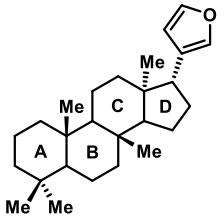
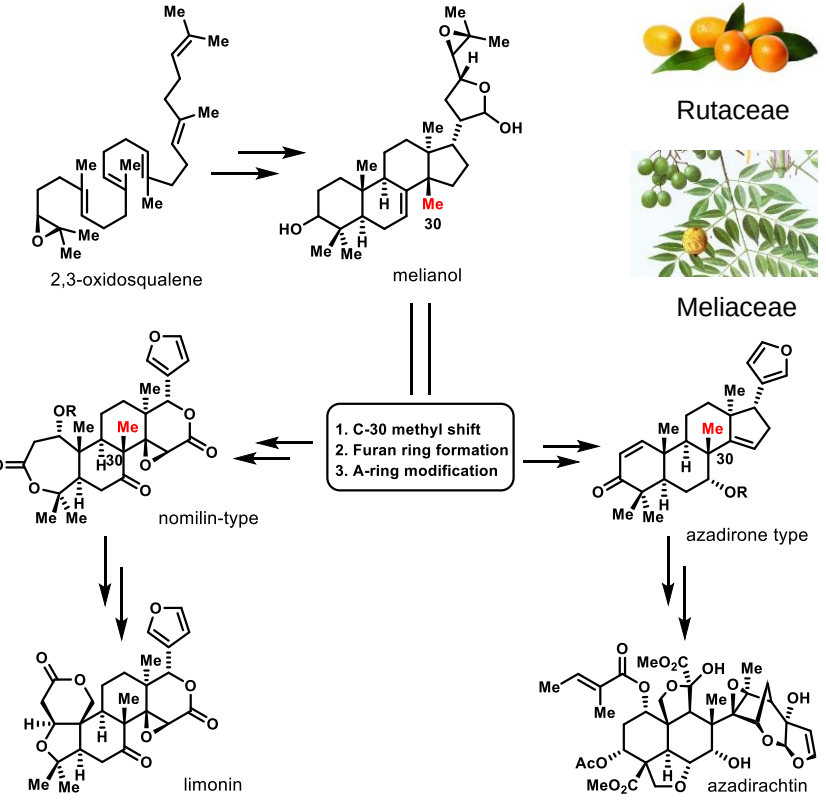


basic limonoid skeleton

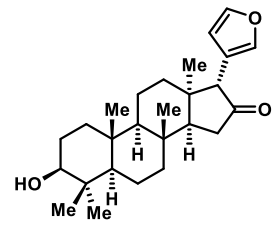
Limonoid famliy feature

- the most impressive symbol sturcture is the furan ring
- classfied by completion of A/B/C/D Rrings if one of these rings fractured is called "X ring-*seco* type limonoid"
- majorly found in *Meliaceae* and *Rutaceae*
- nearly 2500 limonoids with over 35 unique carbon frameworks have been observed

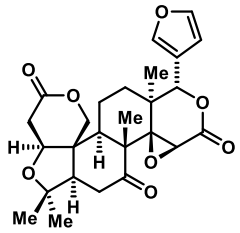
Proposed biosynthetic pathway



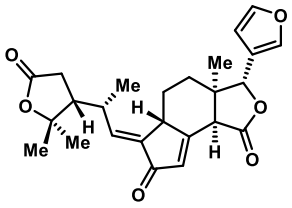
Presentative total synthesis works of the limonoid family



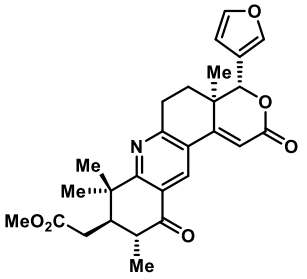
Protolimonoid
intact



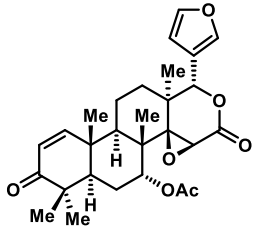
Limonin
A/D *seco*



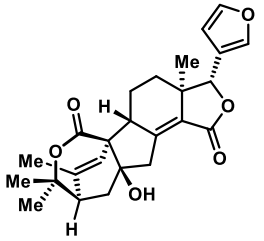
Perforanoid A
A/B *seco*



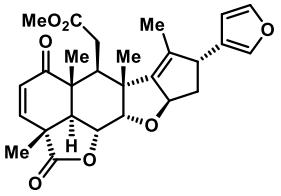
Xylogranatopyridine
B/D *seco*



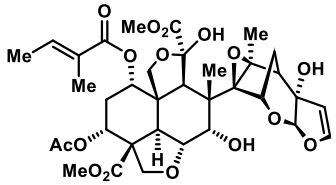
Gedunin
D *seco*



Haperforin G
A/B/D *seco*

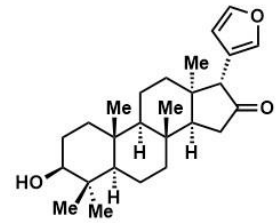


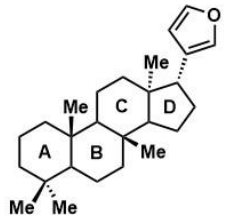
Nimbolide
C *seco*



Azadirachitin
C *seco*

I. Protolimonoid





four intact rings type 4,4,8-trimethyl-17-furyl-13α-androstane

Structure feature

- tetranortriterpenoid family
- preplex chiral centers
- relatively low oxidation state compared to other limonoids

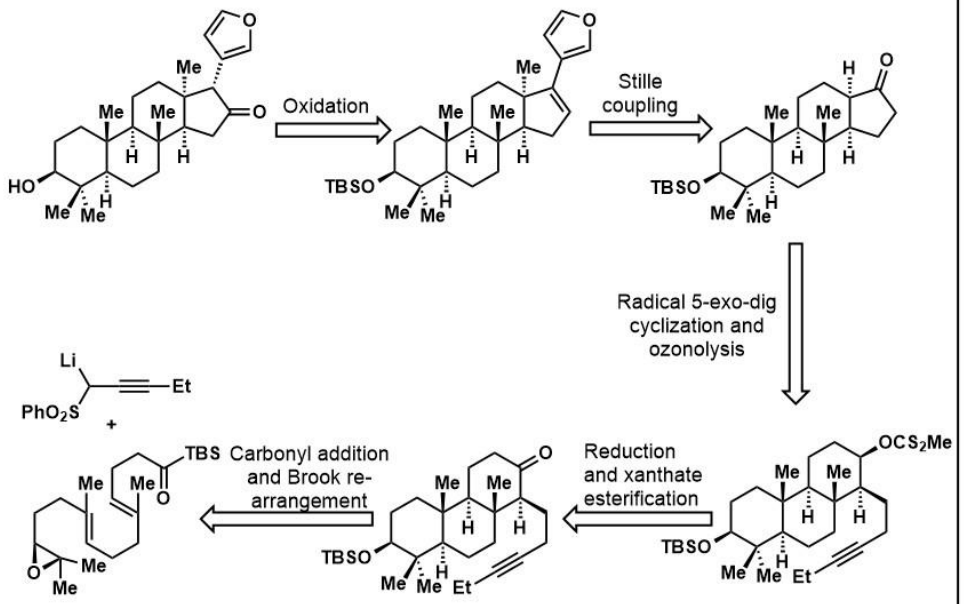
Main issues

- 7 consecutive chiral centers
- easily oxidizable furan ring

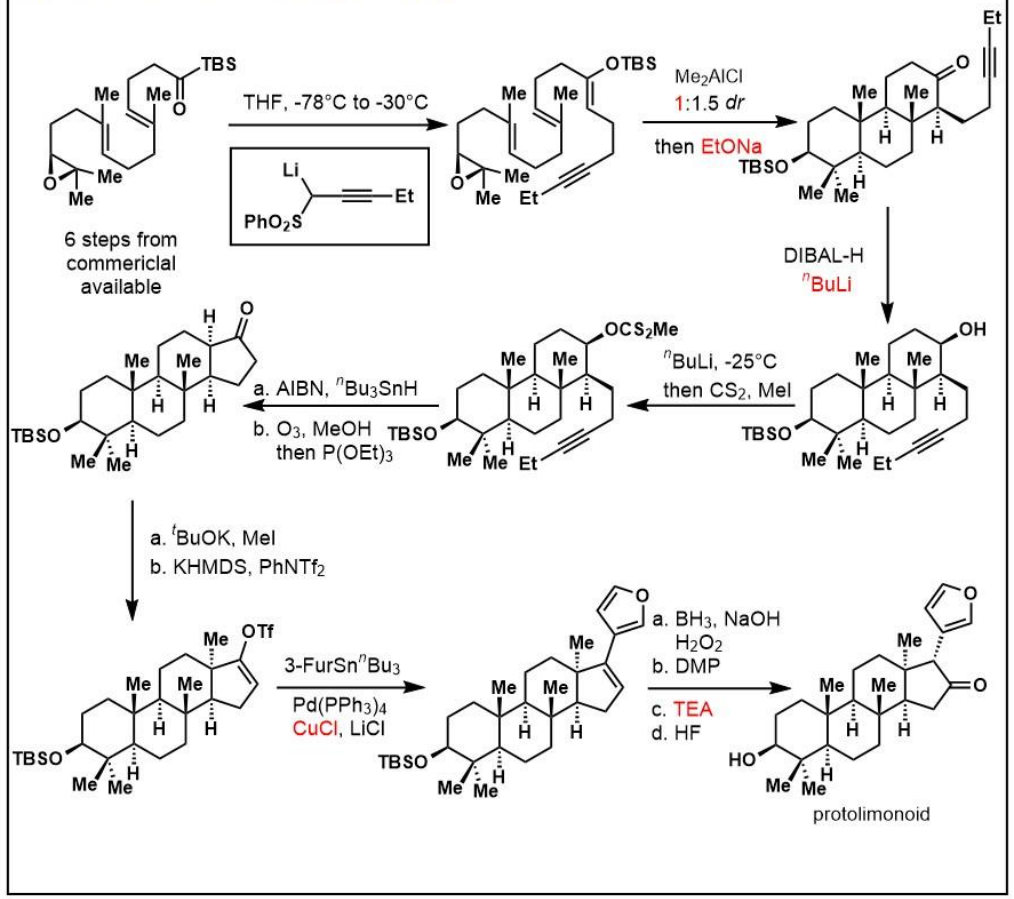
Main strategy

- cationic triple annulation
- radical ring closure
- bimetallic coupling

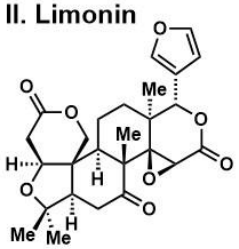
Retrosynthetic analysis

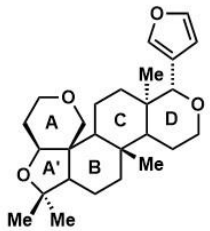


Synthesis of Protoliminoid (20 steps)



II. Limonin



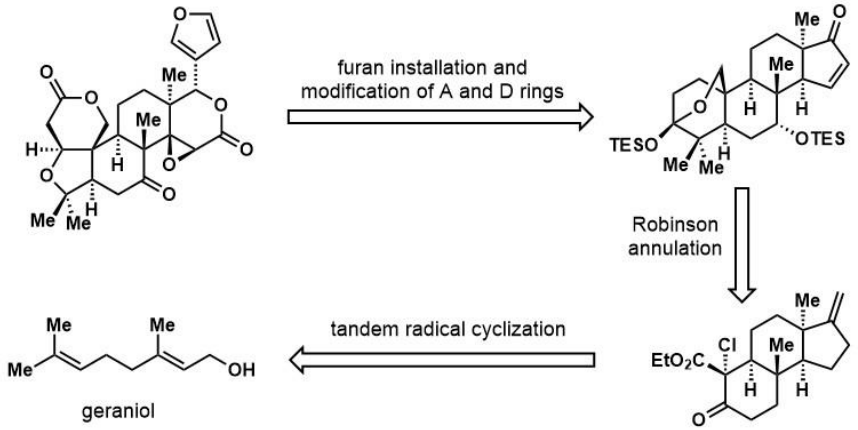


A/D rings seco type limonoid

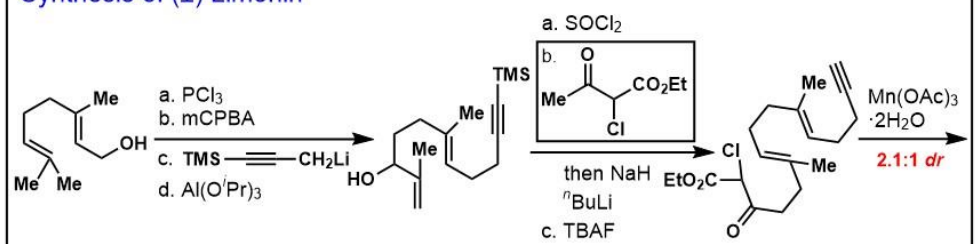
Structure feature

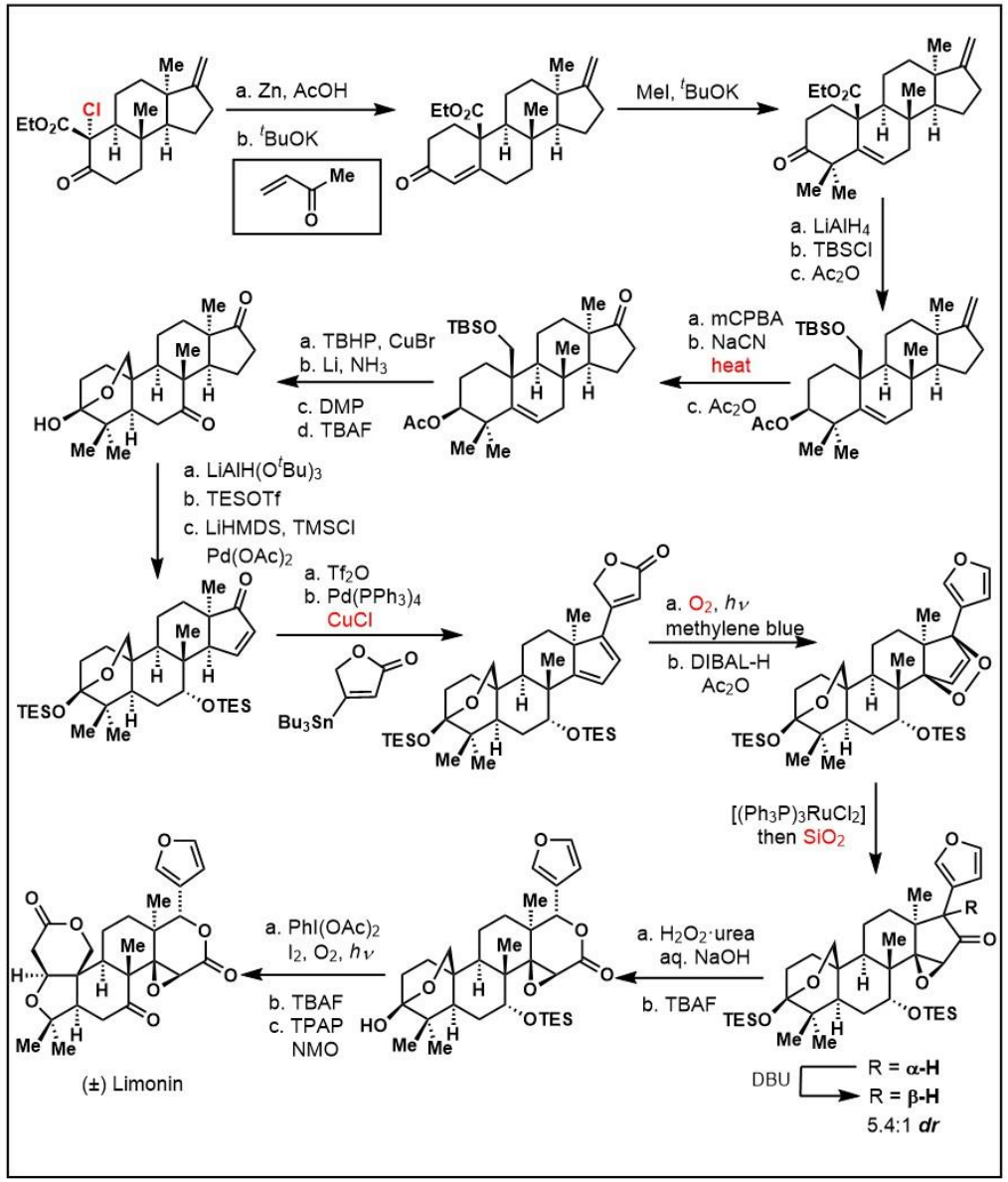
- **flagship congener** in the tetranortriterpenoid family
- preplex chiral centers
- relatively **high** oxidation state

Retrosynthetic analysis

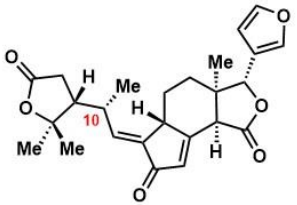


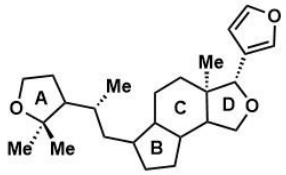
Synthesis of (±) Limonin





III. Perforanoid A





A/B/D rings seco type limonoid

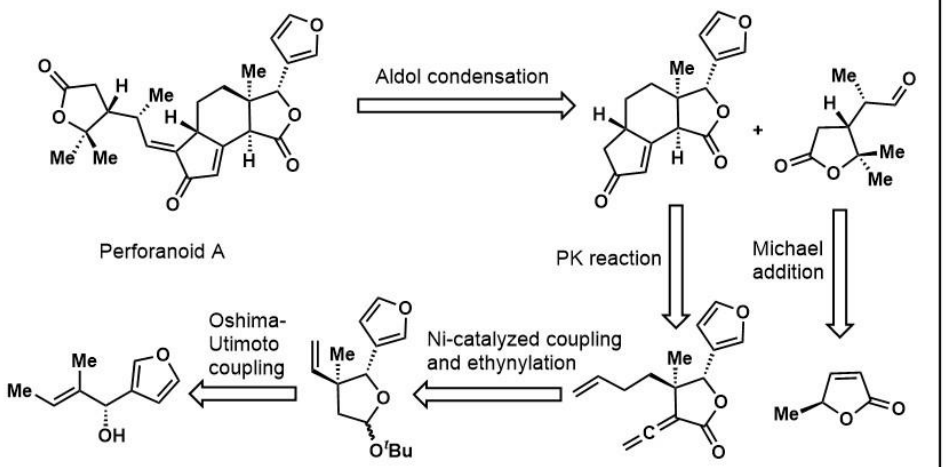
Structure feature

- tetranortriterpenoid family
- preplex chiral centers
- relatively low oxidation state
- novel **BCD** ring system

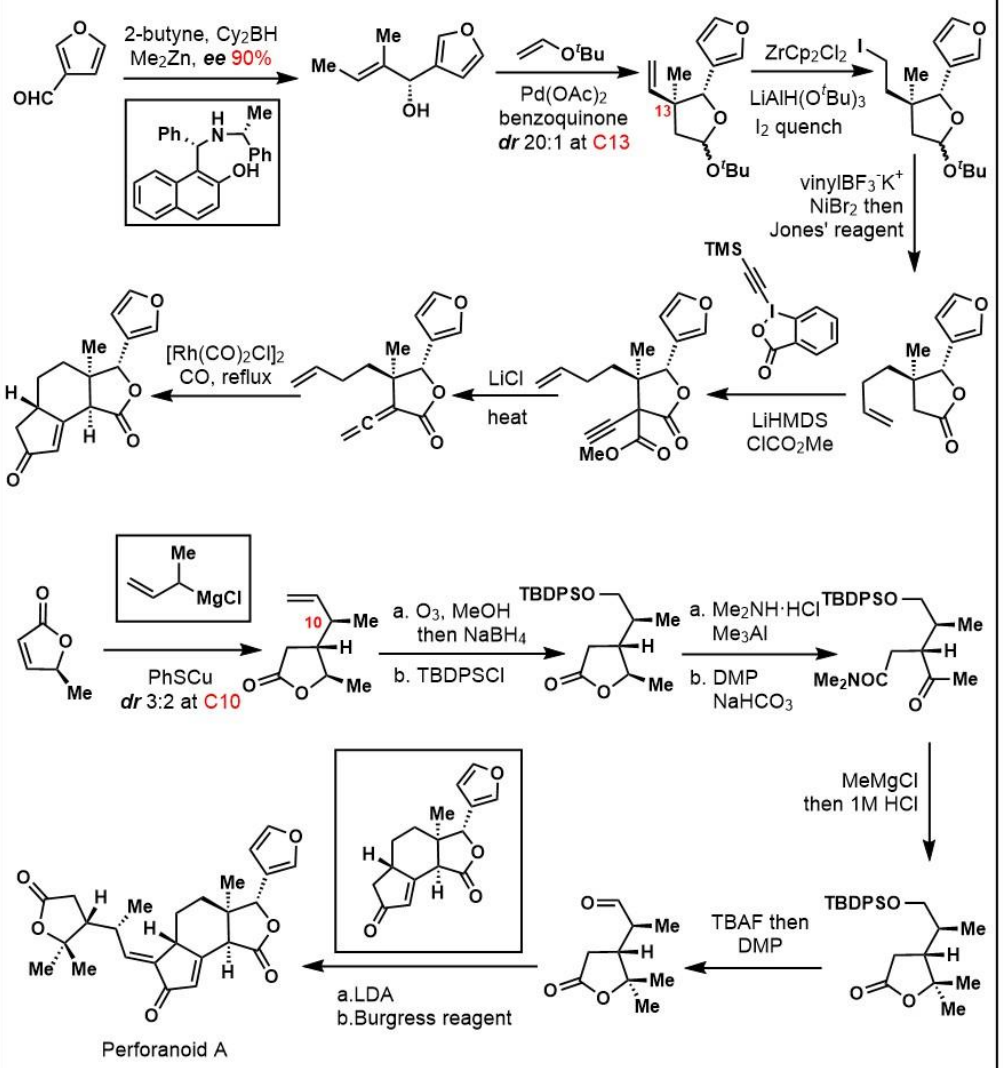
Background

- isolated by Xiaojiang Hao and co-workers, but configuration was uncertain at C10, eventually, proved by total synthesis with Zhen Yang and co-workers
- C10 absolute stereochemistry was comfirmed by Mosher esterification *via* ^{1}H, ^{19}F NMR
- veryfied biological activities(IC_{50}) against HEL(6.17μM), CB3(3.91μM), K562(4.24μM) indicating potential antileukemia activity.

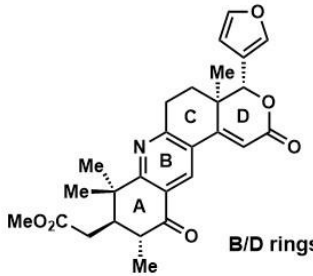
Retrosynthetic analysis



Synthesis of Perforanoid A (10 steps)



IV. (–)-Xylogranatopyridine



B/D rings seco type limonoid

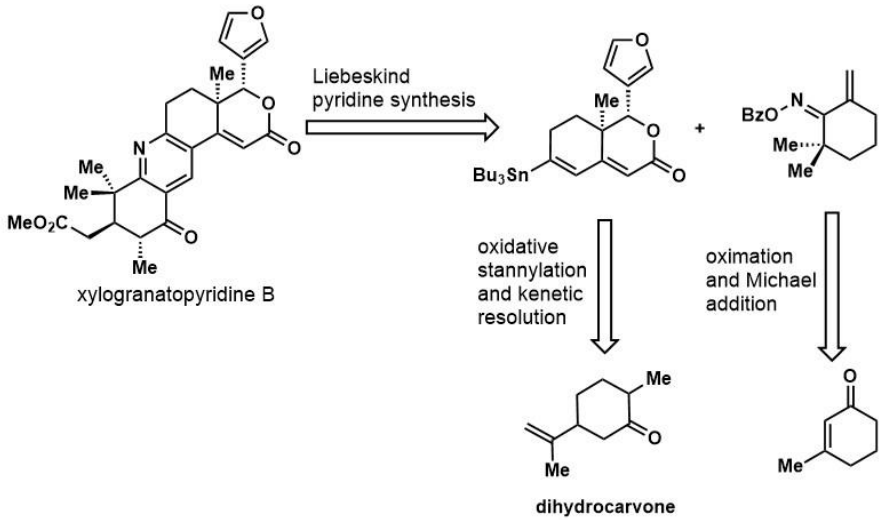
Structure feature

- tetranortriterpenoid family
- prossess a rare pyridine ring
- relatively low oxidation state
- flat skeleton structure of four rings

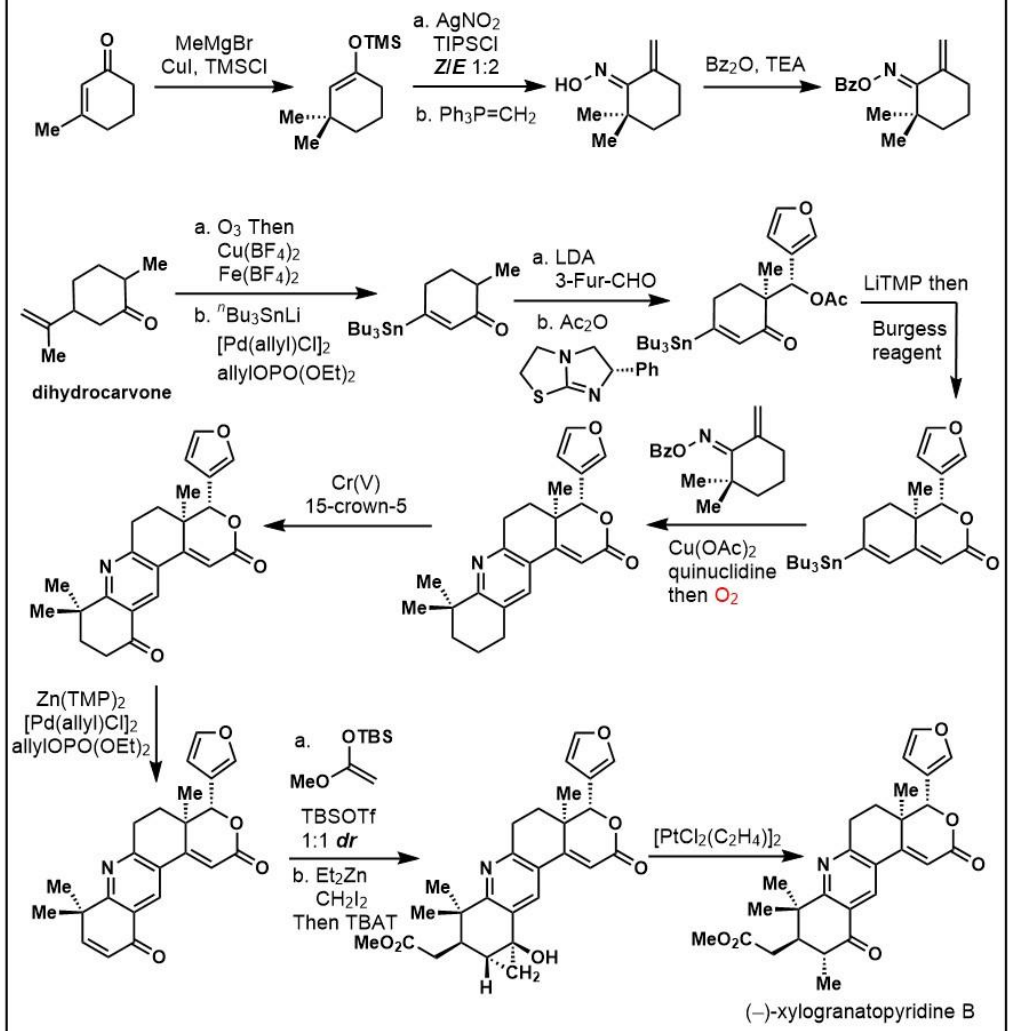
Background

- isolated from Chinese mangrove (Xylocarpus granatum)
- involved oxidative stannylation and kenetic resolution using (–)-Levamisole, providing a novel method for construction of the CD rings

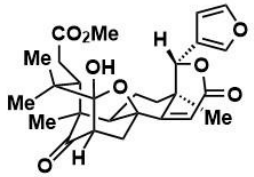
Retrosynthetic analysis



Synthesis of (–)-Xylogranatopyridine B(11 steps)



V. Andirolide N



A/B/D rings seco type limonoid

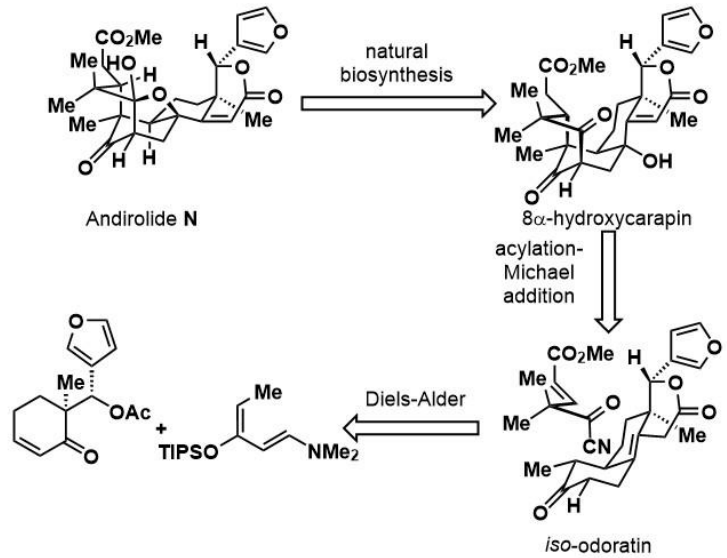
Structure feature

- tetranortriterpenoid family
- prossess complex cage like scaffold
- relatively high oxidation state

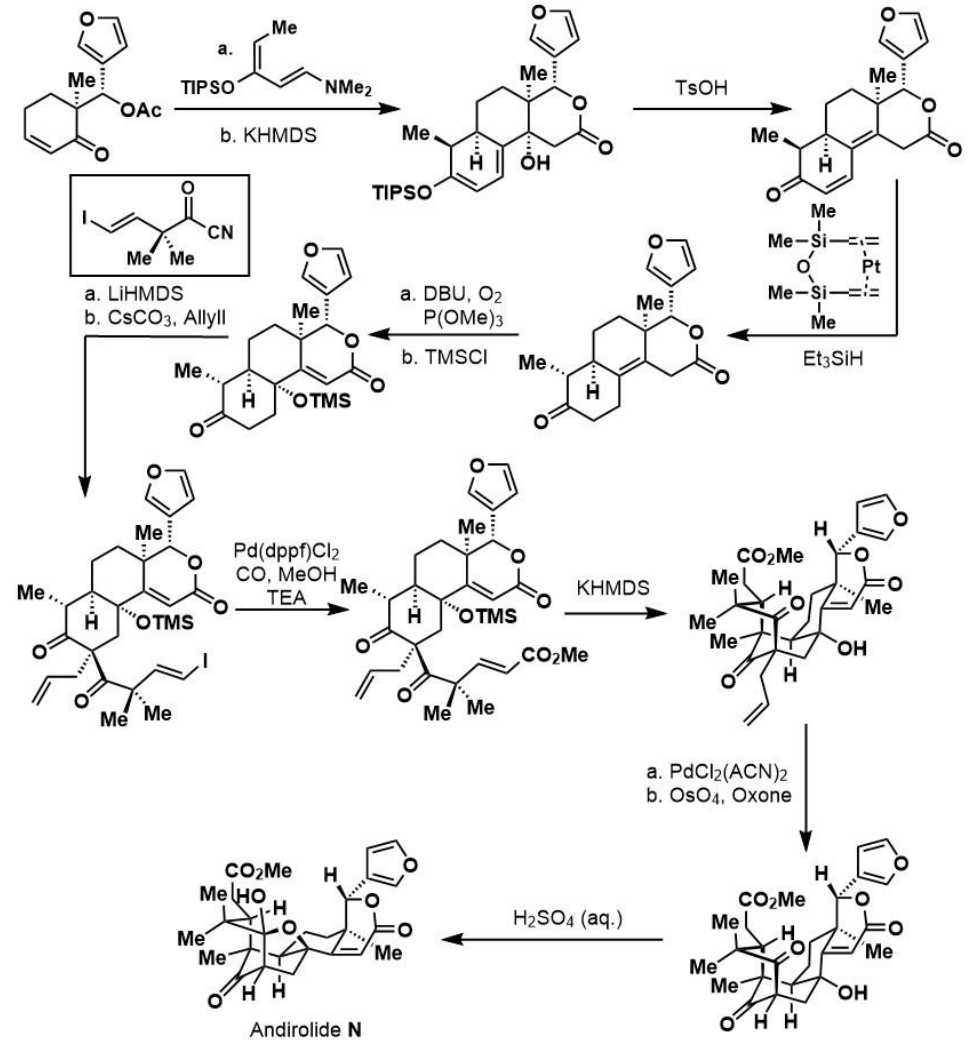
Background

- isolated from flower of mahogany (*Carapa guianensis*)
- simulate natural synthesis pathway to build the complex cage rings
synthetic target is aim at a natural product degradation named *iso*-odoratin

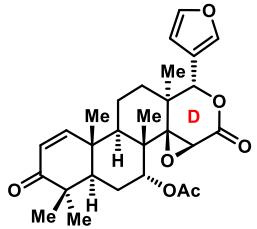
Retrosynthetic analysis



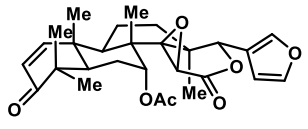
Synthesis of Andirolide N (12 steps)



VI. Gedunin



D ring *seco* type limonoid



3D structure

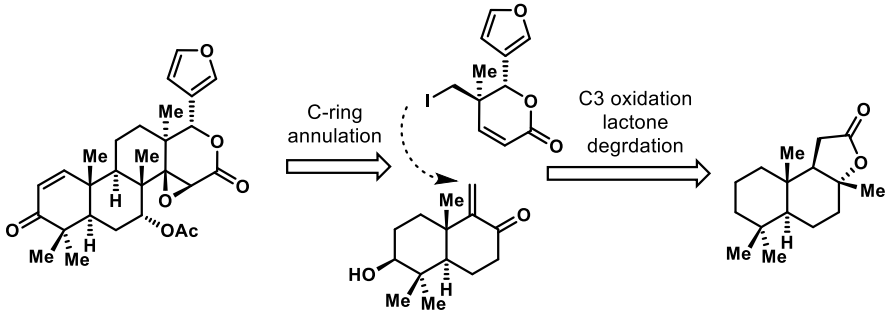
Background

- isolated from mangrove (Xylocarpus Koenig)
- potent inhibitory for heat shock protein 90 (HSP 90) engenders anticancer effect to various cancers
- one of the most potent antimalarial limonoid due to conjugated enone system and furan ring
- combination of traditional transition metal asymmetric catalysis and immature but novel chemoenzymatic catalysis

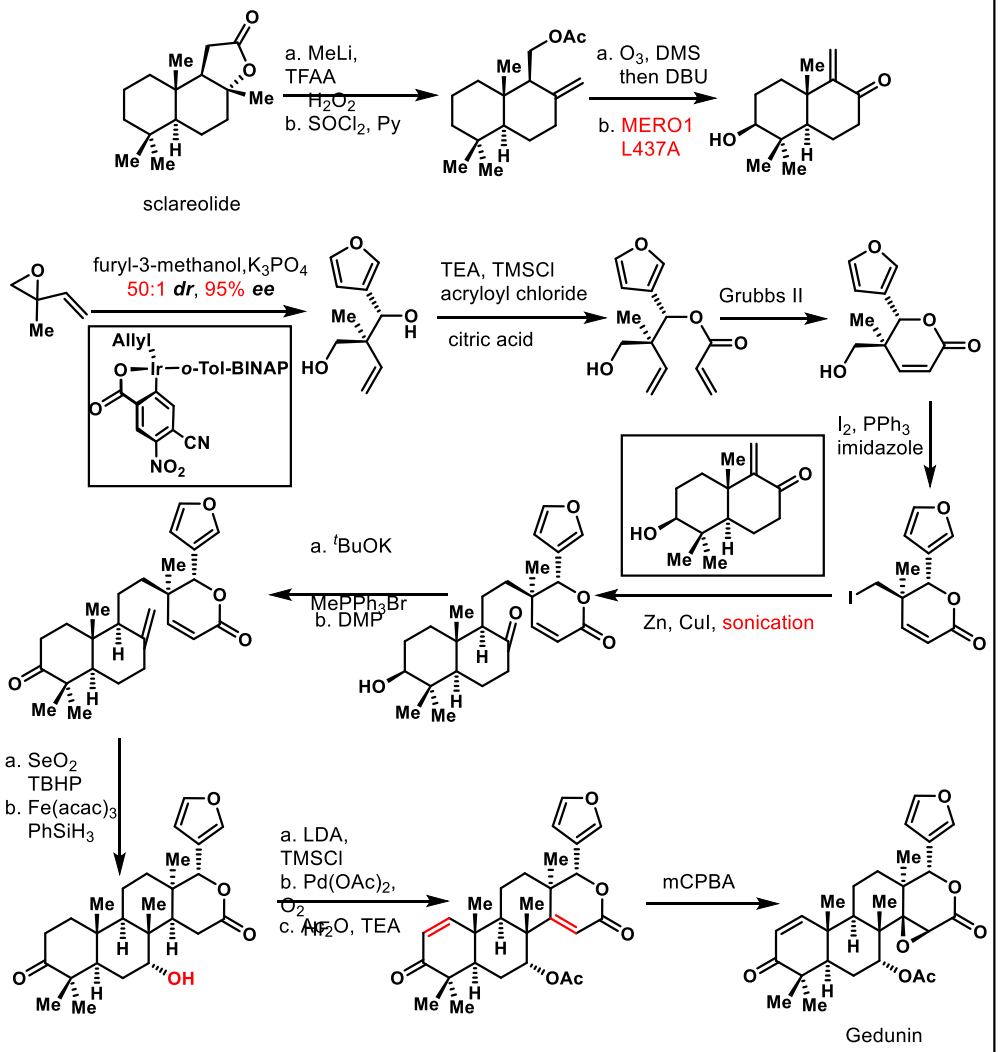
Structure feature

- tetranortriterpenoid family
- preplex stereocenters
- four almost intact rings
- CD-bicycle in unfavored boat-boat configuation
- relatively low oxidation state

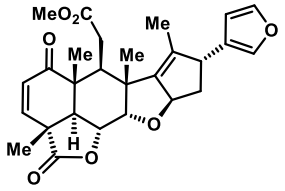
Retrosynthetic analysis



Synthesis of Gedunin (13 steps)



VII. Nimbolide

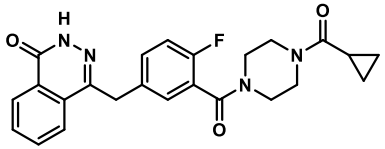


C ring seco type limonoid

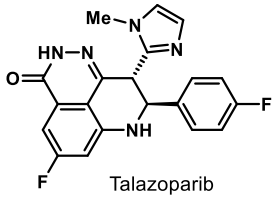
Structure feature

- tetranortriterpenoid family
- preplex chiral centers
- prossess a lactone ring
- prossess a full stereocenters ring
- relatively high oxidation state

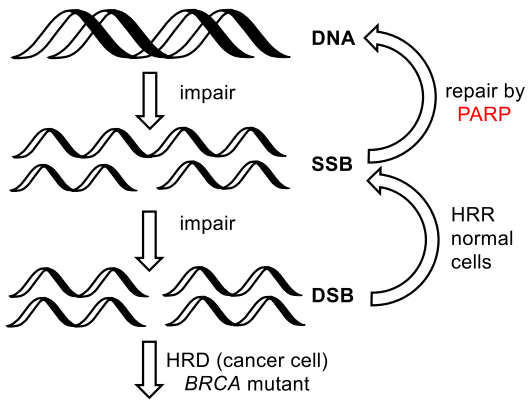
Marketed drugs of PARPIs and synthetic lethality mechanism



Olaparib (2014)

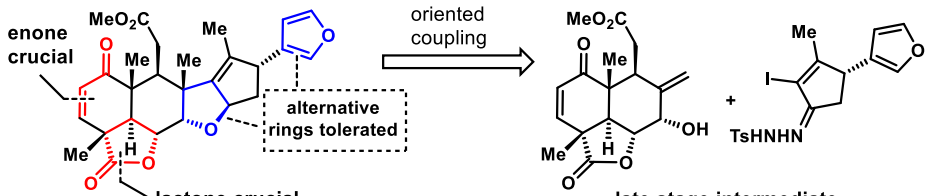


Talazoparib
the most effective PARPIs
in tapping mechanism

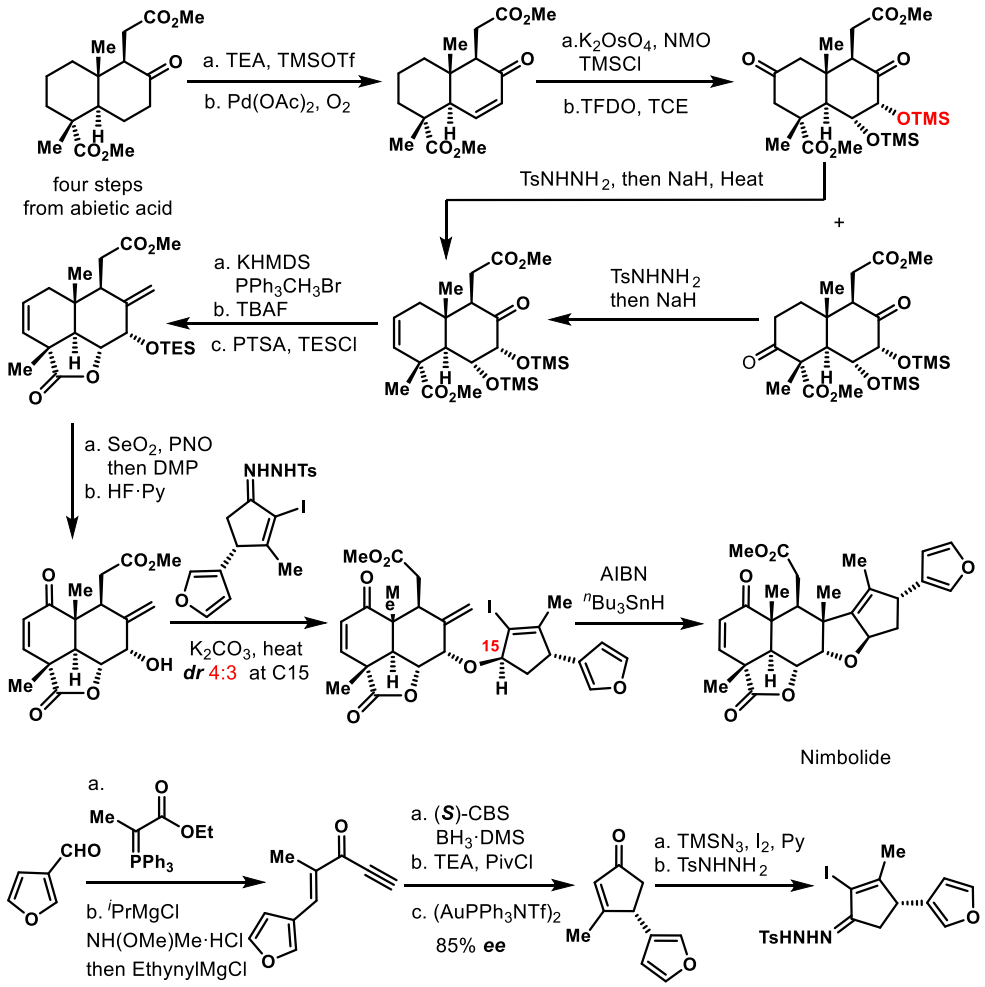


cancer Apoptosis
normal cells survive

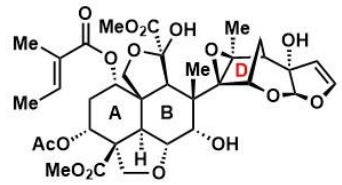
Retrosynthetic analysis and SAR



Synthesis of Nimbolide (14 steps)



VIII. azadirachtin



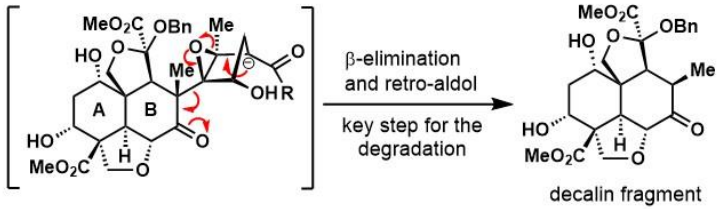
C ring seco type limonoid

Structure feature

- tetranortriterpenoid family
- terrified chiral centers
- prossess 16 contiguous stereocenters
- extremely high oxidation state
- various oxygen functional groups

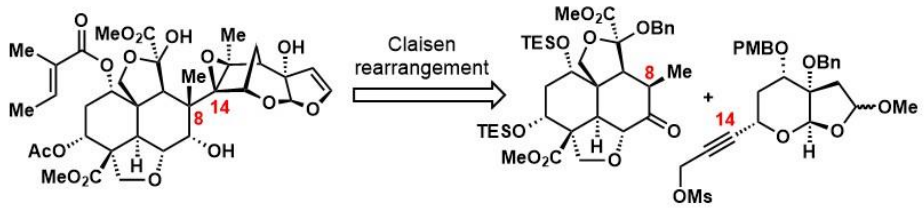
Background

- first isolated from the Indian neem tree by J. H. Butterworth and E. D. Morgan in 1968 first total synthesis reported by Steven V. Ley and co-workers using 40 years
- one of the most notably antifeedant against insect species (>200)
- furan ring oxidates to form bicyclic rings with D ring
- after plenty of auther's investgation and other literature the hardest problem is to construct C_8-C_{14}carbon bond due to steric constraints from C_8 position
- be unendure with both acid and base presenting fairly unstable by investgation
- vital decalin fragment could obtain from degradation of azadirachtin itself even devised a mature route to degrade the natural product into the intermediate

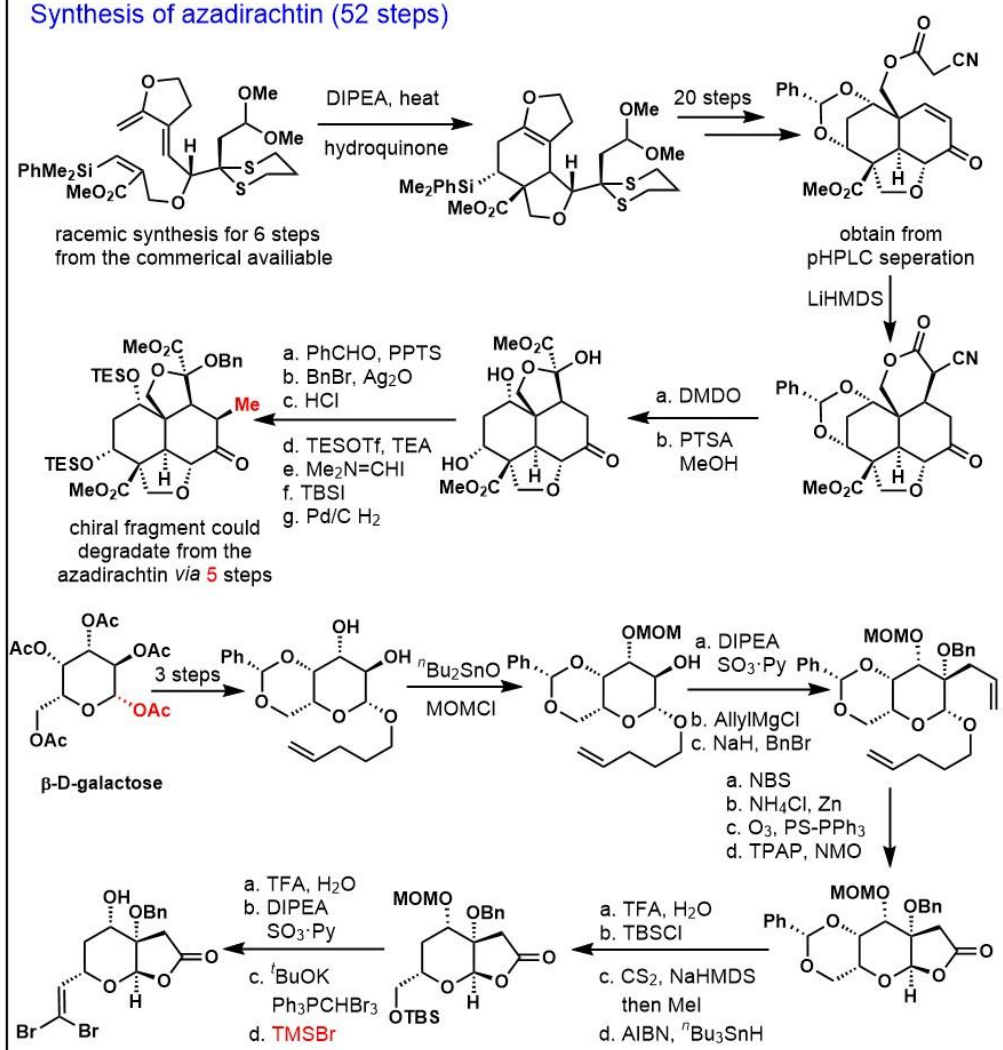


decalin fragment

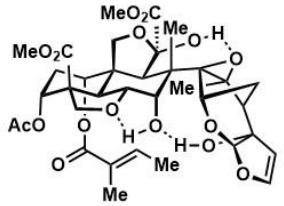
Retrosynthetic analysis



Synthesis of azadirachtin (52 steps)



VIII. azadirachtin

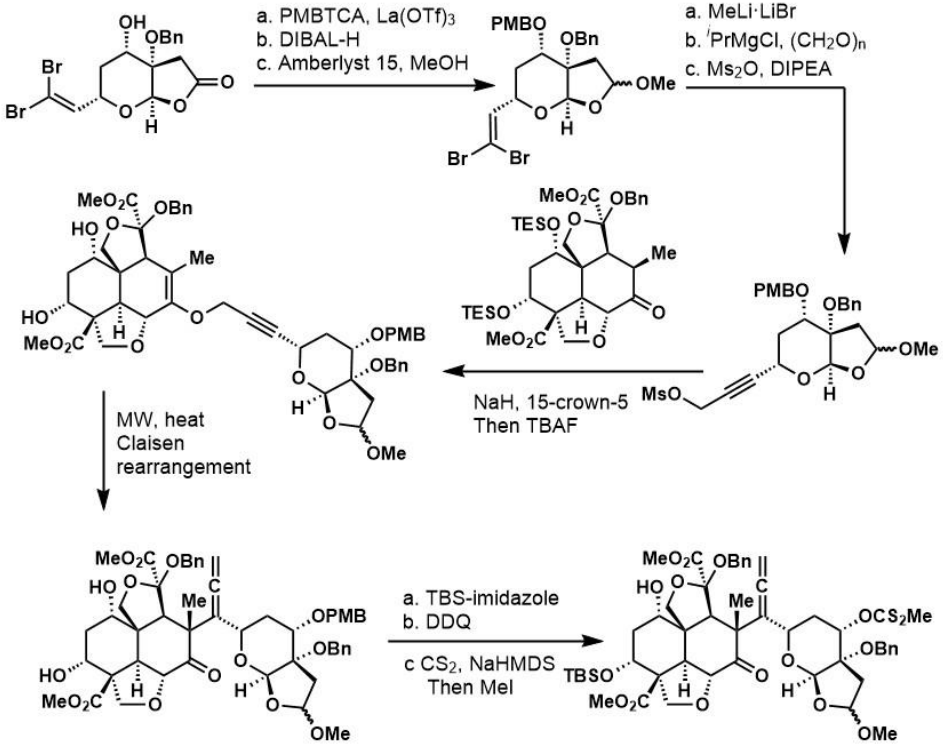


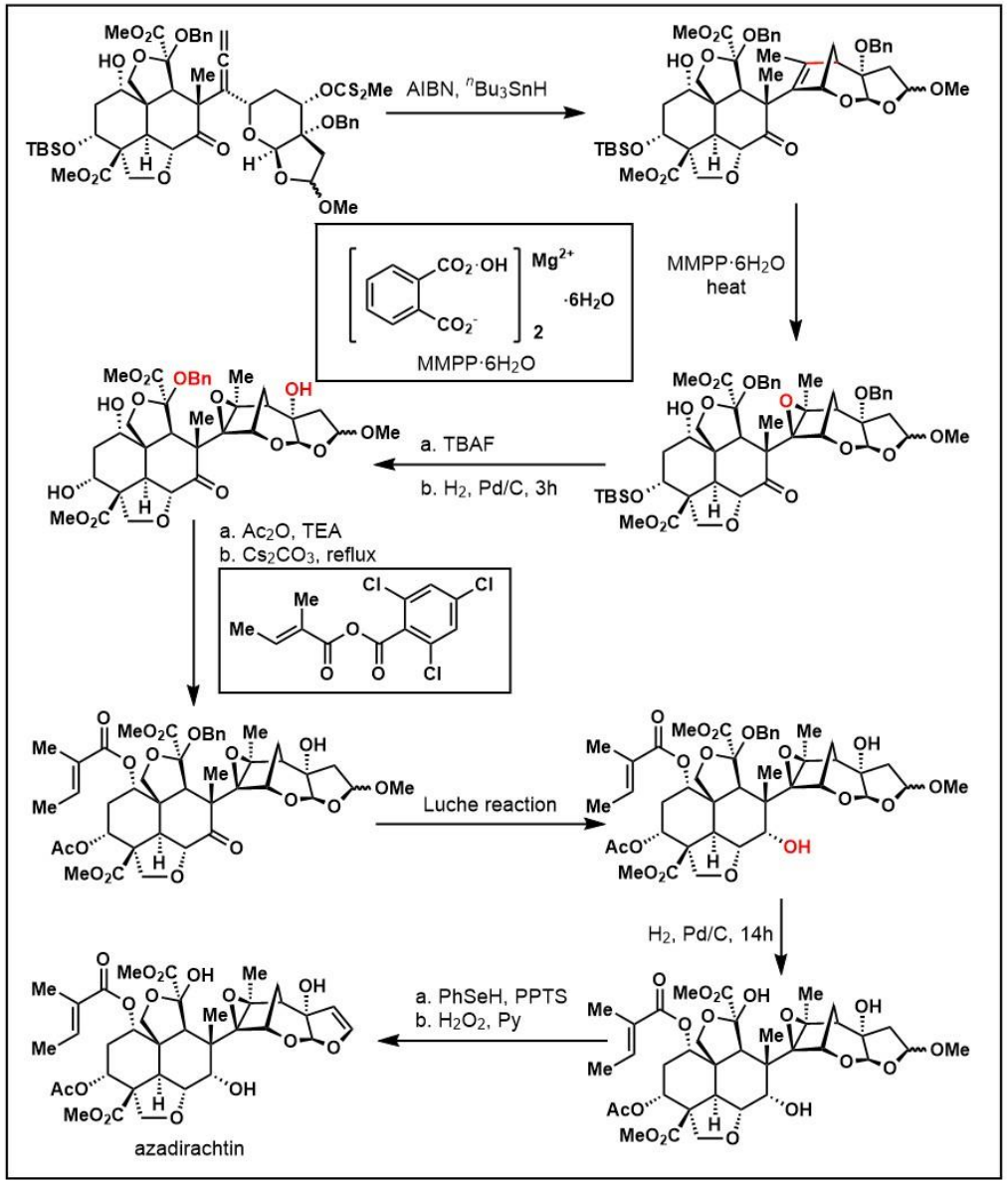
Hydrogen-bonding pattern in azadirachin

Structure feature

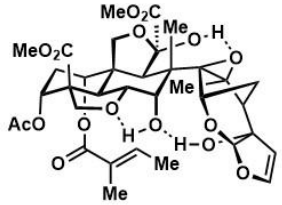
- tetranortriterpenoid family
- terrified chiral centers
- prossess 16 contiguous stereocenters
- extremely high oxidation state
- various oxygen functional groups

Synthesis of azadirachtin





VIII. azadirachtin



Hydrogen-bonding pattern in azadirachin

Structure feature

- tetranortriterpenoid family
- terrified chiral centers
- prossess 16 contiguous stereocenters
- extremely high oxidation state
- various oxygen functional groups

Formal synthesis of azadirachtin by Watanabe