

Oxidative Coupling Approach to Sarpagine Alkaloids: Total Synthesis of (−)-Trinervine, Vellosimine, (+)-Normacusine B, and (−)-Alstomutinine C

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Abstract: Sarpagine alkaloids are bioactive indole natural products that contain a highly rigid indole-fused 1-azabicyclo[2.2.2]octane, more than 100 members of which have been identified. Herein, a detailed examination of the intramolecular oxidative coupling between a ketone and a Weinreb amide for assembling the complex 1-azabicyclo[2.2.2]octane core structure of sarpagine family alkaloids is described. Precise late-stage manipulations of the ketone and Weinreb amide enable the divergent syntheses of (−)-trinervine, (+)-vellosimine, (+)-normacusine B, and (−)-alstomutinine C. Other notable transformations of the synthesis featured an aza-Achmatowicz/indole cyclization cascade to generate the azabicyclo[3.3.1]nonane structure, a regioselective elimination reaction to form the ethylidene motif embedded in the (+)-vellosimine and (+)-normacusine B structures, and a diastereoselective indole oxidative rearrangement to form the spirooxindole structure in (−)-alstomutinine C.

Introduction

Sarpagine alkaloids are isolated from the Apocynaceae plant family and display a range of biological activities, including anti-inflammatory, analgesic, anticancer, and antiplasmodial activities.^[1] To date, more than 100 sarpagine alkaloids have been identified. A common structural feature of sarpagine alkaloids is a 1-azabicyclo[2.2.2]octane ring system together with a fully integrated indole-fused azabicyclo[3.3.1]nonane architecture. This highly rigid and strained polycyclic structure has seven contiguous stereogenic centers, including an inflexible stereogenic nitrogen atom (Figure 1). Triner-

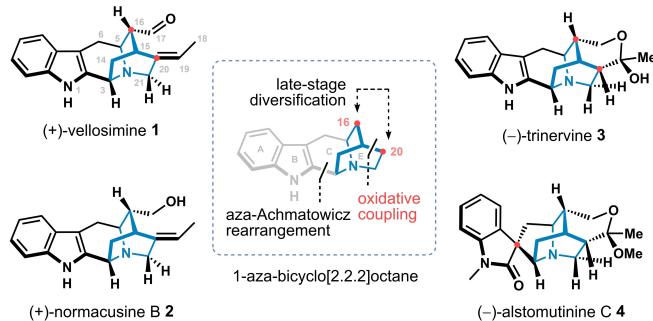


Figure 1. Representative sarpagine alkaloids.

vine is a representative member of this family, containing the core structure mentioned above and a hemiacetal motif connected to the E ring. Vellosimine and normacusine B have the same ethylidene substituent at C20 and different oxidation states at C17 (an aldehyde or hydroxy group, respectively). Alstomutinine C is one of the most complex molecules of this family; it has an additional all-carbon quaternary stereogenic center that stems from the spiro[pyrrolidine-3,3'-oxindole] structure.^[2]

Owing to their intriguing bioactivities and complex architectures, the sarpagine alkaloids have attracted considerable interest from numerous research groups worldwide and have been synthetic targets for more than half a century. The first total synthesis of ajmaline was published by Masamune^[3] in 1967, and biomimetic total syntheses of ajmaline and (+)-N-methylvellosimine were completed by Tamelen^[4] and Martin,^[5] respectively. The first asymmetric syntheses of (+)-koumidine and (+)-koumine were disclosed by Magnus^[6] in 1989. Subsequently, other asymmetric syntheses of sarpagine alkaloids were reported by Kutney,^[7] Cook,^[8] Gaich,^[9] Takayama,^[10] Kerr,^[11] She,^[12] Zhang,^[13] Zhang,^[14] and Qin.^[15] Other interesting synthetic studies toward the 1-azabicyclo[2.2.2]octane core structures of the sarpagine alkaloids have also been documented.^[16] A survey of previous syntheses revealed that significant efforts were mainly focused on the synthetic challenge of the highly strained N-bridgehead 1-azabicyclo[2.2.2]octane ring system, which has also served to demonstrate innovative methodology development. For example, a notable C5–C16 bond formation through iminium-ion-mediated nucleophilic substitution was developed to mimic the concise biosynthesis pathway.^[4,5] Gold-catalyzed alkyne activation and 6-exo cyclization can provide the vinyl group that is suitable for

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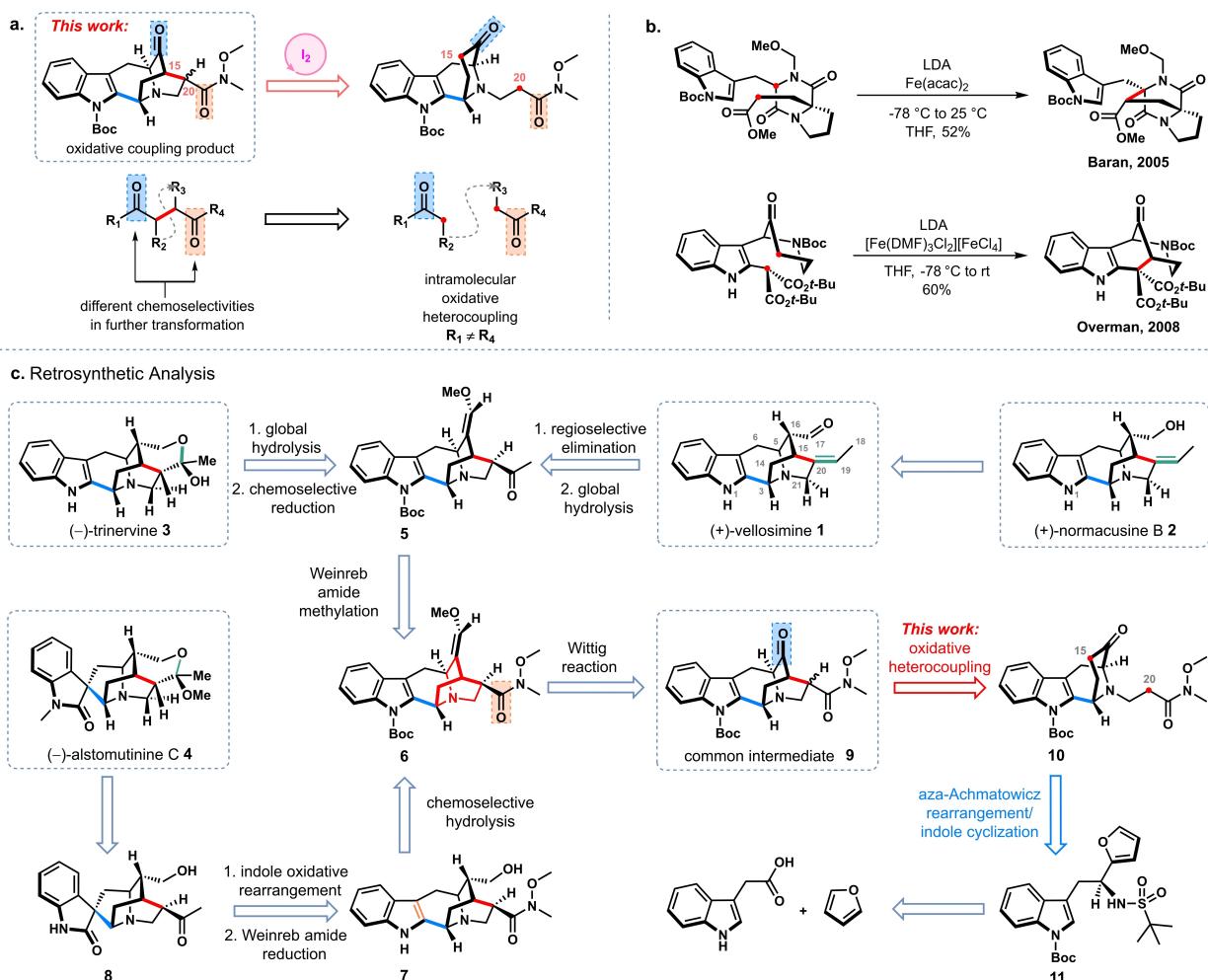
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divergent synthesis.^[6,10,12,13] Other innovative strategies include transition-metal-catalyzed cross-coupling,^[8c, 9a, 15] oxy-anion-Cope rearrangement,^[8b] and radical-type cycloaddition.^[14, 16a] The common features of previous syntheses—which require either the prefunctionalization of coupling partners or the participation of transition-metal catalysts—have motivated us to pursue a distinct strategy that simplifies the assembly of the 1-azabicyclo[2.2.2]octane moiety by adopting a step-economic oxidative coupling strategy.

In 1935, Ivanoff and Spassoff reported the dimerization of α -carbon carboxylate dianions, with the net loss of two protons, providing a symmetrical succinic acid.^[17] This enolate oxidative coupling reaction joins two sp^3 carbon atoms in a single step, without prefunctionalization of each coupling partner. Owing to the intrinsic distinct oxidation potential of α -C–H bonds of distinct carbonyl groups, intermolecular oxidative coupling has been broadly utilized in the syntheses of natural products and medicinal compounds.^[18] In contrast to intermolecular coupling, intramolecular oxidative coupling between two carbonyl groups has received less attention, and the successful application of

such intramolecular coupling in the syntheses of natural products remains limited.^[19] In 2005, the Baran group used oxidative coupling of an amide and an ester for the synthesis of bicyclo[2.2.2]diazaoctane in their elegant total synthesis of stephacidin A (Scheme 1b).^[19c] In 2008, the Overman group applied an oxidative coupling reaction between a ketone and a malonate to quickly build the core skeleton in their concise synthesis of actinophyllic acid (Scheme 1b).^[19c] Inspired by these two successful applications of intramolecular oxidative heterocoupling in the total synthesis of natural products, we envisioned that the challenging N-bridgehead 1-azabicyclo[2.2.2]octane rings of sarpagine alkaloids could be assembled by an intramolecular oxidative heterocoupling reaction between two distinguishable carbonyl groups, such as a ketone and a Weinreb amide (Scheme 1a). Herein, we present our development of an intramolecular oxidative heterocoupling and summarize the asymmetric total syntheses of (−)-trinevine, (+)-vellosimine, and (+)-normacusine B, and the first total synthesis of (−)-alstomutinine C.



Scheme 1. a) Our plan for preparing the 1-azabicyclo[2.2.2]octane core by intramolecular oxidative heterocoupling. b) Selected examples of intramolecular oxidative heterocoupling in natural product total synthesis. c) Retrosynthetic analysis. LDA = lithium diisopropylamide.

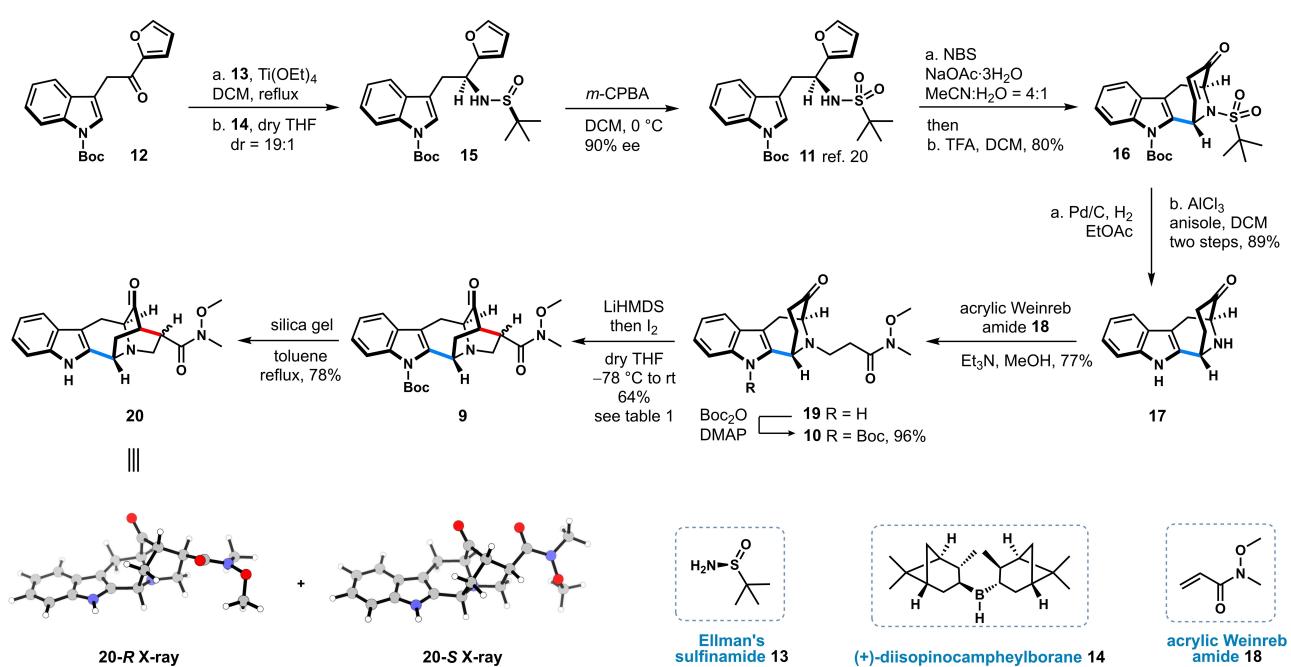
Results and Discussion

Retrosynthetically, sarpagine alkaloids could be targeted by diversifying the ketone and the Weinreb amide of the common 1-azabicyclo[2.2.2]octane intermediate **9** (Scheme 1c). Specifically, the hemiketal motif in trinervine (**3**) could be assembled through a global hydrolysis/aldehyde reduction sequence from **5**, which could be formed from ketone **9** through a Wittig reaction and a selective Weinreb amide methylation. The C20 ethylidene motif in yellosimine (**1**) and normacusine B (**2**) could be constructed from **5** by a reaction sequence of ketone reduction, regioselective elimination, and enol ether hydrolysis. The spirooxindole skeleton **8** in alstomutinine C (**4**) could be assembled from the intermediate **6** through chemoselective hydrolysis and a diastereoselective indole oxidative rearrangement reaction. An intramolecular oxidative heterocoupling reaction was mapped out for the construction of the 1-azabicyclo[2.2.2]-octane scaffold based on the ketone and the Weinreb amide of the indole-fused azabicyclo[3.3.1]nonane **10**, which could be readily prepared by an aza-Achmatowicz rearrangement/indole cyclization cascade^[20] of indole derivative **11**.

Our synthesis began with the preparation of the aza-Achmatowicz rearrangement precursor **11** (Scheme 2). Chiral sulfonamide **15** was obtained as a 19:1 diastereomeric mixture from ketone **12** through amination in the presence of Ellman's sulfonamide **13** and Ti(OEt)₄, followed by reduction of the imine using (+)-diisopinocampheylborane **14**. Sulfonamide **15** was then oxidized to **11** with *m*-CPBA. An aza-Achmatowicz rearrangement/indole cyclization cascade was conducted, resulting in the formation of an unsaturated azabicyclo[3.3.1]nonane (in its doubly protected form **16**) in 80% yield. The reduction of the C14 and C15

double bond was followed by global deprotection in the presence of AlCl₃ to give the ketone **17** in 89% yield (2 steps). Compound **17** was treated with the acrylic Weinreb amide **18** through an aza-Michael addition reaction to give **19** in 77% yield. The indole nitrogen atom was protected with a Boc group to deliver the indole-fused azabicyclo[3.3.1]nonane **10** in 96% yield.

With the oxidative coupling precursor in hand, a variety of reaction conditions were screened to optimize the formation of the oxidative coupling product **9**. Cu^{II} or Fe^{III} salts were explored as oxidants (Table 1, entry 1; Table S1, entry 1); however, no product was isolated, with only decomposition of the starting material detected. The [Fe-(DMF)₅Cl₂][FeCl₄] complex reported by Overman^[19e] is not suitable for this N-bridgehead 1-aza-bicyclo[2.2.2]octane ring formation (Table 1, entry 2). Numerous transition-metal-based oxidative coupling methods were screened and proved fruitless. Hypervalent iodine species, including PIDA and Koser's reagent used by Zhu and co-workers^[21] in their total synthesis of (-)-arborisidine, as well as PIFA reported by Vincent^[22] in their total synthesis of strictamine, were tested (Table S1, entry 2; Table 1, entries 3 and 4); however, no desired product could be detected, and the substrate decomposed quickly. Inspired by Ma's work on I₂-promoted intramolecular oxidative coupling between the indole 3-position and an enolate for the total synthesis of indole alkaloids,^[23] we applied the same reaction conditions to couple the dicarbonyl groups of the substrate **10** using molecular iodine as the oxidant. To our delight, the target molecule **9** was generated as a mixture of diastereomers (dr = 1.6:1; (Table 1, entry 5). After removal of the Boc group, the structures of these two diastereomers were



Scheme 2. Synthesis of ketone **9** by intramolecular oxidative heterocoupling. DCM = dichloromethane, *m*-CPBA = *m*-chloroperoxybenzoic acid, NBS = *N*-bromosuccinimide, DMAP = 4-dimethylaminopyridine, LiHMDS = lithium bis(trimethylsilyl)amide.

Table 1: Optimization of the conditions for the intramolecular oxidative heterocoupling.

Entry	Base (2.2 equiv)	Oxidant (1.2 equiv)	Yield [%]	dr ^[a]
1	LiHMDS	Cu(OTf) ₂	n/d	
2	LiHMDS	[Fe(DMF) ₃ Cl ₂][FeCl ₄]	n/d	
3	LiHMDS	Koser's reagent	n/d	
4	LiHMDS	PIFA	n/d	
5	LiHMDS	I ₂	61 % ^[b] (60 % ^[c])	1.6:1
6	LiHMDS	ICl	60 % ^[b] (63 % ^[c])	1:1.3
7	LiHMDS	IBr	59 % ^[b] (59 % ^[c])	1:1
8	LiHMDS ^[d]	I ₂	64 % ^[b] (61 % ^[c] , 52 % ^[b,e])	1.4:1
9	NaHMDS	I ₂	21 % ^[b] (23 % ^[c])	1:6.2
10	KHMDS	I ₂	n/d	
11	LiHMDS	I ₂ ^[f]	56 % ^[b] (57 % ^[c])	2.0:1

These reactions were performed on a 0.05 mmol scale, –78 °C, THF. [a] The diastereomeric ratio was determined by ¹H NMR analysis of the crude material. [b] Yield of the isolated product. [c] Yield determined by ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as the internal standard. [d] LiHMDS (2.5 equiv). [e] This reaction was performed on a 1.0 mmol scale. [f] This reaction was performed in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO) (1.0 equiv). n/d = not detected, NaHMDS = sodium bis(trimethylsilyl)amide, KHMDS = potassium bis(trimethylsilyl)amide, PIFA = (bis(trifluoroacetoxy)iodo)benzene.

unambiguously confirmed by X-ray diffraction experiments.^[24]

Encouraged by this preliminary result, we examined several halonium ion sources to improve efficiency. NBS (Table S1, entry 3) was found to be unsuitable for this transformation.^[25] We then focused on the screening of I⁺ reagents. NIS (Table S1, entry 4) was not as efficient as I₂. ICl and IBr generated the coupling product in comparable yields to I₂, but lower diastereoselectivities were observed (Table 1, entries 6 and 7). Besides the oxidant, combinations of solvent and base were also evaluated for this transformation. Incomplete conversion of the starting material was observed in toluene (Table S1, entry 5), whereas a complex mixture was detected in diethyl ether (Table S1, entry 6). The yield was highly dependent on the base used in the reaction. LiHMDS (2.5 equiv) afforded the highest yield (Table 1, entry 8). As compared to LiHMDS, the stronger base NaHMDS led to decreased yield but higher diastereoselectivity (Table 1, entry 9), and KHMDS resulted in decomposition of the starting material (Table 1, entry 10).

Seeking insight into this transformation, we performed this reaction with LiHMDS/I₂ at –78 °C in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO) as the radical scavenger (Table 1, entry 11). The coupling product **9** was still generated in 57 % yield. Besides the intermolecular radical capture experiment with TEMPO, we also conducted a radical clock experiment under the same reaction conditions using substrate **27** (Scheme 3b), which bears a cyclopropane group next to the Weinreb amide. The coupling product **28** was isolated and radical-induced ring-opening products were not detected during the whole process of the reaction, suggesting that the radical species was unlikely to be involved in this intramolecular coupling reaction (Scheme 3a, path A). Alternatively, upon the addition of iodine solution at –78 °C, C15 was iodinated to form intermediate **26** (Scheme 3a, path B), which may undergo intramolecular S_N2 displacement to give the coupling product **9**. Deuterium incorporation at the α-position of ketone **22** and iodination at the α-position of the ketone

of a by-product (see the Supporting Information for more details) further supported the possibility of the generation of intermediate **26**. Notably, owing to low diastereoselectivity (dr = 1:1), the dianion-Li chelation model noted for the oxidative dianion coupling for C–N bond formation in Sarpong's synthesis of lycopodium alkaloids does not seem relevant to the transformation examined in the current study.^[26] A plausible mechanism for this unique transformation is depicted in Scheme 3.

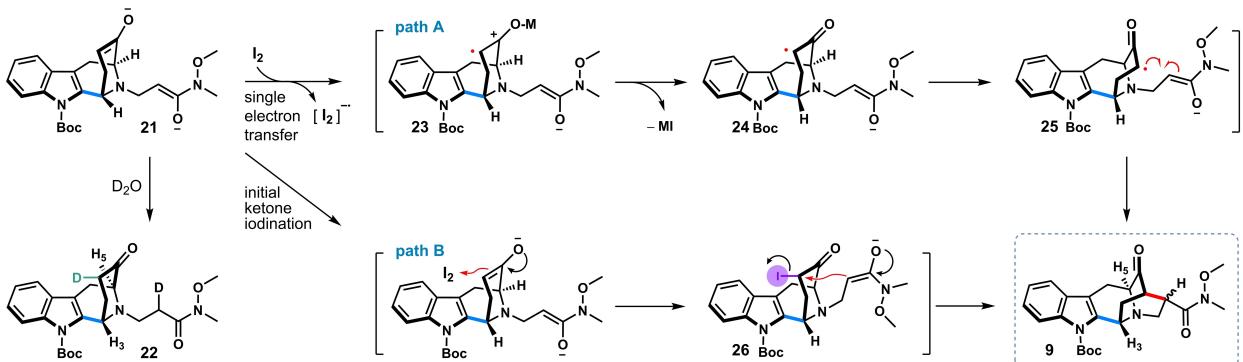
Total Synthesis of (–)-Trinervine

The coupling product **9** (mixture of diastereomers, dr = 1.6:1) was then treated with Wittig reagent **29** to achieve homologation at C16. We found that product **6** of the Wittig reaction is a single diastereomer formed in 64 % yield (Scheme 4). 2D NMR analysis revealed that the newly generated enol ether motif was invariably the Z isomer and that the C20 stereogenic center adopts the R configuration, indicating exclusive selectivity of the double-bond geometry upon simultaneous epimerization of the C20 stereogenic center during the Wittig reaction. In the presence of excess methylmagnesium bromide, Weinreb amide **6** was transformed to ketone **5** in 86 % yield. The hydrolysis of the enol ether using TFA led to the aldehyde **30** in 74 % yield, and selective reduction of the aldehyde in the presence of n-Bu₄N·BH₄ resulted in the formation of the primary alcohol **31** in 60 % yield.^[27] We then treated **31** with K₂CO₃ in MeOH: The expected epimerization at C20 occurred, resulting in the formation of (–)-trinervine (**3**) in 93 % yield.

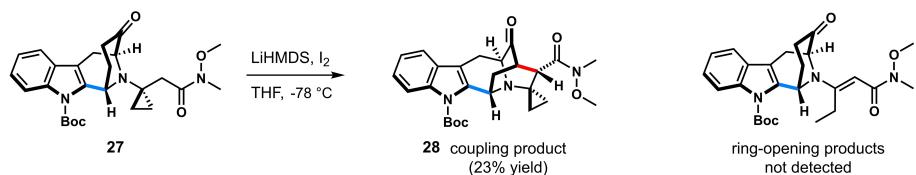
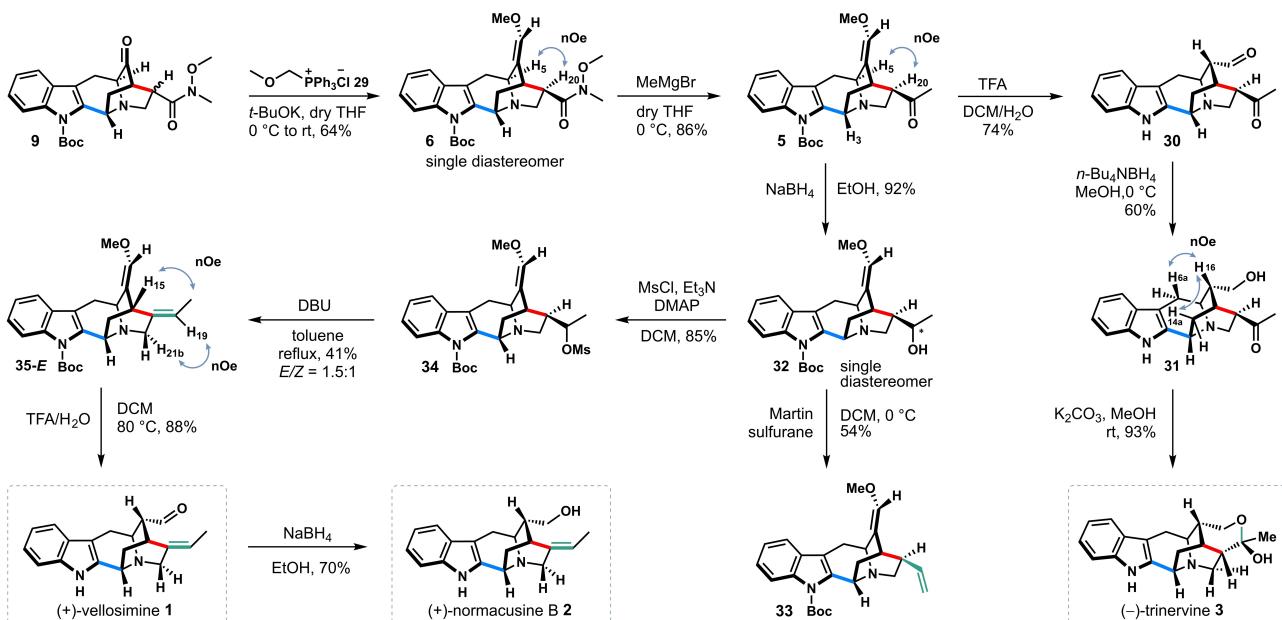
Total Syntheses of (+)-Vellosimine and (+)-Normacusine B

Compound **5** was treated with NaBH₄ in EtOH to give the secondary alcohol **32** in 90 % yield. A variety of reagents were explored for the elimination of the secondary alcohol **32** to form the exocyclic alkene. Common dehydration

a. Proposed Mechanism



b. Radical Clock Experiment

**Scheme 3.** Proposed mechanism and radical clock experiment.**Scheme 4.** Total syntheses of (-)-trinervine, (+)-vellosimine, and (+)-normacusine B. TFA = trifluoroacetic acid, DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene.

reagents, such as POCl_3 and SOCl_2 , resulted in disappointing yields (Table 2, entries 1 and 2). Dehydration with the Burgess reagent resulted in a complex mixture (entry 3). However, in the presence of the Martin sulfurane, elimination of the hydroxy group led to the terminal alkene **33** in 54 % yield (entry 4). We reasoned that the regioselectivity arises from the distinct kinetic acidities of the C20 and C18 hydrogen atoms. The C18 methyl hydrogen atoms were less hindered, and the kinetic terminal alkene product was

predominant in the presence of the highly reactive sulfurane reagent. Alternatively, the secondary alcohol was converted into the mesylate ester group **34**, and E2 elimination provided the desired internal C19–C20 double bond as a separable mixture of the *E/Z* isomers (1.5:1) in the presence of the strong base DBU (entry 5). Subsequent global hydrolysis of **35-E** gave (+)-vellosimine (**1**) in 88 % yield, and further reduction of the aldehyde group gave (+)-normacusine B (**2**) in 70 % yield.

Table 2: Dehydration/elimination conditions.

Entry	R	Reagent	Solvent	T	Yield [%] ^[a]	
					33: C20-R, $\Delta^{18,19}$	35: E, $\Delta^{19,20}$ 35: Z, $\Delta^{19,20}$
1	OH	POCl ₃	pyridine	0°C→rt	n/d	
2	OH	SOCl ₂	pyridine	0°C→rt	trace	
3	OH	Burgess reagent	toluene	120°C	complex mixture	
4	OH	Martin sulfuran	DCM	0°C→rt	33: 54%	35-E: n/d, 35-Z: n/d
5	OMs	DBU	toluene	120°C	33: n/d	35-E: 24%, 35-Z: 16%

[a] Yield of the isolated product.

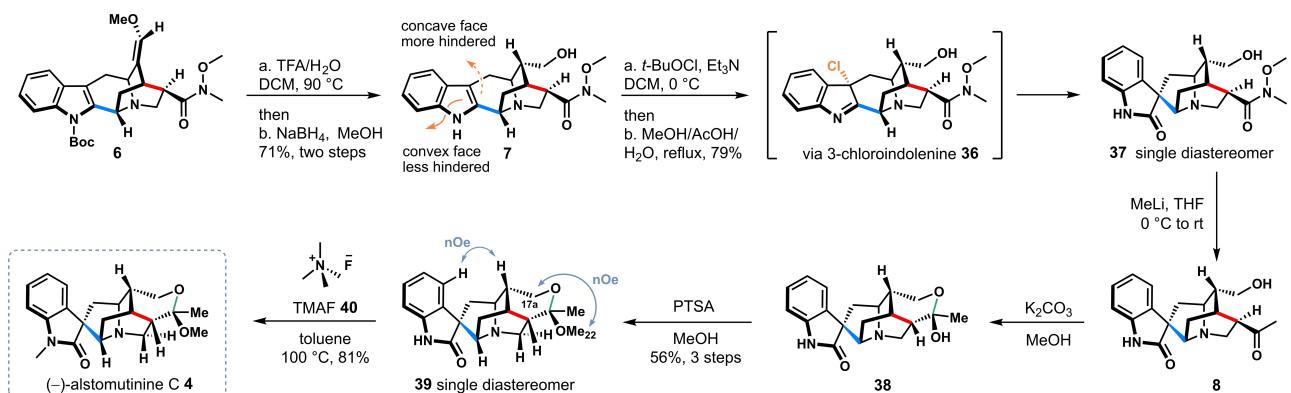
Total Synthesis of (–)-Alstomutinine C

To complete the synthesis of alstomutinine C (Scheme 5), which has a complex spiro[pyrrolidine-3,3'-oxindole] ring system, we further transformed compound **6** into the primary alcohol **7** by selective hydrolysis of the enol ether and the Boc group, followed by selective reduction of the aldehyde. Although Oxone and Davis oxaziridine/Lewis acid mediated oxidative rearrangement failed to generate the desired oxindole product, *t*-BuOCl showed promising results.^[28] Alcohol **7** was treated with *t*-BuOCl in the presence of Et₃N, followed by heating of the crude chloroindolenine **36** at reflux in a mixture of MeOH/AcOH/H₂O, and the desired spirooxindole skeleton **37** was delivered smoothly as a single diastereomer in 79% yield. The configuration at C7 was confirmed by NOESY analysis of compound **39**. Structural analysis of **7** revealed that the concave face of the 2,3-indole double bond is more hindered than the opposite face, suggesting that in the presence of halogenating reagents, the halogenation of C3 would take place from the less hindered face to generate a stereocenter with the *S* configuration.

For the following stereospecific 1,2-shift, the migrating group was positioned opposite to the C3 halogen bond and resulted in the final oxindole with the correct configuration. Next, Weinreb amide **37** was converted into ketone **8** in the presence of methylolithium. Inversion of the configuration of the C20 stereogenic center was required to obtain the final acetal: This epimerization was successful using K₂CO₃ in MeOH, and spontaneously delivered the hemiketal **39**, which was further transformed into the acetal **38** in the presence of PTSA in MeOH (56% yield, over 3 steps). The configurations of the C7 and C19 stereocenters were confirmed by NOESY. Chemoselective methylation of the amide nitrogen N1 of the oxindole (over N4) was achieved by using TMAF **40** (tetramethylammonium fluoride) as the methylation reagent,^[29] and the final product (–)-alstomutinine C (**4**) was obtained in 81% yield.

Conclusion

In conclusion, we have developed an efficient iodine-mediated intramolecular oxidative heterocoupling reaction



Scheme 5. Total synthesis of (–)-alstomutinine C. PTSA = *p*-toluenesulfonic acid, TMAF = tetramethylammonium fluoride.

for the rapid construction of the 1-azabicyclo[2.2.2]octane core structure of sarpagine alkaloids. The simple transition-metal-free conditions highlight the advantage of oxidative coupling of the α -positions of two carbonyl groups in the construction of a highly strained polycyclic ring system. Chemoselective functional-group interconversions of the C16 ketone and the C20 Weinreb amide enabled divergent total syntheses of (–)-trinervine (16 steps), (+)-vellosimine (17 steps), (+)-normacusine B (18 steps), and (–)-alstomutinine C (19 steps). A regioselective elimination of the secondary hydroxy group was developed to construct the internal ethylenic motif, which emphasized the utility of mechanism-based fine tuning of conditions in regioselective olefination. This concise synthetic strategy is likely to be suitable for producing other sarpagine alkaloids or congeners to support biomedical investigations. The exploration of the utility of oxidative heterocoupling reactions in the syntheses of other natural products is under investigation.

Acknowledgements

This research was supported by the National Natural Science Foundation of China (21971018 and 82225041). We gratefully acknowledge the Beijing Municipal Government and Tsinghua University for their financial support.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are openly available in figshare at <https://doi.org/10.6084/m9.figshare.22347076>, reference number 22347076.

Keywords: Iodine · Oxidative Coupling · Rearrangement · Sarpagine Alkaloids · Total Synthesis

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Manuscript received: March 28, 2023

Accepted manuscript online: May 9, 2023

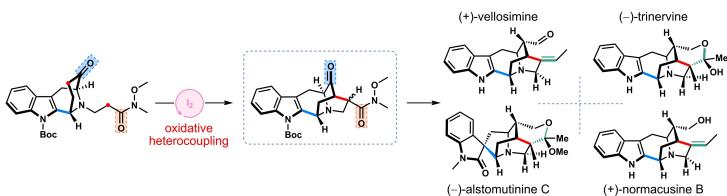
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Research Articles

Natural Products Synthesis

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Oxidative Coupling Approach to Sarpagine Alkaloids: Total Synthesis of (−)-Trinervine, Vellosimine, (+)-Normacusine B, and (−)-Alstomutininine C



An innovative intramolecular oxidative coupling between a ketone and a Weinreb amide was developed for the assembly of the complex 1-azabicyclo[2.2.2]-octane core structure of sarpagine alkaloids. Precise late-stage functional-

group manipulation of the ketone and the Weinreb amide enabled the divergent synthesis of (−)-trinervine, (+)-vellosimine, (+)-normacusine B, and (−)-alstomutininine C.