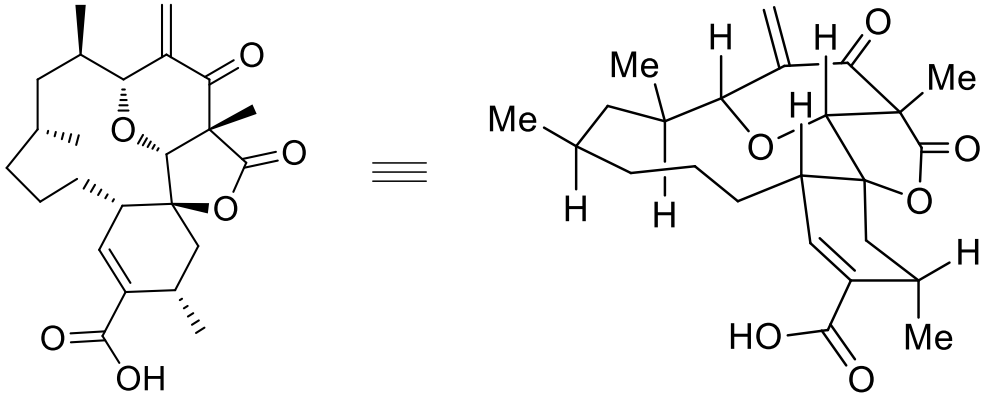
# Synthesis of (-)-Okilactomycin by a Prins-Type Fragment-Assembly Strategy




Jason M. Tenenbaum, William J. Morris, Daniel W. Custer, and Karl A. Scheidt*

*Angew. Chem. Int. Ed*. **2011**, *Early View*

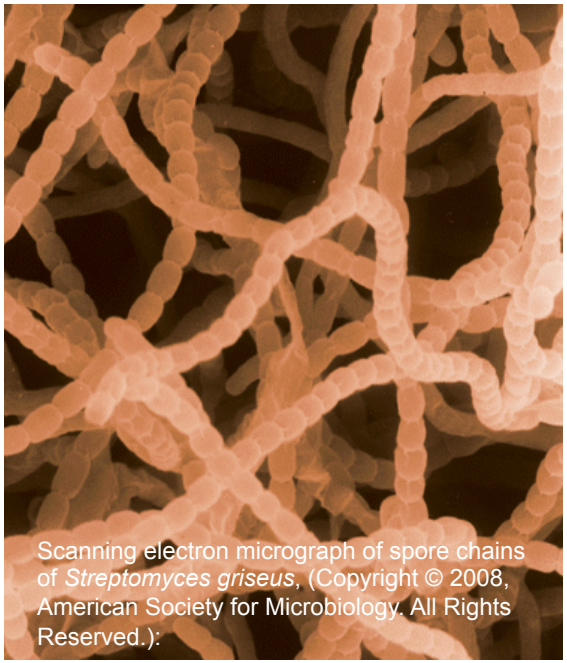
Wipf Group Current Literature
John Goodell – 5/21/11

# Isolation and Biological Evaluation

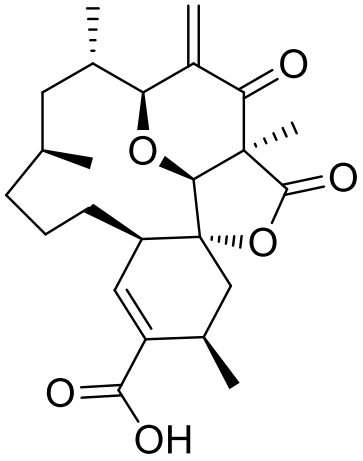
Isolated in 1987 from *Streptomyces griseoflavus* found in a soil sample collected on Zamami Island, Okinawa, Japan.

Structure originally assigned using MS and NMR techniques, then later by X-ray analysis which confirmed the relative stereochemistry.

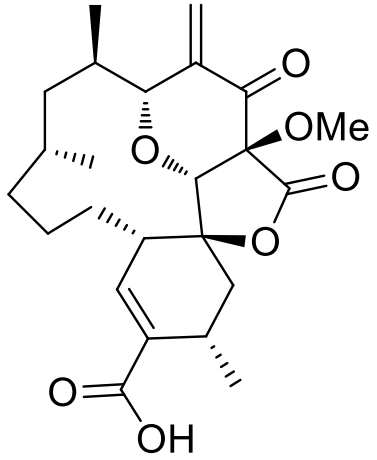
Absolute stereochemistry confirmed after first synthesis of (-)-okilactomycin by Smith et al. *JACS* **2007**, *129*, 14872.



Scanning electron micrograph of spore chains of *Streptomyces griseus*, (Copyright © 2008, American Society for Microbiology. All Rights Reserved.):




(+)-okilactomycin




(-)-chrolactomycin

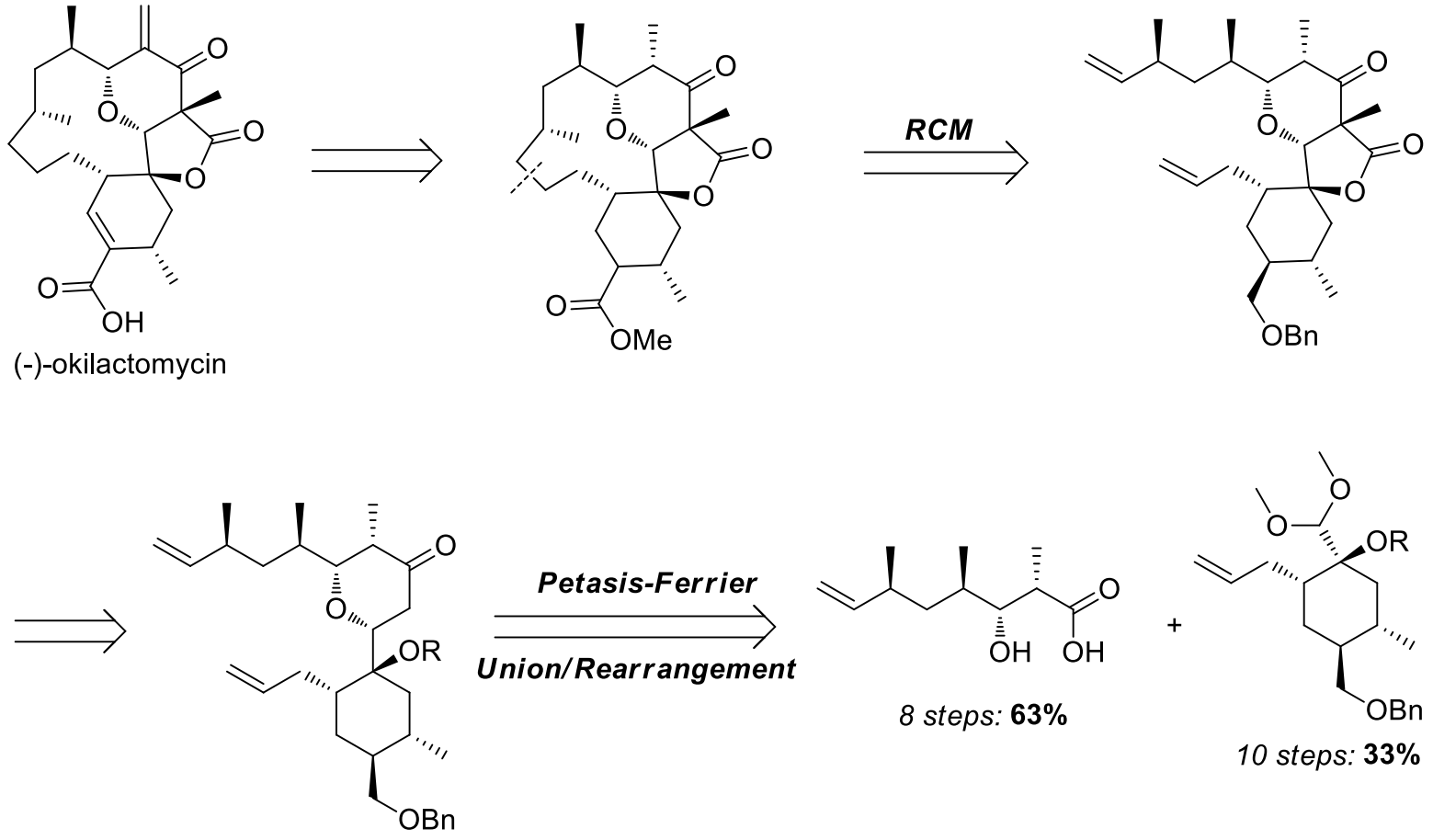
*relative stereochemistry*

Exhibits *in vitro* cytotoxicity against human lymphoid leukemia L1210 cells ($IC_{50}$ = 216 nM) P388 leukemia cells ($IC_{50}$ = 89 nM).

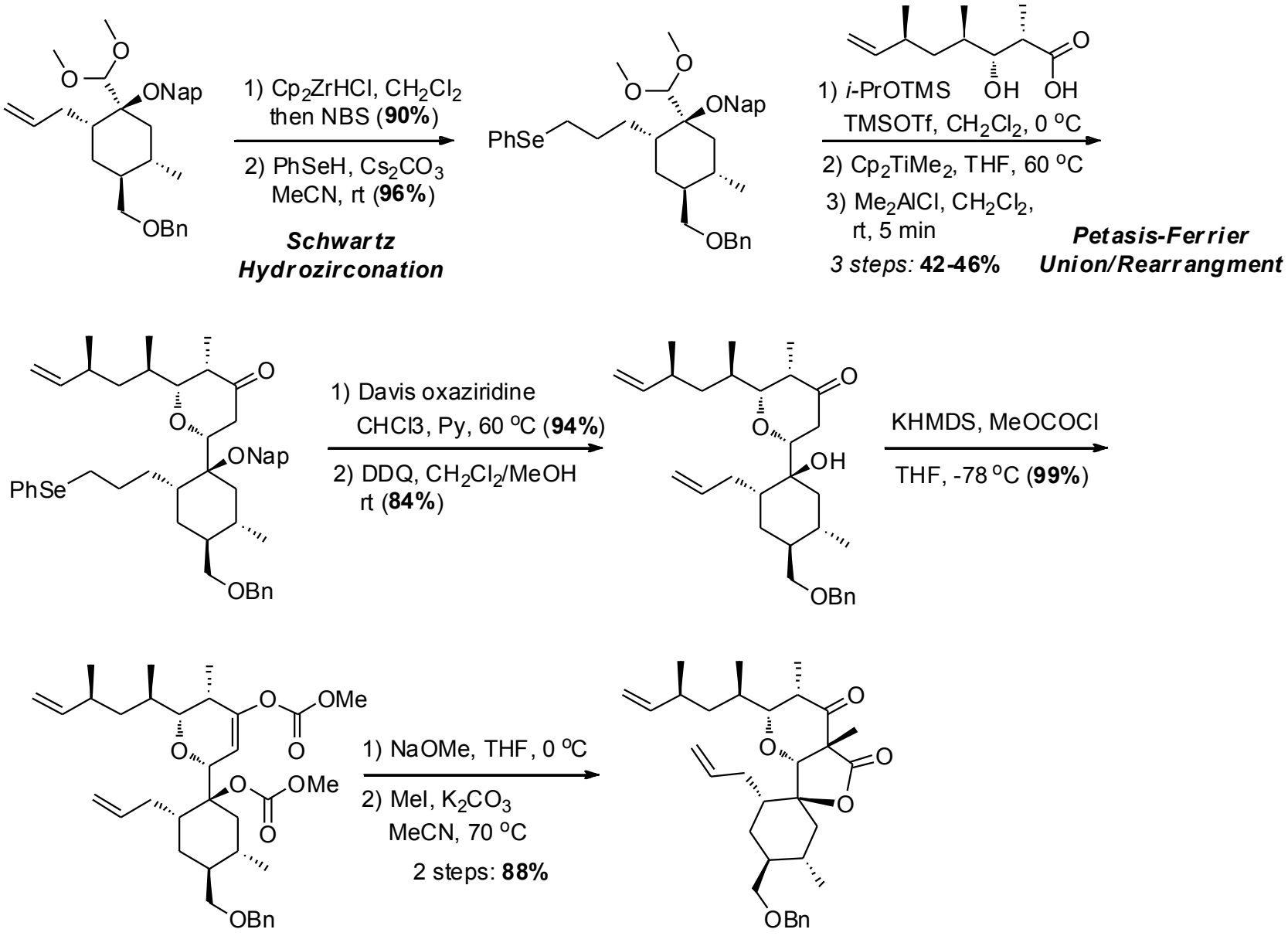
Despite this potent inhibition, only found two additional reports of activity and no reports of follow-up SAR.

(-)-Chrolactomycin has shown antitumor, antibiotic, and telomerase inhibition.

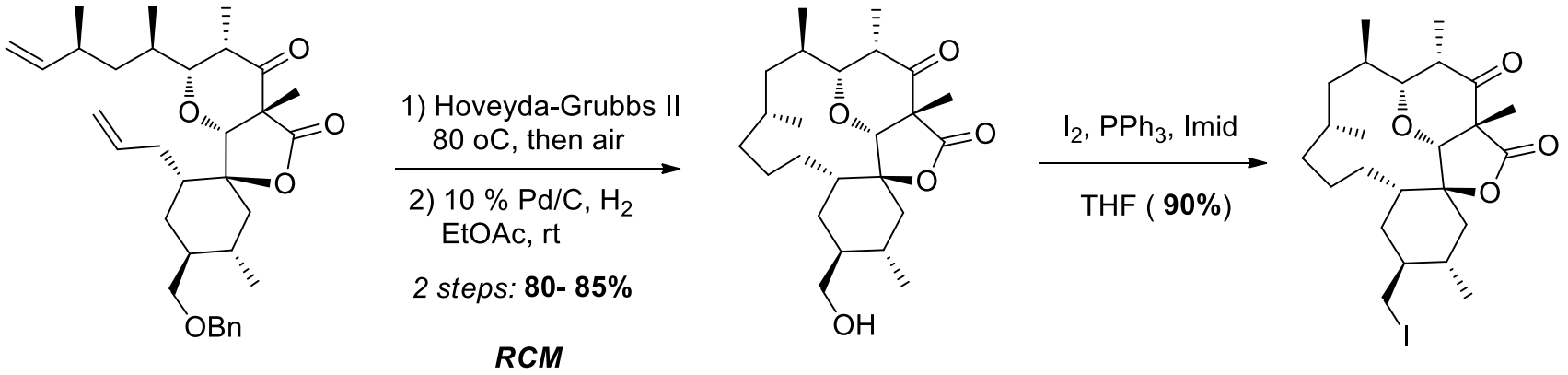
# Smith's Retrosynthetic Analysis



# Smith's Construction of Core Framework



# Smith's Construction of Core Framework



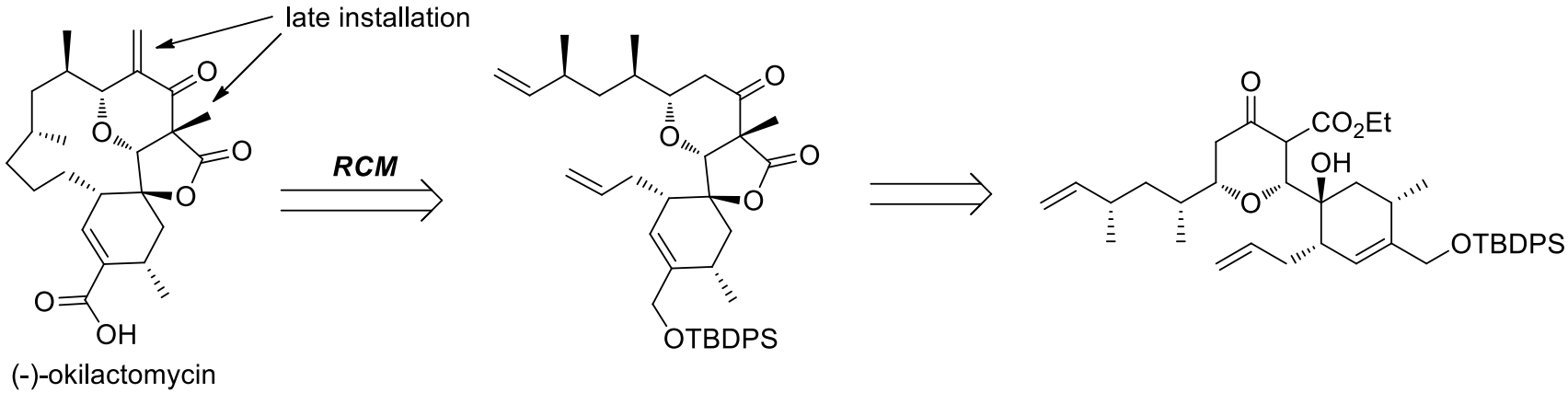

X-ray analysis confirmed absolute stereochemistry of (-)-Okilactomycin

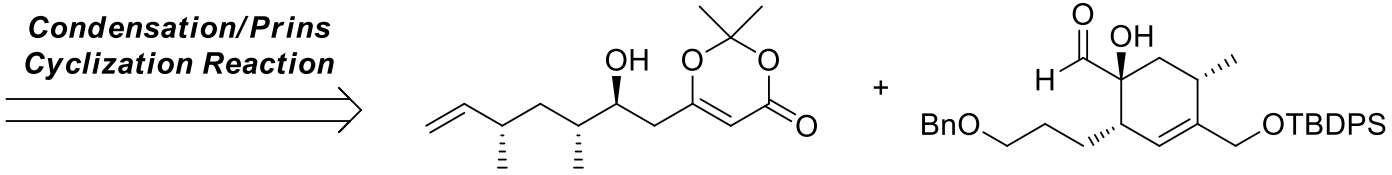
*(-)-Okilactomycin achieved in 7 steps from alcohol; 29 overall (longest linear sequence)

*Utilized a Petasis-Ferrier union/rearrangement to construct 2,6-cis-tetrahydropyanone core.

*Established absolute stereochemistry of natural (+)-okilactomycin.

# Retrosynthetic Analysis: Title Paper

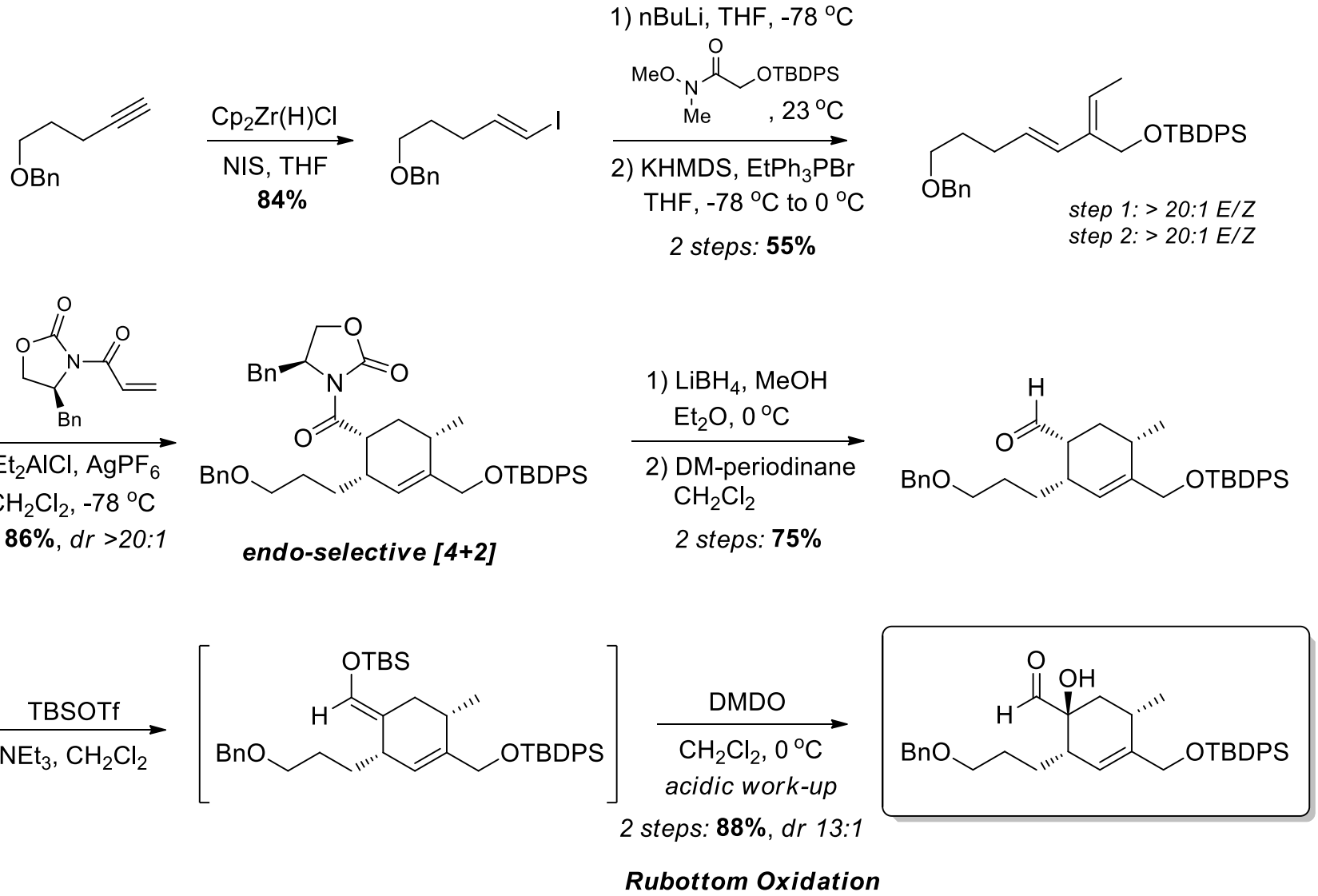


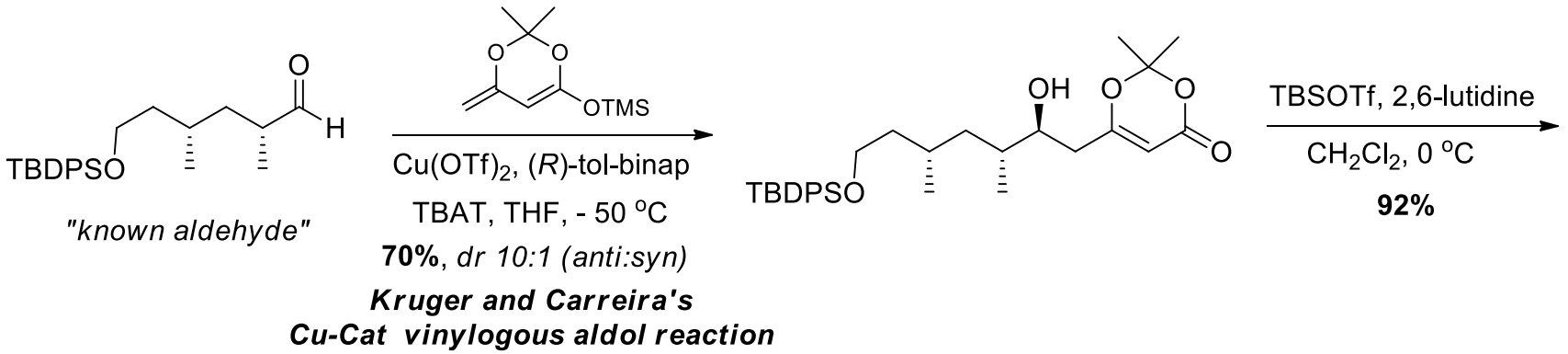

-hydroxy dioxinone fragment

-hydroxy aldehyde fragment

# Synthesis of α-Hydroxy Aldehyde Fragment

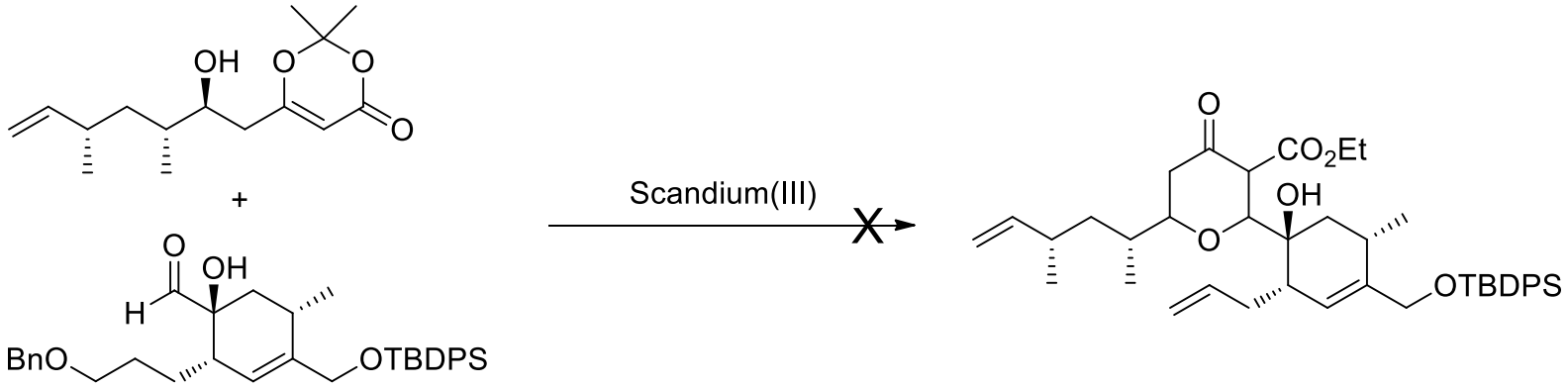


# Synthesis of β-Hydroxy Dioxinone Fragment

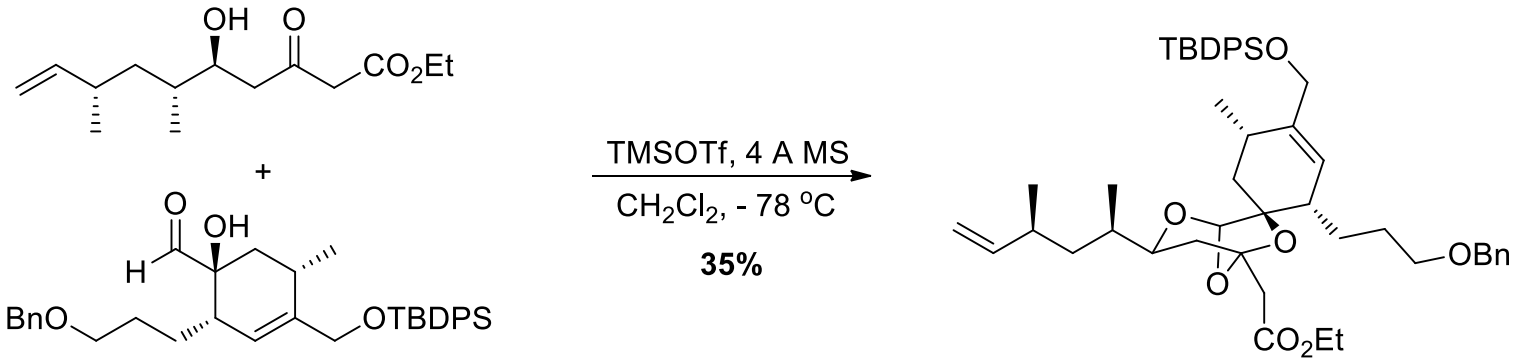


# Connection of Key Fragments

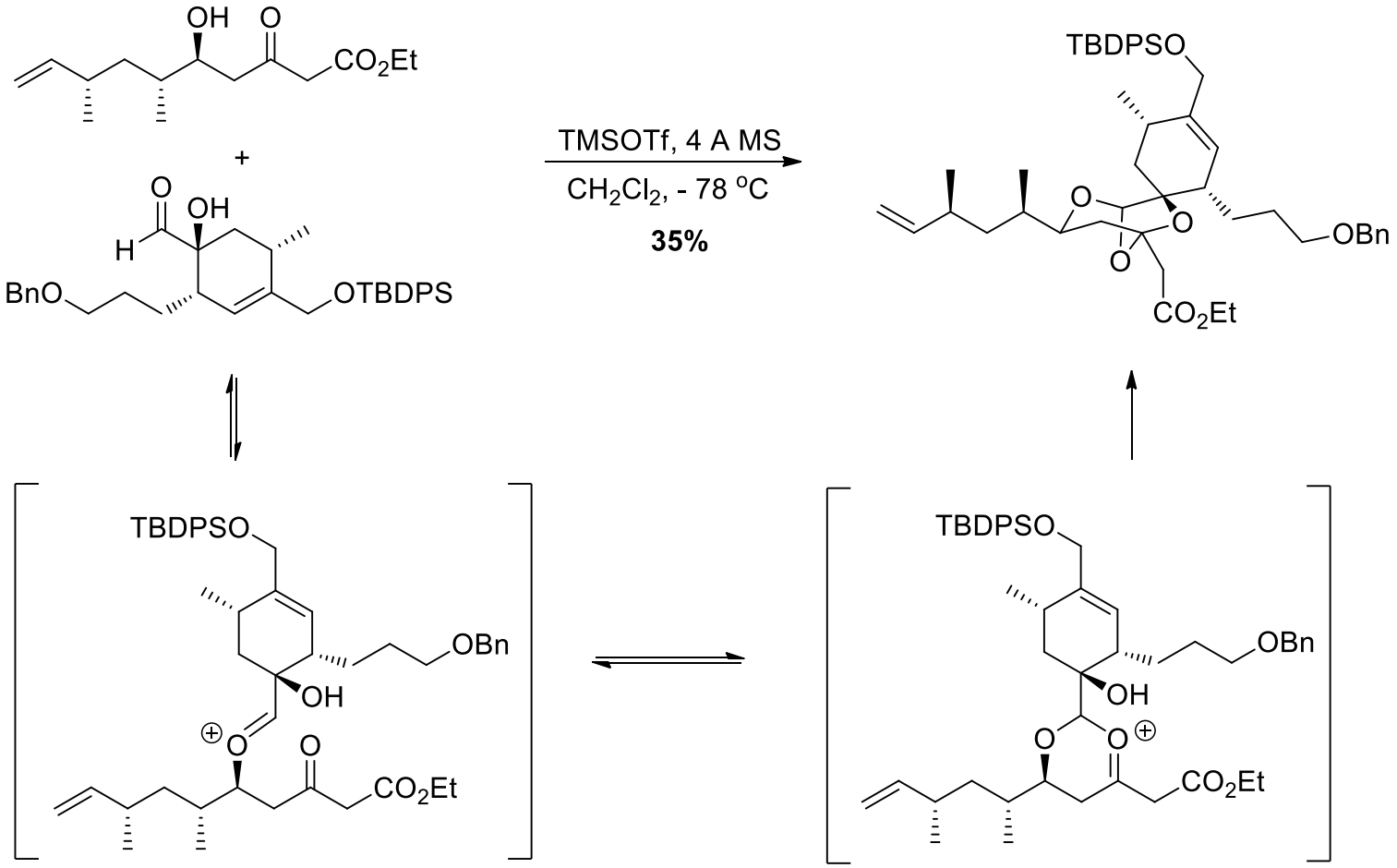
***condensation/Prins cyclization approach***



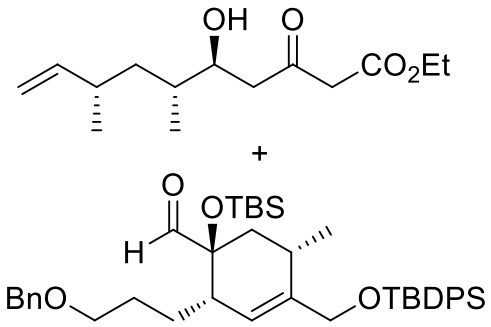

***Maitland-Japp reaction approach***



# Proposed Mechanism for Trioxabicyclo[3.2.1] ocatane



# Fragment Coupling and RCM Reactions

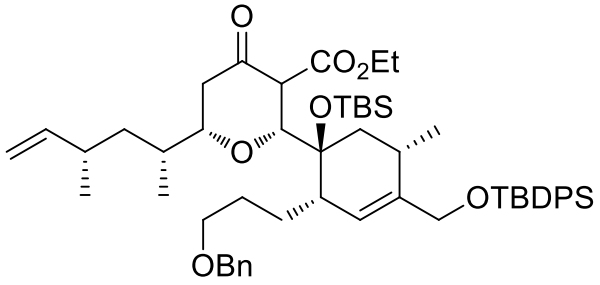



***Prins-Type***
***Maitland-Japp reaction***

TMSOTf, 4 A MS

$CH_2Cl_2$, - 78 to -40 °C

**60%**, dr 13:1

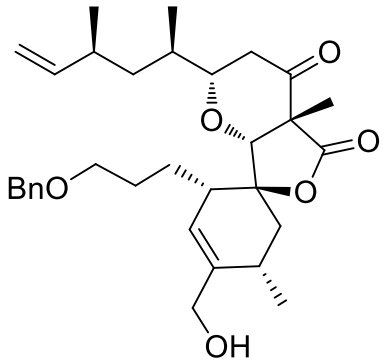



1) *aq* HF, $CH_3CN$

2) KOtBu, $CH_2Cl_2$

3) $K_2CO_3$, MeI, $CH_3CN$, 70 °C

*3 steps:* **58%**




1) TBDPSCl, imidazole, $CH_2Cl_2$

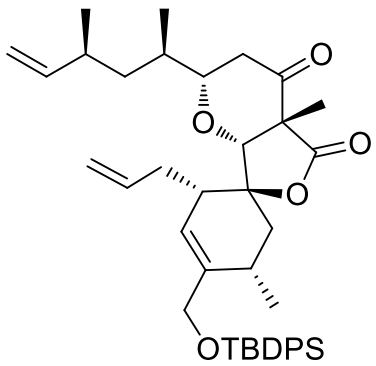
2) DDQ (30 equiv), $CH_2Cl_2$

3) *o*-nitrophenyl-selenocyanate
$PBu_3$, THF

4) $H_2O_2$, THF

*4 steps:* **33%**

***Grieco elimination***

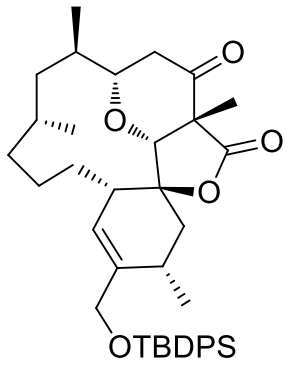



1) Grubbs 2nd Gen (40 mol%)
$CH_2Cl_2$, 40 °C

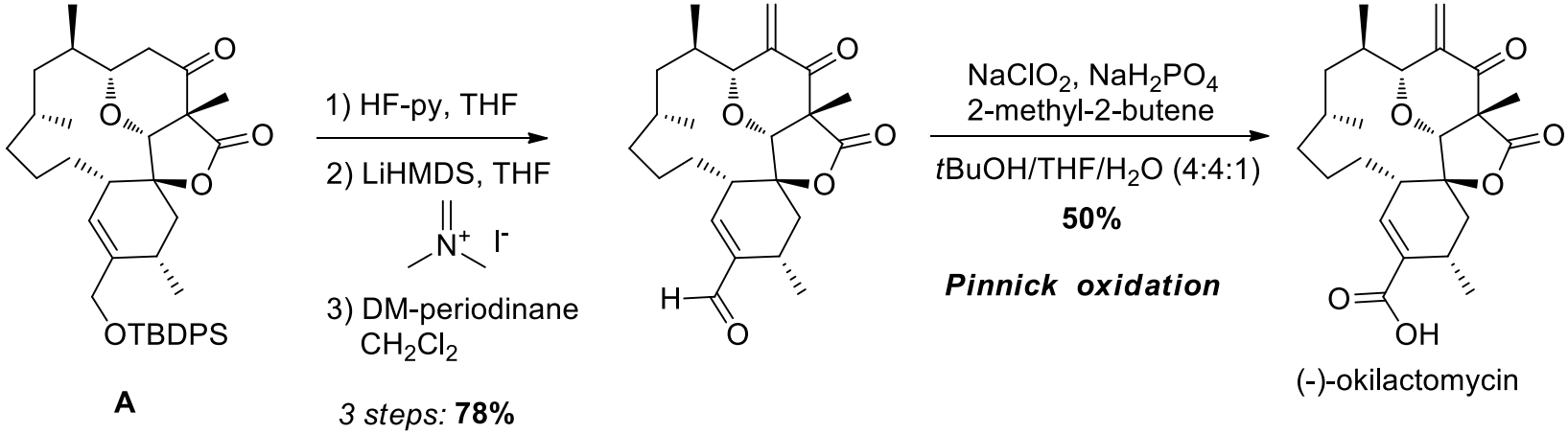
2) $H_2$, $PtO_2$, EtOAc

*2 steps:* **65%**

***RCM***



# Completion of the Synthesis




Synthetic Material: [□]$^{20}_D$ = - 20 (c = 0.04, MeOH)
Natural Product: [□]$^{20}_D$ = + 34 (c = 1, MeOH)
Smith's Material: [□]$^{20}_D$ = - 37 (c = 0.03, MeOH)

*All intermediates up to and including compound **A** , had (+) optical rotation.

*Authors believed to this point that they were in route to the desired natural (+)-okilactomycin.

*Similar phenomenon reported by Smith et al. 2007 (*prior to RCM*)

# Conclusion

(-)-Okilactomycin achieved in 1.0% overall yield over 26 steps (longest linear sequence).

Stereoselective alkylation and Diels-Alder routes gave the δ-hydroxy β-ketoester and α-silyloxy aldehyde fragments, respectively.

Lewis acid promoted Maitland-Japp reaction established the full carbon core with high diastereoselectivity for the 2,6-*cis* tetrahydropyran core.

Late installation of exocyclic olefin and overall convergent nature of the synthesis makes this synthesis amendable to derivatization and SAR.