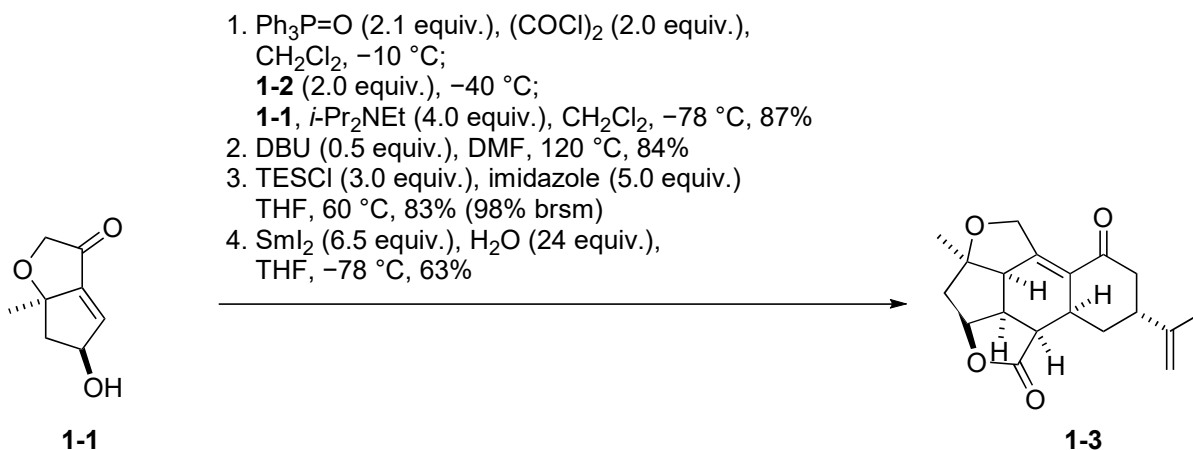
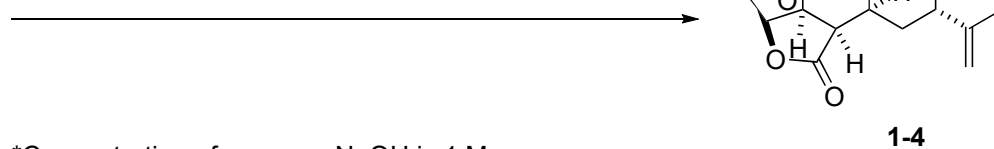


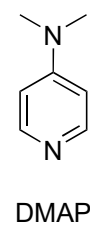
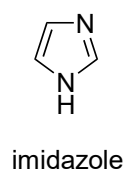
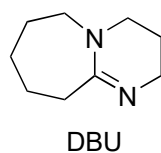
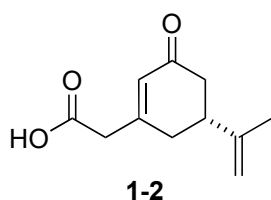
Problem Please provide following reaction mechanisms.



5. DBU (4.8 equiv.), O_2 atmosphere,
 benzene, $70\text{ }^\circ\text{C}$, 67%
 6. Ac_2O (1.4 equiv.), Et_3N (2.0 equiv.), DMAP (0.10 equiv.),
 CH_2Cl_2 , $23\text{ }^\circ\text{C}$, 85%
 7. SmI_2 (3.0 equiv.), THF/aq. NaOH^* (8/1),
 $-78\text{ }^\circ\text{C}$, 45%



*Concentration of aqueous NaOH is 1 M.



Problem Session (5) -Answer-

2023/07/08 Yuma Komori

Topic: Total synthesis of (+)-ineleganolide

Introduction

Isolation

Formosan soft coral

Sinularia inelegans

(Duh, C. Y.; Wang, S. K.; Chia, M. C.; Chiang, M. Y. *Tetrahedron Lett.* **1999**, *40*, 6033.)

Structural features

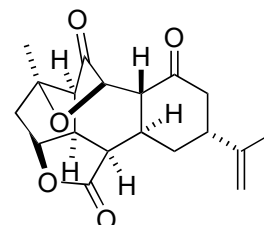
- 5 rings containing β -keto tetrahydrofuran
- 9 stereocenters

Bioactivity

Cytotoxicity against P-380 leukemia cell lines ($ED_{50} = 3.82 \mu\text{g/mL}$)

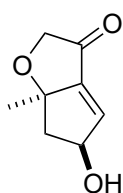
Total syntheses

- Wood's group (2022, also see 230107_PS_Shintaro_Fukaya)
- Stoltz's group (2023→**problem**)



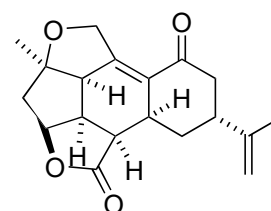
(+)-ineleganolide

Problem



1-1

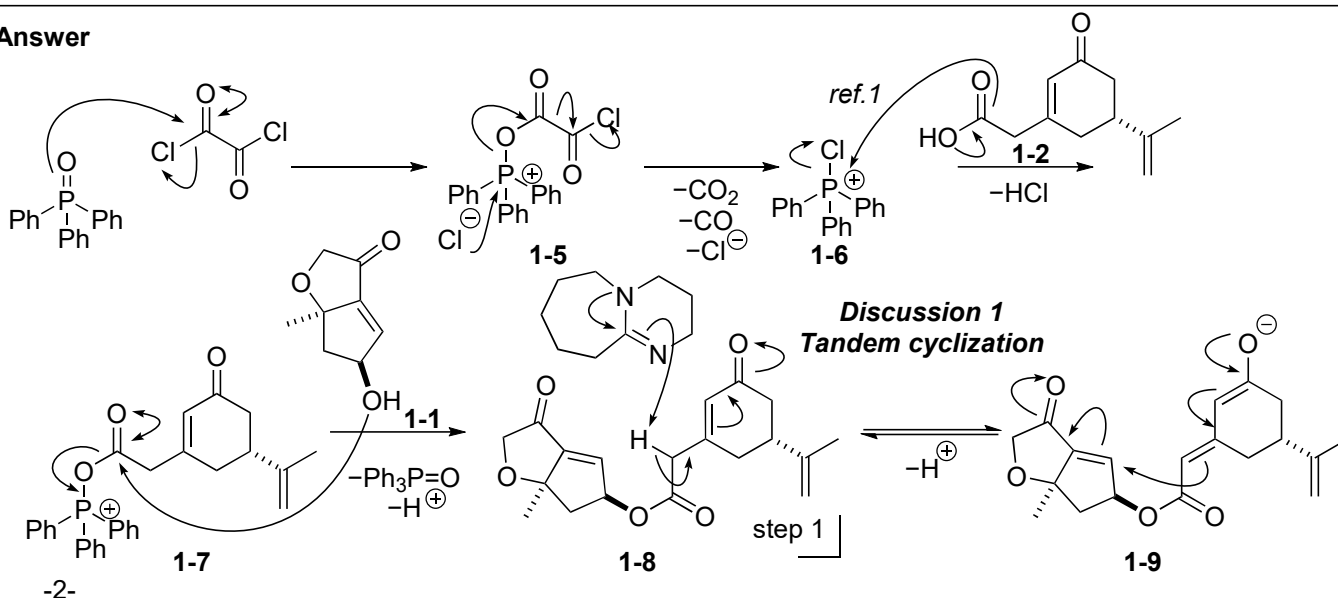
1. $\text{Ph}_3\text{P}=\text{O}$ (2.1 equiv.), $(\text{COCl})_2$ (2.0 equiv.), CH_2Cl_2 , -10°C ; **1-2** (2.0 equiv.), -40°C ; **1-1**, $i\text{-Pr}_2\text{NEt}$ (4.0 equiv.), CH_2Cl_2 , -78°C , 87%
2. DBU (0.5 equiv.), DMF, 120°C , 84%
3. TESCl (3.0 equiv.), imidazole (5.0 equiv.) THF, 60°C , 83% (98% brsm)
4. SmI_2 (6.5 equiv.), H_2O (24 equiv.), THF, -78°C , 63%

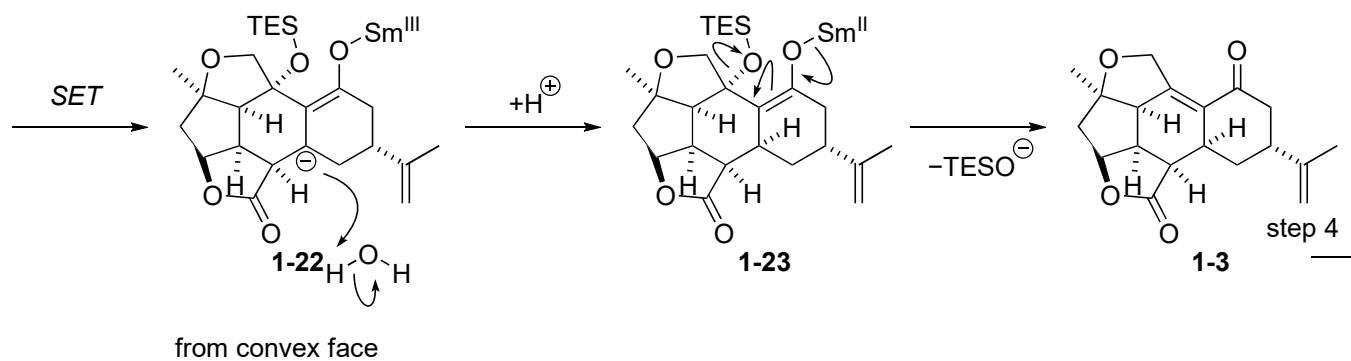
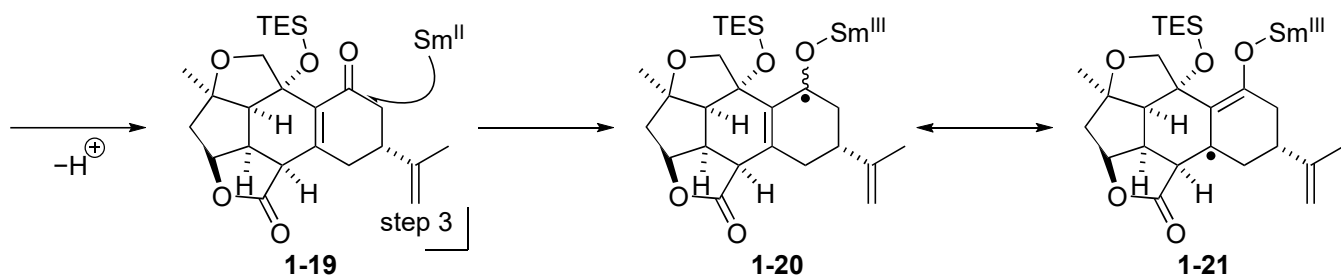
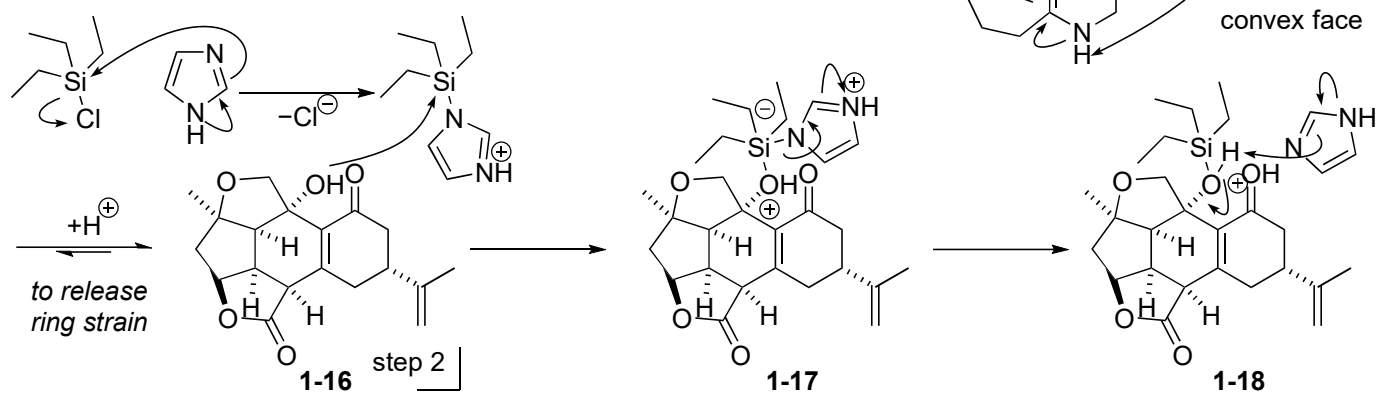
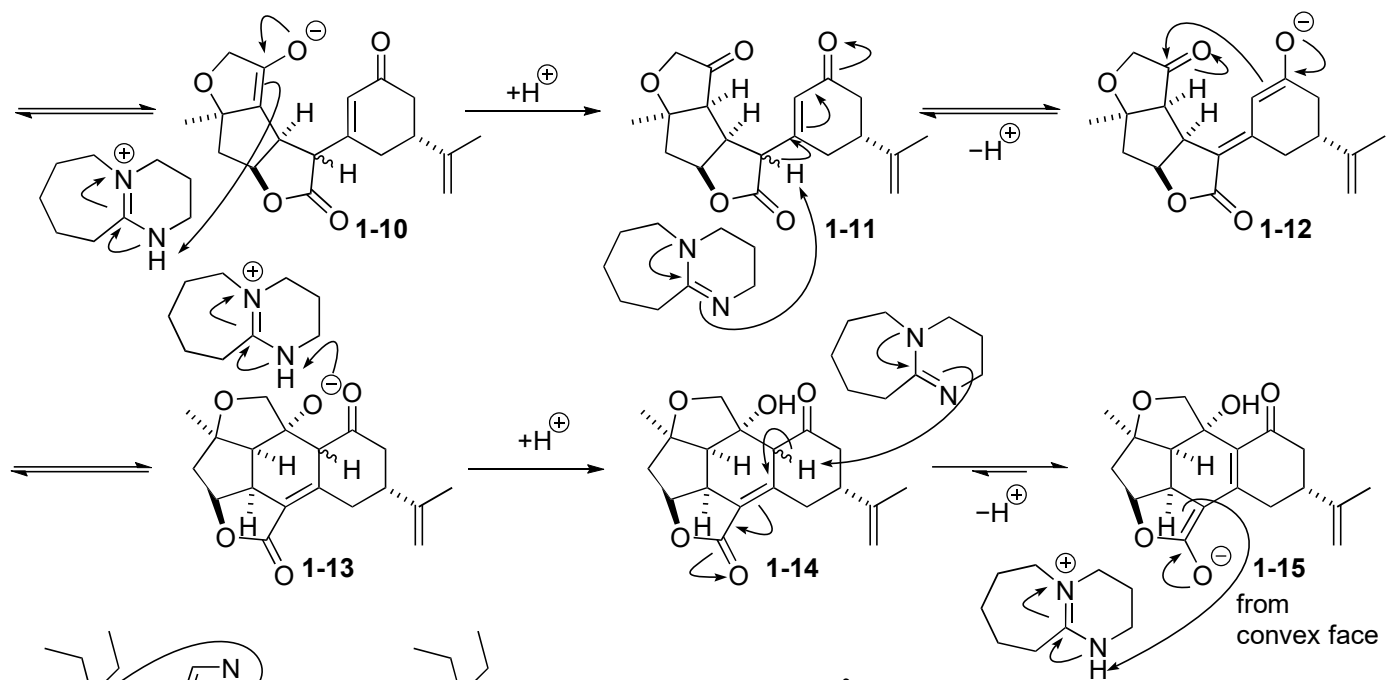


1-3

Gross, B. M.; Han, S.-J.; Virgil, S. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2023**, *145*, 7763.

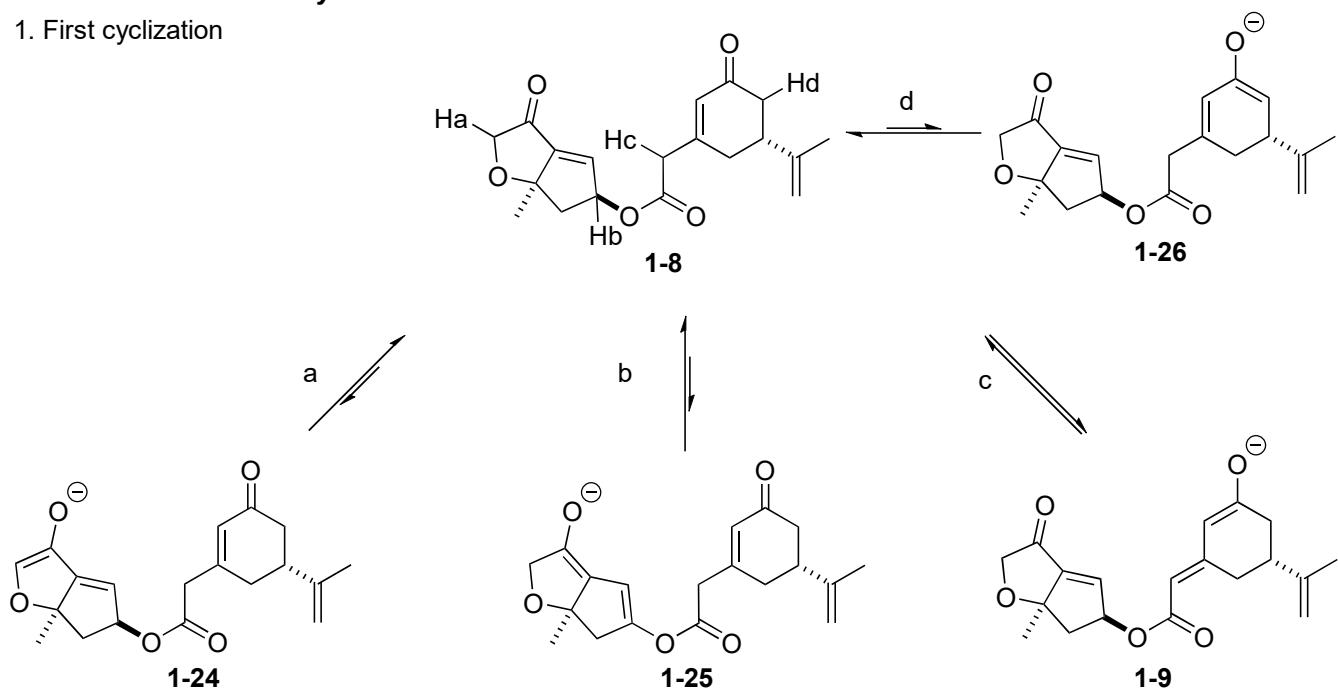
Answer



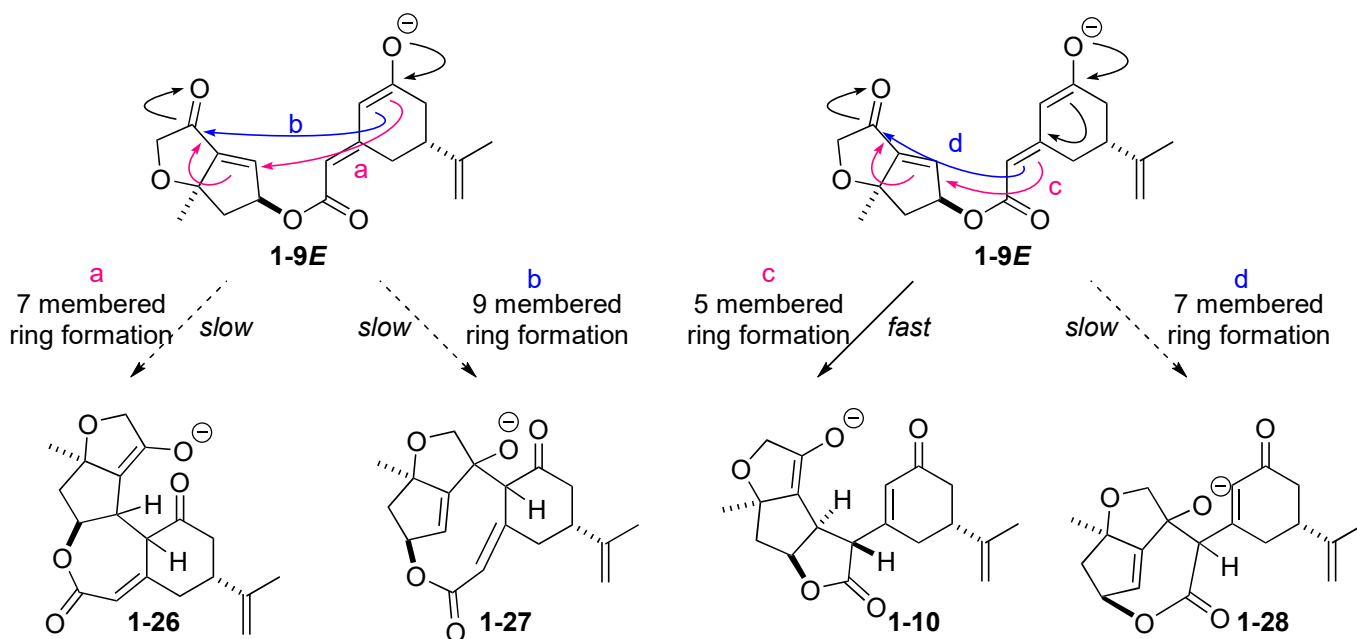
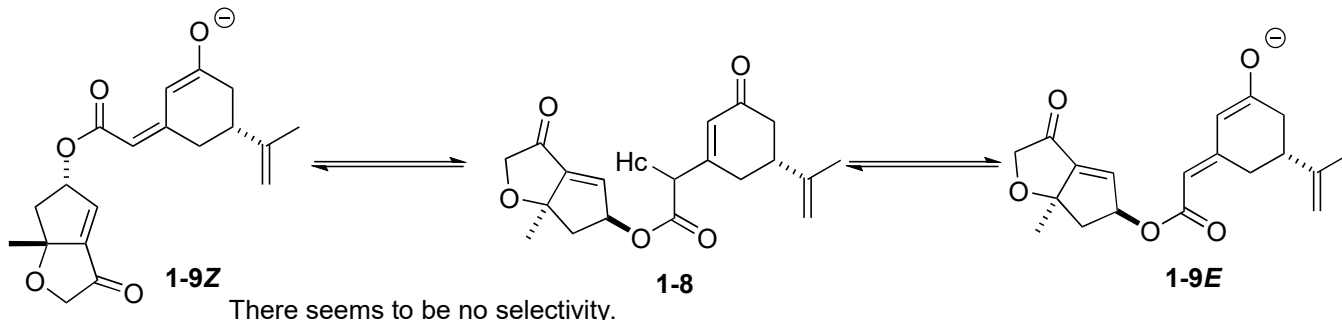
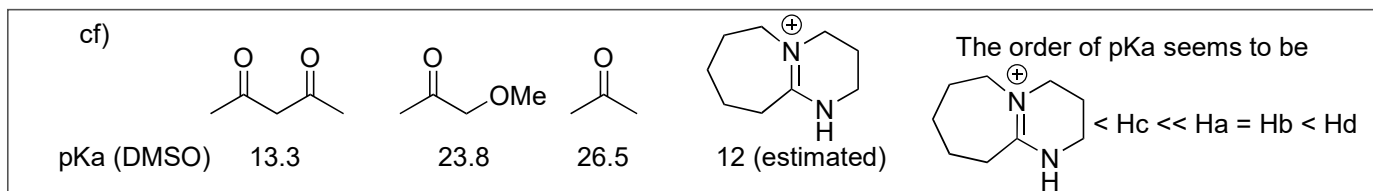


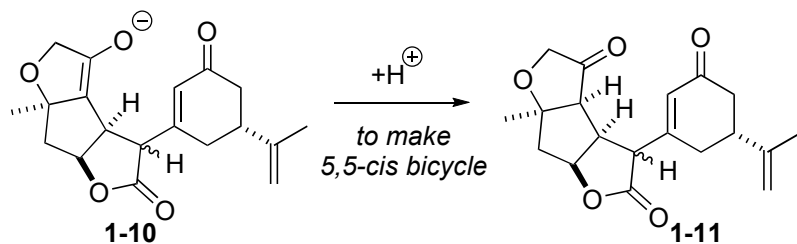
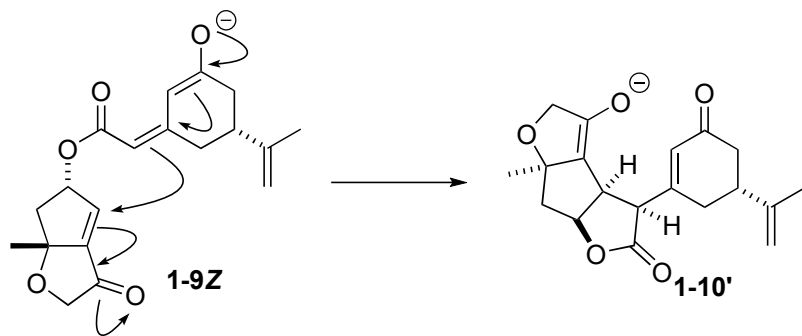
Discussion 1: Tandem cyclization

1. First cyclization

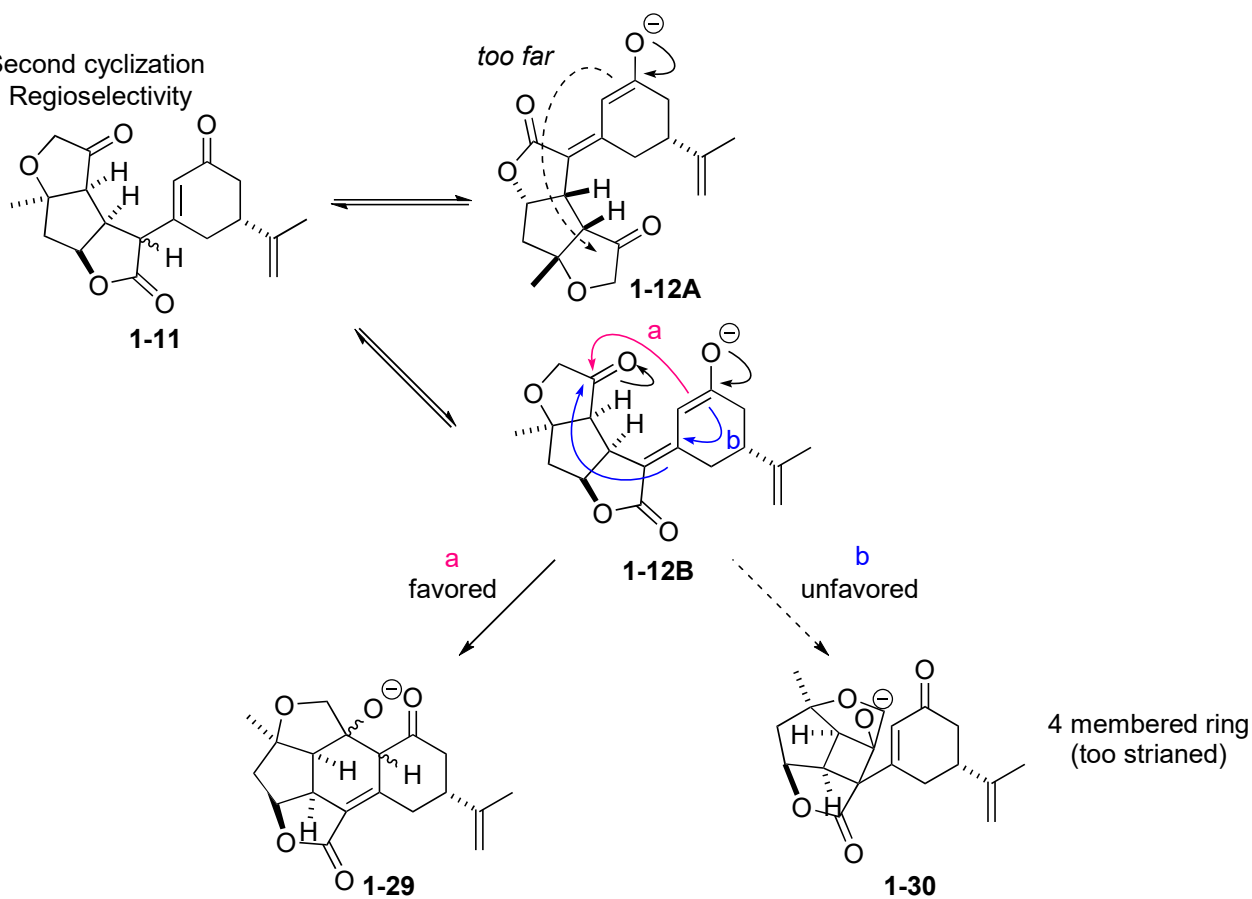


Path c seems to be most favorable.

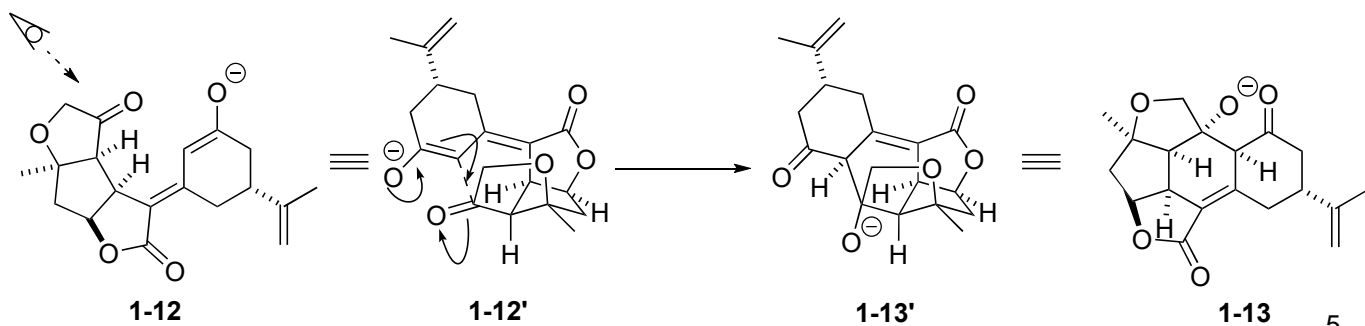




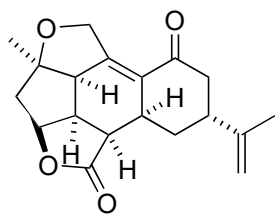
2. Second cyclization
2.1. Regioselectivity



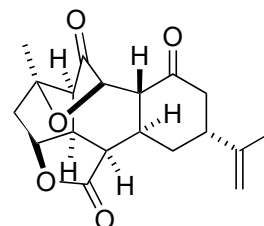
2.2. Stereoselectivity



5. DBU (4.8 equiv.), O₂ atmosphere, benzene, 70 °C, 67%
 6. Ac₂O (1.4 equiv.), Et₃N (2.0 equiv.), DMAP (0.10 equiv.), CH₂Cl₂, 23 °C, 85%
 7. SmI₂ (3.0 equiv.), THF/aq. NaOH (8/1), -78 °C, 45%

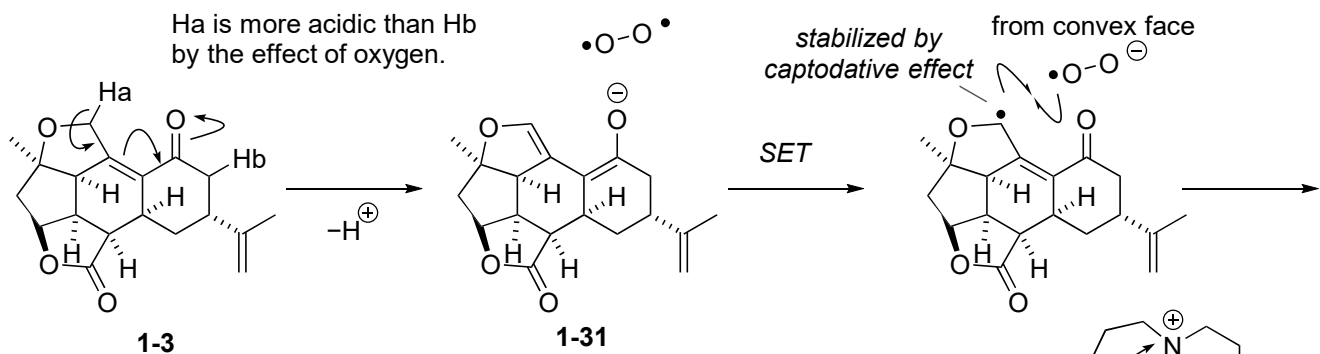


1-3



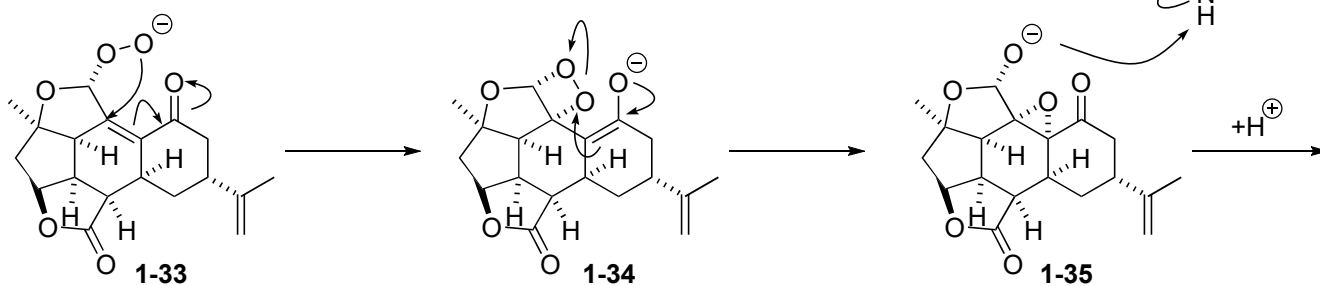
1-4

Ha is more acidic than Hb by the effect of oxygen.



1-3

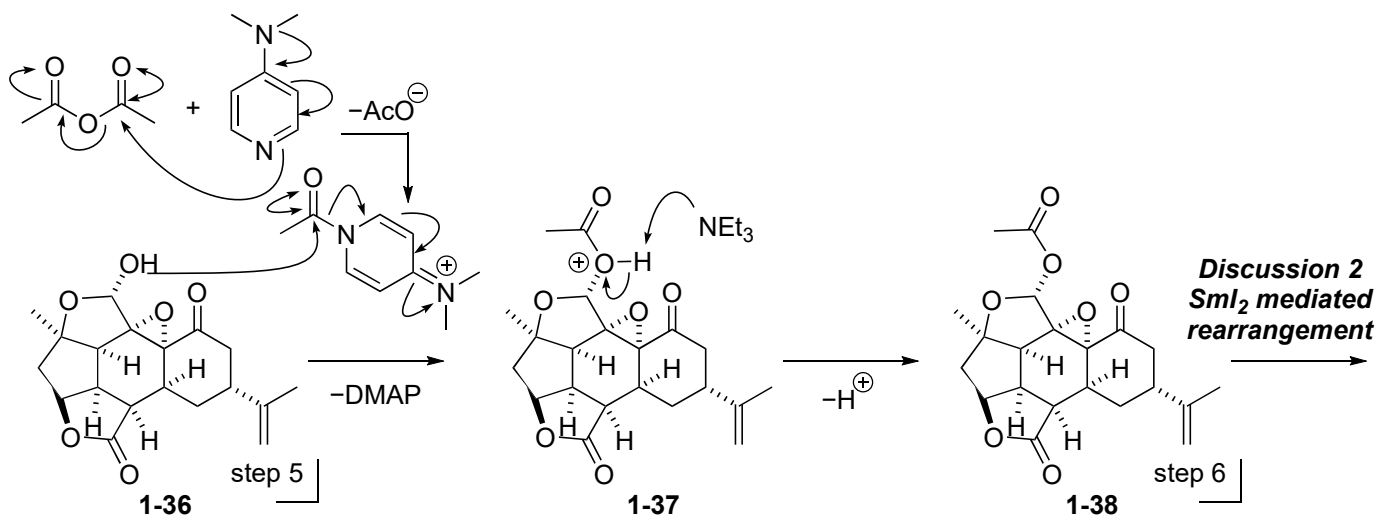
1-31



1-33

1-34

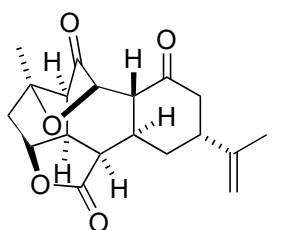
1-35



1-36

1-37

1-38

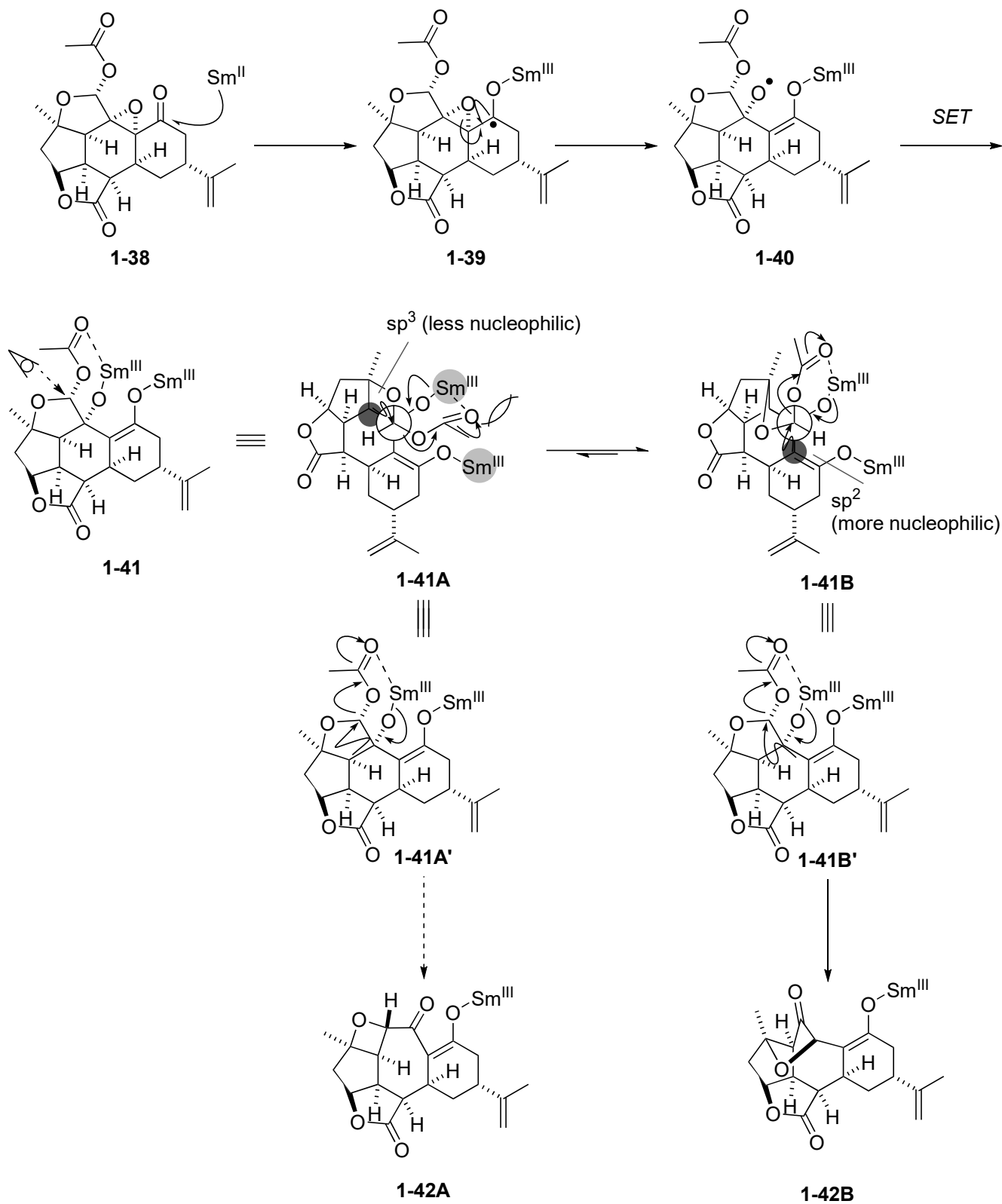


1-4

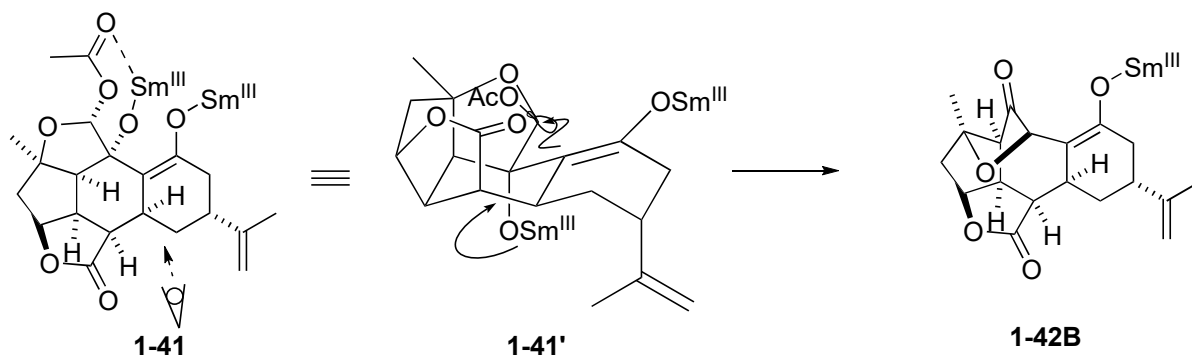
step 7

Discussion 2: SmI_2 mediated rearrangement

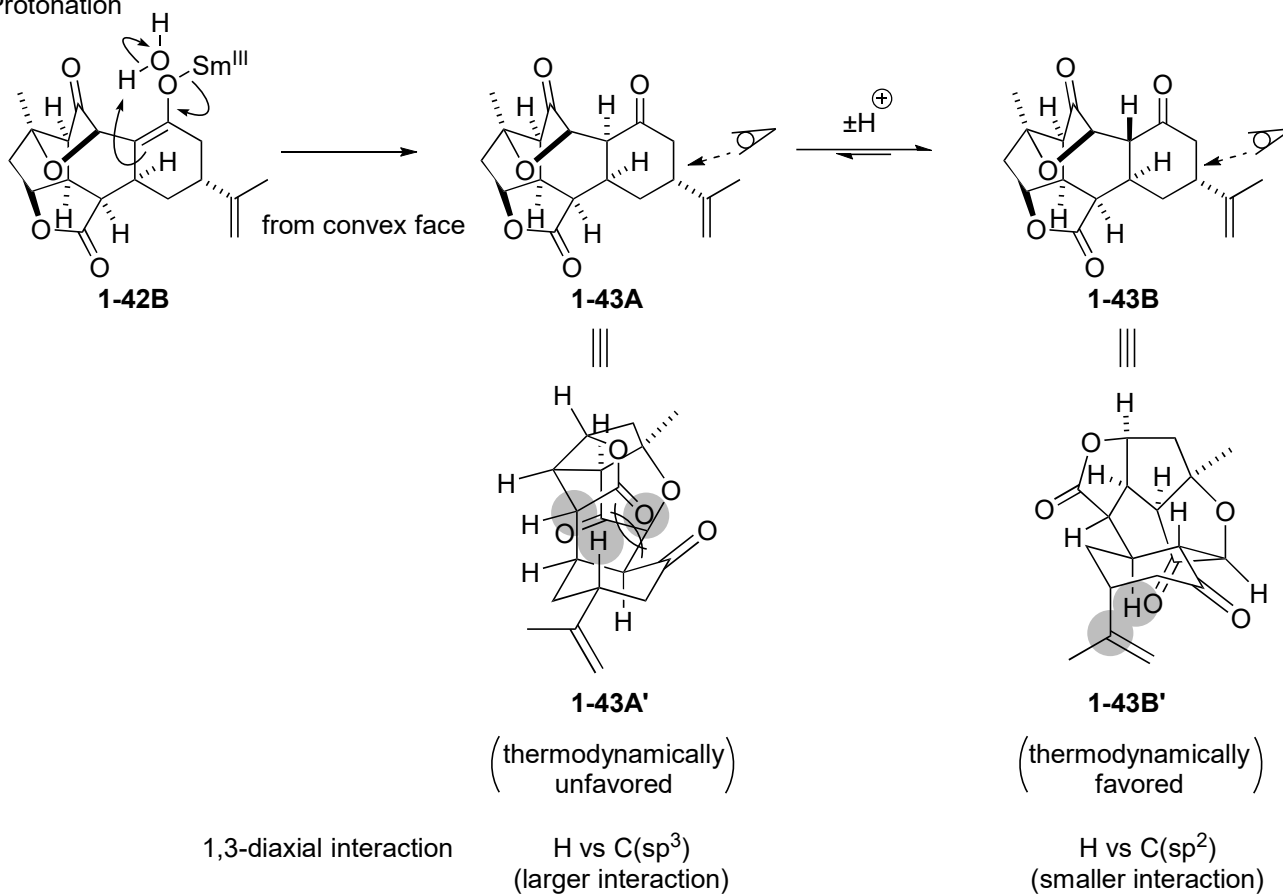
1. Rearrangement



Another view point of **1-41**



2. Protonation



References

- 1) Jia, M.; Jiang, L.; Niu, F.; Zhang, Y.; Sun, X. *R. Soc. Open Sci.* **2018**, *5*, 171988.