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Letter

Stereocontrolled Total Synthesis of (−)-Isocelorbicol and Its Elaboration to Natural Dihydro-β-agarofuran Esters

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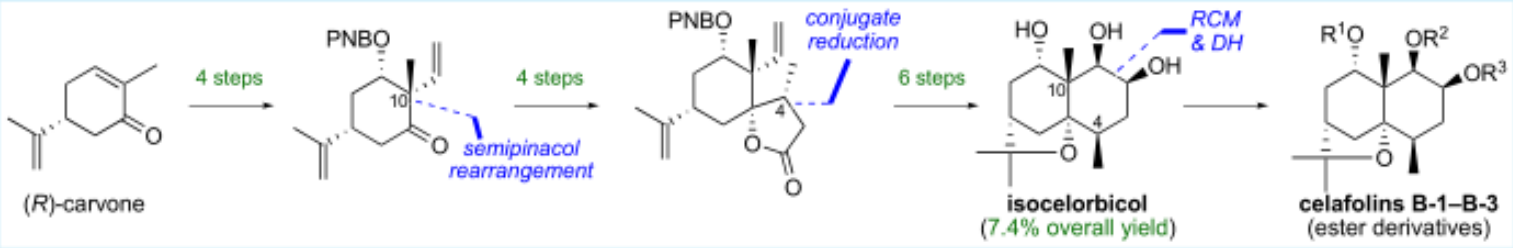
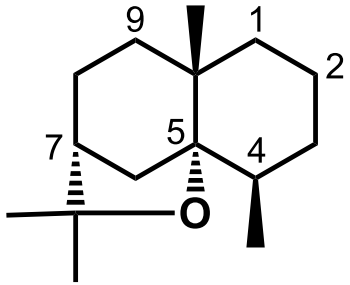
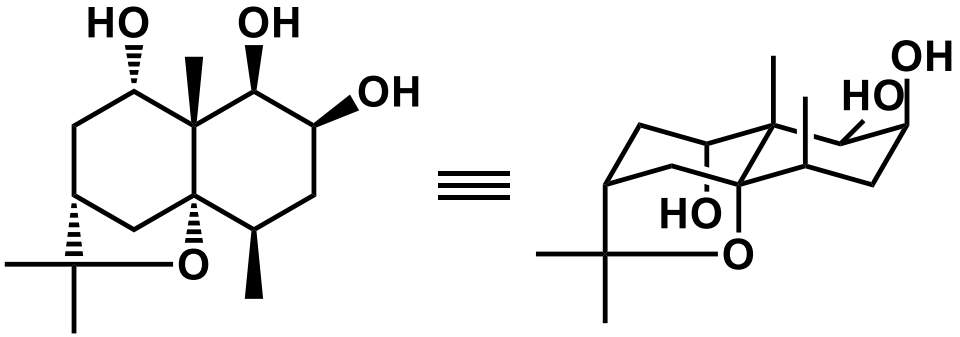


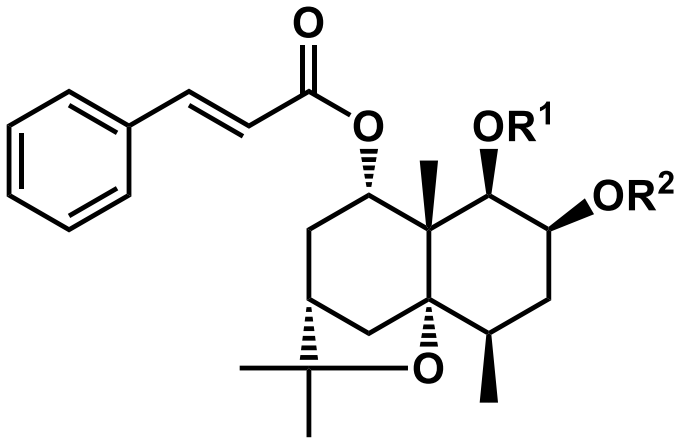
背景介绍



dihydro-β-agarofuran **(1)**



(-)-isocelorbicol **(2)**



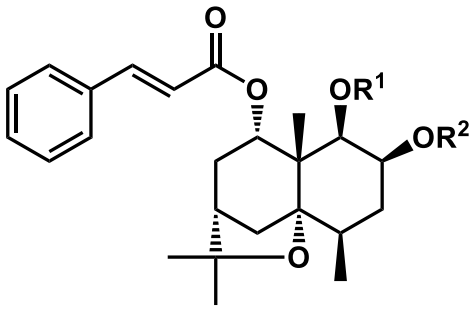
3. R^1=Ac, R^2=H (celafolin B-1)

4. R^1=H, R^2=Ac (celafolin B-2)

5. R^1=Ac, R^2=Bz (celafolin B-3)

6. R^1=R^2=Ac

逆合成分析



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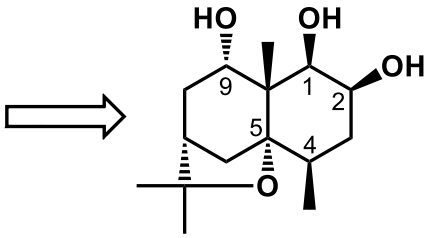

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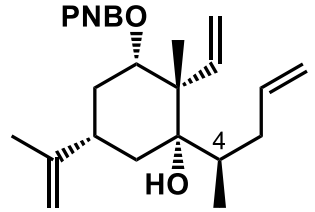

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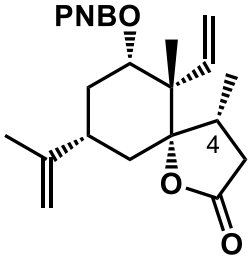

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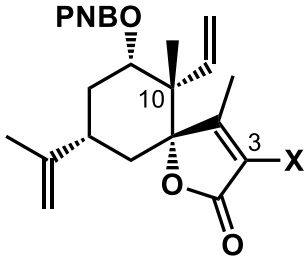

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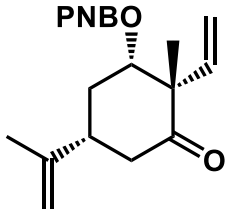

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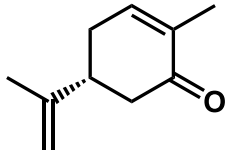
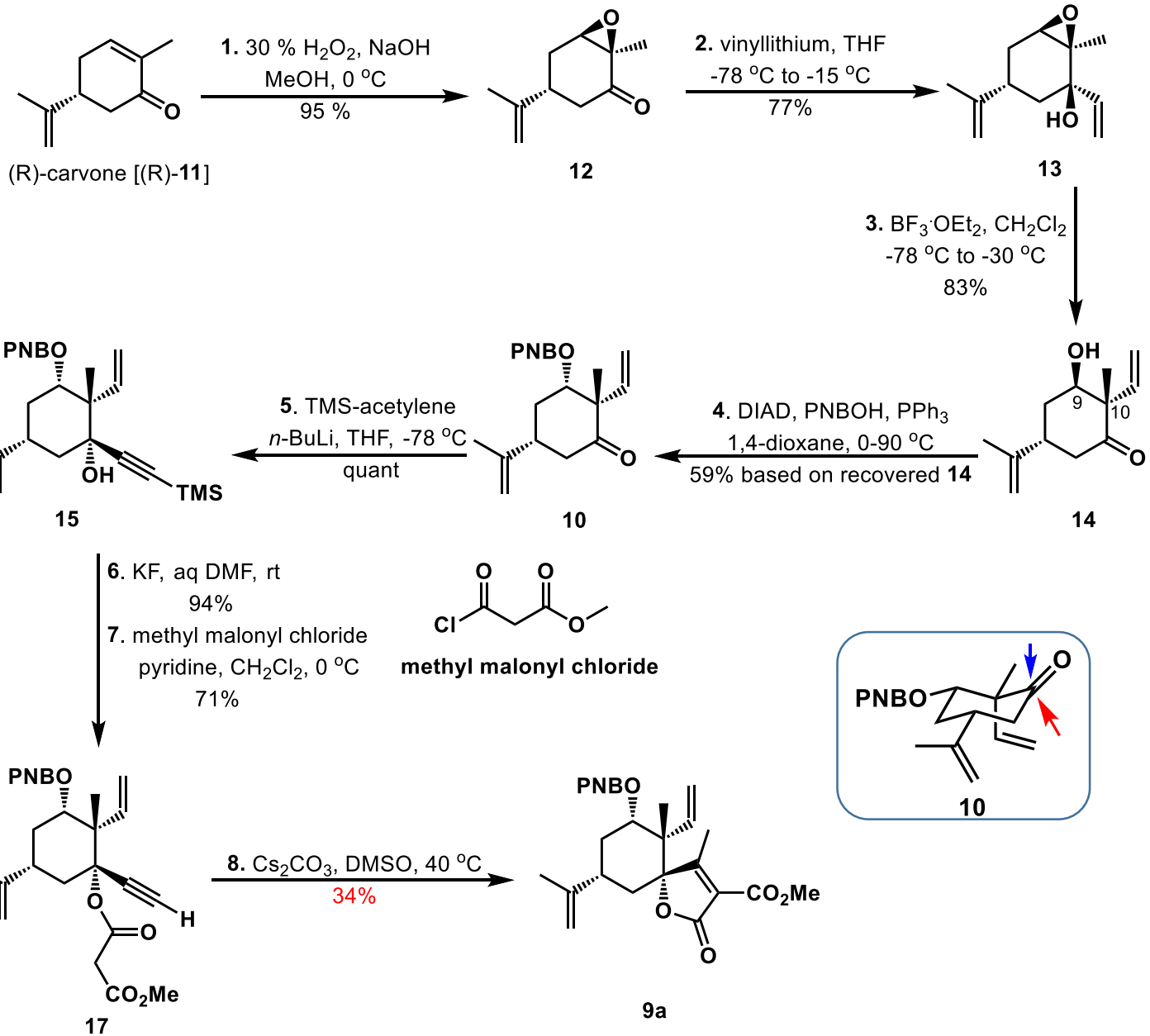
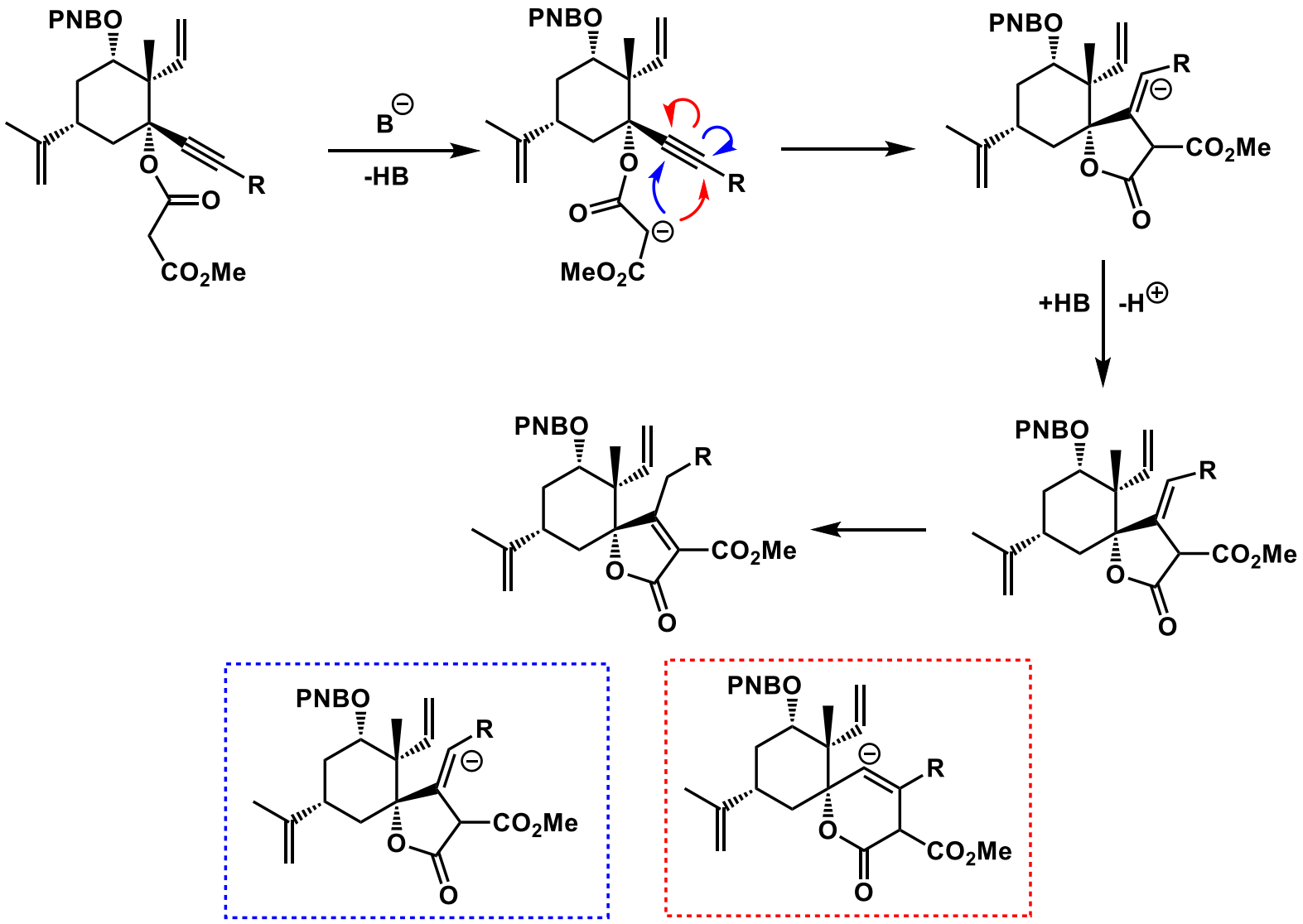


(R)-carvone [(R)-**11**]

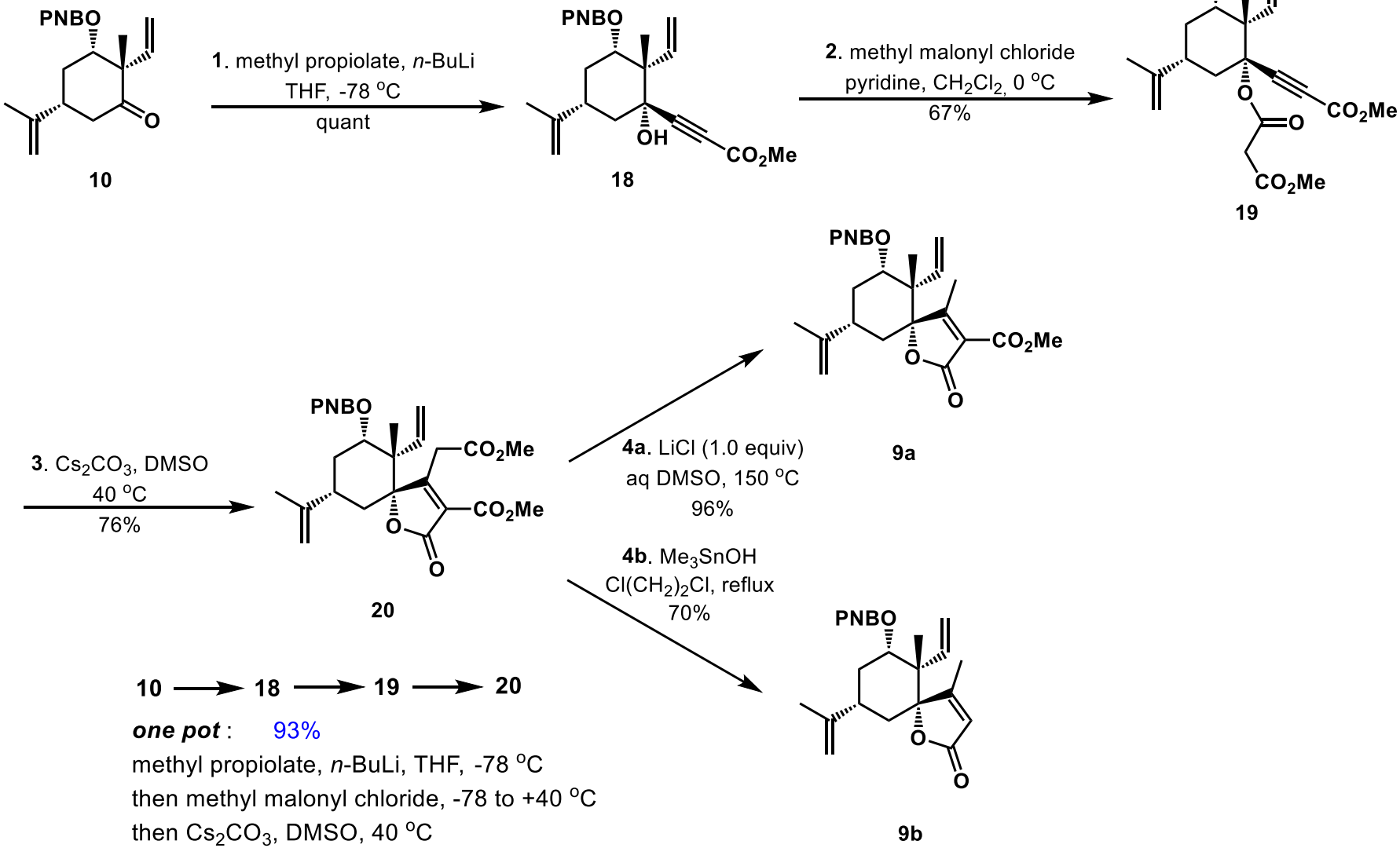
螺环中间体9的制备


1. 30 % H2O2, NaOH
MeOH, 0 °C
95 %
2. vinyllithium, THF
-78 °C to -15 °C
77%
(R)-carvone [(R)-11]
12
13
3. BF3·OEt2, CH2Cl2
-78 °C to -30 °C
83%
PNBO
OH
TMS
15
5. TMS-acetylene
n-BuLi, THF, -78 °C
quant
10
4. DIAD, PNBOH, PPh3
1,4-dioxane, 0-90 °C
59% based on recovered 14
14
6. KF, aq DMF, rt
94%
7. methyl malonyl chloride
pyridine, CH2Cl2, 0 °C
71%
methyl malonyl chloride
17
8. Cs2CO3, DMSO, 40 °C
34%
9a
10

螺环关环机理



螺环中间体9的制备



10 → 18 → 19 → 20

one pot : 93%

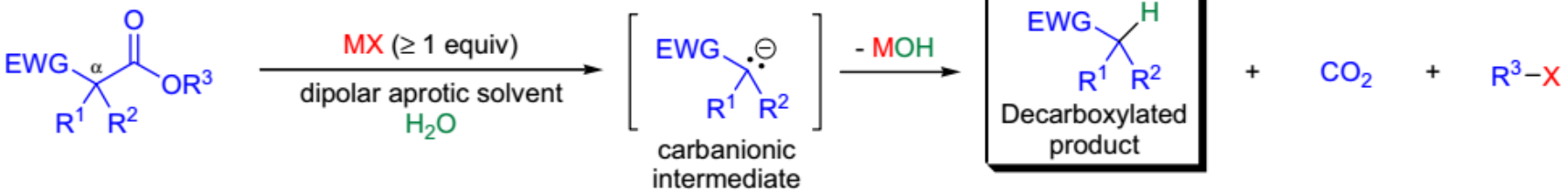
methyl propiolate, *n*-BuLi, THF, -78 °C

then methyl malonyl chloride, -78 to +40 °C

then Cs_2CO_3, DMSO, 40 °C

Krapcho dealkoxycarbonylation

Krapcho dealkoxycarbonylation:

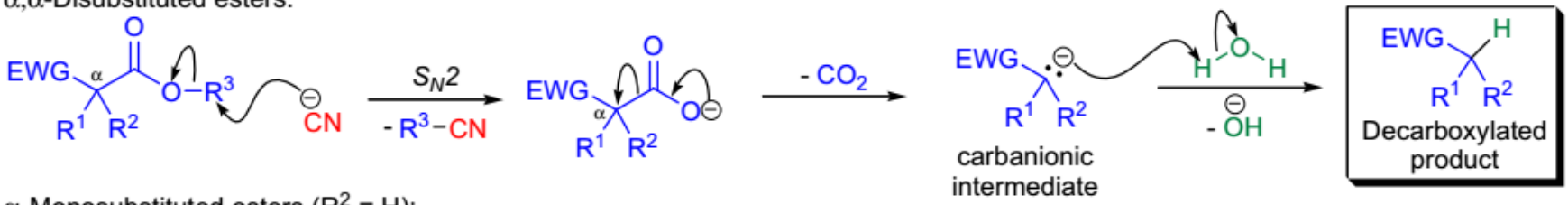


EWG = CO_2-alkyl, CO_2-aryl, CN, CO-alkyl, SO_2-alkyl, SO_2-aryl; R^{1-2} = H, alkyl, aryl; R^3 = Me, Et; MX = NaCN, KCN, LiCl, NaCl, NaBr, NaI, LiI·H_2O, Na_2CO_3·H_2O, Na_3PO_4·$12H_2O$, Me_4NOAc ; solvent: DMSO, DMF, DMA, HMPT

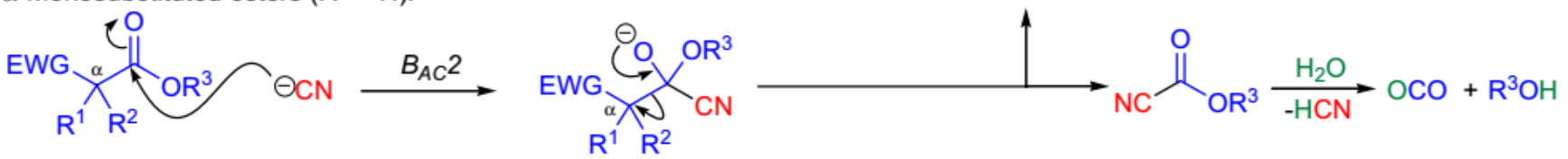
Mechanism: [16,17,9,18,19]

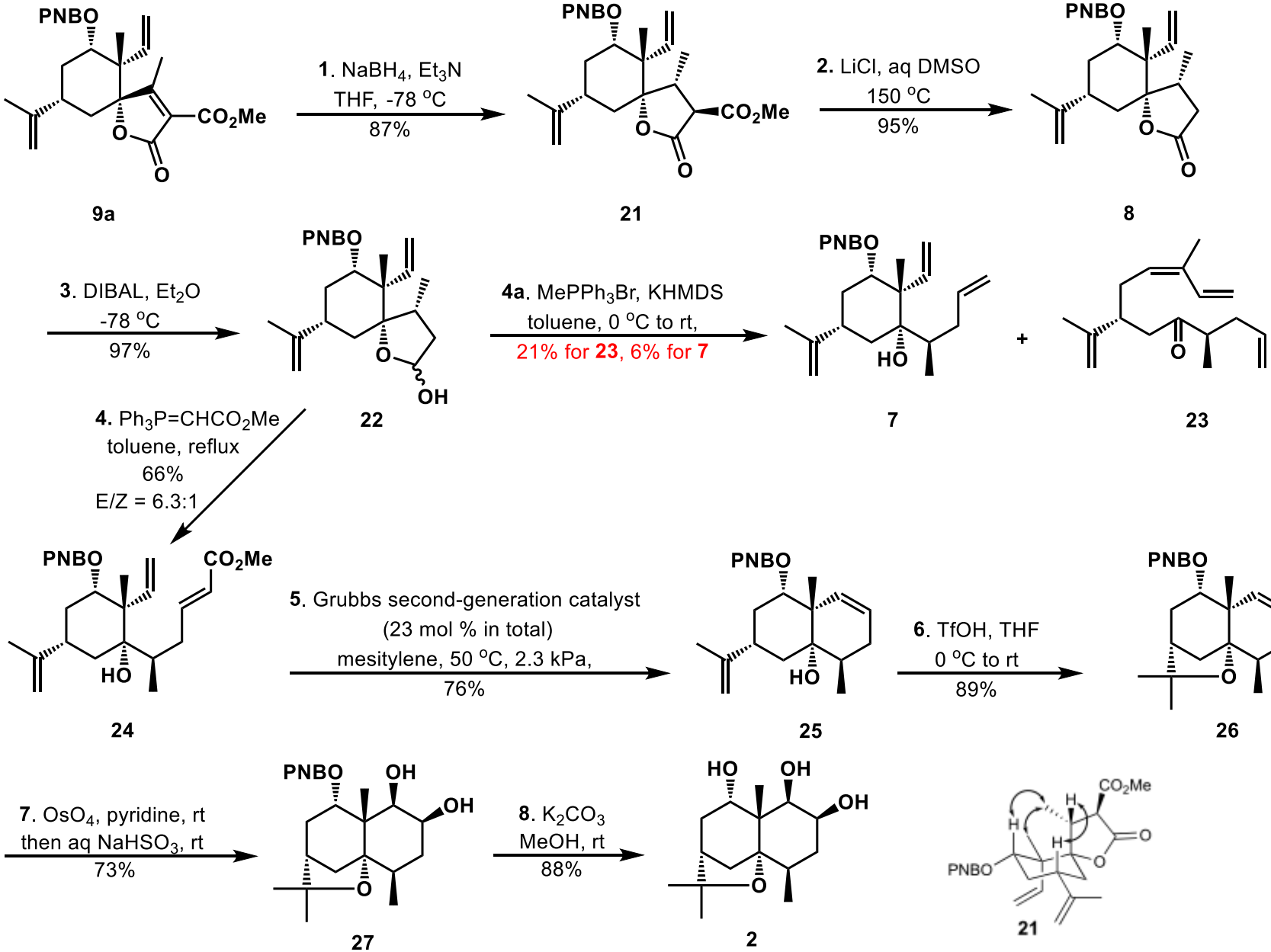
The mechanism of the *Krapcho dealkoxycarbonylation* is dependent on the structure of the substrate ester and the type of anion used. In the case of α,α-disubstituted diesters (especially the methyl esters), the anion from the salt (cyanide ion in the scheme) attacks the alkyl group of the ester in an S_N2 fashion and the decarboxylation results in the formation of a carbanionic intermediate that is quenched by the water. In the case of α-monosubstituted diesters the cyanide attacks the carbonyl group to form a tetrahedral intermediate, which breaks down to give the same carbanionic intermediate and a cyanoformate, which is hydrolyzed to give carbon dioxide and an alcohol.

α,α-Disubstituted esters:

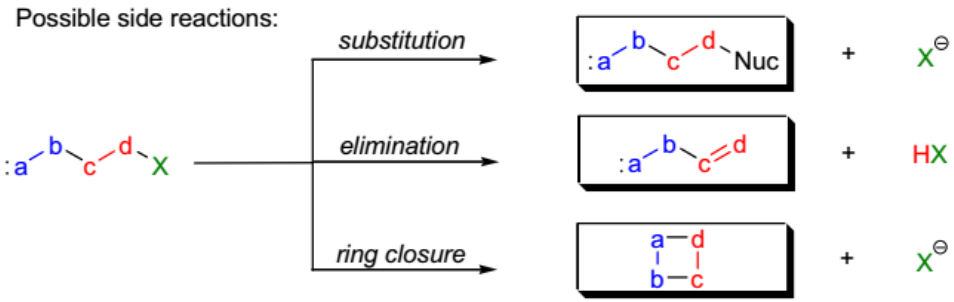


α-Monosubstituted esters (R^2 = H):




PNBO
CO2Me
O
O
9a
1. NaBH4, Et3N
THF, -78 °C
87%
21
2. LiCl, aq DMSO
150 °C
95%
8
3. DIBAL, Et2O
-78 °C
97%
OH
22
4a. MePPh3Br, KHMDS
toluene, 0 °C to rt,
21% for 23, 6% for 7
HO
7
+
23
4. Ph3P=CHCO2Me
toluene, reflux
66%
E/Z = 6.3:1
24
5. Grubbs second-generation catalyst
(23 mol % in total)
mesitylene, 50 °C, 2.3 kPa,
76%
25
6. TfOH, THF
0 °C to rt
89%
26
7. OsO4, pyridine, rt
then aq NaHSO3, rt
73%
27
8. K2CO3
MeOH, rt
88%
2
H
21

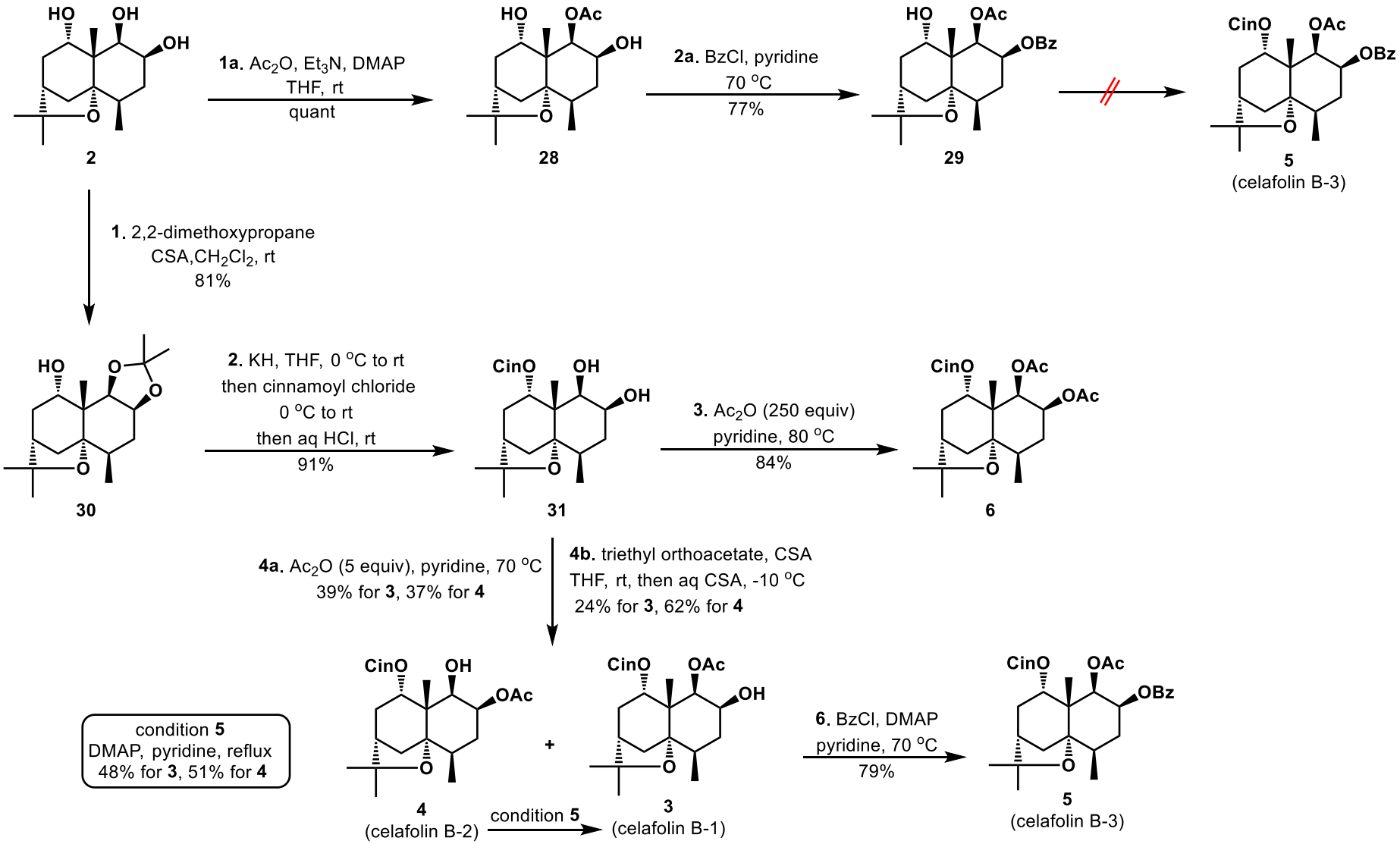
Grob碎片化反应



1) one-step synchronous

2) two-step cationic

3) two-step anionic


HO
OH
OH
O
2
1a. Ac2O, Et3N, DMAP
THF, rt
quant
HO
OAc
OH
O
28
2a. BzCl, pyridine
70 °C
77%
HO
OAc
OBz
O
29
CinO
OAc
OBz
O
5
(celafolin B-3)
1. 2,2-dimethoxypropane
CSA,CH2Cl2, rt
81%
HO
O
O
O
30
2. KH, THF, 0 °C to rt
then cinnamoyl chloride
0 °C to rt
then aq HCl, rt
91%
CinO
OH
OH
O
31
3. Ac2O (250 equiv)
pyridine, 80 °C
84%
CinO
OAc
OAc
O
6
4a. Ac2O (5 equiv), pyridine, 70 °C
39% for 3, 37% for 4
4b. triethyl orthoacetate, CSA
THF, rt, then aq CSA, -10 °C
24% for 3, 62% for 4
condition 5
DMAP, pyridine, reflux
48% for 3, 51% for 4
CinO
OH
OAc
O
4
(celafolin B-2)
+
CinO
OAc
OH
O
3
(celafolin B-1)
condition 5
6. BzCl, DMAP
pyridine, 70 °C
79%
CinO
OAc
OBz
O
5
(celafolin B-3)