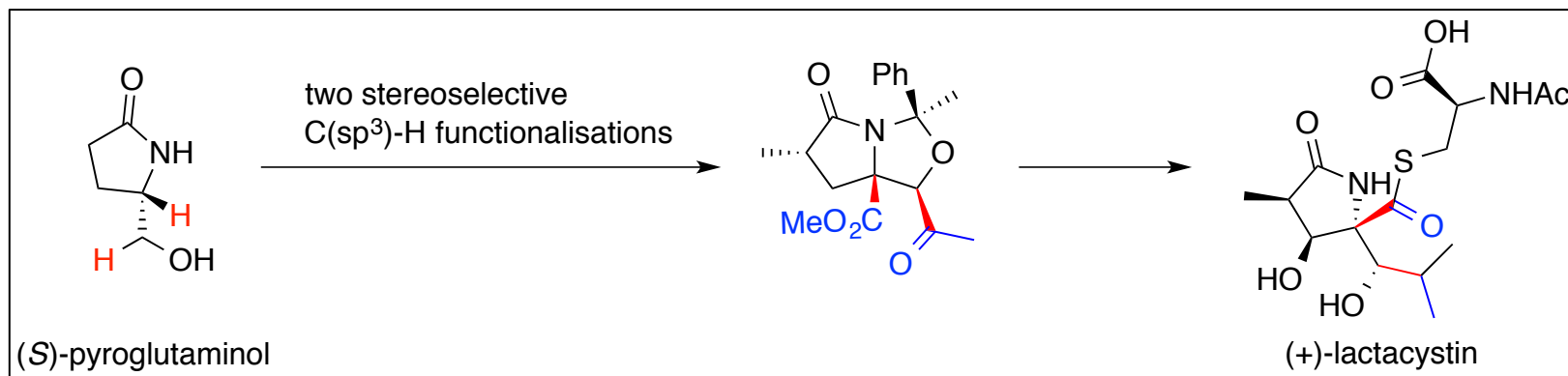


Application of Two Direct C(sp³)-H Functionalizations for the Total Synthesis of (+)-Lactacystin



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History

Previous Studies and Synthesis

- Isolated from *Streptomyces* sp. OM-6519 by Omura in 1991
- Proteasom Inhibitor, Cancer Treatment

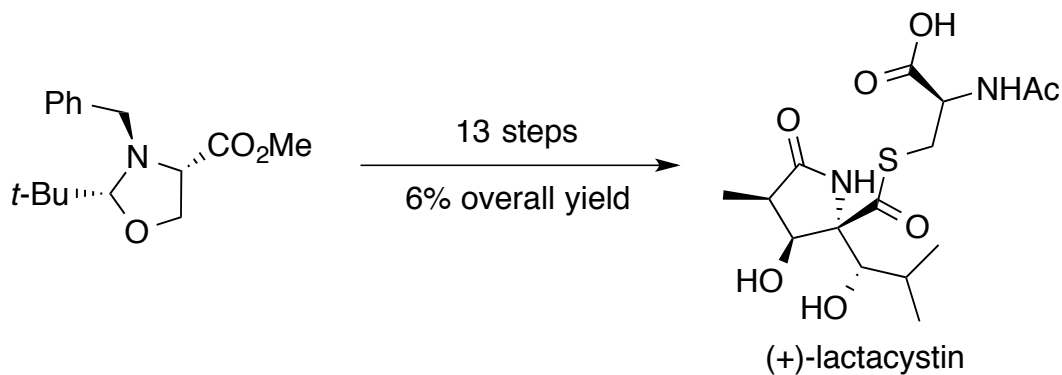
- Significant attention as synthetic target:
 - Total Synthesis (**13**)
 - Corey (1992), Smith (1993), Russel (1994), Ogawa (1995), Corey (1998), Corey (1998), Masse (1999), Plamondon (1999), Hatakeyama (2004), Shibasaki (2006), Jacobsen (2006), Prodger (2008), Silverman (2011)

 - Formal Total Synthesis (**12**)
 - Jun (1998), Youn (1998), Ohfuné (2000), Harling (2005), Bowen (2005), Jung (2007), Kobayashi (2007), Langlois (2007), Rescourio (2008), Hayes (2010), Hayes (2013), Chandrasekhar (2014)

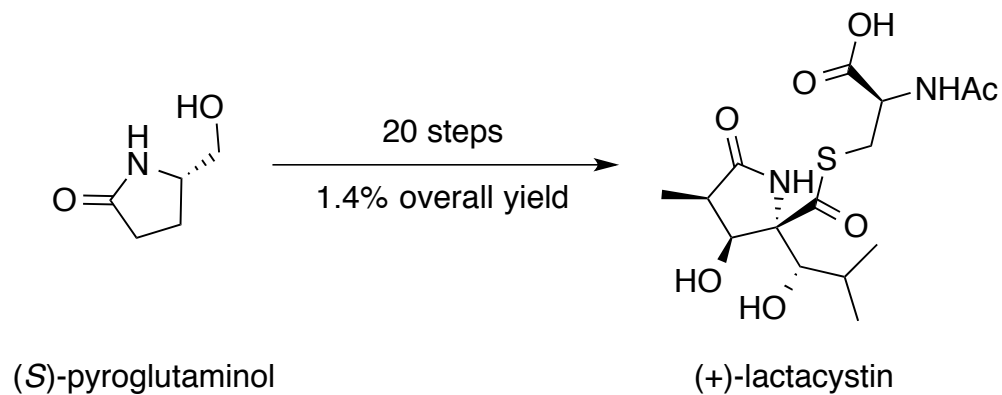
Development

Comparison to first TS

- Corey's approach (1992)

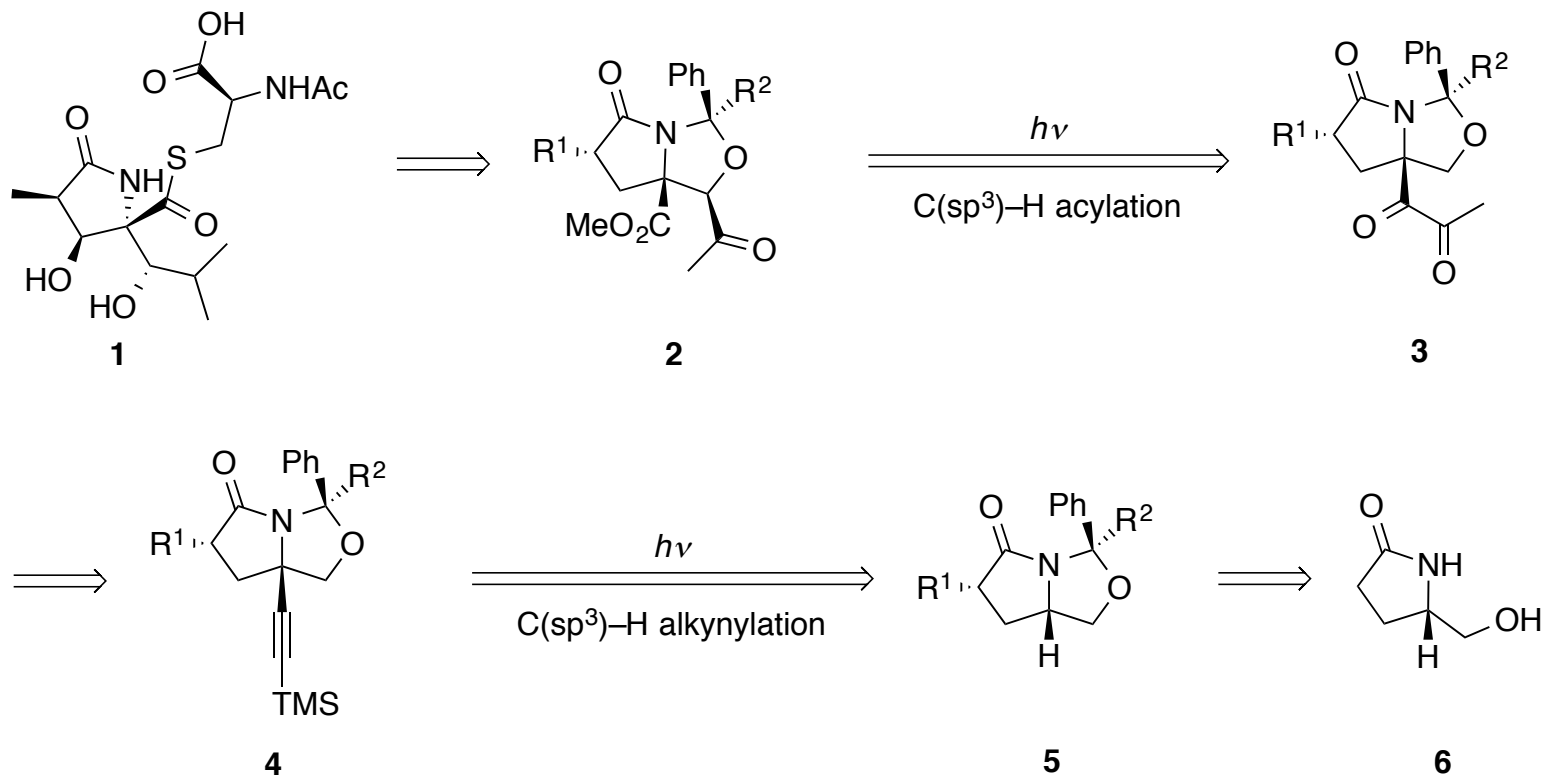


- This approach (2014)



Retrosynthetic Pathway

Starting from (S)-pyroglutaminol (6)

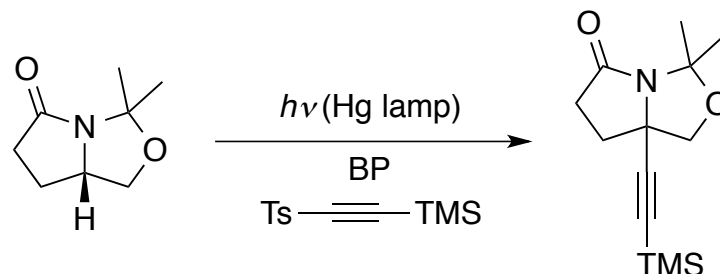


Direct transformation of C(sp³)-H bonds to C(sp³)-C bonds eliminates the preactivation → Permits design of **simpler** synthetic schemes

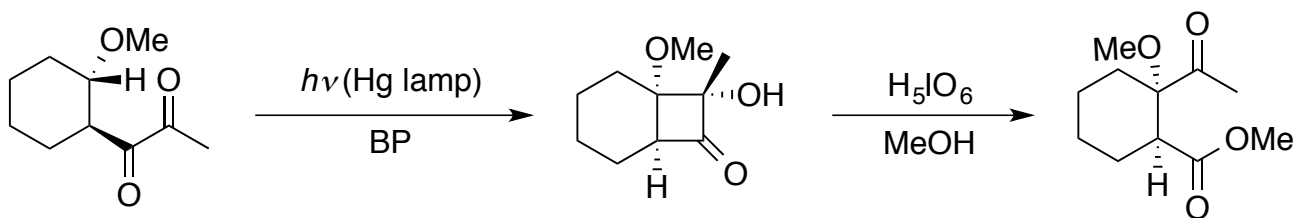
Synthesis

Preliminary Studies, Developments

- Intermolecular C(sp³)-H functionalization



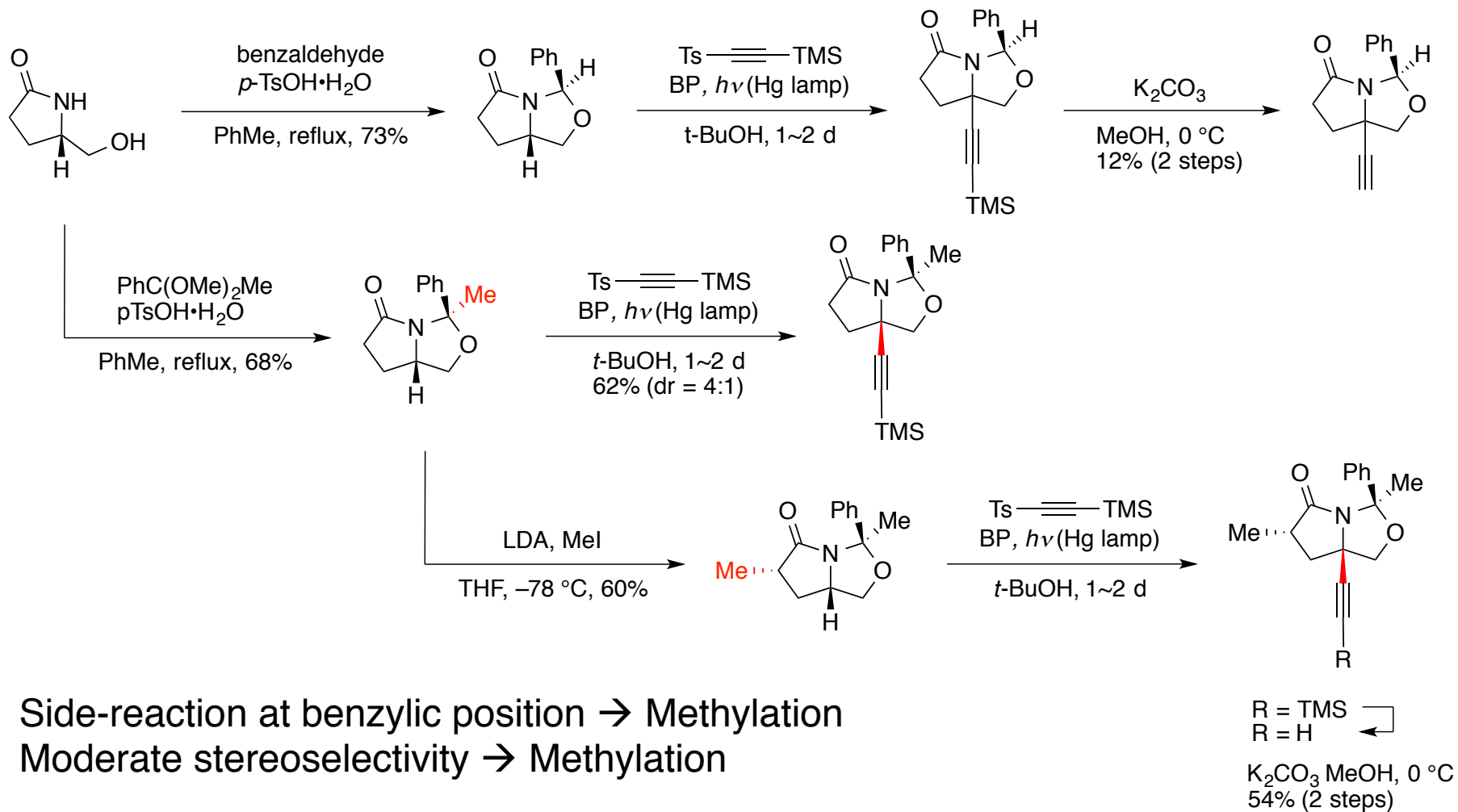
- Selectivity (α -N Hydrogen \rightarrow α -O Hydrogen \rightarrow aliphatic Hydrogen)
- Intramolecular C(sp³)-H functionalization



- Norrish-Yang cyclization followed by oxidative ring opening

Synthesis

Exploring the Selectivity Towards Alkynylation Product

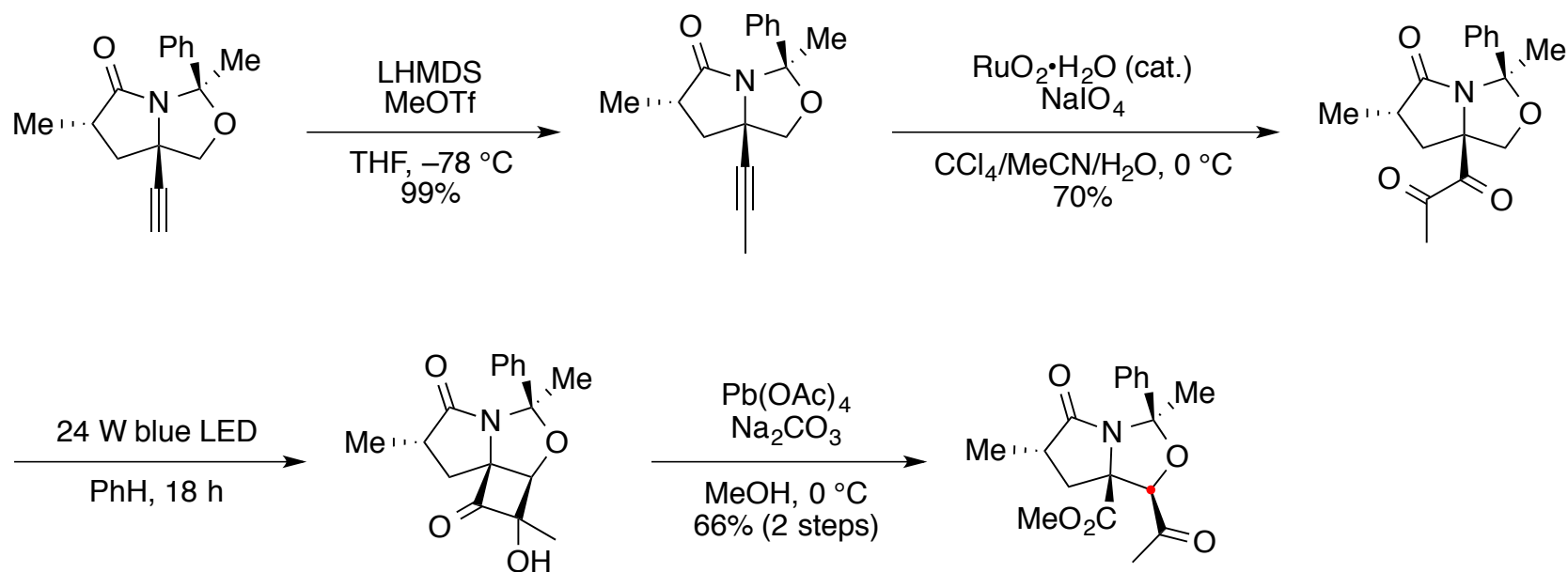


Side-reaction at benzylic position → Methylation

Moderate stereoselectivity → Methylation

Synthesis

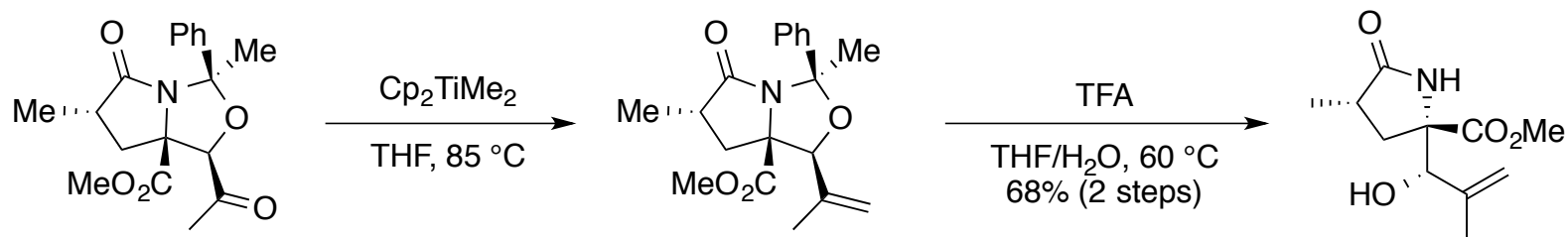
Second C(sp³)-H Functionalization



- Norrish-Yang cyclization not working with Hg lamp, photoexcitation of ketol → LED longer wavelength
- Epimerization observed without Na₂CO₃

Synthesis

Construction of (+)-Lactacystin I



1. Ac₂O, DMAP, py
2. Boc₂O, DMAP, Et₃N, CH₂Cl₂

3. H₂, Pd/C, EtOAc, 63% (3 steps)

1. LHMDS, PhSeBr, THF, -78 °C

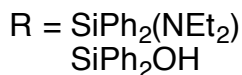
2. H₂O₂, NaHCO₃, THF/EtOAc, 0 °C, 73% (2 steps)

- Et₂Zn, Et₂NPh₂SiLi, THF, -78 °C

then methyl salicylate

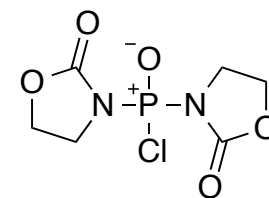
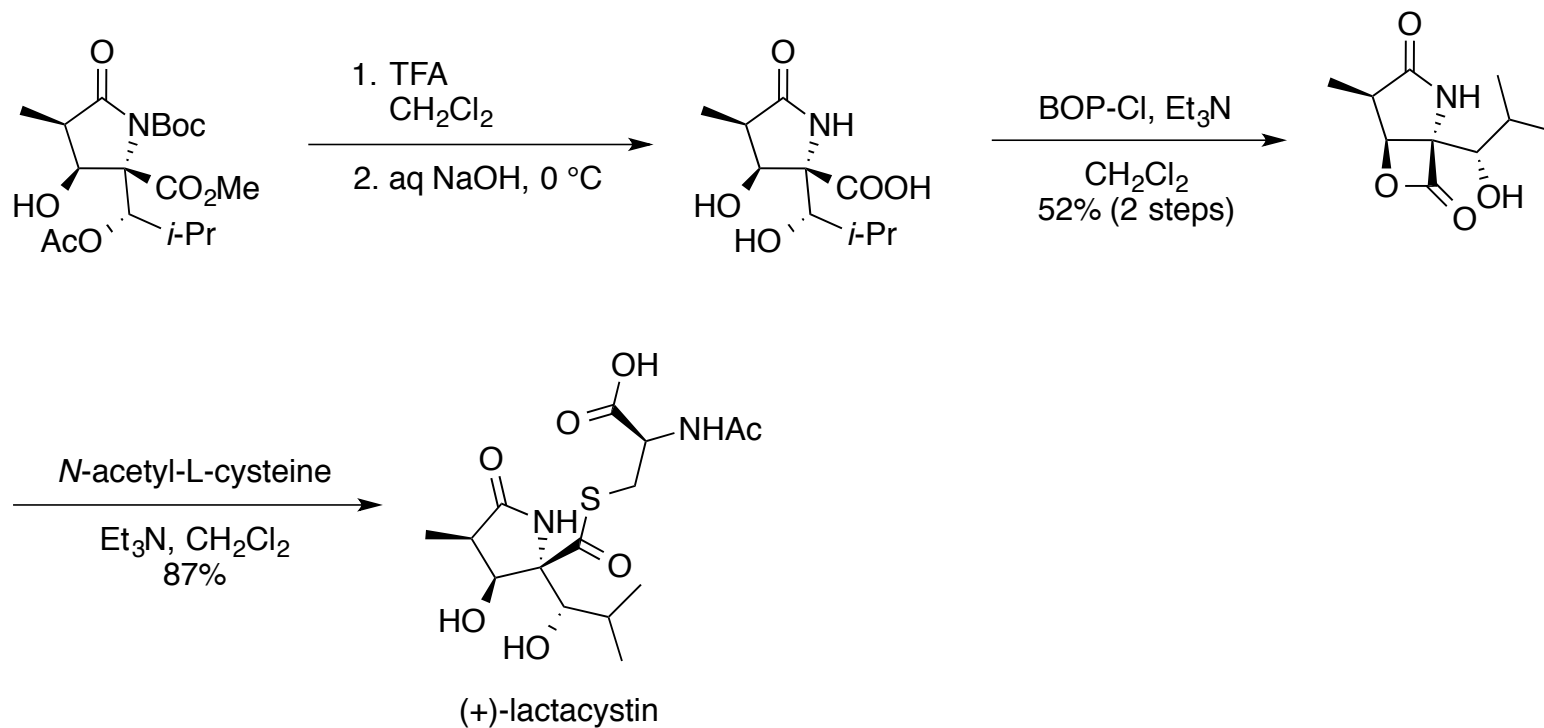
- m*-CPBA, KHF₂, DMF

66% (2 steps)



Synthesis

Construction of (+)-Lactacystin II



BOP-Cl

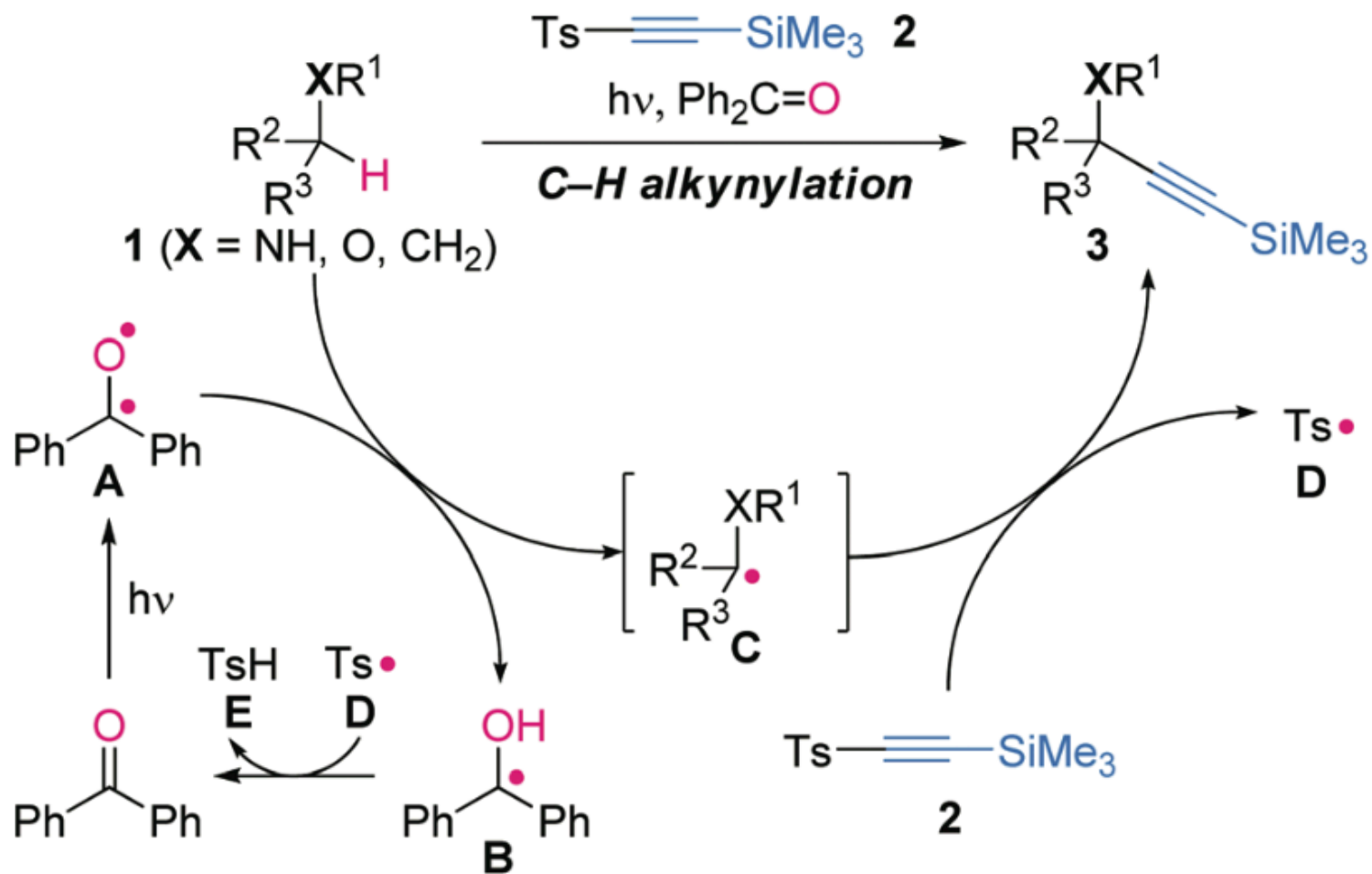
Conclusion

- **Novel route** to (+)-lactacystin from (*S*)-pyroglutaminol
- “Reasonable” application of intermolecular **C–H alkynylation** and intramolecular **C–H acylation**
- **High applicability** of the two C(sp³)–H functionalizations
- **High predictability** of their chemoselectivities (α -N–H \rightarrow α -O–H \rightarrow aliphatic H)
- Further applications are under investigation

Thank you for your attention

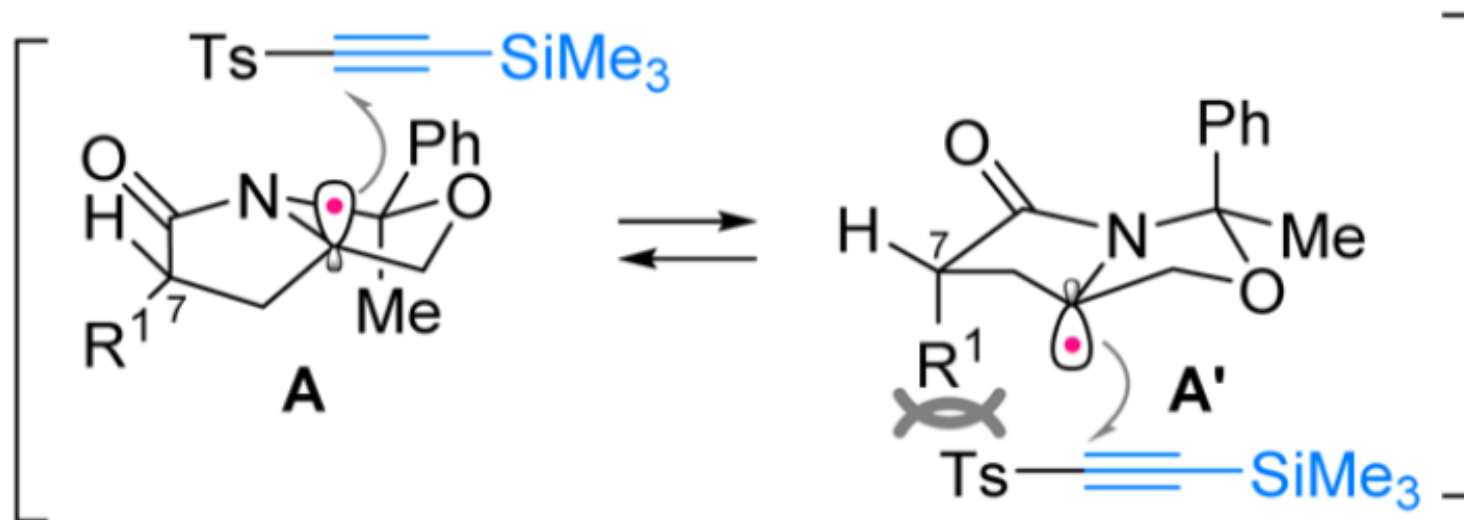
Supplementary Information

Intermolecular C(sp³)-H Functionalization



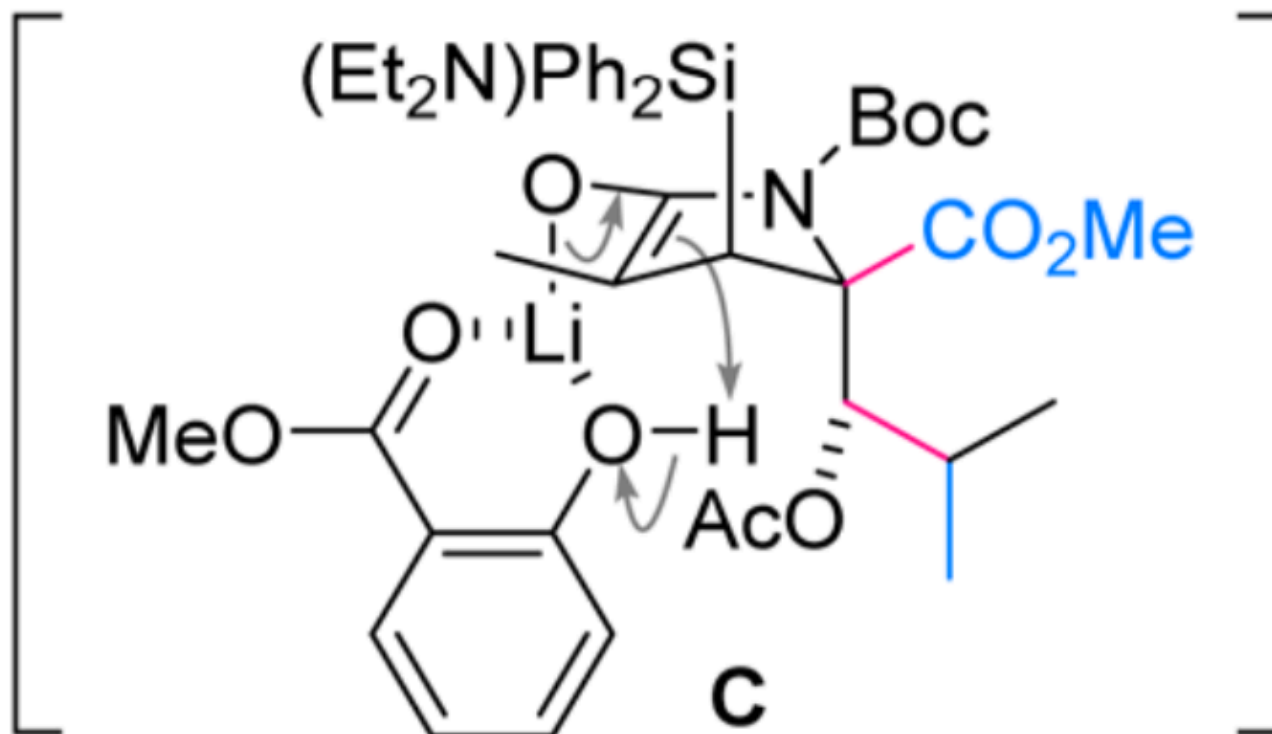
Supplementary Information

Explanation for Stereochemical Outcome of Alkynylation



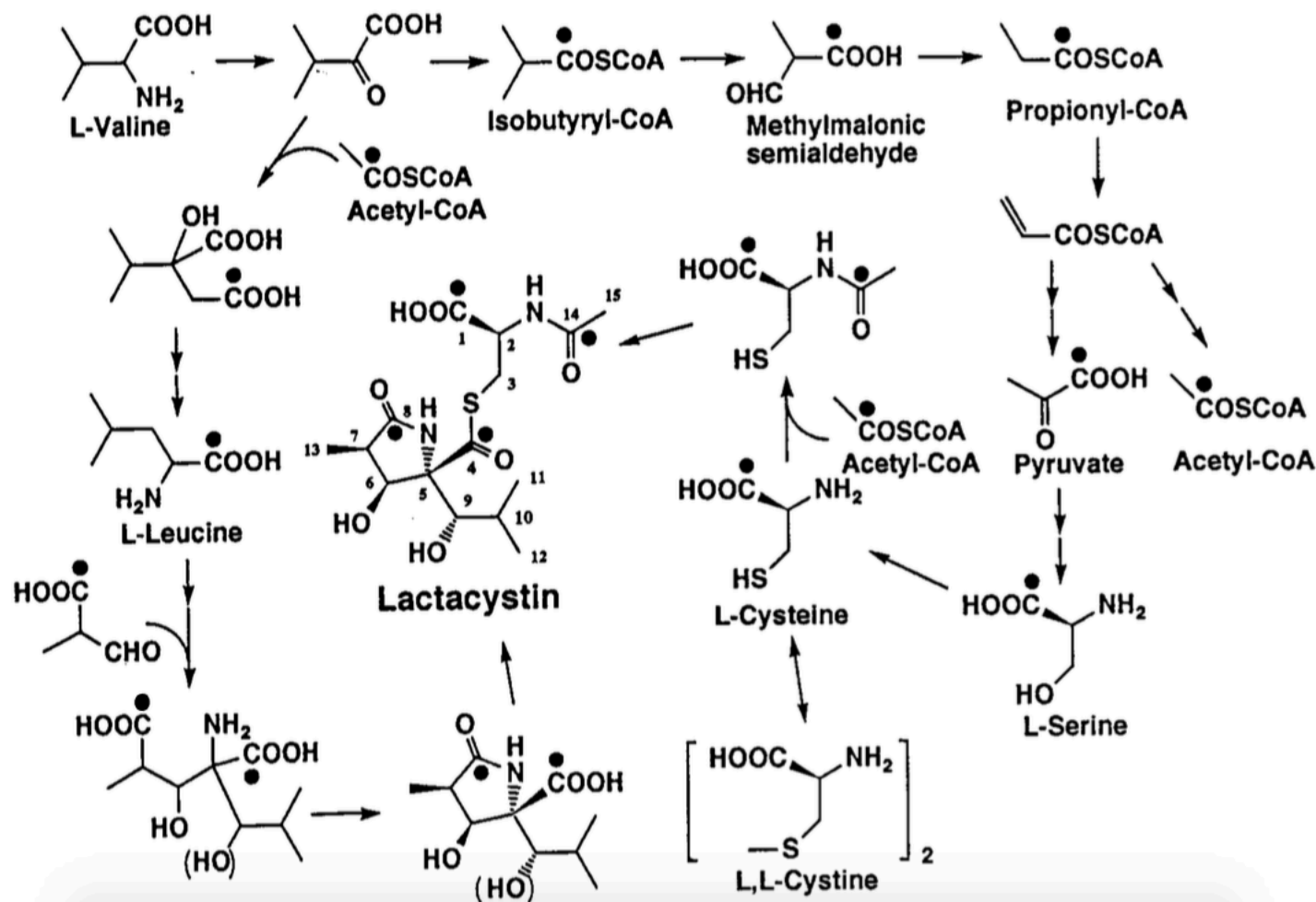
Supplementary Information

Protonation of Fleming-Tamao Oxidation Enolate



Supplementary Information

Biosynthesis



Supplementary Information

Norrish-Yang Cyclization

