Literature Report IV

Total Syntheses of (−)-Caulamidine D and (−)-Isocaulamidine D and Their Absolute Configuration Reassignment

Reporter: Bao-Qian Zhao

Checker: Tong Niu

Yu, H.; Zhang, J.; Ma, D.; Xu, T. *J. Am. Chem. Soc.* 2023, *145*, 22335

2024.03.11

CV of Prof. Tao Xu (徐涛)

Research:

- Highly efficient synthesis of fused- and bridged-ring frameworks
- Natural product total synthesis and Synthetic organic methodology development

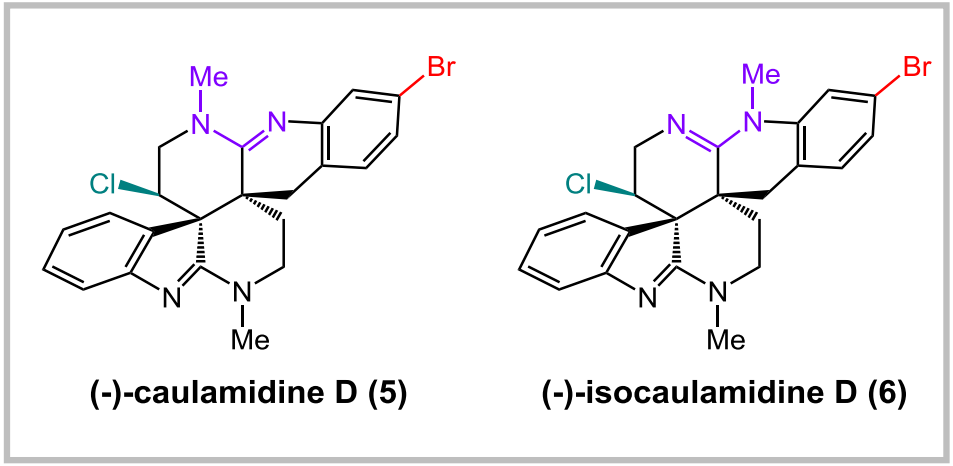
Education & Professional Experience:

- **2006** B.S., Dalian University of Technology
- **2011** Ph.D., Peking University (Prof. Yang Zhen)
- **2011-2015** Postdoc., University of Texas at Austin (Prof. Dong Guangbin)
- **2015-** Professor, Ocean University of China

Contents

Introduction

Isolation of their first congener—2004

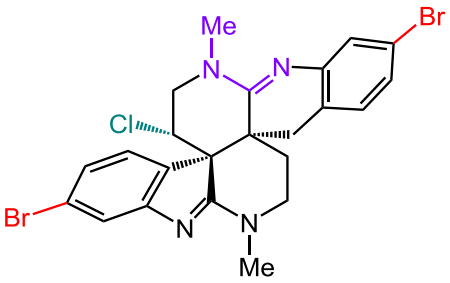


- Halogen incorporation to altered biological activity
- Inhibited plasmodium falciparum at low micromolar concentrations
- This congeners possessed moderate cytotoxicity in the NCI-60 cell lines

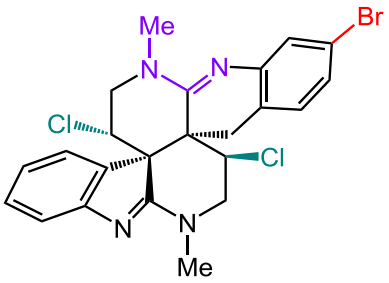
Milanowski, D. J.; Gustafson, K. R.; McMahon, J. B. *J. Nat. Prod*. **2004**, *67*, 70
Tian, X. R.; Wang, D.; Bokesch, H. R.; Gustafson, K. R. *J. Nat. Prod*. **2023**, *86*, 1855

Introduction

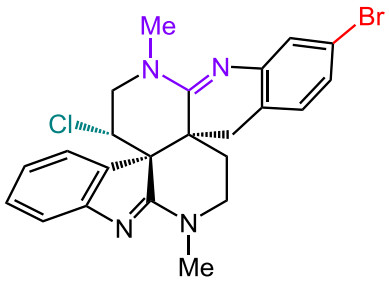
Caulamidines Isolated from Ascidians



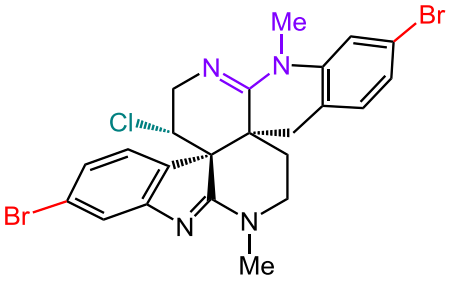
caulamidine B (1)



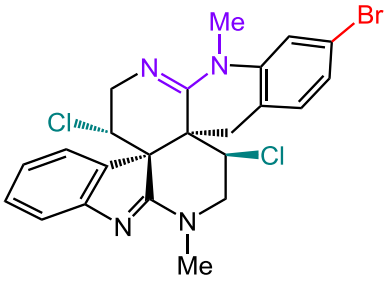
caulamidine C (3)



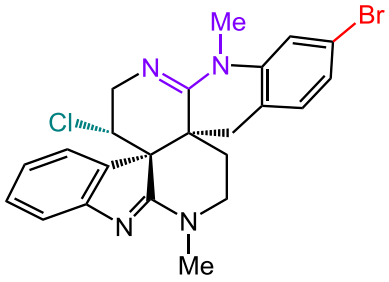
caulamidine D (5)
orginal assignment



isocaulamidine B (2)



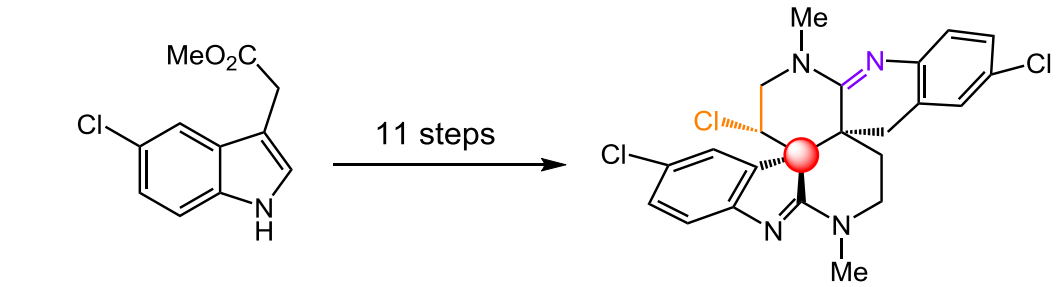
isocaulamidine C (4)



isocaulamidine D (6)
orginal assignment

Introduction

Synthesis of Caulamidine A



methyl 5-Cl indole-3-acetate

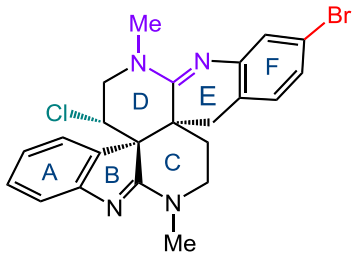
caulamidine A (7)

- ✓ **Pd-Catalyzed Asymmetric Prenylation**
- ✓ **Diastereoselective Ketone-Amidine Annulation Reaction**
- ✓ **Highly Diastereoselective Hydrogen Atom Transfer**

Zhu, Z.; Maimone, T. J. *J. Am. Chem. Soc.* 2023, *145*, 14215

Retrosynthetic Analysis

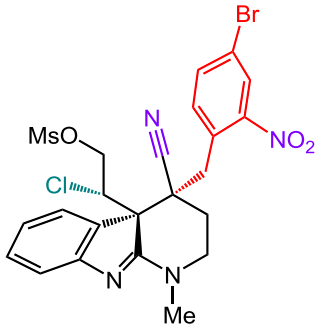
Retrosynthetic Analysis



caulamidine D (5)

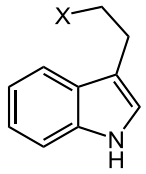
cascade cyclization

divergent methylation



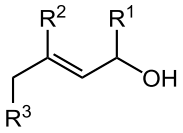
8

electrophilic
chlorination / alkylation



10

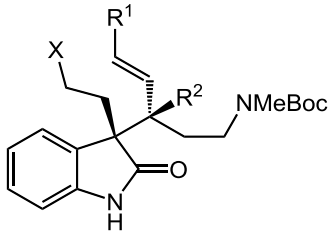
+



11

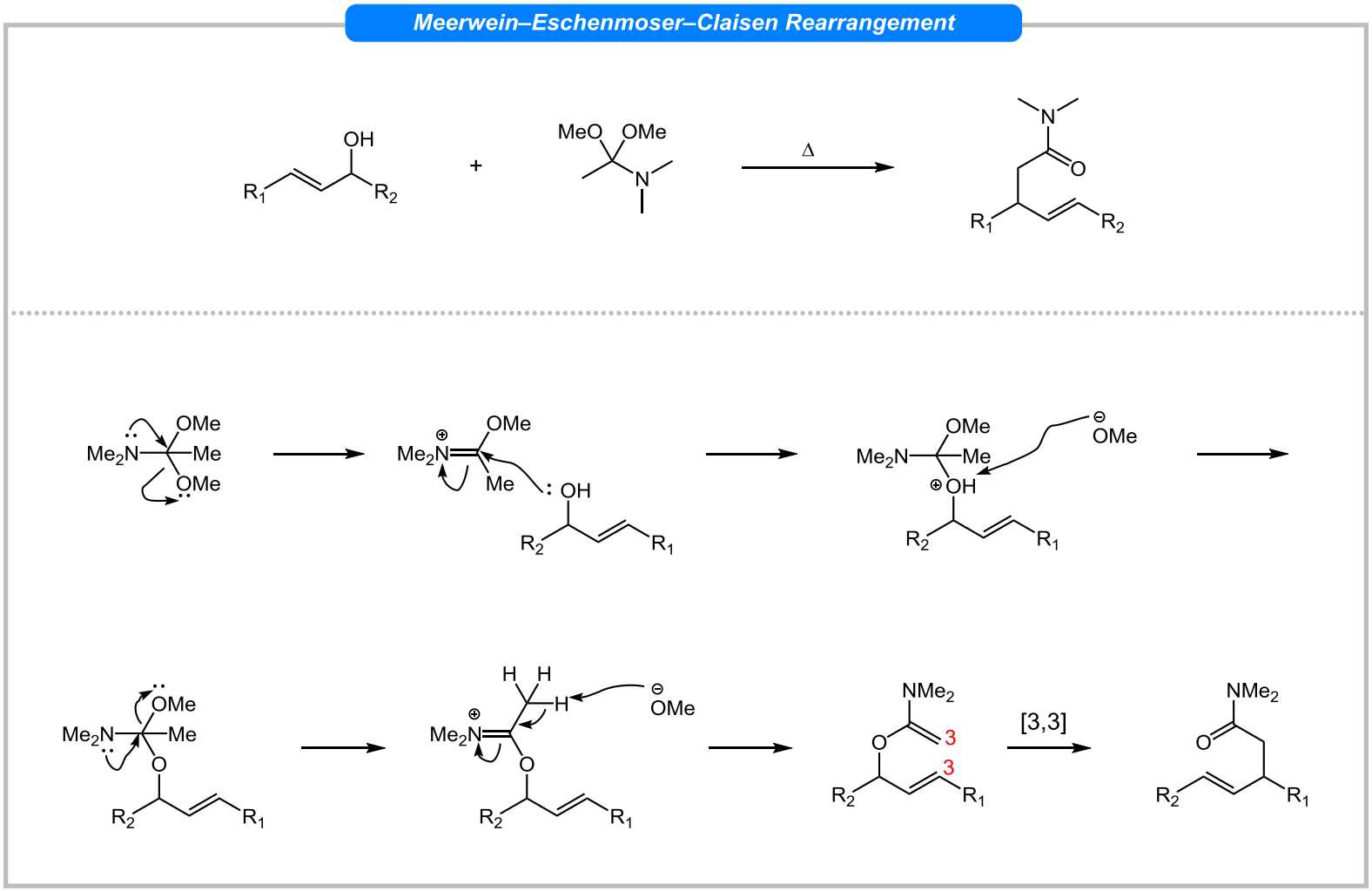
AMEC rearrangemt

vicinal stereocenters in one step

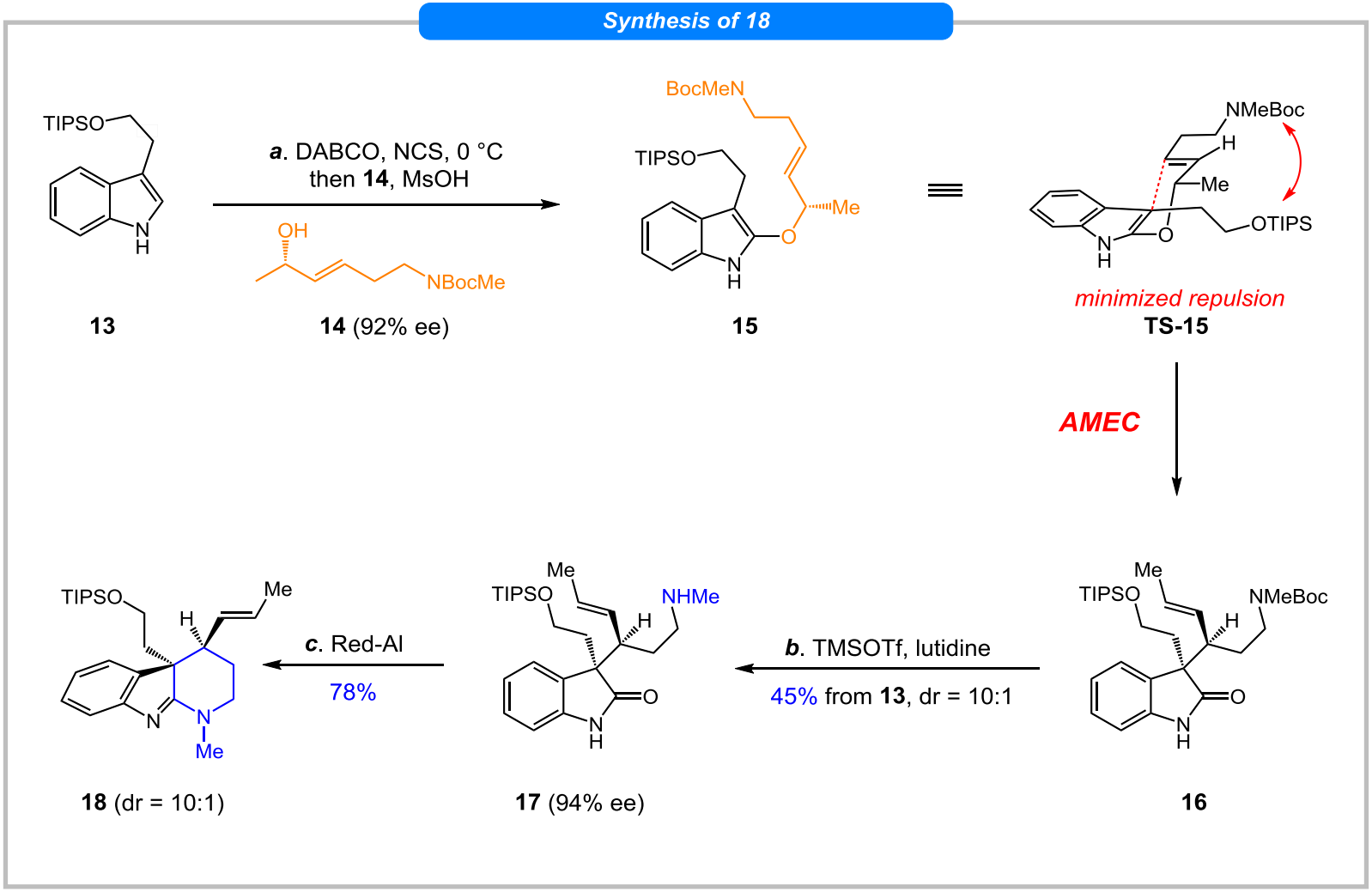


9 X = N, O etc

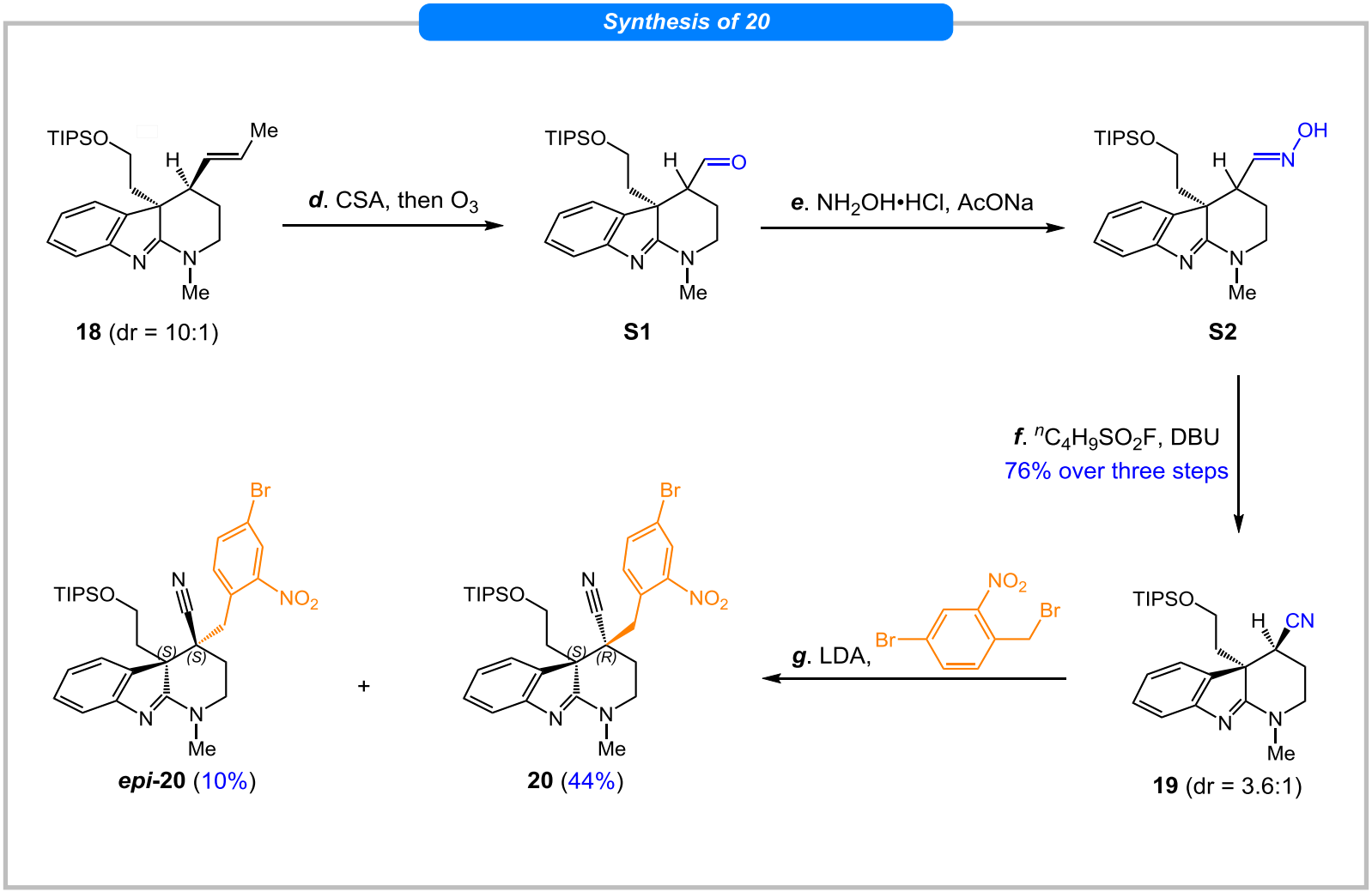
Meerwein–Eschenmoser–Claisen Rearrangement



Stage 1—Synthesis of Key Intermediate 8

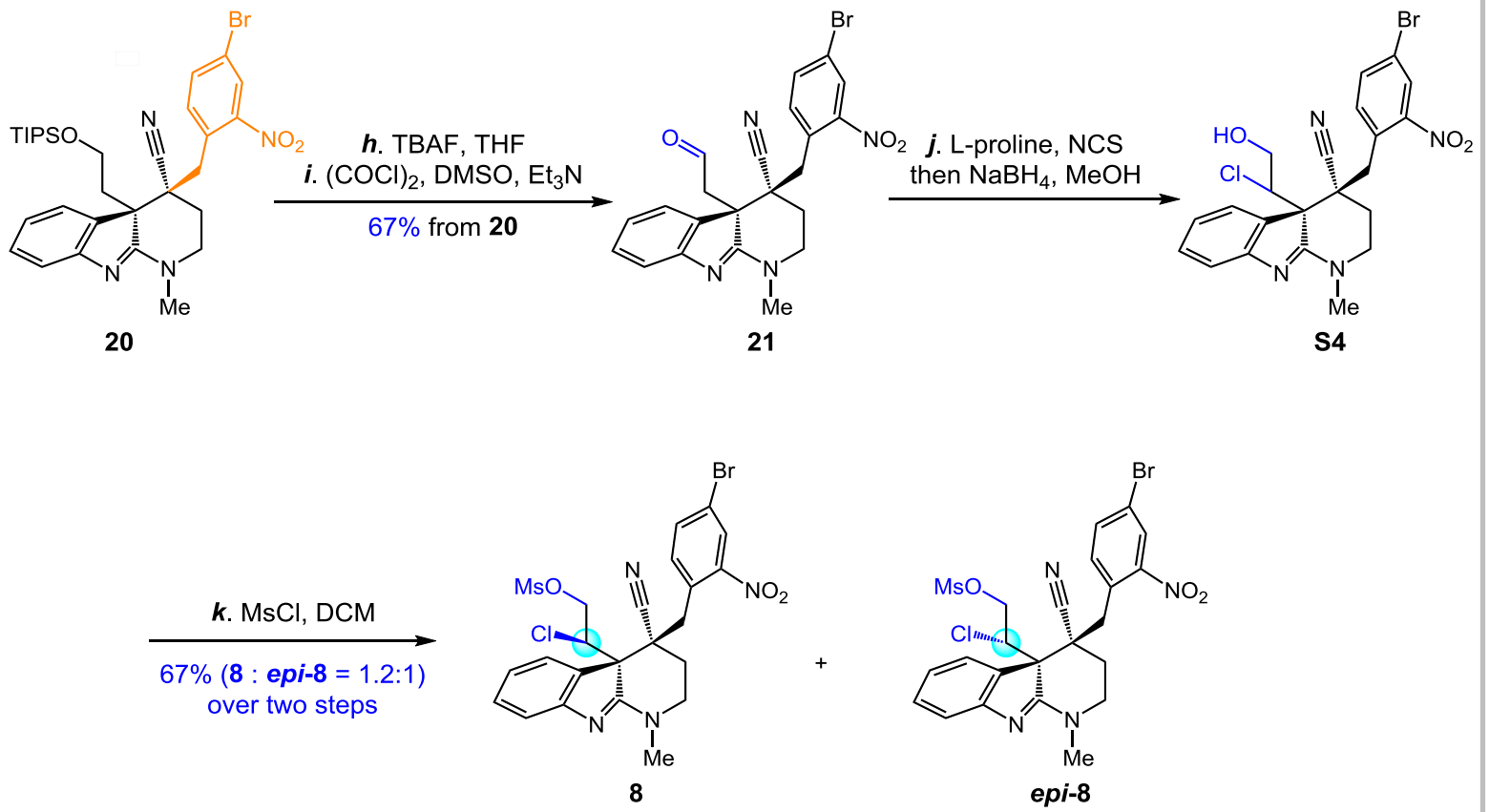


Stage 1—Synthesis of Key Intermediate 8

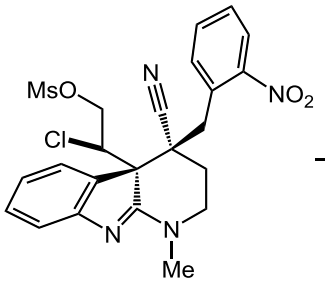


Stage 1—Synthesis of Key Intermediate 8

Synthesis of 8

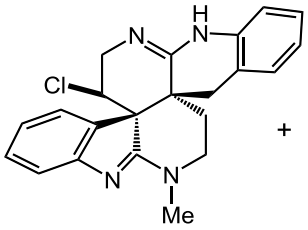


Stage 2— Condition Optimization



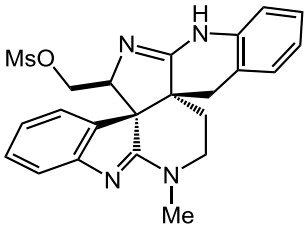
24

conditions



25a

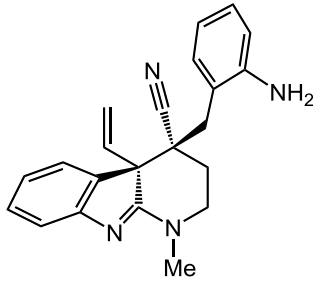
+



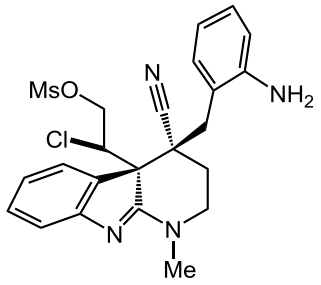
25b

Entry	Conditions	Time	25a (%)	25b (%)	25c (%)	25d (%)
1	Zn powder, NH_4Cl	2 h	38	16	20	3
2	Fe powder, NH_4Cl	0.5 h	43	28	0	24
3	In powder, NH_4Cl	2 h	25	31	3	3
4	Fe powder, HCl	0.5 h	23	53	0	3
5	Fe powder, NH_4Cl	2 h	49	16	0	3
6	Fe powder, NH_4Cl	3 h	53	24	0	0

Reaction Condition: [a]EtOH (0.5 mL) and NH_4Cl (aq.) (0.25 mL) solution containing **24** (0.06 mmol, 1 equiv) was added metal powder (4 equiv) at room temperature, and the mixture was stirred at 90 °C. [b]Isolated yields.



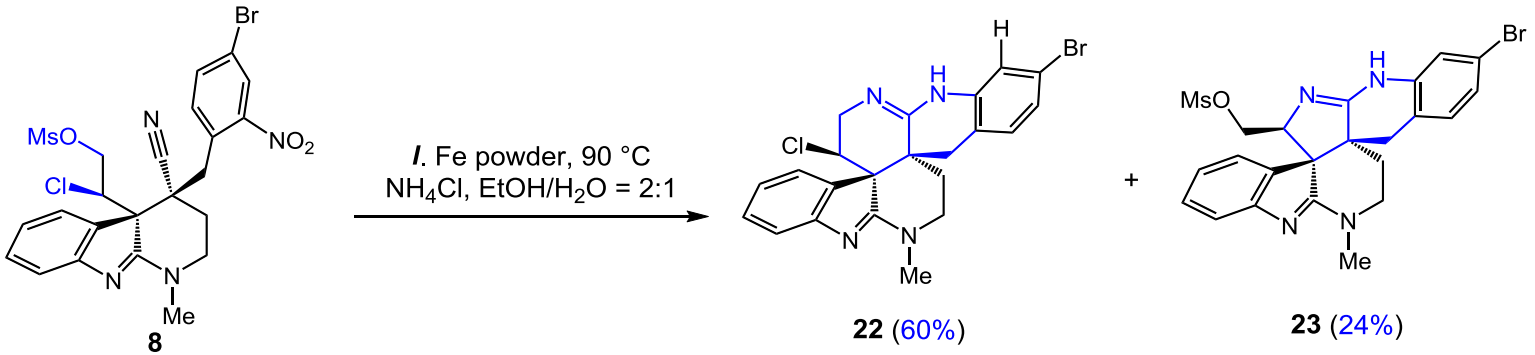
25c



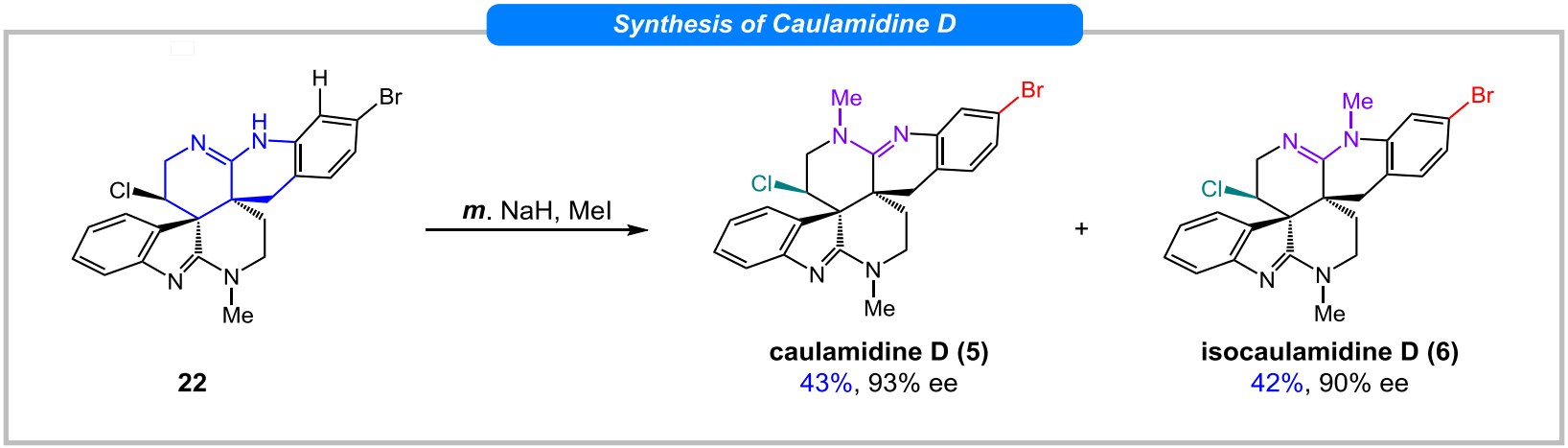
25d

Stage 2— Synthesis of 22

Synthesis of 22

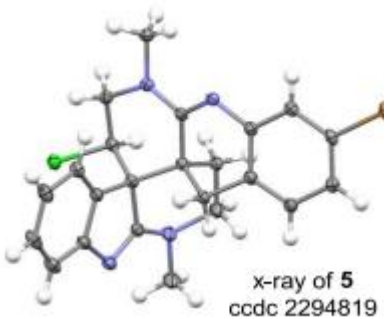


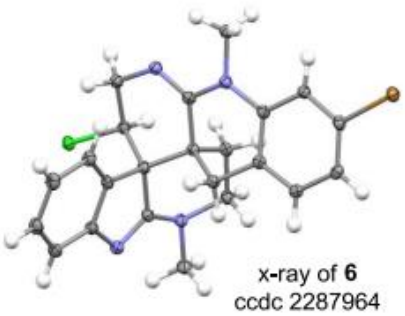
Stage 3—Synthesis of 5 and 6



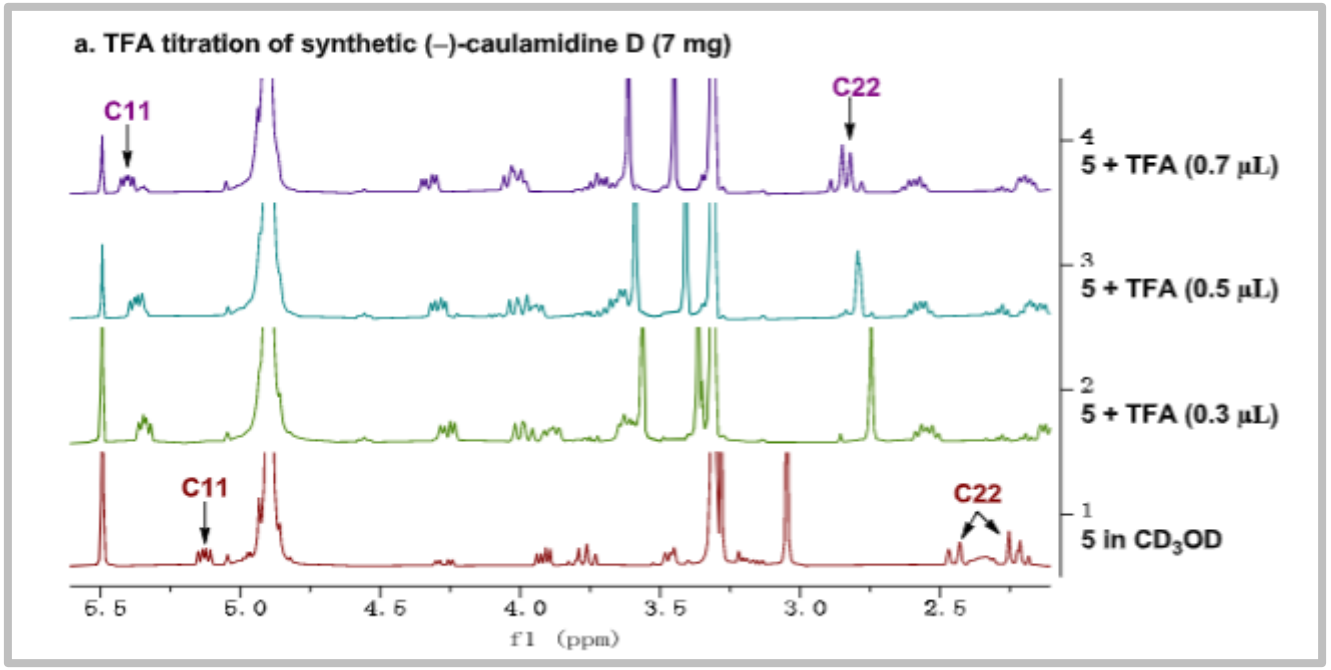
$[\alpha]^{20}_D = -60$ (c 0.05, CH_2Cl_2) for **5**
Original report: $[\alpha]^{20}_D = -62$ (c 0.01, MeOH)

$[\alpha]^{20}_D = -59$ (c 0.1, CH_2Cl_2) for **6**
Original report: $[\alpha]^{20}_D = -60$ (c 0.02, MeOH)

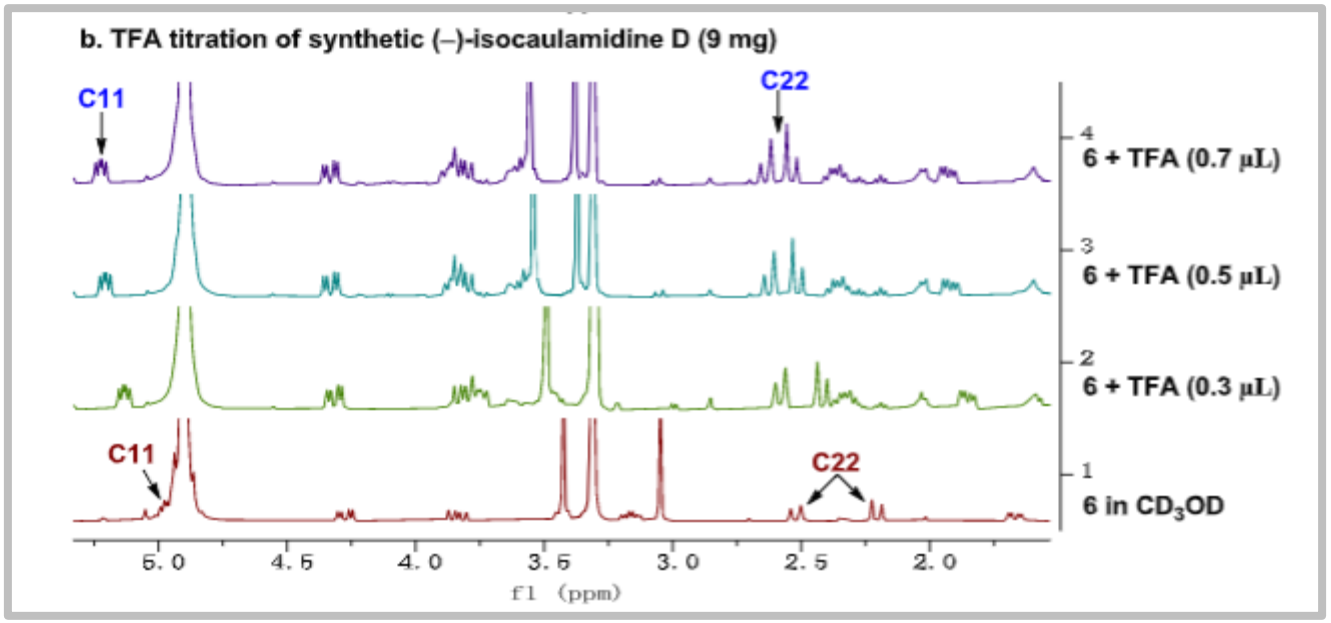




TFA Titration of Synthetic 5 and 6 in CD_3OD

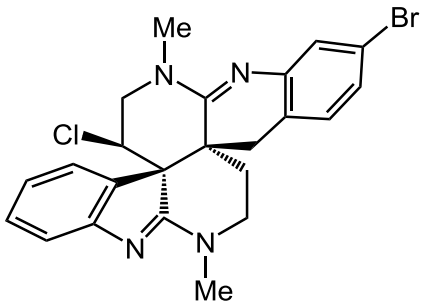


TFA Titration of Synthetic 5 and 6 in CD_3OD

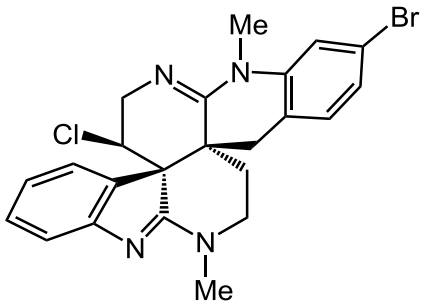


Summary

Total Synthesis of 5 and 6



caulamidine D (5)



isocaulamidine D (6)

» ***The First Enantioselective Total Syntheses of 5 and 6, 0.03% Overall Yield***

» ***Asymmetric MECR to Construct the Key Consecutive Stereocenters***

» ***Conception and Implementation of A Cascade Amine/Nitrile Cyclization Strategy***

Writing Strategies

☐ The First Paragraph

Source and Bioactivities of Caulamidines A-D

↓

Previous work of Caulamidines A-D

↓

Main Content of This Work

- ✓ Ascidians are a very important class of marine invertebrates in terms of providing structurally intriguing and biologically promising secondary metabolites. Halogen incorporation is a unique tactic that marine organisms use to decorate their multipurpose metabolites and usually results in altered biological activities.
- ✓ During the preparation of this Letter, Zhu and Maimone reported the first elegant total synthesis of caulamidine A over 11 steps (longest linear sequence) starting from methyl 5-chloroindole-3-acetate based on three key reactions.
- ✓ However, the structures and absolute configurations of newly reported (iso)caulamidines B–D have not been rigorously determined, although contemporary NMR techniques and DFT calculations have been applied.

Writing Strategies

☐ The Last Paragraph

Summary of this Work

- ✓ The first enantioselective total syntheses of (−)-caulamidine D and its congener (−)-isocaulamdine D were completed. A major finding when comparing NMR data is that the natural samples of **5** and **6** were actually TFA salts.

Highlights of this Work

- ✓ The key reactions include (1) the development and application of an asymmetric Meerwein–Eschenmoser–Claisen rearrangement to construct the key C10, C23 consecutive stereocenters and (2) the conception and implementation of a cascade 6-exo-dig/6-exo-tet amine/nitrile cyclization strategy.

Outlook of this Work

- ✓ It is hoped that the scalable nature of this synthetic route may serve as a platform to solve the “supply issue” of these natural samples in future medicinal research.

Representative Examples

- ✓ **Architecturally** (*adv.* **在结构上**), the caulamidines share a hydrogenated 2,6-naphthyridine core fused indole unit and a quinoline fragment that form a novel 21-carbon hexacyclic alkaloid. .
- ✓ When we compared the NMR spectra of our synthetic **6** with the reported data, an **astonishing** (*adj.* **惊人的，意想不到的**) observation was that they did not match at all. Neither did the data for **5**.
- ✓ It is hoped that the scalable nature of this synthetic route may serve as a platform to solve the "**supply issue**" (**供应问题，本文指代海洋药物的来源**) of these natural samples in future medicinal research.

Acknowledgement

Thanks for your attentions!