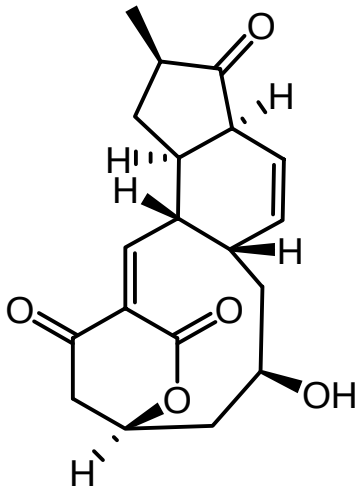
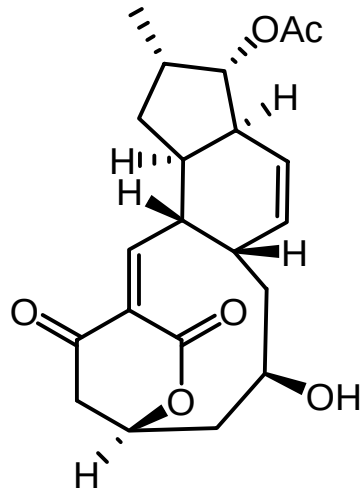


Macquarimicin A



Cochleamycin A

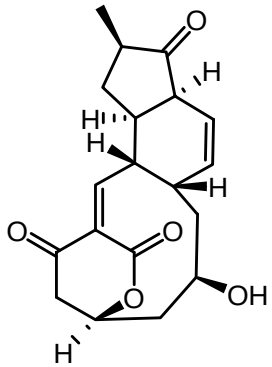
Approaches to the Synthesis of Macquarimicins and Cochleamycins

Drew Adams

Friday Seminar

March 18, 2005

Isolation and Activity



Macquarimicin A

Isolated in 1995 from *Micromonospora* bacteria

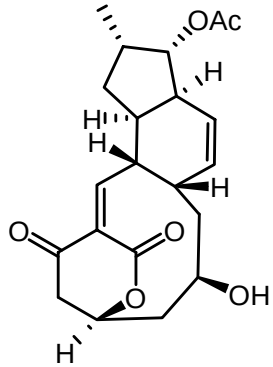
Macquarie University, Sydney, Australia

Weak activity against anaerobes

Cytotoxic against P388 leukemia line (0.3 μg/ml)

Selective but weak activity against N-SMase, as outlined below

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



Cochleamycin A

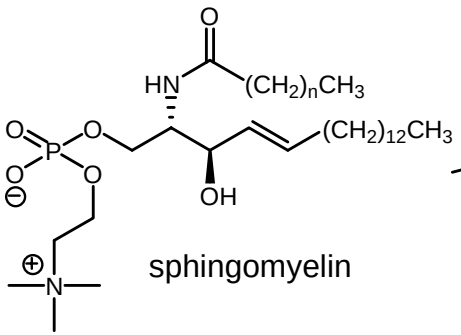
Isolated in 1992 from *Streptomyces* bacteria

Nishimeya-cho, Aomori, Japan

Weak activity against Gram-positive bacteria

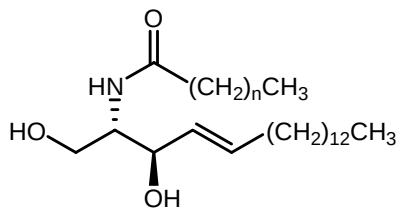
Cytotoxic against a variety of tumor lines

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



sphingomyelin

Neutral, Mg^{++}-dependent Sphingomyelinase



ceramide

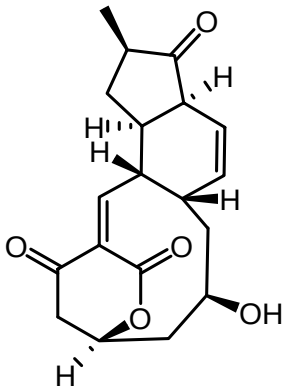
$IL\text{-}1\beta$, PGE_2

inflammation
cell proliferation
apoptosis

For more on ceramide signalling pathways:

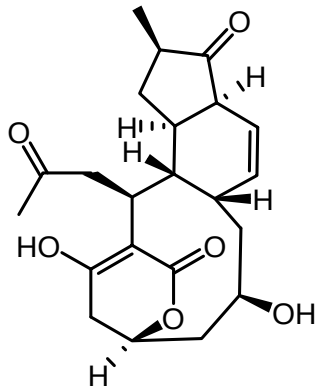
Ogita, T. *J. Antibiotics*, **1999**, *52*, 531.
Ohanian, J. *Cell. Mol. Life Sci*, **2001**, *58*, 2053.
Andrieu-Abidie, N., *Biochim. Biophys. Acta*, **2002**, *1585*, 126.

Derivatives



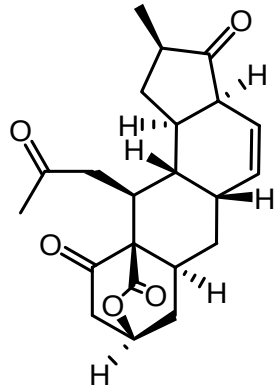
Macquarimicin A

Michael Reaction

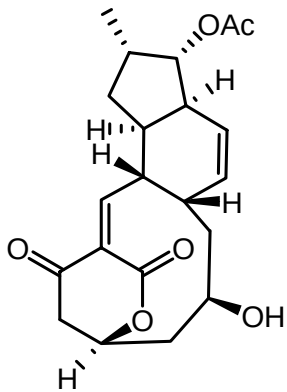


Macquarimicin B

S_N2 alkylation



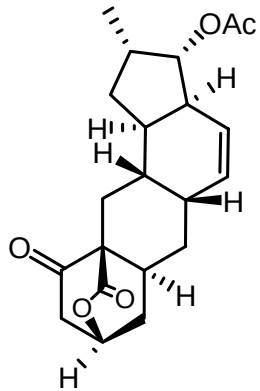
Macquarimicin C



Cochleamycin A

Reduction;

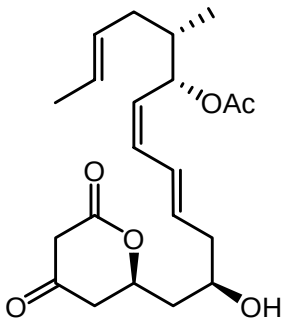
S_N2 alkylation



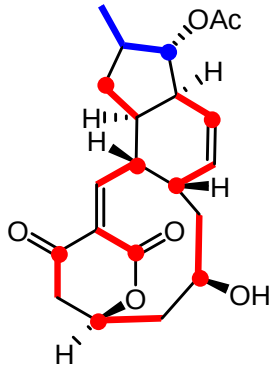
Cochleamycin B

Tadano, *JACS*, **2004**, *126*, 11254.

Biosynthetic Proposal



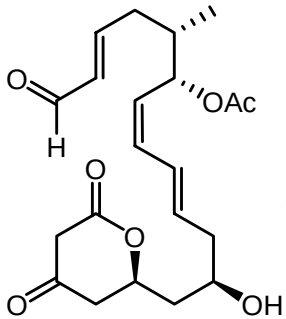
linear polyketide precursor



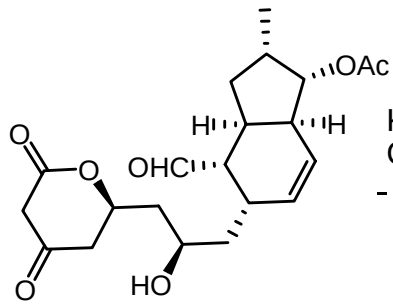
Cochleamycin A

Feeding studies indicate incorporation of six acetate subunits and a single propionate.

allylic oxidation

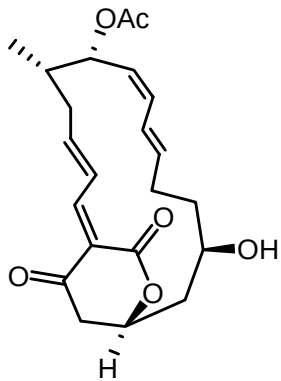


IMDA

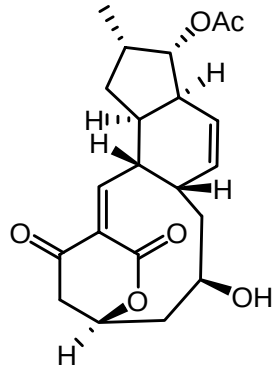


Knoevenagel Condensation

Knoevenagel Condensation



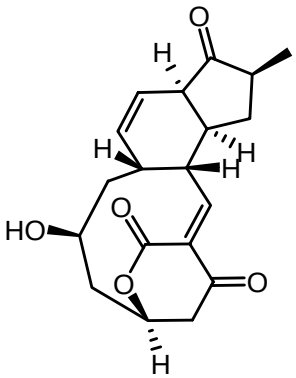
TADA



Cochleamycin A

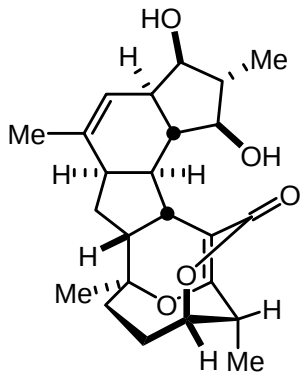
Shindo, K. *J. Antibiotics*, **1996**, *49*, 244.

Biosynthetic Proposal, Tested



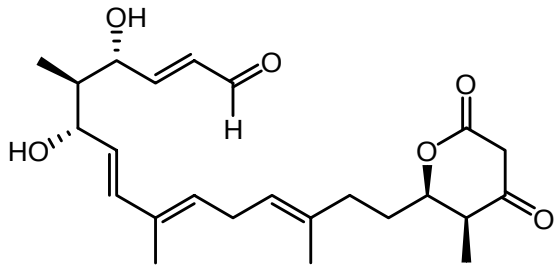
Macquarimicin A

+



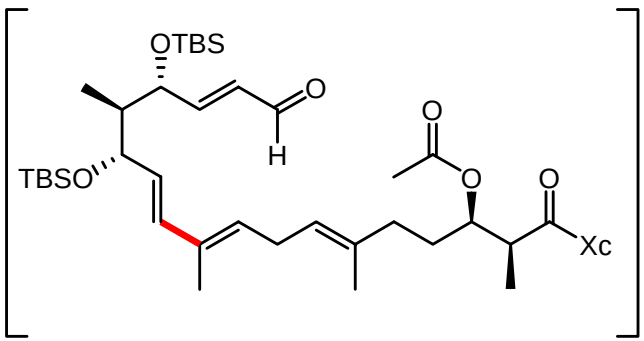
FR182877

(see also Hexacyclinic Acid)



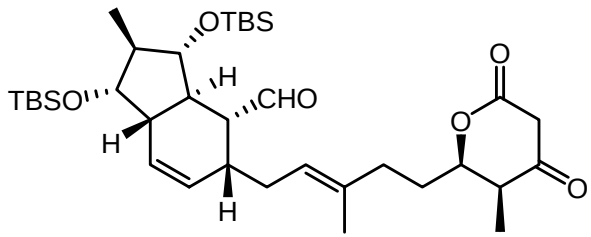
Pd(0)

(Stille)



1. RT

2. KHMDS, -78 C



Diels-Alder selectivity poor

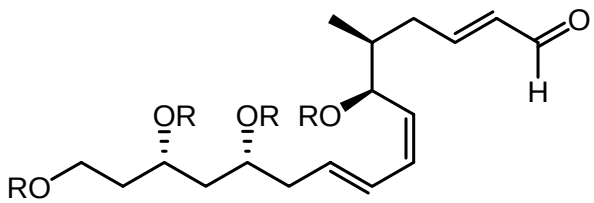
various Knoevenagel conditions

Cyclization of medium rings is difficult using reversible reactions.

macrocycle

Sorenson, *JACS*, **2003**, *125*, 5393.

A Summary of Approaches



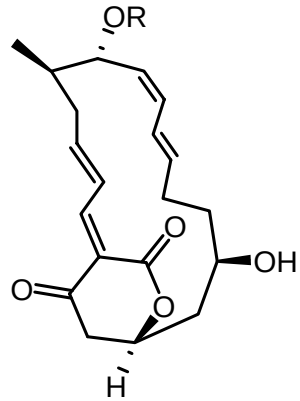
IMDA

Tatsuta (2003, Cochleamycin)

Roush

Tadano

Paquette



TADA

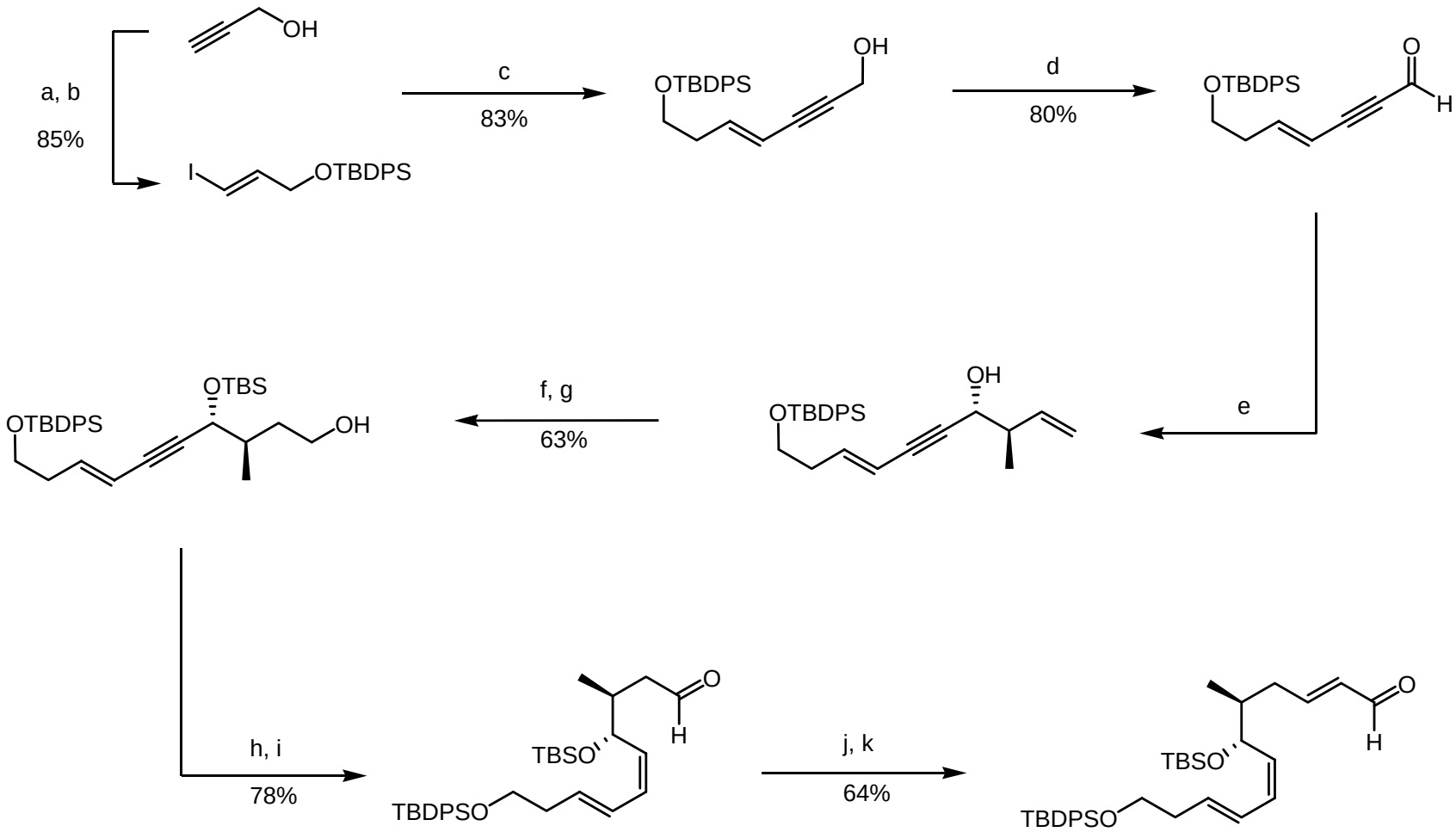
Tadano (2003, Macquarimicins)

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

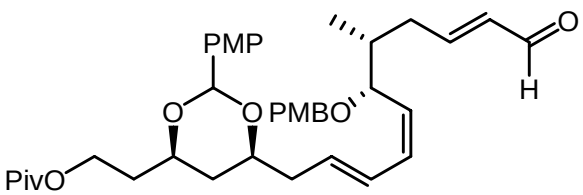


a) TBDPSCl, imid., DMAP; b) $Cp_2Zr(H)Cl$, CH_2Cl_2; I_2; c) $Pd(PPh_3)_2Cl_2$, CuI, NEt_3; d) MnO_2, CH_2Cl_2; e) diisopropyl(S,S)-tartrate-(E)-crotylboronate, PhMe, -78 °C; f) TBSCl, imid.; g) 9-BBN, THF, 0°C, then aq. H_2O_2, aq. NaOH; h) Zn, $Cu(OAc)_2 \cdot H_2O$, $AgNO_3$, MeOH/H_2O; i) DMP, pyr., wet CH_2Cl_2; j) diethyl (N-methoxy-N-methylcarbamoylmethyl)phosphonate, NaH, THF; k) DIBAL-H, THF, -78 °C

Roush, *OL*, **2003**, *5*, 4725

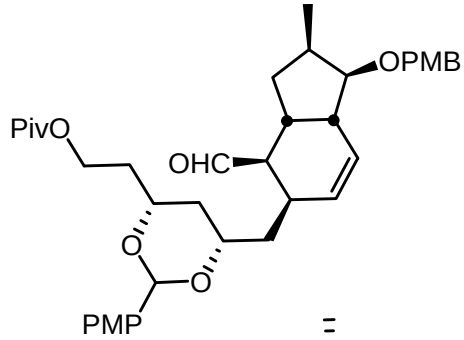
Key IMDA Reactions

Paquette

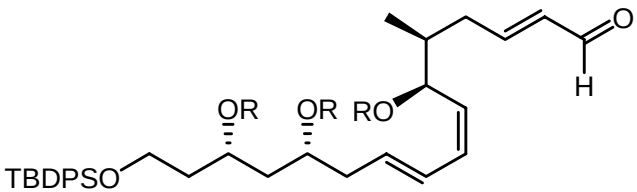


cat. BHT, PhMe, 195 °C,
26 h

moderate yield, one isomer



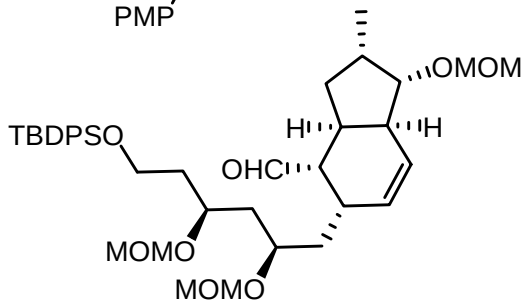
Tatsuta



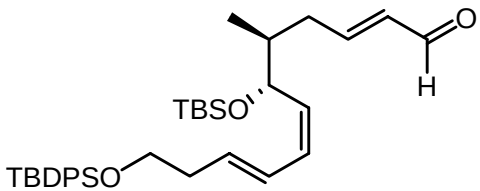
R = MOM

$Yb(fod)_3$, BHT, xylene, 140 °C,
4 h

high yield, one isomer

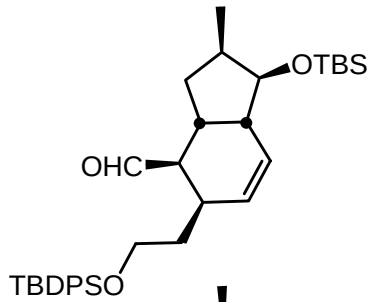


Roush

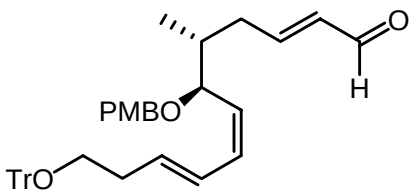


cat. BHT, PhMe, 160 °C,
16 h

83% (minor isomer, 3%)

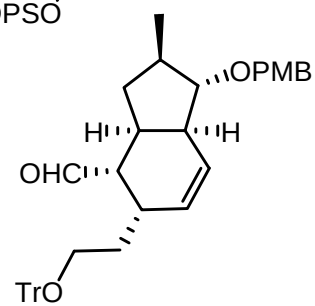


Tadano



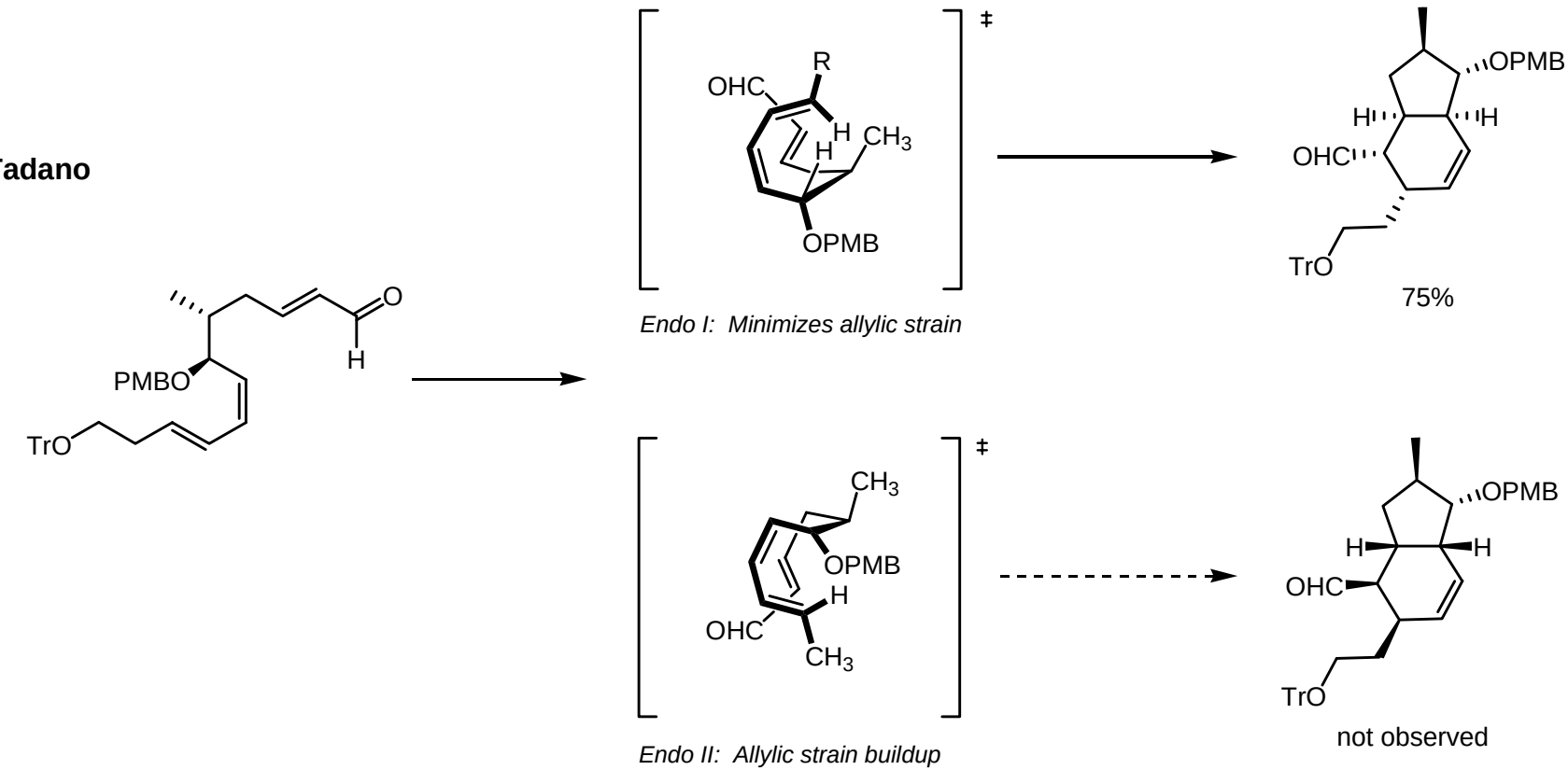
cat. BHT, PhMe, 150 °C

75%, single isomer



IMDA Diastereoselectivity

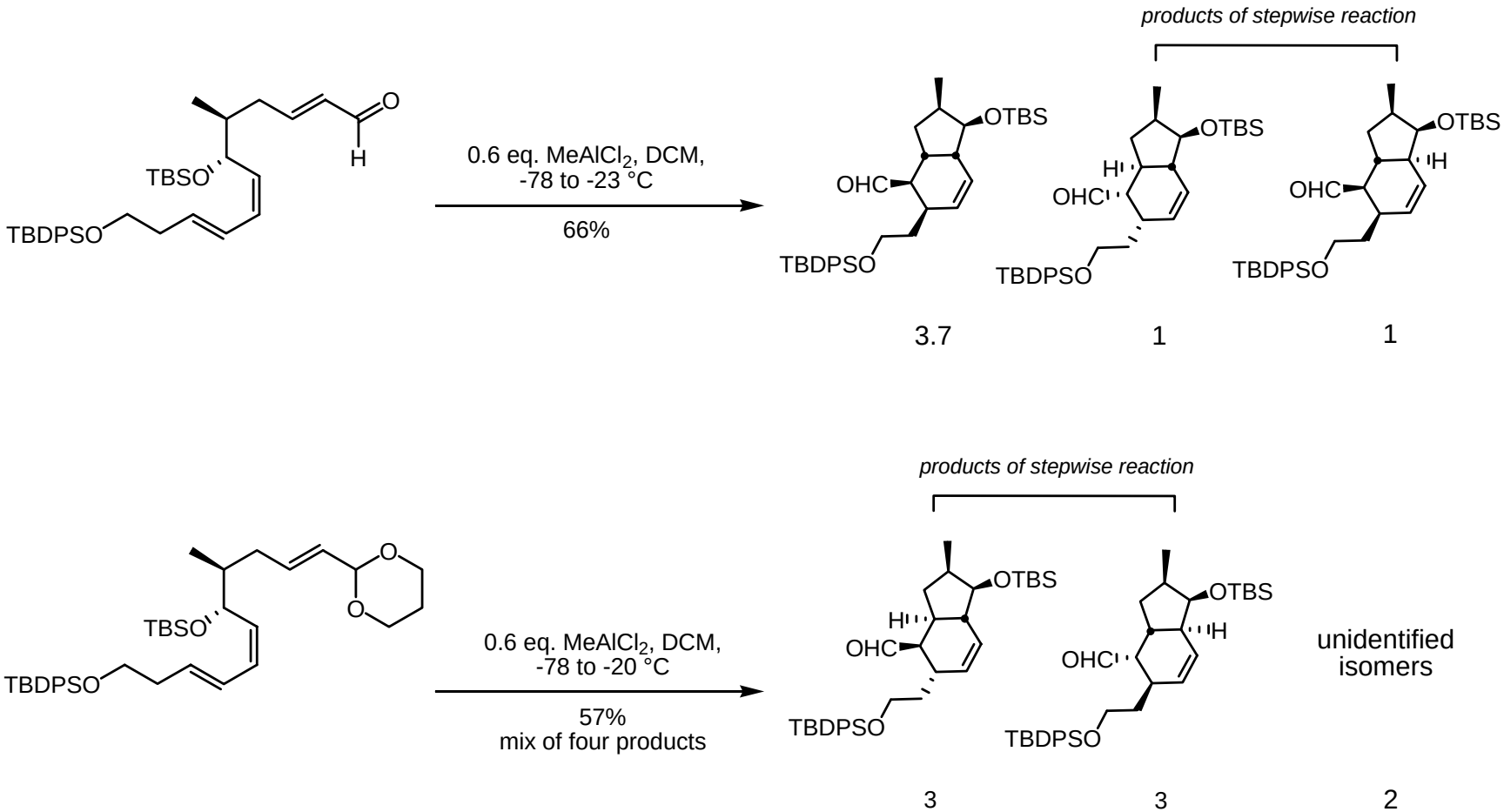
Tadano



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

Tadano, *OL*, **2001**, *3*, 3029

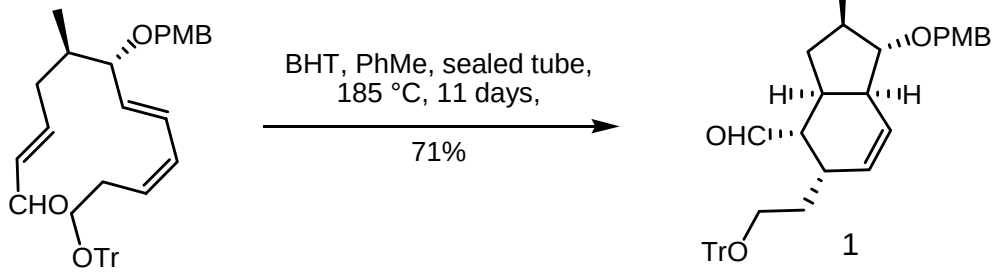
Roush's Lewis Acid Activation Experiments



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

Roush, *OL*, **2003,** *5,* 4725.

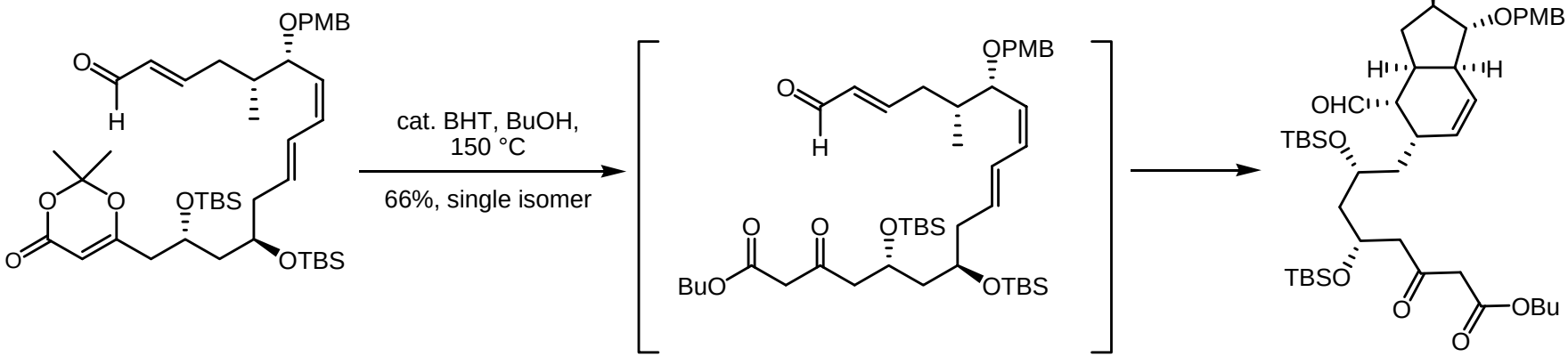
Tadano's Diverse IMDA Targets



1

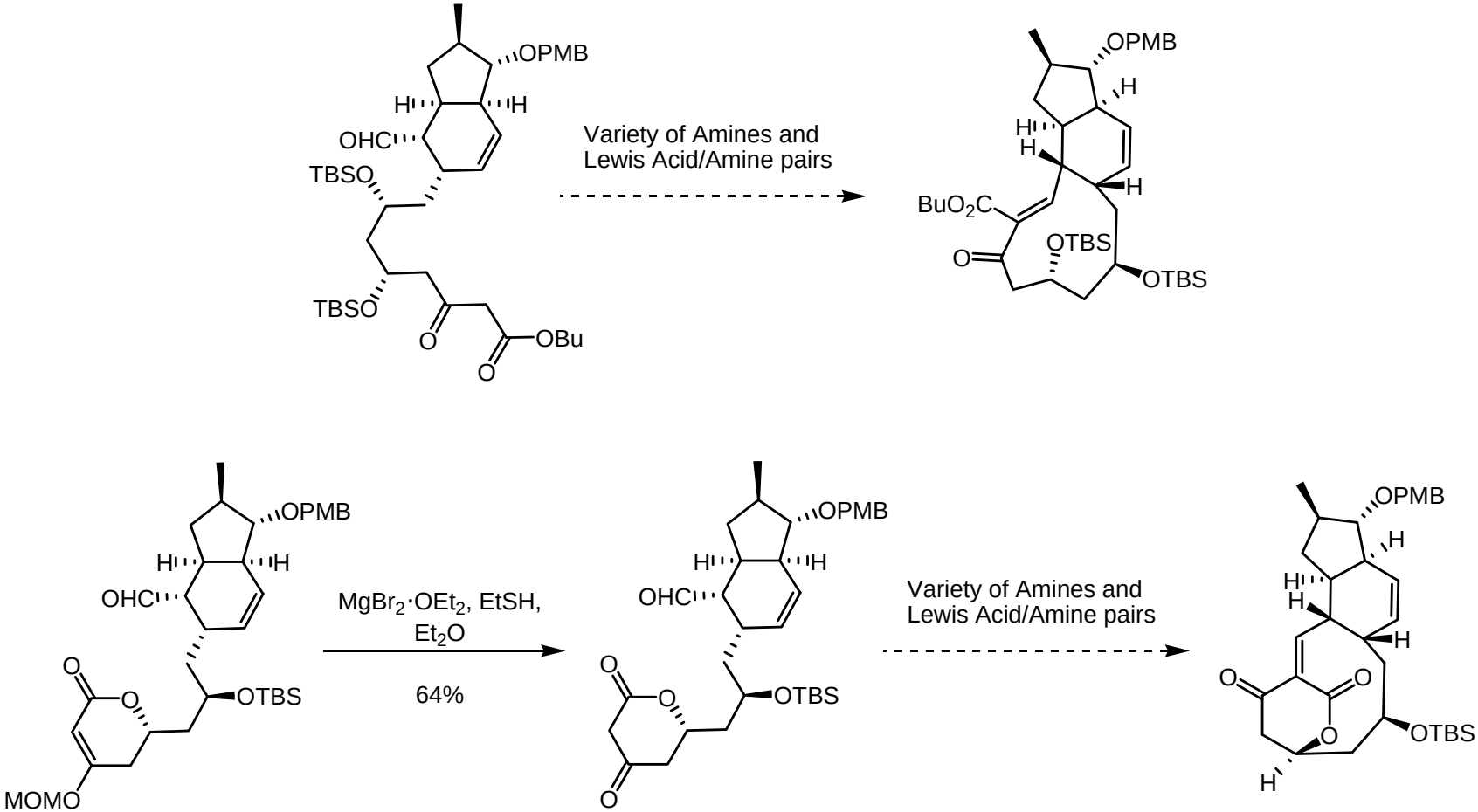
five unidentified isomers

2.3



Tadano, *OL*, **2001,** *3,* 3029.

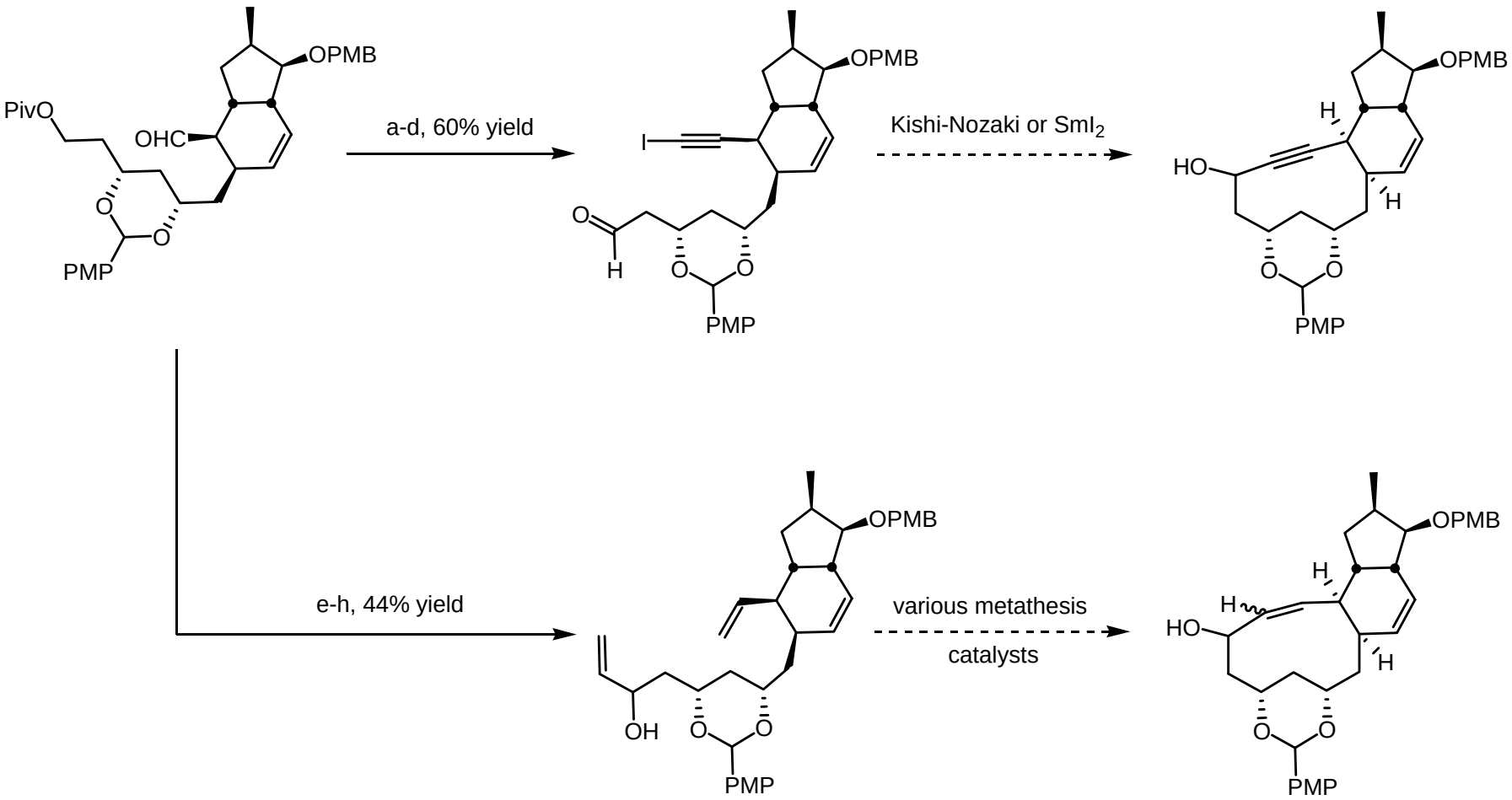
Tadano's Knoevenagel Macrocyclization Efforts



Route abandoned in favor of TADA approach.

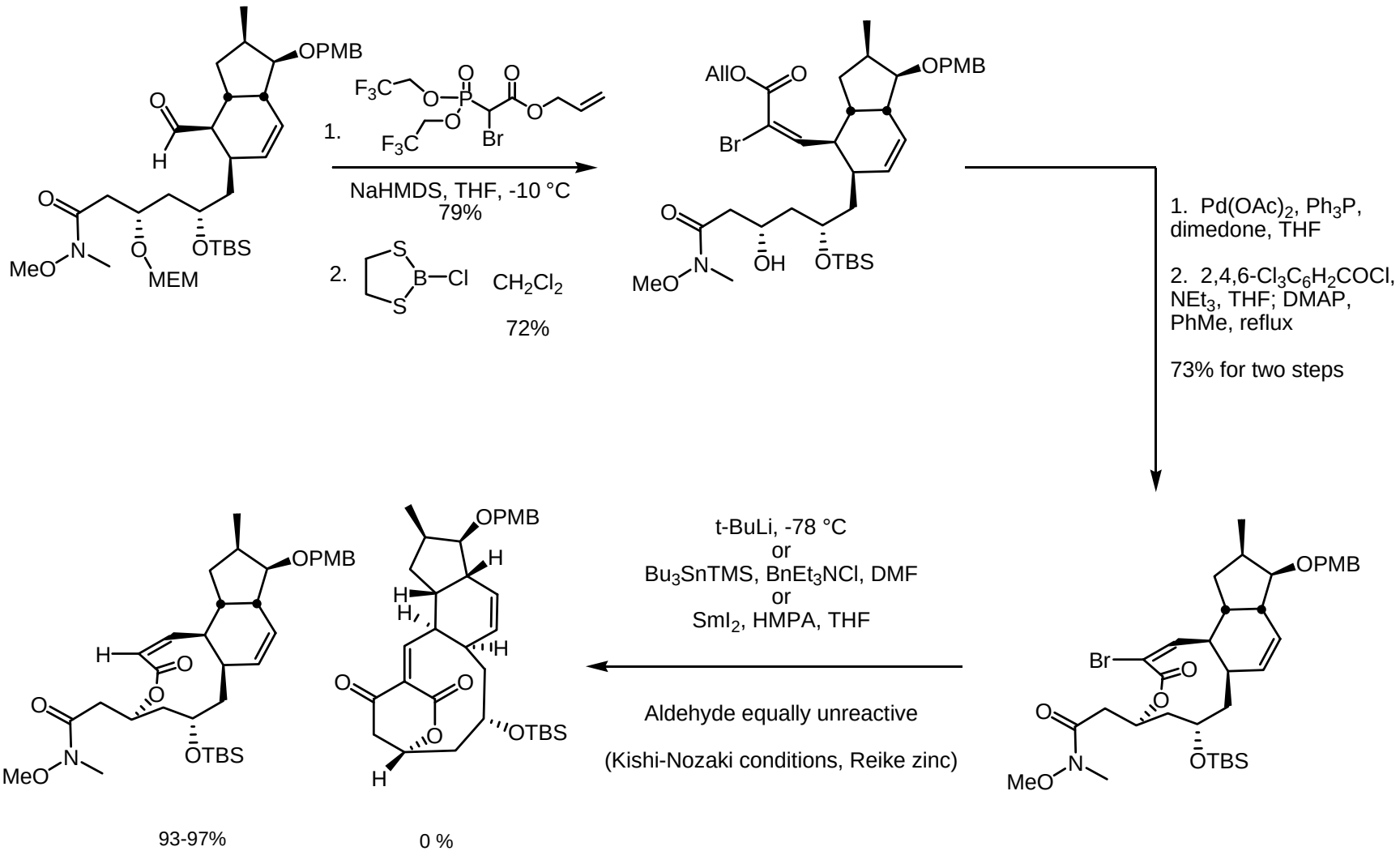
Tadano, *OL*, **2001,** *3,* 3029.

Paquette's Organometallic Macrocyclization Efforts



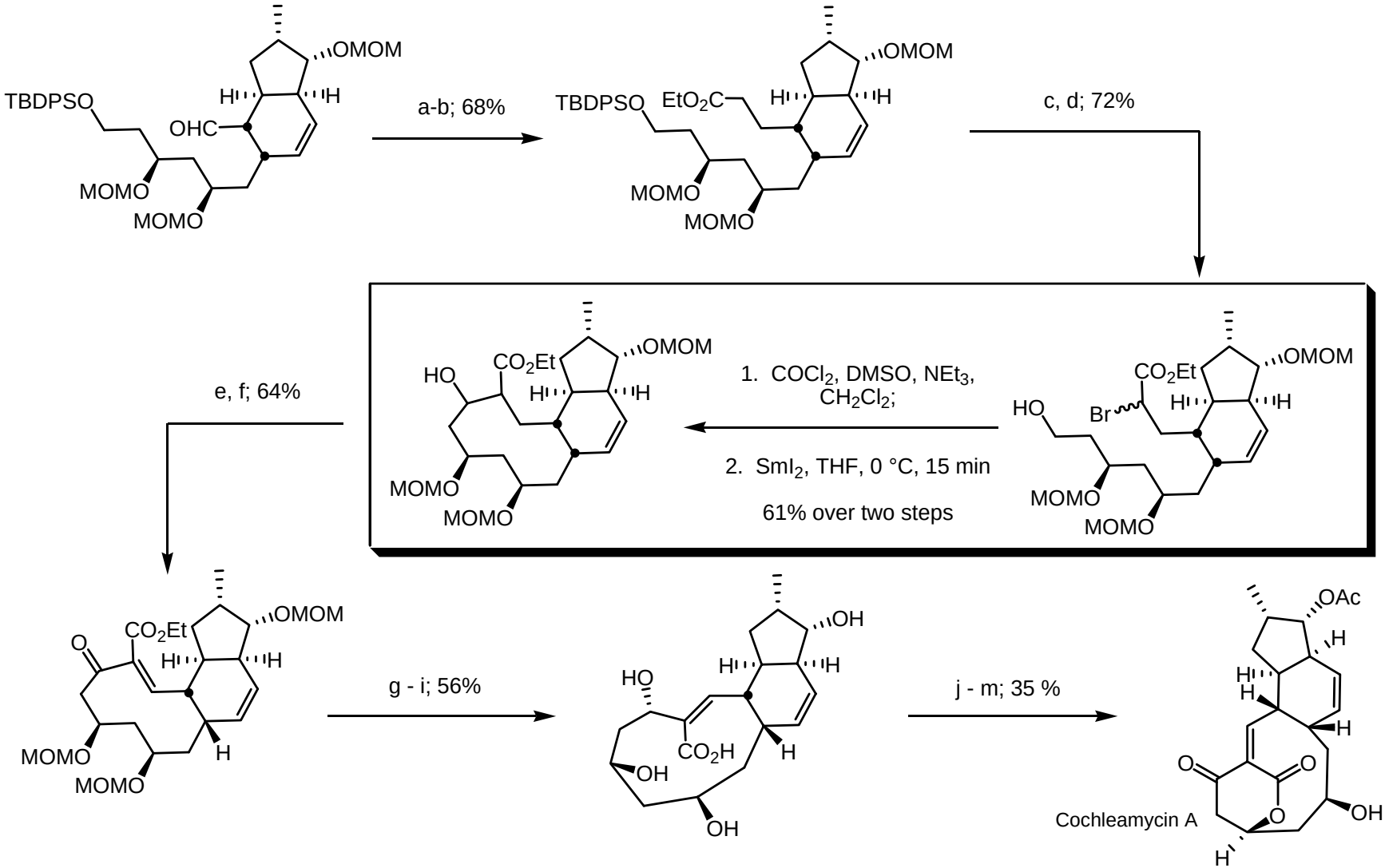
a) CBr_4, PPh_3, pyr., CH_2Cl_2, 0 °C, 98%; b) n^-BuLi, THF, -78 °C, 86%; c) I_2, morpholine, PhH, 50-60 °C, 90%; d) PCC, NaOAc, seives, CH_2Cl_2, 78%.
e) $Ph_3PCH_3^+Br^-$, n-BuLi, THF, -78 °C, 76%; f) n-BuLi, THF, -78 °C, 76%; g) PCC, NaOAC, seives, CH_2Cl_2, 76%; h) $CH_2CHMgBr$, THF, -78 to 0° C, 96%.

Paquette's Macrolactonization Efforts



Paquette, *JOC*, **2004,** *69,* 6441.

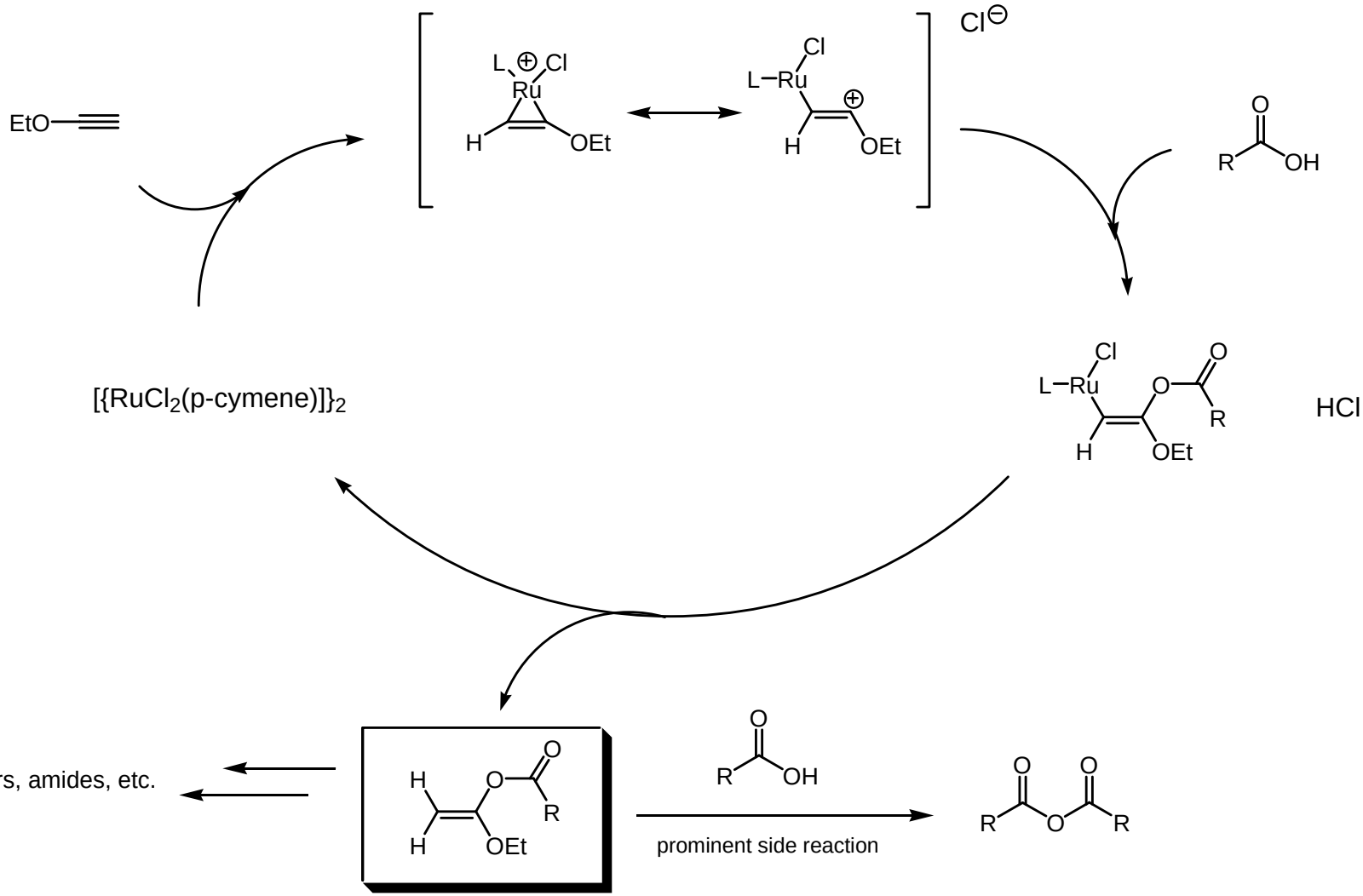
Tatsuta: First Synthesis of Cochleamycin A



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) $NaBH_4$, $CeCl_3 \cdot 7\ H_2O$, EtOH, 0 °C, 70%; h) HCl, EtOH; i) LiOH, H_2O, THF, 60 °C, 80% over two steps; j) ethyl ethynyl ether, $[RhCl_2(p\text{-cymene})]_2$, DMF, 0 °C, 68%; k) CSA, THF, 83%; l) MnO_2, EtOAc, 85%; m) NaOAc, Ac_2O, 60 C, 72%

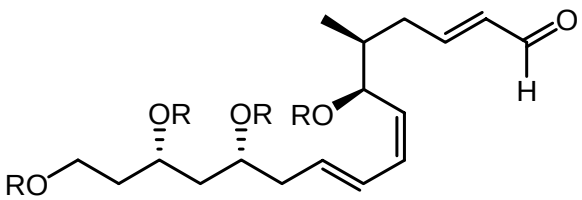
Tatsuta, *J. Antibiotics*, **2003,** *56*, 584.

Kita's Acylation Method



Kita, *J. Chem. Soc. Perkin 1*, **1993,** 2999.

A Summary of Approaches



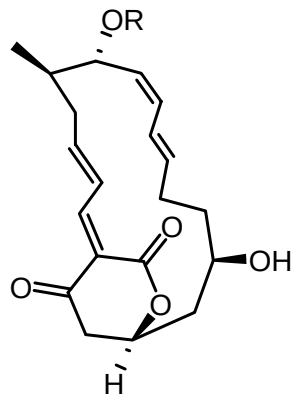
IMDA

Tatsuta (2003, Cochleamycin)

Roush

Tadano

Paquette



TADA

Tadano (2003, Macquarimicins)

Roush (2004, Cochleamycin)

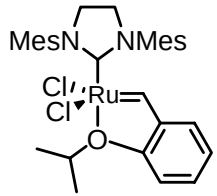
(Evans)

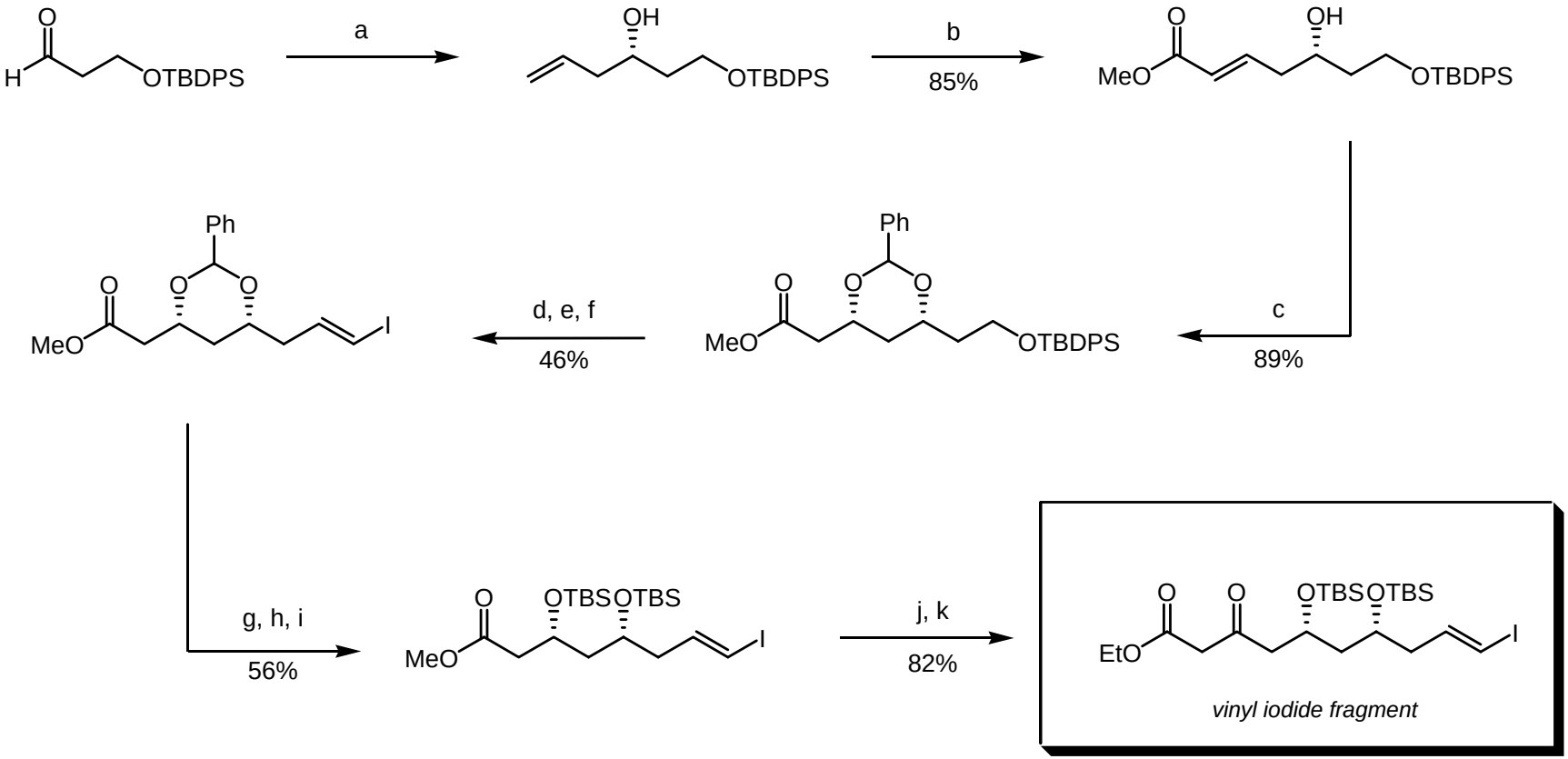
Tadano, *JACS*, **2004**, *126*, 11254
Roush, *OL*, **2004,** *6,* 2043.
Beaver, Ph.D. dissertation, Harvard U., 2002

Synthesis of TADA Substrates

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

Hoveyda catalyst



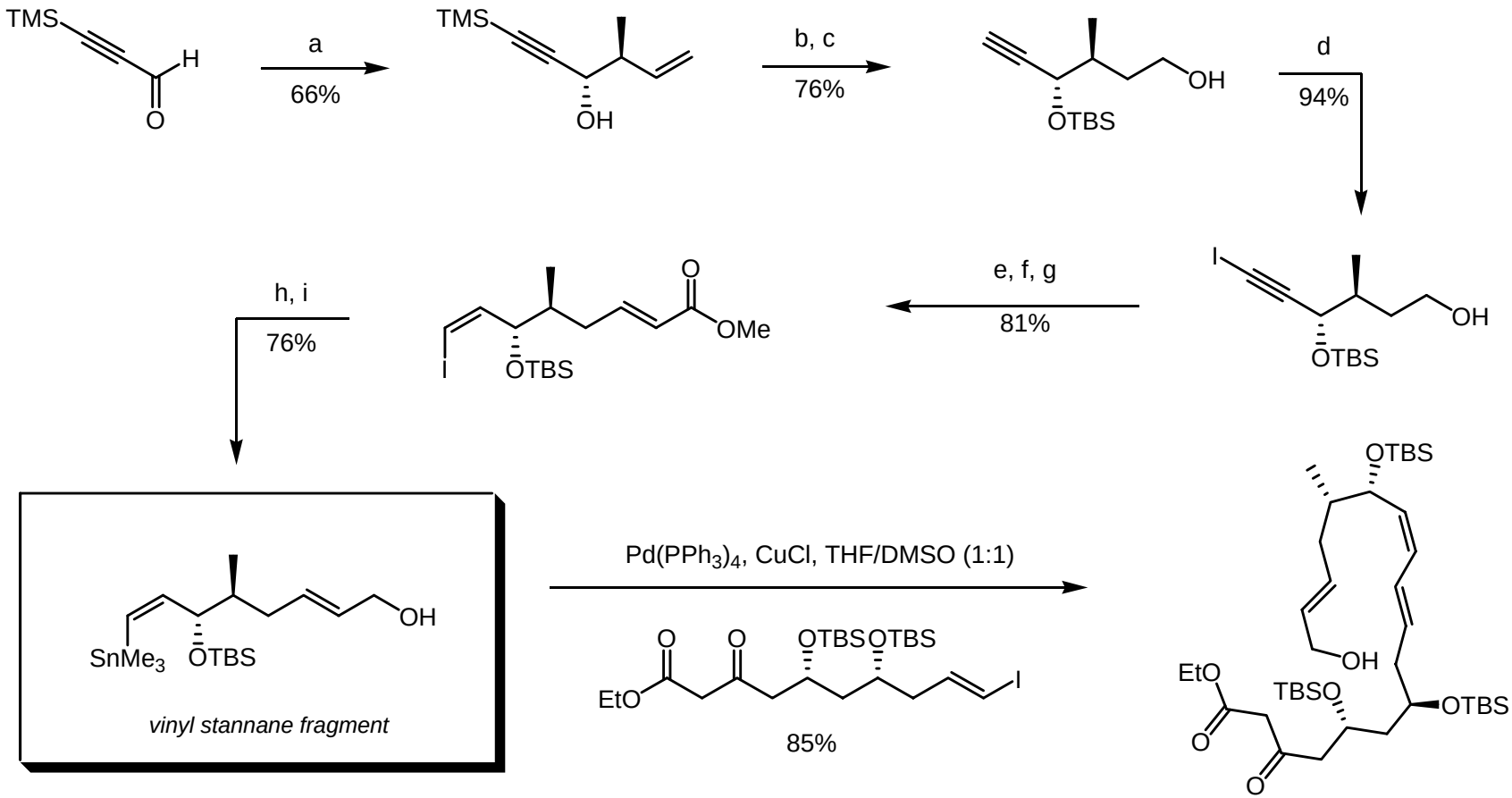


a) (^{d}Ipc)$_2$-B-allyl, THF, -78 °C; b) methyl acrylate, 1.5 mol% Hoveyda catalyst, CH_2Cl_2, reflux; c) PhCHO, tBuOK, THF, 0 °C; d) $(HF)_3Et_3N$, MeCN, 40 °C; e) SO_3·pyr, DMSO, iPr_2NEt, CH_2Cl_2, 0 °C; f) $CrCl_2$, CHI_3, dioxane/THF; g) 80% AcOH, THF, 95 °C; h) Amberlite IRA-400(OH), MeOH; i) TBSOTf, 2,6-lutidine, CH_2Cl, -78 °C; j) DIBAL-H, -78 °C; k) ethyl diazoacetate, $SnCl_2$, CH_2Cl_2.

Roush, *OL*, **2004**, *6*, 2043

Synthesis of TADA Substrates

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

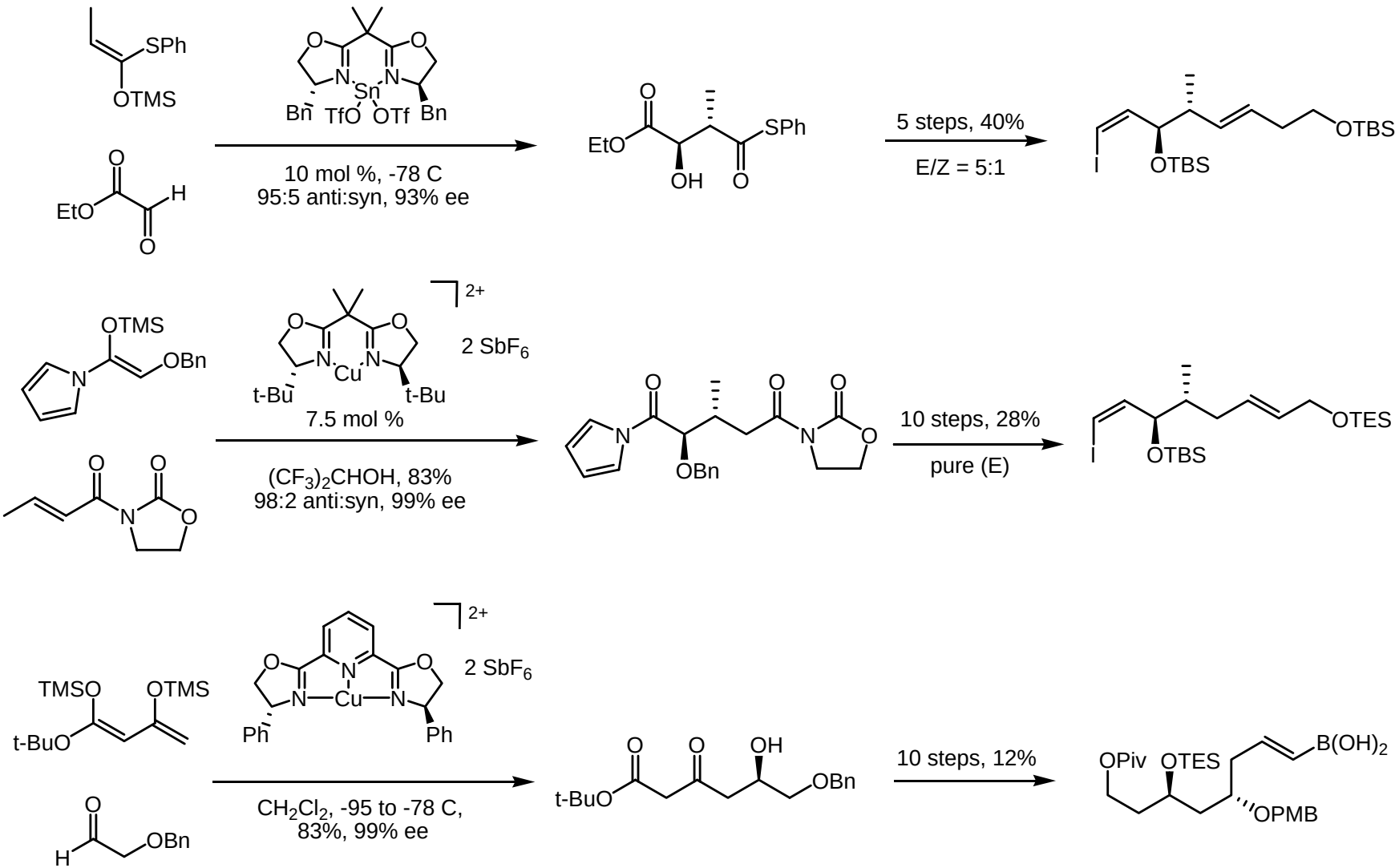


a) (^{d}Ipc)$_2$-B-allyl, THF, -78 °C; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, -78 °C; c) 9-BBN, THF; then aq. NaOH/H_2O_2; d) n-BuLi, THF, -50 C, then I_2; e) o-Nitrobenzenesulfonylhydrazide, Et_3N, THF/i-PrOH (1:1); f) SO_3*pyr, DMSO, iPr_2NEt, CH_2Cl_2, 0 °C; g) Trimethyl phosphonoacetate, LiCl, NEt_3,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

Roush, *OL*, **2004**, *6*, 2043

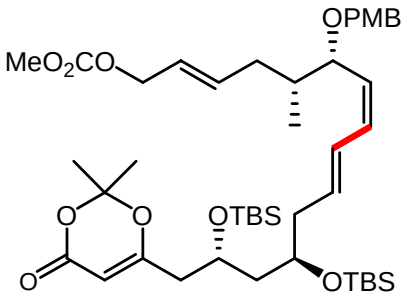
Synthesis of TADA Substrates

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



Beaver, Ph.D. thesis, Harvard, 2002

Tadano's First TADA Target



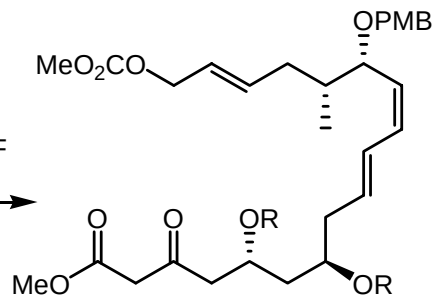
Formed via Stille coupling

Optional:

1. HF·pyr., pyr., THF
2. MOMCl

Then:

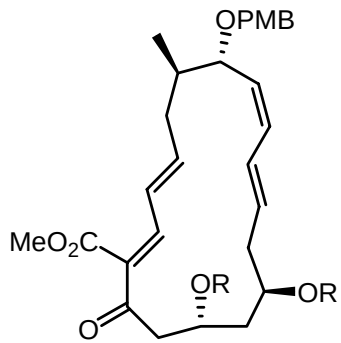
MeOH, PhMe,
110 °C, 98%
(90% over 3 steps)



R = TBS or MOM

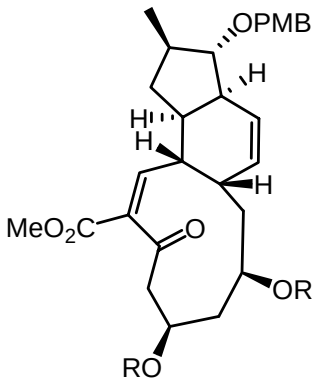
1. Pd(PPh$_3$), dppe, THF, 84%
2. NaHMDS, THF, -78 °C; PhSeCl, PhMe
3. mCPBA, CH_2Cl_2

51-59%



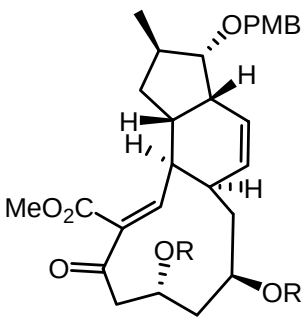
Exclusively (Z)

BHT, 130 °C,
PhMe



10%

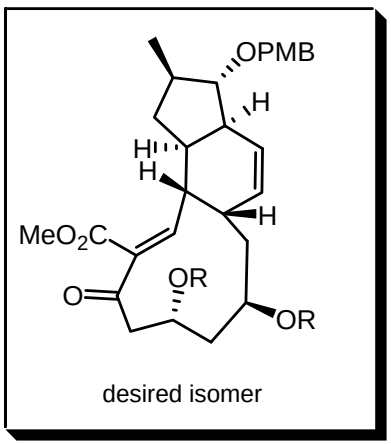
R = TBS



29%

<10%?

R = MOM



desired isomer

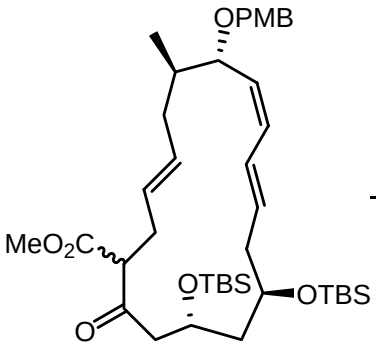
0%

29%

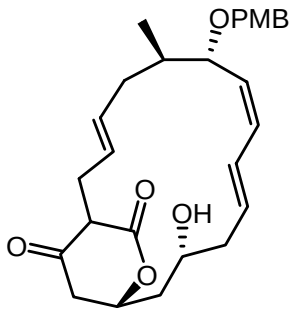
(worse, efforts to deprotect failed)

Tadano, *JACS*, **2004**, *126*, 11254

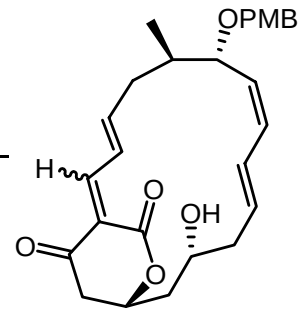
Tadano's Second TADA Target



1. HF·pyr., pyr.
2. iPr_2NEt, MeOH

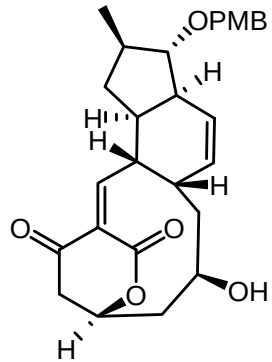


1. $PhSeCl$, NEt_3, CH_2Cl_2, -78 °C
2. mCPBA, CH_2Cl_2, -50 °C



BHT, PhMe, 130 °C

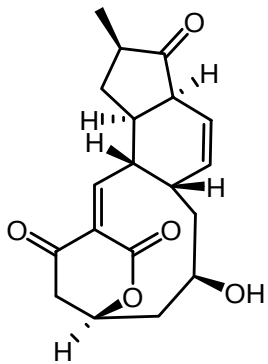
47% over five steps



1. TESOTf, lutidine
2. DDQ, pH 7 buffer

3. DMP, $NaHCO_3$
4. PPTS, MeOH

66%

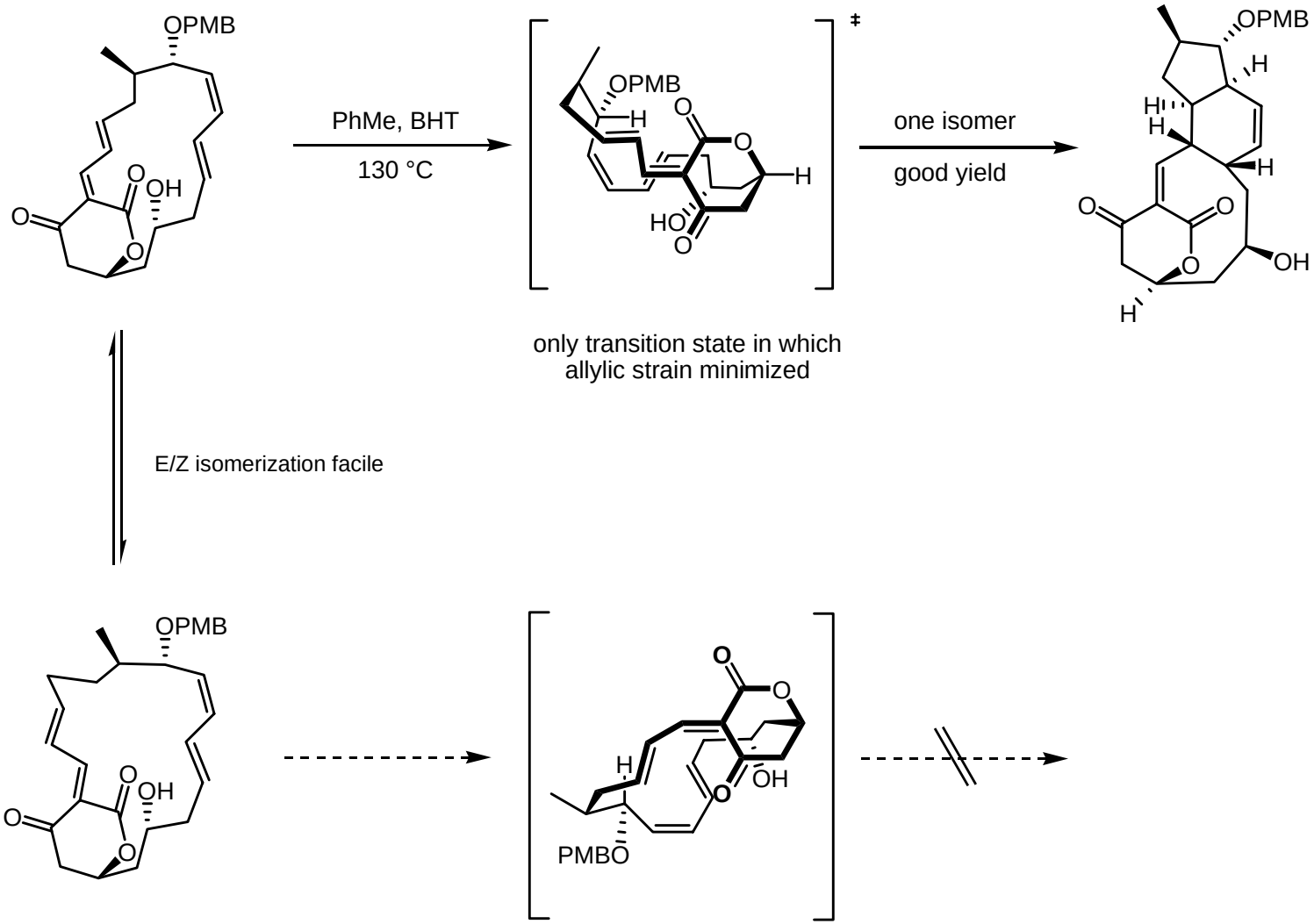


Macquarimicin A

"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..."

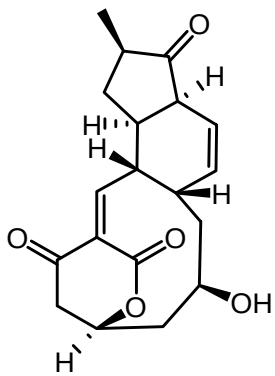
Tadano, *JACS*, **2004**, *126*, 11254

TADA Stereoselectivity

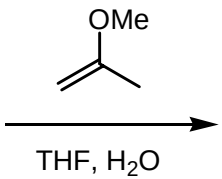


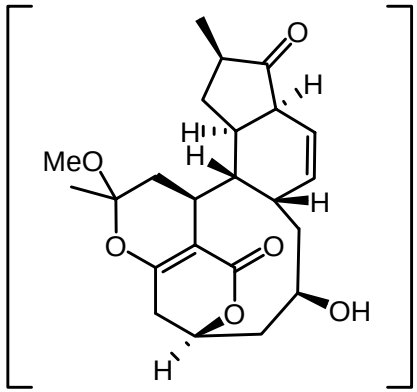
Tadano, *JACS*, **2004**, *126*, 11254

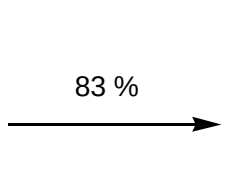
Tadano: Macquaramicins B and C

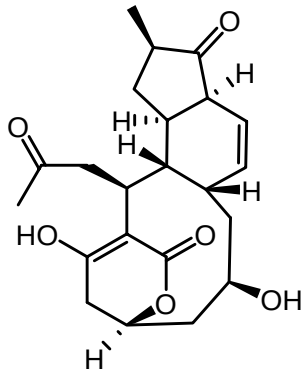


Macquarimicin A

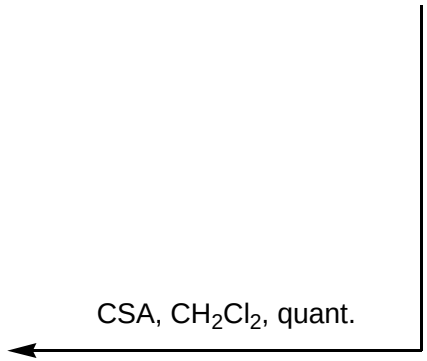


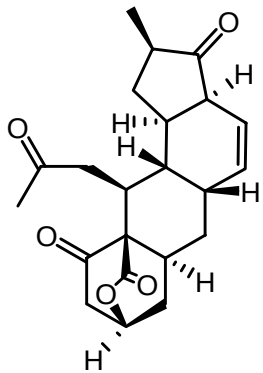






Macquarimicin B

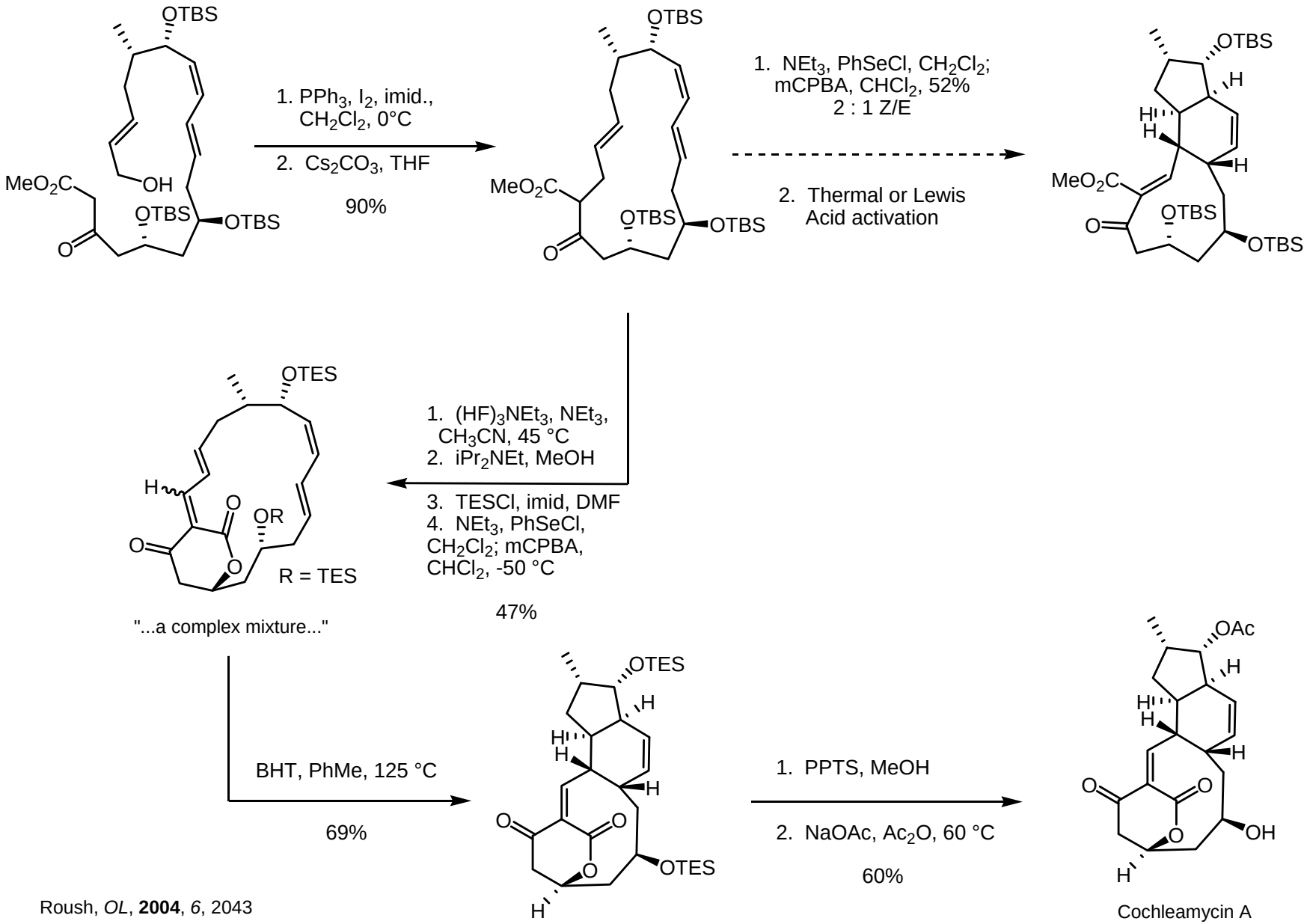




Macquarimicin C

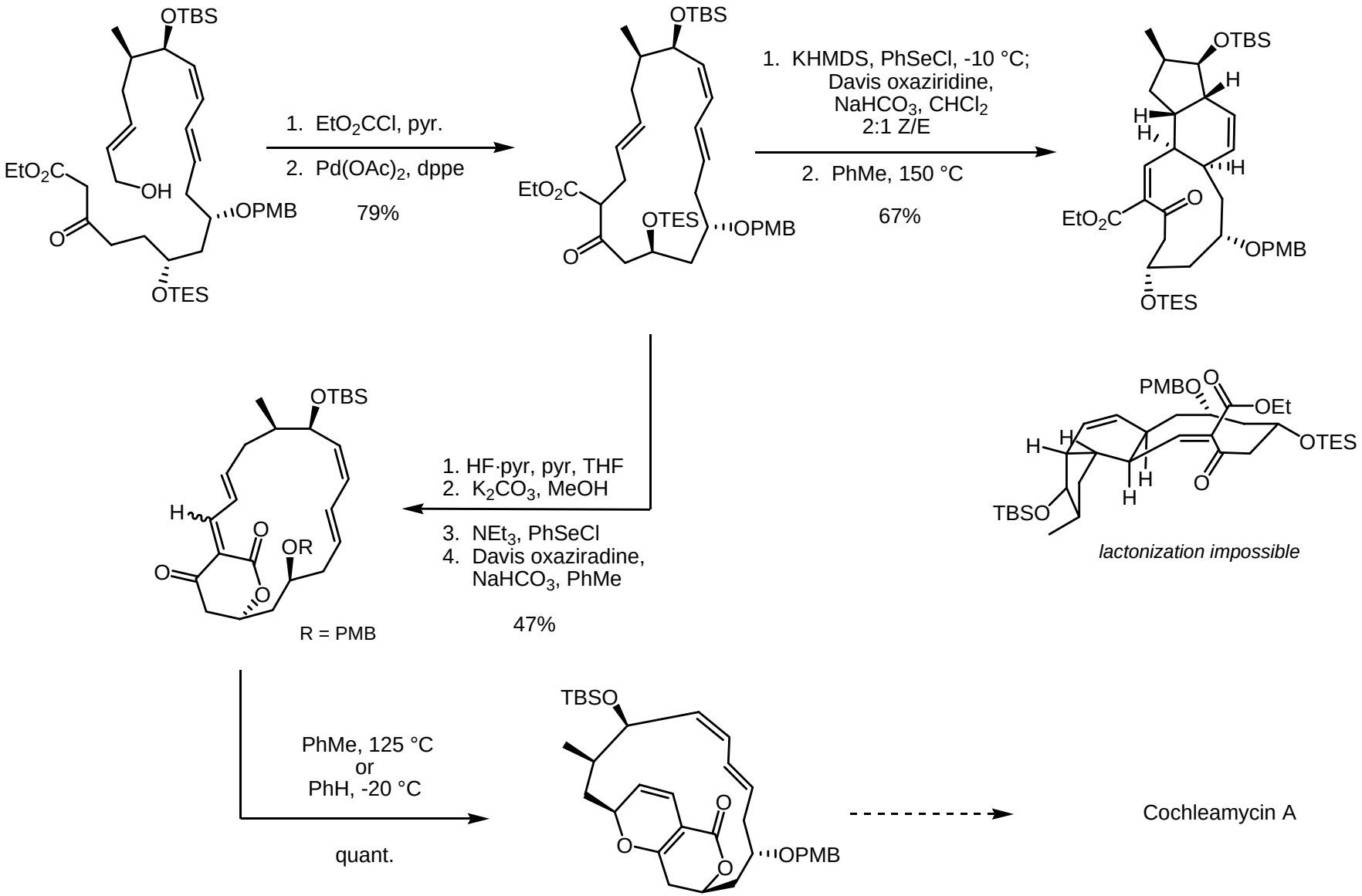
Tadano, *JACS*, **2004**, *126*, 11254

Roush's TADA Efforts



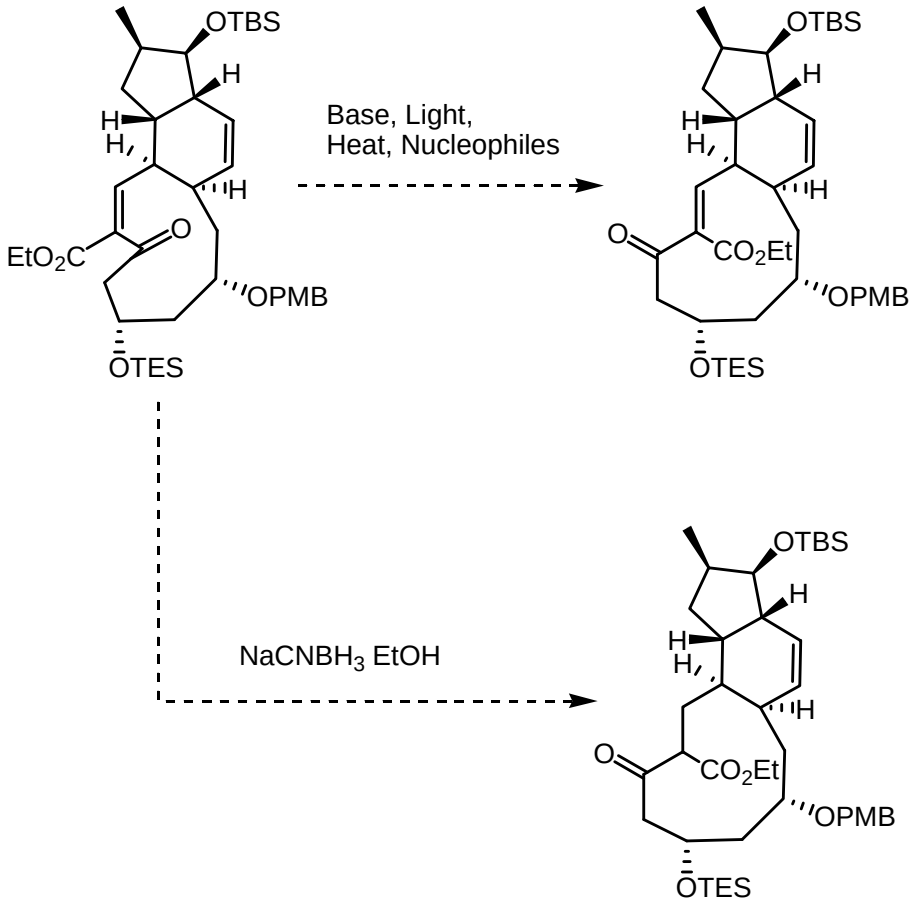
Roush, *OL*, **2004**, *6*, 2043

Evans' TADA Approach



Beaver, Ph.D. dissertation, Harvard U., 2002

Evans' TADA Approach



Calculations suggest thermodynamic preference strongly opposed to desired geometry.

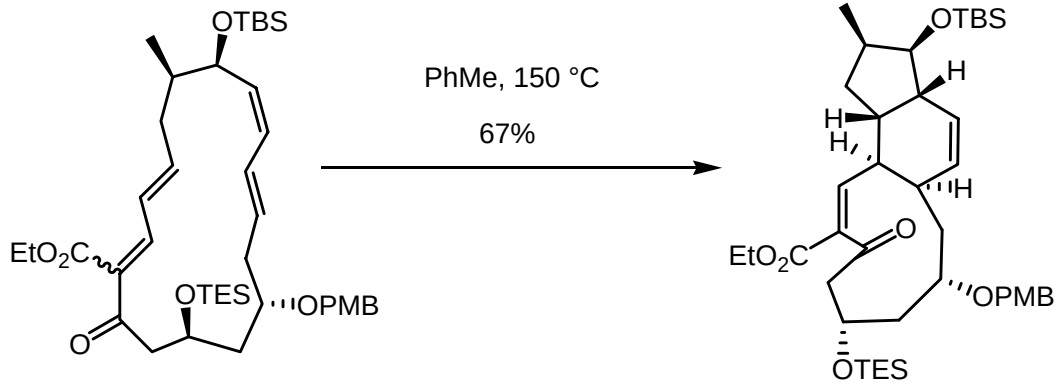
More vigorous conditions over-reduced or decomposed a model system.

Beaver, Ph.D. dissertation, Harvard U., 2002

Summary of TADA Reactions

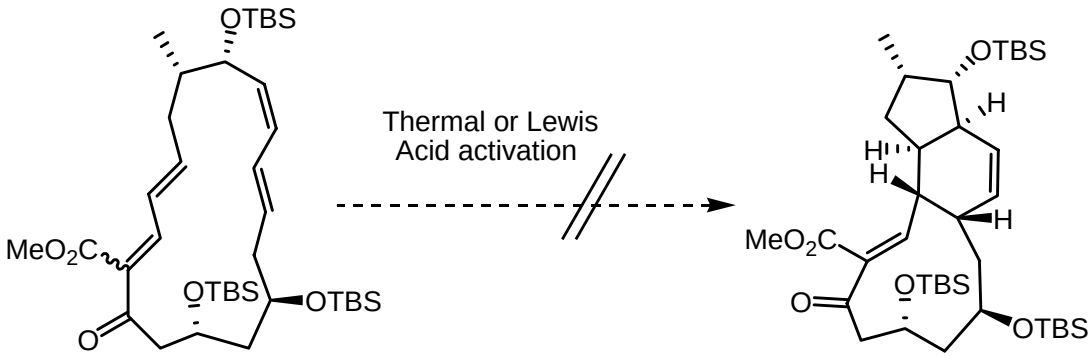
Evans

Z / E = 2 : 1



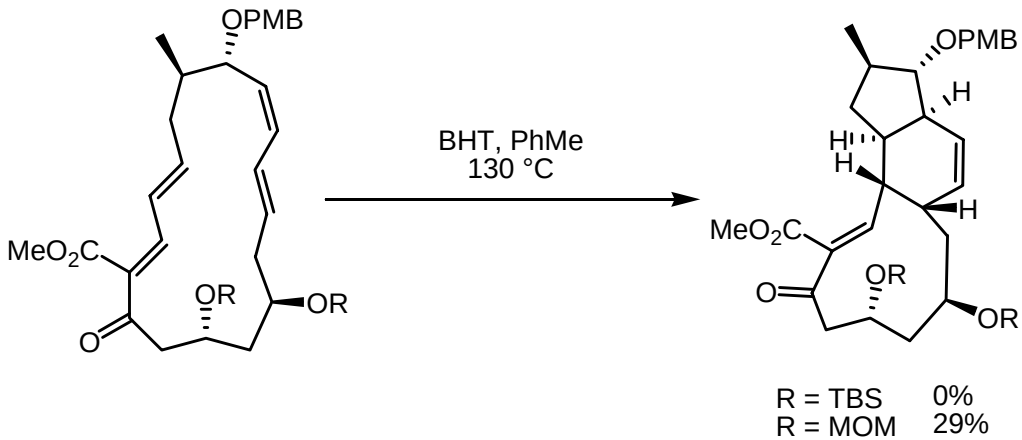
Roush

Z / E = 2 : 1



Tadano

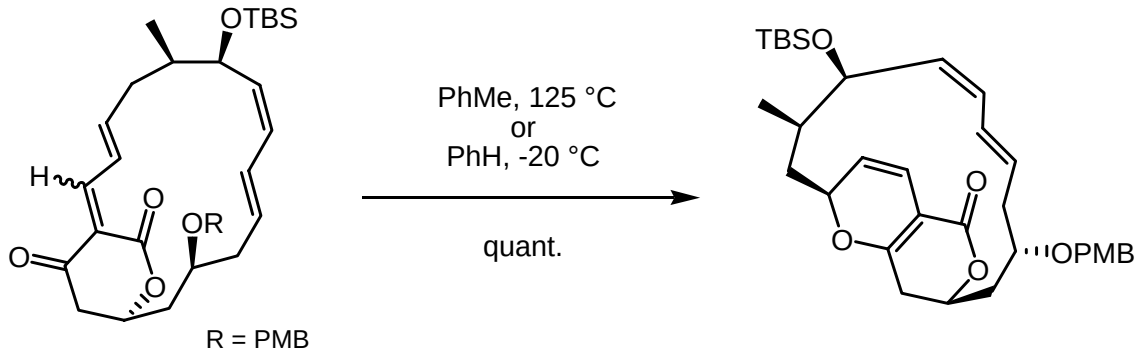
Z / E > 20 : 1



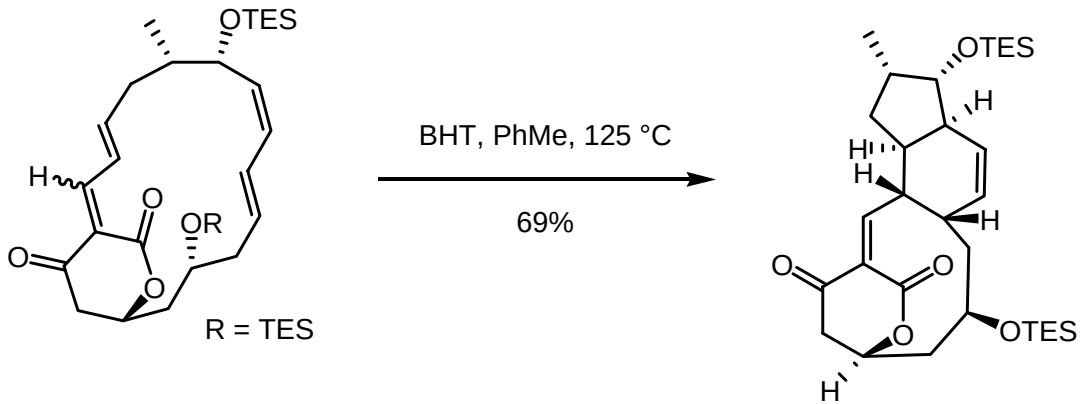
R = TBS 0%
R = MOM 29%

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.