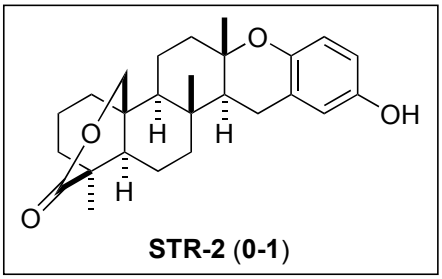
Problem Session (5) Answer

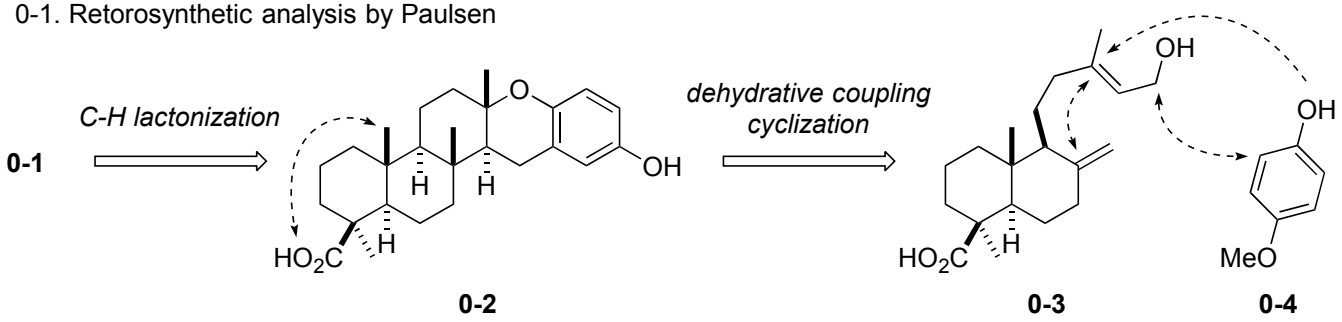
2016/7/23 Satoshi Hashimoto

Strongylophorine-2
Isolation & structural determination: from *Strongylophora durissima*
Breakman, J. C. et al. *Bull. Soc. Chem. Belg.* **1978**, *87*, 917.
Biological Activity: HIF-1 inhibition (EC_{50} 8 μM)
Ireland, C. M. et al. *J. Med. Chem.* **2008**, *51*, 1402.
Total Synthesis:
Poulsen, T. B. et al. *Angew. Chem. Int. Ed.* **2016**, *55*, 8294.



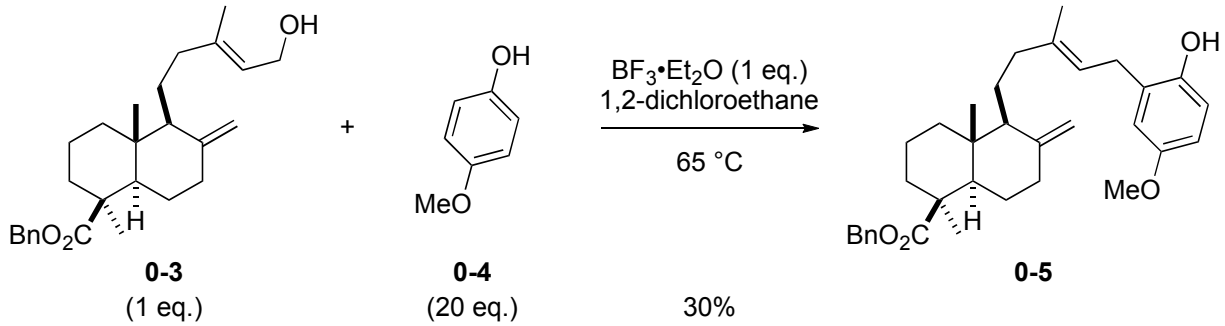
STR-2 (**0-1**)

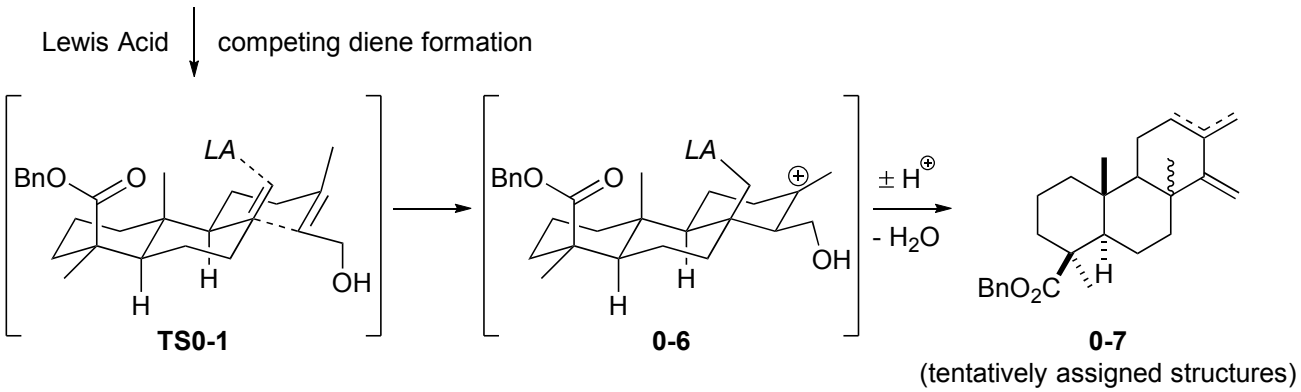
0-1. Retorosynthetic analysis by Paulsen



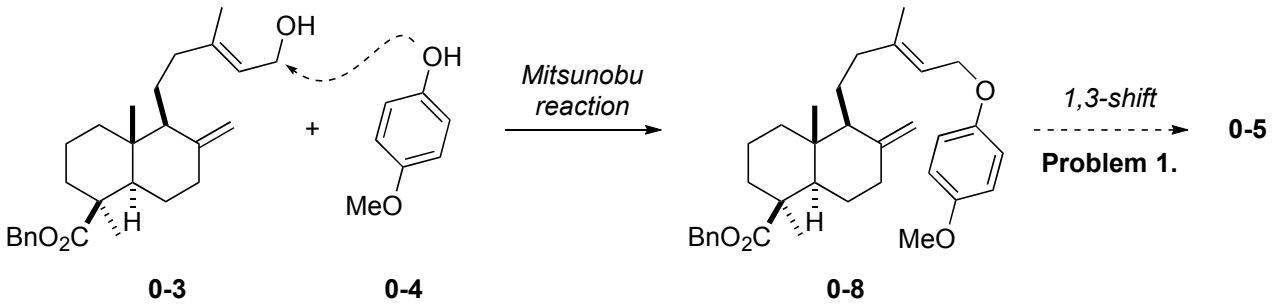
Poulsen, T. B. et al. *Angew. Chem. Int. Ed.* **2016**, *55*, 8294.

0-2. Initially attempted dehydrative coupling

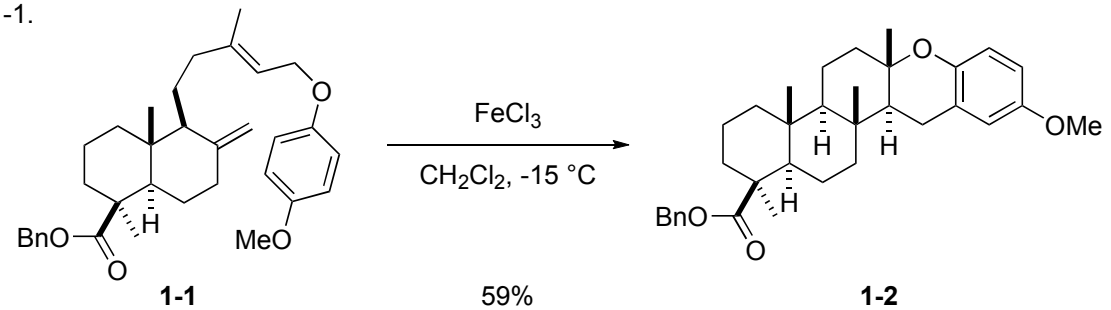




0-3. Alternative synthetic plan



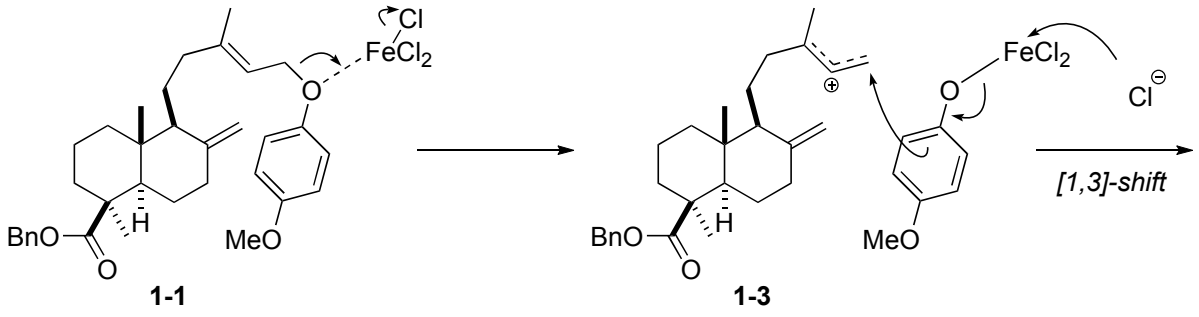
1-1.



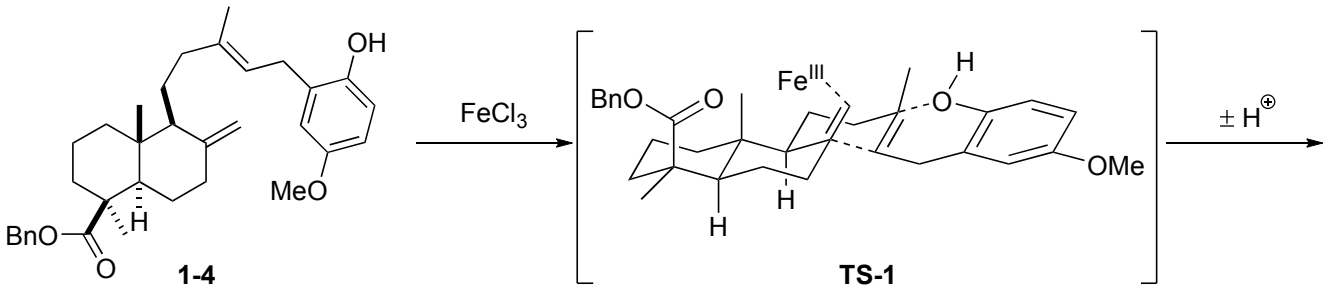
1-1 59% **1-2**

Answer:

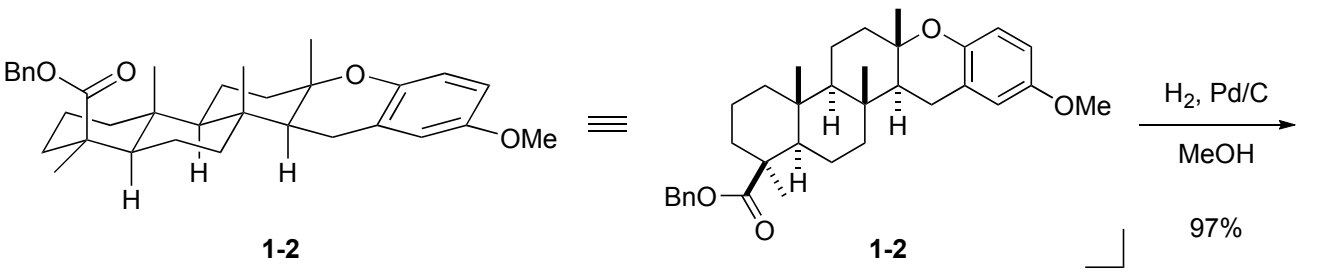
1-1. **1-1**→**1-2**



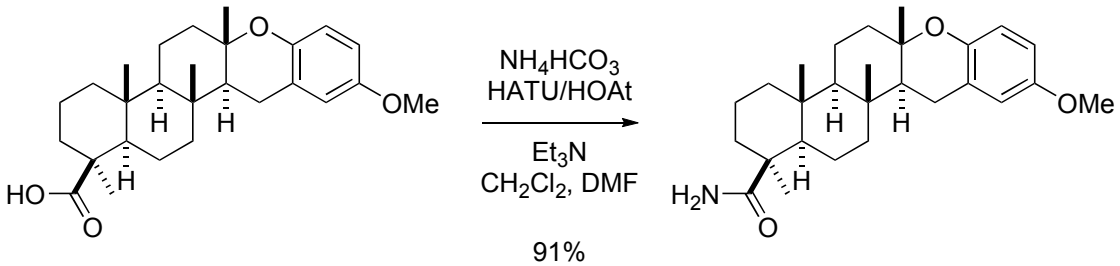
1-1 **1-3**



1-4 **TS-1**



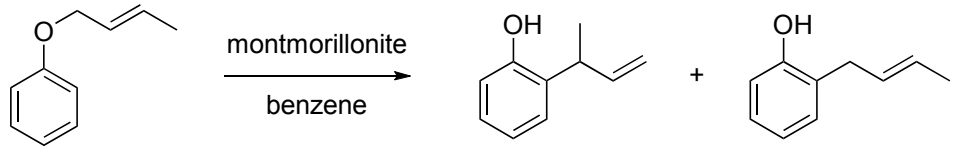
1-2 **1-2**



1-5 **1-6**

Discussion: 1,3-allyl shift

1-2. [1,3] vs [3,3] rearrangement



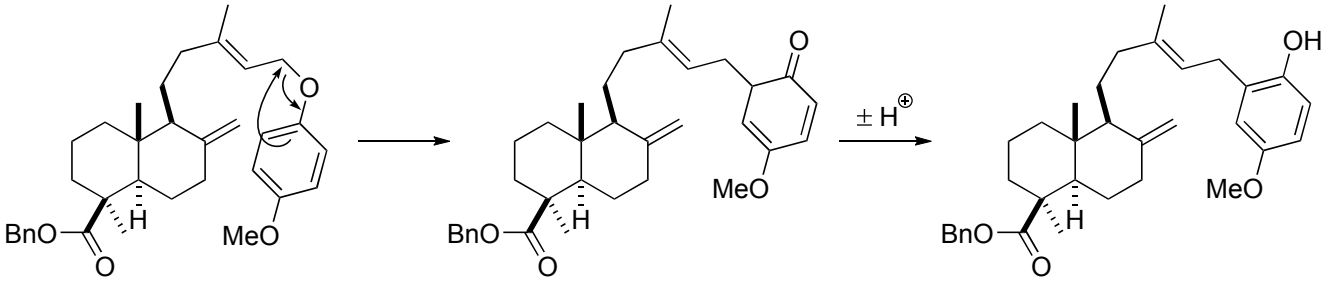
1-7 **1-8** [3,3] **1-9** [1,3]

50%

(**1-8**:**1-9** = 1.3:1)

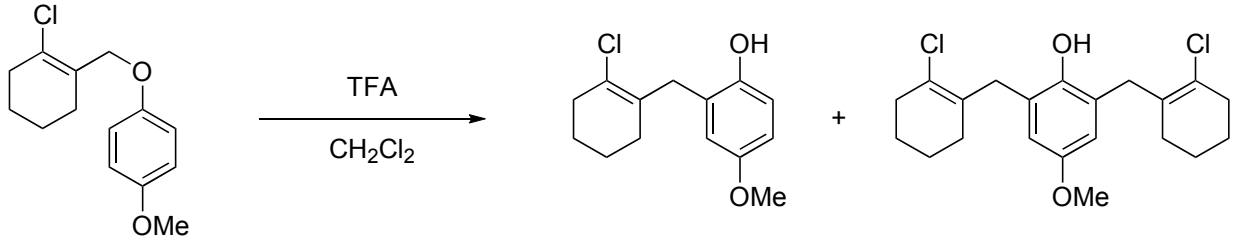
Dauben, W. G.; Cogen, J. M.; Behar, V. *Tetrahedron Lett.* **1990**, *31*, 3241.

1-3. Concerted pathway



1-1 **1-10** **1-4**

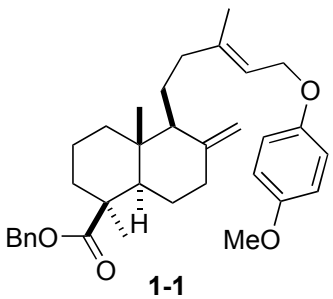
1-4. Formation of diallylated product supported stepwise pathway



1-11 **1-12** 70% **1-13** <5%

Geetha, N.; Balasubramanian, K. K. *Tetrahedron Lett.* **1998**, *39*, 1417.

1-5. Experimental result:

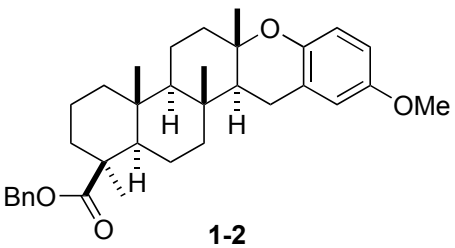


1-1

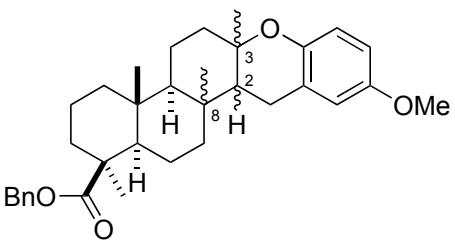
LA (2 eq.)

CH_2Cl_2

0 °C, 30 min

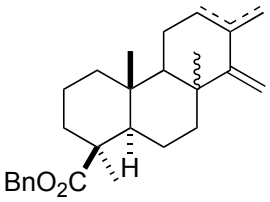


1-2



1-2b,c,d

(stereoisomers at C2, C3, C8)

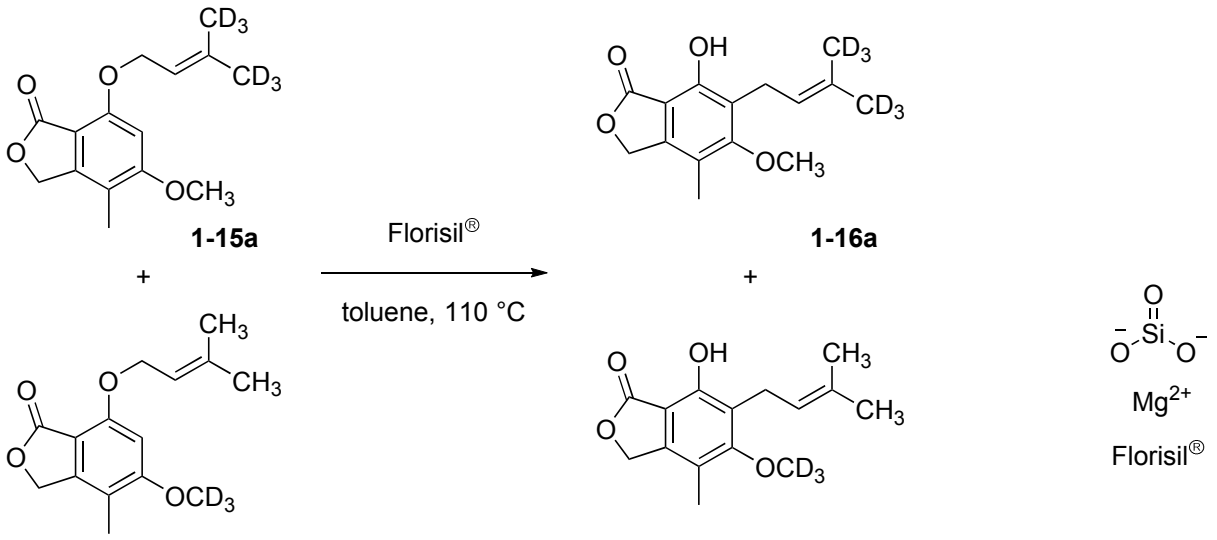


1-14

(eliminated products)

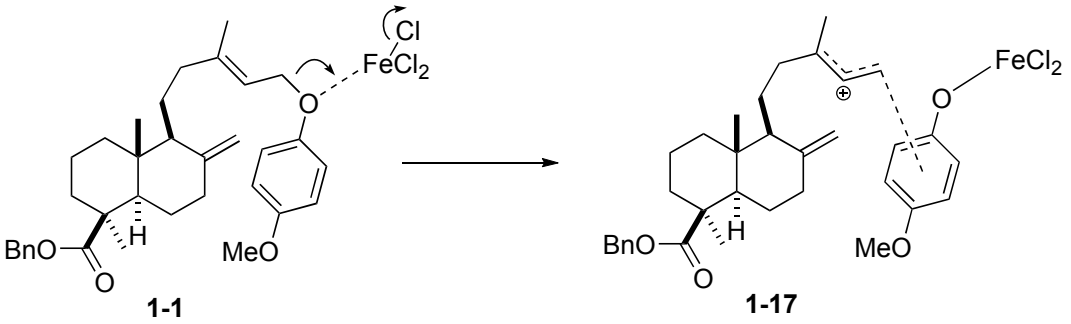
entry	LA	**1-2**/**1-2b-d**/**1-14**
1	$SnCl_4$	21:19:60
2	$InBr_3$	66:23:11
3	$FeCl_3$	48:24:28

1-6. Crossover experiment: reaction is intramolecular.



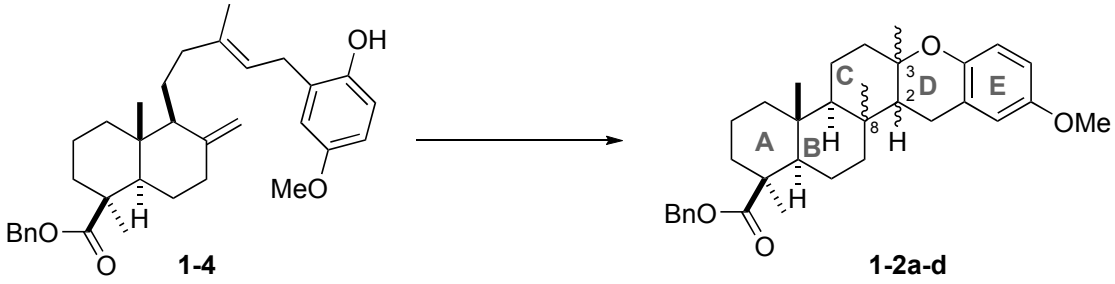
Talamás, F. X. et al. *Tetrahedron Lett.* **1997**, *38*, 4725.

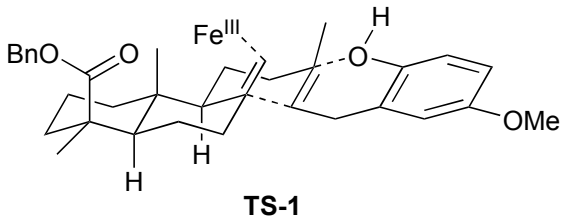
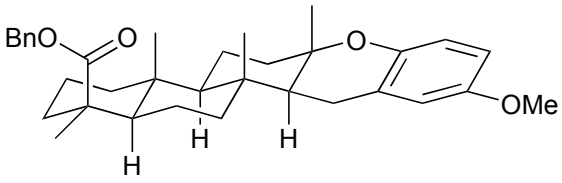
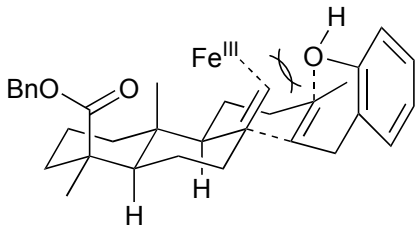
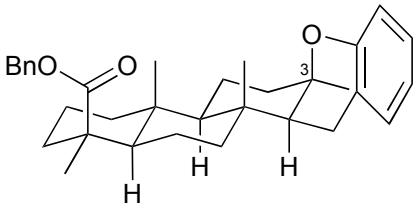
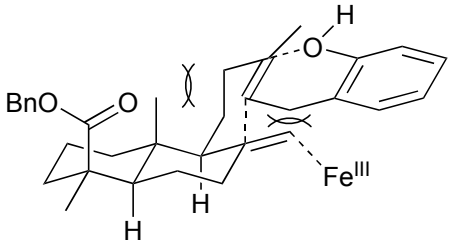
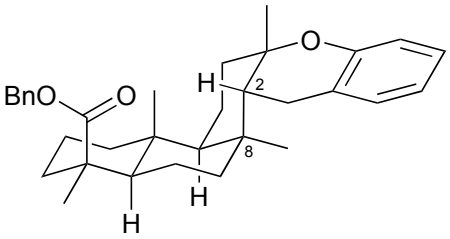
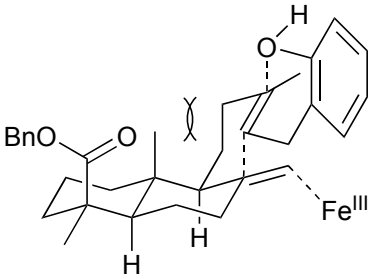
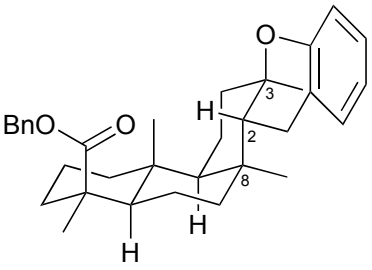
1-7. Possible cation-π interaction:



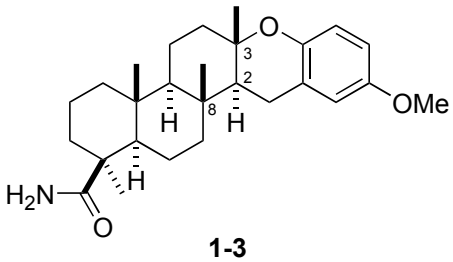
Cation-π interaction could improve the yield of 1,3 rearrangement.

1-8. Explanation of stereoselectivity of polycyclization



transition state	→ product	
 **TS-1**	 **1-2**	favor
 **TS-2**	 **1-2b** (C3 epimer)	unfavor
 **TS-3**	 **1-2c** (diastereomer at C2,8)	
 **TS-4**	 **1-2d** (diastereomer at C2,3,8)	

1-2.

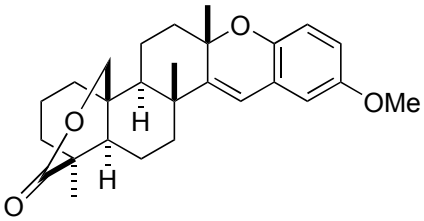


1-3

$Pb(OAc)_4$, I_2, $h\nu$, benzene;

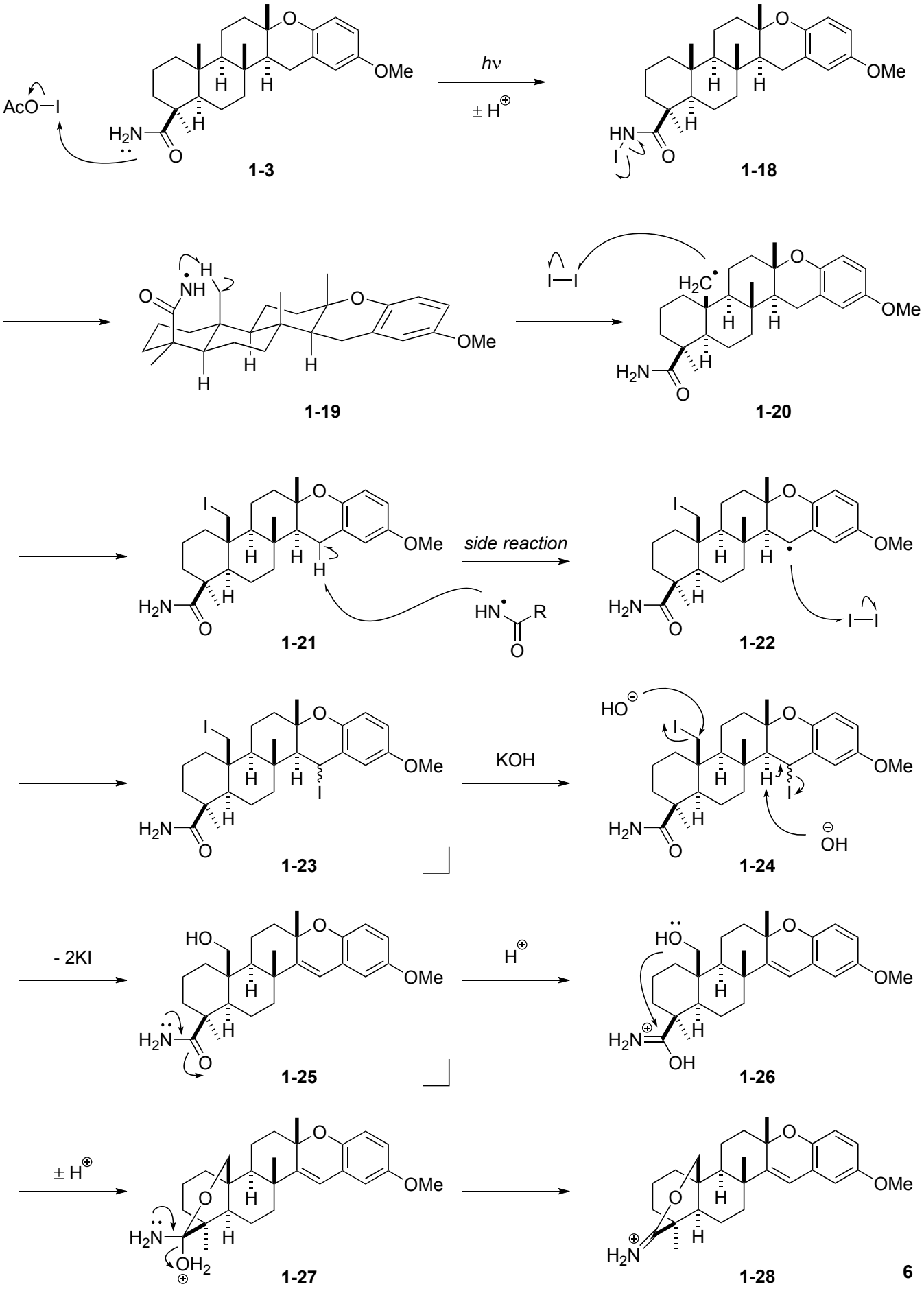
KOH, MeOH, reflux;
aq. HCl, CH_3CN, 100 °C

58%

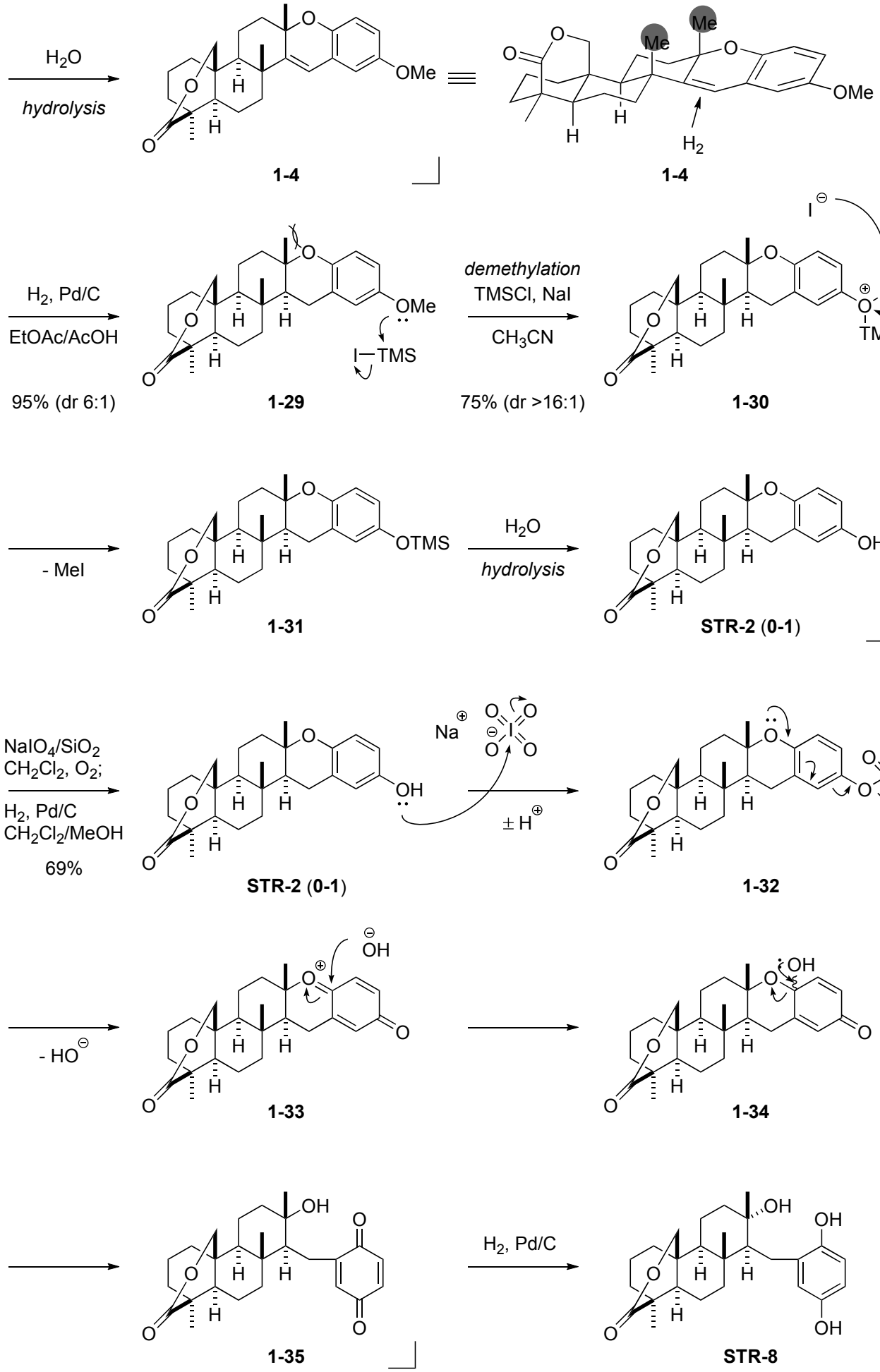


1-4

Answer: 1-9. **1-3**→**1-4**



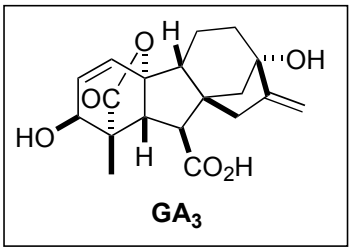
1-10. Total synthesis of STR-2 and STR-8



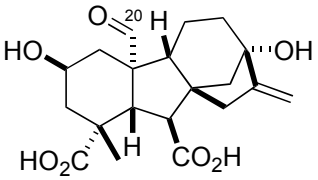
Dixson, D. D.; Lockner, J. W.; Zhou, Q.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 8432.

2. Total synthesis of gibberellic acid (GA_3)

gibberellic acid (GA_3)
Isolation: from *Gibberella fujikuroi*
Yabuta, T. et al. *J. Agric. Chem. Soc. Jpn.* **1938**, *14*, 1526.
structural elucidation:
McCapra, F. et al. *Proc. Chem. Soc., London*, **1962**, 185.
Biological Activity: GID1 agonist (IC_{50} 4 μM)
Ueguchi-Tanaka, M. et al. *Nature*, **2005**, *437*, 693.
Total synthesis:
Corey, E. J. et al. *J. Am. Chem. Soc.* **1978**, *100*, 8034.
Lombardo, L.; Mander, L. N.; Turner, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6626.
Nagaoka, H.; Shimano, M.; Yamada, Y. *Tetrahedron Lett.* **1989**, *8*, 971.
many formal syntheses and syntheses of related compounds.
foe review of gibberellins: Mander, L. N. *Nat Prod. Rep.* **2003**, *20*, 49.

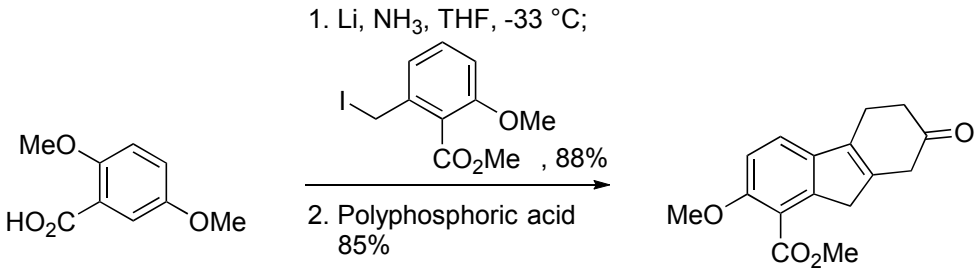


GA_3



C_{20} gibberellin (**GA_{99}**)

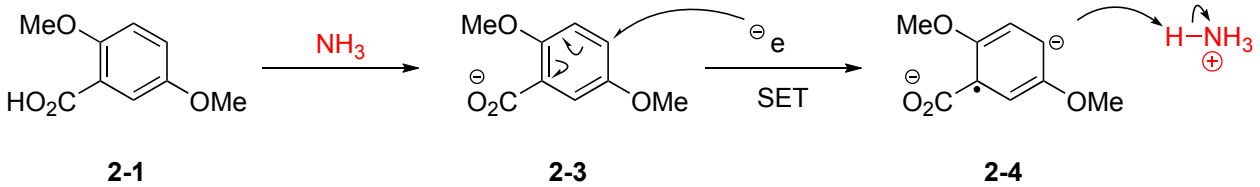
2.



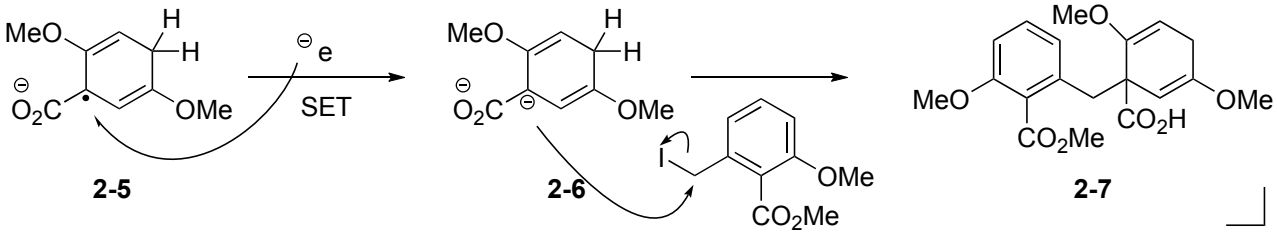
2-1 **2-2**

Hook, J. M.; Mander, L. N. *J. Org. Chem*. **1980**, *45*, 1722.

Answer:
2-1. Birch reduction

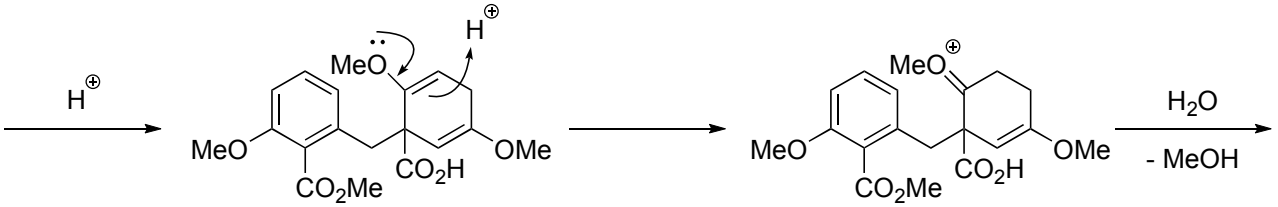


2-1 **2-3** **2-4**

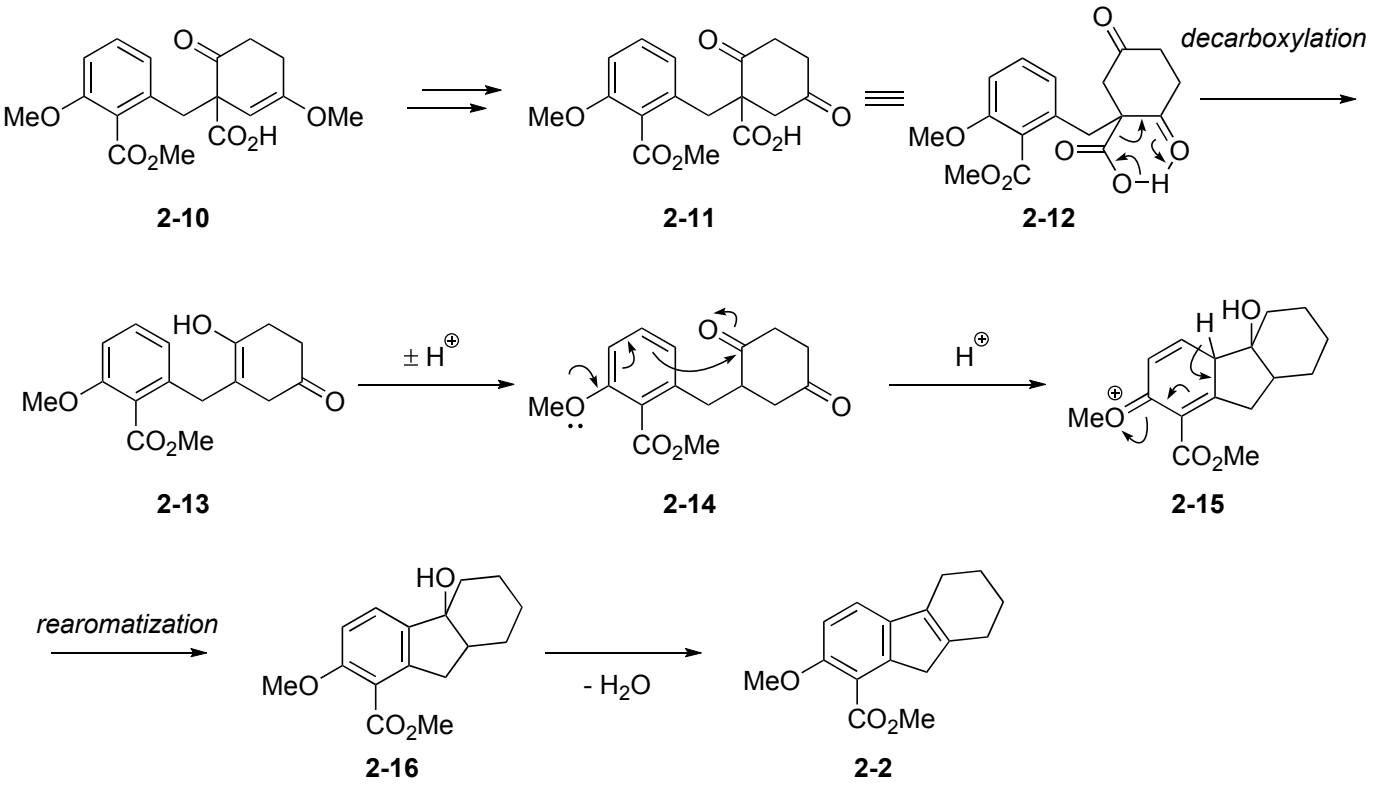


2-5 **2-6** **2-7**

2-2. Cyclization

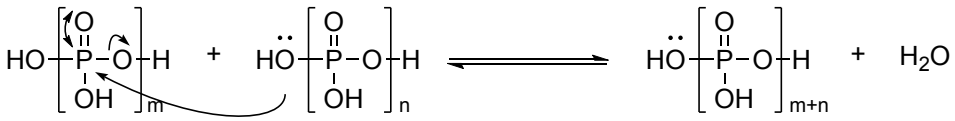


2-8 **2-9**

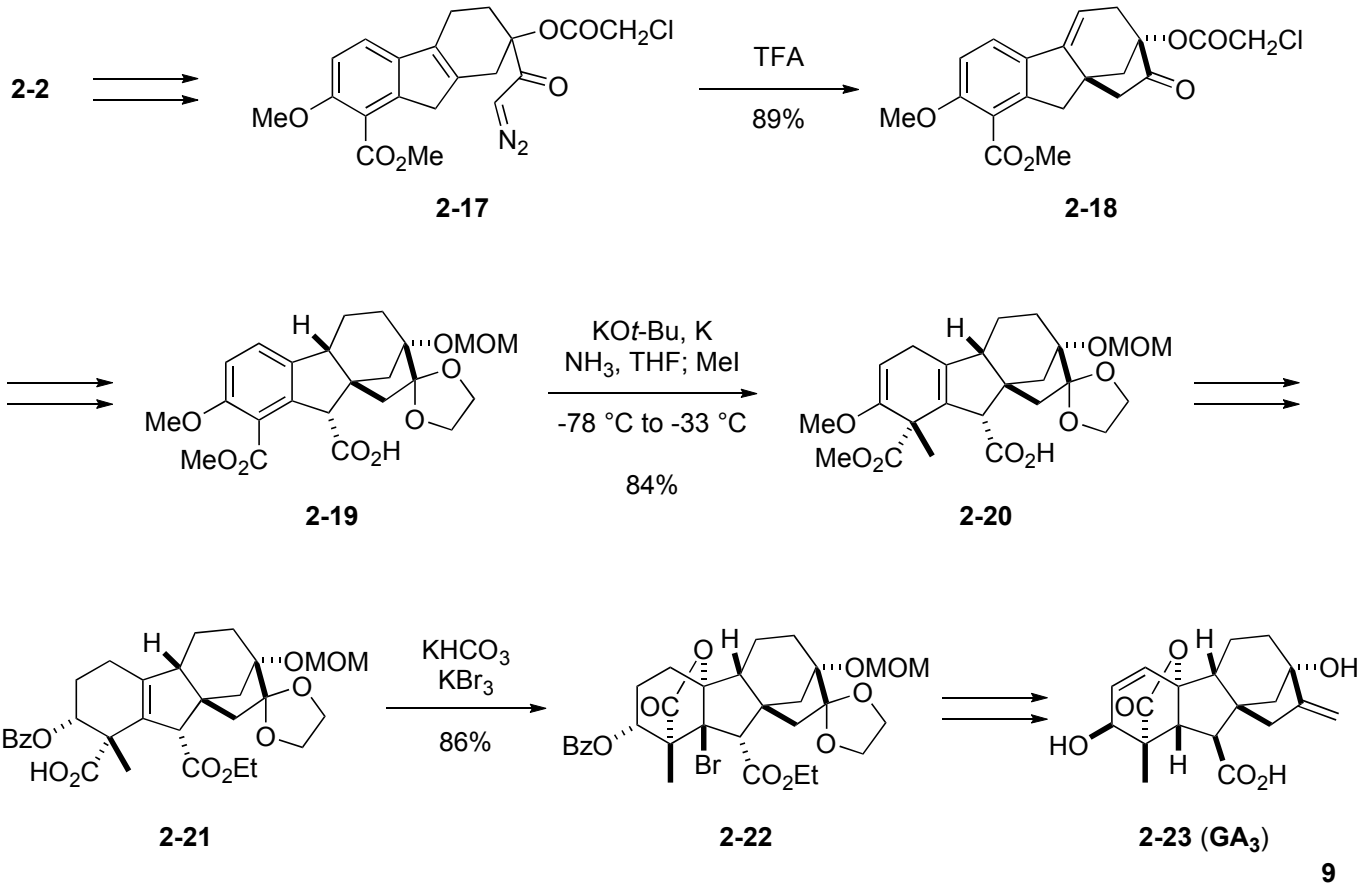


2-10 **2-11** **2-12** **2-13** **2-14** **2-15** **2-16** **2-2**

• Polyphosphoric acid



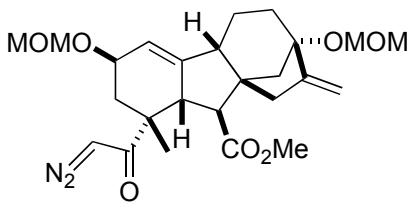
2-3. Overview of Mander's GA_3 synthesis:



2-17 **2-18** **2-19** **2-20** **2-21** **2-22** **2-23** (**GA_3**)

3. Transformation of C_{19} GA to C_{20} GAs

3.

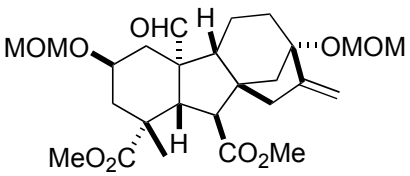


3-1

1. $Cu(acac)_2$, $(ClCH_2)_2$ reflux, 58%
2. Li, NH_3, *t*-BuOH, -78 °C
3. Dess-Martin periodinane CH_2Cl_2, 90% (2 steps)

3-2

1. KH, DMF, THF 0 °C; O_2
2. CH_2N_2 88% (2 steps)

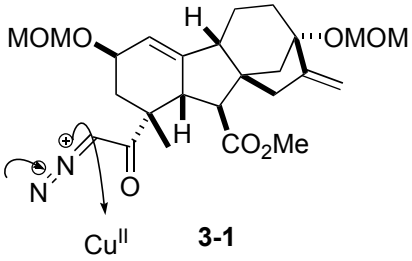


3-3

Mander, L. N.; Owen, D. J. *Tetrahedron Lett.* **1996** *5*, 723.

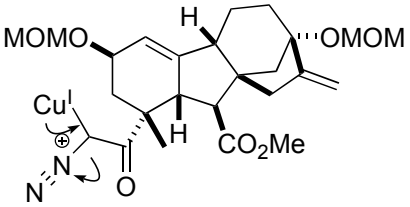
Answer:

3-1. **3-1**→**3-2**



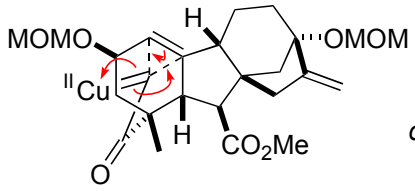
3-1

$Cu(acac)_2$



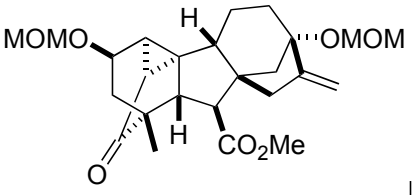
3-4

$-N_2$



3-5

cyclopropanation

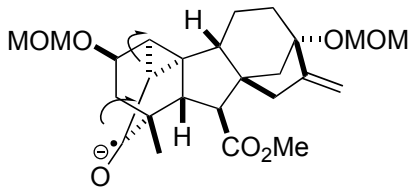


3-6

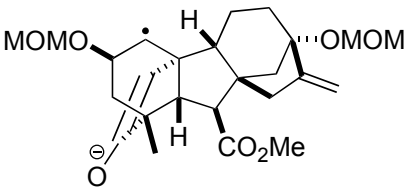
Birch reduction

Li/NH_3

$^{\ominus}e$

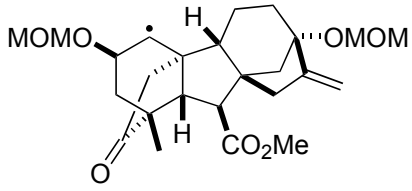


3-7



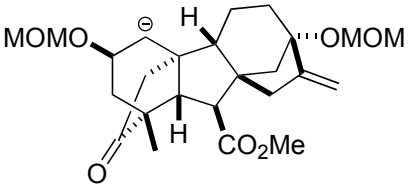
3-8

t-BuOH



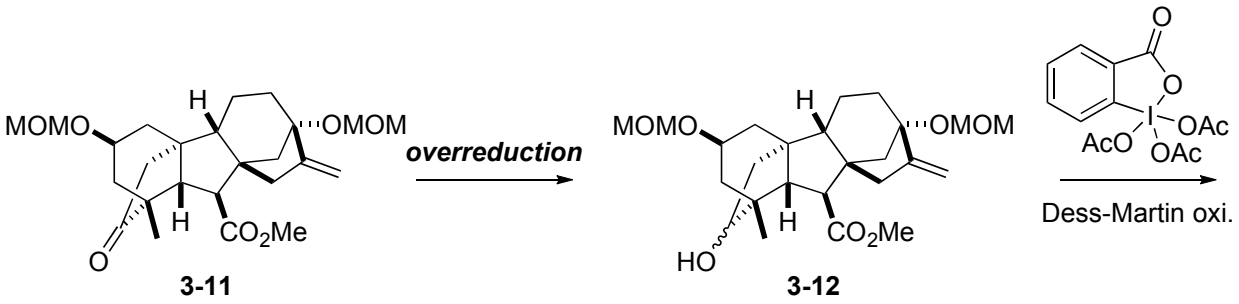
3-9

$^{\ominus}e$

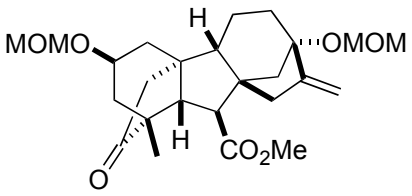


3-10

t-BuOH

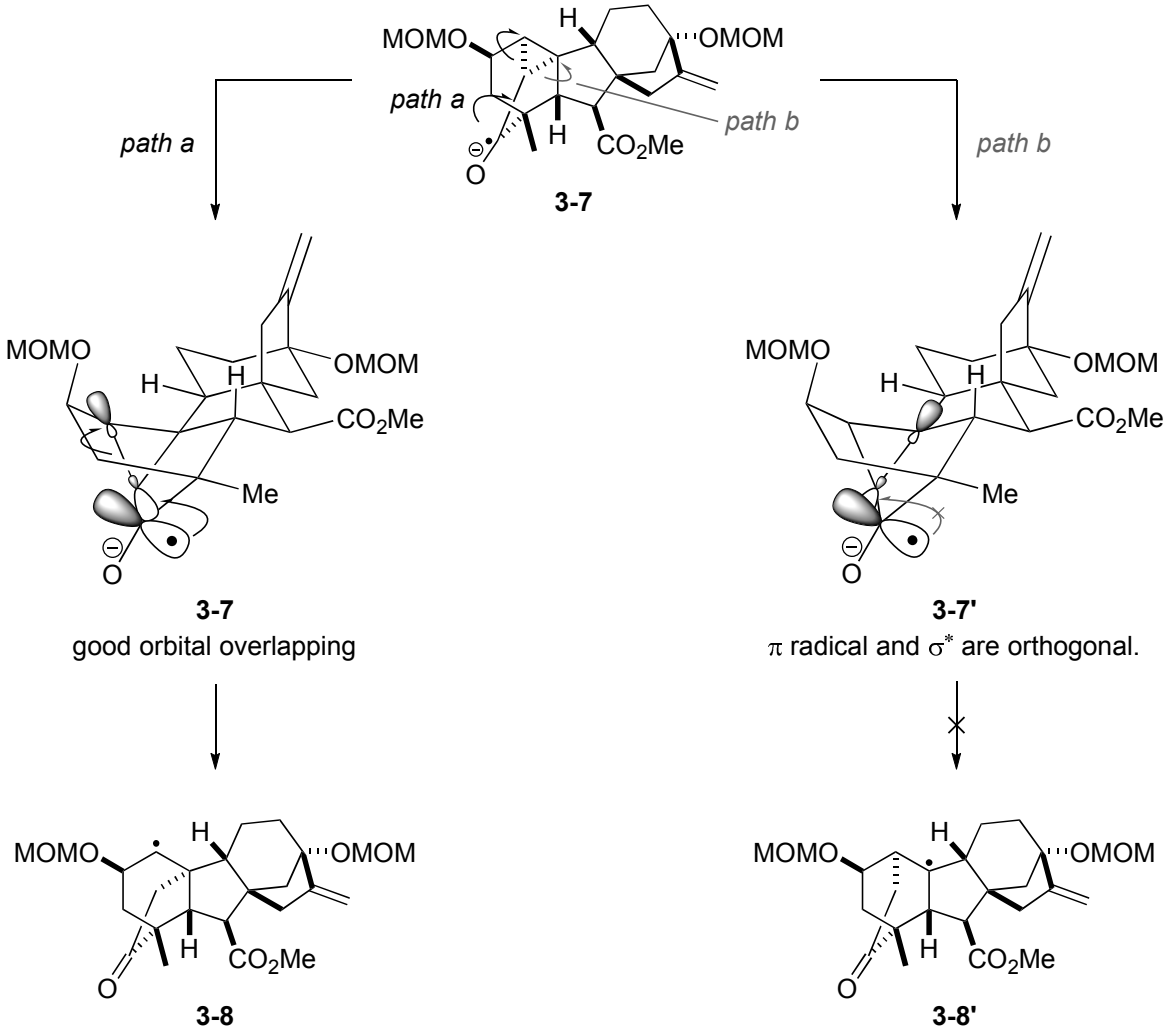


3-11 **3-12**



3-2

3-2. Selective cleavage of cyclopropane



3-7

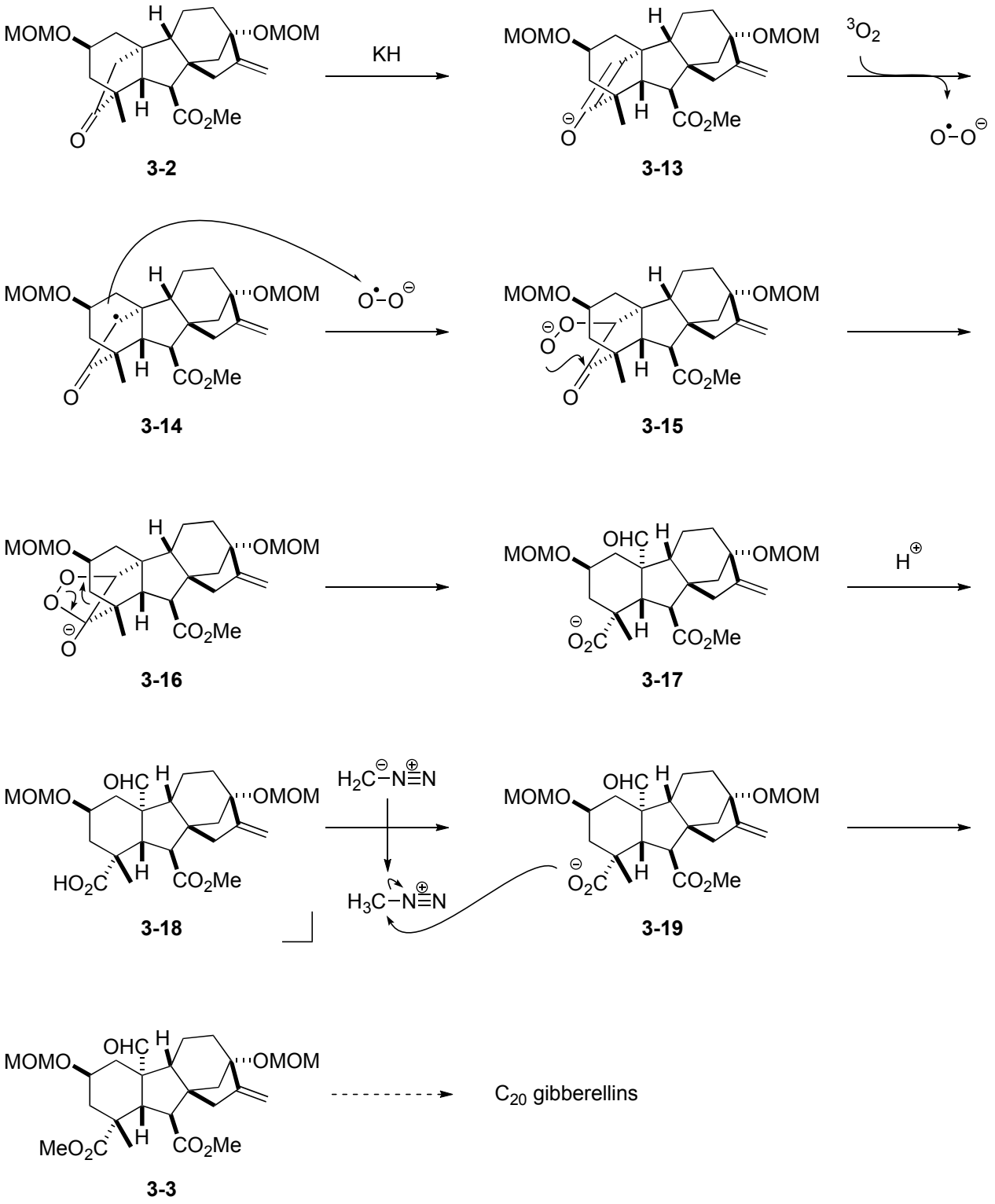
good orbital overlapping

3-7'

π radical and σ* are orthogonal.

3-8 **3-8'**

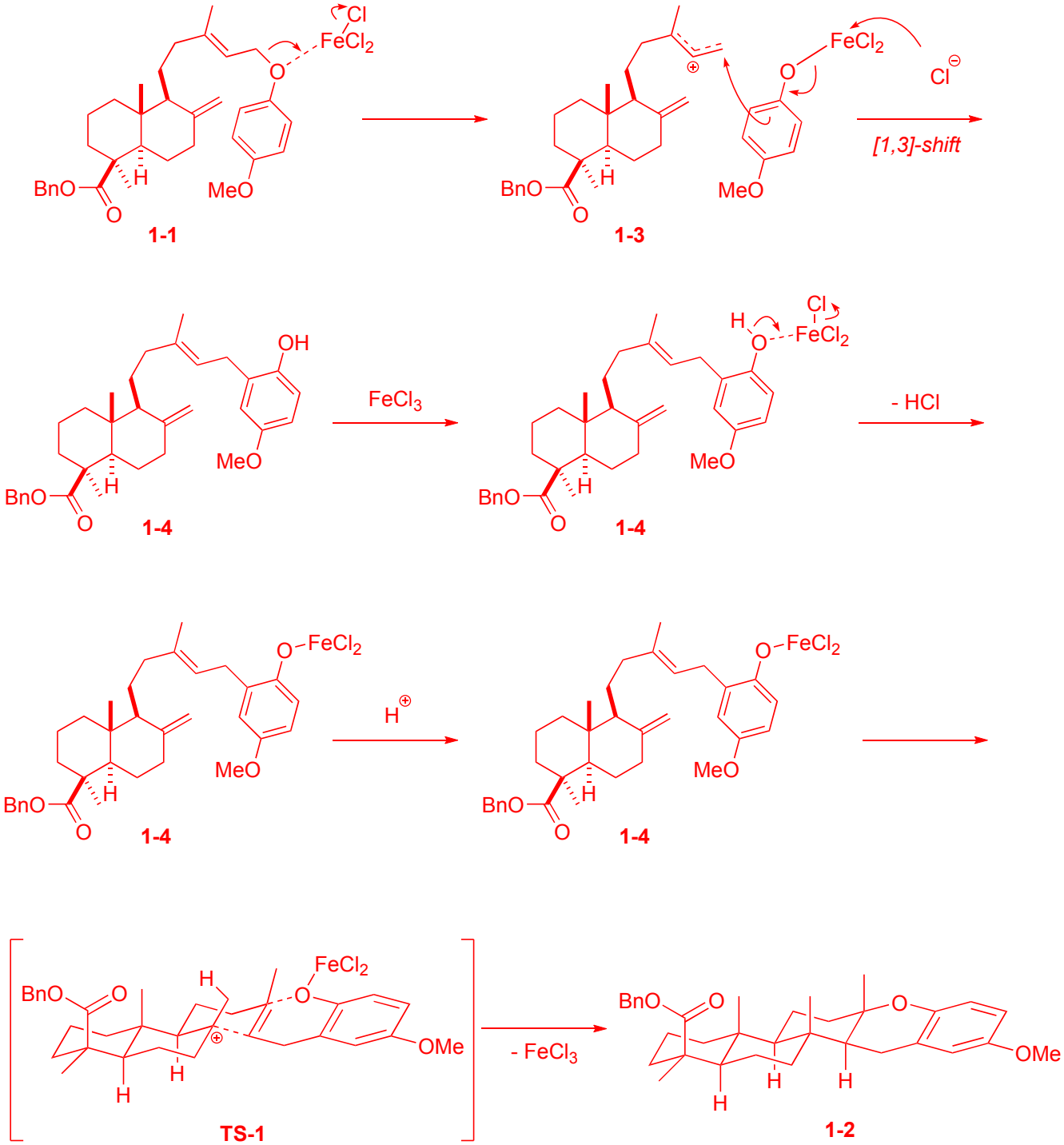
3-3. **3-2→3-3**



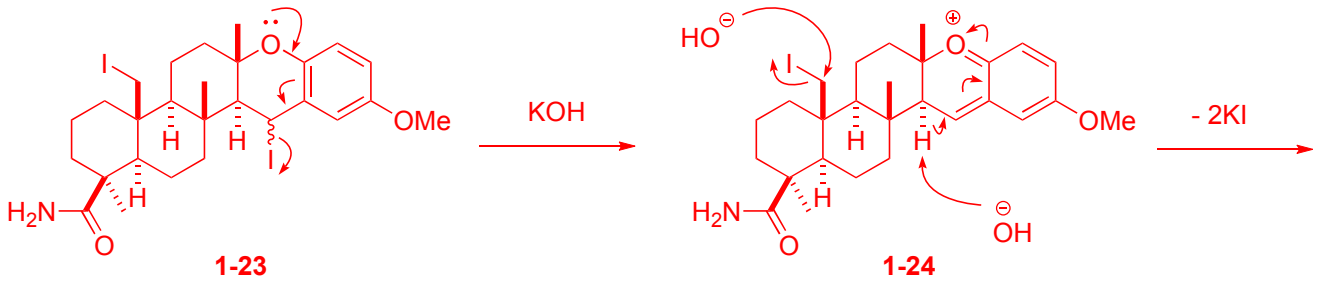
For related enolate oxidation: 100703_LS_Tamaki_HOSHIKAWA, 160716_PS_Atsushi_HAYATA

Revised answer:

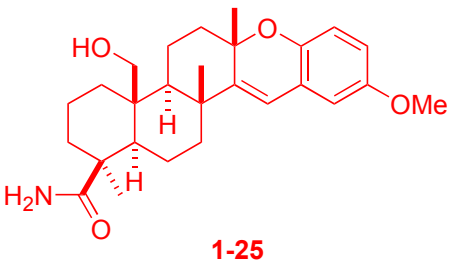
1-1. **1-1→1-2**



1-9. **1-23→1-25**



1-23 **1-24**



1-25