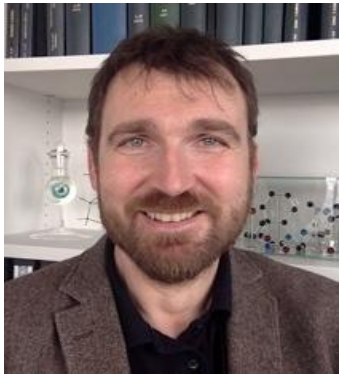
Literature Report I

Total Synthesis of Crocagin A

Reporter : Yang Zhao
Checker : Zhong Yan
Date : 2017-12-13

Bihelovic, F.; Stichnoth, D; Surup, F.; Müller, R.; **Trauner, D.***
Angew. Chem. Int. Ed. **2017**, *56*, 12848

CV of Prof. Dirk Trauner



Research:

- Chemical synthesis, natural product chemistry, cell biology, neuroscience, and photopharmacology.

Education:

- **1986–1995** Diplom, University of Vienna & Free University of Berlin
- **1995–1997** Ph.D., University of Vienna (Johann Mulzer)
- **1998–2000** Postdoctor, Columbia University (Samuel J. Danishefsky)
- **2000–2006** Assistant Professor, University of California, Berkeley
- **2006–2010** Associate Professor, University of California, Berkeley
- **2008–now** Professor, University of Munich

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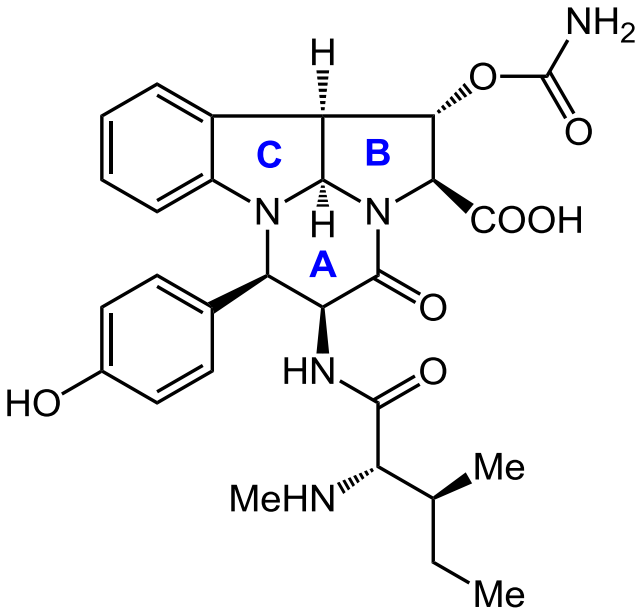
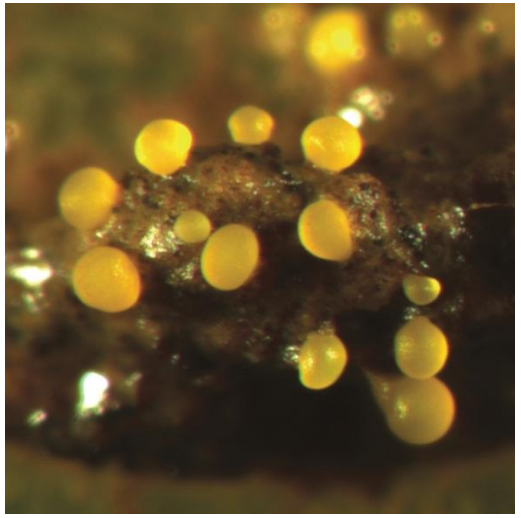
Introduction



Crocagin A



Myxobacteria

- Isolated from the *myxobacterium chondromyces crocatus*;
- Active in a screen for inhibitors of carbon storage regulator protein A;
- Novel polycyclic peptides and a tetrahydropyrrolo[2,3-*b*]indole core.

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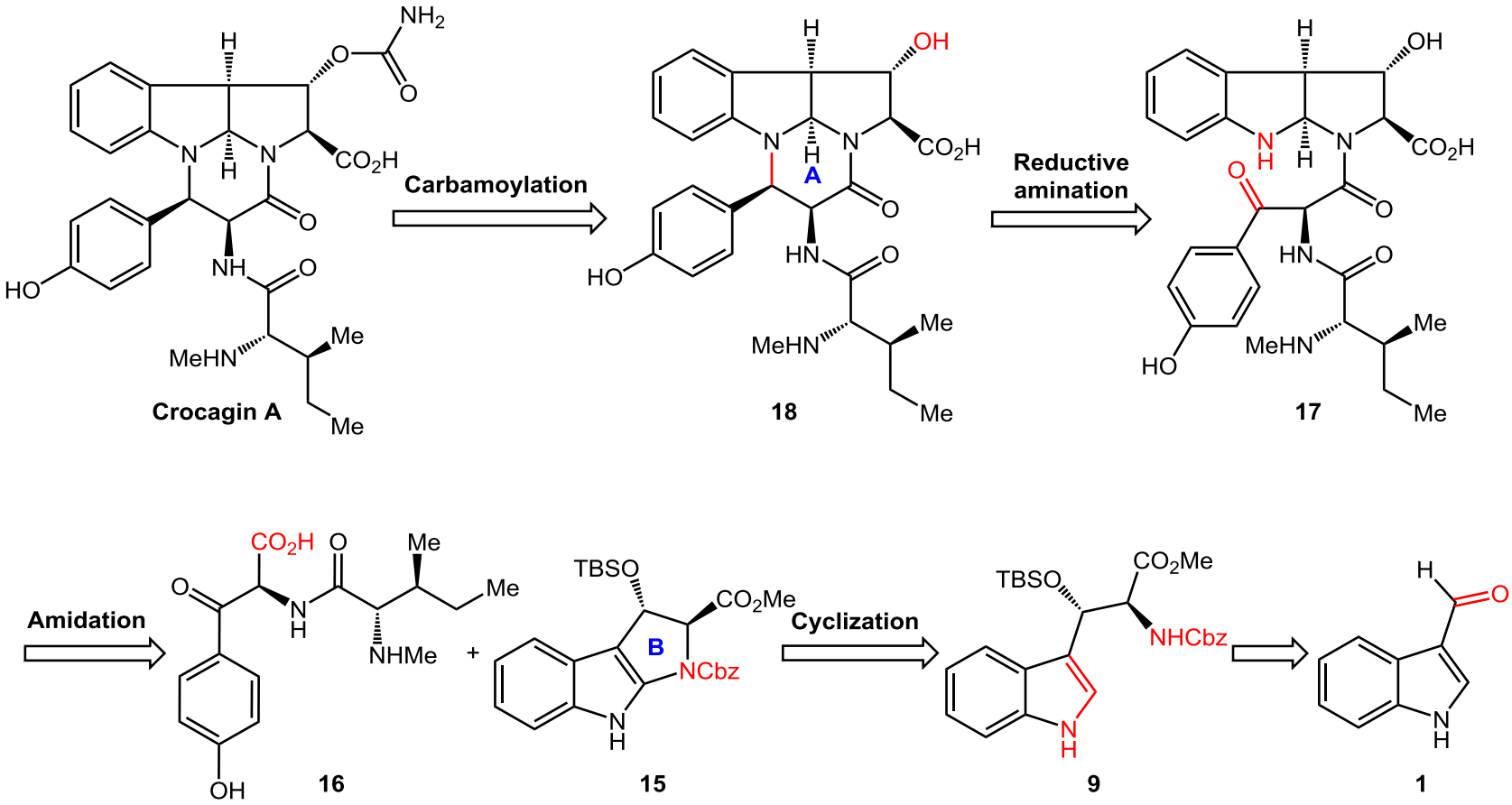
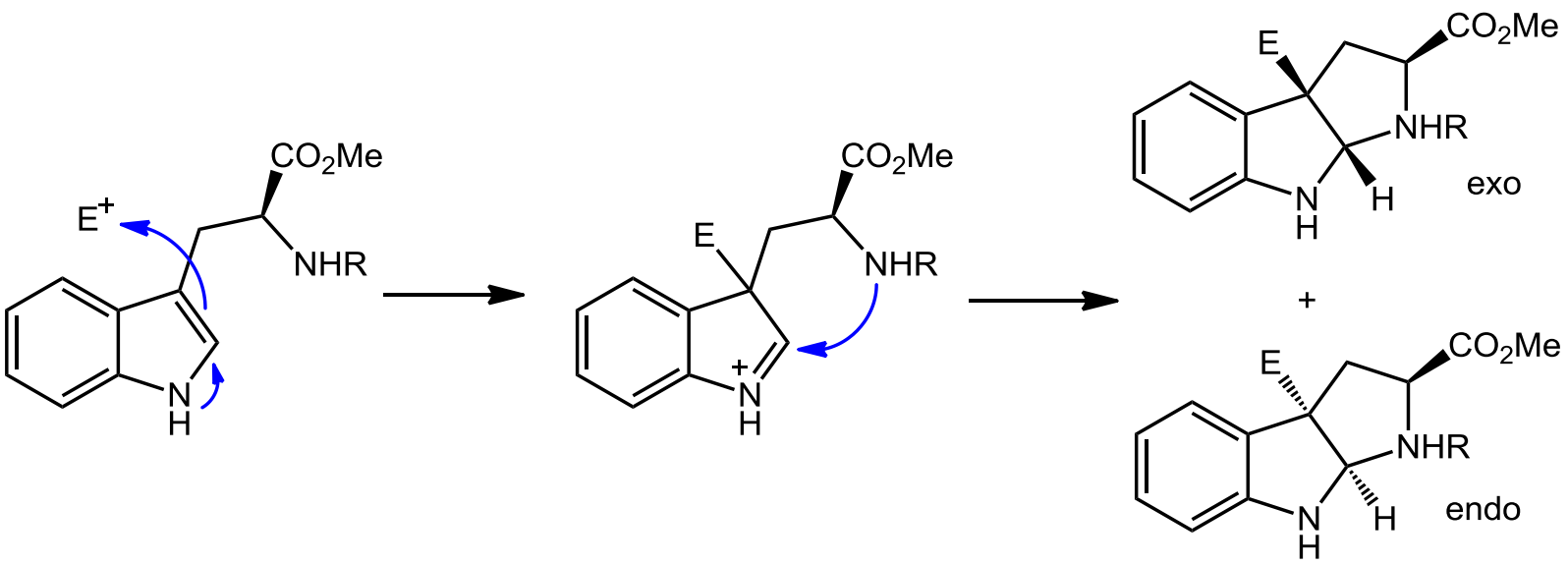
Retrosynthetic Analysis

The First Synthetic Attempt of Crocagin A



The First Cyclization Strategy

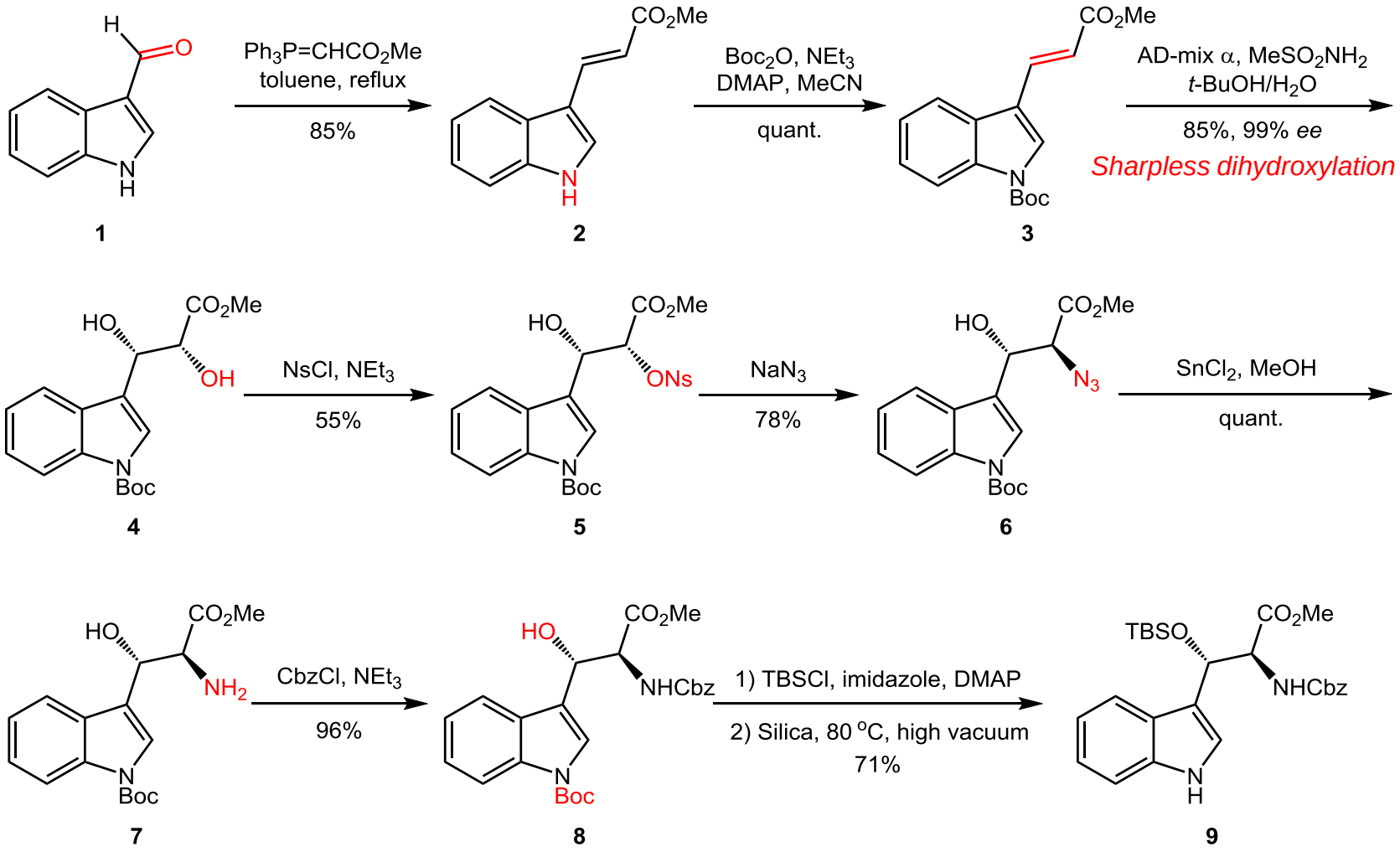


The Electrophile can either be a proton (cyclization with Brønsted acids like TFA, H_3PO_4) or a halogen (cyclization with NBS, NIS, NCS) or selenium (with PhSeCl, *N*-Phenylselenophtalimide).

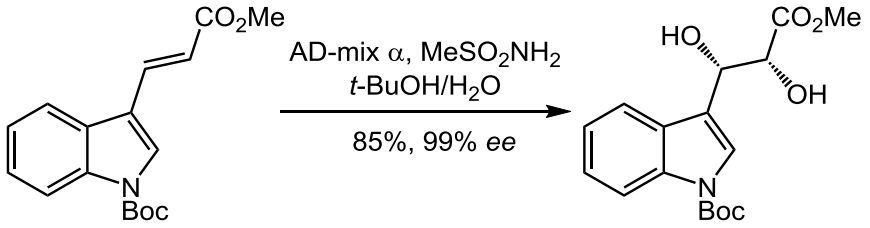
Crich, D.; Huang, X. H. *J. Org. Chem.* **1999**, *64,* 7218

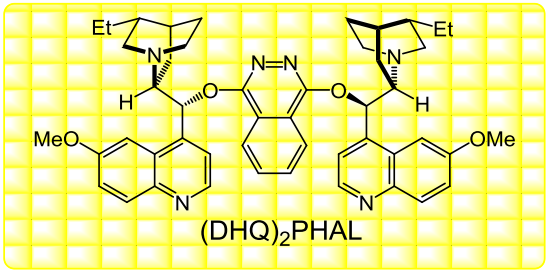
Ohno, M.; Spande T. F.; Witkop B. *J. Am. Chem. Soc.* **1970**, *92,* 343

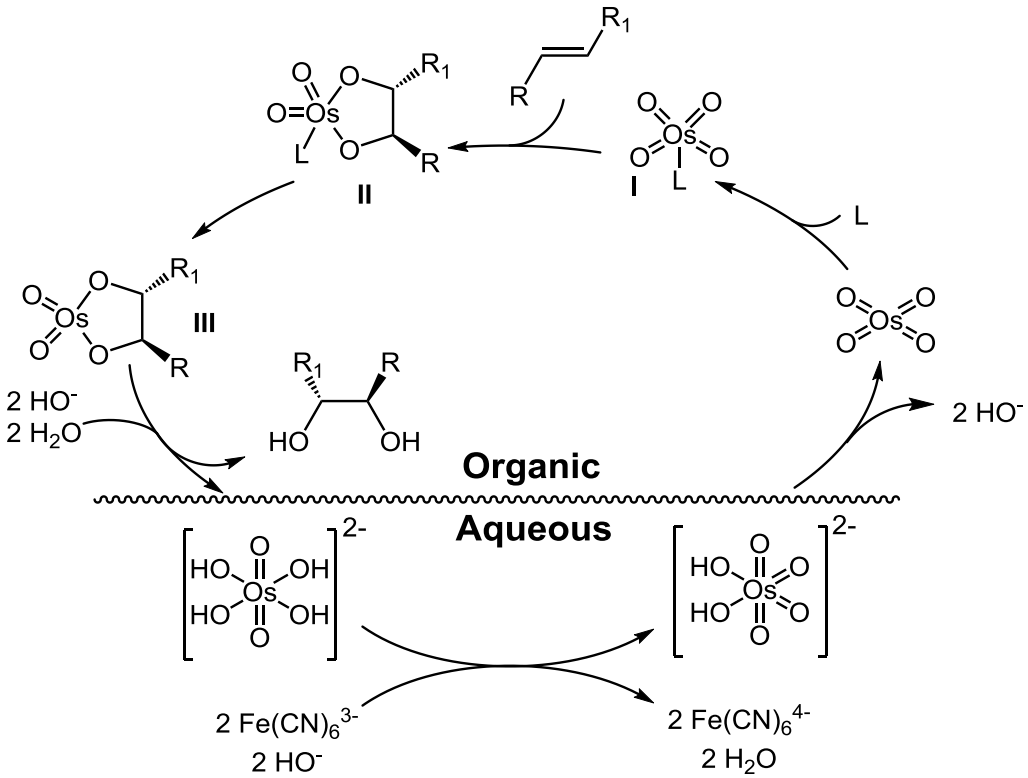
The First Synthetic Attempt of Crocagin A



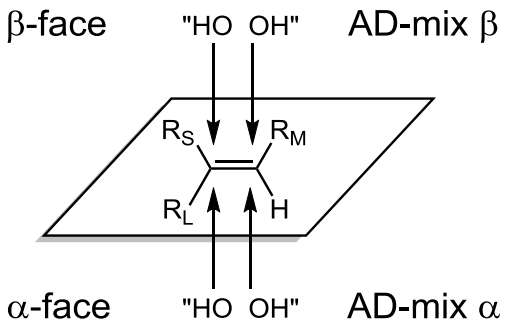
Sharpless Asymmetric Dihydroxylation







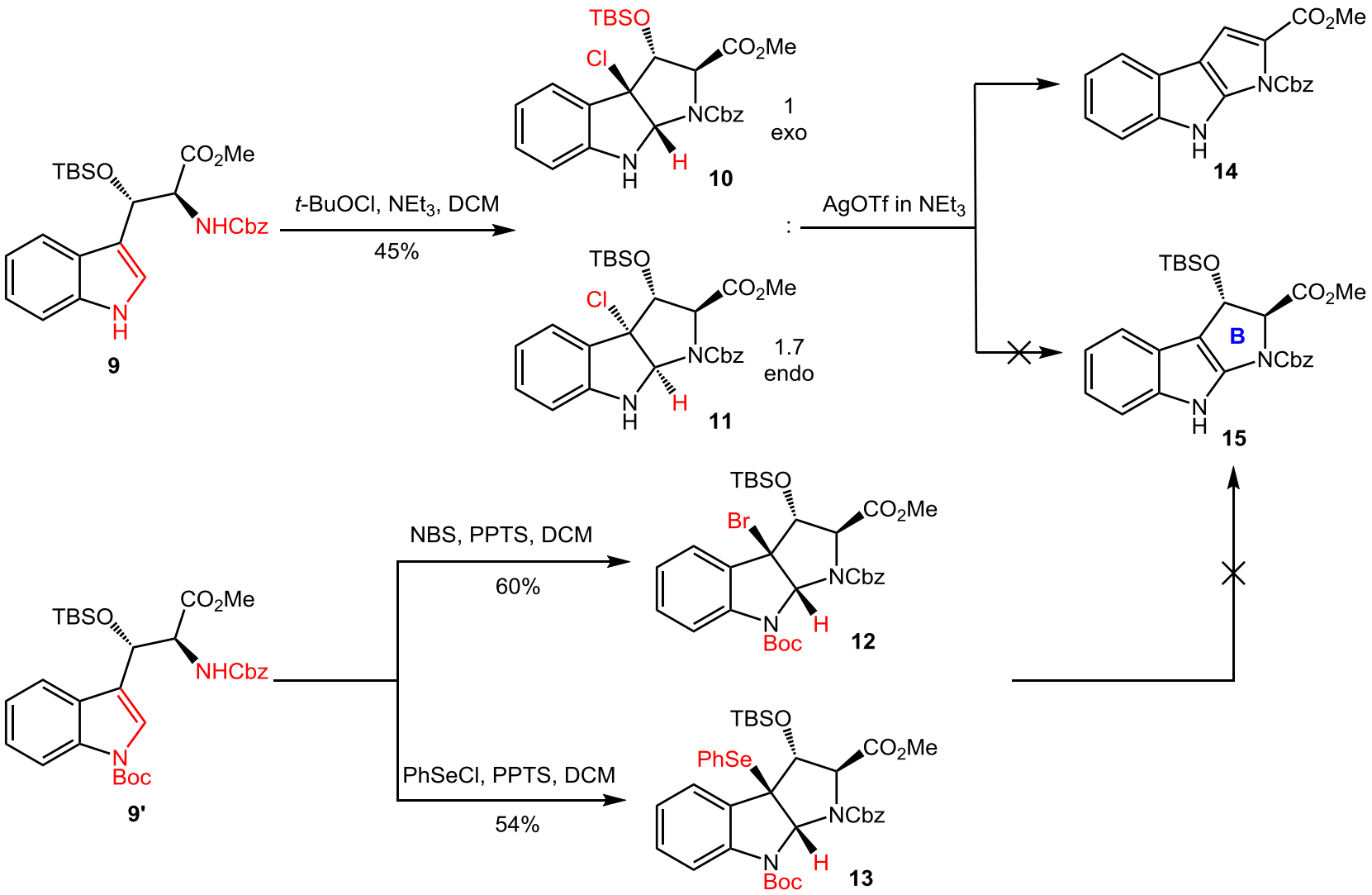
Empirical Model:



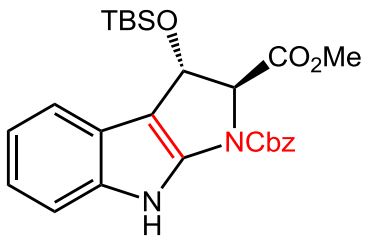
AD-mix α: $(DHQ)_2PHAL + K_2OsO_2(OH)_4 + K_3Fe(CN)_6$

AD-mix β: $(DHQD)_2PHAL + K_2OsO_2(OH)_4 + K_3Fe(CN)_6$

Unsuccessful Cyclization Attempt



The First Synthetic Attempt



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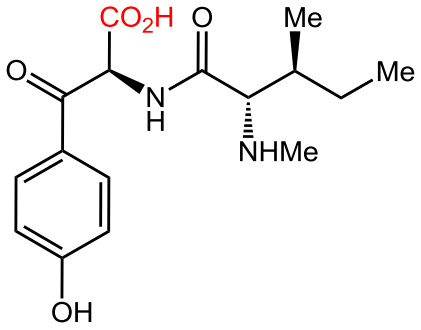

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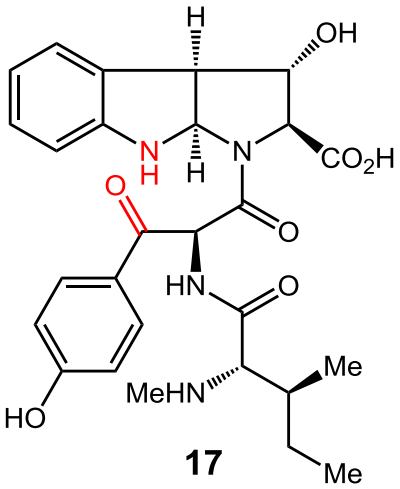
1) Hydrogenation
2) Amidation



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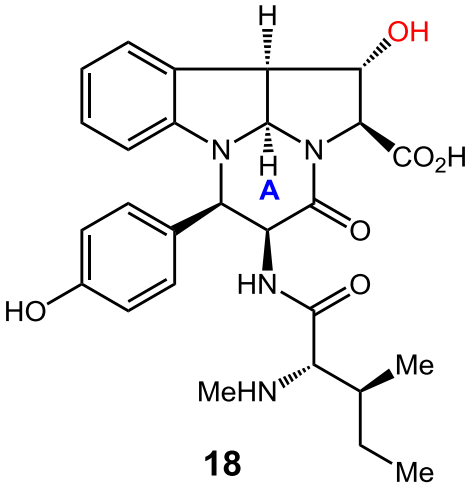
Reductive amination



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Carbamoylation

Crocagin A

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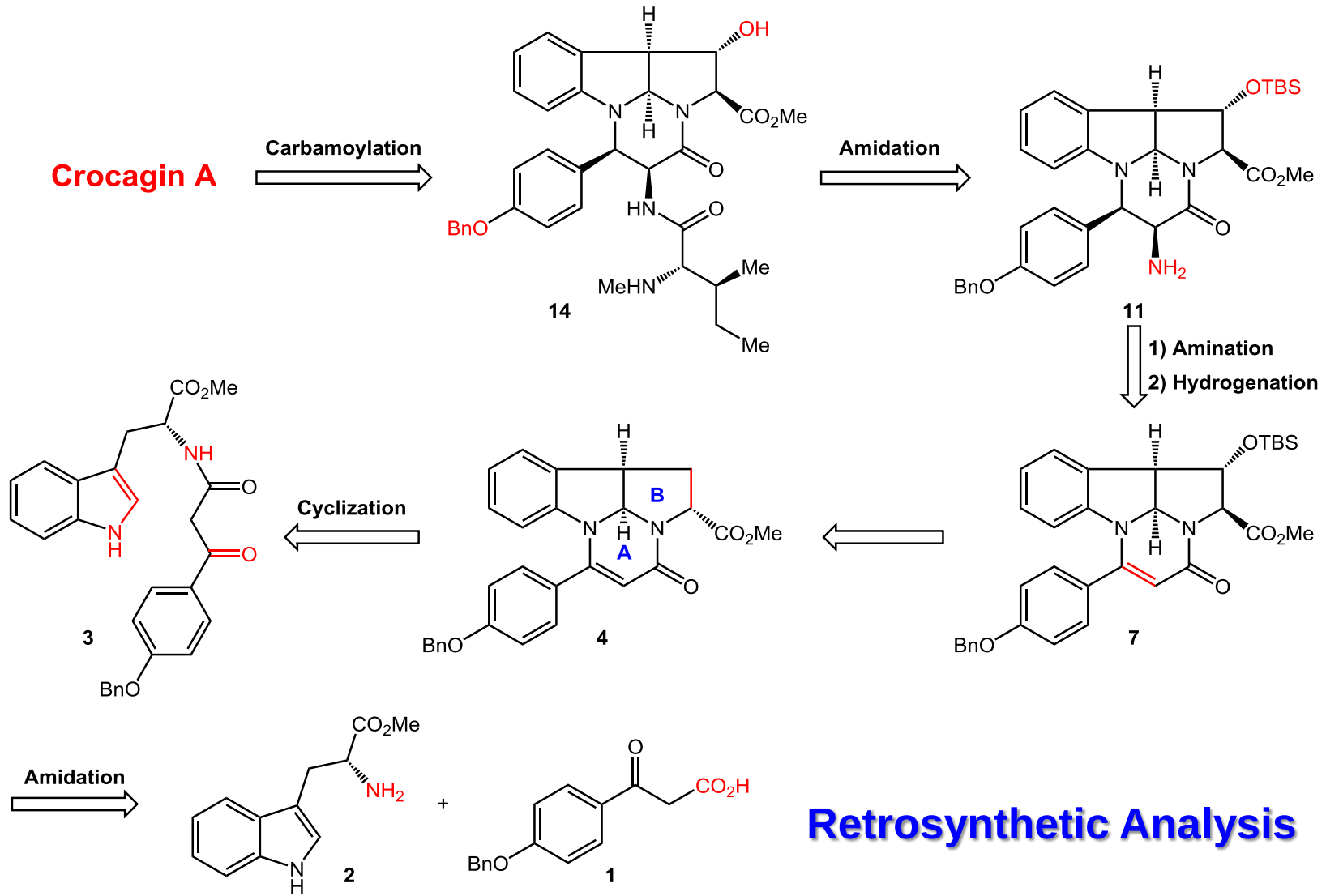
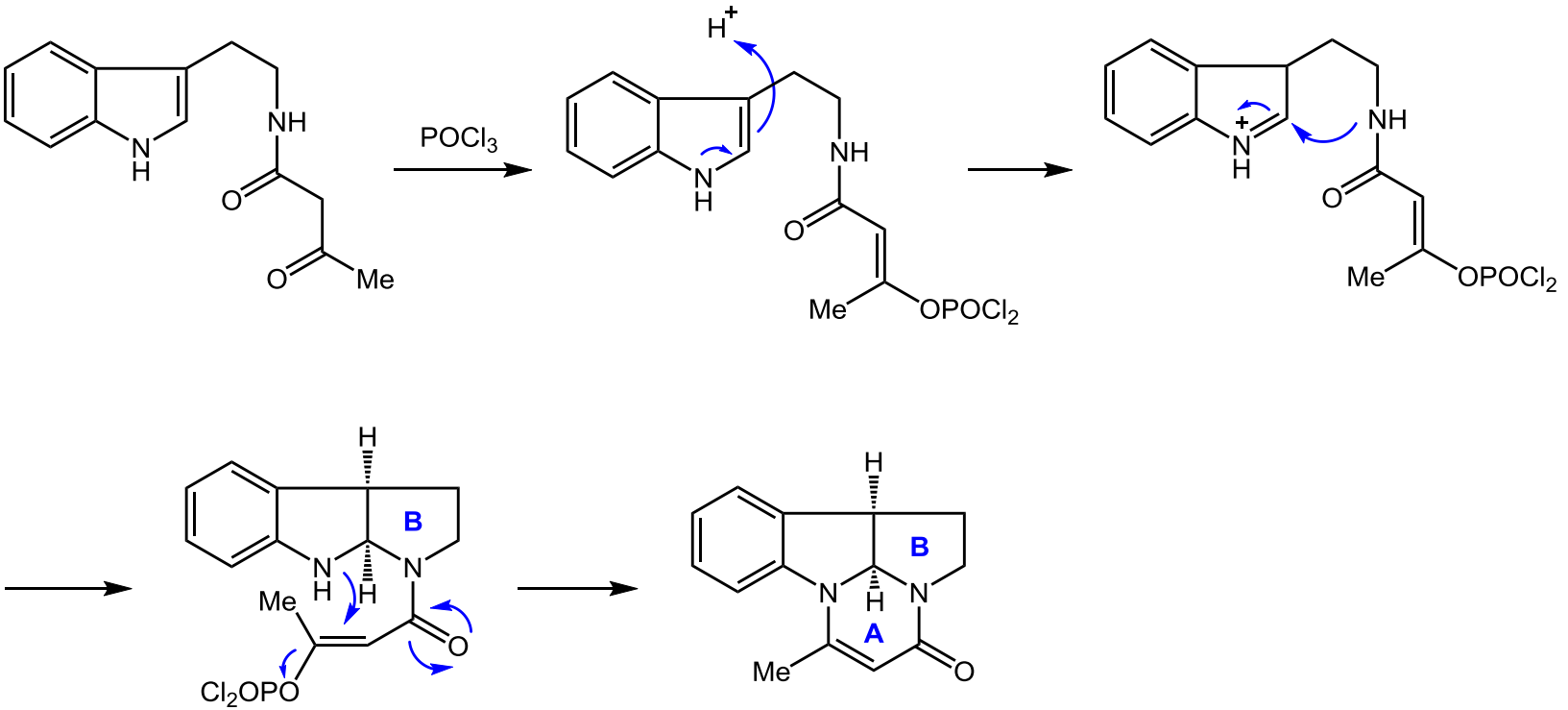
The Second Synthetic Strategy

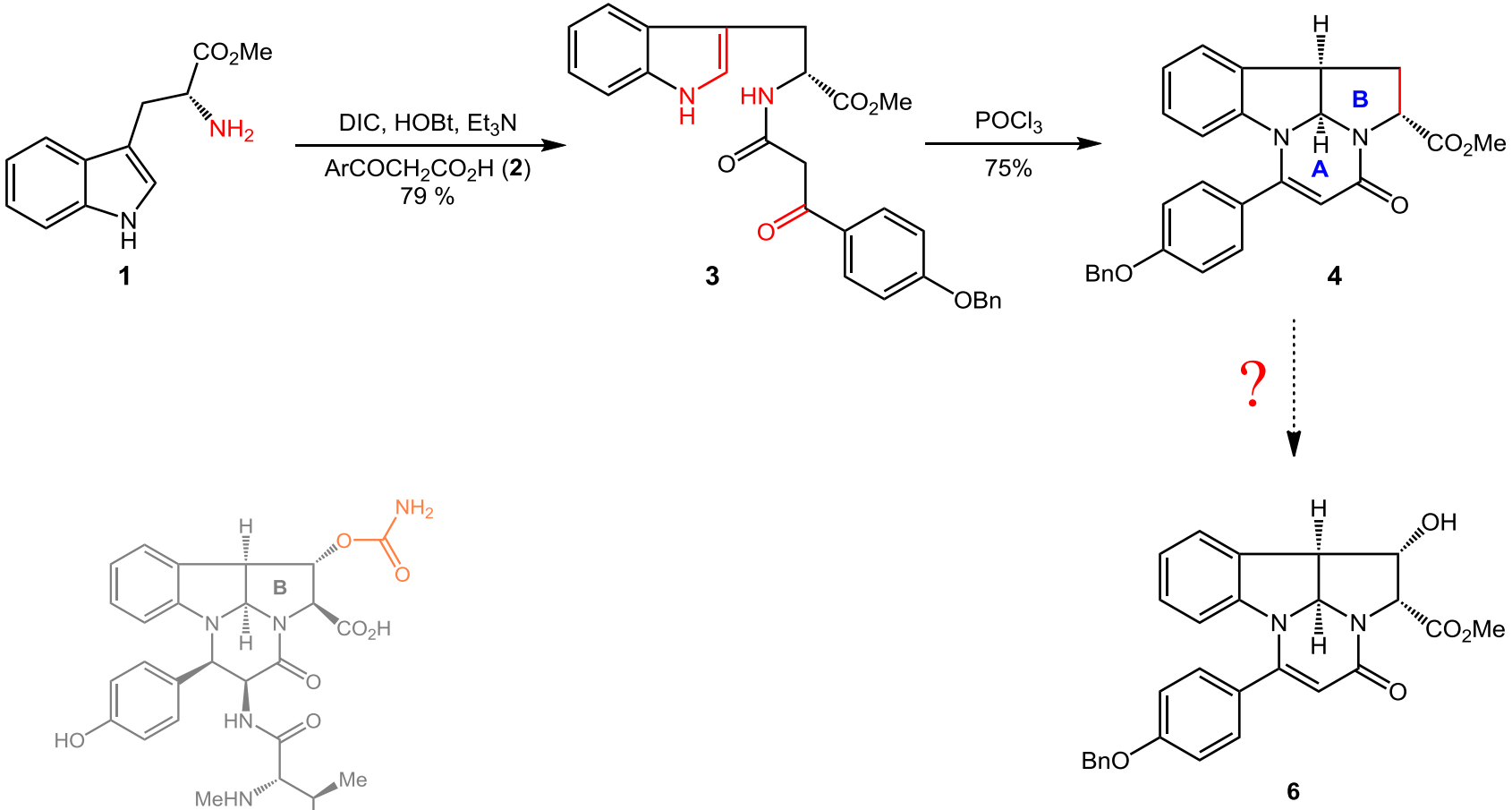


The Second Cyclization Strategy

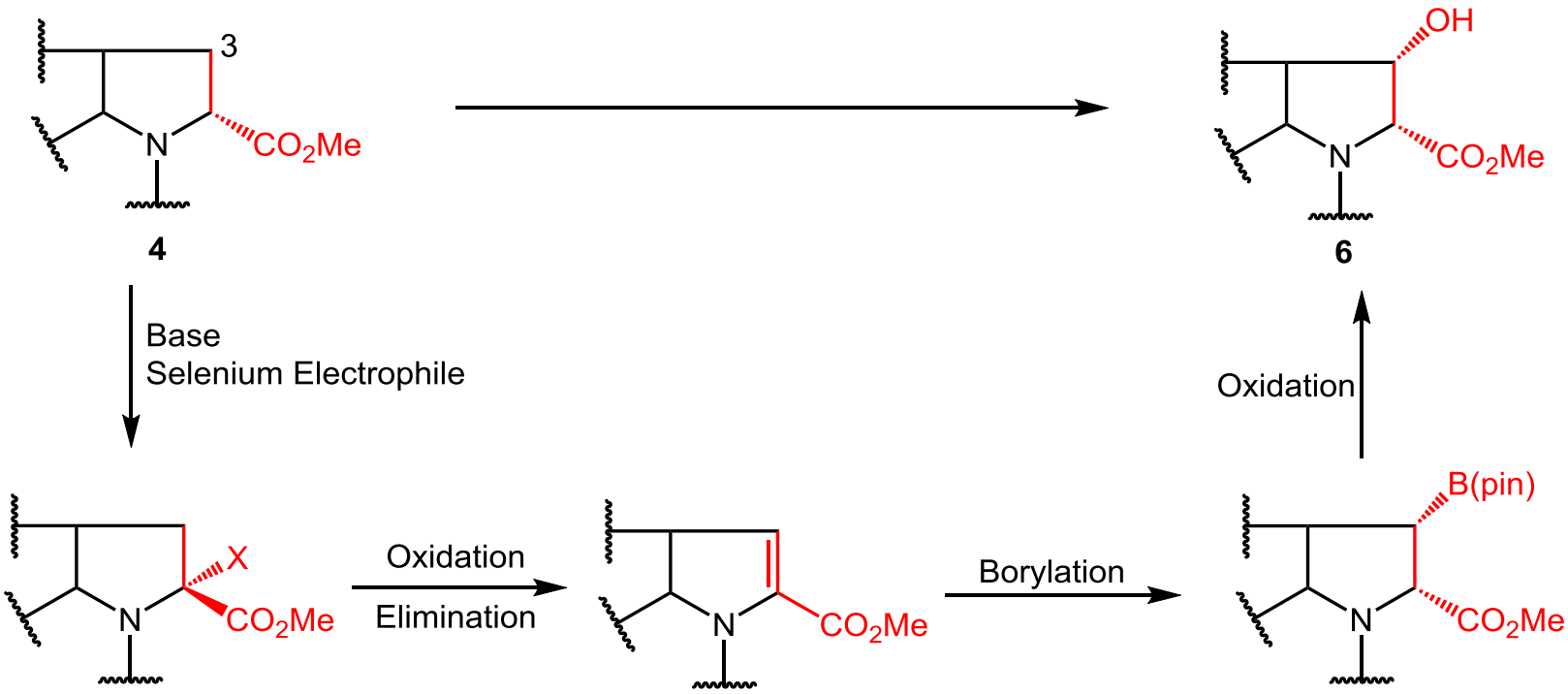


Wilkins, D. J.; Shannon P. V. R. *J. Chem. Soc. Perkin Trans. 1,* **1994**, 299

The Second Cyclization Strategy

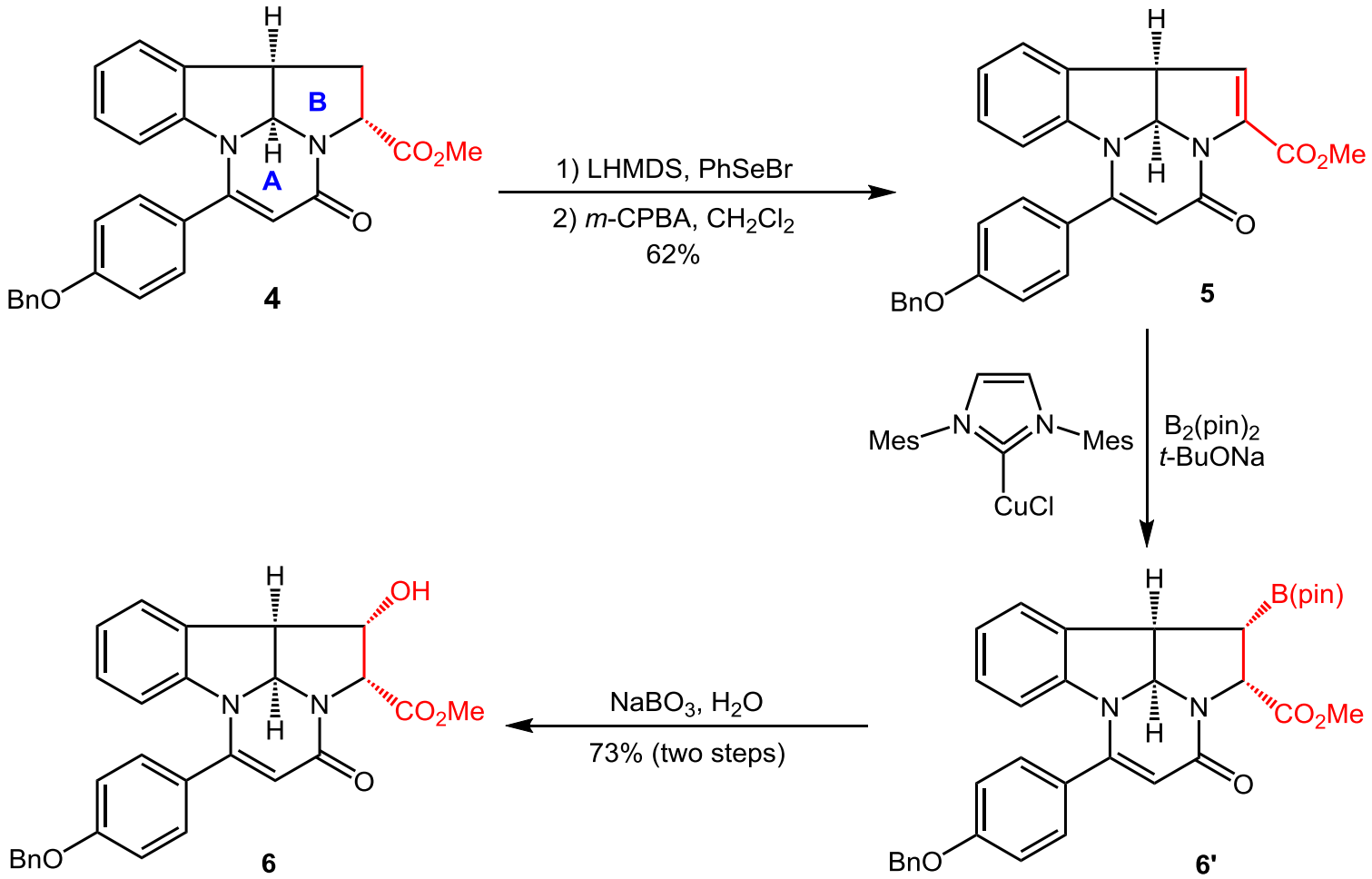


Introduction of Chiral Hydroxy Group

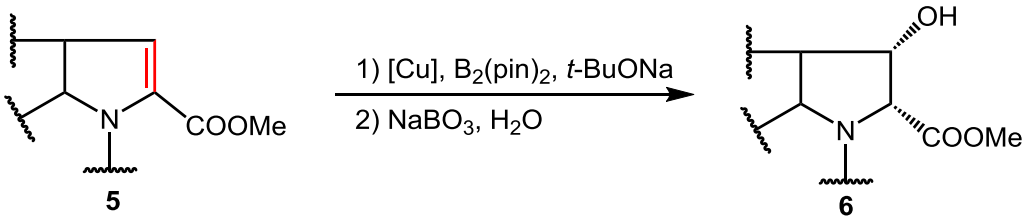


Lillo, V.; Prieto, A.; Fernández, E. *Organometallics,* **2009**, *28*, 659

The Second Cyclization Strategy



Michael Addition/Oxidation



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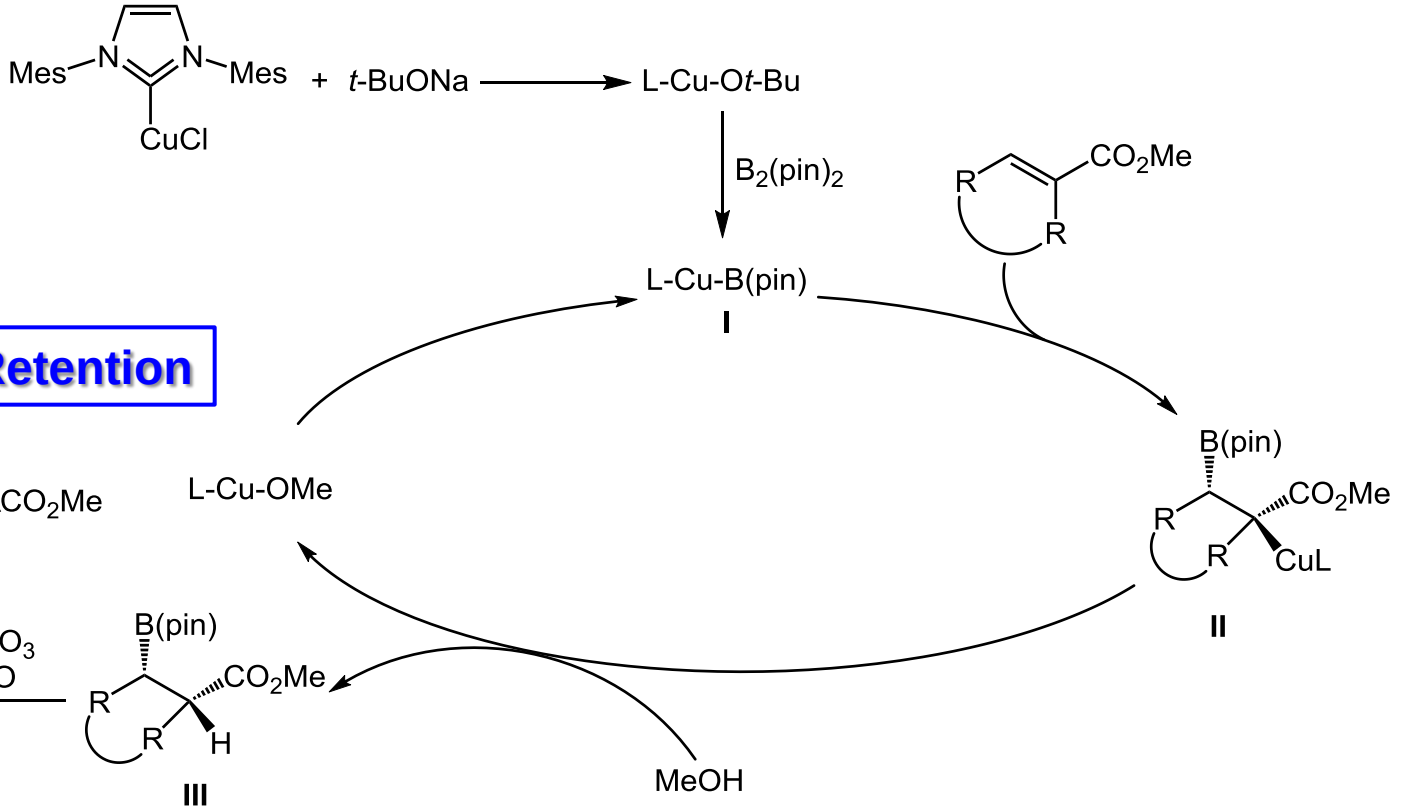
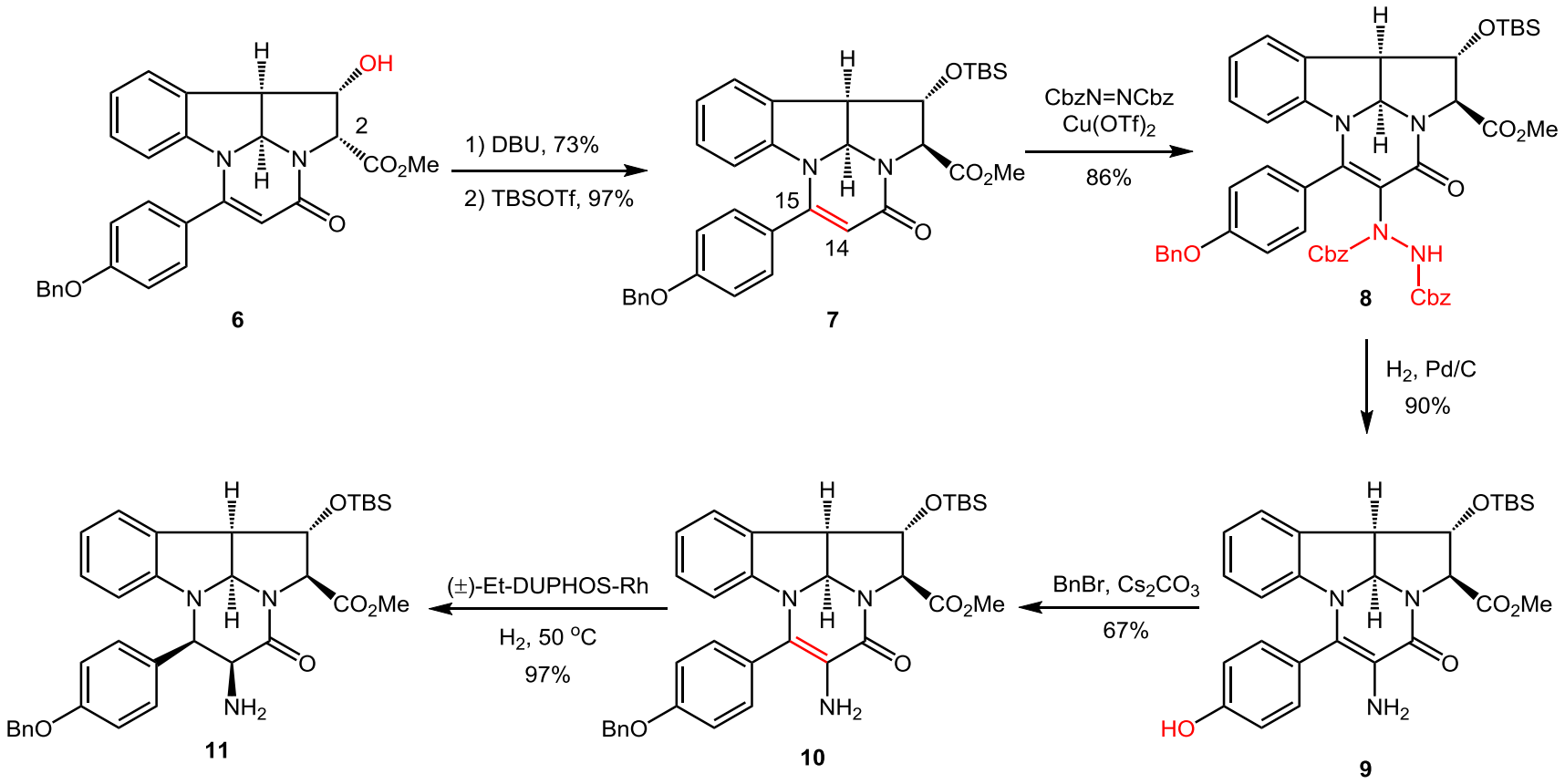
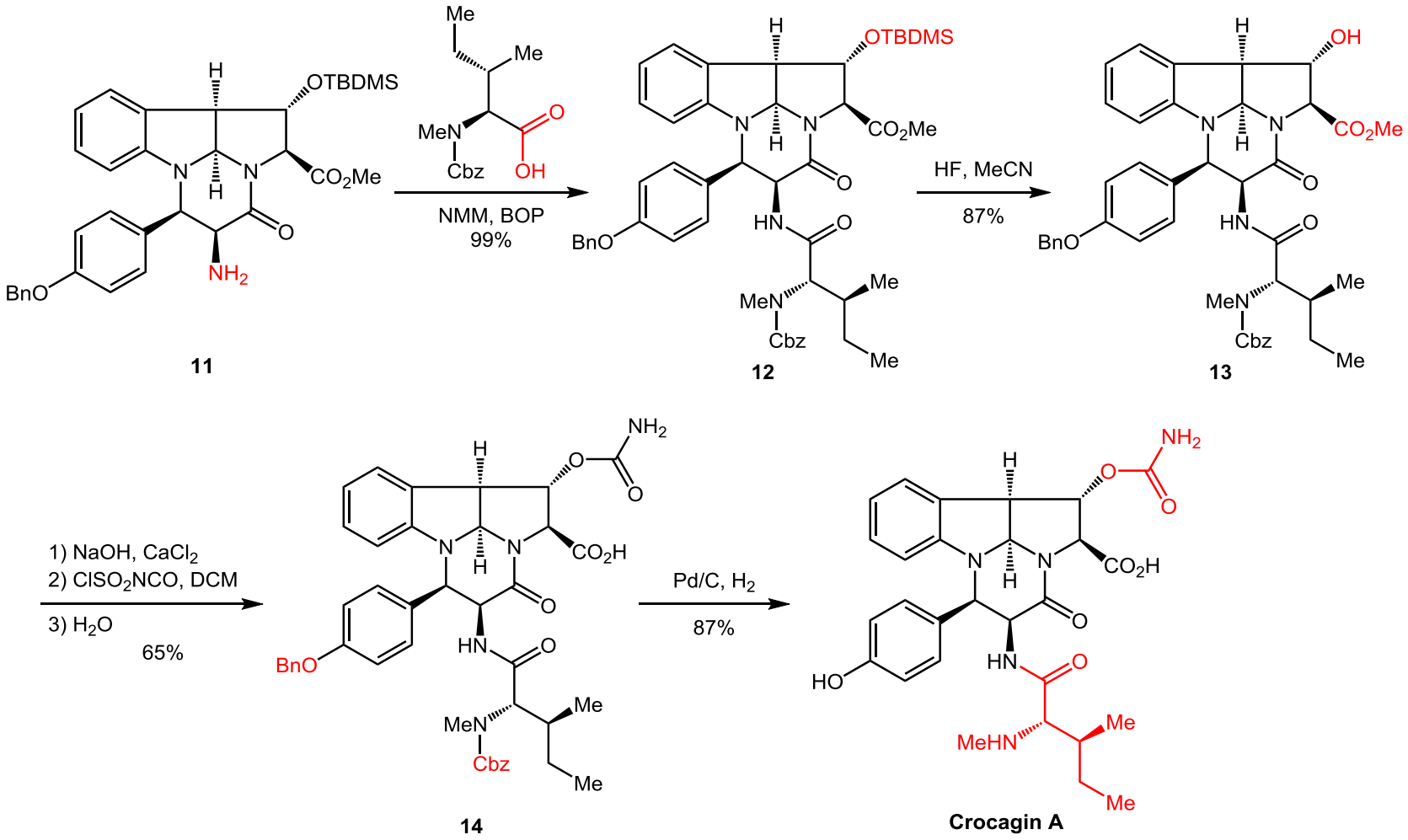


The Second Synthetic Strategy



Yamashita, Y.; Ishitani, H.; Kobayashi, S. *Can. J. Chem*. **2000**, *78*, 666

The Second Synthetic Strategy



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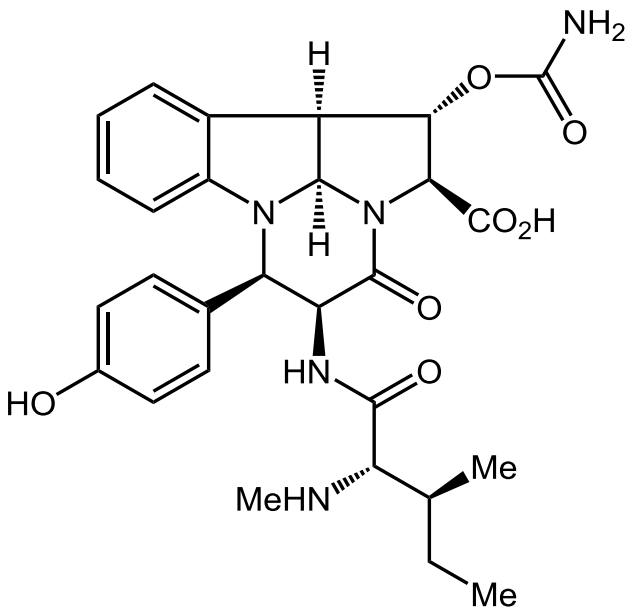
Summary



Crocagin A

- Stereoselective synthesis of Crocagin A
- 14 steps, 4.6% overall yield
- Pyrroloindole cyclization strategy
- Electrophilic amination strategy
- Stereoselective hydrogenation strategy

The Structure of First Paragraph

Crocagin A的生物来源

↓

Crocagin A的生源合成途径

↓

Crocagin A独特的分子结构

↓

提出该研究工作及其意义

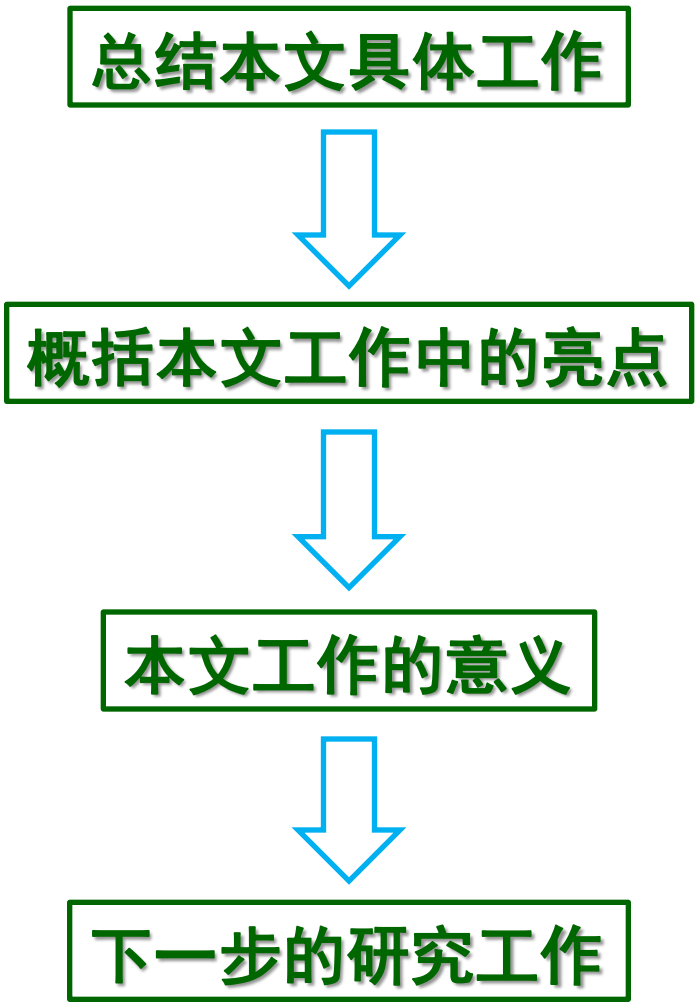
The First Paragraph

Ribosomally produced and post-translationally modified peptides account for some of the most complex small molecules found in nature. A very recent addition to this fascinating class is Crocagin A (**1**), which was isolated by Müller et al. from the myxobacterium Chondromyces crocatus, a prolific producer of biologically active metabolites. Crocagin A is unusual in several respects. Biosynthetically, it stems from the terminus of a precursor peptide, which undergoes cleavage, oxidation, and cyclization to yield the novel heterotricyclic system of **1**. Although its origin from a peptide cannot be denied, **1** also has features that are more characteristic of alkaloids. For instance, it contains a tetrahydropyrrolo[2,3-*b*]indoline moiety, which is quite common amongst these natural products, albeit rarely found with a bridgehead methine.

The First Paragraph

In the case of **1**, however, aromatization to an indole through elimination of an amide would yield a highly strained nine-membered lactam and is therefore unfavorable. Furthermore, all substituents on the heterotricyclic core of **1**, with the exception of a carbamoyl group at C(3), reside on its concave face. In combination with the novel skeleton, these features pose special challenges for synthesis and render Crocagin A a very attractive target. Herein, we report a short and stereoselective synthesis of **1** that confirms the relative and absolute configuration of the natural product and provides ample material for biological testing.

The Structure of Last Paragraph



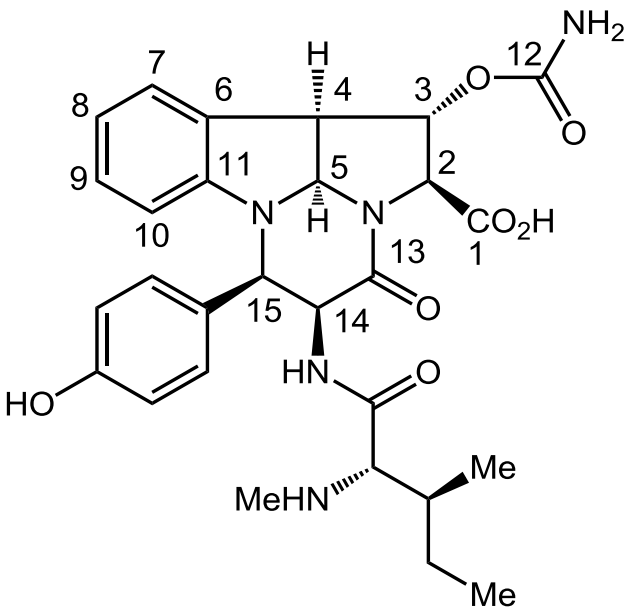
The Last Paragraph

In summary, we have achieved a concise and stereoselective synthesis of Crocagin A that incorporates several unusual steps. The hydrogenation of a tetrasubstituted double bond to yield a 1,2-diamino motif is particularly noteworthy. Our synthesis confirms the unusual structure of Crocagin A and can serve as a template for the design and procurement of numerous analogues and congeners, such as Crocagin B. It will also enable structure-activity studies of this fascinating natural product. Further synthetic attempts will be directed at photoaffinity labels and other chemical tools with which to identify the binding site of **1** on the carbon storage regulator CsrA and, potentially, additional biological targets.

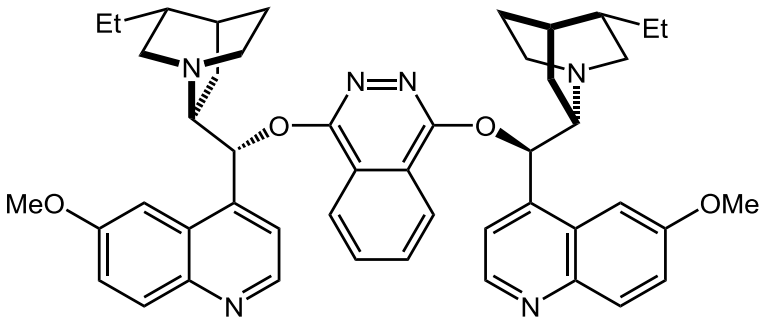
Acknowledgement

Thanks
for your kind attention !

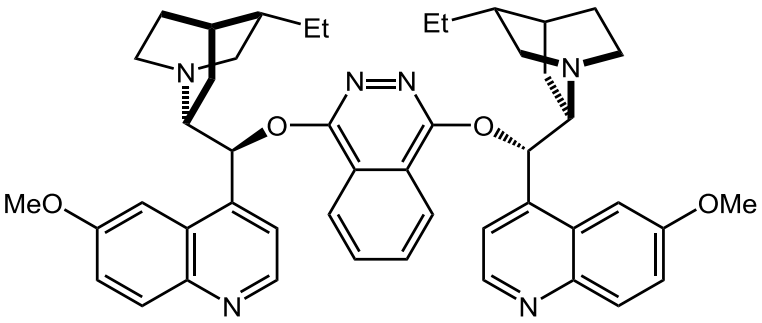
The Structure of Crocagin A



$(DHQ)_2PHAL$ and $(DHQD)_2PHAL$



$(DHQ)_2PHAL$



$(DHQD)_2PHAL$