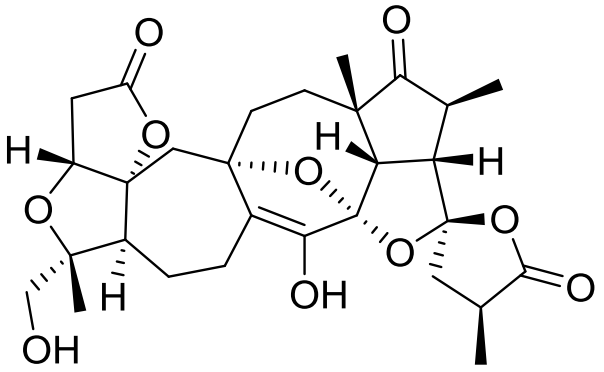
Asymmetric Total Synthesis of Lancifodilactone G Acetate

Dong-Dong Liu, Tian-Wen Sun, Kuang-Yu Wang, Yong Lu, Su-Lei Zhang, Yuan-He Li, Yan-Long Jiang, Jia-Hua Chen, and Zhen Yang

J. Am. Chem. Soc., 2017, 139, 5732–5735

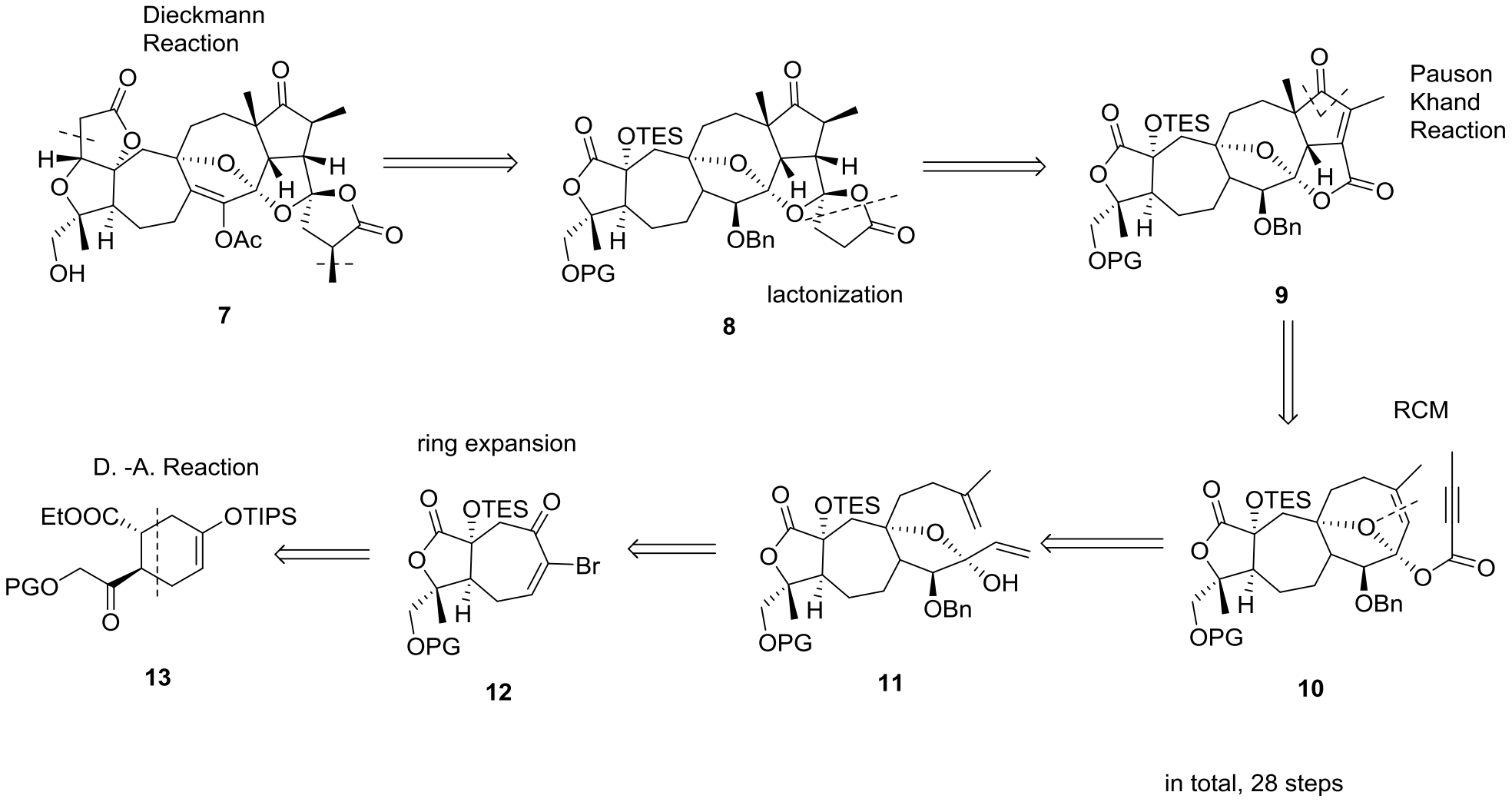
- Lancifodilactone G was isolated from the medicinal plant *Schisandra lancifolia* by Sun and co-workers in 2005, and its structure has been determined by X-ray crystallographic analysis.
- It contains a rare nonresonance-stabilized aliphatic enol, a highly congested tricyclic ring system and an unusual 2- fold anomerically stabilized bis-spiro system.
- Many Schinortriterpenoids have shown the usefulness in antihepatitis, antitumor, and anti-HIV agents.



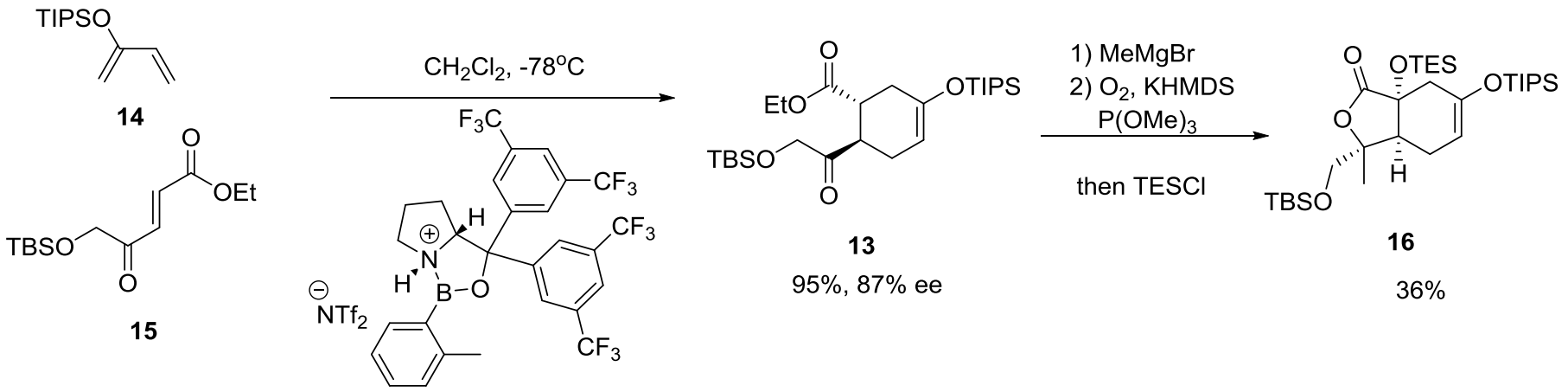
Lancifodilactone G

Presented by Yuanzhe Zhang, Liu group.

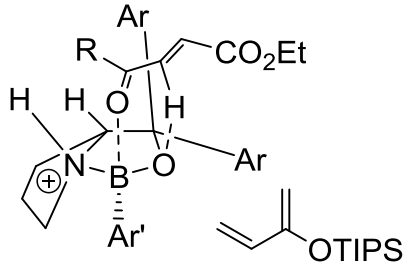
Retro-synthetic Route



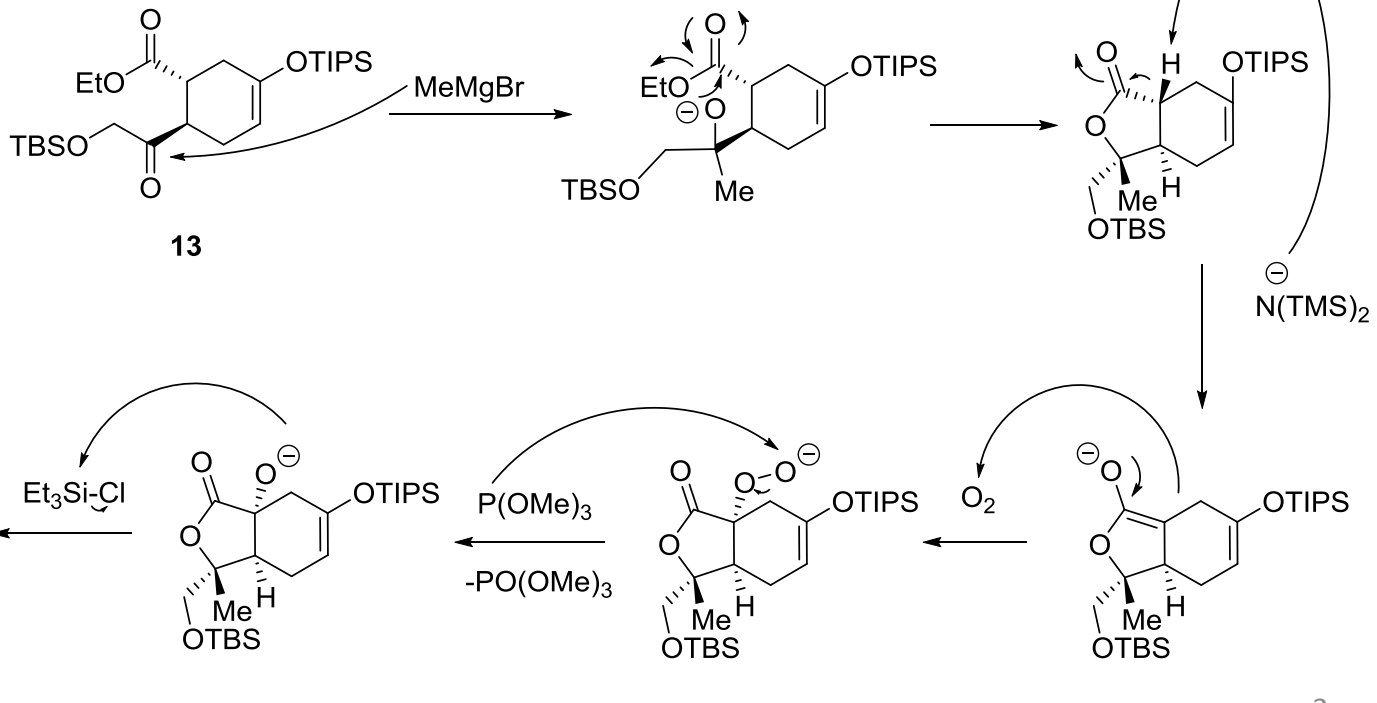
A very similar product, see: Yang, Z. *Nat. Commun*. **2017**, *8*, 14233.

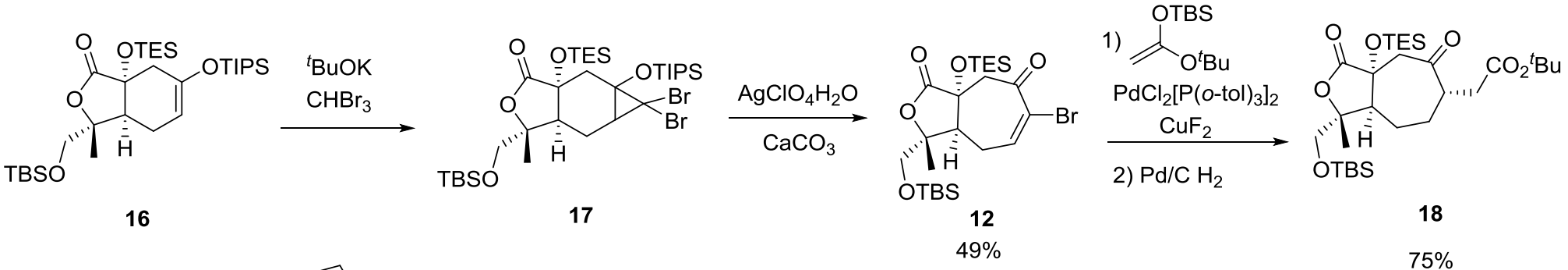


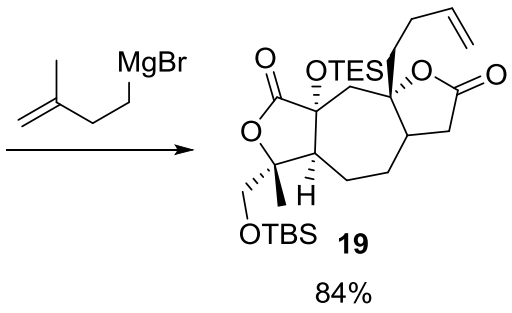
Oxazaborolidine catalyzed 4+2

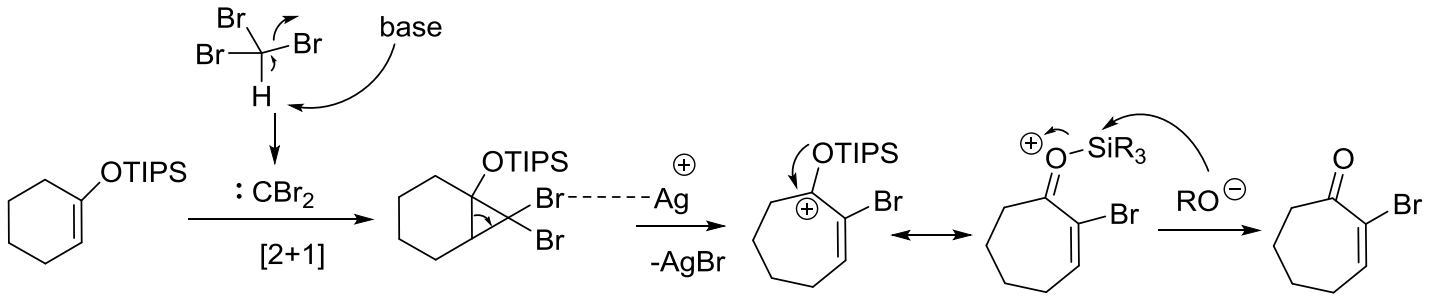


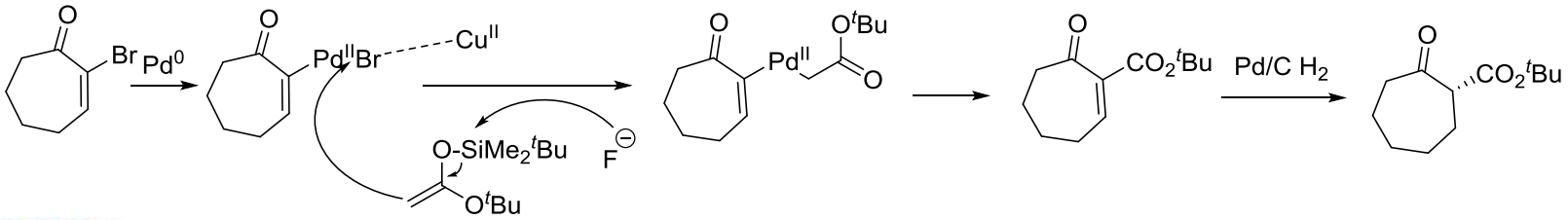
coordination from top
dienophile perpendicular to NBO ring

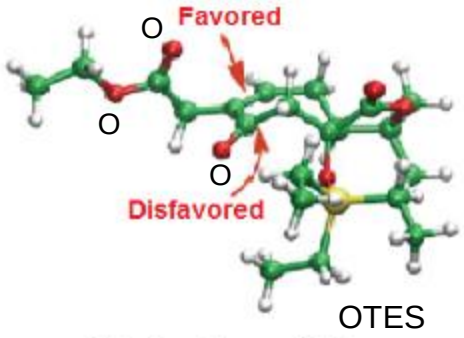




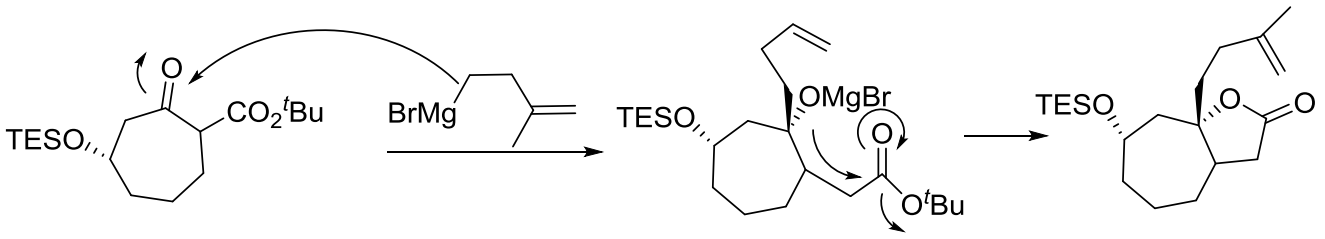


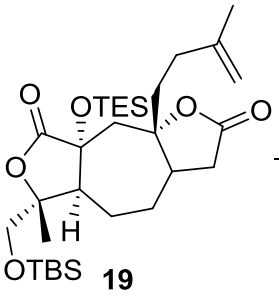






3D structure of **18**

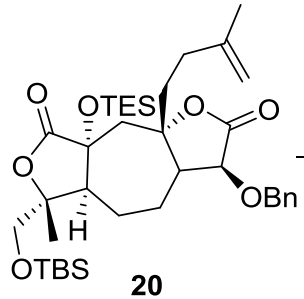




19

1) LiHMDS, LiCl, MoOPH

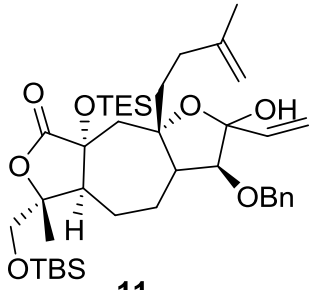
2) BnBr, Ag_2O



20

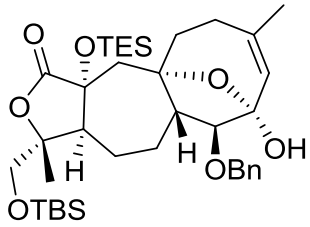
80%

MgBr



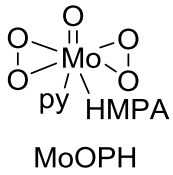
11

H -G II



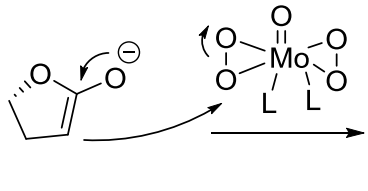
21

75%

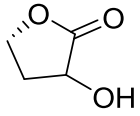


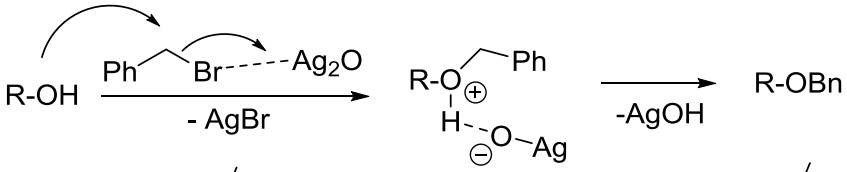
MoOPH

LiHMDS



hydrolysis





R-OH

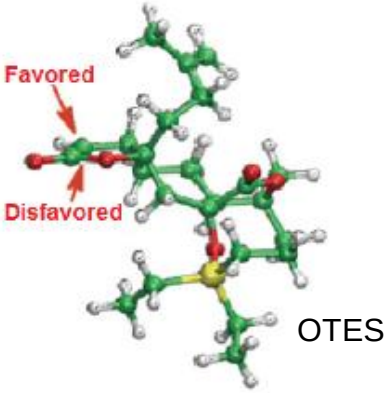
Ph Br Ag_2O

- AgBr

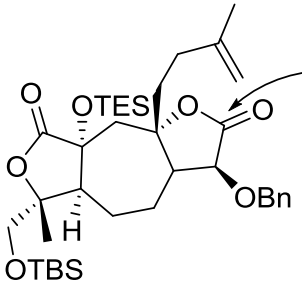
R-O Ph H O Ag

-AgOH

R-OBn

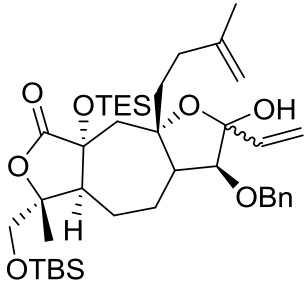


19



20

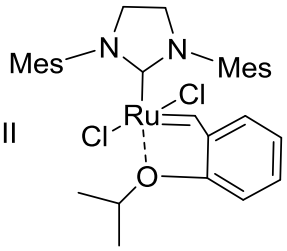
MgBr



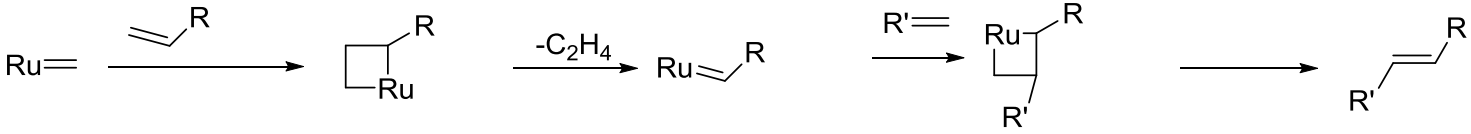
5:1 selectivity

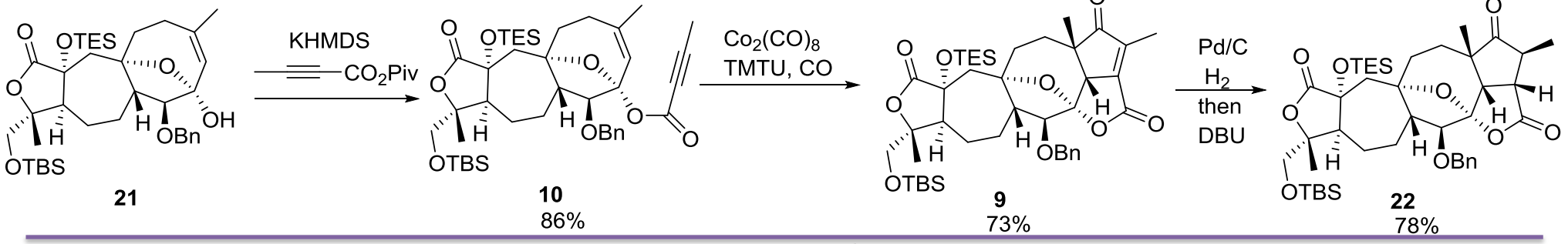
relatively unstable

in situ epimerize when treated the mixture with HG II



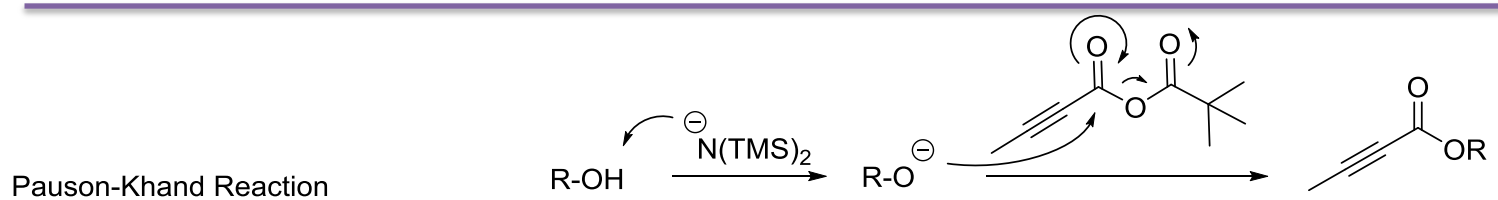
H -G II

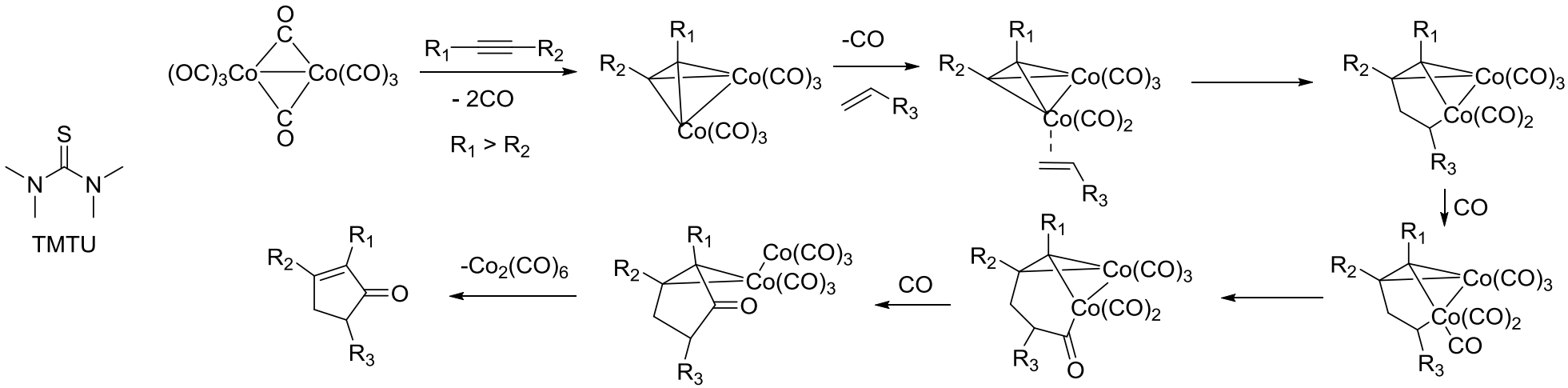


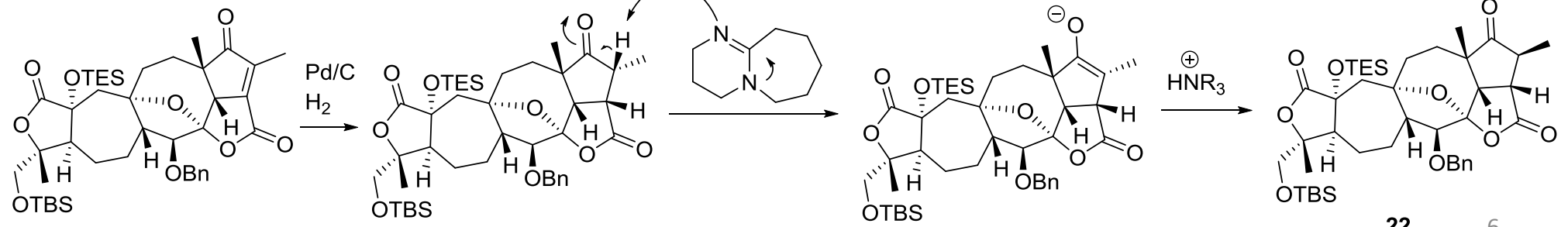


21 → **10** 86% → **9** 73% → **22** 78%

Pauson-Khand Reaction



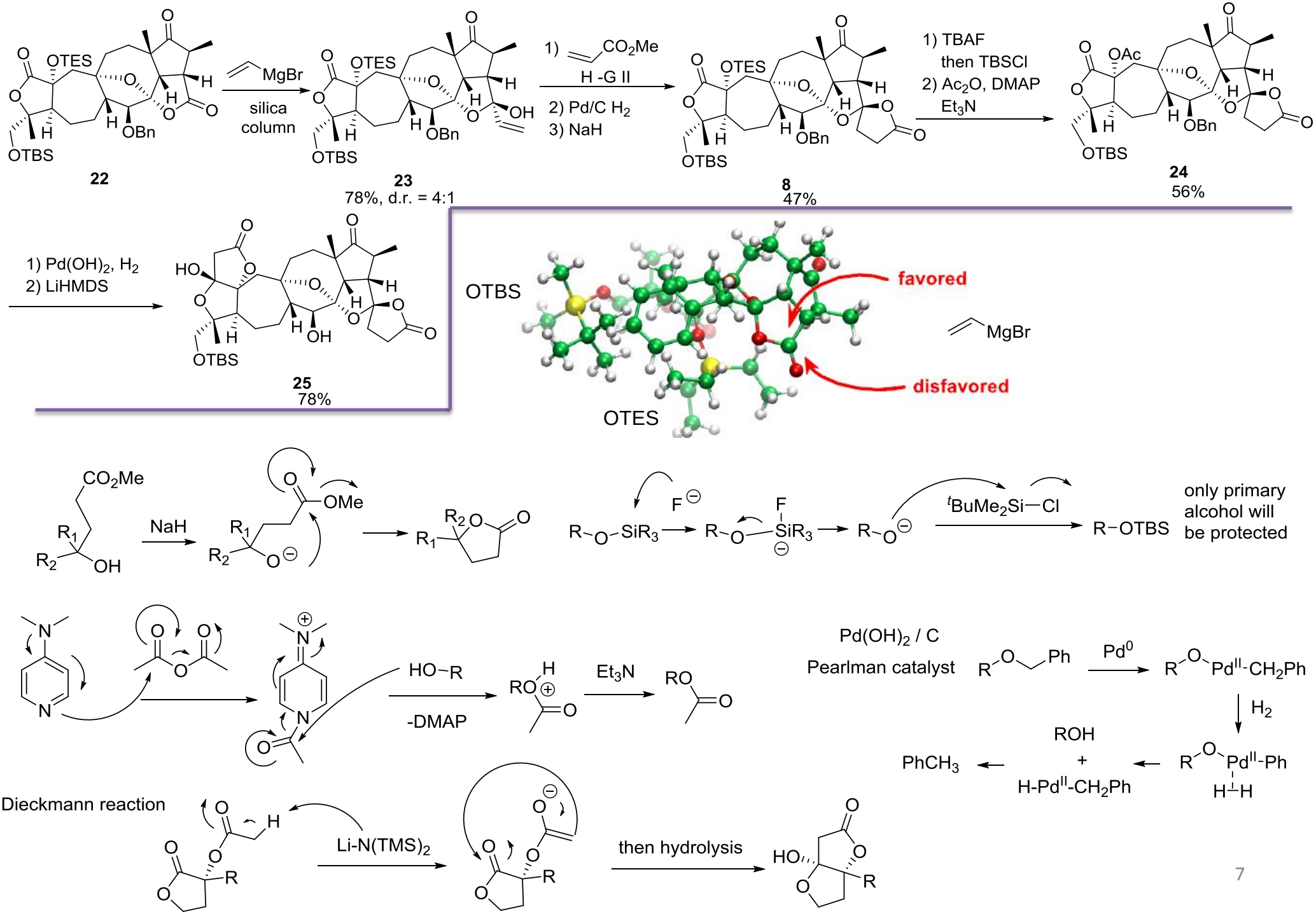


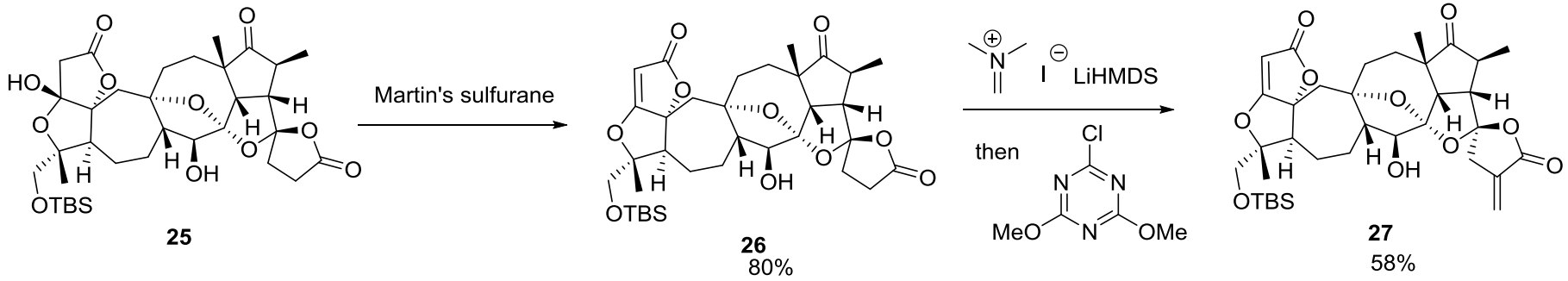


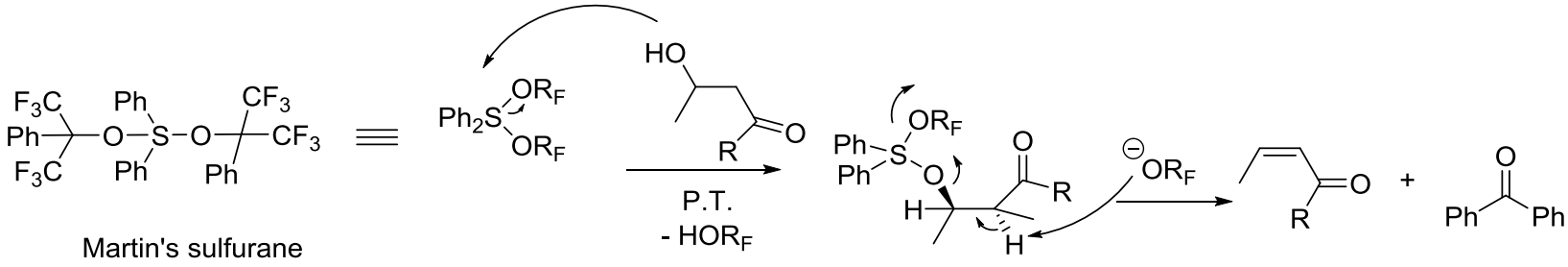
9 Based on crystal structure, the OTES blocks one way

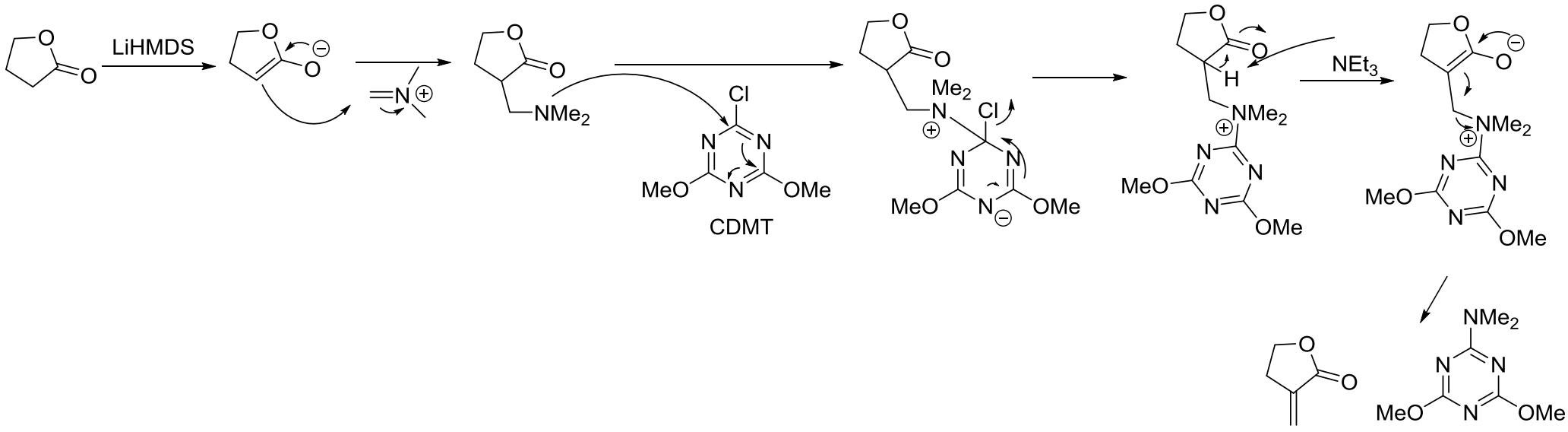
epimerization

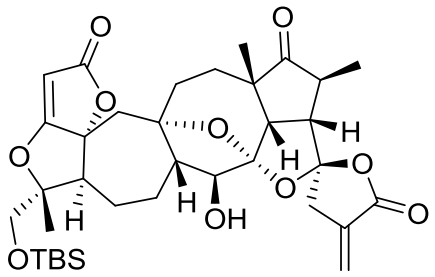
22


OTES
OTBS
OBn
MgBr
silica column
1) CO2Me
H -G II
2) Pd/C H2
3) NaH
1) TBAF
then TBSCl
2) Ac2O, DMAP
Et3N
OAc
22
23
78%, d.r. = 4:1
8
47%
24
56%
1) Pd(OH)2, H2
2) LiHMDS
HO
OH
25
78%
favored
disfavored
CO2Me
NaH
OMe
F
SiR3
tBuMe2Si—Cl
R—OTBS
only primary alcohol will be protected
HO—R
-DMAP
Et3N
RO
Pd(OH)2 / C
Pearlman catalyst
Pd0
PdII-CH2Ph
H2
PdII-Ph
H-PdII-CH2Ph
ROH
PhCH3
Dieckmann reaction
Li-N(TMS)2
then hydrolysis


Martin's sulfurane
LiHMDS
then
25
26
80%
27
58%

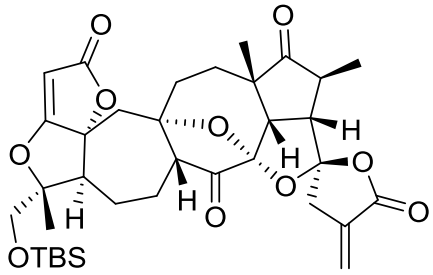

Martin's sulfurane
P.T.
- HORF


LiHMDS
CDMT
NEt3



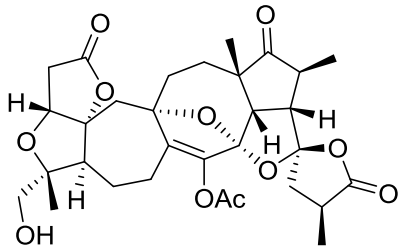
27

DMP, $NaHCO_3$



28

1) Ac_2O,Et_3N
DMAP
2) Pd/C, H_2
MeOH

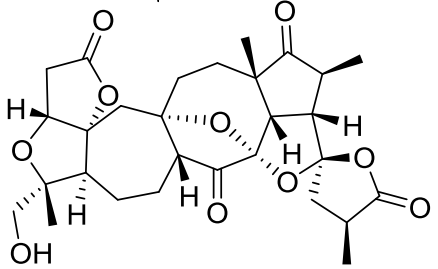


7

80%

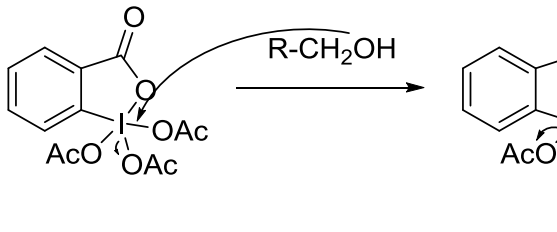
All the OAc deprotect methods failed.

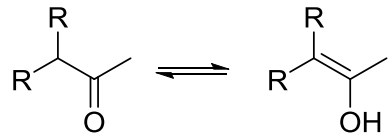
Pd/C, H_2
MeOH



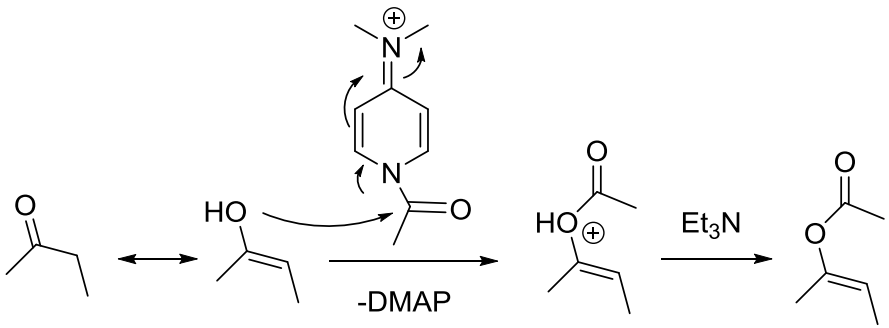
29

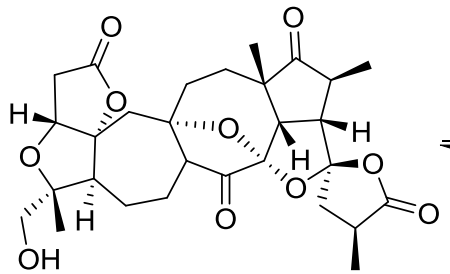
Decomposed anyway





R = H, +13.0 kcal/mol
R = Me, +9.3 kcal/mol





-0.8kcal/mol