Alois Fürstner

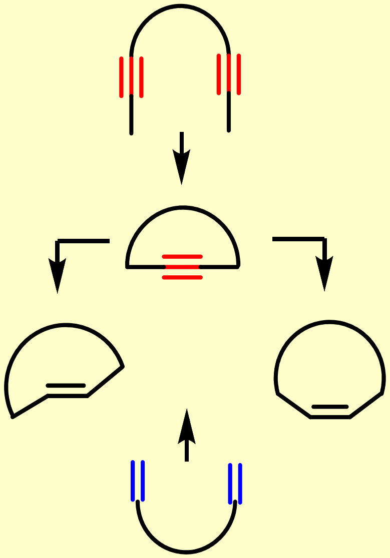
Max-Planck-Institut für Kohlenforschung

Mülheim/Ruhr, Germany

TINKERING WITH NATURES MACROLIDES

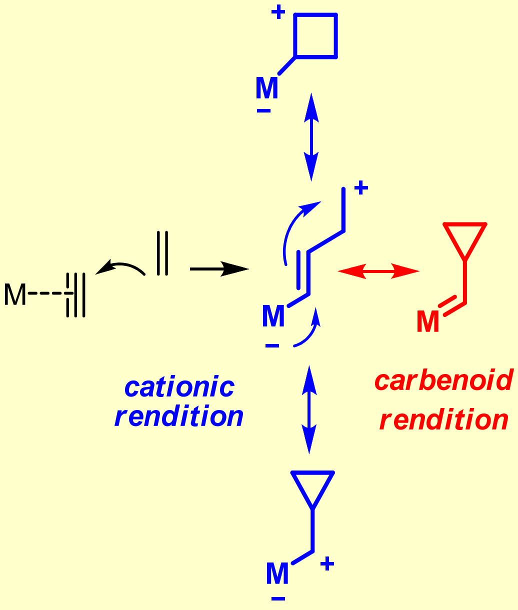
OUR AGENDA

METATHESIS



A. Fürstner,
ACIE **2000**, *39*, 3012

PLATINUM / GOLD



A. Fürstner, P. W. Davies,
ACIE **2007**, *46*, 3410

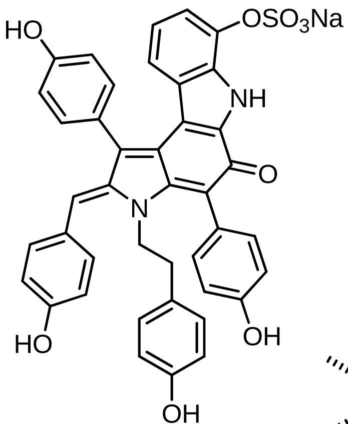
IRON CATALYSIS

Fe^{-II}: [Ar] $3d^8$ $4s^2$

Pd^0: [Kr] $3d^{10}$ $4s^0$

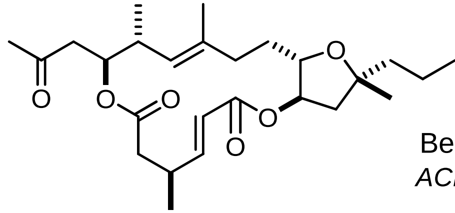
Cu^{+I}: [Kr] $3d^{10}$ $4s^0$

B. D. Sherry, A. Fürstner,
Acc. Chem. Res., in press



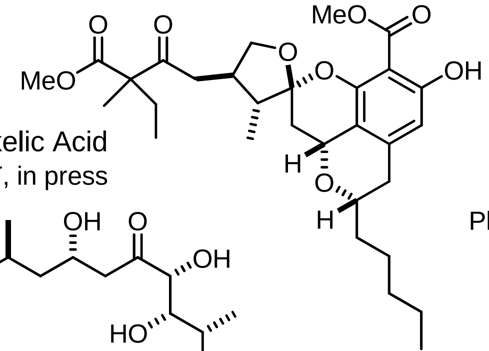
Dictyodendrin E

JACS **2006**, *128*, 8087



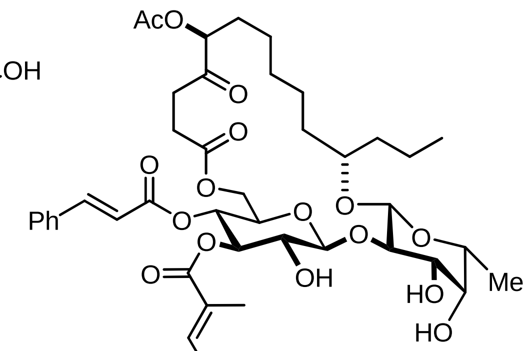
Amphidinolide X

JACS **2004**, *126*, 15970



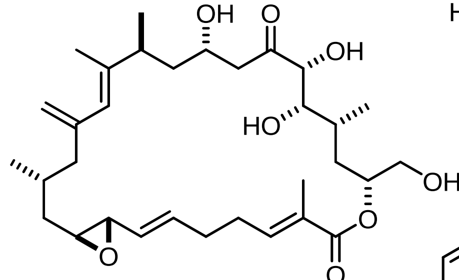
Berkelic Acid

ACIE, in press



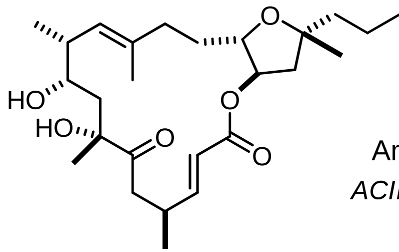
Ipomoeassin E

JACS **2007**, *129*, 1906



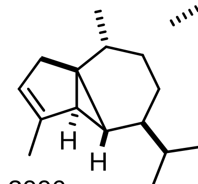
Amphidinolide H

ACIE **2007**, *46, 9265*



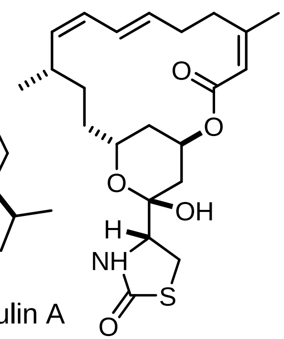
Amphidinolide Y

JACS **2006**, *128*, 9194



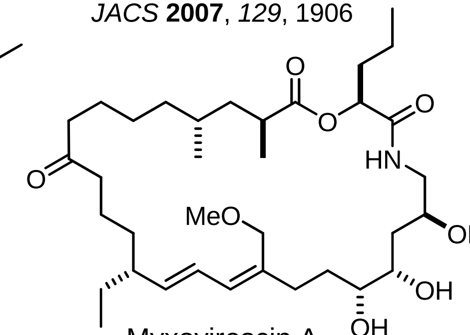
Cubebene

Chem. Eur. J., **2006**, *12,* 3006



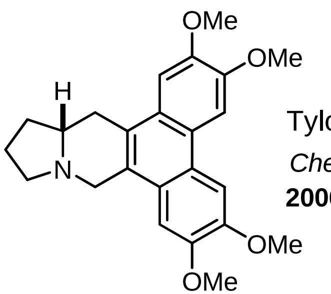
Latrunculin A

PNAS **2005**, *102*, 8103



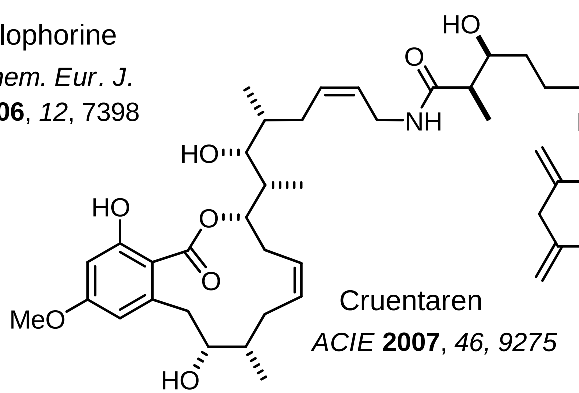
Myxovirescin A_1

Chem. Eur. J. **2007**, *13*, 8762



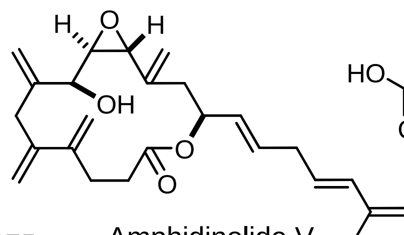
Tylophorine

Chem. Eur. J.
2006, *12*, 7398



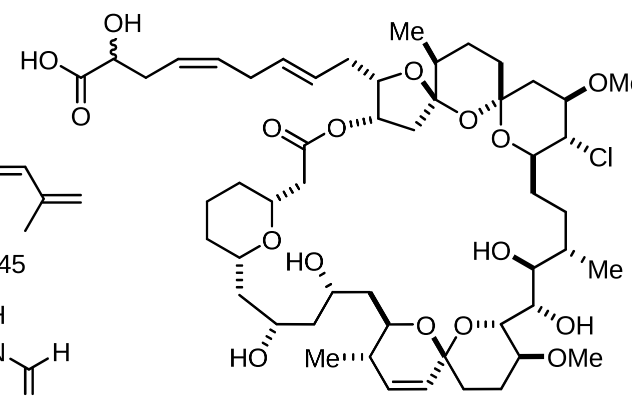
Cruentaren

ACIE **2007**, *46, 9275*



Amphidinolide V

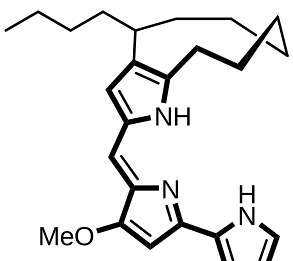
ACIE **2007**, *46*, 5545



Spirastrellolide A (all fragments)

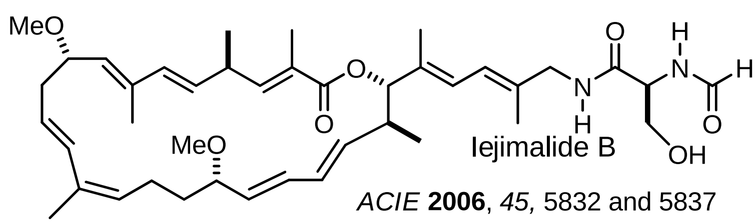
ACIE **2006**, *45,* 5506 and 5510

Chem. Commun. **2007**, 3045



Butylcycloheptylprodigiosin

Chem. Eur. J. **2007**, *13*, 1929



Iejimalide B

ACIE **2006**, *45,* 5832 and 5837

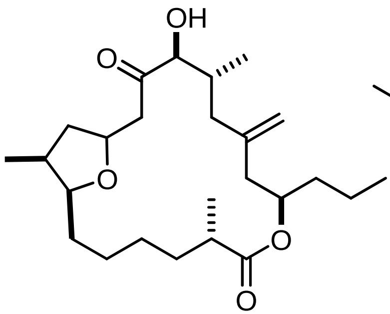
JACS **2007**, *129*, 9150

THE AMPHIDINOLIDES

secondary metabolites produced by marine dinoflagellates (*Amphidinium* sp.) living in symbiosis with Okinawan marine flatworms

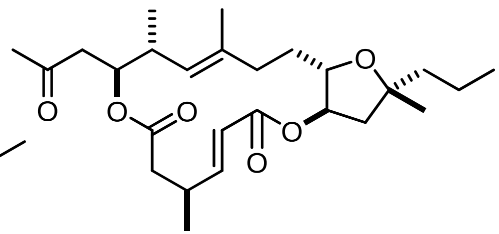
Review: J.-I. Kobayashi et al., *Nat. Prod. Rep*. **2004**, *21*, 77

“OUR” AMPHIDINOLIDES



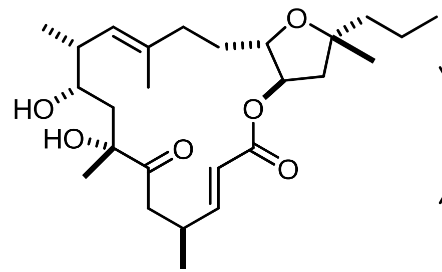
Amphidinolide T1

JACS **2003**, *125*, 15512



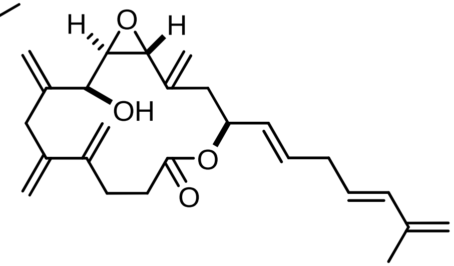
Amphidinolide X

JACS **2004**, *126*, 15970



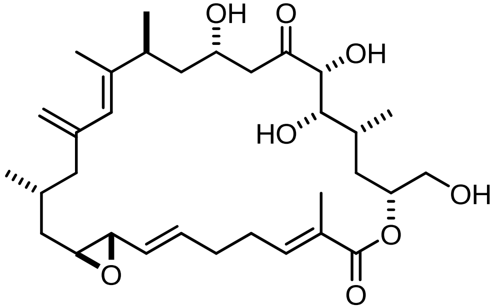
Amphidinolide Y

JACS **2006**, *128*, 9194



Amphidinolide V

ACIE **2007**, *46*, 5545



Amphidinolide H

ACIE **2007**, 46, 9265

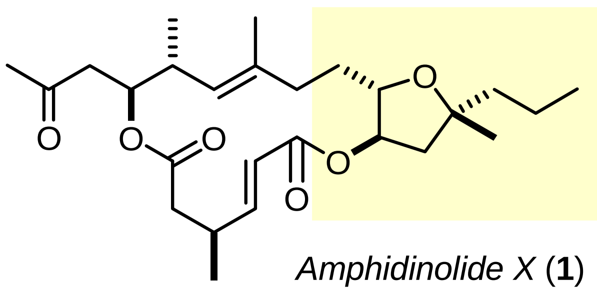
very scarce

mixed polyketide biosynthesis

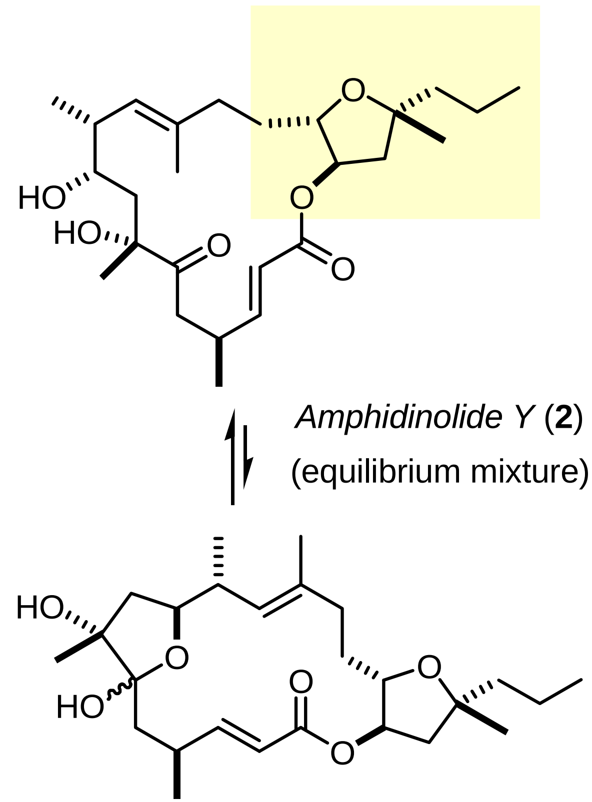
(very) potent cytotoxicity

generally unknown mode of action

AMPHIDINOLIDE X AND Y



Amphidinolide X (**1**)



Amphidinolide Y (**2**)

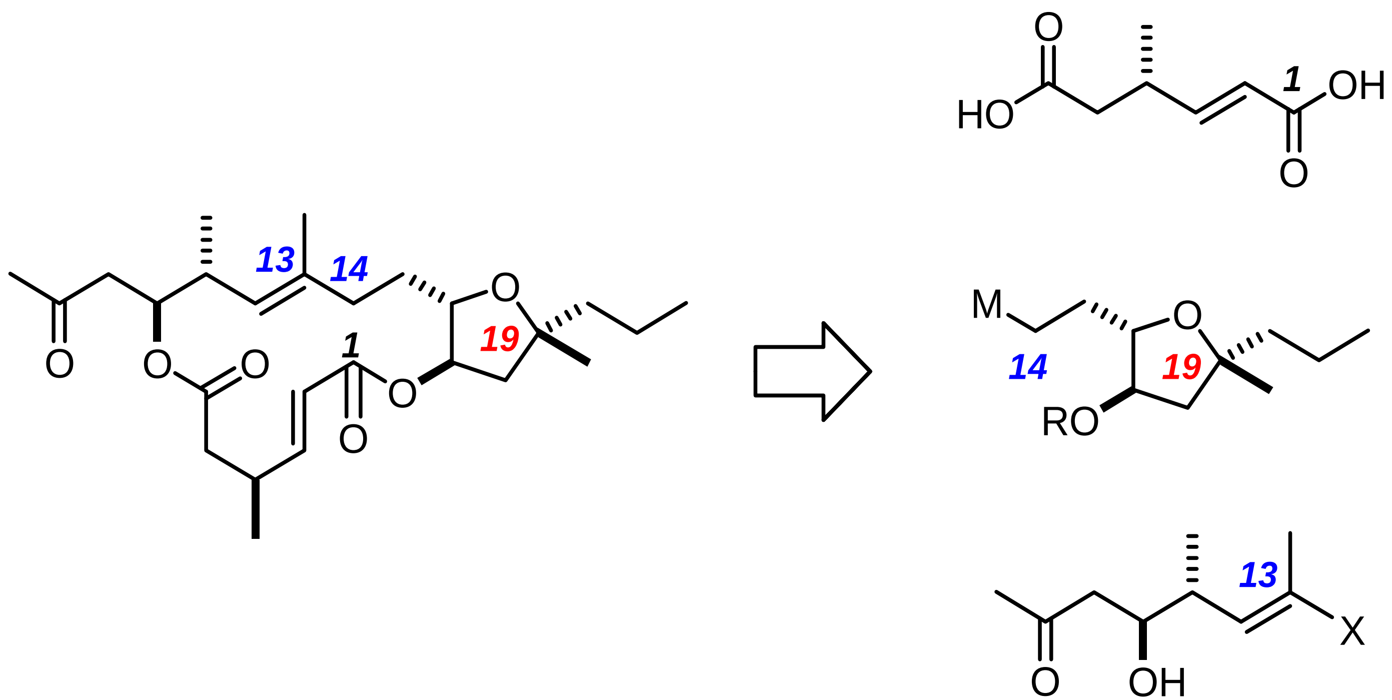
(equilibrium mixture)

very scarce cytotoxic secondary metabolite of symbiotic dinoflagellate *Amphidinium sp*., cf. :

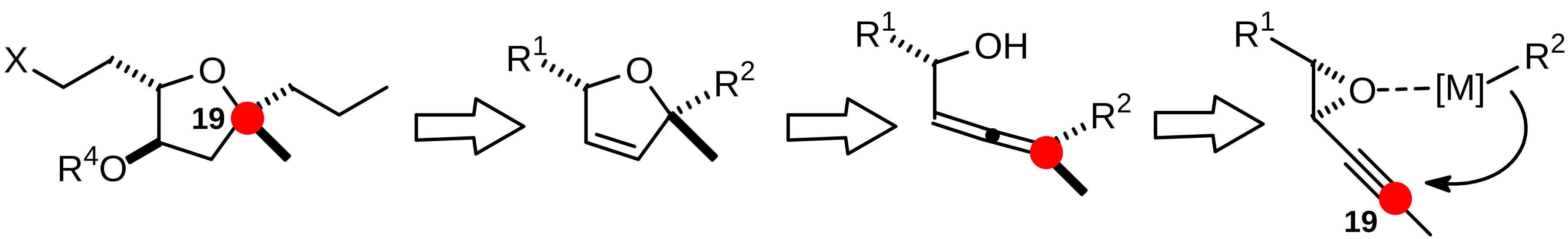
J. Kobayashi et al., *JOC* **2003**, *68*, 5339 (A_X); *JOC* **2003**, *68*, 9109 (A_Y)

for a review on the amphidinolides see: J. Kobayashi et al., *Nat. Prod. Rep*. **2004**, *21*, 77

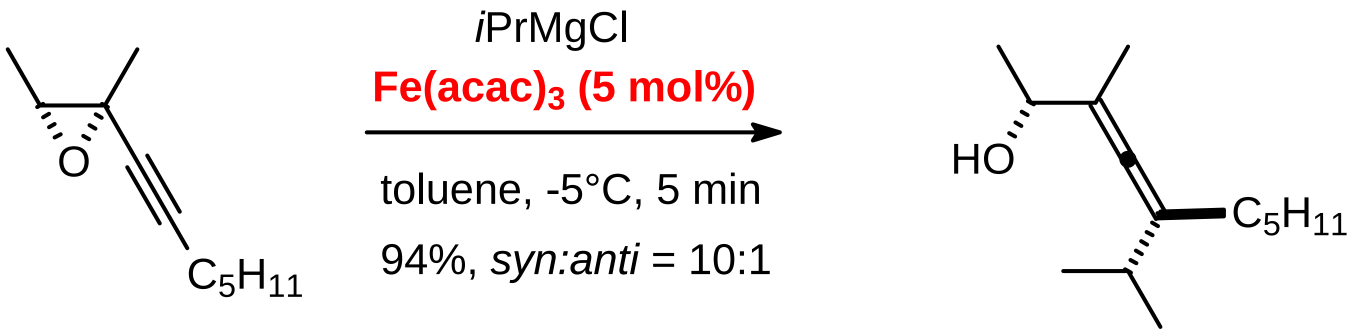
AMPHIDINOLIDE X: RETROSYNTHETIC ANALYSIS



AMPHIDINOLIDE X: STRATEGIC DISCONNECTION



IRON CATALYZED SYNTHESIS OF ALLENOLS



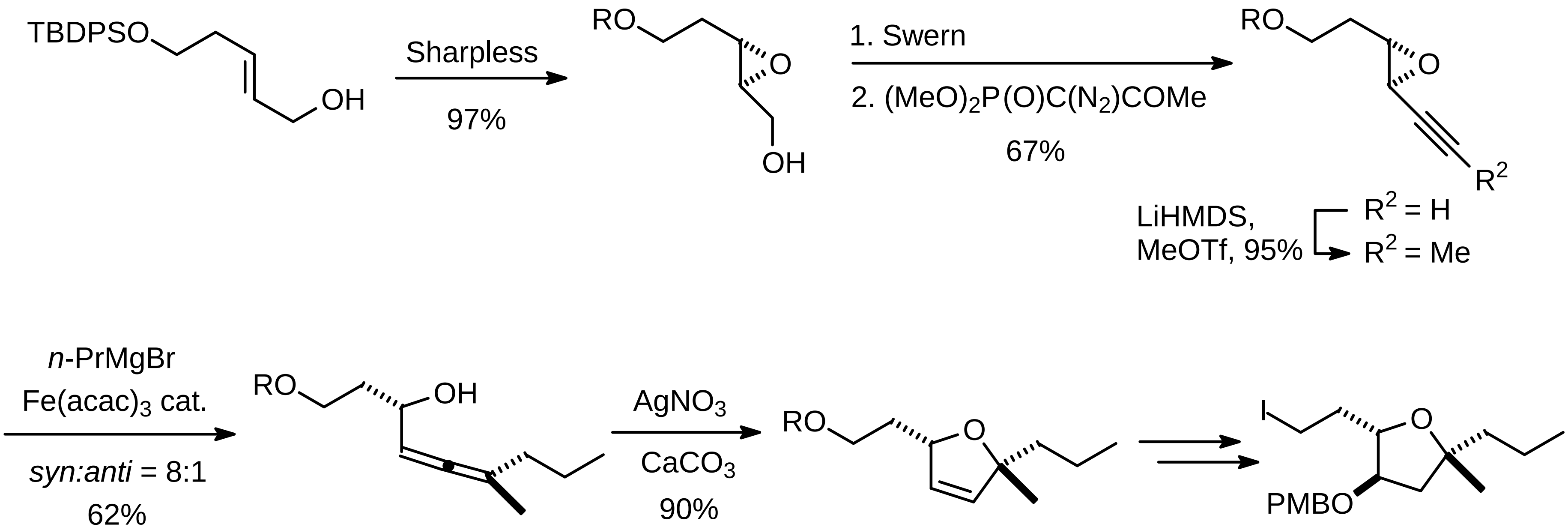
ee = 93%

ee = 93% (*syn*)

A. Fürstner, M. Méndez, *Angew*. *Chem*. *Int*. *Ed*. **2003**, *42*, 5355

for a short review on Fe-catalyzed cross coupling, see: A. Fürstner, R. Martin *Chem. Lett*. **2005**, *34*, 624

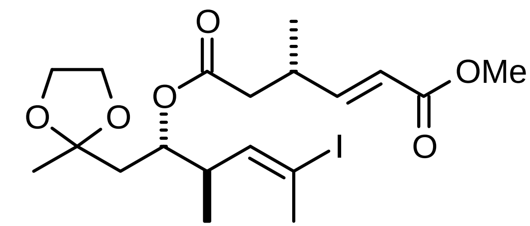
TOTAL SYNTHESIS OF AMPHIDINOLIDE X

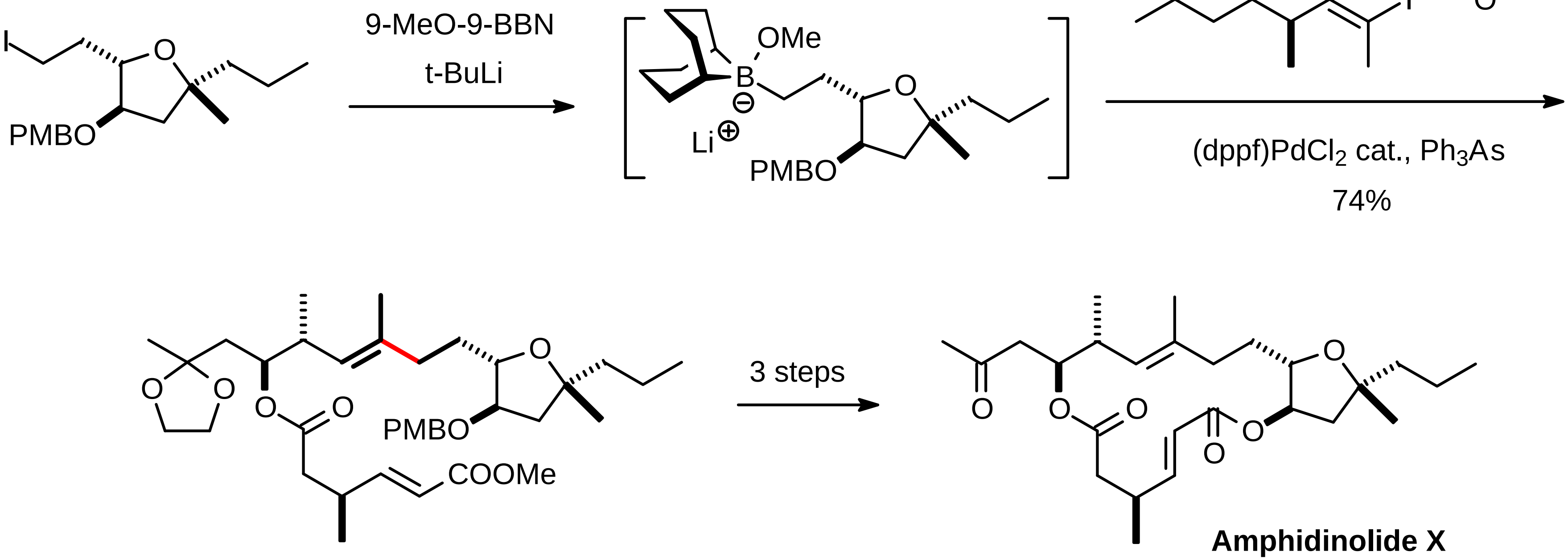


FIRST TOTAL SYNTHESIS OF AMPHIDINOLIDE X

for the „9-MeO-9-BBN“ variant of the Suzuki coupling, see:

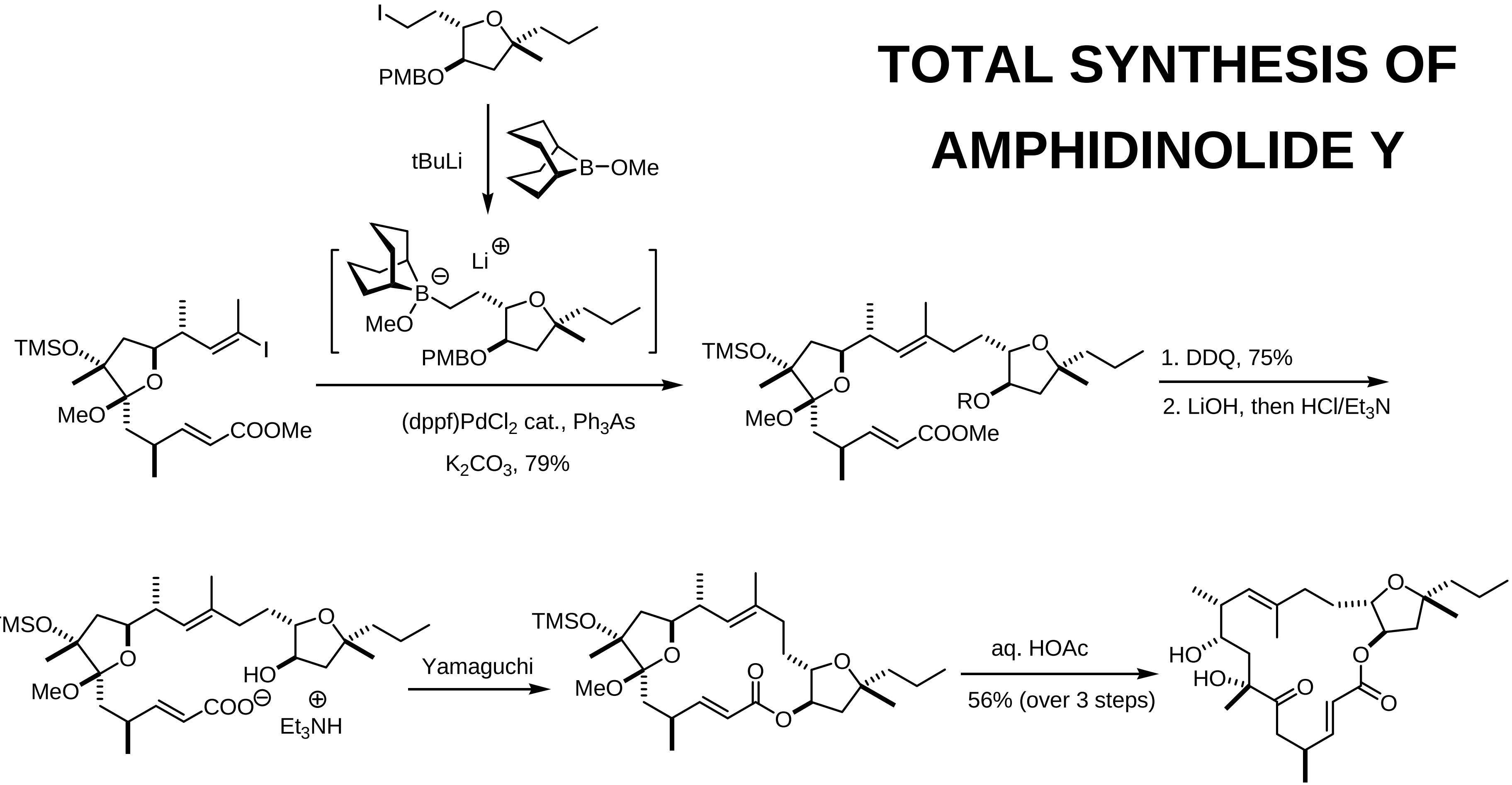
A. Fürstner, G. Seidel, *Tetrahedron* **1995**, *51*, 11165



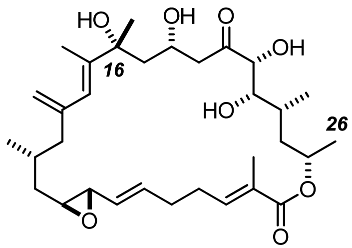


O. Lepage, E. Kattnig, A. Fürstner, *J. Am. Chem. Soc.* **2004**, *126*, 15970

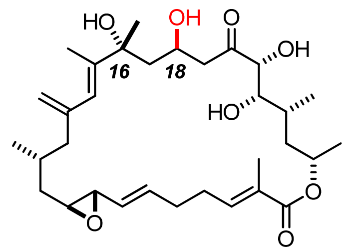
TOTAL SYNTHESIS OF AMPHIDINOLIDE Y



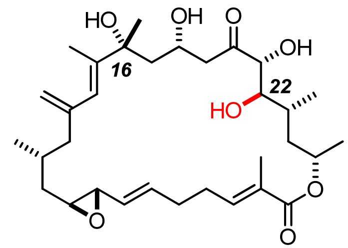
A. Fürstner, E. Kattnig, O. Lepage *J. Am. Chem. Soc.* **2006**, *128*, 9194



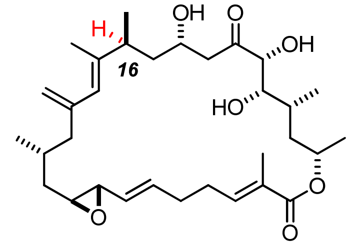
Amphidinolide B1 (**1**)



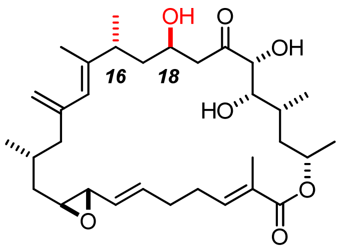
Amphidinolide B2 (**2**)



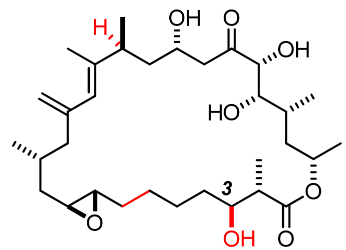
Amphidinolide B3 (**3**)



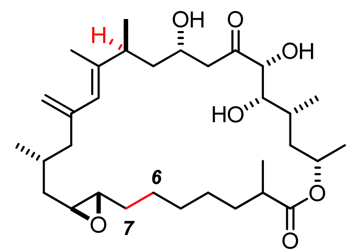
Amphidinolide B4 (**4**)



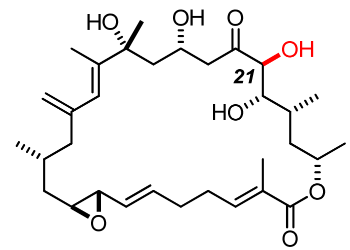
Amphidinolide B5 (**5**)



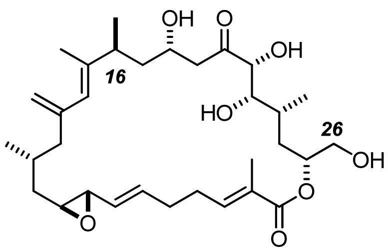
Amphidinolide B6 (**6**)



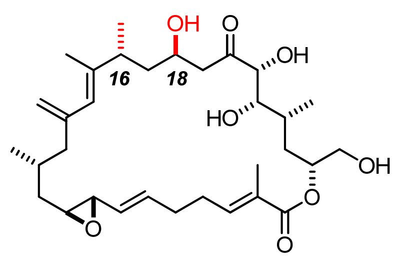
Amphidinolide B7 (**7**)



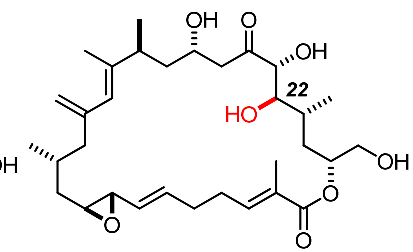
Amphidinolide D (**8**)



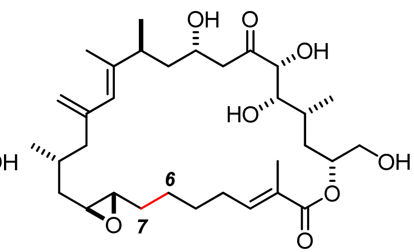
Amphidinolide H1 (**9**)



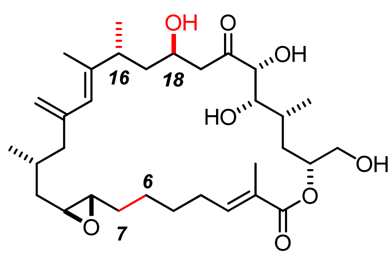
Amphidinolide H2 (**10**)



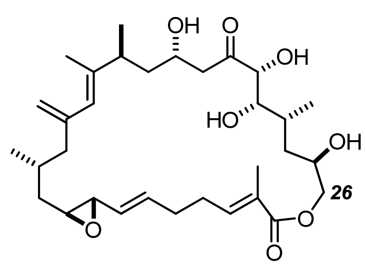
Amphidinolide H3 (**11**)



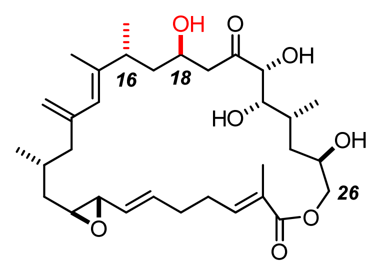
Amphidinolide H4 (**12**)



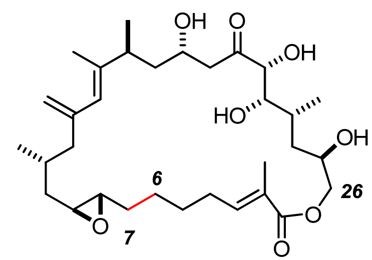
Amphidinolide H5 (**13**)



Amphidinolide G1 (**14**)

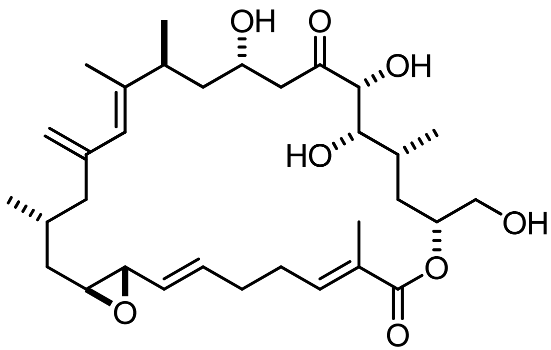


Amphidinolide G2 (**15**)



Amphidinolide G3 (**16**)

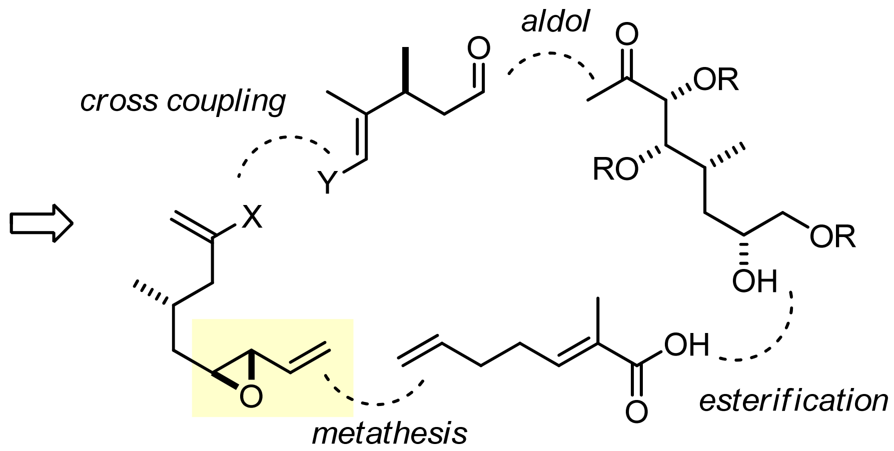
J. Kobayashi et al., *Nat. Prod. Rep*. **2004**, *21*, 77



Amphidinolide H

IC_{50} 0.52 ng/mL

(KB human epidermoid carcinoma)



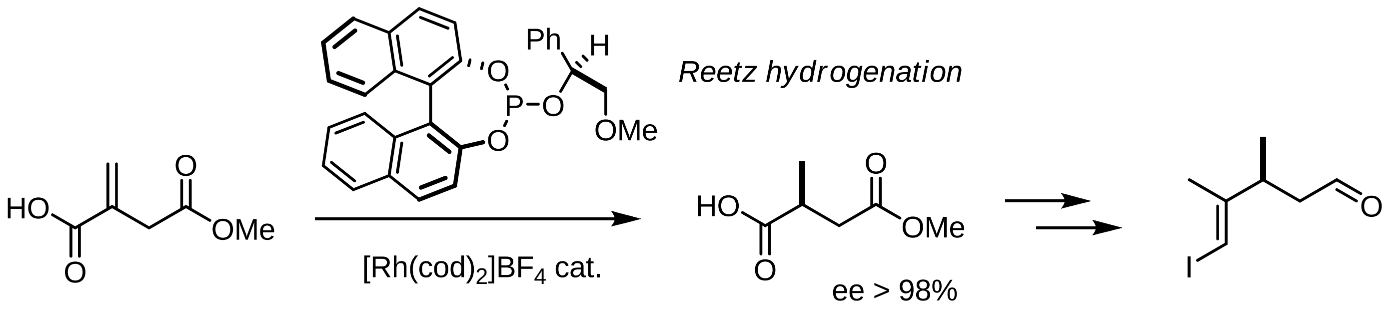
very scarce

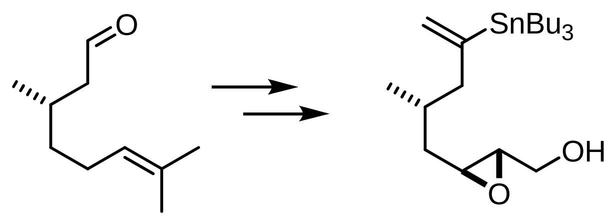
mixed polyketide biosynthesis

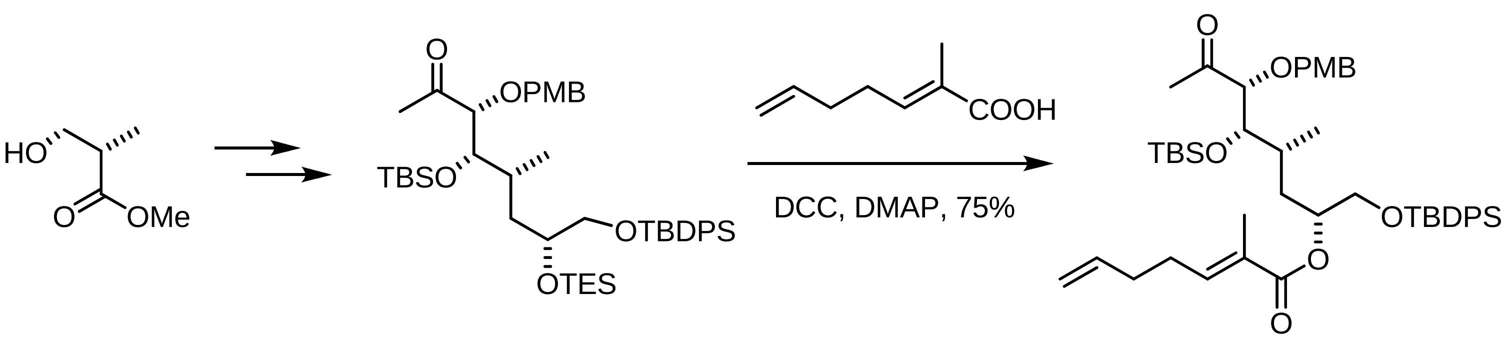
(very) potent cytotoxicity

interferes with actin

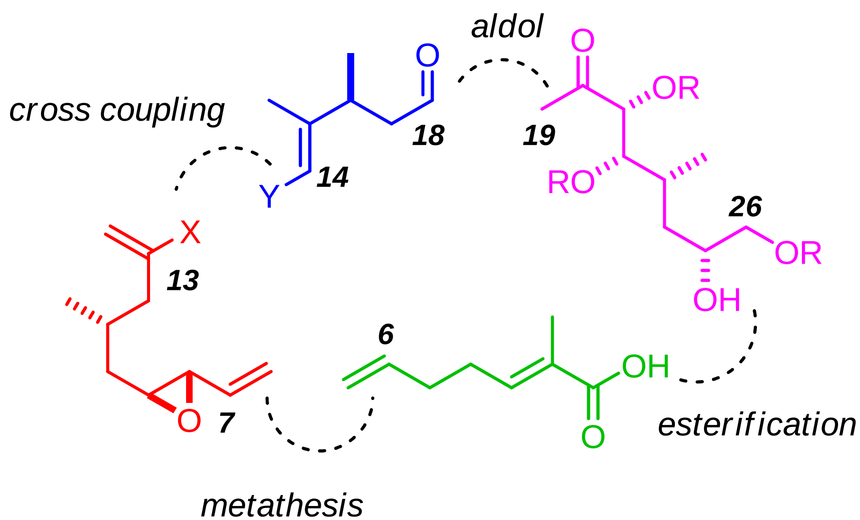
other biological targets?


Reetz hydrogenation
[Rh(cod)2]BF4 cat.
ee > 98%
Ph
H
OMe
HO
OMe
I

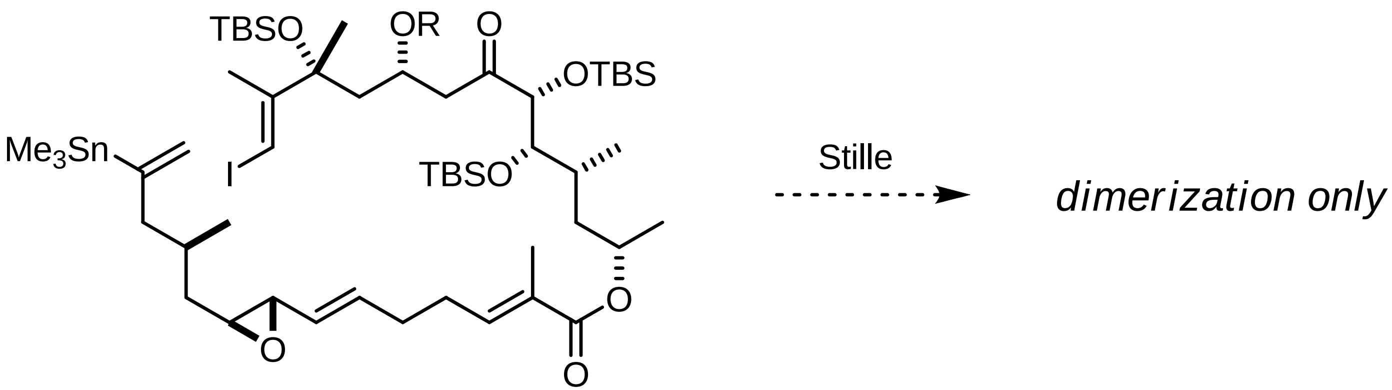

SnBu3
OH


HO
OMe
OPMB
TBSO
OTBDPS
OTES
COOH
DCC, DMAP, 75%

WHAT IS THE RIGHT ORDER?



LITERATURE PRECEDENT

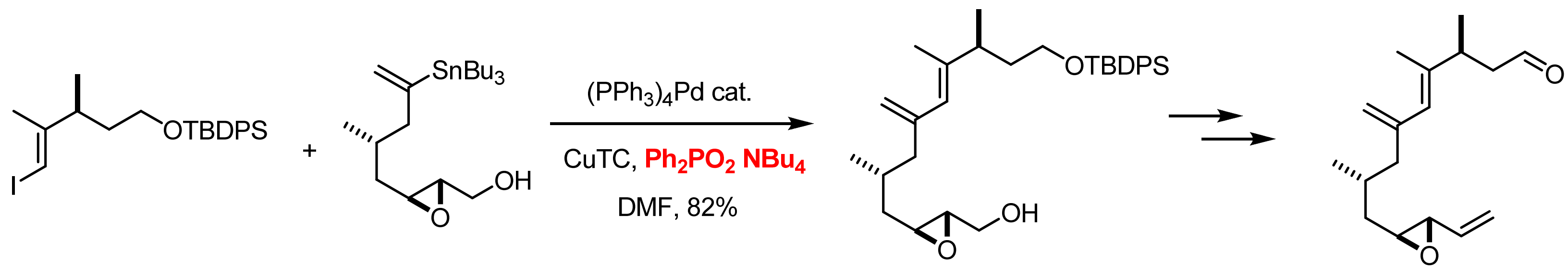


G. Pattenden et al., *Tetrahedron Lett.* **2000**, *41*, 7373

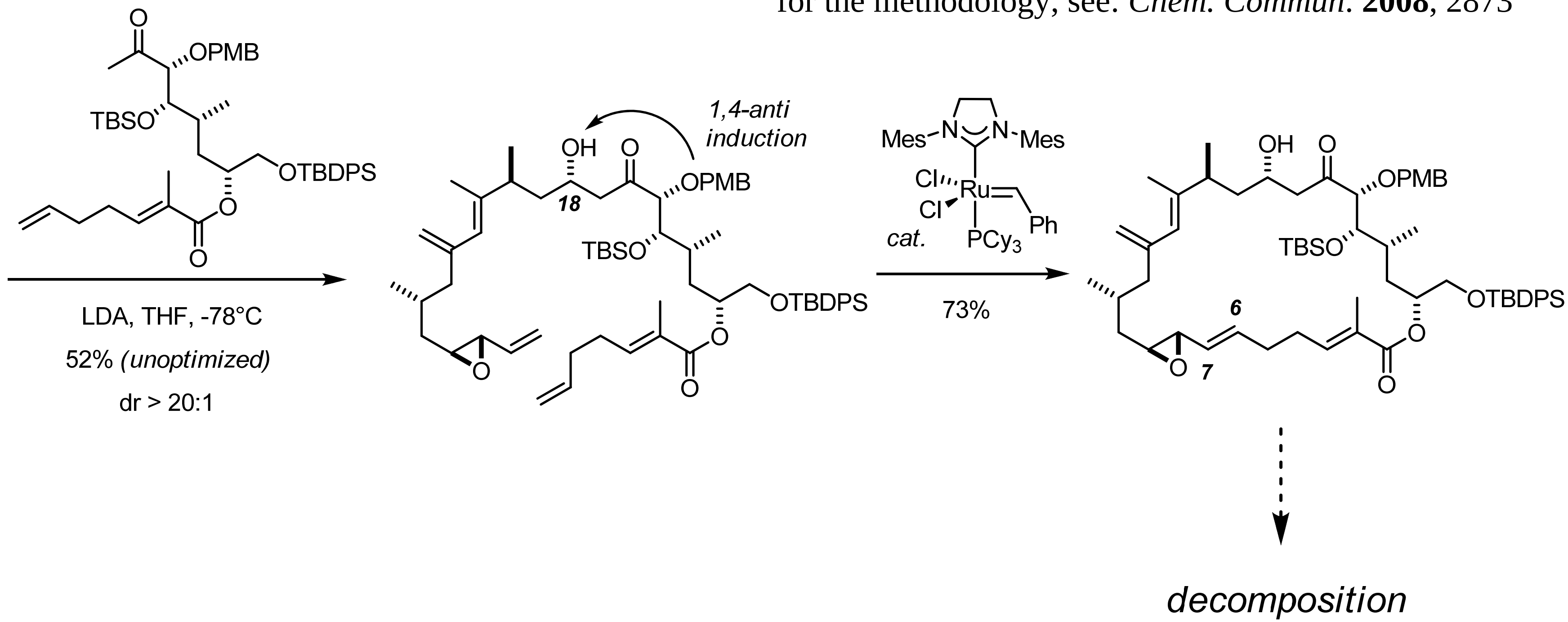
other studies toward amphidinolides B, H and G were reported by

Kobayashi, Chakraborty, Nishiyama, Myles, Carter, Crews, Nelson, Marco, Kalesse, Zhao

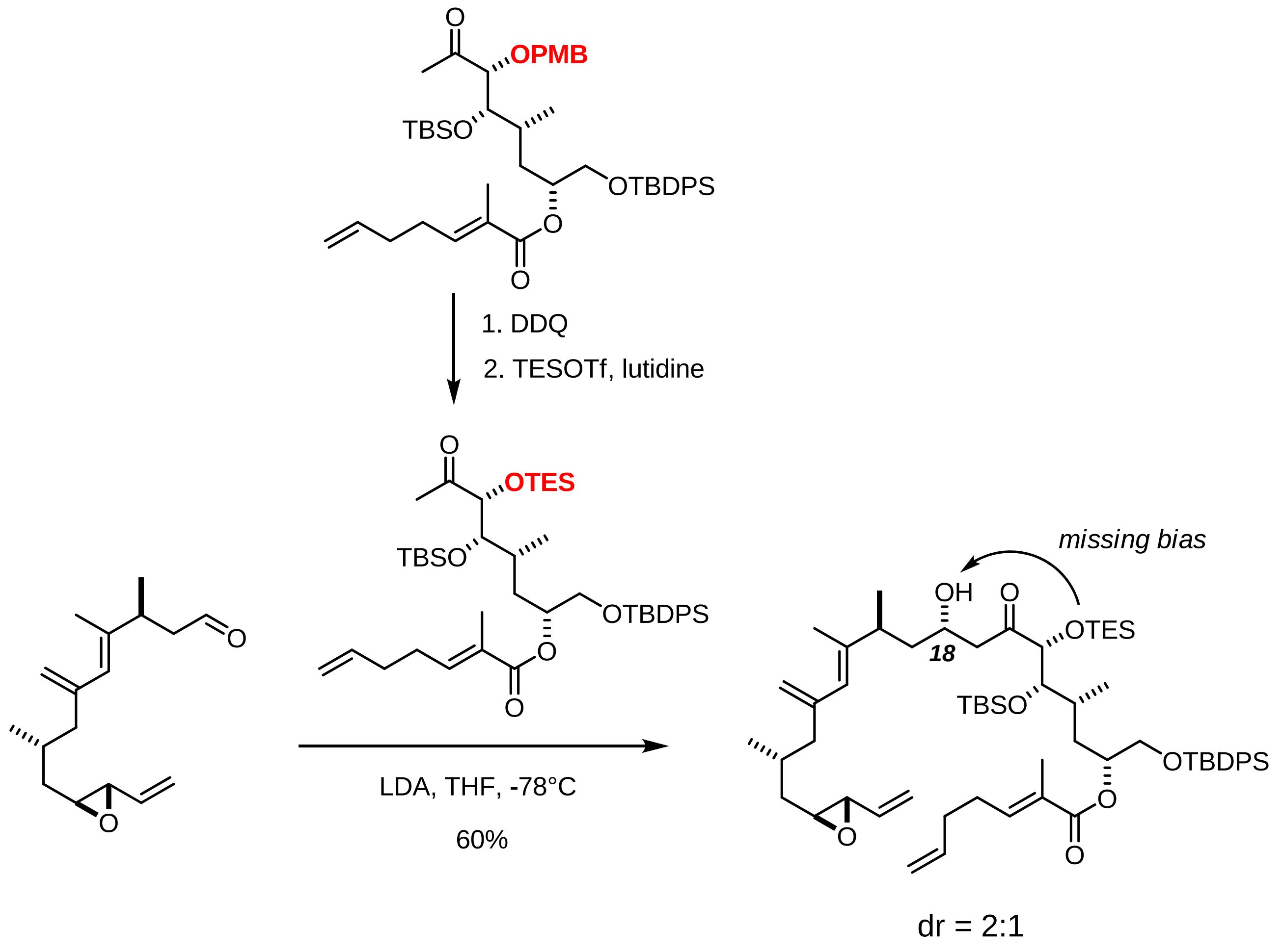
TOWARD AMPHIDINOLIDE H

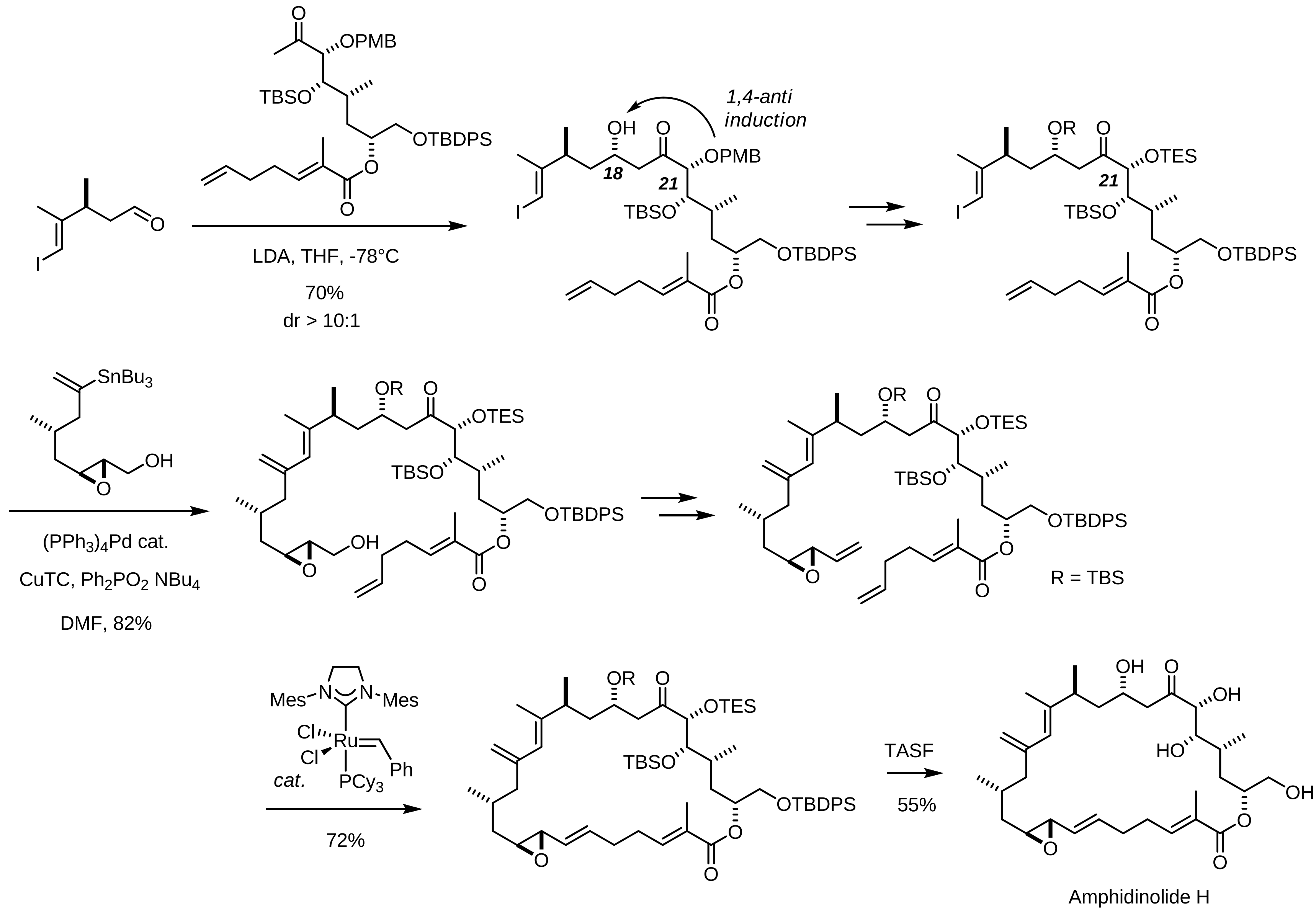


for the methodology, see: *Chem. Commun*. **2008**, 2873



TOWARD AMPHIDINOLIDE H (II)

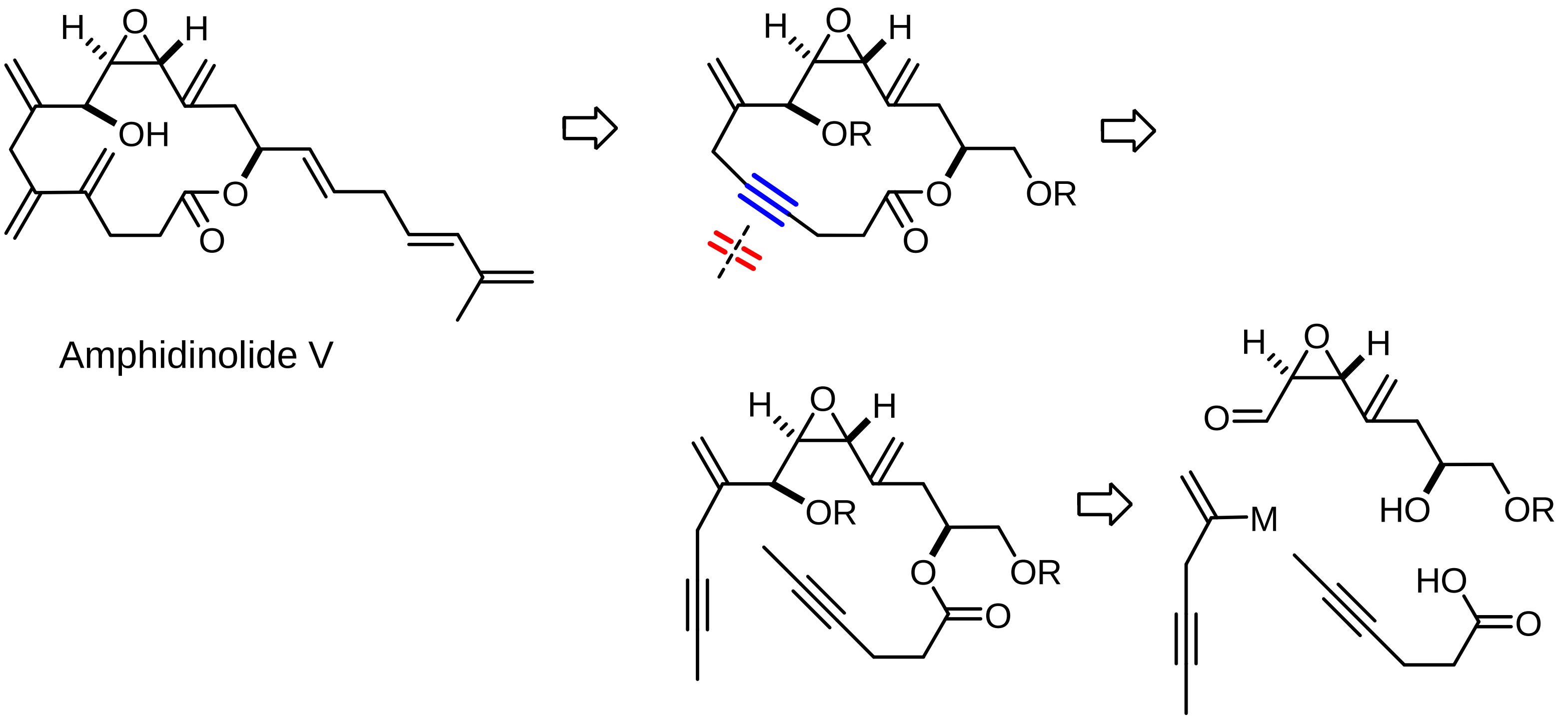




A. F. with L. C. Bouchez, J.-A. Funel, V. Lipins, F.-H. Porée, R. Gilmour, F. Beaufils, D. Laurich, M. Tamiya

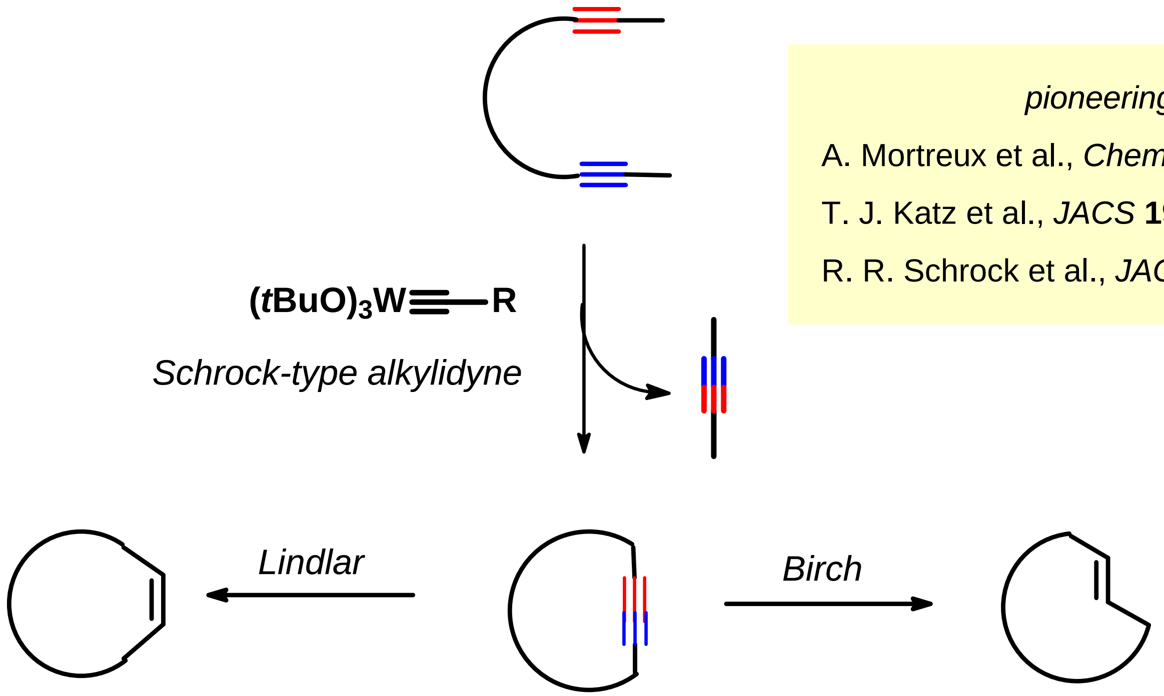
Angew. Chem. Int. Ed. **2007**, *46*, 9265

AMPHIDINOLIDE V



Isolation: J.-I. Kobayashi et al., *Tetrahedron Lett.* **2000**, *41*, 713

RING CLOSING ALKYNE METATHESIS (RCAM)



pioneering studies:

A. Mortreux et al., *Chem. Commun*. **1974**, 786

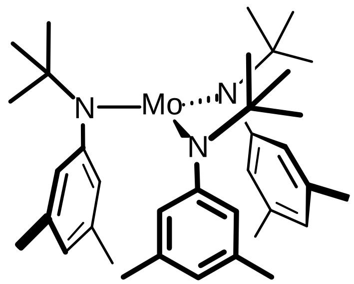
T. J. Katz et al., *JACS* **1975**, *97*, 1592

R. R. Schrock et al., *JACS* **1981**, *103*, 3932

A. Fürstner, G. Seidel, *Angew. Chem. Int. Ed*. **1998**, *110*, 1758

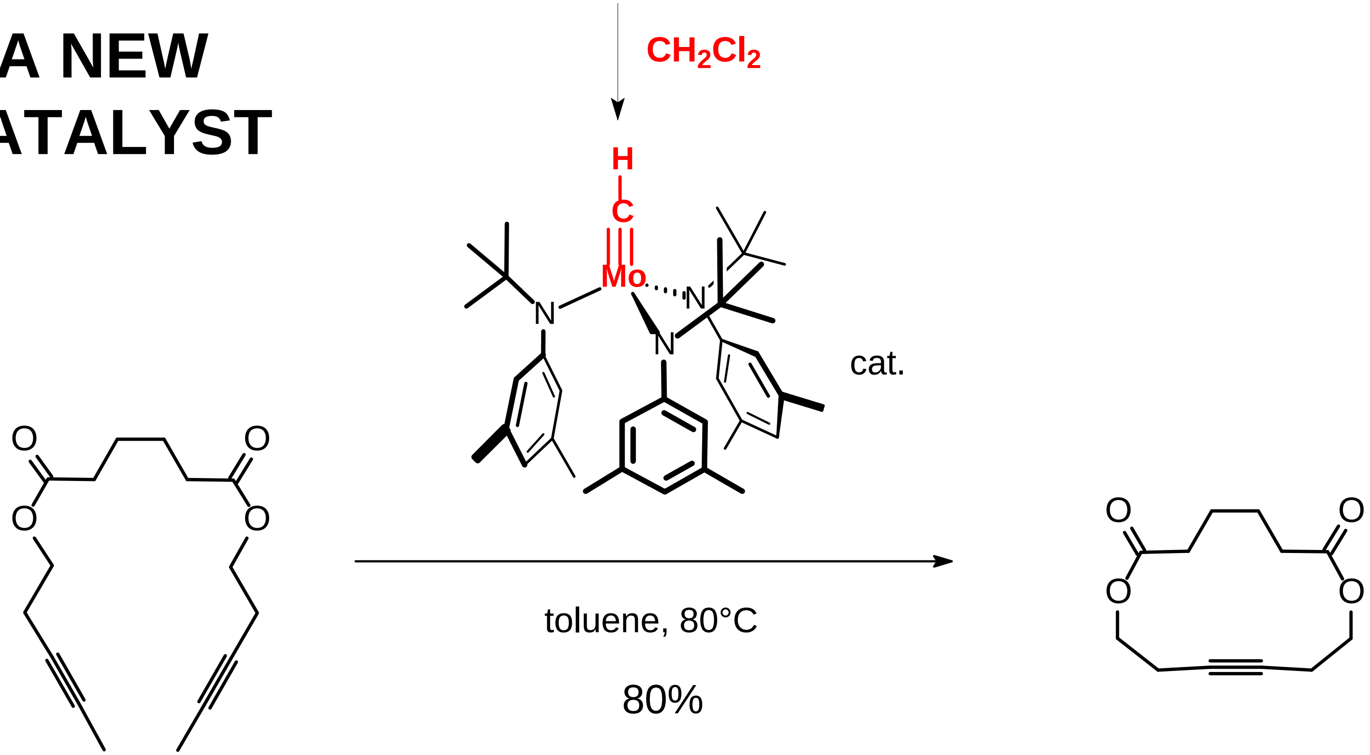
Review on alkyne metathesis: A. Fürstner, P. W. Davies, *Chem. Commun*. **2005**, 2307

A NEW CATALYST



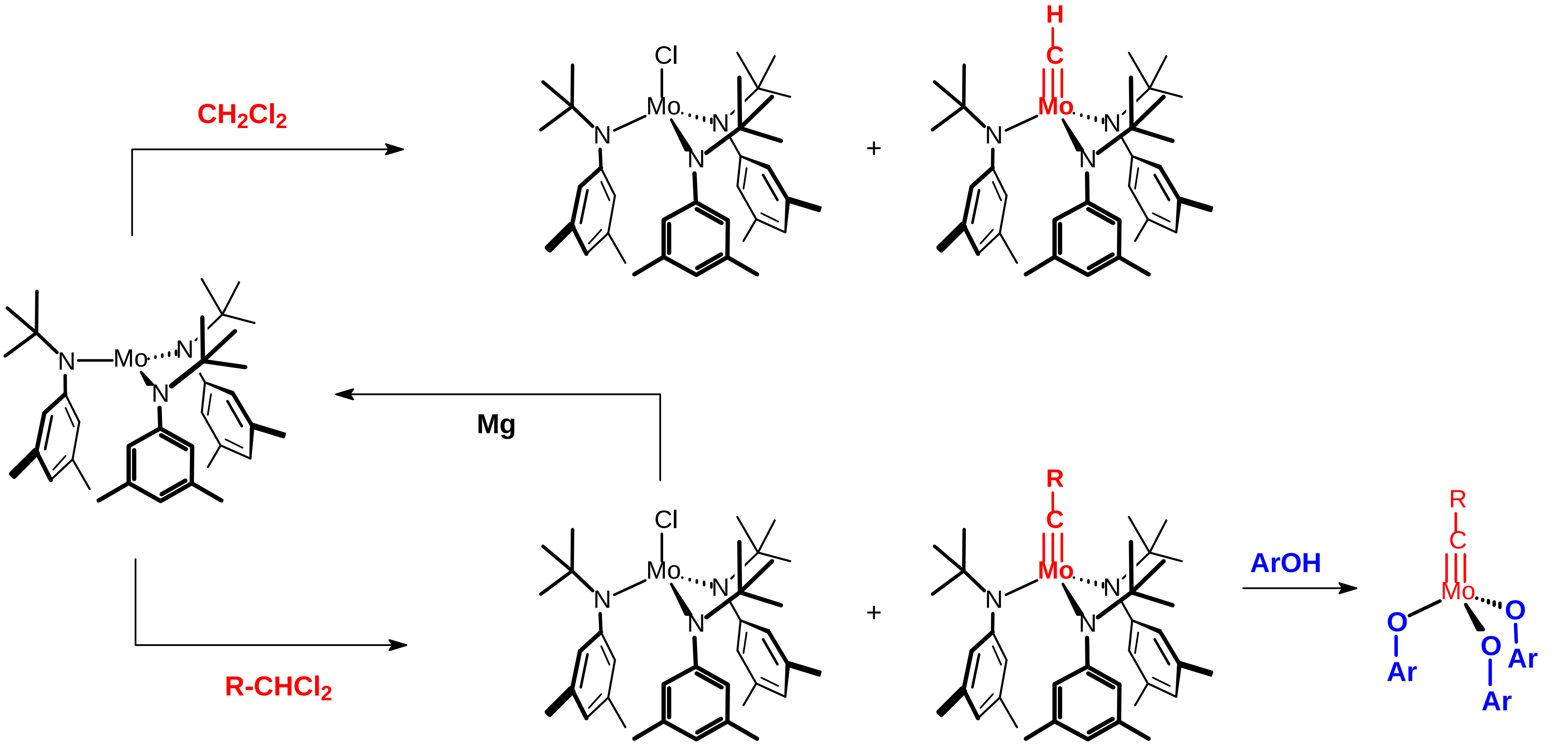
designed for the stoichiometric cleavage of N_2

C. C. Cummins et al., *Chem. Commun*. **1998**, 1777



A. Fürstner, C. Mathes, C. W. Lehmann, *J. Am. Chem. Soc*. **1999**, *121*, 9453

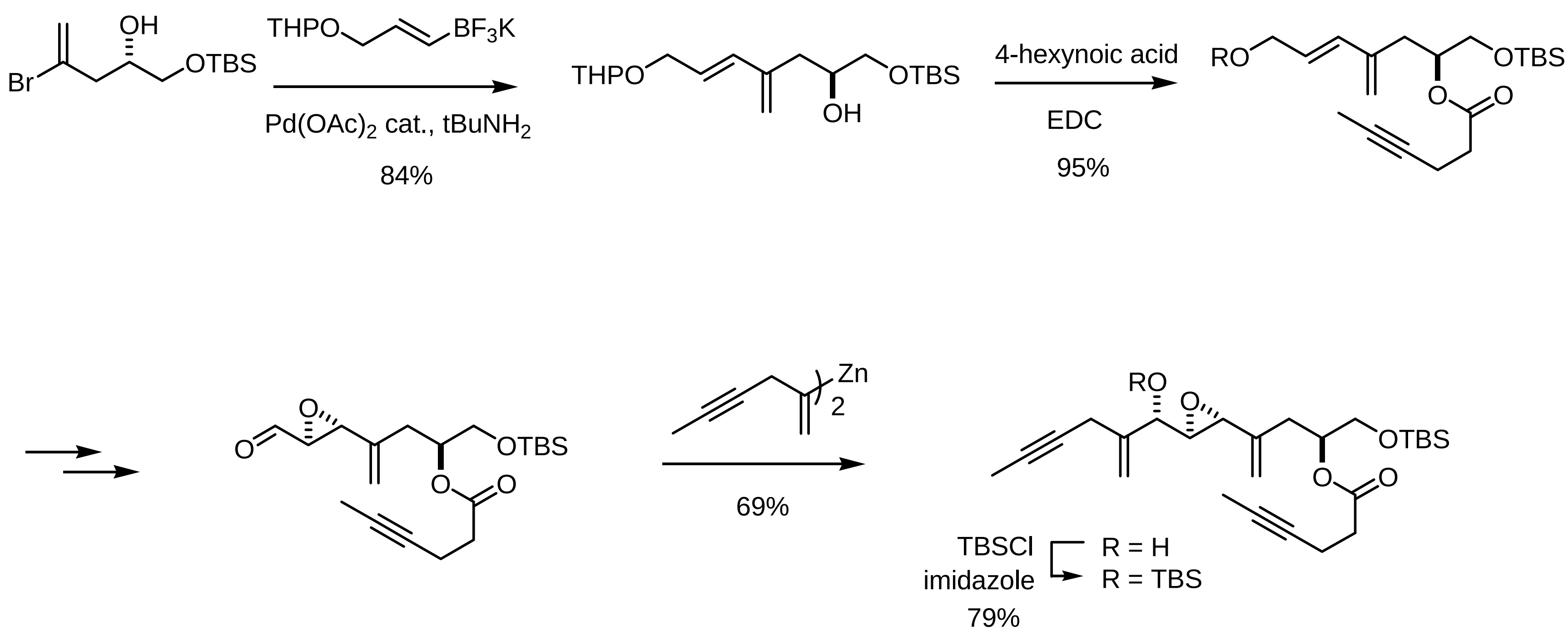
FURTHER IMPROVEMENT



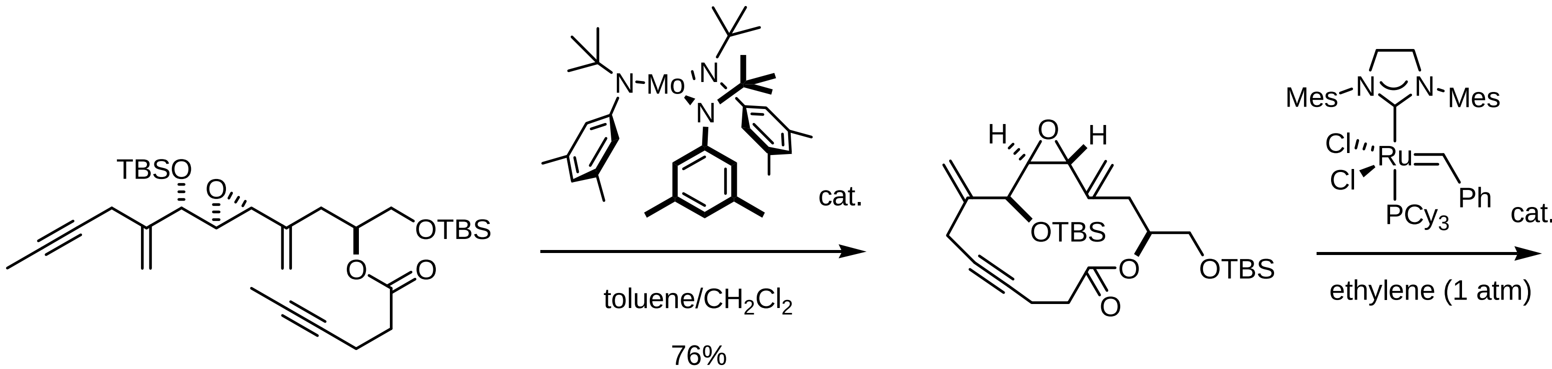
W. Zhang, S. Kraft, J. S. Moore, *Chem. Commun*. **2003**, 832; idem, *J. Am. Chem. Soc*. **2004**, *126*, 392;

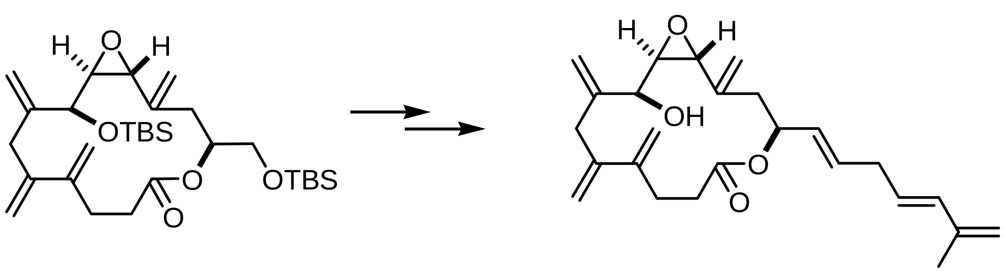
See also: C. C. Cummins et al., *Organometallics* **2003**, *22*, 3351.

TOWARDS AMPHIDINOLIDE V



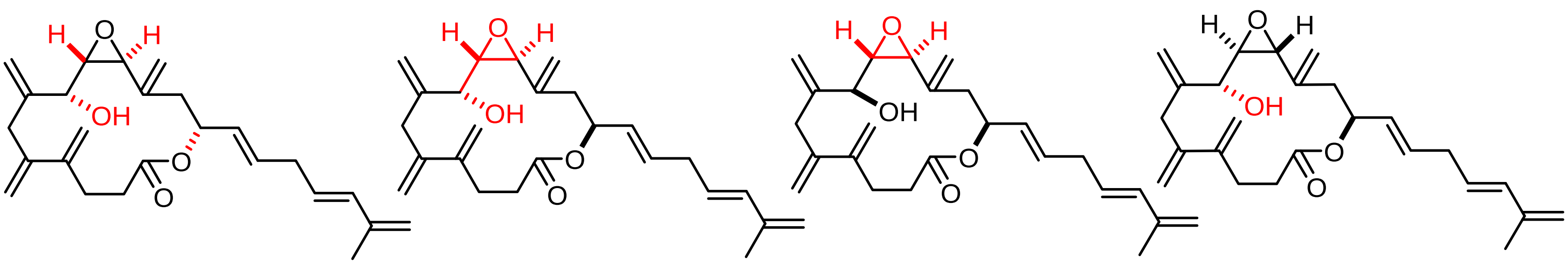
TOTAL SYNTHESIS OF AMPHIDINOLIDE V



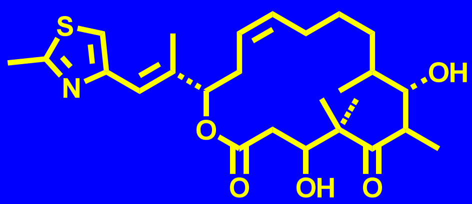


A. F. with O. Larionov, S. Flügge

Angew. Chem. Int. Ed. **2007**, *46*, 5545

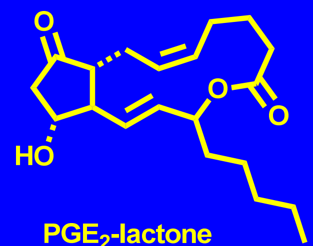


ALKYNE METATHESIS



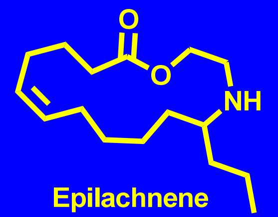
Epothilone A and C

Chem. Eur. J. 2001, *7*, 5299



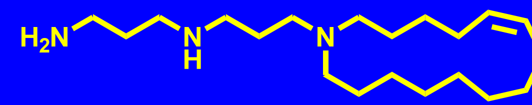
PGE$_2$-lactone

JACS 2000, *122*, 11799



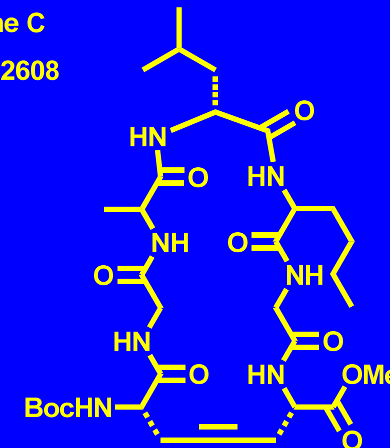
Epilachnene

JACS 1999, *121*, 11108



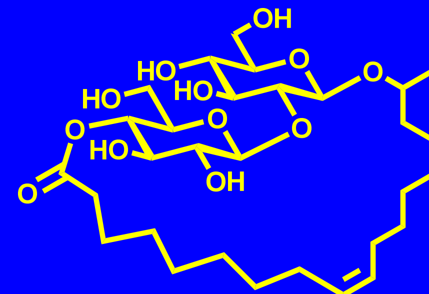
Motuporamine C

JOC 2000, *65*, 2608



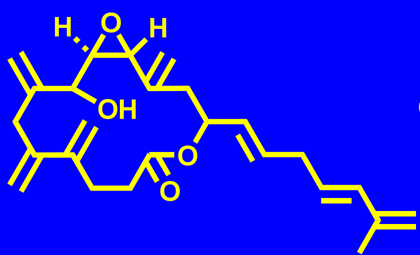
Nysin-loop isostere

Org. Lett. 2005, *7*, 2961



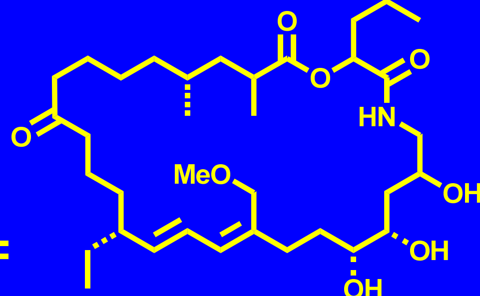
Sophorolipid Lactone

JOC 2000, *65*, 8758



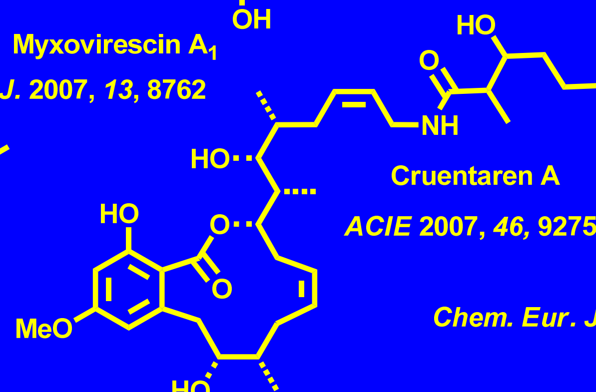
Amphidinolide V

ACIE 2007, *46*, 5545



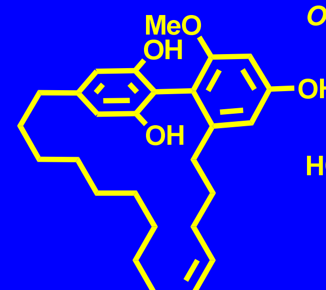
Myxovirescin A$_1$

Chem. Eur. J. 2007, *13*, 8762



Cruentaren A

ACIE 2007, *46*, 9275

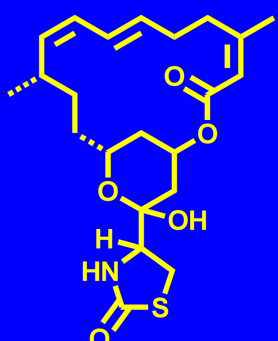


Turriane

Chem. Eur. J. 2003, *8*, 1856

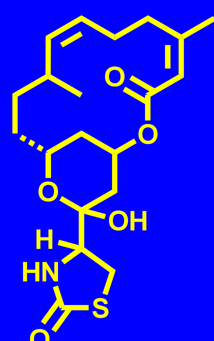
Citreofuran

JOC 2002, *67*, 1521



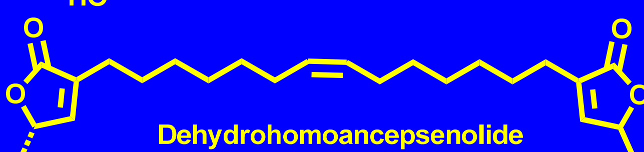
Latrunculin A

ACIE 2005, *44*, 3462



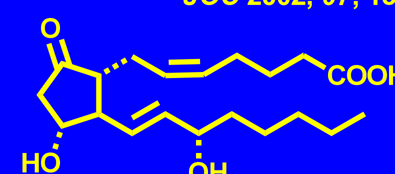
Latrunculin B

ACIE 2003, *42*, 5358



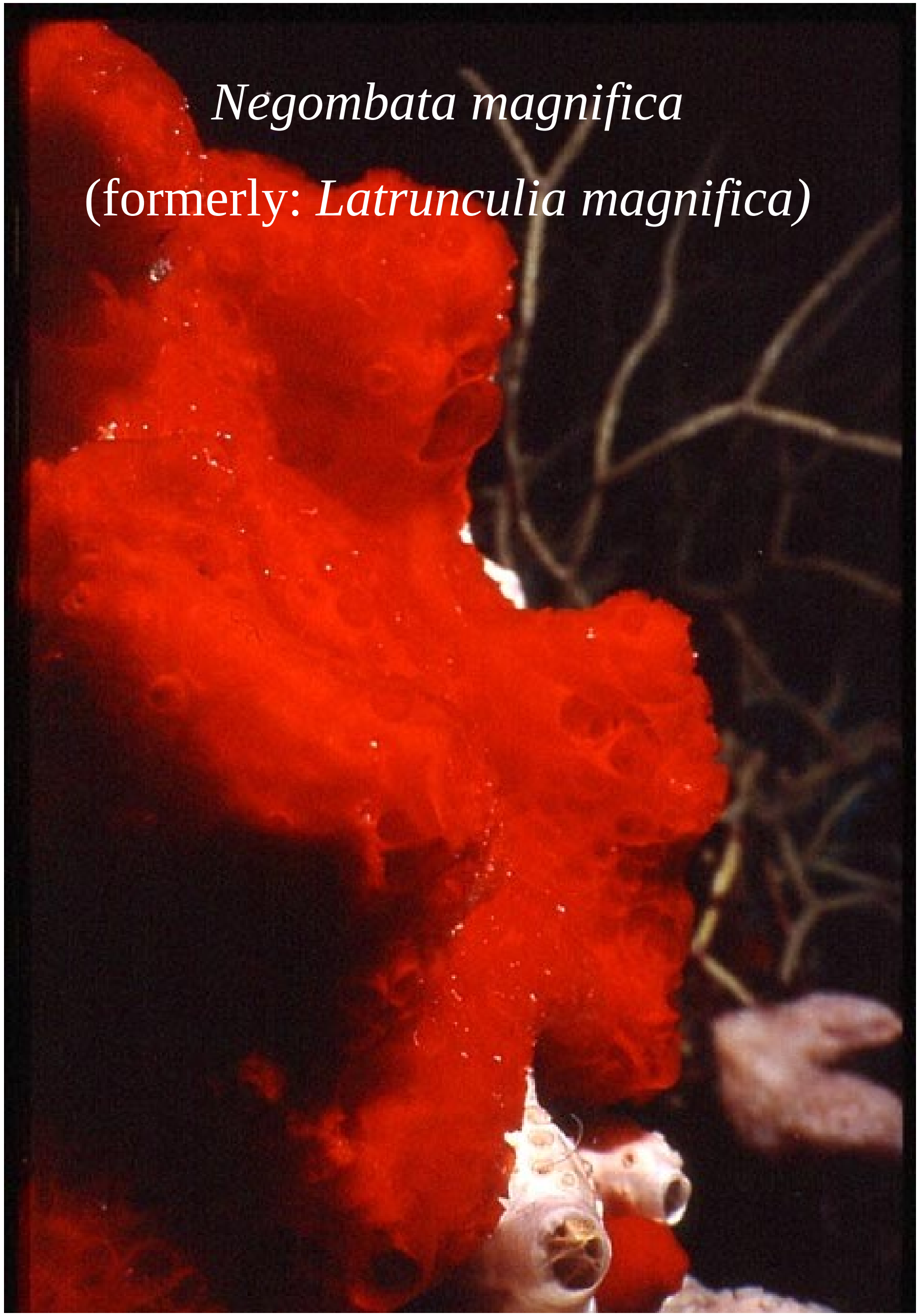
Dehydrohomoancepsenolide

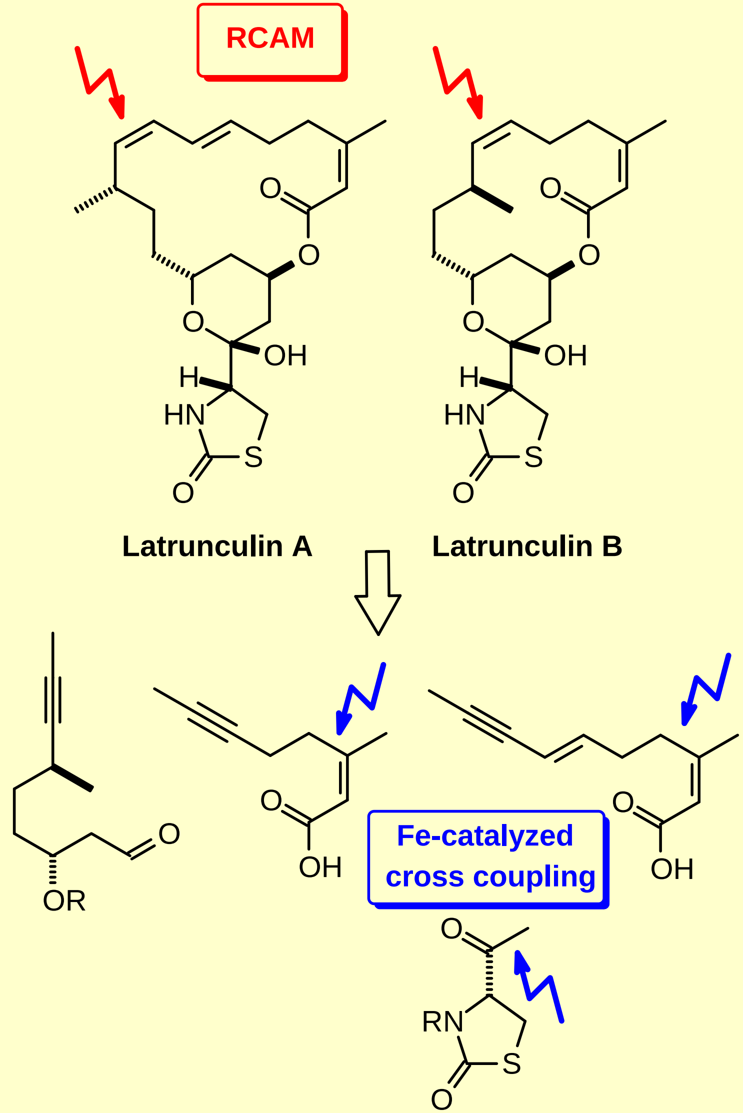
Org. Lett. 2000, *2*, 2463



Prostaglandin E$_2$

Org. Lett. 2001, *3*, 221

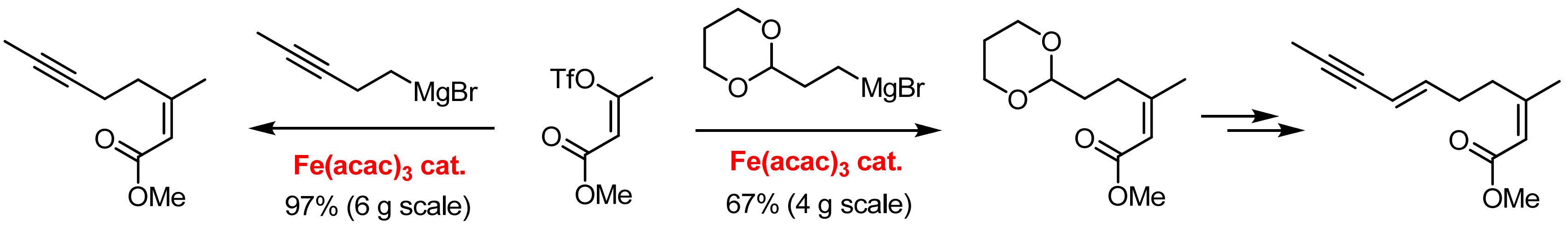




previous syntheses (1992) by A. B. Smith and J. White

potent actin microfilament disrupting agents: I. Spector et al., *Science* **1983**, *219*, 493

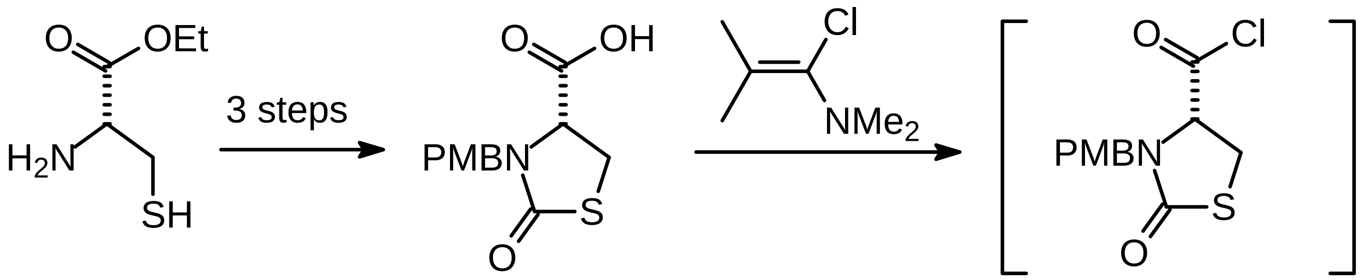
EN ROUTE TO THE LATRUNCULINS

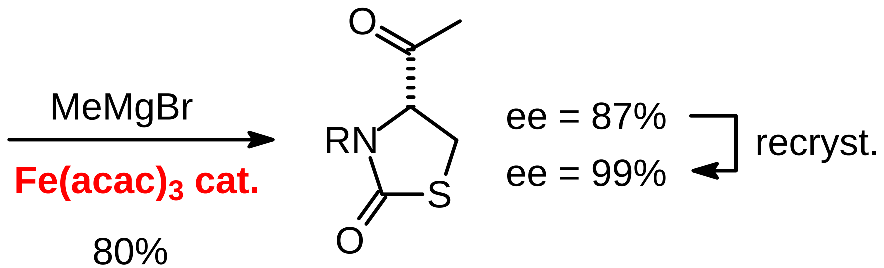


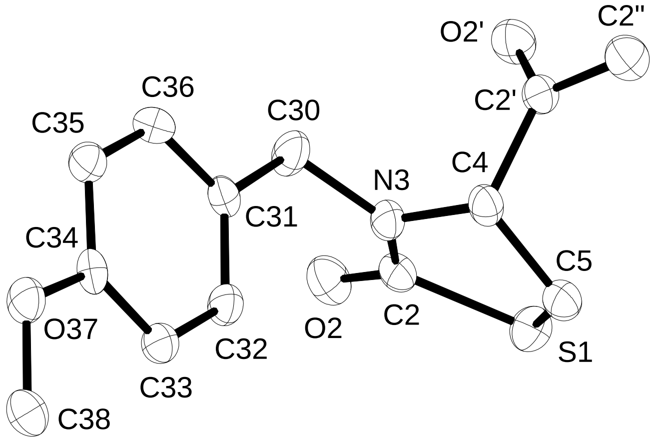
for a comprehensive study on Fe-catalyzed cross coupling reactions of enol triflates see:

B. Scheiper, M. Bonnekessel, H. Krause, A. Fürstner, *J. Org. Chem*. **2004**, *69*, 3943

TOTAL SYNTHESIS OF LATRUNCULIN B





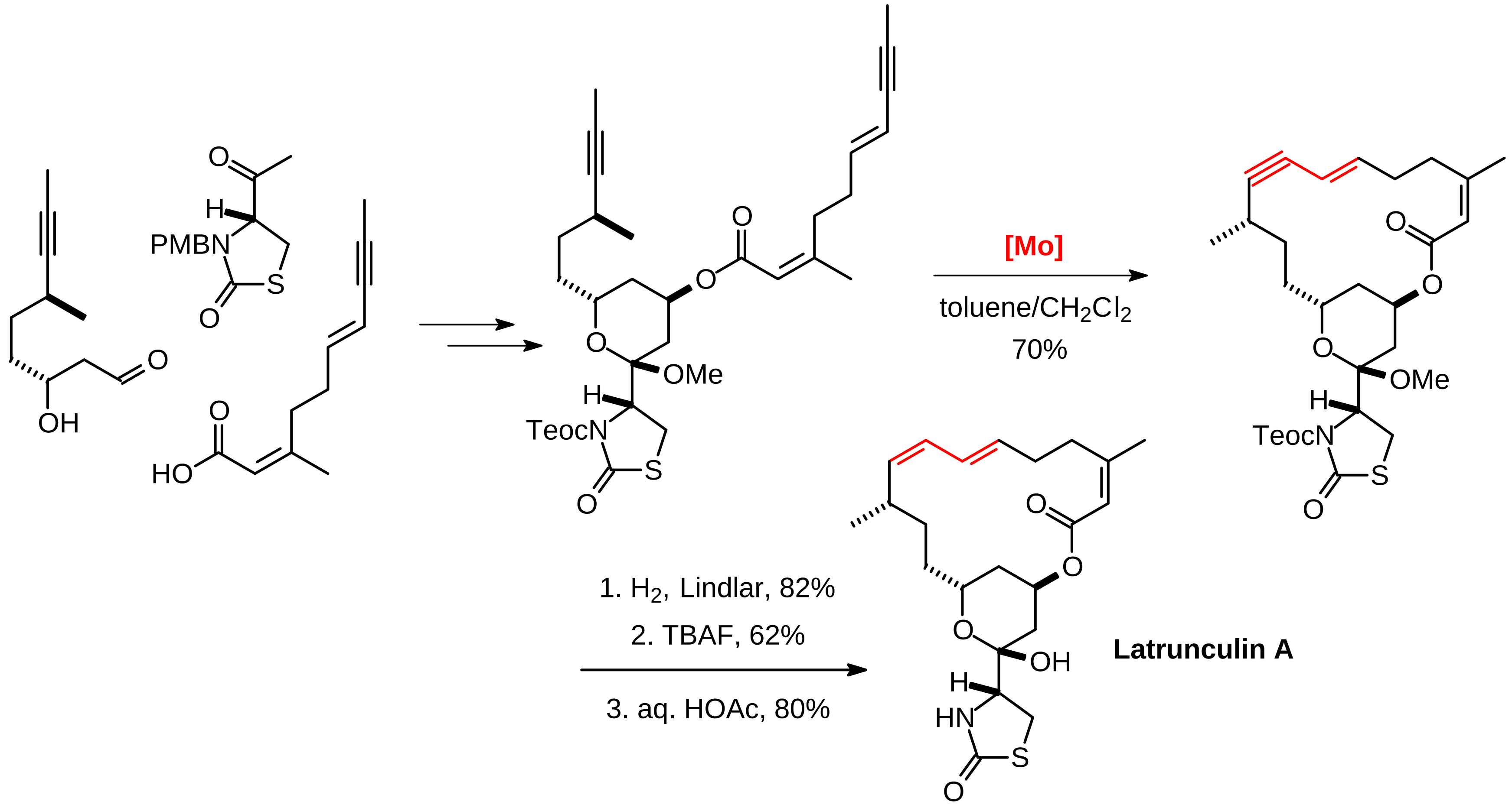


in the absence of Fe cat.: < 30% yield

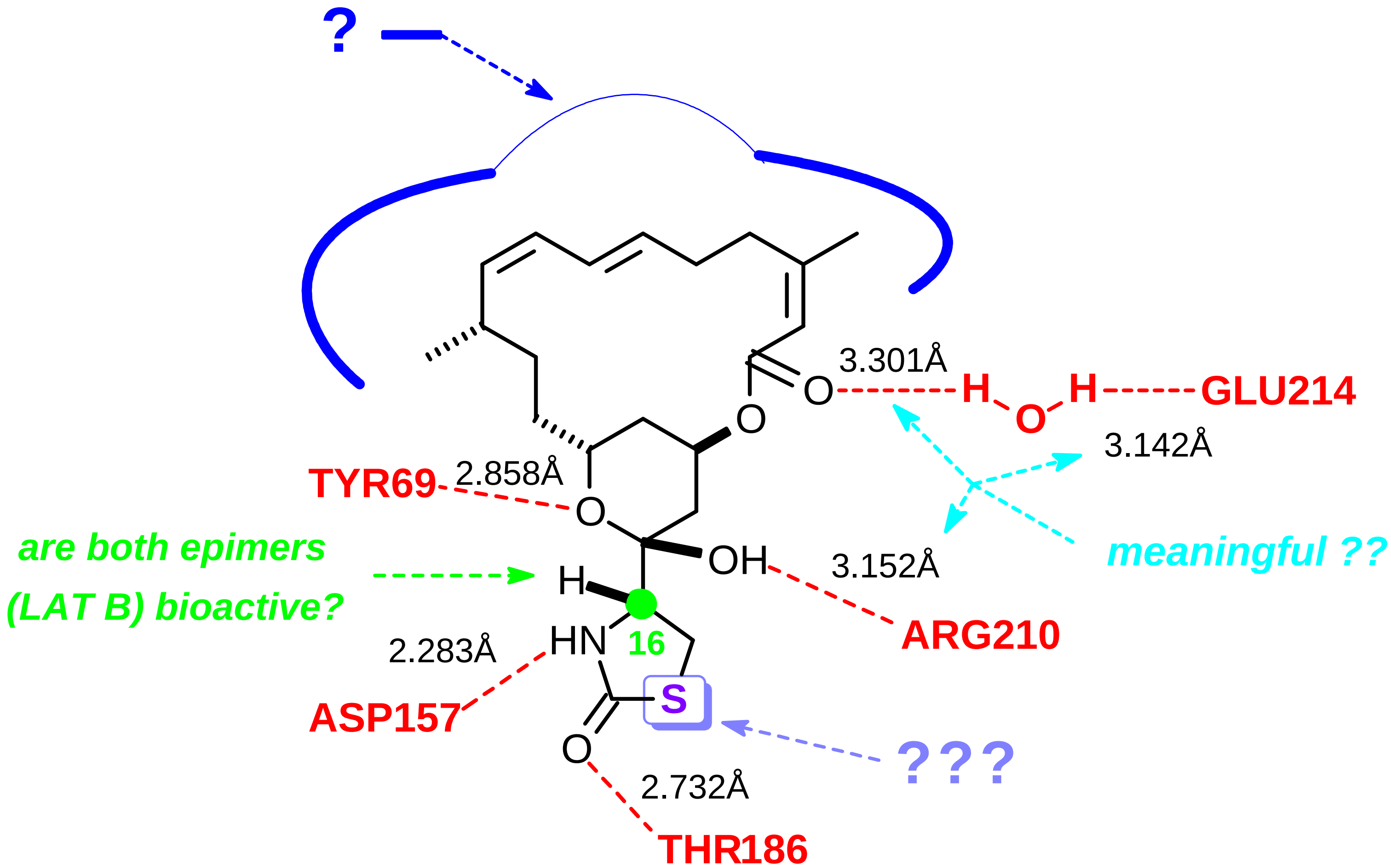
using Cu(I) in catalytic or stoichiometric amounts instead of Fe cat. leads to decomposition

for a short review on Fe-catalyzed cross coupling, see: A. Fürstner, R. Martin *Chem. Lett*. **2005**, *34*, 624

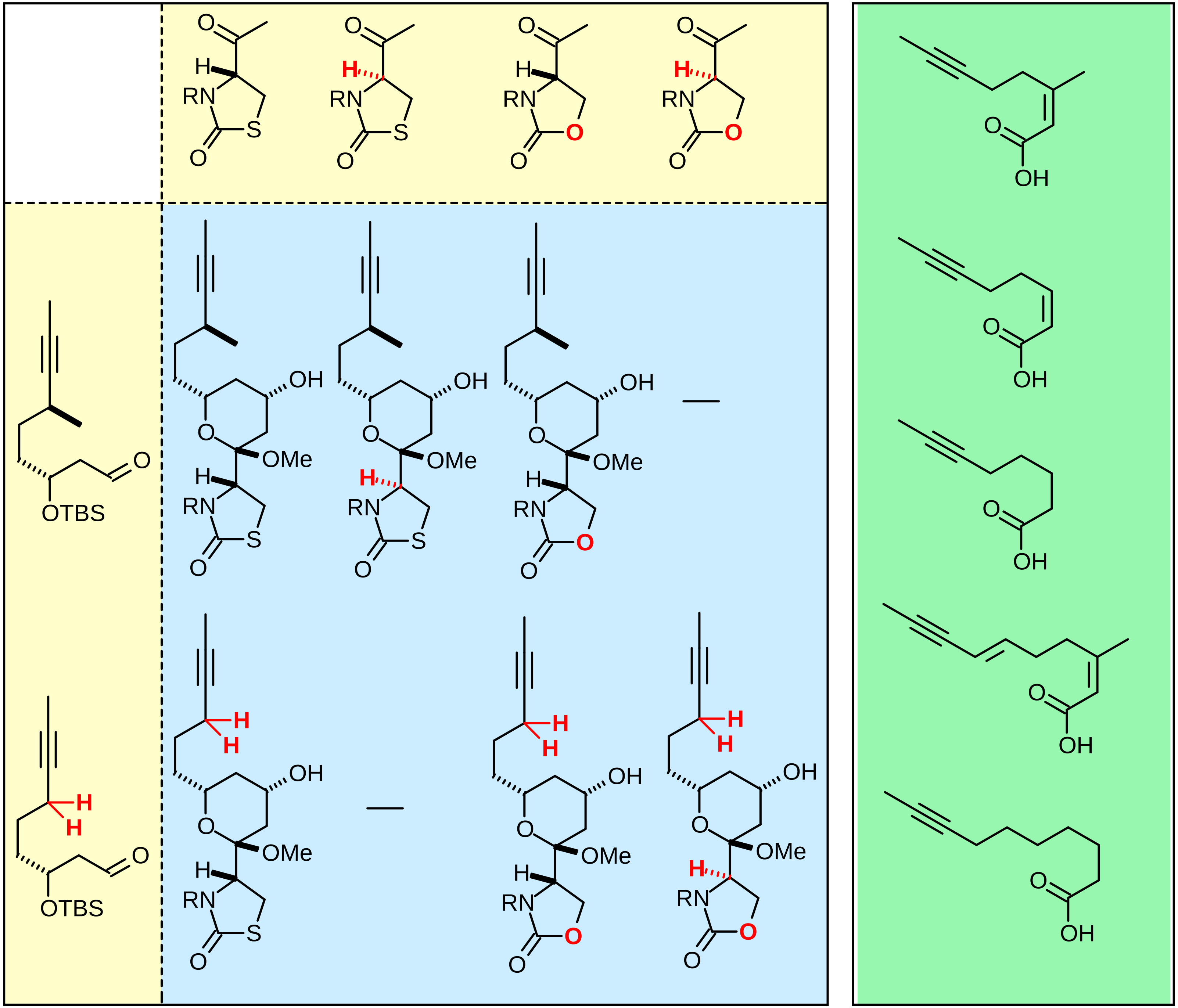
ENYNE-YNE METATHESIS



L. Turet, A. Fürstner, *Angew. Chem. Int. Ed.* **2005**, *44*, 3462

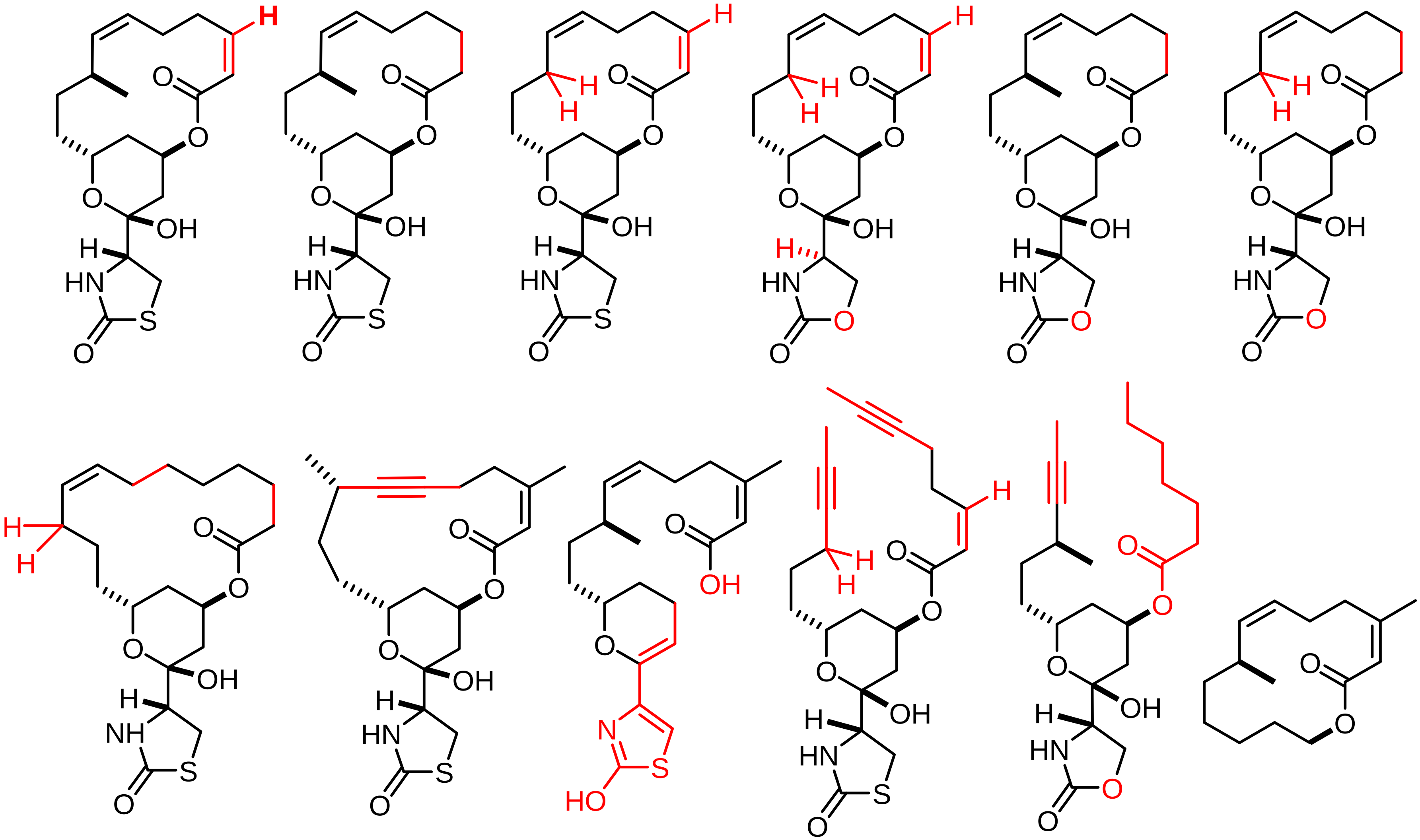


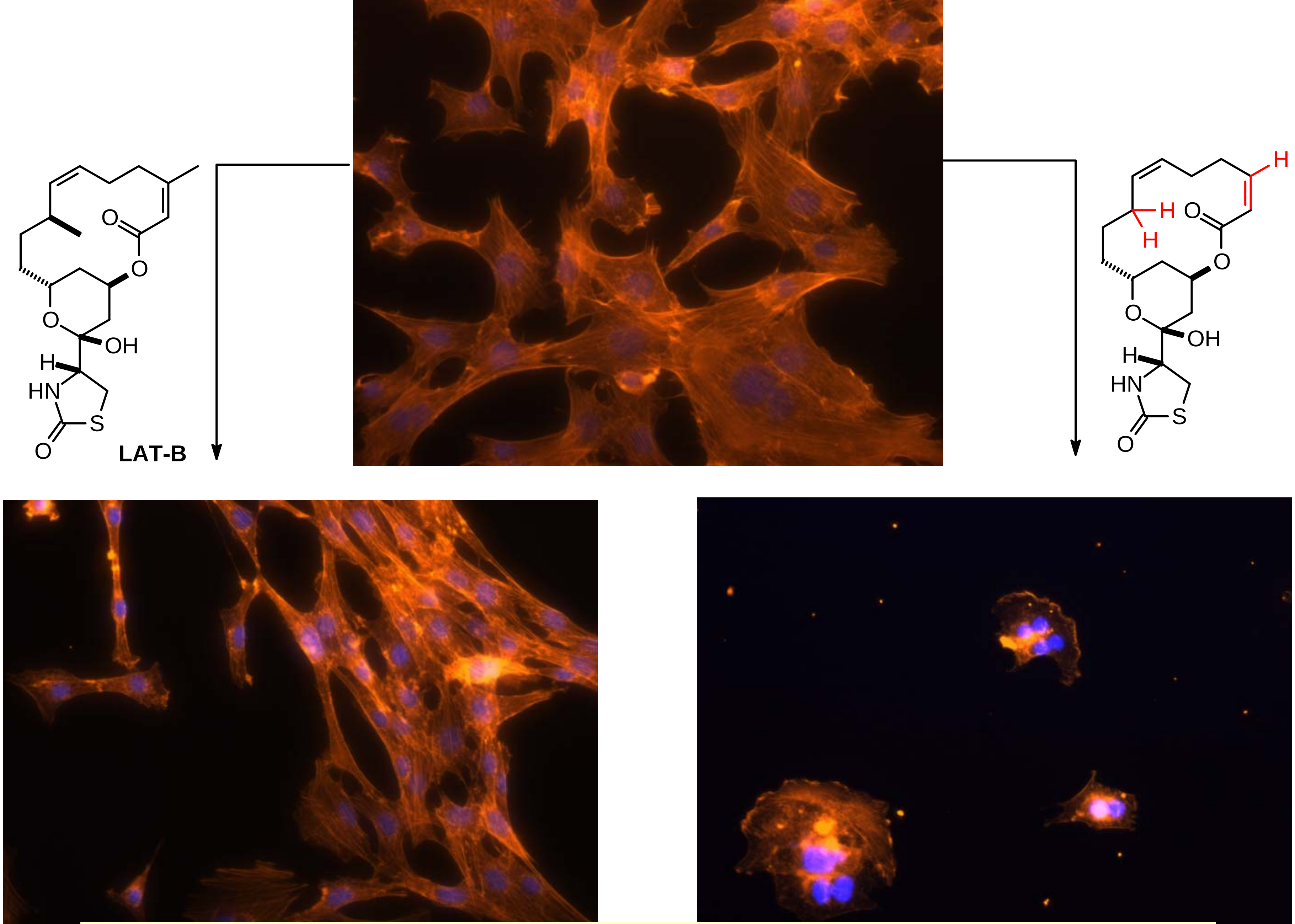
no derivative of the natural product known that retains any significant bioactivity



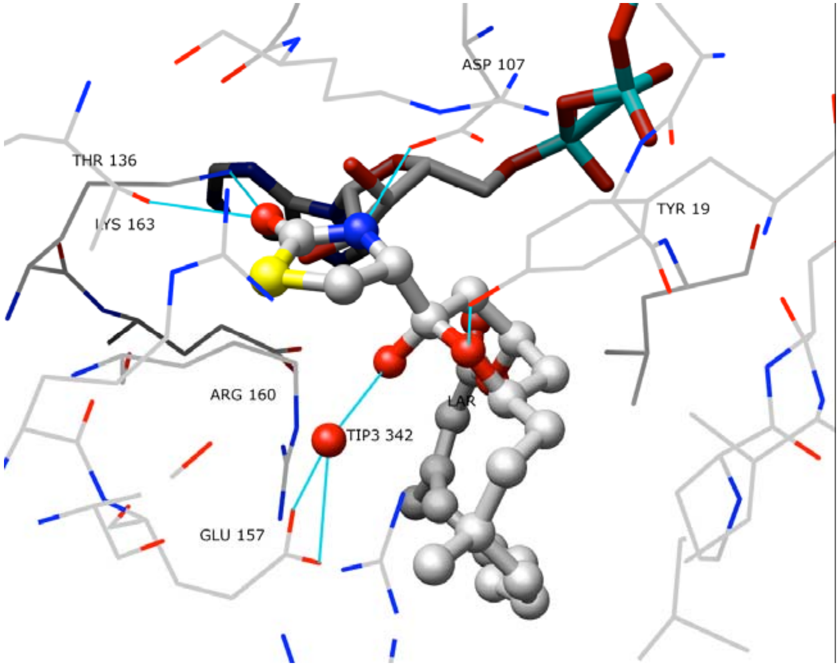
OTBS
OTBS
OH
OMe
RN
OH

DIVERTED TOTAL SYNTHESIS





A. Fürstner, D. Kirk, M. Fenster, C. Aissa, D. De Souza, O. Müller, *PNAS* **2005**, *102*, 8103



QM/MM CALCULATIONS

Latrunculin A / Actin Complex

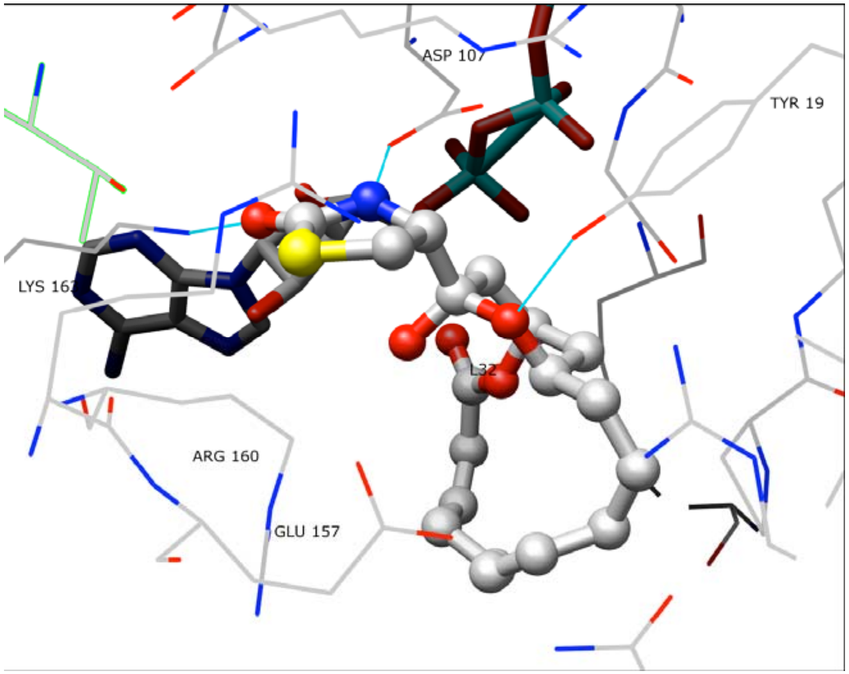
refined and corrected picture of H-bonding network

importance of hydrophopic interactions

“Lat 32” / Actin Complex

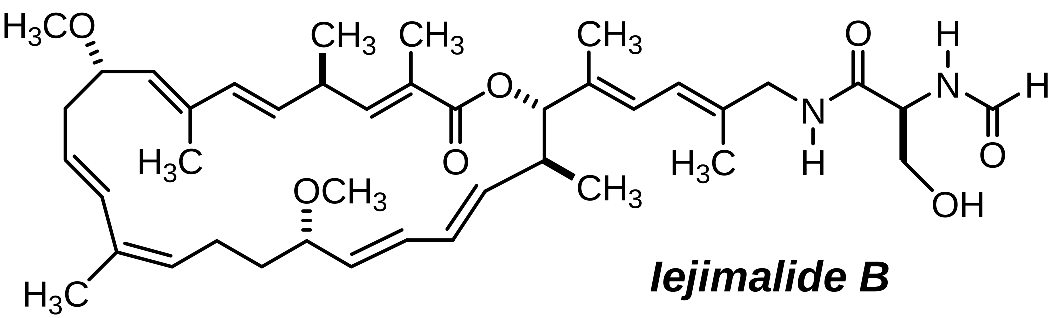
different but equally strong hydrogen bond network

hydrophobic interactions optimized



with Prof. W. Thiel, Dr. T. Tuttle, Dr. C. Nevado,
Chem. Eur. J. **2007**, *13*, 135

A RELEVANT TARGET?



Iejimalide B

J. Kobayashi et al., *J. Org. Chem*. **1988**, *53,* 6147
Bioorg. Med. Chem. **2006**, *14*, 1063

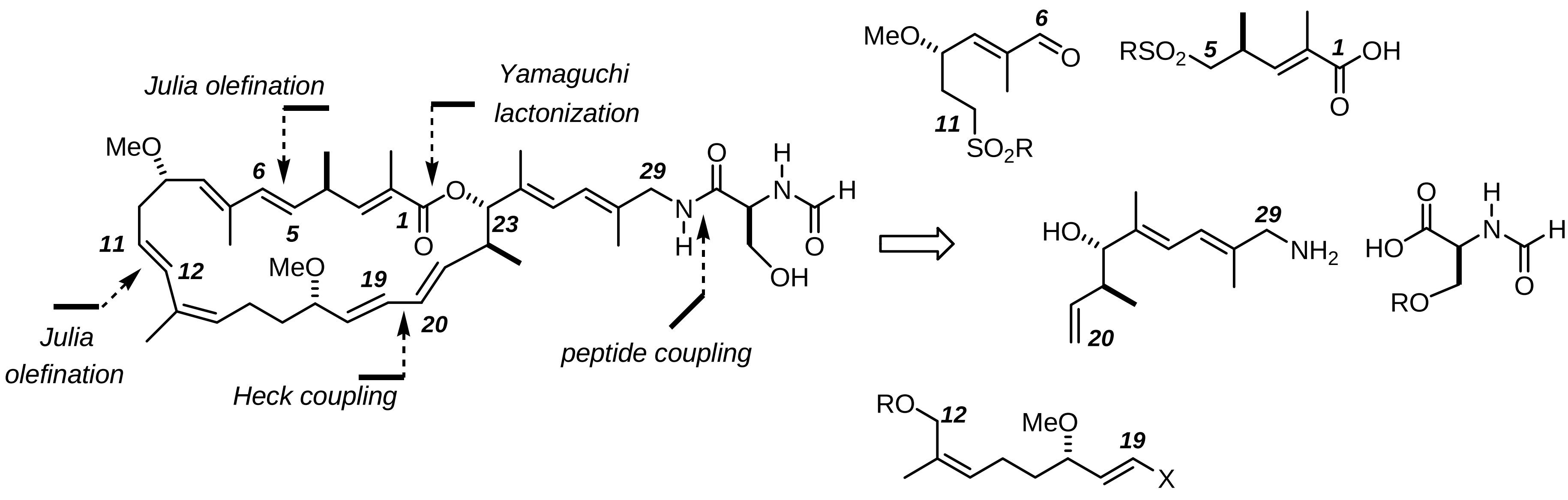
extremely scarce, very cytotoxic (average GI_{50} = 13 nM)

in vivo **activity (T/C = 150%)**

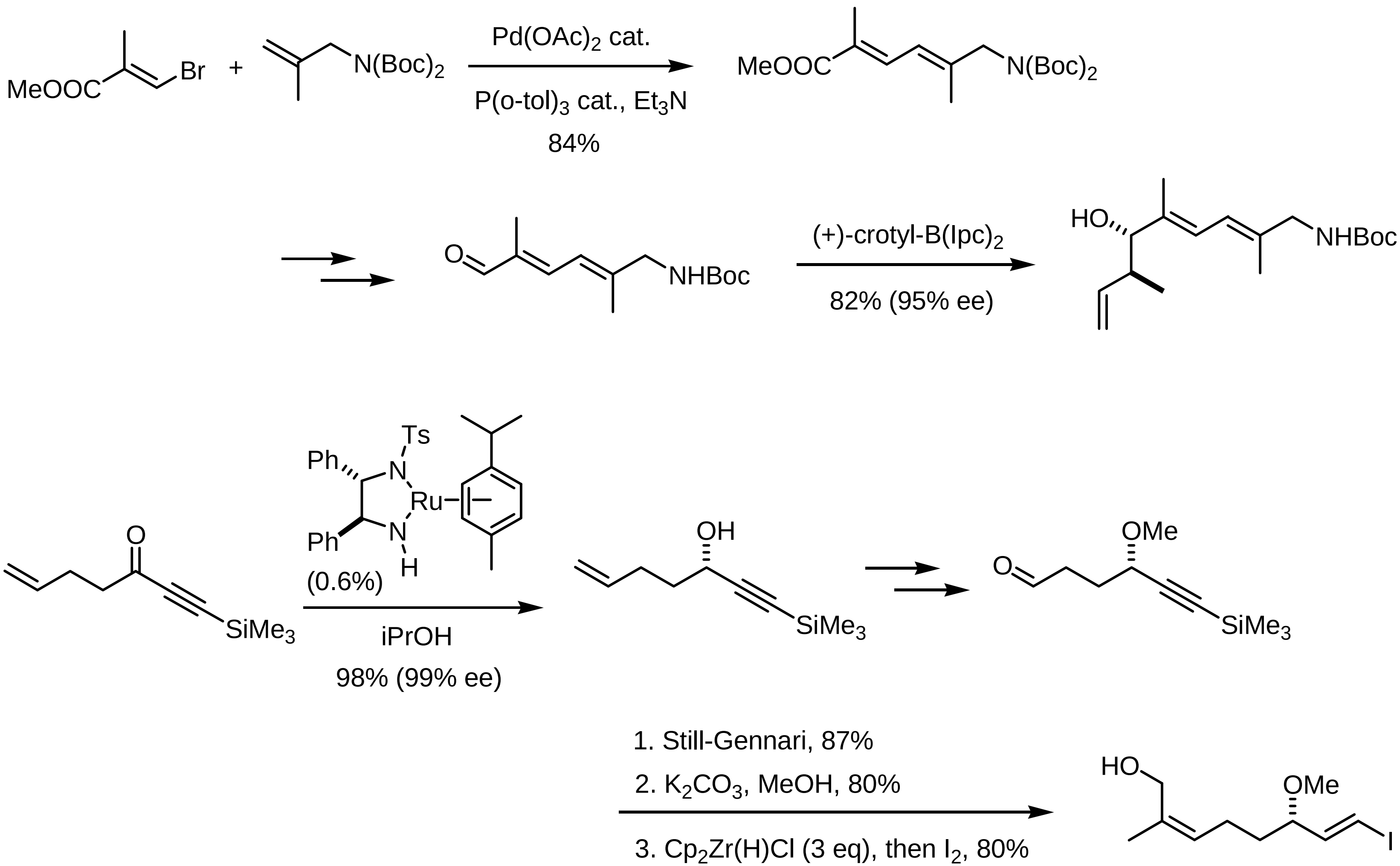
no "COMPARE" correlation with any standard anticancer agent

unknown mode of action

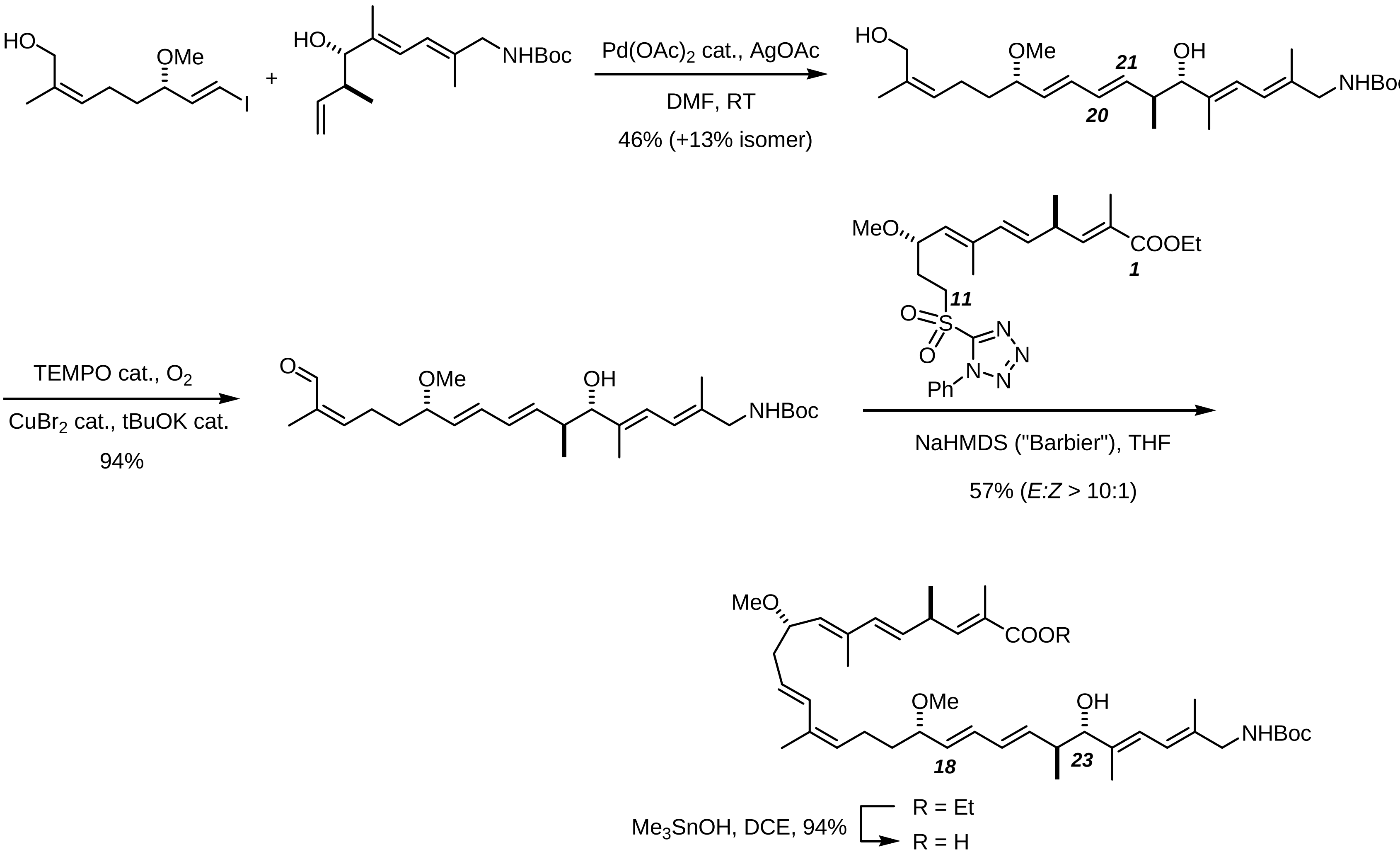
RETROSYNTHETIC ANALYSIS

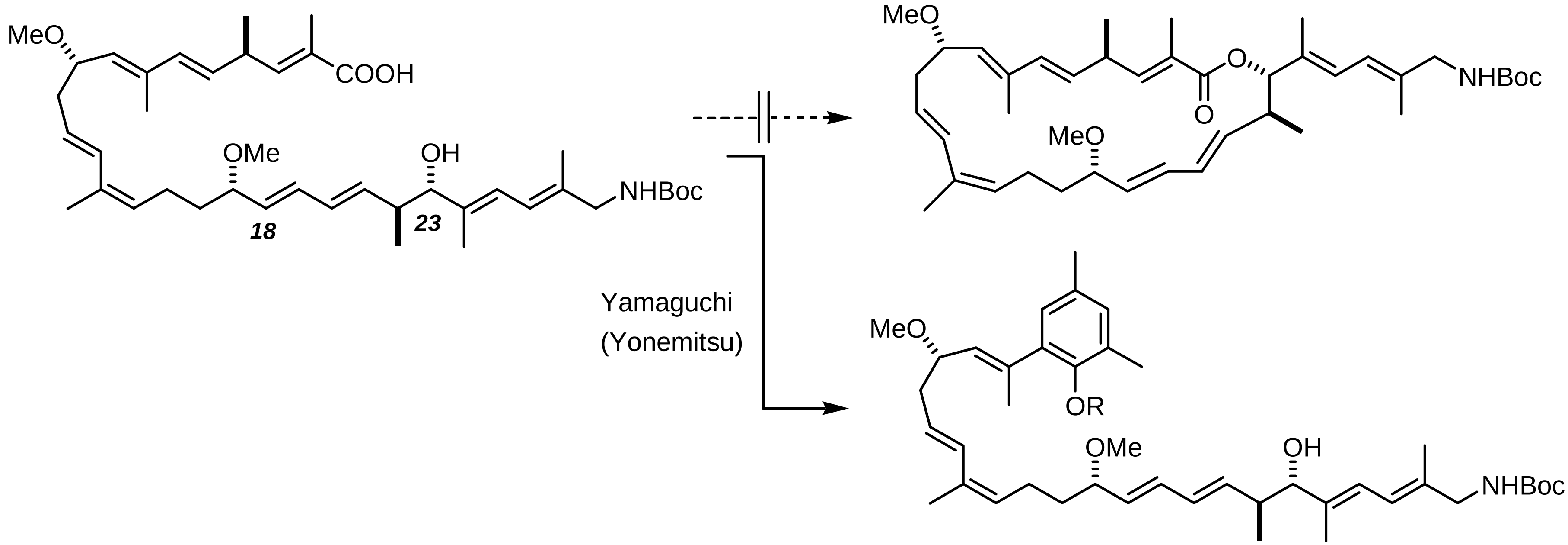


BUILDING BLOCKS

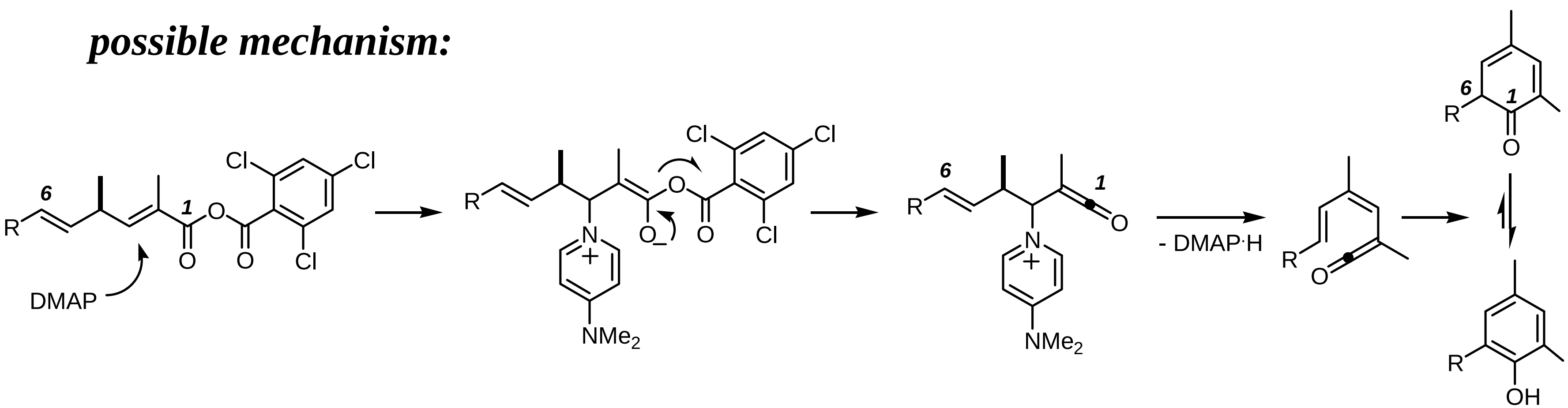


PREPARATION OF THE SECO-ACID





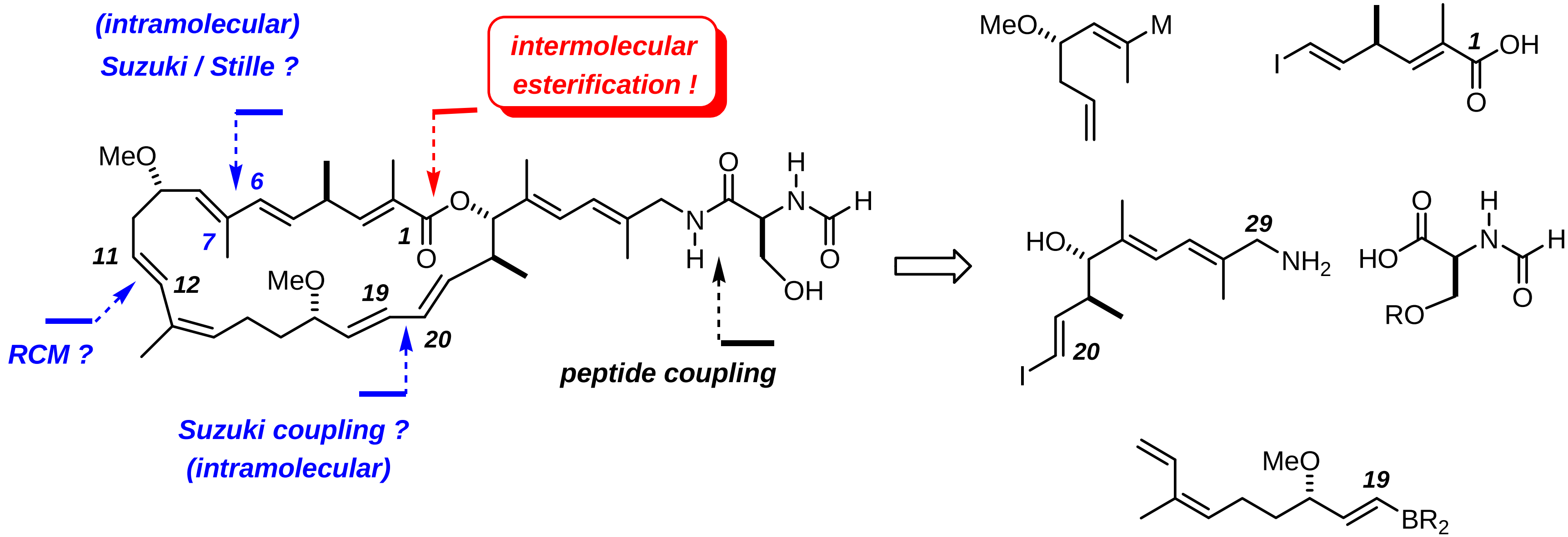
possible mechanism:



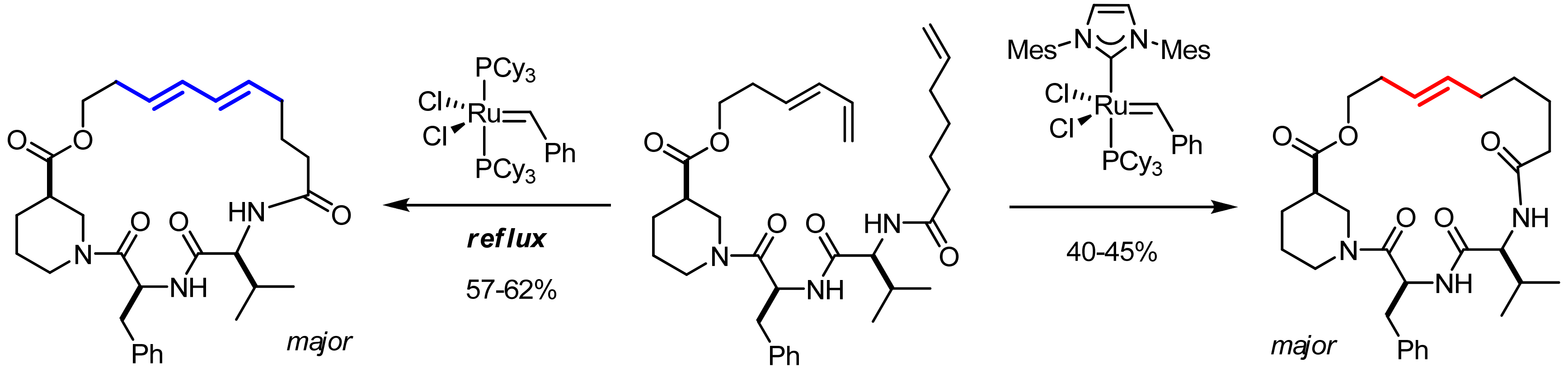
A. Fürstner, C. Aissa, C. Chevrier, F. Teplý, C. Nevado, M. Tremblay *Angew. Chem. Int. Ed.* **2006**, *45*, 5832

for a low yielding Shiina-macrolactonization approach, see: P. Helquist et al., *Org. Lett.* **2007**, *9*, 4619

RETROSYNTHETIC ANALYSIS (II)



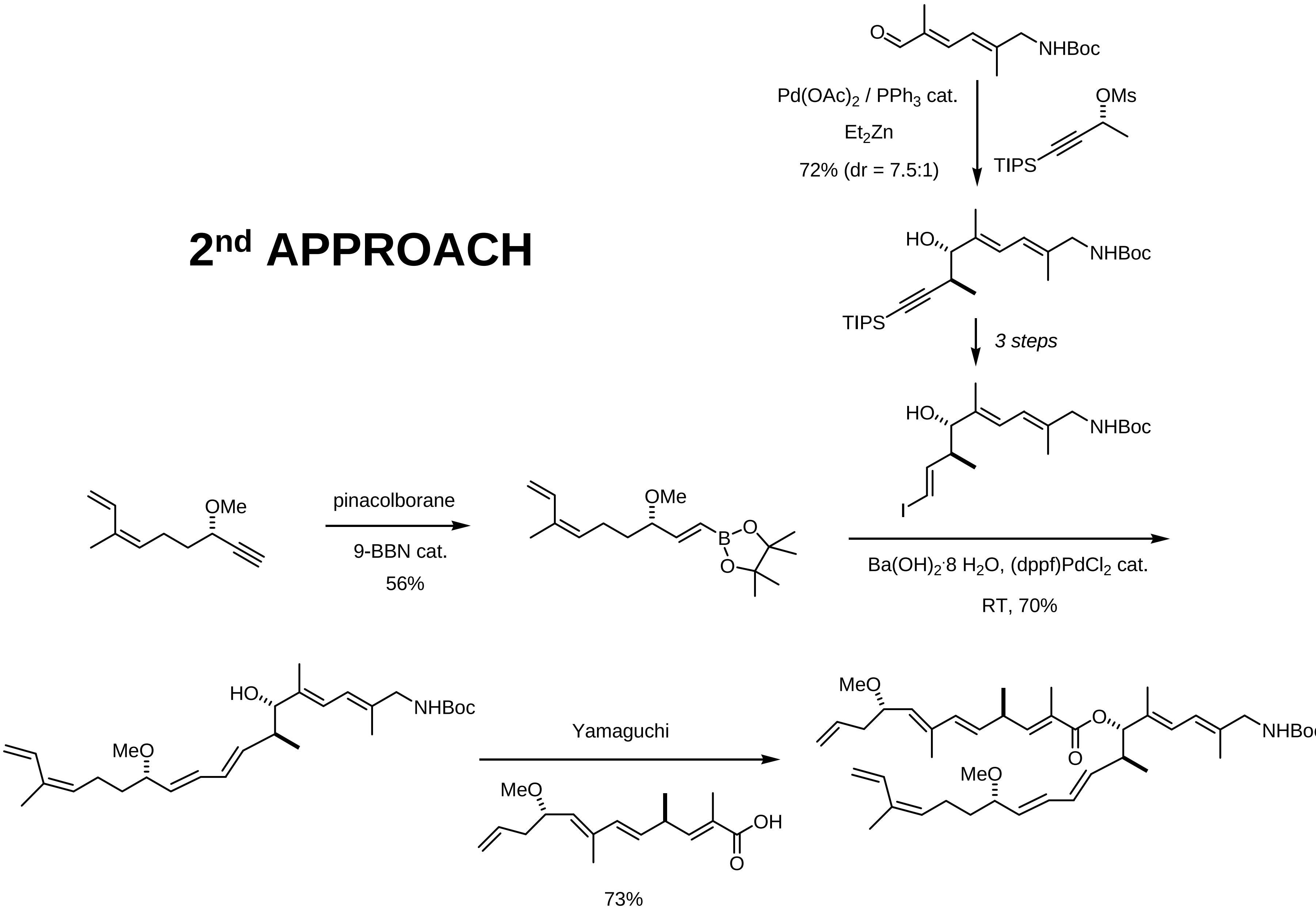
LITERATURE PRECEDENCE



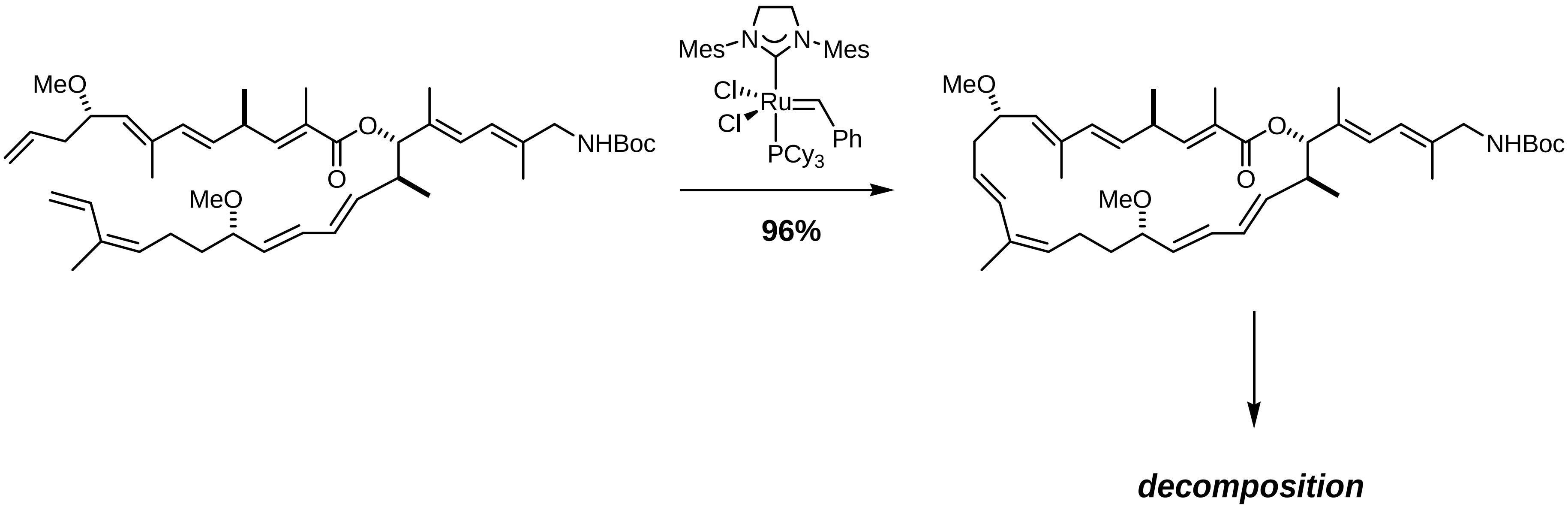
independent of temperature, solvent, concentration

J. Wagner et al., *JACS* **2003**, *125*, 3849; L. A. Paquette et al., *Helv. Chim. Acta* **2002**, *85*, 3033

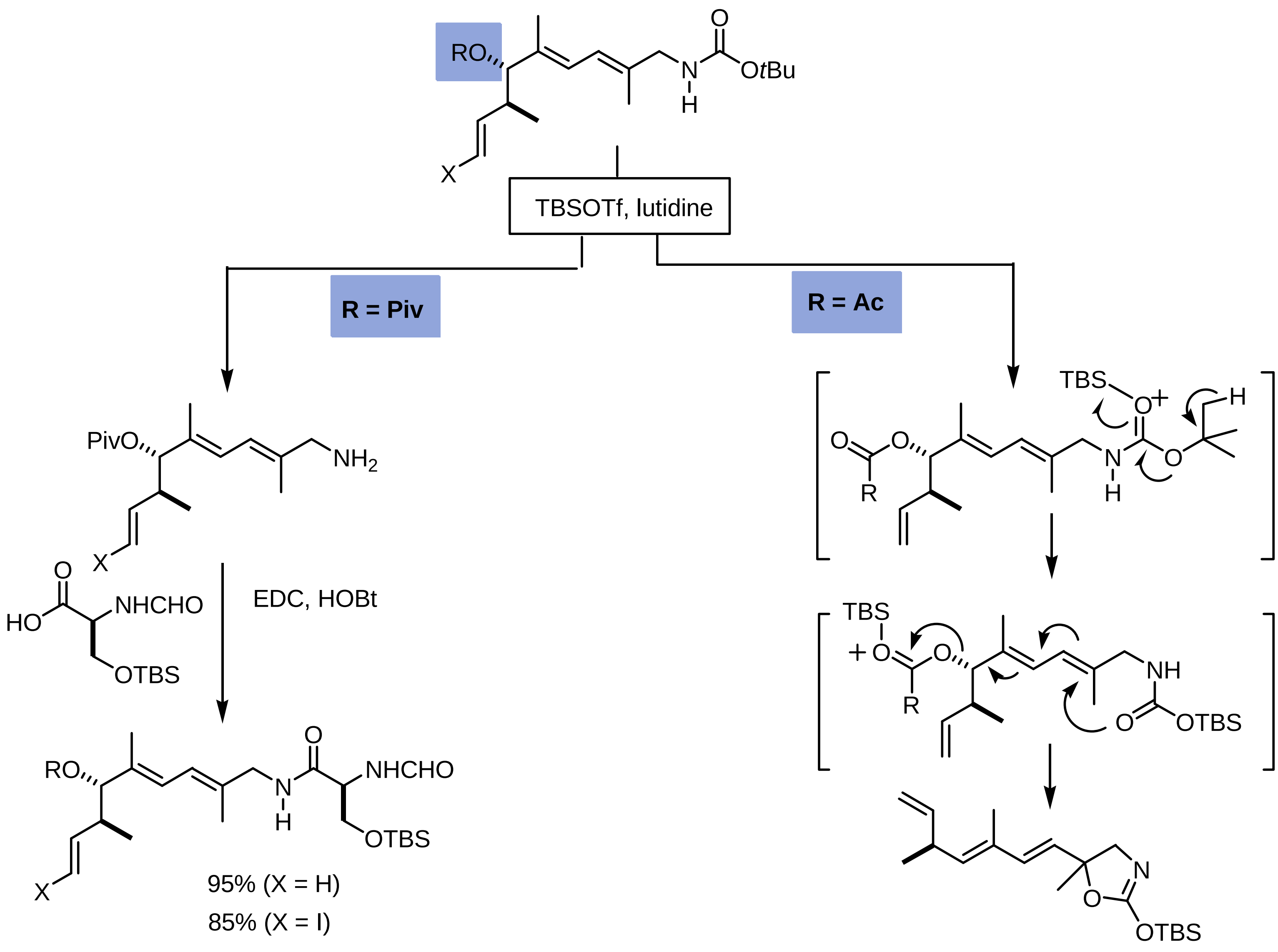
2nd APPROACH

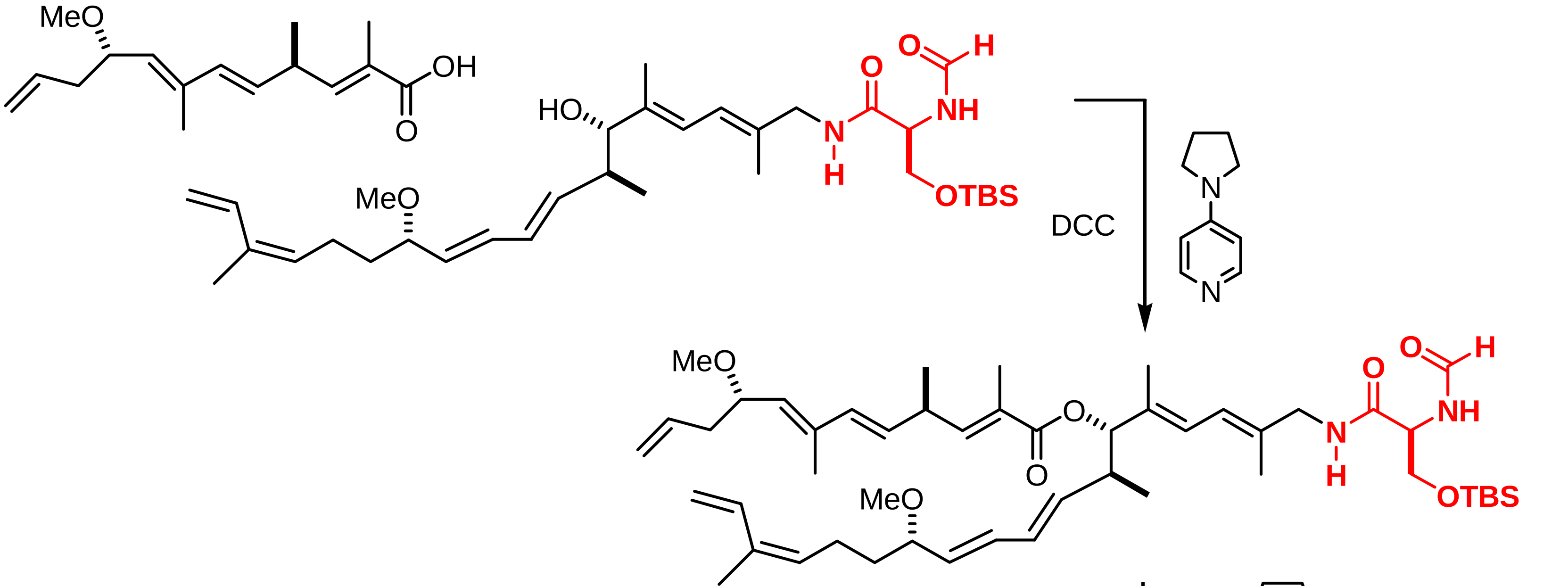


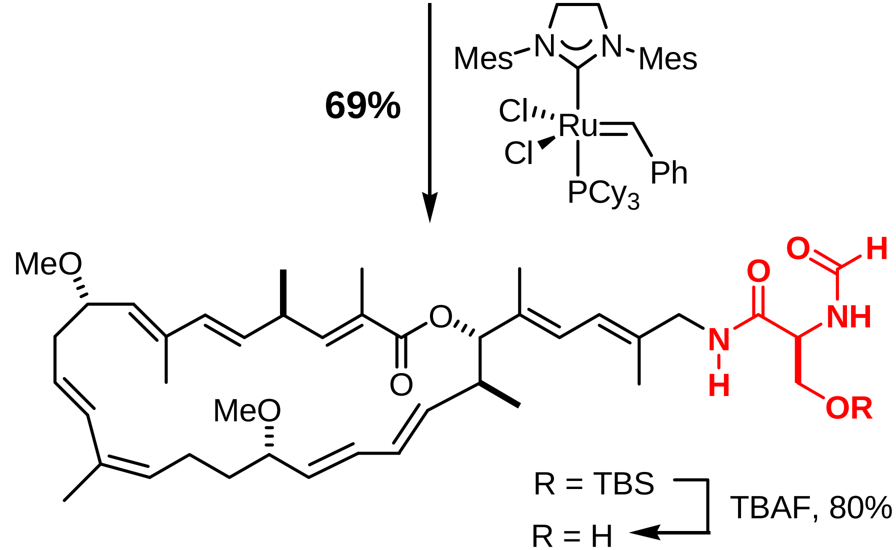
2nd APPROACH



"PROFUMO SYNDROME"





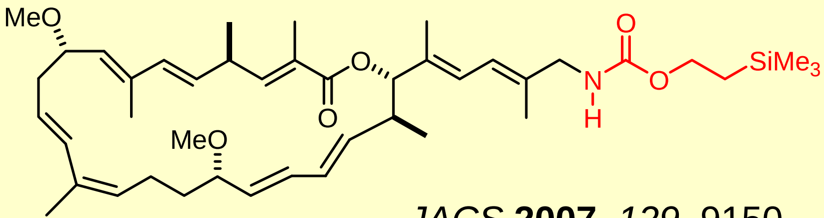


A. F. with C. Nevado, M. Tremblay, C. Chevrier, F. Teplý, C. Aissa, M. Waser

Angew. Chem. Int. Ed. **2006**, *45*, 5837

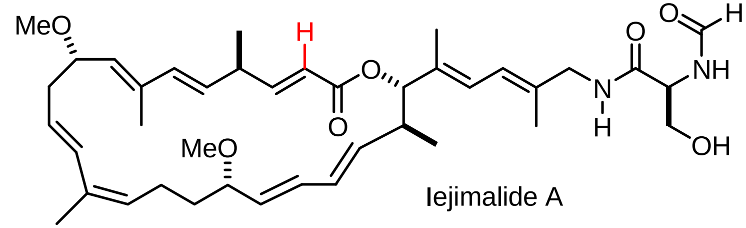
J. Am. Chem. Soc. **2007**, *129*, 9150

3rd GENERATION APPROACH



JACS **2007**, *129*, 9150

MOLECULAR EDITING



Iejimalide A