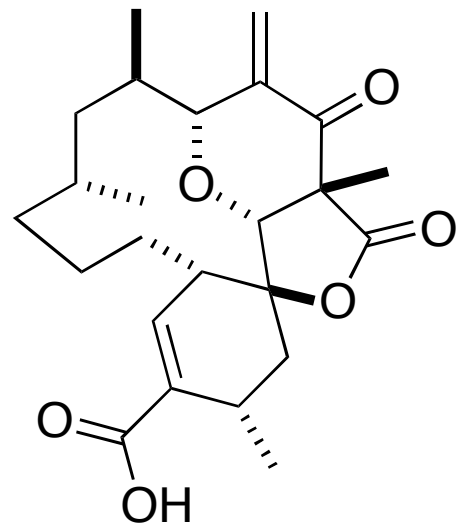
Total Synthesis of (-)-Okilactomycin



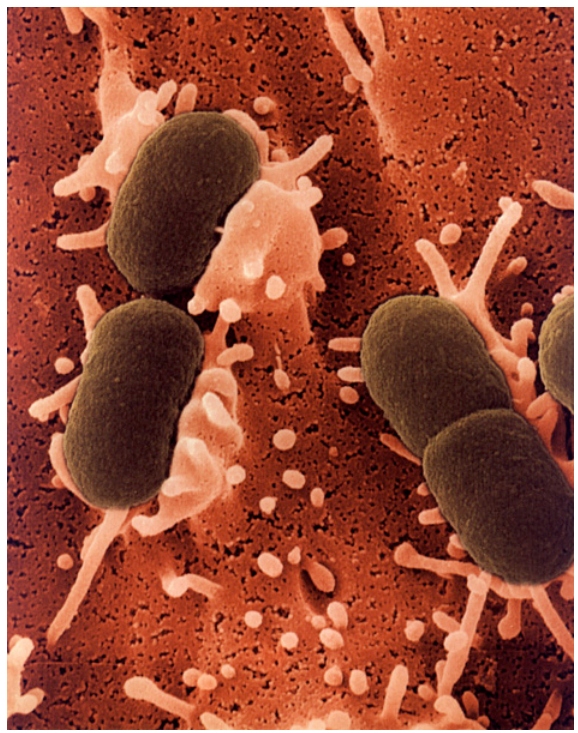
Amos B. Smith, III, Kallol Basu and Todd Bosanac
JACS ASAP (11/13/2007)

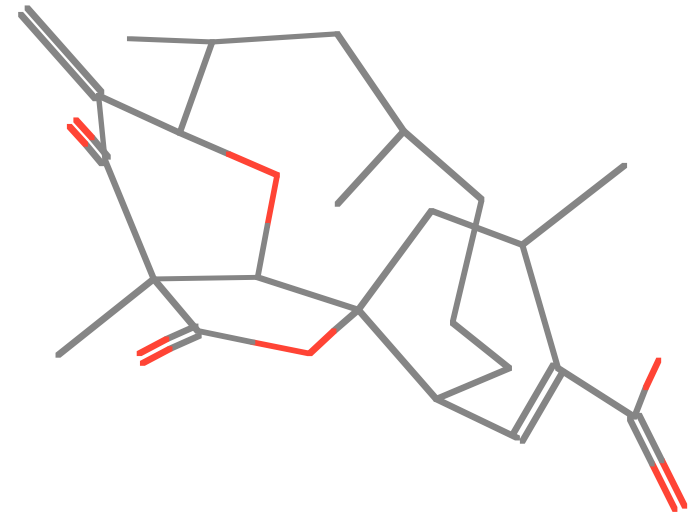
Wipf Group Current Literature
Joshua Pierce - 11/24/07

Isolation and Structure Determination

Isolated in 1987 from bioactive filtrate of Streptomyces griseoflavus

Exhibits cytotoxicity against human cell lines P388 and lymphoid leukemia L1210 (IC_{50} = 0.09, 0.037 μg/mL)

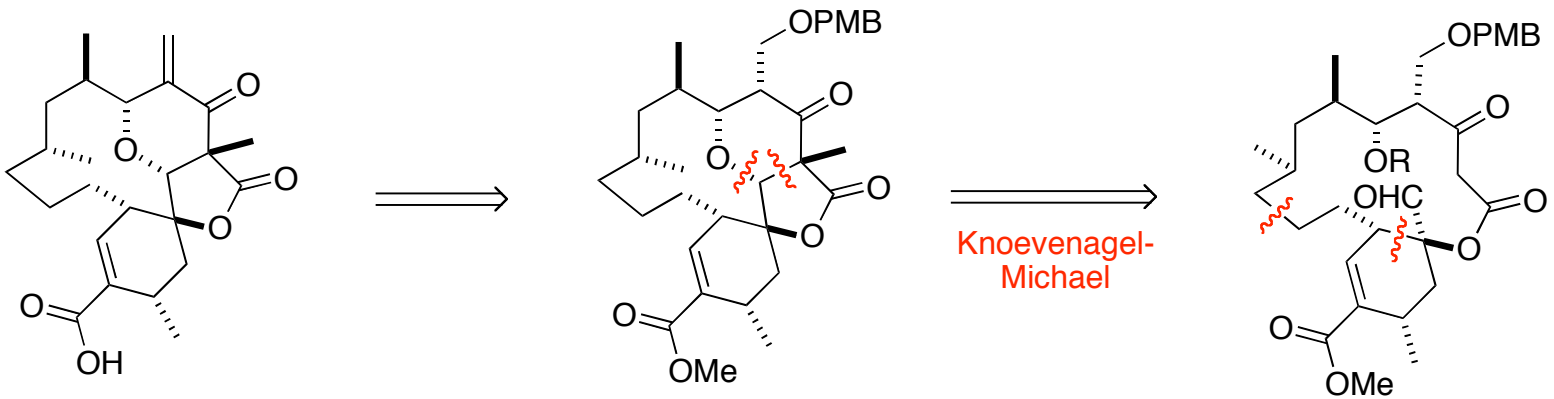




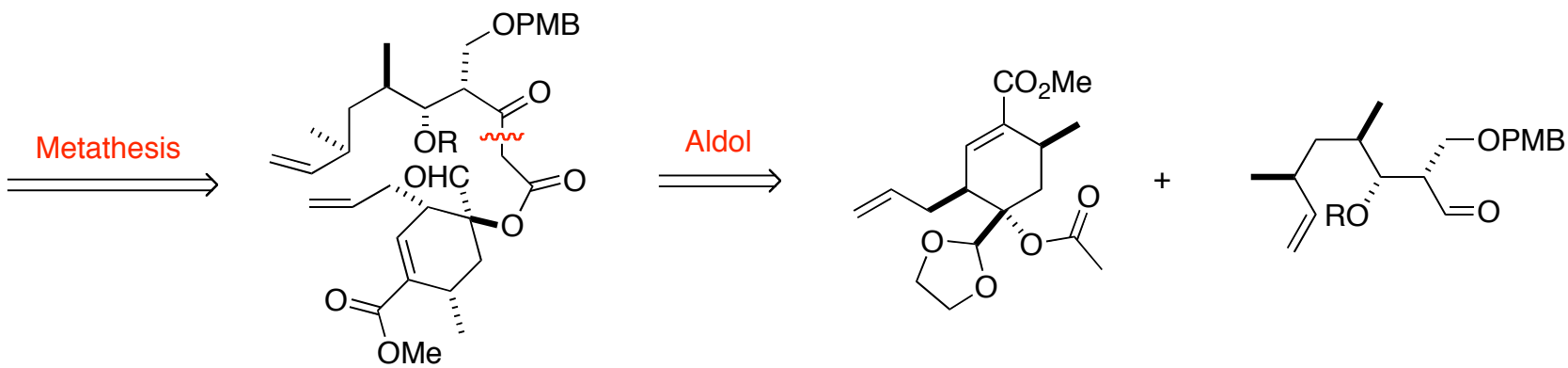
Structure contains functionalized cyclohexane with spirocenter, 2,6-*cis*-tetrahydropyranone and 13 membered ring

Initially assigned by NMR, later confirmed by X-ray analysis. Absolute stereochemisty remained unknown until present work.

Previous Synthetic Studies



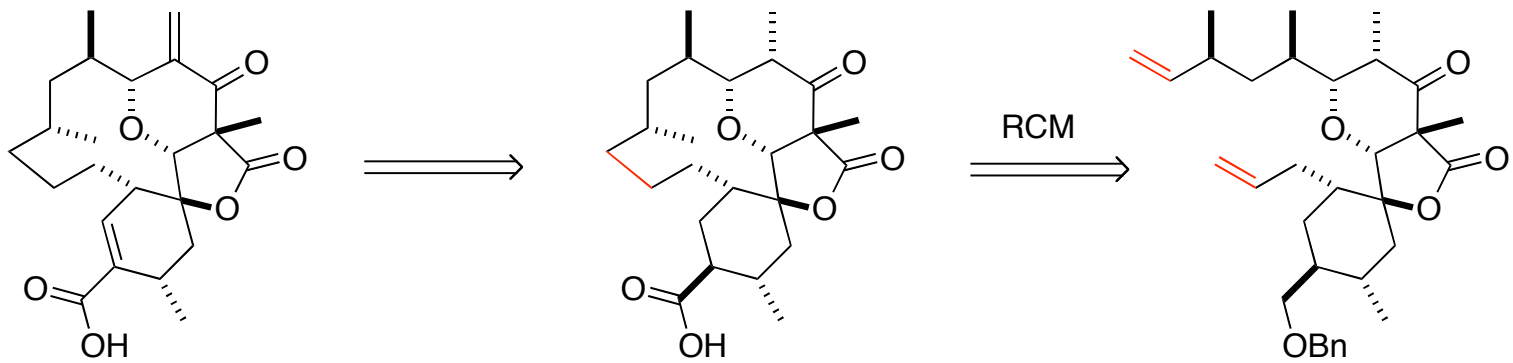
Okilactomycin

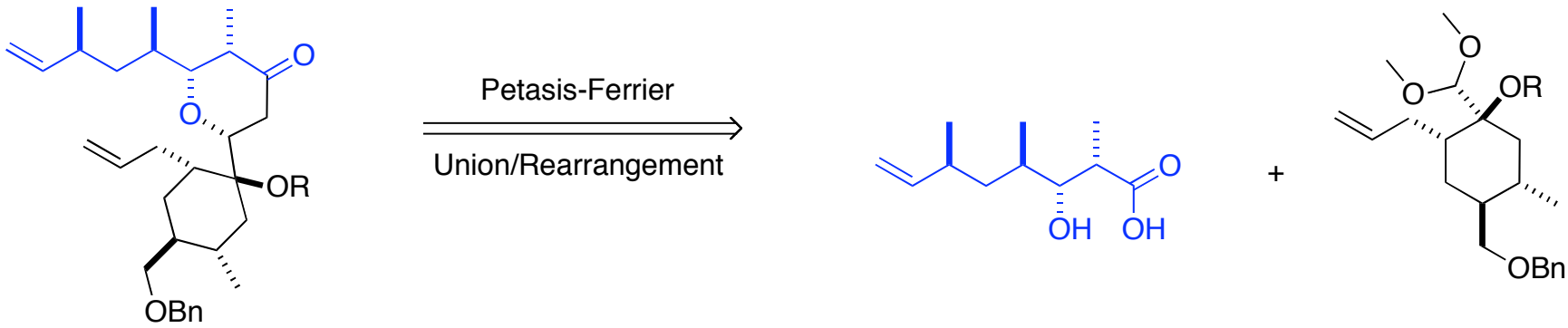


Paquette *et al.*, *Synthesis*, **2002**, 888-894.

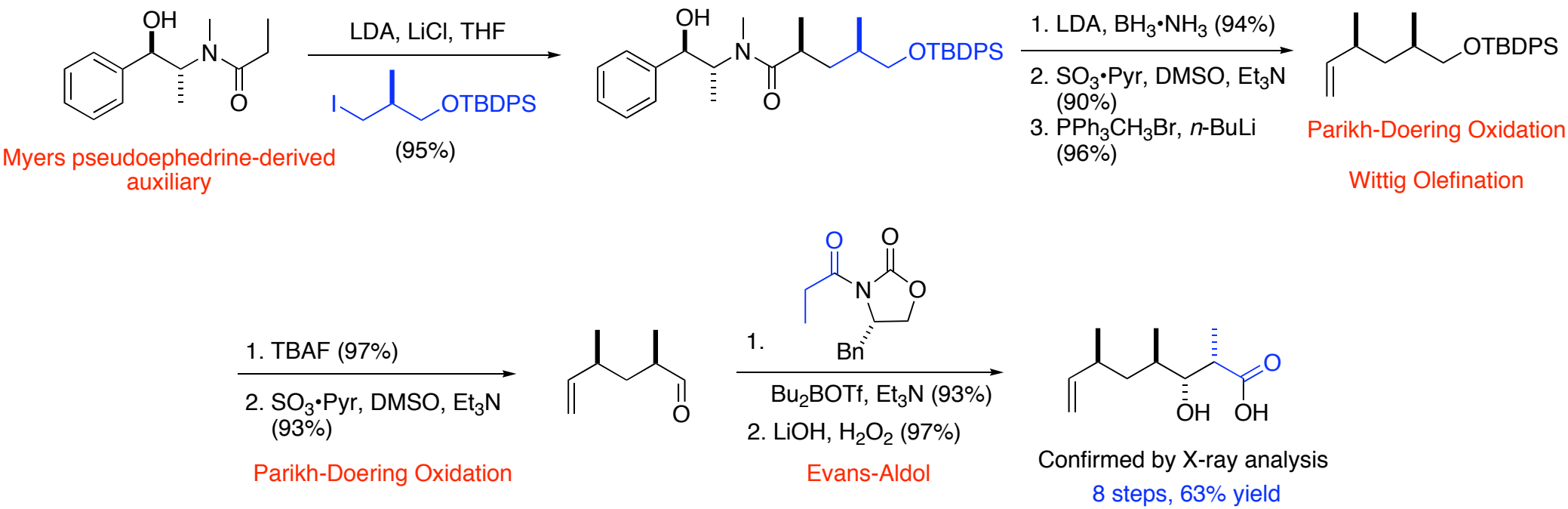
Paquette *et al.*, *Synthesis*, **2002**, 895-900.

Retrosynthetic Analysis

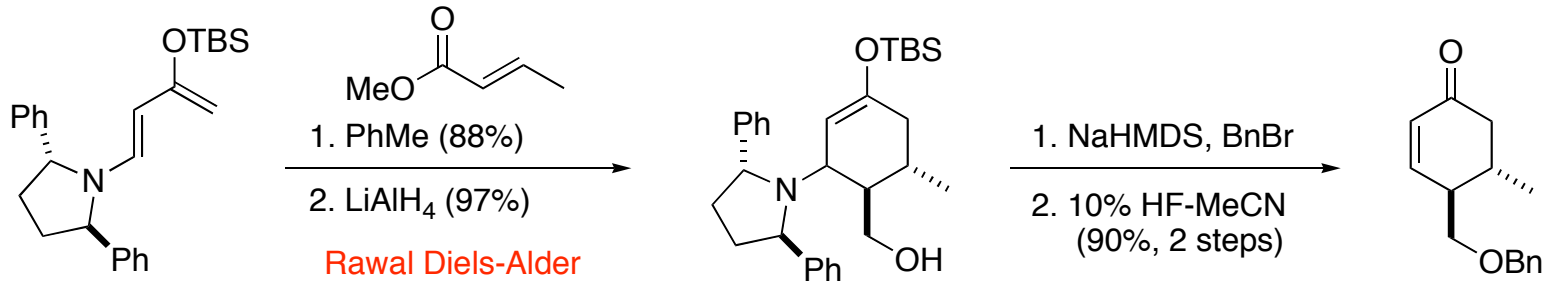


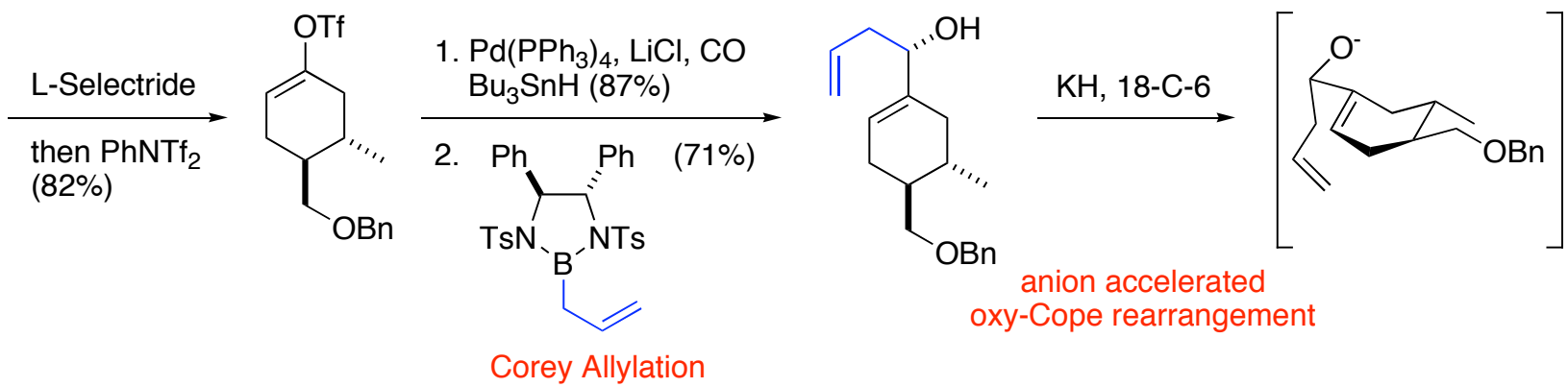


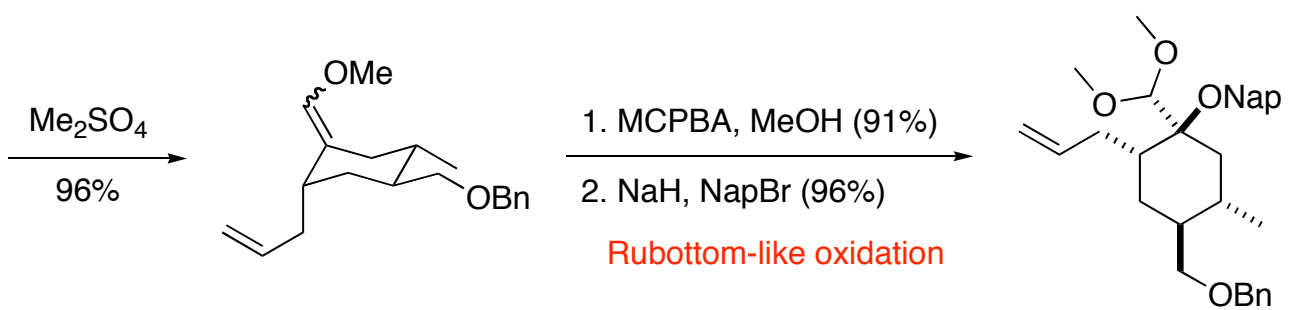
Synthesis of Acid Fragment



Synthesis of Cyclohexyl Fragment

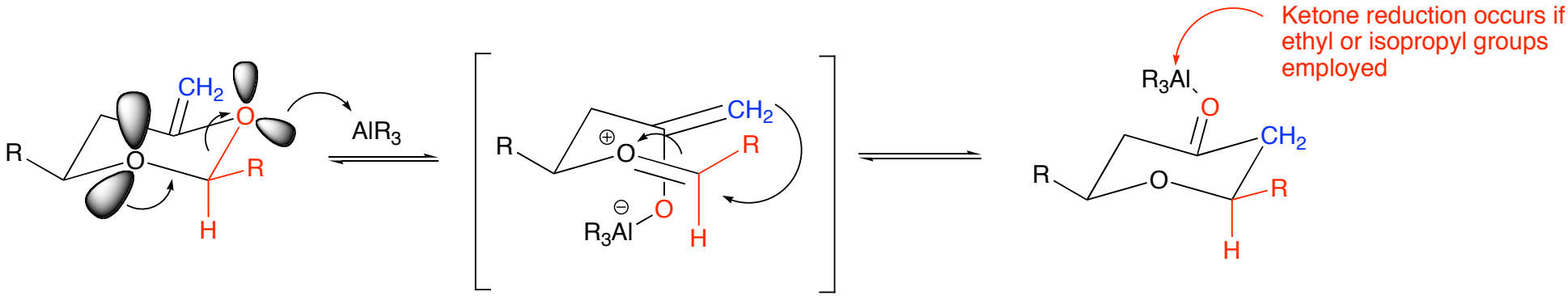






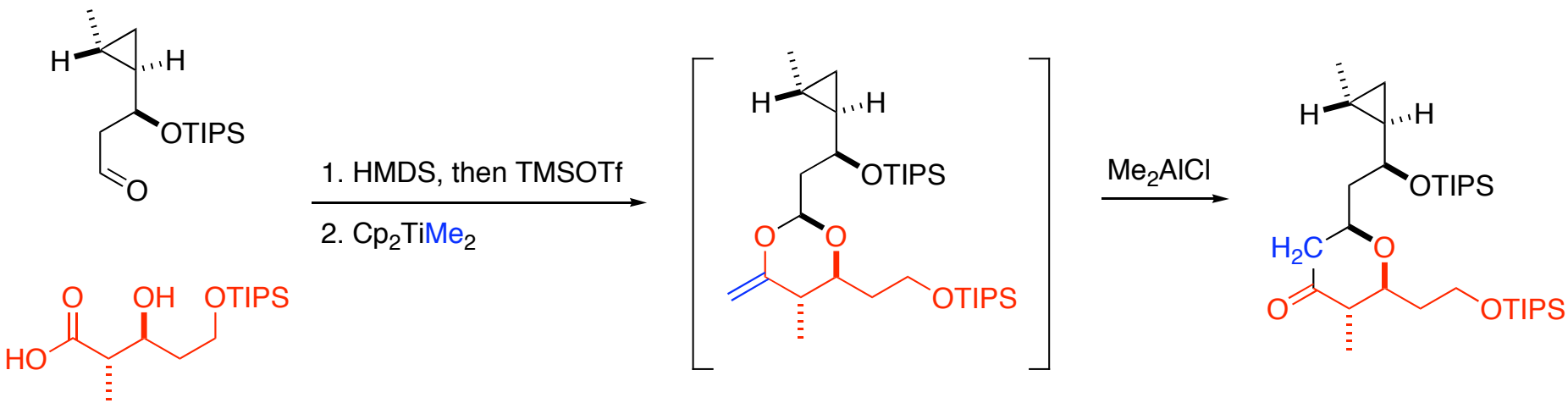
Petasis-Ferrier Union/Rearrgangement

Petasis-Ferrier Reaction (1995):



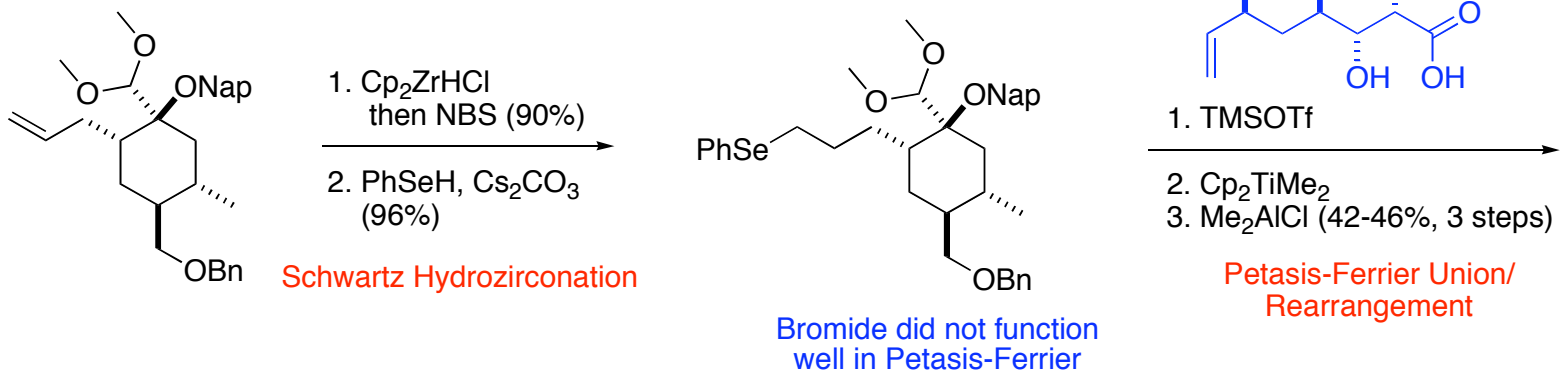
Petasis *et al. JACS*, **1995**, *117*, 6394.

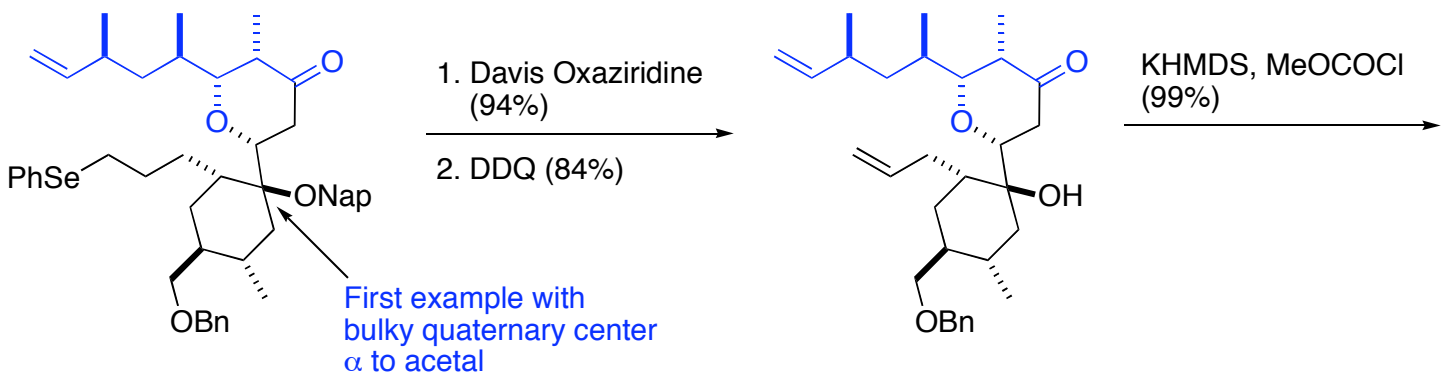
Smith has utilized coupling of complex fragments via acetalization followed by P-F rearrangement:

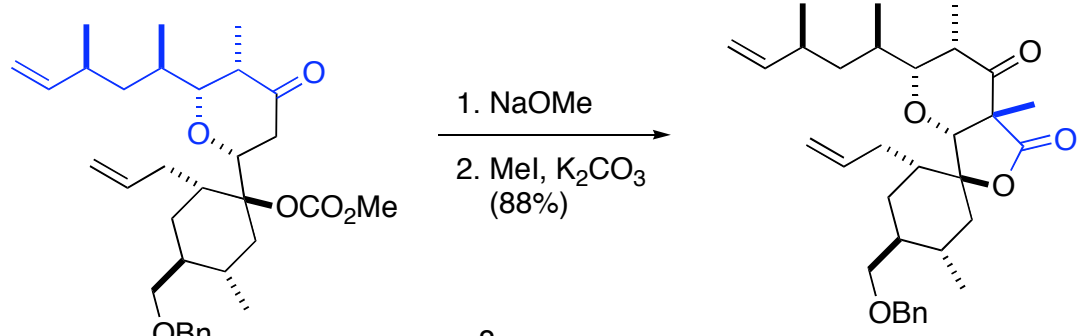


Smith *et al. JACS*, **2001**, *123*, 10942.
Smith *et al. OL*, **2006**, *8*, 3315,

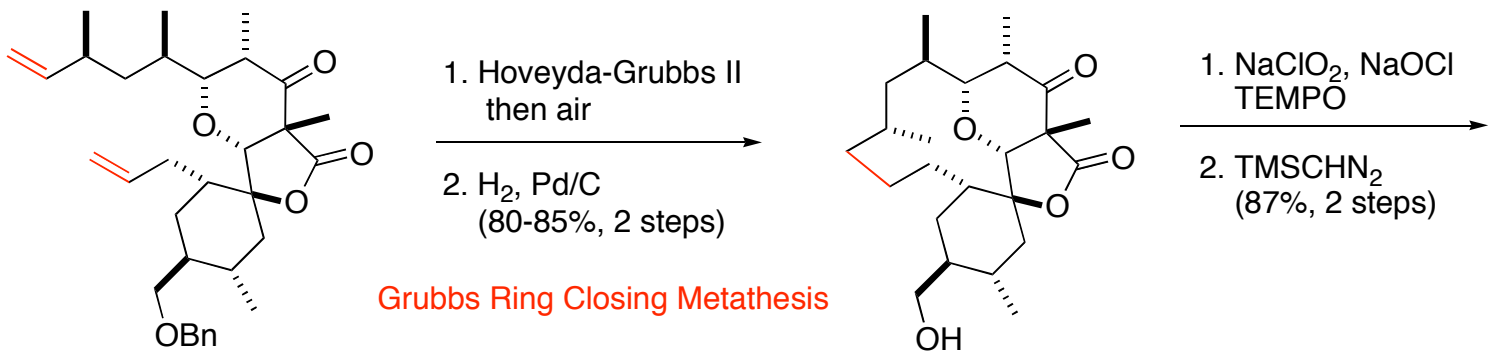
Petasis-Ferrier Union/Rearrgangement Applied

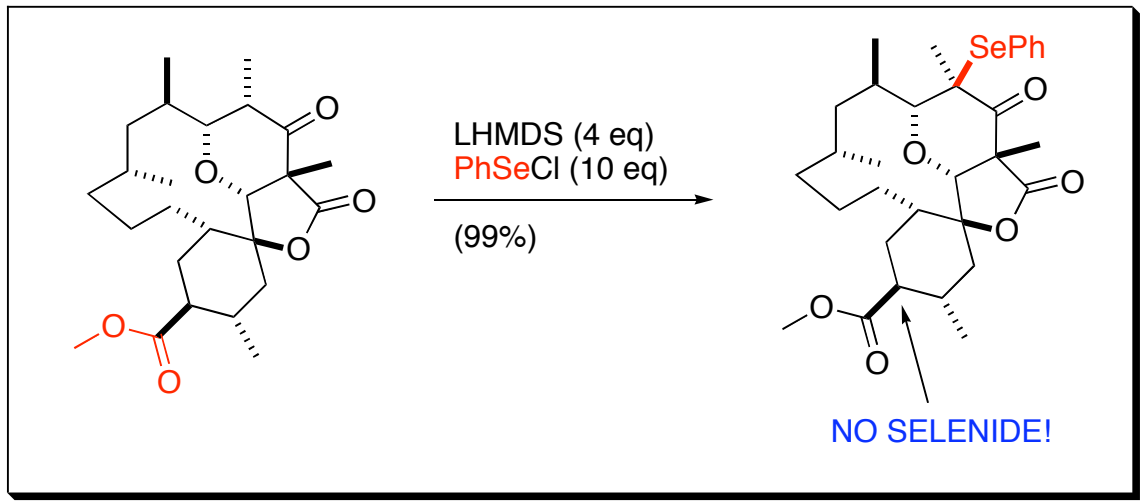




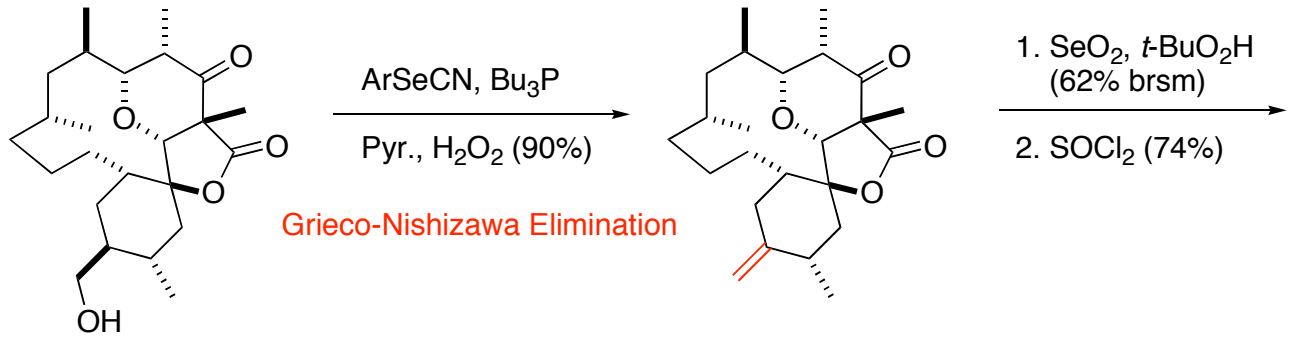


Ring Closing Metathesis

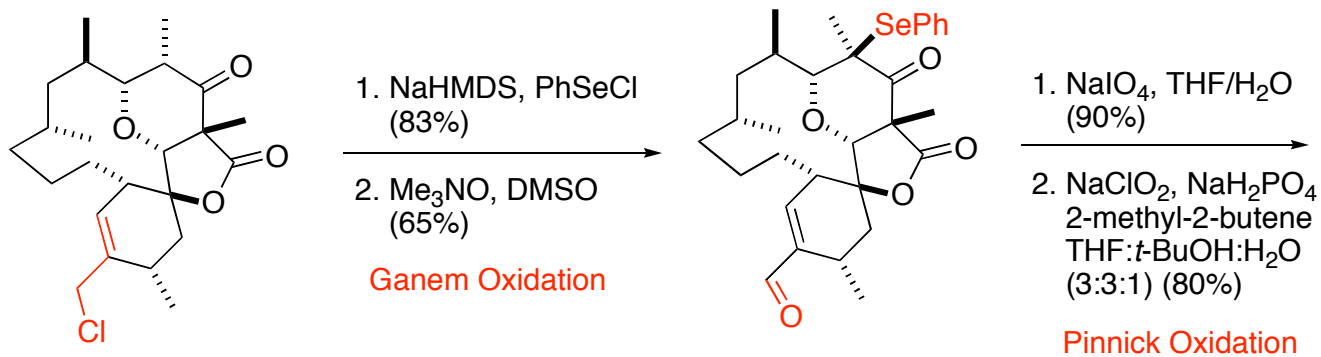


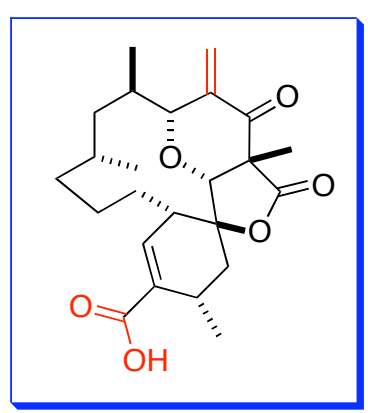


Completion of the Synthesis



Confirmed by X-ray analysis of Iodide





Synthetic Material: $[\alpha]^{20}_D$ = = -37 (*c* = 0.03, MeOH)

Natural Product: $[\alpha]^{20}_D$ = = +34 (*c* = 1, MeOH)

Conclusions

First total synthesis of okilactomycin has been achieved in 29 steps (longest linear sequence).

Synthesis establishes absolute configuration through formation of incorrect enantiomer.

Utilization of a variety of classical reaction in conjunction of effective Petasis-Ferrier union/rearrangement provided access to the functionalized core.

Biological evaluation and analog development should provide insight into the potential of this compound as a therapeutic agent.