Progress in Total Synthesis: A Highly Convergent Total Synthesis of **Leustroducsin B**

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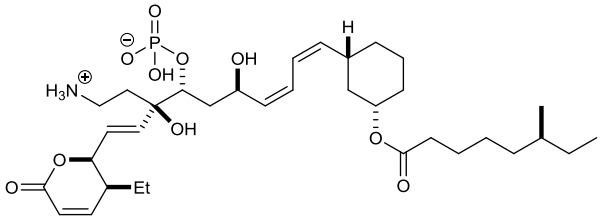
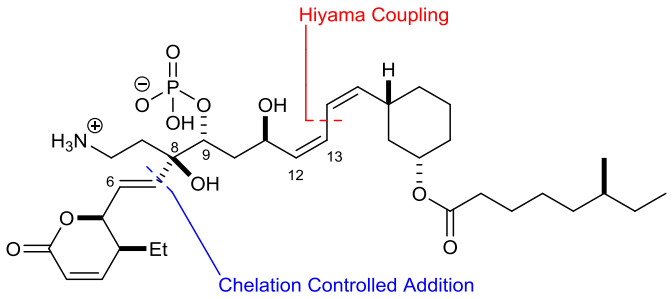
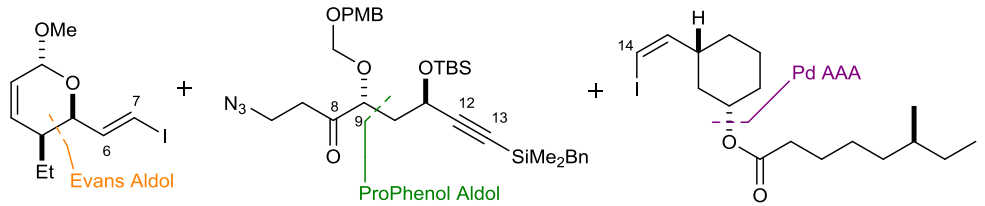
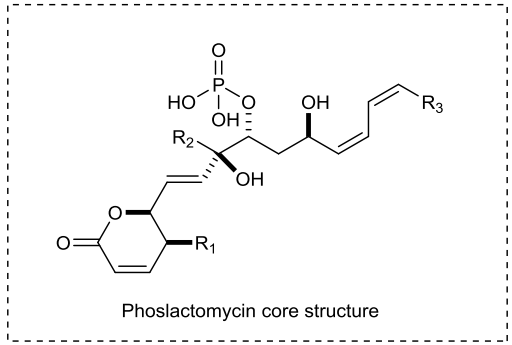

Leustroducsin B

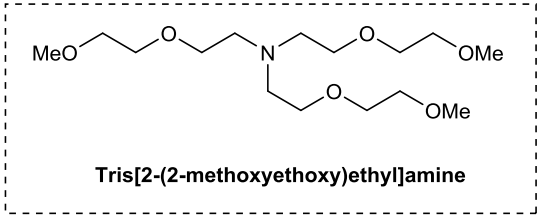
- Leustroducsin A-C first isolated 1993 by Kohama et al. at Sankyo.
- Bioactivities ranging from antibacterial, antifungal, and antitumor activity.
- Showed high potency and selectivity toward inhibition of protein serine/threonine phosphatase 2A.
- Leustroducsin B, specifically, shows potent *in vitro* induction of cytokine production by KM-102 cells as well as increased host *in vivo* resistance to *E. coli* infections and thrombocytosis induction.

Retrosynthetic Analysis

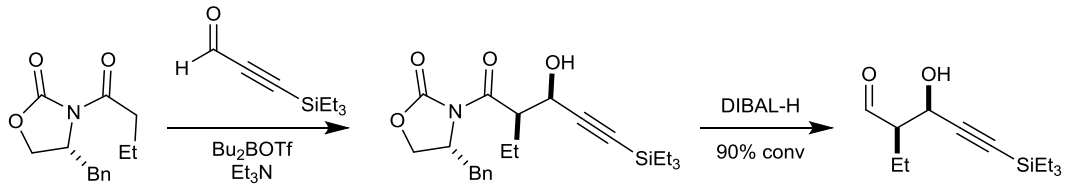


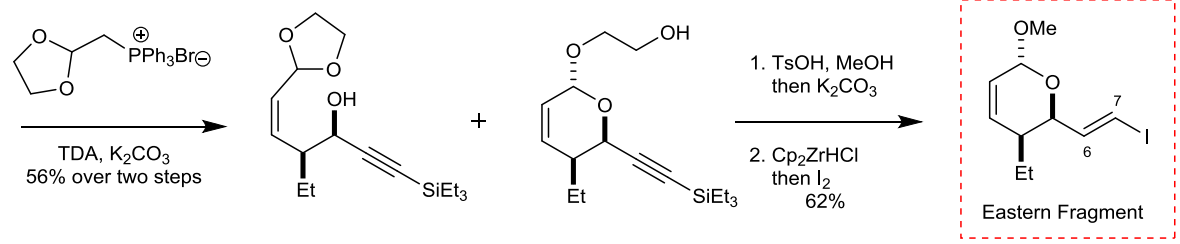



Phoslactomycin core structure

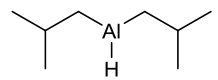

Tris[2-(2-methoxyethoxy)ethyl]amine

Synthesis of Eastern Fragment





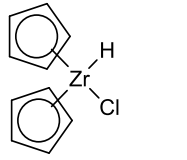
Eastern Fragment


Diisobutyl Aluminum Hydride (DIBAL-H)

Strong bulky reducing agent.

Can stop at the aldehyde unlike Lithium Aluminum Hydride

Can reduce ester, ketone, aldehyde, amide, nitrile.

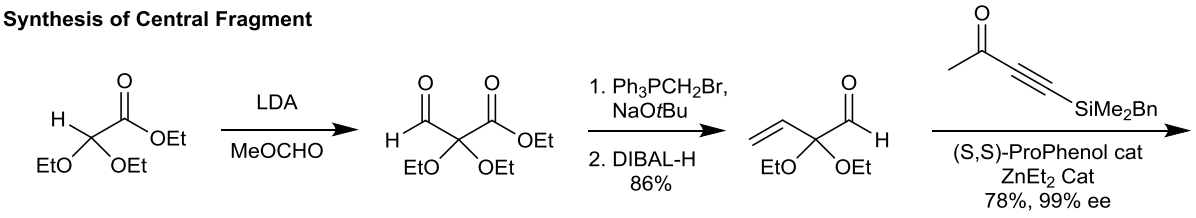

Schwartz's reagent

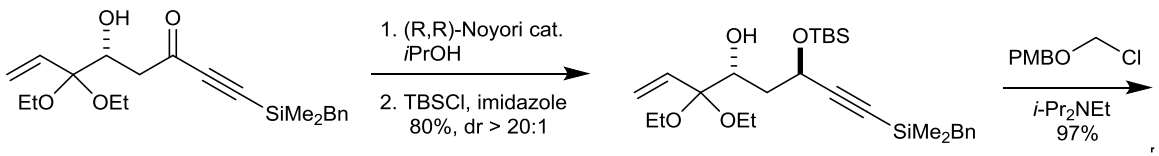
First prepared by Wailes and Weigold in 1970. Named after Jeffery Schwartz at Princeton University

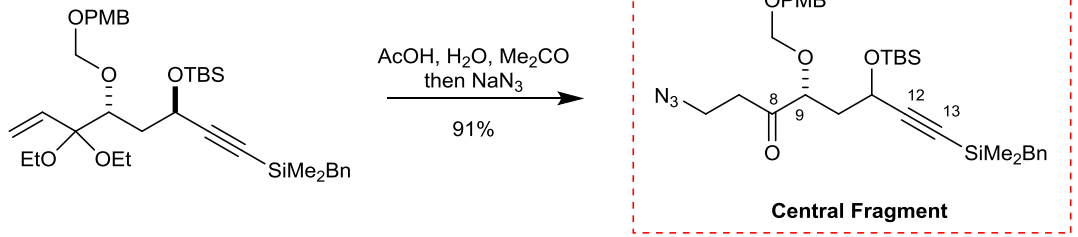
Know for alkene/alkyne chemistry. Syn-additon of Zr-H across the double bond. Alkynes react faster than alkenes and terminal groups faster than internal.

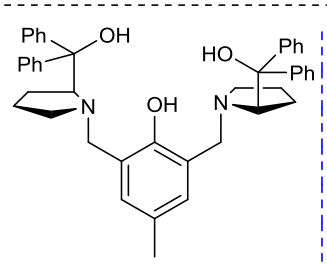
*Can reduce amides to aldehydes in the presence of esters

Synthesis of Central Fragment





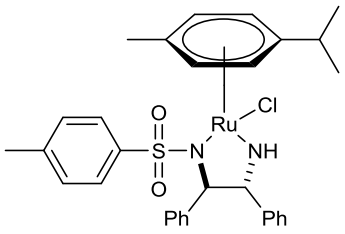



(S,S)-ProPhenol cat

Prophenol cat was developed by Trost in 2000 for the enantioselective adol reaction.

Evans' oxazolidinone
Heathcock
Mukaiyama
Crimmins thiazolidinethione
Organocatalysis (Proline)

Others: Oppolzer's Sultam, Abiko/Masamune's norephedrin-derived, Masamune/Reetz chiral Boron


(R,R)-Noyori cat

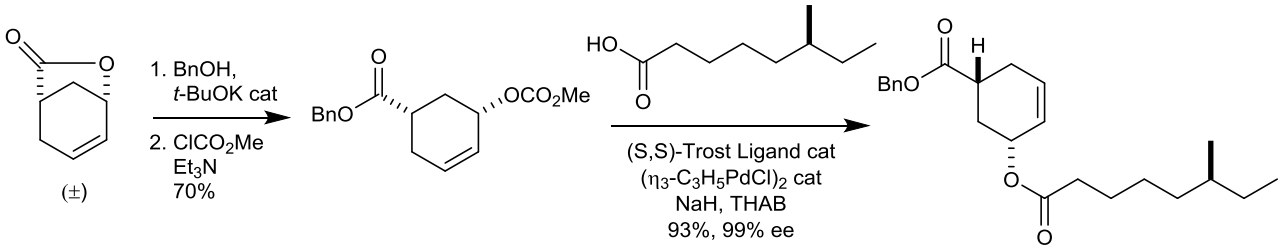
1956 a heterogeneous cat of palladium deposited on silk ws shown to effect asymmetric hydrogentation (HA).

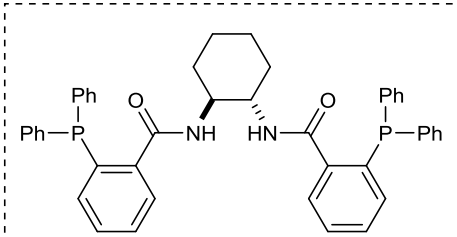
1968 William Knowles and Leopold Horner indepentdently published AH using homogenous cat.

Noyori introduced Ru-based cat for hydrogentation of polar substrates.

Nobel prize in 2001to Knowles and Noyori

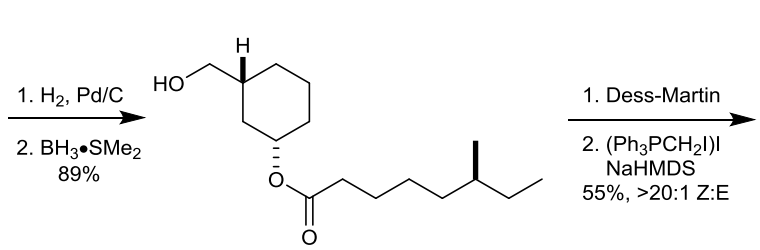
Synthesis of Western Fragment

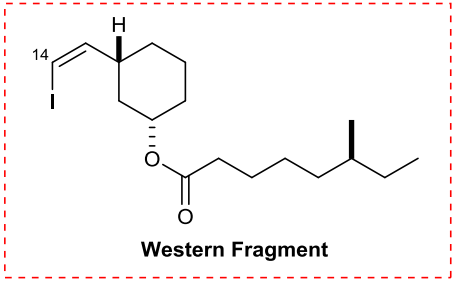


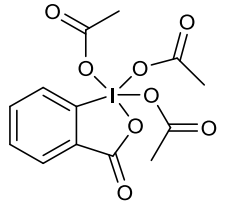

(S,S)-Trost Ligand

Asymmetric Allylic Alkylation

Hard Vs. Soft Nu
Hard Nu - net inversion
Soft Nu - net retention

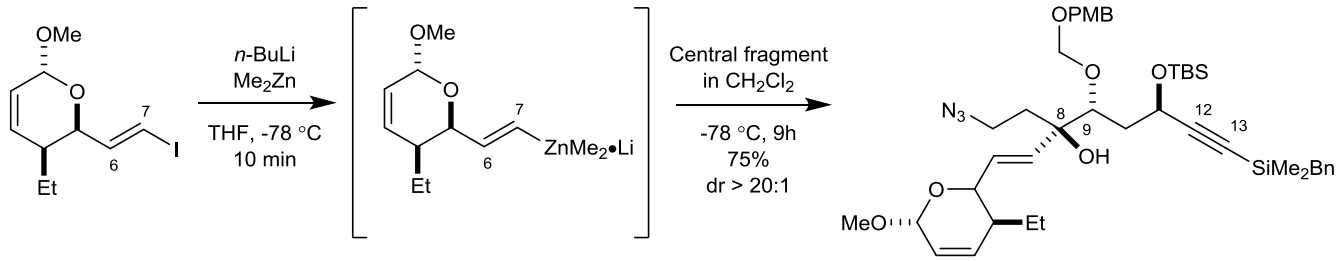


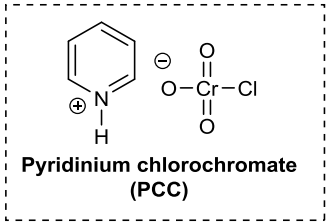

Western Fragment

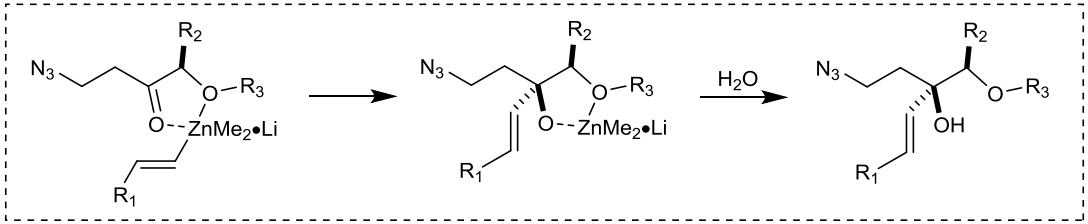

Dess-Martin periodinane

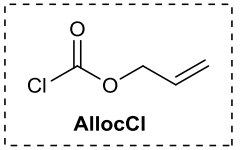
Developed by Daniel Dess and James Martin in 1983. It is based on IBX but due to the acetate groups DMP is more reactive and much more soluble in organic solvents

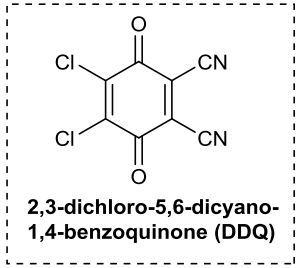
Chelation Controlled Addition of Eastern Fragment to Central Fragment



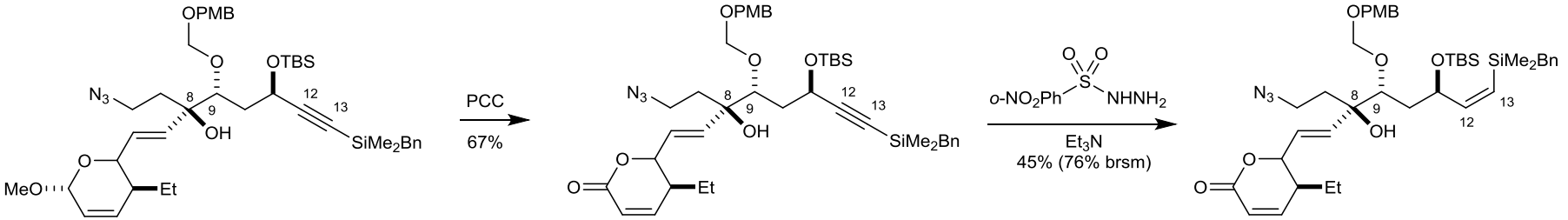


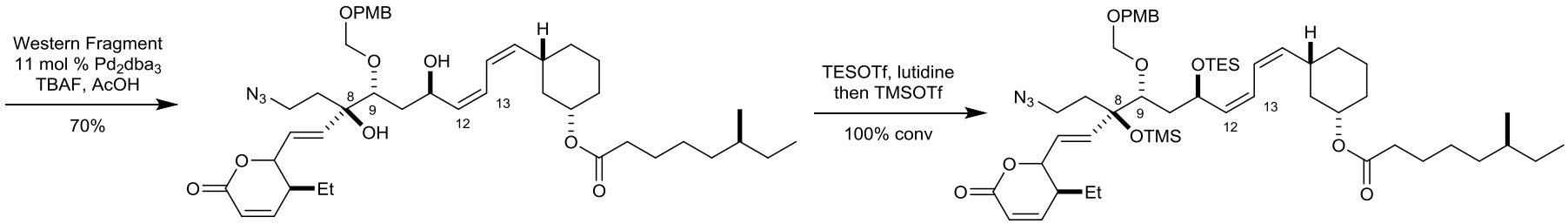


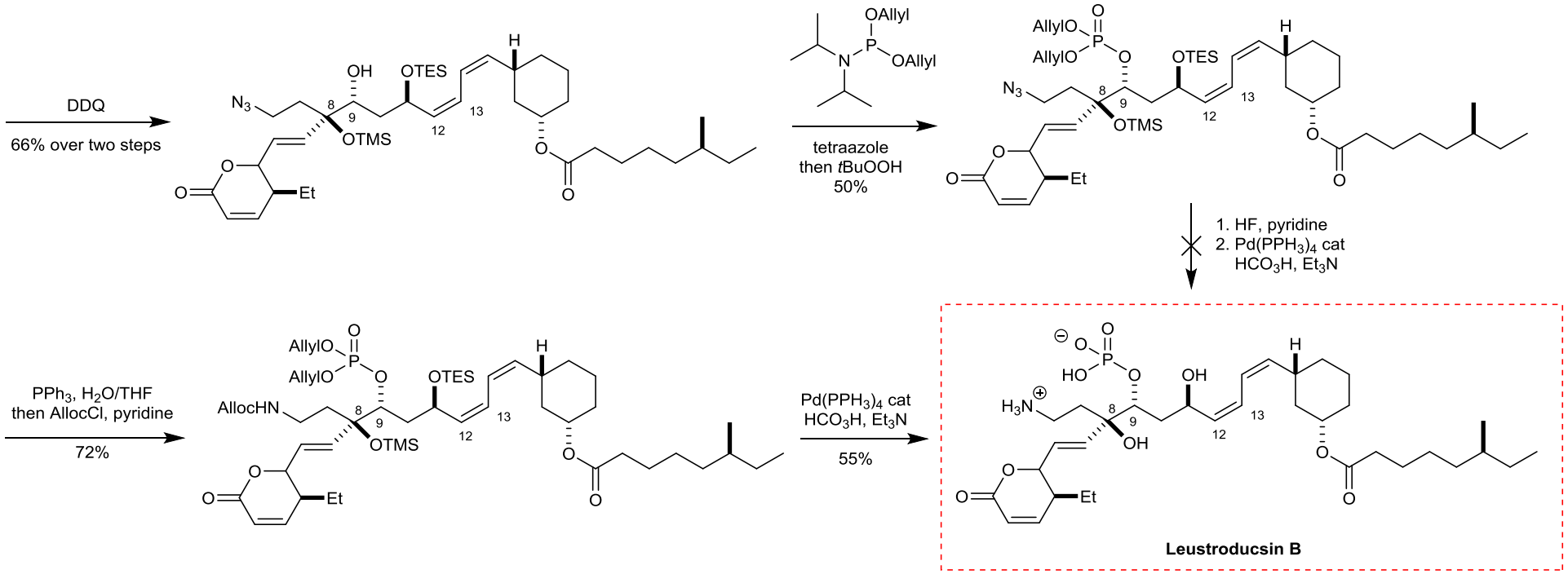




End Game to Leustroducsin B






DDQ
66% over two steps
tetraazole
then tBuOOH
50%
1. HF, pyridine
2. Pd(PPH3)4 cat
HCO3H, Et3N
PPh3, H2O/THF
then AllocCl, pyridine
72%
Pd(PPH3)4 cat
HCO3H, Et3N
55%
Leustroducsin B