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

(S)-pyroglutaminol

two stereoselective C(sp³)-H functionalisations

(S)-pyroglutaminol

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Samuel Rieder, 8. Jan. 2015
- Isolated from *Streptomyces* sp. OM-6519 by Omura in 1991
- Proteasom Inhibitor, Cancer Treatment

- Significant attention as synthetic target:
  
  - Total Synthesis (13)

  - Formal Total Synthesis (12)
Development
Comparison to first TS

- Corey’s approach (1992)

![Chemical structure](image1)

13 steps
6% overall yield

(+)-lactacystin

- This approach (2014)

![Chemical structure](image2)

20 steps
1.4% overall yield

(S)-pyroglutaminol

(+)-lactacystin

Retrosynthetic Pathway
Starting from (S)-pyroglutaminol (6)

\[
1 \rightarrow 2 \xrightarrow{h\nu} 3 \\
\text{C(sp}^3\text{)--H acylation}
\]

\[
4 \xrightarrow{h\nu} 5 \\
\text{C(sp}^3\text{)--H alkynylation}
\]

Direct transformation of C(sp\(^3\))–H bonds to C(sp\(^3\))–C bonds eliminates the preactivation → Permits design of simpler synthetic schemes
Synthesis
Preliminary Studies, Developments

- Intermolecular $\text{C}(\text{sp}^3)\text{–H}$ functionalization

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{O} \\
\text{H} \\
\end{array}
\xrightarrow{h\nu\text{(Hg lamp)}}
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{O} \\
\text{H} \\
\end{array}
\]

- Selectivity ($\alpha$-N Hydrogen $\rightarrow$ $\alpha$-O Hydrogen $\rightarrow$ aliphatic Hydrogen)

- Intramolecular $\text{C}(\text{sp}^3)\text{–H}$ functionalization

\[
\begin{array}{c}
\text{OMe} \\
\text{H} \\
\text{O} \\
\text{O} \\
\end{array}
\xrightarrow{h\nu\text{(Hg lamp)}}
\begin{array}{c}
\text{OMe} \\
\text{H} \\
\text{O} \\
\text{O} \\
\end{array}
\xrightarrow{\text{H}_5\text{IO}_6\text{MeOH}}
\begin{array}{c}
\text{MeO} \\
\text{O} \\
\text{OMe} \\
\end{array}
\]

- 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

Synthesis
Construction of (+)-Lactacystin II

1. TFA
   CH$_2$Cl$_2$

2. aq NaOH, 0 °C

BOP-Cl, Et$_3$N
CH$_2$Cl$_2$
52% (2 steps)

$N$-acetyl-L-cysteine
Et$_3$N, CH$_2$Cl$_2$
87%

(+)-lactacystin
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(sp$^3$)–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(sp\(^3\))–H Functionalization

Supplementary Information
Explanation for Stereochemical Outcome of Alkynylation

Supplementary Information
Protonation of Fleming-Tamao Oxidation Enolate
Supplementary Information
Biosynthesis

A. Nakagawa, M. Kainosho and S. Ōmura, Pure Appl. Chem. 1994, 66(10-11), 2411-2413
Supplementary Information
Norrish-Yang Cyclization