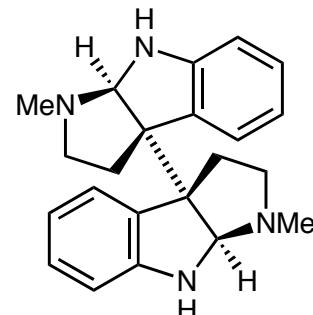
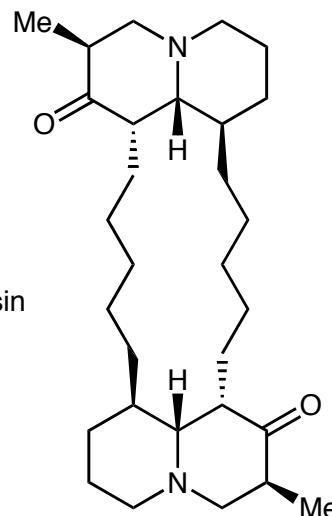
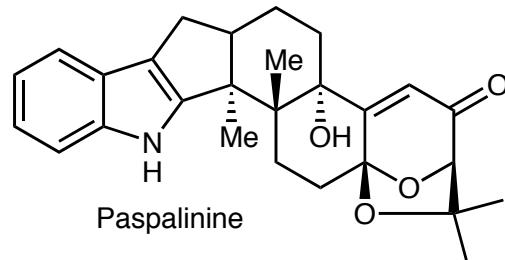


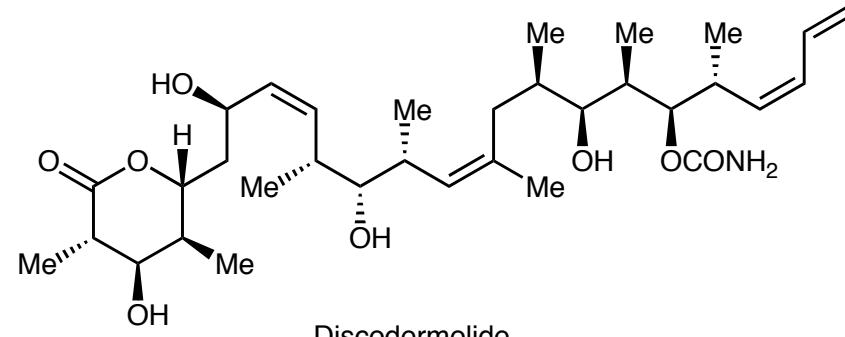
Basic Reactions for Fragments Couplings

- ***C-X Bond Forming Reactions***
- ***C-C Bond Forming Reactions***
 - Stabilized-carbanion chemistry
 - Enolate Dimerization (Baran, Movassaghi)
- ***C=C Bond Forming Reactions - See Supplementary Material***
 - Wittig reaction
 - Horner-Emmons-Wadsworth
 - Julia reaction
 - Modified Julia reaction
 - Olefin metathesis
 - Peterson olefination
 - Warren olefination

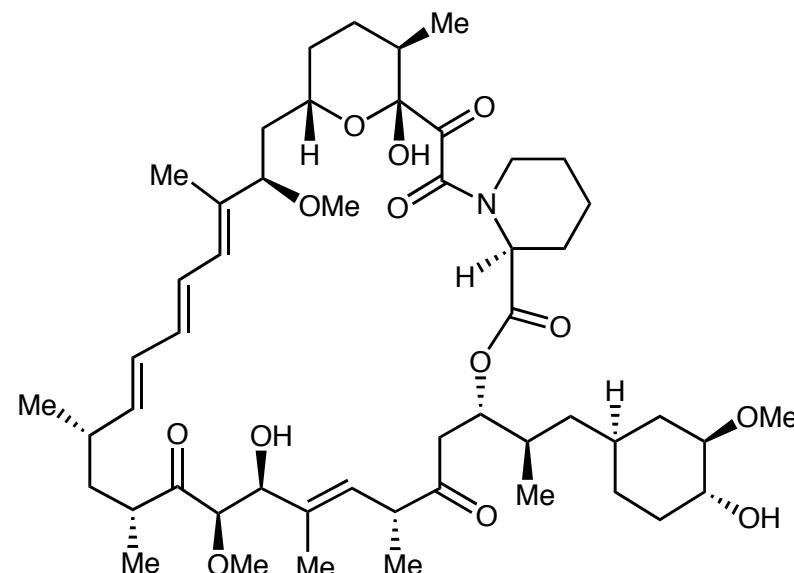
Retrosynthesis Analysis of Natural Products: Any Symmetry Elements?



Chimonanthine

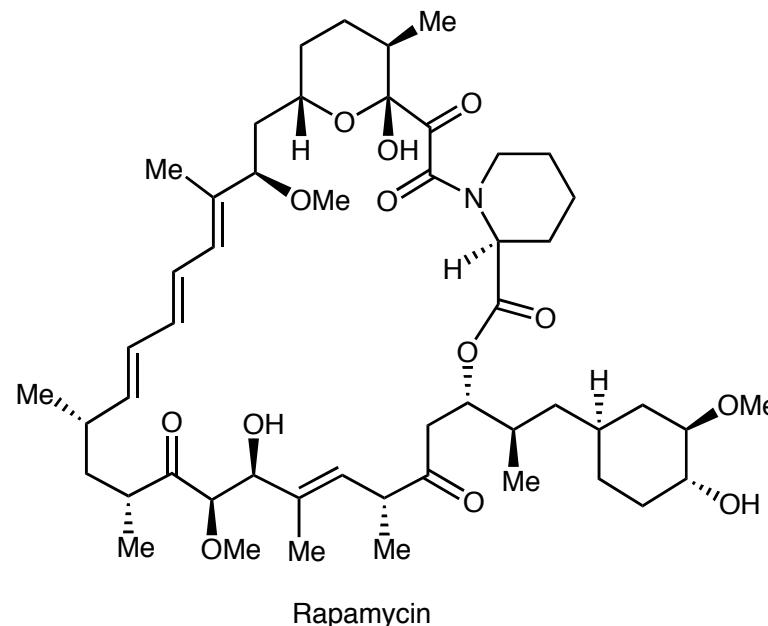
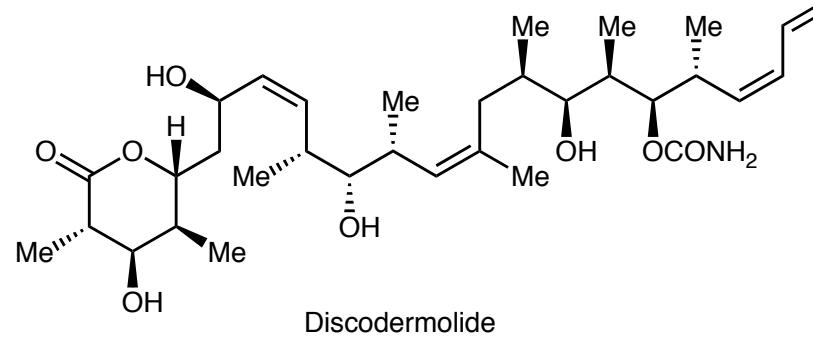
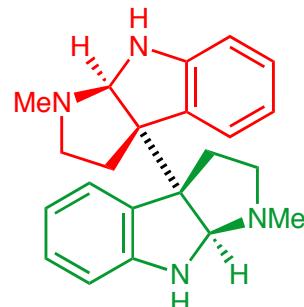
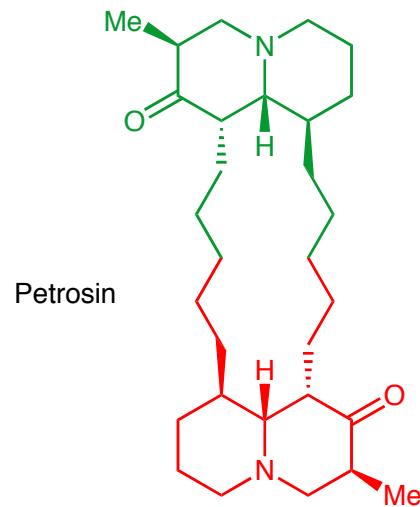
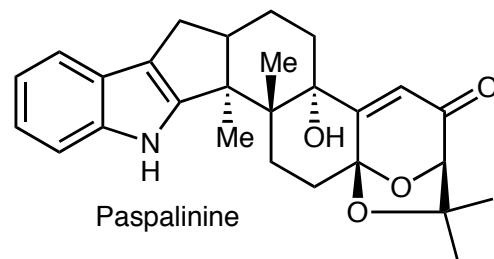


Discodermolide



Rapamycin

Retrosynthesis Analysis: Are There Any Symmetry Elements?



- Bidirectional Chain Synthesis
- Subunit Dimerization (new reaction development)

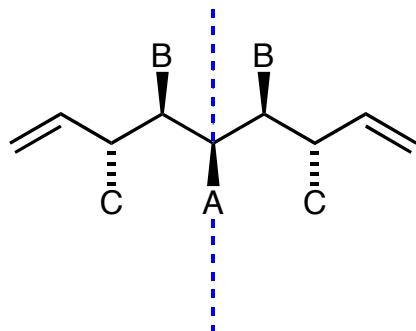
Review:

Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, 27, 9-17.

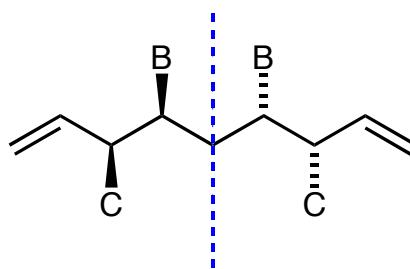
Two-directional chain synthesis:

Homologation of a chain in *two directions at the same time*. Requirements: The substrate must contain some symmetry elements.

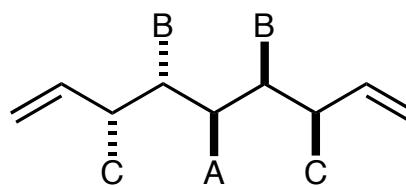
Achiral and meso Chains
Plane of symmetry



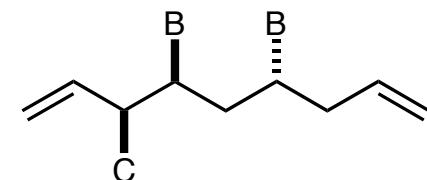
C_2 Symmetric Chain
 C_2 Symmetry axis



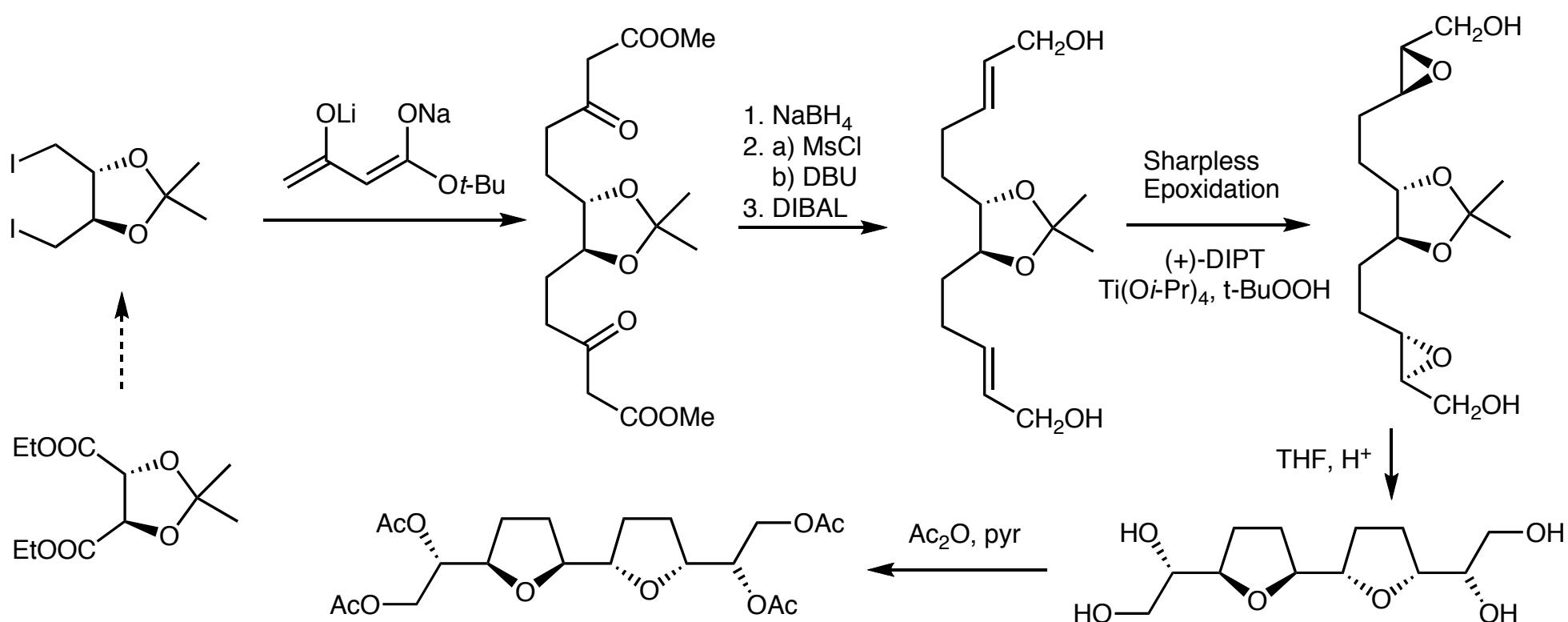
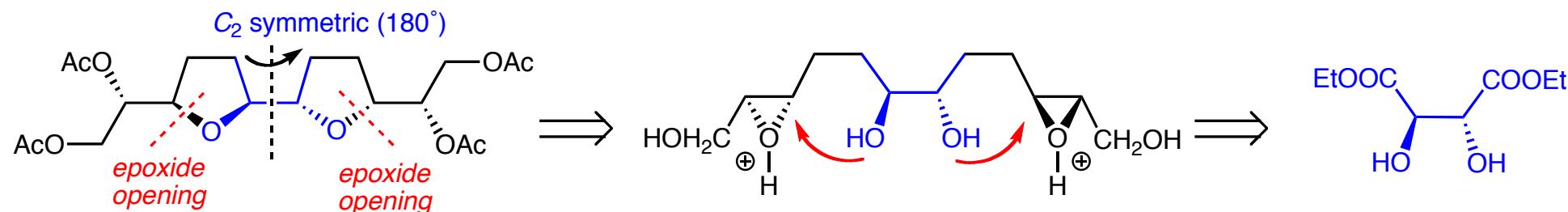
Pseudo C_2 Symmetric Chain



Non Symmetric Chain

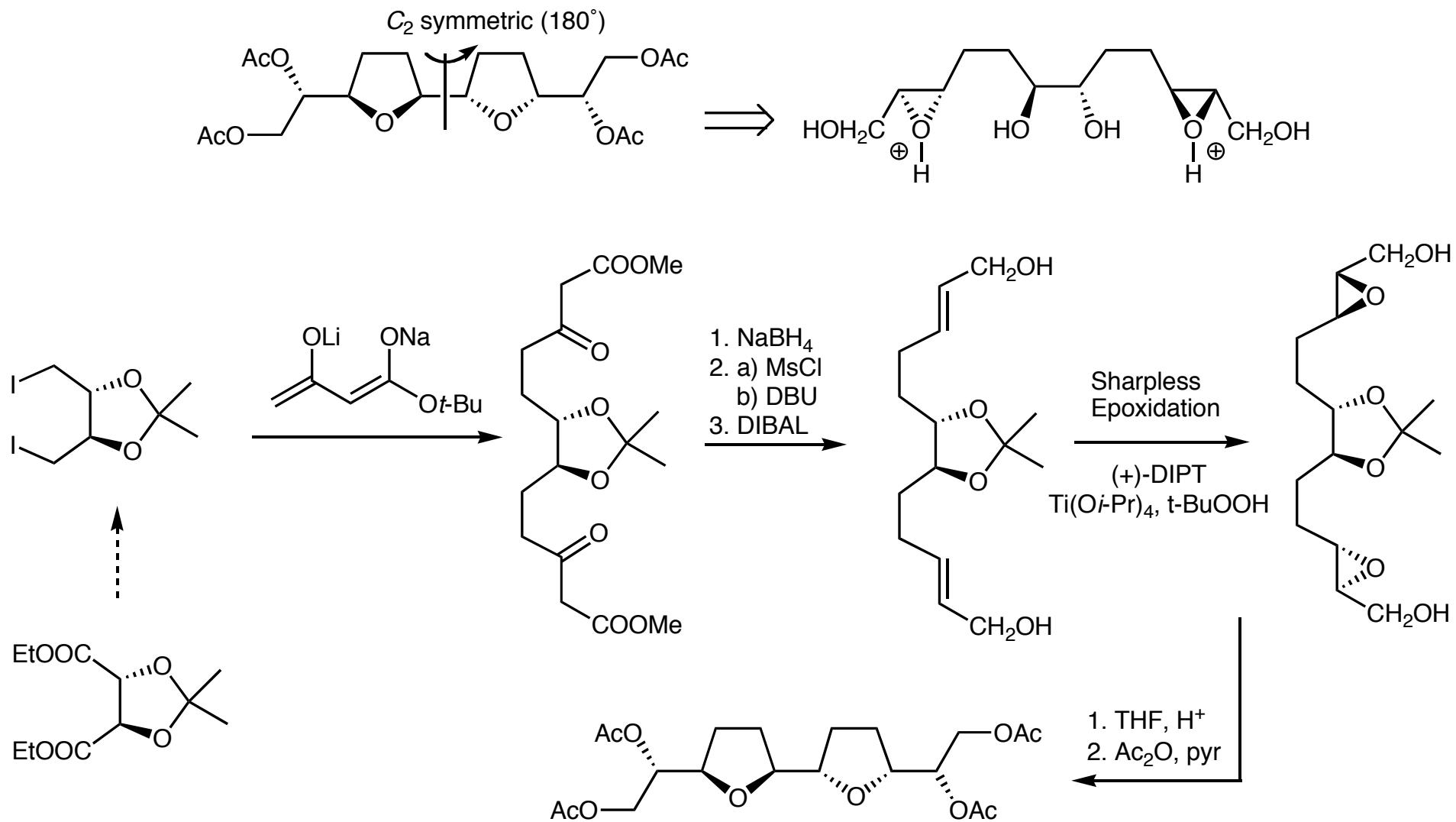


A Simple Case of Bidirectional Chain Synthesis



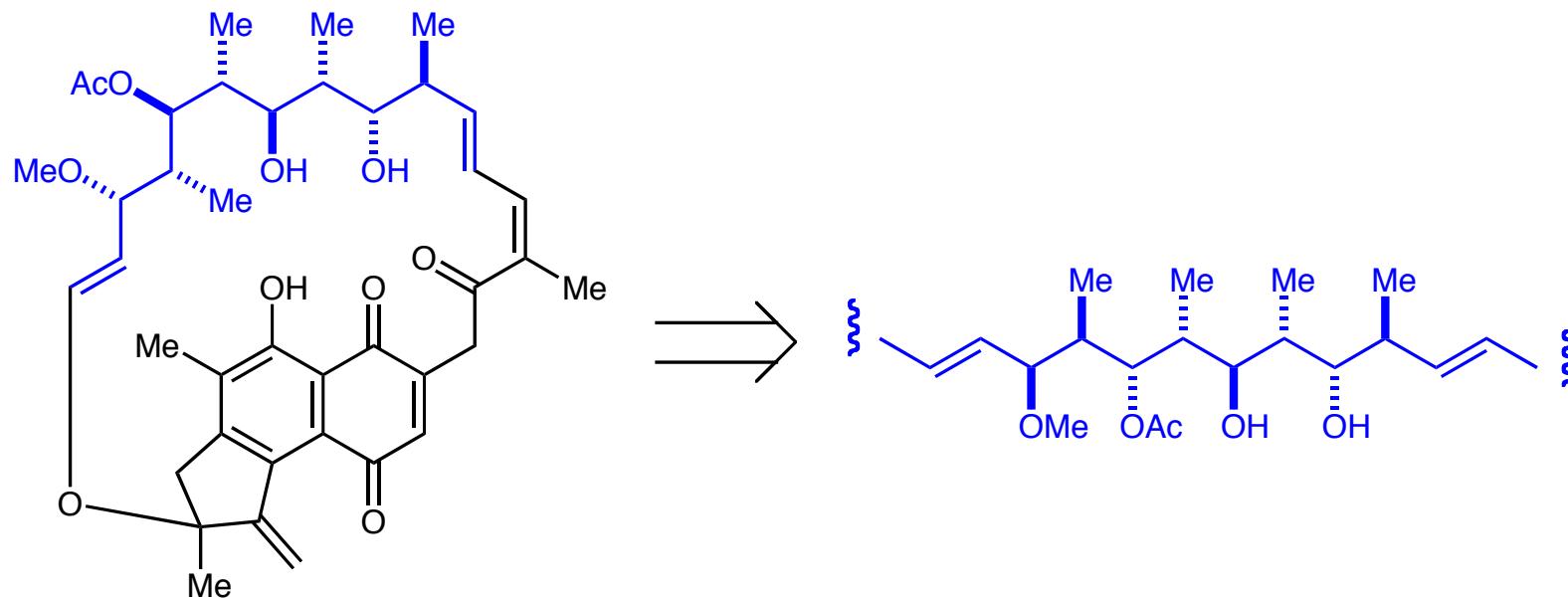
Hoye *Tetrahedron* **1986**, 42, 2855

A Simple Case of Bidirectional Chain Synthesis



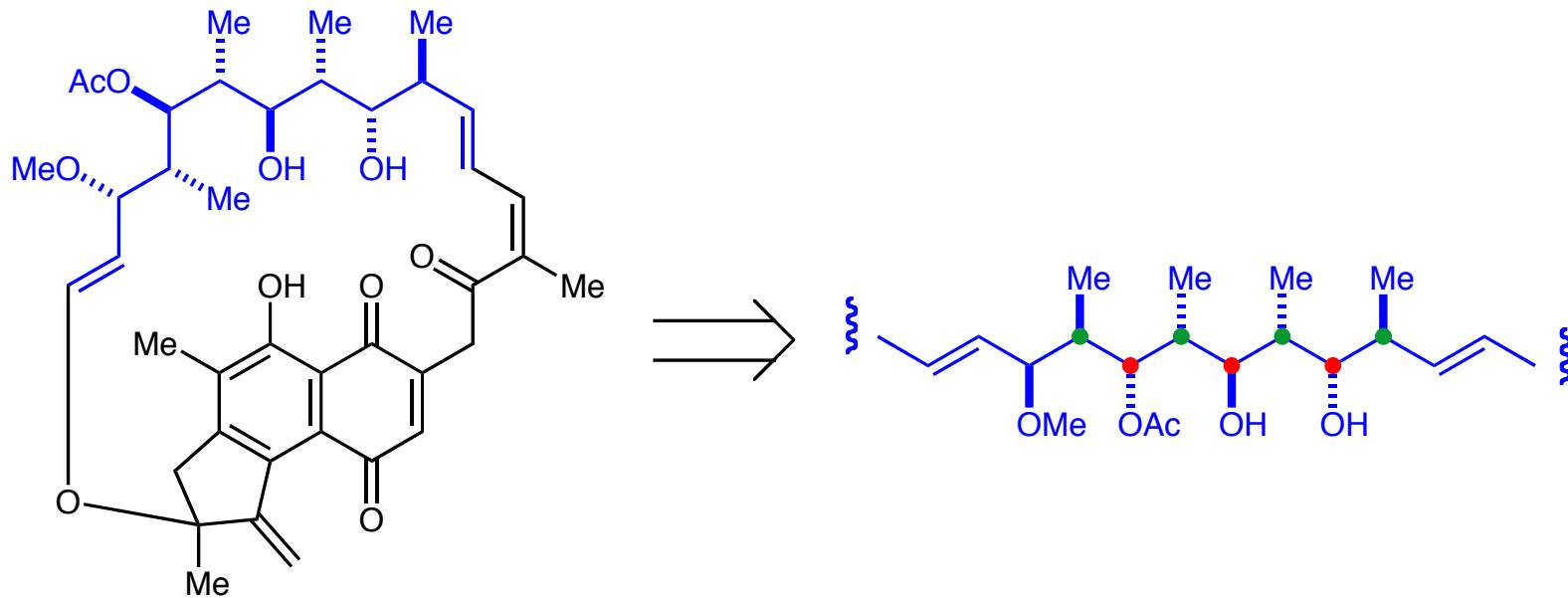
Hoye *Tetrahedron* **1986**, *42*, 2855

Still's Ryfamincin S Synthesis

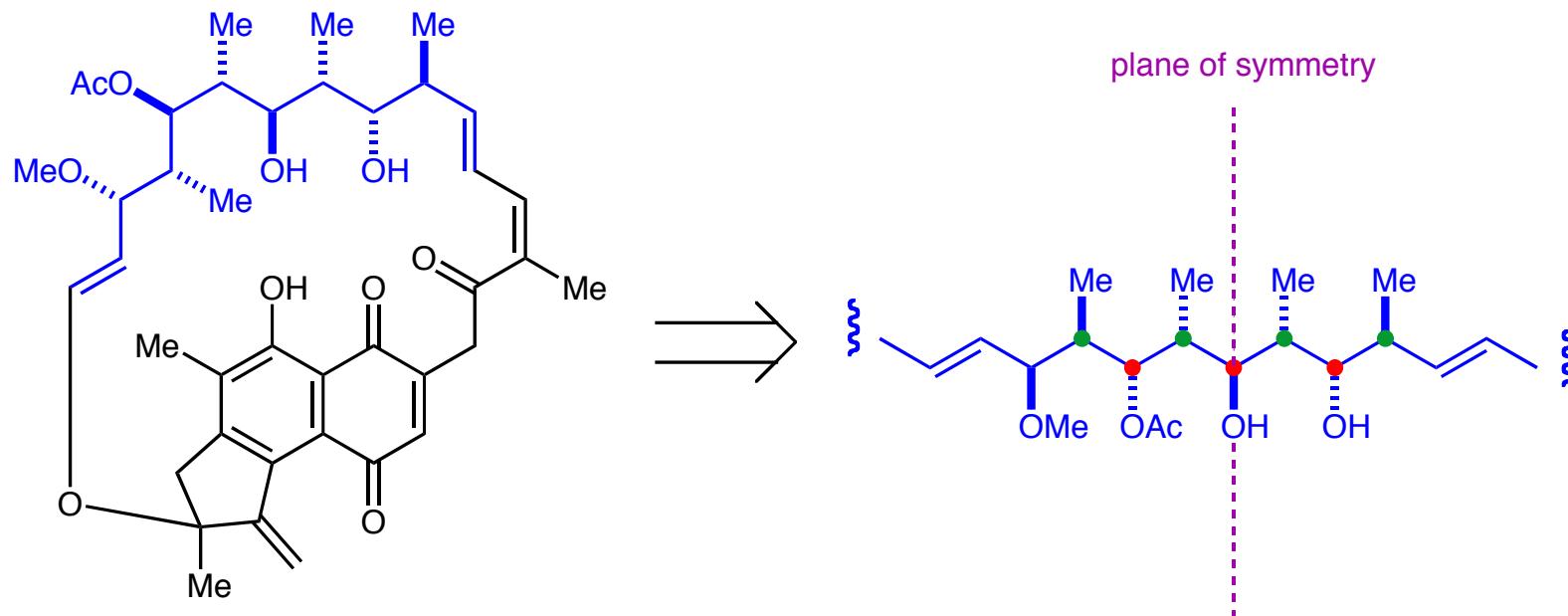


Still, W. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487-2489.

Still's Ryfamincin S Synthesis

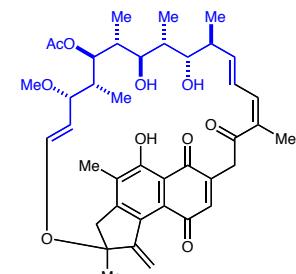
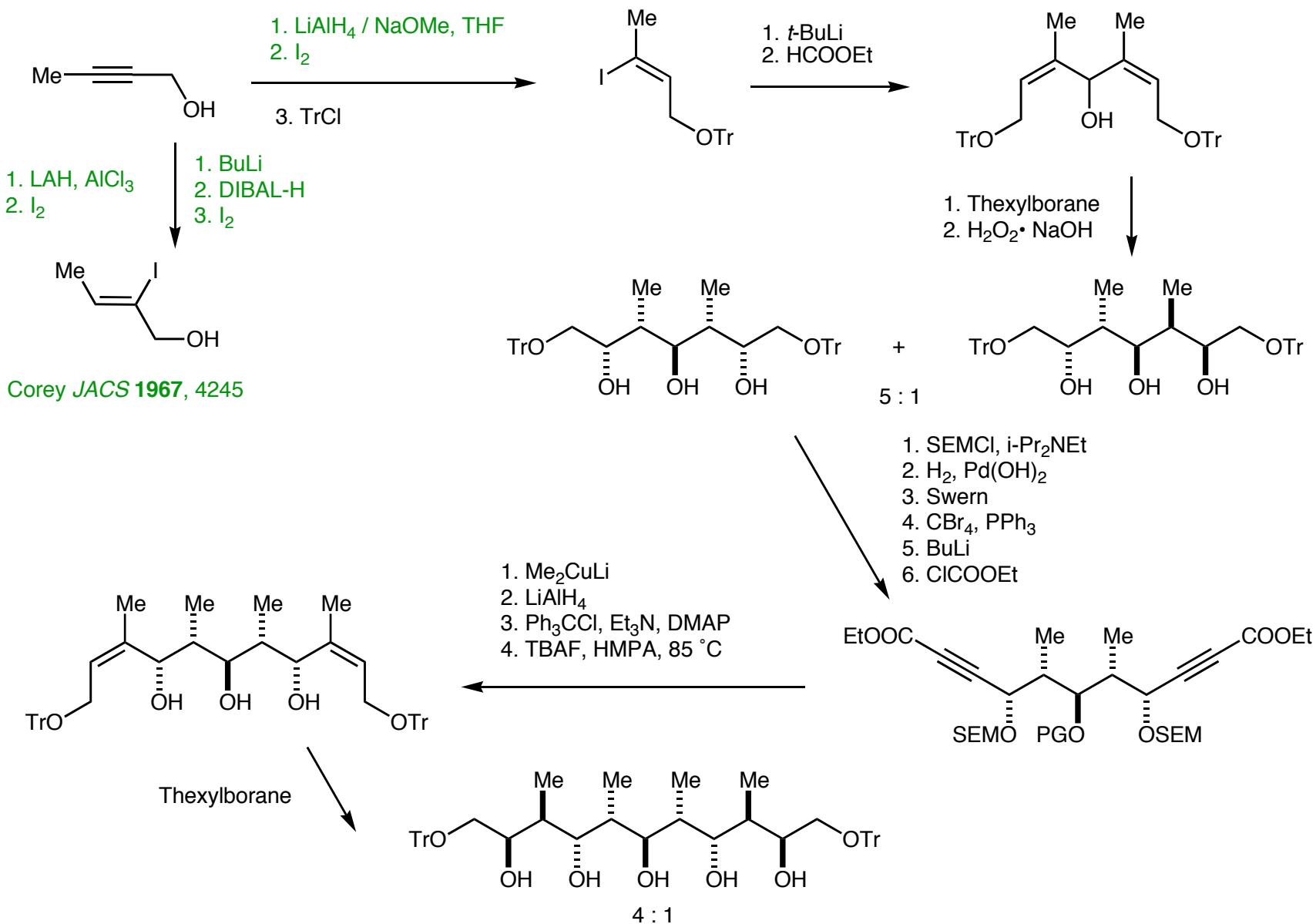


Still, W. C. *J. Am. Chem. Soc.* 1983, 105, 2487-2489.

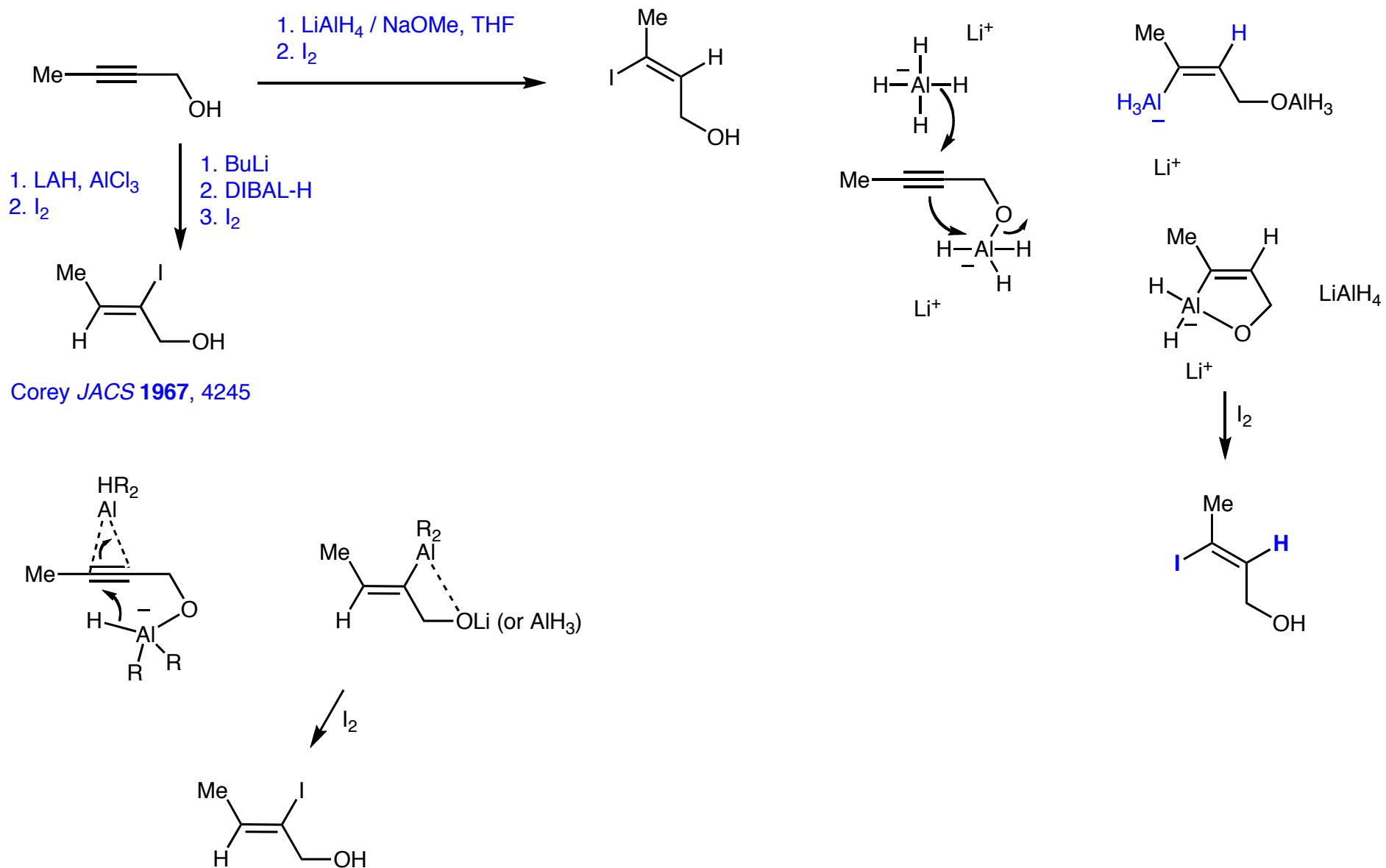


Still, W. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487-2489.

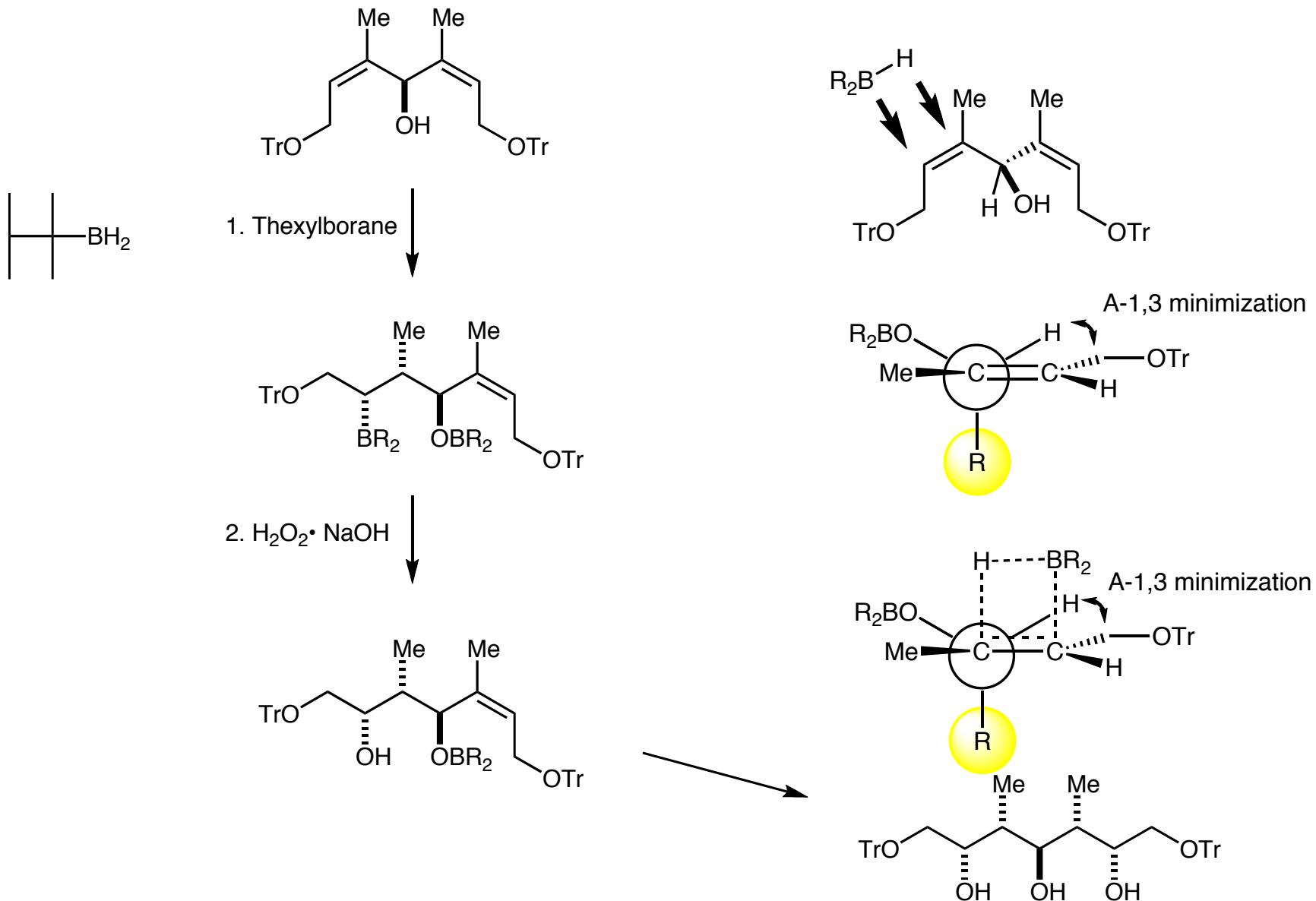
Still's Ryfamycin S Synthesis



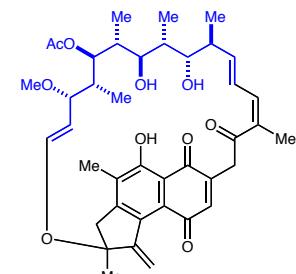
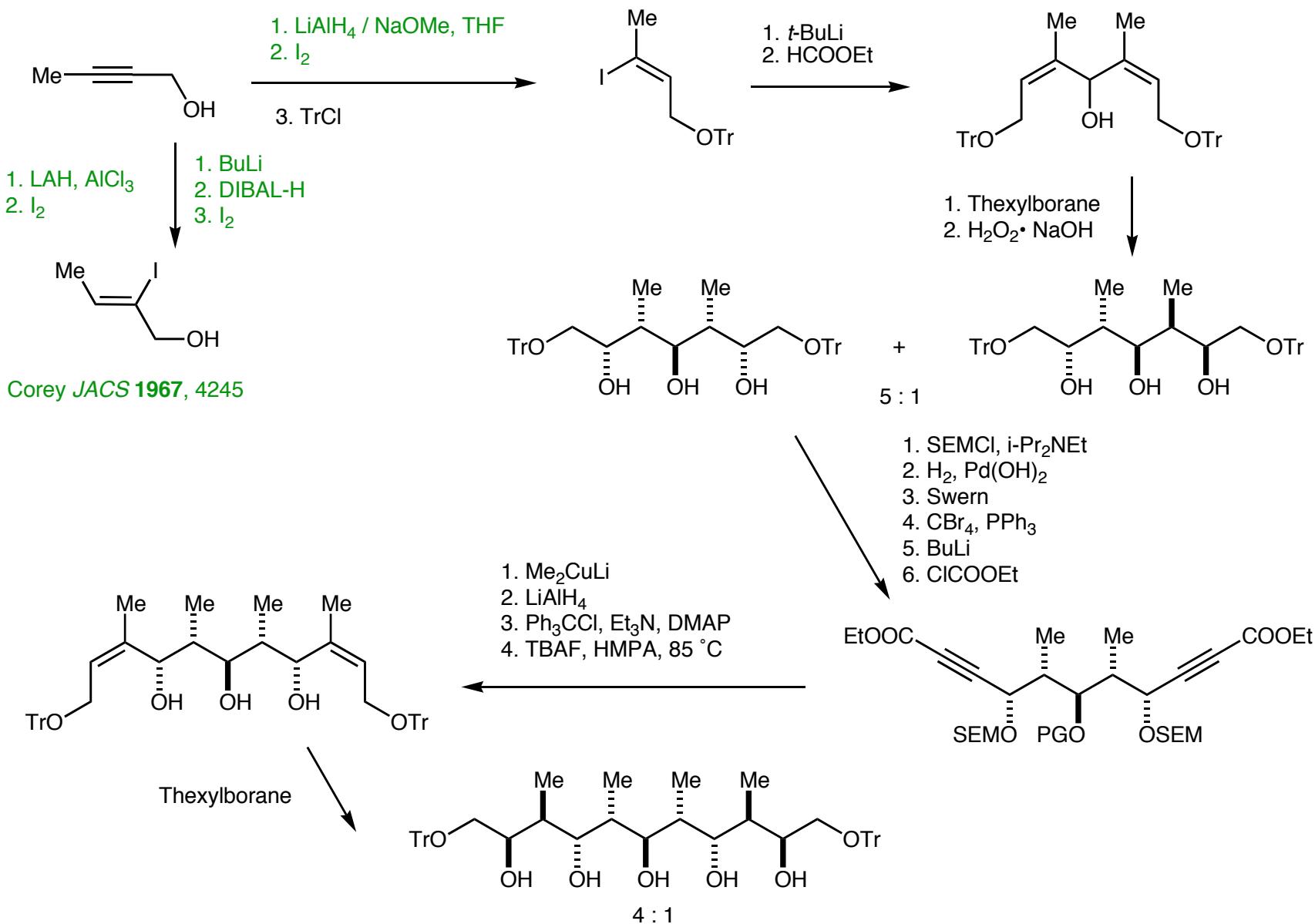
Reduction of Propargyl Alcohols (Corey)



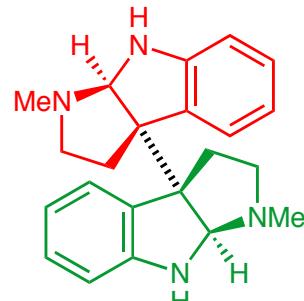
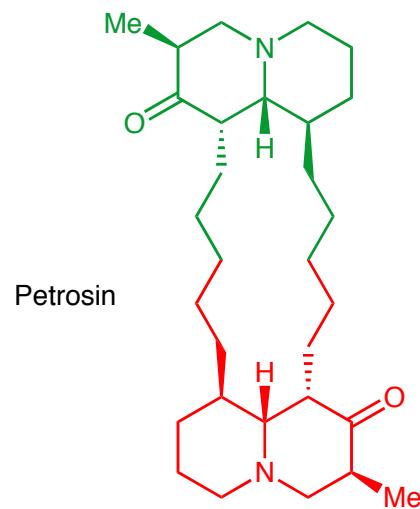
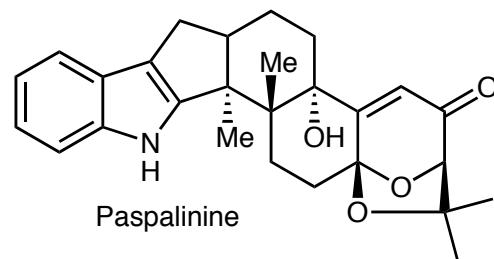
Minimization of the A-1,3 Strain



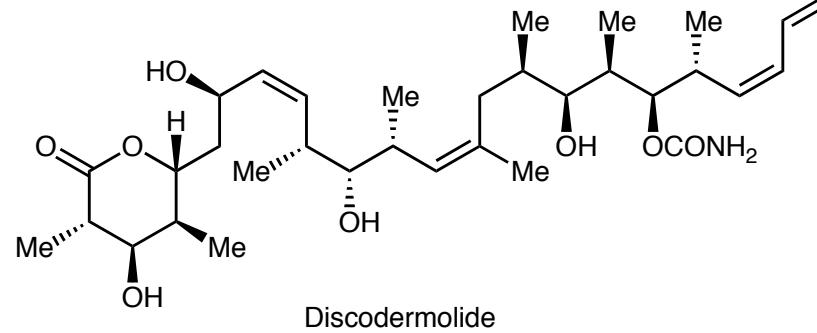
Still's Ryfamincin S Synthesis



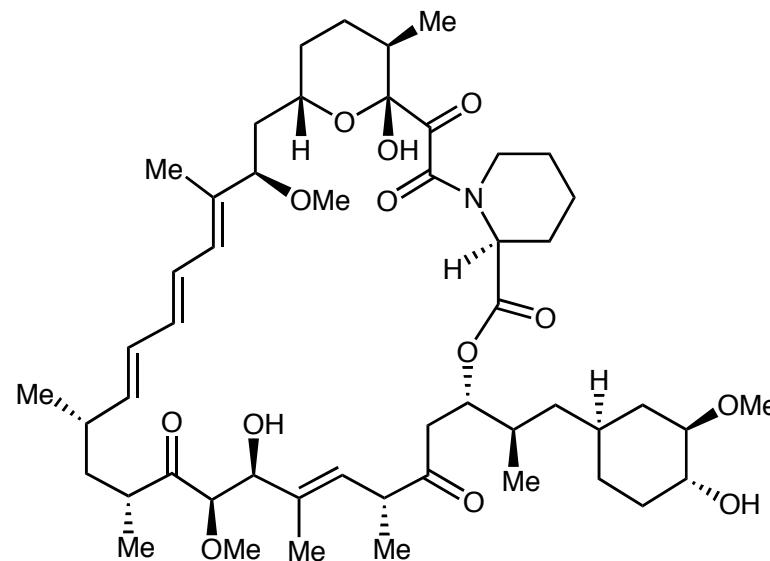
Retrosynthesis Analysis: Are There Any Symmetry Elements?



Chimonanthine



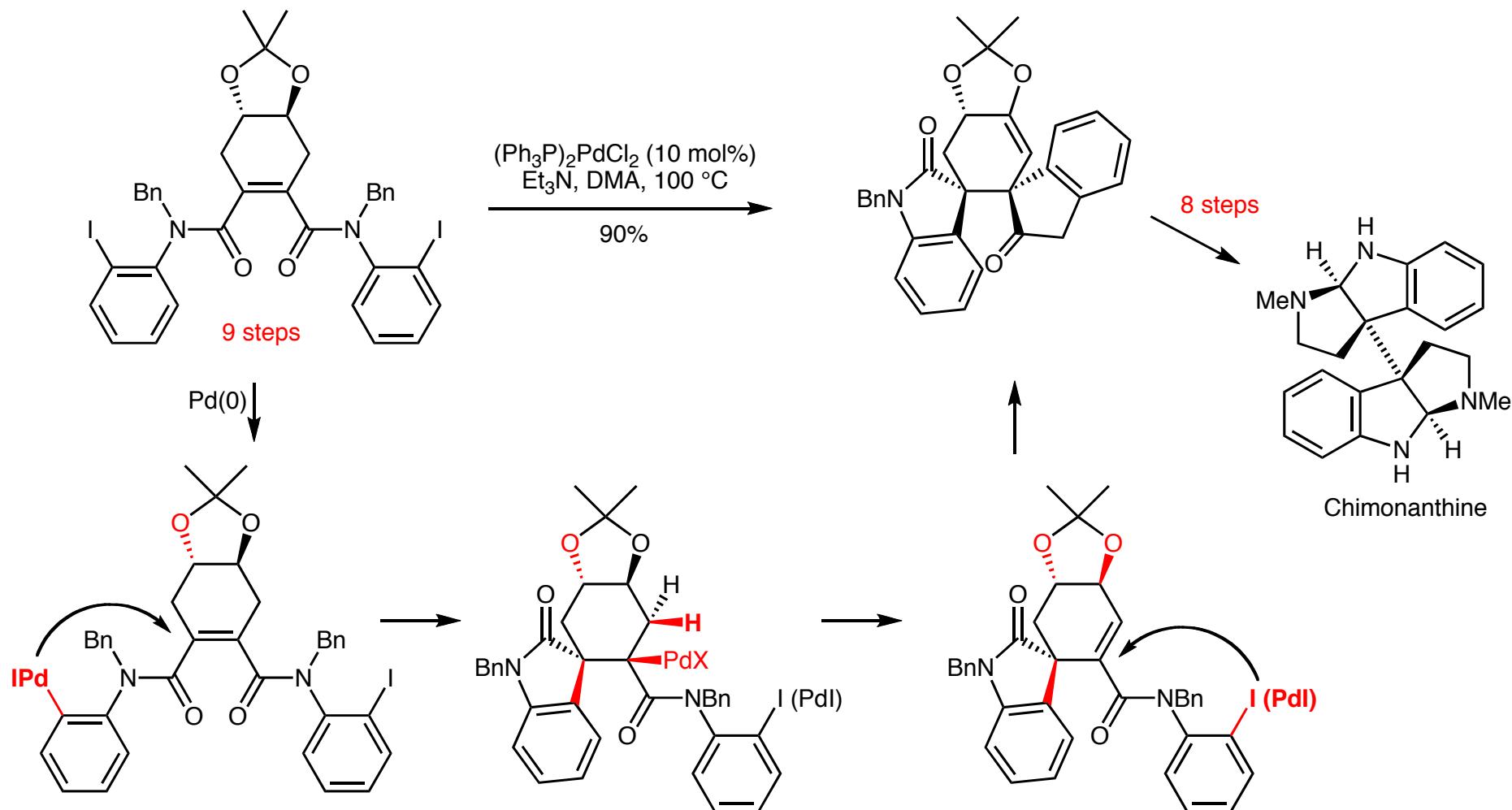
Discodermolide



Rapamycin

- Bidirectional Chain Synthesis
- Subunit Dimerization (new reaction development)

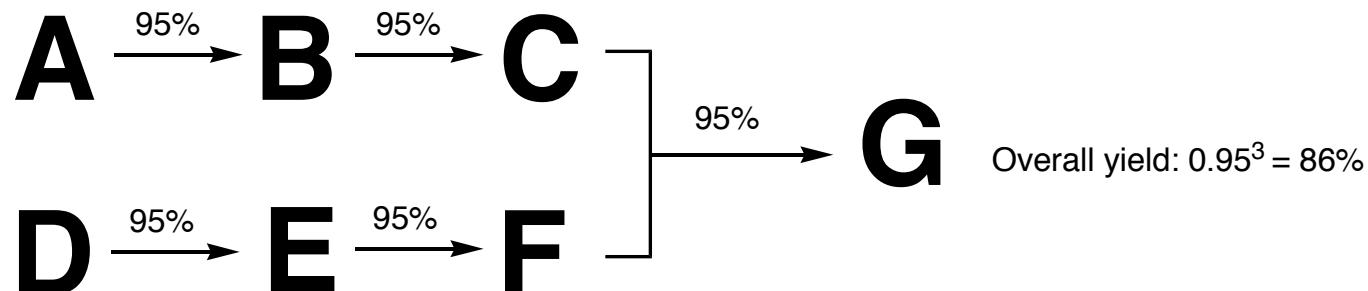
Chimonanthine Synthesis: Overman's Bidirectional Synthesis



Overman, L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 7702.
Overman, L. E.; Rosen, M. D. *Angew. Chem. Int. Ed.* **2000**, *39*, 4596.



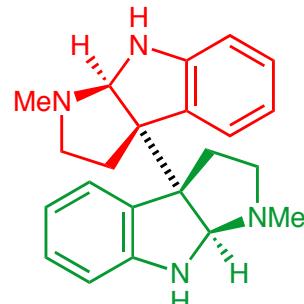
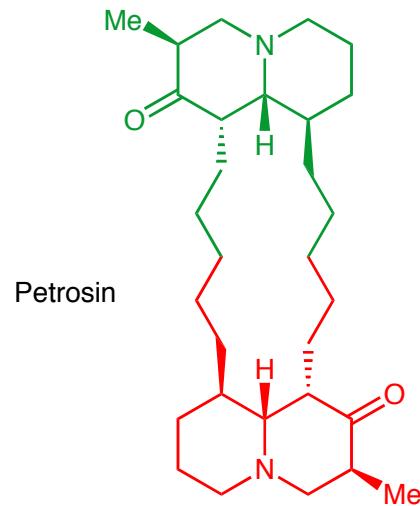
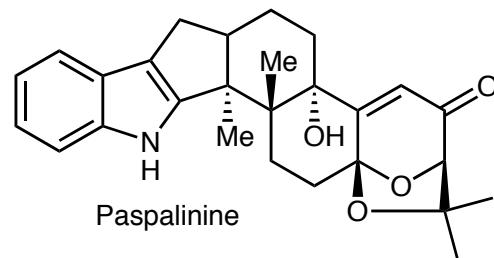
Overall yield: $0.95^6 = 73.5\%$



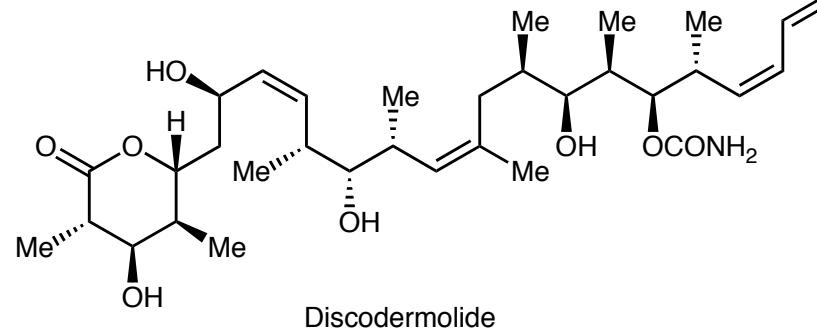
Faster to modify the structure of C or F (i.e. Protecting group, Olefination precursor, etc.) in a convergent synthesis. A small change in the structure of F in a linear sequence would require 5 steps (vs 2 in the convergent synthesis).

A convergent synthesis is almost always more efficient than a linear one.

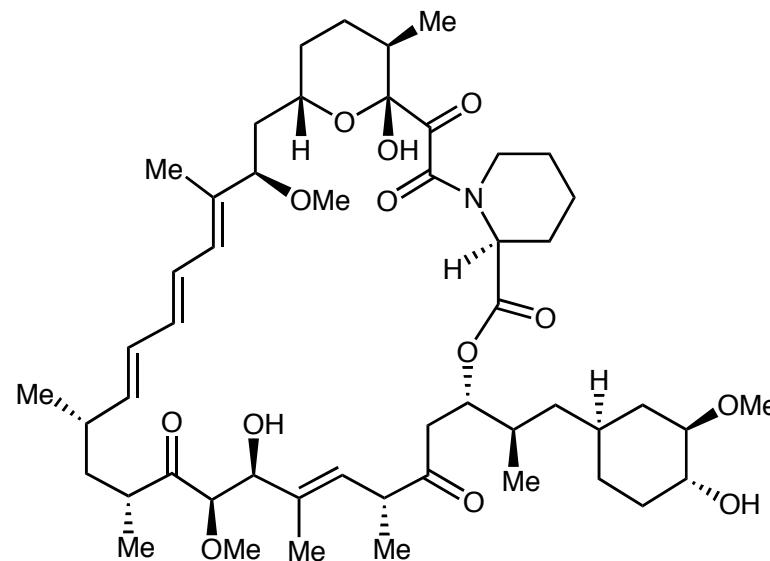
Retrosynthesis Analysis: Are There Any Symmetry Elements?



Chimonanthine



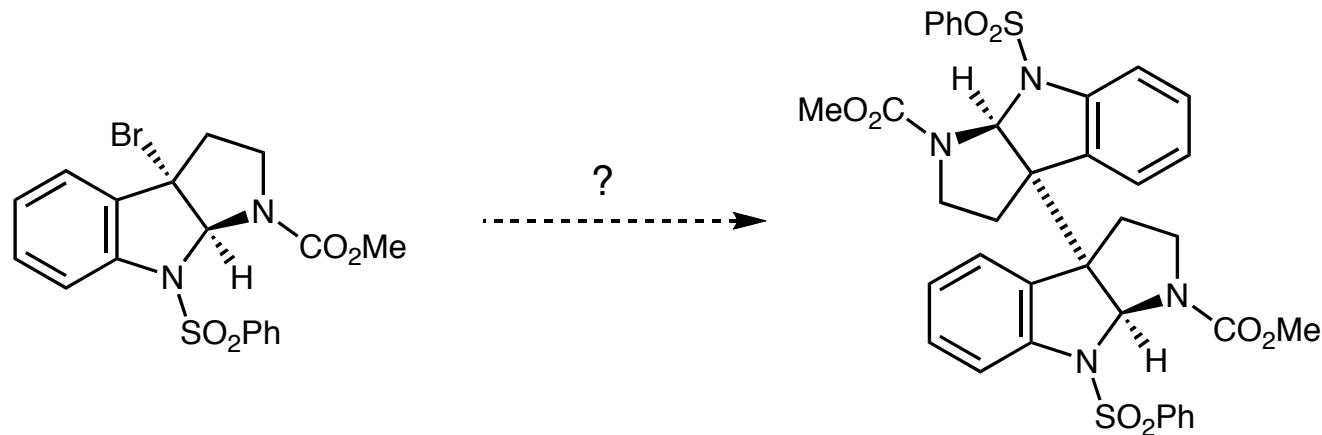
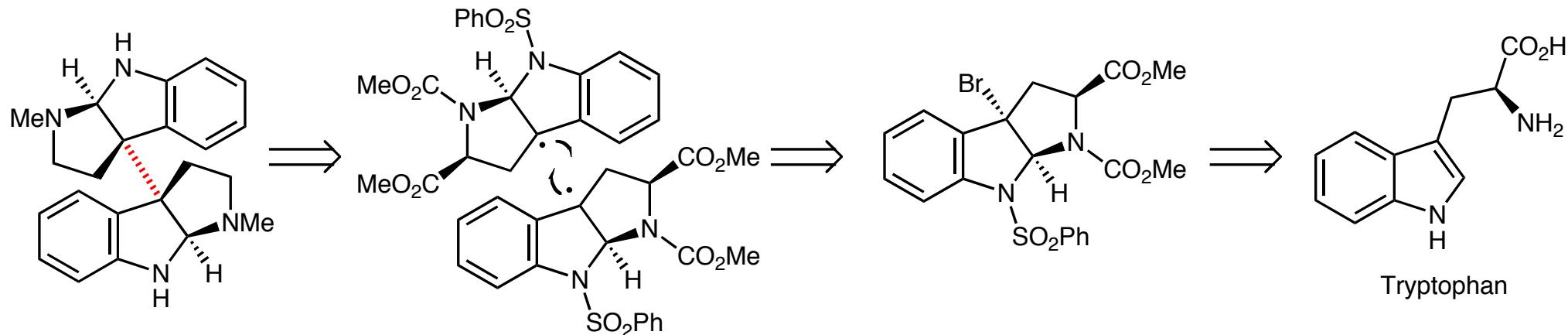
Discodermolide



Rapamycin

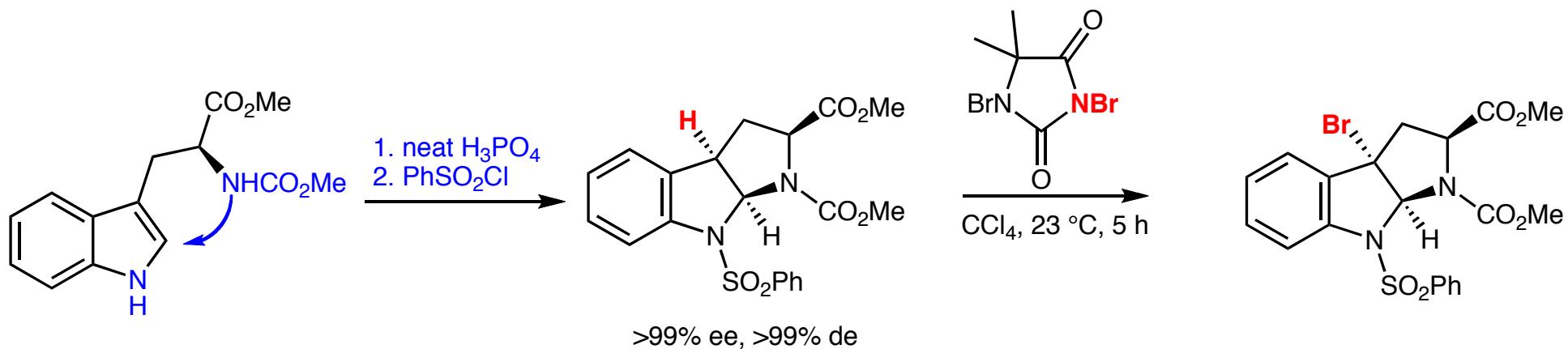
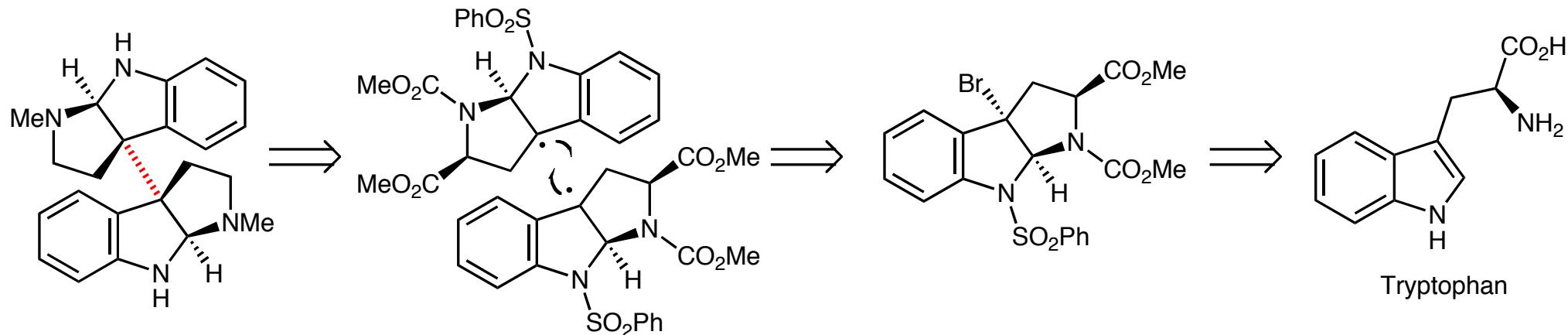
- Bidirectional Chain Synthesis
- Subunit Dimerization (new reaction development)

Retrosynthetic Analysis: Are There Any Symmetry Elements?



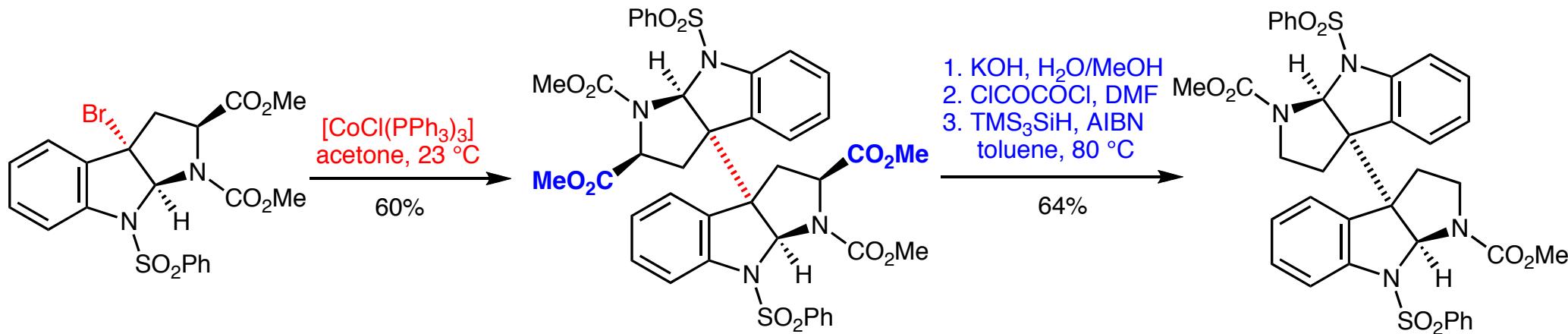
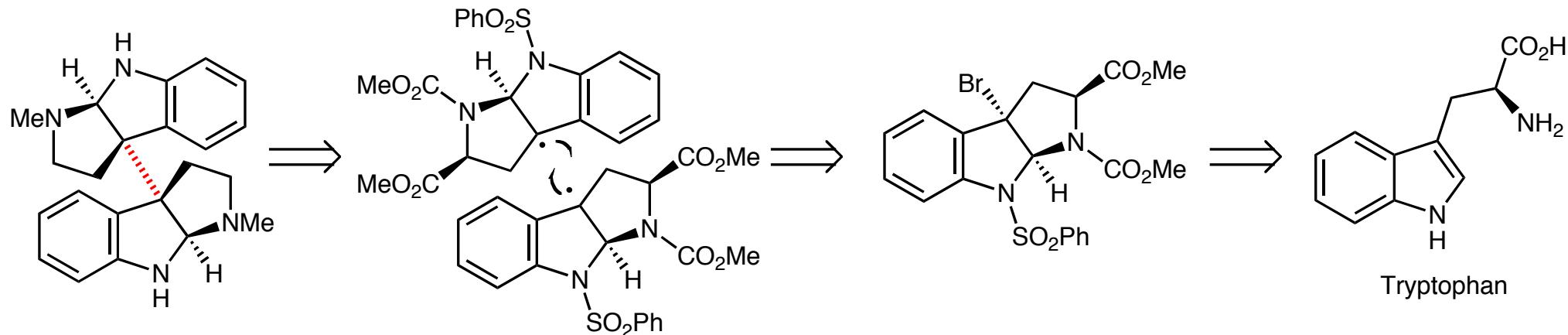
Movassaghi, M.; Schmidt, M. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 3725.

Retrosynthetic Analysis: Are There Any Symmetry Elements?



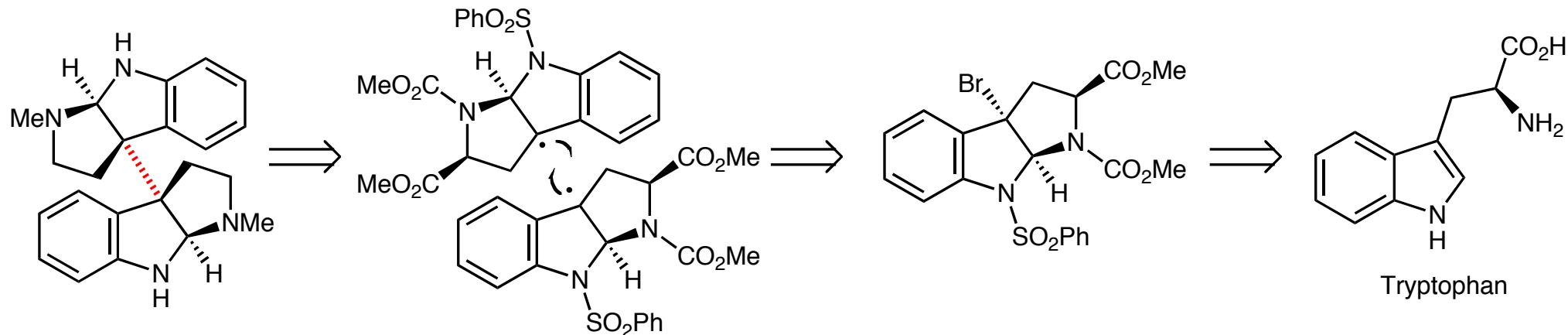
Movassaghi, M.; Schmidt, M. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 3725.

Retrosynthetic Analysis: Dimerization of Identical Fragments

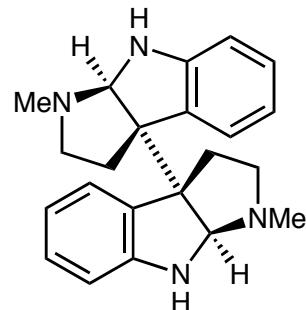
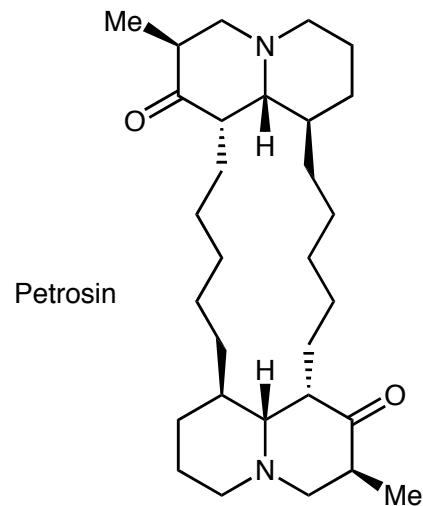
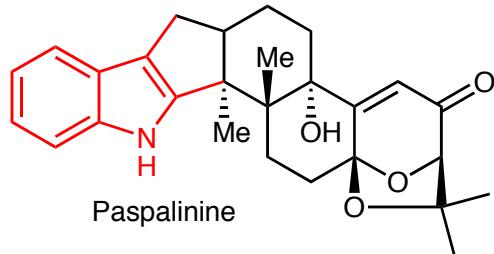


Movassaghi, M.; Schmidt, M. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 3725.

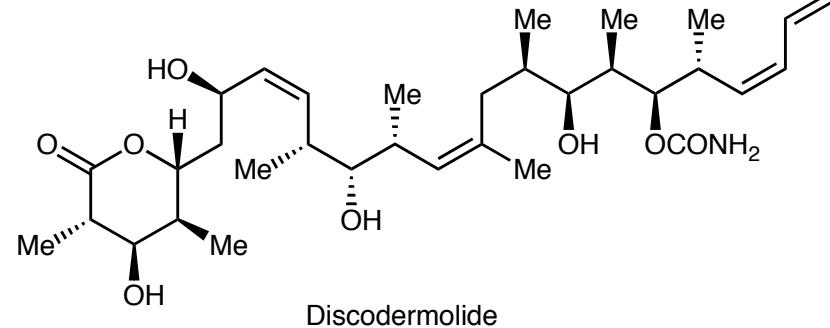
Retrosynthetic Analysis: Dimerization of Identical Fragments



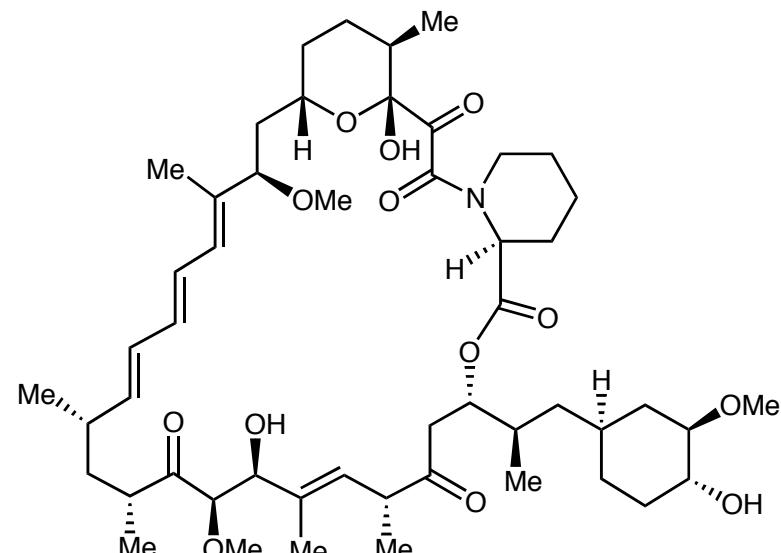
Movassaghi, M.; Schmidt, M. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 3725.



Chimonanthine

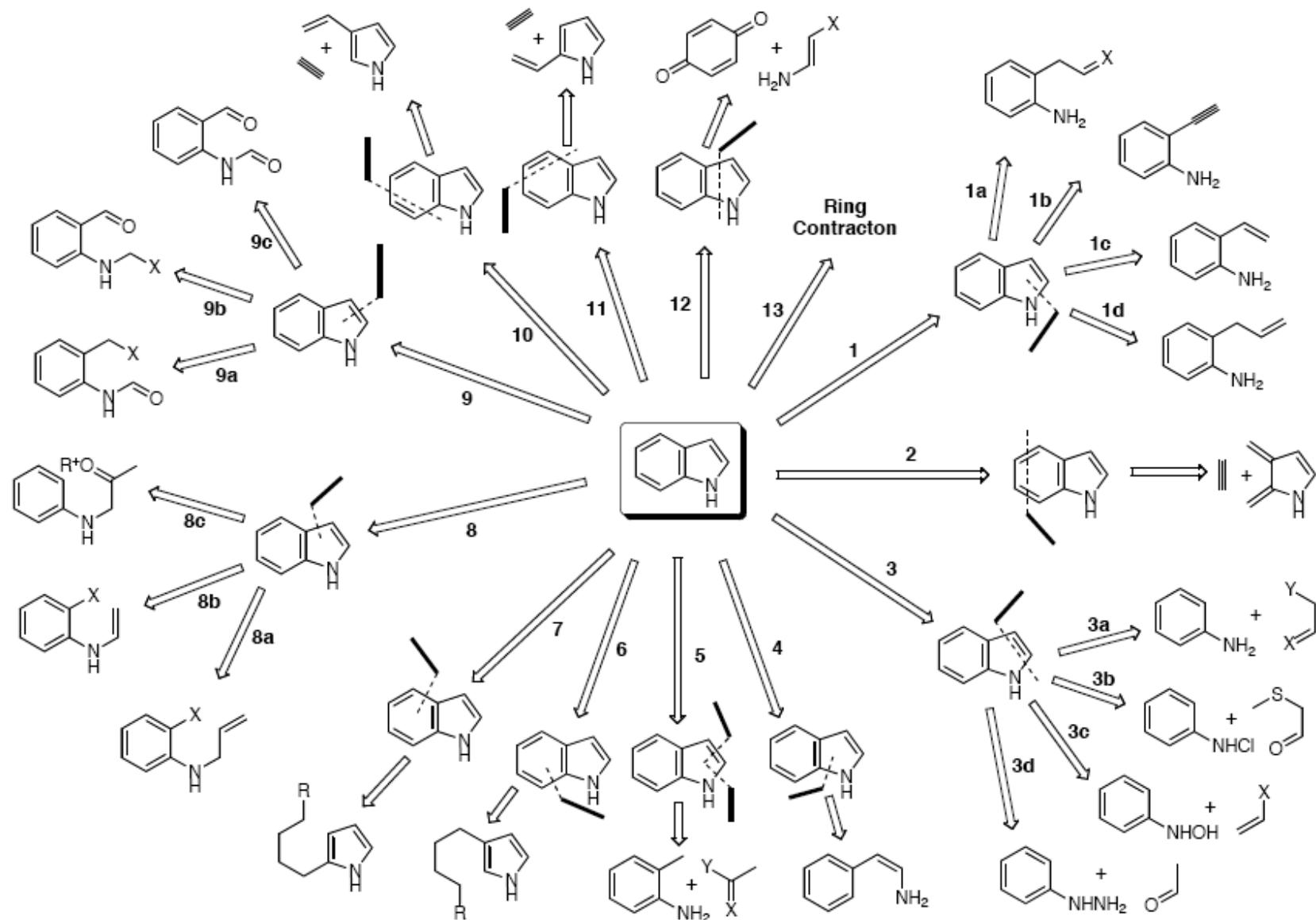


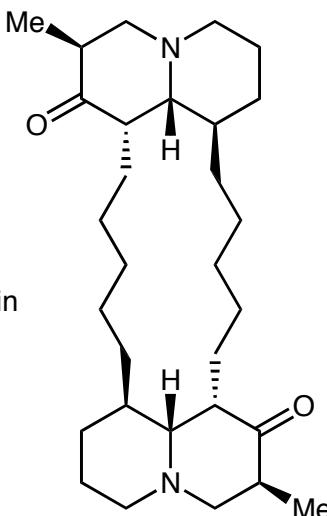
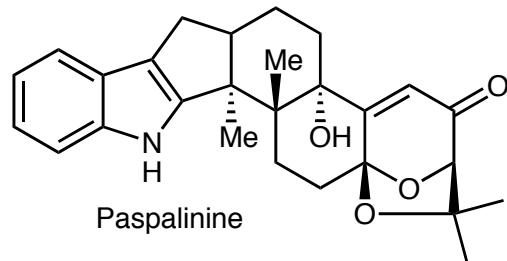
Discodermolide



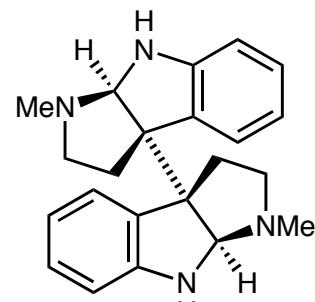
Rapamycin

Indole Synthesis

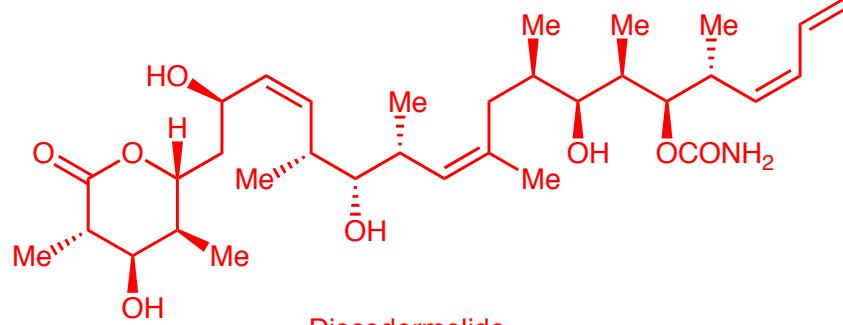




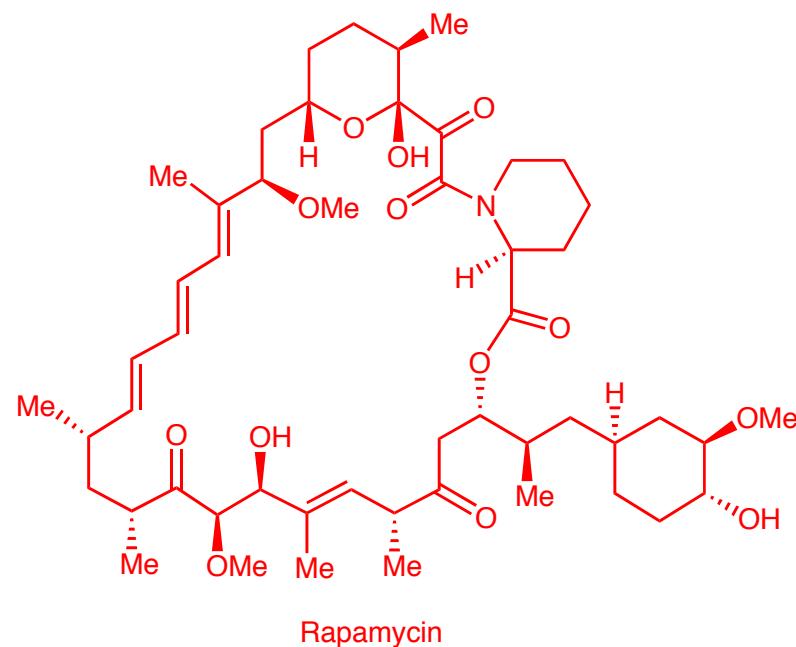
Petrosin



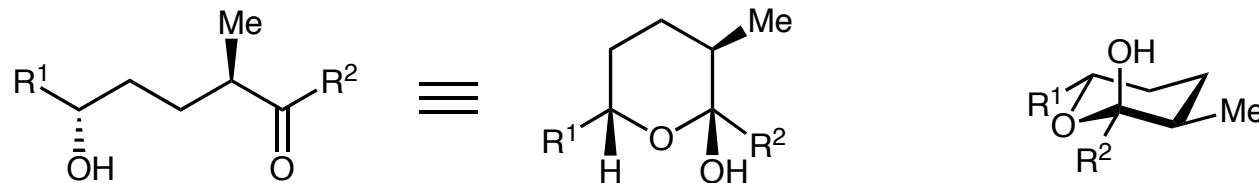
Chimonanthine



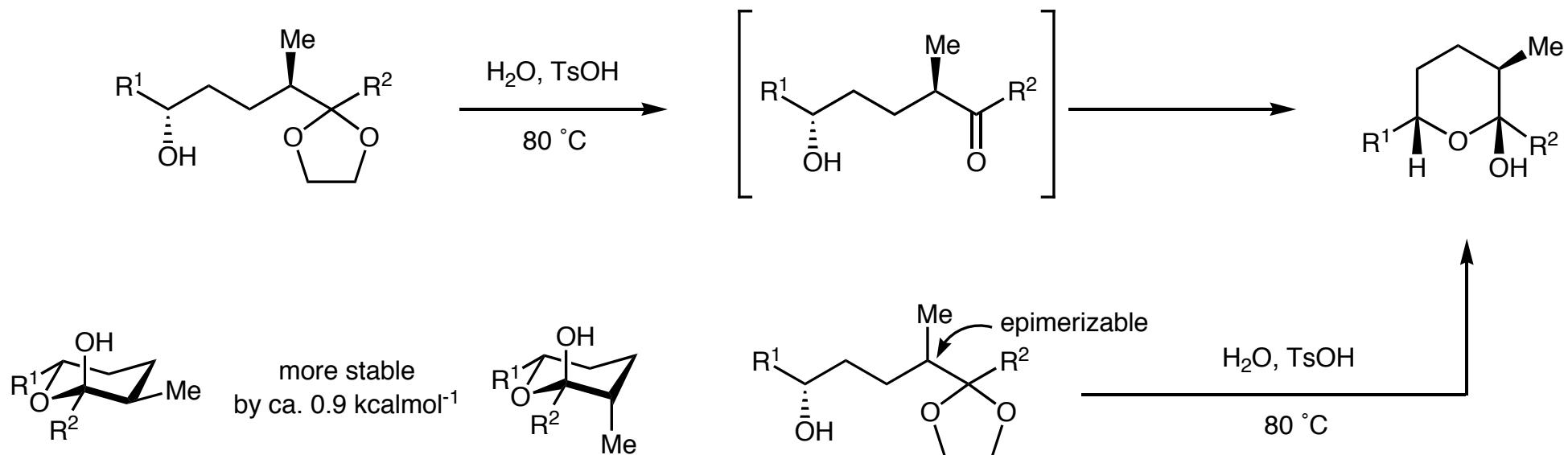
Discodermolide



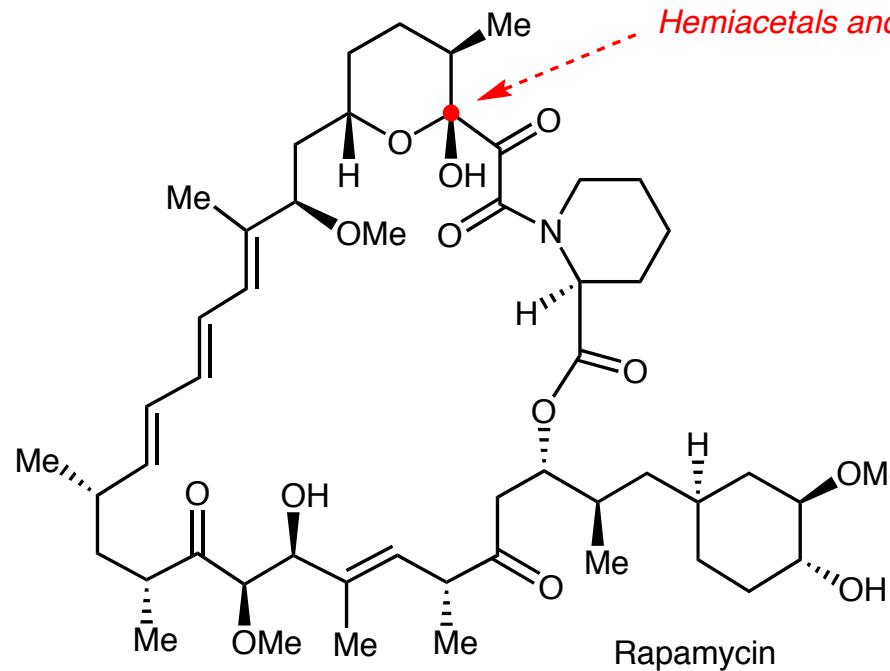
Rapamycin



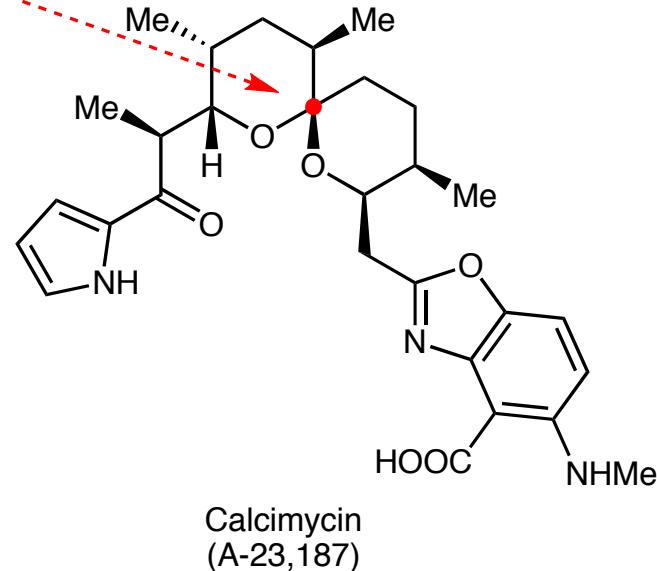
→ Usually, hemiacetal in which the hydroxy group ends up axial are thermodynamically favored (anomeric effect)



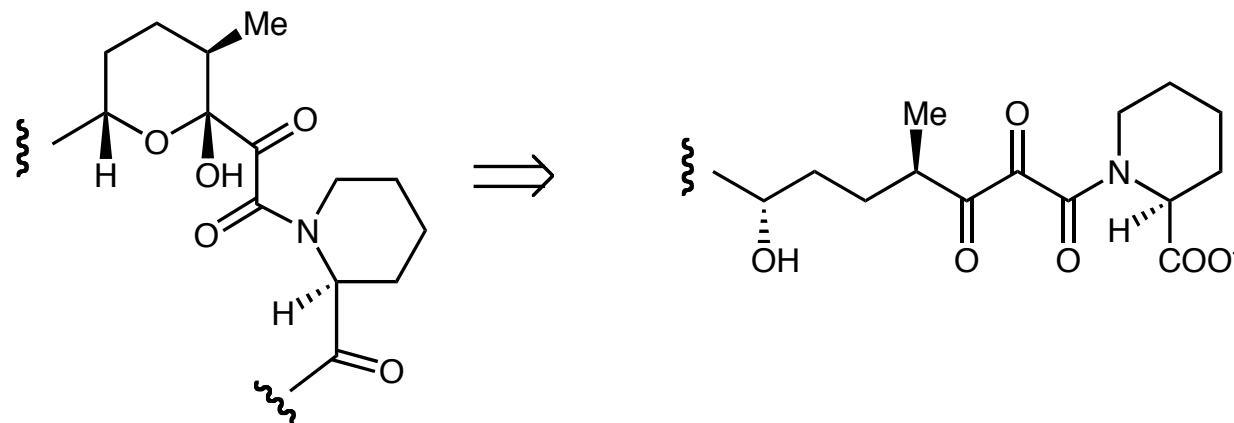
Hemiacetal, Spiroketal Centers: A Logical Disconnection

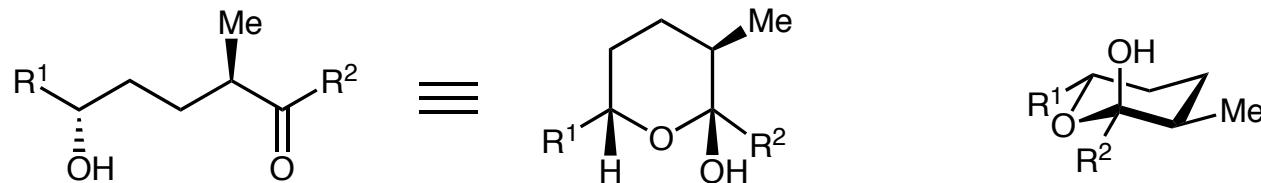


Hemiacetals and acetals

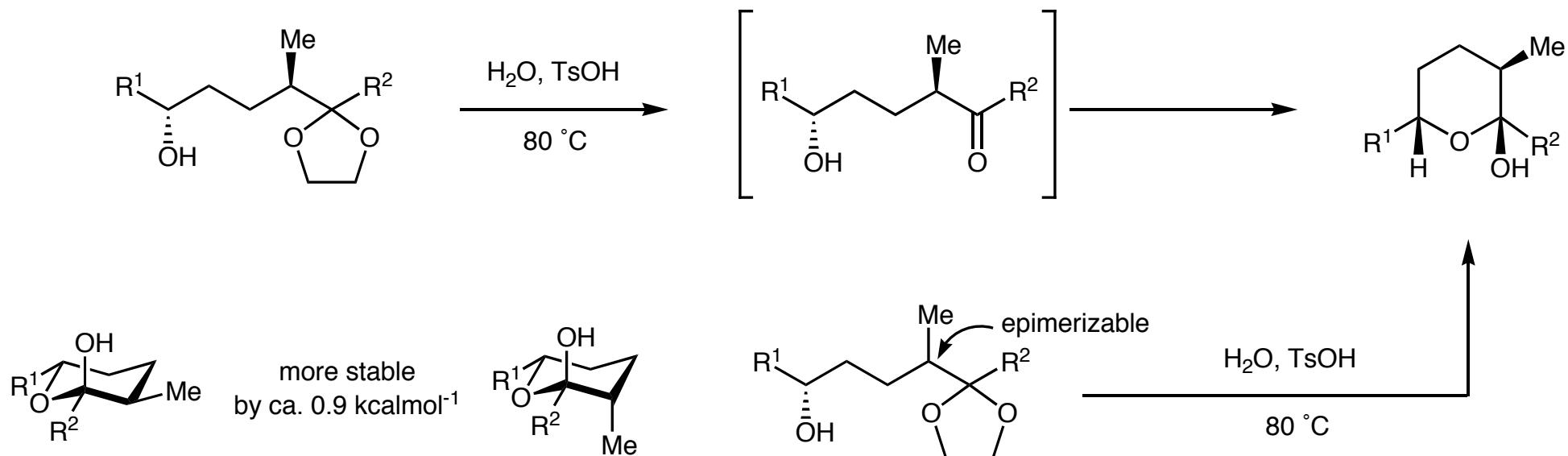


Calcimycin
(A-23,187)

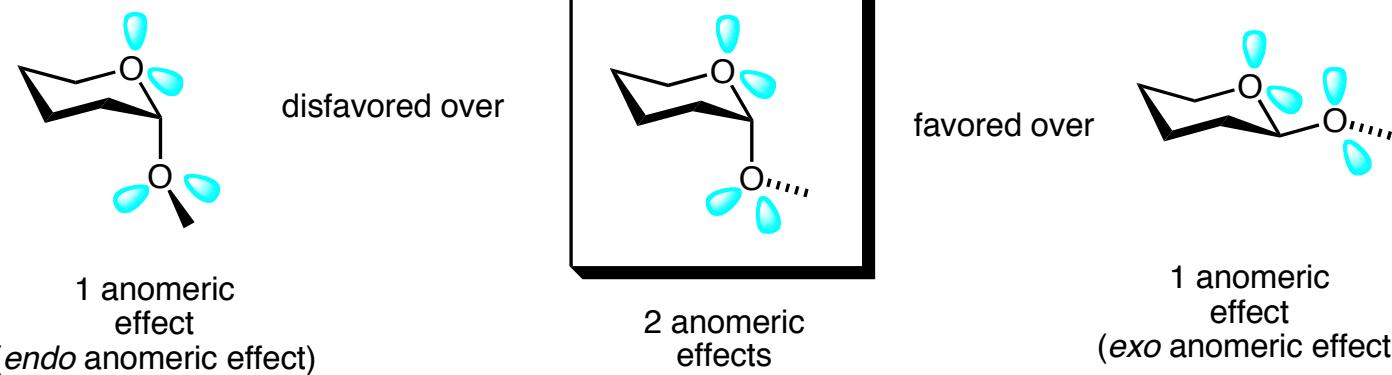
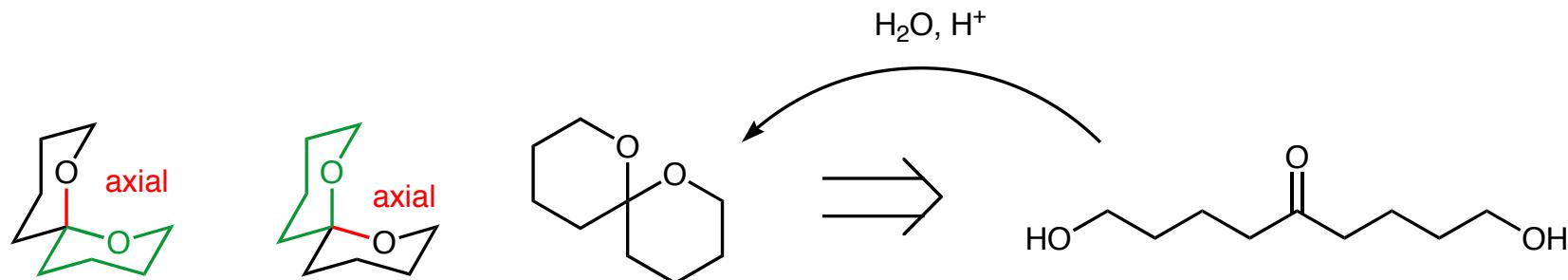




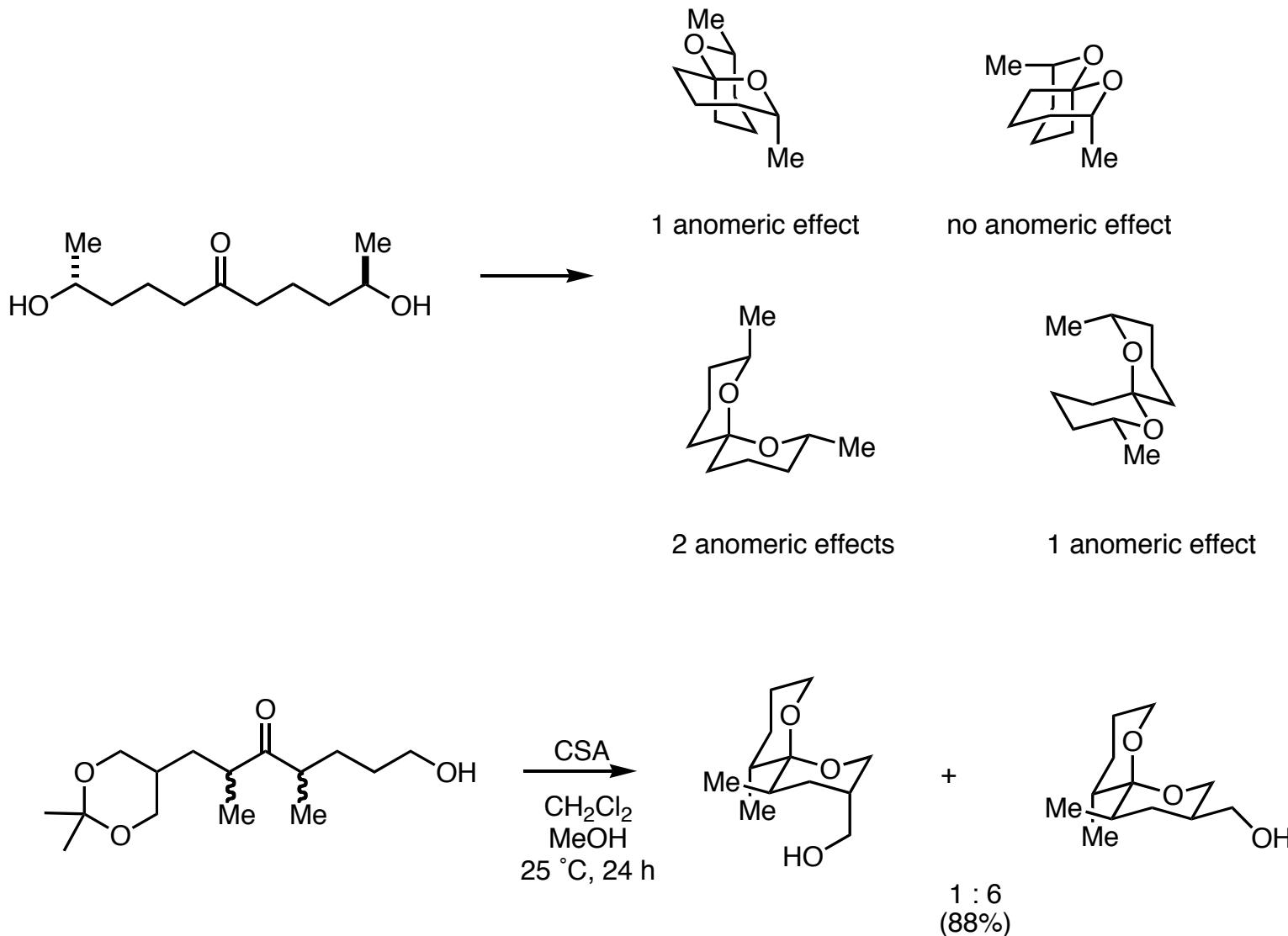
→ Usually, hemiacetal in which the hydroxy group ends up axial are thermodynamically favored (anomeric effect)



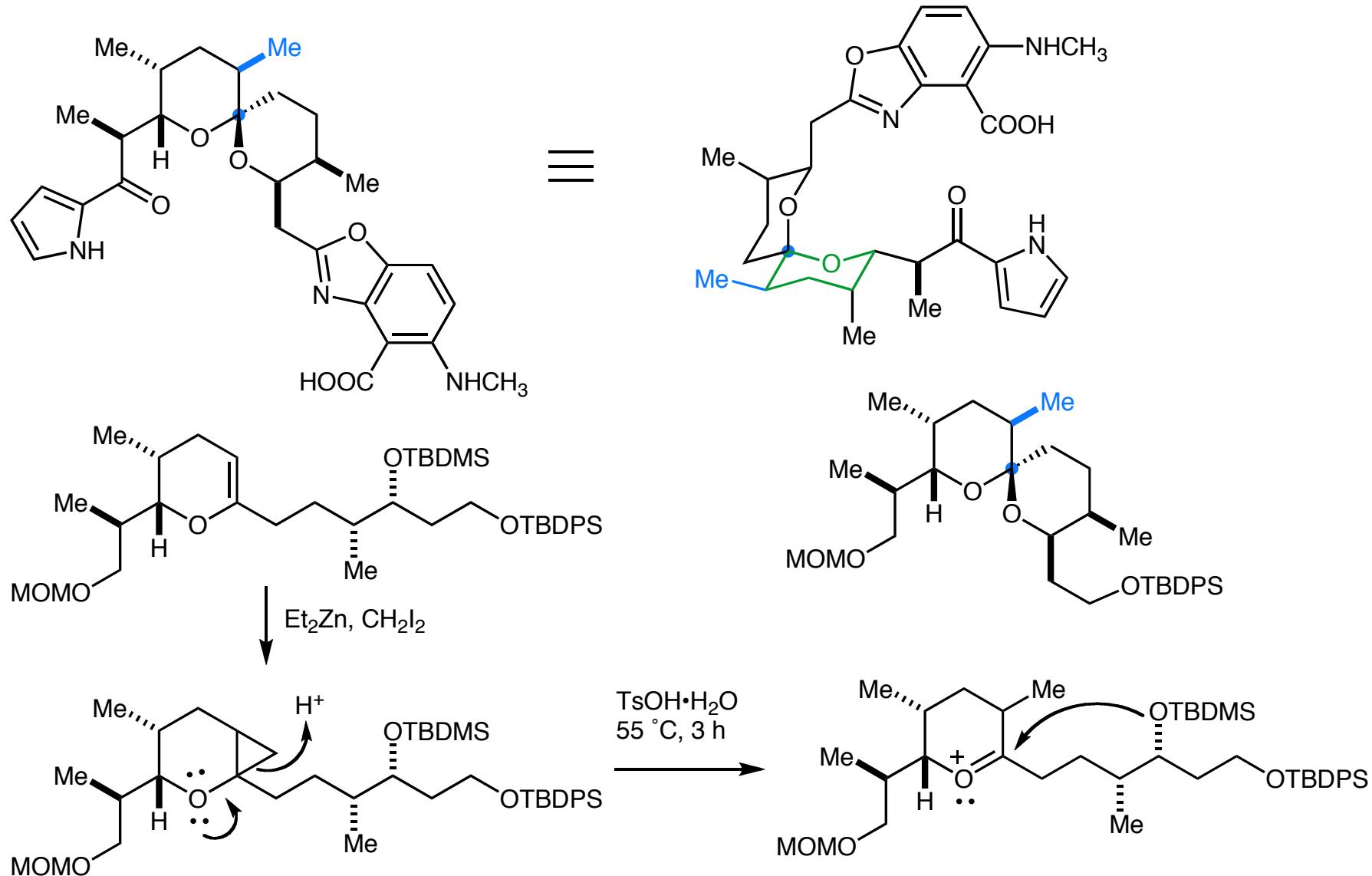
Review: Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617.



$$1 \text{ anomeric effect} = \text{ca. } 1.4 \text{ kcal mol}^{-1}$$

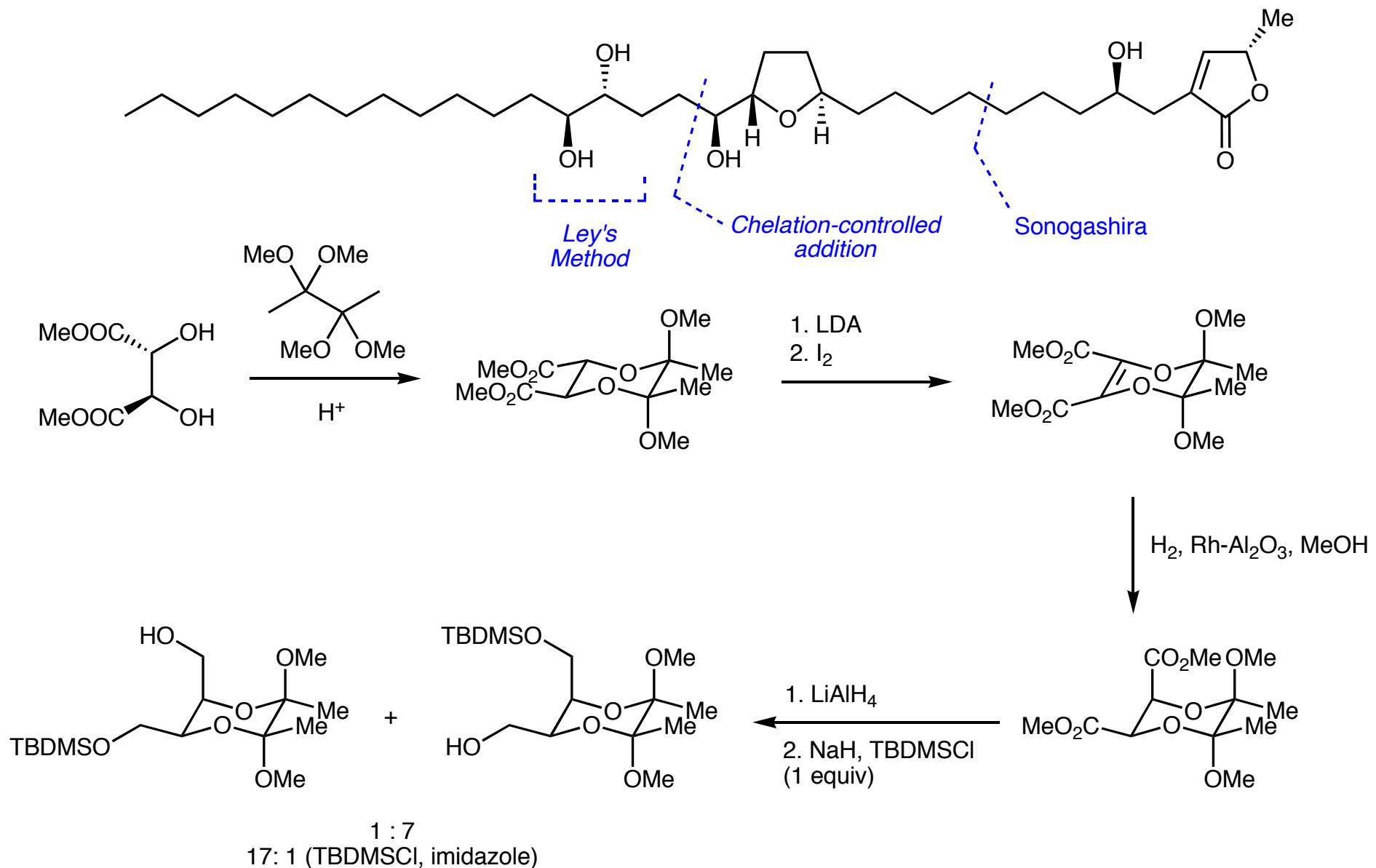


Spiroketal: Calcimycin Synthesis

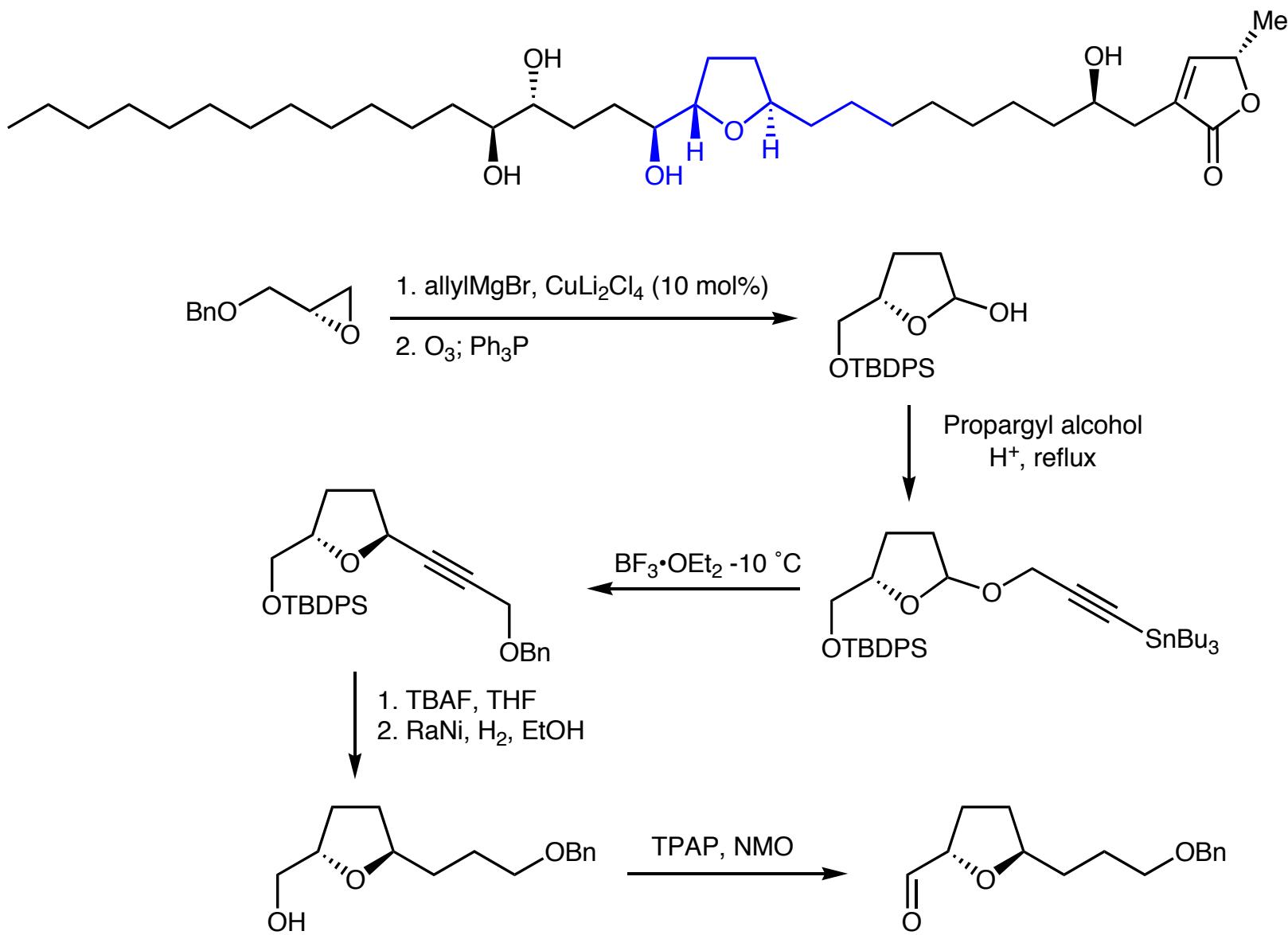


JACS 1987, 7553. JACS 1991, 5337.

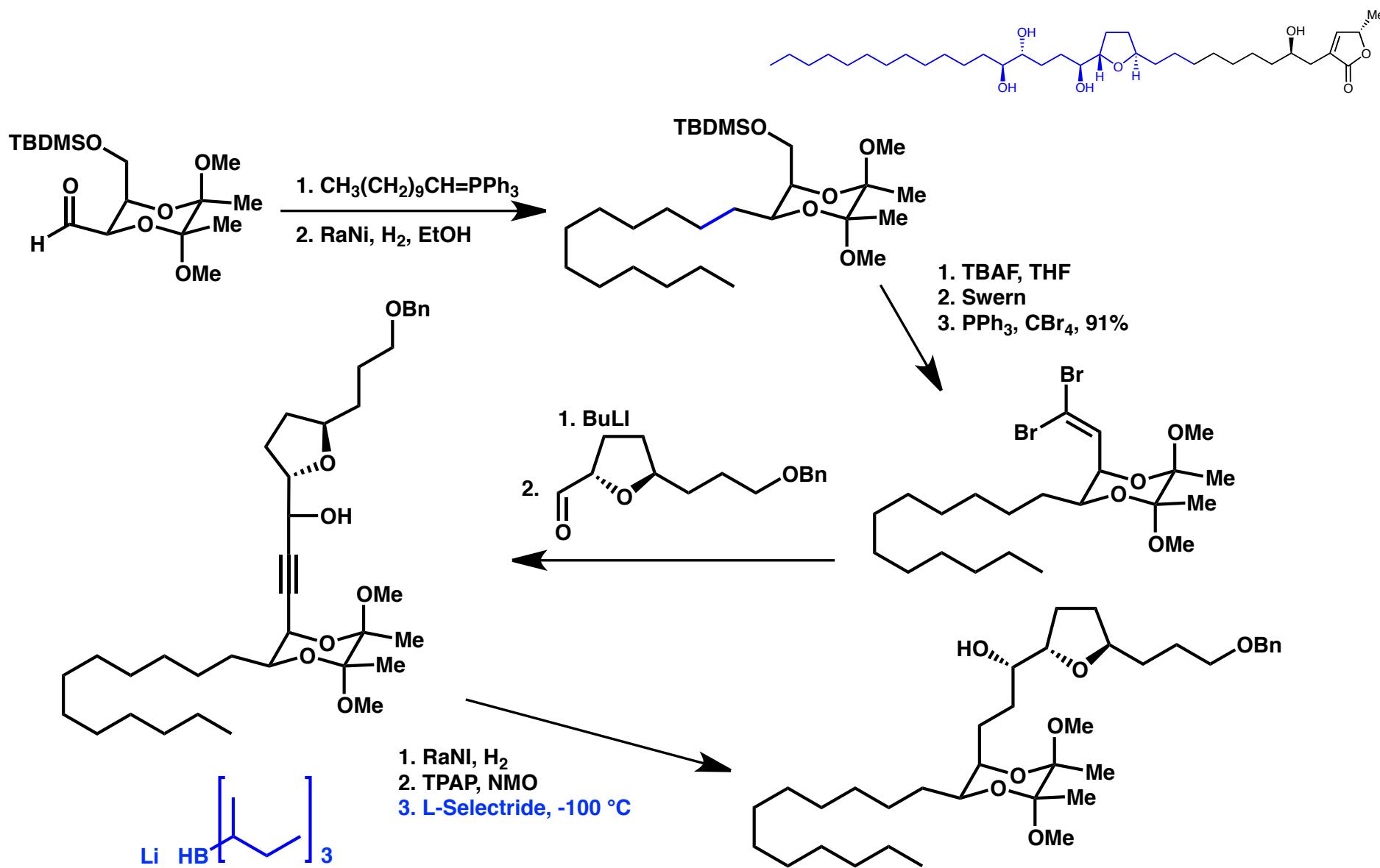
Synthesis of Muricatetron C: Ley's Diacetol Method



Ley's Synthesis

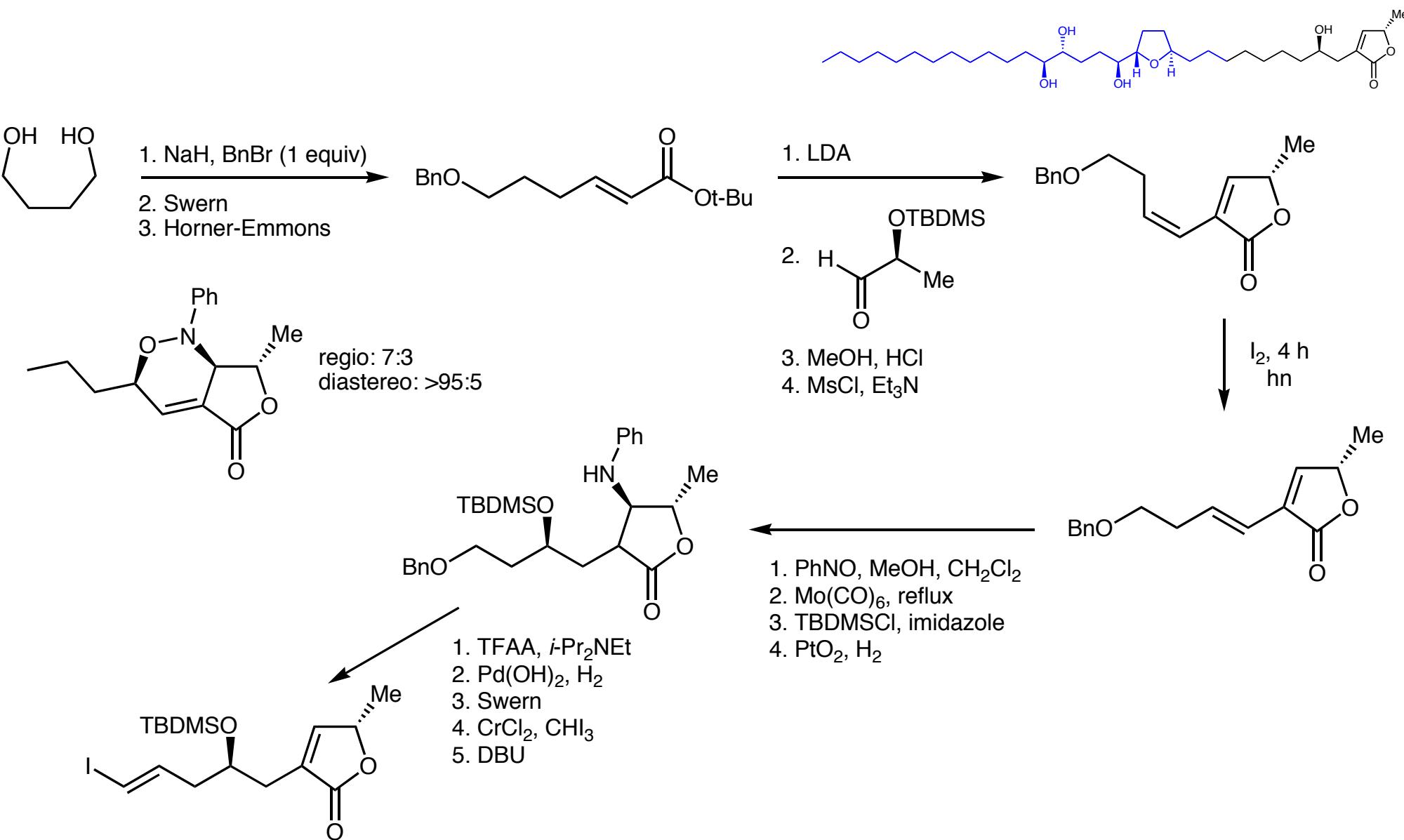


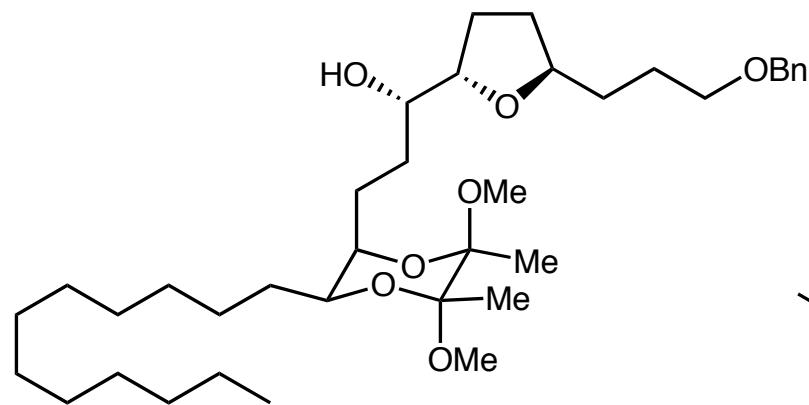
Ley's Synthesis



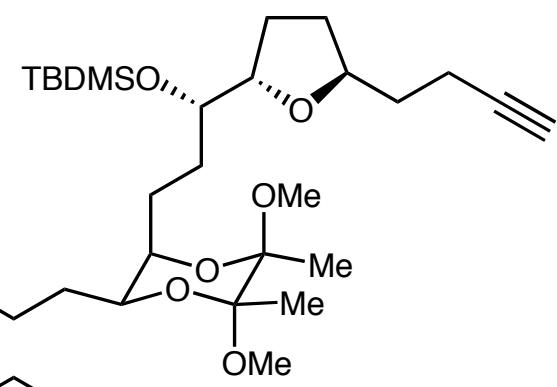
Ley's Synthesis

CHM-6315





1. TBDMSCl, imidazole
2. $\text{Pd}(\text{OH})_2, \text{H}_2$
3. Dess-Martin
4. $(\text{EtO})_2\text{P}(\text{O})\text{CHN}_2, \text{KO}t\text{-Bu}$

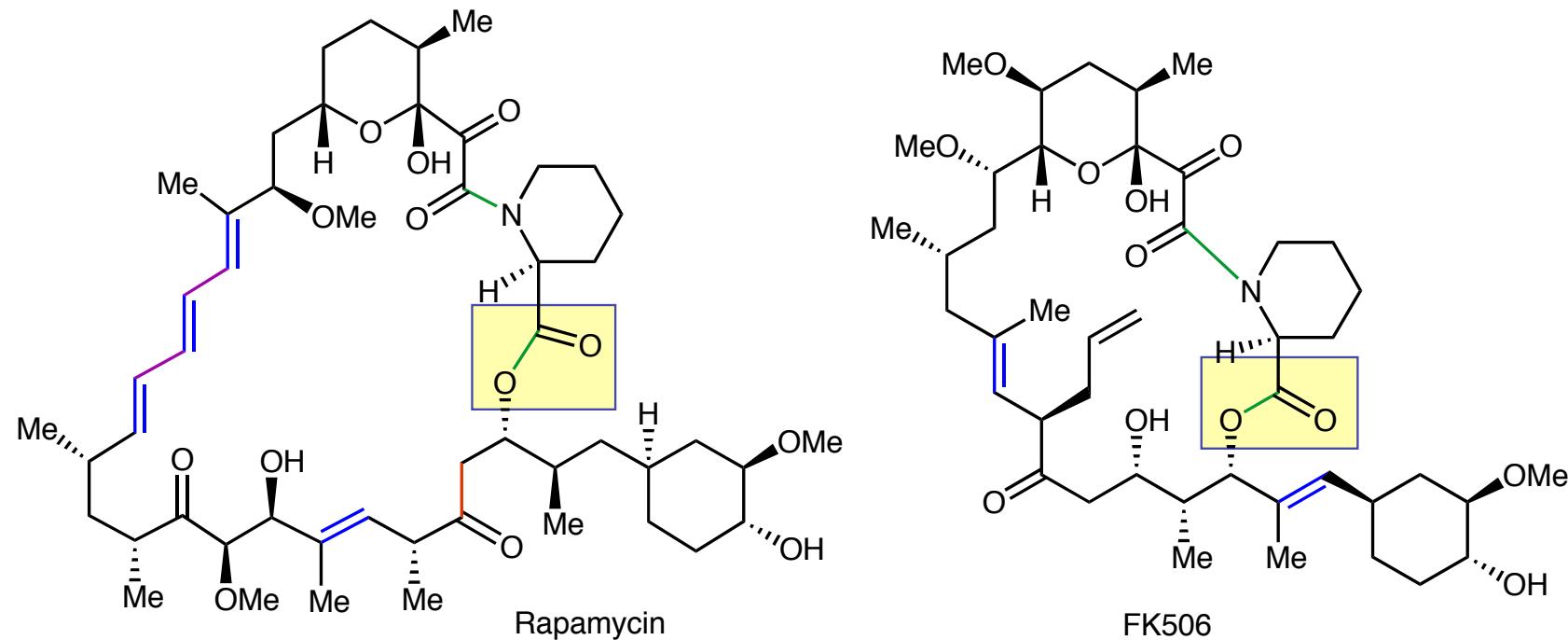


1. $\text{Pd}(0), \text{CuI}, \text{Et}_3\text{N}$

Muricatetrocin C



2. $\text{Rh}(\text{PPh}_3)_3\text{Cl}, \text{H}_2$
3. $\text{TFA}, \text{H}_2\text{O}$



-

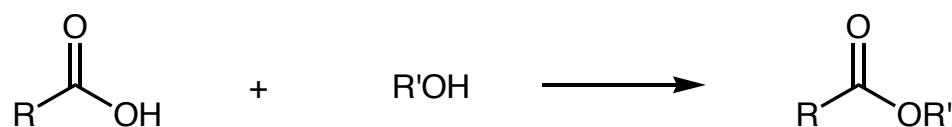
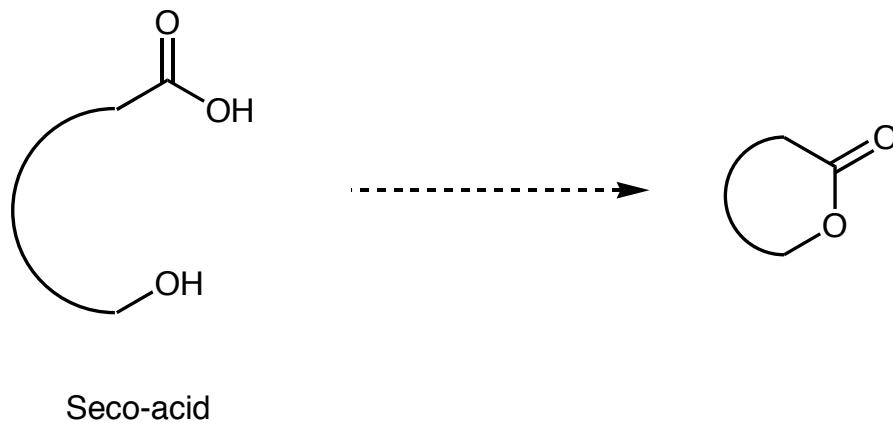
Lactonization and Macrolactonization

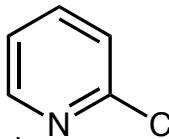
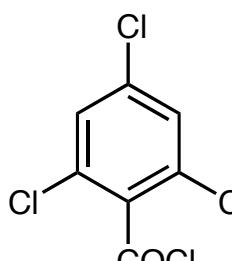
Lactamization and Macrolactamization

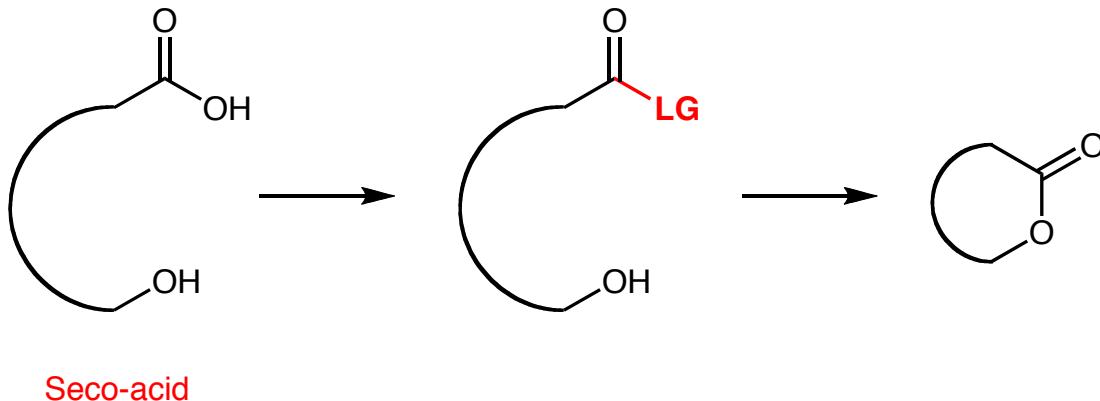
Olefination Reactions (Wittig, Horner-Emmons, Julia, Julia-Kocienski, etc.)

Transition Metal Catalyzed Cross-coupling Reactions

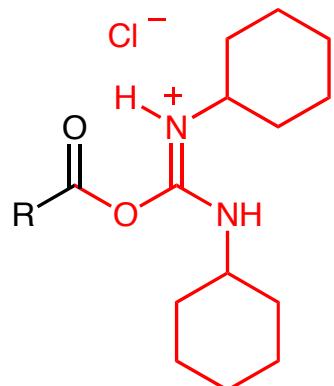
Alkylation of Stabilized Anions



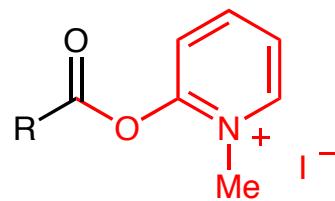
Reagents	Reference
DCC, DMAP, DMAP-HCl, CHCl ₃	Keck <i>J. Org. Chem.</i> 1985 , <i>50</i> , 2394.
 + Et ₃ N I ⁻	Mukaiyama <i>Ang. Chem. Int. Ed. Engl.</i> 1979 , <i>18</i> , 707
 Et ₃ N; then DMAP, toluene	Yamaguchi <i>Bull. Chem. Soc. Jpn.</i> 1979 , <i>52</i> , 1989
Pyridyl- or Imidazole thio ester	Corey <i>Tet. Lett.</i> 1976 , <i>17</i> , 3409
t-Buthioester; then CuOTf	Ley <i>JCS Chem. Comm.</i> 1985 , 1805
(PhO) ₂ PPOCl, Et ₃ N; DMAP	Masamune <i>J. Org. Chem.</i> 1982 , <i>47</i> , 1612.
Pivaloyl-Cl, Et ₃ N; pyrrolidinopyridine	Roush <i>J. Org. Chem.</i> 1983 , <i>48</i> , 758.
BOP-Cl, Et ₃ N, r.t.	Corey <i>J. Am. Chem. Soc.</i> 1982 , <i>104</i> , 6818.



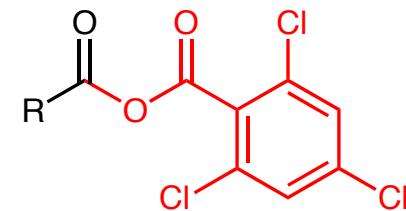
Seco-acid



DCC, DMAP, DMAP·HCl
(Keck)

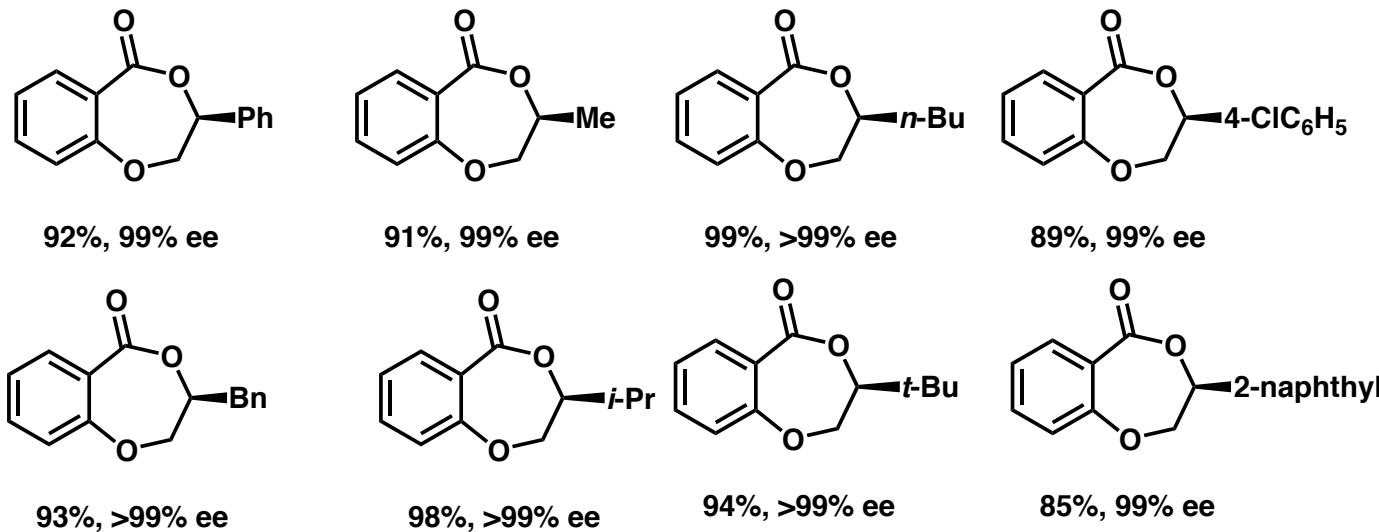
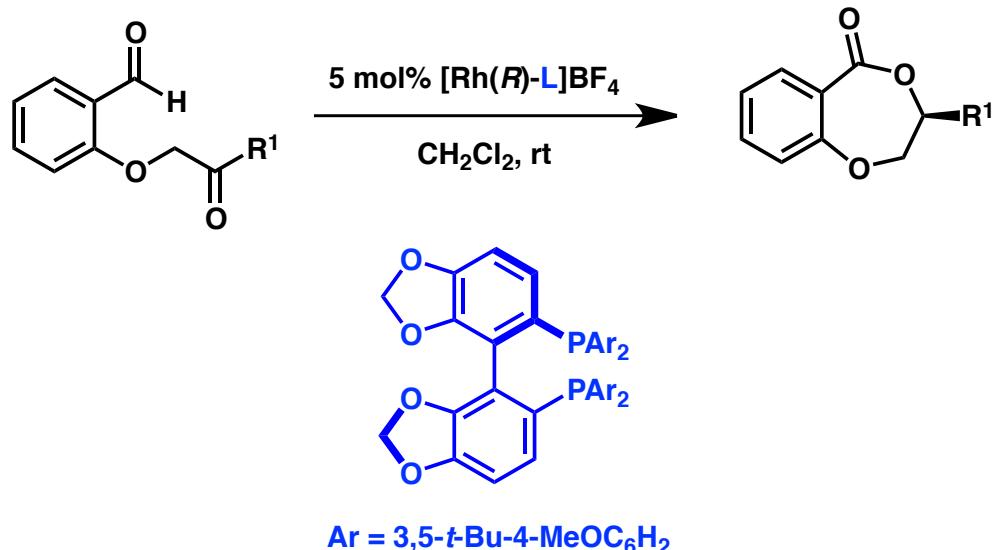
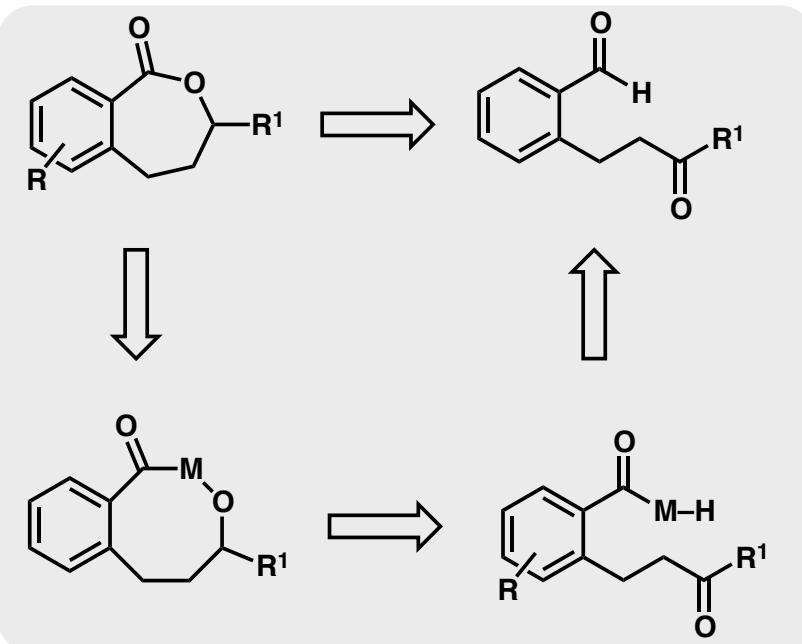


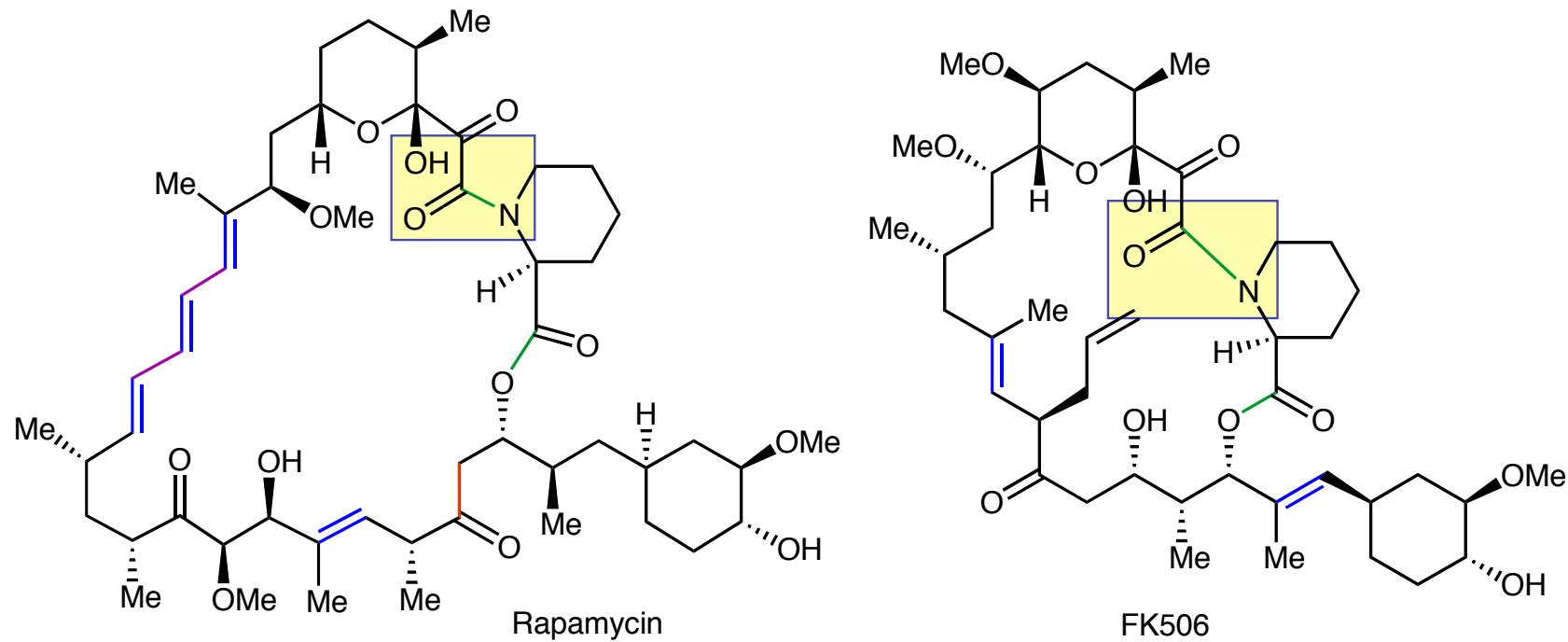
N-Methyl 2-chloropyridinium iodide
(Mukaiyama)



2,4,6-Trichlorobenzoyl Chloride
(Yamaguchi)

Alternative Approach to Macrolactone Formation





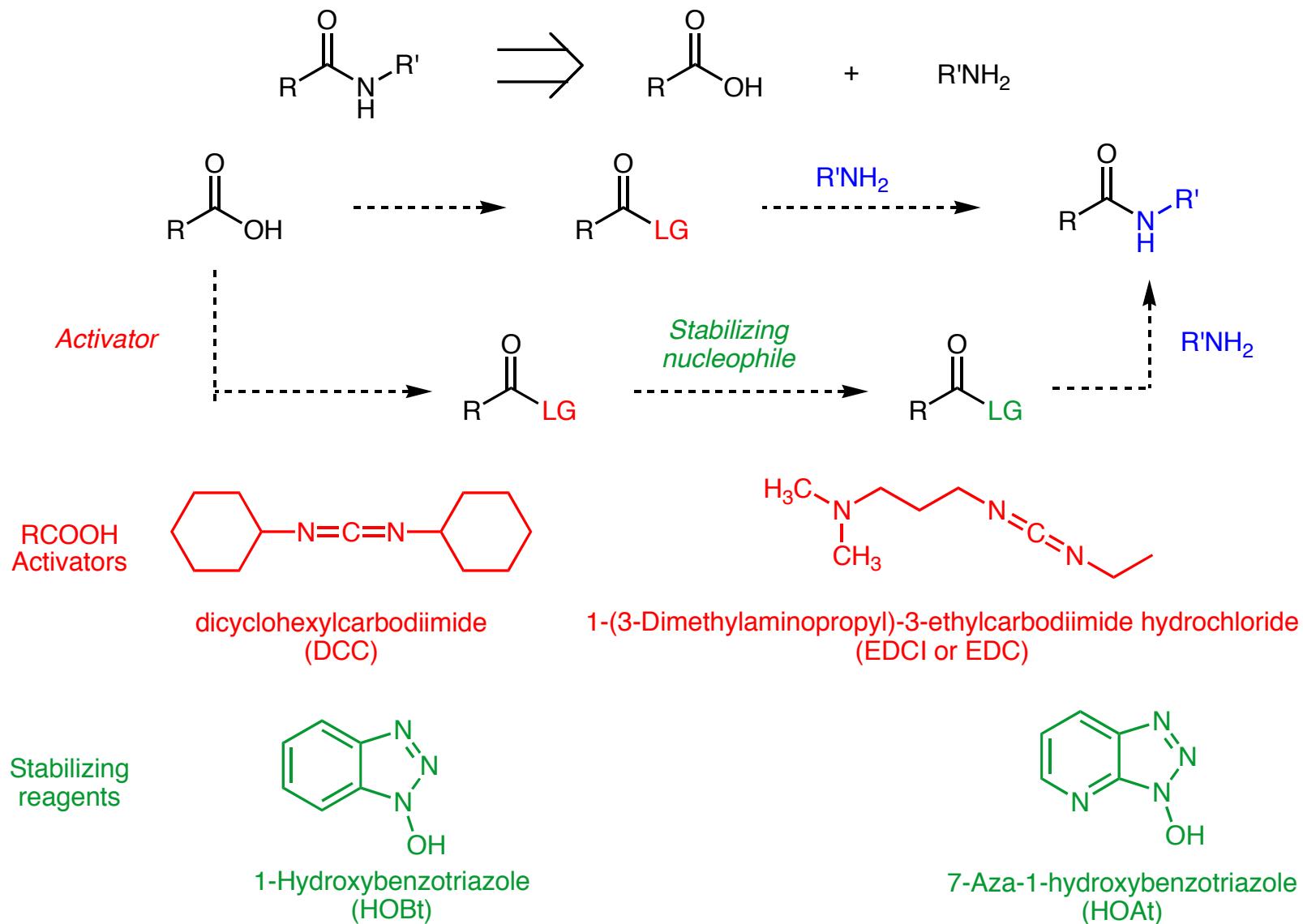
Lactonization and Macrolactonization

Lactamization and Macrolactamization

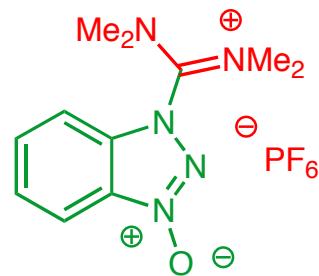
Olefination Reactions (Wittig, Horner-Emmons, Julia, Julia-Kocienski, etc.)

Transition Metal Catalyzed Cross-coupling Reactions

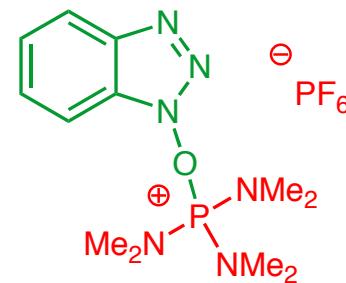
Alkylation of Stabilized Anions



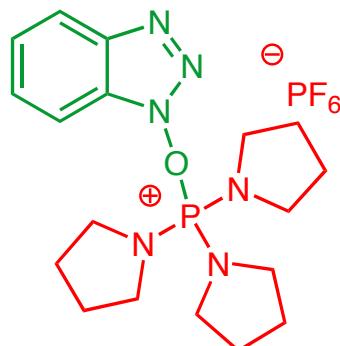
Dual
reagents



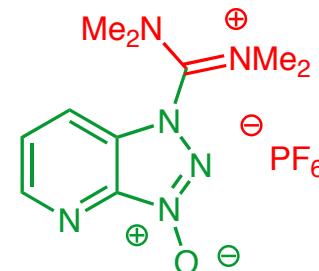
O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium
hexafluorophosphate
(HBTU)



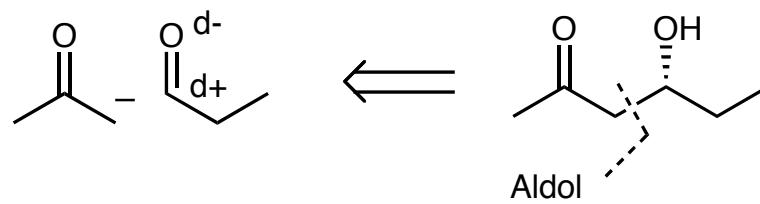
1-benzotriazolyloxytris(dimethylamino)-
phosphonium hexafluorophosphate
(BOP)



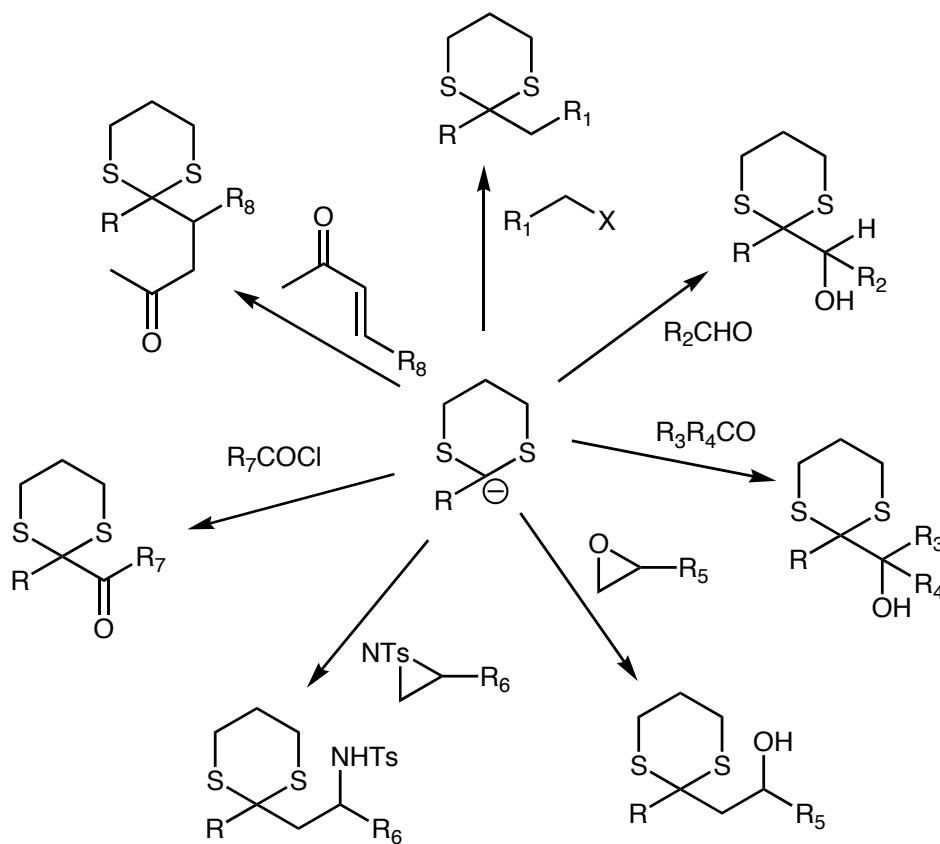
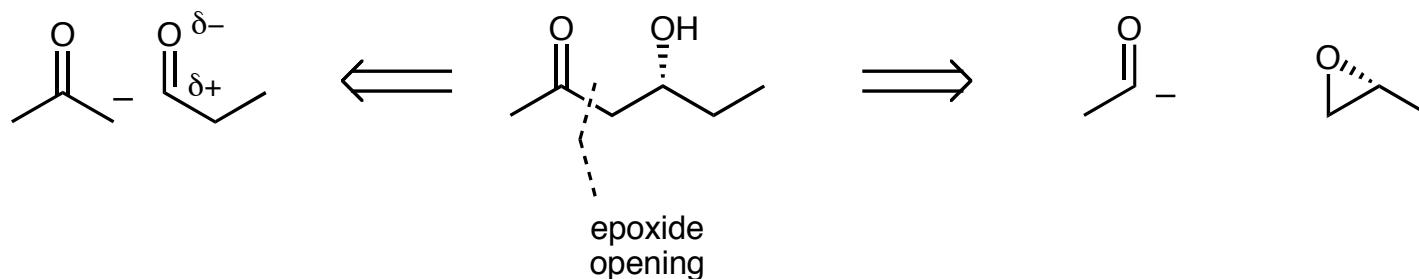
Benzotriazol-1-yloxytritypyrrolidinophosphonium
hexafluorophosphate
(PyBOP)

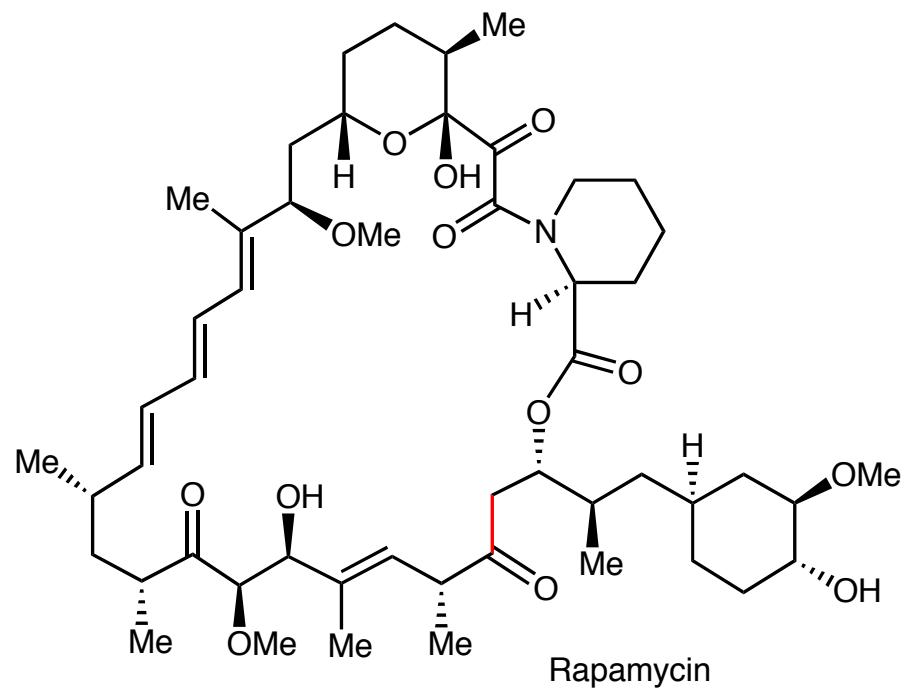


O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
(HATU)

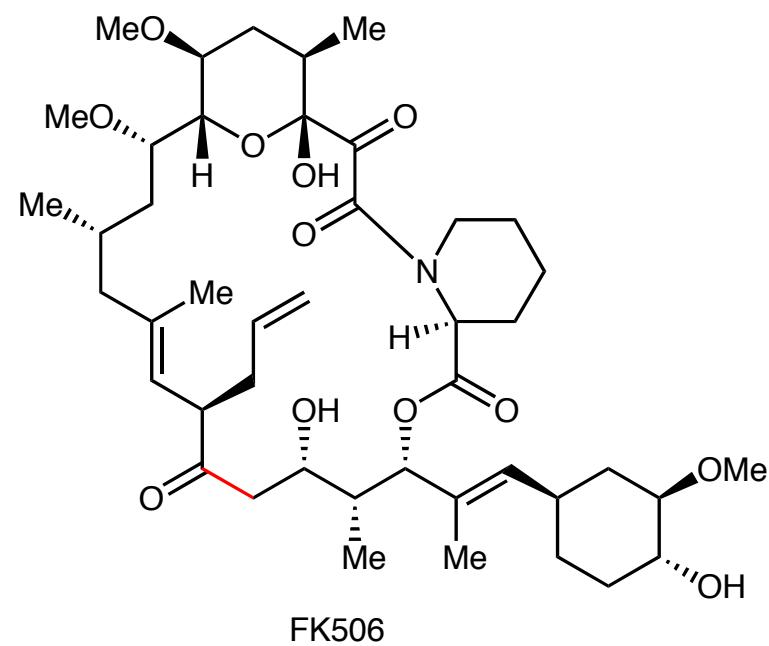


Umpolung Approach for Efficient C-C Bond Forming Process



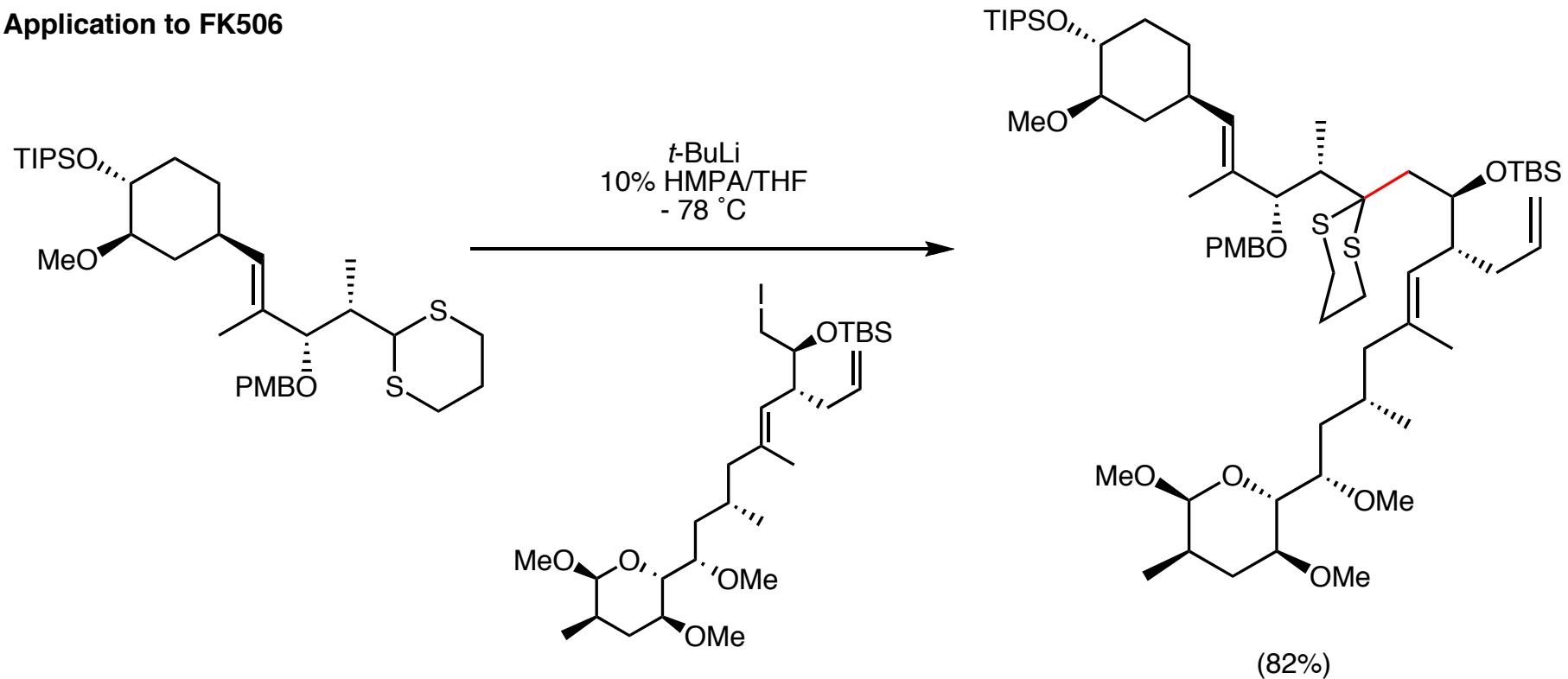


Rapamycin



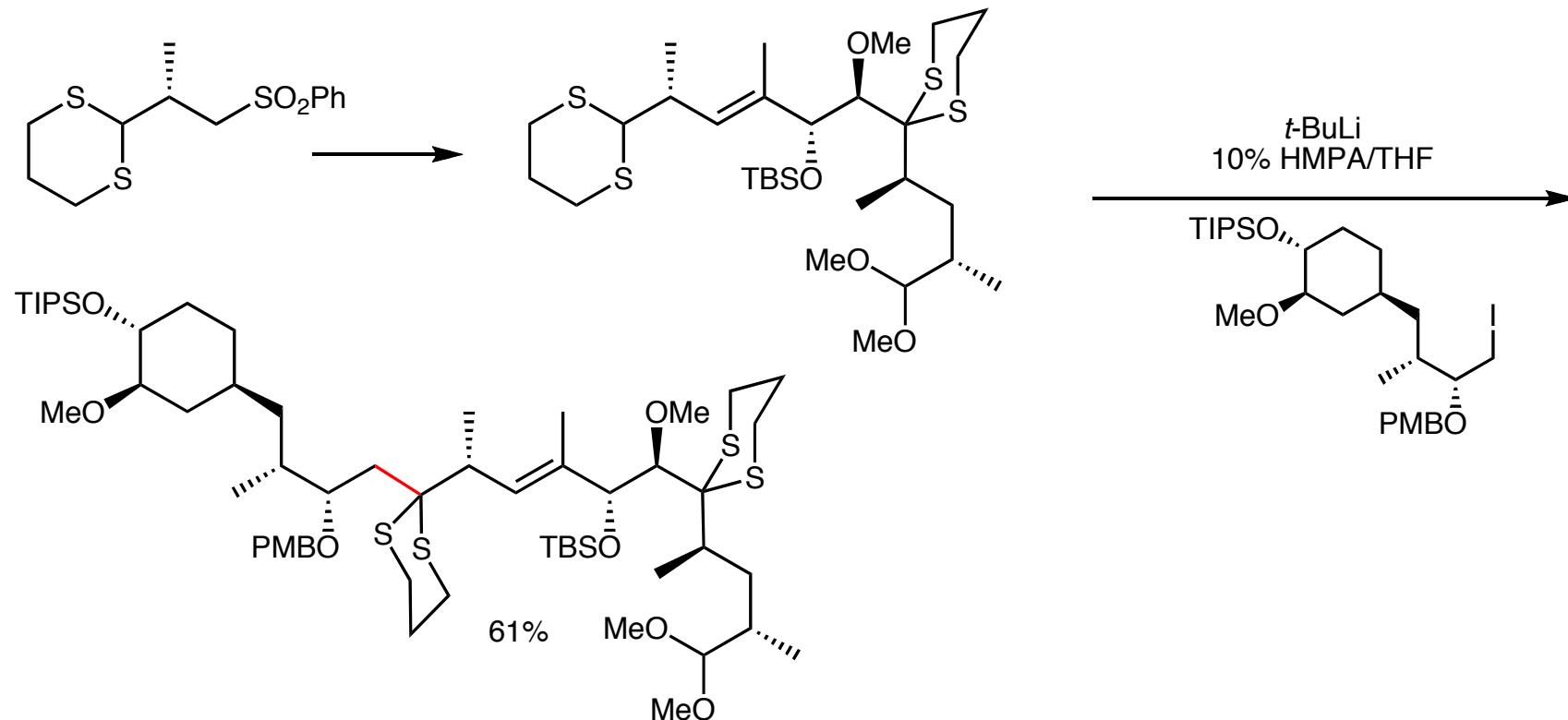
FK506

Application to FK506

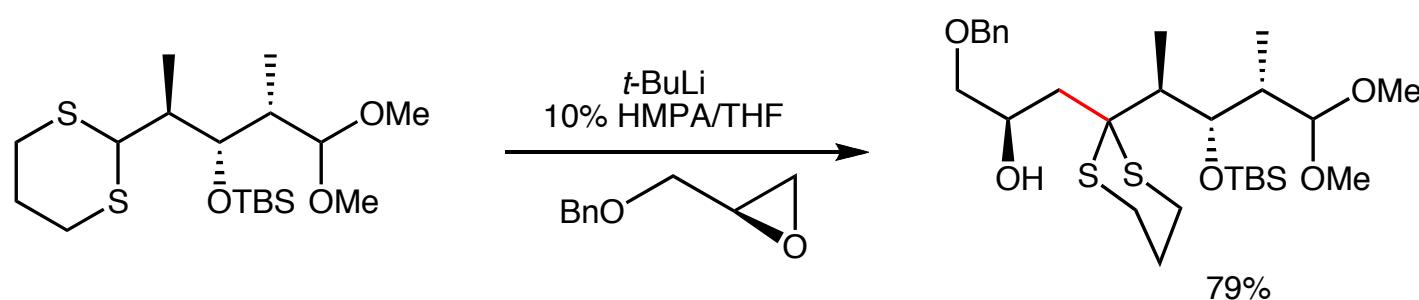


Umpolung Approach for Efficient C-C Bond Forming Process

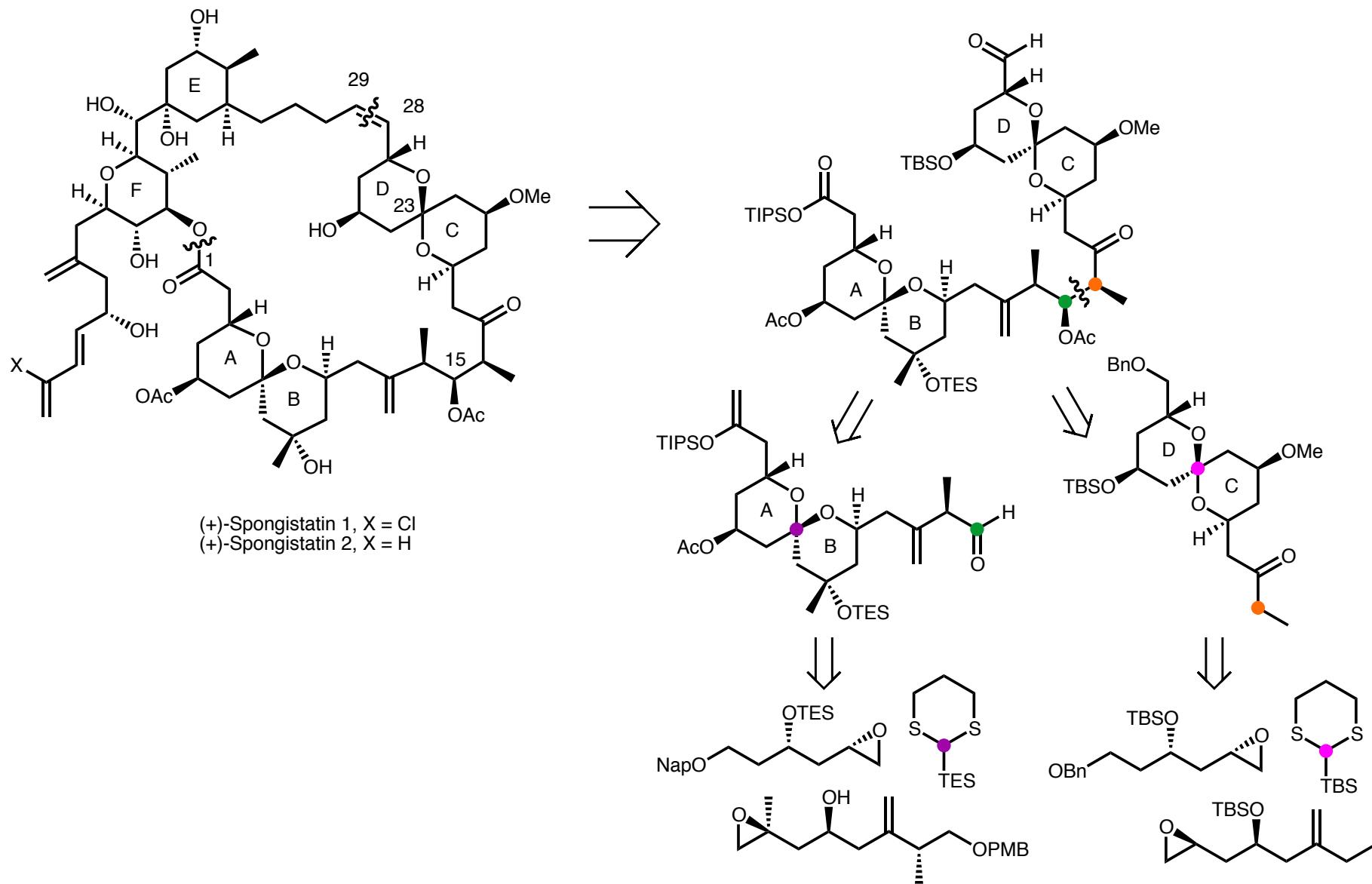
Rapamycin



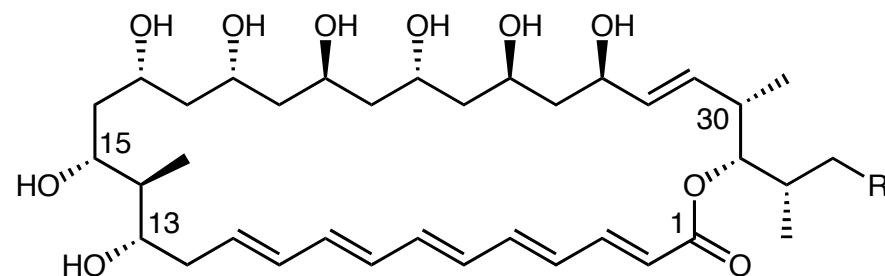
Discodermolide



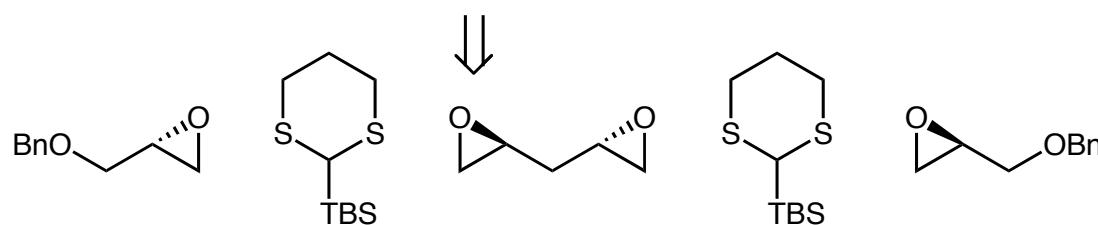
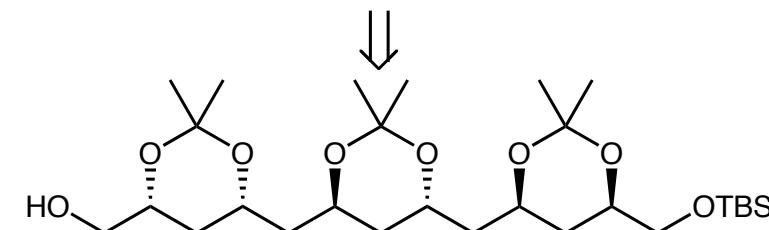
Umpolung Approach for Efficient C-C Bond Forming Process



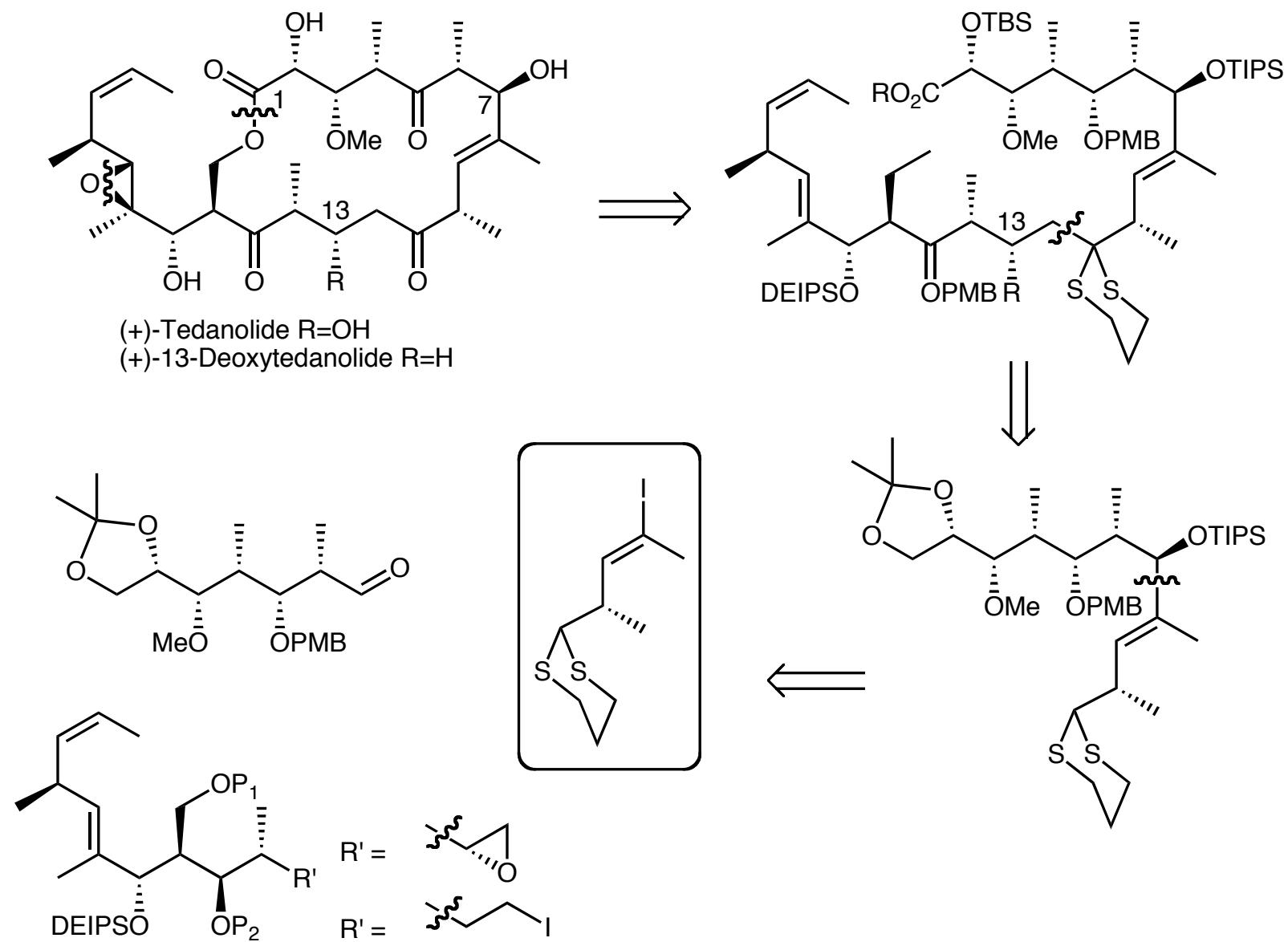
Umpolung Approach for Efficient C-C Bond Forming Process



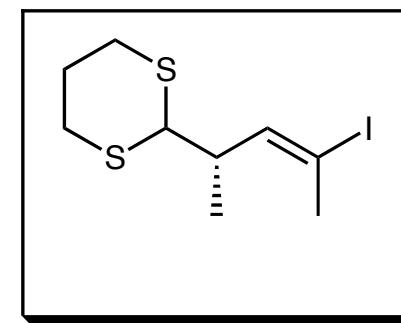
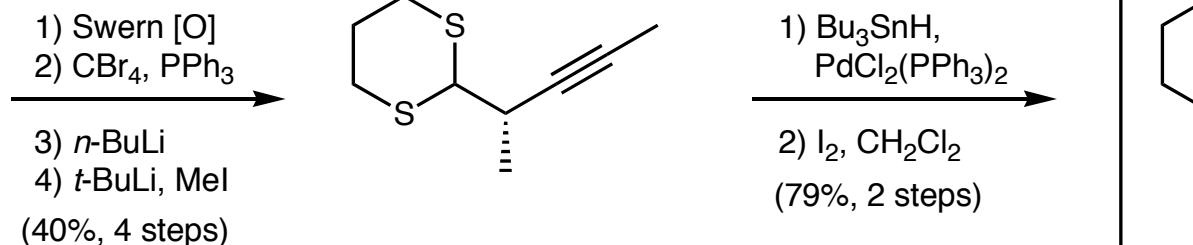
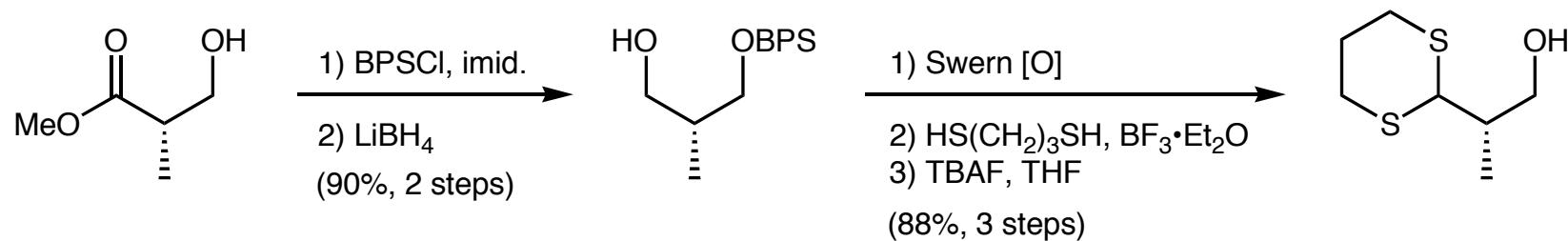
(+)-Mycoticin A R=H
(+)-Mycoticin B R=Me

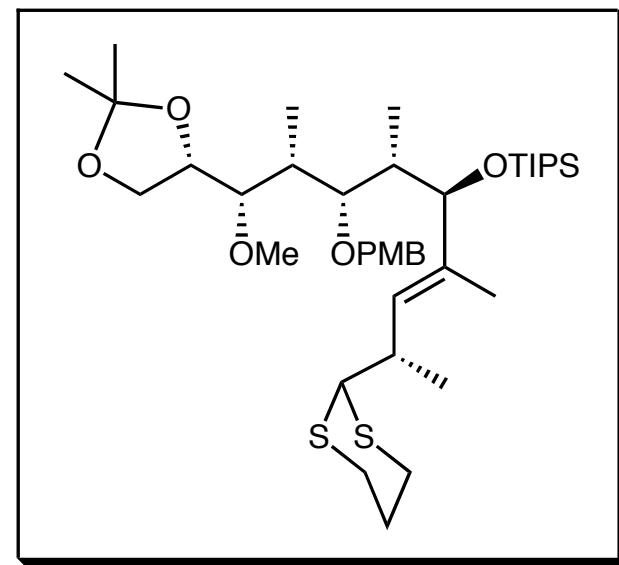
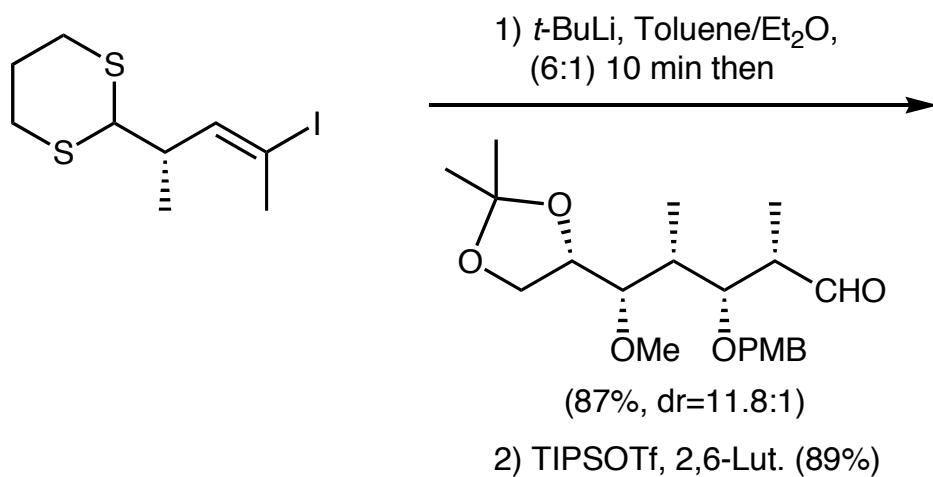


Dithiane in Synthesis: (+)-13-Deoxytedanolide



Dithiane in Synthesis: (+)-13-Deoxytedanolide





Dithiane in Synthesis: (+)-13-Deoxytedanolide

CHM-6315

