

Problem Session (4) -Answer-

2022/06/18 Yuuki Watanabe

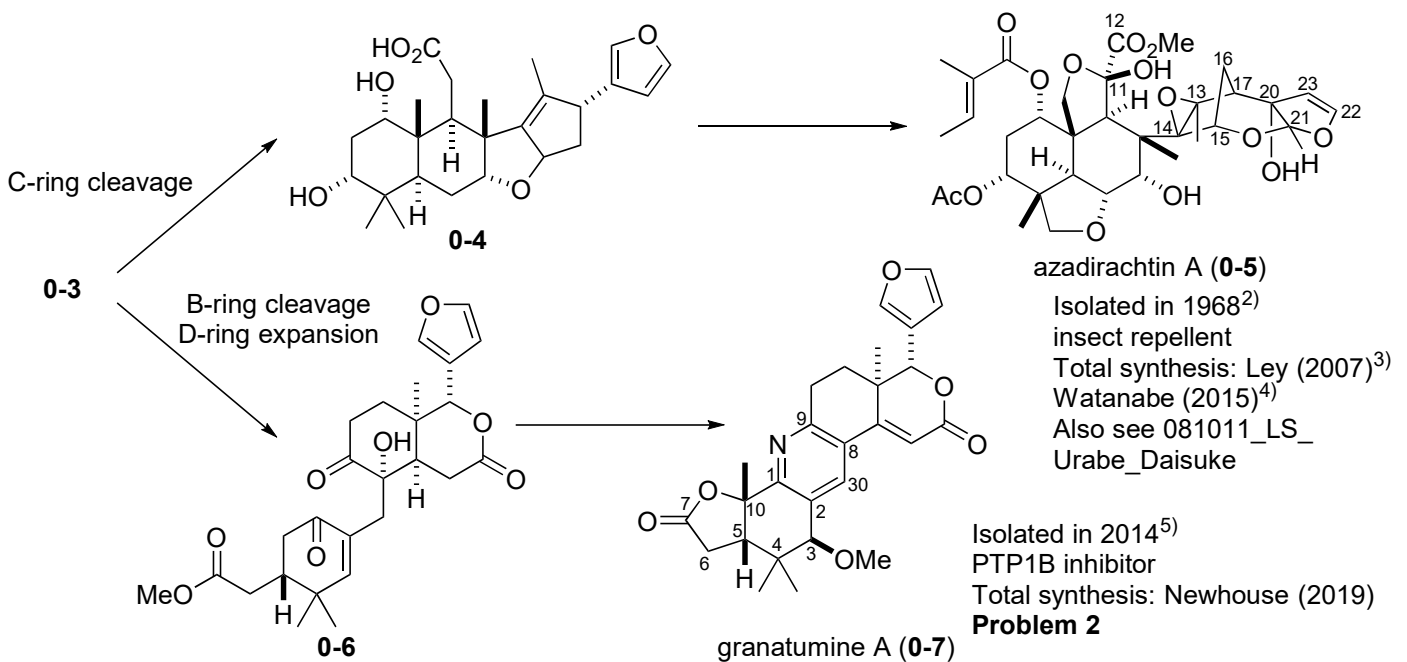
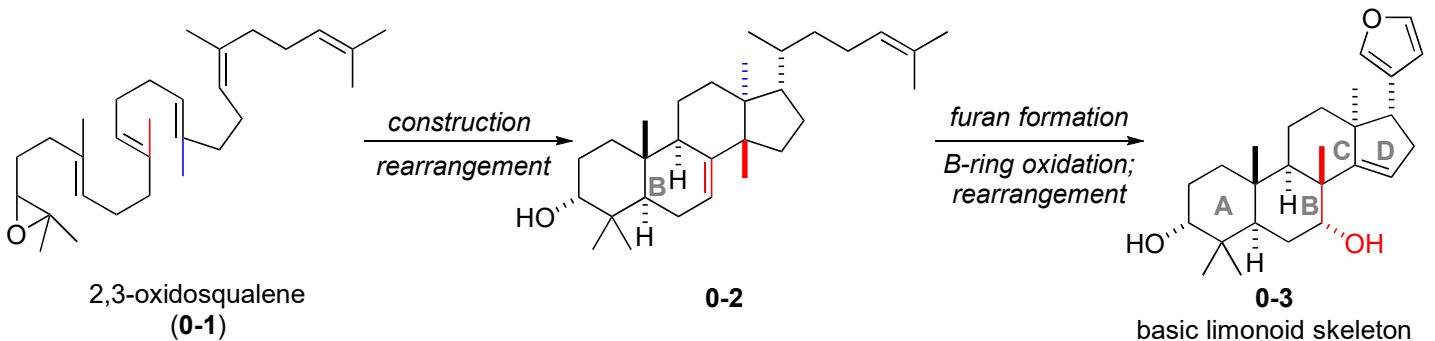
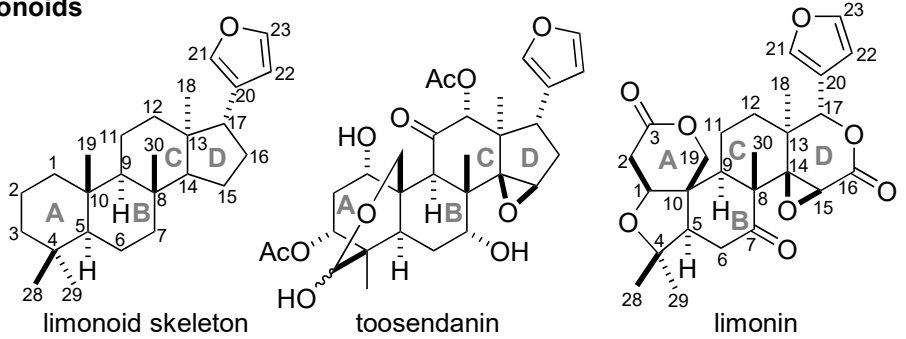
Topic: Synthetic study of rearranged limonoids

0. Introduction

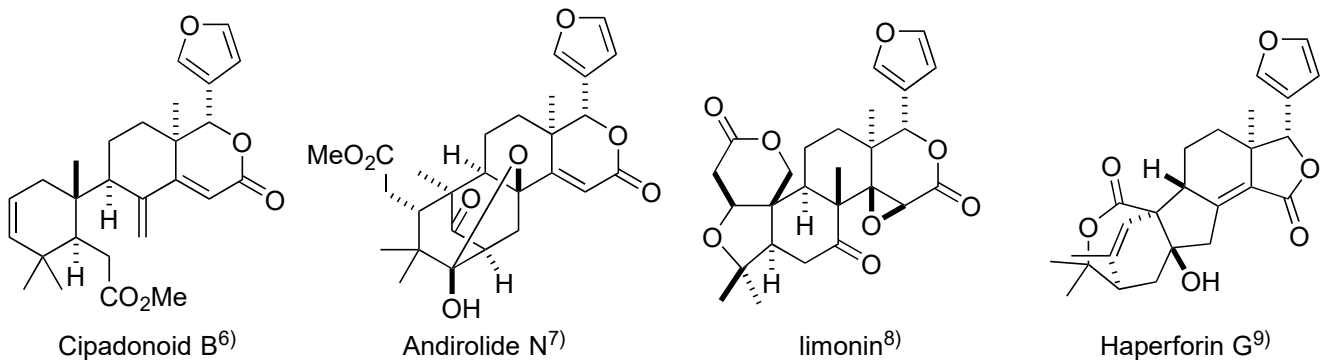
0-1. Outline

- Highly oxygenated triterpenes
- AB-trans/BC-trans ring system
- C28~C30 carbons/ α -oriented furan at C17
- Various bioactivities were reported.
- Many rearranged limonoids were isolated.

0-2. Proposed biosynthesis¹⁾



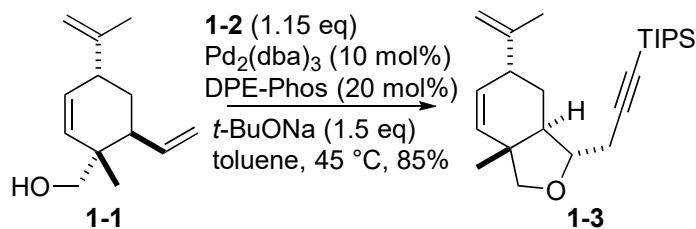
0-3. Total synthesis of rearranged limonoids



For the total synthesis of limonin, see 150926_PS_Yinghua_Wang

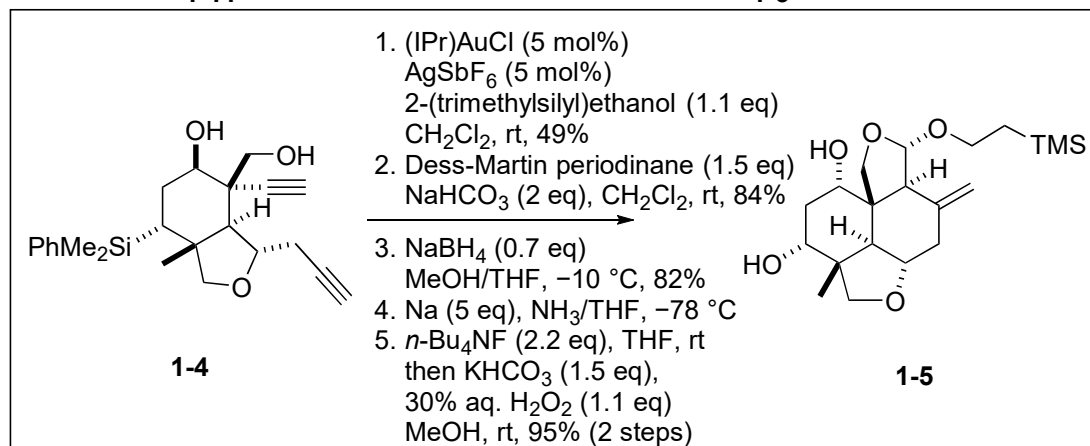
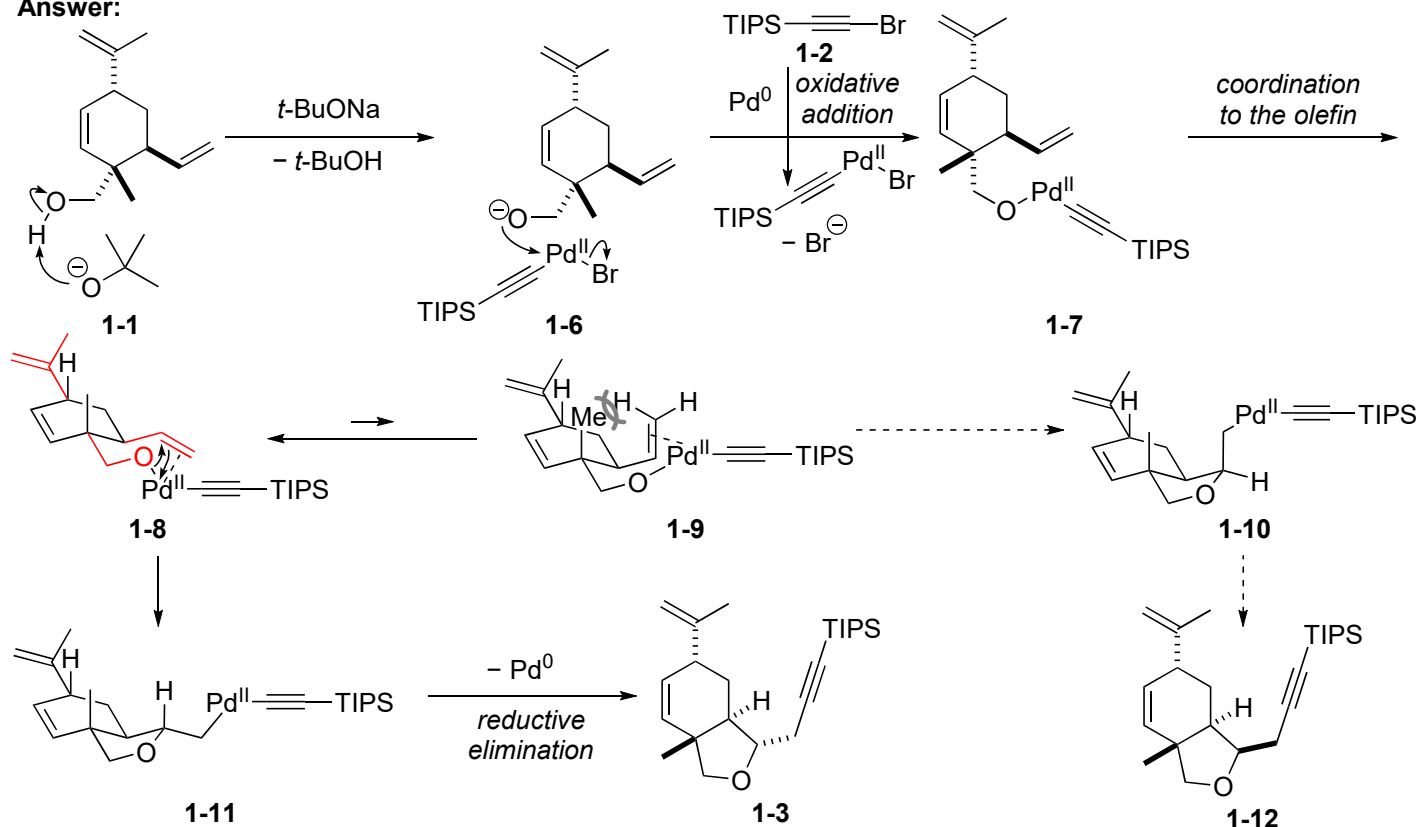
(1) Synthetic study of azadirachtins

Shi, H.; Tan, C.; Zhang, W.; Zhang, Z.; Long, R.; Luo T.; Yang, Z. *Org. Lett.* **2015**, *17*, 2342.

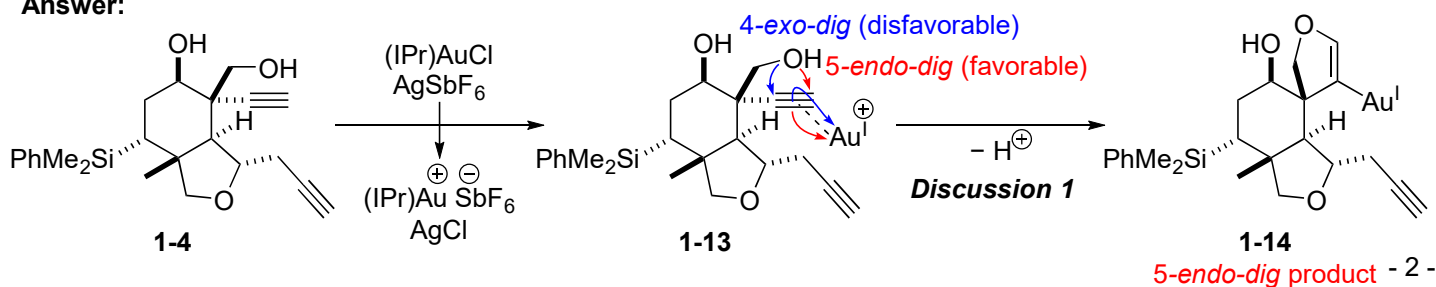


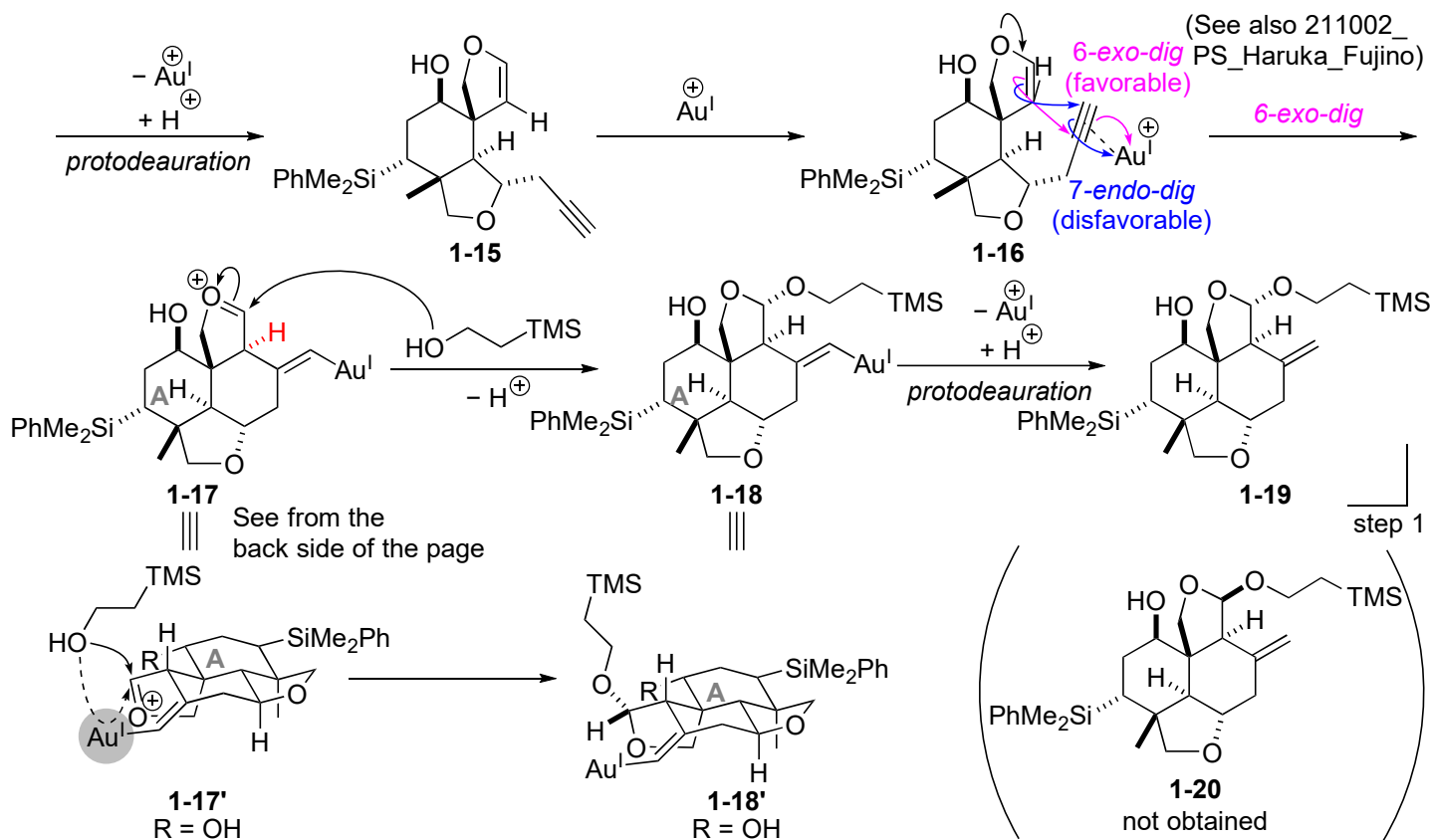
For the full articles,
Shi, H.; Tan, C.; Zhang, W.; Zhang, Z.; Long, R.;
Gong, J.; Luo T.; Yang, Z. *J. Org. Chem.* **2016**, *81*, 751.

Answer:

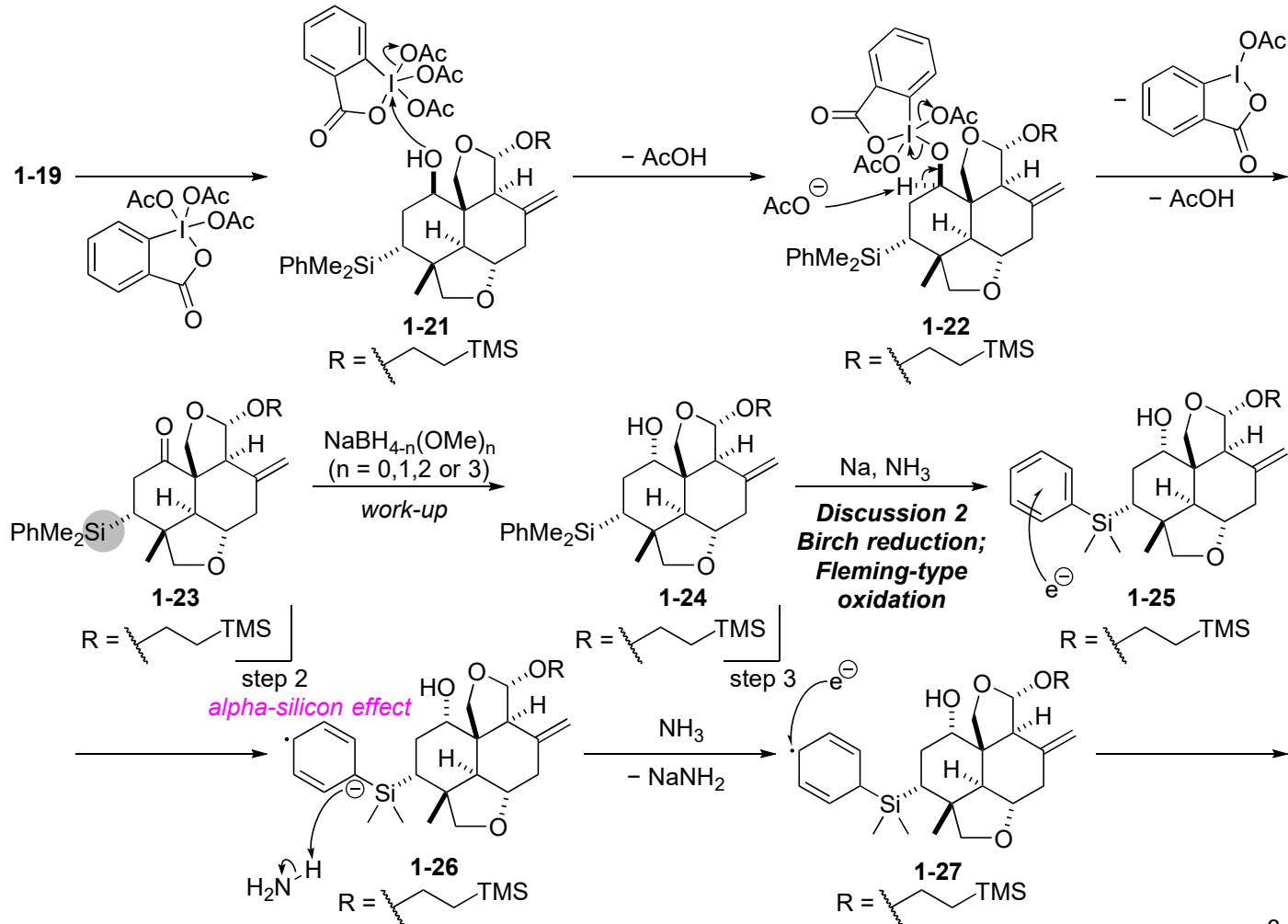


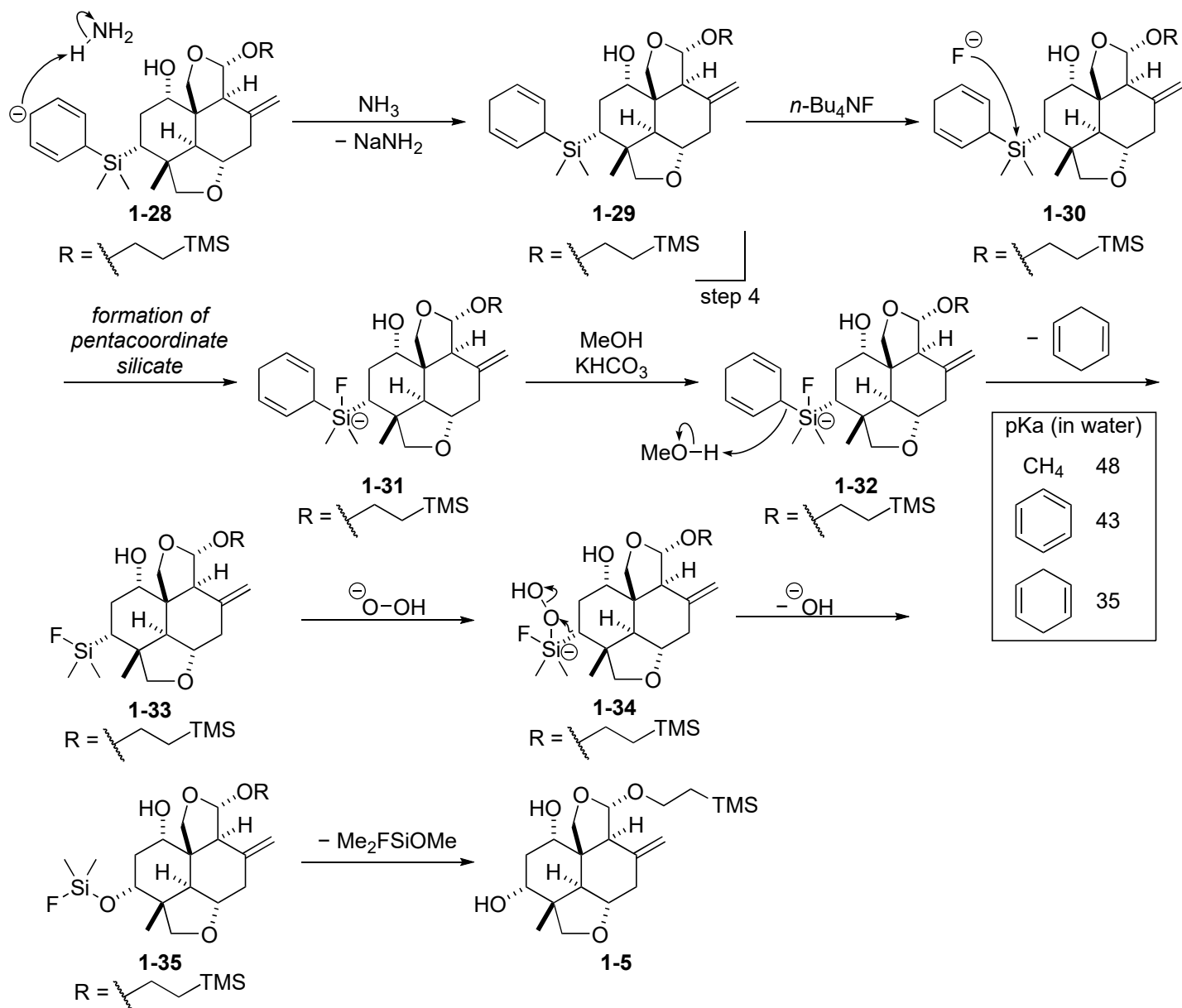
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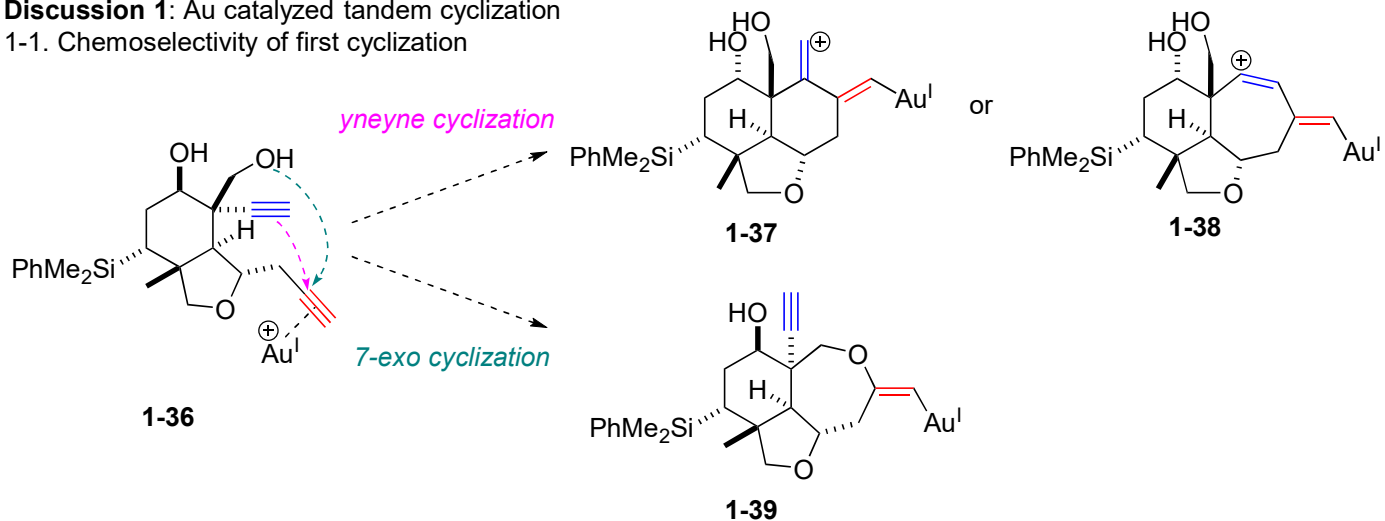


Due to the bulkiness of dimethyl phenyl silyl group, the conformation of A-ring should be a boat form.

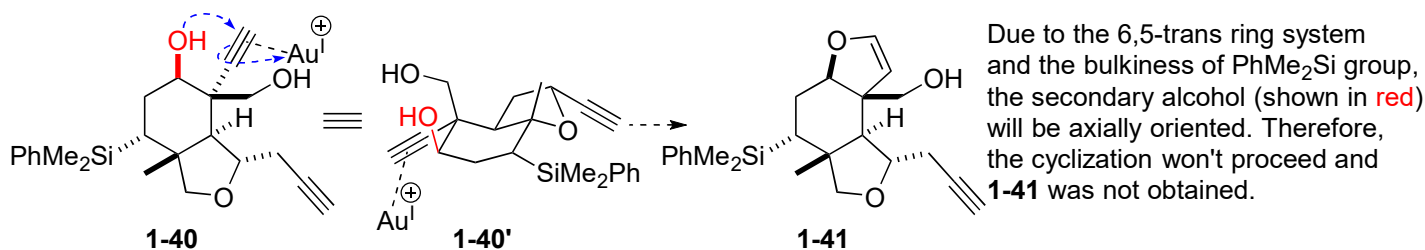




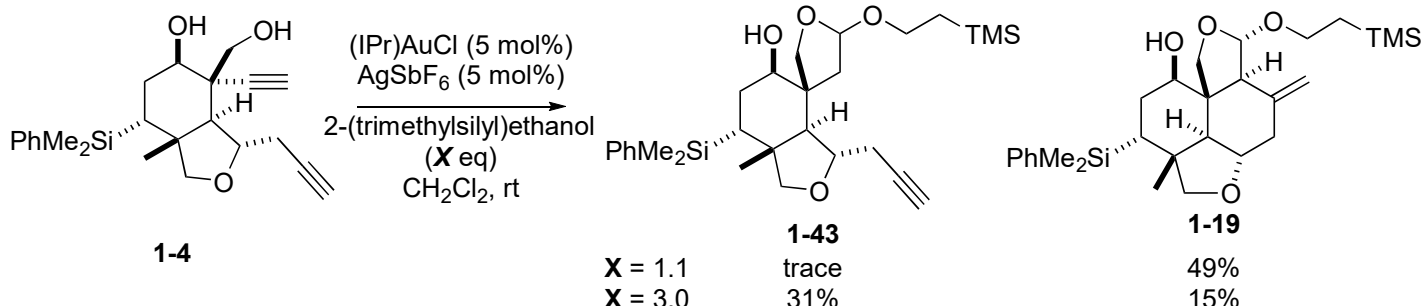
Discussion 1: Au catalyzed tandem cyclization
 1-1. Chemoselectivity of first cyclization



Considering the steric hindrance, the **red alkyne** may be more reactive with Au complex. However, following cyclization reaction should be disfavorable as the obtained cation species are unstable. Also, the cyclization of the **red alkyne** and the primary alcohol is 7-exo form (relatively slow reaction). Therefore, the first cyclization proceeded with the **blue alkyne** and the primary alcohol.



1-2. The effect of the equivalent of TMS ethanol

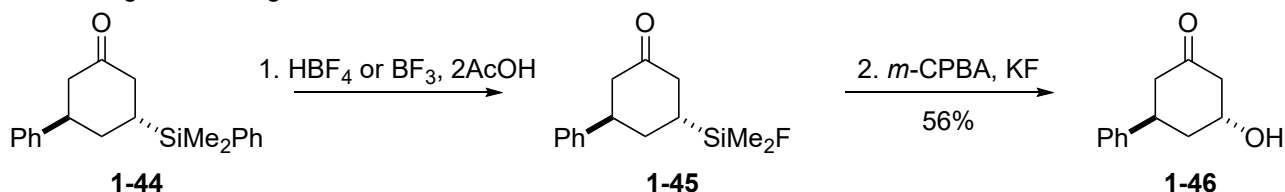


The excess amount of TMS ethanol suppressed the second cyclization and **1-43** was obtained as a byproduct. These results also suggest that the alcohol-alkyne cyclization proceeded first, and vinyl ether-alkyne cyclization followed.

Discussion 2: Birch reduction and following oxidation

2-1. Fleming's report

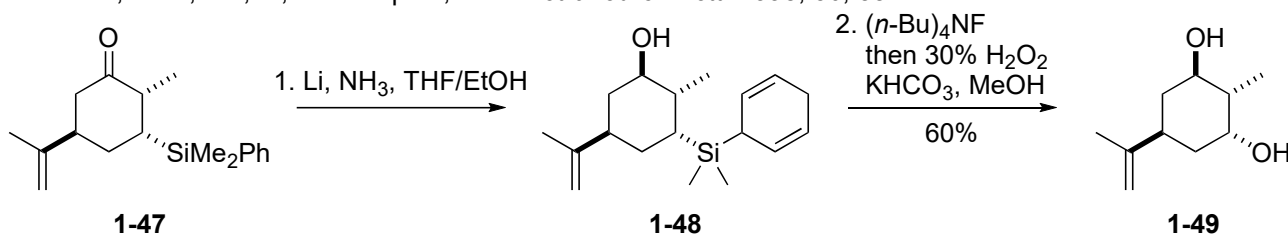
Fleming, I.; Henning, R.; Plait, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29.



This reaction (known as Fleming oxidation) is widely used in the organic syntheses. However, it is necessary to replace Ph group to fluorine atom by the strong acidic conditions.

2-2. Taber's report

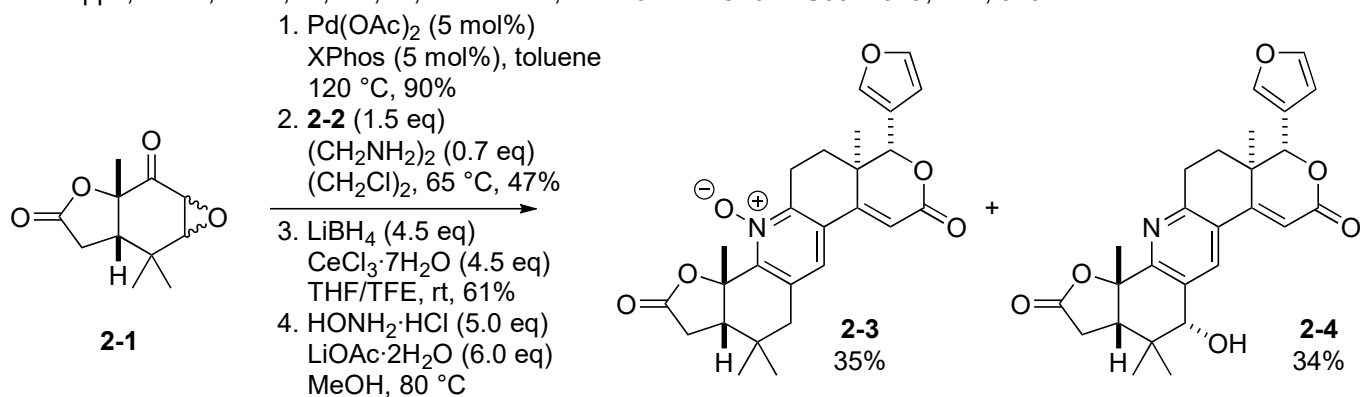
Taber, D. F.; Yet, L.; Bhamidipato, R. S. *Tetrahedron Lett.* **1995**, 36, 351.



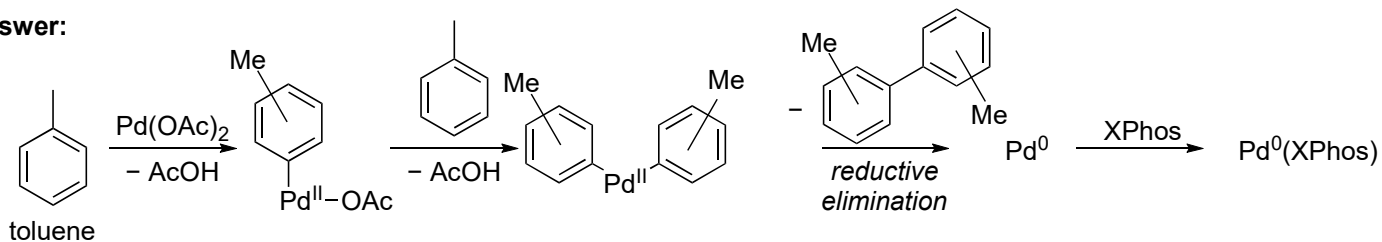
These conditions can be useful when the substrates are unstable on the acidic conditions. On the other hand, silyl protective groups and carbonyl groups can react.

(2) Total synthesis of granatumine A by Newhouse

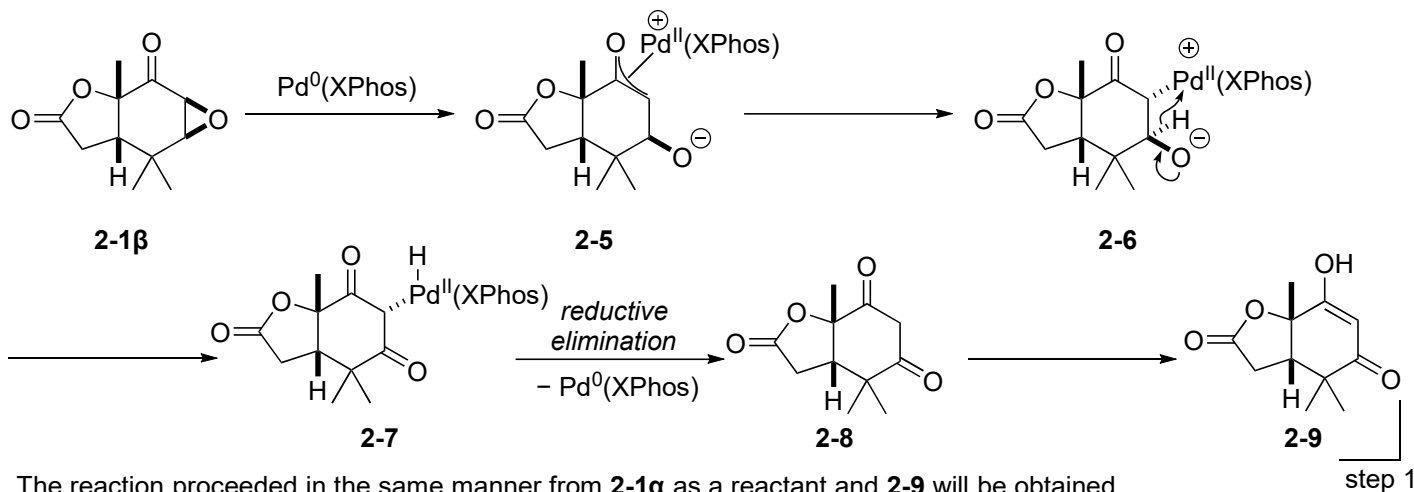
Schuppe, A. W.; Zhao, Y.; Liu, Y.; Newhouse, T. R. *J. Am. Chem. Soc.* **2019**, 141, 9191.



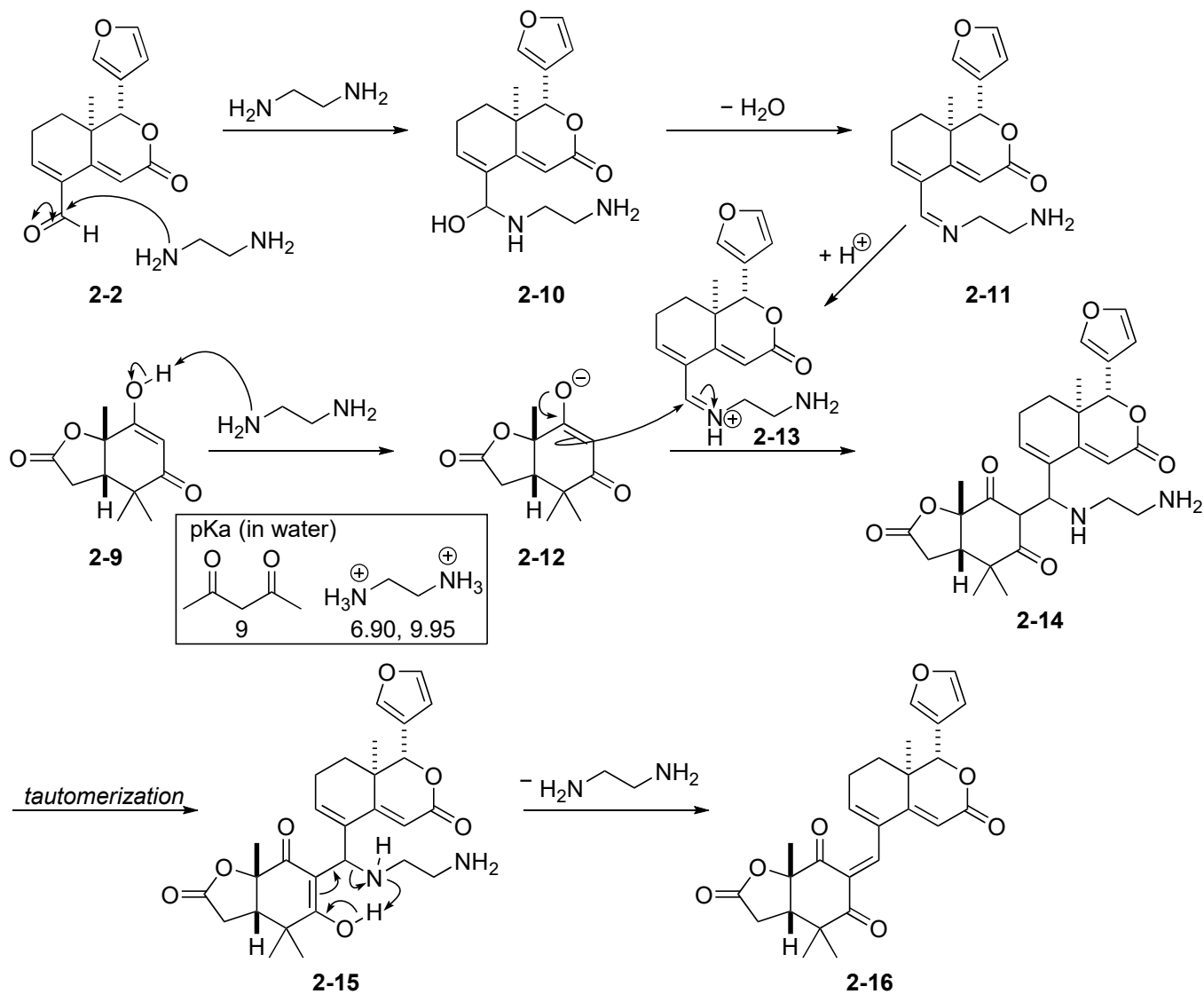
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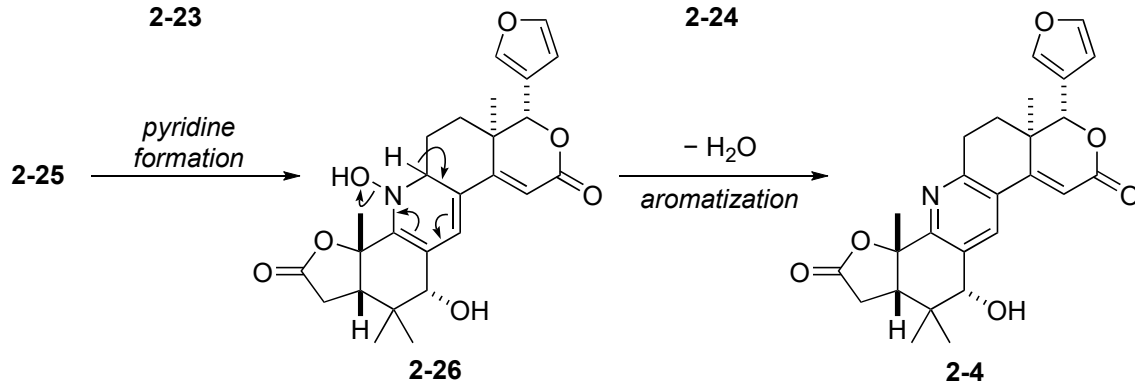
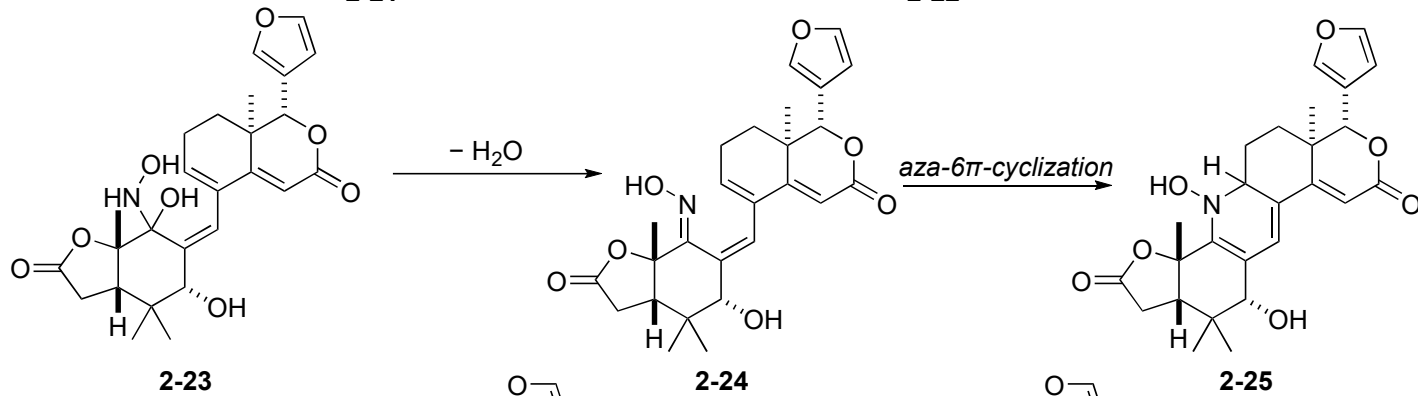
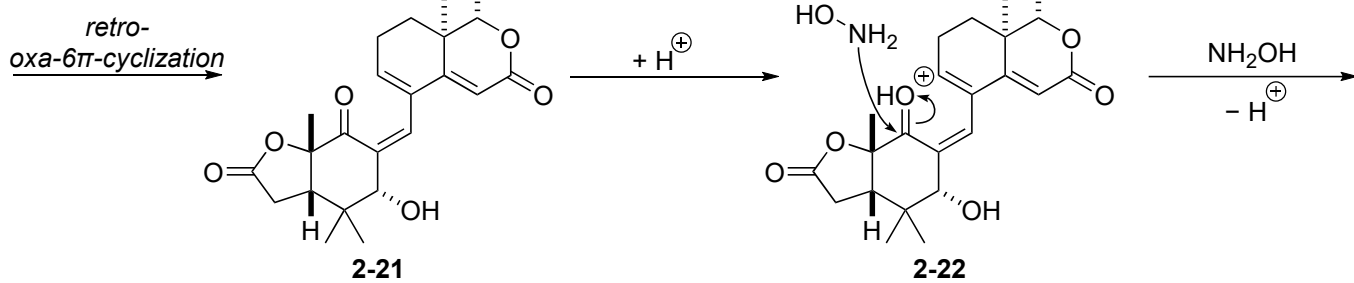
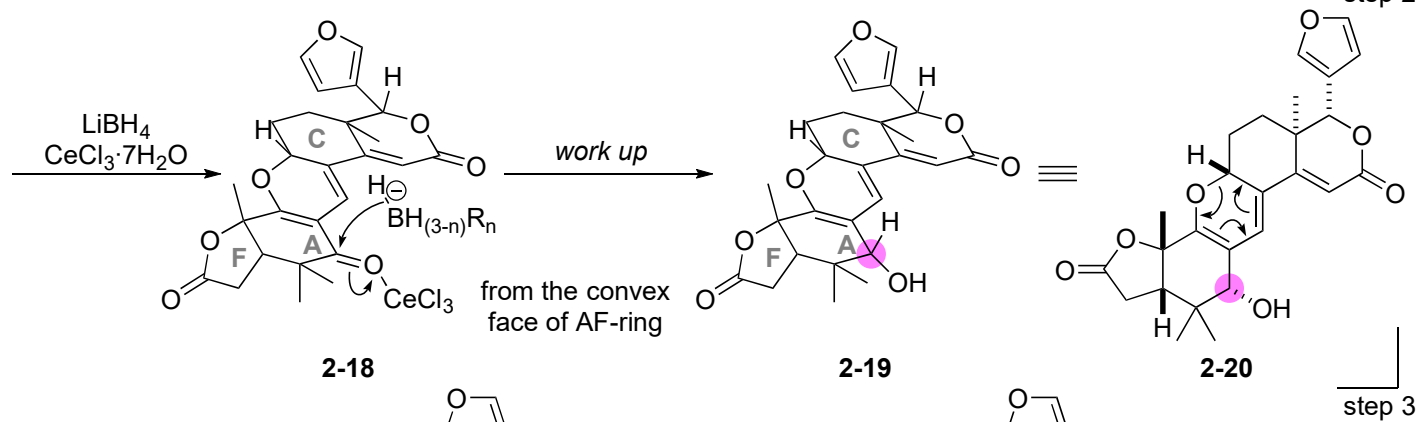
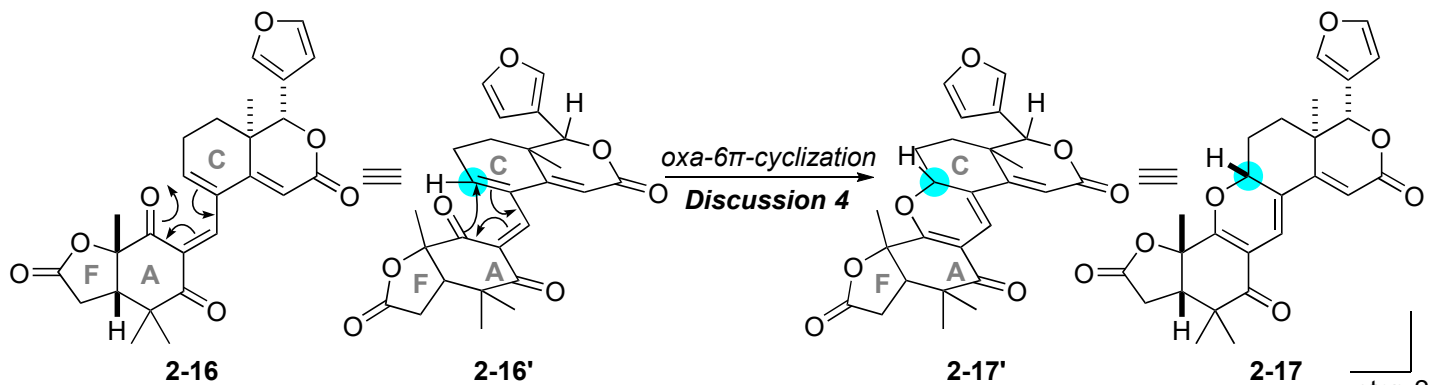


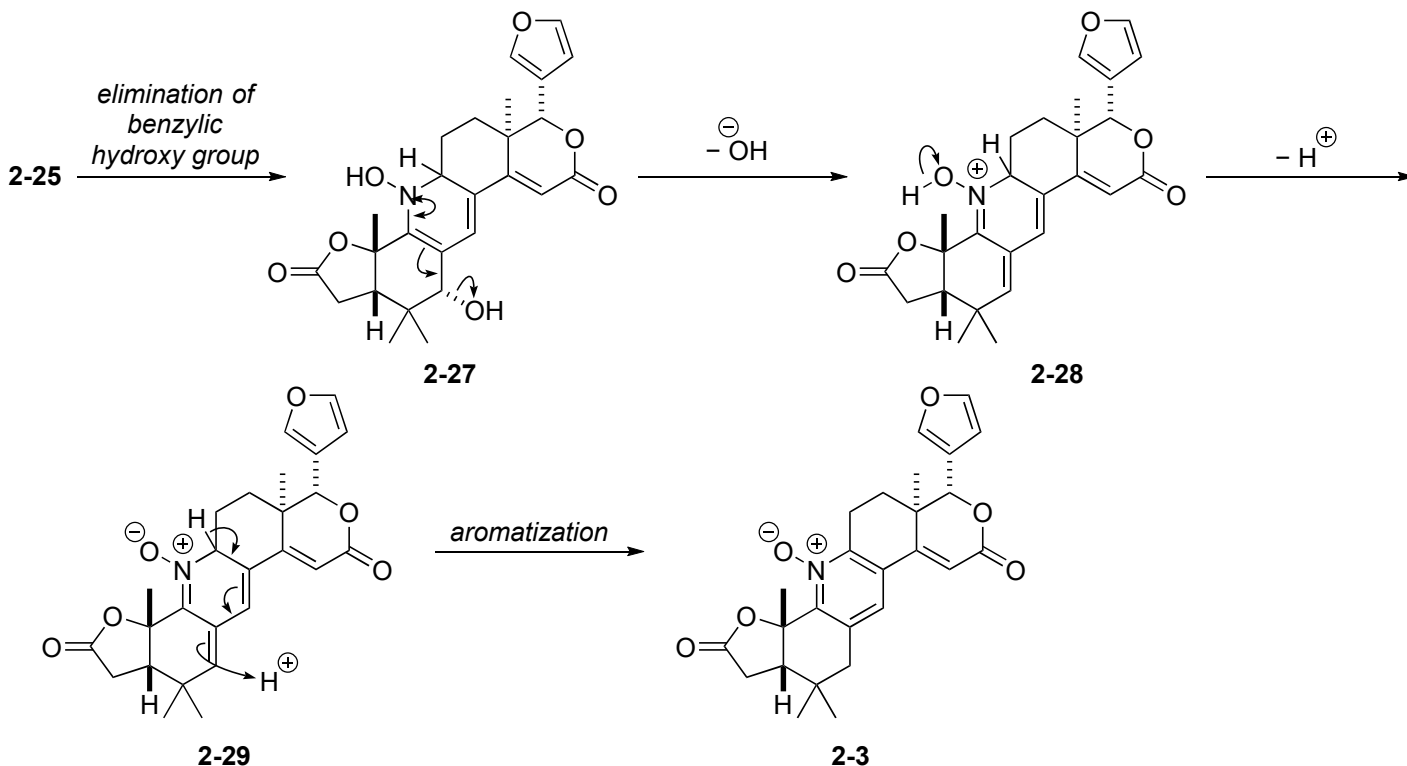
Discussion 3: Formation of Pd⁰



The reaction proceeded in the same manner from **2-1α** as a reactant and **2-9** will be obtained.

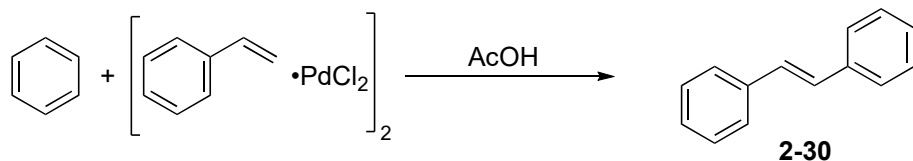






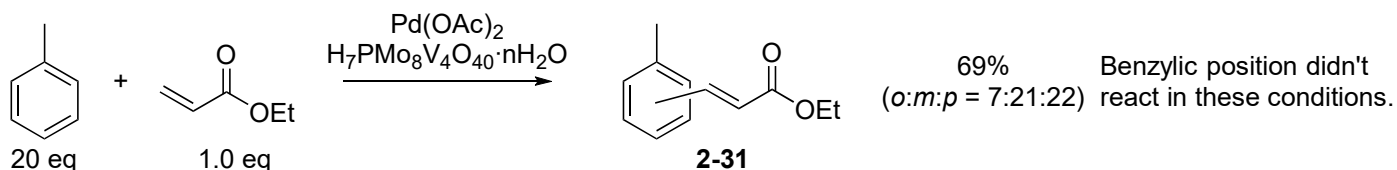
Discussion 3: Formation of Pd⁰ from arene (Fujiwara-Moritani reaction)

3-1. Original reaction (Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, 8, 1119.)

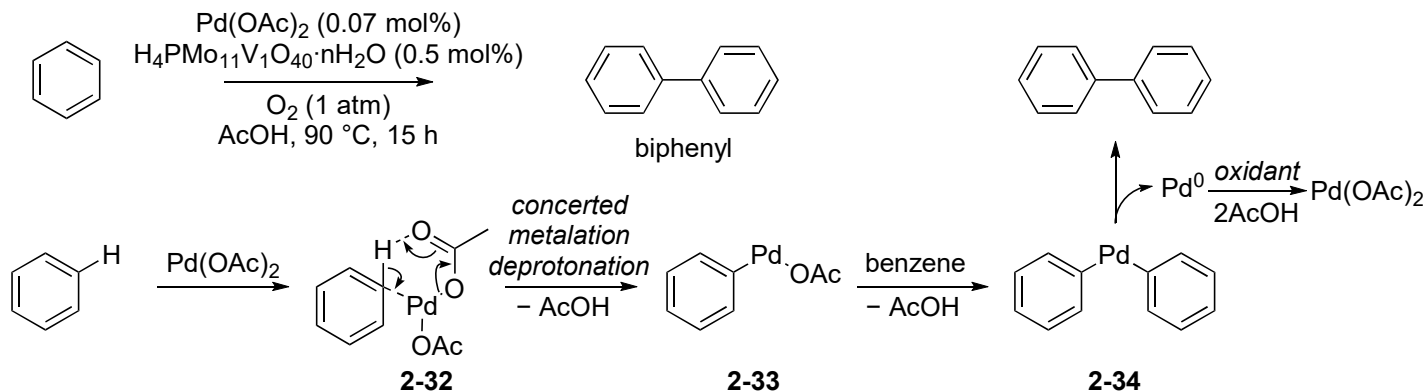


3-2. Cross coupling with toluene and acrylate

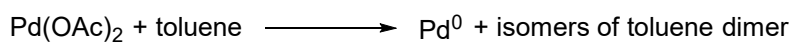
(Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, 125, 1476.)



3-3. Formation of biphenyl (Yokota, T.; Sakaguchi, S.; Ishii, Y. *Adv. Synth. Catal.* **2002**, 344, 849.)

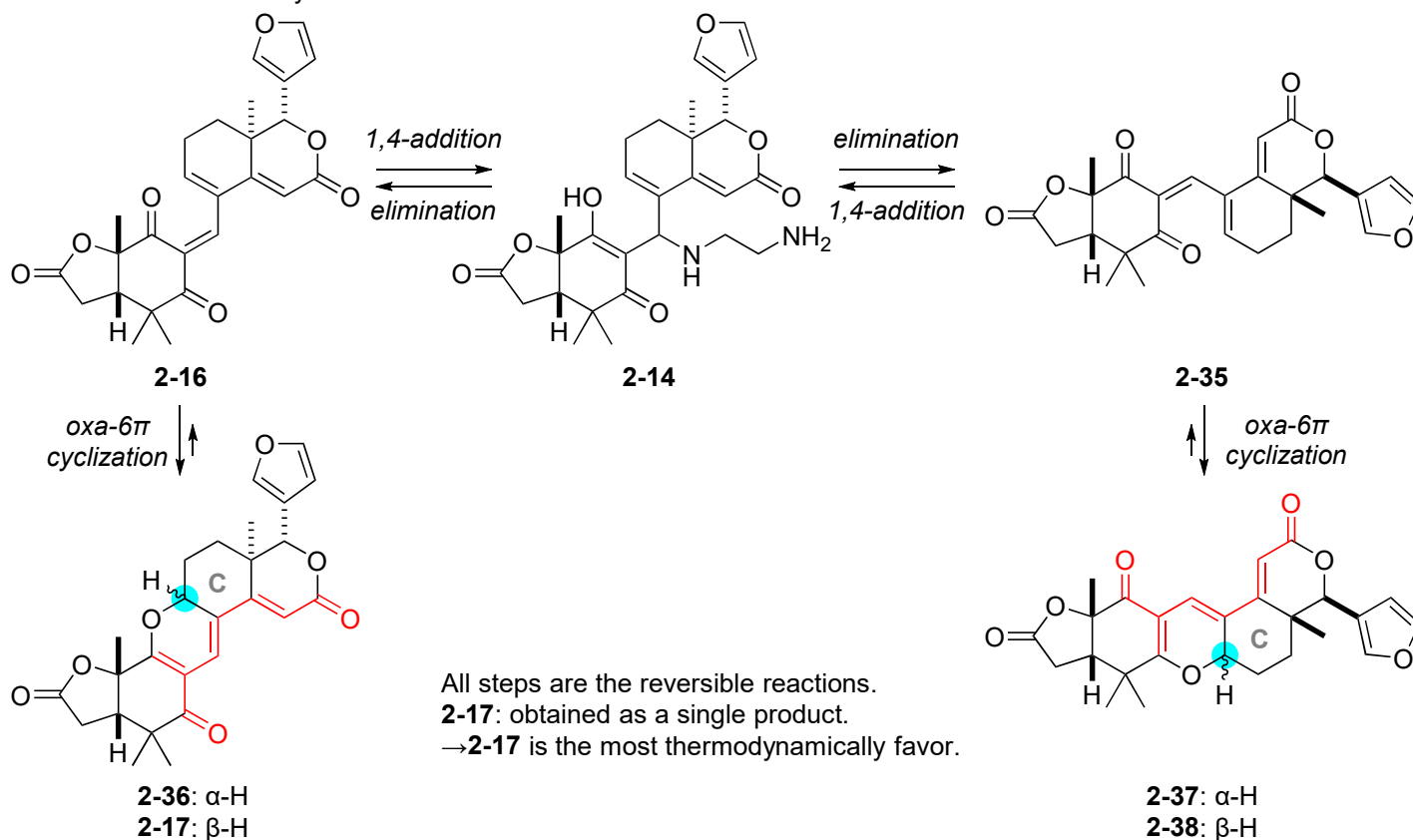


In the conditions of problem...



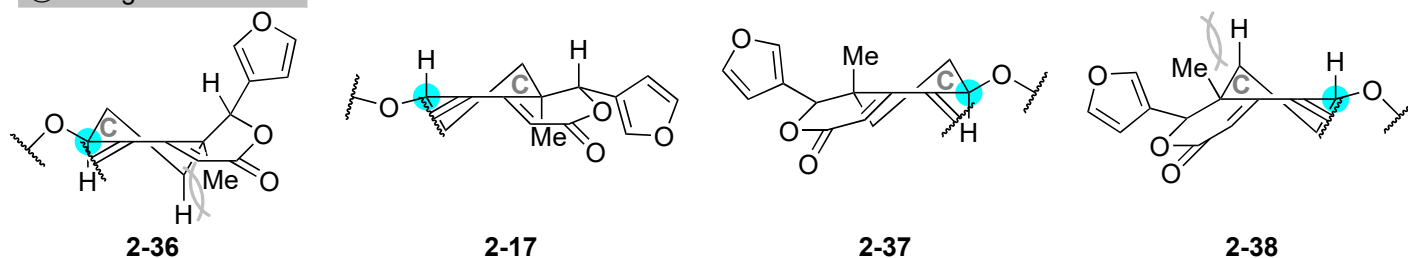
In the absence of the oxidant, Pd⁰ catalyzes the reaction.

Discussion 4: Oxa-6π-cyclization



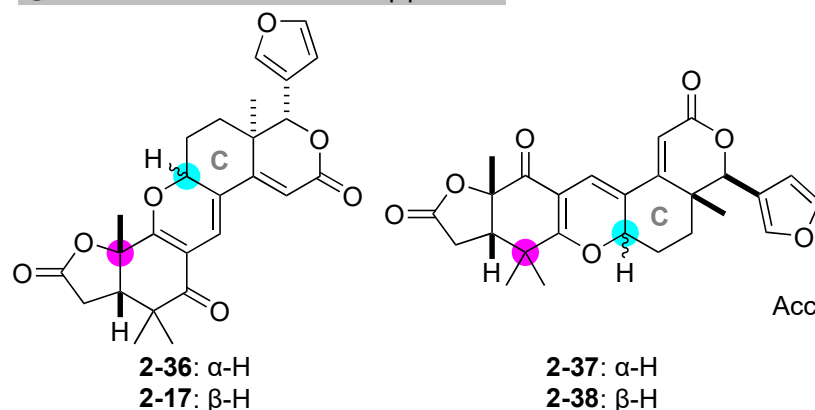
This reaction is the thermodynamic control. Therefore, the selectivity can be discussed by the stability of products. These 4 products have the conjugation system (shown in red). Therefore, the most stable conformation will maintain the conjugation system.

① C-ring conformation



To maintain the conjugation system, 2-36 and 2-38 have a large 1,2-steric repulsion. Therefore, 2-17 and 2-37 are more stable.

② Tetra-substituted carbon at γ -position

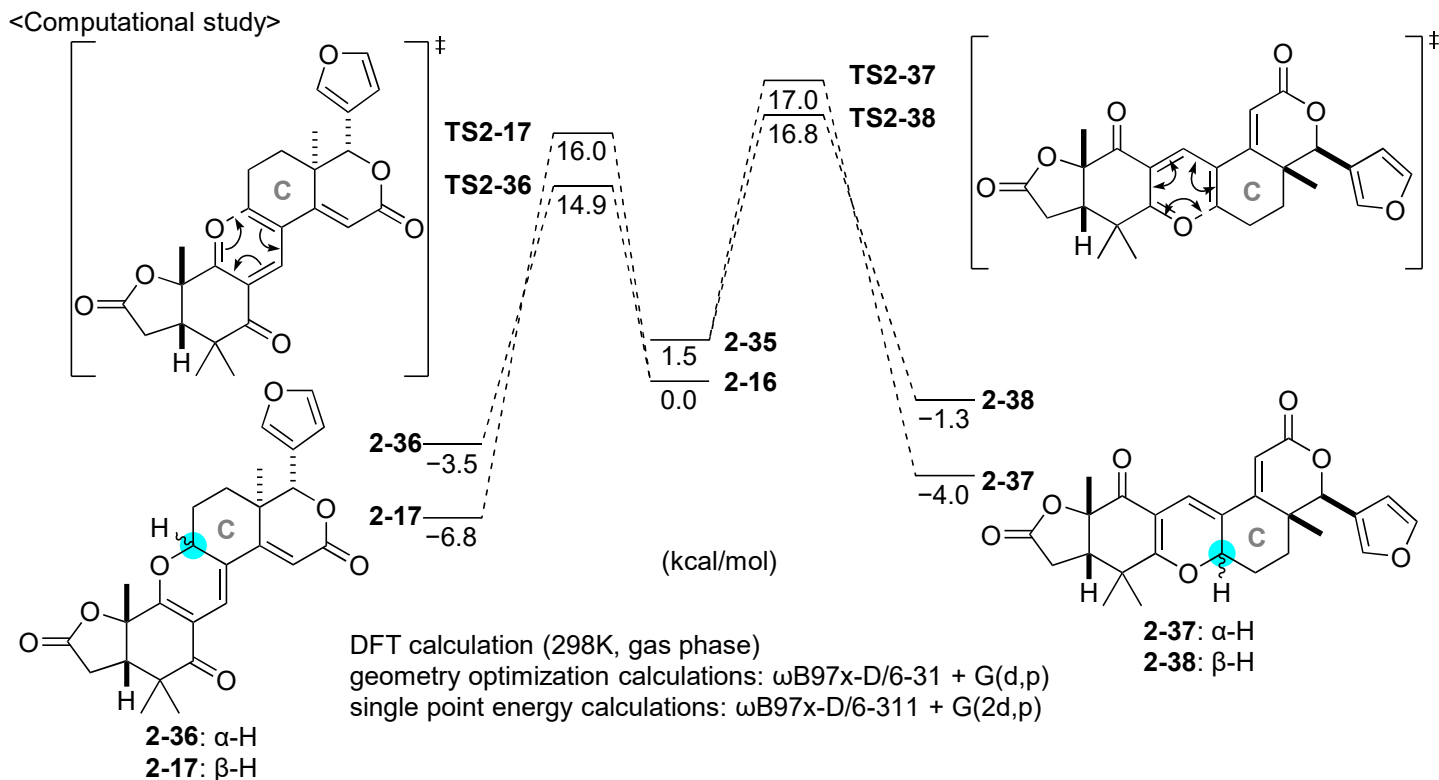


2-36, 2-17: The tetra-substituted carbon at the γ -position of blue highlighted hydrogen contains Me group and oxygen atom.

2-37, 2-38: The tetra-substituted carbon at the γ -position of blue highlighted hydrogen contains two Me groups.

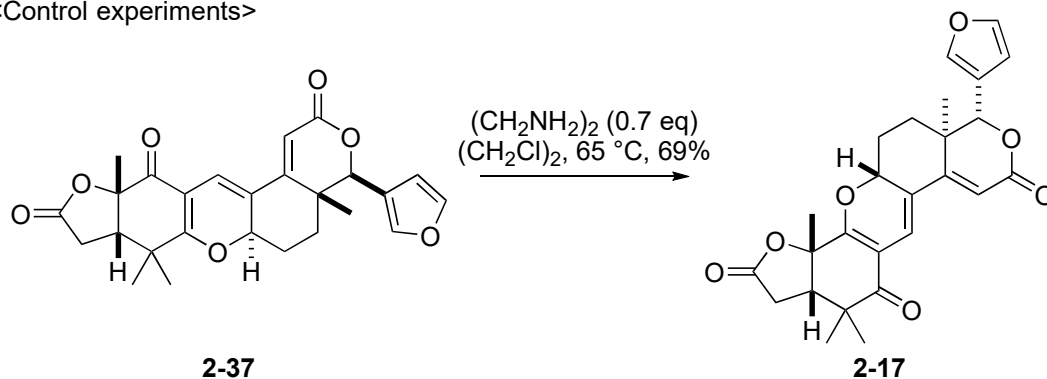
According to this point, 2-36 and 2-17 are more stable.

Considering ① and ②, the stability can be expected as follows: 2-17 > 2-36 \approx 2-37 > 2-38
Therefore, 2-17 is the most thermodynamically favored product.



These computational results also suggest that **2-17** is the most stable product.

<Control experiments>



Based on these results, **2-17** is the thermodynamically favored product.

Reference

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