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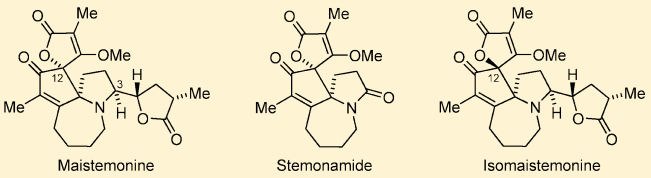
Total Synthesis of (±)-Maistemonine, (±)-Stemonamide, and (±)-Isomaistemonine

Zhi-Hua Chen, Zhi-Min Chen, Yong-Qiang Zhang, Yong-Qiang Tu,* and Fu-Min Zhang*

State Key Laboratory of Applied Organic Chemistry and Department of Chemistry, Lanzhou University, Lanzhou 730000, P. R. China

Supporting Information

ABSTRACT: A full account of the total synthesis of (±)-maistemonine, (±)-stemonamide, and (±)-isomaistemonine is presented. Two approaches have been developed to construct the basic pyrrolo[1,2-*a*]azepine core of the *Stemona* alkaloids, featuring a tandem semipinacol/Schmidt rearrangement of a secondary azide and a highly stereoselectively desymmetrizing intramolecular Schmidt reaction, respectively. To build the common spiro-γ-butyrolactone, a new protocol was carried out by utilizing an intramolecular ketone-ester condensation as the key transformation. The vicinal butyrolactone moiety of (±)-maistemonine was stereoselectively introduced via a one-pot procedure involving the epimerization at C-3 and carbonyl allylation/lactonization. Moreover, (±)-stemonamide was divergently synthesized from a common intermediate, and (±)-isomaistemonine was obtained via the epimerization of (±)-maistemonine at C-12.



INTRODUCTION

The *Stemona* alkaloids represent a class of polycyclic alkaloids with relatively complex structures. More than 130 *Stemona* alkaloids have been isolated to date from the monocotyledonous family Stemonaceae.[1−4] Recently, Pilli and co-workers classified *Stemona* alkaloids into eight groups according to their structural features.[4] The stemonamine group (Figure 1), which

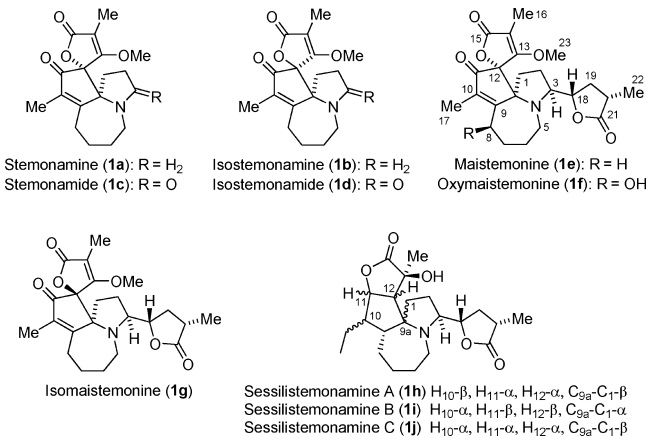


Figure 1. Structures of 10 alkaloids of the stemonamine group.

is characterized by the presence of a cyclopenta[1,2-*b*]pyrrolo[1,2-*a*]azepine nucleus, includes stemonamine (**1a**),[5] isostemonamine (**1b**),[5] stemonamide (**1c**),[5] isostemonamide (**1d**),[5] maistemonine (**1e**),[5,6] oxymaistemonine (**1f**),[5,6] isomaistemonine (**1g**),[7] and sessilistemonamines A−C (**1h**−**1j**).[8] Since the plants from which the *Stemona* alkaloids are obtained have been used in folk medicine in East Asia for thousands of years to treat respiratory diseases and as anthelmintics,[9−11] it is not surprising that the pure natural products possess interesting bioactivities. For example, maistemonine (**1e**) has been shown to display significant antitussive activity.[12]

Maistemonine (**1e**) is a pentacyclic *Stemona* alkaloid that was originally isolated by Xu et al. in 1991 from the roots of *Stemona mairei*.[6] The striking molecular architecture of **1e** includes an azatetracyclic 7,5,5,5-ring system and an α-methyl-γ-butyrolactone moiety annexed to C-3 as a side chain. The azatetracyclic system, which is common to stemonamide (**1c**) and isomaistemonine (**1g**), possesses two contiguous heteroquaternary stereocenters.

Since the report of the first total synthesis of (+)-croomine by Williams' group in 1989,[13] the challenging structural complexity and various biological activities of the *Stemona* alkaloids have attracted considerable interest from the synthetic community.[1,4,14−19] Among them, a number of elegant total syntheses of the stemonamine group alkaloids **1a**−**1d** have been reported in the literature.[20−27] However, maistemonine (**1e**) and isomaistemonine (**1g**), which have more intricate skeletons, had not been synthesized until we disclosed our first total synthesis of **1e** in 2010.[28] Herein, we provide a full account of the development and execution of our strategy, which culminated in the total synthesis of maistemonine (**1e**) and isomaistemonine (**1g**) and divergent synthesis of stemonamide (**1c**).

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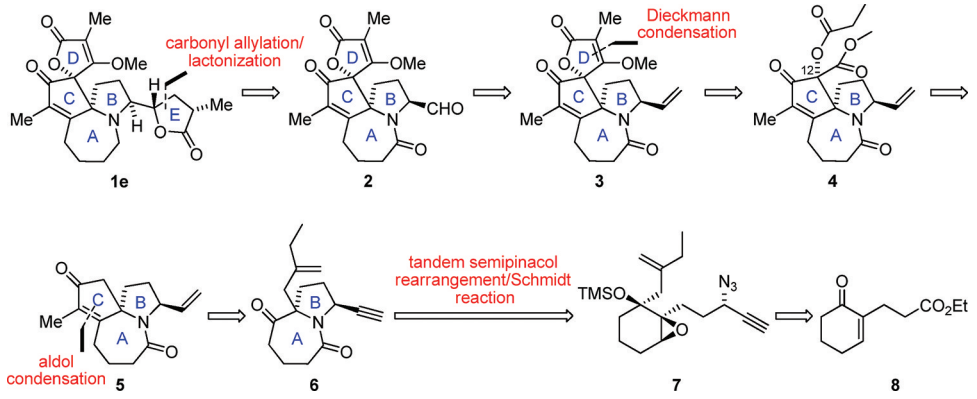
Scheme 1. First-Generation Retrosynthetic Analysis of (±)-Maistemonine

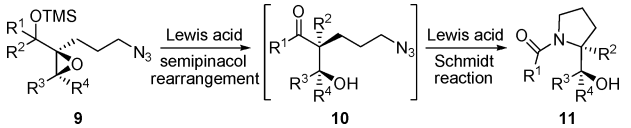


RESULTS AND DISCUSSION

Our initial retrosynthetic analysis of maistemonine (**1e**) is depicted in Scheme 1. We anticipated that the lactone ring **E** of the natural product **1e** could be conveniently formed via a stereoselective carbonyl allylation/lactonization[29,30] of aldehyde **2**, which could be derived via oxidative cleavage of alkene **3**. Ring **D** could be formed by means of Dieckmann condensation and subsequent *O*-methylation of diester **4**. Simplification of **4** according to our previously developed strategy[23] reveals tricycle **5**. Key reaction in this section of the synthesis would be the stereoselective establishment of the oxa-quaternary center (C-12). Construction of the enone and terminal vinyl moieties of **5** by a sequence of ozonolysis, Lindlar reduction, and aldol condensation leads back to ketone **6**, which has the common pyrrolo[1,2-*a*]azepine core of most *Stemona* alkaloids. We hoped to rapidly fashion the bicyclic core of **6** via a tandem semipinacol rearrangement/Schmidt reaction[31] developed by our group. Precursor **7** could be derived from the known ester **8**[32] by a route featuring DIBAL-H reduction, Grignard addition, S_N2 displacement, and regioselective epoxidation.

In 2006, our laboratory developed a general method for the efficient construction of aza-quaternary carbon units via a Lewis acid promoted tandem semipinacol/Aubé's type intramolecular Schmidt reaction of α-siloxy-epoxy-azide (Scheme 2).[31] Shortly

Scheme 2. Tandem Semipinacol/Schmidt Rearrangement



thereafter, we applied this methodology as part of an efficient total synthesis of stemonamine (**1a**).[23] Despite the fact that the tandem process is effective for a wide scope of substrates, the secondary azide, such as **7** (Scheme 1), was not investigated until recently. Although some precedent existed for the intramolecular Schmidt reaction of secondary azide,[33−35] we were unsure if the secondary azide **7** would undergo the tandem reaction to give the desired bicyclic product.

Our attempt at constructing **6** according to the plan described above commenced with the preparation of the known ester **8**,[32] as depicted in Scheme 3. Treatment of enone **12** and ethyl acrylate with a catalytic amount of DBU in DMF at 185 °C (sealed tube) afforded **8**. Protection of the keto carbonyl group provided 1,3-dioxolane **13**, which underwent DIBAL-H reduction of the ester group to afford aldehyde **14**. Then, Grignard addition to **14** with ethynylmagnesium bromide gave alcohol **15**, which is followed by the mesylation to form the mesylate **16**. Substitution of mesylate **16** with NaN_3 was conducted at 40 °C, affording secondary azide **17**. It should be noted that the introduction of the alkynyl group was elaborated to be an aldehyde precursor for the convenient establishment of ring **E** and also made it possible to obtain stemonamide (**1c**) in the later stage. We initially chose a vinyl group as the aldehyde precursor and found that the S_N2' reaction was a prominent side reaction, giving a double bond migration product in the subsequent NaN_3 displacement process.[36] The dioxolane group of **17** was rapidly removed under standard conditions (PTS, acetone) to give enone **18**. Next, 1,2-addition of the (2-methylenebutyl)magnesium reagent, derived from 2-(bromomethyl)but-1-ene,[37] with **18** proceeded in good yield, affording diastereoisomers **19**, which are not separable on silica gel. Regioselective epoxidation of **19** was conducted to furnish **20** in 86% yield via optimization of the reaction conditions. Increasing the amount of ^{t}BuOOH or prolonging the reaction time gave a prominent diepoxidation byproduct. TMS protection of the labile tertiary alcohol **20** resulted in the formation of the key intermediate **21**. We elected not to optimize the 1,2-addition (**18** → **19**) to get the single diastereoisomer **7** mentioned in our retrosynthetic analysis (Scheme 1), as diastereoisomers **21** were competent to permit the examination of the subsequent tandem reaction. When we exposed **21** to $TiCl_4$ in CH_2Cl_2 at −78 °C to room temperature, the expected rearrangement proceeded smoothly to afford the separable diastereoisomers **22** and **23** in the ratio of 5:1. The relative configurations of the newly formed stereocenters of **22** and **23** were assigned by X-ray analysis.[38]

Unfortunately, by comparing the relative configurations of the major diastereoisomer **22** and maistemonine (**1e**), we found that their stereochemistries at C-3 and C-9a were inconsistent. Apparently, the ratio of the diastereoisomers **19** formed in the 1,2-addition step (**18**→**19**) ultimately enabled the undesired rearrangement product **22** to be primarily generated. Then, **22** and **23** were oxidized to yield ketones **24** and **6**, respectively. Although the designed bicyclic intermediate **6** was obtained via the anticipated tandem semipinacol/Schmidt rearrangement of the secondary azide substrate (Scheme 3), its lengthy preparation course (12 steps) and low stereoselectivity in the tandem reaction impelled us to seek a more concise approach toward the synthesis of **6**.

A modified retrosynthesis of **1e**, based on the concept mentioned above, is portrayed in Scheme 4. We did not

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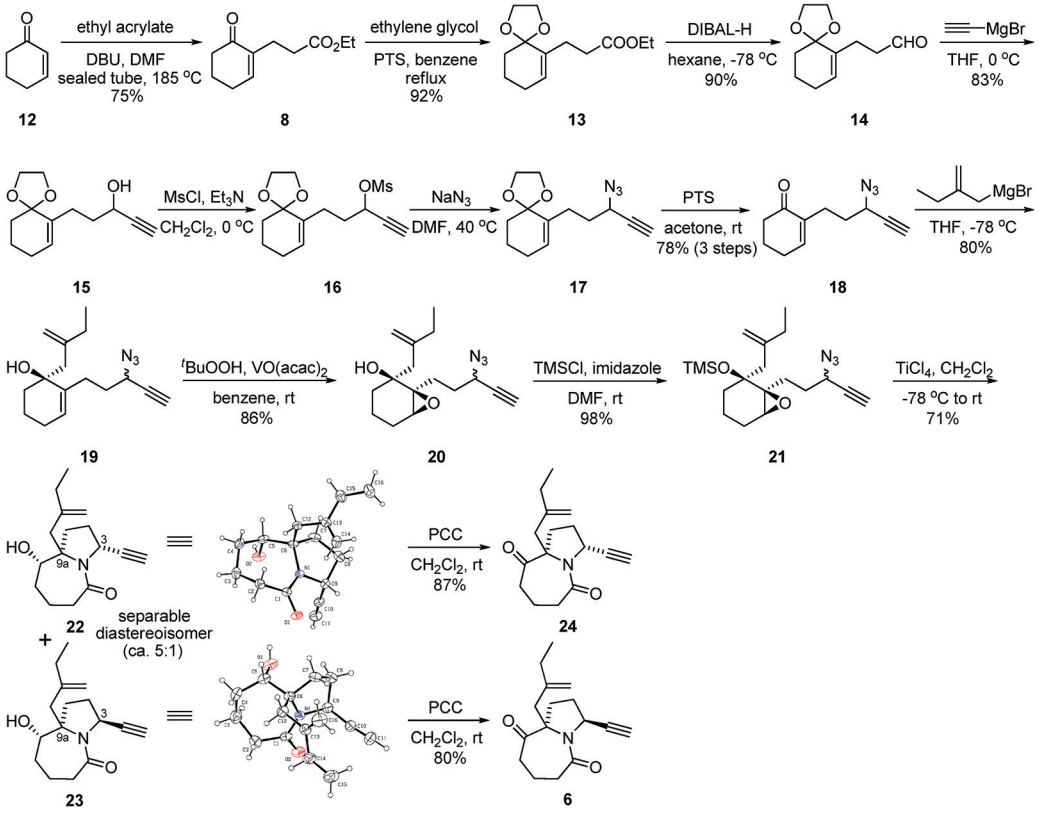
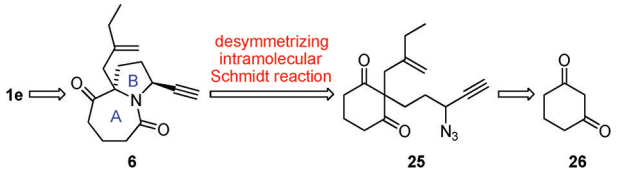
Scheme 3. Preparation and Tandem Semipinacol/Schmidt Rearrangement of Secondary Azide 21



Scheme 4. Second-Generation Retrosynthetic Analysis of (±)-Maistemonine

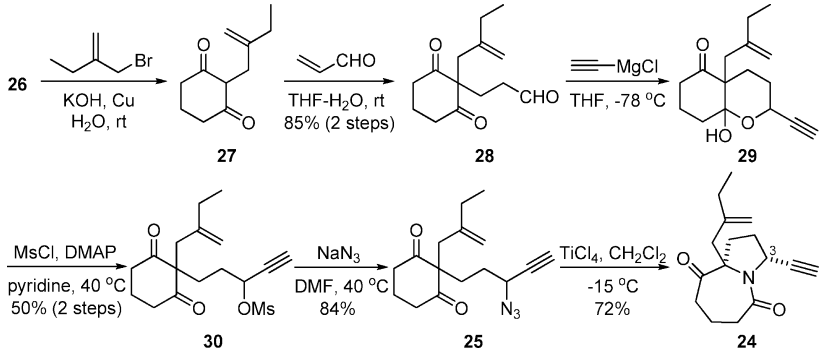


envision our new strategy requiring changes to the **6**→**1e** stages of the synthesis. However, **6** would now be derived from a desymmetrizing intramolecular Schmidt reaction[33,39−43] of azido-ketone **25**, which could be easily obtained in five steps from inexpensive material **26**.

As shown in Scheme 5, treatment of cyclohexane-1,3-dione with 2-(bromomethyl)but-1-ene in the presence of copper powder afforded the *C*-alkylation product **27**, which was subjected to Michael addition with acrolein to yield the keto-aldehyde **28**. Selective Grignard addition of ethynylmagnesium chloride to **28** was performed at low temperature to give hemiketal **29**. Mesylation of **29** with MsCl and Et_3N or pyridine in CH_2Cl_2 proceeded in low yield (10−20%, 2 steps). After optimization of the reaction conditions, it was found that changing the solvent to pyridine with a catalytic amount of DMAP could afford the desired keto-mesylate **30** in 50% yield over two steps. Mesylate substitution of **30** with NaN_3 gave the secondary azide **25**. Then, the key desymmetrizing intramolecular Schmidt reaction of the secondary azide was investigated. The rearrangement was enabled by treatment of **25** with 1.2 equiv of $TiCl_4$ in CH_2Cl_2 at −15 °C to afford the bicyclic product **24** as a single product in 72% yield.

To verify the high stereoselectivity of the desymmetrizing intramolecular Schmidt reaction, an analogue of **25** with a terminal ethyl moiety instead of the alkynyl group was

Scheme 5. Preparation and Desymmetrizing Intramolecular Schmidt Reaction of Azide 25



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Scheme 6. Preparation and Desymmetrizing Intramolecular Schmidt Reaction of Azide 33

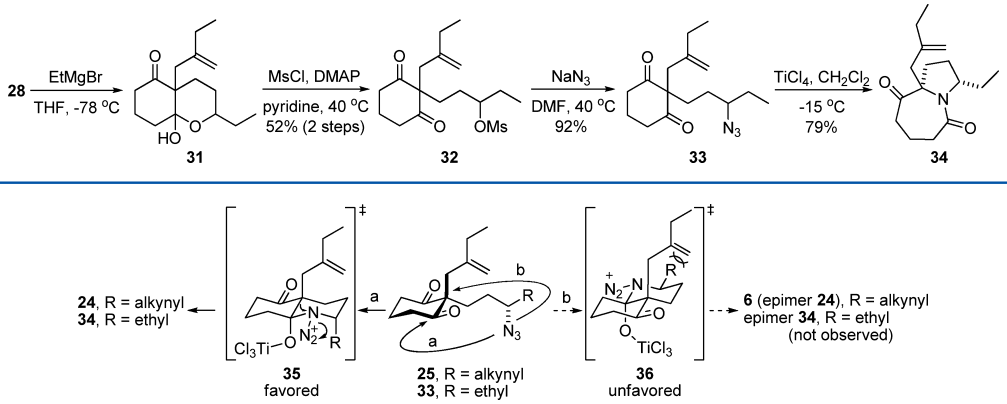
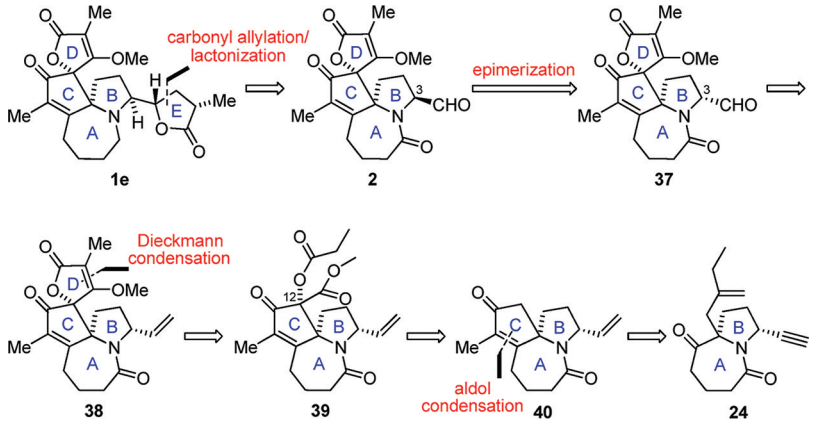
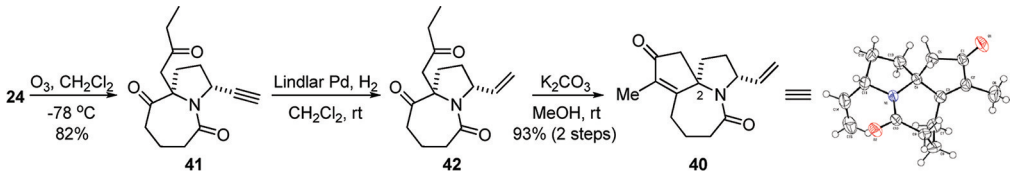


Figure 2. Proposed process for the diastereotopic group selective Schmidt reaction.

Scheme 7. Third-Generation Retrosynthetic Analysis of (±)-Maistemonine



Scheme 8. Synthesis of Tricyclic Skeleton 40



prepared. The synthesis of **33**, which parallels the above route used to prepare **25**, is shown in Scheme 6. Similarly, treatment of **33** with $TiCl_4$ in CH_2Cl_2 at −15 °C afforded another rearrangement product **34** in the form of a single diastereoisomer.

This result might rule out the possibility that the metal−π interaction of the titanium alkoxide with the alkynyl moiety was responsible for the stereochemical outcome of the Schmidt reaction (**25**→**24**). Presumably, the unfavored steric hindrance between the 2-methylenebutyl and alkynyl moieties (or ethyl moieties) in the transition state (**36**) might result in the observed high stereoselectivity of the diastereotopic group selective intramolecular Schmidt reaction (Figure 2).

Apparently, the relative configuration of the rearrangement product **24** was still inconsistent with that of the designed bicyclic intermediate **6**. However, by comparing the two different approaches to the bicyclic core **24** (Schemes 3 and 5), we found that the first route to the bicyclic intermediates **24** and **6** (ca. 5:1) would need 12 steps in 16% overall yield, but the second process to the single diastereoisomer **24** would only need 6 steps in 26% overall yield. Furthermore, all of the procedures in Scheme 5 could be conveniently and rapidly performed and **24** could be easily obtained on a gram scale. Given that more manipulations and a large mass of bicyclic precursor would be required in the subsequent exploration of the synthesis, the second approach was chosen as the material supplying route to complete the total synthesis of **1e**. As depicted in Scheme 7, we therefore planned to slightly modify our strategy and take advantage of the aldehyde intermediate **37**, which would be formed in the final stages, to adjust the C-3 stereochemistry. Comparison of the two strategies, listed in Schemes 1 and 7, shows that the transformations of the bicyclic intermediates **6** or **24** into **1e** involve the same process, except for epimerization of **37** at C-3 in Scheme 7.

After drafting the new synthetic route to **1e** from the readily available **24**, we turned our attention to forge ring **C** in **1e** (Scheme 8). Ozonolysis of **24**, by bubbling ozone through the reaction mixture very slowly at −78 °C (approximately 11 h), proceeded in good yield to furnish diketone **41**. Slightly accelerating the rate of ozone bubbling resulted in reduction of

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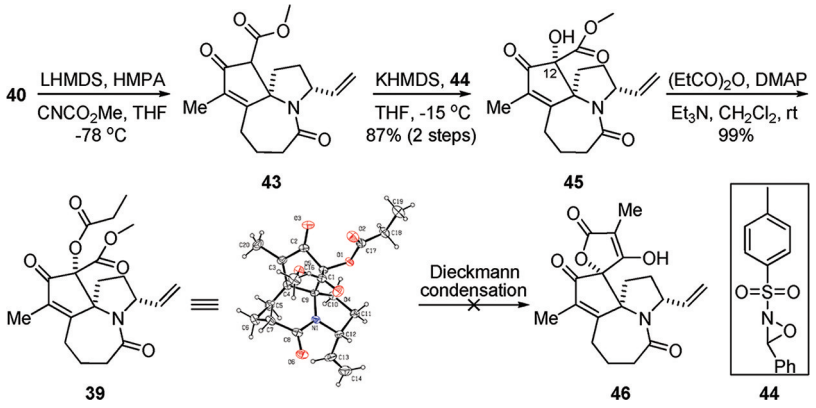
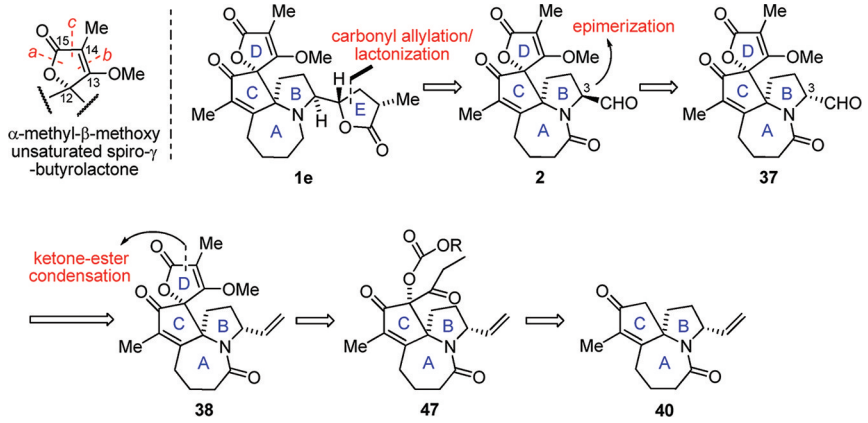
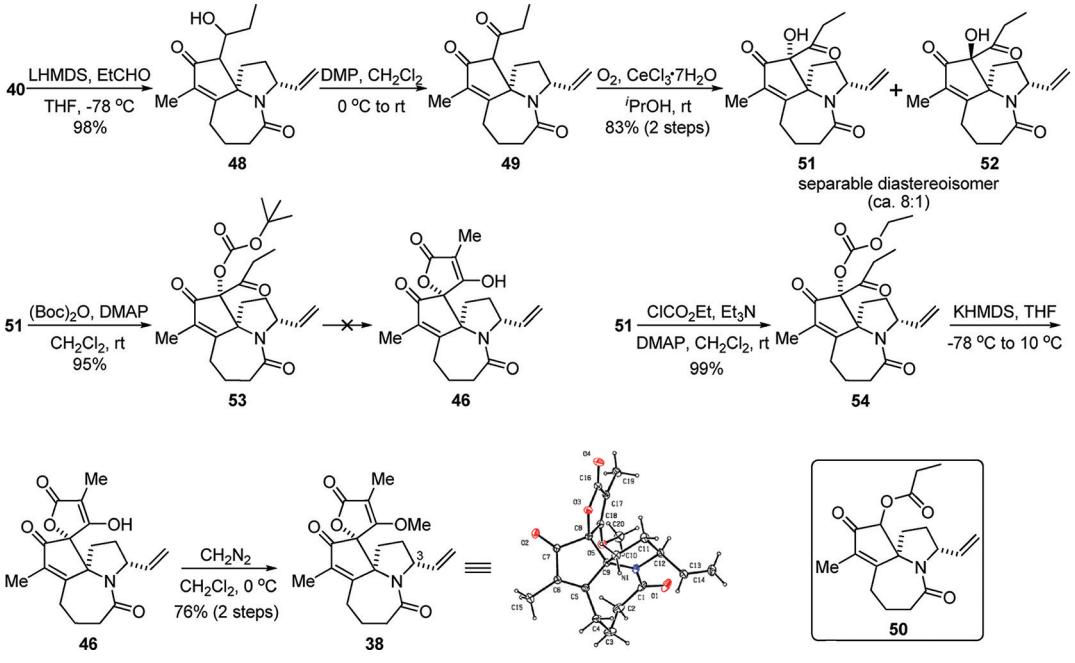
Scheme 9. Preparation and Examination of Dieckmann Condensation



Scheme 10. Fourth-Generation Retrosynthetic Analysis of (±)-Maistemonine



Scheme 11. Preparation and Construction of Ring D via Ketone-Ester Condensation



reaction time but a significantly decreased yield of **41**. At this point, we envisioned that some of the subsequent procedures to the tetracyclic intermediate **38** would be performed under basic conditions, and therefore, the terminal alkynyl moiety containing an active hydrogen atom might interfere with the procedures. As a consequence, reduction of **41** was carried out, using Lindlar Pd as catalyst,[44] to give alkene **42**. Then, the key aldol condensation for formation of ring **C** was examined. Surprisingly, exposure of **42** to ^{t}BuOK in ^{t}BuOH afforded a 5:1 mixture of enone **40** and its diastereoisomer, which could not

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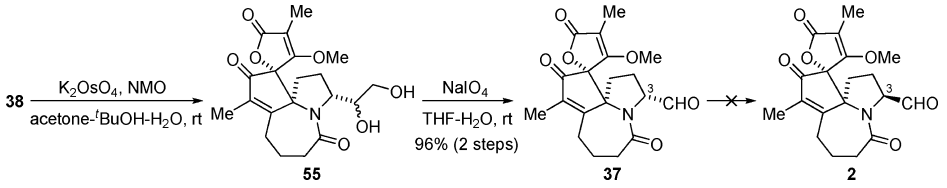
Scheme 12. Preparation and Examination of Epimerization of Aldehyde 37



be separated by column chromatography. In fact, the diastereoisomer of **40** was a desired intermediate, mentioned in Scheme 1 as compound **5**, whose relative configuration was consistent with that of **1e**. In order to form **5** as the sole product, a series of bases (^{t}BuOK, NaOEt, NaH, and LHMDS) in combination with various solvents (^{t}BuOH, benzene, EtOH, and THF) were carefully examined for the aldol condensation of **42**; however, similar results to the generation of **40** and **5** in an approximate ratio of 5:1 were obtained. It was assumed that the epimerization at C-2 of **40** via a retro-aza-Michael process[45] might account for the formation of **5** in the aldol condensation. During this study, we found that treatment of **42** with K_2CO_3 in MeOH produced **40** without formation of its diastereoisomer **5**, and the structure of **40** was confirmed by X-ray analysis.[38]

With tricycle **40** in hand, we commenced our investigation of the construction of ring **D** (Scheme 9). Reaction of the lithium enolate of **40** with Mander's reagent[46] in THF at −78 °C provided *β*-ketoester **43**. The introduction of oxa-quaternary center C-12 was accomplished by direct addition of Davis' reagent **44**[47] to the potassium enolate of **43** in THF at −15 °C, affording tertiary alcohol **45** as a single compound in 87% yield over two steps. The supposed Dieckmann condensation precursor **39** was obtained by treatment of **45** with propionic anhydride/DMAP/Et_3N in nearly quantitative yield, and its stereochemistry was verified by X-ray crystallography.[38] Then, the key Dieckmann condensation for formation of ring **D** was examined. Unfortunately, all attempts (^{t}BuOK/18-crown-6/benzene, ^{t}BuOK/DMF, ^{t}BuOK/^{t}BuOH, ^{t}BuOK/THF, LDA/THF, LHMDS/THF, and NaH/THF, etc.) failed to furnish the desired tetracycle **46** and resulted in no reaction or substrate decomposition. After extensive examinations without any success, we had to give up the Dieckmann condensation and explore an alternative method for building ring **D**.

The *α*-methyl-*β*-methoxy unsaturated spiro-*γ*-butyrolactone (ring **D**) is a common structural feature of *Stemona* alkaloids **1a**−**1g**. As depicted in Scheme 10, previous studies showed that ring **D** could be constructed by ultimate formation of the C15−O bond (path a)[22] or the C13−C14 bond (path b).[23] However, to our knowledge, the ultimate formation of the C14−C15 bond (path c) to build the spiro-*γ*-butyrolactone has not been reported. Therefore, we would like to design a new protocol to access the spirolactone **D** (path c) via an intramolecular ketone-ester condensation.[48] Accordingly, tricycle **40** was still projected as a key precursor to tetracycle **38**, and the final stages of the synthesis would not need to be changed (Scheme 10).

According to the aforementioned idea, we started to explore the establishment of spirolactone **D** over again, as described in Scheme 11. Aldol reaction of **40** was carried out by treatment of propanal with the lithium enolate of **40** in THF at −78 °C, affording *β*-hydroxy ketone **48** as a single diastereoisomer in 98% yield. Considering that the hydroxyl in **48** would be oxidized to form a ketone, we did not identify the relative configuration of the newly formed stereocenter. Then, oxidation of **48** to *β*-diketone **49** was achieved using the Dess−Martin periodinane.[49] To install the oxa-quaternary center (C-12), the potassium enolate of **49** was initially treated with Davis' reagent, which was used to prepare **45**, providing an unexpected rearrangement product **50**.[50] The successful introduction of hydroxyl group was conducted by bubbling O_2 to **49** with a catalytic amount of $CeCl_3{\cdot}7H_2O$ in ^{i}PrOH at room temperature,[51,52] furnishing an 8:1 mixture of separable diastereoisomeric alcohols **51** and **52**. Reaction of the major isomer **51** with di-*tert*-butyl dicarbonate and DMAP in CH_2Cl_2 afforded carbonate **53** in 95% yield.

Then, the key intramolecular ketone-ester condensation was attempted. To our disappointment, the ring-closure product **46** was not obtained once again by treatment of **53** with a series of basic systems such as LDA/THF, LHMDS/THF, NaHMDS/THF, KHMDS/THF, ^{t}BuOK/18-crown-6/benzene, and ^{t}BuOK/^{t}BuOH. On the basis of molecular model studies, we reasoned that the bulky *tert*-butoxy group might retard the nucleophilic attack of the enolate anion on the carbonyl carbon. Thus, replacement of the bulky *tert*-butoxy group in **53** by a less sterically hindered group such as an ethoxy group might enable the ketone-ester condensation to proceed. Exposure of **51** to Et_3N, DMAP, and ethyl chloroformate in CH_2Cl_2 at room temperature generated carbonate **54** in nearly quantitative yield (Scheme 11). Fortunately, the designed ketone-ester condensation for accessing spirolactone **D** was achieved by treatment of **54** with KHMDS in THF at −78 to 10 °C, giving tetracycle **46**, which was labile on column chromatography. It should be noted that treatment of **54** with other bases (LDA, LHMDS, NaHMDS, and ^{t}BuOK) resulted in substrate decomposition and no observation of the ring-closure product **46**. *O*-Methylation of the crude product **46** with Me_2SO_4 in CH_2Cl_2 afforded **38** in low yield (20%, 2 steps). An acceptable result was obtained when the methylation reagent was changed to CH_2N_2: 76% yield over two steps. Furthermore, the structure of **38** was confirmed by X-ray analysis.[38]

After the tetracyclic skeleton had been set up, adjustment of the C-3 stereochemistry was envisaged to generate the correct relative configurations in line with **1e**. As shown in Scheme 12, oxidation of **38** with K_2OsO_4/NMO followed by treatment of the resulting crude diol **55** with $NaIO_4$, affording aldehyde **37** in 96% yield. Then, the epimerization of aldehyde **37** at C-3 was investigated. At the outset, we did not anticipate that this task would be problematic, and two approaches for this purpose were explored. Initially, we hoped to carry out the epimerization by subjecting **37** to a catalytic amount of DBU;[53,54] however, no C-3 epimer was observed. Subsequently, a strategy involving enolization and protonation from the *α*-face was attempted.[55] Examinations of a variety of bases (LDA, LHMDS, NaHMDS, KHMDS, and ^{t}BuOK, etc.) and proton sources (H_2O, phenol, and 2,6-di-*tert*-butyl-4-methylphenol) only resulted in substrate recovery. At this point, we noticed that a report by Boger and co-workers describing a

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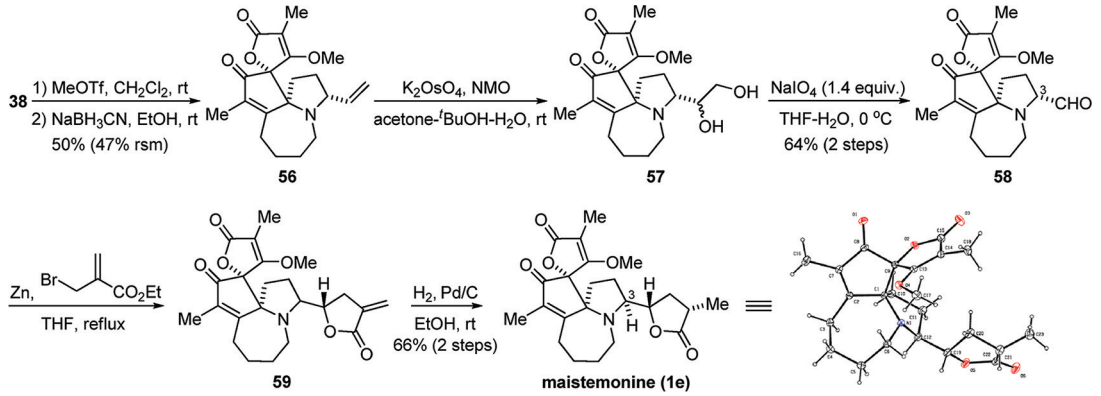
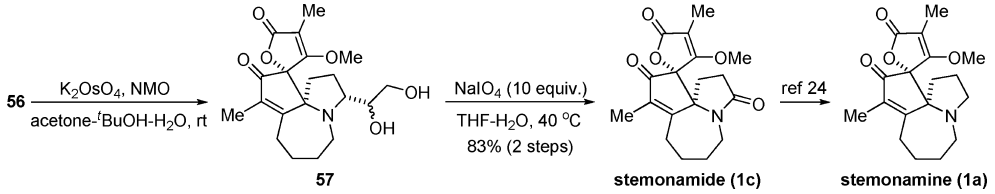
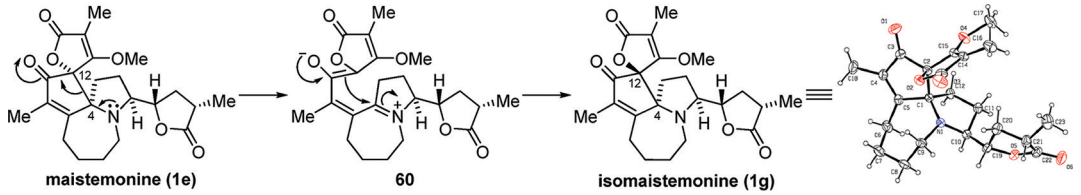
Scheme 13. Completion of Total Synthesis of (±)-Maistemonine (1e)



Scheme 14. Synthesis of (±)-Stemonamide (1c)



Scheme 15. Conversion of (±)-Maistemonine (1e) into (±)-Isomaistemonine (1g) via a Proposed Retro-Mannich and Mannich Processes



rapid epimerization of an unstable α-aminoaldehyde.[56] This report gave us an enlightenment that the neighboring lactam carbonyl in **37** might retard the epimerization at C-3 as a result of unfavored steric hindrance effect or electronic effect. Therefore, we decided to modify our synthetic plan once more and to perform reduction of the lactam carbonyl in advance.

In fact, selective reduction of the lactam carbonyl without touching the double bond and other carbonyls in **38** was proved to be a troublesome task. Initial attempt to reduce the amide group in **38** with $BH_3{\cdot}Me_2S$[57] gave a complex mixture of products. Then, a series of featured reduction reagents including 9-BBN,[58] Tf_2O/Hantzsch ester,[59] $RhH(CO)(PPh_3)_3/Ph_2SiH_2$,[60] and $Et_3OBF_4/NaBH_4$/2,6-di-*tert*-butylpyridine[61] were examined but resulted in no reaction. Treatment of **38** with Lawesson's reagent or P_4S_{10} in refluxing toluene[62] afforded a thioamide in 11% yield, which was subjected to Raney Ni[63] in EtOH at room temperature to generate an undesired terminal double bond saturated amine. During this study, we noticed that treatment of the tertiary amide with methyl trifluoromethanesulfonate could afford an alkoxy imminium salt,[64] which might be reduced by $NaBH_3CN$ to furnish the corresponding tertiary amine. Then, a one-pot protocol ($MeOTf/CH_2Cl_2$, then $NaBH_3CN$/EtOH) to selectively reduce the lactam was attempted, and fortunately, the desired amine **56** was obtained in 50% yield (47% of recovered starting material, Scheme 13). Oxidation of **56** with K_2OsO_4/NMO in a mixed solvent provided diol **57** as a crude product, which was converted to aldehyde **58** using 1.4 equiv of $NaIO_4$ at 0 °C in 64% yield.

Noteworthy, a slow epimerization of α-aminoaldehyde **58** at room temperature was observed. This phenomenon was similar to Boger's observation mentioned above. At this juncture, we conceived that epimerization of **58** at C-3 and construction of ring **E** via carbonyl allylation/lactonization might be carried out through a one-pot process. With this idea, direct addition of ethyl 2-(bromomethyl)acrylate[65] in THF to Zn and **58** in refluxing THF afforded **59**, which was unstable on column chromatography. Subsequently, hydrogenation of the *exo*-double bond in the nonpurified adduct **59**, using palladium on carbon as catalyst, generated maistemonine (**1e**) stereoselectively. Its NMR spectra were in all aspects identical to the spectra of the natural product. The relative configuration of **1e** was unambiguously established, for the first time, by X-ray analysis.[38]

During the preparation of **58**, a byproduct was obtained in 15% yield, and its spectroscopic data (^1H NMR and ^{13}C NMR) exactly matched with the authentic data of stemonamide (**1c**).[5] Although appropriate experiments were not performed to verify the mechanism, it is likely that stemonamide (**1c**) was an oxidation product of **58**. Indeed, stemonamide (**1c**) was obtained in 83% yield (2 steps) by increasing the amount of $NaIO_4$ (10 equiv), elevating the reaction temperature (40 °C) and prolonging the reaction time (Scheme 14). Thus, the divergent total synthesis of stemonamide (**1c**) was accomplished from a same synthetic intermediate **56** by varying the

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reaction conditions. Additionally, stemonamide (**1c**) could be converted into stemonamine (**1a**) by reduction of the lactam carbonyl group in **1c**.[24]

In particular, we observed that an NMR sample of (±)-maistemonine (**1e**) in $CDCl_3$ was smoothly converted into (±)-isomaistemonine (**1g**) at room temperature. This process could not be accelerated by heat, and the ratio of **1e** and **1g** approximately remained 1:1. It was assumed that the epimerization of (±)-maistemonine (**1e**) at the stereogenic center C-12 via a retro-Mannich and Mannich processes might account for the generation of (±)-isomaistemonine (**1g**) (Scheme 15).[24] The ^{1}H NMR and ^{13}C NMR spectra of (±)-isomaistemonine (**1g**) were in agreement with that of the natural product provided by Ye's group.[7,66−69] However, there have been some reports of the isolation of (−)-isomaistemonine, which gave different relative configurations at C-4 and C-12.[70,71] Finally, the synthetic (±)-isomaistemonine (**1g**) was crystallized, and for the first time, an X-ray crystal structure was obtained which fully confirmed the structural assignment.[38]

CONCLUSION

We have achieved the total synthesis of (±)-maistemonine (**1e**), (±)-stemonamide (**1c**), and (±)-isomaistemonine (**1g**). Two approaches were developed to construct the basic pyrrolo[1,2-*a*]azepine core of the *Stemona* alkaloids. Initially, we investigated the feasibility of the tandem semipinacol/Schmidt rearrangement of a secondary azide **21** and utilized the cascade protocol to build the bicyclic subunit. However, the lengthy preparation course of substrate **21** (12 steps) prompted us to explore a more efficient route to the bicycle **24**, featuring a highly stereoselectively desymmetrizing intramolecular Schmidt reaction. A subsequent strategy based on Dieckmann condensation for construction of the spiro-γ-butyrolactone **D** was unsuccessful. Therefore, we designed and developed a new method to establish the spiro-lactone via an intramolecular ketone-ester condensation. To selectively reduce the lactam carbonyl without touching double bond and other carbonyls in **38**, a variety of reduction procedures were attempted, and MeOTf/$NaBH_3CN$ was proved to be a very effective approach. In the final stage of the synthesis of (±)-maistemonine (**1e**), a one-pot protocol involving the epimerization at C-3 and carbonyl allylation/lactonization was successfully performed to stereoselectively install the vicinal butyrolactone moiety. Moreover, (±)-stemonamide (**1c**) was synthesized from intermediate **56** using a divergent approach and (±)-isomaistemonine (**1g**) was obtained via the epimerization of **1e** at C-12. The structures of the synthetic (±)-maistemonine (**1e**) and (±)-isomaistemonine (**1g**) were unambiguously confirmed, for the first time, by X-ray crystallographic analysis. Finally, it is noteworthy that the synthetic strategies of the total synthesis of **1e**, **1c**, and **1g** from cyclohexane-1,3-dione **26** are step-economic processes, and no extra protecting-group manipulations were required.

EXPERIMENTAL SECTION

General Experimental Details. All reactions requiring anhydrous conditions were carried out under an argon atmosphere using oven-dried glassware (120 °C), which was cooled under argon. Anhydrous tetrahydrofuran and benzene were distilled from sodium metal under argon. Anhydrous dichloromethane was dried by distillation from CaH_2 immediately prior to use under argon. Anhydrous *N*,*N*-dimethylformamide was dried by distillation from $MgSO_4$ under reduced pressure. Anhydrous methanol, ethanol, and isopropyl alcohol were distilled from activated magnesium under argon. All other solvents and reagents were used as received. Analytical TLC was carried out on precoated plates (silica gel 60, F254). Column chromatography was performed with silica gel (200−300 mesh). ^{1}H NMR spectra were recorded at 400 or 600 MHz. ^{13}C NMR spectra were recorded at 100 or 150 MHz. Chemical shifts are recorded in parts per million, and coupling constants *J* are recorded in hertz. IR spectra were recorded on a Fourier transform infrared spectrometer. The MS data were obtained with EI (70 eV). HRMS data were determined on an APEXII 47e FT-ICR spectrometer. Melting point was measured on a melting point apparatus and was uncorrected.

Ester (8). To a solution of cyclohex-2-enone (1.70 mL, 17.500 mmol) in DMF (32 mL) was added DBU (523 μL, 3.500 mmol) and ethyl acrylate (2.48 mL, 22.739 mmol). The reaction tube was sealed and heated at 185 °C for 24 h. After cooling to room temperature, the reaction mixture was poured into ice water (30 mL), and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with water (2 × 10 mL) and brine (10 mL), then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (5% EtOAc/petroleum ether to 10% EtOAc/petroleum ether) to give ester **8** (2.57 g, 75%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72−6.70 (t, *J* = 4.0 Hz, 1H), 4.06−4.01 (dd, *J* = 14.4, 7.2 Hz, 2H), 2.44−2.41 (m, 2H), 2.37−2.32 (m, 4H), 2.30−2.26 (dd, *J* = 10.4, 5.6 Hz, 2H), 1.93−1.87 (ddd, *J* = 12.8, 6.4, 6.4 Hz, 2H), 1.18−1.14 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 172.9, 146.1, 138.0, 60.0, 38.3, 33.1, 25.9, 25.3, 22.9, 14.1.

1,3-Dioxolane (13). A solution of ester **8** (3.94 g, 20.102 mmol), ethylene glycol (4.40 mL, 80.194 mmol), and *p*-TsOH·H_2O (173.0 mg, 1.005 mmol) in benzene (80 mL) was refluxed for 24 h in a Dean−Stark apparatus. The reaction mixture was cooled, poured into saturated aqueous $NaHCO_3$ solution (10 mL), the aqueous layer extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with water (2 × 10 mL) and brine (10 mL), then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (2% EtOAc/petroleum ether to 5% EtOAc/petroleum ether) to give 1,3-dioxolane **13** (4.44 g, 92%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71−5.69 (t, *J* = 4.0 Hz, 1H), 4.14−4.08 (dd, *J* = 14.4, 7.2 Hz, 2H), 4.00−3.97 (m, 4H), 2.48−2.44 (m, 2H), 2.36−2.32 (m, 2H), 2.01−2.00 (t, *J* = 2.0 Hz, 2H), 1.74−1.67 (m, 4H), 1.25−1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 136.6, 129.4, 107.6, 64.9, 60.1, 33.9, 33.7, 25.2, 25.0, 20.6, 14.2; HRMS (ESI) calcd for $C_{13}H_{21}O_4$ $(M + H)^+$: 241.1434, found 241.1428.

Aldehyde (14). To a solution of 1,3-dioxolane **13** (809.5 mg, 3.373 mmol) in hexane (16 mL) was added DIBAL-H (1.0 M in cyclohexane, 3.71 mL, 3.710 mmol) dropwise under argon at −78 °C. The resultant mixture was stirred at −78 °C for 10 min, then treated with water (1 mL), and warmed to room temperature. The mixture was filtered through a plug of Celite and washed with CH_2Cl_2 (3 × 10 mL). The filtrate was washed with water (3 × 10 mL) and brine (10 mL), then dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (5% EtOAc/petroleum ether to 15% EtOAc/petroleum ether) to give aldehyde **14** (595.0 mg, 90%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74−9.73 (t, *J* = 2.0 Hz, 1H), 5.70−5.69 (m, 1H), 3.98 (s, 4H), 2.60−2.56 (m, 2H), 2.38−2.34 (m, 2H), 2.02−1.99 (m, 2H), 1.74−1.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 136.3, 129.8, 107.5, 64.8, 43.1, 33.6, 25.2, 22.1, 20.5; HRMS (ESI) calcd for $C_{11}H_{17}O_3$ $(M + H)^+$: 197.1172, found 197.1165.

Alcohol (15). To a solution of aldehyde **14** (662.1 mg, 3.378 mmol) in anhydrous THF (10 mL) was added ethynylmagnesium bromide (0.5 M in THF, 8.11 mL, 4.055 mmol) dropwise under argon at −78 °C. The resultant mixture was stirred at 0 °C for 1 h, then treated with water (1 mL), and warmed to room temperature. The mixture was diluted with Et_2O (10 mL) and saturated aqueous NH_4Cl (5 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL), then the combined organic extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (10% EtOAc/

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petroleum ether to 20% EtOAc/petroleum ether) to give alcohol **15** (622.4 mg, 83%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80−5.78 (t, J = 4.0 Hz, 1H), 4.41−4.39 (t, J = 5.6 Hz, 1H), 4.05−3.97 (m, 4H), 2.57 (s, 1H), 2.45−2.44 (d, J = 2.4 Hz, 1H), 2.24−2.16 (m, 2H), 2.04−2.03 (t, J = 2.0 Hz, 2H), 1.92−1.87 (dd, J = 14.4, 7.2 Hz, 2H), 1.75−1.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 130.3, 107.9, 85.1, 72.6, 64.9, 64.8, 61.9, 37.2, 33.7, 25,3, 24.7, 20.6; HRMS (ESI) calcd for $C_{13}H_{18}O_3Na$ $(M + Na)^+$: 245.1148, found 245.1157.

Enone (18). A solution of alcohol **15** (486.6 mg, 2.192 mmol) in anhydrous CH_2Cl_2 (5 mL) under argon was treated with Et_3N (762 μL, 5.482 mmol) and methanesulfonyl chloride (339 μL, 4.380 mmol) at 0 °C. The reaction mixture was stirred for 30 min and then quenched with water (1 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), then the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give the crude mesylate **16** as a yellow oil.

The crude mesylate **16** was dissolved in anhydrous DMF (4 mL) under argon, and then NaN_3 (427.5 mg, 6.577 mmol) was added. After being stirred at 40 °C for 4 h, the solution was allowed to cool on an ice−water bath. Then, the reaction mixture was diluted with Et_2O (10 mL) and quenched with water (5 mL). The aqueous phase was extracted with Et_2O (3 × 5 mL), and the combined organic phase was washed with water (2 × 5 mL) and brine (5 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated to give the crude azide **16** as a yellow oil.

To a solution of azide **16** in acetone (5 mL) was added p-TsOH·H_2O (75.5 mg, 0.438 mmol) at room temperature. The resultant mixture was stirred at room temperature for 30 min and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (2% EtOAc/petroleum ether to 5% EtOAc/petroleum ether) to give enone **18** (347.0 mg, 78%, 3 steps) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78−6.76 (t, J = 4.0 Hz, 1H), 4.06−4.02 (ddd, J = 6.8, 6.8, 2.0 Hz, 1H), 2.58−2.57 (d, J = 2.4 Hz, 1H), 2.44−2.40 (t, J = 6.8 Hz, 2H), 2.38−2.32 (m, 4H), 2.01−1.95 (m, 2H), 1.85−1.79 (dd, J = 14.4, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 146.2, 138.2, 79.2, 75.2, 52.3, 38.5, 33.9, 26,2, 26.1, 23.0; HRMS (ESI) calcd for $C_{11}H_{14}N_3O$ $(M + H)^+$: 204.1131, found 204.1138.

Alcohol (19). To dry magnesium powder (403.7 mg, 16.821 mmol) covered with anhydrous THF (5 mL) under argon was added $HgCl_2$ (1 mg), and a few drops of freshly distilled 2-(bromomethyl)-but-1-ene (501.3 mg, 3.364 mmol) in THF (5 mL) were added while heating the mixture to reflux. When the formation of the Grignard reagent had started, the rest of 2-(bromomethyl)but-1-ene in THF was added at room temperature and the stirring was continued for 1 h. Then, the resultant mixture was used for the following Grignard addition.

To a solution of enone **18** (455.3 mg, 2.243 mmol) in anhydrous THF (5 mL) was added the above prepared (2-methylenebutyl)-magnesium bromide dropwise under argon at −78 °C. The resultant mixture was stirred at −78 °C for 30 min, then treated with water (1 mL), and warmed to room temperature. The mixture was diluted with Et_2O (10 mL) and water (5 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL), then the combined organic extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (2% EtOAc/petroleum ether to 5% EtOAc/petroleum ether) to give diastereomers **19** (489.7 mg, 80%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51−5.50 (t, J = 4.0 Hz, 1H), 4.92−4.91 (d, J = 1.6 Hz, 1H), 4.80 (s, 1H), 4.14−4.10 (t, J = 6.4 Hz, 1H), 2.58−2.57 (t, J = 2.0 Hz, 1H), 2.47−2.44 (m, 3H), 2.21−1.83 (m, 7H), 1.82−1.71 (m, 2H), 1.68−1.57 (m, 3H), 1.06−1.02 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 140.5, 125.1, 125.0, 112.2, 79.5, 75.0, 74.9, 72.2, 52.6, 44.9, 36.1, 36.0, 34.7, 34.6, 30.6, 26.6, 25.5, 19.3, 12.5; HRMS (ESI) calcd for $C_{16}H_{24}N_3O$ $(M + H)^+$: 274.1914, found 274.1916.

Epoxide (20). A solution of alcohol **19** (441.9 mg, 1.619 mmol) in anhydrous benzene (5 mL) under argon was treated with ^{t}BuOOH (5.5 M in decane, 353 μL, 1.942 mmol) and $VO(acac)_2$ (23.2 mg, 0.087 mmol) at room temperature. The reaction mixture was stirred for 30 min and then treated with water (1 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), then the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (2% EtOAc/petroleum ether to 5% EtOAc/petroleum ether) to give diastereomers **20** (402.5 mg, 86%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90−4.89 (d, J = 1.2 Hz, 1H), 4.77 (s, 1H), 4.15−4.11 (ddd, J = 6.4, 6.4, 2.0 Hz, 1H), 3.20−3.19 (t, J = 1.6 Hz, 1H), 2.58−2.49 (m, 2H), 2.30−2.11 (m, 4H), 1.92−1.73 (m, 4H), 1.72−1.66 (m, 2H), 1.56−1.51 (m, 1H), 1.47−1.25 (m, 3H), 1.07−1.03 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 112.2, 79.2, 79.1, 75.2, 75.1, 73.9, 64.6, 61.5, 61.4, 52.8, 42.1, 42.0, 32.4, 30.1, 29.9, 26.0, 25.9, 23.1, 17.7, 12.4; HRMS (ESI) calcd for $C_{16}H_{24}N_3O_2$ $(M + H)^+$: 290.1863, found 290.1858.

Trimethylsiloxy (21). A solution of epoxide **20** (174.0 mg, 0.602 mmol) in anhydrous DMF (2 mL) under argon was treated with imidazole (246.0 mg, 3.613 mmol) and chlorotrimethylsilane (228 μL, 1.805 mmol) at room temperature. The reaction mixture was stirred for 24 h and then was diluted with Et_2O (5 mL) and water (1 mL). The aqueous phase was extracted with Et_2O (3 × 5 mL), and the combined organic phase was washed with water (2 × 5 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified via silica gel chromatography (petroleum ether to 1% EtOAc/petroleum ether) to give diastereomers **21** (212.8 mg, 98%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87−4.86 (d, J = 1.6 Hz, 1H), 4.73 (s, 1H), 4.13−4.07 (m, 1H), 3.05−3.04 (d, J = 2.0 Hz, 1H), 2.58−2.57 (t, J = 2.0 Hz, 1H), 2.48−2.43 (d, J = 13.6 Hz, 1H), 2.27−2.12 (m, 4H), 1.85−1.74 (m, 4H), 1.70−1.59 (m, 1H), 1.58−1.52 (m, 2H), 1.46−1.35 (m, 2H), 1.06−1.02 (t, J = 7.2 Hz, 3H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 112.1, 79.2, 78.8, 75.1, 75.0, 64.2, 58.9, 58.8, 52.9, 52.8, 42.3, 29.9, 29.7, 29.5, 24.4, 24.2, 21.9, 19.0, 12.6, 2.6,; HRMS (ESI) calcd for $C_{19}H_{31}N_3O_2SiNa$ $(M + Na)^+$: 384.2078, found 384.2074.

Amides (22) and (23). To a solution of trimethylsiloxy **21** (116.0 mg, 0.321 mmol) in anhydrous CH_2Cl_2 (3 mL) at −78 °C under argon was added $TiCl_4$ (1.0 M in CH_2Cl_2, 707 μL, 0.707 mmol). The resultant mixture was stirred at −78 °C for 15 min. After being warmed slowly to 10 °C for additional times (about 3 h), it was quenched with water (1 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), then the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (50% EtOAc/petroleum ether to 75% EtOAc/petroleum ether) to give amide **22** (49.6 mg, 59%) and amide **23** (9.9 mg, 12%) as white crystalline solid, respectively. Amide **22**: mp 115−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94−4.93 (d, J = 1.2 Hz, 1H), 4.89−4.87 (d, J = 8.0 Hz, 1H), 4.84 (s, 1H), 3.74 (s, 1H), 2.87−2.79 (m, 2H), 2.75−2.62 (m, 2H), 2.37−2.36 (d, J = 2.0 Hz, 1H), 2.21−2.17 (d, J = 14.0 Hz, 1H), 2.05−1.79 (m, 8H), 1.72−1.64 (m, 1H), 1.05−1.01 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 146,9, 113.9, 84.4, 71.0, 70.7, 69.3, 51.2, 42.2, 37.4, 34.0, 30.2, 29.7, 28.5, 16.3, 12.6; HRMS (ESI) calcd for $C_{16}H_{24}NO_2$ $(M + H)^+$: 262.1801, found 262.1805. Amide **23**: mp 127−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99−4.98 (d, J = 1.2 Hz, 1H), 4.91−4.89 (m, 2H), 3.92 (s, 1H), 2.77−2.62 (m, 4H), 2.58−2.51 (m, 1H), 2.25−2.03 (m, 6H), 1.89−1.78 (m, 3H), 1.71−1.66 (m, 1H), 1.07−1.04 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 146.5, 114.0, 84.1, 73.2, 70.2, 69.0, 51.2, 44.0, 37.5, 37.4, 31.5, 30.4, 30.2, 17.0, 12.5; HRMS (ESI) calcd for $C_{16}H_{24}NO_2$ $(M + H)^+$: 262.1801, found 262.1807.

Ketone (24). To a solution of pyridinium chlorochromate (PCC) (40.0 mg, 0.185 mmol) in anhydrous CH_2Cl_2 (3 mL) at room temperature under argon were added silica (40.0 mg) and NaOAc (15.1 mg, 0.184 mmol). After 10 min of stirring at room temperature, a solution of amide **22** (16.0 mg, 0.061 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise. The resultant mixture was stirred for 12 h at room temperature under argon, then filtered through a plug of Celite and washed with CH_2Cl_2 (3 × 10 mL). The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (10% EtOAc/petroleum ether to 30% EtOAc/petroleum ether) to give ketone **24** (13.8 mg, 87%) as a white

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amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92−4.91 (d, J = 1.6 Hz, 1H), 4.86 (s, 1H), 4.81−4.80 (d, J = 6.4 Hz, 1H), 3.33−3.25 (m, 1H), 2.72−2.53 (m, 3H), 2.56−2.41 (m, 1H), 2.34−2.16 (m, 5H), 2.08−1.92 (m, 5H), 1.01−0.98 (t, J = 3.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 171.1, 146.2, 114.6, 82.7, 74.5, 71.0, 50.0, 40.5, 35.9, 34.8, 33.0, 29.6, 29.1, 22.6, 12.2; IR (neat) 3254, 1713, 1661, 907 cm^{-1}; MS (EI) m/z 259, 230, 217, 202, 190, 162, 136; HRMS (ESI) calcd for $C_{16}H_{22}NO_2$ $(M + H)^+$: 260.1645, found 260.1649.

Ketone (6). To a solution of pyridinium chlorochromate (PCC) (17.4 mg, 0.081 mmol) in anhydrous CH_2Cl_2 (2 mL) at room temperature under argon were added silica (17.4 mg) and NaOAc (6.6 mg, 0.080 mmol). After 10 min of stirring at room temperature, a solution of amide **23** (7.0 mg, 0.027 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise. The resultant mixture was stirred for 12 h at room temperature under argon, then filtered through a plug of Celite and washed with CH_2Cl_2 (3 × 10 mL). The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (20% EtOAc/petroleum ether to 50% EtOAc/petroleum ether) to give ketone **6** (5.6 mg, 80%) as a white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (s, 1H), 4.95−4.94 (d, J = 1.6 Hz, 1H), 4.93−4.88 (ddd, J = 4.4, 4.4, 2.0 Hz, 1H), 2.97−2.93 (d, J = 14.0 Hz, 1H), 2.85−2.77 (ddd, J = 11.2, 11.2, 8.4 Hz, 1H), 2.65−2.57 (ddd, J = 13.6, 13.6, 7.6 Hz, 1H), 2.53−2.49 (d, J = 13.6 Hz, 1H), 2.41−2.35 (m, 4H), 2.27−2.06 (m, 4H), 2.04−1.93 (m, 3H), 1.04−1.00 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 171.2, 146.3, 115.7, 83.3, 75.6, 71.5, 49.7, 40.1, 37.8, 35.6, 33.3, 30.1, 29.9, 22.8, 12.5; IR (neat) 2964, 1722, 1392, 960 cm^{-1}; MS (EI) m/z 259, 234, 216, 208, 190, 174, 146, 91; HRMS (ESI) calcd for $C_{16}H_{22}NO_2$ $(M + H)^+$: 260.1645, found 260.1641.

Keto-aldehyde (28). A solution of KOH (3.47 g, 61.964 mmol) in water (26 mL) was treated with cyclohexane-1,3-dione (5.78 g, 51.607 mmol), copper powder (0.33 g, 5.156 mmol), and 2-(bromomethyl)but-1-ene (9.23 g, 61.946 mmol) at room temperature. The reaction mixture was stirred for 24 h and then cooled to 0 °C. NaOH (2.48 g, 62.000 mmol) was added portionwise to the mixture, and it was stirred at 0 °C for 2 h. The resultant mixture was filtered, and the filtrate was extracted with Et_2O (2 × 10 mL). The water phase was neutralized to pH = 1 using concentrated hydrochloric acid at 0 °C, then filtered under reduced pressure to give the crude *C*-alkylation product **27** as a light yellow amorphous solid.

To a solution of the crude **27** in THF (25 mL) and H_2O (25 mL) was added acrolein (8.62 mL, 129.008 mmol) at room temperature. After stirring for 24 h at room temperature, the mixture was diluted with Et_2O (50 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL), then the combined organic extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (10% EtOAc/petroleum ether to 30% EtOAc/petroleum ether) to give keto-aldehyde **28** (10.34 g, 85%, 2 steps) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 4.83−4.82 (d, J = 0.8 Hz, 1H), 4.55 (s, 1H), 2.64−2.60 (m, 4H), 2.51 (s, 1H), 2.29−2.26 (t, J = 7.2 Hz, 2H), 2.10−1.98 (m, 3H), 1.92−1.85 (m, 3H), 0.97−0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.2, 200.8, 146.1, 113.1, 67.6, 43.6, 39.4, 39.3, 30.0, 27.4, 16.8, 12.2; MS (EI) m/z 236, 218, 207, 192, 55, 41; HRMS (ESI) calcd for $C_{14}H_{24}NO_3$ $(M+NH_4)^+$: 254.1751, found 254.1755.

Keto-mesylate (30). To a solution of keto-aldehyde **28** (5.03 g, 21.297 mmol) in anhydrous THF (140 mL) at −78 °C under argon was added ethynylmagnesium chloride (0.6 M in THF, 35.50 mL, 21.300 mmol). The mixture was stirred for 7.5 h at −78 °C and then quenched with water (5 mL). After warming up to room temperature, the reaction mixture was diluted with Et_2O (100 mL) and saturated aqueous NH_4Cl (50 mL). The aqueous phase was extracted with Et_2O (3 × 50 mL), then the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Chromatography (15% EtOAc/petroleum ether) afforded the crude hemiketal **29** as a white amorphous solid.

The crude hemiketal **29** was dissolved in pyridine (35 mL) at 40 °C under argon, and DMAP (350.0 mg, 2.869 mmol) and methanesulfonyl chloride (7.00 mL, 90.441 mmol) were added. After stirring for 30 min, the solution allowed to cool on an ice−water bath. The reaction was diluted with Et_2O (30 mL) and quenched with water (10 mL). The biphasic mixture was vigorously stirred for 30 min prior to separation of the layers. The organic phase was washed with water (2 × 20 mL) followed by back-extraction of the combined aqueous extracts with Et_2O (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to yield a yellow oil which was then purified via column chromatography (15% EtOAc/petroleum ether to 25% EtOAc/petroleum ether) to afford keto-mesylate **30** (3.62 g, 50%, 2 steps) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08−5.05 (dt, J = 6.4, 2.0 Hz, 1H), 4.82−4.81 (d, J = 1.2 Hz, 1H), 4.54 (s, 1H), 3.09 (s, 3H), 2.72−2.71 (d, J = 2.4 Hz, 1H), 2.62−2.59 (m, 4H), 2.51 (s, 2H), 2.04−1.89 (m, 3H), 1.88−1.84 (m, 3H), 1.69−1.63 (m, 2H), 0.97−0.93 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3, 210.2, 146.2, 113.0, 78.6, 77.3, 70.5, 67.7, 43.6, 39.6, 39.1, 31.0, 30.9, 30.0, 16.7, 12.2; IR (neat) 3269, 1691, 1360, 903 cm^{-1}; MS (EI) m/z 340, 311, 261, 245, 201, 173, 131; HRMS (ESI) calcd for $C_{17}H_{28}NO_5S$ $(M + NH_4)^+$: 358.1683, found 358.1676.

Azide (25). A solution of keto-mesylate **30** (406.6 mg, 1.196 mmol) in anhydrous DMF (4 mL) was treated with NaN_3 (233.2 mg, 3.588 mmol) at 40 °C under argon. After 1.5 h, the mixture was cooled to 0 °C and then diluted with Et_2O (10 mL). The resultant mixture was washed with water (2 × 10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated to yield a yellow oil which was purified via column chromatography (15% EtOAc/petroleum ether) to give the azide **25** (288.3 mg, 84%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82−4.81 (d, J = 1.6 Hz, 1H), 4.54−4.53 (d, J = 0.8 Hz, 1H), 4.02−3.98 (dt, J = 6.8, 2.4 Hz, 1H), 2.61−2.57 (m, 5H), 2.50 (s, 2H), 2.03−1.95 (m, 1H), 1.93−1.82 (m, 5H), 1.49−1.42 (m, 2H), 0.97−0.93 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4, 146.3, 112.9, 78.5, 75.4, 67.8, 52.5, 43.7, 39.7, 39.6, 32.3, 30.5, 30.0, 16.7, 12.2; IR (neat) 3268, 2104, 1693, 906 cm^{-1}; MS (EI) m/z 287, 258, 244, 216, 188, 136; HRMS (ESI) calcd for $C_{16}H_{25}N_4O_2$ $(M + NH_4)^+$: 305.1972, found 305.1969.

Amide (24). To a solution of the azide **25** (2.58 g, 8.974 mmol) in anhydrous CH_2Cl_2 (90 mL) at −15 °C under argon was added $TiCl_4$ (1.0 M in CH_2Cl_2, 10.83 mL, 10.830 mmol). The resultant mixture was stirred at −15 °C for 20 min, then it was quenched with water (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), then the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (20% EtOAc/petroleum ether to 35% EtOAc/petroleum ether) to give amide **24** (1.67 g, 72%) as a yellow amorphous solid.

Keto-mesylate (32). To a solution of keto-aldehyde **28** (500.0 mg, 2.119 mmol) in anhydrous THF (5 mL) at −78 °C under argon was added ethylmagnesium bromide (1.0 M in THF, 2.12 mL, 2.120 mmol). The mixture was stirred for 10 min at −78 °C and then quenched with water (1 mL). After warming up to room temperature, the reaction mixture was diluted with Et_2O (10 mL) and saturated aqueous NH_4Cl (5 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL), then the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Chromatography (10% EtOAc/petroleum ether to 20% EtOAc/petroleum ether) afforded the crude hemiketal **31** as a light yellow oil.

The crude hemiketal **31** was dissolved in pyridine (5 mL) at 40 °C under argon, and DMAP (30.0 mg, 0.246 mmol) and methanesulfonyl chloride (600 μL, 7.752 mmol) were added. After stirring for 30 min, the solution allowed to cool on an ice−water bath. The reaction was diluted with Et_2O (10 mL) and quenched with water (5 mL). The biphasic mixture was vigorously stirred for 30 min prior to separation of the layers. The organic phase was washed with water (2 × 5 mL) followed by back-extraction of the combined aqueous extracts with Et_2O (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to yield a yellow oil which was then purified via column chromatography (20% EtOAc/petroleum ether to 30% EtOAc/petroleum ether) to afford keto-mesylate **32** (378.9 mg, 52%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83−4.82 (d, J = 1.2 Hz, 1H), 4.59−4.53 (m, 2H), 3.01 (s, 3H), 2.62−2.59 (m, 4H),

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2.50 (s, 2H), 2.05−1.93 (m, 1H), 1.91−1.81 (m, 5H), 1.72−1.65 (m, 2H), 1.47−1.40 (m, 2H), 0.98−0.92 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8, 210.6, 146.3, 113.1, 84.1, 68.0, 44.1, 39.8, 38.7, 31.2, 30.0, 29.1, 27.0, 16.7, 12.2, 9.2; HRMS (ESI) calcd for $C_{17}H_{32}NO_5S$ $(M + NH_4)^+$: 362.1996, found 362.1990.

Azide (33). A solution of keto-mesylate **32** (105.0 mg, 0.305 mmol) in anhydrous DMF (1 mL) was treated with NaN_3 (59.5 mg, 0.915 mmol) at 40 °C under argon. After 1.5 h, the mixture was cooled to 0 °C and then diluted with Et_2O (5 mL). The resultant mixture was washed with water (2 × 5 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated to yield a yellow oil which was purified via column chromatography (5% EtOAc/petroleum ether to 10% EtOAc/petroleum ether) to give the azide **33** (81.8 mg, 92%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80−4.79 (d, J = 1.2 Hz, 1H), 4.52 (s, 1H), 3.11−3.05 (ddd, J = 16.8, 11.6, 5.2 Hz, 1H), 2.59−2.56 (t, J = 6.8 Hz, 4H), 2.49 (s, 2H), 2.01−1.83 (m, 5H), 1.79−1.72 (m, 1H), 1.53−1.45 (m, 2H), 1.28−1.17 (m, 2H), 0.96−0.90 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8, 210.7, 146.5, 112.6, 68.0, 64.2, 43.7, 39.8, 39.7, 33.4, 30.0, 29.2, 27.0, 16.6, 12.2, 10.2; HRMS (ESI) calcd for $C_{16}H_{29}N_4O_2$ $(M + NH_4)^+$: 309.2285, found 309.2280.

Amide (34). To a solution of the azide **33** (23.4 mg, 0.080 mmol) in anhydrous CH_2Cl_2 (1 mL) at −15 °C under argon was added $TiCl_4$ (1.0 M in CH_2Cl_2, 96 μL, 0.096 mmol). The resultant mixture was stirred at −15 °C for 20 min, then it was quenched with water (1 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), then the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (10% EtOAc/petroleum ether to 25% EtOAc/petroleum ether) to give amide **34** (16.7 mg, 79%) as a yellow amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92−4.91 (d, J = 1.2 Hz, 1H), 4.86 (s, 1H), 4.05−4.01 (t, J = 8.0 Hz, 1H), 3.09−3.01 (dd, J = 20.4, 10.8 Hz, 1H), 2.74−2.70 (d, J = 14.0 Hz, 1H), 2.64−2.55 (m, 2H), 2.42−2.31 (m, 2H), 2.24−2.06 (m, 2H), 2.03−1.88 (m, 6H), 1.70−1.60 (m, 1H), 1.22−1.15 (m, 1H), 1.04−1.00 (t, J = 7.6 Hz, 3H), 0.94−0.90 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.8, 171.2, 146.9, 114.5, 75.3, 61.9, 41.0, 35.5, 35.1, 34.3, 29.8, 25.5, 25.2, 22.4, 12.5, 11.2; HRMS (ESI) calcd for $C_{16}H_{26}NO_2$ $(M + H)^+$: 264.1958, found 264.1950.

Diketone (41). Amide **24** (201.0 mg, 0.776 mmol) was dissolved in CH_2Cl_2 (12 mL) at room temperature. The reaction mixture was cooled to −78 °C, after a brief oxygen purge (ca. 5 min), ozone was bubbled through the reaction mixture very slowly until the reaction was completed by tlc (approximately 11 h). After dimethylsulfide (5 mL) addition, the reaction was stirred at room temperature for 3 days. Concentration of the reaction mixture to give a yellow oil. Chromatography afforded diketone **41** (165.4 mg, 82%) as a sticky oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81−4.79 (d, J = 5.6 Hz, 1H), 3.27−3.19 (m, 1H), 2.92−2.77 (m, 2H), 2.72−2.62 (m, 1H), 2.54−2.38 (m, 4H), 2.36−2.17 (m, 5H), 2.14−2.00 (m, 2H), 1.08−1.05 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.4, 207.4, 170.3, 82.5, 74.6, 71.2, 49.7, 44.4, 38.8, 34.4, 33.5, 33.4, 29.4, 22.9, 7.6; IR (neat) 3302, 1712, 1661 cm^{-1}; MS (EI) m/z 261, 232, 204, 190, 176, 148, 108; HRMS (ESI) calcd for $C_{15}H_{20}NO_3$ $(M + H)^+$: 262.1438, found 262.1431.

Enone (40). To a solution of diketone **41** (421.0 mg, 1.613 mmol) in CH_2Cl_2 (10 mL) were added Lindlar catalyst (299.1 mg) and quinoline (38 μL, 0.322 mmol). The mixture was exposed to an atmosphere of H_2 at room temperature. After 1.5 h, the resulting mixture was filtered and concentrated to give the crude ene **42** as a yellow oil.

The crude ene **42** was dissolved in anhydrous MeOH (10 mL), followed by addition of K_2CO_3 (262.4 mg, 1.901 mmol). After stirring at room temperature for 1 h, the solution was diluted with $CHCl_3$ (20 mL) and water (10 mL). The aqueous phase was extracted with $CHCl_3$ (3 × 10 mL), then the combined organic extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (50% EtOAc/petroleum ether to 75% EtOAc/petroleum ether) to give enone **40** (367.5 mg, 93%, 2 steps) as a white crystalline solid: mp 152−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89−5.80 (ddd, J = 16.8, 10.4, 6.4 Hz, 1H), 5.23−5.15 (m, 2H), 4.63−4.59 (t, J = 6.8 Hz, 1H), 2.86−2.81 (dd, J = 8.0, 4.8 Hz, 1H), 2.67−2.58 (m, 2H), 2.48−2.41 (m, 1H), 2.32−2.10 (m, 5H), 1.93−1.83 (m, 2H), 1.76 (s, 3H), 1.50−1.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 172.3, 170.7, 137.4, 135.9, 115.4, 70.7, 60.0, 50.7, 38.6, 33.1, 29.1, 23.9, 22.3, 8.1; IR (neat) 1700, 1654, 1000 cm^{-1}; MS (EI) m/z 245, 230, 202, 178, 135, 91; HRMS (ESI) calcd for $C_{15}H_{20}NO_2$ $(M + H)^+$: 246.1489, found 246.1482.

Alcohol (45). To a solution of enone **40** (123.6 mg, 0.504 mmol) in anhydrous THF (5 mL) at −78 °C under argon was added LHMDS (1.0 M in THF, 757 μL, 0.757 mmol). After 30 min of stirring at −78 °C, $NCCO_2Me$ (68 μL, 0.857 mmol) was added and followed HMPA (132 μL, 0.759 mmol). The resultant mixture was stirred for 30 min and then quenched with water (1 mL). After warming up to room temperature, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and water (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), then the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give the crude β-ketoester **43** as a yellow oil.

The crude β-ketoester **43** was dissolved in anhydrous THF (7 mL) at −15 °C under argon followed by addition of KHMDS (0.91 M in THF, 666 μL, 0.606 mmol). After 30 min of stirring, Davis' reagent **44** (167.0 mg, 0.607 mmol) was added. The resulting mixture was stirred for 1.5 h and then quenched with water (1 mL). After warming up to room temperature, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and water (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), then the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified via silica gel chromatography (20% EtOAc/petroleum ether to 50% EtOAc/petroleum ether) to give alcohol **45** (140.0 mg, 87%, 2 steps) as a white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83−5.74 (ddd, J = 17.2, 10.0, 7.2 Hz, 1H), 5.21−5.12 (m, 2H), 4.50−4.46 (t, J = 8.0 Hz, 1H), 3.84 (brs, 1H), 3.72 (s, 3H), 2.93−2.88 (dd, J = 12.4, 10.4 Hz, 1H), 2.81−2.73 (ddd, J = 14.0, 14.0, 6.4 Hz, 1H), 2.58−2.44 (m, 2H), 2.22−2.09 (m, 3H), 2.00−1.94 (m, 2H), 1.89 (s, 3H), 1.77−1.72 (dd, J = 6.4, 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 172.4, 170.8, 170.3, 138.7, 136.9, 115.1, 84.4, 77.4, 60.8, 53.4, 34.1, 33.1, 29.3, 22.9, 22.5, 8.7; MS (EI) m/z 319, 301, 260, 231, 203, 175, 91; HRMS (ESI) calcd for $C_{17}H_{22}NO_5$ $(M + H)^+$: 320.1492, found 320.1486.

Ester (39). A solution of alcohol **45** (140.0 mg, 0.439 mmol) in anhydrous CH_2Cl_2 (8 mL) under argon was treated with Et_3N (366 μL, 2.638 mmol), DMAP (33.1 mg, 0.271 mmol), and propionic anhydride (281 μL, 2.192 mmol) at room temperature. The reaction mixture was stirred for 48 h and then concentrated. The residue was purified via silica gel chromatography (15% EtOAc/petroleum ether to 35% EtOAc/petroleum ether) to give ester **39** (164.0 mg, 99%) as a white crystalline solid: mp 138−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84−5.75 (ddd, J = 17.6, 10.4, 7.2 Hz, 1H), 5.20−5.10 (m, 2H), 4.56−4.52 (t, J = 8.0 Hz, 1H), 3.63 (s, 3H), 2.85−2.79 (dd, J = 12.4, 9.2 Hz, 1H), 2.65−2.50 (m, 2H), 2.48−2.35 (m, 3H), 2.15−2.03 (m, 3H), 2.01−1.94 (m, 2H), 1.86 (s, 3H), 1.77−1.72 (dd, J = 6.4, 6.4 Hz, 1H), 1.19−1.15 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 172.1, 171.9, 167.3, 166.2, 138.6, 136.7, 115.0, 88.1, 75.9, 60.8, 52.9, 35.2, 32.6, 28.9, 27.5, 23.3, 22.1, 8.8, 8.5; MS (EI) m/z 375, 319, 301, 260, 231, 203, 175; HRMS (ESI) calcd for $C_{20}H_{26}NO_6$ $(M + H)^+$: 376.1755, found 376.1750.

β-Hydroxy Ketone (48). To a solution of enone **40** (172.0 mg, 0.702 mmol) in anhydrous THF (10 mL) at −78 °C under argon was added LHMDS (1.0 M in THF, 1.06 mL, 1.060 mmol). After 1 h of stirring at −78 °C, propanal (103 μL, 1.420 mmol) was added. The resultant mixture was stirred for 1 h and then quenched with water (1 mL). After warming to room temperature, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and water (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), then the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Chromatography (40% EtOAc/petroleum ether to 75% EtOAc/petroleum ether) afforded β-hydroxy ketone **48** (208.2 mg, 98%) as a white crystalline solid: mp 161−163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88−5.79 (ddd, J = 17.2, 10.4, 6.8 Hz, 1H), 5.21−5.13 (m, 2H),

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4.58−4.54 (t, J = 7.2 Hz, 1H), 3.59−3.55 (ddd, J = 8.0, 5.6, 2.4 Hz, 1H), 3.09−3.00 (m, 1H), 2.88−2.82 (dd, J = 12.4, 9.6 Hz, 1H), 2.49−2.41 (m, 1H), 2.30−2.15 (m, 3H), 2.13−1.99 (m, 3H), 1.91−1.79 (m, 4H), 1.75 (s, 3H), 1.42−1.38 (dd, J = 11.6, 4.8 Hz, 1H), 0.97−0.94 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 173.3, 170.6, 138.2, 137.3, 115.0, 73.4, 73.0, 61.2, 60.6, 40.0, 33.5, 29.4, 29.2, 22.6, 22.4, 10.5, 7.9; IR (neat) 3333, 1702, 1629, 1000 cm^{-1}; MS (EI) m/z 303, 274, 246, 204, 175, 148, 91; HRMS (ESI) calcd for $C_{18}H_{26}NO_3$ $(M + H)^+$: 304.1907, found 304.1904.

Alcohols (51) and (52). To a solution of β-hydroxy ketone **48** (278.5 mg, 0.919 mmol) in anhydrous CH_2Cl_2 (10 mL) under argon at 0 °C was added Dess−Martin periodinane (549.4 mg, 1.296 mmol) followed by slow warming of the reaction mixture to room temperature. After stirring for 1.5 h, the reaction was quenched via addition of saturated aqueous $NaHCO_3$ (10 mL) and $Na_2S_2O_3$ (10 mL) and diluted with CH_2Cl_2 (20 mL). The biphasic mixture was vigorously stirred at room temperature for 30 min, and then the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to yield the crude β-diketone **49** as a yellow oil.

The β-diketone **49** was dissolved in anhydrous ^{i}PrOH (10 mL) at room temperature, followed by addition of $CeCl_3{\cdot}7H_2O$ (34.2 mg, 0.092 mmol). The flask was then evacuated to 300 mbar and flushed with O_2, and the reaction mixture was stirred at room temperature for 20 h, while a slow stream of oxygen (ca. 50 cm^3 h^{-1}) was passed through. After removal of the solvent, the residue was purified by column chromatography (25% EtOAc/petroleum ether to 50% EtOAc/petroleum ether) to give alcohol **51** (214.7 mg, 74%, 2 steps) and alcohol **52** (27.1 mg, 9%, 2 steps) as white amorphous solids. Alcohol **51**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82−5.73 (ddd, J = 17.6, 10.4, 7.2 Hz, 1H), 5.20−5.09 (m, 2H), 4.57−4.53 (t, J = 8.0 Hz, 1H), 4.42 (brs, 1H), 2.84−2.64 (m, 3H), 2.63−2.52 (m, 1H), 2.51−2.32 (m, 2H), 2.06−1.99 (m, 2H), 1.98−1.89 (m, 3H), 1.82 (s, 3H), 1.77−1.72 (dd, J = 12.4, 5.6 Hz, 1H), 0.92−0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.4, 203.4, 172.7, 170.6, 138.3, 135.7, 115.5, 89.8, 76.6, 61.3, 34.9, 32.9, 31.5, 29.1, 23.5, 22.5, 8.2, 7.3; IR (neat) 3284, 1723, 1700, 1625, 984 cm^{-1}; MS (EI) m/z 317, 260, 232, 204, 178, 132, 105; HRMS (ESI) calcd for $C_{18}H_{24}NO_4$ $(M + H)^+$: 318.1700, found 318.1708. Alcohol **52**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84−5.76 (ddd, J = 17.2, 10.0, 7.2 Hz, 1H), 5.19−5.13 (m, 2H), 4.57−4.53 (t, J = 4.0 Hz, 1H), 3.04−2.95 (m, 1H), 2.90−2.80 (m, 2H), 2.76−2.66 (m, 1H), 2.48−2.40 (m, 1H), 2.15−2.04 (m, 4H), 1.93−1.86 (m, 1H), 1.82 (s, 3H), 1.72−1.69 (m, 1H), 1.62−1.54 (m, 1H), 1.14−1.10 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 201.2, 174.4, 173.0, 138.1, 134.7, 115.4, 86.0, 77.4, 60.5, 34.9, 34.1, 32.8, 28.8, 23.5, 22.4, 8.3, 7.5; IR (neat) 2922, 1728, 1689, 1383, 1026 cm^{-1}; MS (EI) m/z 317, 260, 236, 218, 188, 123, 91; HRMS (ESI) calcd for $C_{18}H_{24}NO_4$ $(M + H)^+$: 318.1700, found 318.1706.

Carbonate (53). A solution of alcohol **51** (13.0 mg, 0.041 mmol) in anhydrous CH_2Cl_2 (2 mL) under argon was treated with di-*tert*-butyl dicarbonate (21.0 mg, 0.096 mmol) and DMAP (1.1 mg, 0.009 mmol) at room temperature. The reaction mixture was stirred for 5 h and then concentrated. The residue was purified via silica gel chromatography (15% EtOAc/petroleum ether to 35% EtOAc/petroleum ether) to give carbonate **53** (16.2 mg, 95%) as a white crystalline solid: mp 138−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85−5.76 (ddd, J = 17.6, 10.4, 7.2 Hz, 1H), 5.30−5.16 (m, 2H), 4.61−4.57 (t, J = 8.0 Hz, 1H), 2.85−2.79 (dd, J = 12.8, 9.2 Hz, 1H), 2.69−2.52 (m, 3H), 2.38−2.26 (m, 2H), 2.12−1.95 (m, 5H), 1.88−1.81 (m, 4H), 1.52 (s, 9H), 1.06−1.02 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 197.1, 172.9, 165.7, 151.8, 138.3, 137.0, 115.8, 93.3, 84.3, 75.7, 61.5, 35.3, 33.0, 32.0, 29.2, 27.6, 23.4, 22.2, 8.4, 7.6; IR (neat) 2921, 1721, 1650, 1259, 932 cm^{-1}; MS (EI) m/z 417, 360, 344, 316, 270, 216, 188, 133; HRMS (ESI) calcd for $C_{23}H_{32}NO_6$ $(M + H)^+$: 418.2224, found 418.2231.

Carbonate (54). A solution of alcohol **51** (285.2 mg, 0.900 mmol) in anhydrous CH_2Cl_2 (10 mL) under argon was treated with Et_3N (1.50 mL, 10.792 mmol), DMAP (439.1 mg, 3.599 mmol), and ethyl chloroformate (860 μL, 9.037 mmol) at room temperature. The reaction mixture was stirred for 24 h and then concentrated. The residue was purified via silica gel chromatography (15% EtOAc/petroleum ether to 35% EtOAc/petroleum ether) to give carbonate **54** (350.0 mg, 99%) as a white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84−5.76 (ddd, J = 17.6, 10.4, 7.2 Hz, 1H), 5.26−5.16 (m, 2H), 4.60−4.56 (t, J = 8.0 Hz, 1H), 4.33−4.22 (m, 2H), 2.86−2.80 (dd, J = 12.4, 8.8 Hz, 1H), 2.67−2.51 (m, 3H), 2.40−2.31 (m, 2H), 2.13−2.02 (m, 4H), 2.01−1.92 (m, 1H), 1.88 (s. 3H), 1.86−1.82 (m, 1H), 1.37−1.33 (t, J = 6.8 Hz, 3H), 1.05−1.01 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 196.7, 172.7, 166.1, 153.5, 138.1, 137.0, 115.8, 93.4, 75.8, 65.3, 61.4, 35.1, 33.0, 32.2, 29.2, 23.3, 22.1, 14.0, 8.4, 7.5; IR (neat) 1760, 1729, 1710, 1655, 954 cm^{-1}; MS (EI) m/z 389, 332, 299, 260, 214, 175, 120; HRMS (ESI) calcd for $C_{21}H_{28}NO_6$ $(M + H)^+$: 390.1911, found 390.1918.

Lactone (38). To a solution of the carbonate **54** (77.0 mg, 0.198 mmol) in anhydrous THF (14 mL) at −78 °C under argon was added KHMDS (0.91 M in THF, 436 μL, 0.397 mmol). The reaction mixture was warmed slowly to 10 °C over 5 h, and then it was quenched with water (3 mL) at 0 °C. The resultant mixture was diluted with CH_2Cl_2 (10 mL) and treated with 2N HCl to PH = 2. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), then the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give the crude **46** as a yellow amorphous solid.

The crude **46** was dissolved in anhydrous CH_2Cl_2 (16 mL) under argon, followed by addition of CH_2N_2 (1.0 M in CH_2Cl_2, 1.00 mL, 1.000 mmol). After stirring at 0 °C for 1 h, the solution was quenched with acetic acid (1 mL). Removal of solvent in vacuo resulted in a yellow solid which was purified by chromatography (50% EtOAc/petroleum ether to 70% EtOAc/petroleum ether) to give lactone **38** (53.9 mg, 76%, 2 steps) as a white crystalline solid: mp 178−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80−5.71 (ddd, J = 17.2, 10.0, 7.2 Hz, 1H), 5.20−5.12 (m, 2H), 4.44−4.40 (t, J = 7.6 Hz, 1H), 3.98 (s, 3H), 2.98−2.92 (m, 1H), 2.86−2.77 (dt, J = 14.4, 6.4 Hz, 1H), 2.57−2.49 (m, 1H), 2.30−2.25 (ddd, J = 14.4, 4.4, 2.8 Hz, 1H), 2.16−2.07 (m, 4H), 2.03 (s, 3H), 1.97−1.90 (m, 1H), 1.87 (s, 3H), 1.77−1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 173.6, 173.1, 170.7, 169.7, 138.6, 137.4, 115.3, 98.6, 88.1, 75.9, 60.9, 59.1, 35.6, 33.8, 29.2, 22.5, 21.8, 8.9, 8.8; IR(neat) 1761, 1719, 1647, 1000 cm^{-1}; MS (EI) m/z 357, 302, 242, 202, 175, 149, 83; HRMS (ESI) calcd for $C_{20}H_{24}NO_5$ $(M + H)^+$: 358.1649, found 358.1646.

Aldehyde (37). Potassium osmate dehydrate (1.0 mg) was added to a stirred solution of lactone **38** (22.0 mg, 0.062 mmol) and *N*-methylmorpholine *N*-oxide (41.7 mg, 0.309 mmol) in acetone (1 mL), ^{t}BuOH (500 μL), and water (500 μL). After stirring for 5.5 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (10 mL). The resultant mixture was dried over $MgSO_4$, filtered and evaporated under reduced pressure to give the crude diol **55** as a sticky oil.

The crude diol **55** was dissolved in THF (4 mL) and water (2 mL) under argon, followed by addition of $NaIO_4$ (26.2 mg, 0.122 mmol). After stirring at room temperature for 2 h, the solution was diluted with CH_2Cl_2 (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and then the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Chromatography (50% EtOAc/petroleum ether to 75% EtOAc/petroleum ether) afforded the aldehyde **37** (21.2 mg, 96%, 2 steps) as a white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65−9.64 (d, J = 0.8 Hz, 1H), 4.56−4.53 (d, J = 9.2 Hz, 1H), 3.99 (s, 3H), 2.94−2.84 (m, 3H), 2.34−2.29 (m, 1H), 2.23−2.07 (m, 4H), 2.04 (s, 3H), 2.01−1.94 (m, 1H), 1.89 (s, 3H), 1.87−1.86 (d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 195.4, 173.4, 170.0, 169.6, 137.8, 98.8, 88.2, 75.3, 65.0, 59.2, 35.6, 32.2, 23.0, 22.4, 22.2, 8.9, 8.7; MS (EI) m/z 359, 330, 290, 256, 202, 149, 83; HRMS (ESI) calcd for $C_{19}H_{22}NO_6$ $(M + H)^+$: 360.1442, found 360.1440.

Amine (56). Methyl trifluoromethanesulfonate (748 μL, 6.819 mmol) was added in one portion to a solution of **38** (64.0 mg, 0.179 mmol) in anhydrous CH_2Cl_2 (10 mL) under argon. The reaction mixture was stirred at room temperature for 12 h and concentrated. The residue was dissolved in anhydrous EtOH (3 mL), and treated with $NaCNBH_3$ (53.5 mg, 0.849 mmol). The reaction mixture was stirred at room temperature for 10 min, treated with a mixture of acetic

acid and water (3 mL, ca. 1:1), and sequentially stirred at room temperature for 30 min. The resultant mixture was diluted with CH_2Cl_2 (10 mL) and treated with saturated aqueous $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and then the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Chromatography (15% EtOAc/petroleum ether to 65% EtOAc/petroleum ether) afforded the tertiary amine **56** (30.9 mg, 50%) as a white amorphous solid and recovered starting material **38** (30.0 mg, 47% of recovered starting material). Amine **56**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37−5.28 (ddd, J = 18.0, 10.0, 8.0 Hz, 1H), 5.11−5.01 (m, 2H), 3.96 (s, 3H), 3.66−3.61 (dd, J = 15.2, 8.8 Hz, 1H), 3.09−3.05 (d, J = 15.6 Hz, 1H), 2.92−2.81 (m, 2H), 2.18−2.09 (m, 2H), 2.03 (s, 3H), 2.01−1.90 (m, 2H), 1.82−1.74 (m, 4H), 1.68−1.53 (m, 2H), 1.39−1.34 (dd, J = 14.0, 3.6 Hz, 1H), 1.29−1.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 175.0, 174.2, 172.4, 141.5, 135.7, 115.9, 97.0, 91.3, 77.7, 63.9, 58.5, 45.7, 36.3, 31.8, 28.3, 26.6, 24.8, 8.8, 8.3; IR(neat) 1758, 1710, 1663, 992 cm^{-1}; MS (EI) m/z 343, 300, 284, 256, 216, 174, 132; HRMS (ESI) calcd for $C_{20}H_{26}NO_4$ $(M + H)^+$: 344.1856, found 344.1859.

Aldehyde (58). Potassium osmate dehydrate (1.0 mg) was added to a stirred solution of **56** (15.7 mg, 0.046 mmol) and *N*-methylmorpholine *N*-oxide (31.0 mg, 0.229 mmol) in acetone (800 μL), ^{t}BuOH (400 μL), and water (400 μL). After stirring for 3.5 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (10 mL). The resulting mixture was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude diol **57** as a sticky oil.

The crude diol **57** was dissolved in THF (3 mL) and water (1.5 mL) under argon, followed by addition of $NaIO_4$ (13.8 mg, 0.065 mmol). After stirring at 0 °C for 3 h, the solution was diluted with CH_2Cl_2 (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and then the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Chromatography (20% EtOAc/petroleum ether) afforded the aldehyde **58** (10.0 mg, 64%, 2 steps) as a white amorphous solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.99−8.98 (d, J = 4.2 Hz, 1H), 4.02 (s, 3H), 3.68−3.65 (m, 1H), 3.08−3.04 (m, 1H), 2.95−2.93 (d, J = 13.2 Hz, 2H), 2.27−2.25 (dd, J = 12.0, 5.4 Hz, 1H), 2.18−2.14 (m, 1H), 2.03−2.01 (m, 5H), 1.93−1.84 (m, 2H), 1.81 (s, 3H), 1.71−1.64 (m, 1H), 1.49−1.46 (m, 1H), 1.33−1.24 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.9, 198.0, 174.5, 172.2, 172.0, 137.0, 97.4, 90.8, 78.1, 68.3, 58.8, 47.9, 36.6, 28.2, 26.5, 25.5, 25.4, 8.8, 8.5; IR (neat) 2779, 1759, 1713, 1662 cm^{-1}; MS (EI) m/z 345, 316, 283, 266, 188, 162, 83; HRMS (ESI) calcd for $C_{19}H_{24}NO_5$ $(M + H)^+$: 346.1649, found 346.1643.

Maistemonine (1e). Zinc powder (16.5 mg, 0.254 mmol) was added to a solution of aldehyde **58** (17.9 mg, 0.052 mmol) in anhydrous THF (6 mL) under argon. The solution was heated, and when reflux started, a solution of ethyl 2-(bromomethyl)acrylate (16.9 mg, 0.088 mmol) in anhydrous THF (5 mL) was added dropwise for 5 min. After stirring for additional 5 min, the resultant mixture was cooled to room temperature, quenched with water (10 μL), and concentrated. The residue was dissolved in anhydrous EtOH (7 mL), and treated with 10% Pd/C (8.0 mg). The reaction mixture was stirred in an atmosphere of H_2 for 15 h, filtered, and concentrated. Chromatography (75% chloroform/petroleum ether) afforded maistemonine **1e** (14.2 mg, 66%, 2 steps) as a white crystalline solid: mp 189−190 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.00 (s, 3H), 3.87−3.83 (ddd, J = 11.4, 7.8, 6.0 Hz, 1H), 3.60−3.58 (d, J = 15.6 Hz, 1H), 3.40−3.36 (m, 1H), 2.95−2.88 (m, 2H), 2.60−2.55 (m, 1H), 2.36−2.32 (ddd, J = 13.8, 8.4, 5.4 Hz, 1H), 2.28−2.24 (m, 1H), 2.13−2.10 (m, 1H), 2.02 (s, 3H), 1.98−1.97 (m, 1H), 1.89−1.85 (m, 2H), 1.82−1.75 (m, 4H), 1.54−1.46 (m, 3H), 1.39−1.33 (m, 1H), 1.26−1.25 (d, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.9, 179.7, 175.0, 173.2, 172.5, 136.4, 96.9, 91.6, 85.1, 79.3, 63.6, 58.8, 47.2, 35.8, 34.8, 34.5, 28.4, 26.6, 25.5, 24.9, 14.9, 8.9, 8.4; IR (neat) 1760, 1709, 1662 cm^{-1}; MS (EI) m/z 415, 372, 316, 272, 188, 162, 83; HRMS (ESI) calcd for $C_{23}H_{30}NO_6$ $(M + H)^+$: 416.2068, found 416.2058.

Stemonamide (1c). Potassium osmate dehydrate (1.0 mg) was added to a stirred solution of **56** (8.7 mg, 0.025 mmol) and *N*-methylmorpholine *N*-oxide (17.4 mg, 0.129 mmol) in acetone (480 μL), ^{t}BuOH (240 μL), and water (240 μL). After stirring for 3.5 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (10 mL). The resulting mixture was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude diol **57** as a sticky oil.

The crude diol **57** was dissolved in THF (2 mL) and water (1 mL) under argon, followed by addition of $NaIO_4$ (54.3 mg, 0.254 mmol). After stirring at 40 °C for 10 h, the solution was diluted with CH_2Cl_2 (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and then the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Chromatography (70% EtOAc/petroleum ether) afforded stemonamide **1c** (7.0 mg, 83%, 2 steps) as a white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21−4.17 (d, J = 14.8 Hz, 1H), 4.00 (s, 3H), 3.02−2.97 (dd, J = 10.0, 5.6 Hz, 1H), 2.88−2.82 (t, J = 12.8 Hz, 1H), 2.66−2.56 (m, 1H), 2.41−2.27 (m, 2H), 2.18−2.11 (m, 2H), 2.02 (s, 3H), 2.00−1.91 (m, 1H), 1.87 (s, 3H), 1.84−1.81 (d, J = 11.2 Hz, 1H), 1.47−1.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 175.8, 172.9, 170.9, 168.7, 137.0, 99.7, 90.0, 74.5, 59.2, 41.3, 31.9, 30.2, 29.9, 27.5, 27.4, 9.1, 8.4; IR (neat) 2925, 1766, 1699, 1662 cm^{-1}; MS (EI) m/z 331, 286, 221, 181, 164, 131, 83; HRMS (ESI) calcd for $C_{18}H_{21}NO_5$ $(M + H)^+$: 332.1492, found 332.1495.

Isomaistemonine (1g). A white crystalline solid: mp 219−221 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.34−4.31 (ddd, J = 10.8, 5.4, 5.4 Hz, 1H), 4.13 (s, 3H), 3.72−3.68 (ddd, J = 10.8, 5.4, 5.4 Hz, 1H), 3.33−3.29 (dd, J = 15.6, 3.6 Hz, 1H), 2.95−2.88 (m, 2H), 2.64−2.57 (m, 1H), 2.42−2.39 (dd, J = 13.2, 6.6 Hz, 1H), 2.27−2.23 (ddd, J = 13.8, 8.4, 5.4 Hz, 1H), 2.11−2.08 (m, 4H), 2.03−2.01 (d, J = 11.4 Hz, 1H), 1.90−1.86 (m, 1H), 1.77−1.69 (m, 5H), 1.51−1.45 (m, 3H), 1.30−1.19 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.5, 179.1, 175.2, 173.2, 169.6, 135.4, 102.3, 88.4, 81.0, 60.8, 59.5, 47.2, 34.9, 32.5, 32.2, 27.9, 26.9, 25.5, 24.1, 15.0, 9.2, 8.1; IR (neat) 2925, 1826, 1659, 1073 cm^{-1}; MS (EI) m/z 415, 386, 356, 316, 288, 162, 134, 91; HRMS (ESI) calcd for $C_{23}H_{30}NO_6$ $(M + H)^+$: 416.2068, found 416.2062.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full spectroscopic data for all new compounds and X-ray crystallographic data in CIR format of **22**, **23**, **40**, **39**, **38**, **1e**, and **1g**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tuyq@lzu.edu.cn; zhangfm@lzu.edu.cn.

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