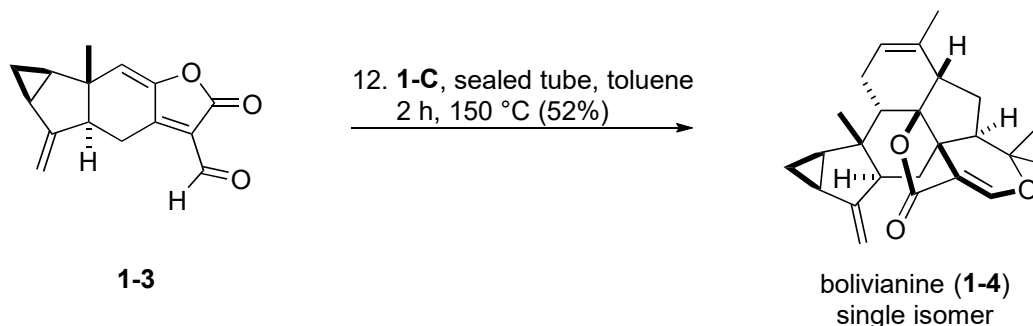
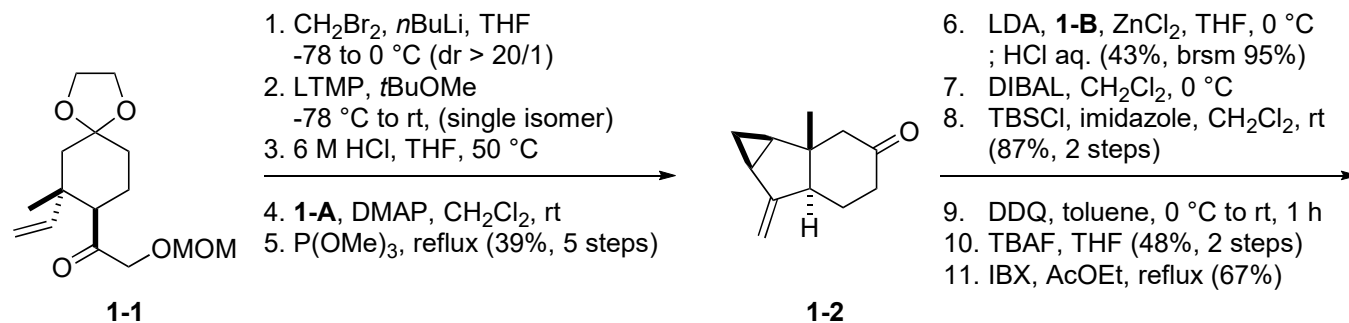


Problem Session (1)

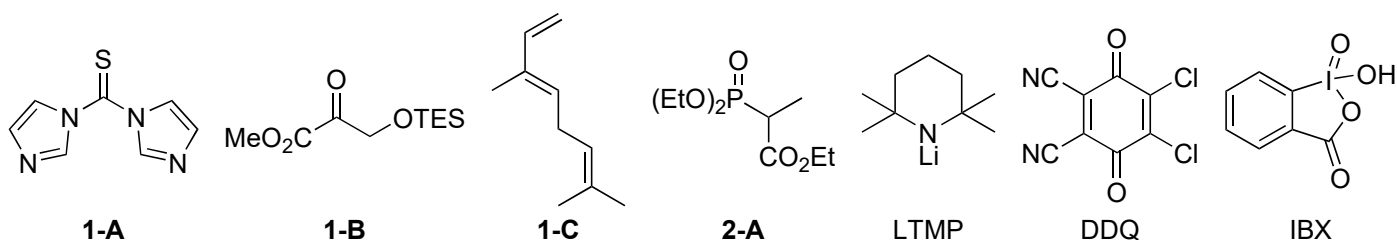
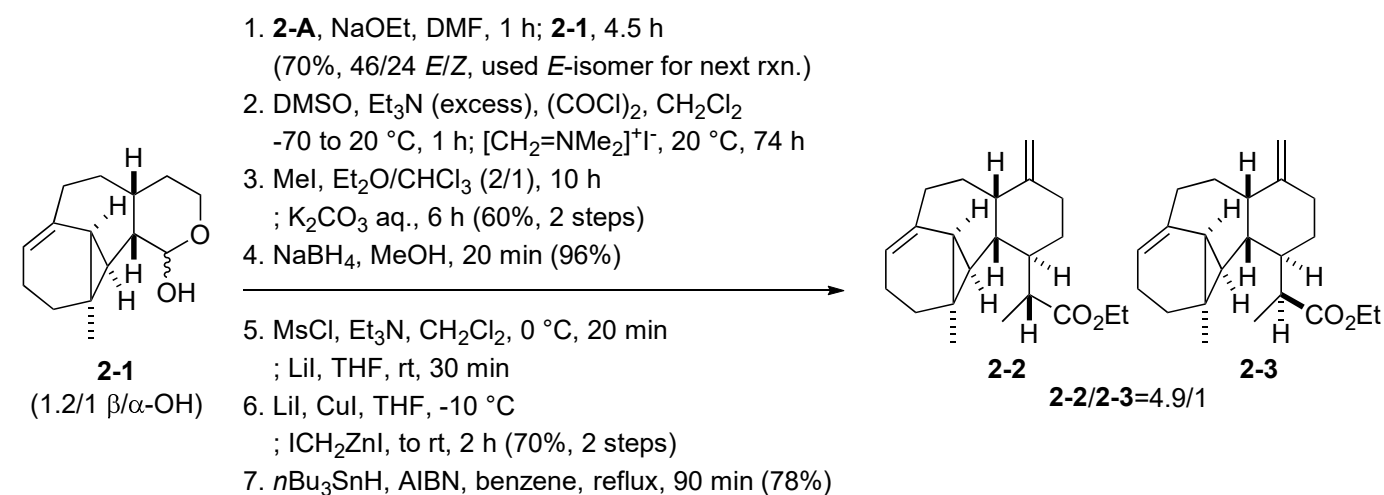
20170203 Shimizu Shinsuke

Please provide following reaction mechanisms

Problem 1



Problem 2



Problem Session (1) Answer

20170203 Shimizu Shinsuke

topic: Total synthesis of bolivianine and ceruberubic acid III

problem 1: **bolivianine**

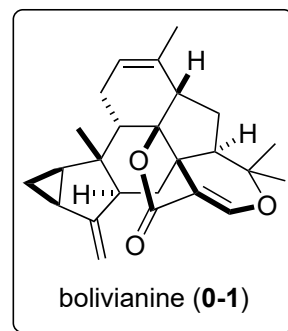
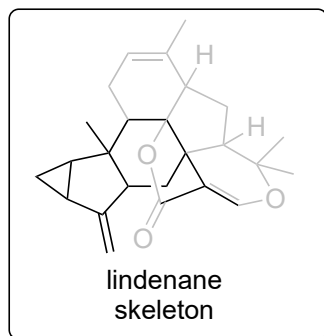
isolation & structural determination: from trunk bark of *Hedyosmum angustifolium*
Jullian, V. et. al. *Org. Lett.* **2007**, 9, 4693.

growing in the Andean forest of
Bolivia, Peru, Ecuador

bioactivity: no activity was reported (*Plasmodium falciparum* or on the MCF cell line)
Jullian, V. et. al. *Org. Lett.* **2007**, 9, 4693.

structural feature:

- unique 3/5/6 ring junction
- angular methyl group
- congested heptacyclic skeleton
- nine-contiguous stereogenic centers (including two quaternary chiral centers and a tetra-substituted carbon)



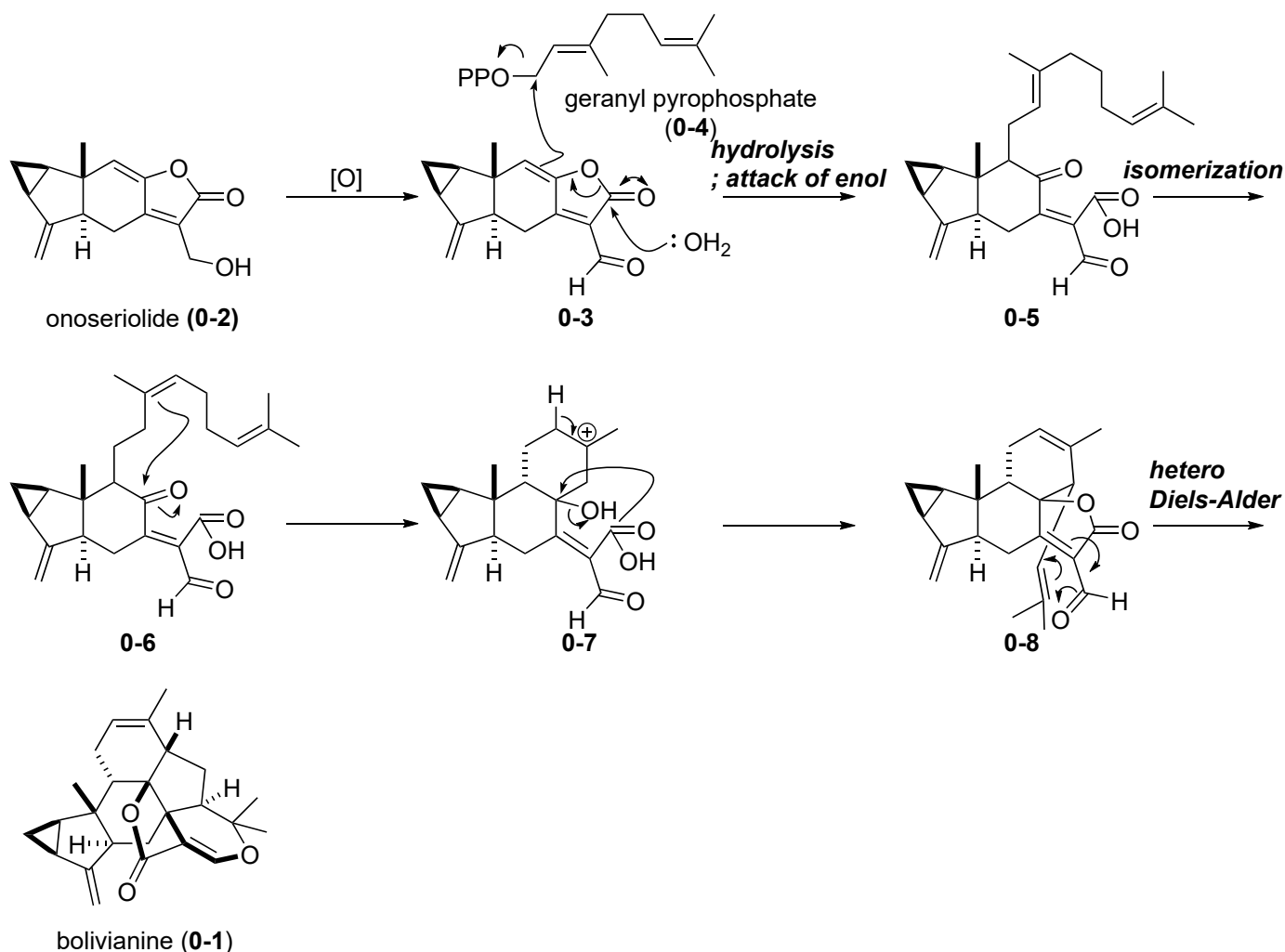
total synthesis:

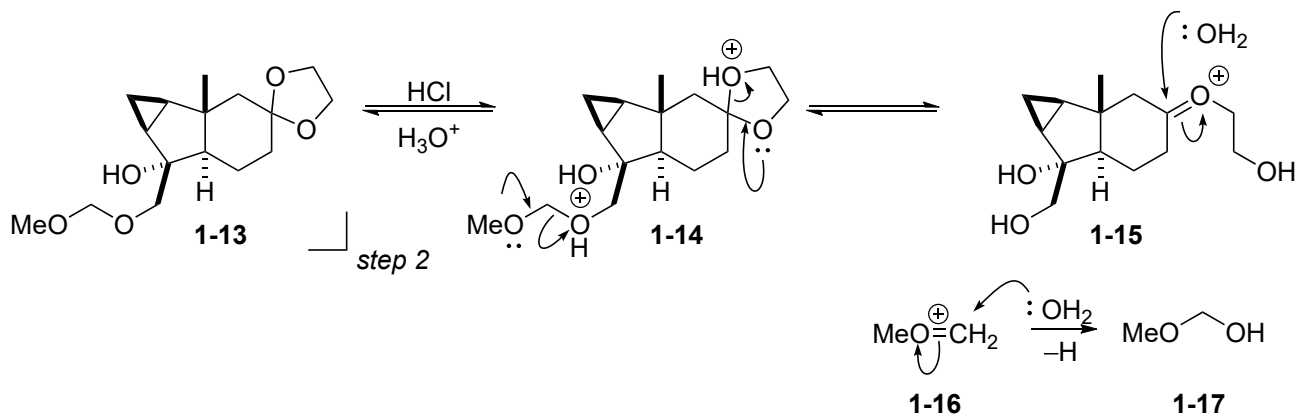
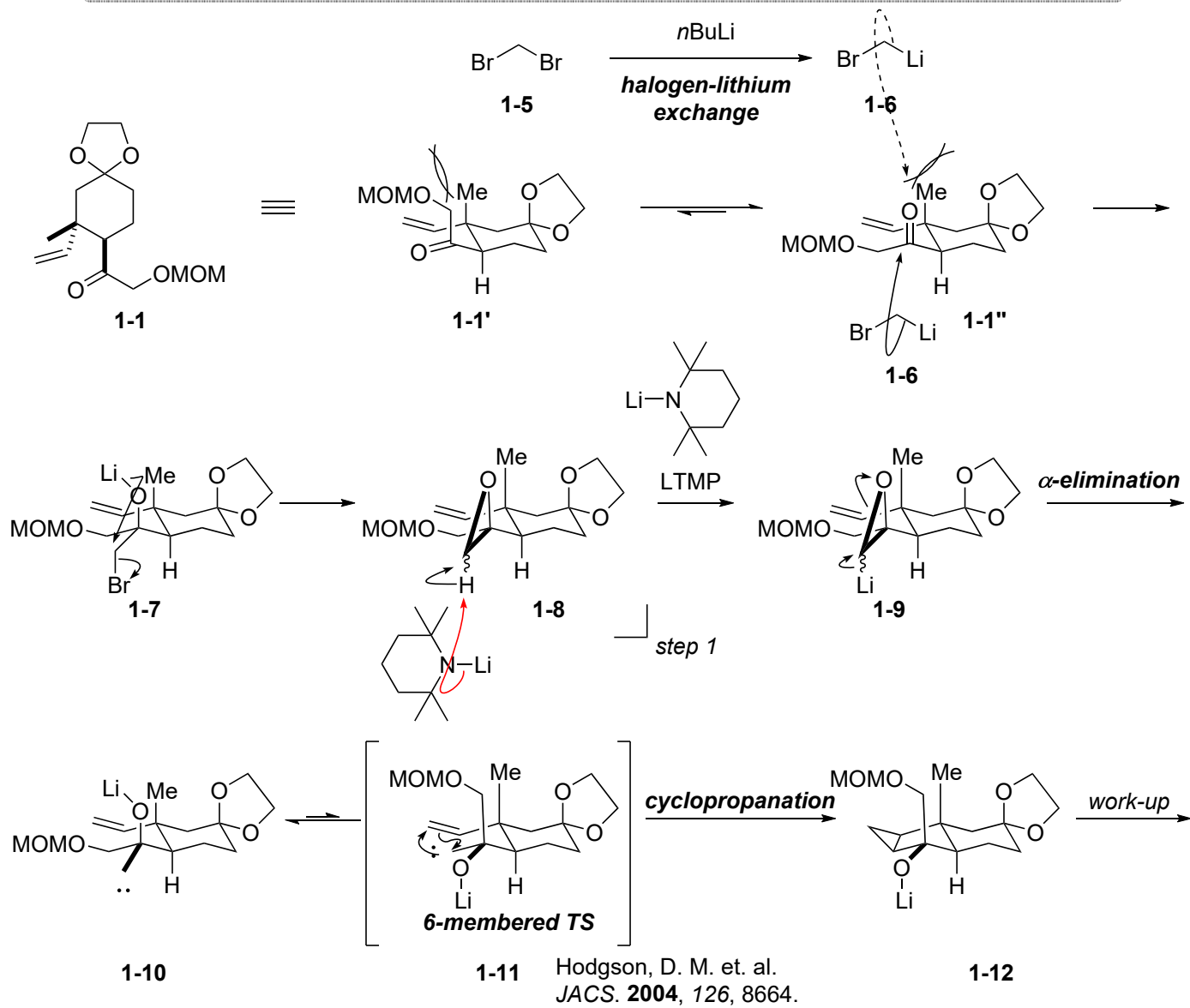
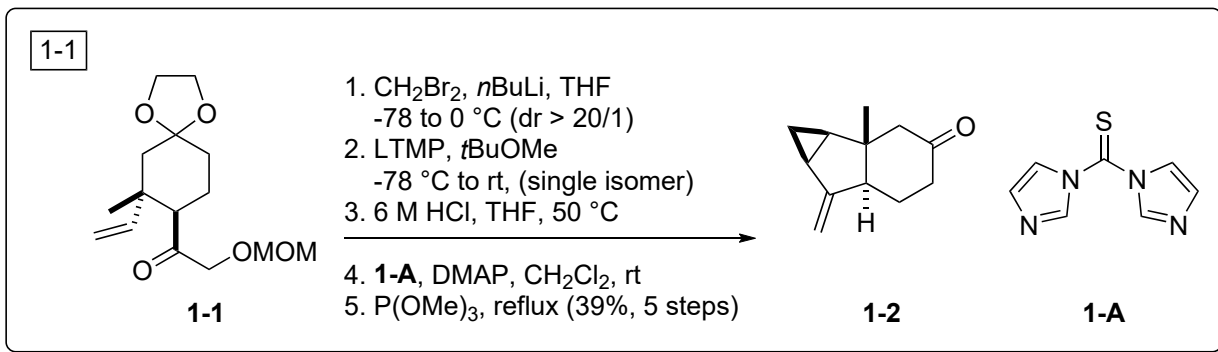
Liu, B. et. al. *Chem. Eur. J.* **2014**, 20, 2613. (**problem 1**)

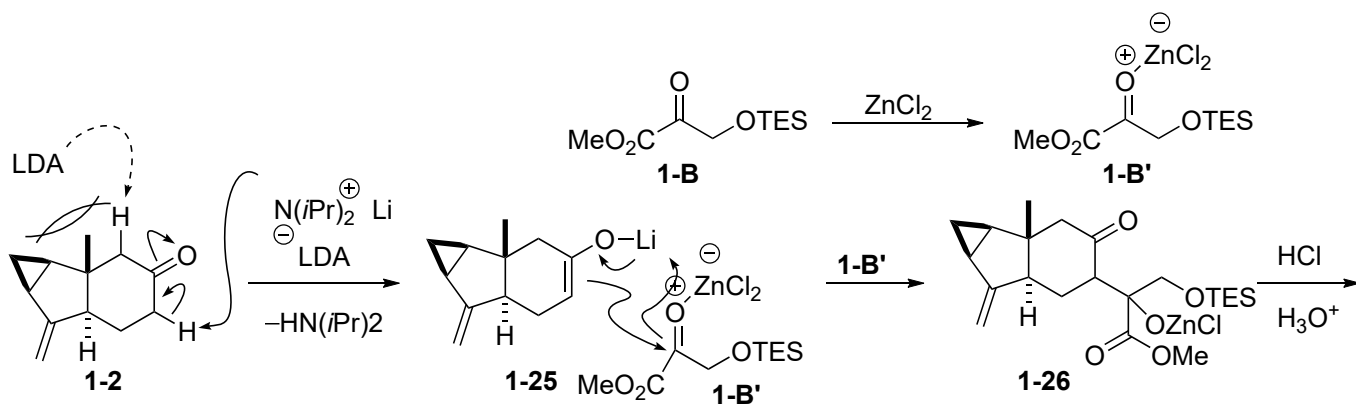
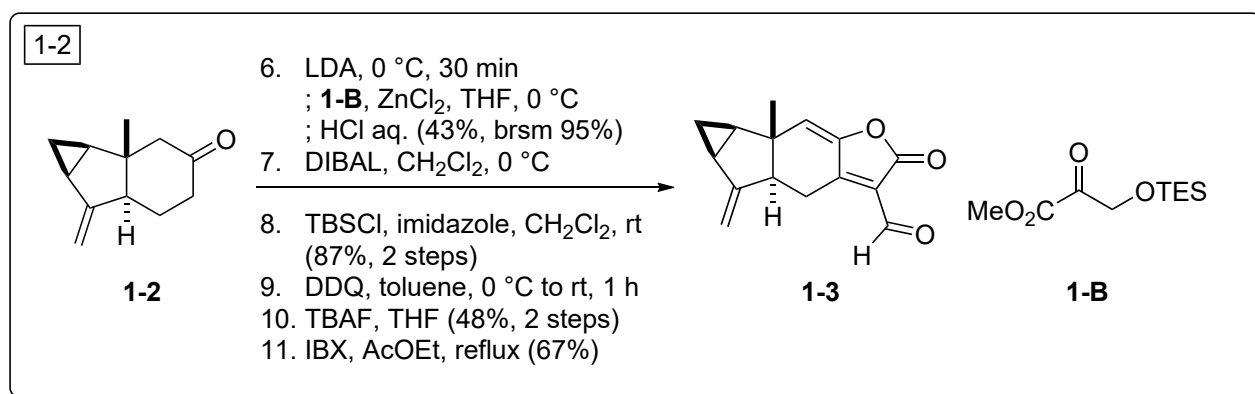
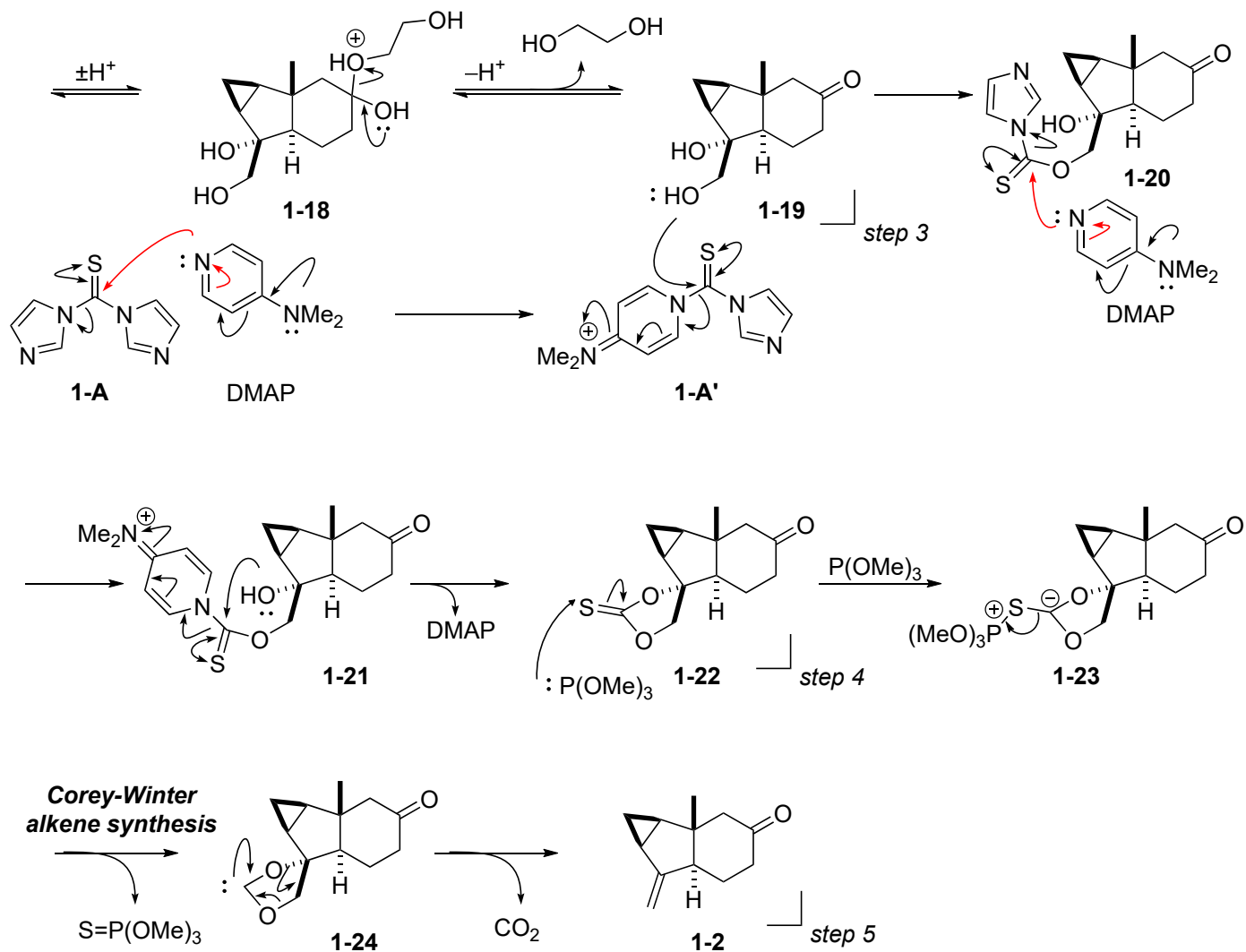
biosynthesis:

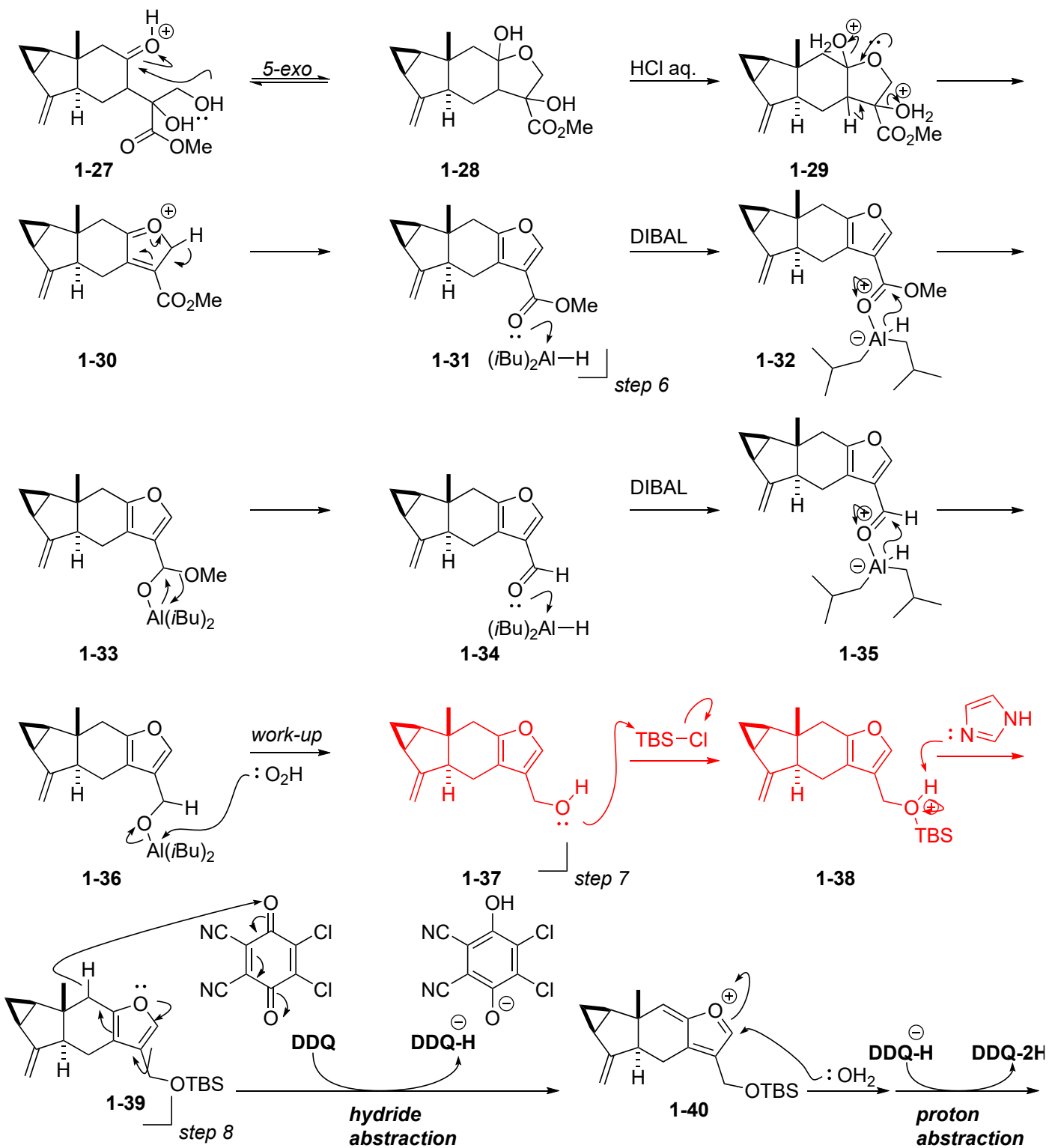
proposed Jullian group

Jullian, V. et. al. *Org. Lett.* **2007**, 9, 4693.

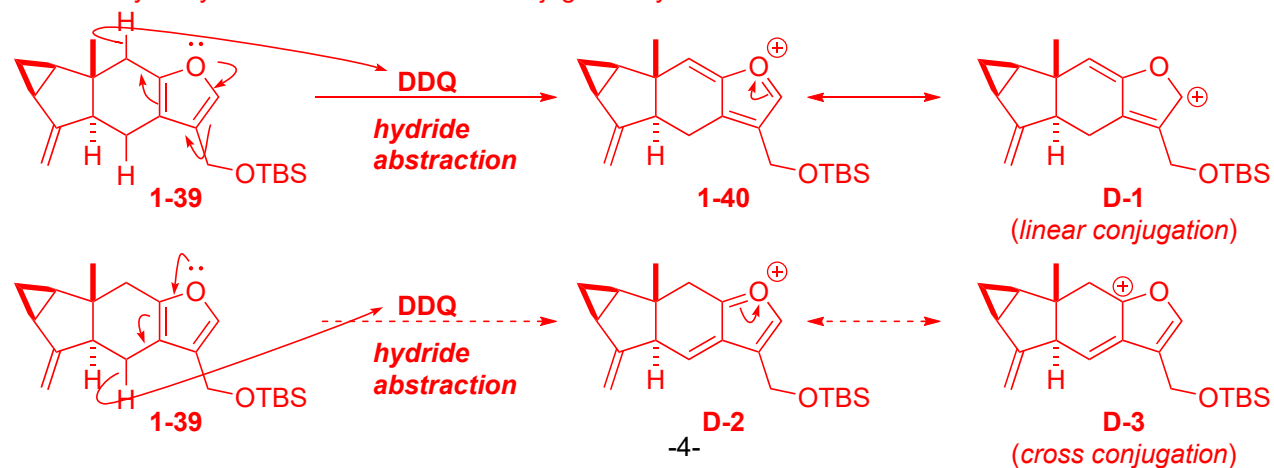


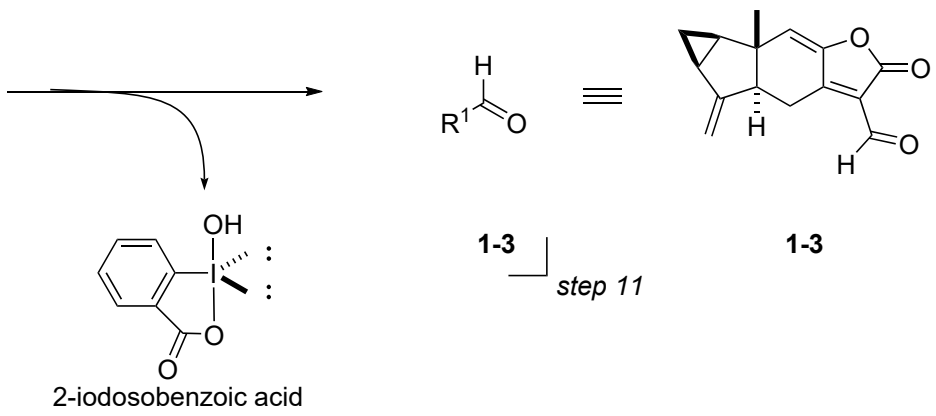
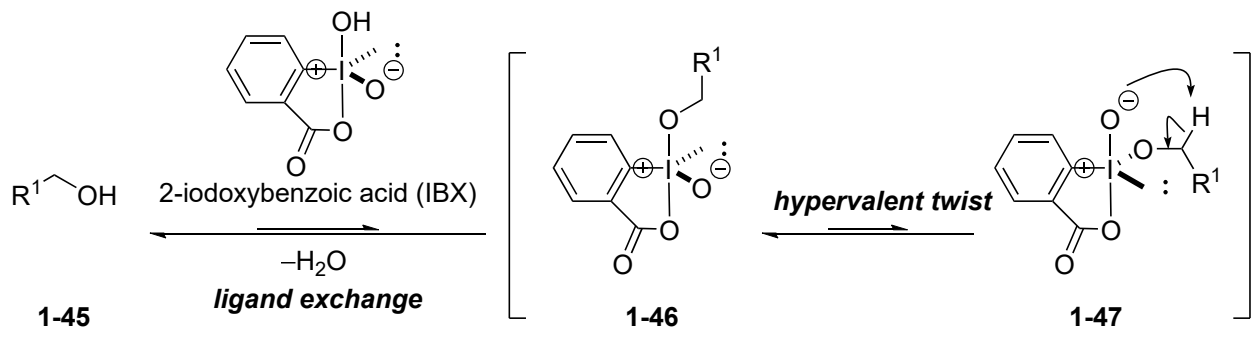
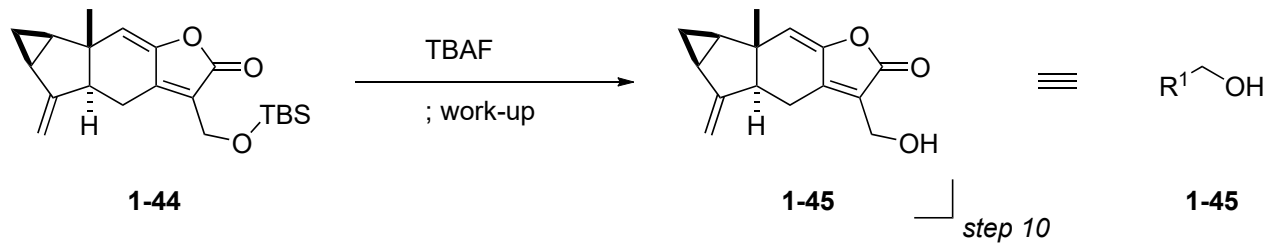
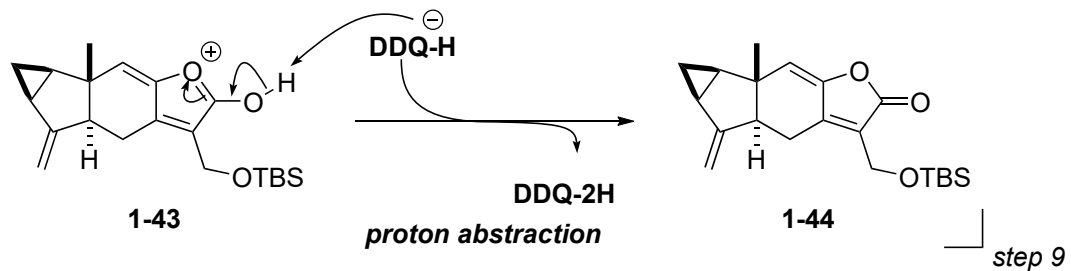
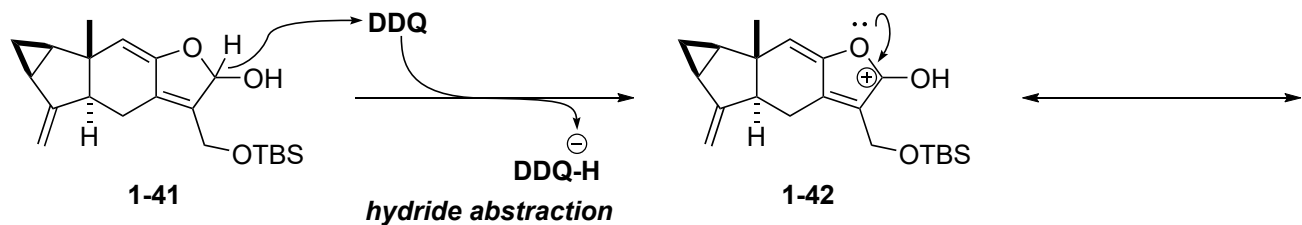


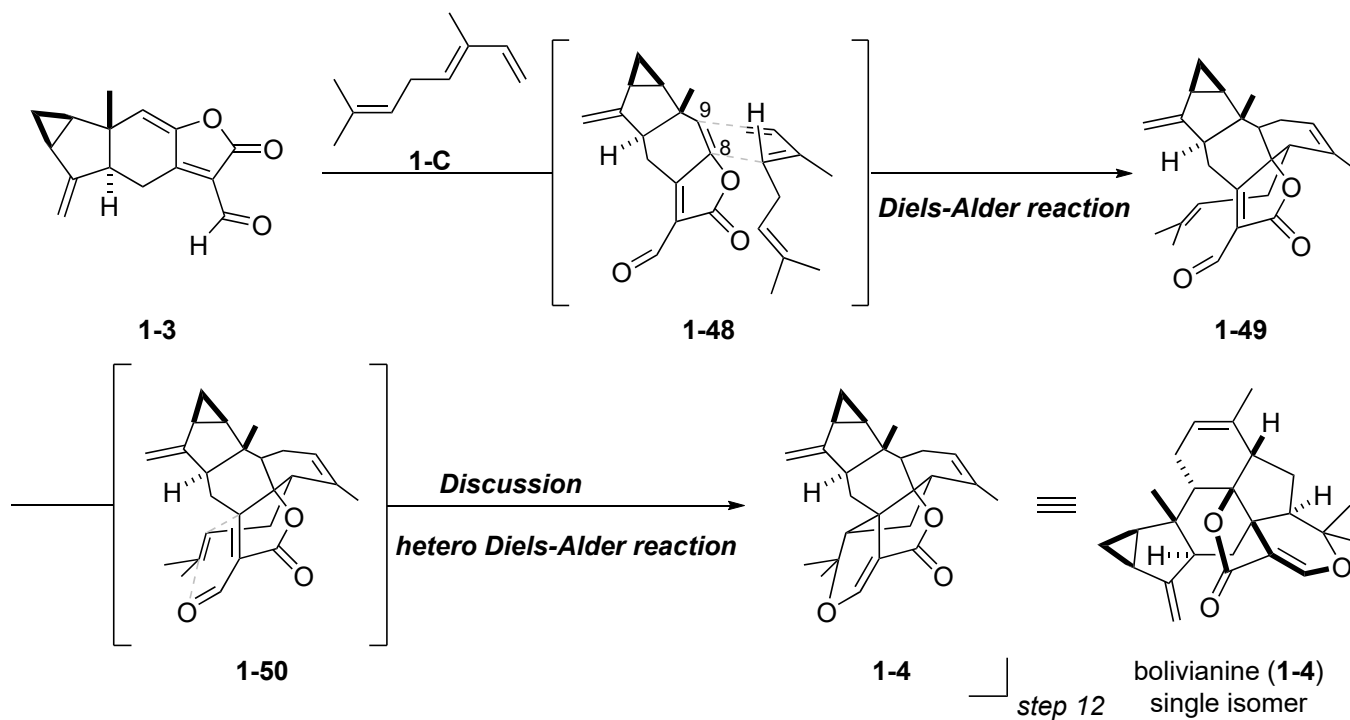
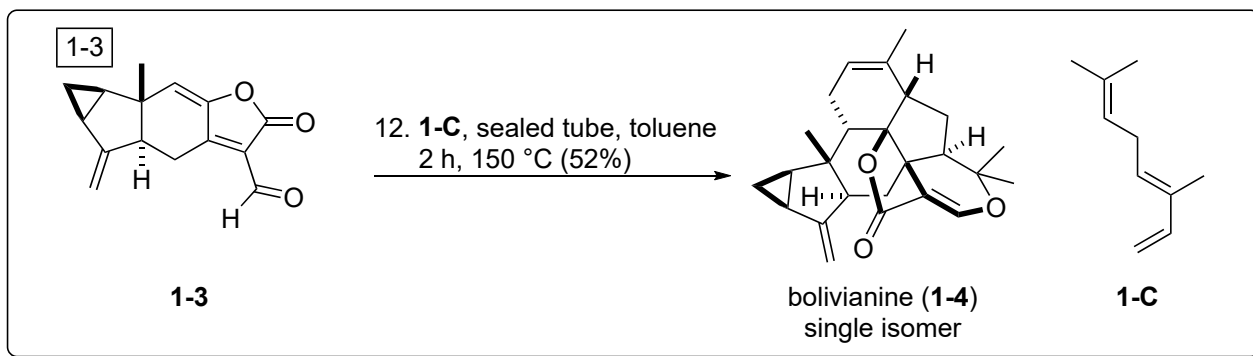




∅selectivity of hydride abstraction: linear conjugation system is more stable than cross one.







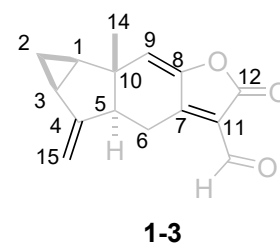
Discussion: Diels-Alder reaction (DA) & hetero Diels-Alder reaction (HDA)

∅chemo-selectivity...why did the C8=C9 double bond react?



C8=C9 double bond is...

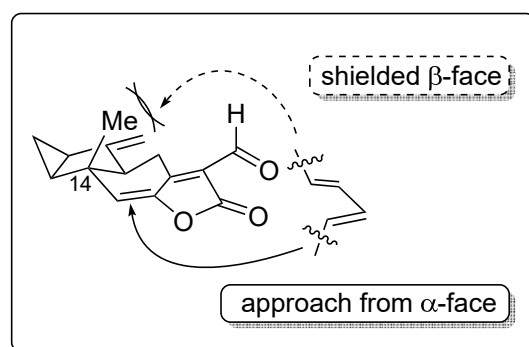
- more electron deficient than the C4=C15 double bond
- less substituted and less hindered than the C7-C11 double bond



∅facial-selectivity...α-face or β-face?



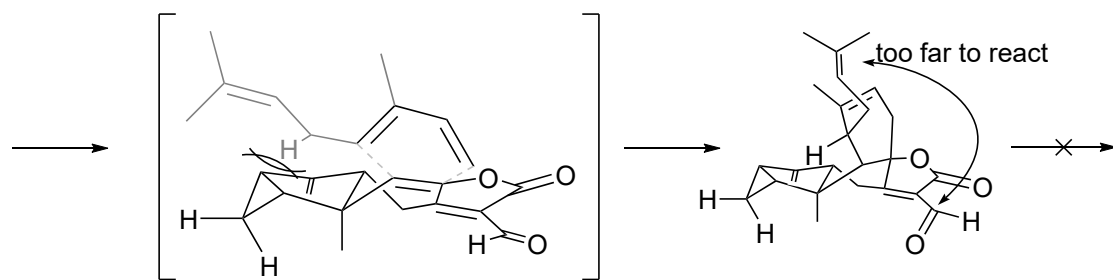
- because of rigid tetracyclic skeleton of **1-3** and C14 methyl group, diene **1-C** could attack to dienophile from the α-face



∅regioselectivity

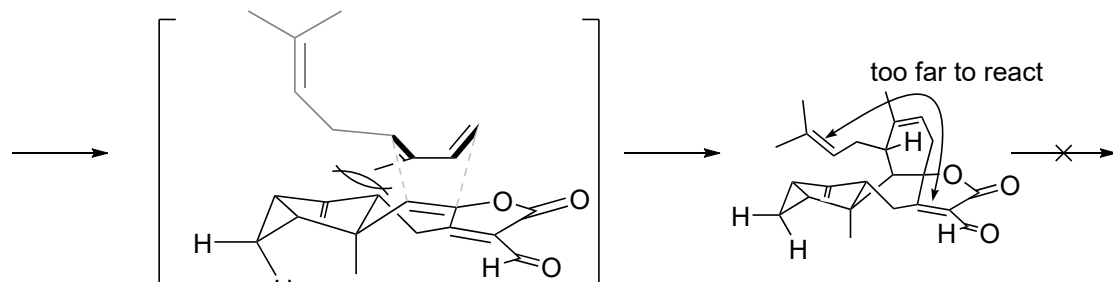
∅endo-selectivity

∅priority of DA to HDA



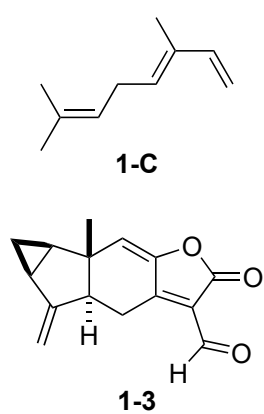
exo-TS1a

exo-IM1a



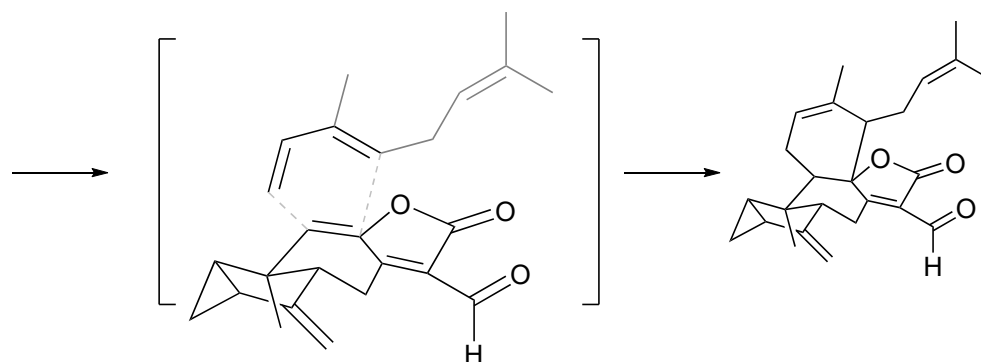
endo-TS1a

endo-IM1a



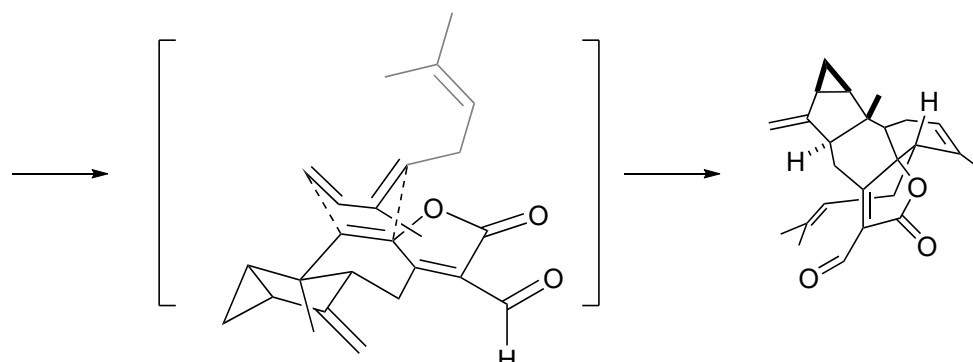
1-C

1-3



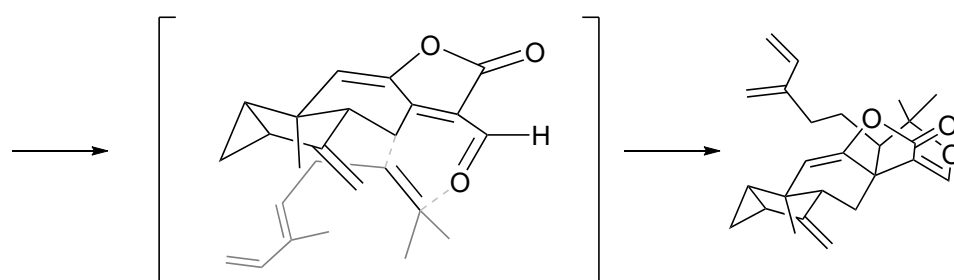
exo-TS1b

exo-IM1b



endo-TS1b

endo-IM1b



TS1c

IM1c

- because of the remote location of the double bond from the enal segment, in both **exo-IM1a** and **endo-IM1a**, the corresponding HDA is thwarted.
- from *endo*-rule, transition energy of **endo-TS1b** is lower than **exo-TS1b**.

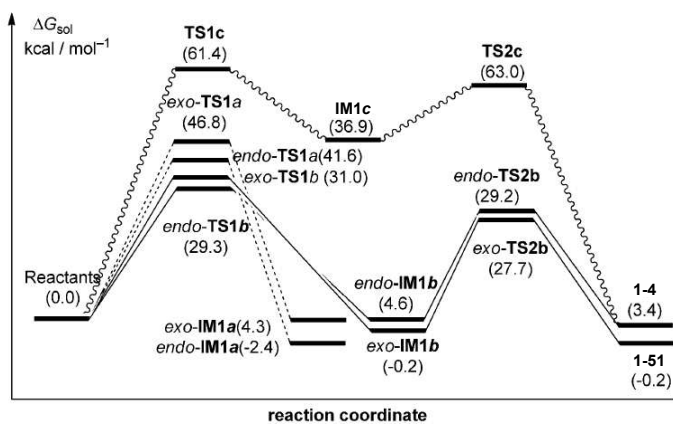
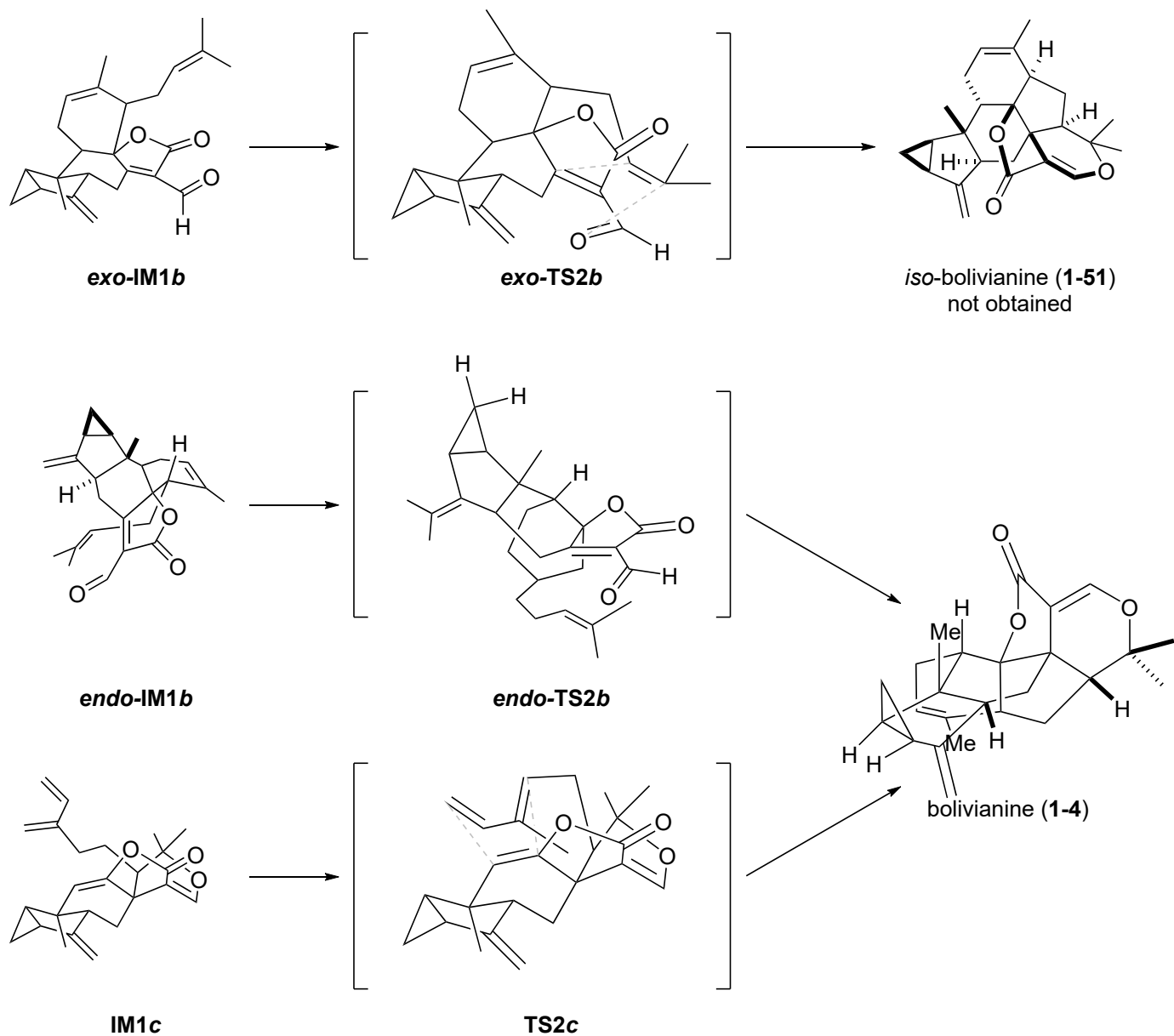


Figure 2. Calculated relative energies (in parentheses) of various species at the B3LYP/6-31G* level on the potential energy surface (PES) in system 1 (4+8).



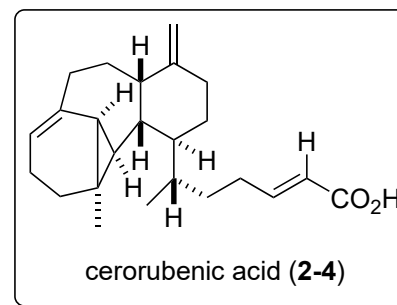
problem 2: **cerorubenic acid III**

isolation & structural determination: from *Ceroplastes rubens*
Naya, Y. et. al. *J. Chem. Soc., Chem. Commun.* **1983**, 1182.

bioactivity: kairomone for the ovipositional behavior
of the parasitic wasp *Anicetus beneficus* towards *C. rubens*
Naya, Y. et. al. *J. Chem. Soc., Chem. Commun.* **1983**, 1182.

structural feature:

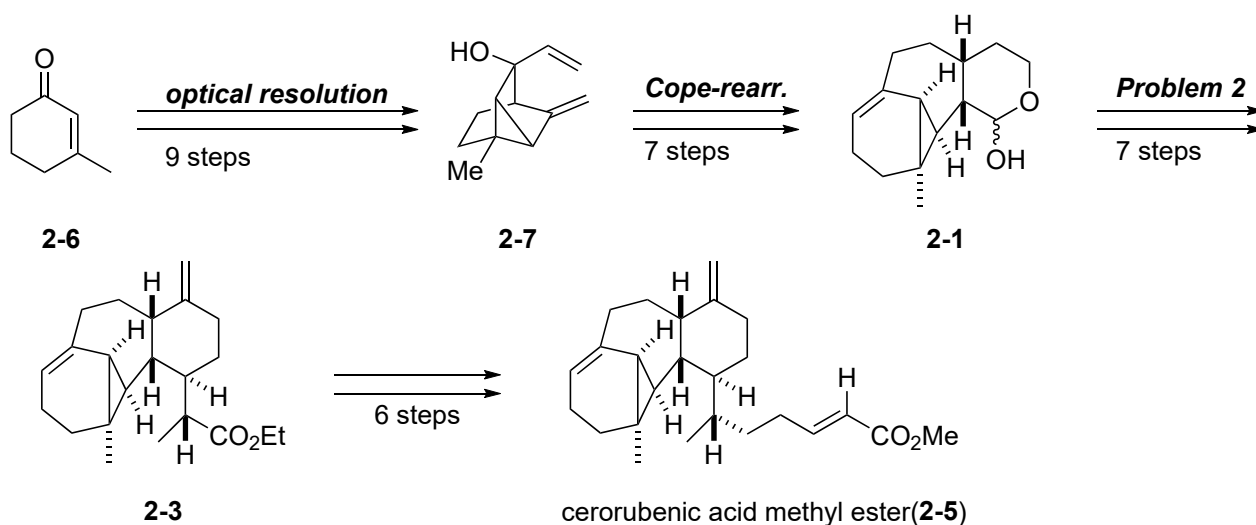
- unique tetracyclo[8.4.1.0.0]pentadecane skeleton
 - seven contiguous stereogenic centers
 - embedded vinylcyclopropane motif (its alkene moiety residing at a bridgehead site)
- Trauner, D. et. al. *Nat. Prod. Rep.* **2012**, 29, 752.



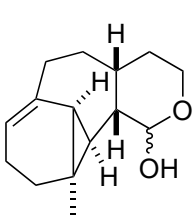
total synthesis:

methyl ester (**2-5**): Paquette, L. A.; Dyck, B. P. *J. Am. Chem. Soc.* **1998**, 120, 5953. (**problem 2**)

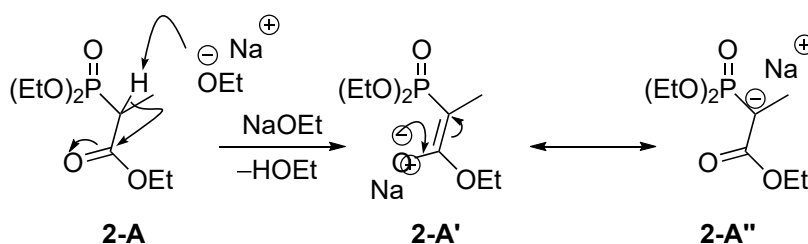
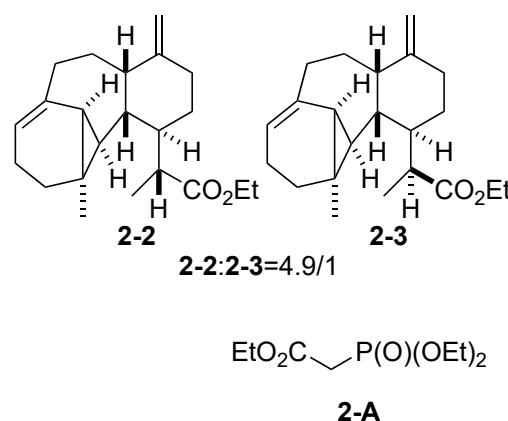
synthetic approach (by Paquette)

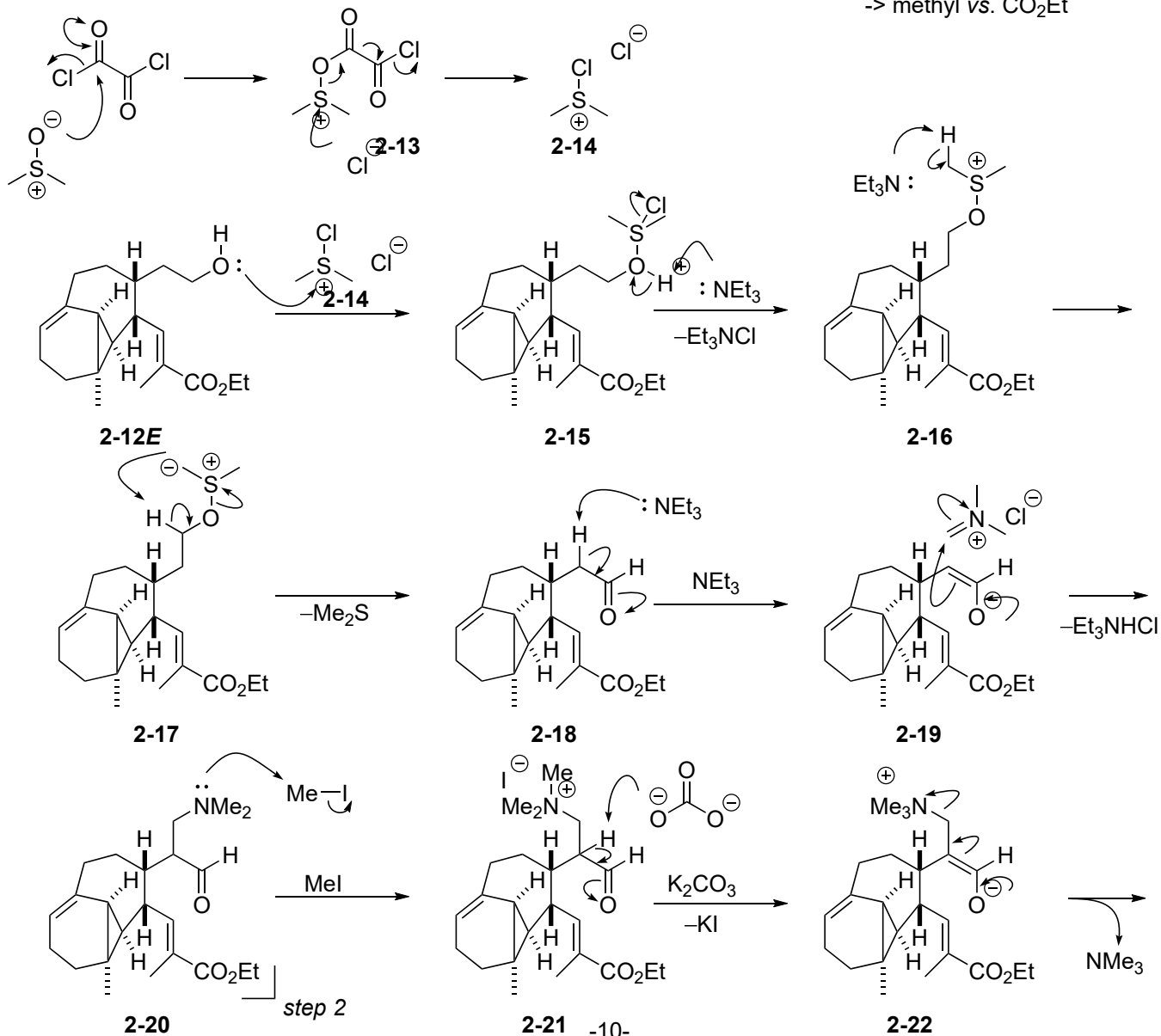
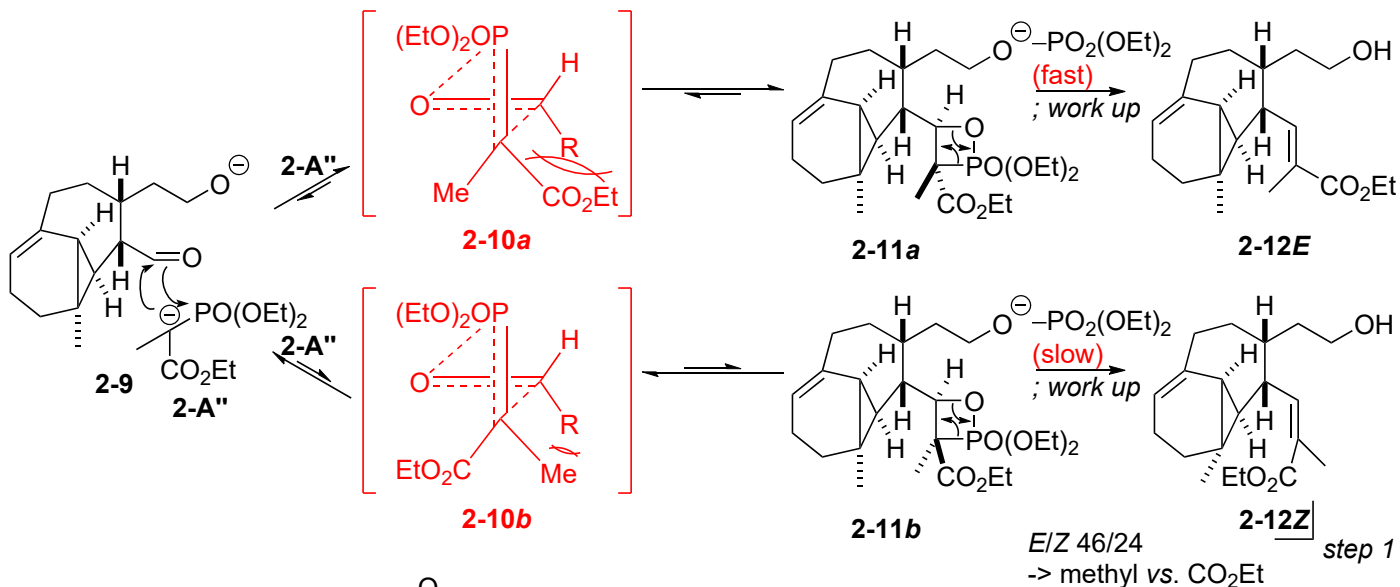
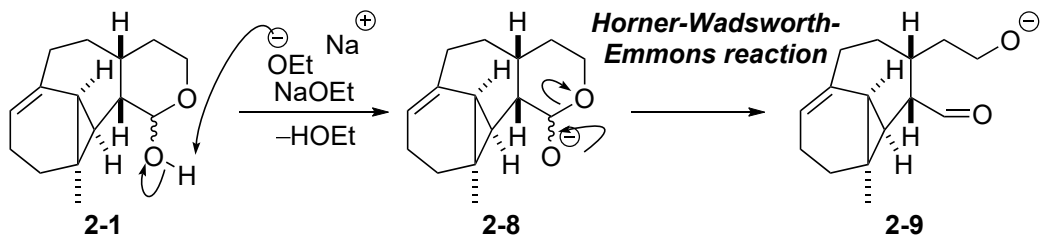


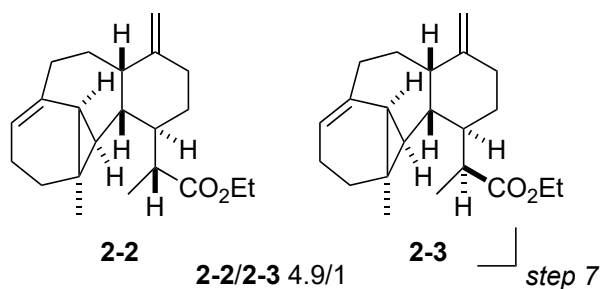
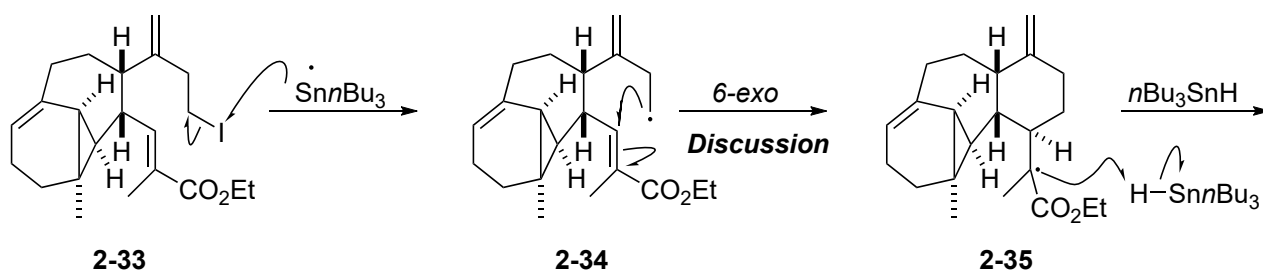
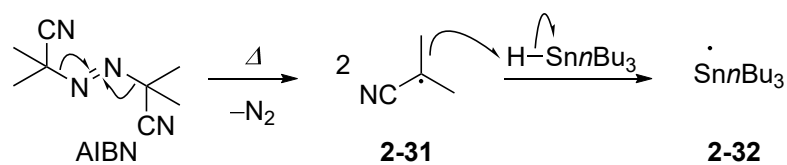
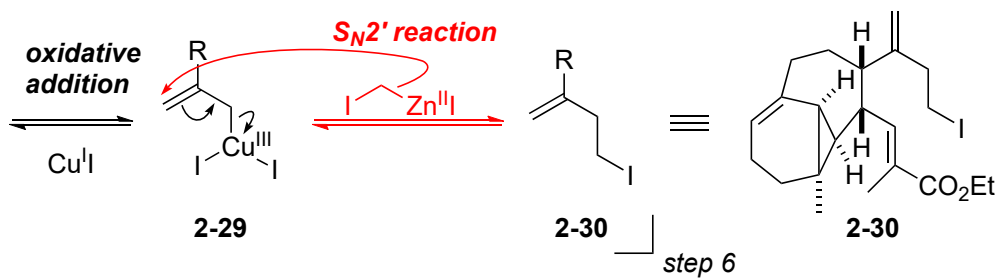
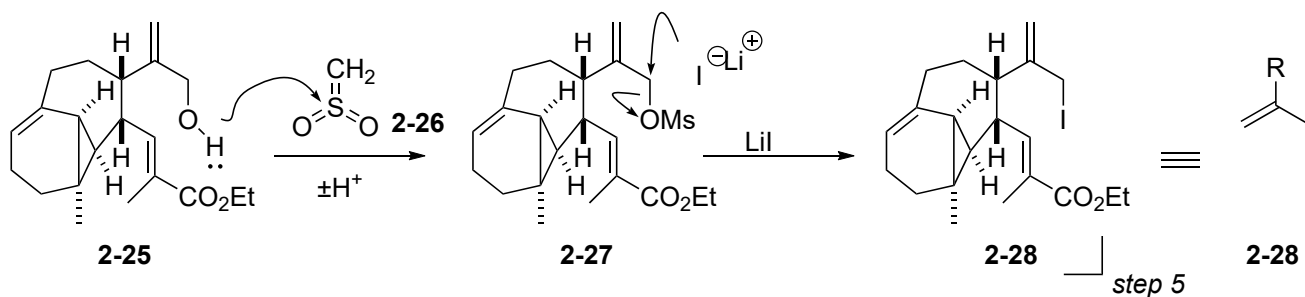
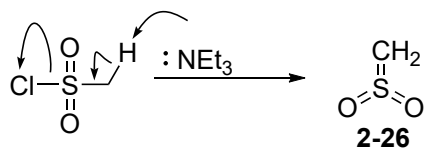
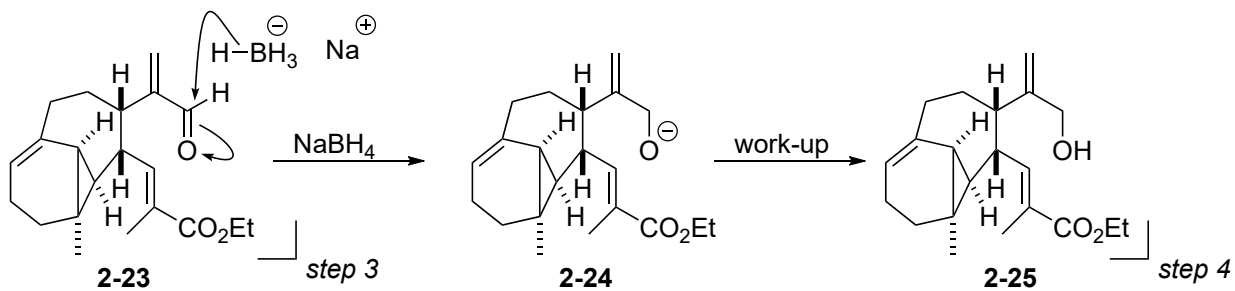
Problem 2



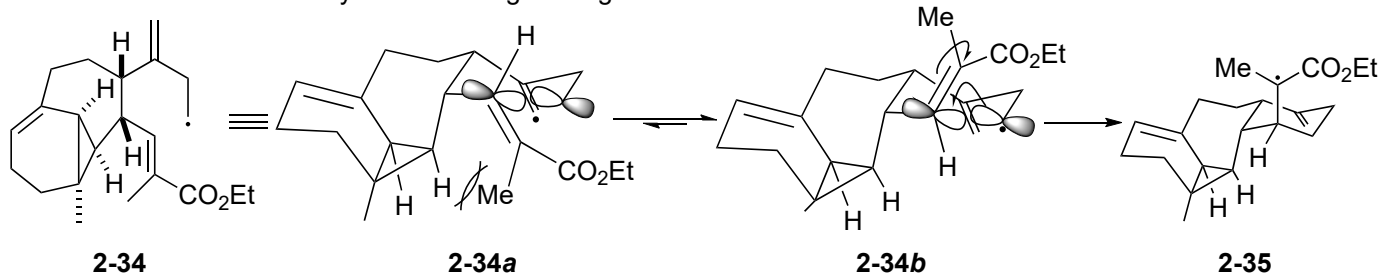
- 2-A**, NaOEt, DMF, 1 h; **2-1**, 4.5 h
(70%, 46/24 *E/Z*, used *E*-isomer for next rxn.)
- DMSO, Et₃N (excess), (COCl)₂, CH₂Cl₂
-70 to 20 °C, 1 h; [CH₂=NMe₂]⁺Cl⁻, 20 °C, 74 h
- MeI, Et₂O/CHCl₃ (2/1), 10 h
; K₂CO₃ aq., 6 h (60%, 2 steps)
- NaBH₄, MeOH, 20 min (96%)
- MsCl, Et₃N, CH₂Cl₂, 0 °C, 20 min
; Lil, THF, rt, 30 min
- Lil, CuI, THF, -10 °C
; ICH₂ZnI, to rt, 2 h (70%, 2 steps)
- n*Bu₃SnH, AIBN, benzene, reflux, 90 min (78%)





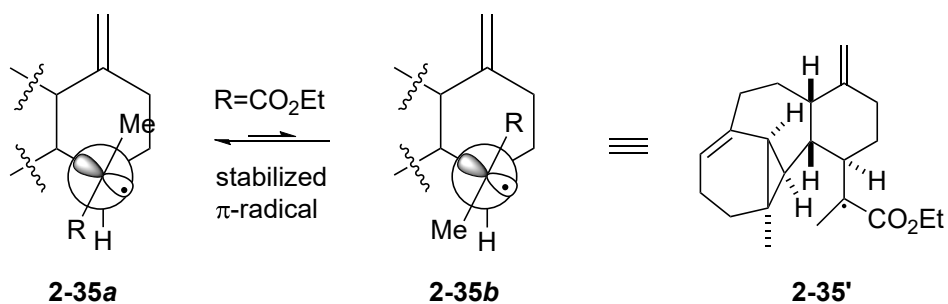


Discussion: stereoselectivity of radical ring-closing

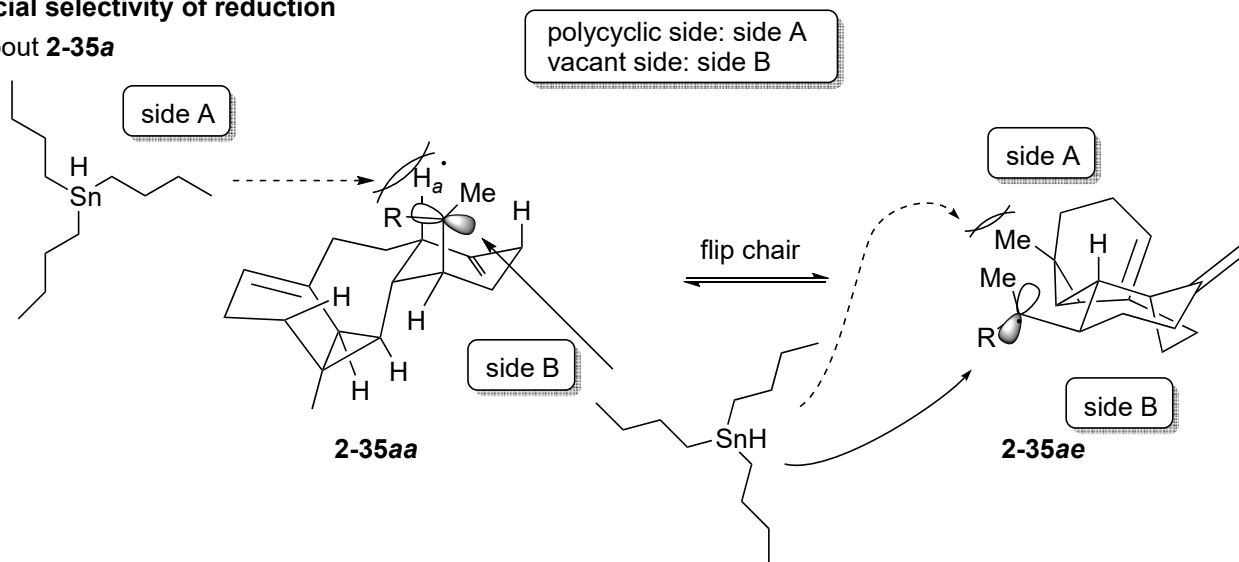


∅ **conformation**

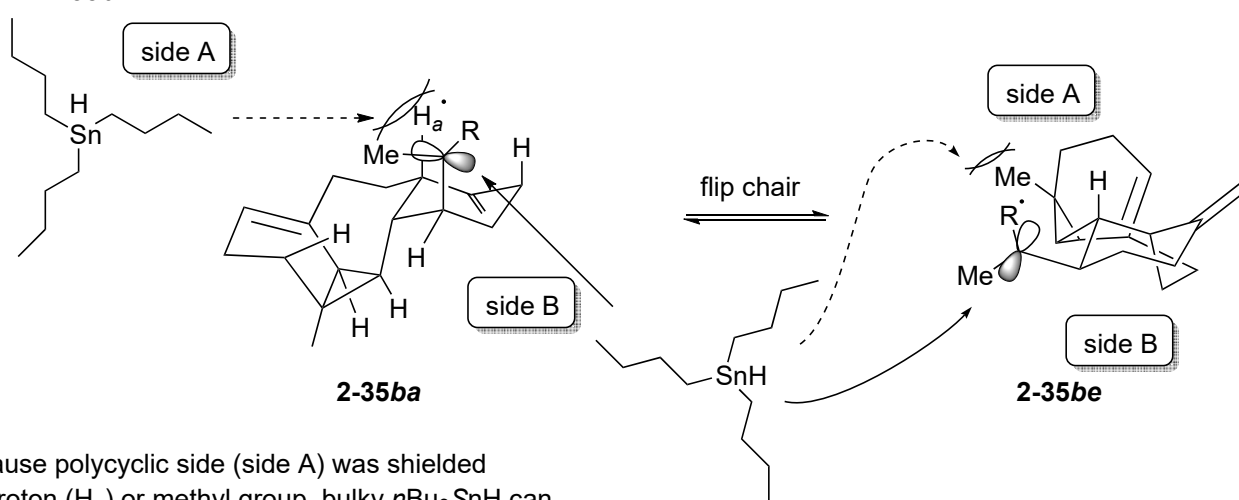
to minimize gauche interactions, **2-35a** is preferred conformer. (Giese, B. et al. *Tetrahedron Lett.* **1992**, *33*, 1863.)



∅ **facial selectivity of reduction**
about **2-35a**

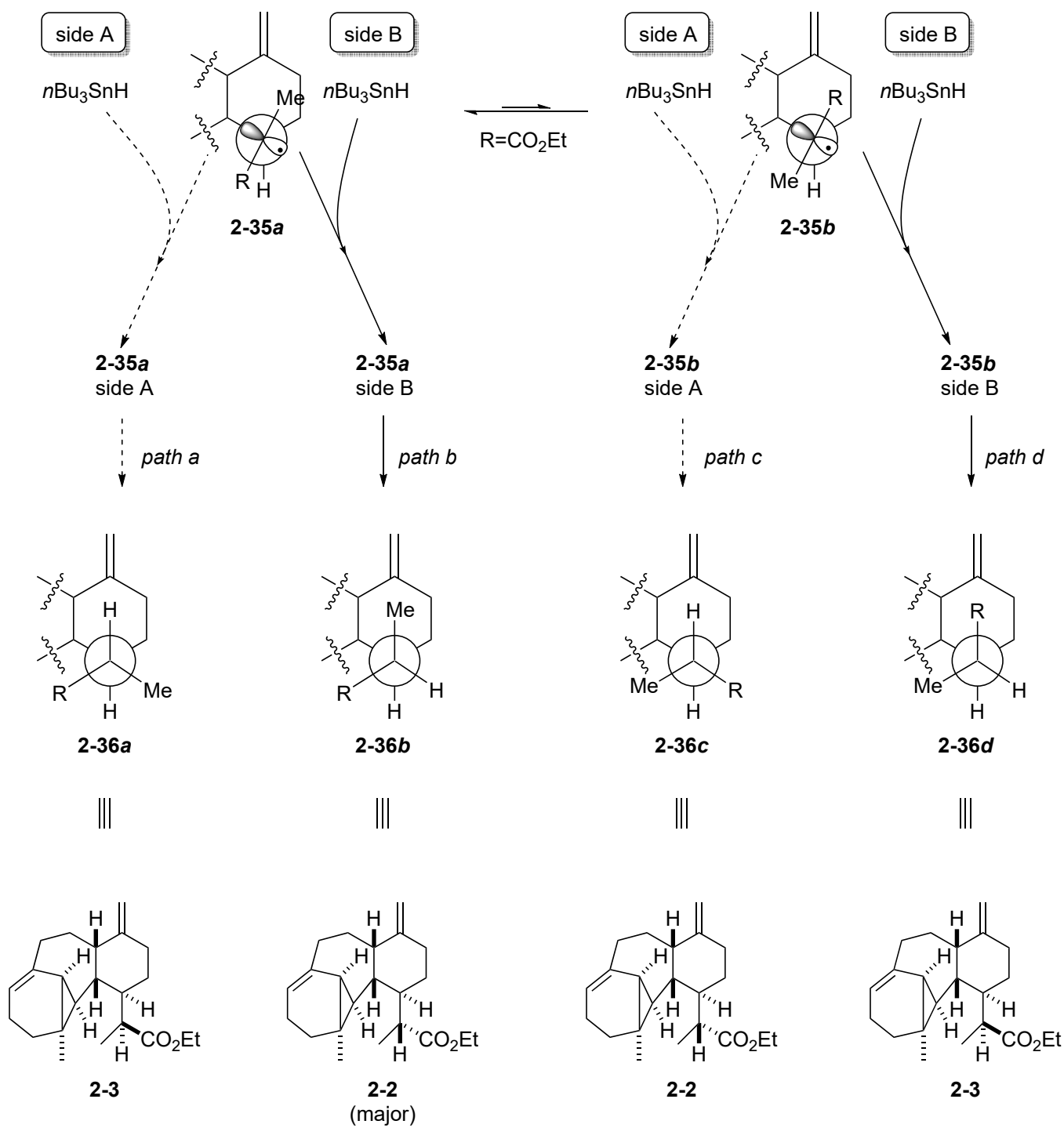


about **2-35b**



because polycyclic side (side A) was shielded by proton (H_a) or methyl group, bulky nBu_3SnH can approach from another side (side B) mainly.

2 conformers x 2 facial selectivities = 4 reaction path ways



2-2/2-3 4.9/1