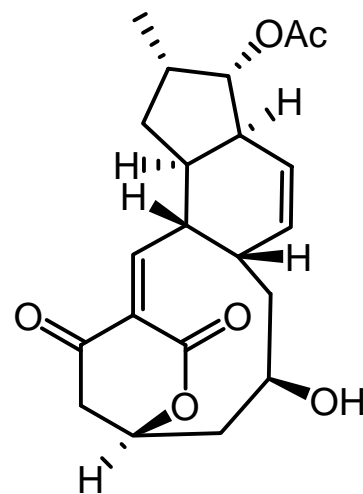


Macquarimicin A



Cochleamycin A

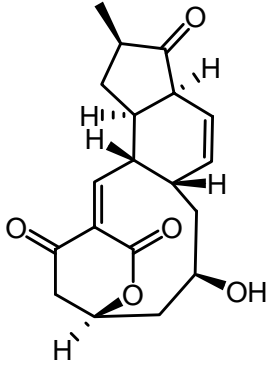
Approaches to the Synthesis of Macquarimicins and Cochleamycins

Drew Adams

Friday Seminar

March 18, 2005

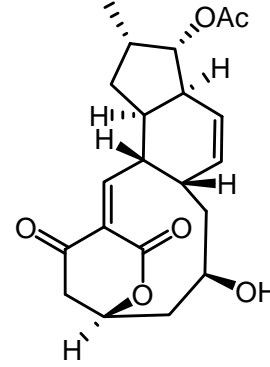
Isolation and Activity



Isolated in 1995 from *Micromonospora* bacteria
 Macquarie University, Sydney, Australia
 Weak activity against anaerobes
 Cytotoxic against P388 leukemia line (0.3 $\mu\text{g/ml}$)
 Selective but weak activity against N-SMase,
 as outlined below

Macquarimicin A

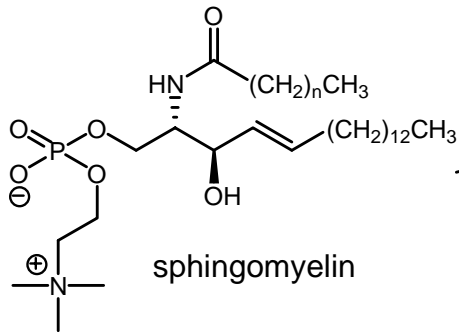
Jackson, M. *J. Antibiotics*, **1995**, *48*, 462-470.
 Ogita, T. *J. Antibiotics*, **1999**, *52*, 670.



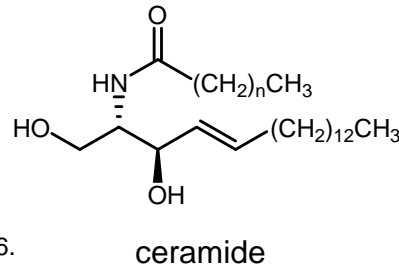
Isolated in 1992 from *Streptomyces* bacteria
 Nishimeya-cho, Aomori, Japan
 Weak activity against Gram-positive bacteria
 Cytotoxic against a variety of tumor lines

Cochleamycin A

Shindo, K. *J. Antibiotics*, **1996**, *49*, 241-252.



Neutral, Mg^{++} -dependent
 Sphingomyelinase



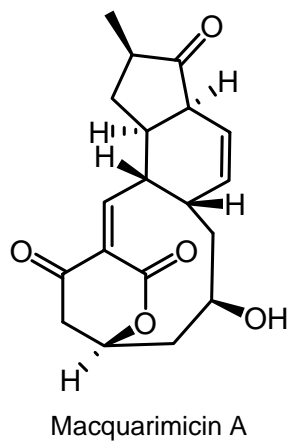
IL-1 β , PGE₂

inflammation
 cell proliferation
 apoptosis

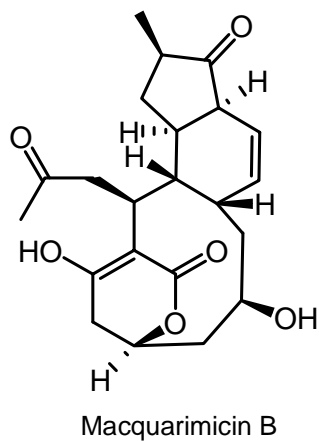
For more on ceramide signalling pathways:

Ogita, T. *J. Antibiotics*, **1999**, *52*, 531.
 Ohanian, J. *Cell. Mol. Life Sci*, **2001**, *58*, 2053.
 Andrieu-Abidie, N., *Biochim. Biophys. Acta*, **2002**, *1585*, 126.

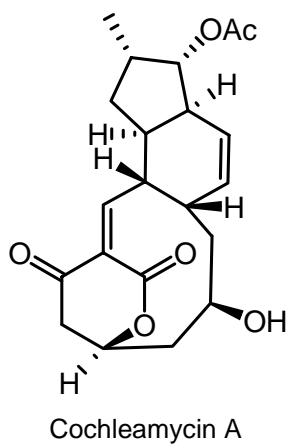
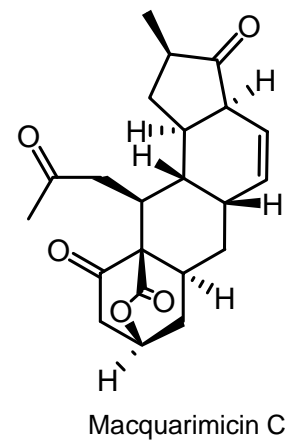
Derivatives



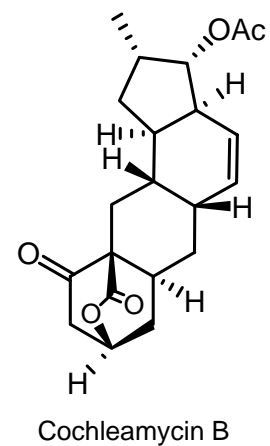
Michael Reaction



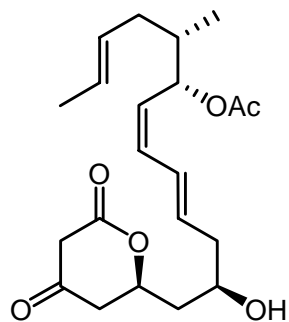
S_N2 alkylation



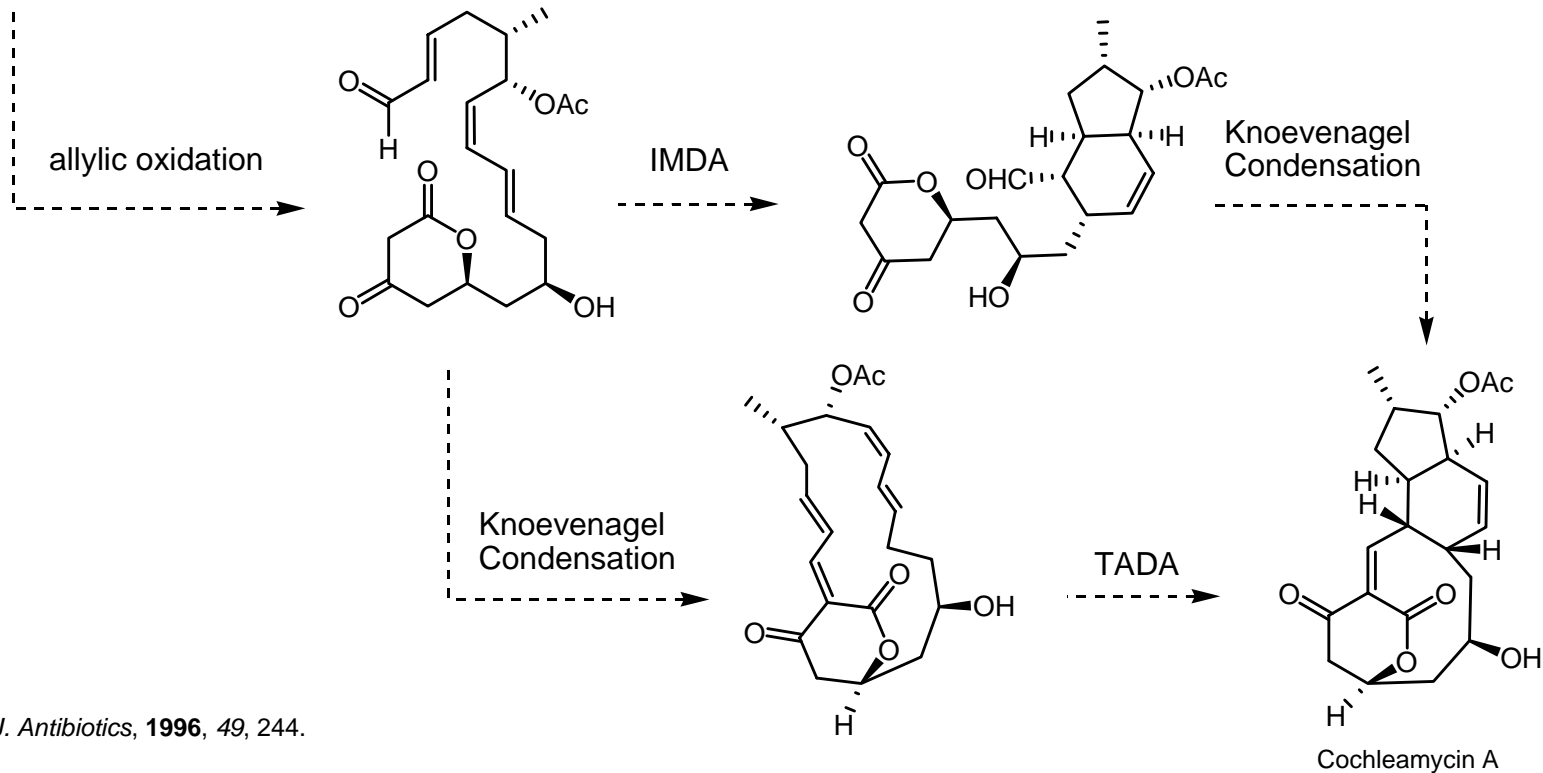
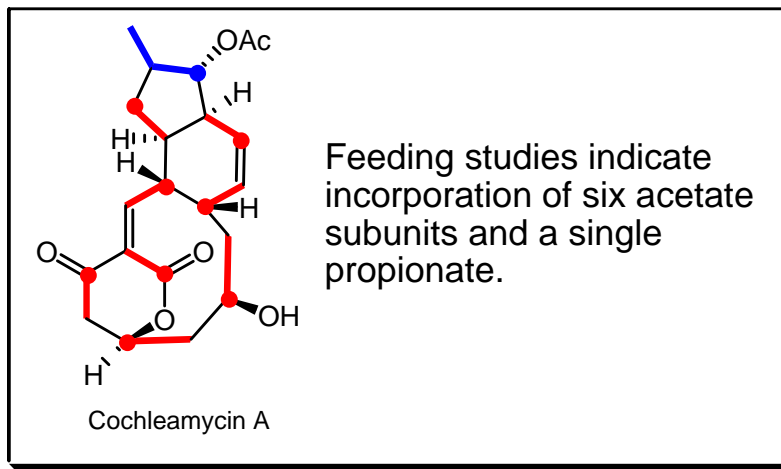
Reduction;
S_N2 alkylation



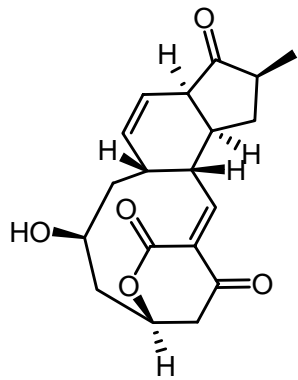
Biosynthetic Proposal



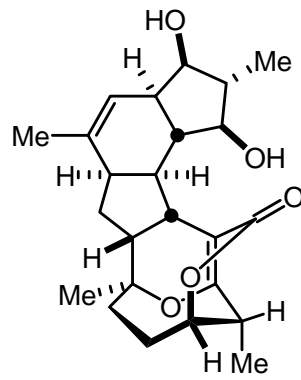
linear polyketide precursor



Biosynthetic Proposal, Tested

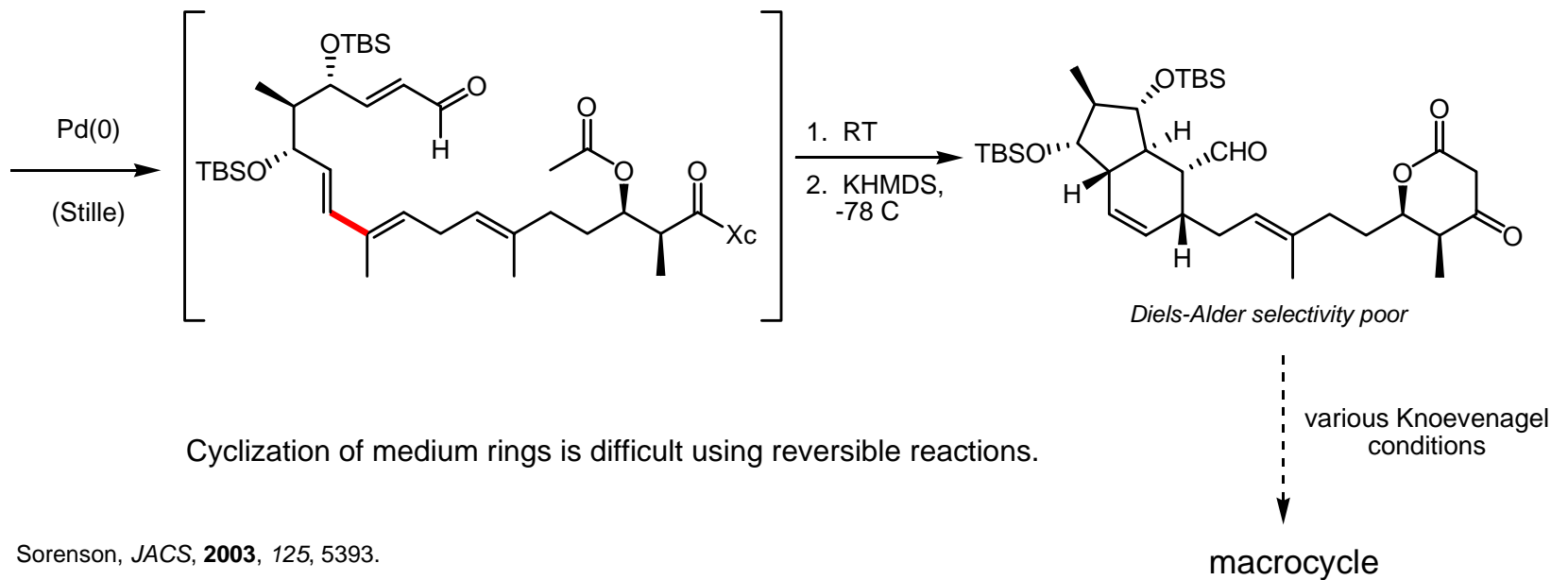
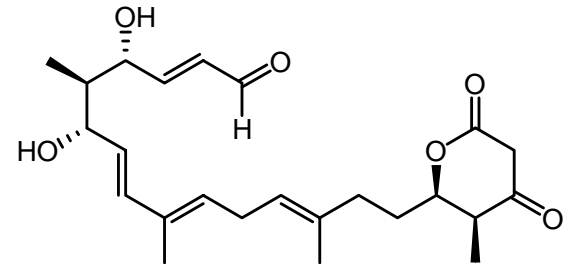
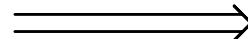


Macquarimicin A

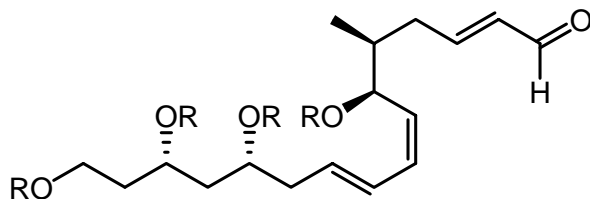


FR182877

(see also Hexacyclinic Acid)



A Summary of Approaches



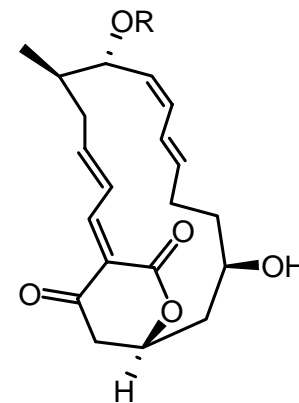
IMDA

Tatsuta (2003, Cochleamycin)

Roush

Tadano

Paquette



TADA

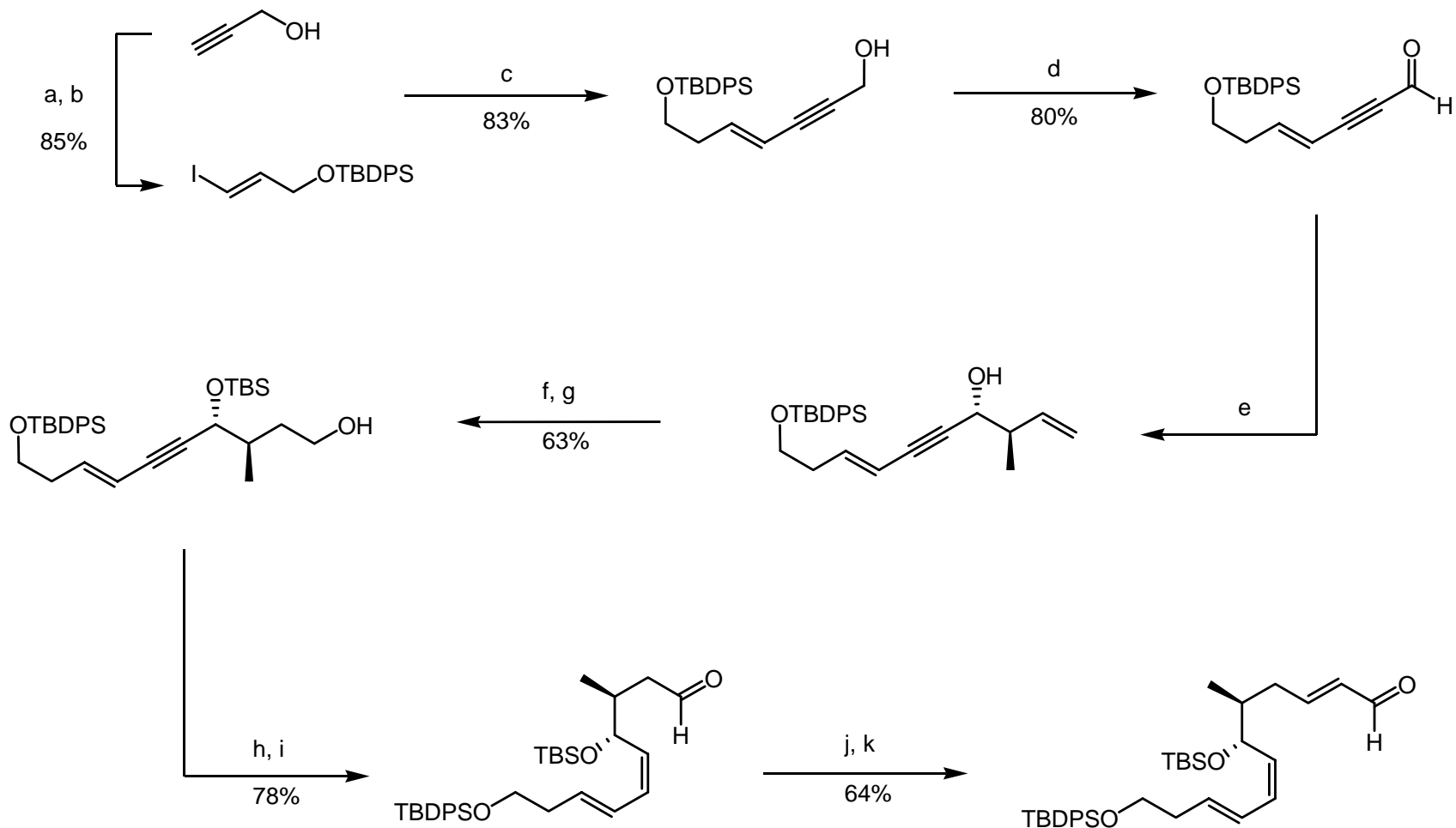
Tadano (2003, Macquarimicins)

Roush (2004, Cochleamycin)

(Evans)

Tatsuta, *J. Antibiotics*, **2003**, 56, 584.
Roush, *OL*, **2003**, 5, 4725.
Tadano, *OL*, **2001**, 3, 3029.
Paquette, *OL*, **2002**, 4, 253.
Paquette, *JOC*, **2004**, 69, 6441.

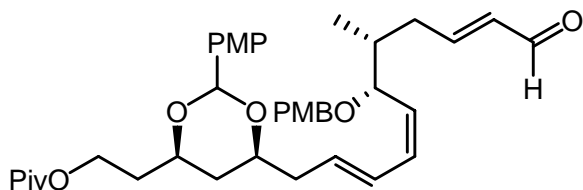
Synthesis of IMDA Substrates



a) TBDPSCI, imid., DMAP; b) $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$, CH_2Cl_2 ; I_2 ; c) $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, CuI , NEt_3 ; d) MnO_2 , CH_2Cl_2 ; e) diisopropyl(*S,S*)-tartrate-(*E*)-crotylboronate, PhMe , -78°C ; f) TBSCl , imid.; g) 9-BBN, THF, 0°C , then aq. H_2O_2 , aq. NaOH ; h) Zn , $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, AgNO_3 , $\text{MeOH}/\text{H}_2\text{O}$; i) DMP, pyr., wet CH_2Cl_2 ; j) diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate, NaH , THF; k) DIBAL-H, THF, -78°C

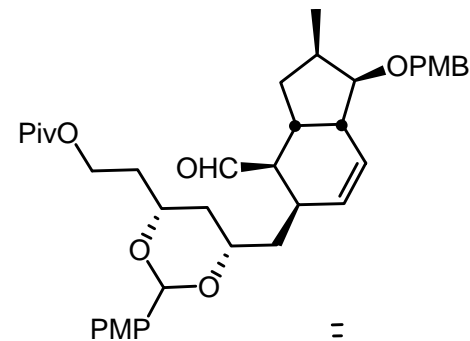
Key IMDA Reactions

Paquette

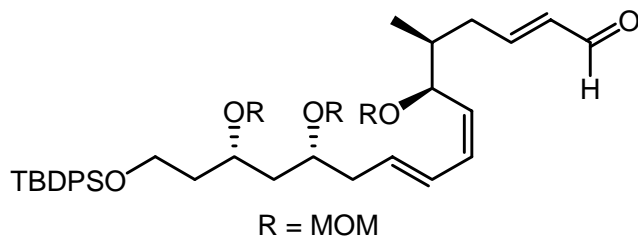


cat. BHT, PhMe, 195 °C,
26 h

moderate yield, one isomer

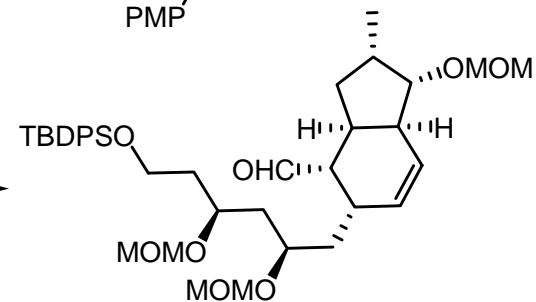


Tatsuta

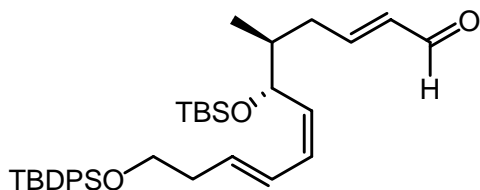


Yb(fod)₃, BHT, xylene, 140 °C,
4 h

high yield, one isomer

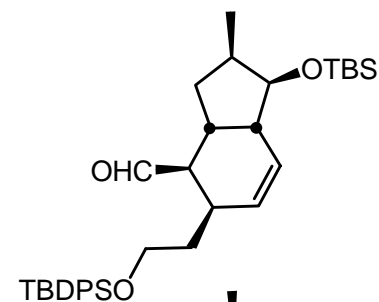


Roush

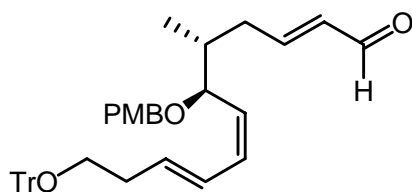


cat. BHT, PhMe, 160 °C,
16 h

83% (minor isomer, 3%)

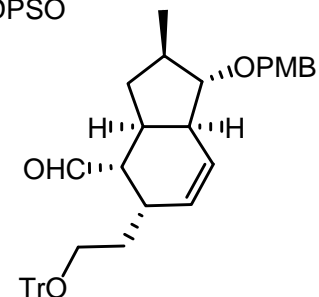


Tadano



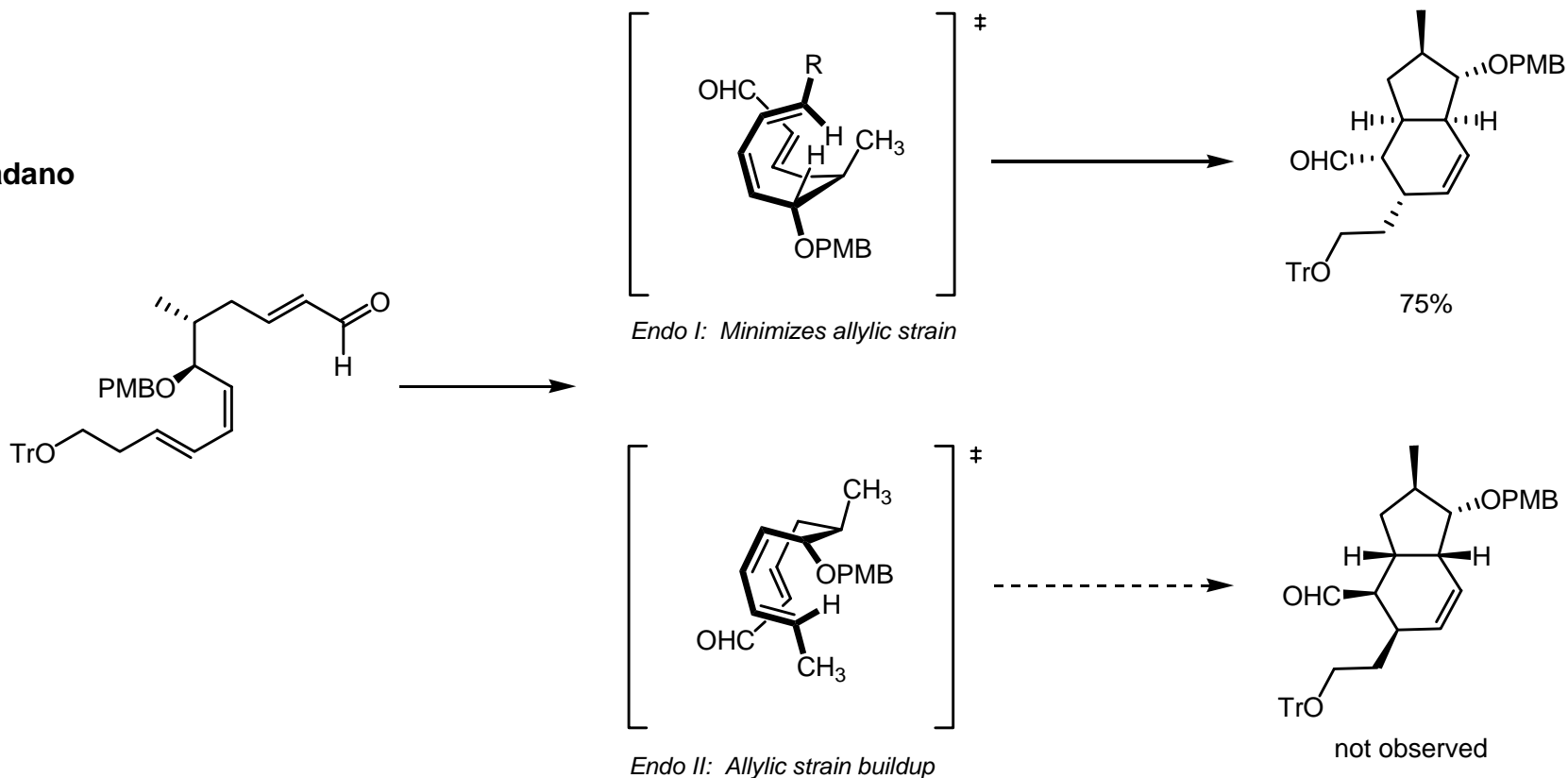
cat. BHT, PhMe, 150 °C

75%, single isomer



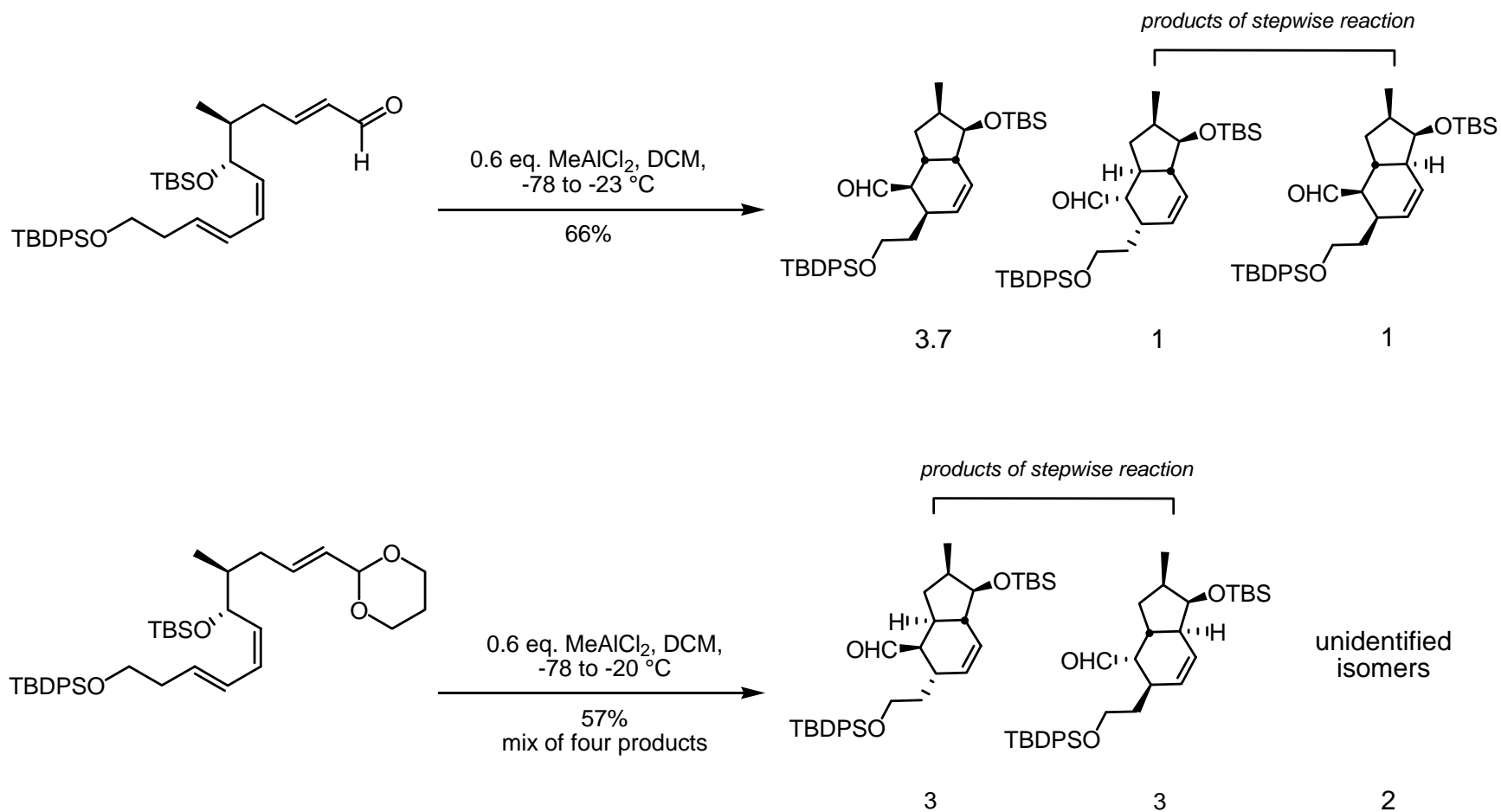
IMDA Diastereoselectivity

Tadano



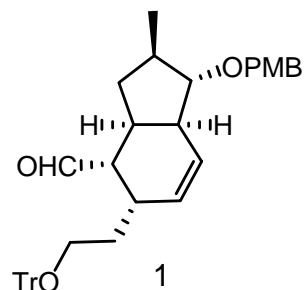
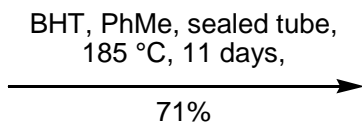
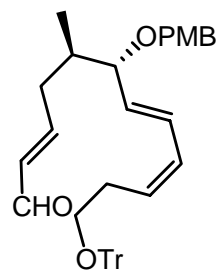
Exo TS not feasible given the orientation of the (E, Z) diene.

Roush's Lewis Acid Activation Experiments



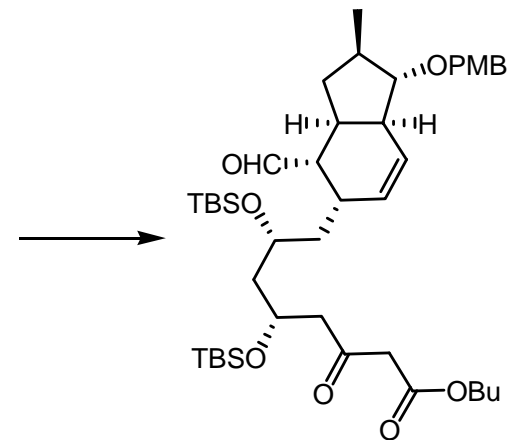
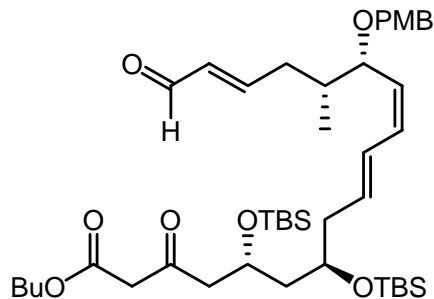
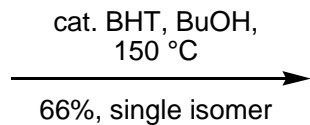
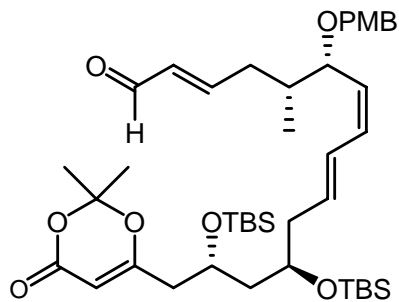
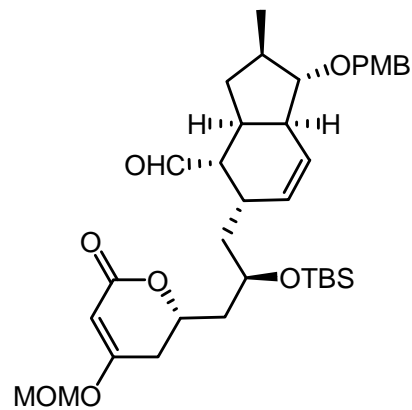
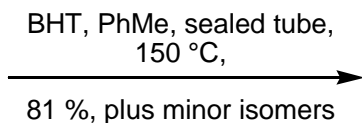
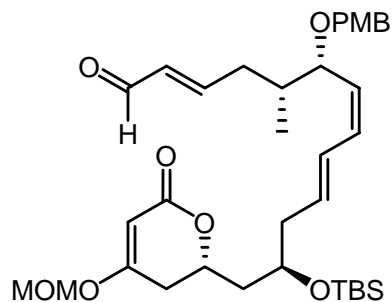
Increasing activation of the dienophile hinders diastereocontrol: stepwise pathways preferred.

Tadano's Diverse IMDA Targets

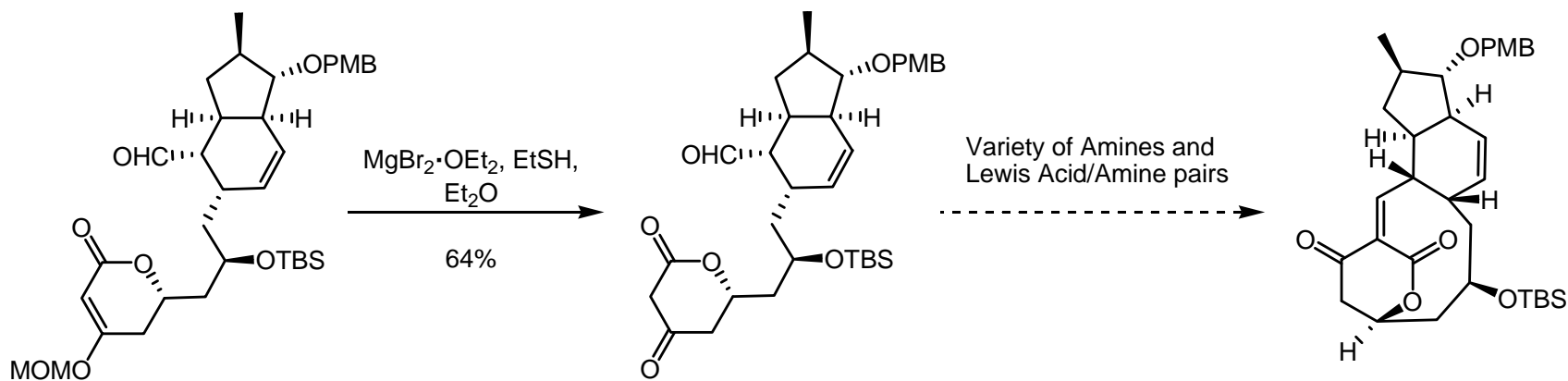
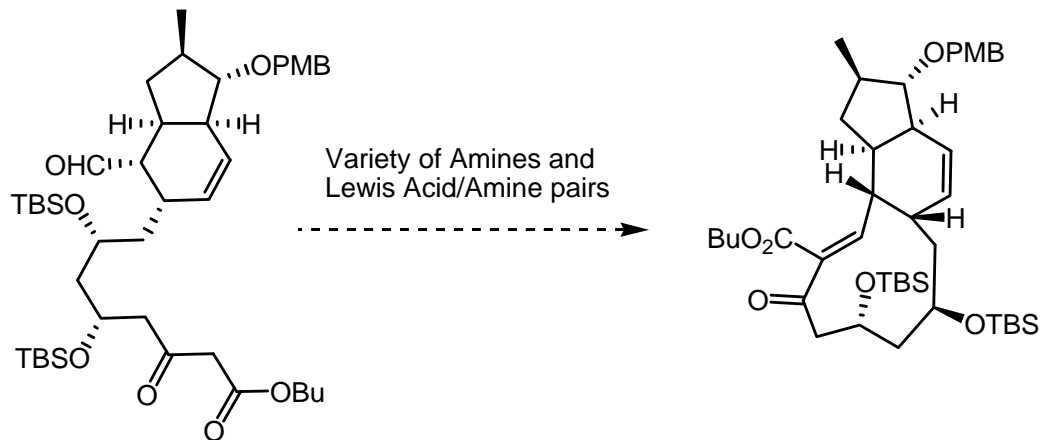


five unidentified isomers

2.3

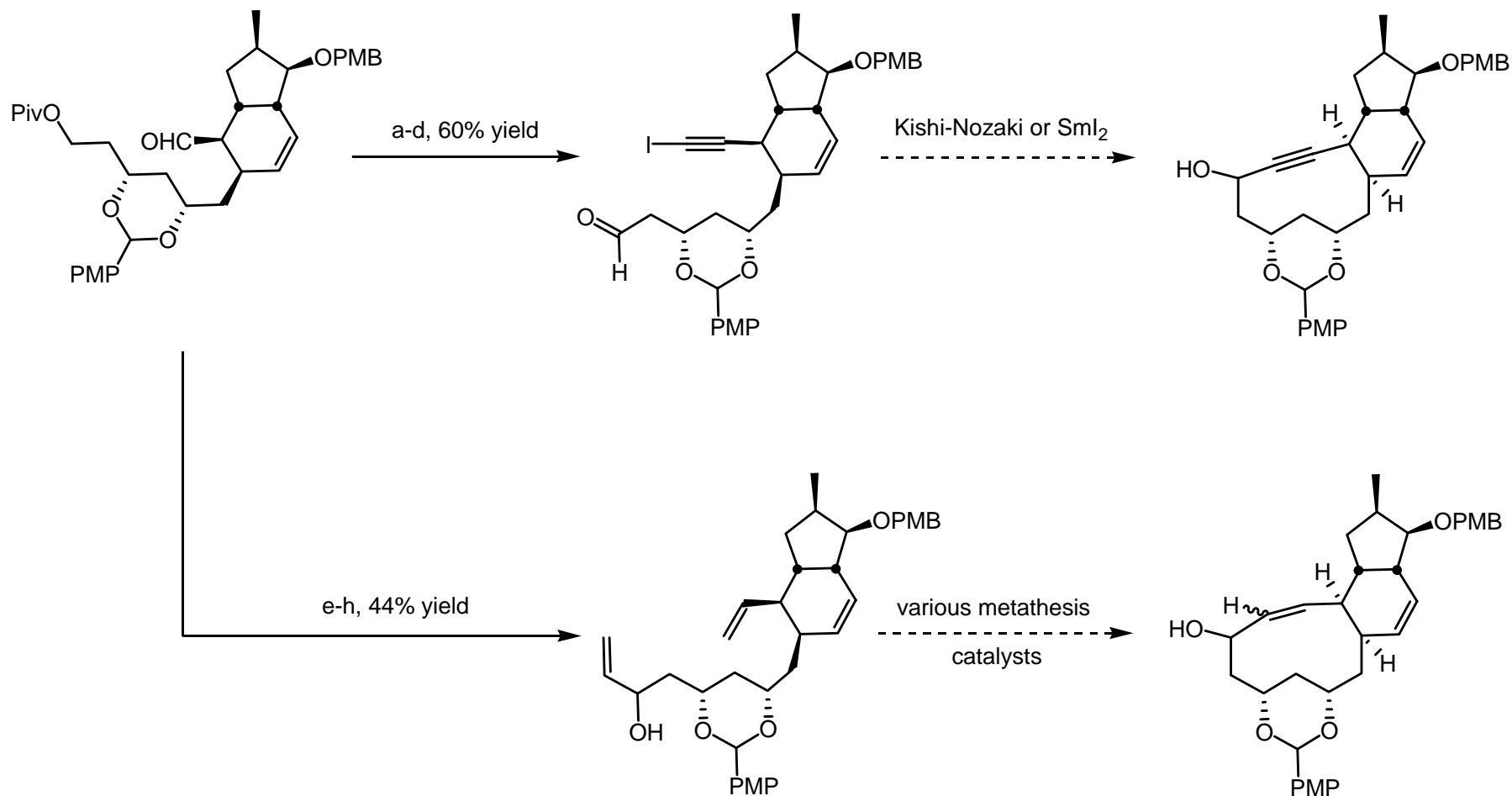


Tadano's Knoevenagel Macrocyclization Efforts



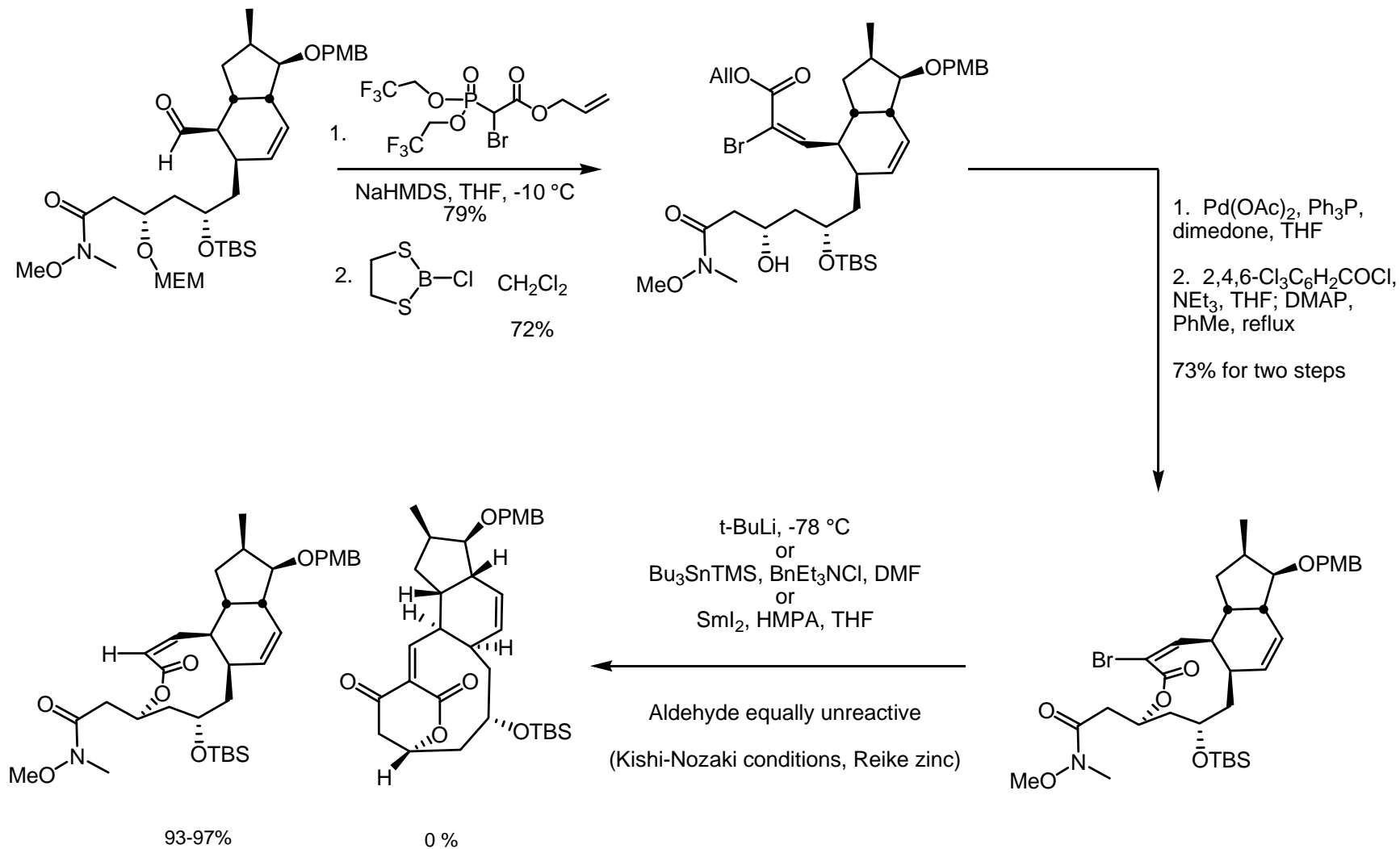
Route abandoned in favor of TADA approach.

Paquette's Organometallic Macrocyclization Efforts

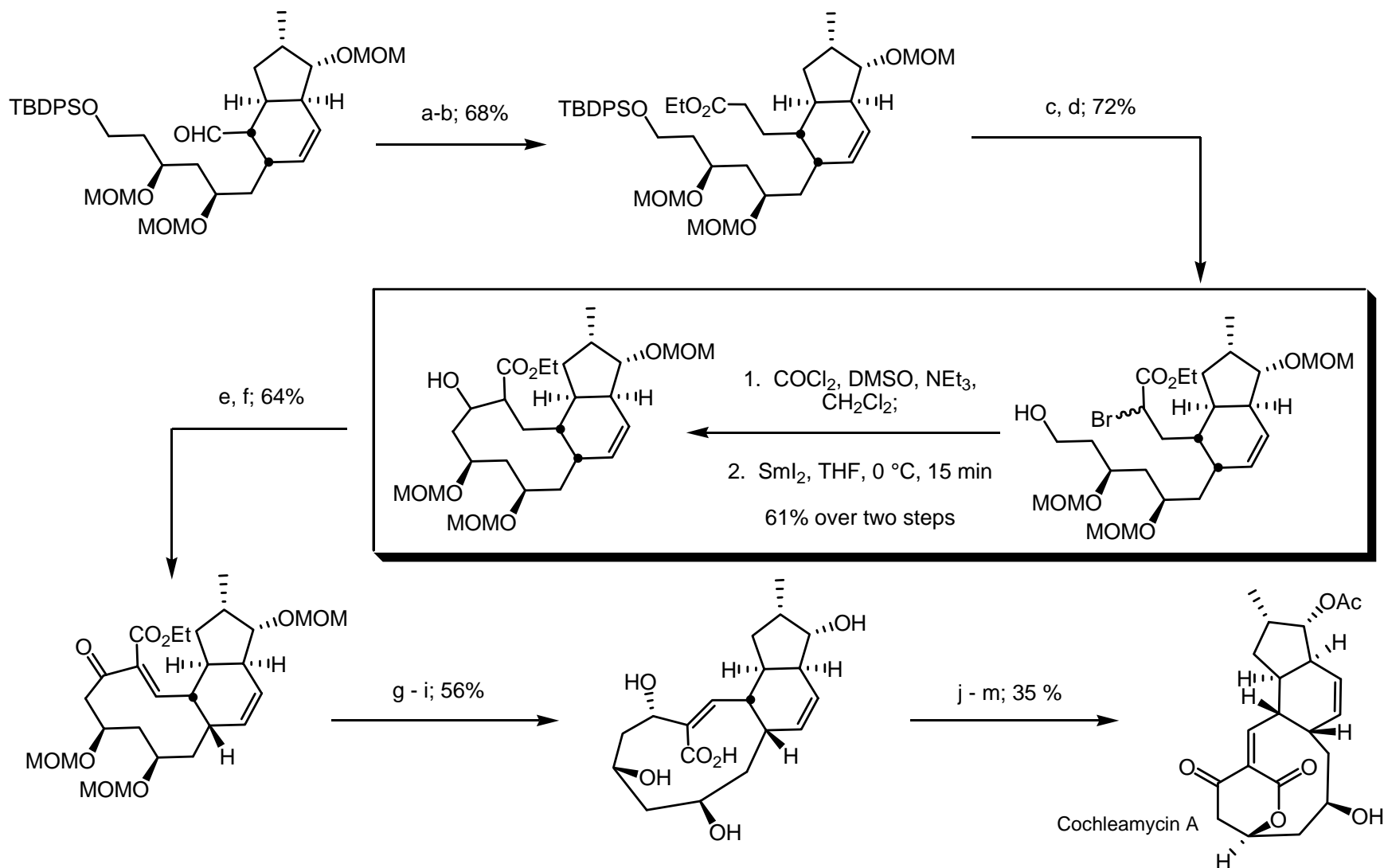


- a) CBr_4 , PPh_3 , pyr., CH_2Cl_2 , 0°C , 98%; b) $n\text{-BuLi}$, THF, -78°C , 86%; c) I_2 , morpholine, PhH, $50\text{-}60^\circ\text{C}$, 90%; d) PCC, NaOAc, sieves, CH_2Cl_2 , 78%.
 e) $\text{Ph}_3\text{PCH}_3^+\text{Br}^-$, $n\text{-BuLi}$, THF, -78°C , 76%; f) $n\text{-BuLi}$, THF, -78°C , 76%; g) PCC, NaOAc, sieves, CH_2Cl_2 , 76%; h) CH_2CHMgBr , THF, -78 to 0°C , 96%.

Paquette's Macrolactonization Efforts

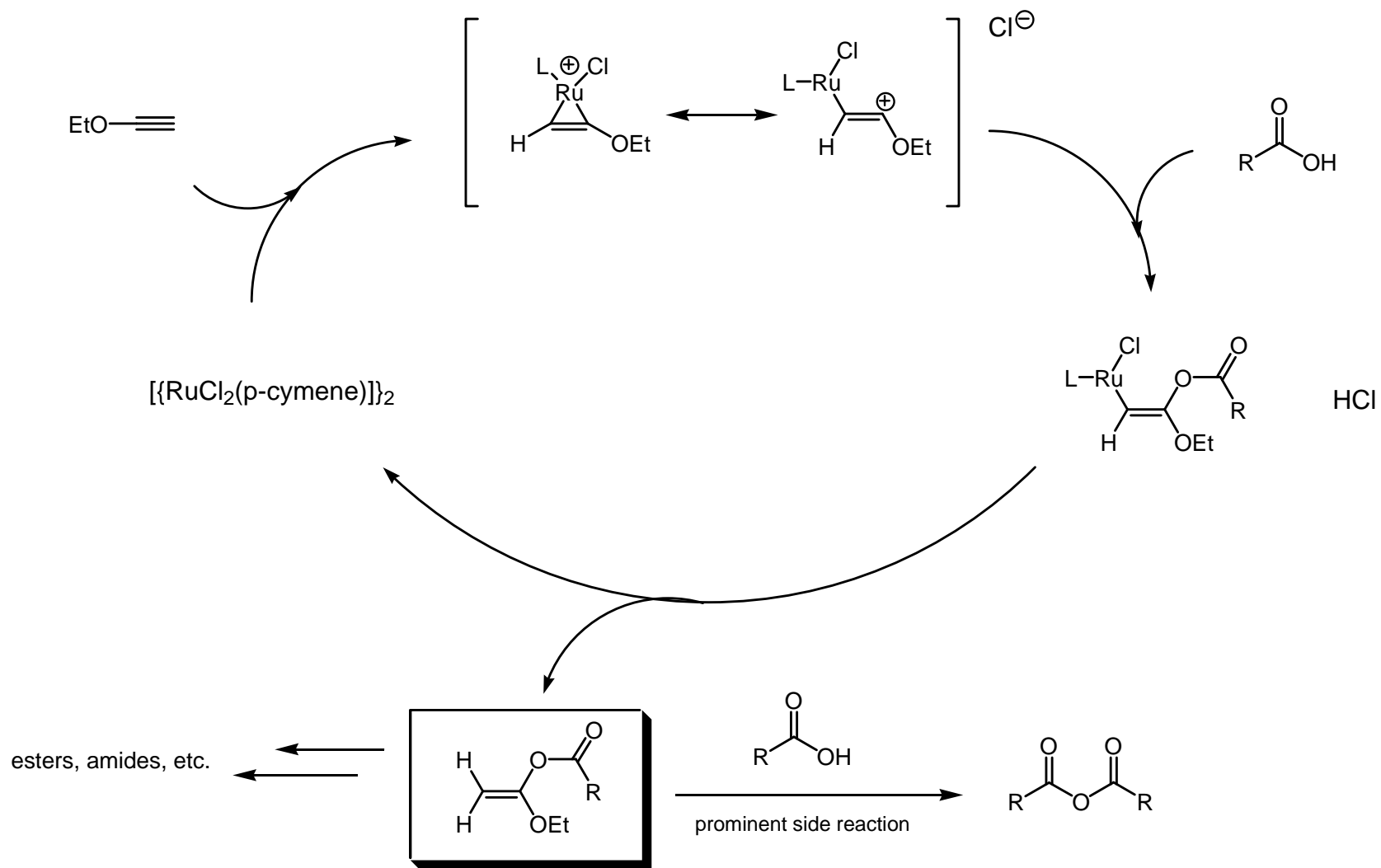


Tatsuta: First Synthesis of Cochleamycin A

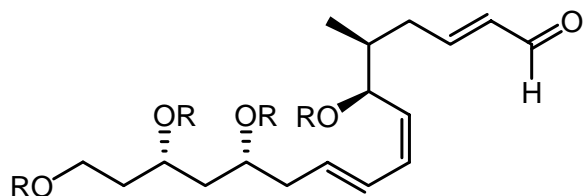


a) triethyl phosphonoacetate, NaH, THF, -30 °C, 80%; b) H_2 , Rh-C, PhMe, 85%; c) TBAF, THF, 50 °C, quant.; d) LDA, THF, -78 °C; CBr_4 , 72%; e) IBX, PhMe, DMSO, 89%; f) PhSeCl, LHMDS, THF; then H_2O_2 , 0 °C, 62%; g) NaBH_4 , $\text{CeCl}_3 \cdot 7 \text{H}_2\text{O}$, EtOH, 0 °C, 70%; h) HCl, EtOH; i) LiOH, H_2O , THF, 60 °C, 80% over two steps; j) ethyl ethynyl ether, $[\text{RhCl}_2(\text{p-cymene})]_2$, DMF, 0 °C, 68%; k) CSA, THF, 83%; l) MnO_2 , EtOAc, 85%; m) NaOAc, Ac_2O , 60 °C, 72%

Kita's Acylation Method



A Summary of Approaches



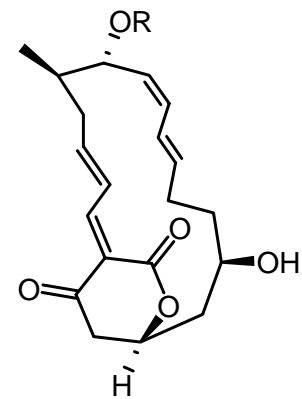
IMDA

Tatsuta (2003, Cochleamycin)

Roush

Tadano

Paquette



TADA

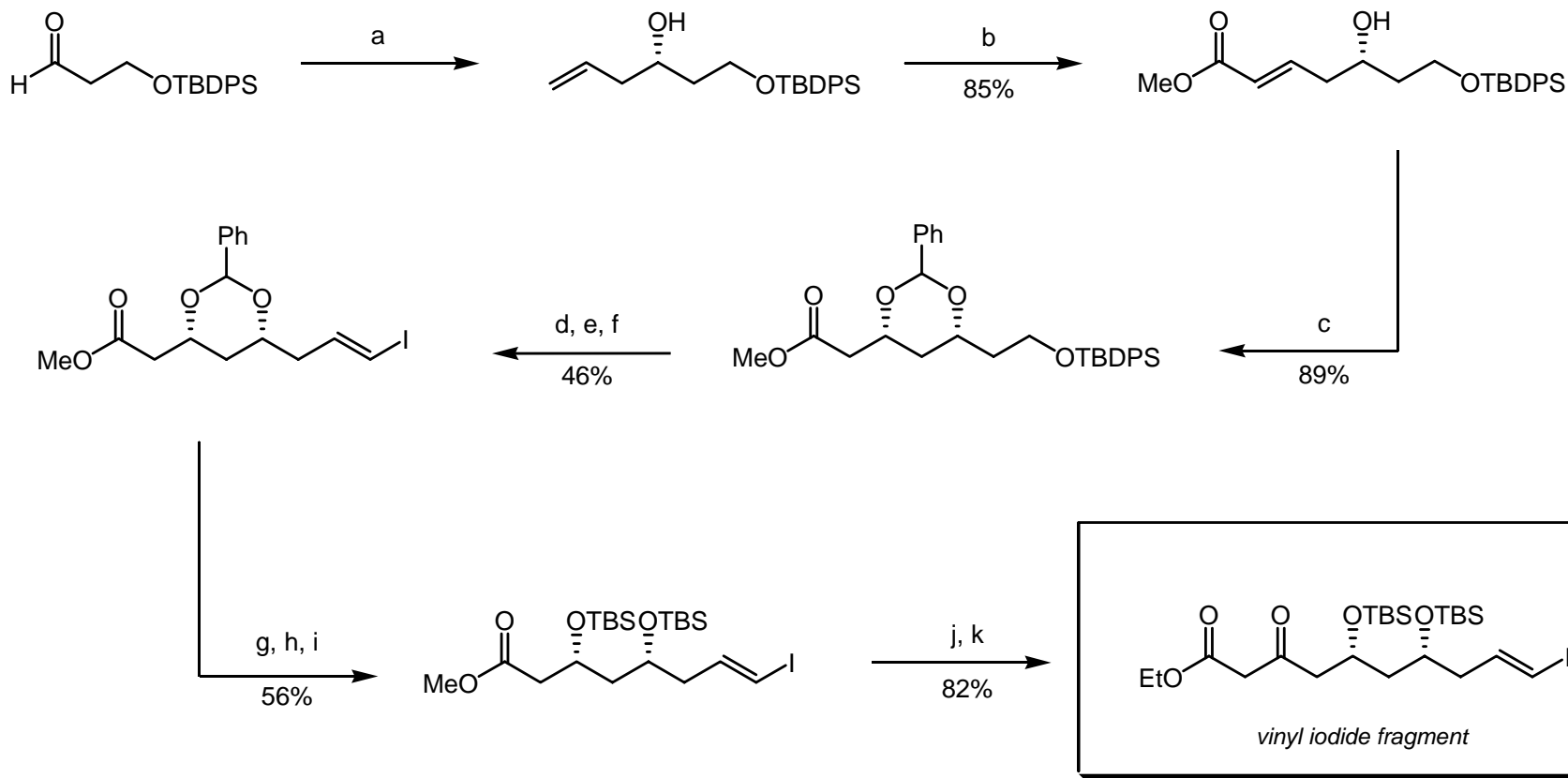
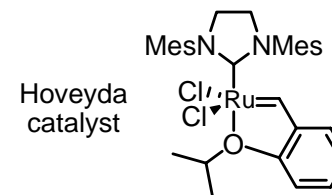
Tadano (2003, Macquarimicins)

Roush (2004, Cochleamycin)

(Evans)

Synthesis of TADA Substrates

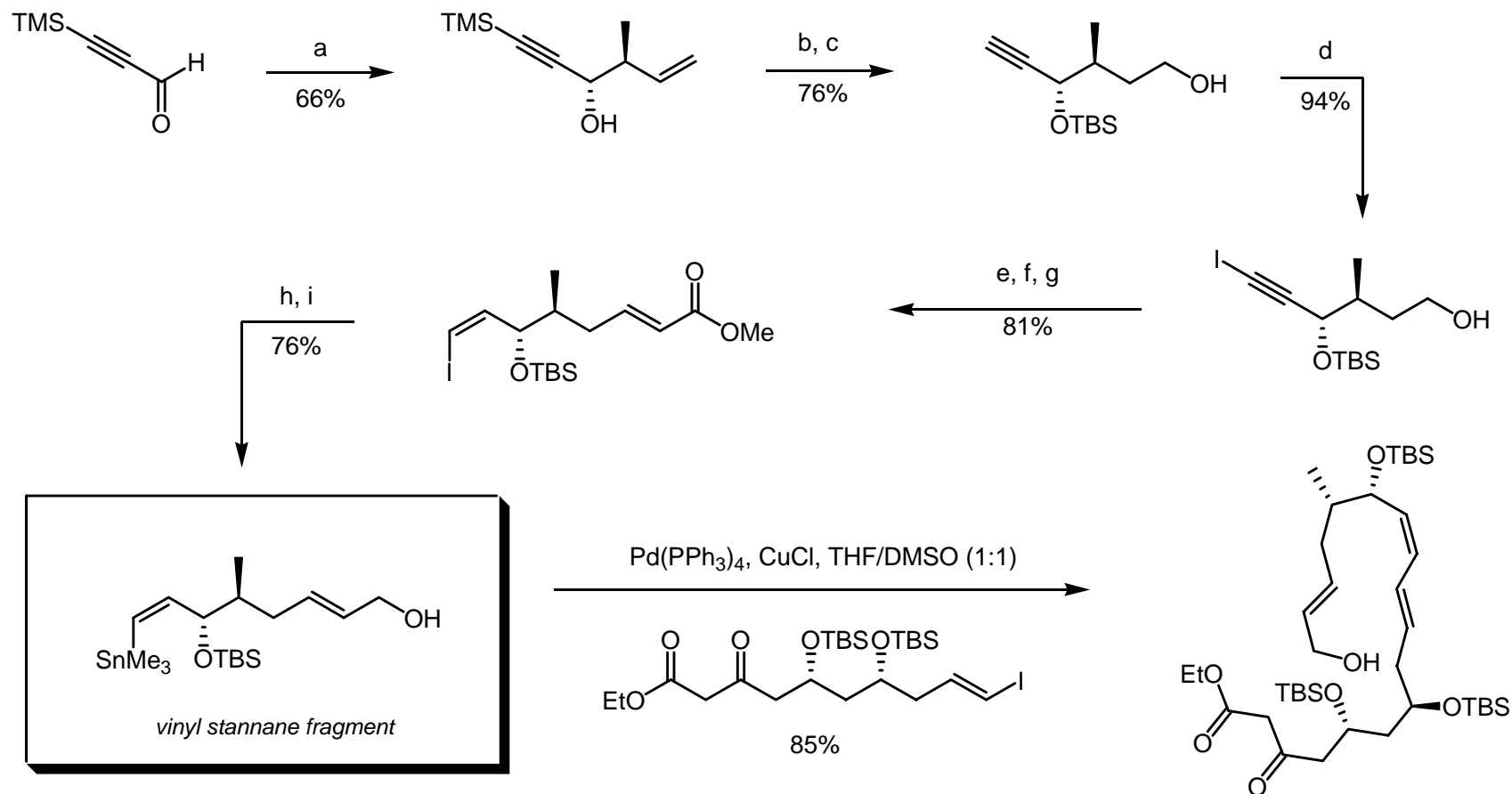
Sonigashira coupling/partial reduction no longer attractive; Stille approach now dominant



a) $(^d\text{Ipc})_2\text{-B-allyl}$, THF, $-78\text{ }^\circ\text{C}$; b) methyl acrylate, 1.5 mol% Hoveyda catalyst, CH_2Cl_2 , reflux; c) PhCHO, tBuOK, THF, $0\text{ }^\circ\text{C}$; d) $(\text{HF})_3\text{Et}_3\text{N}$, MeCN, $40\text{ }^\circ\text{C}$; e) $\text{SO}_3\cdot\text{pyr}$, DMSO, $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , $0\text{ }^\circ\text{C}$; f) CrCl_2 , CHCl_3 , dioxane/THF; g) 80% AcOH, THF, $95\text{ }^\circ\text{C}$; h) Amberlite IRA-400(OH), MeOH; i) TBSOTf, 2,6-lutidine, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$; j) DIBAL-H, $-78\text{ }^\circ\text{C}$; k) ethyl diazoacetate, SnCl_2 , CH_2Cl_2 .

Synthesis of TADA Substrates

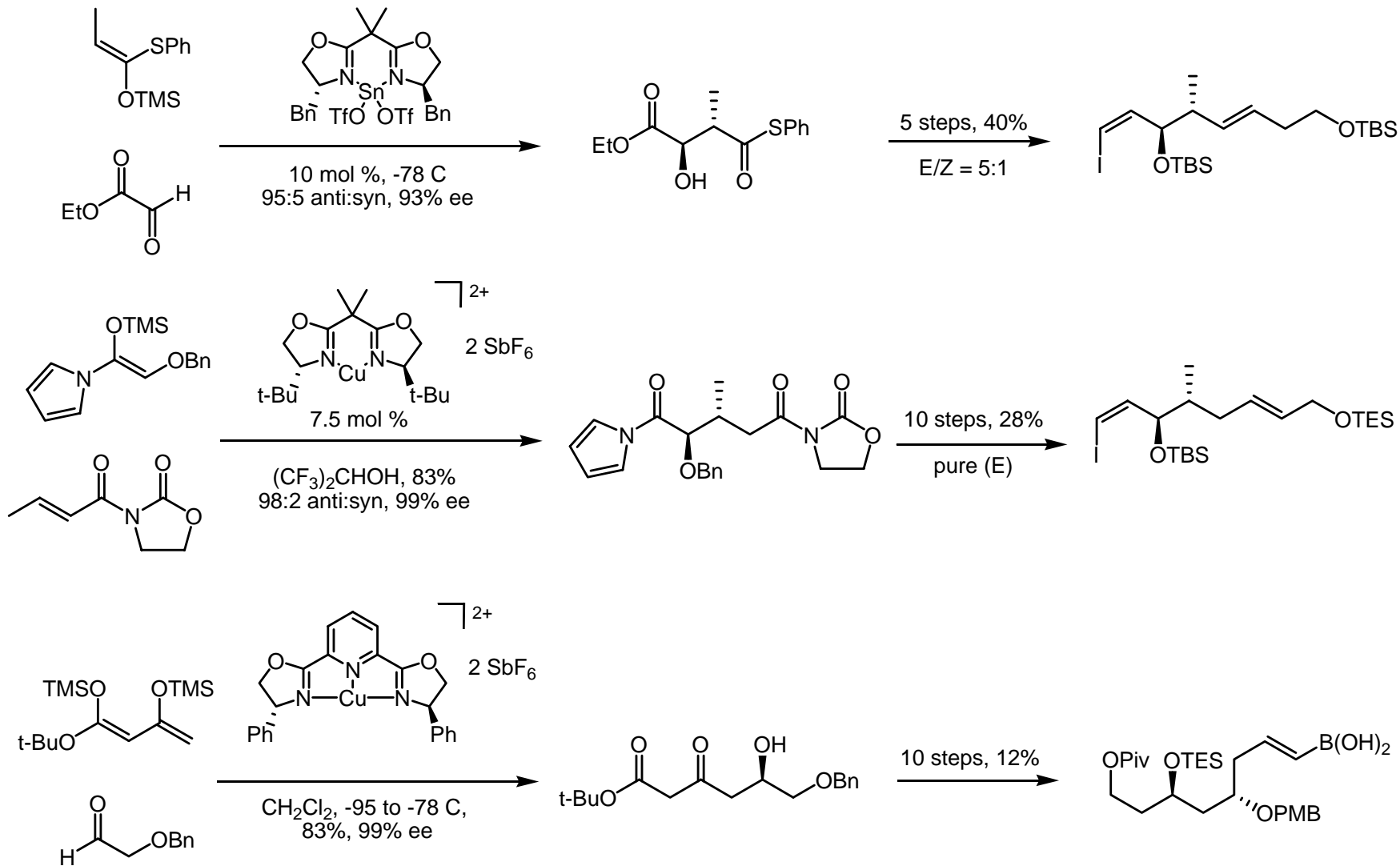
Sonigashira coupling/partial reduction no longer attractive; Stille approach now dominant



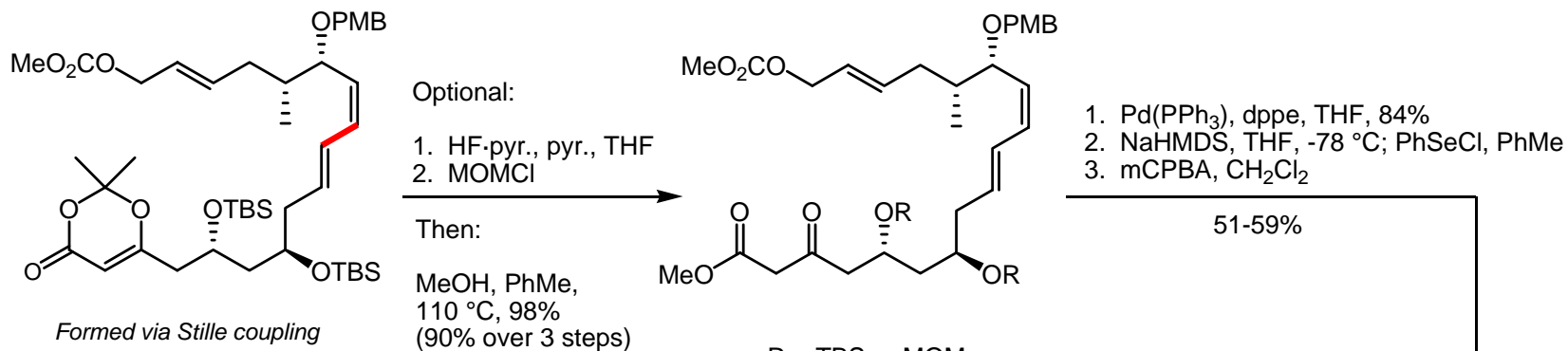
a) $(^d\text{Ipc})_2\text{-B-allyl}$, THF, -78°C ; b) TBSOTf, 2,6-lutidine, CH_2Cl_2 , -78°C ; c) 9-BBN, THF; then aq. NaOH/ H_2O_2 ; d) n-BuLi, THF, -50°C , then I_2 ; e) o-Nitrobenzenesulfonylhydrazide, Et_3N , THF/*i*-PrOH (1:1); f) SO_3^*pyr , DMSO, iPr_2NEt , CH_2Cl_2 , 0°C ; g) Trimethyl phosphonoacetate, LiCl, NEt_3 , MeCN; h) DIBAL-H, CH_2Cl_2 ; i) MeLi, Et_2O , -40 to 23°C ; n-BuLi, -78°C ; then Me_3SnCl , THF, -78°C .

Synthesis of TADA Substrates

Group methodology, Suzuki coupling employed in Krista Beaver's approach.

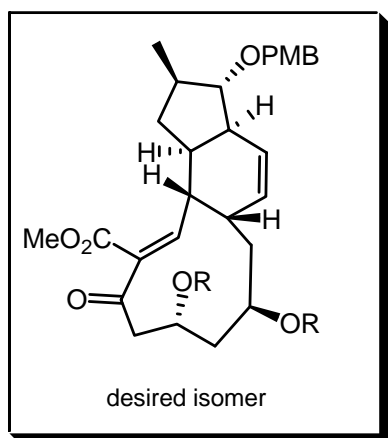


Tadano's First TADA Target



1. Pd(PPh₃), dppe, THF, 84%
2. NaHMDS, THF, -78 °C; PhSeCl, PhMe
3. mCPBA, CH₂Cl₂

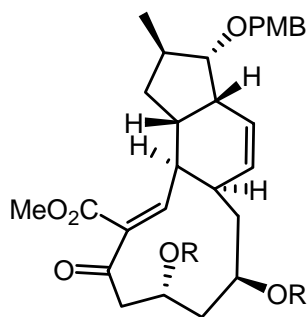
51-59%



0%

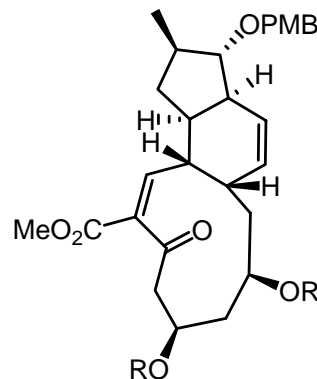
29%

(worse, efforts to deprotect failed)



29%

<10%?



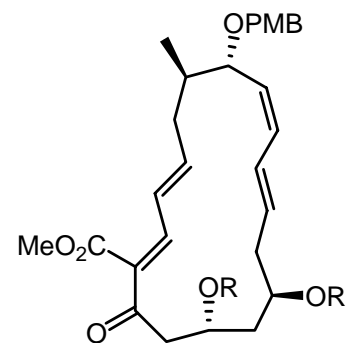
10%

<10%?

BHT, 130 °C,
PhMe

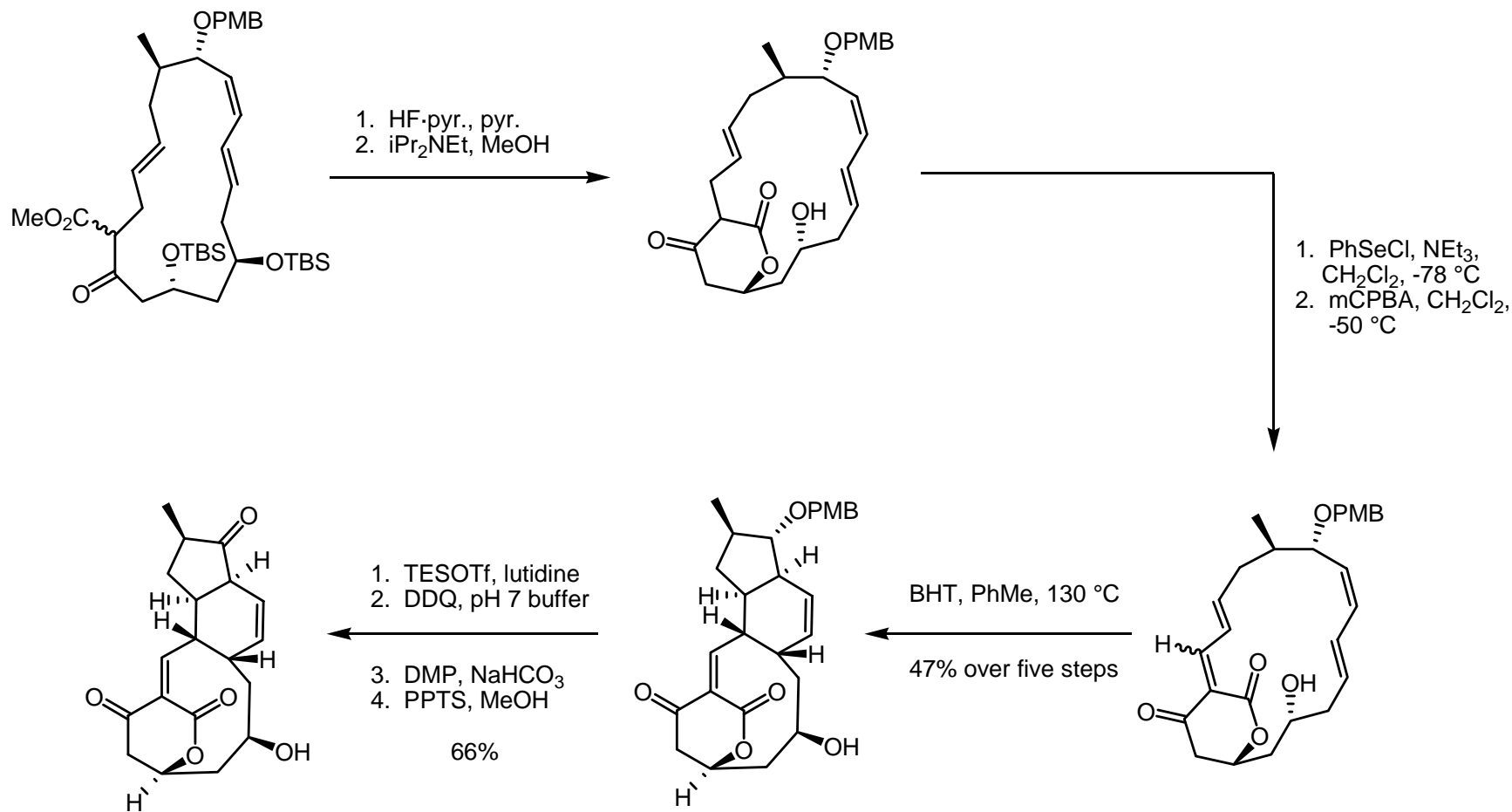
R = TBS

R = MOM



Exclusively (Z)

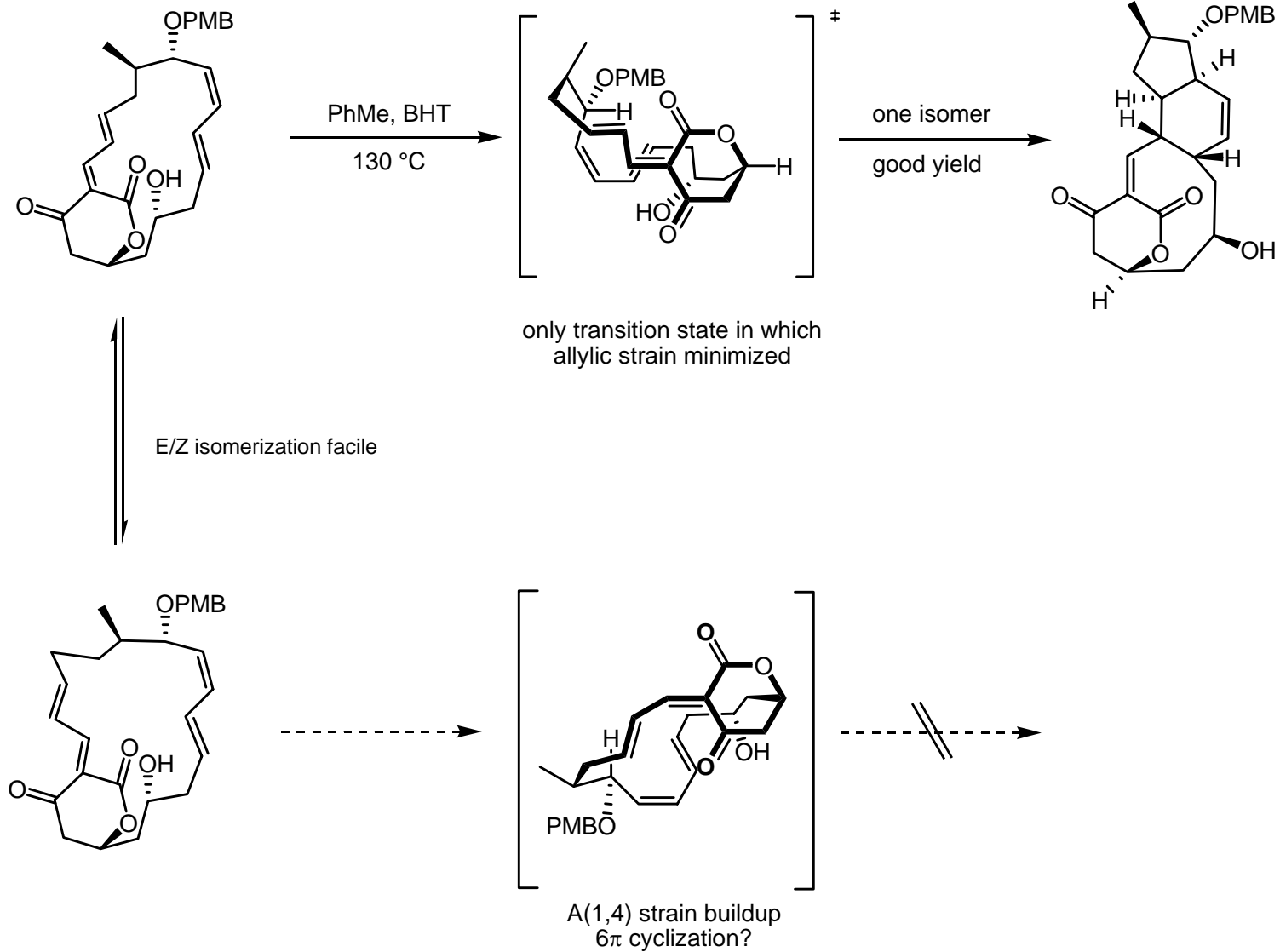
Tadano's Second TADA Target



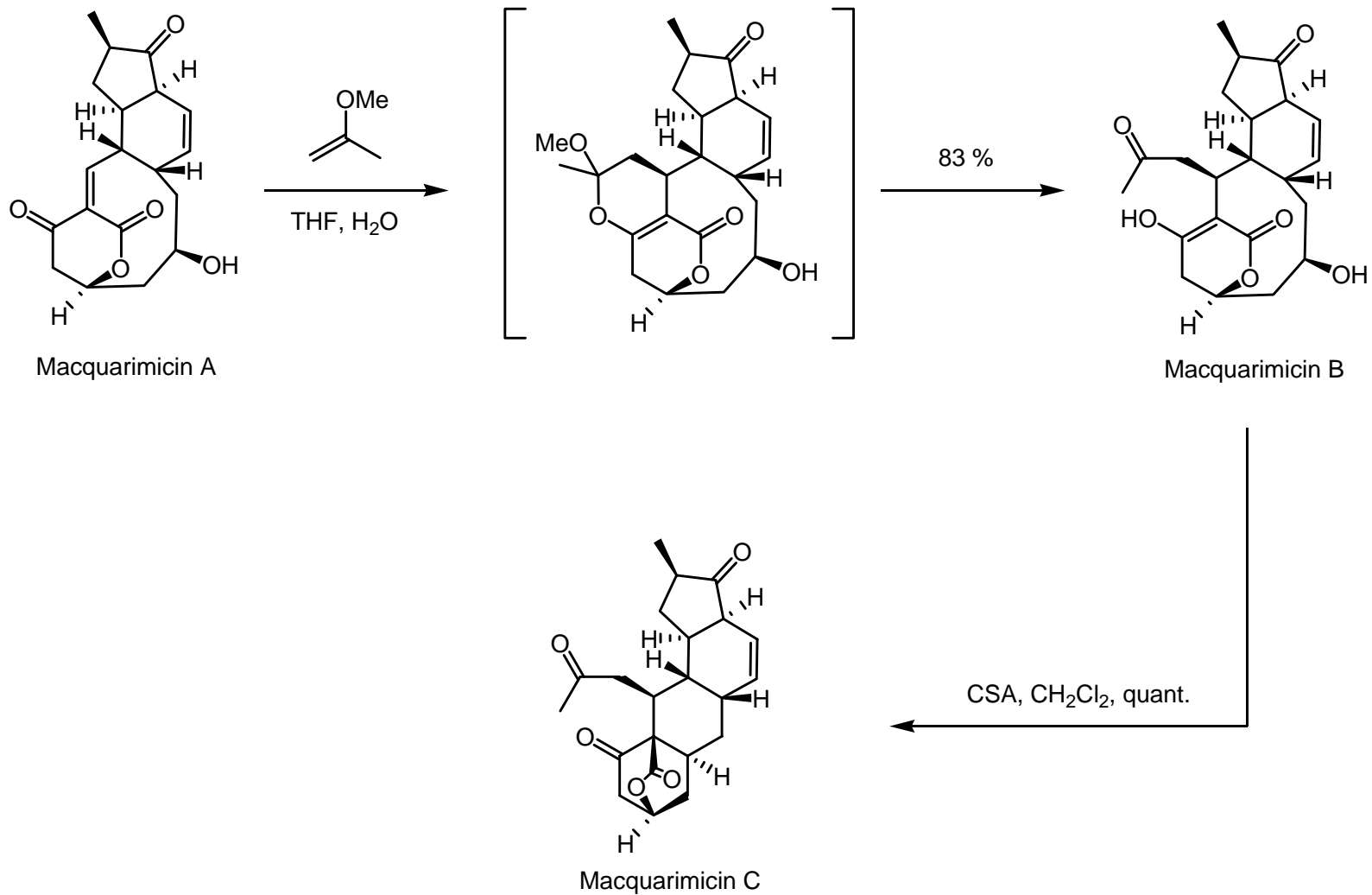
Macquarimicin A

"The TADA substrate showed a complicated ^1H NMR spectrum, making determination of the E/Z ratio extremely difficult. We attribute this complication to the presence of tautomers such as hemiketal forms and/or rotamers..."

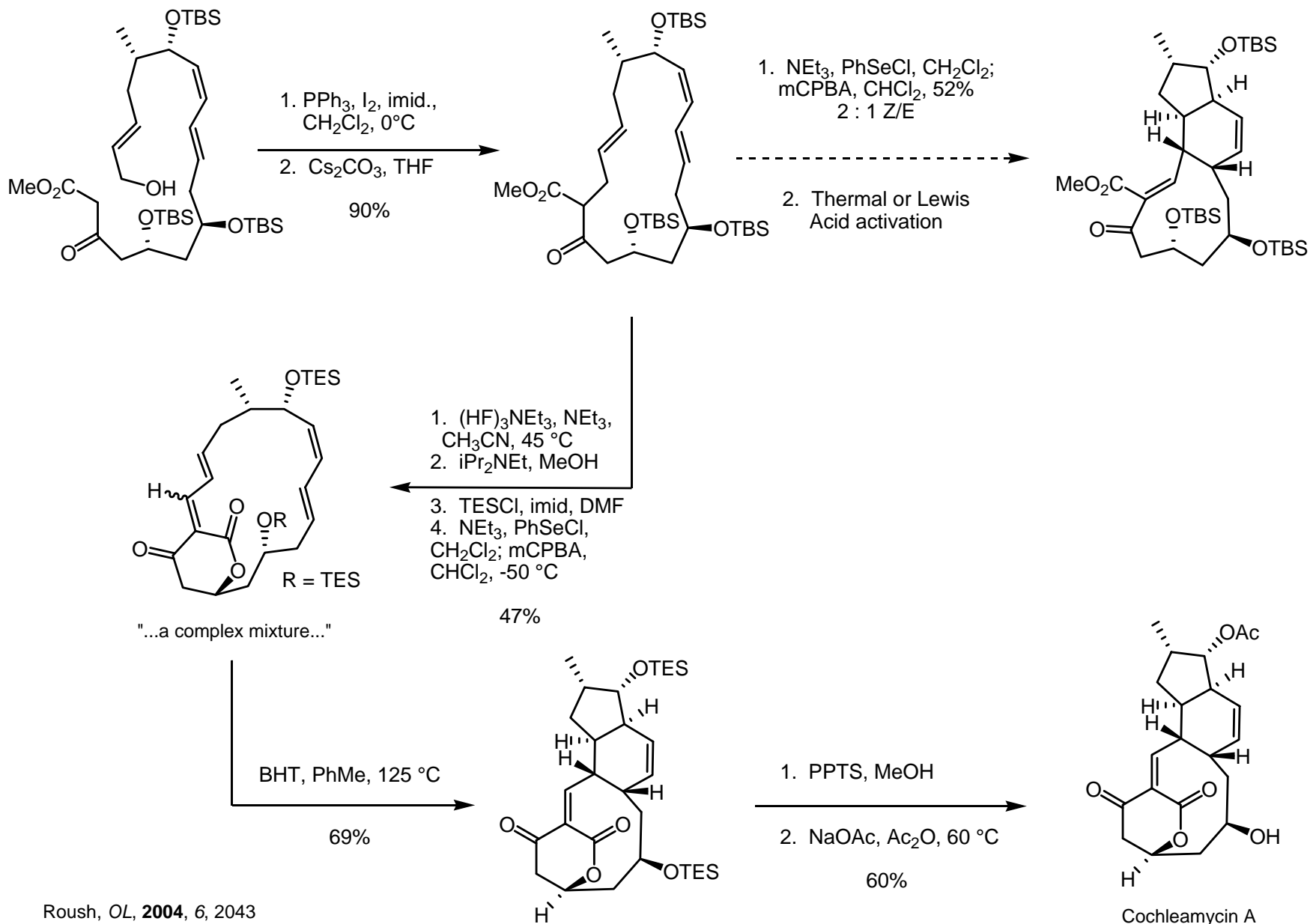
TADA Stereoselectivity



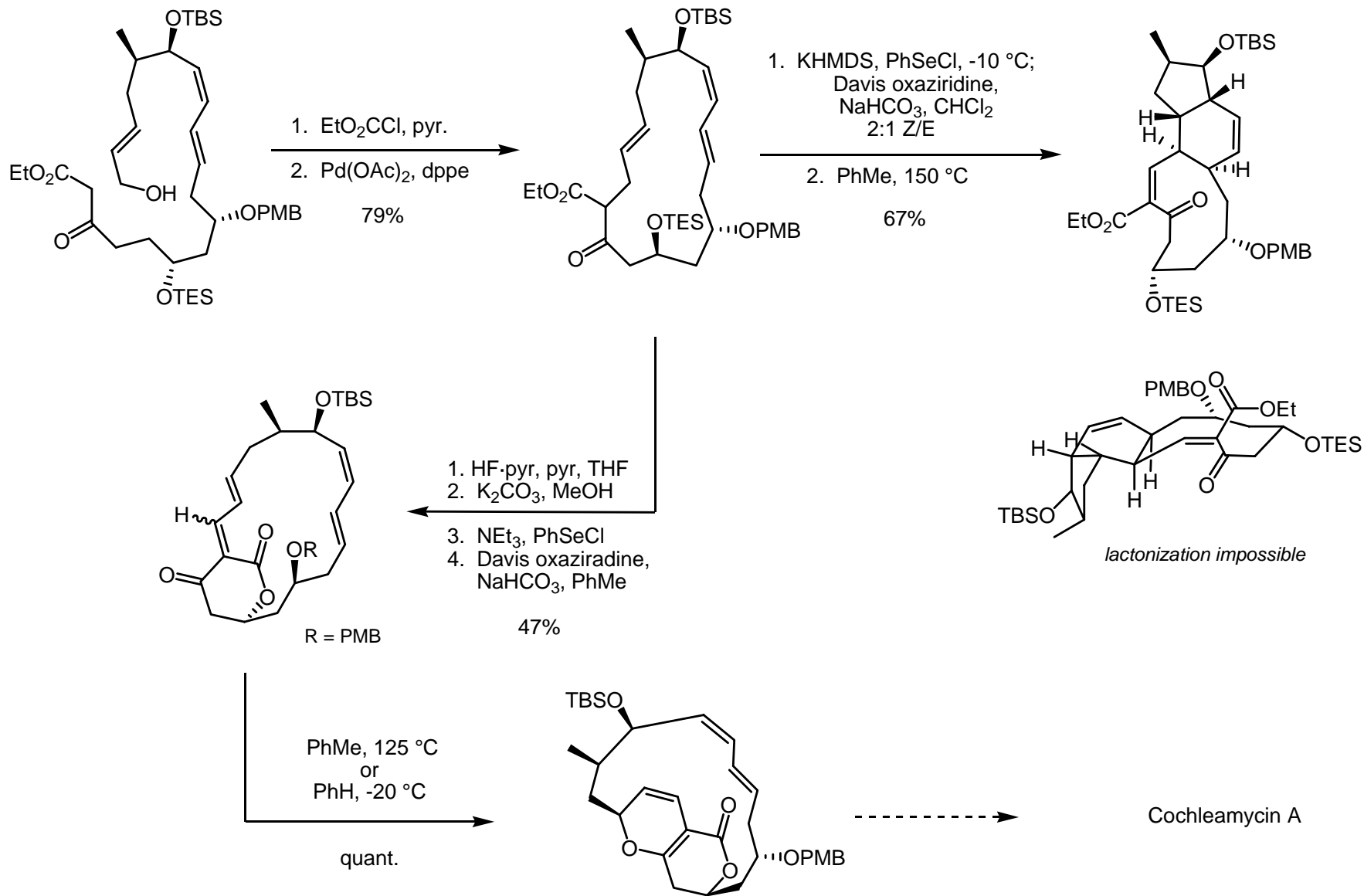
Tadano: Macquaramicins B and C



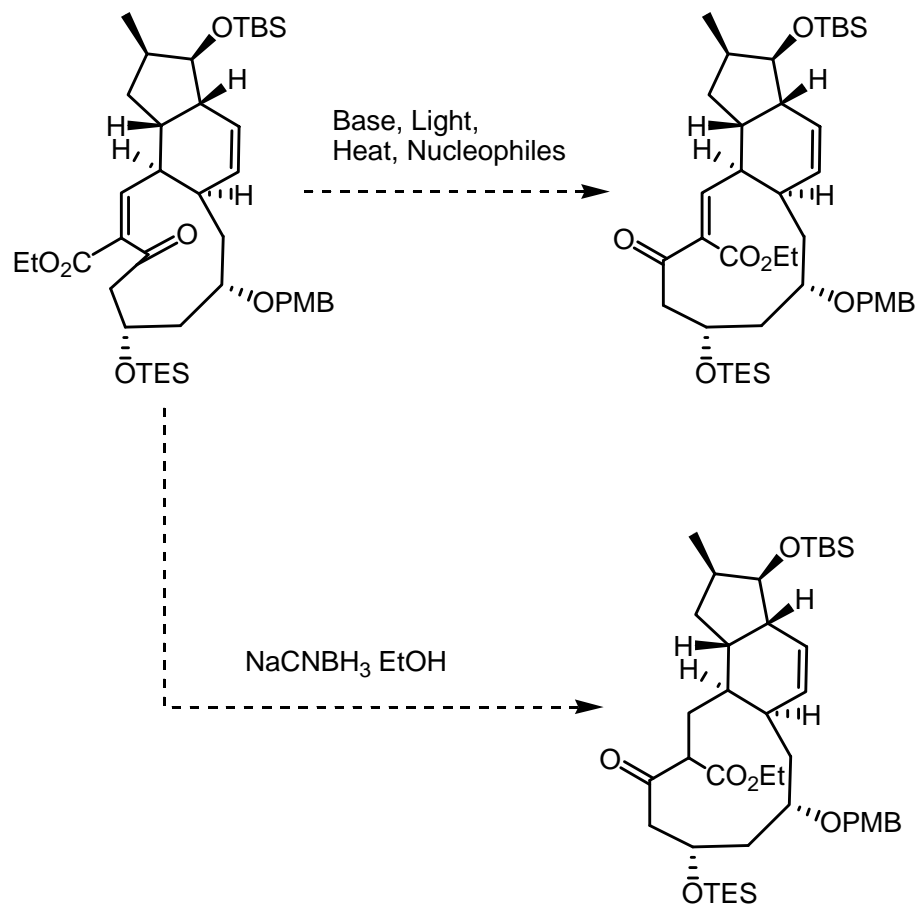
Roush's TADA Efforts



Evans' TADA Approach



Evans' TADA Approach

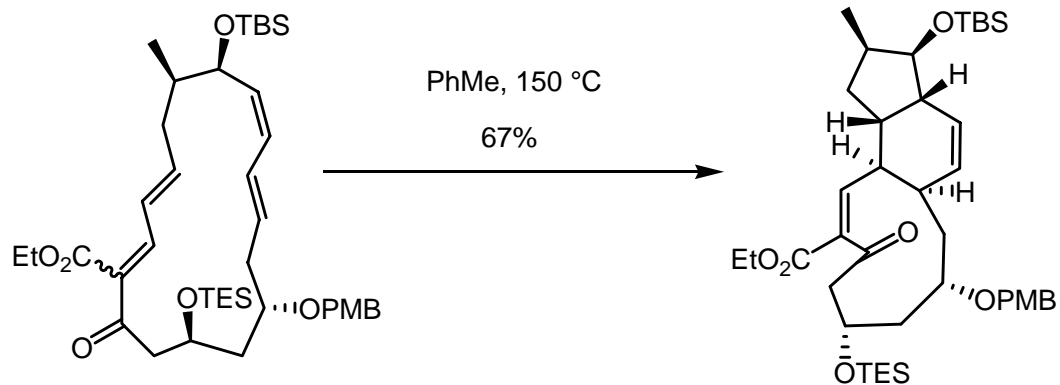


Calculations suggest thermodynamic preference strongly opposed to desired geometry.

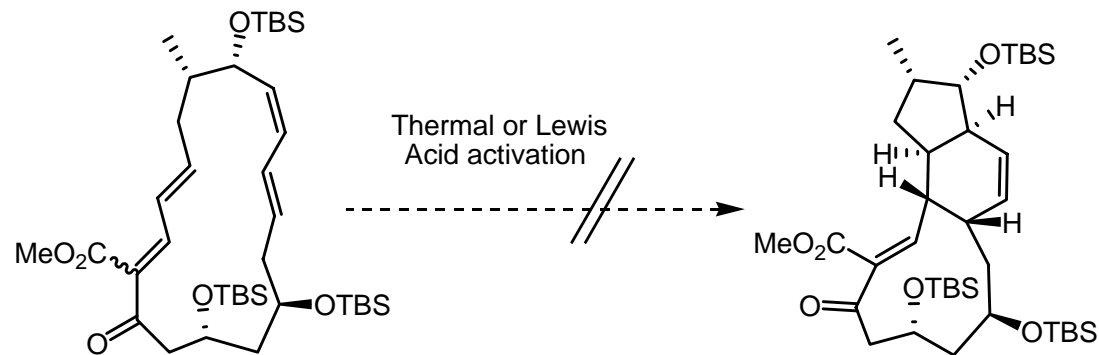
More vigorous conditions over-reduced or decomposed a model system.

Summary of TADA Reactions

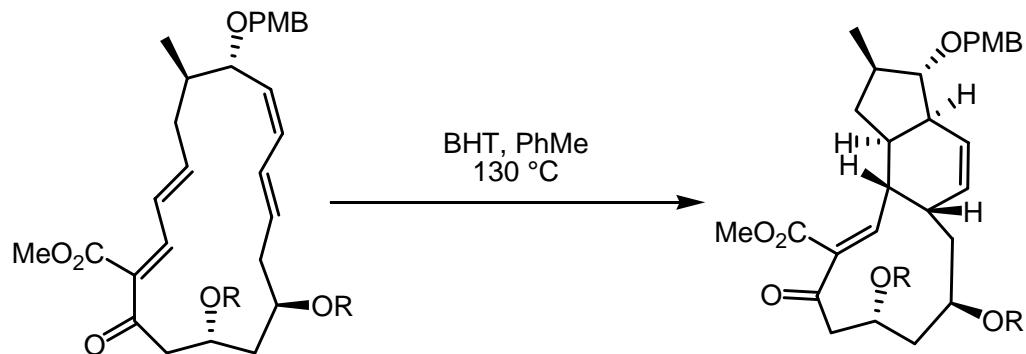
Evans
Z / E = 2 : 1



Roush
Z / E = 2 : 1



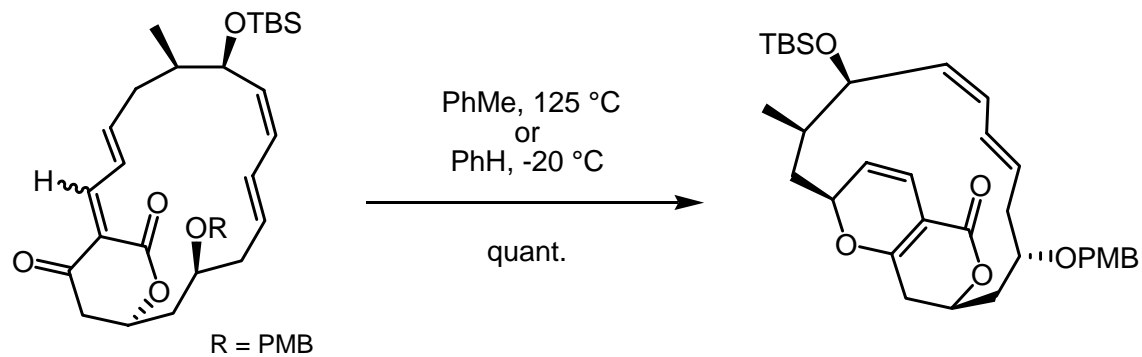
Tadano
Z / E > 20 : 1



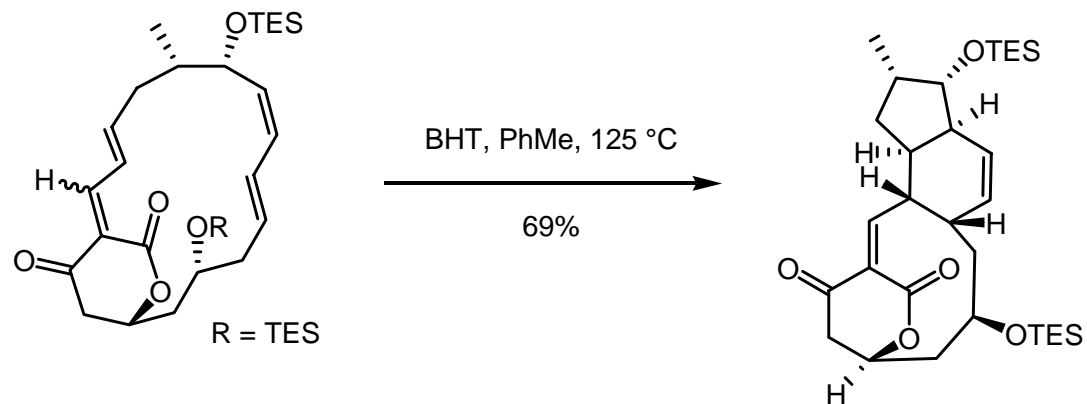
R = TBS 0%
R = MOM 29%

Summary of TADA Reactions

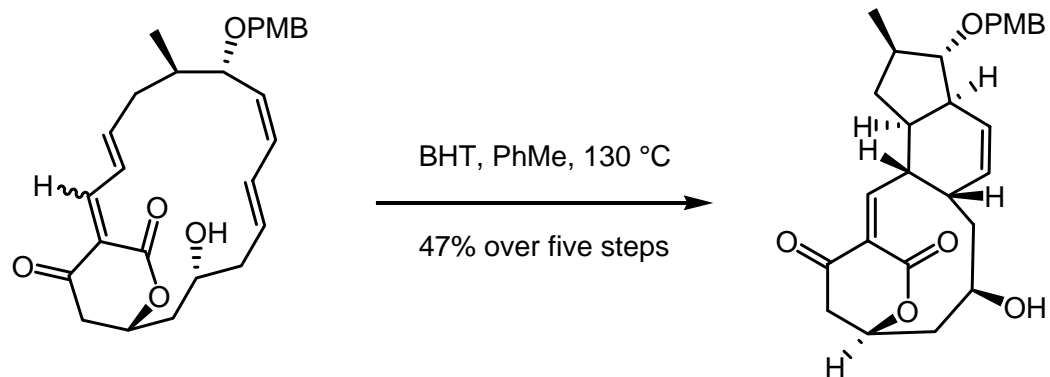
Evans



Roush



Tadano



Conclusions

One completed synthesis using IMDA (Tatsuta)

Closing 10 membered ring after IMDA challenging:

Only a Samarium-mediated Reformatsky reaction succeeded.

Two completed syntheses using TADA (Tadano, Roush)

Palladium π -allyl and malonate alkylation effectively closed macrocycle.

Protecting group choices far more important than expected:

Evans carried out a TADA that Roush and Tadano could not,

But Roush and Tadano achieved the TADA that led swiftly to the natural product.