Literature Report 5

Total Synthesis of Corymine

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Checker: Li-Xia Liu
Date: 2020-07-20

Li, C. *et al*. *Angew. Chem. Int. Ed.* **2017**, *56*, 7484.
Li, C. *et al*. *J. Am. Chem. Soc*. **2020**, *142*, 3269.

CV of Prof. Chaozhong Li

Education:

- **1983-1988** B.A., USTC
- **1988-1993** Ph.D., SIOC
- **1993-1994** Research Assistant, SIOC
- **1994-1998** Postdoc, Iowa State University
- **1999-Present** Research Associate, Research Fellow, SIOC

Research:

- Free Radical Chemistry
- Natural Product Synthesis
- Organometallic Chemistry

Contents

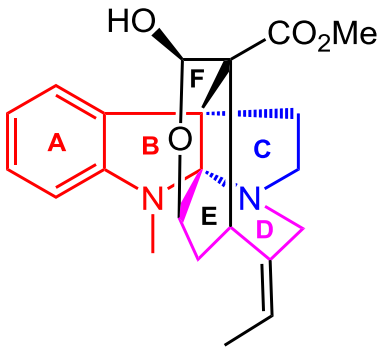
1 Introduction

2 Total Synthesis of (+/-)-Corymine

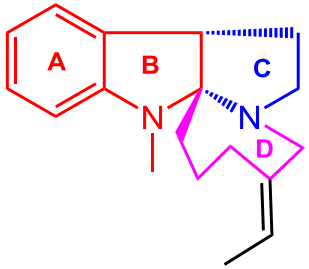
3 Enantioselective Total Synthesis of (+)-Corymine

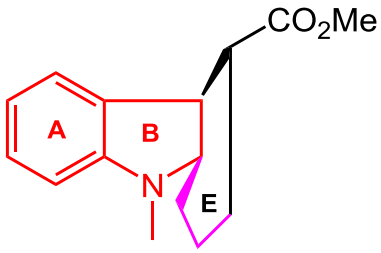
4 Summary

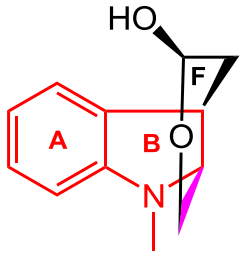
Introduction



Corymine





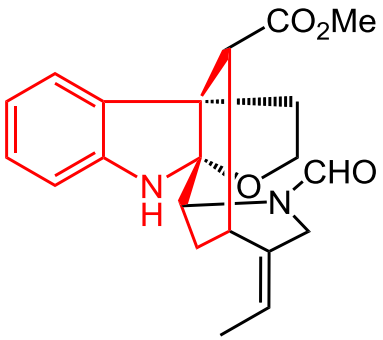


Hunteria zeylanica

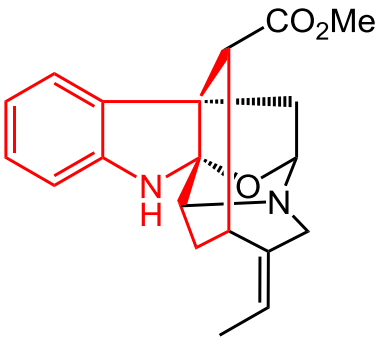
仔榄树

- Corymine is a member of the **Akuammiline** family and was first isolated from the seeds of **Hunteria unbellata** in 1965. It is a **non-competitive antagonist** of the gamma-aminobutyric acid receptor and has a highly **condensed six-ring backbone** structure.

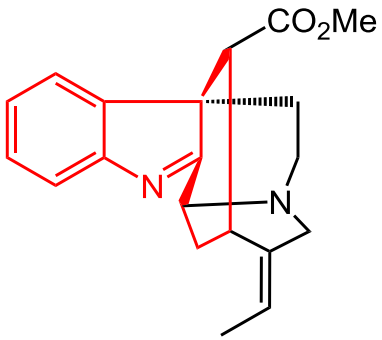
Akuammiline Alkaloids



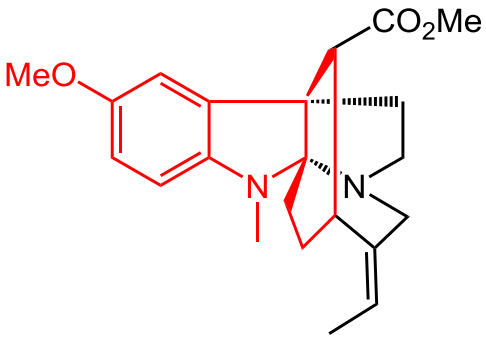
Aspidophylline A



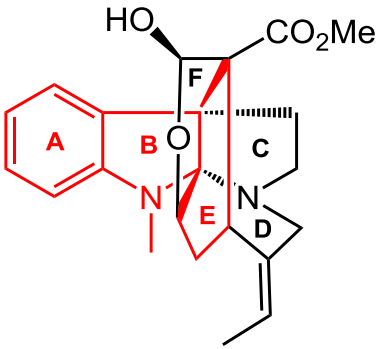
Picrinine



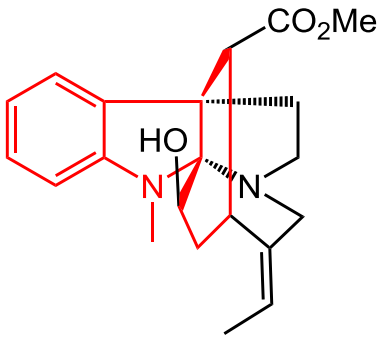
Strictamine



Vincorine

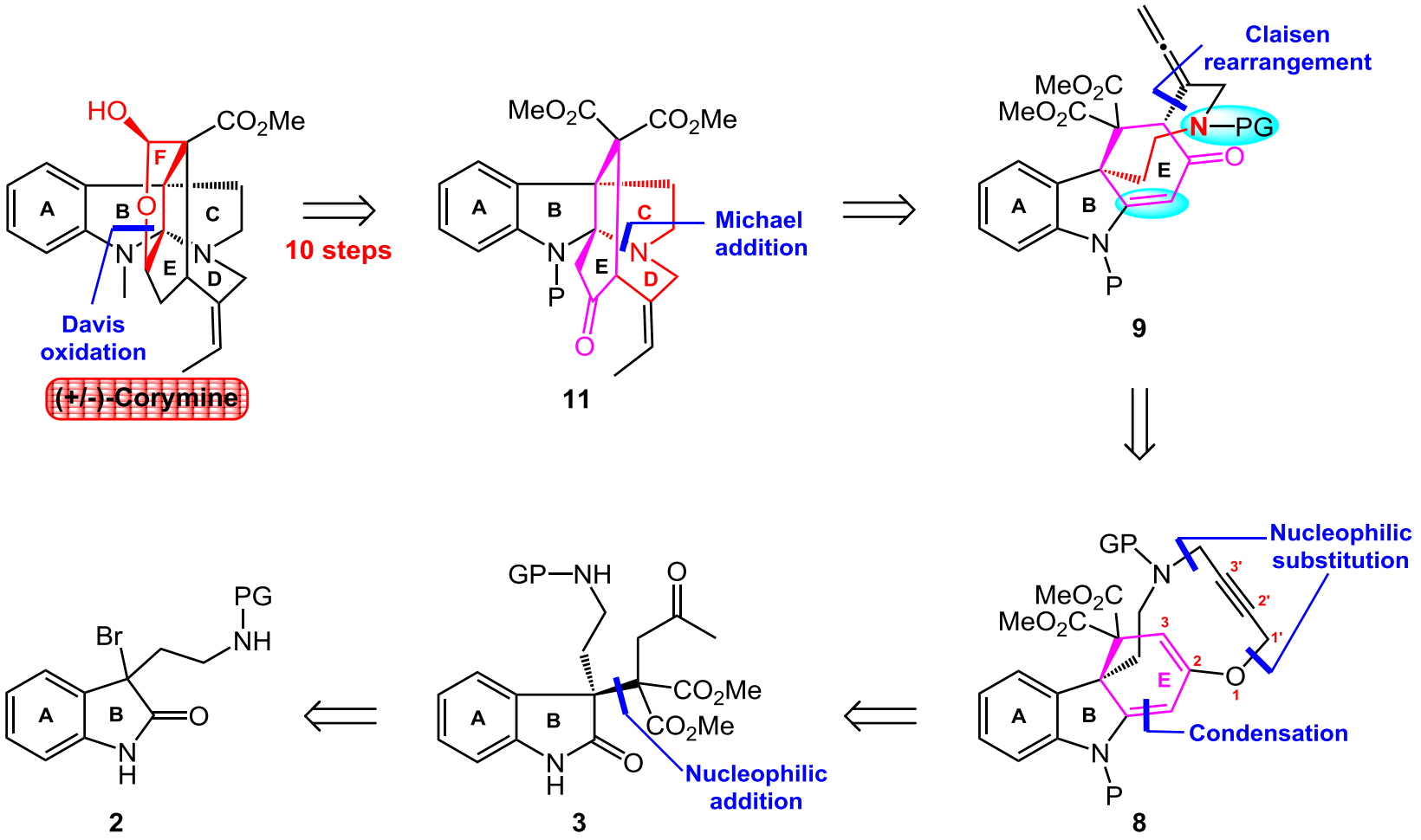


Corymine



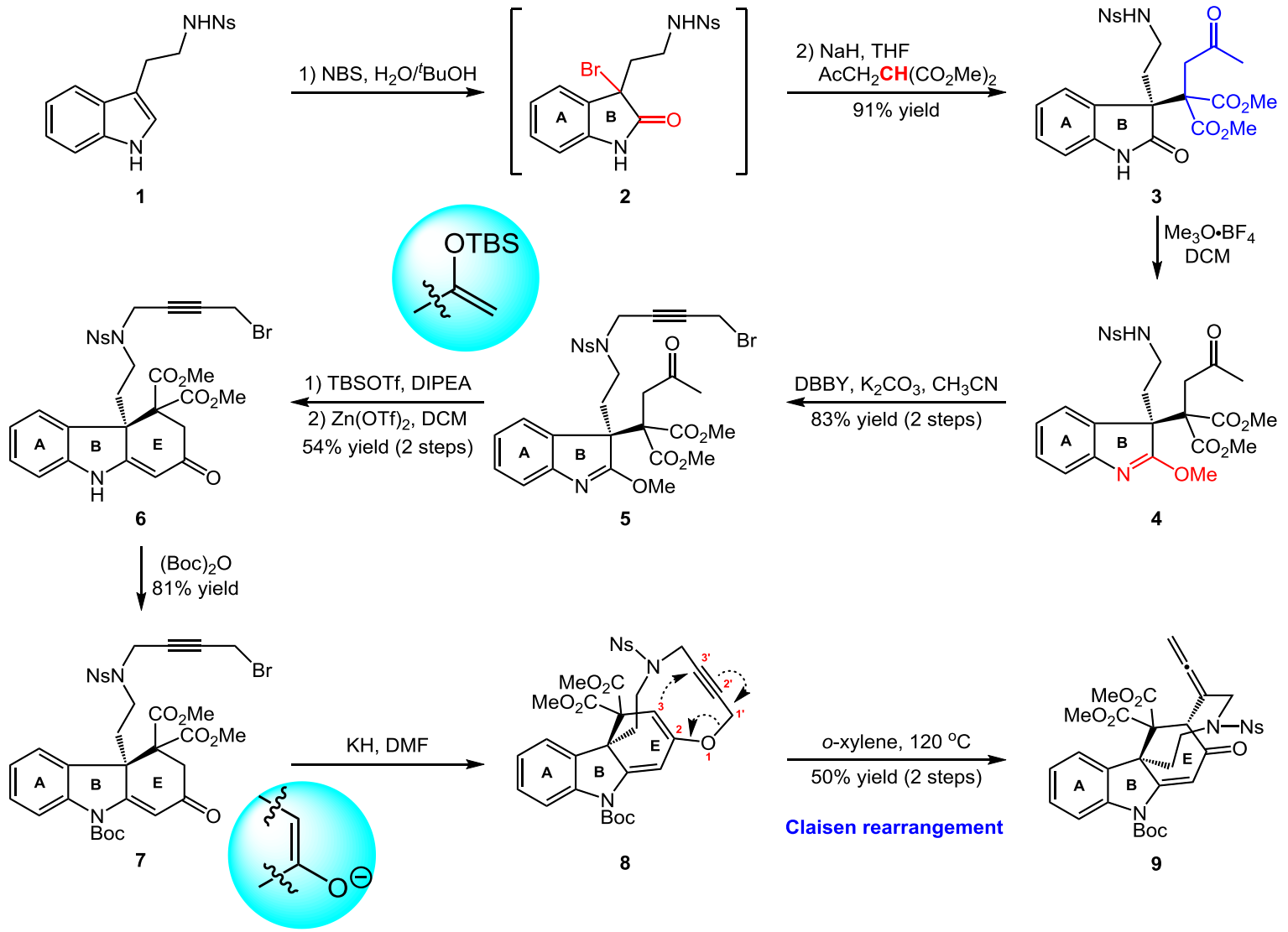
Deformylcorymine

Retrosynthetic Analysis of (+/-)-Corymine

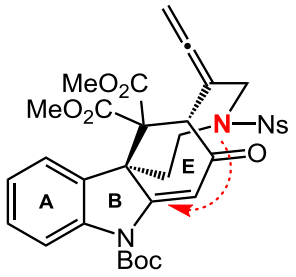


Li, C. *et al*. *Angew. Chem. Int. Ed.* **2017**, *56*, 7484.

Synthesis of 9



Synthesis of 11



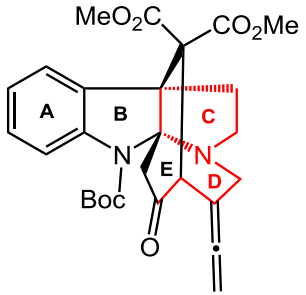
9

K_2CO_3, *p*-thiocresol

CH_3CN

70% yield

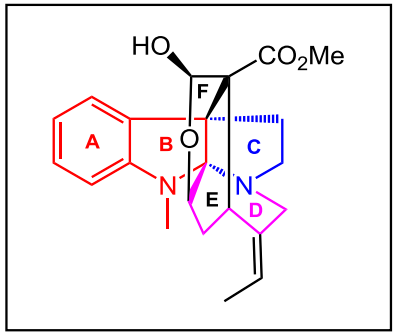
Michael addition

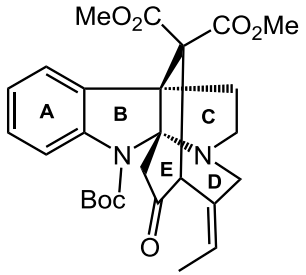


10

Pd/C, H_2, THF

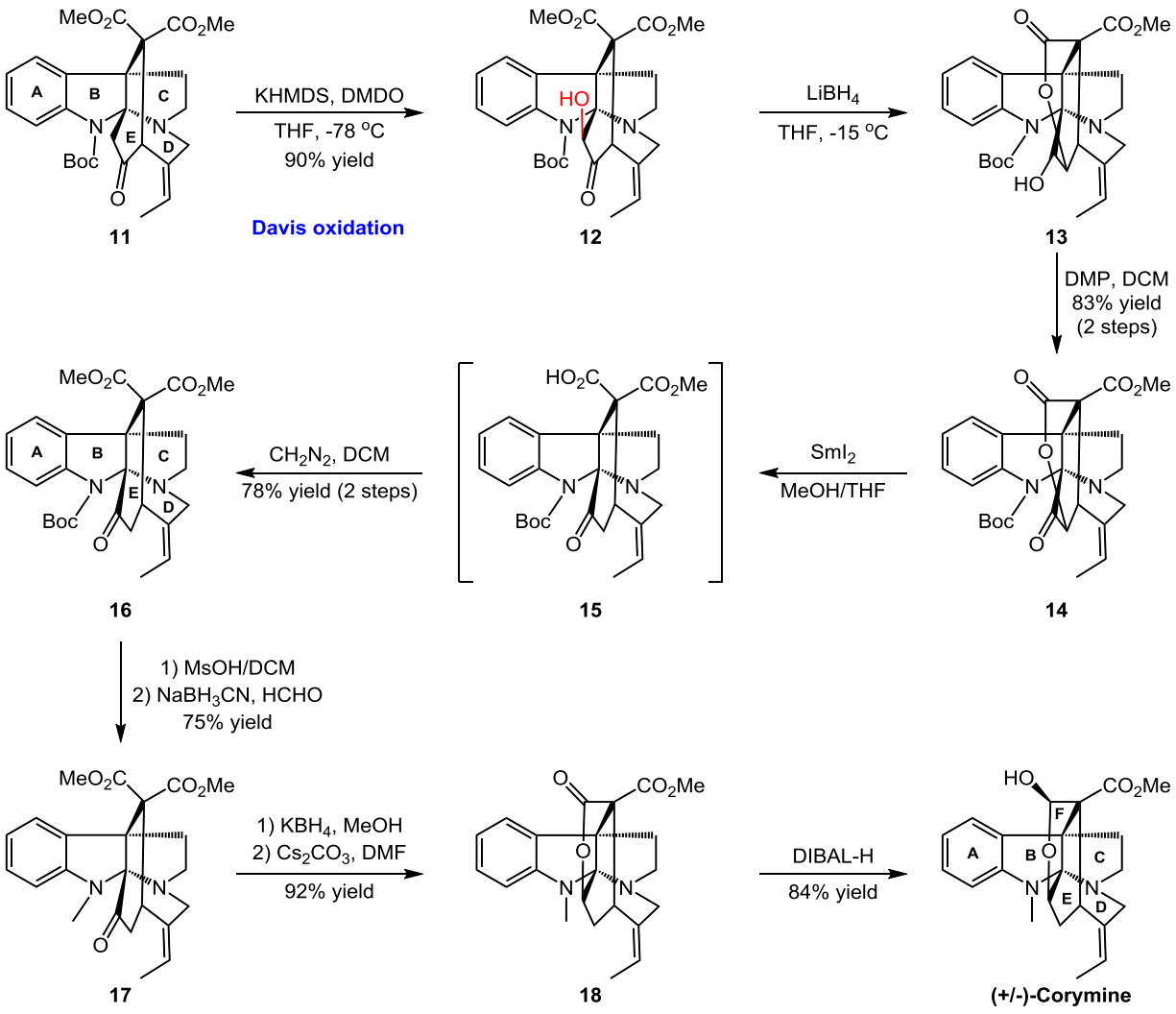
87% yield



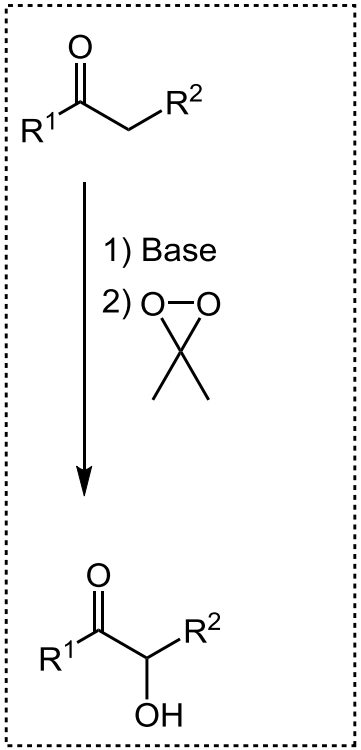


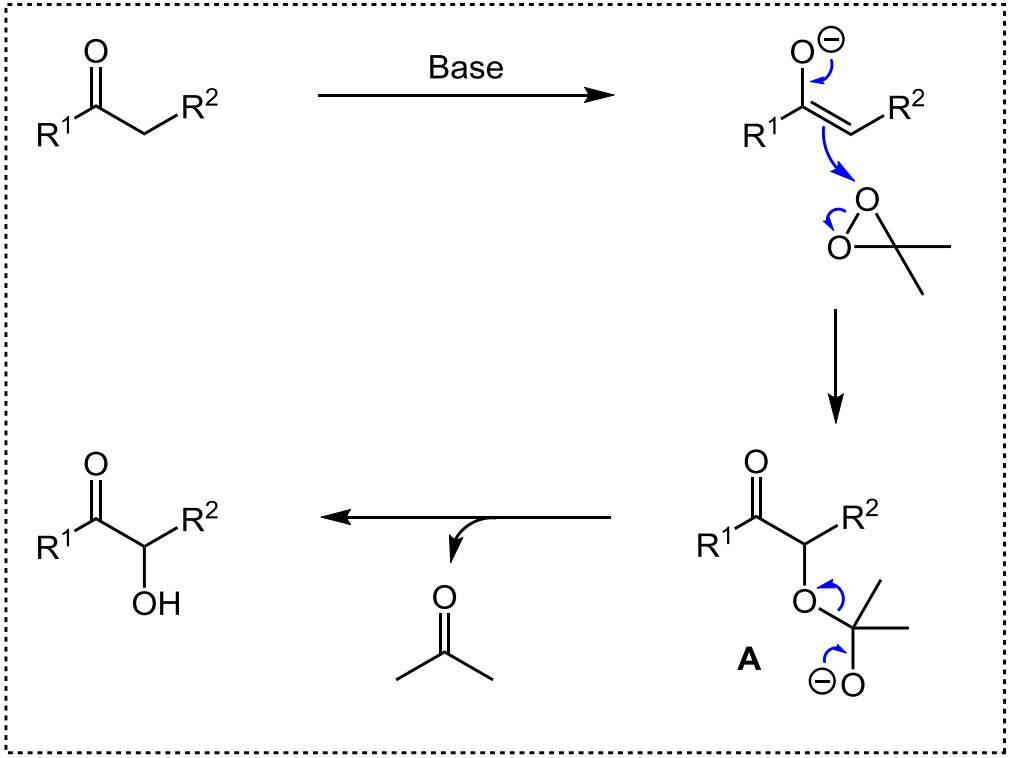
11

Synthesis of (+/-)-Corymine

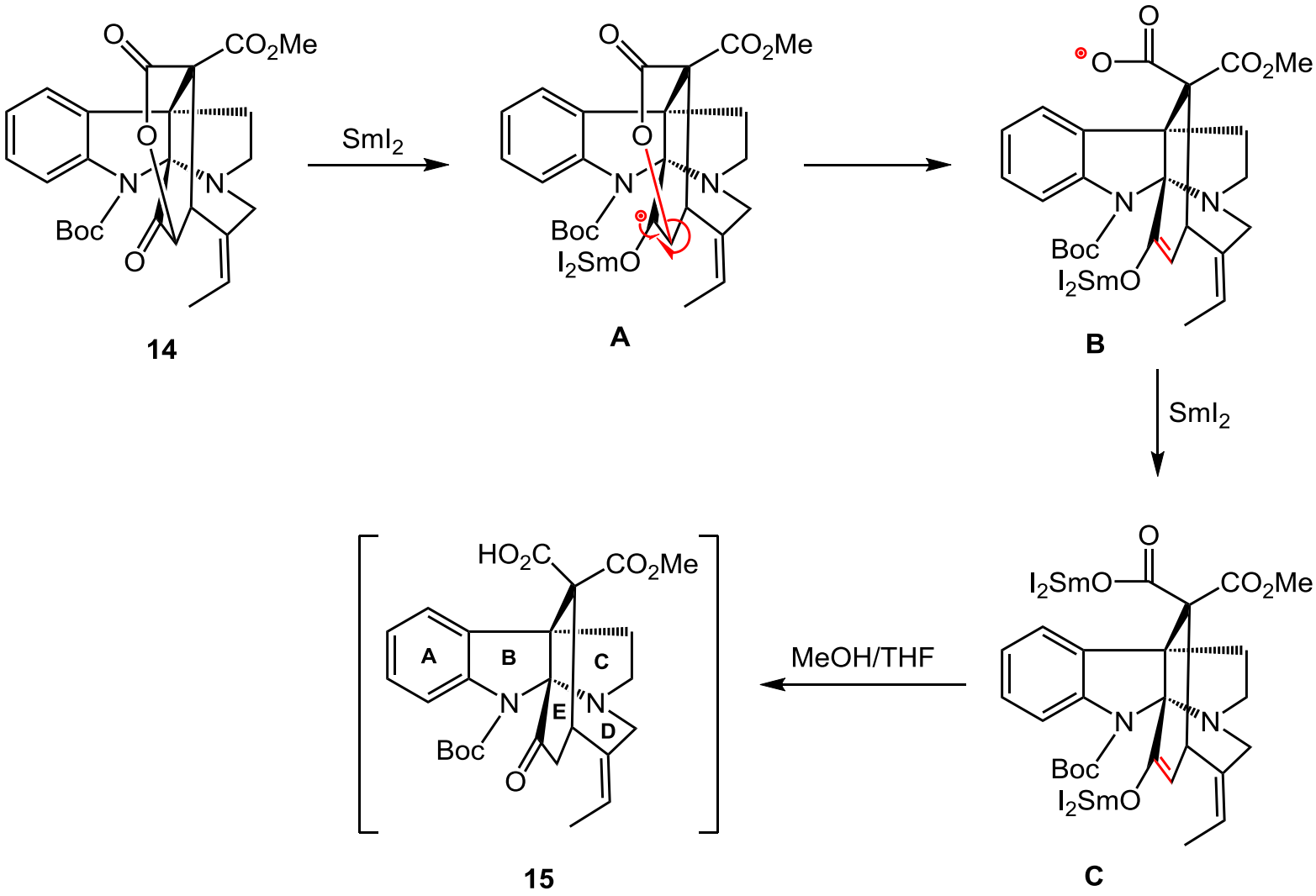


Davis Oxidation

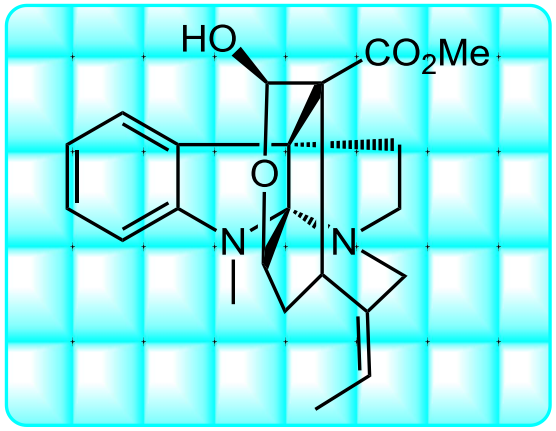




Synthesis of (+/-)-Corymine

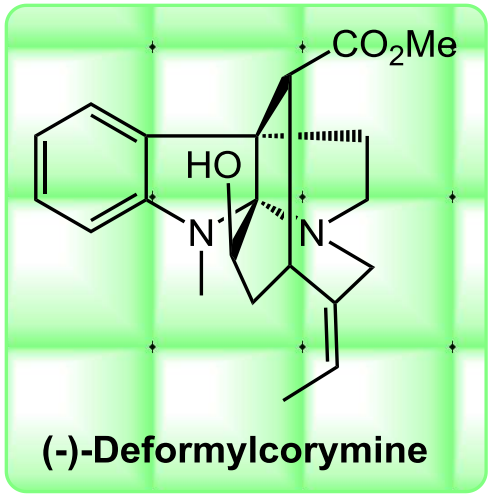


Total Synthesis of Corymine



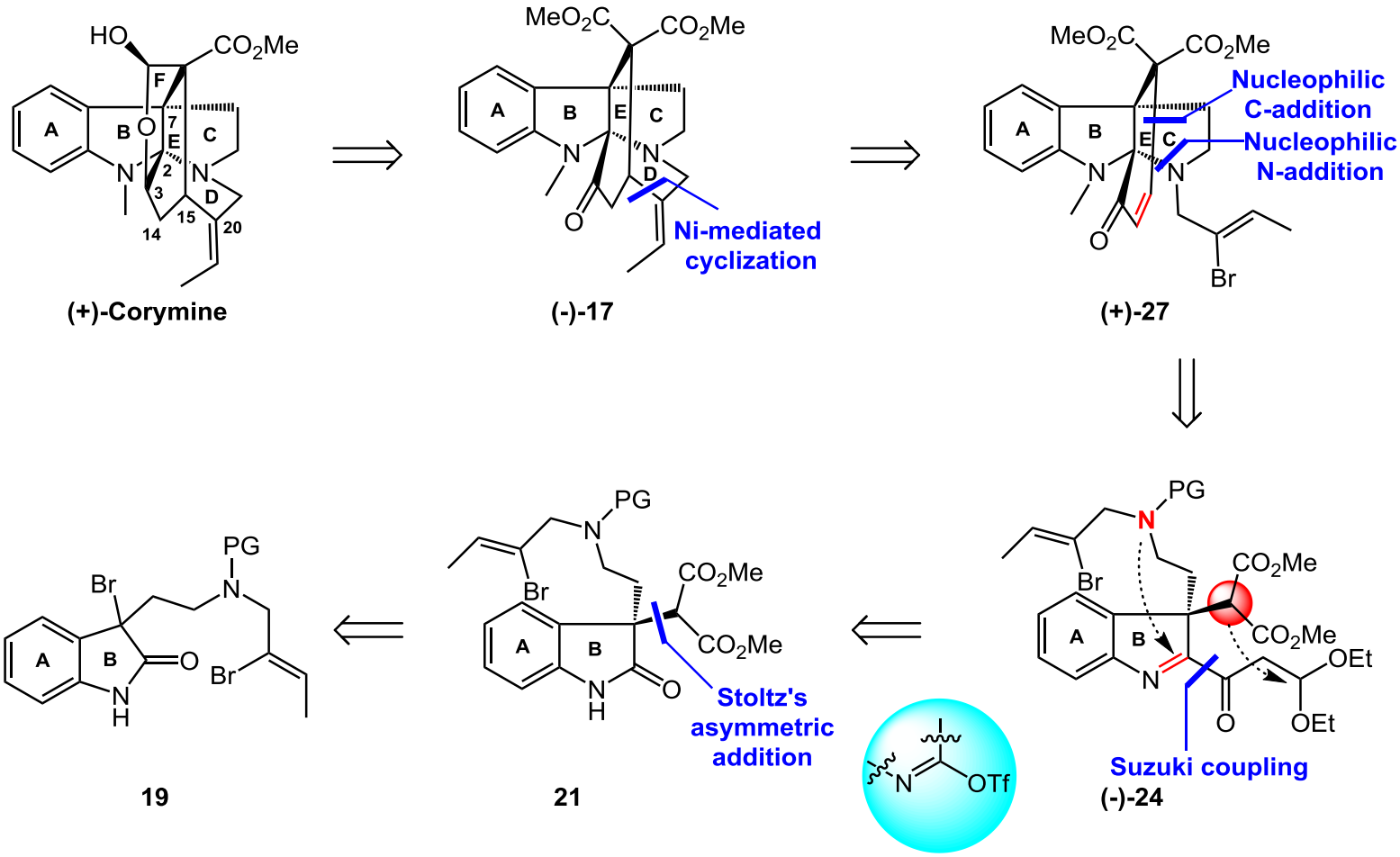
(+/-)-Corymine
21 steps, 3.48% yield
Li, C. *et al. ACIE*. **2017**, *56*, 7484.

(+)-Corymine
11 steps, 3.60% yield
Li, C. *et al. JACS*. **2020**, *142*, 3269.



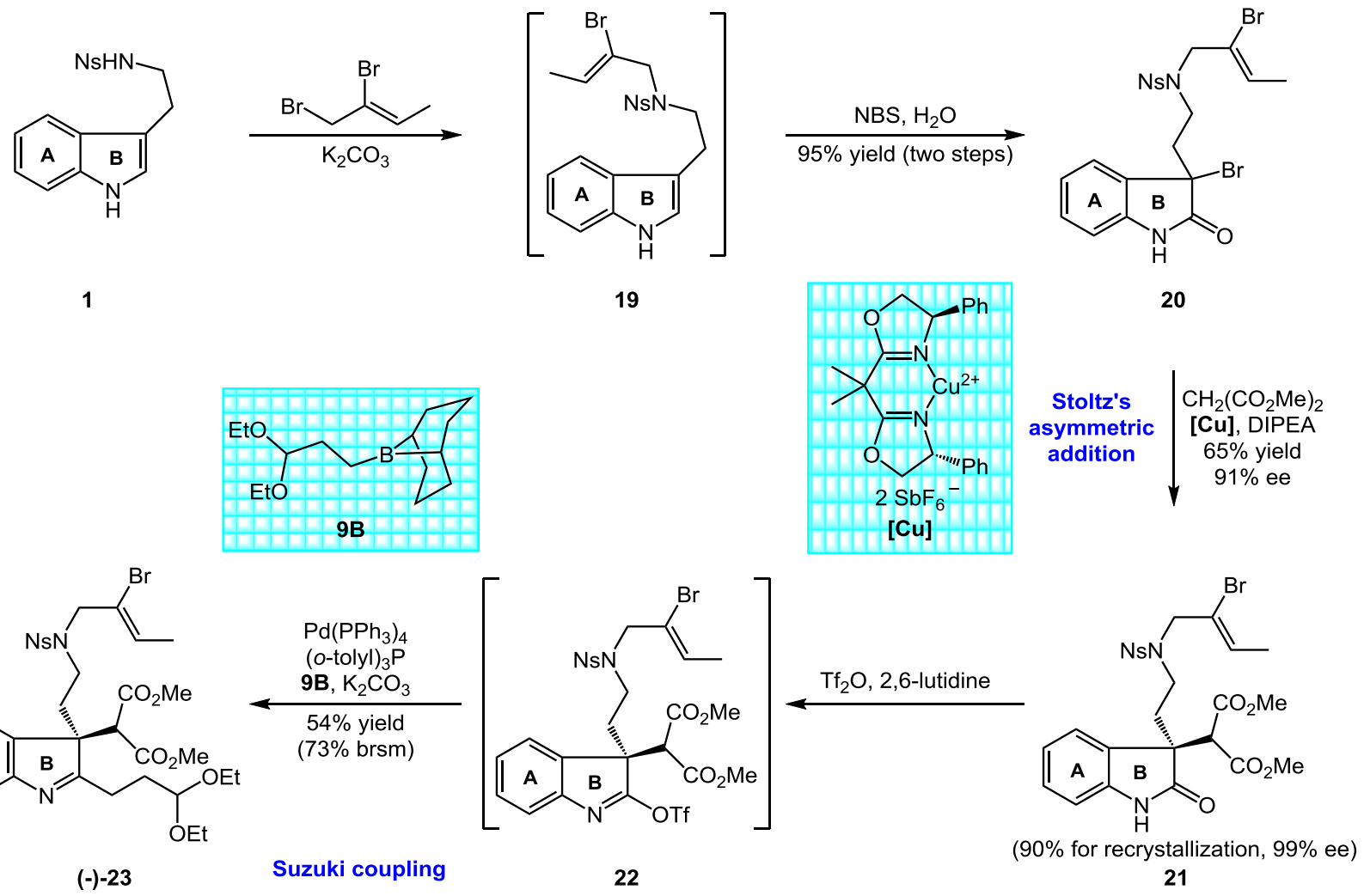
(-)-Deformylcorymine

Retrosynthetic Analysis of (+)-Corymine

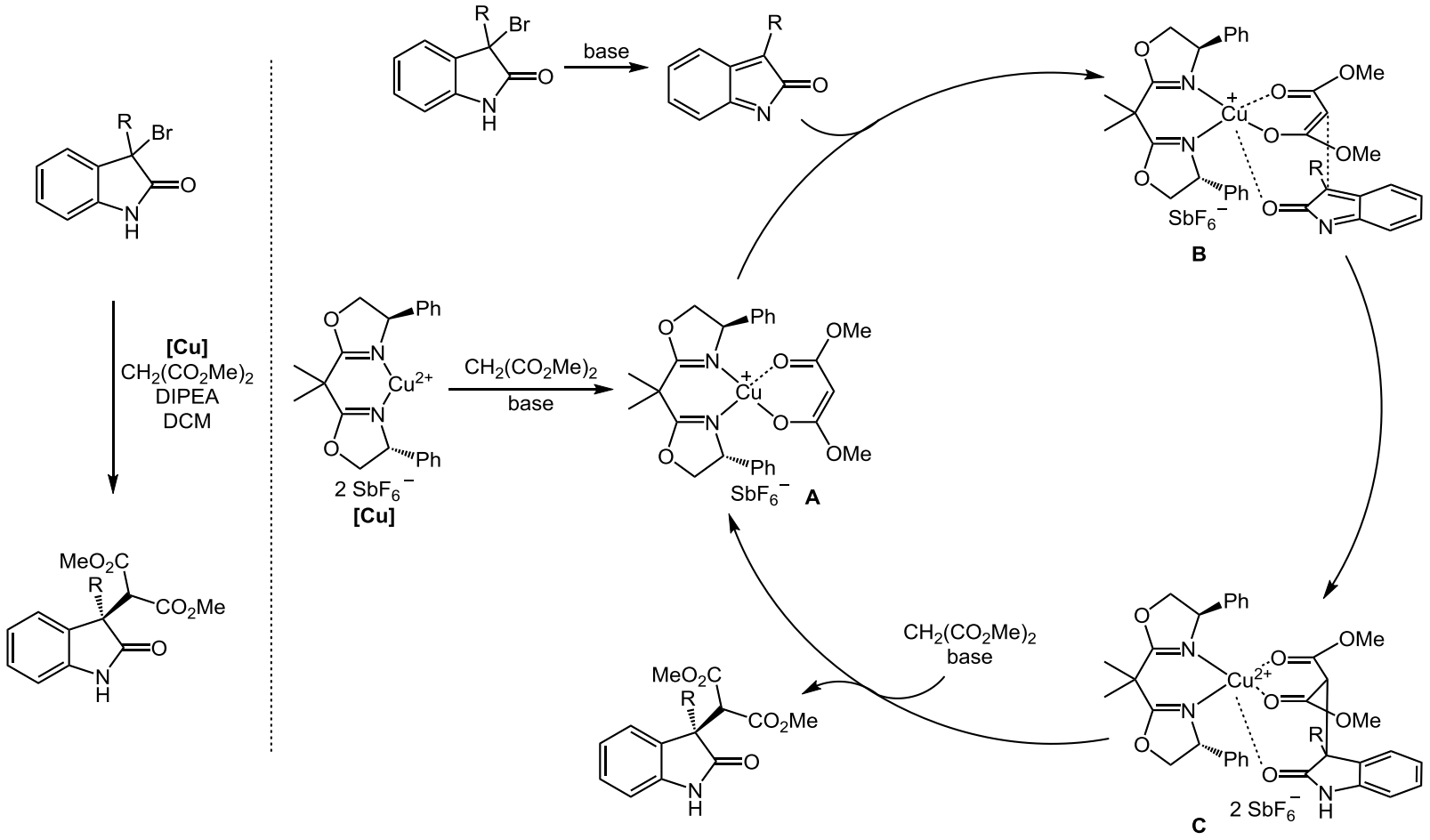


Li, C. *et al*. *J. Am. Chem. Soc.* **2020**, *142*, 3269.

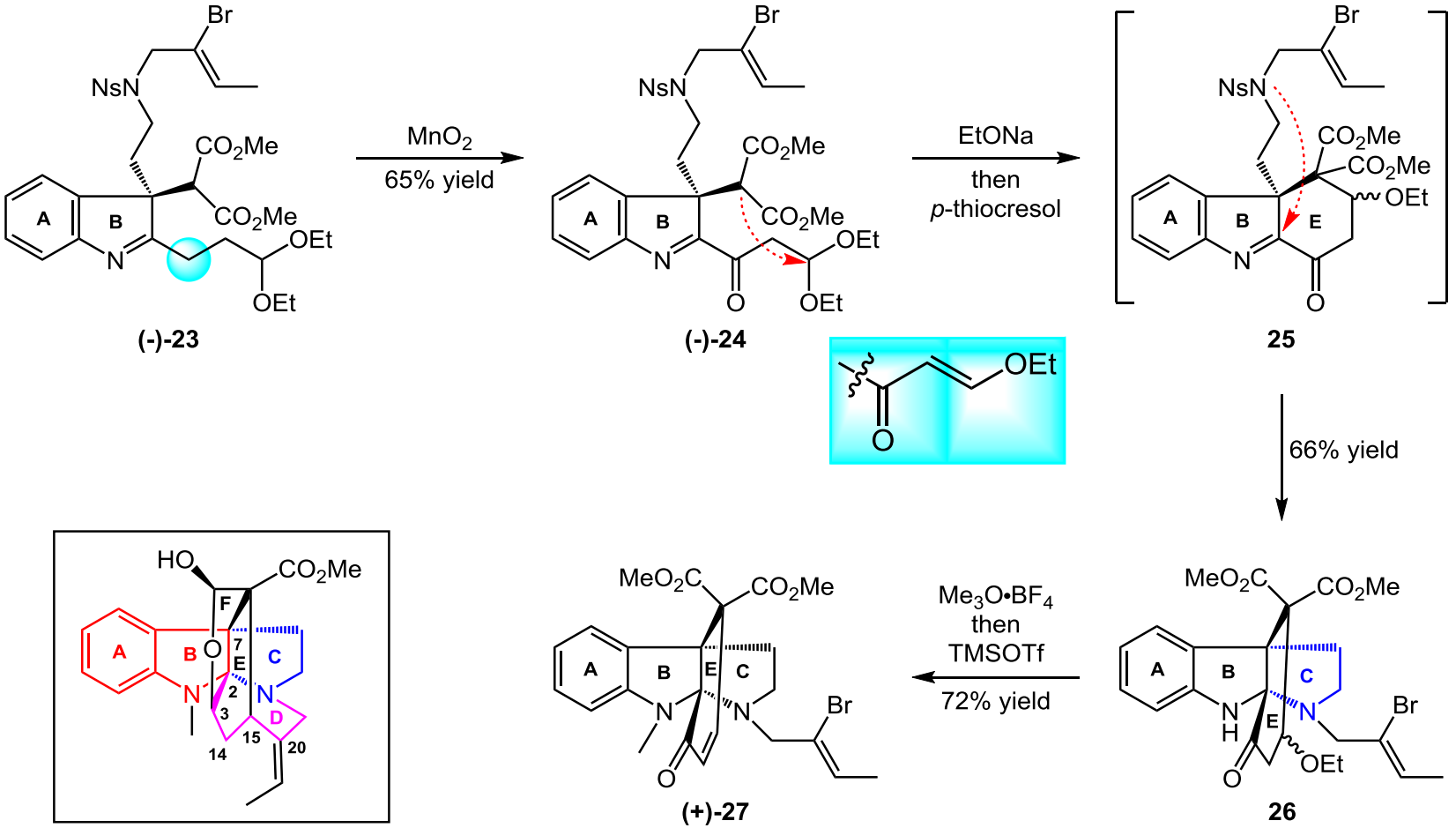
Synthesis of (-)-23



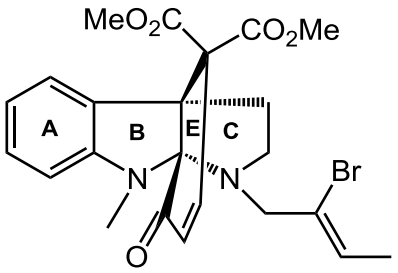
Stoltz's Asymmetric Addition



Synthesis of (+)-27



Synthesis of (+)-Corymine

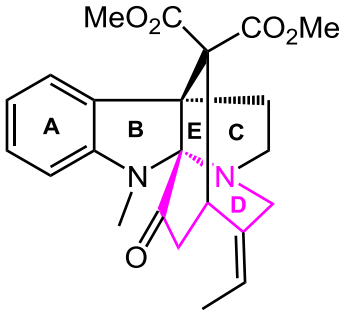


(+)-27

$Ni(cod)_2$, NaI
$Mg(OTf)_2$

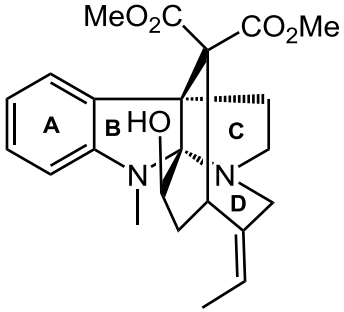
50% yield

$Ni(cod)_2$-mediated cyclization



(-)-17

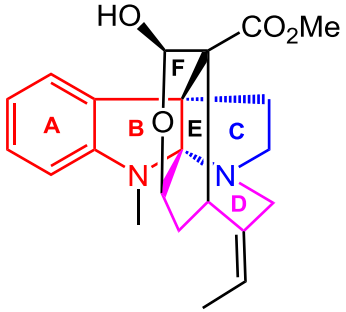
KBH_4
95% yield



(-)-18

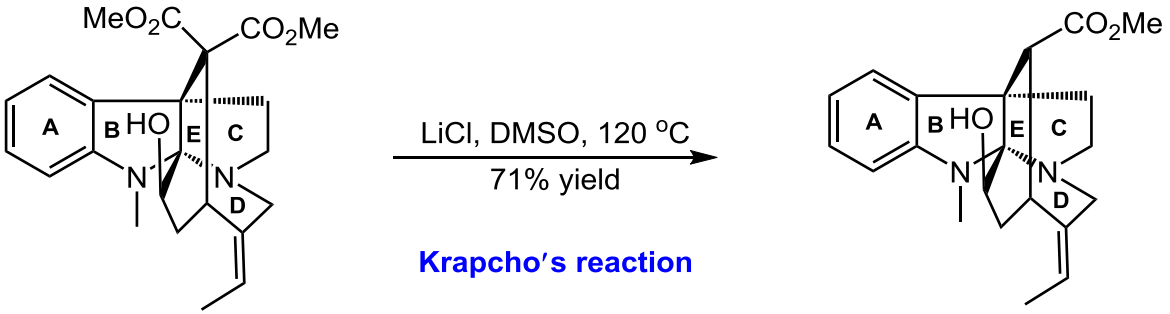
Cs_2CO_3
then DIBAL-H

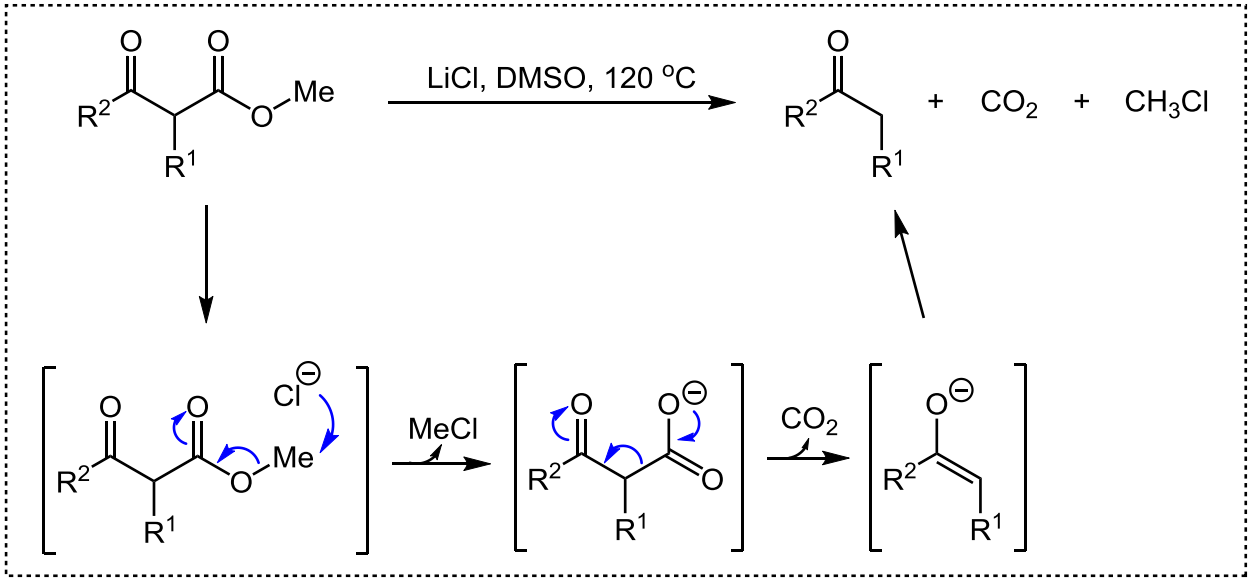
82% yield



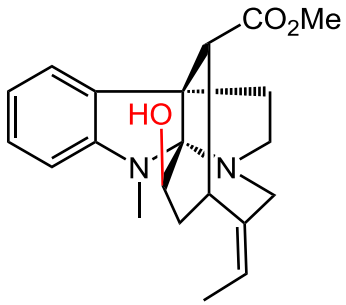
(+)-Corymine

Synthesis of (-)-28



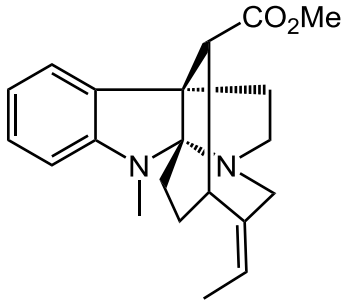


Synthesis of (-)-29

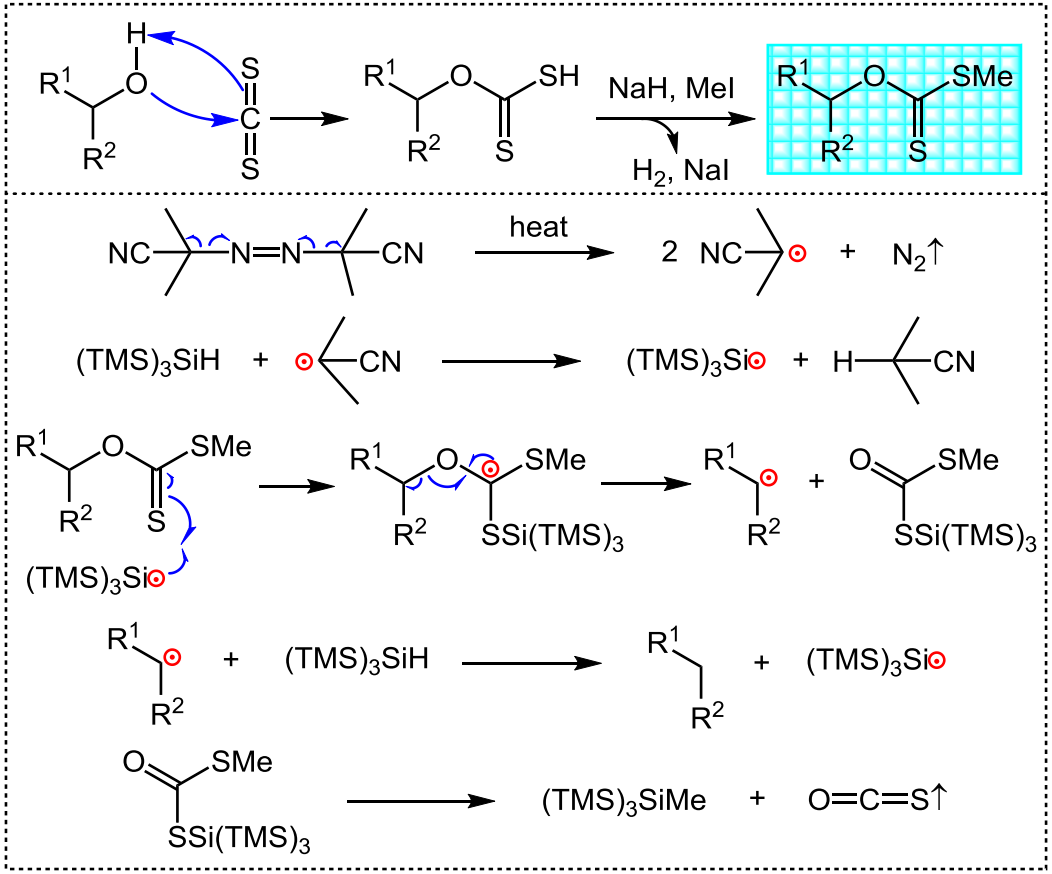


(-)-Deformylcorymine (-)-28

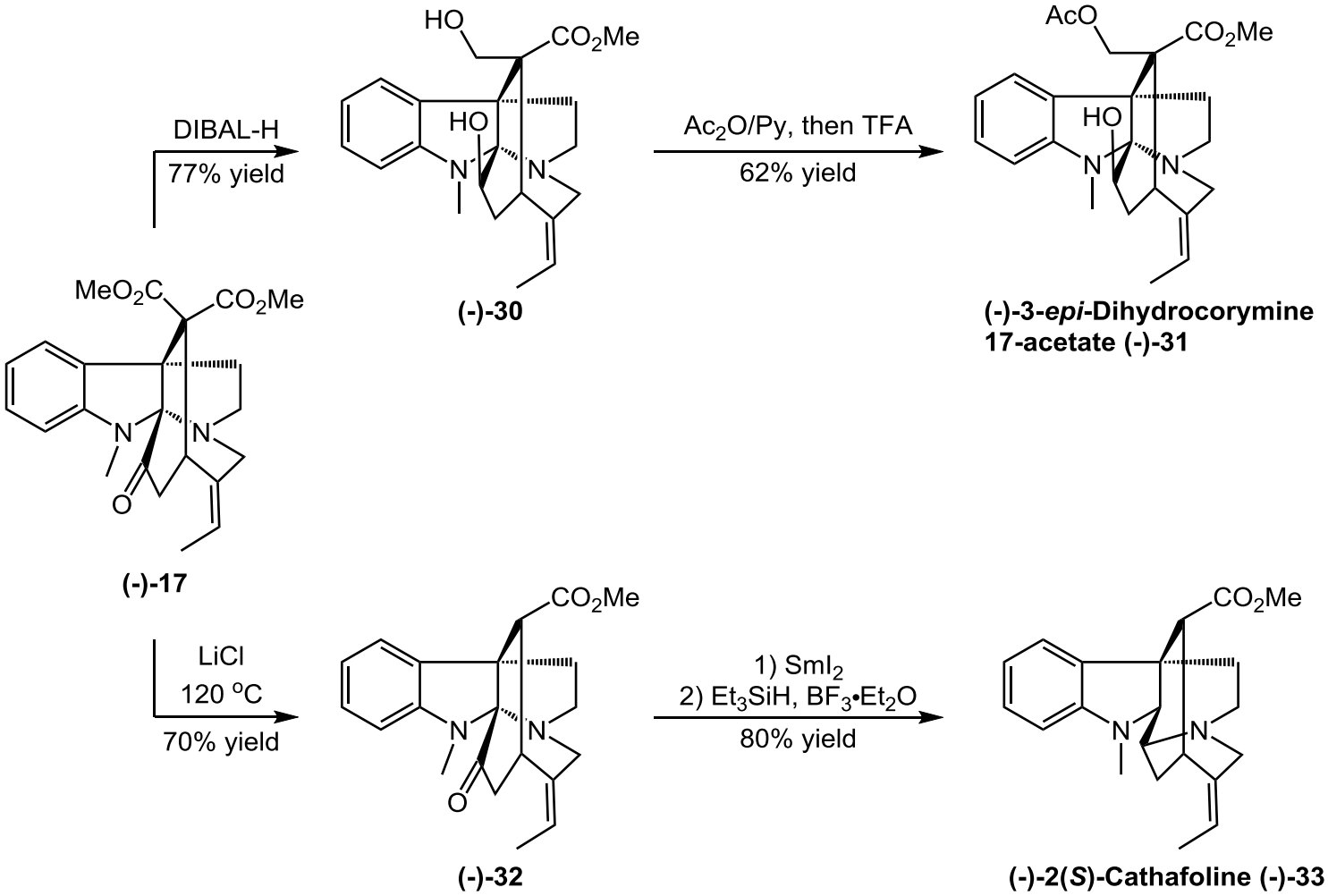
1) CS_2, NaH, MeI
2) $(TMS)_3SiH$, AIBN
82% yield



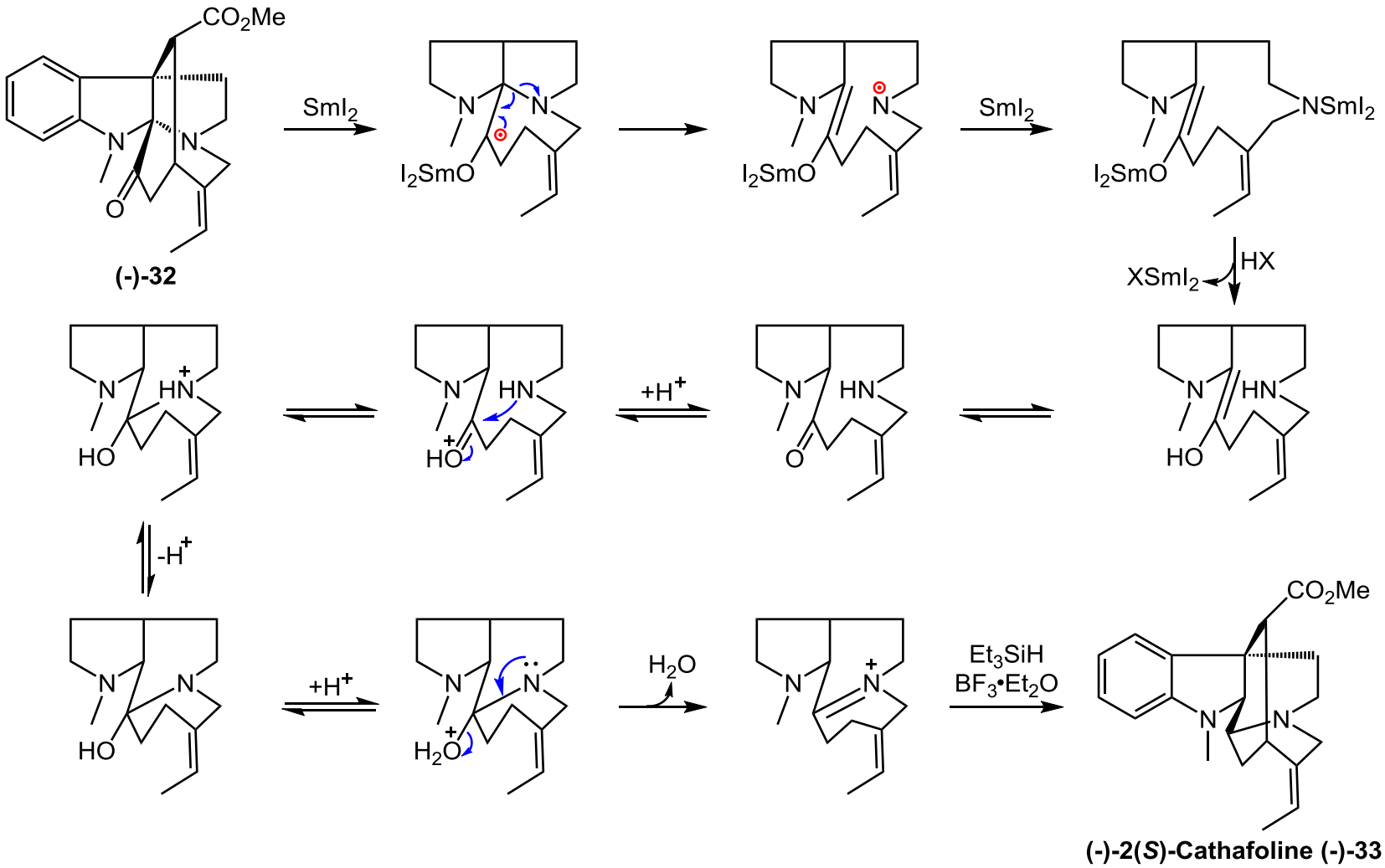
(-)-10-Demethoxyvincorine (-)-29



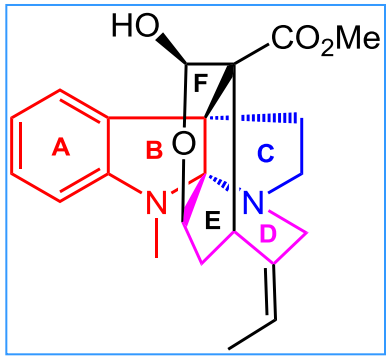
Synthesis of (-)-31 and (-)-33



Synthesis of (-)-33



Summary



(+/-)-Corymine

- 21 Steps, 3.48% overall yield;
- The first total synthesis of (+/-)-corymine;
- Claisen rearrangement and Michael addition;
- Davis oxidation.

Li, C. *et al*. *Angew. Chem. Int. Ed.* **2017**, *56*, 7484.

(+)-Corymine

- 11 Steps, 3.60% overall yield;
- Stoltz's asymmetric addition;
- Suzuki coupling;
- Ni-mediated cyclization.

Li, C. *et al. J. Am. Chem. Soc.* **2020**, *142*, 3269.

Introduction

写作思路

化合物的重要性

↓

目前文献成功报道，合成该类化合物家族的一些例子。

↓

介绍了该化合物结构上的复杂性，合成非常有挑战性。引出文献先前报道消旋版本全合成上的不足，进而引出作者工作。

The First Paragraph

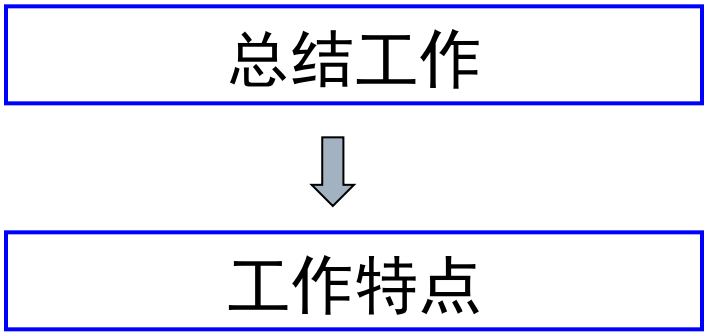
Akuammiline alkaloids are a rich family of monoterpene indole alkaloids with a pentacyclic framework. They display a wide variety of pharmacological activities and have been the subject of medicinal interest for over a century. However, the structural complexity of akuammiline alkaloids deterred them from being the target of organic synthesis until only a decade ago. The structures of representative family members are shown in Figure 1. Over the years the total syntheses of aspidophylline A, prcrinine, strictamine, vincorine, scholarisine A, calophyline A, akuammiline, and a few other family members and related natural products, have been accomplished by a number of research groups. These synthetic endeavors have also spurred the discovery of new synthetic methodologies that demonstrate significant impact on natural product synthesis. For example,

The First Paragraph

the Qin group developed the strategy of cyclopropanation/ring-opening/iminium cyclization (the CRI reaction) for assembling indoline alkaloid skeletons. The Garg group introduced the interrupted Fischer indolization methodology for the construction of fused indoline scaffolds. The Ma group created the intramolecular dearomative oxidative coupling of indoles to install the all-carbon quaternary stereocenter. The MacMillan group introduced the collective natural product synthesis on the basis of organocascade catalysis.

The Last Paragraph

写作思路



The Last Paragraph

In conclusion, we have successfully accomplished the first asymmetric total syntheses of akuammiline alkaloids (+)-corymine. Enabled by our rational design, the title compounds are both achieved in only 11 steps from the commercially available N-nosyltryptamine. The synthesis features (a) the successful establishment of the C7 all-carbon quaternary stereocenter by copper-catalyzed enantioselective malonate addition to a 3-bromooxindole, (b) the formations of cyclohexyl and pyrrolidinyl rings in one step via nucleophilic C- and N-addition and (c) the $Ni(cod)_2$-mediated 7-endo cyclization of alkenyl bromide to secure the azepanyl ring. The strategy is then extended to the total syntheses of (-)-10-demethoxyvincorine (in 13 steps), (-)-2(*S*)-cathafoline (in 11 steps) and (-)-3-epi-dihydrocorymine 17-acetate (in 12 steps), another three members of the akuammiline family.

Representative Examples

They display a wide variety of pharmacological activities and have been the subject of medicinal interest for over a century. (化合物重要性)

The structures of representative family members are shown in Figure 1. (引出其它类似化合物)

These synthetic endeavors have also spurred the discovery of new synthetic methodologies that demonstrate significant impact on natural product synthesis. (研究意义)

Enabled by our rational design, the title compounds are both achieved in only 11 steps from the commercially available N-nosyltryptamine. (该方法的优点)

Acknowledgement

Thanks
for your attention