Total synthesis of (±)-maistemonine and (±)-stemonamide†

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The first total synthesis of polycyclic *Stemona* alkaloid maistemonine has been achieved. The efficient approach features a stereoselective intramolecular Schmidt reaction, a ketone–ester condensation, and a Reformatsky reaction. Additionally, another *Stemona* alkaloid stemonamide was divergently synthesized from a common intermediate.

The traditional Chinese and Japanese medicine *Stemona* has long been used for the treatment of respiratory diseases, such as pertussis and tuberculosis, and also used as vermifuges and insecticides.[1] So far, more than 80 alkaloids have been isolated from the *Stemona* plants, and Pilli *et al*. have classified them into eight groups according to their structural features,[2] wherein a family of stemonamine group including six *Stemona* alkaloids (**1a–1f**) is characterized by the inclusion of a spirolactone ring at C-12 of the basic azatricyclic 7,5,5-ring system (Fig. 1). Among them, maistemonine (**1e**) was isolated from the roots of *Stemona mairei* as one of the structurally complex major components by Xu and co-workers in 1991,[3] and has been shown to display significant antitussive activity.[4]

In the past decade, a number of ingenious synthetic efforts towards (±)-stemonamine (**1a**),[5c,e,f] (±)-isostemonamine (**1b**),[5e] (±)-stemonamide (**1c**),[5a,b,d,e] and (±)-isostemonamide (**1d**)[5a,b,d,e] have been reported, including the first total synthesis of (±)-stemonamine (**1a**) by our group. However, total synthesis of maistemonine (**1e**) with more intricate skeleton has not been reported to date.

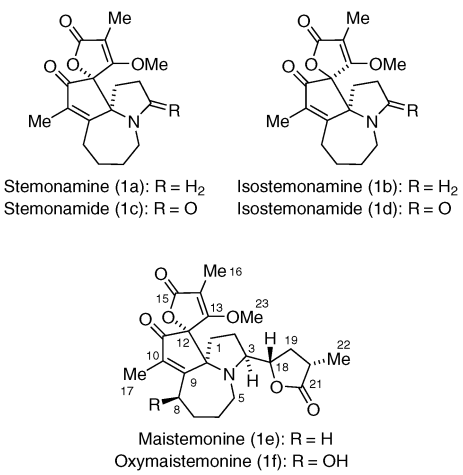
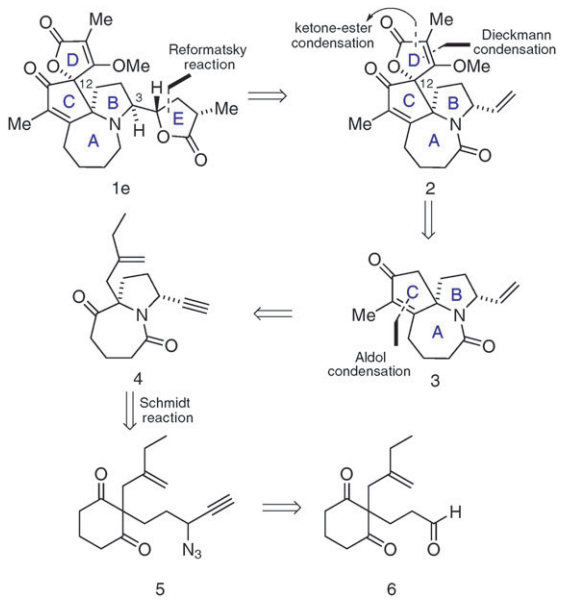


Fig. 1 Six alkaloids of the stemonamine group.

Maistemonine with a relatively complex polycyclic structure consists of a tetracyclic nucleus and an α-methyl-γ-butyrolactone moiety annexed to C-3 as a side-chain, and contains five stereogenic carbons including two contiguous hetero-quaternary centers. Its challenging molecular architecture and potential biological activities prompted us to develop an efficient and economical synthesis based on rational synthetic design. Herein, we report the first synthetic strategy that leads back to a readily available compound to the pentacyclic alkaloid, (±)-maistemonine (**1e**).

A retrosynthetic analysis of **1e** is shown in Scheme 1. We envisioned that the right-side butyrolactone unit **E** of **1e** could be forged through a Reformatsky-type reaction. The spirolactone ring **D** at C-12 might be established by the Dieckmann condensation or ketone–ester condensation. Construction of the enone ring **C** from **4** would involve sequential oxidation, reduction and aldol cyclization. A particularly appealing entry to bicycle **4** was conceived *via* a highly stereoselective intramolecular Schmidt reaction of precursor **5** which could be derived from the known aldehyde **6**[5f] in three steps.

The convenient preparation of the key precursor **3** is outlined in Scheme 2. Selective Grignard addition of ethynylmagnesium chloride to the known tricarbonyl compound **6**, followed by the mesylation, resulted in the formation of the ketone mesylate **7**. The mesylate group in **7** was subsequently substituted by NaN_3 to give the secondary azide **5**. With **5** in hand, the key intramolecular Schmidt



Scheme 1 Retrosynthetic analysis of (±)-maistemonine.

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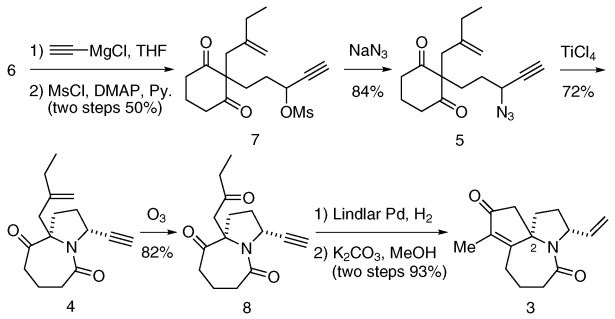
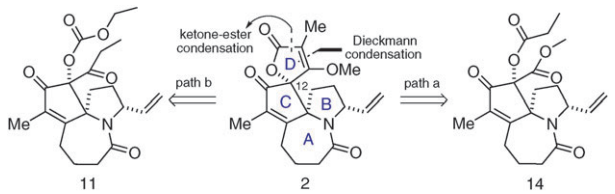


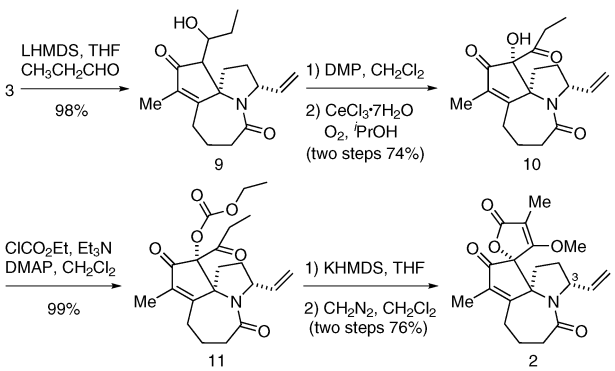
Scheme 2

reaction[6] of secondary azide was then investigated. To our delight, the desired amide **4** was obtained by using Lewis acid $TiCl_4$ in a stereoselective form.[7] The remarkable stereoselectivity might be understood by considering the unfavored steric hindrance between 2-methylenebutyl and alkynyl moieties in the transition state.[8] The introduction of the alkynyl group was elaborate for the convenient establishment of ring **E** and also made it possible to obtain stemonamide (**1c**) in the later stage. Ozonolysis and subsequent Lindlar reduction[9] produced the corresponding terminal olefin, which was subjected to aldol condensation without purification with K_2CO_3 in MeOH to provide the crucial tricyclic product **3** in 23% overall yield from **6**. It should be noted that the use of stronger bases such as ^{t}BuOK was not suitable for this cyclization in which a reto-aza-Michael process might account for the observed epimerization at C-2 of **3**.[10]

The next steps of the synthesis required the construction of ring **D**. According to our previous study in the total synthesis of (±)-stemonamine (**1a**), the spirolactone **D** might be established by the Dieckmann condensation[5c] in path a (Scheme 3). A series of bases with the combination of various solvents were carefully examined for the cyclization of **14**, however no expected ring closure product was obtained. Therefore, an alternative strategy for the construction of ring **D** based on a ketone–ester condensation[11] was designed (path b). As depicted in Scheme 4, reaction of ketone **3** with LHMDS and propanal efficiently provided β-hydroxy ketone **9** as a single diastereoisomer. Oxidation using Dess–Martin periodinane[12] afforded the desired β-dicarbonyl compound. To introduce the contiguous spirocyclic quaternary center, the nonpurified β-dicarbonyl compound was initially treated with Davis' reagent, resulting in the unexpected rearrangement product.[13] Gratifyingly, reaction of the crude β-dicarbonyl compound with 10 mol% $CeCl_3{\cdot}7H_2O$ in ^{i}PrOH under an atmosphere of oxygen[14] furnished α-hydroxylation adduct **10** accompanied by its epimer in the ratio of 8 : 1, which were readily separated by column chromatography. The desired major isomer was converted to carbonate **11** by treatment with ethyl chloroformate in CH_2Cl_2 at room temperature. With the vital intermediate in hand, the unique intramolecular ketone–ester condensation to access the spirolactone **D** was attempted. After extensive investigation, it was found that treatment of **11** with KHMDS in THF at −78 to 10 °C for 5 h, followed by *O*-methylation with diazomethane, provided tetracyclic skeleton **2** in good yield. Its relative stereochemistry was confirmed by X-ray crystallography.[15] Indeed, exposure of **11** to other bases (LDA, LHMDS, NaHMDS, or ^{t}BuOK) only resulted in the substrate decomposition, and the selection of less bulky ethoxy as leaving group is crucial in this ring closure reaction.[16] This method provides a novel approach for the construction of similarly unsaturated spirolactone skeleton.[5a,c,d]



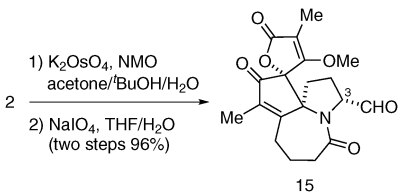
Scheme 3 Two designed strategies for construction of ring **D**.



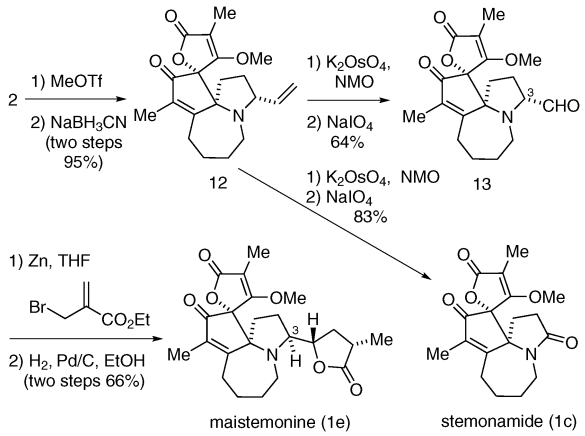
Scheme 4

With the tetracyclic core of maistemonine completed, the final challenge was stereoselective establishment of ring **E**. By comparing the relative configurations of **2** and **1e**, we found the inconsistency of the C-3 stereochemistry. After accessing aldehyde **15** by oxidative cleavage of **2** (Scheme 5), we investigated the epimerization of C-3 *via* the enolization/protonation sequence from α-face. A variety of bases and proton sources were attempted, however, no desired epimerization product was observed.

As an alternative synthetic approach to **1e** (Scheme 6), we explored the reduction of the lactam carbonyl without touching double bond and other carbonyls in **2**. Pleasingly, after extensive experimentation, the desired tertiary amine **12** was obtained by means of *O*-methylation and reductive removal of lactam carbonyl in a chemoselective reduction manner. Oxidative cleavage of the terminal vinyl moiety in **12** with K_2OsO_4–$NaIO_4$ provided the requisite aldehyde **13** in 64% yield. Notably, a slow C-3 epimerization of **13** in $CDCl_3$ at room temperature was observed during the NMR analysis, and a one pot protocol of epimerization and construction of ring **E** was conceived. To our delight, treatment of **13** with ethyl bromomethylacrylate and zinc in THF,[17] followed by



Scheme 5



Scheme 6

subsequent hydrogenation of the *exo*-double bond of the resulting unstable α-methylen-γ-lactone intermediate in the presence of Pd/C under atmospheric pressure, produced (±)-maistemonine (**1e**) stereoselectively.[18] Its NMR spectra were in all aspects identical with the spectra of natural product. The relative configuration of **1e** was unambiguously established by the later X-ray analysis.[15]

Interestingly, another *Stemona* alkaloid (±)-stemonamide (**1c**) was obtained in 83% yield from **12** in the oxidative cleavage reaction by increasing the amount of $NaIO_4$, elevating the reaction temperature and prolonging the reaction time (Scheme 6). Spectral data of **1c** were in agreement with the authentic data of stemonamide.[3b] Thus, we have accomplished a new route to stemonamide.[5a,d]

In summary, the first total synthesis of (±)-maistemonine (**1e**) was achieved in 19 steps with an overall yield of 5% from known compound **6**. Key transformations include a highly stereoselective intramolecular Schmidt reaction of secondary azide to form the central perhydroazaazulene ring system, a new protocol for the construction of the spirolactone ring through a ketone–ester condensation, and a sequence of Reformatsky reaction and hydrogenation involving epimerization of C-3 to introduce the vicinal butyrolactone moiety. Besides, (±)-stemonamide (**1c**) was divergently synthesized from intermediate **12** in the later stage. It is noteworthy that the synthetic strategy described here is a step economy process and no extra protecting-group manipulations were required in the current total synthesis.

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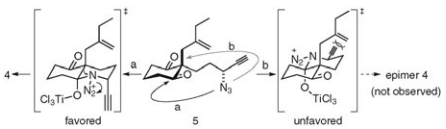
8 Proposed process for the stereoselective Schmidt reaction.



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18 It was assumed that simple epimerization of the aldehyde α-stereocenter or a retro-Mannich and Mannich process (see ref. 5*e*) might account for the epimerization of the stereogenic center C-3 (or C-4 and C-12) in the epimerization/Reformatsky reaction.