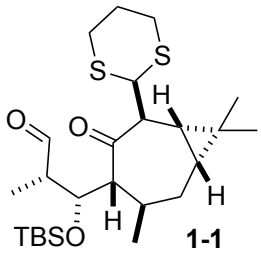
Problem session (2)

2022/04/30 Hiromu Kakizawa

Please provide the mechanism for each reaction.

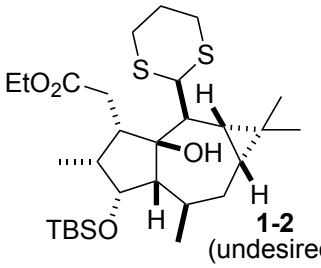
1.



1-1

1'. **A** (7.0 eq)*, NaH (7.0 eq)*
THF (0.038 M), 0 °C, 65%
2'. SmI_2 (2.5 eq), MeOH (4.1 eq)
THF (5.9 mM), rt, 78%

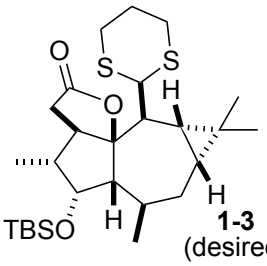
*pre-mixed before addition of **1-1**



1-2
(undesired)

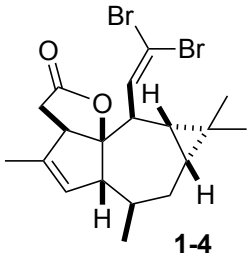
1. **B** (1.8 eq)*, $KN(TMS)_2$ (1.5 eq)*
18-crown-6 (5.0 eq)*
THF (0.064 M), − 78 °C, 78%
2. SmI_2 (2.4 eq), MeOH (4.0 eq)
THF (0.018 M), rt, 89%

*pre-mixed before addition of **1-1**



1-3
(desired)

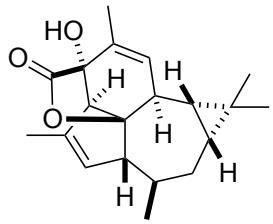
4 steps



1-4

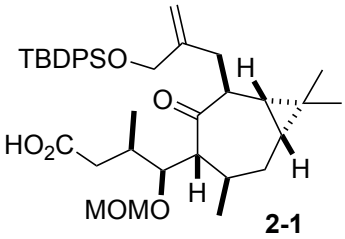
3. MeLi (6.0 eq)*, CuI (3.0 eq)*, Et_2O (0.036 M), 0 °C
then I_2 (6.0 eq), − 78 °C to rt, 74%
4. $KN(TMS)_2$ (1.25 eq), **C** (5.0 eq), THF (0.053 M), − 78 °C to rt
5. DMP (2.0 eq), CH_2Cl_2**, 0 °C to rt, 49% over 2 steps
6. *t*-BuLi (3.9 eq), Et_2O (9.8 mM), − 78 °C, 40%

*pre-mixed before addition of **1-4**
**Concentration was not mentioned in the paper.



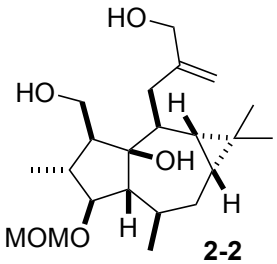
(+)-euphorikanin A

2.



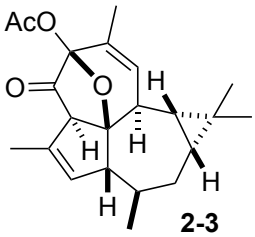
2-1

1. 4-PPY (3.0 eq), TsCl (2.0 eq)
Et_3N (4.0 eq), CH_2Cl_2 (0.093 M), 40 °C
then $LiAlH_4$ (2.0 eq), THF (0.14 M), 30 °C
2. *n*-Bu_4NF (2.0 eq), THF (0.12 M)
35 °C, 85% over 2 steps



2-2

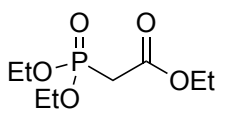
13 steps



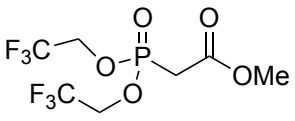
2-3

3. KOH (5.0 eq), MeOH (0.019 M)
rt, 91%

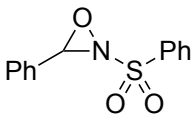
(+)-euphorikanin A



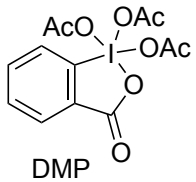
A



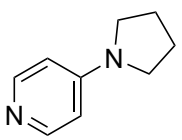
B



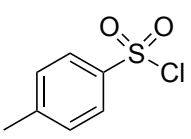
C



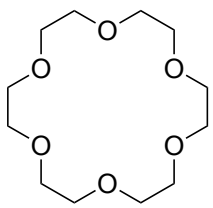
DMP



4-PPY



TsCl



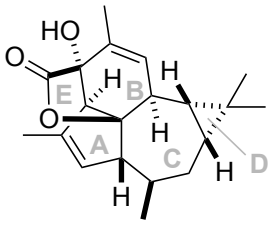
18-crown-6

Problem session (2) -answer-

2022/04/30 Hiromu Kakizawa

Topic: Total synthesis of (+)-euphorikanin A

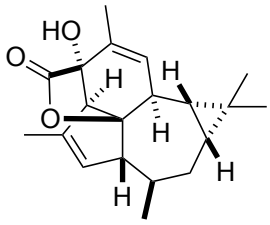
1. Introduction



(+)-euphorikanin A

- a diterpenoid isolated from the roots of *Euphorbia kansui* in 2016 by Zhang[1]
- exhibits cytotoxicity against human tumor cell (NCI-446 and HeLa)
- 5/6/7/3-fused tetracyclic skelton and lactone bridge, contiguous eight stereocenters
- total synthesis: Carreira (2021)[2] and Jia (2022)[3]

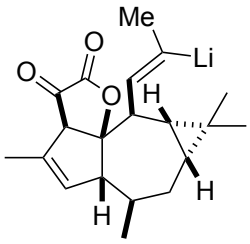
Carreira's total synthesis (problem 1): 19 steps, 0.12%



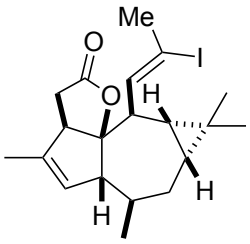
(+)-euphorikanin A

nucleophilic addition of vinyl lithium

construction of lactone-fused B-ring

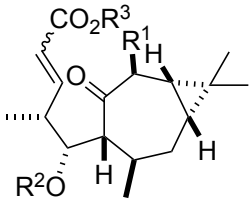


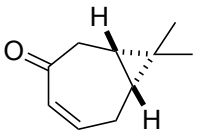
α-oxidation

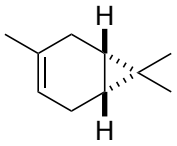


radical cyclization

simultaneous construction of A-ring and lactone

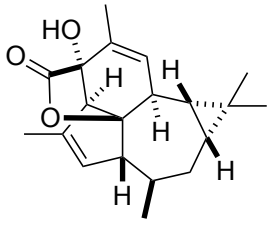






(+)-3-carene

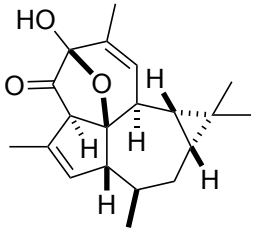
Jia's total synthesis (problem 2): 29 steps, 4%

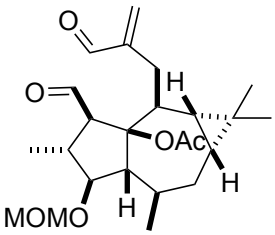


(+)-euphorikanin A

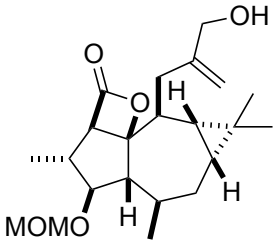
benzilic acid type rearrangement

construction of B-ring and lactone



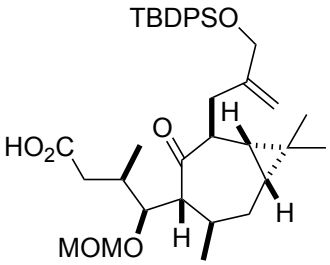


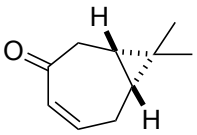
reduction

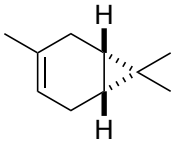


intramolecular aldol reaction

stereoselective construction of A-ring

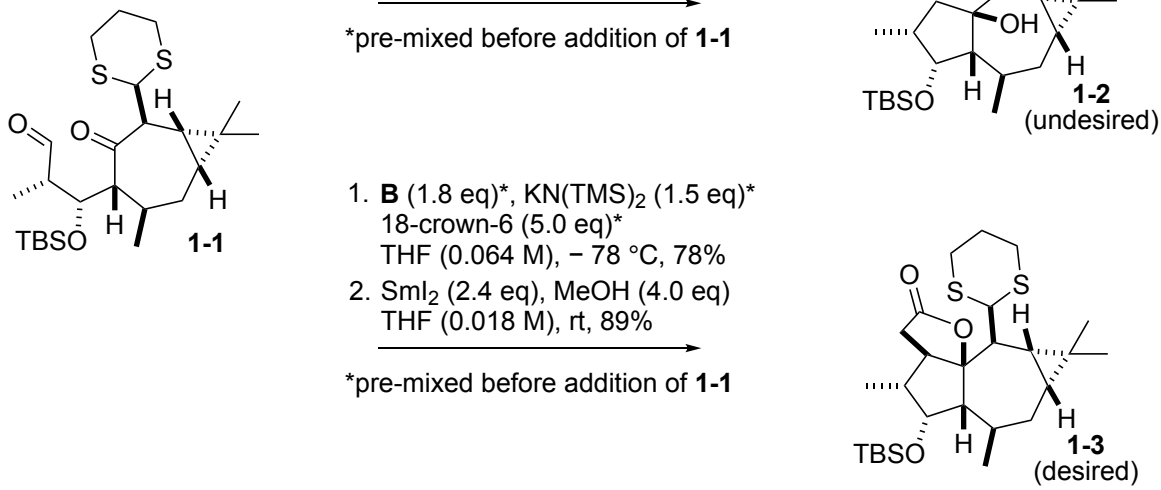






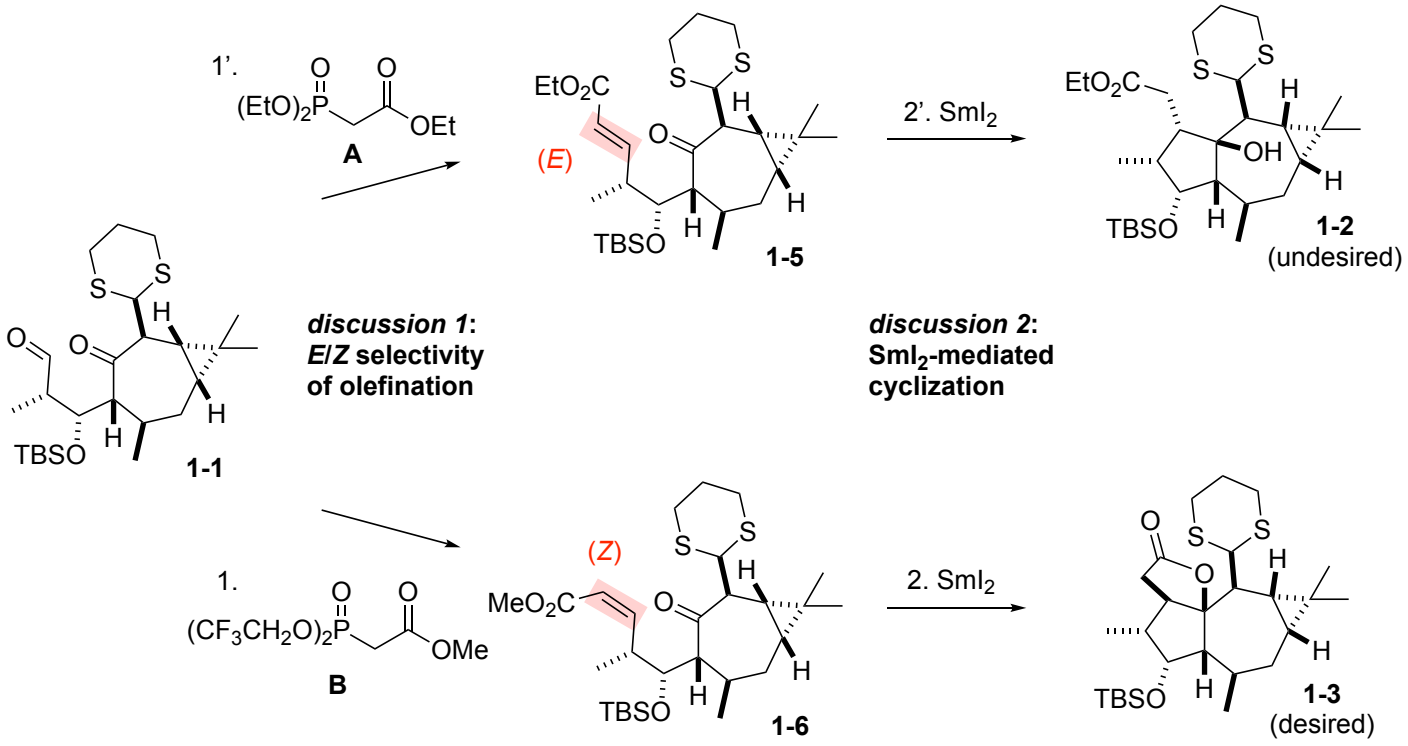
2. Answer for problem 1

2-1. Steps 1 and 2: simultaneous formation of 5-membered A-ring and lactone



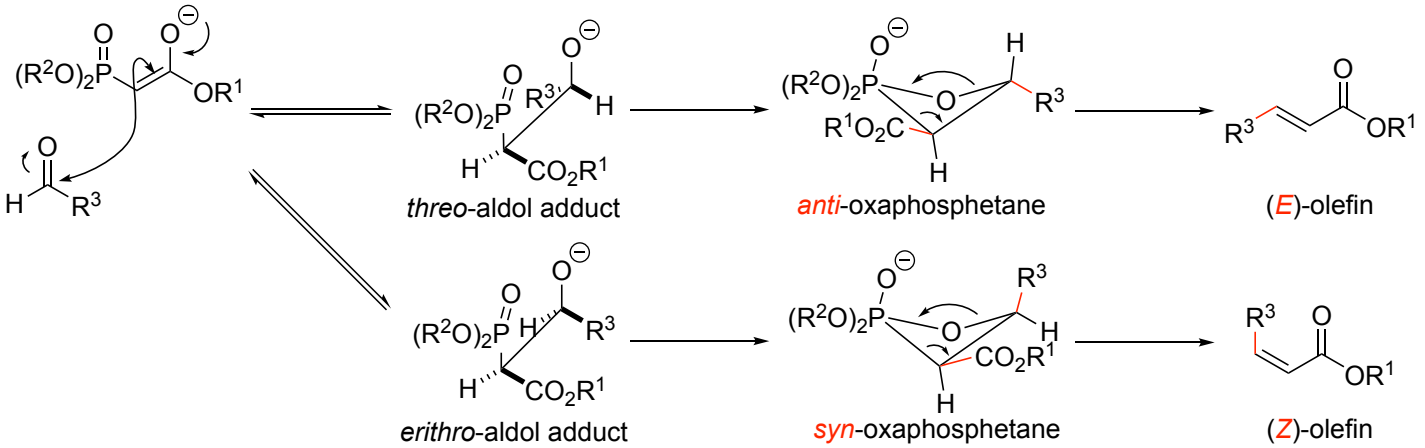
M. J. Classen; M. N. A. Böcker; R. Roth; W. M. Amberg; E. M. Carreira. J. Am. Chem. Soc. **2021**, *143*, 8261.

2-1-1. Overview of the reactions

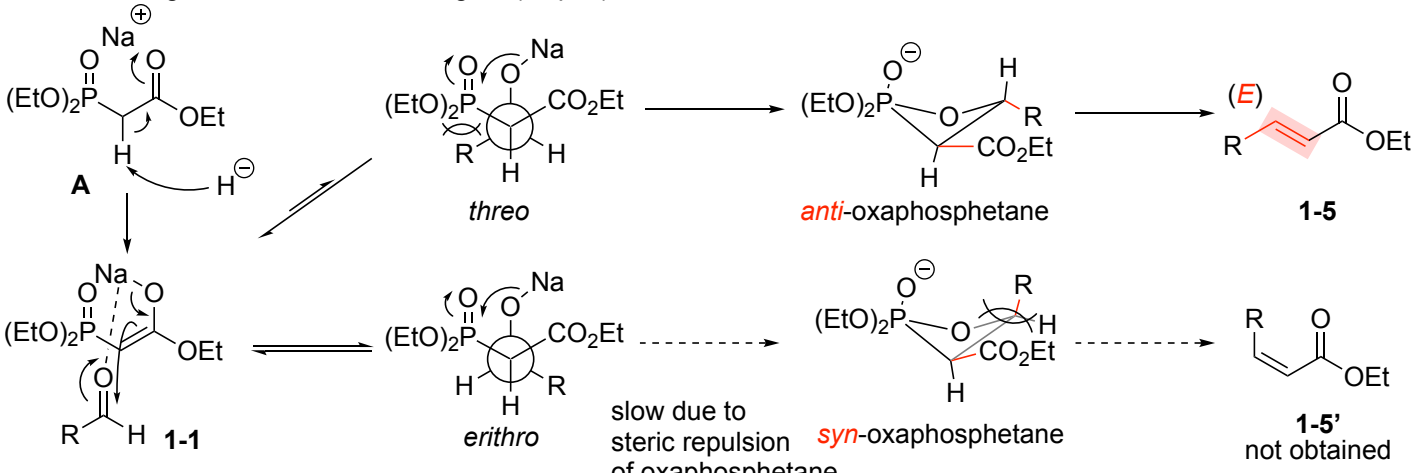


2-1-2. **Discussion 1**: *E*/*Z* selectivity of Horner-Wadsworth-Emmons-type olefination

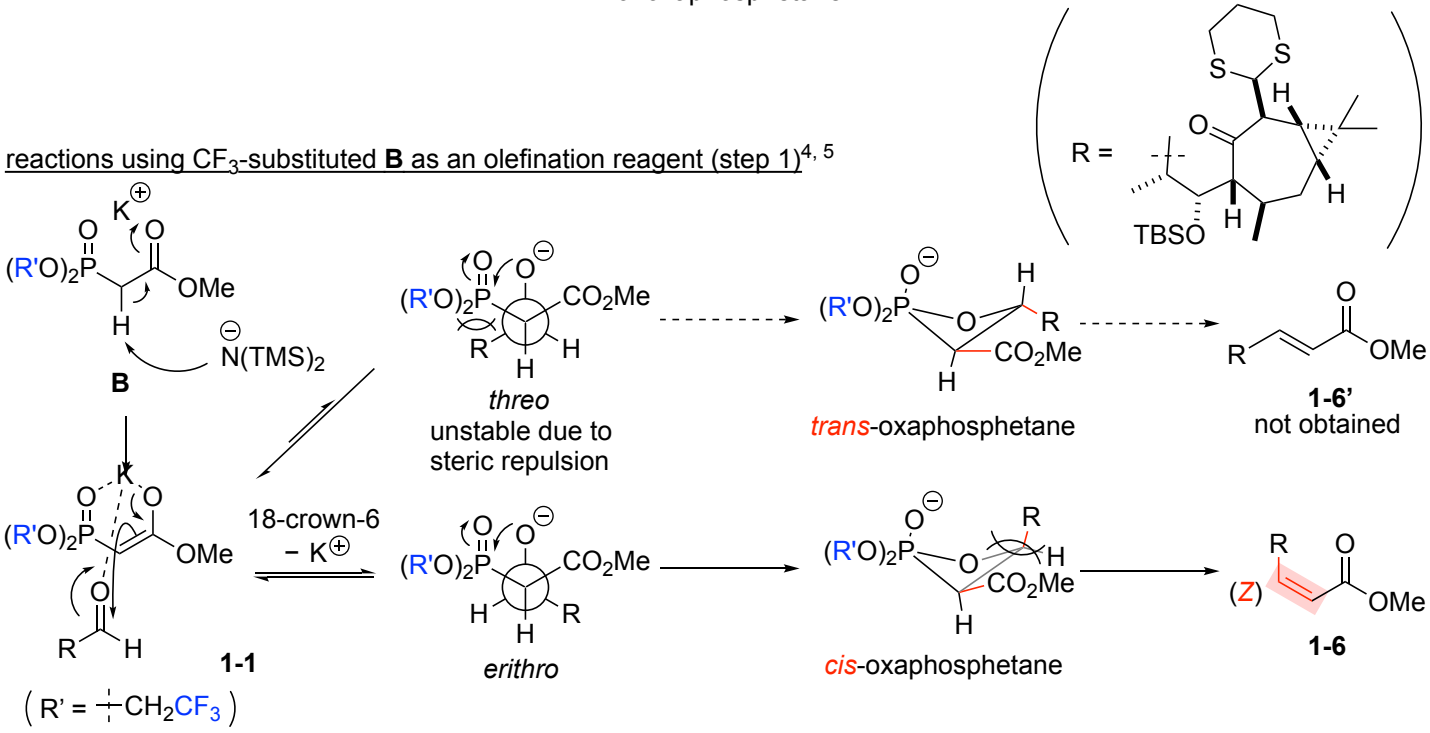
The stereochemistry of resultant olefin is determined by that of the aldol adduct and the oxaphosphetane[4]:



reactions using **A** as an olefination reagent (step 1')



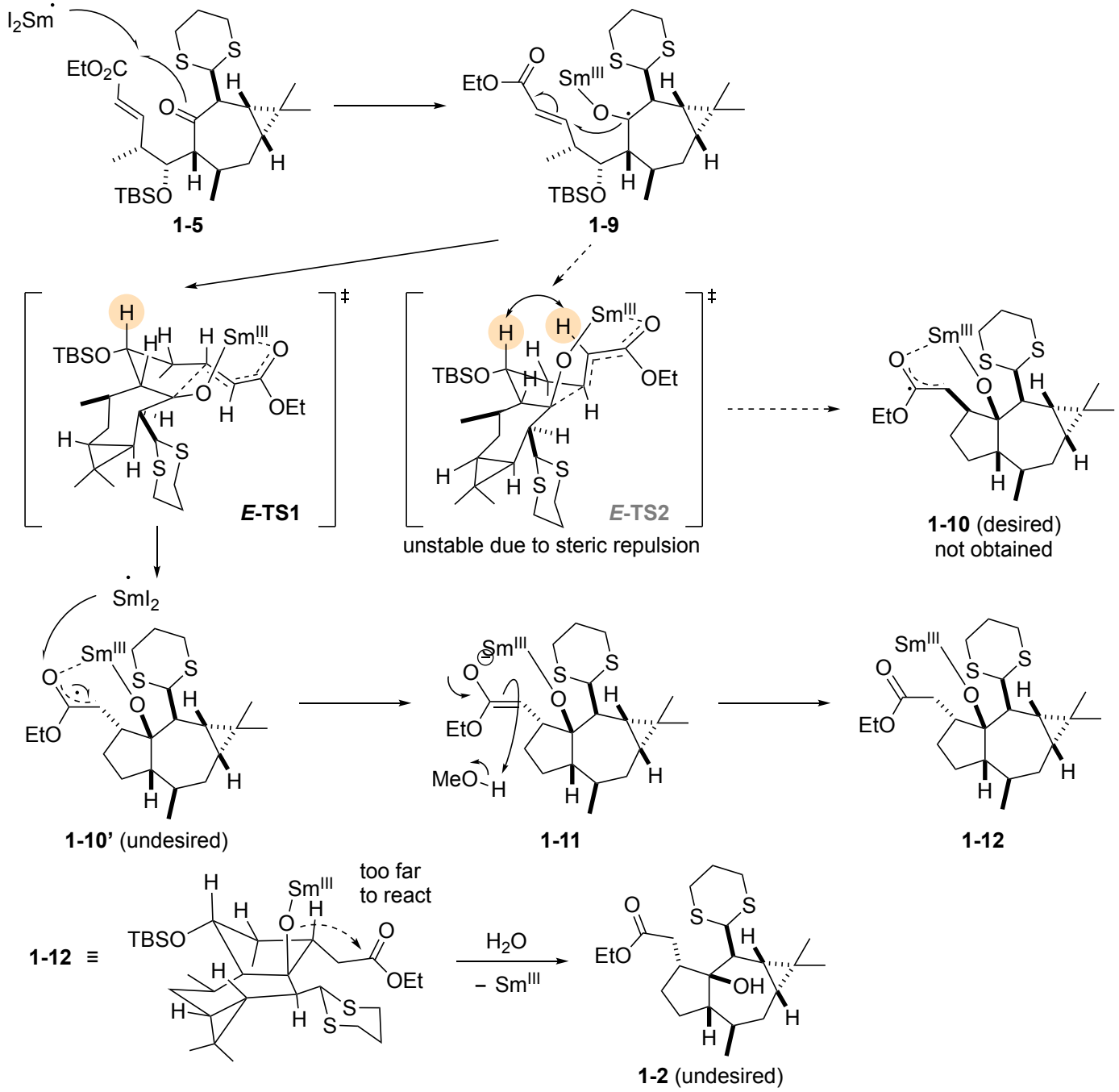
reactions using CF_3-substituted **B** as an olefination reagent (step 1)[4, 5]



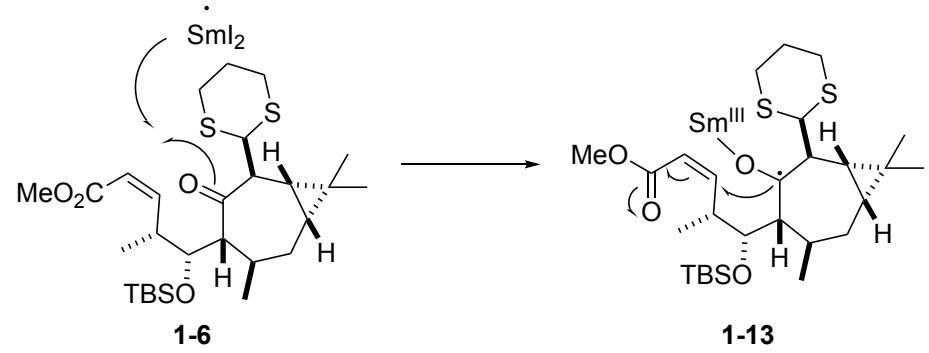
Formation of oxaphosphetane is fast enough due to the electrophilicity of phosphate (affected by inductive effect of CF_3).

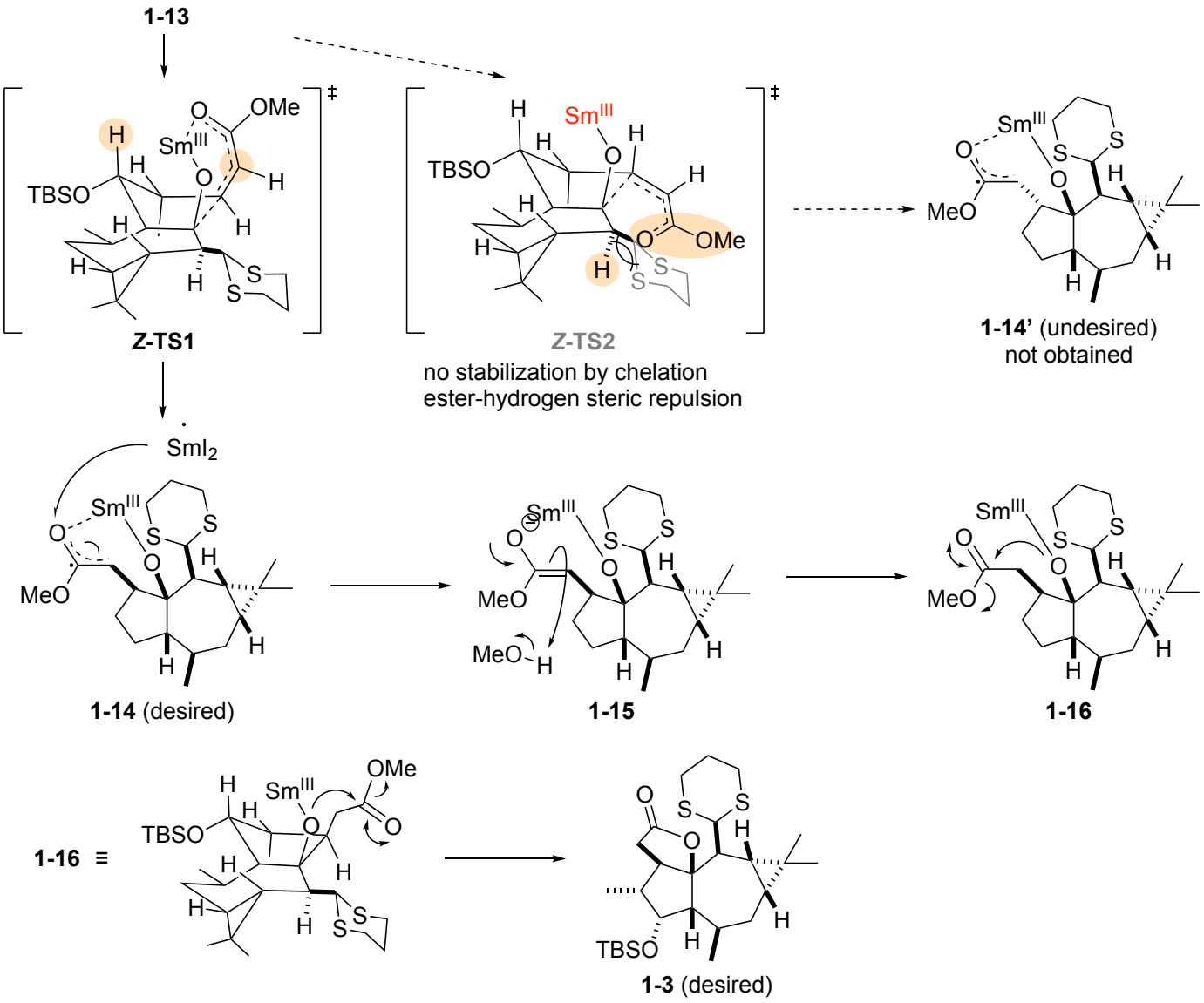
2-1-3. **Discussion 2**: SmI_2-mediated cyclization

for (*E*)-enone **1-5** (step 2'):

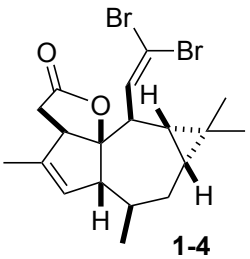


for (*Z*)-enone **1-6** (step 2):





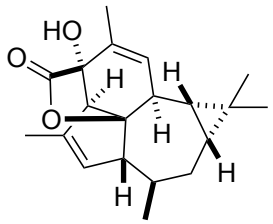
2-2. Steps 3 to 6: construction of B-ring via nucleophilic attack of vinyllithium



1-4
(4 steps from **1-3**)

3. MeLi (6.0 eq)*, CuI (3.0 eq)*, Et_2O (0.036 M), 0 °C
   then I_2 (6.0 eq), − 78 °C to rt, 74%
4. $KN(TMS)_2$ (1.25 eq), **C** (5.0 eq), THF (0.053 M), − 78 °C to rt
5. DMP (2.0 eq), CH_2Cl_2**, 0 °C to rt, 49% over 2 steps
6. *t*-BuLi (3.9 eq), Et_2O (9.8 mM), − 78 °C, 40%

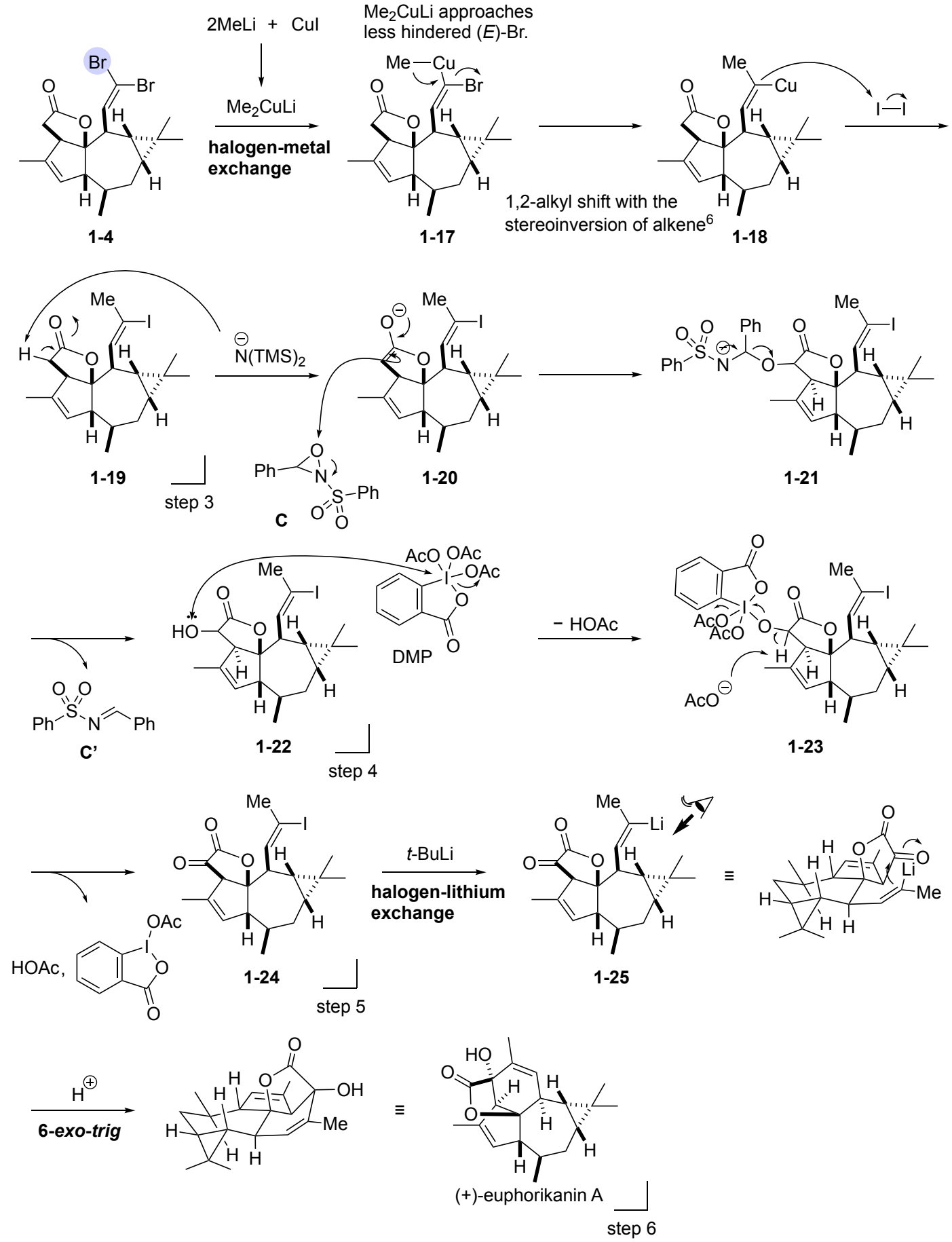
*pre-mixed before addition of **1-4**
**Concentration was not mentioned in the paper.



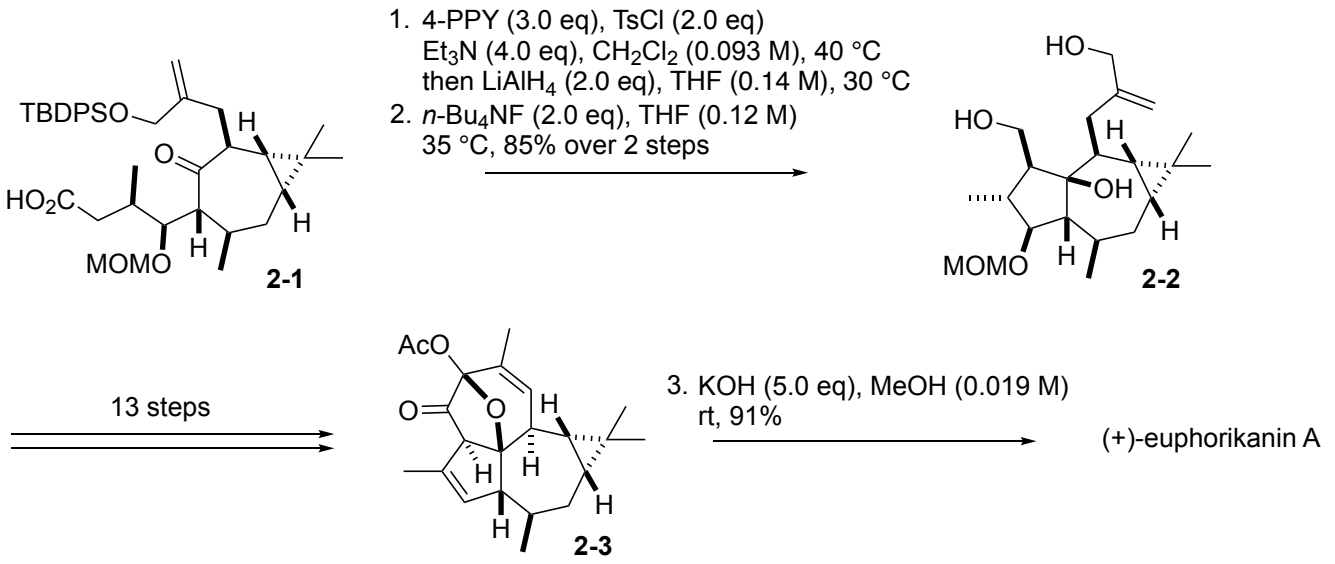
(+)-euphorikanin A

M. J. Classen; M. N. A. Böcker; R. Roth; W. M. Amberg; E. M. Carreira. J. Am. Chem. Soc. **2021**, *143*, 8261.

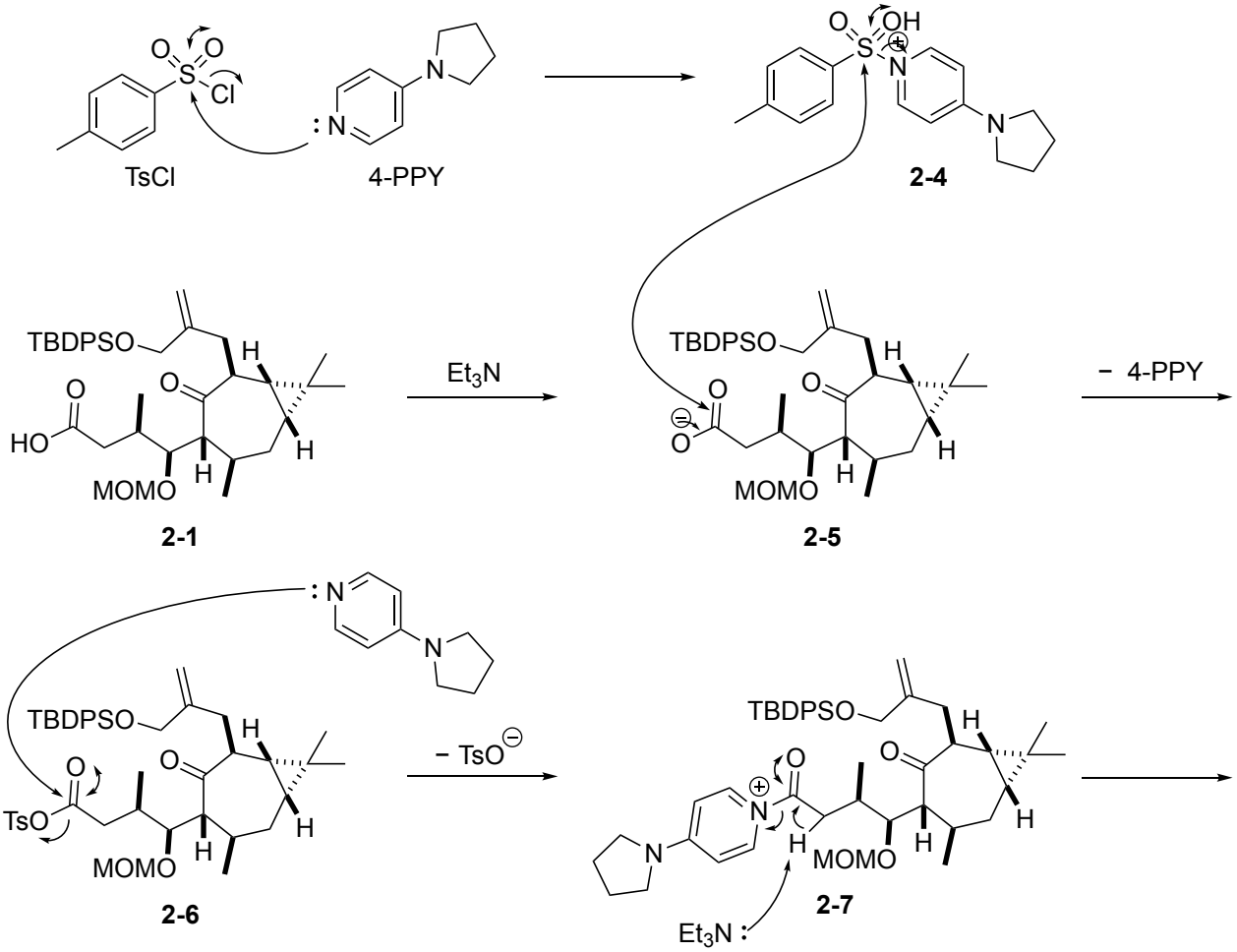
Reaction mechanisms:

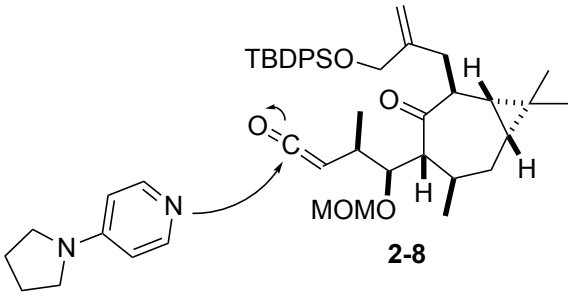


3. Answer for problem 2: total synthesis of (+)-euphorikanin A by Jia's group

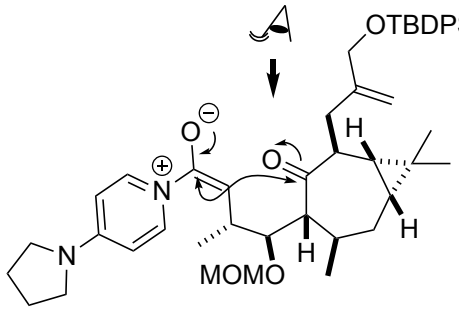


Z. Chen; K. Zhao; Y. Jia. *Angew. Chem. Int. Ed.* **2022**, *51*, e202200576





2-8



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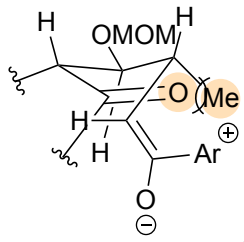
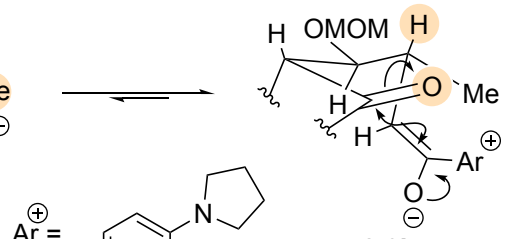
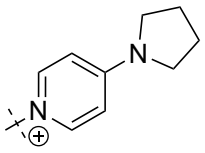


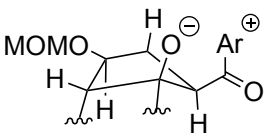
2-9a
unfavored



2-9b
favored

Ar⊕ =





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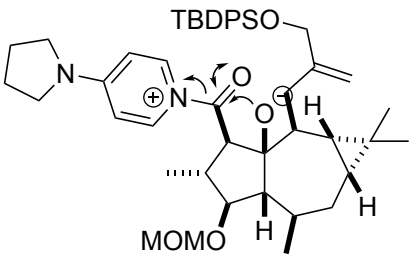
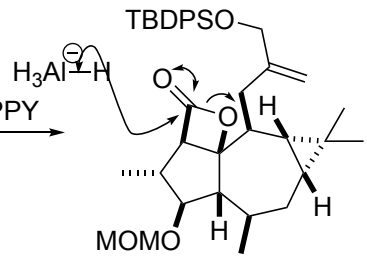
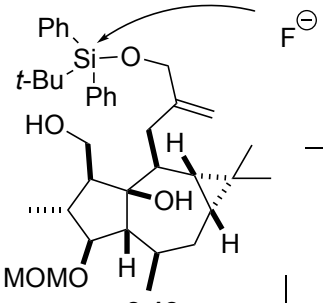


– 4-PPY



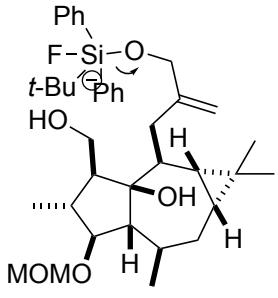
2-11

H⊕



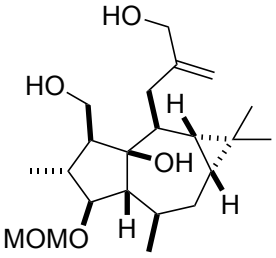
2-12

step 1



2-13

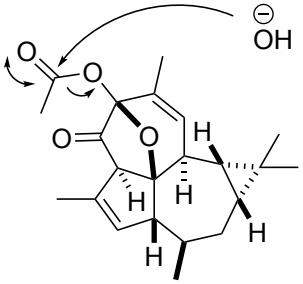
H⊕



2-2

step 2

13 steps



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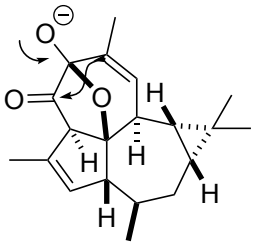
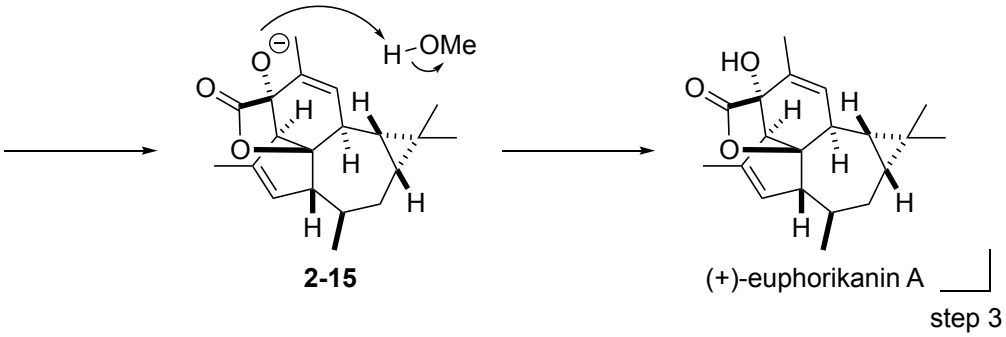
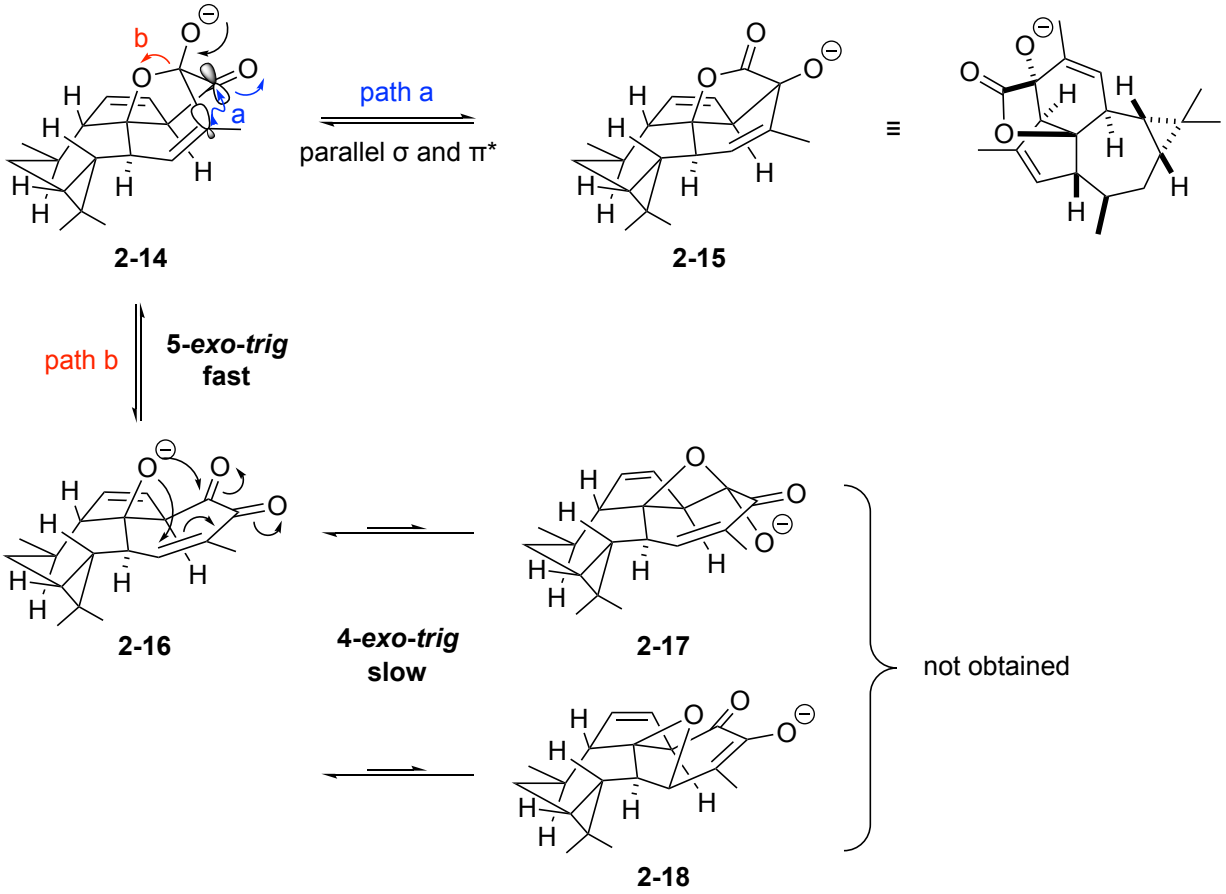


2-14

***discussion 3*:**
mechanism and stereochemistry of lactone formation



3-2. **Discussion 3**: mechanism and stereoselectivity of lactone formation



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