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Synthesis of the Proposed Structures of Parvistemoamide and Their Transformations to Stemoamide Derivatives

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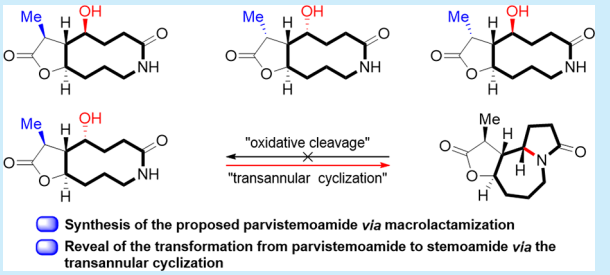
ABSTRACT: The proposed structures of parvistemoamide have been achieved by macrolactamization, but none of the characterization data of synthetic samples matched with those of the natural sample. The transformation of the highly strained 10-membered lactam ring in parvistemoamide into the pyrrolo[1,2-*a*]-azepine nucleus in stemoamide is accomplished for the first time by either transannular cyclization or Pilli's transformation. This research may promote the total synthesis of other more complex stemoamide-type or medium-sized-ring-containing *Stemona* alkaloids.



Medium-sized rings (8−11 atoms) play an important role in biologically active natural products, medicines, and cyclic peptides,[1] but the syntheses of medium-sized rings still remain a challenge because of their unfavorable transannular interactions and entropic factors.[2] *Stemona* is a traditional herbal medicine in China and Japan that, besides containing a large number of bioactive seven-membered azepine skeletons, possesses medium-sized alkaloids as some of its main components.[3] Although medium-sized alkaloids are most likely some of the indispensable active components of *Stemona*,[4] they have never been investigated in pharmacology, which is mainly due to limitations such as the low yields in the plant, the low isolation efficiency, and the high difficulty of the synthesis. Therefore, accomplishing the total syntheses of medium-sized-ring-containing *Stemona* alkaloids may promote research on the substance basis of the activities of *Stemonaceae* plants.

Parvistemoamide (**3**), which was isolated from *Stemona parviflora* by Xu and co-workers, was the first identified and one of the most representative medium-sized *Stemona* alkaloids.[4e] It belongs to the miscellaneous group in Pilli's classification[4d] and is characterized by a highly strained 10-membered lactam and four continuous stereocenters. However, the stereochemistry at the C9a and C10 positions remains ambiguous; Xu and co-workers proposed two kinds of stereochemistry, one is C9a−*α*-OH and C10−*α*-Me[4e,5b] and the other one is C9a−*β*-OH and C10−*β*-Me.[5c] After Xu's seminal research, the topic of *Stemona* alkaloids has been reviewed by several groups, and the two structures proposed by Xu and co-workers appeared in some of these publications.[4d,5a] In 2006, Greger and co-workers showcased the structure of parvistemoamide as C9a−*α*-OH and C10−*α*-Me,[4c] whereas the stereochemistry at C9a was reversed in their latest review (Figure 1).[4a] The above confusing stereochemistry at the C9a

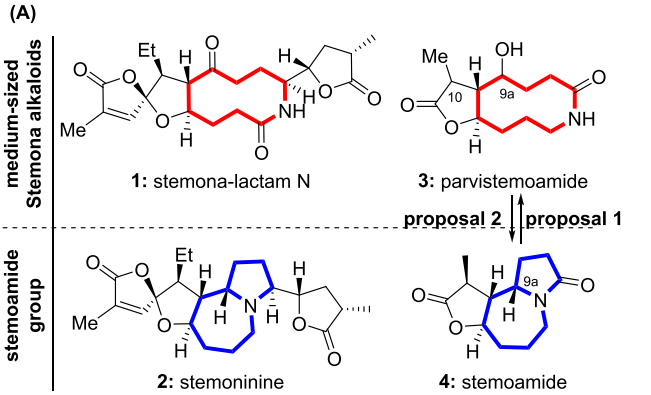


Figure 1. (A) Stemoamide-type and medium-sized *Stemona* alkaloids and the reported transformation between parvistemoamide and stemoamide. (B) Reported structures of parvistemoamide at present.

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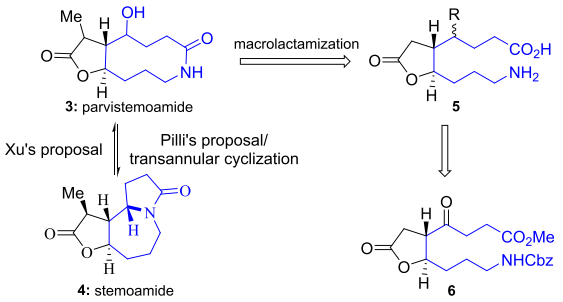
and C10 positions of parvistemoamide largely hinders the synthetic and pharmacological studies on parvistemoamide and medium-sized-ring-containing *Stemona* alkaloids.

At same time as reporting the isolation of parvistemoamide, Xu simultaneously reported that the 10-membered lactam in parvistemoamide (**3**) may come from the pyrrolo[1,2-*a*]-azepine nucleus in stemoamide (**4**) by C9a−N oxidative cleavage.[4e] Afterward, Pilli and co-workers revealed their synthetic study on parvistemoamide in 2005 and proposed a possible biomimetic conversion of parvistemoamide to stemoamide via oxidation at C9a, a nucleophilic attack by an activated form of the amide nitrogen, and the following dehydration and reduction of the intermediate N-acyliminium ion,[5a] which is different from Xu's proposal[4e] (Figure 1). However, in Pilli's work only a 5:1 mixture of two lactams with C9a−*α*-OH and C10−*α*-Me and C9a−*β*-OH, C10−*β*-Me was achieved, and no any NMR data were provided.[5a] More importantly, neither Xu's nor Pilli's viewpoint on the transformation relationship between parvistemoamide and stemoamide has been studied by experiments until now, although many elegant formal or total synthesis studies toward stemoamide have been revealed.[6] Therefore, the relative configuration of parvistemoamide and its transformation relationship with stemoamide are still unsolved mysteries.

In this regard, accomplishing the total syntheses of the possible structures of parvistemoamide may help to confirm its stereochemistry and, more importantly, promote the study of the transformation relationship of *Stemona* alkaloids. In the continuation of our research interest in *Stemona* alkaloids,[7] we herein (A) report the total syntheses of four stereoisomers of parvistemoamide (**3**) via macrolactamization and (B) reveal the transformations of the possible structures of parvistemoamide (**3**) to stemoamide (**4**) and 9a-*epi*-stemoamide by transannular cyclization or Pilli's transformation, although the unambiguous structural determination for parvistemoamide was not accomplished in this work.

Based on the structural characters of parvistemoamide, we propose the following retro-synthetic strategy (Scheme 1). The

Scheme 1. Retro-Synthetic Analysis of Stemoamide and Parvistemoamide



10-membered lactam ring in parvistemoamide is proposed to be constructed via the macrolactamization of the amphoteric compound **5**, which can be further traced back to ketone **6** via the protection of the keto-carbonyl group and the deprotection of the ester and amine. Ketone **6** is a known compound and could be easily obtained.[8] On the other hand, parvistemoamide may be derived from stemoamide via the C9a−N oxidative cleavage proposed by Xu,[4e] or stemoamide could come from parvistemoamide via the C−N bond formation proposed by Pilli[5a] or transannular cyclization. If the above proposal is successfully achieved, parvistemoamide (**3**) could be synthesized and, more importantly, the stereochemistry of parvistemoamide and its transformation relationship with stemoamide (**4**) would be clearly revealed, which may further promote the total syntheses of other more complex stemoamide-type alkaloids.

With the above retrosynthetic analysis in mind, we commenced the synthesis of stereoisomers **3a**−**3d**, which encompass the two structures proposed for parvistemoamide (**3**) by Xu and co-workers[4e,5c] (Scheme 2). Starting from ketone **6**,[8] the protection of the ketone carbonyl group with 1,3-dimercaptopropane and the hydrolysis of the methyl ester with LiOH generated carboxylic acid **7**. Under the promotion of TMSI, the carboxybenzyl group (Cbz) in **7** was deprotected to render the unprotected amine, which was then subjected to the Corey−Nicolaou macrolactamization reaction to construct the 10-membered lactam **8** in a 50% yield in a rather high-dilution solvent ($c = 1.0 \times 10^{-3}$ M). Then, the above-generated unprotected amide was protected by Boc to deliver **9** in a 71% yield, which was identified by X-ray analysis. Sequentially, **9** underwent the oxidative deprotection of the 1,3-dithiane protecting group by PIFA, affording ketone **10** in a 72% yield.

We subsequently studied the stereoselective reduction of ketone **10**. When subjecting ketone **10** to reducing reagents such as sterically hindered $LiAl(^tBuO)_3H$, the Boc-protected 10-membered lactam in the desired product was susceptible to nucleophilic ring opening, and an unexpected lactam−lactone exchange product formed via the ring opening of lactam and the lactonization of the amide carbonyl group with the newly formed hydroxyl group (see the Supporting Information (SI)). This is mainly due to the existence of Boc weakening the p−*π* conjugation effect between the amide nitrogen atom and the amide carbonyl group, thus weakening the C−N bond and increasing the electrophilicity of amide carbonyl group.[9] Pleasingly, when the reaction mixture was flash-quenched with 3 M HCl, only a single diastereoisomer with C9a−*α*-OH was afforded in a 73% yield. The subsequent sequential C9a−*α*-OH protection by TES and the stereospecific methylation at C10 rendered **11a** smoothly. When **11a** was treated with $BF_3{\cdot}OEt_2$, TES was removed prior Boc, the lactam−lactone exchange byproduct was formed (see the SI). After exhaustive attempts, $Mg(ClO_4)_2$, which was compatible with the sensitive TES, was considered as the most appropriate reagent to remove Boc.

Then, TES was deprotected by CAN, accomplishing the synthesis of **3a**. After the attempted introduction of a double bond in C10 failed (see the SI), the most commonly employed chiral adjustment method in the synthetic studies on *Stemona* alkaloids was used. As a result, **3a** (*β*-Me) and **3b** (*α*-Me) were obtained in a 39% total yield in a diastereoselective ratio of 1:1 when **3a** was subjected to K_2CO_3/MeOH. The structures of **3a** (CCDC 2068248) and **3b** (CCDC 2068262) were confirmed by X-ray crystallographic analysis, and **3b** was found to be identical to the structure proposed by Xu.[4e,5b] However, the ^1H and ^{13}C NMR data of neither **3a** nor **3b** are the same as those of the natural sample. One of the most significant differences in the ^1H NMR data is that there is an additional set of peaks at 2.80−3.0 ppm in our reported data. As for the ^{13}C NMR data, it is obvious that both **3a** and **3b** are not the naturally occurring parvistemoamide.

Thus, we have to resort to the epimers at the C9a position. After several trials, $NaBH_4$ gave a 3.8:1 ratio of two diastereoisomers in favor of *β*-OH (see the SI). Following a

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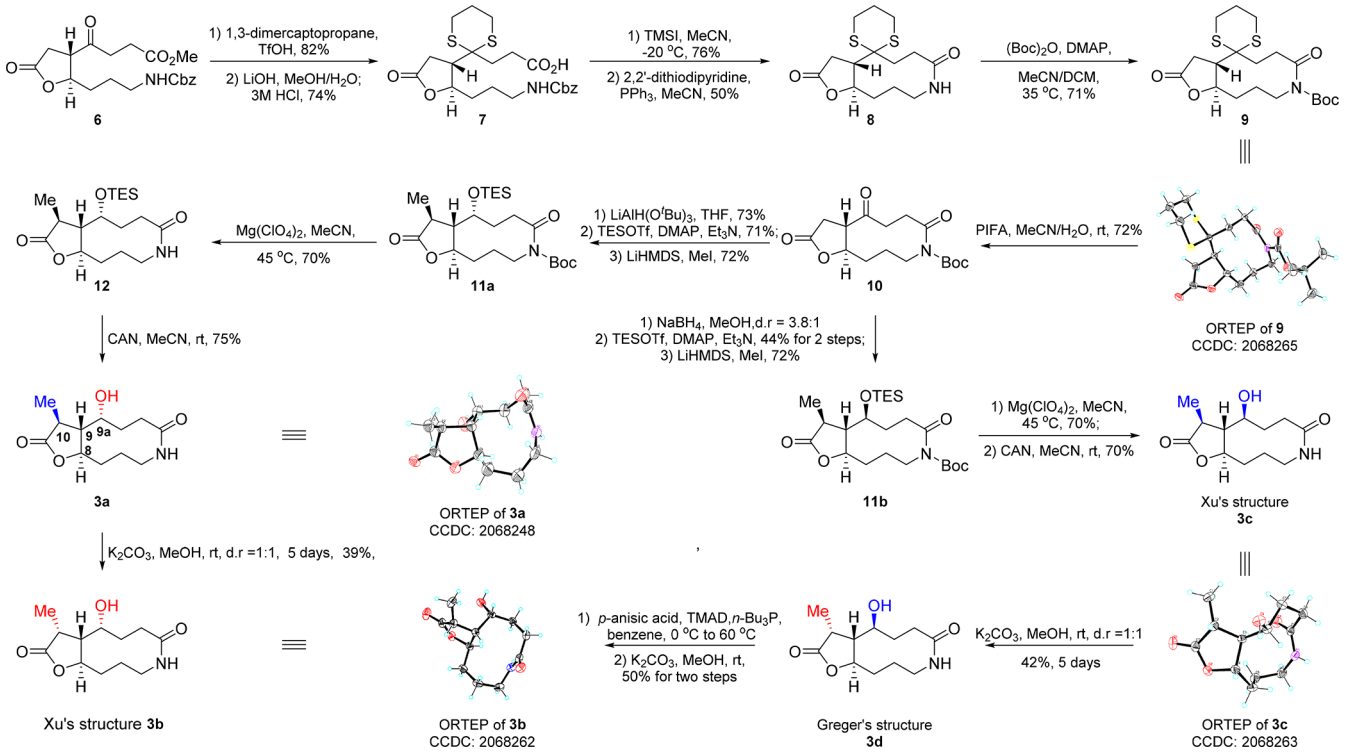
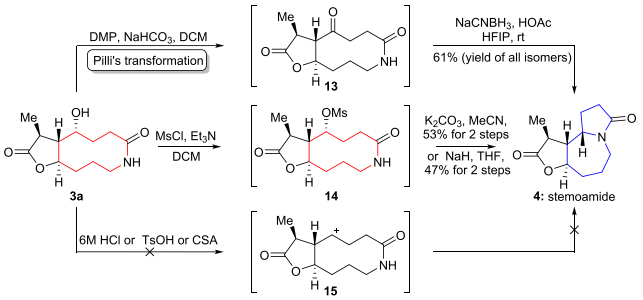
Scheme 2. Total Syntheses of Parvistemoamide (3) and Three of Its Epimers[a]



[a]Non-hydrogen atoms are shown as 30% ellipsoids.

similar reaction sequence, including TES protection, methylation, and the removal of Boc and TES, the newly formed alcohol was further transformed into another epimer of parvistemoamide **3c** (CCDC 2068263) with C9a–β-OH and unexpected C10–β-Me, which was proposed by Xu.[5c] Then, Greger's structure **3d** was synthesized through the epimerization of **3c** under the promotion of K_2CO_3 or the Mitsunobu reaction and ester hydrolysis of **3b**. Nevertheless, the ^{1}H and ^{13}C NMR data of **3c** and **3d** were still not in accordance with those of the reported compound, which is analogous to the cases of **3a** and **3b**. At this point, stereoisomers **3a**–**3d** proposed for parvistemoamide have been synthesized, but none of the characterization data of the synthetic compounds were in accordance with those originally reported, indicating that in the original paper the proposed structure of parvistemoamide may be incorrect. We hypothesize that the following transformation relationship studies may help to confirm the real stereochemistry of parvistemoamide. Among the four synthesized epimers of parvistemoamide, we chose **3a** to study Pilli's transformation relationship between parvistemoamide and stemoamide (Scheme 3). Under the conditions of DMP oxidation and $NaCNBH_3$ reduction, **3a** was proven to convert to stemoamide through the ketone intermediate **13**. In order to find more direct evidence to reveal the transformation relationship between parvistemoamide and stemoamide, we investigated the conditions of the direct conversion of parvistemoamide into stemoamide. When subjecting **3a** to 6 M HCl, TsOH, or CSA, the desired carbocation intermediate **15** was not formed, which further blocked the C–N bond formation in stemoamide (**4**) through the nucleophilic attack of a nitrogen atom to the carbocation **15**. Pleasingly, treating **3a** with MsCl could render the methanesulfonylated intermediate **14**. OMs as a good leaving group in **14** was

Scheme 3. Transformation Studies from the 5/10 Skeleton of Parvistemoamide to the 5/7/5 Skeleton of Stemoamide



easily substituted by a nitrogen atom in the presence of either K_2CO_3 or NaH, thus providing the thermodynamically more stable stemoamide (**4**) in a 53% or 47% yield, respectively. In addition, isomers **3b**–**3d** were respectively subjected to the same nucleophilic transannular cyclization. As a result, **3b** with C9–α-OH was transformed into stemoamide (**4**), while **3c** and **3d** bearing C9–β-OH were transformed into 9a-*epi*-stemoamide, indicating that the C10–Me could epimerize in this reaction process (see the SI). We hypothesized that the feasibility of the above transformations may be supported by releasing the high ring tension of the 10-membered lactam.[10] Noteably, this transannular cyclization from the 5/10 bicyclic skeleton of parvistemoamide to the 5/7/5 tricyclic skeleton of stemoamide (**4**) was first proposed and identified by experiments.

Since the transformation of parvistemoamide to stemoamide *via* C–N bond formation in our transannular cyclization or Pilli's proposal has been identified by experiments, we wondered if Xu's transformation relationship scheme is feasible

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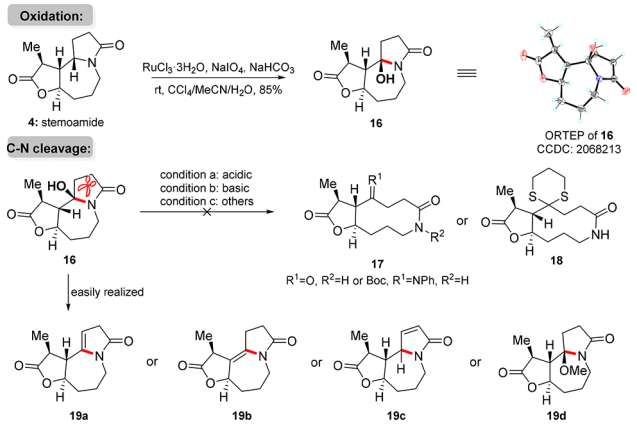
in chemical transformations (Scheme 4). After obtaining a large amount of stemoamide, which was synthesized by

Scheme 4. Verification of Xu's Transformation Relationship[a]



[a]Non-hydrogen atoms are shown as 30% ellipsoids.

employing Chida and Sato's concise synthetic strategy,[11] stemoamide (**4**) underwent an oxidation at the position adjacent to the amide nitrogen atom by $RuCl_3{\cdot}3H_2O/NaIO_4$.[12] However, the desired 5/10 skeleton was not observed, and only compound **16** was obtained in a 85% yield. Unfortunately, subsequent extensive attempts at C−N cleavage to accomplish the direct or indirect conversion of the 5/7/5 skeleton into the 5/10 skeleton proved to be in vain, and only the corresponding dehydration products **19a**−**19c** or the methylated product **19d** were generated (see the SI). From the failure of the above attempts, we realize that although a strong resonance effect between the nitrogen lone pair and the antibonding orbital (π^*) of the carbonyl group exists,[13] which may further weaken the adjacent C9a−N bonds, cleaving the adjacent C9a−N bonds seems to still be difficult due to the high C−N bond dissociation energy (BDE).[14] Meanwhile, it would be tough for a thermodynamically more stable 5/7/5 tricyclic skeleton to overcome a high strain energy to form a highly strained ten-membered lactam in classic transformations (see the SI).

In conclusion, we accomplished the total syntheses of the possible structures of parvistemoamide. More importantly, we verified the transformations of the possible structures of parvistemoamide to stemoamide and 9a-*epi*-stemoamide *via* either the transannular cyclization or Pilli's transformation proposal. This transformation may promote the collective total syntheses of other parvistemoamide- or stemoamide-related *Stemona* alkaloids. Synthetic and biological studies on other *Stemona* alkaloids are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01045.

Experimental procedures, spectroscopic data, and checkcif reports for crystallographic data (PDF)

Accession Codes

CCDC 2068213, 2068248, 2068262−2068263, 2068265−2068266, and 2068268 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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