Literature Report VIII

Total Synthesis of Isodaphlongamine H by Ir-Catalyzed Reductive [3 + 2] Cycloaddition of *N*-Hydroxylactam

Reporter: Bao-Qian Zhao
Checker: Qing-Xian Xie
Date: 2025-06-30

Iwamoto, S.; Nakano, R.; Sasaki, K.; Okamura, T.; Sato, T. *Angew. Chem., Int. Ed.* **2025***, 62,* e202508062

CV of Prof. Takaaki Sato (佐藤 孝明)

Research:

Natural Products Chemistry & Organic Synthesis & Development of New Synthetic Methodology

Background:

- ☐ **1997-2001** B.S., Tohoku University
- ☐ **2001-2006** Ph.D., Tohoku University
- ☐ **2006-2008** Postdoc., University of California, Irvine
- ☐ **2008-now** Assistant Professor, Professor, Keio University

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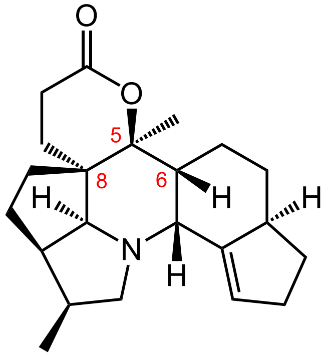
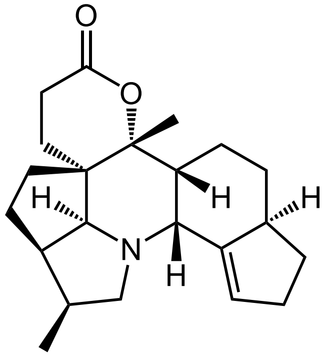


daphlongamine H **4**



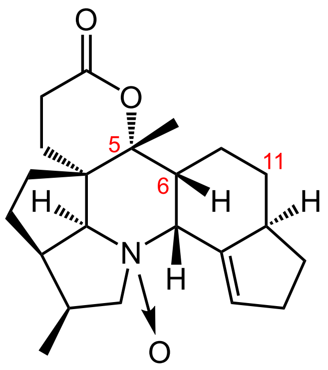
isodaphlongamine H **5**

- First isolated from the daphniphyllum longeracemosum by the Hao group in 2009
- A central piperidine moiety decorated with seven contiguous stereocenters
- Unique hexacyclic framework and exhibit antiproliferative effects

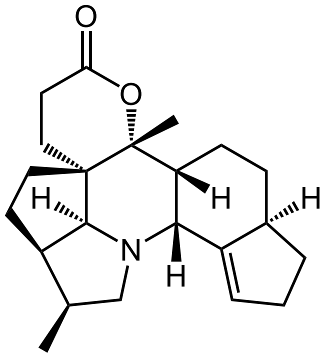
Li, C.-S.; Di, Y.-T.; Zhang, Q.; Hao, X.-J. *Helv. Chim. Acta* **2009**, *92*, 653

Introduction

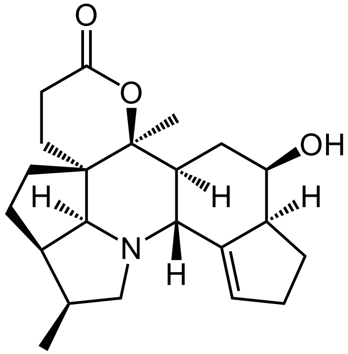
Representative Calyciphylline B-type Alkaloids



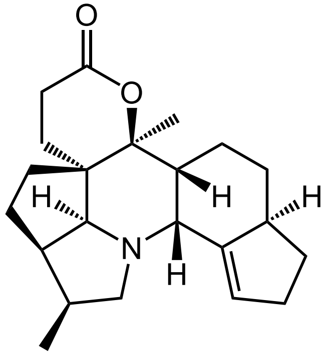
calyciphylline B **1**



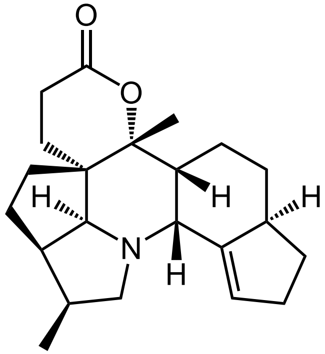
deoxycalyciphylline B **2**



oldhamiphylline A **3**



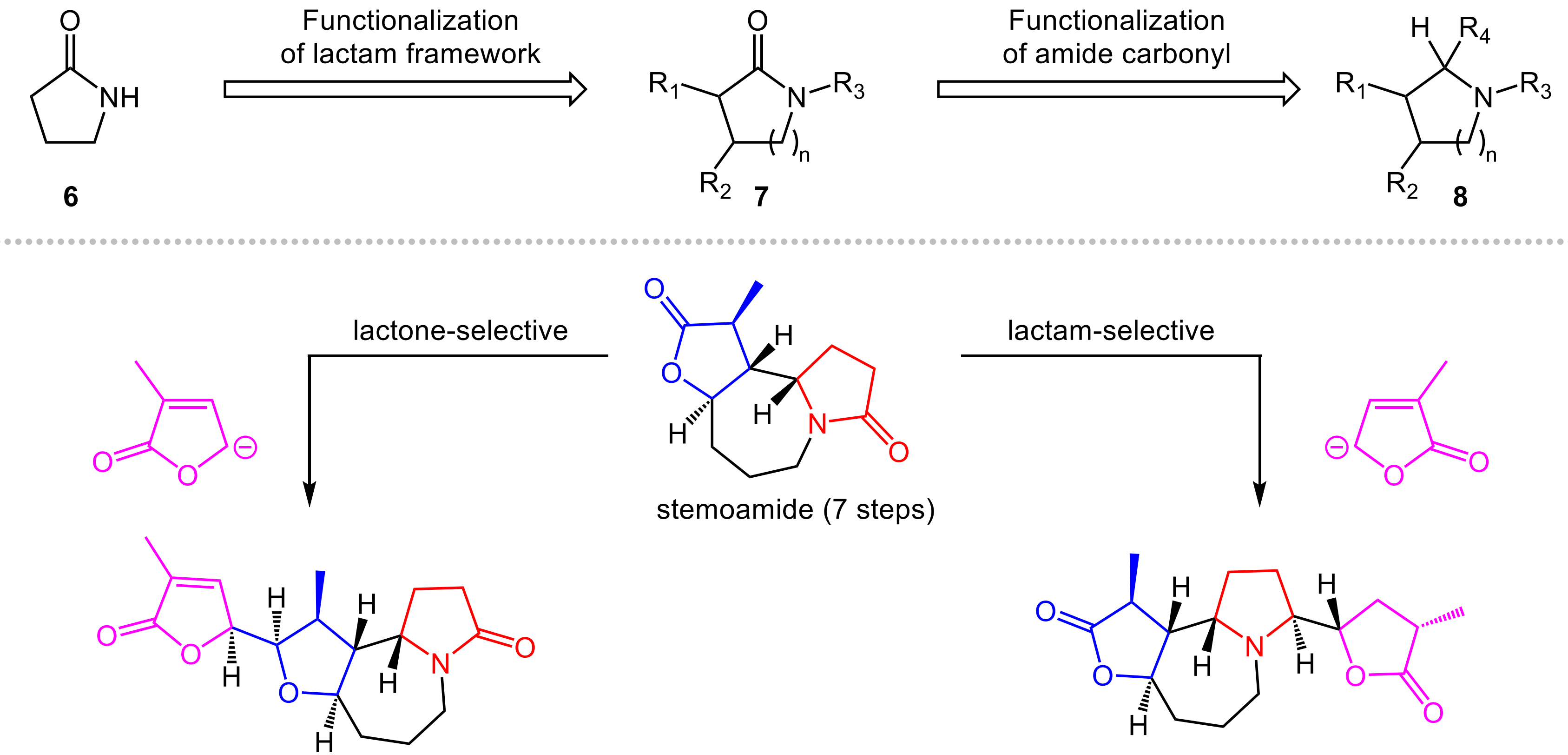
daphlongamine H **4**



isodaphlongamine H **5**
unnatural

Introduction

Lactam Strategy for Synthesis of Complex Alkaloids



Functionalization of lactam framework

Functionalization of amide carbonyl

6 **7** **8**

lactone-selective

lactam-selective

stemoamide (7 steps)

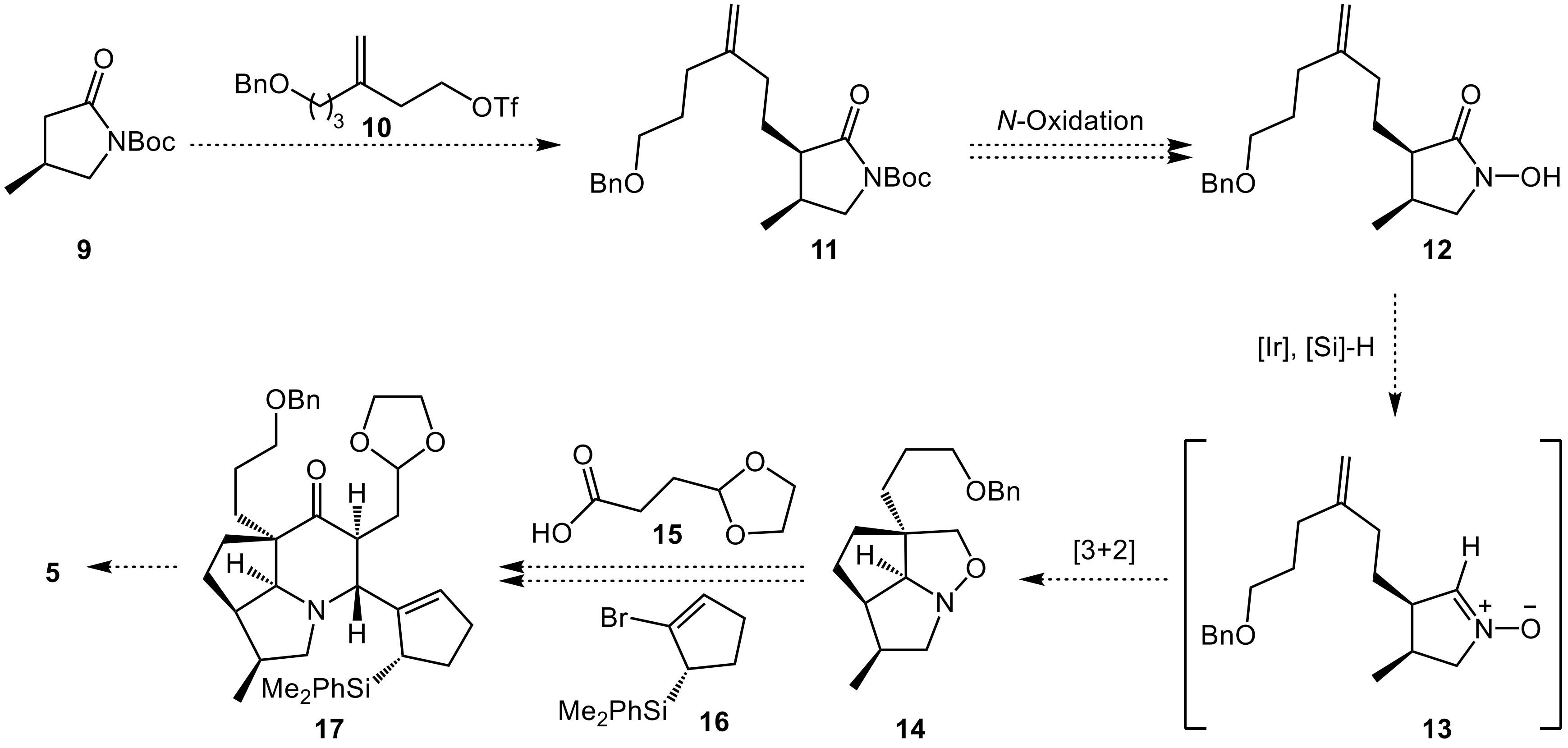
saxorumamide (11 steps)

stemonine (9 steps)

Yoritate, M.; Takahashi, Y.; Tajima, H.; Sato, T.; Chida, N. *J. Am. Chem. Soc.* **2017**, *139*, 18386

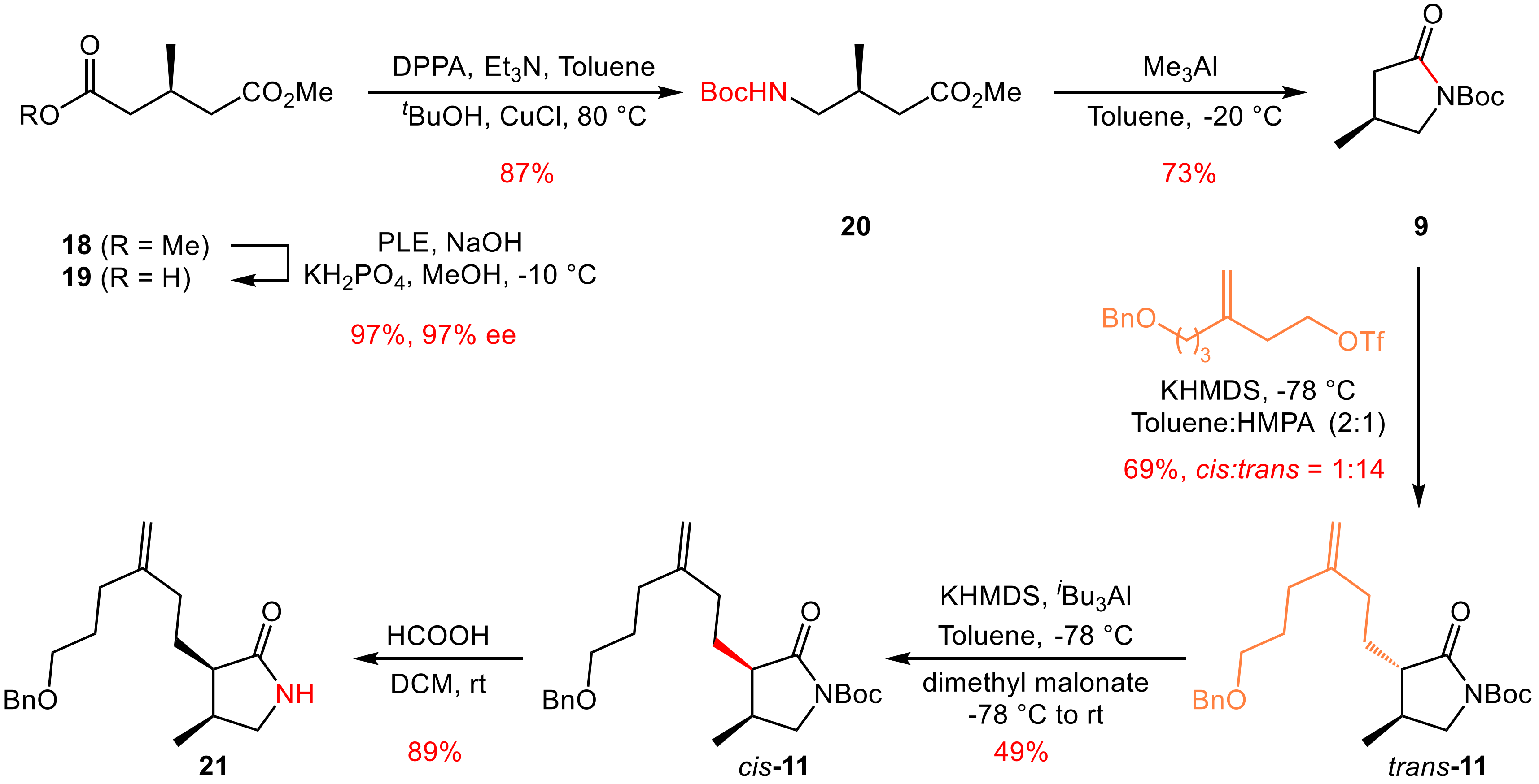
Introduction

Synthetic Plan to Calyciphylline B-type Alkaloids



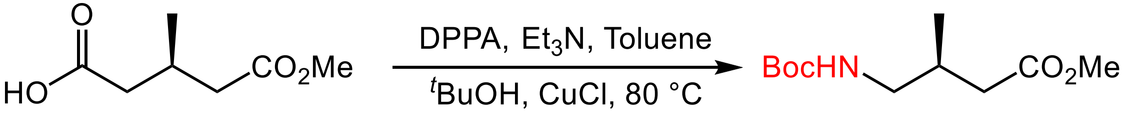
Synthetic Chiral Blocks

Synthesis of Chiral *cis*-Lactam 21

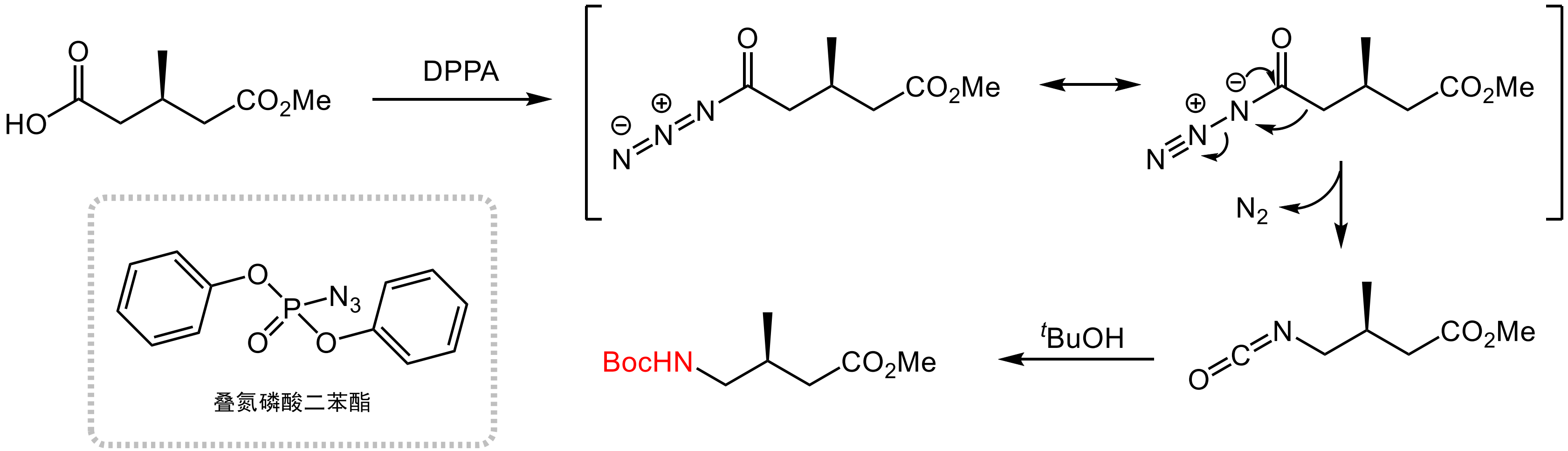


Curtius Rearrangement

Curtius Rearrangement



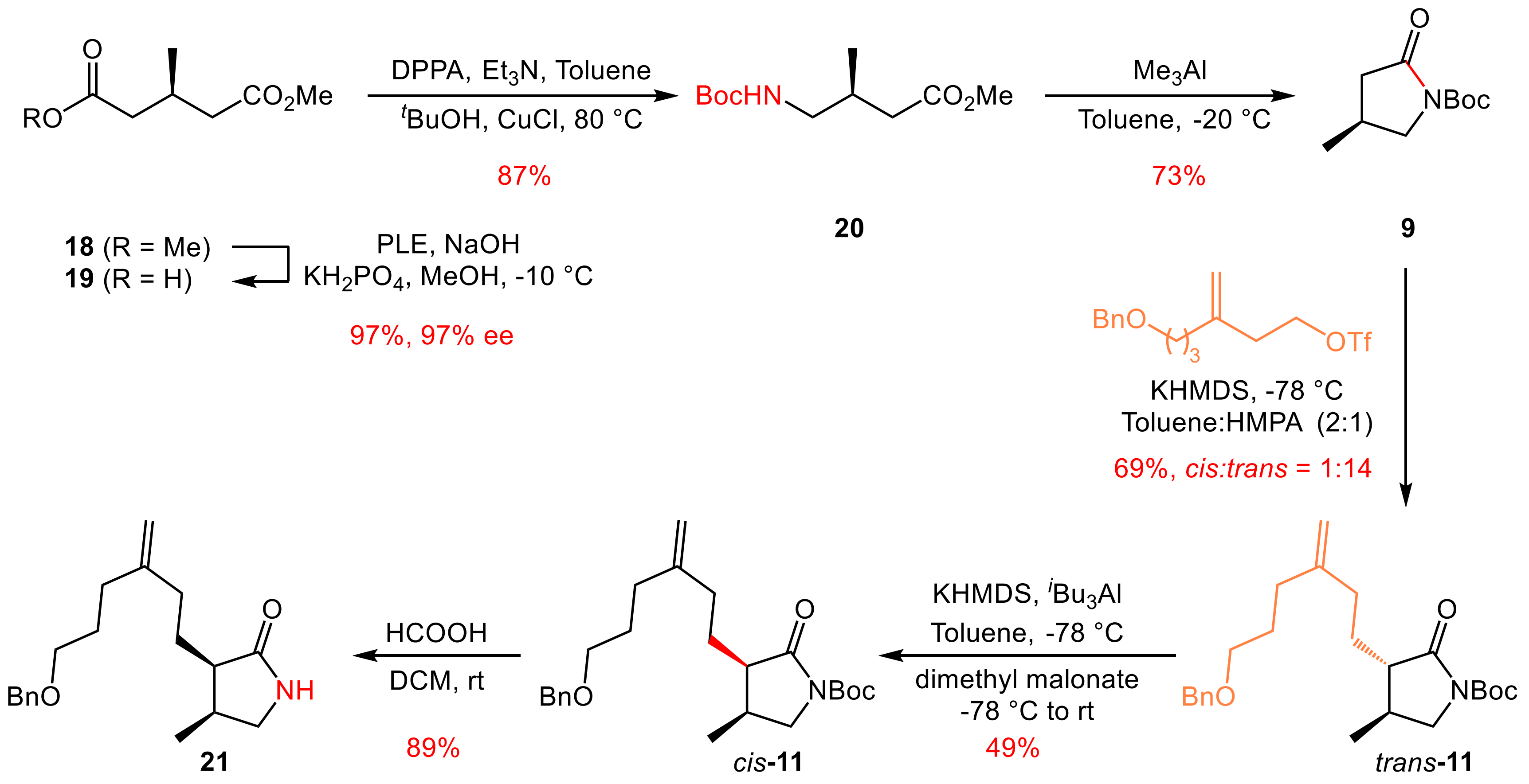
19 87% **20**



叠氮磷酸二苯酯

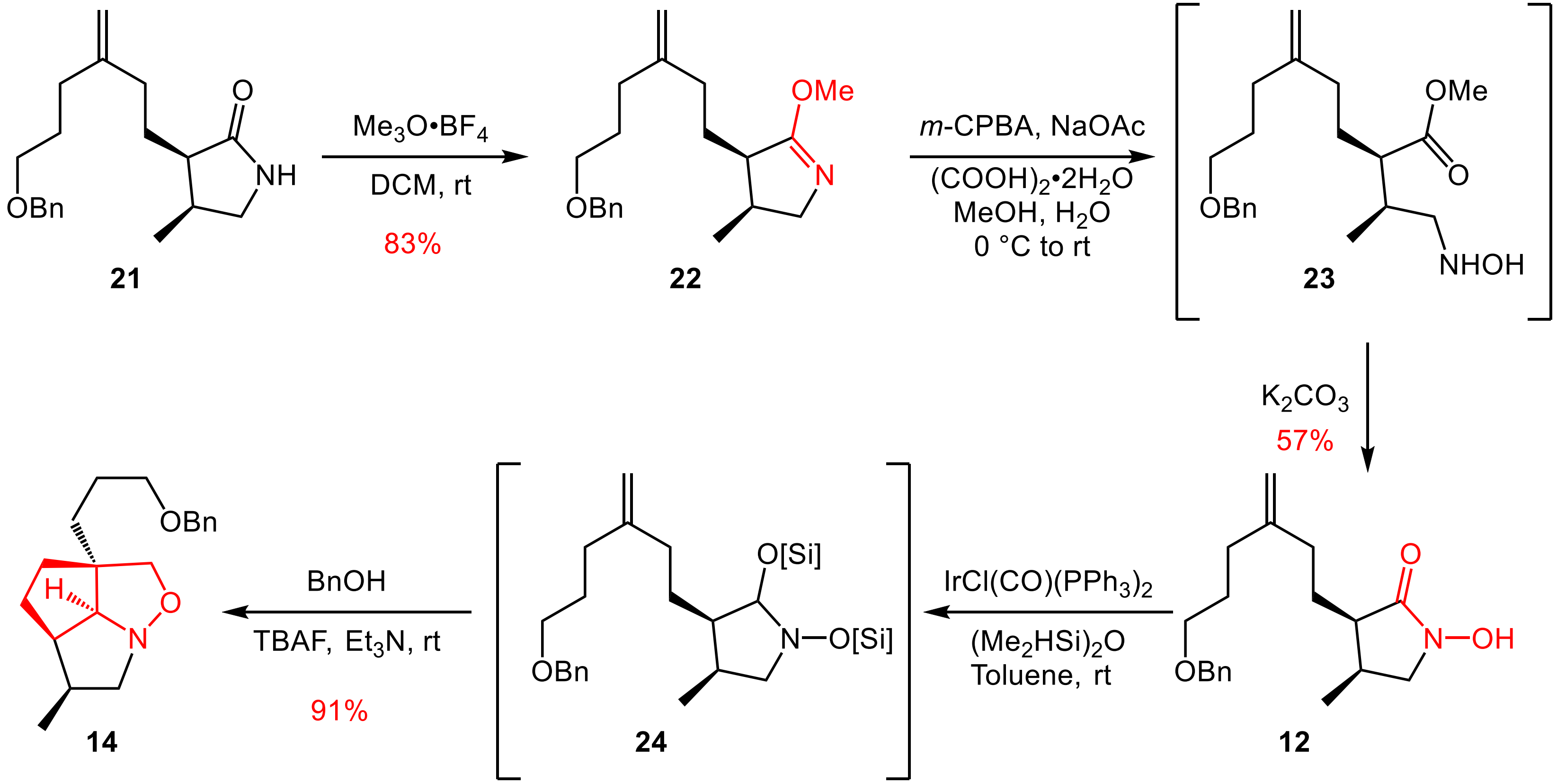
Synthetic Chiral Blocks

Synthesis of Chiral *cis*-Lactam 21



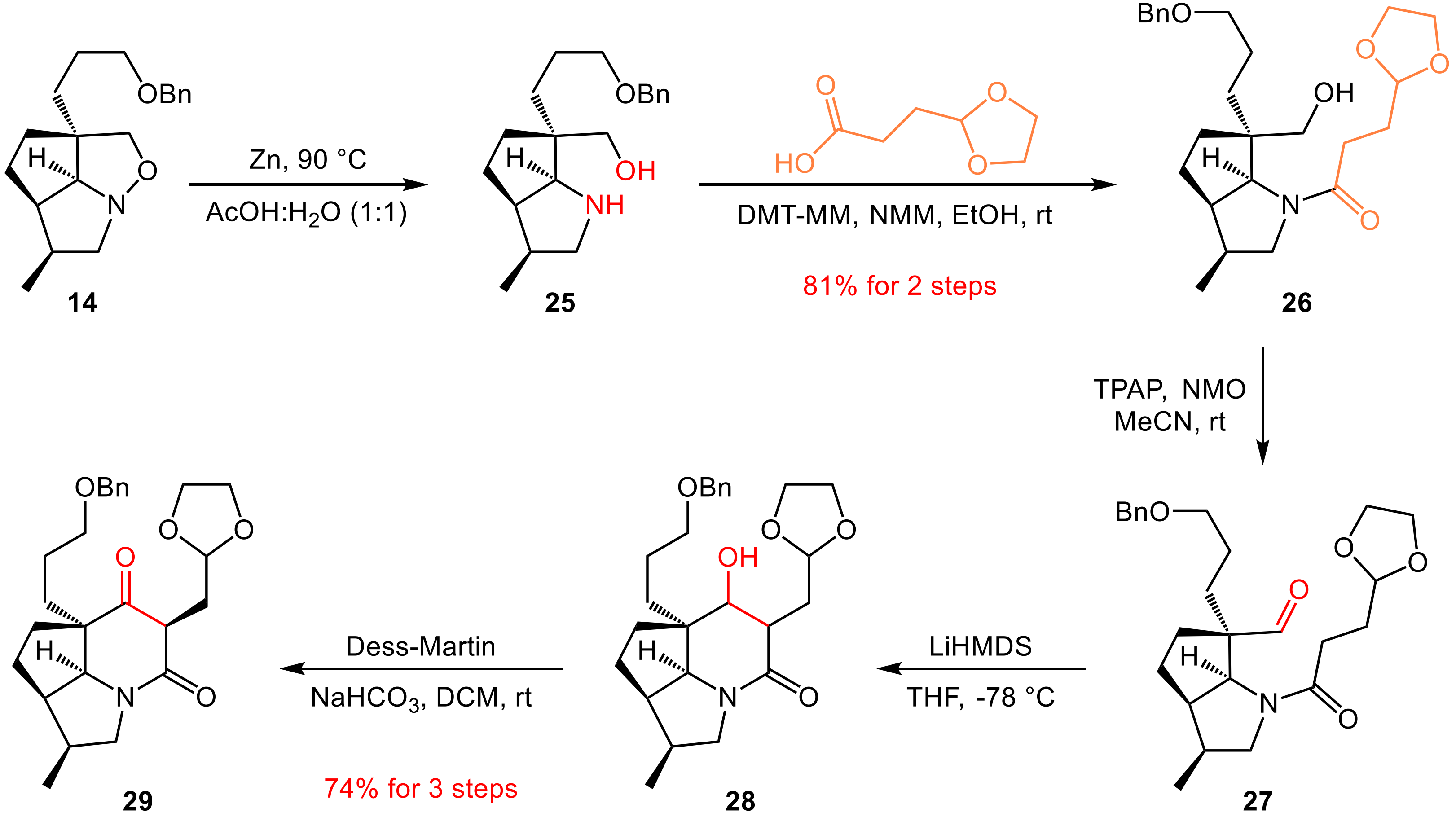
Synthetic Chiral Blocks

N-oxidation of Chiral Secondary Lactam 21



Synthesis of Cyclic β-Ketoamide

Synthesis of Cyclic β-ketoamide 29



Zn, 90 °C

AcOH:H_2O (1:1)

DMT-MM, NMM, EtOH, rt

81% for 2 steps

TPAP, NMO
MeCN, rt

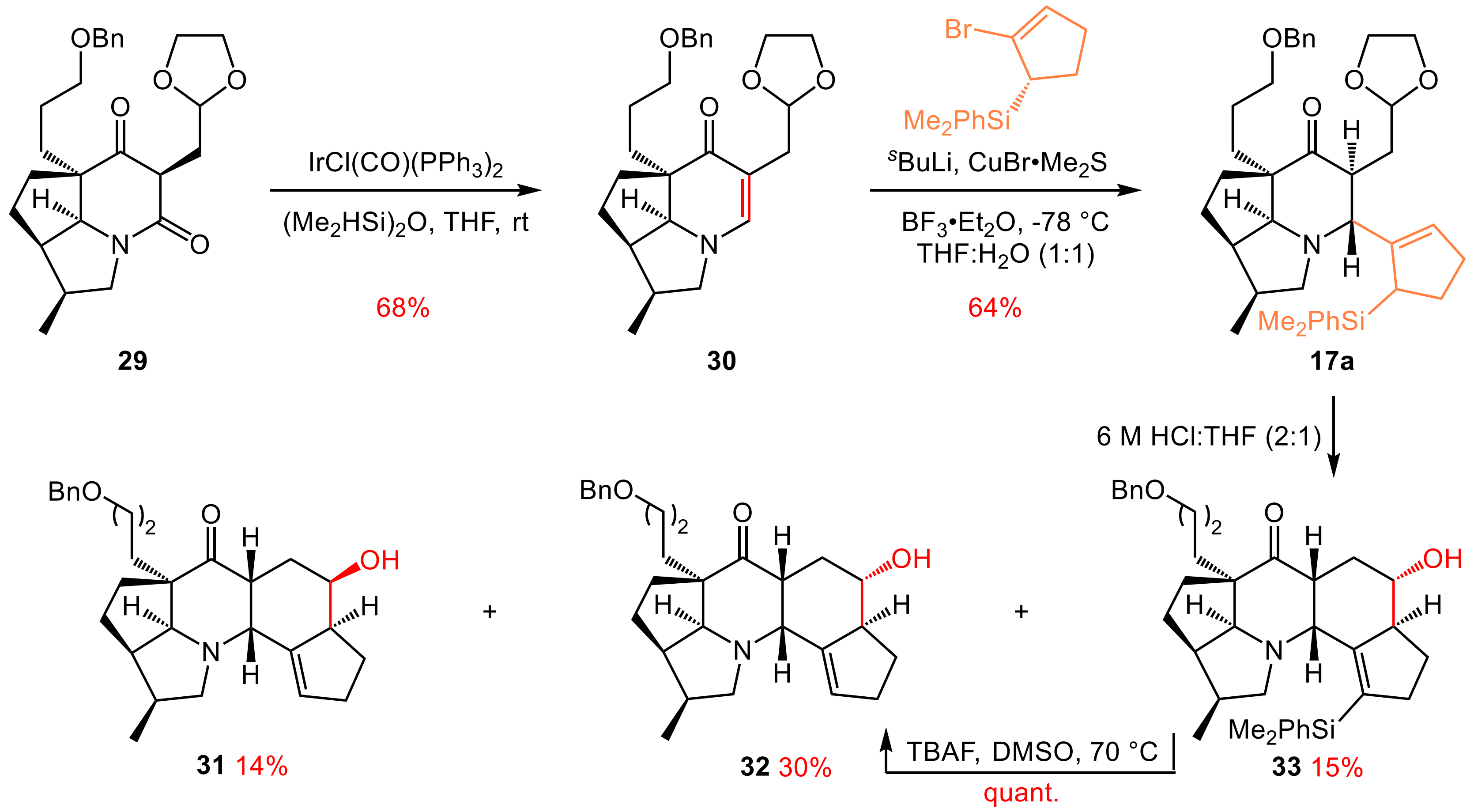
LiHMDS
THF, -78 °C

Dess-Martin
$NaHCO_3$, DCM, rt

74% for 3 steps

Intramolecular Hosomi–Sakurai Allylation

Intramolecular Hosomi–Sakurai Allylation of 17α



29 → **30**: $IrCl(CO)(PPh_3)_2$, $(Me_2HSi)_2O$, THF, rt, 68%

30 → **17a**: Br, Me_2PhSi cyclopentene, ${}^{s}BuLi$, $CuBr•Me_2S$, $BF_3•Et_2O$, -78 °C, $THF:H_2O$ (1:1), 64%

17a → **31** + **32** + **33**: 6 M HCl:THF (2:1)

31 14%

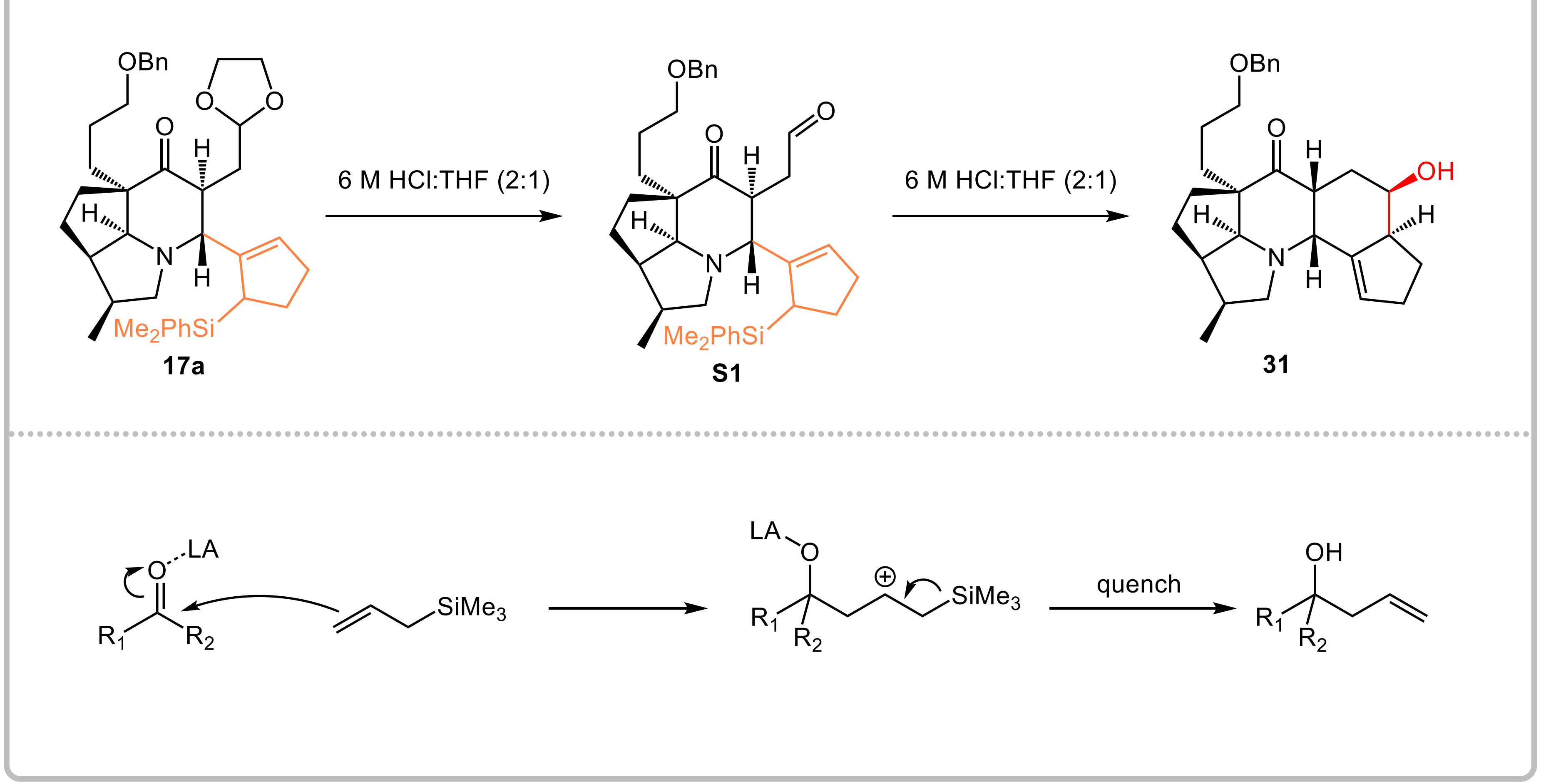
32 30%

33 15%

33 → **32**: TBAF, DMSO, 70 °C, quant.

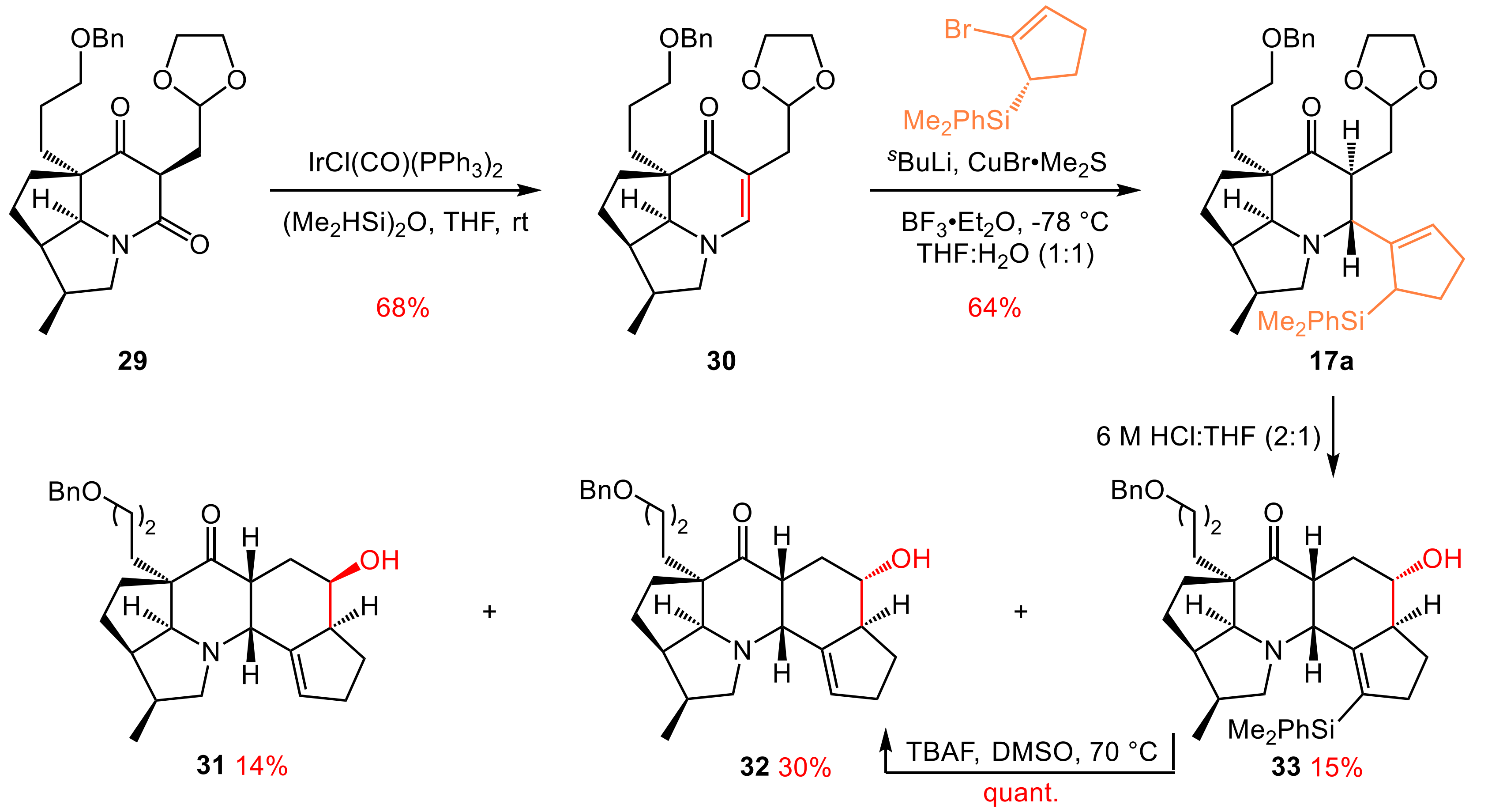
Hosomi–Sakurai Allylation

Hosomi-Sakurai Allylation



Intramolecular Hosomi–Sakurai Allylation

Intramolecular Hosomi–Sakurai Allylation of 17α



29

$IrCl(CO)(PPh_3)_2$

$(Me_2HSi)_2O$, THF, rt

68%

30

Me_2PhSi

$^{s}BuLi$, $CuBr{\bullet}Me_2S$

$BF_3{\bullet}Et_2O$, -78 °C

$THF:H_2O$ (1:1)

64%

17a

6 M HCl:THF (2:1)

31 14%

+

32 30%

+

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TBAF, DMSO, 70 °C

quant.

Total Synthesis of Isodaphlongamine H

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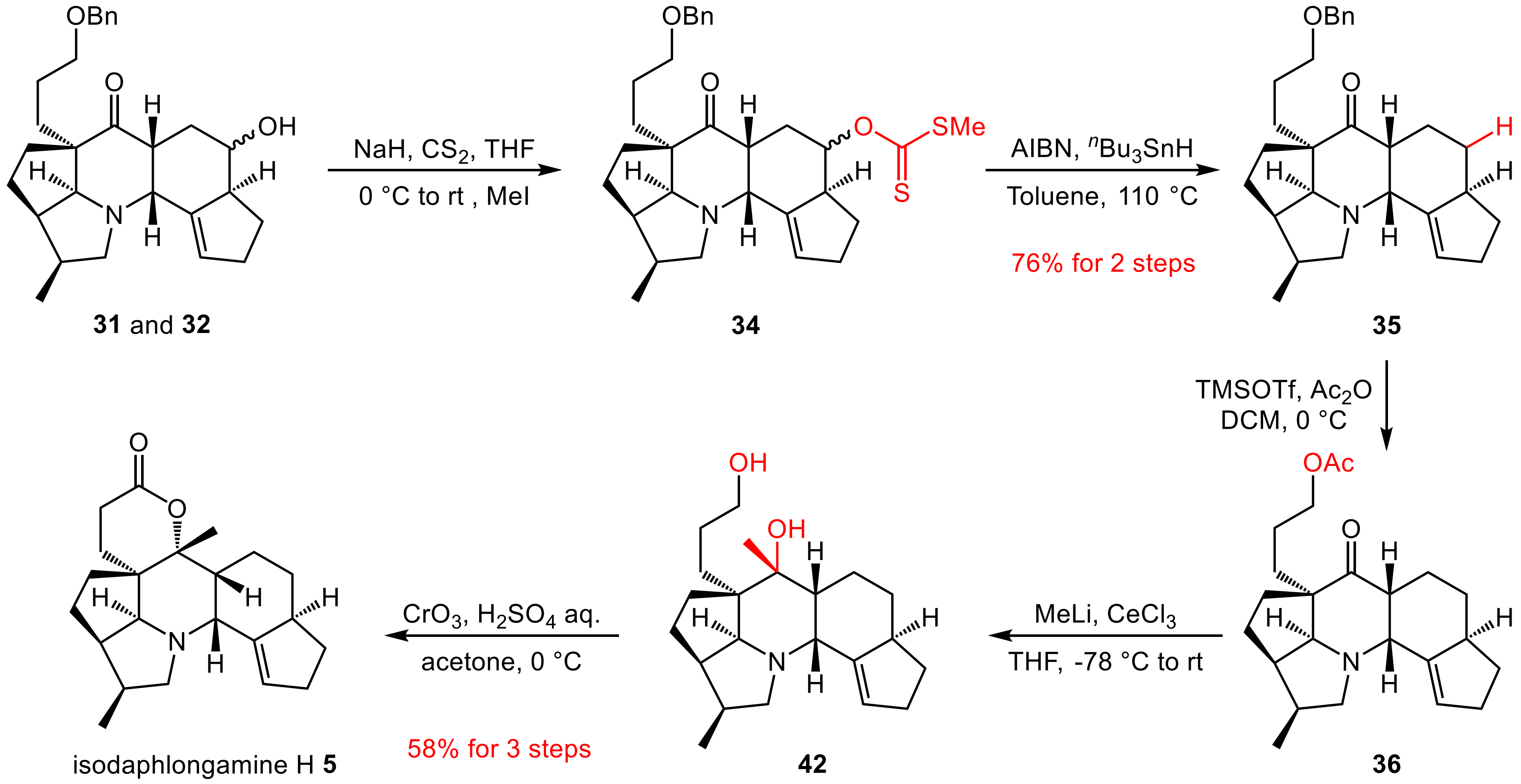
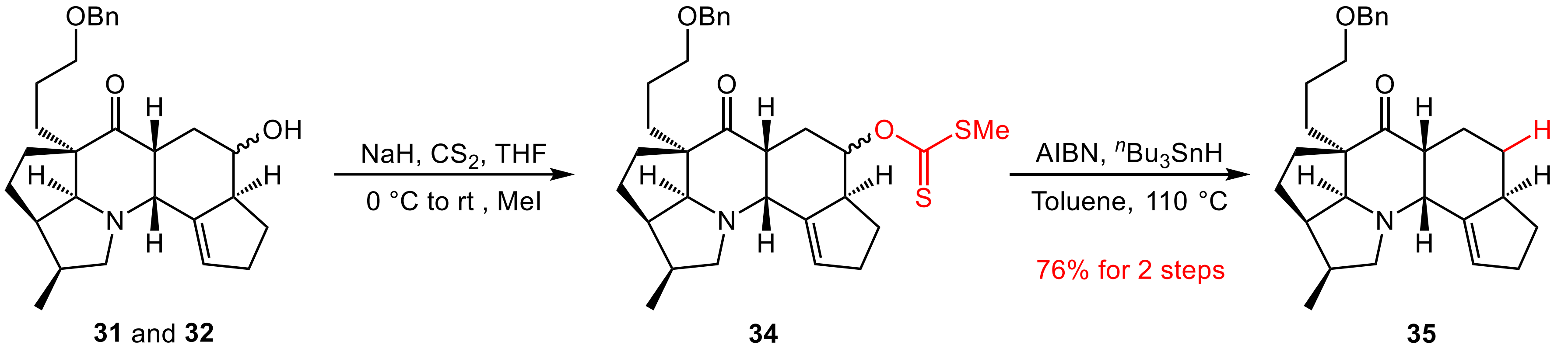
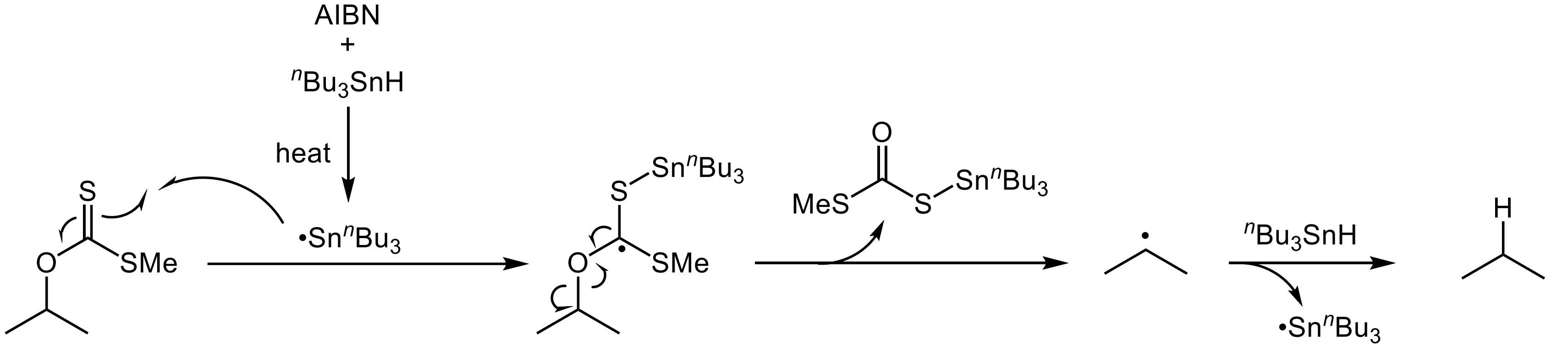


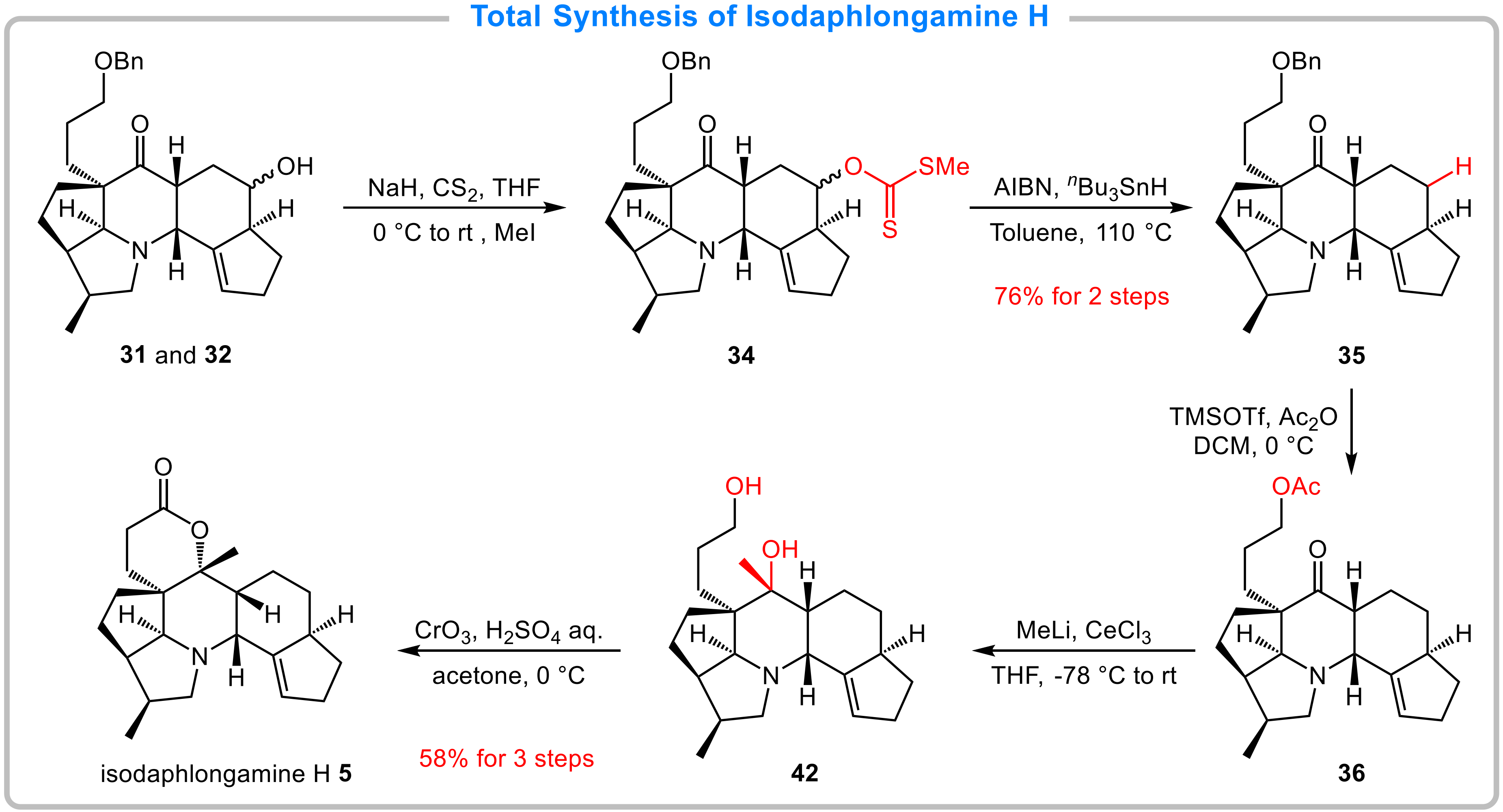
Barton-Mccombie Deoxygenation

Barton-McCombie Deoxygenation



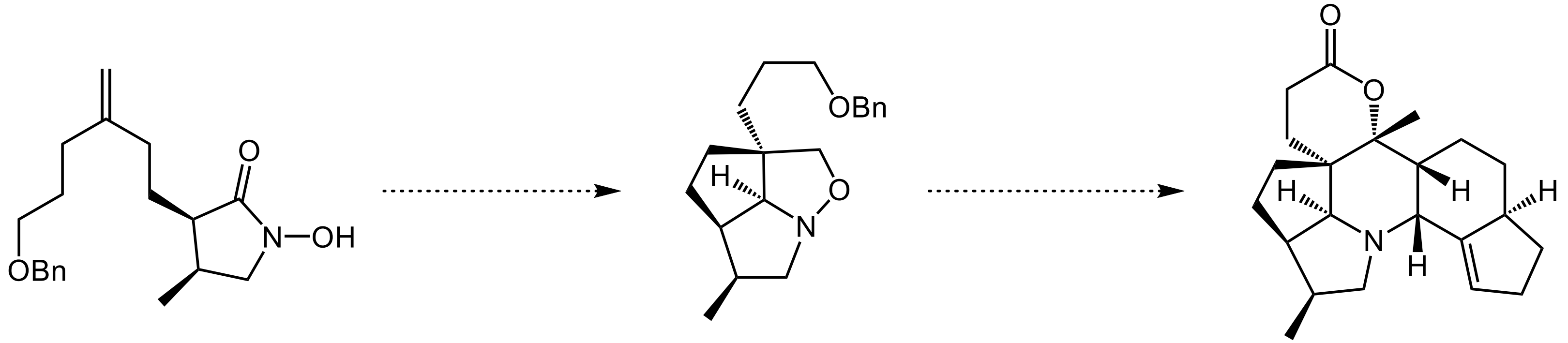


Total Synthesis of Isodaphlongamine H



Summary

Summary



isodaphlongamine H **5**

- Ir-catalyzed reductive [3 + 2] cycloaddition of the N-hydroxylactam
- Intramolecular Hosomi–Sakurai allylation constructed a pentacyclic framework
- Utility of the lactam strategy in the total synthesis of complex alkaloids

Writing Strategies

☐ The First Paragraph

The Importance of Daphniphyllum Alkaloids

- ✓ The Daphniphyllum alkaloids are one of the largest families belonging to the genus of Daphniphyllaceae, and consist of over 300 polyazacyclic natural products. The large family of these alkaloids is further divided into fourteen classes. Their diverse structures have encouraged extensive investigation of their biosynthesis, total synthesis, and biological activities.

Previous Work

- ✓ In 2003, the Kobayashi group reported isolation of calyciphylline B (**1**) as a new class of the Daphniphyllum alkaloids from the leaves of Daphniphyllum calycnum.

Main Content of This Work

- ✓ An overarching objective of our research group is the development of a general synthetic strategy for biologically active complex alkaloids.

Writing Strategies

☐ The Last Paragraph

Summary
of This Work

- ✓ The present synthesis of isodaphlongamine H (**5**) by the lactam strategy was accomplished in 23 steps with 0.8% total yield from commercially available diester **18**.

Highlights of
the Current Method

- ✓ The key transformation in the lactam strategy was iridium-catalyzed reductive [3 + 2] cycloaddition of the N-hydroxylactam. A sequence including N-oxidation and iridium-catalyzed reduction proved to be useful for the synthesis of chiral cyclic nitrones, which are not quickly accessible by other conventional methods. After Michael addition of an allylic silane fragment, intramolecular Hosomi–Sakurai allylation constructed a pentacyclic framework accompanied by epimerization at the C6 carbon center.

Outlook
of This Work

- ✓ We expect that the deoxygenated pentacyclic intermediate could become a lead compound for further biological study.

Representative Examples

- ✓ Considering the cis-junction of rings B and C in **27**, it is not surprising that the **trajectory** (**轨迹**) of approach of the MeLi reagent toward the carbonyl group favored the less hindered α-face.
- ✓ Considering the proposed biosynthetic pathway, it is **intriguing** (**有趣的是**) that intermediate A would preferentially give the tetrasubstituted intermediate olefin B…then to cyclize to deoxycalyciphylline B (**2**) and deoxyisocalyciphylline B (**3**).
- ✓ In contrast, the C6 stereocenter **underwent** （**经历**） the complete epimerization, resulting in the cis-configuration between C6 and C7.

Acknowledgment

Thanks for your attention !