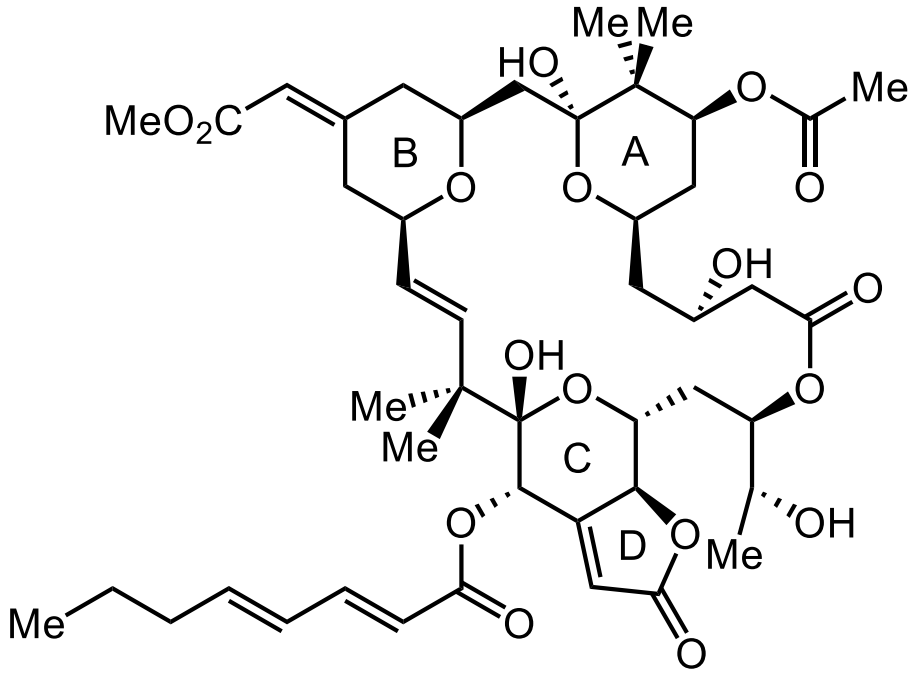
Total Synthesis of Bryostatin 3



unique butenolide unit

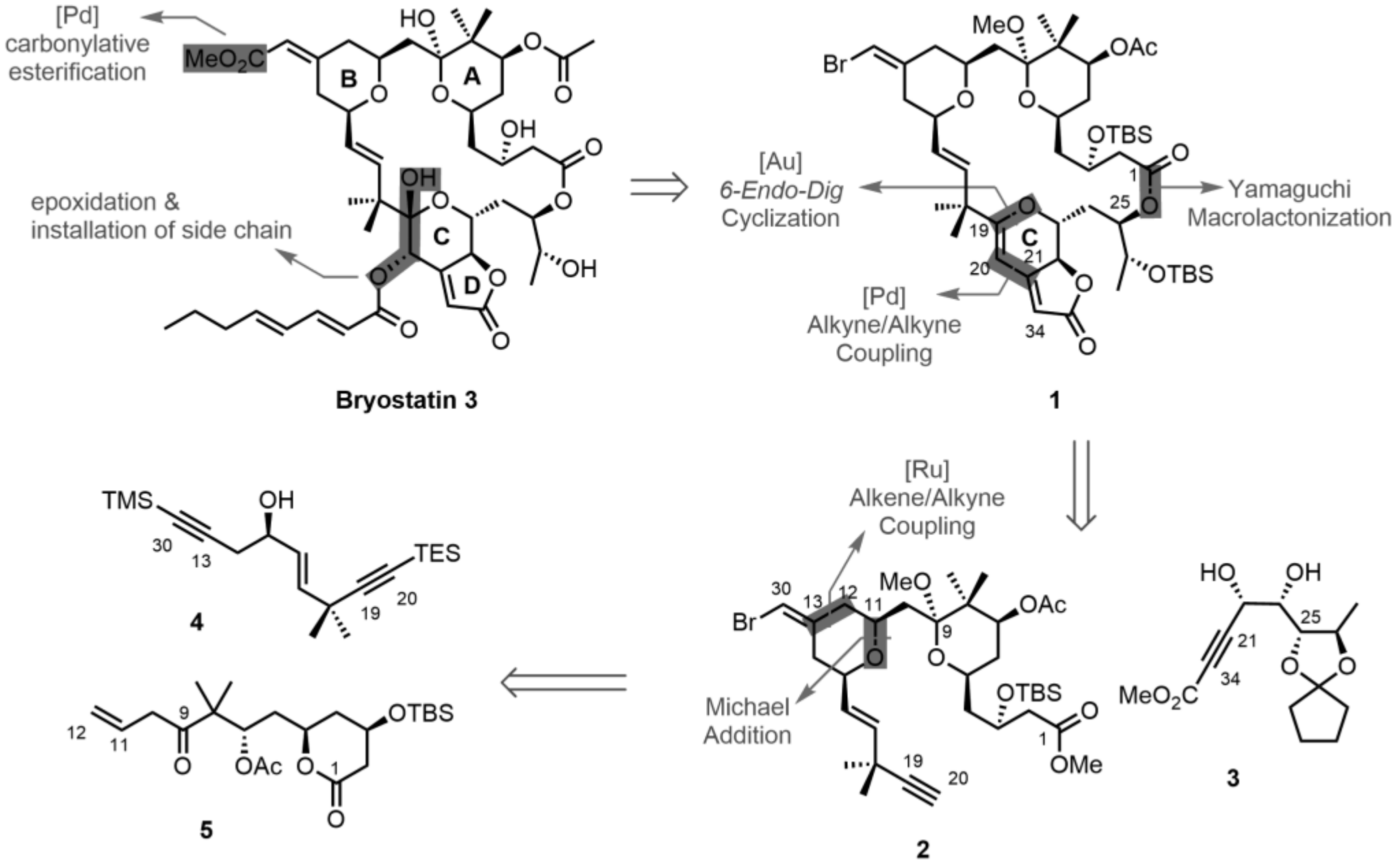
Bryostatin 3: PKC Ki = 2.75 nM
Yamamura 2000, 43 steps (LLS), 88 steps (TS)
This work, 22 steps (LLS), 31 steps (TS)

- First isolated by Pettit from the marine bryozoan, are a family of 21 macrolides.
- Potent antineoplastic, immunopotentiating, synaptogenesis inducing, and latent HIV–modulating activity.
- Beneficial effects as a post-stroke treatment and for restoring the blood-brain barrier after traumatic blast injuries.
- 26-membered lactone and three highly functionalized tetrahydropyrans integrated in the macrocycle.

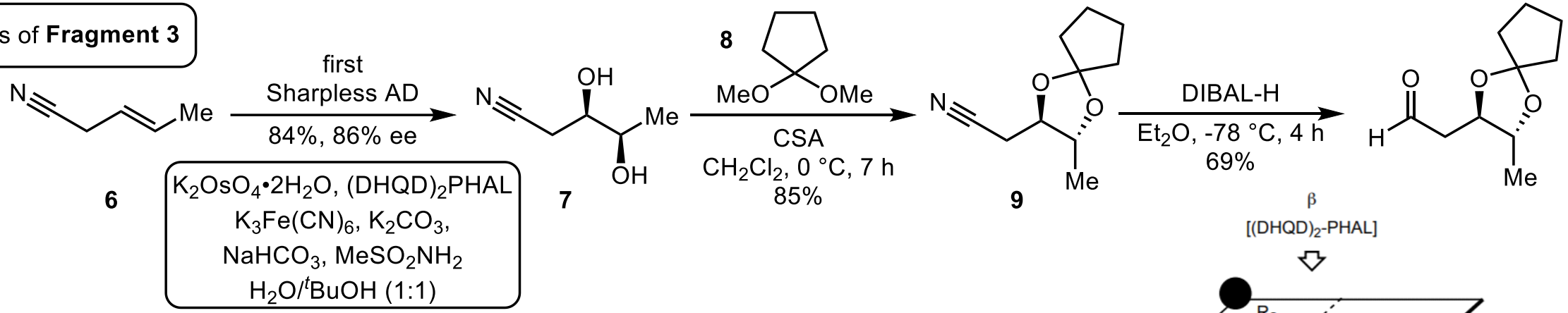
Ziyong Wang
Liu Research Group
Total Synthesis Presentation
12/9/2020

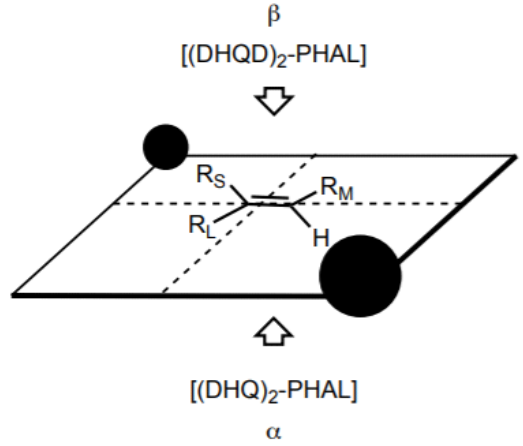
Trost, B. M.; Wang, Y.; Buckl, A. K.; Huang, Z.; Nguyen, M. H.; Kuzmina, O., *Science* **2020,** *368*, 1007-1011.

Retrosynthetic analysis of Bryostatin 3

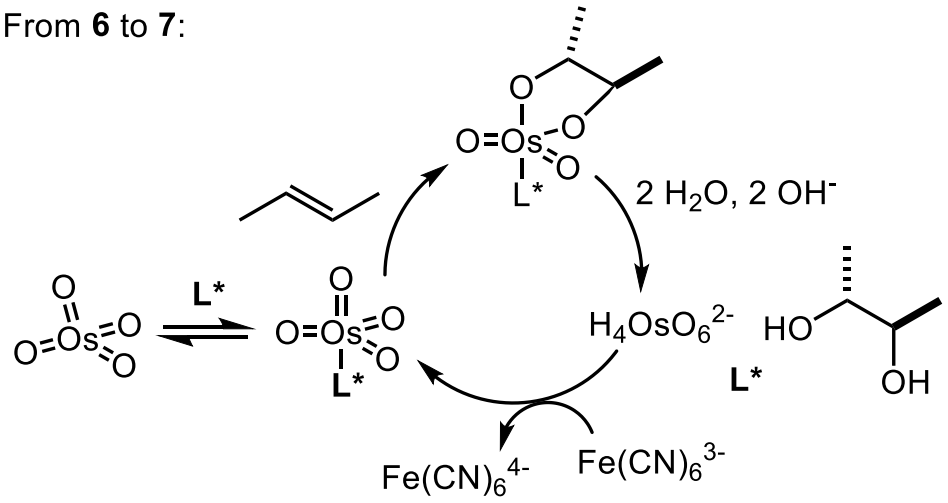


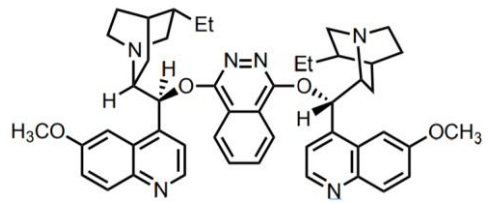
Synthesis of **Fragment 3**

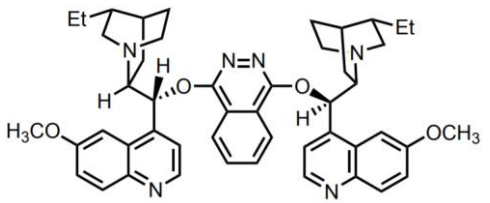




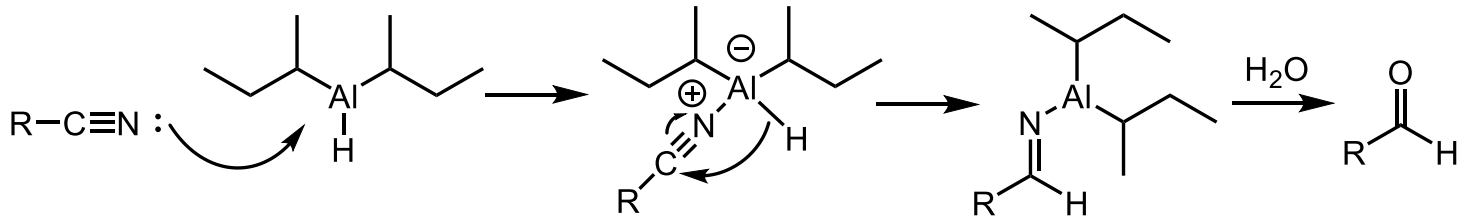
From **6** to **7**:



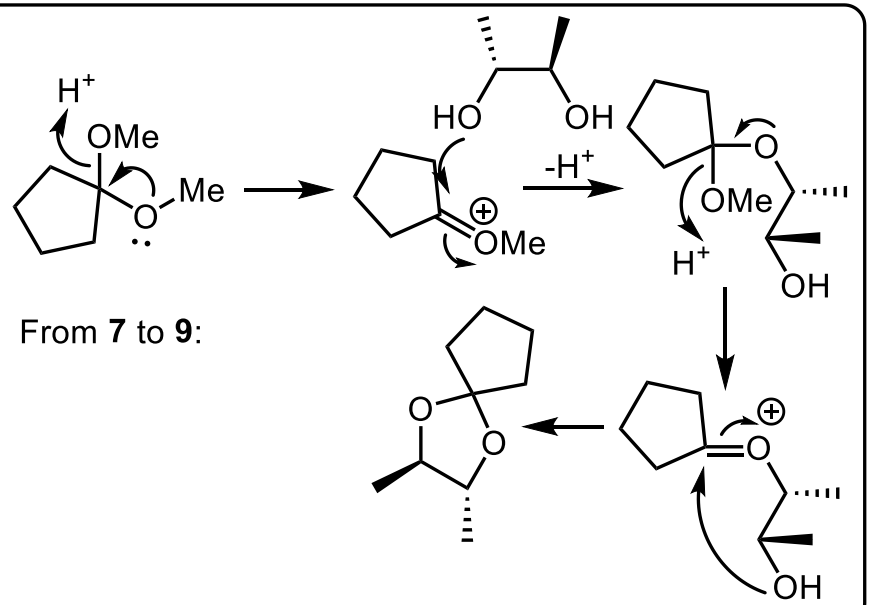




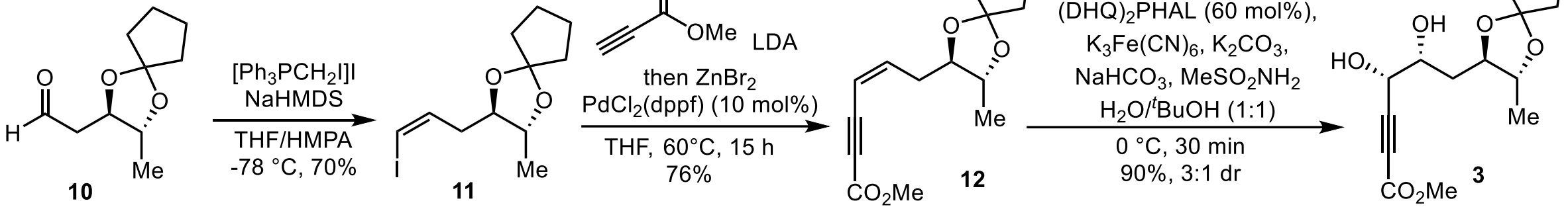
From **9** to **10**:



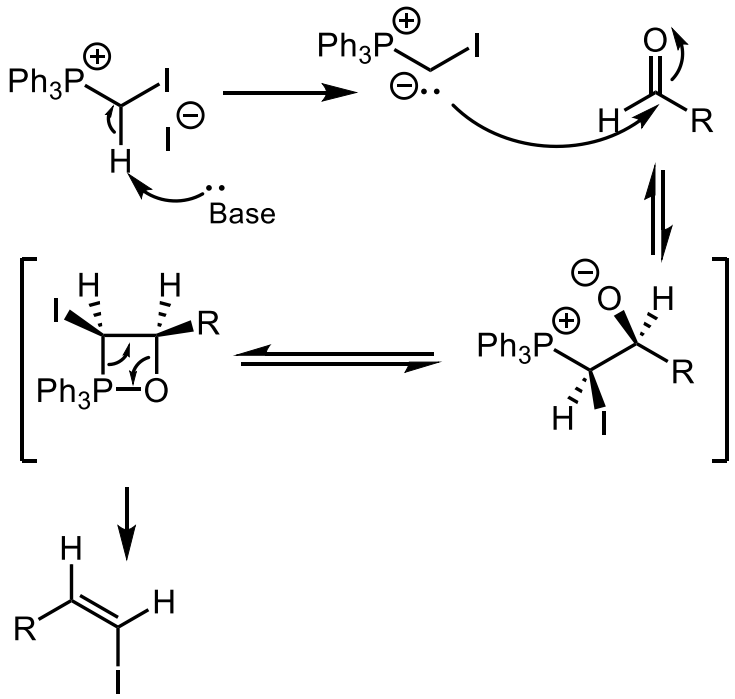
From **7** to **9**:



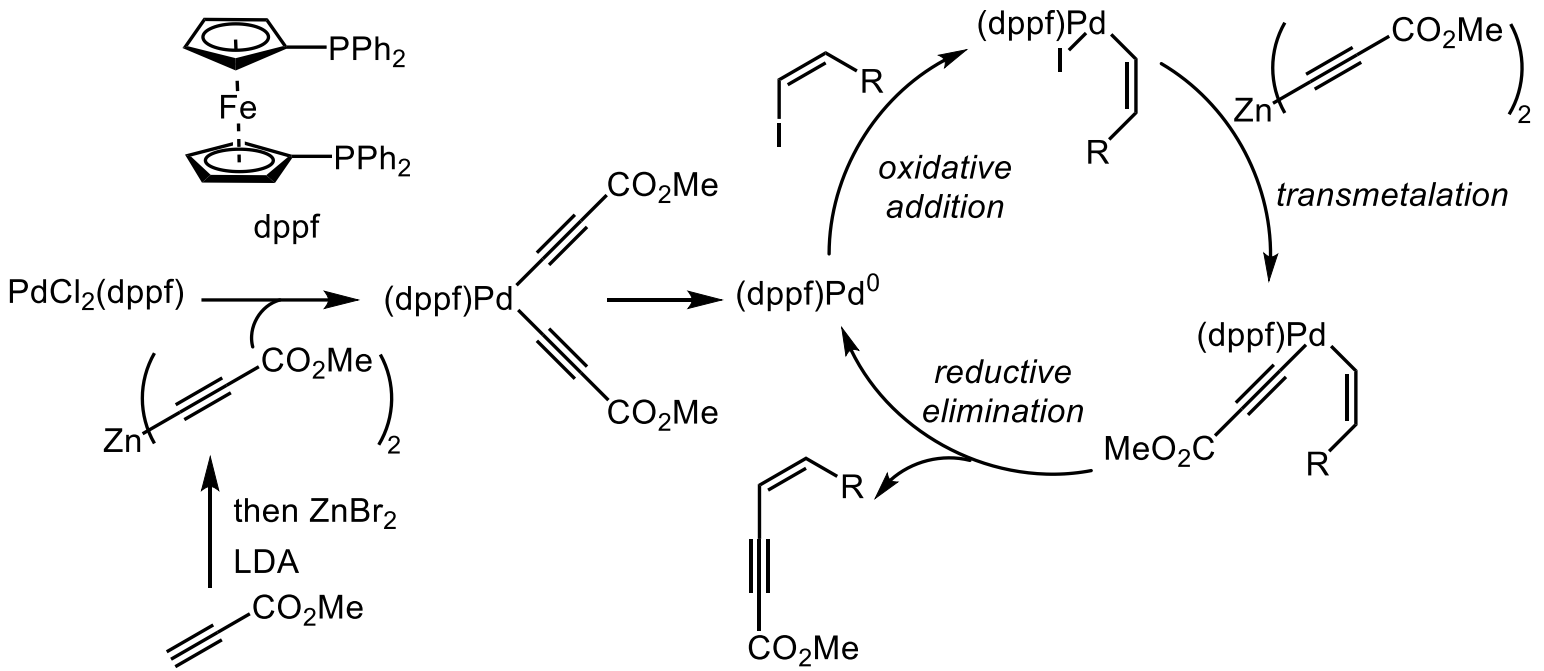
Synthesis of **Fragment 3**

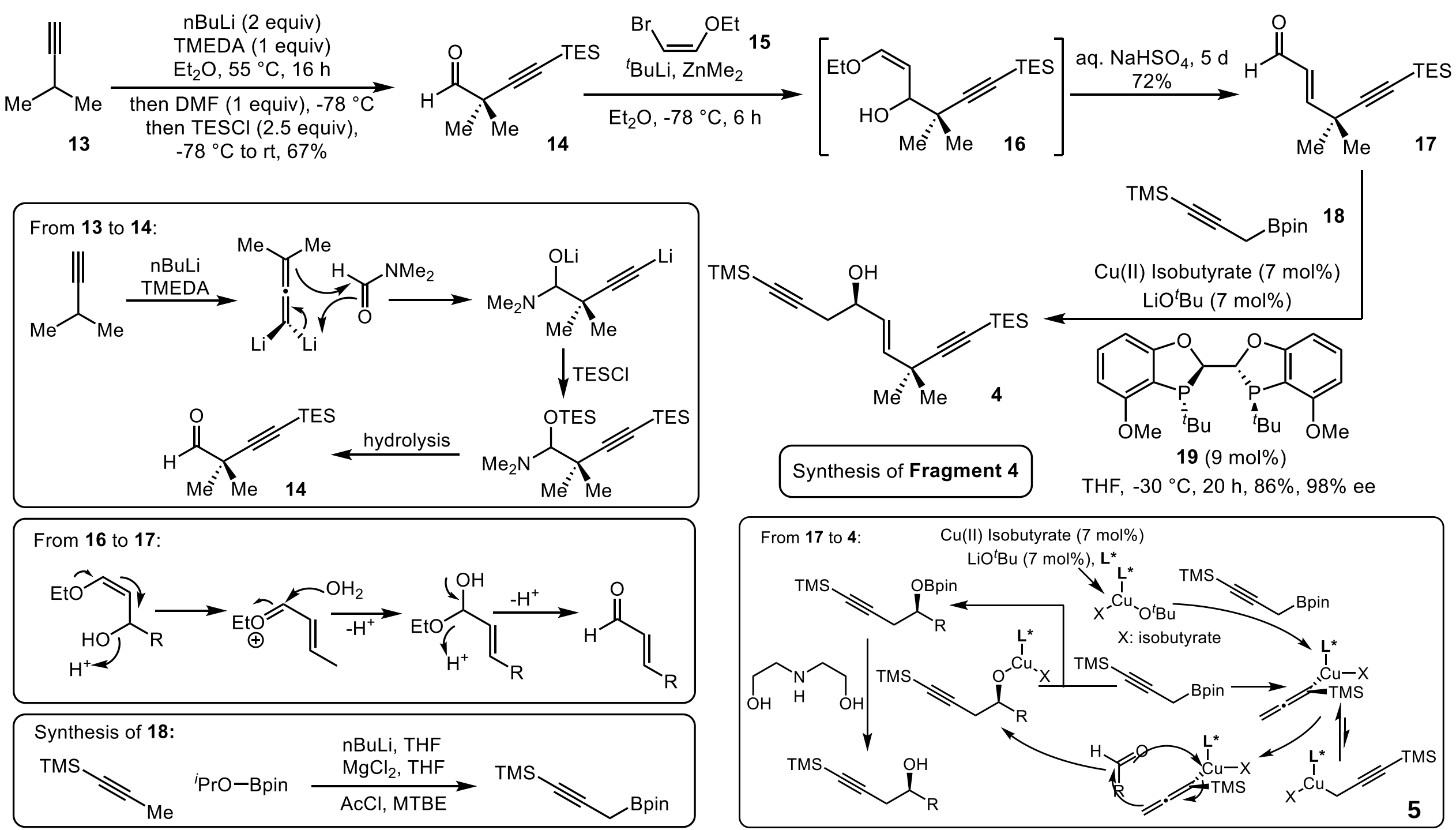


From **10** to **11**: Wittig Olefination

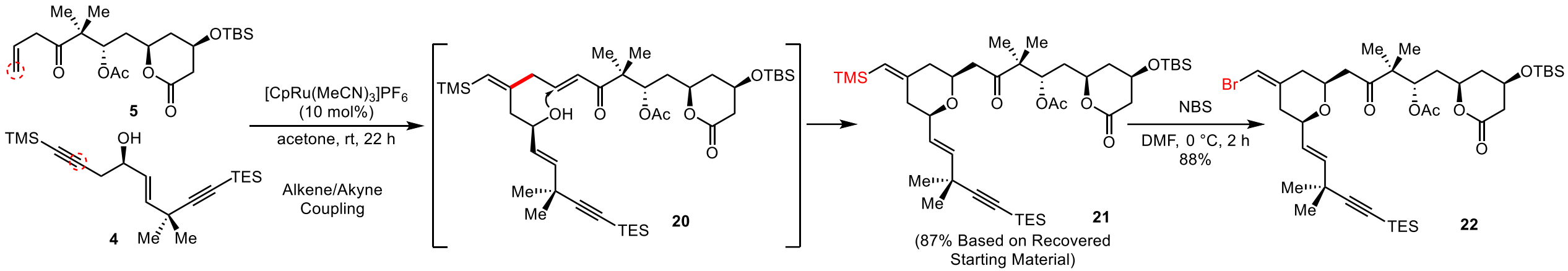


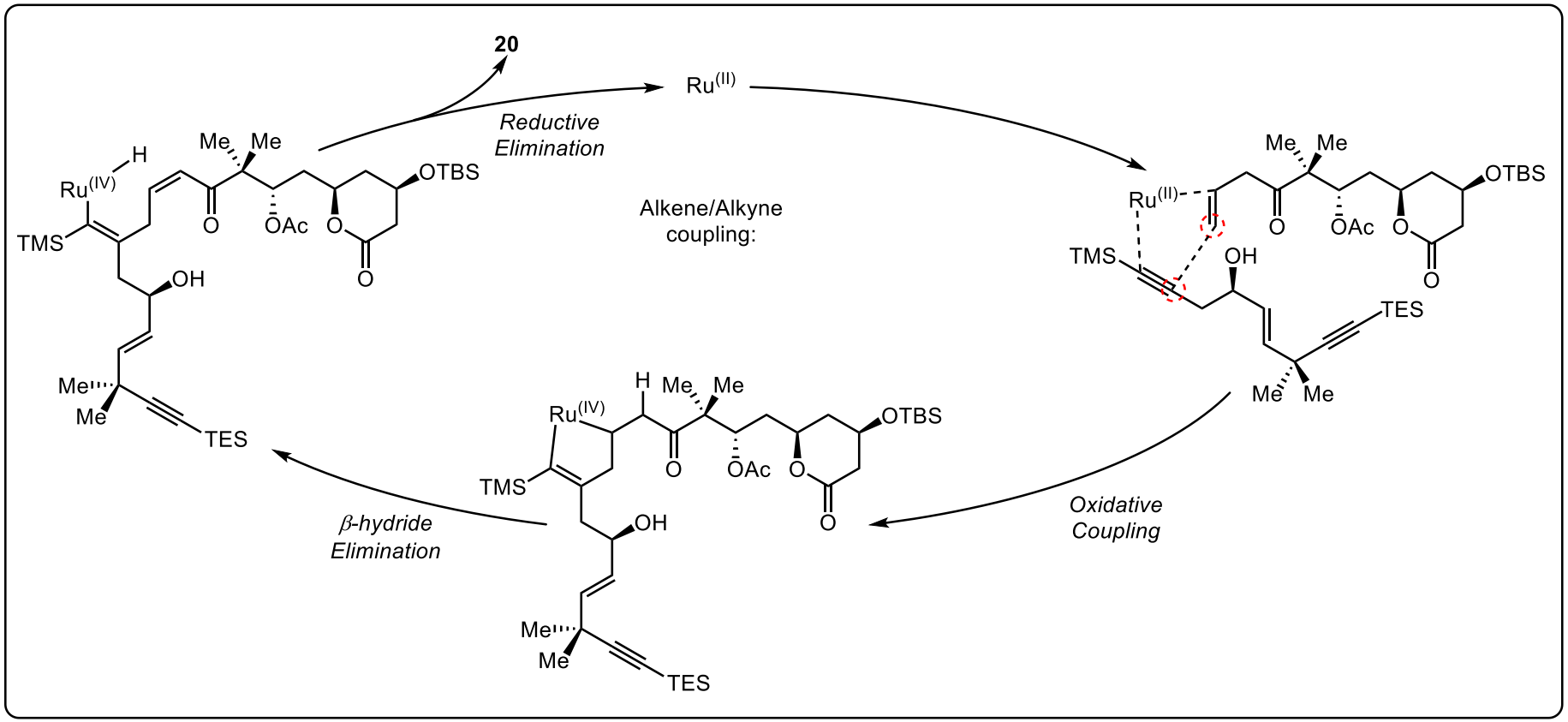
From **11** to **12**: Negishi cross-coupling

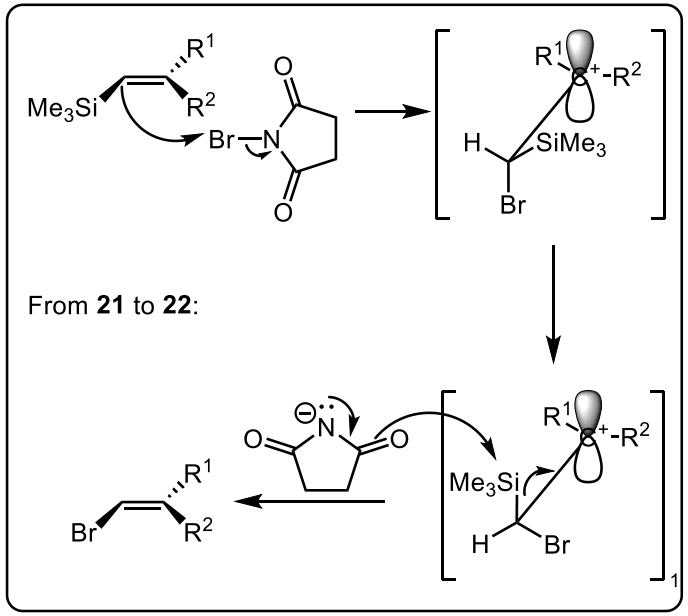



nBuLi (2 equiv)
TMEDA (1 equiv)
Et2O, 55 °C, 16 h
then DMF (1 equiv), -78 °C
then TESCl (2.5 equiv),
-78 °C to rt, 67%
13
14
15
tBuLi, ZnMe2
Et2O, -78 °C, 6 h
16
aq. NaHSO4, 5 d
72%
17
18
Cu(II) Isobutyrate (7 mol%)
LiOtBu (7 mol%)
19 (9 mol%)
THF, -30 °C, 20 h, 86%, 98% ee
4
Synthesis of Fragment 4
From 13 to 14:
nBuLi
TMEDA
TESCl
hydrolysis
From 16 to 17:
From 17 to 4:
Cu(II) Isobutyrate (7 mol%)
LiOtBu (7 mol%), L*
X: isobutyrate
5
Synthesis of 18:
nBuLi, THF
MgCl2, THF
AcCl, MTBE

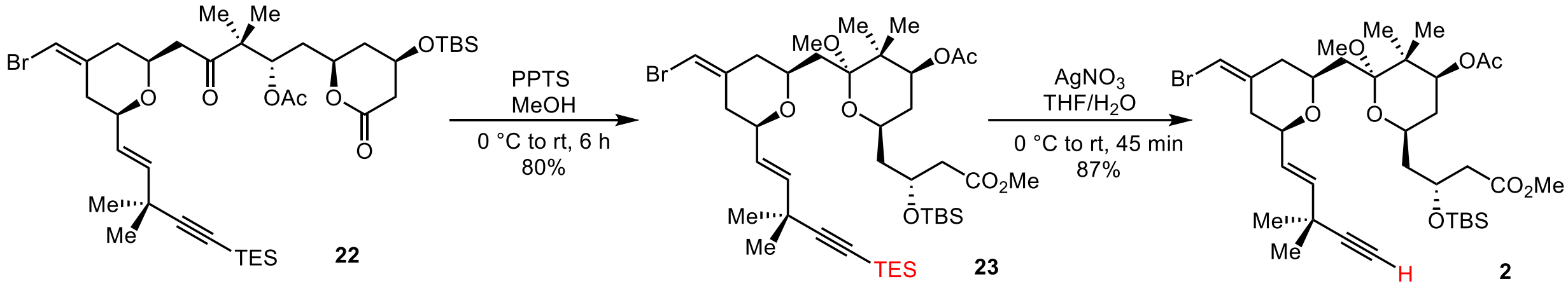
Synthesis of **Fragment 2**



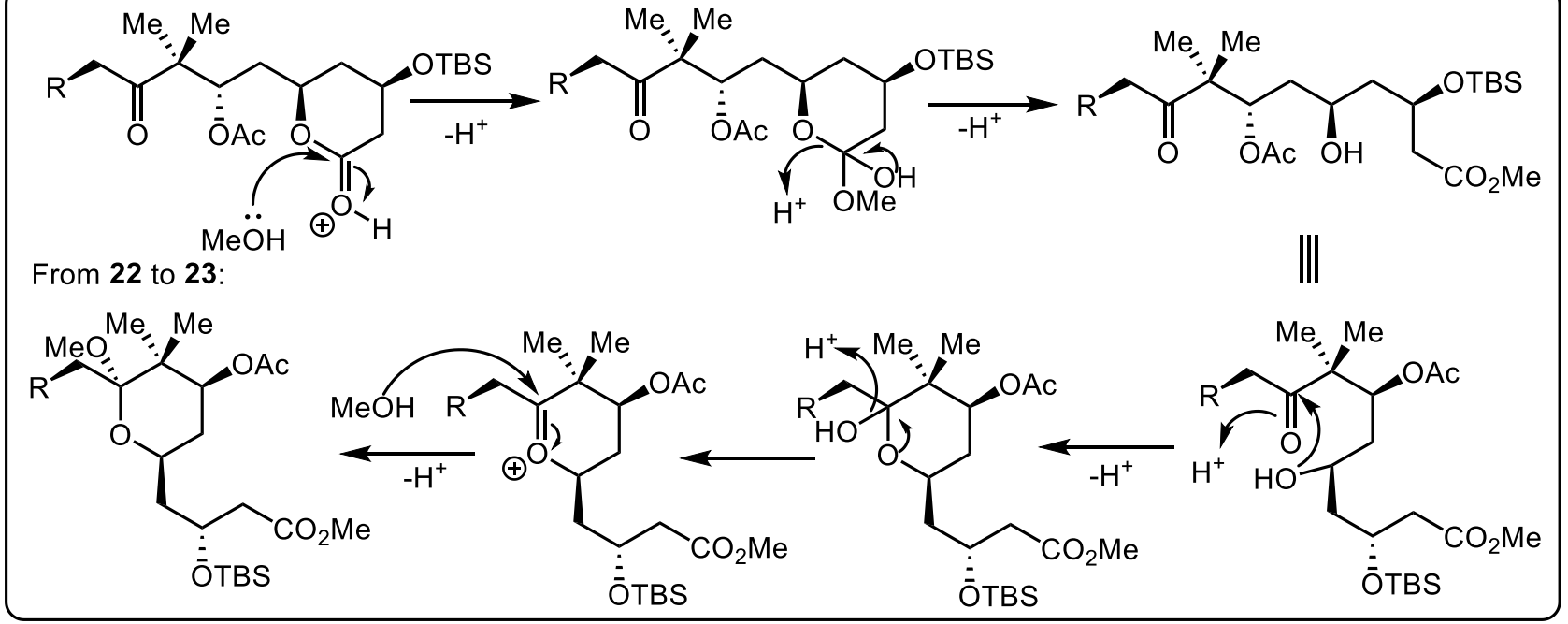




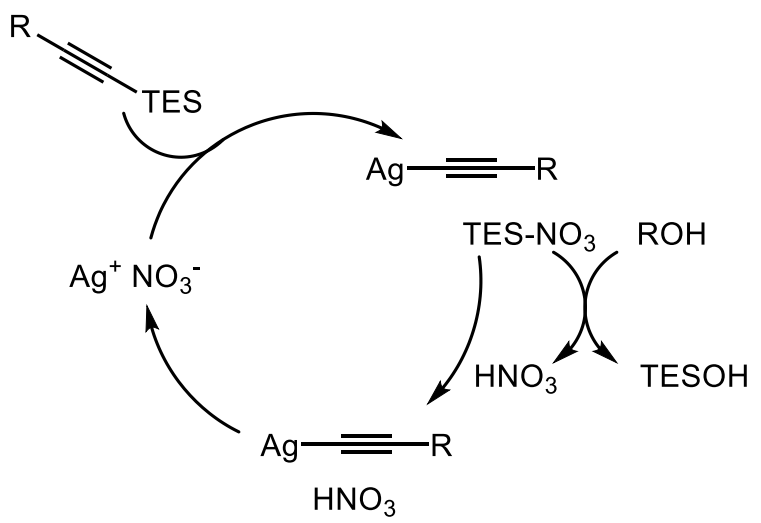
Synthesis of **Fragment 2**



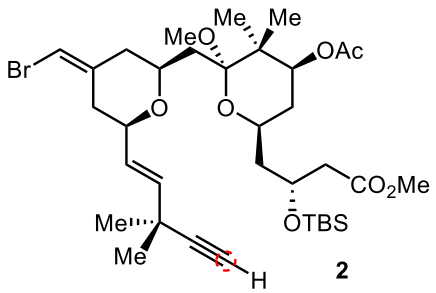
From **22** to **23**:



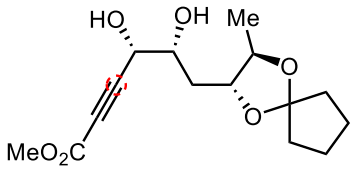
From **23** to **2**:



Coupling of **Fragment 2 & 3**

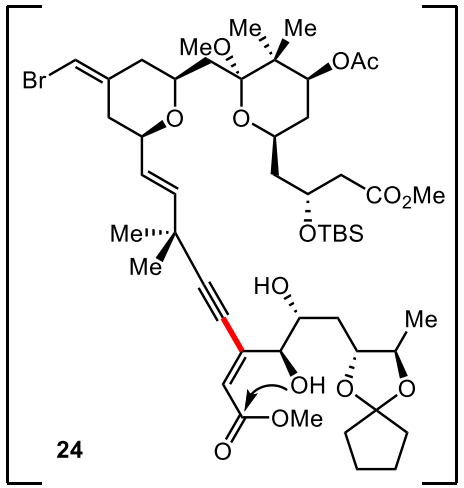


2



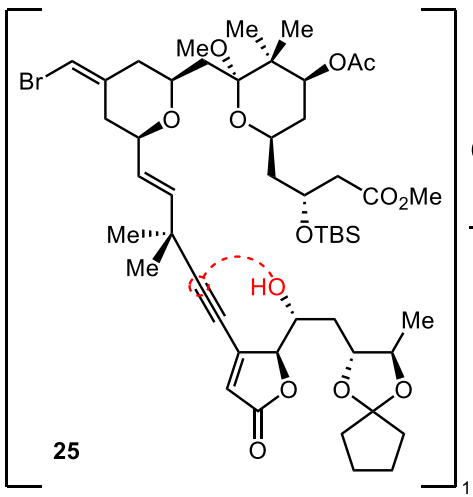
3

$Pd(OAc)_2$ (5 mol%)
TDMPP (7.5 mol%)
benzene, rt, air free
25 h
Alkyne/Alkyne Coupling



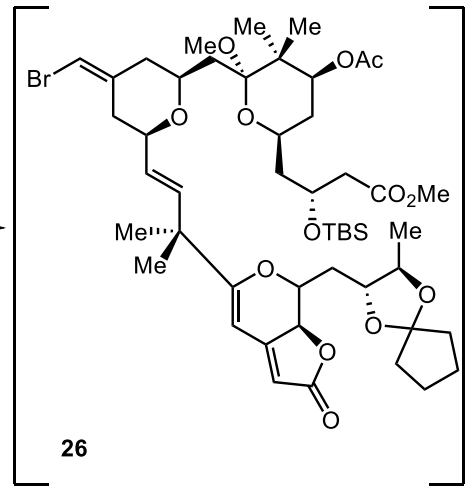
24

-MeOH



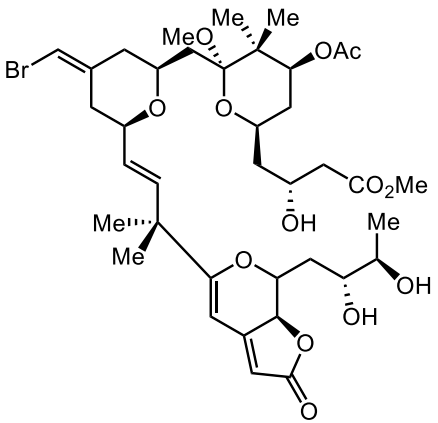
25

(IPr)AuCl (10 mol%)
$AgSbF_6$ (20 mol%)
CH_2Cl_2, rt, 24 h
6-Endo-Dig Cyclization

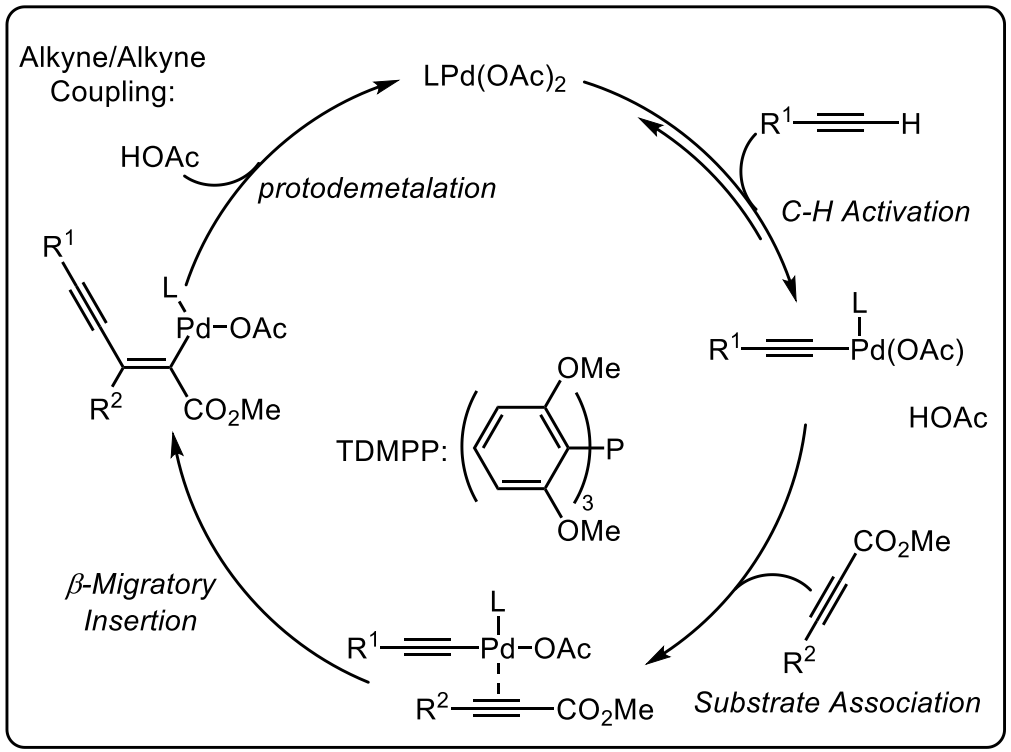


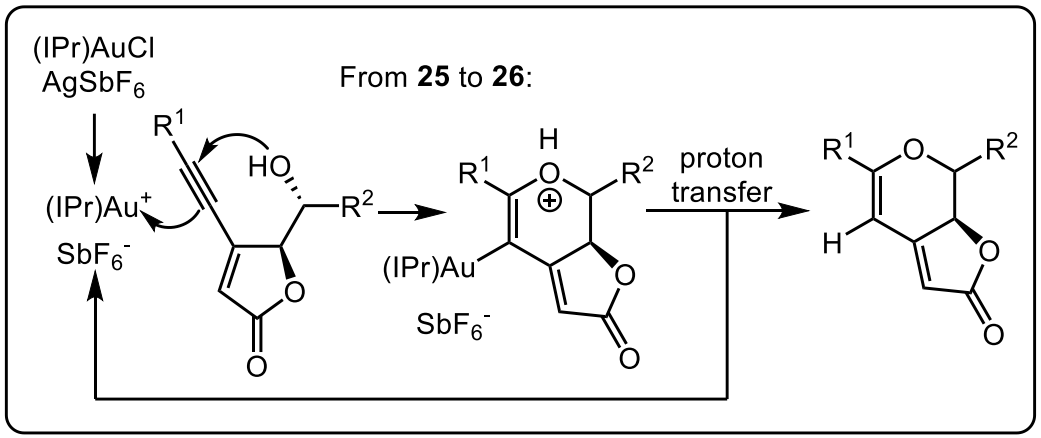
26

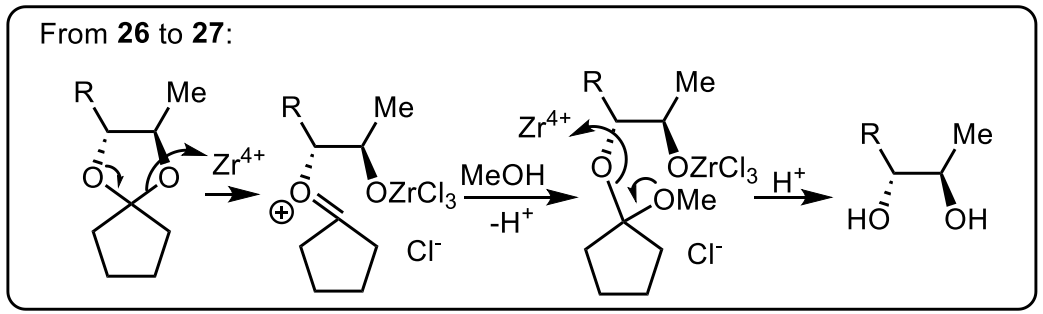
$ZrCl_4$
(250 mol%)
MeOH
0 °C to rt,
1.5 h



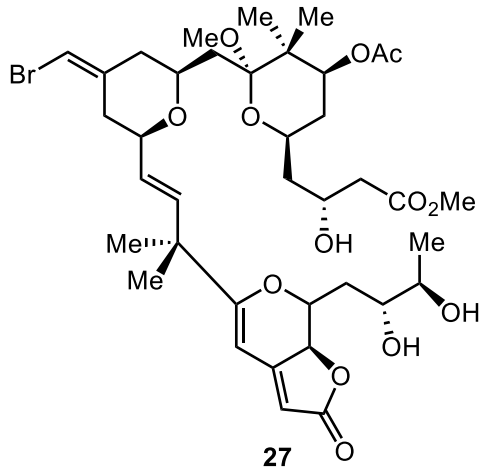
27 48%, three operations in one pot without solvent removal or exchange





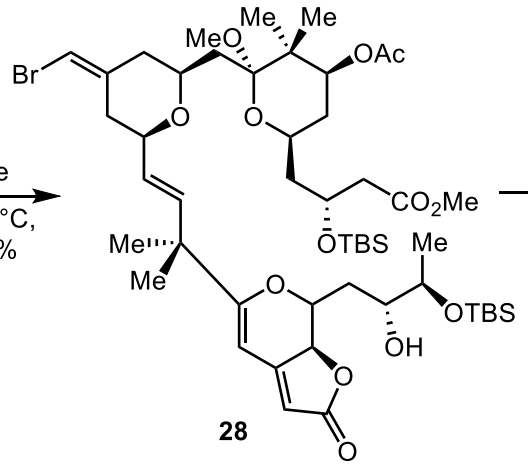


Completion of **bryostatin 3** synthesis



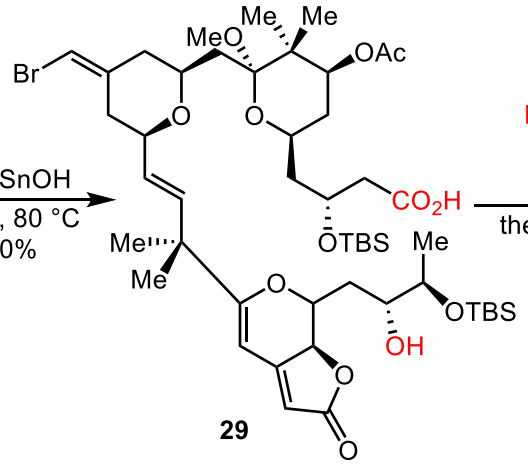
27

TBSOtf
2,6-lutidine
CH_2Cl_2, -78 °C,
15 min, 60%



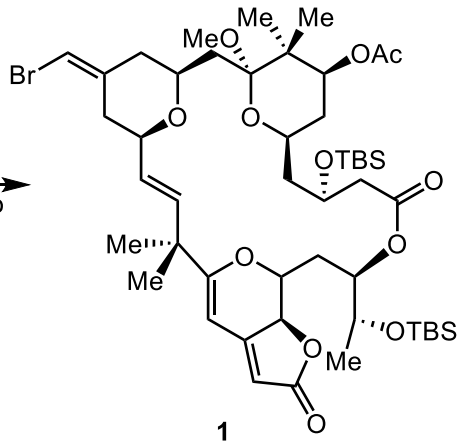
28

Me_3SnOH
DCE, 80 °C
80%



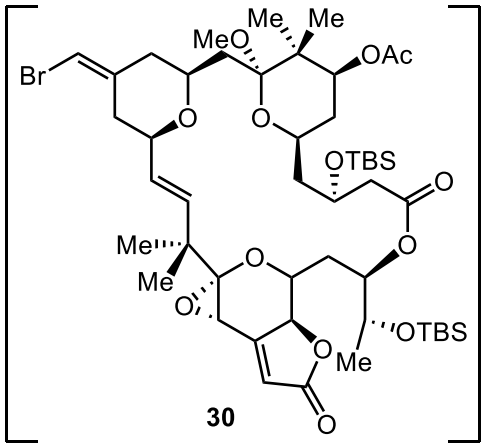
29

Yamaguchi
Macrolactonization
2,3,6-$Cl_3PhCOCl$
Et_3N, THF, rt, 4 h
then slow addition into
DMAP in toluene
14 h, 40 °C
96%



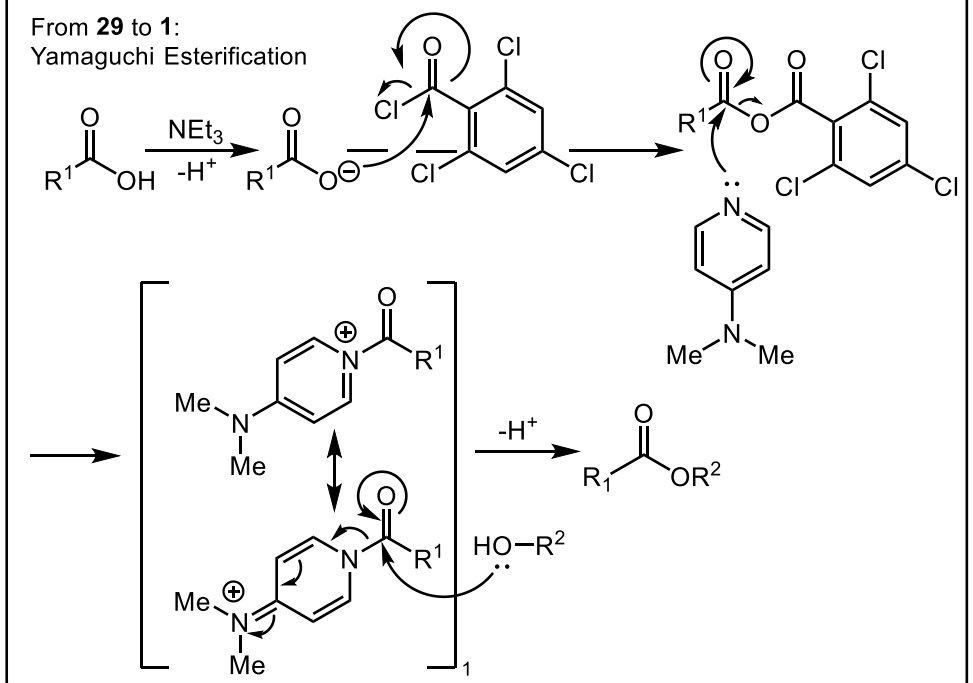
1

methylrhenium trioxide
UHP (Urea Hydroperoxide)
1-methylimidazole
MeOH, rt, 24 h

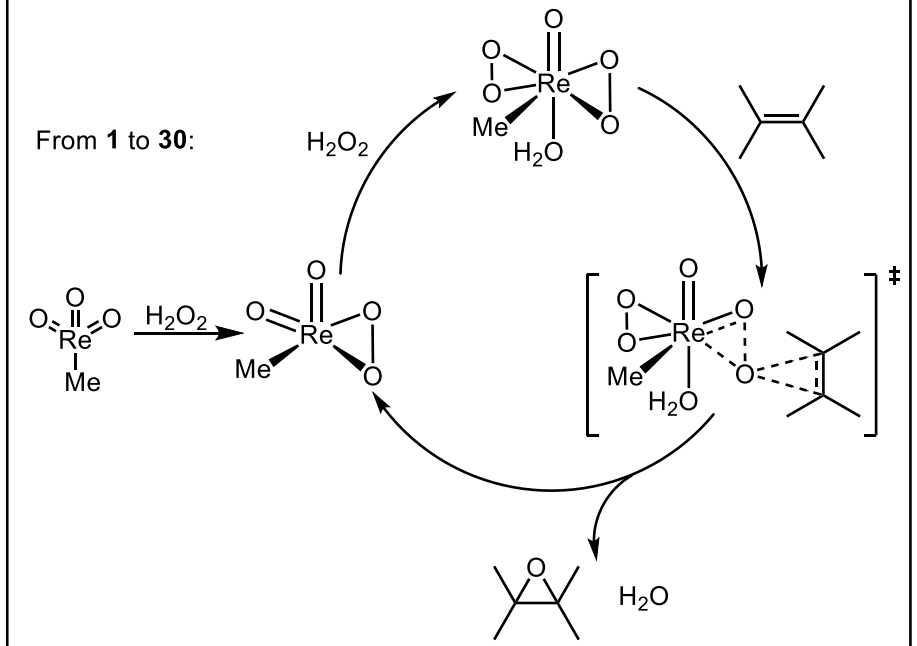


30

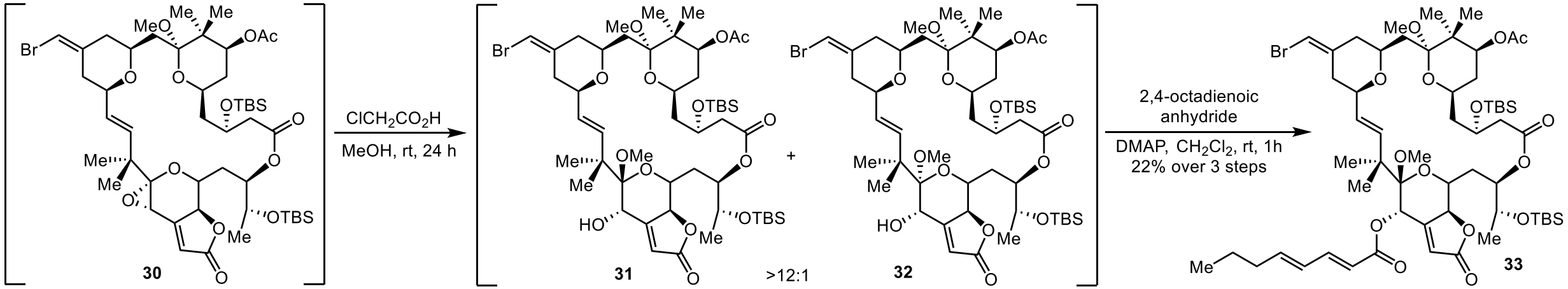
From **29** to **1**:
Yamaguchi Esterification



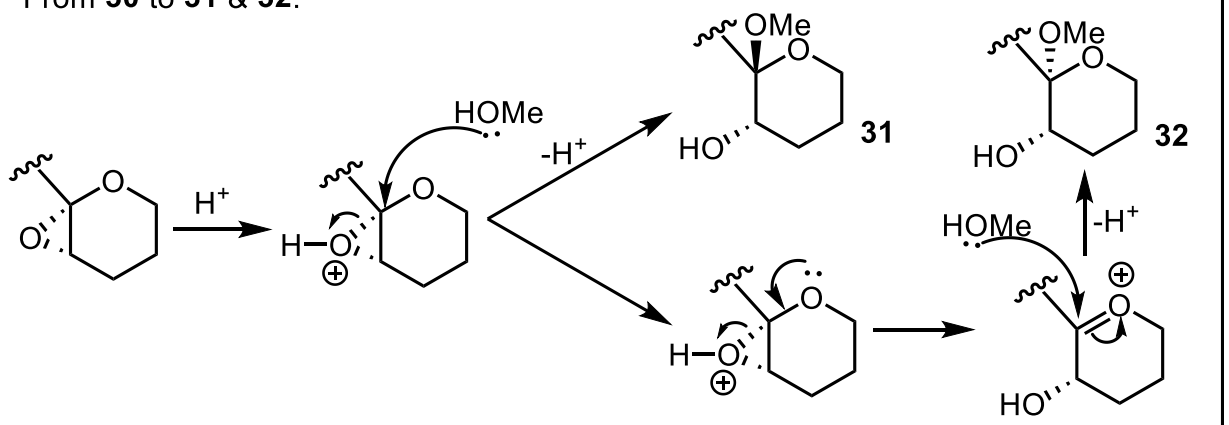
From **1** to **30**:



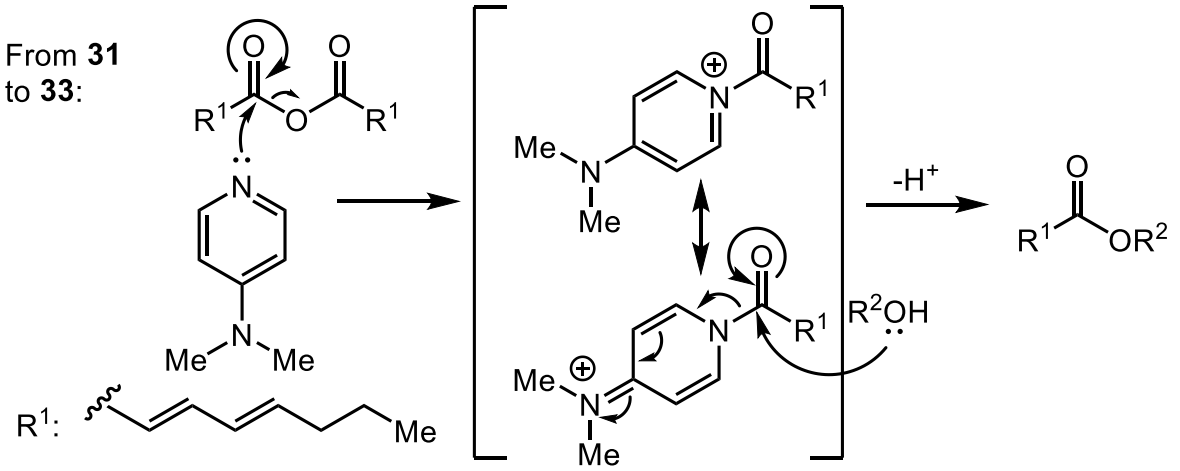
Completion of **bryostatin 3** synthesis



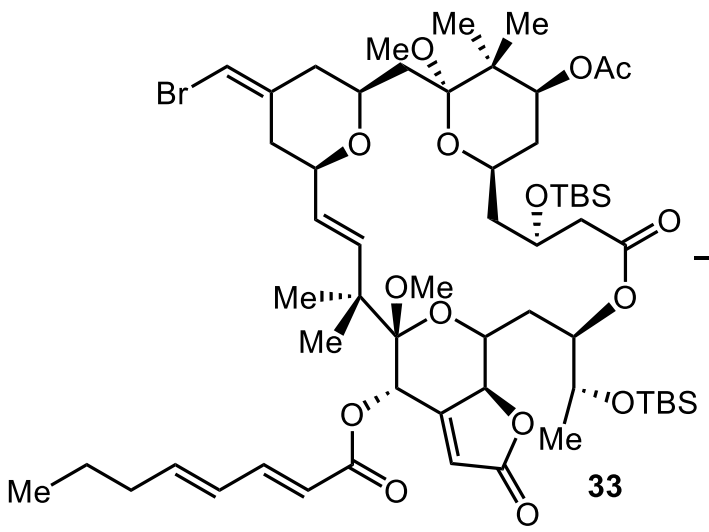
From **30** to **31** & **32**:



From **31** to **33**:

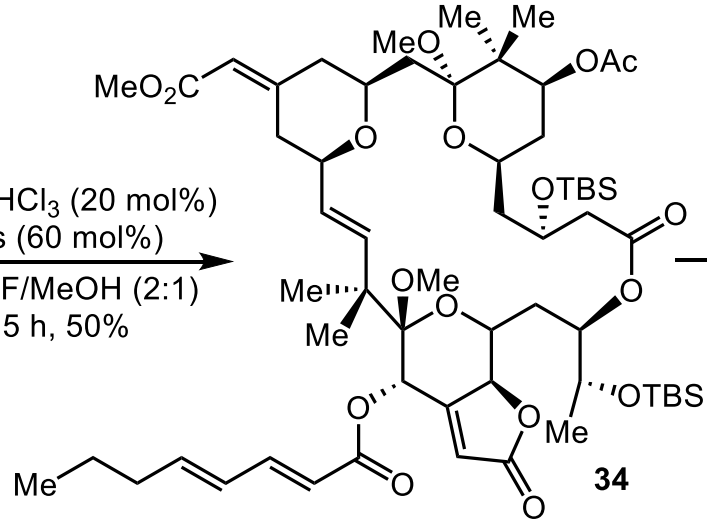


Completion of **bryostatin 3** synthesis



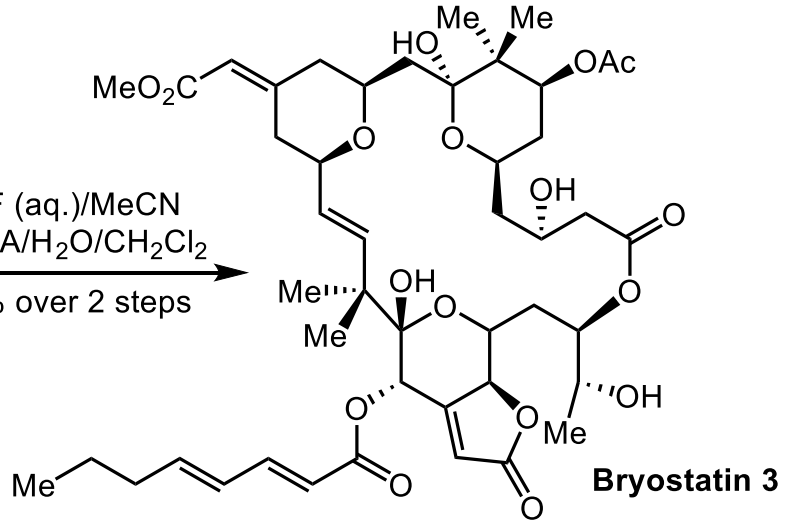
$Pd_2(dba)_3 \cdot CHCl_3$ (20 mol%)
Xantphos (60 mol%)

DIPEA, DMF/MeOH (2:1)
90 °C, 5 h, 50%

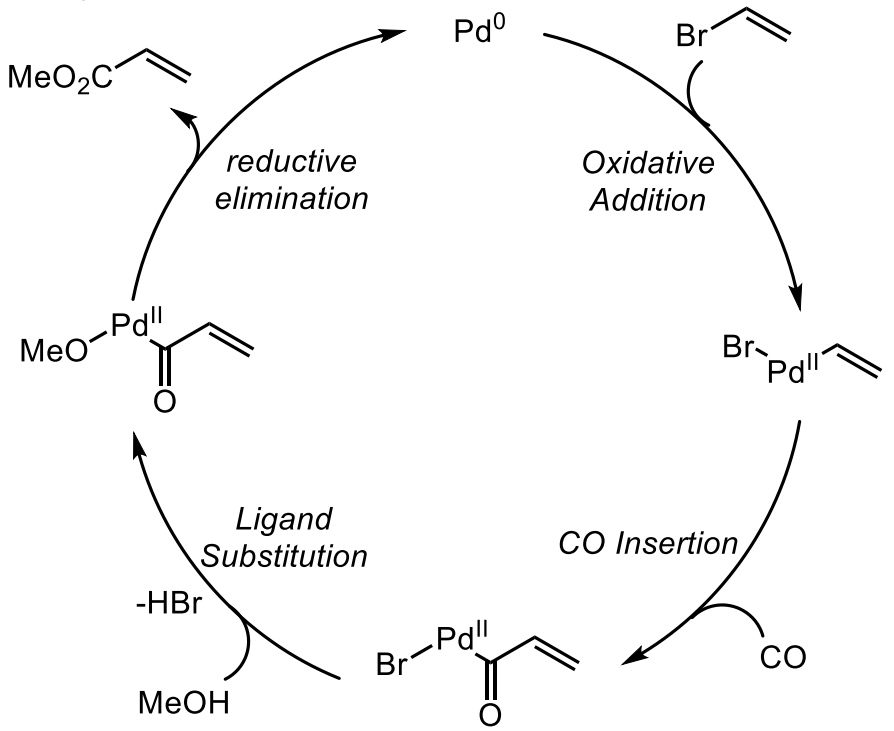


1. HF (aq.)/MeCN
2. TFA/H_2O/CH_2Cl_2

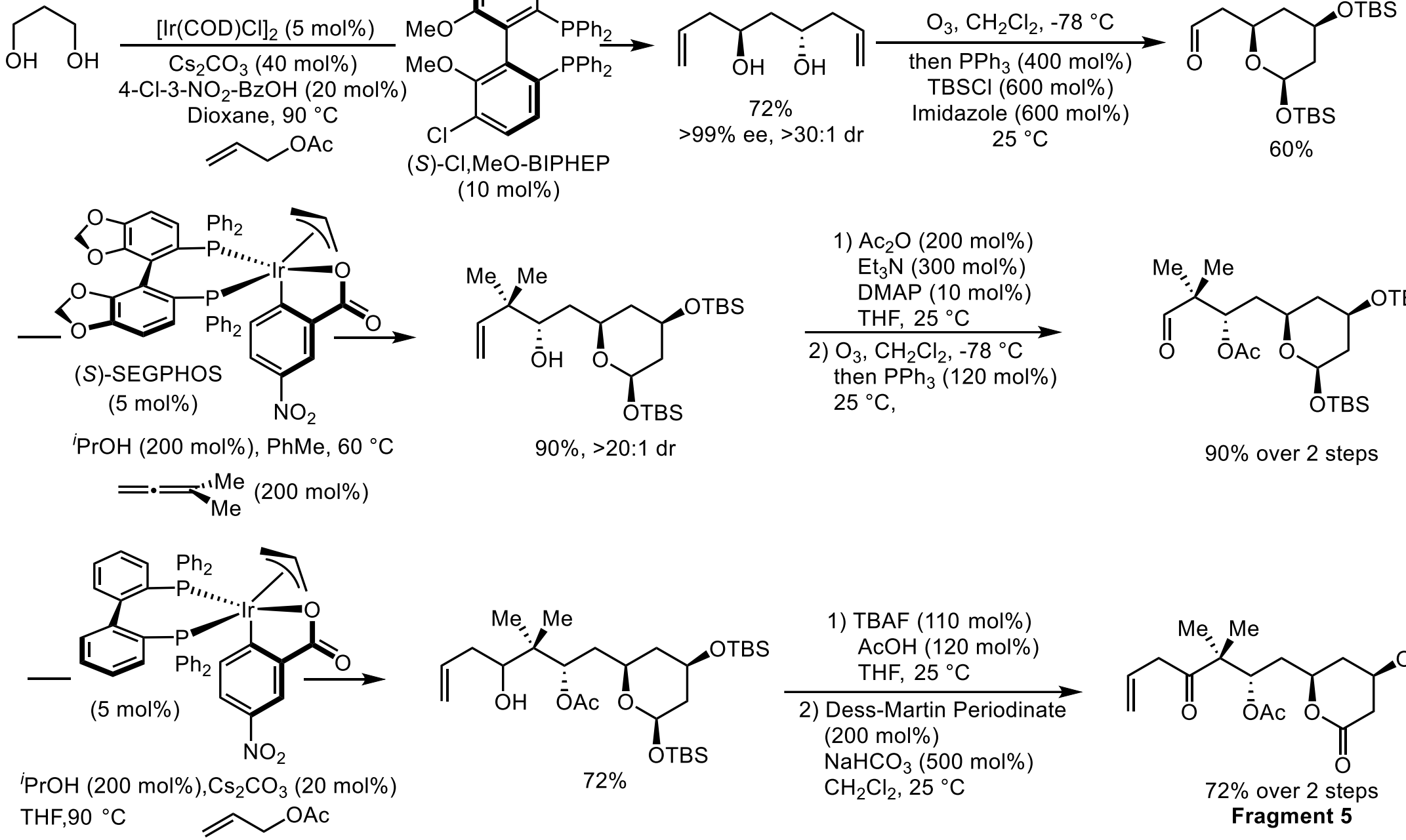
60% over 2 steps



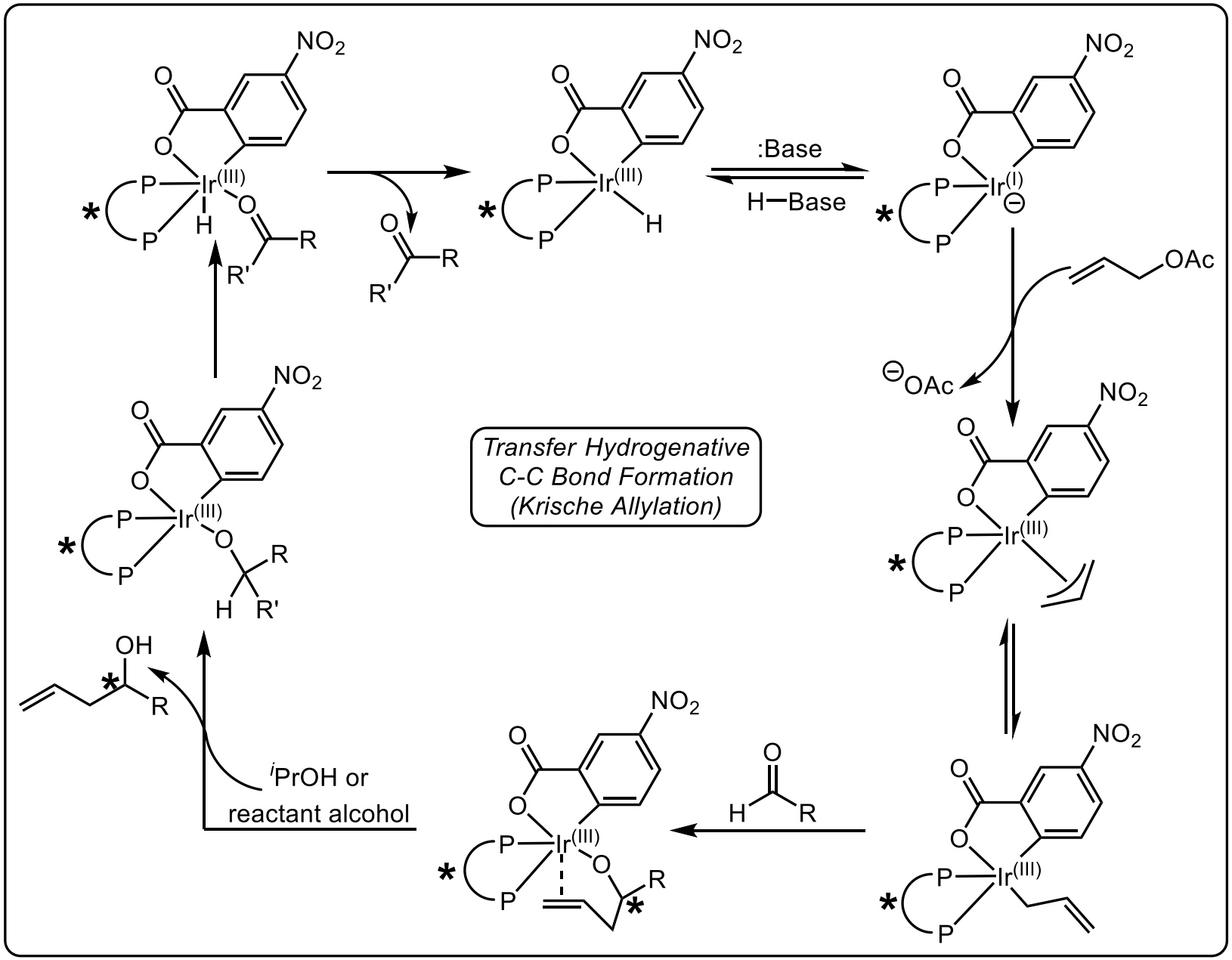
From **33** to **34**:

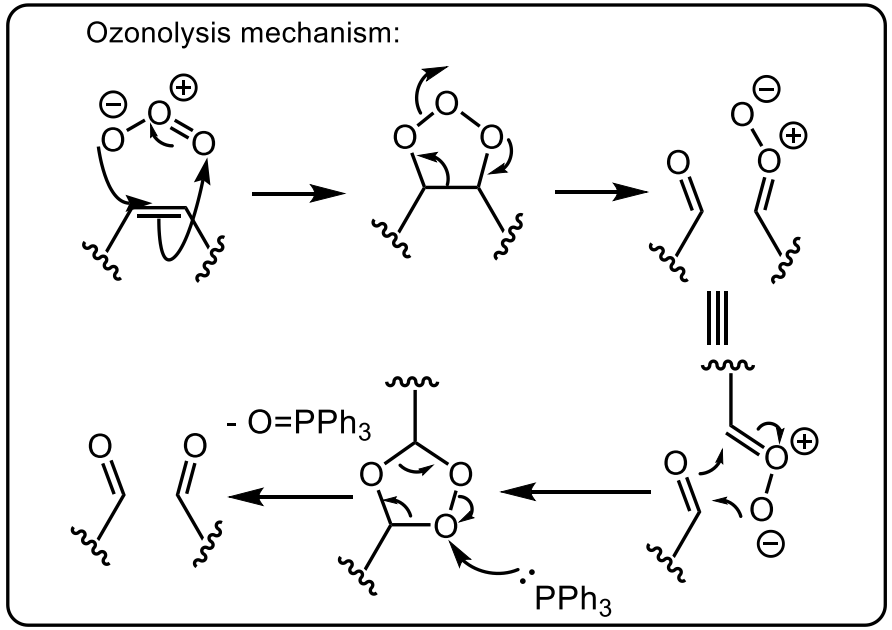


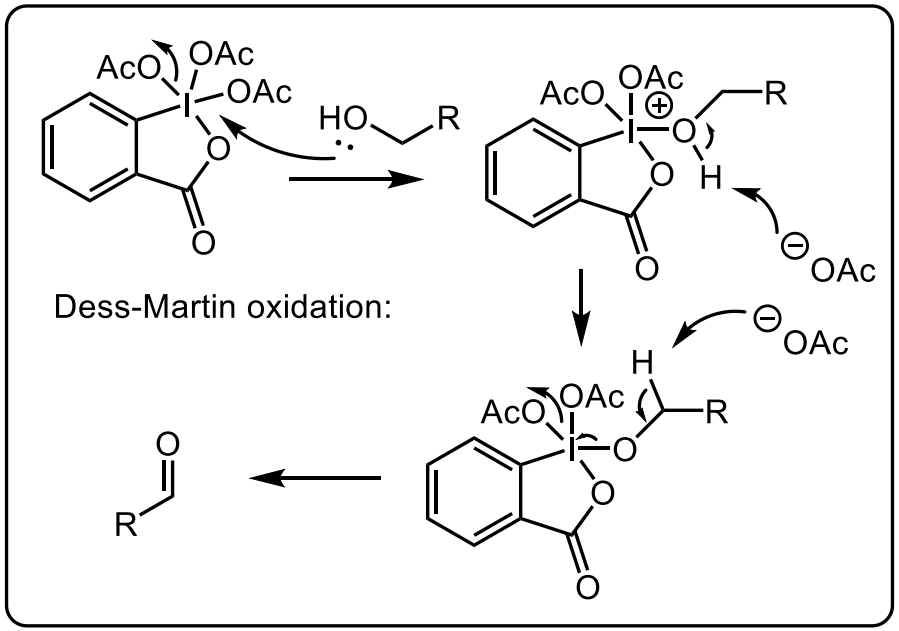
Synthesis of **Fragment 5**



Y. Lu, S. K. Woo, M. J. Krische, *J. Am.Chem. Soc.* **2011**, *133*,13876–13879.


Transfer Hydrogenative
C-C Bond Formation
(Krische Allylation)
:Base
H–Base
OAc
OAc
iPrOH or
reactant alcohol


Ozonolysis mechanism:
- O=PPh3
PPh3


Dess-Martin oxidation:
OAc
OAc