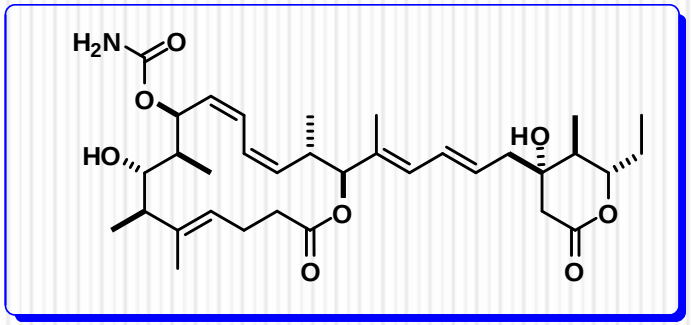
Angewandte Communications

Natural Product Synthesis

Total Synthesis of the Antimitotic MarineMacrolide (-)- Leiodermatolide

Sankar Rao Suravarapu

Prof. Dr. Philippe Renaud
University of Bern, Department of Chemistry and Biochemistry



I. Paterson et al., *Angew. Chem. Int. Ed.* **2014**, *53*, 12988

Introduction

1. Leiodermatolide was isolated in 2008 by the Wright group from the marine sponge *Leiodermatium sp*.
2. These samples were collected by submersible off the Florida coastline
3. Exhibits potent anti proliferative activity against a panel of human cancer cell lines

IC_{50} = 3.3 nM for A549 lung adenocarcinoma cells
= 5.0 nM for PANC-1 pancreatic carcinoma cells

A. E. Wright, J. K. Reed, J. Roberts, R. E. Longley, U.S. Pat. Appl. Publ. (USA), US2008033035, 14 pp. [*Chem. Abstr*. **2008**, *148*, 230103]

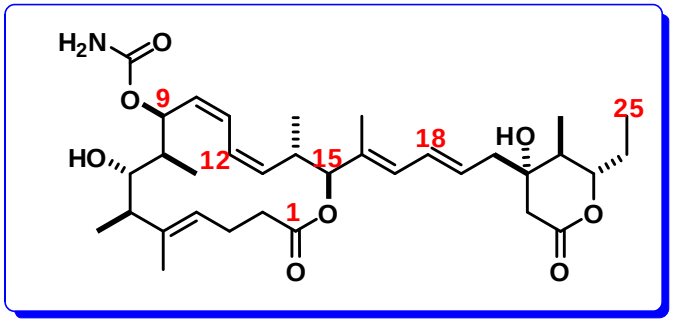
Introduction

Structural features

1. Triply unsaturated 16-membered macrolide contains carbamate group at C9

2. *E*,*E*- dienyl side chain at C15 and a δ- lactone ring at terminal

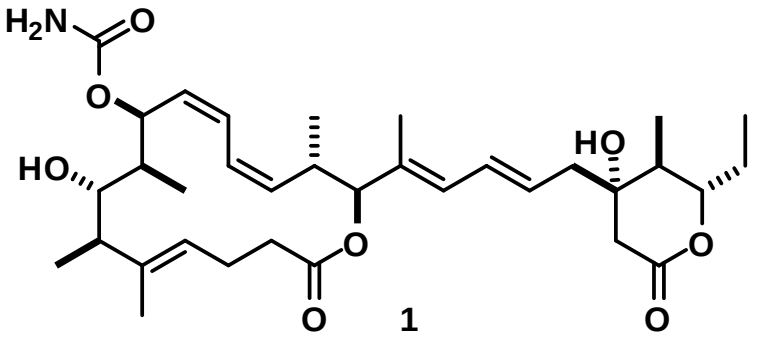
3. Contains 9 stereogenic centers

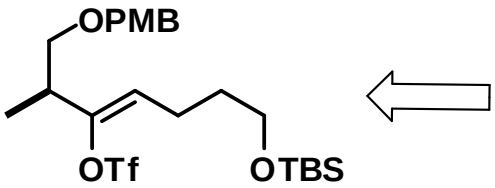


4. Relative configuration was elucidated by suing a combination of

- Homo- and heteronuclear spectroscopic analysis
- Molecular modeling and
- Computational DP4 NMR prediction

Retrosynthetic analysis





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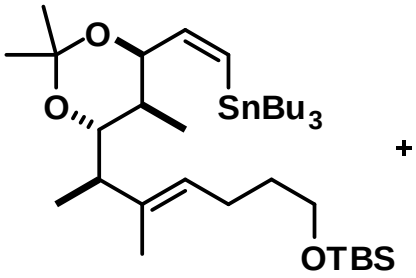
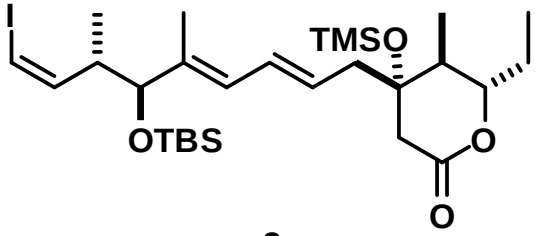


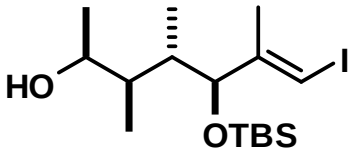
2

+



3

Heck



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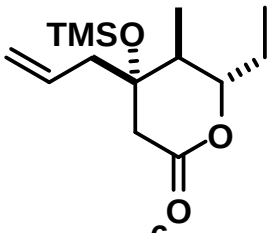
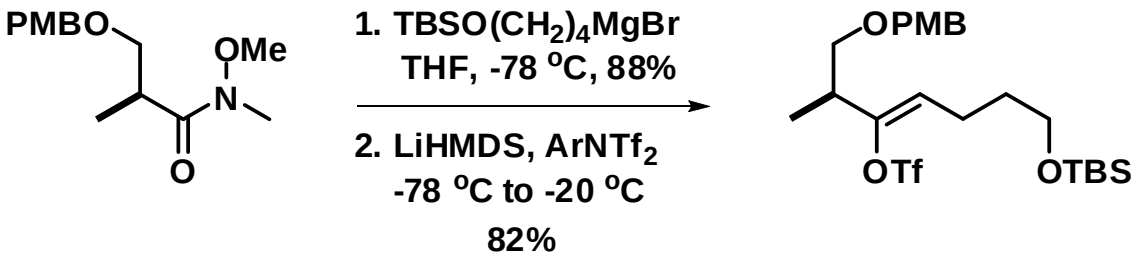
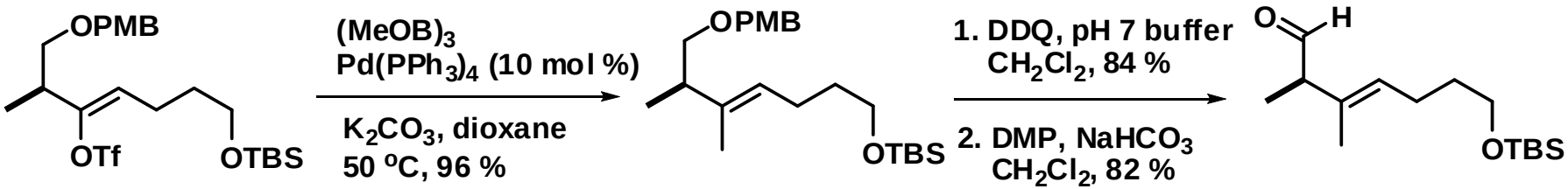
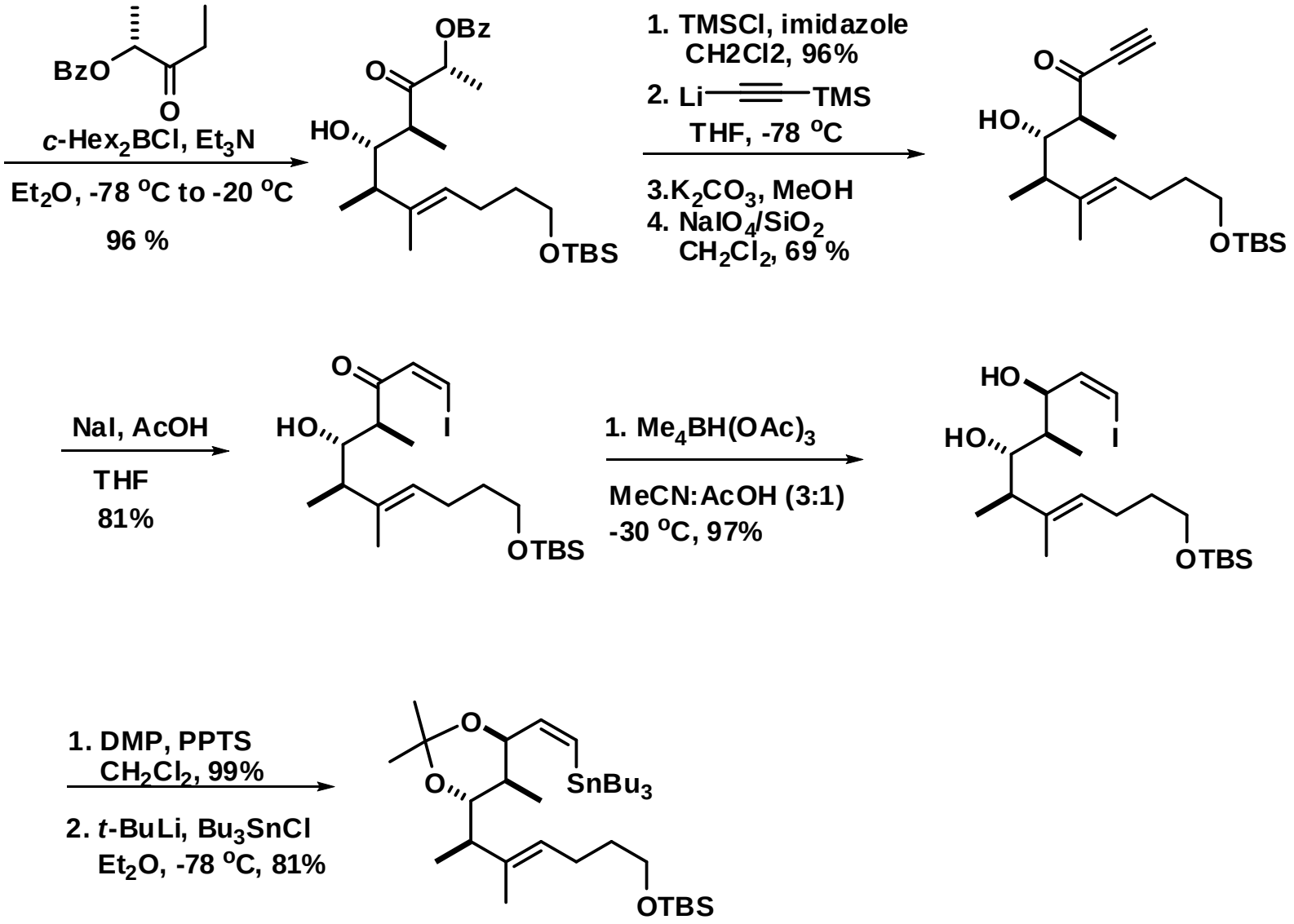


6

Synthesis of fragment 2

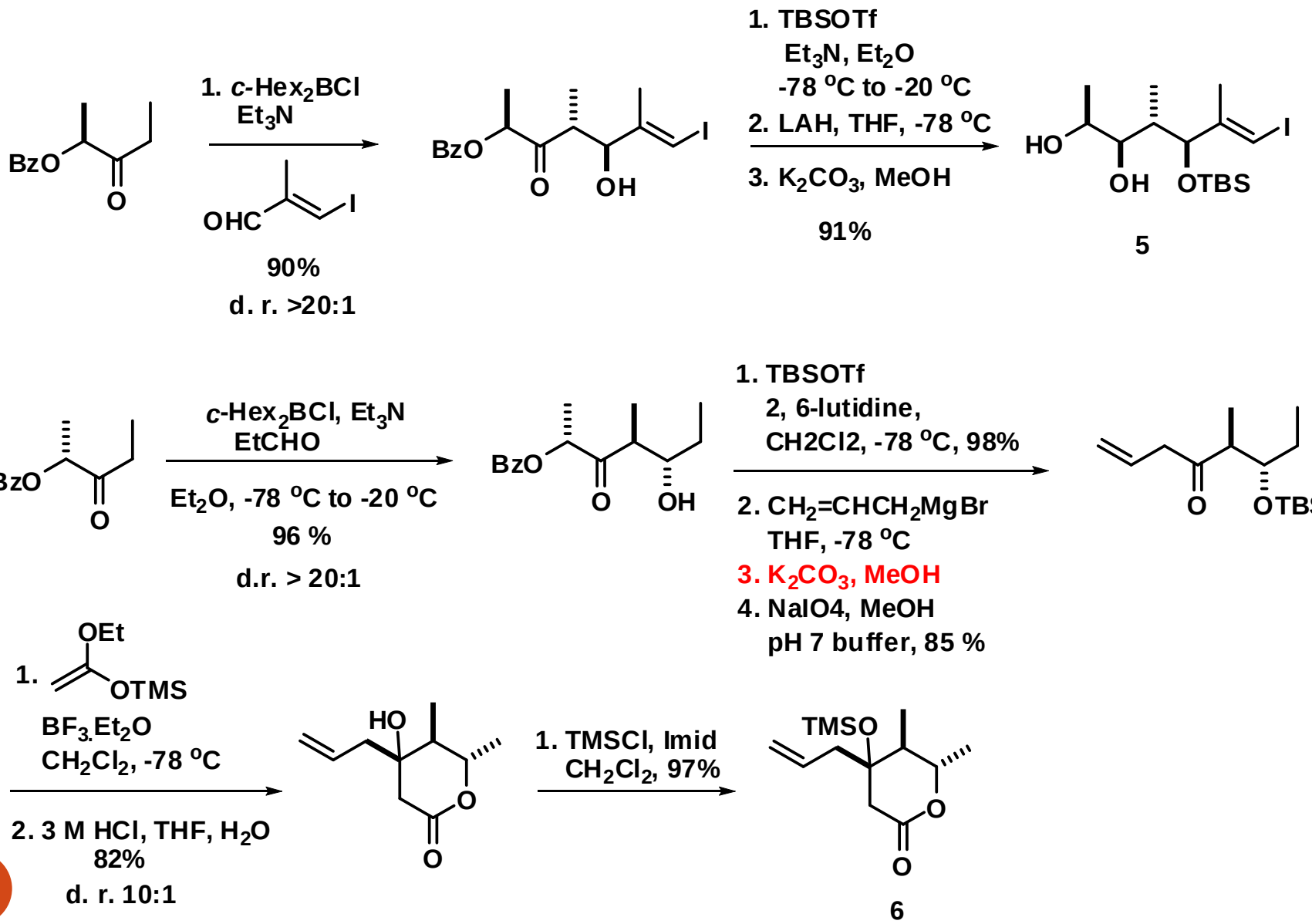


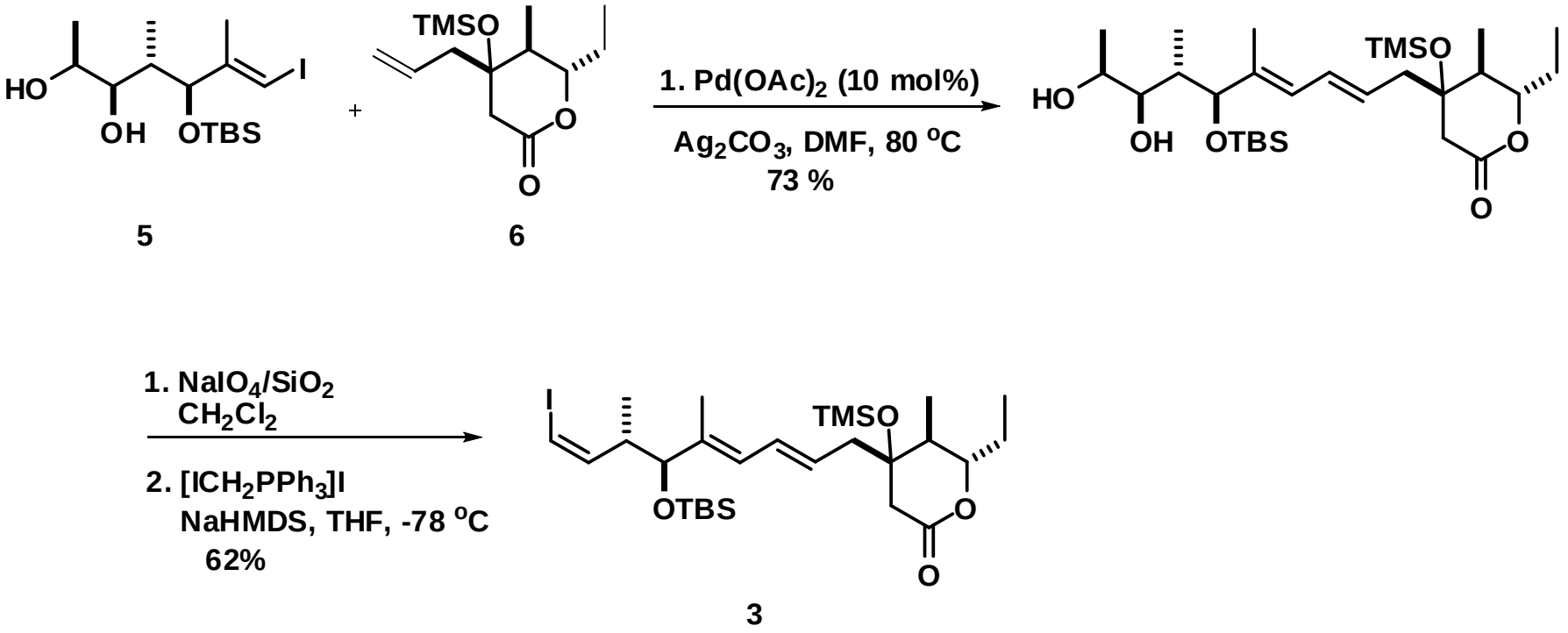



BzO
O
c-Hex2BCl, Et3N
Et2O, -78 °C to -20 °C
96 %
OBz
O
HO
OTBS
1. TMSCl, imidazole
CH2Cl2, 96%
2. Li
TMS
THF, -78 °C
3.K2CO3, MeOH
4. NaIO4/SiO2
CH2Cl2, 69 %
O
HO
OTBS
NaI, AcOH
THF
81%
O
HO
I
OTBS
1. Me4BH(OAc)3
MeCN:AcOH (3:1)
-30 °C, 97%
HO
HO
I
OTBS
1. DMP, PPTS
CH2Cl2, 99%
2. t-BuLi, Bu3SnCl
Et2O, -78 °C, 81%
O
O
SnBu3
OTBS

2

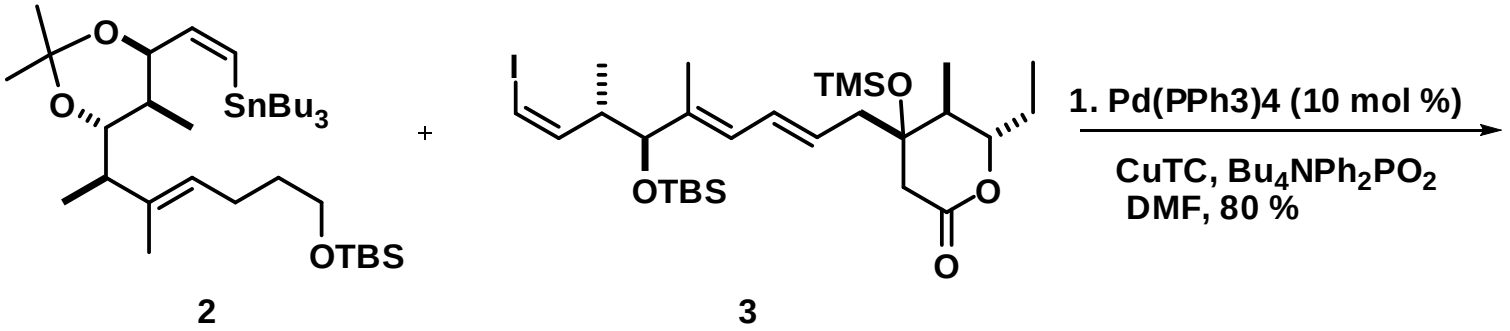
Synthesis of fragment 3

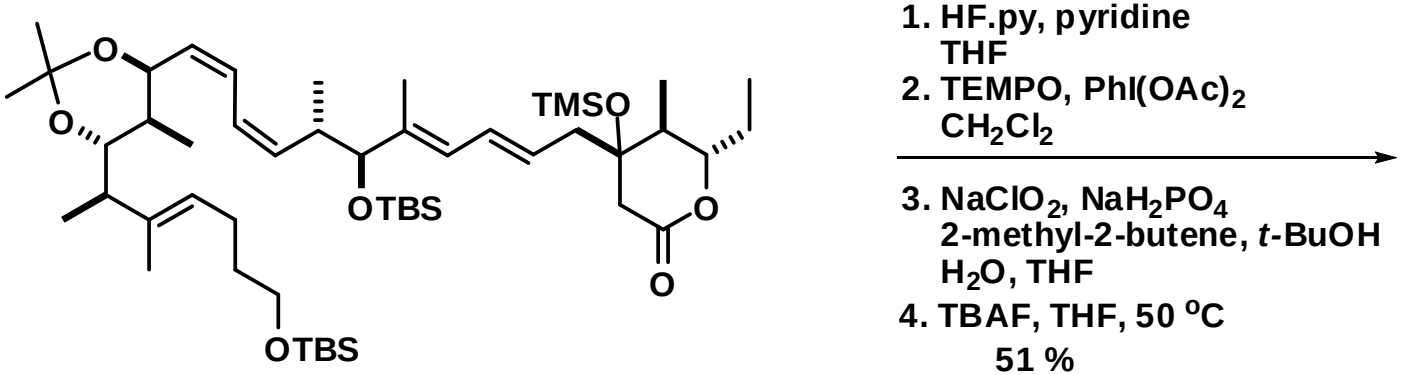


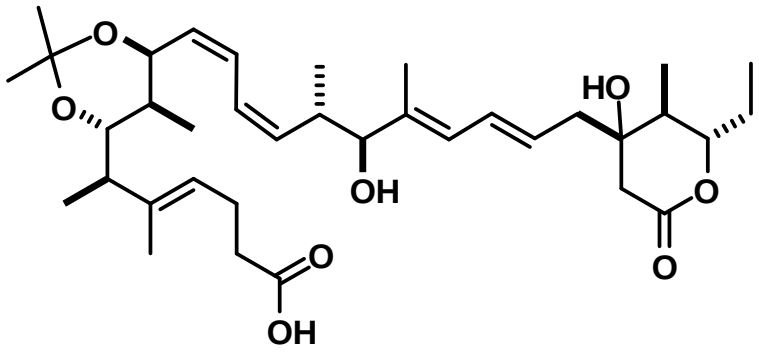

HO
OH
OTBS
I
TMSO
O
O
1. Pd(OAc)2 (10 mol%)
Ag2CO3, DMF, 80 °C
73 %
HO
OH
OTBS
TMSO
O
O
1. NaIO4/SiO2
CH2Cl2
2. [ICH2PPh3]I
NaHMDS, THF, -78 °C
62%
I
OTBS
TMSO
O
O

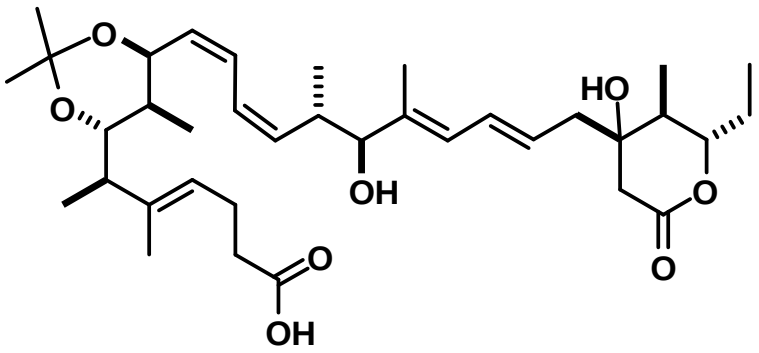
5 6 3

Completion of synthesis



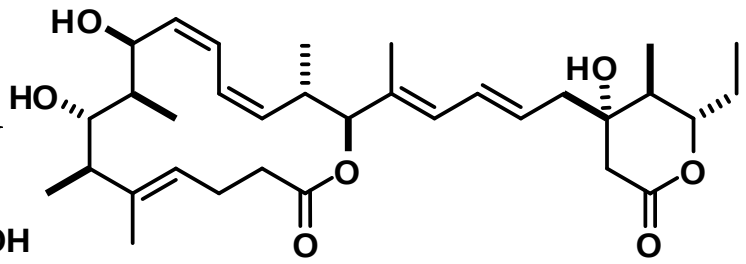






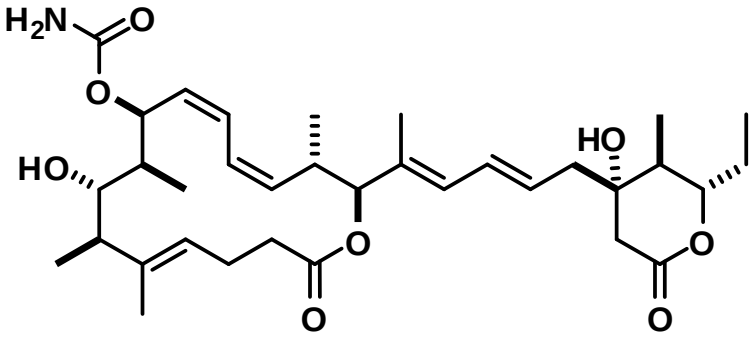
1. TCBC, Et_3N

THF, DMAP, PhMe
80 %
2. Dowex resin, MeOH



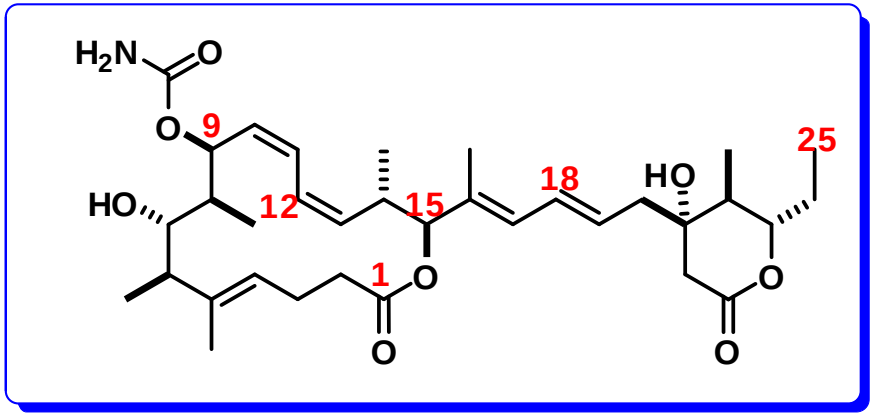
TMS-imidazole
PPTS

CCl_3CONCO
PPTS, Al_2O_3
53%



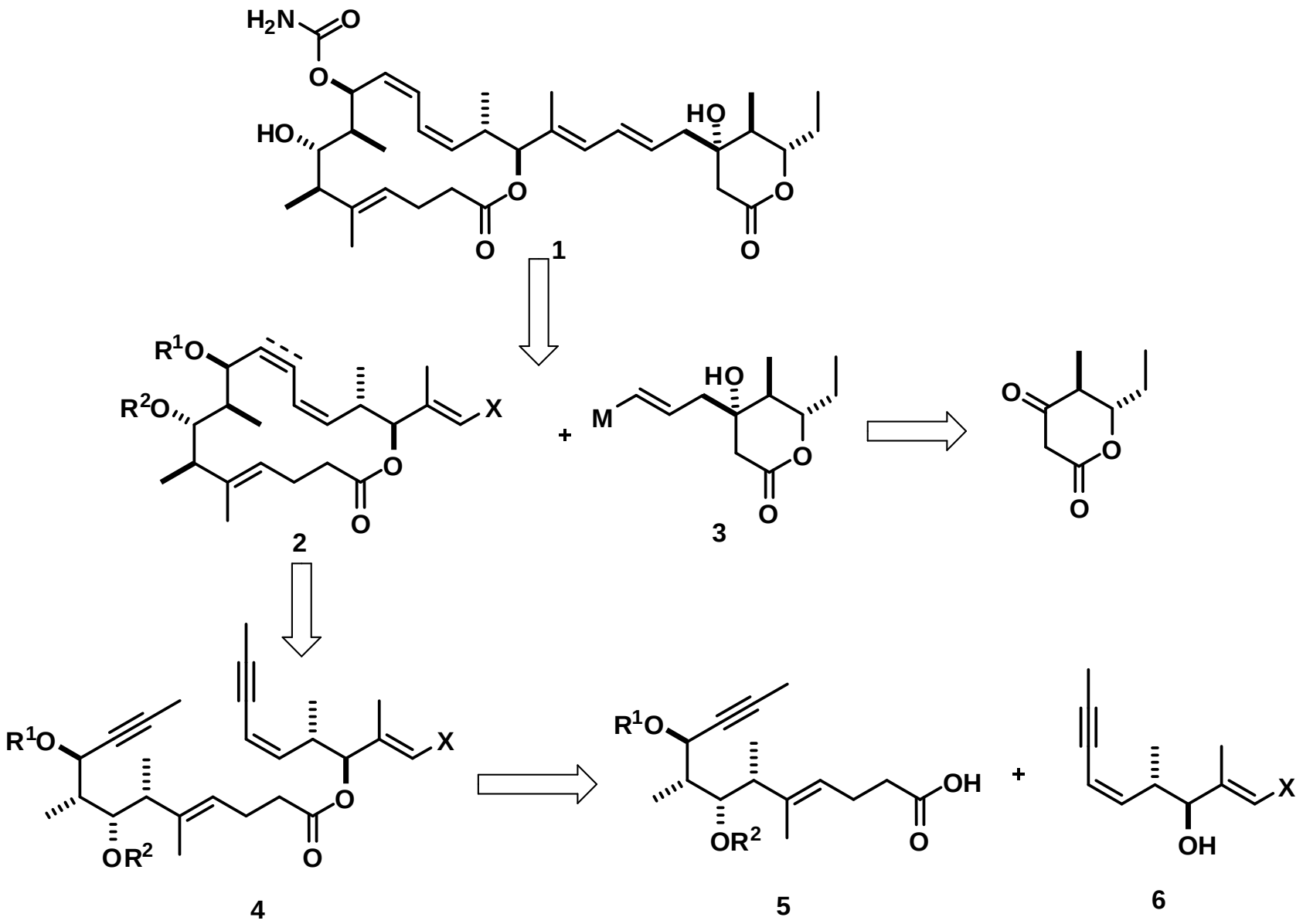
Leiodermatolide

Divergent Total Synthesis of the Antimitotic Agent Leiodermatolide

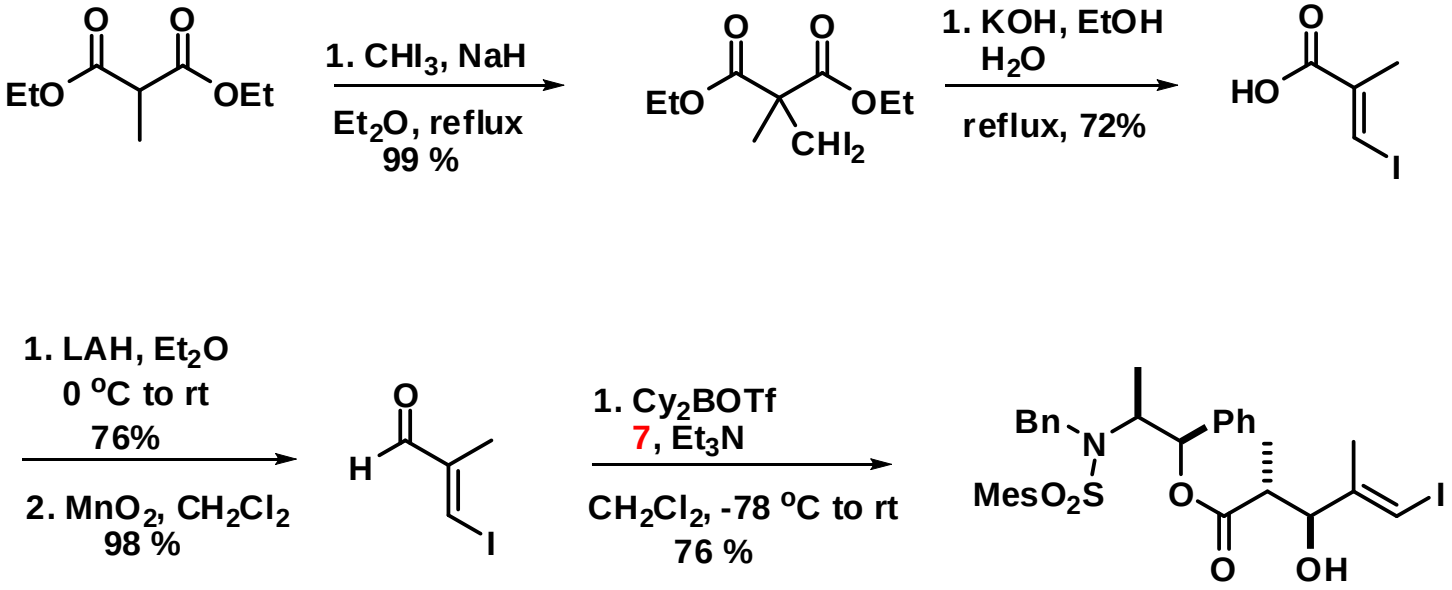


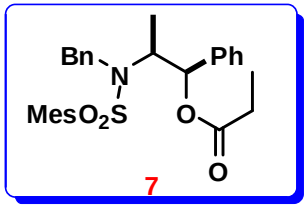
A. Furstner et al., *Angew. Chem. Int. Ed.* **2012**, *51*, 12041

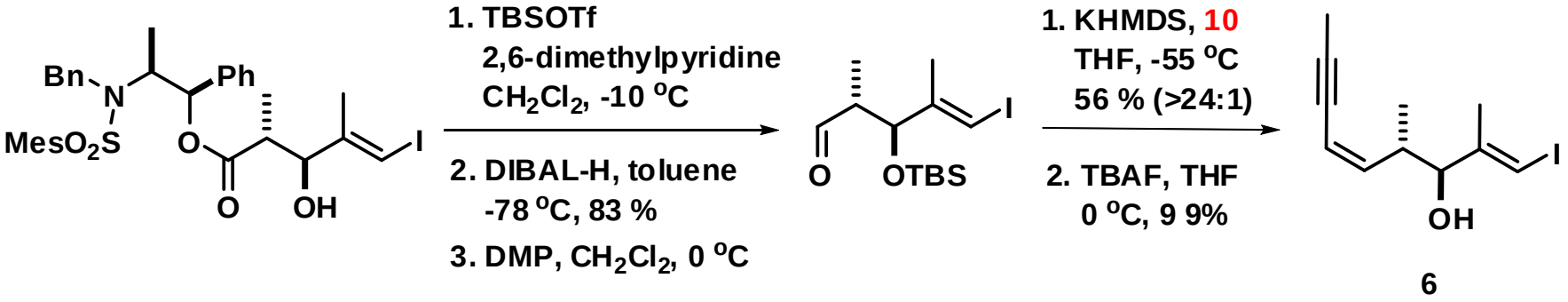
Retrosynthetic analysis

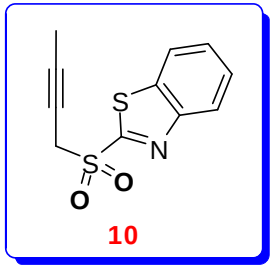


Synthesis of fragment 6

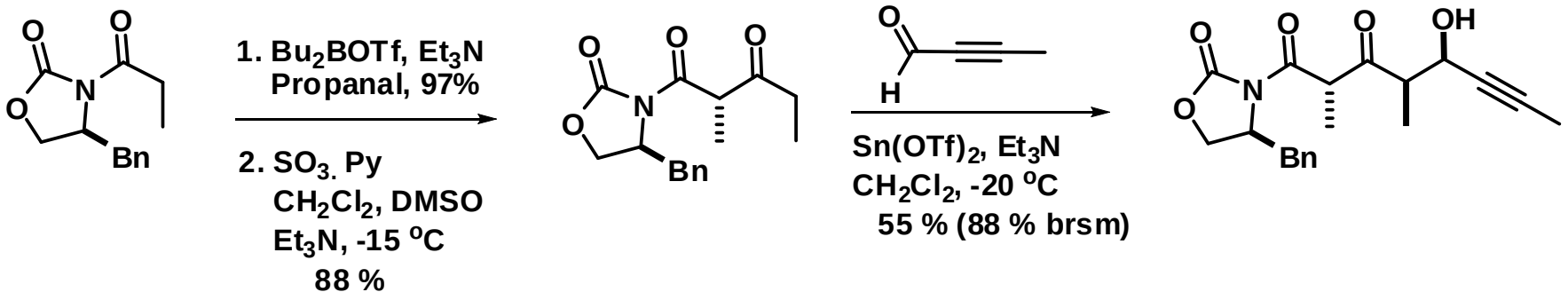


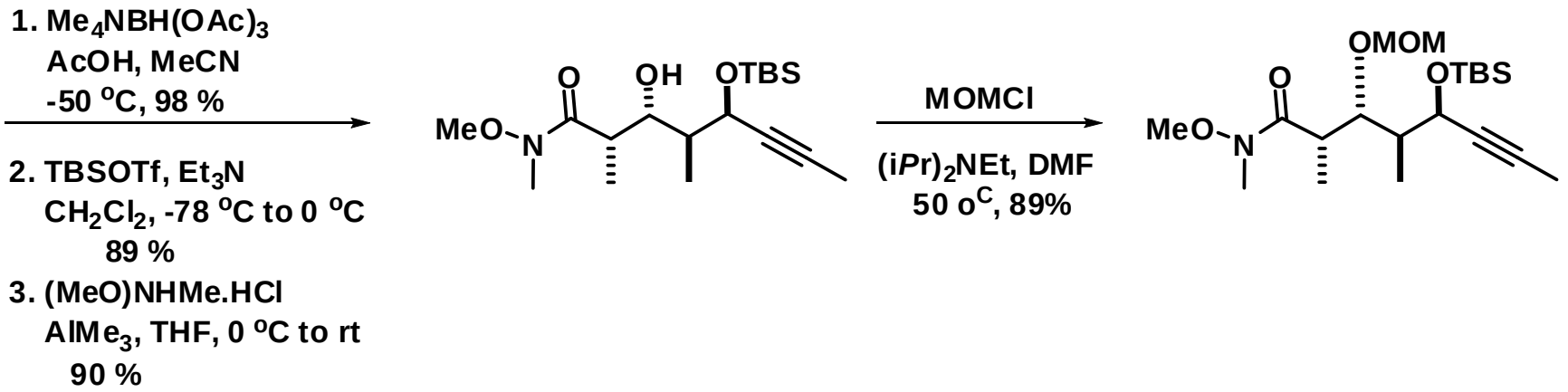


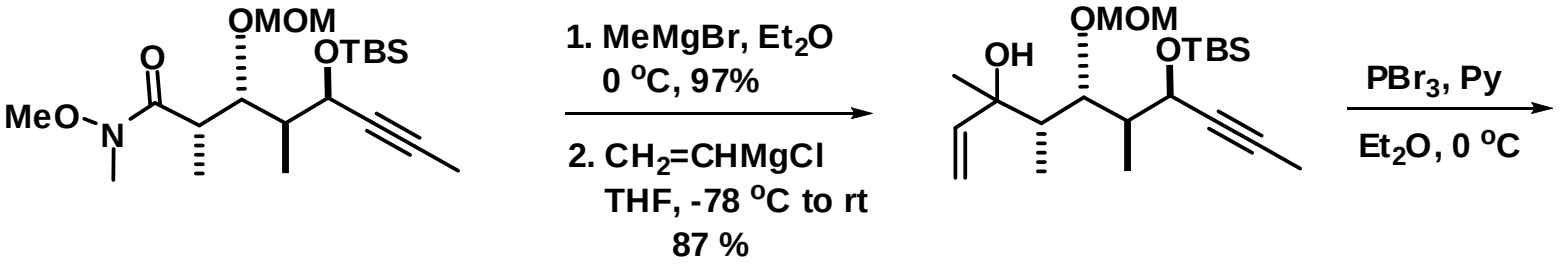

Bn
N
Ph
MesO2S
O
O
OH
I
1. TBSOTf
2,6-dimethylpyridine
CH2Cl2, -10 °C
2. DIBAL-H, toluene
-78 °C, 83 %
3. DMP, CH2Cl2, 0 °C
O
OTBS
I
1. KHMDS, 10
THF, -55 °C
56 % (>24:1)
2. TBAF, THF
0 °C, 9 9%
OH
I
6


S
N
S
O
O
10

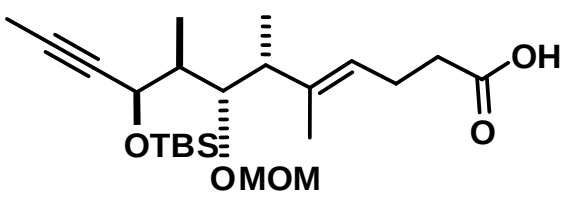
Synthesis of fragment 5






OMOM
OTBS
O
MeO
N
1. MeMgBr, Et2O
0 °C, 97%
2. CH2=CHMgCl
THF, -78 °C to rt
87 %
OMOM
OH
OTBS
PBr3, Py
Et2O, 0 °C
OMOM
OTBS
Br
1. EtOAc, LDA, CuI
THF, -110 °C to -30 °C
63 % over two steps
2. Me3SiOK, Et2O
quant.
OMOM
OTBS
O
HO
5

Synthesis of 2



6

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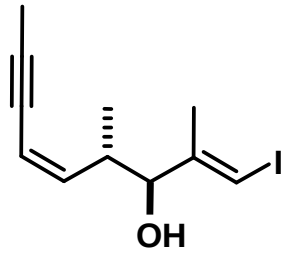
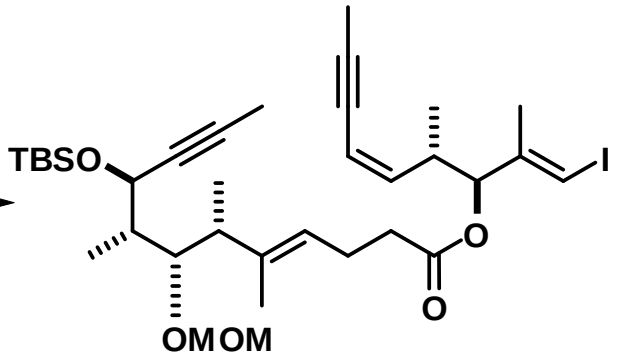


5

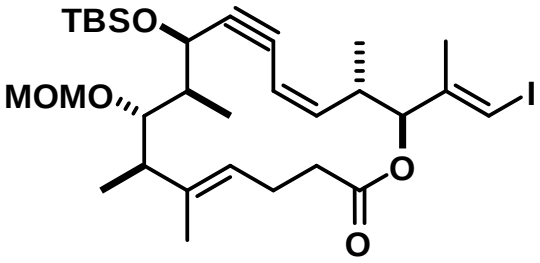
EDCI.HCl
DMAP

CH_2Cl_2, 0 °C
89%

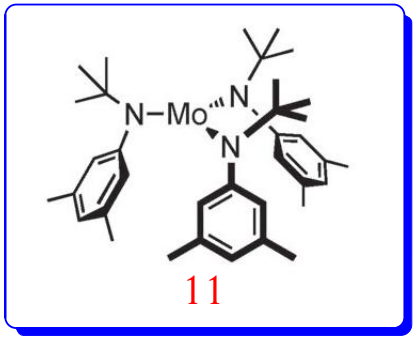


11 (40 mol%)

CH_2Cl_2, toluene
100 °C, 72%

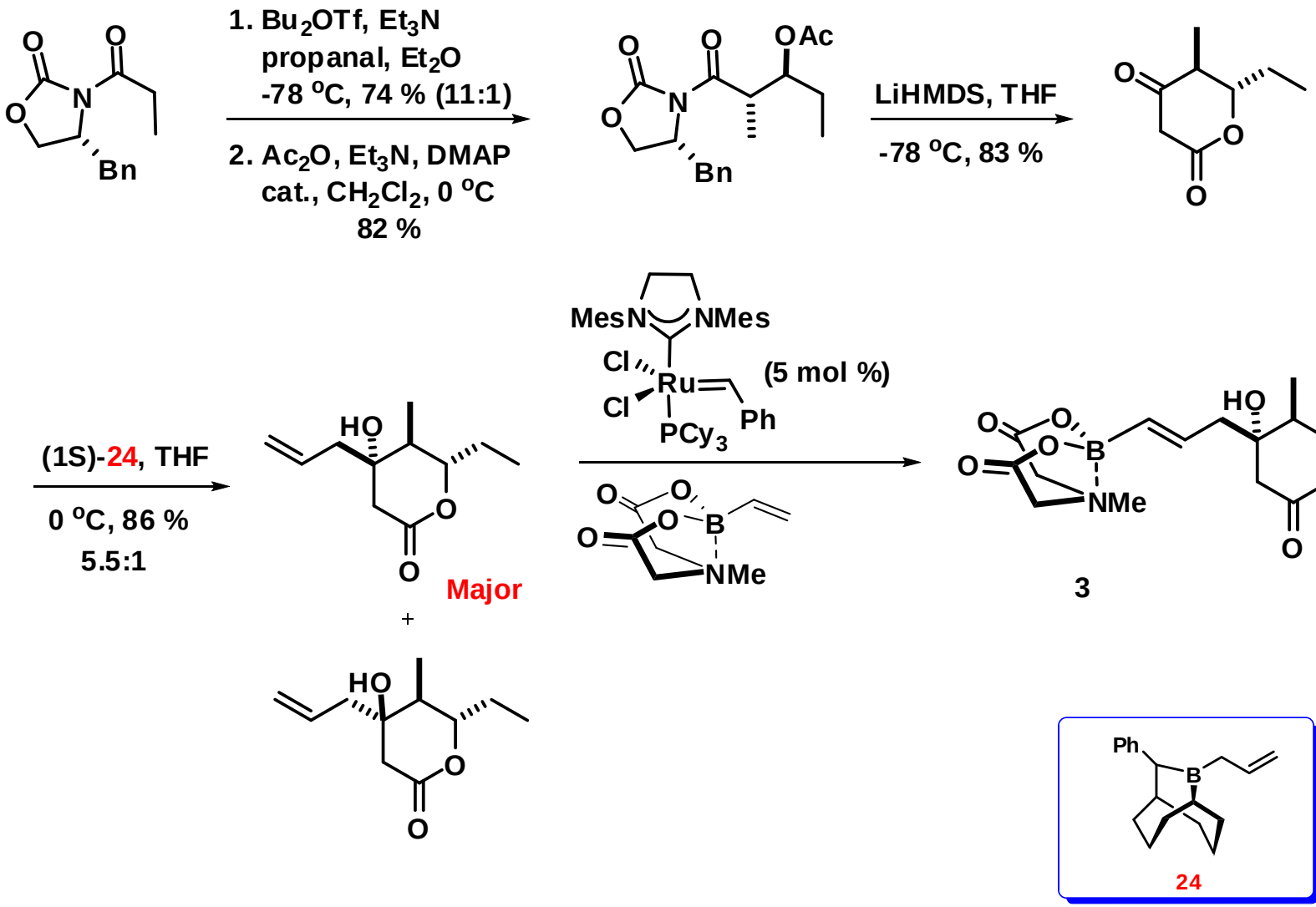


2

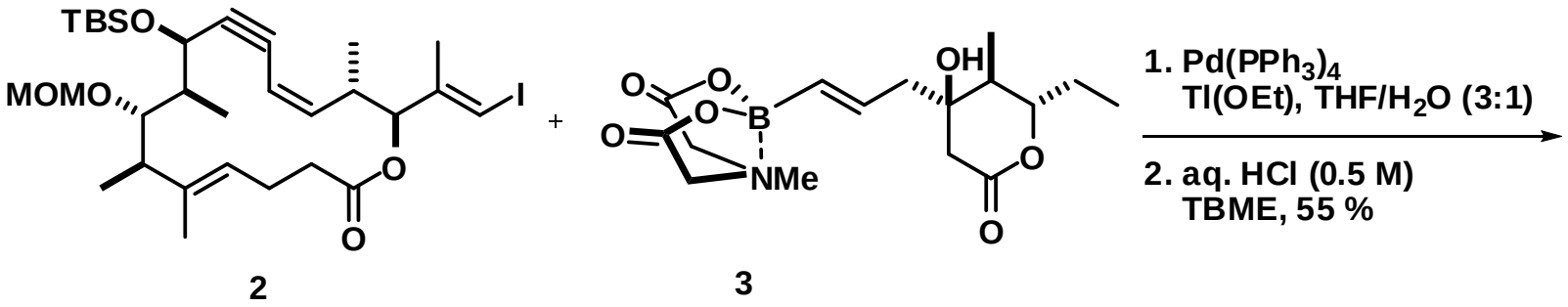


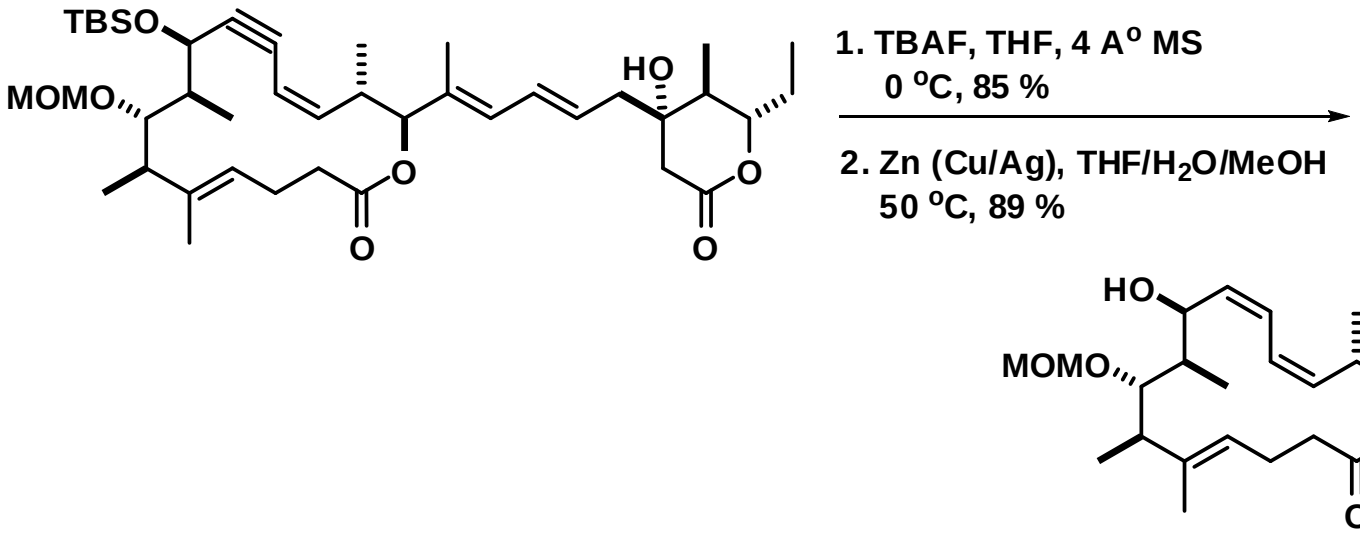
11

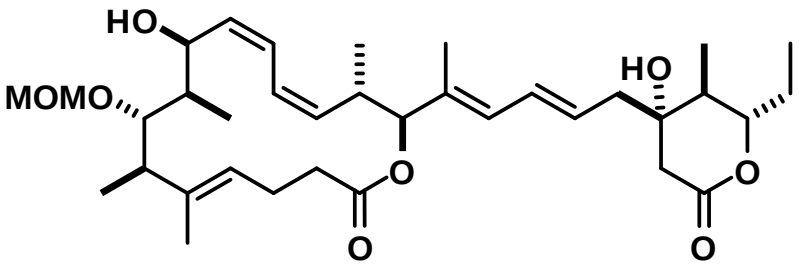
Synthesis of 3

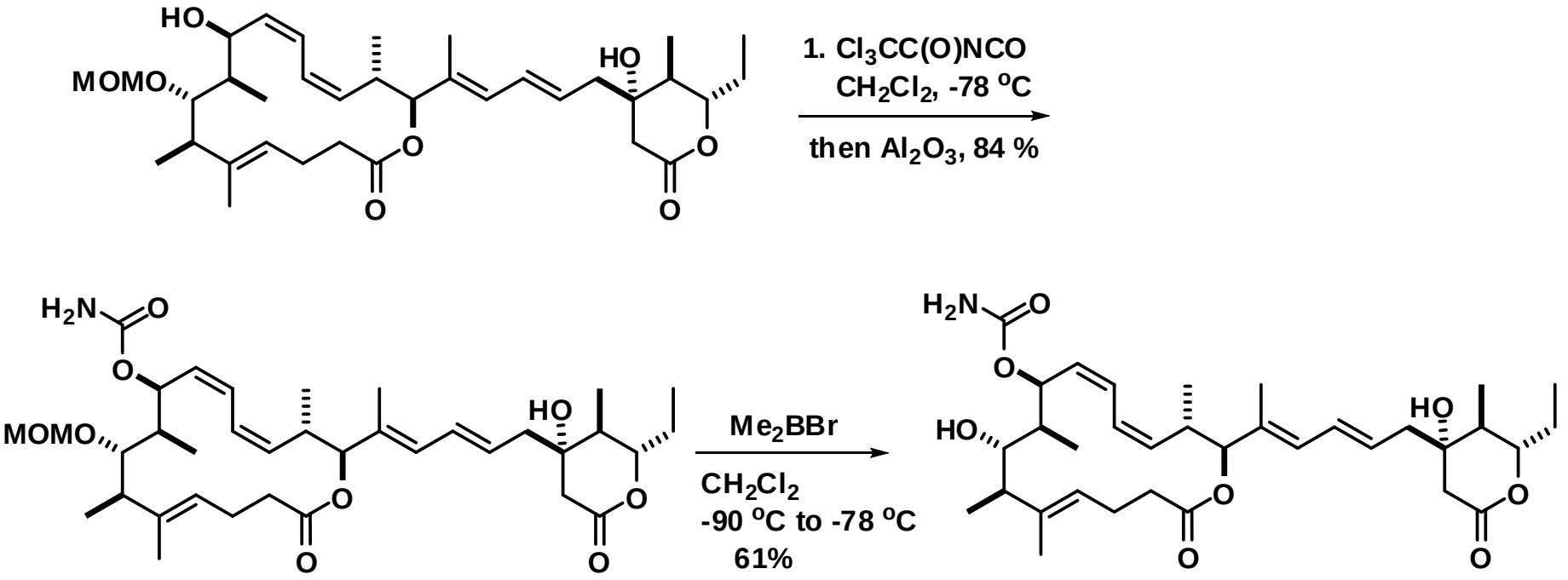


End game of the synthesis









1

Leiodermatolide

Conclusion

Paterson's approach (convergent synthesis)

Total no. of steps = 23, overall yield 3.2%

Key steps: stereo controlled aldol reactions and palladium-catalyzed coupling s

Frustner's approach (highly convergent synthesis)

Total no. of steps = 19, overall yield ….

Key steps: RCAM/semi reduction, Julia olefination, Brown's asymmetric allylation

Thank you
For your attention