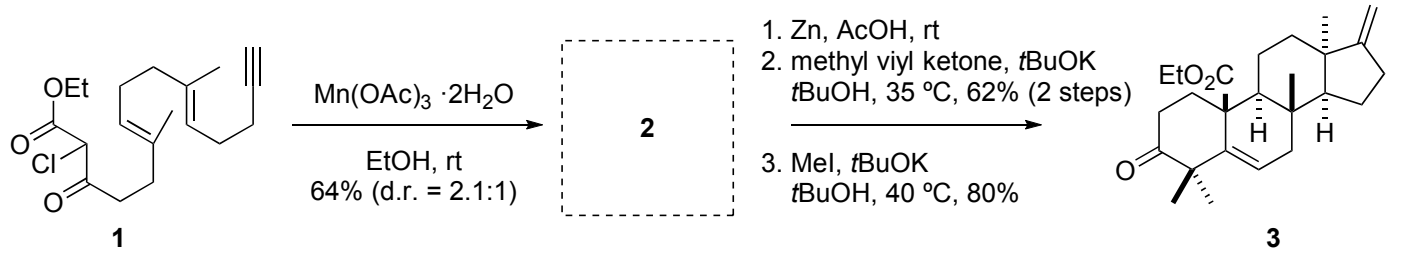
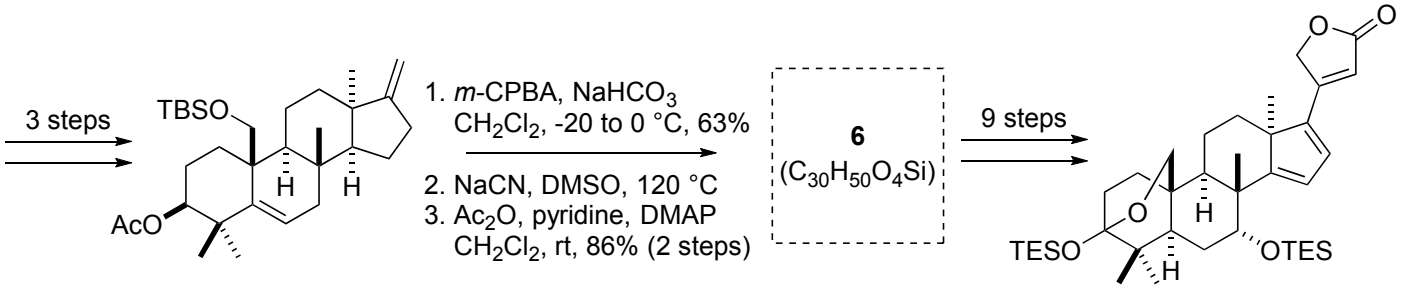
Problem Session (1)

2015.09.26. Yinghua Wang

Please fill in the blanks and provide each reaction mechanisms.

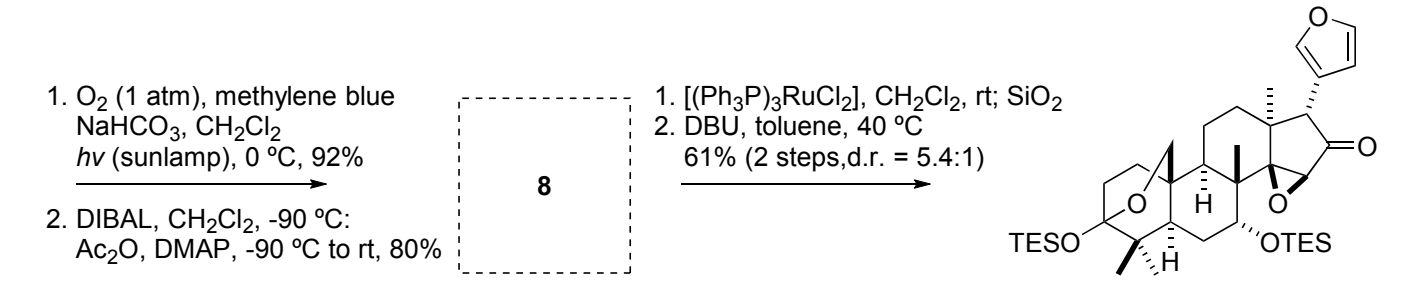


1 **3**



5
($C_{31}H_{52}O_3Si$)

7



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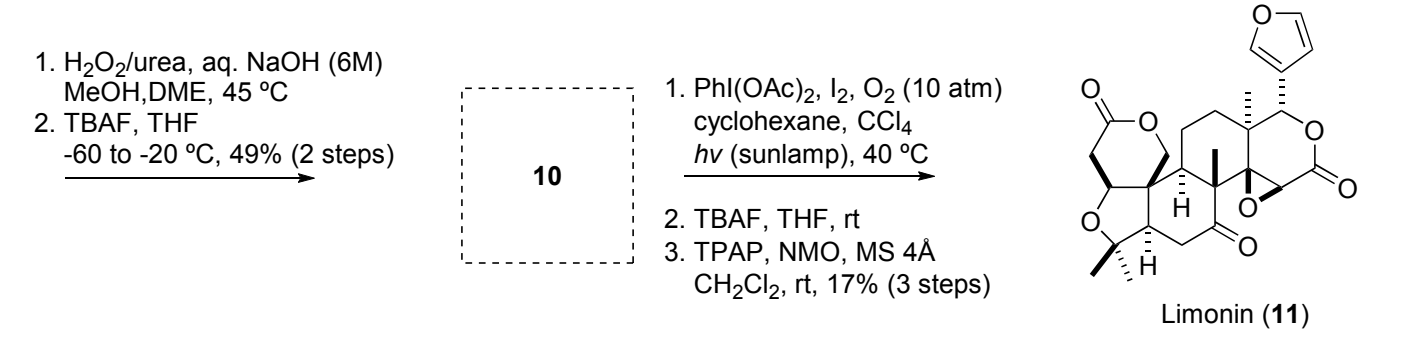
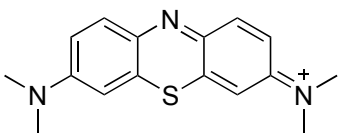


Limonin (**11**)



methylene blue

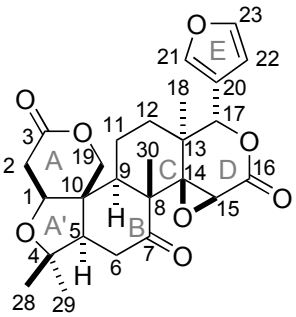
Problem Session (1) -Answer-

2015.09.26. Yinghua Wang

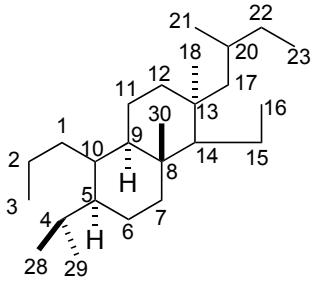
Topic: Total Synthesis of Limonin

0. Introduction
0-1. Isolation
Isolated in 1841 from the citrus fruit
Bernays. *Justus Liebigs Ann. Chem.* **1841**, *40*, 317.

Structure determined in 1960
Arigoni, D. et al. *Experientia* **1960**, *16*, 41.
Arnott, A. W. et al. *Experientia* **1960**, *16*, 49.



Limonin

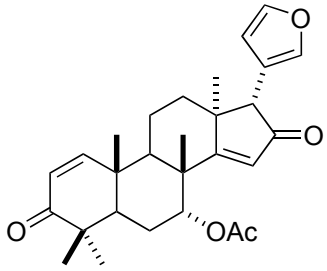


limonoid skelton

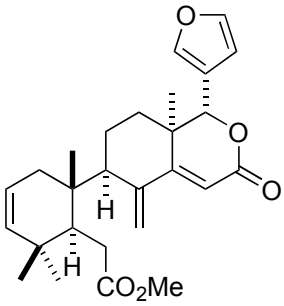
0-2. limonoids
0-2-1. Outline
highly oxgenated triterpenes
characterized by a 4,4,8-trimethyl-17-furyl-3α-androstane framework
known out of over 300 limonoids

0-2-2. Biological activity of limonoids
activities on insects
anti-cancer, anti-malarial, anti-microbial, anti-HIV activity
reported many other activities

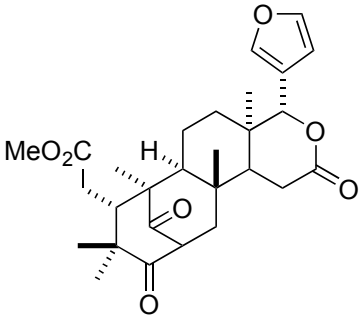
0-2-3. Total synthesis of limonoids



Azadiradione[1)]



Cipadonoid B[2)]

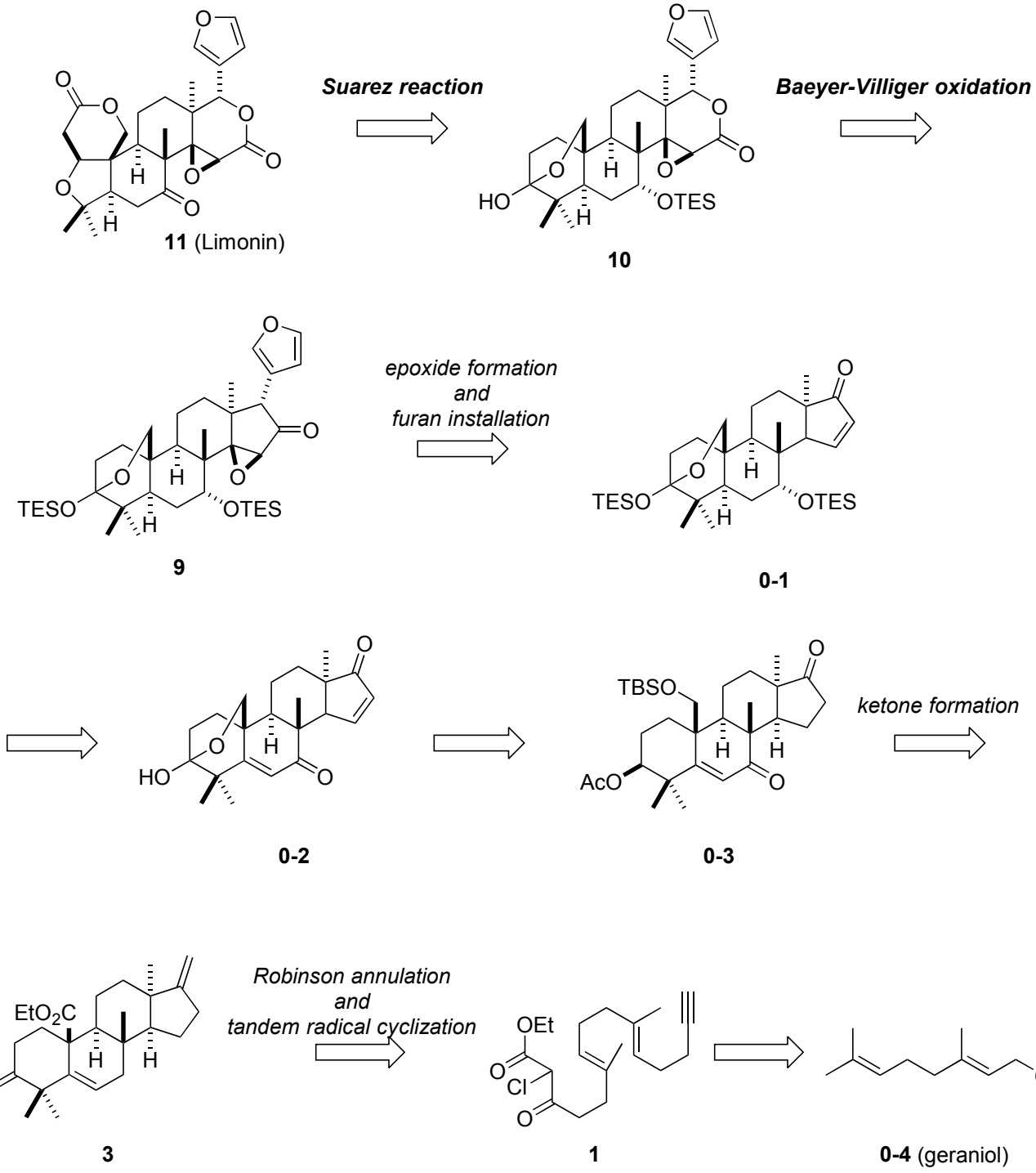


Mexicanolide[3)]

1) Corey, E. J.; Hahl, R.H. *Tetrahedron Lett.* **1989**, *30*, 3023.
2) Faber, J.M.; Williams, C. M. *Chem. Commun.* **2011**, 2258.
3) Faber, J.M.; Eger, W. A.; Williams, C. M. *J. Org. Chem.* **2012**, *77*, 8913.

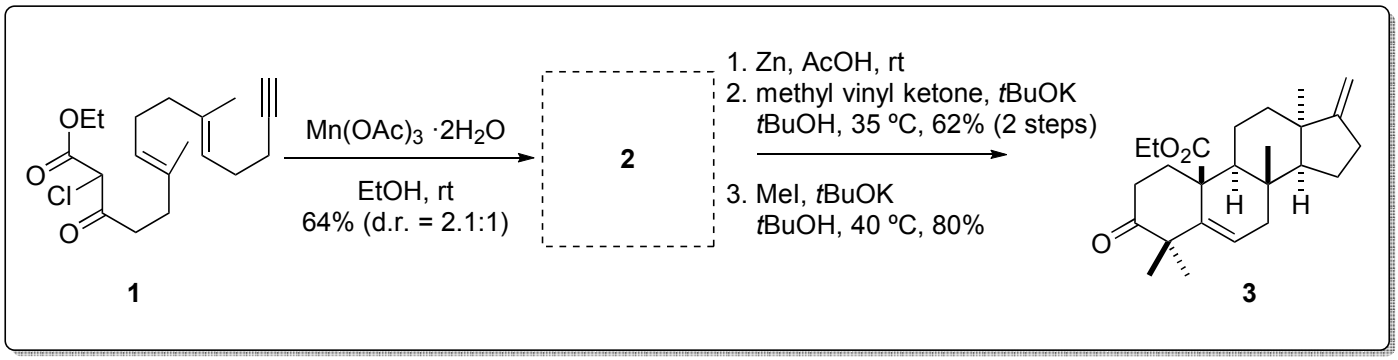
0-2-4. Reviews on limonoids
Roy, A.; Saraf, S. *Biol. Pharm. Bull.* **2006**, *29*, 191.
Champagne, D. E. et al. *Phytochemistry* **1992**, *31*, 377.
Heasley, B. *Eur. J. Org. Chem.* **2011**, 19.

0-3. Retrosynthetic analysis

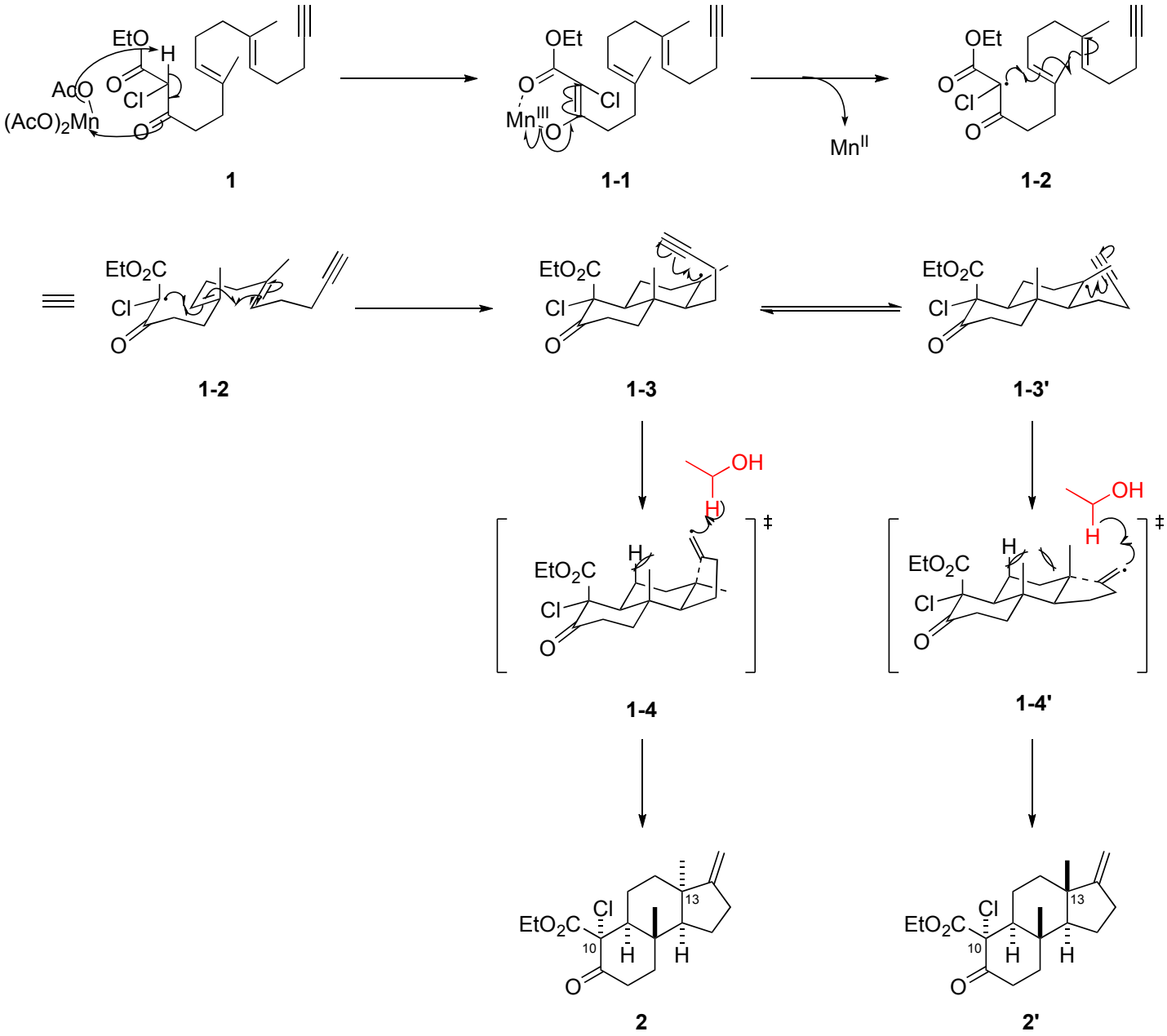


-Answer-

1. Construction of BCD rings

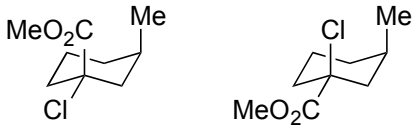


• **2** > **3**: **tandem radical cyclization**



2:**2'** = 2.1:1

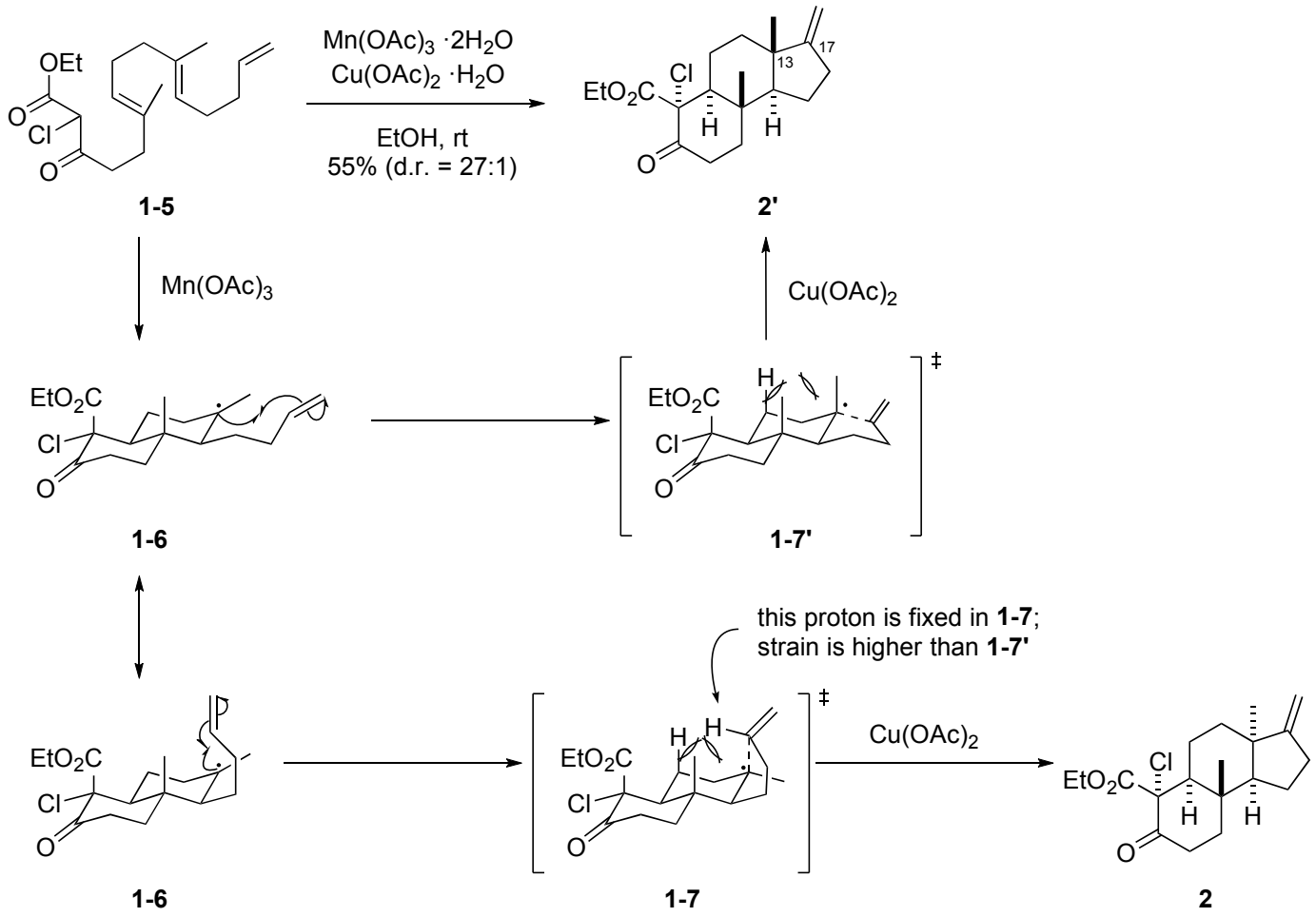
support for the stereochemistry of C10



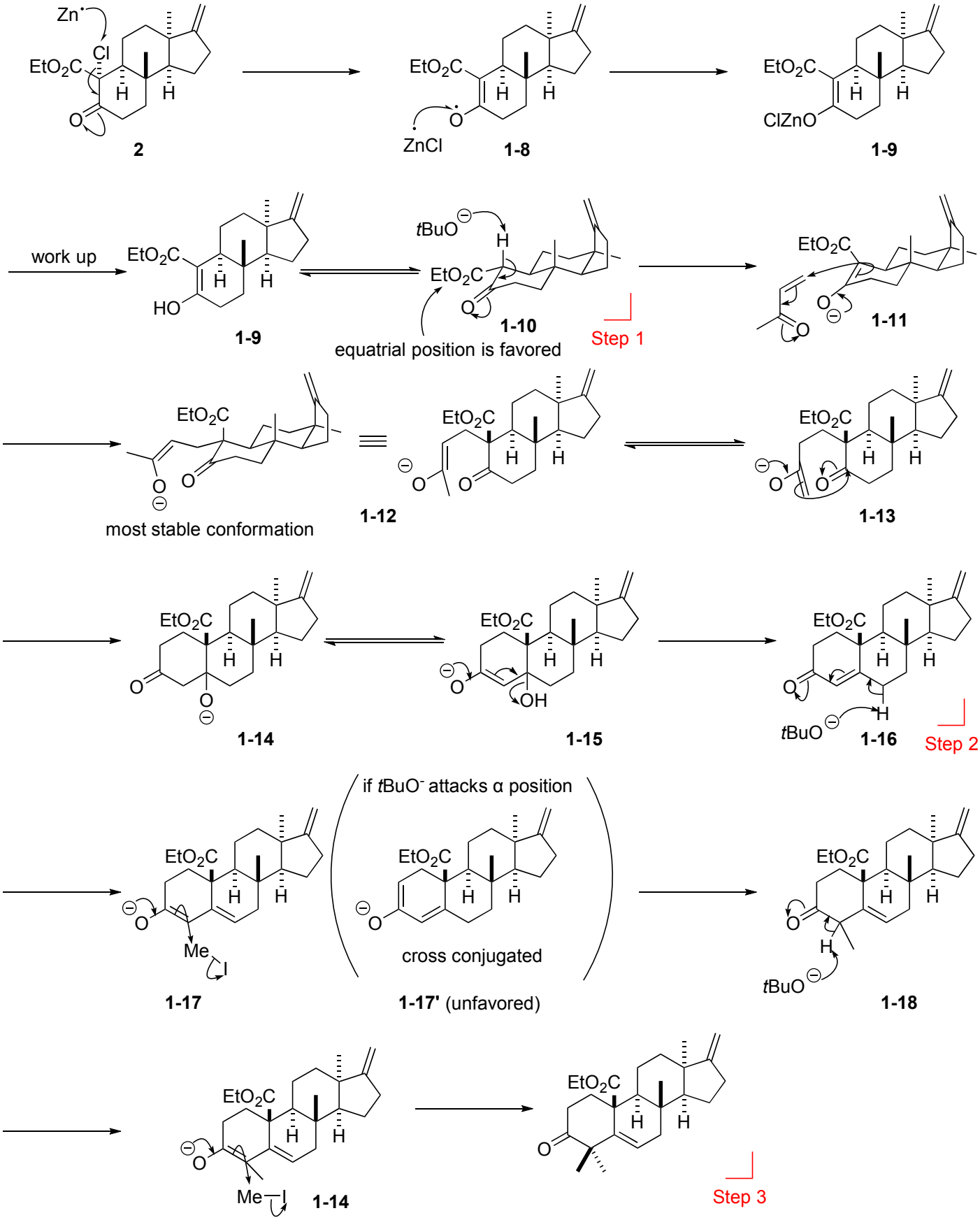
G_{rel}	0.0	0.48	(HF/6-31G*)
(kcal/mol)	0.0	0.36	(Becke3LYP)

Yang, D.; Xu, M. *Org. Lett.* **2013**, *54,* 1589.

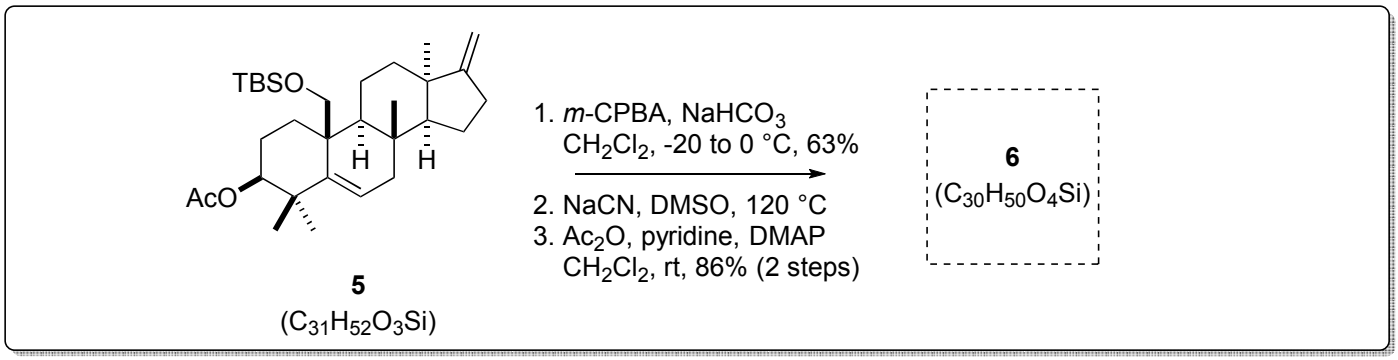
stereochemistry of C13



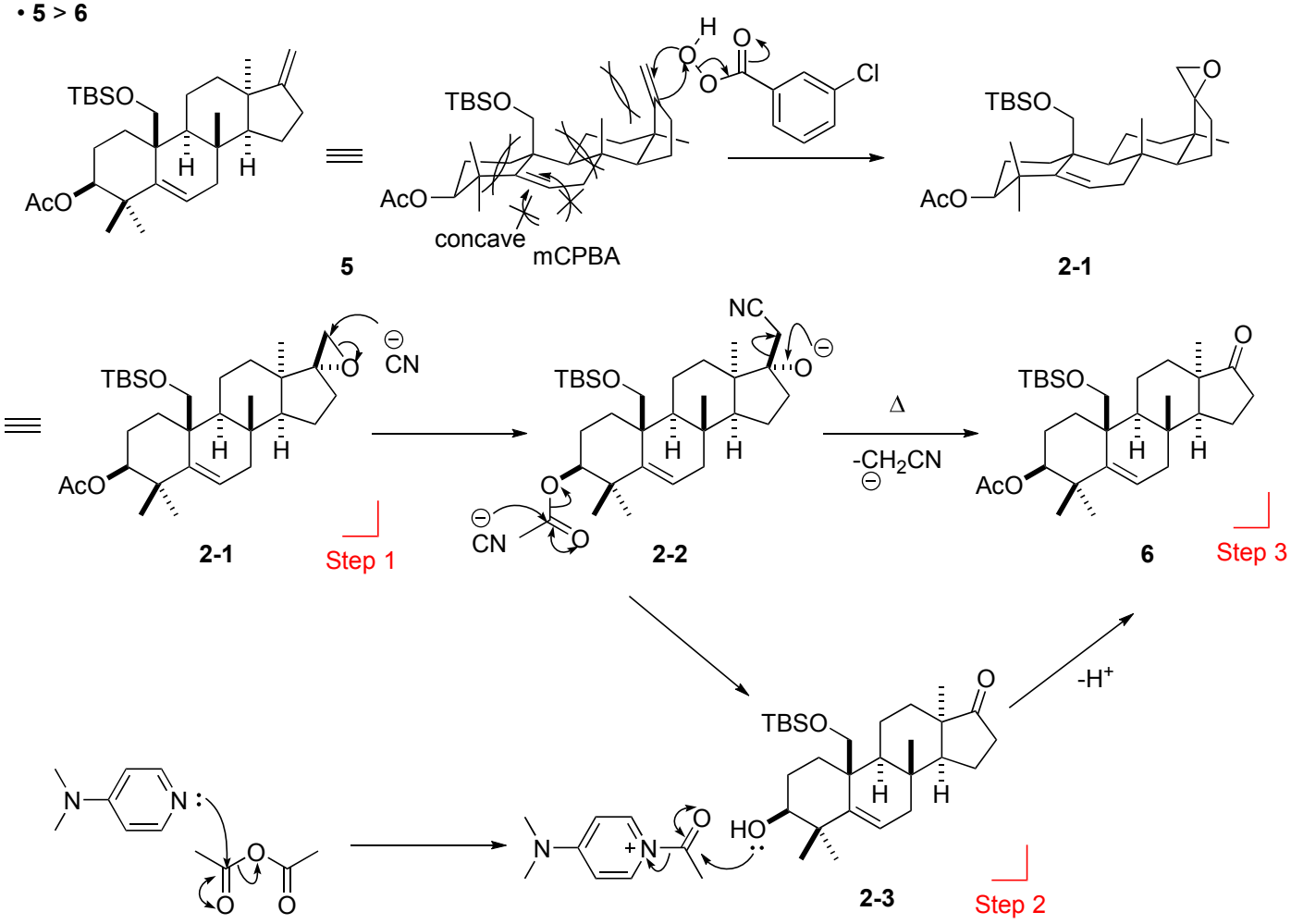
• **3** > **4**: **Robinson annulation**



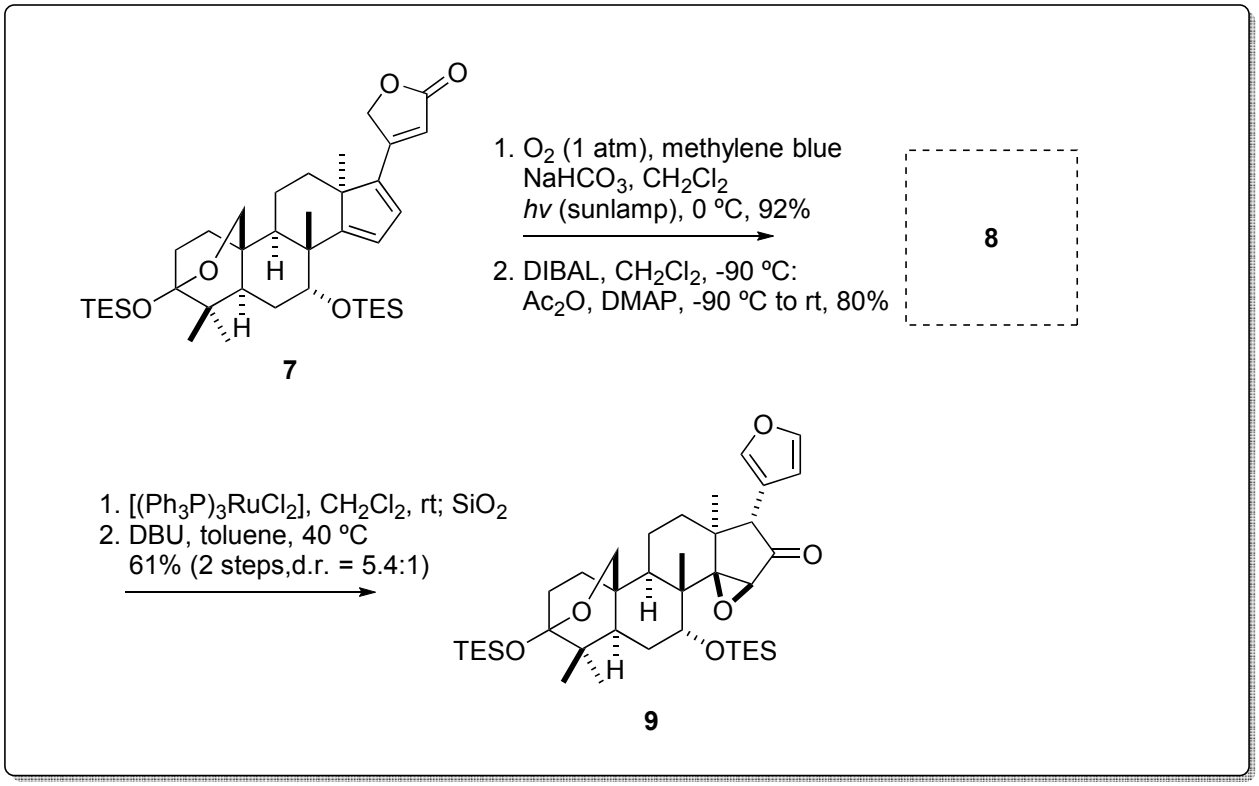
2. Formation of a ketone



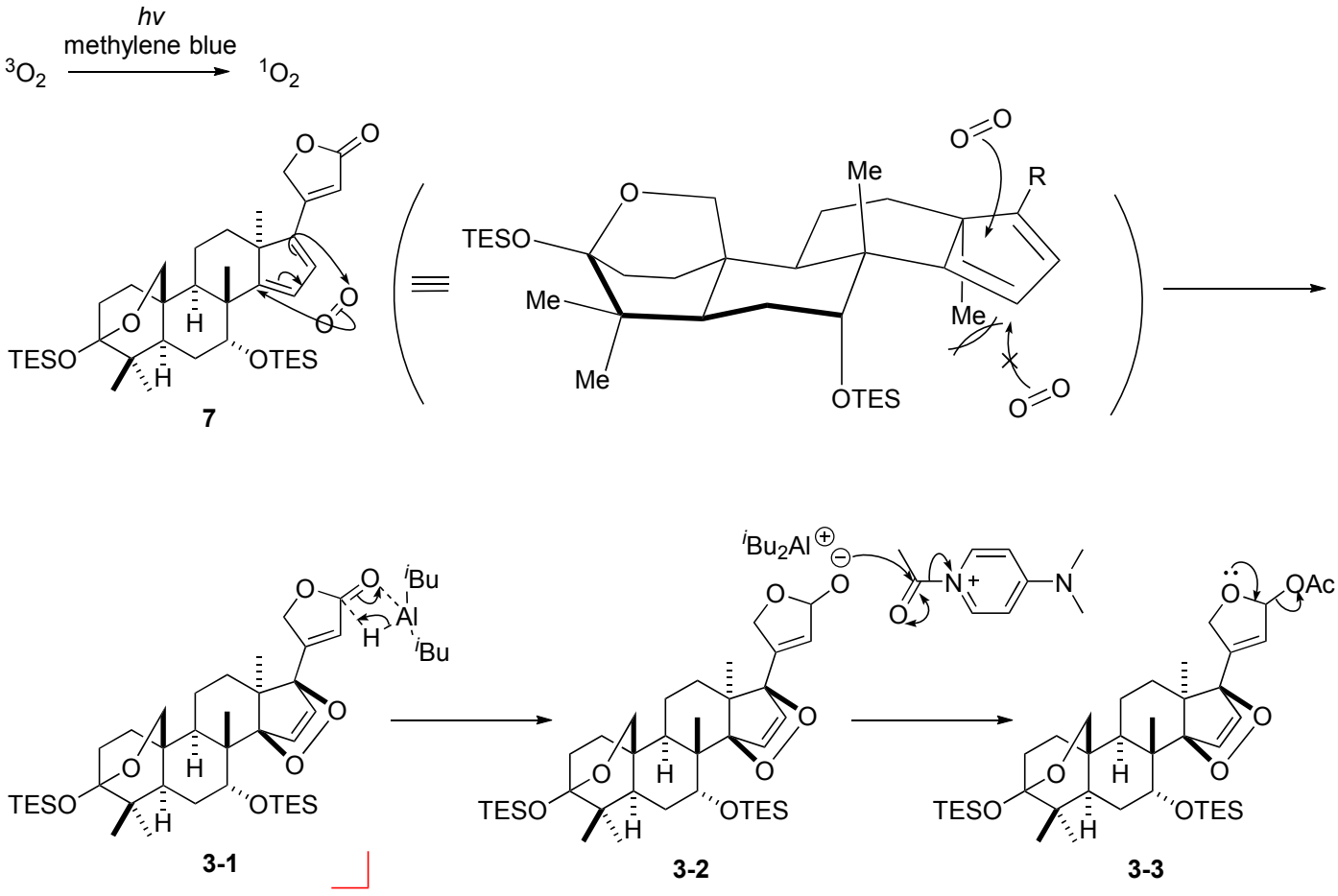
• **5 > 6**

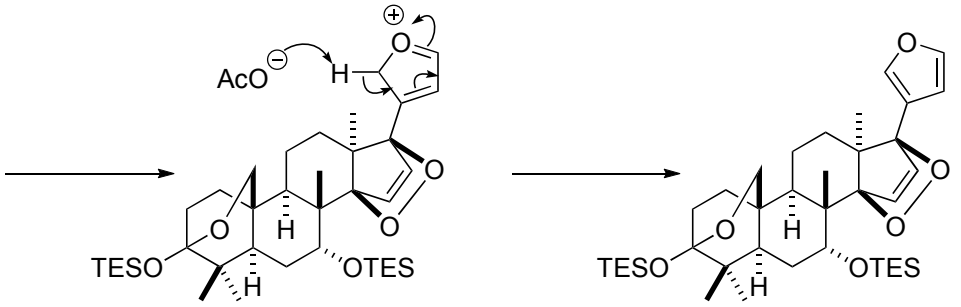


3. Installation of epoxylactone.



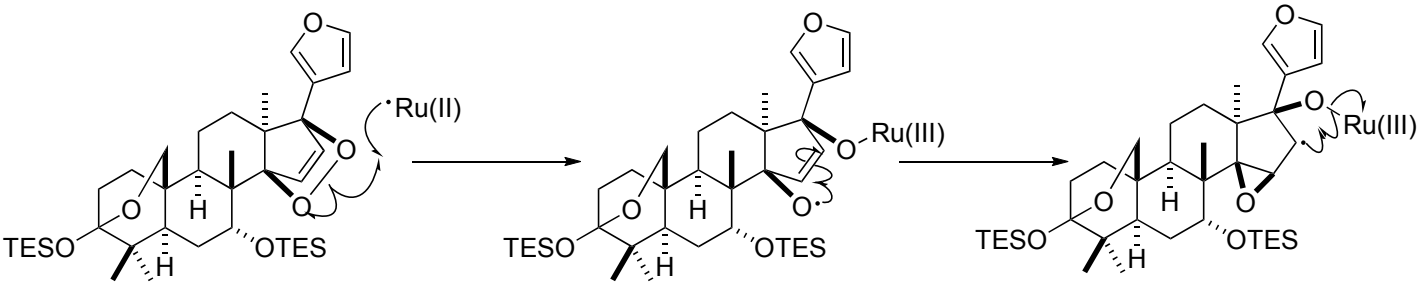
• **7 > 8**



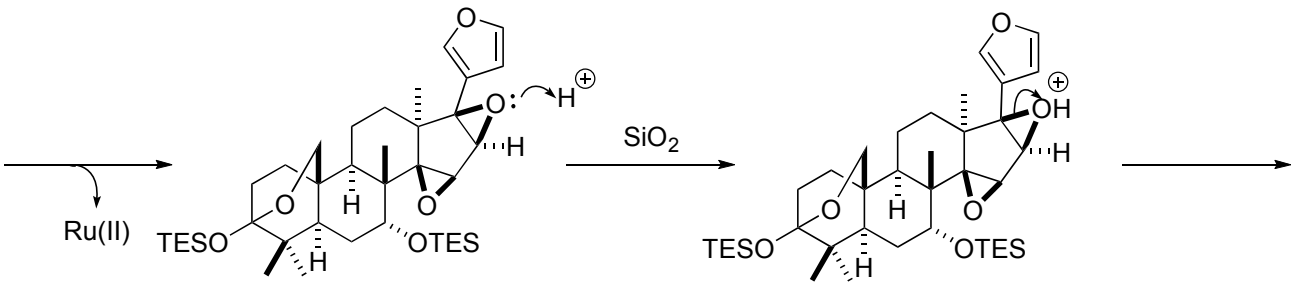


3-4 **8** Step 2

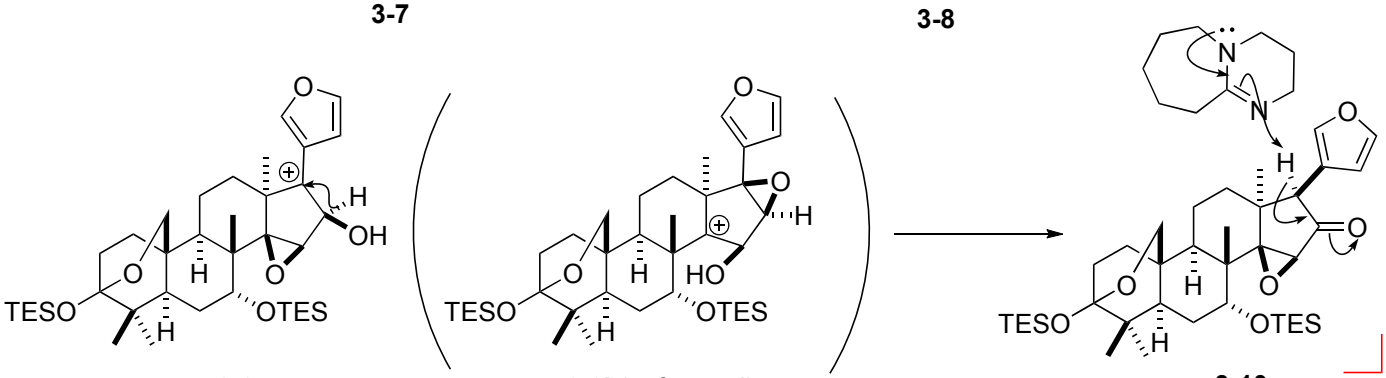
• **8** > **9**



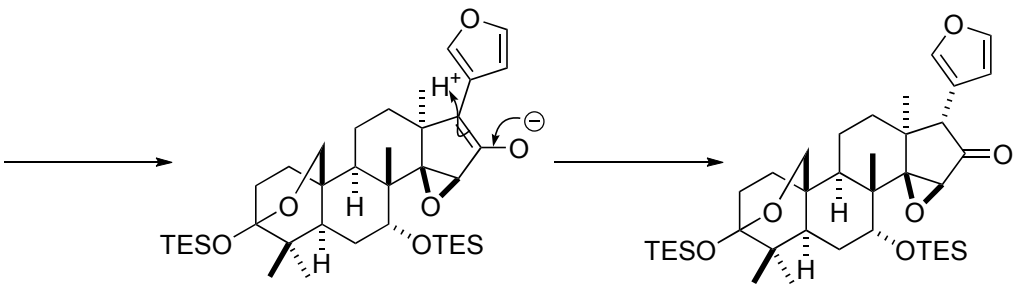
8 **3-5** **3-6**



3-7 **3-8**



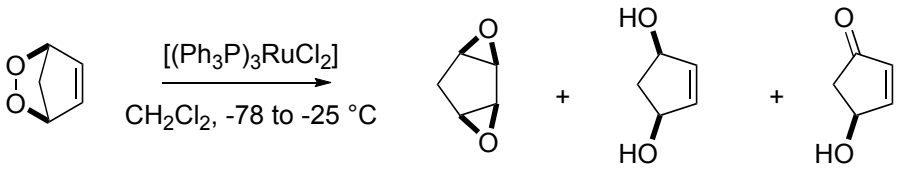
3-9 **3-9'** (unfavored) Not stabilized by a furan ring **3-10** Step 1



3-11

9 (**9**:**3-10** = **5.4**:**1**) Step 2

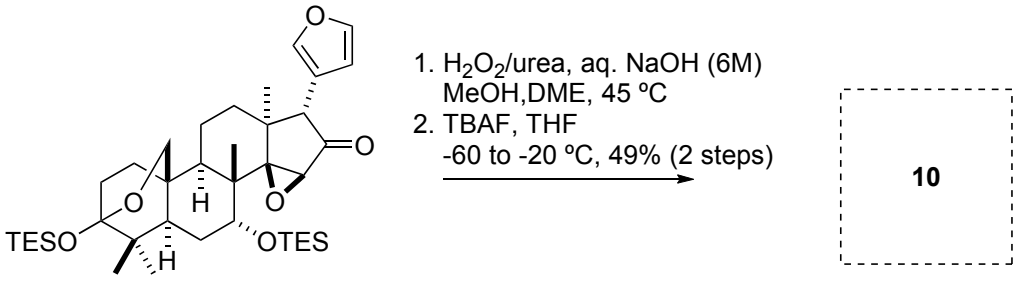
support for formation of diepoxide (**8** to **3-7**)



3-10 **3-11** 78% **3-12** 3% **3-13** 5%

Suzuki, M; Ohtake, H.; Kameya, Y.; Hamanaka, N.; Noyori, R. *J. Org. Chem.* **1989**, *54,* 5292.

4. Construction of AA' rings.



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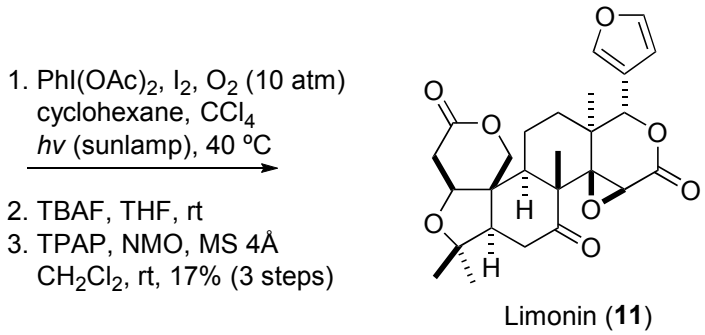
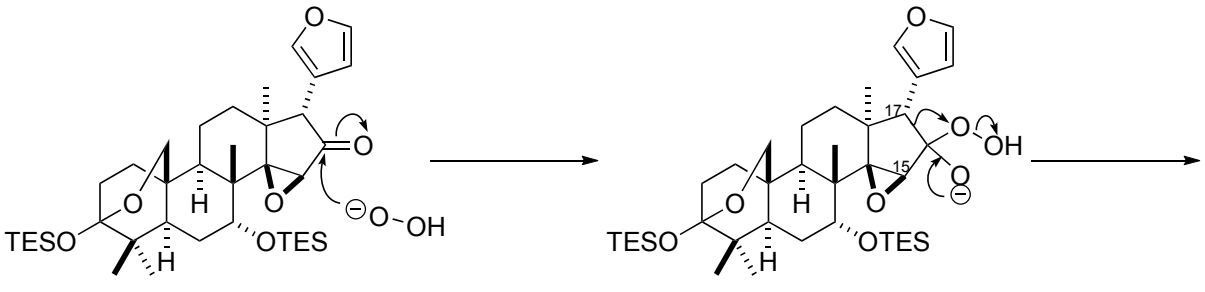


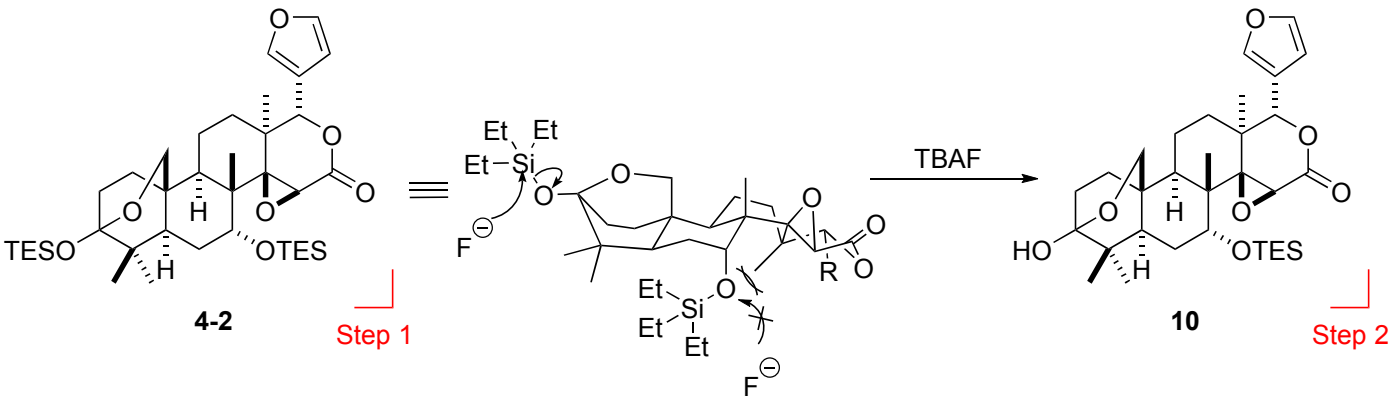
Limonin (**11**)

• **9** > **10**: **Baeyer-Villiger oxidation**



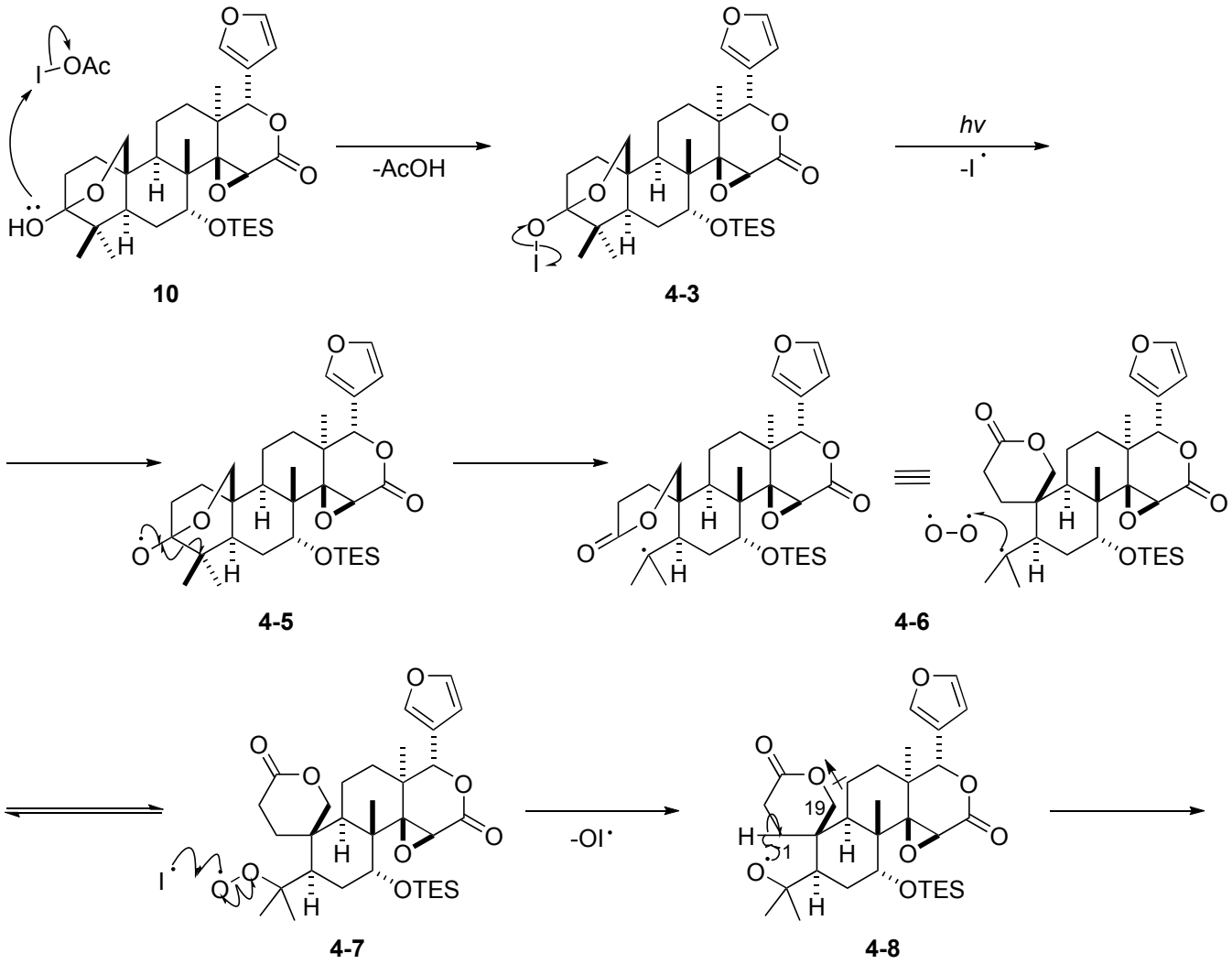
9 **4-1**

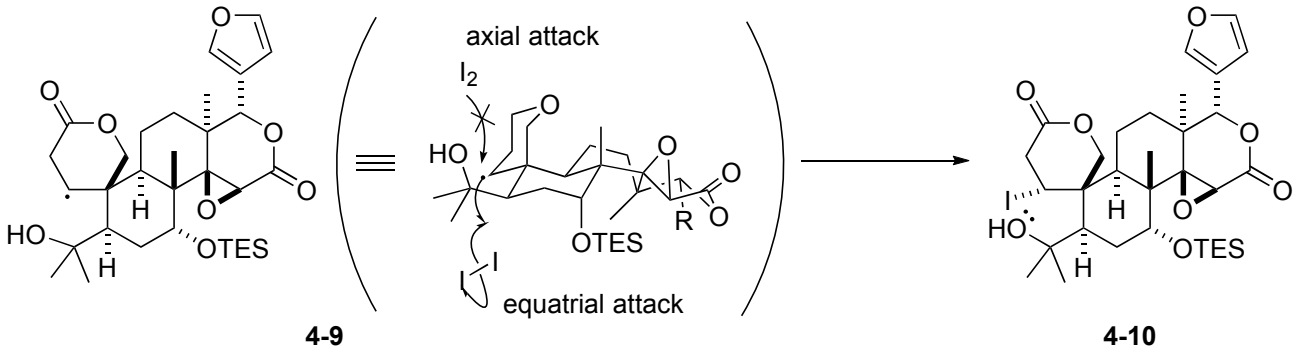
Since a furan ring exists, C17 is more electoron rich than C15

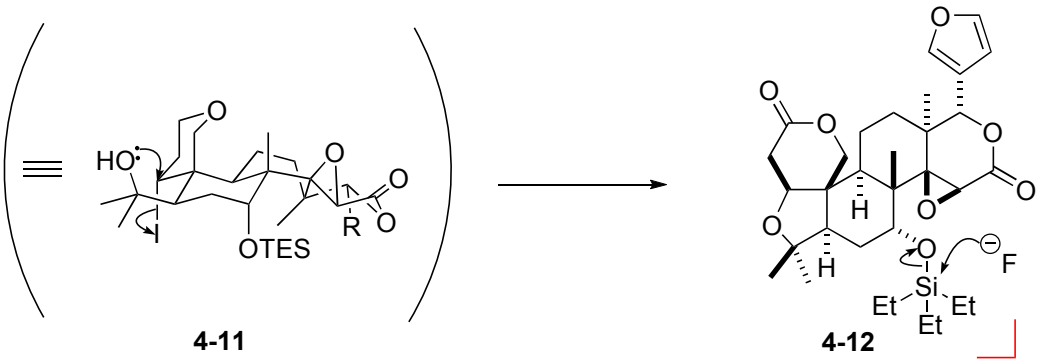


• **10** > **11**

$PhI(OAc)_2 + I_2 \longrightarrow 2\ AcOI + PhI$

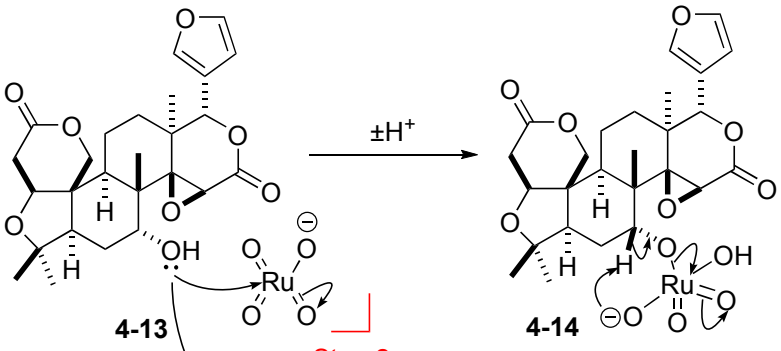




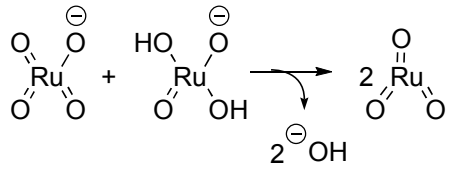


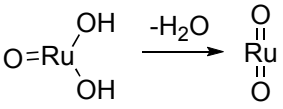
Step 1

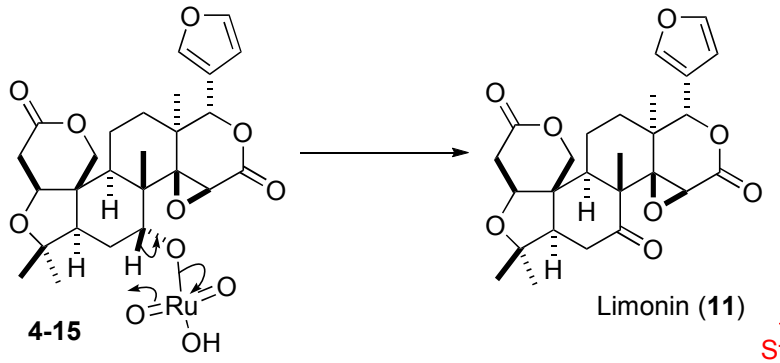
TBAF



Step 2







Step 3