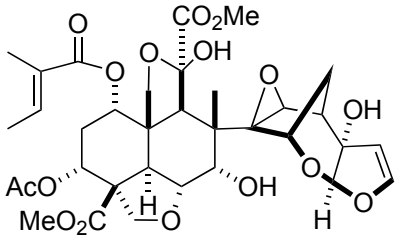
Studies toward the Synthesis of Azadirachtin: Total Synthesis of a Fully Functionalized ABC Framework and Coupling with a Norbornene Domain

Nicolaou and Co-workers

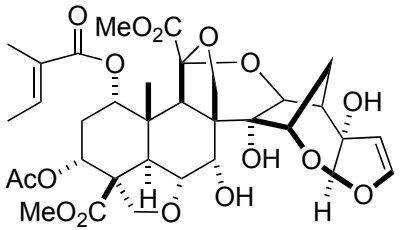
Angew. Chem. Int. Ed. **2005**, *44*, 3443



Azadirachtin: Structural Mystery for 20 years

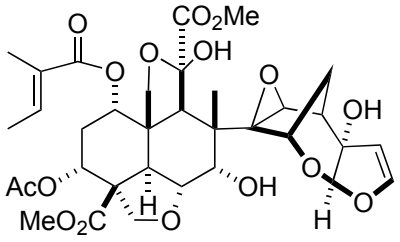
-Isolated in 1968 from Azadirachta indica, the indian Neem tree, with no structure proposed.

-Controversial structure proposed in 1975 by Nakanishi.



1975 Structure

-In 1987, Kraus and Co-workers published the accepted structure.



Revised Structure

16 contiguous chiral centers

7 tetrasubstitued carbons

7 rings

Extremely dense oxygenation

-Azadirachtin is a potent insect anti-feedant, as well as growth inhibitor.

-It is non-toxic, biodegradable, and "natural", and therefore an attractive pesticide.

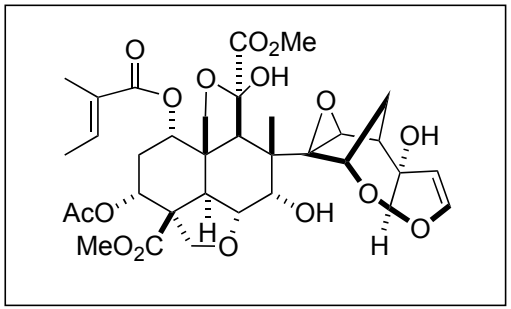
-Azadirachtin is unstable to mild acidic, basic and photolytic conditions.

-Its biological mode of action is unknown.

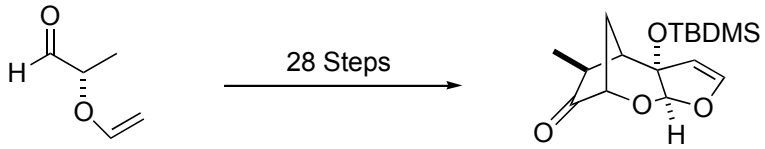
-Given is limited availability, simpler analogs are often targeted in hopes of maintaing effectiveness in the field.
-Several groups have investigated its total synthesis.

J. Chem. Soc. Chem. Commun. **1968**, 23.
J. Am. Chem. Soc. **1975**, *97*, 1975.
Tetrahedron 1987, 43, 2779

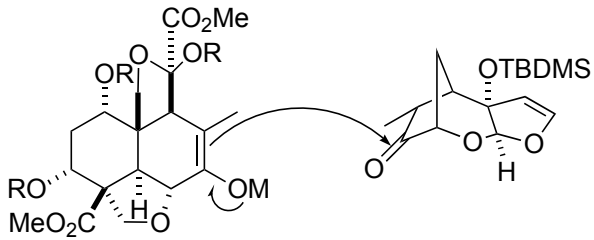
Some Other Approaches to Azadirachtin



Shibasaki and Co-workers



3 steps from (-)-ethyl lactate

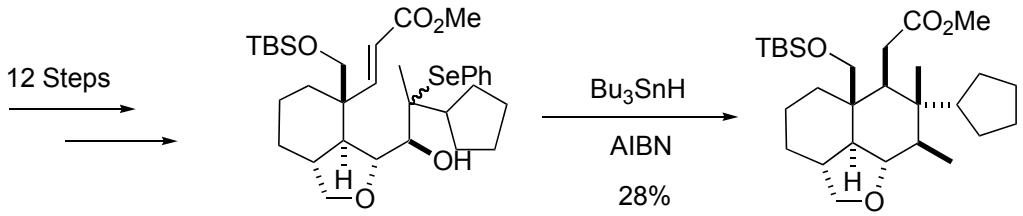


[O]

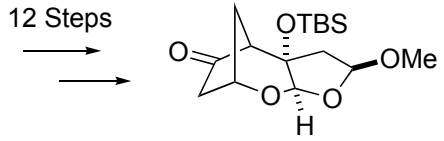
(-)-Azadirachtin

J. Org. Chem. **1989**, *54*, 3354

Mori and Co-workers



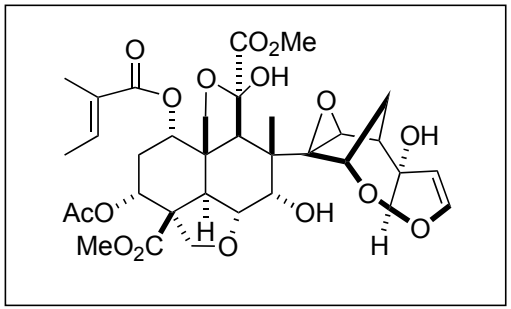
Tetrahedron Lett. **1997**, *38*, 4429

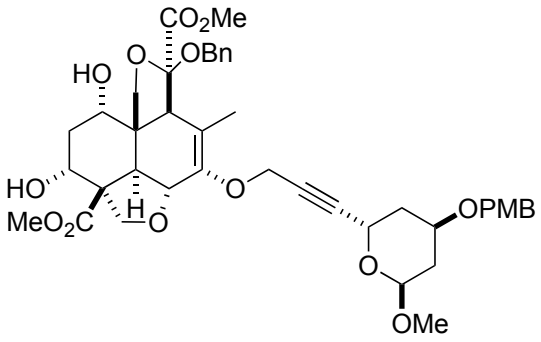


Tetrahedron **1996**, *52*, 13939

Claisen-Radical Cyclization Approach

Ley and Co-workers



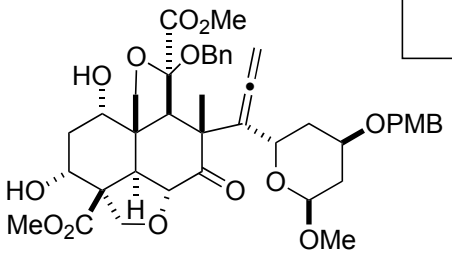


MWI (15 x 1 min)

o-DCB

180 °C

88%

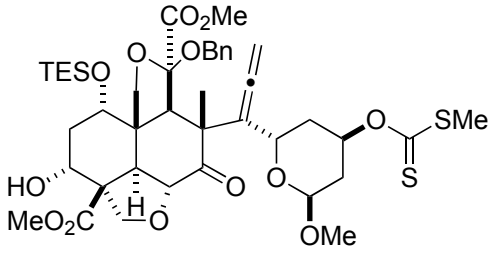


-All Lewis acid catalysis failed.

1) TESOTf

2) DDQ

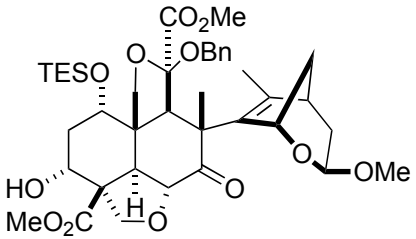
3) NaH, CS_2, MeI

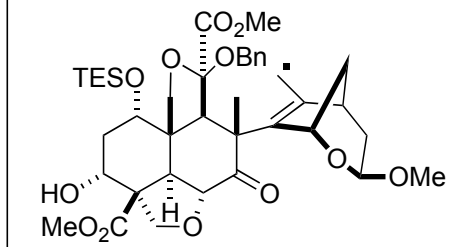


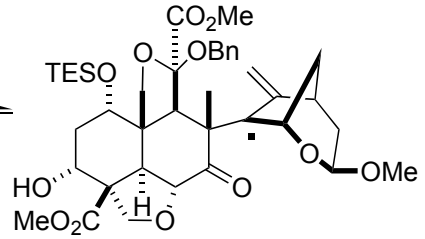
Bu_3SnH

AIBN

81%



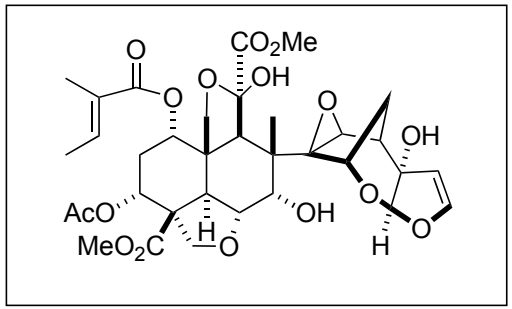




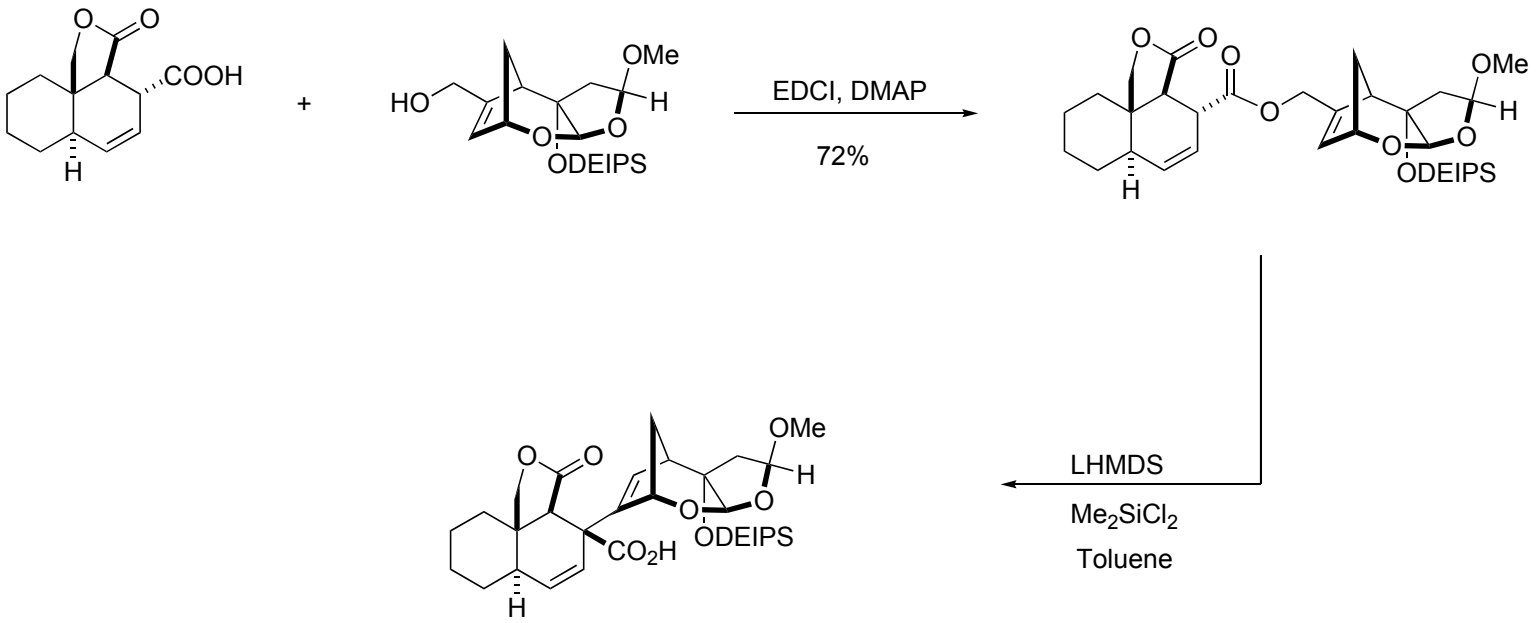
Sterically Unprotonatable?

Org. Lett. **2002**, *4*, 3847

An Ireland-Claisen Approach



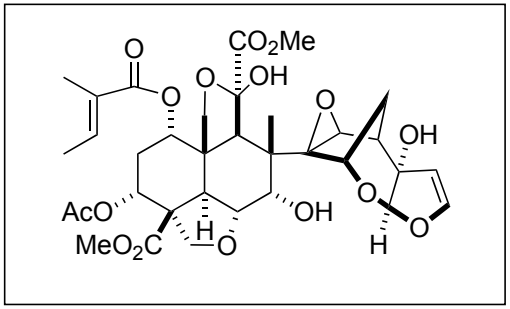
Murai and Co-workers

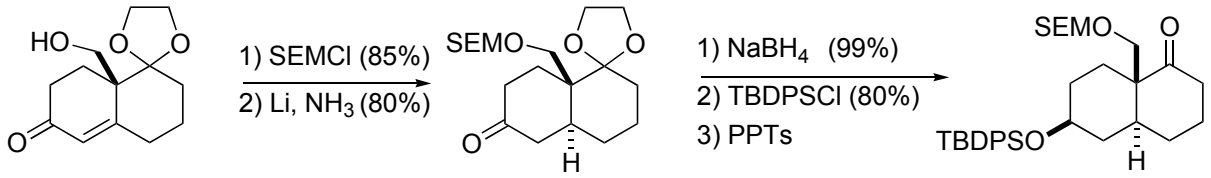


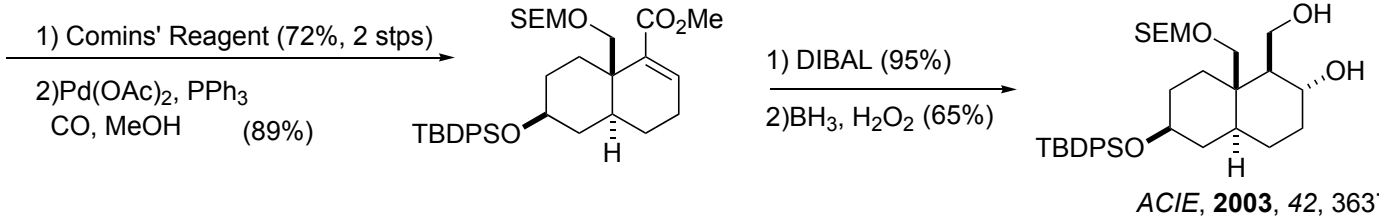
Org. Lett. **2002**, *4*, 2877

-System lacks functionalization on decalin system.

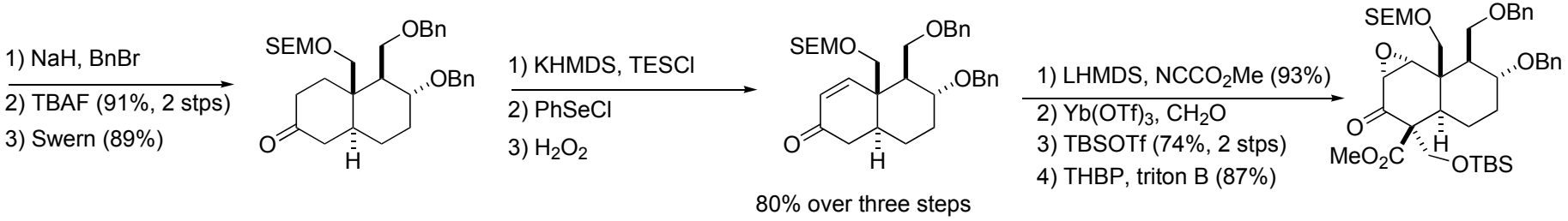
Construction of the decalin system: Installation of dense oxygenation





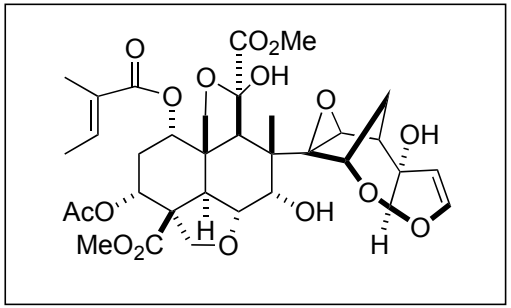


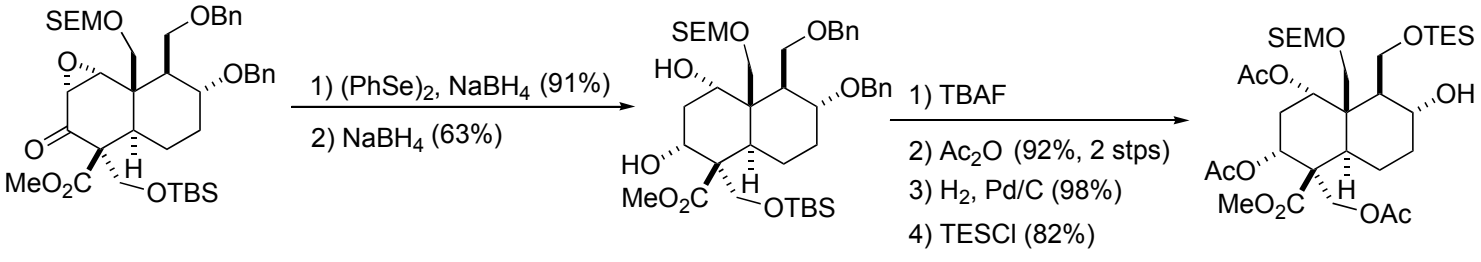
ACIE, **2003**, *42*, 3637

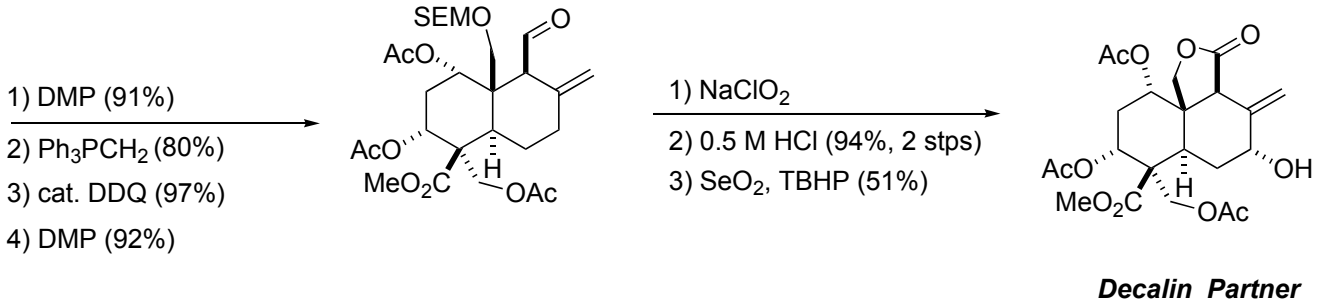


80% over three steps

Final manipulation of the decalin system

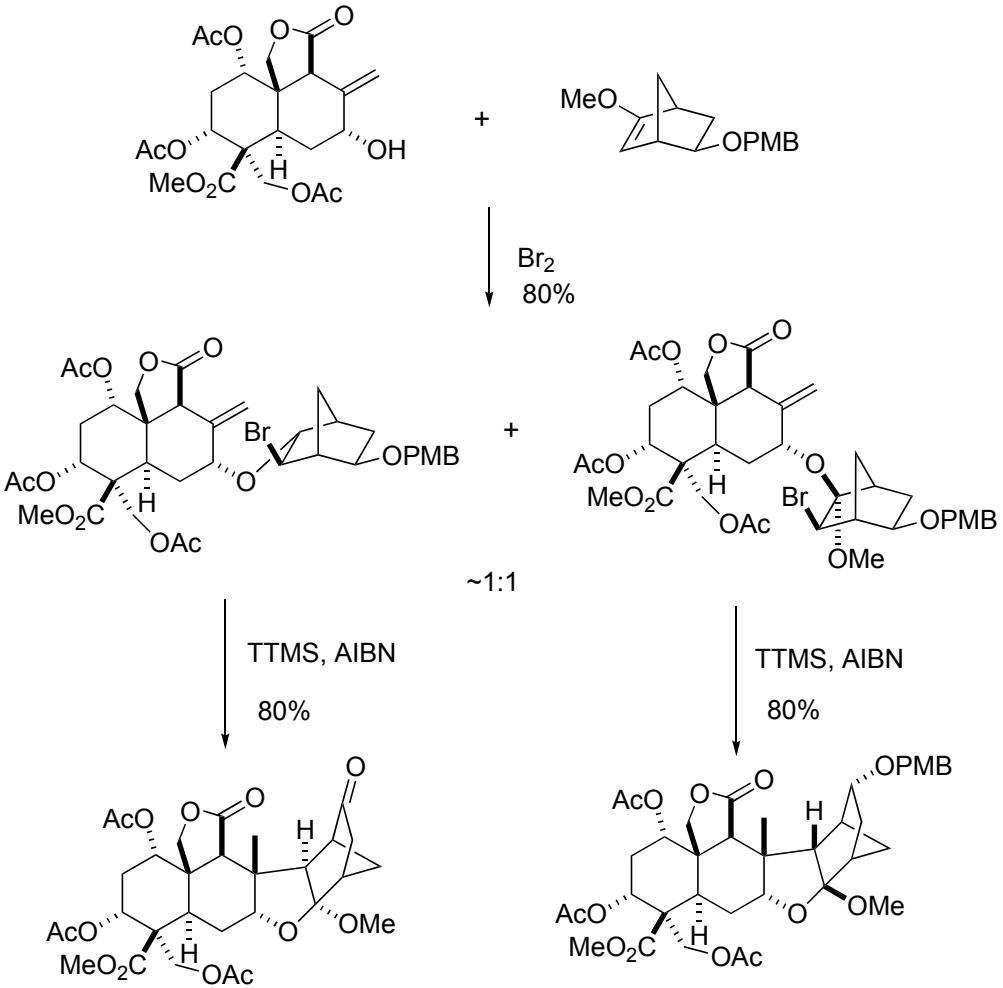






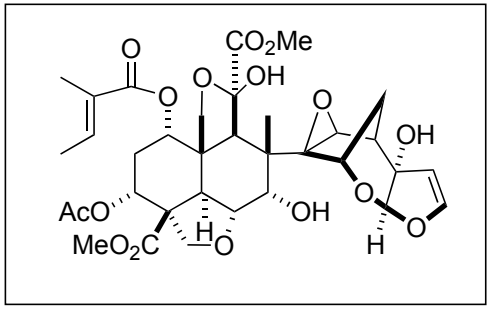
Decalin Partner

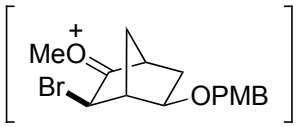
Temporary Linkage and Radical Cyclization



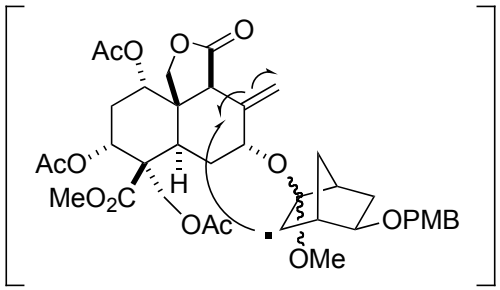
5-*exo*-trig cyclization followed by 1,5-H shift and PMB loss

5-*exo*-trig cyclization followed by intermolecular quench





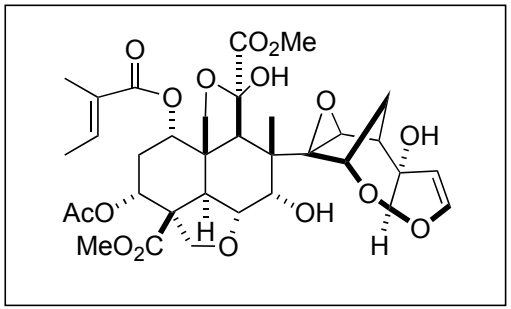
Oxonium Intermediate

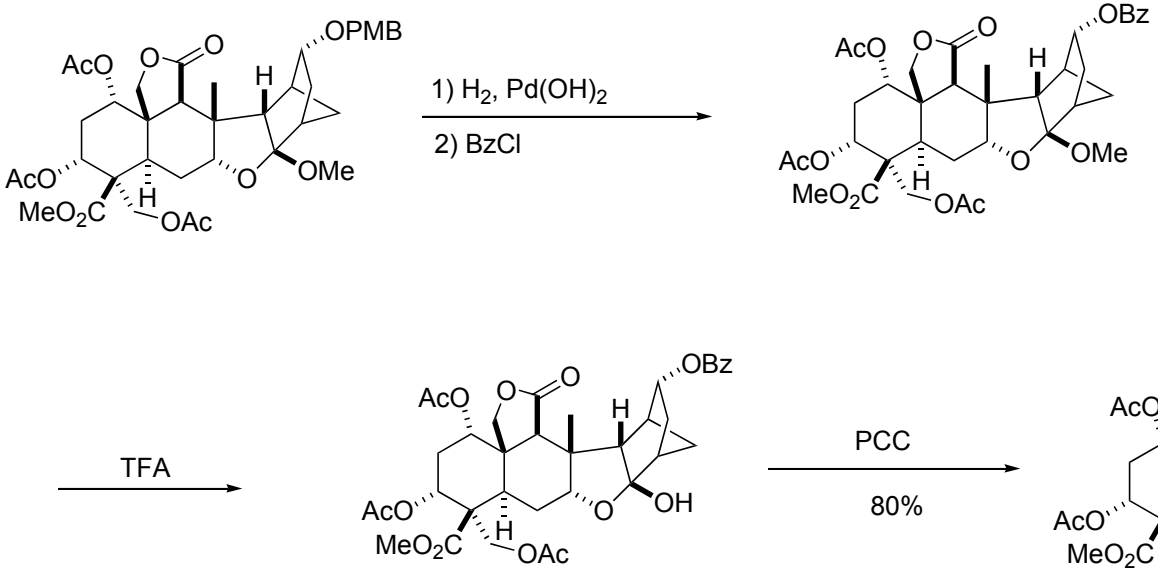


Radical Cyclization Pathway

-Cyclization extremely substrate dependant!

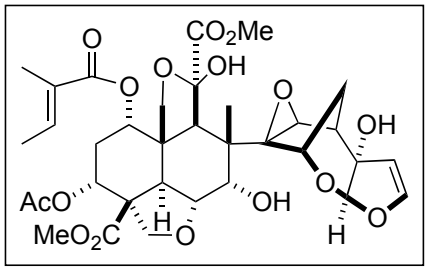
Towards Azadirachtin: Oxidative opening of the Acetal Linkage





75% over three steps

Conclusions

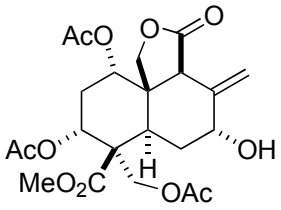


-A fully oxygenated decalin system was prepared and coupled to a model bicycle.

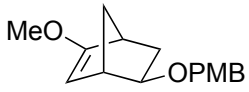
-Radical cyclization and subsequent cleavage of the oxo-linkage provides high-yielding access to the sterically congested C8-C14 bond of Azadirachtin.

-Bicycle lacks functionalization

-Route to decalin partner is 32+ steps, often falling into protecting group traps, a consequence of the dense oxygenation.



Decalin Partner



Model Bicycle