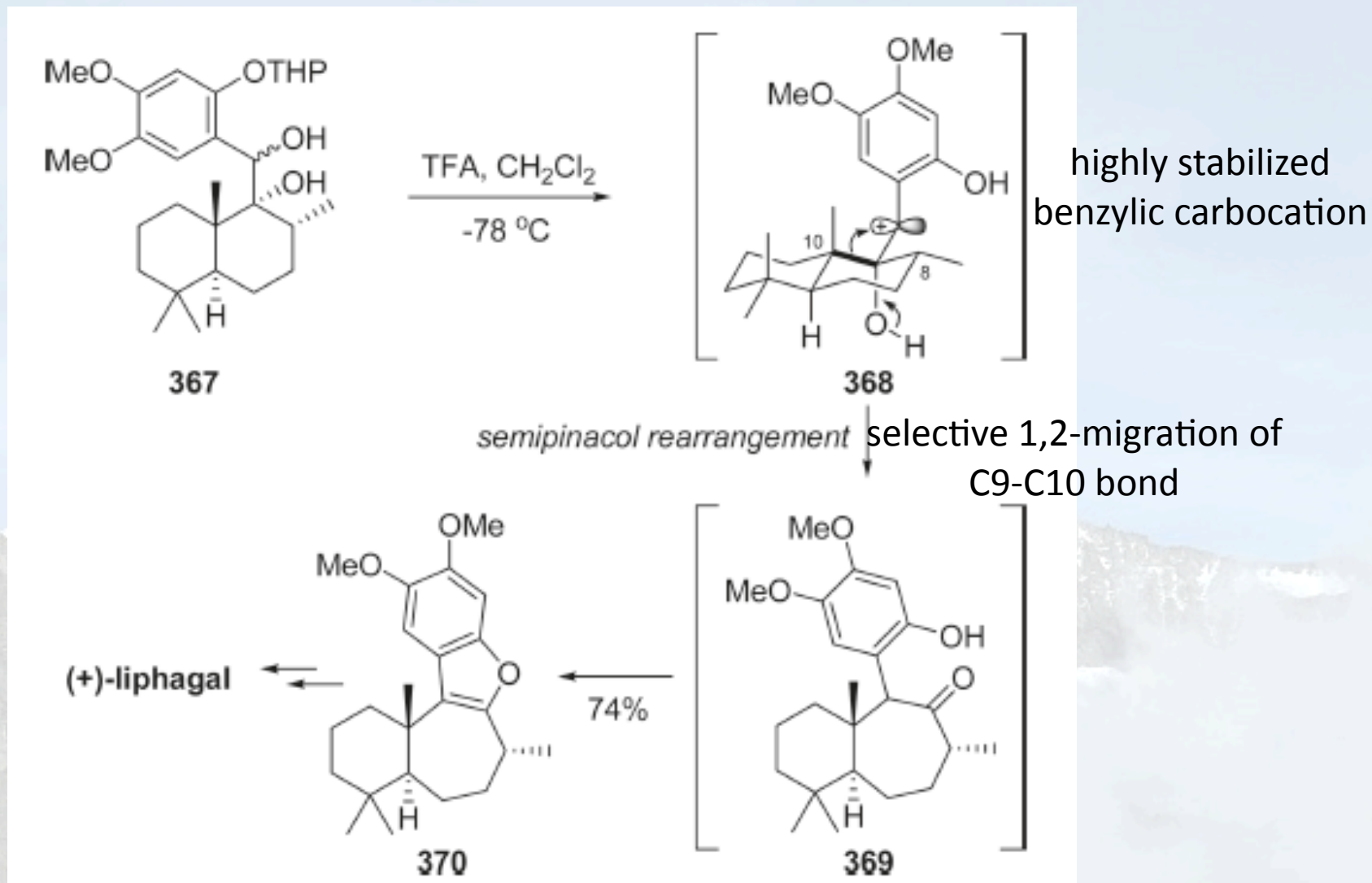
6. Biosynthesis and Biomimetic Synthesis Involving Semipinacol Rearrangement

oxidase-catalyzed oxidation generating an active intermediate such as a carbocation or epoxide => rearrangement (probably without interacting with any enzyme)

Andersen's Proposed Biosynthesis of (+)-Liphagal:

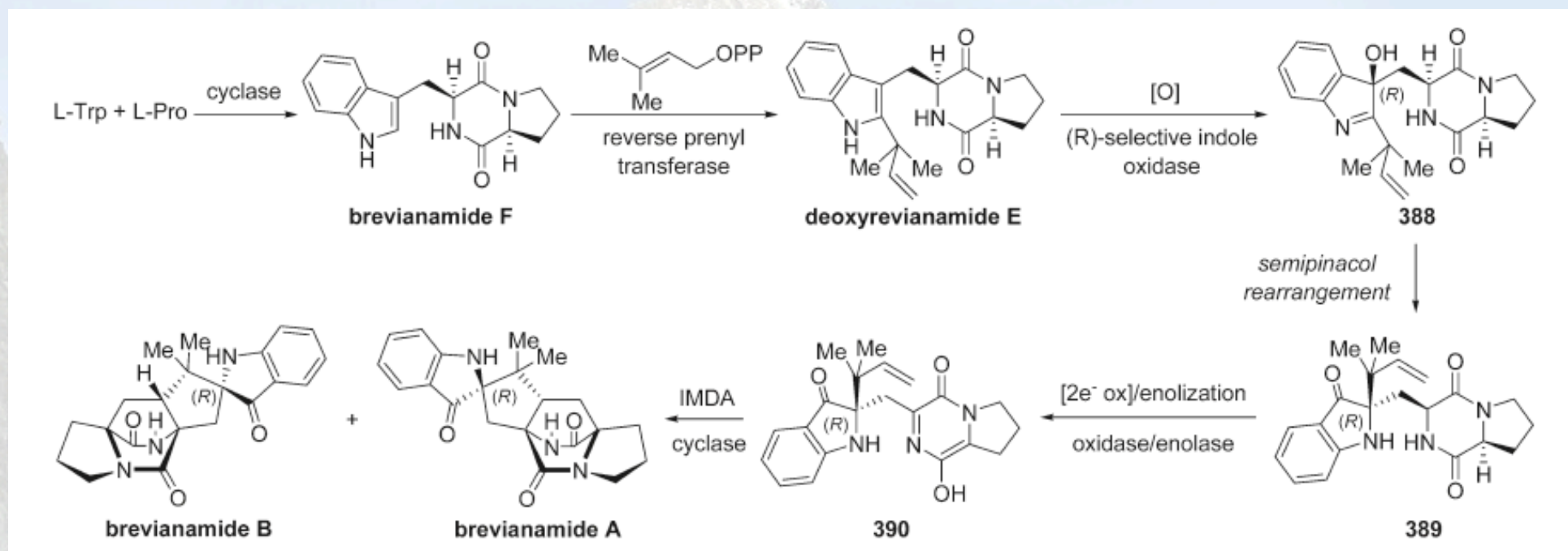


George's Biomimetic Synthesis of (+)-Liphagal:



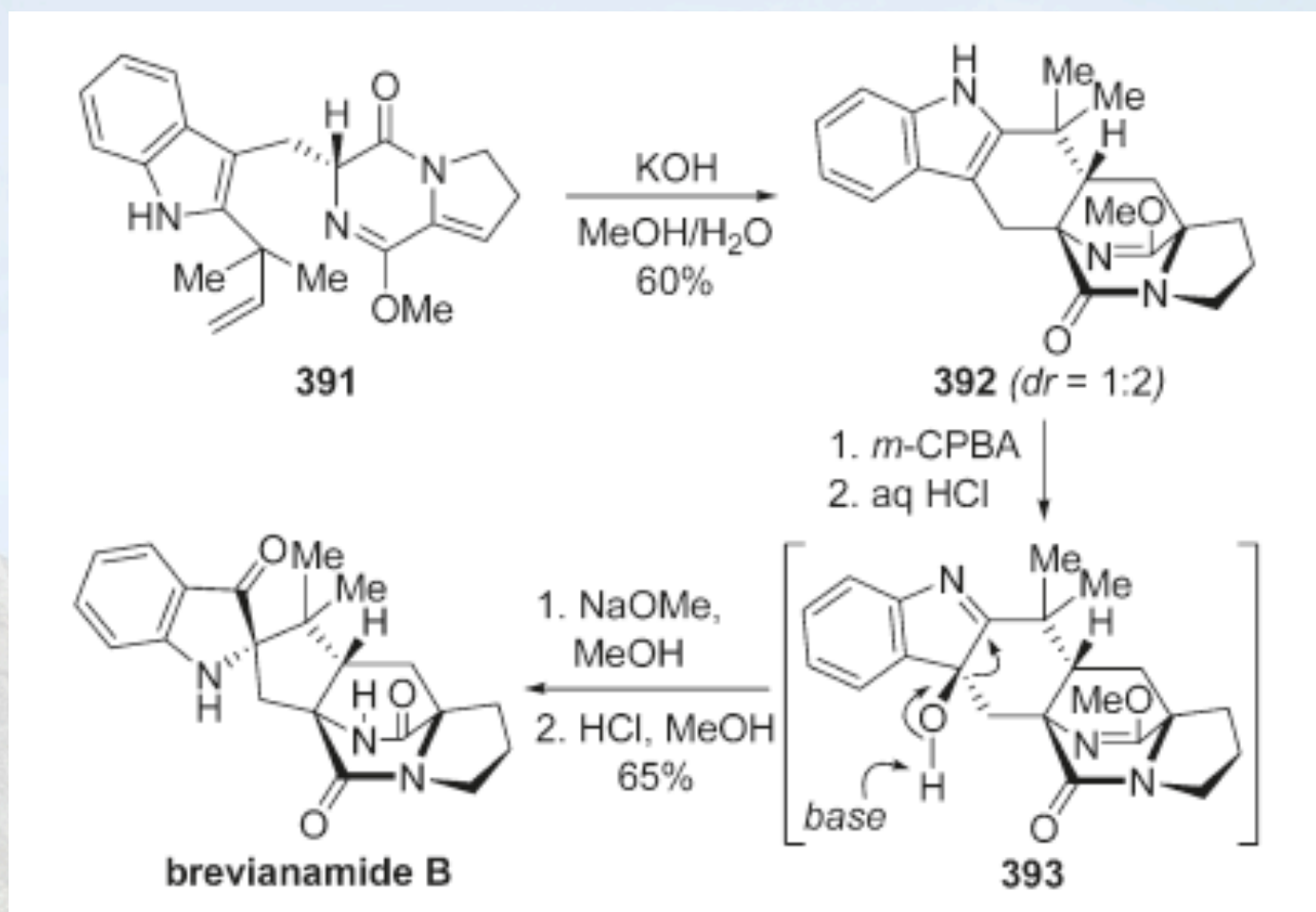
Williams' Proposed Biosynthesis of Brevianamides:

unique bicycle-[2.2.2]-diazooctane core and spiroindoxyl ring system

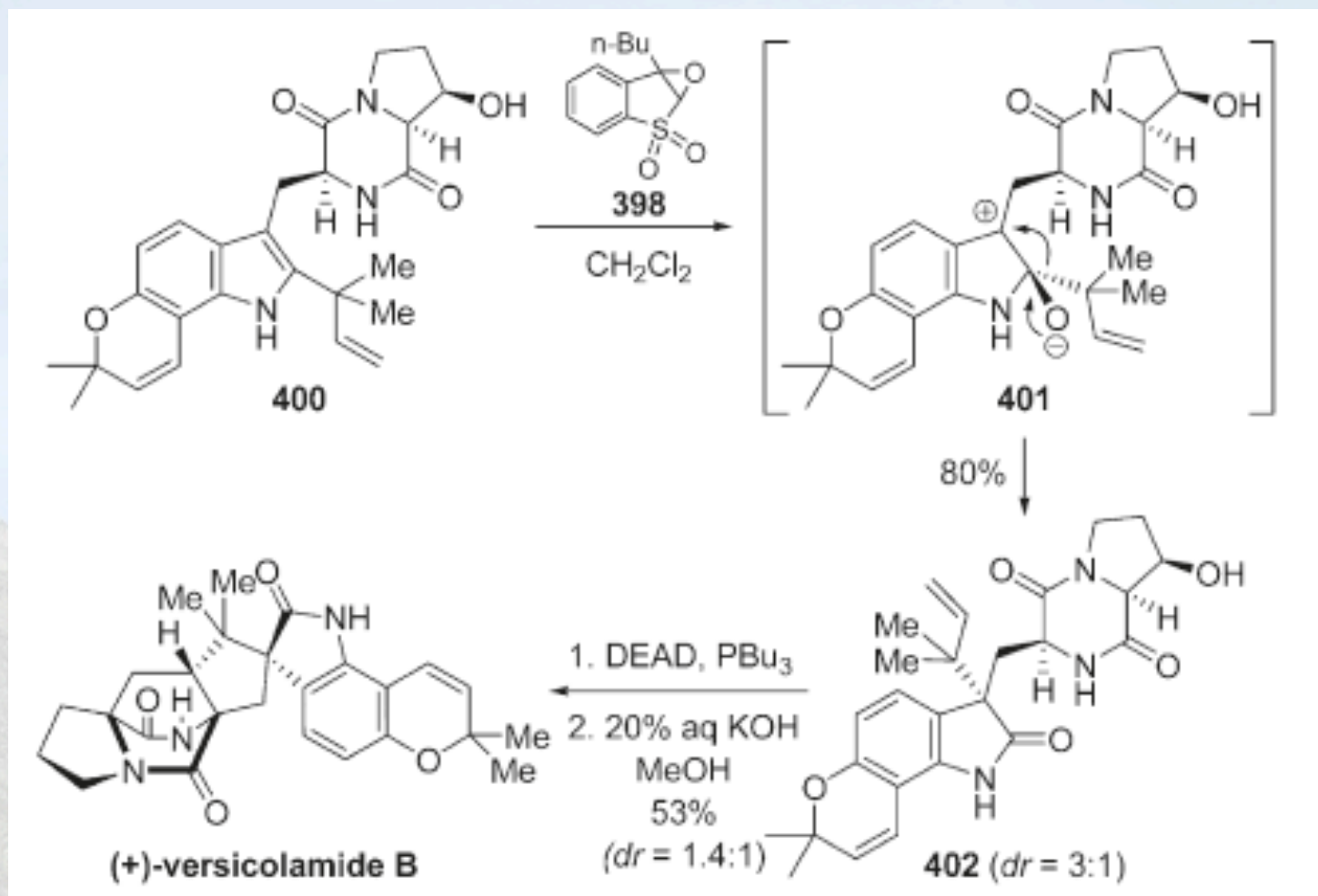


IMDA: intramolecular Diels-Alder cycloaddition

Williams' Biomimetic Synthesis of Brevianamide B:

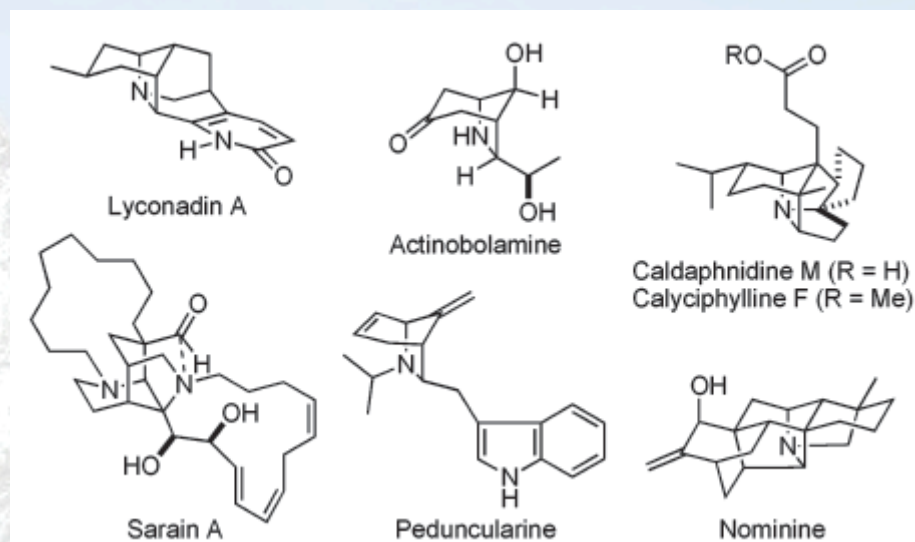
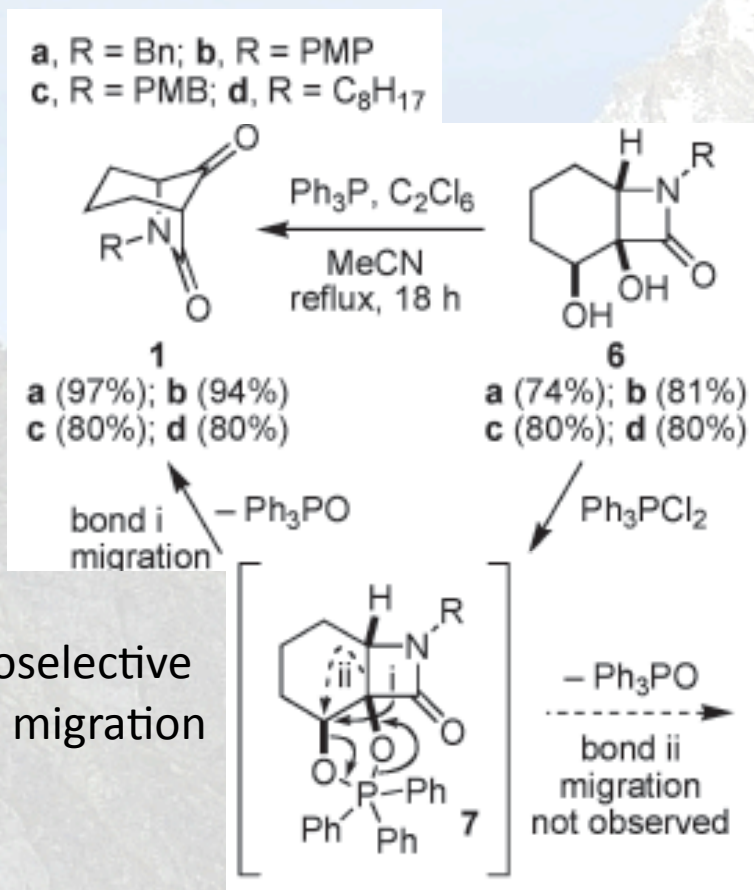


Williams' Biomimetic Synthesis of (+)-Versicolamide B:



7. Recent example


Grainger's Semipinacol Rearrangement of Cis-Fused β -Lactam Diols into Keto-Bridged Bicyclic Lactams:



representative Natural products with 6-azabicyclo[3.2.1] octane ring system

8. Conclusion

- broad applicability to various structural systems (especially ring systems)
- tandem reactions => highly efficient construction of complex molecules
- exceptionally good for constructing synthetically challenging quaternary carbon centers, which are usually impossible or extremely difficult to create by other methods



End