

Literature Report V

Asymmetric Total Synthesis of Hetidine-Type C₂₀-Diterpenoid Alkaloids: (+)-Talassimidine and (+)-Talassamine

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Checker: Wen-Jun Huang

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Zhang, M. *et al.* *Angew. Chem. Int. Ed.* **2018**, *57*, 937

Zhang, M. *et al.* *J. Am. Chem. Soc.* **2021**, *143*, 7088

CV of Professor Min Zhang



Research:

- ◆ Total synthesis of complex natural products;
- ◆ The development of new organic reaction methodology.

Background:

- **1999-2003** B.S. , West China School of Pharmacy Sichuan University;
- **2003-2009** Ph.D., West China School of Pharmacy Sichuan University;
- **2009-2013** Postdoc., University of Wisconsin, Madison;
- **2013-Now** Professor, School of Pharmaceutical Sciences, Chongqing University .

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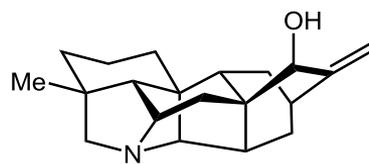
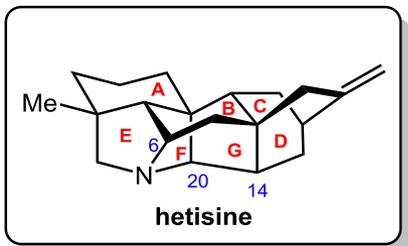
Total Synthesis of (+)-Talassimidine and (+)-Talassamine

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Summary

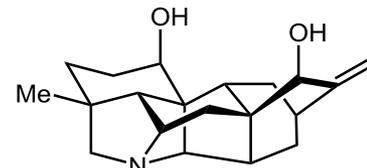
Introduction

Representative members of hetisine-type and hetidine-type alkaloids



nominine

Natsume, M. *et al.* 2004

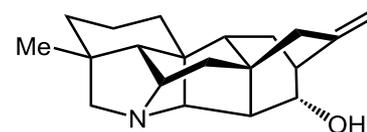


cossondine

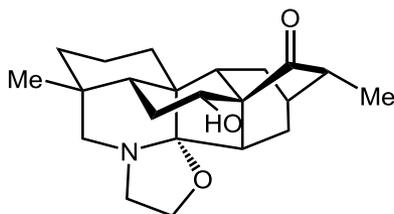
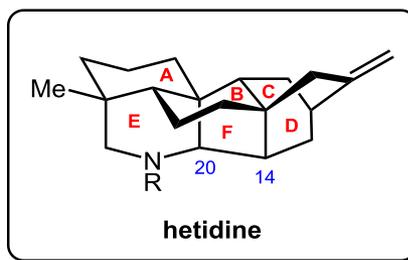
Sarpong, R. *et al.* 2018



spirasine IV

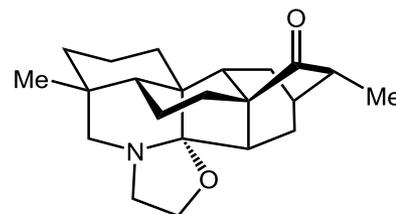


spirasine XI

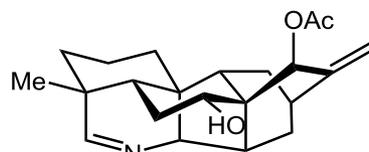


septedine

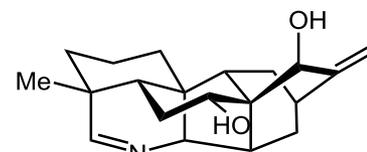
Li, A. *et al.* 2018



7-deoxyseptedine

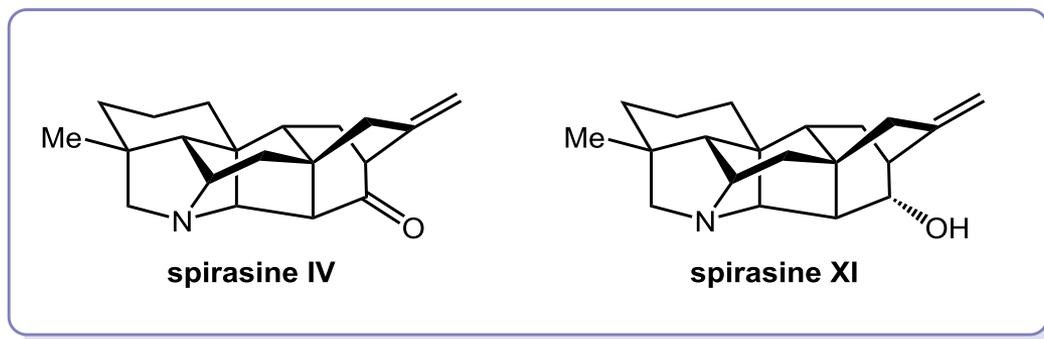


talassimidine

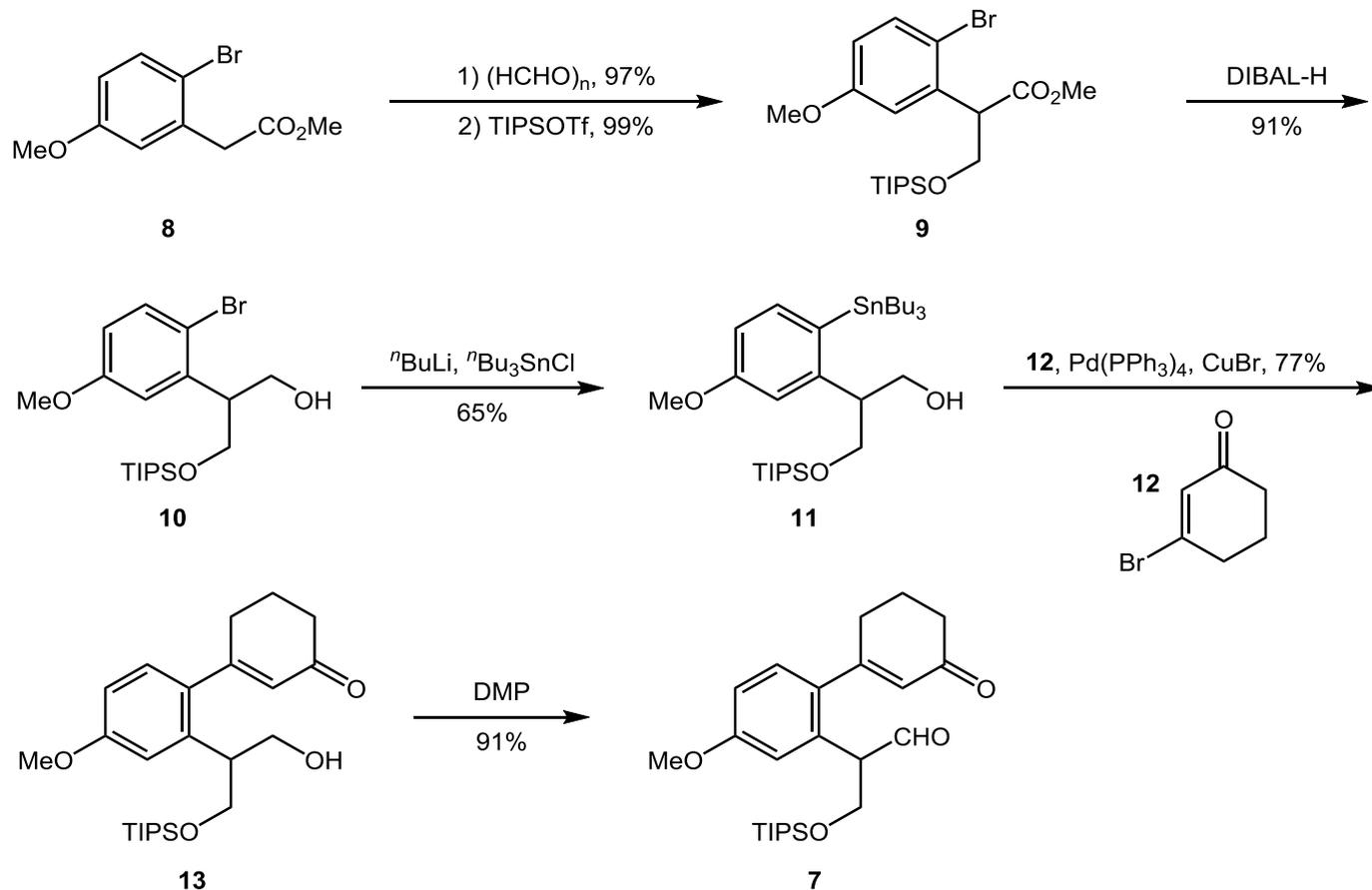


talassamine

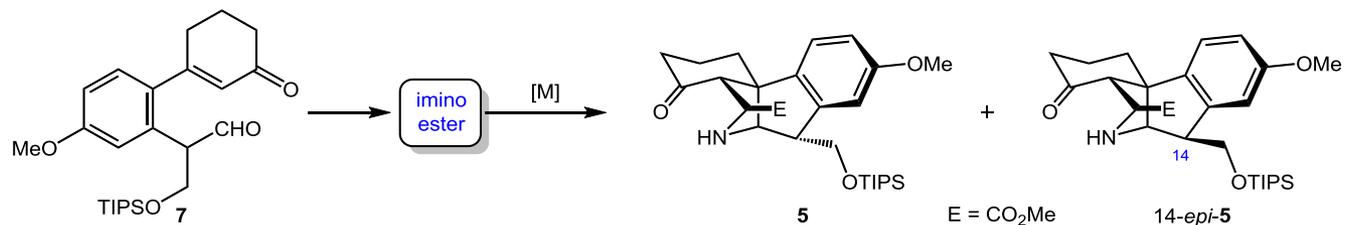
Total Synthesis of Spirasine IV and XI



Synthesis of compound 7



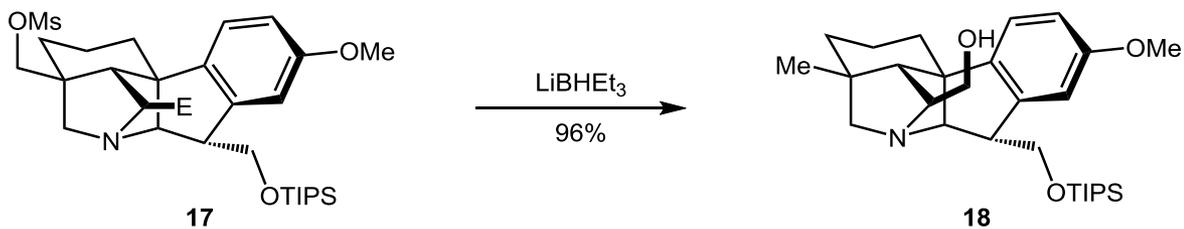
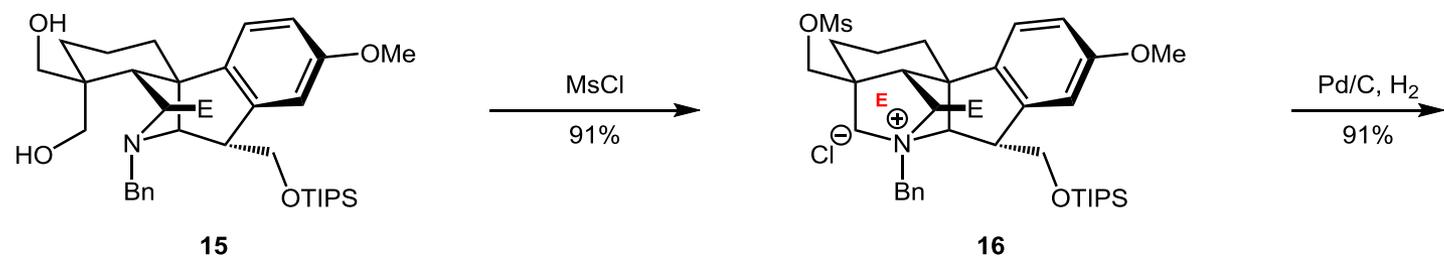
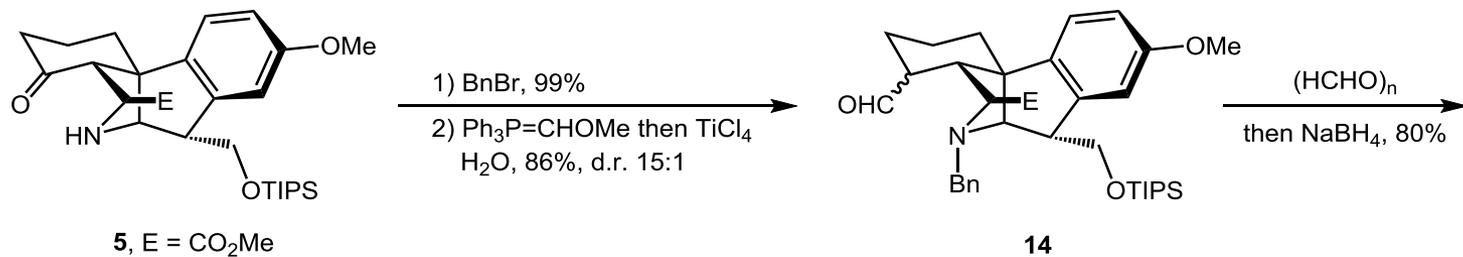
Construction of A/F/C rings system



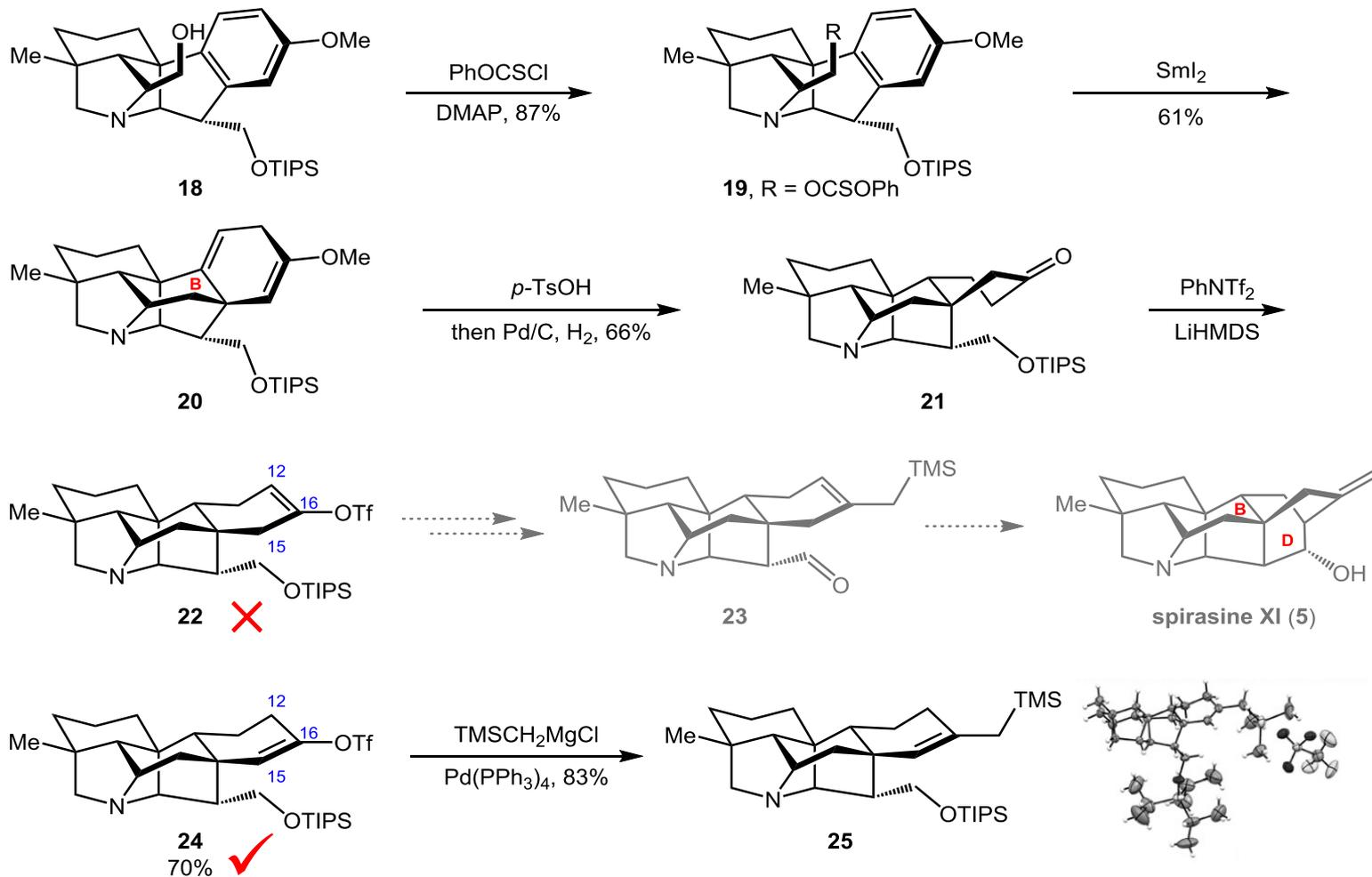
entry	[M]	amino ester source	yield (%) ^b	dr ^c
1	CuBF ₄	Ph ₃ P=NCH ₂ CO ₂ Me	21	2.1:1
2	CuPF ₆	Ph ₃ P=NCH ₂ CO ₂ Me	20	2.7:1
3	AgOTf	Ph ₃ P=NCH ₂ CO ₂ Me	59	5.3:1
4	AgTFA	Ph ₃ P=NCH ₂ CO ₂ Me	56	5:1
5	AgBF ₄	Ph ₃ P=NCH ₂ CO ₂ Me	60	3.5:1
6	AgClO ₄	Ph ₃ P=NCH ₂ CO ₂ Me	53	2.5:1
7	Ag ₃ PO ₄	Ph ₃ P=NCH ₂ CO ₂ Me	50	2.3:1
8	AgOAc	Ph ₃ P=NCH ₂ CO ₂ Me	68	7:1
9	AgOAc	NH ₂ CH ₂ CO ₂ Me	45	5:1
10 ^d	AgOAc	Ph ₃ P=NCH ₂ CO ₂ Me	63	7:1

^aConditions unless otherwise stated: **7** (0.12 mmol, 1 equiv), N₃CH₂CO₂Me/PPh₃ (1.1 equiv) or NH₂CH₂CO₂Me (1.1 equiv), metal salt (0.1 equiv), DBU (2 equiv), toluene (2 mL), 0 °C, 1 h. ^bYield of the isolated major isomer **5**. ^cRatio of the yields of **5** and **14-epi-5** (isolated products). ^dThe reaction was conducted on a 27 g scale.

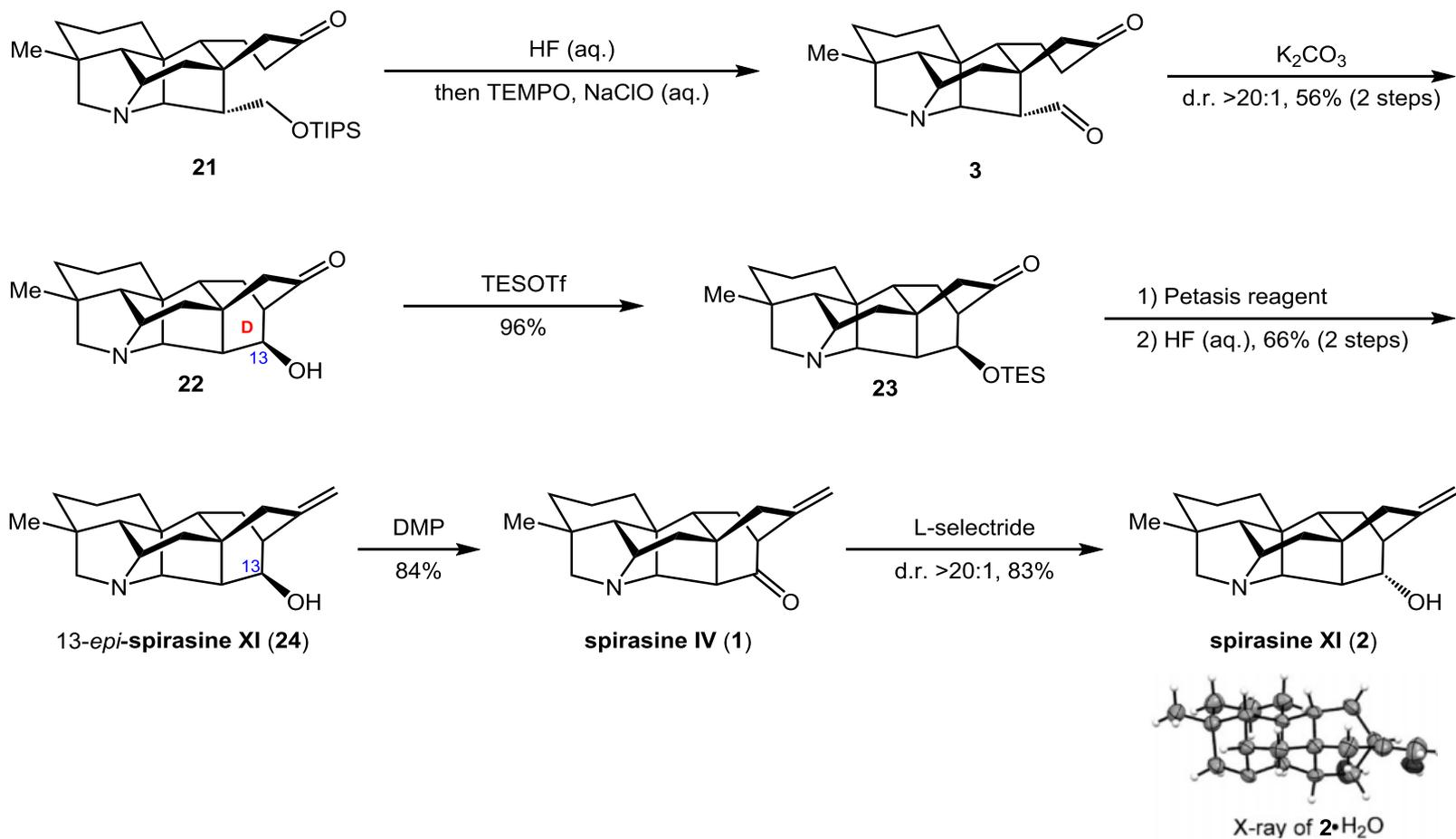
Construction of the E ring



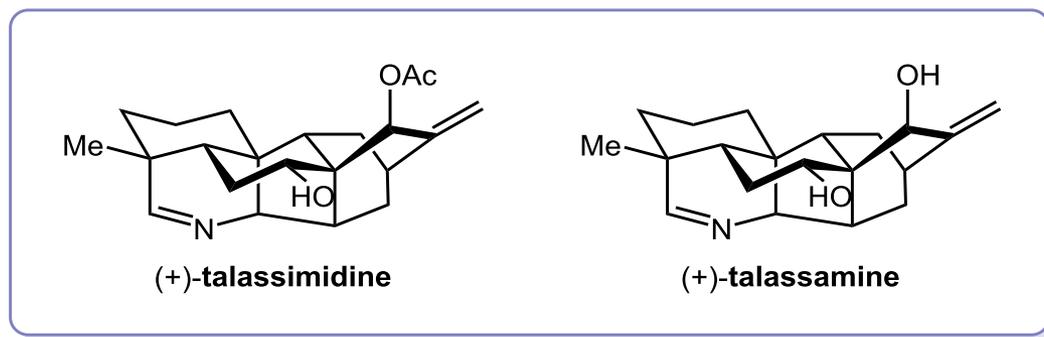
Construction of the B and D rings



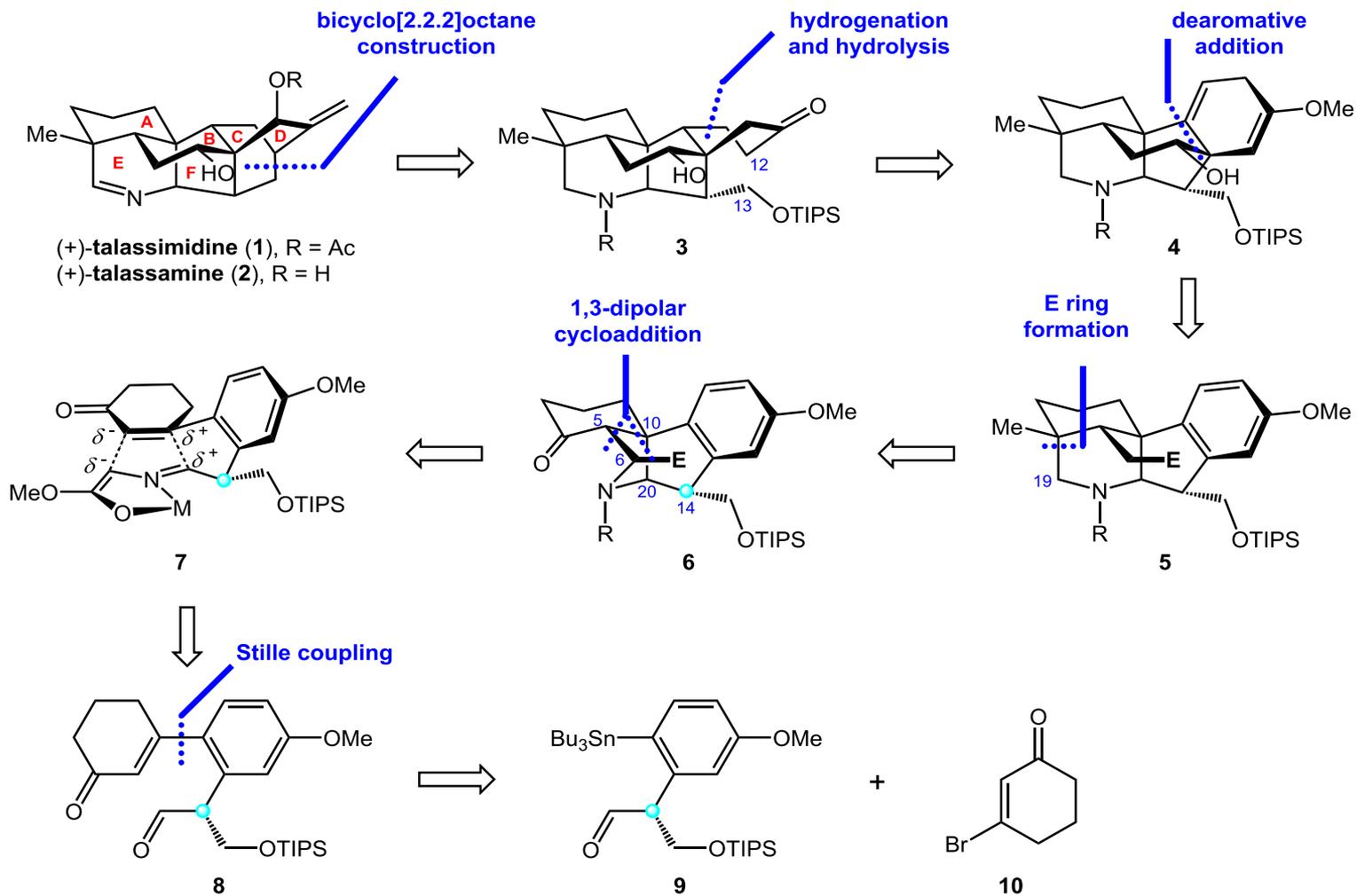
Completion of the total synthesis



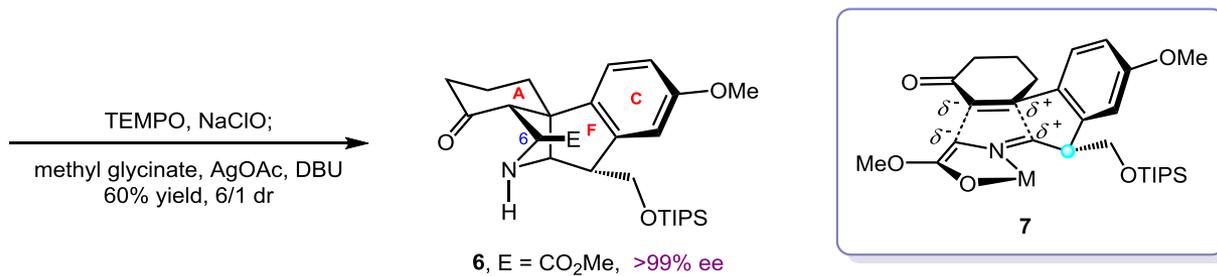
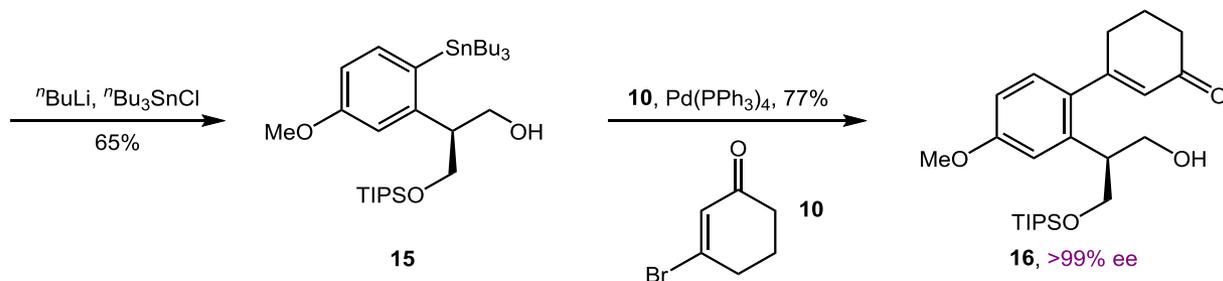
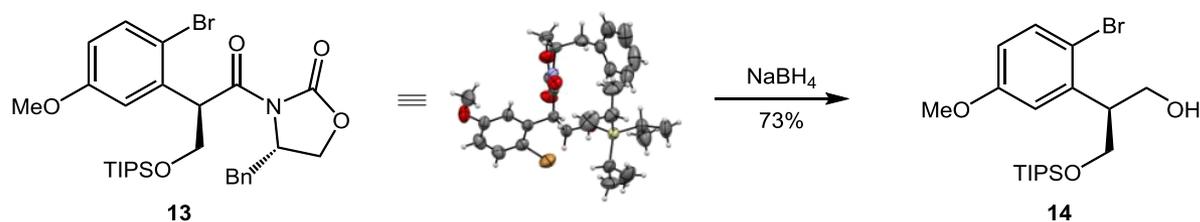
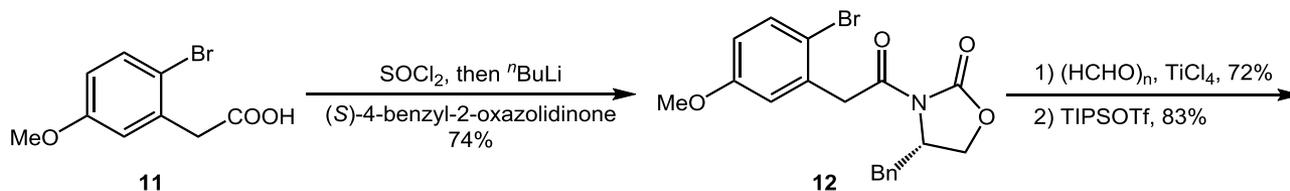
Total Synthesis of Talassimidine and Talassamine



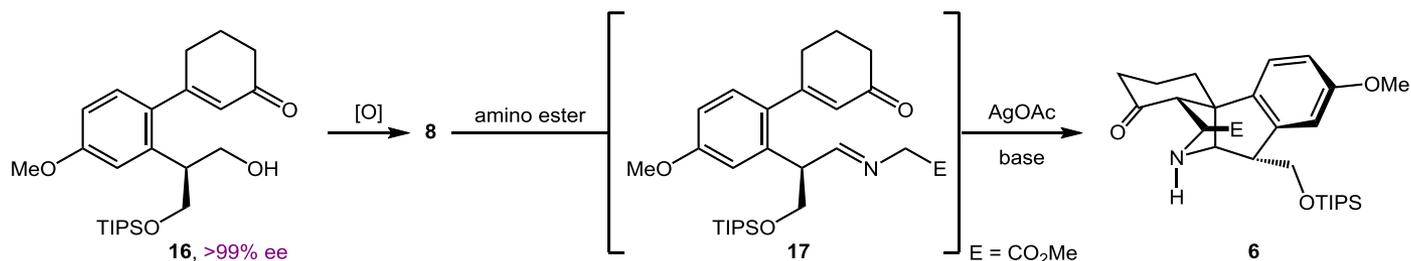
Retrosynthetic Analysis



Construction of A/F/C rings system



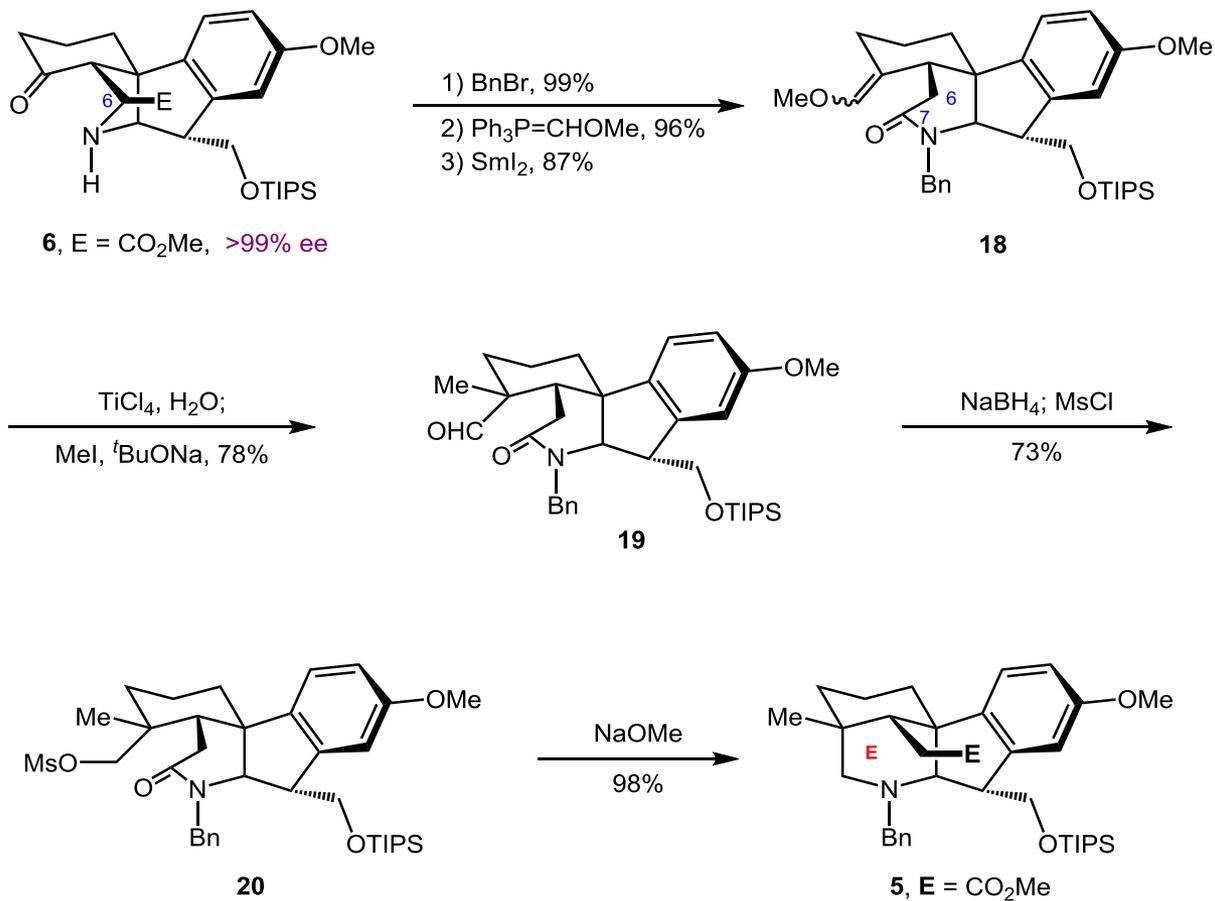
Optimization of the Asymmetric Cycloaddition



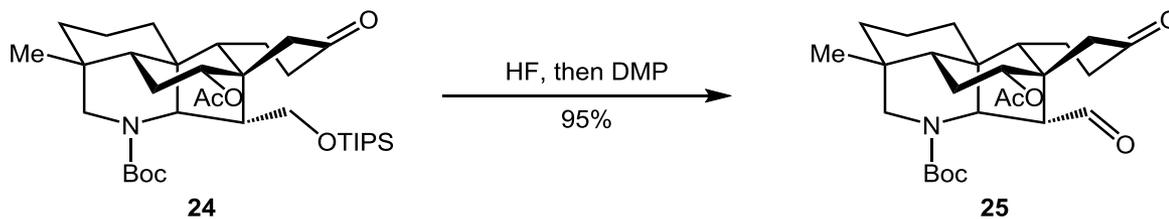
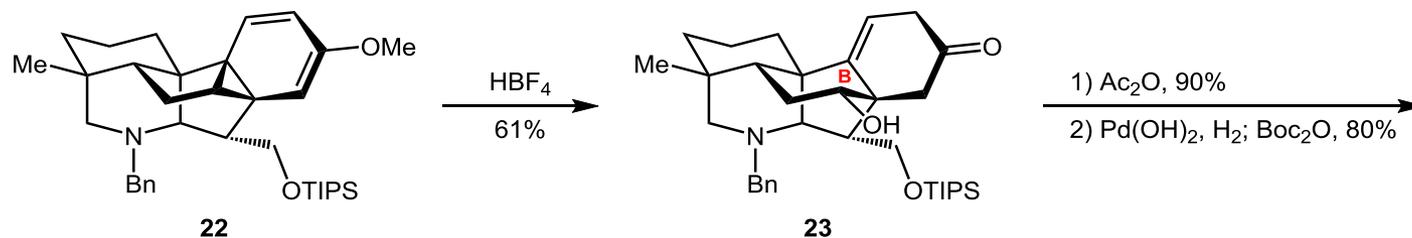
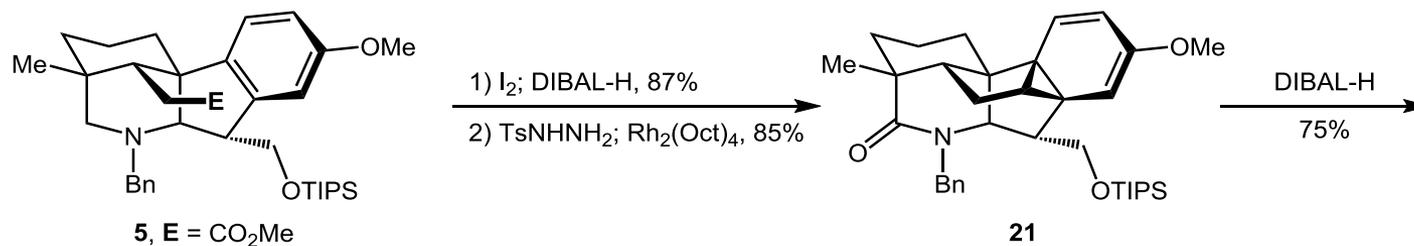
entry	[O] ^{a,b}	amino ester source ^{c,d}	base ^e	yield (%) ^f	dr ^g	ee (%) ^h
1	[DMP]	Ph ₃ P=NCH ₂ CO ₂ Me	DBU	54	7:1	45
2	[DMP]	Ph ₃ P=NCH ₂ CO ₂ Me	Et ₃ N	45	5:1	54
3	[DMP]	NH ₂ CH ₂ CO ₂ Me	Et ₃ N	40	4:1	50
4 ⁱ	[DMP]	NH ₂ CH ₂ CO ₂ Me	Et ₃ N	<5	-	-
5 ⁱ	[TEMPO]	NH ₂ CH ₂ CO ₂ Me	Et ₃ N	51	4:1	>99
6 ⁱ	[TEMPO]	NH ₂ CH ₂ CO ₂ Me	DIPEA	53	4:1	>99
7 ⁱ	[TEMPO]	NH ₂ CH ₂ CO ₂ Me	TMG	56	4:1	>99
8 ⁱ	[TEMPO]	NH ₂ CH ₂ CO ₂ Me	DBU	65	6:1	>99
9 ⁱ	[TEMPO]	NH ₂ CH ₂ CO ₂ Me	Cs ₂ CO ₃	37	4:1	>99
10 ⁱ	[TEMPO]	NH ₂ CH ₂ CO ₂ Me	K ₂ CO ₃	42	4:1	>99
11 ⁱ	[TEMPO]	Ph ₃ P=NCH ₂ CO ₂ Me	DBU	45	5:1	36

^a[DMP] oxidation: **16** (0.10 mmol), Dess-Martin periodinane (0.15 mmol), CH₂Cl₂ (3 mL), rt, 0.5 h, chromatography on silica gel.
^b[TEMPO] oxidation: **16** (0.10 mmol), TEMPO (0.01 mmol), KBr (0.20 mmol), NaClO (10% in H₂O, 0.20 mmol), NaHCO₃ (saturated aqueous solution, 2 mL), CH₂Cl₂ (3 mL), 0 °C to rt, 3 min, aqueous workup. ^c**8**, N₃CH₂CO₂Me/PPh₃ (0.11 mmol), CH₂Cl₂ (2 mL), 0 °C, 1 h. ^d**8**, NH₂CH₂CO₂Me·HCl (0.20 mmol), Et₃N (0.22 mmol), MgSO₄ (0.60 mmol), CH₂Cl₂ (2 mL), 0 °C, 1 h. ^eCrude **17**, AgOAc (0.01 mmol), base (0.11 mmol), toluene (2 mL), rt, 1 h. ^fIsolated yield of the major diastereoisomer from **16**. ^gRatio of yields of the two isolated diastereoisomers. ^hOf the major diastereoisomer; determined by chiral HPLC analysis. ⁱCrude **8** was used for the next step without chromatography purification.

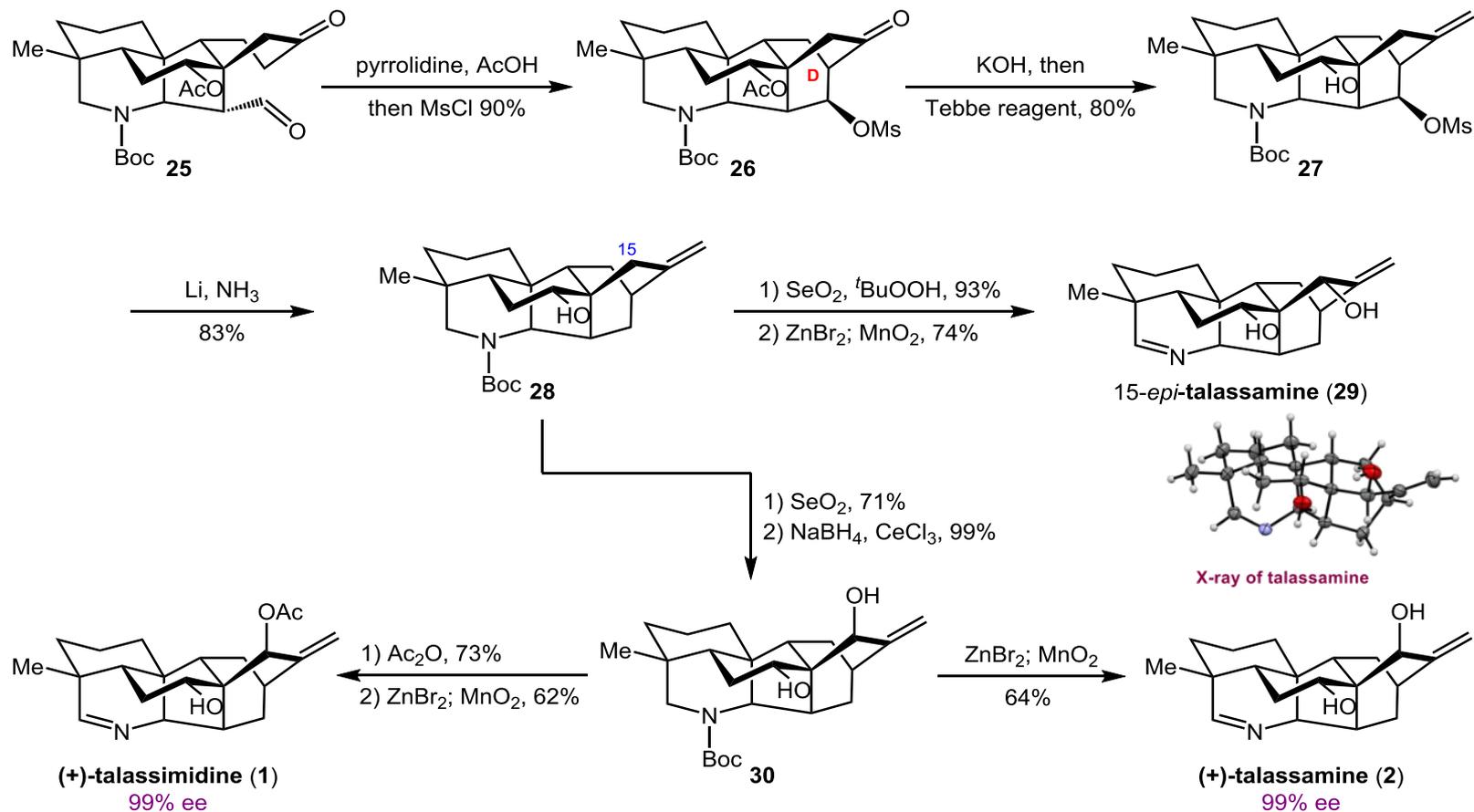
Construction of E ring



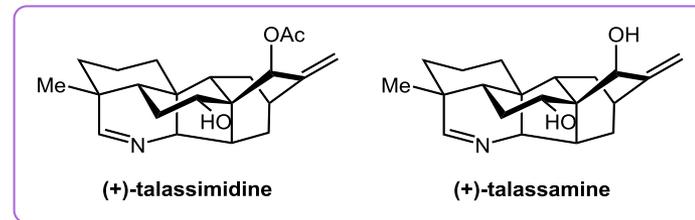
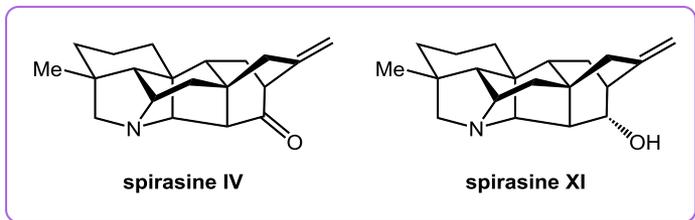
Construction of B ring



Completion of the total synthesis



Summary



- 22 Total steps for spirasine IV, 1.2% overall yield
- 23 Total steps for spirasine XI, 1.0% overall yield
- 1,3-Dipolar cycloaddition
- Sml₂-mediated free-radical addition

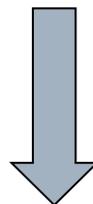
- 27 Total steps for (+)-talassimidine, 0.20% overall yield
- 26 Total steps for (+)-talassamine, 0.28% overall yield
- 1,3-Dipolar cycloaddition
- Dearomative cyclopropanation of the benzene ring
- S_N2-like ring opening of the cyclopropane

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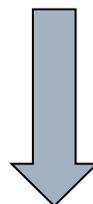
The First Paragraph

Writing Strategy

Source of C₂₀-diterpenoid alkaloids



**Several subtypes of
C₂₀-diterpenoid alkaloids**



**Synthetic strategy of several
subtypes of C₂₀-diterpenoid alkaloids**

The First Paragraph

The C₂₀-diterpenoid alkaloids constitute a large family of natural products, which are mainly isolated from the *Aconitum*, *Consolidum*, *Delphinium*, and *Spiraea* genera of plants that have a history of use in traditional medicine. Architecturally, the C₂₀-diterpenoid alkaloids can be classified into several subtypes (selected subtypes and representative hetidine-type members are shown in Scheme 1A). Of the biosynthetically related atisine-, hetidine-, and hetisine-type C₂₀-diterpenoid alkaloids, the hexacyclic hetidine core has a characteristic C14–C20 linkage; besides the C14–C20 linkage, the hetisine core has an additional C6–N linkage, forming a complex heptacyclic framework. The unique biological profiles and structural complexity of C₂₀-diterpenoid alkaloids render them highly sought-after synthetic targets.

The First Paragraph

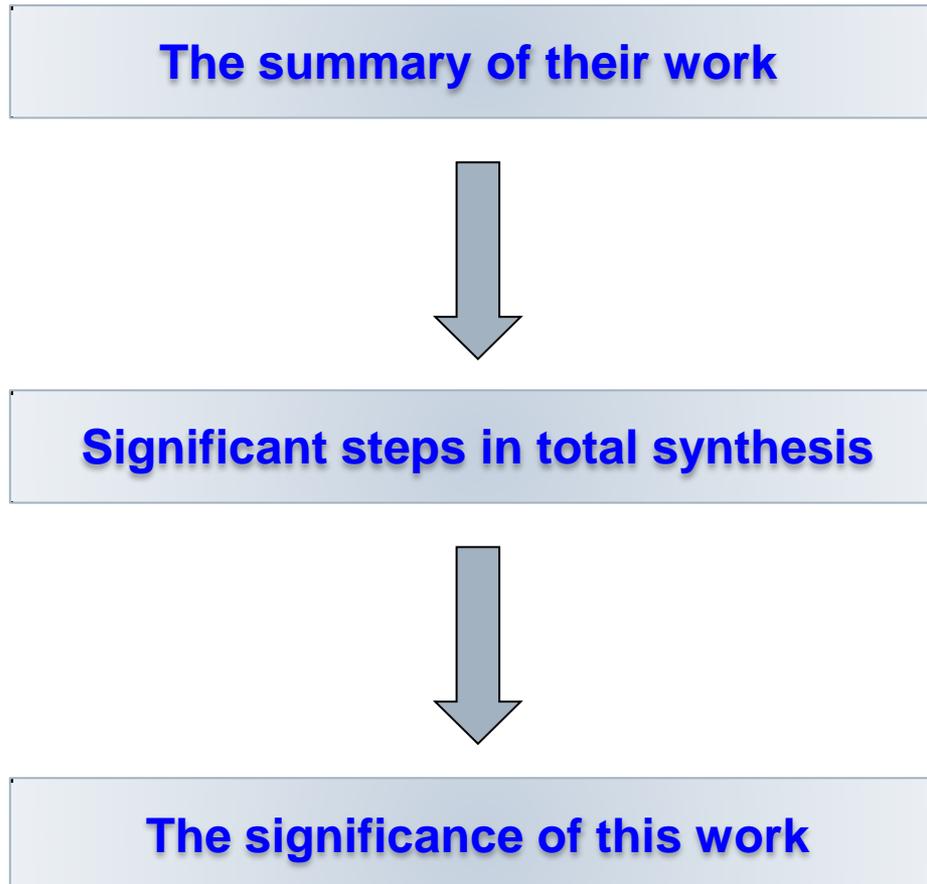
Successful total syntheses of hetisine-type alkaloids have been reported by the groups of Muratake/Natsume, Gin, and Sarpong, as well as our group, reflecting considerable achievements toward total synthesis of various C₂₀-diterpenoid alkaloids in recent years. However, there has been limited success in the synthesis of the seemingly less complex hetidine-type alkaloids, despite considerable efforts having been made toward this subtype. Guided by network analysis, Sarpong's group accomplished a unified total synthesis of C₁₈-, C₁₉-, and C₂₀-diterpenoid alkaloids and developed an elegant approach of Ga-catalyzed cycloisomerization to synthesize dihydronavirine, a structurally very similar analogue of navirine. Baran's group applied a two-phase synthetic strategy to synthesize the atisine alkaloids and construct the hetidine skeleton from a readily available *ent*-kaurane.

The First Paragraph

Qin and Liu developed an efficient biomimetic approach to access the denudatine- and atisine-type alkaloids and the hetidine skeleton from an atisine-type precursor. Ma, Liu, and colleagues used a hydrogen atom transfer-based radical cyclization as the key step to build the hetidine scaffold and accomplished an efficient synthesis of the proposed structure of navirine C. Recently, Li and co-workers reported an elegant synthesis of septedine and 7-deoxyseptedine, which represents the first and only route to hetidine-type C₂₀-diterpenoid alkaloids reported to date (Scheme 1B). Key steps of this synthesis included a Carreira polyene cyclization to construct the core framework and a Sanford Csp³-H functionalization to install the equatorial C7-OH.

The Last Paragraph

Writing Strategy



The Last Paragraph

We have accomplished the first asymmetric total synthesis of (+)-talassamine and (+)-talassimidine in 0.28 and 0.20% total yields from known compound **26** over 26 and 27 total steps, respectively. A regio- and diastereo-selective 1,3-dipolar cycloaddition of azomethine ylide generated the fundamental tetracyclic skeleton with five continuous stereogenic carbon centers in high enantiopurity (>99% ee). Besides the hetidine-type alkaloids, this chiral tetracyclic intermediate should also enable asymmetric access to the hetisine-type alkaloids.

The Last Paragraph

An efficient sequence of dearomative cyclopropanation of the benzene ring and subsequent S_N2 -like ring opening of the cyclopropane moiety with a water nucleophile was developed to stereospecifically install the challenging equatorial C7-OH group and to concurrently construct the B ring. This cyclopropanation strategy also allowed preparation of natural product analogues with unnatural functionalities at C7.

Representative Examples

- Guided by network analysis, Sarpong's group accomplished a unified total synthesis of C₁₈-, C₁₉-, and C₂₀-diterpenoid alkaloids and developed an elegant approach of Ga-catalyzed cycloisomerization to synthesize dihydronavirine, a structurally very similar analogue of navirine. (由...来指导; 完成; 优雅的、优美的)
- To develop ..., we embarked on ... (为了..., 我们着手于...)
- ... be potentially prone to racemization (...可能容易发生消旋化)

Acknowledgement

Thanks for your attention !