Total Synthesis of (-)-Sarain A

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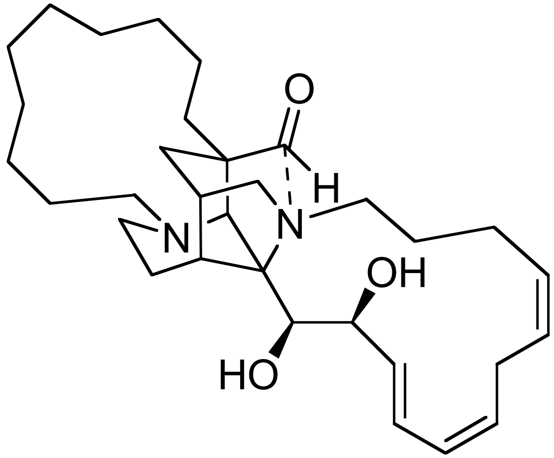
J. AM. CHEM. SOC. 2007, 129, 11987-12002

Erikah Englund
Current Lit
Synthetic Approaches
10/27/07

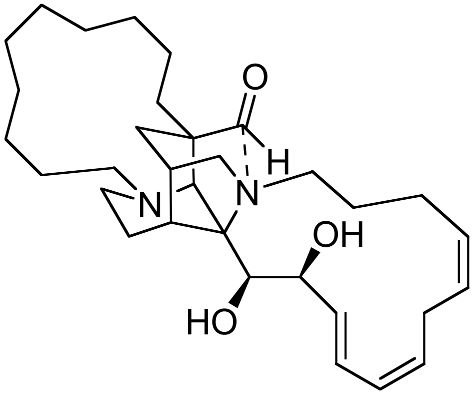


Outline

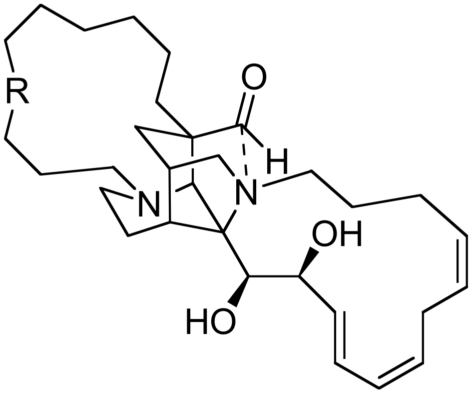
- Isolation
- Biosynthesis
- Syntheses from other groups
- Current route
- Overall picture
- Conclusions

Isolation

- In 1986, Cimino isolated Sarains A-C at the Bay of Naples from the marine sponge *Reniera sarai.* (Tetrahedron, **1989**, *45*, 3863)



Sarain A



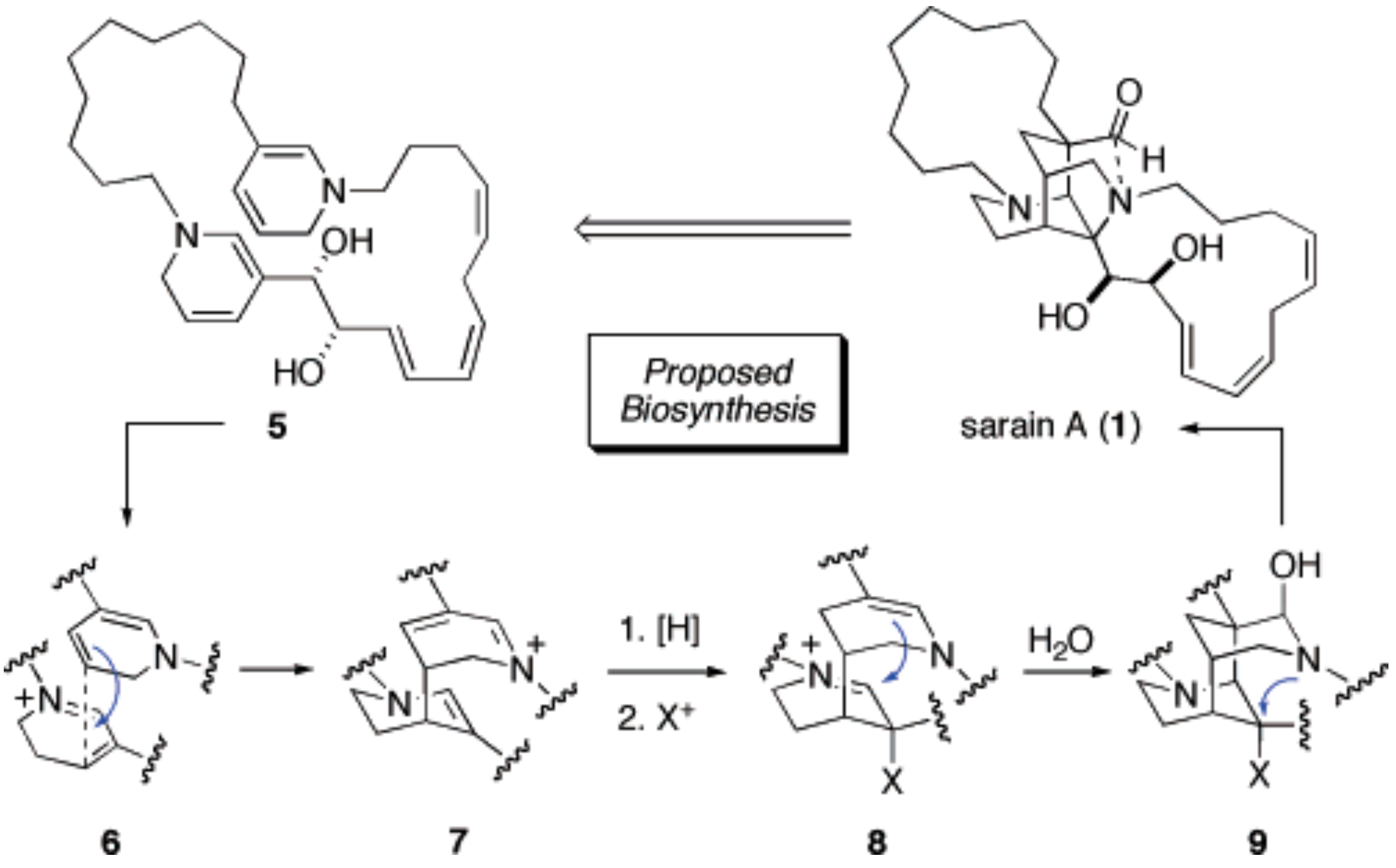
Sarain B, R = -(*Z*)-$CH_2CH{=}CH$-
Sarain C, R = -(*Z*)-$CH{=}CHCH_2$

- Products were characterized through MS, NMR, IR and 2D NMR: COSY, HETCOR, long range HETCOR. Structure was confirmed through X-ray of diacetate crystal (J. Nat. Prod. **1990**, *53*, 1519)

- Absolute conformation determined through Mosher ester analysis (Tetrahedron, **1996**, *52*, 8341)

- Sarains A-C display modest antibacterial, insecticidal and antitumor activities (Comp.Biochem.Physiol. B, **1992**, *103B*, 293)

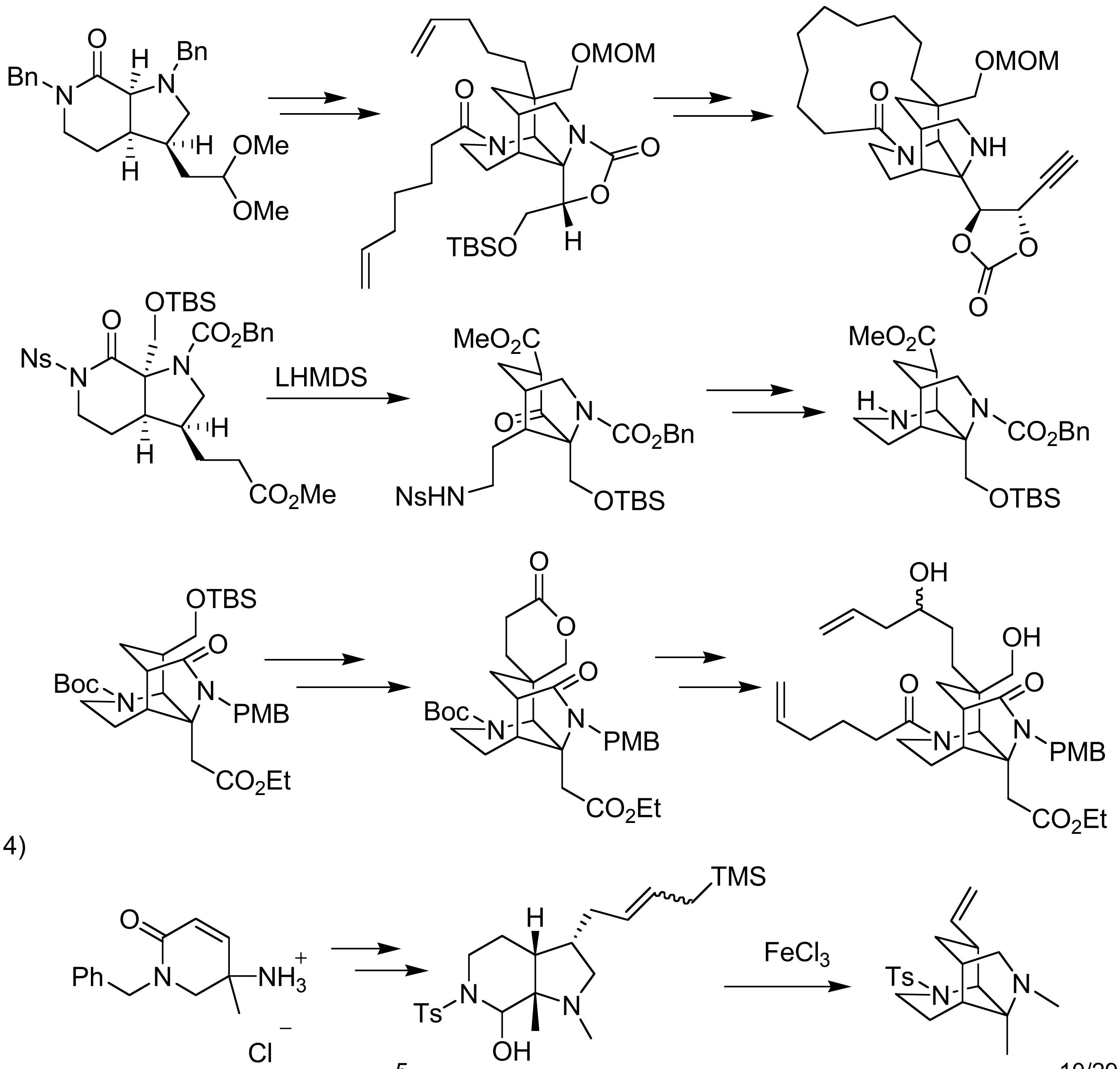
Proposed Biosynthesis



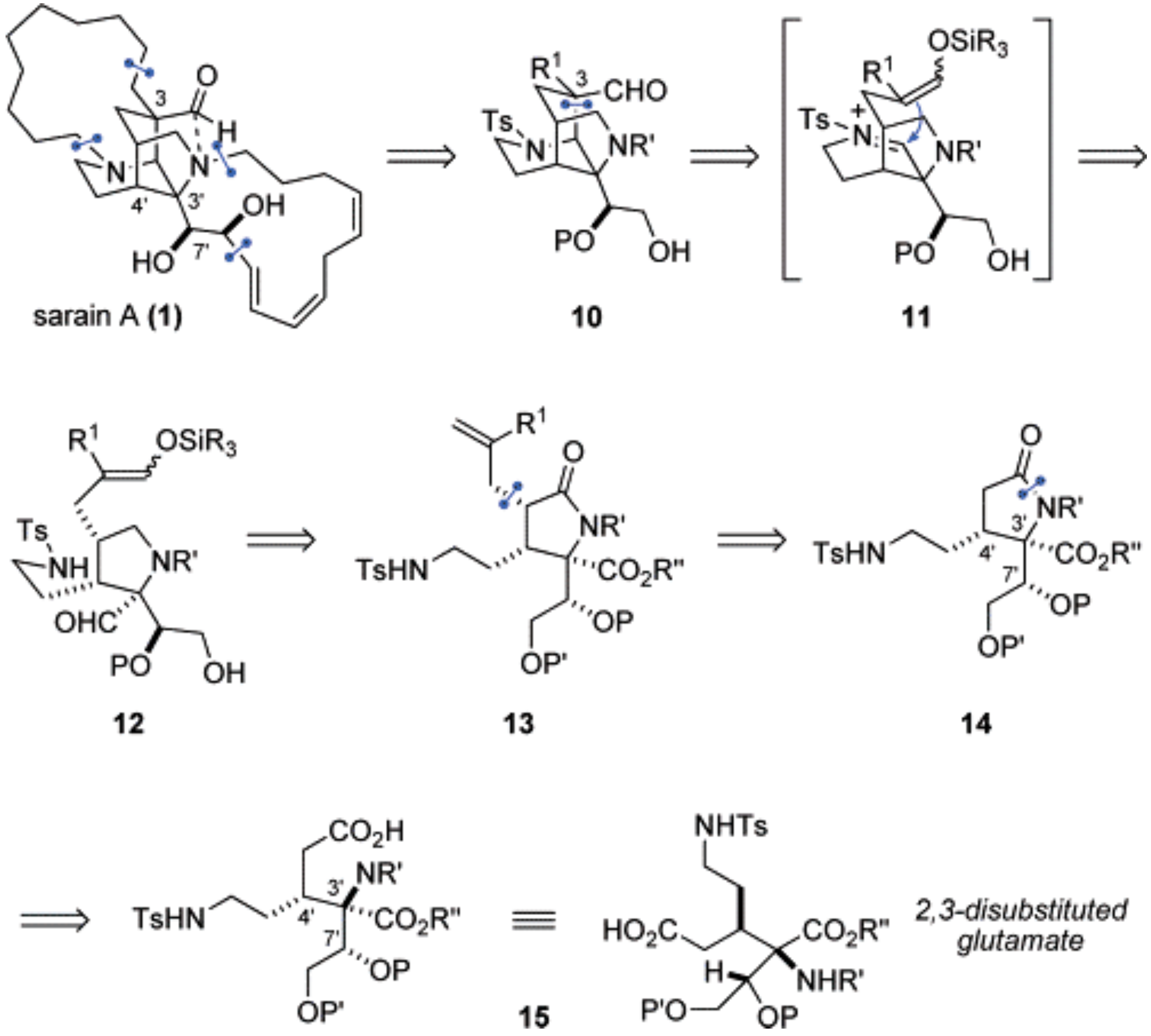
Tet. Lett. **1995**, *36*, 707

Previous Synthetic Efforts

- **Weinreb**
  (J.O.C. **2006**, *71*, 2078)
- **Heathcock**
  (J.O.C. 1998, 63, 9616)
- **Cha**
  (J.O.C. 2003, 68, 2205)
- **Marazano**
  (Eur.J.O.C. 2006, 4106-4114)



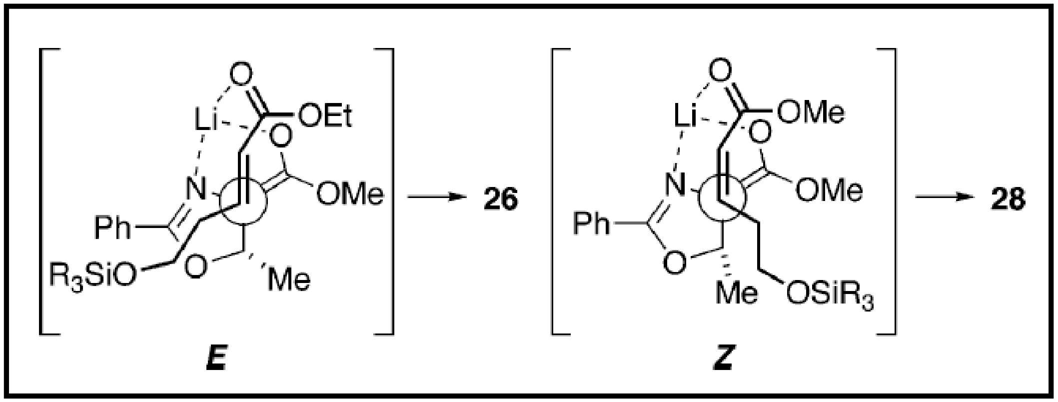
Initial Retrosynthesis

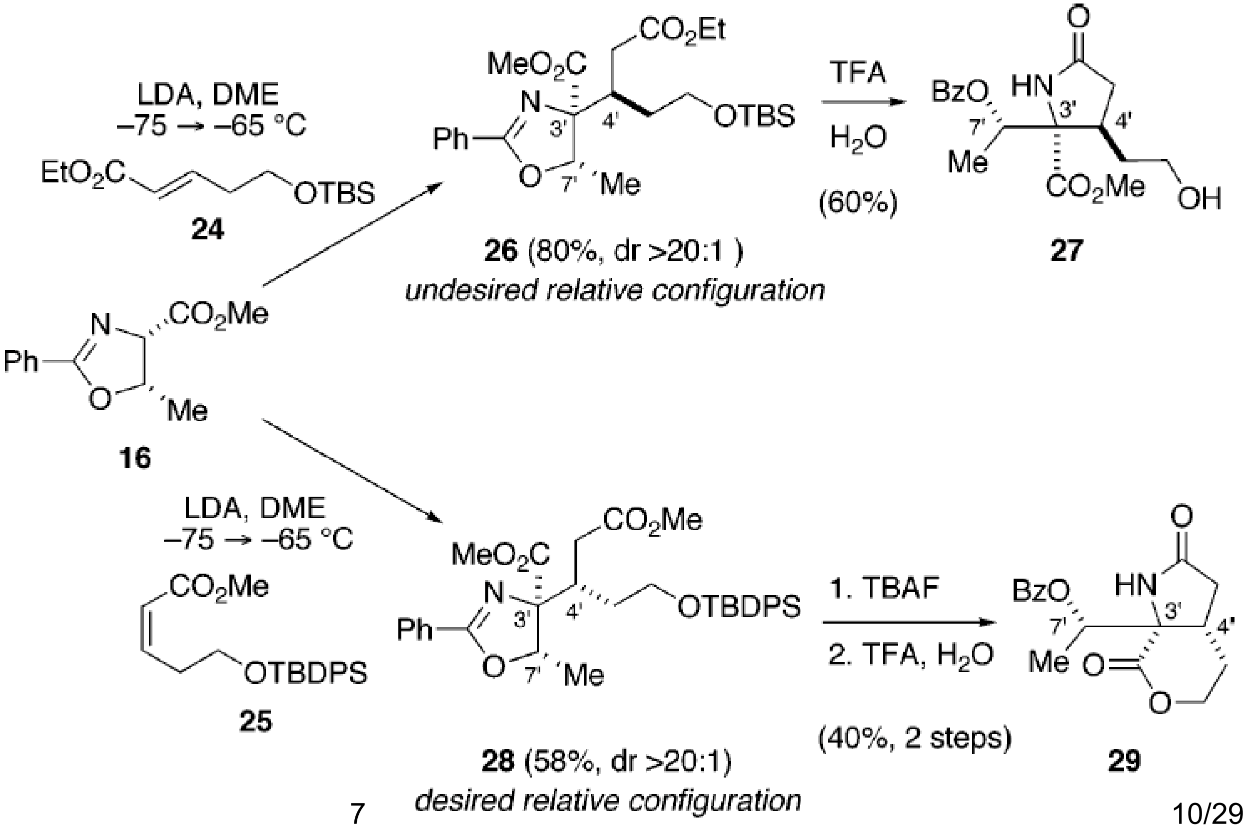


Overman Communication: Angew.Chem.Int.Ed **2006**, *45*, 2912

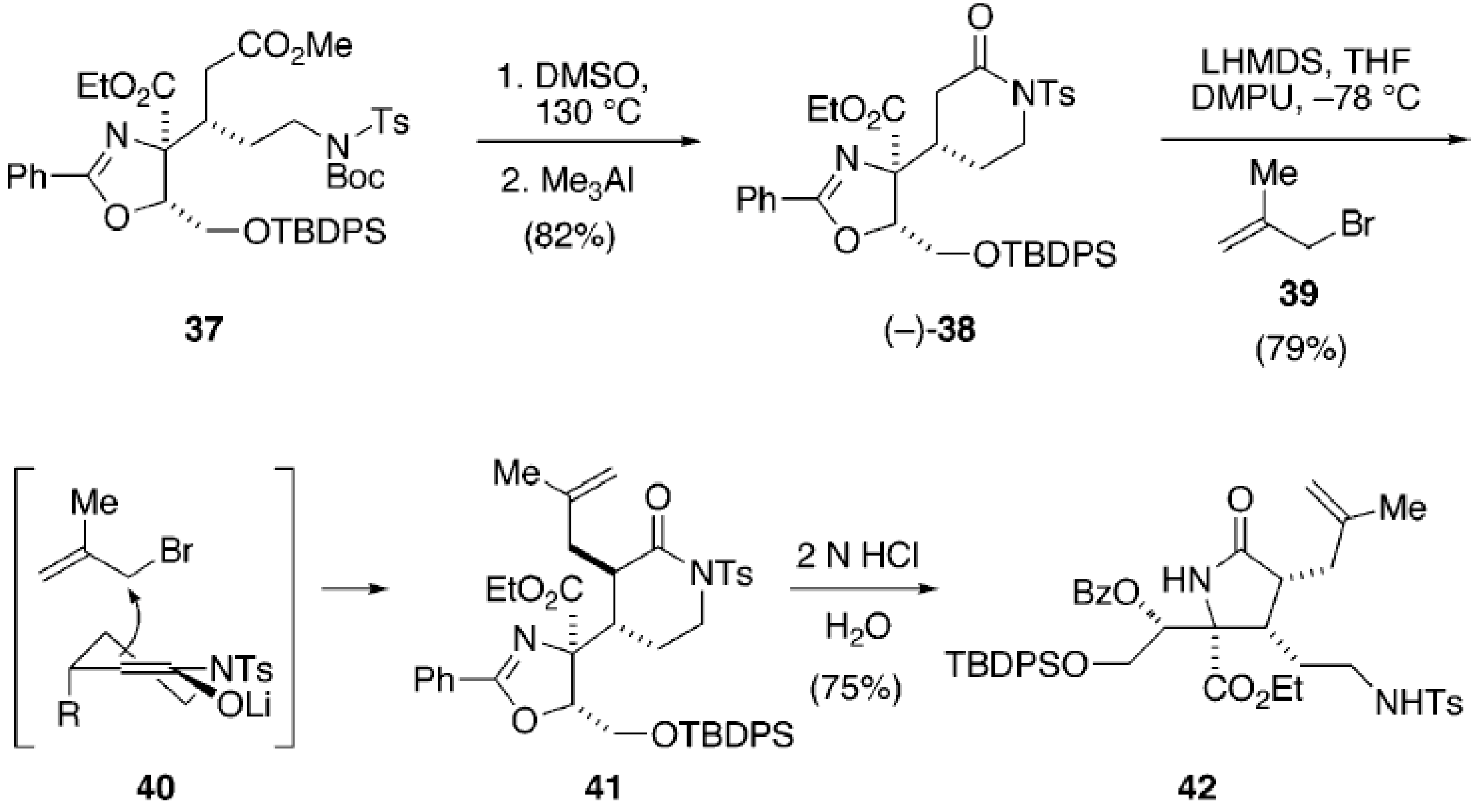
First Models

- Seebach chemistry
  - Tet. Lett **1983**, *24*, 3311
- Benefit: Both enantiomers are accessible
- Early work done with unnatural enantiomer
- Model System: Z-enone needed
- 71% 20:1 dr
- Stereochem confirmed via derivatization



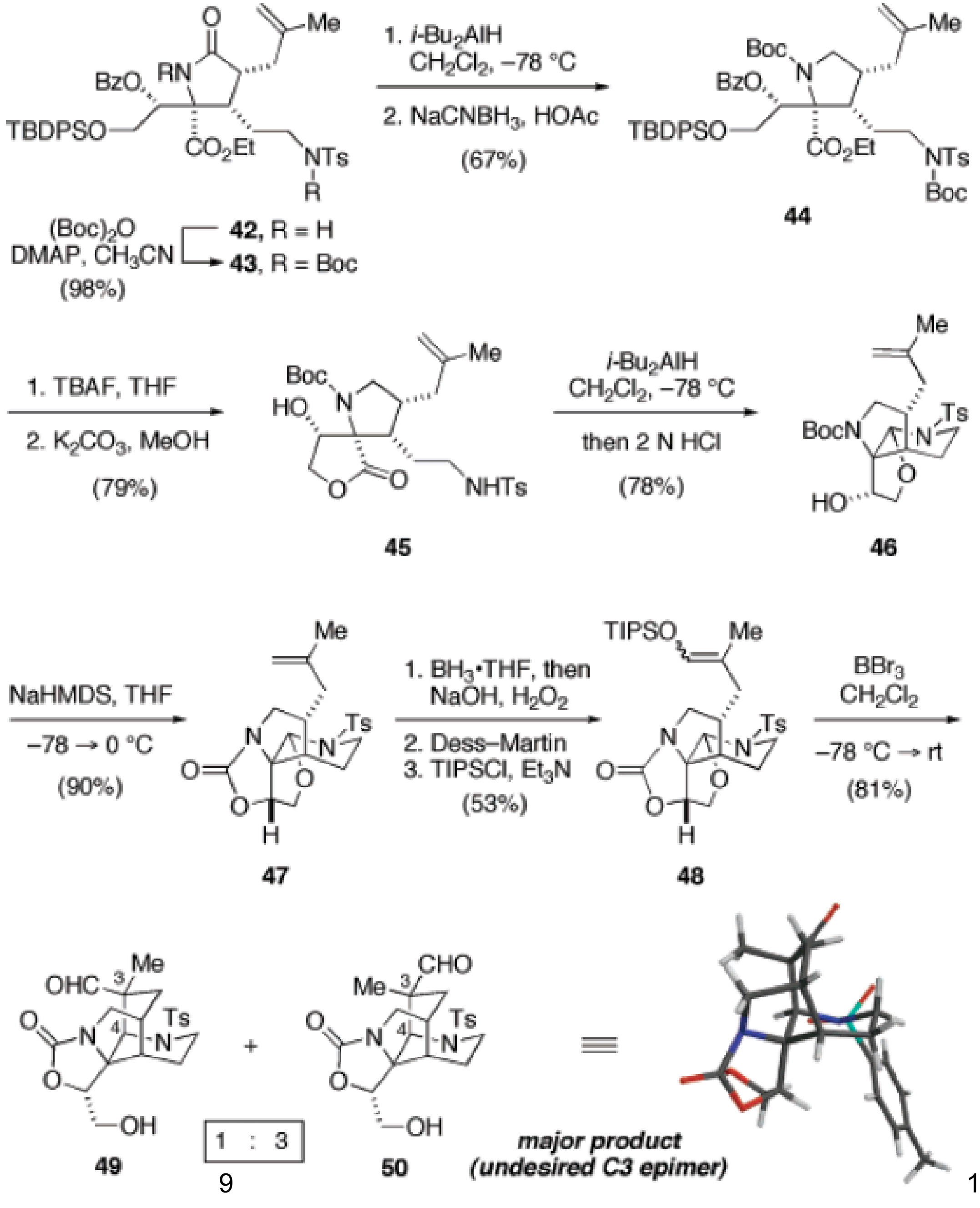


Model

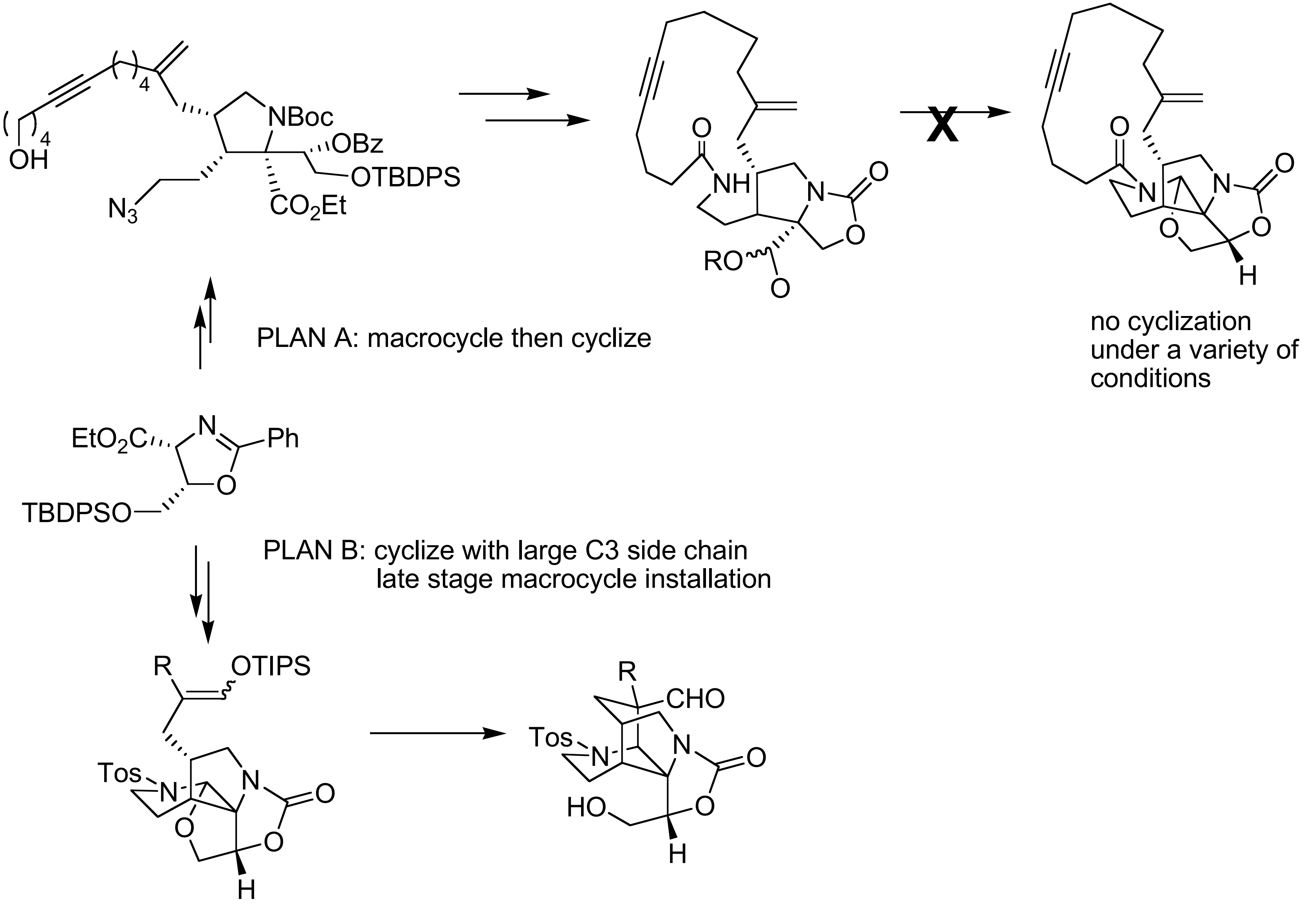

CO2Me
EtO2C
N
Ts
Boc
Ph
O
OTBDPS
37
1. DMSO, 130 °C
2. Me3Al
(82%)
O
NTs
(–)-38
LHMDS, THF
DMPU, –78 °C
Me
Br
39
(79%)
NTs
OLi
R
40
Me
41
2 N HCl
H2O
(75%)
BzO
HN
TBDPSO
CO2Et
NHTs
42

Model Findings

- Many Lewis Acids screened for cyclization to **49**
  - $SnCl_4$, $BF_3.OEt_2$, Me_3Al
- Further exploration deemed necessary on real system
- 2 Plans
  - Plan A
    - Form macrocycle before cyclization
  - Plan B
    - Have larger C3 group on prior to cyclization



Plan A or Plan B



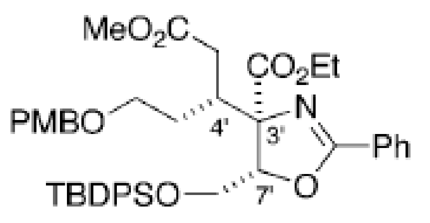
PLAN A: macrocycle then cyclize

no cyclization
under a variety of
conditions

PLAN B: cyclize with large C3 side chain
late stage macrocycle installation

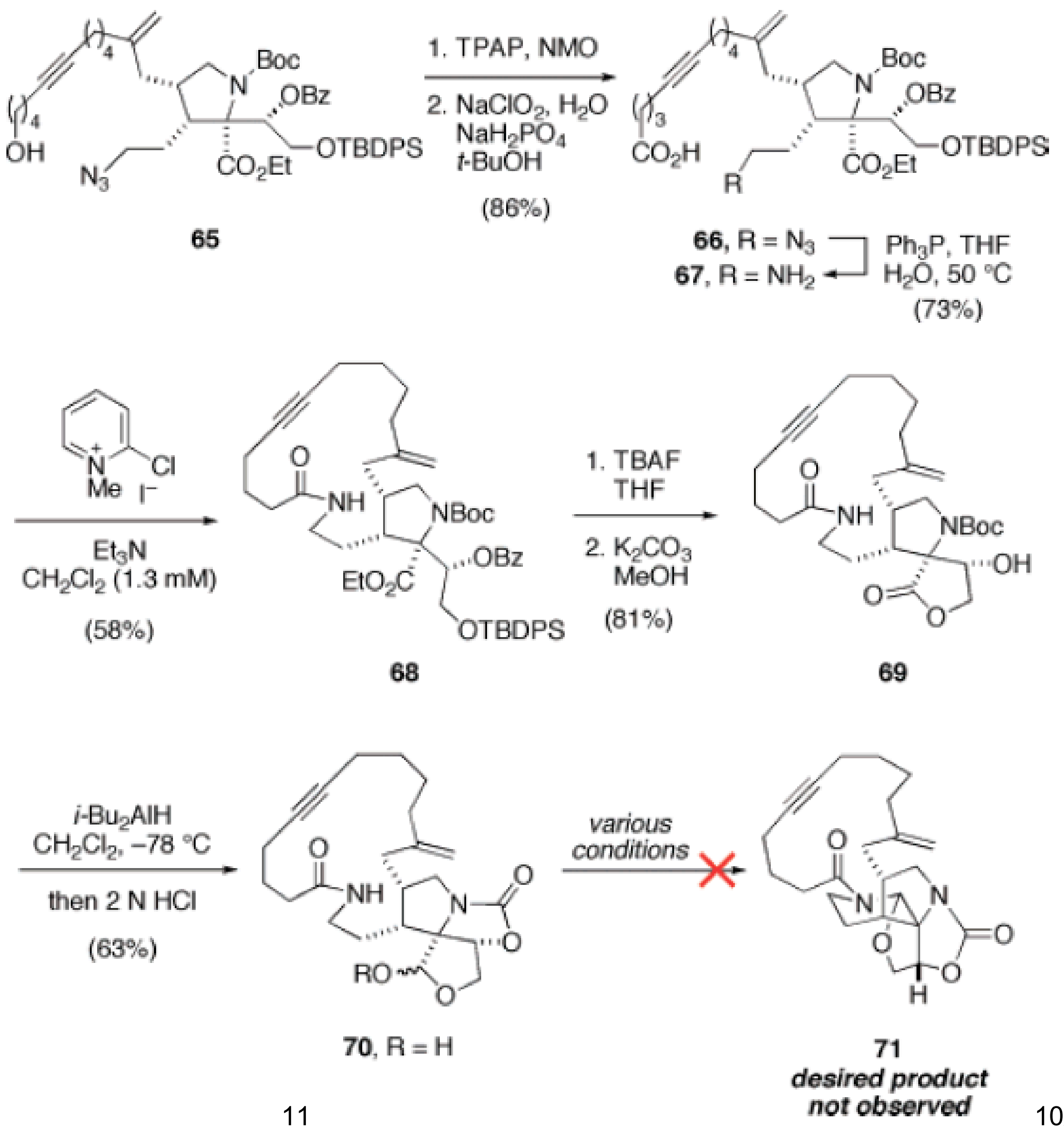
Plan A & Problems

- Macrocycle formed prior to cyclization
- The synthesis commenced with:

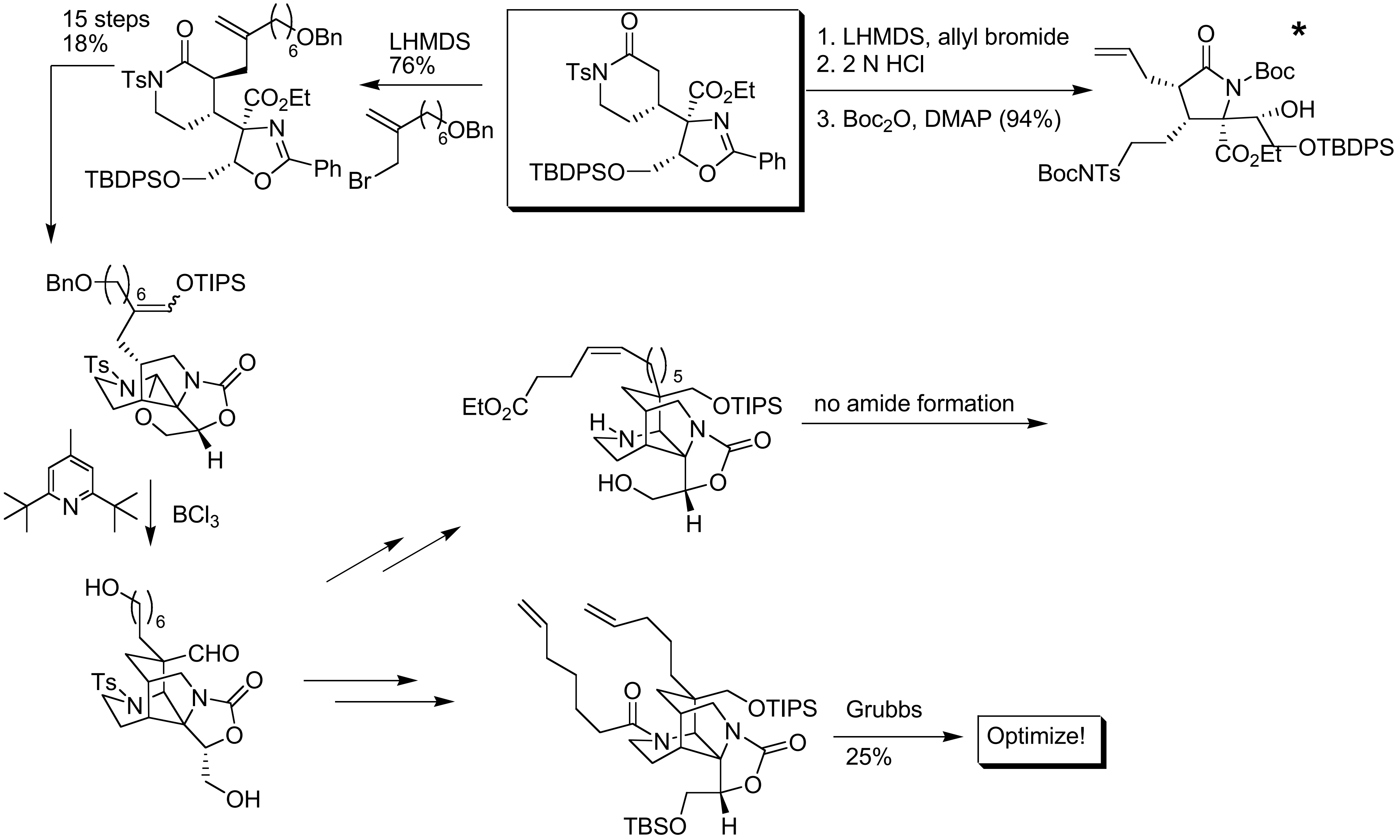


58

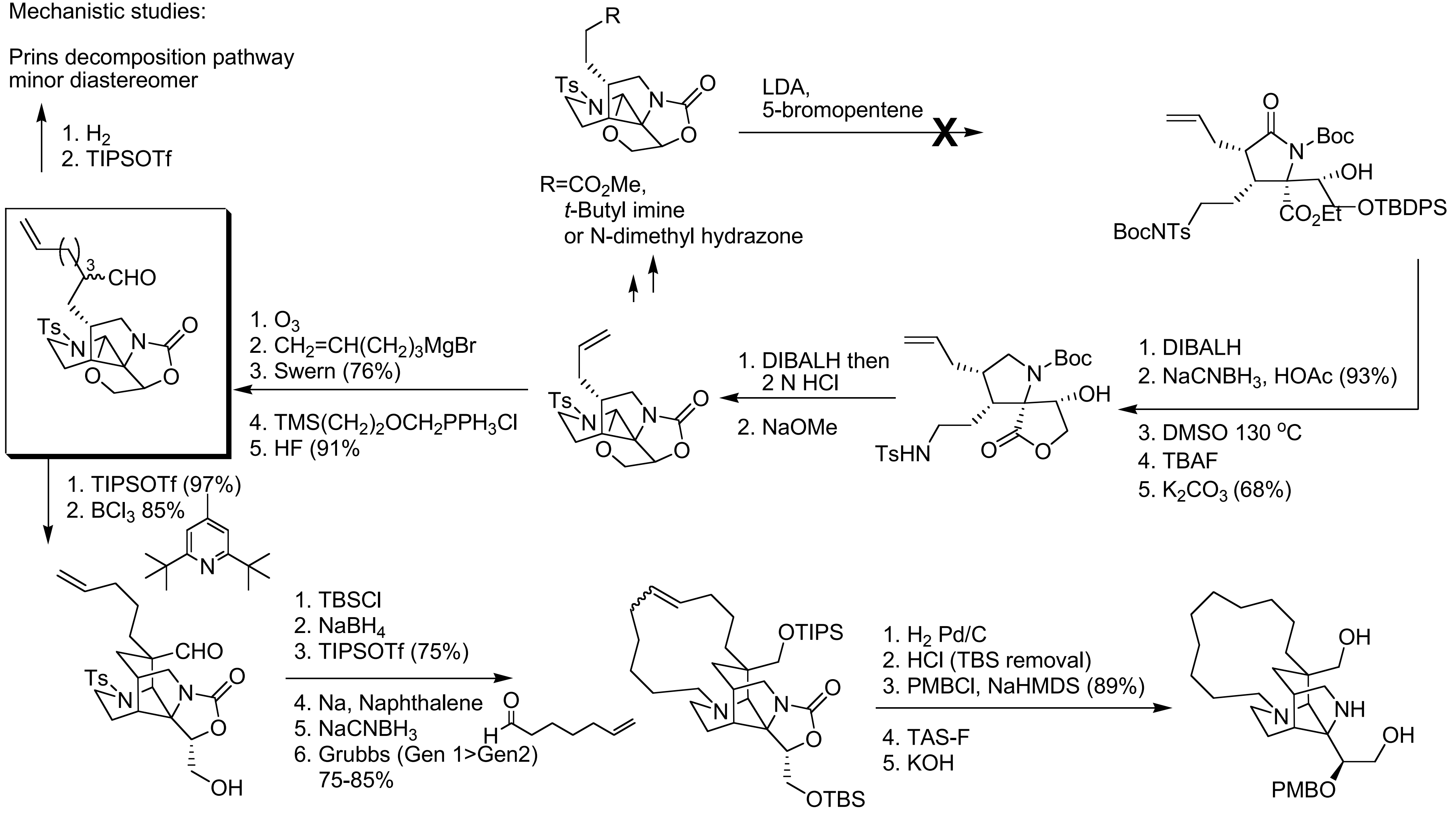
- Converted to 65 in 8 steps



Plan B


15 steps
18%
LHMDS
76%
1. LHMDS, allyl bromide
2. 2 N HCl
3. Boc$_2$O, DMAP (94%)
*
TsN
CO$_2$Et
TBDPSO
Ph
OBn
Br
Boc
OH
OTBDPS
BocNTs
BnO
OTIPS
Ts
BCl$_3$
CHO
EtO$_2$C
no amide formation
TBSO
Grubbs
25%
Optimize!

Cyclization Optimization



Mechanistic studies:

Prins decomposition pathway
minor diastereomer

1. H_2
2. TIPSOTf

LDA,
5-bromopentene

R=CO_2Me,
t-Butyl imine
or N-dimethyl hydrazone

1. DIBALH
2. $NaCNBH_3$, HOAc (93%)
3. DMSO 130 °C
4. TBAF
5. K_2CO_3 (68%)

1. DIBALH then
2 N HCl
2. NaOMe

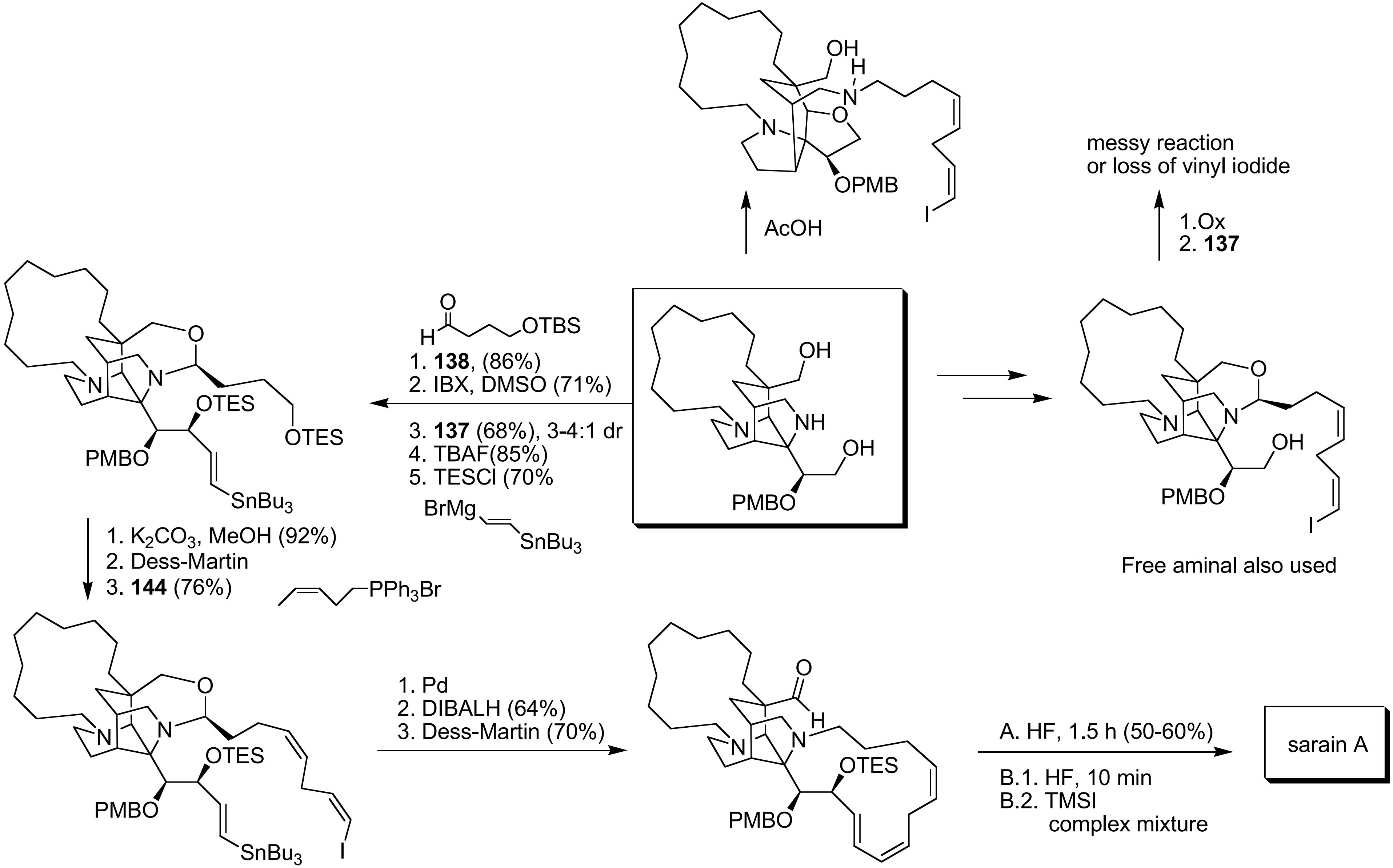
1. O_3
2. CH_2=CH$(CH_2)_3$MgBr
3. Swern (76%)
4. TMS$(CH_2)_2OCH_2PPH_3Cl$
5. HF (91%

1. TIPSOTf (97%)
2. BCl_3 85%

1. TBSCl
2. $NaBH_4$
3. TIPSOTf (75%)
4. Na, Naphthalene
5. $NaCNBH_3$
6. Grubbs (Gen 1>Gen2)
75-85%

1. H_2 Pd/C
2. HCl (TBS removal)
3. PMBCl, NaHMDS (89%)
4. TAS-F
5. KOH

Finale



AcOH

messy reaction
or loss of vinyl iodide

1.Ox
2. **137**

1. **138**, (86%)
2. IBX, DMSO (71%)
3. **137** (68%), 3-4:1 dr
4. TBAF(85%)
5. TESCl (70%

Free aminal also used

1. K_2CO_3, MeOH (92%)
2. Dess-Martin
3. **144** (76%)

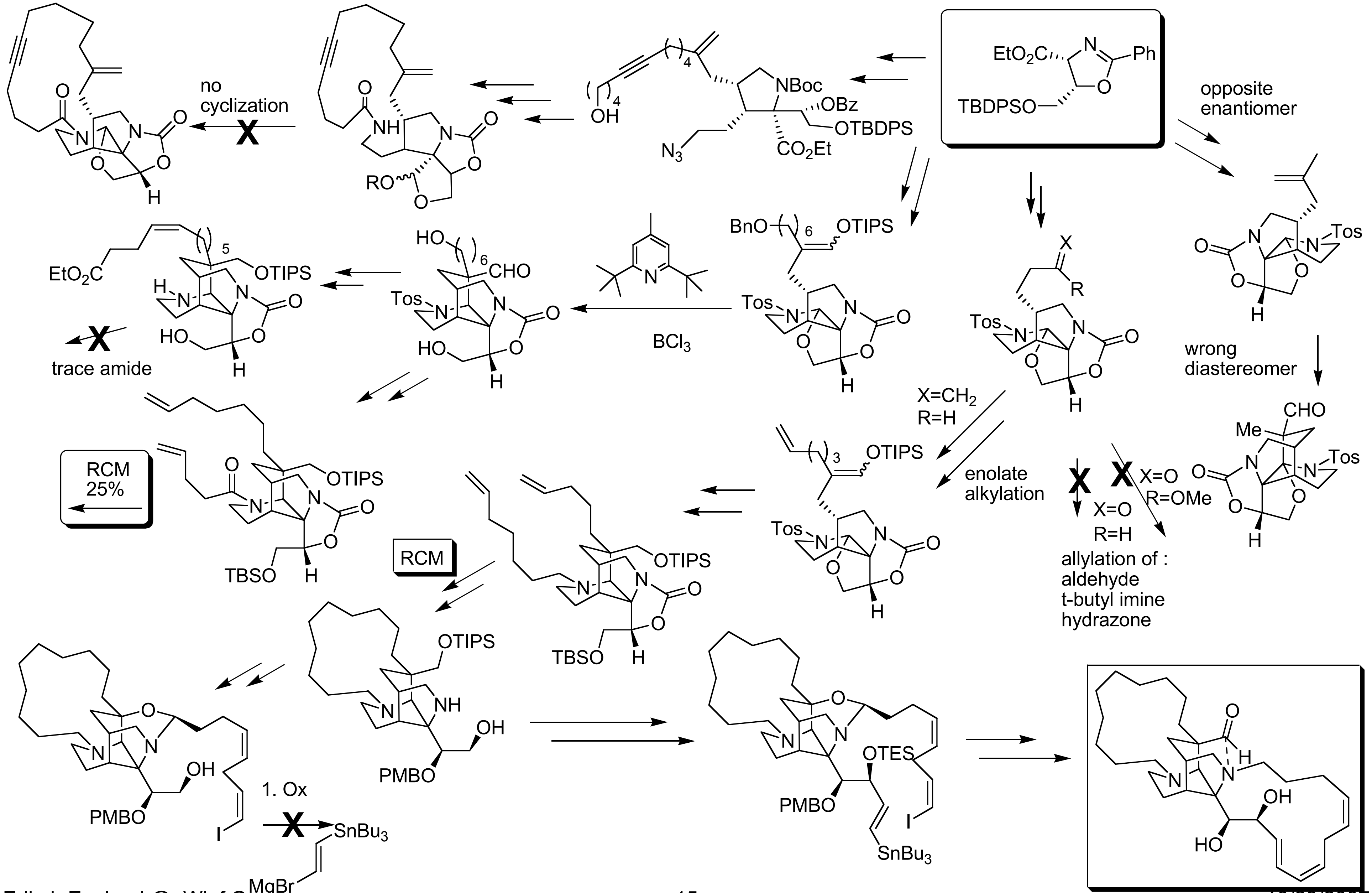
1. Pd
2. DIBALH (64%)
3. Dess-Martin (70%)

A. HF, 1.5 h (50-60%)

B.1. HF, 10 min
B.2. TMSI
complex mixture

sarain A

Synthesis Maze



Conclusions

- After extensive optimization, the total synthesis of sarain A was completed in 45 steps and 0.13% overall yield from diethyl D-tartrate
- Weinreb, Heathcock, Cha and Marazano have independently developed methadology to synthesize the core
- The Highlights:
  - Seebach oxazoline chemistry sets three key stereocenters that influence all the remainder stereocenters in the molecule
  - Congested core constucted via novel enoxysilane addition to N-sulfonyliminium species
  - Ring closing metathesis sets western ring
  - Stille coupling on a sensitive substrate sets eastern ring