

Problem Session (3)

Topic: Construction of 5/7/6-tricycles

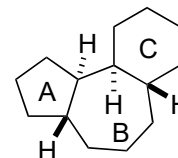
0. Introduction of 5/7/6-tricycles:

Common skeleton of tigliane, rhamnolane, and daphnane diterpenes

Natural products known as its unique biological activity

A lot of synthetic studies reported

(Especially original construction strategy of the 5/7/6-tricycles)



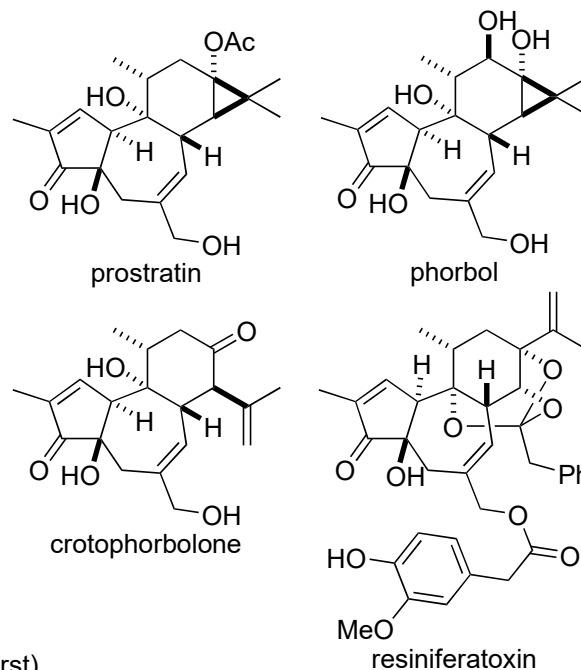
Biological activity:

- phorbol ester: Promoter effect of the cancer
- prostratin: Anti latent HIV effect
- resiniferatoxin: Analgesic effect by activating the TRPV1

Structure:

• **Common trans 5/7/6-tricycles**

- Highly oxygenated (more than 4)
- Cyclopropane moiety (tigliane)
- Orthoester moiety (daphnane)



Total synthesis:

(±)-phorbol:

Wender's group, *J. Am. Chem. Soc.* **1989**, *111*, 8957–8958.

(+)-phorbol:

Wender's group, *J. Am. Chem. Soc.* **1997**, *119*, 7897–7898. (First)

Cha's group, *J. Am. Chem. Soc.* **2001**, *123*, 5590–5591. (Formal)

Baran's group, *Nature* **2016**, *532*, 90–93.

(±)-prostratin:

Li's group, *Chem* **2018**, *13*, 2944–2954.

(+)-crotophorbolone:

Inoue's group, *Angew. Chem., Int. Ed.* **2015**, *54*, 14457–14461. (First)

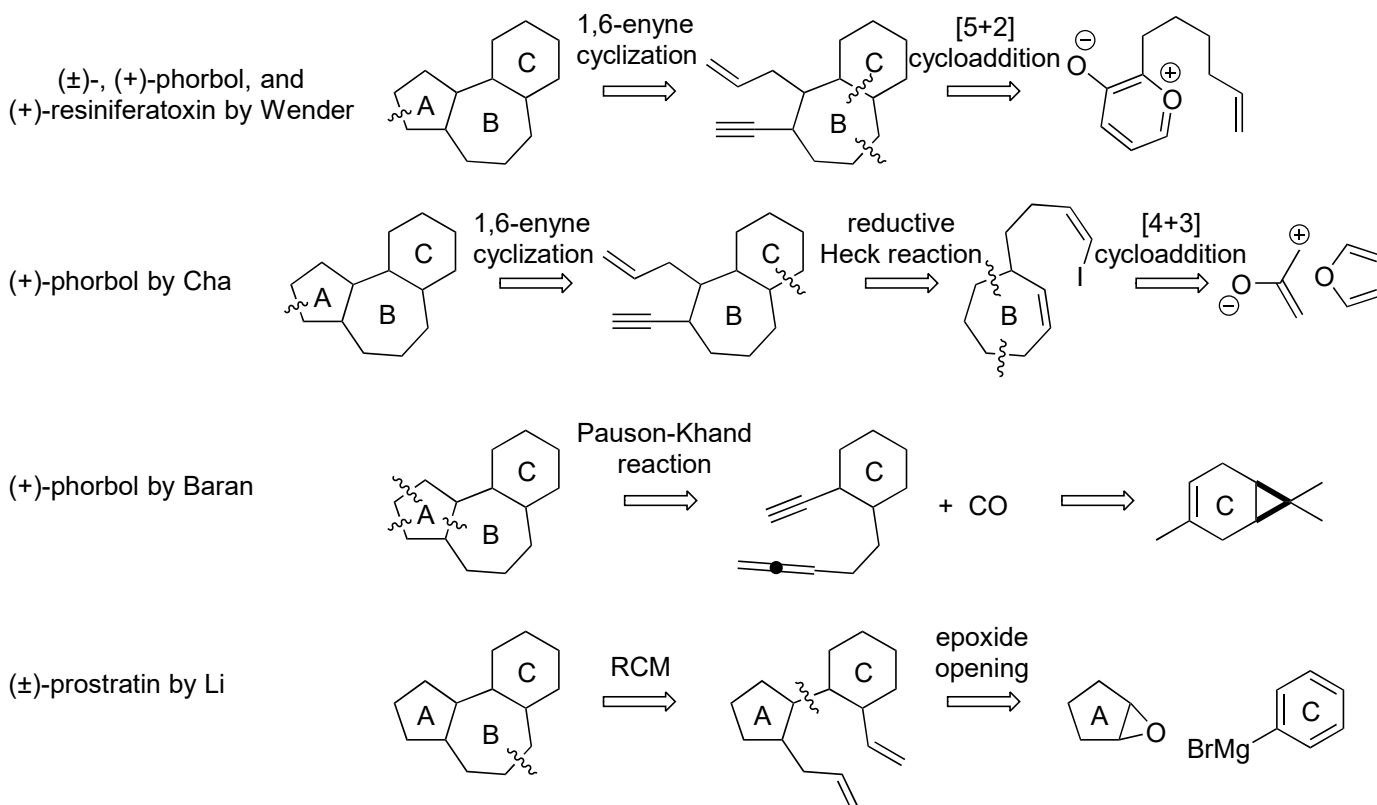
Liu's group, *Chem. Sci.* **2020**, *11*, 7177–7181.

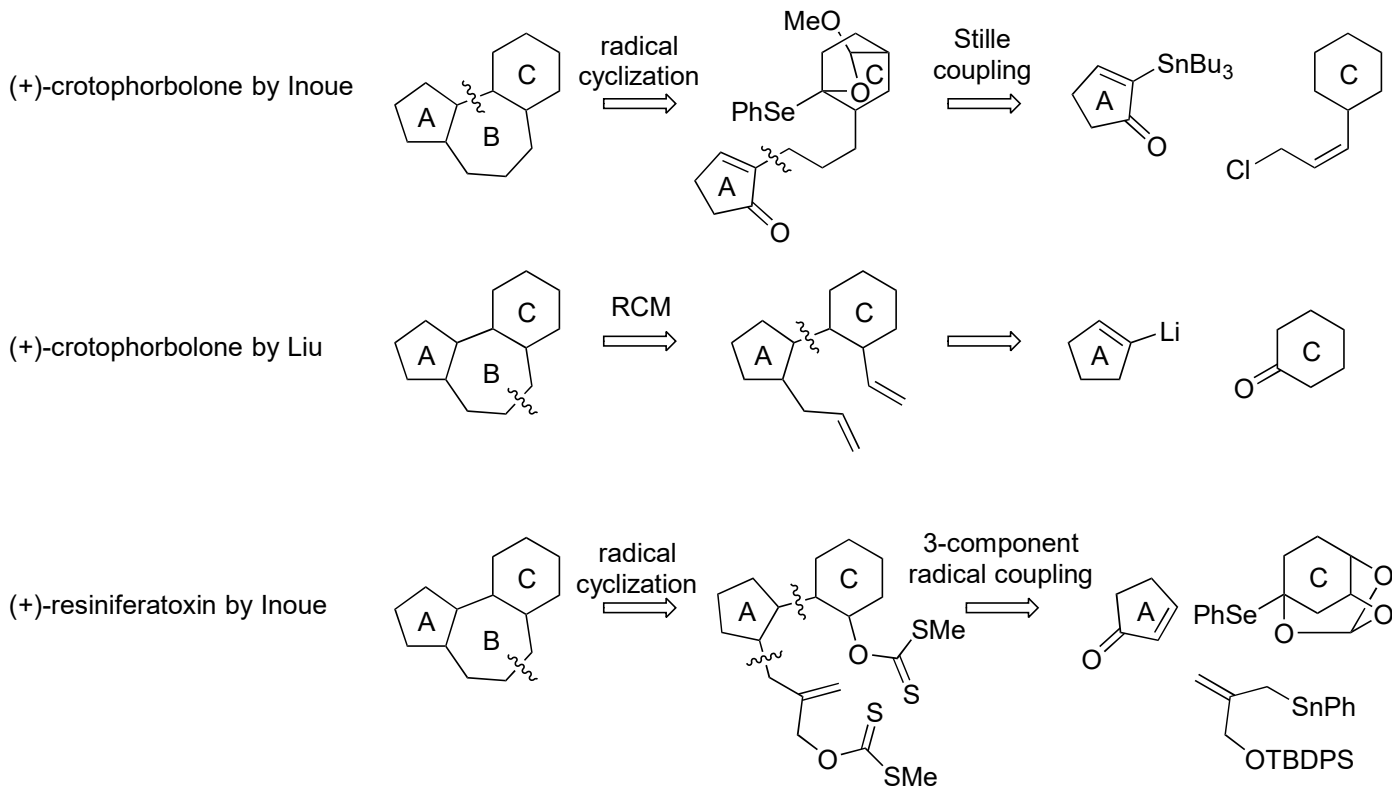
(+)-resiniferatoxin

Wender's group, *J. Am. Chem. Soc.* **1997**, *119*, 12976–2977. (First)

Inoue's group, *J. Am. Chem. Soc.* **2017**, *139*, 16420–16429.

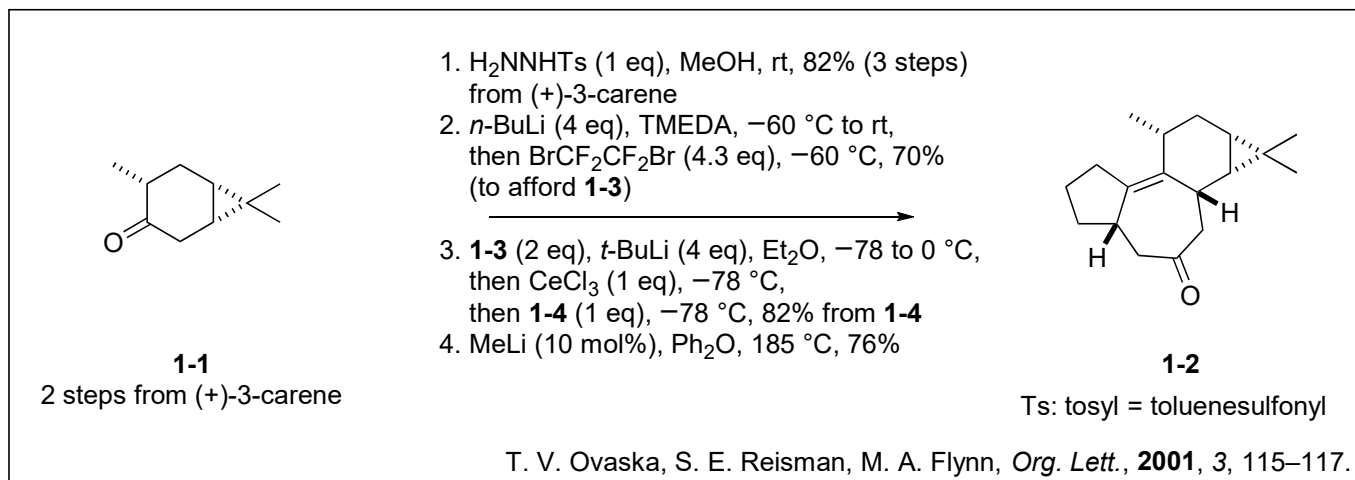
An overview of construction of 5/7/6-tricycles:



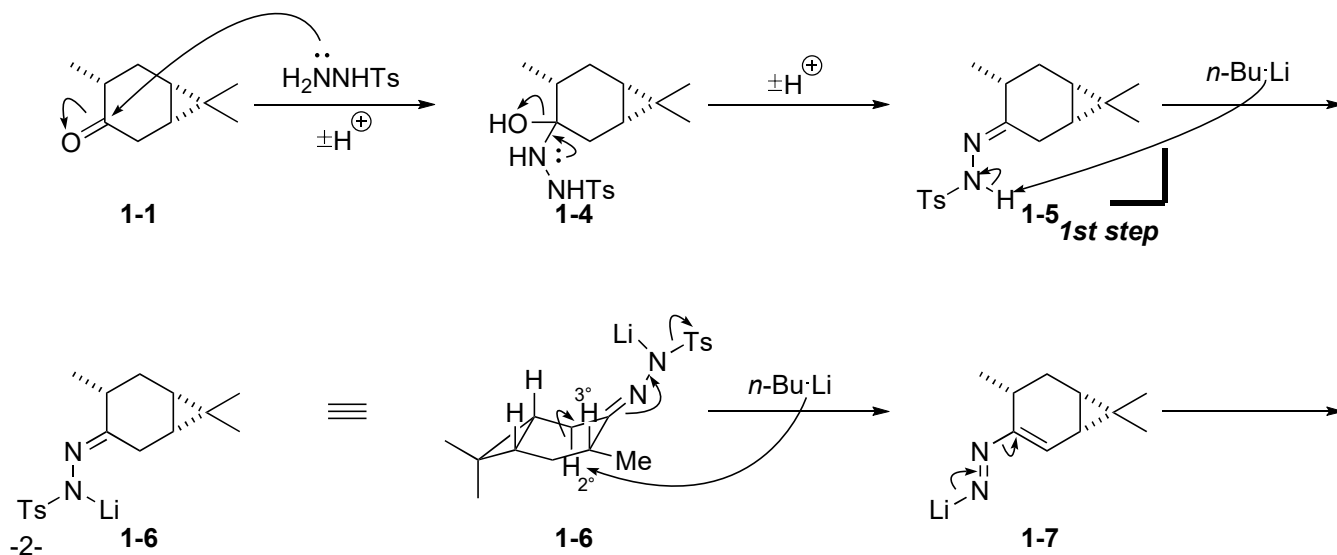


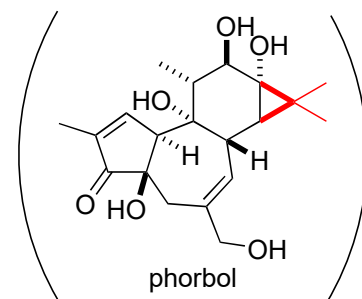
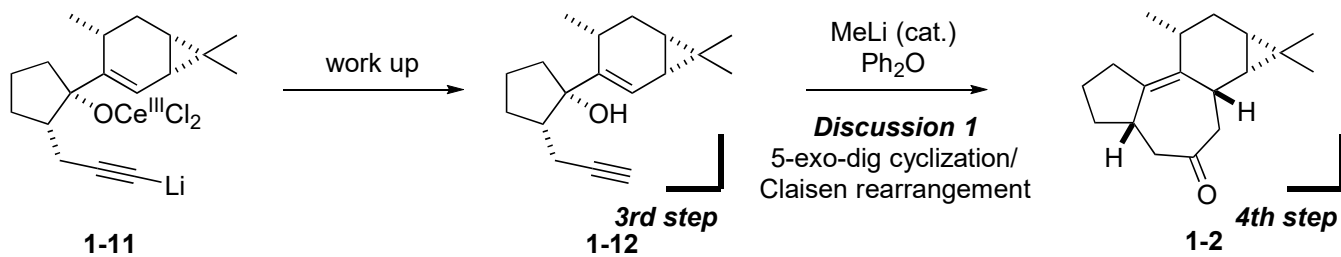
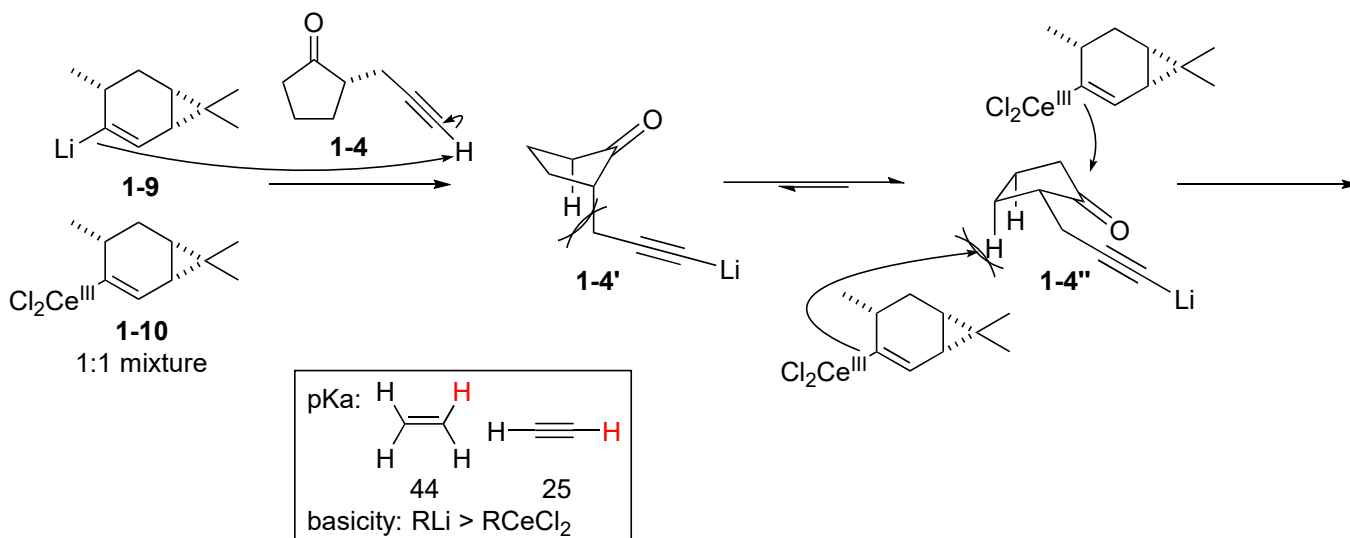
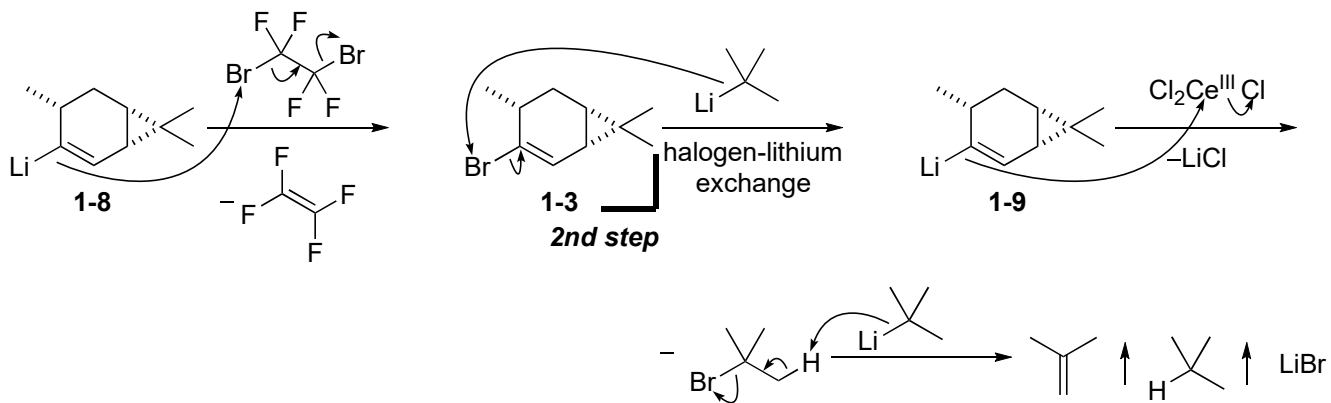
Answer:

1. Phorbol-type 5/7/6/3-ring system by Ovaska's group

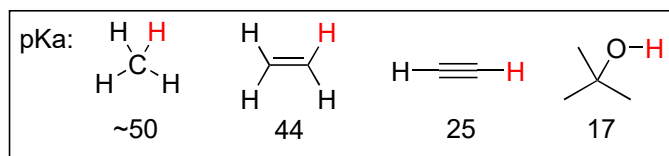
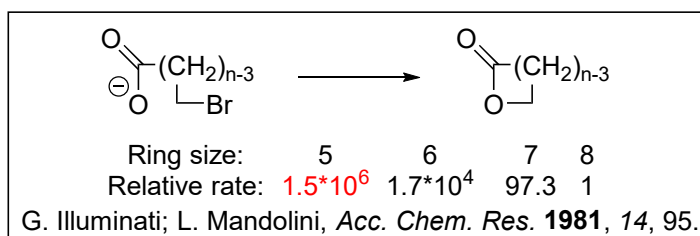
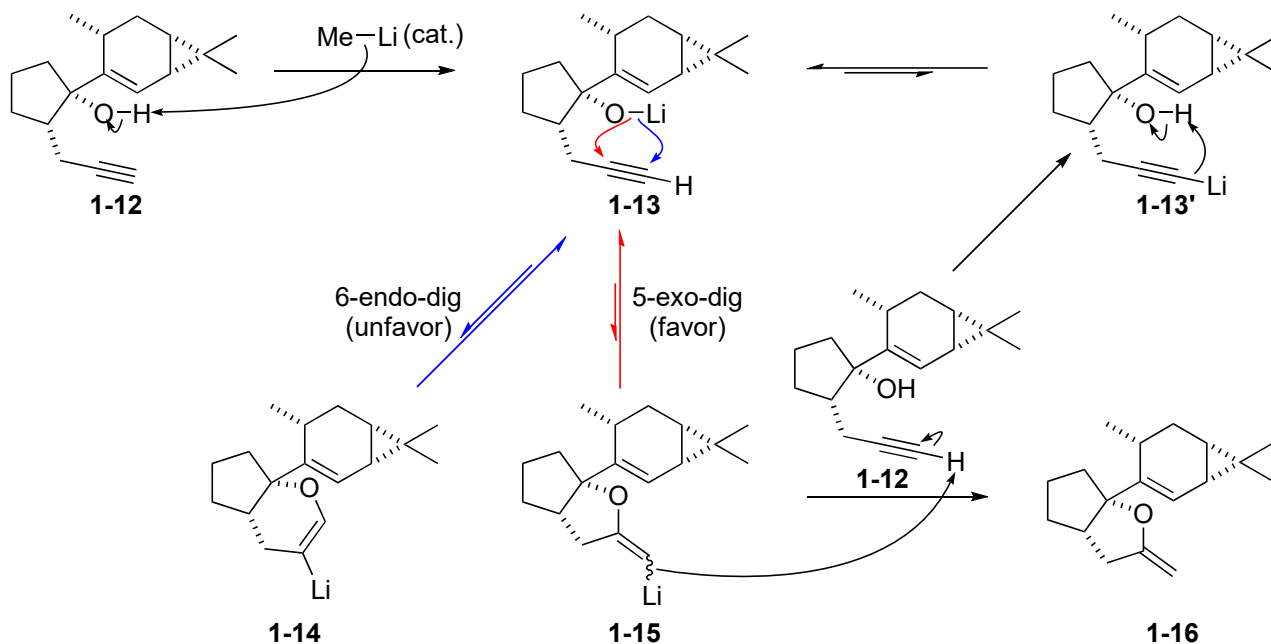


1-1. Reaction mechanism

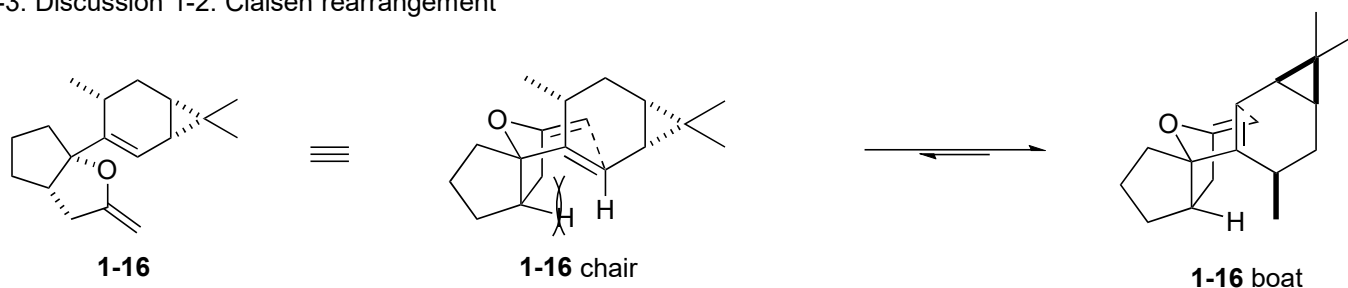




1-2. Discussion 1-1: 5-exo-dig cyclization



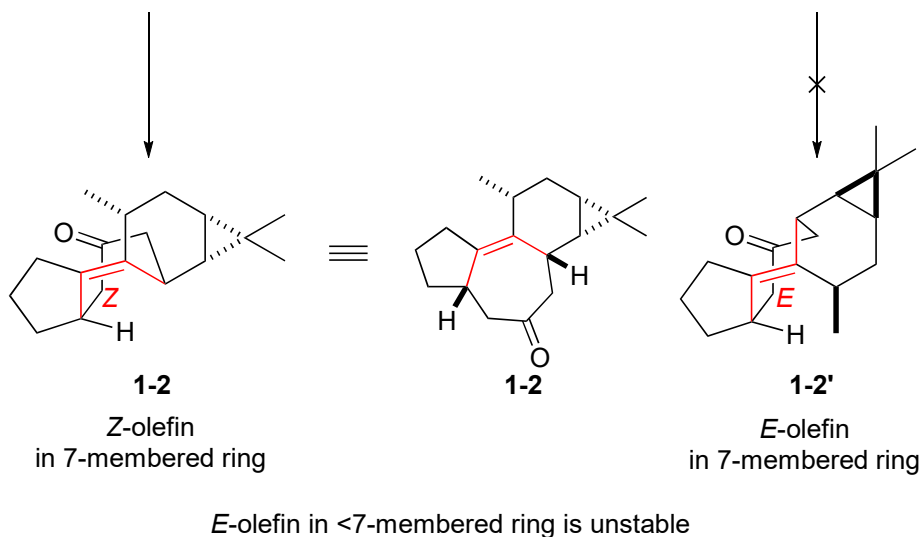
1-3. Discussion 1-2: Claisen rearrangement



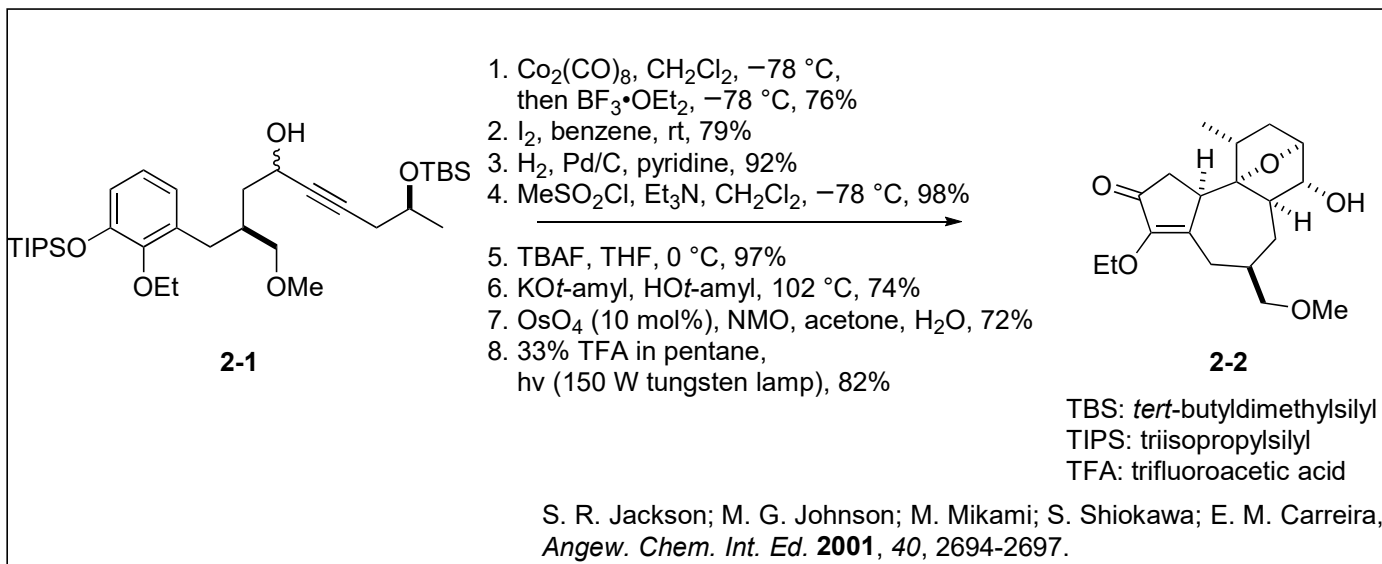
Relative stability of *E*- and *Z*-cycloalkenes²⁾

ΔH (kcal/mol)

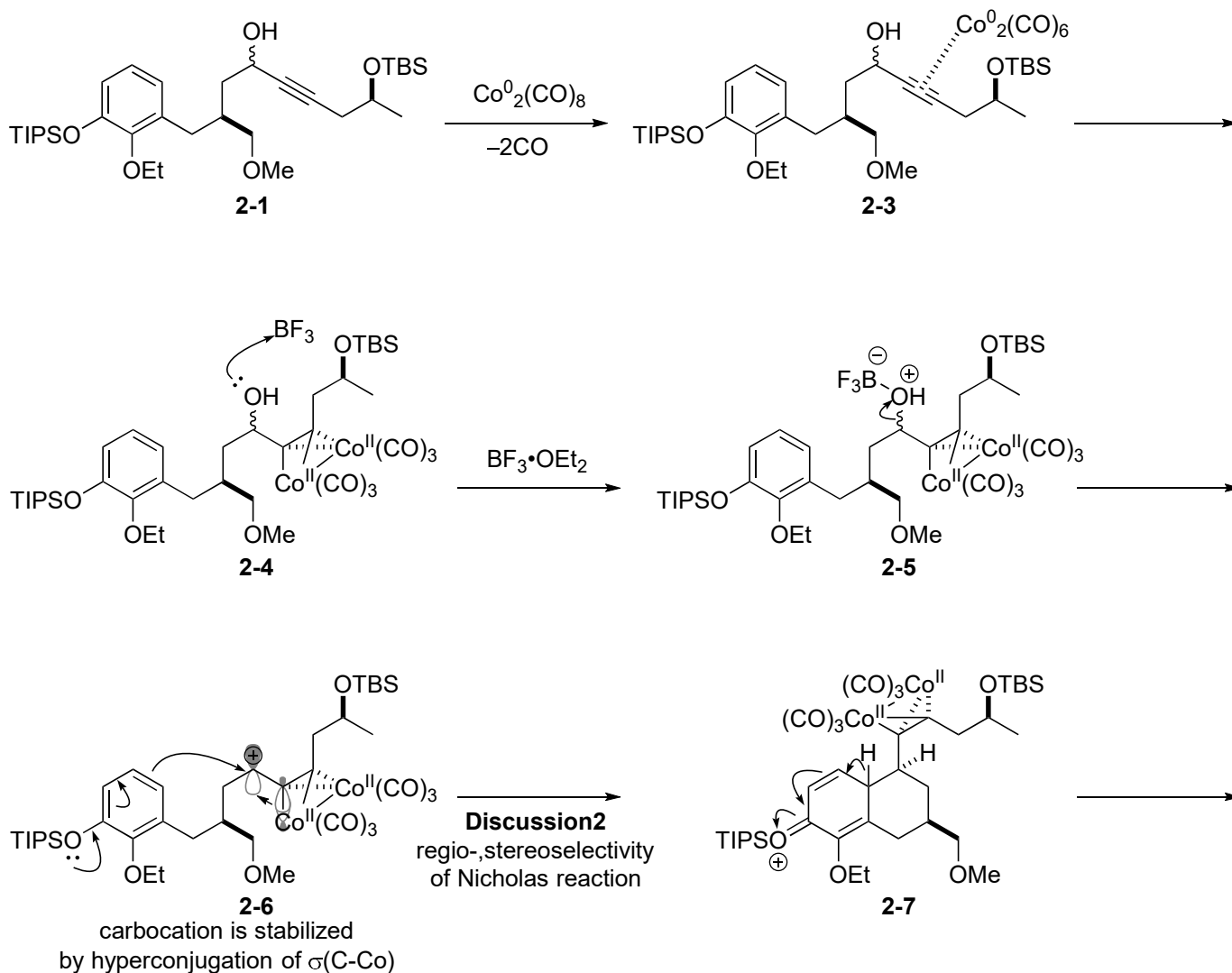
cycloalkene	$\Delta H^\circ (E \rightleftharpoons Z)$ (kcal/mol)
7	-20.3
8	-9.7
9	-2.8
10	-3.5
11	+0.1
12	+0.4

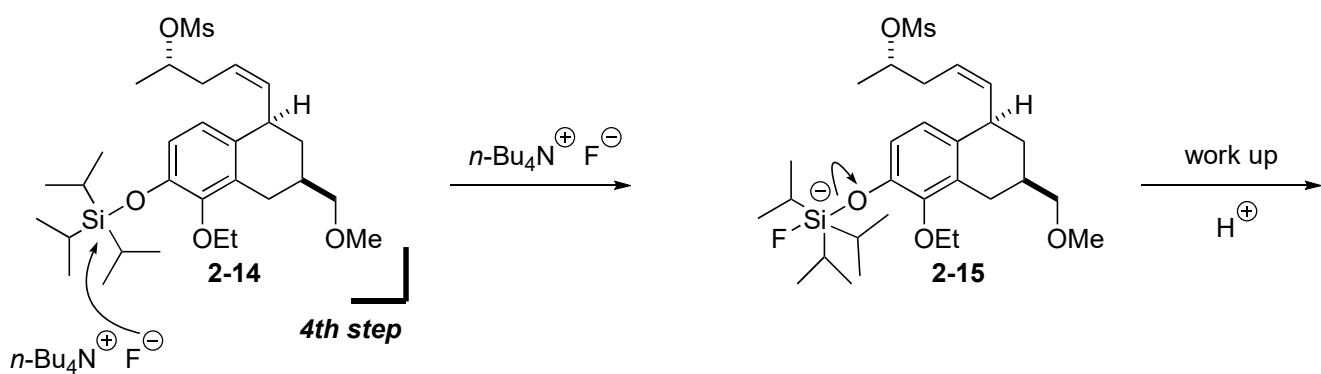
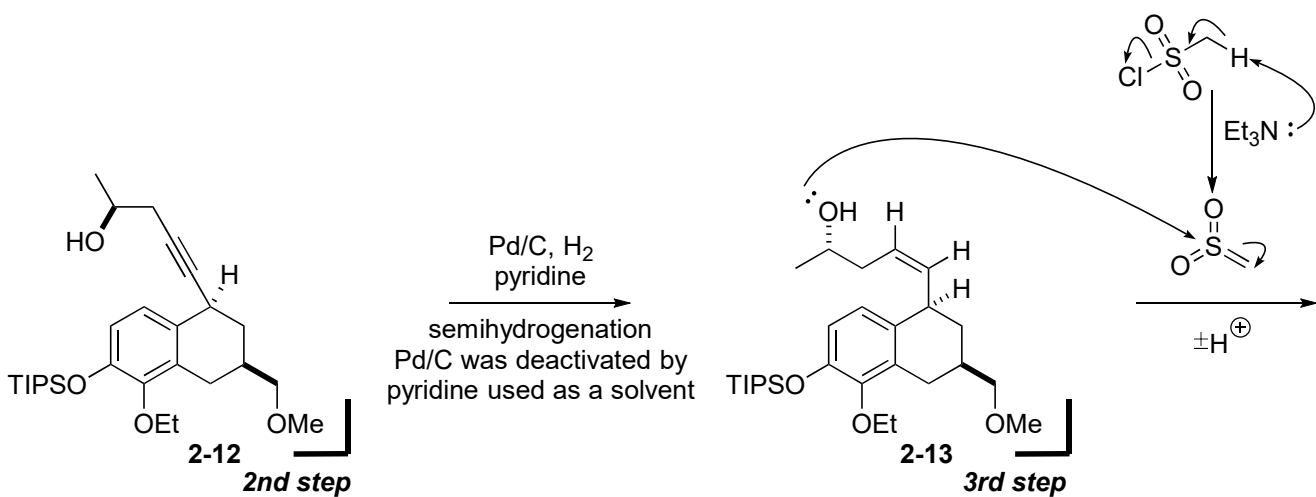
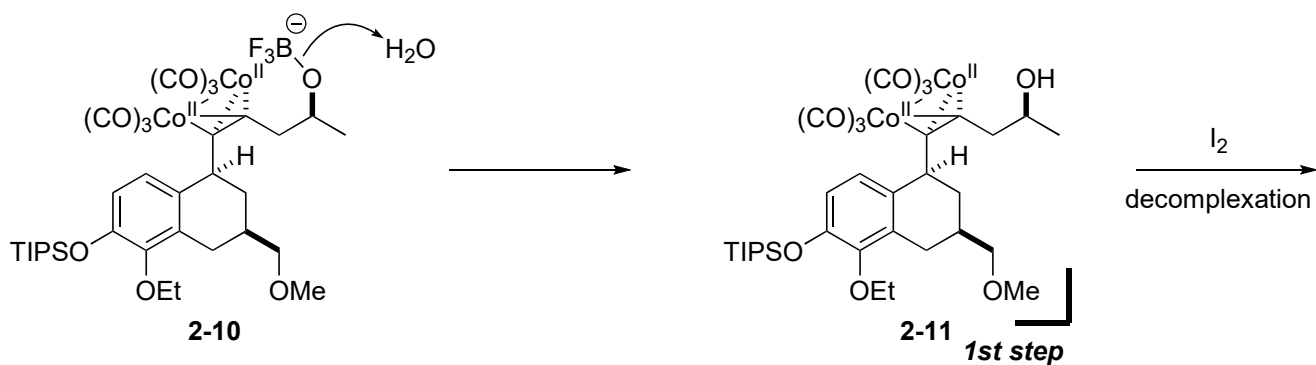
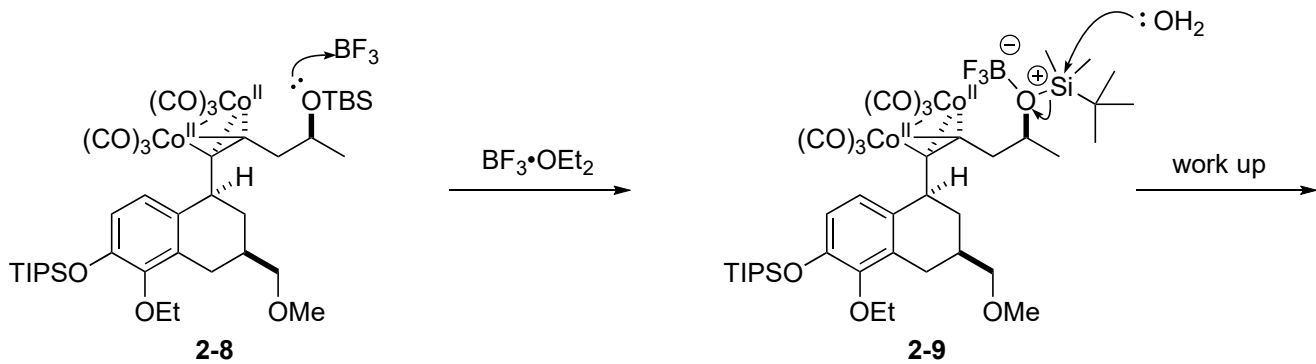


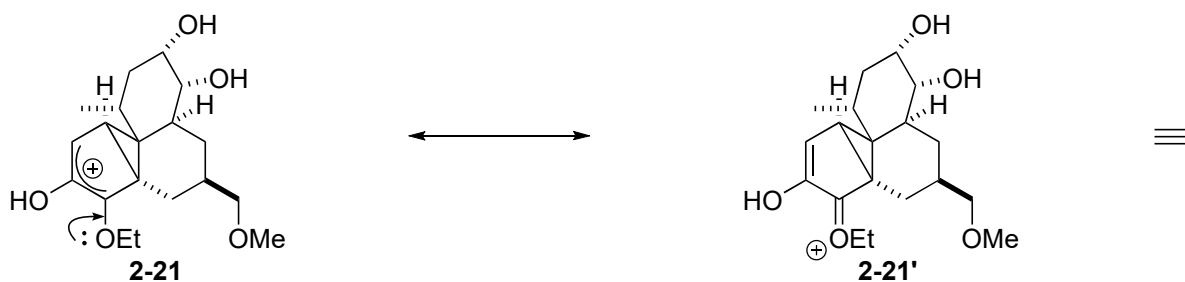
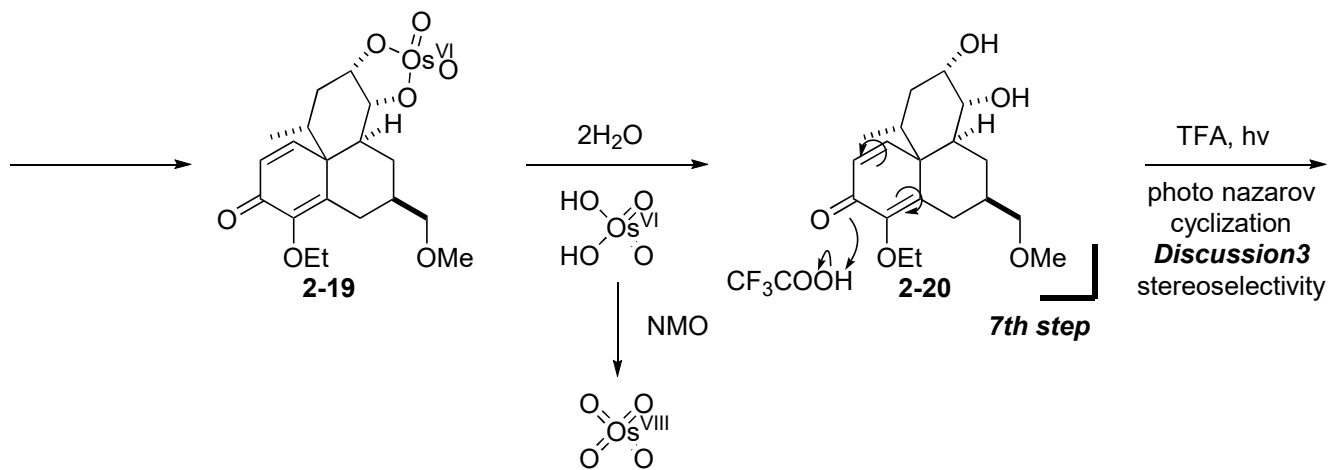
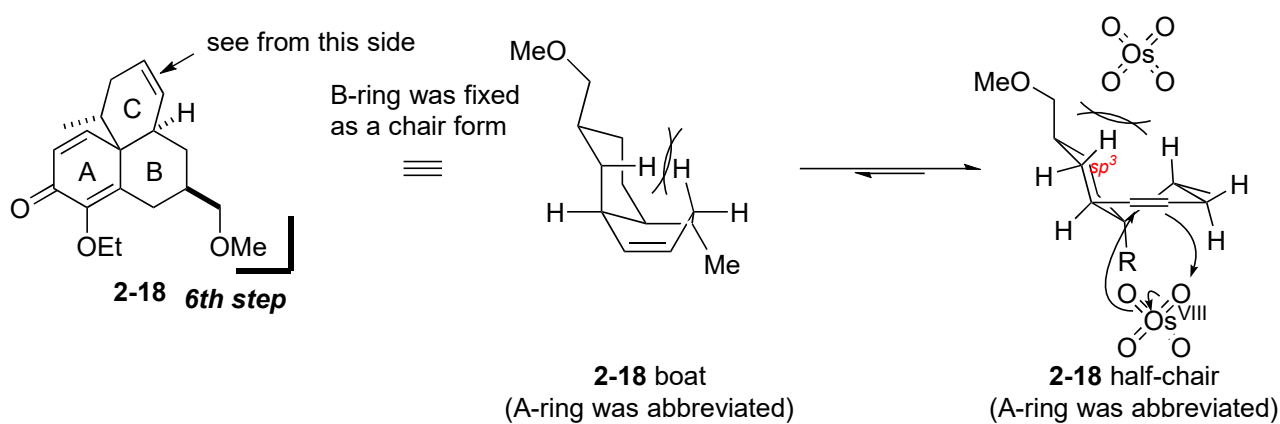
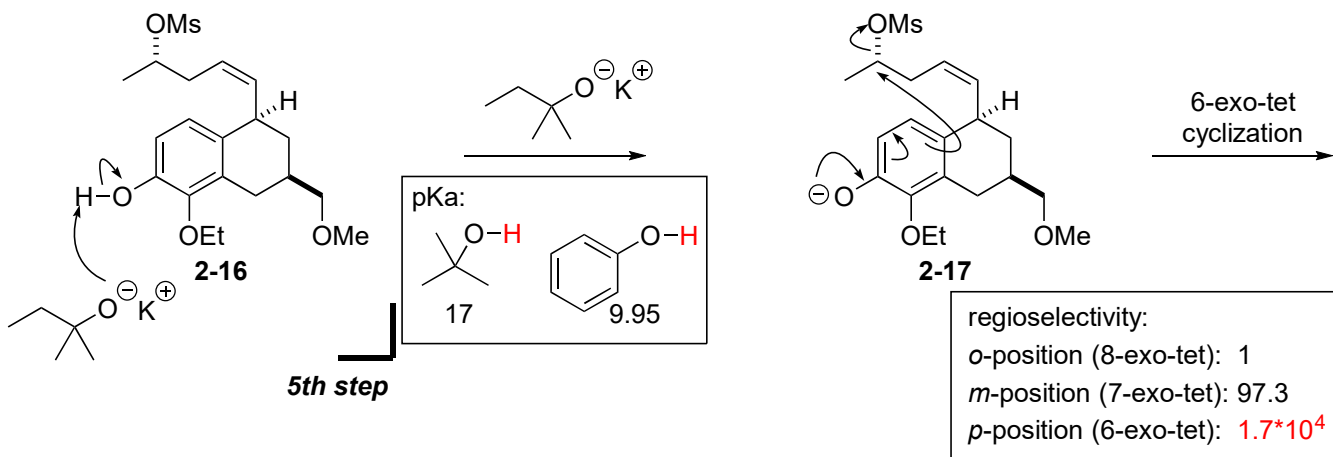
2. resiniferatoxin-type 5/7/6-ring system by Carreira's group

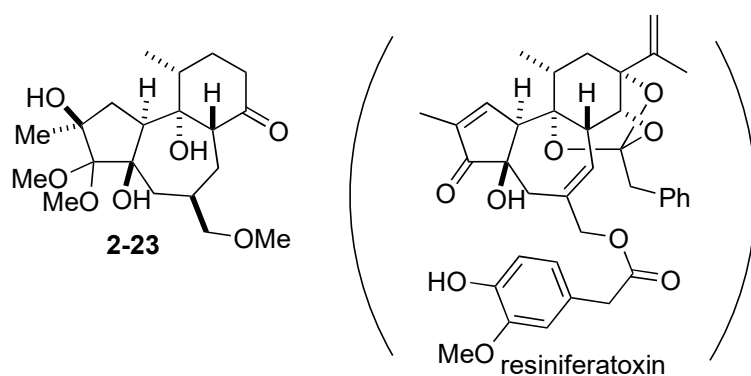
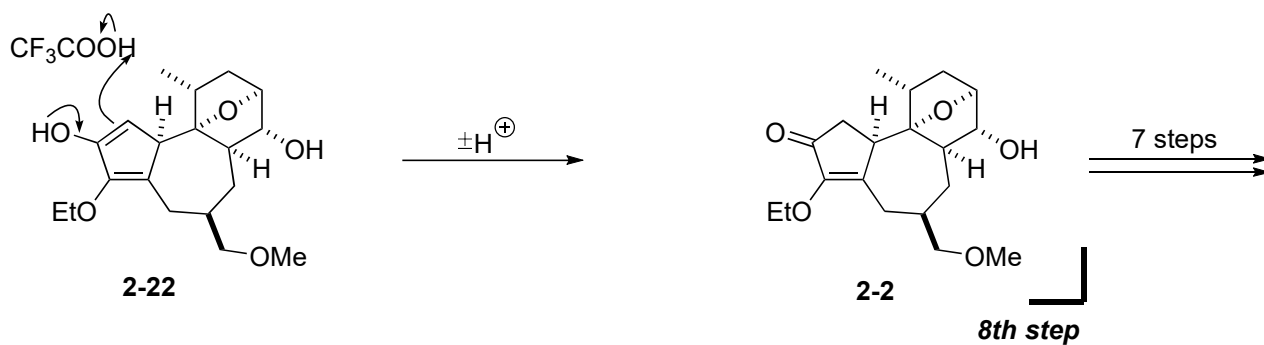
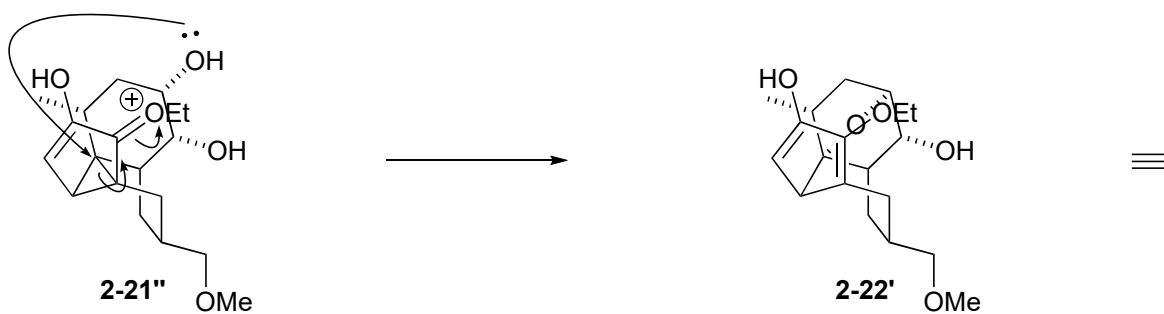


2-1. Reaction mechanism

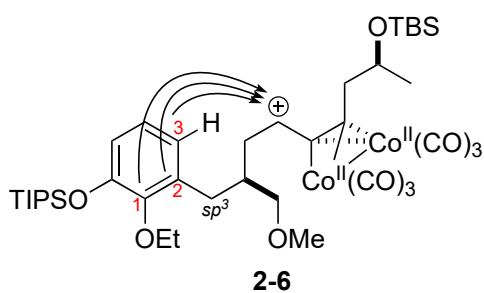




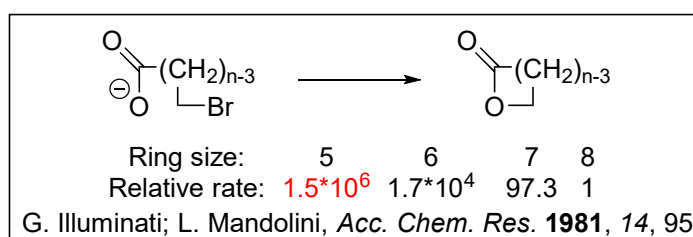




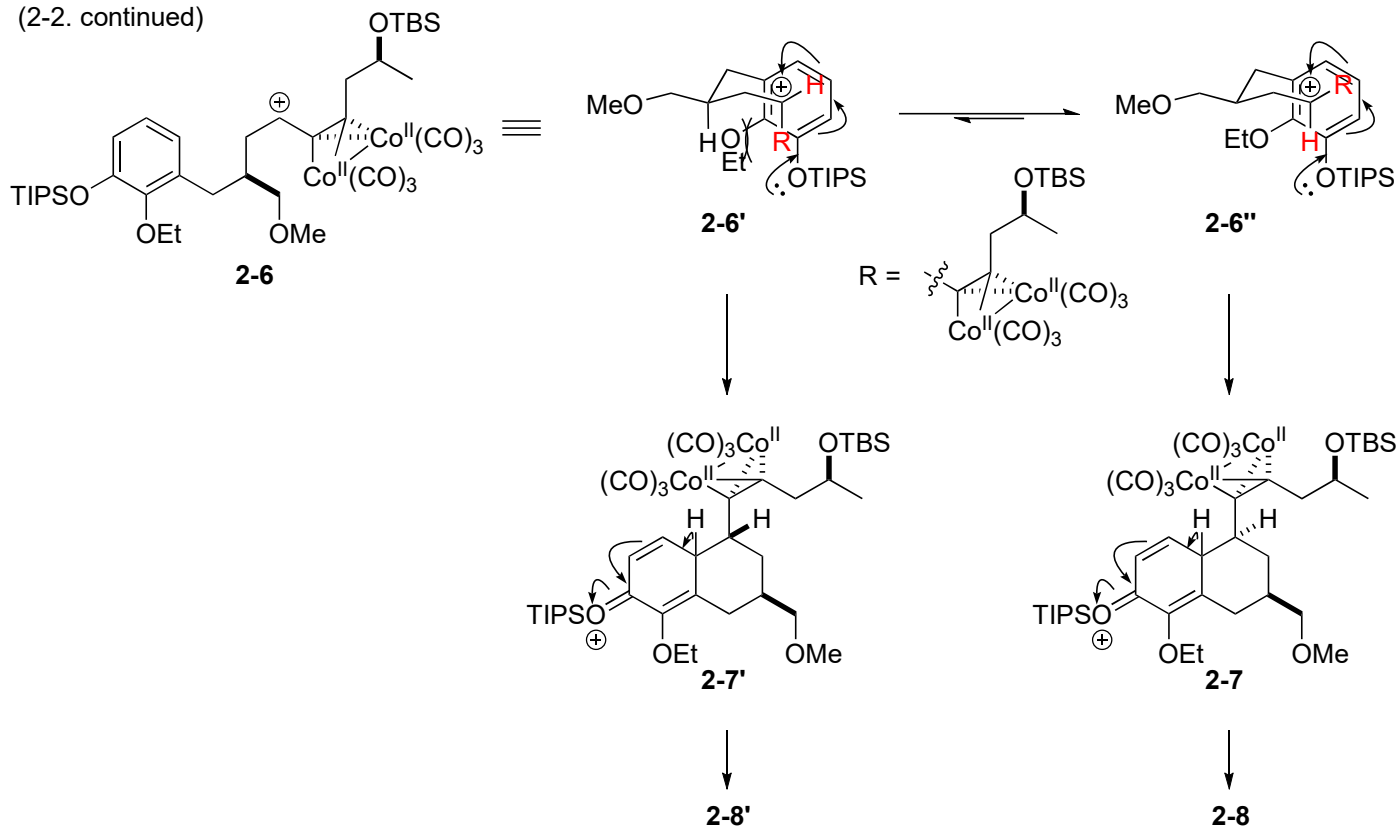
2-2. Discussion 2: regio-, stereoselectivity of Nicholas reaction



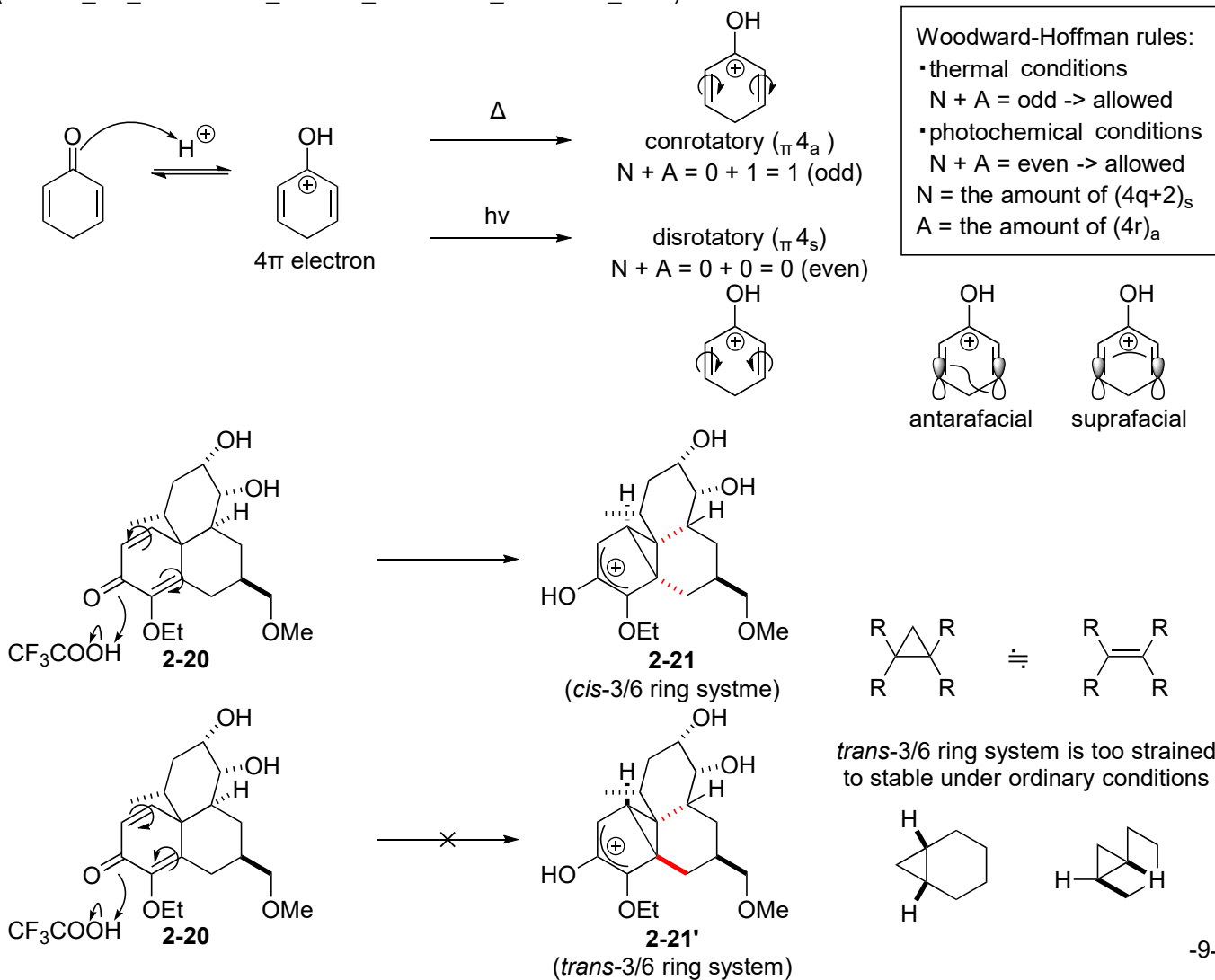
- cyclization rate: 2 (5) > 1 (6) = 3 (6)
- steric effect: 2 (C_{sp^3}) > 1 (OR) > 3 (H)
- electronic effect: 3 > 2 > 1
- conjugative effect: 1 \approx 3 \geq 2 (OTIPS \geq OMe)
- inductive effect: 1 > 2 > 3
- > steric effect and electronic effect were dominant



(2-2. continued)



2-3. Discussion 3: Stereoselectivity of photo Nazarov cyclization
(150509_PS_Shunichiroh_KATOH_Woodward_Hoffmann_rules)



References:

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- 2) N. L. Allinger; J. T. Sprague, *J. Am. Chem. Soc.*, **1972**, *94*, 5734.
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