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Asymmetric Total Synthesis of Hetidine-Type C_{20}-Diterpenoid Alkaloids: (+)-Talassimidine and (+)-Talassamine

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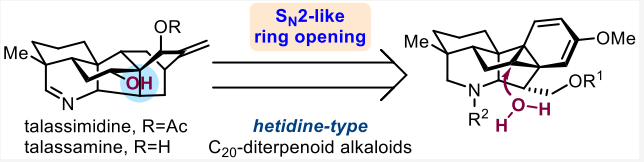
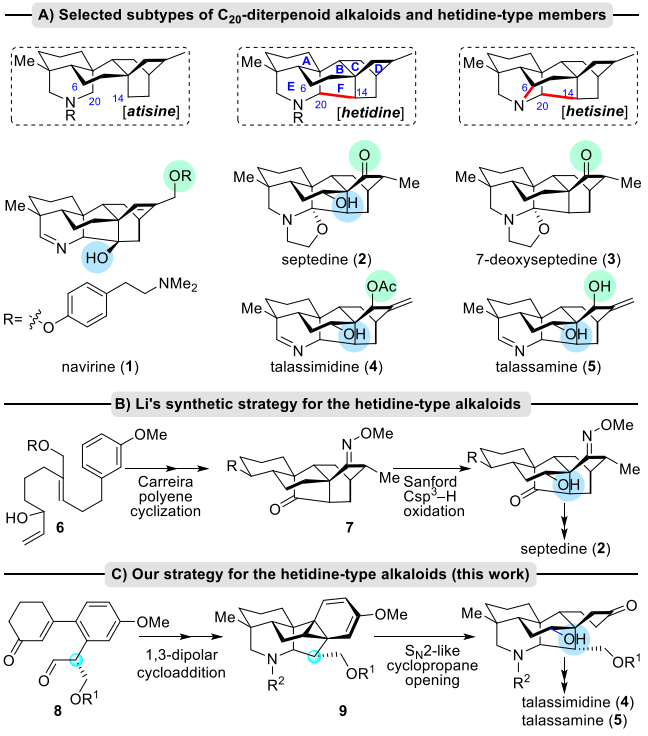
ABSTRACT: Here, we report the first asymmetric total synthesis of (+)-talassimidine and (+)-talassamine, two hetidine-type C_{20}-diterpenoid alkaloids. A highly regio- and diastereoselective 1,3-dipolar cycloaddition of an azomethine ylide yielded a chiral tetracyclic intermediate in high enantiopurity, thus providing the structural basis for asymmetric assembly of the hexacyclic hetidine skeleton. In this key step, the introduction of a single chiral center induces four new continuous chiral centers. Another key transformation is the dearomative cyclopropanation of the benzene ring and subsequent S_N2-like ring opening of the resultant cyclopropane ring with water as a nucleophile, which not only establishes the B ring but also precisely installs the difficult-to-achieve equatorial C7−OH group.



INTRODUCTION

The C_{20}-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.[1] Architecturally, the C_{20}-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 C_{20}-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 C_{20}-diterpenoid alkaloids render them highly sought-after synthetic targets.[2−10] Successful total syntheses of hetisine-type alkaloids have been reported by the groups of Muratake/Natsume, Gin, and Sarpong, as well as our group,[4] reflecting considerable achievements toward total synthesis of various C_{20}-diterpenoid alkaloids in recent years.[3−8] 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.[6,7] Guided by network analysis, Sarpong's group accomplished a unified total synthesis of C_{18}-, C_{19}-, and C_{20}-diterpenoid alkaloids[2h,5c,8b,9e] and developed an elegant approach of Ga-catalyzed cycloisomerization to synthesize dihydronavirine, a structurally very similar analogue of navirine.[6a,b] 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.[3i] 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.[3k] Ma, Liu, and colleagues used a hydrogen atom transfer-based radical cyclization as the key step to build the hetidine scaffold

Scheme 1. Background and Study Synopsis



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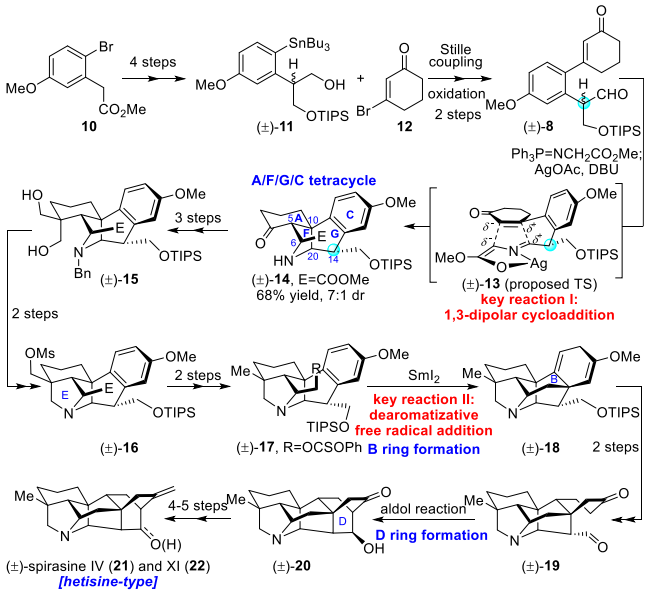
and accomplished an efficient synthesis of the proposed structure of navirine C.[3l] Recently, Li and co-workers reported an elegant synthesis of septedine (**2**) and 7-deoxyseptedine (**3**), which represents the first and only route to hetidine-type C_{20}-diterpenoid alkaloids reported to date (Scheme 1B).[7] Key steps of this synthesis included a Carreira polyene cyclization to construct the core framework and a Sanford Csp^3–H functionalization to install the equatorial C7–OH.

The limited success in the synthesis of hetidine-type alkaloids can be attributed to the synthetic challenge associated with the rigid hexacyclic cage-shaped skeleton and more problematically, the different oxygen substitutions at various positions of the core frameworks.[2,6,7] To develop new synthetic strategies to access diterpenoid alkaloids with complex oxygen substitution patterns, we embarked on a synthetic program toward the synthesis of talassimidine (**4**) and talassamine (**5**), two hetidine-type alkaloids initially isolated from *Aconitum talassicum* M. Pop. by Nishanov[11a] and then reisolated from *Delphinium campylocentrum* Maxim. by Wang[11b] (Scheme 1A). We report here the first asymmetric total synthesis of (+)-talassimidine and (+)-talassamine through 1,3-dipolar cycloaddition and cyclopropanation/ring opening as the key transformations to build the polycyclic hetidine scaffold and to install the oxygen functionalities (Scheme 1C).

RESULTS AND DISCUSSION

In 2018, our group realized the first racemic total synthesis of hetisine-type alkaloids spirasine IV (**21**) and XI (**22**) (Scheme 2).[4d] Key reactions of the synthesis involve a diastereoselective

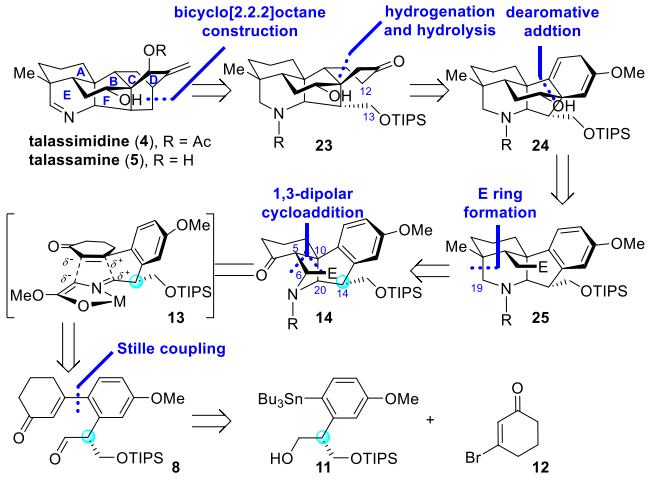
Scheme 2. Our Previous Synthesis of the Hetisine-Type C_{20}-Diterpenoid Alkaloids (±)-Spirasine IV and XI



intramolecular 1,3-dipolar cycloaddition of azomethine ylide to access the tetracycle (±)-**14** with linkages of C14–C20 and C6–N and a SmI_2-mediated, dearomative free radical addition to the arene moiety to construct the B ring. Highly enolizable aldehyde **8** was prepared in a racemic form via a modular coupling of two simple building blocks, **11** and **12**, with known compound **10** as the starting material. Condensation of aldehyde (±)-**8** with the phosphinimine $Ph_3P{=}CH_2CO_2Me$ and subsequent treatment with AgOAc and DBU provided tetracycle (±)-**14** in good yield with a regioselectivity opposite to the intrinsic selectivity observed in the intermolecular reactions. In this key reaction, four continuous chiral carbon centers at C6, C5, C10, and C20 were established in a single step (in addition to the retained C14 chiral center). With (±)-**14** as the key intermediate, the E ring was constructed by an intramolecular alkylation. Thereafter, a SmI_2-mediated free radical addition to the arene moiety without prior dearomatization was used as the second key reaction to build the B ring (**17** to **18**). Last, a diastereoselective aldol reaction constructed the remaining D ring of the hetisine core (**19** to **20**). Finally, installation of requisite functionalities furnished (±)-spirasine IV (**21**) and (±)-spirasine XI (**22**) in 0.88 and 0.73% total yields from **10** over 22 and 23 total steps, respectively. From a biogenetic perspective, the hetidine scaffold generates a hetisine core via formation of a C6–N bond. Retrosynthetically, breakage of the C6–N bond of the hetisine scaffold would lead to a hetidine core. On basis of these analyses, we envisioned that using tetracycle **14** as the foundational intermediate and breaking the C6–N bond at an appropriate stage would provide a new strategy to access hetidine-type alkaloids. Additionally, if tetracycle **14** could be prepared in high enantiopurity, asymmetric synthesis of both hetisine- and hetidine-type alkaloids could be achieved.

Retrosynthetic Analysis. Our retrosynthetic analysis of hetidine-type alkaloids (+)-talassimidine (**4**) and (+)-talassamine (**5**) is illustrated in Scheme 3. Disassembly of the

Scheme 3. Retrosynthetic Analysis of (+)-Talassimidine and (+)-Talassamine



bicyclo[2.2.2]octane motif in talassimidine and talassamine led back to **23**. Instead of the commonly used Diels–Alder cycloaddition strategy,[2] formation of the C12–C13 bond of **23** would give the bicyclo[2.2.2]octane motif and establish the hetidine core. Inspired by our previous success in constructing the B ring of hetisine through a dearomative free radical addition, we posited that addition of a ketyl radical to the arene moiety would yield the B ring and concurrently install a hydroxyl group. The ketyl radical precursor could be formed by single-electron reduction of an aldehyde, which can be traced back to tetracyclic ester **25**.[12,14] Through the use of tetracyclic **14** as the key intermediate, **25** can be obtained by a sequence of C6–N cleavage and C19–N formation. The fundamental step for our proposed scheme is the asymmetric synthesis of **14**. If chiral erosion of the potentially

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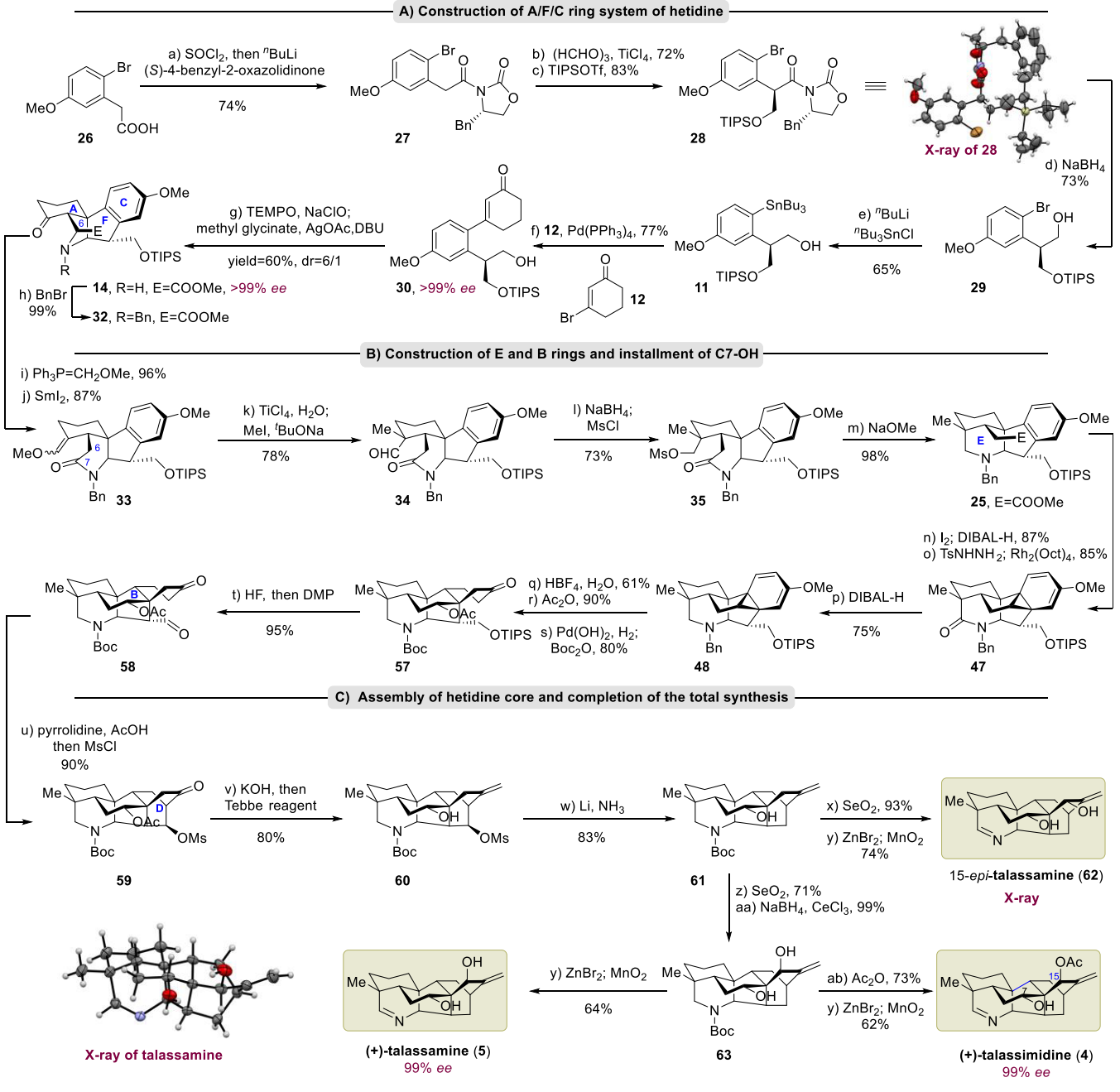
Scheme 4. Asymmetric Total Synthesis of (+)-Talassimidine and (+)-Talassamine[a]



[a]Reagents and conditions: (a) $SOCl_2$, DMF, CH_2Cl_2, 0 °C to room temperature (rt), 4 h, then (*S*)-4-benzyl-2-oxazolidinone, ^{n}BuLi, THF, −78 °C, 1 h, 74%; (b) $TiCl_4$, DIPEA, $(HCHO)_3$, 0 to −20 °C, 1 h, 72%; (c) TIPSOTf, 2,6-lutidine, 0 °C to rt, 2 h, 83%, >20/1 dr; (d) $NaBH_4$, MeOH/THF, 0 °C to rt, 3 h, 73%; (e) ^{n}BuLi, ^{n}Bu$_3$SnCl, THF, −78 °C, 30 min, 65%; (f) **12**, $Pd(PPh_3)_4$, CuBr, dioxane, 85 °C, 12 h, 77%; (g) TEMPO, KBr, aqueous NaClO, $NaHCO_3$, CH_2Cl_2/H_2O, 0 °C to rt, 3 min, then $NH_2CH_2COOMe{\cdot}HCl$, Et_3N, $MgSO_4$, CH_2Cl_2, 1 h, then AgOAc, DBU, toluene, rt, 1 h, 60% (gram-scale yield), 6/1 dr; (h) BnBr, K_2CO_3, CH_3CN, 80 °C, 5 h, 99%; (i) $Ph_3PCH_2OMe{\cdot}Cl$, ^{n}BuLi, THF, −78 to 0 °C, 2 h, 96%; (j) SmI_2, HMPA, HCl, MeOH/THF, 0 °C, 6 h, 87%; (k) $TiCl_4$, H_2O, CH_2Cl_2, 0 °C, 1 h, then MeI, ^{t}BuONa, THF, 0 °C to rt, 10 h, 78%, >20/1 dr; (l) $NaBH_4$, MeOH, 0 °C, 30 min, then MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 30 min, 73%; (m) NaOMe, MeOH, 90 °C (microwave), 2 h, 98%; (n) I_2, $NaHCO_3$, THF/H_2O, rt, 1 h, then DIBAL-H, CH_2Cl_2, −78 °C, 10 min, 87%; (o) $TsNHNH_2$, THF, rt, 1 h, then $Rh_2(Oct)_4$, K_2CO_3, dioxane, 130 °C, 1.5 h, 85%; (p) DIBAL-H, toluene, 0 °C to rt, 2 h, 75%; (q) HBF_4, THF/H_2O, 60 °C, 1 h, 61%; (r) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 90%, >20/1 dr; (s) H_2, $Pd(OH)_2$, MeOH, rt, 8 h, then Boc_2O, Et_3N, CH_2Cl_2, reflux, 24 h, 80%; (t) HF, H_2O/THF, rt, 4 h, then Dess−Martin periodinane, CH_2Cl_2, rt, 1 h, 95%; (u) pyrrolidine, AcOH, CH_2Cl_2, rt, 5 h, then MsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C to rt, 30 min, 90%; (v) KOH, THF/H_2O, 80 °C, 8 h, then Tebbe reagent, THF, rt, 2 h, 80%; (w) Li, liquid NH_3, ^{t}BuOH, THF, −78 °C, 2 h, 83%; (x) SeO_2, ^{t}BuOOH, CH_2Cl_2, 0 °C to rt, 30 min, 93%, >20/1 dr; (y) $ZnBr_2$, CH_2Cl_2, rt, 3 h, then MnO_2, CH_2Cl_2, rt, 4 h, 74% for 15-*epi*-talassamine (**62**), 62% for talassimidine (**4**), 64% for talassamine (**5**); (z) SeO_2, dioxane, 80 °C, 6 h, 71%; (aa) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 30 min, 99%, >20/1 dr; (ab) Ac_2O, DMAP, Et_3N, CH_2Cl_2, −30 °C, 30 min, 73%.

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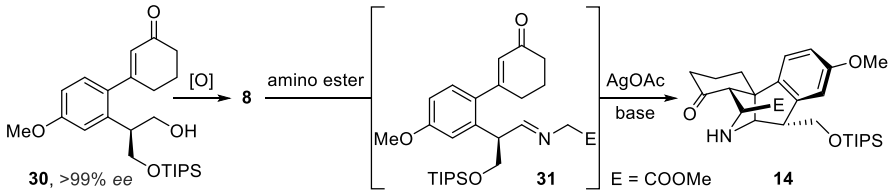
Table 1. Optimization of the Asymmetric 1,3-Dipolar Cycloaddition



entry	[O][a,b]	amino ester source[c,d]	base[e]	yield (%)[f]	dr[g]	ee (%)[h]
1	[DMP]	$Ph_3P{=}NCH_2CO_2Me$	DBU	54	7:1	45
2	[DMP]	$Ph_3P{=}NCH_2CO_2Me$	Et_3N	45	5:1	54
3	[DMP]	$NH_2CH_2CO_2Me$	Et_3N	40	4:1	50
4[i]	[DMP]	$NH_2CH_2CO_2Me$	Et_3N	<5		
5[i]	[TEMPO]	$NH_2CH_2CO_2Me$	Et_3N	51	4:1	>99
6[i]	[TEMPO]	$NH_2CH_2CO_2Me$	DIPEA	53	4:1	>99
7[i]	[TEMPO]	$NH_2CH_2CO_2Me$	TMG	56	4:1	>99
8[i]	**[TEMPO]**	**$NH_2CH_2CO_2Me$**	**DBU**	**65**	6:1	**>99**
9[i]	[TEMPO]	$NH_2CH_2CO_2Me$	Cs_2CO_3	37	4:1	>99
10[i]	[TEMPO]	$NH_2CH_2CO_2Me$	K_2CO_3	42	4:1	>99
11[i]	[TEMPO]	$Ph_3P{=}NCH_2CO_2Me$	DBU	45	5:1	36

[a][DMP] oxidation: **30** (0.1 mmol), Dess−Martin periodinane (0.15 mmol), CH_2Cl_2 (3 mL), rt, 0.5 h, chromatography on silica gel. [b][TEMPO] oxidation: **30** (0.10 mmol), TEMPO (0.01 mmol), KBr (0.20 mmol), NaClO (10% in H_2O, 0.20 mmol), $NaHCO_3$ (saturated aqueous solution, 2 mL), CH_2Cl_2 (3 mL), 0 °C to rt, 3 min, aqueous workup. [c]**8**, N_3CH_2COOMe/PPh_3 (0.11 mmol), CH_2Cl_2 (2 mL), 0 °C, 1 h. [d]**8**, $NH_2CH_2COOMe{\cdot}HCl$ (0.20 mmol), Et_3N (0.22 mmol), $MgSO_4$ (0.60 mmol), CH_2Cl_2 (2 mL), 0 °C, 1 h. [e]Crude **31**, AgOAc (0.01 mmol), base (0.11 mmol), toluene (2 mL), rt, 1 h. [f]Isolated yield of the major diastereoisomer from **30**. [g]Ratio of yields of the two isolated diastereoisomers. [h]Of the major diastereoisomer; determined by chiral HPLC analysis. [i]Crude **8** was used for the next step without chromatography purification.

racemization-prone azamethine ylide **13** or its precursors could be avoided, then chiral **14** could be obtained through a regio- and diastereo-selective intramolecular 1,3-dipolar cycloaddition of a chiral imino ester. Chiral aldehyde **8** for preparation of the imino ester could be synthesized from chiral stannane **11** and commercially available bromide **12** through a Stille coupling.

Construction of the A/F/C Ring System. As depicted in Scheme 4A, our synthetic efforts commenced with the preparation of chiral precursor **30** from commercially available acid (*S*)-4-benzyl-2-oxazolidinone. A sequence involving amidation, Evans asymmetric aldol reaction,[15] and silylation of the resultant free hydroxyl group afforded chiral amide **28** in good yield with a >20:1 diastereomeric ratio (dr). The absolute configuration of the newly generated stereogenic carbon center was determined by X-ray crystallographic analysis.[16,17] Reduction of amide **28** with $NaBH_4$ provided alcohol **29**, which was transformed to **11** by treatment with $^nBu_3SnCl$ after a Br−Li exchange. A Stille coupling of **11** and **12** with $Pd(PPh_3)_4$ as the catalyst and CuBr as the cocatalyst yielded **30** in 77% yield with >99% enantiopurity (ee).

With decagram quantities of chiral **30** in hand, we next explored the feasibility of an asymmetric synthesis of tetracyclic **14** via 1,3-dipolar cycloaddition (Table 1). Aldehyde **8**, imino ester **31**, and ylide **13** (structures are shown in Scheme 3) are potentially prone to racemization; therefore, the protocols for oxidation of alcohol **30**, formation of imine ester **31**, and Lewis acid catalyzed 1,3-dipolar cycloaddition are key to successfully preparing chiral **14**. Initially, a sequence of oxidation of **30** with Dess−Martin periodinane, imino ester formation with an aza-Wittig reagent, and 1,3-dipolar cycloaddition with AgOAc/DBU following our previous work produced **14** with low and inconsistent ee values (entry 1). We posited that the basic aza-Wittig reagent (i.e., $Ph_3P{=}NCH_2CO_2Me$)[18] and DBU may induce racemization and alternatively tested the less basic methyl glycinate and Et_3N. However, the reaction outcome did not improve (entries 2 and 3). Monitoring of the ee values of all precursors and reacting intermediates throughout the process indicated that silica gel chromatography of crude **8** resulted in its racemization. Hence, crude **8** was then used directly in the next step without silica gel chromatography; however, the cycloaddition was inhibited (entry 4). Thus, the oxidation protocol for this step must directly provide **8** in the required chemical purity without the need for silica gel chromatography. After screening, we were delighted to find that crude **8** prepared via a TEMPO-catalyzed oxidation afforded **14** in good yield with >99% ee (entry 5).[19] After further investigation of various amino ester sources and bases (entries 6−11), methyl glycinate and DBU were determined to be the best options (entry 8). Through this protocol, we smoothly prepared batches of chiral **14** on a gram scale.

Construction of the E Ring. Having successfully obtained the fundamental framework of hetidine skeleton, we next focused on construction of the E ring (Scheme 4B). After benzyl protection and Wittig olefination, a SmI_2-promoted domino reductive elimination/lactamization afforded formal skeleton-rearranged product **33** with breakage of the C6−N bond.[20] A sequence of enol ether hydrolysis and diastereoselective methylation gave aldehyde **34** in 78% yield. Reduction of the aldehyde group and subsequent mesylation of the resulting hydroxyl group gave **35**, which underwent a cascade of lactam opening and intramolecular alkylation in the presence of NaOMe to afford **25** with formation of the E ring.

Construction of the B Ring and Installment of the C7−OH Group. Inspired by our experience with constructing the B ring of hetisine-type alkaloids by a SmI_2-mediated, dearomative free radical addition to arene moiety, we initially envisioned that a ketyl radical generated from an aldehyde could undergo a dearomative addition to the phenyl ring, thus constructing the B ring likewise and installing the C7−OH group concurrently (Scheme 5A). However, our early attempts

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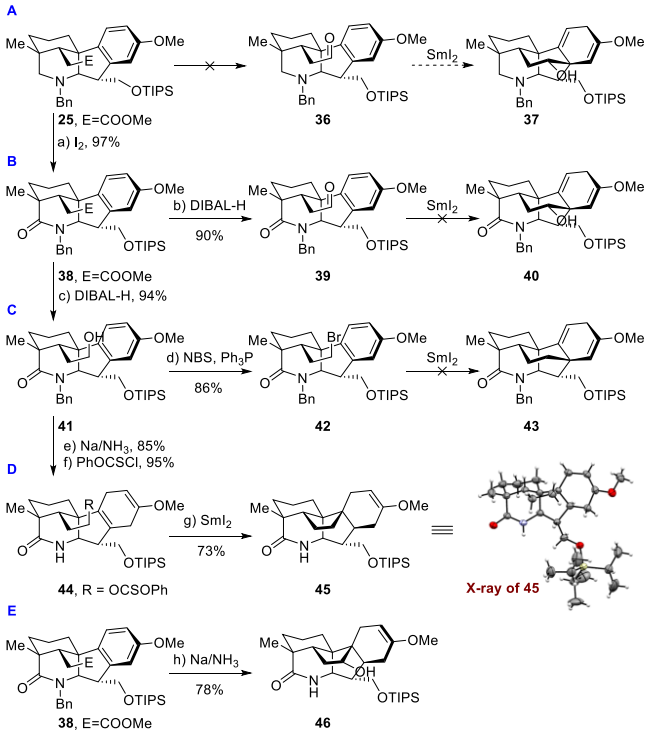
Scheme 5. Failed Attempts to Construct the B Ring[a]

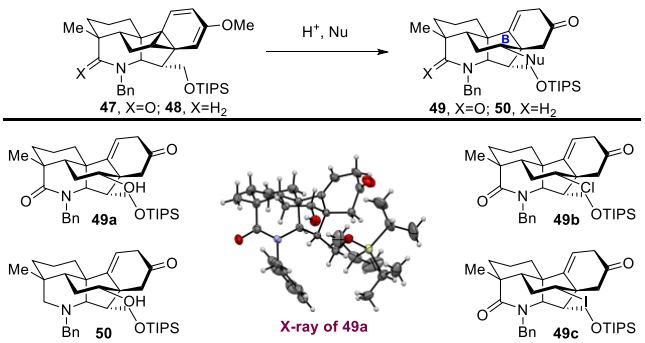


[a]Reagents and conditions: (a) I_2, $NaHCO_3$, THF/H_2O, rt, 1 h, 97%; (b) DIBAL-H, CH_2Cl_2, −78 °C, 10 min, 90%; (c) DIBAL-H, CH_2Cl_2, −30 °C, 10 min, 94%; (d) NBS, Ph_3P, rt, 1 h, 86%; (e) Na, liquid NH_3, ^{t}BuOH, THF, −78 °C, 2 h, 85%; (f) PhOCSCl, DMAP, CH_2Cl_2, rt, 2 h, 95%; (g) SmI_2, HMPA, THF, rt, 2 h, 73%; (h) Na, liquid NH_3, ^{t}BuOH, THF, −78 °C, 2 h, 78%.

to prepare aldehyde **36** from ester **25** were unfruitful, and only the suspected quaternary ammonium byproducts were observed. This can be attributed to tendency toward quaternization of the basic tertiary amine moiety of **25**. Accordingly, amine **25** was oxidized to amide **38** by treatment with I_2 (Scheme 5B). DIBAL-H reduction of the ester afford aldehyde **39** in high yield. However, treatment of **39** with SmI_2 under various conditions resulted in complex reaction mixtures (Scheme 5B). To explore the feasibility of constructing the B ring via dearomative addition with a primary free radical intermediate, as we did previously, primary bromide **42** was prepared from **38** by a sequential reduction and bromination and was tested with SmI_2 or Bu_3SnH. However, only unidentified products were generated (Scheme 5C). After several unsuccessful dearomative additions, we then turned to free radical addition to the alkene group after an arene dearomatization. Thus, precursor **44** was prepared by a sequence of Birch reduction and esterification and was then subjected to SmI_2. Notably, only **45** was isolated in a high yield with formation of a five-membered ring (Scheme 5D). Interestingly, Birch reduction of ester **38** led to compound **46** with a similar five-membered ring (Scheme 5E). We hypothesized that formation of a five-membered ring is favored over the six-membered ring without the tethering C6−N bond, which is present in our hetisine-type alkaloid synthesis.

After unsuccessful attempts to construct the B ring via free radical addition, we were ultimately drawn to a dearomative cyclopropanation strategy. As indicated in Scheme 4B, the diazo precursor was generated by condensation of aldehyde **39** withTsNHNH$_2$, which was then treated with a base and $Rh_2(Oct)_4$ to give **47** in 85% yield along with 10% yield of a 1,2-H shift alkene byproduct. Using copper salts as the catalyst in substitute for $Rh_2(Oct)_4$, only the alkene product was observed.[17] Amide reduction of **47** with DIBAL-H gave **48** in good yield. We envisioned that opening the cyclopropane ring with a hydroxyl nucleophile would not only establish the B ring but also introduce a hydroxyl group at C7. As shown in Scheme 6, a cascade of hydrolysis of the enol ether and S_N2-

Scheme 6. Nucleophilic Ring Opening of the Cyclopropane[a]



[a]Reagents and conditions: **47** or **48**, acid (5 equiv), THF, 60 °C, 1 h. **49a** (48% HBF_4 in H_2O, 80% yield, >20/1 dr); **49b** (37% HCl in H_2O, 86% yield, >20/1 dr); **49c** (57% HI in H_2O, 83% yield, >20/1 dr); **50** (48% HBF_4 in H_2O, 61% yield, >20/1 dr).

like ring opening of cyclopropane moiety by treating **47** or **48** with an aqueous solution of HBF_4 formed the B ring and stereospecifically installed the problematic equatorial C7−OH. Although attempts to introduce fluoro, benzenesulfonyl, or phenylthio groups at C7 were unfruitful, treatment of **47** with an aqueous solution of HCl or HI generated **49b** or **49c** with a halogen atom introduced, which would facilitate preparation of natural product analogues with unnatural functionalities at C7.[13] The stereochemistry of the newly formed C7−OH of **49a** was determined by X-ray crystallographic analysis, and the same configuration was assigned to other products by analogy.[16,17]

Construction of the D Ring. With the B ring established, the next task was to construct the D ring. As shown in Scheme 7, our initial plan to construct the B ring was an intramolecular alkylation. Mesylate **52** was prepared by a sequence of desilylation, mesylation, cyclopropane ring opening, and hydrogenation. To our surprise, attempts to construct the bicyclo[2.2.2]octane motif by treatment of **52** with a base (e.g., LDA, ^{t}BuOK, NaH, and K_2CO_3) only resulted in generation of **54** with a four-membered ring. The structure of **54** was confirmed by X-ray analysis of a single crystal of its derivative **56**, which was prepared by sequential olefination and allylic oxidation.[16,17] Generally, formation of a six-membered ring is favored over a four-membered ring. A possible rationale for this unusual selectivity is the specific and rigid architecture of compound **52**. We next resorted to a reversible aldol reaction with the expectation of generating the thermodynamically favored six-membered ring product. As shown in Scheme 4C, sequential reactions of acetylation, one-step alkene hydrogenation/Bn-hydrogenolysis, and Boc-protection delivered **57**, which was then elaborated to aldehyde **58** via desilylation and oxidation. Exposure of **58** to the classic aldol reaction

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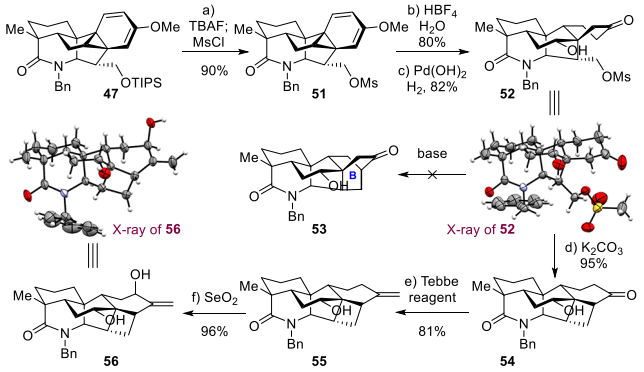
Scheme 7. Failed Attempts to Construct the D Ring by Alkylation[a]



[a]Reagents and conditions: (a) TBAF, THF, 70 °C, 4 h, then MsCl, DMAP, Et_3N, CH_2Cl_2, rt, 3 h, 90%; (b) HBF_4, THF/H_2O, 60 °C, 1 h, 80%; (c) $Pd(OH)_2$, H_2, MeOH, rt, 2 h, 82%; (d) K_2CO_3, MeOH, 75 °C, 3 h, 95%; (e) Tebbe reagent, THF, rt, 2 h, 81%; (f) SeO_2, ^{t}BuOOH, CH_2Cl_2, 0 °C to rt, 30 min, 96%.

conditions of pyrrolidine/AcOH and subsequent treatment with MsCl provided mesylate **59** with the D ring successfully constructed, thus completing the hetidine core.

Total Synthesis of (+)-Talassimidine and (+)-Talassamine. With the hetidine core constructed, the remaining task for completion of the synthesis of (+)-talassimidine and (+)-talassamine was the installation of the requisite functionalities (Scheme 4C). Mesylate **59** was transformed to **61** by sequential deacetylation, olefination, and sulfonate reduction. Using **61** as the branch point, we prepared 15-*epi*-talassamine **62**, a natural product analogue, by a sequence of diastereoselective allylic oxidation with SeO_2/^{t}BuOOH at 0 °C, Boc deprotection, and amine oxidation; the total synthesis of (+)-talassamine **5** was achieved by reactions including allylic oxidation with SeO_2 at 80 °C, diastereoselective Luche reduction of the resultant ketone, Boc deprotection, and amine oxidation. The total synthesis of (+)-talassimidine **4** was achieved by a similar reaction sequence except with an additional acetylation of C15−OH. The structure of our synthetic talassamine **5** and 15-*epi*-talassamine **62** were unambiguously confirmed by X-ray crystallographic analysis.[16,17] Notably, the ee values of the final products, as measured by chiral HPLC analysis, indicated that our synthetic approach provided (+)-talassimidine **4** and (+)-talassamine **5** with 99% ee.

CONCLUSION

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. 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.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c01865.

Experimental procedures and compound characterization (PDF)

Accession Codes

CCDC 2059195, 2059198, 2059200, 2059202, 2070613, 2070620, and 2070622 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

DIPEA, *N*,*N*-diisopropylethylamine; TIPS, triisopropylsilyl; TEMPO, 2,2,6,6-tetramethylpiperidine 1-oxide; Tebbe reagent, bis(cyclopentadienyl)-μ-chloro(dimethylaluminum)-μ-methylenetitanium

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