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A Pyrrole Strategy to the γ-Lactam-Containing *Stemona* Alkaloids: (±)Stemoamide, (±)Tuberostemoamide, and (±)Sessilifoliamide A

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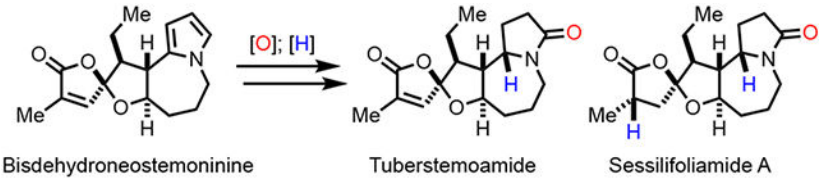
Abstract

Stemona alkaloids contain family members with diverse structural scaffolds. Many of them feature a γ-lactam ring embedded in their characteristic 5-7-5 fused tricyclic core. Herein, a pyrrole strategy was developed to enable the total syntheses of three *Stemona* alkaloids: (±)stemoamide, (±)tuberostemoamide, and (±)sessilifoliamide A. In these cases, a substituted pyrrole was used as the γ-lactam precursor. A sequential pyrrole oxidation and enamide reduction were realized to convert the pyrrole to the corresponding γ-lactam in those three natural products. The use of a pyrrole in an early stage of the synthesis offers the advantage of rapid construction of the key intermediates by exploiting its nucleophilicity.

Graphical Abstract



The *Stemona* alkaloids (also called "Bai Bu" alkaloids[1a]) are a large family of natural products isolated from the *Stemona genus* including *S. tuberosa, S. japonica*, and *S. sessilifolia*. These species are often used as antitussive herb medicines in east Asia. So far, over 215 *Stemona* alkaloids have been isolated. They are classified into eight groups: stenine, stemoamide, tuberostemospironine, stemonamine, parvistemoline, stemofoline, stemocurtisine, and a miscellaneous group.[1] These natural products feature either a hidden pyrrolo[1,2-*a*]azepine or a pyrido[1,2-*a*]azepine core often embedded in a polycyclic skeleton. Despite the long time uses of the *Stemona genus* as herb medicines, biological

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and spectra data (PDF file)

Crystallographic data for compounds **23**, **7** and **8** (cif files)

The authors declare no competing financial interest.

evaluation of these purified *Stemona* alkaloids is quite limited. Nevertheless, the *Stemona* alkaloids have attracted a significant amount of synthetic attention due to their characteristic and diverse structures.[2] These synthetic efforts have facilitated biological function studies of these alkaloids by providing precious materials as well as their synthetic analogs.[3] Among the groups of the *Stemona* alkaloids, total syntheses of the stemoamide group members are quite limited. While stemoamide (**1**, Figure 1) itself has been a popular target for total synthesis,[4] only a few more complex group members have been synthesized. Notably, stemonine (**2**) with a γ-butyrolactone appended on the pyrrolidine was synthesized by the groups of Williams and Chida/Sato in 2003[5] and 2017,[6] respectively. Chida and Sato also achieved the total synthesis of saxorumamide (**3**) with an α,β-unsaturated γ-butyrolactone linked on the tetrahydrofuran moiety.

We recently took note of members of the stemoamide group with a unique oxaspirolactone moiety (**4**-**9**, Figure 1) and applied our palladium-catalyzed carbonylative spirolactonization of hydroxycyclopropanol[7] to build this key structural moiety. Our initial efforts have led to the total syntheses of (±)bisdehydroneostemoninine(**4**) and (±) bisdehydrostemoninine (**5**) with a pyrrole moiety (Figure 2A).[8] The pyrrole group has significantly facilitated our synthesis by enabling the formation of two key C-C bonds due to its nucleophilicity. Meanwhile, we envisioned the possibility of synthesizing the γ-lactam or pyrrolidine-containing stemoamide group members such as tuberostemoamide (**7**), sessilifoliamide A (**8**), and stemoninine (**9**) by chemical manipulations of the pyrrole group. Herein, we report our total syntheses of stemoamide (**1**), tuberostemoamide (**7**), and sessilifoliamide A (**8**) in their racemic forms via a pyrrole oxidation strategy. Notably, while we were optimizing our syntheses, Wang and co-workers reported their elegant asymmetric total syntheses of tuberostemoamide (**7**), sessilifoliamide A (**8**), and their synthetic analogs via a completely different strategy.[9] Further biological evaluation led them to identify 11,13-bis-*epi*-sessilifoliamide A as a butyrylcholinesterase (BChE) inhibitor for treating neurodegenerative disorders, which highlights the importance of chemical syntheses of these stemoamide alkaloids.

Our previous syntheses of bisdehydroneostemoninine (**4**) and bisdehydrostemoninine (**5**) used tricyclic pyrrole **10** as a key intermediate (Figure 2A), from which hydroxycyclopropanol **11** was prepared in two steps. A palladium-catalyzed carbonylative spirolactonization delivered **12** in good yield, which eventually led to bisdehydroneostemoninine (**4**) and bisdehydrostemoninine (**5**). In order to realize the conversion of bisdehydroneostemoninine (**4**) to tuberostemoamide (**7**) and sessilifoliamide A (**8**), a mild oxidation reaction needs to be identified to install the γ-lactam carbonyl group because the spirolactone moiety is very labile under either acidic or basic conditions (Figure 2B). While oxidation of indole to oxindole is prevalent in the literature with a broad range of reaction conditions,[10] the corresponding case for pyrrole oxidation is extremely rare. Our literature resulted in one example using more than 90% pure *m*CPBA as the oxidant.[11] The reaction presumably goes through an epoxidation of the pyrrole followed by an epoxide-carbonyl rearrangement to a dihydro-2*H*-pyrrol-2-one intermediate. In our case, the dihydro-2*H*-pyrrol-2-one intermediate (**14** or **15**) needs to be reduced, which is nontrivial as

well. If intermediate **14** is produced, the ethyl group will sterically block the top side to make the desirable reduction more difficult.

With the above concerns in mind, we decided to use compound **10** as a model substrate, which could also lead to a total synthesis of stemoamide (**1**). Compound **10** was previously synthesized by us in 6 steps at gram scale from commercially available starting materials **16** (Scheme 1A). The key steps involve Clauson-Kaas pyrrole synthesis, Weinreb ketone synthesis, Luche reaction, cross metathesis, and Lewis acid-promoted tandem Friedel-Crafts cyclization and lactonization (cf. **17**→**10**). The use of the pyrrole is essential for the success of the last tandem process due to its strong nucleophilicity. When compound **10** was subjected to the oxidation conditions with commercially available *m*CPBA (less than 77% purify), the reaction was quite messy with only a small amount of product **18** obtained. Further condition optimization failed to improve the reaction yield. Dimethyldioxirane (DMDO) was used as well, but only a trace amount of product was observed. We then decided to purify the commercial *m*CPBA by washing with buffer solution and evaporation **with caution**.[12] The purified *m*CPBA gave better results. When 1,2-dichloroethane (DCE) was used as solvent at −35 °C, we were able to get consistent oxidation of **10** to **18** in 65% yield. Pd/C-catalyzed hydrogenation of **18** gave **19** in almost quantitatively yield with the desired stereochemistry at the newly generated carbon center. Regio- and stereo-selective α-methylation on the γ-butyrolactone completed the total synthesis of (±)stemoamide (**1**). The analytic data, including ^{1}H, ^{13}C, and HRMS of our synthetic sample, match well with the reported ones.

We then wondered how the α-methyl group on the γ-butyrolactone will influence the oxidation and reduction steps, because for the proposed syntheses of tuberostemoamide (**7**) and sessilifoliamide A (**8**), there is an ethyl group on the tetrahydrofuran ring. Therefore, α-methylation of compound **10** was explored. Surprisingly, unlike the α-methylation of **19**, in this case, a 9:1 mixture of **20** and **21** was obtained kinetically favoring **20** with undesired stereochemistry at the α-position. This result indicates that the stereochemistry of the lactam γ-position (cf. **19**) is important to control the stereochemistry of the lactone α-methylation. Epimerization of **20** under the conditions of DBU in MeOH at 50 °C gave **21** in 92% yield. To our delight, the purified *m*CPBA oxidation worked smoothly with **21** bearing the α-methyl group. However, reduction of the double bond became problematic. The aforementioned Pd/C-catalyzed hydrogenation resulted in a 1:1 mixture of (±) stemoamide (**1**) and its isomer. Thus, the stereochemistry of the lactone α-position does significantly influence the reduction. We then opted for a hydride reduction of the acyl iminium ion derived from **22** under mild acidic conditions with the rationale that hydride reduction could be less steric demanding, and the acyl iminium ion is highly reactive. After comprehensive investigations, we identified that the combination of $NaCNBH_3$ with acetic acid in hexafluoro-2-propanol (HFIP) is the best for the task. A 3.6:1 mixture of (±)stemoamide (**1**) and its isomer was produced in 95% yield. Other solvents we investigated were much less effective than HFIP.[13]

With two different approaches to convert compound **10** to stemoamide (**1**) by successfully converting the pyrrole group to the corresponding γ-lactam, we began the total syntheses of

tuberostemoamide (**7**) and sessilifoliamide A (**8**, Scheme 2). Following our previously reported procedures, compound **10** was advanced to bisdehydroneostemoninine (**4**) in six steps. To our delight, the oxaspirolactone moiety of bisdehydroneostemoninine survived the *m*CPBA oxidation, and γ-lactam **14** was obtained in 40% yield with 40% of starting material recovered. Our efforts to increase the conversion led to a decreased overall yield of **14**. Similar to the stemoamide (**1**) case, with the steric effect from the ethyl group, we encountered difficulties in reducing the dihydro-2*H*-pyrrol-2-one with catalytic hydrogenation. When Pd/C was used in EtOH under hydrogen atmosphere, hemiaminal ethyl ether **23** was produced in almost quantitative yield. Its structure was confirmed by x-ray analysis.[14] While **23** was not our desired product, it indicated that the α,β-unsaturated γ-butyrolactone could be reduced in a stereoselective manner by delivering the reducing reagent from the less hindered side to form the required stereochemistry for sessilifoliamide A (**8**) synthesis. Switching the solvent from EtOH to other solvents led to starting material decomposition. We then took recourse to the hydride reduction conditions established for the reduction of **22** to stemoamide (**1**, Scheme 1) and were able to selectively reduce the dihydro-2*H*-pyrrol-2-one of **14** in the presence of the α,β-unsaturated γ-butyrolactone. (±)Tuberostemoamide (**7**) was produced in 33%, which was further reduced with Pd/C-catalyzed hydrogenation in EtOH to complete the total synthesis of (±) sessilifoliamide A (**8**). Additionally, compound **23** could be reduced to (±)sessilifoliamide A (**8**) as well by using the $NaCNBH_3$ reduction conditions. The structural assignments for both (±)tuberostemoamide (**7**) and (±)sessilifoliamide A (**8**) were unambiguously confirmed by x-ray analysis.[14]

In summary, we have developed a pyrrole strategy to synthesize γ-lactam-containing *Stemona* alkaloids, including stemoamide (**1**), tuberostemoamide (**7**), and sessilifoliamide A (**8**) in their racemic forms. A protocol which combines a purified *m*CPBA oxidation with catalytic hydrogenation or $NaCNBH_3$ reduction in HFIP was developed to achieve the task. Meanwhile, we learned that the reduction of the dihydro-2*H*-pyrrol-2-one intermediates derived from the corresponding *m*CPBA oxidation is very sensitive to the steric effect implemented by the substituents on the adjacent tetrahydrofuran ring. These syntheses together with our previous syntheses of bisdehydroneostemoninine (**4**), bisdehydrostemoninine (**5**), and their synthetic analogs, will allow us to comprehensively evaluate and understand the biological function of these *Stemona* alkaloids, which will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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(14). CCDC 1996683, 1996684, and 1996685 contains the supplementary crystallographic data for compounds **23, 7** and **8**, respectively.

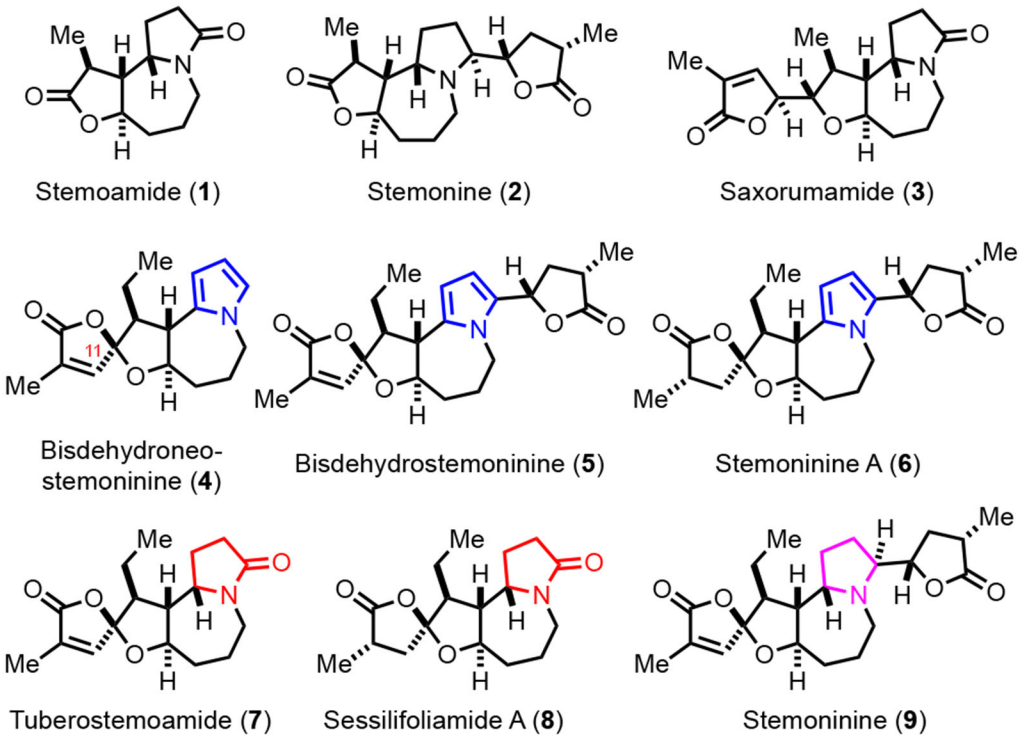


Figure 1.
Selected stemoamide alkaloids.

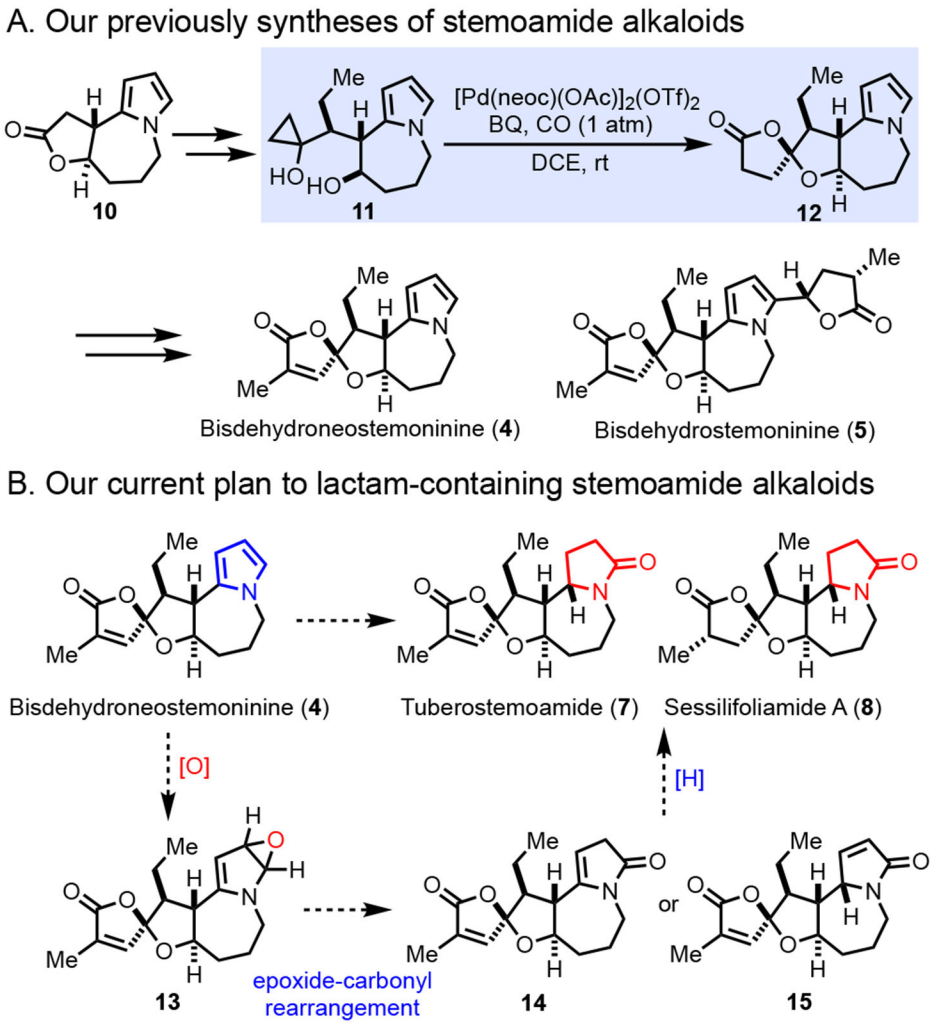
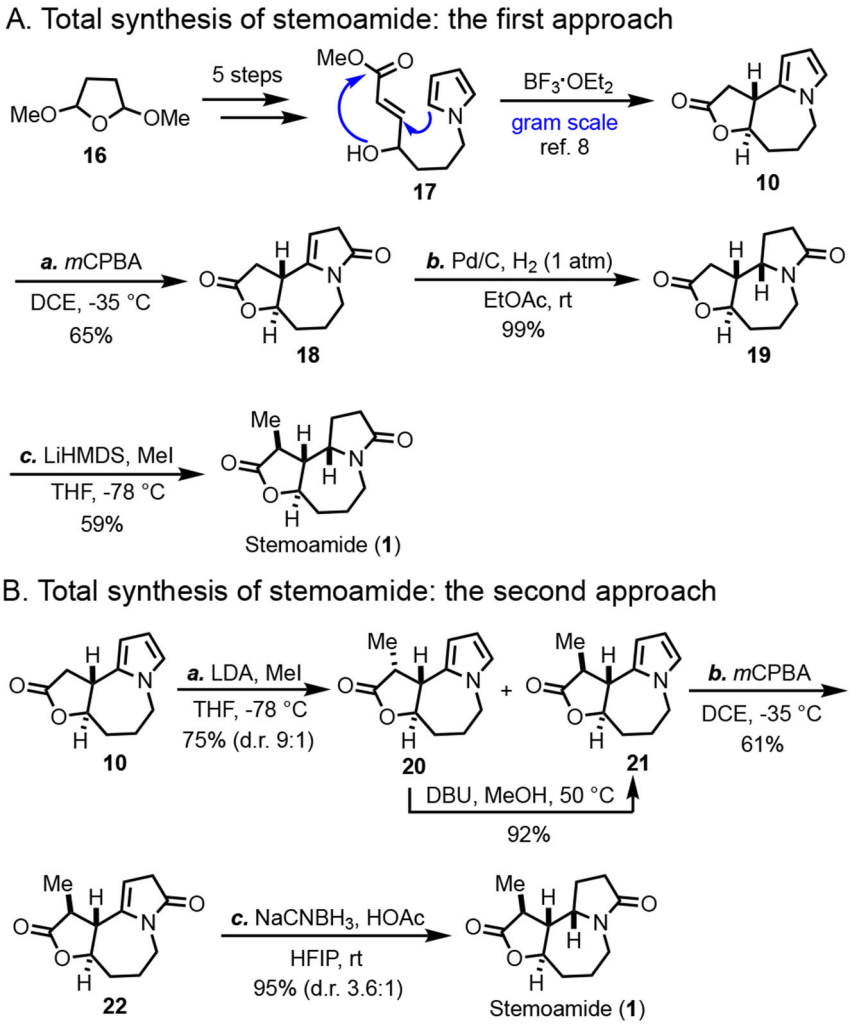
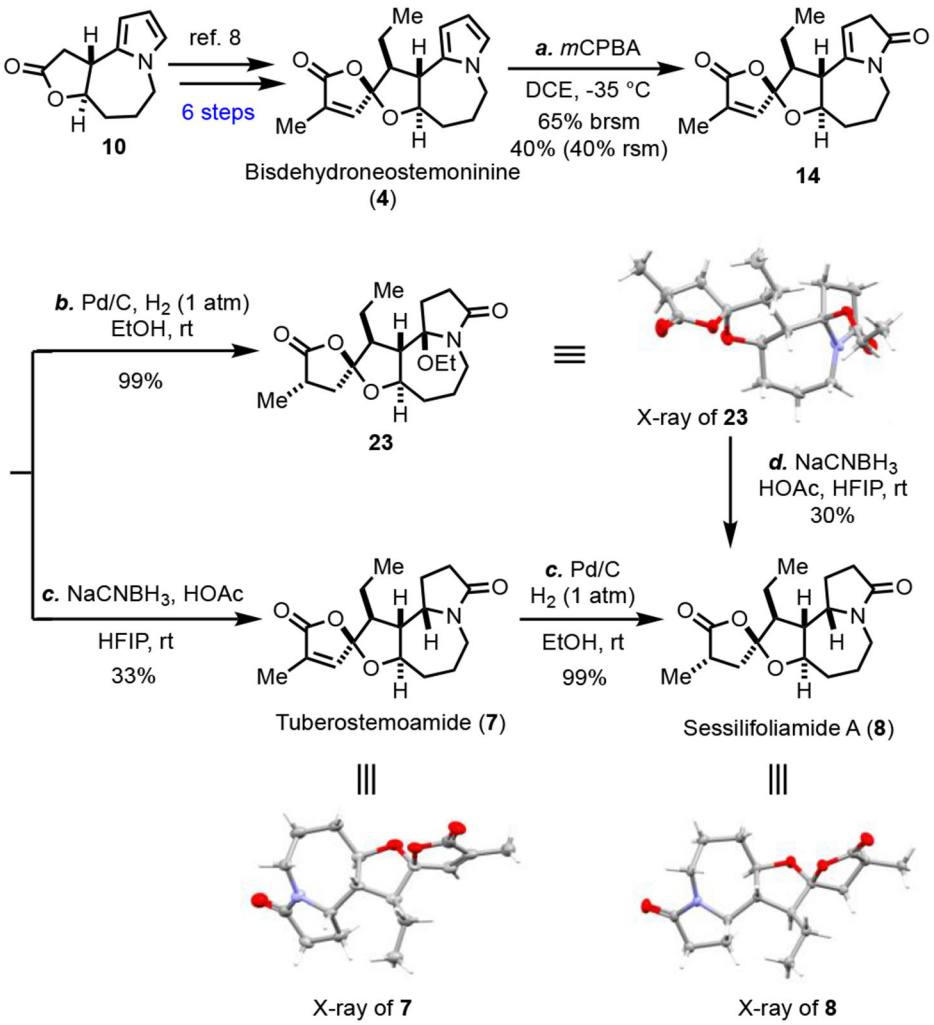


Figure 2.
Our previous total synthesis and current synthetic plan.



Scheme 1.

Approaches for the total synthesis of (±) stemoamide.



Scheme 2.

Total syntheses of (±)tuberostemoamide and (±) sessilifoliamide A.