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

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Abstract − More than 140 *Stemona* alkaloids have been isolated from Stemona plants (of the Stemonaceae species). These alkaloids represent a unique pyrrolo[1,2-*a*]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.

CONTENTS

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.[1-4] The extracts of these roots contain more than 140 types of *Stemona* alkaloids,[4] 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).[3] Moreover, Pilli et al. suggested an alternative classification into eight groups on the basis of their chemical aspects: stenine, stemoamide, tuberostemospironine, stemonamine, parbistemoline, stemofoline, stemocurtisine, and a miscellaneous group (Figure 1-2).[4] Although *Stemona* alkaloids are used as traditional medicines and the biological studies on *Stemona* alkaloids have been reviewed by Greger[3] and Pilli,[2] 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.[5]
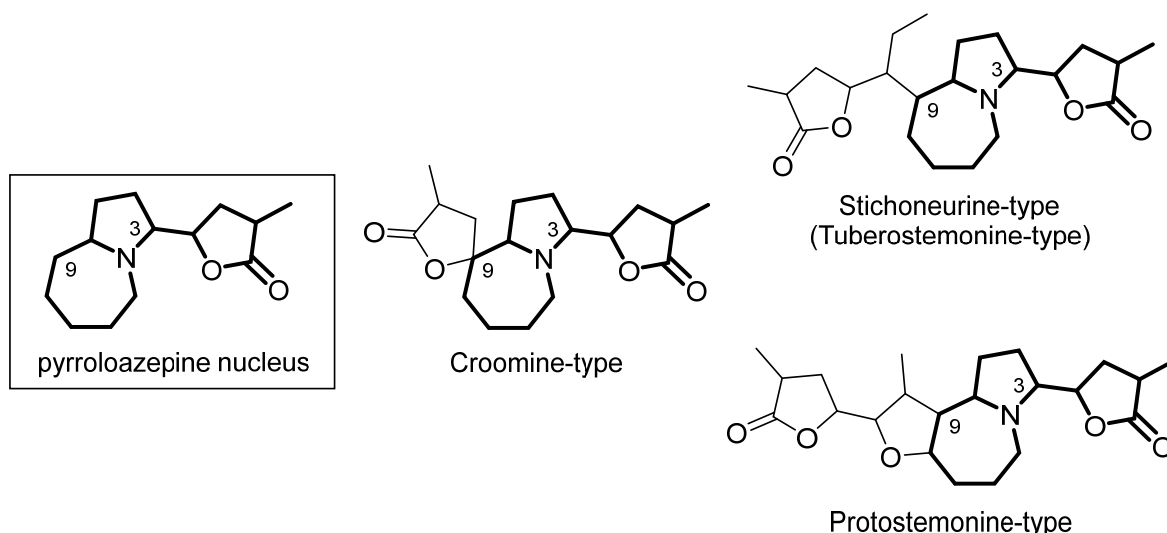

Figure 1-1. Greger's classification of *Stemona* alkaloids into three skeletal types
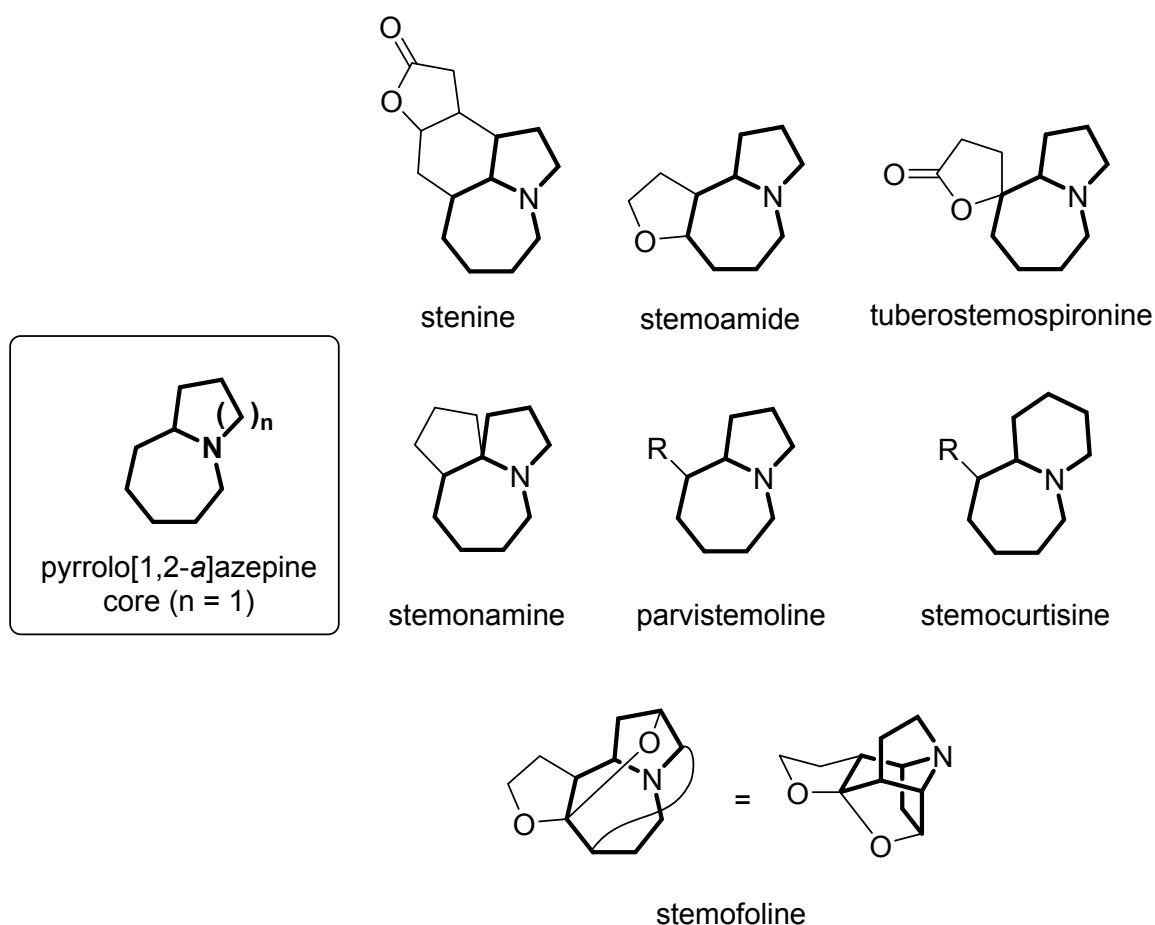
(reproduced from ref 3)

Figure 1-2. Pilli's classification of *Stemona* alkaloids into eight skeletal groups
(Reproduced from ref 4)

Among the various *Stemona* alkaloids, the stemonamine group has the cyclopenta[1,2-*b*]pyrrolo[1,2-*a*]azepine skeleton [tetracyclic 1'*H*, 11*H*-spiro[1*H*-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,[5,6] the first synthesis of the stemonamine group was delayed and at last published in 2001, which was still a racemic product.[7,8] 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**),[9,10] isostemonamine (**2**),[9,10] stemonamide (**3**),[10] isostemonamide (**4**),[10] maistemonine (protostemotinine) (**5**),[10,11] isomaistemonine (**6**),[12] oxymaistemonine (**7**),[10,11] isooxymaistemonine (**8**),[12] sessilistemonamines A, B,

and C (**9-11**),[13] 3β-*n*-butylstemonamine (**12**),[14] 8-oxo-3β-*n*-butylstemonamine (**13**),[14] 8-oxo-oxymaistemonine (**14**)[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.[9] 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*).
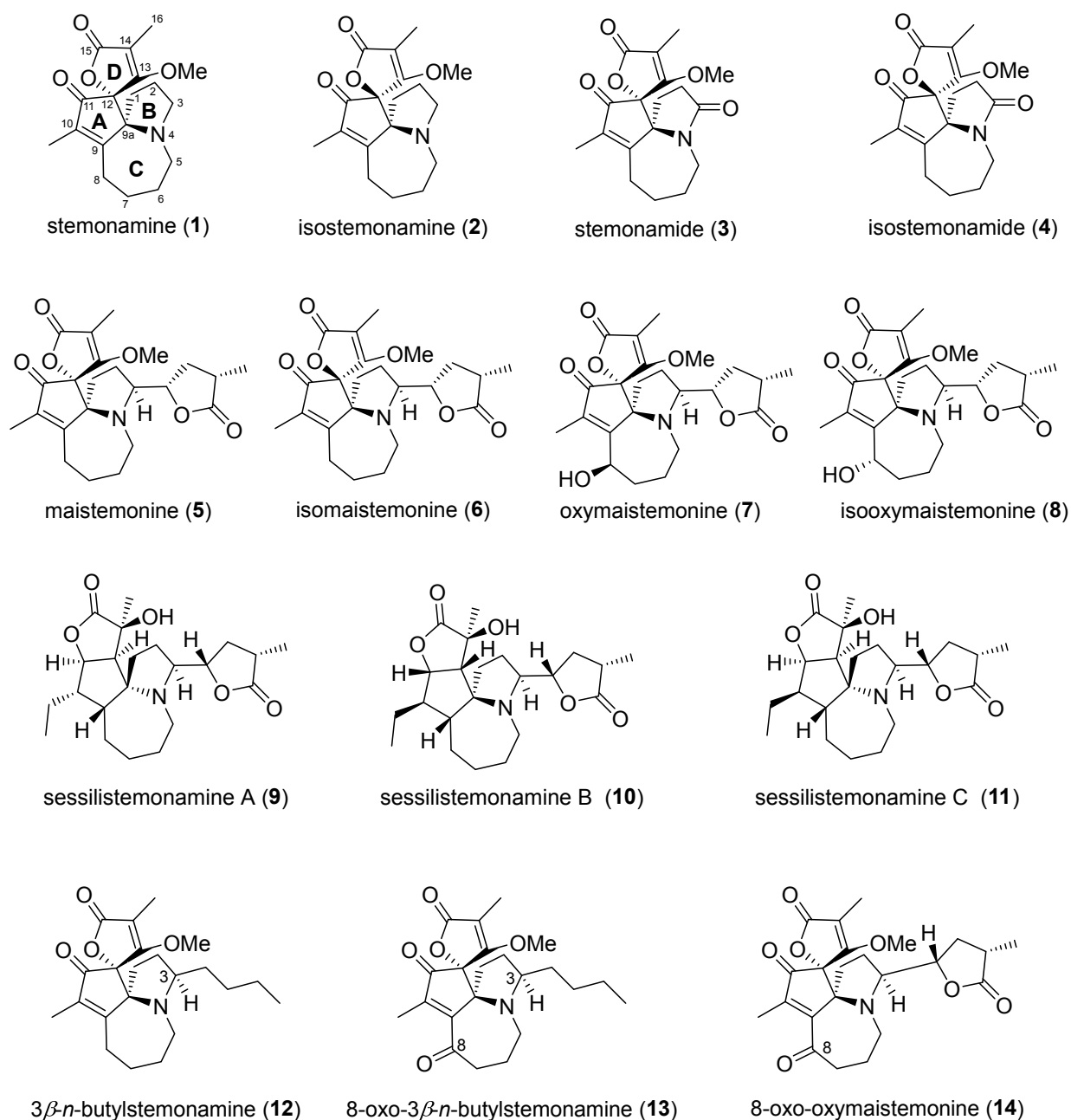

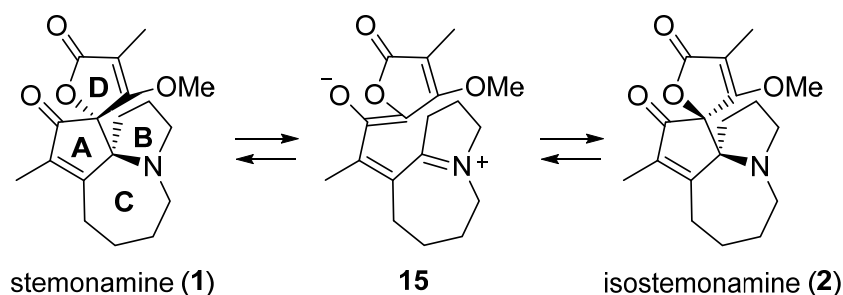Figure 1-3. Stemonamine group alkaloids

Figure 1-4. Racemization and epimerization of stemonamine and isostemonamine

2. TOTAL SYNTHESIS

2-1. Overview

Till now, four groups (Kende,[15,16] Ishibashi,[17,18] Tu (and Zhang),[19-21] and Shindo[22,23]) 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[24,25] and Rhee[26]) 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.
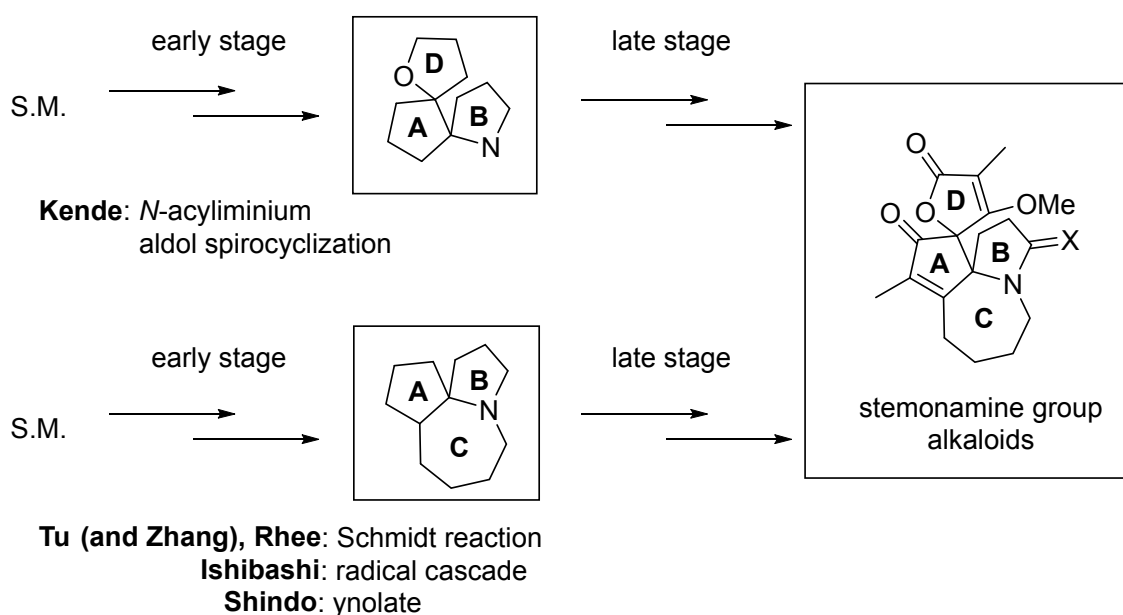

Figure 2-1. Overview of the strategies for synthesis of stemonamine group alkaloids

2-2. Kende's synthesis of (±)-stemonamide and (±)-isostemonamide (2001)[15,16]

In 2001, Kende et al. reported the first total synthesis of a stemonamine group alkaloid.[15] In that study, these authors succeeded in the synthesis of racemic stemonamide (**3**) and isostemonamide (**4**) using *N*-acyliminium chemistry[27] 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**.
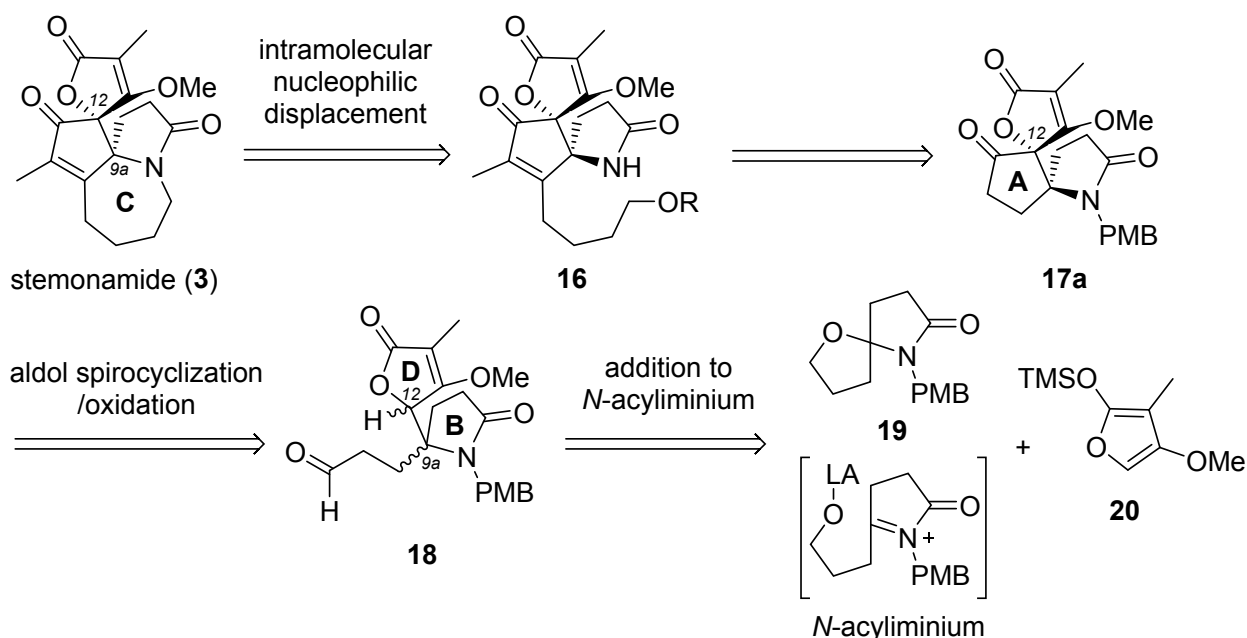

Scheme 2-1. Kende's retrosynthetic plan for (±)-stemonamide (**3**)

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 BF₃•Et₂O 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[28] 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 RhCl₃. 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 isostemamide were achieved with 4% and 7% total yield, respectively.
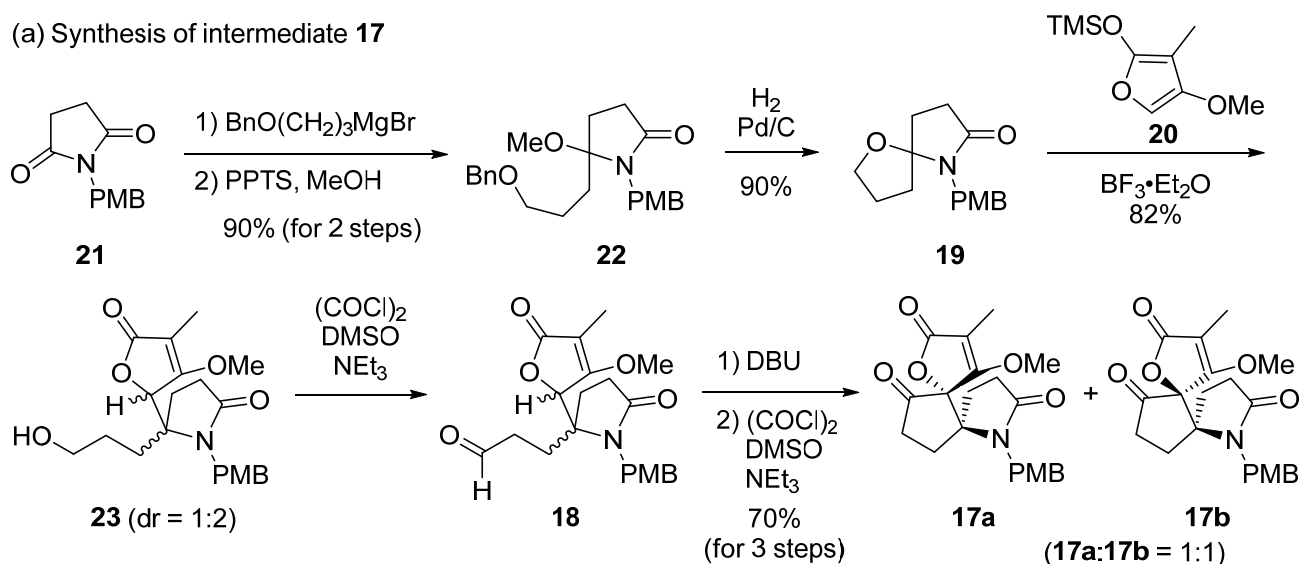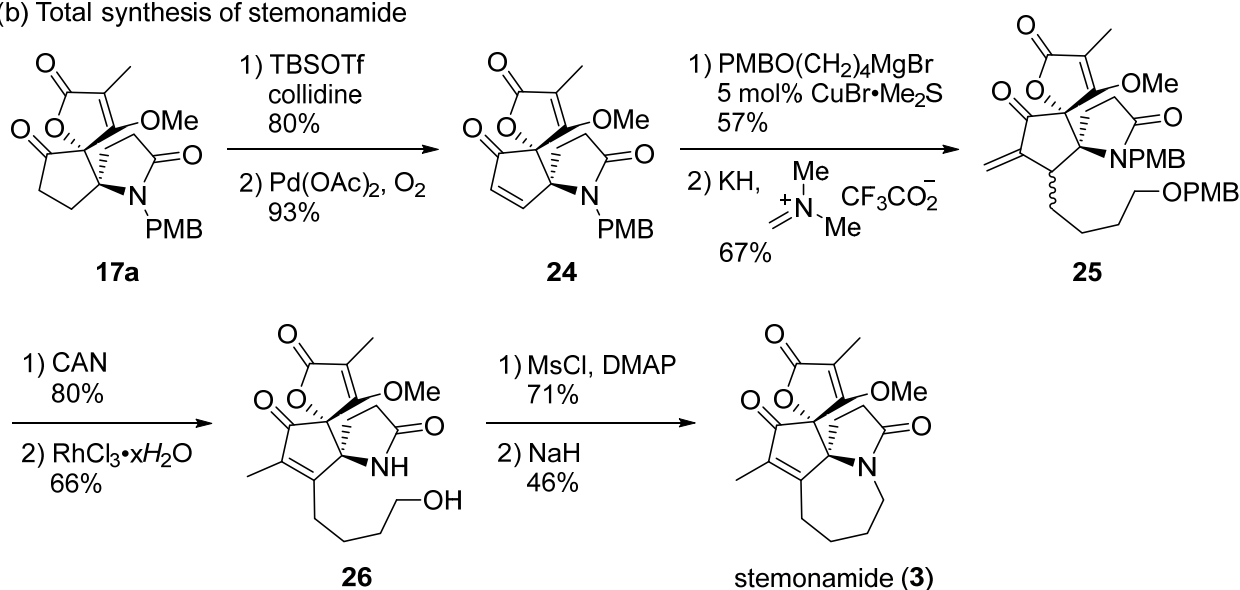

Scheme 2-2. Kende's synthesis of stemonamide (**3**)

Summarizing Kende's total synthesis, the construction of the tricyclic system (A, B, and D rings) was shortly achieved using *N*-acyiminium 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 *Stemona* alkaloids,[29] 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)[17,18]

The second total synthesis of stemonamine group alkaloids was reported by Ishibashi et al. in 2008.[17] 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.[18] 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**),[30] which is generally disfavored according to Baldwin's rule and 7-*endo-trig* cyclization (**29** to **28**).[31]
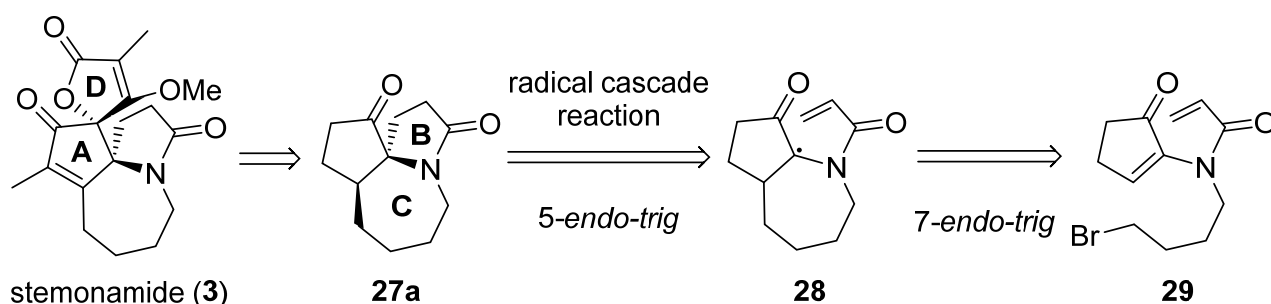
Scheme 2-3. Ishibashi's retrosynthetic plan for (±)-stemonamide (**3**)

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.
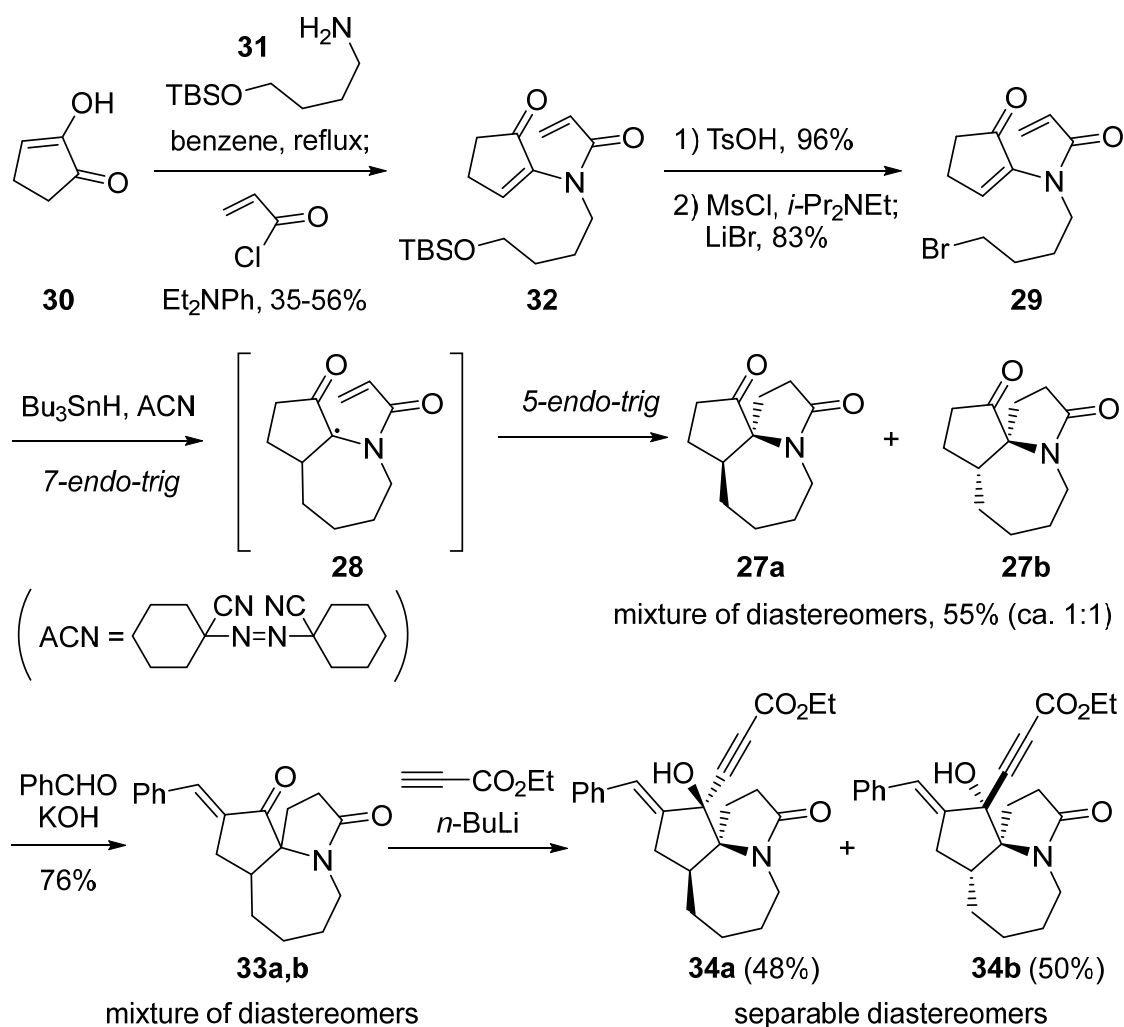
Scheme 2-4. Ishibashi's synthesis of intermediates **34a** and **b**

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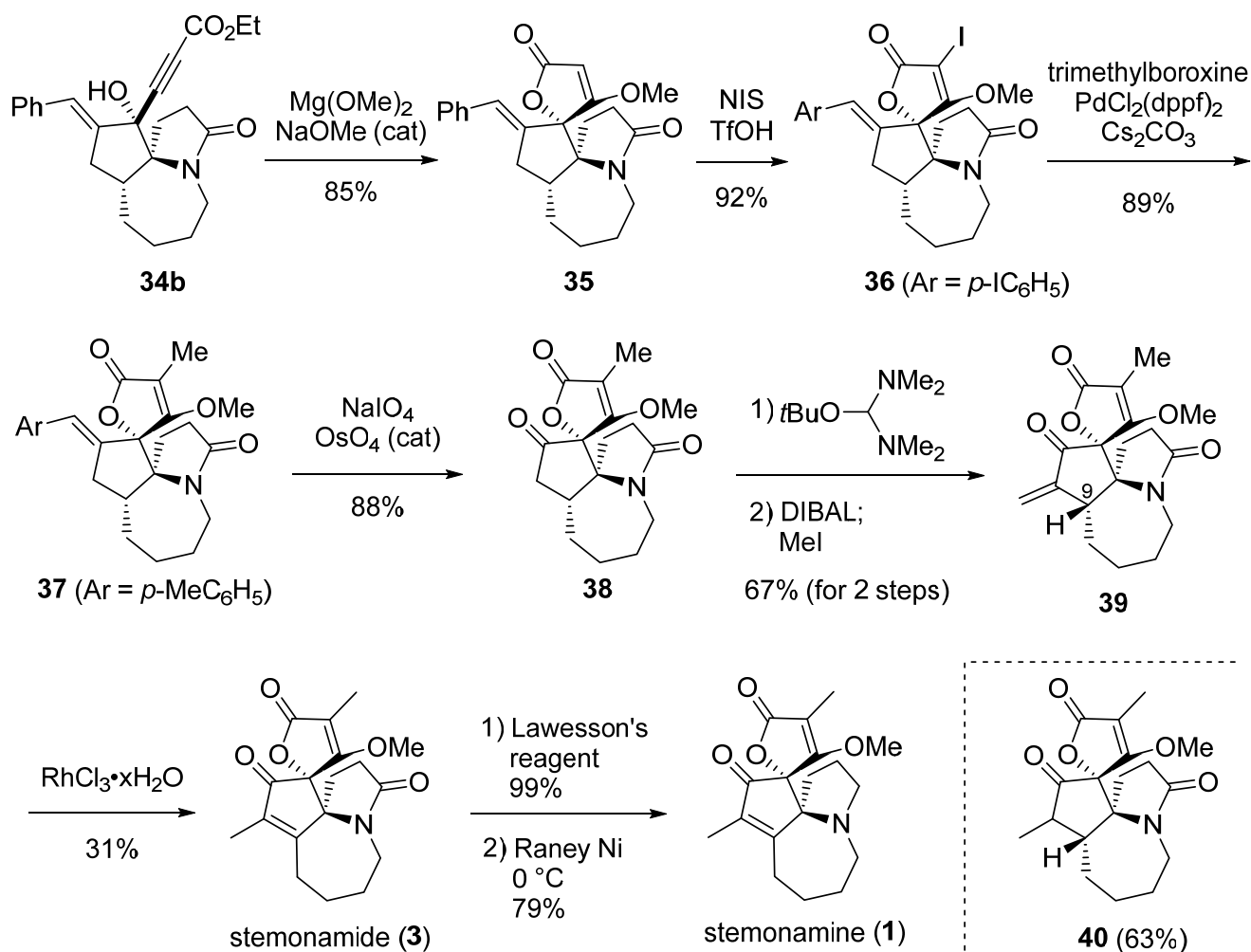
Scheme 2-5. Ishibashi's synthesis of stemonamide (**3**) and stemonamine (**1**)

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)[19]

The first total synthesis of stemonamine (**1**) was reported by Tu et al. in 2008, prior to Ishibashi's study.[19] In that study, a racemic stemonamine was synthesized using tandem semipinacol/Schmidt reaction as a key reaction.[32] 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**.
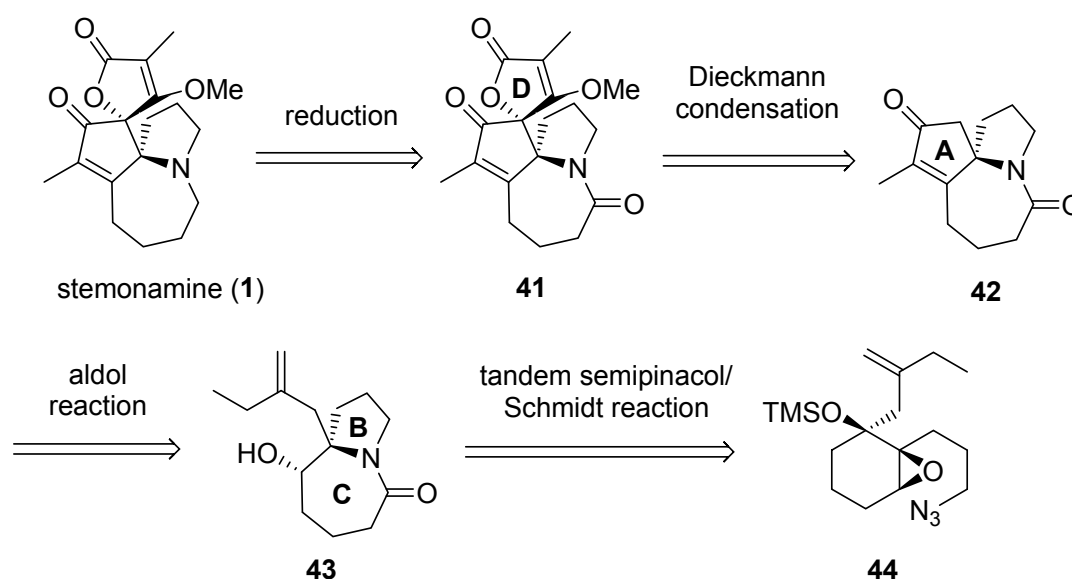
Scheme 2-6. Tu's retrosynthetic plan for (±)-stemonamine (**1**)

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**).
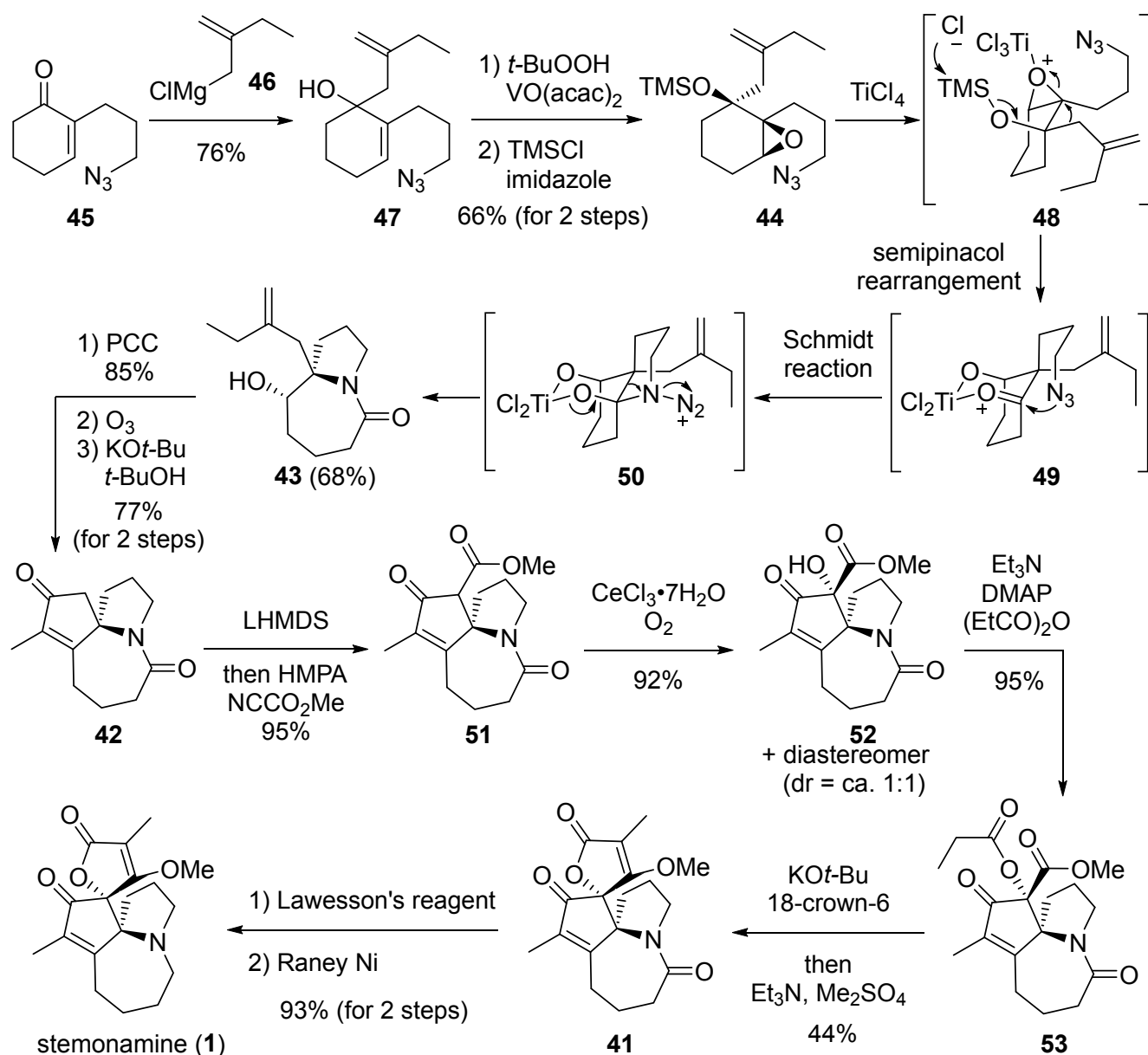

Scheme 2-7. Tu's synthesis of stemonamine (**1**)

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,[33] 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)[24,25]

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.[24,25] 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).
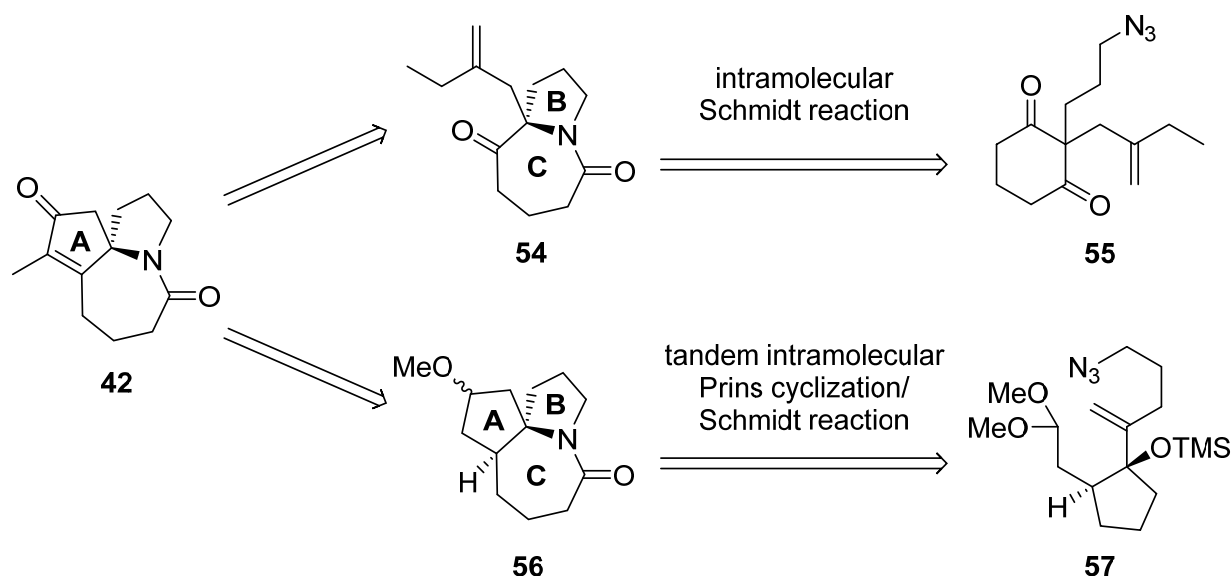
Scheme 2-8. Tu's retrosynthetic plans for key intermediate **42**

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 NaBH$_3$CN, mesylation to give **60** and sequential treatment of NaN$_3$ produced azide dione **55**. The key intramolecular Schmidt reaction using TiCl$_4$ 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).
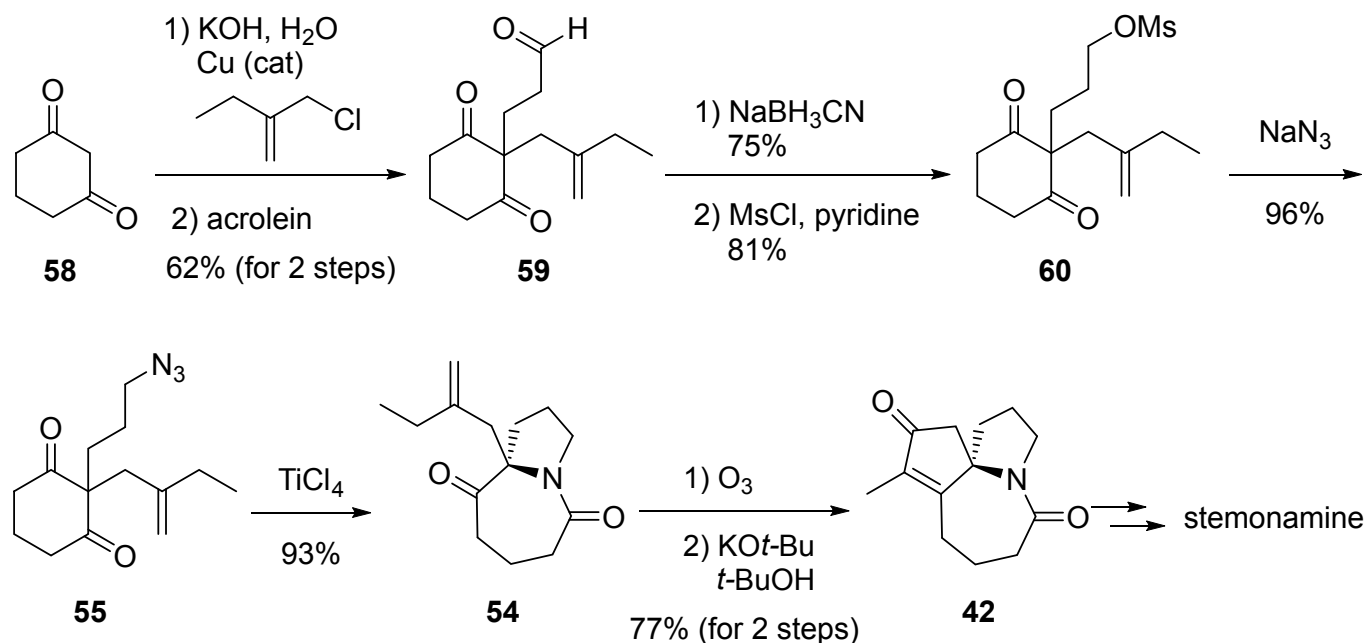
Scheme 2-9. Tu's second generation synthesis of the tricyclic intermediate **42**

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 NaN$_3$ 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 TiCl$_4$ 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**.
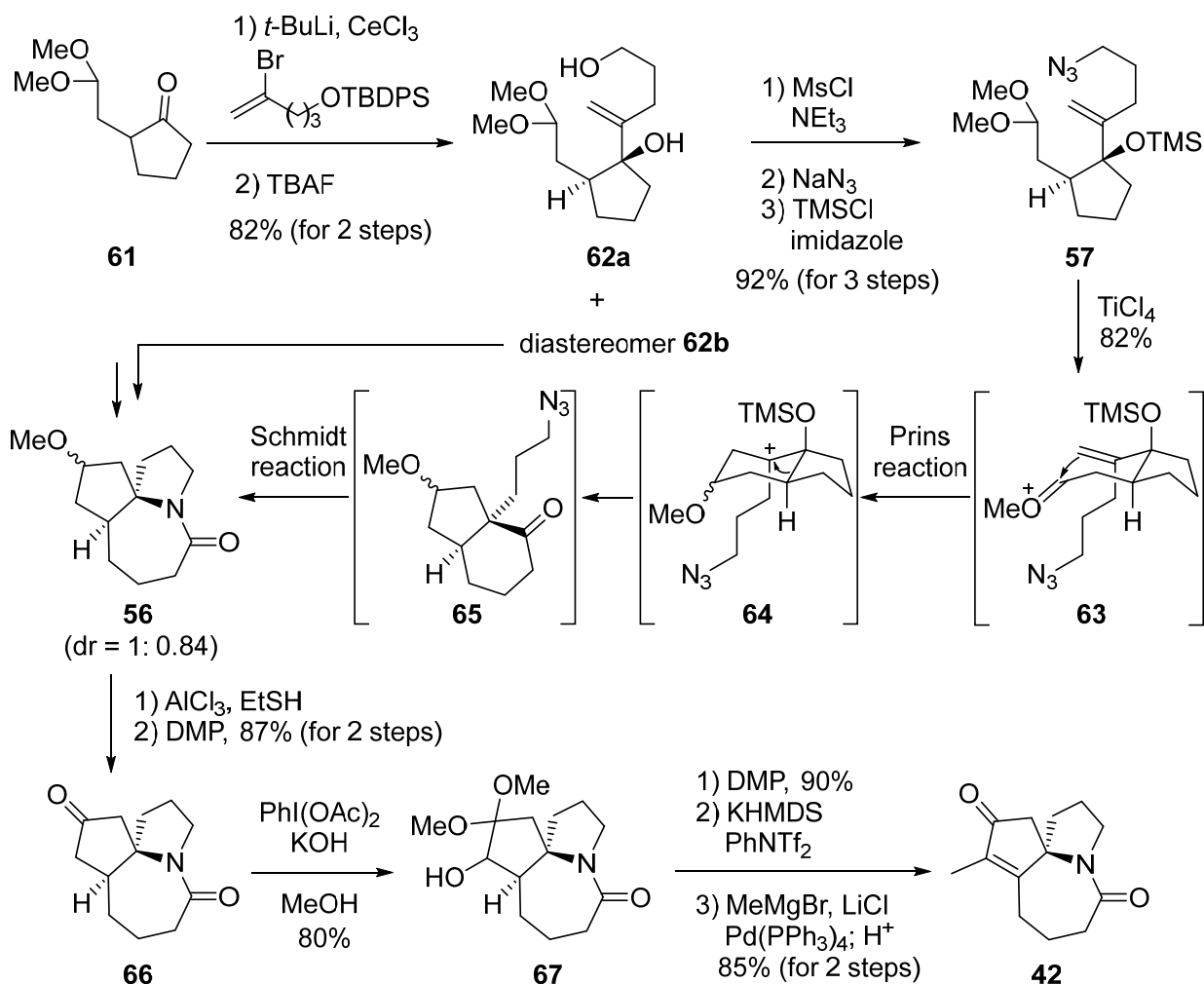
Scheme 2-10. Tu's third generation synthesis of the tricyclic intermediate **42**

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,[34] 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)[20,21]

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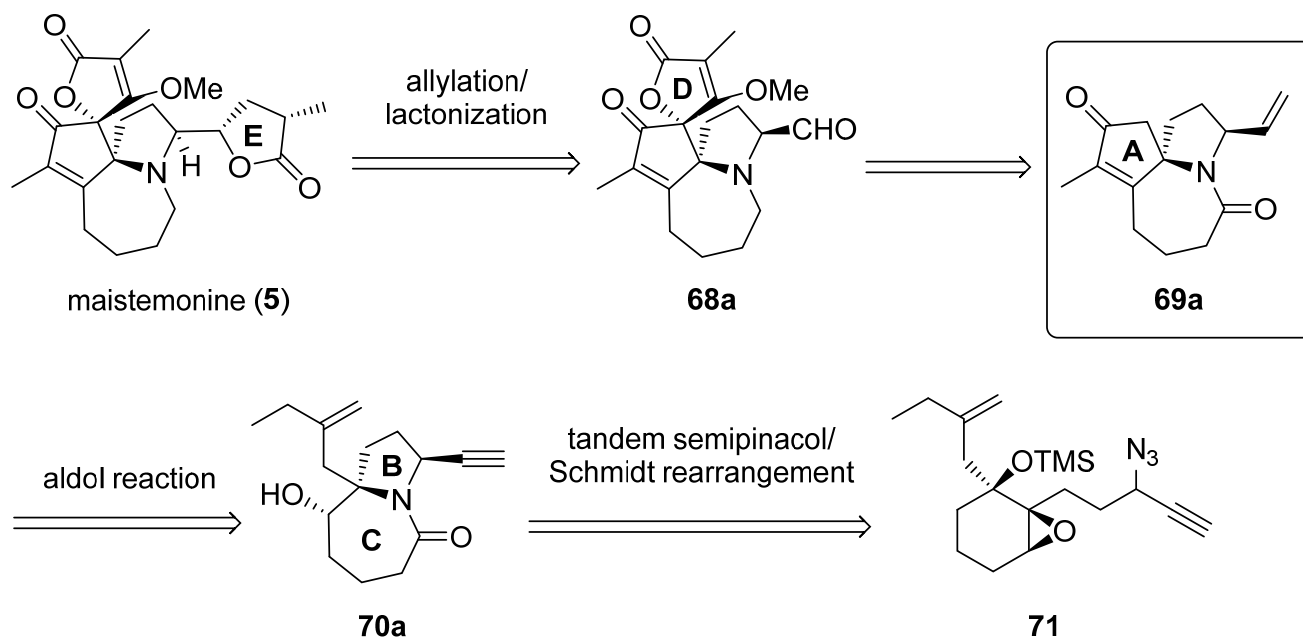
Scheme 2-11. Tu and Zhang's retrosynthetic plan for (±)-maistemonine (**5**)

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**.
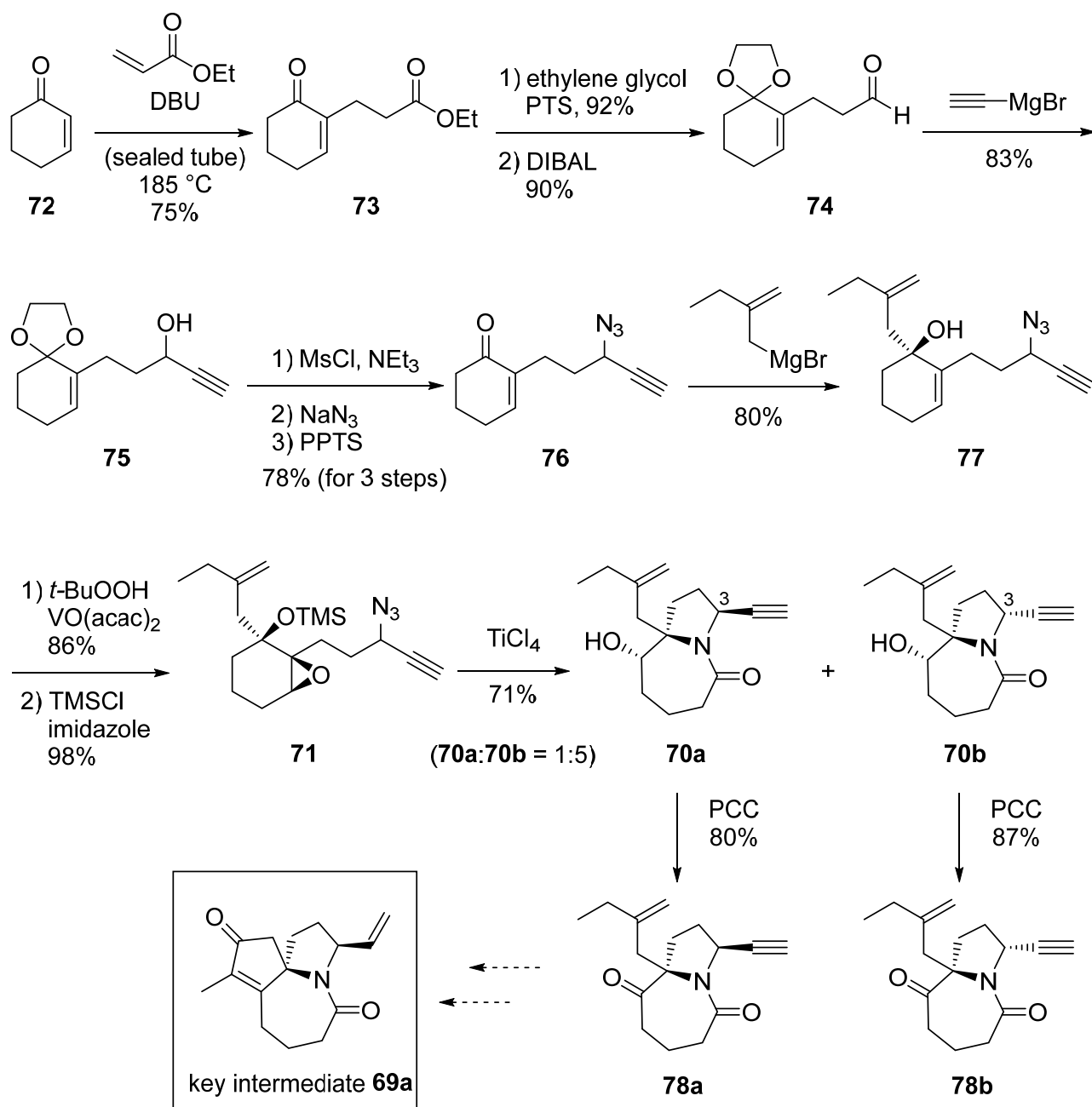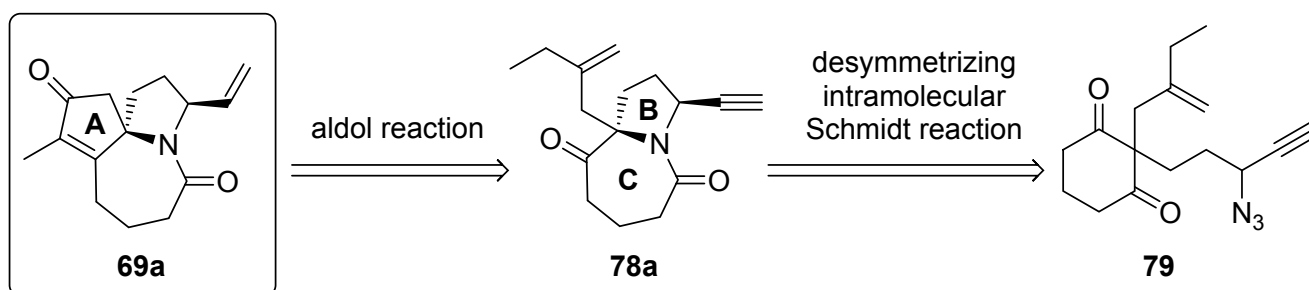
Scheme 2-12. Tu and Zhang's first generation synthesis of key intermediate **69a**

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 (refer 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 NaN$_3$. The obtained precursor **79** was then subjected to desymmetrizing intramolecular Schmidt reaction by the treatment of TiCl$_4$. 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**.

(a) second generation retrosynthetic plan for intermediate **69a**

(b) second generation synthesis of intermediare **69a**
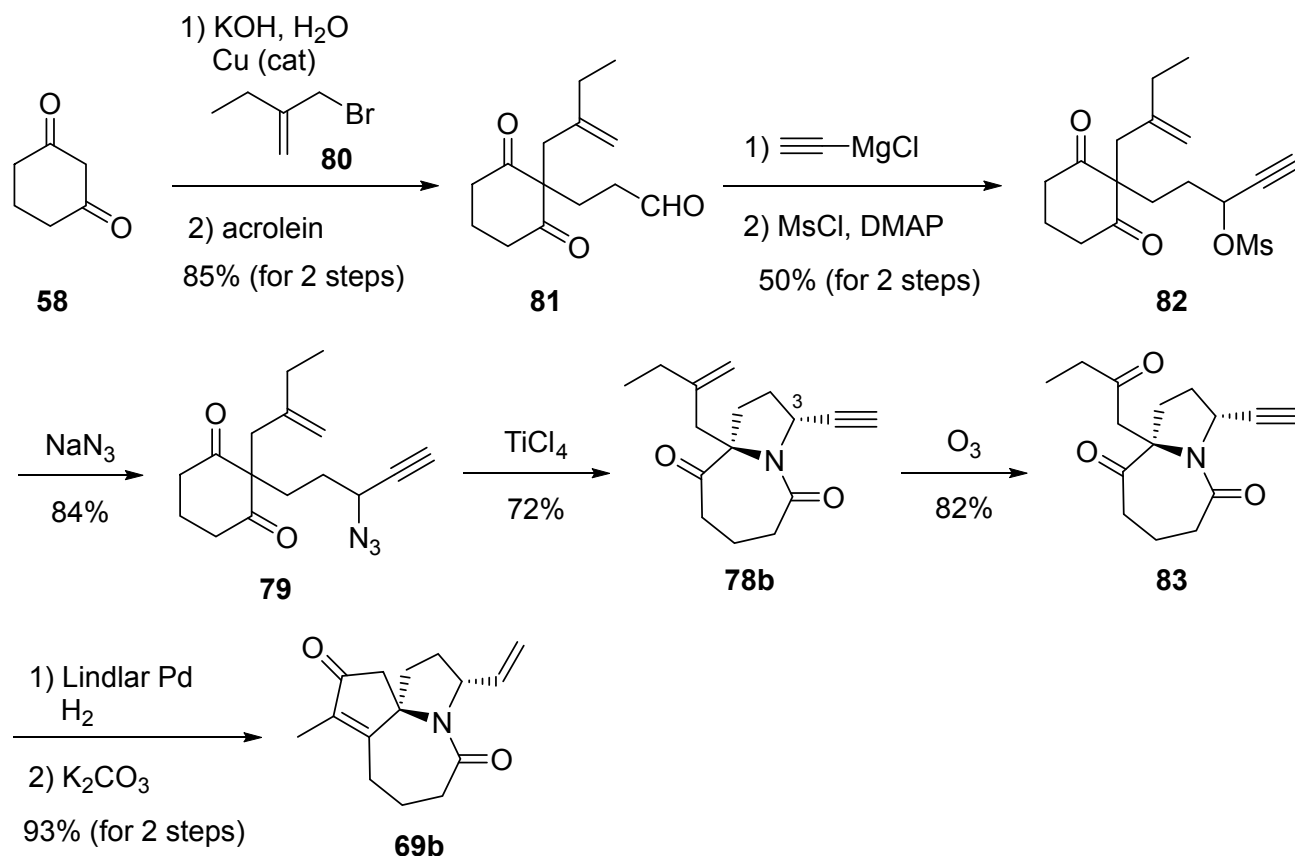
Scheme 2-13. Tu and Zhang's second generation synthesis of intermediate **69**

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 CeCl$_3$•7H$_2$O under oxygen bubbling conditions, which provided separable diastereomers **85a** and **b** 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 NaBH$_3$CN reduction of the resulting alkoxy iminium salt. The obtained tertiary amine **88** was used as the common intermediate to access maistemonine, isomaistemonine, and stemonamide.
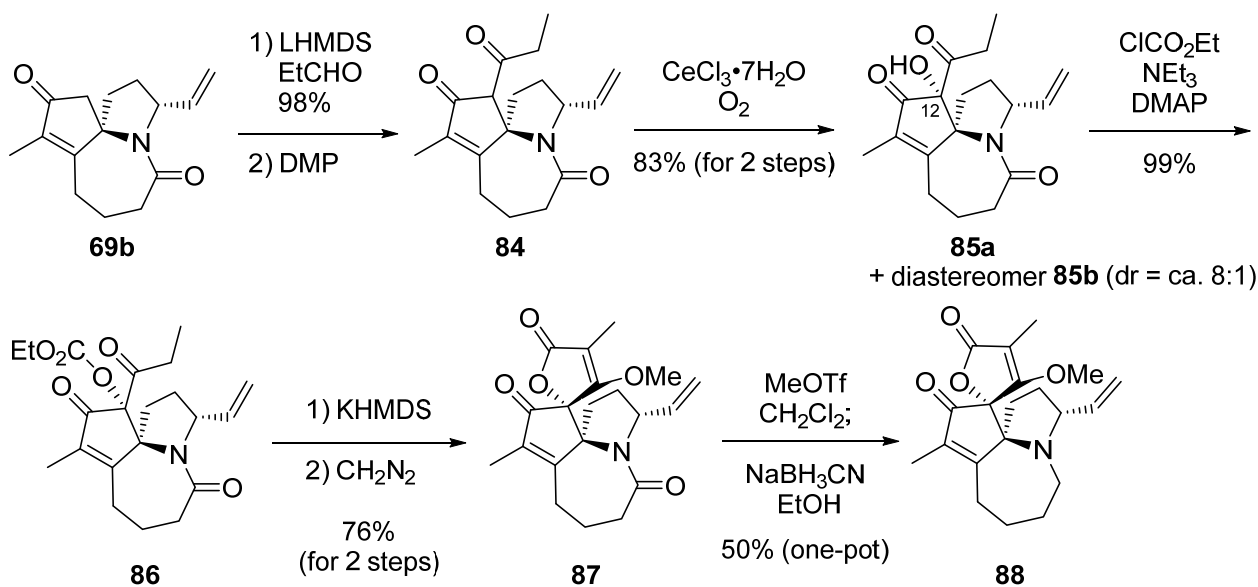
Scheme 2-14. Tu and Zhang's synthesis of common intermediate **88**

Tetracyclic compound **88** was then converted into maistemonine and isostemonine by the following transformations (Scheme 2-15). Oxidation of **88** with K$_2$OsO$_4$/NMO afforded diol **89**, which was exposed to 1.4 equivalents of NaIO$_4$ 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.[35] 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.
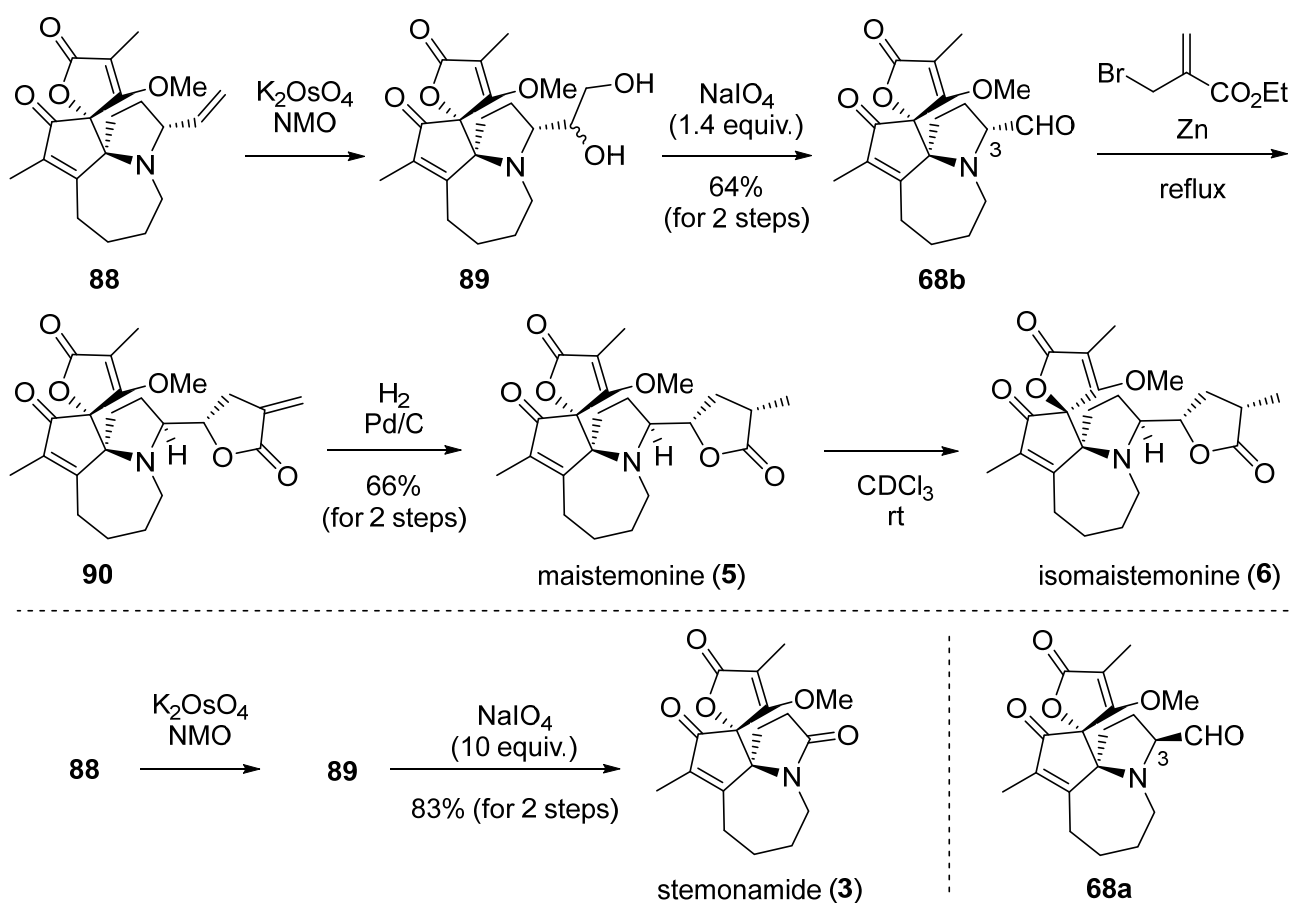
Scheme 2-15. Tu and Zhang's synthesis of maistemonine (**5**), isomaistemonine (**6**) and stemonamide (**3**)

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)[26]
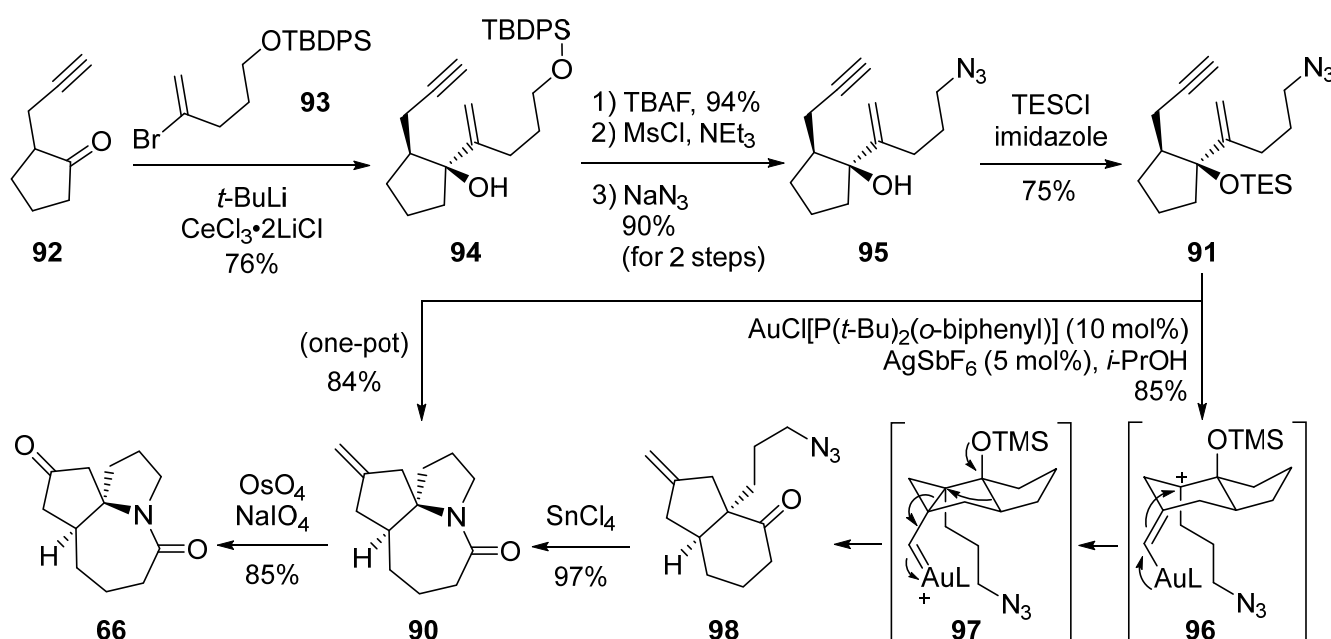
In 2014, Rhee et al. reported a formal total synthesis of (±)-stemonamine.[26] They focused on the synthesis of Tu's intermediate **66** (See Section 2-5) based on synthesis of **90** using gold-catalyzed cyclization and subsequent intramolecular Schmidt reaction of ene-yne-azide **91** (Scheme 2-16a). Ketone **92** was treated with a vinyllithium reagent (derived from vinyl bromide **93**) in the presence of CeCl$_3$ to afford tertiary alcohol **94** (Scheme 2-16b). Sequential transformations including deprotection of TBDPS group, mesylation, and treatment of NaN$_3$ 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$_4$ 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$_4$ and NaIO$_4$ to produce Tu's intermediate **66** en route for stemonamine (See Section 2-5).


Scheme 2-16. Rhee's synthesis of tricyclic intermediate **66**

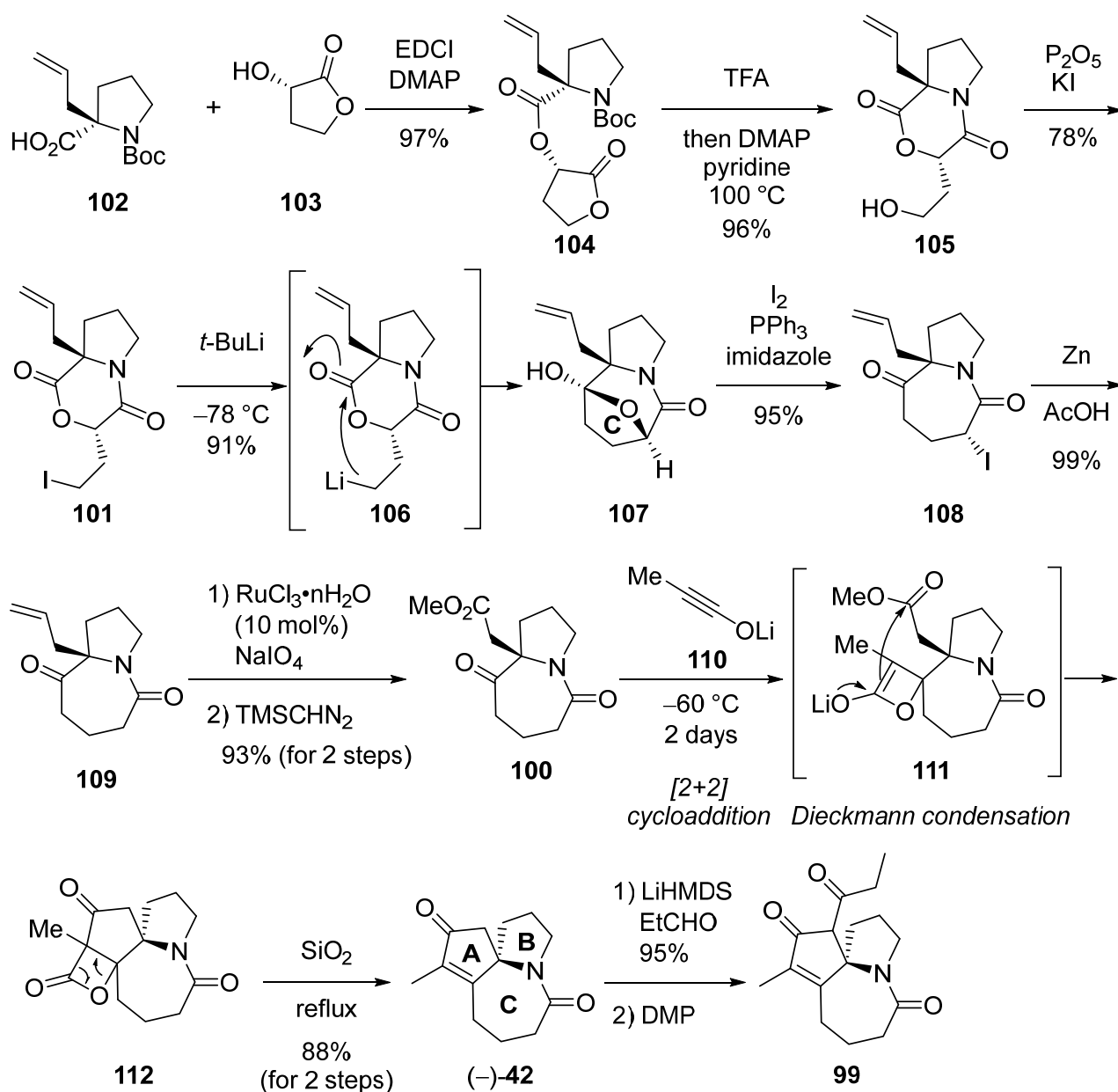## 2-8. Shindo's synthesis of (−)-stemonamine and (−)-isostemonamine (2018)[22,23]

In 2018, Shindo et al. reported the first asymmetric total synthesis of (−)-stemonamine (**1**)[22] and (−)-isostemonamine (**2**).[23] 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**.[36] The C ring would be formed by intramolecular acylation of iodide **101**,[37] which can be prepared from the known compounds **102** and **103**.
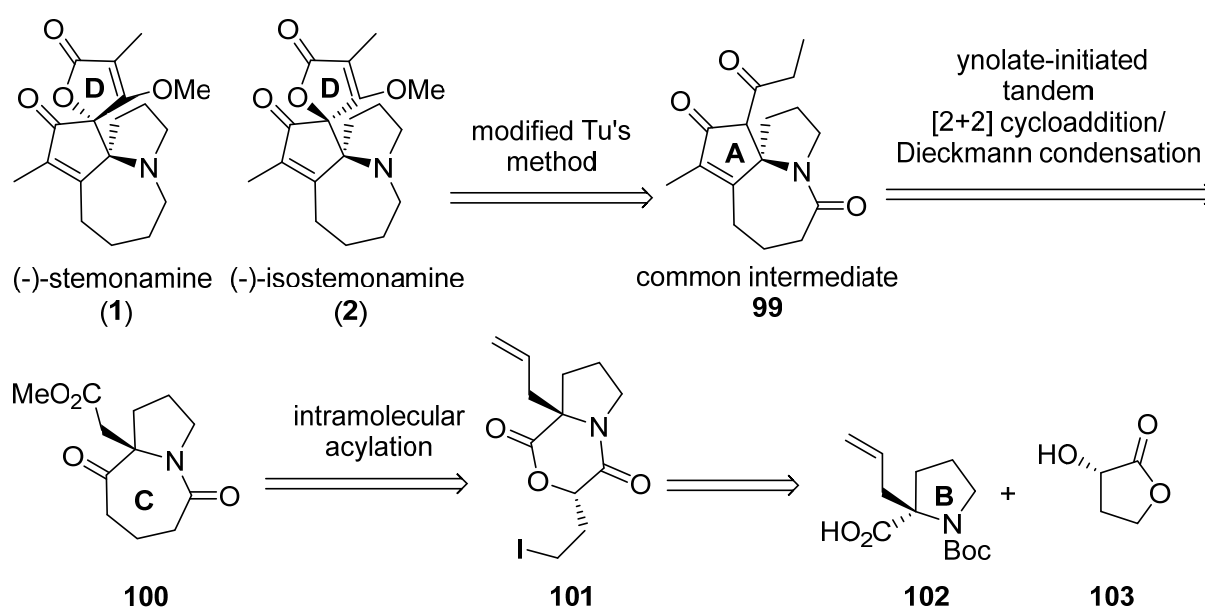
Scheme 2-17. Shindo's retrosynthetic plan for enantiomer-enriched stemonamine (**1**) and isostemonamine (**2**)

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 cyclobutenone enolate **111** via formal [2+2] cycloaddition reaction, which subsequently proceeded Dieckmann condensation reaction to afford β-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**.
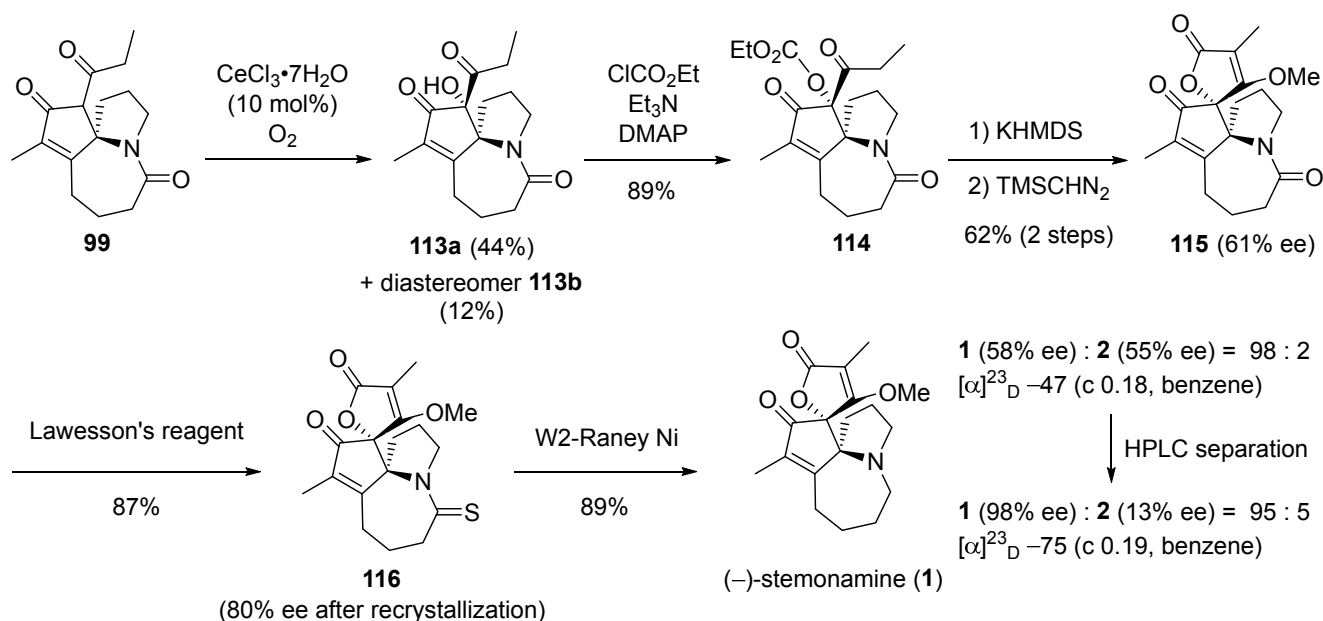

Scheme 2-18. Shindo's synthesis of the common intermediate **99**

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, α-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.
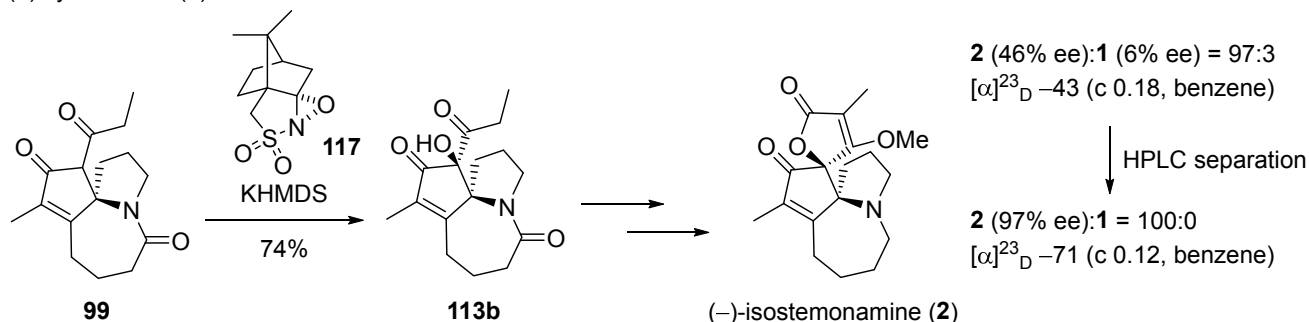
Scheme 2-19. Shindo's synthesis of (−)-stemonamine (**1**) and (−)-isostemonamine (**2**)

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.[18] 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).[22,23] 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 23)

Entry	Solvent	Temp. (°C)	(−)-stemonamine (**1**)				(−)-isostemonamine (**2**)			
			Racemization		Epimerization		Racemization		Epimerization	
			k^a	$t_{1/2}$ (h)	k^a	$t_{1/2}$ (h)	k^a	$t_{1/2}$ (h)	k^a	$t_{1/2}$ (h)
1	20% i-PrOH in hexane	60	0.74	2.6	0.026	74	11	0.18	0.066	29
2	20% i-PrOH in hexane	45	0.22	9.0	0.0071	270	2.9	0.67	0.010	190
3	20% i-PrOH in hexane	25	0.035	55	<0.001	>1000	0.53	3.6	<0.001	>1000
4	20% i-PrOH in hexane	10	0.0097	200	-^{b}	-^{b}	0.11	18	-^{b}	-^{b}
5	CHCl$_3$	25	0.0072	270	-^{b}	-^{b}	0.16	12	-^{b}	-^{b}

^{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**).[20,21] 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 *Stemona* alkaloids have not been clarified enough. Many biological investigations have been conducted using the plant extracts without identifying the actual active compounds.[38] Therefore, studies on biological activity of the *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 α (ERα)-negative breast cancer cell lines (MDA-MB-231) with an IC_{50} value of 9.3 µM.[39]

5. CONCLUSION

In this review, we summarized the synthetic effort toward *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 *Stemona* alkaloids, there is huge scope for a synthetic chemist to further contribute to the assessment of *Stemona* alkaloids based on a synthetic study.

Devices."

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