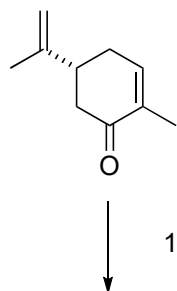


# Total Synthesis of (+)-Pleuromutilin

Neal J. Fazakerley, Dr. Matthew D. Helm, David J. Procter  
*Chem. Eur. J.* **2013**, *19*, 6718 – 6723.



↓ 7-10



↓ 11 - 16

- 1) benzylamine,  $\Delta$ ; then  $\text{KO}^t\text{-Bu}$ , diglyme; then  $\text{AcOH}/\text{H}_2\text{O}$
- 2)  $\text{O}_3$ ,  $\text{MeOH}$ ,  $-78\text{ }^\circ\text{C}$ ; then  $\text{Cu}(\text{OAc})_2$ ,  $\text{FeSO}_4$ , rt
- 3)  $\text{TBSOCH}_2\text{CH}_2\text{CH}_2\text{MgBr}$ ,  $\text{CuCN LiCl}$ ,  $\text{TMSCl}$ ,  $\text{THF}$ ,  $-45\text{ }^\circ\text{C}$  to rt
- 4)  $\text{Pd}(\text{OAc})_2$  (cat.),  $\text{DMSO}$ ,  $\text{O}_2$
- 5)  $\text{CuI}$ ,  $\text{TMSCH}_2\text{C}(\text{MgBr})\text{CH}_2$ ; then Comins' reagent  $-45$  to  $0\text{ }^\circ\text{C}$
- 6)  $\text{Pd}(\text{OAc})_2$ ,  $\text{Ph}_3\text{P}$ ,  $\text{Et}_3\text{N}$ ,  $\text{MeOH}/\text{DMF}$ ,  $\text{CO}$  balloon,  $40\text{ }^\circ\text{C}$

- 7)  $\text{TBSOCH}_2\text{CH}_2\text{CHO}$ ,  $\text{BF}_3\cdot\text{OEt}_2$ ,  $\text{TBAT}$ ,  $4\text{ \AA}$  MS  
 $\text{CH}_2\text{Cl}_2$ ,  $-78$  to  $-20\text{ }^\circ\text{C}$
- 8)  $\text{PivCl}$ , pyridine,  $\text{DMAP}$ ,  $\text{CH}_2\text{Cl}_2$
- 9)  $\text{HF}$ , pyridine,  $\text{MeCN}$ ,  $0\text{ }^\circ\text{C}$  to rt
- 10)  $\text{DMP}$ ,  $\text{CH}_2\text{Cl}_2$ ,

- 11)  $\text{SmI}_2$ ,  $\text{THF}/t\text{-BuOH}$ ,  $0\text{ }^\circ\text{C}$
- 12)  $\text{Et}_3\text{N}$ ,  $\text{TBSOTf}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0\text{ }^\circ\text{C}$
- 13)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$
- 14)  $\text{DMP}$ ,  $\text{CH}_2\text{Cl}_2$
- 15)  $\text{H}_2$ , 10%  $\text{Pd}/\text{C}$ ,  $\text{EtOH}$
- 16) ethylene glycol,  $\text{HC}(\text{OMe})_3$ ,  $\text{Amberlyst}$  (cat.),  $\text{toluene}/\text{MeCN}$

Step 1: Mechanism?

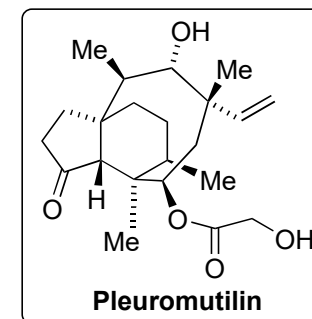
Step 2: Role of  $\text{Cu}(\text{OAc})_2$  and  $\text{FeSO}_4$ ?

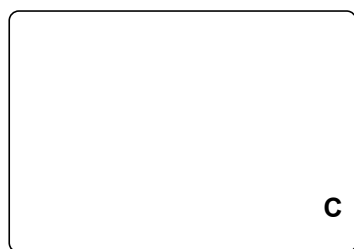
Step 4: Name Reaction?

Step 7: Suggest a possible role for  $\text{TBAT}$

Step 11: Mechanism?

*Hint: two new carbocycles are formed*





17-21



22-26

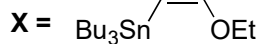


27-31

- 17)  $\text{SnI}_2/\text{pyrrolidine}/\text{H}_2\text{O}$
- 18) LDA (2 eq), *p*-methylbenzoyl chloride (2 eq), THF,  $-78\text{ }^\circ\text{C}$
- 19) NaOMe, MeOH,  $0\text{ }^\circ\text{C}$  to rt
- 20) 1,1'-Thiocarbonyldiimidazole, THF,  $\Delta$
- 21) *n*- $\text{Bu}_3\text{SnH}$ , AIBN, PhMe,  $\Delta$

- 22)  $\text{FeCl}_3$  on  $\text{SiO}_2$ , acetone
- 23) HF, MeCN
- 24) MOMCl, DIPEA,  $\text{CH}_2\text{Cl}_2$
- 25) HMDS, TMSI; then *m*-CPBA,  $\text{NaHCO}_3$ ; then TBAF
- 26) MOMCl, DIPEA,  $\text{CH}_2\text{Cl}_2$

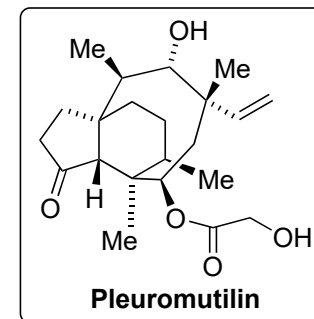
- 27) treat **X** with *n*-BuLi, add to **E**, THF,  $-78\text{ }^\circ\text{C}$
- 28)  $\text{FeCl}_3$  on  $\text{SiO}_2$ , acetone
- 29)  $\text{NaBH}_4$ , THF/ $\text{H}_2\text{O}$
- 30) NCS,  $\text{Me}_2\text{S}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0\text{ }^\circ\text{C}$
- 31)  $\text{Me}_2\text{Zn}$ , CuCN, DMF,  $-20\text{ }^\circ\text{C}$



Step 17: Why does the reaction work in the presence of water and pyrrolidine, and not without amine additive, water?

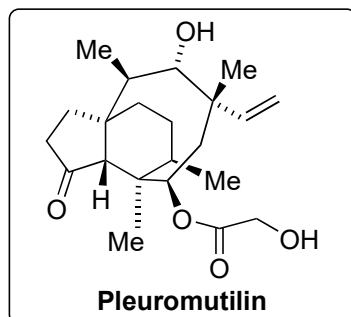
Step 20/21: Name reaction?

Step 25: Name reaction? Why is TBAF added?





32-36



- 32)  $\text{LiAlH}_4$ , THF
- 33) DMP,  $\text{CH}_2\text{Cl}_2$
- 34) AcCl, EtOH
- 35) trifluoroacetyl imidazole (1 eq), EtOAc,  $-45\text{ }^\circ\text{C}$
- 36) **Y**, EDCI, DMAP,  $\text{CH}_2\text{Cl}_2$ , *then* MeOH,  $\text{Et}_3\text{N}$

