

Problem Session (2) -Answer-

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Topic: Recent synthetic works of scabrolide A.

Introduction

• **Isolation:** Isolated from soft coral *Sinularia scabra*. in 2002, along with three other novel norcembranoids (scabrolides B-D) and four known norcembranoids (e.g., ineleganolide). Sheu, J.; Ahmed, A. F.; Shiue, R.; Dai, C.; Kuo, Y.; *J. Nat. Prod.* **2002**, 65, 1904-1908.

• **Bioactivities:** Scabrolide A is shown to inhibit IL-6 and IL-12 production *in vitro* and has a potential as an anti-inflammatory agent.

• **Structural features:** A fused [5,6,7] carbocyclic framework featuring 6 stereogenic centers, five of which are contiguous.

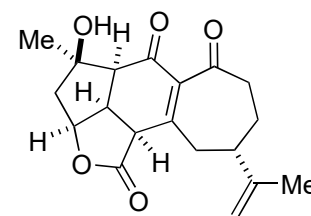
Total synthesis

Hafeman, N. J.; Loskot, S. A.; Reimann, C. E.; Pritchett, B. P.; Virgil, S. C.; Stoltz, B. M.

J. Am. Chem. Soc. **2020**, 142, 8585. see 200606_PS_Takahiro_Watanabe

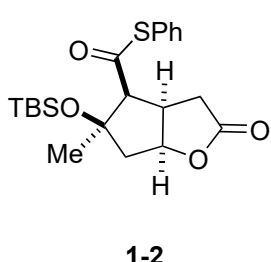
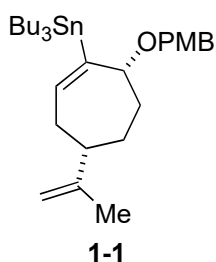
Meng, Z. C.; Furstner, A. *J. Am. Chem. Soc.* **2022**, 144, 1528. → **problem 2**

Serrano, R.; Boyko, Y. D.; Hernandez, L. W.; Lotuzas, A.; Sarlah, D. *J. Am. Chem. Soc.* **2023**, 145, 8805. → **problem 1**

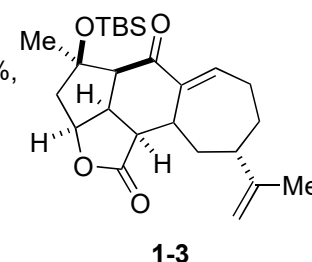


scabrolide A

Problem 1



1. Pd₂(dba)₃ (0.1 eq), P(o-furyl)₃ (0.4 eq)
CuDPP (1.5eq), THF, 60 °C, 89%
2. LiN(*i*-Pr)₂ (4.0 eq), ZnI₂ (2.0 eq)*, 0 °C, 53%,
d.r. = 20 : 1

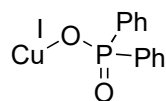
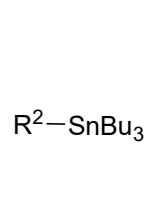
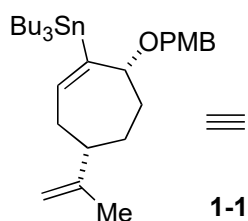


* ca. 1.1-1.2 eq newly formed base was added.

Serrano, R.; Boyko, Y. D.; Hernandez, L. W.; Lotuzas, A.; Sarlah, D. *J. Am. Chem. Soc.* **2023**, 145, 8805.

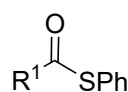
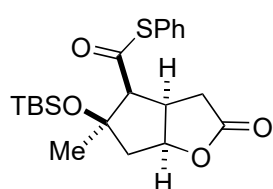
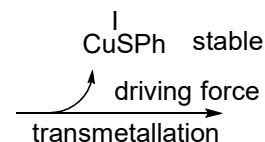
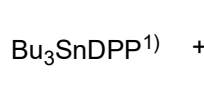
Answer

Liebeskind-Srogl coupling

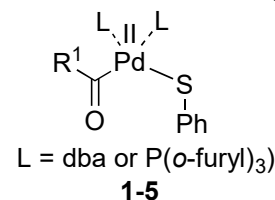


CuDPP

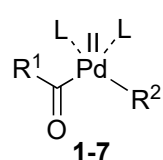
the effectiveness of the Ph₂P(O)O⁻ counterion facilitate the precipitation of tin residues (as *n*Bu₃SnOP(O)Ph₂) from the reaction mixture.



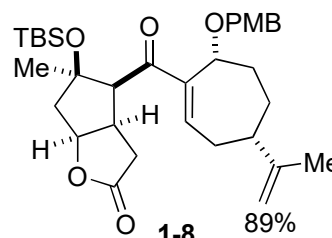
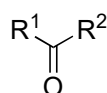
oxidative addition



1-6

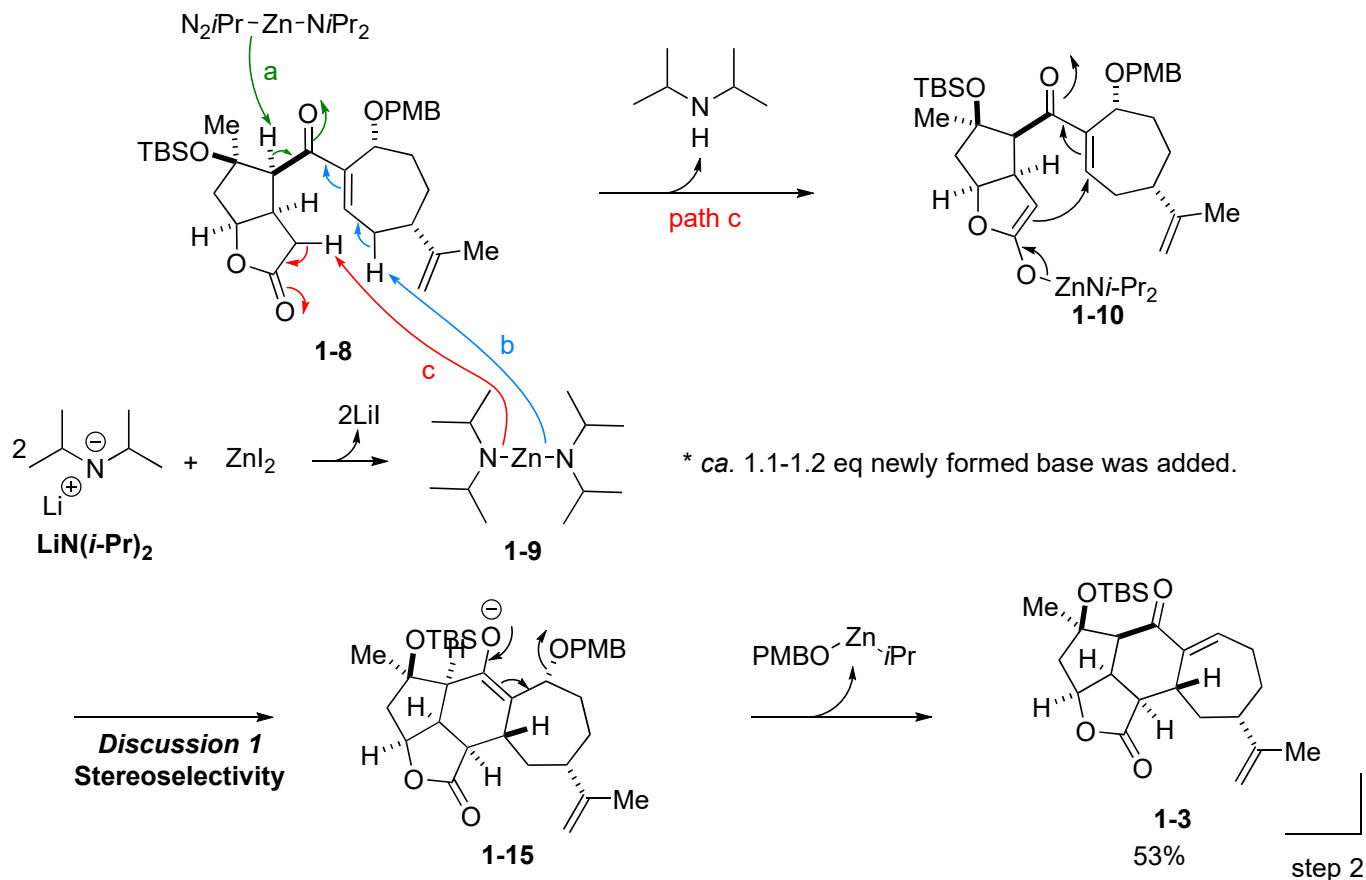


reductive elimination



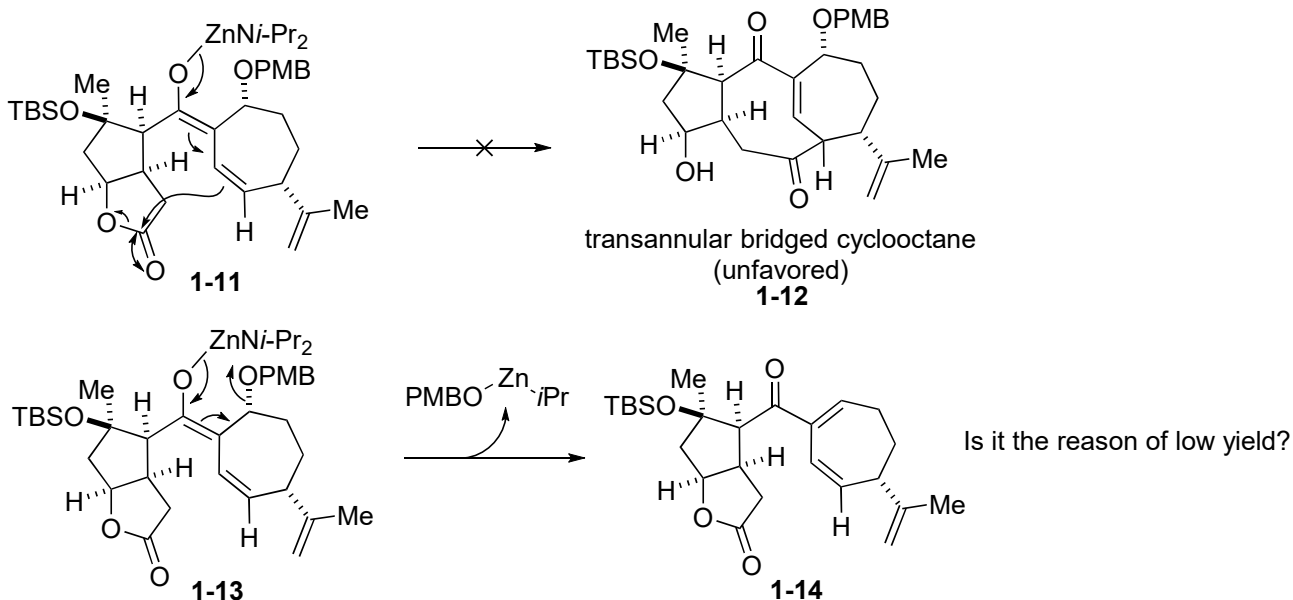
step 1

1



path a : the proton is shielded by the methyl group, deprotonation is hard.

path b:



Discussion 1

Stereoselectivity of coupling reaction

1. Screening of base & additives

The decomposition and low yield may result from the strong basicity of the base (bad tolerance of base-sensitive functionalities).

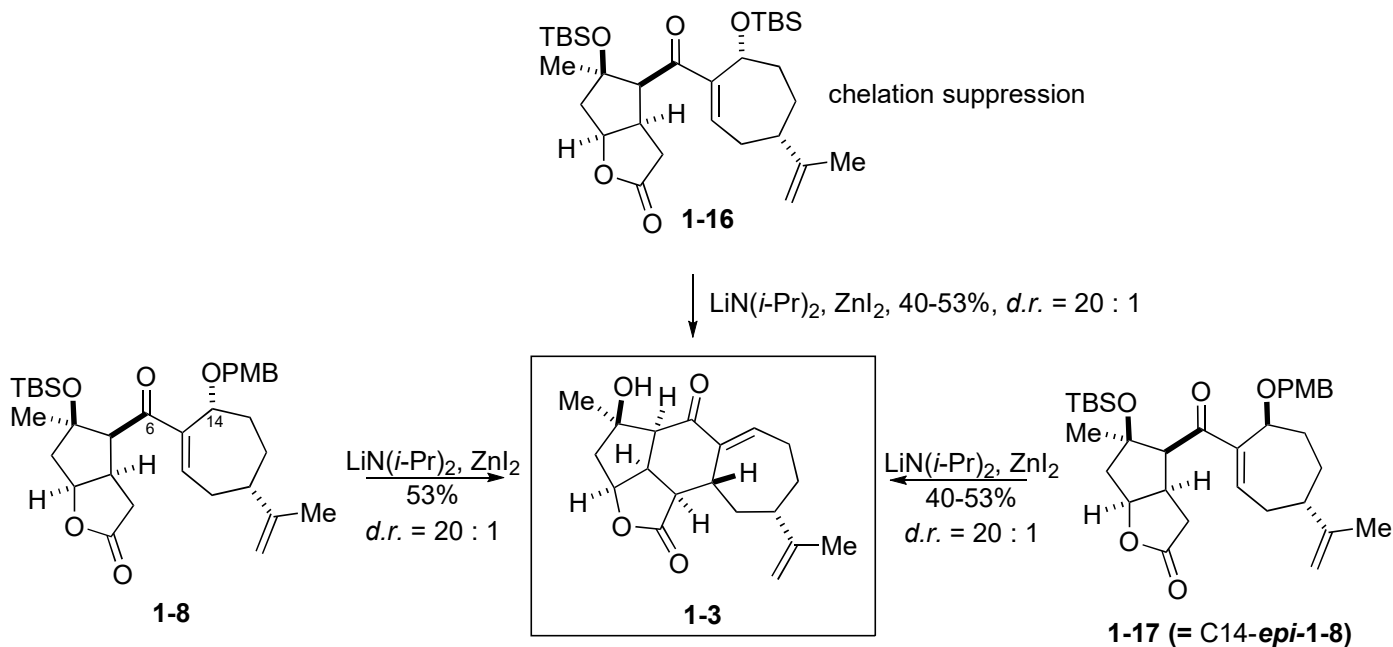
It is reported ^{ref2} that organozinc base (less basic) could deprotonate wide ranges of functionalized organics under mild conditions. Finally, the author found that premixing of ZnI₂ and LDA in 1 : 2 ratio proved critical, suggesting the bis-amidozinc base is operative in the coupling reaction.

base & additives	yield
NaN(TMS) ₂ or KN(TMS) ₂	decomp.
LiN(<i>i</i> -Pr) ₂ or LiN(TMS) ₂	5-10%
LiN(<i>i</i> -Pr) ₂ , ZnCl ₂	30-40%
LiN(<i>i</i> -Pr) ₂ , ZnI ₂	53%
LiN(<i>i</i> -Pr) ₂ , MgBr ₂	decomp.

2. Reaction mechanism

Chelation control studies

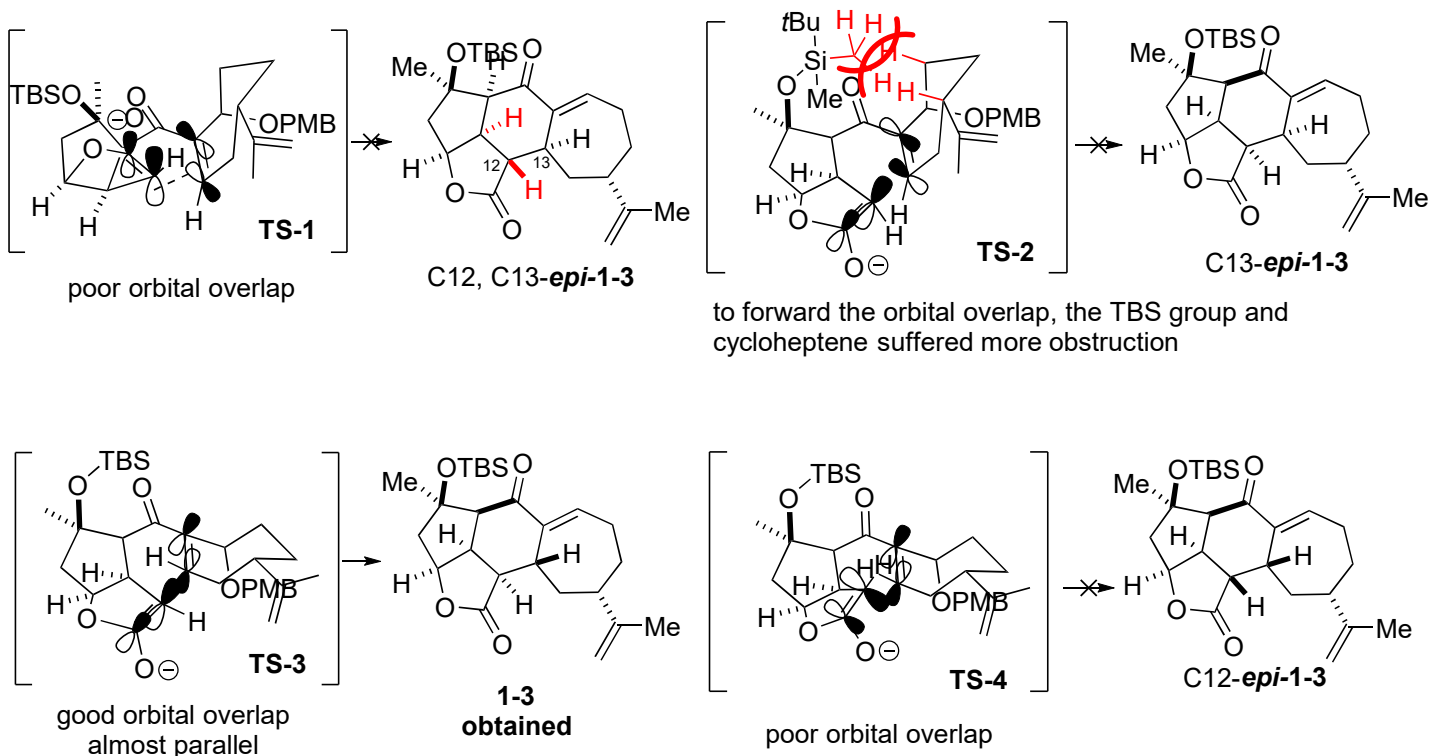
The author declared the chelation effect of zinc with oxygens of ketone and OPMB fix the reaction conformation; however, even in substrate **1-13** whose chelation effect is suppressed, desired compound could be obtained in moderate yield. That's contradictory.

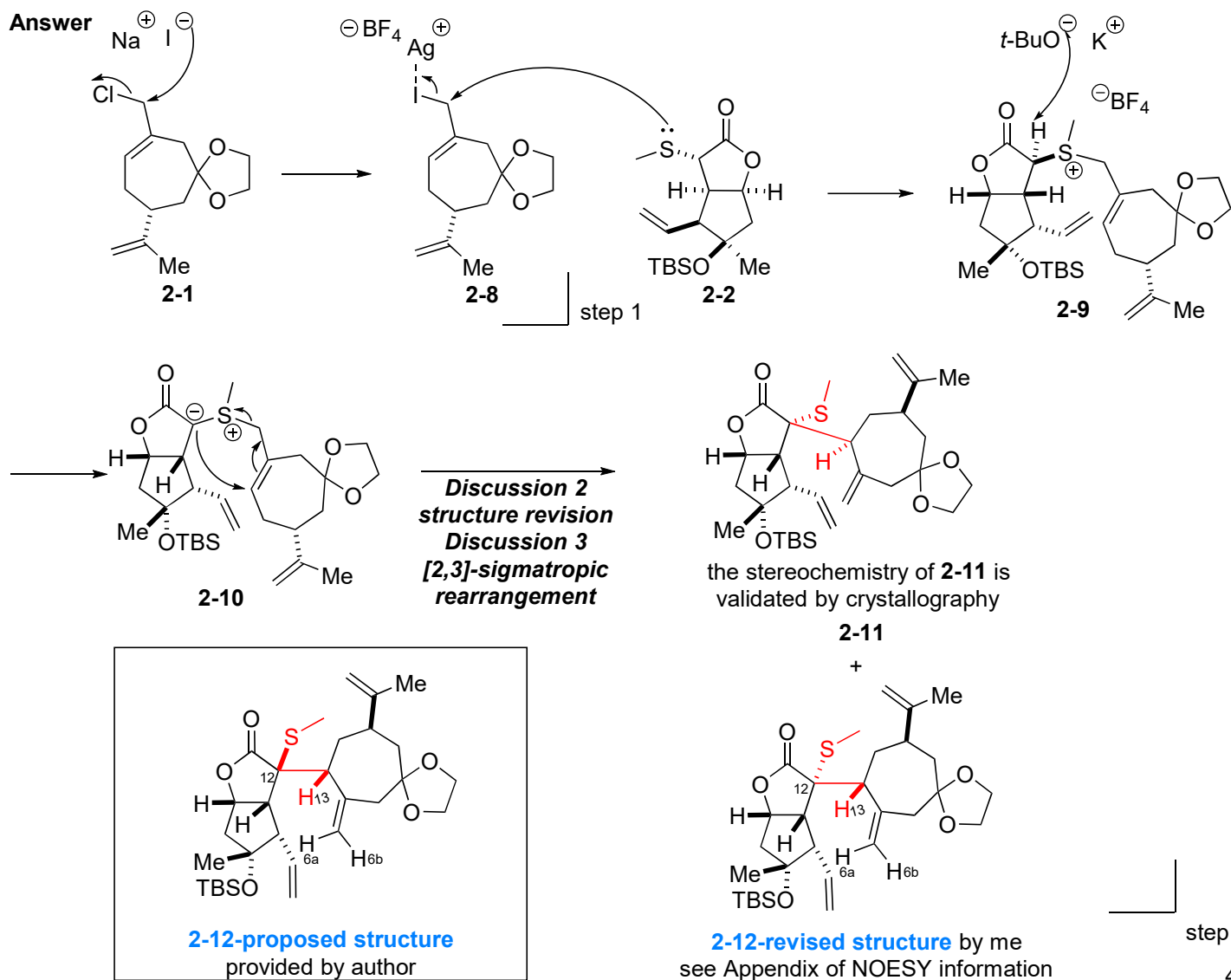
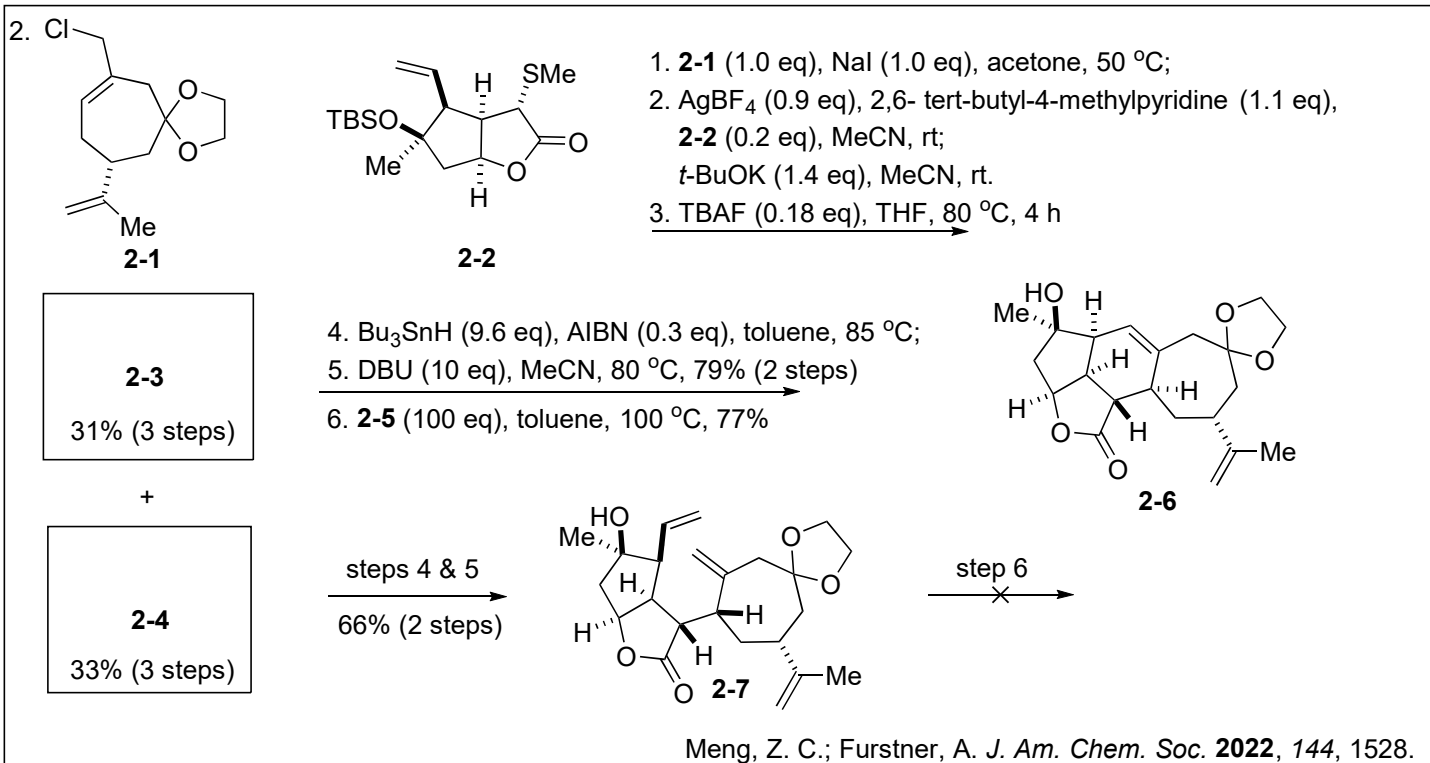


My opinion: substrates with opposite stereochemistry at C14 could provide same result, indicating no chelation.

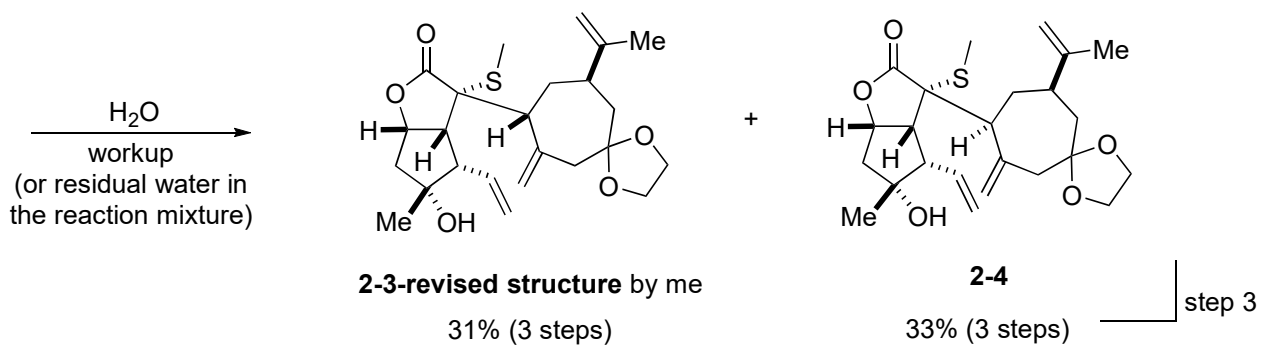
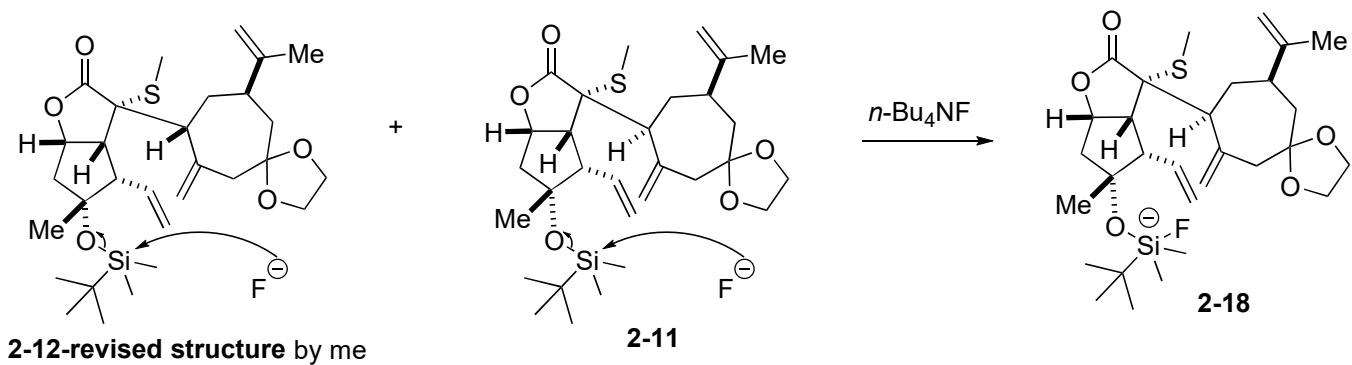
3. Stereoselectivity

The highly congested cyclohexenone is formed by coupling of lactone and cycloheptenone. Four transition states are described below.





The mixtures of **2-11** and **2-12** are subjected to next step.

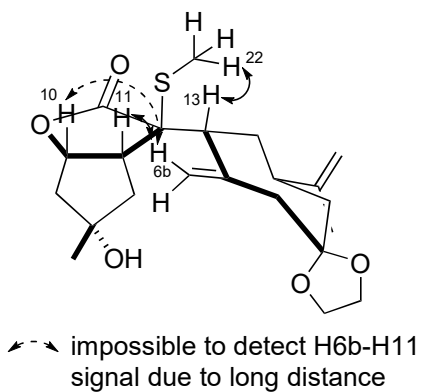


desilylation of isomer mixtures enable the **seperation** and yield calculation (3 steps).

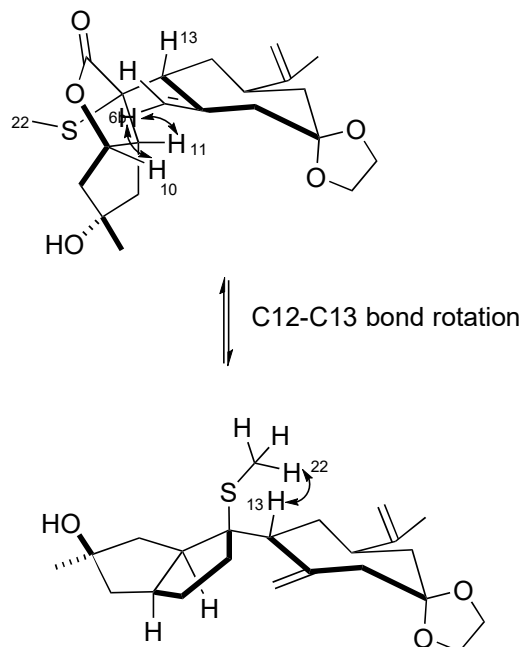
Discussion 2 structure revision

Key NOESY correlation signals in Supporting information: H6b-H10, H6b-H11, H13-H22

2-3-proposed structure provided by author



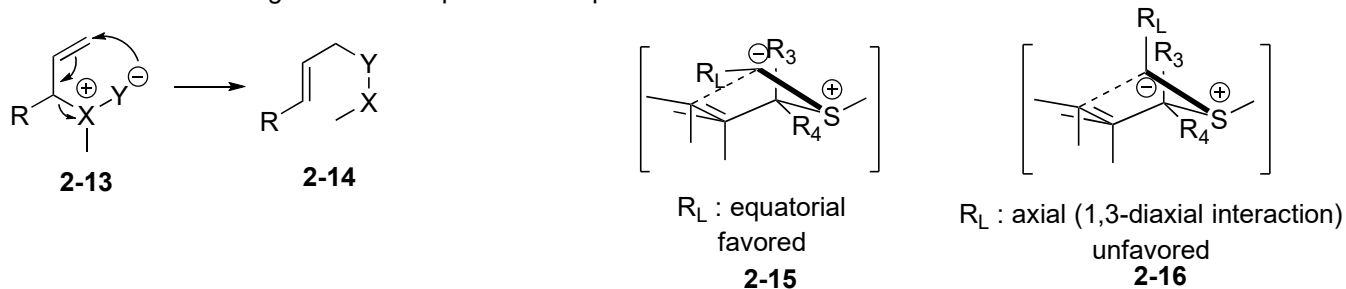
2-3-revised structure by me



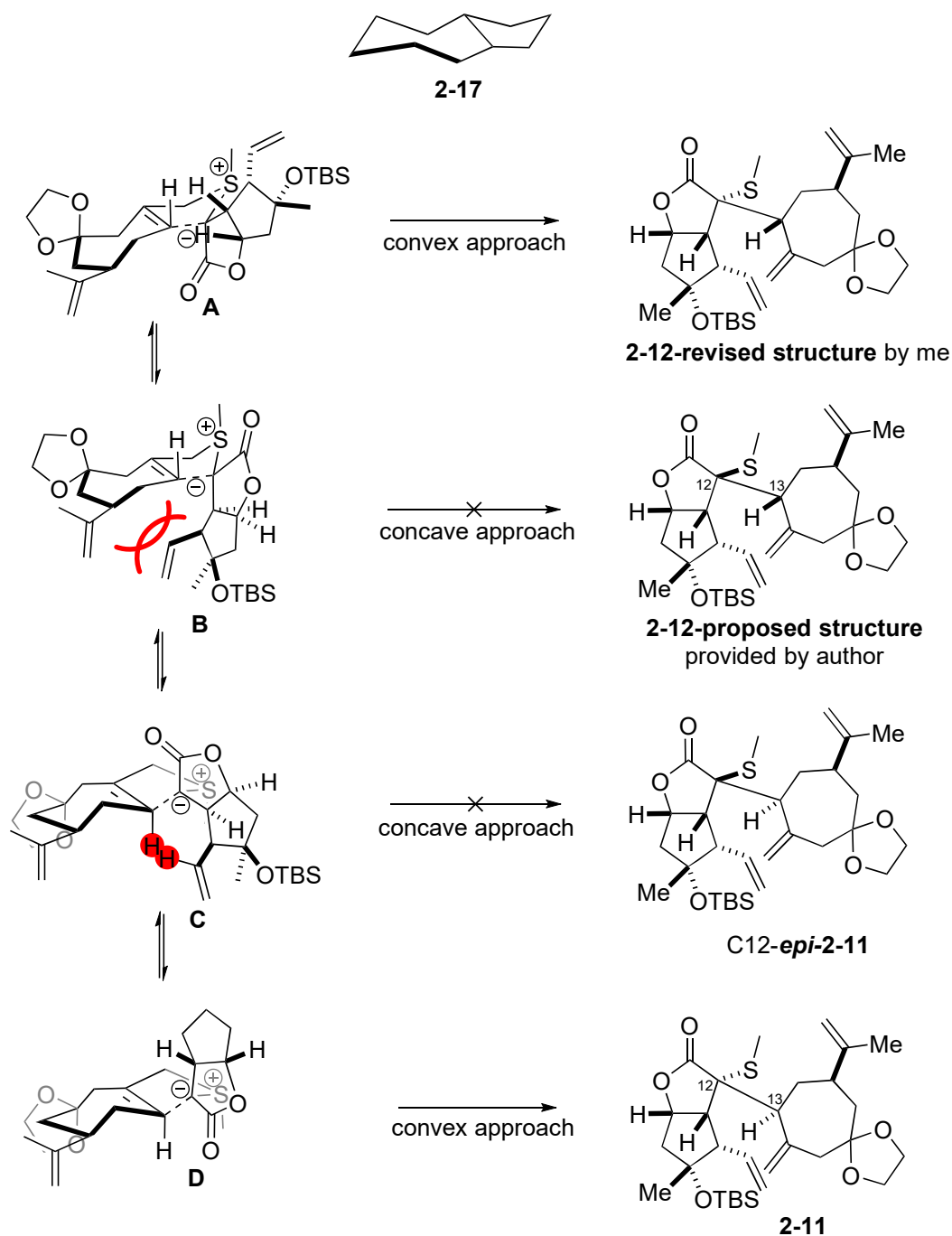
Discussion 3

[2,3]-sigmatropic rearrangement

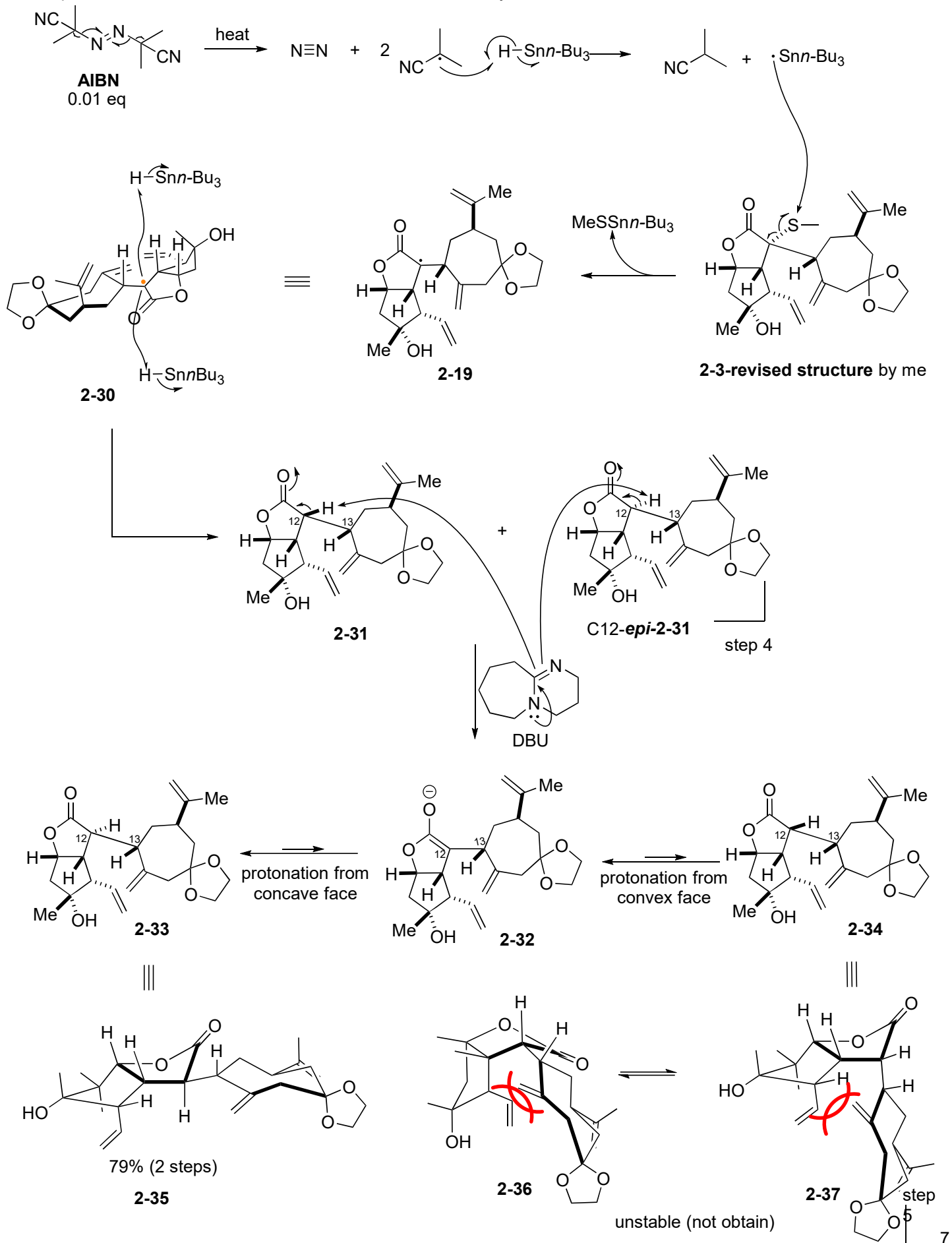
Allylic sulfonium ylide undergo [2,3]-sigmatropic rearrangement to produce sulfide in a concerted pattern. Generally, the stereochemistry of this rearrangement can be predicted in terms of a cyclic five-membered envelope-like transition state in which large substituent prefers an equatorial orientation.

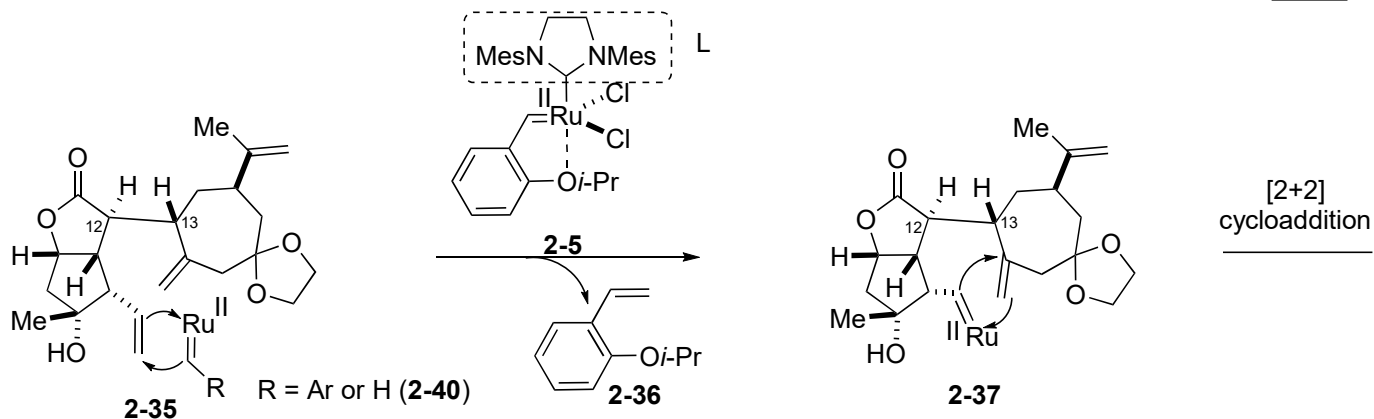


Considering the conformation of fused [7,5]-bicyclo ring system, only favored transition state 2-17 is discussed here.

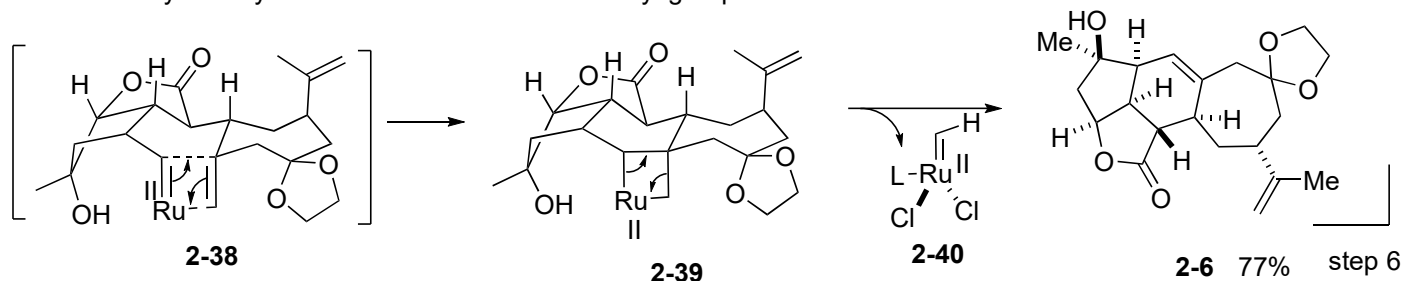


Subsequent transformation from isomer **2-3-revised structure by me** by me.



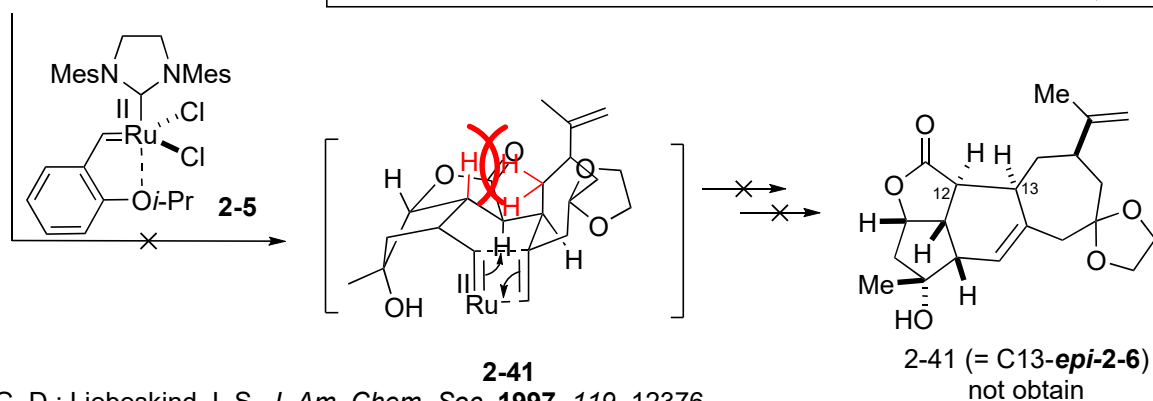
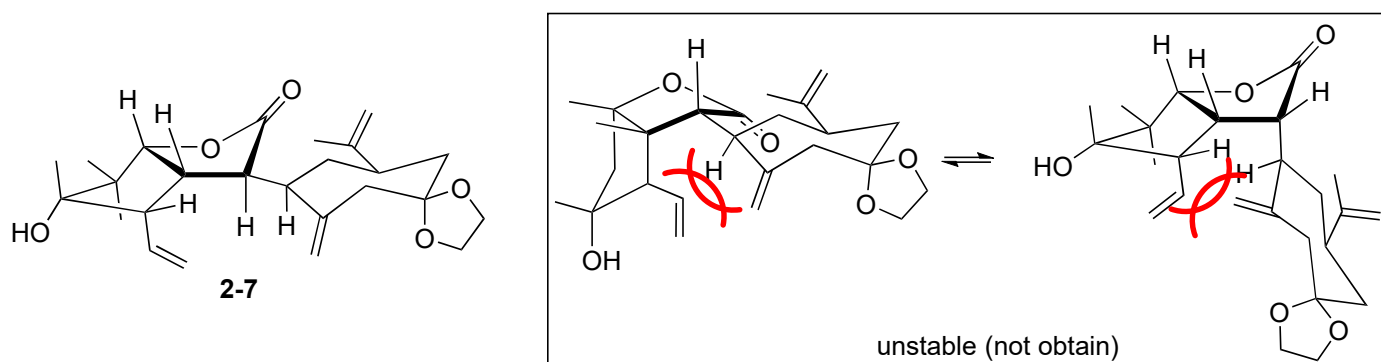
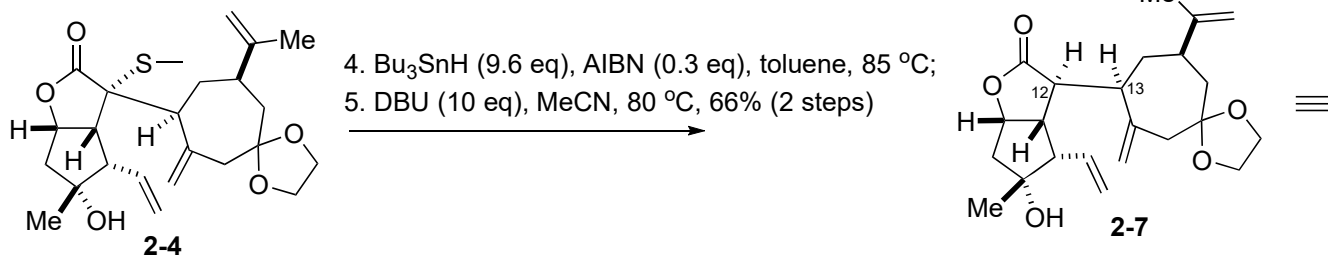


Ruthium catalyst firstly react with mono-substituted vinyl group.



It is too far for isopropene to participate the cyclization, the resulting cyclooctene with a bridged ring is highly strained.

Transformation from isomer 2-4.



1) Srogl, J.; Allred, G. D.; Liebeskind, L.S. *J. Am. Chem. Soc.* **1997**, *119*, 12376.

2) Hlavinka, M.L. Hagadorn, J.R. *Organometallics* **2007**, *26*, 4105.