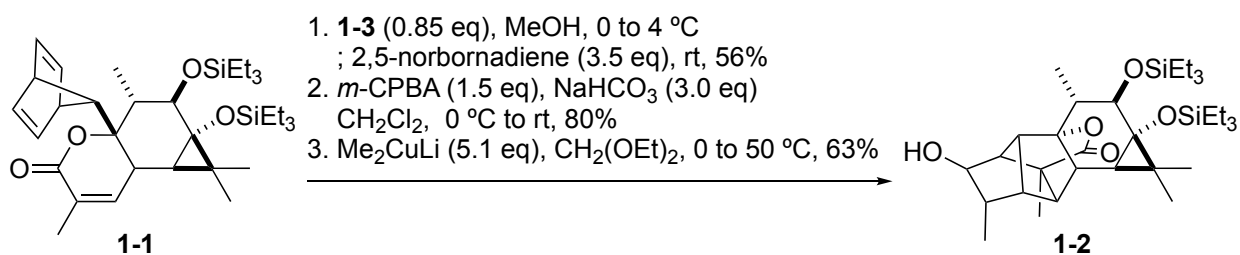
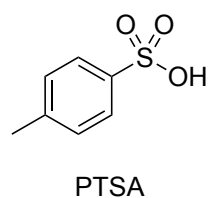
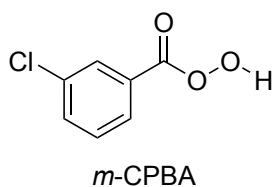
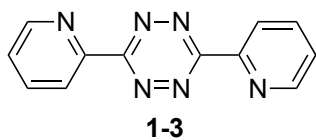
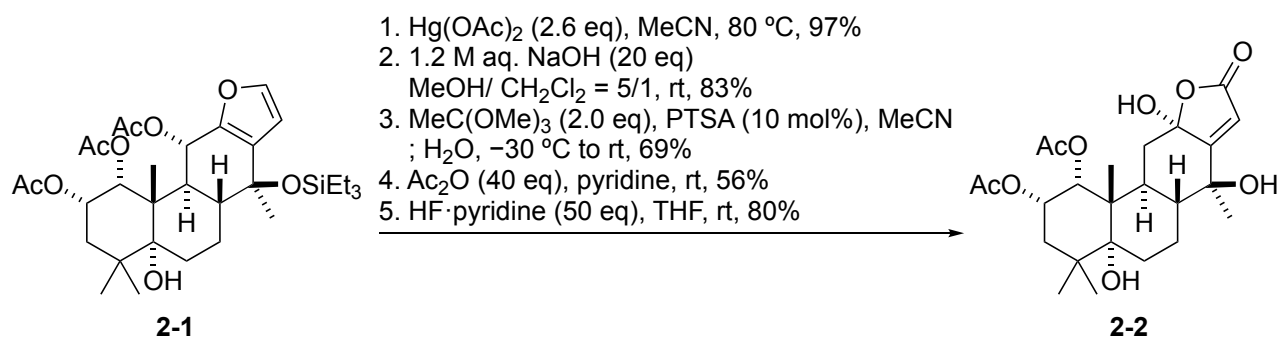


Please provide the reaction mechanisms.

1



2



## Problem Session (2) Answer

2023.11.25 Manaka Matsumoto

**Topic:** Recent total synthesis by Carreira's group

### Introduction:

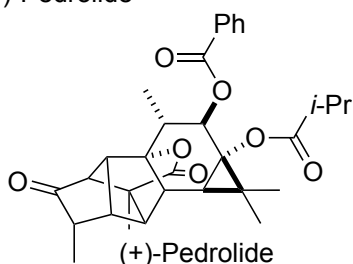
1. Prof. Erick M. Carreira<sup>1)</sup>



1984 B. S., @ University of Illinois at Urbana-Champaign (Prof. Denmark)  
1990 Ph.D., @ Harvard University (Prof. Evans)  
1990- Postdoctoral fellow @ California Institute of Technology  
1992- Assistant Professor @ California Institute of Technology  
1996- Associate Professor @ California Institute of Technology  
1997- Professor @ California Institute of Technology  
1998- Professor @ ETH Zürich

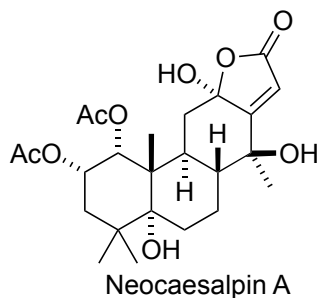
Research topic: Asymmetric synthesis of biologically active, stereo-chemically complex, natural products

2. (+)-Pedrolide



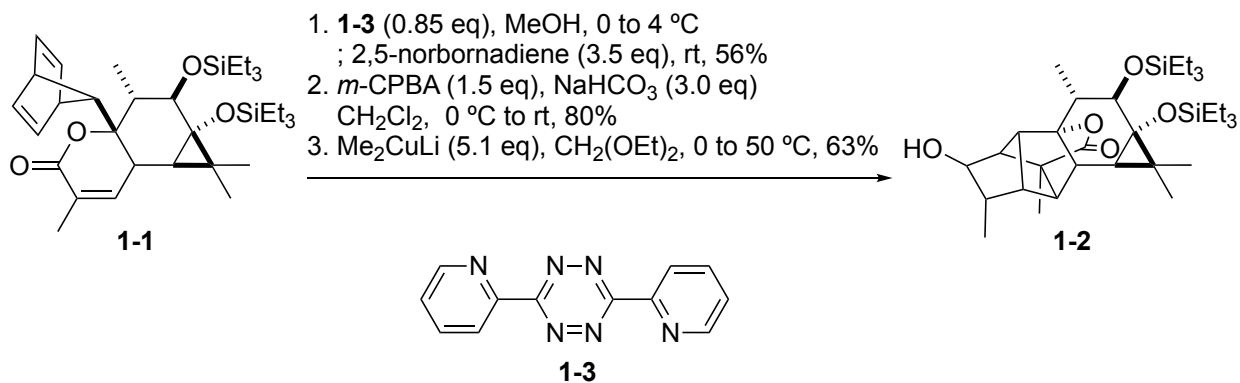
isolation: from *Euphorbia pedroi* (2021)<sup>2)</sup>  
biological activity: P-glycoprotein inhibitory properties  
structural features: 5-5-6-3 fused pentacyclic carbon skelton, bicyclo [2,2,1] heptane  
total synthesis: Carreira's group (2023) → **Problem 1**

3. Neocaesalpin A (**Problem 2**)



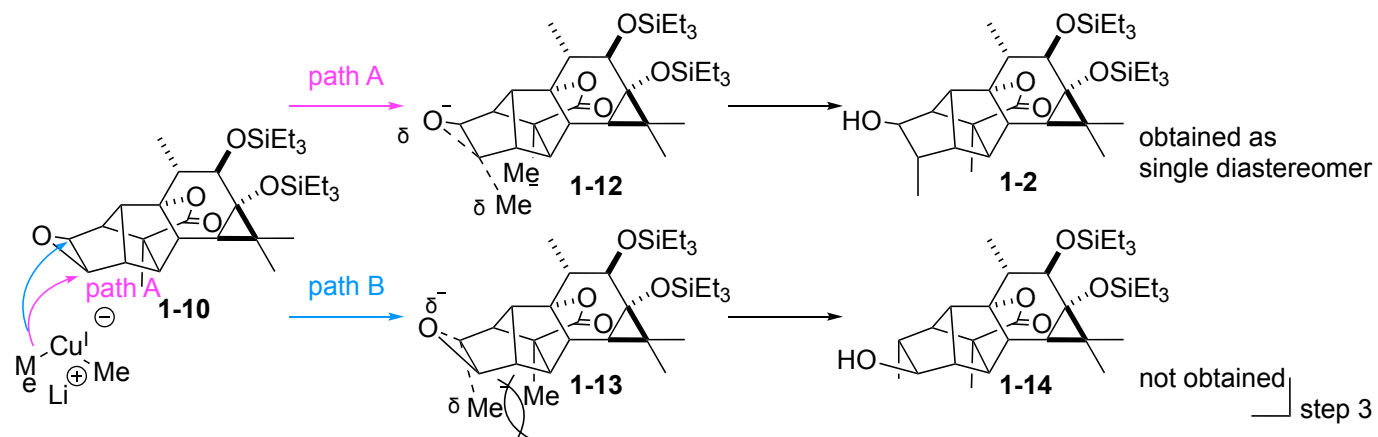
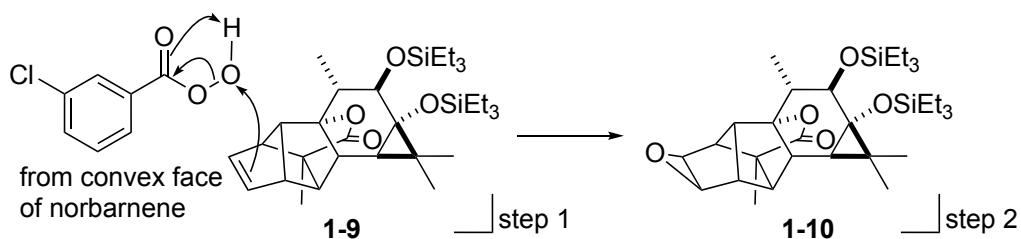
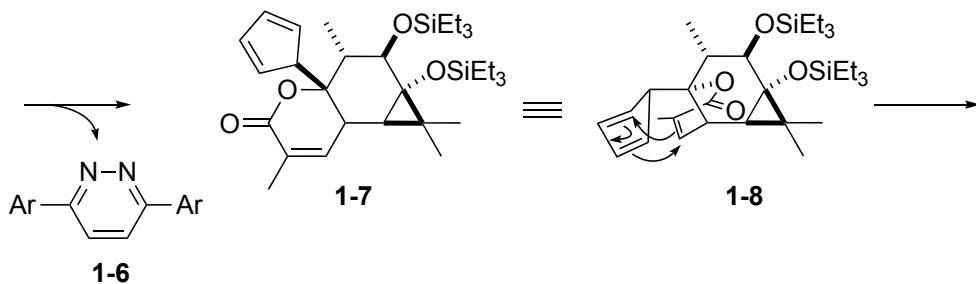
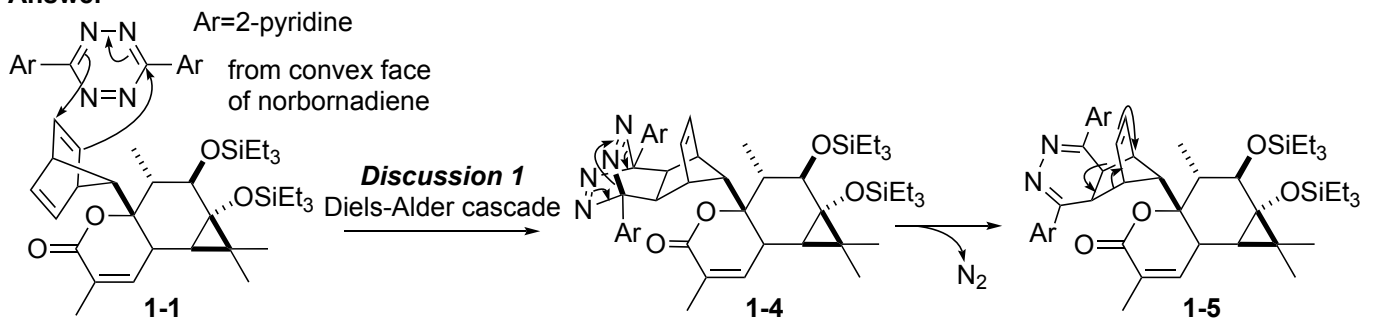
isolation: from *Caesalpinia bonduc* (1996)<sup>3)</sup>  
biological activity: unknown  
structural features: 6-6-6-5 fused cassane type skelton, butenolide ring  
total synthesis: Carreira's group (2023) → **Problem 2**

### Problem 1: Total synthesis of (+)-Pedrolide



Fadel, M.; Carreira, E. M. *J. Am. Chem. Soc.* **2023**, *145*, 8332.

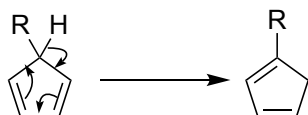
## Answer



## Discussion 1: Diels-Alder cascade

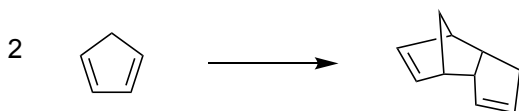
1-0. Difficulties to use 5-alkyl-substituted cyclopentadienes

- 1,5-sigmatropic hydrogen shifts



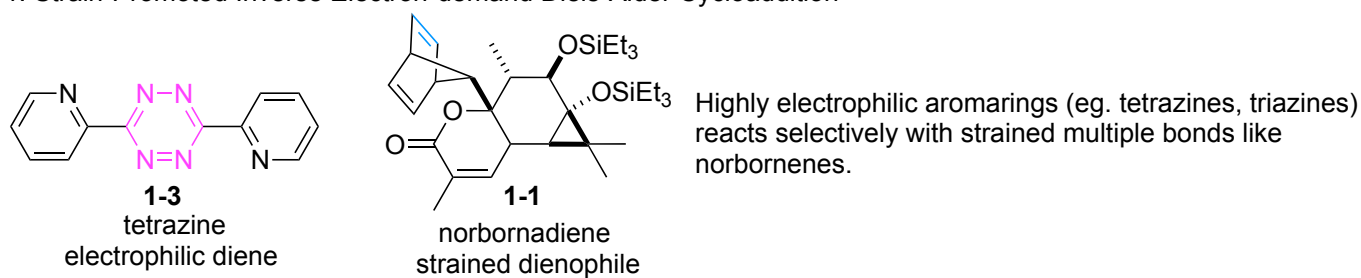
Isomerization to the thermodynamically more stable isomers occurs even at 25 °C.

- dimerization

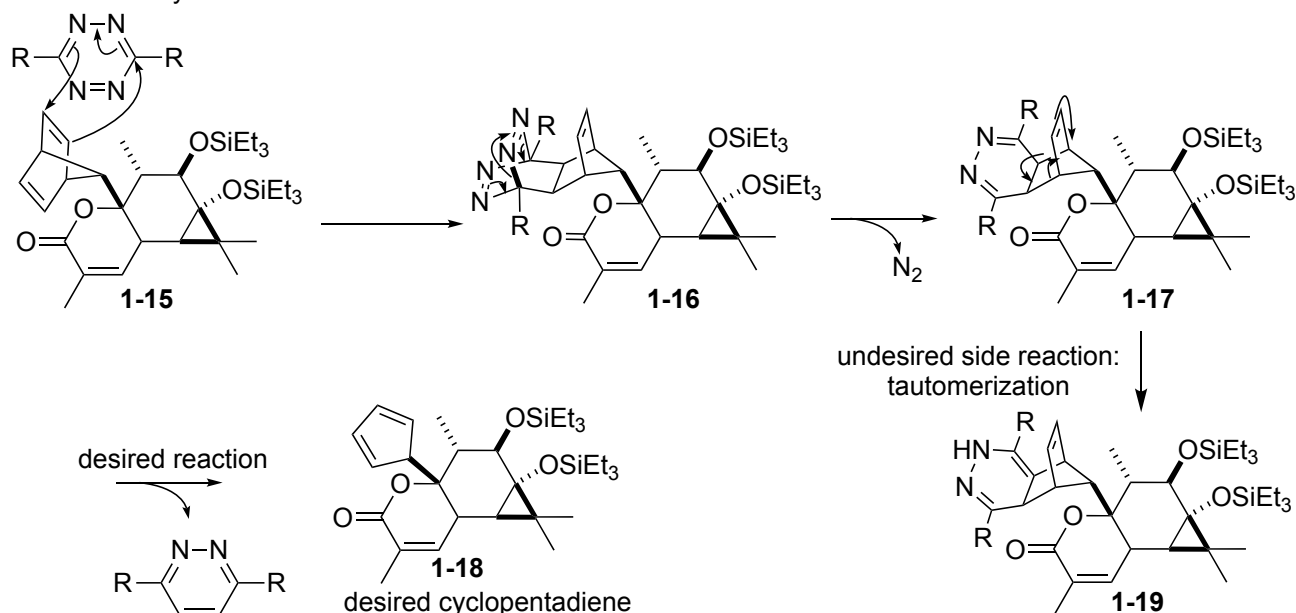


Because of these difficulties, application of 5-alkyl-substituted cyclopentadienes to total synthesis is very limited. Authors decided to generate cyclopentadiene in situ from a norbornadiene derivative.

## 1-1. Strain-Promoted Inverse Electron-demand Diels-Alder Cycloaddition



## 1-2. Reactivity of tetrazine



The reactivity of tetrazines was highly dependent on the 3,6-substituents.

### 1. R=Me, Ph

Tetrazines are least electron deficient, so the first Diels-Alder reaction with norbornadiene did not take place.

### 2. R= CO<sub>2</sub>Me, Cl

Tetrazines are very electron deficient, so the first Diels-Alder reaction with norbornadiene readily took place.

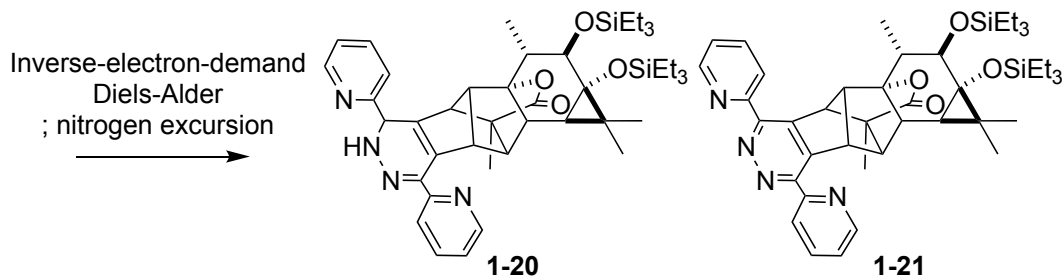
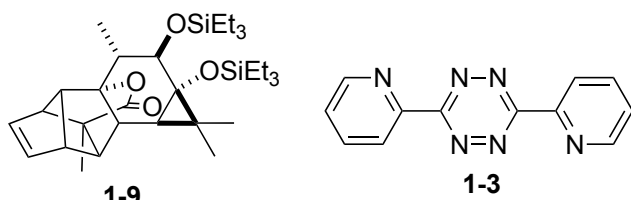
However, tautomerization from **1-17** to **1-19** was dominant and desired fragmentation to cyclopentadiene hardly took place.

### 3. R= 2-pyridine

Tetrazines are less electron deficient, so the first Diels-Alder reaction with norbornadiene slowly took place.

Fragmentation readily occurred but overreaction was problematic. (see 1-3.)

### 1-3. Over reaction

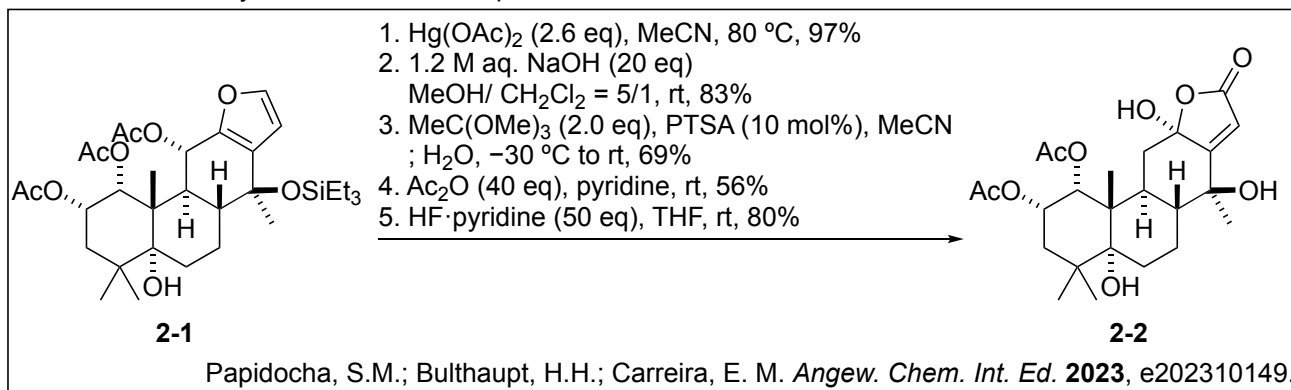


In order to suppress this over reaction, reaction conditions were optimized.

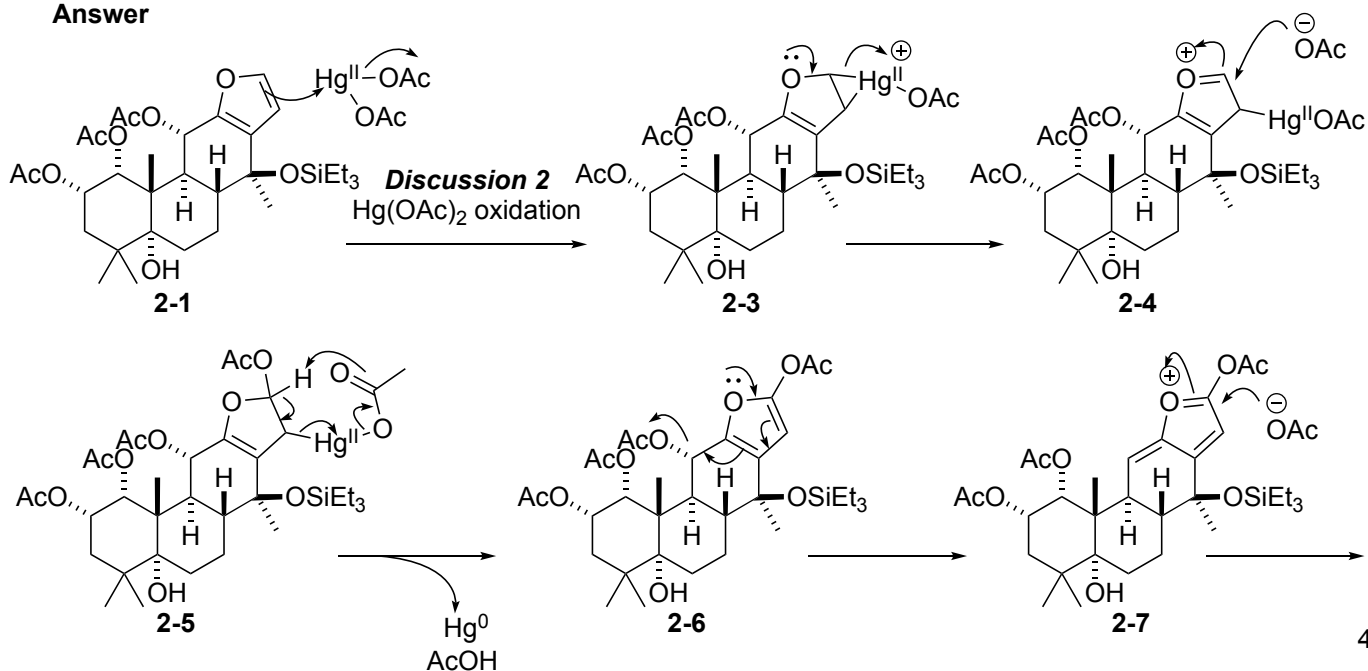
- equivalent of **1-3** was decreased to 0.85 eq
- concentration was lowered to 0.4 °C
- 2,5-norbornadiene was used as additive to react with excess **1-3**

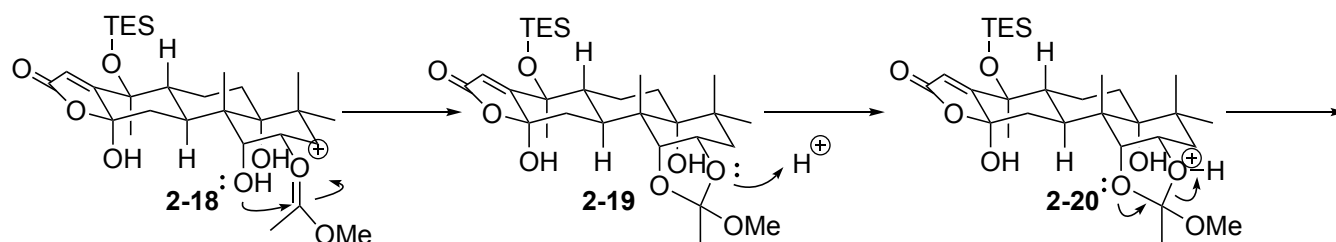
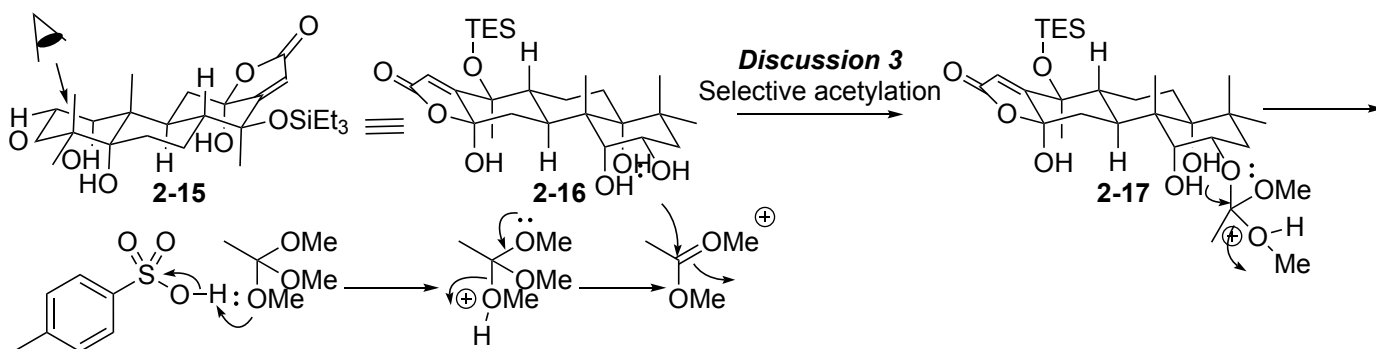
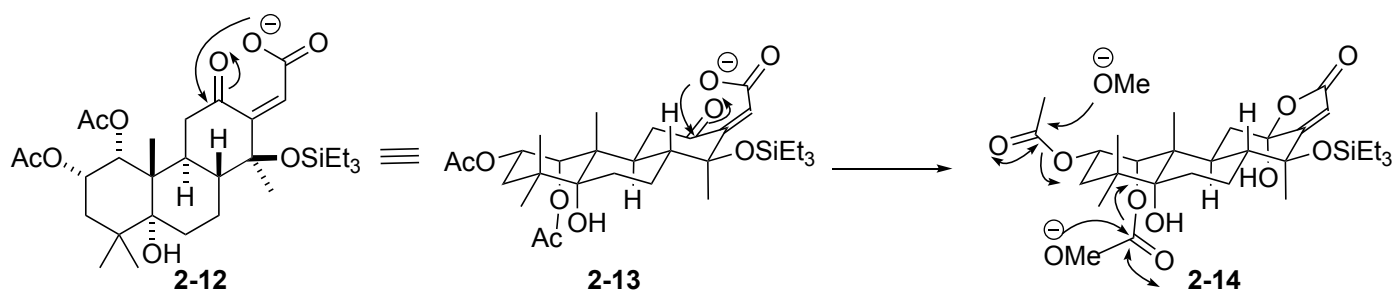
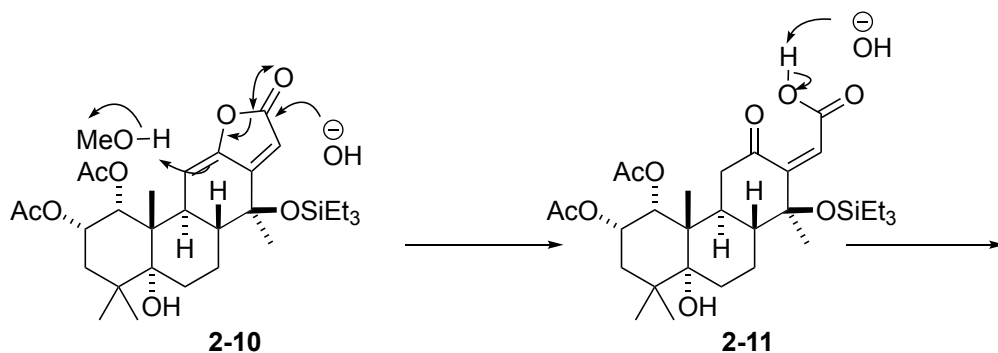
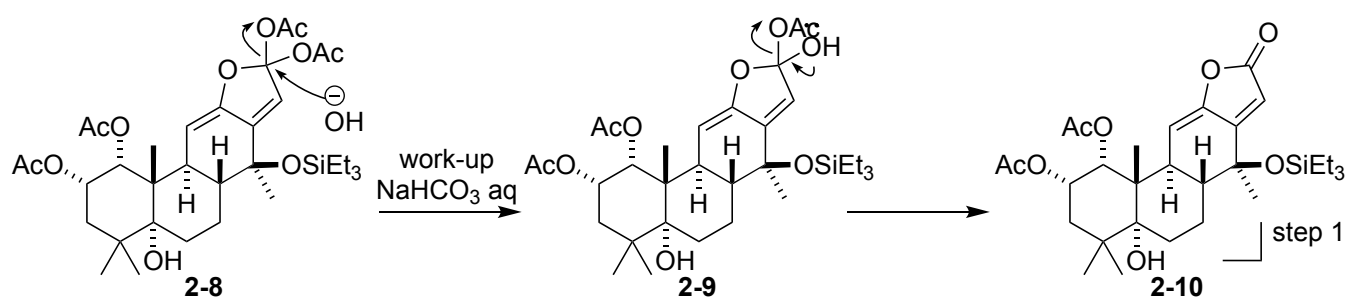


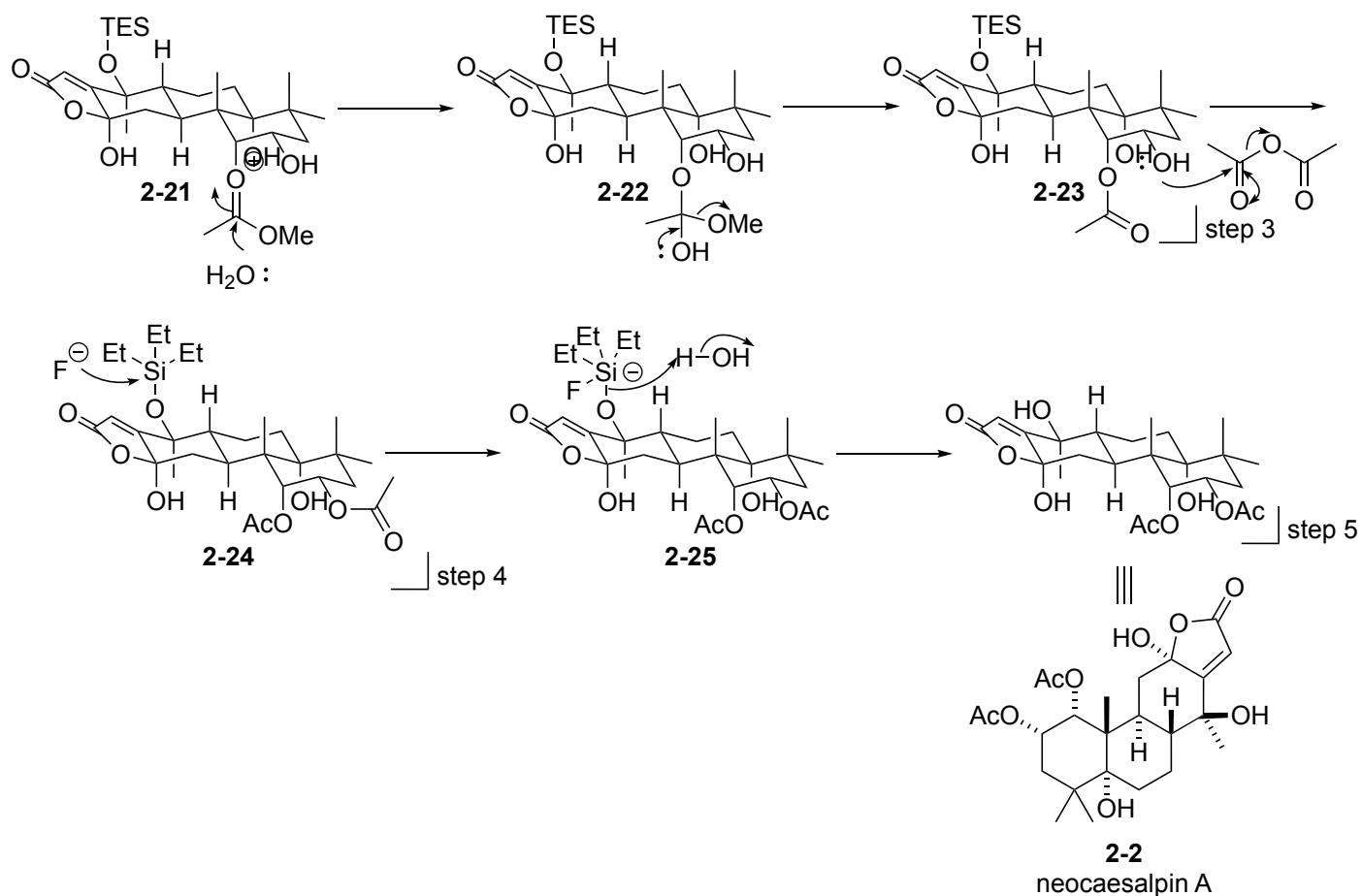
### Problem 2: Total synthesis of neocaesalpin A



### Answer

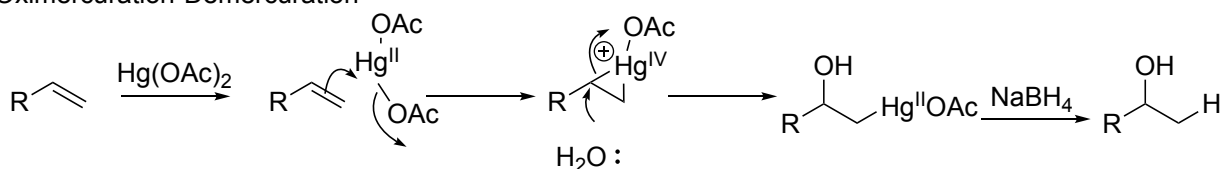




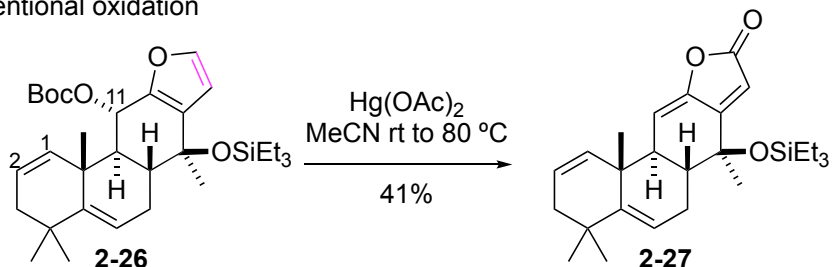


## Discussion 2: $\text{Hg}(\text{OAc})_2$ oxidation

### 2-1. Oximercuriation-Demercuriation



### 2-2. Unintentional oxidation



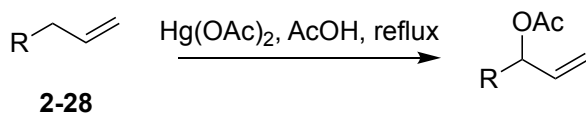
Authors intended to use C11 Boc alcohol as a neighboring group which participates in selective intramolecular oximercuriation of C1-C2 olefin.

However, the product of above reaction was  $\gamma,\delta$ -unsaturated butenolide.

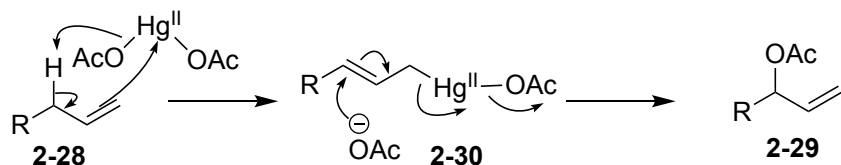
This result suggests that the least hindered and electron rich olefin (highlighted in pink) reacted in these conditions.

With this result, authors adopted the same conditions to **2-1** and successfully obtained oxidized product.

2-3. examples of oxidation with  $\text{Hg}(\text{OAc})_2$   
 2-3-1. Allylic oxidation reported by Rappoport<sup>4)</sup>

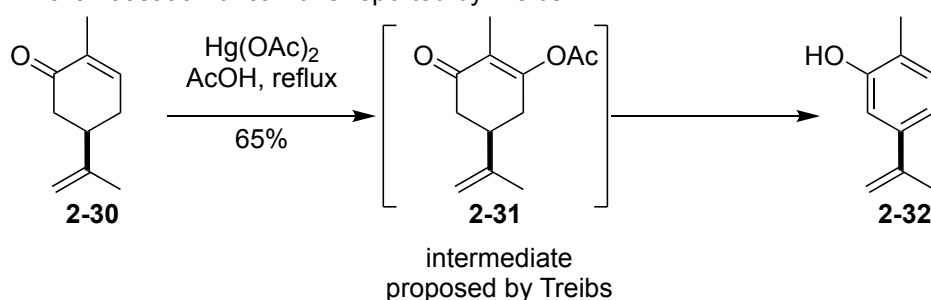


mechanism explained by authors

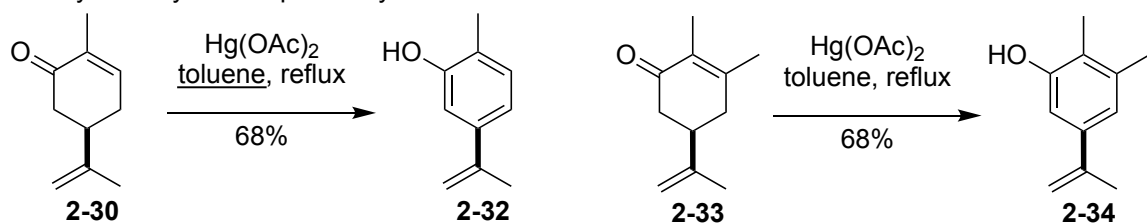


They report that  $\text{Hg}^0$  was obtained when the substrate was excess, and  $\text{Hg}_2^{2+}(\text{OAc})_2$  was obtained when  $\text{Hg}(\text{OAc})_2$  was excess.

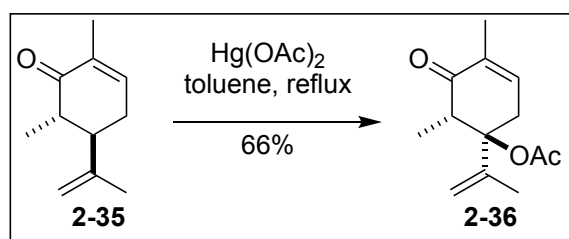
2-3-2. aromatisation of carvone reported by Treibs<sup>5)</sup>



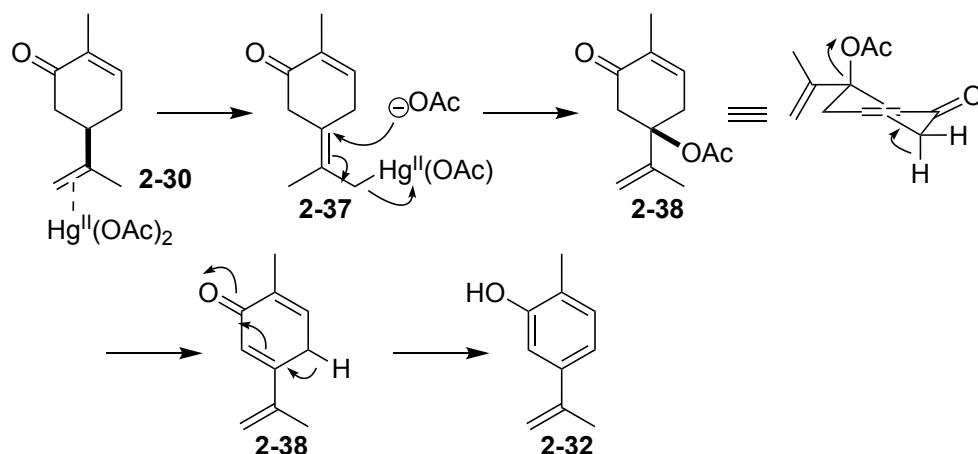
2-3-3. allylic acetylation reported by Dethe<sup>6)</sup>



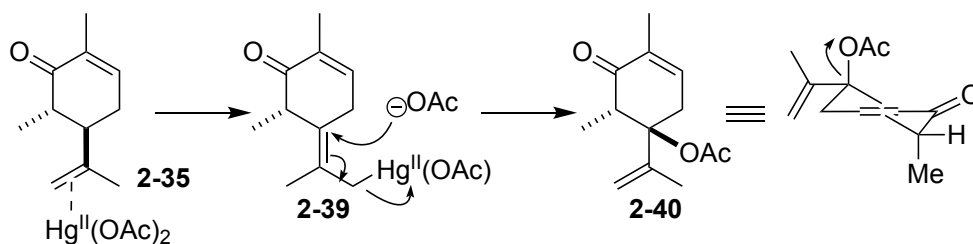
mechanism proposed by Treibs was incorrect.



corrected mechanism of aromatization



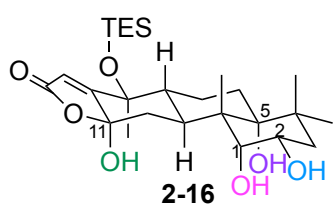




In case of 2-35, there is no H in the antiperiplanar relationship with OAc.

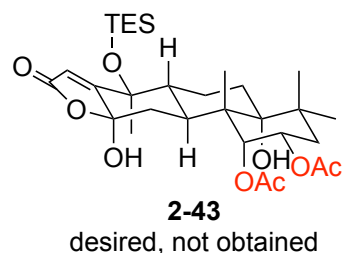
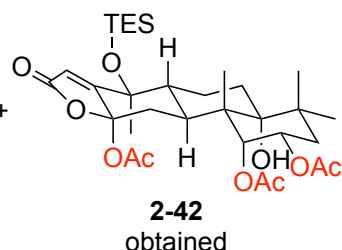
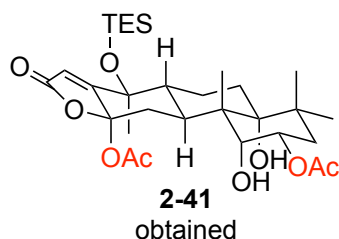
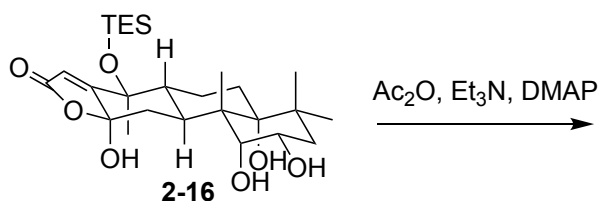
Therefore, the reaction stopped at **2-40**. Isolation of reaction intermediate validated the above mechanism.

### Discussion 3: Selective acetylation



There are four hydroxyl groups in 2-  
**C1-OH** secondary but hindered by adjacent quaternary carbon, 1,3 diaxial OH)  
**C2-OH** secondary  
**C5-OH** tertiary, hindered by adjacent quaternary carbons  
**C11-OH** tertiary but less hindered (adjacent: O, sp<sup>2</sup> carbon, secondary carbon)

reactivity: C2 > C11 > C1 > C5



In order to selectively acethylate C1 and C2, the authors adopted 2 step conversion.

C1(selectively acetylated using orthoester)  $\rightarrow$  C2 (acetylated selectively in mild conditions)

### References

- 1) <https://carreira.ethz.ch/the-group/people/prof-dr-erick-m-carreira.html>
- 2) Ferreira, R. J.; Spengler, G.; Orthaber, A.; dos Santos, D. J. V. A.; Ferreira, M.-J. U. *Org. Lett.* **2021**, 23, 274.
- 3) Kinoshita, T.; Kaneko, M.; Noguchi, H.; Kitagawa, I. *Heterocycles* **1996**, 43, 409.
- 4) Rappoport, Z.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1972**, 94, 2320.
- 5) Treibs, W. *Justus Liebigs Ann. Chem.* **1953**, 581, 59.
- 6) Dethe, D. H.; Dherange, B. D.; Boda, R. *Org. Chem. Front.* **2015**, 2, 159.