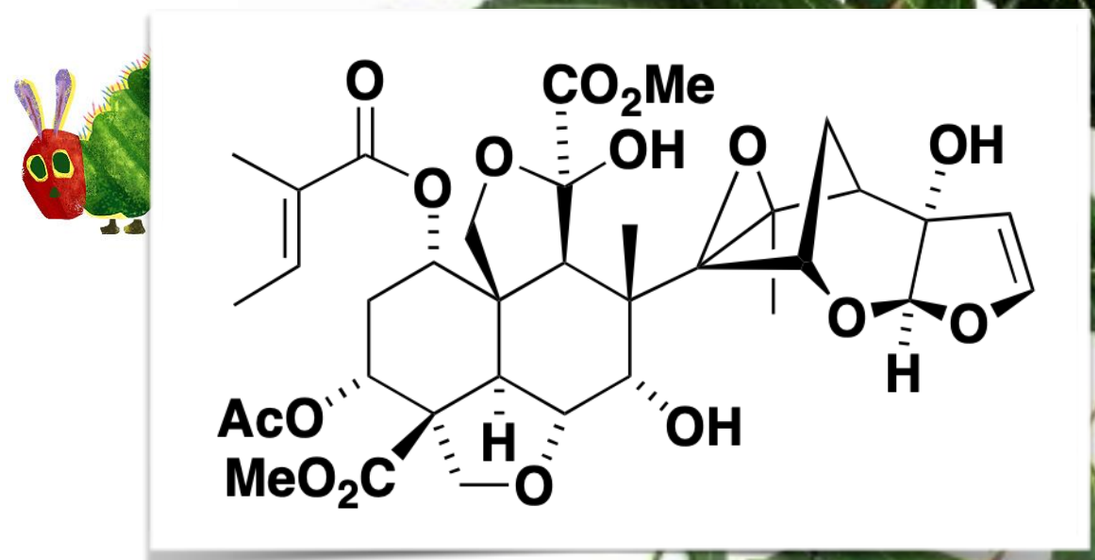
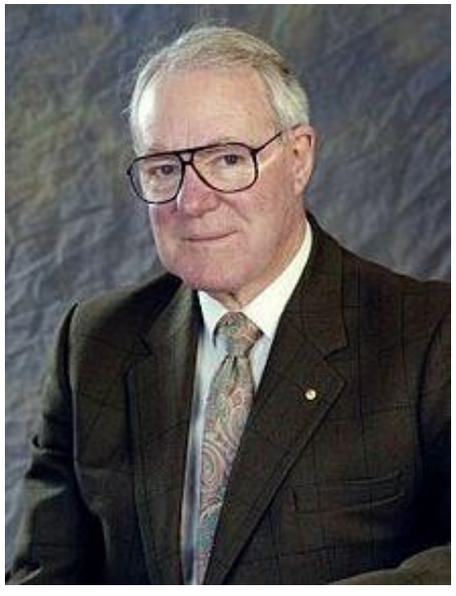



# The Azadirachtin Story: Slimming Pills for Insects

*Australia 2016*

***Cornforth Lecture***

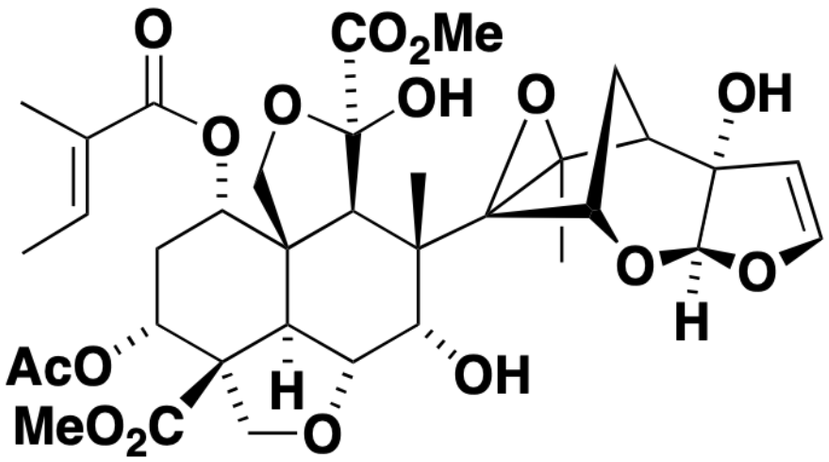


Steven Ley
Department of Chemistry
University of Cambridge

http://leygroup.ch.cam.ac.uk

# *Azadirachta indica* A. Juss - The Neem Tree

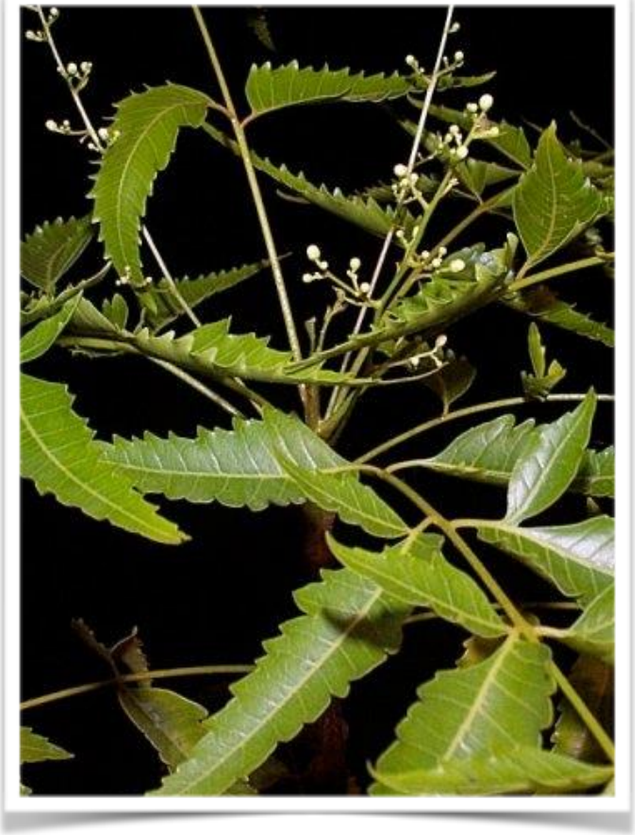









# *Azadirachtin – Neem Products*





















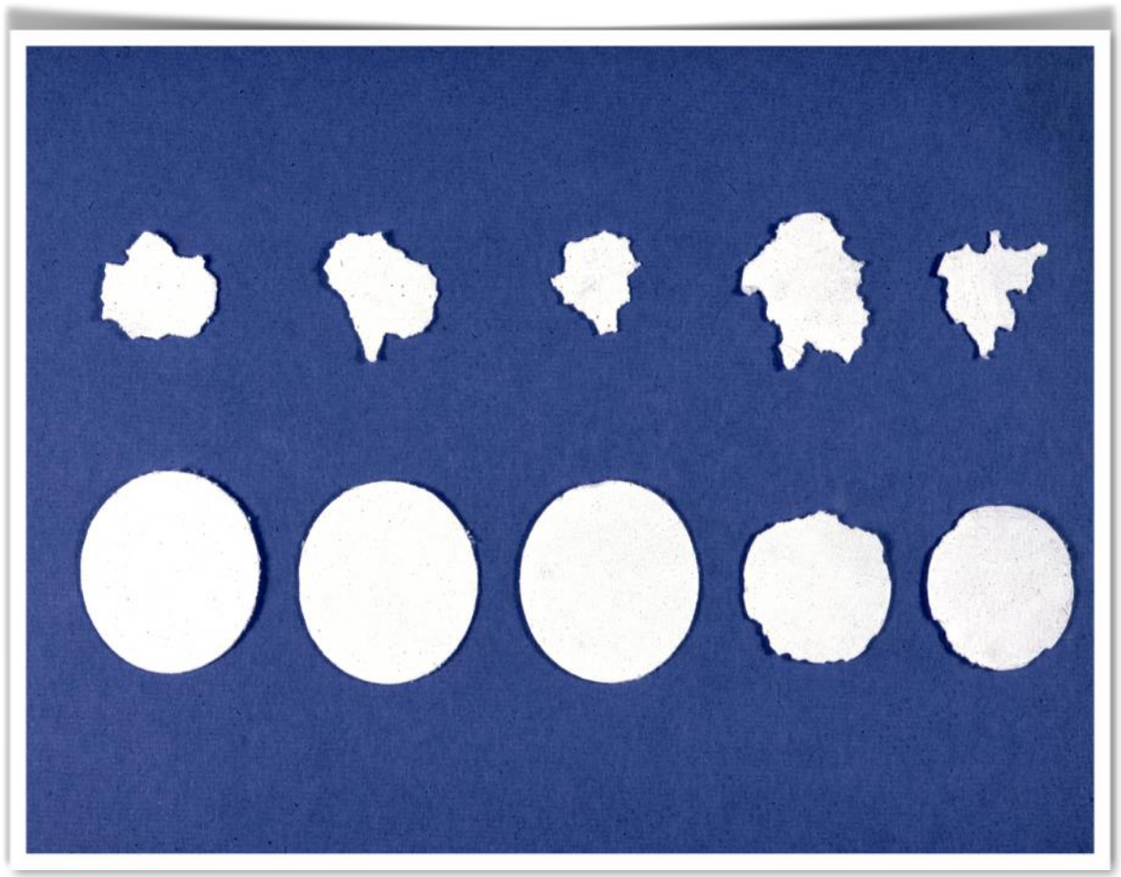



## Whole Plant



Treated Untreated

## Laboratory Screening Discs



# *Azadirachtin – Other screening protocols*

Haemolymph Injection

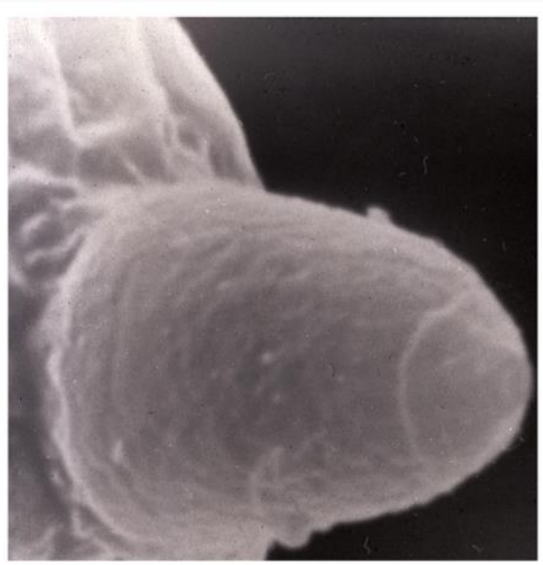


Gut Injection

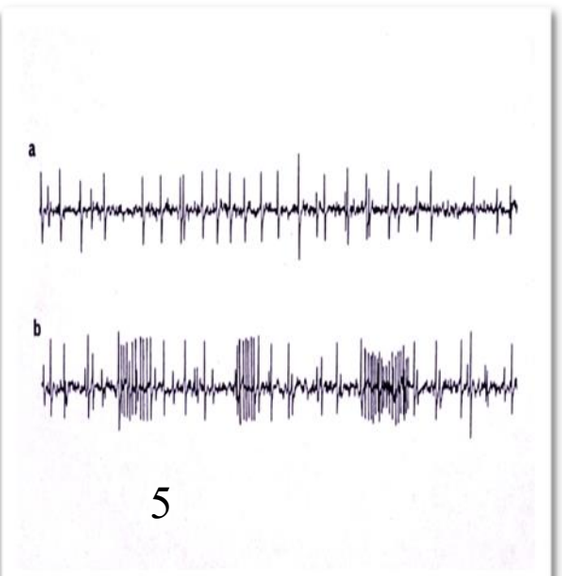


Electrophysiology

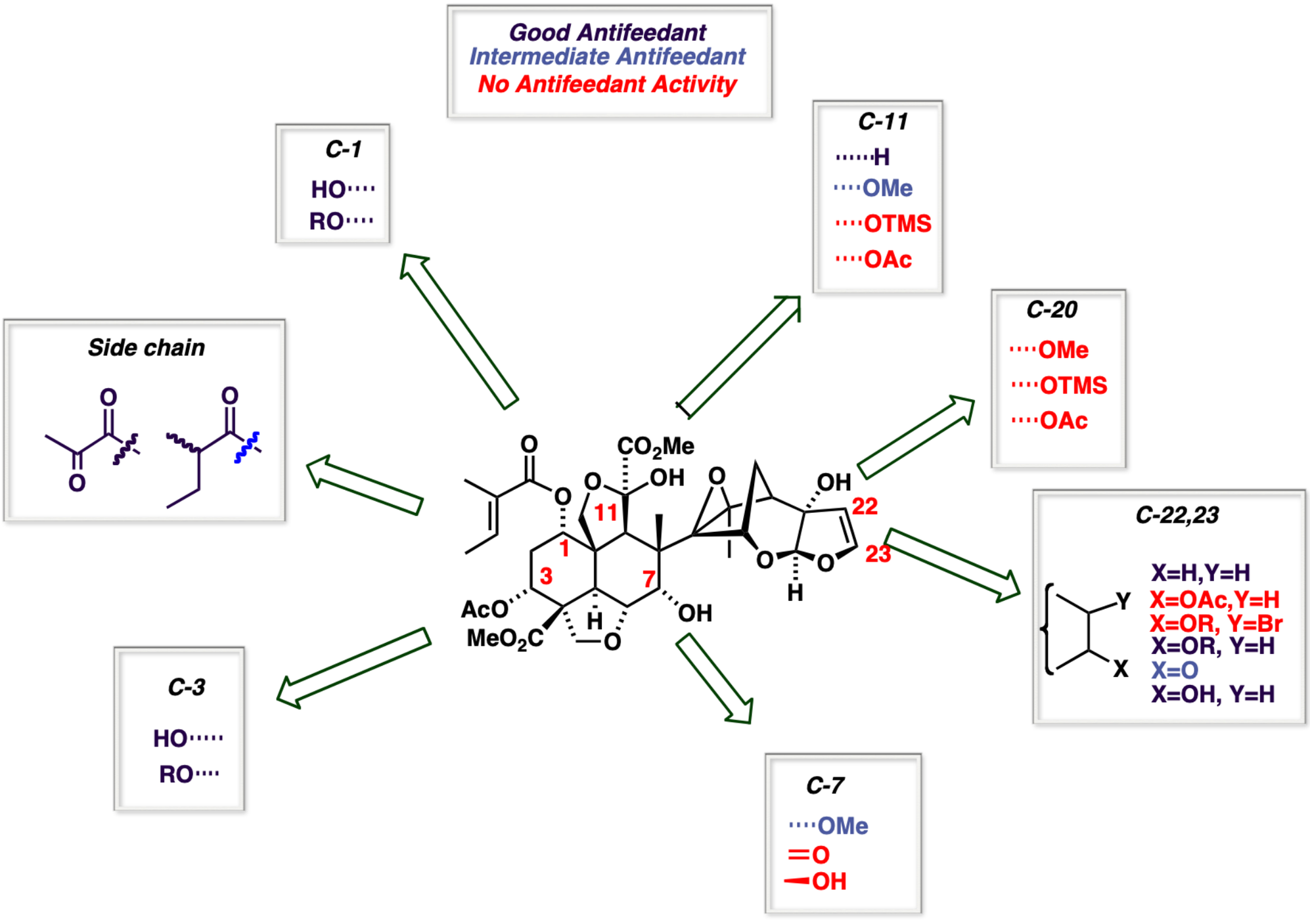






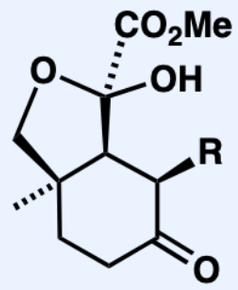


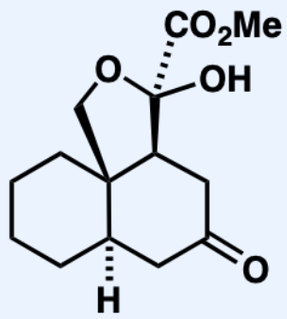
# *Azadirachtin – Structure-Activity Relationships*

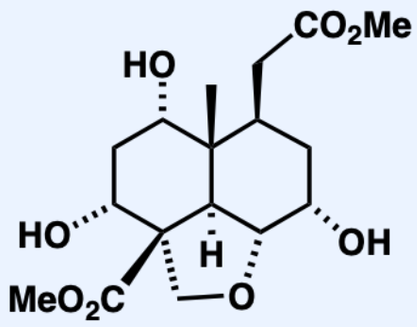


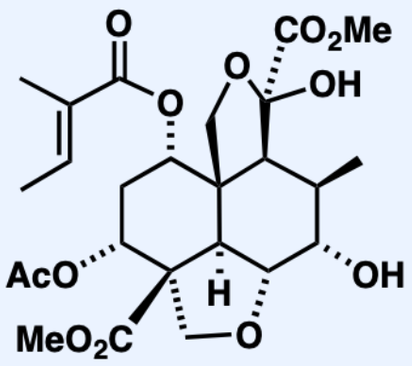
# *Azadirachtin – Minimum structural requirements*

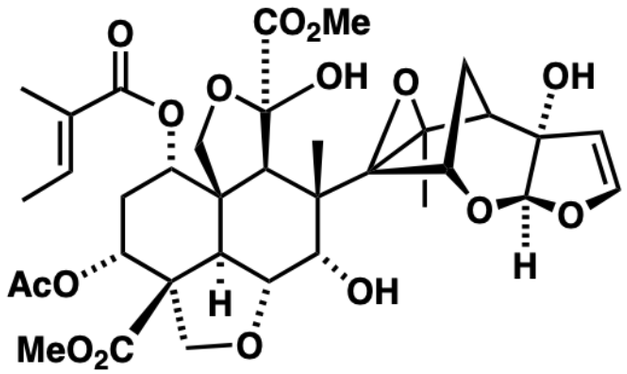
## Growth Regulation



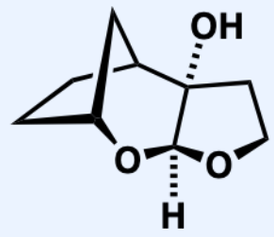



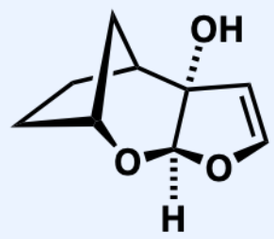



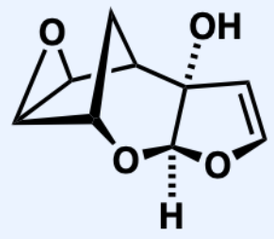



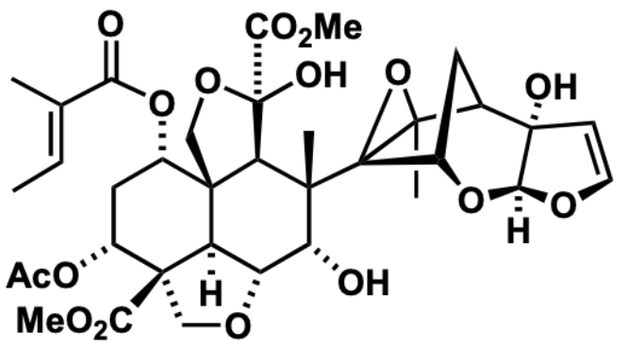

## Antifeedant



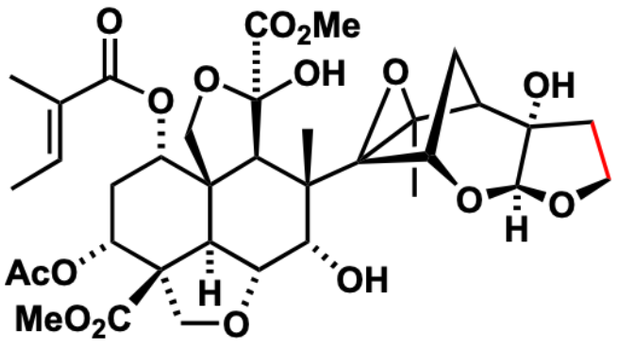



# *Azadirachtin – Modifications*



Pd / C

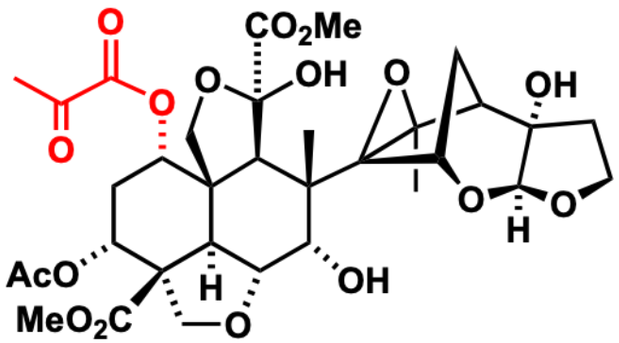
$H_2$ 3.5 h



76%

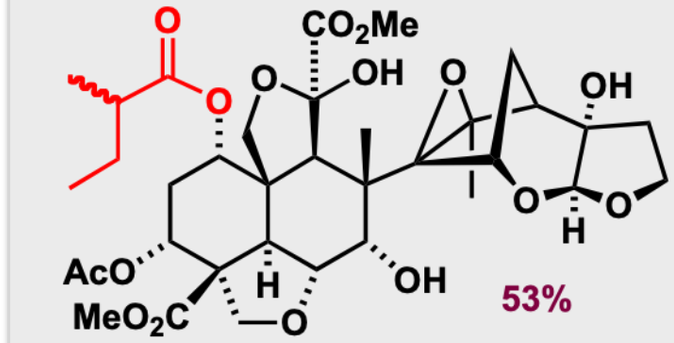
$O_3$, MeOH, -50°C

Pd / C
$H_2$ 24h



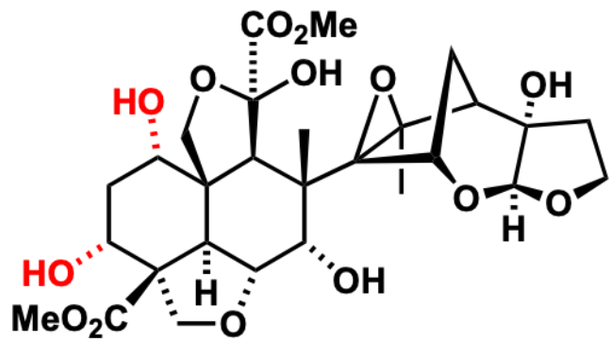
61%

More stable fully active derivative



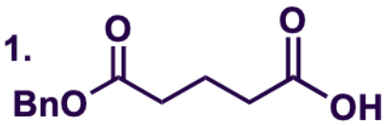
53%

$NaHCO_3$ / MeOH
3 days



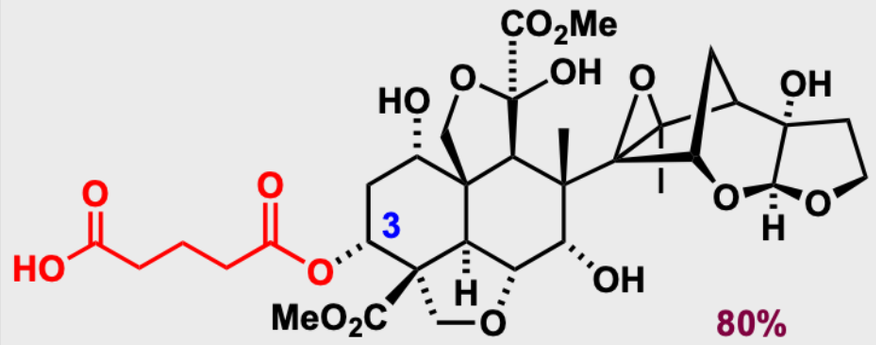
50%

1.



DIC, DMAP, $CH_2Cl_2$

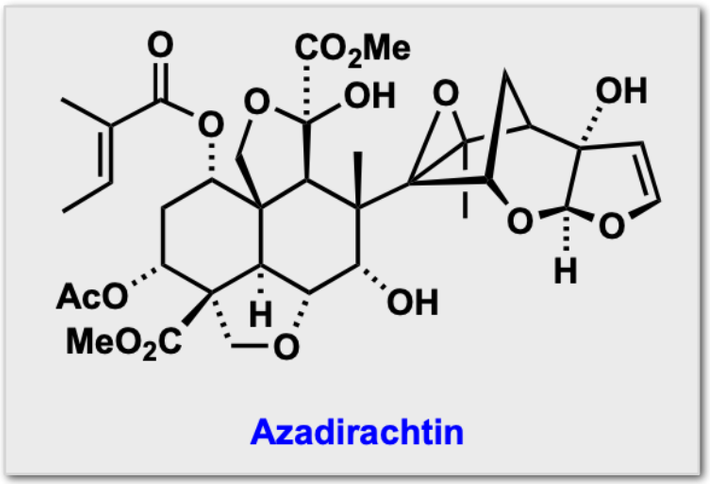
2. $H_2$, Pd / C, MeOH



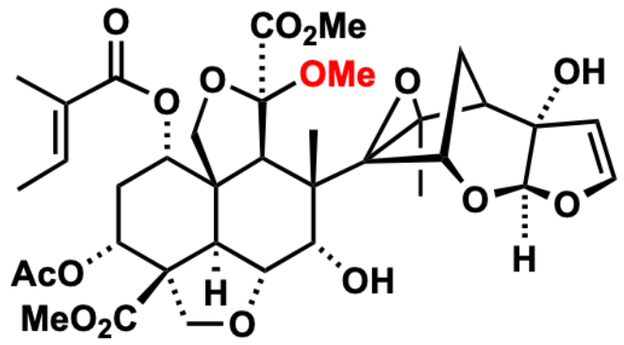
80%

3-Glutaryl-Derivative for biological studies

# *Azadirachtin – Methylation*




$Ag_2O$, MeI, 40° 2h

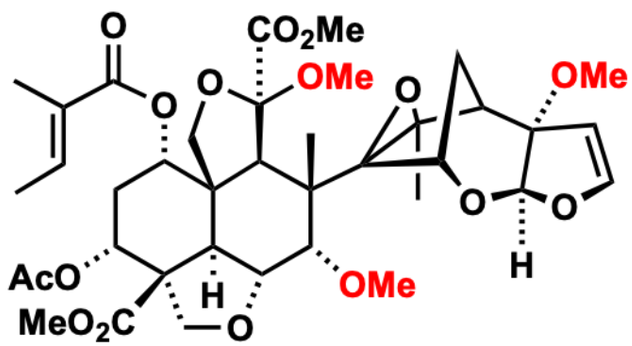


**86%**

11- monomethyl derivative

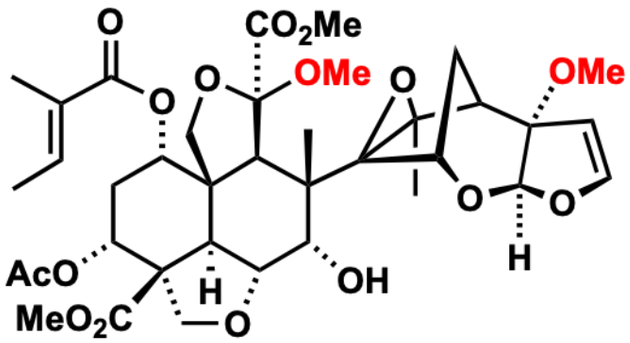
$Ag_2O$, MeI, 40° 8h

KOH, DMSO,
MeI
15 min.



**24%**

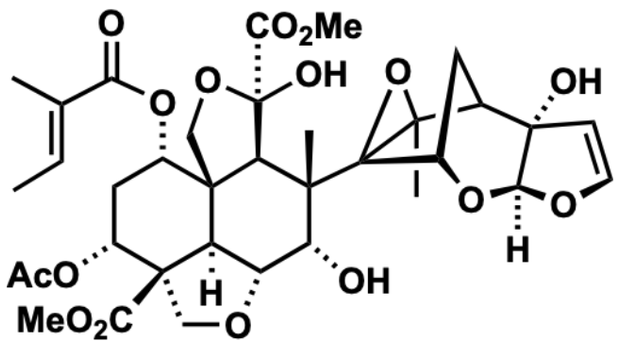
7,11,20-trimethyl derivative



**73%**

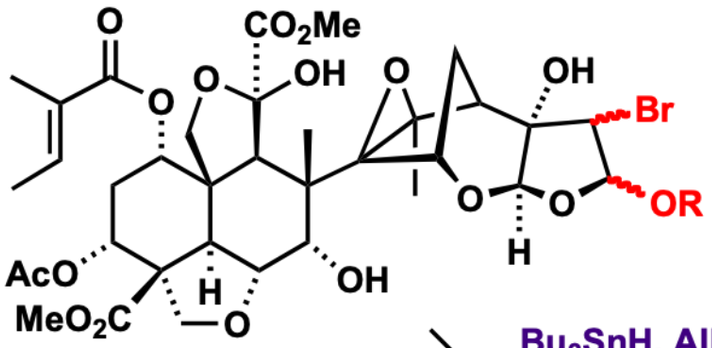
11,20- dimethyl derivative

# *Azadirachtin – Addition reactions*



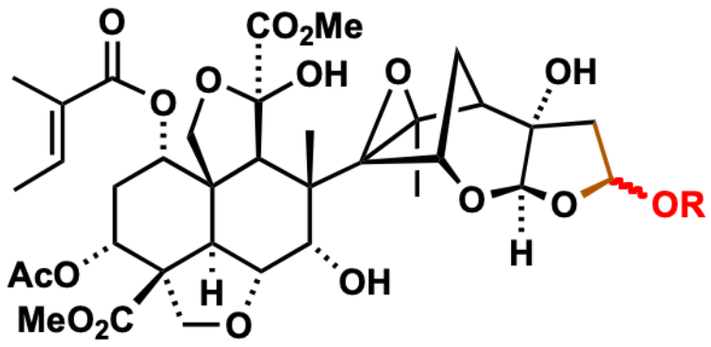
$Br_2$, ROH

0°C



R = Me 83%
R = Et 97%
R = iPr 96%

$Bu_3SnH$, AIBN,
PhMe, 110°C, 95%

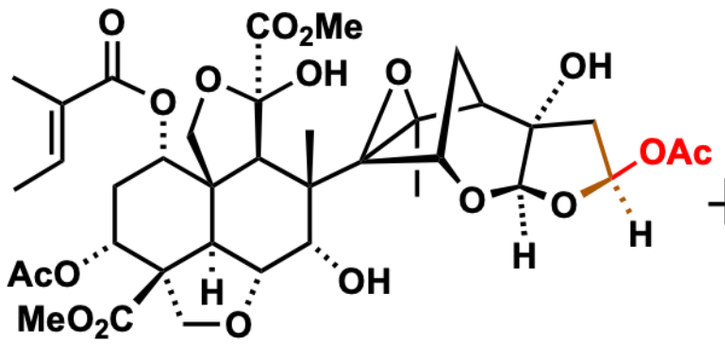


HOAc, 36 h, r.t

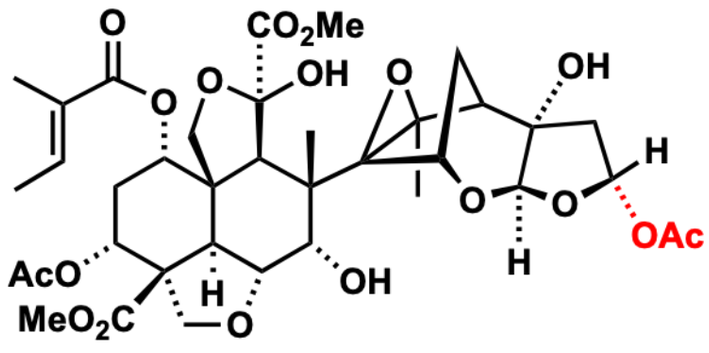
95%

$10^{-1}$ mm Hg, 165°C

97% !

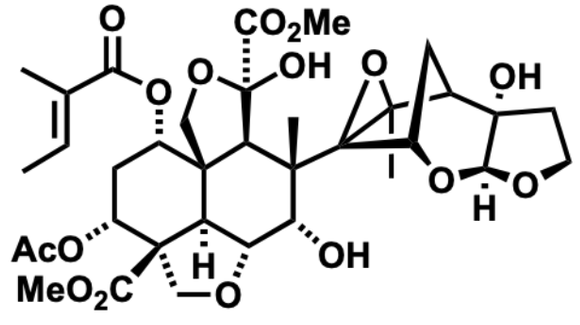


+

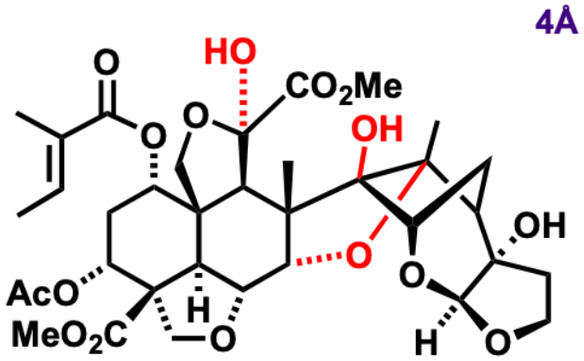


1 : 2

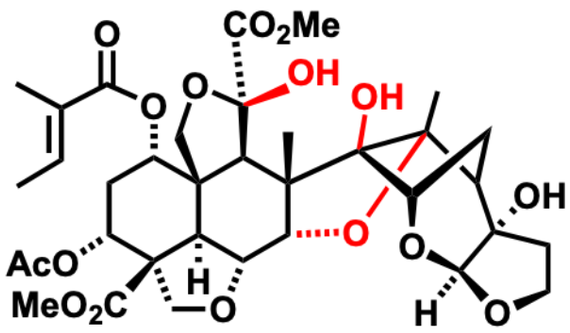
# *Azadirachtin – Acid-Catalysed Rearrangements*





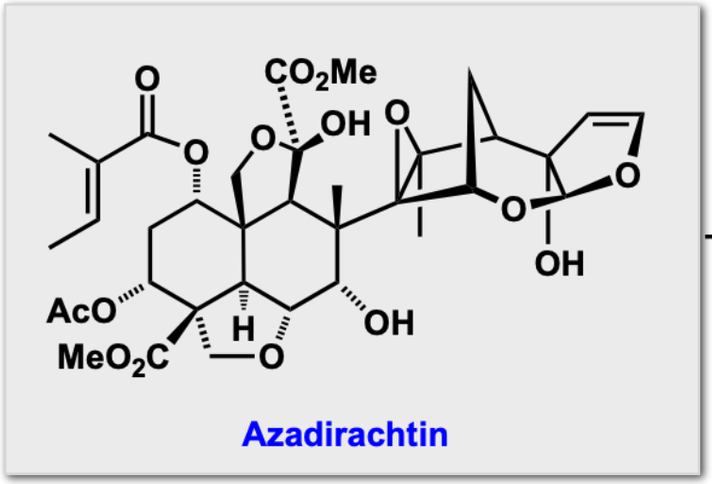



1



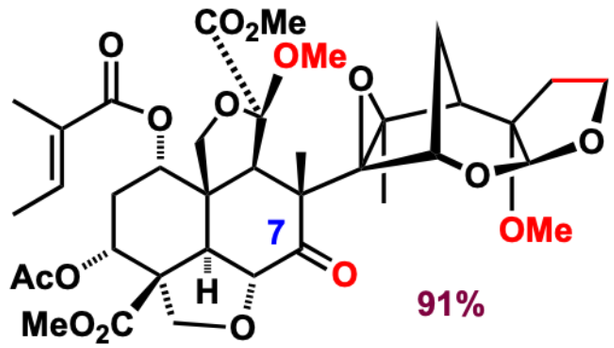
3

# *Azadirachtin – Other Acid-Catalysed Rearrangements*

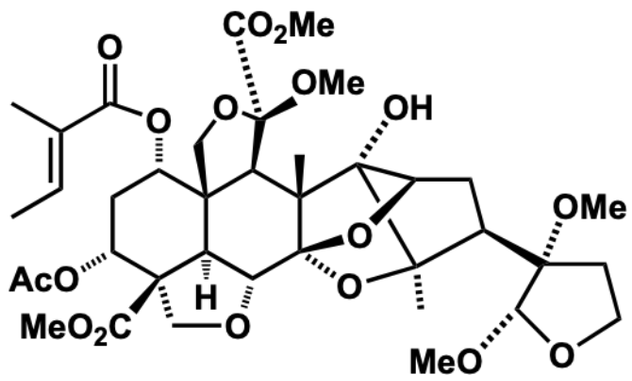



1) $Ag_2O$, MeI, 40°C, 8 h, 80%
2) $H_2$, Pd/C, MeOH, 73%

3) PDC, DCM, 4Å sieves

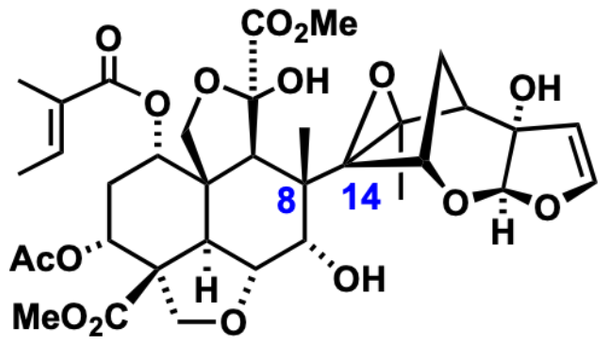


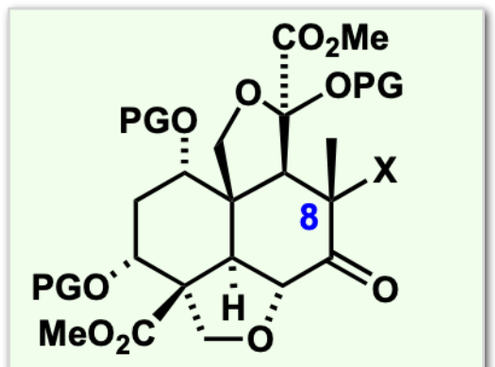

A-15 $SO_3H$ MeOH



59%

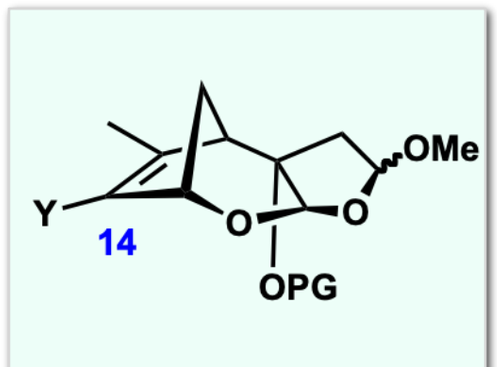
# *Azadirachtin – Synthesis Plan...'first thoughts'*




Decalin fragment

?




Hydroxyfuranacetal fragment

***Synthesis Problems***

16 Stereogenic centres

7 Quaternary centres

Acid labile

Base labile

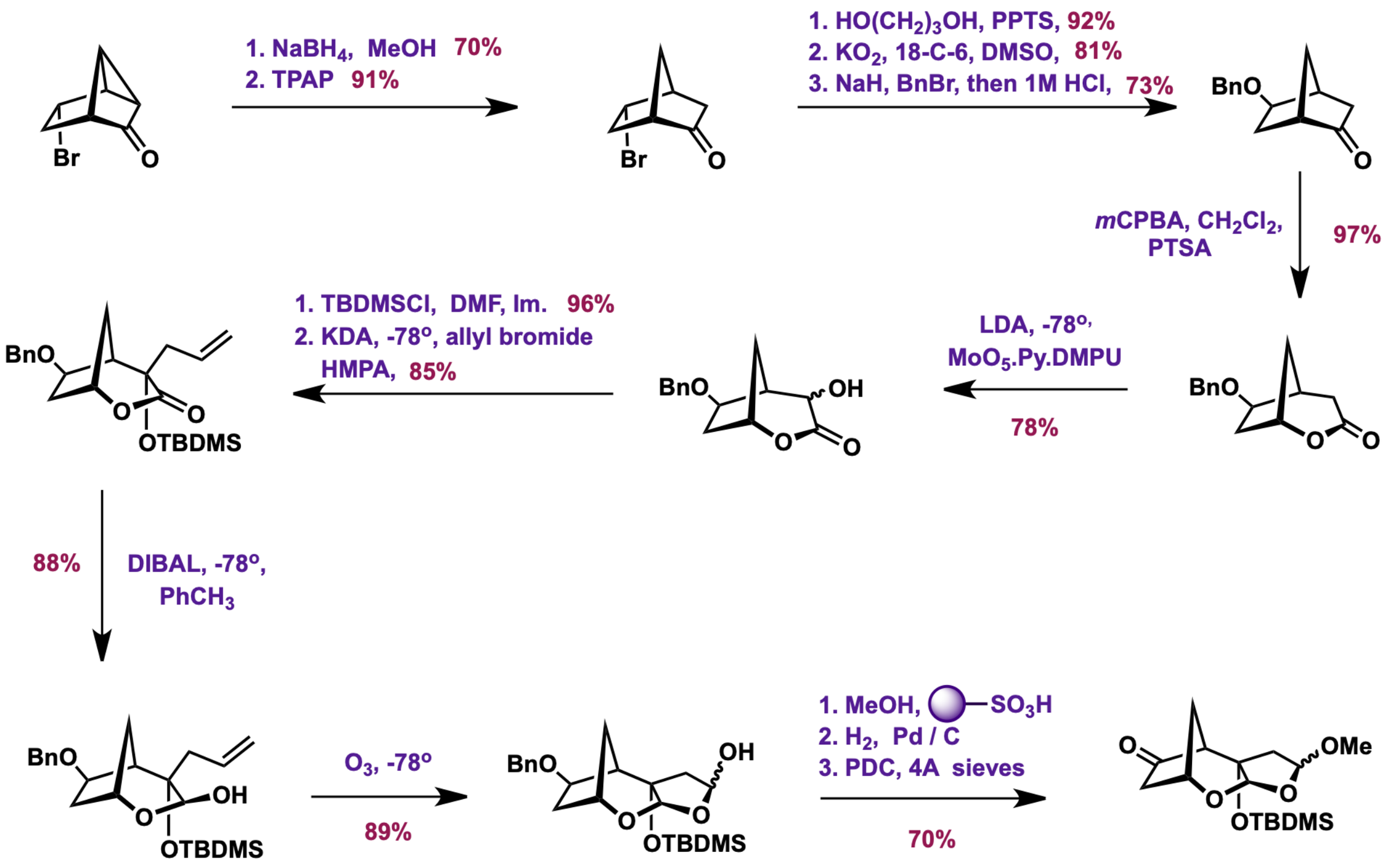
Photo sensitive

Prone to rearrangement

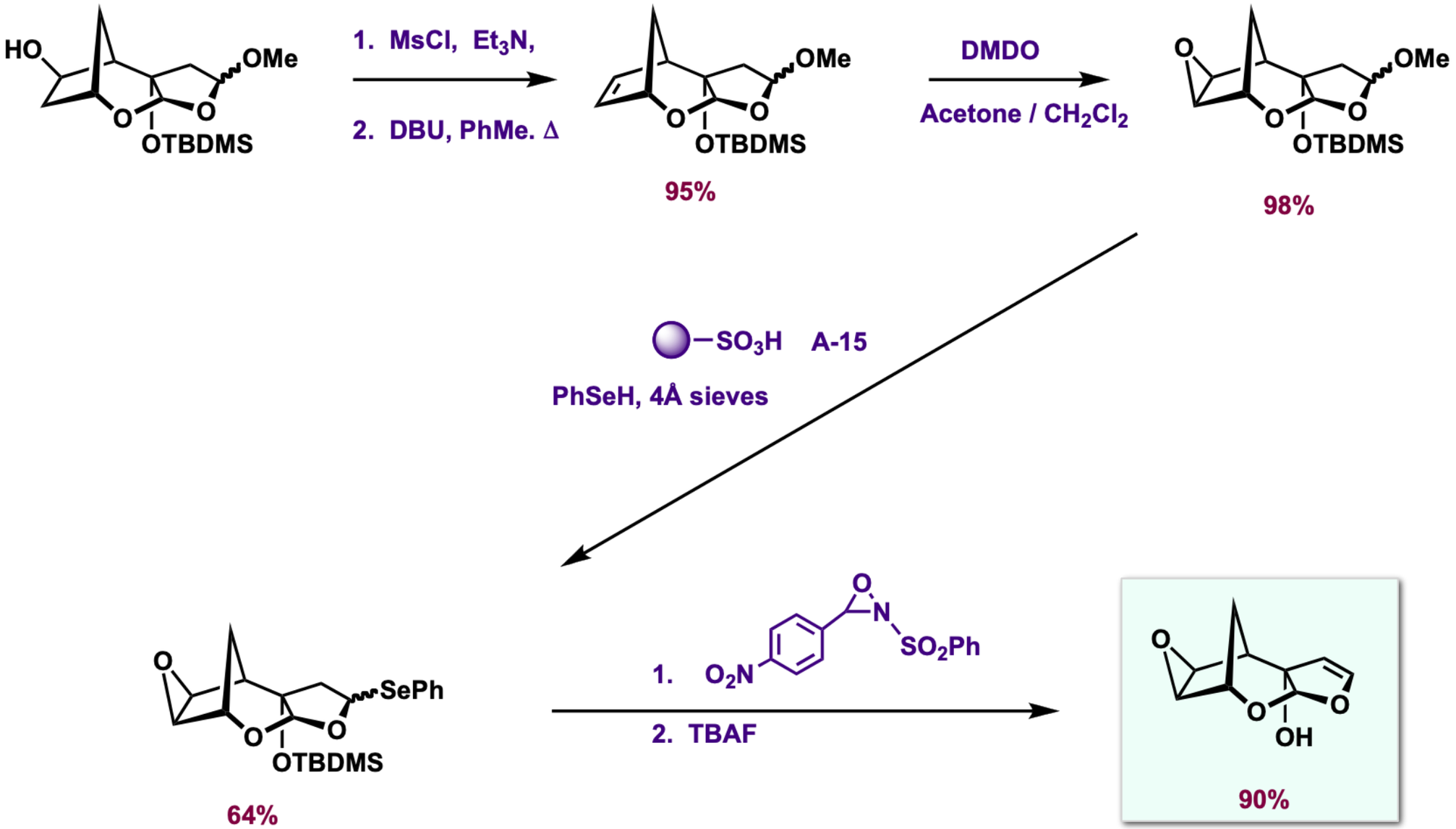
High density of different oxygen atoms

Complex hydrogen bonding pattern

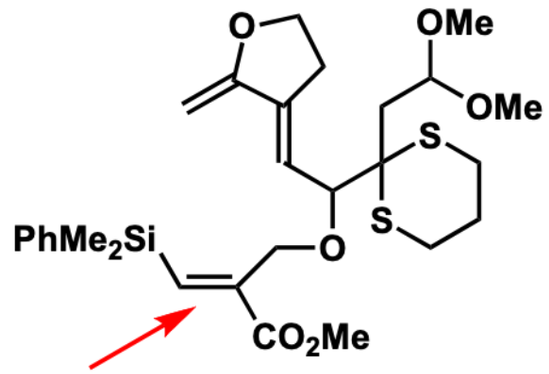
# *Azadirachtin – Acetal Fragment Synthesis*



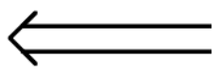
# *Azadirachtin – Epoxide Model Synthesis*

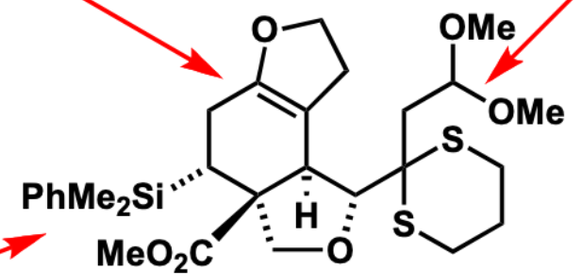


# *Azadirachtin – Synthesis Plan to the Decalin Fragment*




***Cis-endo* Intramolecular Diels-Alder Reaction**

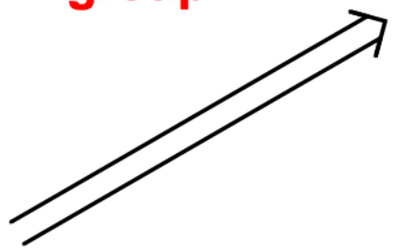




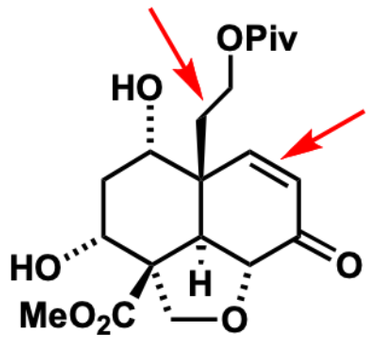

**Electron rich alkene**

**Electrophilic acceptor group**

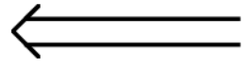
**Masked hydroxyl group**

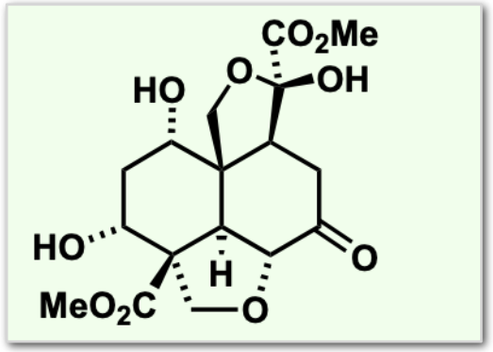


**Degrade side-chain**



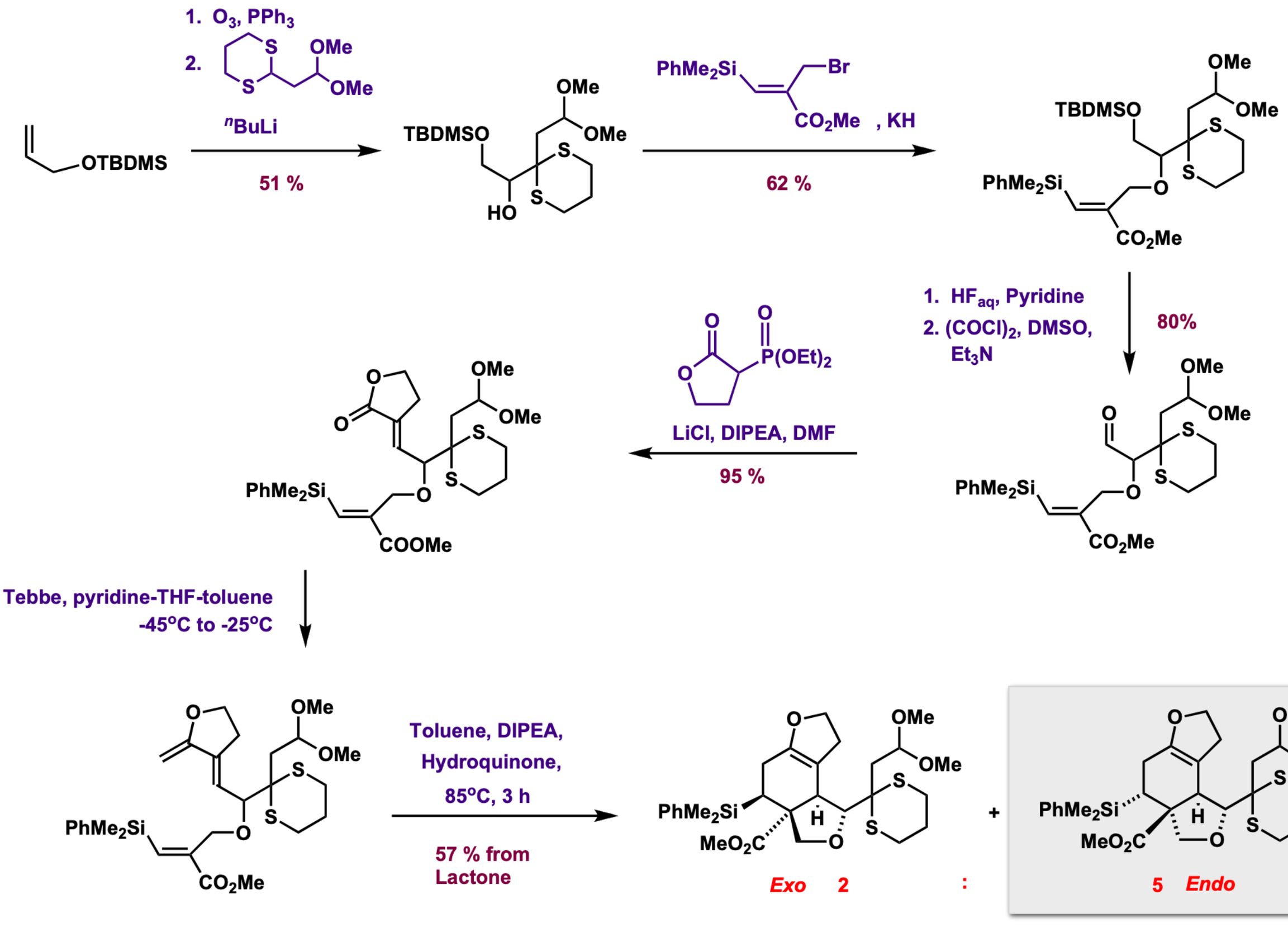

**Michael acceptor**



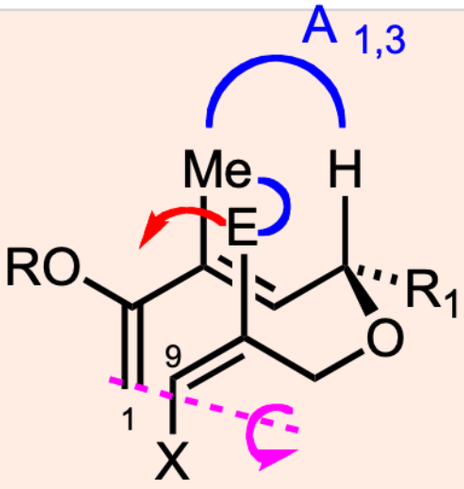



**Target Molecule**

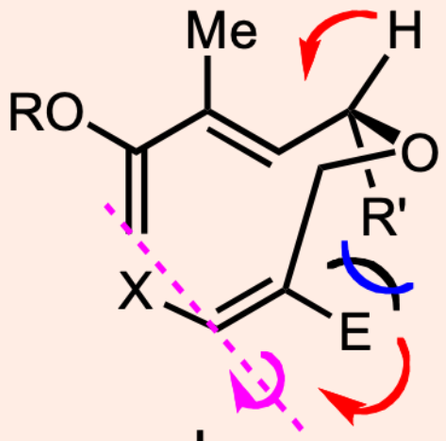
# *Azadirachtin – Decalin Fragment*



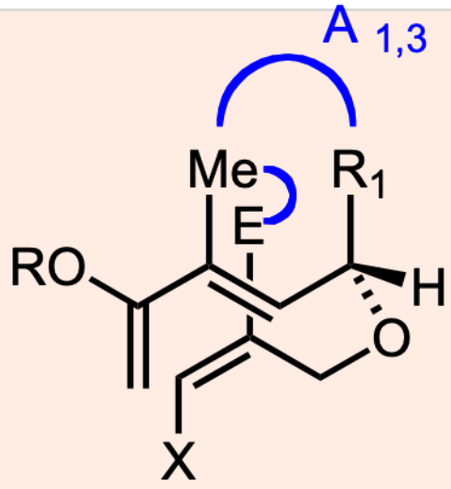
# *Azadirachtin – Intramolecular Diels-Alder Transition States*



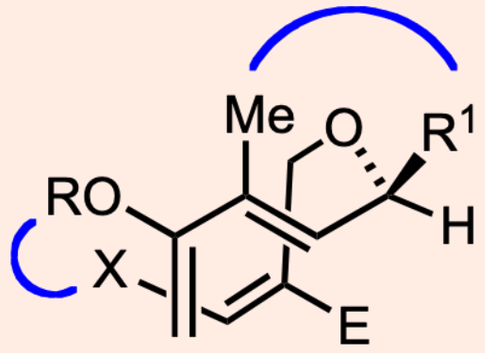

*endo*
*A*



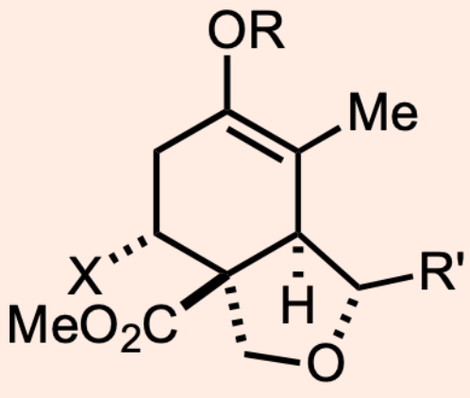

*exo*
*B*

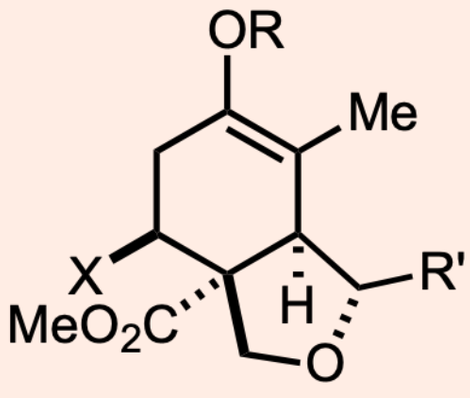


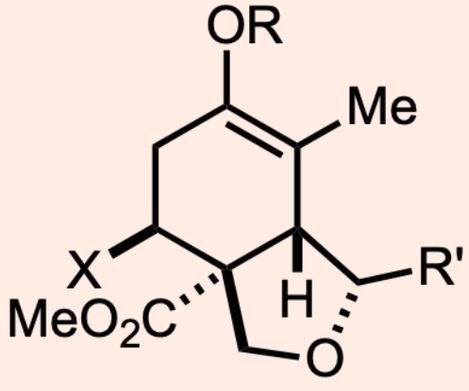

*endo*
*C*

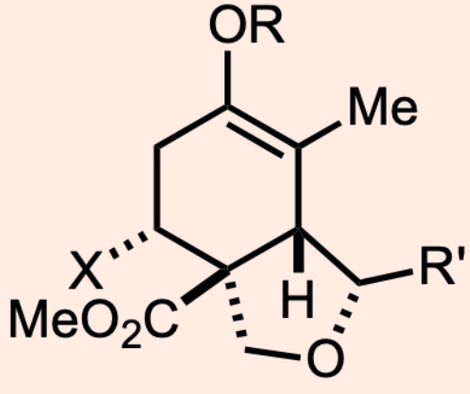



*exo*
*D*

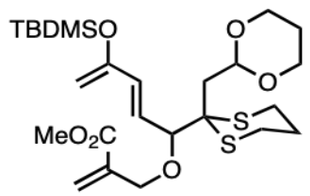
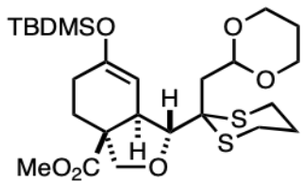
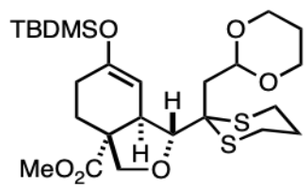
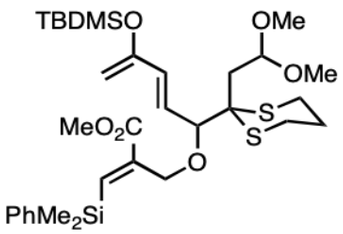
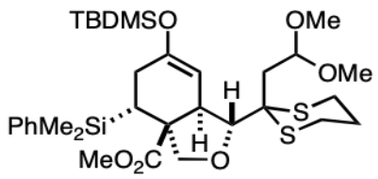
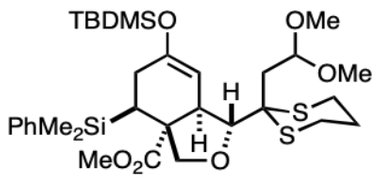
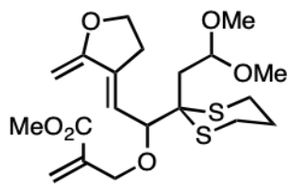
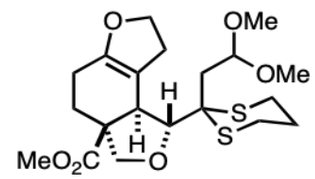
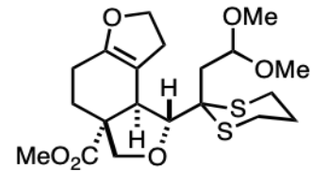
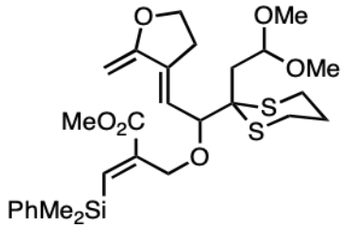
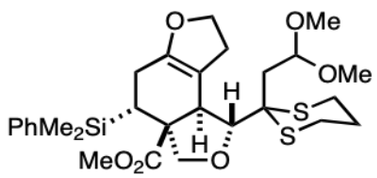
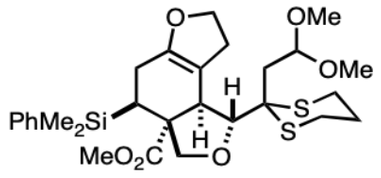
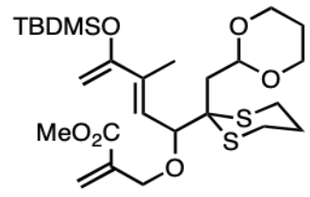
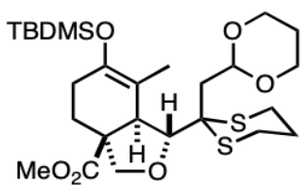
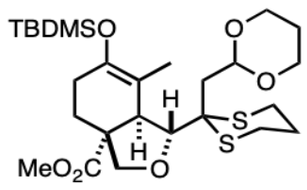
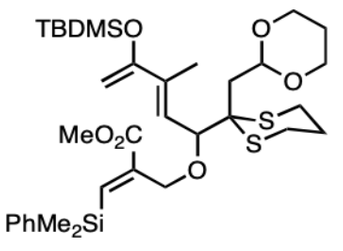
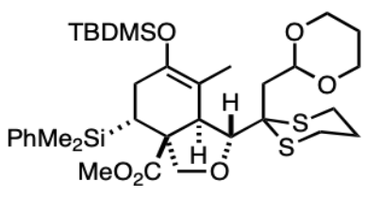
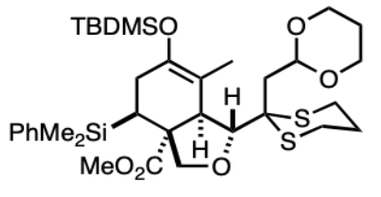


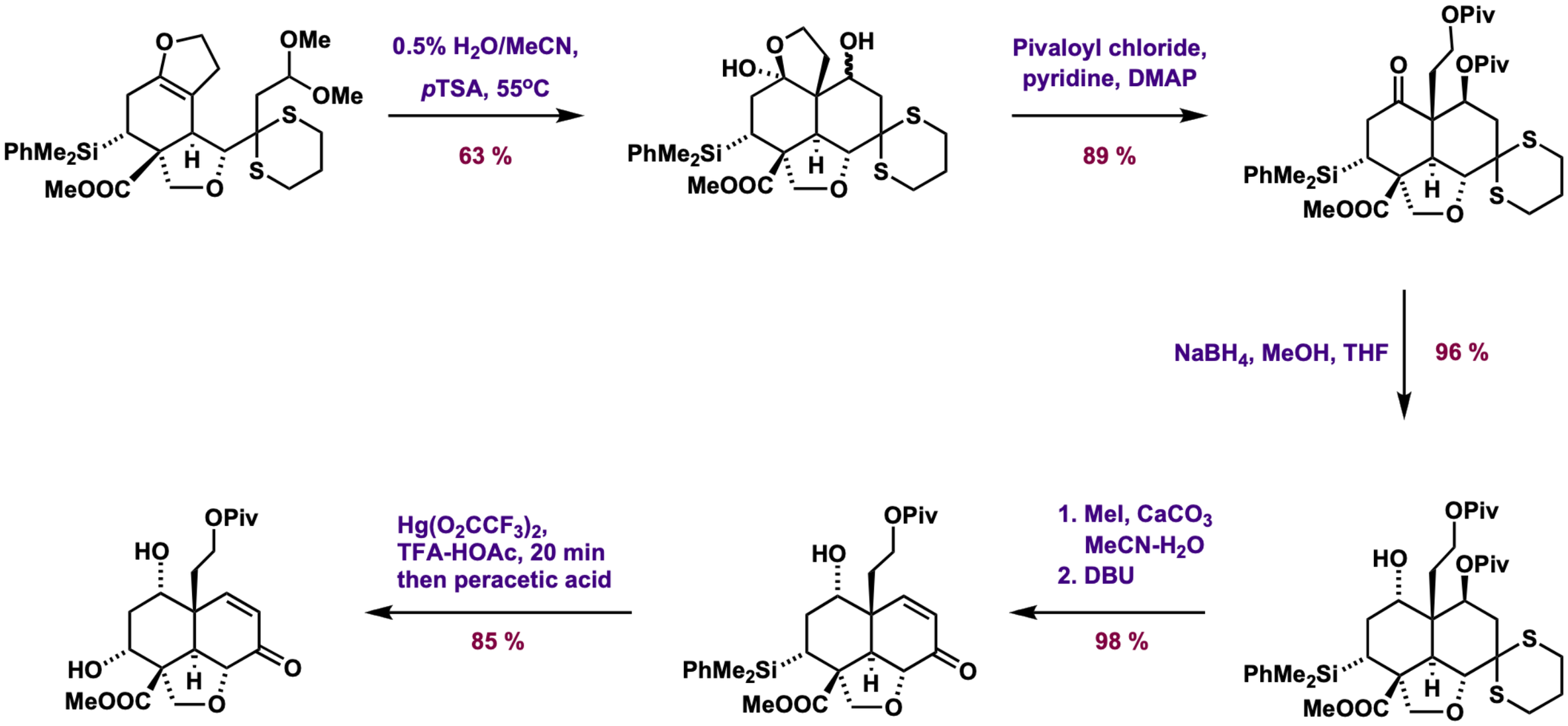



# *Azadirachtin – Intramolecular Diels-Alder*

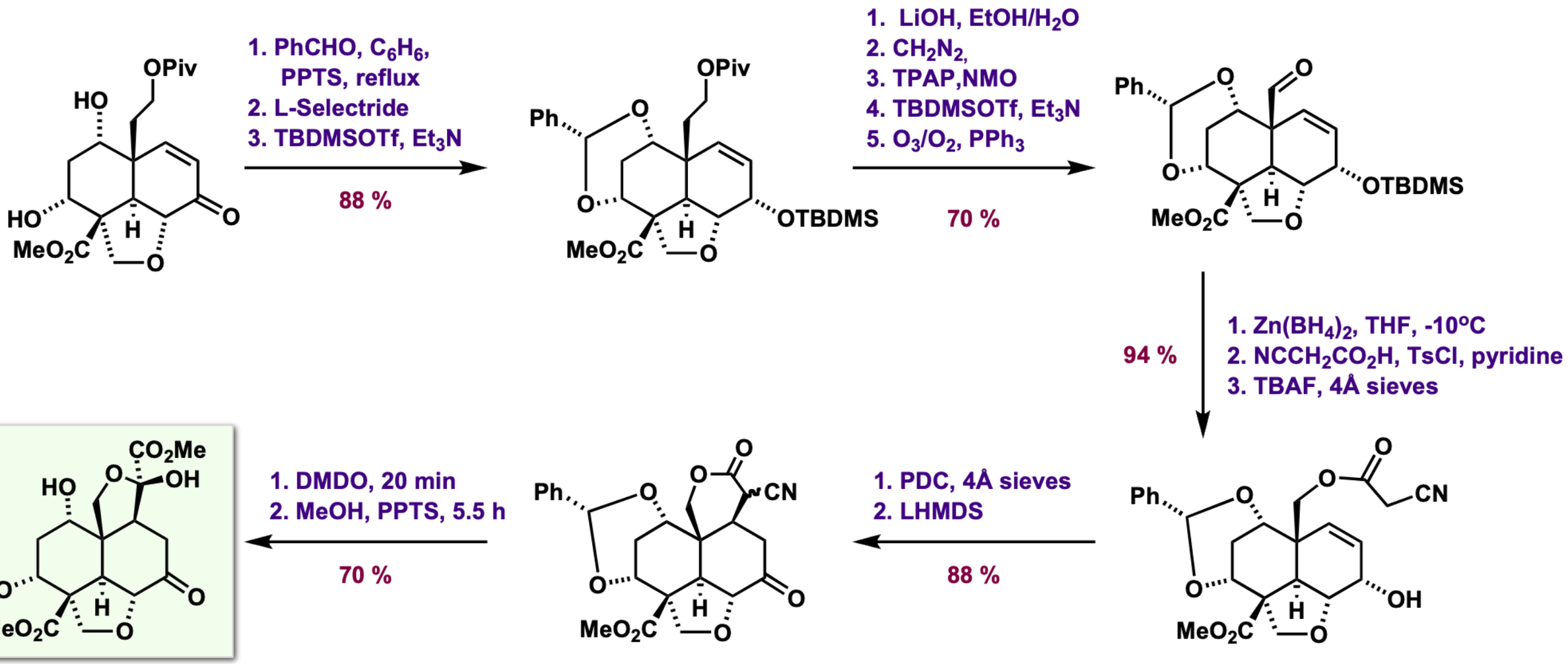
| Starting triene | Conditions | Yield (%) | Product ratio, *endo : exo* | | |
|---|---|---|---|---|---|
|  | 7h, 111˚C, toluene | 84 |  | <1 : 10 |  |
|  | 14h, 111˚C, toluene | 77 |  | 1 : 3.4 |  |
|  | 5h, 60˚C, toluene | 18* |  | 1 : 8 |  |
|  | 4h, 85˚C, toluene | 29* |  | 2.4 : 1 |  |
|  | 0.75h, 135˚C,DMSO | 84 |  | 2.1 : 1 |  |
|  | 3h, 111˚C, toluene | 77 |  | >12 : 1 |  |

*Yield for Tebbe methylenation and IMDA cyclisation.

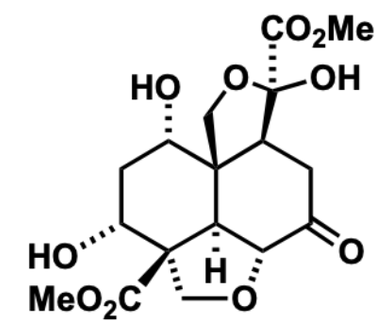
# *Azadirachtin – Decalin Fragment – the next steps*



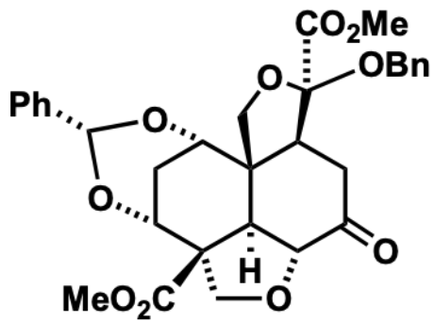
# *Azadirachtin – Decalin Fragment – the next steps*



# *Azadirachtin – Decalin Fragment – further steps*

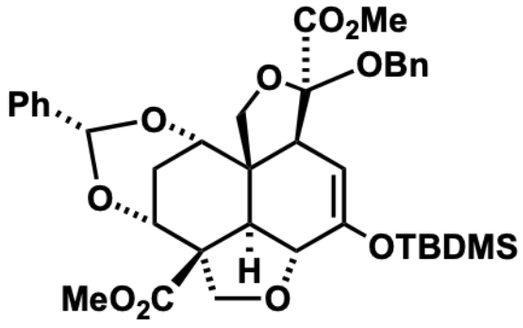



1. PhCHO, PPTS, 75%
2. BnBr, $Ag_2O$, DMF, 61%

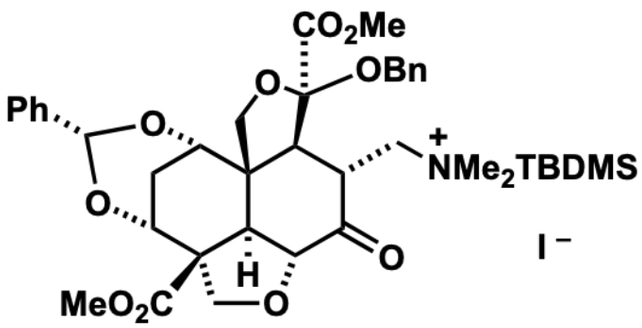



TBDMSOTf
$Et_3N$, MeCN

77%

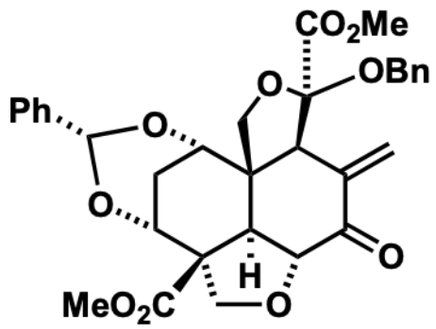



$CH_2{=}\overset{+}{N}(Me)_2\,I^-$, $CH_2Cl_2$, 35°C
then TBDMSI, $CH_2Cl_2$



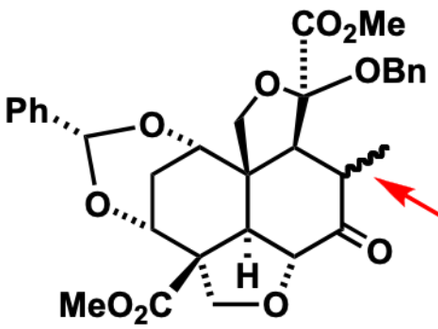

$SiO_2$

68%
over 2 steps



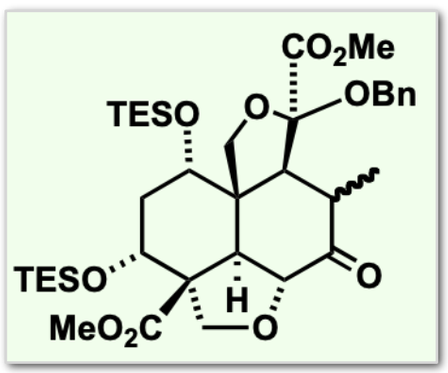

$H_2$, Pd / C. MeOH

65%



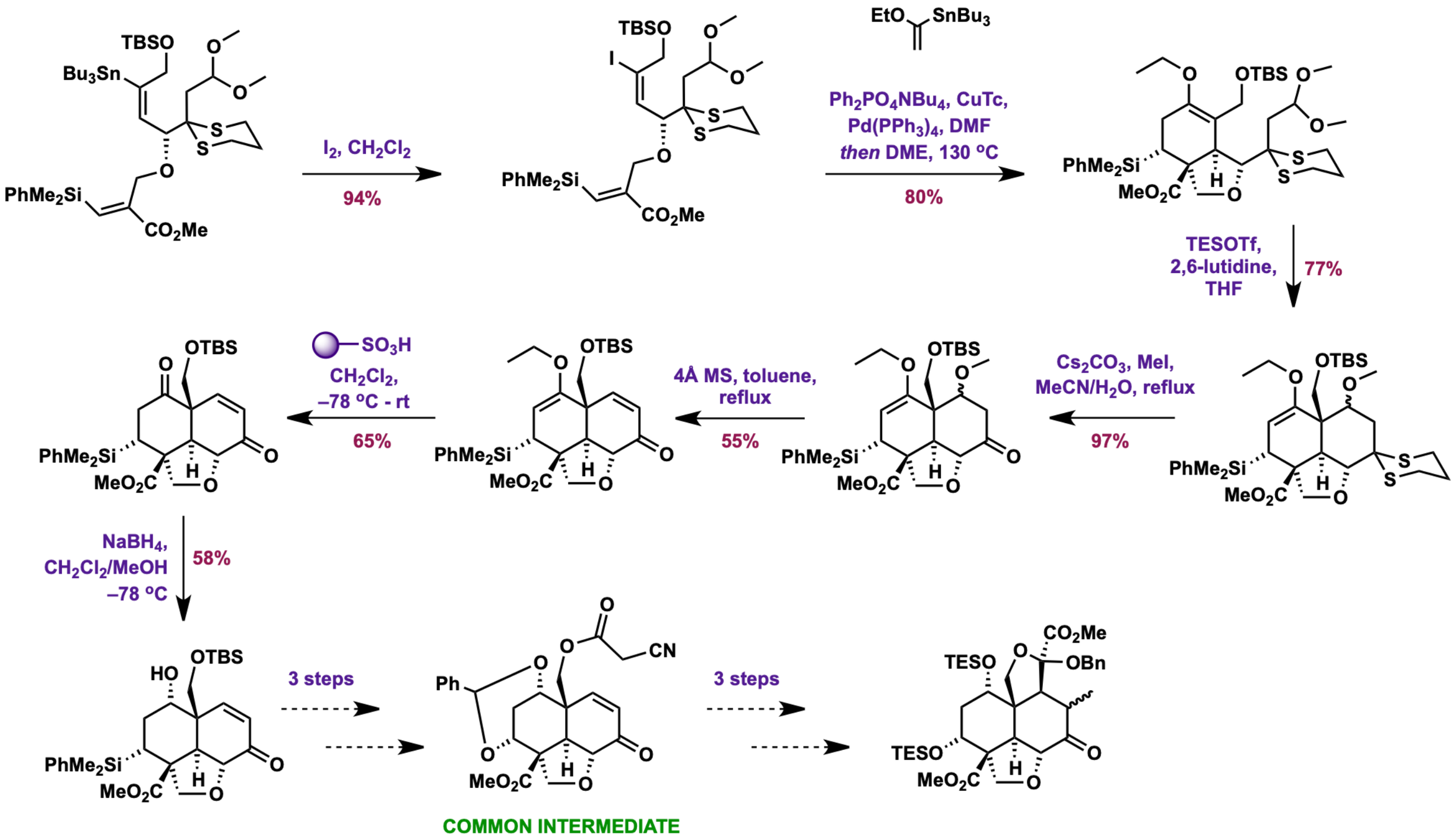

4:1 β:α

1. PPTS, MeCN, 85%
2. TESOTf, DIPEA, $CH_2Cl_2$, 90%



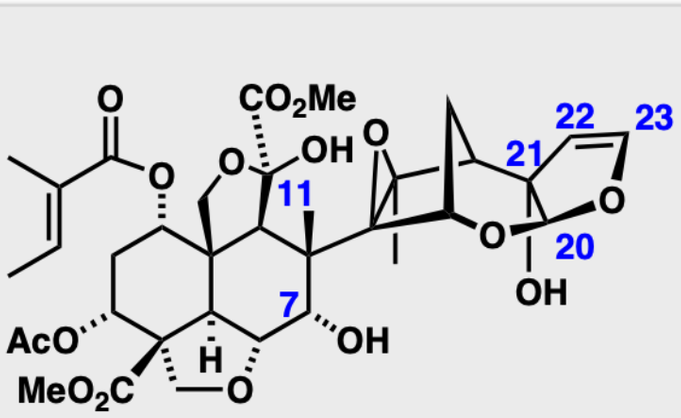

***Same as the fragment from degradation***

# *Azadirachtin – Second Generation Decalin Fragment*



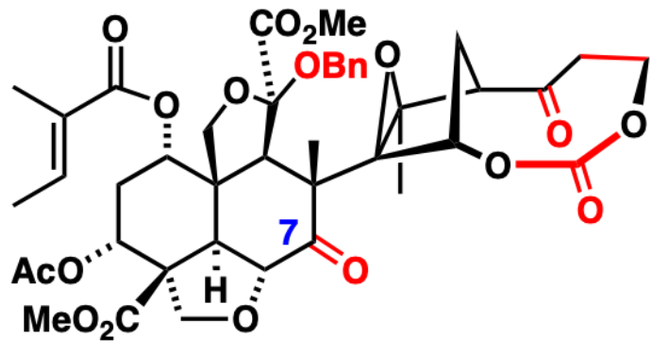

**COMMON INTERMEDIATE**

# *Azadirachtin – Degradation Studies*

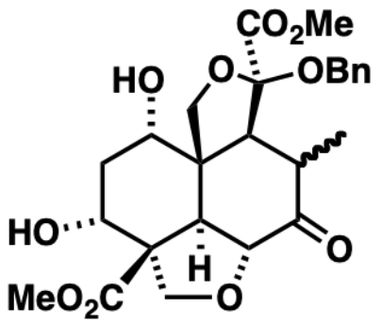



1) $H_2$, Pd/C, MeOH, 81%
2) BnBr, $Ag_2O$, DMF, 82%

3) PCC (5 eq), 4Å MS, DCM, 48hr, 62%

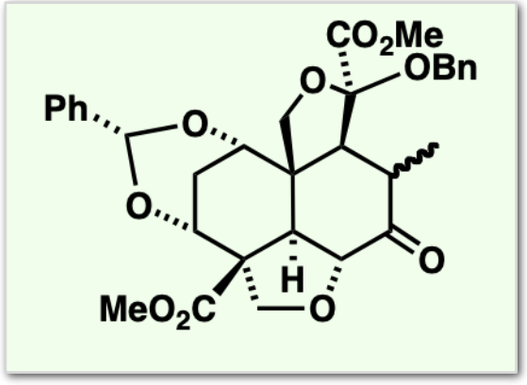



NaOMe, MeOH
O°C, then r.t., 24h
72%

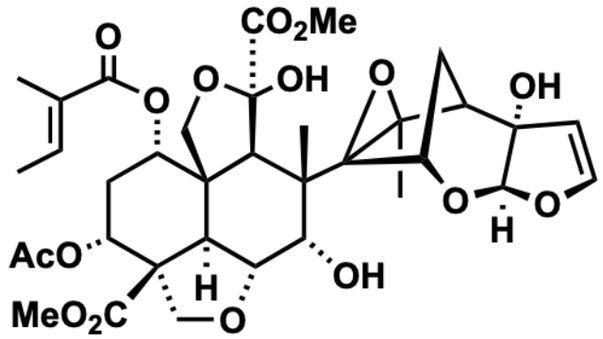


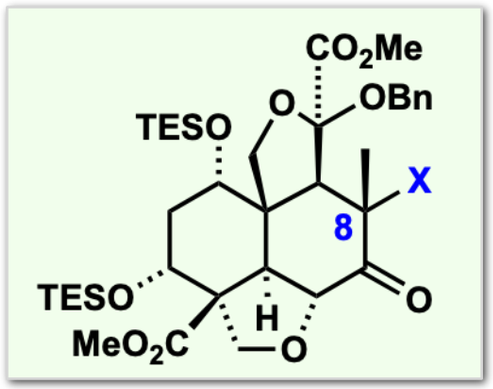

$PhCH(OMe)_2$, PPTS

91%

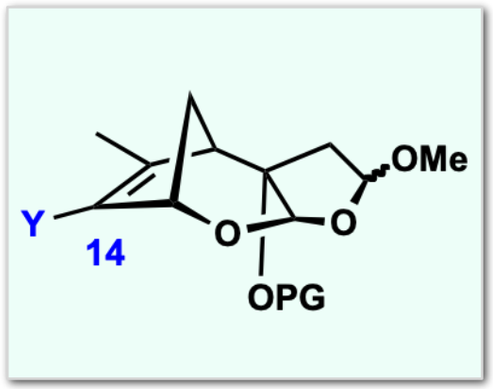


# *Azadirachtin – The Synthesis Plan*



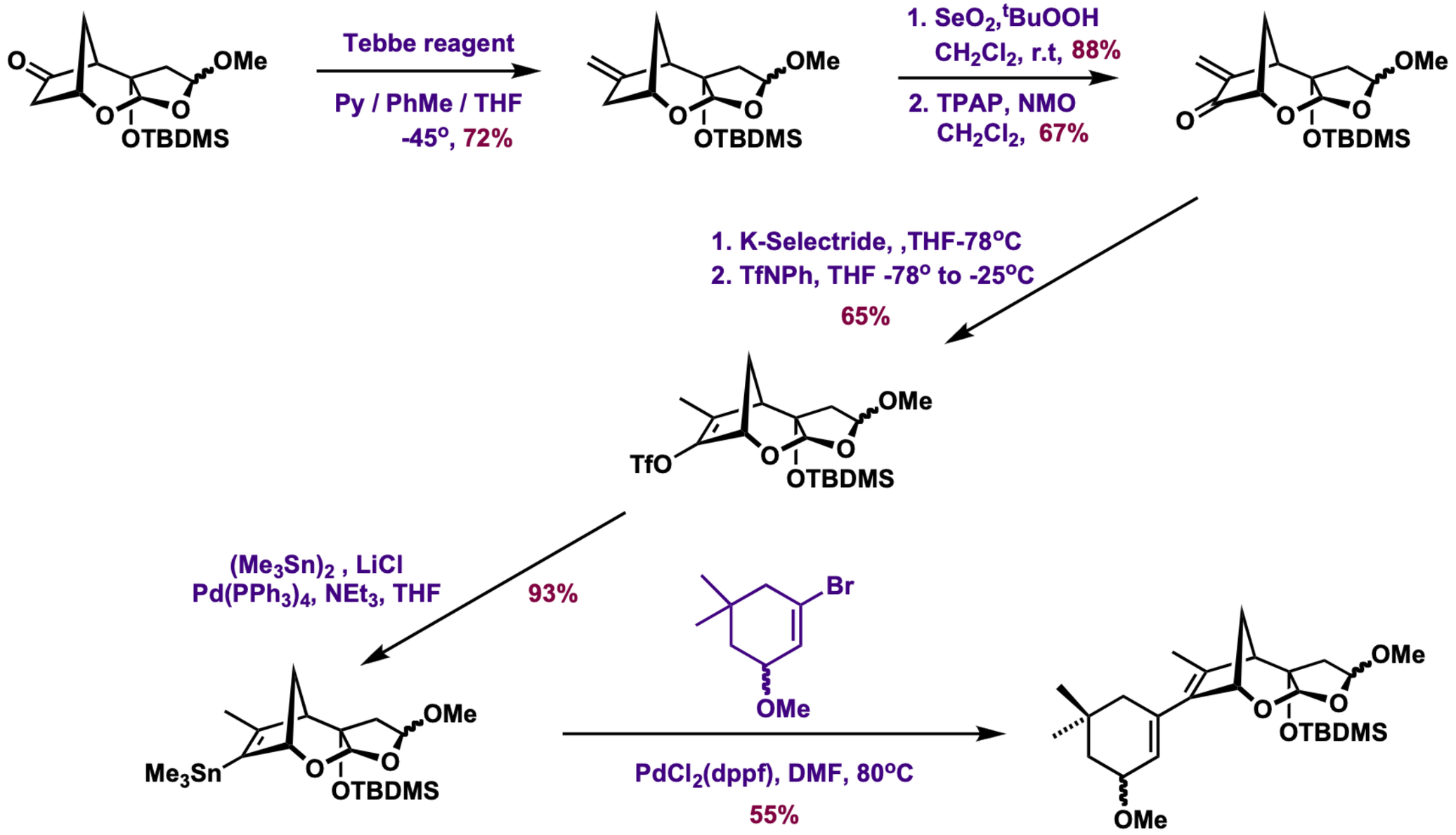




**Decalin fragment**

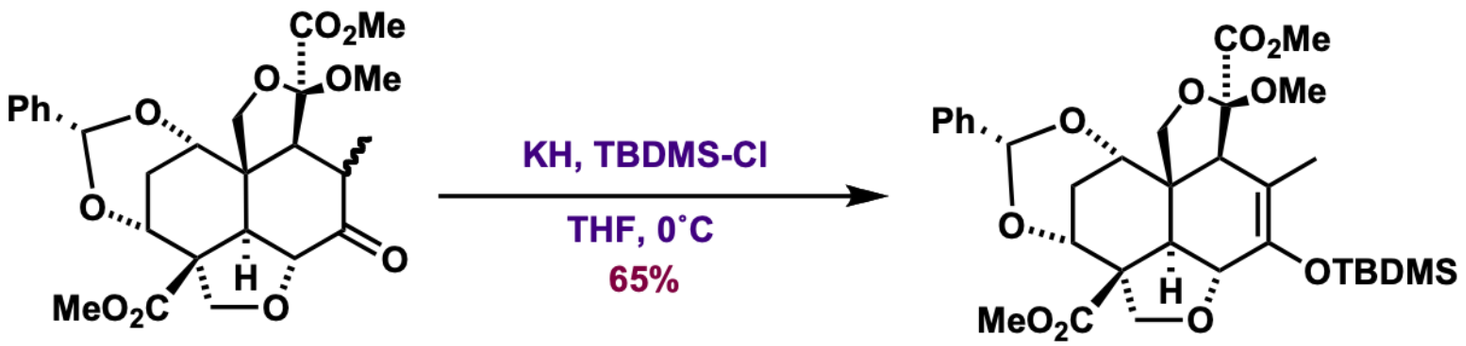



**Hydroxyfuranacetal fragment**

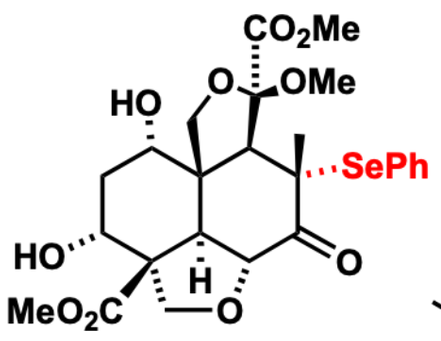
# *Azadirachtin – Acetal Coupling Plan*

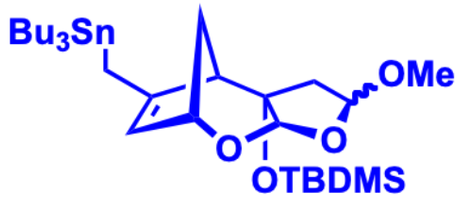


# *Azadirachtin – Radical Coupling at C8*



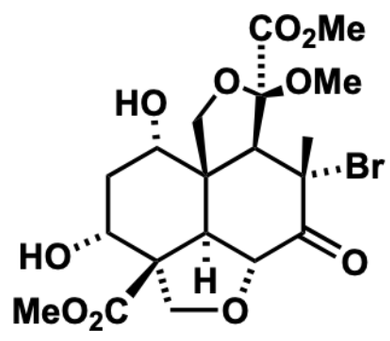

1. PhSeCl, $CH_2Cl_2$, -78˚C, 74%
2. PPTS, aq $CH_3CN$, 92%





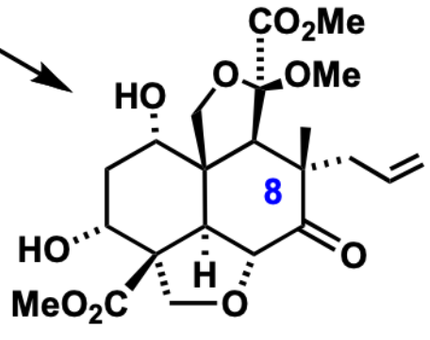
But the real system fails !

1. NBS, THF, -20˚C, 85%
2. PPTS, aq $CH_3CN$, 98%





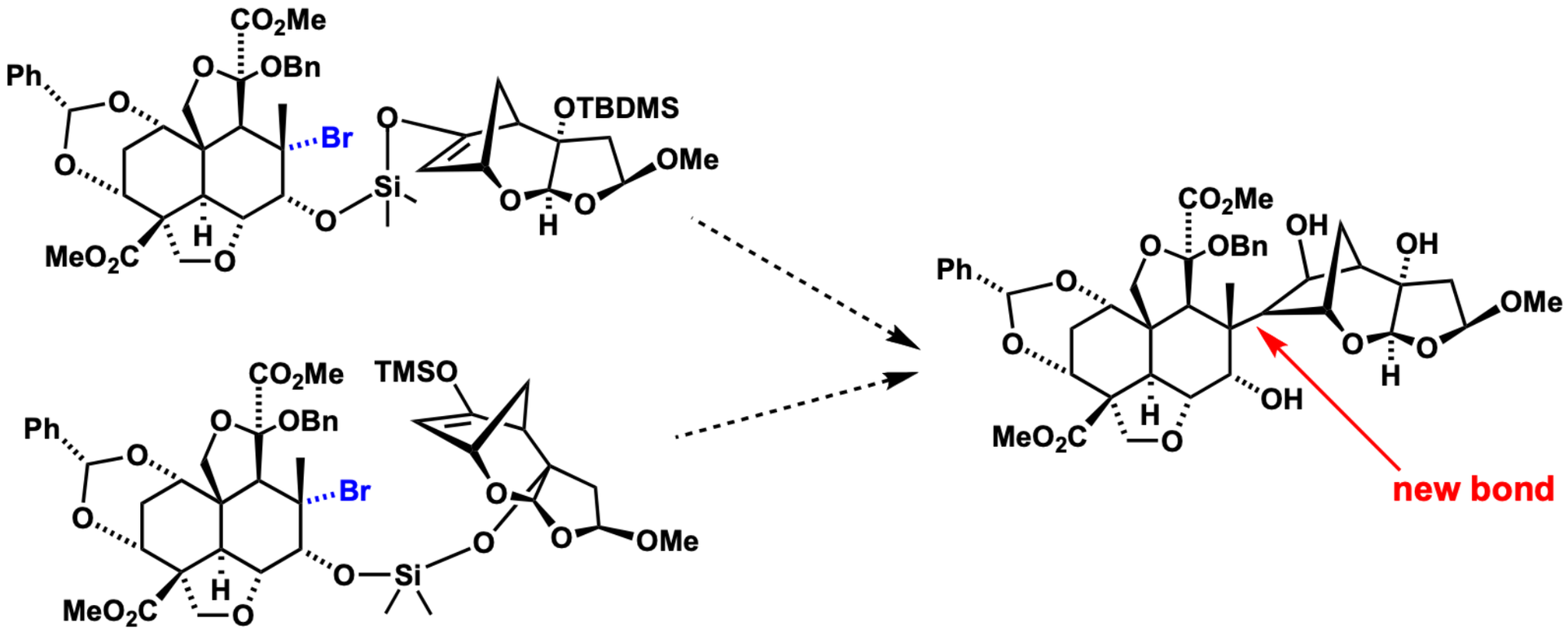
hv, benzene, 27%





hv, benzene, 70%

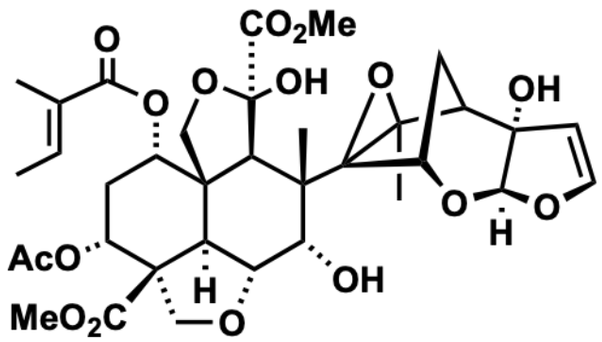
# *Azadirachtin – Radical Tether Route*

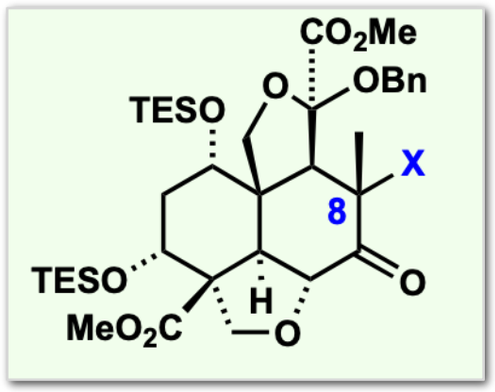



**A Model System**

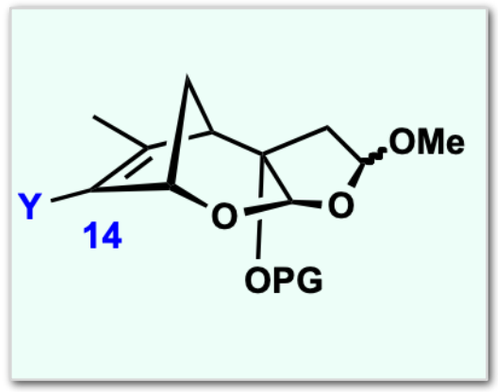


# *Azadirachtin – The Synthesis Plan*



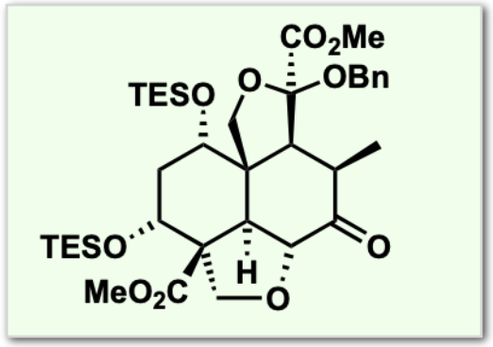

**Decalin fragment**



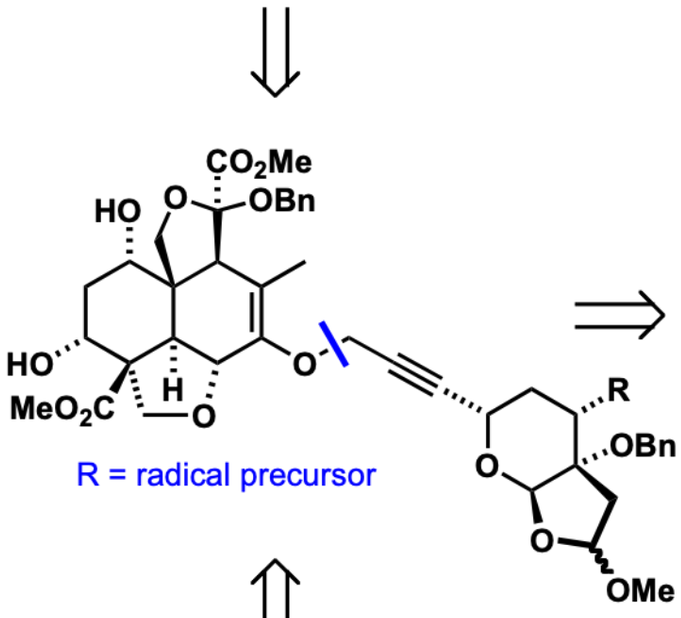

**Hydroxyfuranacetal fragment**

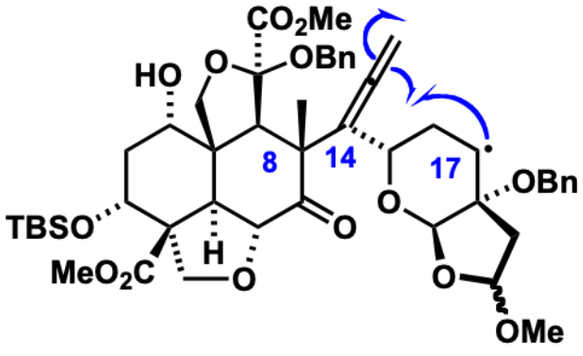
*All the couplings failed, we need a new plan*

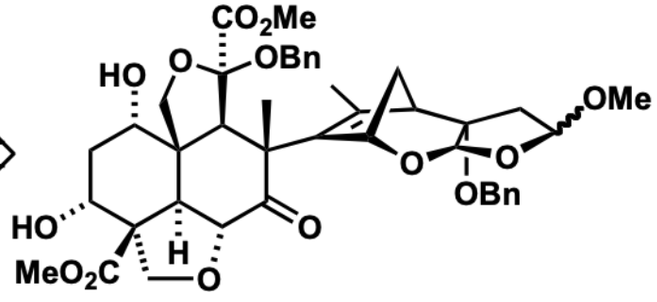
# *Azadirachtin – The New Synthesis Plan: The Claisen Radical Cyclisation Route*



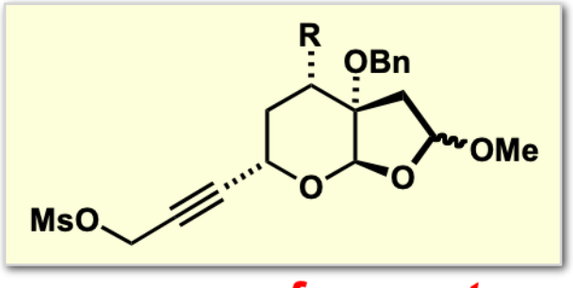

***decalin fragment***



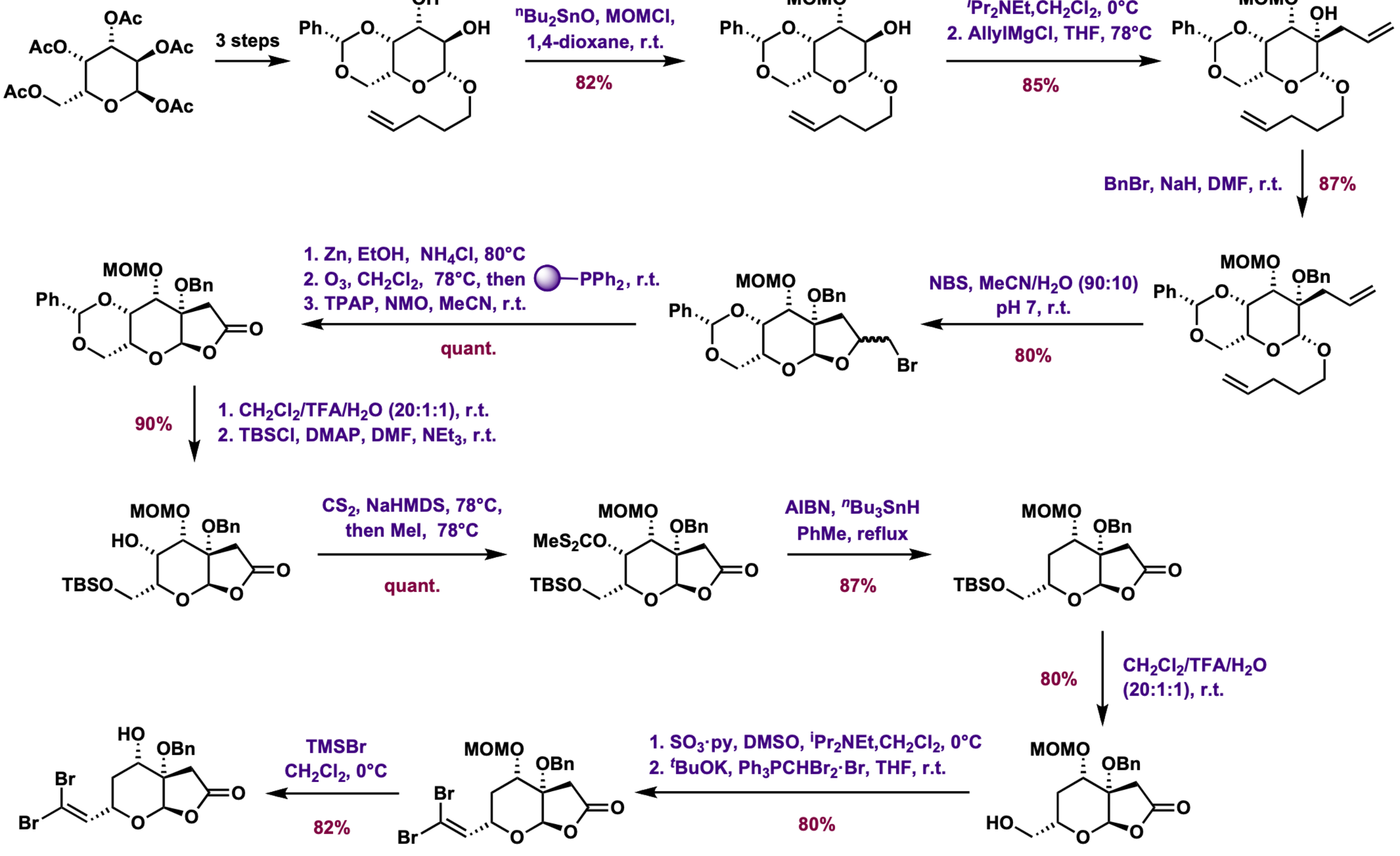




***azadirachtin***

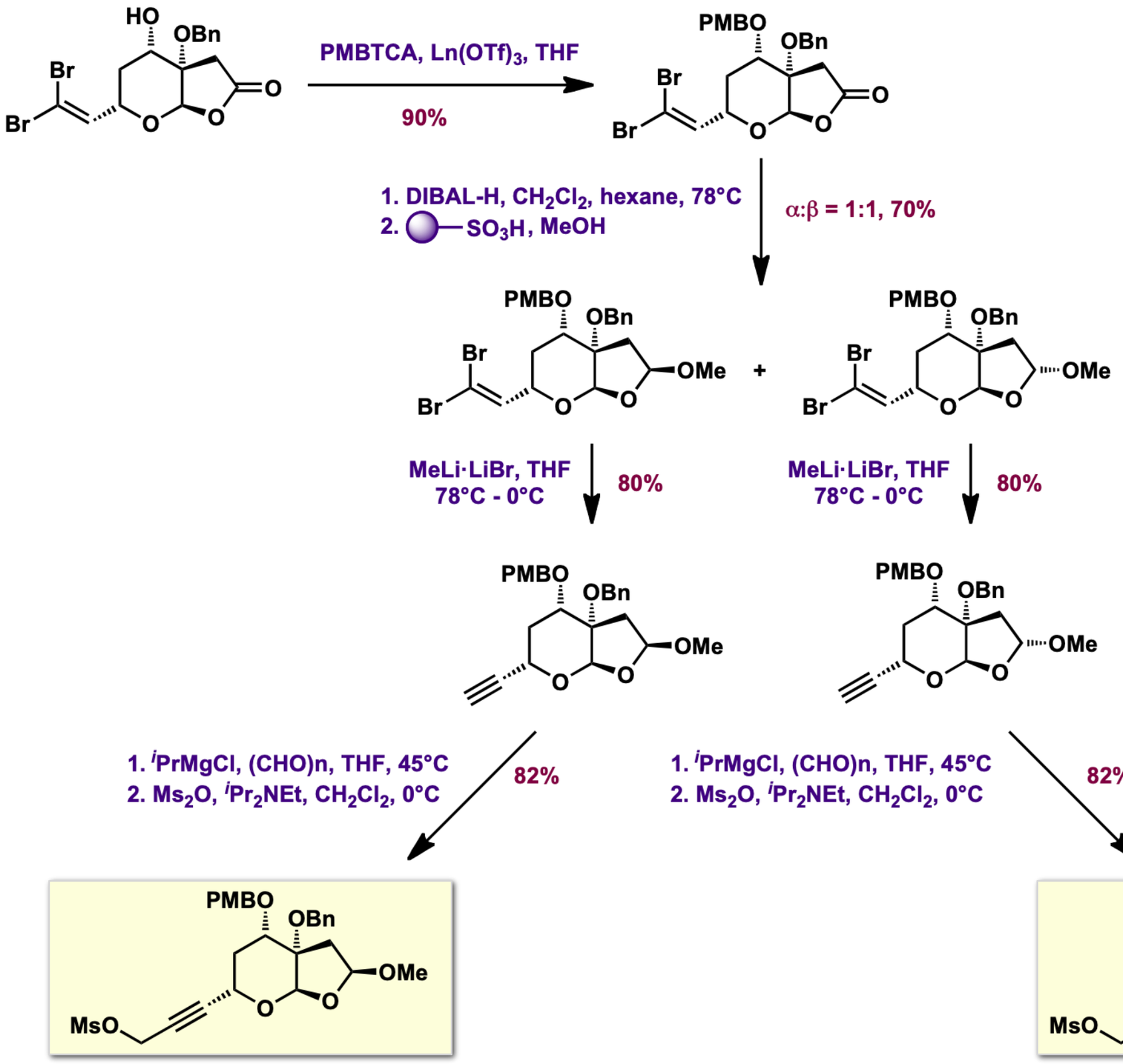



***pyran fragment***

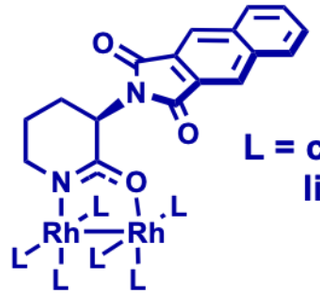
# *Azadirachtin – The Pyran Fragment*



# *Azadirachtin – The Pyran Fragment*

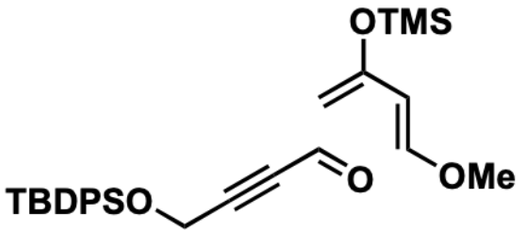


# *Azadirachtin – The Pyran Fragment*



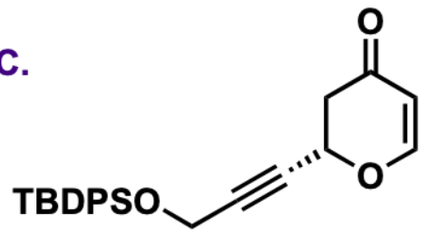
L = carboxamidate ligand

Hashimoto, Angew., Chem. Int. Ed., 43, 2004, 2665.



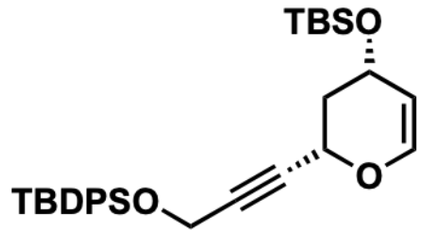
1% catalyst, $CH_2Cl_2$, -20 °C.

63%, 94% *ee*

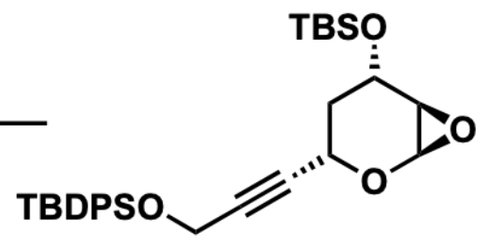


1. $NaBH_4$, $CeCl_3 \cdot 7H_2O$, $CH_2Cl_2$, -20 °C.
2. TBSCl, $CH_2Cl_2$, rt.

82%

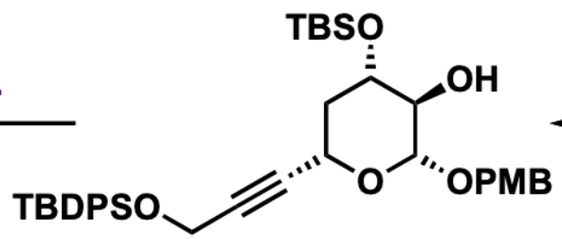


DMDO
acetone,
0 °C.

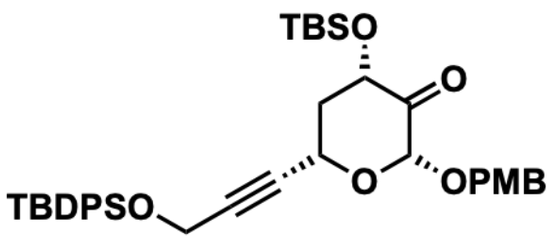


50 equiv. PMBOH,
$ZnCl_2$, $CH_2Cl_2$, rt.

86%

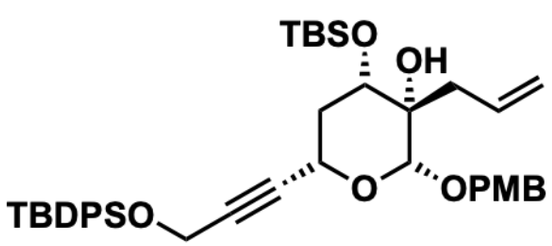


DMP, $CH_2Cl_2$, rt.



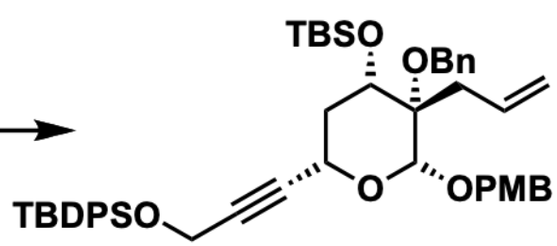
AllylMgBr,
$Et_2O$, THF,
-110 °C.

79%

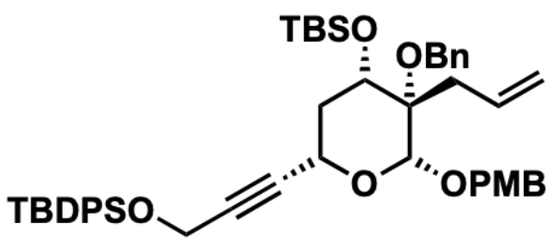


NaH, BnBr,
TBAI, DMF, rt.

87%

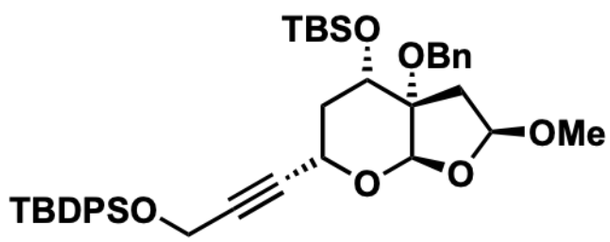


# *Azadirachtin – The Pyran Fragment*



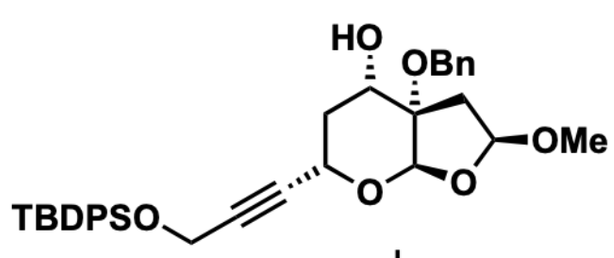

1. $O_3$, $CH_2Cl_2$, -78 °C, *then* $PPh_3$, rt.
2. TFA, $CH_2Cl_2$ (1:9), rt.
3. MeOH, MeCN, $SO_3H$ , 3Å MS, rt.

45%

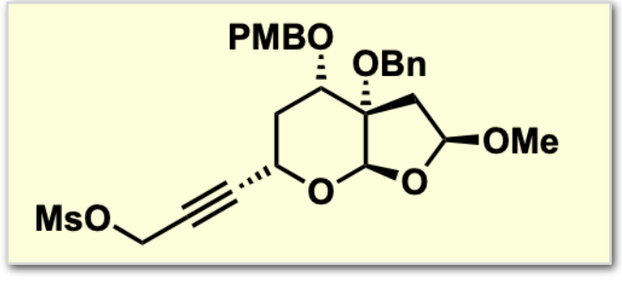



1. TBAF, THF, rt.
2. TBDPSCl, imid., $CH_2Cl_2$, rt.

87%

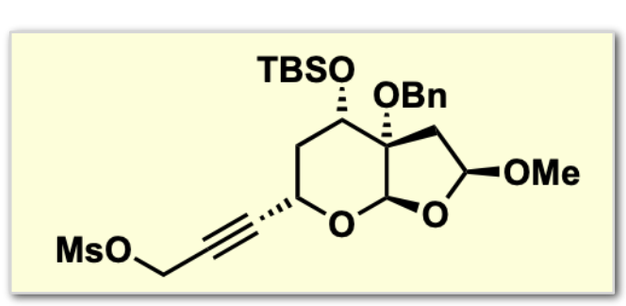



1. PMB-TCA, $Ln(OTf)_3$, THF (70%)
3. TBAF, THF, rt (82%)
3. $Ms_2O$, $^iPr_2NEt$, $CH_2Cl_2$, 0 °C (90%)



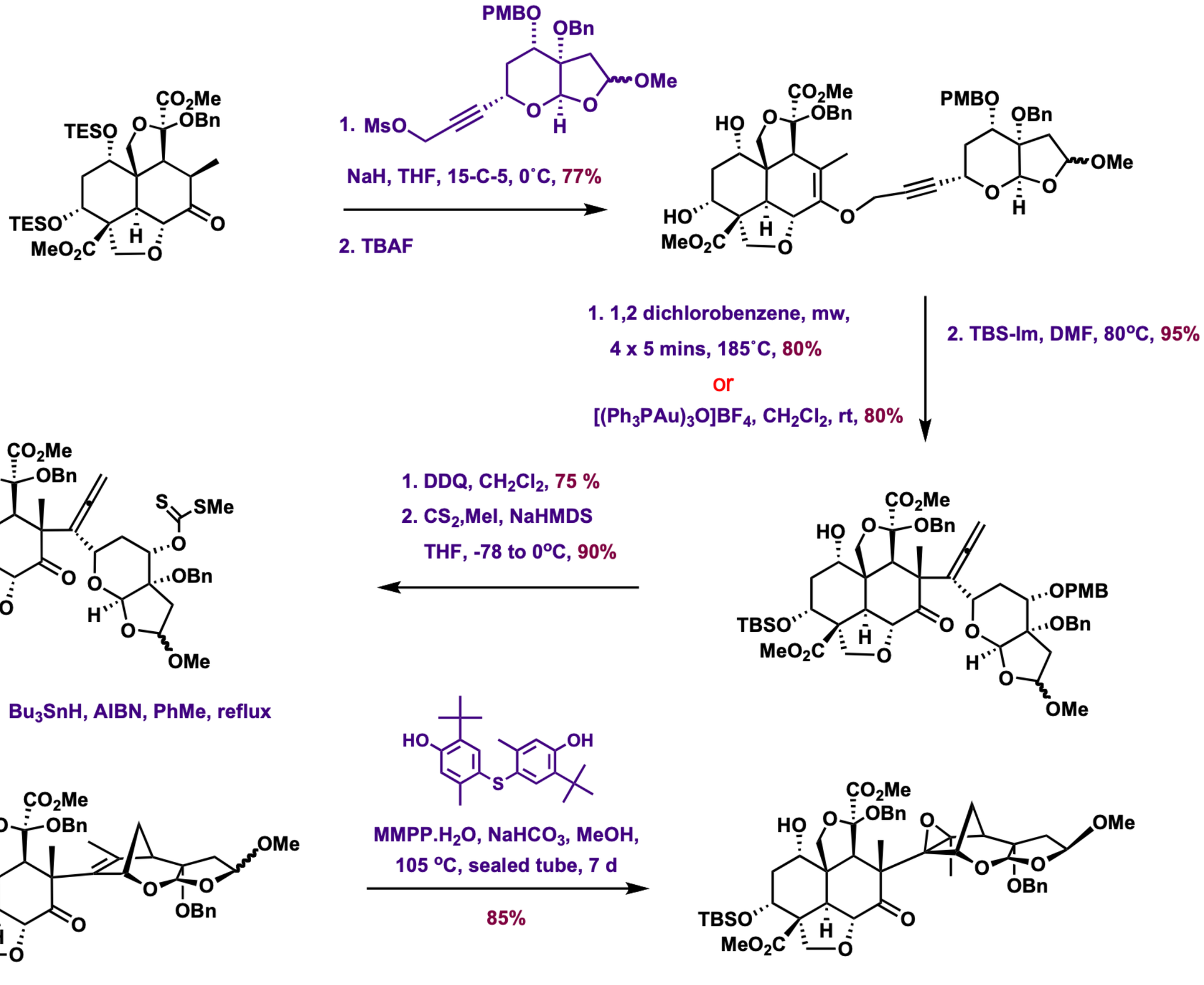

71%

1. TBAF, THF, rt.
2. $Ms_2O$, $^iPr_2NEt$, $CH_2Cl_2$, 0 °C.

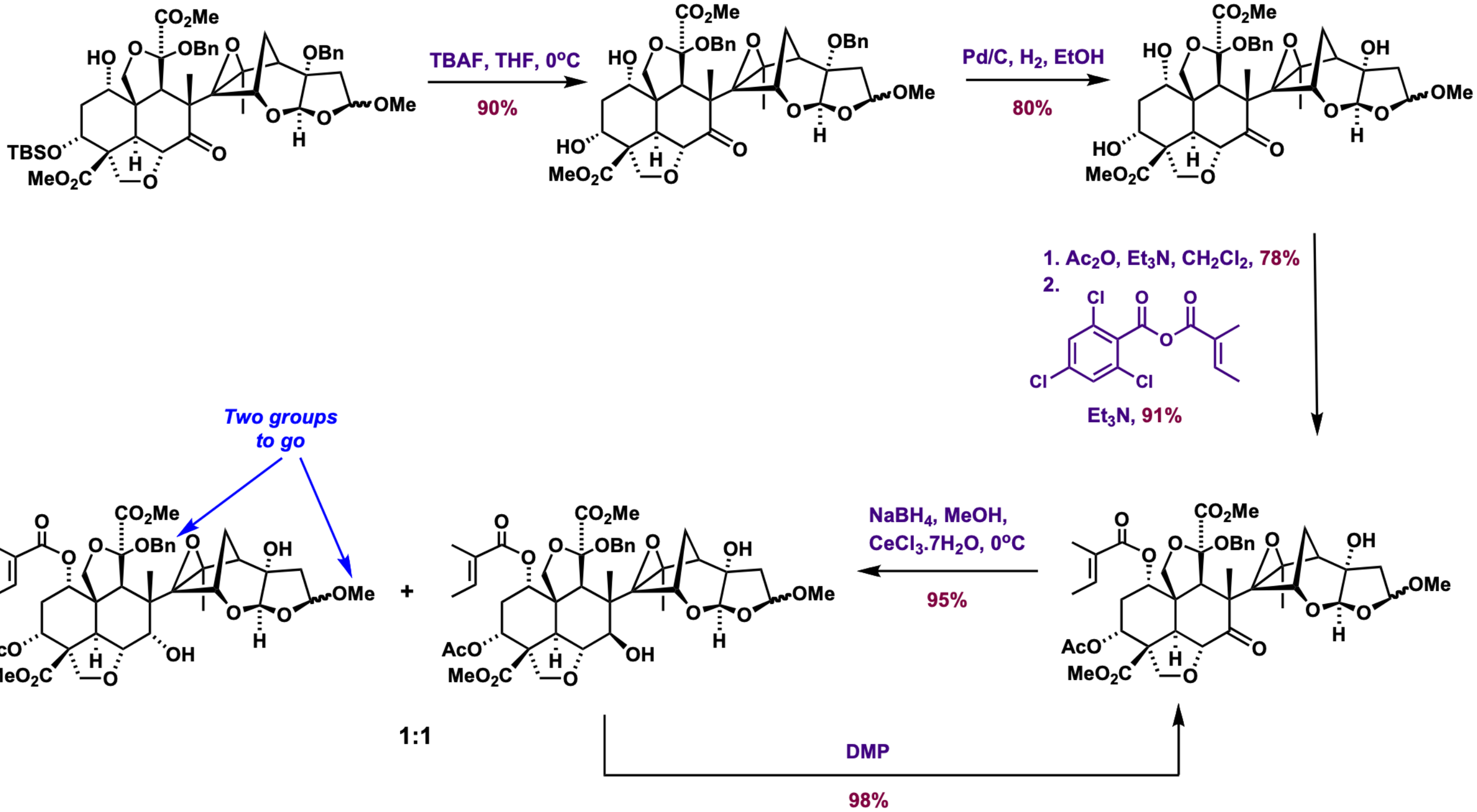



Previous route from galactose: 26 steps
New route: 15 steps

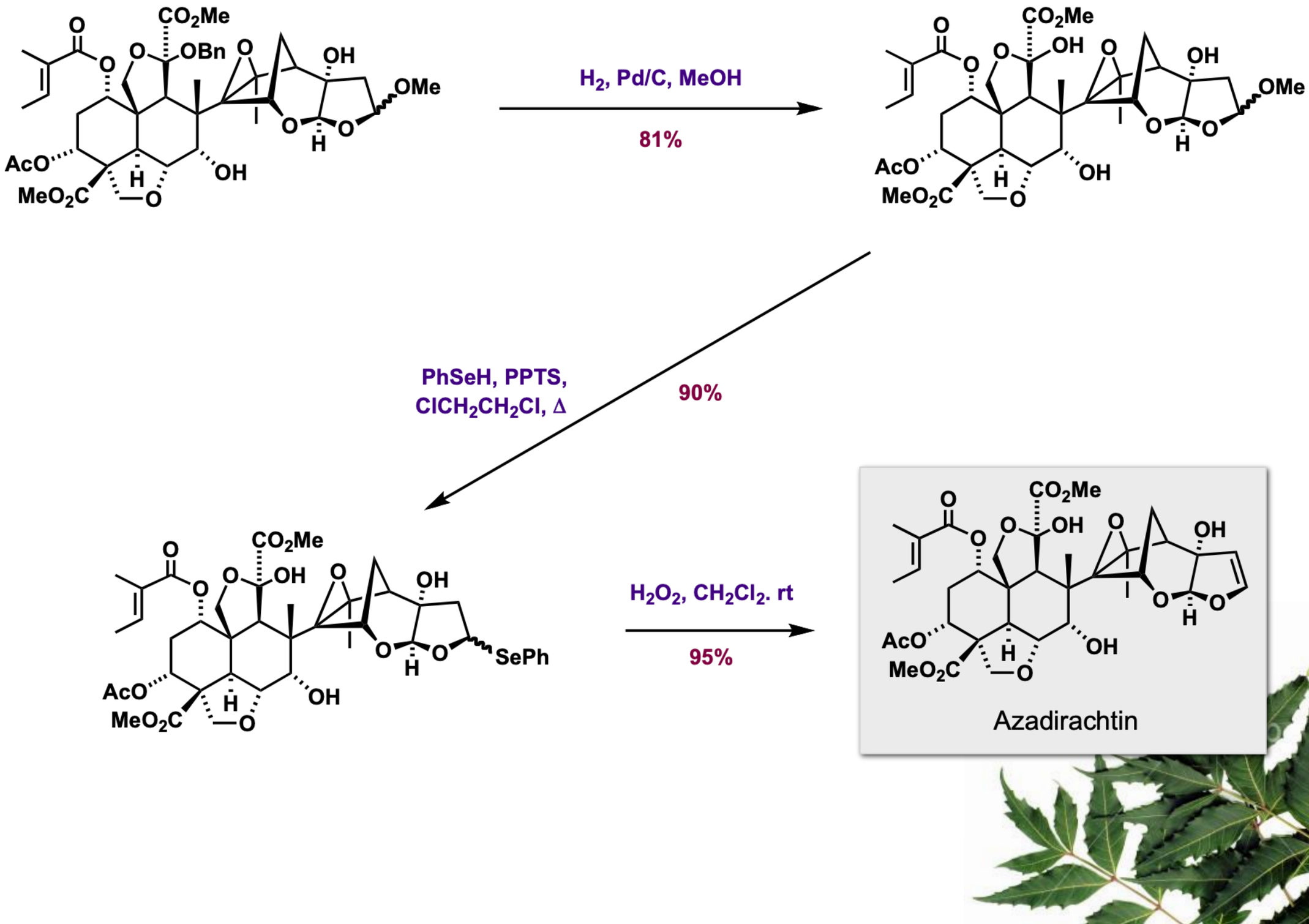
# *Azadirachtin – The New Route - Coupling and Claisen*



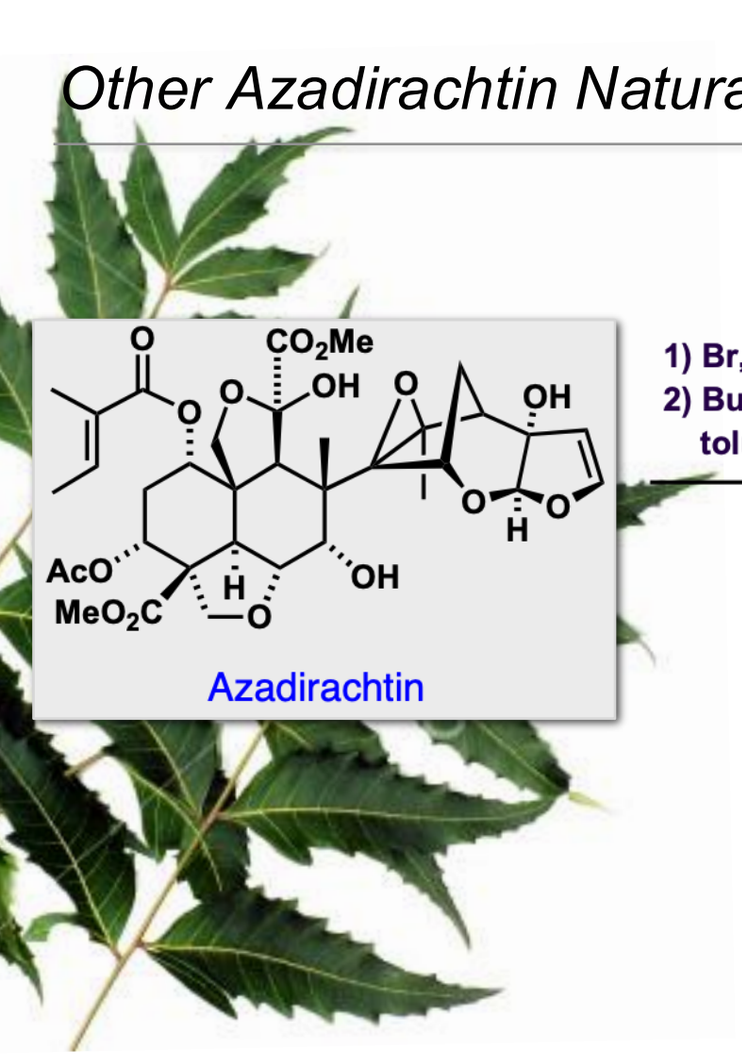
# *Azadirachtin – The Final Steps*



# *Azadirachtin – The Final Steps*



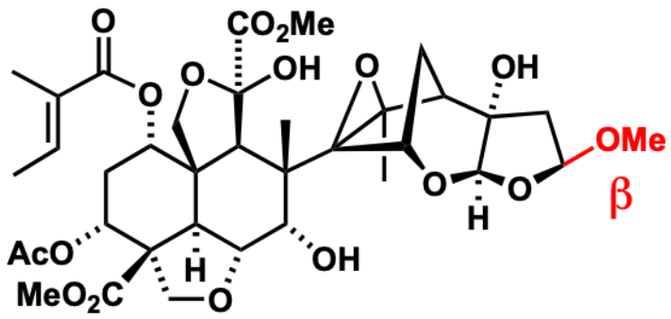
# *Other Azadirachtin Natural Products*





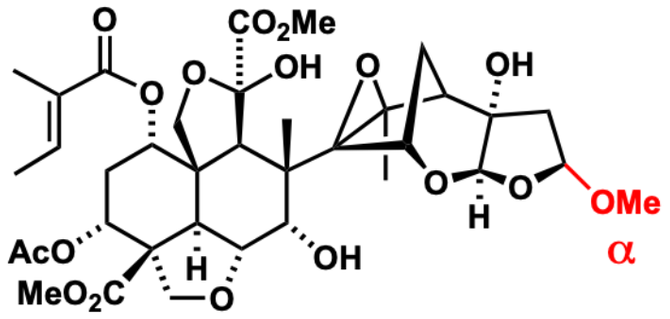
Azadirachtin

1) Br, MeOH, 83%
2) $Bu_3SnH$, AIBN, toluene, Δ 95%



Vepaol

\+

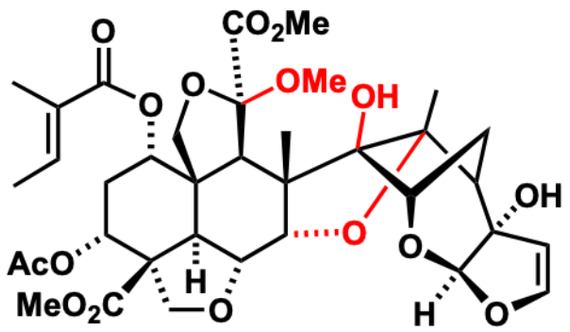


Iso-Vepaol

1) MeI, DMF, $Ag_2O$, 82%

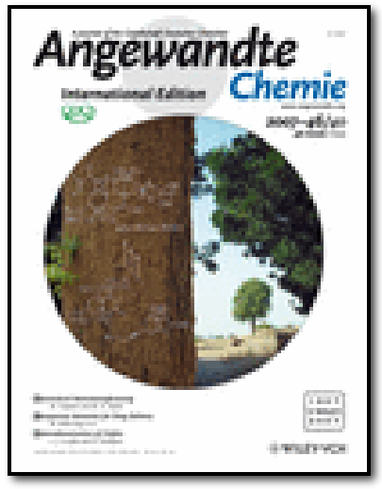
2) HSePh,  $SO_3H$, $CH_2Cl_2$, reflux, 94%

3) $H_2O_2$, $CH_2Cl_2$, rt, 1 min, 96%



Azadirachtinnin

*G.E.Veitch, A.Pinto, A.Boyer, E.Beckmann, J.C. Anderson, S.V. Ley. Org.Lett.*, **2008**,*10*, 569




# Synthesis of Azadirachtin: A Long but Successful Journey

Gemma E. Veitch, Dr Edith Beckmann, Dr Brenda J. Burke, Alistair Boyer, Sarah L. Maslen, Prof Steven V. Ley *

*Angew. Chemie, Int. Edn.*, **2007**, *46*, 7629 - 7632.

# A Relay Route for the Synthesis of Azadirachtin

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*Angew. Chemie, Int. Edn.*, **2007**, *46*, 7633 - 7635.

# The Azadirachtin Story

G. Veitch, A. Boyer and S.V. Ley.

*Angew. Chem. Int. Ed*. **2008**, *47*, 9402-9429.

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*Chem. Eur. J.,* **2008**, *14*, 10683-10704.

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