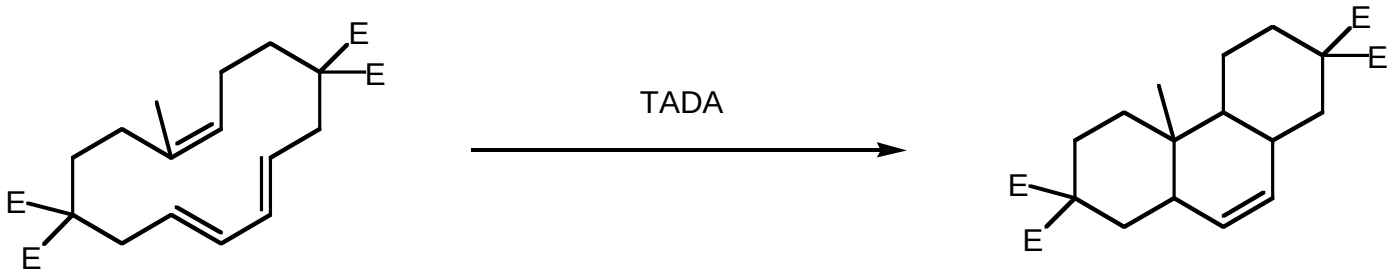
The Transannular Diels-Alder Reaction

Drew Adams
Evans Group Seminar
May, 2004



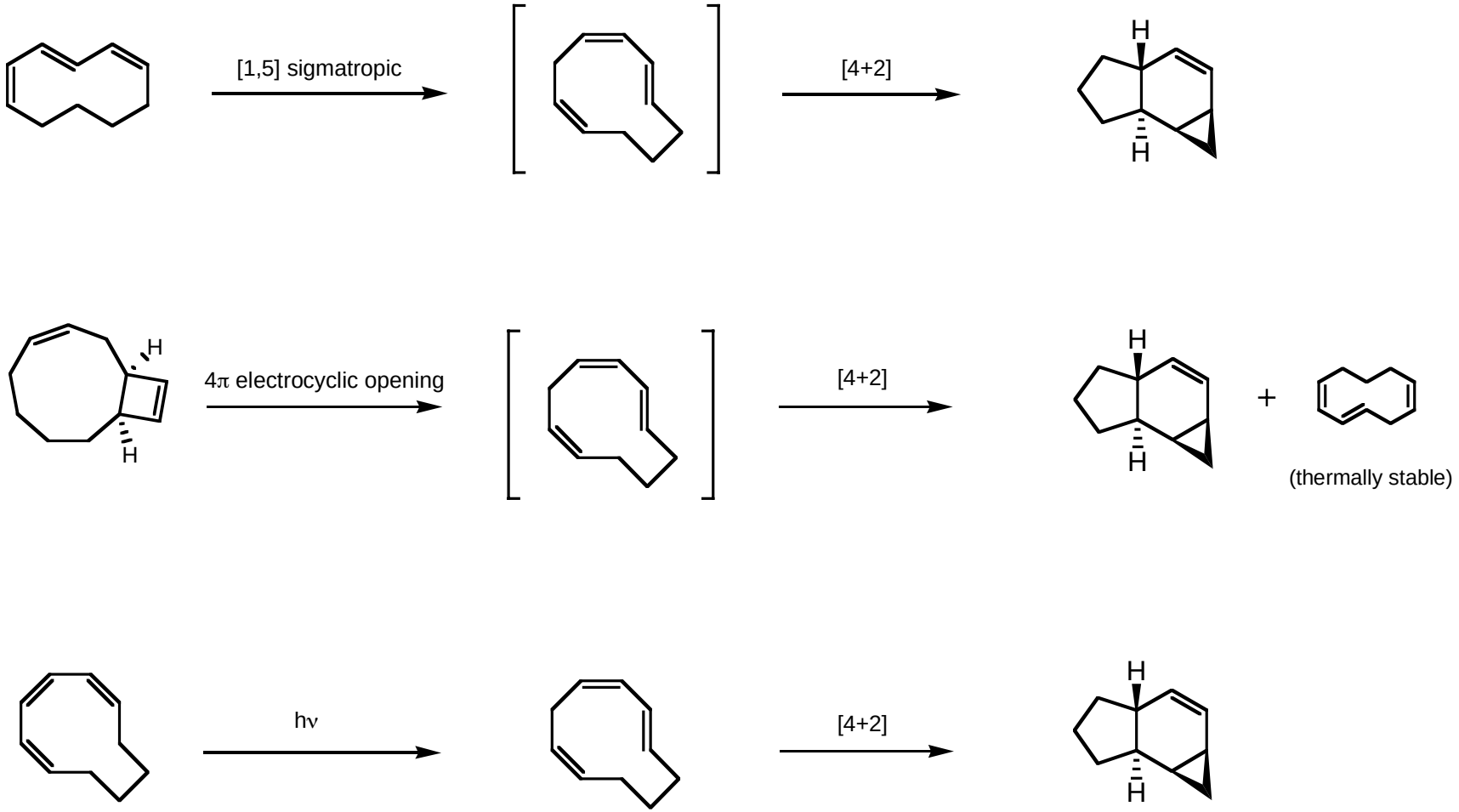
I. Background, Utility, Scope

II. Insights and Oddities From Model Studies

III. Total Syntheses

E = CO_2Me

TADA: Accidental discovery

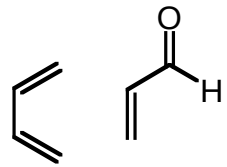


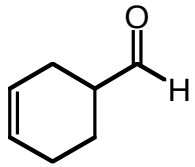
only example of cyclopropane formation via TADA.

Dauben, W.G. *JOC*, **1981**, 687.

Diels Alder reaction types

Standard Diels-Alder

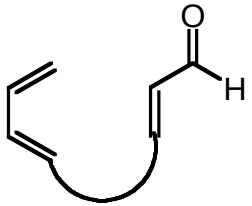


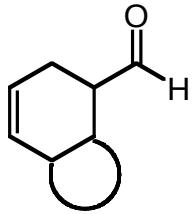


cyclic product

high entropy of activation

Intramolecular Diels-Alder (IMDA)

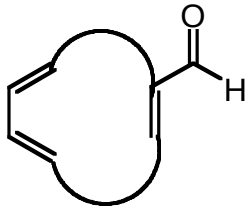


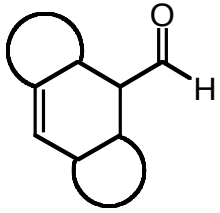


one tether yields a bicyclic product

lowered entropy of activation because unimolecular

Transannular Diels-Alder (TADA)





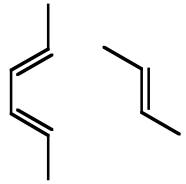
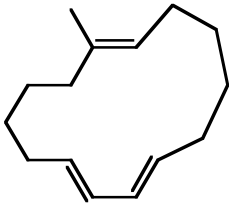
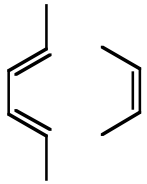
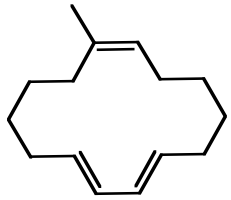
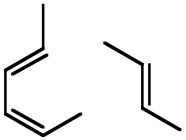
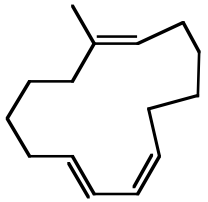
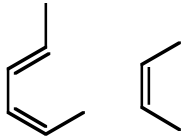
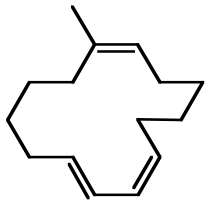
two tethers yields a tricyclic product

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

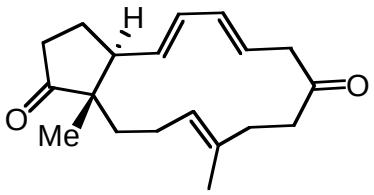
	$\Delta H^{\ddagger}$	$T\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta G_{CH}^{\ddagger}$	$T\Delta S_{CH}^{\ddagger}$	$\Delta H_{CH}^{\ddagger}$	
 trans, trans: trans	37.01	*-16.83*	**53.84**	**36.36**	*-5.46*	30.90	
 trans, trans: cis	37.19	*-16.27*	**53.46**	**34.88**	*-2.78*	32.01	
 cis, trans: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

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

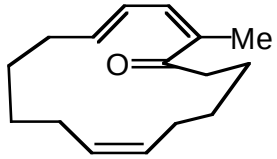
Wolfe, S. *Can. J. Chem.*, **79**, 2001, 1284

TADA Benefits: Diene Scope

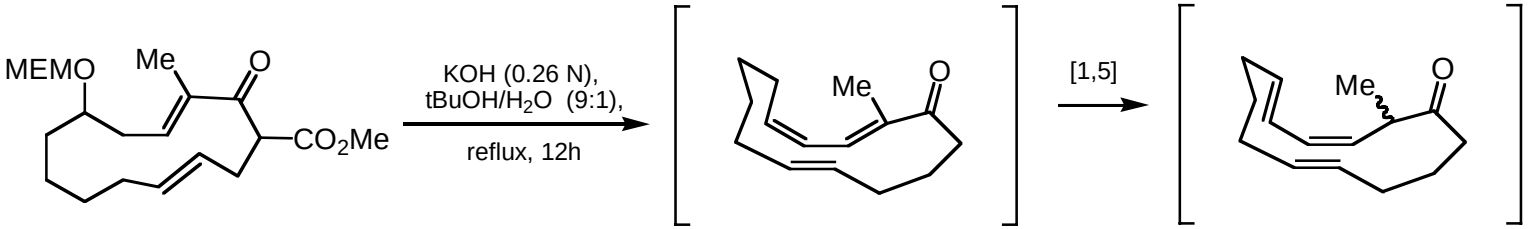
Trans, Trans



Cis, Trans



Cis, Trans (substituted)



In one step:

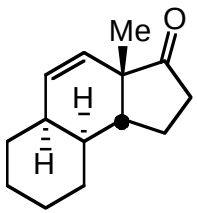
establish γ, δ unsaturation;

saponify ester;

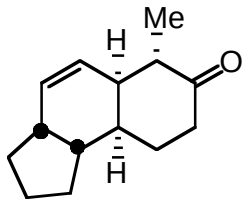
decarboxylate;

[1,5] rearrangement (optional);

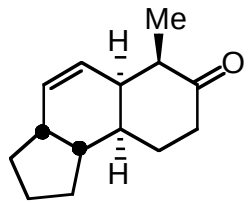
[4+2] cycloaddition



34%



38%

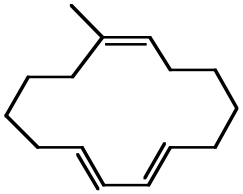


19%

Deslongchamps, P. *TL*, **1987**, *28*, 5249.

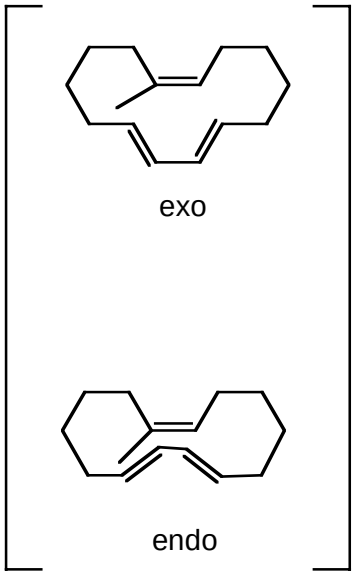
Diene reactivity

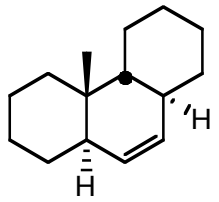
Trans, Trans dienes



trans, trans; cis

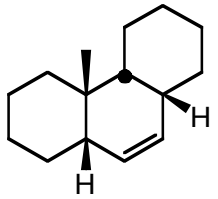
< 80 °C





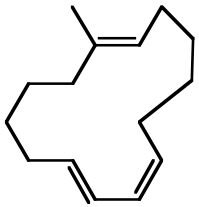
100%
trans, syn, trans (TST)

A trans dienophile gives only 2:1 selectivity.



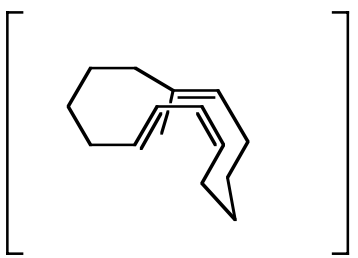
0%
cis, syn, cis (CSC)

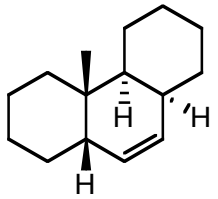
Cis, Trans dienes



cis, trans; trans

350 °C



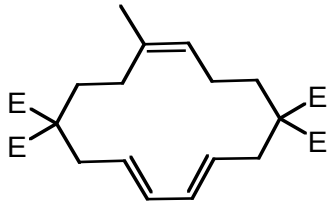


100%
cis, anti, cis (CAC)

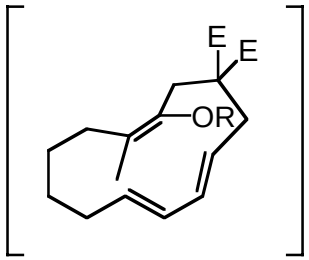
Deslongchamps, *Tet.*, **2001**, *57*, 4243

TADA Benefits: Dienophile Scope

Unactivated dienophile

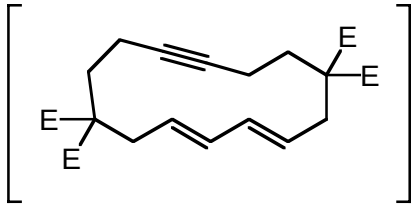


Tetrasubstituted enol ether

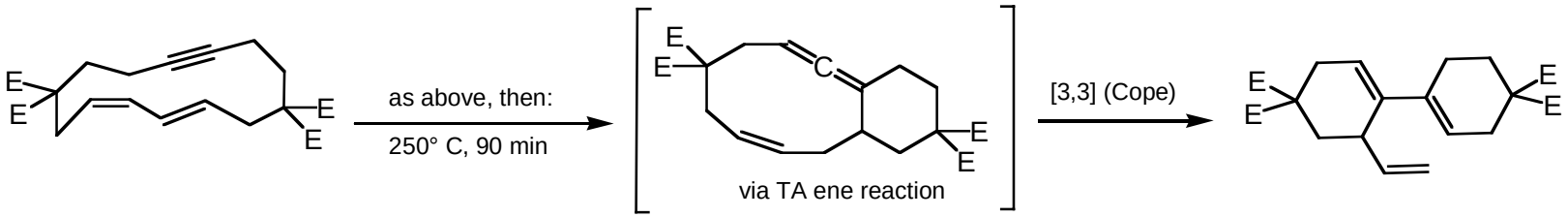


R = MOM

Acetylene



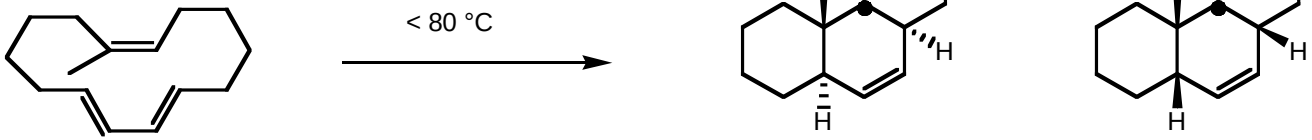
The corresponding cis, trans diene gave some TADA product (23%) but mostly rearranged product (63%):



Deslongchamps, P. *TL*, 1987, **28**, 5255.
Deslongchamps, P. *JACS*, 2001, **123**, 8213.

TADA Benefits: Stereoselectivity

The macrocyclic environment is often highly differentiating:



trans, trans; cis

100%

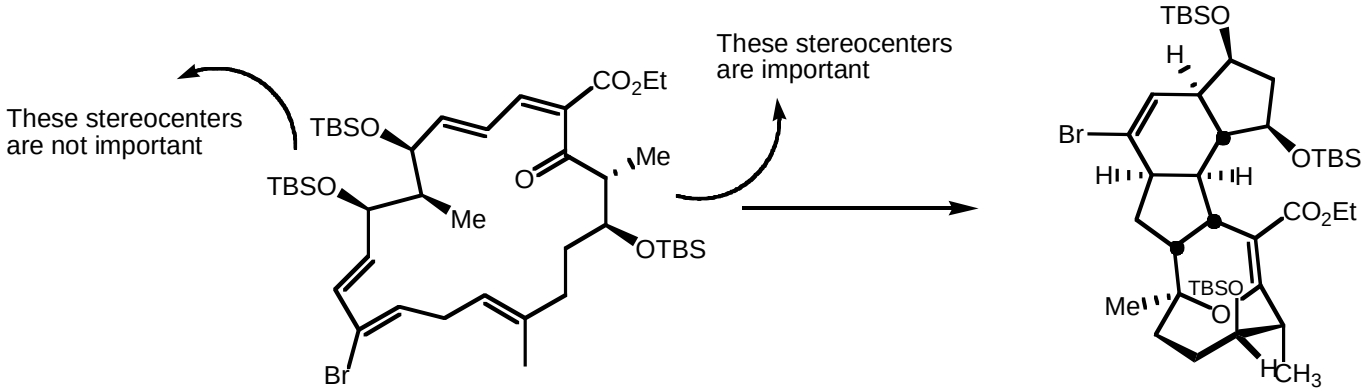
trans, syn, trans (TST)

0%

cis, syn, cis (CSC)

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

The impact of remote stereocenters can be strong:

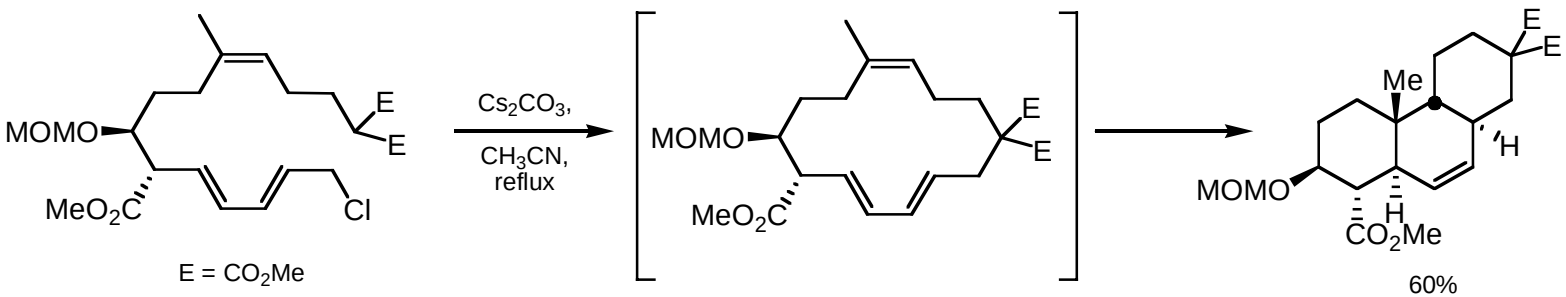


single isomer

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

TADA Challenges: Macrocyclization

Malonate alkylations

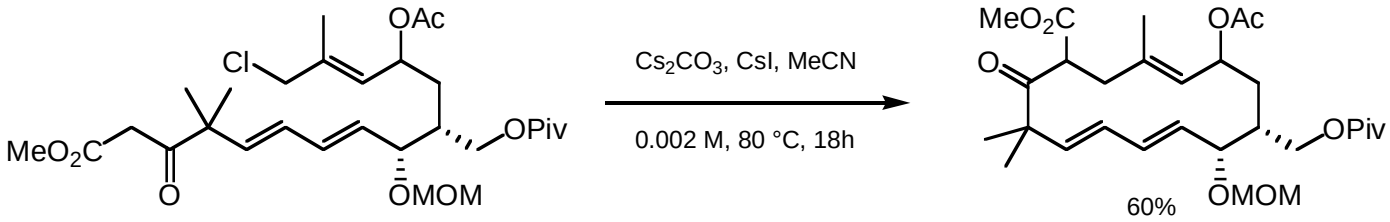


Allows quick, reliable construction of macrocycles: method of choice for model studies

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

Not common for total synthesis: transformations of malonates cumbersome

β-keto-ester alkylations

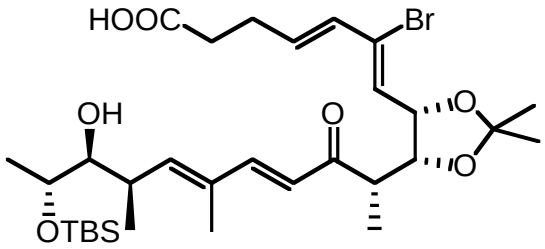


Ease of decarboxymethylation (often under TADA conditions) makes this method more useful for synthesis.

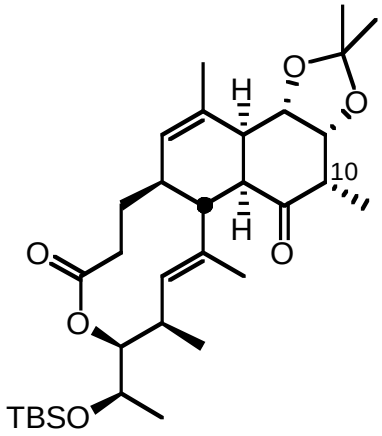
Deslongchamps, P. and Dory, Y. *JOC*, **2003**, *68*, 2390

TADA Challenges: Macrocyclization

Macrolactonization



1. $Cl_3C_6H_2COCl$, NEt_3, DCM
2. DMAP, toluene, 100 °C

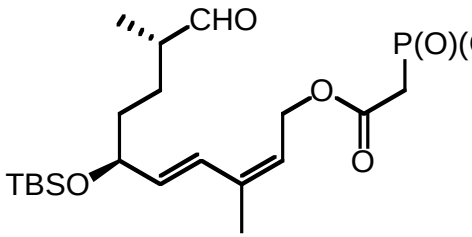


Yields not always high, especially when forming smaller TTT rings

63% (+13% C10 epimer)

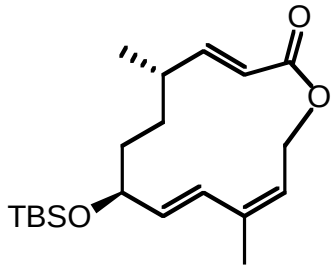
Roush, *JACS*, **1996**, *118*, 7502

Horner-Wadsworth-Emmons



K_2CO_3, 18-crown-6, PhMe

0.005 M, rt



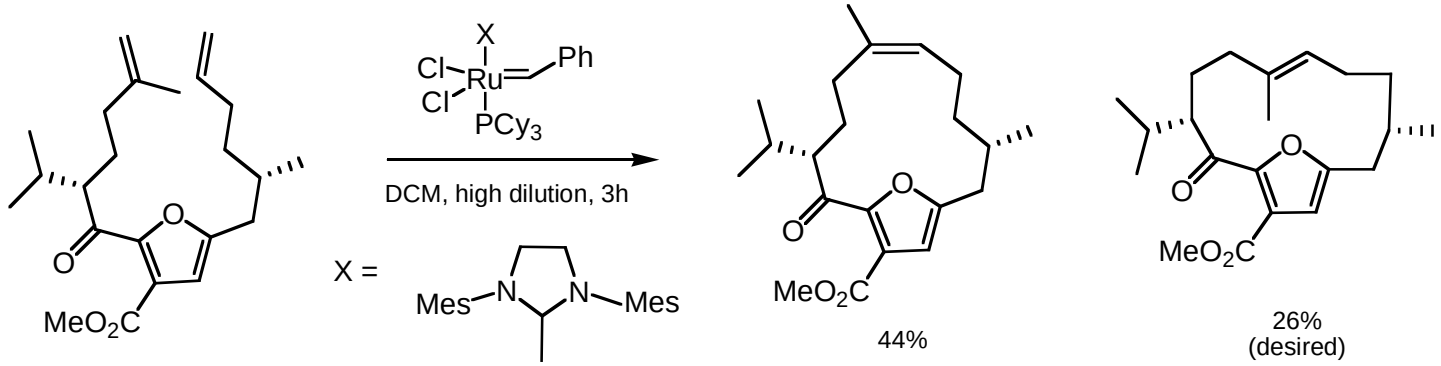
> 78 %

Applicability to trans-trans-trans macrocycles?

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

TADA Challenges: Macrocyclization

Ring-Closing Metathesis



44%

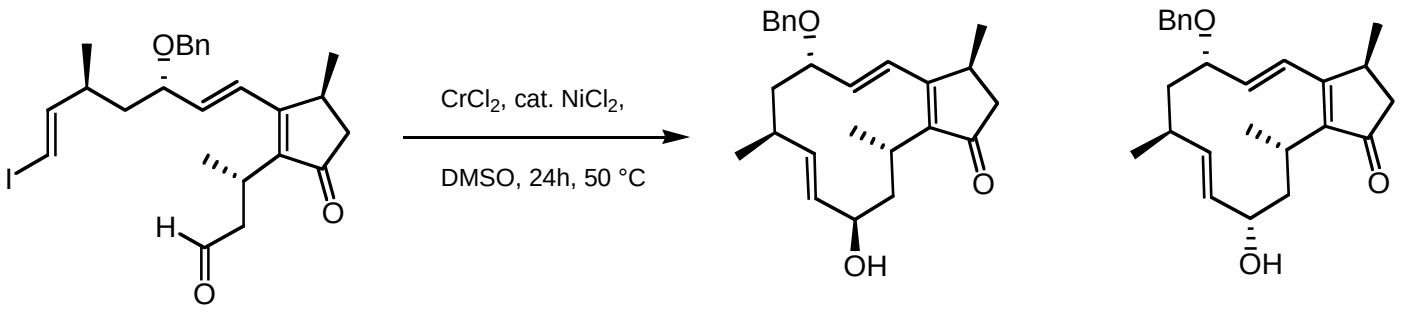
26%
(desired)

Preference for Z olefin seems strong: if C=O is reduced to an α -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..."



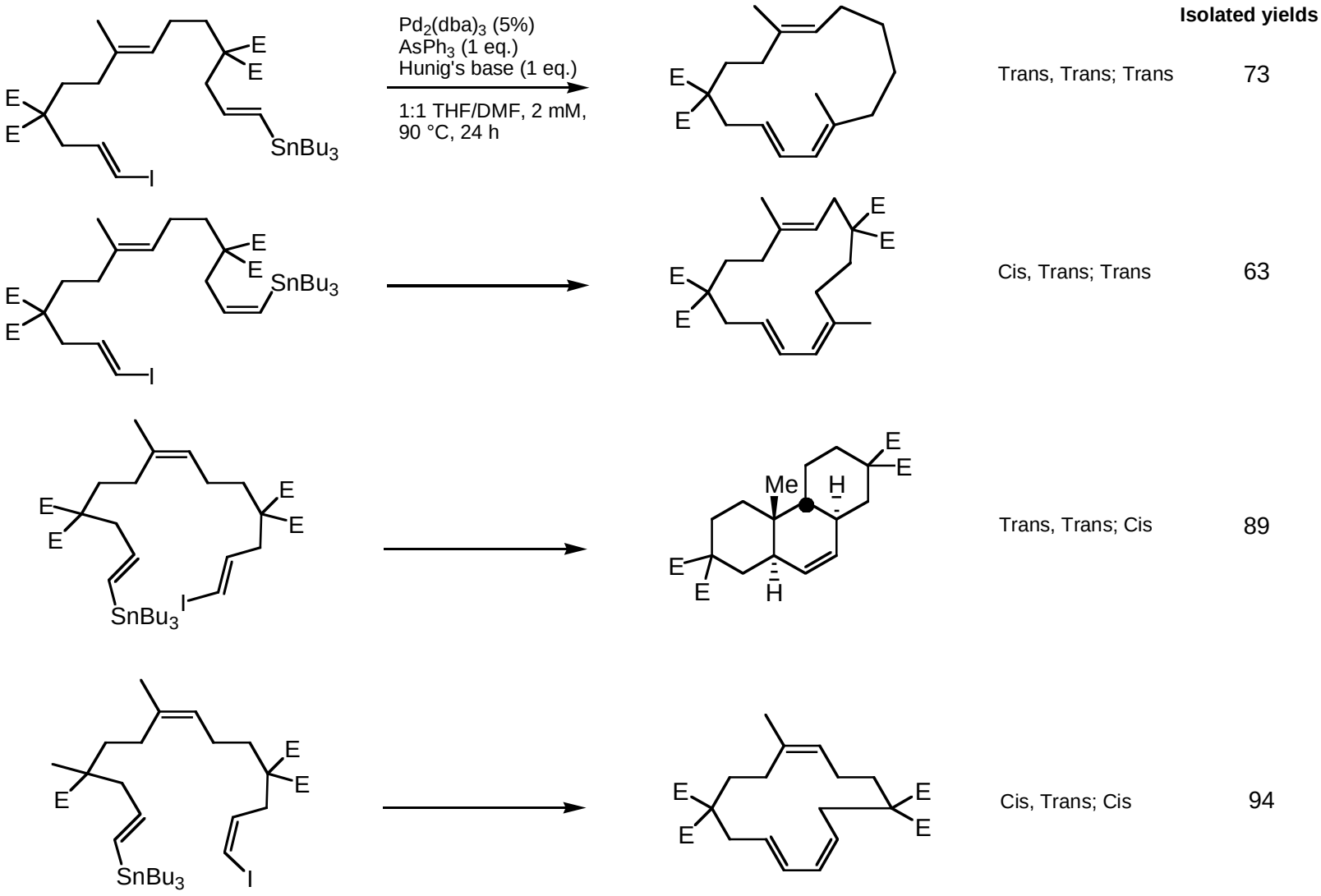
62%

14%

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

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

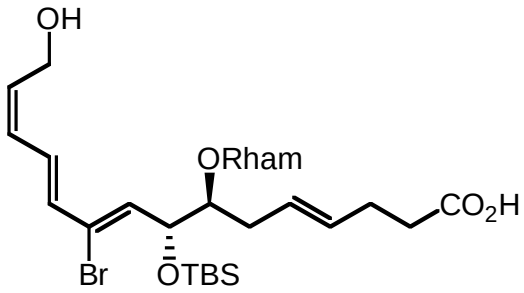
Efficient Stille Cyclization Conditions



	Isolated yields
Trans, Trans; Trans	73
Cis, Trans; Trans	63
Trans, Trans; Cis	89
Cis, Trans; Cis	94

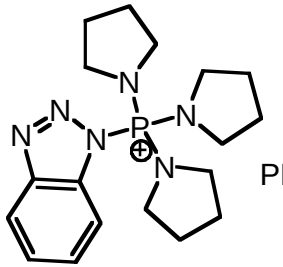
Deslongchamps, P. *Org. Lett.*, **2000**, 3317.

Roush's Ireland-enolate Ring Contraction

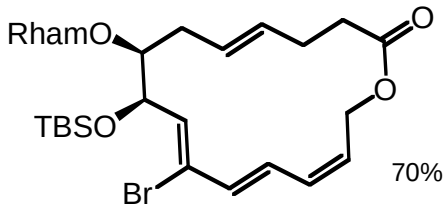


PyBOP, DMAP, DCM,
slow addition to 0.003 M

PyBOP =

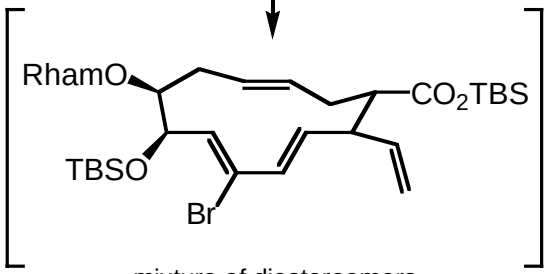


PF_6^-



70%

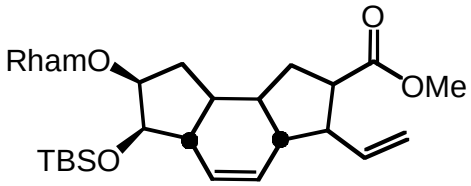
KHMDS, TBSOTf,
4:1 THF/HMPA,
-78 °C to 140 °C, 15 h



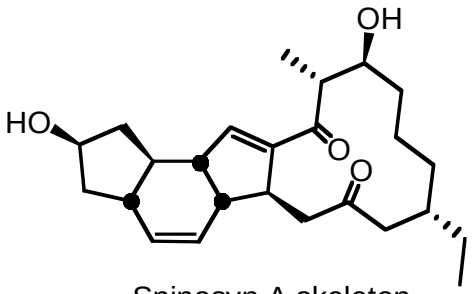
mixture of diastereomers

TADA;

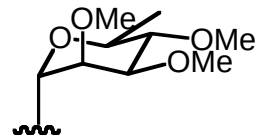
aqueous workup,
then $TMSCHN_2$



53% yield
mixture of four diastereomers



Spinosyn A skeleton



Rham = rhamnopyranosyl

Roush, *JOC*, **2002**, *67*, 4316

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

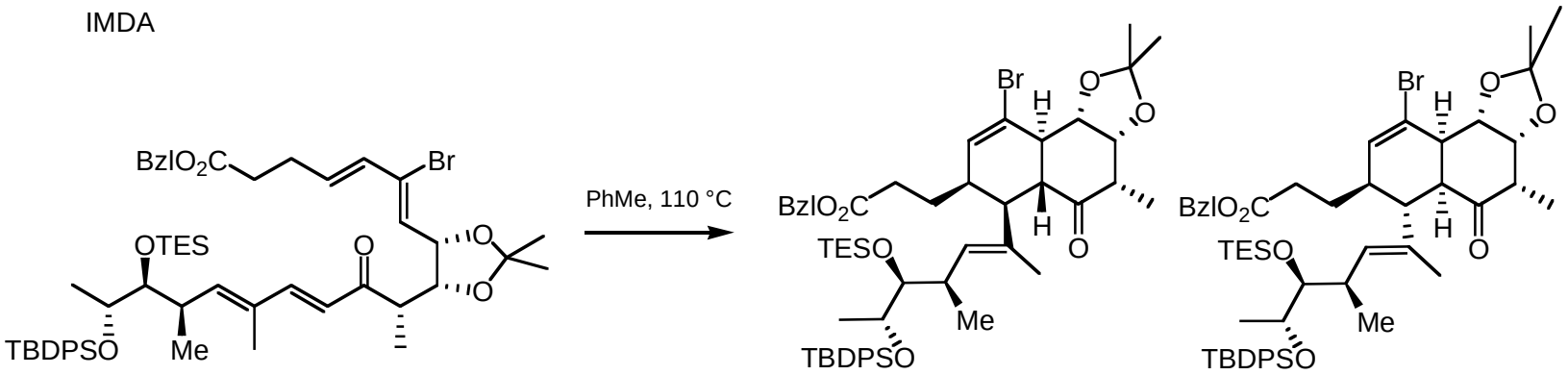
Conjugation of dienophile in TS; activation
by EWG, Lewis Acid catalysis

Planarity of diene in TS

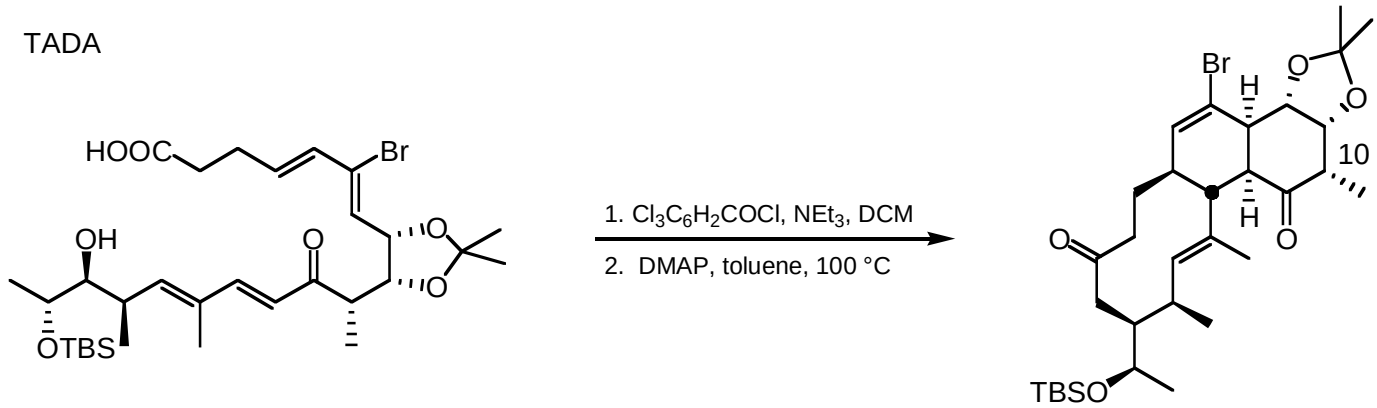
Effects are often countervailing; predicting the dominant effect is difficult.

IMDA v. TADA

IMDA



TADA

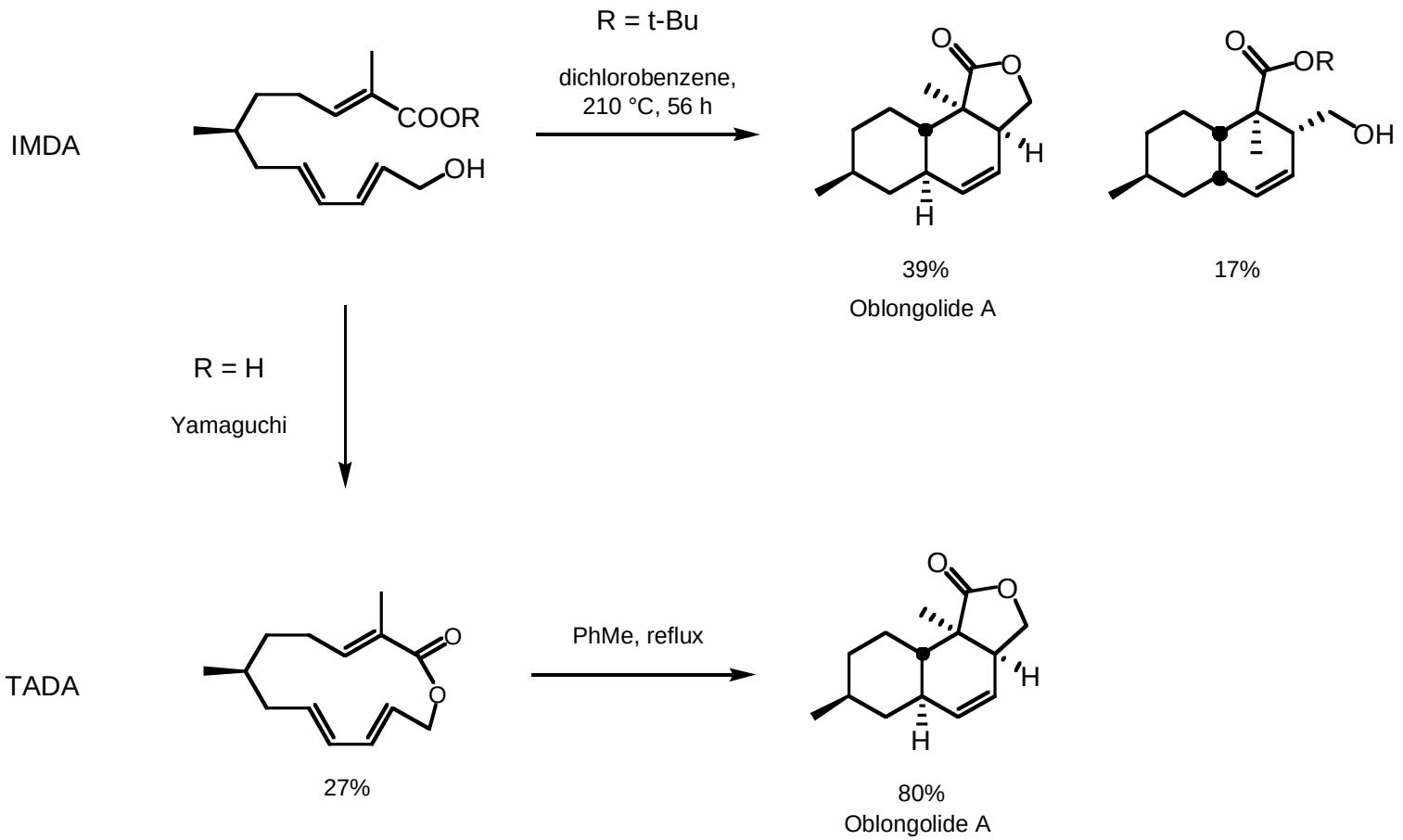


Macrocyclization at 80 °C followed by heating in PhMe at 100 °C reduces epimerization.

63% (+13% C10 epimer)

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

IMDA v. TADA



Shing, T.K. *JOC*, **1995**, *60*, 5785.

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

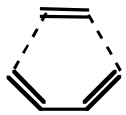
wisdom from Pierre:

"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."

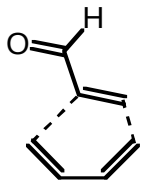
The Issue of Dienophile Activation

Experimental $\Delta G^{\ddagger}$

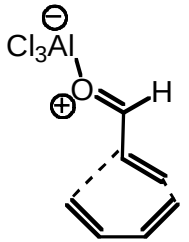
26-35 kcal/mol



20 kcal/mol



10 kcal/mol



Calculations:

Synchronous TS

both bonds = 2.21A

Asynchronous TS

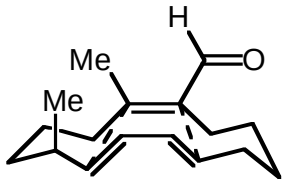
short bond = 2.088A
long bond = 2.353A

Highly Asynchronous TS

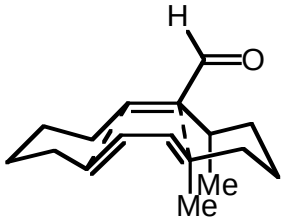
short bond = 1.932A
long bond = 2.96A

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

Asynchronicity affects the macrocyclic environment:



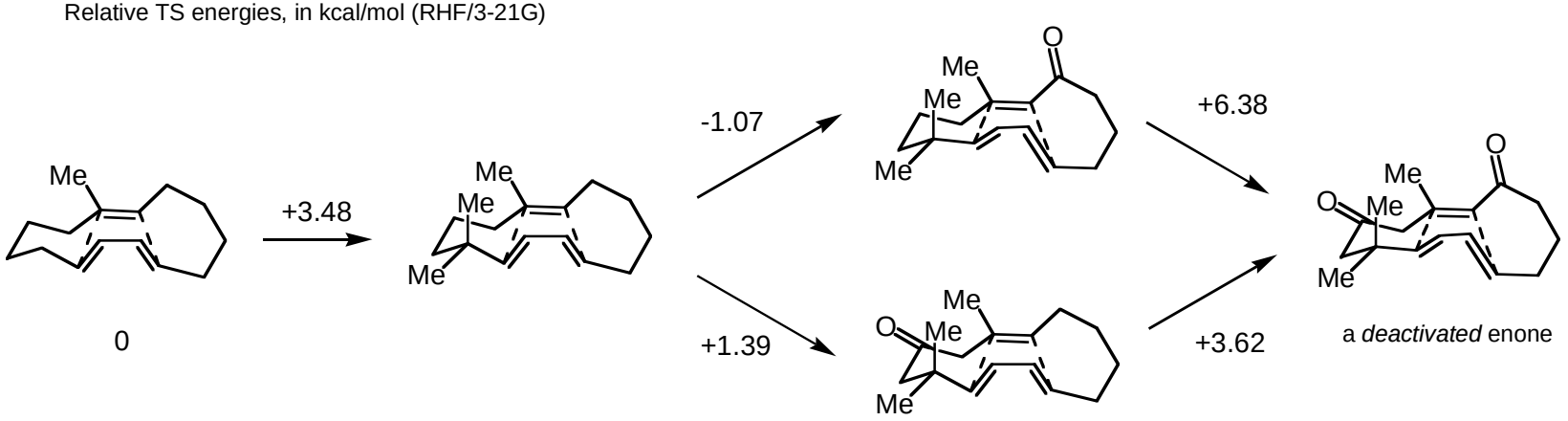
steric congestion near the short bond



steric congestion near the long bond

The Issue of Dienophile Activation

Relative TS energies, in kcal/mol (RHF/3-21G)



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.

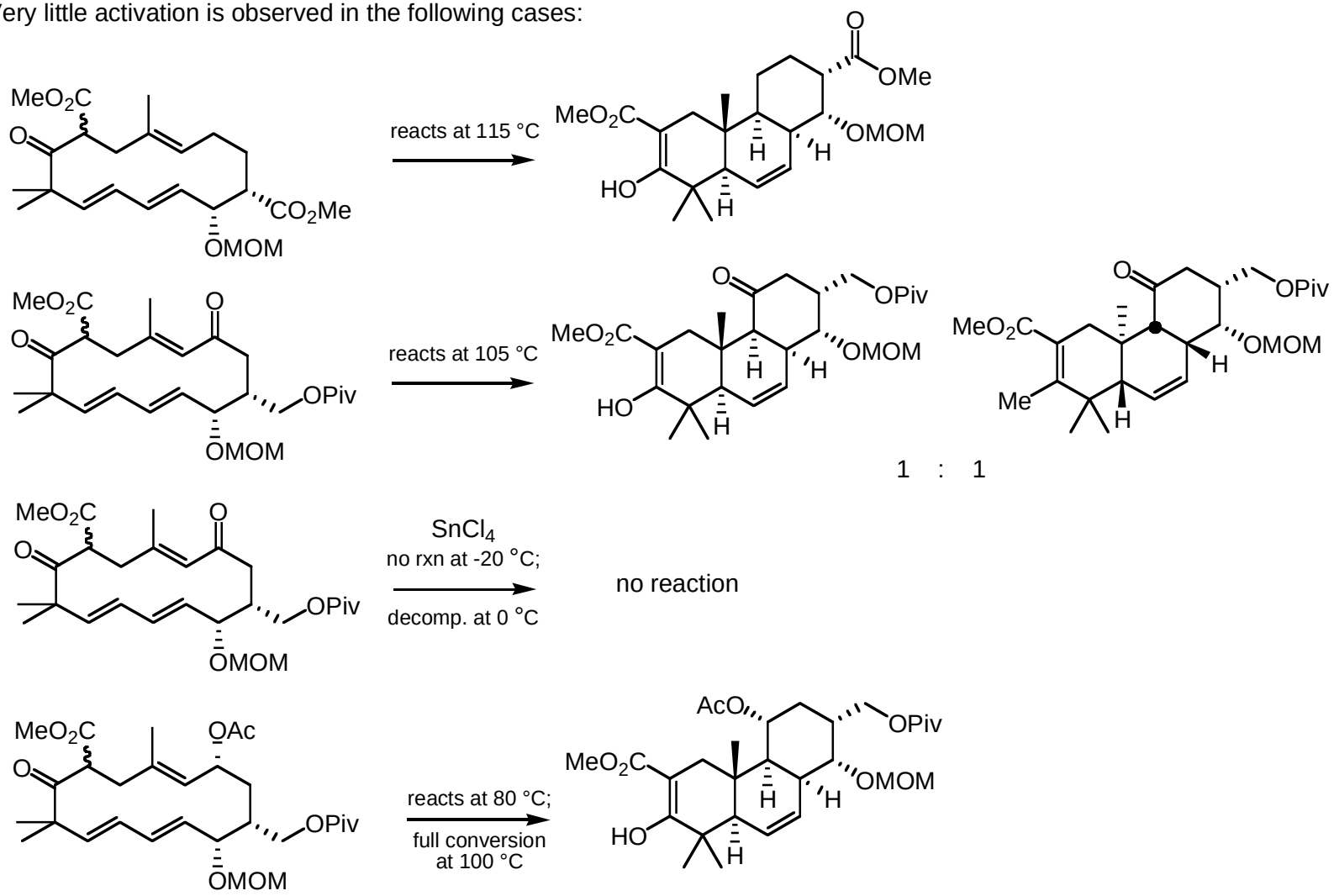
Adding a carbonyl at C(11) separates diene/dienophile and is deactivating.

Combining effects leads to a deactivated enone.

Deslongchamps, *JOC*, **2003**, *68*, 4027.

The Issue of Dienophile Activation

Very little activation is observed in the following cases:

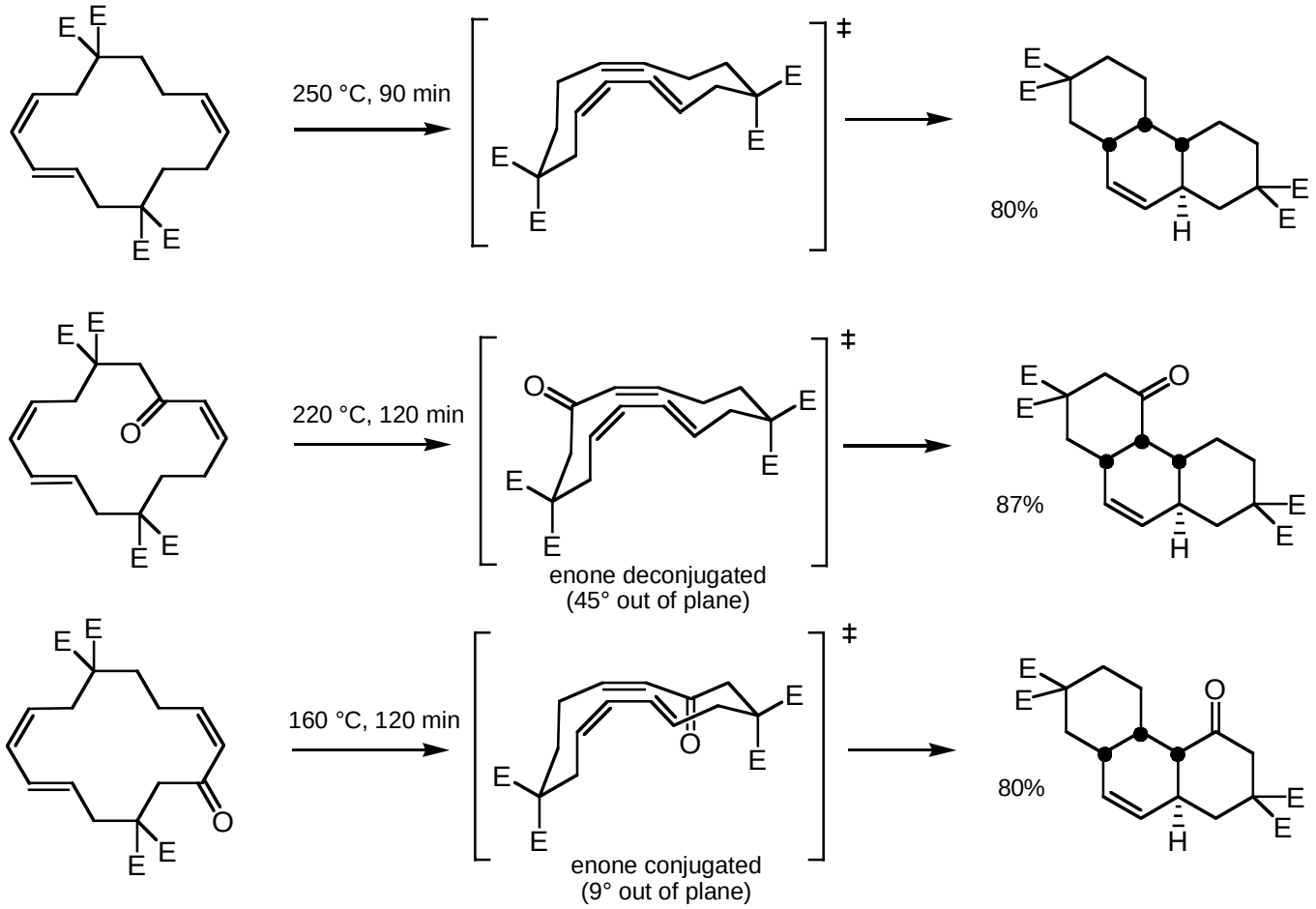


Deslongchamps, *JOC*, **2003**, *68*, 4027.

The Issue of Dienophile Activation

Ground state: conjugation easy to maintain

Transition state: minimization of transannular strain may entail breaking conjugation

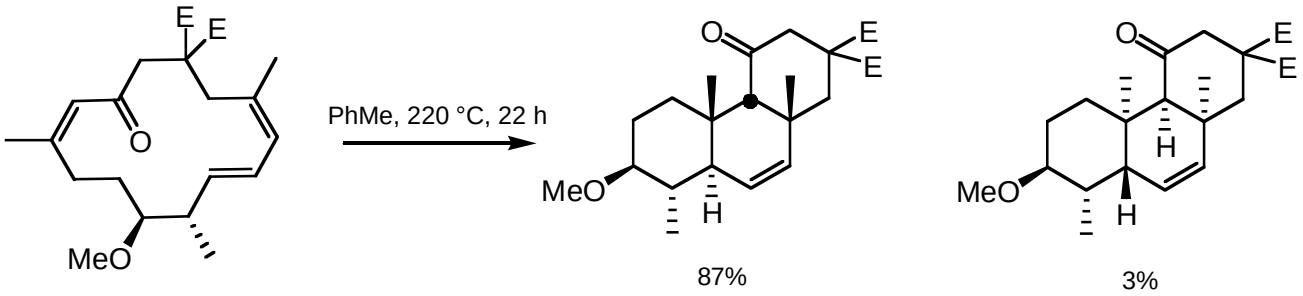


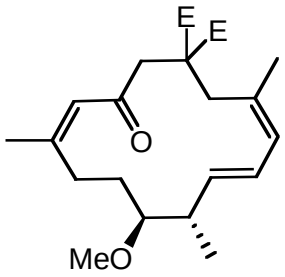
Deslongchamps, *Org. Lett.*, **2003**, *5*, 4799.

The Issue of Dienophile Activation

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

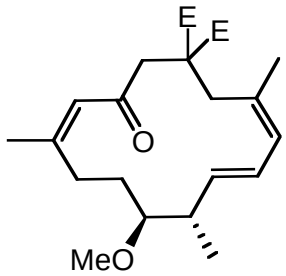
Calculations show Lewis Acids enforce planarity: can be *deactivating.*





Lewis Acid, 60 °C

no reaction



Lewis Acid, 110 °C

decomposition

Lewis Acids screened:

$SnCl_4$

BF_3OEt_2

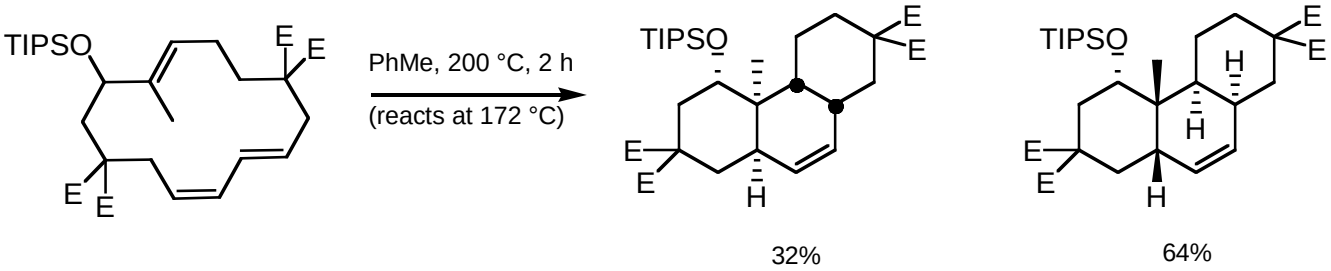
Me_2AlCl

$TiCl_4$

Deslongchamps, *Tet.*, **1997**, *43*, 14937

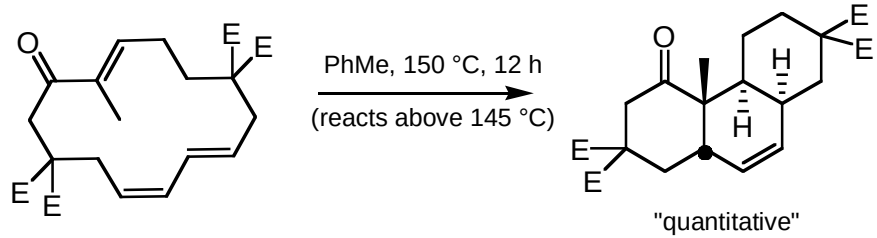
The Issue of Dienophile Activation

Lewis Acids perform as expected when dienophile is truly activated:

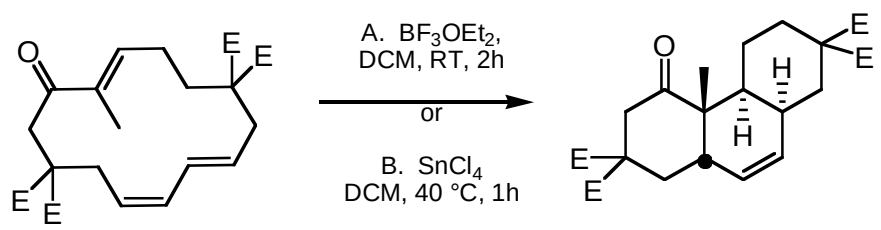


32%

64%



"quantitative"

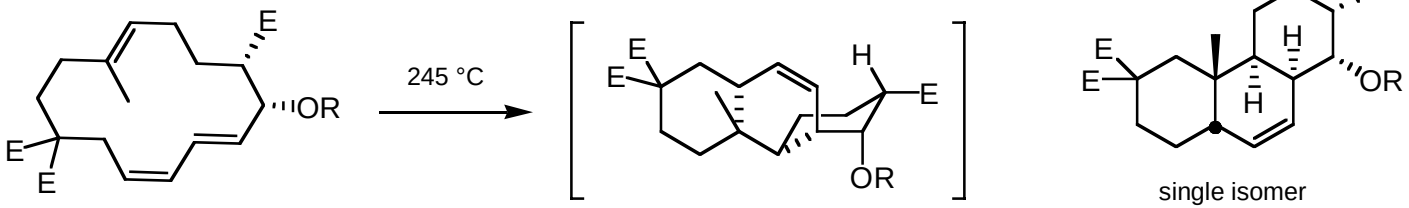


A. 83%

B. 73%

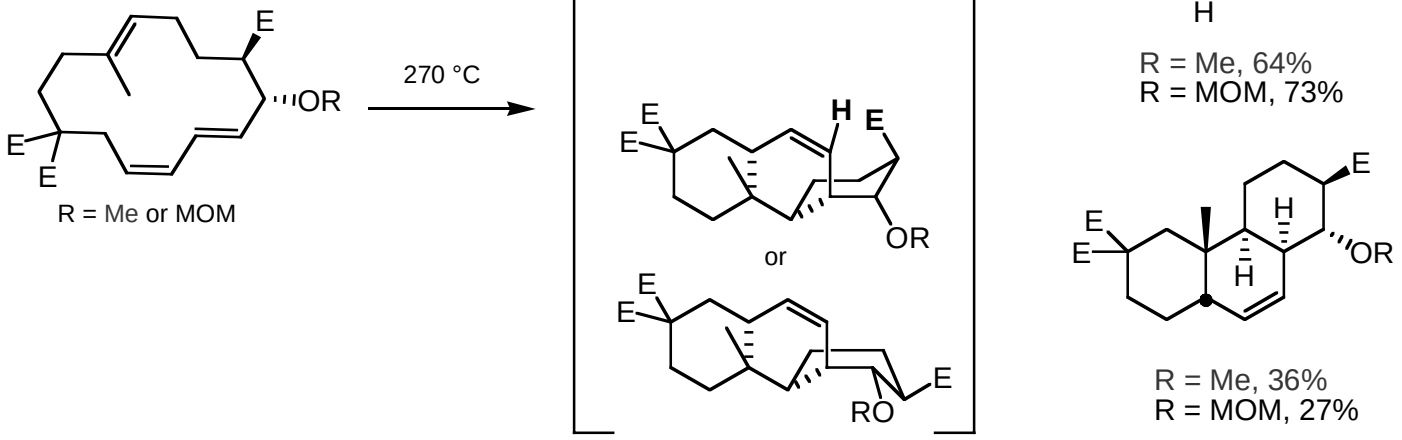
Deslongchamps, *Tet.*, **2000**, *56*, 5509.

A Stereoelectronic effect?



R = Me or MOM

single isomer



R = Me or MOM

R = Me, 64%
R = MOM, 73%

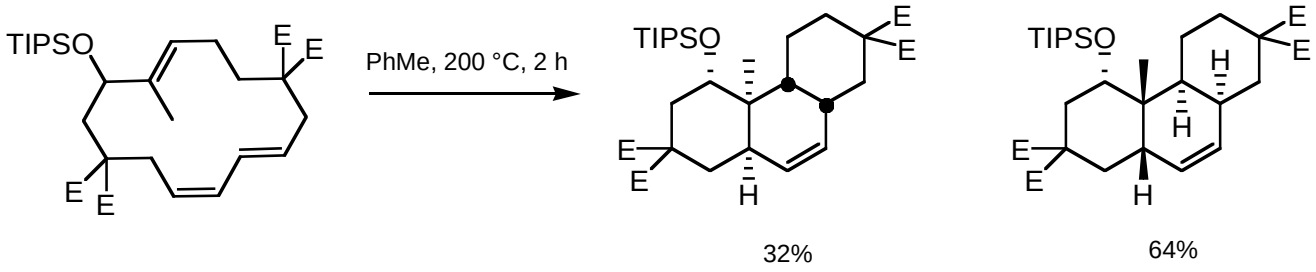
R = Me, 36%
R = MOM, 27%

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

Origin of the effect unclear: is it stereoelectronic?

Deslongchamps, *Bull. Soc. Chim. Fr.*, **1994**, *131*, 121.

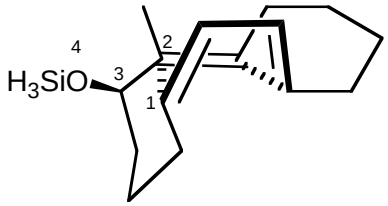
A Stereoelectronic effect?

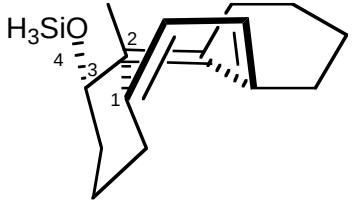


3.21G/3.21G* ab initio calcs:

Chair-Boat-Chair TS

-$OSiH_3$: axial
θ(1,2,3,4): 65°
contribution: 9%

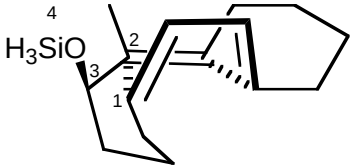


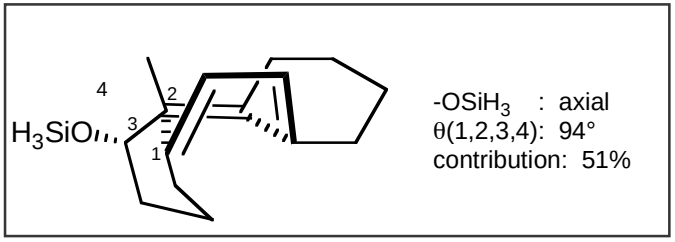


-$OSiH_3$: equatorial
θ(1,2,3,4): 173°
contribution: 15%

Boat-Boat-Chair TS

-$OSiH_3$: equatorial
θ(1,2,3,4): 152°
contribution: 25%





-$OSiH_3$: axial
θ(1,2,3,4): 94°
contribution: 51%

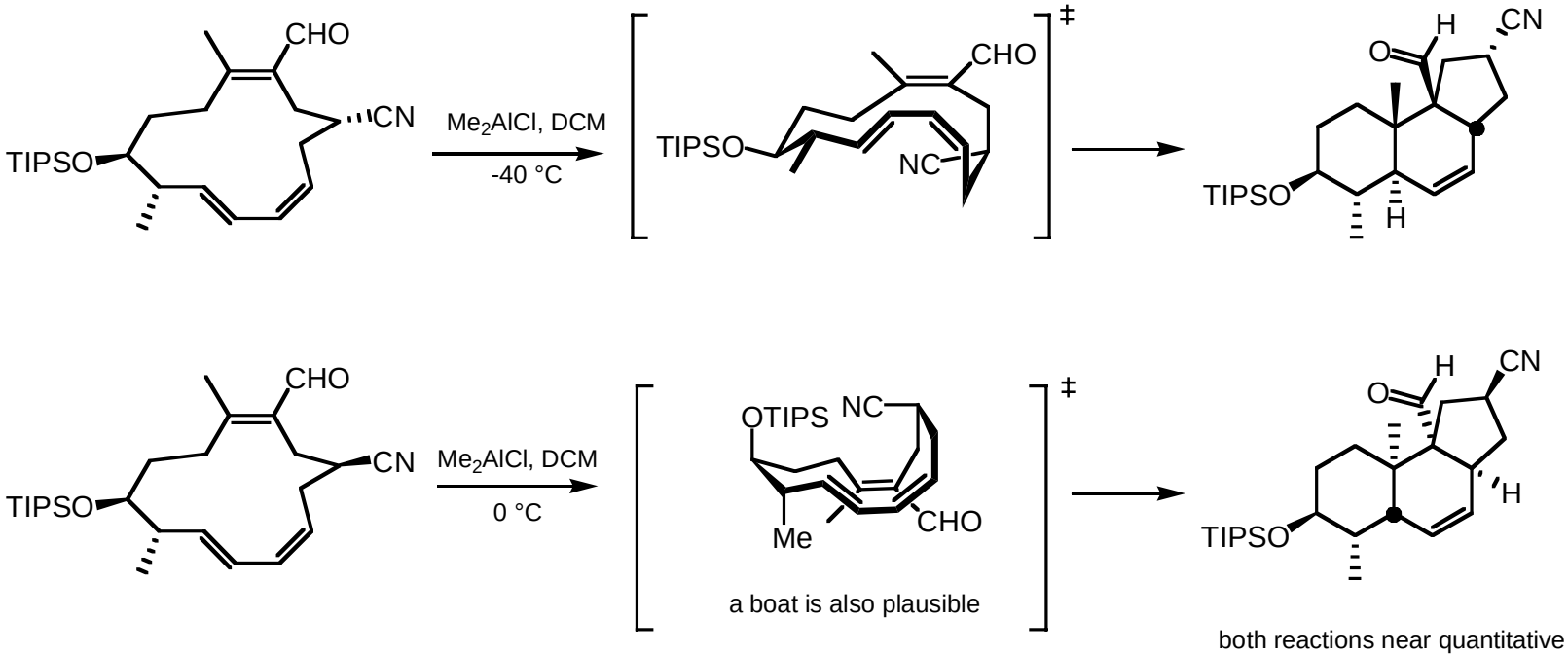
expected total: 34%

expected total: 66%

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

Deslongchamps, *Tet.*, **2000**, *56*, 5509.

Maritimol model studies: an electrostatic effect?



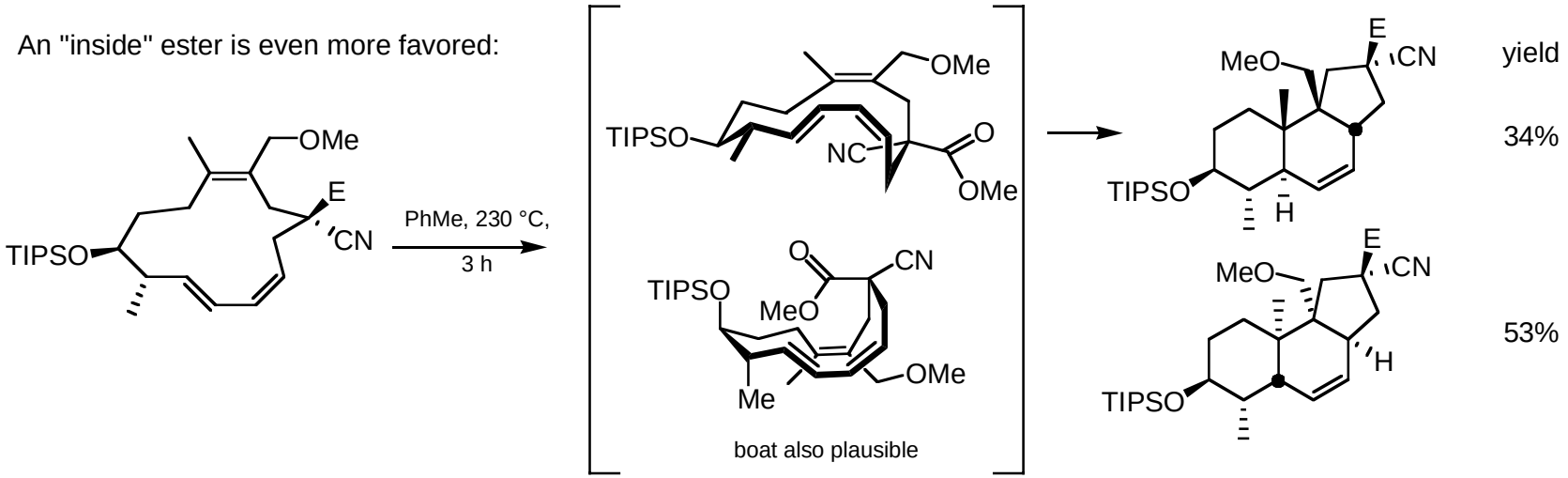
Gem-dicyano compound gave a 9:2 mixture favoring product of top transition state.

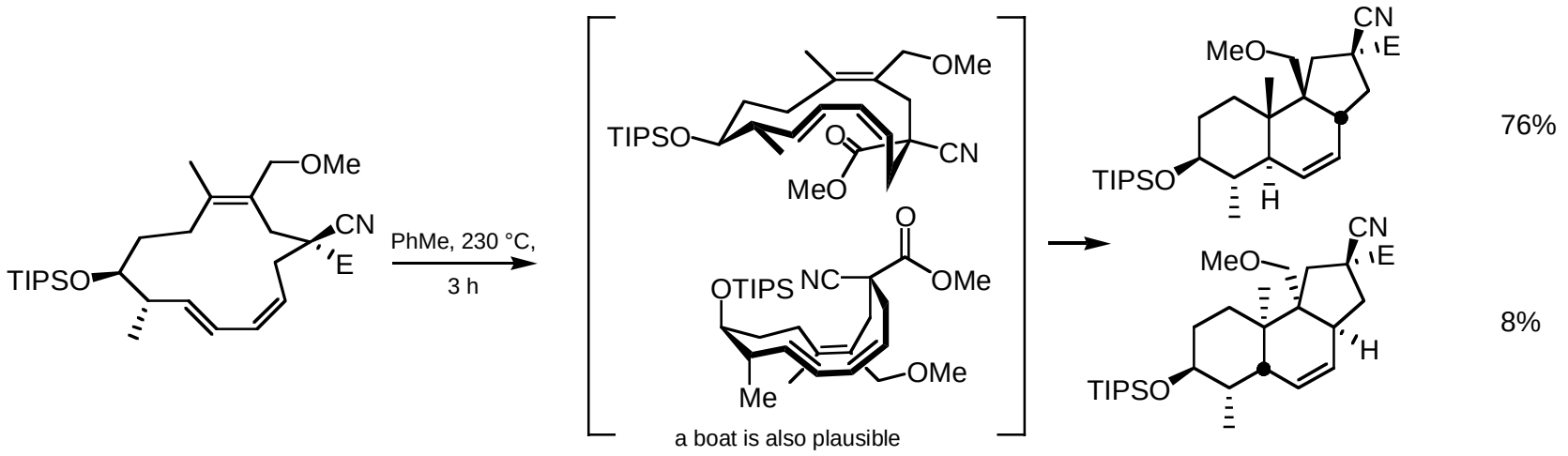
Charge separation in TS stabilized by cyano dipole?

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

Maritimol model studies: an electrostatic effect?

An "inside" ester is even more favored:

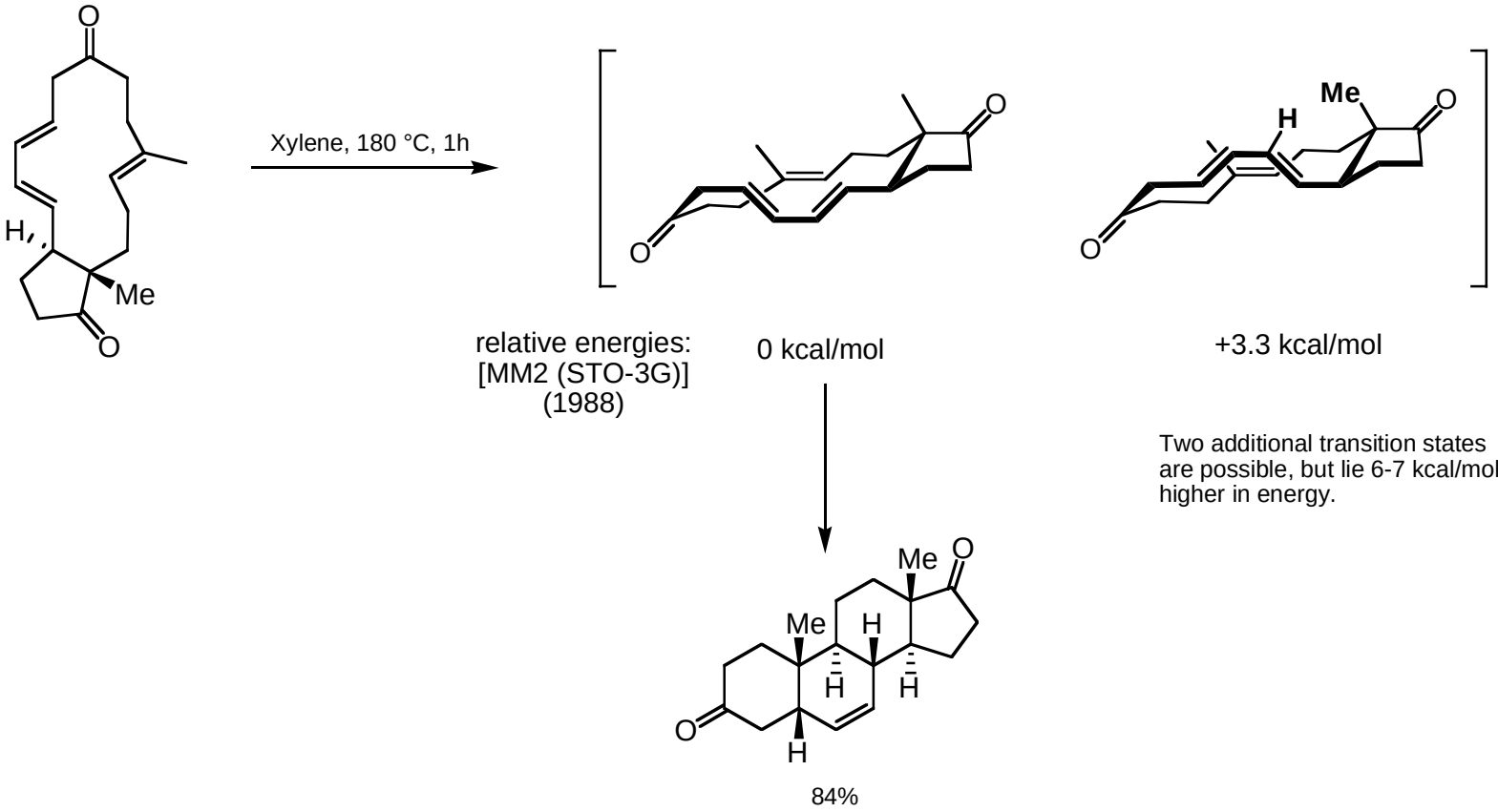




Given more synchronous TS, is an electrostatic explanation tenable?

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

TTT: Takahashi, Steroid ring system

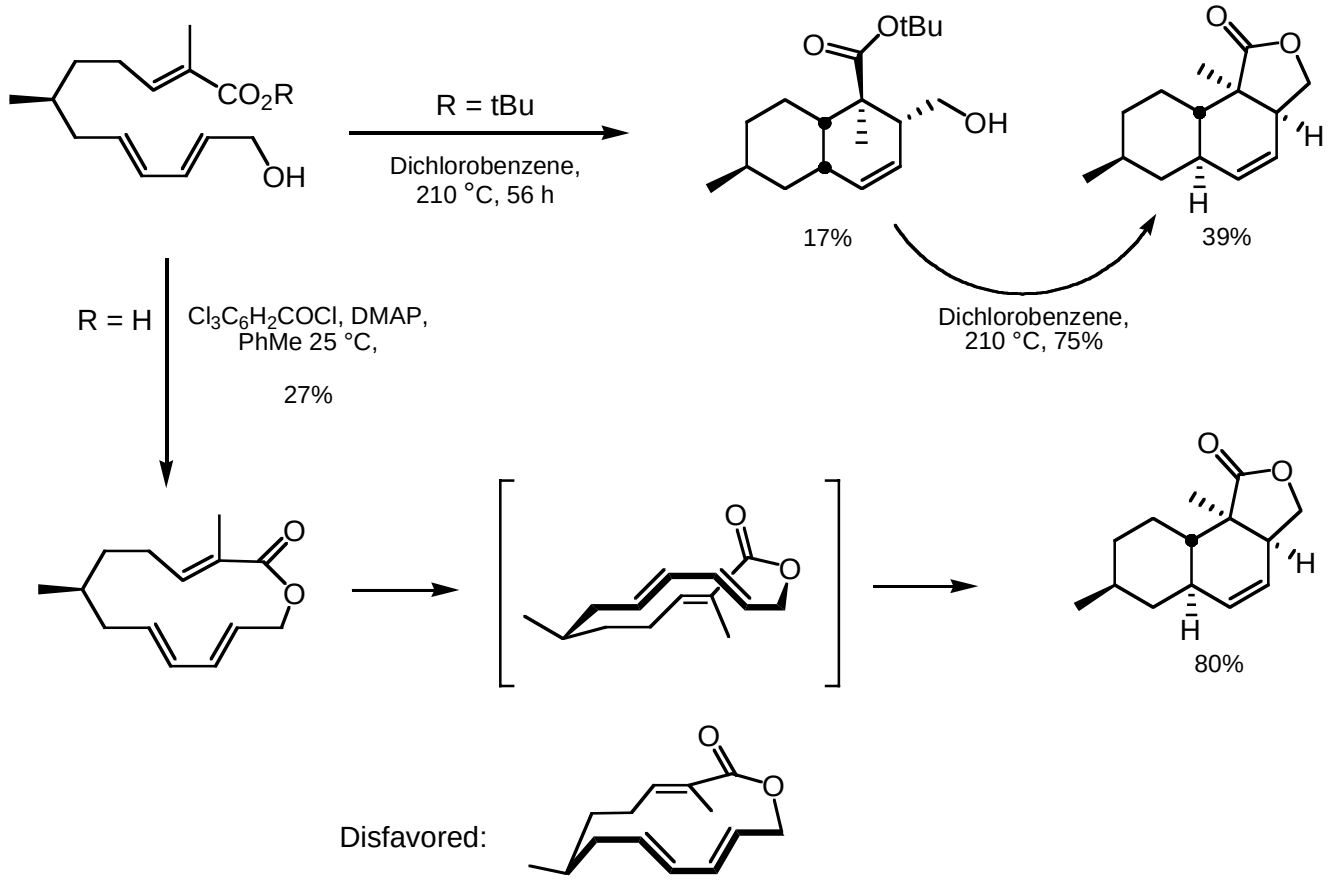


If macrocyclic ketone is replaced by $(CO_2Me)_2$, $(CN)_2$, or $(SO_2Ph)_2$, a mixture results:

Major product arises from opposite dienophile orientation.

Takahashi, T. *JACS*, 1988, **110**, 2674.
Deslongchamps, P. *Tet.*, **2001**, *57*, 2674.

TTT: Shing, Oblongolide A

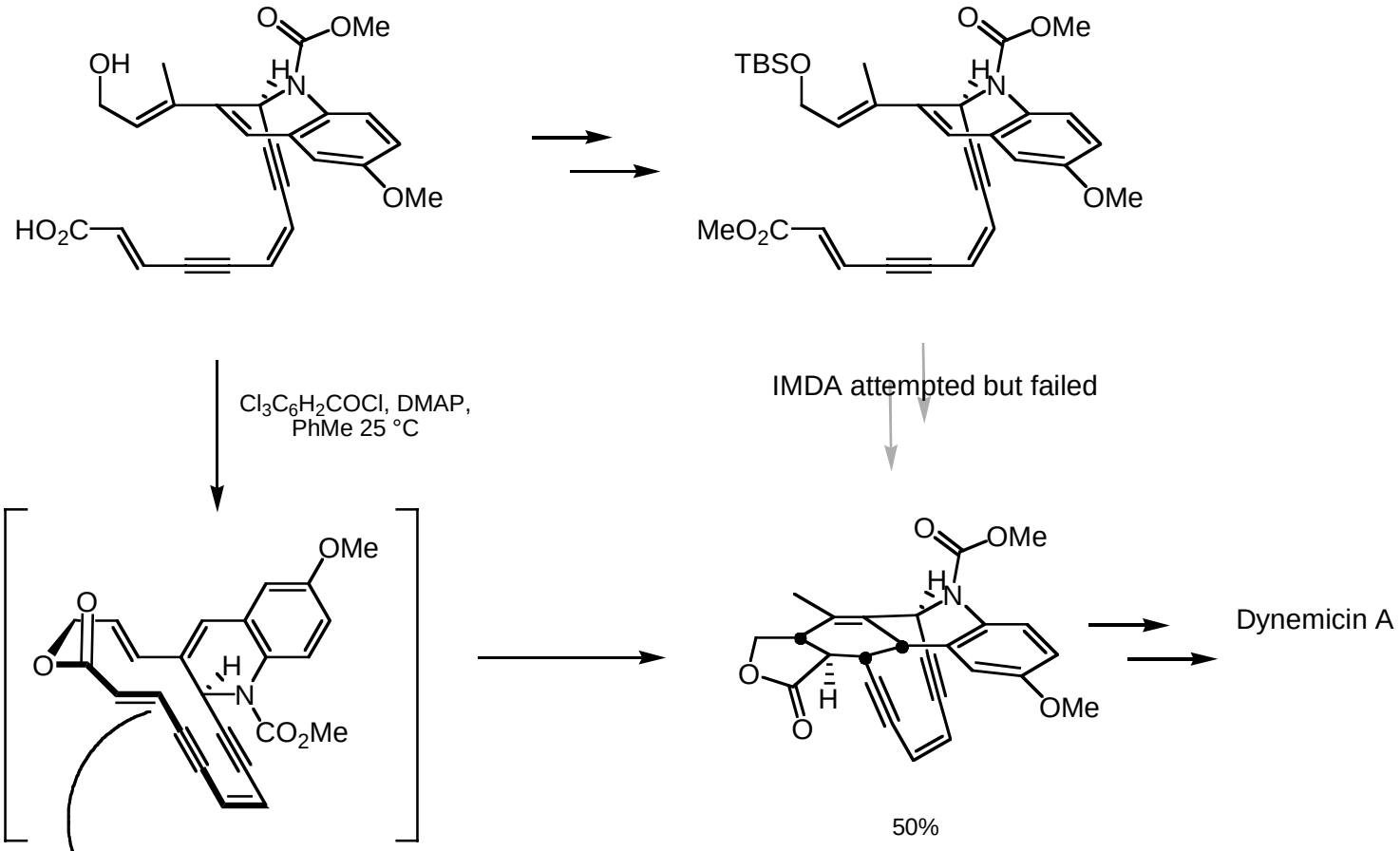


exo

diene/dienophile methyl
steric interaction

Shing, T.K. *JOC*, **1995**, *60*, 5785.

TTT: Schreiber, Dynemicin A

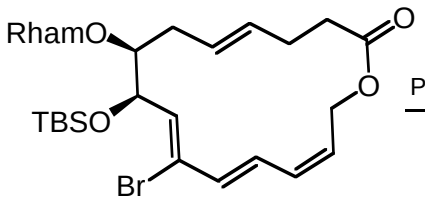


Macrocyclization could also be effected by Sonigashira coupling to form this bond.

Rigidity of ene-diyne and dihydroquinoline system leads to remarkably facile and selective reaction.

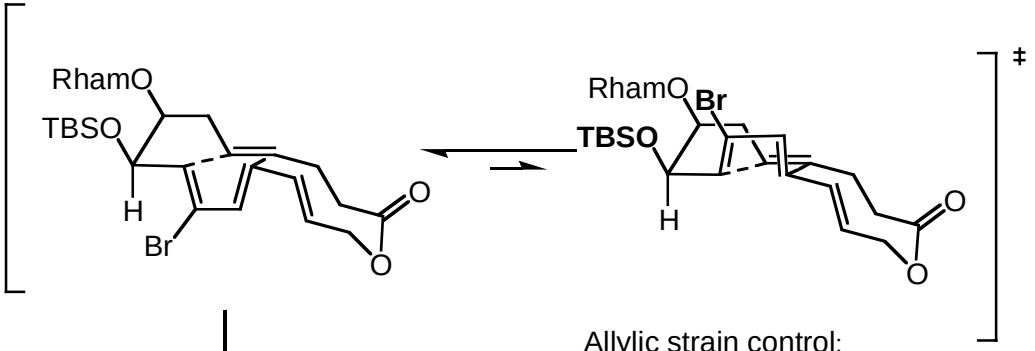
Schreiber, *JACS*, **1990**, *112*, 7411

TTT: Roush, Spinosyn A



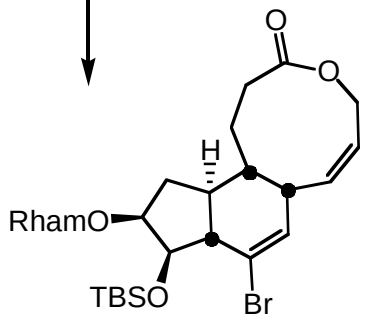
PhMe, 180 °C,

36 h



Allylic strain control:

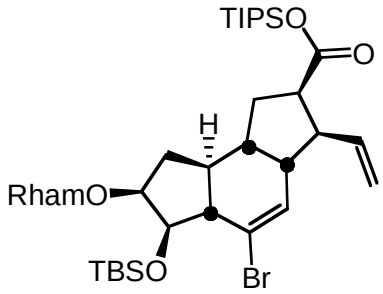
both -Br and -OTBS were added for this purpose; subsequently removed



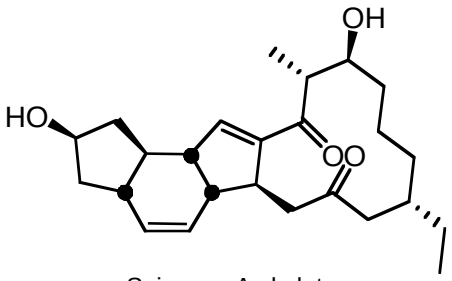
46%

(41% recovered SM)

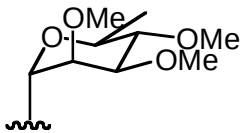
LiTMP, TIPSOTf,
DCM, rt, 48 h



53-71%



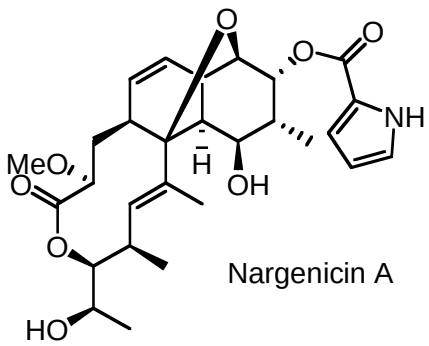
Spinosyn A skeleton



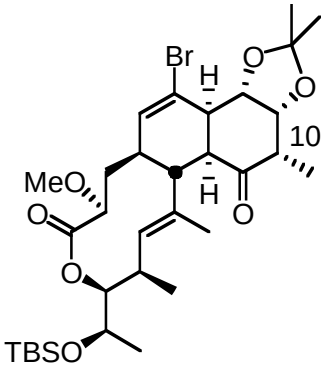
Rham = rhamnopyranosyl

Roush, *JOC*, **2002**, *67*, 4322.

TTT: Roush, Nargenicin A

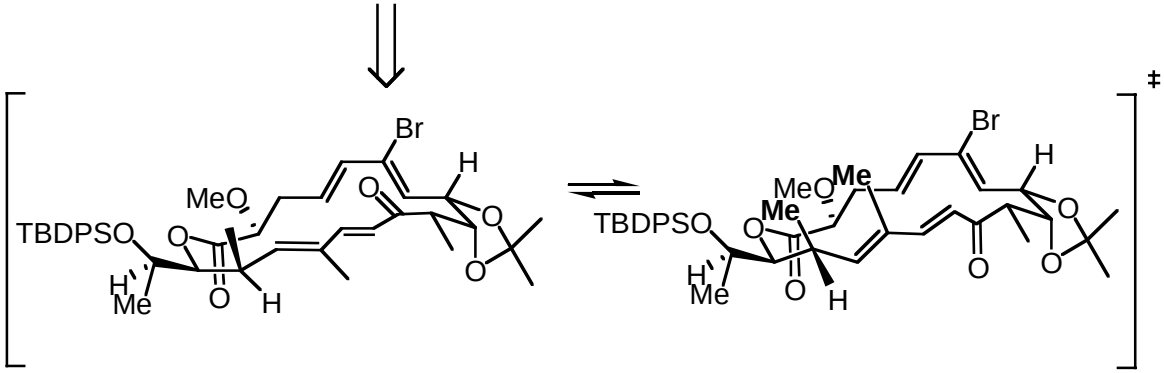


Nargenicin A



simplified target;

advanced intermediate?



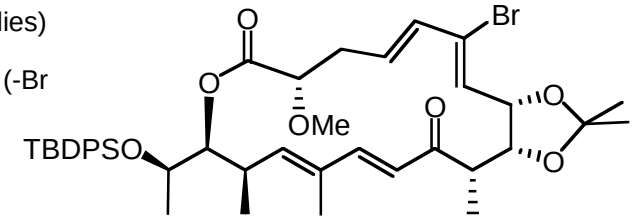
Left transition state was predicted to be favored:

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

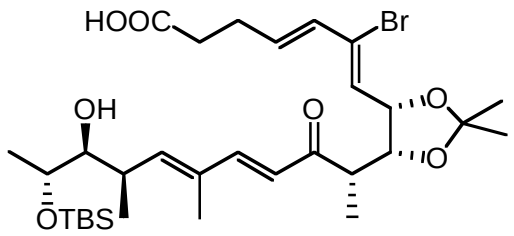
Endo Rule



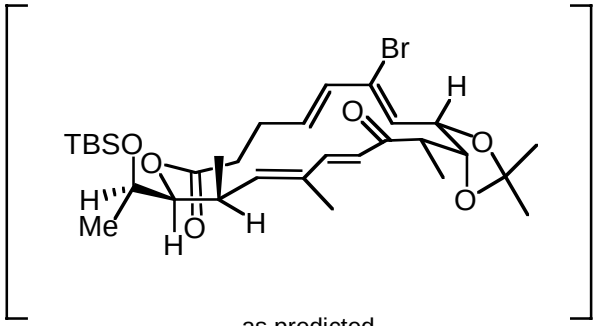
Roush, *JACS*, **1996**, *118*, 7502

TTT: Roush, Nargenicin A

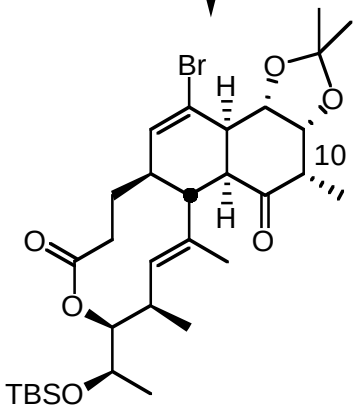
The target macrocycle, minus one stereocenter, was synthesized:



1. $Cl_3C_6H_2COCl$, NEt_3, DCM
2. DMAP, toluene, 100 °C



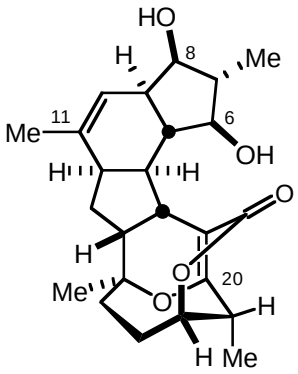
as predicted



63% (+13% C10 epimer)

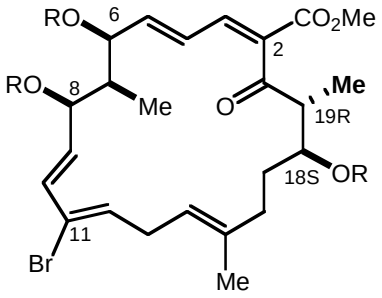
Roush, *JACS*, **1996**, *118*, 7502

TTT+CTT: Evans, FR182877



FR182877

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



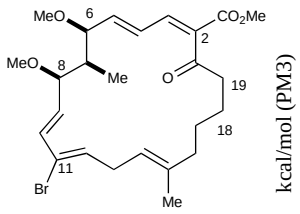
Which reaction starts the cacade?

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

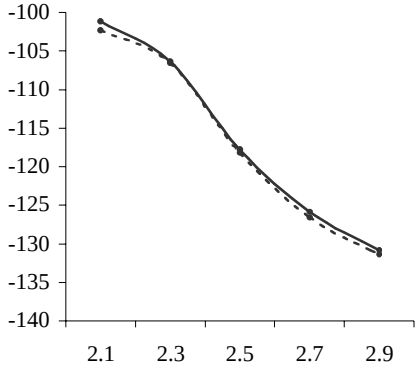
Evans, *JACS*, **2003**, *125*,13536.

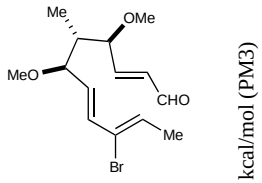
TTT: Evans, FR182877

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

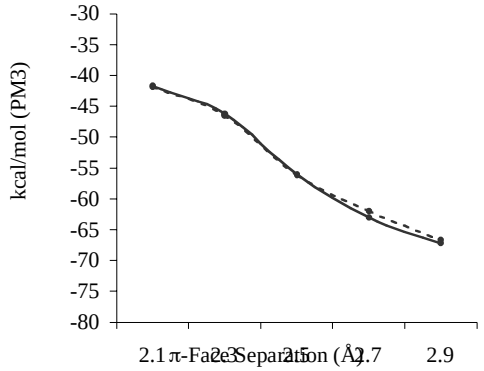


53; control TADA

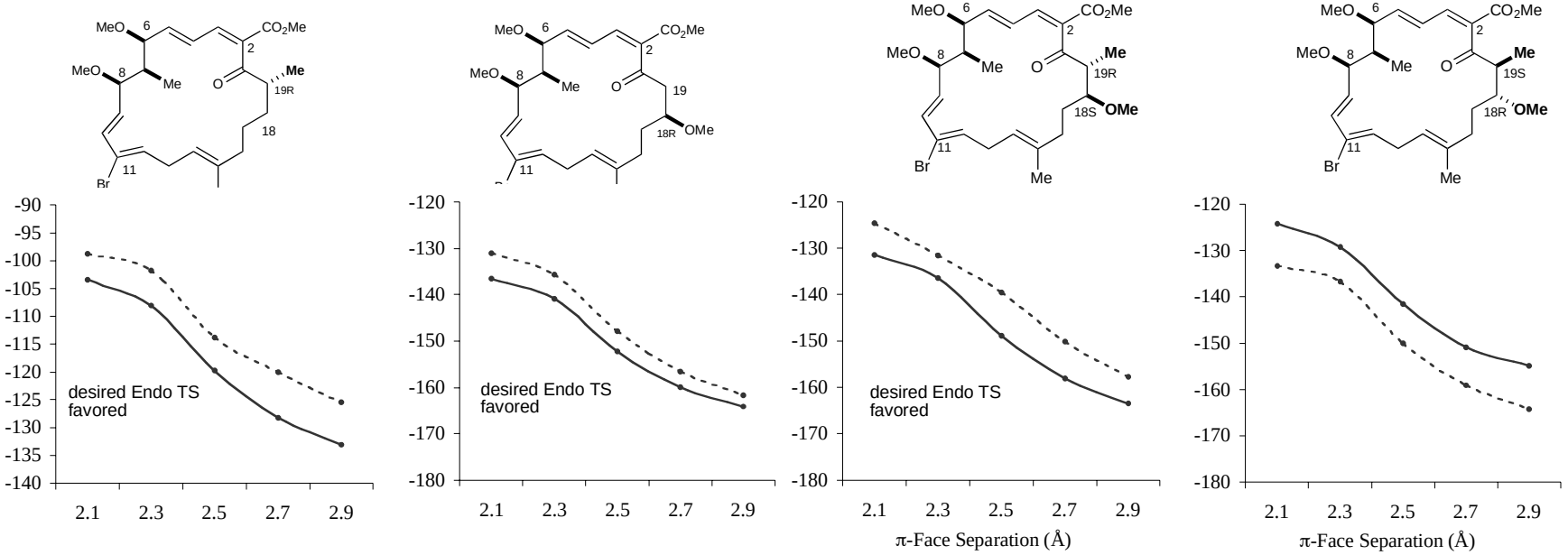




64; control IMDA

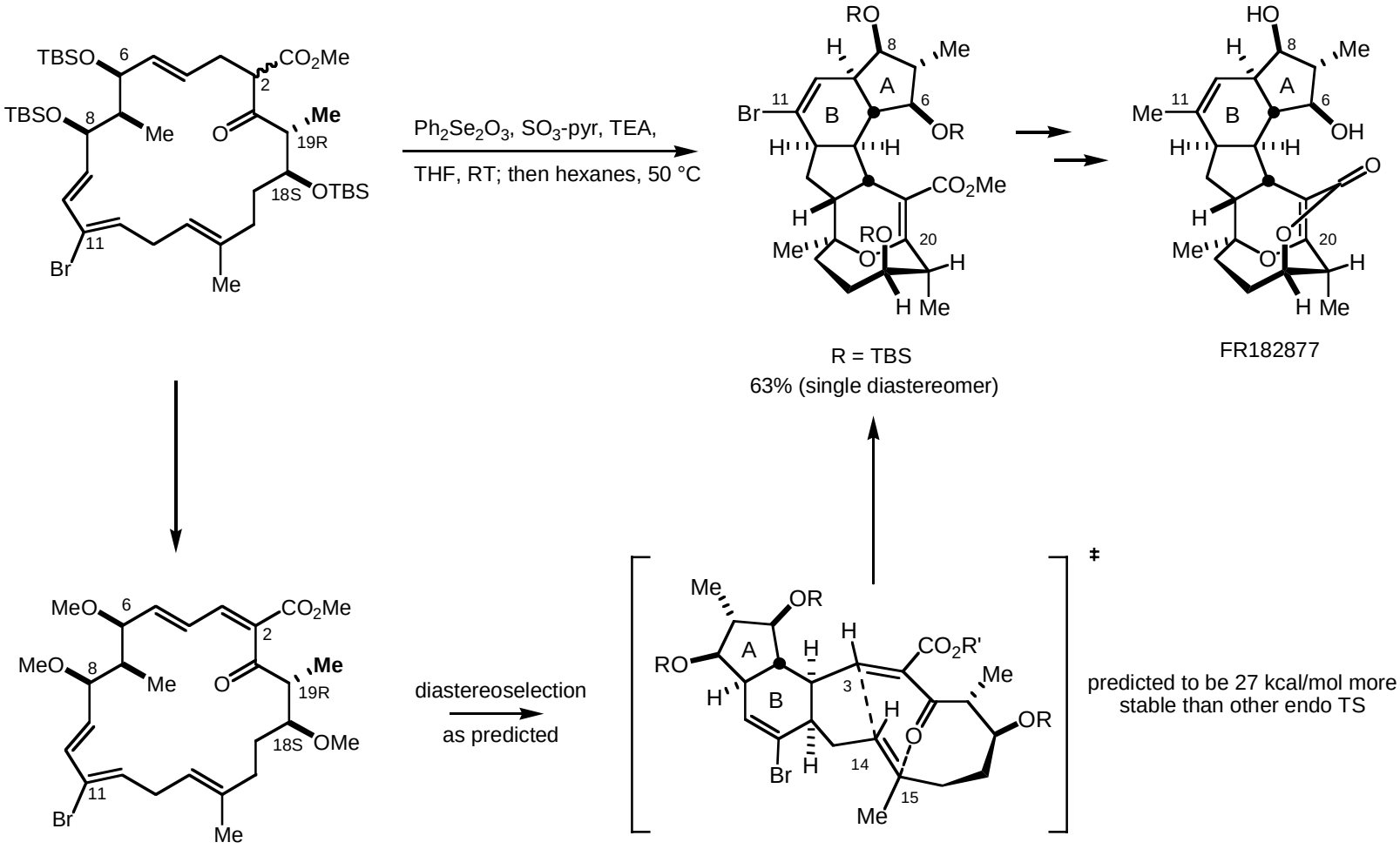


Stereocenters at C(19), C(20) should confer desired selectivity



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

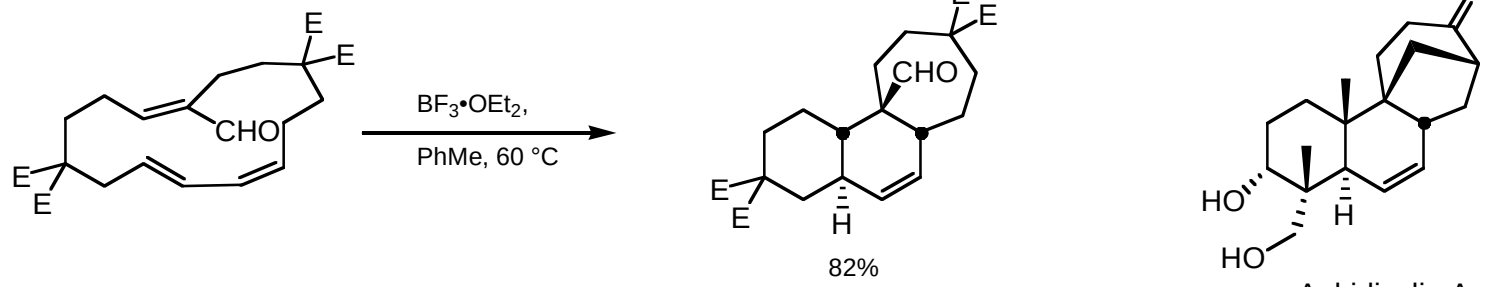
TTT+CTT: Evans, FR182877



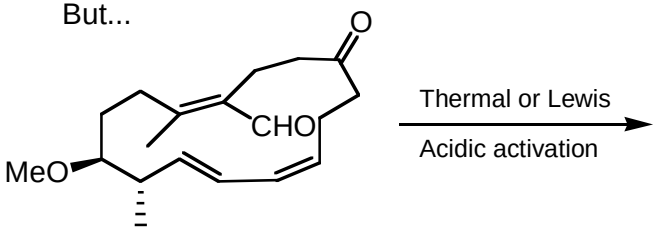
Evans, *JACS*, **2003**, *125*,13536.

CTC/TTC: Deslongchamps, Aphidicolin A

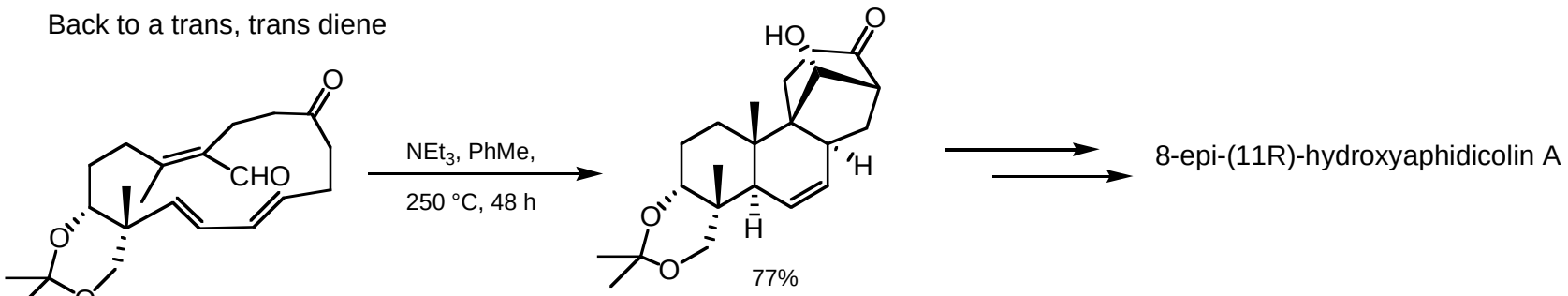
Model study success



But...



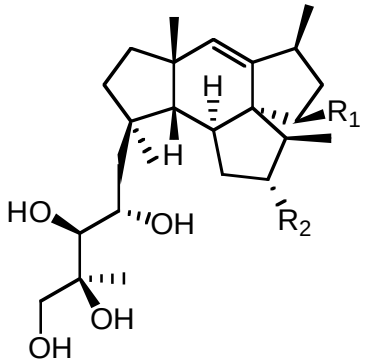
Back to a trans, trans diene



Endo Rule controlling factor?

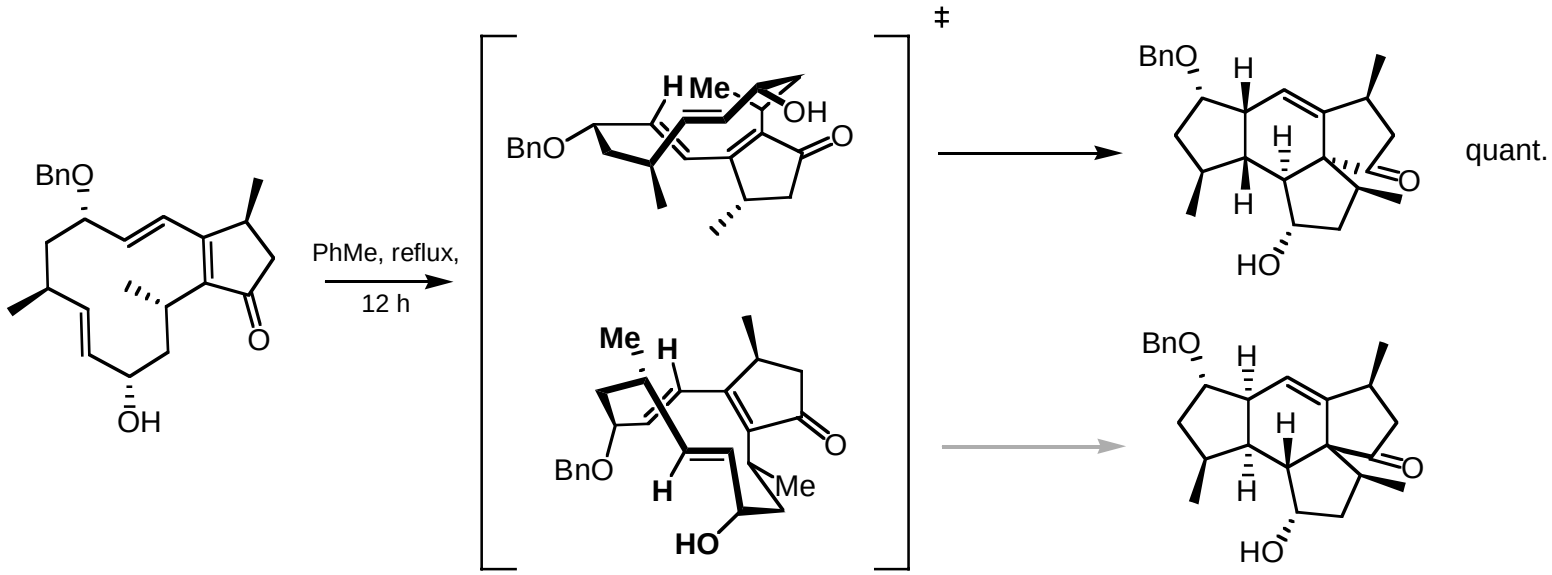
Deslongchamps, P. *Tet.*, **2003**, *59*, 2781.
Deslongchamps, P. *Tet.*, **2001**, *57*, 4243.

CTT: Uemura, Mangicol core



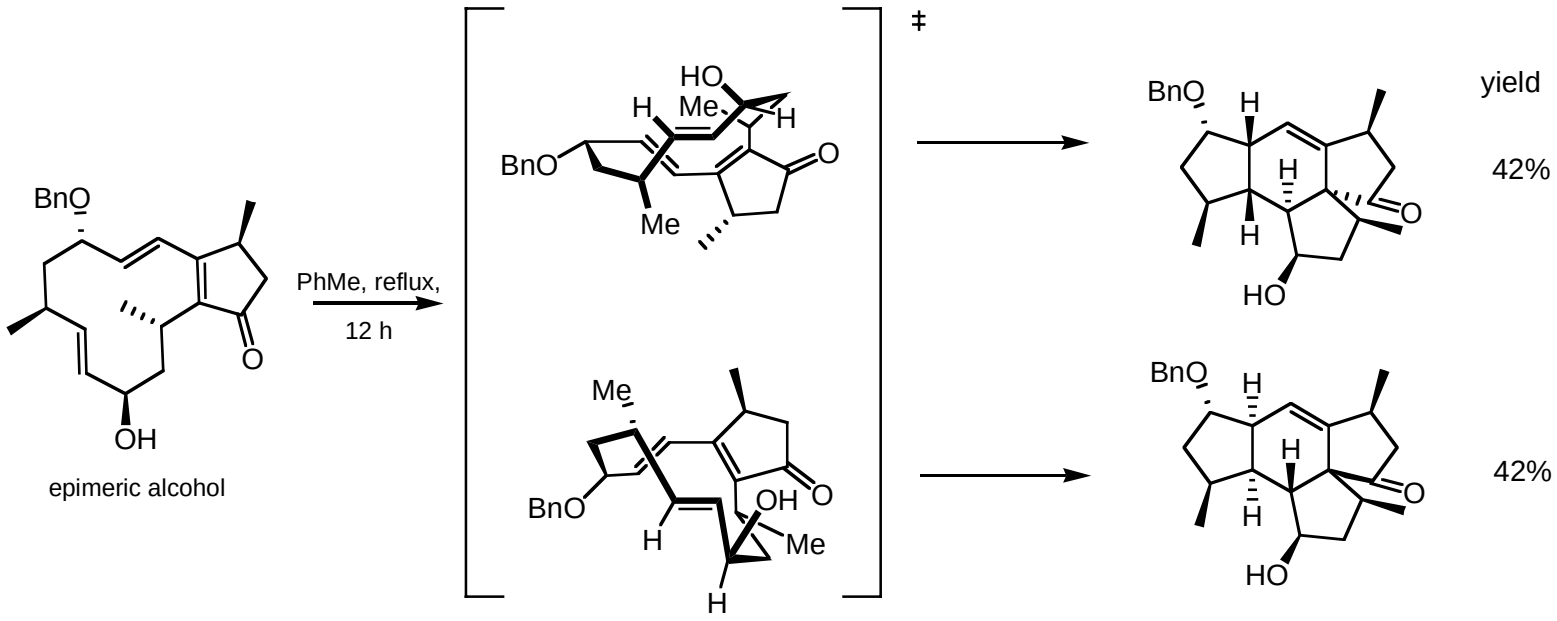
Mangicols

A: R_1 = OH, R_2 = H
B: R_1 = H, R_2 = OH
C: R_1 = R_2 = H



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

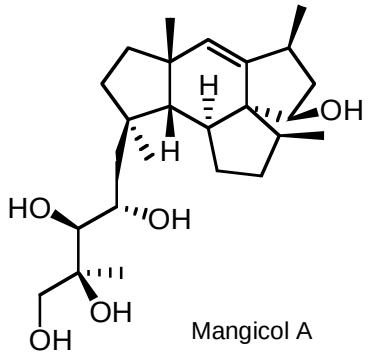
CTT: Uemura, Mangicols



Authors invoke steric argument to explain erosion in stereoselectivity

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

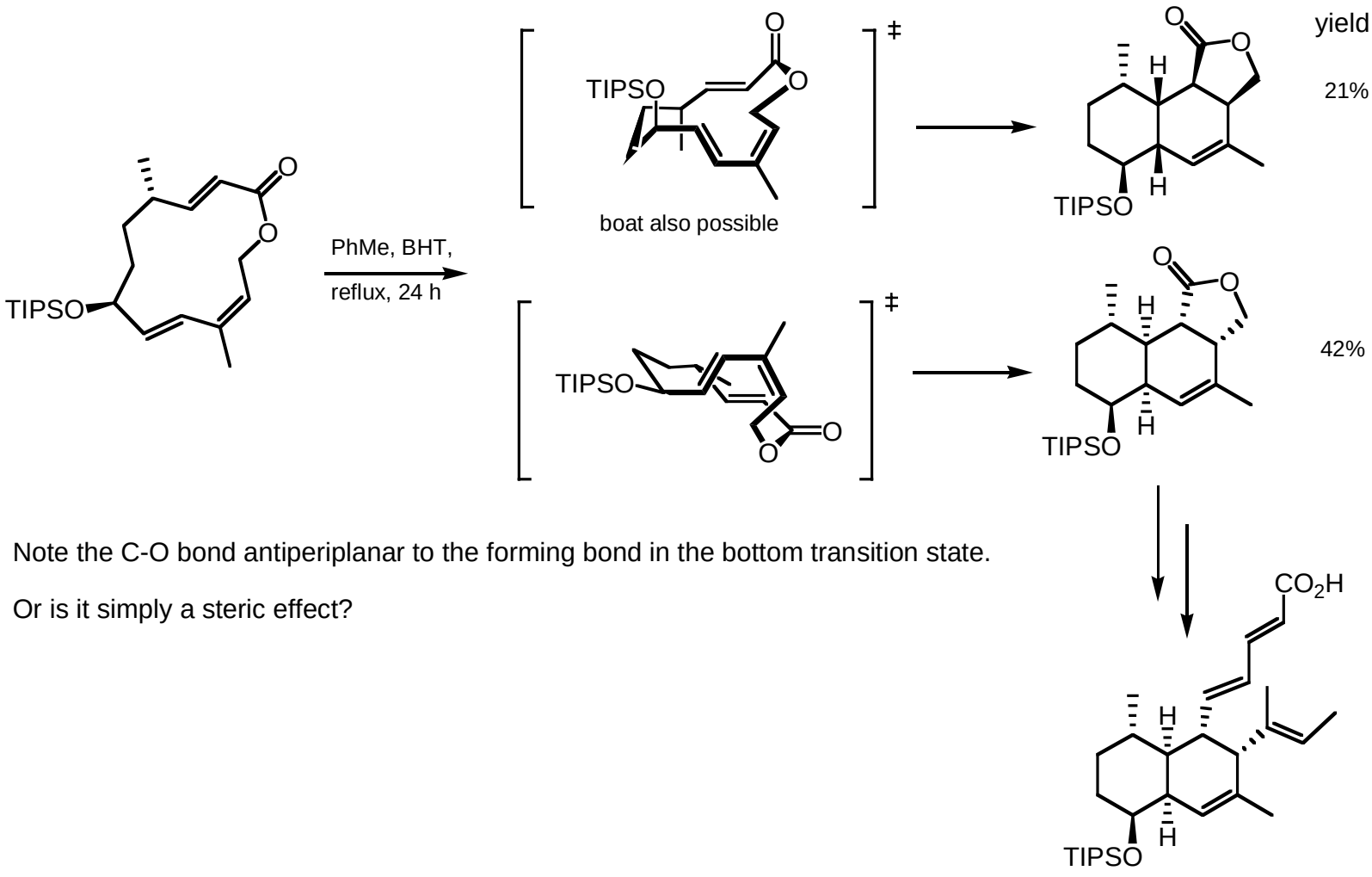
No experiments on the oxidized, activated dienophile?



Mangicol A

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

CTT: Nakada, Phomopsidin



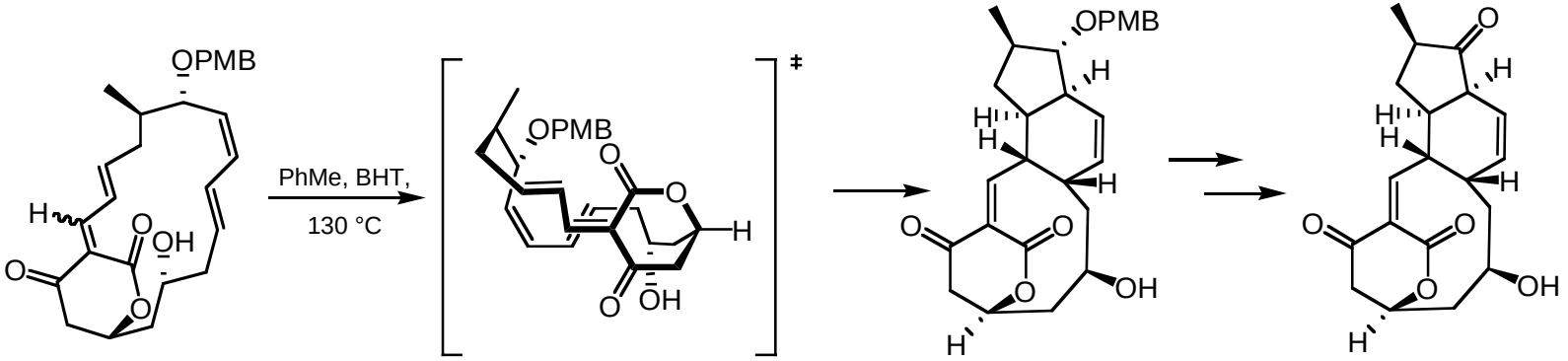
Phomopsidin A

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

Or is it simply a steric effect?

Nakada, M. *Org. Lett*, **2004**, *6*, 553.

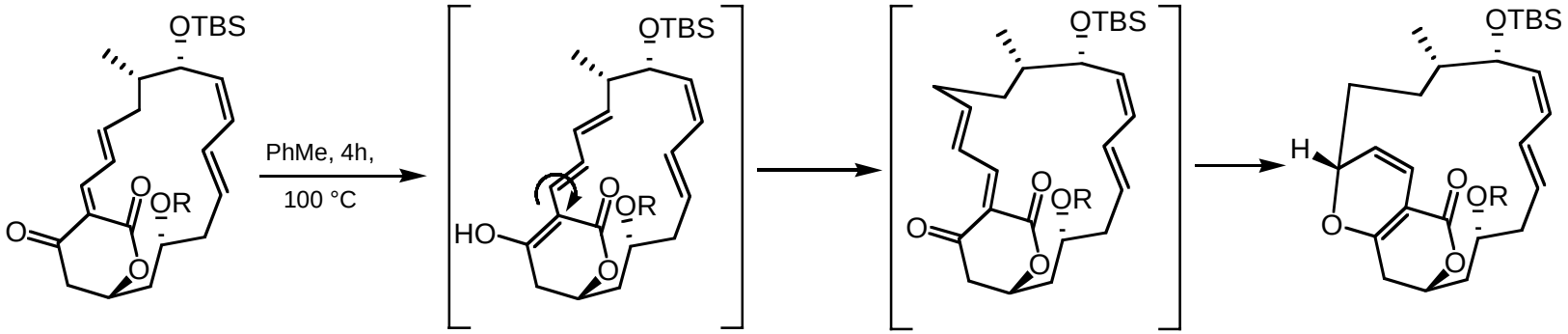
CTT: Tadano, Macquarimicin A



"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:

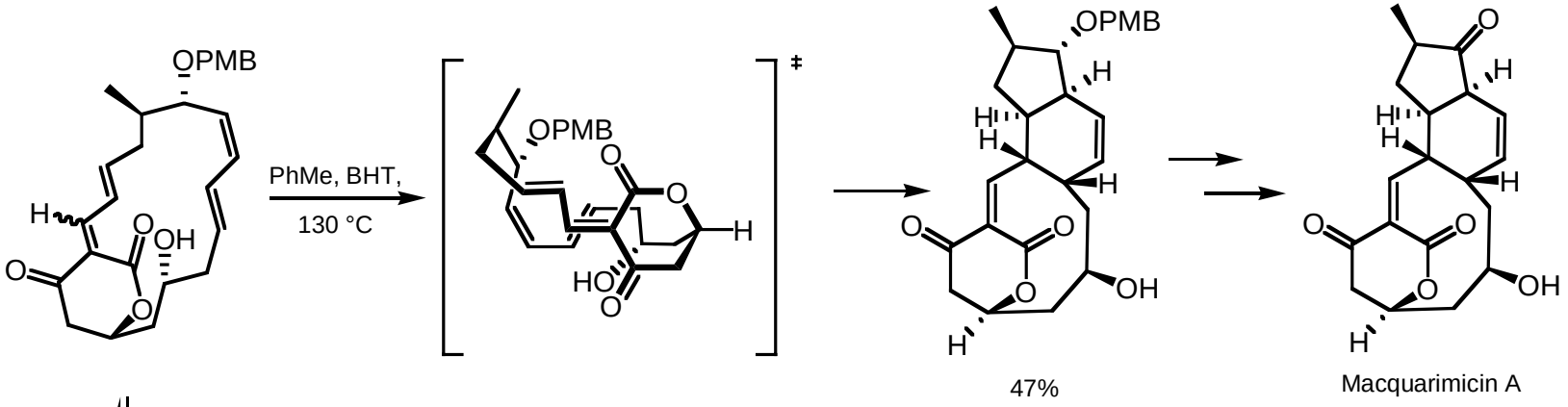


R = PMB

or adventitious nucleophile addition/elimination?

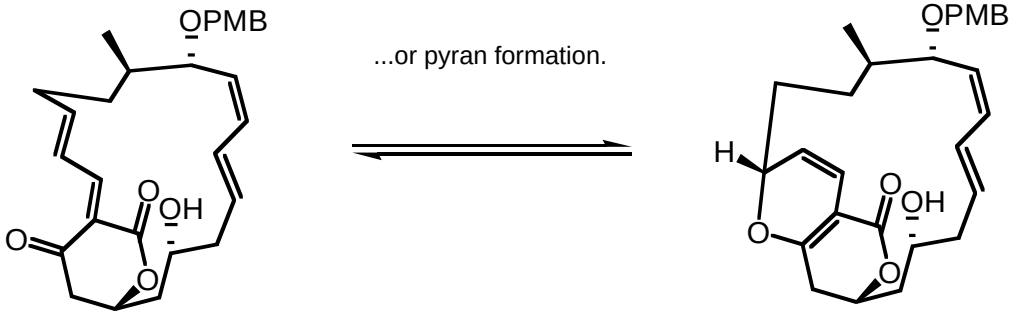
Beaver, Evans, unpublished.

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

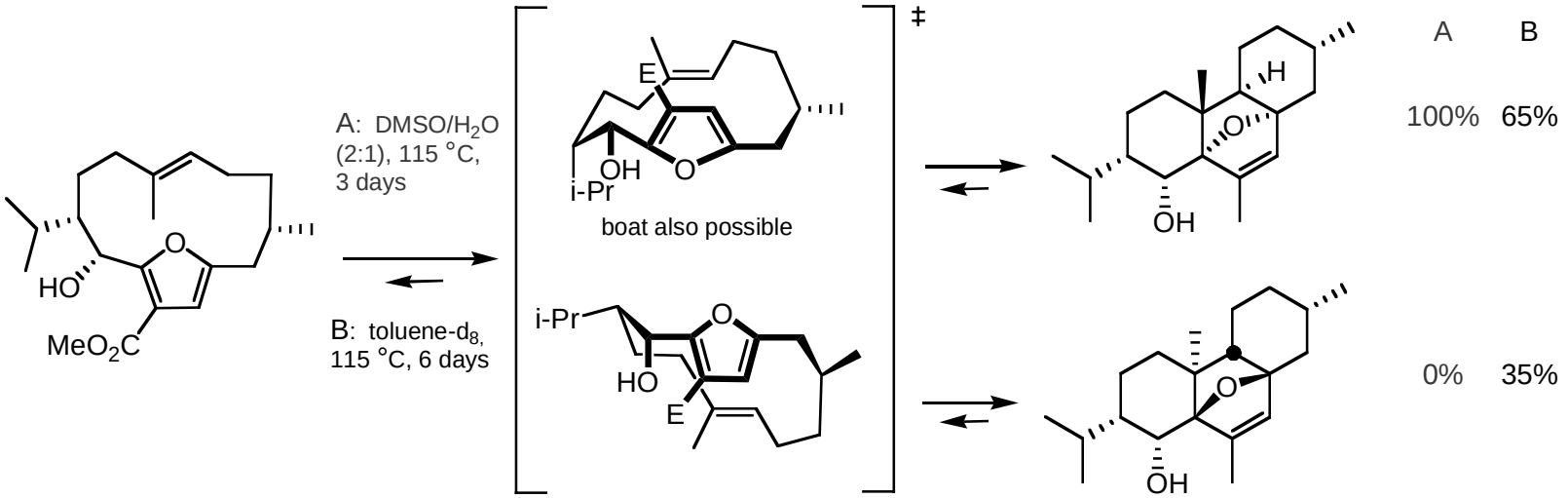


Reversibility in this case could result from:

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

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

Furan as diene: Deslongchamps, Chatancin

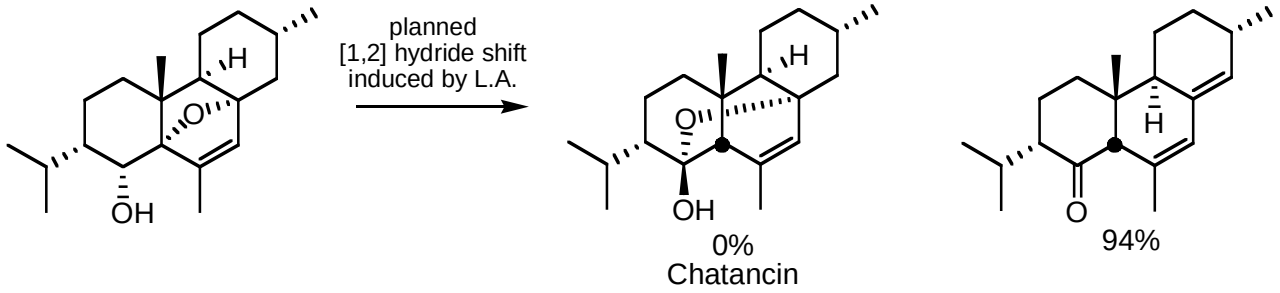


Solvent dependence may reflect disruption of intramolecular H-bond between alcohol and ester.

Diastereoselectivity not fully explained.

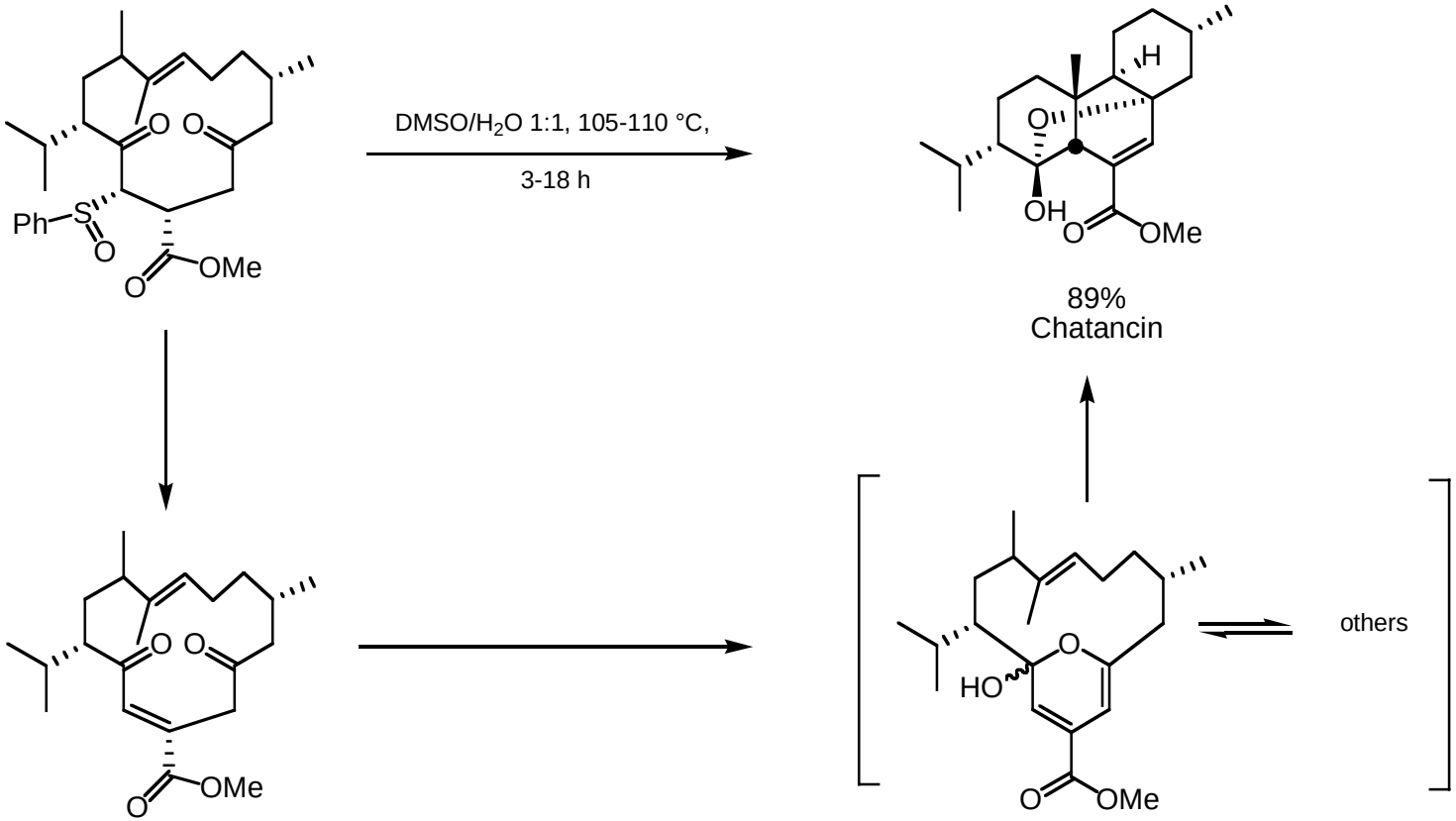
Note antiperiplanar -OH in top TS can be avoided by adopting a boat-like geometry.

Endgame strategy not viable:



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

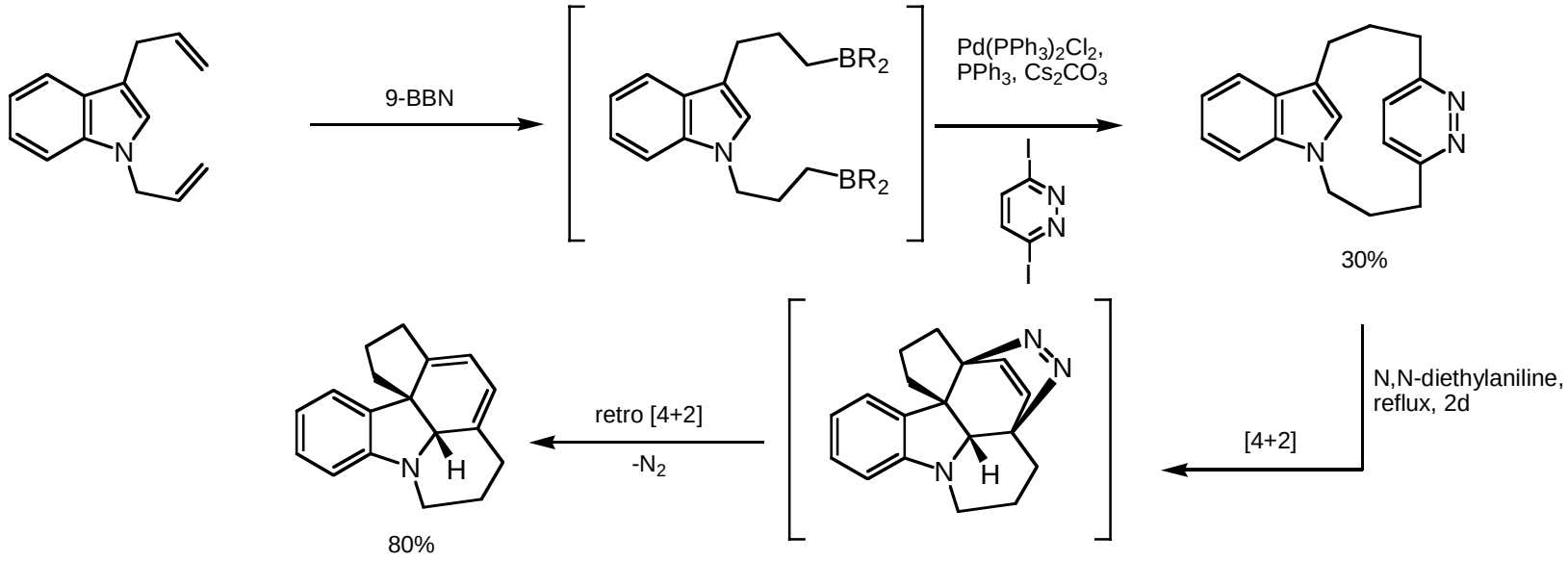
Pyran as diene: Deslongchamps, Chatancin



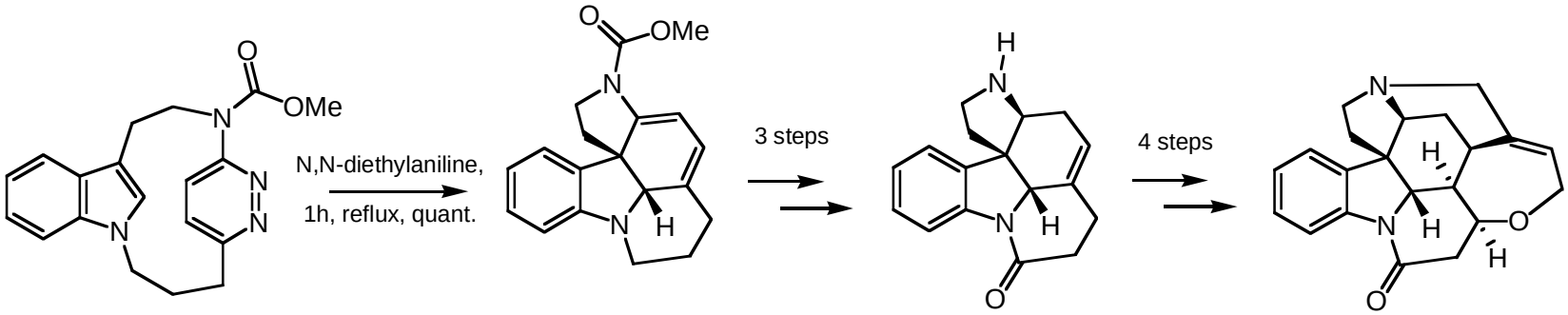
Deslongchamps. P. *JOC,* **2003**, *68*, 9983

Cyclophanes as TADA Substrates: Strychnine

Model system

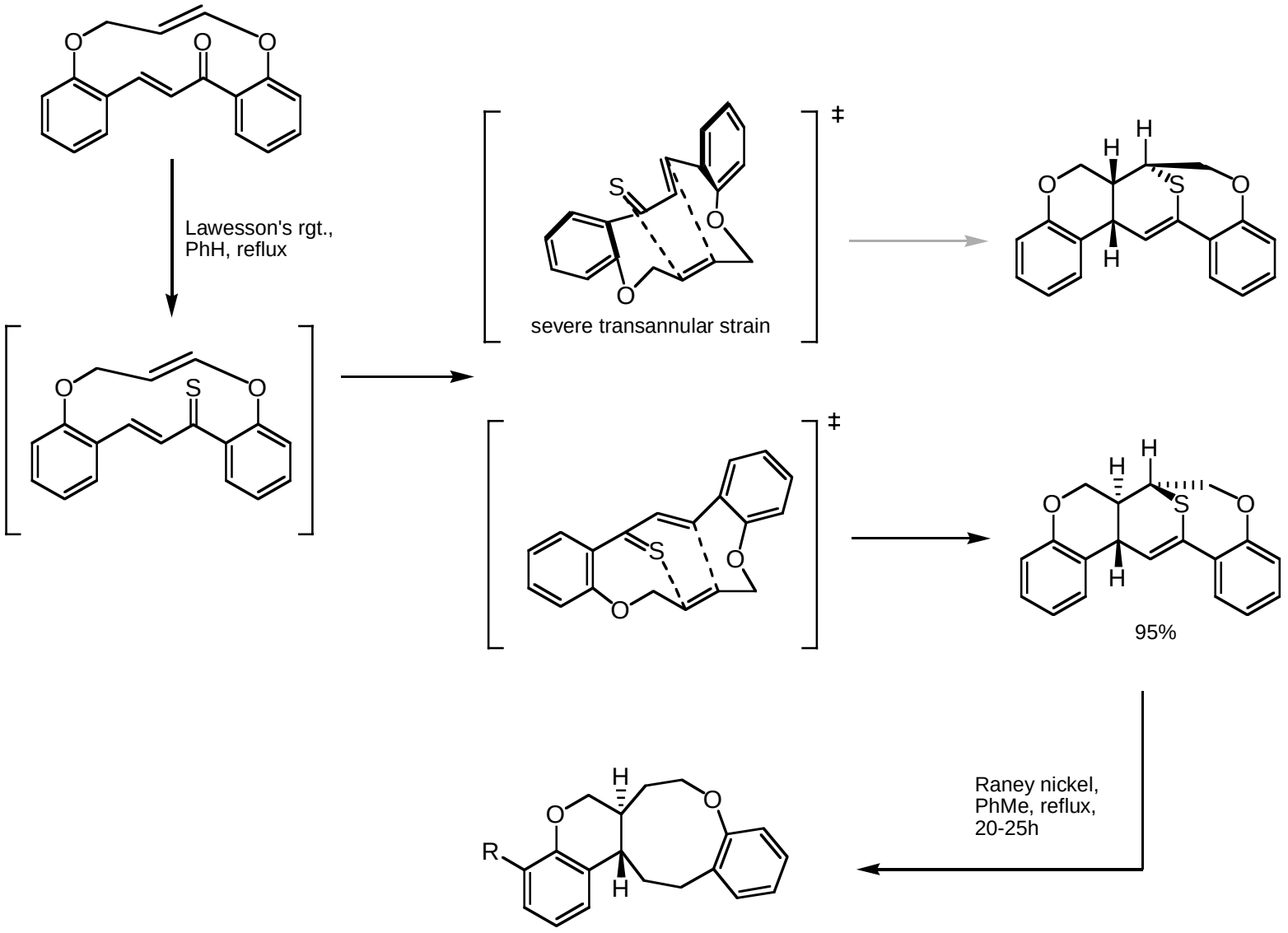


Formal synthesis of strychnine in 12 steps



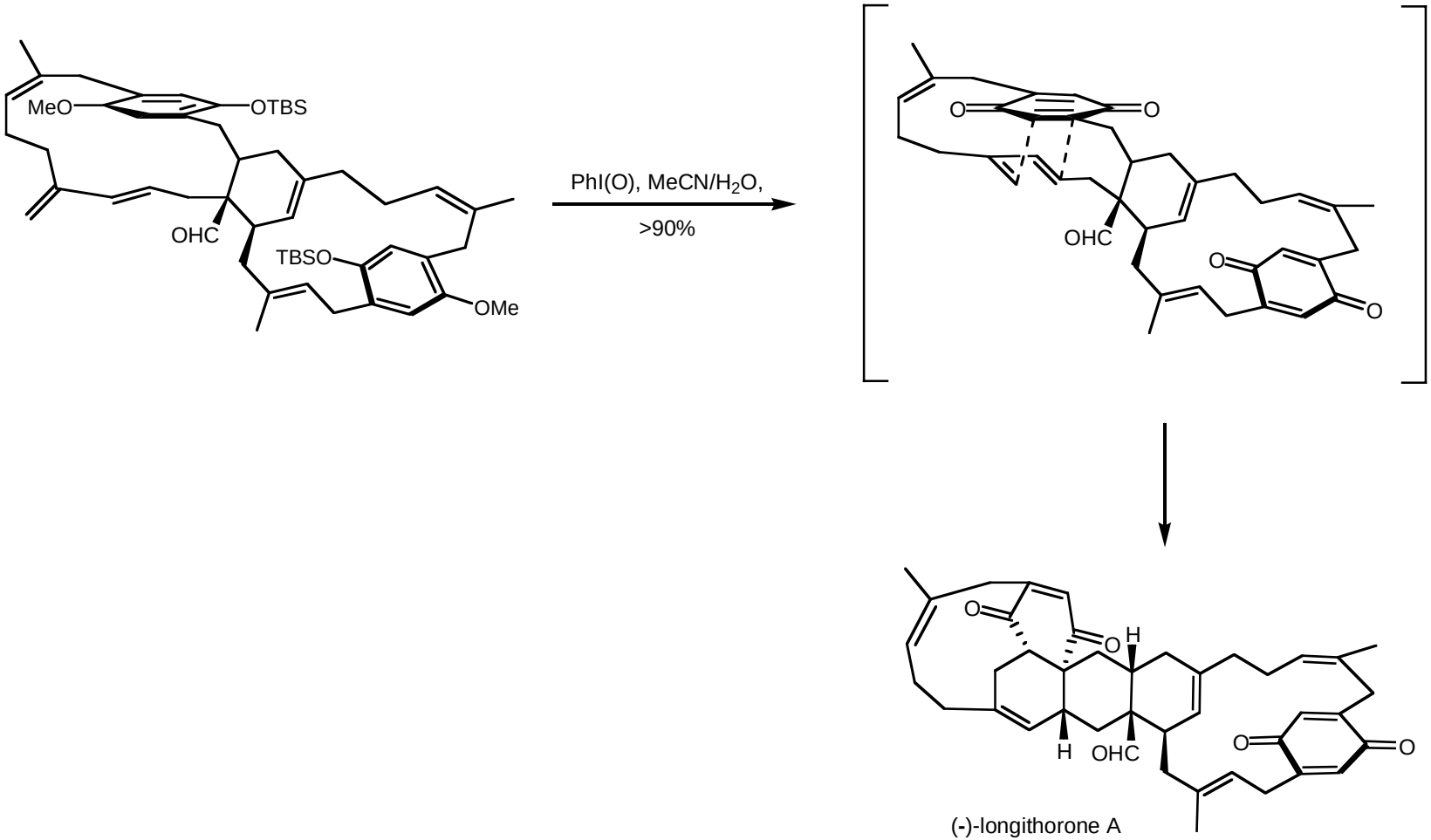
Bodwell, G.J. *ACIEE*, **2002**, 41, 3261
Bodwell, G.J. *Org. Lett.*, **2002**, 4, 127.

Type II TADA: an approach to oxonins



Saito, T., *Synlett*, **1996**, 72

Type II TADA: Longithorone A



Shair, *JACS*, **2002**, 124, 773