

Problem Session (4)

Topic: Recent Total syntheses

Introduction: hyperelodione D

Biological activity:

• Cytotoxic effects against HeLa and HepG-2 cell lines

Structure:

• Polycyclic polyprenylated acylphloroglucinols (PPAPs) family (e.g. hyperforin)

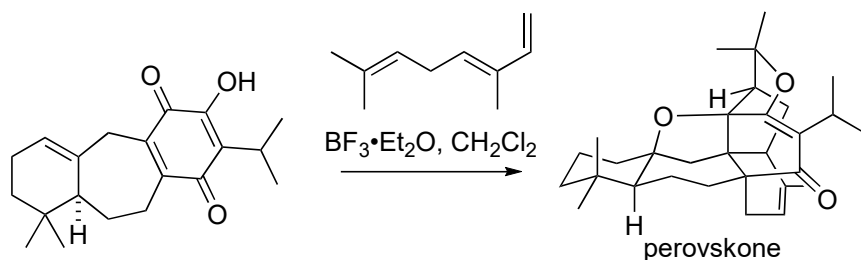
• 6/6/5/5 fused tetra cyclic core

Total synthesis:

• Not reported (isolation reported in 2021)

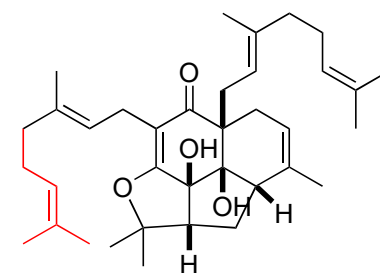
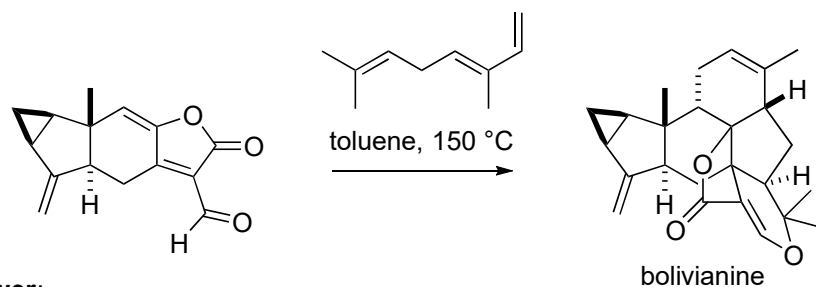
Key reaction (Diels–Alder reaction with *E*- β -ocimene):

Majetich et. al. *Tetrahedron*, **2011**, *67*, 10129



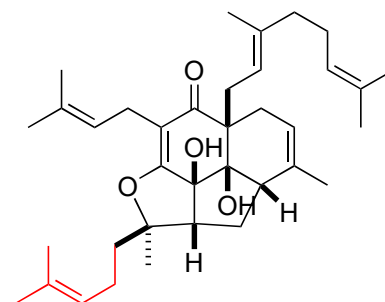
Liu et. al. *J. Am. Chem. Soc.*, **2013**, *135*, 9291

(Please see: 170203_PS_Shimizu_Shinzuke)



1-2

proposed structure of hyperelodione D

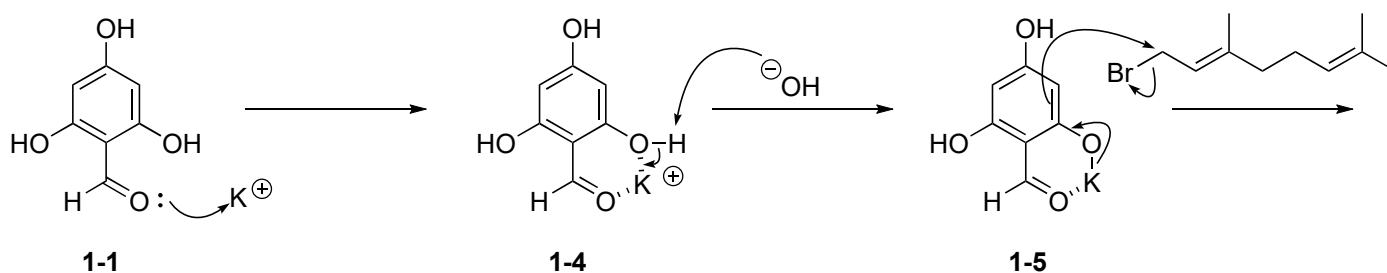
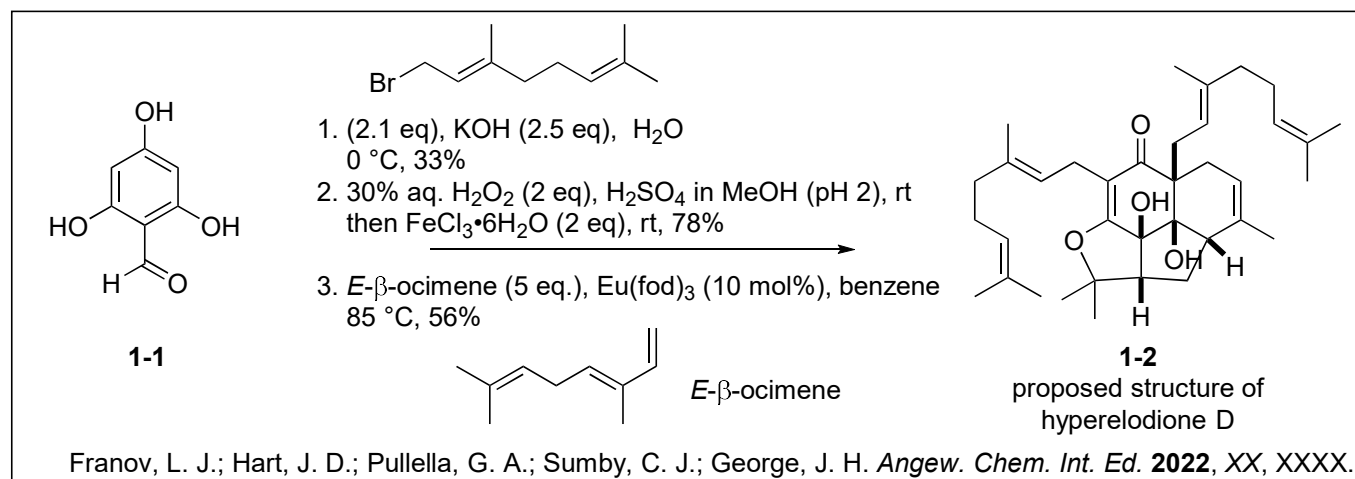


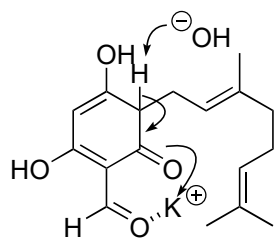
1-3

revised structure of hyperelodione D

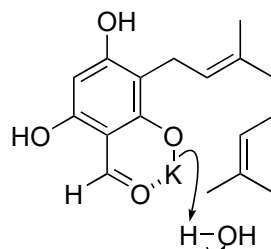
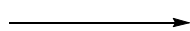
Answer:

1-1. Reaction mechanism

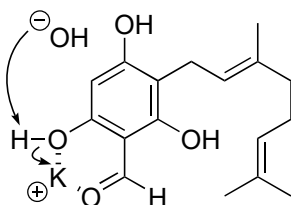
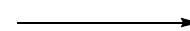




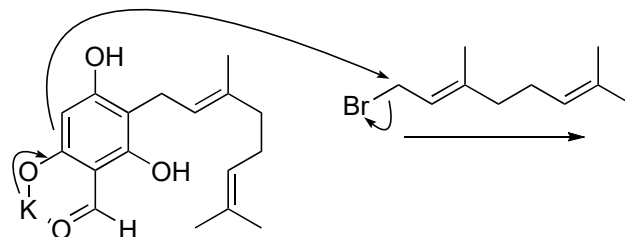
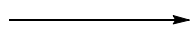
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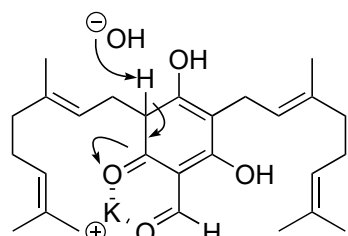
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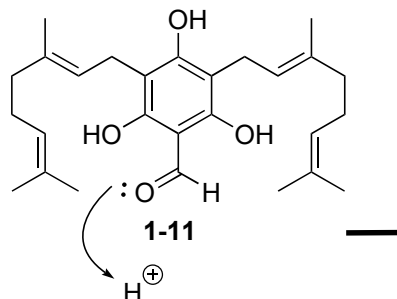
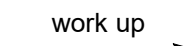
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1-9

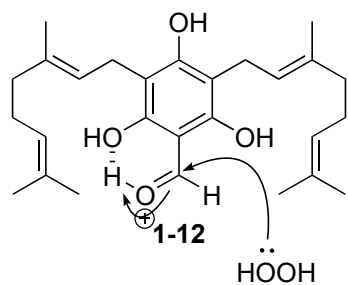
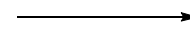


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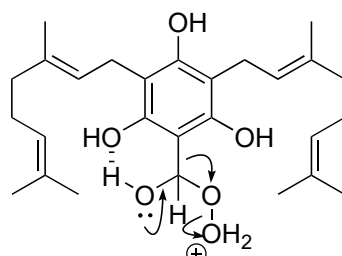
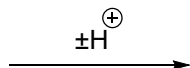


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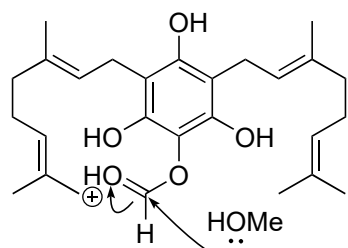
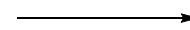
1st step



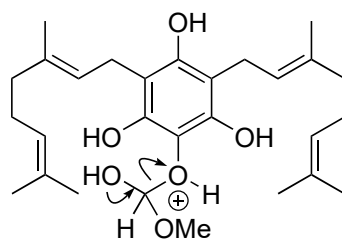
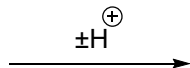
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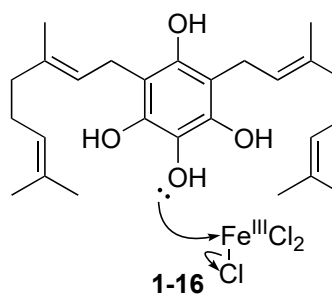
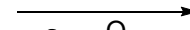
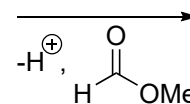
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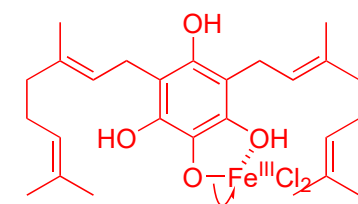
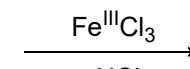
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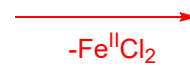
1-15



1-16



1-17



Introduction: crinipellins**Biological activity:**

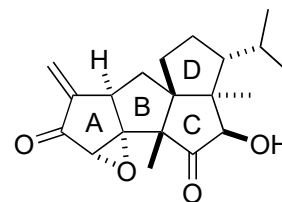
- Antibacterial and anticancer activities

Structure:

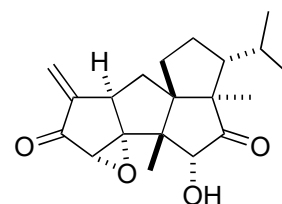
- Linear cis,anti,cis-triquinane (ABC rings) and angular triquinane (BCD rings)
- 8-10 stereogenic centers containing 3 quaternary carbon

Total synthesis:

- First total synthesis of (±)-crinipellin B by Piers's group (*J. Org. Chem.*, **1993**, 58, 11.)
- First asymmetric total synthesis of (-)-crinipellin A by Lee's group (*J. Am. Chem. Soc.*, **2014**, 136, 10274.)
(Please see: 180602_PS_Kotaro_Tokumoto and 200208_PS_Yuto_Hikone)
- Recent asymmetric total synthesis of (-)-crinipellin A and B by Yang's group (*Angew. Chem., Int. Ed.*, **2018**, 57, 8744.)
(Please see: 200208_PS_Yuto_Hikone)



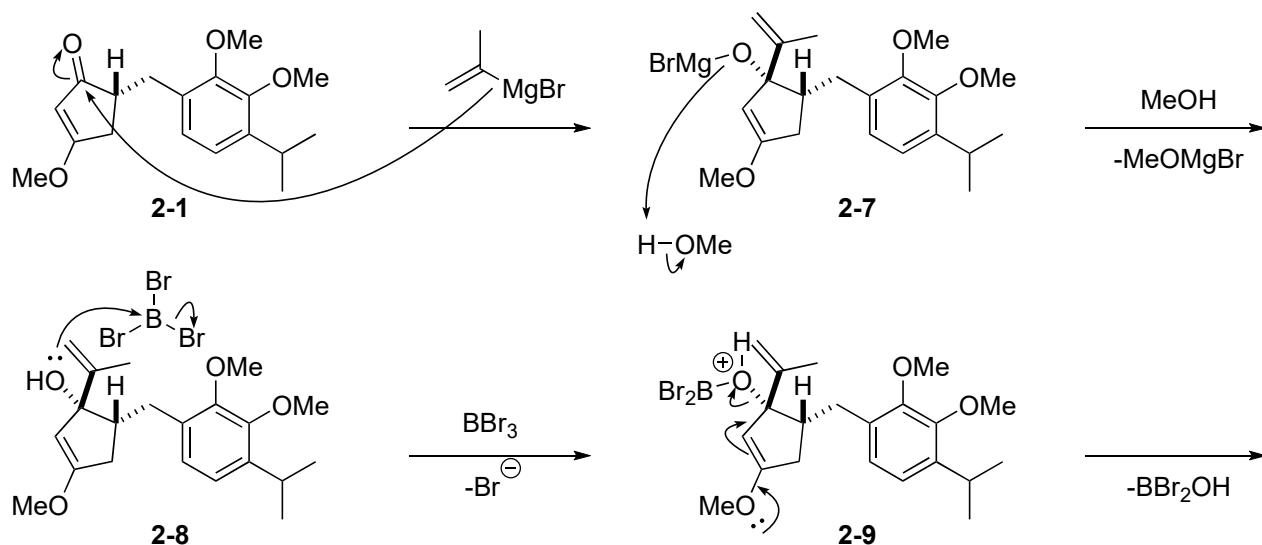
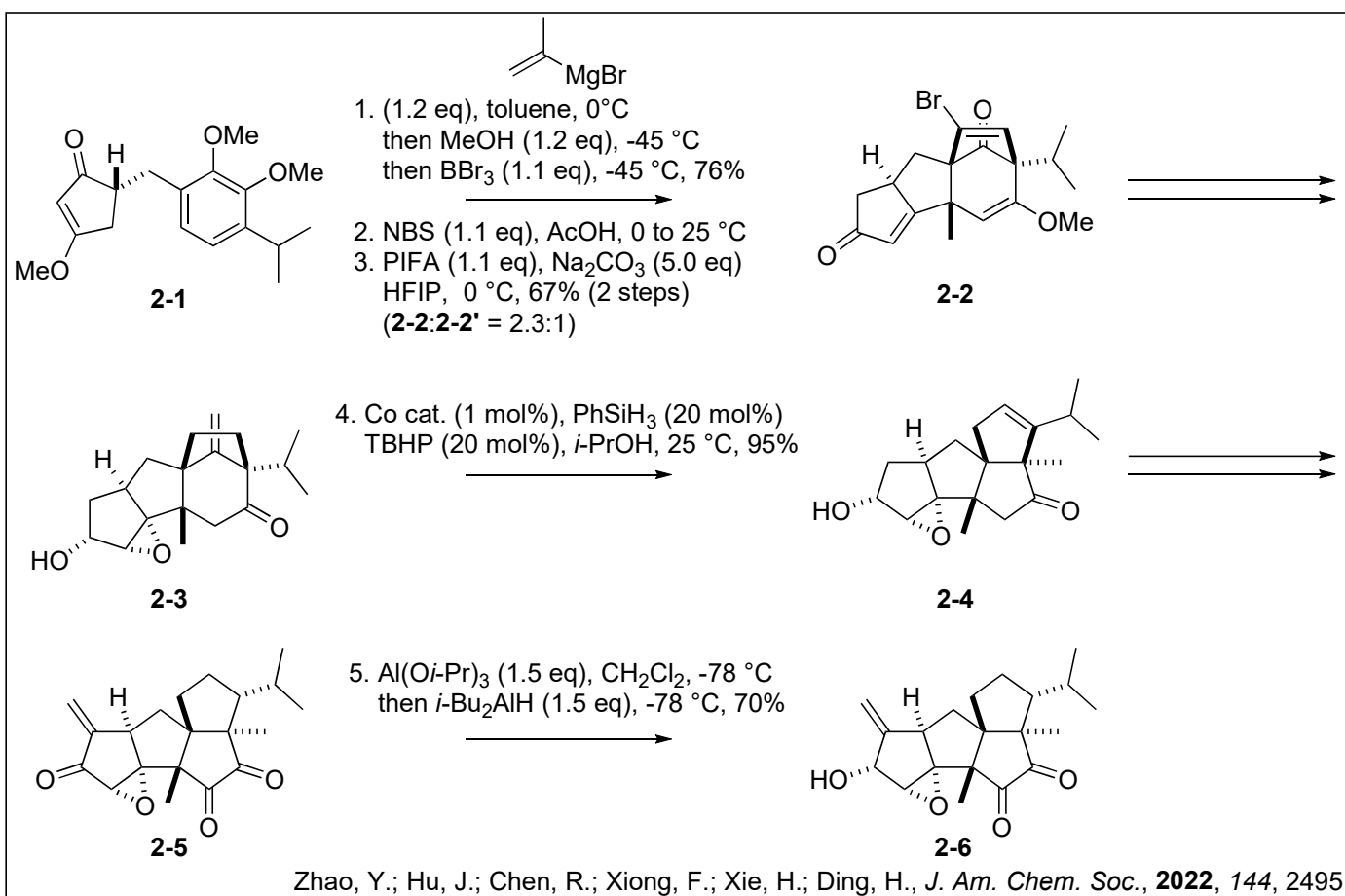
crinipellin A

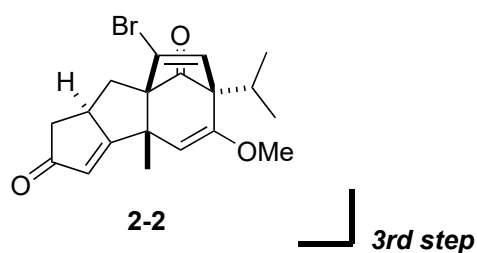
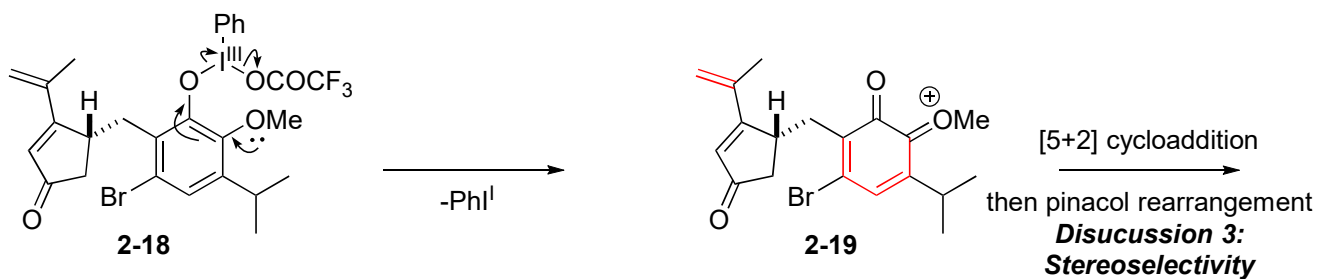
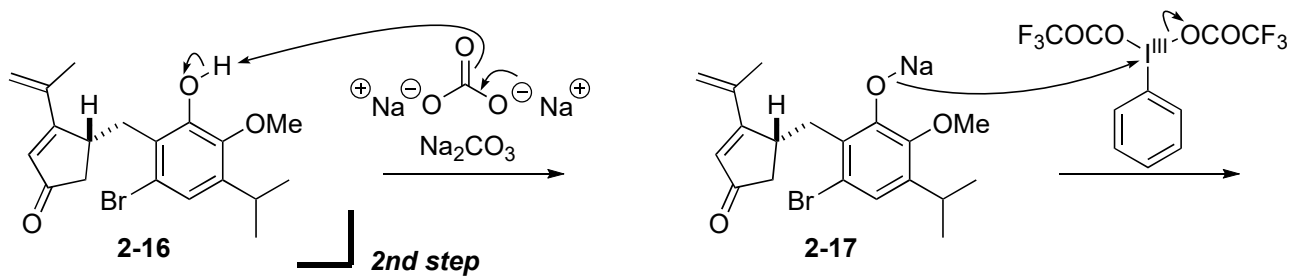
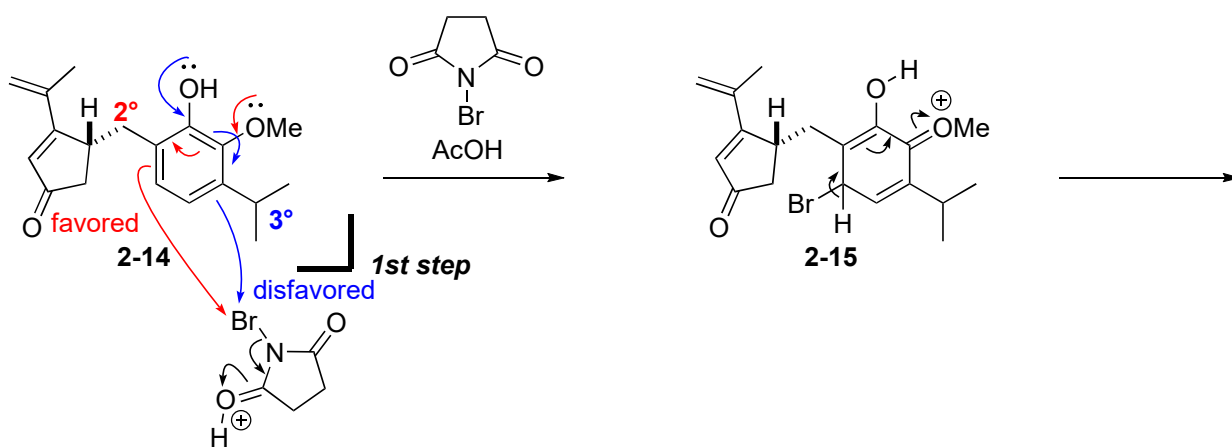
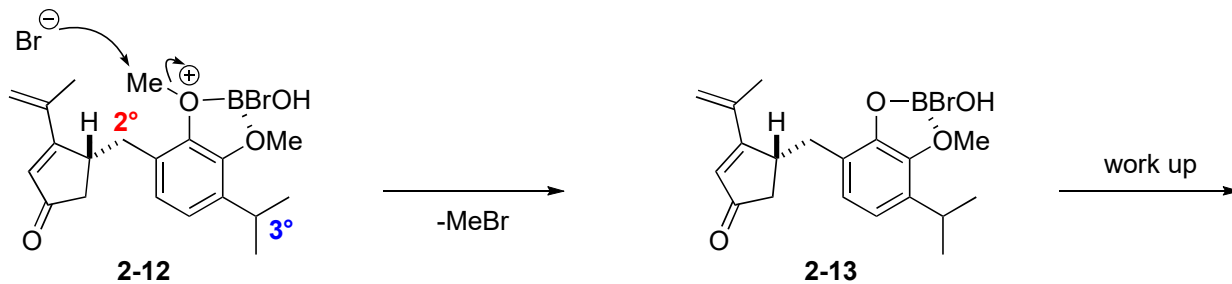
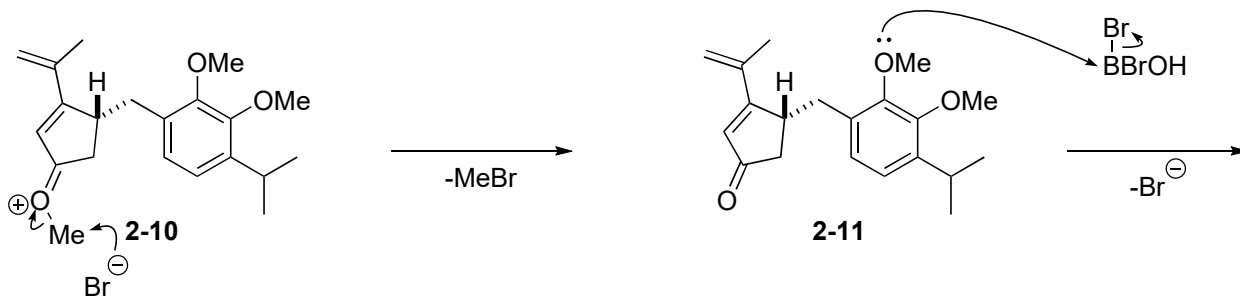


crinipellin B

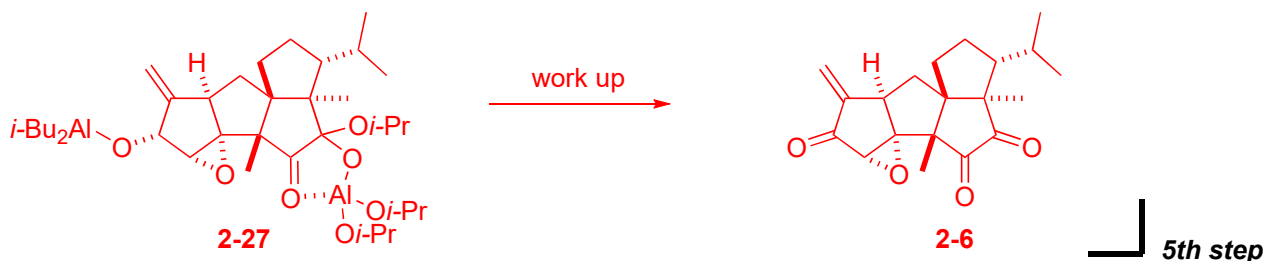
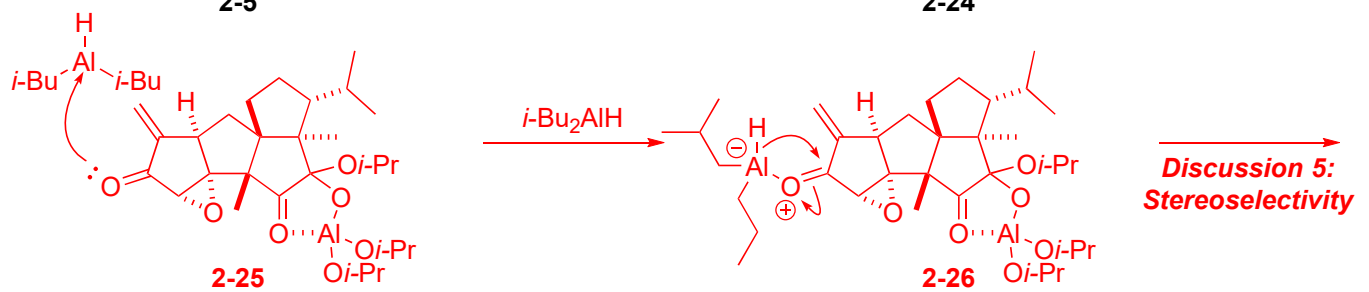
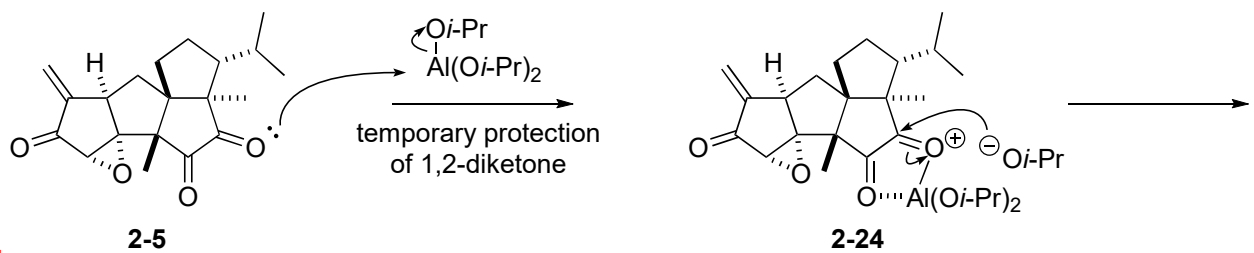
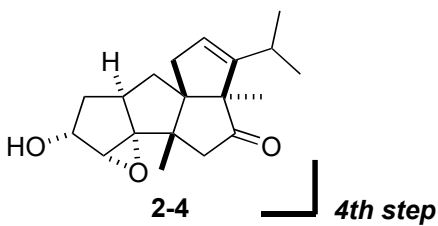
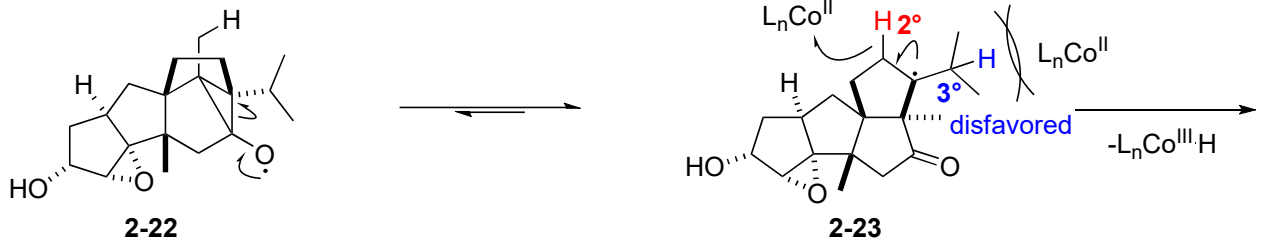
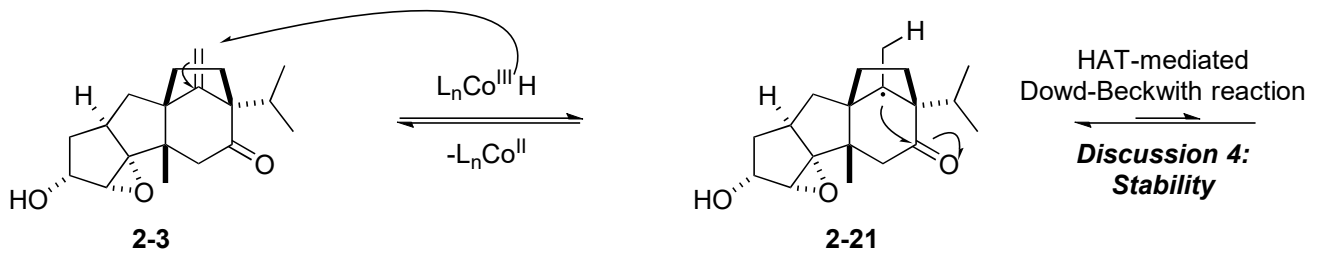
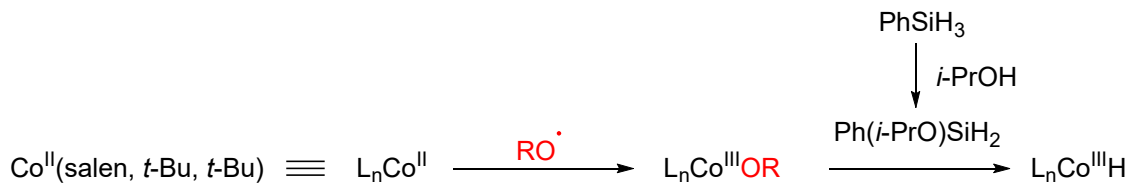
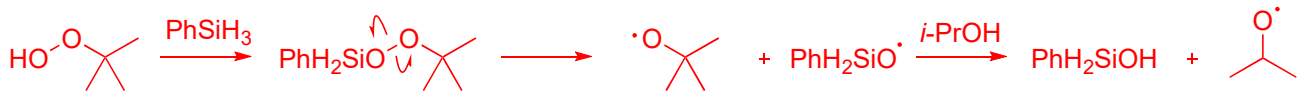
Answer:

1-1. Reaction mechanism

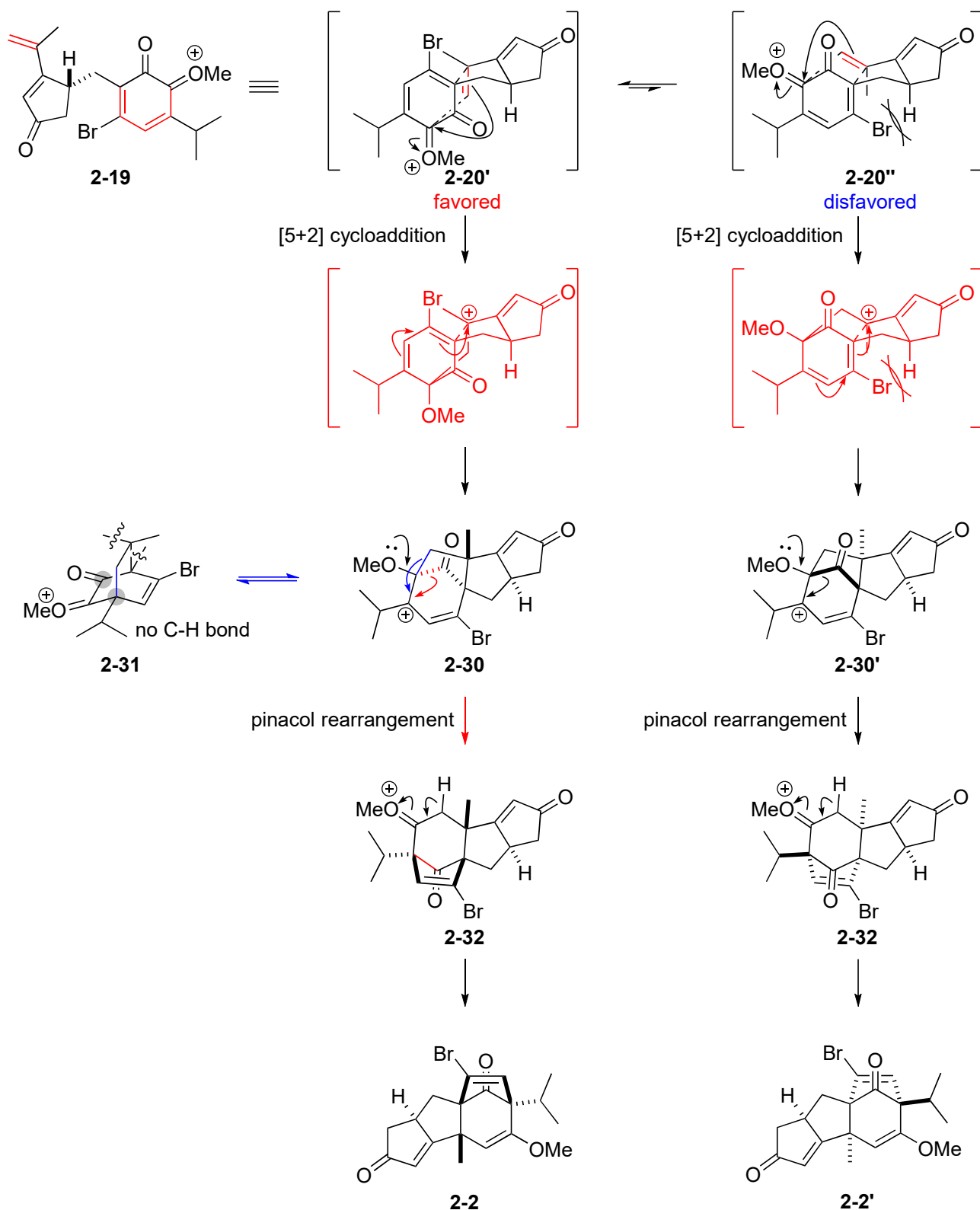




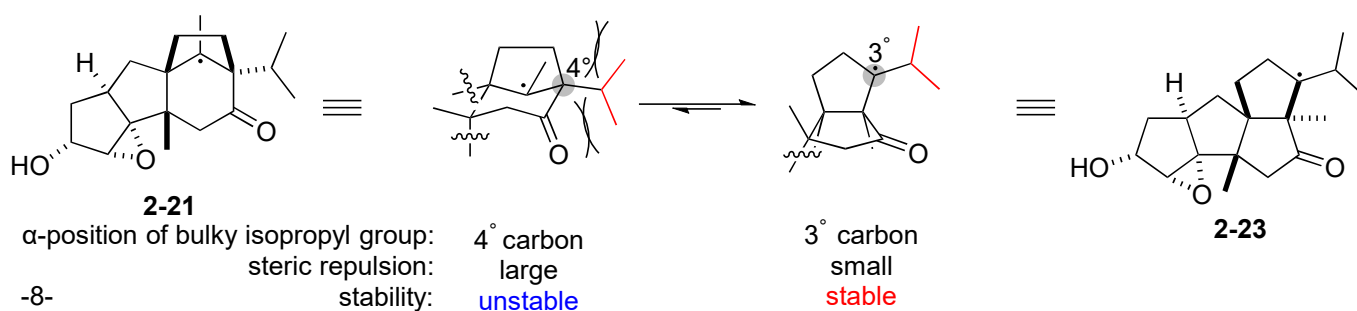
[5+2] cycloaddition
then pinacol rearrangement
Discussion 3:
Stereoselectivity



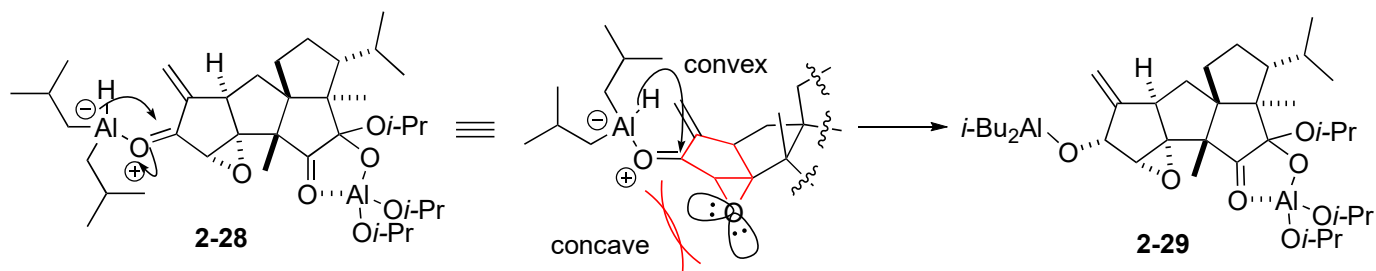
2-2. Discussion 3: Stereoselectivity of [5+2] cycloaddition and pinacol rearrangement



2-3. Discussion 4: Relative stability between compounds **2-21** and **2-23**



2-4. Discussion 5: Stereoselectivity of *i*-Bu₂AlH reduction



1. attack from the face avoiding from repulsion against lone pair of epoxide
2. attack from convex face of bicyclo [3.1.0]

