Literature Report 1

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

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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



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^{1,5}]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^{1,5}]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



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

C–C Activation by Temporary Chelation Assistance

C-C Activation for [5+2] Cycloaddition



C-C Activation for Acyl Transfer



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



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

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

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

Retrosynthetic Analysis of Penicibilaenes



Completing the Synthesis of Penicibilaenes A and B



Completing the Synthesis of Penicibilaenes A and B



Summary



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)₂) Effects

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Writing Strategies

□ The First Paragraph



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 2π -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



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 β -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