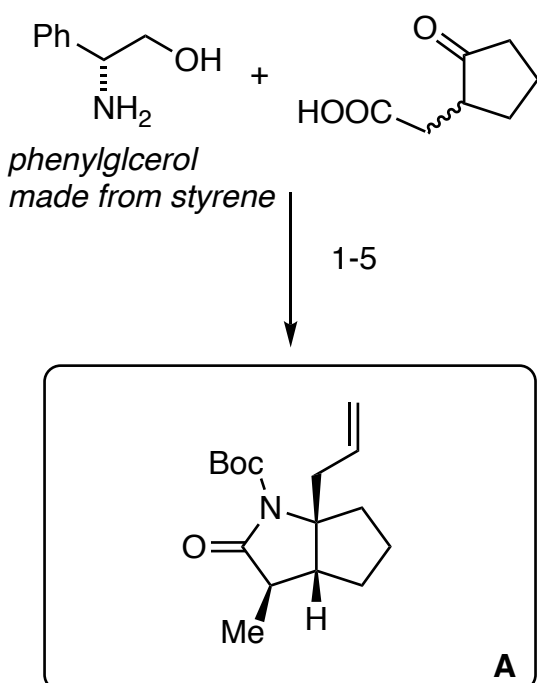
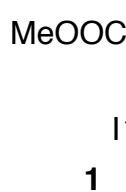


**Total Synthesis of (+)-Halichlorine: An Inhibitor of VCAM-1 Expression**

D. Trauner, J. B. Schwarz, and S. J. Danishefsky  
*Angew. Chem. Int. Ed.* **1999**, *38*, 3542-3545.



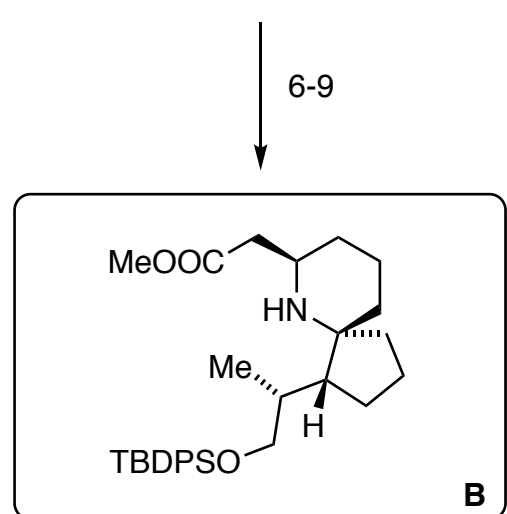
- 1) PhMe, reflux
- 2) allyltrimethylsilane,  $\text{TiCl}_4$
- 3) Na,  $\text{NH}_3$
- 4)  $\text{Boc}_2\text{O}$ , DMAP
- 5) LHMDS then MeI



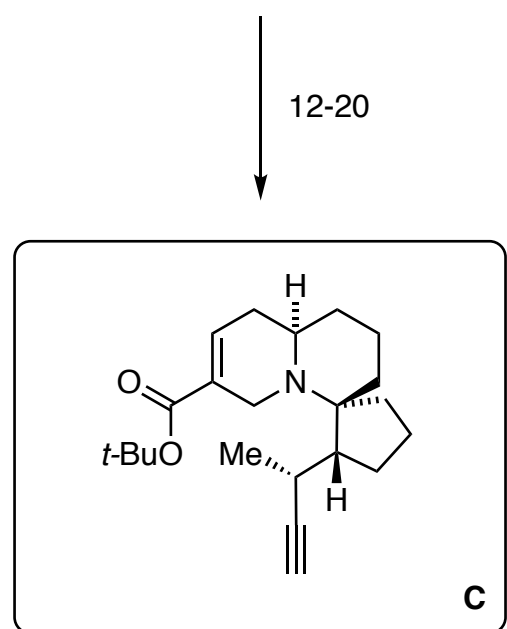
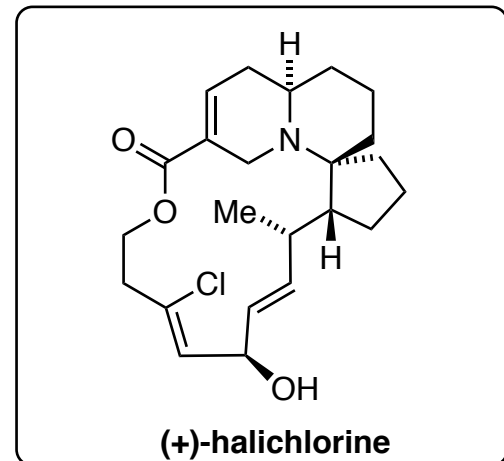
1) What is the name of the structure formed in 1? *Meyers lactam, one isomer formed (thermodynamic control). epimerization likely at acyl-imminium stage*

2) Please name the reaction and explain the Mechanism.  
*Hosomi-Sakurai reaction mention  $\beta$ -Si-effect*

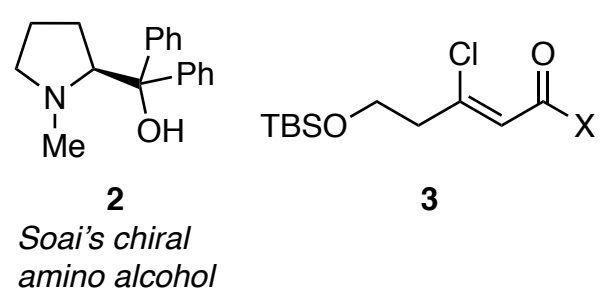
5) stereoselectivity? Me from convex site



- 6) LiOH,  $\text{H}_2\text{O}/\text{THF}$
- 7)  $\text{ClCOOEt}$ ,  $\text{NEt}_3$  then  $\text{NaBH}_4$ , MeOH
- 8)  $\text{TBDPSCl}$ ,  $\text{NEt}_3$ , DMAP
- 9) 9-BBN, THF then **1**,  $[\text{Pd}(\text{dppf})\text{Cl}_2]$ ,  $\text{AsPh}_3$ ,  $\text{Cs}_2\text{CO}_3$ , DMF/ $\text{H}_2\text{O}$
- 10) TFA, DCM then  $\text{K}_2\text{CO}_3$ ,  $\text{H}_2\text{O}$



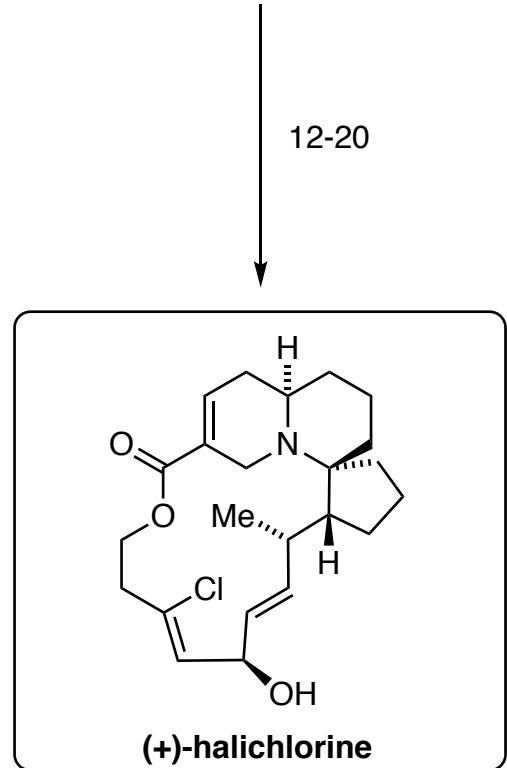
- 11) *t*-BuOAc, LHMDS
- 12)  $\text{H}_2\text{CO}$ , EtOH
- 13) LHMDS, then  $[\text{Cp}_2\text{Zr}(\text{H})\text{Cl}]$
- 14) HF/py
- 15) TPAP, NMO
- 16)  $\text{N}_2\text{CHP}(\text{O})(\text{OMe})_2$ ,  $\text{KO}^t\text{-Bu}$



11+12) please name the steps  
 11: *crossed Claisen condensation*  
 12: *Mannich reaction*

15) which other methods can achieve this transformation? *Ley-Griffith oxidation, other methods: DMP, PCC, Swern, ...*

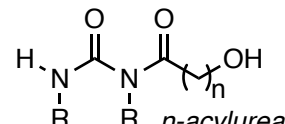
16) Please name the transformation and give the Mechanism. *Seyferth-Gilbert Homologation*



- 17)  $[\text{Cp}_2\text{Zr}(\text{H})\text{Cl}]$  then  $\text{ZnMe}_2$ , then **2** then **3**
- 18) DIBAL-H
- 19) TBSOTf, 2,6-lutidine
- 20)  $\text{NH}_4\text{F}$ , MeOH/ $\text{H}_2\text{O}$
- 21) EDCI, DMAP, DMAP  $\cdot$  HCl
- 22) HF/py

17) d.r.: 4:1 (sequence by Wipf 1998)

21) What is the role of DMAP  $\cdot$  HCl?  
*Keck-conditions of Steglich esterification; proton transfer agent; avoids formation of the N-acyl urea side-product*



**Bonus Question: what is VCAM-1?**

*VCAM-1: Vascular Cell Adhesion Molecule 1: inducible surface glycoprotein that is predominantly expressed in endothelial cells. It's expression is, among others, activated by pro-inflammatory cytokines, high glucose concentration and shear stress. VCAM-1 is involved in inflammation, immunological disorders and tumor angiogenesis and metastasis. (see: *Int. J. Mol. Sci.* **2018** *19*, 1057).*

