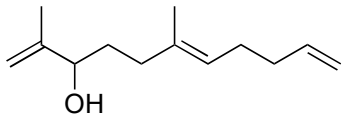
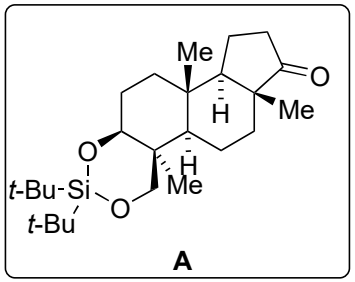
Bidirectional Total Synthesis of Phainanoid A via Strategic Use of Ketones

Jiaxin Xie, Xin Liu, Nan Zhang, Shinyoung Choi, Guangbin Dong *J. Am. Chem. Soc.* **2021**, *143*, 19311–19316.

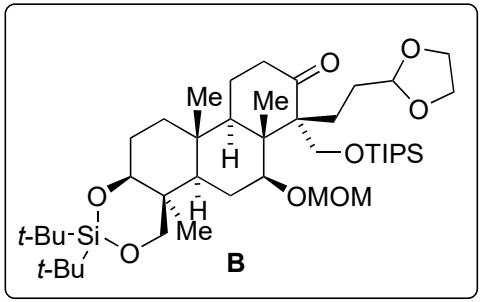


1-6



A

7-13



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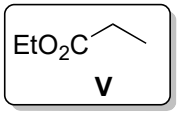
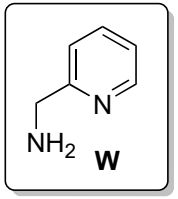
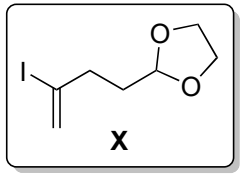


V

1) $MeC(OEt)_3$, cat. $EtCO_2H$
2) **V**, LDA
3) $Mn(OAc)_3•2H_2O$, $Cu(OAc)_2•H_2O$
4) $LiAlH_4$
5) O_3; SMe_2
6) *t*-$Bu_2Si(OTf)_2$, 2,6-lutidine



W

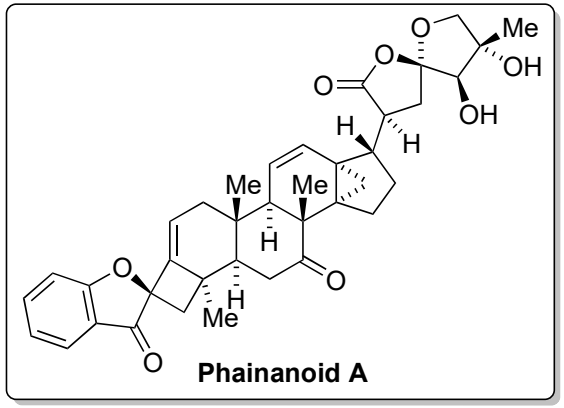


X

7) **W**, *then* $Cu(NO_3)_2•3H_2O$, H_2O_2
8) MOMCl, TBAI, DIPEA
9) **X**, *n*-BuLi
10) TMSCl, HMDS, imidazole
11) *m*-CPBA, $NaHCO_3$
12) $AlMe_3$, $AlMe_2Cl$
13) TIPSOTf, 2,6-lutidine

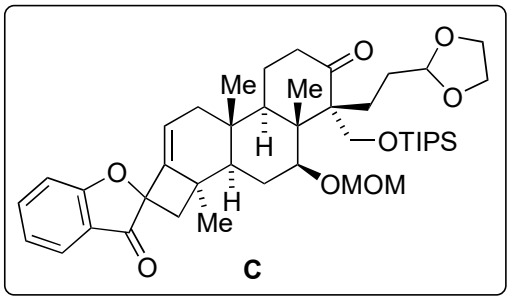
step 1: Name? Classify the reaction!
Johnson-Claisen rearrangement
[3,3]-sigmatropic rearrangement
step 2: Name?
Claisen condensation

step 7: Name? Mechanism?
Schönecker oxidation
(Baran modification)
step 12: Name?
semipinacol rearrangement



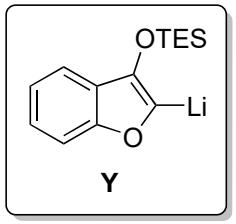
Phainanoid A

14-21

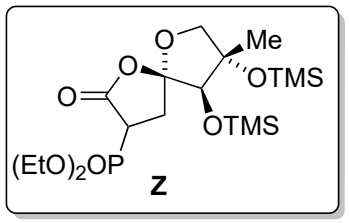


C

14) TBAF/HOAc
15) TEMPO, NaClO, KBr, $NaHCO_3$
16) TESCl, imidazole
17) **Y**
18) TBAF/HOAc
19) DMP, $NaHCO_3$
20) KHMDS, $PhNTf_2$
21) Pd/C, H_2 *then* Pd-QPhos-G3, Cs_2CO_3



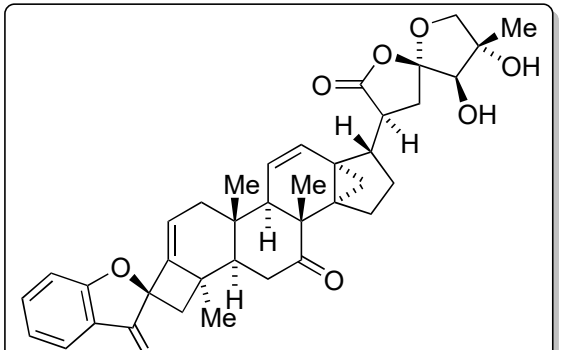
Y



Z

22-29

22) KHMDS, $PhNTf_2$
23) TBAF/HOAc
24) TsCl, NEt_3, DMAP
25) HCl
26) **Z**, DIPEA, LiCl
27) $Ni(cod)_2$, LiBr, NEt_3
28) DMP, $NaHCO_3$
29)TBAF/HOAc



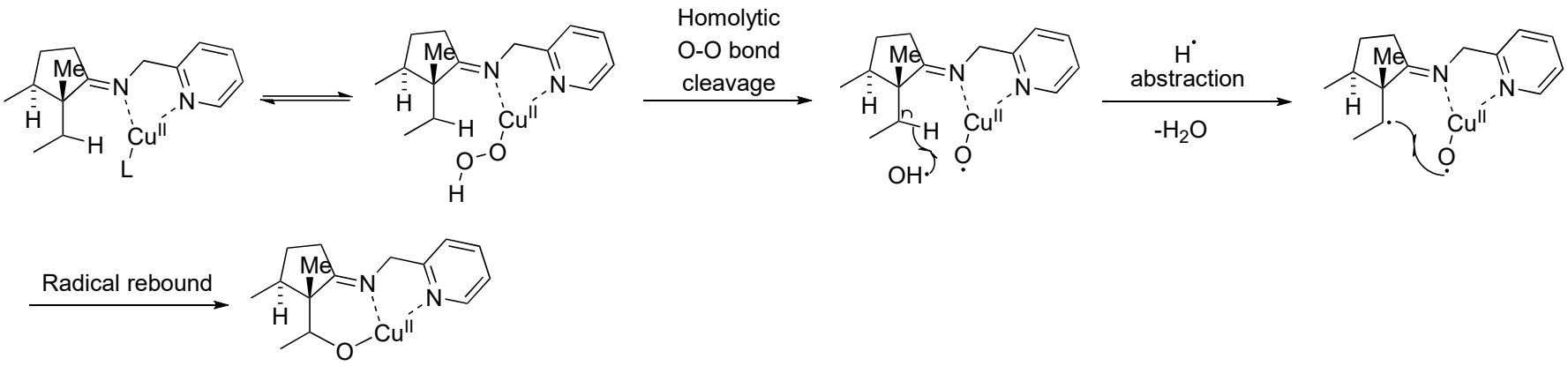
Phainanoid A

step 26: Name? Role of LiCl?

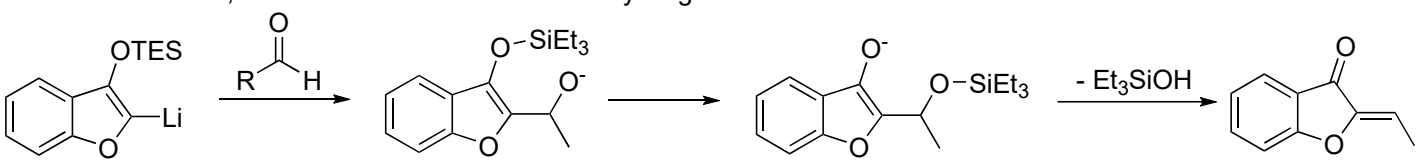
Masamune-Roush variation of the HWE reaction

LiCl enhances the acidity of the phosphonate, allowing for the utilization of mild amine bases

Mechanism of step 7 (*J. Org. Chem.* **2017**, *82*, 7887-7904):



step 17:



step 27: