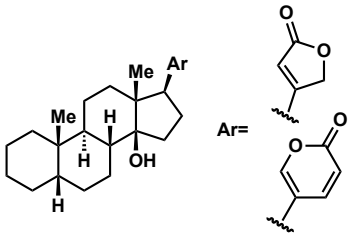
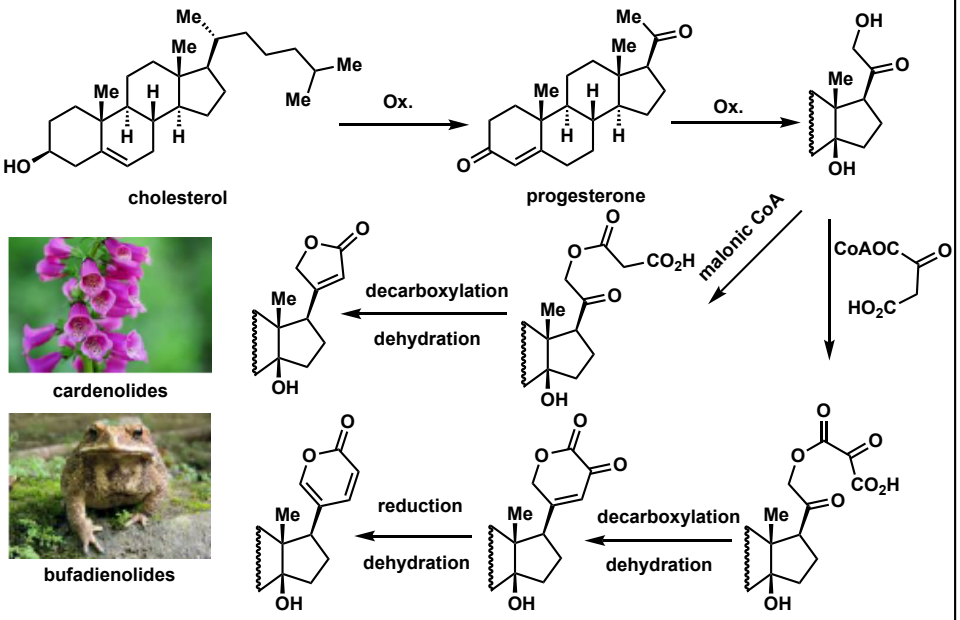


basic cardiotonic steroids skeleton

Cardiotonic steroids famliy feature

- the unsaturated heterocycle in C-17: 5 / 6 member rings dividended into cardenolides (furan ring) and bufadienolides(pyrone rings)
- intact steroid structure the steroid configuation of AB, CD rings is almost cis
- cardenolides were majorly found in plants bufadienolides were found in amphibians (mainly in toads)

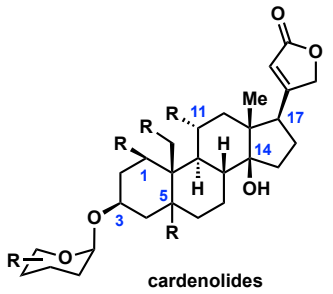
Proposed biosynthetic pathway



Biologicial activity

1. **heart failure, cardiogenic shock and certain arrhythmias (Na^+/K^+-ATPase inhibitor, increase concentration of Ca^{2+} narrow theraputic index, often over treated with 60% toxic dose)**
2. **anti cancer activity (Na^+/K^+-ATPase inhibitor for tumor or modulate signal pathway and DNA repair)**

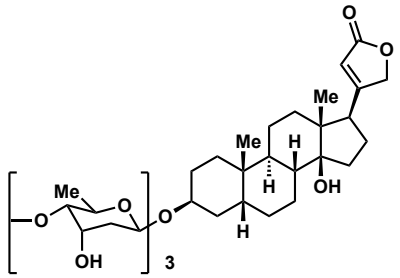
The SAR studies of cardenolides



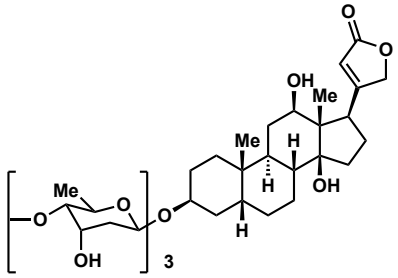
cardenolides

1. C1, C5, C11 and C19 hydroxyls may enhance the activity, but not essential
2. Sugar residue at C3 is important, Rhamnose is better than others
3. the unsaturated heterocycle in C17 is essential and its β oriented position is also vital
4. the cis configuation of CD rings and AB rings could enchance the activity

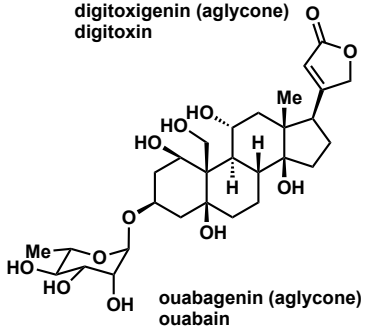
Representative cardiotonic steroids



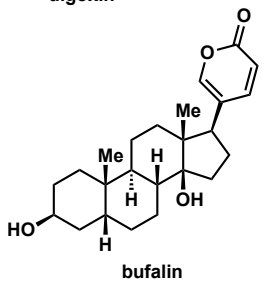
digitoxigenin (aglycone)
digitoxin



digoxigenin (aglycone)
digoxin

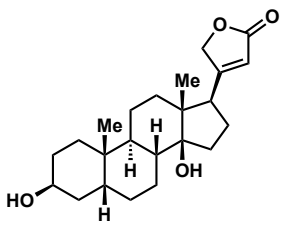


ouabagenin (aglycone)
ouabain



bufalin

I. digitoxigenin (Stork's synthesis)



intact steriod structure

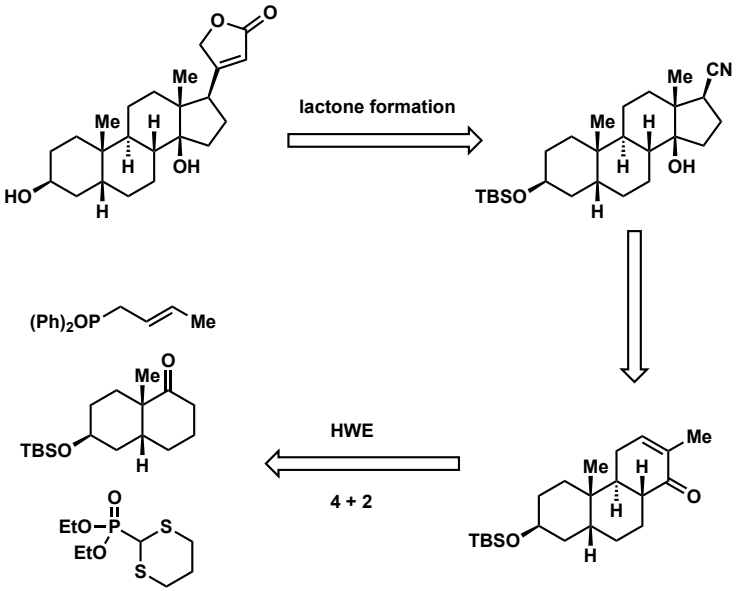
Structure feature

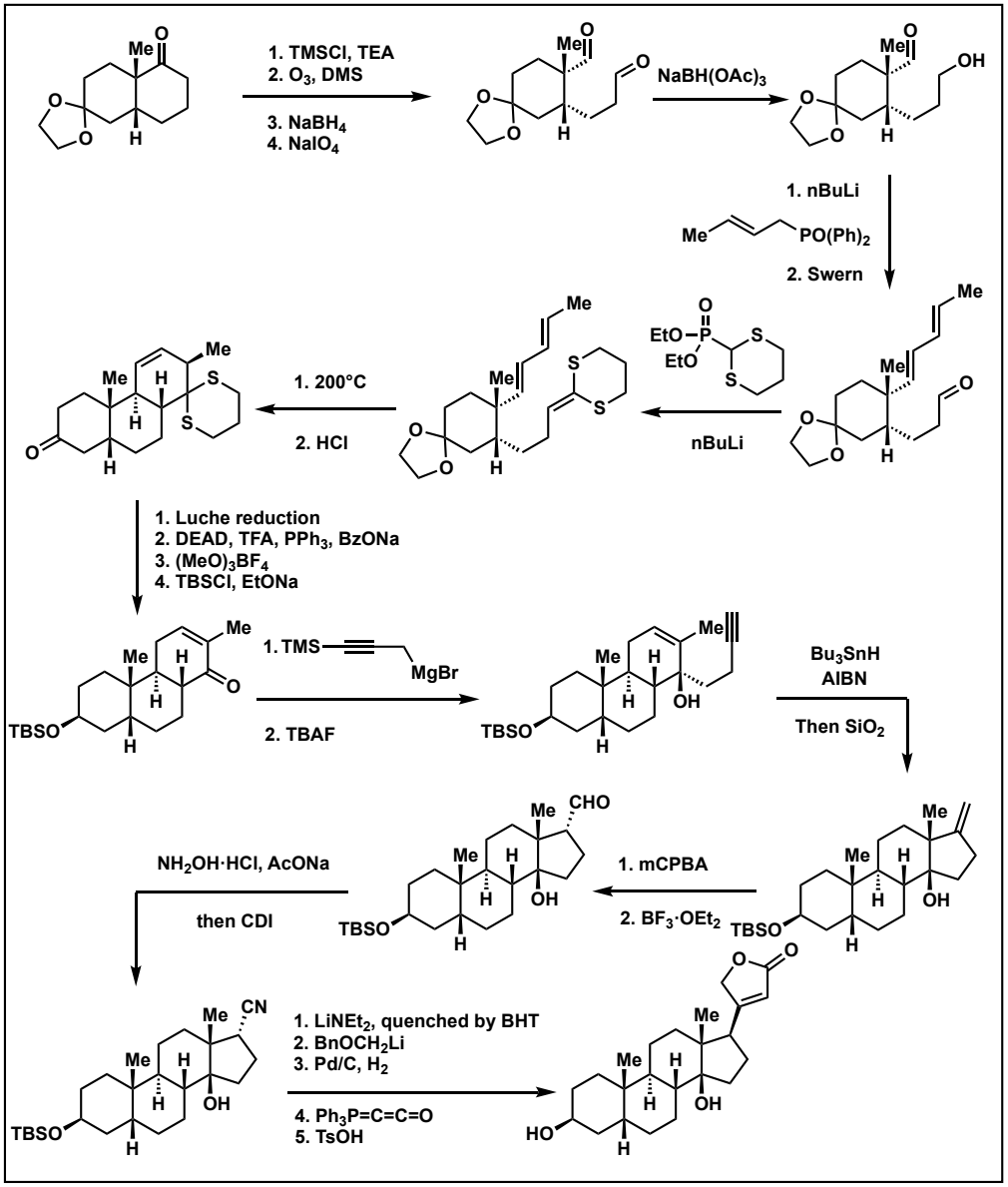
- flagship congener in the cardiac glycoside family
- 7 conseutive chiral centers
- relatively low oxidation state

Background

- the active components in the *Digitalis*(the most ingested drugs)

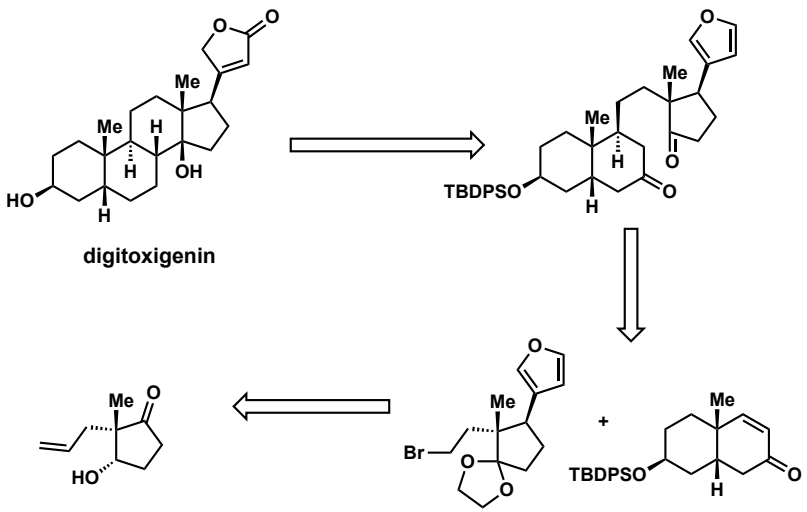
Retrosynthetic analysis



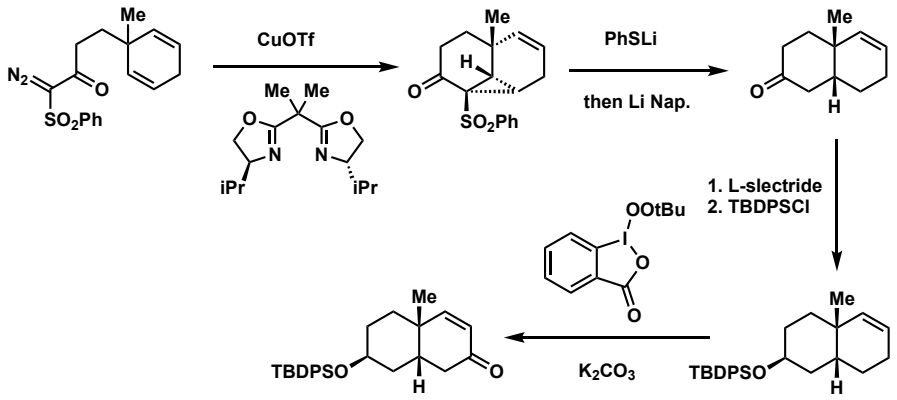


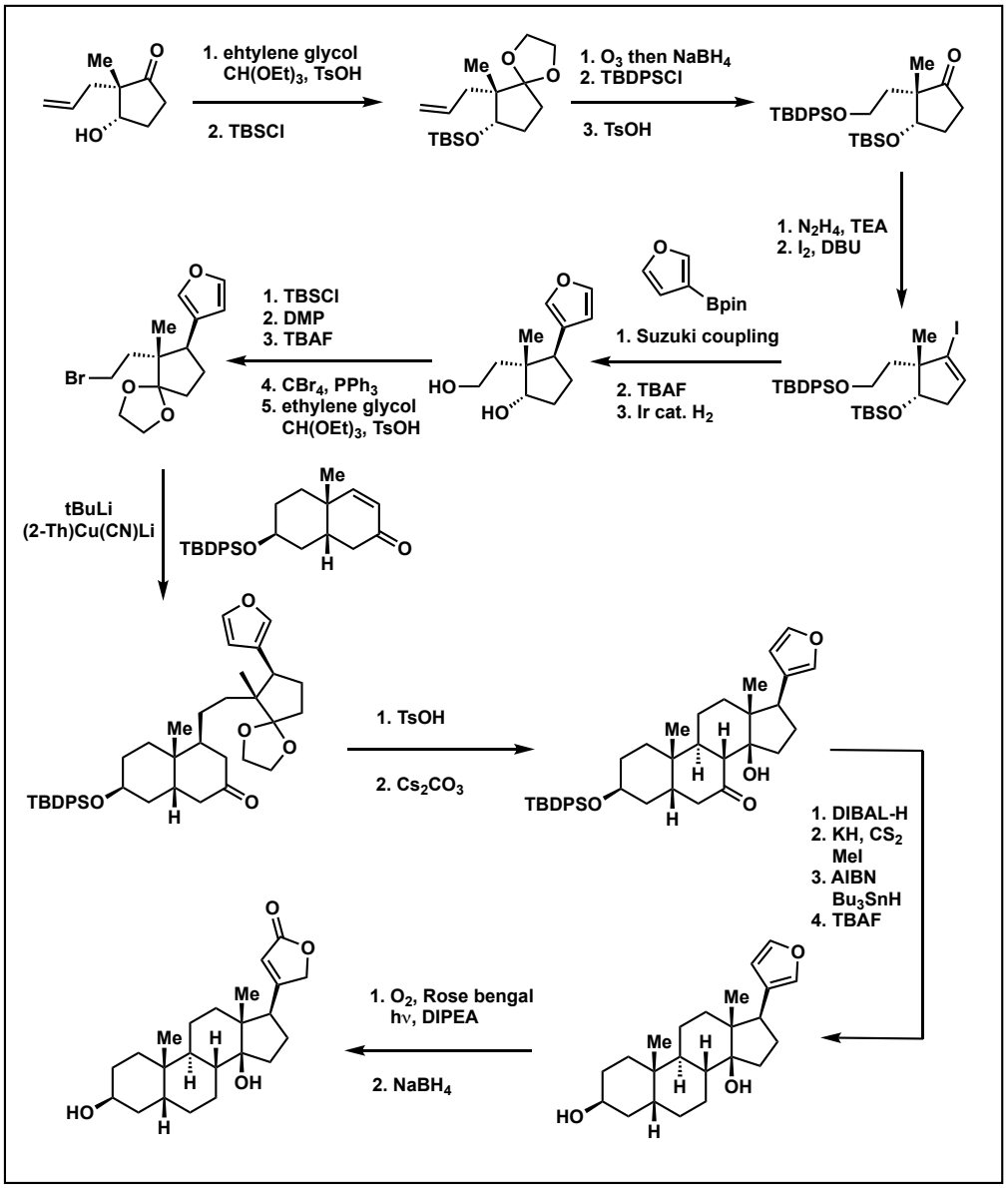
II. digitoxigenin (Nakada's synthesis)

Retrosynthetic analysis

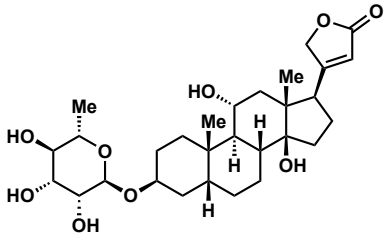


synthetic route (24 steps **LLS**)





III. Rhodexin A



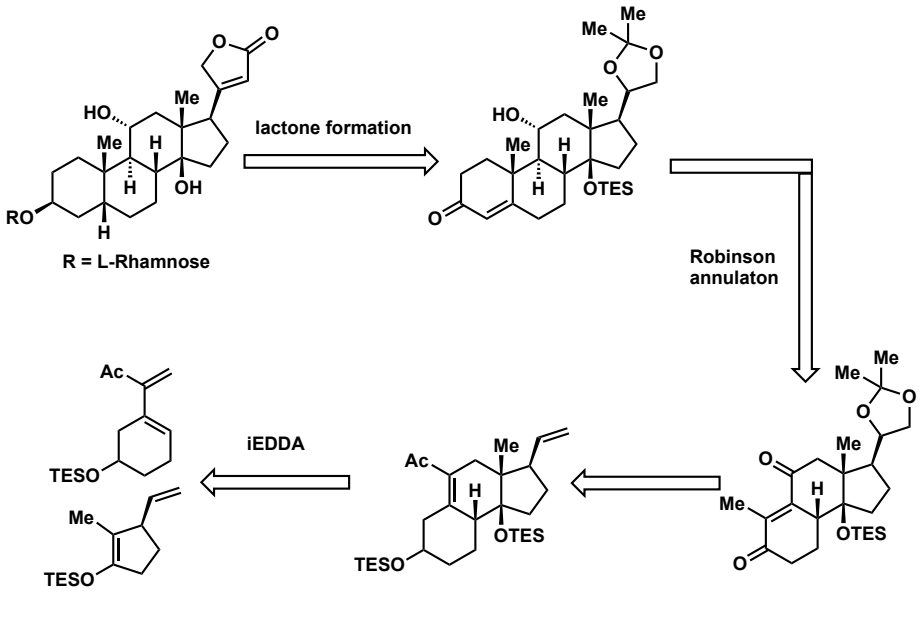
Structure feature

- L-Rhamnoside of sarmentogenin
- 7 conseutive chiral centers
- relatively low oxidation state

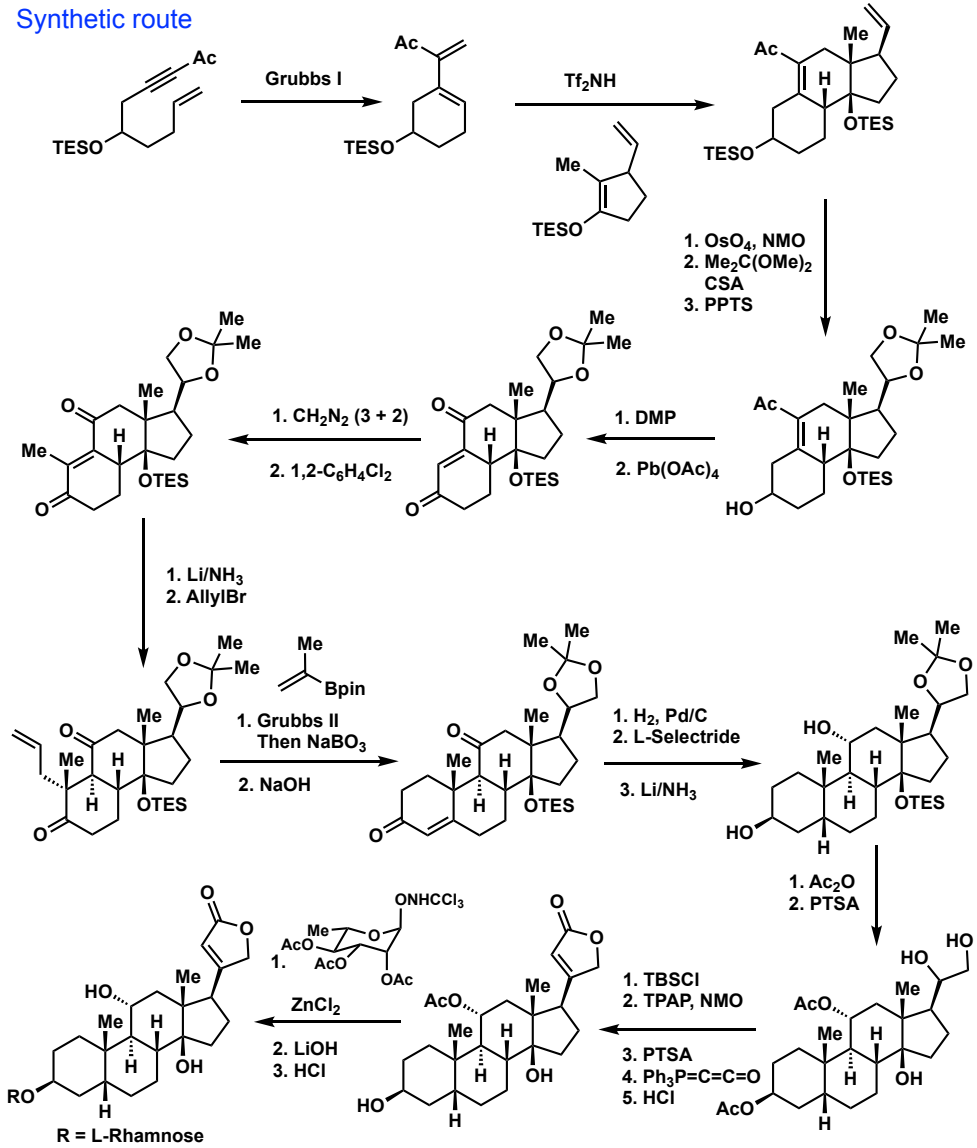
Background

- against human leukemia K_{562} cells (IC_{50} 19 nm)
- potent antiproliferative activity (inhibit HIF-1α)

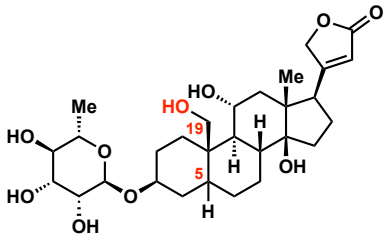
Retrosynthetic analysis



Synthetic route



IV. trewianin



trewianin (α-H5)
5-epi-trewianin (β-H5)

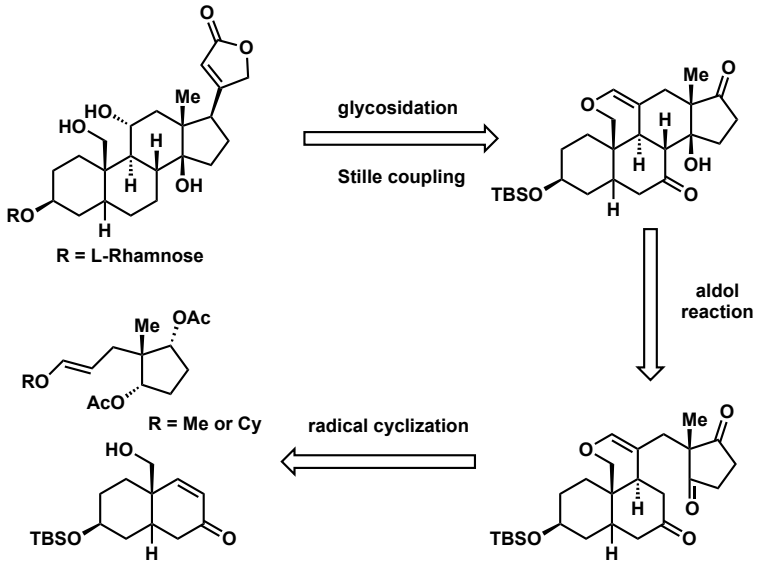
Structure feature

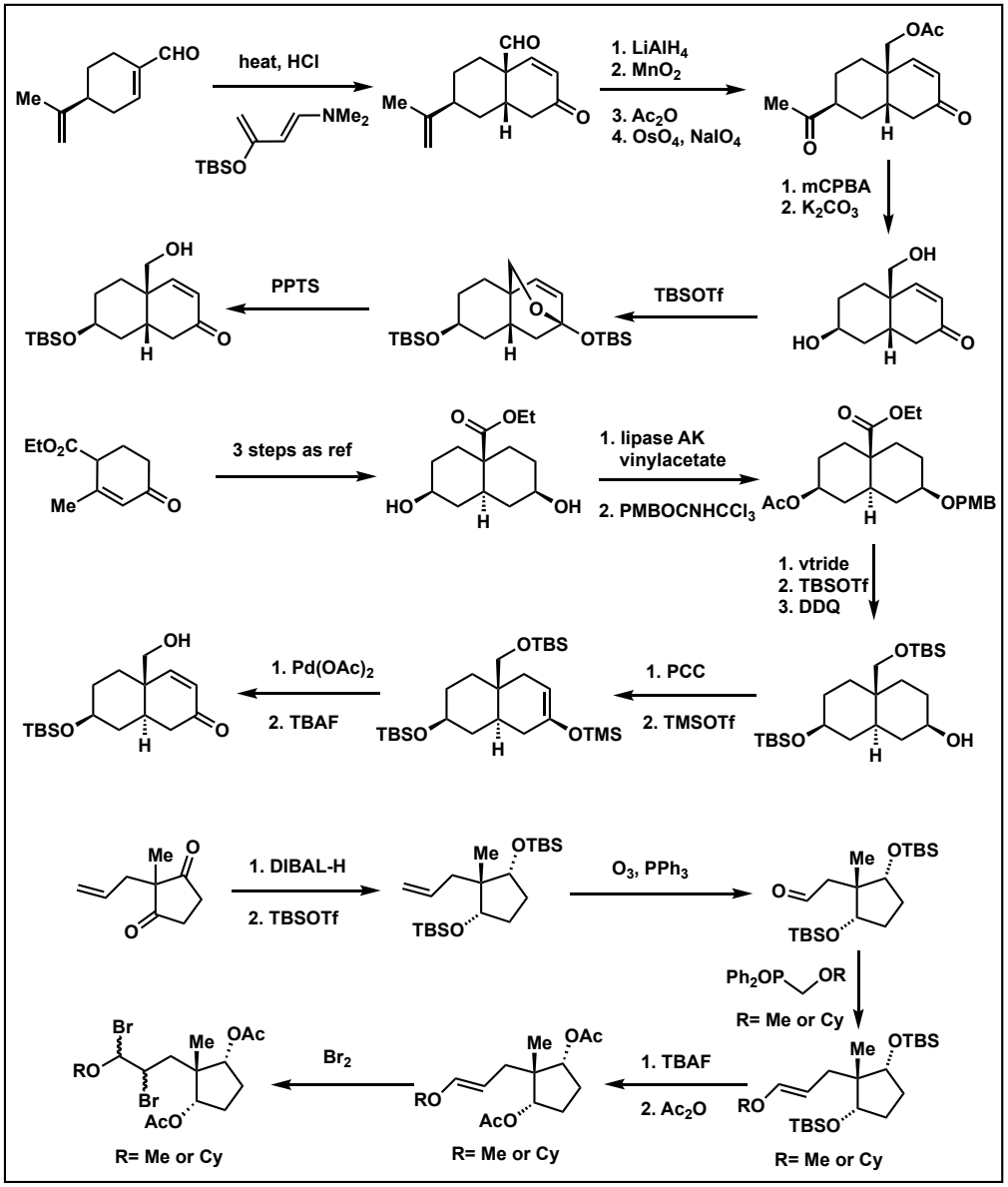
- unusual trans decalin for AB ring
- 7 conseutive chiral centers
- relatively high oxidation state

Background

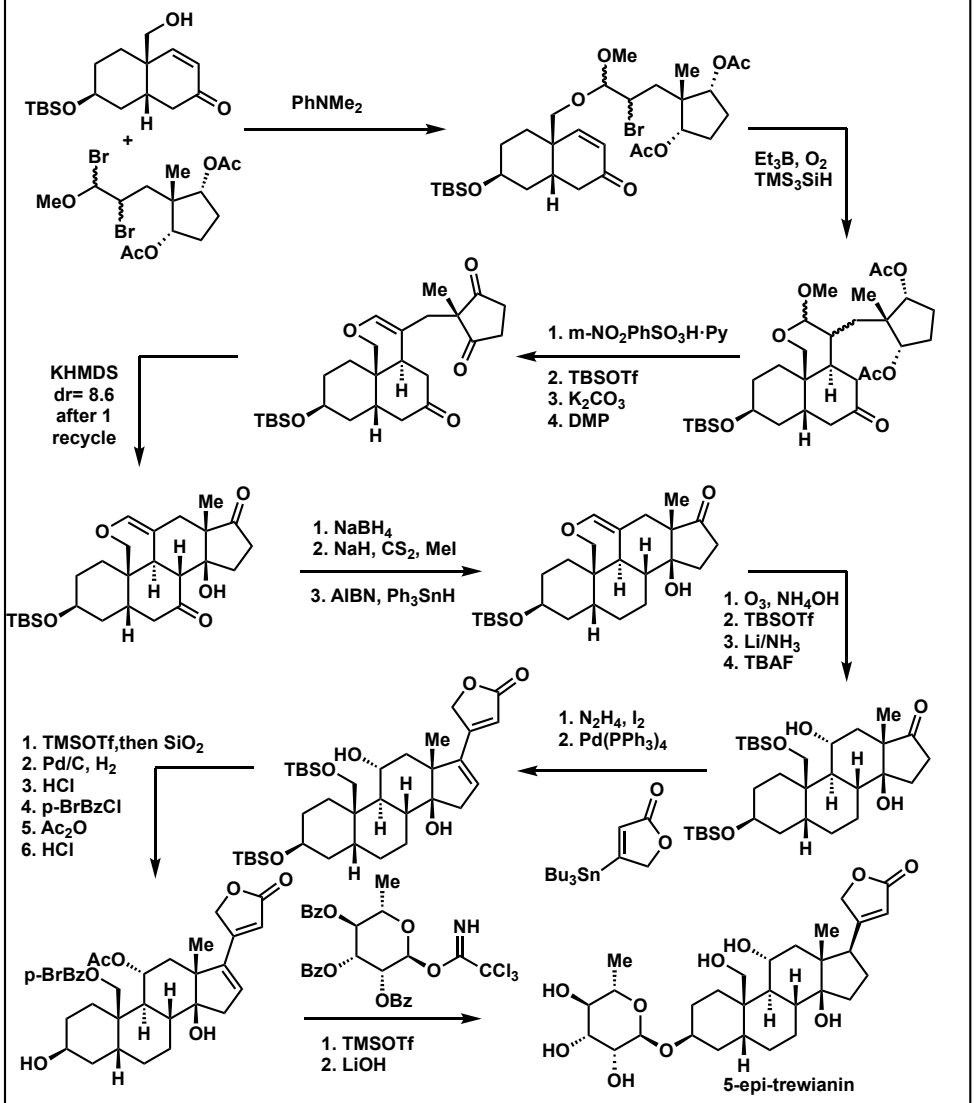
- against MCF-7 human breast carcinoma cells
  GI_{50} of 5-epi-trewianin= 108 nM,
  but GI_{50} of the aglycon > 10μM

Retrosynthetic analysis

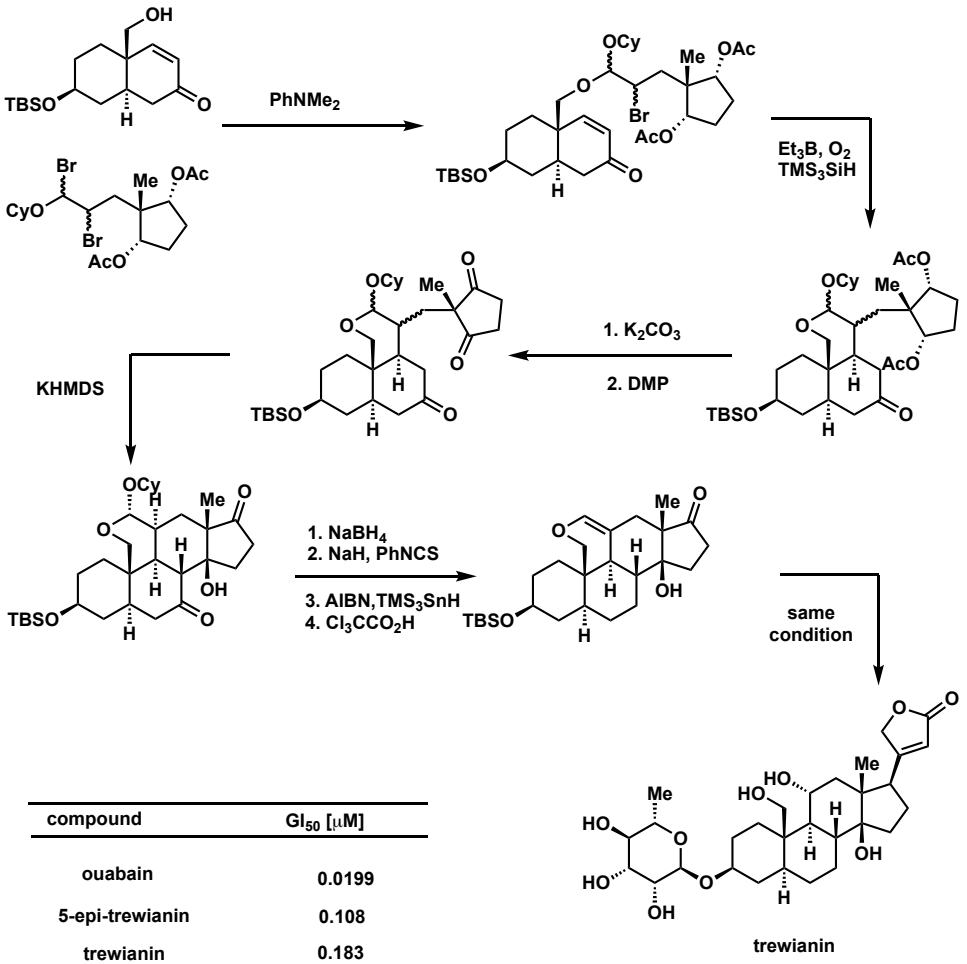




Completion synthesis of 5-epi trewianin

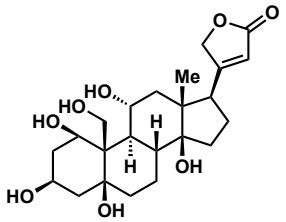


Completion synthesis of trewianin



compound	GI_{50} [μM]
ouabain	0.0199
5-epi-trewianin	0.108
trewianin	0.183
5-epi-trewianin aglycon	3.27
trewianin aglycon	> 10

V. ouabagenin (Baran's synthesis)



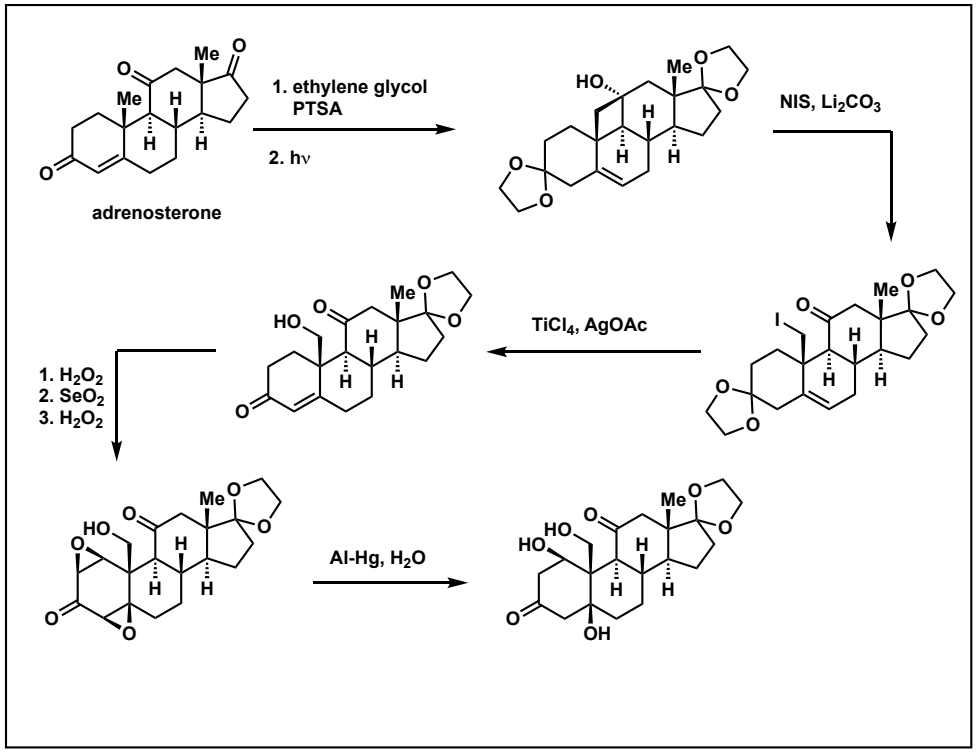
ouabagenin

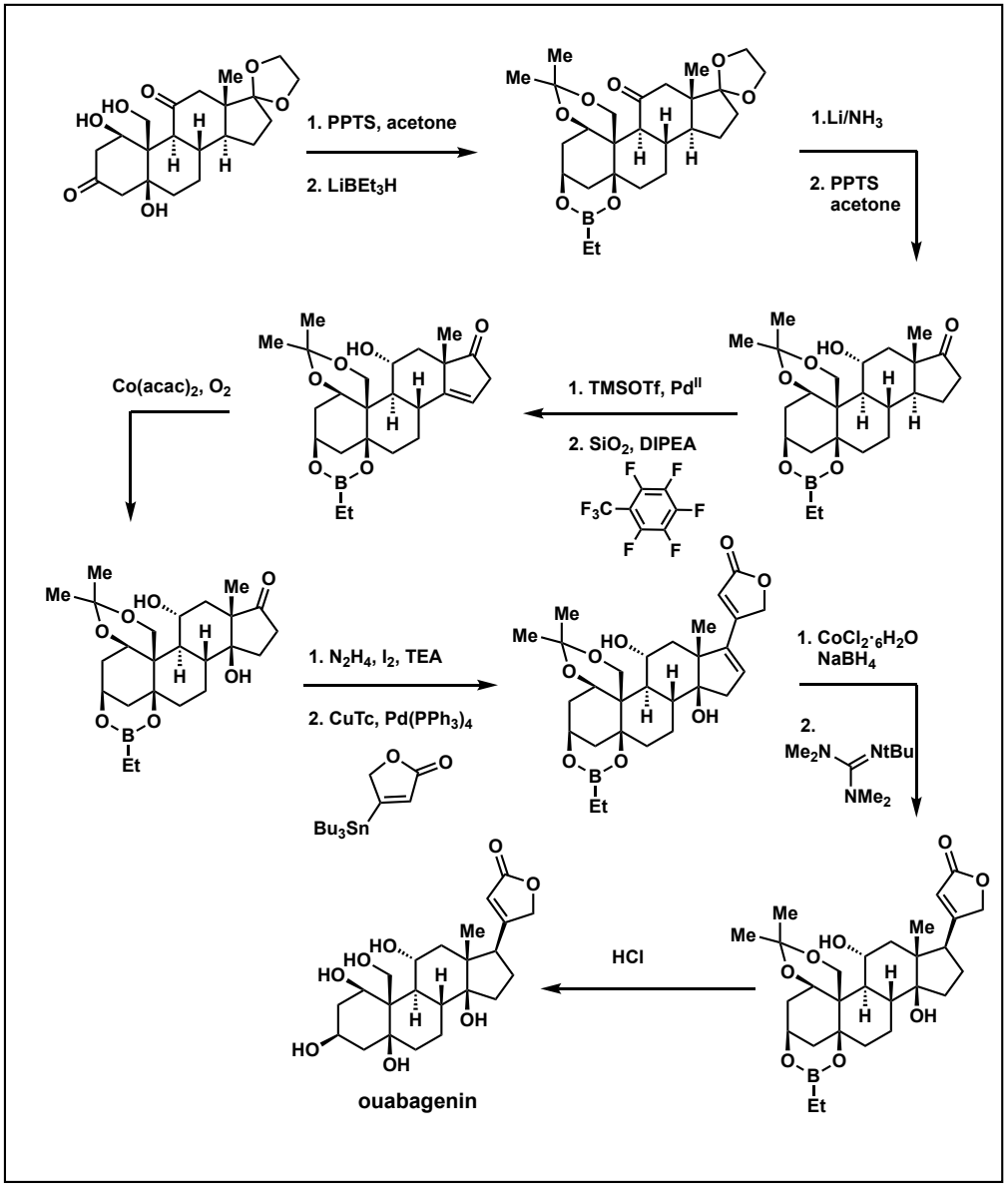
Structure feature

- aglycon part of ouabain
- 7 conseutive chiral centers
- high oxidation state

Background

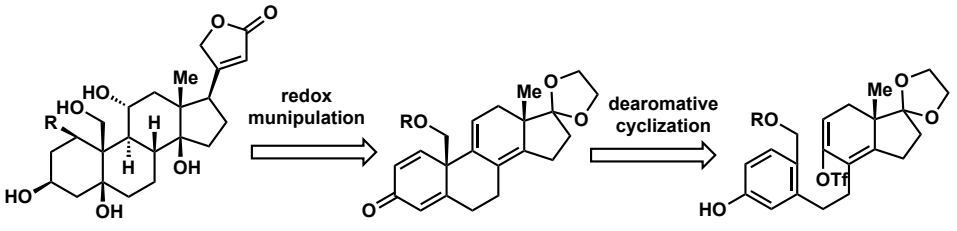
- supposed to be arisen from progesterone
- partial synthesis, 21 steps LLS from cortisone
- apply quasibiomimetic oxidation strategy

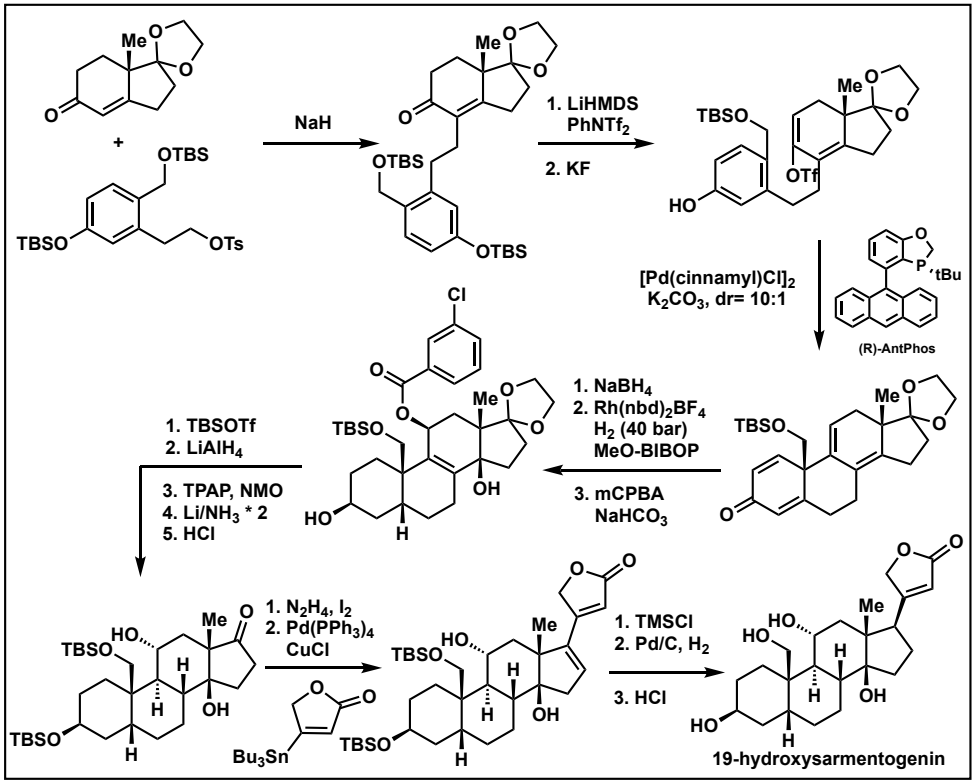


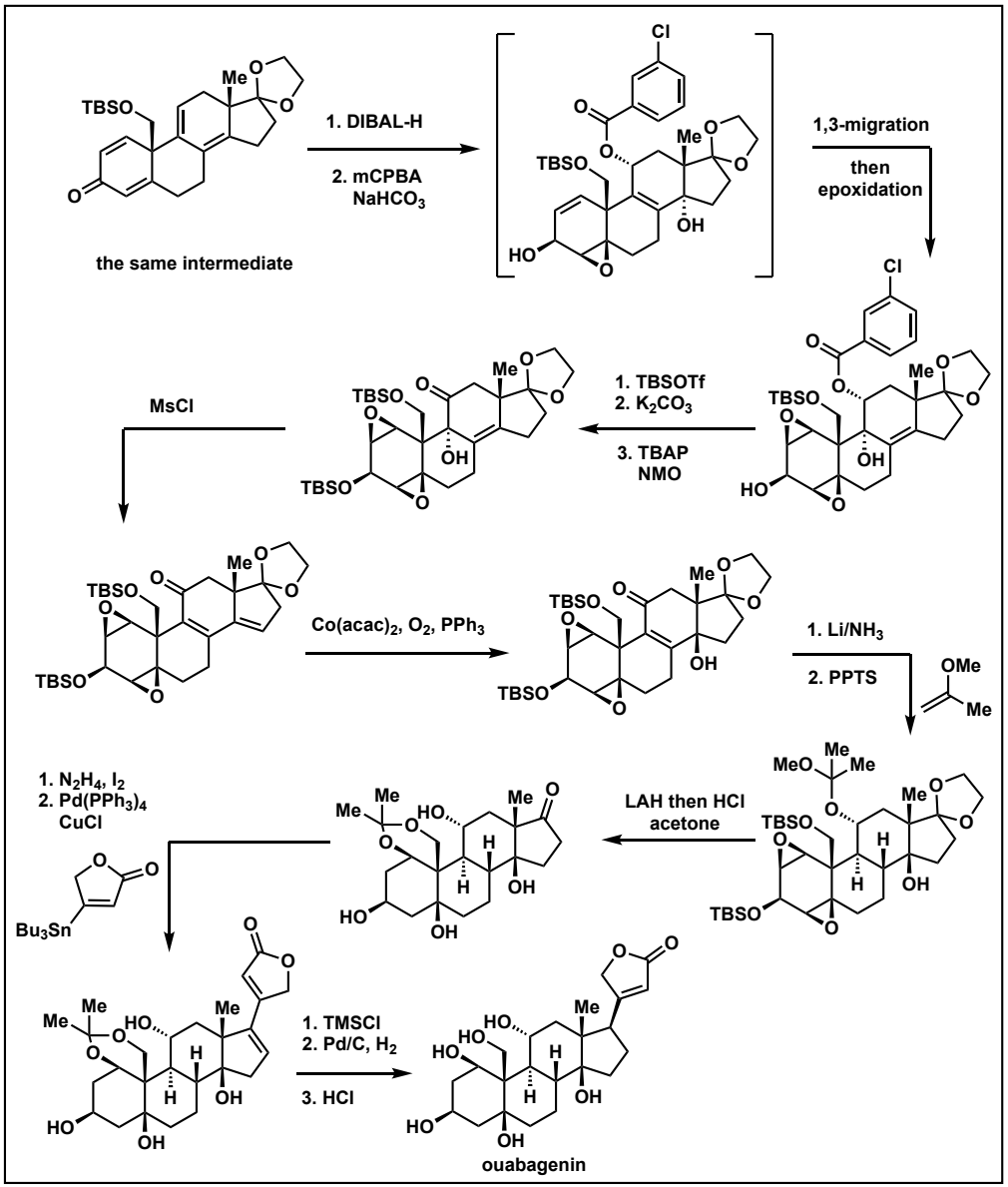


VI. ouabagenin and 19-hydroxysarmentogenin (Tang's synthesis)

Retrosynthetic analysis

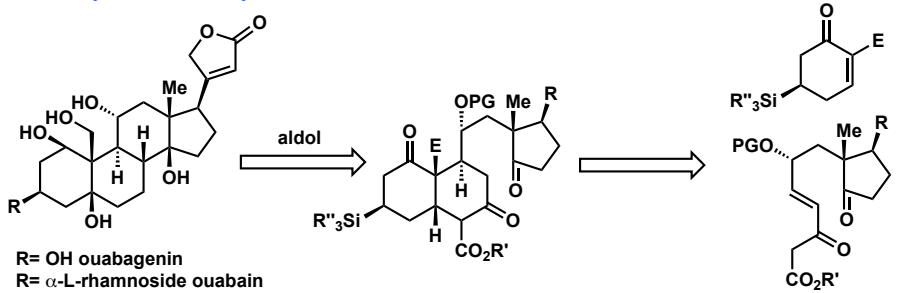




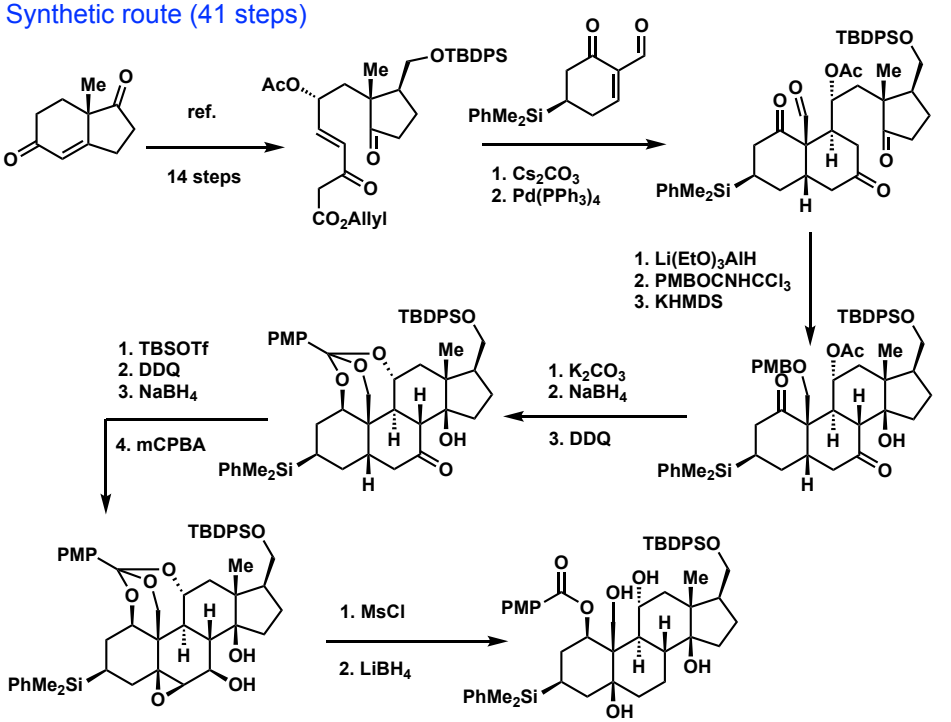


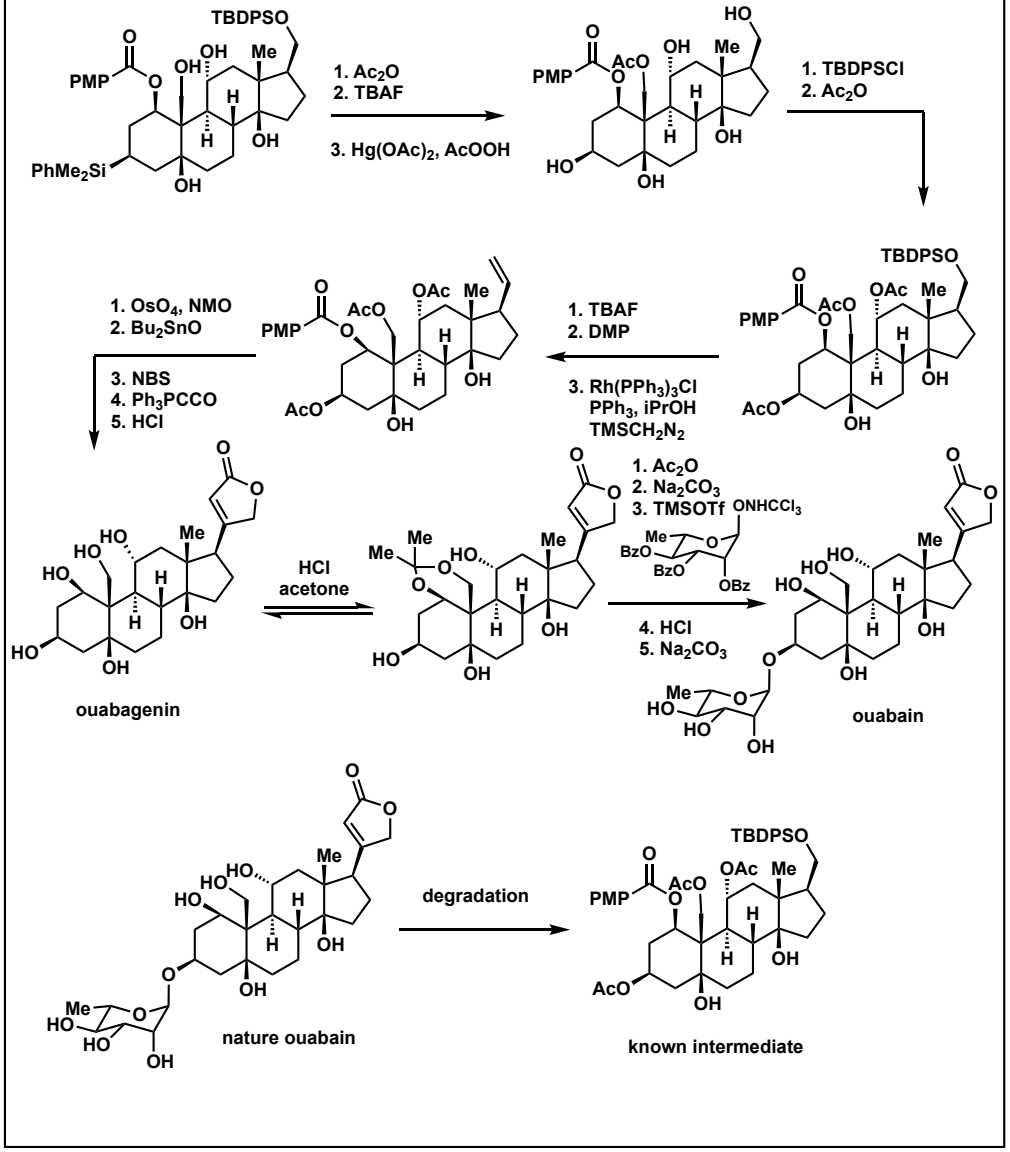
VII. ouabagenin and ouabain (Deslongchamps's synthesis)

Retrosynthetic analysis



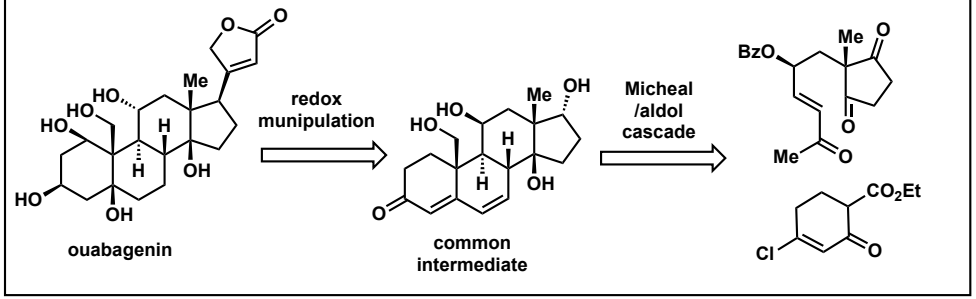
Synthetic route (41 steps)

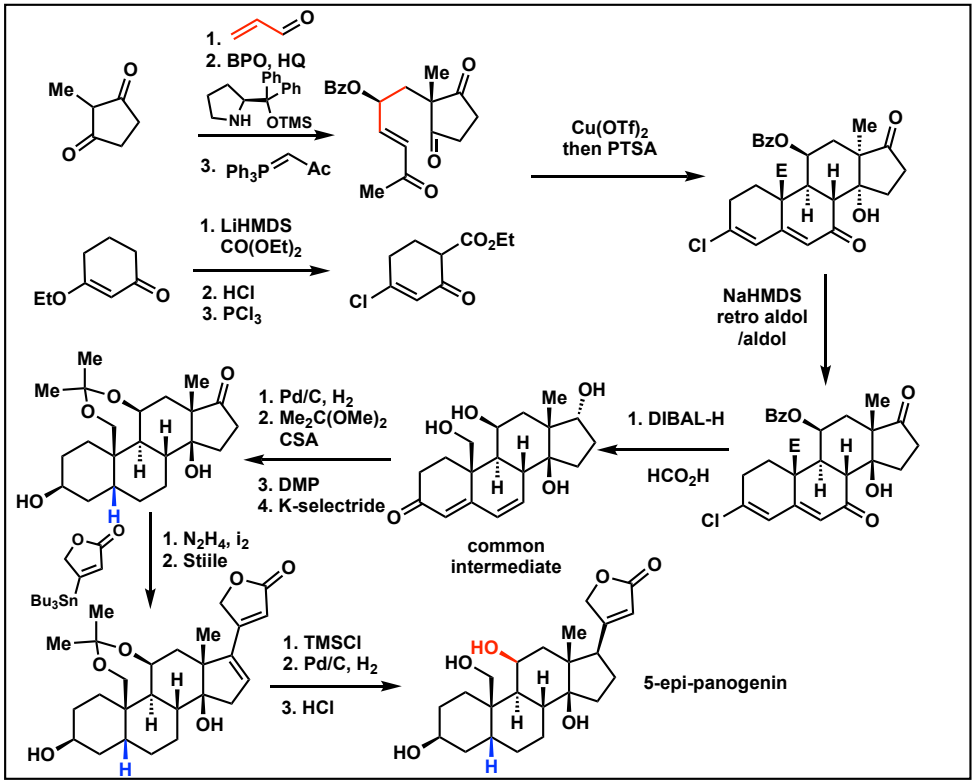


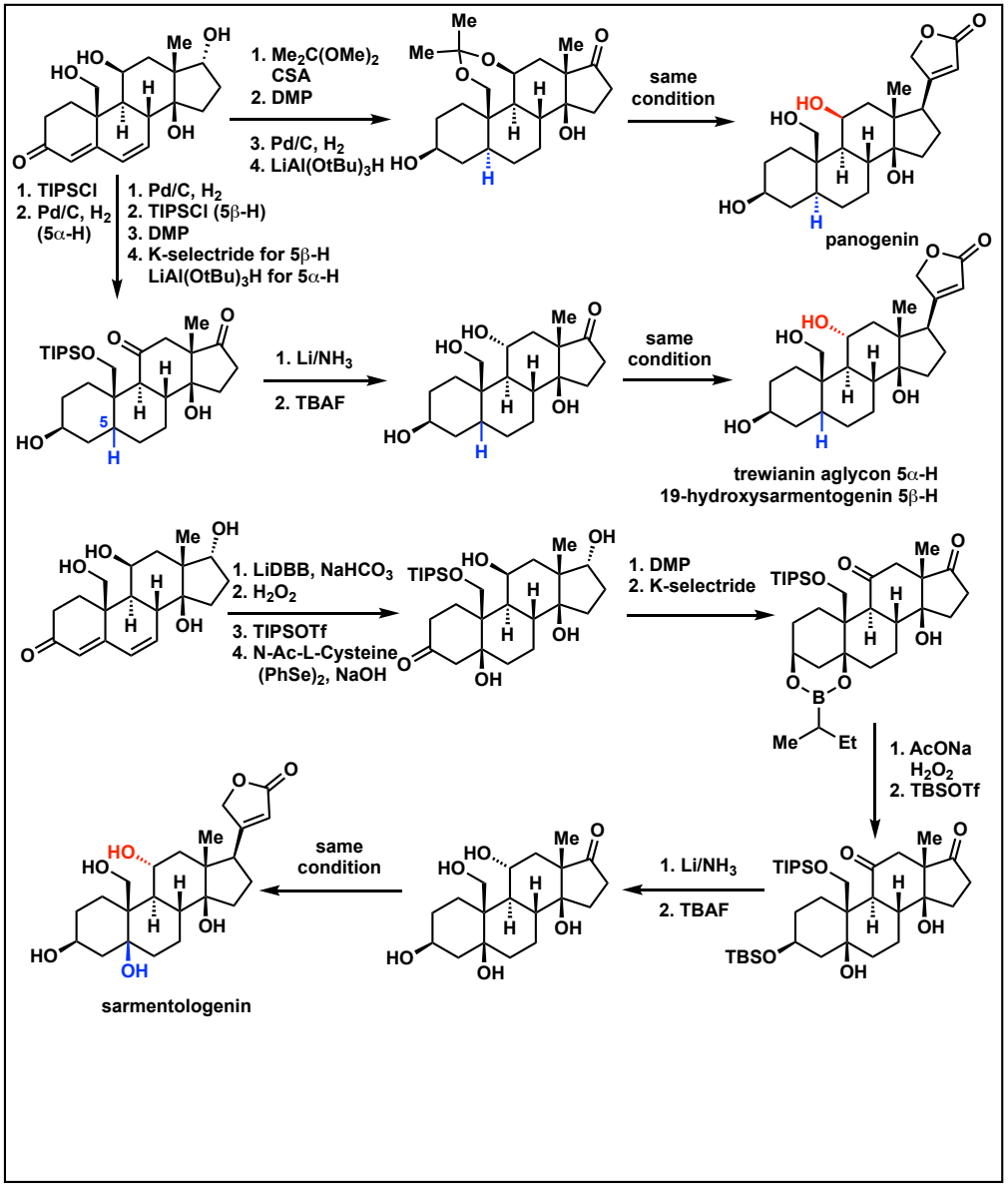


VIII. ouabagenin and 7 other cardenolides (Nagorny's synthesis)

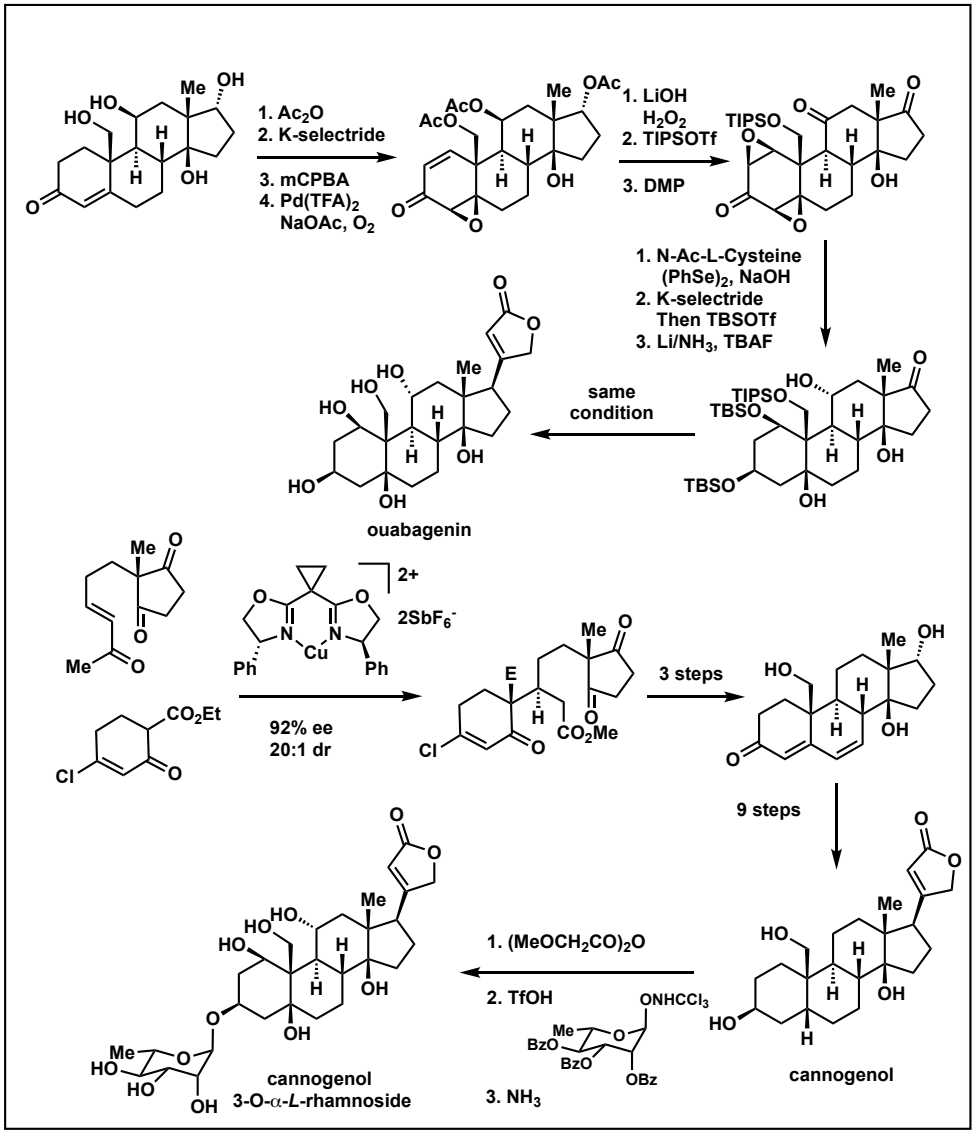
Retrosynthetic analysis



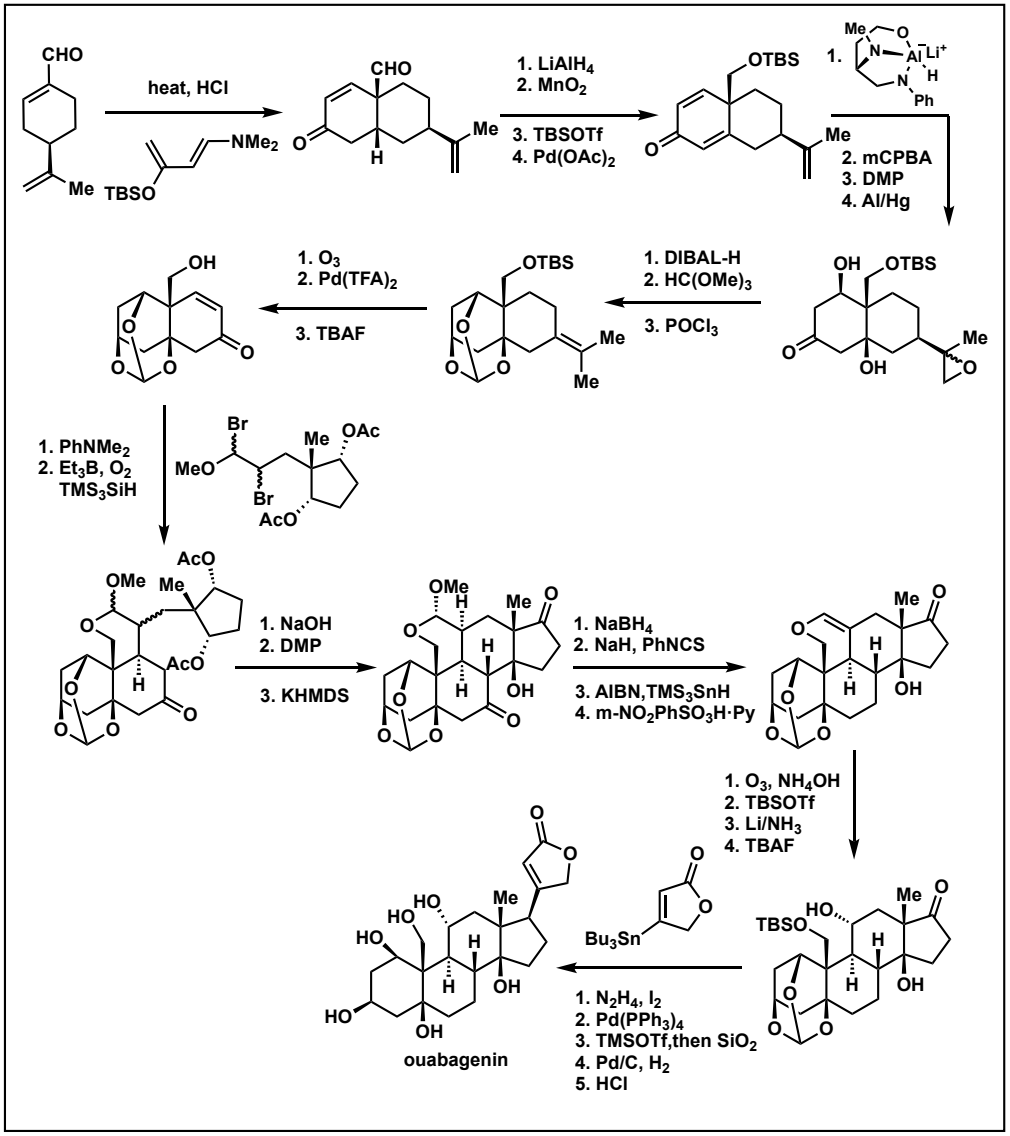




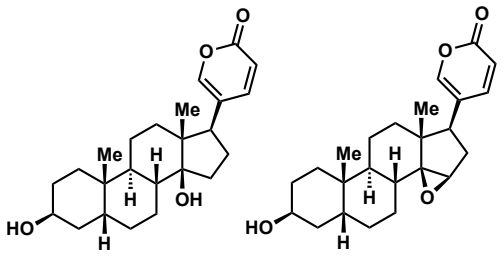
VIII. ouabagenin and 7 other cardenolides (Nagorny's synthesis)



IX. ouabagenin (Inoue's synthesis)



X. bufalin and resibufogenin

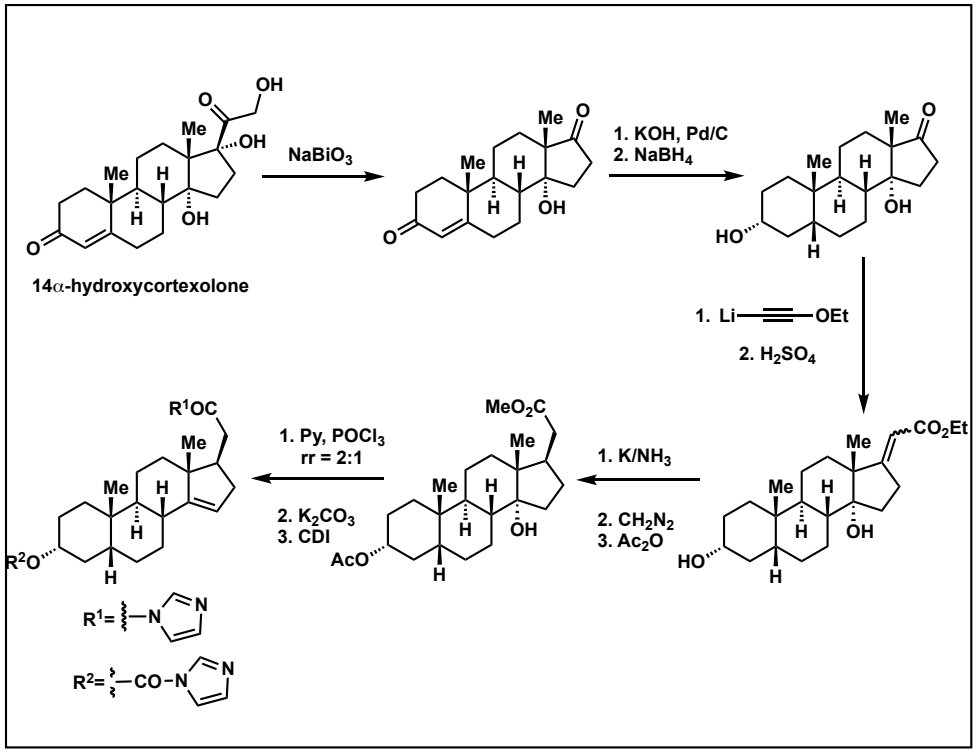


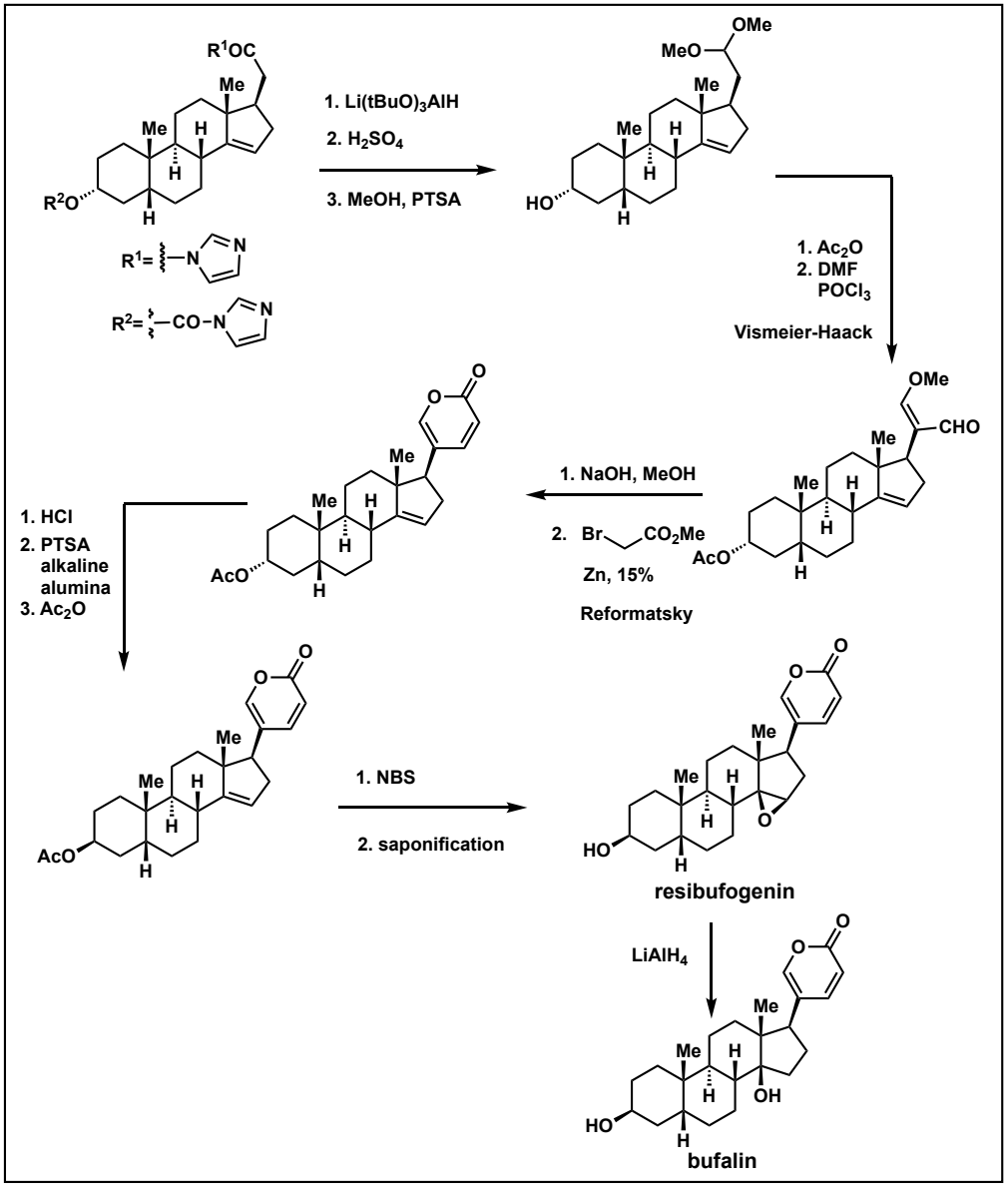
Structure feature

- intact steriod structure
- 7 conseutive chiral centers
- relatively low oxidation state

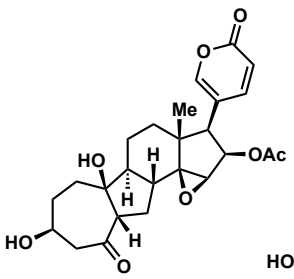
Background

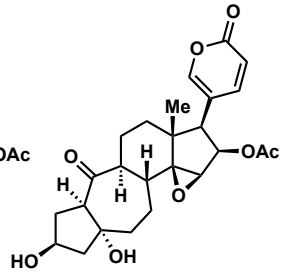
- derived from the dried venom of Chinese toad (Ch'an Su)





XI. bufogargarizins A and B


bufogargarizins A


bufogargarizins B

Structure feature

- abeo steroids
- unique 7/5 or 5/7 rings at A/B rings
- 7 conseutive chiral centers
- relatively high oxidation state

Background

- derived from the dried venom of *Bufo bufo gargarizans*
- scarcity of biological evaluation
- interconvertion of two compounds could be *via* retro- aldol/aldol