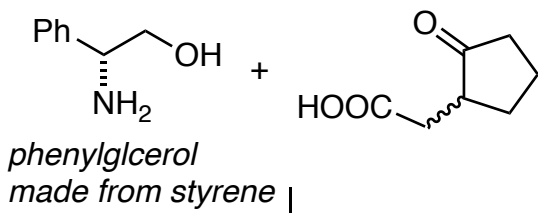
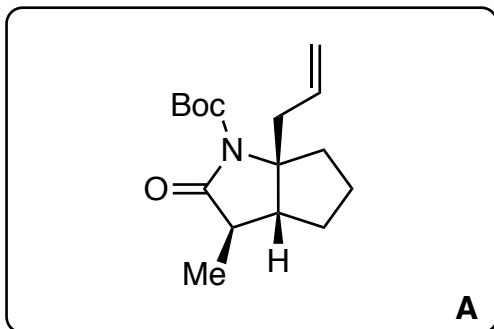


Total Synthesis of (+)-Halichlorine: An Inhibitor of VCAM-1 Expression

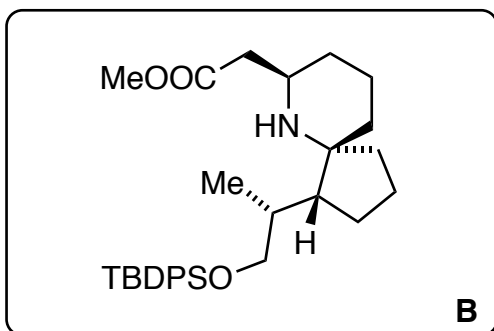
D. Trauner, J. B. Schwarz, and S. J. Danishefsky
Angew. Chem. Int. Ed. **1999**, *38*, 3542-3545.



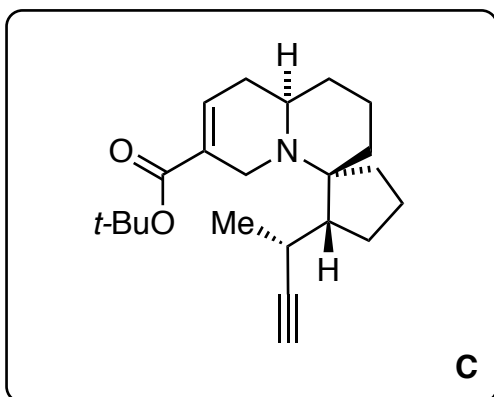
1-5



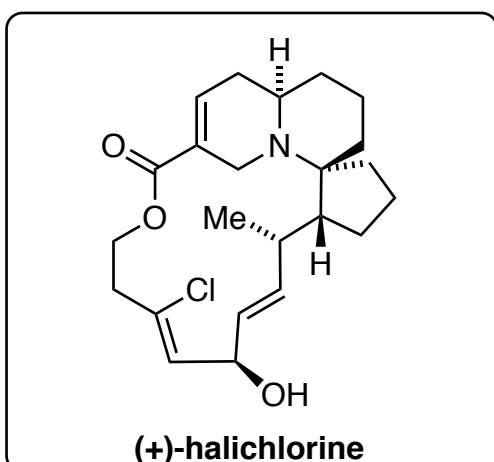
6-9



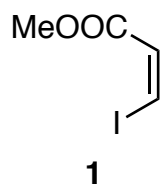
12-20



12-20

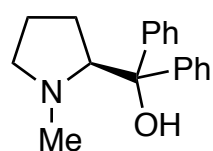


- 1) PhMe, reflux
- 2) allyltrimethylsilane, TiCl₄
- 3) Na, NH₃
- 4) Boc₂O, DMAP
- 5) LHMDS then MeI

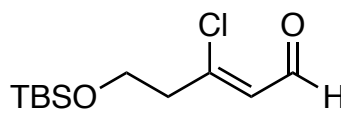


- 6) LiOH, H₂O/THF
- 7) ClCOOEt, NEt₃ then NaBH₄, MeOH
- 8) TBDPSCI, NEt₃, DMAP
- 9) 9-BBN, THF then **1**, [Pd(dppf)Cl₂], AsPh₃, Cs₂CO₃, DMF/H₂O
- 10) TFA, DCM then K₂CO₃, H₂O

- 11) *t*-BuOAc, LHMDS
- 12) H₂CO, EtOH
- 13) LHMDS, then [Cp₂Zr(H)Cl]
- 14) HF/py
- 15) TPAP, NMO
- 16) N₂CHP(O)(OMe)₂, KO^t-Bu



Soai's chiral amino alcohol



- 17) [Cp₂Zr(H)Cl] then ZnMe₂, then **2** then **3**
- 18) TBSOTf, 2,6-lutidine
- 19) NH₄F, MeOH/H₂O
- 20) EDCI, DMAP, DMAP · HCl
- 21) HF/py

Bonus Question: what is VCAM-1?

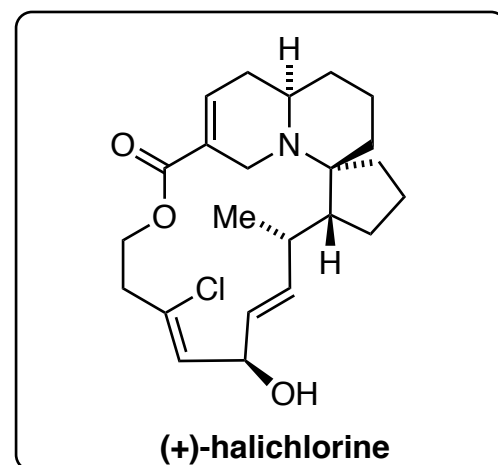
VCAM-1: Vascular Cell Adhesion Molecule 1: inducible surface glycoprotein that is predominantly expressed in endothelial cells. It's expression is, among others, activated by pro-inflammatory cytokines, high glucose concentration and shear stress. VCAM-1 is involved in inflammation, immunological disorders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

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 β-Si-effect

5) stereoselectivity? Me from convex site



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

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

