SYNTHESIS, STEREOCHEMICAL STABILITY, AND BIOLOGICAL ACTIVITY OF STEMONAMINE AND ITS RELATED STEMONA ALKALOIDS

Takayuki Iwata and Mitsuru Shindo*

Institute for Materials Chemistry and Engineering, Kyushu University, Kasuga-koen, Kasuga 816-8580, Japan. E-mail: shindo@cm.kyushu-u.ac.jp

Abstract – More than 140 Stemona alkaloids have been isolated from Stemona plants (of the Stemonaceae species). These alkaloids represent a unique pyrrolo[1,2-α]azepine nucleus, and can be classified into eight groups on the basis of their chemical aspects. This study is focused on the synthesis of stemonamine group alkaloids, in addition to their chemical stability and biological activity.

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1. INTRODUCTION

1-1. Stemona alkaloids

The tuberous roots of Stemona plants (of the Stemonaceae species), such as *Stemona japonica* Miq., *Stemona tuberosa* Lour., *Stemona sessilifolia* Miq., and related Stemona plants (ca 30 species) are used as anthelmintic and antitussive agents in traditional medicines in China (Bai Bu), Japan (Byakubu), and other East Asian countries. The extracts of these roots contain more than 140 types of *Stemona* alkaloids, which represent a unique pyrrolo[1,2-a]azepine nucleus (or pyrido[1,2-a]azepine in minor) in their structures. Based on their biosynthetic considerations and various distributions, Greger classified *Stemona* alkaloids into three skeletal types in his study: stichoneurine-, protostemonine-, and croomine-type alkaloids, distinguished by the carbon chains attached to C-9 of the core (Figure 1-1). Moreover, Pilli et al. suggested an alternative classification into eight groups on the basis of their chemical aspects: stenine, stemoamide, tuberostemospironine, stemonamine, parvistemoline, stemofoline, stemocurtisine, and a miscellaneous group (Figure 1-2). Although *Stemona* alkaloids are used as traditional medicines and the biological studies on *Stemona* alkaloids have been reviewed by Greger and Pilli, the detailed bioactivities of each component of the *Stemona* alkaloids have not been investigated well so far, partially because of their complex mixture of various components. Thus, separation, isolation, and purification of these alkaloids is not easy for determining their quantities. Furthermore, their complicated and congested structure stimulated synthetic organic chemists. Therefore, a total synthesis of *Stemona* alkaloids and their derivatives is important for medicinal chemistry, molecular biology, and synthetic organic chemistry.

Figure 1-1. Greger’s classification of *Stemona* alkaloids into three skeletal types
(reproduced from ref. 3)
Among the various *Stemona* alkaloids, the stemonamine group has the cyclopenta[1,2-b]pyrrolo[1,2-a]azepine skeleton [tetracyclic 1’H, 11H-spiro[1H-cyclopenta[b]pyrrolo-[1,2-a]azepine-11,2’-furan]-5’,10-dione nucleus], which includes four condensed rings containing characteristic α-methyl-β-methoxy spiro-butenolide (Figure 1-3). Especially, the A-ring is highly congested, which is fully substituted (C-9a is a tetrasubstituted stereogenic center) and connected with all the other rings. Although total syntheses of the *Stemona* alkaloids has been reported since 1989, the first synthesis of the stemonamine group was delayed and at last published in 2001, which was still a racemic product. This review is focused on the synthetic study of the stemonamine group.

1-2. Stemonamine group

The stemonamine group includes the following natural products: stemonamine (1), isostemonamine (2), stemonamide (3), isostemonamide (4), maistemonine (protostemotinine) (5), isomaistemonine (6), oxymaistemonine (7), isooxymaistemonine (8), sessilistemonamines A, B, and C (9-11), 3β-n-butylstemonamine (12), 8-oxo-3β-n-butylstemonamine (13),
8-oxo-oxymaistemonine (14) (Figure 1-3). These stemonamine groups’ natural products were isolated from the Stemonaceae species of *Stemona japonica* Miq., *Stemona sessilifolia*, *Stemona sazorum*, and *Stemona mairei*. Interestingly, only stemonamine and isostemonamine were isolated as the racemic compounds. The racemization mechanism through retro-Mannich/Mannich reaction via intermediate 15 was proposed (Figure 1-4), and later, experimentally exemplified by the non-racemic synthesis (*vide infra*).
2. TOTAL SYNTHESIS

2-1. Overview

Till now, four groups (Kende, Ishibashi, Tu (and Zhang), and Shindo) have reported a total synthesis of six alkaloids belonging to the stemonamine group, namely stemonamide, isostemonamide, stemonamine, isostemonamine, maistemonine, and isomaistemonine. In addition, two groups (Tu and Rhee) have reported formal total synthesis. The strategies for the construction of tetracyclic scaffold of the stemonamine group alkaloids can be roughly classified into two routes (Figure 2-1). In Kende’s synthesis, the tricyclic A, B, and D ring system bearing the consecutive spiro-tetrasubstituted centers were constructed in the early stage of the synthesis, and later the formation of C ring was explored. Moreover, all the other groups planned to obtain the tricyclic A, B, and C ring system before the installation of the D ring at the late stage of the synthesis. Therefore, all groups focused on the construction of these tricyclic systems using their original chemistry. In Figure 2-1, the key words for each group’s synthesis are summarized, and the details of the syntheses will be depicted in the following sections.
2-2. Kende’s synthesis of (±)-stemonamide and (±)-isostemonamide (2001)\textsuperscript{2,15}

In 2001, Kende et al. reported the first total synthesis of a stemonamine group alkaloid.\textsuperscript{2} In that study, these authors succeeded in the synthesis of racemic stemonamide (3) and isostemonamide (4) using N-acyliminium chemistry\textsuperscript{26} and aldol spirocyclization as a key step. Their retrosynthetic plan for stemonamine is illustrated in Scheme 2-1. The C ring would be elaborated in the final step through intramolecular nucleophilic displacement from 16. The formation of A ring (construction of the C-12 tetrasubstituted center) can be accomplished by aldol spirocyclization of 18. The B and D rings can be connected by making C-9a tetrasubstituted center using addition of furan 20 to N-acyliminium intermediate derived from the spiro compound 19.

![Scheme 2-1. Kende’s retrosynthetic plan for (±)-stemonamide (3)](image)

The synthesis began with the readily available PMB-protected succinimide 21, which was converted into a spiro compound 19 through the three-step transformation involving desymmetrization by Grignard addition, acetal formation (21 to 22), and deprotection of the benzyl group (22 to 19) (Scheme 2-2a). Further, the spiro compound 19 was treated with siloxyfuran 20 in the presence of BF$_3$•Et$_2$O to create C-9a tetrasubstituted center through N-acyliminium ion intermediate. The resulting alcohol 23 was a diastereomeric mixture in the ratio of 1:2. Oxidation of this mixture under Swern conditions produced corresponding aldehydes 18, which upon treatment with DBU produced corresponding spiro aldols, followed by Swern oxidation to produce separable diastereomeric spiro ketones 17a and b (1:1). The ketones 17a and b were used for total synthesis of stemonamide and isostemonamide, respectively. These syntheses are similar and only the route to stemonamide is depicted in details in Scheme 2-2b. The ketone
17a was transformed into silyl enol ether, which was followed by Larock modified Ito-Saegusa oxidation\textsuperscript{22} to produce enone 24. The conjugate addition of the Grignard reagent to 24 in the presence of a Cu catalyst allowed a 6.4:1 ratio of diastereomers. The exo-methylene was installed by treating the mixture with KH and dimethylmethyleneammonium trifluoroacetate to produce compound 25. After deprotection of both PMB groups, isomerization of the exocyclic double bond was achieved by treating it with RhCl\textsubscript{3}. Finally, the conversion of 26 to mesylate followed by intramolecular nucleophilic displacement produced racemic stemonamide (3). Isostemonamide (4) was also synthesized from spiro compound 17b using the similar method. Overall, the 14-step total syntheses of stemonamide and isostemamid were achieved with 4% and 7% total yield, respectively.

Scheme 2-2. Kende’s synthesis of stemonamide (3)
Summarizing Kende’s total synthesis, the construction of the tricyclic system (A, B, and D rings) was shortly achieved using \(N\)-acyliminium chemistry and aldol spirocyclization. The formation of the consecutive spiro-tetrasubstituted centers in the early stage makes Kende’s study distinct from other studies. This strategy is considered to be based on the idea of avoiding the conceivable difficulty on the formation of these two spiro centers from sterically congested intermediate in the later stage. However, the stereochemistry of these tetrasubstituted centers is not highly controlled in this case. The late stage transformations involved functionalization of the A ring and final step formation of the C ring, which efficiently provided stemonamide and isostemonamide. It is noteworthy that although the formation of the azepane ring (C ring) by intramolecular nucleophilic displacement is observed in many synthetic reports on other groups of \textit{Stemona} alkaloids,\(^{26}\) this method is applied only in Kende’s total synthesis among the series of synthesis of stemonamine group alkaloids.

2-3. Ishibashi’s synthesis of (±)-stemonamide, (±)-isostemonamide, (±)-stemonamine, and (±)-isostemonamine (2008)\(^{16,17}\)

The second total synthesis of stemonamine group alkaloids was reported by Ishibashi et al. in 2008.\(^{16}\) They reported a racemic total synthesis of stemonamide (3) and isostemonamide (4) using their developed radical cascade reaction as a key step. In the same year, they also reported synthesis of stemonamine (1) and isostemonamine (2) from stemonamide and isostemonamide, respectively.\(^{17}\) In their retrosynthetic plan for stemonamide (Scheme 2-3), the A and D ring can be constructed at a later stage of the synthesis using the carbonyl group as a steppingstone. Consequently, the key radical cascade reaction was envisioned to form the tricyclic intermediate 27a via 5-endo-trig cyclization (28 to 27a),\(^{26}\) which is generally disfavored according to Baldwin’s rule and 7-endo-trig cyclization (29 to 28).\(^{30}\)

![Scheme 2-3. Ishibashi’s retrosynthetic plan for (±)-stemonamide (3)](image)

Ishibashi’s synthesis commenced with the condensation of cyclopentane-1,2-dione (30) and TBS-protected aminoalcohol 31, followed by acylation with acryloyl chloride (Scheme 2-4). After silyl ether 32 was converted into corresponding bromide 29, the key radical cascade reaction was conducted.
In this reaction, the primary radical added onto β-position of enone in a 7-endo-trig cyclization fashion to give intermediate 28, which was followed by 5-endo-trig cyclization to afford the tricyclic compounds 27a,b as a ca. 1:1 diastereomer mixture. The mixture was then converted into α,β-unsaturated ketones 33a,b using aldol reaction with benzaldehyde. Sequentially, the compounds were treated with lithium ethyl propiolate to afford the separable adducts 34a and b in 48% and 50%, respectively. Both the products might be formed by convex addition of lithium ethyl propiolate.

Further, alkyne 34b was treated with magnesium dimethoxide in the presence of a catalytic amount of sodium methoxide (Scheme 2-5). Michael addition of methoxide to propiolate moiety, followed by lactonization, provided lactone 35. To install a methyl group on the lactone ring, 35 was subjected to iodination reaction using N-iodosuccinimide and sequentially the Suzuki coupling reaction of the resulting iodide 36 with trimethylboroxine. Olefin 37 was converted into ketone 38 by the treatment with osmium tetroxide. 38 was then converted into corresponding enamine by the treatment of Bredereck’s
reagent, which followed by reduction with DIBAL and methylation with iodomethane to provide exo-methylenated product 39. Finally, isomerization of olefin by exposure of 39 to RhCl₃ gave stemonamide (3) in 31% yield along with the reduced product 40 as a major product (63%). Isostemonamide (4) was also synthesized according to the similar transformations from 34a. In addition, stemonamide (3) and isostemonamide (4) were converted into stemonamine (1) and isostemonamine (2), respectively, through thiolactamization using Lawesson’s reagent, followed by reduction with Raney nickel at 0 °C. It is noteworthy that when Raney nickel reduction of isostemonamide (4) was conducted at room temperature, isostemonamine (2) was obtained along with stemonamine (1). This suggested the existence of an interconversion process between stemonamine and isostemonamine (vide infra).

Scheme 2-5. Ishibashi’s synthesis of stemonamide (3) and stemonamine (1)

Overall, Ishibashi’s synthesis can be classified into three parts. 1) One-step formation of the tricyclic system (A, B, and C rings) using radical cascade reaction; 2) construction of the D ring; and 3) functionalization of the A ring. The radical cascade reaction demonstrates impressive efficiency, and it proved to be a powerful tool for construction of the Stemona alkaloid core structure. However, this total
synthesis cannot be easily applied for asymmetric synthesis of *Stemona* alkaloids because stereochemistry is generally lost in radical reactions. In addition, diastereoselectivity in the radical cascade reaction did not appear in this synthesis.

### 2-4. Tu’s synthesis of (±)-stemonamine (2008)

The first total synthesis of stemonamine (1) was reported by Tu et al. in 2008, prior to Ishibashi’s study. In that study, a racemic stemonamine was synthesized using tandem semipinacol/Schmidt reaction as a key reaction. Their retrosynthetic plan is shown in Scheme 2-6. Stemonamine was planned to be synthesized from the corresponding amide 41, in which the carbonyl group is used as protecting group for tertiary amino moiety. The D ring could be installed at a later stage of the synthesis using Dieckmann condensation reaction. The tricyclic intermediate 42 would be accessed from olefin 43 using aldol reaction to build the A ring. Further, the tandem semipinacol/Schmidt reaction was envisioned to occur in the single-step formation of both B and C rings from epoxide-azide 44.

![Scheme 2-6. Tu’s retrosynthetic plan for (±)-stemonamine (1)](image)

This synthesis commenced with the addition of allylmagnesium chloride 46 to enone 45. The resulting allyl alcohol 47 was subjected to epoxidation reaction using the vanadium reagent, which was followed by silylation of tertiary alcohol to produce epoxide 44 (Scheme 2-7). The five-seven bicyclic system was then constructed using the key tandem semipinacol/Schmidt reaction. In this reaction, titanium chloride-mediated semipinacol rearrangement proceeded from 48 to oxonium intermediate 49, which underwent Schmidt reaction via intermediate 50 to afford bicyclic amide 43 with 68% yield. Subsequent PCC and ozone oxidation led to diketone intermediate, which was treated with potassium t-butoxide in
t-butanol to induce an intramolecular aldol reaction. The resulting tricyclic product 42, which is the key intermediate not only in this synthesis but also in the course of Tu's study, about Stemona alkaloid synthesis (*vide infra*), was then used for the construction of the γ-lactone ring (D-ring). Deprotonation of 42 with LHMDS and subsequent treatment of Mander’s reagent afforded ketoester 51. Further, this compound was oxidized by a catalytic amount of CeCl₃•7H₂O in oxygen atmosphere to produce alcohol 52 (its diastereomer was also obtained in about 1:1 ratio). This alcohol was converted into diester 53 via acylation using propionic anhydride, followed by Dieckmann condensation using potassium t-butoxide to give tetracyclic intermediate 41. Finally, the two-step transformation including thiolactamization using Lawesson’s reagent and reduction using Raney nickel delivered a racemic stemonamine (1).

Scheme 2-7. Tu’s synthesis of stemonamine (1)
Tu’s synthesis of stemonamine is achieved in 13 total steps with an overall yield of 3.7%. This approach is conducted in three parts. 1) The construction of the five-seven bicyclic structure (B, C rings) using tandem semipinacol/Schmidt reaction, 2) construction of the A ring by aldol reaction, and 3) late stage installation of the D ring by Dieckmann condensation. The most impressive process is the formation of the seven-membered ring (B ring), which is generally not easy to form, using the ring expansion strategy in the early stage of the synthesis. Tu et al. also used the ring expansion strategy using Schmidt reaction into the synthesis of other natural products, which demonstrates their Schmidt reaction as a powerful tool for construction of aza-polycyclic ring systems. The late stage installation of the D ring into the sterically congested tricyclic intermediate is also a remarkable point in this synthesis.

2-5. Tu’s formal syntheses of (±)-stemonamine (2009, 2011)

After their report on the first total synthesis of stemonamine, Tu et al. reported two formal total syntheses of stemonamine, both of which were focused on the construction of a tricyclic key intermediate 42 using intramolecular Schmidt reaction. The second generation synthesis of 42 was planned to obtain ketoamide 54 via intramolecular Schmidt reaction of the azide dione compound 55 (construction of B and C rings), while the third generation synthesis was aimed to synthesize the tricyclic compound 56 using tandem intramolecular Prins cyclization/Schmidt reaction of 57 (one-pot construction of A, B, and C rings) (Scheme 2-8).

Tu’s second generation synthesis of 42 began with allylation and Michael addition using 1,3-cyclohexanedione (58) as the starting material (Scheme 2-9). After the resulting aldehyde 59 was selectively reduced by NaBH₃CN, mesylation to give 60 and sequential treatment of NaN₃ produced azide...
dione 55. The key intramolecular Schmidt reaction using TiCl₄ then provided the aza-bicyclic compound 54 with 93% yield. This compound was converted into a tricyclic intermediate 42 by the same procedure as described above (see Section 2-4).

Scheme 2-9. Tu’s second generation synthesis of the tricyclic intermediate 42

Tu’s third generation synthesis made use of a known ketone 61, which was treated with vinyl cerium reagent and subsequent deprotection of TBDPS group to afford alcohol 62a and its diastereomer 62b in the ratio of 5:1 (Scheme 2-10). 62a was then subjected to mesylation, displacement with NaN₃ and TMS-protection of tertiary alcohol to give azido acetal 57. The tandem intramolecular Prins cyclization/Schmidt reaction was then conducted by treatment of 57 with TiCl₄ to provide the tricyclic compound 56 as a diastereomer mixture (dr = 1:0.84). In this reaction, the oxonium cation 63 was first generated, and subsequent cyclization reaction led to tertiary carbocation 64, which provide azido ketone 65 via Meerwein rearrangement from the favored conformation. Finally, the subsequent Schmidt reaction afforded a tricyclic intermediate 56. Interestingly, it is noted that when the diastereomer of 57 (derived from 62b, not shown here) was applied to this tandem reaction under the same conditions, 56 was produced as a major diastereomer (dr = 1:0.53) as well. Continuing the synthesis, 56 was converted into ketoamide 66 via demethylation followed by DMP oxidation. 66 was then transformed into α-hydroxy dimethyl acetal 67 using the hypervalent iodine reagent. Finally, 67 was oxidized to a corresponding α-hydroxy ketone, which was subsequently subjected to enol triflate formation and Kumada coupling using methylmagnesium bromide to provide a key tricyclic intermediate 42.
Overall, these formal synthesis delivers the key tricyclic intermediate 42 in 8 and 12 total steps, which theoretically leads to stemonamine in 14 and 18 total steps, respectively. Although chiral Brønsted acid-promoted asymmetric version of the Schmidt reaction was also reported by Tu and Zhang, this reaction has not been applied to asymmetric synthesis of Stemona alkaloids yet.

2-6. Tu and Zhang’s synthesis of (±)-maistemonine, (±)-stemonamide, and (±)-isomaistemonine (2011)\textsuperscript{19,20}

In 2011, Tu, Zhang et al. reported the first total synthesis of (±)-maistemonine (5), (±)-isomaistemonine (6), and (±)-stemonamide (3), based on their previous study on Stemona alkaloids. Their retrosynthetic plan is illustrated in Scheme 2-11. They envisioned the construction of the E ring, which is a characteristic additional ring as compared to stemonamine, using allylation of the carbonyl group in 68a and subsequent lactonization. The tetracyclic ring system was planned to be accessed in a manner similar to the total synthesis of stemonamine discussed in Section 2-4. The D ring could be installed into the
tricyclic intermediate 69a, which is the key intermediate having vinyl group substituted onto the B ring. Further, access to the key compound 69a would be envisioned through aldol reaction of 70a to construct the A ring and the tandem semipinacol/Schmidt rearrangement from 71 to build the bicyclic ring system (B and C rings).

Scheme 2-11. Tu and Zhang’s retrosynthetic plan for (±)-maistemonine (5)

2-Cyclohexen-1-one (72) was treated with ethyl acrylate in the presence of DBU under the sealed tube conditions to afford ketoester 73 (Scheme 2-12). Ethylene acetal protection, which was followed by DIBAL reduction, furnished aldehyde 74. 1,2-Addition of Grignard reagent to 74 produced propargyl alcohol 75, which was converted into azido-ketone 76 after three-step transformation including mesylation, displacement of azide, and deprotection of acetal moiety. The resultant 76 was then transformed into tertiary alcohol 77 with the addition of Grignard reagent. Epoxidation by treatment of t-BuOOH and VO(acac)2 and subsequent TMS-protection of tertiary hydroxy group provided the requisite tandem reaction precursor 71. In a key step, it was possible to construct the tricyclic ring system through titanium-mediated tandem semipinacol/Schmidt rearrangement (for more details, refer Section 2-4). However, the products were 1:5 ratio of diastereomers 70a and b, and the main product (70b) had an inconsistent stereochemistry at C-3 position. This result indicates that the Grignard addition reaction (76 to 77) mainly provided a diastereomer having undesired stereochemistry. The separable diastereomers were then oxidized to ketoamides 78a and b, respectively. However, because of lengthy preparation course and low diastereoselectivity in the key tandem reaction, Tu and Zhang changed their approach to access the bicyclic intermediate 69a.
In the second generation retrosynthetic plan toward 69a (Scheme 2-13a), a ring would be constructed using aldol reaction, and the corresponding intermediate 78a was envisioned to be accessed by desymmetrizing intramolecular Schmidt reaction of 79, which was used in their formal total synthesis of stemonamine (see Section 2-5). 1,3-Cyclohexanedione (58) was treated with allyl bromide 80 in the presence of copper powder and potassium hydroxide to provide alkylated intermediate, which was sequentially treated with acrolein to undergo one-pot Michael addition to produce tricarbonyl product 81 (Scheme 2-13b). Grignard addition to the aldehyde moiety in 81, which was followed by mesylation reaction with MsCl, pyridine and catalytic amount of DMAP, led to mesylate 82. The precursor of Schmidt reaction, azido-diketone 79, was prepared through displacement with NaN₃. The obtained
precursor 79 was then subjected to desymmetrizing intramolecular Schmidt reaction by the treatment of TiCl₄. Although the bicyclic product was obtained through this reaction in good yield, the product was again found to be 78b, which is a diastereomer having undesired stereochemistry at C-3 position. Therefore, the authors decided to epimerize the C-3 position at the late stage. Proceeding with the synthesis, 78b was subjected to ozonolysis to yield diketone 83. The terminal alkynyl moiety of 83 was reduced by the treatment of Lindlar catalyst to produce the corresponding olefin, which was subjected into intramolecular aldol condensation to construct tricyclic key intermediate 69b.

Scheme 2-13. Tu and Zhang’s second generation synthesis of intermediate 69
Thus, the subsequent task was to construct the D ring (Scheme 2-14). Aldol condensation of tricyclic compound 69b with propanal, and subsequent oxidation of the resulting alcohol afforded diketone 84. Introduction of the hydroxy group to the α-position of diketone was achieved by treatment of 84 with catalytic amount of CeCl₃·7H₂O under oxygen bubbling conditions, which provided separable diastereomers 85a and 85b in 8:1 ratio. 85a, which has a desired stereochemistry at the C-12 position, was next exposed to ethyl chloroformate to give carbonate 86. Treatment of 86 with KHMDS induced intramolecular keto-ester condensation reaction to give the tetracyclic intermediate, which without purification was subsequently subjected to O-methylation using diazomethane to furnish 87. Selective reduction of the carbonyl group of lactam was then achieved by one-pot protocol including treatment of methyl trifluoromethanesulfonate and subsequent NaBH₃CN reduction of the resulting alkoxy iminium salt. The obtained tertiary amine 88 was used as the common intermediate to access maistemonine, isomaistemonine, and stemonamide.

Scheme 2-14. Tu and Zhang’s synthesis of common intermediate 88

Tetracyclic compound 88 was then converted into maistemonine and isostemonine by the following transformations (Scheme 2-15). Oxidation of 88 with K₂OsO₄/NMO afforded diol 89, which was exposed to 1.4 equivalents of NaIO₄ to produce aldehyde 68b. It is noteworthy that α-aminoaldehyde 68b was found to slowly epimerize to its diastereomer 68a which has identical stereochemistry at C-3 position with maistemonine. The authors explained that this phenomenon is similar to Boger’s report on lability of stereochemistry of α-aminoaldehyde. Additionally, we consider that the absence of the carbonyl group adjacent to the tertiary amine might enhance the epimerization via retro-Mannich/Mannich process (vide infra). Based on this phenomenon, installation of the E ring and epimerization at the C-3 position were
simultaneously accomplished in a one-pot process by exposure of 68b with allyl zinc reagent under refluxing conditions. Finally, hydrogenation of exo-methylene 90 produced maistemonine (5) stereoselectively. Furthermore, an NMR sample of maistemonine dissolved in CDCl₃ epimerized to isomaistemonine (6) at room temperature, which provided the 1:1 mixture of maistemonine and isomaistemonine. Relative configuration of both natural products was confirmed by X-ray crystallographic analysis. Moreover, stemonamide (3) was synthesized from terminal olefin 88 by two-step oxidation including dihydroxylation using K₂OsO₄/NMO, and subsequent oxidative cleavage using 10 equivalents of NaIO₄.

Scheme 2-15. Tu and Zhang’s synthesis of maistemonine (5), isomaistemonine (6) and stemonamide (3)

Considering together, Tu and Zhang’s total synthesis of maistemonine and isomaistemonine was accomplished based on their previously developed methods to construct stemonamine scaffold using the tandem semipinacol/Schmidt rearrangement or desymmetrizing intramolecular Schmidt reaction as a key reaction. In addition, this synthesis is the only one study on synthesis of stemonamine group alkaloids bearing additional E ring. Installation of this characteristic ring was efficiently achieved using olefin moiety as the foothold without any protecting groups on other rings.
2-7. Rhee’s formal synthesis of (±)-stemonamine (2014)\textsuperscript{25}

In 2014, Rhee et al. reported a formal total synthesis of (±)-stemonamine.\textsuperscript{25} They focused on the synthesis of Tu’s intermediate 66 (see Section 2-5) based on synthesis of 90 using gold-catalyzed cyclization and subsequent intramolecular Schmidt reaction of ene-yne-azide 91 (Scheme 2-16a). Ketone 92 was treated with a vinyllithium reagent (derived from vinyl bromide 93) in the presence of CeCl\textsubscript{3} to afford tertiary alcohol 94 (Scheme 2-16b). Sequential transformations including deprotection of TBDPS group, mesylation, and treatment of NaN\textsubscript{3} provided azide 95. After TES-protection of tertiary alcohol, the key gold-catalyzed cyclization reaction was conducted using azide 91. In this reaction, the initial carbocyclization reaction gave the tertiary cation intermediate 96, which underwent pinacol type-rearrangement via cyclopropane intermediate 97 to afford ketone 98. The sequential Schmidt reaction by the treatment of SnCl\textsubscript{4} efficiently provided amide 90. These two steps were also conducted in one-pot fashion, which provided 90 with 84% yield. Finally, the oxidative cleavage of exo methylene was performed using catalytic amount of OsO\textsubscript{4} and NaIO\textsubscript{4} to produce Tu’s intermediate 66 en route for stemonamine (see Section 2-5).

(a) Rhee’s retrosynthetic plan

(b) synthesis of Tu’s intermediate 66

Scheme 2-16. Rhee’s synthesis of tricyclic intermediate 66
In 2018, Shindo et al. reported the first asymmetric total synthesis of (−)-stemonamine (1) and (−)-isostemonamine (2). They envisioned that both stemonamine and isostemonamine could be synthesized from a common intermediate 99 using the modified Tu’s method to construct the D ring (Scheme 2-17). Construction of the A ring was planned to use their own original reaction, that is the ynolate-initiated tandem [2+2] cycloaddition/Dieckmann condensation reaction of ketoamide 100. The C ring would be formed by intramolecular acylation of iodide 101, which can be prepared from the known compounds 102 and 103.

This synthesis began with condensation reaction between both chiral proline derivative 102 and hydroxy lactone 103 (Scheme 2-18). The subsequent deprotection of the Boc group of ester 104 and lactamization of the resulting amine afforded lactam 105. After conversion of the primary hydroxy group of 105 into iodo group, the intramolecular acylation reaction, which is the first key reaction, was performed. Lithium-iodine exchange of 101 by the treatment of t-BuLi at −78 °C efficiently induced intramolecular acylation reaction of intermediate 106 to give hemiacetal 107, which has an azepane ring (C ring). Further, the α-oxygen atom adjacent to the carbonyl group of lactam was removed by a two-step sequence involving Appel reaction (107 to 108) and reduction by zinc (108 to 109). The resultant product 109 with terminal olefin was converted into ketoester 100 by oxidative cleavage reaction followed by methylation using TMSCHN₂. Ketoester 100 was then treated with ynolate 110 to perform the key tandem reaction.
The ynolate reacted with the ketone moiety of 100 to produce the cyclobutene enolate 111 via formal [2+2] cycloaddition reaction, which subsequently proceeded Dieckmann condensation reaction to afford \( \beta \)-propiolactone 112. The product without purification was treated with an acidic silica gel under the reflux conditions to provide (-)-enantiomer-enriched Tu’s tricyclic intermediate 42. The aldol reaction of 42 with propanal, which was followed by DMP oxidation yielded a common intermediate 99.

Scheme 2-18. Shindo’s synthesis of the common intermediate 99

With a common intermediate 99 in hand, synthesis of both the natural products was attempted using modified version of Tu and Zhang’s method (Scheme 2-19a). In the synthesis of stemonamine, \( \alpha \)-hydroxy group was installed into diketone 99 using cerium chloride as an oxidant. The products were 4:1 mixture of 113a and its diastereomer 113b, both of which have identical stereochemistry to stemonamine and...
isostemonamine, respectively. The stemonamine-type product 113a was then converted into a carbonate 114, and subsequent intramolecular keto-ester condensation reaction followed by methylation provided butenolide 115. It is observed that enantiomeric excess of 115 was observed to be 61%, thereby insisting the possibility that racemization could occur over the course of the synthesis and/or in basic conditions used for the intramolecular keto-ester condensation reaction. 115 was treated with Lawesson’s reagent to form thioamide 116, which have 80% ee after recrystallization. Finally, the reductive removal of the thiocarbony group by the treatment of Raney nickel afforded stemonamine (1). Although the resultant stemonamine upon proper workup process had 58% ee and $[\alpha]^{23}_D -47$, HPLC separation using chiral column provided more optically pure (−)-stemonamine with 98% ee and $[\alpha]^{23}_D -75$. Moreover, in the synthesis of isostemonamine (2) (Scheme 2-19b), the common intermediate 99 was diastereoselectively oxidized using chiral oxaziridine 117 to form 113b. The same subsequent transformations, as mentioned above, produced (−)-isostemonamine with 97% ee and $[\alpha]^{23}_D -71$ after HPLC separation.

Scheme 2-19. Shindo’s synthesis of (−)-stemonamine (1) and (−)-isostemonamine (2)
Overall, although Shindo’s total syntheses of stemonamine and isostemonamine are based on Tu’s method to construct the D ring, their original reactions, such as intramolecular acylation reaction and ynolate-initiated tandem [2+2] cycloaddition/Dieckmann condensation reaction, are observed to be a rapid and efficient approach to construct the C and A rings.

3. STEREOCHEMICAL STABILITY
Natural products are generally produced in an optically pure form. However, some natural products are also known to be isolated as a racemic or scalemic mixture. Stemonamine (1) and isostemonamine (2) are examples of this class of natural products. The isolation report of these alkaloids was first published in 1973; thus, it has been anticipated that they had a racemic and epimeric pathway through the retro-Mannich/Mannich process (Figure 1-4). Ishibashi et al. reported the reduction of isostemonamide (4) provided isostemonamine along with stemonamine.12 This fact supported epimerization between the two alkaloids. However, there were still unclear questions about their stereostability. Moreover, racemization had not been experimentally explored for a long time, because nonracemic stemonamine and isostemonamine had not been obtained until Shindo et al. accomplished asymmetric synthesis of the alkaloids. Using nonracemic alkaloids, Shindo et al. experimentally demonstrated racemization and epimerization, and reported kinetic analysis of their processes (Table 3-1).21,22 This study revealed that both alkaloids racemize faster than epimerize, and the interconversion processes of isostemonamine are faster than those of stemonamine.

Table 3-1. Rate constants and half-lives of racemization and epimerization of (−)-stemonamine (1) and (−)-isostemonamine (2) (reproduced from ref. 22)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Racemization</th>
<th>Epimerization</th>
<th>Racemization</th>
<th>Epimerization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(−)-stemonamine (1)</td>
<td>(−)-isostemonamine (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$k_a$</td>
<td>$t_{1/2}$ (h)</td>
<td>$k_a$</td>
<td>$t_{1/2}$ (h)</td>
</tr>
<tr>
<td>1</td>
<td>20% $i$-PrOH in hexane</td>
<td>60</td>
<td>0.74</td>
<td>2.6</td>
<td>0.026</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>20% $i$-PrOH in hexane</td>
<td>45</td>
<td>0.22</td>
<td>9.0</td>
<td>0.0071</td>
<td>270</td>
</tr>
<tr>
<td>3</td>
<td>20% $i$-PrOH in hexane</td>
<td>25</td>
<td>0.035</td>
<td>55</td>
<td>&lt;0.001</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>4</td>
<td>20% $i$-PrOH in hexane</td>
<td>10</td>
<td>0.0097</td>
<td>200</td>
<td>- b</td>
<td>- b</td>
</tr>
<tr>
<td>5</td>
<td>CHCl₃</td>
<td>25</td>
<td>0.0072</td>
<td>270</td>
<td>- b</td>
<td>- b</td>
</tr>
</tbody>
</table>

a rate constants ($\times 10^{-4}$s$^{-1}$). b not determined.
Moving on to other stemonamine group alkaloids, all of them were isolated in an optically active form. Stemonamide (3) and isostemonamide (4) have an amide in their structure, which is anticipated to be the suppress ring opening process, while other compounds except sessilistemonamines have similar structures with only different substitutions on the B ring, which insists that they could racemize and epimerize. Moreover, Tu et al. observed epimerization of maistemonine (5).\textsuperscript{19,20} This fact interests us to explore the details of stereochemical stability of these compounds.

4. BIOLOGICAL ACTIVITY

Although Stemonaceae extracts have been used as a traditional medicine for curing respiratory diseases and infections with worms, the biological activities of \textit{Stemona} alkaloids have not been clarified enough. Many biological investigations have been conducted using the plant extracts without identifying the actual active compounds.\textsuperscript{37} Therefore, studies on biological activity of the \textit{Stemona} alkaloids are very few. Among the stemonamine group alkaloids, the situation is same, and there has been only one study on the anti-proliferative effects of isostemonamine. Takeda et al. elucidated that isostemonamine displays the strong cell-killing effects on a highly aggressive estrogen receptor \( \alpha \) (ER\( \alpha \))-negative breast cancer cell lines (MDA-MB-231) with an IC\textsubscript{50} value of 9.3 \( \mu \text{M}. \textsuperscript{38}

5. CONCLUSION

In this review, we summarized the synthetic effort toward \textit{Stemona} alkaloids, which are classified into stemonamine groups, focusing on strategies to construct a fused polycyclic skeleton. As mentioned above, the most challenging and interesting part in the syntheses of this class of alkaloids is the construction of consecutive spiro-tetrasubstituted centers. Therefore, each group presents a strategic and unique chemistry to achieve total synthesis. Especially, it is demonstrated that cascade reactions are highly useful for construction of the fused ring system even in the synthesis of stemonamine group alkaloids. Considering the insufficient number of studies on biological investigation of \textit{Stemona} alkaloids, there is huge scope for a synthetic chemist to further contribute to the assessment of \textit{Stemona} alkaloids based on a synthetic study.

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Devices.”

REFERENCE AND NOTES
8. Kohno and Narasaka reported synthesis of “stemoamide,” mistakenly designated as “stemonamide” (Bull. Chem. Soc. Jpn., 1996, 69, 2063); for discussion, also see refs. 2 and 7.


37. For biological activities of *Stemona* alkaloids, also see refs. 2, 3, and 4.

**Takayuki Iwata** received his Ph.D. from Osaka University, Japan, under the direction of Prof. Koichi Fukase and Prof. Katsunori Tanaka in 2015. After a postdoctoral fellow with Prof. John A. Porco Jr. at Boston University (2015-2016), he joined Prof. Mitsuru Shindo’s group in Institute for Materials Chemistry and Engineering, Kyushu University, Japan, as an Assistant Professor. His research interests include natural products chemistry and iptycene chemistry.

**Mitsuru Shindo** was born in Tokyo, Japan, in 1963. He graduated from the Faculty of Pharmaceutical Sciences, University of Tokyo, in 1986, and then entered the Graduate School of the University of Tokyo. He was appointed as Research Associate in Prof. Koga’s group at the University of Tokyo in 1990 and received his Ph. D. from the University of Tokyo under the supervision of Professors Kenji Koga and Kiyoshi Tomioka. After working with Professor R. A. Holton’s group as a postdoctoral fellow for two years, he returned to the University of Tokyo, and was then promoted to Associate Professor at Tokushima University in 1996. After joining Kyushu University in 2005, he was appointed as Full Professor at the Institute for Materials Chemistry and Engineering at Kyushu University in 2010. His research interests include the development of new reactions as well as the design and synthesis of biologically useful compounds.