

# Literature Report

## Total Synthesis of Pyrroloazocine Indole Alkaloids Sheds Light on Their Biosynthetic Relationship

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Reporter: Chang-Bin Yu

Checker: Shu-Bo Hu

May 14, 2018



Miloserdov, F. M.; Echavarren, A. M. *et al.* *J. Am. Chem. Soc.* **2018**, *140*, 5393

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# CV of Prof. Antonio M. Echavarren

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1977 MS Universidad Autónoma de Madrid (UAM)

1982 Ph.D Universidad Autónoma de Madrid (UAM)

1992-2009 Professor UAM (1992-2009)

2004-now Institute of Chemical Research of Catalonia

**Prof. Echavarren, A. M**

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**Research Fields:**

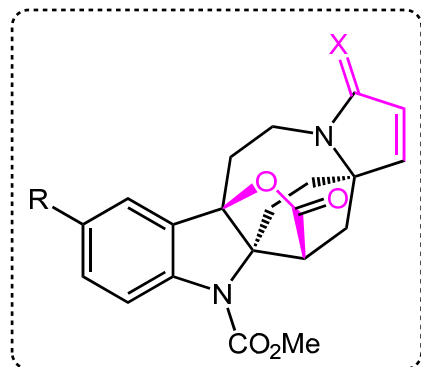
1. Organic Synthesis
2. Organometallic Chemistry

# Contents

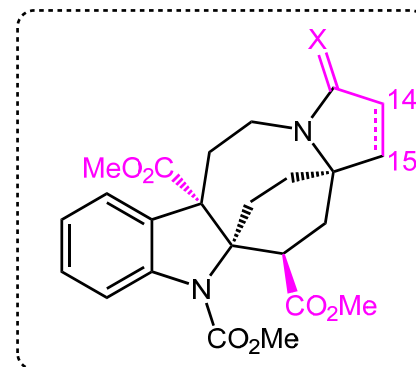
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- ◆ **Introduction**
- ◆ **Total Synthesis of (+)-Grandilodine & (+)-Lapidilectine**
- ◆ **Total Synthesis of Pyrroloazocine Indole Alkaloids**
- ◆ **Summary**

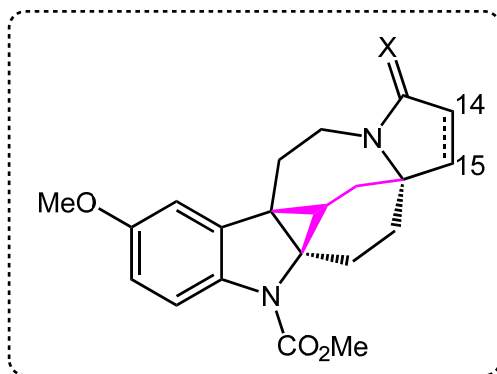
# Pyrroloazocine Indole Alkaloids



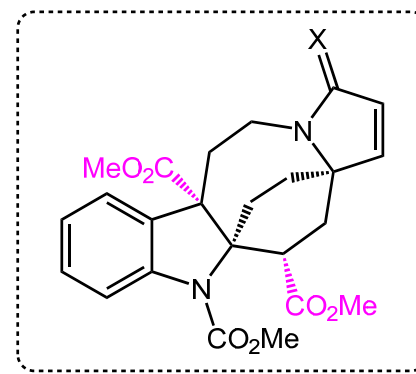
- (+)-Lapidilectine B R = H, X = H<sub>2</sub>
- (+)-Grandilodine C R = H, X = O
- (+)-Tenuisine A R = OMe, X = H<sub>2</sub>
- (+)-Tenuisine C R = OMe, X = O



- (-)-Lapidilectine A  $\Delta^{14,15}$ , X = H<sub>2</sub>
- (-)-Lapidilectam  $\Delta^{14,15}$ , X = O
- (-)-Grandilodine A X = H<sub>2</sub>

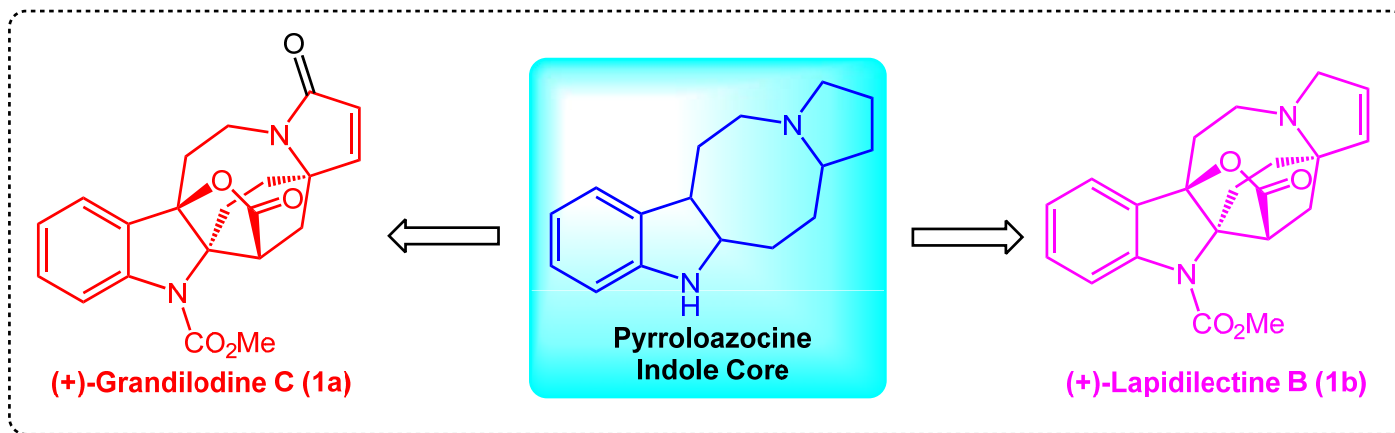


- (-)-Lundurine A  $\Delta^{14,15}$ , X = O
- (-)-Lundurine B  $\Delta^{14,15}$ , X = H<sub>2</sub>



- (+)-Isolapidilectine A X = H<sub>2</sub>
- (+)-Grandilodine B X = O

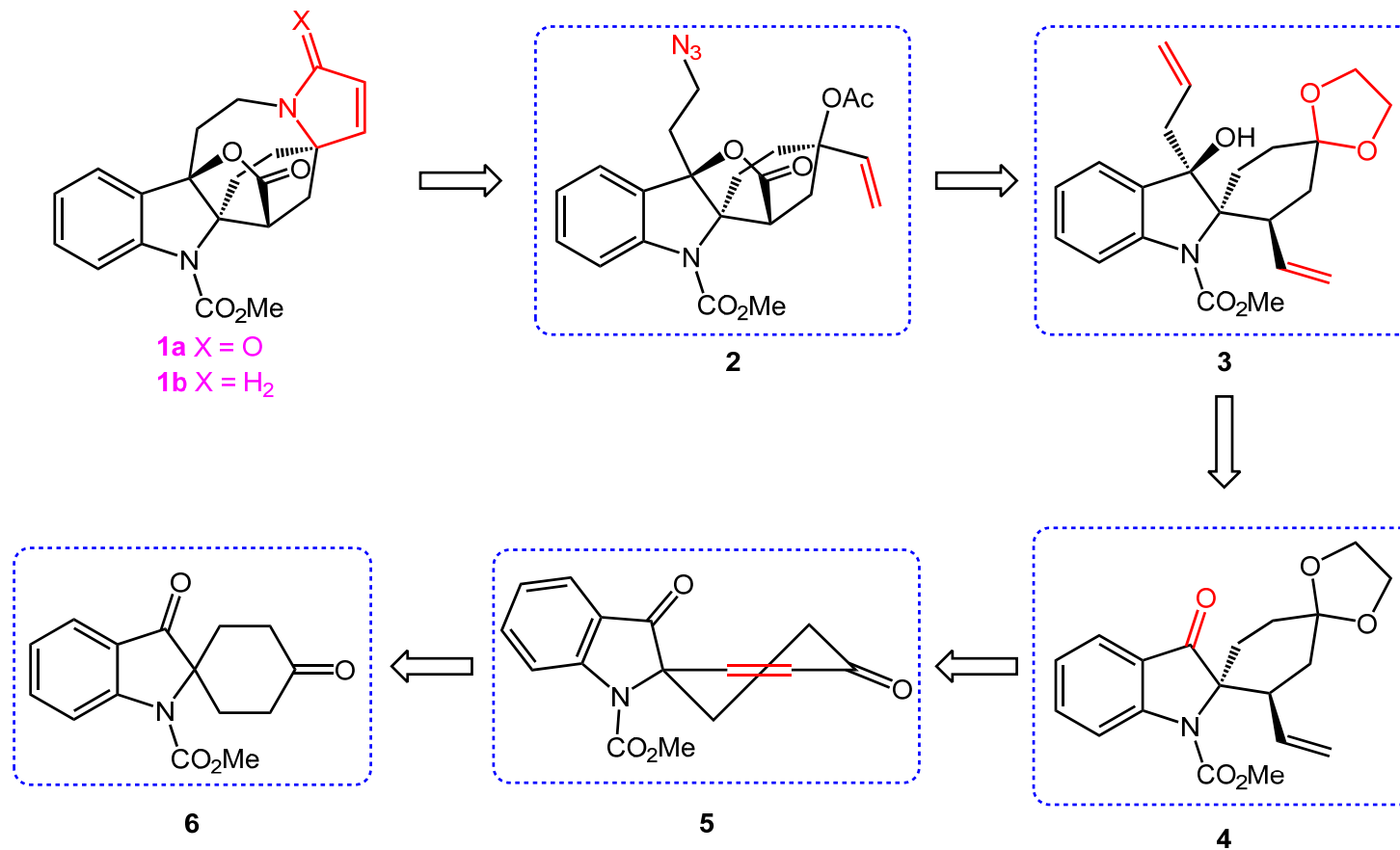
# (+)-Grandilodine C and (+)-Lapidilectine B



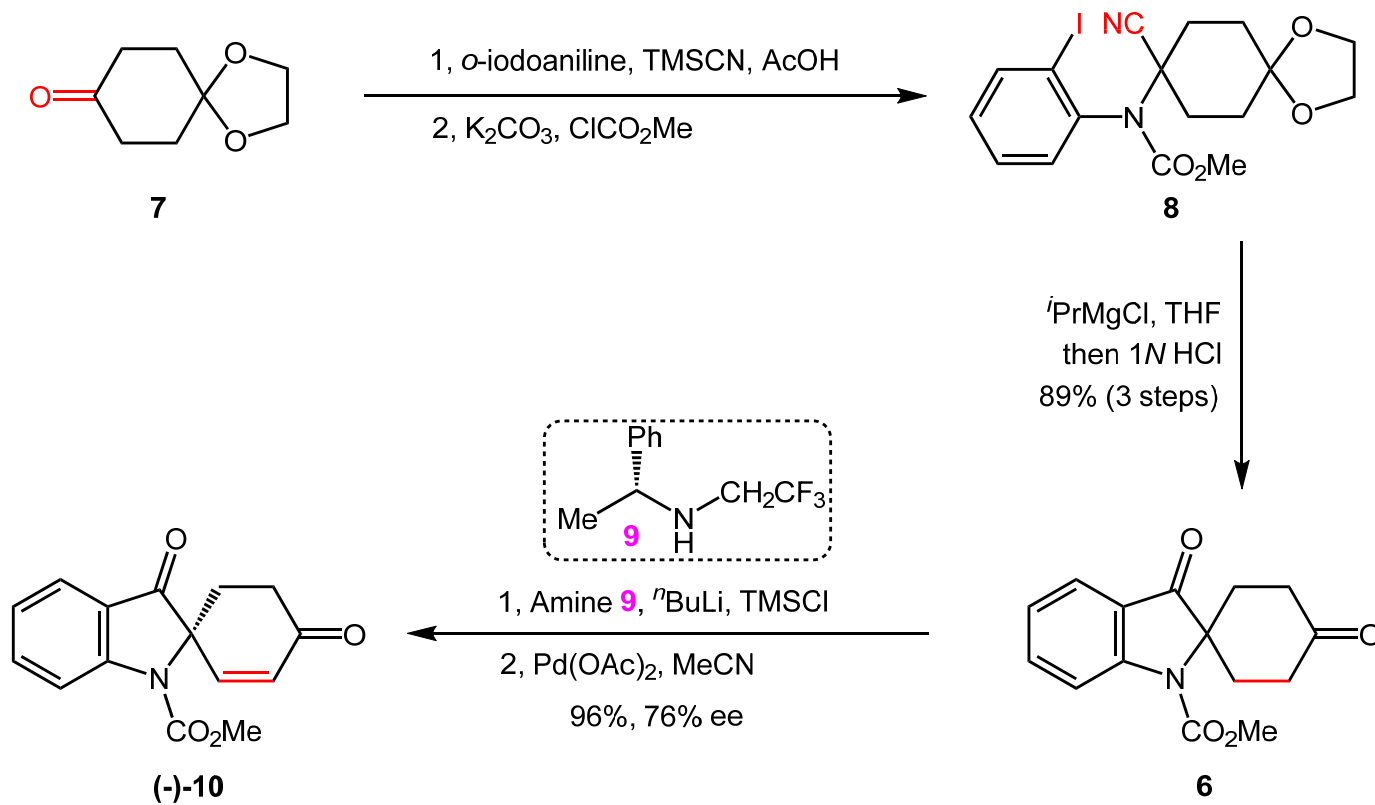
- ◆ Isolated from Malaysia species *Kopsia grandifolia* in 1992
- ◆ Three quaternary carbon centers and a polycyclic ring system

Nishida, A. *et al. Angew. Chem. Int. Ed.* **2016**, *55*, 3473

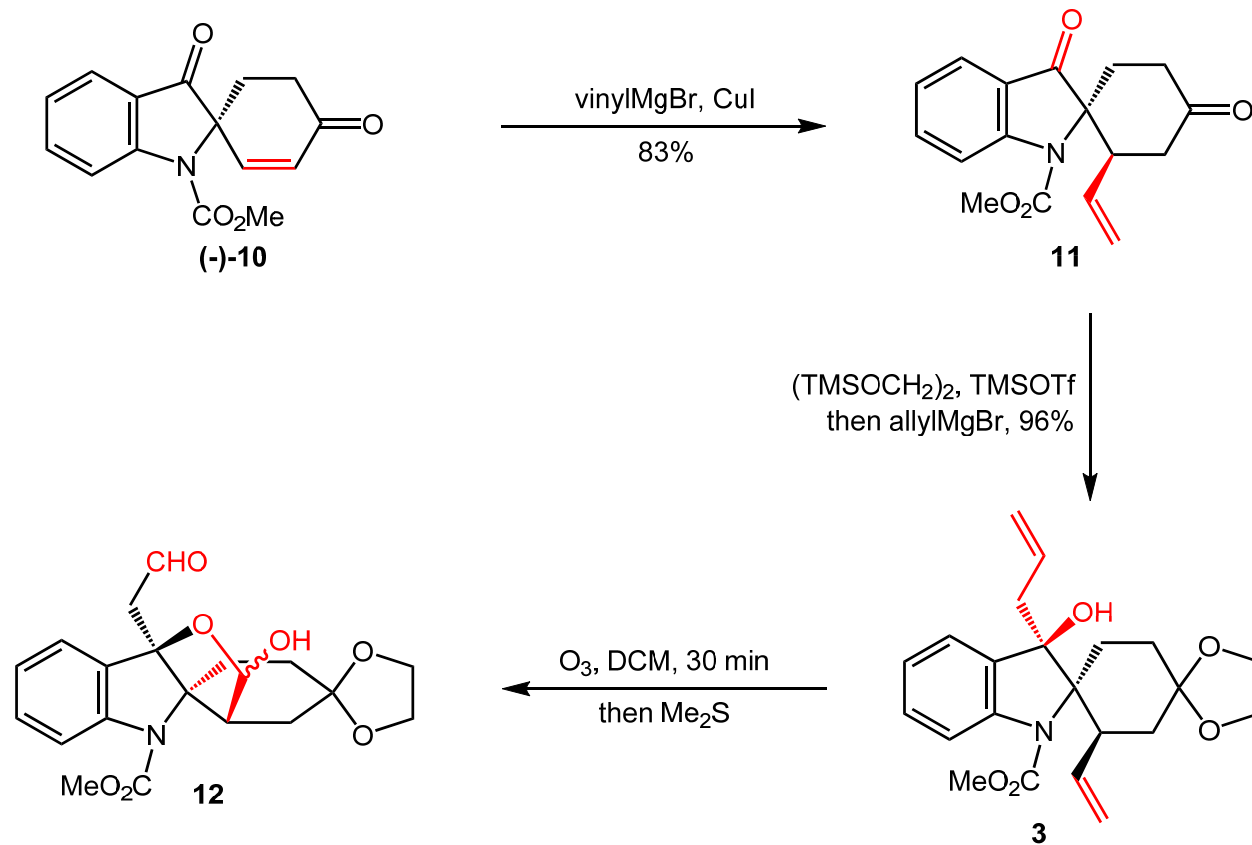
# Retrosynthetic Analysis of 1



# Synthesis of 10

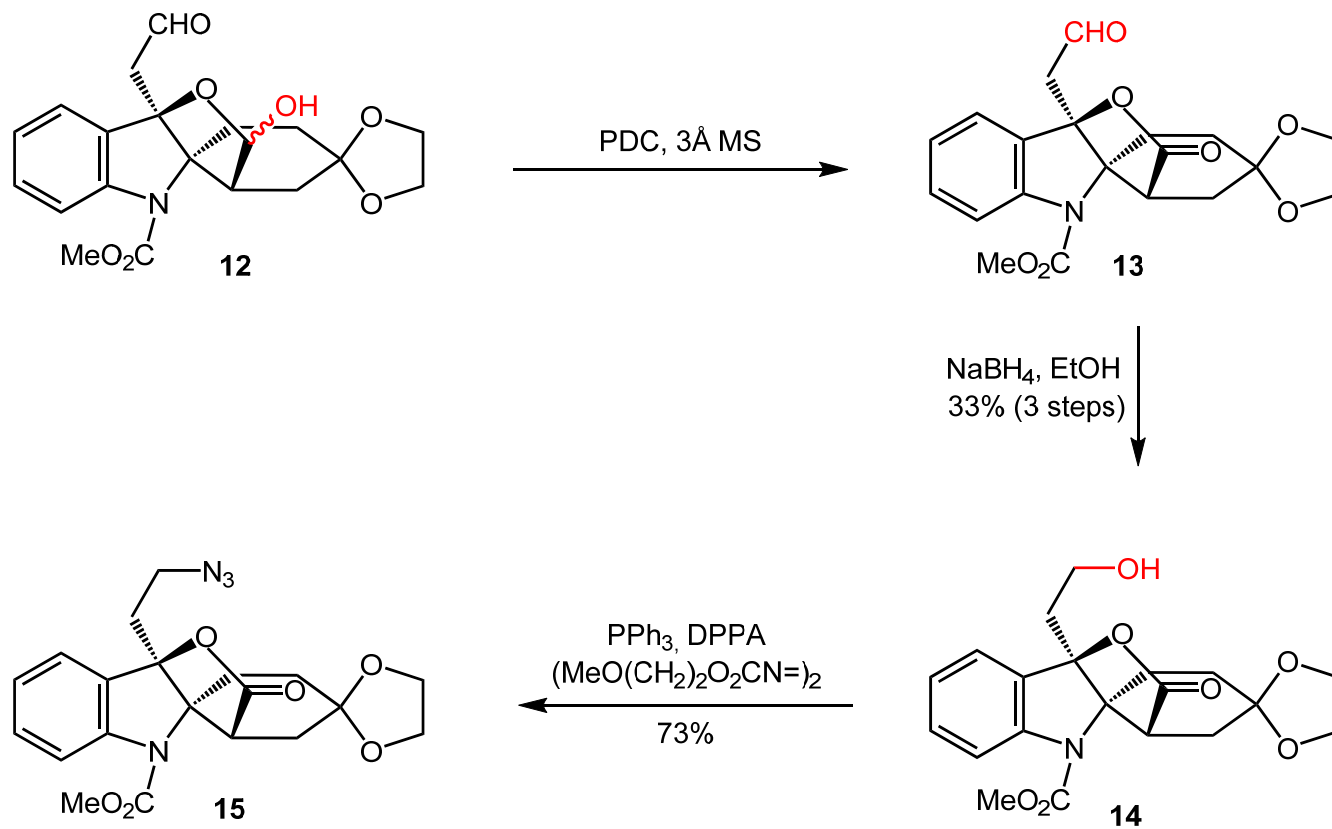


# Synthesis of 12

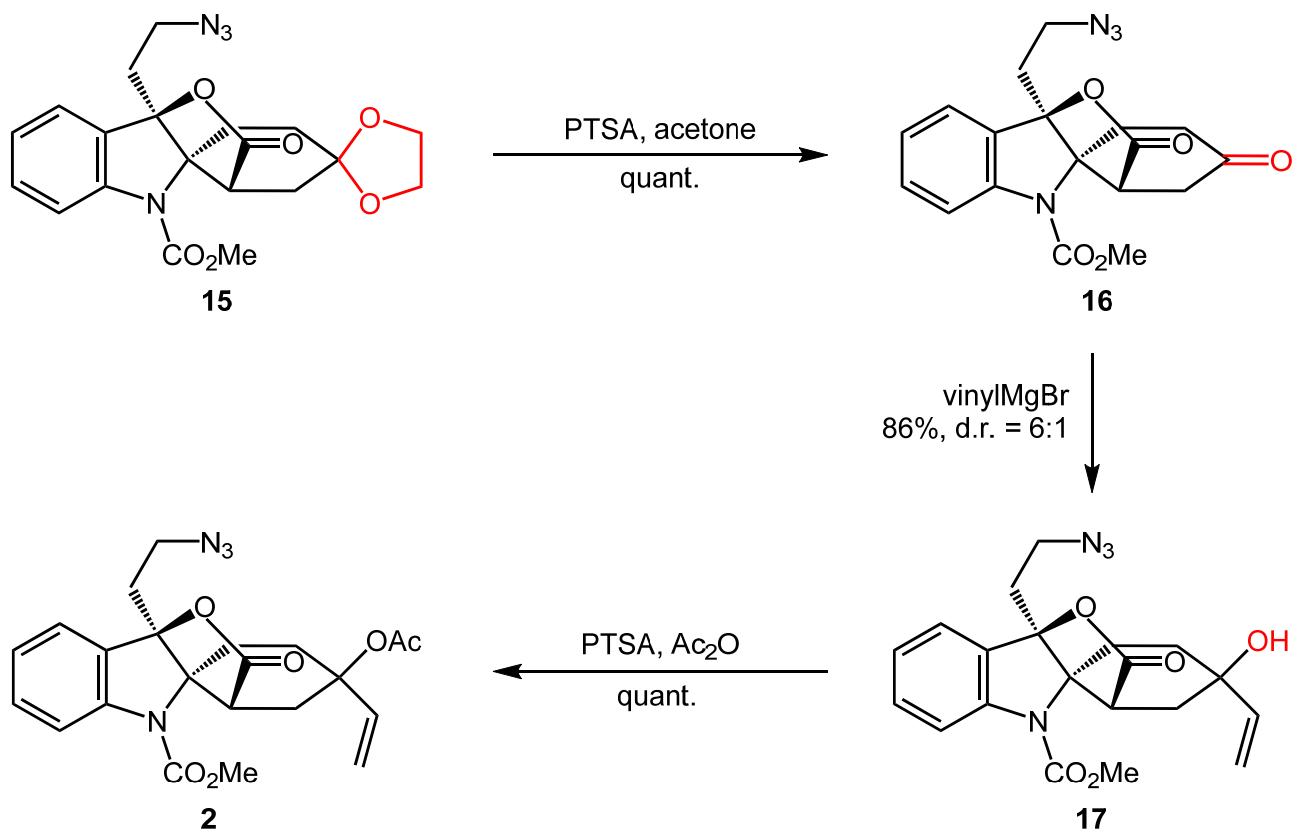




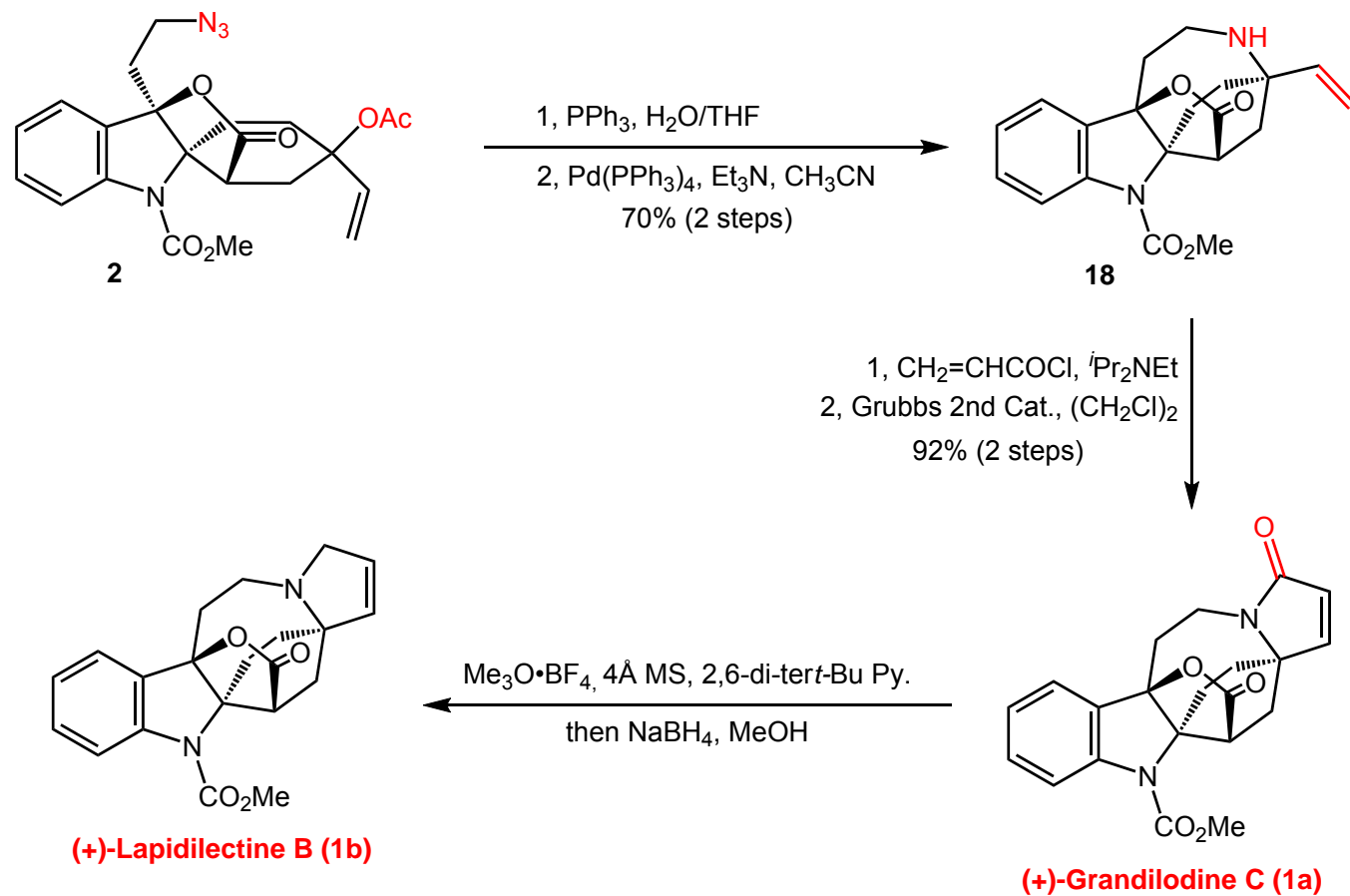
# Synthesis of 15



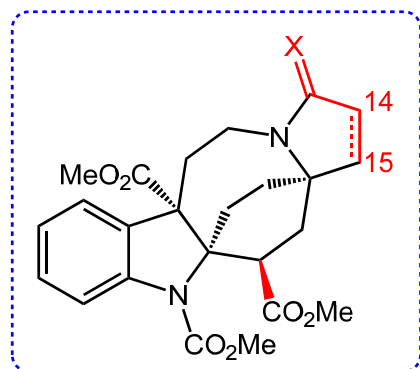
# Synthesis of 2



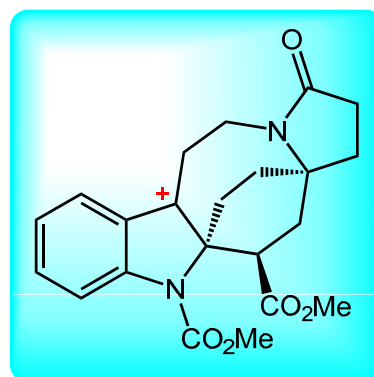
# Synthesis of (+)-1a and (+)-1b



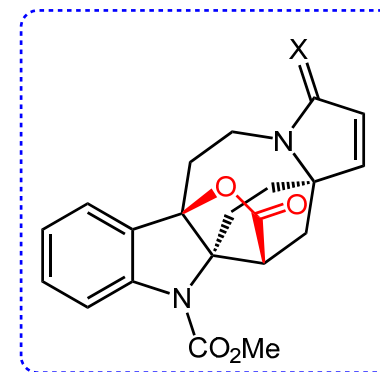
# Pyrroloazocine Indole Alkaloids



- (-)-Lapidilectine A  $\Delta^{14,15}$ , X = H<sub>2</sub> (1c)  
(-)-Lapidilectam  $\Delta^{14,15}$ , X = O (1d)  
(-)-Grandilodine A X = H<sub>2</sub> (1e)  
(+)-Isolapidilectine A X = H<sub>2</sub> (1f)  
(+)-Grandilodine B X = O (1g)



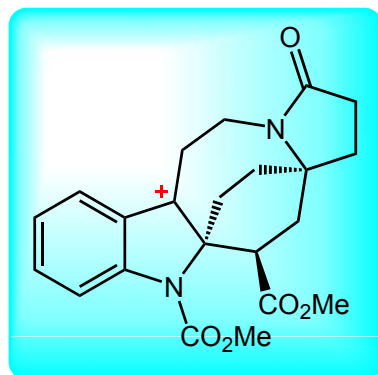
Key intermediate



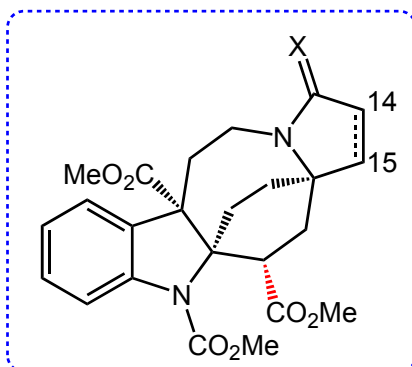
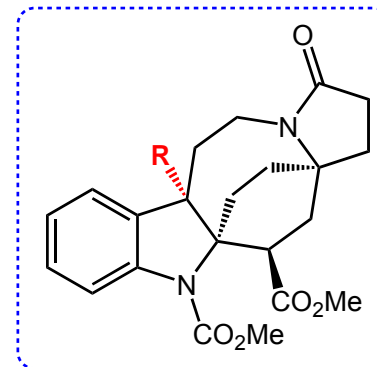
- (+)-Grandilodine C X = O (1a)  
(+)-Lapidilectine B X = H<sub>2</sub> (1b)

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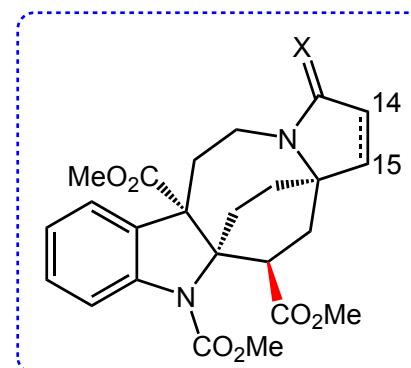
# Retrosynthetic Analysis of Indole Alkaloids



Key intermediate

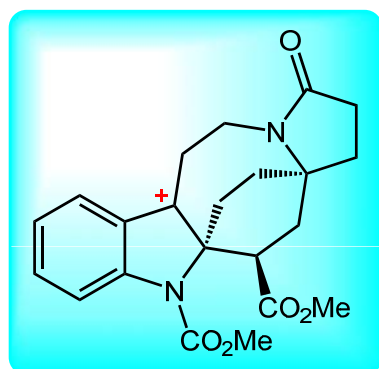


(+)-Isolapidilectine A X = H<sub>2</sub> (1f)  
 (+)-Grandilodine B X = O (1g)



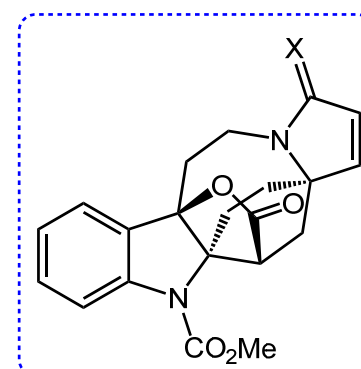
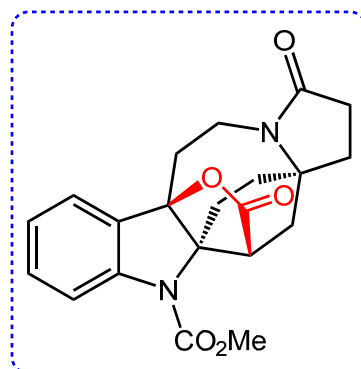
(-)-Lapidilectam  $\Delta^{14,15}$ , X = O (1d)  
 (-)-Grandilodine A X = H<sub>2</sub> (1e)

# Retrosynthetic Analysis of Indole Alkaloids



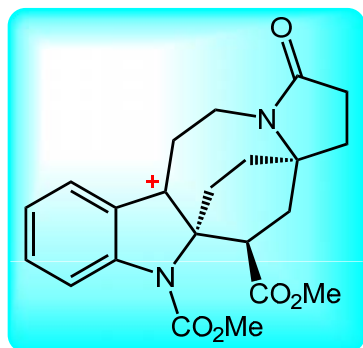
Key intermediate

Lactonization

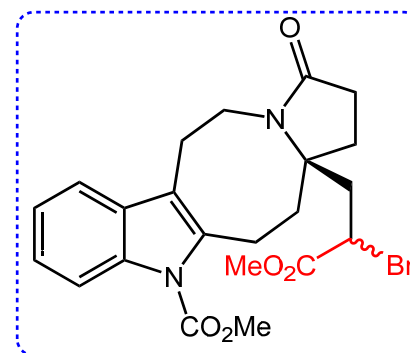
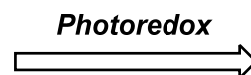
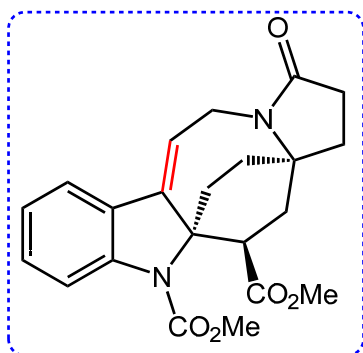
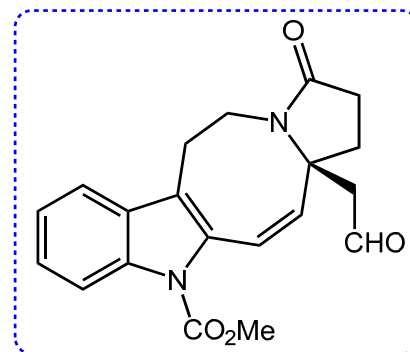


(+)-Grandilodine C X = O (1a)  
(+)-Lapidilectine B X = H<sub>2</sub> (1b)

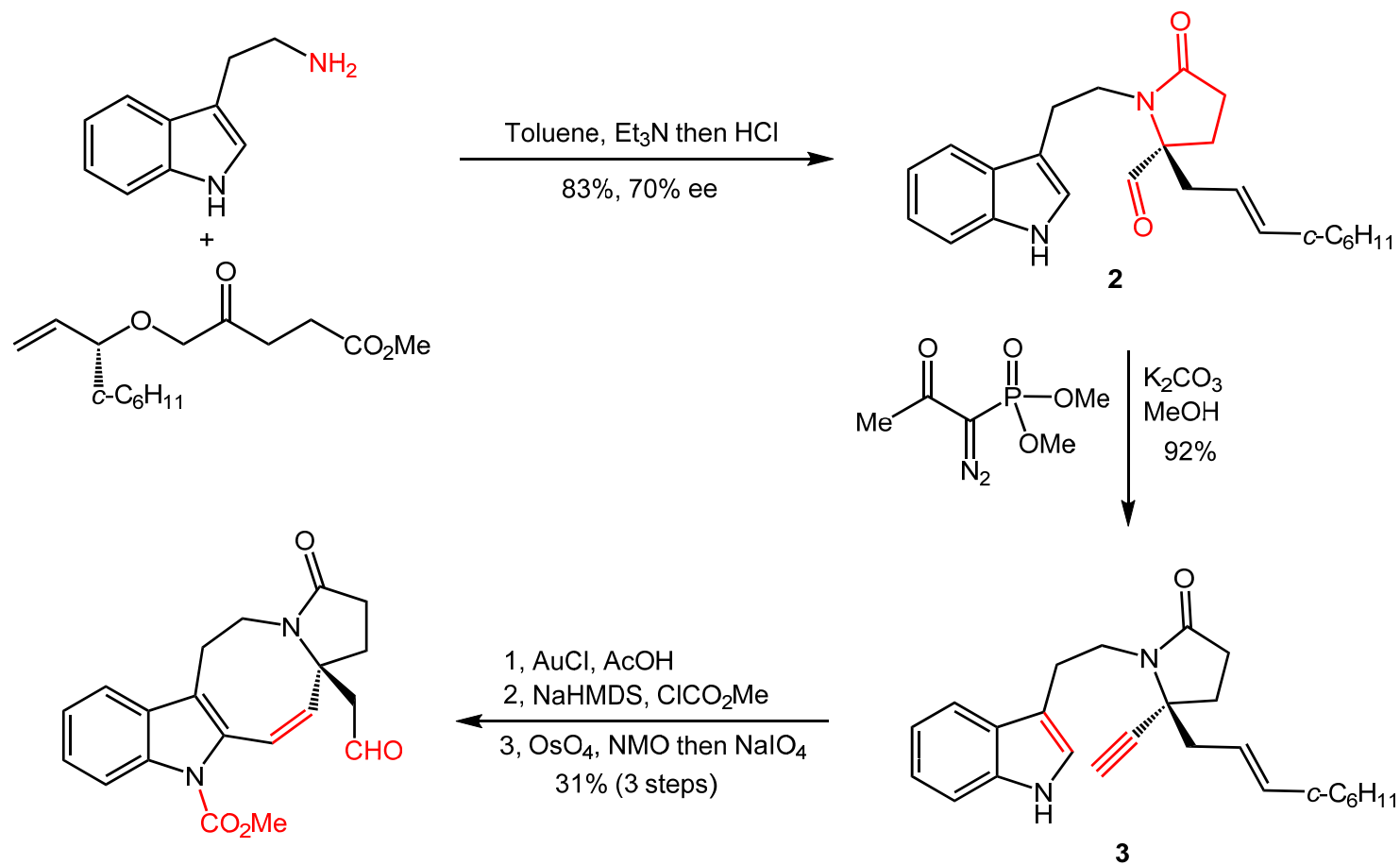
# Retrosynthetic Analysis of Intermediate



Key intermediate

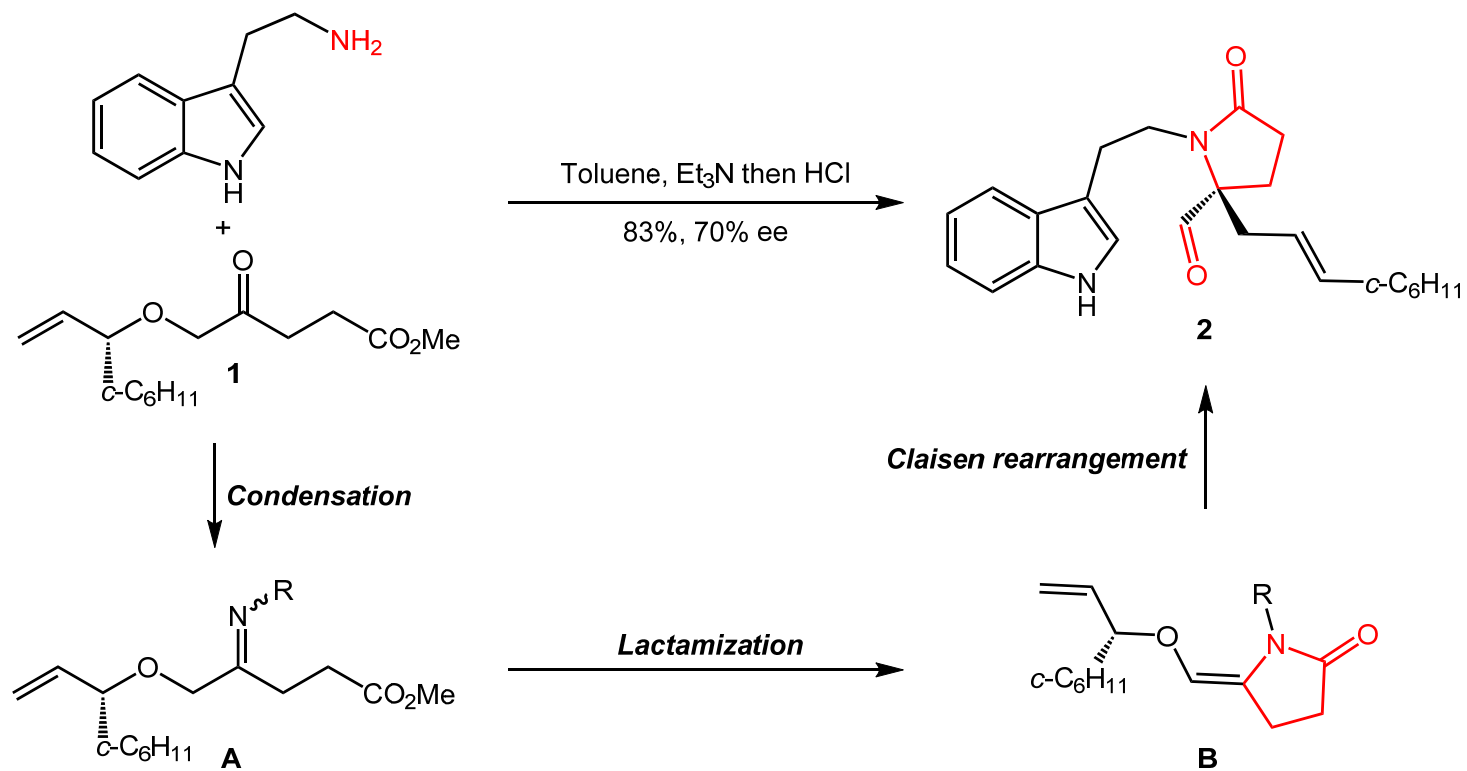


# Synthesis of Aldehyde Intermediate



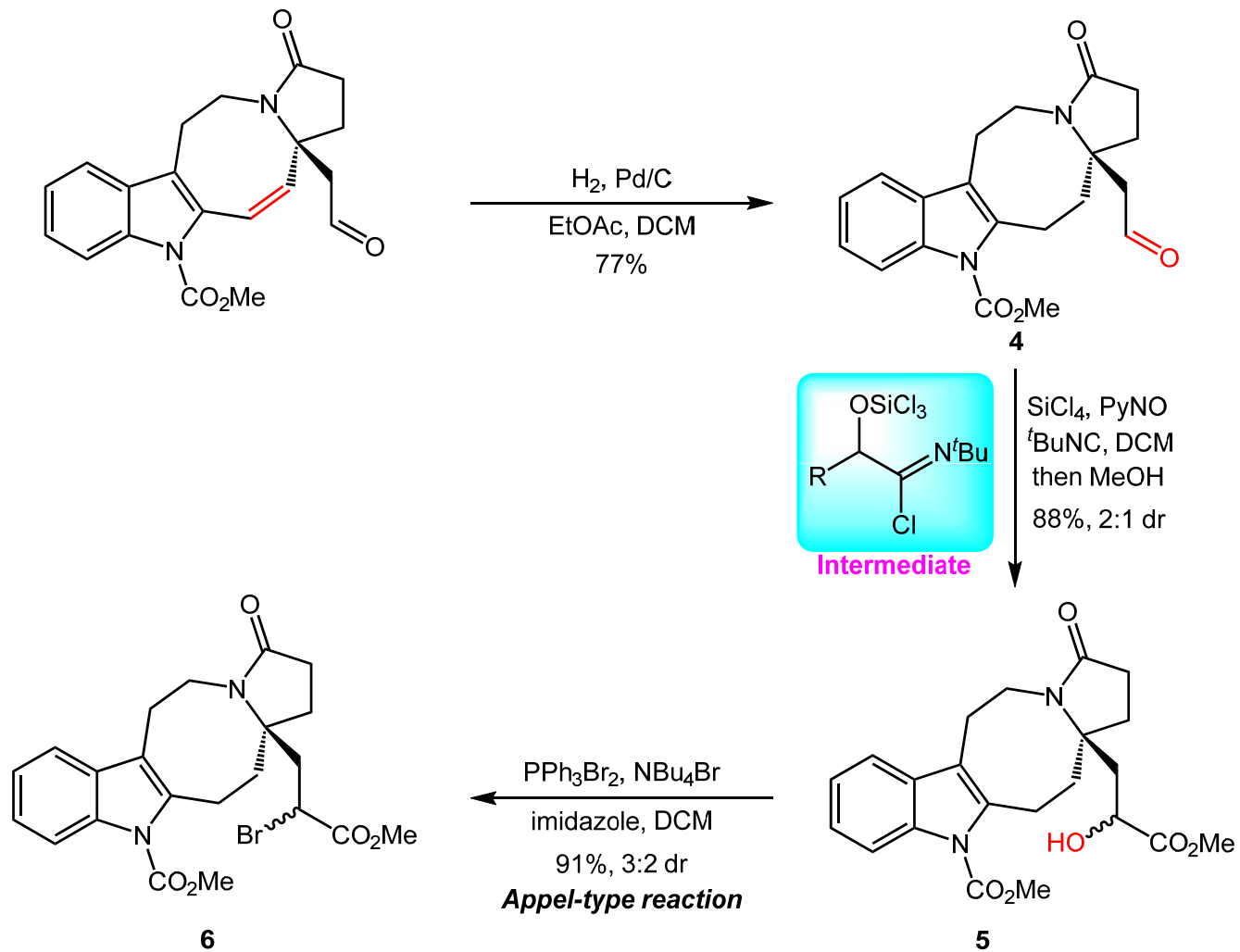


# Enantioselective Claisen Rearrangement

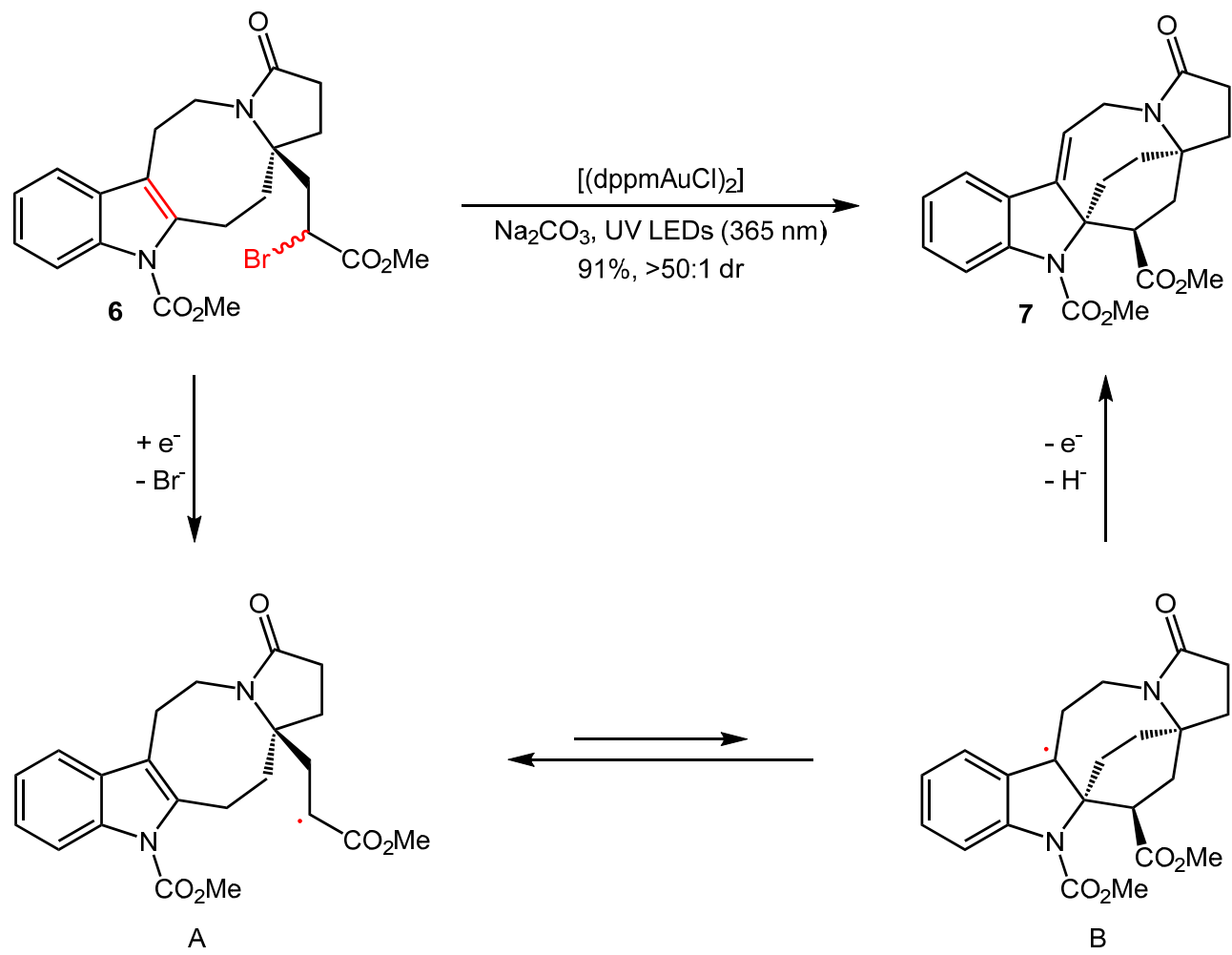


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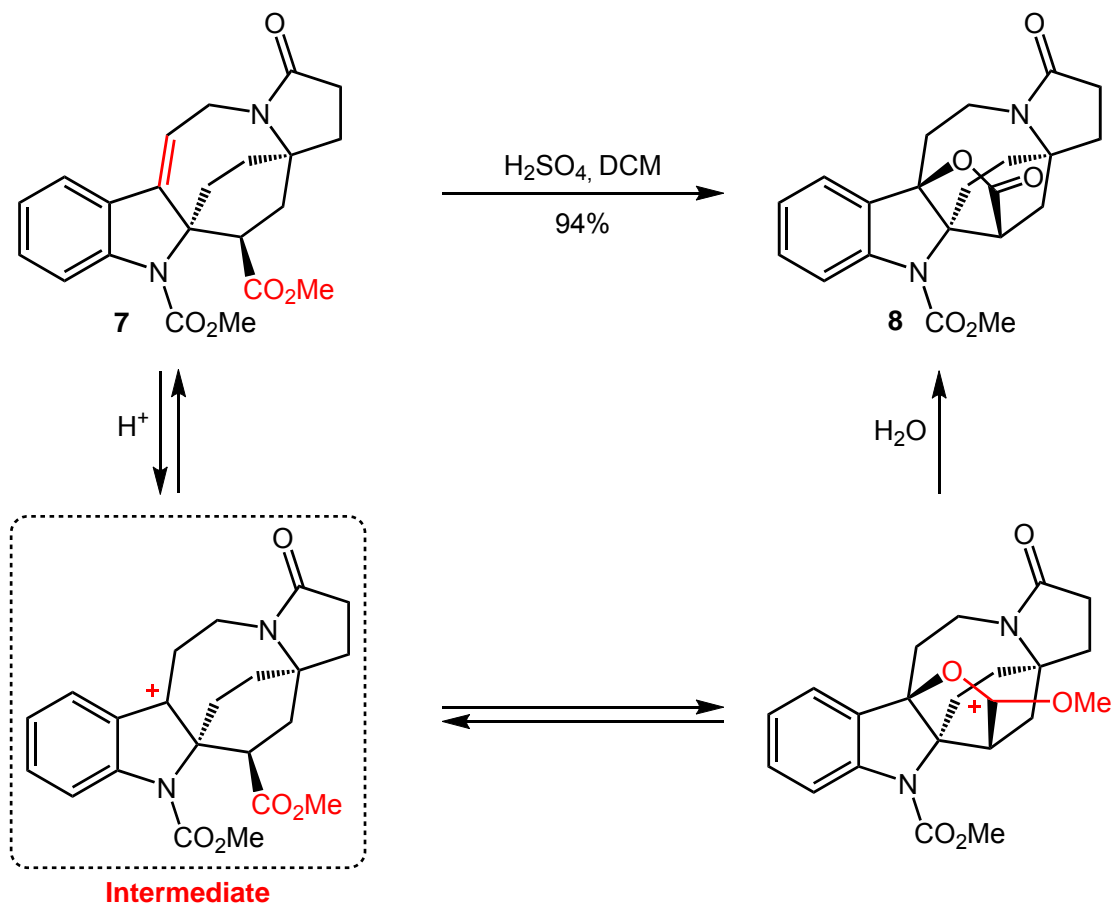
# Synthesis of $\alpha$ -Bromo Ester 6



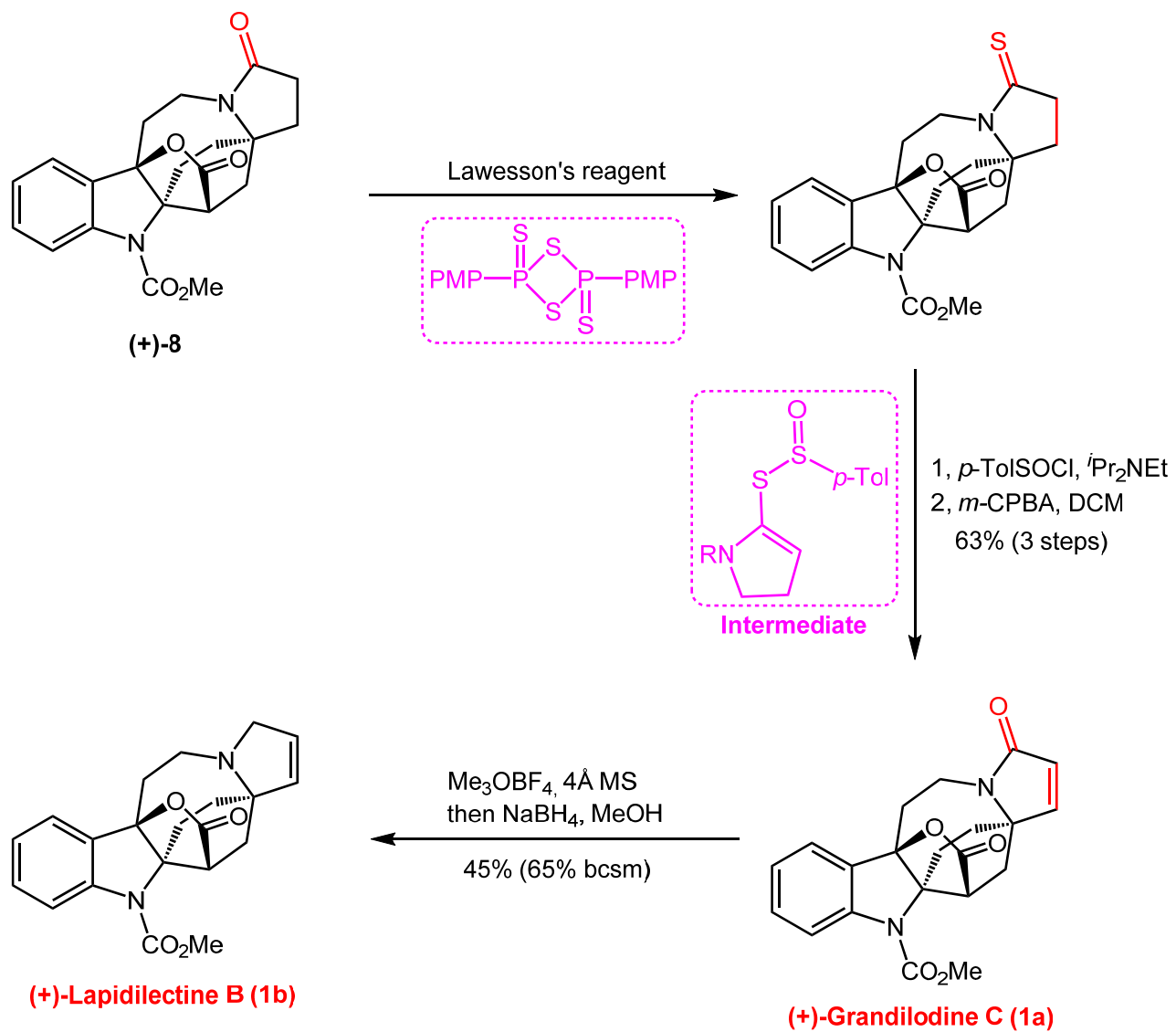
# Photoredox Cyclization of 6 into 7



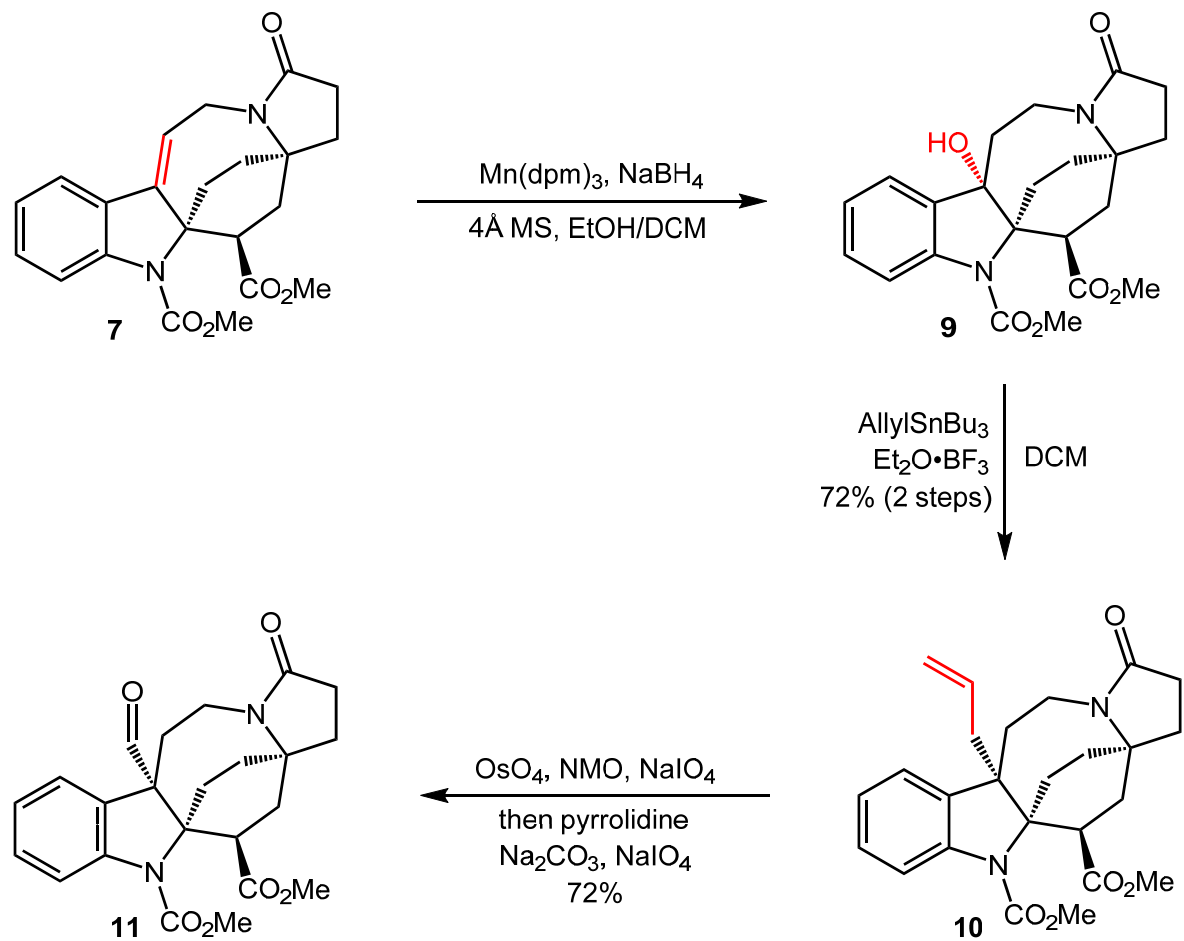
# Lactonization of 7



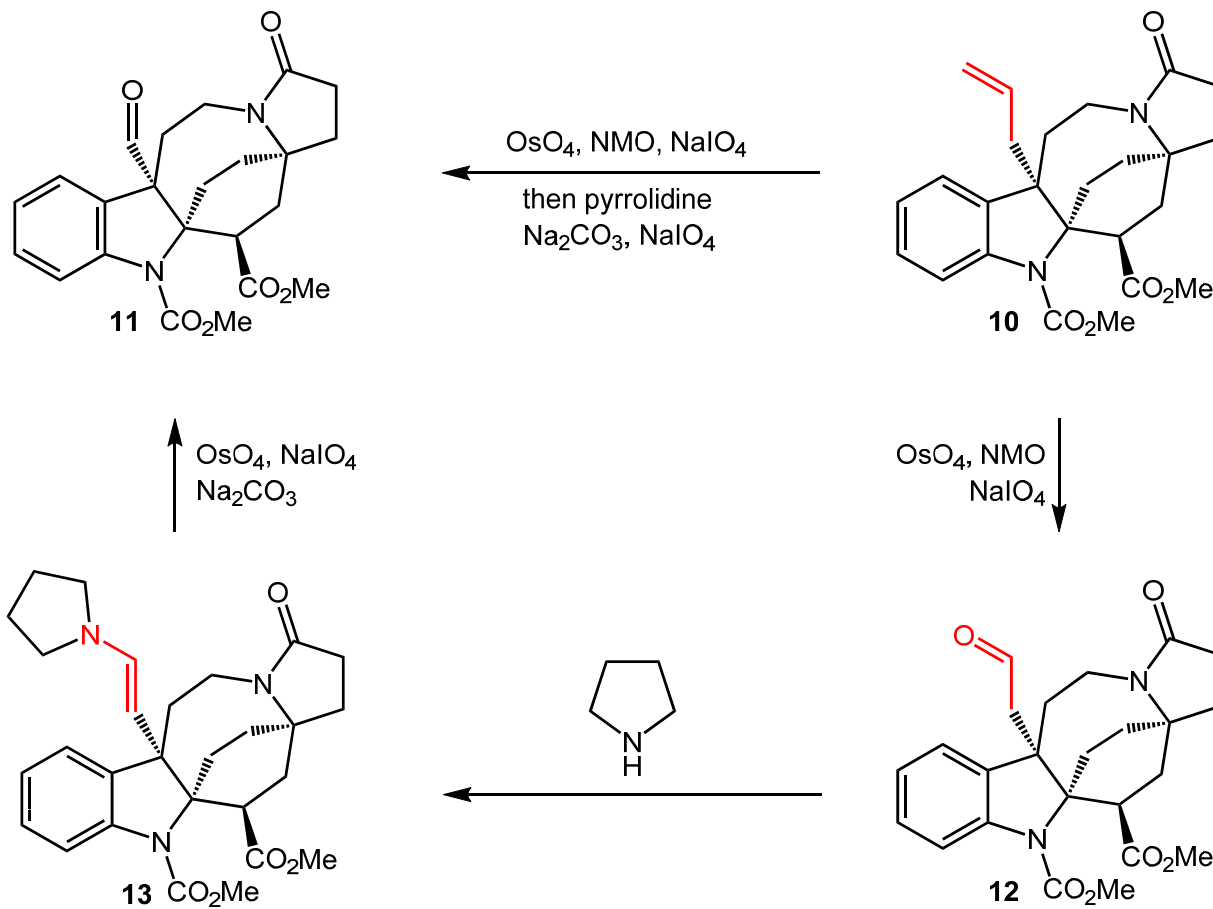
# Synthesis of 1a and 1b



# Synthesis of 11

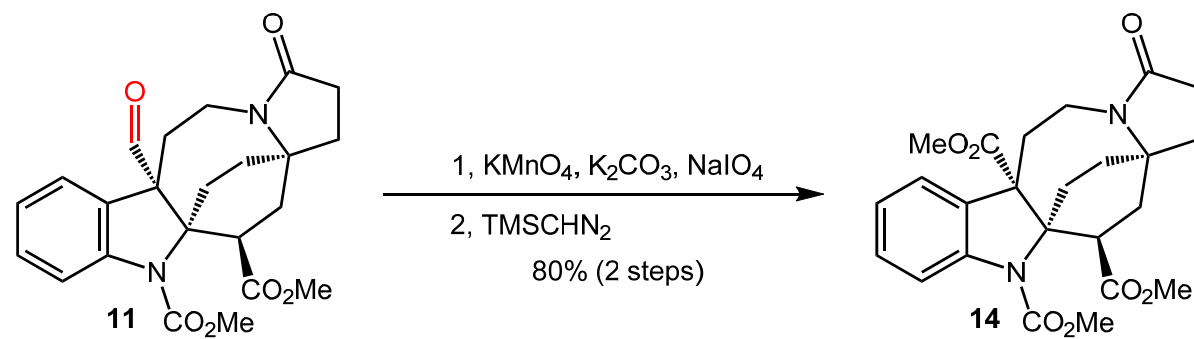


# Synthesis of 11



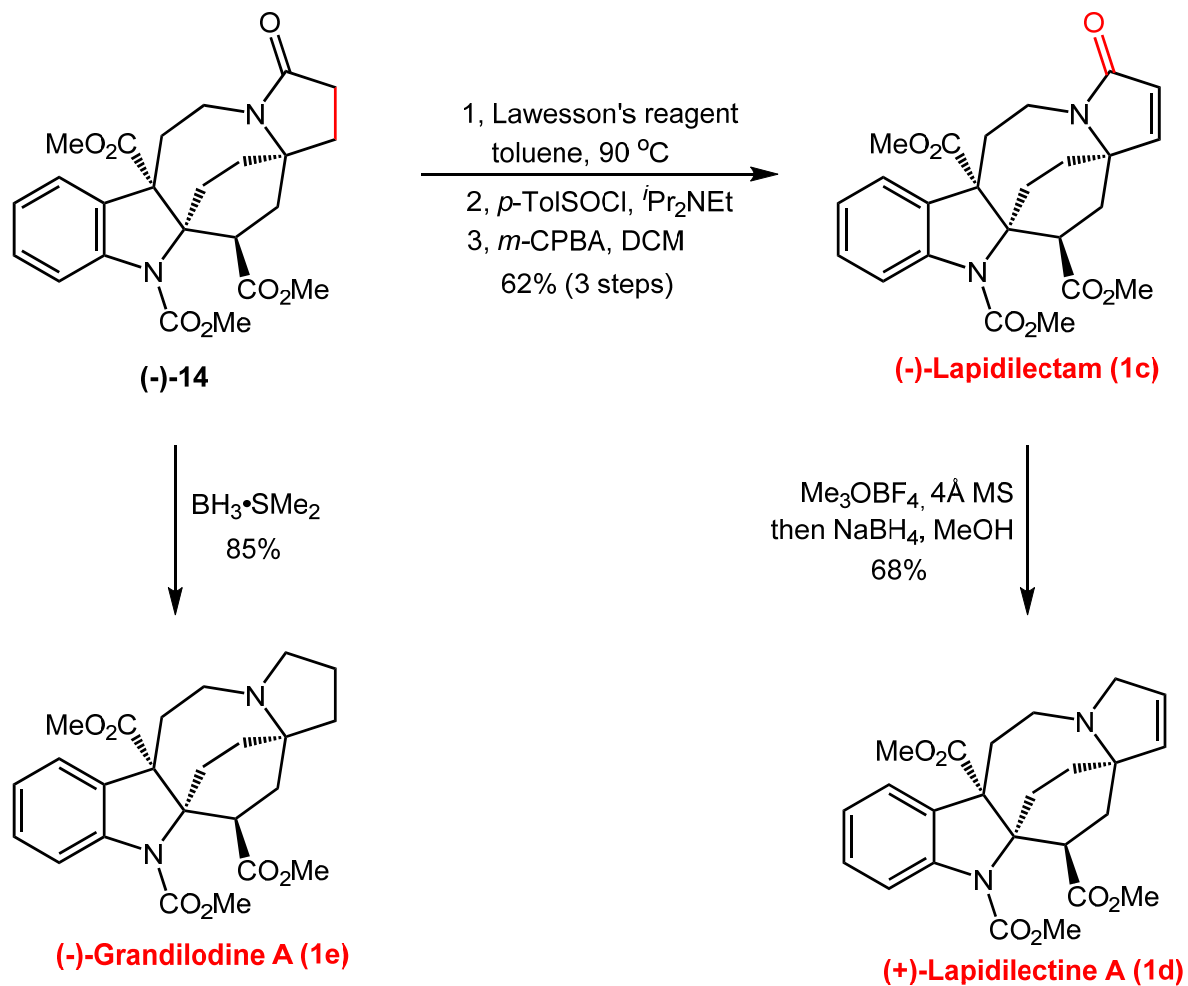
# Introduction of Benzylic CO<sub>2</sub>Me Group

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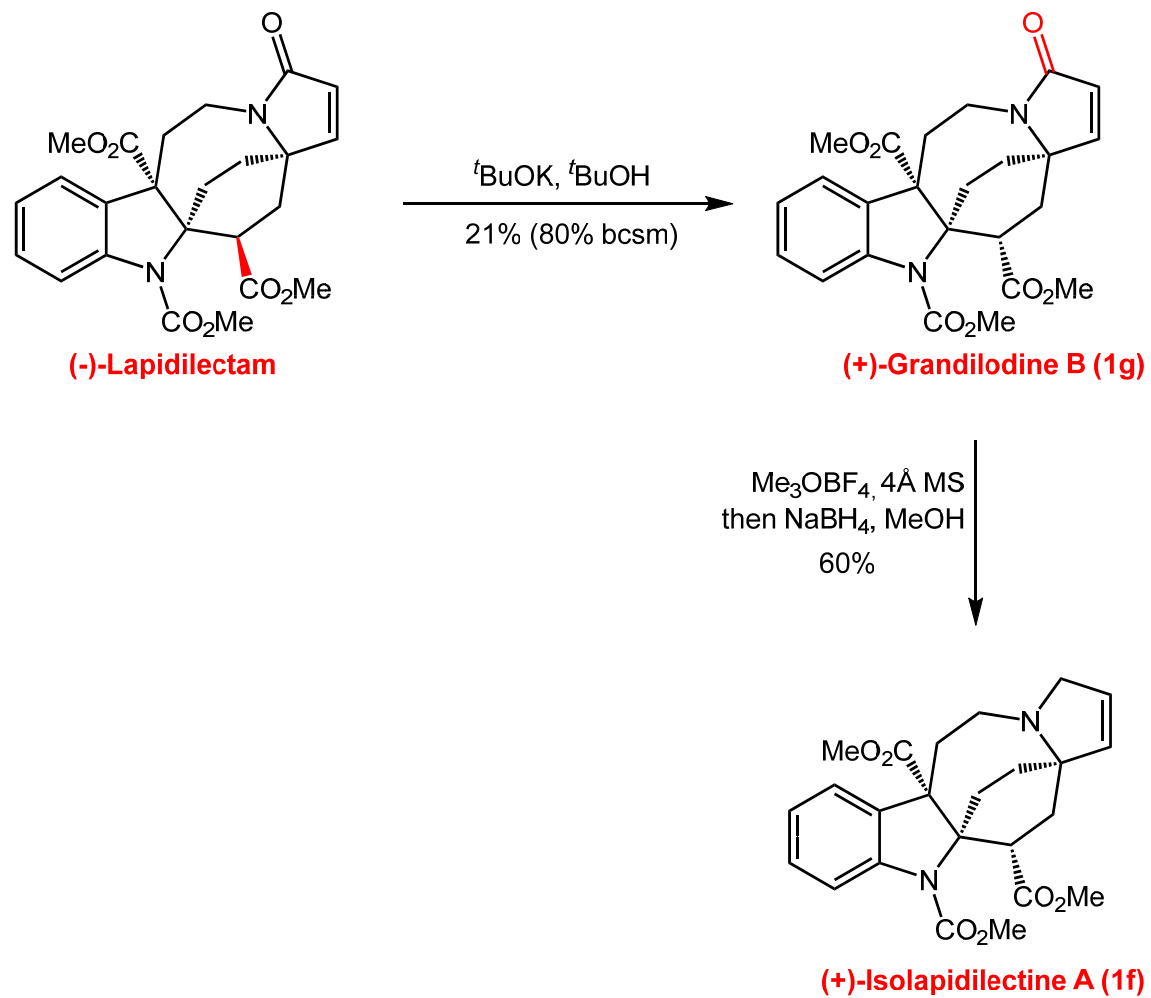




# Synthesis of (+)-1c, (-)-1d, (-)-1e

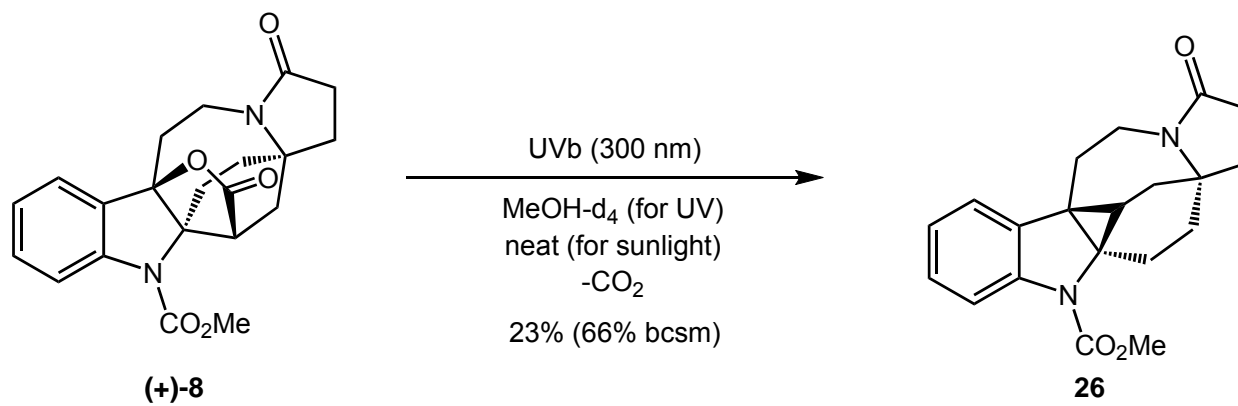


# Synthesis of (+)-1f, (+)-1g

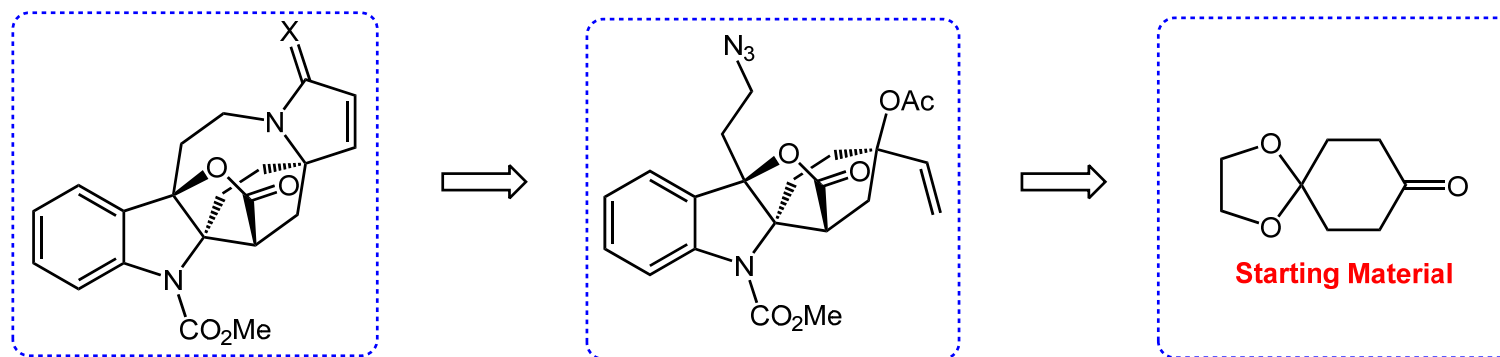


# Biosynthesis of 26

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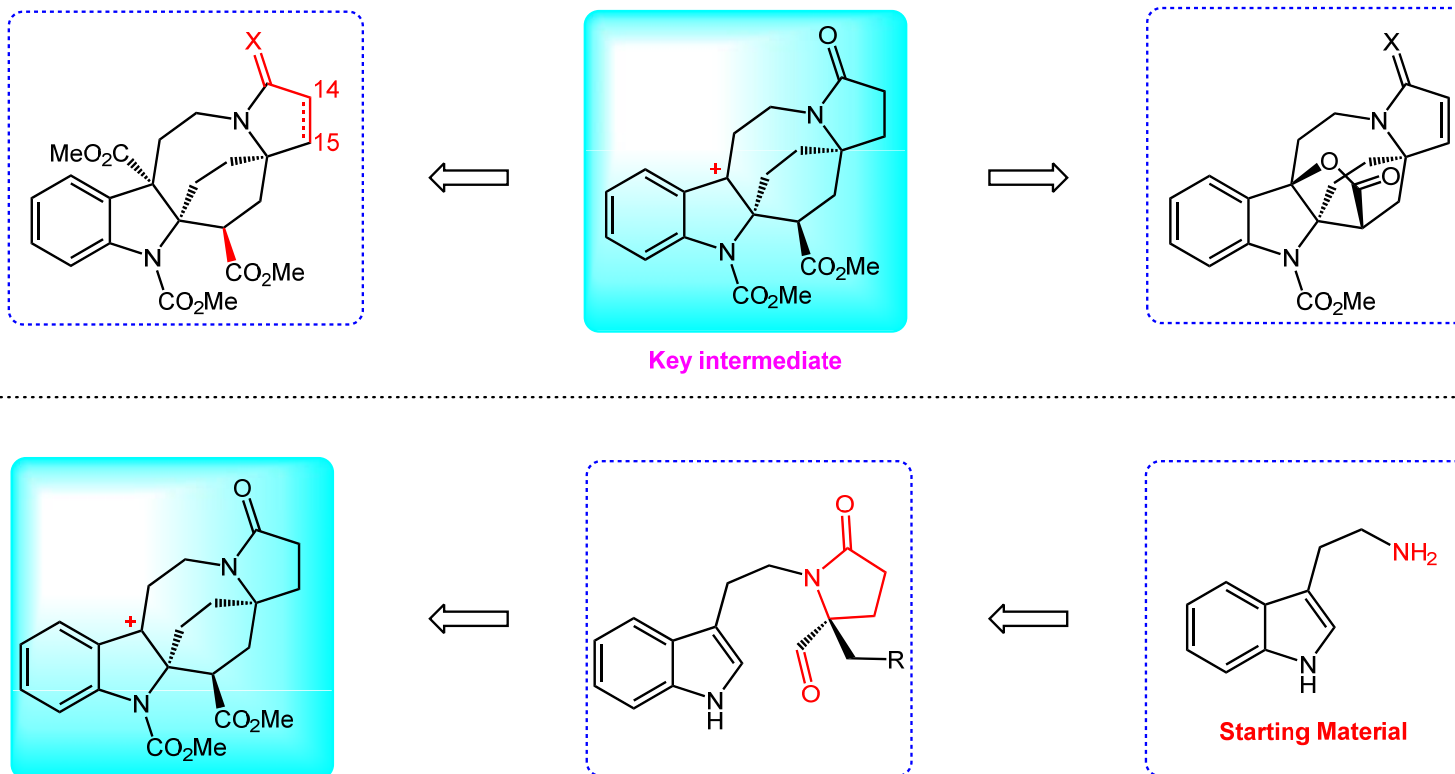
# Summary



- ◆ 18-19 linear steps, 8.4%-7.4% overall yield
- ◆ Stereoselective vinylation–allylation
- ◆ Strecker synthesis and enantioselective deprotonation

Nishida, A. *et al. Angew. Chem. Int. Ed.* **2016**, *55*, 3473

# Summary



◆ 11-19 linear steps

◆ Two gold-catalyzed cyclization processes

◆ Without protection/deprotection of functional groups

## The First Paragraph: Introduction

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Lapidilectines and grandilodines are indole alkaloids, isolated from Malaysia species *Kopsia grandifolia*, that feature lactone or diester motifs. Together with tenuisines and the cyclopropane-containing lemurines isolated from *Kopsia* species, they represent a family of 16 indole alkaloids containing the common pyrroloazocine core. Preliminary studies on the biological activity of lapidilectines and grandilodines demonstrated their ability to reverse multidrug resistance in vincristine-resistant cancer cells.

## The Last Paragraph: Summary

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In summary, we have developed concise total syntheses of enantiomerically pure (+)-lapidilectine B, (+)-grandilodine, (-)-lapidilectine A, (-)-lapidilectam, (-)-grandilodine A, (+)-isolapidilectine A, (+)-grandilodine B, by means of two highly efficient gold-catalyzed cyclization processes. We also propose a new hypothesis of biosynthetic relationship among Kopsia pyrroloazocine indole alkaloids by means of decarboxylation event: the elimination of a carboxylic acid to form a lactone and a photoinduced conversion into the cyclopropane present in the lundurines.