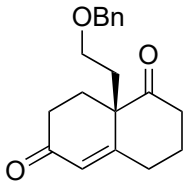
Total Synthesis of Dapholdhamine B and Dapholdamine B Lactone

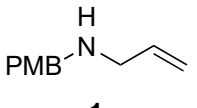
L.-D. Guo, J. Hou, W. Tu, Y. Zhang, Y. Zhang, L. Chen, J. Xu, *J. Am. Chem. Soc.* **2019** *141*, 11613–11720.



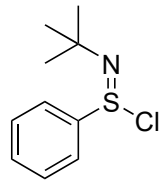
1 - 9

B

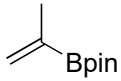
1) $CH(OMe)_3$, PTSA *then* **1,** HCHO
2) $Pd(PPh_3)_4$, 1,3-dimethylbarbituric acid, $Pd(PPh_3)_4$, *then* $NaHCO_3$, TsCl
3) $ZnMe_2$, LiBr, $Ni(acac)_2$
4) LHMDS, -78 °C, then **2**
5) H_2O_2, NaOH
6) LiBr, CH_3CN, MW, 120°C
7) XPhos Pd G2, **3**, K_3PO_4
8) CAN
9) KHMDS, TBSCl, -78°C then KHMDS, $PhNTf_2$, 0°C



1



2



3

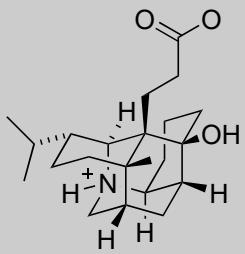
1) Name the reaction.

1) *Hint: start with forming a dienol.*

4) Draw a mechanism for the dehydrogenation.

6) *Hint: a vinyl bromide is formed.*

9) *Hint: cyclization. Two heteroatoms are triflated.*



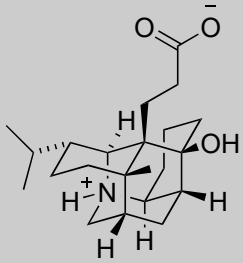
dapholdamine B

B

10 – 14

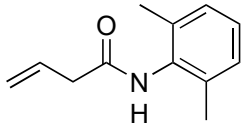
C

15 - 20



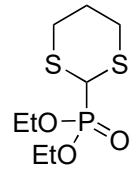
dapholdamine B

10) Crabtree's catalyst, H_2, *then* TBAF, HOAc
11) $NaBH_4$
12) $SOCl_2$, pyridine
13) **4**, 9-BBN *then* $Pd_2(dba)_3$•$CHCl_3$, $AsPh_3$, K_3PO_4
14) Tf_2O, 2-F-Pyr. *then* 2 *N* HCl



4

15) Pd/C, H_2 (80 bar)
16) TEMPO, PIDA *then* $NaClO_2$, NaH_2PO_4, *then* 2 *N* HCl
17) BH_3•THF then H_2O_2, NaOH aq.
18) Na-Naph, -78°C
19) PPh_3, CBr_4, DMAP, TEA
20) NaH, **5** *then* 2 *N* HCl *then* NaOH aq.



5

14) *Hint: cyclization. Start with creating an activated amine. The product is an α,β-unsaturated ketone.*

15) *Hint: 1 deprotection and 2 hydrogenations. The remaining π bond is critical for step 16.*
16) *Hint: cyclization. Start with a selective oxidation.*
17) *Hint: the lactone is also reduced to the corresponding lactol.*
18) *Hint: deprotection.*