Scalable Total Synthesis of Portimine A and B Reveals the Basis of Their Potent and Selective Anti-cancer Acitvity

J. Tang, W. Li, T.-Y. Chiu, Z. Luo, C. T. Chong, Q. Wei, F. Martinez-Peňa, N. Gazaniga, Y. Y. See, L. L. Lairson, C. G. Parker, P. S. Baran

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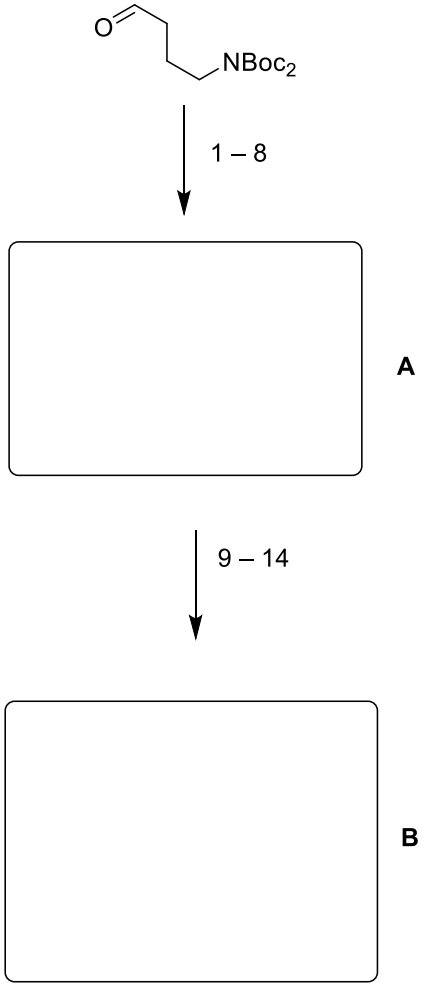
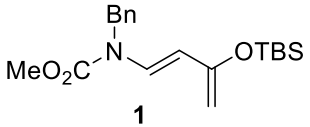


1. HCHO, pyrrolidine, propionic acid, H_2O, *i*-PrOH
2. **1**, [Co(*t*-Bu-Salen)]SbF_6, 4Å MS, DCM, r.t.
3. $NaBH_4$, MeOH, DCM, 0 °C
4. TBAF, THF, r.t.
5. TEMPO, NaOCl, KBr, $NaHCO_3$, DCM, H_2O, 0 °C
6. **2**, THF, –78 °C
7. DMP, $NaHCO_3$, DCM, 0 °C
8. TFA, DCM, r.t.



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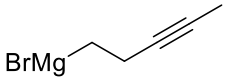

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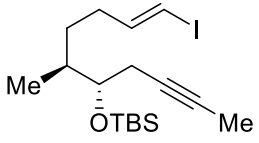
9. **3**, *t*-BuLi, THF, –78 °C *then* **4**, *n*-Bu_3P, THF, –78 °C *then* **A**, THF, –78 °C *then* Comins´ rgt., THF, 0 °C
10. TrocCl, DMAP, DCM, reflux
11. **5**, 5Å MS, PhMe, 80 °C
12. PTSA, DCM, MeOH, H_2O, 50 °C
13. $XPhosAuNTf_2$, DCM, reflux
14. $Ru(PPh_3)_2Cl_2$, TBHP, TBAI, MeCN, PhMe, H_2O, r.t.



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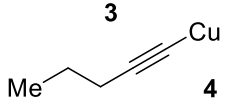

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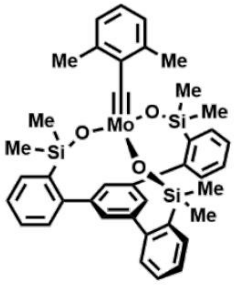

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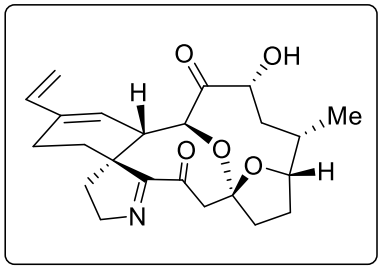
Step 2: Please, name the reaction, the reagent **1** and show structure of the salen ligand.

Step 5: Please, show the mechanism.

Step 11: Who developed this type of catalyst?

Hint step 12: Concomitant silyl deprotection.

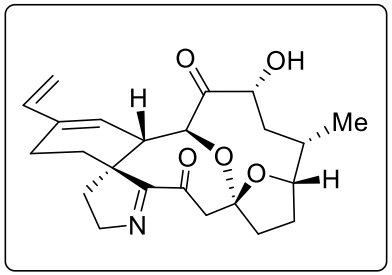
Hint step 13: Three heterocycles are formed.



Portimine B

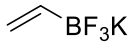
B

15 – 25



Portimine B

15. L-selectride, THF, –78 °C
16. $NaBH_4$, MeOH, 0 °C
17. TEMPO, NaOCl, KBr, $NaHCO_3$, DCM, H_2O, 0 °C
18. Zn, AcOH, H_2O, 70 °C
19. TBSOTf, Et_3N, DCM, reflux
20. DMDO (excess), acetone, DCM, 0 °C
21. Ac_2O (excess), Et_3N, DCM, 35 °C
22. LiOH, THF, H_2O, 0 °C
23. **6**, $Pd(dppf)Cl_2$, Et_3N, *n*-PrOH, 90 °C
24. DMP, $NaHCO_3$, DCM, r.t.
25. NH_3, H_2O, MeOH



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Step 18: Please, suggest a mechanism.

Hint step 20: Oxidation at 2 positions.

Step 21: Please, show the mechanism. Which analogous named rearrangement uses 2-alkylpyridine-*N*-oxides as substrates? Classify the rearrangement.

Hint step 22: Selective mono-deprotection.