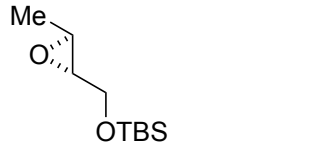
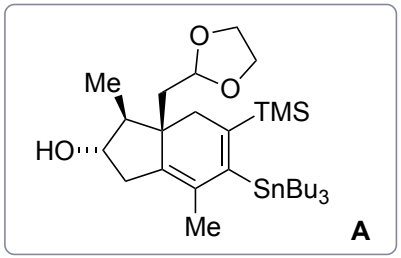
Total Synthesis of (−)-Jiadifenin

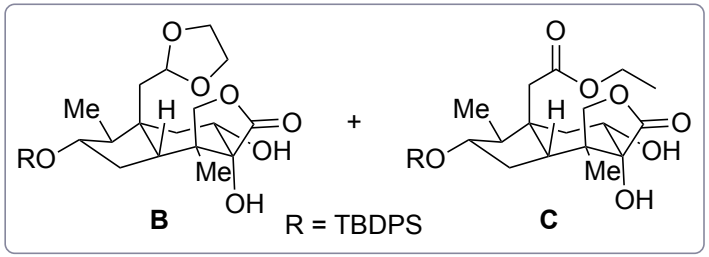
X. Cheng, G. C. Micalizio, *J. Am. Chem. Soc*. **2016**, *138*, 1150



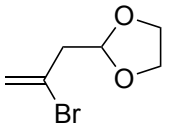
1 ñ 6



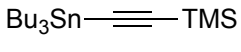
7 − 12



1) **1**, Mg, CuI
2) TBAF
3) TsCl (1.2 equiv), Et_3N, DMAP
4) NaH
5) Propyne, *n*-BuLi, BF_3ïOEt_2
6) Ti(O*i*-Pr)$_4$, *n*-BuLi, *then* **2**, *then* *n*-BuLi and substrate, *then* PhCHO



1

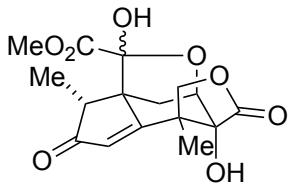


2

7) TBAF
8) TBDPSCl, imH
9) MeLi, *then* CO_2
10) $PhSeCH_2Cl$, *i*-Pr_2NEt, NaI
11) OsO_4
12) *n*-Bu_3SnH, AIBN

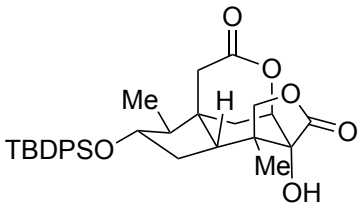
6) Mechanism? See below.

12) Hint: An additional unexpected HAT gives rise to the second product. Propose a mechanism how both products are formed. See below.



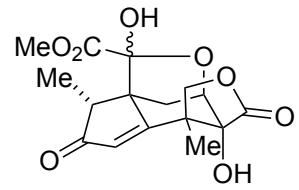
(−)-jiadifenin

B → 13 – 16 → **C** → 17 – 19 →



D

20 – 25 →

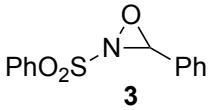


(–)-jiadifenin

13) $(COCl)_2$, DMSO, Et_3N
14) HCl, THF/H_2O
15) $NaClO_2$, 2-methylbut-2-ene, NaH_2PO_4
16) $NaBH_4$, *then* TsOH

17) $(COCl)_2$, DMSO, Et_3N
18) $NaBH_4$
19) TsOH

20) TBAF
21) IBX
22) LDA, TMSCl, *then* $Pd(OAc)_2$
23) TBAF
24) NaHMDS, **3**
25) CrO_3, H_2SO_4, *then* MeOH

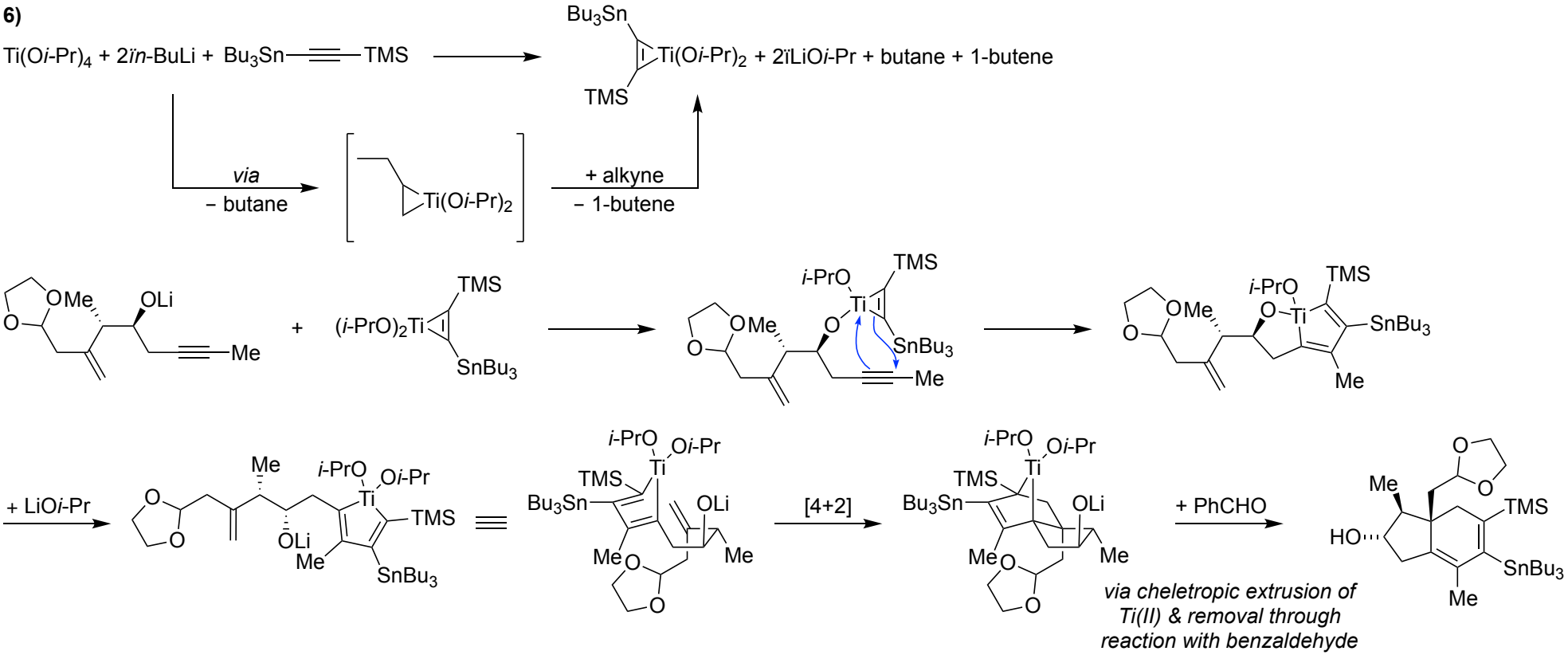


3

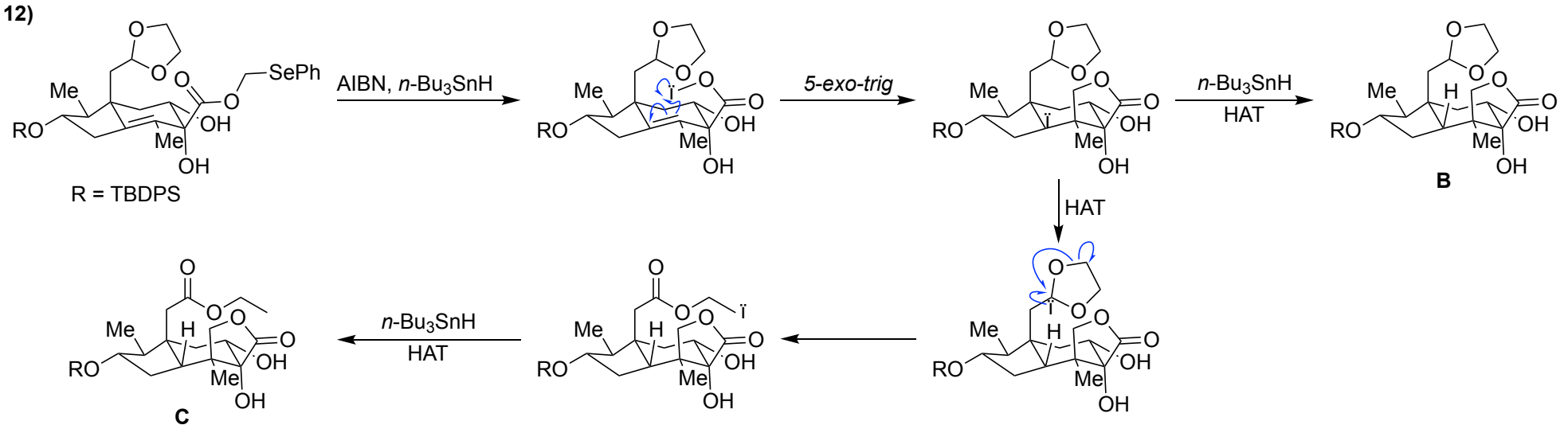
13) Name of the reaction? Swern oxidation
15) Name of the reaction? Pinnick–Lindgren–Kraus oxidation

22) Name of the reaction? A hydroxyl group is also protected.
24) Hint: Additionally, an epimerization takes place.
25) Name of the oxidation reaction?

6)


Ti(Oi-Pr)4 + 2ïn-BuLi + Bu3Sn—≡—TMS
Bu3Sn
TMS
Ti(Oi-Pr)2 + 2ïLiOi-Pr + butane + 1-butene
via
− butane
Ti(Oi-Pr)2
+ alkyne
− 1-butene
OMe
OLi
Me
+
(i-PrO)2Ti
TMS
SnBu3
i-PrO
Ti
O
SnBu3
Me
+ LiOi-Pr
Me
i-PrO
Oi-Pr
Ti
TMS
OLi
Me
SnBu3
Bu3Sn
[4+2]
+ PhCHO
HO
via cheletropic extrusion of
Ti(II) & removal through
reaction with benzaldehyde

12)


SePh
AIBN, n-Bu3SnH
5-exo-trig
n-Bu3SnH
HAT
RO
Me
OH
R = TBDPS
B
HAT
n-Bu3SnH
HAT
C