# **Literature Report 1**

# Total Synthesis of Penicibilaenes via C–C Activation-Enabled Skeleton Deconstruction and Desaturation Relay-Mediated C–H Functionalization

Reporter: Shanshan Xun Checker: Yi-Xuan Ding Date: 2021-07-19

Xue, Y. B.; Dong, G. B. J. Am. Chem. Soc. 2021, 143, 8272

# **CV of Prof. Guangbin Dong**

**Guangbin Dong** 

## **Background:**

□ 1999-2003	B.S., Peking University
□ 2004-2009	Ph.D., Stanford University (Barry M. Trost)
□ 2009-2011	Postdoctoral, CalTech (Robert H. Grubbs)
□ 2011-2016	Assistant Professor, University of Texas at Austin
□ 2016-	Professor, University of Texas at Austin
□ 2016-now	Professor, University of Chicago

### **Research Interests:**

- Developing Novel Catalytic C-H and C-C Bond Activation
- Developing Transition-metal Catalysts Based on Supramolecular Chemistry
- Establishing Efficient Synthetic Routes to Access Natural Products

# 1 Introduction

## 2 Total Synthesis of Penicibilaenes

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# Introduction



Penicillium bilaiae (拜赖青霉菌)



- First isolated from the marine fungus *Penicillium bilaiae* MA-267 in 2014;
- Selective and potent activity against the plant pathogenic fungus Colletotrichum gloeosporioides;
- Tricyclo[6.3.1.0<sup>1,5</sup>]dodecane skeleton as well as five adjacent stereocenters with one being all-carbon quaternary.

Meng, L. H.; Li, X. M.; Wang, B, G. Org. Lett. 2014, 16, 6052

# **Hunsdiecker Reaction**



From Name Reactions by J. J. Li, p. 327

# **Barton Decarboxylation Reaction**



From Name Reactions by J. J. Li, p. 26

# **Key Points of Synthesis**



**Construct the Tricyclo**[6.3.1.0<sup>1,5</sup>]dodecane Skeleton

Functionalization to Introduce the Substituents

(The tricyclic skeleton exhibit a 1,3,5-triad pattern)

# **Approaches for Terpene Synthesis**

#### A. The "two-phase" Strategy



Chen. K.; Baran, P. S. Nature 2009, 459, 824

#### B. The "C-C/C-H" Strategy



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# Synthesis 1,3,5-Triads



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# **Retrosynthetic Analysis of Penicibilaenes**



# Synthesis of the "Cut-and-Sew" Precursor



# **Retrosynthetic Analysis of Penicibilaenes**



## Linker Effect in the "Cut-and-Sew" Reaction



# **C–C Activation by Temporary Chelation Assistance**



Jun, C. H.; Lee, H. J. Am. Chem. Soc. 1999, 121, 880

# **C–C Activation by Temporary Chelation Assistance**

![](_page_14_Figure_1.jpeg)

Xia, Y.; Dong, G. B. Nat. Chem. 2014, 6, 739

# **C–C Activation by Temporary Chelation Assistance**

### C-C Activation for [5+2] Cycloaddition

![](_page_15_Figure_2.jpeg)

**C-C Activation for Acyl Transfer** 

![](_page_15_Figure_4.jpeg)

Xia, Y.; Ochi, S.; Dong, G. B. *J. Am. Chem. Soc.* **2019**, *141*, 13038 Rong, G. Q.; Lim, H. N.; Dong, G. B. *Angew. Chem. Int. Ed.* **2018**, *57*, 475

# Selected Optimization of the "Cut-and-Sew" Step

![](_page_16_Figure_1.jpeg)

# Selected Optimization of the "Cut-and-Sew" Step

Entry <sup>a</sup>	Additives	Solvent	Directing Group	Time	Yield (%) <sup>b</sup>
1		1,4-dioxane	DG-1 (100 mol%)	12 h	trace
2	ZnCl <sub>2</sub>	1,4-dioxane	DG-1 (100 mol%)	12 h	12%
3	Zn(OTf) <sub>2</sub>	1,4-dioxane	DG-1 (100 mol%)	12 h	20%
4	Zn(OTf) <sub>2</sub>	1,4-dioxane	DG-1 (20 mol%)	12 h	23%
5	Zn(OTf) <sub>2</sub>	1,4-dioxane	DG-1 (20 mol%)	48 h	34%
6	Zn(OTf) <sub>2</sub>	1,4-dioxane	DG-2 (20 mol%)	48 h	35%
7	Zn(OTf) <sub>2</sub>	1,4-dioxane	DG-3 (20 mol%)	48 h	47%
8	Zn(OTf) <sub>2</sub>	Toluene	DG-3 (20 mol%)	48 h	48%
9	Zn(OTf) <sub>2</sub> 2,6-di- <sup>#</sup> Bu-py	Toluene	DG-3 (20 mol%)	48 h	42% <sup>c</sup>
	N NH <sub>2</sub>	Me NH2		Me Me NH <sub>2</sub>	
	DG1		DG2	DG3	

<sup>*a*</sup> Unless otherwise mentioned, the reaction was run on a 0.05 mmol scale. <sup>*b*</sup> Determined by GC using 1-methylnaphthalene as the internal standard. <sup>*c*</sup> The reaction was run on a gram scale.

# **Retrosynthetic Analysis of Penicibilaenes**

![](_page_18_Figure_1.jpeg)

# **Completing the Synthesis of Penicibilaenes A and B**

![](_page_19_Figure_1.jpeg)

# **Completing the Synthesis of Penicibilaenes A and B**

![](_page_20_Figure_1.jpeg)

# Summary

![](_page_21_Figure_1.jpeg)

13 or 14 Total Steps, Penicibilaene A or Penicibilaene B

- □ The "C-C/C-H" Strategy
- The Rh-catalyzed "Cut-and-Sew" Reaction
- Critical Linker and Lewis Acid (Zn(OTf)<sub>2</sub>) Effects

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# **Writing Strategies**

## □ The First Paragraph

![](_page_22_Figure_2.jpeg)

Terpenes and their derivatives have been a rich source of therapeutic agents, agrochemicals, and fragrances. In addition, they often exhibit intriguing and complex chemical structures, such as bridged/fused rings and diverse substitutions. As such, terpenes have been highly attractive target molecules in the synthetic community. Inspired by the biosynthesis of terpenes, a "two-phase" strategy has been advanced by Baran and coworkers, leading to a number of elegant total syntheses since 2009. This strategy involves a cyclase phase to first build the carbon backbone from a linear or less complex precursor, followed by an oxidase phase to install oxygen functionalities at proper positions. Notably, in the cyclase phase, polyene cyclization and various cycloadditions, such as Diels-Alder reaction and Robinson annulation, are commonly employed for synthesizing multiring systems.

On the other hand, the transition-metal-catalyzed C-C activation of cyclic ketones followed by insertion of an unsaturated  $2\pi$ -unit, namely, a "cut-andsew" process, has been found useful for constructing various bridged and fused rings. Thus, terpene synthesis could also be envisioned to go through a closely related but complementary strategy, which utilizes C-C activation to construct the core skeleton and then ketone-directed or -mediated C-H functionalization to introduce the substituents. Comparing to the "two-phase" strategy, one subtle difference with this "C-C/C-H" approach is that not all carbons in the terpene core need to be introduced in the "C-C" stage, as some carbon substituents can be installed in the later "C-H" stage. Herein, we describe a proof-of-concept of utilizing this "C-C/C-H" strategy in a concise total synthesis of penicibilaenes A and B.

# **Writing Strategies**

□ The Last Paragraph

![](_page_25_Figure_2.jpeg)

In summary, we have described the first total synthesis of penicibilaenes A and B in 13 and 14 steps, respectively, in the longest linear sequence from commercially available starting materials. The synthesis features a deconstructive formation of the tricyclic skeleton via C-C activation of cyclobutanones and the use of carbonyl desaturation relay to replace  $\beta$ -C-H bonds with the desired functional groups. Such a "C-C/C-H" approach may inspire alternative bond-disconnecting strategies for natural product syntheses. In addition, the discovery of a new linker system and a Lewis acid effect in the Rh-catalyzed "cut-and-sew" reaction between cyclobutanones and bulky alkenes could have broader implications on preparing other all-carbon bridged/fused rings.

- As such, terpenes have been highly attractive target molecules in the synthetic community. (极具吸引力的目标分子)
- X-ray structures of the carboxylic acid and the hydrazone derivative of the decarboxylation product were obtained to allow unambiguous charac-terization. (得到明确的表征)
- It can be further envisaged that the C4 oxygen functional group can also be installed via a similar desaturation-based beta-functionalization sequence from ketone. (可以进一步设想...)

# Thanks for your attention