Literature Report 1

Total Synthesis of Leiodermatolide A

Reporter: Jian Chen

Checker: Wen-Jun Huang

Siu, Y.-M.; Krische, M. J.* *J. Am. Chem. Soc.* **2021**, *143*, 10590

2021-12-20

CV of Prof. Michael J. Krische

Background:

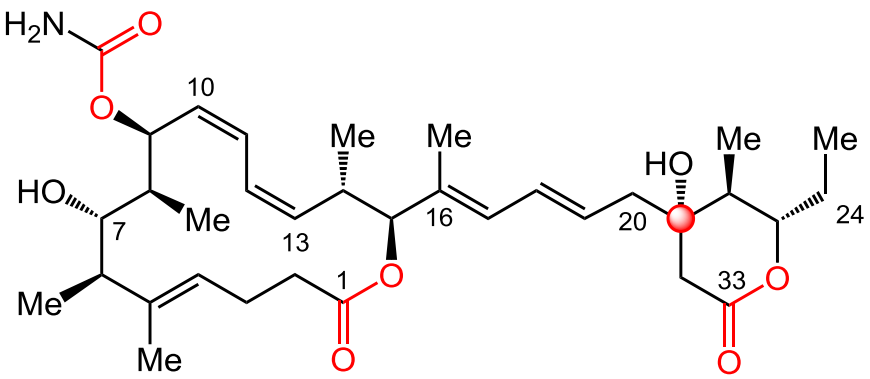
- **1986-1989** B.S., UC-Berkeley
- **1989-1990** Fulbright Fellow, Helsinki University
- **1990-1996** Ph.D., Stanford University (Barry Trost)
- **1997-1999** Post-Doc., Université Louis Pasteur
- **1999-2003** Assistant Professor, UT-Austin
- **2004-Now** Professor, University of Texas at Austin

Research:

- Total Synthesis of Complex Natural Products
- Hydrogen Gas-Mediated C-C Coupling

Contents

Introduction

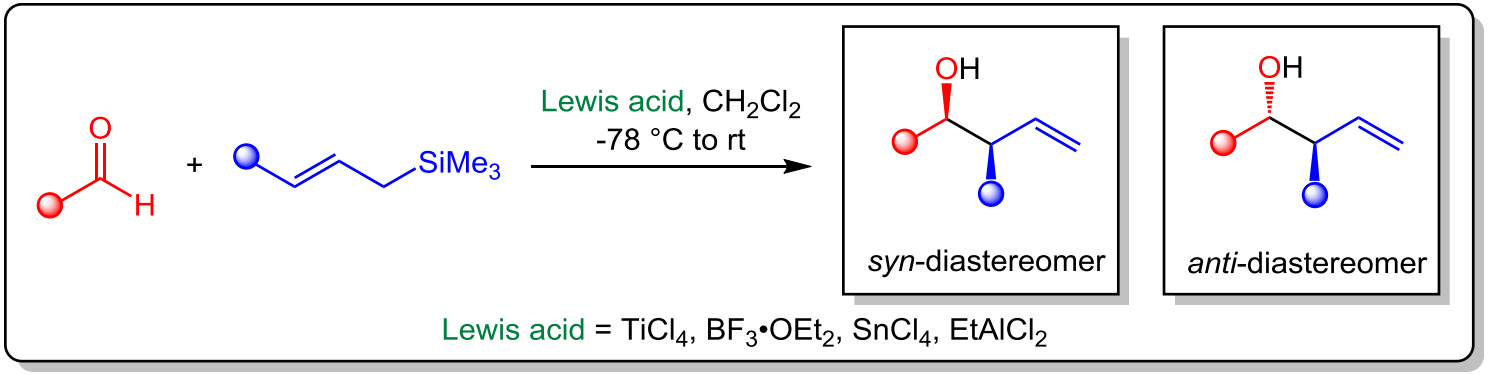


Leiodermatolide A

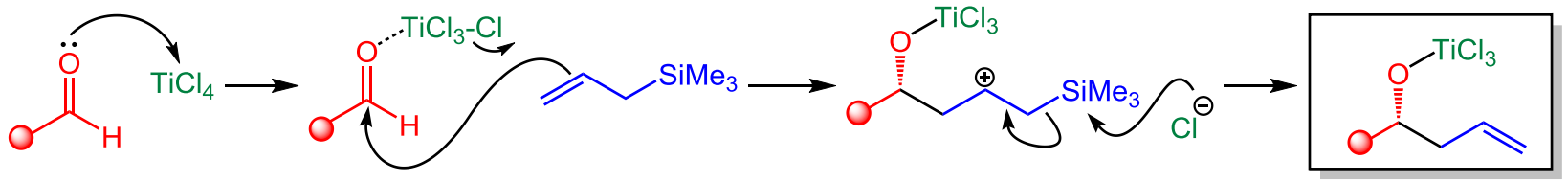
Leiodermatium

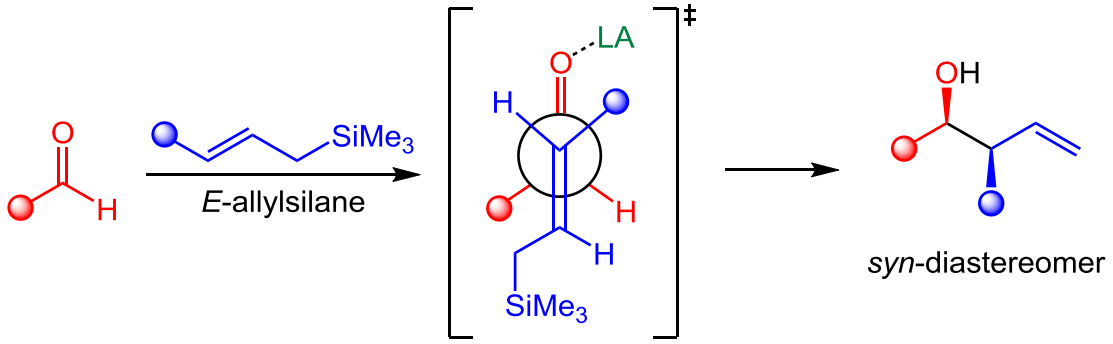
- Leiodermatolide A was isolated by Wright's group in 2008;
- Leiodermatolide A has a macrolide skeleton and contains 9 stereocenters (4 contiguous stereocenters), including 1 quaternary center and 3 ester groups;
- Leiodermatolide A exhibited potent antiproliferative effects, selectively pertur -bing tubulin dynamics at nM concentrations.

Sakurai Allylation

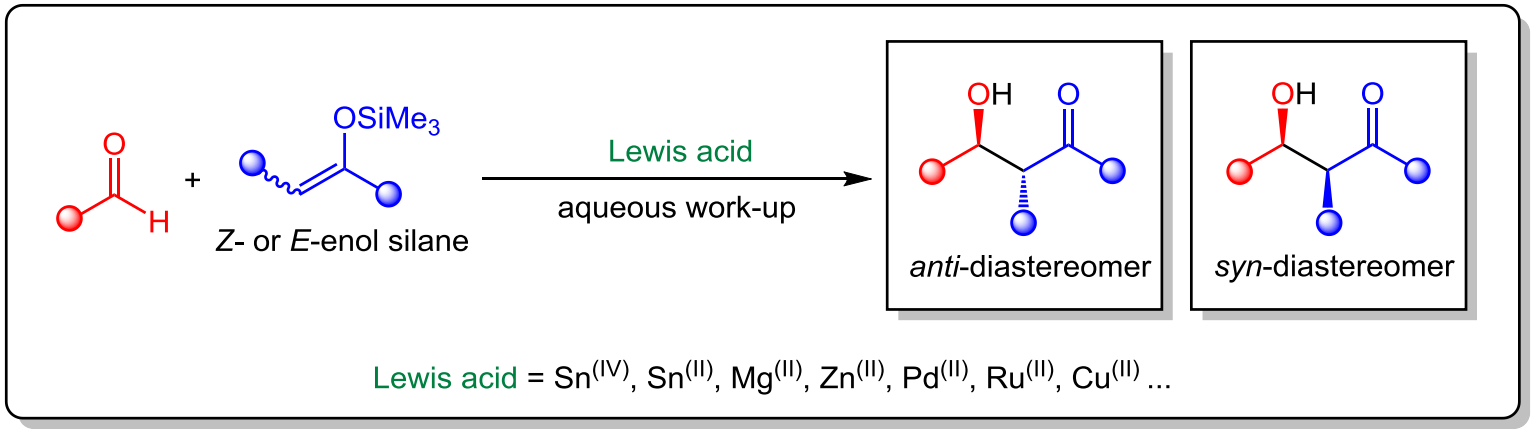


Mechanism:





Mukaiyama Aldol Reaction



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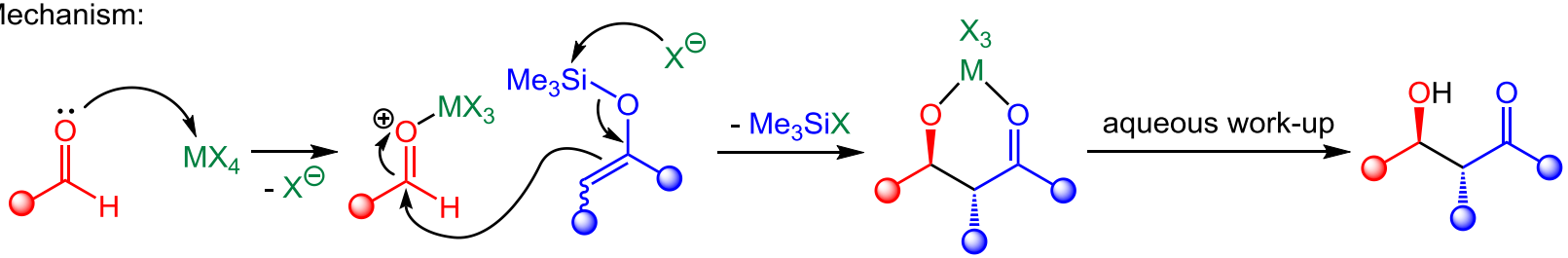
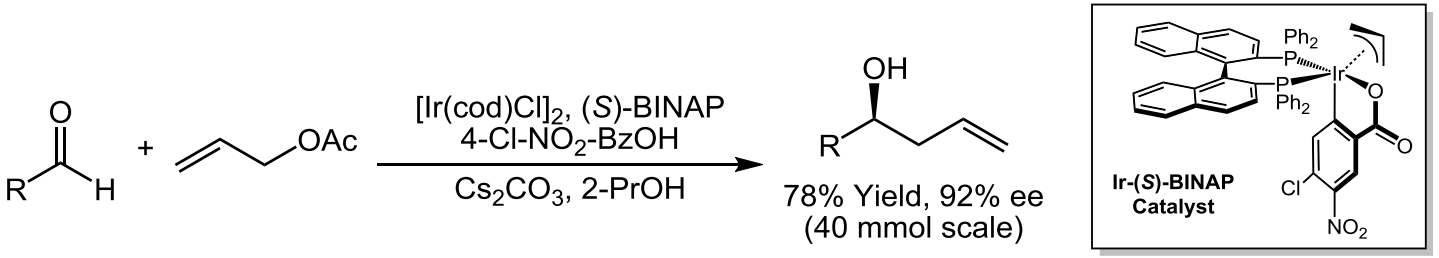
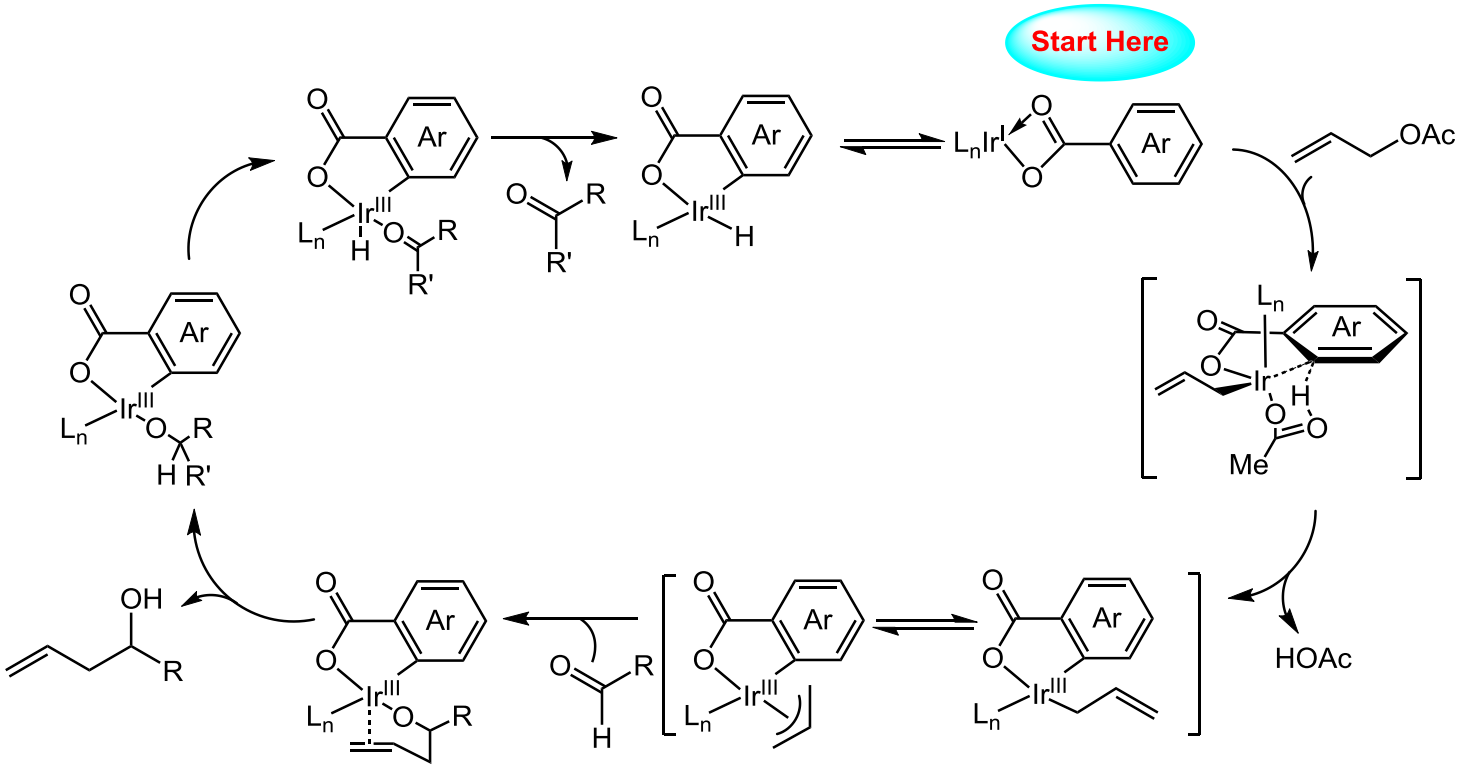


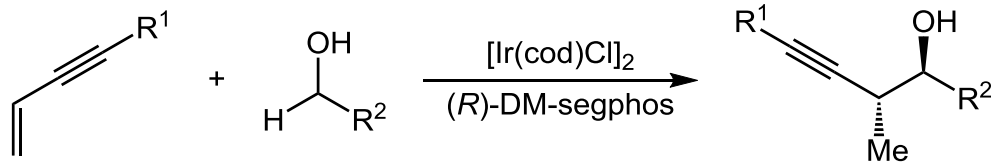
Mechanism

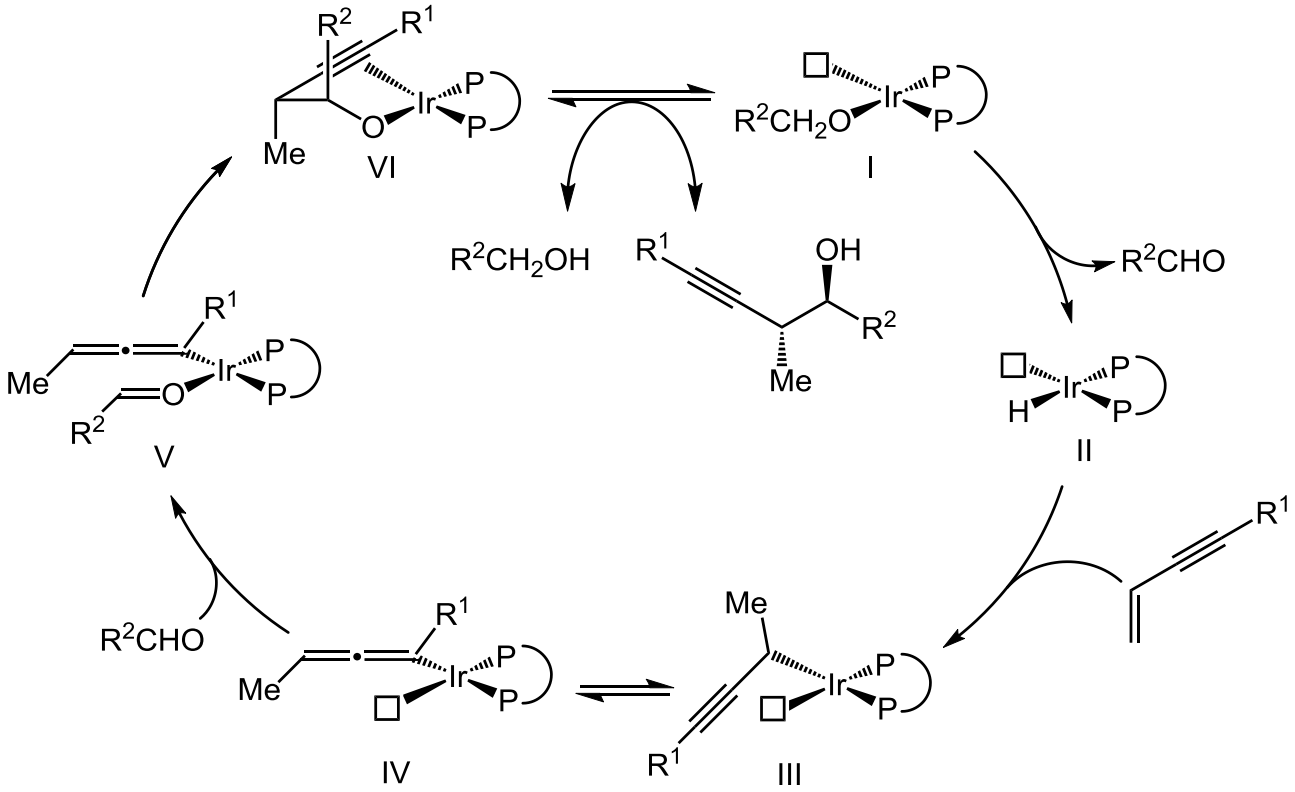




Kim, I. S.; Krische, M. J.* *J. Am. Chem. Soc.* **2008**, *130*, 14891

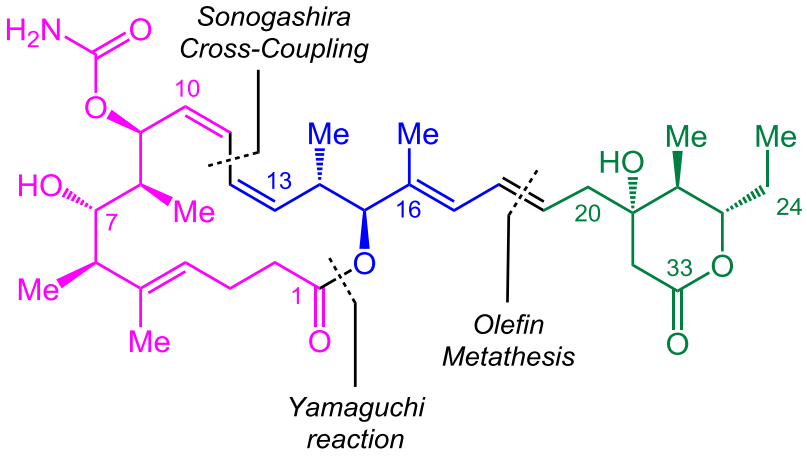
Mechanism



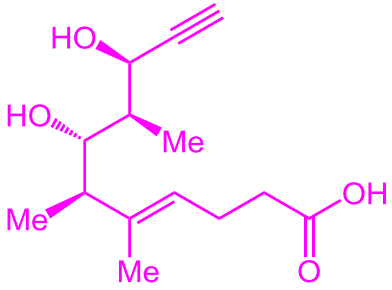


Geary, L. M.; Krische, M. J.* *Angew. Chem. Int. Ed.* **2012**, *51*, 2972

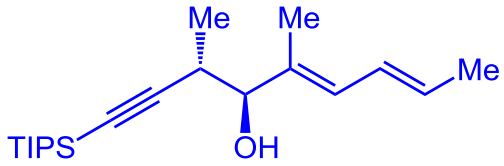
Retrosynthetic Analysis



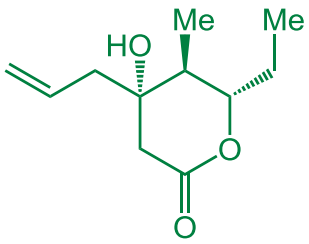
Leiodermatolide A



Fragment A
9 Steps (LLS)

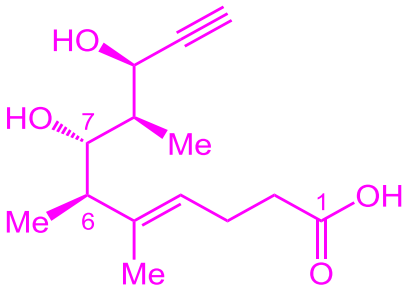


Fragment B
3 Steps (LLS)



Fragment C
5 Steps (LLS)

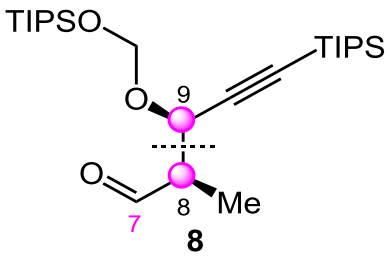
Retrosynthetic Analysis



Fragment A

C6-C7

Sakurai Reaction



8

Alcohol-Mediated Crotylation

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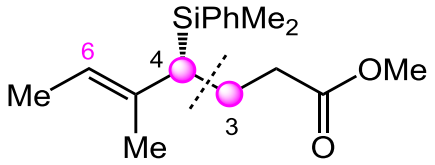

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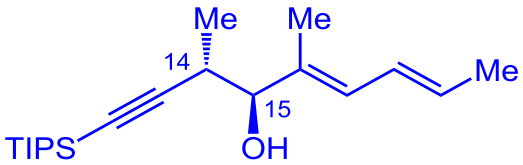
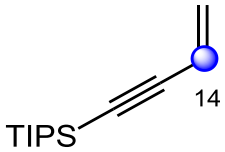
Alcohol-Mediated Allylation



Fragment B

C14-C15

Alcohol-Mediated Propargylation



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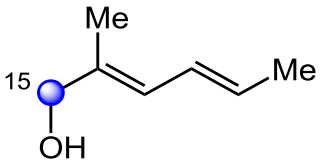

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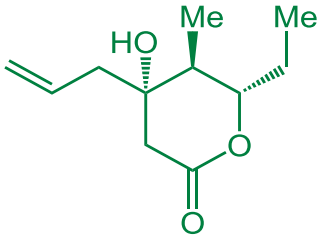
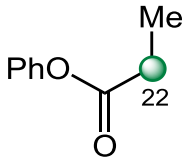


Fragment C

C22-C23

Mukaiyama Aldol
Birman KR, Dieckmann
Ketone Allylation



11

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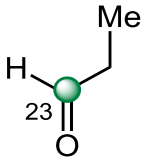

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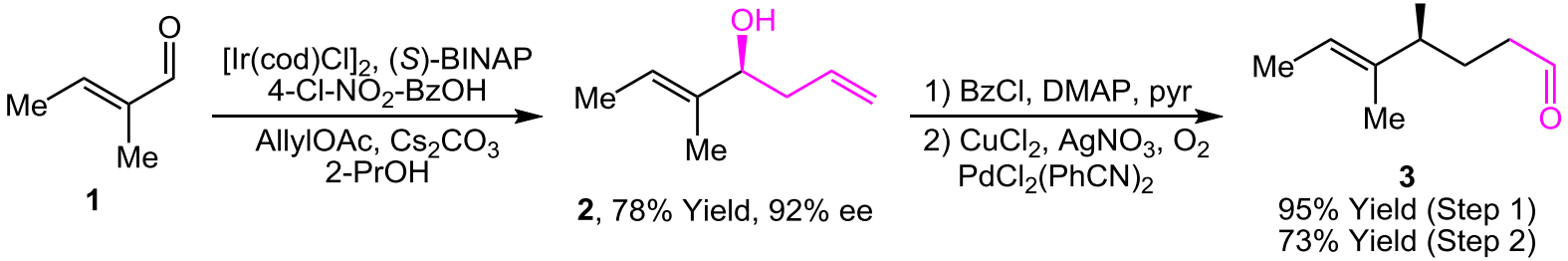
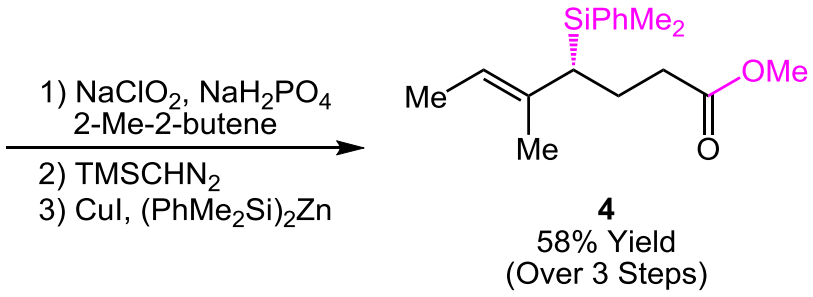
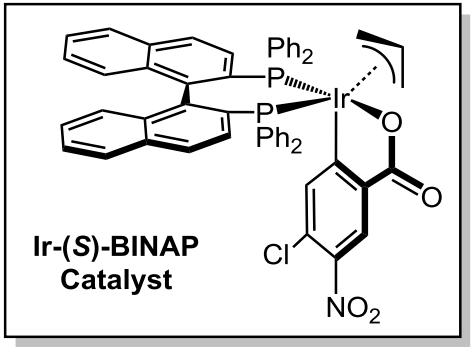
Synthesis of Fragment A







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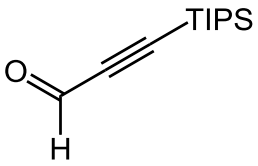
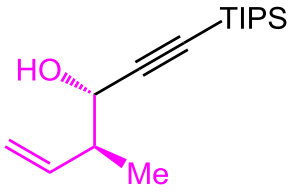


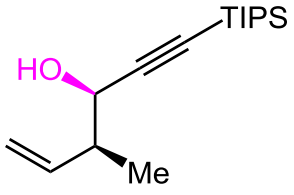
5
Made in 1 Step

Ir-(*S*)-SEGPHOS
2-PrOH, K_3PO_4
α-Me-AllylOAc, H_2O



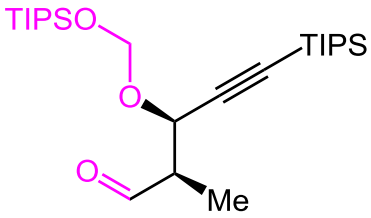
6
58% Yield, >20:1 dr
98% ee

1) 4-O_2N-$C_6H_4CO_2H$
DIAD, PPh_3
2) K_2CO_3, MeOH

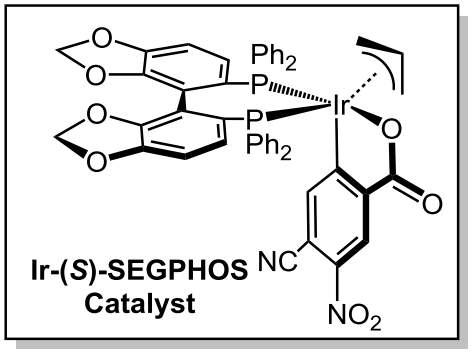


7
84% Yield, >20:1 dr
(Over 2 Steps)

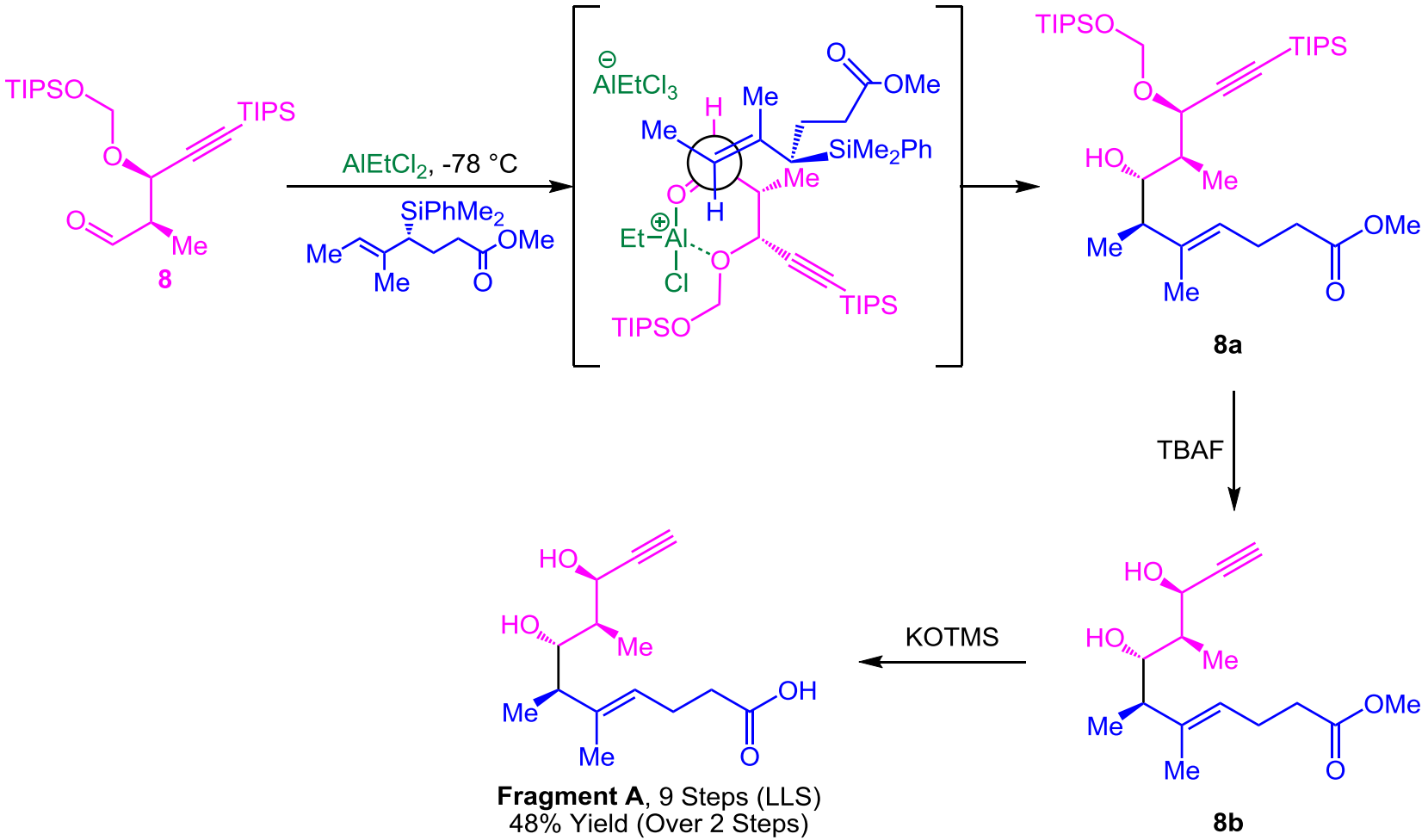
1) $ClCH_2OTIPS$
$^iPr_2EtN$, TBAI
2) O_3, TTMPP
Sudan Red 7B



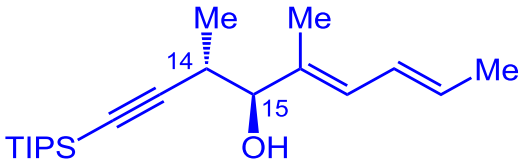
8
74% Yield
(Over 2 Steps)



Synthesis of Fragment A



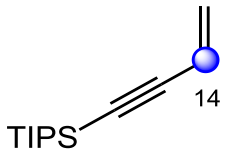
Synthesis of Fragment B



Fragment B

C14-C15

Alcohol-Mediated Propargylation



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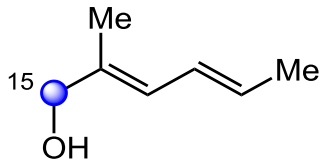

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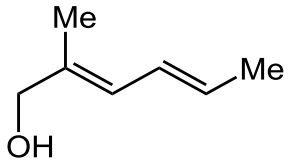
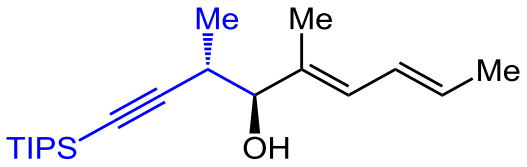


10
(Made in 2 Steps)

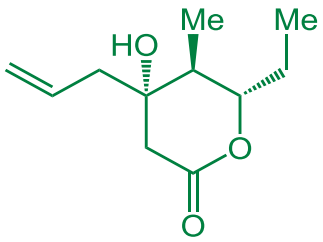
$[Ir(cod)Cl]_2$
(*S*)-DM-SEGPHOS

9



Fragment B, 3 Steps (LLS)
63% Yield, 90% ee
(1.07 gram scale)

Synthesis of Fragment C



Fragment C

C22-C23

Mukaiyama Aldol
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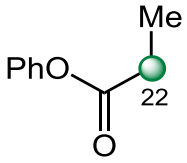
Ketone Allylation



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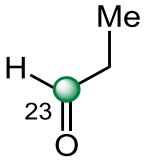

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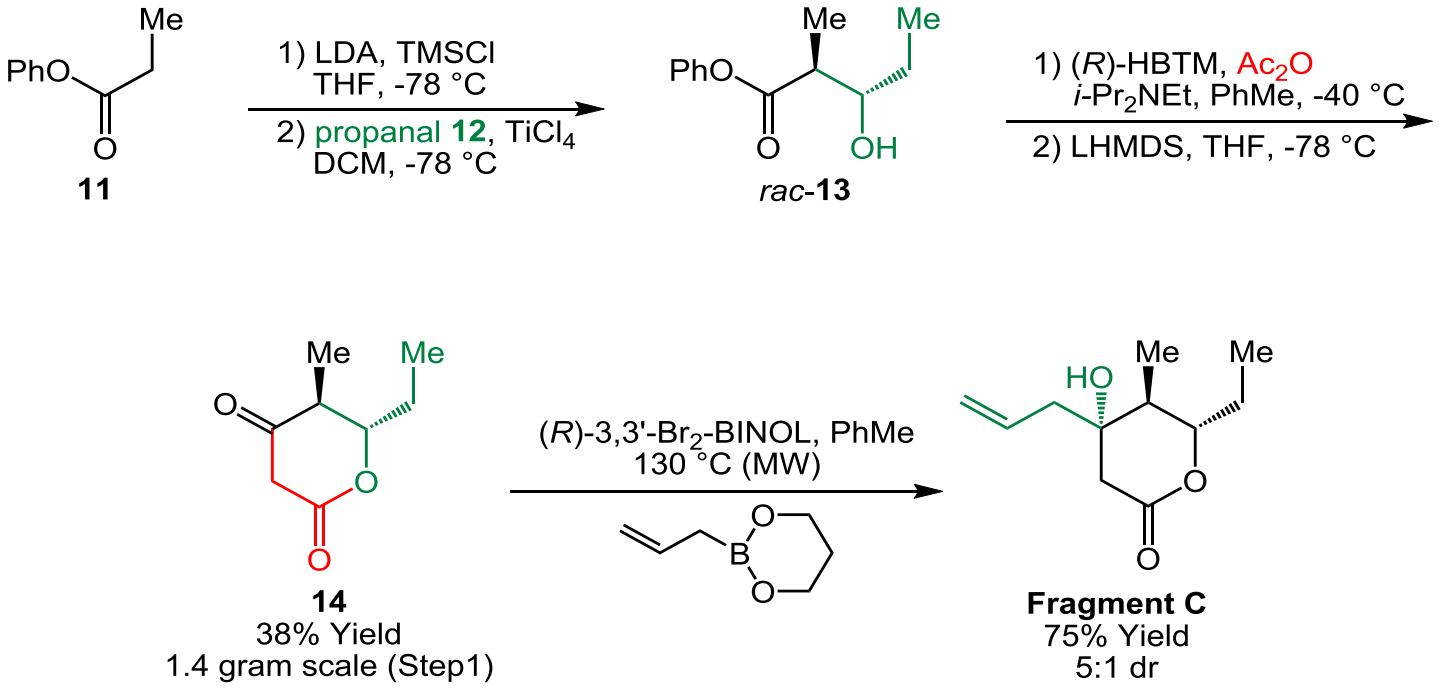
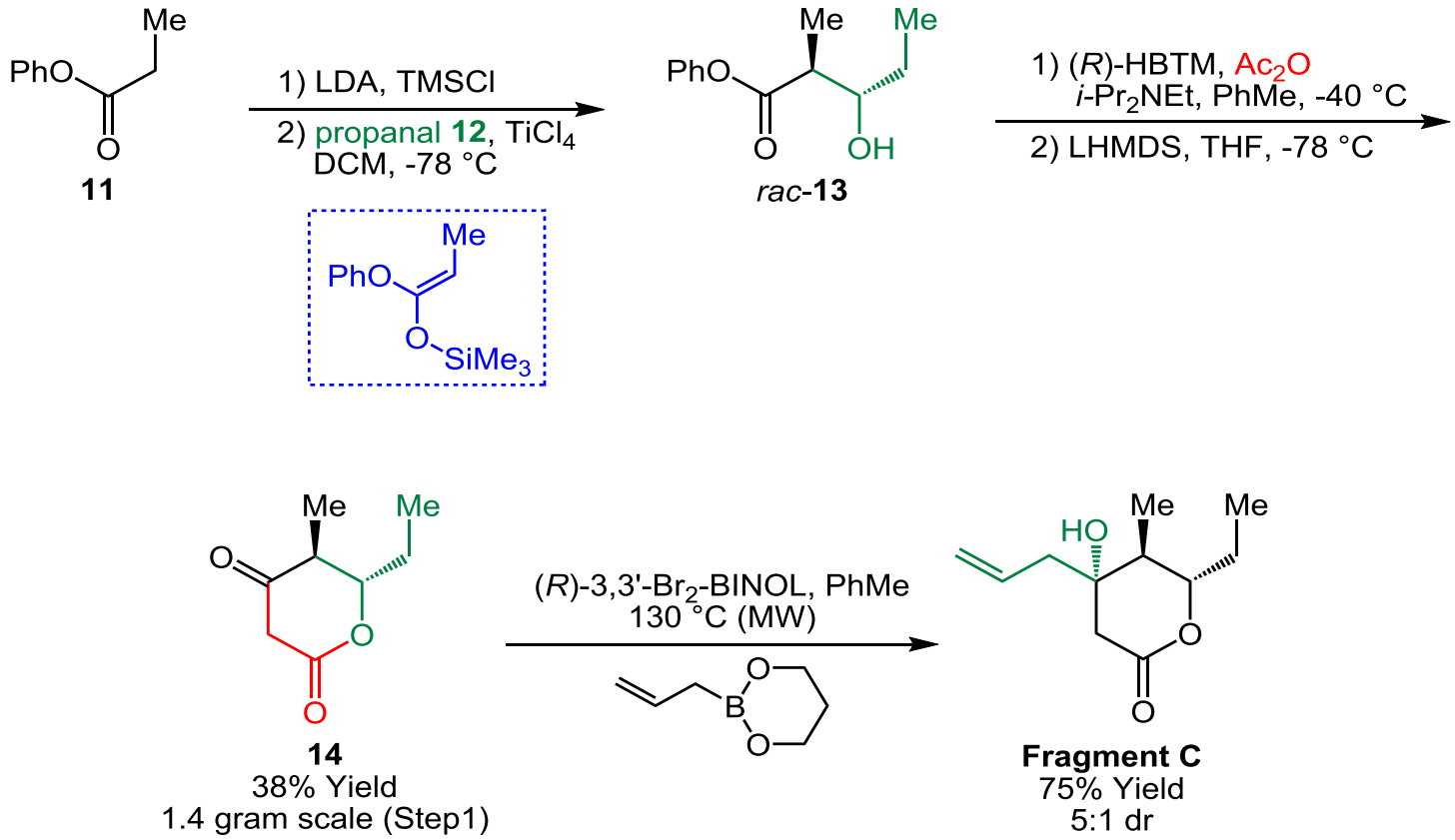
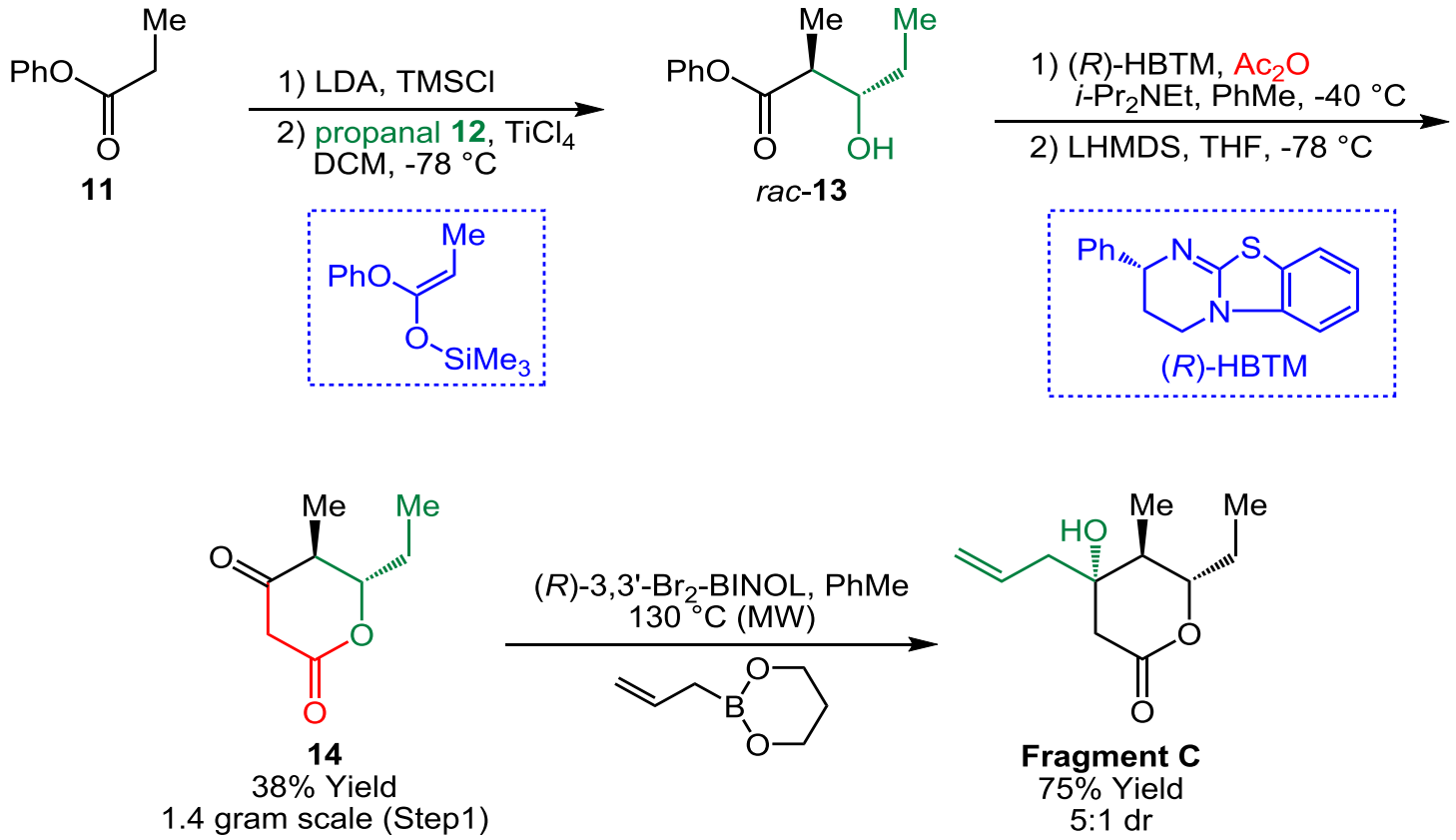
Synthesis of Fragment C



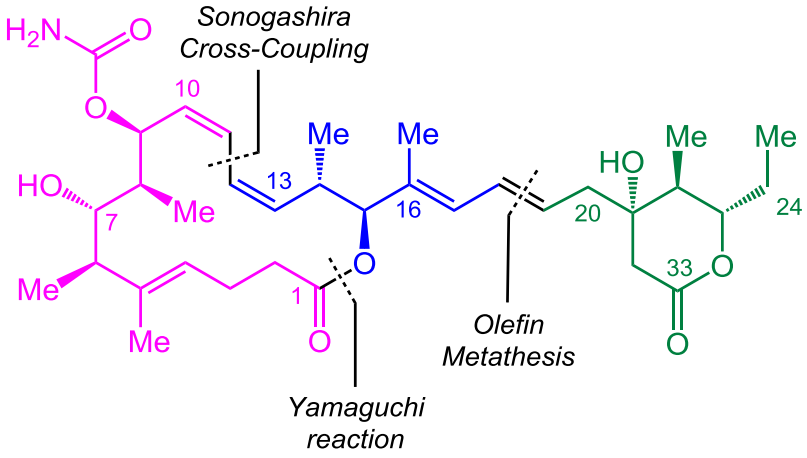
Synthesis of Fragment C



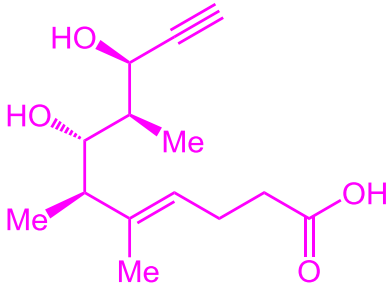
Synthesis of Fragment C



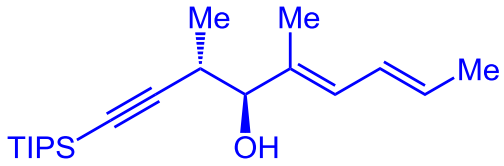
Retrosynthetic Analysis



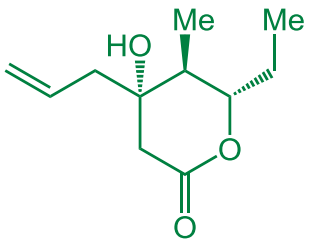
Leiodermatolide A



Fragment A
9 Steps (LLS)

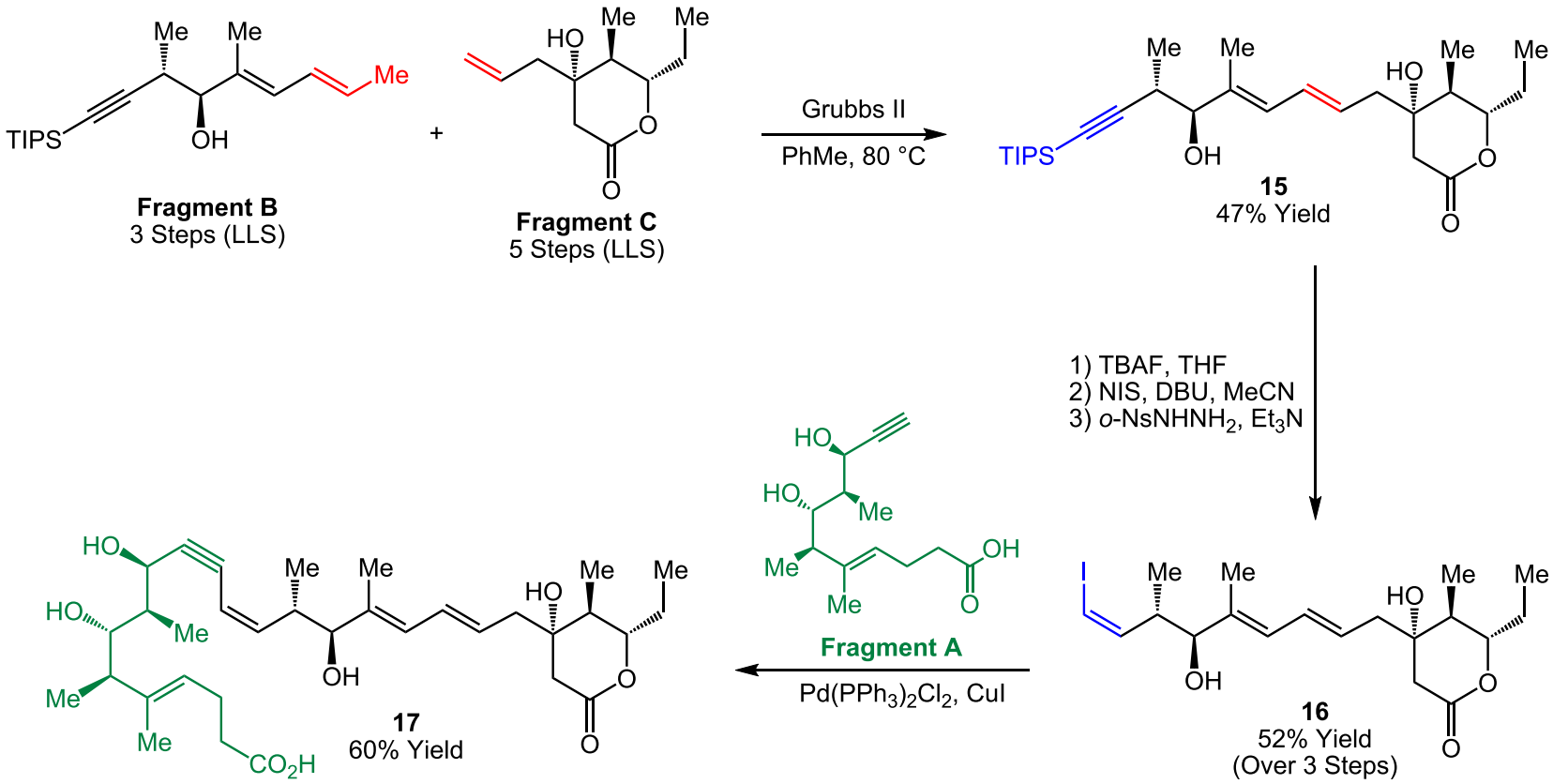


Fragment B
3 Steps (LLS)



Fragment C
5 Steps (LLS)

Synthesis of Leiodermatolide A



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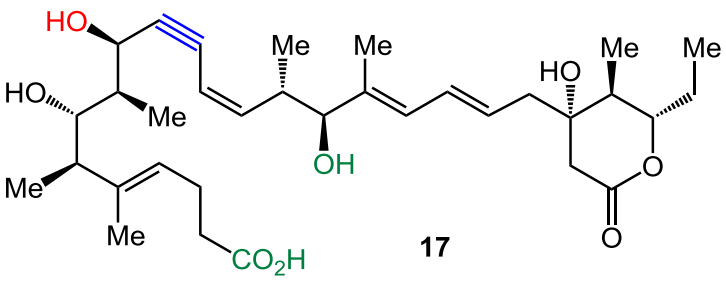
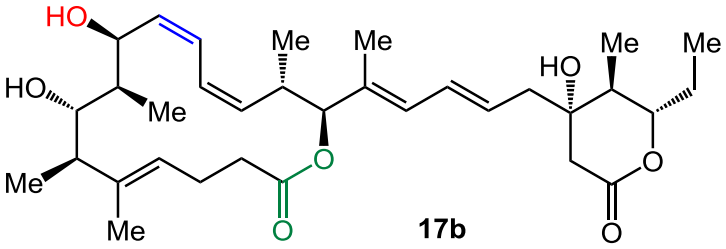
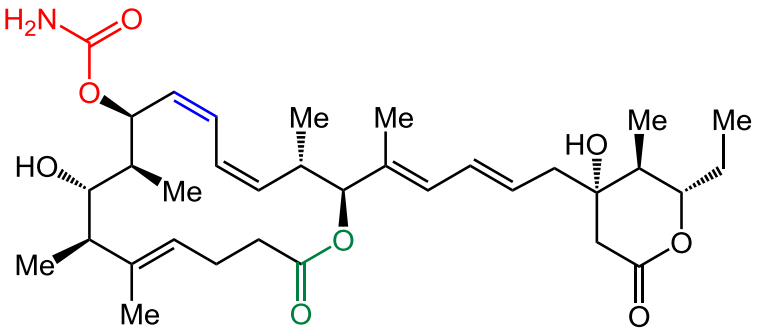


17

1) 2,4,6-Cl_3BzCl
DMAP, Et_3N
2) $Rh(cod)_2BAr^F$
rac-BINAP, H_2



17b



Leiodermatolide A

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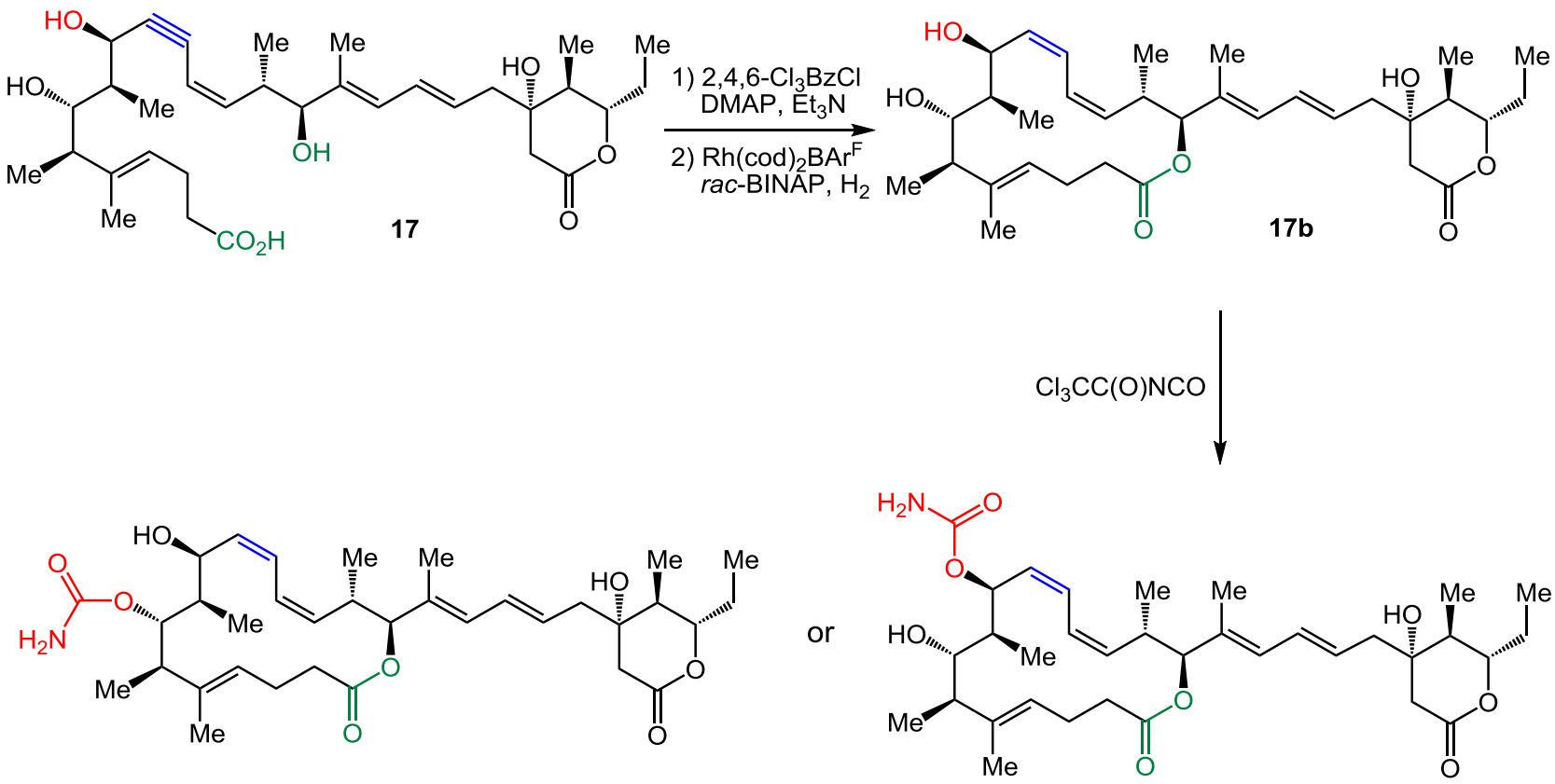

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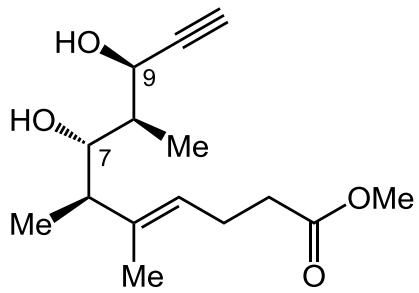
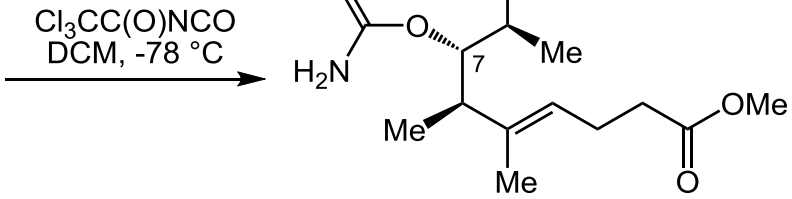
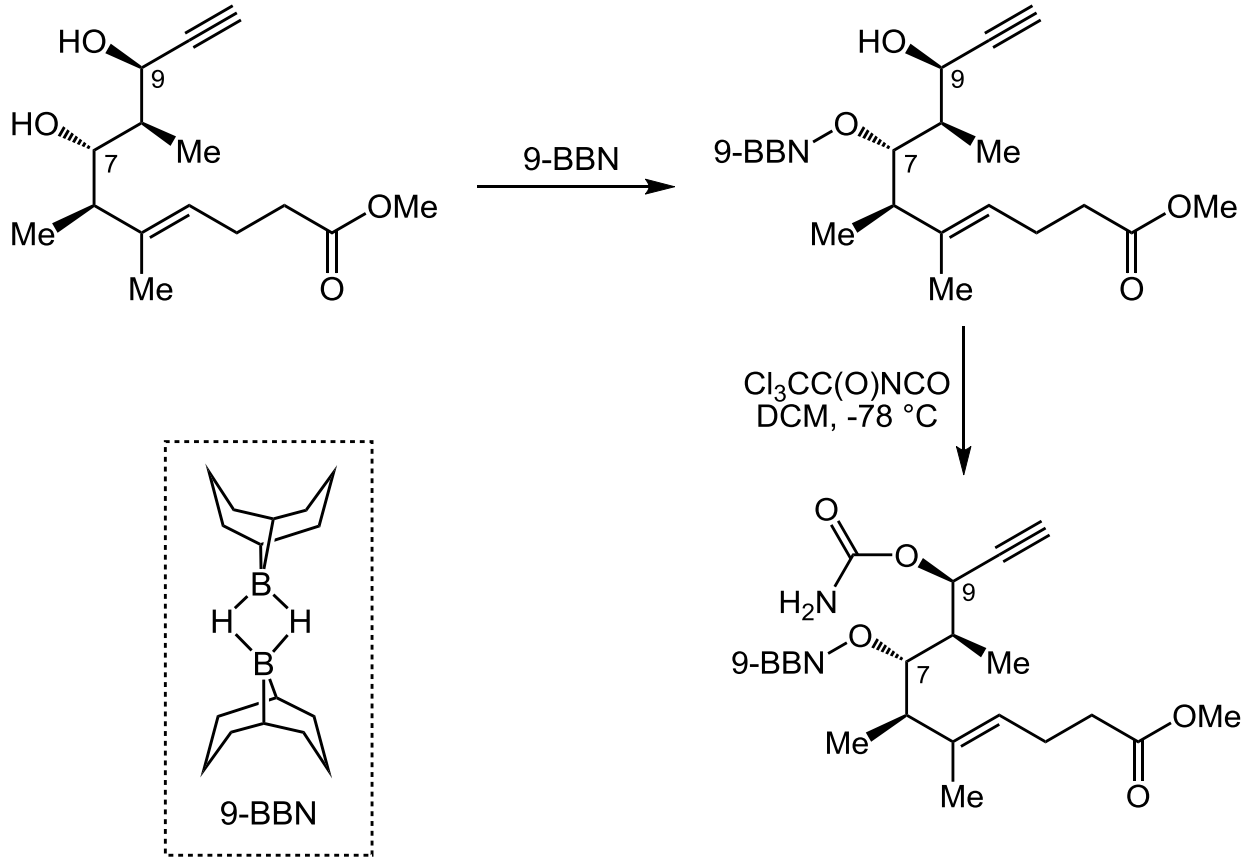


Fragment A
Methyl Ester

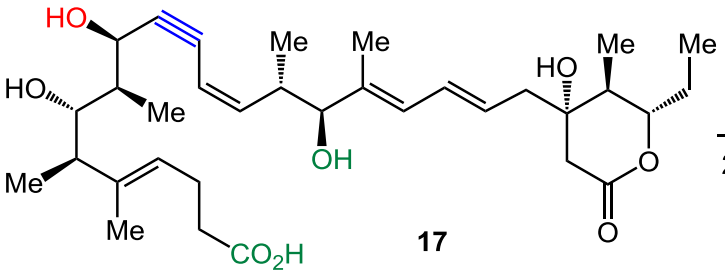


C7 vs C9 Isomers
72% Yield, 8:1 dr (without 9-BBN)
65% Yield, 1:10 dr (9-BBN 95 mol%)

Synthesis of Leiodermatolide A



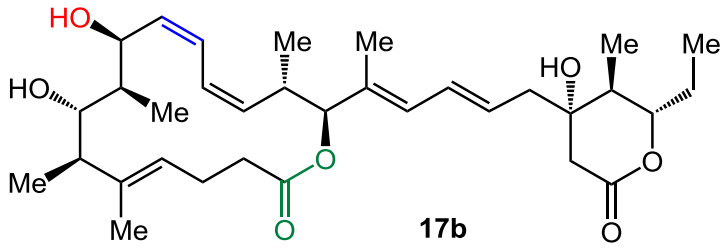
Synthesis of Leiodermatolide A



17

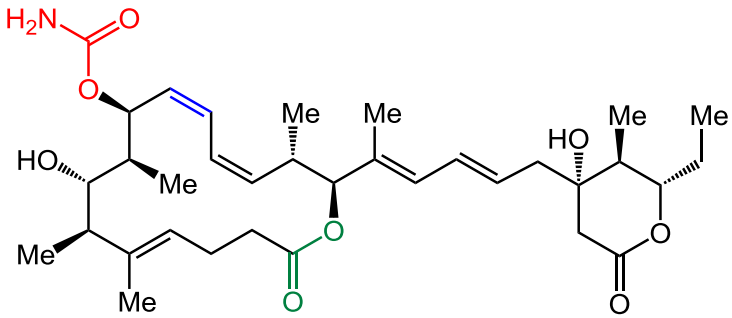
1) 2,4,6-Cl_3BzCl
DMAP, Et_3N

2) $Rh(cod)_2BAr^F$
rac-BINAP, H_2



17b

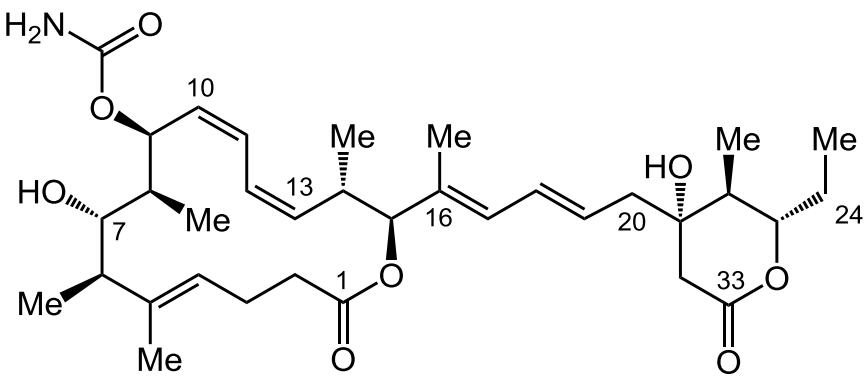
9-BBN
$Cl_3CC(O)NCO$



Previously
19 & 25 Steps (LLS)
Now 13 Steps (LLS)

Leiodermatolide A
42% Yield (Over 3 Steps)

Summary



Leiodermatolide A
13 steps (LLS)

- Total synthesis of Leiodermatolide A: 13 steps (LLS), constituting the most concise route to this compound reported;
- Transfer hydrogenative variants of three carbonyl additions that traditionally rely on premetalated reagents (allylation, crotylation, and propargylation) are deployed together in one total synthesis.

The First Paragraph

Writing Thought

Bioactivities of Leiodermatolide A

↓

Previous Work on Synthesis

↓

Significance of Developing New Methodologies

The First Paragraph

Natural products that disrupt microtubule dynamics have found broad use as anticancer agents. Leiodermatolide A is an antimitotic marine macrolide that was isolated in 2008 from crude extracts of a deep sea lithistid sponge of the genus Leiodermatium found off the Florida coast. In a panel of human cancer cell lines, Leiodermatolide A exhibited potent antiproliferative effects, selectively perturbing tubulin dynamics at nM concentrations through a novel mechanism: while incurring abnormal spindle formation at nM concentrations in two different cancer cell lines, purified tubulin remained undisturbed in vitro even at much higher concentrations.

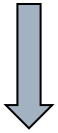
The First Paragraph

The scarce supply and compelling biology of Leiodermatolide A has driven efforts toward its de novo chemical synthesis, resulting in truly impressive total syntheses by Paterson and Fürstner and substructure syntheses by Maier. The synthesis of Leiodermatolide analogues have led to additional biological data that reveal mitotic arrest, micronucleus induction, centrosome amplification, and tubulin disruption in human U2OS cells without evidence for direct binding of tubulin in cell-free analyses. On the basis of these data, centrosome declustering was suggested as a possible mechanism of action. Further investigations into Leiodermatolide's unique biology have been prohibited due to lack of material.

The Last Paragraph

Writing Thought

Summary of Our Work



Illustrate the Highlights of Our Work

The Last Paragraph

To conclude, the synthetic challenges posed by the structural complexity of polyketide natural products have evoked numerous advances in acyclic stereocontrol, especially in the context of carbonyl addition. Whereas the initial lexicon of asymmetric methods that emerged focused on the use of premetalated C-nucleophiles and chiral auxiliaries, we aim to advance a suite of catalytic enantioselective C−C couplings that bypass discrete organometallic reagents and stoichiometric chiral inducing elements. The present total synthesis of Leiodermatolide A, which exploits asymmetric alcohol-mediated allylation, crotylation, and propargylation, exemplifies how time-honored transformations that have traditionally relied on premetalated reagents can now be conducted catalytically from tractable π-unsaturated pronucleophiles.

Representative Examples

●Kinetic resolution of the racemic aldol rac-**13**, which is accessible via anti-diastereoselective Mukaiyama-aldol addition, was deemed an attractive alternative.

被认为；被视为

●To conclude, the synthetic challenges posed by the structural complexity of polyketide natural products have evoked numerous advances in acyclic stereocontrol, especially in the context of carbonyl addition.

唤起；引起

●The issues surrounding Leiodermatolide A are emblematic of the persistent challenges associated with the construction of structurally complex secondary metabolites that continue to evoke innovation across the field of chemical synthesis.

标志的；典型的；有代表性的

Acknowledgement

Thanks for Your Attention