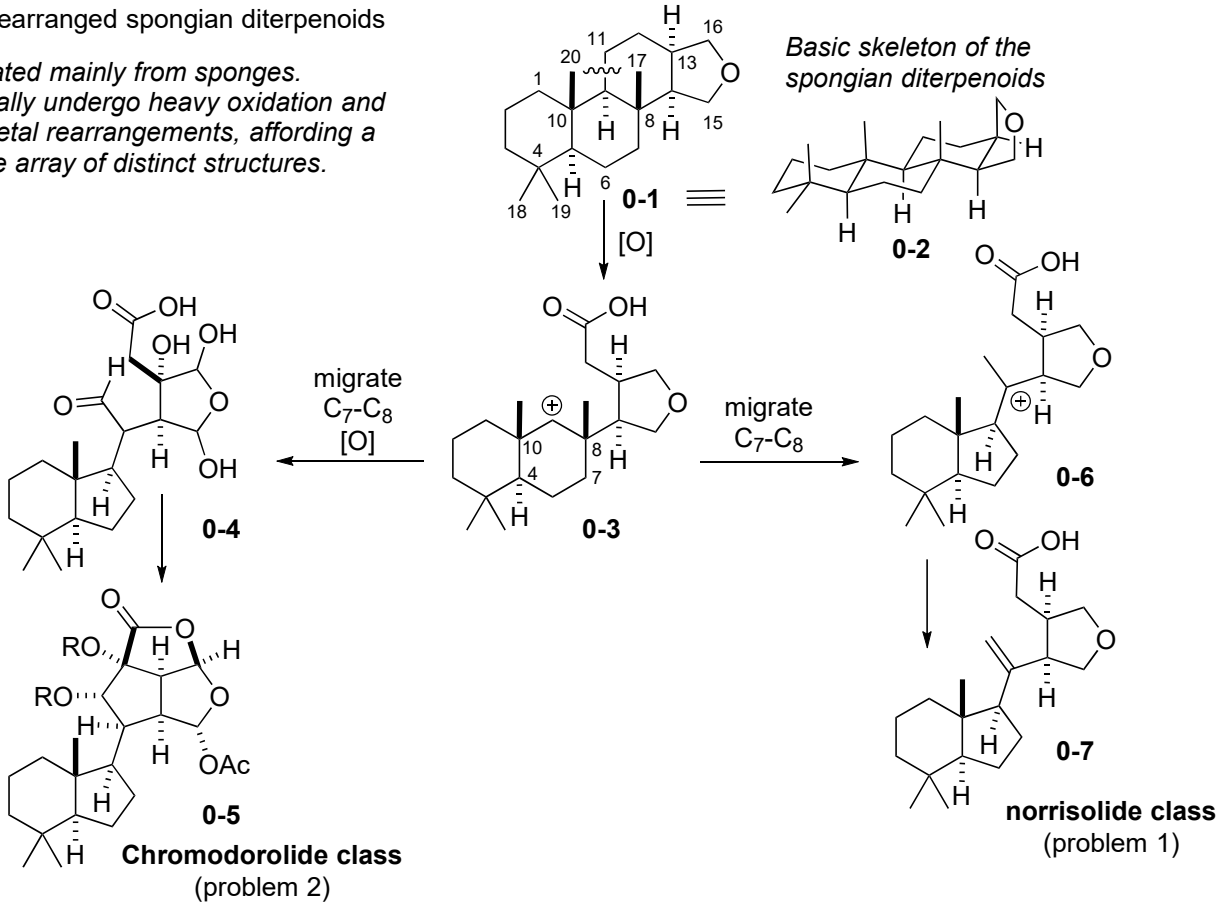
Problem Session (4) [Answer]

2020.10.3 Keshu Zhang

topic: Total Synthesis of Spongian Diterpenes Seconorrisolide C and Chromodorolide B

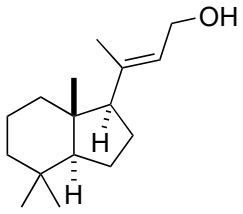
0. Rearranged spongian diterpenoids

Isolated mainly from sponges.
Usually undergo heavy oxidation and skeletal rearrangements, affording a large array of distinct structures.



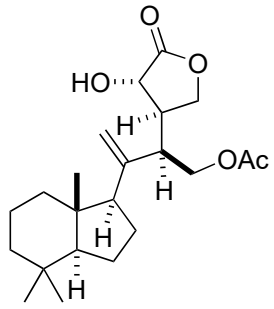
Answer :

Problem 1

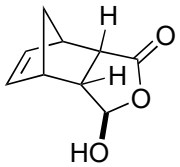


1-1

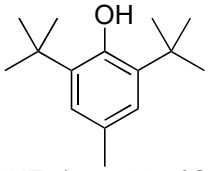
1. **A** (1.2 eq.), TsOH (0.1 eq.), toluene, 100 °C, 72%
2. BHT (0.1 eq.), Ph_2O, 245 °C, 84%
3. LiHMDS (3.0 eq.), MoOPH (2.0 eq.)
   THF, -78 °C to 0 °C, 77%
4. TBSCl (2.0 eq.), Imidazole (2.0 eq.), CH_2Cl_2, rt, 85%
5. KOH (2.0 equiv), THF/MeOH/H_2O = 2:1:1, 0 °C
   then $NaBH_4$ (5.0 equiv), then AcCl (8.8 eq.), 52%
6. Ac_2O (20 eq.), Et_3N (20 eq.), CH_2Cl_2, rt
   then TBAF·$3H_2O$ (6.0 eq.), THF, rt, 66%



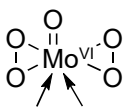
1-2
seconorrisolide C



A

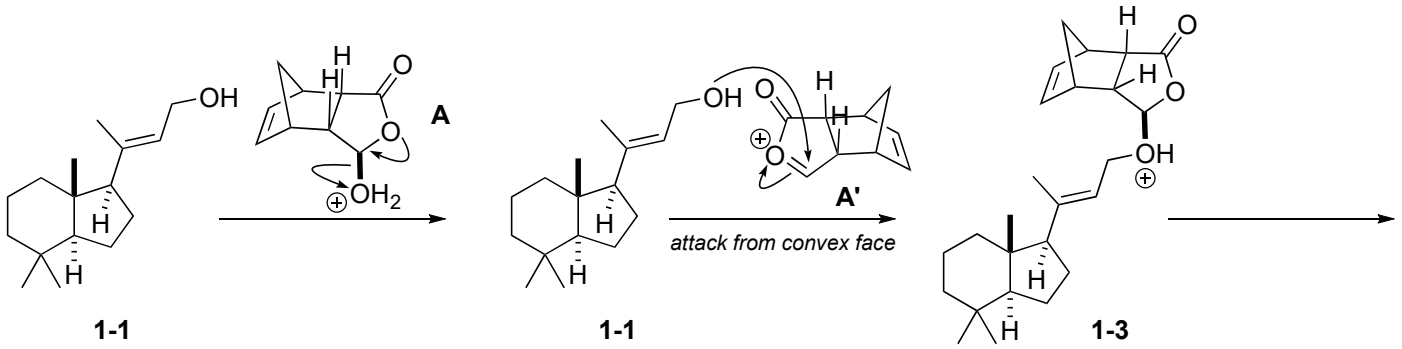


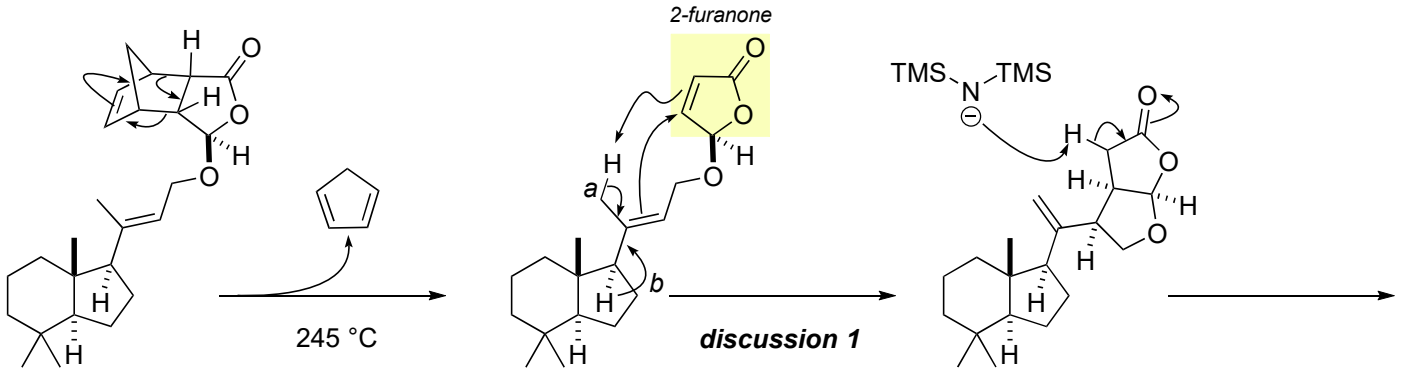
BHT (m.p. 265 °C)
butylated hydroxytoluene



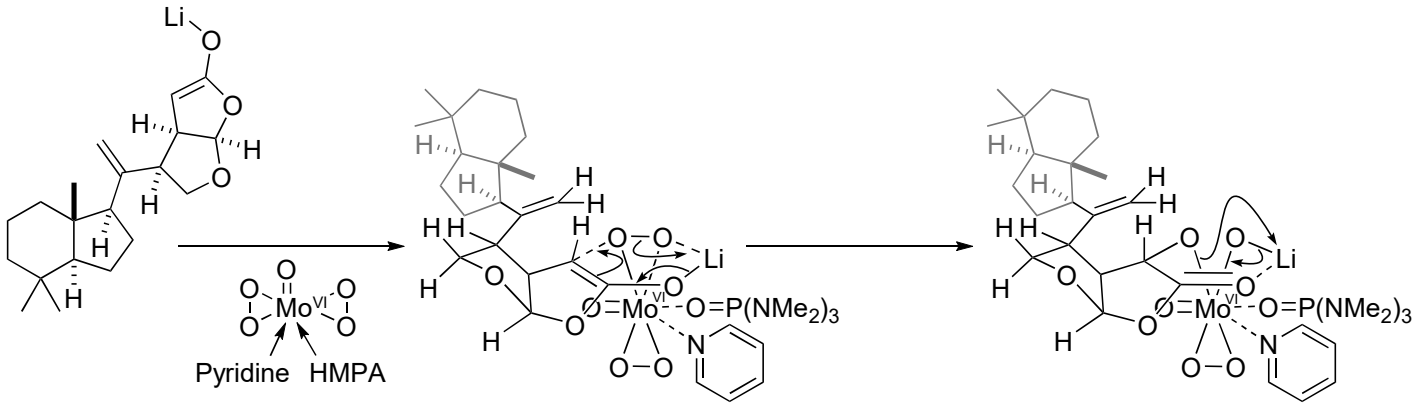
Pyridine HMPA
MoOPH

T. Qiao, Y. Wang, S. Zheng, H. Kang, G. Liang, *Angew. Chem. Int. Ed*. **2020**, *59*, 14111

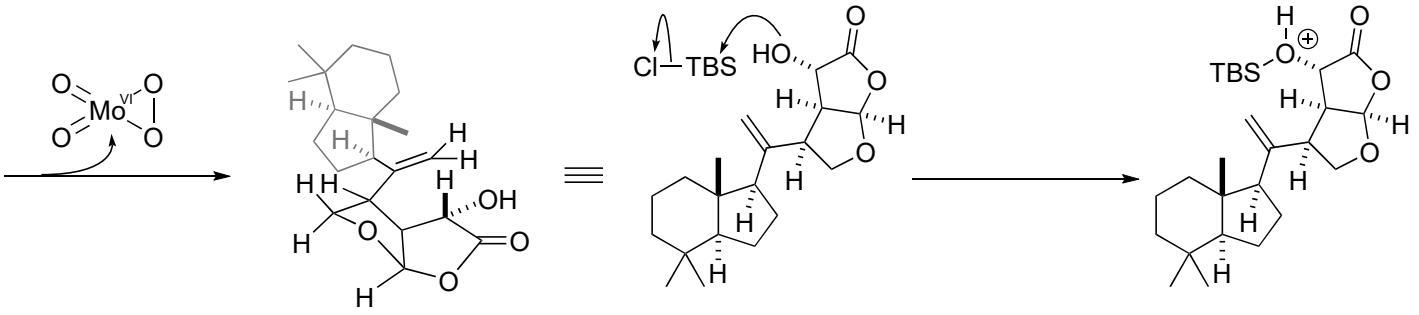




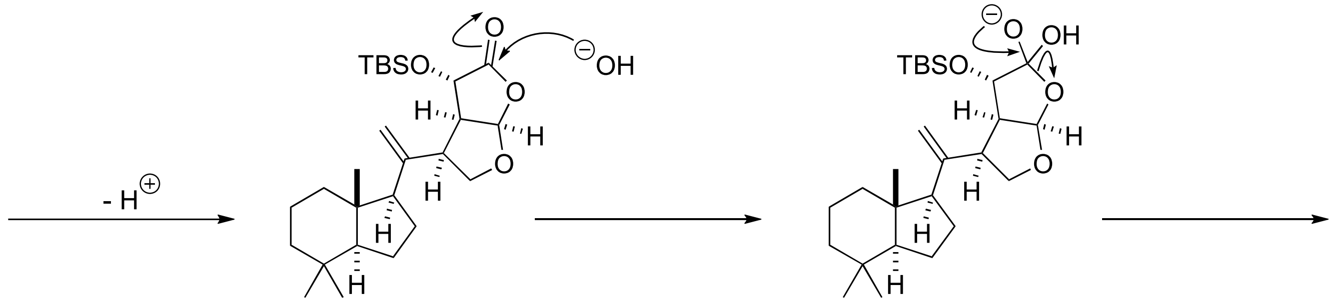
step 1 step 2



MoOPh = MoO_5·Py·HMPA (*J. Am. Chem. Soc*. **1974**, *96*, 5944.)
mechanistic discussion on the epoxidation (*J. Am. Chem. Soc.* **1972**, *94*, 295.)

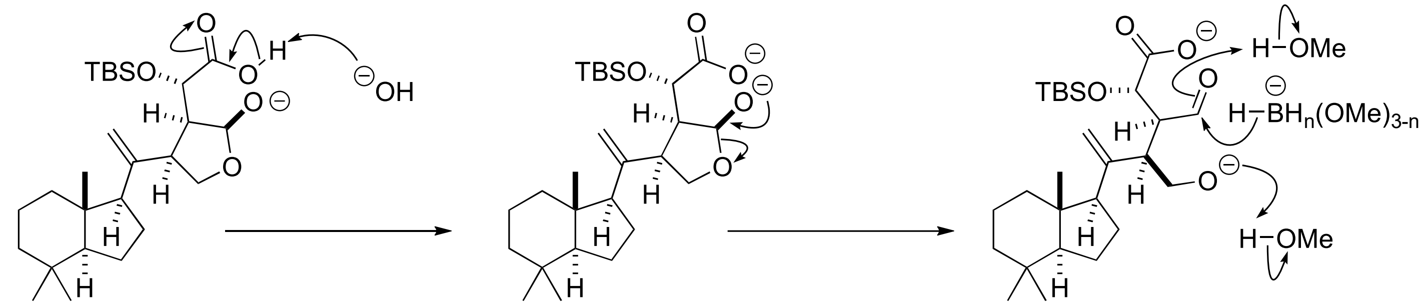


step 3

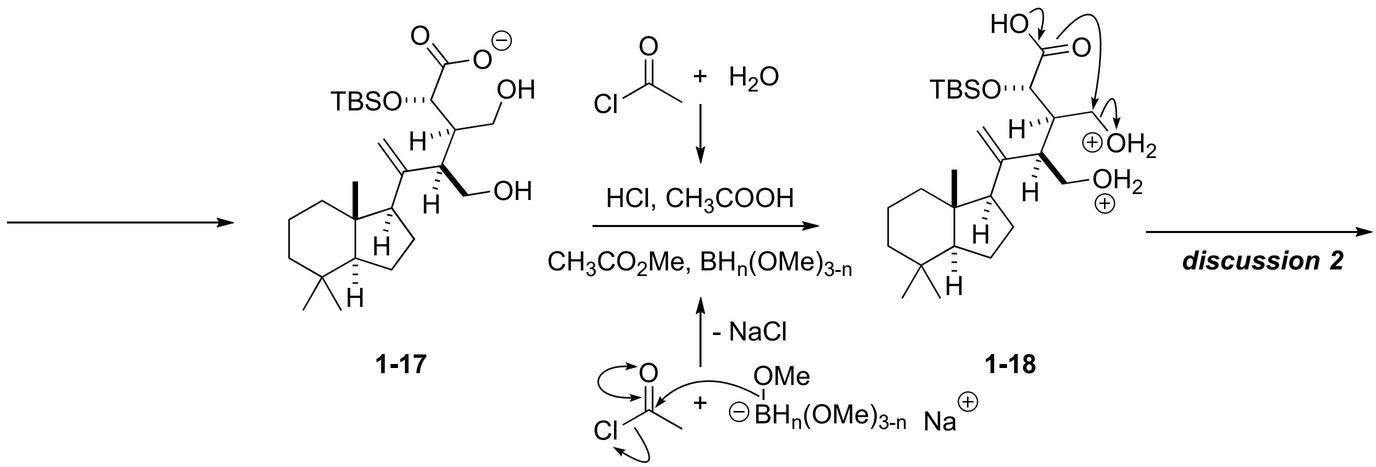


1-12 1-13

step 4

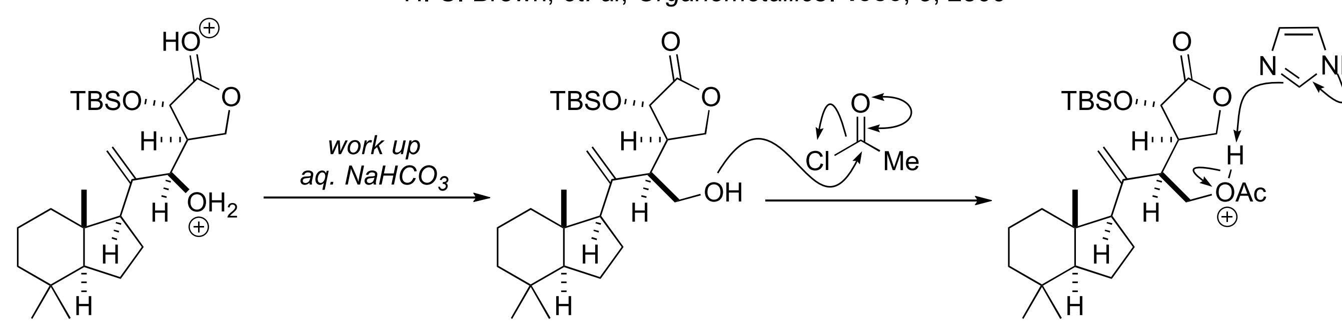


1-14 1-15 1-16



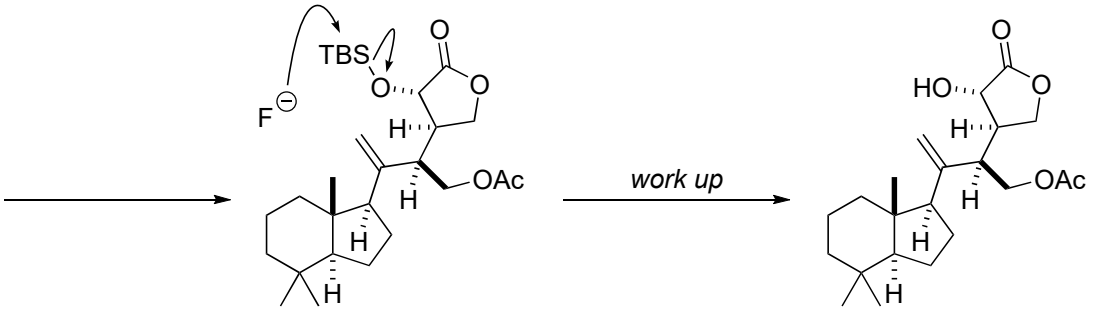
1-17 1-18

H. C. Brown, *et. al*, *Organometallics*. **1986**, *5*, 2300



1-19 1-20 1-21

step 5

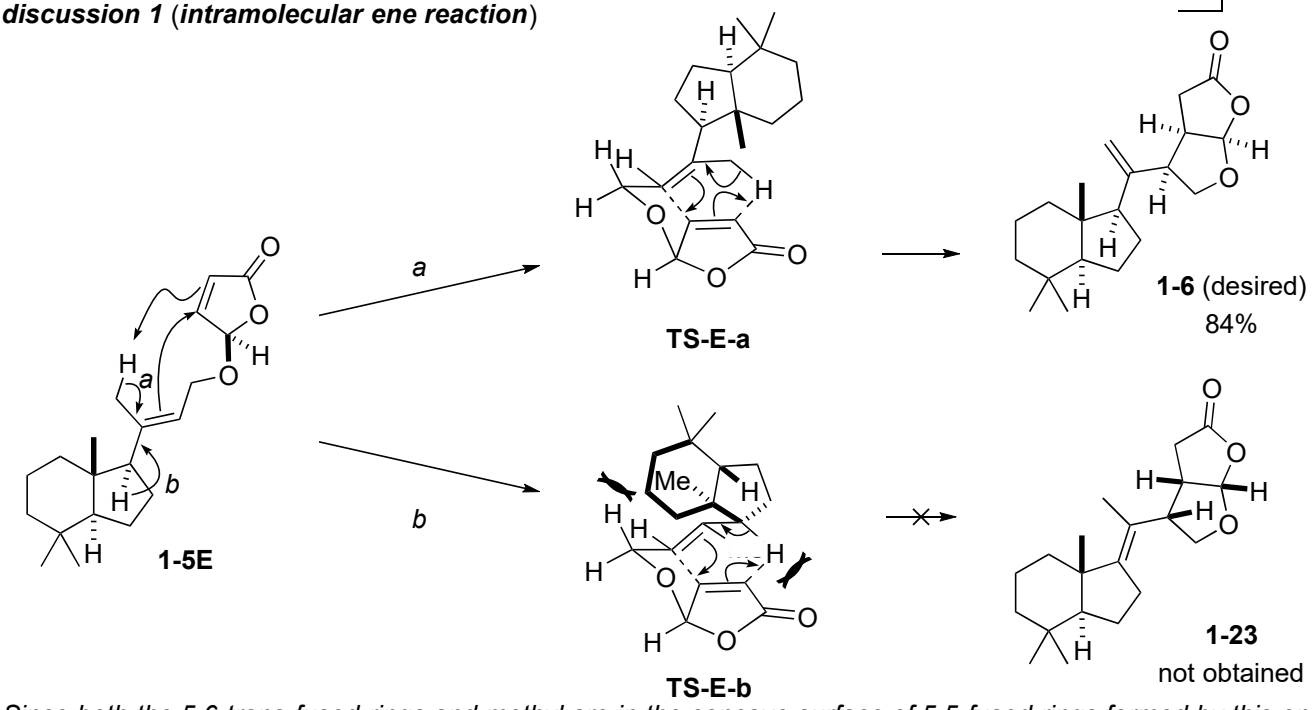


1-22 **1-2**

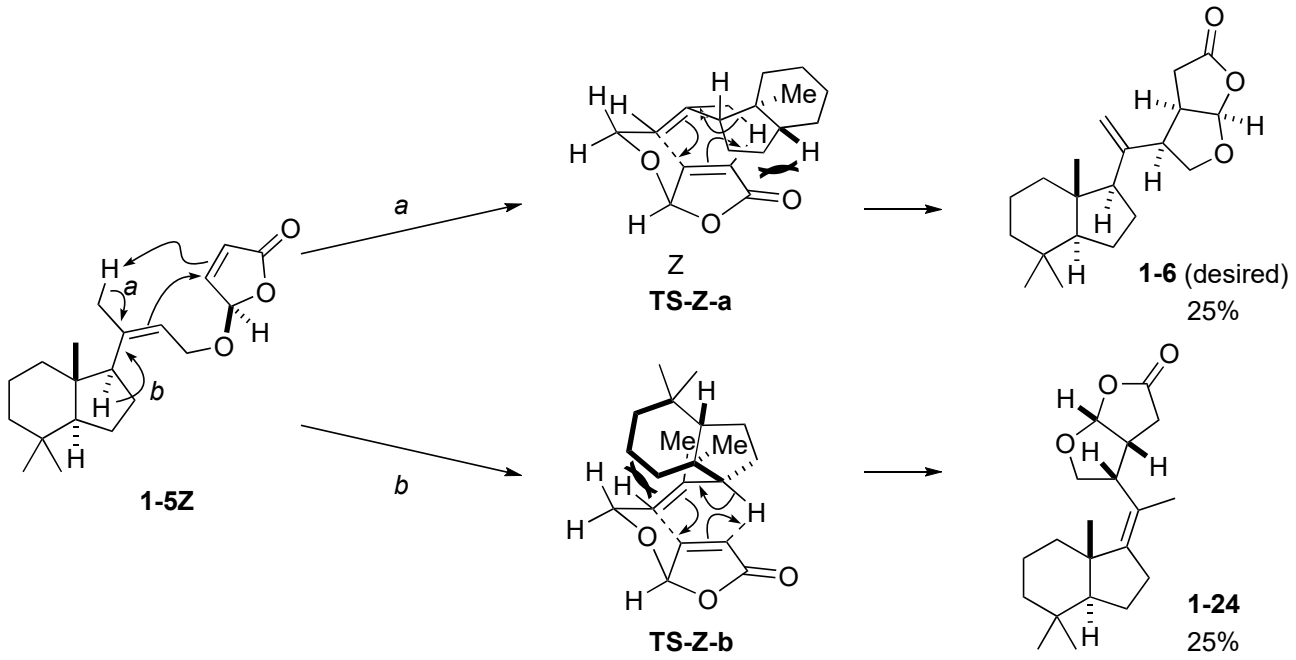
seconorrisolide C

step 6

discussion 1 (***intramolecular ene reaction***)

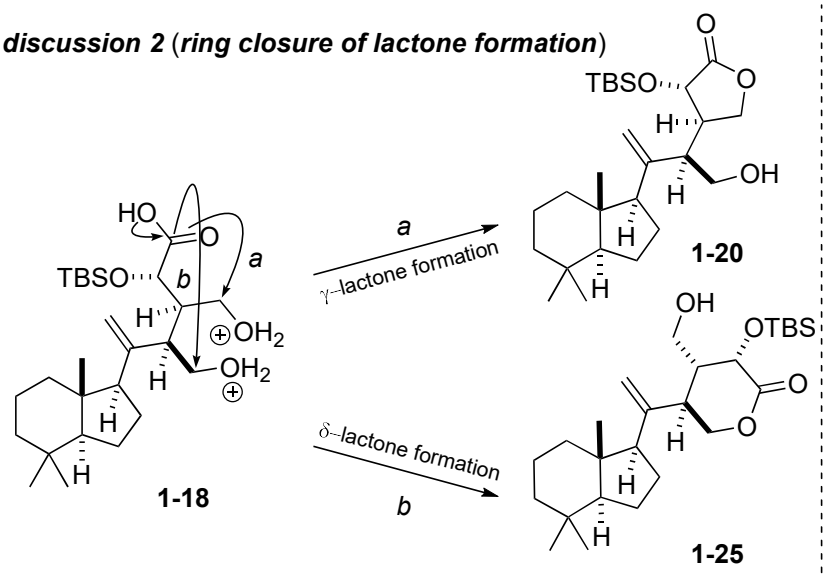


*Since both the 5,6-trans-fused rings and methyl are in the concave surface of 5,5-fused rings formed by this ene-reaction, there is a great steric hindrance in **TS-E-b**, thus only **1-6** was obtained in the reaction with E-olefin **1-5E**.*

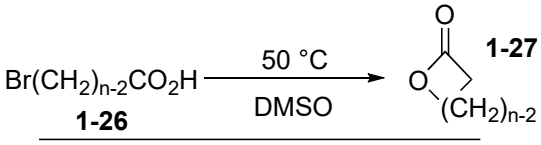


*Although there are steric hindrances of 5,6-trans-fused rings and furanone ring in both **TS-Z-a** and **TS-Z-b**, desired **1-6** and **1-24** was obtained in 25% yield respectively in the ene-reaction with Z-olefin **1-5Z**.*

discussion 2 (***ring closure of lactone formation***)



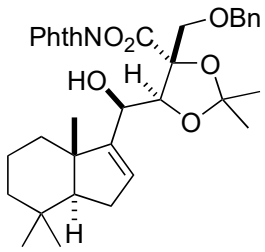
Kinetic Data for the Formation of Lactones from $Br(CH_2)_{n-2}CO_2H$ in Me_2SO



n	k_{intra} (s^{-1})
3	(2.41 ± 0.02) x 10^{-3}
4	2.6
5	3.1 x 10^{2}
6	2.9
7	(1.08 ± 0.02) x 10^{-2}
8	(1.11 ± 0.02) x 10^{-5}

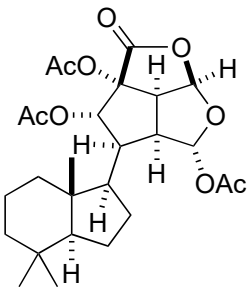
C. Galli, *et. al*, *J. Am. Chem. Soc*. **1977**, *99*, 2591

Problem 2

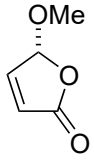


2-1

1. $SOCl_2$ (2.0 eq.), pyridine, Et_2O, -45 °C, 62%
2. **B** (4.0 eq.), $[Ru(bpy)_3](PF_6)_2$ (1 mol%)
   D_2-HE (1.5 eq.), 450 nm light, CH_3CN, rt, 28%
3. DIBAL-H (1.7 eq.), toluene, -78 °C
   then Ac_2O (6.0 eq.), DMAP (2.1 eq.), pyridine, 83%
4. HCO_2H, Pd/C, MeOH, rt.
5. Pt_2O, H_2, MeOH, 41% (2 steps)
6. DMP (1.5 eq.), CH_2Cl_2, rt
7. $NaClO_2$ (7.9 eq.), **C** (2.5 eq.), NaH_2PO_4 (11 eq.)
   ^{t}BuOH/THF = 1:1, rt
8. 4 M aq HCl, THF
9. Ac_2O (15 eq.), DMAP (1.0 eq.), pyridine (2.0 eq.), rt
   49% (4 steps)

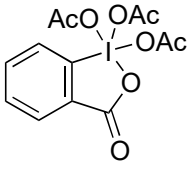


2-2
Chromodorolide B

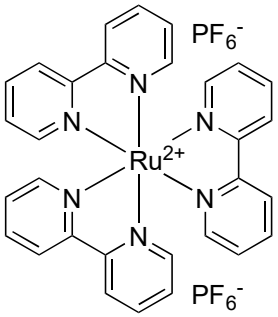


B

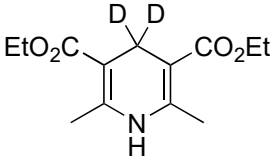
C
2-methyl-2-butene



DMP
Dess-Martin periodinane



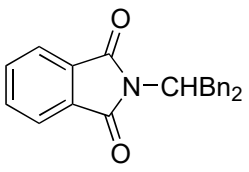
$[Ru(bpy)_3](PF_6)_2$



D_2-HE (Hantzsch ester)

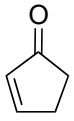
D. J. Tao, S. Yuriy, L. E. Overman, *J. Am. Chem. Soc*. **2016**, *138*, 2186

Photosensitized Decarboxylative Michael Addition of N-(Acyloxy)phthalimides to Electron-Deficient Olefins



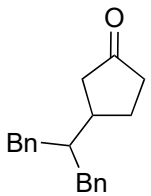
2-3

$[Ru(bpy)_3]Cl_2$ (cat.), BNAH (1 eq.)
>460 nm light, THF-H_2O, rt

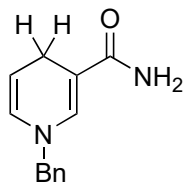


(1 eq.)

2-4

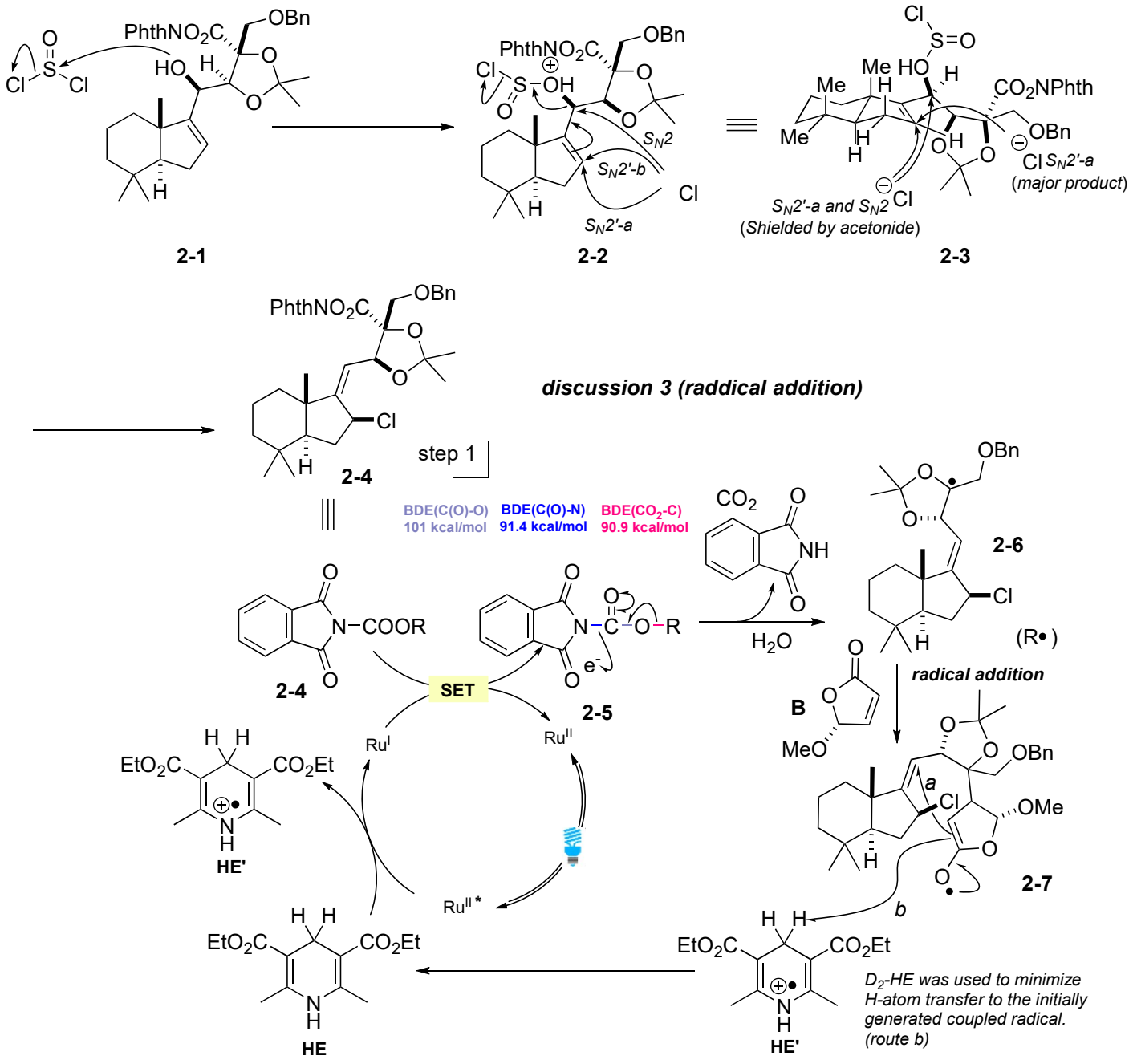


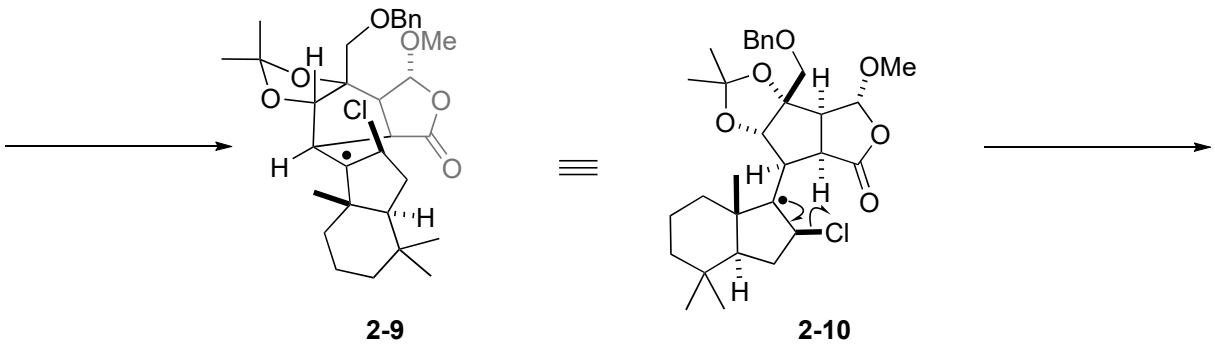
68%



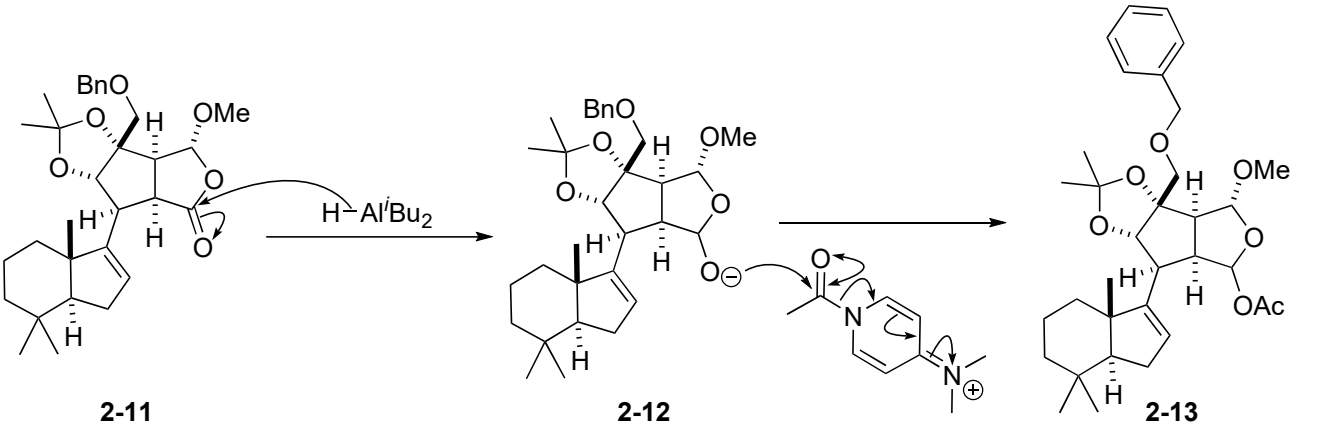
BNAH
($E_{1/2}^{red}$ = +0.76 V vs.SCE)

K. Okada, *et al*, *J. Am. Chem. Soc*. **1991**, *113*, 9401


PhthNO2C
OBn
HO
H
O
Cl
S
Cl
2-1
SN2
SN2'-b
SN2'-a
2-2
Me
CO2NPhth
OBn
SN2'-a
(major product)
SN2'-a and SN2
(Shielded by acetonide)
2-3
discussion 3 (raddical addition)
step 1
2-4
BDE(C(O)-O) 101 kcal/mol
BDE(C(O)-N) 91.4 kcal/mol
BDE(CO2-C) 90.9 kcal/mol
N–COOR
SET
e-
2-5
CO2
NH
H2O
2-6
(R•)
radical addition
B
MeO
a
OMe
2-7
b
RuI
RuII
RuII*
EtO2C
CO2Et
HE'
HE
D2-HE was used to minimize H-atom transfer to the initially generated coupled radical. (route b)
Addition from bottom face of radical
2-8



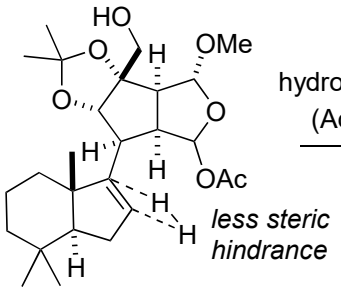
2-9 ≡ **2-10**



2-11 → **2-12** → **2-13**

step 2 | step 3

deprotection of Bn ether
(Pd/C hydrogenation)

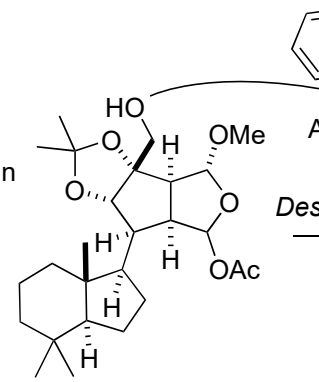


less steric hindrance

2-14

step 4

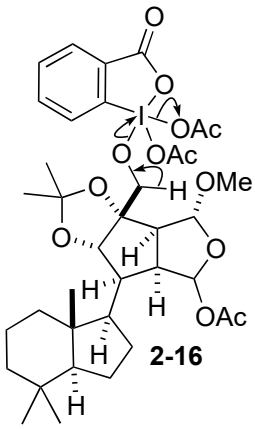
hydrogenation of olefin
(Adams' catalyst)



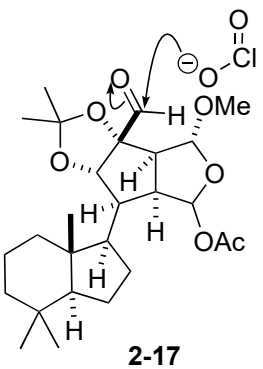
2-15

step 5

Dess-Martin oxidation



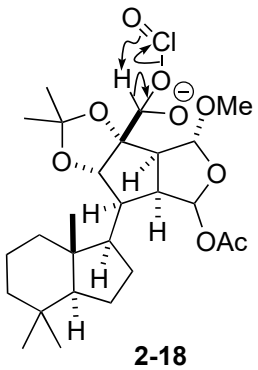
2-16



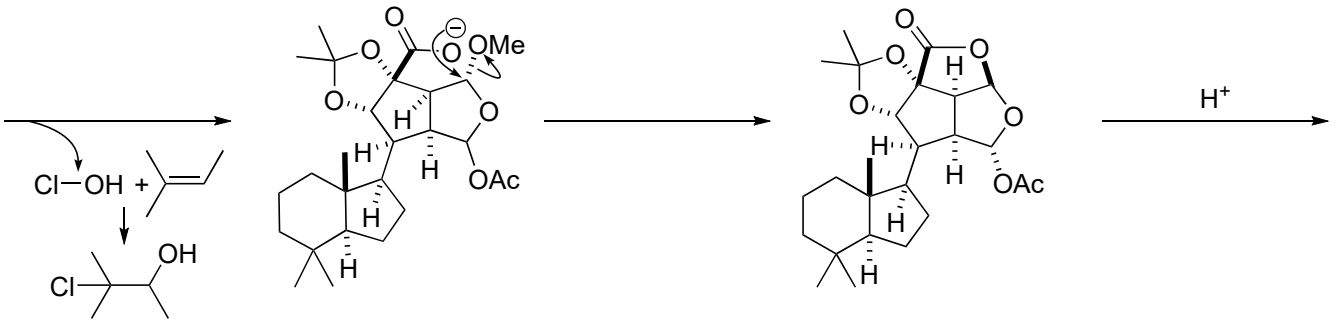
2-17

step 6

Pinnick oxidation

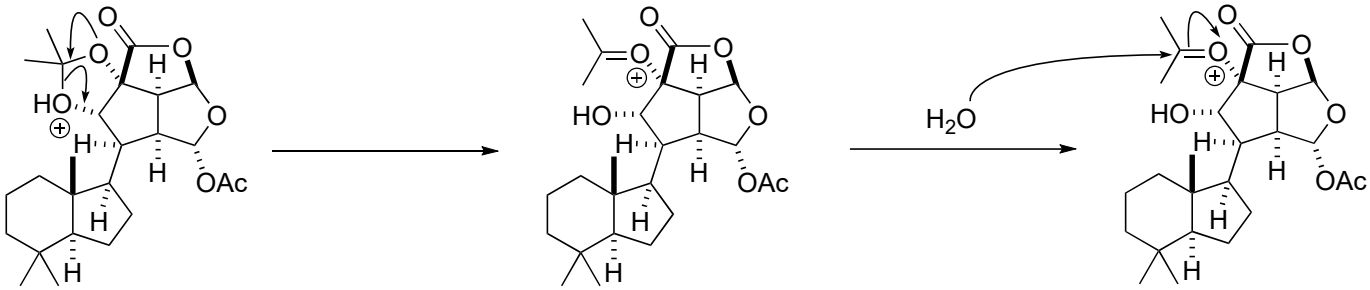


2-18

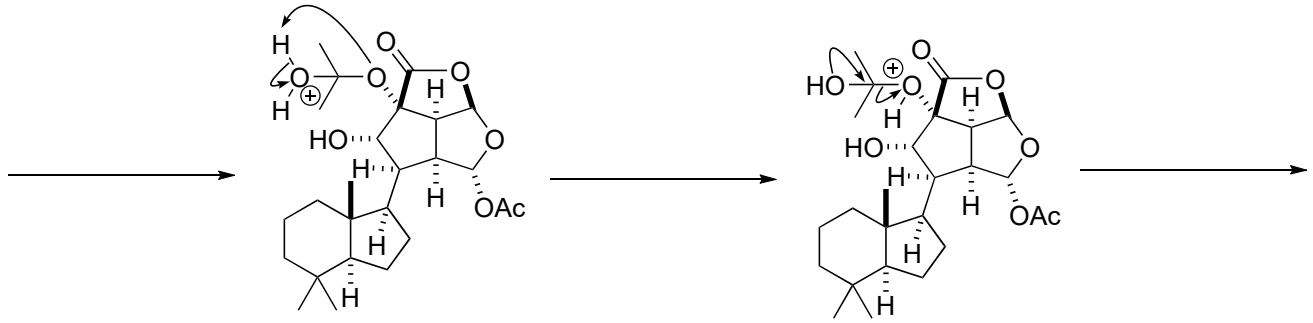


2-19 **2-20**

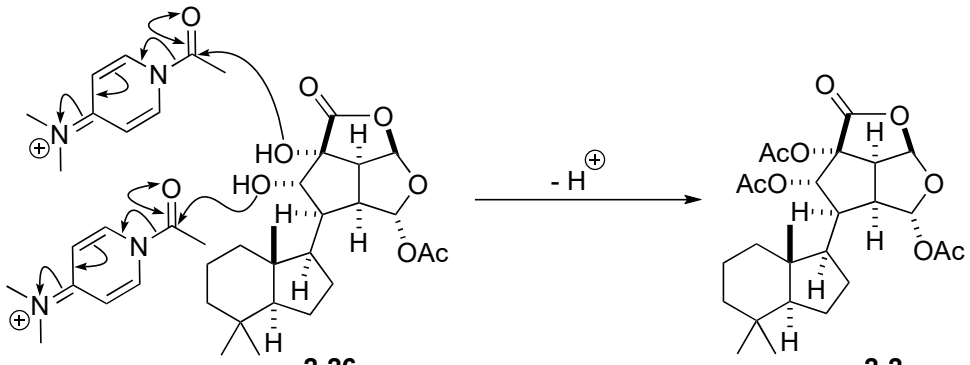
step 7



2-21 **2-22** **2-23**



2-24 **2-25**



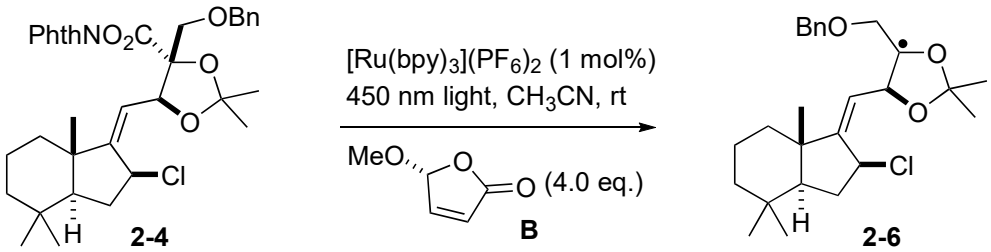
2-26

step 8

2-2
Chromodorolide B

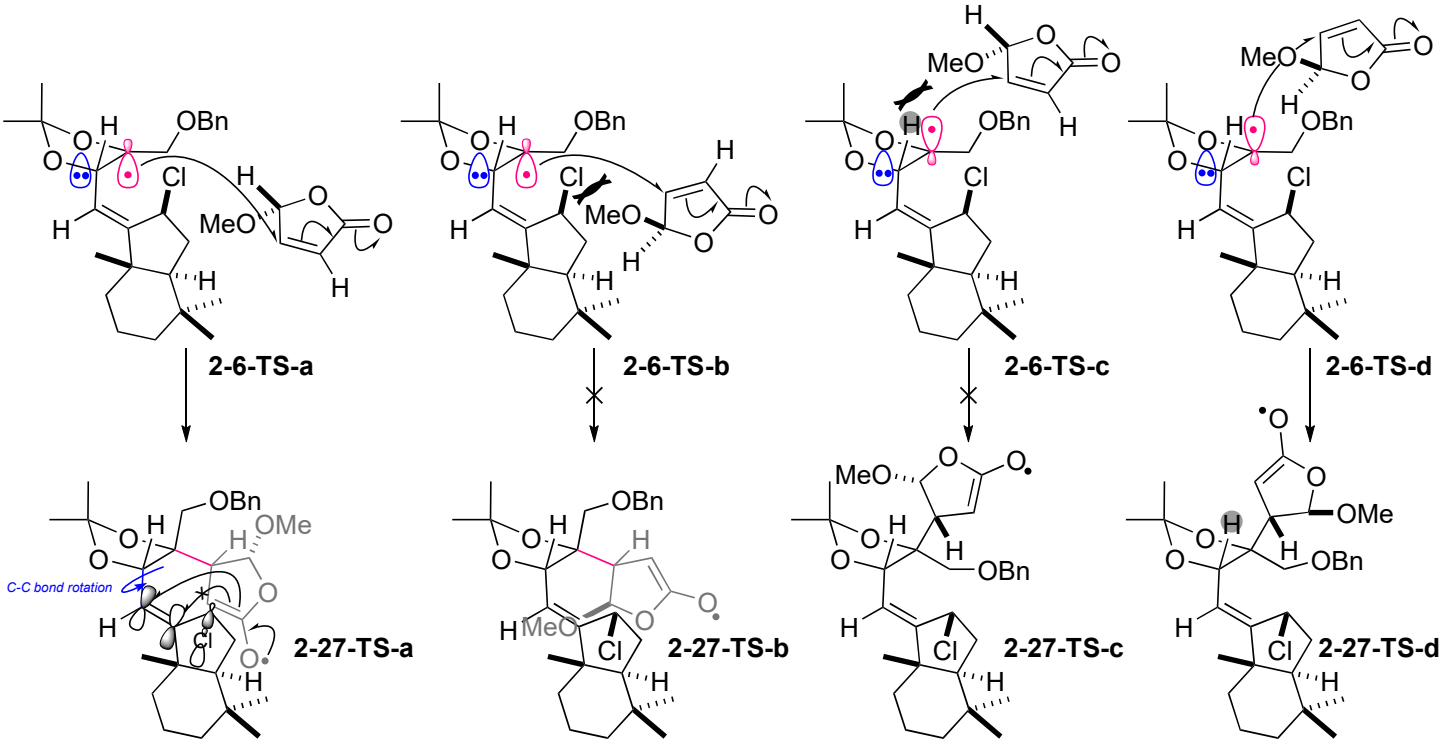
step 9

discussion 3 (raddical addition)



Addition from bottom face (desired) **TS-a**, **TS-b**

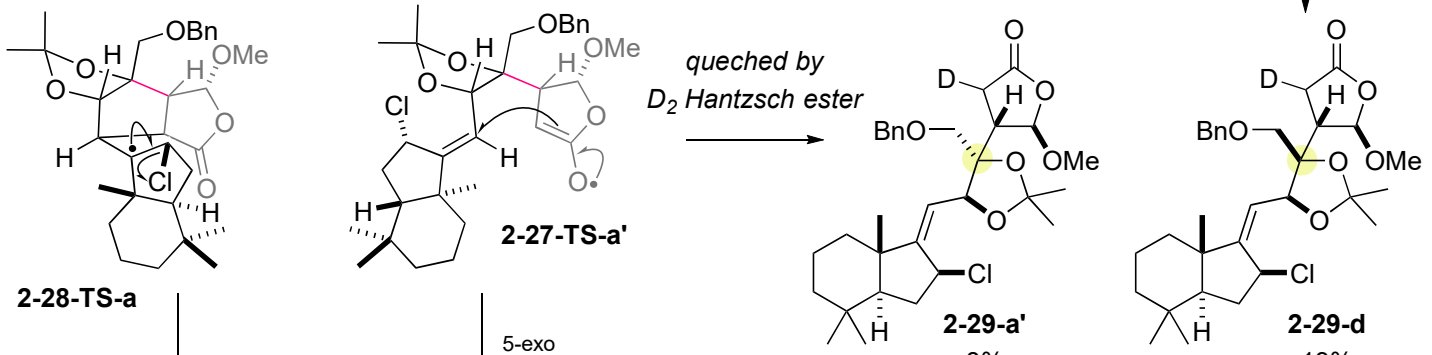
Addition from top face (undesired) **TS-c**, **TS-d**



5-exo

C-C bond rotation to avoid steric repulsion between H atom, methyl and furanone ring

quenched by D_2 Hantzsch ester



5-exo