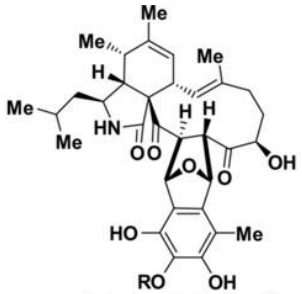
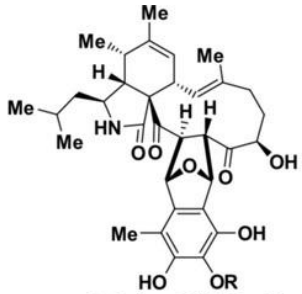
Total Syntheses of Asperchalasines A-E

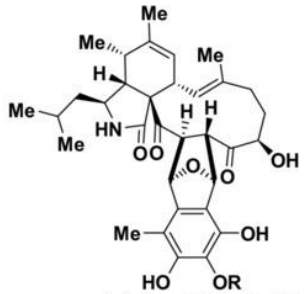
Bao R. etc. *Angew. Chem. Int. Ed.* **2018**, *57*, 14216



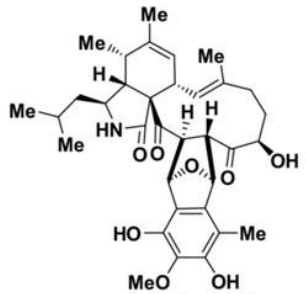
asperchalasine B (**1**): R = Me
asperchalasine G (**5**): R = H



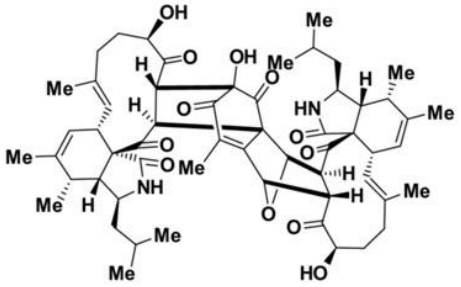
asperchalasine C (**2**): R = Me
asperchalasine F (**6**): R = H



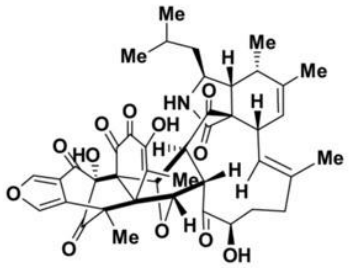
asperchalasine D (**3**): R = Me
asperchalasine H (**7**): R = H



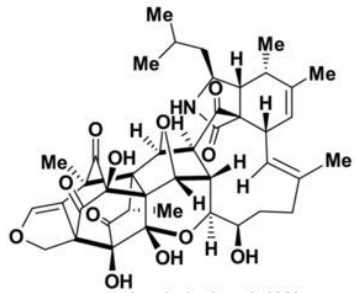
asperchalasine E(**4**)



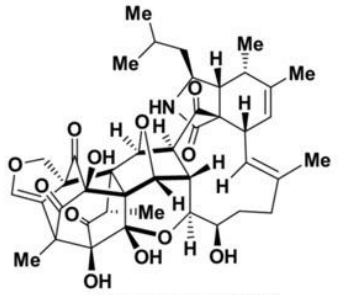
asperchalasine A (**8**)



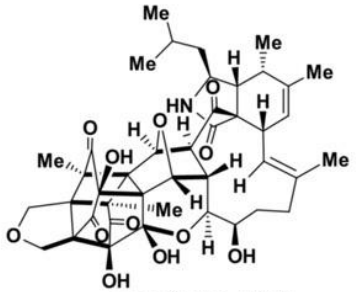
asperflavipine B (**9**)



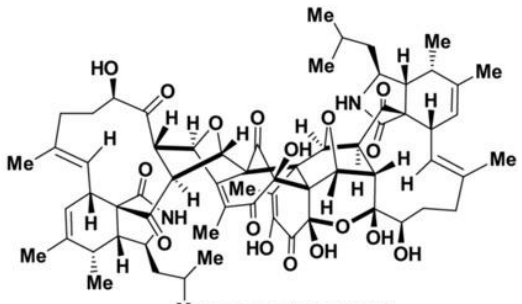
epicochalasine A (**10**)



epicochalasine B (**11**)



aspergilasine A (**12**)

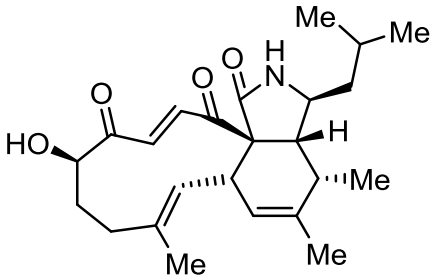


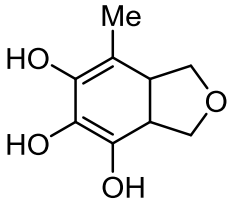
asperflavipine A (**13**)

Representative merocytochalasans

Asperchalasines is a collection of merocytochalasans from fermentation broth of Aspergillus flavipes

They are series of fungal secondary metabolites consisting of two types of subunits :
the tricyclic cytochalasan and **bicyclic epicoccine.**

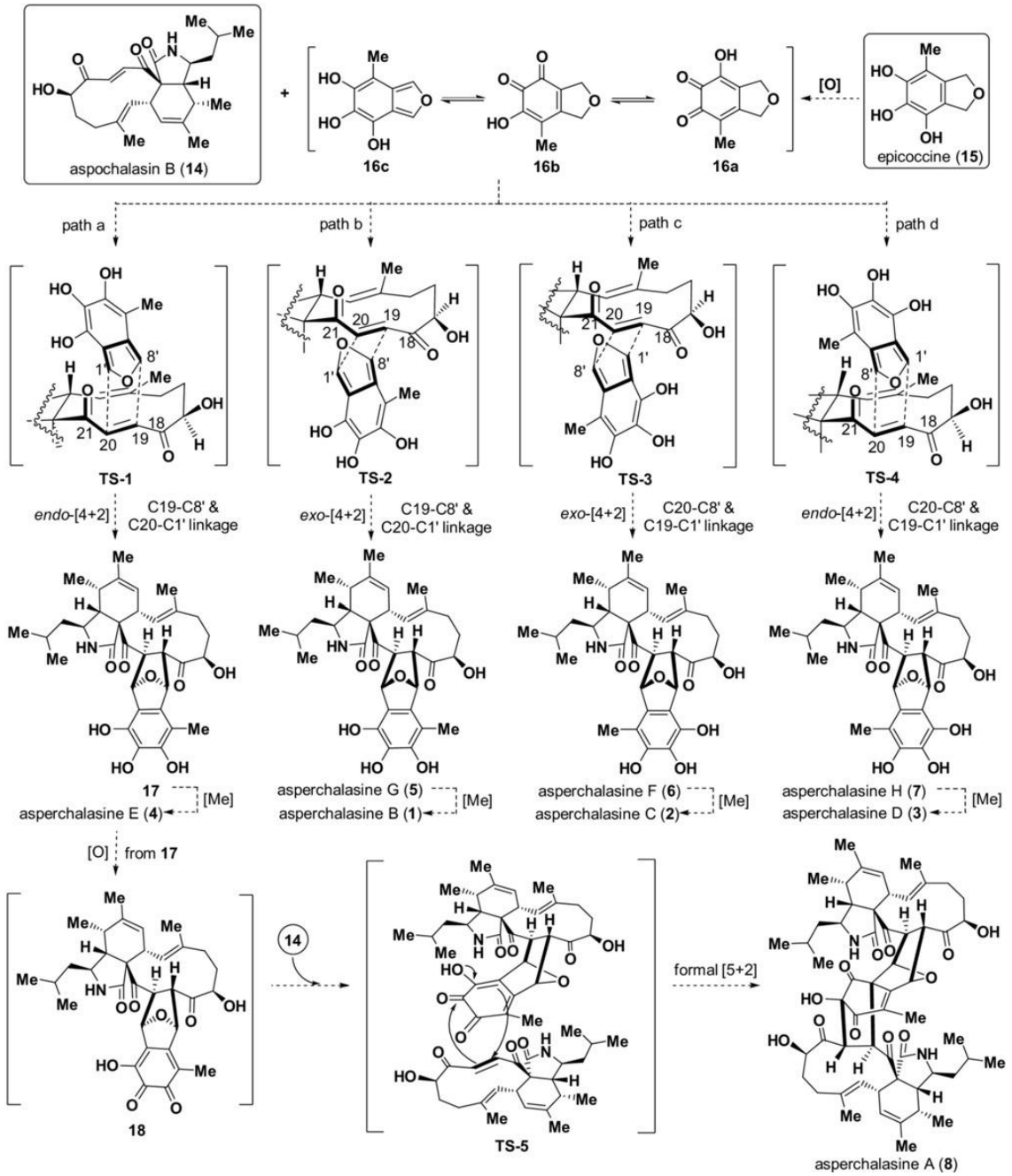




Some of merocytochalasans can serve as a selective cell cycle regulor against cancer cells.

Synthetically, intricate polycyclic ring systems, high degrees of functionalities and multiple stereogenic centers pose formidable challenges to synthetic chemists.

12/18/2018 Xinyu Yang



The plausible biosynthetic origin of asperchalasines

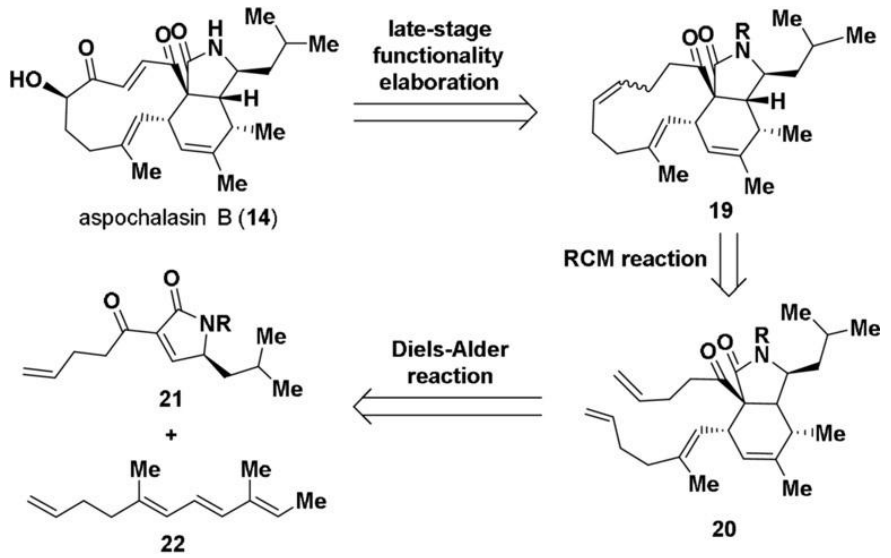
Synthetic strategy mainly built on biosynthetic origin:

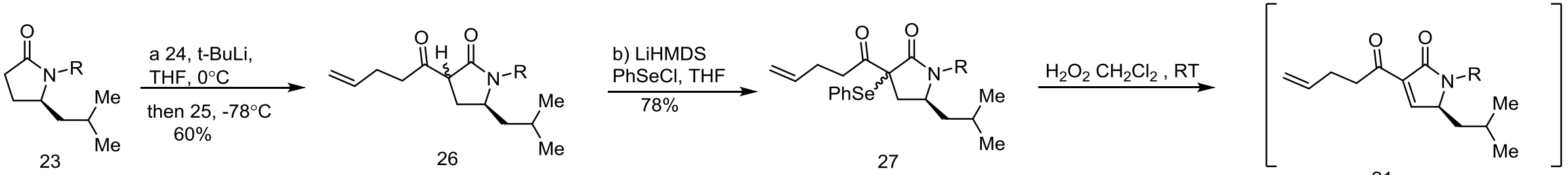
Two common precursors, aspochalasinB (**14**) and epicoccine(**15**)

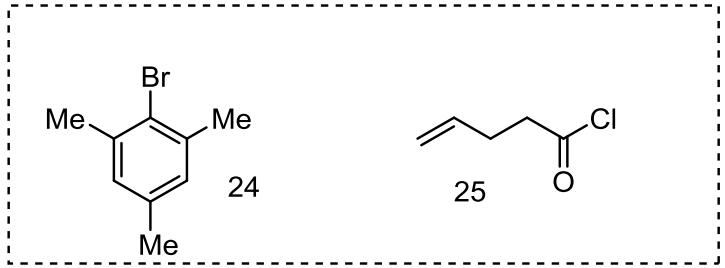
Due to underlying endo/exo selectivity and regioselectivity, the Diels-Alder reaction could lead to four heterodimers asperchalasines **F-H** and **17.**
17 could undergo further transformations to form hetero-trimer asperchalasine **A**

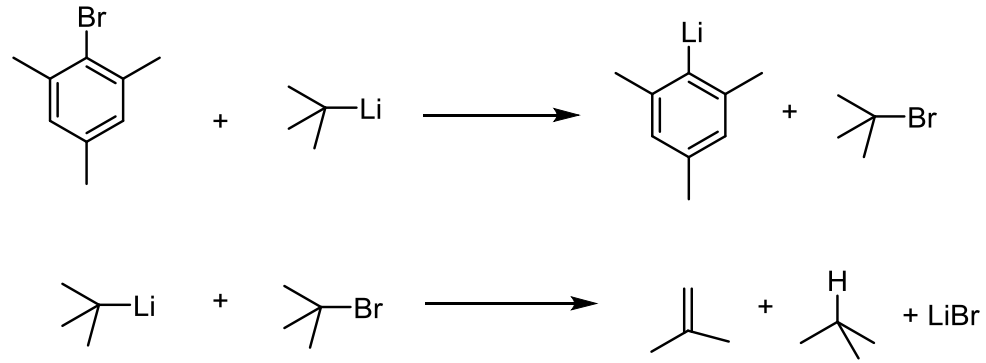
To validate the biosynthetic hypothesis, they start with 14 and 15 precursor synthesis.

Retrosynthetic analysis of aspochalasin B (14)

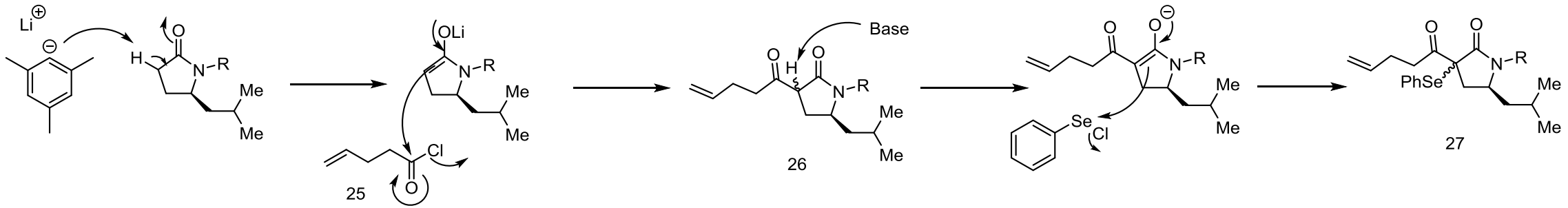


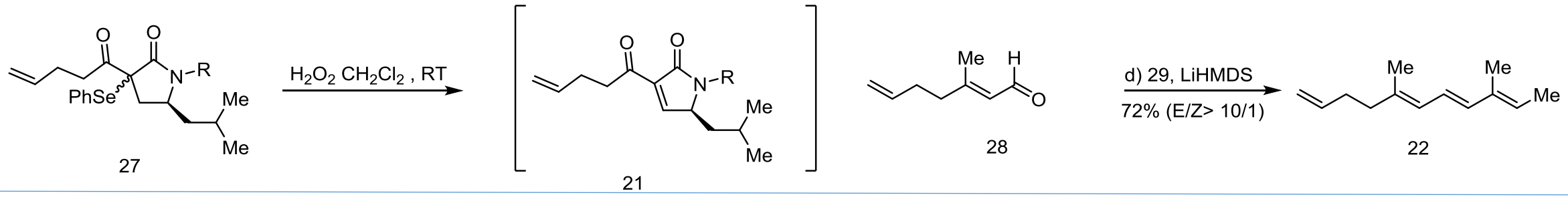




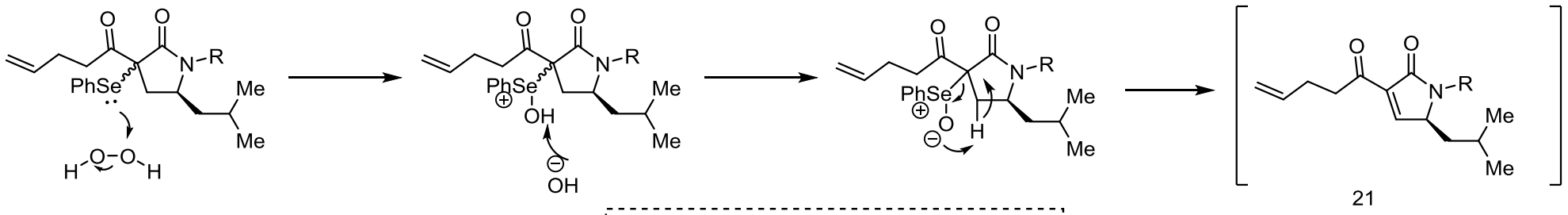


Sequential selenylation and oxidative elimination

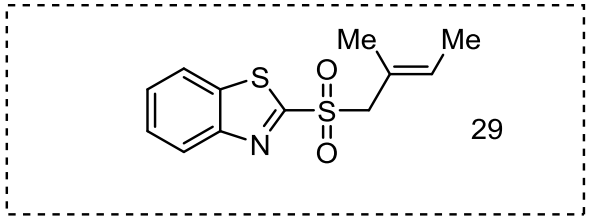


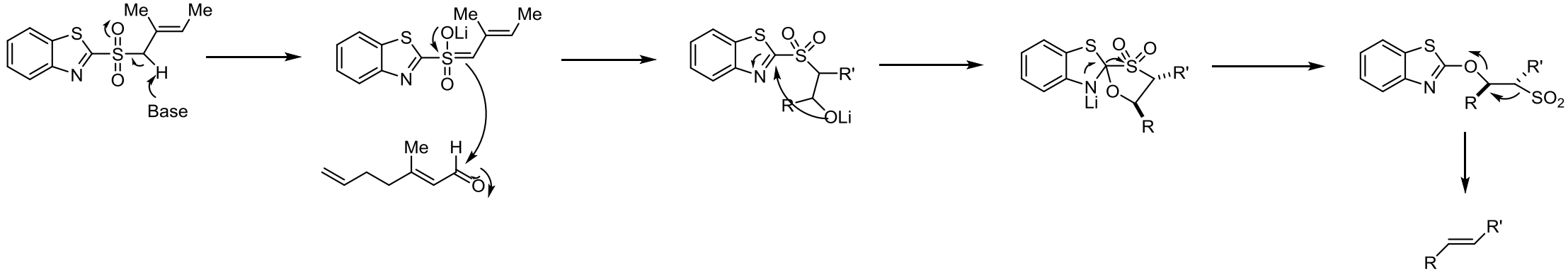


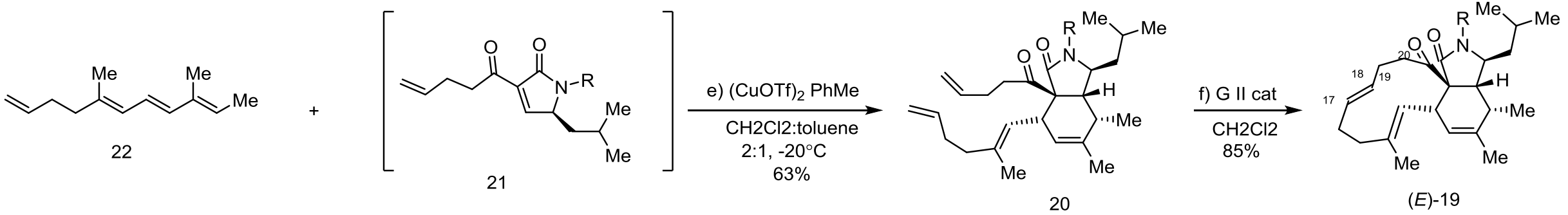
Sequential selenylation and oxidative elimination



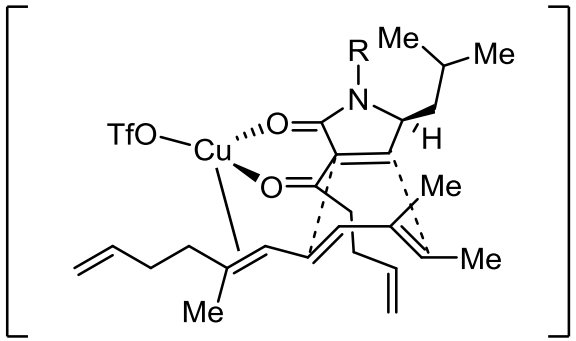
Julia Olefination



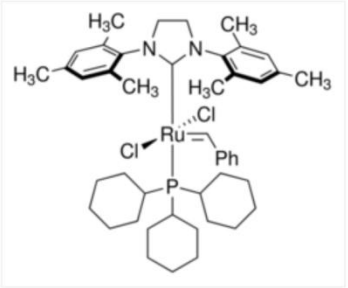




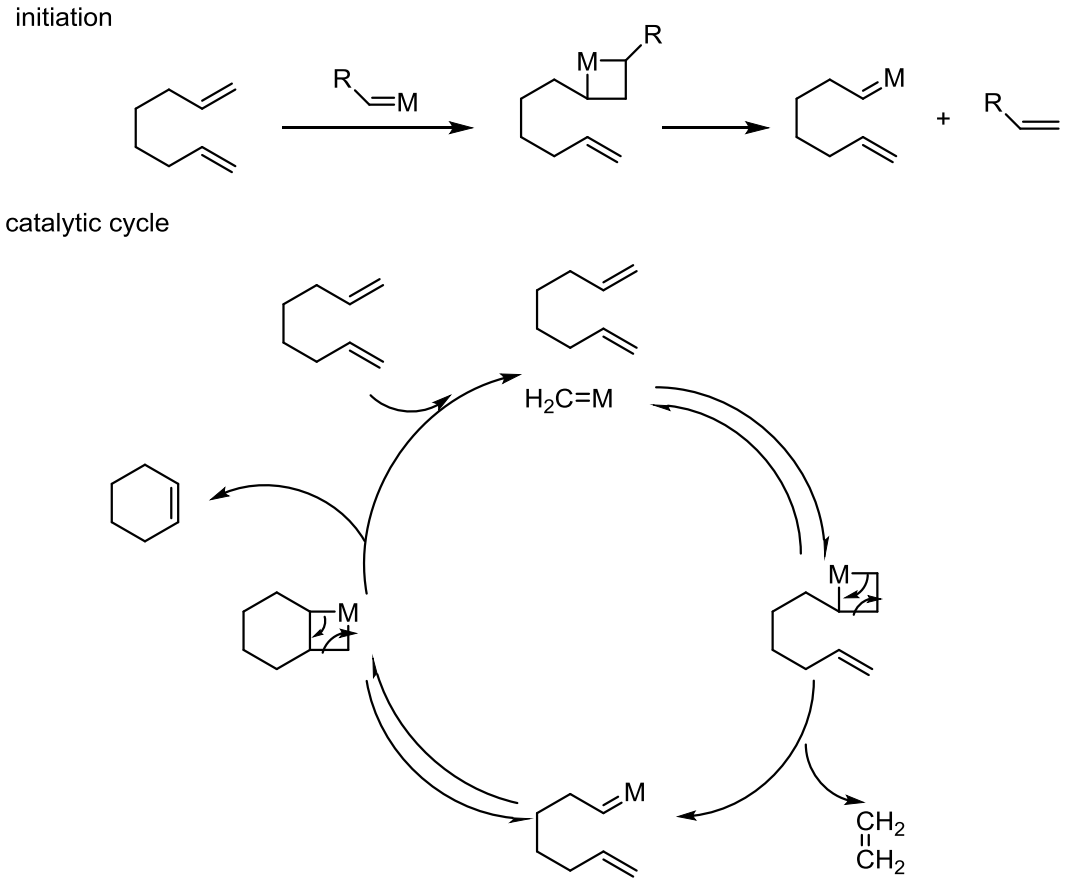
Lewis acid-promoted Diels-Alder reaction:

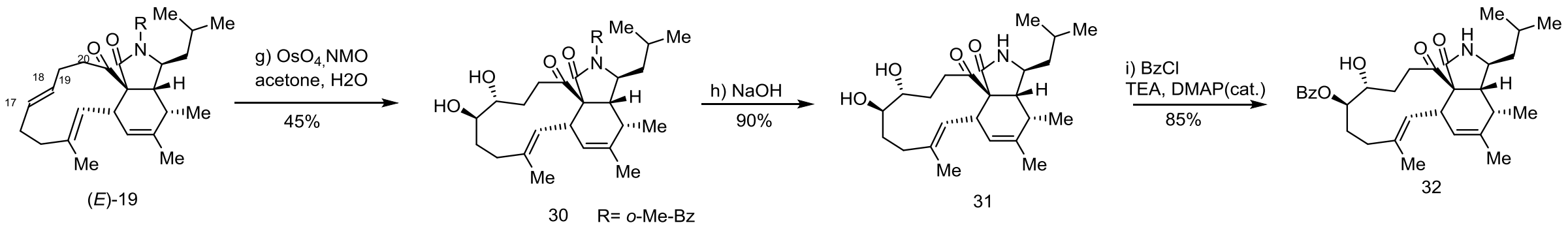


endo-TS-6

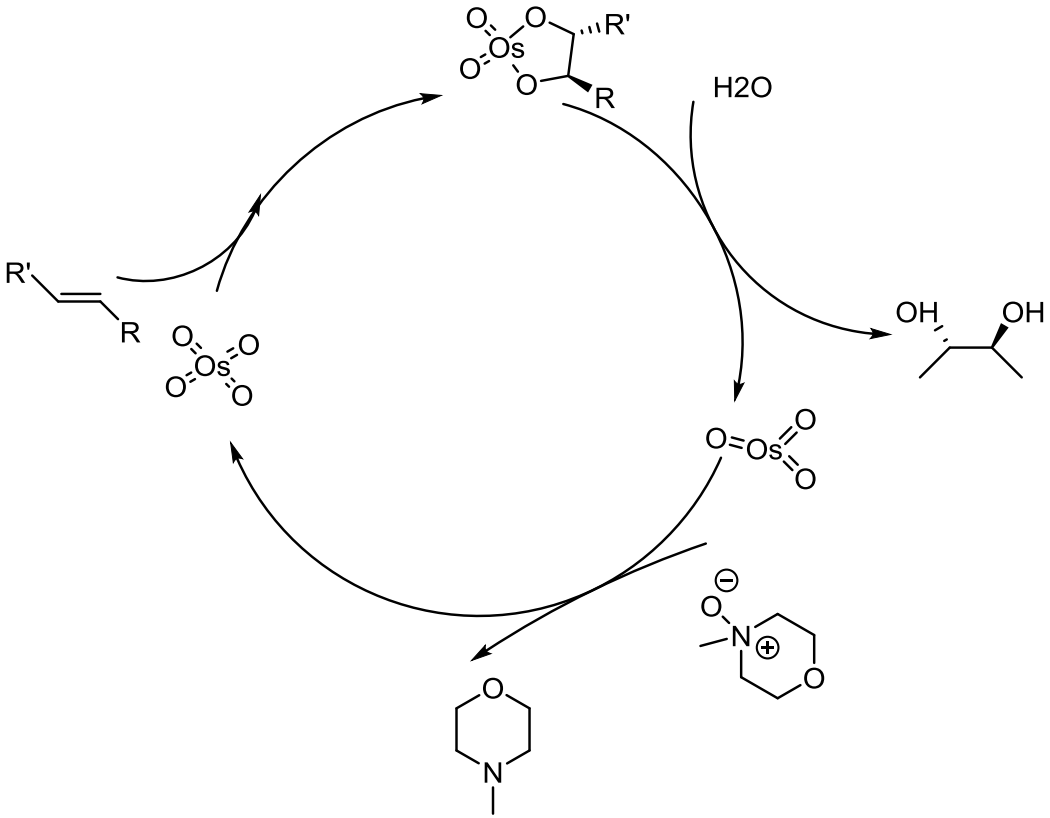


Grubb's second generation Catalyst catalyzed Ring Closing metathesis:

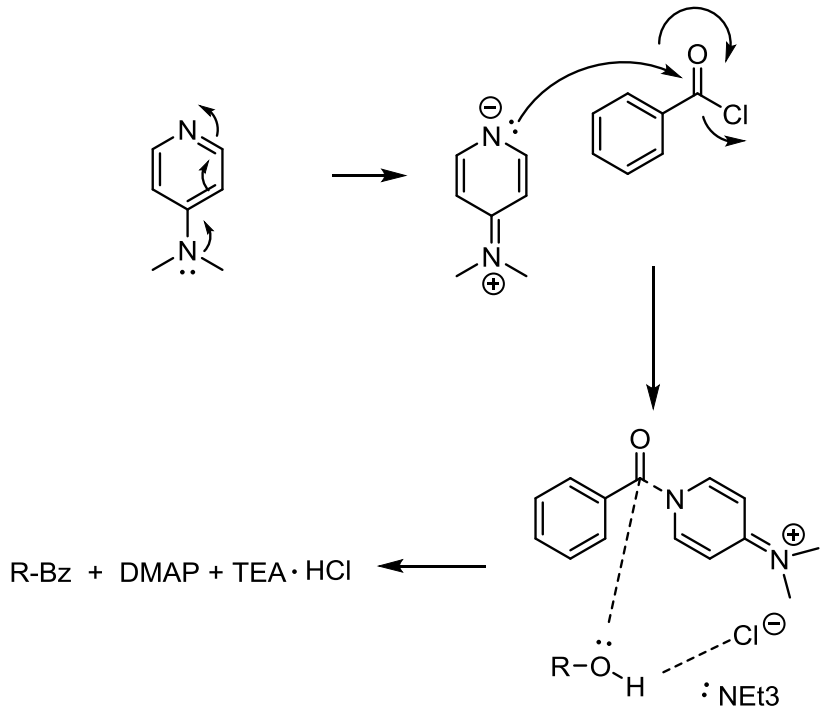


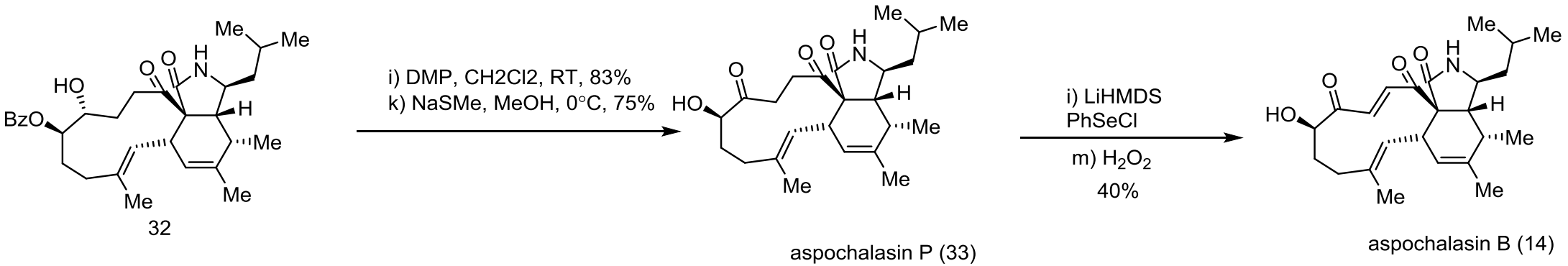


Upjohn dihydroxylation



Selective 17-OH protection





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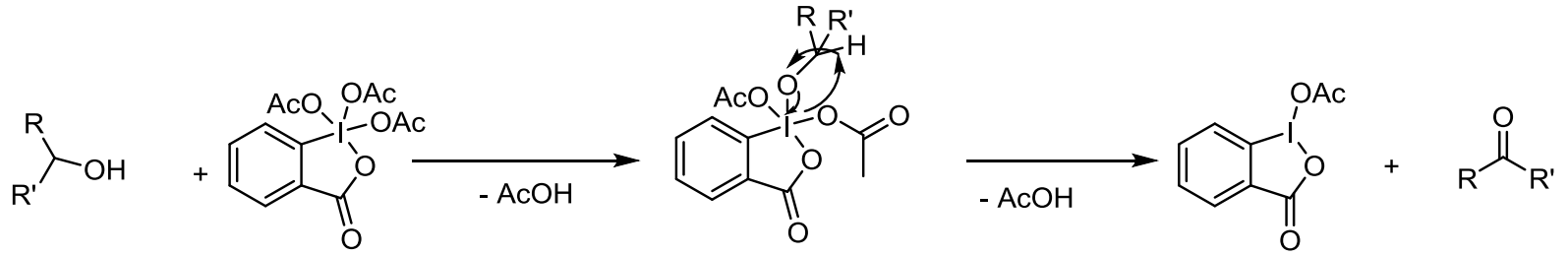
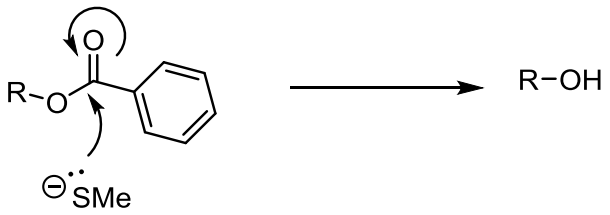
aspochalasin P (33)

aspochalasin B (14)

Dess-Martin Oxidation



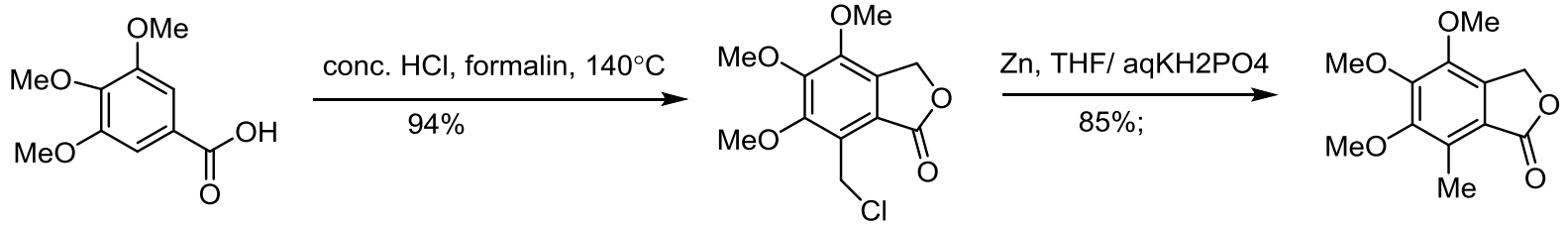
Benzoyl group deprotection



Another sequential selenylation and oxidative elimination:

Forming unsaturated carbonyl (mechanism see before)

Syntheses of epicoccine part



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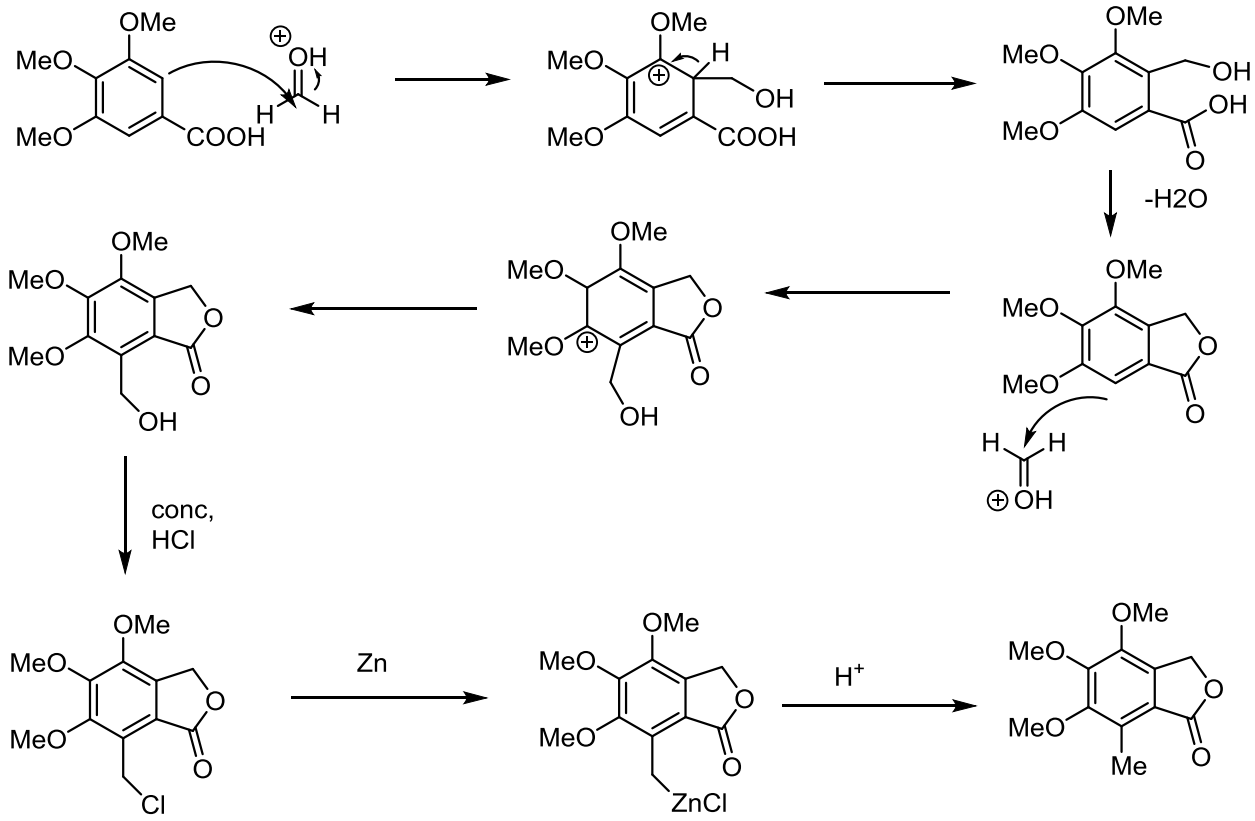
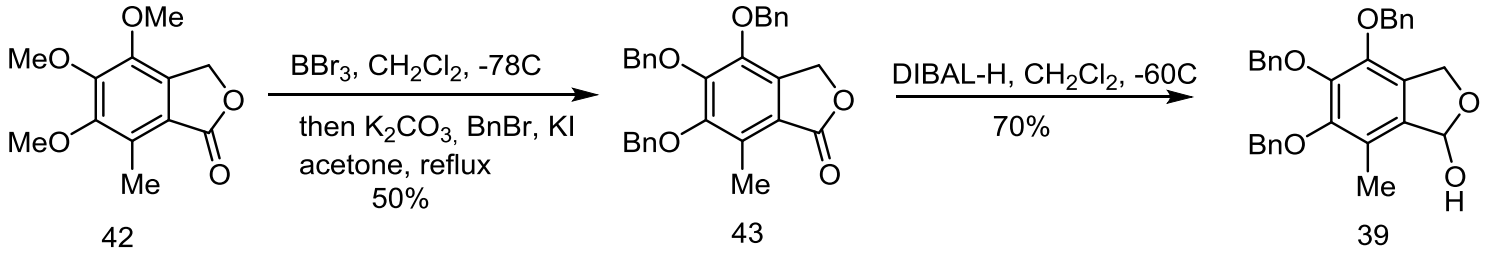
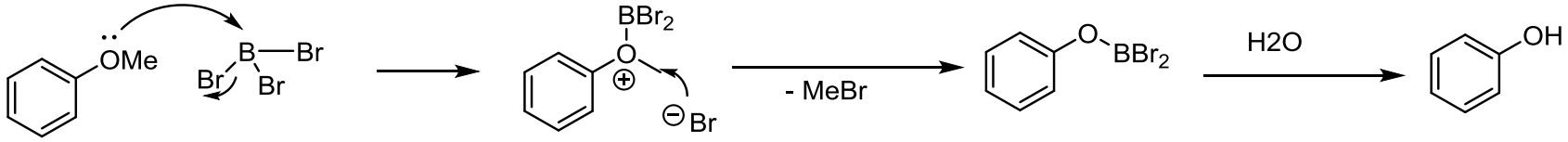
Blanc Chloromethylation and dechlorination



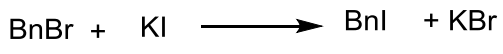
Trauner D. *Angew. Chem. Int. Ed.* **2014**,*126*,13632

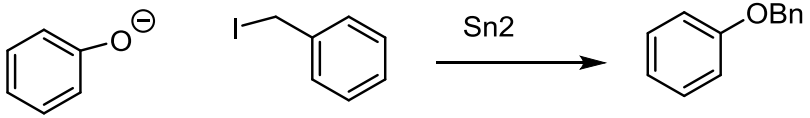


Demethylation:

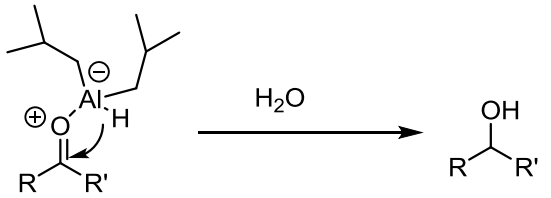


Benzyl protection

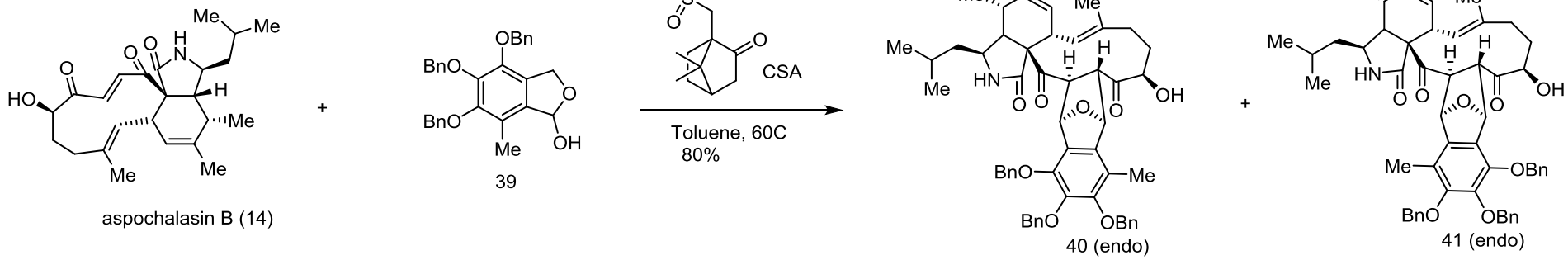


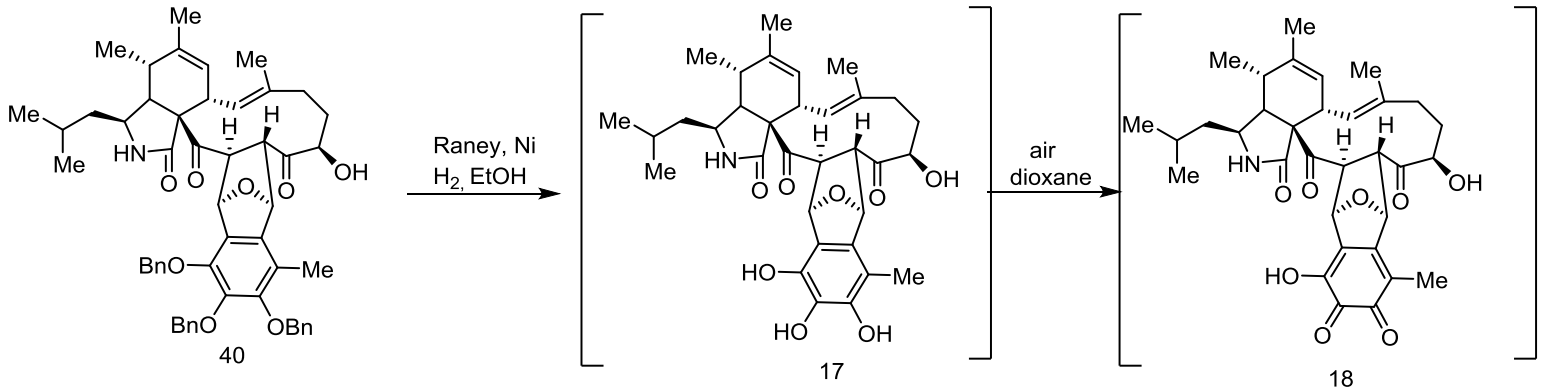


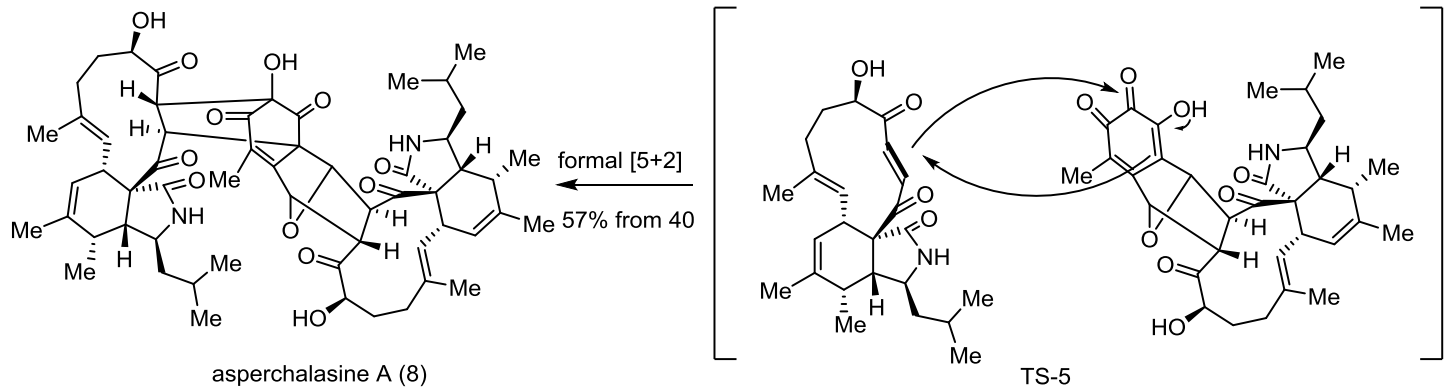
DIBAL reduction:



Finishing syntheses Of asperchalasine A

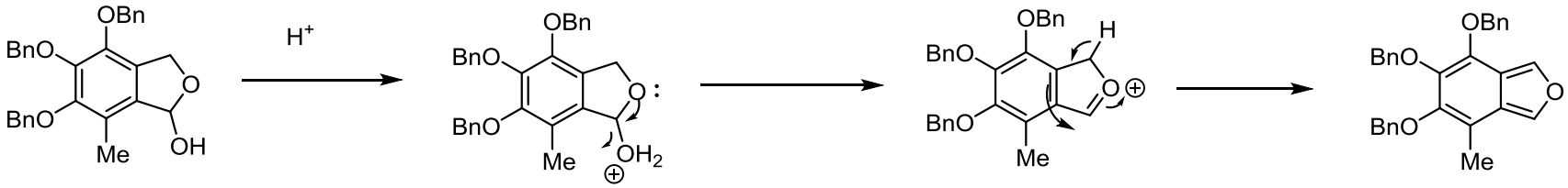






Back-up mechanism of last page:

Diels-Alder reaction forming **40** :



Hydrogenolysis of benzyl group: