

Literature Report I

Concise and Stereoselective Total Syntheses of Annotinolides C, D, and E

Reporter: Zheng Liu

Checker: Yu-Qing Bai

Qu, P.; Snyder, S. A.* *J. Am. Chem. Soc.* **2021**, *143*, 11951

CV of Prof. Scott A. Snyder

Background:



- ❑ **1995-1999** B.S., Williams College
- ❑ **1999-2004** Ph.D., The Scripps Research Institute (TSRI)
- ❑ **2004-2006** NIH Postdoctoral Fellow, Harvard University
- ❑ **2006-2011** Assistant Professor, Columbia University
- ❑ **2011-2013** Associate Professor, Columbia University
- ❑ **2013-2015** Associate Professor, TSRI
- ❑ **2015-now** Professor, University of Chicago

Research:

1. Development of chemoselective halogenating reagents;
2. Strategies and methods for rapid polycycle construction;
3. Total syntheses of natural products.

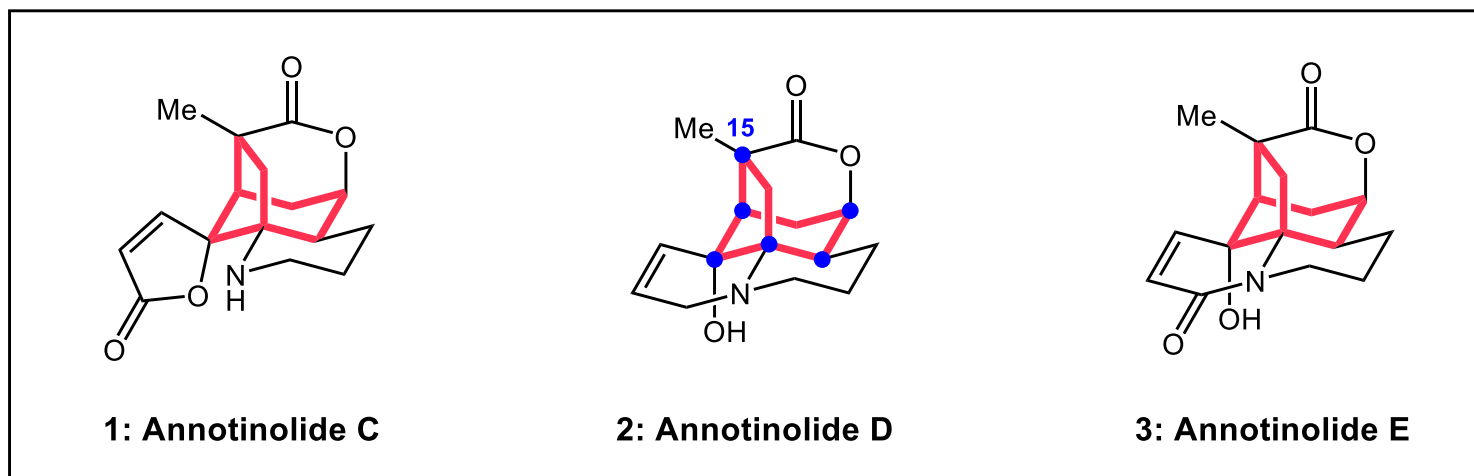
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2 Total Syntheses of Annotinolides C, D, and E

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Introduction



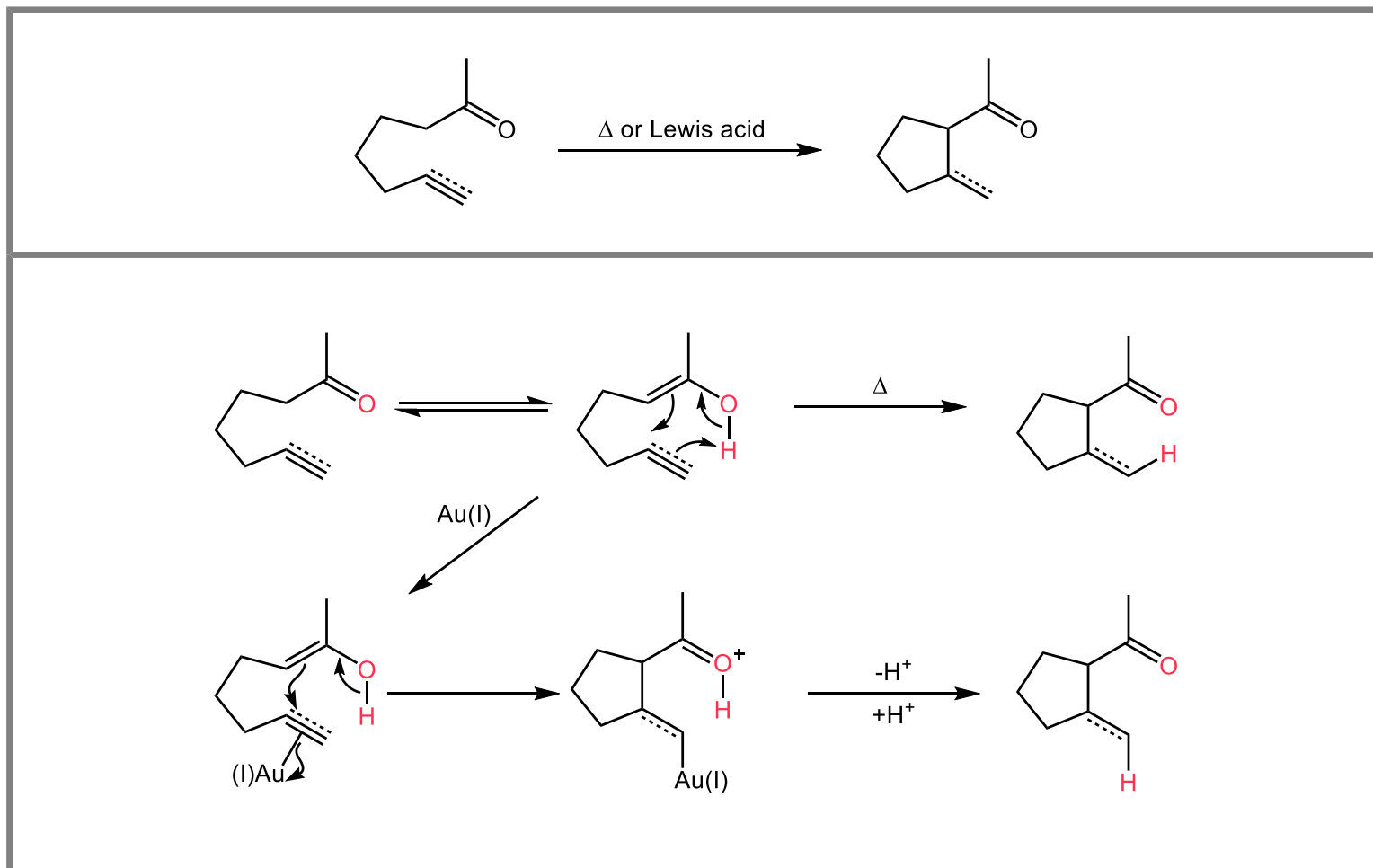
- They were isolated from *Lycopodium annotinum* and characterized in 2016;
- They have [3.2.1]-bicyclic core with 6 contiguous chiral centers.



Lycopodium annotinum

Tang, Y.; Xiong, J.; Zhang, J.-J.; Zhang, W.; Zhang, H.-Y.*; Hu, J.-F*. *et al. Org. Lett.* **2016**, *18*, 4376

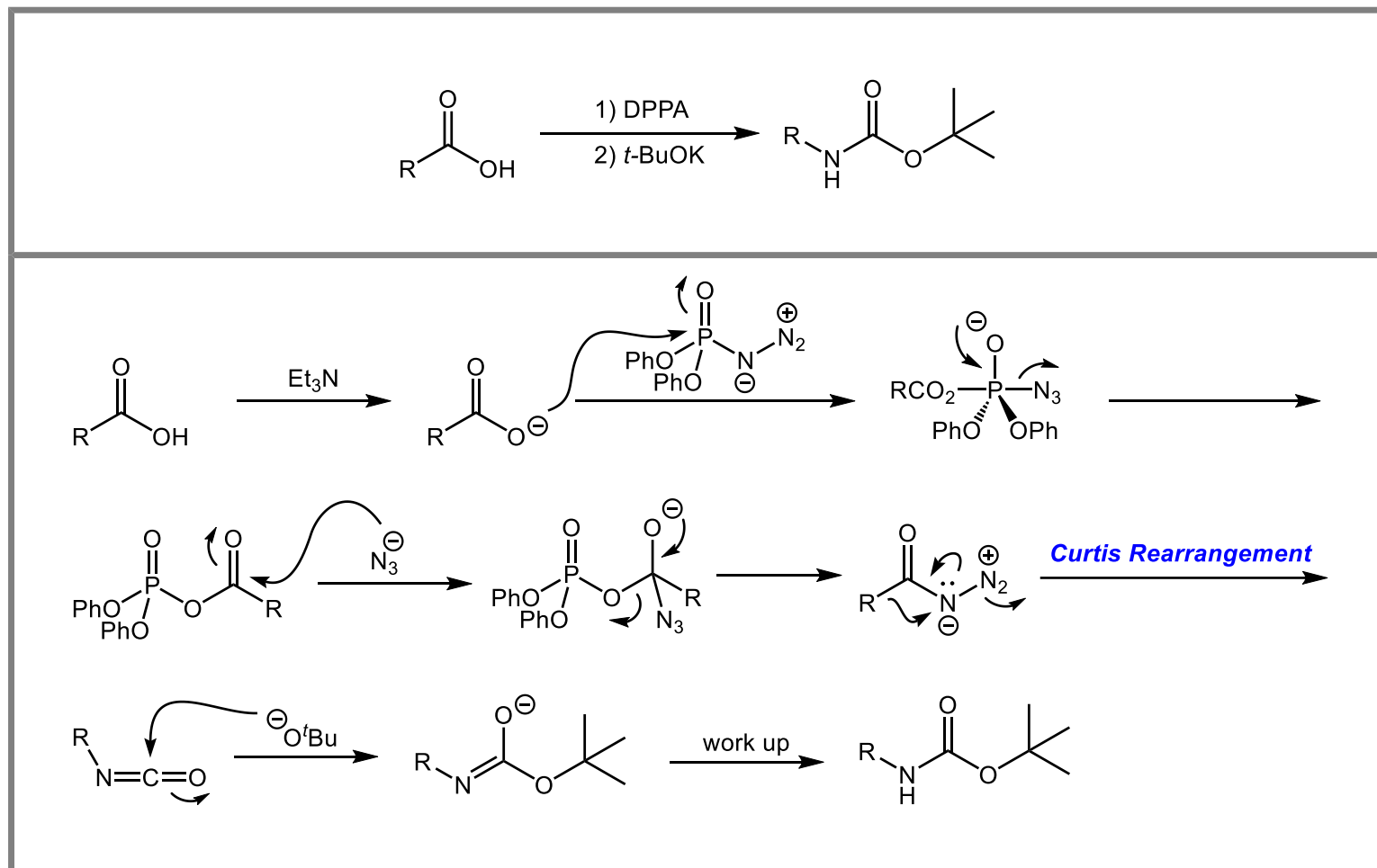
Conia-ene Reaction



Conia, J. M.; Le Perchec, P. *Synthesis* **1975**, 1, 1

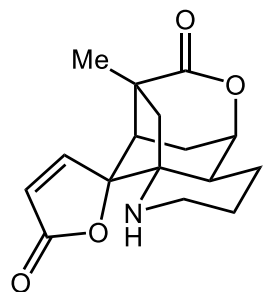
Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, 126, 4526

Fukuyama Amination

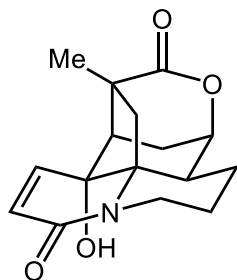
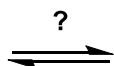


Adachi, Y.; Kamei, N.; Fukuyama, T. *Org. Lett.* **2011**, 13, 4446

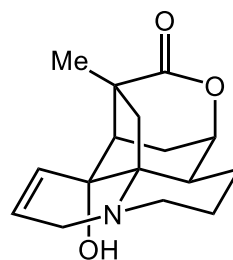
Retrosynthetic Analysis



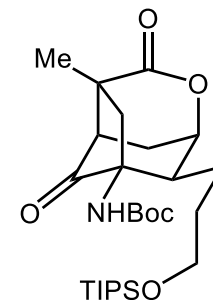
1: Annotinolide C



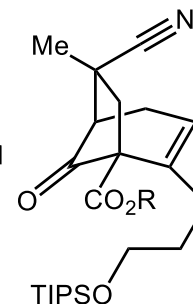
3: Annotinolide E



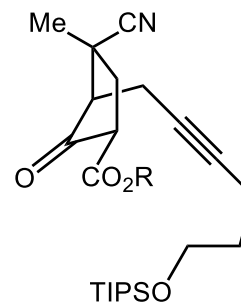
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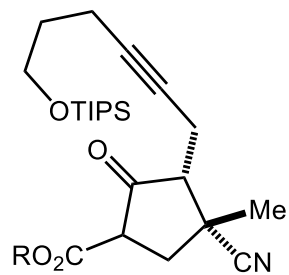
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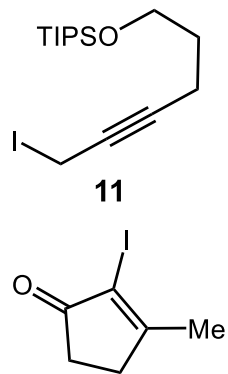
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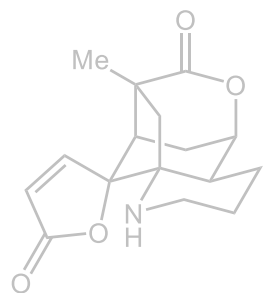
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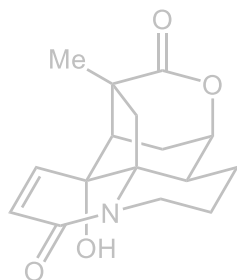
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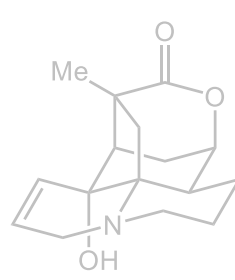
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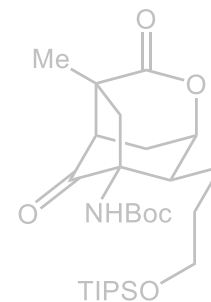
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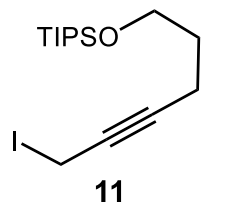
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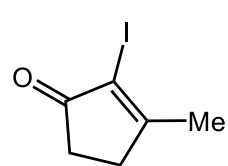
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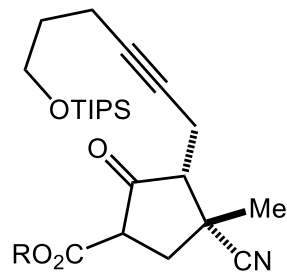
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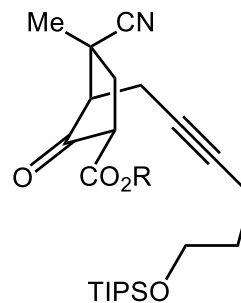
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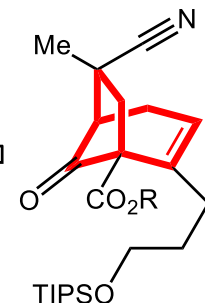
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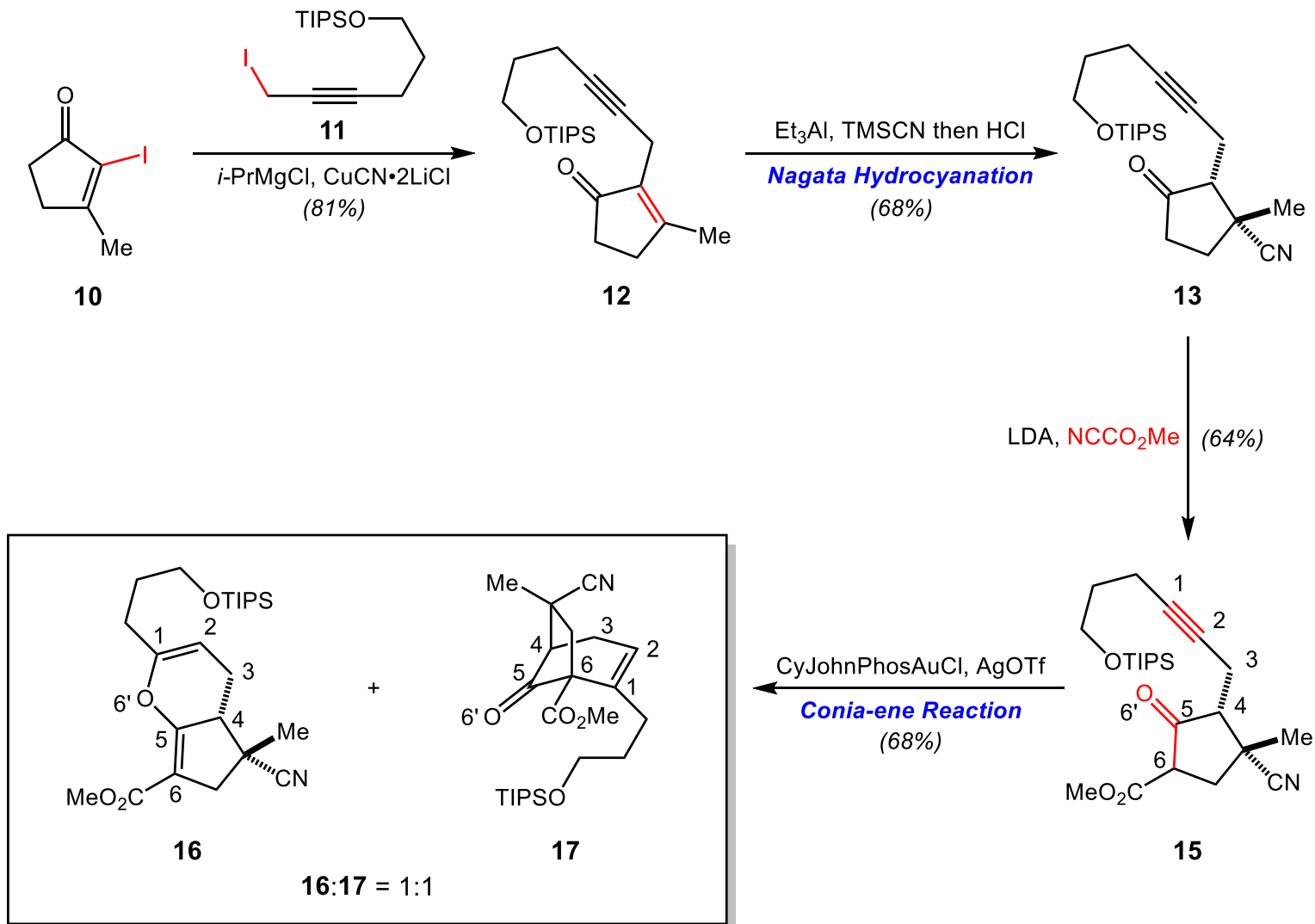


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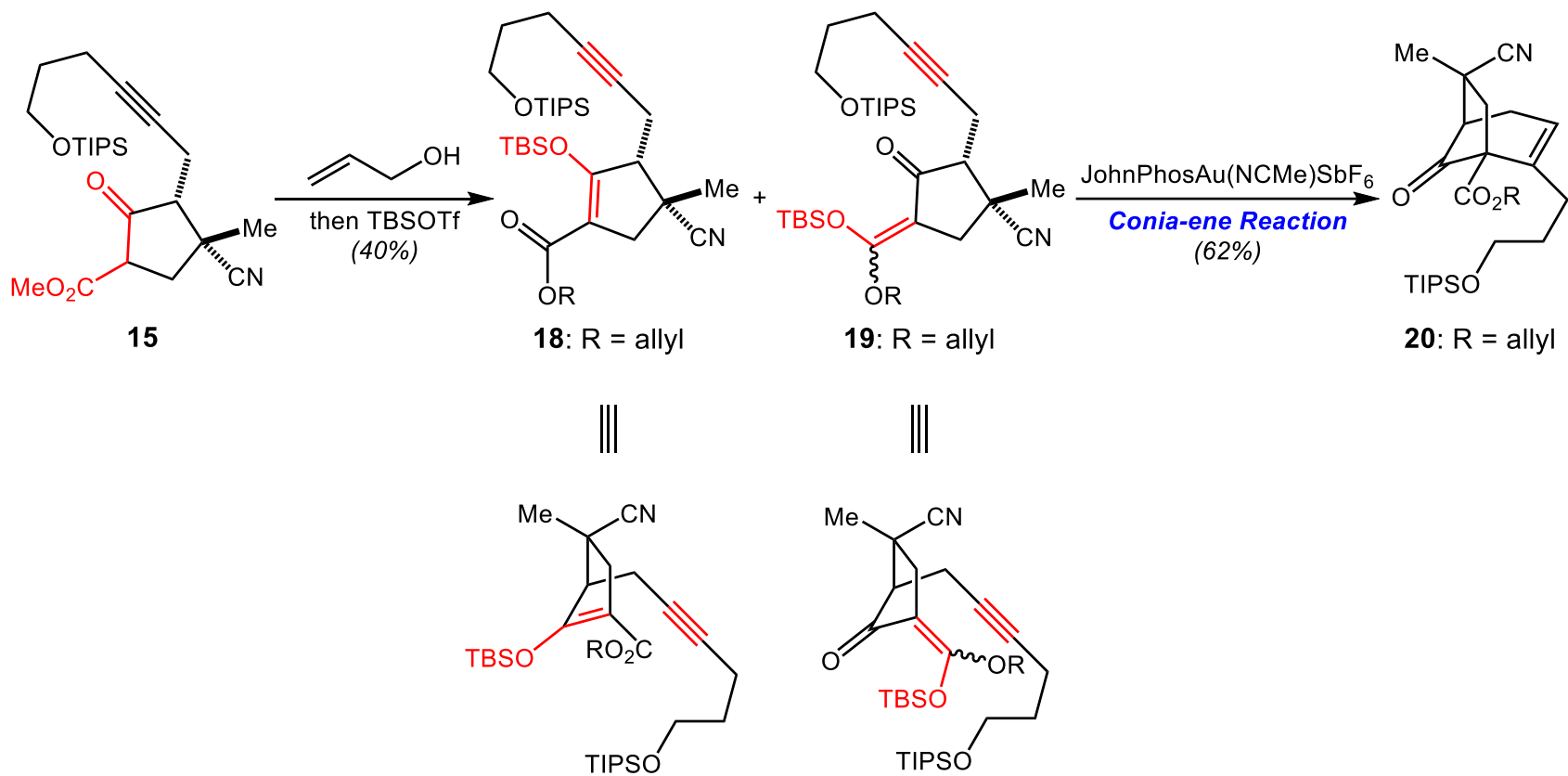


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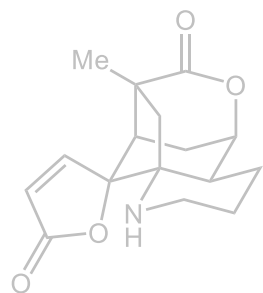
Synthesis of Intermediate 17



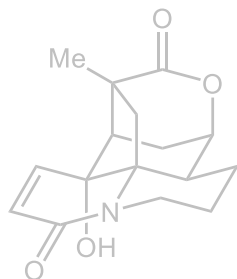
Synthesis of Intermediate 20



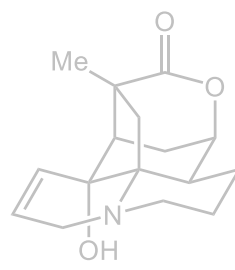
Retrosynthetic Analysis



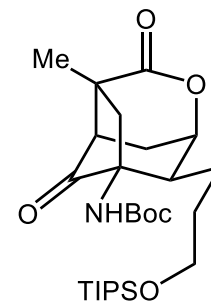
1: Annotinolide C



3: Annotinolide E



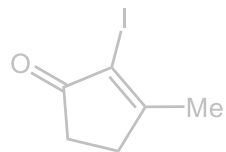
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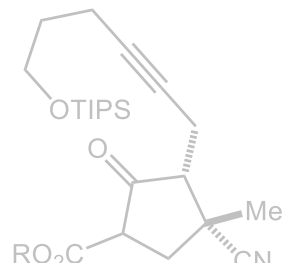
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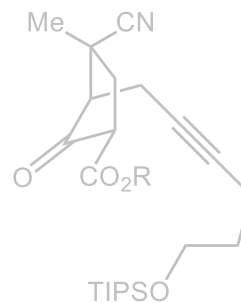
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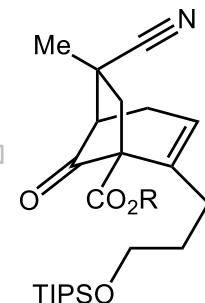
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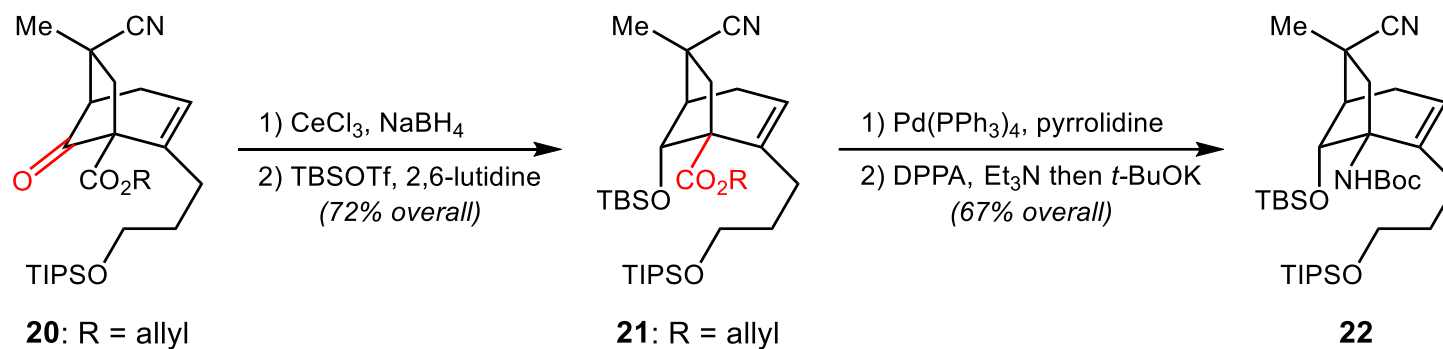


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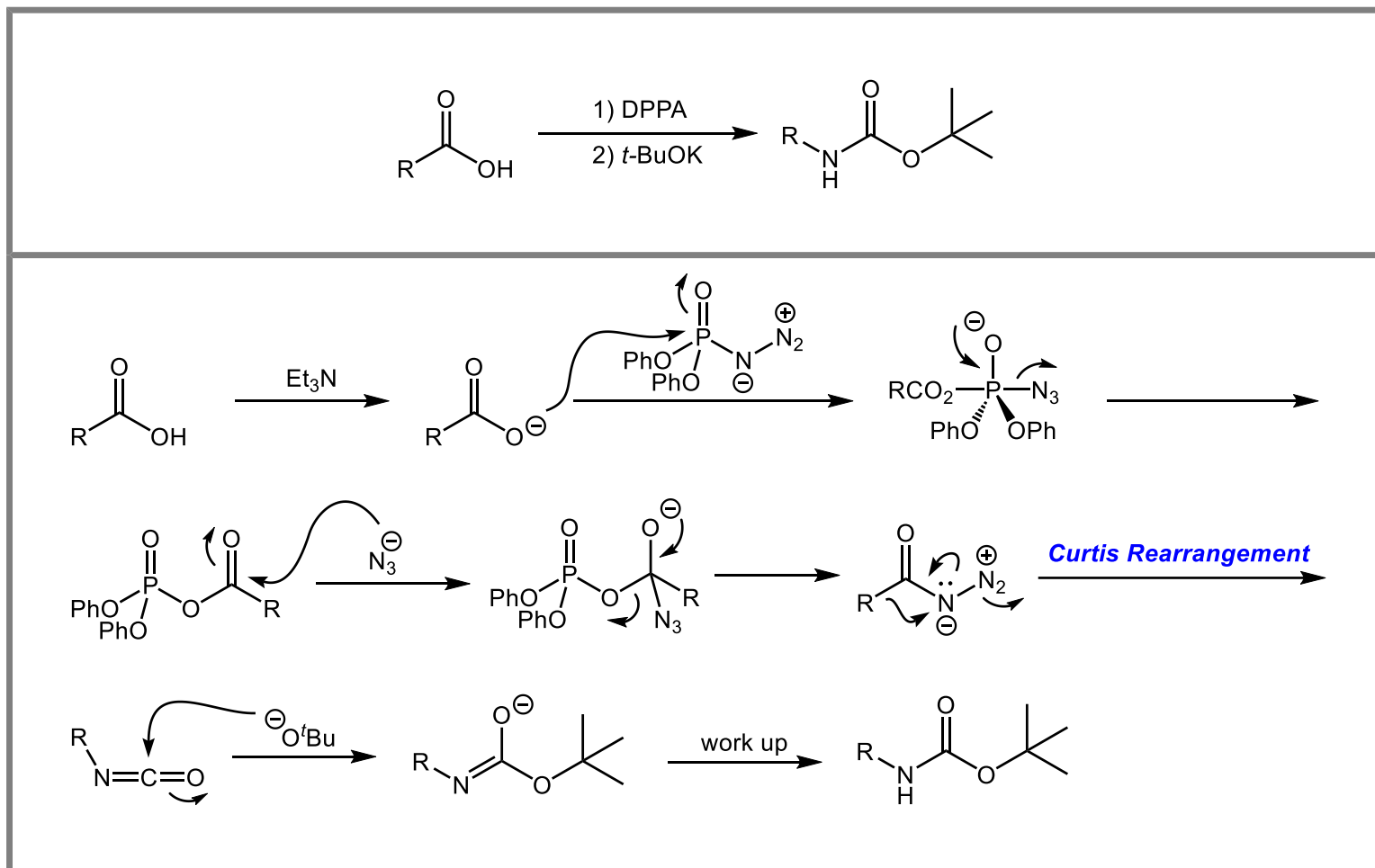


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Synthesis of Intermediate 22

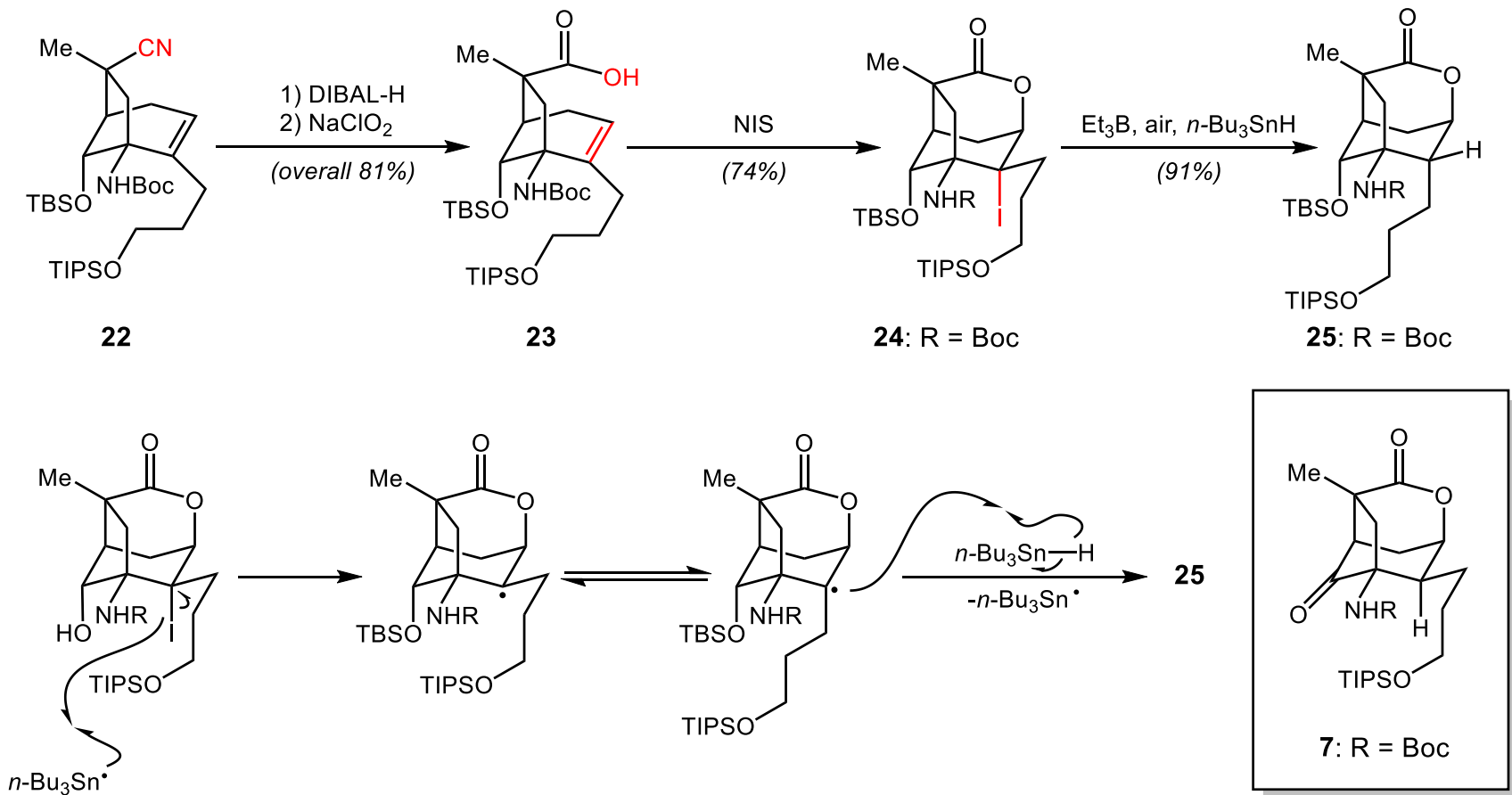


Fukuyama Amination

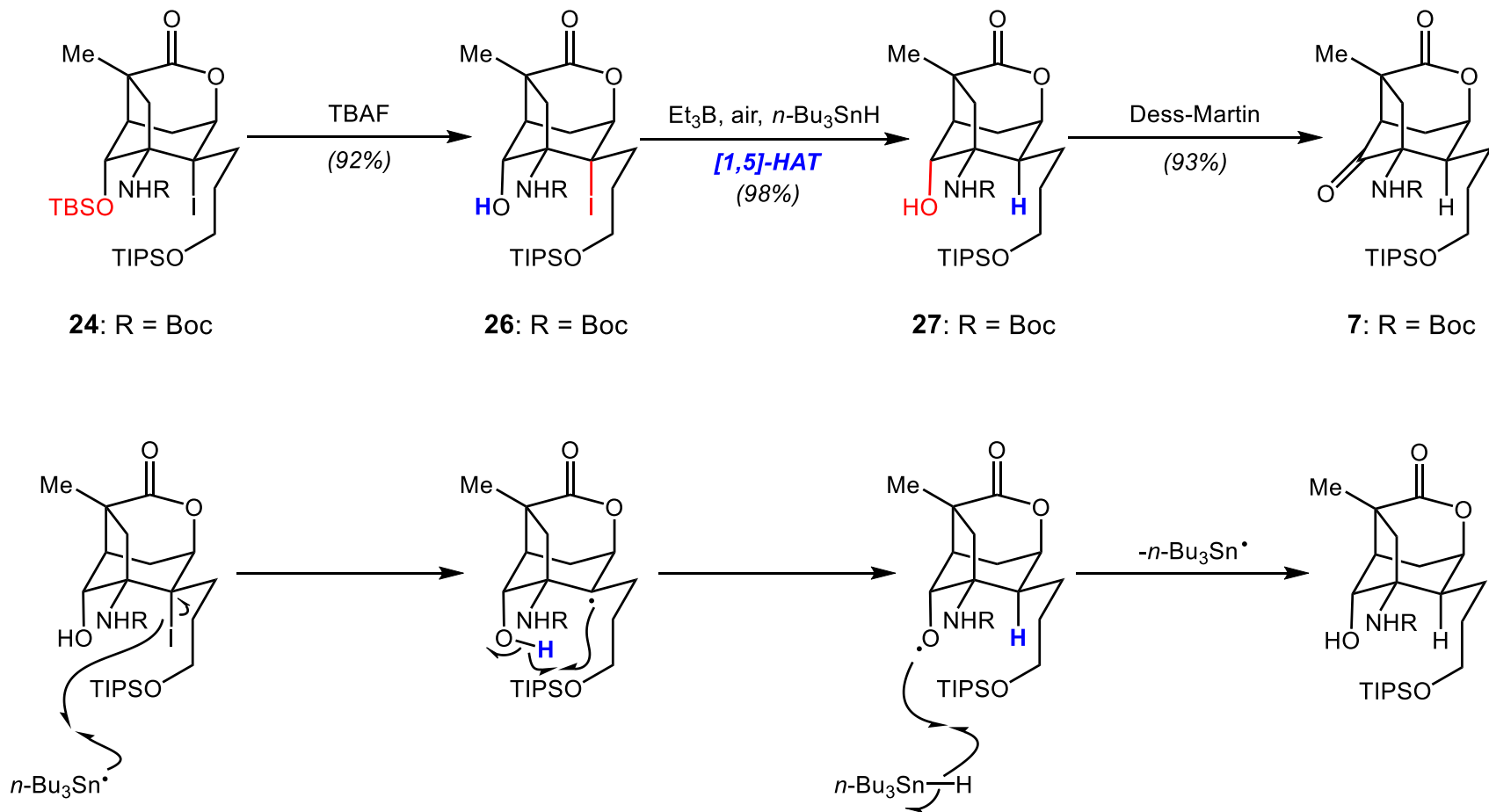


Adachi, Y.; Kamei, N.; Fukuyama, T. *Org. Lett.* **2011**, *13*, 4446

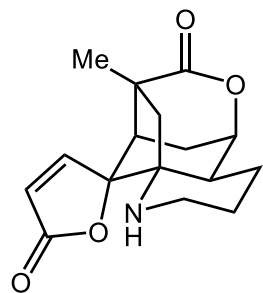
Synthesis of Intermediate 7



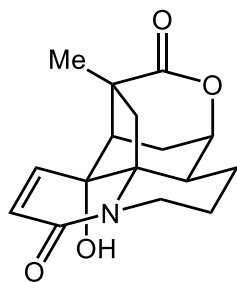
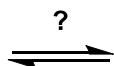
Synthesis of Intermediate 7



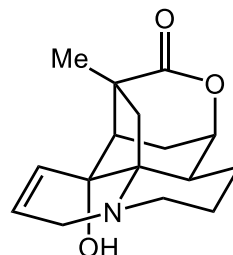
Retrosynthetic Analysis



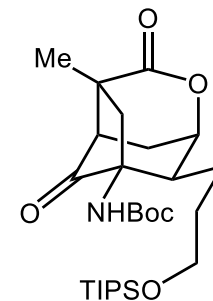
1: Annotinolide C



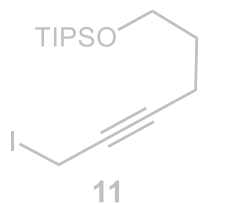
3: Annotinolide E



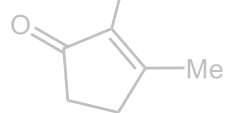
2: Annotinolide D



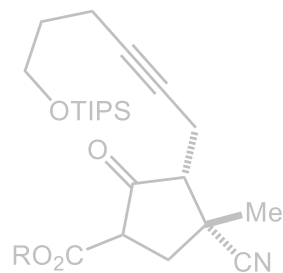
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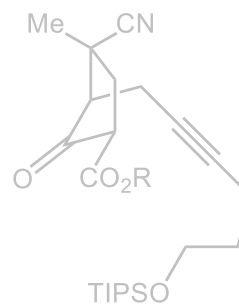
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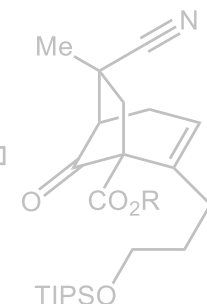
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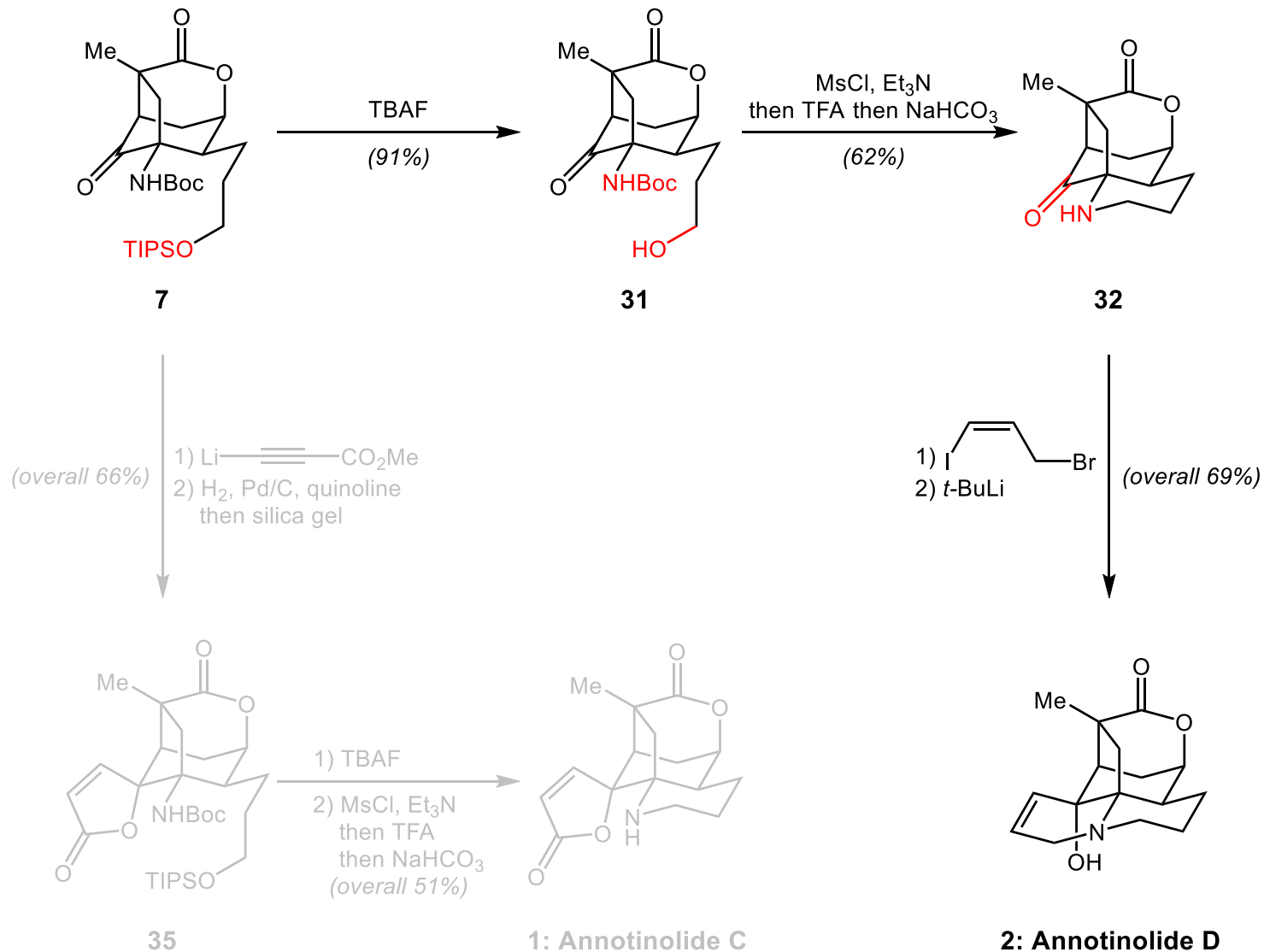


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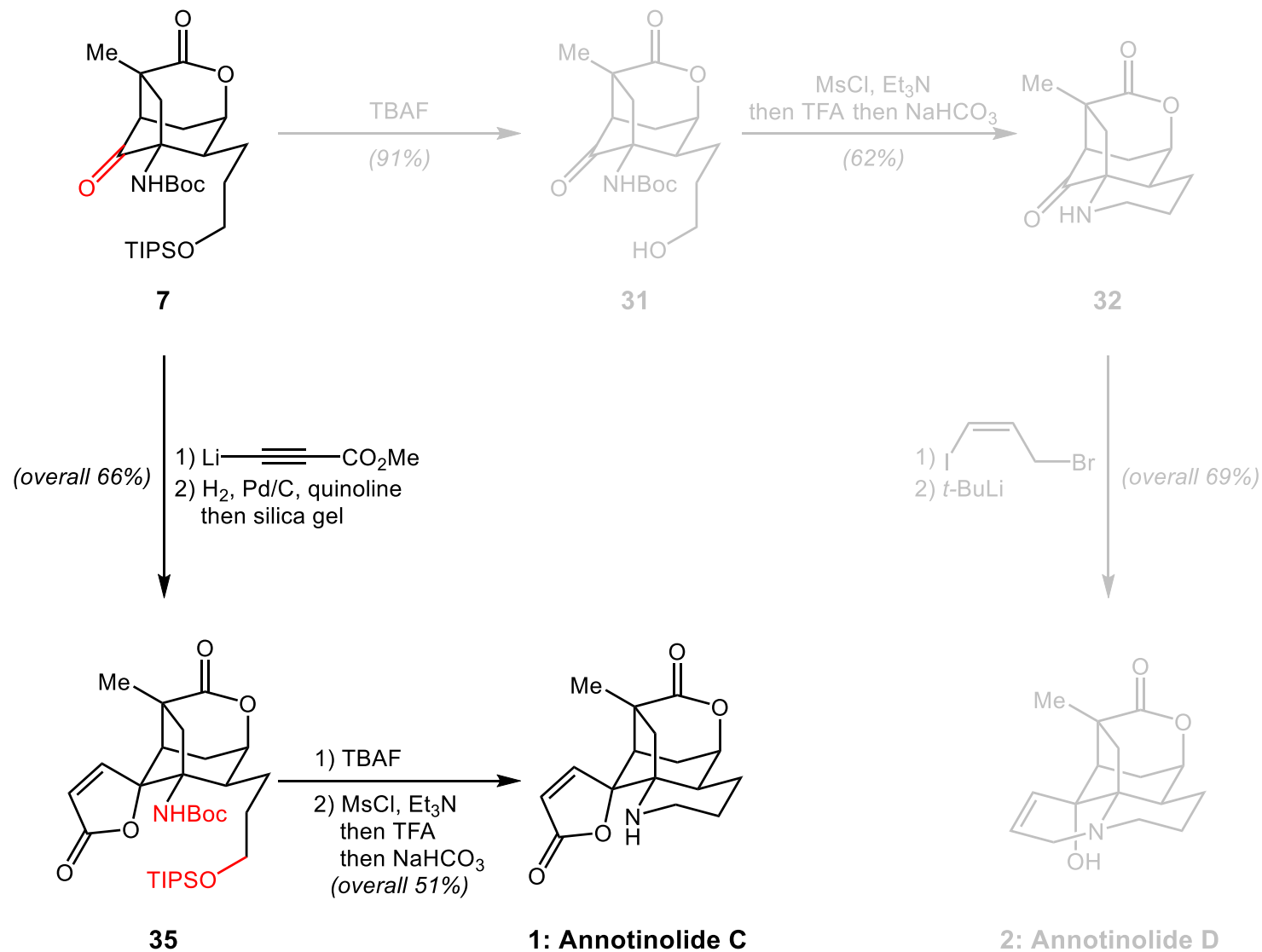


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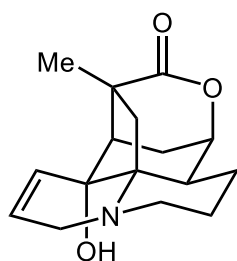
Syntheses of Annotinolides C and D



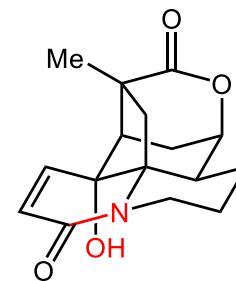
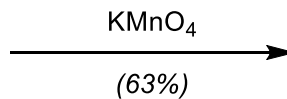
Syntheses of Annotinolides C and D



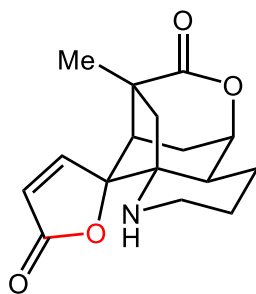
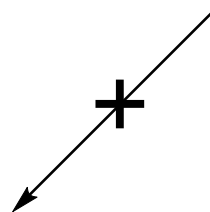
Synthesis of Annotinolide E



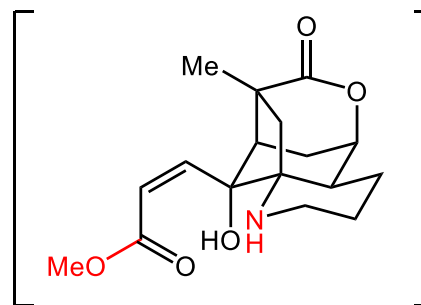
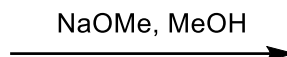
2: Annotinolide D



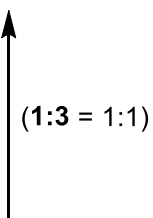
3: Annotinolide E



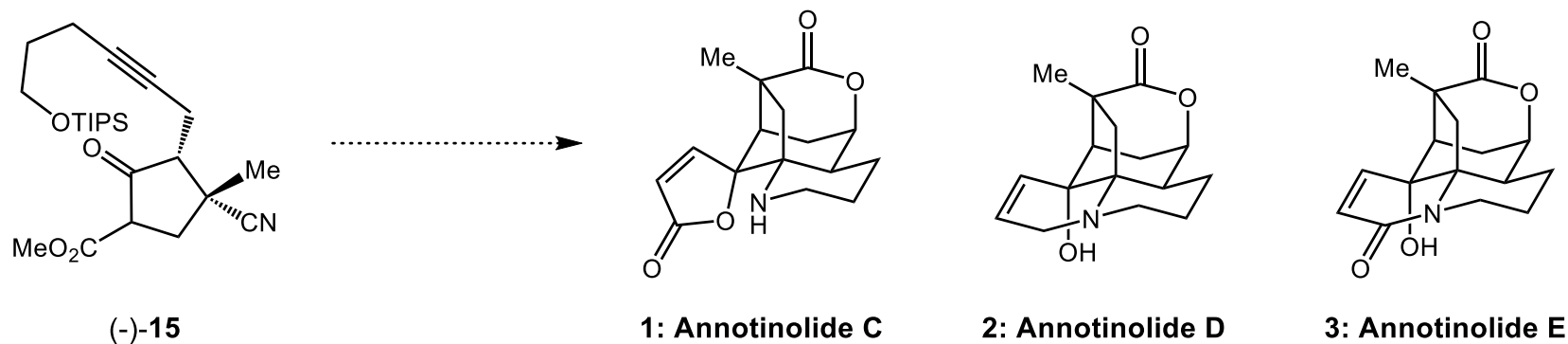
1: Annotinolide C



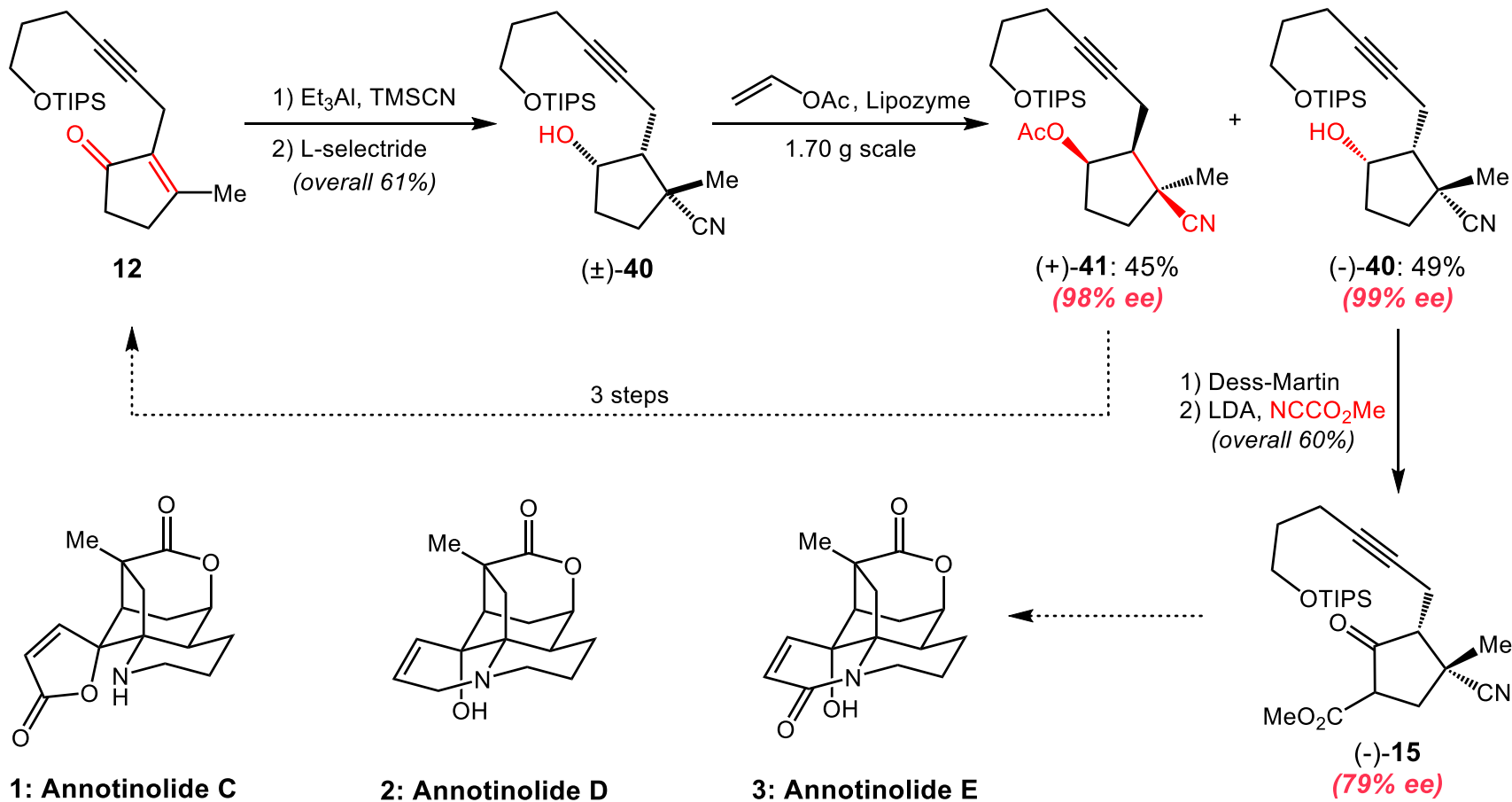
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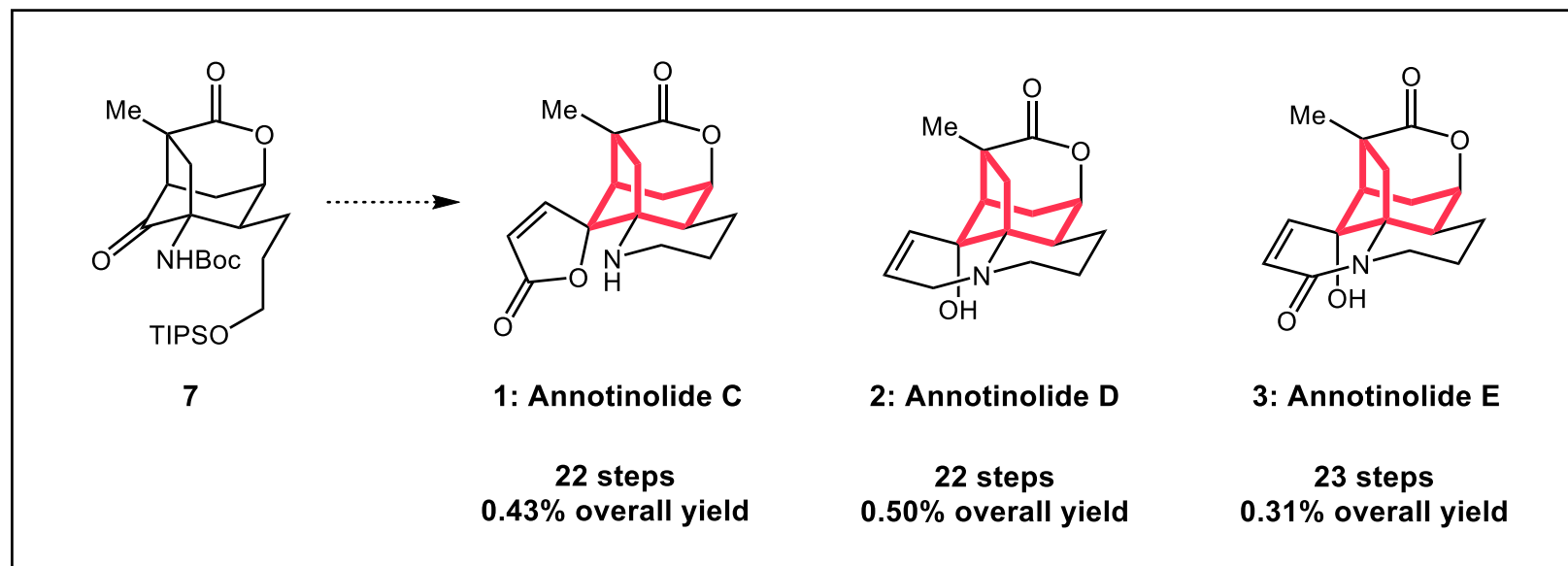
Development of a Formal Asymmetric Route



Development of a Formal Asymmetric Route



Summary

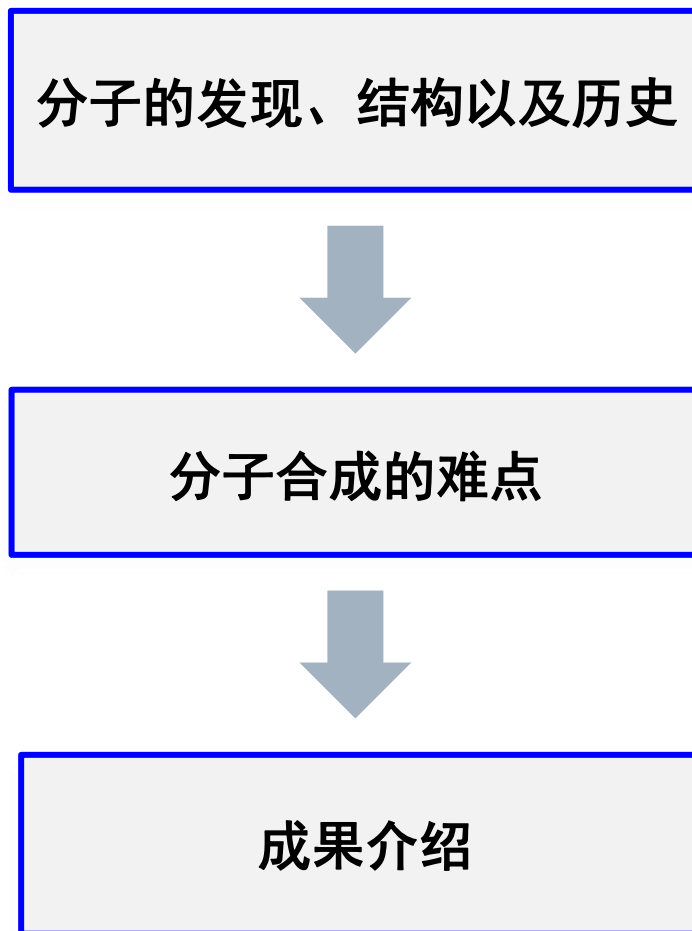


- Conia-ene reaction ([3.2.1]-bicycle)
- Curtius rearrangement (aza-quaternary center)
- 1,5-Hydrogen atom transfer (core lactone motif)

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The First Paragraph

写作思路



The First Paragraph

In 2016, Zhang, Hu, and co-workers reported the isolation and characterization of a unique collection of alkaloid-based natural products from *Lycopodium annotinium*, including **1–3**. While structurally related to the famous lycopodine family, of which **4** is the flagship member given its historic isolation in 1881, these compounds possess a truncated and more highly oxidized [3.2.1]-bicyclic core in contrast to the standard [3.3.1]-framework of the parent class. This domain within the annotinolides, while generally rare, has been found in other alkaloid classes as exemplified by the structures of gelsemine and isopalhinine A, and can be quite challenging to fashion as revealed by published syntheses of these particular targets over the past decade.

The First Paragraph

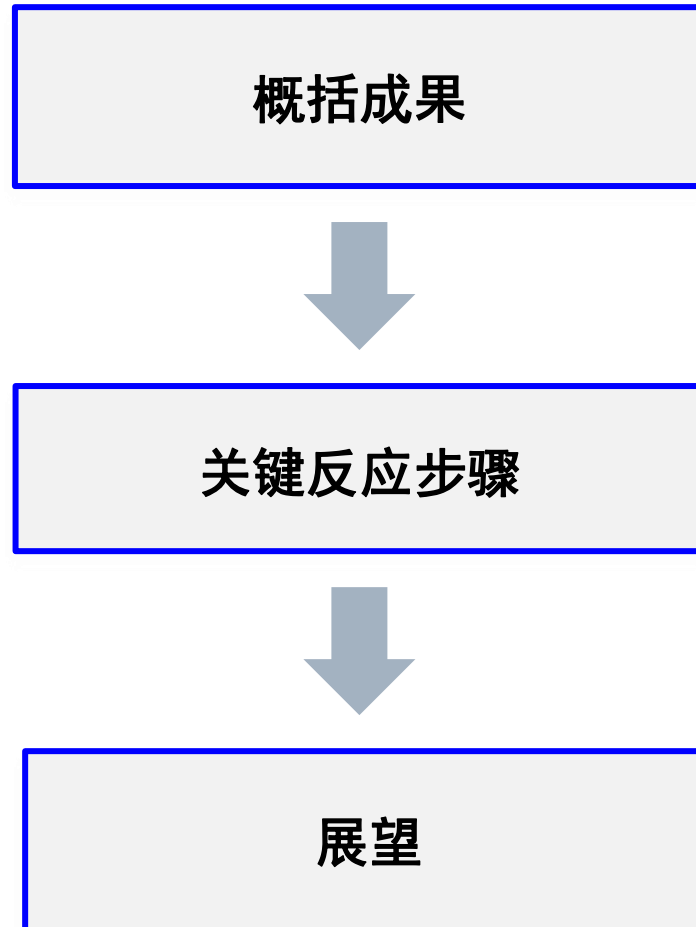
For **1–3** specifically, this [3.2.1]-bicycle leads to the presence of 6 contiguous chiral centers within the main core, of which 3 are fully substituted, with 1 being a quaternary center. The remaining structural variations among the drawn annotinolides reflect further changes in oxidation state and/or peripheral ring patterning. To date, no member of this collection has succumbed to laboratory synthesis, with only a recent model study by Tu illustrating a potential approach to fashion their common core.

The First Paragraph

Herein, we report the first route capable of achieving their total syntheses through a cohesive strategy featuring several carefully orchestrated transformations to both fashion and manipulate their structural elements despite their intricate and sterically encumbered environments. Additionally, a series of chemical operations performed on the synthesized natural products offer insights into their biosynthetic relationships, in one case suggesting a connection counter to the original biogenetic proposals posited by the isolation team. Finally, a formal asymmetric synthesis of a key building block is presented.

The Last Paragraph

写作思路



The Last Paragraph

In conclusion, we have synthesized three members of the annotinolide family through an approach that leveraged the presence of an initial cyanide-containing quaternary center in a cyclopentanone precursor to stereospecifically fashion the remaining rings and chiral centers of these formidable caged compounds. Critical operations leading to that success include the following: (1) a challenging Conia-ene reaction to forge the entire [3.2.1]-core in a single operation using silyl enol ethers to circumvent alternate modes of cyclization, (2) subsequent use of the ester to generate a hindered aza-quaternary center through a Curtius rearrangement, (3) intramolecular 1,5-hydrogen atom transfer to finalize the core lactone motif, and (4) diastereoselective additions and terminating cyclizations to fashion the periphery.

The Last Paragraph

In addition, we established a viable means for the interconversion of two family members and developed a scalable route to access our key cyanide-containing building block in an enantioenriched fashion. Efforts to extend the lessons learned from these endeavors to other members of the family, as well as additional alkaloid classes, are the subject of current study.

Representative Examples

- Additionally, a series of chemical operations performed on the synthesized natural products offer insights into their biosynthetic relationships. (为…提供一个视角)
- We have synthesized three members of the annotinolide family through an approach that leveraged the presence of an initial cyanide-containing quaternary center in a cyclopentanone precursor to stereospecifically fashion... (利用…来…)
- We established a viable means for the interconversion of two family members and developed a scalable route to access our key cyanide-containing building block in an enantioenriched fashion. (发展一种方法)

Acknowledgement

*Thanks
for your attention*