Literature Report III

Enantioselective Total Synthesis of (–)-Caulamidine A

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Checker: Tong Niu

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

2023.10.09

CV of Prof. Thomas. J. Maimone

Research:

- Natural product total synthesis
- Synthetic organic methodology development

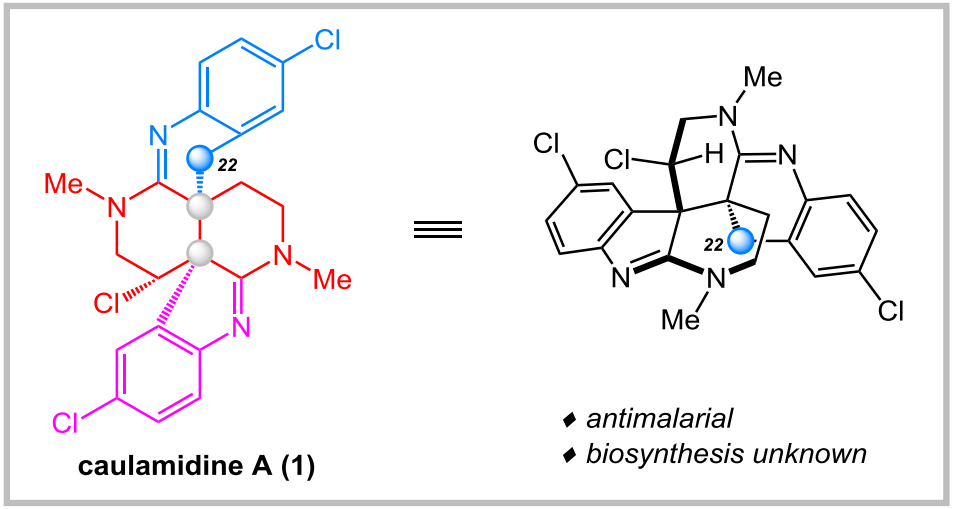
Education & Professional Experience:

- **2004** B.S., UC, Berkeley
- **2009** Ph.D., The Scripps Research Institute
- **2009-2012** NIH Postdoctoral Fellow, MIT
- **2012-** Assistant Professor, UC, Berkeley

Contents

Introduction

Isolation of their first congener—2004

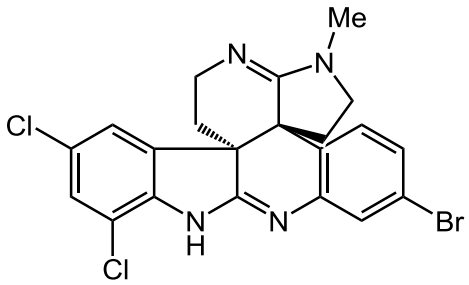


- Inhibited plasmodium falciparum at low micromolar concentrations
- Hexahydro-2,6-naphthyridine core
- Fused to a dihydroindole-derived and tetrahydroquinoline-based ring

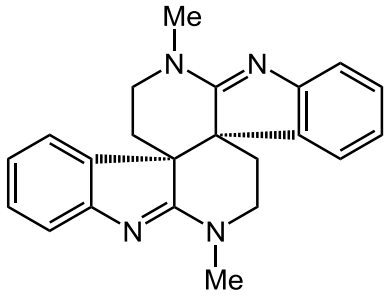
Milanowski, D. J.; Gustafson, K. R.; McMahon, J. B. *J. Nat. Prod*. **2004**, *67*, 70

Introduction

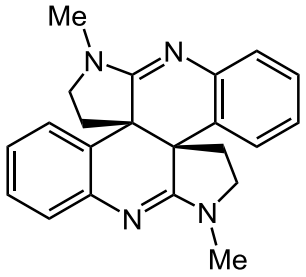
Dimeric Cyclotryptamine Alkaloids



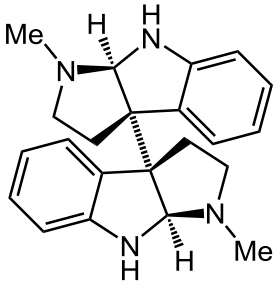
(+)-perphoramidine (4)



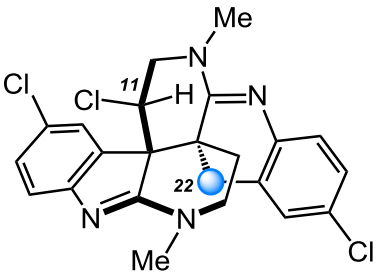
psychotriadine (5)



dehydrobhesine (6)

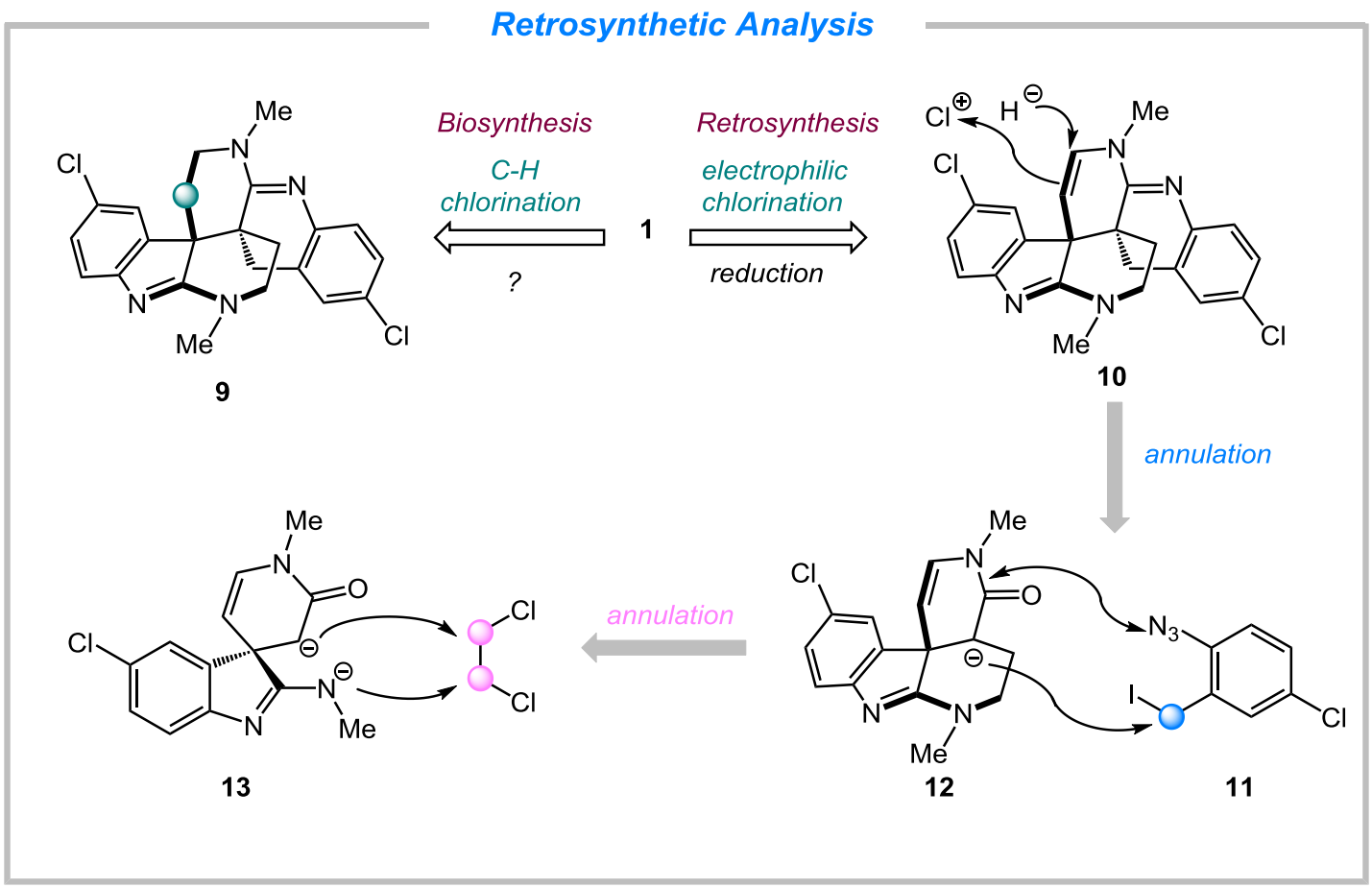


(+)-chimonanthine (7)



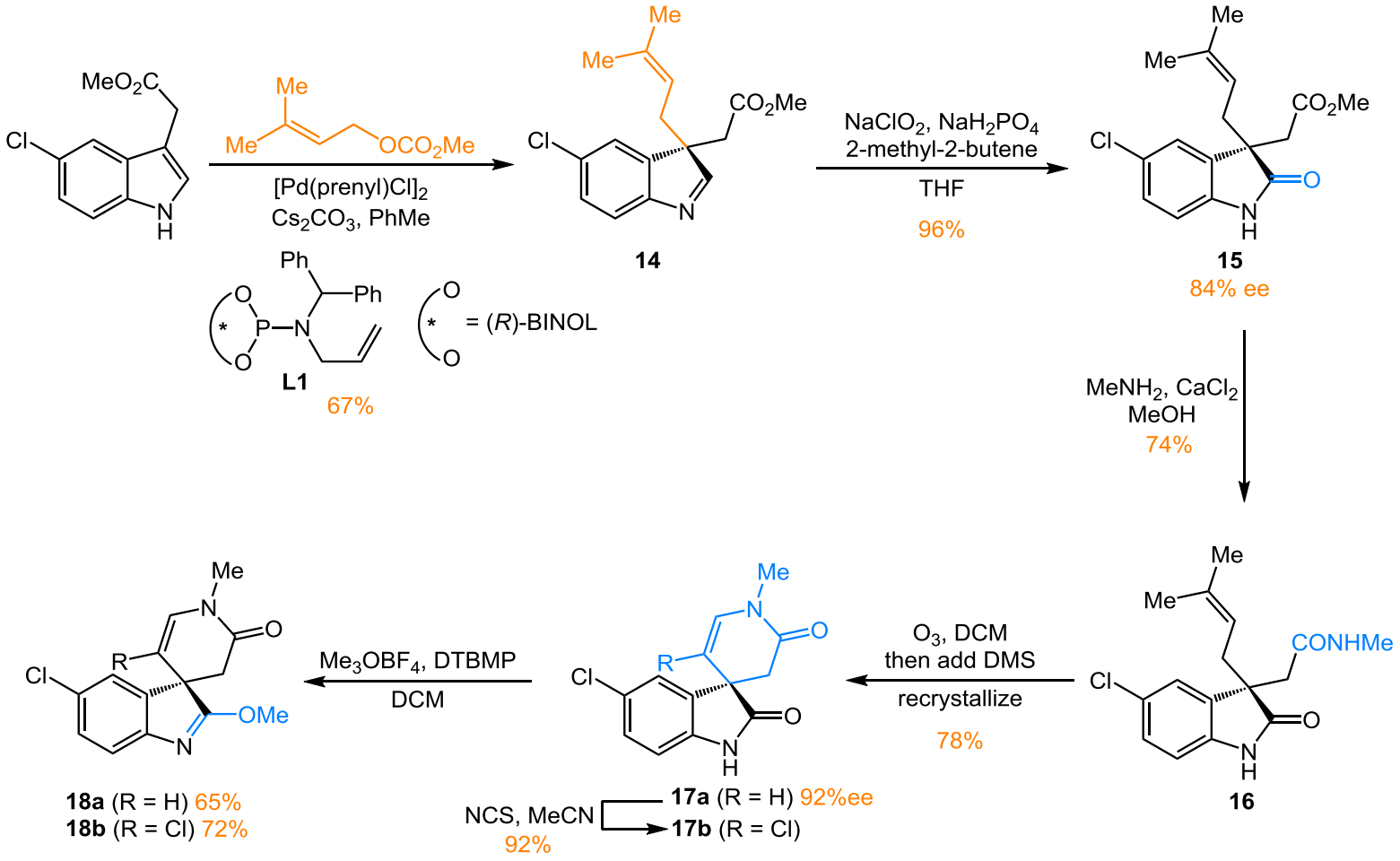
caulamidine A (1)

Retrosynthetic Analysis of (–)-Caulamidine A

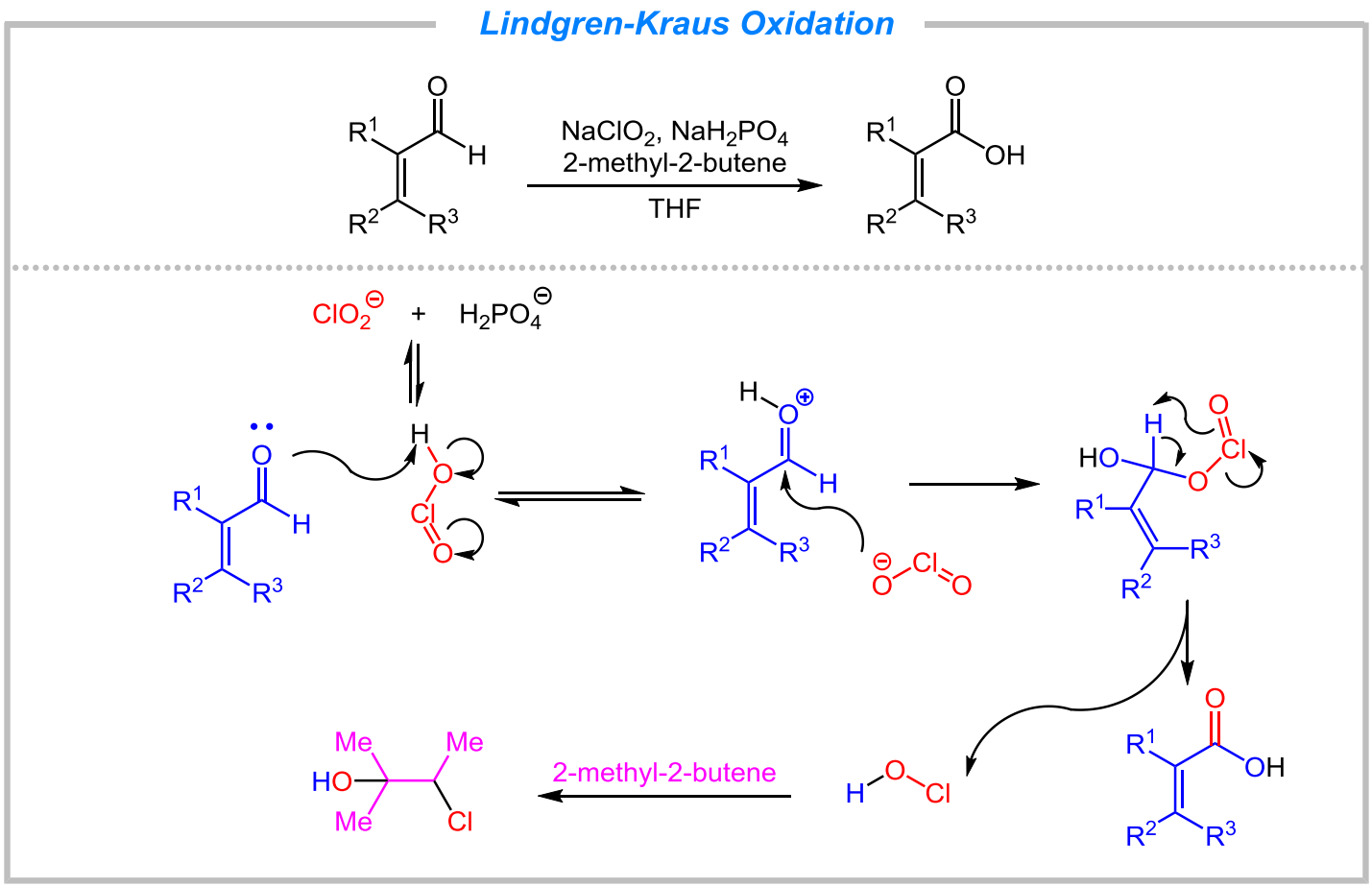


Stage 1

Enantioselective Total Synthesis of (–)-Caulamidine A

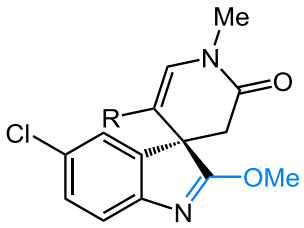


Lindgren–Kraus Oxidation



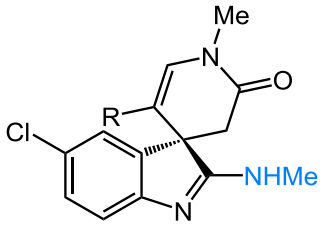
Stage 2

Enantioselective Total Synthesis of (–)-Caulamidine A



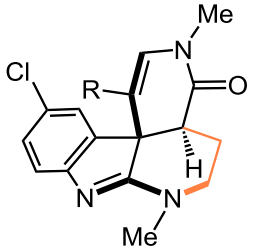
18a (R = H) 65%
18b (R = Cl) 72%

$MeNH_2$, $Ti(O^iPr)_4$
MeOH

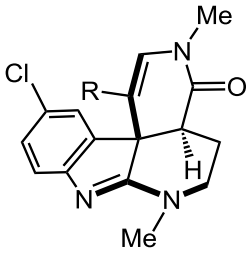


13a (R = H) 93%
13b (R = Cl) 91%

LDA, THF
then add

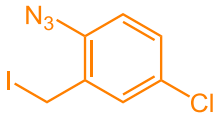


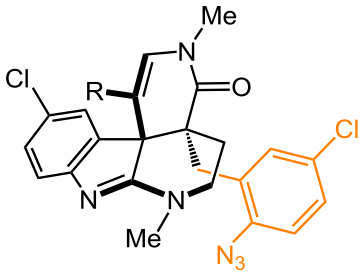
12a (R = H) 40%
12b (R = Cl) 58%
single diastereomer



12a (R = H) 40%
12b (R = Cl) 58%
single diastereomer

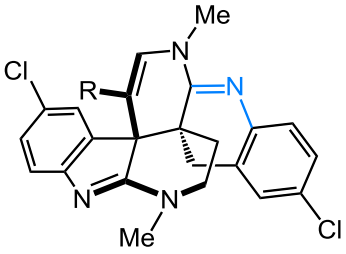
LDA, THF
then add HMPA





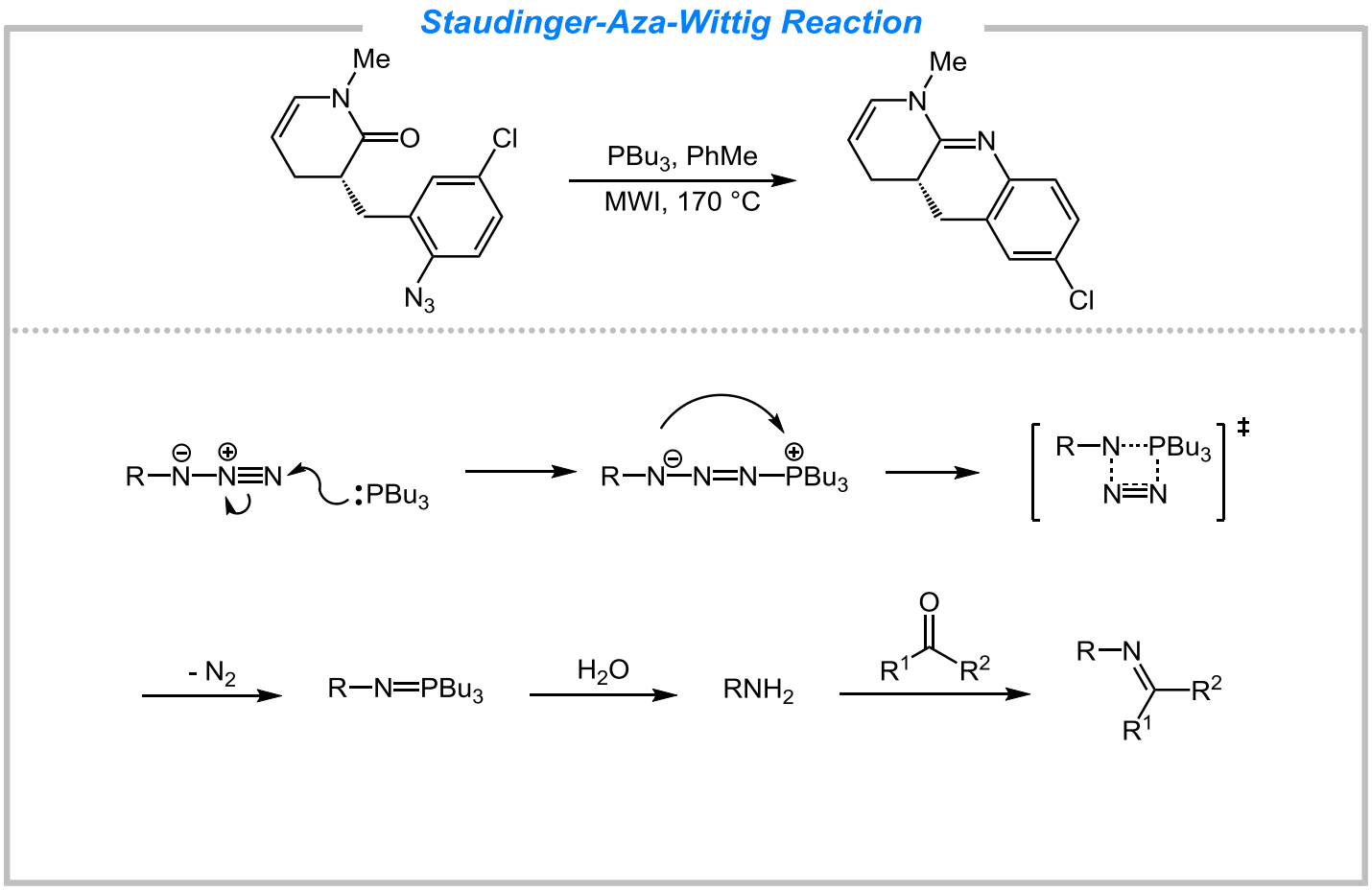
20a (R = H) 75%
20b (R = Cl) 54%
single diastereomer

PBu_3, PhMe
MWI



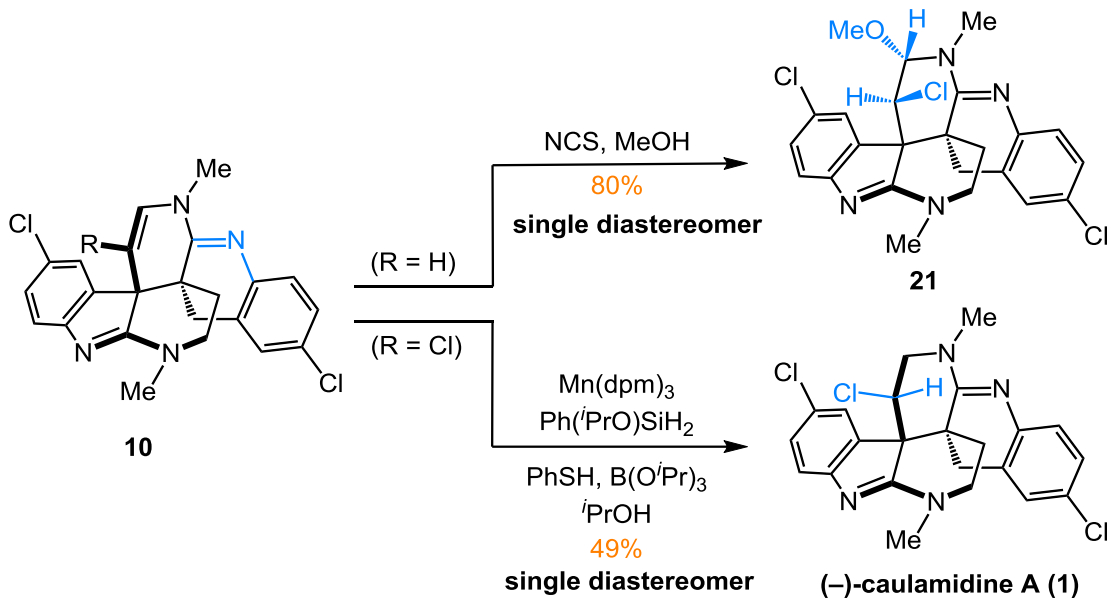
10a (R = H) 74%
10b (R = Cl) 94%

Staudinger-Aza-Wittig Reaction

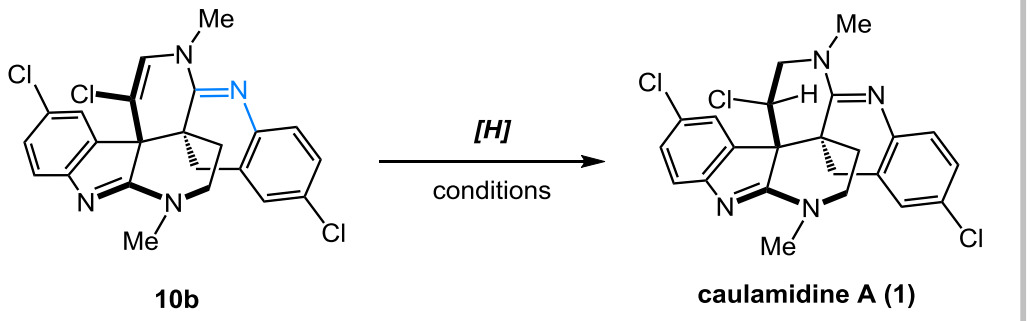


Stage 3

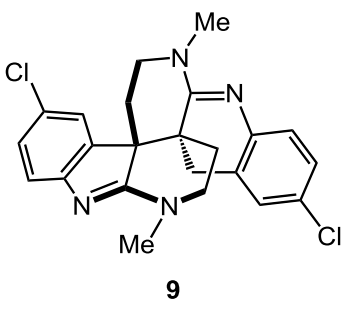
Enantioselective Total Synthesis of (–)-Caulamidine A



Optimization and Mechanistic Studies



10b **caulamidine A (1)**

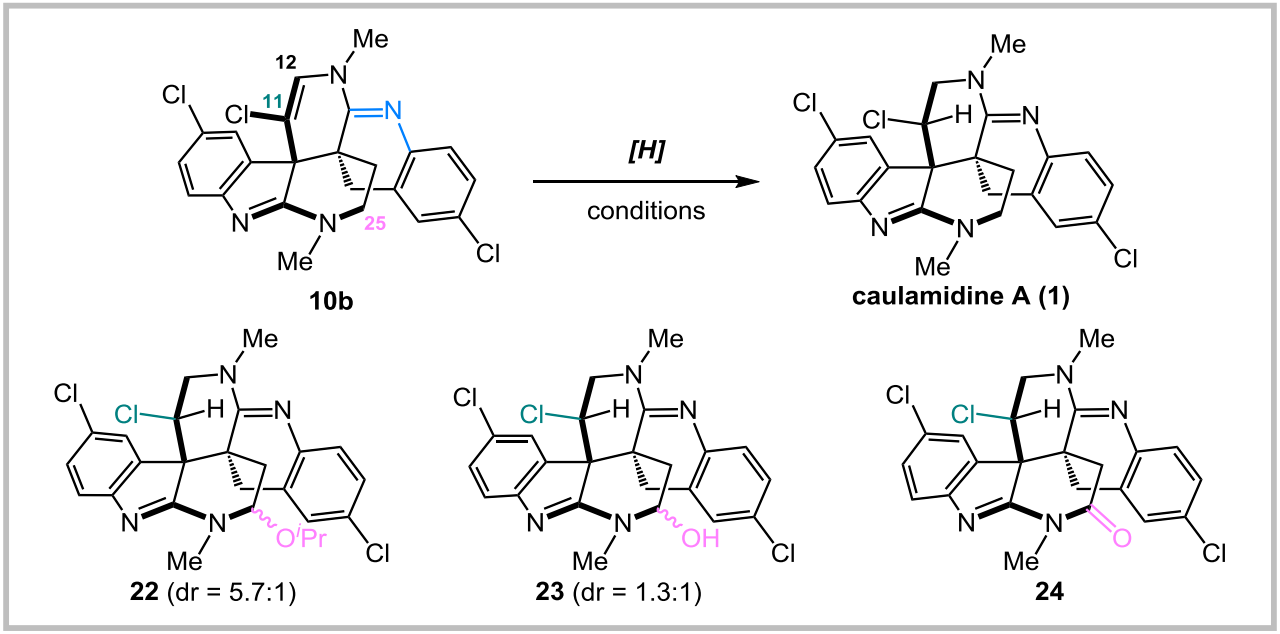


9

Entry	Conditions	Reaction Products [a]
1	TFA, Et_3SiH, DCM	**10b**
2	H_2, PtO_2, AcOH/EtOAc	**10b**, **9** (14%), **1** (6%)
3	$Fe_2(ox)_3$, $NaBH_4$, EtOH/H_2O	**10b**
4	$Co(acac)_2$, Et_3SiH, 1,4-CHD, TBHP, ^{n}PrOH, air	**10b**
5	$Fe(acac)_3$, $PhSiH_3$, PhSH, EtOH	**10b**
6	$Mn(dpm)_3$, $PhSiH_3$, TBHP, ^{i}PrOH	**10b**

Reaction Condition: [a]Yields determined by 1H NMR analysis. [b]Mn^{III} (5 mol%), silane (2 eq.), TBHP (2 eq.). [c]Mn^{III} (2 eq.), silane (4 eq.), TBHP (2 eq.). [d]Mn^{III} (2 eq.), silane (2 eq.), PhSH (2 eq.). [e]Mn^{III} (10 eq.), silane (10 eq.), PhSH (10 eq.), $B(^{i}PrO)_3$ (2 eq.), with aq. NH_4OH workup. [f]Isolated yield.

Optimization and Mechanistic Studies

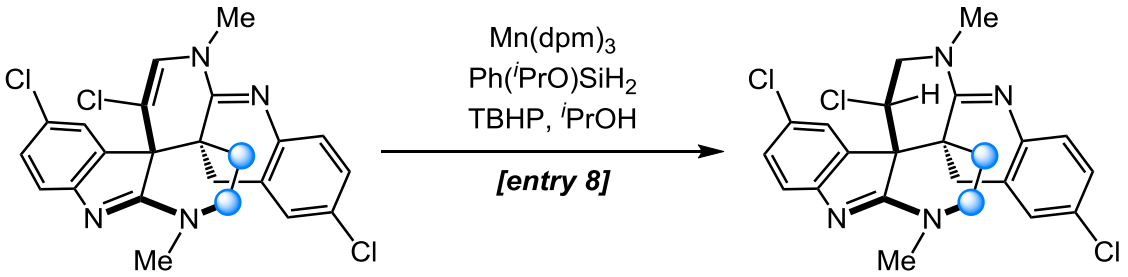


Entry	Conditions	Reaction Products [a]
6	$Mn(dpm)_3$, $PhSiH_3$, TBHP, ^{i}PrOH	**10b**
7[b]	$Mn(dpm)_3$, $Ph(^iPrO)SiH_2$, TBHP, ^{i}PrOH	**10b**, **1** (trace)
8[c]	$Mn(dpm)_3$, $Ph(^iPrO)SiH_2$, TBHP, ^{i}PrOH	**10b** (21%), **1** (15%) **22** (16%), **23** (9%), **24** (7%)
9[d]	$Mn(dpm)_3$, $Ph(^iPrO)SiH_2$, PhSH, ^{i}PrOH	**10b** (62%), **1** (12%)
10[e]	$Mn(dpm)_3$, $Ph(^iPrO)SiH_2$, PhSH, ^{i}PrOH , $B(^iPrO)_3$	**10b** (24%), **1** (49%)[f]

Reaction Condition: [a]Yields determined by 1H NMR analysis. [b]Mn^{III} (5 mol%), silane (2 eq.), TBHP (2 eq.). [c]Mn^{III} (2 eq.), silane (4 eq.), TBHP (2 eq.). [d]Mn^{III} (2 eq.), silane (2 eq.), PhSH (2 eq.). [e]Mn^{III} (10 eq.), silane (10 eq.), PhSH (10 eq.), $B(^iPrO)_3$ (2 eq.), with aq. NH_4OH workup. [f]Isolated yield.

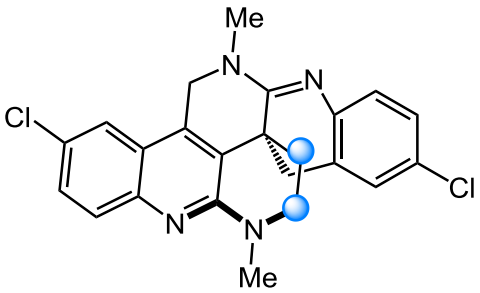
Optimization and Mechanistic Studies

Deuterium labeling Experiments

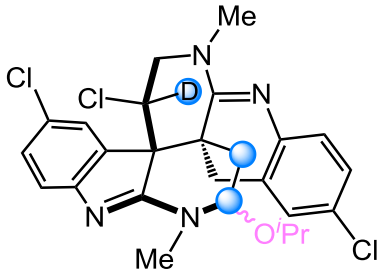


10b-d_4(form **19-d_4)**

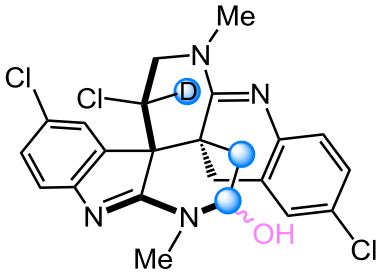
1-d_4



25-d_4 (13%)



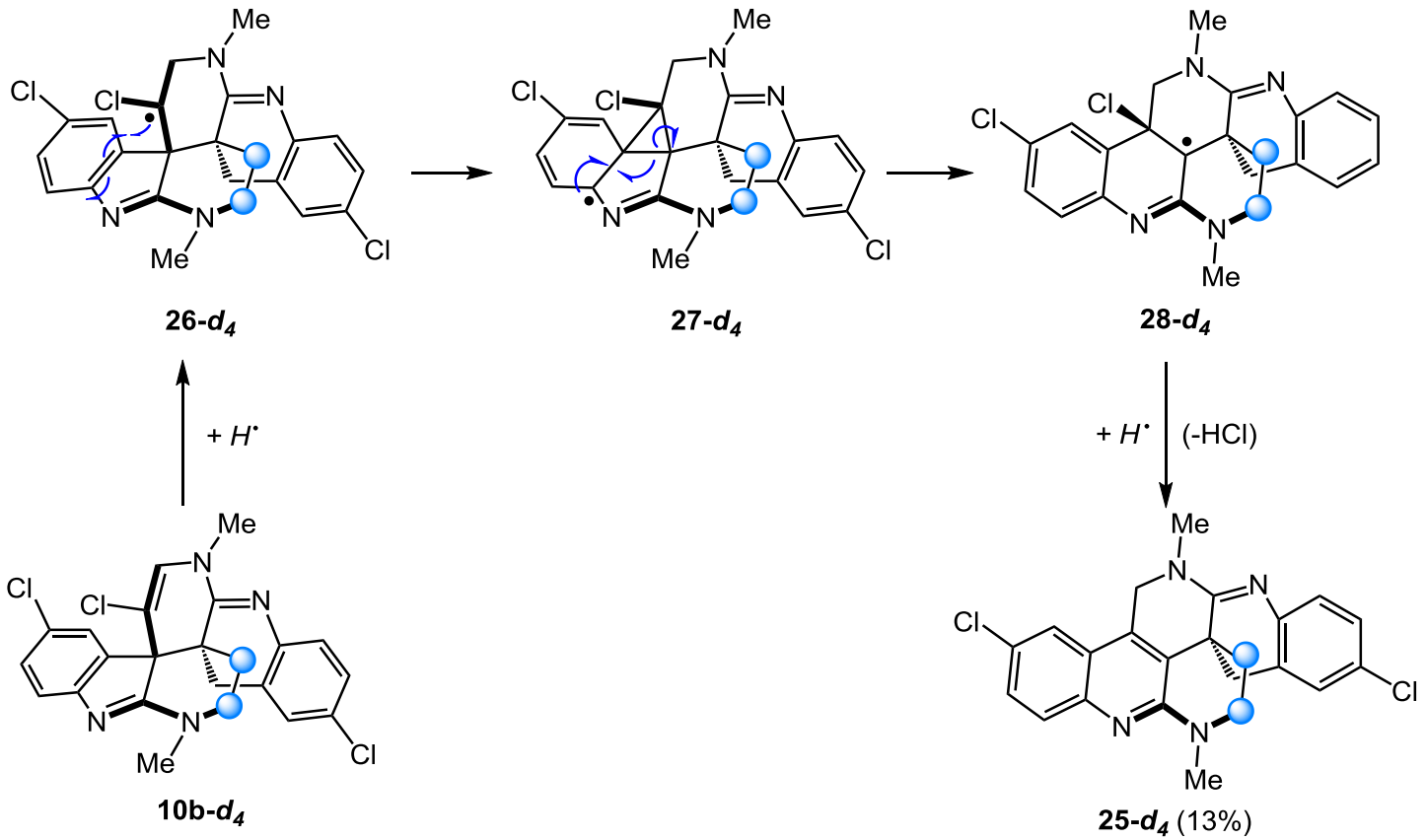
22-d_4 (trace)



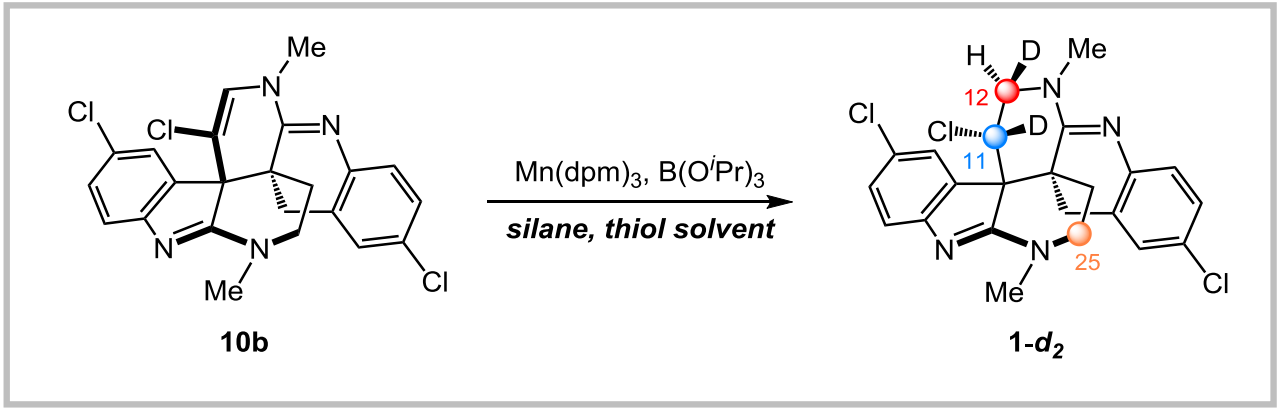
23-d_4 (trace)

Optimization and Mechanistic Studies

Deuterium labeling Experiments

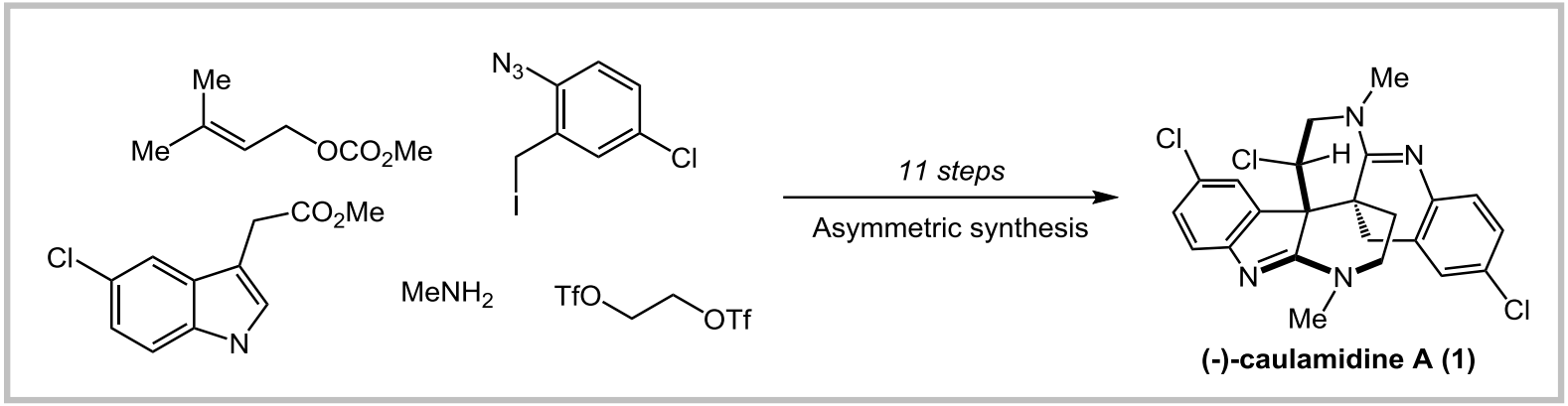


Optimization and Mechanistic Studies



Conditions	Results
Ph(^{i}PrO)SiH$_2$, PhSD, CD$_3$OD	C12 0% D
	C11 0% D
	C25 0% D
Ph(^{i}PrO)SiD$_2$, PhSH, ^{i}PrOH	C12 97% D
	C11 94% D
	C25 0% D

Summary



- ✓ **Pd-Catalyzed Asymmetric Prenylation**
- ✓ **Diastereoselective Ketone-Amidine Annulation Reaction**
- ✓ **Highly Diastereoselective Hydrogen Atom Transfer**
- ✓ **First Total Synthesis of (–)-1: 11 Steps, 3.2% Overall Yield**

Writing Strategies

☐ The First Paragraph

Source and Bioactivities of Caulamidine A

↓

The Synthetic Challenge of Caulamidine A

↓

Main Content of This Work

✓ **1** were initially isolated as minor constituents from extracts of the Caulibugula intermis by Gustafson in 2004. The natural product inhibited chloroquine-sensitive and -resistant strains of Plasmodium falciparum at low micromolar concentrations with little cytotoxicity to human cells.

✓ While this hexacyclic scaffold is reminiscent of the dimeric cyclotryptamine alkaloids, caulamidines are neither symmetric nor dimeric due to the presence of a single additional carbon atom (C22) of unknown biosynthetic origins.

✓ Herein, we explore elements of this blueprint, culminating in the first total synthesis of **1** in 11 steps, rigorously confirming both its structure and its absolute configuration.

Writing Strategies

☐ The Last Paragraph

Summary of This Work

✓ In summary, we have developed the first total synthesis of the structurally unique antimalarial alkaloid caulamidine A in 11 steps, thus confirming its mysterious and elusive structure.

Highlights of the Current Method

✓ An enantioselective prenylation highlights the rapid formation of an enantioenriched spirocyclic oxindole in only four steps from commercial materials. A glycol bistriflate-mediated annulation reaction then quickly constructs the hexahydro-2,6-naphthyridine core with complete diastereoselectivity.

Outlook of This Work

✓ A one-pot azide reduction or cyclization forges the caulamidine core in 10 steps, setting the stage for a diastereoselective HAT hydrogenation to form the key neopentylic chlorine stereocenter of the target.

Representative Examples

- ✓ While this hexacyclic scaffold is **reminiscent** (*adj*. **使人联想的**) of the dimeric cyclotryptamine alkaloids, caulamidines are neither symmetric nor dimeric due to the presence of a single additional carbon atom of unknown biosynthetic origins.
- ✓ Given the possibility that the Lewis basic nitrogens in **10b** interfere with the manganese complexes formed in this reaction, we included $B(O^iPr)_3$ to the reaction as a **sacrificial** (*adj*. **牺牲的**) Lewis acid and found it to be beneficial to the reaction outcome.
- ✓ A glycol bistriflate-mediated annulation reaction then quickly constructs the hexahydro-2,6-naphthyridine core with complete diastereoselectivity. Given the importance of spirocyclic oxindoles in drug discovery, we feel this **maneuver** (*n*. **策略，妙招**) may have uses in other contexts.

Acknowledgement

Thanks for your attentions!