

# Synthesis Challenge #79

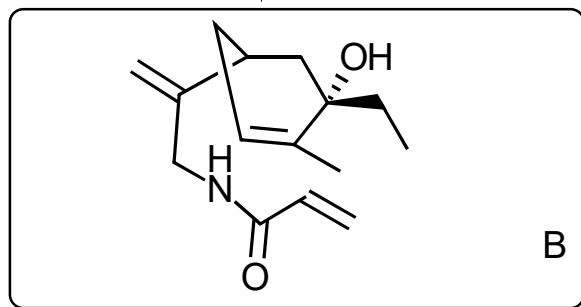
Total Synthesis of (-)-Daphenylline

B. Xu, B. Wang, W. Xun, F. G. Qiu, *Angew. Chem. Int. Ed.* **2019**, *58*, 5754 –5757

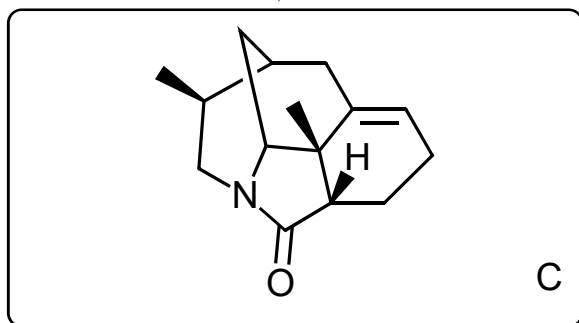
18.04.2019

Carvone A

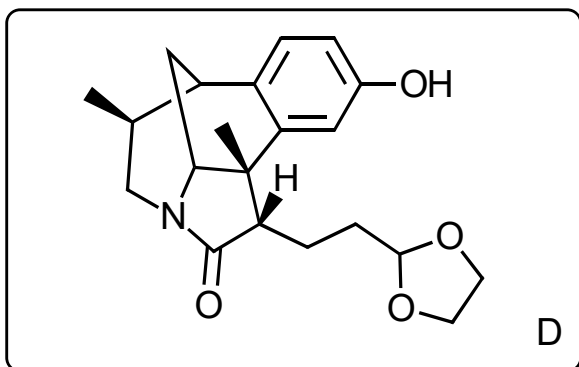
↓ 1-3



↓ 4-6



↓ 7-10



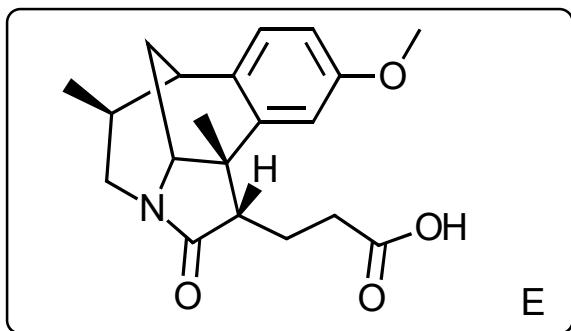
1)  $\text{SO}_2\text{Cl}_2$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{CH}_2\text{Cl}_2$ , RT, 7 h;  
then  $\text{NaN}_3$ , DMF, RT  
2)  $\text{CH}_2=\text{CHMgBr}$ , THF,  $-78^\circ\text{C}$  to  $0^\circ\text{C}$ ;  
then  $\text{H}_2\text{O}$ ,  $\text{PPh}_3$ , RT  
3) acryloyl chloride,  $\text{CH}_2\text{Cl}_2$ ,  $\text{Et}_3\text{N}$ ,  $0^\circ\text{C}$ ,

4)  $\text{Mg}(\text{ClO}_4)_2$ ,  $\text{CH}_3\text{CN}$ , reflux  
5) BHT, xylene,  $200^\circ\text{C}$   
6)  $\text{H}_2/\text{Ar}$  (1:2), Crabtree's catalyst,  
 $\text{CH}_2\text{Cl}_2$ , RT, 2 h; then  $\text{H}_2$ , RT

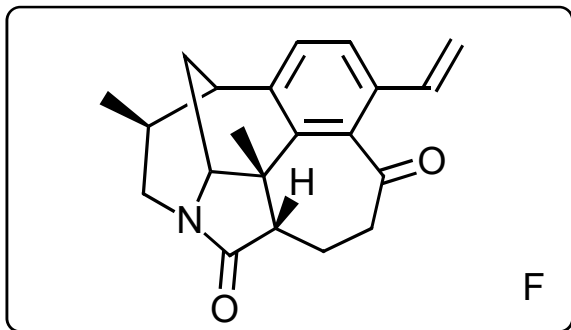
7) Sudan III,  $\text{O}_3$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ,  $-78^\circ\text{C}$   
then pyridine,  $\text{Me}_2\text{S}$ ,  $-78^\circ\text{C}$  to RT  
8)  $\text{TMSOCH}_2\text{CH}_2\text{OTMS}$ , TMSOTf,  
 $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$  to  $0^\circ\text{C}$   
9) LDA, Stork-Ganem reagent, THF,  
 $-78^\circ\text{C}$  to  $0^\circ\text{C}$ ; then KOH, MeOH, RT  
10) NaOMe, MeOH, reflux

11) NaH, MeI, DMF, 0°C, 0.5 h;  
then *p*-TsOH, acetone/H<sub>2</sub>O, 60°C  
12) NaH<sub>2</sub>PO<sub>4</sub>, NaClO<sub>2</sub>,  
2-methyl-2-butene, THF/*t*-BuOH/THF

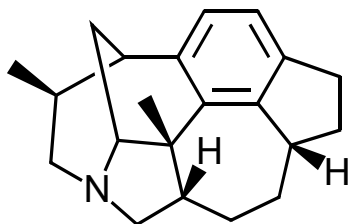
↓ 11, 12



↓ 13, 14



↓ 15-17



13) (COCl)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, RT, 2 h;  
then AlCl<sub>3</sub>, reflux  
14) Tf<sub>2</sub>O, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 4 h;  
then potassium vinyltrifluoroborate,  
Pd(dppf)Cl<sub>2</sub>, Et<sub>3</sub>N, MeOH, 55°C

15) NaBH<sub>4</sub>, MeOH, 0°C, 0.5 h;  
then *p*-TsOH, toluene, 55°C  
16) H<sub>2</sub>, Pd/C, MeOH, RT, 15 min  
17) Lawesson's reagent, 2-dichloro-  
benzene, 140°C, 15 min ;  
then Raney Ni, THF, RT, 15 min