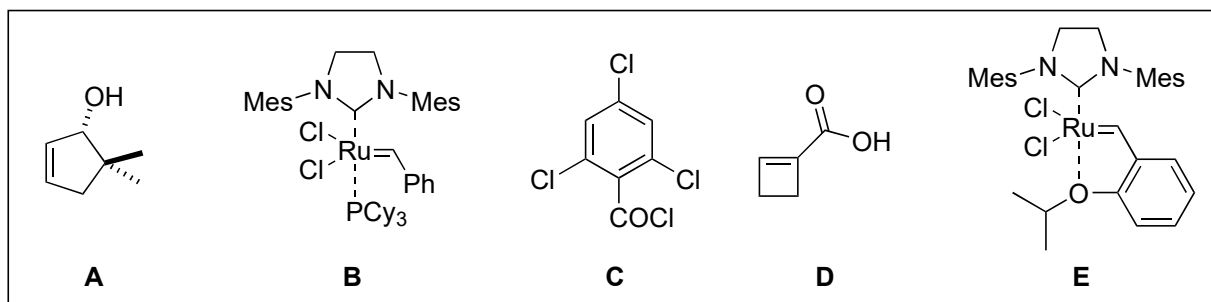
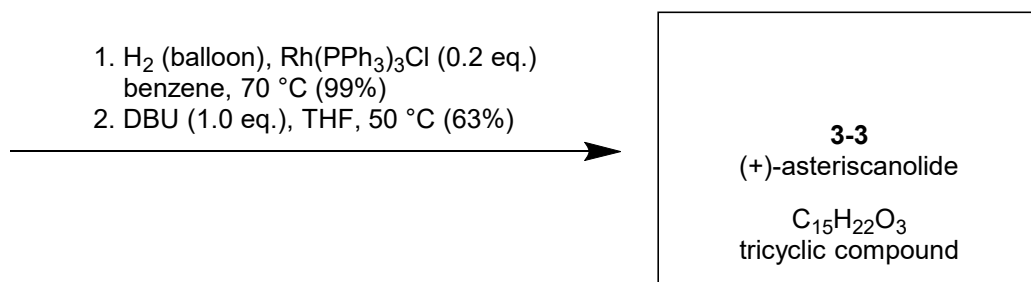
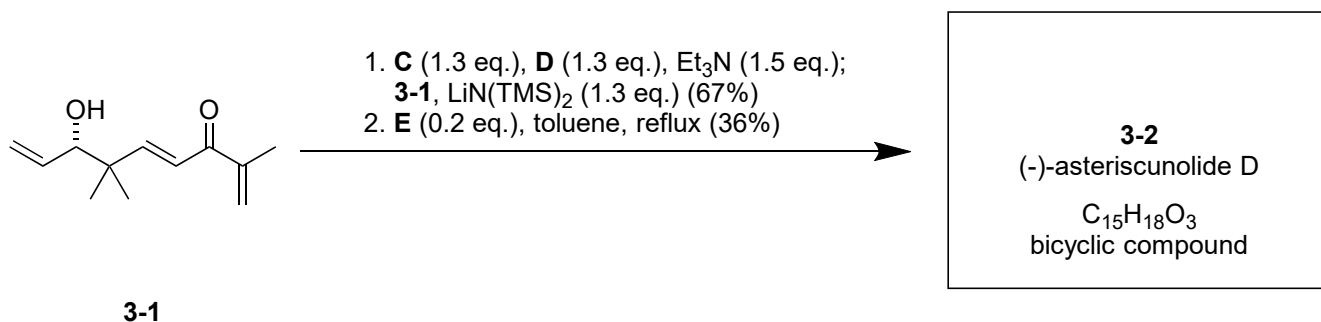
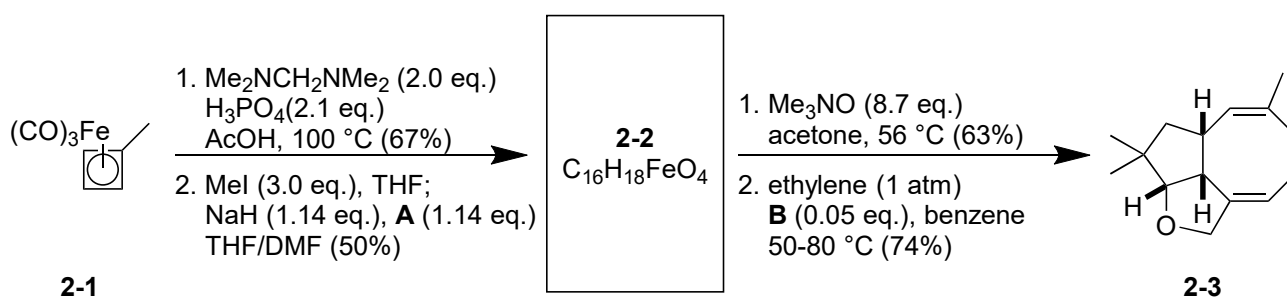
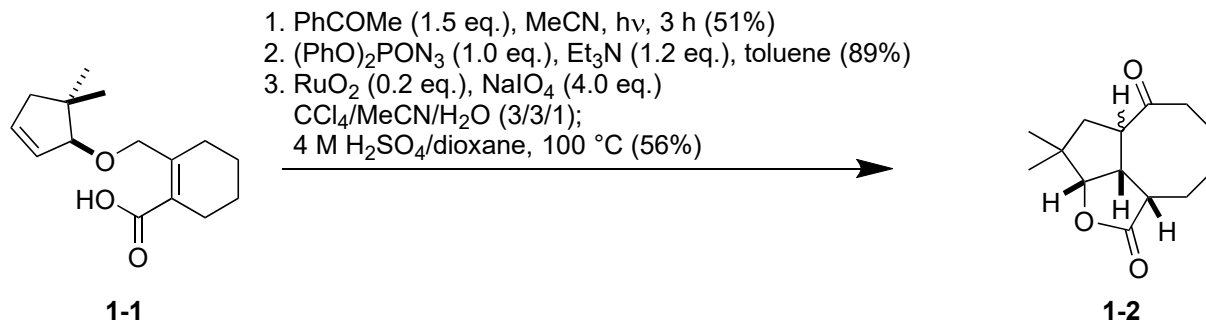


Problem Session (1)

2016/10/14 Takehiro Kato

Please provide the reaction mechanisms and fill in the blanks.



Problem Session (1) -Answer-

2016/10/14 Takehiro Kato

Topics: Total syntheses of asteriscanolide

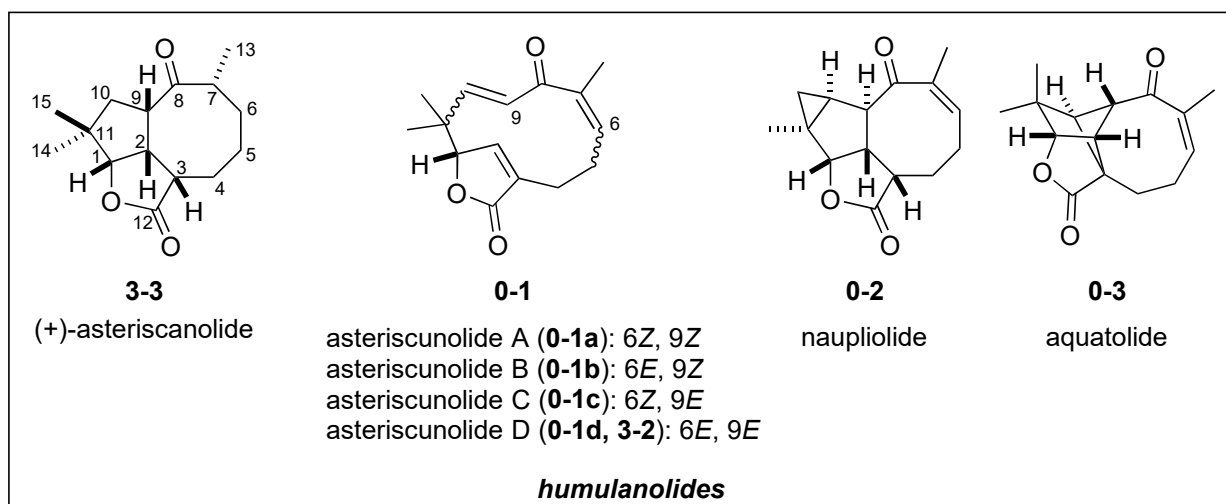
0. Introduction

Isolation

Isolated from *Asteriscus aquaticus* L

A. San Feliciano. *et al. Tetrahedron Lett.* **1985**, 26, 2369.)

Some other terpenoids called asteriscunolides were isolated from *Asteriscus aquaticus* L.



Biological Activity

Bioactivity of asteriscanolide has not been investigated.

Asteriscunolide A induces apoptosis in human cancer cells, and asteriscunolide D has cytotoxicity against the HT-29 (human colon carcinoma), A-549 (human lung carcinoma), and MEL-28 (human melanoma) cell lines.

Structural Feature

C₁₅ sesquiterpene

Bicyclo[6,3,0]undecane skeleton and adjoining butyrolactone

5 stereo centers

Total Synthesis

7-desmethylasteriscanolide (asymmetric)

K. I. Booker-Milburn. *et al. Tetrahedron*, **1997**, 37, 12319. (**Problem 1**)

asteriscanolide (asymmetric)

P. A. Wender. *et al. J. Am. Chem. Soc.* **1988**, 110, 5904

L. A. Paquette. *et al. J. Am. Chem. Soc.* **2000**, 122, 2742

M. L. Snapper. *et al. J. Am. Chem. Soc.* **2000**, 122, 8071 (**Problem 2**)

Z.-X. Yu. *et al. Chem. Commun.* **2011**, 47, 6659

Z.-X. Yu. *et al. Chem. Asian J.* **2012**, 7, 593

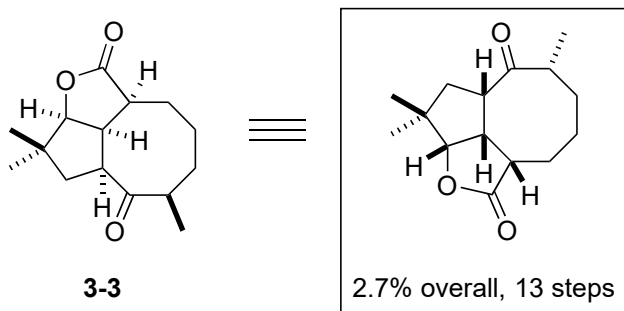
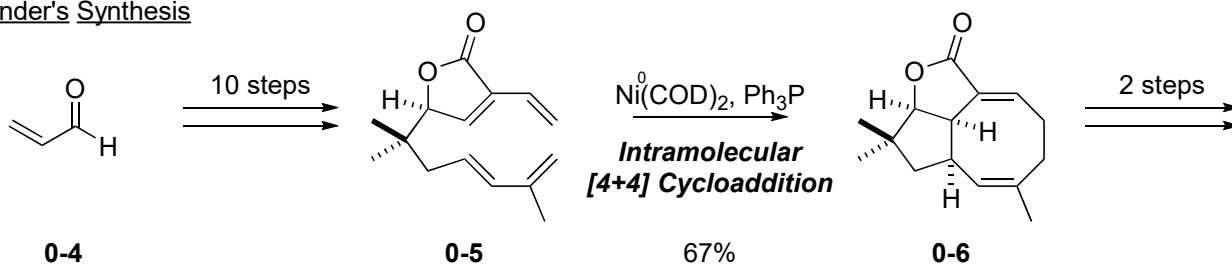
C. -C, Li. *et al. J. Am. Chem. Soc.* **2014**, 136, 13610 (**Problem 3**)

asteriscanolide (racemic)

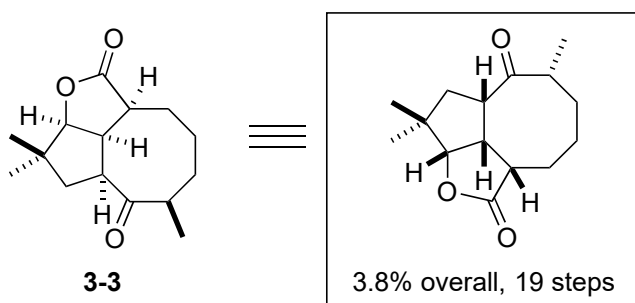
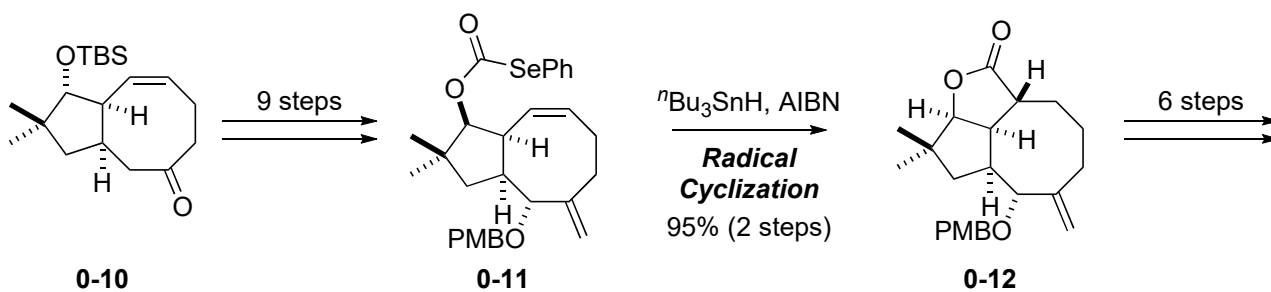
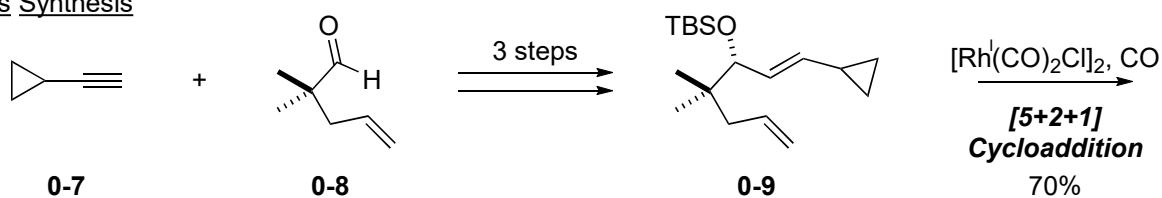
M. E. Krafft. *et al. Synthesis* **2000**, 1020

M. E. Krafft. *et al. J. Org. Chem.* **2001**, 66, 7443

Wender's Synthesis

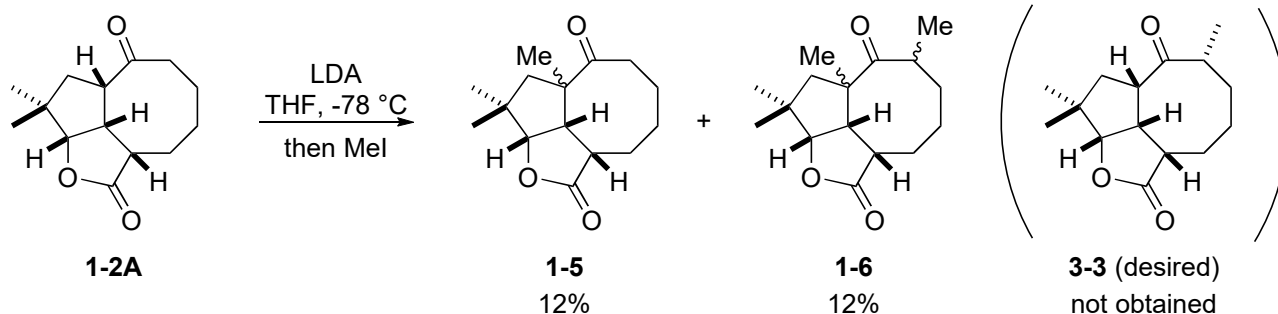
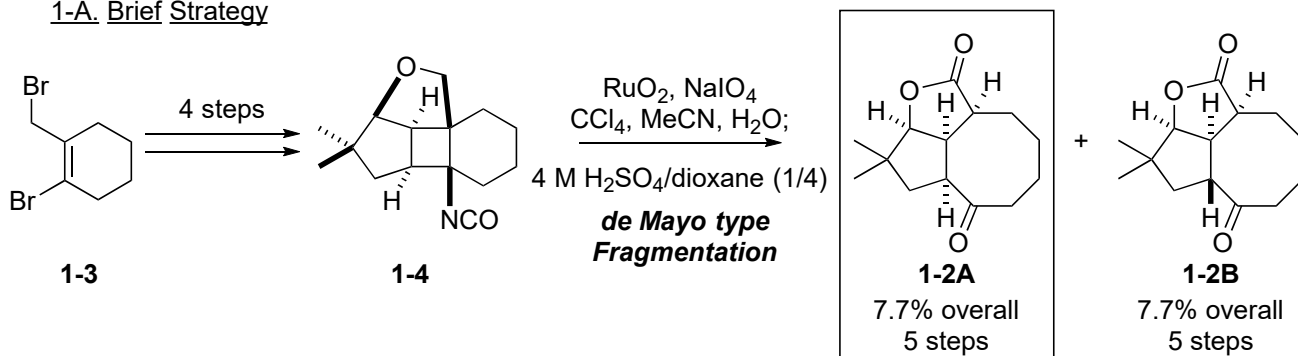


Yu's Synthesis

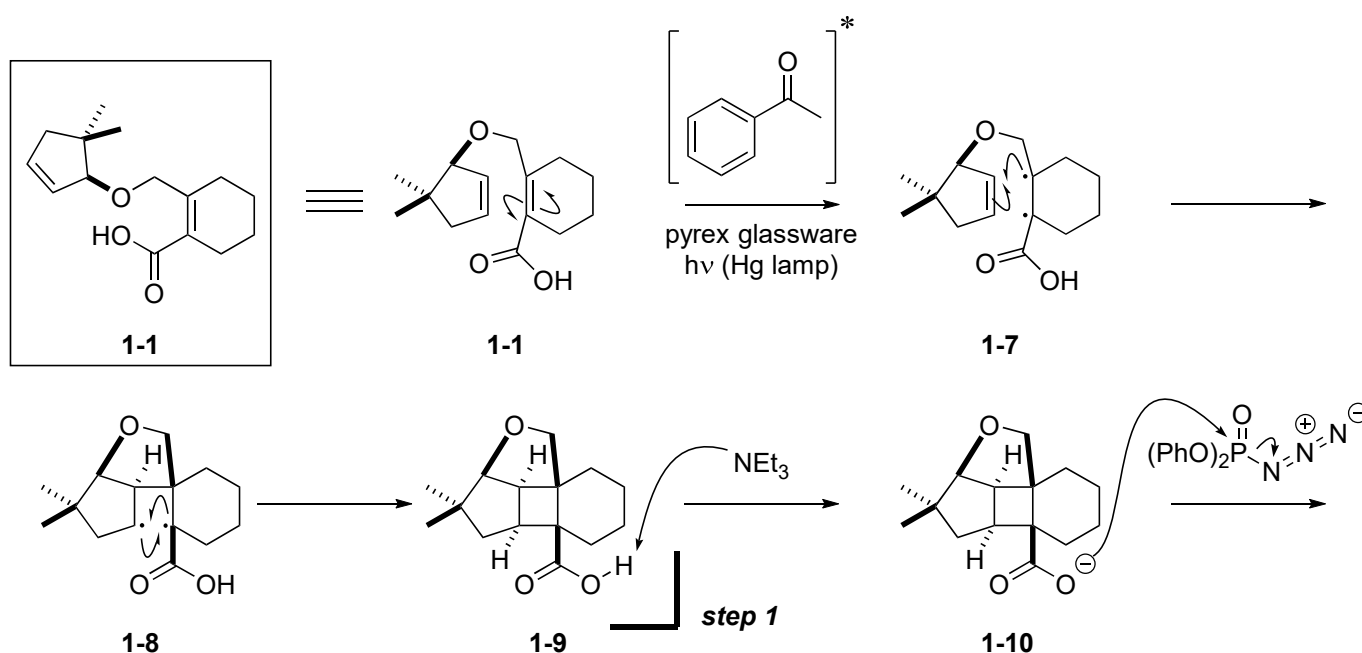
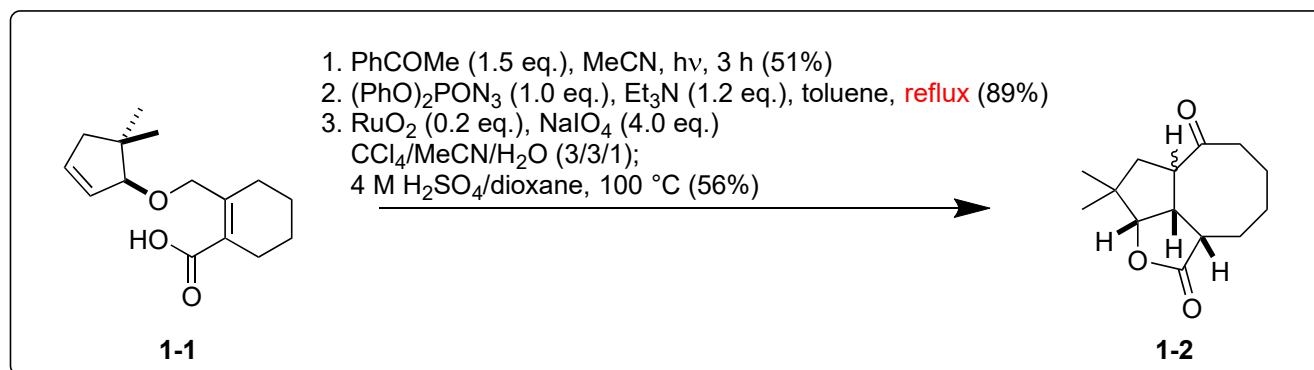


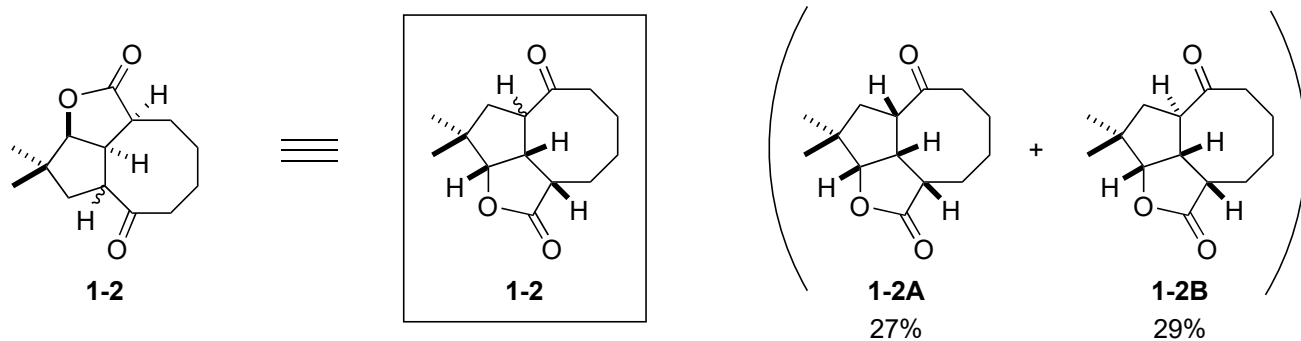
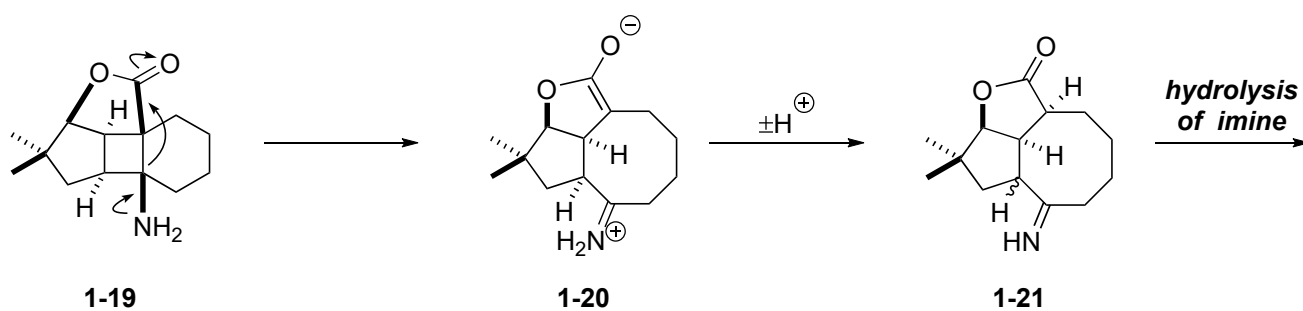
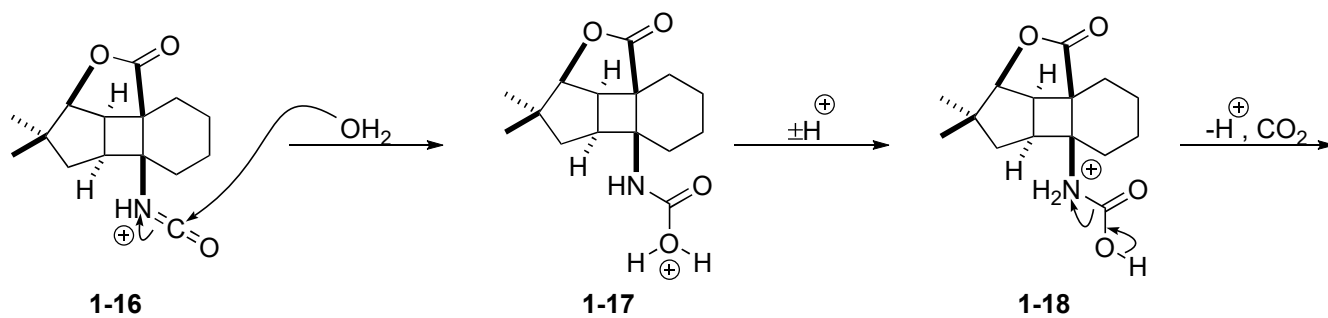
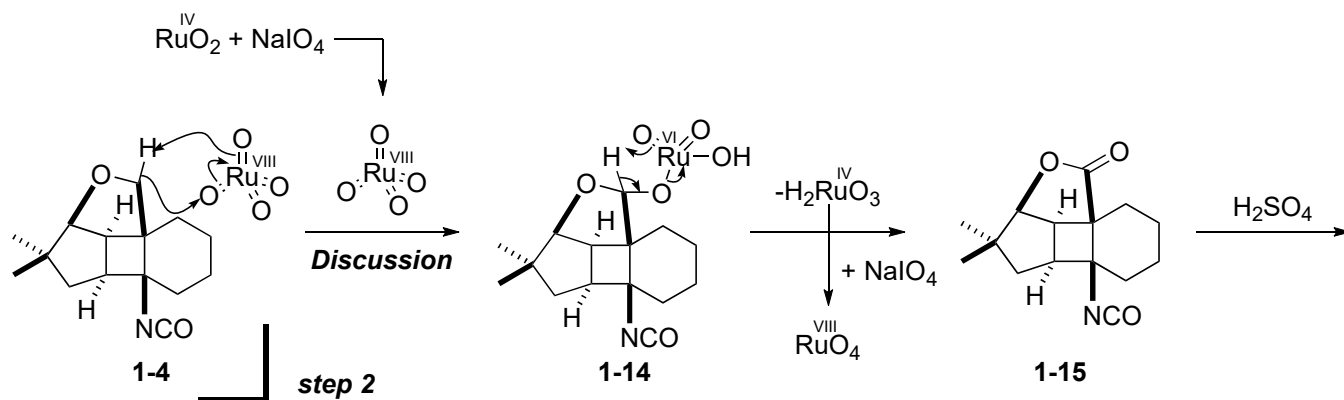
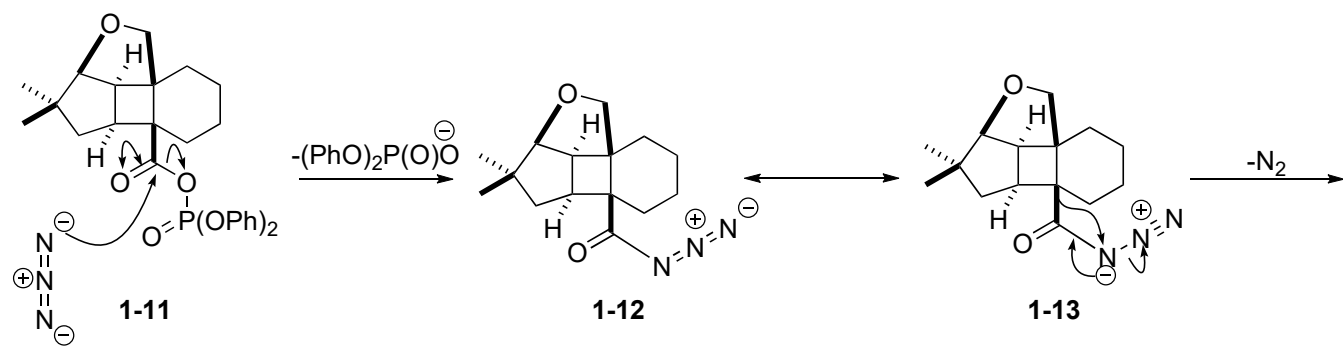
1. Booker-Milburn's Synthesis of 7-desmethyleriscanolid

1-A. Brief Strategy



1-B. Reaction Mechanism

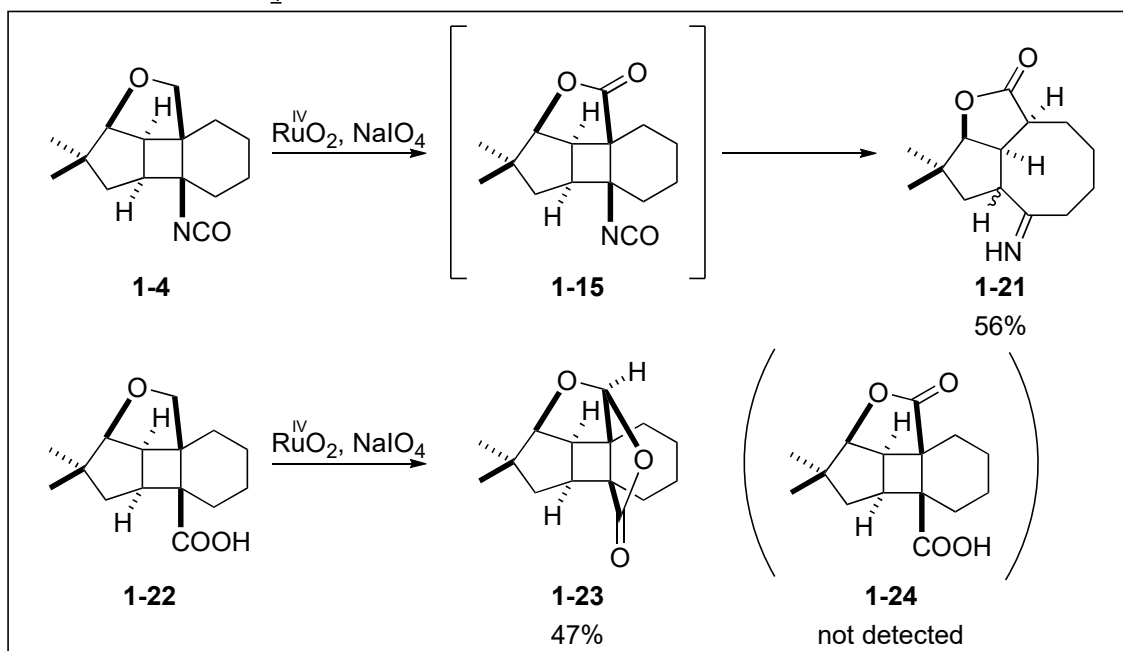




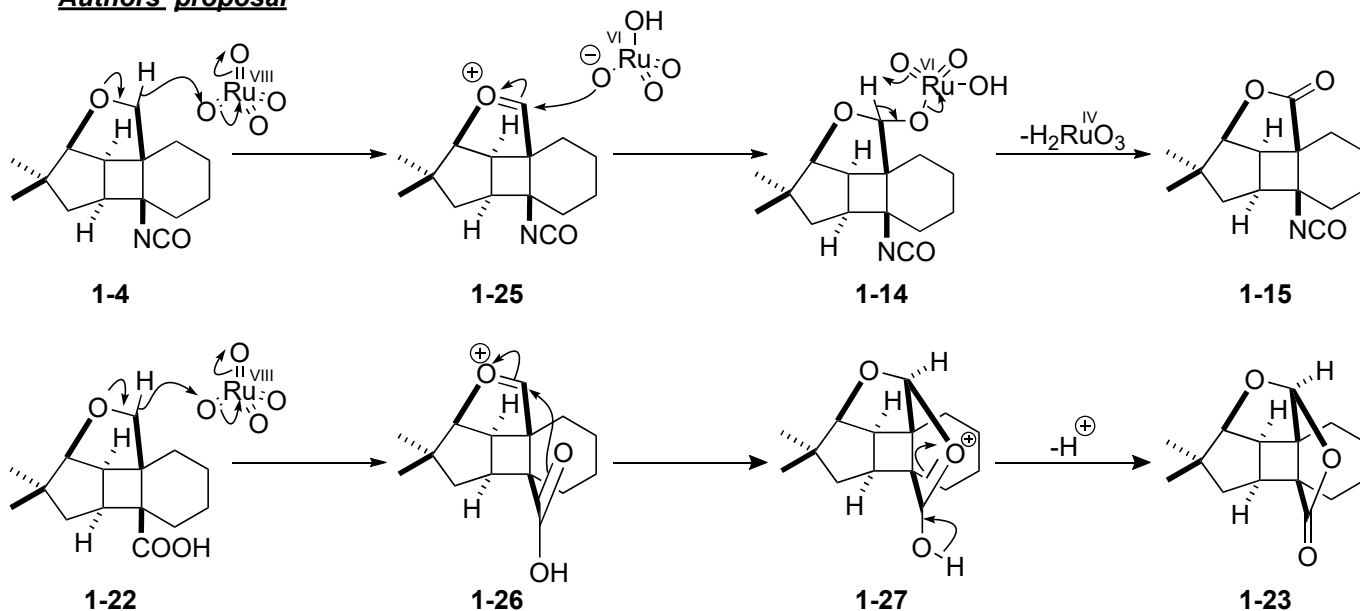
7-desmethylasteriscanolide (**1-2A**)
9-*epi*-7-desmethylasteriscanolide (**1-2B**)

1-C. Discussion

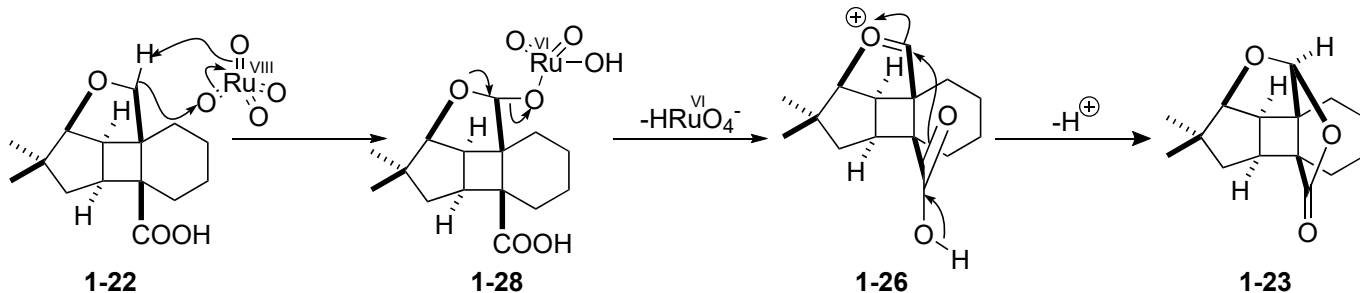
1-C-1. Mechanism of RuO₄ Oxidation of **1-4**



Authors' proposal



My proposal



The authors proposed that RuO₄ oxidation proceeds via hydride abstraction to give an intermediate carbocation. But it is confirmed that concerted mechanism shown above fits the experimental data of kinetic isotope effects and calculated conformation of transition state[†].

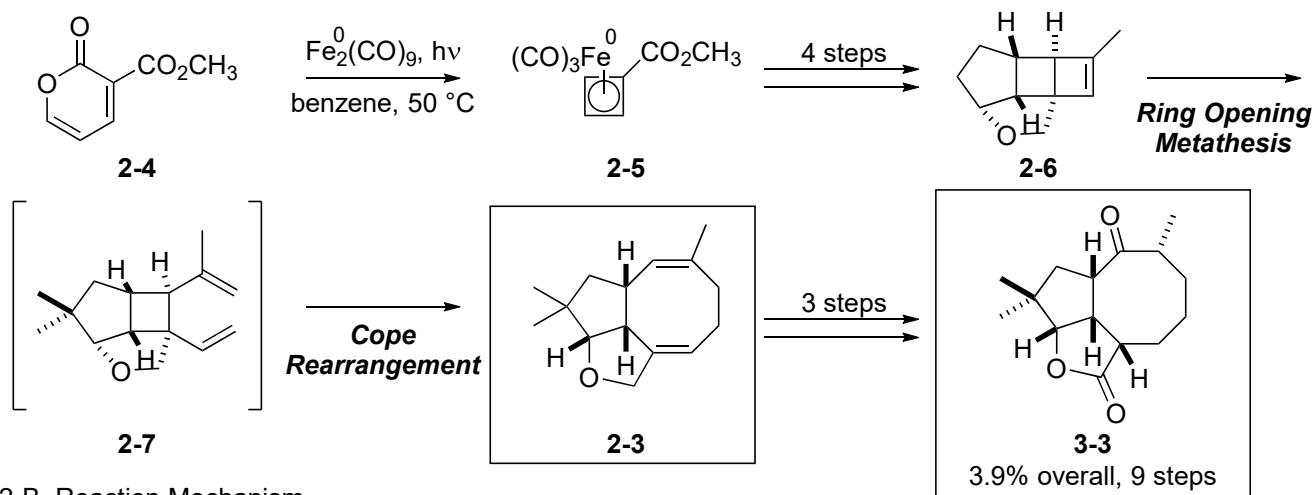
Strassner, *et al.* stated that their results of the calculation were in good agreement with experimental results from earlier work of Bakke*. Bakke, *et al.* investigated the solvent effects, solvent isotope effects, substituent effects, and isotope effects.

[†]M. Drees; T. Strassner. *J. Org. Chem.* **2006**, *71*, 1755

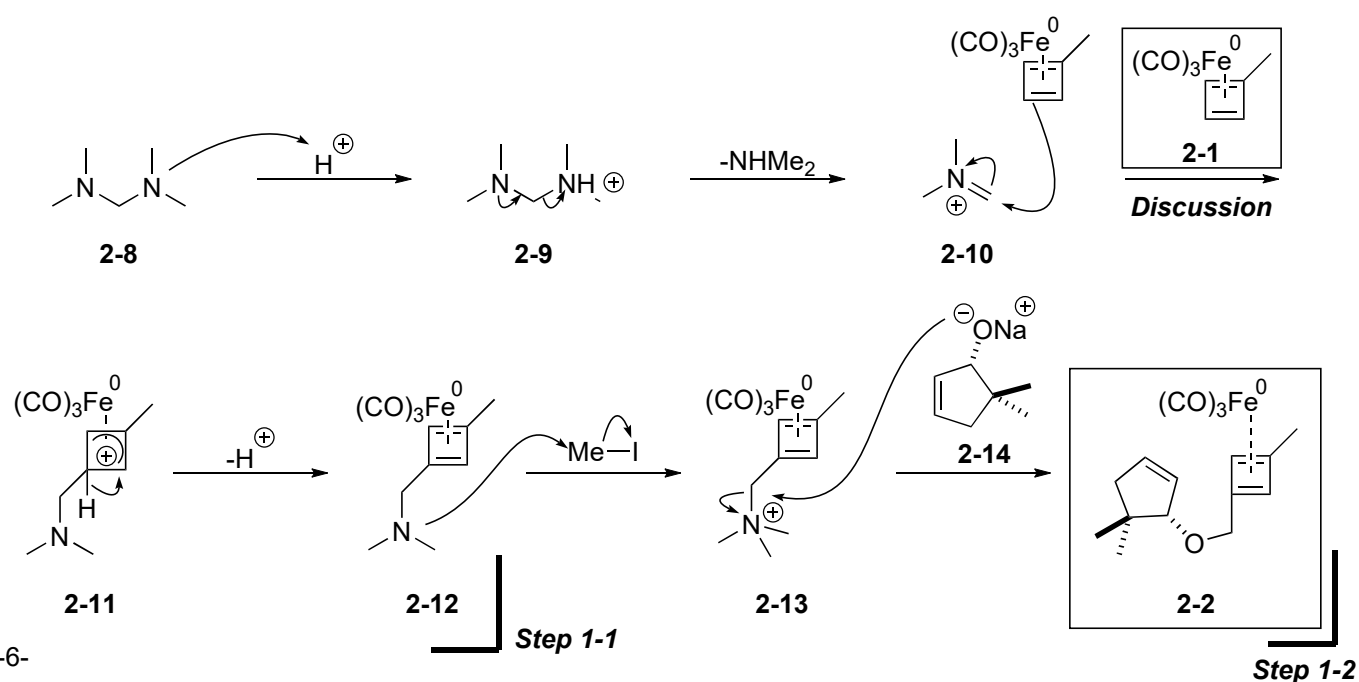
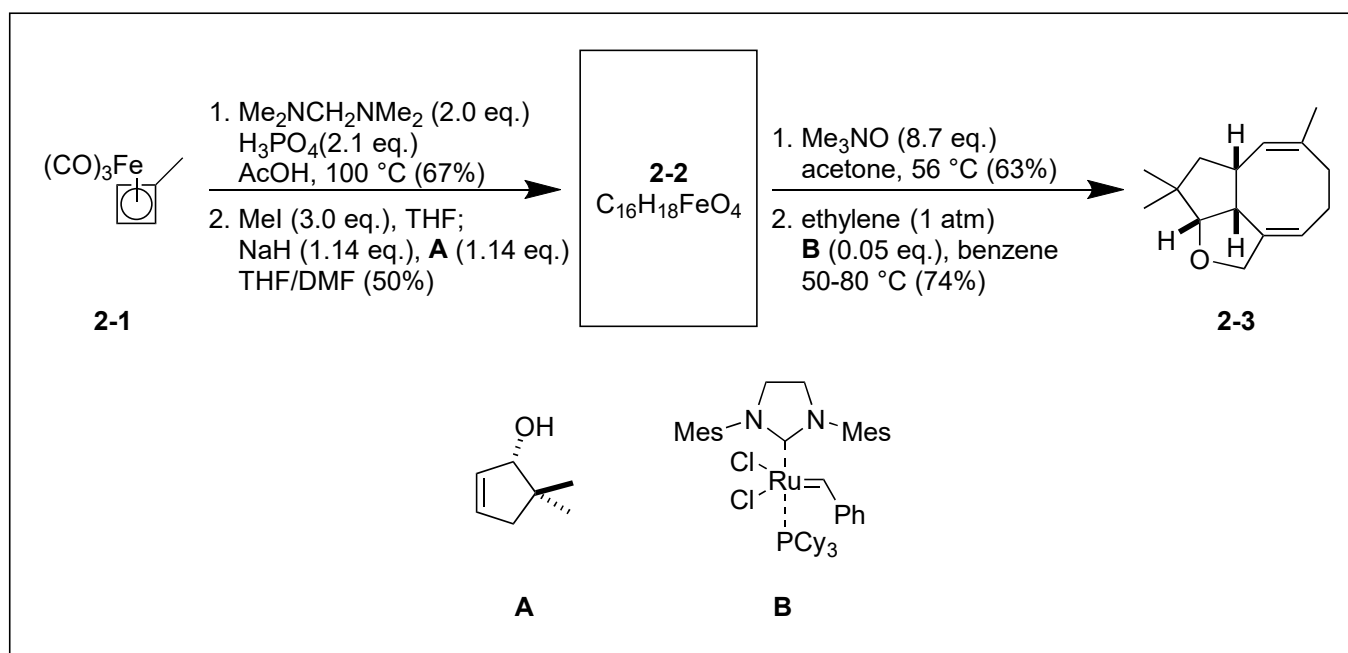
*J. M. Bakke; A. E. Frøhaug. *J. Phys. Org. Chem.* **1996**, *9*, 310

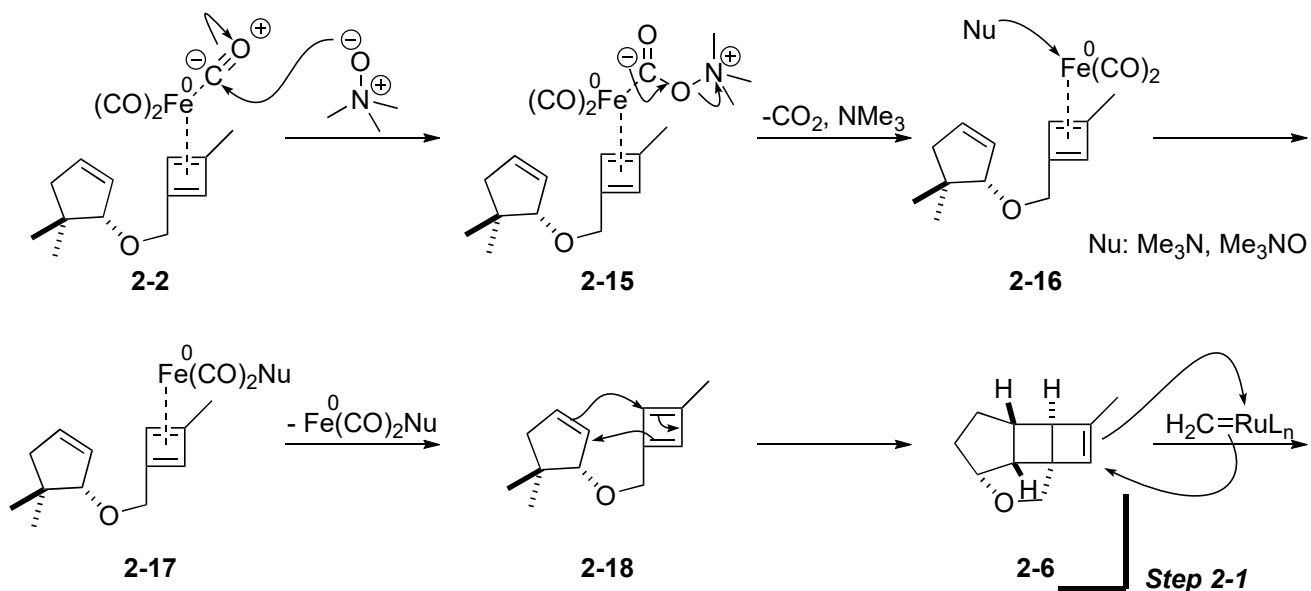
2. Snapper's Synthesis of Asteriscanolid

2-A. Brief Strategy

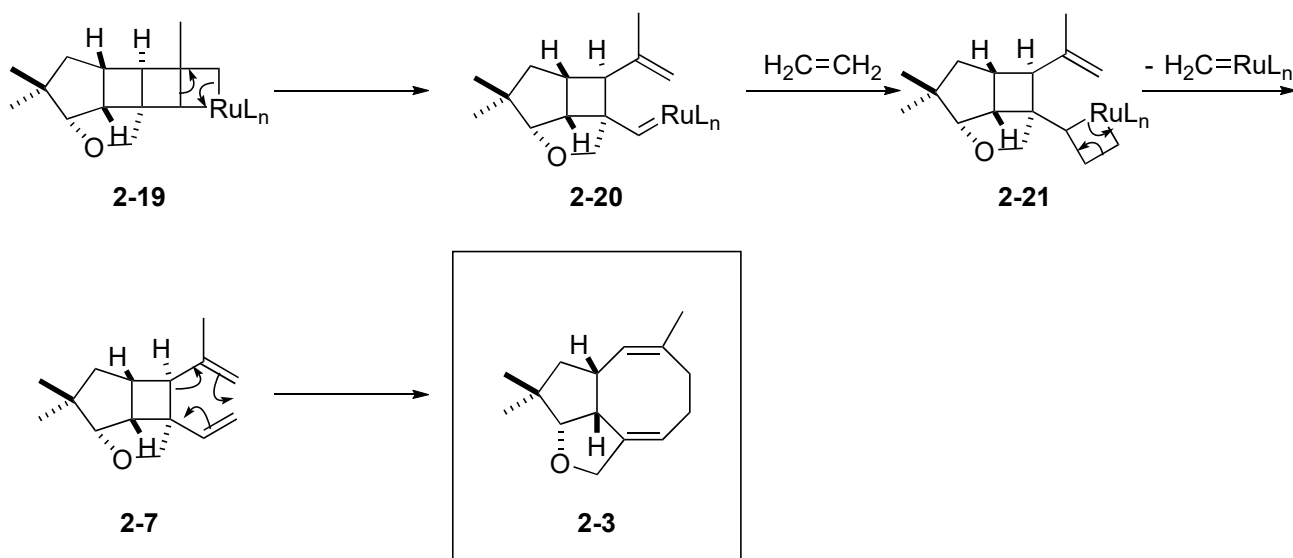


2-B. Reaction Mechanism



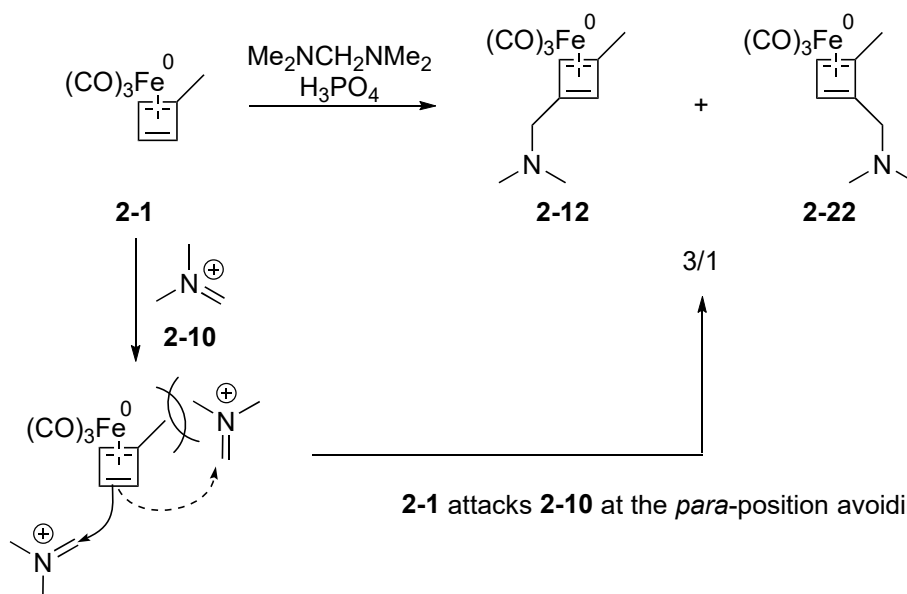


Note: The mechanism of the conversion from **2-16** to **2-18** is my proposal. It is known that one of the carbonyl ligand would be removed by Me₃NO as shown above, but how iron eliminates from cyclobutadiene is not elucidated.



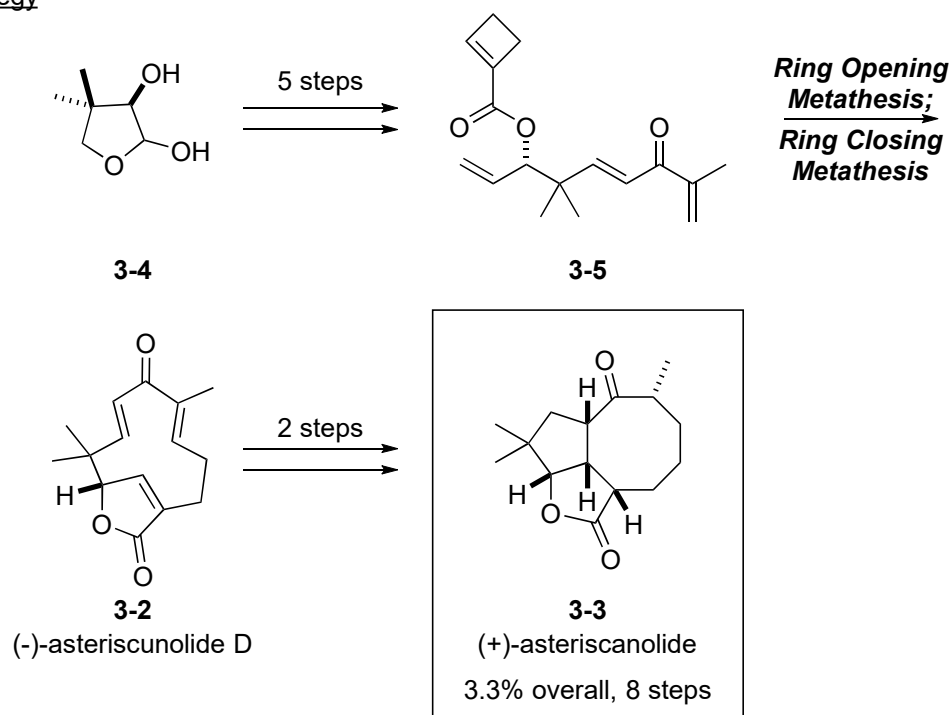
2-B. Discussion

2-B-1. Regioselectivity of Electrophilic Addition of **2-10** to **2-1**

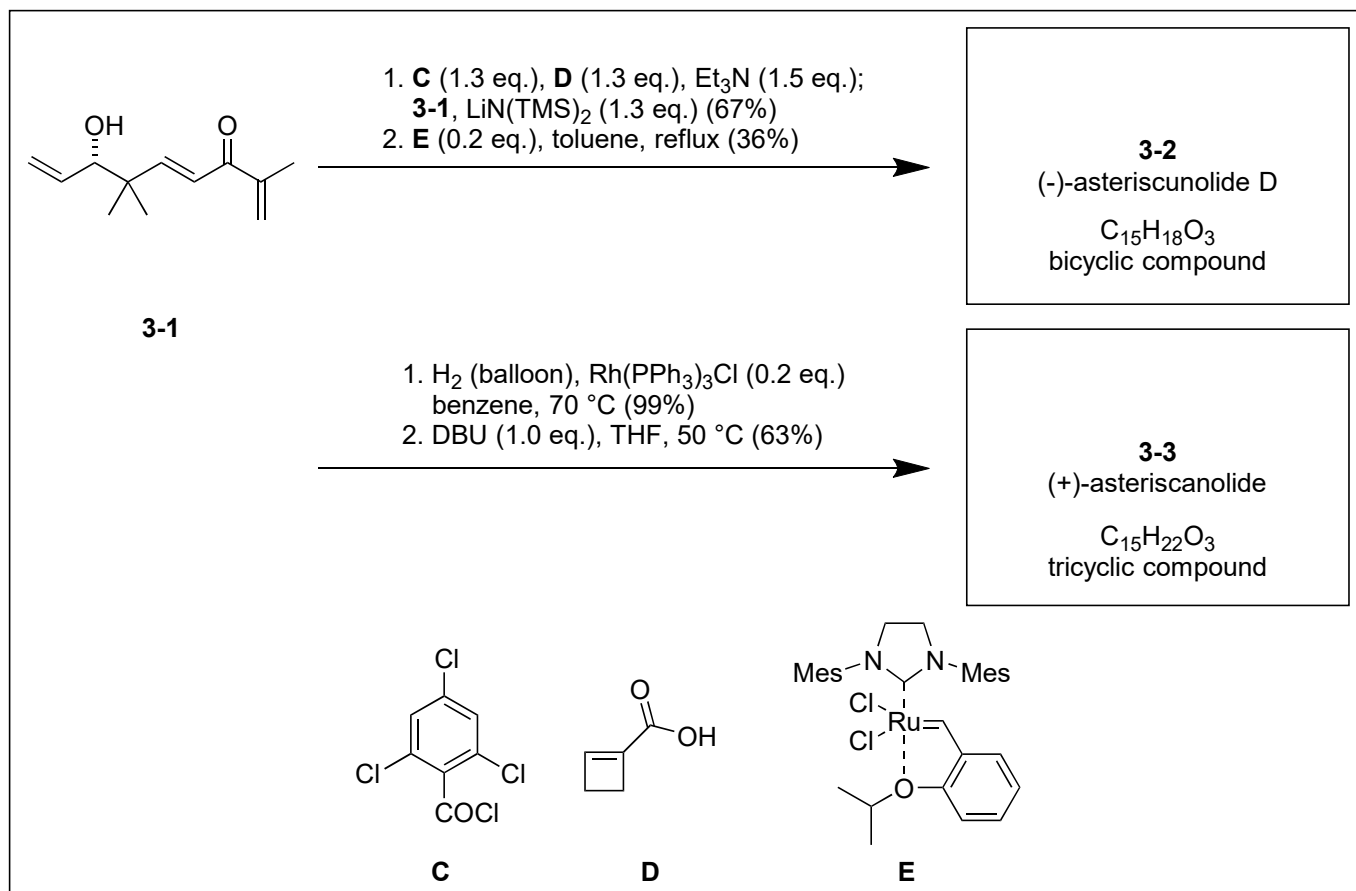


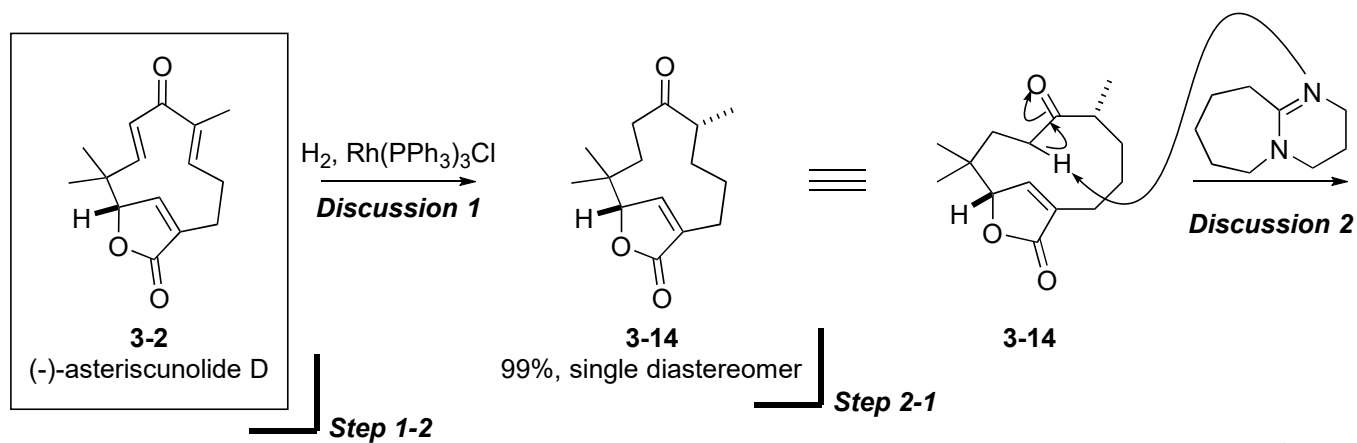
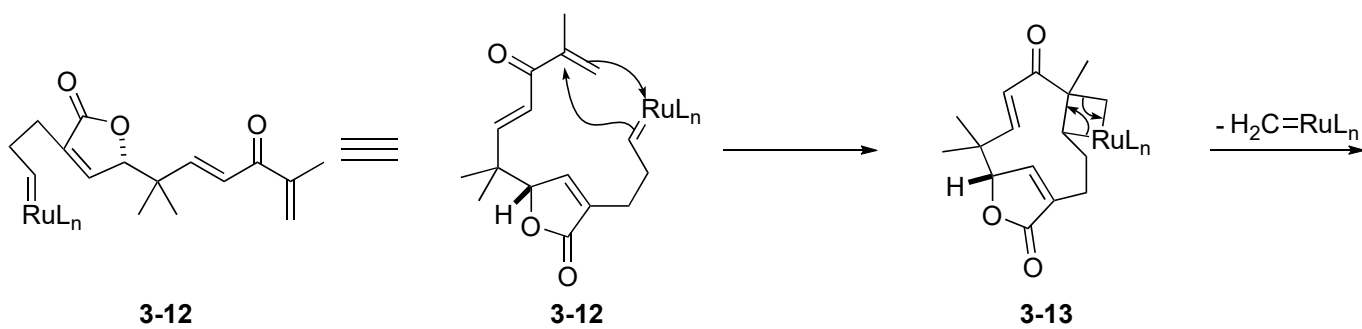
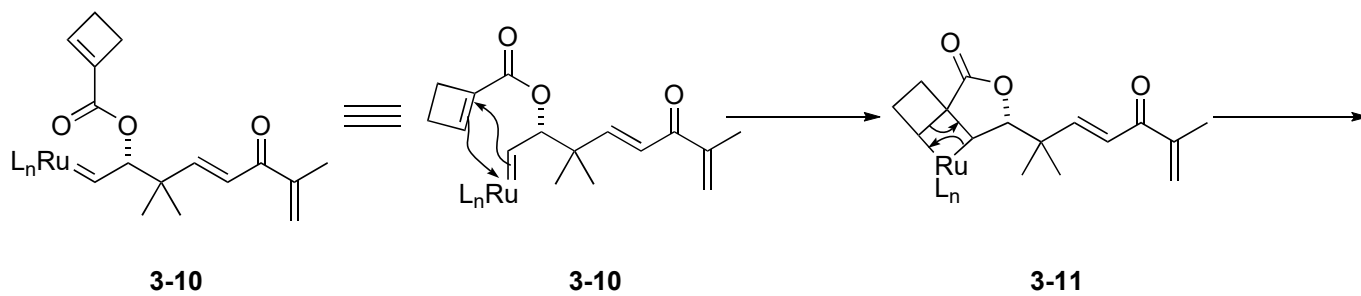
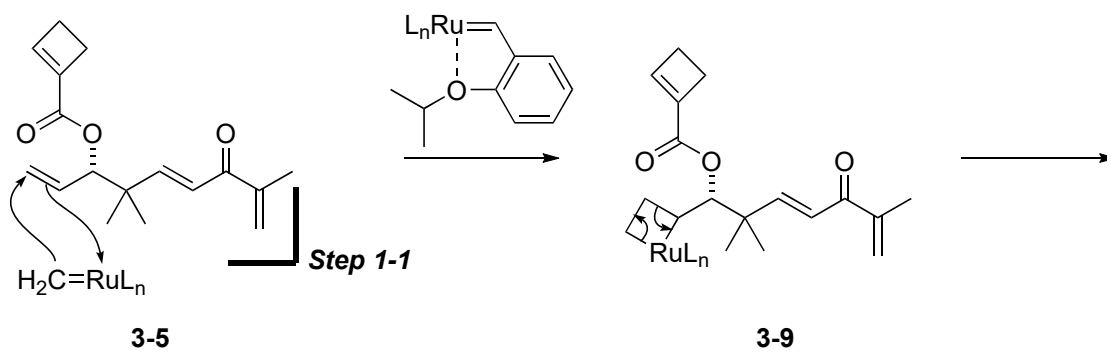
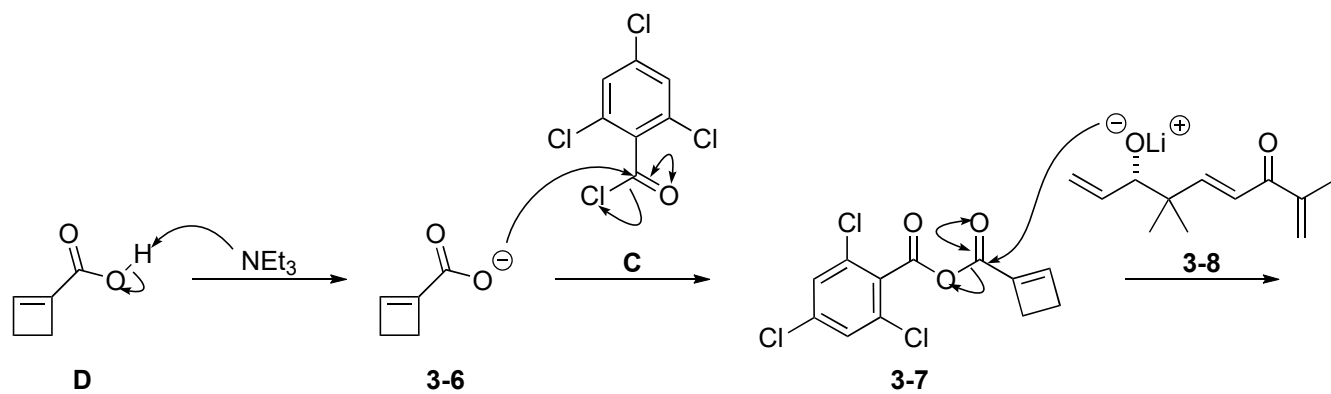
3. Li's Synthesis of Asteriscunolide D and Asteriscanolide

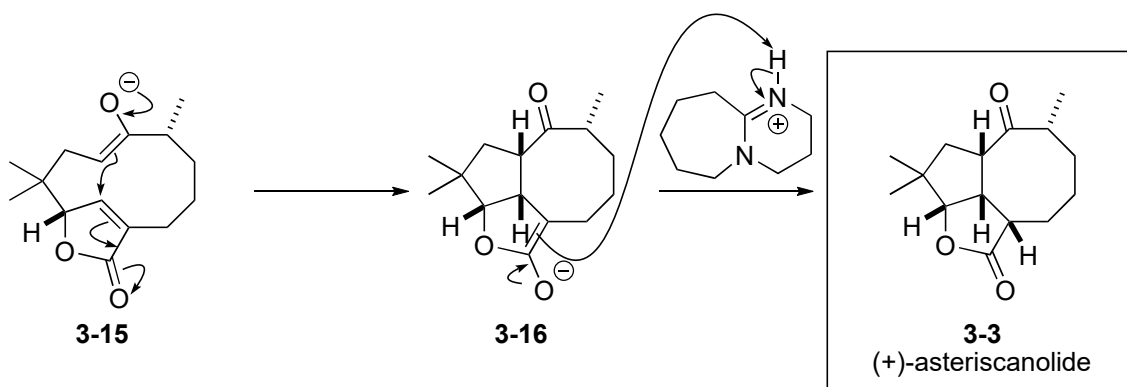
3-A. Brief Strategy



3-B. Reaction Mechanism

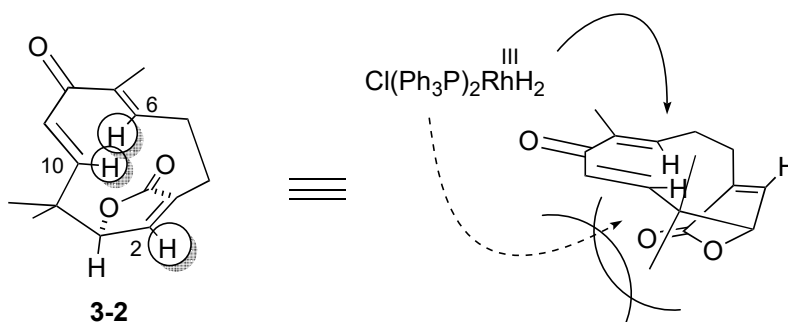




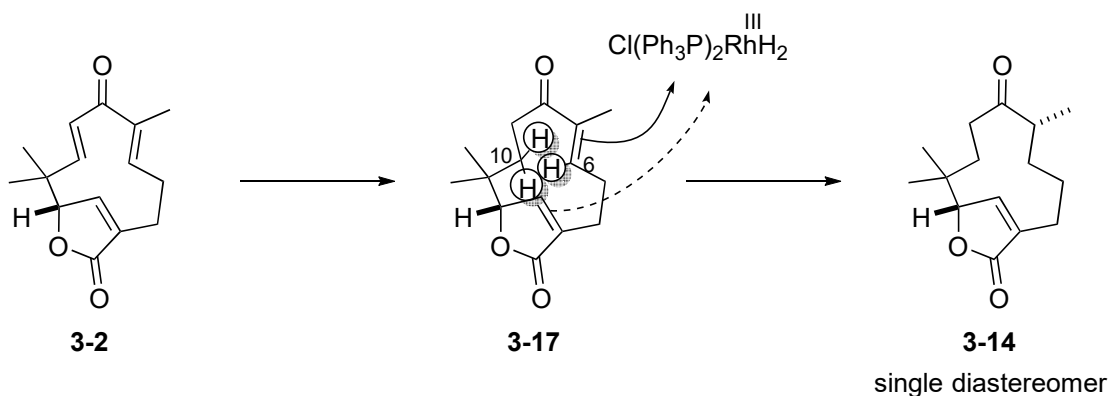


3-B. Discussion

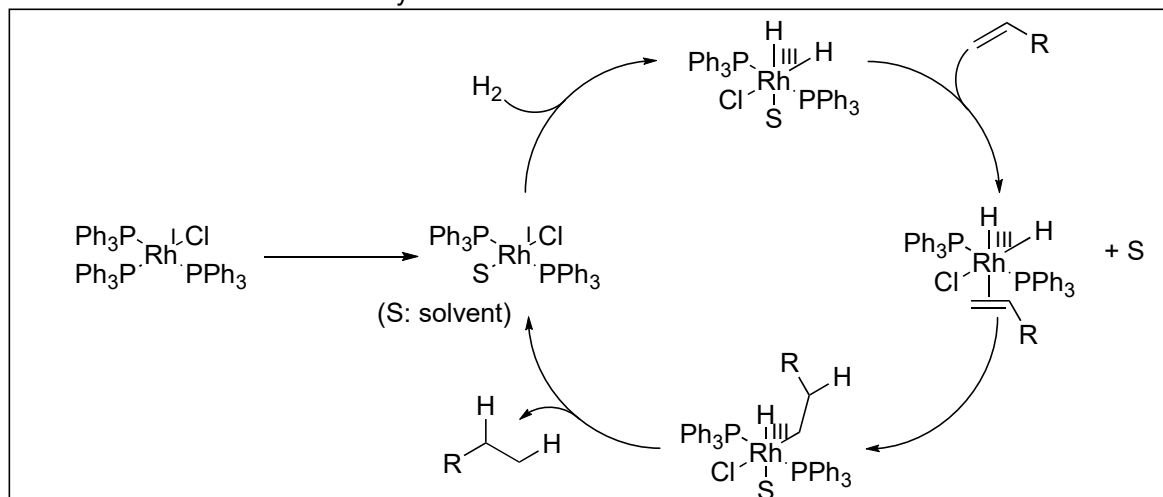
3-B-1. Stereo- and Chemoselectivity of Hydrogenation of **3-2**



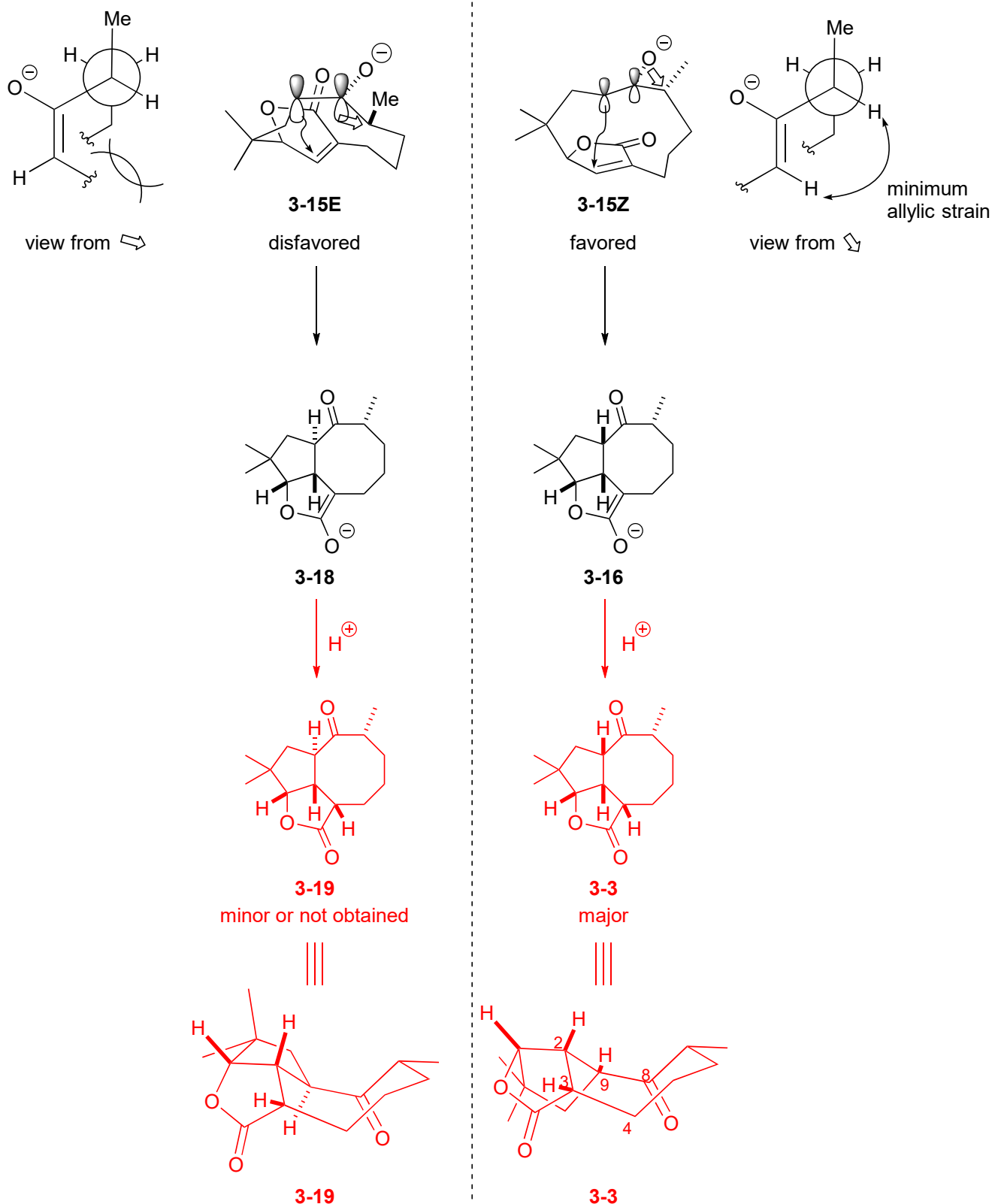
H6 and H10 exist inside the macroring and repel H2.
To avoid steric repulsion, the butenolide covers α side of **3-2** and Wilkinson's catalyst approaches from β side.



The two-substituted olefin would be hydrogenated first, producing **3-17**.
Because of the repulsion between H6 and H10, the enone plane of **3-17** is twisted and electron withdrawal of carbonyl group becomes weaker.
So the enone olefin is electron-richer than butenolide olefin and coordinates to Wilkinson's catalyst faster.



3-B-3. Stereoselectivity of Michael Addition



The supposed conformation of **3-19** and **3-3** are shown above as both of the eight-membered rings form boat-chair. But considering the strain of the lactone bridge, C2, 3, 4, 8 and 9 of **3-3** is supposed to form flatter plane than the above.