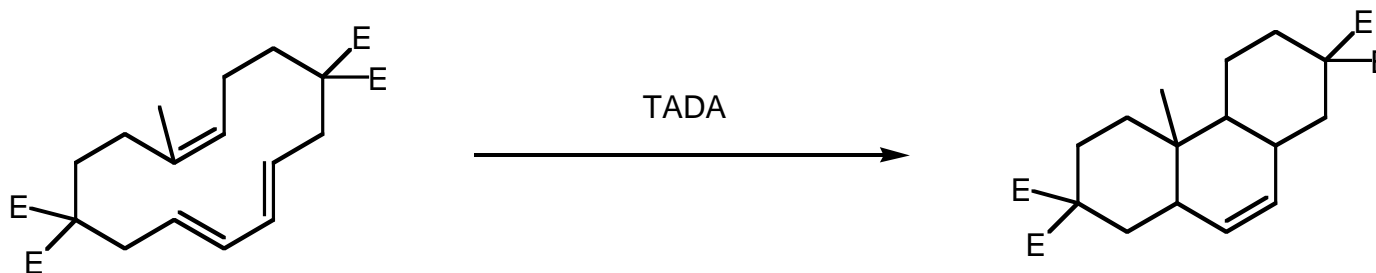


# The Transannular Diels-Alder Reaction

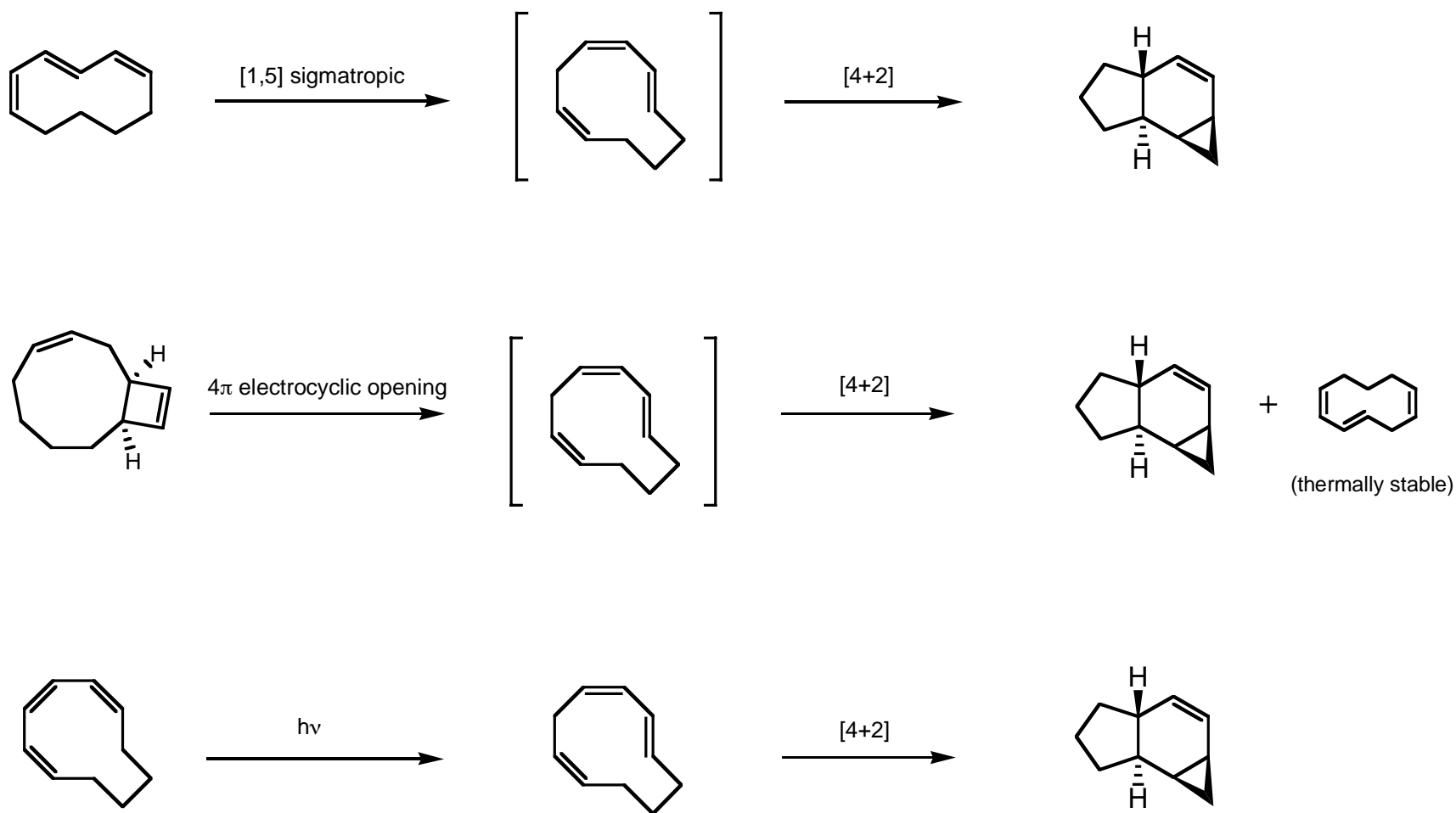
Drew Adams  
Evans Group Seminar  
May, 2004



- I. Background, Utility, Scope
- II. Insights and Oddities From Model Studies
- III. Total Syntheses

E = CO<sub>2</sub>Me

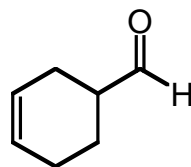
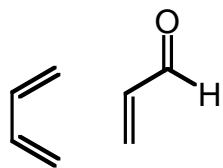
## TADA: Accidental discovery



only example of cyclopropane formation via TADA.

## Diels Alder reaction types

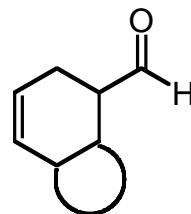
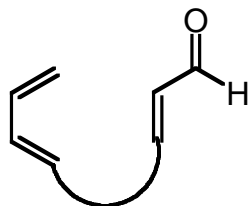
### Standard Diels-Alder



cyclic product

high entropy of activation

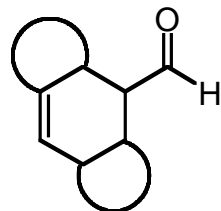
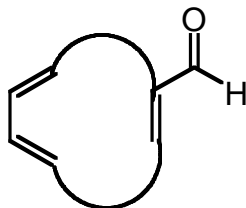
### Intramolecular Diels-Alder (IMDA)



one tether yields a bicyclic product

lowered entropy of activation because unimolecular

### Transannular Diels-Alder (TADA)



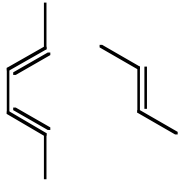
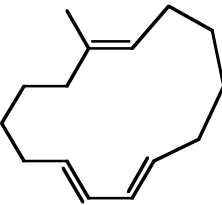
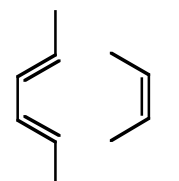
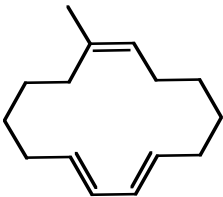
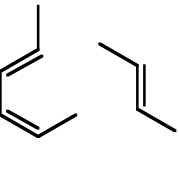
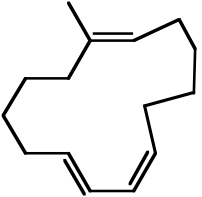
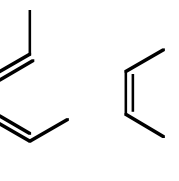
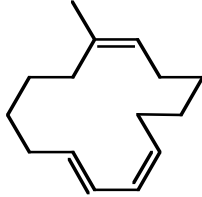
two tethers yields a tricyclic product

lowest entropy of activation because unimolecular  
and forced proximity of reactive centers

*Inverse-electron demand/hetero-DA versions possible for all three situations*

## TADA Benefits: Thermodynamics, Reactivity

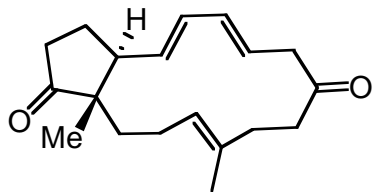
all values are kcal/mol; obtained by MM3, PM3, and author's own macocycle algorithm

	$\Delta H^\ddagger$	$T\Delta S^\ddagger$	$\Delta G^\ddagger$	$\Delta G_{CH}^\ddagger$	$T\Delta S_{CH}^\ddagger$	$\Delta H_{CH}^\ddagger$	
 trans, trans: trans	37.01	-16.83	<b>53.84</b>	<b>36.36</b>	-5.46	30.90	
 trans, trans: cis	37.19	-16.27	<b>53.46</b>	<b>34.88</b>	-2.78	32.01	
 cis, trans: trans	44.63	-16.28	<b>60.90</b>	<b>45.89</b>	-4.84	41.05	
 cis, trans: cis	42.92	-15.60	<b>58.52</b>	<b>45.21</b>	-4.09	41.12	

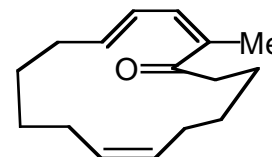
**Prediction:** lowered activation energy of TADA will make typically marginal D-A reactions feasible.

## TADA Benefits: Diene Scope

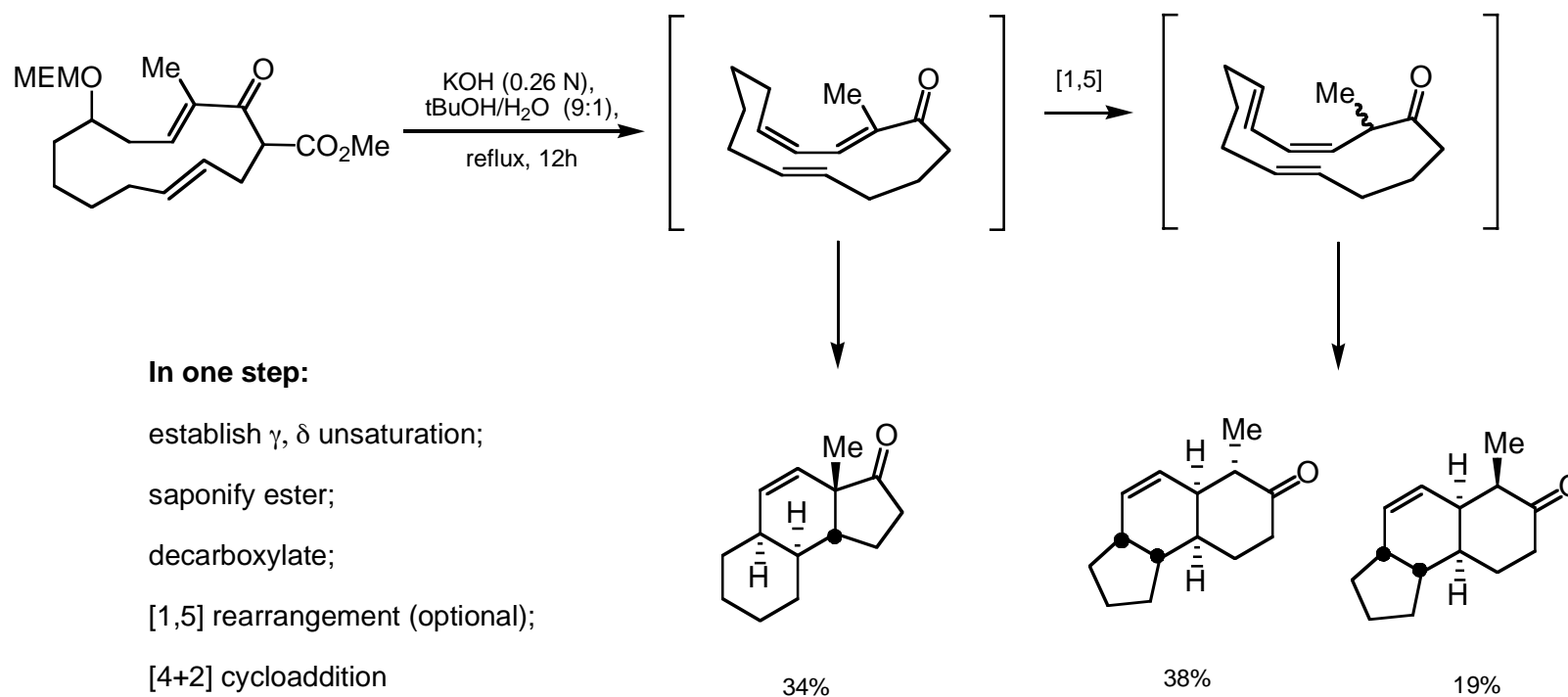
Trans, Trans



Cis, Trans

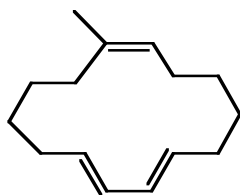


Cis, Trans (substituted)



## Diene reactivity

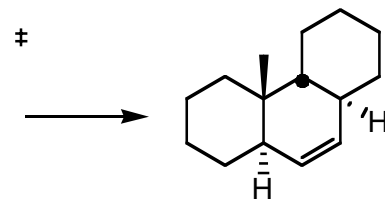
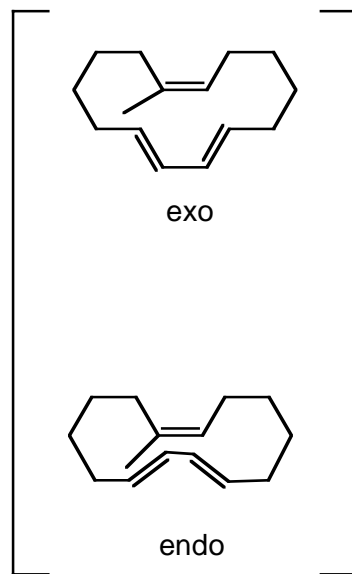
Trans, Trans dienes



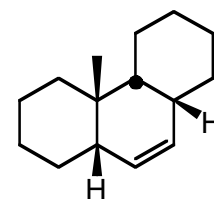
trans, trans; cis

A trans dienophile gives only 2:1 selectivity.

< 80 °C

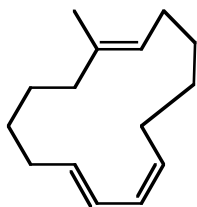


100%  
trans, syn, trans (TST)



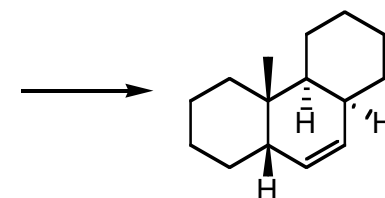
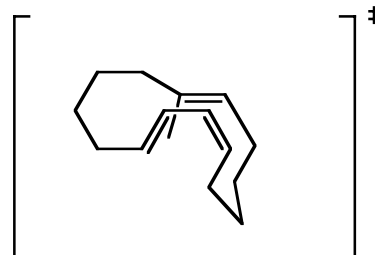
0%  
cis, syn, cis (CSC)

Cis, Trans dienes



cis, trans; trans

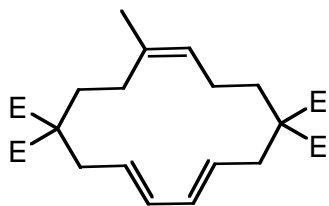
350 °C



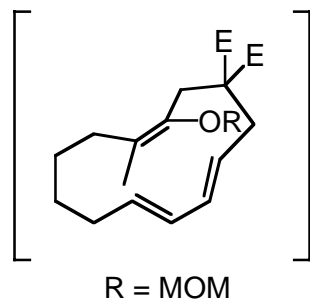
100%  
cis, anti, cis (CAC)

## TADA Benefits: Dienophile Scope

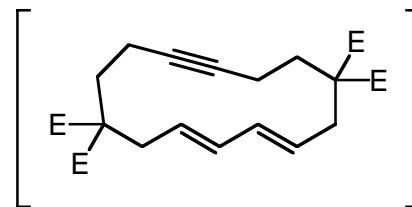
Unactivated dienophile



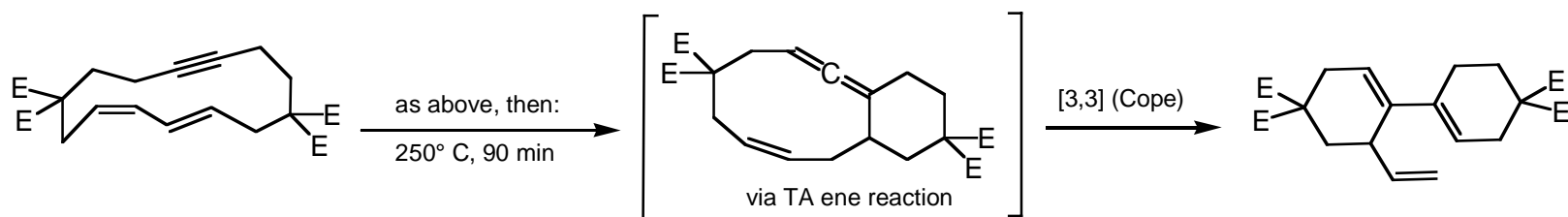
Tetrasubstituted enol ether



Acetylene



The corresponding cis, trans diene gave some TADA product (23%) but mostly rearranged product (63%):

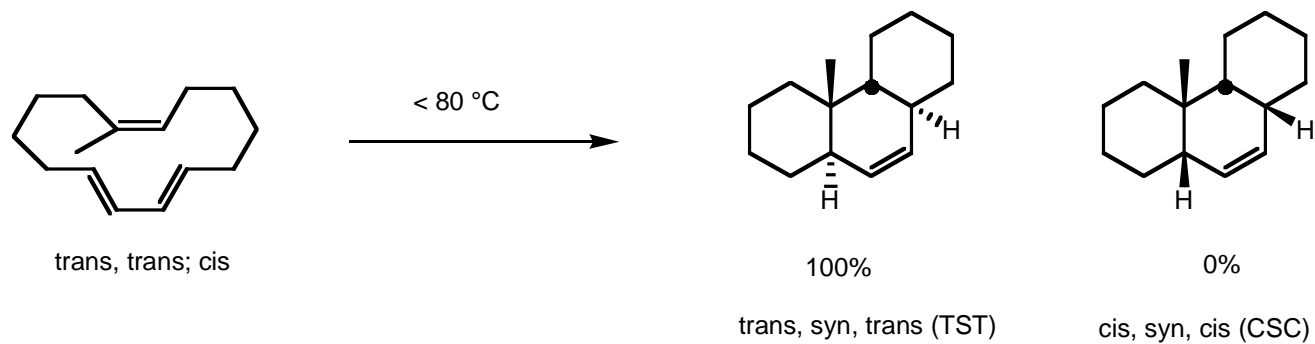


Deslongchamps, P. *TL*, 1987, **28**, 5255.

Deslongchamps, P. *JACS*, 2001, **123**, 8213.

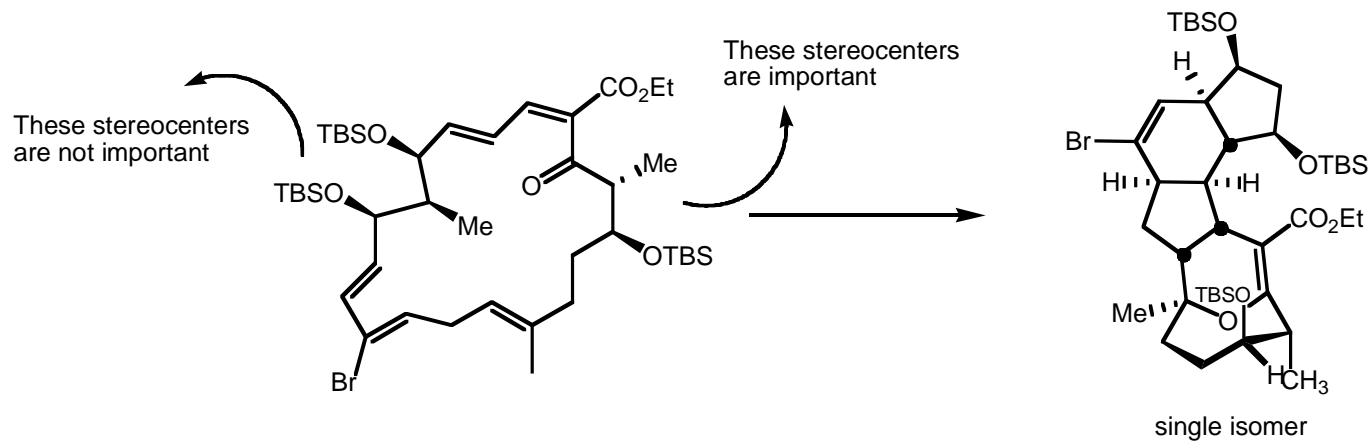
## TADA Benefits: Stereoselectivity

The macrocyclic environment is often highly differentiating:



Deslongchamps, *Tet.*, **2001**, 57, 4243

The impact of remote stereocenters can be strong:

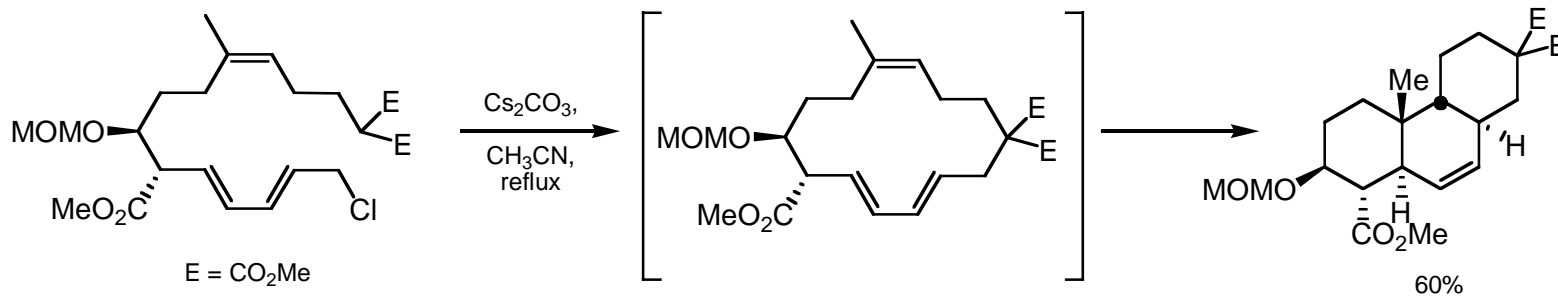


Evans, *JACS*, **125**, 2003, 13531



## TADA Challenges: Macrocyclization

### Malonate alkylations

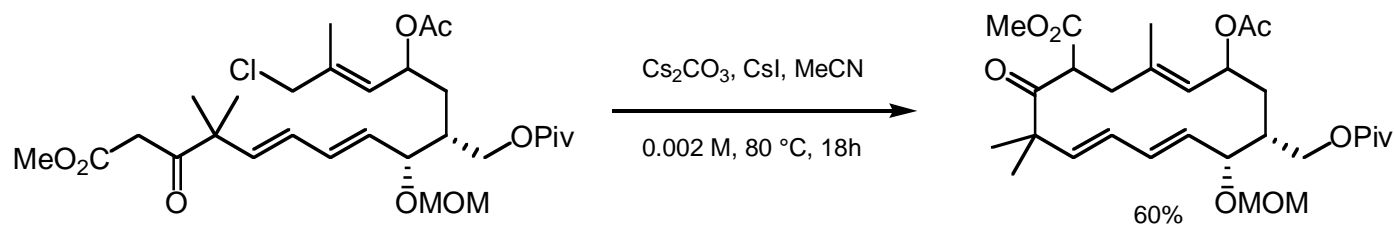


Allows quick, reliable construction of macrocycles: method of choice for model studies

Deslongchamps, P. *JOC*, **2002**, 67, 5269

Not common for total synthesis: transformations of malonates cumbersome

### β-keto-ester alkylations

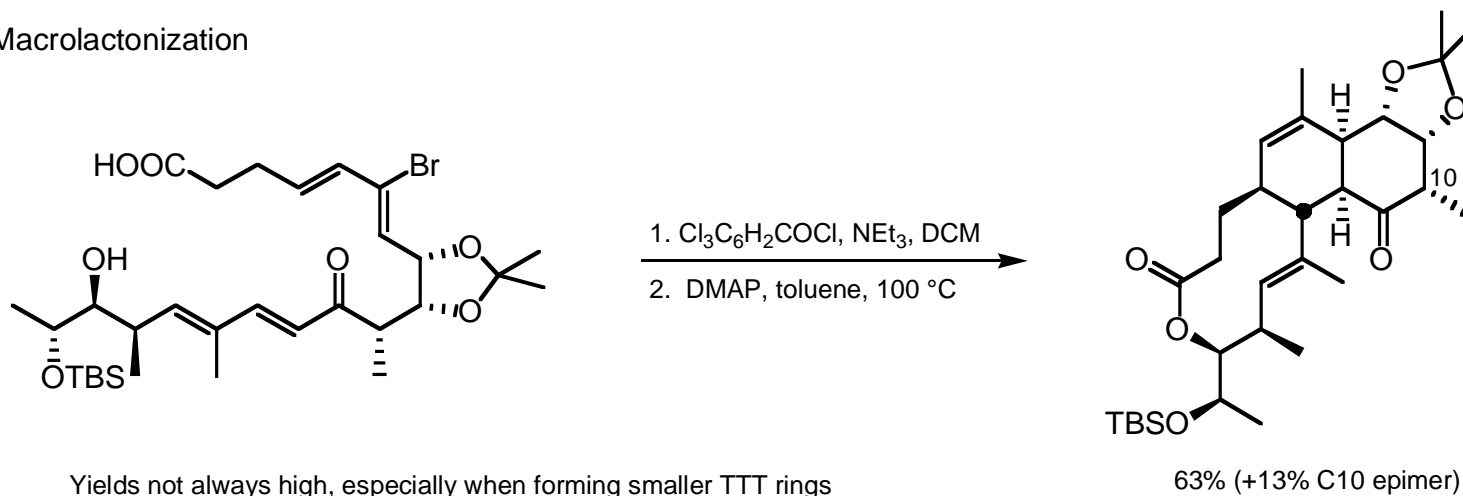


Ease of decarboxymethylation (often under TADA conditions) makes this method more useful for synthesis.

Deslongchamps, P. and Dory, Y. *JOC*, **2003**, 68, 2390

## TADA Challenges: Macrocyclization

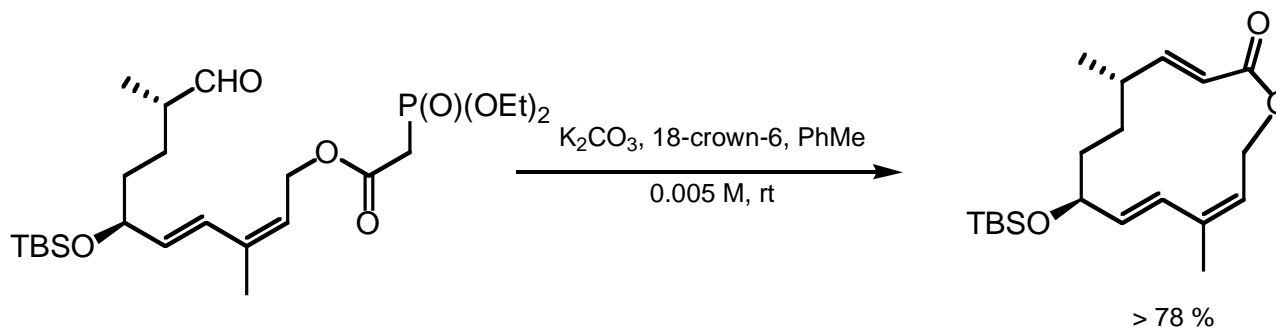
### Macrolactonization



Yields not always high, especially when forming smaller TTT rings

Roush, *JACS*, **1996**, 118, 7502

### Horner-Wadsworth-Emmons

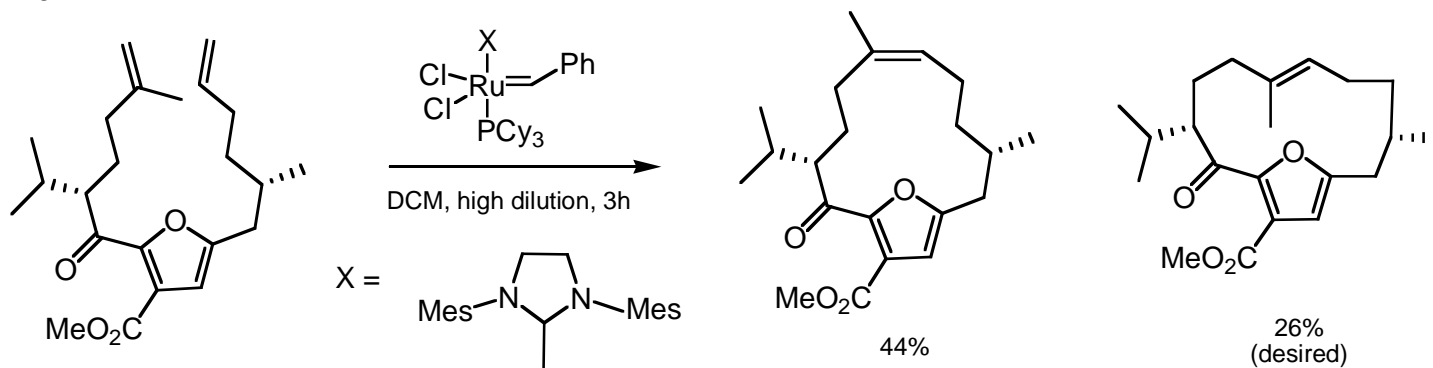


Applicability to trans-trans-trans macrocycles?

Nakada, M. *Org. Lett.*, **2003**, 68, 2390

## TADA Challenges: Macrocyclization

### Ring-Closing Metathesis

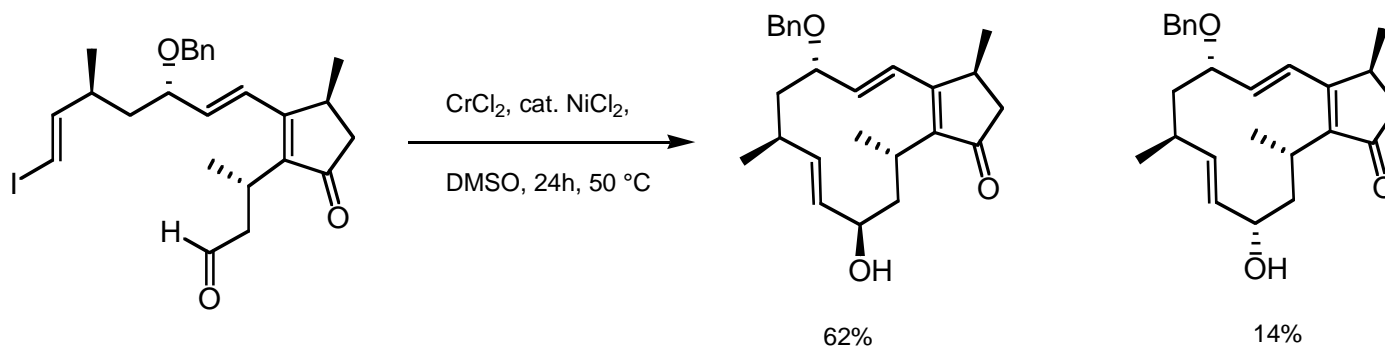


Preference for Z olefin seems strong: if C=O is reduced to an  $\alpha$ -OTBS, only Z olefin is isolated (93%)

Deslongchamps, P. *JOC*, **2003**, 68, 6847.

### Intramolecular "Nozaki-Hiyama-Kishi"

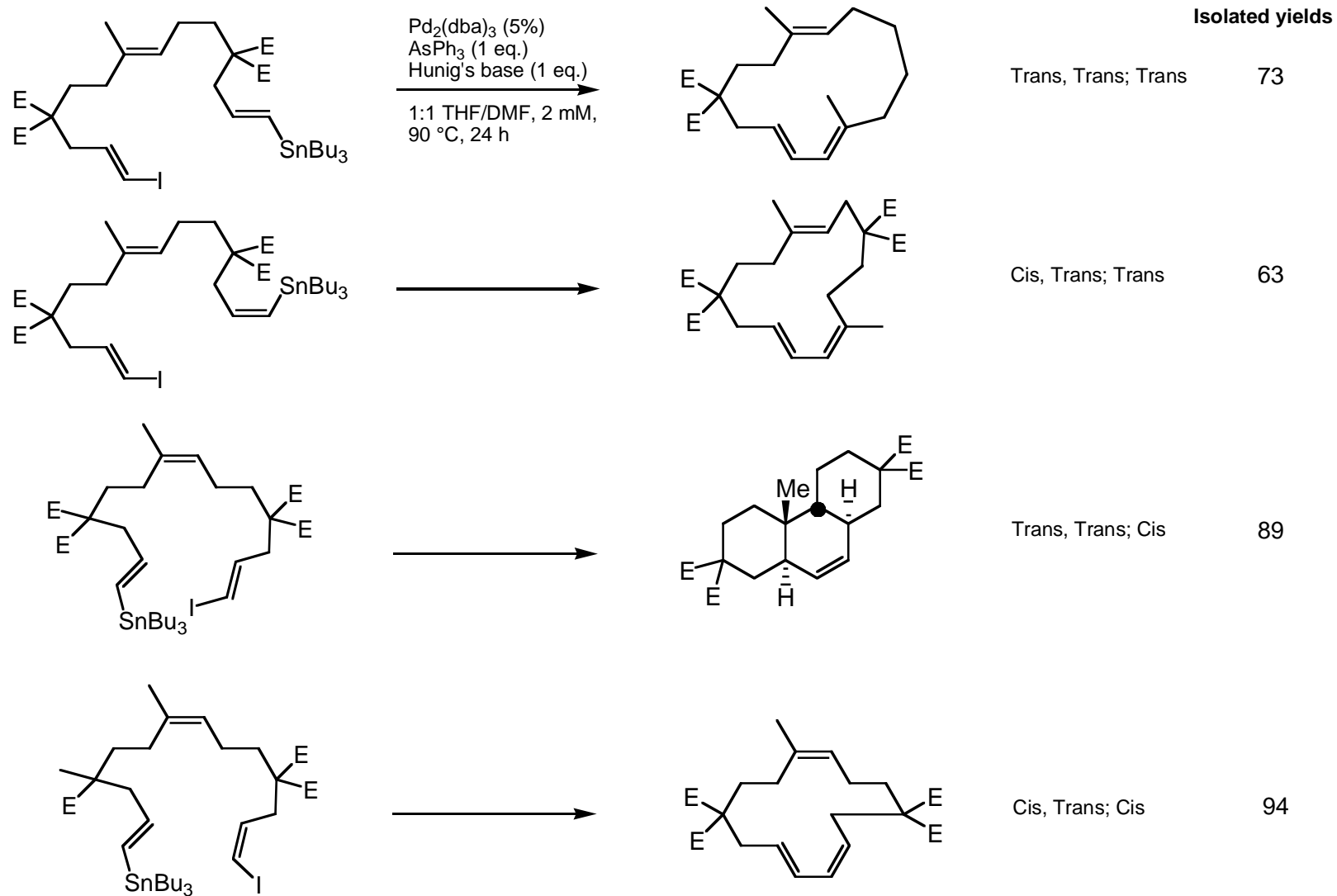
"Although intramolecular NHK's reported to date have given poor yields..."



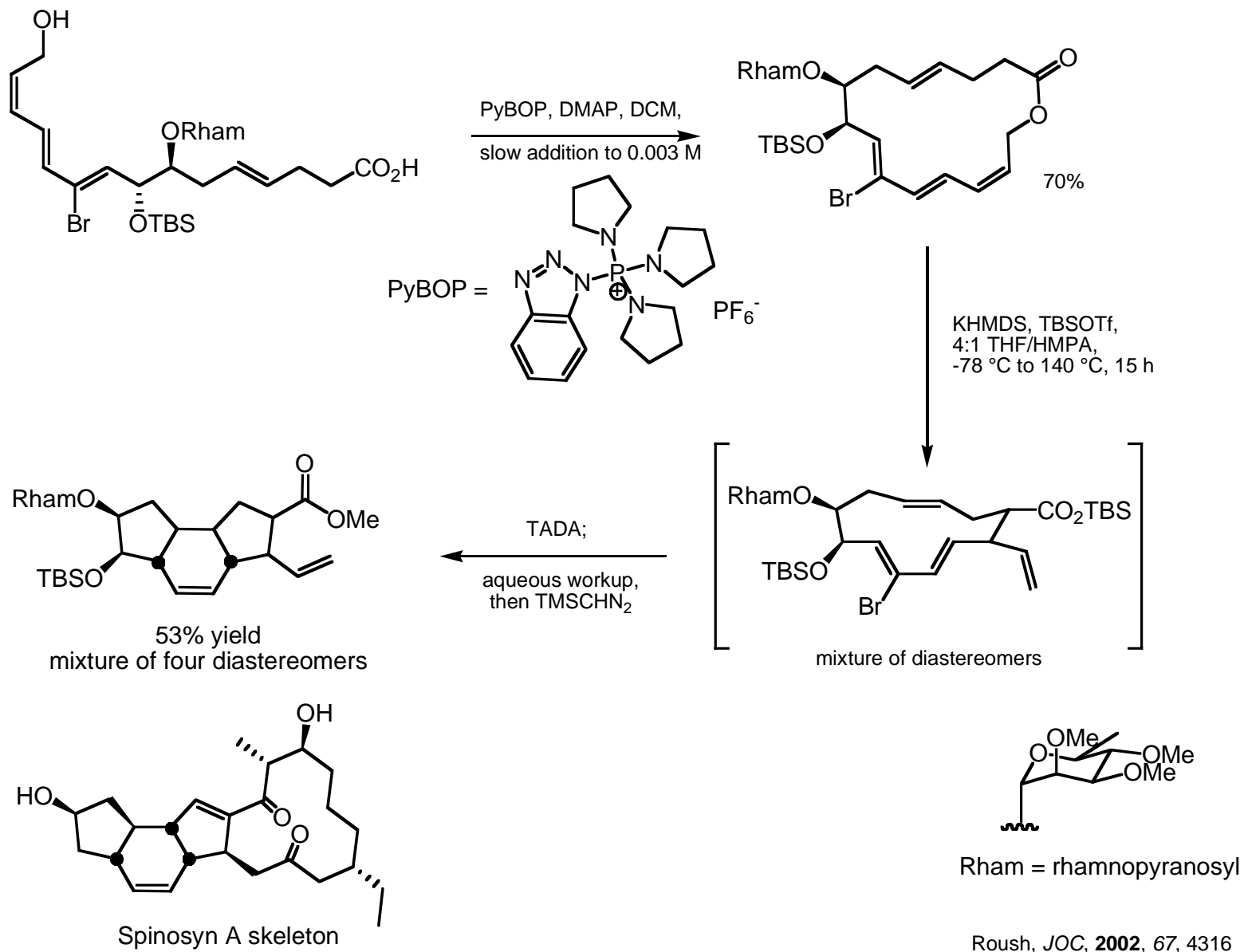
Making unsaturated 12-membered macrocycles is known to be especially difficult.

Uemura, D. *ACIEE*, **2004**, 43, 81.

## Efficient Stille Cyclization Conditions



# Roush's Ireland-enolate Ring Contraction



## *TADA Challenges: Macrocyclic Conformational Analysis*

*Can we reliably predict favored transition state(s)?*

computation

model studies

conformational analysis

*Minimizing transannular strain often trumps standard tools of conformational analysis, e.g.*

Endo Rule

Minimization of allylic strain

Pseudo-equatorial substituents preferable  
to pseudo-axial substituents

Chair-like TS preferable to boat-like TS

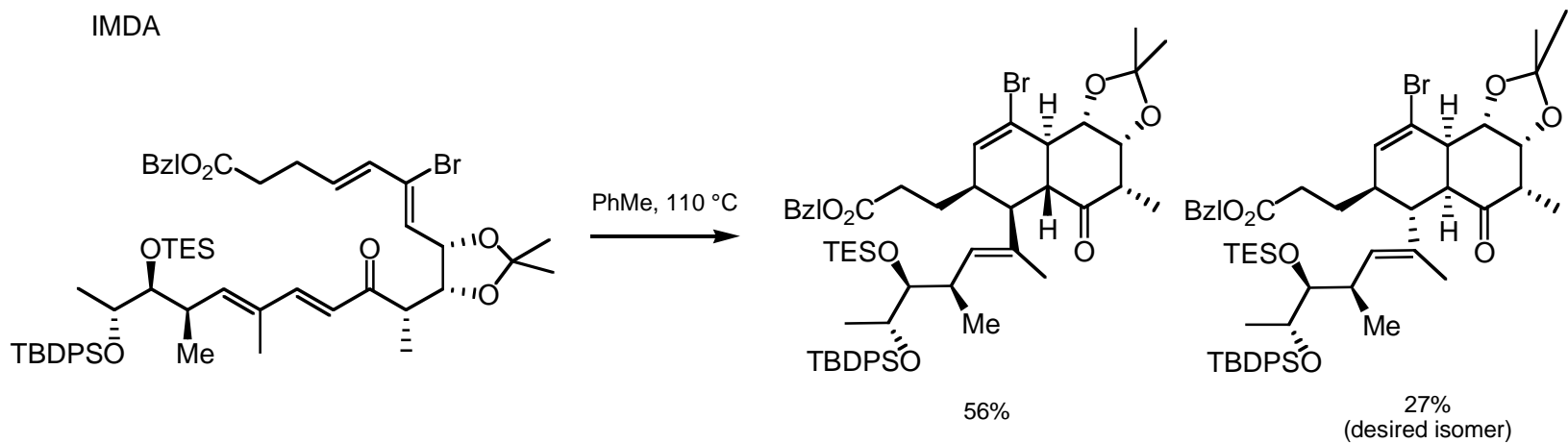
Conjugation of dienophile in TS; activation  
by EWG, Lewis Acid catalysis

Planarity of diene in TS

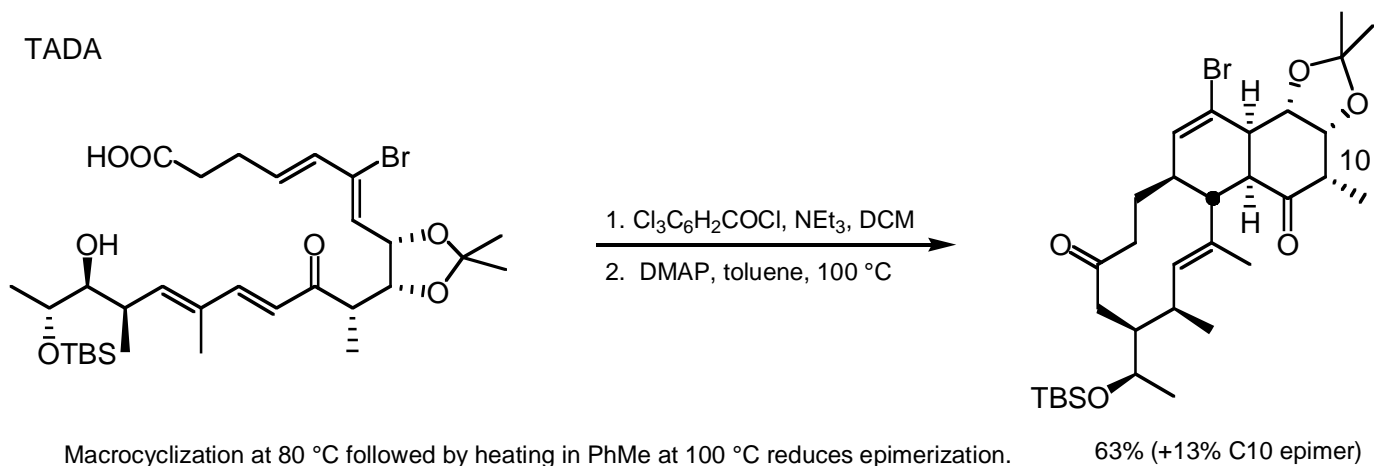
*Effects are often countervailing; predicting the dominant effect is difficult.*

## IMDA v. TADA

IMDA

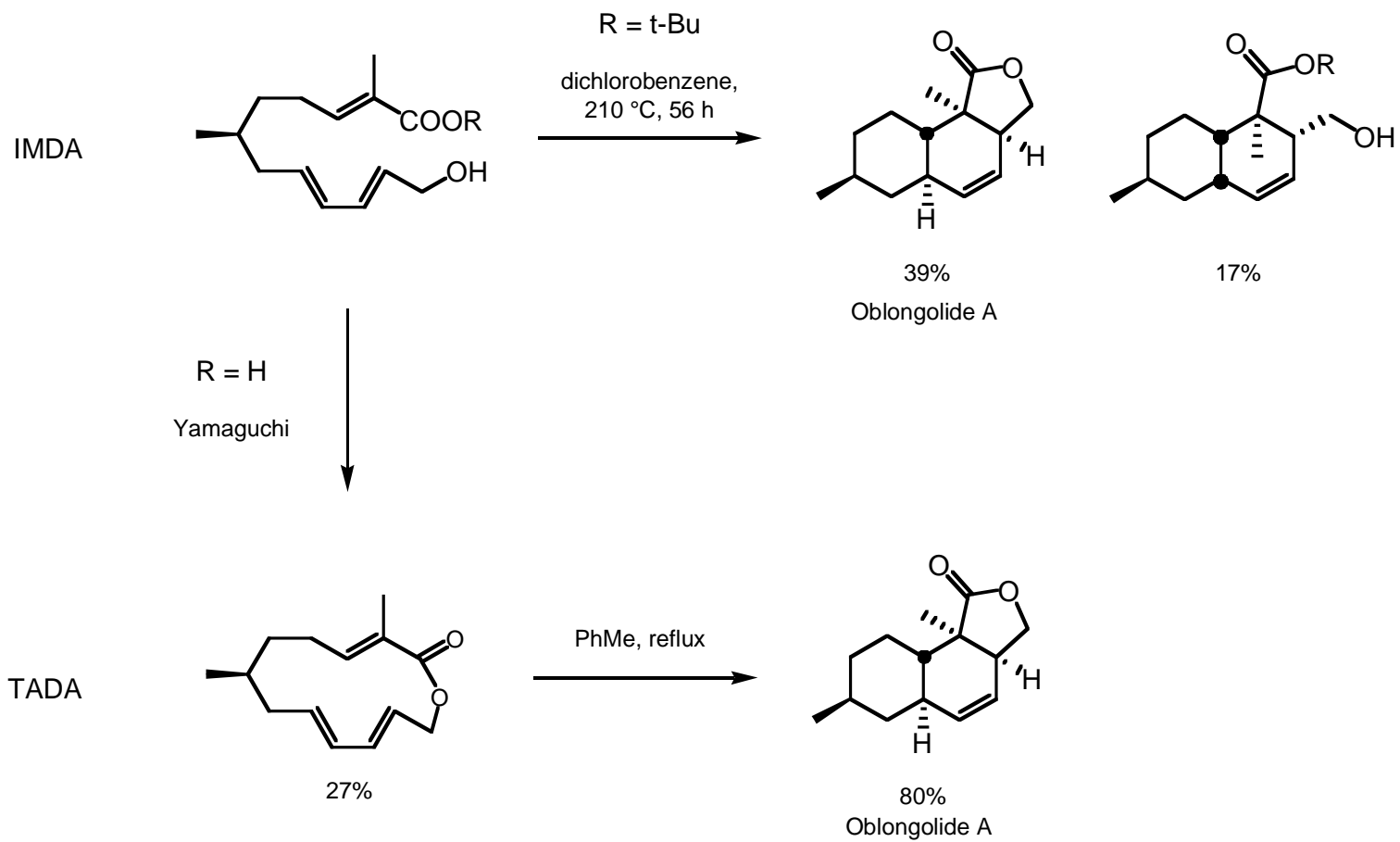


TADA



Macrocyclization at 80 °C followed by heating in PhMe at 100 °C reduces epimerization.

# IMDA v. TADA





# IMDA v. TADA

*Can I make the requisite macrocycle?*

macrocyclization methodologies continue to improve

*Am I confident I can predict and control the stereochemical course of the transannular reaction?*

computer modeling

model studies

literature precedent

careful consideration of competing TS's

*If so, the TADA can offer:*

enhanced reactivity/mild conditions

enhanced diene/dienophile scope

enhanced (distal) stereocontrol

high yields

atom economy

**wisdom from Pierre:**

*"The complexity and power of the TADA strategy arises from a judicious choice of substituents that will govern the conformation adopted by the macrocycle at the transition state level, via transannular steric repulsion and electronic interactions."*

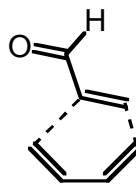
## The Issue of Dienophile Activation

Experimental  $\Delta G^\ddagger$

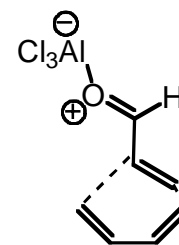
26-35 kcal/mol



20 kcal/mol



10 kcal/mol



Calculations:

Synchronous TS

both bonds = 2.21Å

Asynchronous TS

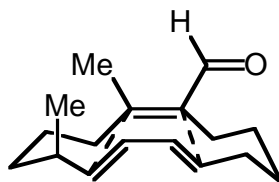
short bond = 2.088Å  
long bond = 2.353Å

Highly Asynchronous TS

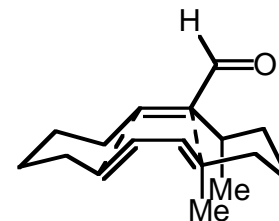
short bond = 1.932Å  
long bond = 2.96Å

Houk, *JACS*, **1990**, 112, 4027.

Asynchronicity affects the macrocyclic environment:

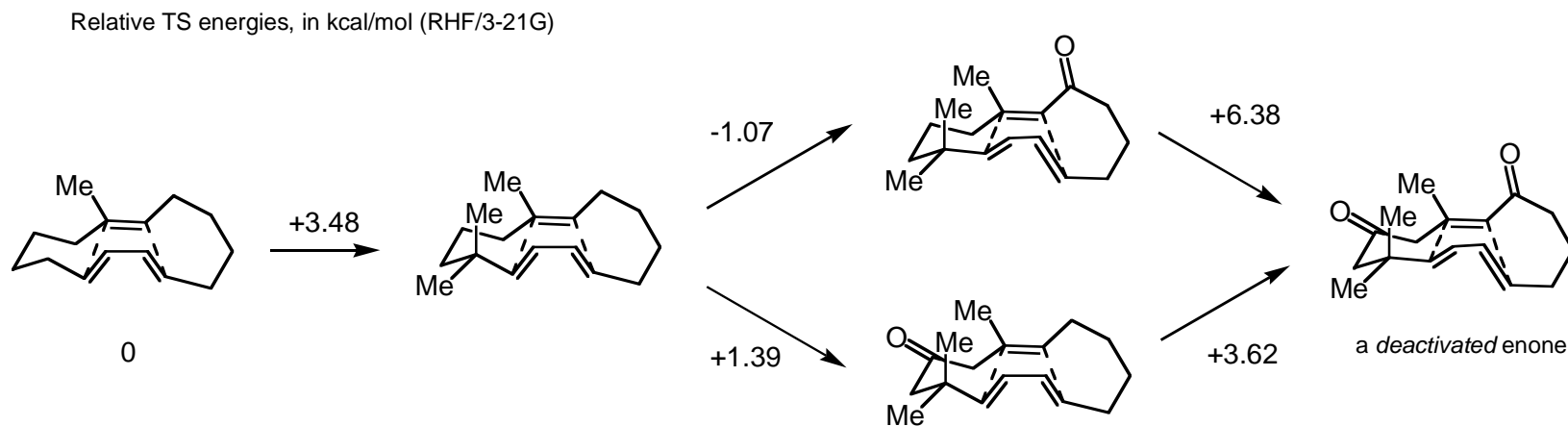


steric congestion near the short bond



steric congestion near the long bond

## The Issue of Dienophile Activation



Adding a gem-dimethyl introduces a 1,3 diaxial interaction.

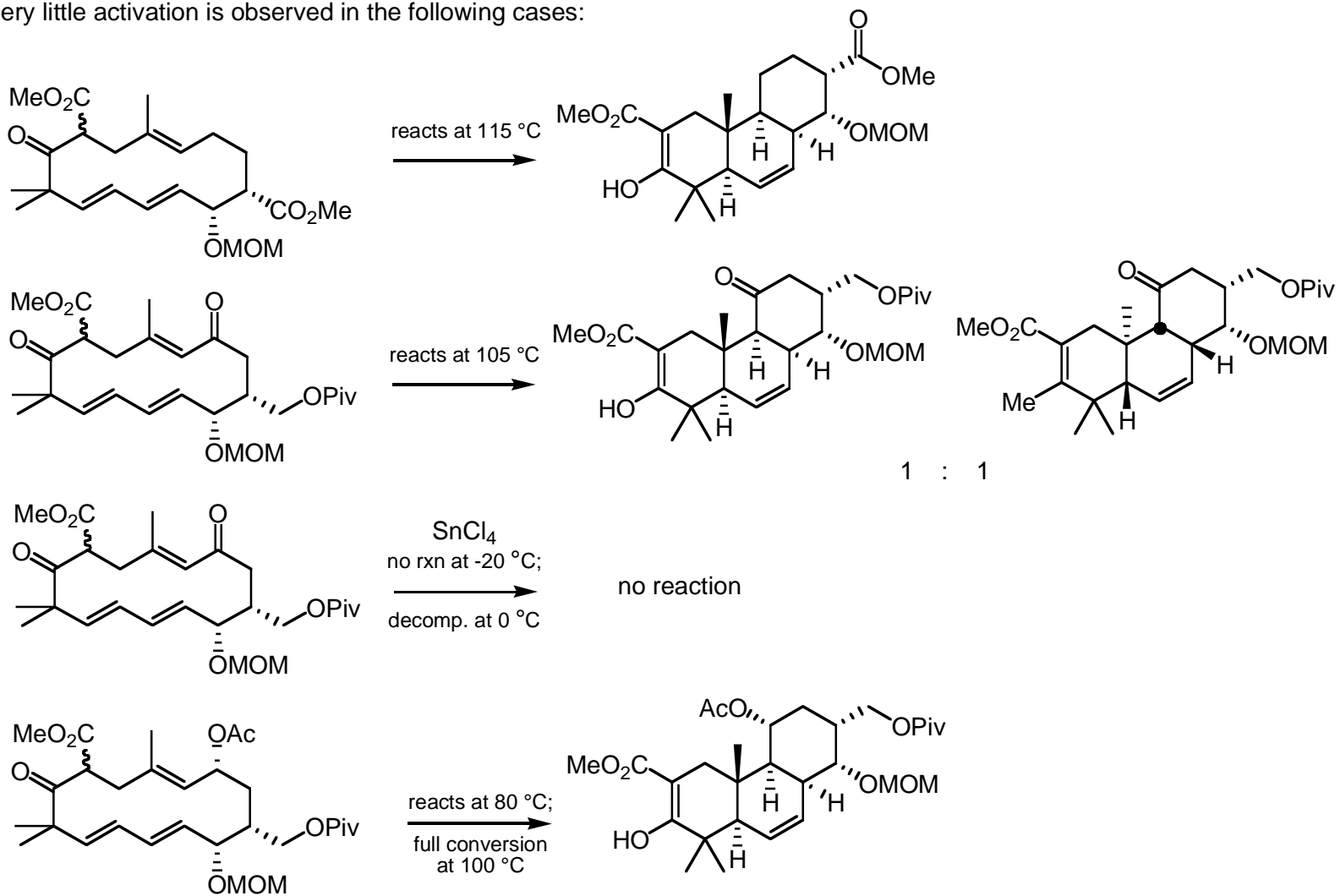
Adding a carbonyl at C(11) aggravates the 1,3 diaxial interaction but is activating.

Adding a carbonyl at C(11) separates diene/dienophile and is deactivating.

Combining effects leads to a deactivated enone.

## The Issue of Dienophile Activation

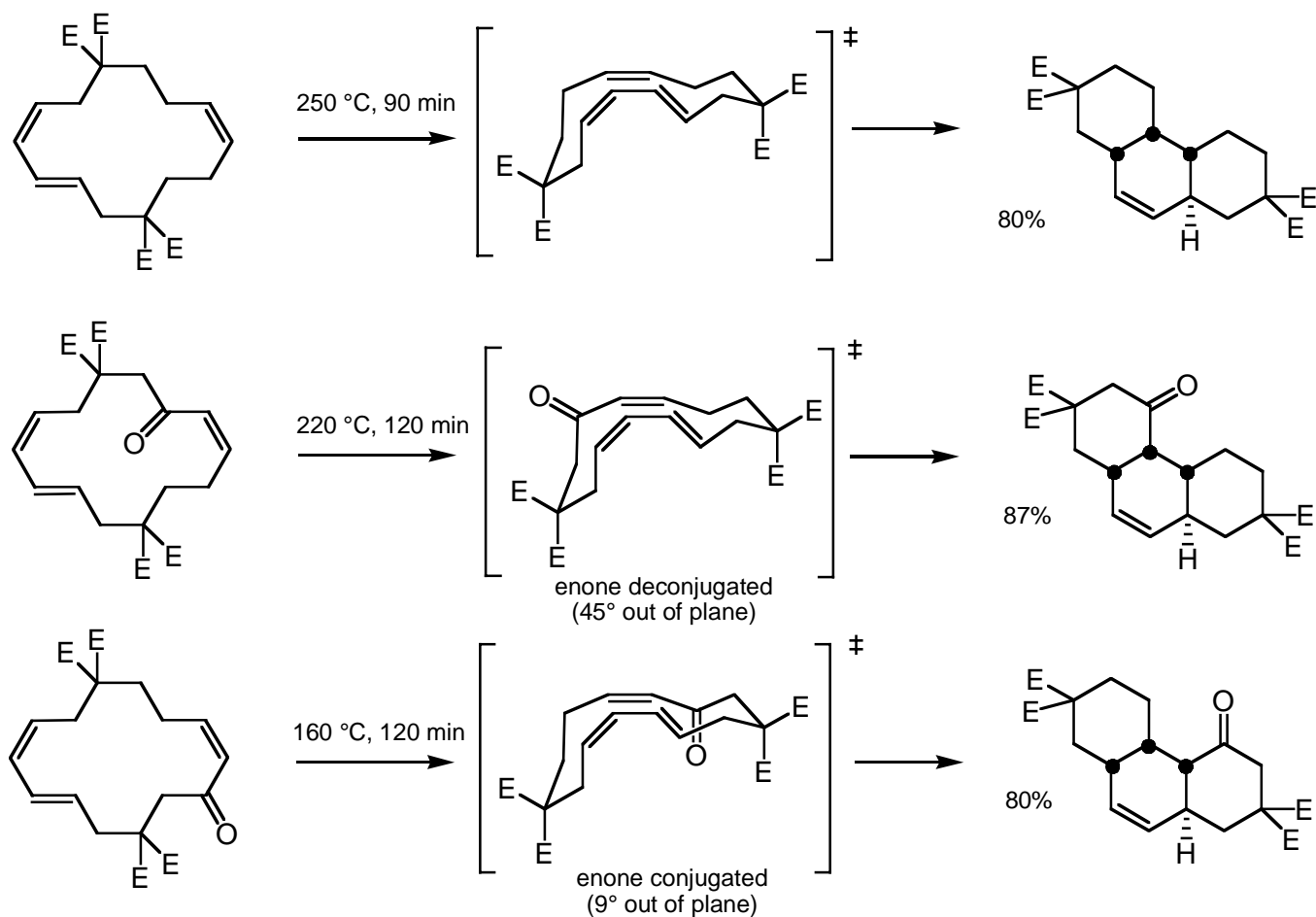
Very little activation is observed in the following cases:



## The Issue of Dienophile Activation

Ground state: conjugation easy to maintain

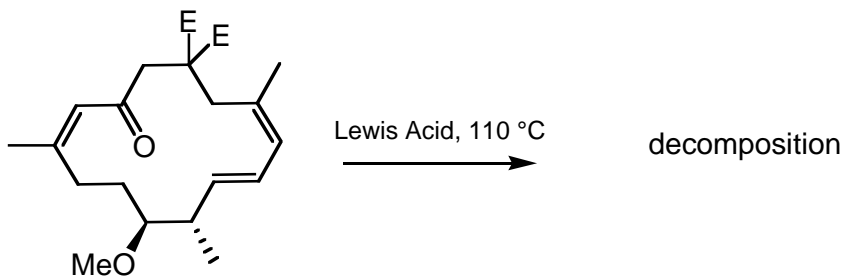
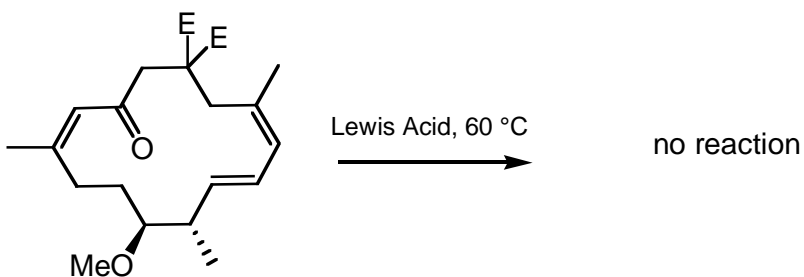
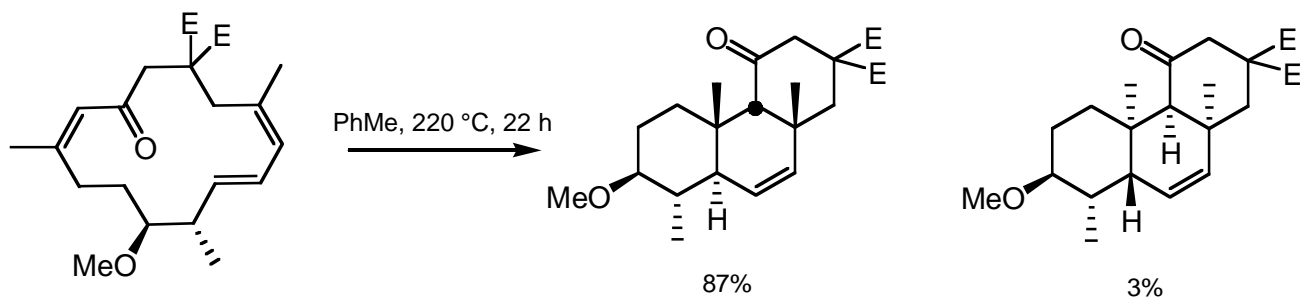
Transition state: minimization of transannular strain may entail breaking conjugation



## The Issue of Dienophile Activation

Dienophile planarity: electronically favorable, but can be sterically disfavored.

Calculations show Lewis Acids enforce planarity: can be *deactivating*.



Lewis Acids screened:

SnCl<sub>4</sub>

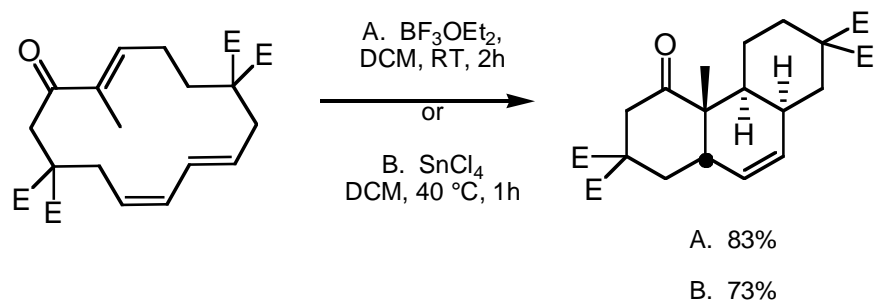
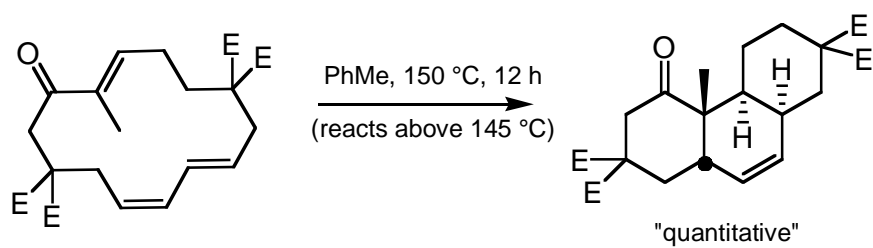
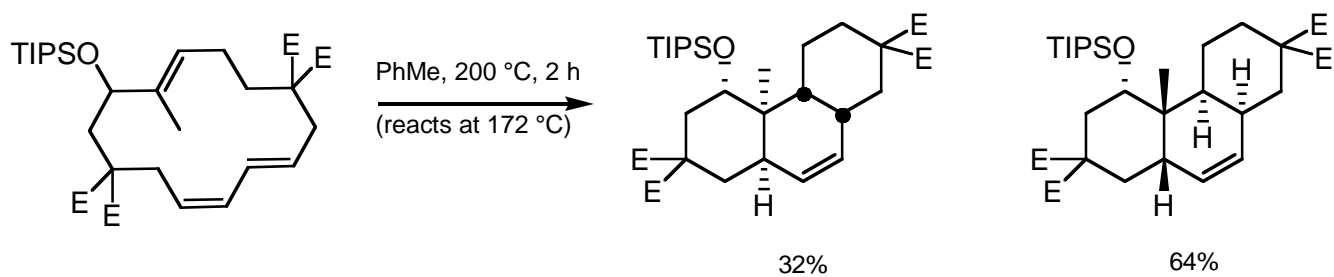
BF<sub>3</sub>OEt<sub>2</sub>

Me<sub>2</sub>AlCl

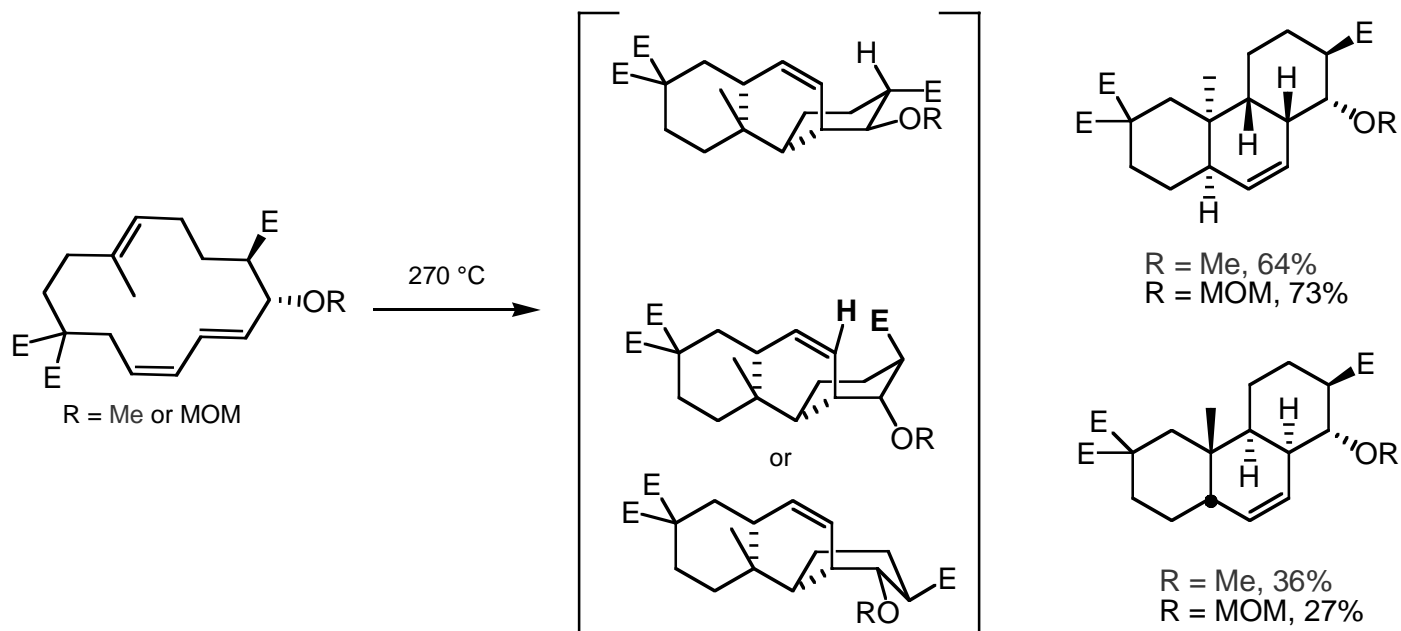
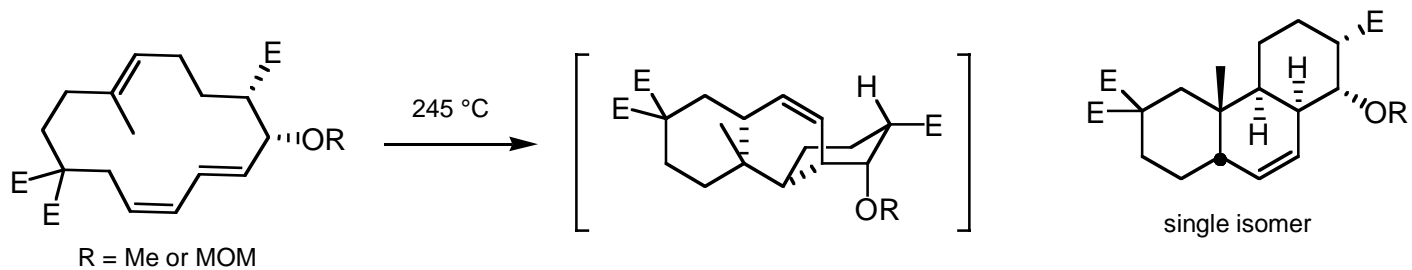
TiCl<sub>4</sub>

## The Issue of Dienophile Activation

Lewis Acids perform as expected when dienophile is truly activated:



## A Stereoelectronic effect?

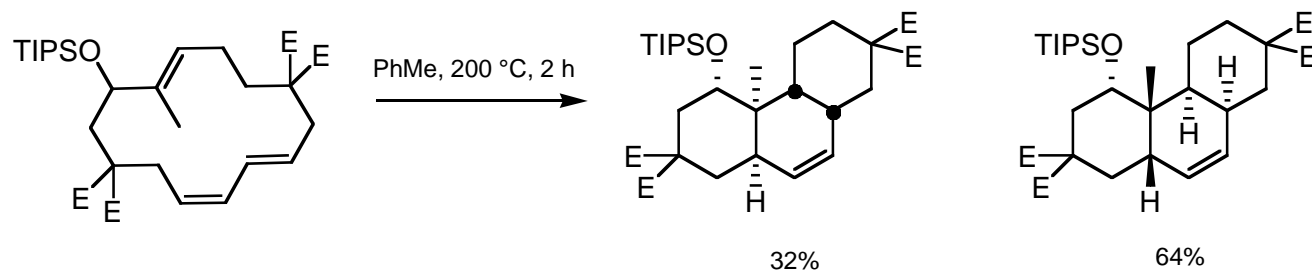


Avoiding antiperiplanar alignment of -OTIPS and forming bond seems to trump equatorial/chair bias.

Origin of the effect unclear: is it stereoelectronic?



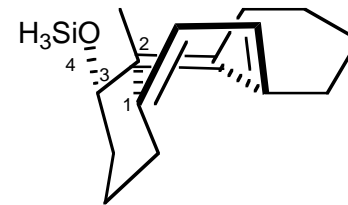
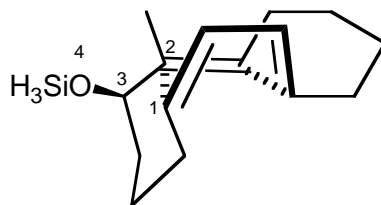
## A Stereoelectronic effect?



3.21G/3.21G\* ab initio calcs:

Chair-Boat-Chair TS

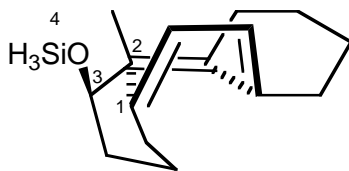
-OSiH<sub>3</sub> : axial  
θ(1,2,3,4): 65°  
contribution: 9%



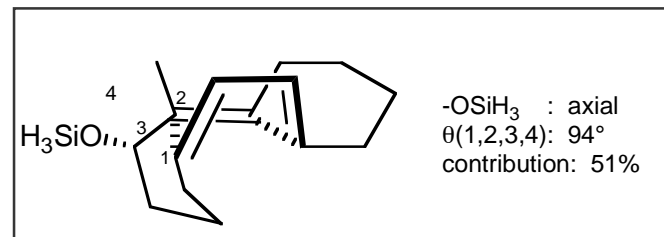
-OSiH<sub>3</sub> : equatorial  
θ(1,2,3,4): 173°  
contribution: 15%

Boat-Boat-Chair TS

-OSiH<sub>3</sub> : equatorial  
θ(1,2,3,4): 152°  
contribution: 25%



expected total: 34%

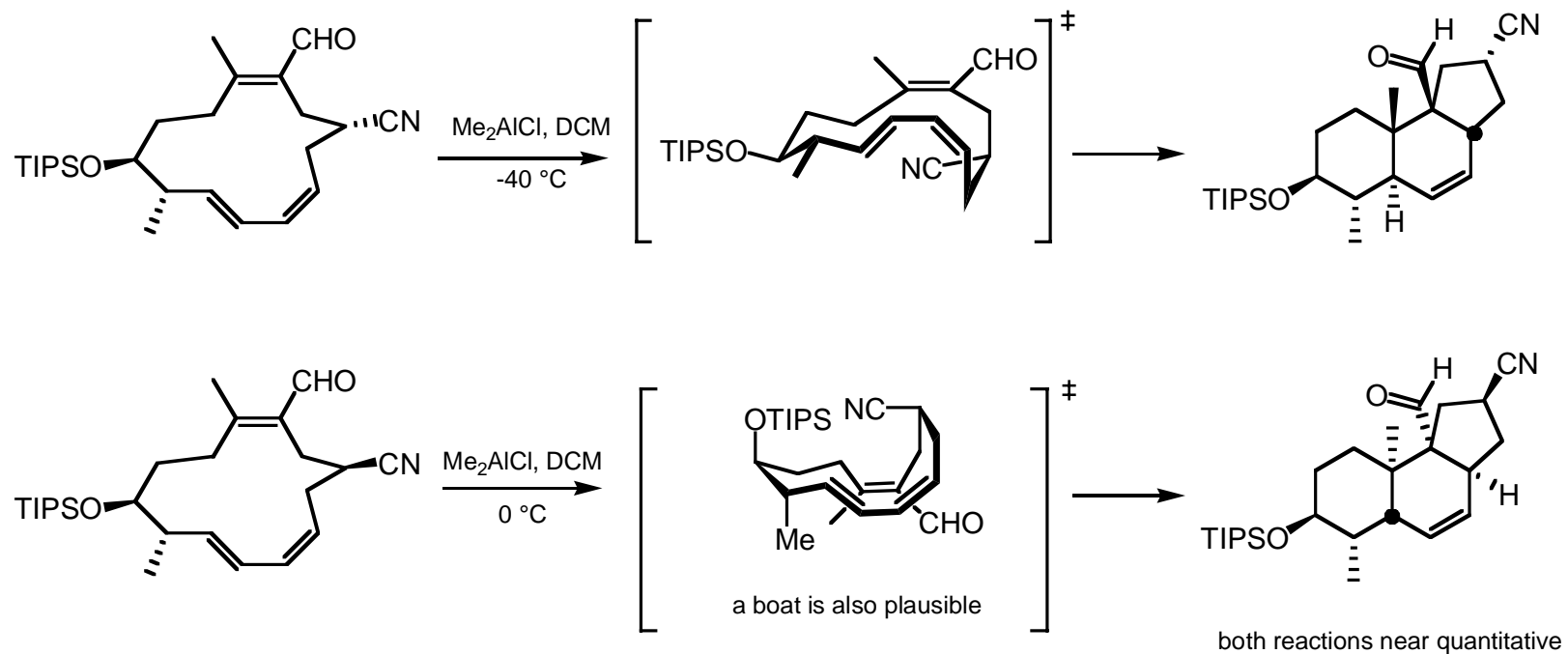


-OSiH<sub>3</sub> : axial  
θ(1,2,3,4): 94°  
contribution: 51%

expected total: 66%

Avoiding antiperiplanar alignment of -OTIPS and forming bond seems to trump chair/equatorial bias.

## Maritamol model studies: an electrostatic effect?

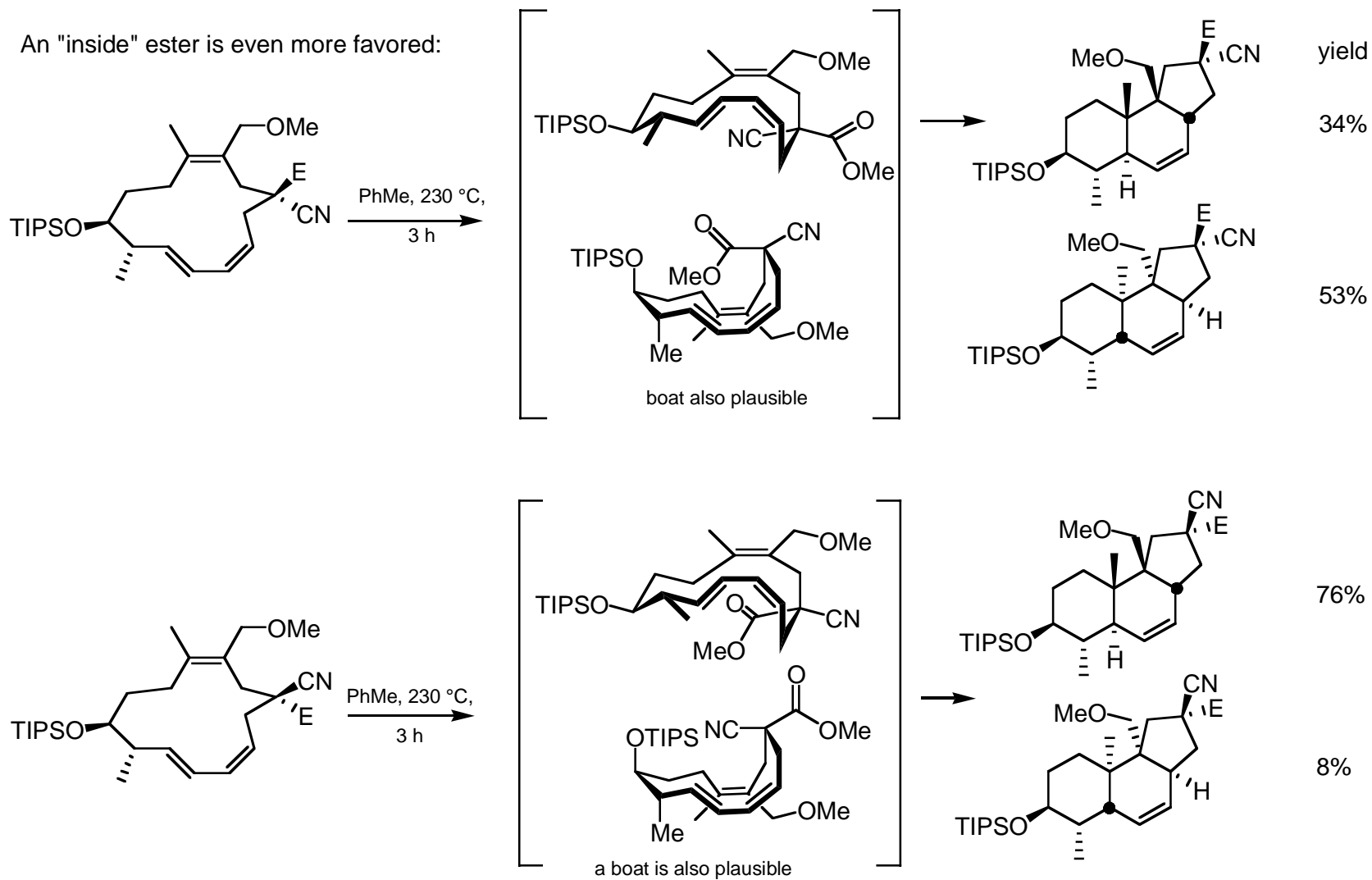


Gem-dicyano compound gave a 9:2 mixture favoring product of top transition state.

Charge separation in TS stabilized by cyano dipole?

## Maritamol model studies: an electrostatic effect?

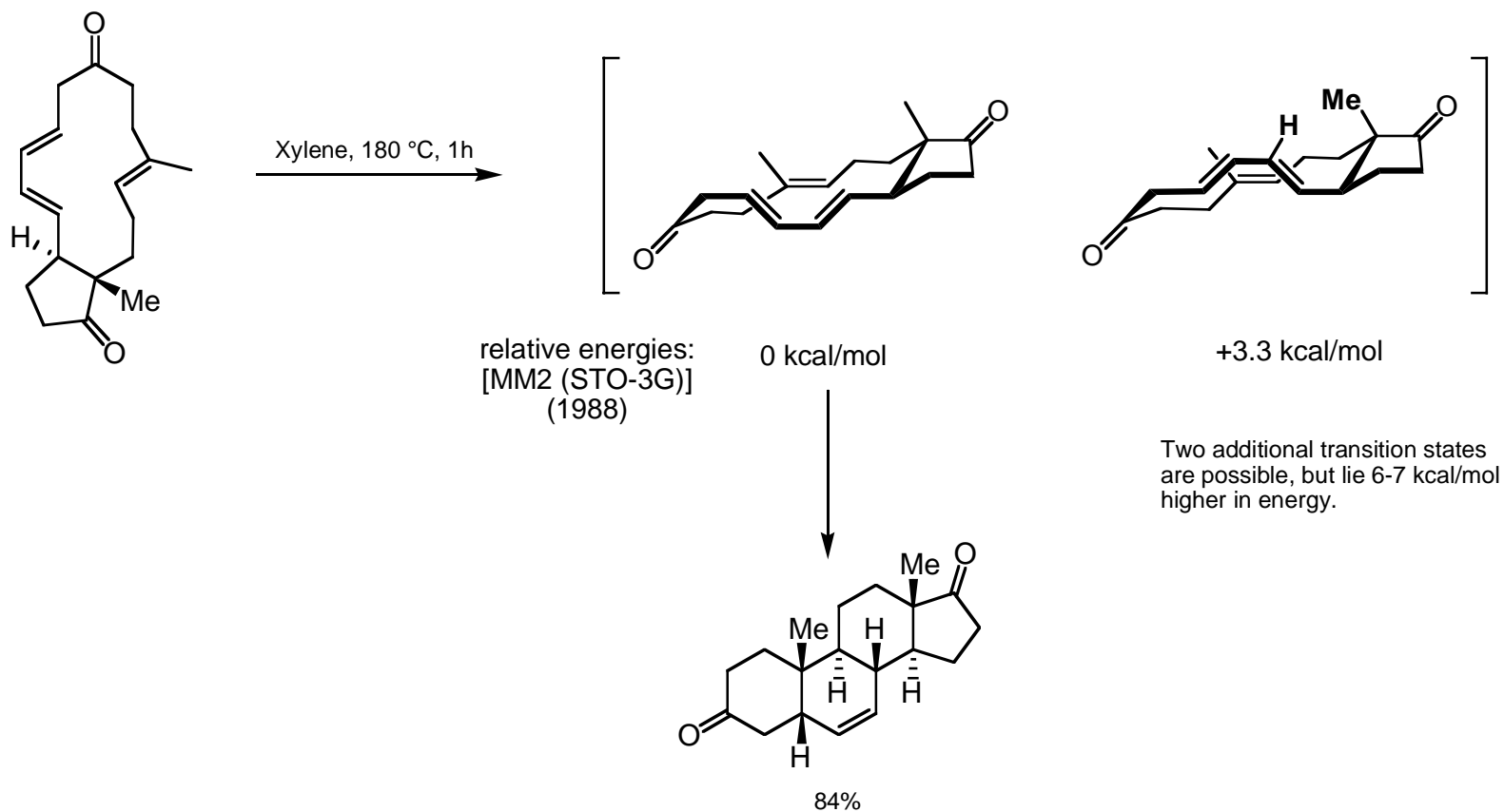
An "inside" ester is even more favored:



Given more synchronous TS, is an electrostatic explanation tenable?

Deslongchamps, *Tet.*, **1999**, 55, 4655.

## TTT: Takahashi, Steroid ring system



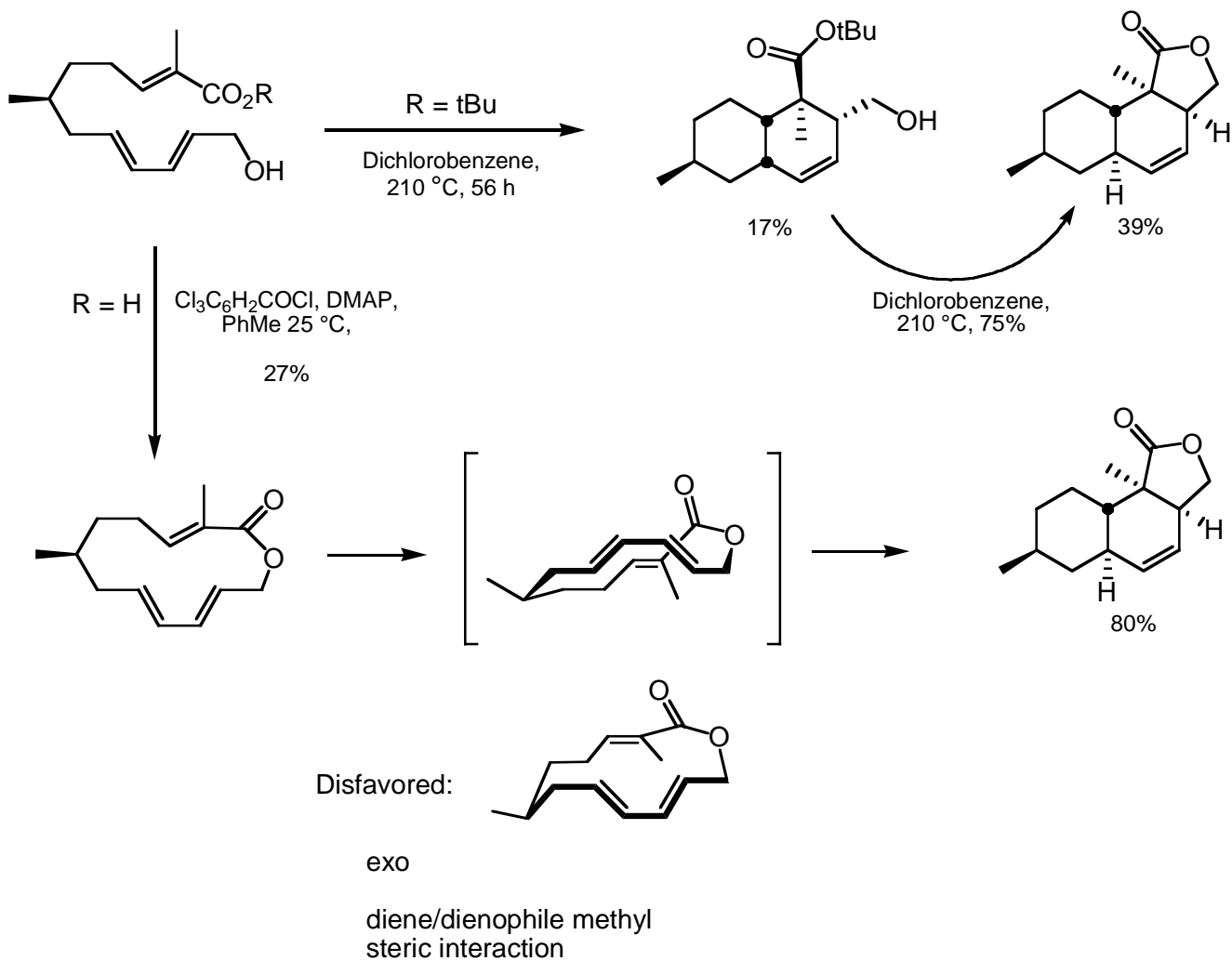
If macrocyclic ketone is replaced by  $(\text{CO}_2\text{Me})_2$ ,  $(\text{CN})_2$ , or  $(\text{SO}_2\text{Ph})_2$ , a mixture results:

Major product arises from opposite dienophile orientation.

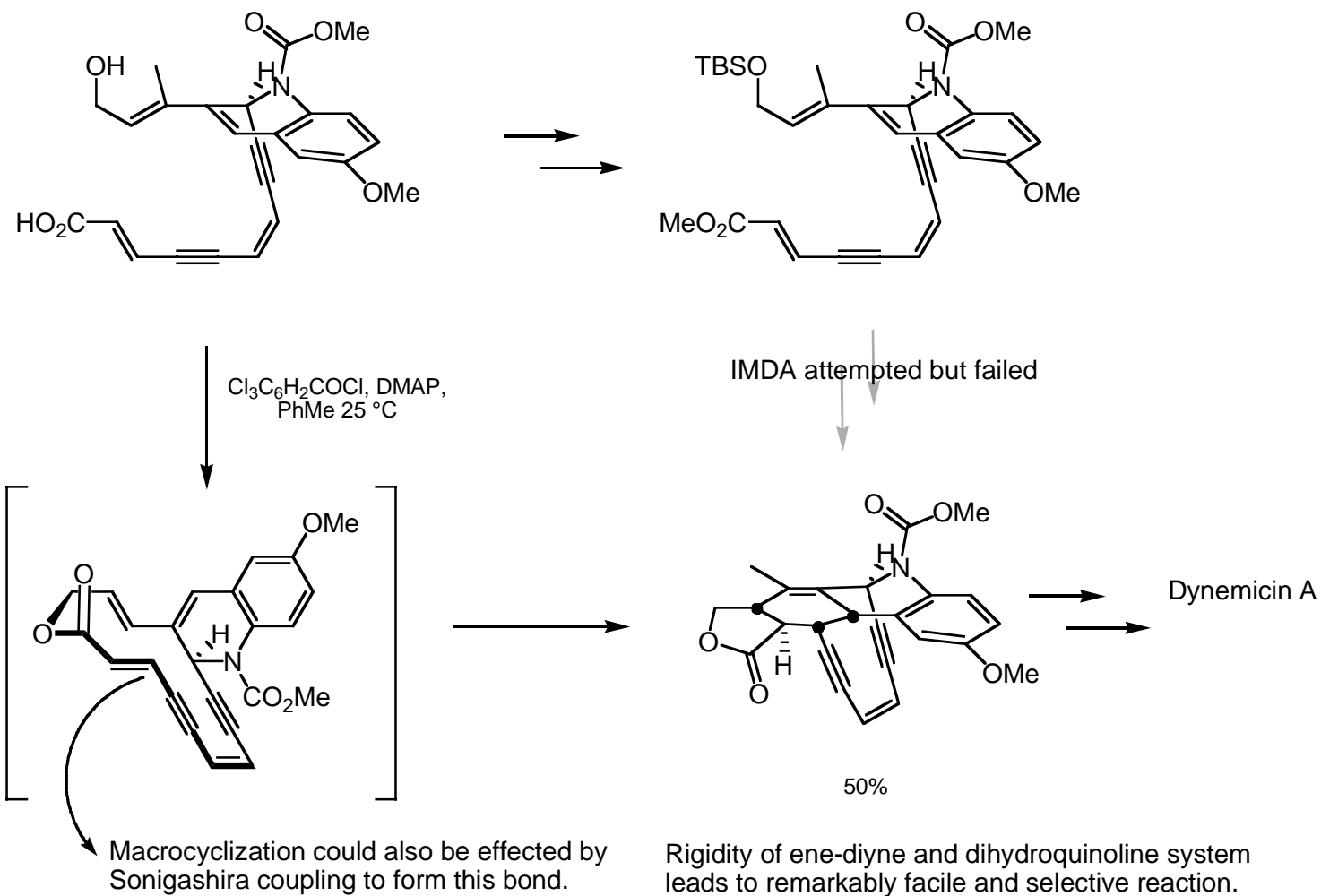
Takahashi, T. *JACS*, 1988, **110**, 2674.

Deslongchamps, P. *Tet.*, **2001**, 57, 2674.

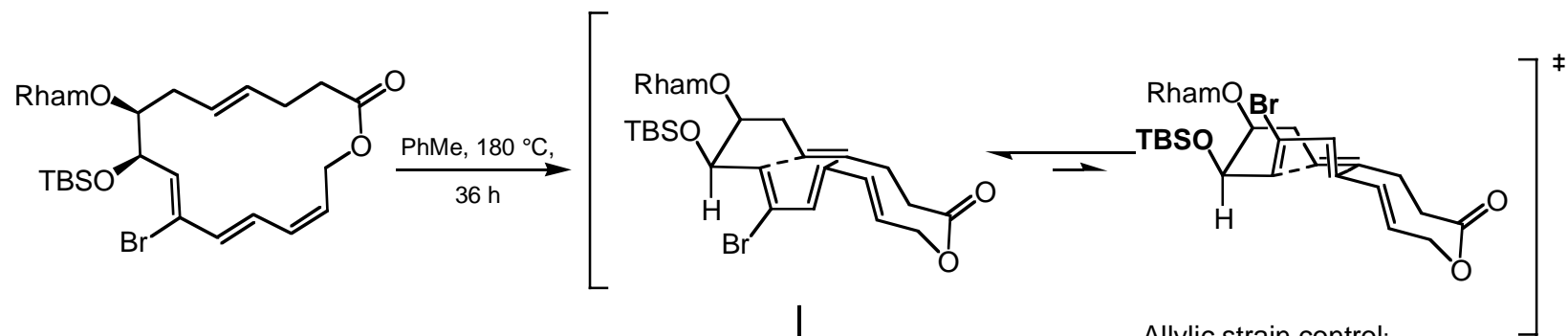
TTT: Shing, Oblongolide A



# TTT: Schreiber, Dynemicin A

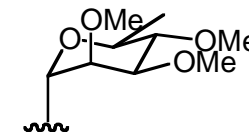
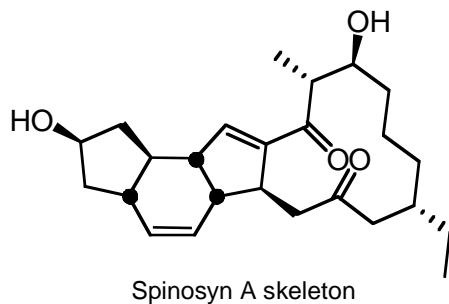
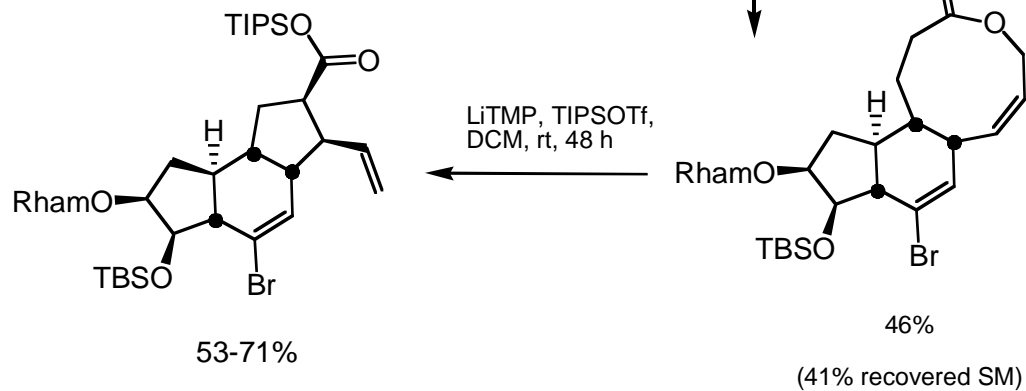


# TTT: Roush, Spinosyn A



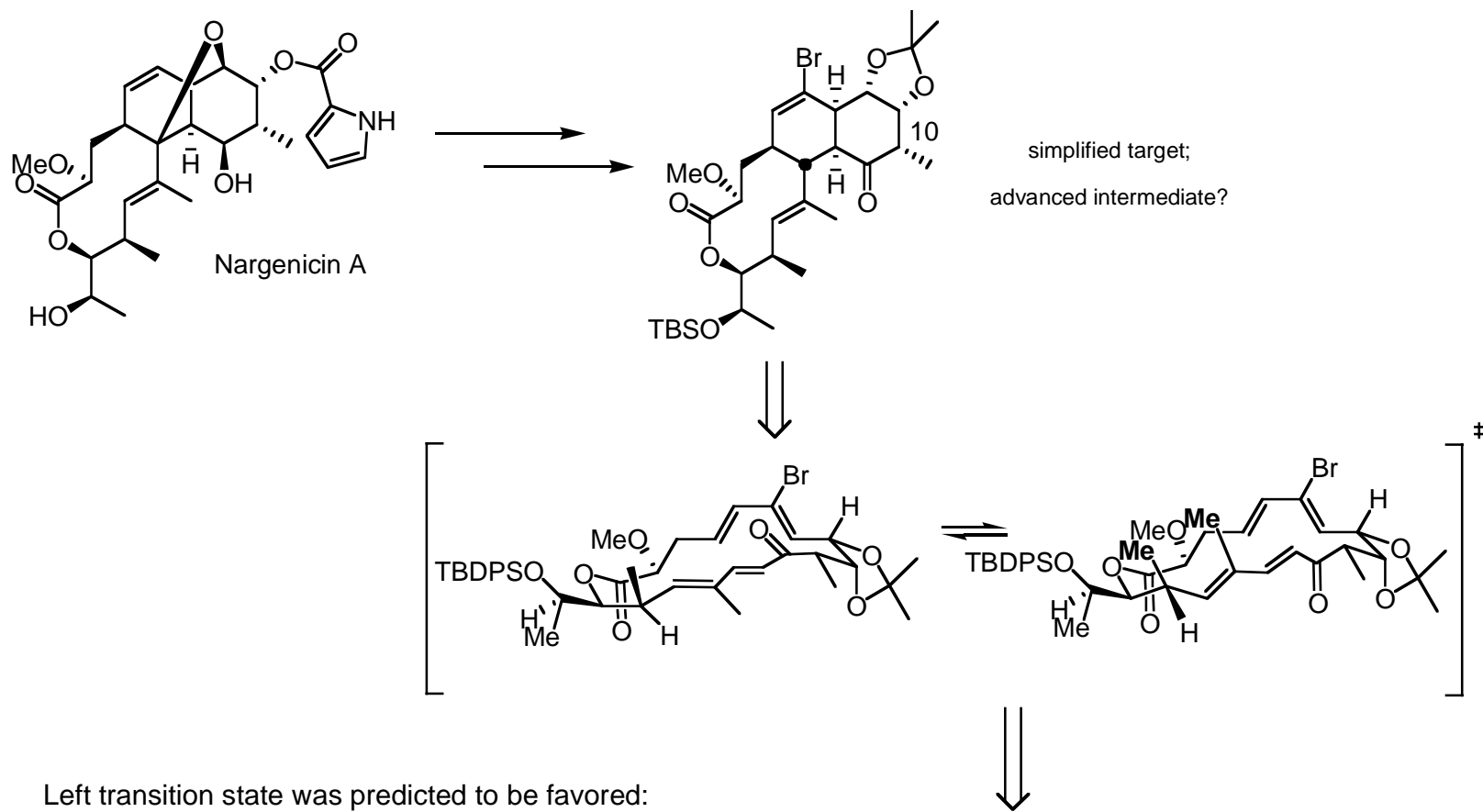
Allylic strain control:

both -Br and -OTBS were added for this purpose; subsequently removed



Rham = rhamnopyranosyl

## TTT: Roush, Nargenicin A

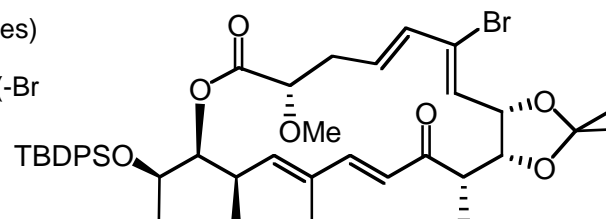


Acetonide encourages boat-like TS (established in IMDA studies)

Opposite orientation of diene (not shown) strongly disfavored (-Br substituent as steric directing group)

Avoidance of syn-pentane type interaction

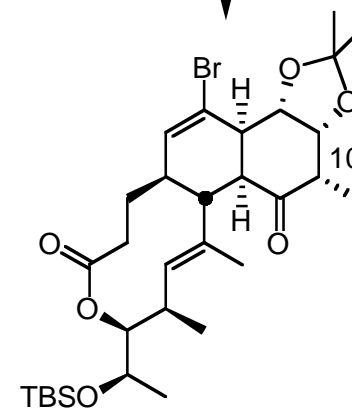
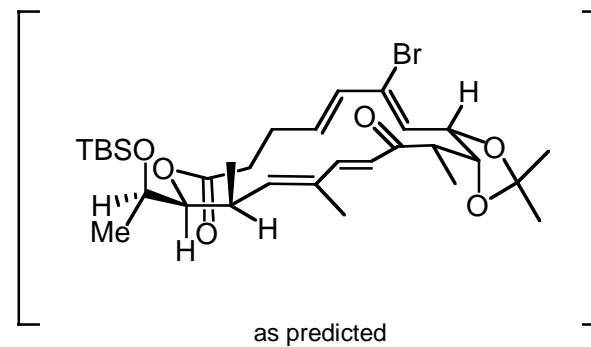
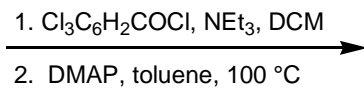
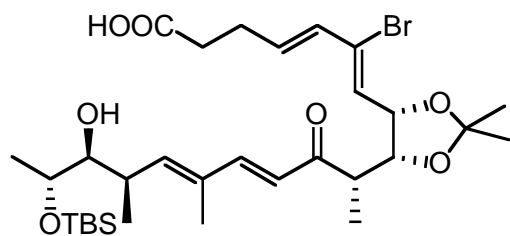
Endo Rule





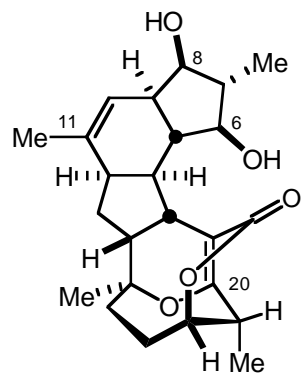
# TTT: Roush, Nargenicin A

The target macrocycle, minus one stereocenter, was synthesized:



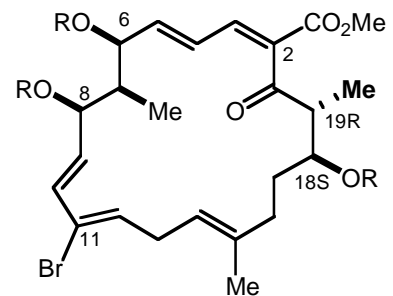
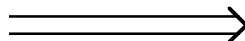
63% (+13% C10 epimer)

## TTT+CTT: Evans, FR182877



FR182877

Transannular cycloaddition cascade  
(one Diels-Alder, one Hetero-Diels-Alder)

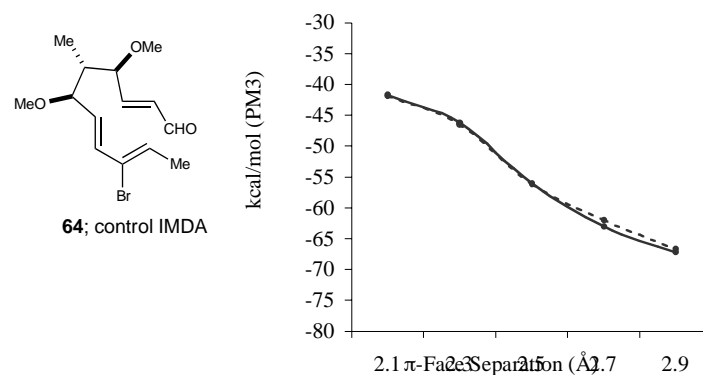
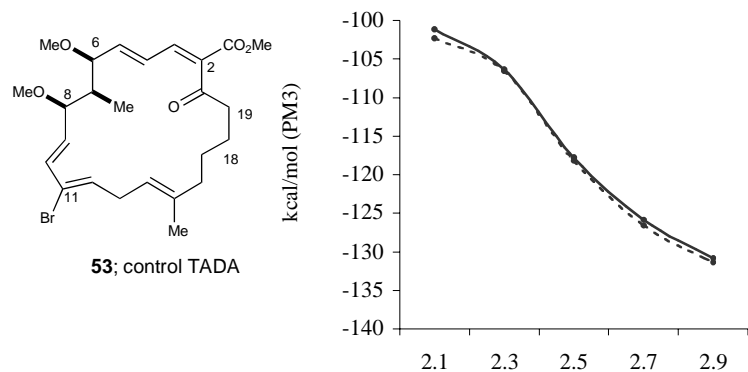


Which reaction starts the cascade?

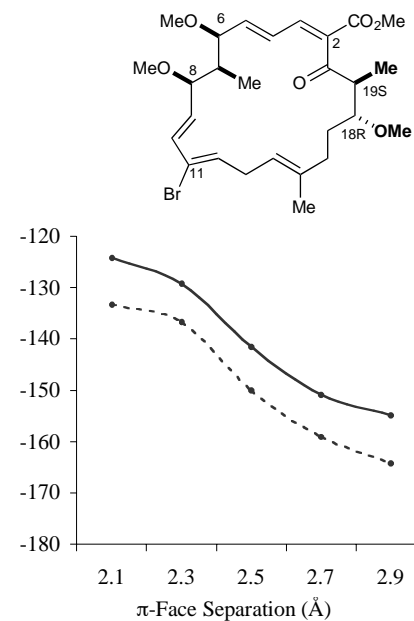
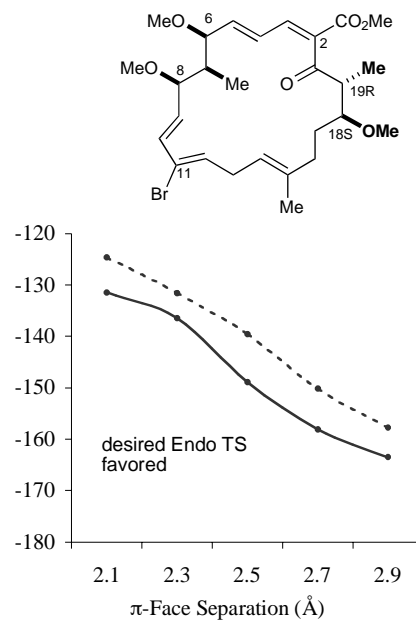
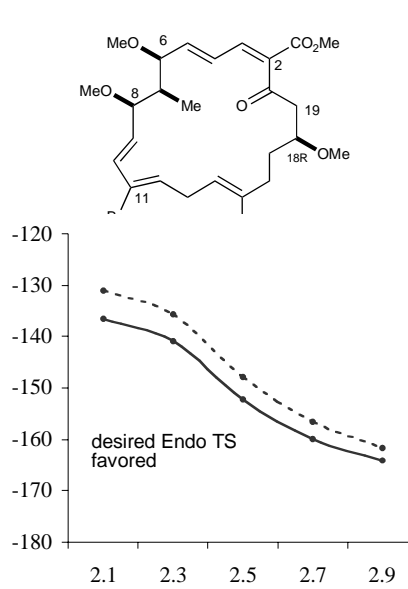
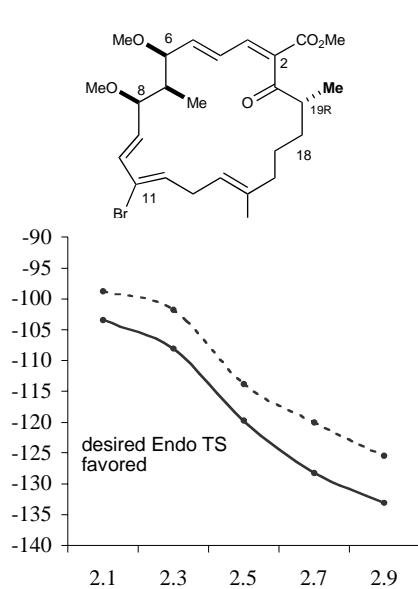
Calculations suggest the standard Diels-Alder has better orbital overlap, should proceed first.

# TTT: Evans, FR182877

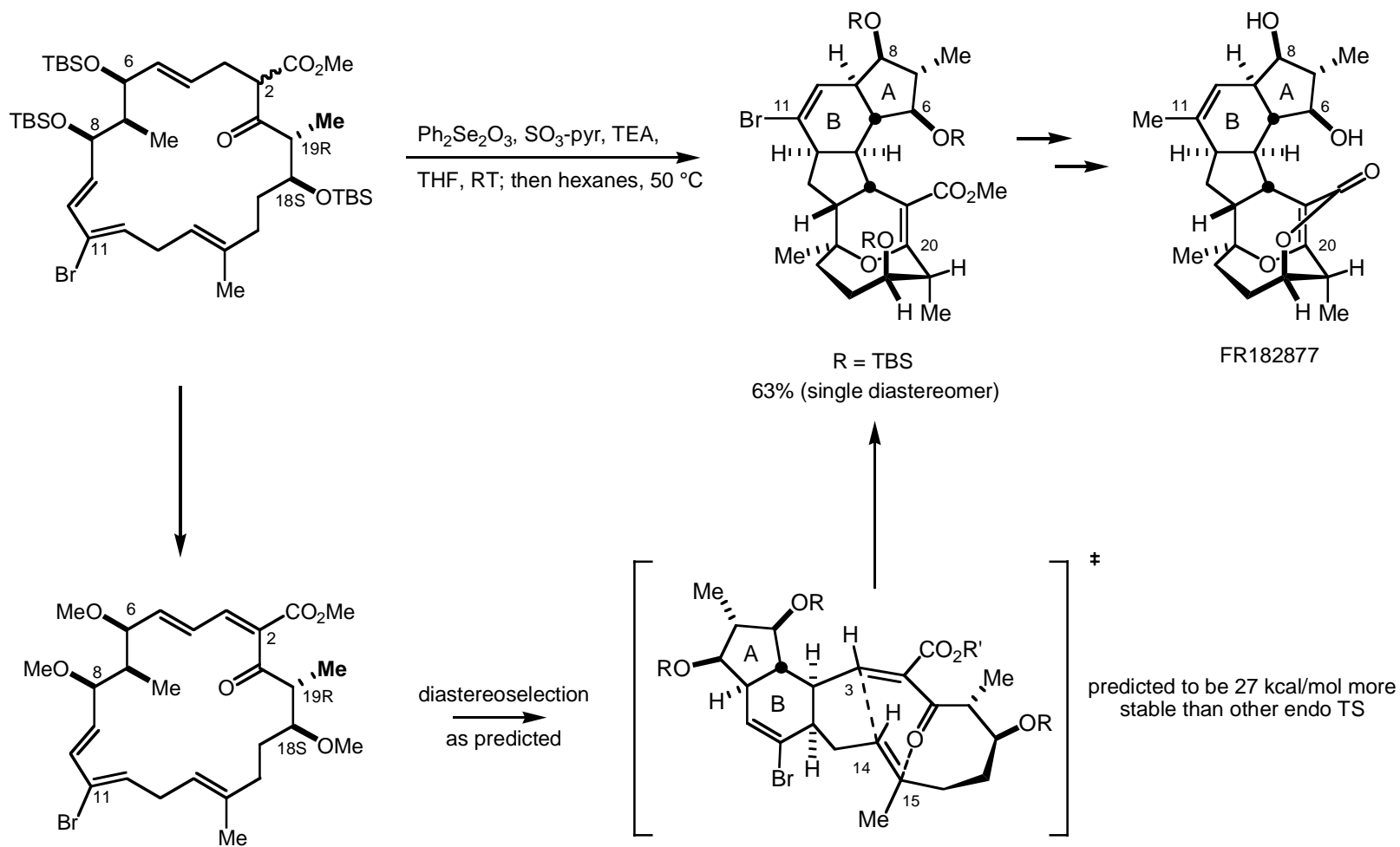
Stereocenters at C(6)-C(8) have little impact



Stereocenters at C(19), C(20) should confer desired selectivity

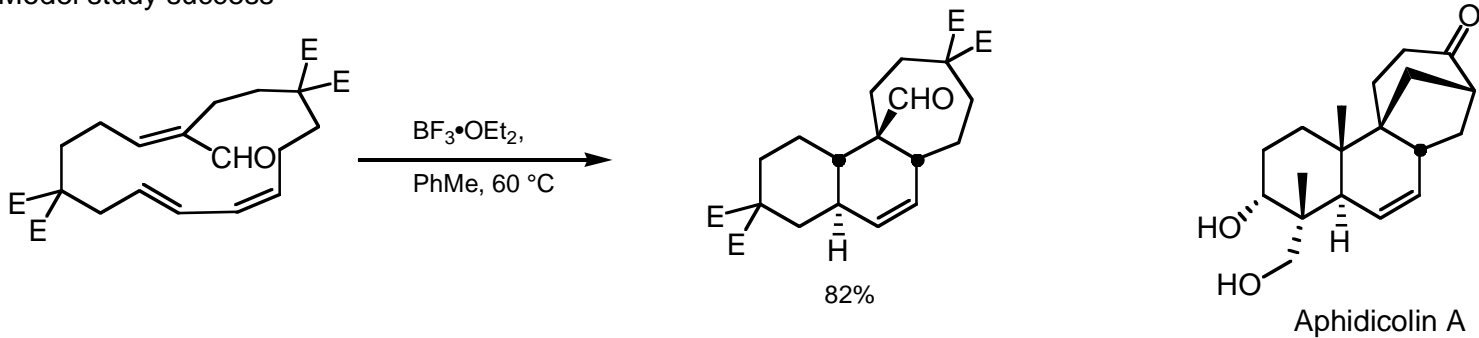


*TTT+CTT: Evans, FR182877*

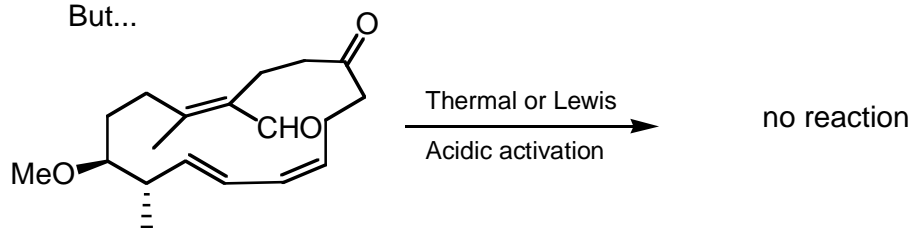


## CTC/TTC: Deslongchamps, Aphidicolin A

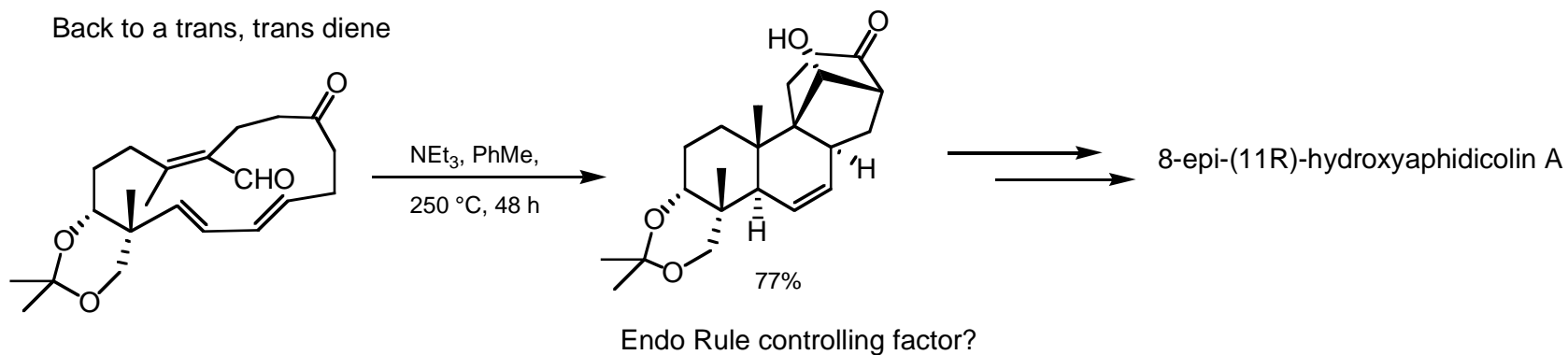
Model study success



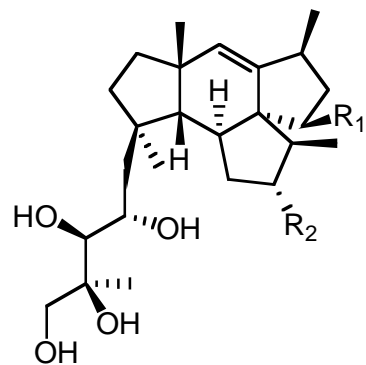
But...



Back to a trans, trans diene



# CTT: Uemura, Mangicol core

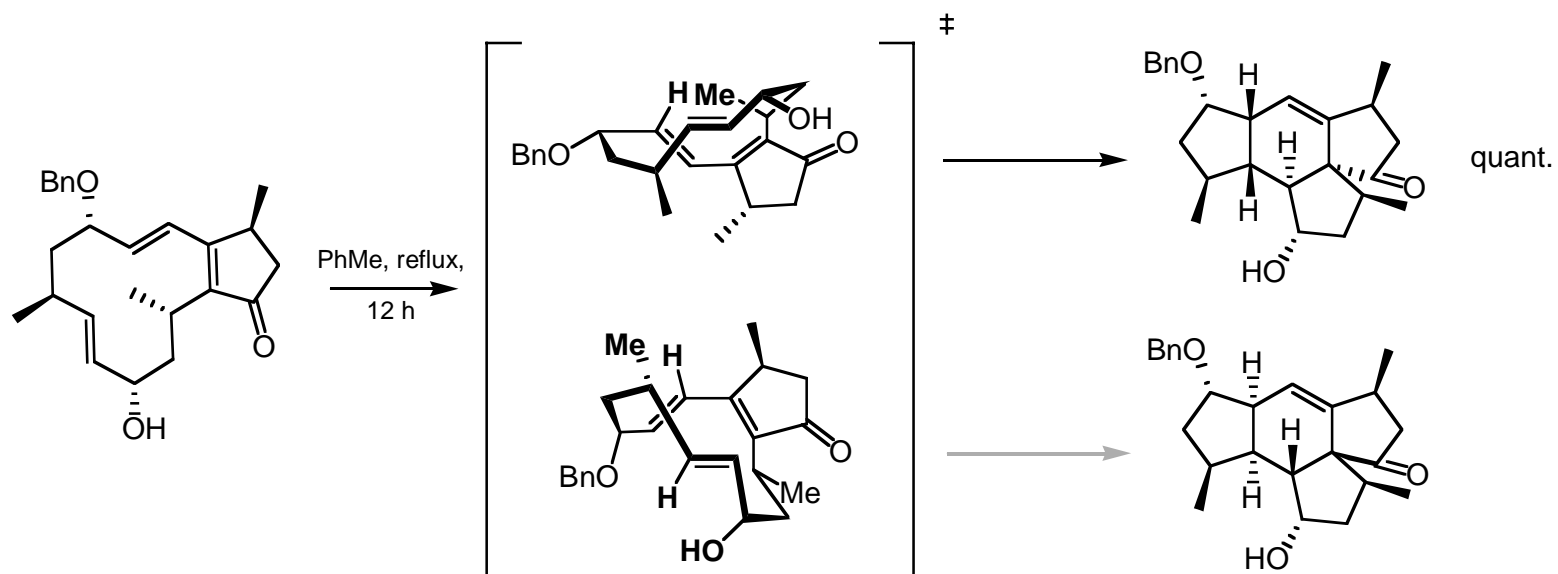


Mangicols

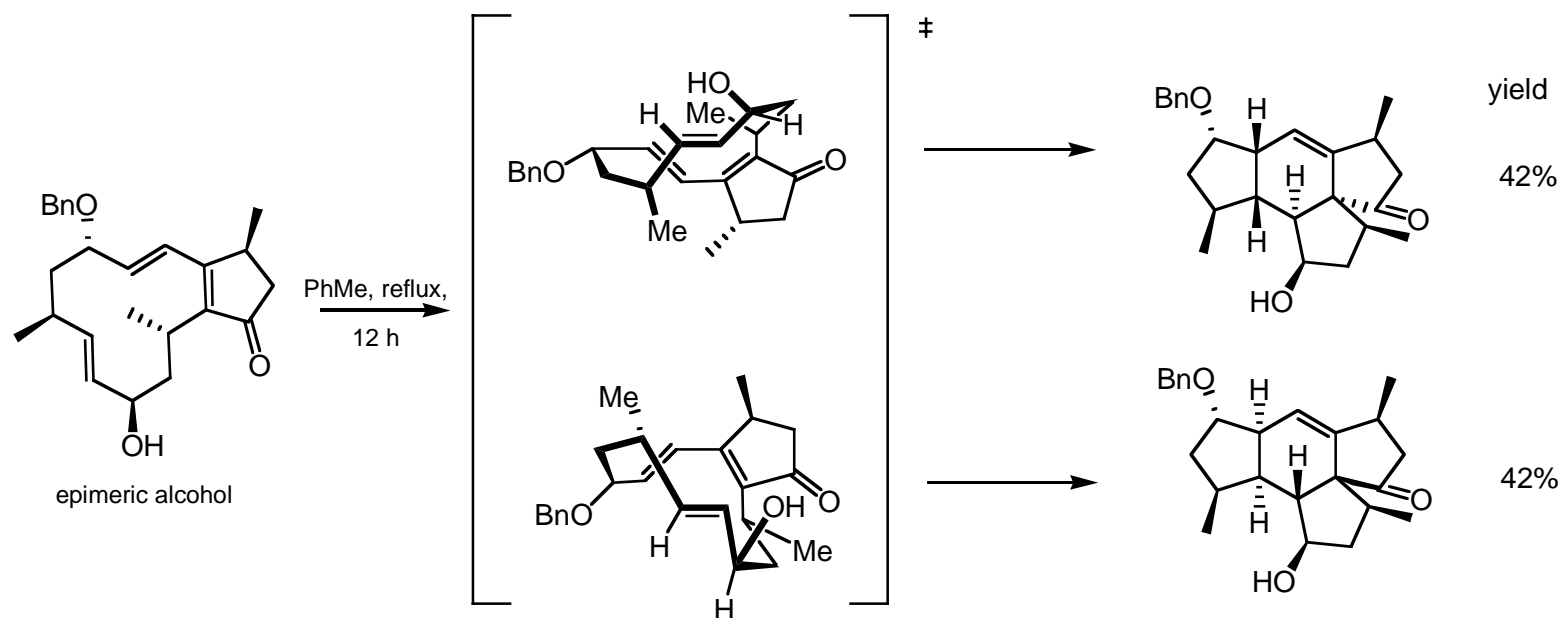
A: R<sub>1</sub> = OH, R<sub>2</sub> = H

B: R<sub>1</sub> = H, R<sub>2</sub> = OH

C: R<sub>1</sub> = R<sub>2</sub> = H



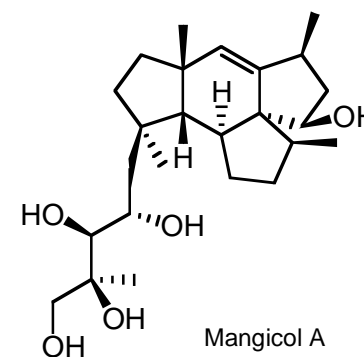
*CTT: Uemura, Mangicols*



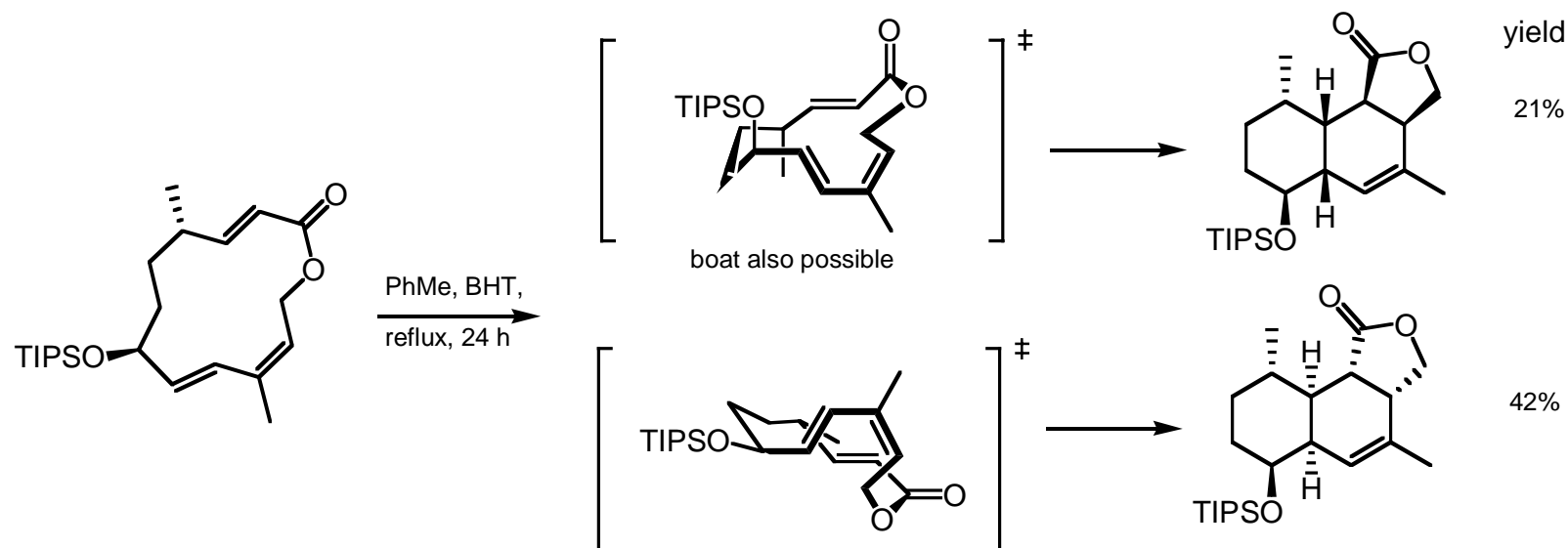
Authors invoke steric argument to explain erosion in stereoselectivity

Note the two C-O bonds antiperiplanar to the forming bonds in the top TS.

No experiments on the oxidized, activated dienophile?

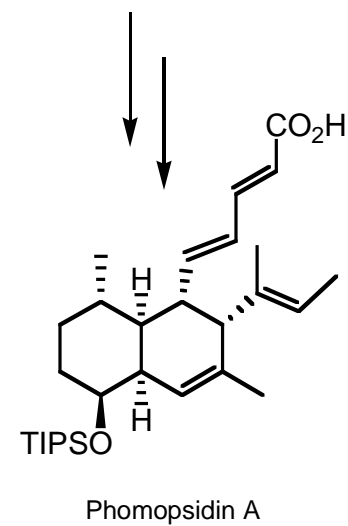


# CTT: Nakada, Phomopsidin



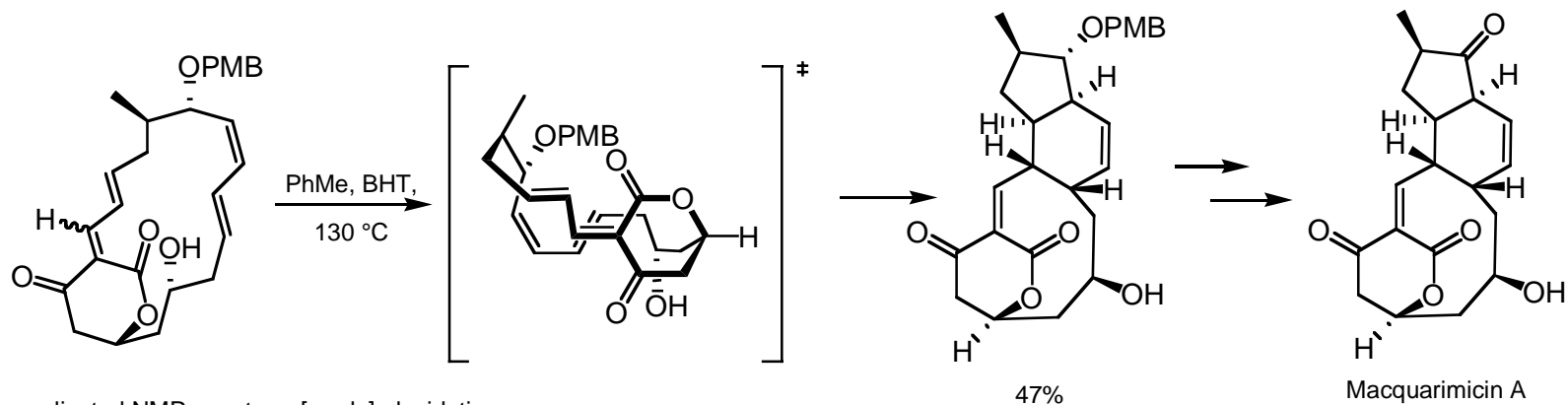
Note the C-O bond antiperiplanar to the forming bond in the bottom transition state.

Or is it simply a steric effect?





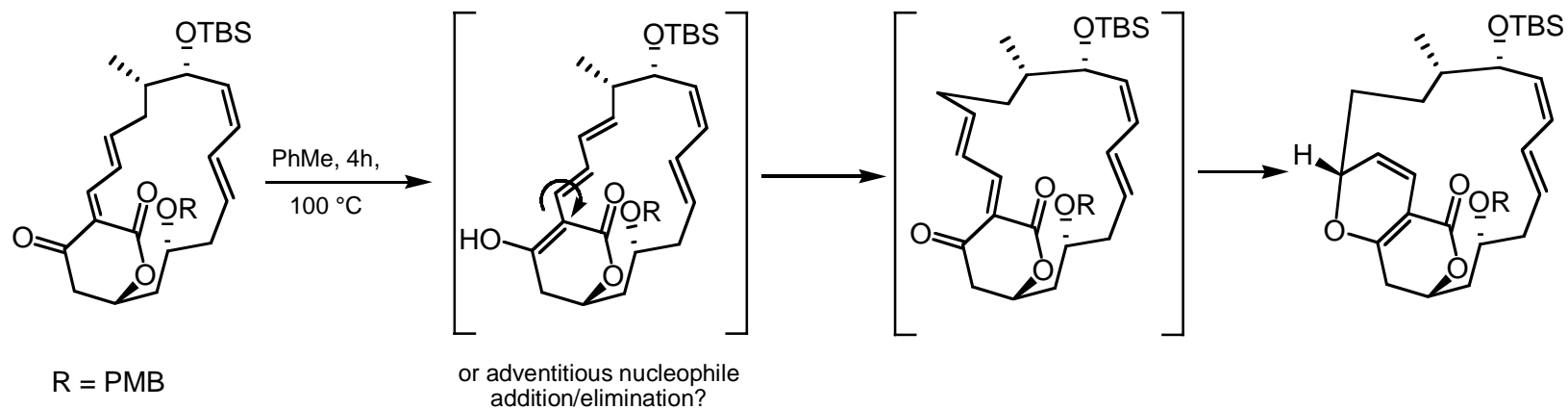
## CTT: *Tadano, Macquarimicin A*



"a complicated NMR spectrum [made] elucidation of the E/Z ratio difficult. We attribute the complication to...ketalization."

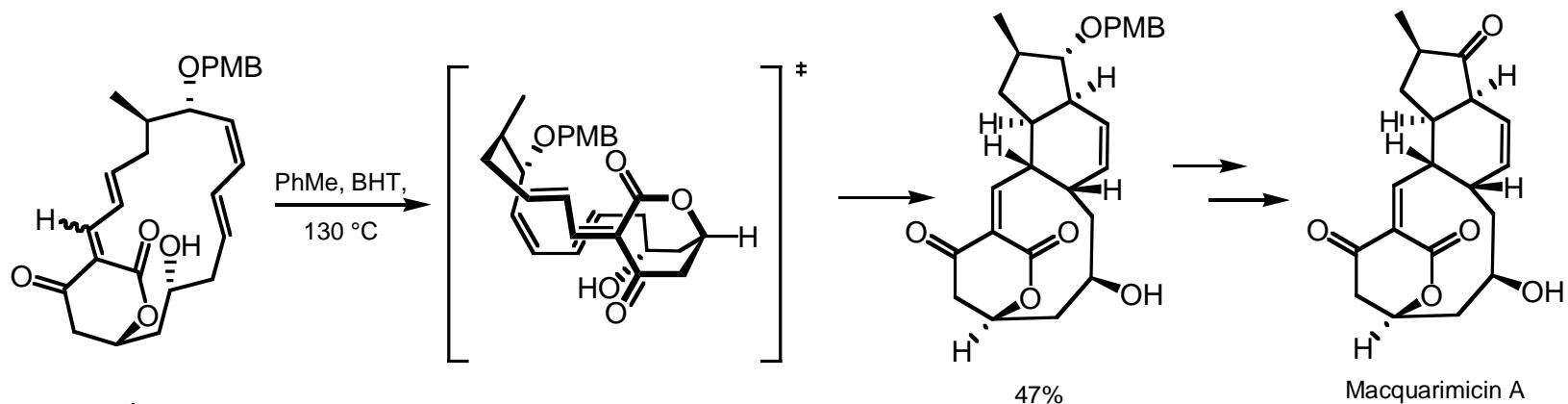
Tadano, *JACS*, **2003**, 125, 13536

But this closely related reaction failed:



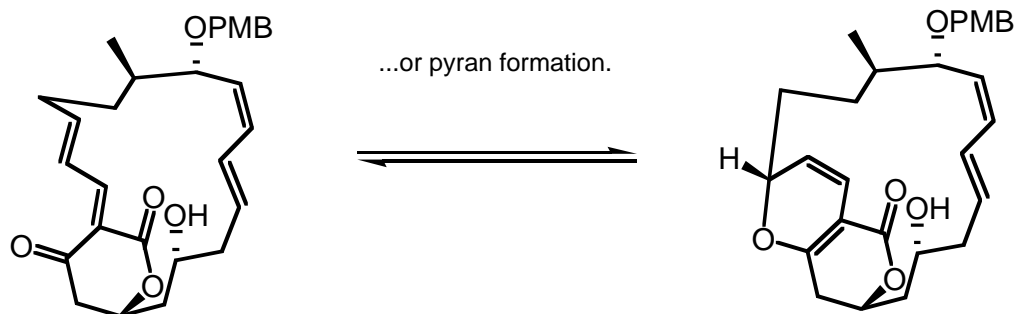
Beaver, Evans, unpublished.

# CTT: Tadano, Macquarimicin A



"a complicated NMR spectrum [made] elucidation of the E/Z ratio difficult. We attribute the complication to...ketalization."

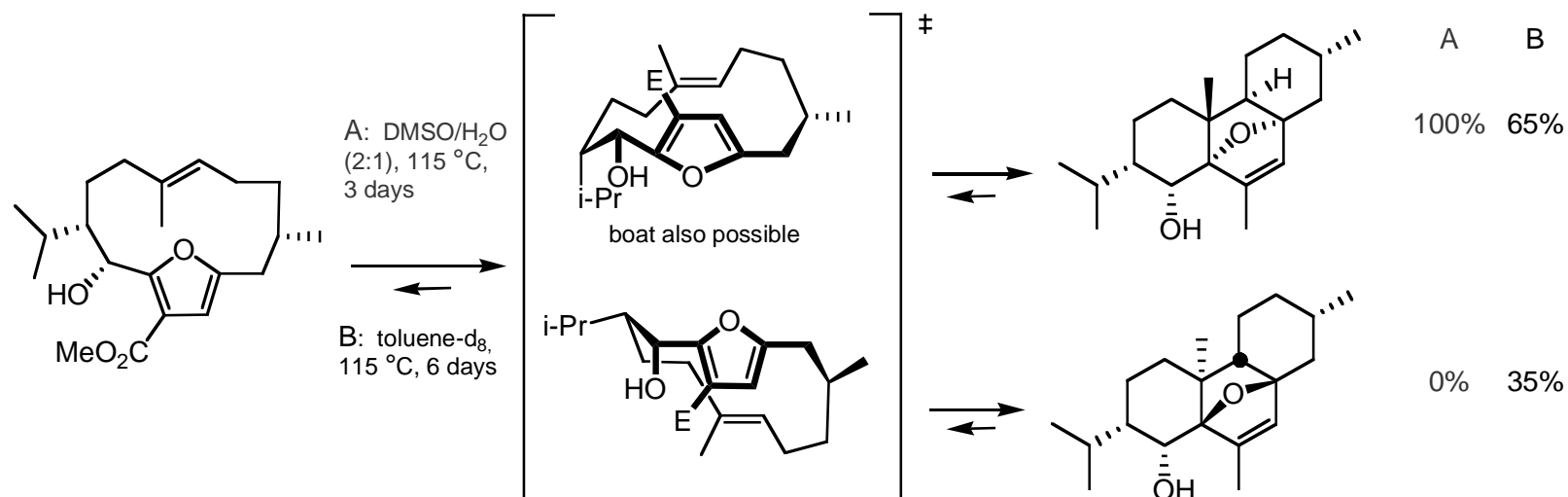
Is ketalization plausible?  
Spectral information not disclosed



Reversibility in this case could result from:

- anti stereocenters
- PMB v. TBS
- free hydroxyl v. PMB

## Furan as diene: Deslongchamps, Chatancin

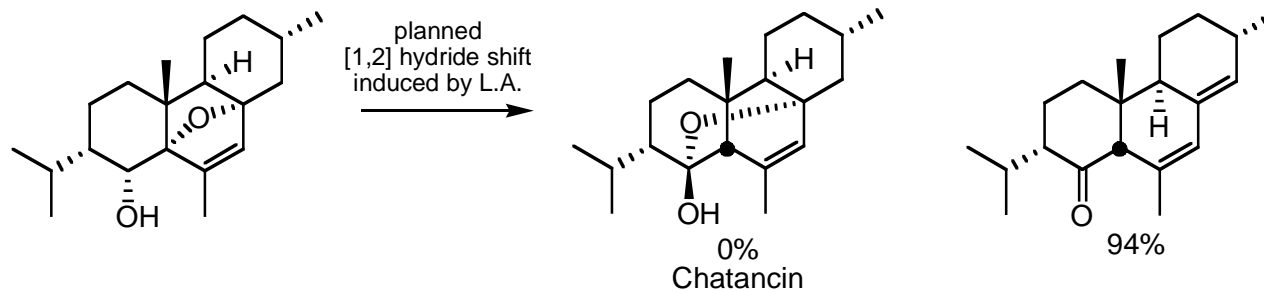


Solvent dependence may reflect disruption of intramolecular H-bond between alcohol and ester.

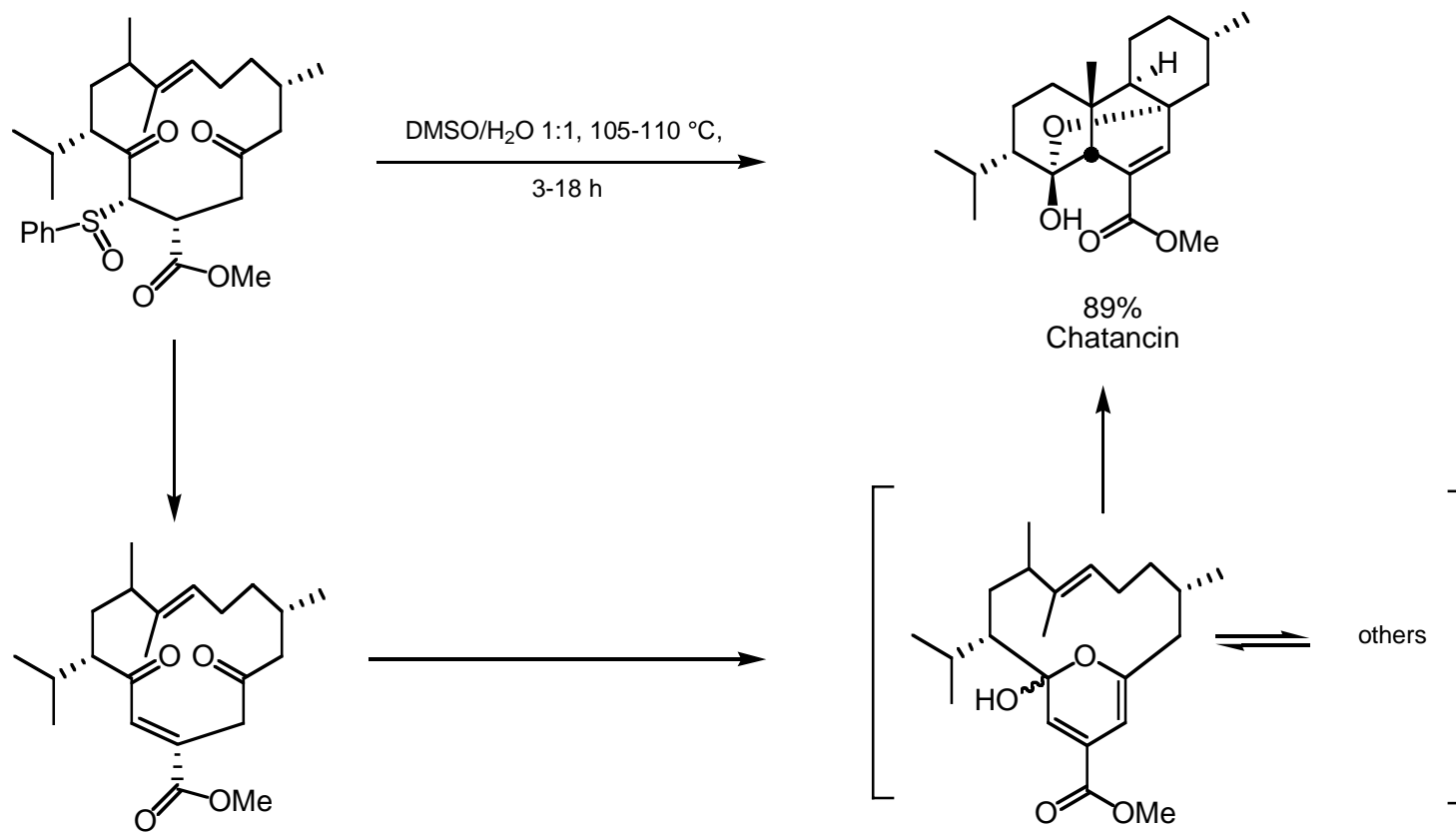
Diastereoselectivity not fully explained.

Note antiperiplanar -OH in top TS can be avoided by adopting a boat-like geometry.

Endgame strategy not viable:

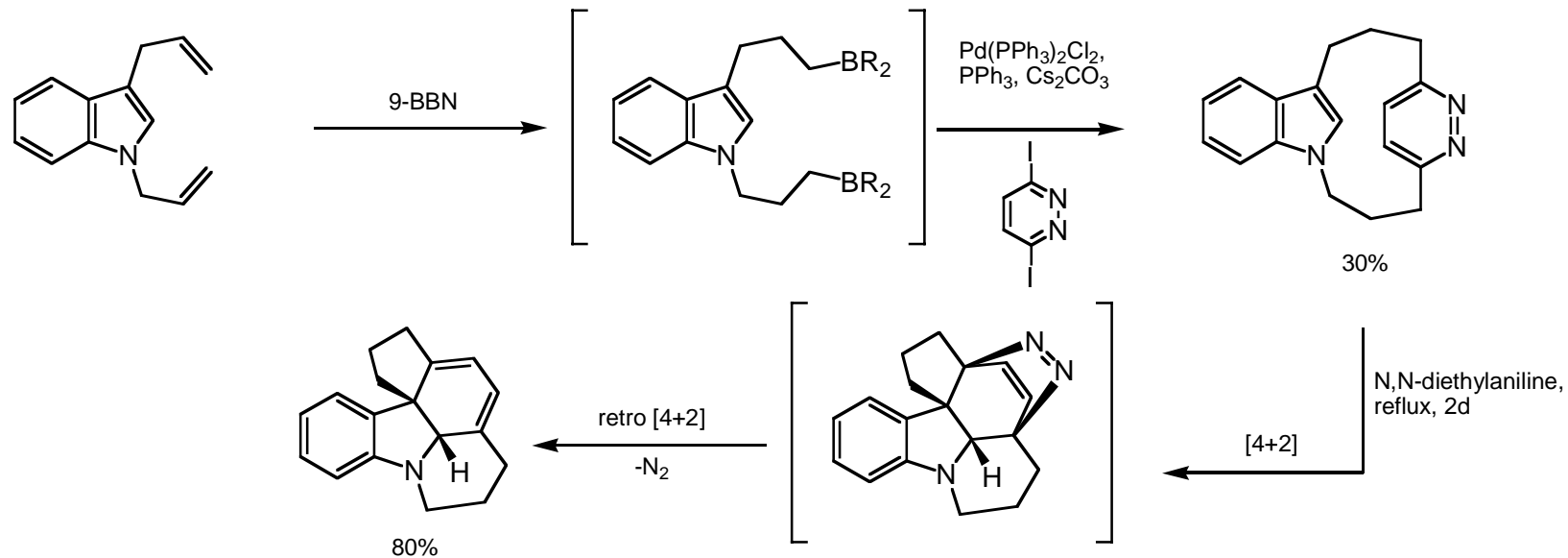


*Pyran as diene: Deslongchamps, Chatancin*

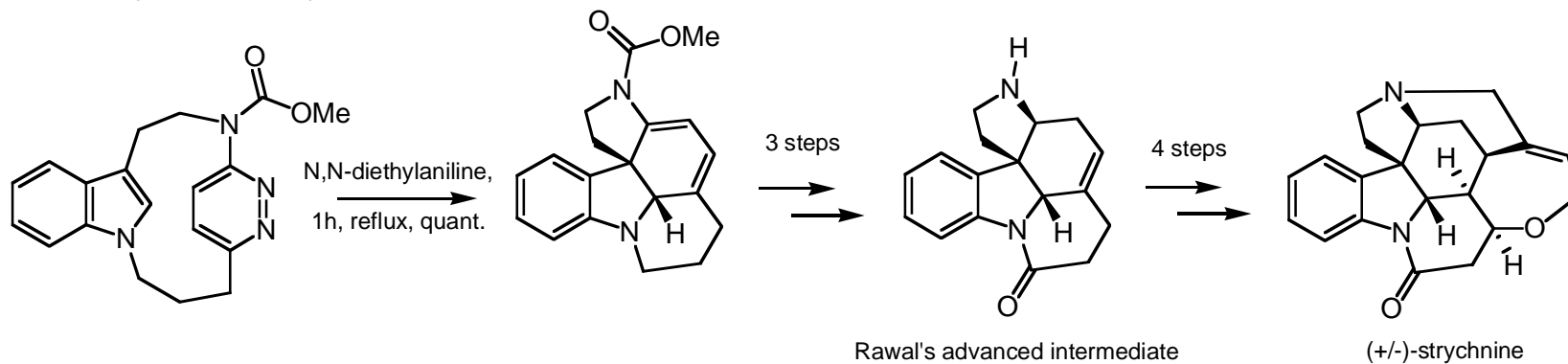


## Cyclophanes as TADA Substrates: Strychnine

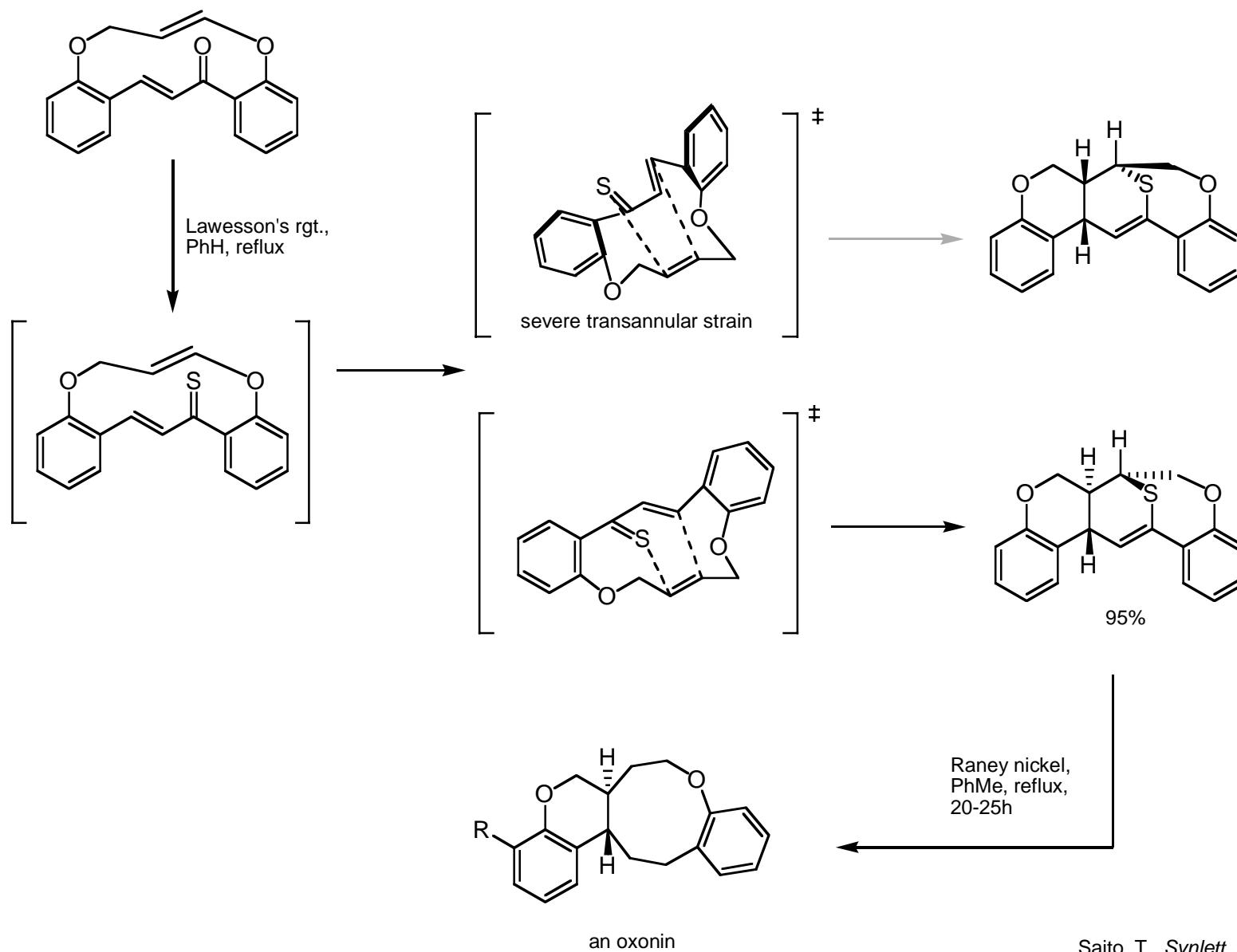
Model system



Formal synthesis of strychnine in 12 steps



*Type II TADA: an approach to oxonins*



## Type II TADA: Longithorone A

