TOTAL SYNTHESIS OF STEMONA ALKALOIDS VIA PALLADIUM CATALYZED CARBONYLATION

by

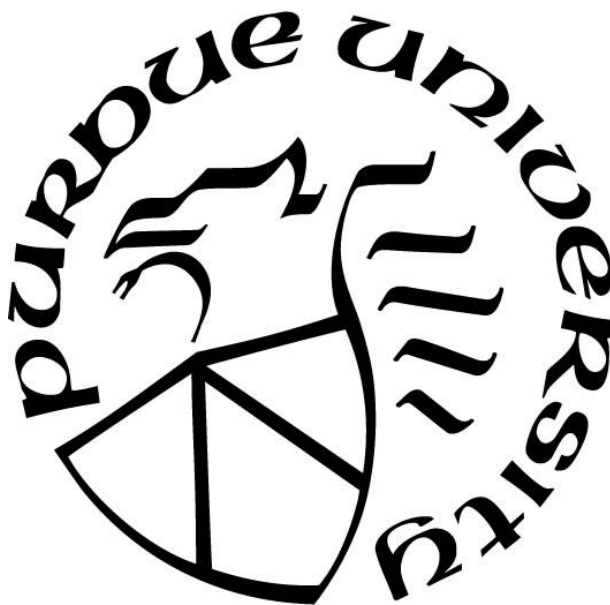**Xianglin Yin**

A Dissertation

Submitted to the Faculty of Purdue University

In Partial Fulfillment of the Requirements for the degree of

Doctor of Philosophy

Department of Chemistry

West Lafayette, Indiana

May 2020

THE PURDUE UNIVERSITY GRADUATE SCHOOL
STATEMENT OF COMMITTEE APPROVAL

Dr. Mingji Dai, Chair

Department of Chemistry, School of Science

Dr. Hilkka Kenttämaa

Department of Chemistry, School of Science

Dr. Jianguo Mei

Department of Chemistry, School of Science

Dr. Christopher Uyeda

Department of Chemistry, School of Science

Approved by:

Dr. Christine Hrycyna

To my family and friends for their love and support

ACKNOWLEDGMENTS

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

ABSTRACT

Carbon monoxide is a useful carbon linchpin to construct complex molecules of natural products by stitching different pieces of target molecules together. Recently, our group reported a novel and efficient palladium-catalyzed spirolactonization by Dr. Dexter Davis to construct oxaspirolacones from esters or lactones. As an essential motif, oxaspirolactone structures in natural products exhibit diverse and exciting structures and biological activities. The first part of this thesis mainly describes the total synthesis of stemoamide alkaloids in the stemona family and the application of our palladium-catalyzed spirolactonization, which was developed by our group to complete total synthesis of bisdehydroneostemoninine and bisdehydrostemoninine with Prof. Kaiqing Ma. The total synthesis features a one-pot ring-closing cross-metathesis, Lewis acid-mediated Friedel-Crafts reaction and lactonization, and accomplished bisdehydrostemonine in 15 steps. The total synthesis of stemoamide, tuberostemoamide, and sessilifoliamide A were finished, and the critical step features an mCPBA oxidation to convert pyrrole to lactam in one step without destructing other functional groups.

In the second part of this thesis, we developed a novel and efficient palladium-catalyzed cascade amino-carbonylative lactonization to streamline the synthesis of dihydropyrrole-fused furanones in collaboration with Prof. Seleem's lab for biological activities. Using this method, we quickly expanded this method to construct different ring structures, such as β-lactone and dihydropyrrole-fused pyrrolone. This method was applied to the total synthesis study towards stemofoline alkaloids. Our palladium-catalyzed spirolactonizaiton was also used in this total synthesis study for target molecules.

CHAPTER 1. TOTAL SYNTHESIS OF STEMOAMIDE ALKALOIDS

1.1 Introduction

The dry roots of Stemonaceae plants called "Bai Bu" in traditional Chinese medicine were utilized to treat persistent coughing since 200 A. D. The herbal extracts have been widely used in treating respiratory diseases, anthelmintic reagents, antitussive reagents, and insecticides for thousands of years in Chinese and Japanese medicine.[1, 2] As a rich resource of bioactive molecules with complex structures, there are over 150 stemona alkaloids having been isolated, and most of them feature pyrrolo[1,2-a]azepine nucleus.[3, 4, 5] All the alkaloids are categorized into eight subgroups (Figure 1.1).
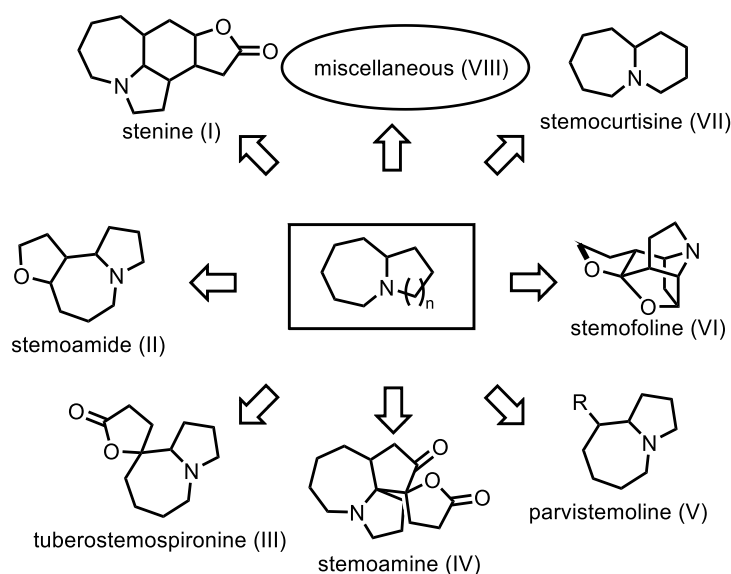
Figure 1.1 *Stemona* alkaloid groups

In these eight groups of *stemona* alkaloids, our attention was brought to stemoamide group because of its oxaspirolactone moiety (Figure 1.2), such as bisdehydroneostemoninine (**1.1**), (iso)bisdeydrostemoninine (**1.2** and **1.3**)[6], stemoninine A and B (**1.4** and **1.5**)[7], tuberostemoamide

$(\mathbf{1.6})^8$, sessilifoliamide A $(\mathbf{1.7})^9$, (dihydro)stemoninine $(\mathbf{1.8}$ and $\mathbf{1.9})^{10}$ and stemoenonine $(\mathbf{1.10})^{11}$. Interestingly, natural products with tricyclic core and lactone moiety (from $\mathbf{1.12}$ to $\mathbf{1.16}$) in the stemoamide group also provide a significant chance to apply our spirolactonizaiton methodology.

Figure 1.2 Stemoamide group members

12

In the recent total synthesis of stemoamide alkaloids in the *stemona* family, only limited alkaloids in the stemoamide group were synthesized. Although there are over 20 total syntheses of stemoamide (**1.13**), there are a few total synthesis of stemoamide group members with oxaspirolactone moiety. In 1994, Williams and coworkers[12] firstly finished the total synthesis of (-)-stemoamide from methyl (R)-3-hydroxy-2-methyl propionate to afford imide (**1.18**) by 7 steps (Scheme 1.1). The asymmetric Evans adol reaction provided a *syn*-adol derivative followed by silyl group deprotection and butyrolactonizaiton under basic condition to form butyrolactone, which was protected by silyl ether (**1.19**). After 5 steps, **1.19** was converted to **1.20** which was directly oxidized, followed by methyl esterification. Reduction of azide and two cyclizations were performed to obtain lactam (**1.21**). Then, stemoamide (**1.13**) was obtained via deprotections and oxidations from **1.21**.
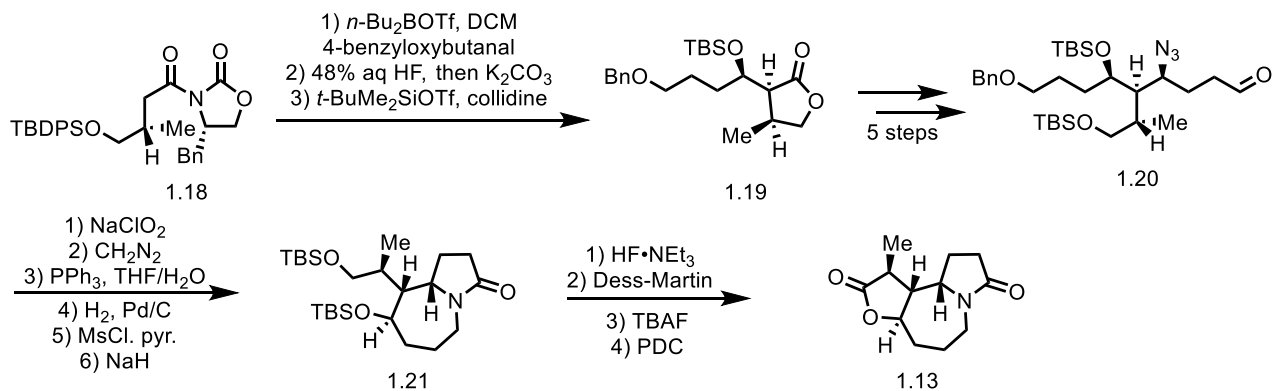
Scheme 1.1 Williams' total synthesis of stemoamide

In 1996, Narasaka and Kojno[13] reported a total synthesis of (±)-stemoamide by oxidative coupling (Scheme 1.2). Starting from silyl enol ether **1.22**, a oxidative coupling of stannyl reagents was applied to obtain **1.23**. With the same method, Boc protected pyrrolidine ring was installed to form **1.24** which was converted lactone **1.26** via hydrogenation, reduction, protection group

switching, and oxidation. The final natural product (±)-stemoamide **1.13** was accessed by substitution and methylation.
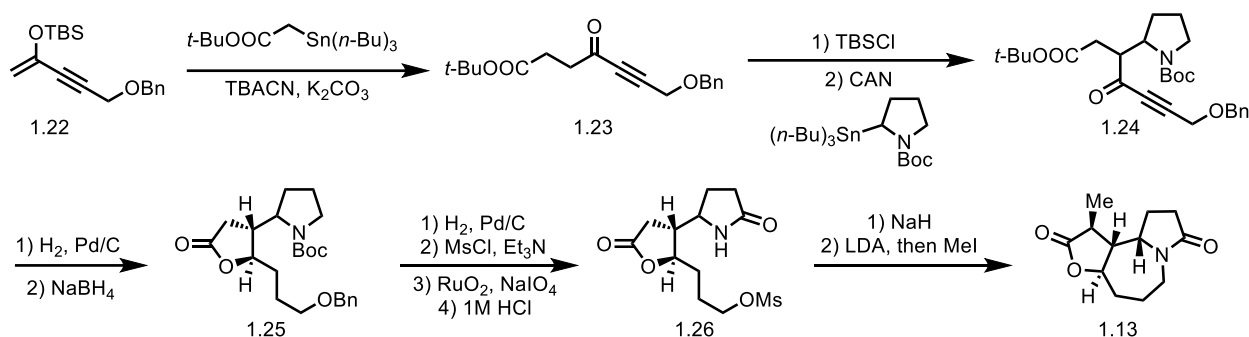
Scheme 1.2 Narasaka's total synthesis of stemoamide

After one year, Mori and Kinishita[14] finished a second total synthesis of (-)-stemoamide via ruthenium-catalyzed enyne metathesis (Scheme 1.3). Starting from (-)-pyroglutamic, the total synthesis features a ruthenium-catalyzed metathesis to convert lactam **1.28** to pyrrolo[1,2-α]azepine 1.29 which was transformed to (-)-stemoamide (**1.13**) after 4 steps.
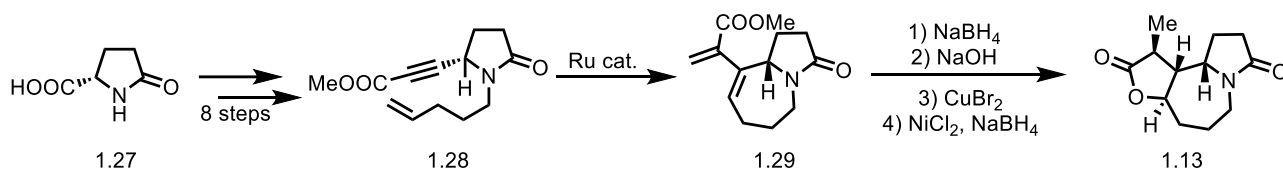
Scheme 1.3 Mori's total synthesis of stemoamide

In 1997, Jacobi and Lee[15] provided an efficient method to obtain (±)-stemoamide, and the total synthesis features an intramolecular Diels-Alder/retro Diels-Alder reaction (Scheme 1.4). Starting with commercially available starting material **1.30**, **1.31** was obtained by condensation and substitution. After reduction and Lewis acid-catalyzed condensation, the target oxazole 1.32

was accessed. The molecule (±)-stemoamide (**1.13**) was finally finished by Diels-Alder/retro Diels-Alder reaction and nickel catalyzed reduction.
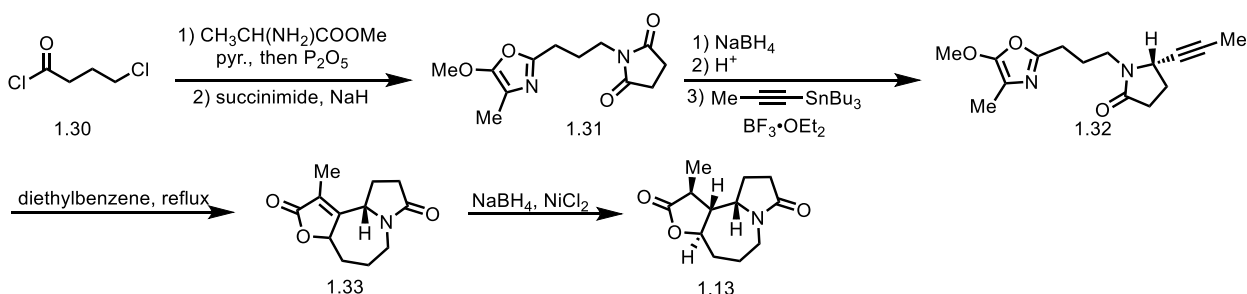
Scheme 1.4 Lee's total synthesis of stemoamide

A formal synthesis of (-)-stemoamide (**1.13**) was reported by Gurjar and Reddy[16]. Starting from all of the furanose, the total synthesis features a zinc-mediated allylation and Barton-McCombie reaction. Kohno and Narasaka's method was applied to finalize the molecule. In 2004, Sibi and Subramanian[17] provided an enantioselective total synthesis of (-)-stemoamide. In this total synthesis, a Grubbs catalyst was used for cross-metathesis cyclization to form pyrrolo[1,2-α]azepine intermediate (**1.35**), followed by iodolactonizaiton. By three steps protocol, C9 was epimerized, followed by methylation to complete the natural product.
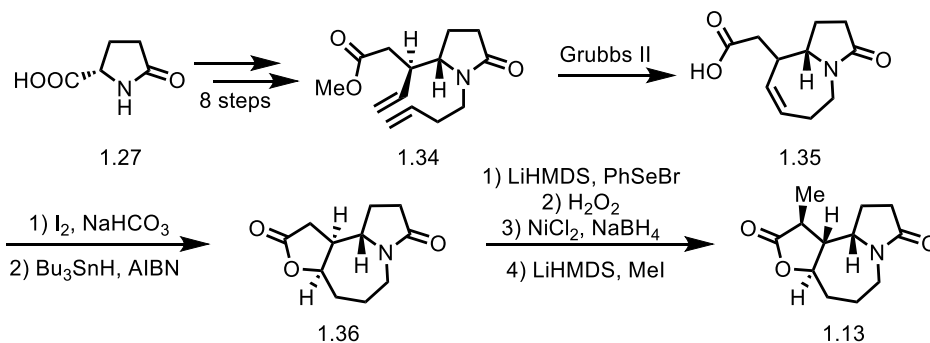
Scheme 1.5 Sibi's total synthesis of stemoamide

15

In 2017, a gram-scale total synthesis of stemoamide was published by Sato and Chida[18] , and the natural product was converted to stemonine (1.14) and saxorumamide (1.15). The total synthesis applied a vinylogous conjugated addition and reduction to build lactam and lactone moieties (1.39) which was converted to stemoamide (1.13) by deprotection, cyclization, and methylation. The chemoselective nucleophilic addition was used to functionalize lactam and lactone separately in stemoamide selectively. The reductive nucleophilic addition to lactam affords stemonine (1.41), and lactone selective nucleophilic addition leads to saxorumaide (1.15) and isosaxorumaide (1.16).
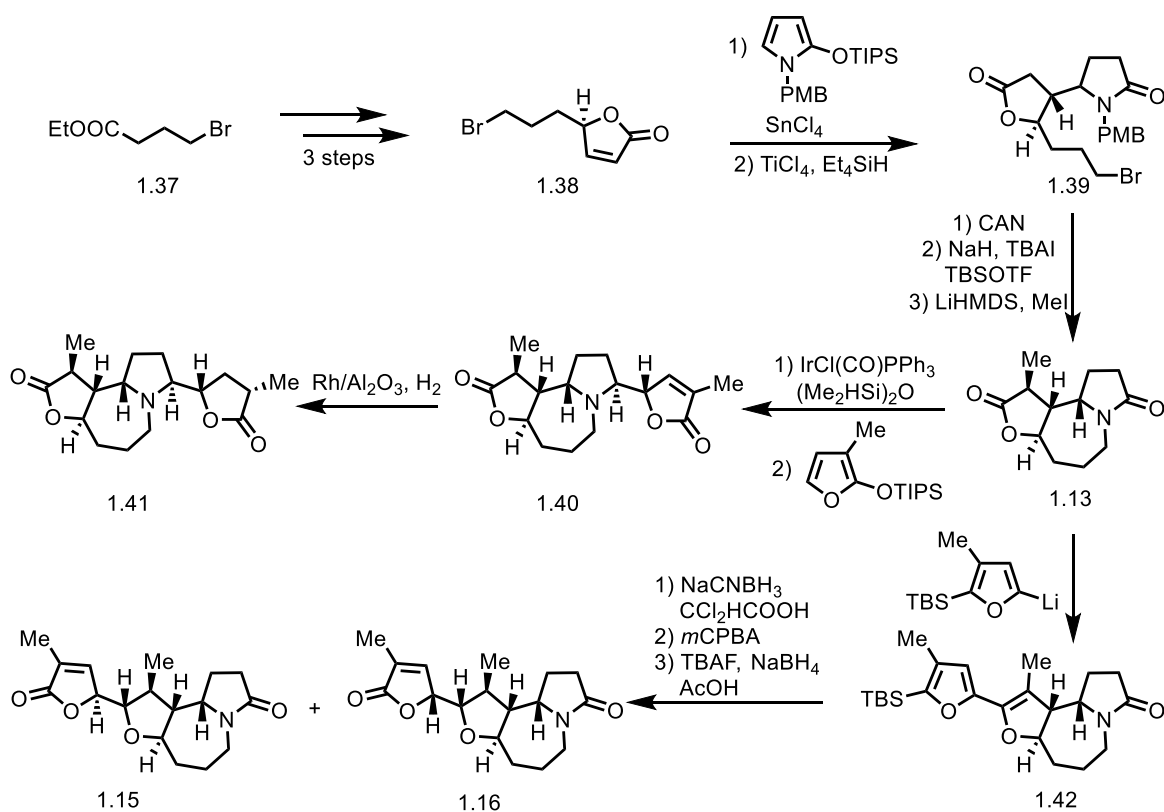
Scheme 1.6 Sato and Chida's total synthesis of stemoamide-type alkaloids

After two years, the first total synthesis of tuberostemoamide (1.6) and sessilifoliamide A (1.7) were accomplished by Wang and Hou[19]. The tricyclic core (1.45) was accessed by SmI$_2$-

mediated conjugated addition, and after 3 steps, ethylstemoamide (**1.46**) was obtained. The lactone selective addition was completed to obtain intermediate **1.48,** and a TEMPO oxidation was directly applied to give sessilifoliamide A (**1.6**). Then, tuberostemoamide (**1.7**) was quickly accessed by bromination and elimination.
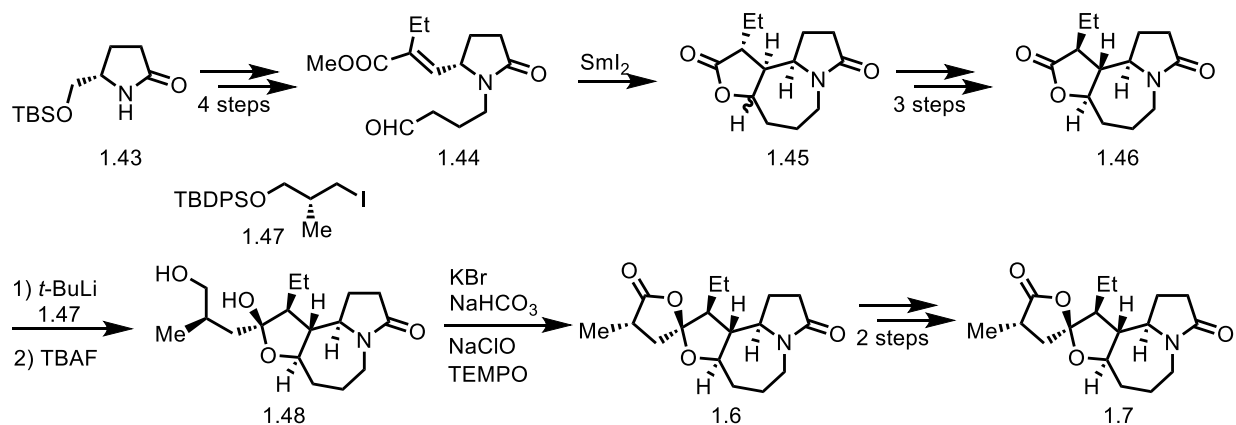
Scheme 1.7 Wang and Hou's total synthesis of tuberostemoamide and sessilifoliamide A

In summary, since the 1990s, over 150 alkaloids in the stemona family were isolated, the unique tricyclic core has drawn significant interests in organic synthesis and biological activity tests. There are over 20 total syntheses of stemoamide (**1.13**) were reported, and except for the examples mentioned above, other syntheses of stemoamide (**1.13**) were also provided in the 21st century. Cossy and Bogliotti[20, 21, 22] reported a radical approach to construct tricyclic core. Olivo and Tovar-Miranda provided a stereoselective anti-Aldol method to complete (-)-stemoamide (**1.13**). Oltra and Munoz-Bascon[23] completed stemoamdie (**1.13**) via a Ti-catalyzed synthesis of exocyclic allenes. Somfai[24] and Pilli[25] also accomplished stemoamide (**1.13**) in 2007 and 2015 separately. Except for stemoamide (1.13) (-)-stemospironinie and (-)-stemonine (**1.14**) have also been achieved by Williams' group. In 2011, Wipf's group presented the first total synthesis of (-)-sessilifoliamide C and (-)-8-*epi*-stemoamide via [3,3]-sigmatropic rearrangements. As an

important intermediate and resource, the tricyclic framework with γ-lactone and γ-lactam provided broad access to divergently synthesize different stemoamide-type alkaloids. And the divergent synthesis will fulfill the requirement of biological activity identification of natural products with low purification yield, which will provide access to these potent molecules and derivative designs.

1.2   Result and Discussion

To expand our recent palladium-catalyzed spirolactonizaiton methodology via a cyclopropanol ring-opening, which features a C-C cleavage, ketal formation with CO insertion, and lactonization (Scheme 1.8)[26], we decided to construct the tricyclic core of stemoamide (1.13) and to apply this methodology to convert lactone to spirolactone. To our surprise, when we start this project, there has been no reported total synthesis of stemoamide alkaloids with oxaspirolactone center.
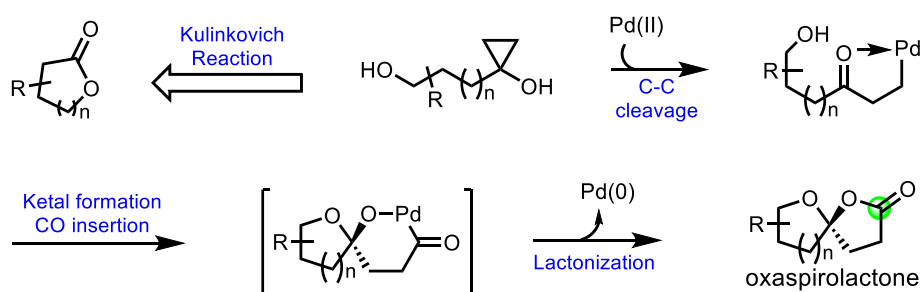
Scheme 1.8 Palladium-catalyzed spirolactonizaiton

The stemoamide alkaloids with oxaspirolactone moiety contain an acid-sensitive spirocenter which give significant challenge in synthesis to install it at an early stage as well as to control the chirality of the spirocenter. Besides, a γ-butyrolactone in bisdehydrostemoninine appended to the C3 position of pyrrole ring, which initiates the epimerization of the C18 stereocenter. So, extra cautions are required to avoid this reconstruction of the stereocenter.

Additionally, many of these alkaloids contain pyrrolidine or oxidized moiety (**1.6**-**1.9**), which generate dramatic challenges to oxidize pyrrole to pyrrolidine with scrambling other function groups at a late stage. These features significantly increase difficulties in accomplishing the complex natural product in total synthesis.
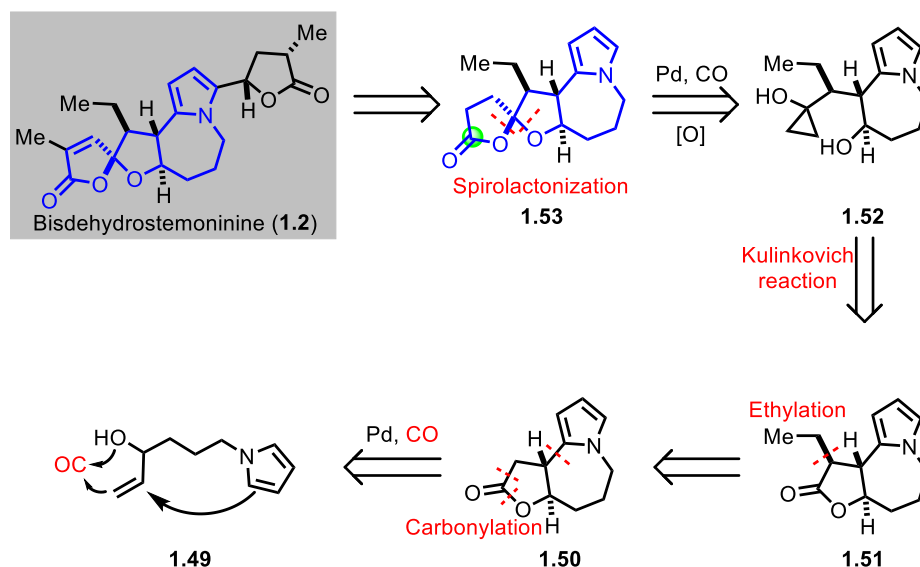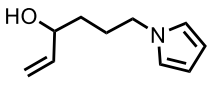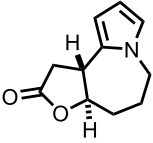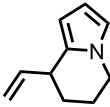
Scheme 1.9 Retro-synthetic analysis of bisdehydrostemoninine

With all these challenges in mind, we proposed a retro-synthetic analysis of bisdehydrostemoninine (**1.2**), which features a palladium-catalyzed oxidative cyclization and carbonylation lactonization (**1.49** to **1.50**) and an oxaspirolactonizaiton (**1.52** to **1.53**). The spirolactonizaiton precursor (**1.52**) is Kulinkovich product from lactone (**1.51**), which was α-ethylated from tricyclic core (**1.50**). Additionally, we planned to convert pyrroles to corresponding pyrrolidines to obtain non-pyrrole-contained alkaloids by developing a new method.

We quickly accessed to vinyl alcohol (**1.49**) and started to screen multiple carbonylative conditions (Table 1.1) to convert **1.49** to tricyclic core **1.50**. After we freshly prepared Pd(MeCN)$_2$Cl$_2$, our visiting scholar Prof. Kaiqing Ma tried different conditions (entry 1 to 7). In

most of the conditions, starting material remained, and some of the conditions provided Tsuji-Trost product. When trace amount of Pd(II) was reduced to Pd(0), oxidative addition happened on vinyl alcohol followed by nucleophilic attacking and decomplexation to access bicyclic product (1.54).

Table 1.1 Condition screening of oxidative cyclization and carbonylative lactonization

Entry	Conditions	Product
1	Pd(MeCN)$_2$Cl$_2$ (10 mol %), CuCl$_2$ (3 equiv.) THF, CO (1atm), 0°C, 1h	No **1.50**; **1.54** observed
2	Pd(MeCN)$_2$Cl$_2$ (1 equiv.), MeCN CO (1atm), rt to 60°C, overnight	**SM** remained
3	Pd(MeCN)$_2$Cl$_2$ (10 mol %), CuCl$_2$ (3 equiv.) di-tert-butyl-pyridine (2 equiv), THF, CO (1atm), 0°C, 1h	No **1.50**; **1.54** observed
4	Pd(OAc)$_2$ (10 mol %), t-BuOOH (1 equiv.) Dioxane:HOAc:DMSO (9:3:1) CO (1atm), 45 °C-75 °C, overnight	**SM** remained
5	Pd(OAc)$_2$ (10 mol %), Cu(OAc)$_2$ (1 equiv.) DMSO, CO (1atm), 70 °C-100 °C, overnight	**SM** remained
6	Pd(MeCN)$_2$Cl$_2$ (10 mol %), MeCN CO (6 atm), DDQ, rt, overnight	**SM** remained
7	Pd(MeCN)$_2$Cl$_2$ (10 mol %), MeCN CO (6 atm), DDQ, 80°C, overnight	**SM** decomposed
8	Pd(MeCN)$_2$Cl$_2$ (10 mol %), AgOTf (20 mol%), MeCN CO (1 atm), DDQ, rt, overnight	**SM** remained
9	Pd(tfa)$_2$ (10 mol %), MeCN CO (1 atm), BQ, rt, overnight	**SM** remained

Our synthesis[27] started from commercially available starting materials 2,5-dimethoxytetrahydro-furan (**1.55**) and amino ester (**1.56**), which was converted to pyrrole by Clauson-Kass pyrrole synthesis[28] followed by Weinreb amide formation to give **1.57**. Vinyl Grignard addition and Luche reduction were applied to provide vinyl alcohol **1.49**. Since the tandem cyclization and lactonization cannot access to the desired product by installing carbonyl

20

group, Prof. Kaiqing Ma started a two-steps method to pre-install carbonyl group via cross-metathesis with methyl acrylate by Grubbs second-generation catalyst[29] and applied a boron trifluoride etherate triggered Friedel-Crafts cyclization/lactonization to obtain a tricyclic core of **1.50**[30, 31, 32]. To improve the yield, we tried different Lewis acids, such as $TiCl_4$ and $SnCl_4$; however, none of them provide any better yield. Under this condition, we also obtained the *cis*-isomer as a 2.6:1 separable mixture. Interestingly, we then combined the cross-metathesis, and Lewis acid promoted Fredel-Crafts cyclization/lactonization into on pot by switching solvent from toluene to dichloromethane and increasing catalyst loading to 10 mol% to obtain similar yield. α-ethylation in mix solvent of THF and HMPA was applied to obtain two epimers as 1.6:1 mixture of **1.51** and **1.59,** which was completely epimerized to the desired product **1.51** under condition of DBU and MeOH at 50 °C. This epimerization significantly saves time for us to accumulate starting material for further steps.
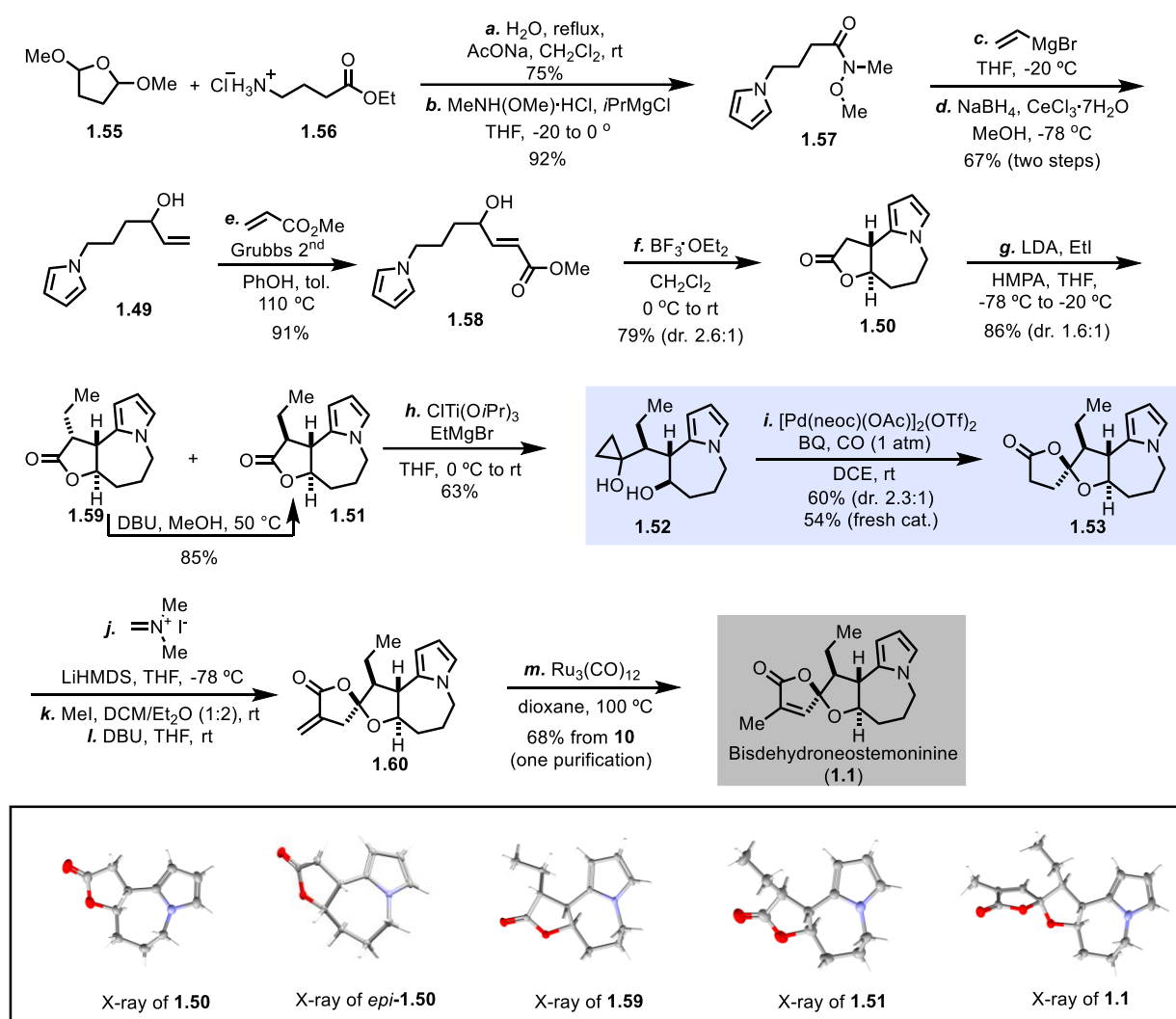
Scheme 1.10 Total synthesis of bisdehydroneostemoninine

With **1.51** in hand, we firstly employed Dreiding-Schmidt reaction to construct *exo*-methylene spirolactone (1.60) with 2-(bromomethyl)acrylate, but the method did not provide any desired product. Then Prof. Kaiqing Ma started to convert it to Kulinkovich product **1.52** by using standard and modified Kulinkovich reaction[33, 34], however, none of them provide fruitful yield. Inspired by Corey's total synthesis of isoedunol[35, 36], Prof. Kaiqing Ma used ClTi(O*i*Pr)$_3$ instead of Ti(O*i*Pr)$_4$ to complete Kulinkovich reaction in 63% yield. To reduce steric hindrance, the isopropoxide group was replaced by a chloride group, and at the same time, this replacement

increases electrophilicity of titanium center. Our methodology, the palladium-catalyzed carbonylative spirolactonizaiton, went smoothly to obtain **1.53** with 10 mol% Waymouth catalyst [Pd(neoc)(OAc)]$_2$(OTf)$_2$. As a 2.3:1 mixture of two stereoisomers, oxaspirolactone **1.53** in 60% yield and the undesired isomer was isomerized to **1.53** by TFA in dichloromethane. Interestingly, freshly prepared Waymouth catalysts may promote epimerization in situ. To install α-*exo*-methylene Eschenmoser protocol was applied, followed by Ru$_3$(CO)$_{12}$-catalyzed isomerization[37] to complete the total synthesis of bisdehydroneostemoninine (**1.1**) in 68% yield for 4 steps with one column purification.
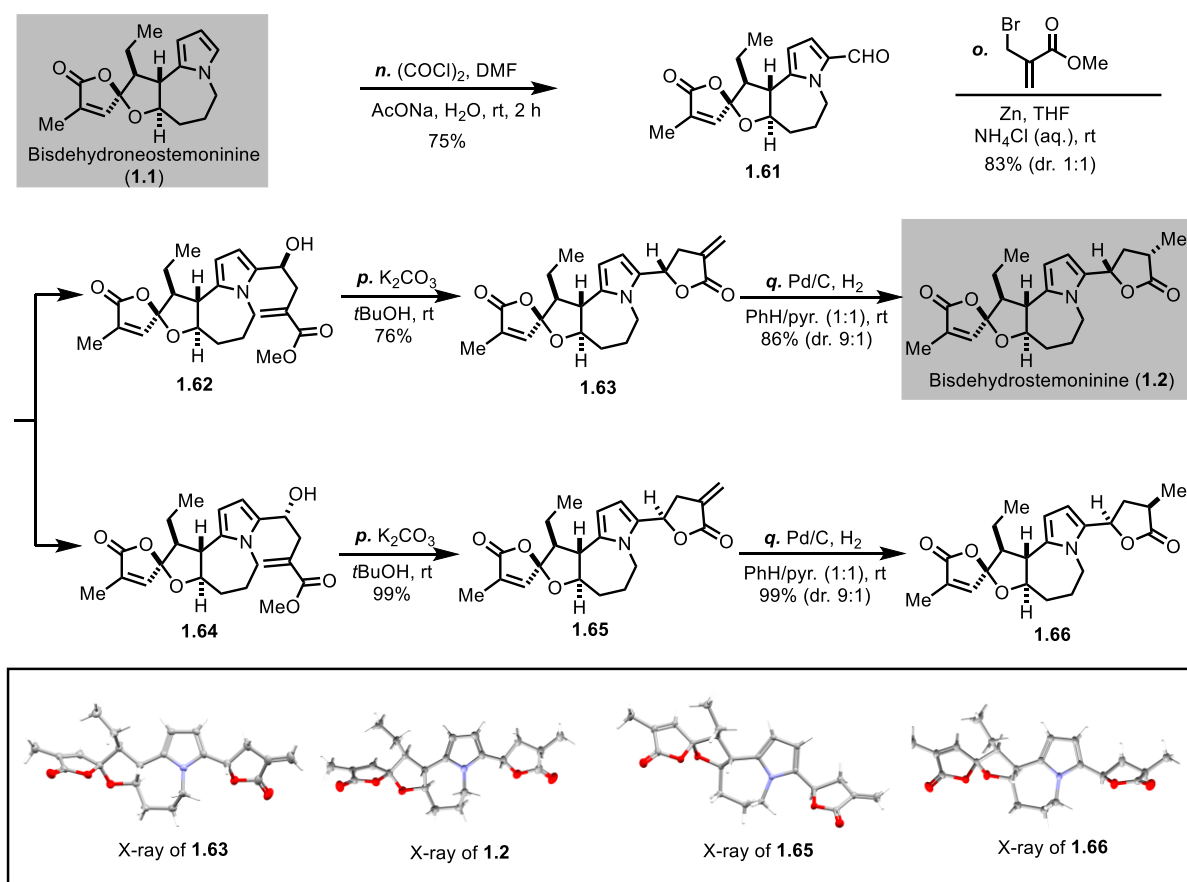
Scheme 1.11 Total synthesis of bisdehydrostemoninine

23

To convert bisdehydroneostemoninine (1.1) to bisdehydrostemoninine (1.2), the first task is to install γ-butyrolactone at C3, which generates several challenges. First of all, the acidic sensitivity of oxaspirolactone restricts the condition for the late-stage substitution, and a mild condition is required. Second, it is difficult to control the newly generated chiral center by substrate, since γ-butyrolactone at C3 is remote to other existing chiral centers. Third, the chiral center at C18 is prone to be epimerized at acid conditions, which may completely scramble the synthesis. With all these challenges in mind, we first tried bromination on our model molecule **1.50**, and a dibromo product at C2 and C3 position was obtained, which not useful for further steps. Then we used the Vilsmeier-Haack reaction[38] to install the carbonyl group on C3 on **1.50** to obtain the desired product in a 30-40% yield. To our surprise, the yield of the Vilsmeier-Haack reaction was significantly improved when it was applied to natural product bisdehydroneostemoninine (**1.1**) to give **1.61** in 75% yield. An organozinc reagent[39] was used to give 1,2 addition product **1.62** and **1.64** in 83% yield. As expected, a 1:1 mixture of **1.62** and **1.64** were obtained and separated by column chromatography. The total synthesis of bisdehydrostemoninine (**1.2**) was accomplished by lactonization[40] with K_2CO_3 and t-BuOH in 76% yield, followed by hydrogenation. As we expected, partial epimerization happened to **1.63** in the column of triethylamine-treated silica gel and standard hydrogenation method. Finally, we used benzene-pyridine (1:1) as co-solvent to avoid acidic epimerization condition and processed a selective hydrogenation in a 86% yield with 9:1 diastereoselectivity.[41] Besides, we used the same method to obtain analogue **1.66** for further biological activity.
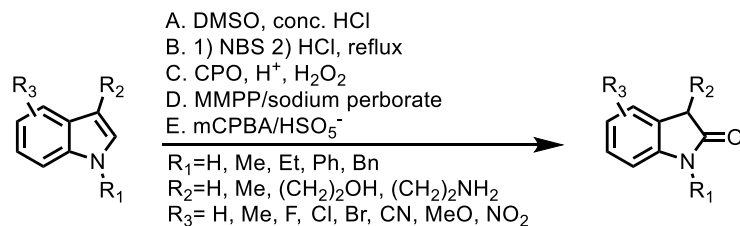
Scheme 1.12 Indole oxidation

After the first total synthesis of bisdehydroneostemoninine (**1.1**) and bisdehydrostemoninine (**1.2**) were accomplished, we started to convert bisdehydroneostemoninine (**1.1**) to its oxidative derivatives. To complete this transformation, a mild oxidation method is necessary to avoid isomerization and deconstruction of the backbone. Although there is limited literature support for pyrrole oxidation, several practical oxidations of indoles into corresponding oxindoles were achieved[42, 43, 44, 45, 46, 47, 48, 49, 50, 51] (Scheme 1.12). Except for the indole oxidation, an oxidation of pyrrolo[1,2-α][1,4]diazepine was reported by *m*CPBA oxidation. To avoid skeleton deconstruction and unnecessary waste of natural products, we selected stemoamide (1.13) as a model molecule to explore oxidation conditions.
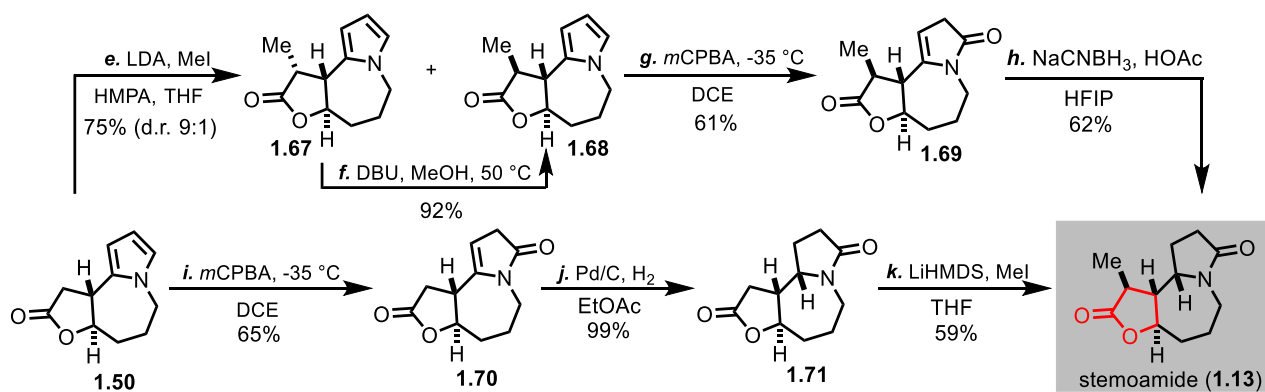
Scheme 1.13 Total synthesis of stemoamide

Starting from tricyclic core **1.50**, a mild *m*CPBA oxidation at -35 °C in DCE was used to achieve lactam **1.71**, followed by hydrogenation. α-Methylation leads to the final product stemoamide (1.13) in 9 steps in total. Methylation of 1.50 provided two diastereomers 1.67 and 1.68 in a mixture of 9:1, which gave an opposite stereoselectivity to α-ethylation. The undesired epimer can also be completely epimerized to desire one, followed by *m*CPBA oxidation and reduction to obtain stemoamide (1.13).
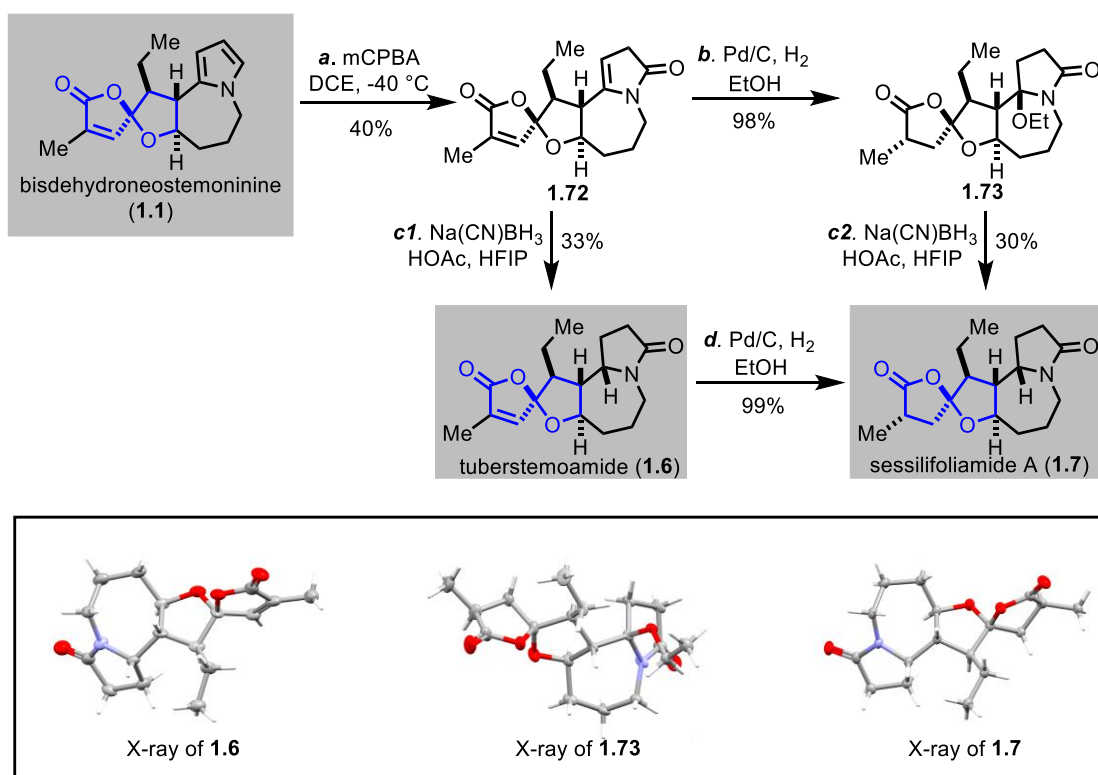
Scheme 1.14 Total synthesis of tuberostemoamide and sessilifoliamide A

After we finished the model study and achieved a total synthesis of stemoamide (**1.13**), we applied the *m*CPBA oxidation to bisdehydroneostemoninine (**1.1**) and quickly accessed to lactam **1.72** in 40% yield. However, hydrogenation did not provide the desired product sessilifoliamide A (**1.7**). To our surprise, we observed an ethoxylated product **1.73** with correct stereochemistry.

An acidic condition was used to isomerize enamine to imine, followed by NaCNBH$_3$ reduction to give tuberostemoamide (**1.6**). HFIP, as a non-nucleophilic source, was used as a solvent to avoid alkoxylation. The hydrogenation of tuberostemoamide (**1.6**) to sessilifoliamide A (**1.7**) went smoothly to complete the total synthesis of tuberostemoamide (**1.6**) and sessilifoliamide A (**1.7**). Under the same reduction condition, the ethoxylated product 1.73 can also be converted to imine followed by reduction to access to sessilifoliamide A (**1.7**).

1.3 Conclusion

In summary, we completed the first total synthesis of bisdehydroneostemoninine (**1.1**) and bisdehydrostemoninine (**1.2**) in stemona alkaloids. A Lewis acid promoted Friedel-Crafts cyclization/lactonization was developed to construct the significant tricyclic core efficiently. A palladium-catalyzed oxaspirolactonization was used to convert build up the tetracyclic core with spirocenter. In this whole process, we optimized the conditions to isomerize undesired products to the desired ones to avoid material waste. Additionally, we finished the total synthesis of stemoamide (1.13), tuberostemoamide (1.6), and sessilifoliamide A (1.7) by developing a mild *m*CPBA oxidation to convert pyrrole to lactam. Also, we obtained different analogues for biological activity test in the future.

1.4 Experimental Data

General Methods: NMR spectra were recorded on Bruker spectrometers (^{1}H at 500 MHz; ^{13}C at 126 MHz. Chemical shifts (δ) were given in ppm with reference to solvent signals [^{1}H NMR: CDCl$_3$ (7.26); ^{13}C NMR: CDCl$_3$ (77.2)]. Column chromatography was performed on silica gel. All reactions sensitive to air or moisture were conducted under argon atmosphere in dry and freshly distilled solvents under anhydrous conditions, unless otherwise noted. Anhydrous THF and

toluene were distilled over sodium and diphenylketone under Argon. Anhydrous CH_2Cl_2 was distilled over calcium hydride under Argon. Anhydrous MeOH was distilled over magnesium under Argon. All other solvents and reagents were used as obtained from commercial sources without further purification.
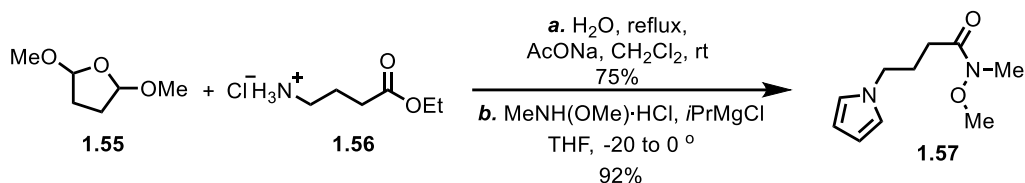
2,5-Dimethoxytetrahydrofuran (13.2 g, 100 mmol) was added to a stirred solution of water (remove the oxygen with argon flux overnight, 180 mL), and the solution was refluxed for 2 h under argon. The light brown mixture was allowed to cool to room temperature before the addition of dichloromethane (100 mL), sodium acetate (13 g, 155 mmol). Ethyl 4-aminobutanoate hydrochloride (8.4 g, 54 mmol) was then added portionwise. The reaction mixture was then stirred vigorously for 15 h with exclusion from light. The color turned to be dark brown. The reaction mixture was treated with 2 M sodium carbonate solution (20 mL) and extracted with CH_2Cl_2. The combined organic layers were concentrated to afford the crude residue, which was purified by column chromatography with EtOAc/Hexane (1:1) to provide the pyrrole derivative 6.8 g in 75% yield as a light-yellow oil.

HRMS (ESI) [M + H$^+$] calculated for $C_{10}H_{16}NO_2$: 182.1176, found: 182.1174;

FTIR (neat, cm^{-1}) ν_{max} 2980, 1732, 1500, 1447, 1375, 1282, 725;

^{1}H NMR (500 MHz, CDCl$_3$) δ: 6.64 (t, J = 2.0 Hz, 2H), 6.14 (t, J = 2.1 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.94 (t, J = 6.9 Hz, 2H), 2.27 (t, J = 7.3 Hz, 2H), 2.05 – 2.11 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H);

^{13}C NMR (126 MHz, CDCl$_3$) δ: 172.8, 120.6, 108.2, 60.5, 48.5, 31.0, 26.8, 14.2.

A solution of 2.0 M *i*PrMgCl (69 ml, 138 mmol) in ~~dry~~ THF was added dropwise to a solution of the above ethyl ester product (10 g, 55 mmol) and Me(MeO)NH·HCl (6.4 g, 66 mmol) in ~~dry~~ THF (150 ml) at −20 ℃. The mixture was warmed slowly to 0 ℃ and stirred at 0 ℃ for 2 h. The reaction was then quenched with saturated aqueous NH$_4$Cl. The mixture was extracted with EtOAc. The organic layers were combined, dried over anhydrous Na$_2$SO$_4$, and filtered. The resulting solution was concentrated in vacuo. Purification with column chromatography of the crude residue [EtOAc/Hexane (1:1)] afforded 10 g of Weinreb amide in 92% yield.

FTIR (neat, cm^{-1}) v_{max} 2937, 1660, 1500, 1445, 1386, 1281, 726;

HRMS (ESI) [M + H$^+$] calculated for C$_{10}$H$_{17}$N$_2$O$_2$: 197.1285, found: 197.1285;

^{1}H NMR (500 MHz, CDCl$_3$) δ: 6.65 (t, J = 2.1 Hz, 2H), 6.13 (t, J = 2.1 Hz, 2H), 3.97 (t, J = 6.8 Hz, 2H), 3.60 (s, 3H), 3.17 (s, 3H), 2.36 (t, J = 7.1 Hz, 2H), 2.12 – 2.06 (m, 2H);

^{13}C NMR (126 MHz, CDCl$_3$) δ: 173.6, 120.6, 108.0, 61.1, 48.7, 32.2, 28.4, 26.2.
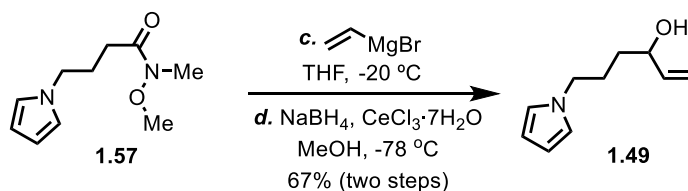
To a solution of amide **1.57** (2.6 g, 13 mmol) in THF (120 ml) at -20 ℃ was added vinyl magnesium bromide (1 M in THF, 16 ml, 16 mmol) dropwise over 20 minutes. The resulting mixture was stirred at this temperature for 30 min, and then another solution of vinyl magnesium chloride (1 M in THF, 4.8 ml, 4.8 mmol) was added dropwise. The reaction mixture was stirred at this temperature for 2 h. The reaction was diluted with ethyl ether (380 ml) at -10 ℃ under Argon and then quenched with water (50 ml). The aqueous layer was extracted with ethyl ether. The

combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a crude residue, which was submitted for the next reaction directly.

To a solution of $CeCl_3$ (12 g, 33 mmol) in MeOH (107 ml) was added $NaBH_4$ (1.6 g, 44 mmol) at 0 ℃. The resulting mixture was cooled to -78 ℃ followed by addition dropwise over 15 min of a solution of the above crude ketone in methanol (36 ml). The mixture was stirred at -78 ℃ for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and concentrated. Then the solution was extracted with EtOAc, and the combined organic layer was concentrated to afford a crude residue, which was purified by column chromatography (Hexane: EtOAc = 1:1) to give 1.5 g of the desired product in 67% yield for two steps.

HRMS (ESI) [M + H^+] calculated for $C_{10}H_{16}NO$: 166.1226, found: 166.1221;

FTIR (neat, cm^{-1}) ν_{max} 3403, 3098, 2942, 2874, 1697, 1500, 1369, 1280.69, 1090, 992, 724;

^1H NMR (500 MHz, $CDCl_3$) δ: 6.65 (t, J = 2.0 Hz, 2H), 6.14 (t, J = 2.1 Hz, 2H), 5.84 (ddd, J = 16.9, 10.4, 6.2 Hz, 1H), 5.22 (dt, J = 17.2, 1.4 Hz, 1H), 5.12 (dt, J = 10.4, 1.3 Hz, 1H), 4.12 – 4.06 (m, 1H), 3.91 (td, J = 7.1, 1.2 Hz, 2H), 1.95 – 1.76 (m, 2H), 1.59 (s, 1H), 1.55 – 1.50 (m, 2H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.7, 120.4, 114.9, 107.8, 72.5, 49.3, 33.8, 27.3.
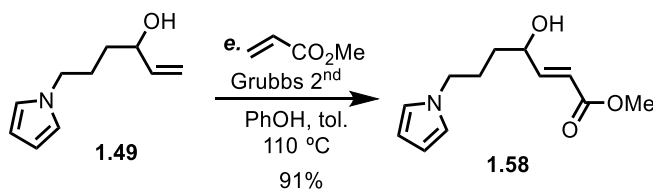
To a solution of alcohol **1.49** (1.3 g, 7.9 mmol) in toluene (7.9 ml) were added methyl acrylate (6.8 g, 79 mmol) , the Grubbs second generation catalyst (167 mg, 0.2 mmol) and phenol (0.37 g, 3.9 mmol) at room temperature in sealed tube. The deep brown reaction mixture was raised

to 110 ℃ and stirred for 0.5 h. The reaction mixture was concentrated to afford a crude residue, which was purified by column chromatography (Hexane: EtOAc = 4:1) to afford 1.6 g of the desired product as brown oil in 91% yield.

FTIR (neat, cm^{-1}) v_{max} 3462, 2950, 1722, 1660, 1500, 1437, 1280, 729;

HRMS (ESI) [M + Na$^+$] calculated for $C_{12}H_{17}NaNO_3$: 246.1101, found: 246.1108;

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.89 (dd, J = 15.7, 4.9 Hz, 1H), 6.64 (t, J = 2.1 Hz, 2H), 6.14 (t, J = 2.1 Hz, 2H), 6.01 (dd, J = 15.7, 1.6 Hz, 1H), 4.35 – 4.11 (m, 1H), 3.91 (td, J = 7.0, 2.1 Hz, 2H), 3.74 (s, 3H), 2.13 (s, 1H), 1.94 – 1.80 (m, 2H), 1.61 – 1.48 (m, 2H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 166.9, 150.0, 120.5, 120.1, 108.1, 70.5, 51.7, 49.3, 33.5, 27.2.
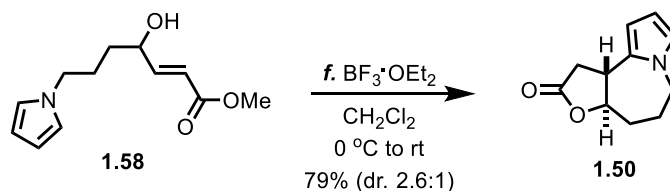
To a solution of ester **1.58** (1.43 g, 6.42 mmol) in DCM (200 ml) was added boron trifluoride diethyl etherate (1.0 ml, 7.70 mmol) at 0 ℃. The reaction mixture was raised to room temperature and stirred overnight. The reaction mixture was quenched with triethylamine and stirred for 30 min. The organic layer was washed with H$_2$O and concentrated to afford a crude residue, which was purified by column chromatography (Hexane: EtOAc = 4:1) to afford 695 mg of the desired product **1.50** as white solid in 57% yield and its epimer (275 mg, 22%).

FTIR (neat, cm^{-1}) v_{max} 2937, 1778, 1487, 1193, 1137, 1019, 716;

HRMS (ESI) [M + H$^+$] calculated for $C_{11}H_{14}NO_2$: 192.1019, found: 192.1017;

^{1}H NMR (500 MHz, CDCl$_3$) δ: 6.62 (t, J = 2.3 Hz, 1H), 6.03 (t, J = 3.3 Hz, 1H), 5.95 – 5.94 (m, 1H), 4.14 – 4.10 (m, 1H), 3.97 (ddd, J = 11.2, 9.9, 3.5 Hz, 1H), 3.88 (ddd, J = 14.6, 11.7, 1.0 Hz,

1H), 3.44 – 3.36 (m, 1H), 2.94 – 2.87 (m, 2H), 2.58 – 2.49 (m, 1H), 2.10 – 2.15 (m, 1H), 1.77 – 1.85 (m, 1H), 1.75 – 1.63 (m, 1H);

^{13}C NMR (126 MHz, CDCl$_3$) δ: 175.2, 128.6, 122.8, 106.4, 105.5, 83.7, 49.1, 42.2, 34.0, 33.7, 26.1.
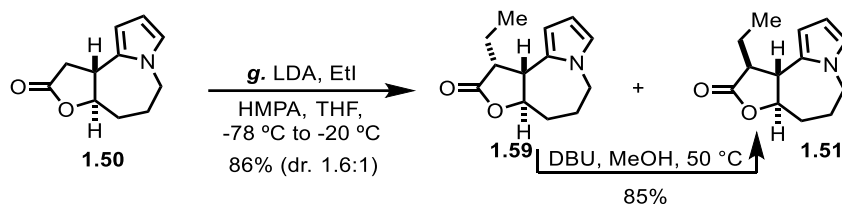
To a stirred solution of lactone **1.50** (191 mg, 1.0 mmol) was added dropwise LDA freshly prepared (0.3 M solution in THF, 10.0 ml, 3.0 mmol) at -78 °C. After stirring for 30 min, HMPA (23 μl) was added, followed by the dropwise addition of ethyl iodide (0.24 ml, 3.0 mmol). The resulting reaction mixture was raised to – 20 °C and stirred for 4 h at this temperature. The reaction was quenched with saturated aqueous NH$_4$Cl and extracted with EtOAc. The combined organic layer was concentrated to afford a crude residue, which was purified by column chromatography (Hexane: EtOAc: DCM = 4:1:1) to afford 60 mg of the desired product **1.51** as a white solid in 37% yield and its epimer **1.59** in 49% yield (108 mg).

To a solution of **1.59** (254 mg, 1.2 mmol) in methanol (30 ml) was added anhydrous K$_2$CO$_3$ (164 mg, 1.2 mmol) at room temperature. The resulting suspension was stirred at the same temperature for 120 h. The reaction was quenched with saturated aqueous NH$_4$Cl and concentrated to remove the methanol. The aqueous residue was extracted with ethyl acetate. The combined organic layer was concentrated to afford a crude residue, which was purified by column chromatography (Hexane: EtOAc: DCM = 4:1:1) to afford 148 mg of the desired product in 58% of yield.

1.51
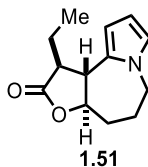
FTIR (neat, cm^{-1}) v_{max} 2934, 1773, 1487, 1453, 1192, 1166, 1019, 712;

HRMS (ESI) [M + H$^+$] calculated for C$_{13}$H$_{18}$NO$_2$: 220.1332, found: 220.1338;

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.62 (dd, J = 2.6, 1.8 Hz, 1H), 6.04 (dd, J = 3.6, 2.7 Hz, 1H), 5.96 (dt, J = 3.2, 1.3 Hz, 1H), 4.13 – 4.08 (m, 1H), 3.94 – 3.81 (m, 2H), 3.21 – 3.08 (m, 1H), 2.98 – 2.93 (m, 1H), 2.58 – 2.45 (m, 1H), 2.08 – 2.14 (m, 1H), 2.00 – 1.82 (m, 2H), 1.81 – 1.62 (m, 2H), 1.07 (t, J = 7.5 Hz, 3H);

^{13}C NMR (126 MHz, CDCl$_3$) δ: 177.5, 128.8, 122.6, 106.4, 105.2, 81.4, 49.0, 45.6, 45.2, 34.1, 26.3, 21.1, 10.8.

1.59
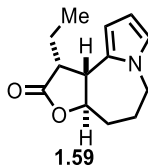
^{1}H NMR (500 MHz, CDCl$_3$) δ 6.61 – 6.60 (m, 1H), 6.14 (dt, J = 3.2, 1.4 Hz, 1H), 6.04 (dd, J = 3.7, 2.7 Hz, 1H), 4.31 (td, J = 10.5, 3.9 Hz, 1H), 4.14 (ddt, J = 14.6, 5.9, 1.4 Hz, 1H), 3.79 (ddd, J = 14.5, 11.2, 1.2 Hz, 1H), 3.44 (dd, J = 10.4, 7.0 Hz, 1H), 2.98 – 2.88 (m, 1H), 2.63 – 2.52 (m, 1H), 2.40 (ddd, J = 14.4, 7.5, 3.8 Hz, 1H), 2.14 – 2.05 (m, 1H), 1.87 – 1.77 (m, 1H), 1.77 – 1.68 (m, 2H), 1.15 (t, J = 7.5 Hz, 3H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 177.2, 126.0, 122.7, 107.6, 106.4, 81.0, 50.0, 45.8, 34.9, 25.4, 19.2, 11.8.
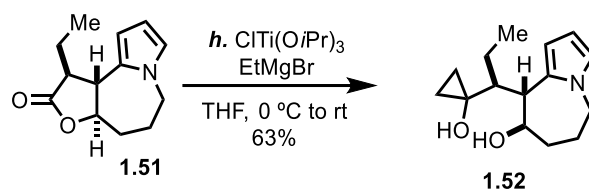
To a solution of lactone **1.51** (1 g, 4.6 mmol) in THF (16 ml) was added a solution of ClTi(O-*i*Pr)$_3$ in THF (1 M in THF, 11 ml, 11 mmol) at room temperature. The reaction mixture was cooled to 0 °C and a solution of EtMgBr in THF (1 M in THF, 22 ml, 22 mmol) was added dropwise from a syringe over 10 min. The addition caused a brown-dark of the reaction mixture. After gas evolution ceased, the reaction mixture was warmed to room temperature. The flask was then sealed tightly with a plastic cap and the thick, dark brown mixture was stirred vigorously at room temperature for 36 h. The reaction mixture was diluted with ethyl acetate and quenched with saturated NH$_4$Cl solution. Triethylamine was added and the reaction was stirred for 30 min. The mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated to afford a crude residue, which was purified by column chromatography (Hexane: EtOAc = 2:1) to afford the cyclopropanol product as colorless oil (Yield: 63%; 680 mg).

FTIR (neat, cm^{-1}) v_{max} 3349, 2929, 2875, 1682, 1487, 1456, 1093, 1075.11, 1018, 709;

HRMS (ESI) [M + H$^+$] calculated for C$_{15}$H$_{24}$NO$_2$: 250.1802, found: 250.1795;

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.52 (t, *J* = 2.3 Hz, 1H), 5.99 (s, 1H) 5.98 (s, 1H), 4.46 (d, *J* = 5.5 Hz, 1H), 4.02 – 3.92 (m, 1H), 3.87 – 3.78 (m, 1H), 3.32 (q, *J* = 8.6, 7.0 Hz, 1H), 2.93 (s, 1H), 2.10 (s, 1H), 1.96 – 1.80 (m, 2H), 1.77 – 1.69 (m, 1H), 1.61 – 1.52 (m, 2H), 1.41 – 1.37 (m, 1H), 1.33 – 1.22 (m, 1H), 0.91 – 0.76 (m, 5H), 0.65 – 0.52 (m, 2H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 130.3, 122.0, 106.0, 73.0, 68.3, 60.3, 55.4, 47.4, 46.6, 31.6, 25.6, 14.4, 12.8.
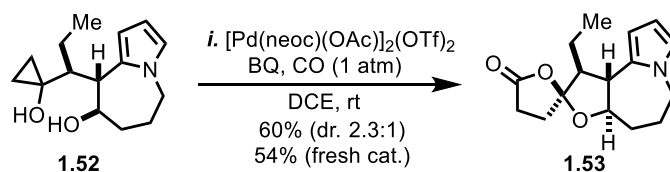
To a solution of cyclopropanol **1.52** (130 mg, 0.53 mmol) in DCE (15.6 ml) was added benzoquinone (115 mg, 1.1 mmol). The resulting solution was evacuated and backfilled three times using a carbon monoxide balloon. [Pd(neoc)(OAc)]$_2$(OTf)$_2$ (27.3 mg, 0.053 mmol) was added in one portion, and the black solution was stirred at 50 °C overnight. To the reaction mixture was added another portion of [Pd(neoc)(OAc)]$_2$(OTf)$_2$ (27.3 mg, 0.053 mmol) and benzoquinone (115 mg, 1.06 mmol). The resulting black solution was stirred at 50 °C for another 8 h. The reaction mixture was quenched with saturated NH$_4$Cl solution. Triethylamine was added and stirred for 30 min. The mixture was extracted with DCM. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated to afford a crude residue, which was purified by column chromatography (Hexane: EtOAc = 4:1) to afford the desired product (Yield: 42%; 60.5 mg) and its epimer (Yield: 18%; 26.5 mg) as purple oil.
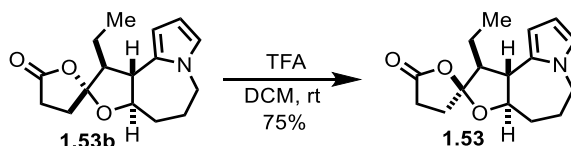
To a solution of the undesired diastereomer (130 mg, 4.7 mmol) in DCM (10 ml) at room temperature was added TFA (53 mg, 4.7 mmol) dropwise. The resulting mixture was stirred at this temperature for 10 min, followed by quenching the reaction with Et$_3$N. The reaction mixture was concentrated to afford a crude residue, which was purified by column chromatography (Hexane: EtOAc = 4:1) to afford the desired product (Yield: 75%; 96 mg) and 22 mg of **1.53b** (15%) was recycled.

The procedure with the freshly prepared [Pd(neoc)(OAc)]$_2$(OTf)$_2$:

To a solution of the cyclopropanol (1.63 g, 6.3 mmol) in DCE (190 ml) was added the benzoquinone (1.36 g, 12.6 mmol). The resulting solution was evacuated and backfilled three times using a carbon monoxide balloon. [Pd(neoc)(OAc)]$_2$(OTf)$_2$ (freshly prepared, 655 mg, 0.63 mmol) was added in one portion, and the black solution was stirred at 50 °C overnight. The reaction mixture was quenched with saturated NH$_4$Cl solution. Triethylamine was added and stirred for 30 min. The mixture was extracted with DCM. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated to afford a crude residue, which was purified by column chromatography (Hexane: EtOAc = 4:1) to afford the desired product (Yield: 54%; 926 mg) as purple oil.
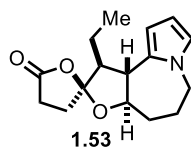
FTIR (neat, cm^{-1}) v_{max} 2932, 1777, 1487, 1452, 1203, 1174, 1062, 1009, 900, 709;

HRMS (ESI) [M + H$^+$] calculated for C$_{16}$H$_{22}$NO$_3$: 276.1594, found: 276.1603;

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.57 (dd, J = 2.7, 1.8 Hz, 1H), 6.02 (dd, J = 3.5, 2.7 Hz, 1H), 5.90 (dt, J = 3.1, 1.3 Hz, 1H), 4.03 (ddt, J = 14.5, 5.5, 1.6 Hz, 1H), 3.87 (ddd, J = 14.5, 11.8, 1.1 Hz, 1H), 3.57 (ddd, J = 11.2, 9.8, 3.5 Hz, 1H), 3.13 – 3.03 (m, 1H), 2.81 (dt, J = 17.5, 9.9 Hz, 1H), 2.55 (ddd, J = 17.6, 9.8, 2.5 Hz, 1H), 2.48 – 2.40 (m, 2H), 2.33 (ddd, J = 13.4, 9.8, 2.5 Hz, 1H), 2.29 – 2.23 (m, 1H), 2.05 – 1.98 (m, 1H), 1.89 – 1.80 (m, 1H), 1.77 – 1.68 (m, 2H), 1.61-1.58 (m, 1H), 1.06 (t, J = 7.6 Hz, 3H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 176.1, 130.1, 121.8, 116.5, 106.0, 104.1, 83.8, 51.1, 48.9, 47.6, 35.3, 32.3, 28.3, 26.6, 20.7, 12.9.

1.53b
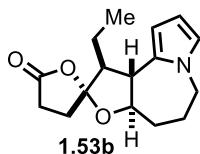
FTIR (neat, cm^{-1}) v_{max} 2933, 2874, 1779, 1487, 1457, 1197, 1148, 902, 712;

HRMS (ESI) [M + H$^+$] calculated for C$_{16}$H$_{22}$NO$_3$: 276.1594, found: 276.1588;

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.56 (t, J = 2.2 Hz, 1H), 6.00 (t, J = 3.1 Hz, 1H), 5.95 (dt, J = 3.1, 1.4 Hz, 1H), 4.06 (dd, J = 14.6, 5.4 Hz, 1H), 3.83 (dd, J = 14.4, 10.9 Hz, 1H), 3.70 (td, J = 10.2, 3.6 Hz, 1H), 2.93 – 2.85 (m, 1H), 2.85 – 2.78 (m, 1H), 2.69 (t, J = 9.9 Hz, 1H), 2.52 – 2.57 (m, 1H), 2.42 – 2.48 (m, 1H), 2.32 – 2.36 (m, 1H), 2.18 (ddd, J = 13.1, 8.9, 1.7 Hz, 1H), 2.06 – 1.98 (m, 1H), 1.67 – 1.77 (m, 2H), 1.66 – 1.58 (m, 2H), 1.01 (t, J = 7.5 Hz, 3H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 176.0, 129.8, 122.0, 117.8, 106.0, 105.6, 81.3, 50.7, 50.0, 49.2, 34.2, 30.0, 28.8, 26.4, 23.6, 12.5.
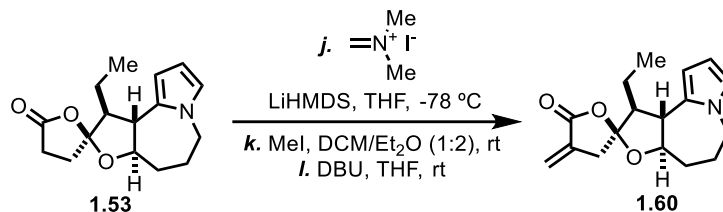
To a solution of **1.53** (48 mg, 0.17 mmol) in THF (8.0 mL) was slowly added fresh prepared lithium bis(trimethylsilyl)amide (2.0 mL, 0.5 M, 1.0 mmol) at -78 °C, and the resultant mixture was then stirred at the same temperature for 0.5 h. To the above solution was added Eschenmoser salt (259 mg, 1.4 mmol), and the resultant mixture was then warmed to -30 °C slowly. The reaction mixture was quenched by addition of a saturated solution of NH$_4$Cl at -30 °C and then raised to room temperature. The reaction mixture extracted by EtOAc three times and the solvent was

removed under vacuum to give a yellow oil, which was used in next step without further purification.

To a solution of the above crude amine compound in ethyl ether (1.0 ml) and DCM (0.5 ml) was added methyl iodide (0.28 ml) at 0 °C. The resulting solution was raised to room temperature and stirred overnight. The solvent was removed under vacuum, and the crude product was re-dissolved in THF (13 ml). To the above solution was added DBU (105 μl) at 0 °C and was raised to room temperature. The reaction mixture was stirred for 2 h and filtered through a short pad of silica. The solvent was concentrated to afford 34 mg crude product, which was submitted for the next reaction without further purification.
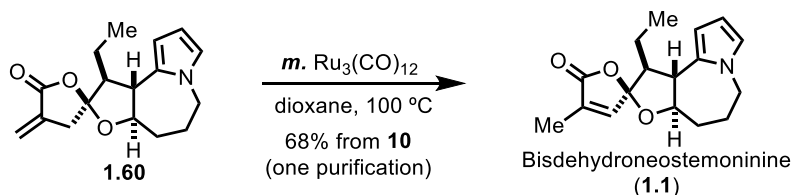
To a solution of **1.60** in dioxane (10 ml) were added Ru$_3$(CO)$_{12}$ (7.4 mg, 0.012 mmol) and triethylamine (17 μl, 0.12 mmol) in a sealed tube. The resulting solution was heated to 100 °C and stirred at this temperature for 1 h. The reaction mixture was concentrated to afford a crude residue, which was purified by column chromatography (Hexane: Acetone = 4:1) to afford **1.1** in 68% yield from **1.53** (34 mg).

FTIR (neat, cm^{-1}) ν_{max} 2934, 1766, 1487, 1451, 1284, 1167, 972, 877, 761, 712;

HRMS (ESI) [M + H$^+$] calculated for C$_{17}$H$_{22}$NO$_3$: 288.1594, found: 288.1585;

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.76 (t, J = 1.6 Hz, 1H), 6.64 – 6.55 (m, 1H), 6.03 (dd, J = 3.6, 2.7 Hz, 1H), 5.89 (dt, J = 3.0, 1.3 Hz, 1H), 4.09 – 4.01 (m, 1H), 3.89 (dd, J = 14.5, 11.8 Hz, 1H), 3.71 – 3.62 (m, 1H), 3.21 (dd, J = 12.1, 9.8 Hz, 1H), 2.57 (ddd, J = 12.3, 9.2, 3.2 Hz, 1H), 2.37 – 2.26

(m, 1H), 2.04 (tq, J = 8.7, 4.4 Hz, 1H), 1.96 (d, J = 1.6 Hz, 3H), 1.86 – 1.73 (m, 2H), 1.66 – 1.60

(m, 1H), 1.59-1.51(m, 1H), 0.91 (t, J = 7.6 Hz, 3H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 171.6, 145.4, 133.2, 129.6, 121.9, 113.2, 106.1, 104.1, 84.8, 50.9,

48.9, 47.3, 35.1, 26.7, 19.9, 13.1, 10.5.
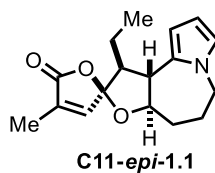
C11-*epi*-1.1

The C11-epimer of **1.1** was prepared via the same sequence described above from **1.53b** in 68%

yield.

FTIR (neat, cm^{-1}) v_{max} 2932, 2875, 1768, 1487, 1451, 1298, 1136, 958, 761, 713;

HRMS (ESI) [M + H$^+$] calculated for C$_{17}$H$_{22}$NO$_3$: 288.1594, found: 288.1590;

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.82 (q, J = 1.6 Hz, 1H), 6.58 (t, J = 2.2 Hz, 1H), 6.02 (dd, J = 3.6,

2.7 Hz, 1H), 5.94 (dt, J = 3.2, 1.3 Hz, 1H), 4.10 – 4.05 (m, 1H), 3.88 – 3.81 (m, 2H), 2.99 (ddd, J

= 10.7, 9.2, 5.2 Hz, 1H), 2.82 (t, J = 10.3 Hz, 1H), 2.37 (ddt, J = 9.8, 4.6, 2.7 Hz, 1H), 2.05 – 2.01

(m, 1H), 1.97 (d, J = 1.7 Hz, 3H) , 1.76 (dtd, J = 15.3, 7.6, 5.3 Hz, 1H), 1.66 – 1.60 (m, 2H), 1.58

– 1.51 (m, 1H), 0.91 (t, J = 7.5 Hz, 3H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 171.3, 143.3, 133.0, 129.1, 122.1, 114.5, 106.1, 105.6, 83.1, 51.9,

50.5, 49.2, 34.3, 26.3, 23.6, 12.4, 10.6.

Bisdehydroneostemoninine
(**1.1**)

n. (COCl)$_2$, DMF

AcONa, H$_2$O, rt, 2 h

75%

1.61
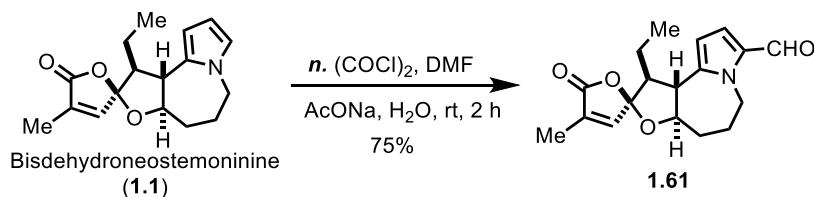
Freshly distilled $(COCl)_2$ (11.7 mg, 8 μl) was added dropwise to anhydrous DMF (11.2 mg, 11.8 μl) at 10 °C, and the white crystals obtained immediately were stirred for 15 min without cooling. Then DCM (1 ml) was added, and a solution of **1.1** (22 mg, 0.077 mmol) in DCM (2 ml) was added dropwise over 10 min at room temperature. The resulting mixture was stirred for 0.5 h at room temperature. Then a solution of NaOAc (33 mg) in 0.55 ml water was added and the stirring was continued for 0.5 h at room temperature. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic phases were washed with saturated $NaHCO_3$ and water, dried with anhydrous Na_2SO_4 and concentrated to afford a crude residue, which was purified by column chromatography (Hexane: Acetone = 4:1) to afford the aldehyde **1.61** (Yield: 75%; 18 mg).

HRMS (ESI) [M + H$^+$] calculated for $C_{18}H_{22}NO_4$: 316.1543, found: 316.1550;

FTIR (neat, cm^{-1}) ν_{max} 2966, 2168, 1767, 1438, 1285, 1204, 972, 880, 761;

^{1}H NMR (500 MHz, CDCl$_3$) δ 9.46 (s, 1H), 6.84 (d, J = 4.1 Hz, 1H), 6.75 (d, J = 1.7 Hz, 1H), 6.02 (d, J = 4.0 Hz, 1H), 5.78 – 5.67 (m, 1H), 3.76 – 3.62 (m, 2H), 3.29 (dd, J = 12.2, 9.9 Hz, 1H), 2.60 (ddd, J = 12.4, 9.0, 3.7 Hz, 1H), 2.34 (ddd, J = 12.0, 5.5, 2.3 Hz, 1H), 2.07 (ddd, J = 18.2, 8.7, 4.1 Hz, 1H), 1.97 (d, J = 1.7, 3H), 1.86 (tdd, J = 13.1, 11.3, 3.7 Hz, 1H), 1.69 (dtd, J = 15.5, 7.7, 3.6 Hz, 1H), 1.65 – 1.51 (m, 2H), 0.91 (t, J = 7.6 Hz, 3H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 179.5, 171.3, 144.7, 141.3, 133.6, 131.9, 124.7, 112.9, 106.2, 83.3, 50.5, 47.1, 45.2, 35.5, 25.8, 19.9, 13.0, 10.6.
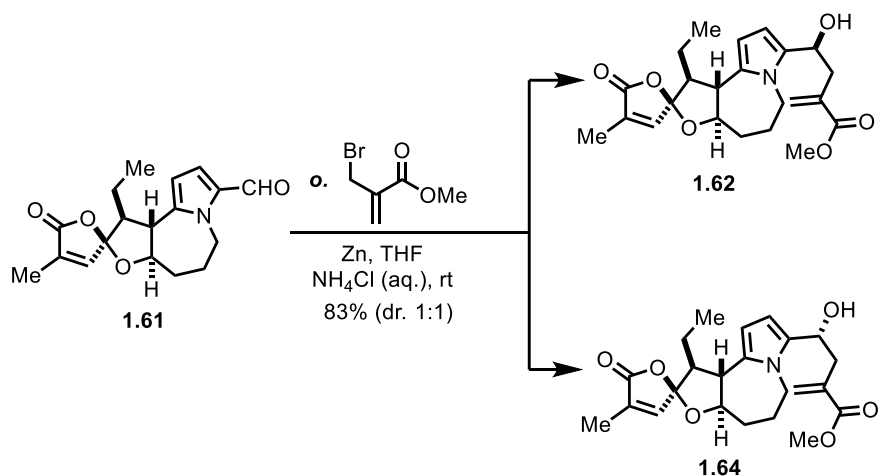
To a solution of aldehyde **1.61** (15 mg, 0.048 mmol) and methyl 2-(bromomethyl)acrylate

(20.4 mg, 13.6 μl, 0.11 mmol) in saturated NH$_4$Cl solution (2.2 ml) and THF (0.45 ml) was added

activated zinc powder (7.6 mg, 0.11 mmol) at room temperature. The resulting reaction mixture

was stirred at room temperature for 2 h and diluted with ethyl ether (5 ml). The aqueous layer was

extracted with ethyl ether. The combined organic phases were dried with anhydrous Na$_2$SO$_4$ and

concentrated to afford a crude residue, which was purified by column chromatography (Hexane:

EtOAc: DCM = 1:1:1) to afford the desired diastereomer **1.62** (Yield: 42%; 8.3 mg) and its epimer

1.64 (Yield: 41%; 8.1 mg).

1.62
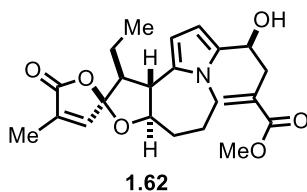
HRMS (ESI) [M + H$^+$] calculated for C$_{23}$H$_{30}$NO$_6$: 416.2068, found: 416.2068;

FTIR (neat, cm^{-1}) ν_{max} 3501, 2928, 1766, 1717, 1438, 1285, 1024, 972, 880, 761;

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.76 (d, J = 1.7 Hz, 1H), 6.32 (d, J = 1.3 Hz, 1H), 6.03 (d, J = 3.6 Hz, 1H), 5.81 (dd, J = 3.7, 0.9 Hz, 1H), 5.73 (d, J = 1.3 Hz, 1H), 4.83 (ddd, J = 9.6, 6.0, 3.6 Hz, 1H), 4.46 (dd, J = 14.6, 5.6 Hz, 1H), 3.78 (s, 3H), 3.72 – 3.62 (m, 2H), 3.28 – 3.18 (m, 1H), 2.97 (ddd, J = 14.0, 3.6, 1.1 Hz, 1H), 2.86 – 2.78 (m, 1H), 2.56 (ddd, J = 12.3, 9.3, 3.3 Hz, 1H), 2.31 (dq, J = 12.1, 3.7 Hz, 1H), 2.10 – 2.01 (m, 2H), 1.96 (d, J = 1.6 Hz, 3H), 1.87 – 1.70 (m, 2H), 1.64 – 1.59 (m, 1H), 1.58-1.54 (m, 1H), 0.90 (t, J = 7.6 Hz, 3H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 171.6, 167.8, 145.3, 137.0, 134.2, 133.2, 131.5, 128.4, 113.2, 104.3, 102.3, 84.7, 65.5, 52.1, 50.7, 47.2, 44.8, 38.9, 35.3, 26.3, 19.9, 13.1, 10.5.

1.64
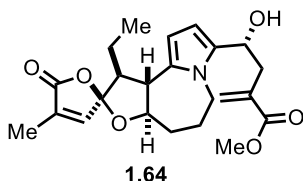
^{1}H NMR (500 MHz, CDCl$_3$) δ 6.75 (q, J = 1.6 Hz, 1H), 6.30 (d, J = 1.3 Hz, 1H), 6.12 – 5.94 (m, 1H), 5.81 (dd, J = 3.6, 1.0 Hz, 1H), 5.73 (q, J = 1.2 Hz, 1H), 4.81 (dd, J = 9.4, 4.6 Hz, 1H), 4.51 (dd, J = 15.0, 5.6 Hz, 1H), 3.77 (s, 3H), 3.75 – 3.62 (m, 2H), 3.21 (ddd, J = 12.1, 9.8, 1.0 Hz, 1H), 2.95 (ddd, J = 14.1, 3.8, 1.1 Hz, 1H), 2.81 (ddd, J = 14.1, 9.5, 0.9 Hz, 1H), 2.56 (ddd, J = 12.3, 9.3, 3.3 Hz, 1H), 2.30 (dq, J = 12.7, 3.7 Hz, 1H), 2.10 – 2.00 (m, 2H), 1.96 (d, J = 1.7 Hz, 3H), 1.87 – 1.68 (m, 2H), 1.66 – 1.44 (m, 2H), 0.90 (t, J = 7.6 Hz, 3H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 171.6, 167.8, 145.3, 137.0, 134.2, 133.2, 131.3, 128.3, 113.2, 104.4, 102.4, 84.7, 65.5, 52.1, 50.7, 47.3, 44.4, 39.4, 35.2, 26.4, 19.9, 13.1, 10.5.

1.62 → **1.63**
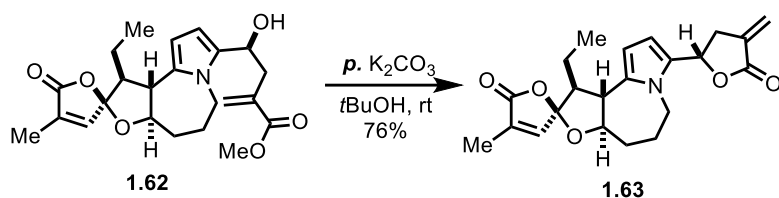
p. K$_2$CO$_3$
*t*BuOH, rt
76%

To a solution of **1.62** (23 mg, 0.055 mmol) in *t*BuOH (1.2 ml) was added K$_2$CO$_3$ (23 mg, 0.17 mmol) at room temperature and stirred for 6 h. The reaction mixture was quenched with water and extracted with DCM. The combined organic layers were concentrated to afford white solid **1.63** (16 mg, 76% yield), which was submitted for the next reaction directly.

HRMS (ESI) [M + H$^+$] calculated for C$_{22}$H$_{26}$NO$_5$: 384.1805, found: 384.1801;

FTIR (neat, cm^{-1}) ν_{max} 2923, 2855, 1764, 1458, 1376, 1277, 1137, 974, 757;

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.76 (q, *J* = 1.6 Hz, 1H), 6.28 (t, *J* = 2.8 Hz, 1H), 6.11 (d, *J* = 3.7 Hz, 1H), 5.87 – 5.85 (m, 1H), 5.74 (t, *J* = 2.5 Hz, 1H), 5.59 (t, *J* = 7.4 Hz, 1H), 4.31 (dd, *J* = 14.5, 5.6 Hz, 1H), 3.81 – 3.74 (m, 1H), 3.67 (ddd, *J* = 11.1, 9.8, 3.6 Hz, 1H), 3.31 – 3.22 (m, 3H), 2.56 (ddd, *J* = 12.4, 9.1, 3.4 Hz, 1H), 2.34 (dq, *J* = 12.7, 3.6 Hz, 1H), 2.10 (dq, *J* = 14.3, 4.3 Hz, 1H), 1.96 (d, *J* = 1.6 Hz, 3H), 1.83 (tdd, *J* = 13.0, 11.2, 3.6 Hz, 1H), 1.76 – 1.66 (m, 1H), 1.58 (ddt, *J* = 14.7, 9.8, 7.4 Hz, 2H), 0.91 (t, *J* = 7.6 Hz, 3H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 171.6, 169.8, 145.2, 134.6, 133.6, 133.4, 129.0, 122.1, 113.1, 106.7, 103.0, 84.3, 70.8, 50.6, 47.3, 45.2, 35.4, 31.7, 26.2, 19.9, 13.1, 10.6.

1.64 → **1.65**

p. K$_2$CO$_3$
*t*BuOH, rt
99%
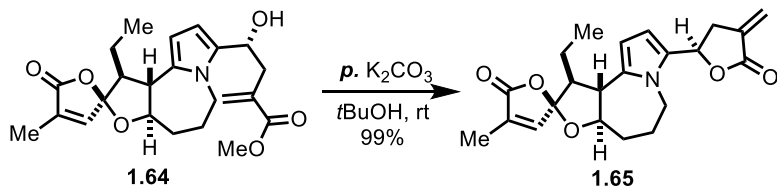
Compound **1.65** was prepared using the same procedure described above. Yield: 99%.

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.75 (d, J = 1.7 Hz, 1H), 6.28 (t, J = 2.8 Hz, 1H), 6.12 (dd, J = 3.8, 0.7 Hz, 1H), 5.85 (dd, J = 3.7, 1.0 Hz, 1H), 5.73 (t, J = 2.4 Hz, 1H), 5.55 (t, J = 7.4 Hz, 1H), 4.37 (dd, J = 15.4, 5.5 Hz, 1H), 3.86 – 3.77 (m, 1H), 3.65 (ddd, J = 11.3, 9.8, 3.6 Hz, 1H), 3.28 (dt, J = 7.4, 2.6 Hz, 2H), 3.22 (ddd, J = 12.4, 9.9, 0.9 Hz, 1H), 2.57 (ddd, J = 12.4, 9.2, 3.4 Hz, 1H), 2.31 (ddd, J = 11.1, 5.9, 2.2 Hz, 1H), 2.13 – 2.03 (m, 1H), 1.96 (d, J = 1.7 Hz, 3H), 1.84 (tdd, J = 13.1, 11.2, 3.8 Hz, 1H), 1.78 – 1.67 (m, 1H), 1.65 – 1.57 (m, 1H), 1.52 (ddt, J = 11.7, 3.3, 1.7 Hz, 1H), 0.90 (t, J = 7.6 Hz, 3H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 171.5, 169.6, 145.1, 134.5, 133.5, 133.4, 128.7, 122.2, 113.1, 107.0, 103.1, 84.4, 70.8, 50.6, 47.3, 44.7, 35.1, 32.0, 26.3, 19.9, 13.1, 10.6.

Bisdehydrostemoninine (**1.2**)
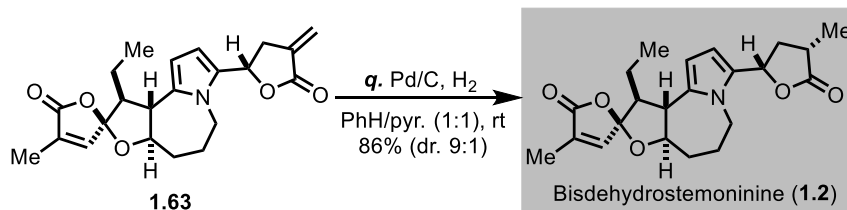
To a solution of **1.63** (5 mg, 0.013 mmol) in 0.66 ml of benzene/pyridine (1:1) was added the 10% Pd/C (1 mg) at room temperature. The reaction was stirred under 1 atm hydrogen for 20 min. before it was diluted with ethyl ether and filtered through a short pad of Celite. The combined organic layer was concentrated to afford the product **1.2** as a white solid (Yield: 86%; 4.3 mg; dr. 9:1).

HRMS (ESI) [M + H$^+$] calculated for C$_{22}$H$_{28}$NO$_5$: 386.1962, found: 386.1970;

FTIR (neat, cm^{-1}) ν_{max} 2933, 1761, 1438, 1343, 1287, 1165, 972, 761

^{1}H NMR (500 MHz, CDCl$_3$) δ 6.76 (q, J = 1.6 Hz, 1H), 6.13 (d, J = 3.8 Hz, 1H), 5.87 (dd, J = 3.8, 1.0 Hz, 1H), 5.38 (dd, J = 11.0, 5.2 Hz, 1H), 4.28 (dd, J = 14.5, 5.5 Hz, 1H), 3.81 – 3.73 (m, 1H), 3.70 – 3.61 (m, 1H), 3.31 – 3.22 (m, 1H), 2.88 – 2.74 (m, 1H), 2.71 (ddd, J = 12.4, 8.3, 5.3 Hz,

1H), 2.57 (ddd, *J* = 12.4, 9.2, 3.5 Hz, 1H), 2.38 – 2.28 (m, 1H), 2.21 (td, *J* = 12.2, 11.0 Hz, 1H), 2.11 – 2.05 (m, 1H), 1.96 (d, *J* = 1.7 Hz, 3H), 1.88 – 1.78 (m, 1H), 1.72 (dtd, *J* = 15.5, 7.7, 3.3 Hz, 1H), 1.68 – 1.57 (m, 2H), 1.35 (d, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 7.6 Hz, 3H);

^{13}C NMR (126 MHz, CDCl$_3$) δ 179.0, 171.7, 145.3, 133.6, 128.8, 113.3, 107.0, 103.1, 84.5, 71.6, 50.8, 47.4, 45.3, 36.2, 35.5, 34.9, 29.7, 26.3, 20.1, 15.2, 13.2, 10.7.

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 7.17 (q, *J* = 1.8 Hz, 1H), 6.13 (d, *J* = 3.7 Hz, 1H), 5.85 (d, *J* = 3.7 Hz, 1H), 5.53 (dd, *J* = 11.1, 5.2 Hz, 1H), 4.18 (dd, *J* = 14.7, 5.5 Hz, 1H), 3.86 (dd, *J* = 14.8, 11.2 Hz, 1H), 3.57 – 3.46 (m, 1H), 3.22 (dd, *J* = 12.1, 9.9 Hz, 1H), 2.89 – 2.79 (m, 1H), 2.70 (ddd, *J* = 12.4, 9.0, 3.5 Hz, 1H), 2.64 – 2.55 (m, 1H), 2.22 – 2.15 (m, 1H), 2.10 (q, *J* = 11.9 Hz, 1H), 2.04 – 1.94 (m, 1H), 1.84 (d, *J* = 1.6 Hz, 3H), 1.69 (qd, *J* = 12.8, 3.7 Hz, 1H), 1.57 (dtt, *J* = 15.4, 7.7, 3.8 Hz, 1H), 1.41 (ddd, *J* = 14.5, 9.0, 7.3 Hz, 2H), 1.17 (d, *J* = 7.0 Hz, 3H), 0.82 (td, *J* = 7.2, 3.6 Hz, 3H);

^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 178.8, 171.3, 146.9, 132.7, 131.6 , 128.6, 113.2, 106.8, 102.7, 84.0, 71.0, 49.1, 46.3, 44.1, 35.5, 34.8, 34.3, 25.9, 19.7, 14.6, 12.4, 10.1.
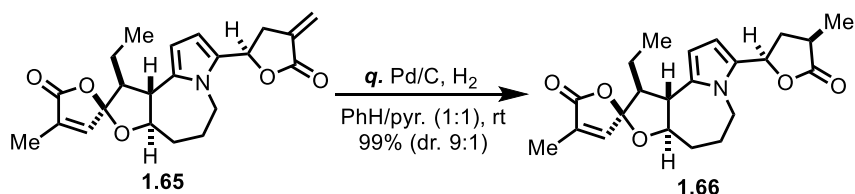
Compound **1.66** was prepared using the same procedure described above. Yield: 99%.

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.17 (q, J = 15 Hz, 1H), 6.14 (d, J = 3.7 Hz, 1H), 5.85 (dd, J = 3.7, 0.8 Hz, 1H), 5.50 (dd, J = 11.0, 5.2 Hz, 1H), 4.22 (dd, J = 14.9, 5.4 Hz, 1H), 3.88 (dd, J = 15.0, 11.5 Hz, 1H), 3.51 (ddd, J = 11.2, 9.7, 3.5 Hz, 1H), 3.26 – 3.15 (m, 1H), 2.84 (ddt, J = 15.2, 12.1, 7.2 Hz, 1H), 2.70 (ddd, J = 12.4, 9.1, 3.5 Hz, 1H), 2.62 (m, 1 H), 2.19 – 2.04 (m, 2H), 2.00 – 1.93 (m, 1H), 1.84 (d, J = 1.6 Hz, 3H), 1.68 (qd, J = 12.6, 12.2, 3.6 Hz, 1H), 1.59 (dtd, J = 15.6, 7.8, 3.5 Hz, 1H), 1.48 – 1.29 (m, 2H), 1.18 (d, J = 7.0 Hz, 3H), 0.82 (t, J = 7.6 Hz, 3H);

^{13}C NMR (126 MHz, DMSO-d_6) δ 178.7, 171.3, 146.9, 132.5, 131.6, 128.5, 113.2, 106.8, 102.7, 84.0, 71.0, 49.1, 46.4, 43.6, 35.5, 34.5, 34.4, 26.0, 19.7, 14.5, 12.4, 10.1.
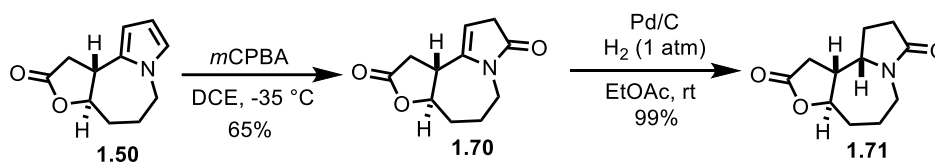
In a flame-dried 8 mL vial, compound **1.50** (10.0 mg, 0.05 mmol) was dissolved in 1 mL anhydrous DCE under argon atmosphere and the solution was cooled to -35 ^{o}C. mCPBA (18.0 mg, 0.1 mmol) was dissolved in 1 mL anhydrous DCE and the solution was added dropwise to the reaction slowly. After the mCPBA was added completely, the reaction was stirred at -35 ^{o}C for 30 mins before 2 mL saturated NaHCO$_3$ solution and 2 mL saturated Na$_2$S$_2$O$_3$ solution were added. The aqueous phase was extracted by DCM for 3 time and dried over Na$_2$SO$_4$. After solid was filtered off, the solution was concentrated and purified by column chromatography (40% ethyl acetate in hexanes) to obtain product (7.1 mg mg, 65% yield) and starting material (3.1 mg, 28%) was recovered. The product was used directly for the next step.

In a flame-dried 8 mL vial, γ-lactam **1.70** (5.0 mg, 0.024 mmol) was dissolved in 2 mL EtOAc under argon atmosphere, and Pd/C (1 mg) was added in one portion. H$_2$ was flushed into

the reaction for 5 times, and the reaction was stirred under H_2 atmosphere for 30 mins before the solution was passed through a plug of celite. The organic layer was dried over Na_2SO_4. After solid was filtered off, the solution was concentrated and purified by Prep TLC (40% EtOAc in hexanes) to obtain compound **1.71** as white solid (4.9 mg, 99% yield).

HRMS (ESI) [M + H$^+$] calculated for $C_{11}H_{15}NO_3$: 210.1125, found: 210.1123;

FTIR (neat, cm^{-1}) v_{max} 2924, 2514, 2159, 2028, 1977, 1777, 1261, 1017, 712;

^{1}H NMR (500 MHz, Chloroform-d) δ 4.28 (td, J = 10.2, 3.0 Hz, 1H), 4.14 (dt, J = 13.1, 3.1 Hz, 1H), 3.99 (dt, J = 10.6, 6.4 Hz, 1H), 2.84 (ddt, J = 12.7, 9.5, 4.6 Hz, 1H), 2.71 – 2.59 (m, 2H), 2.51 (dd, J = 17.4, 12.7 Hz, 1H), 2.46 – 2.34 (m, 4H), 2.07 (dtd, J = 11.8, 5.9, 3.9 Hz, 1H), 1.90 – 1.79 (m, 2H), 1.78 – 1.67 (m, 2H), 1.60 – 1.48 (m, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 174.8, 174.3, 79.9, 56.2, 45.0, 40.4, 34.8, 31.2, 30.7, 25.6, 22.8.
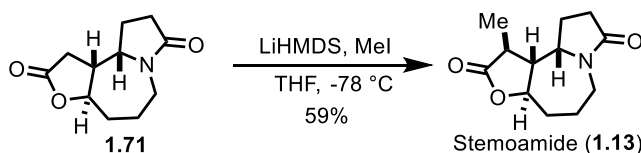
In an 8 mL flame-dried vial, the tricycle compound **1.71** (20.9 mg, 0.1 mmol) was dissolved in anhydrous 1 mL THF and was cooled to -78 °C. Freshly prepared LiHMDS (0.5 M, 0.3 mL, 0.15 mmol) was added dropwise to the solution. The suspension was allowed to warm to –40 °C and stirred for 1 h at this temperature. After the reaction was cooled to-78 °C, methyl iodide (28.2 mg, 0.2 mmol) was added dropwise at –78 °C. The reaction was slowly warmed up to room temperature and was stirring for 2 h at room temperature. The reaction was quenched with aqueous 1 M HCl (2 mL) was extracted with CHCl$_3$ 3 times. The combined organic layer was dried over

Na$_2$SO$_4$. After solid was filtered off, the solution was concentrated and purified by column chromatography (EtOAc/MeOH 1:0 to 19:1) to obtain stemoamide (15.2 mg, 59%) as a white solid.

HRMS (ESI) [M + H$^+$] calculated for C$_{12}$H$_{17}$NO$_3$: 224.1281, found: 224.1283;

FTIR (neat, cm^{-1}) ν_{max} 2925, 2854, 1766, 1671, 1420, 1275, 1189, 1009, 720, 607;

^{1}H NMR (500 MHz, Chloroform-d) δ 4.19 (td, J = 10.2, 3.1 Hz, 1H), 4.16 – 4.11 (m, 1H), 3.98 (dt, J = 10.7, 6.4 Hz, 1H), 2.76 – 2.62 (m, 1H), 2.59 (dd, J = 12.4, 7.0 Hz, 1H), 2.45 – 2.33 (m, 4H), 2.08 – 1.94 (m, 1H), 1.90 – 1.73 (m, 1H), 1.79 – 1.60 (m, 1H), 1.52 (m, 2H), 1.29 (d, J = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, CDCl$_3$) δ 177.5, 174.2, 77.8, 55.9, 52.8, 40.3, 37.4, 34.9, 30.7, 25.7, 22.7, 14.2.
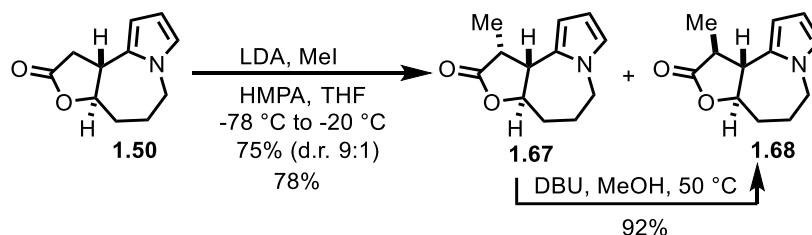
To a stirred solution of lactone **1.50** (191 mg, 1.0 mmol) was added LDA dropwise freshly prepared (0.3 M solution in THF, 10.0 ml, 3.0 mmol) at -78 °C. After stirring for 30 min, HMPA (18 µl) was added, followed by the dropwise addition of methyl iodide (0.31 ml, 5.0 mmol). The resulting reaction mixture was raised to – 20 °C and stirred for 4 h at this temperature. The reaction was quenched with saturated aqueous NH$_4$Cl and extracted with EtOAc. The combined organic layer was concentrated to afford a crude product and was purified by column chromatography (Hexane: EtOAc = 4:1) to obtain the mixture (160 mg, 78% yield).

The mixture (1.2 g, 5.9 mmol) was dissolved in 260 mL MeOH, and DBU (897 mg, 5.9 mmol) was added dropwise. The reaction was stirred at 50 $^{\circ}$C for 24 h before the solution was concentrated. The crude product was purified by column chromatography (Hexane: EtOAc = 4:1) to obtain a single stereoisomer. (1.1 g, 92% yield)

HRMS (ESI) [M + H$^+$] calculated for $C_{12}H_{15}NO_2$: 206.1175, found: 206.1175;

FTIR (neat, cm^{-1}) ν_{max} 2932, 1773, 1454, 1323, 1220, 1201, 1168, 1145, 1012,721;

^{1}H NMR (500 MHz, Chloroform-d) δ 6.63 (m, 1H), 6.05 (dd, J = 3.5, 2.7 Hz, 1H), 5.97 (m, 1H), 4.11 (m, 1H), 3.93 – 3.83 (m, 2H), 3.06 – 2.91 (m, 2H), 2.57 – 2.48 (m, 1H), 2.16 – 2.06 (m, 1H), 1.82 – 1.61 (m, 2H), 1.43 (d, J = 6.5 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 178.4, 128.7, 122.8, 106.6, 105.2, 81.7, 49.4, 49.2, 39.7, 34.2, 26.3, 14.0.
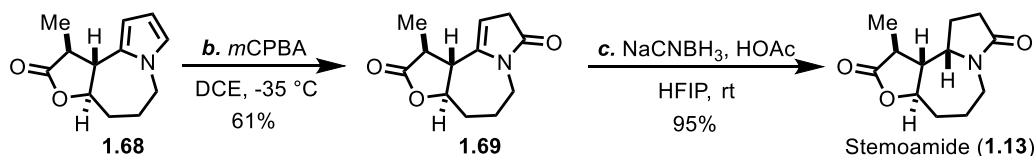
In a flame-dried 8 mL vial, compound **1.68** (41.0 mg, 0.2 mmol) was dissolved in 4 mL anhydrous DCE under argon atmosphere and the solution was cooled to -35 $^{\circ}$C. mCPBA (69.0 mg, 0.4 mmol) was dissolved in anhydrous DCE and the solution was added dropwise to the reaction slowly. After the mCPBA was added completely, the reaction was stirred at -35 $^{\circ}$C for 30 mins before 10 mL saturated NaHCO$_3$ solution and 10 mL saturated Na$_2$S$_2$O$_3$ solution were added. The aqueous phase was extracted by DCM for 3 time and dried over Na$_2$SO$_4$. After solid was filtered off, the solution was concentrated and purified by column chromatography (40% ethyl acetate in hexanes) to obtain product (25.2 mg mg, 61% yield). The product was used

directly for the next step.

Compound 1. In a flame-dried 8 mL vial, γ-lactam **1.69** (5.4 mg, 0.024 mmol) was dissolved in 2 mL HFIP under argon atmosphere, and NaCNBH$_3$ (15.1 mg, 0.24 mmol) was added in one portion followed by 0.1 mL HOAc. The solution was stirred at rt overnight before the solution was passed through a silcal gel plug. Solvent was removed under vacuum before a flush column (EtOAc then 5% MeOH in EtOAc). The second fraction was concentrated to afford stemoamide (**1.13**) as 1:3.6 diastereomers (5.2 mg, 95% yield).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.23 – 4.16 (m, 1H), 4.14 (d, *J* = 3.8 Hz, 1H), 3.99 (dt, *J* = 10.7, 6.4 Hz, 1H), 2.70 – 2.62 (m, 1H), 2.62 – 2.52 (m, 1H), 2.49 – 2.30 (m, 4H), 2.05 (dq, *J* = 12.1, 5.3 Hz, 1H), 1.84 (dt, *J* = 11.6, 6.0 Hz, 1H), 1.78 – 1.61 (m, 1H), 1.59 – 1.43 (m, 2H), 1.30 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, CDCl$_3$) δ 177.5, 174.2, 77.8, 56.0, 52.9, 40.4, 37.5, 35.0, 30.8, 25.8, 22.7, 14.3.

Bisdehydroneostemoninine (**1.1**) — *m*CPBA, DCE, -35 °C, 65% brsm, 40% (40% rsm) → **1.72** — NaCNBH$_3$, HOAc, HFIP, rt, 33% → Tuberostemoamide (**1.6**)
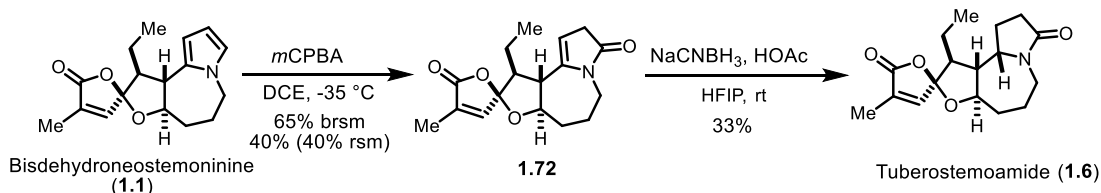
In a flame-dried 8 mL vial, bisdehydroneostemoninine (5.0 mg, 0.017 mmol) was dissolved in 1 mL anhydrous DCE under argon atmosphere, and the solution was cooled to -35 °C. mCPBA (5.8 mg, 0.034 mmol) was dissolved in anhydrous DCE, and the solution was added dropwise to the reaction slowly. After the mCPBA was added completely, the reaction was stirred at -35 °C for 30 mins before 2 mL saturated NaHCO$_3$ solution and 2 mL saturated Na$_2$S$_2$O$_3$ solution were added.

The aqueous phase was extracted by DCM for 3 times and dried over Na_2SO_4. After solid was filtered off, the solution was concentrated and purified by Prep TLC (40% ethyl acetate in hexanes) to obtain the product (2.1 mg, 40% yield) and starting material (2.1 mg, 40%) was recovered. The product was used directly for the next step.

In a flame-dried 8 mL vial, γ-lactam **20** (10.0 mg, 0.03 mmol) was dissolved in 3 mL HFIP under argon atmosphere, and $NaCNBH_3$ (103 mg, 0.6 mmol) was added in one portion. HOAc (18 mg, 0.3 mmol) was added dropwise, and the reaction was stirred for 30 mins before the reaction was quenched by saturated $NaHCO_3$ and extracted by DCM for 3 times. The organic layer was dried over Na_2SO_4. After solid was filtered off, the solution was concentrated and purified by Prep TLC (40% EtOAc in hexanes) to obtain tuberostemoamide (**7**) (3.0 mg, 33% yield).

HRMS (ESI) [M + H$^+$] calculated for $C_{17}H_{23}NO_4$: 306.1701, found: 306.1700;

FTIR (neat, cm^{-1}) v_{max} 2923, 2853, 1766, 1686, 1454, 1274, 974, 874, 714;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.65 (q, *J* = 1.6 Hz, 1H), 4.09 (dt, *J* = 14.3, 3.3 Hz, 1H), 4.05 – 3.97 (m, 2H), 2.74 – 2.58 (m, 2H), 2.47 – 2.33 (m, 2H), 2.21 – 2.10 (m, 2H), 2.00 (m, 1H), 1.94 (d, *J* = 1.7 Hz, 3H), 1.85 – 1.63 (m, 3H), 1.55 – 1.37 (m, 3H), 0.90 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 174.0, 171.4, 144.0, 134.4, 113.8, 80.9, 56.3, 52.0, 49.8, 40.4, 35.9, 30.9, 25.7, 22.2, 20.4, 13.1, 10.8.

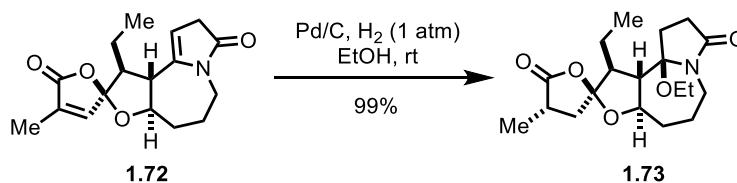

In a flame-dried 8 mL vial, γ-lactam **20** (8.0 mg, 0.026 mmol) was dissolved in 3 mL EtOH under argon atmosphere, and Pd/C (0.8 mg) was added in one portion to the solution. H_2 was

bubbled into the solution for 30 mins. The solution was pass through a plug of celite to remove

Pd/C catalyst and the solution was concentrated to give compound **24** (9.0 mg, 99% yield).

HRMS (ESI) [M + H$^+$] calculated for C$_{19}$H$_{29}$NO$_5$: 352.2118, found: 352.2120;

FTIR (neat, cm^{-1}) v_{max} 2920, 2850, 1667, 1559, 1418, 1260, 1087, 1020, 800, 714;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.84 (d, *J* = 14.1 Hz, 1H), 3.65 – 3.53 (m, 1H), 3.33 – 3.17

(m, 2H), 3.00 – 2.87 (m, 1H), 2.87 – 2.79 (m, 1H), 2.63 (dd, *J* = 11.9, 9.6 Hz, 1H), 2.59 – 2.44

(m, 1H), 2.44 – 2.29 (m, 2H), 2.16 – 2.03 (m, 4H), 2.03 – 1.91 (m, 2H), 1.82 – 1.68 (m, 2H),

1.68 – 1.45 (m, 2H), 1.27 (d, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.0 Hz, 3H), 1.01 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (126 MHz, CDCl$_3$) δ 179.0, 174.1, 114.9, 93.7, 80.2, 58.3, 56.9, 50.0, 39.1, 38.1, 36.5,

34.6, 30.0, 25.4, 24.6, 21.3, 15.4, 15.4, 13.2.

Tuberostemoamide (**1.6**)   Pd/C, H$_2$ (1 atm) / EtOH, rt / 99%   Sessilifoliamide A (**1.7**)
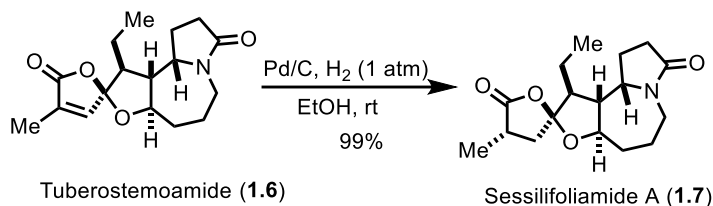
In a flame-dried 8 mL vial, tuberostemoamide (**7**) (5.0 mg, 0.016 mmol) was dissolved in 2

mL EtOH under argon atmosphere, and Pd/C (0.5 mg) was added in one portion to the solution.

H$_2$ was bubbled into the solution for 30 mins and the reaction was stirred under H$_2$ atmosphere at

rt overnight. The solution was pass through a plug of celite to remove Pd/C catalyst and the solution

was concentrated to give sessilifoliamide A (4.9 mg, 99% yield).

HRMS (ESI) [M + H$^+$] calculated for C$_{17}$H$_{25}$NO$_4$: 308.1856, found: 308.1857;

FTIR (neat, cm^{-1}) v_{max} 2922, 2852, 1721, 1668, 1456, 1261, 1096, 1026, 803, 713, 610;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.07 (d, *J* = 14.3 Hz, 1H), 4.01 (dt, *J* = 10.4, 6.3 Hz, 1H),

3.90 (ddd, *J* = 11.3, 9.5, 2.8 Hz, 1H), 2.95 (ddd, *J* = 11.3, 8.6, 7.2 Hz, 1H), 2.66 (ddd, *J* = 14.1,

12.3, 1.6 Hz, 1H), 2.59 – 2.49 (m, 1H), 2.47 – 2.32 (m, 3H), 2.15 – 2.08 (m, 1H), 2.05 – 1.91 (m,

3H), 1.79 – 1.66 (m, 2H), 1.66 – 1.46 (m, 4H), 1.27 (t, J = 7.3 Hz, 3H), 1.03 (t, J = 7.6 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 178.9, 174.2, 114.7, 79.9, 56.5, 52.2, 49.6, 40.4, 39.0,

36.3, 34.7, 30.9, 25.8, 22.3, 21.4, 15.4, 13.1.

CHAPTER 2. SYNTHETIC STUDY TOWARDS STEMOFOLINE ALKALOIDS

2.1 Introduction

Stemofoline (**2.1**) alkaloids were isolated from the family of stemona alkaloids in 1970 by Irie et al. [52] The single-crystal structure was confirmed as hydrobromide salt with provided a pentacyclic core with a conjugated butanolide, and insecticidal activities were reported which attracted synthetic chemist (Figure 2.1).
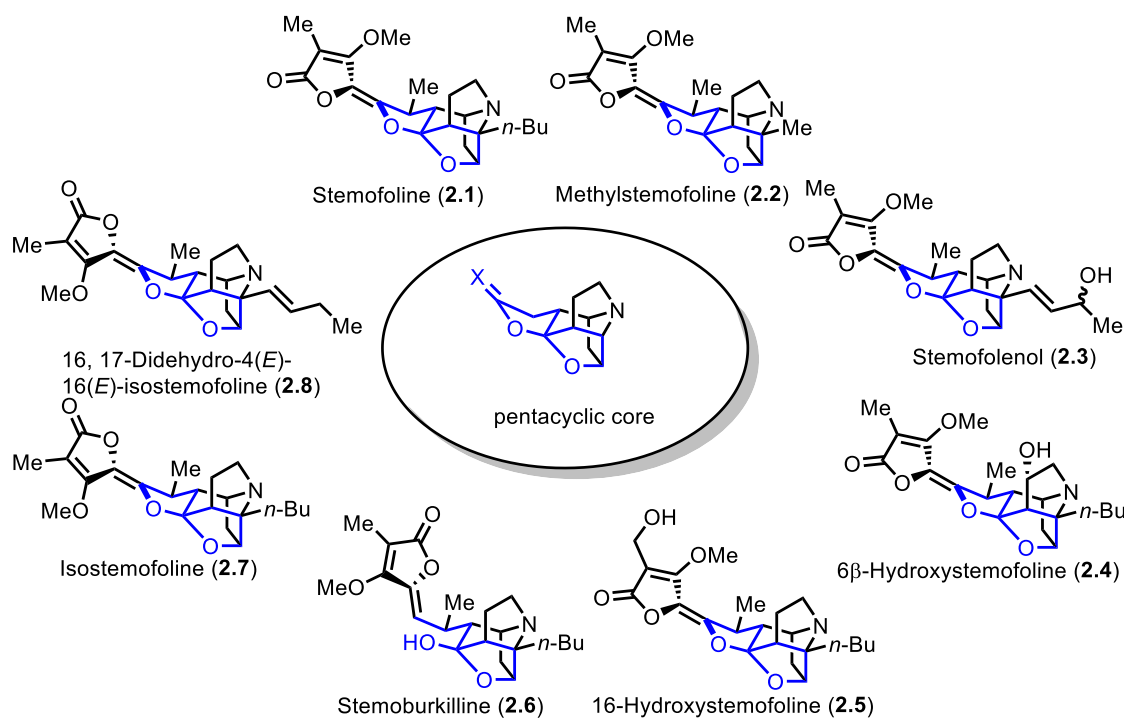
Figure 2.1 stemofoline alkaloids

In 1999, Kende and Smalley reported the first total synthesis of racemic isostemofoline in 25 steps (Scheme 2.1).[53] The total synthesis features a [4+3] cycloaddition. The 1,2-hexanediol (**2.9**) was selectively oxidized and protected as MOM ether followed by condensation to form **2.11** with mono-*N, N*-dimethyl hydrazone of glyoxal. Reductive cyclization was used to obtain pyrrole, followed by Boc protection. [4+3] cycloaddition was used to obtain **2.13** with diazo ester followed

by deprotection, hydrogenation, and decarbomethoxylation to give **2.14**. **2.15** was accessed by condensation of furfural, and alkylation was used to construct **2.16**. Oxidative cleavage and selective reduction were followed by protection to obtain **2.17**. Methylation, desilylation, tosyl protection, and ozonolysis were used to give **2.18** followed by reduction and Dess-Martin oxidation to give **2.19**. Butenolide was installed and was oxidized to give **2.20**. **2.21** was accessed by deprotection and substitution, followed by dehydration to give isostemofoline (**2.7**).
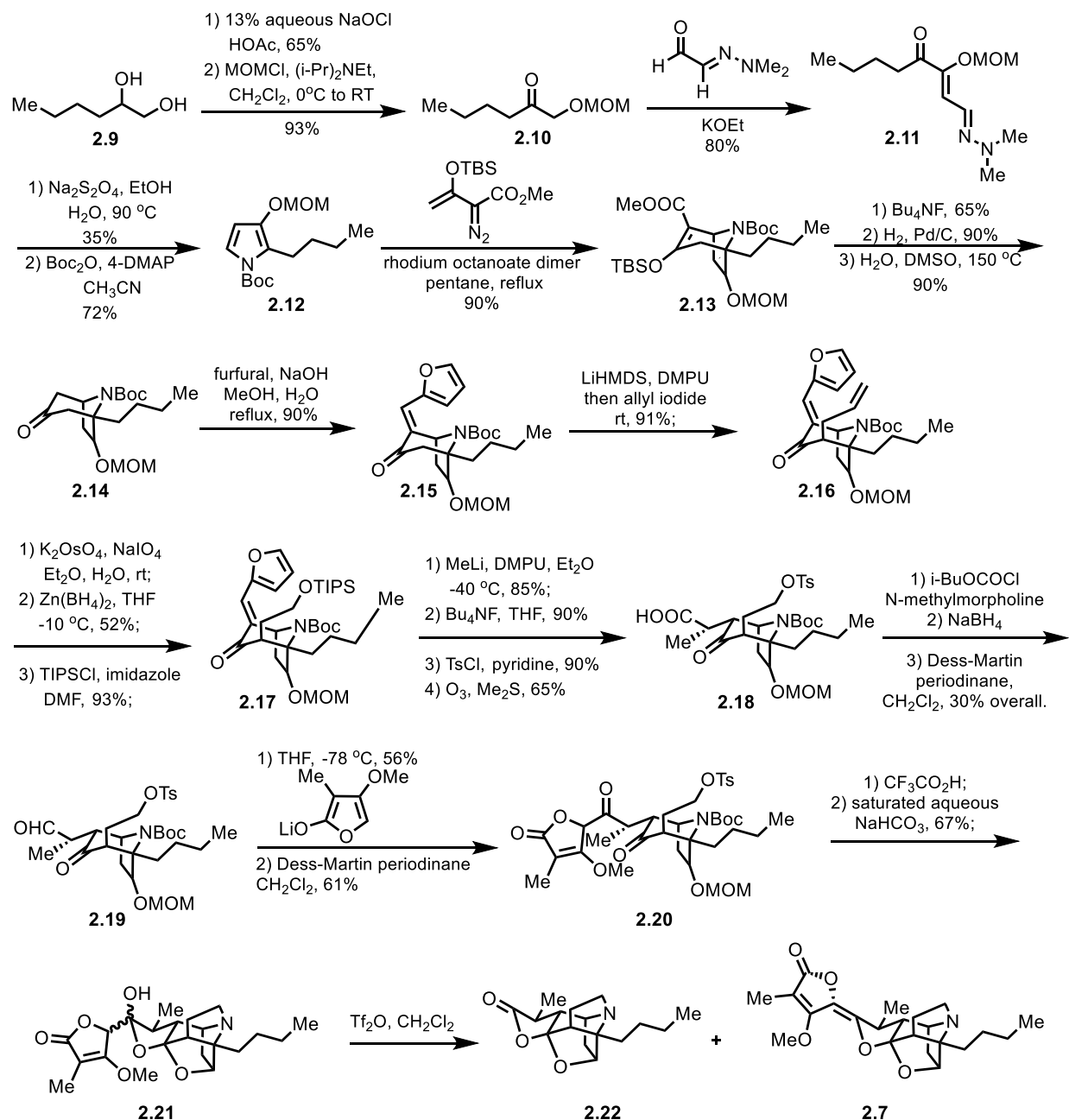
Scheme 2.1 Kende and Smalley's total synthesis of isostemofoline

In 2003, Overman and Bruggemann reported a racemic total synthesis of didehydrostemofoloine and isodidehydrostemofoline in 24 steps (Scheme 2.2) features an aza-Cope-Mannich rearrangement.[54] Pyrrole **2.23** was converted to aza-tricyclodecanone **2.24** via Diels-Alder reaction followed by hydrogenation. Nitro group was removed, and primary alcohol

was protected, followed by DIBALH reduction to obtain **2.25**. **2.25** was then oxidized and converted to enoxysilane followed by ozonolysis to give aza-bicycloheptanone **2.26**. Selective vinylation and treatment of TMSI were used to give **2.27,** which was converted to azatricyclo[5.3.0.0$^{4.10}$]decanone **2.28** in quantitative yield. The side chain was synthesized by TIPS cleavage, oxidation, and Julia-Kocienski olefination to deliver **2.29**. Alkylation and epimerization were used to give **2.30**, followed by selective cleavage, silylation, and methylation to provide **2.31**, which was converted to **2.32** by DIBALH reduction, DMP oxidation and epimerization. Lithium-ion of **2.33** was used to install a tetrahydrofuran ring followed by acidic silyl group deprotection to obtain **2.34**. IBX oxidation and Corey-Winter were used to provide cyclic thionocarbonates **2.36** and **2.37**, which were fragmented to give didehydroisostemofoline (**2.8**) and didehydrostemofoline (**2.38**) respectively.
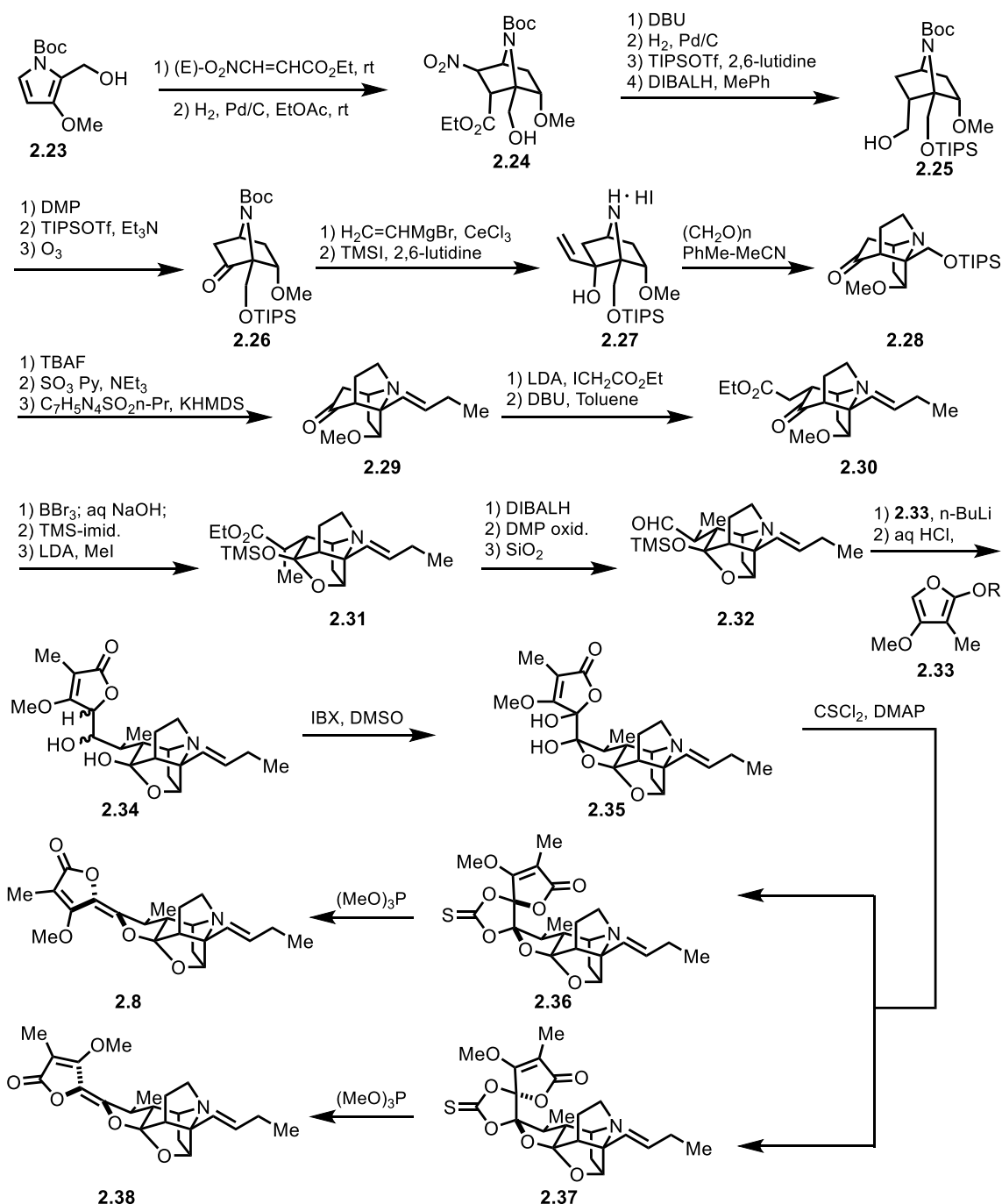
Scheme 2.2 Overman's total synthesis of didehydrostemofoline and isodidehydrostemofoline

The first enantioselective total synthesis of methoxystemofoline and isomethoxystemofoline in 26 steps (Scheme 2.3) were reported by Huang's group in 2015 and featured a halide-assisted bromotropanonation.[55] The total synthesis started from (S)-α-hydroxy-γ-lactone (**2.39**), which was

converted to **2.40** by benzylation and ammonolysis. After 3 steps, lactam **2.41** was synthesized, followed by substitution and reprotection to install side chain of ketone with a small amount *trans*-isomer. Halide-assisted bromotropanonation, which was developed by Huang's group, was used to form 1-bromotropan-3-one (**2.43**) followed by cross-coupling to afford **2.44**. Treatment of LDA and methyl pyruvate provided **2.45** and followed by dehydration to afford **2.46**, which was converted to **2.47** by deprotection and Appel reaction. Cyclization was happened easily under basic condition to deliver **2.48**. To elongate the side chain, a cross-metathesis was applied, followed by hydrogenation to give **2.50**. After TMS protection, reduction, Swern oxidation, and epimerization, 2.51 was achieved. Lithium enolate **2.52** was used for addition, followed by Overman's 3 steps method to give isomethyoxystemofoline (**2.54**) and methoxystemofoline (**2.55**).
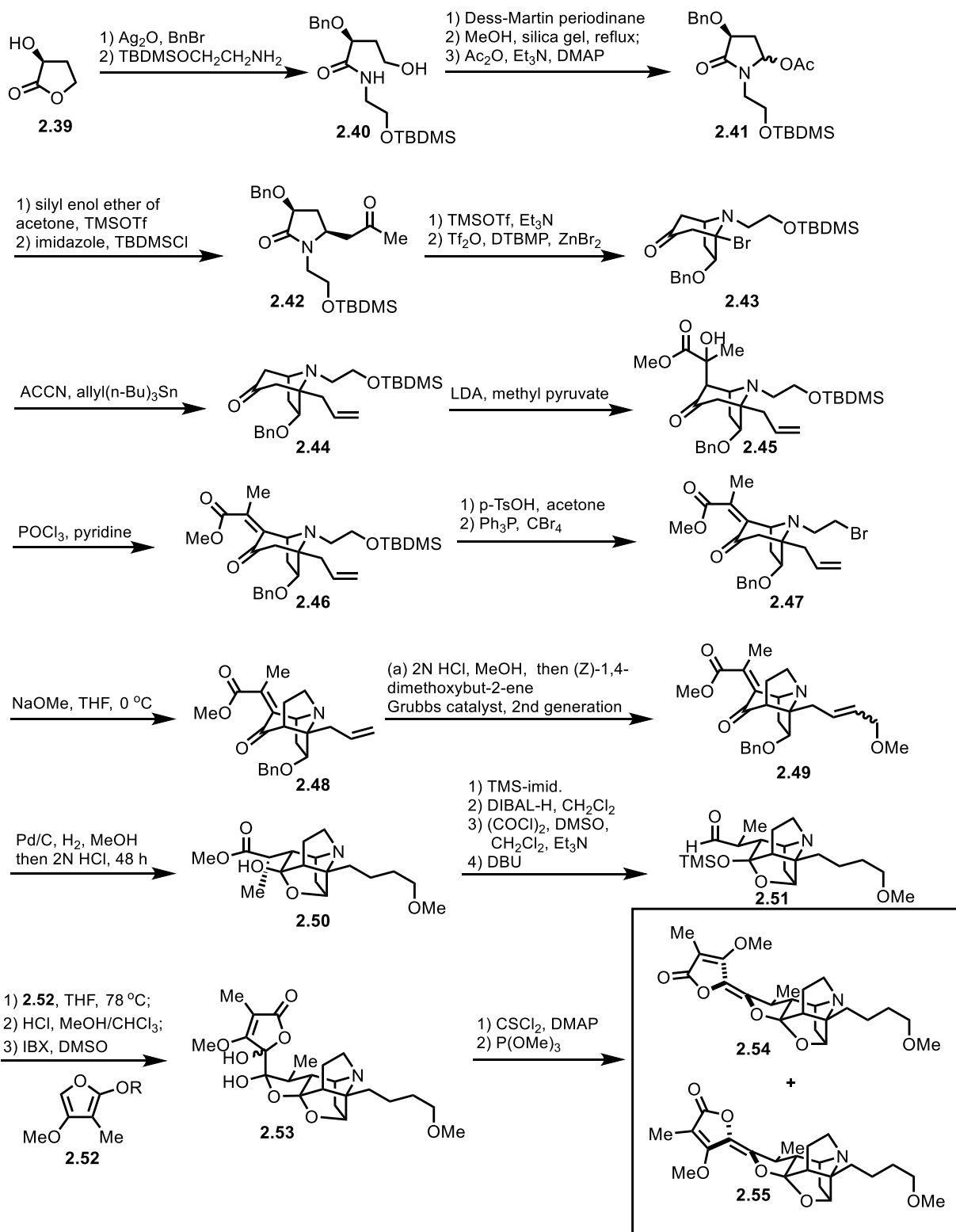
Scheme 2.3 Huang's total synthesis of methoxystemofoline and isomethoxystemofoline

In 2013, Martin's group reported a formal synthesis of stemofoline alkaloids.[56] The synthetic approach started from **2.56**, and after 14 steps, intermediate **2.57** was cyclized by Rh catalyst to access to **2.58**. After 11 steps, the core structure 2.59 was obtained, and the same method to Overman's total synthesis was used to give stemofoline alkaloids.
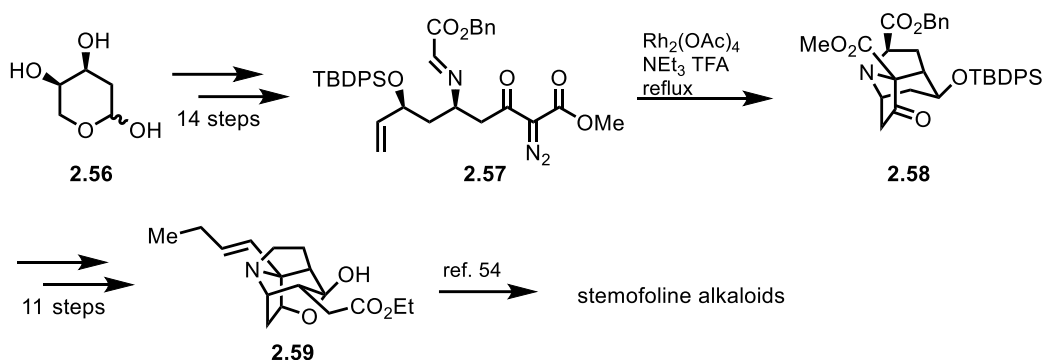
Scheme 2.4 Formal synthesis of stemofoline alkaloids

After 2 years, Fukuyama's group also finished the core of stemofoline alkaloids. The synthesis features a [3+2] cyclization followed by 18 steps to complete the core of stemofoline alkaloids.
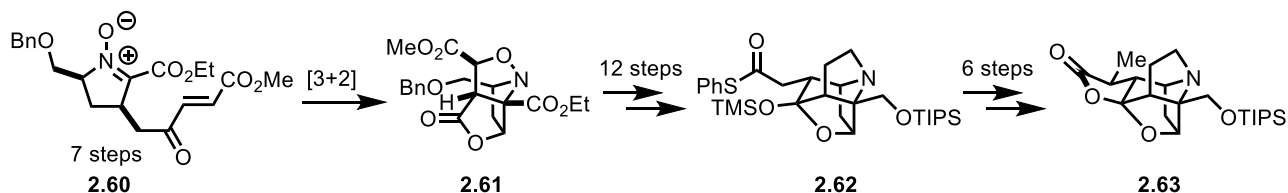
Scheme 2.5 Synthesis of core structure of stemofoline alkaloids

Our recent interest in developing palladium-catalyzed carbonylation reactions for constructing complex natural products resulted in a palladium-catalyzed oxaspirolactonizaiton from cyclopropanol. This new methodology could be a potential method to constructed important intermediate **2.66** (Scheme 2.6) for the total synthesis of stemofoline alkaloids. We proposed that

a tandem Mannich reaction and ketalization could give the core structure **2.64** from **2.66** via intermediate **2.65**. 2.66 could be obtained by palladium-catalyzed oxaspirolactonization, and Kulinkovich reaction from lactone **2.68,** which could be obtained by conjugated addition from bicyclic dihydropyrrole fused furanone **2.69**. To achieve bicyclic intermediate **2.69**, we envision that it could be synthesized by amino carbonylative lactonization from amino propargylic alcohol **2.70**. To our surprise, no reported dihydropyrrole fused furanone was documented, which makes it as a novel scaffold for biological activity tests. Therefore, it proposed to develop a tandem palladium-catalyzed amino carbonylative lactonization for potential biological activities and to access to essential precursors for the total synthesis of stemofoline alkaloids.
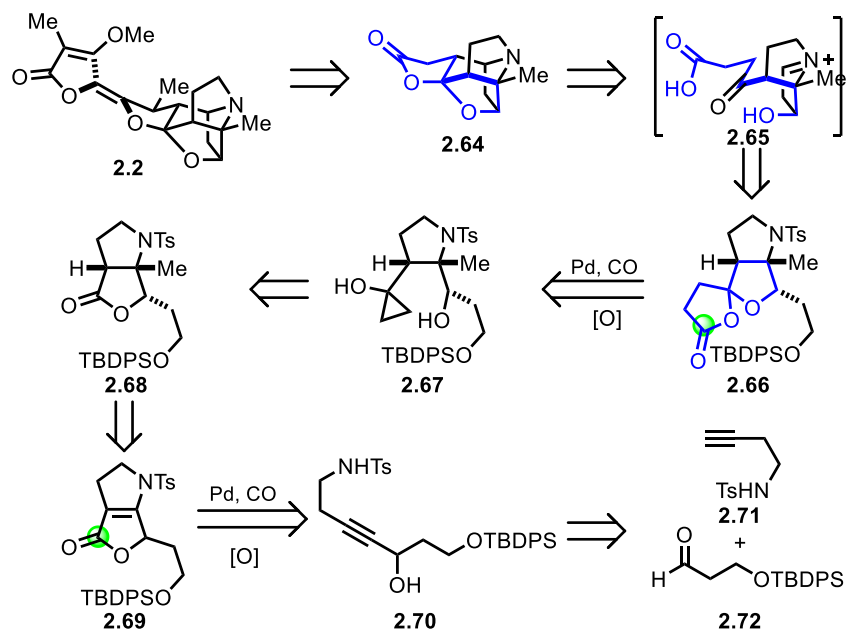
Scheme 2.6 Retro-synthetic analysis of stemofoline alkaloids

In 1979, Murray and Norton reported a palladium-catalyzed carbonylation reaction to obtain α-methylene γ-lactones from acetylenic alcohol (Scheme 2.7A). [57, 58] After that, several palladium-

catalyzed cyclocarbonylations of alkynes were developed. In 1999, Alper reported an efficient way to produce 2(5*H*)-furanones from propargylic alcohols (Scheme 2.7B).[59, 60, 61]

A. Murray and Norton's cyclocarbonylation of acetylenic alcohols

CO, PdI$_2$
Bu$_3$P, MeCN

2.73

2.74
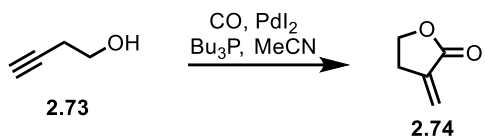
B. Alper's synthesis of 2(5*H*)-furanones

Pd(dba)$_2$, dppb
CO, DME

2.75

2.76
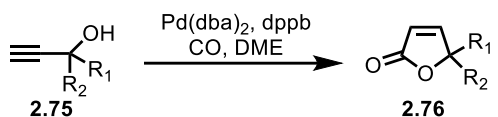
Scheme 2.7 Murray and Alper's carbonylative cyclizations

From 1999 to 2005, Yang's group reported several carbonylative annulations (Scheme 2.8) to construct 2,3-disubstituted benzo[*b*]furans [62, 63], benzo[*b*]furo[3,4-*d*]furan-1-ones [64] and benzo[*b*]furan-3-carboxylic acids[65].

A. Synthesis of 2,3-disubstituted benzo[b]furans

Pd(II), CO
R$_2$OH

2.77

2.78
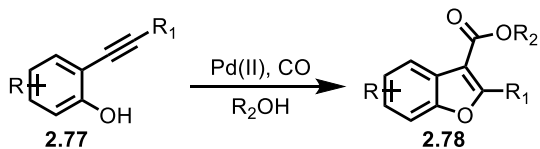
B. Synthesis of benzo[b]furo[3,4-d]furan-1-ones

Pd(II), CO

2.78

2.79
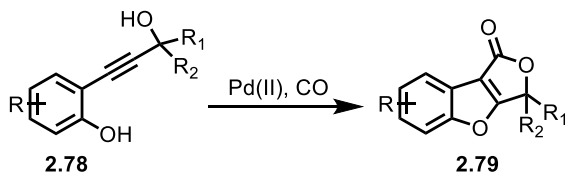
C. Synthesis of benzo[b]furan-3-carboxylic acids

1) Pd(II), CO
2) work up

2.80

2.81
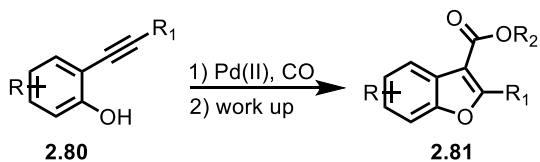
Scheme 2.8 Yang's synthesis of carbonylative cyclizations

In 2002, Lu's group reported palladium-catalyzed cyclization initiated by acetoxypalladation of alkynes (Scheme 2.9A)[66]. In 2004, Li's group developed a palladium-catalyzed carbonylation reaction of terminal alkynes to synthesize (*Z*)-3-haloacrylates (Scheme 2.9B)[67], and Akita's group reported an internal methoxycarbonylation of alkynes (Scheme 2.9C) in 2009[68]. Except for the examples above, other syntheses from Tamaru[69], Negishi[70], Ogawa and Sonoda[71], Yang and Fathi[72], and Gabriele[73] have also developed methodologies to constructed furanones and furans.

A. Lu's palladium catalyzed cyclizaitons
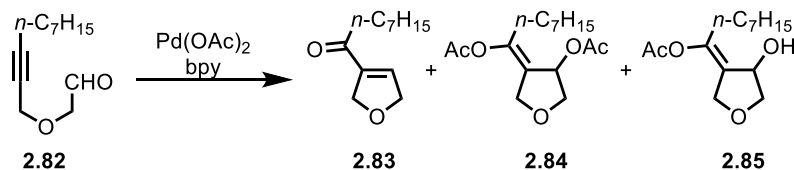
B. Li's synthesis of (Z)-3-haloacrylates
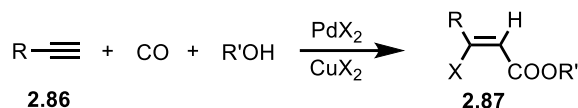
C. Akita's intermolecular methoxycarbonylation
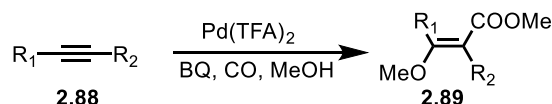
Scheme 2.9 Palladium-catalyzed carbonylations

In summary, since stemofoline was isolated in 1970 and its structure was unambiguously assigned, there are several total synthesis of stemofoline alkaloids reported. The total synthesis of racemic isostemofoline (**2.7**) was firstly completed by Kende's group in 26 steps. Total syntheses of racemic didehydrostemofoline (**2.38**) and isodidehydrostemofoline (**2.8**) were finished by Overman's group in 28 steps. By using the same method developed by Overman's group to install the tetrahydrofuran ring, Huang's group accomplished total syntheses of methoxystemofoline

(**2.55**) and isomethoxystemofoline (**2.54**) in 26 steps. Besides, the formal synthesis of stemofoline

alkaloids and the core structure were accessed by Martin's group and Fukuyama's group,

respectively. Although some stemofoline alkaloids were reached, an efficient approach is still

necessary to obtain stemofoline alkaloids and its analogs for their potential therapeutic applications.

To quickly construct the core structure, we proposed a palladium-catalyzed amino carbonylative

lactonization reaction, and to our surprise, there are no reported structures with dihydropyrrole

fused furanone. This methodology would significantly improve synthetic efficiency and provide a

vital synthesis approach of stemofoline and its analogs.

2.2   Result and Discussion

Started with 1,2-addition of acetylide to the corresponding aldehyde to prepare model

substrate **2.90** (Table 2.1), our investigation firstly used $PdCl_2$ as a carbonylation catalyst with 2,2-

bipyridine ligand A, but no desired product **2.91** was obtained. We proposed that for the amino-

palladation step, an electron-deficient and cationic palladium catalyst should be more efficient to

activate the triple bond. Thus, we explored $Pd(TFA)_2$ with ligand A (0.1 equiv.), p-benzoquinone

(BQ, 1.5 equiv.) as an oxidant, and MeCN as a solvent, and the desired product **2.91** was obtained

in 63% yield. After we screened different ligands (entries 3–6), we found that these ligands do not

provide better yield. We then moved to phosphine ligand Xantphos (entry 7), but trace desired

product was observed, and BOX-ligand F (entry 8) provided a lower yield. We then found that

increasing amounts of ligand (entry 10) and oxidant (entry 11) did not improve the yield. And

decreasing the amount of oxidant slightly reduced the yield to 61% (entry 12). No desired product

was observed when Cs_2CO_3 was added as a base (entry 13), and increasing the pressure of carbon

monoxide decrease the yield (entry 14). To improve the yield, we in situ generated the more

electron-deficient $Pd(OTf)_2$ (0.1 equiv.) by combining of $PdCl_2(MeCN)_2$ (0.1 equiv) and AgOTf

(0.2 equiv) and the yield increase to 72% (entry 15). Then we found the more electron-rich ligand, such as ligand G (entry 16, 81% yield), provided higher yield than ligand C (entry 4) and ligand H (entry 16). We also tried [Pd(neoc)(OAc)]$_2$(OTf)$_2$ (entry 18), a dimeric palladium complex developed by the Waymouth group[74], but the yield is lower. Then we screened different oxidants, and we found CuCl$_2$ as an oxidant was detrimental and 2,3-dichloro-5,6- dicyano-1,4-benzoquinone (DDQ) as oxidant increased the yield to 90% (entry 20). Interestingly, when the protection group was switched to Boc, no desired product was observed (entry 21). However, when the solvent was switched to MeOH and Pd(TFA)2 was used as the catalyst with BQ as the oxidant, product **2.92** was observed (entry 22), which means no lactonization processed. These results indicated that the Boc-protected substrate could have pseudo-A(1,3) interaction between the Boc group and side chain, which makes it difficult to form the furanone ring.

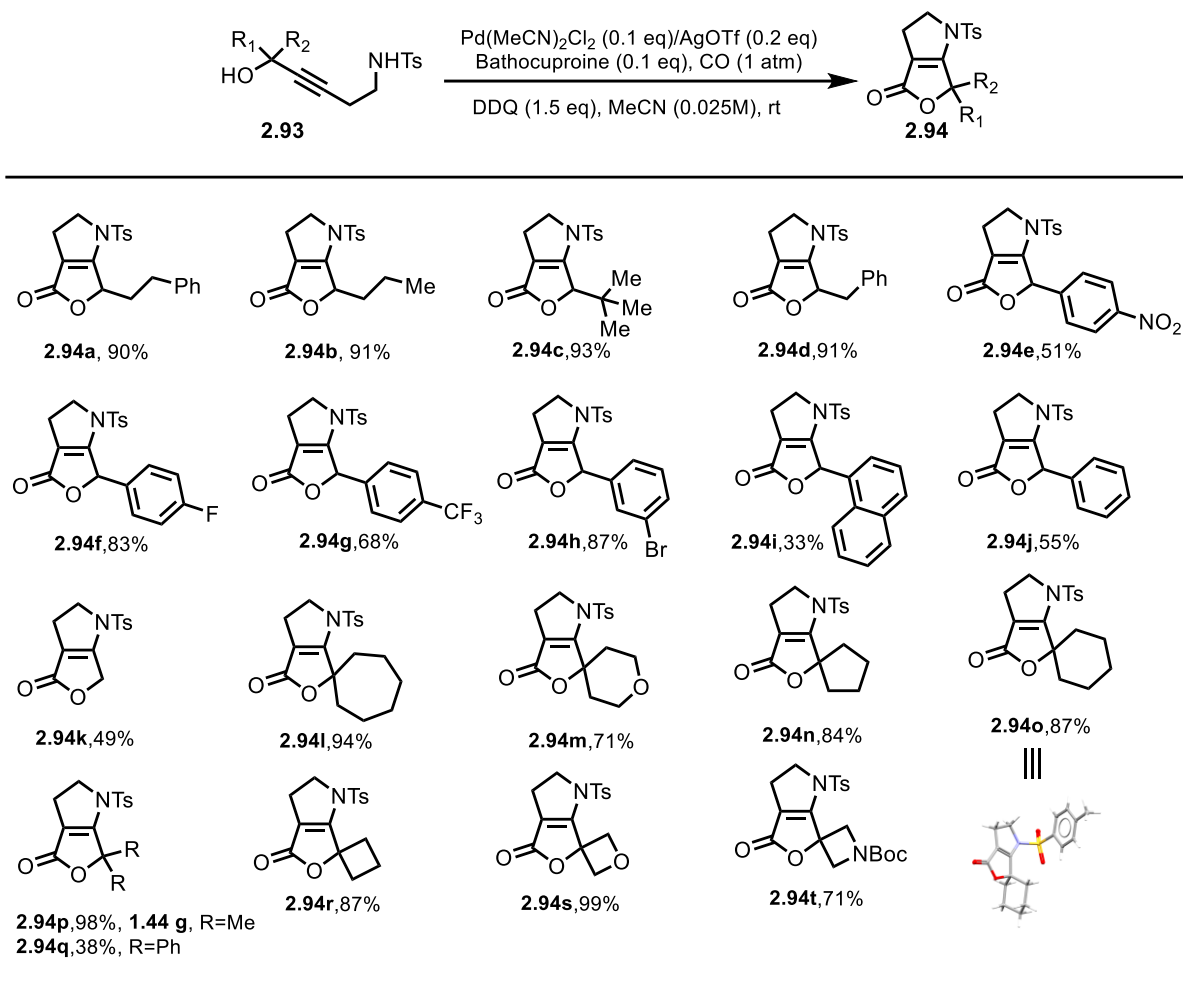Table 2.1 Condition screening of amino carbonylative lactonization

Scheme: **2.90** (Ph—CH2CH2—CH(OH)—C≡C—CH2—NHPG) → Pd cat., ligand / CO (balloon), oxidant / MeCN (0.025M), RT → **2.91**

Ligands: **A** (2,2'-bipyridine), **B** (1,10-phenanthroline), **C** (4,7-diphenyl-1,10-phenanthroline), **D** (6,6'-dimethyl-2,2'-bipyridine), **E** (2,9-dimethyl-1,10-phenanthroline), **G** (4,7-diphenyl-2,9-dimethyl-1,10-phenanthroline), **H** (2,9-diphenyl-4,7-diphenyl-1,10-phenanthroline), **Xantphos**, **F** (bis-oxazoline), **[Pd(neoc)(OAc)]₂(OTf)₂**, product of entry 22 **2.92**

Entry	Reaction conditions (equiv.)	Yield[a] (%)
1	PdCl$_2$ (0.1), **A** (0.1), BQ (1.5), PG=Ts	0
2	Pd(tfa)$_2$ (0.1), **A** (0.1), BQ (1.5), PG=Ts	63
3	Pd(tfa)$_2$ (0.1), **B** (0.1), BQ (1.5), PG=Ts	58
4	Pd(tfa)$_2$ (0.1), **C** (0.1), BQ (1.5), PG=Ts	63
5	Pd(tfa)$_2$ (0.1), **D** (0.1), BQ (1.5), PG=Ts	58
6	Pd(tfa)$_2$ (0.1), **E** (0.1), BQ (1.5), PG=Ts	53
7	Pd(tfa)$_2$ (0.1), **Xantphos** (0.1), BQ (1.5), PG=Ts	Trace
8	Pd(tfa)$_2$ (0.1), **F** (0.1), BQ (1.5), PG=Ts	33
9	PdCl$_2$(MeCN)$_2$ (0.1), **E** (0.1), BQ (1.5), PG=Ts	0
10	Pd(tfa)$_2$ (0.1), **C** (0.2), BQ (1.5), PG=Ts	41
11	Pd(tfa)$_2$ (0.1), **C** (0.1), BQ (3.0), PG=Ts	51
12	Pd(tfa)$_2$ (0.1), **C** (0.1), BQ (1.0), PG=Ts	61
13	Pd(tfa)$_2$ (0.1), **C** (0.1), BQ (1.5), PG=Ts, Cs$_2$CO$_3$ (1.0)	0
14	Pd(tfa)$_2$ (0.1), **C** (0.1), BQ (1.5), PG=Ts, CO (7 atm)	31
15	PdCl$_2$(MeCN)$_2$ (0.1)/AgOTf (0.2), **C** (0.1), BQ (1.5), PG=Ts	72
16	PdCl$_2$(MeCN)$_2$ (0.1)/AgOTf (0.2), **G** (0.1), BQ (1.5), PG=Ts	81
17	PdCl$_2$(MeCN)$_2$ (0.1)/AgOTf (0.2), **H** (0.1), BQ (1.5), PG=Ts	42
18	[Pd(neoc)(OAc)]$_2$(OTf)$_2$, BQ (1.5), PG=Ts	69
19	PdCl$_2$(MeCN)$_2$ (0.1)/AgOTf (0.2), **G** (0.1), CuCl$_2$ (1.5), PG=Ts	0
20	**PdCl$_2$(MeCN)$_2$ (0.1)/AgOTf (0.2), G (0.1), DDQ (1.5), PG=Ts**	**90**
21	PdCl$_2$(MeCN)$_2$ (0.1)/AgOTf (0.2), **G** (0.1), DDQ (1.5), PG=Boc	0
22	Pd(tfa)$_2$ (0.1), BQ (1.5), PG=Boc, MeOH	24

[a] Isolated yield.

With the optimized condition in hand, we expand the substrate scope of the methodology of t amino-carbonylative lactonization (Table 2.2), and several dihydropyrrole-fused furanones were prepared. Generally, with alkyl substituents, secondary propargylic alcohols provided excellent yield (cf. **2.94a–d**). Due to oxidizing the secondary alcohol and other undesired pathways, secondary propargylic alcohols with aryl substituents gave slightly lower yield (cf. **2.94f–h**) or significantly lower yield (cf. **2.94e**, **2.94i–j**) A primary propargylic alcohol provided modest yield (cf. **2.94k**). Surprisingly, most of the tertiary alcohols with alkyl substituents (**2.94l–t**) provided excellent yields even with hetero rings. However, the yield of tertiary alcohols with aryl substituents (**2.94q**) dropped significantly. The structure of **2.94o** was unambiguously confirmed by X-ray analysis. Besides, this mild reaction conditions provided high functional group tolerance

such as Boc-carbamate, sulfonamide, nitro, and bromide groups and a gram-scale (**2.94p**) reaction was also conducted.

Table 2.2 Substrate scope

2.93 → Pd(MeCN)$_2$Cl$_2$ (0.1 eq)/AgOTf (0.2 eq), Bathocuproine (0.1 eq), CO (1 atm); DDQ (1.5 eq), MeCN (0.025M), rt → 2.94

2.94a, 90%   **2.94b**, 91%   **2.94c**, 93%   **2.94d**, 91%   **2.94e**, 51%

2.94f, 83%   **2.94g**, 68%   **2.94h**, 87%   **2.94i**, 33%   **2.94j**, 55%

2.94k, 49%   **2.94l**, 94%   **2.94m**, 71%   **2.94n**, 84%   **2.94o**, 87%

2.94p, 98%, **1.44 g**, R=Me
2.94q, 38%, R=Ph   **2.94r**, 87%   **2.94s**, 99%   **2.94t**, 71%
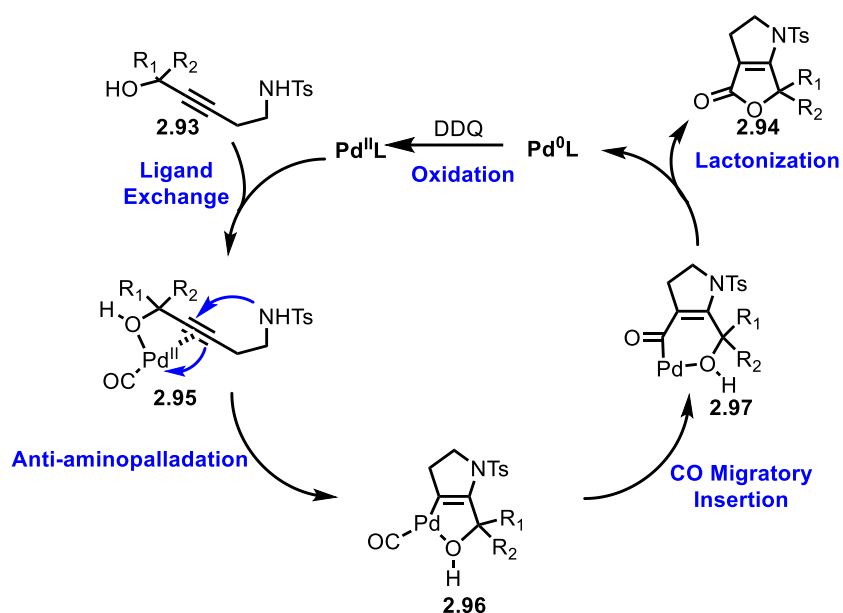
Figure 2.2 Proposed mechanism

Mechanistically (Figure 2.2), after ligand exchange, Pd(II) catalyst activated the alkyne, and the hydroxyl group was directed to trigger a 5-endo-dig cyclization (**2.95**). Anti-aminopalladation processed to build up the dihydropyrrole ring and vinyl-palladium complex (**2.96**). After dihydropyrrole species was formed, a migratory insertion of carbon monoxide accessed to create intermediate **2.97**. Then lactonization leads to product **2.94,** and the palladium catalyst was reduced to a Pd(0) catalyst, which was oxidized to Pd(II) catalyst by DDQ to continue the next cycle.
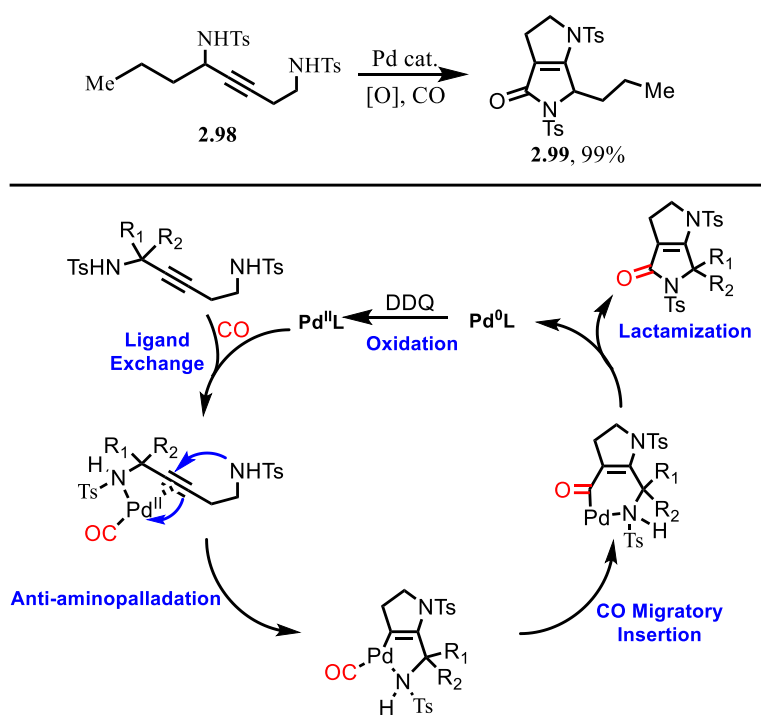
Figure 2.3 Synthesis of dihydropyrrole-fused-pyrrolone

We then switched the hydroxy group to tosyl amine to construct dihydropyrrole fused pyrrolone. The catalytic cycle also goes through ligand exchange, anti-aminopalladation, Co migratory insertion, and lactonization. After ligand exchange, activated alkyne triggered a 5-endo-dig cyclization to give a 5-5 fused ring structure. After reductive elimination, Pd(0) catalyst was oxidized to a Pd(II) catalyst by DDQ for the next catalytic cycle. However, when we started to expand the substrate scope, it is difficult to synthesize the amine substrate with a tertiary carbon.

Figure 2.4 Synthesis of β-lactone

We then prepared propargylic alcohol substrate **2.100** with one more carbon to check the possibility of constructing a 5,6-fused furanone product. However, after adding one carbon between the triple bond and the nitrogen nucleophile, the expected *6-endo-dig* cyclizati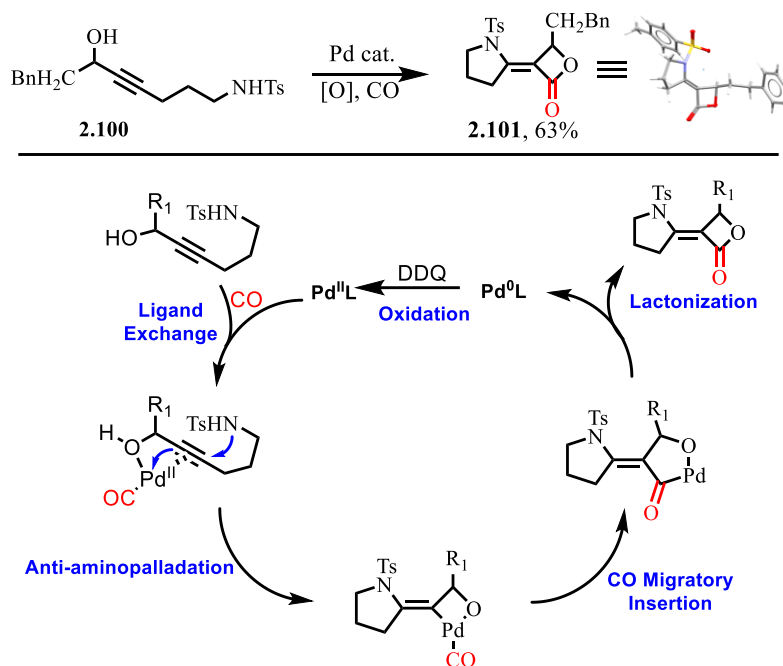on product was not observed under the optimal reaction conditions. Instead of *6-endo-dig* amino-palladation, a competing pathway, a *5-exo-dig* amino-palladation becomes more favored, and a strained β-lactone product (**2.101**) was formed. The structure of the β-lactone product and double bond geometry of **2.101** was unambiguously confirmed by X-ray analysis. Generally, a *5-exo-dig anti*-aminopalladation is more favored than a *6-endo-dig* amino-palladation, and the *trans*-double bond geometry demonstrated that the *anti*-aminopalladation process overrides a *syn*-aminopalladation process.

Since the products of aminocarbonylative lactonization are novel scaffolds and have never been synthesized before, several biological activities had evaluated them against several bacterial, yeast, and mold pathogens. The preliminary results indicated that **2.94h** and **2.94s** showed 128

mM and 64 mM MIC (minimum inhibitory concentration) against *Clostridium difficile*. Besides, there is no side effect on the beneficial intestinal microflora **for 2.94h** and **2.94s**, and these two compounds were nontoxic to Caco-2 cell lines up to 256 mM. Compounds **2.94h**, **2.94k**, **2.94s**, and **2.94b** also showed activity against several fungal pathogens such as *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Cryptococcus gattii*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Aspergillus niger*, and *Aspergillus brasiliensis* with 64–128 mM MIC values.
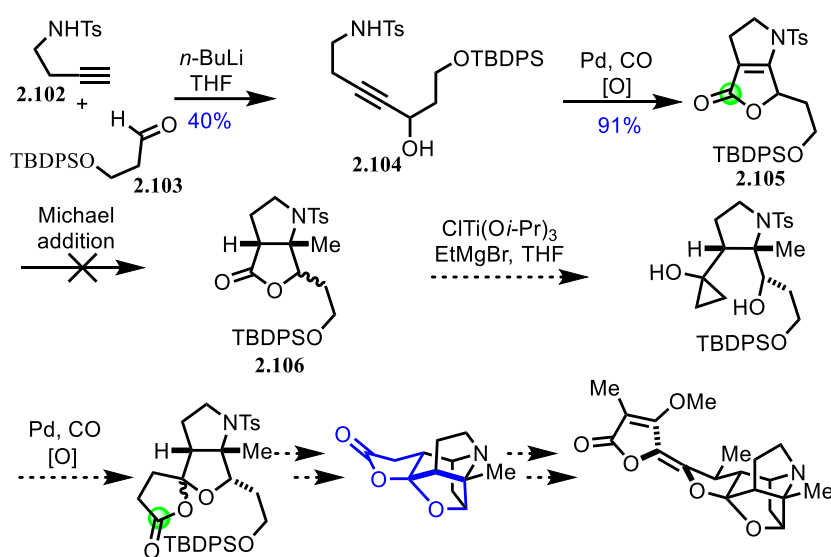
Scheme 2.10 Synthetic plan of stemofoline alkaloids

With this amino-carbonylative lactonization methodology in hand, we started to realize our synthetic plan to check the potential possibility of construct core structure (Scheme 2.10). 1,2 addition was used to synthesize the liner propargylic alcohol **2.104** from compounds **2.102** and **2.103** in 40% yield. Our amino-carbonylative lactonization was applied to construct the corresponding dihydropyrrole-fused-furanone **2.105** smoothly, and the product was accessed in a 91% yield. However, when we started to test the possibility of conjugated addition of compound **2.105**, unfortunately, none of the reaction conditions gave the desired product. To finish the critical

intermediate and check the Mannich rearrangement, we started a detour to construct the corresponding spirolactone compound.
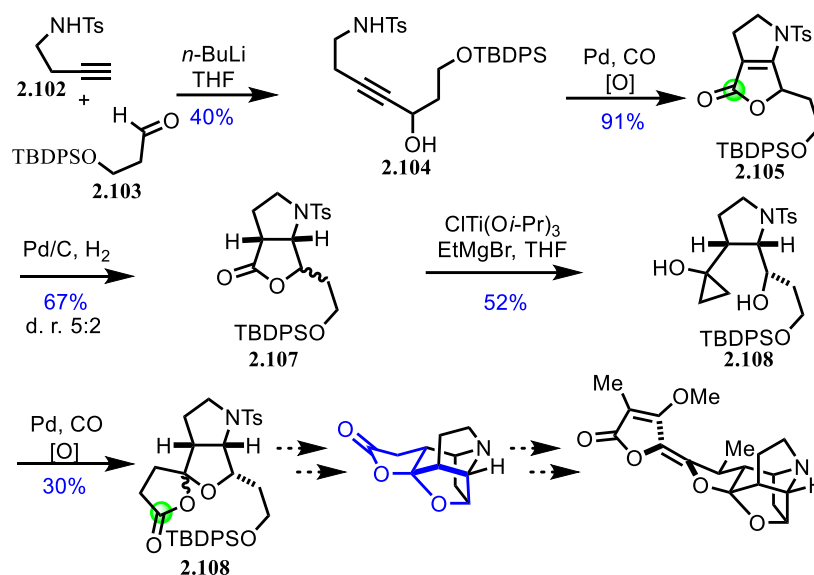
Scheme 2.11 Revised synthetic plan of stemofoline alkaloids

With the dihydropyrrole-fused-furanone **2.105** in hand, we started a model study to obtain the critical intermediate to test our crucial step (Scheme 2.11). We processed hydrogenation instead of conjugated addition to obtain tetrahydropyrrole-fused-furanone **2.107** smoothly in 67% yield as a 5:2 mixture of two stereoisomers. An optimized Kulinkovich reaction condition, which was developed by E. J. Corey's group, was used to convert bicyclic compound **2.107** to cyclopropanol **2.108** successfully. To our surprise, when we started to use Waymouth catalyst [Pd(neoc)(OAc)]$_2$(OTf)$_2$, the desired products were not observed, because of the acidity of the catalyst cause decomposition of the desired products. To overcome this problem, we used Pd(TFA)$_2$ as a catalyst with the same ligand neocuproine instead of [Pd(neoc)(OAc)]$_2$(OTf)$_2$ and the desired spirolactone products were obtained in 30% yield as a 1:1 mixture of two stereoisomers. We are currently using this key intermediate to construct the pentacyclic core.

2.3 Conclusion

In summary, an efficient palladium-catalyzed amino carbonylative lactonization of amino propargylic alcohols was reported to streamline various bicyclic compounds, dihydropyrrole-fused furanones as novel scaffolds. This methodology was also be used for rapid access to dihydropyrrole-fused-pyrrolones (**2.99**) and β-lactone products (**2.101**), which were exhibited as another bioactive novel scaffold. The preliminary biological activity tests of several compounds, such as **2.94h**, **2.94k**, **2.94s**, and **2.101b**, exhibited promising antifungal and antibacterial activities. For example, biological evaluations of compounds **2.94h** and **2.94s** revealed promising activity against Clostridium difficile. Compounds **2.94h**, **2.94k**, **2.94s**, and **2.101b** demonstrated activity against multiple fungal pathogens. Currently, this new methodology was used to explore synthetic capability, which was accessed to facilitate total syntheses of stemofoline alkaloids. Our optimized Kulinkovich reaction and palladium-catalyzed spirolactonization were also used to access to important intermediate 2.108 quickly. This method was also used to prepare analogues of the lead compounds for antibacterial and antifungal activities for therapeutic development.

2.4 Experimental Data

I. General Methods

General Methods: NMR spectra were recorded on Bruker spectrometers (^{1}H at 500 MHz and ^{13}C at 126 MHz). Chemical shifts (δ) were given in ppm with reference to solvent signals [^{1}H NMR: CHCl$_3$ (7.26); ^{13}C NMR: CDCl$_3$ (77.2)]. Column chromatography was performed on silica gel. All reactions sensitive to air or moisture were conducted under argon atmosphere in dry and freshly distilled solvents under anhydrous conditions, unless otherwise noted. Anhydrous THF was distilled over sodium benzophenone ketyl under Argon. Anhydrous CH$_2$Cl$_2$ was distilled over calcium hydride under Argon. Anhydrous MeCN was distilled over calcium hydride under Argon.

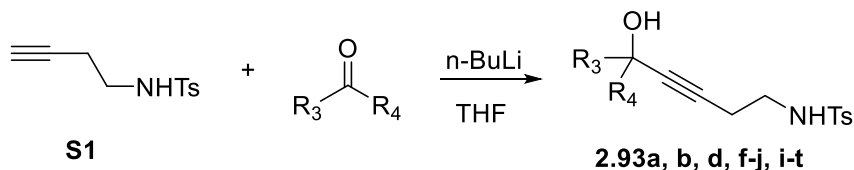All other solvents and reagents were used as obtained from commercial sources without further purification.

## II. Synthesis of starting materials

S1 **S2** **S3**
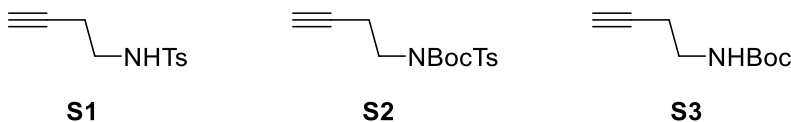
Starting materials **S1**[75], **S2**[76], **S3**[77] are prepared according to the previously reported procedures.

General procedure of preparation of 2.93a, b, d, f-j, i-t :

S1

2.93a, b, d, f-j, i-t

To a stirred solution of **S1** (112 mg, 0.50 mmol) in dry THF (5 mL), a 2.5 M solution of n-BuLi (0.39 mL, 0.98 mmol) in Hexane was added dropwise at -78 ˚C over 10 mins under argon atmosphere. The reaction mixture was allowed to react at the same temperature and stirred for an 1 h. Corresponding aldehyde or ketone (1.5 mmol) was dissolved in 5 mL THF and added at -78 ˚C over 10 mins. The mixture was allowed to warm up to room temperature and react for additional 1 h. The reaction was quenched by saturated NH4Cl solution (5 mL) and extracted by EtOAc for 3 times. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (hexane/ethyl acetate = 3/2) to give **2.94a, b, d, f-j, i-t**.

OH

Ph ⟍⟍⟍≡≡⟍NHTs

2.93a
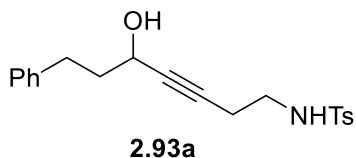
114 mg, 64% yield, colorless oil;

IR (neat): v = 3289,1599, 1496, 1454, 1324, 1157, 1093 cm^{-1};

HRMS (ESI), calcd for $C_{20}H_{23}NO_3SNa$ [M+Na]$^+$ 380.1297, found 380.1280 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.86 – 7.68 (m, 2H), 7.31 – 7.24 (m, 4H), 7.19 (m, 3H), 5.30 (t, J = 6.4 Hz, 1H), 4.31 (s, 1H), 3.09 (q, J = 6.4 Hz, 2H), 2.74 (t, J = 7.9 Hz, 2H), 2.41 (s, 3H), 2.38 (td, J = 6.4, 1.9 Hz, 2H), 2.06 – 1.84 (m, 2H);

^{13}C NMR (125 MHz, Chloroform-d) δ 143.77, 141.46, 137.10, 129.96, 128.63, 128.57, 127.22, 126.11, 83.86, 81.58, 61.87, 42.00, 39.44, 31.57, 21.68, 20.23.

OH

Me ⟍⟍⟍≡≡⟍NHTs

2.93b
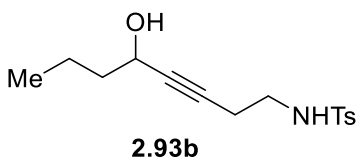
108 mg, 73% yield, colorless oil;

IR (neat): v =3290, 1432, 1331, 1159, 1093 cm^{-1};

HRMS (ESI), calcd for $C_{15}H_{21}NO_3SNa$ [M+Na]$^+$ 318.1141, found 318.1094 m/z;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.84 – 7.70 (m, 2H), 7.35 – 7.28 (m, 2H), 4.94 (t, *J* = 6.4 Hz, 1H), 4.32 (s, 1H), 3.09 (q, *J* = 6.5 Hz, 2H), 2.43 (s, 3H), 2.38 (td, *J* = 6.5, 2.0 Hz, 2H), 1.95 (s, 1H), 1.70 – 1.54 (m, 3H), 1.48 – 1.36 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 143.79, 137.18, 129.97, 127.26, 84.19, 81.11, 62.46, 42.00, 40.19, 21.72, 20.25, 18.65, 13.92.

2.93d
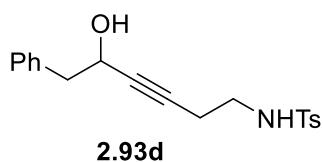
50.2 mg, 29% yield, colorless oil;

IR (neat): $v =$3282, 1598, 1453, 1324, 1157, 1093 cm^{-1};

HRMS (ESI), calcd for $C_{19}H_{21}NO_3SNa$ [M+Na]$^+$ 352.0984, found 352.1004 m/z;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.76 – 7.70 (m, 2H), 7.34 – 7.27 (m, 4H), 7.27 – 7.20 (m, 3H), 5.10 (t, *J* = 6.4 Hz, 1H), 4.62 – 4.44 (m, 1H), 3.04 (q, *J* = 6.4 Hz, 2H), 2.94 (dd, *J* = 6.5, 2.0 Hz, 2H), 2.42 (s, 3H), 2.33 (td, *J* = 6.4, 2.0 Hz, 3H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 143.72, 137.18, 136.88, 129.92, 129.83, 128.57, 127.19, 127.06, 83.20, 82.36, 63.39, 44.26, 41.91, 21.69, 20.23.


2.93f
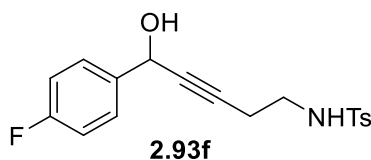
119 mg, 69% yield, white solid;

IR (neat): $v =$3290, 1603, 1507, 1420, 1323, 1223, 1157, 1094, 814, 552 cm^{-1};

HRMS (ESI), calcd for $C_{18}H_{18}FNO_3SNa$ [M+Na]$^+$ 370.0890, found 370.0929 m/z;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.80 – 7.67 (m, 2H), 7.51 – 7.41 (m, 2H), 7.30 – 7.26 (m, 2H), 7.10 – 6.95 (m, 2H), 5.53 – 5.32 (m, 2H), 3.10 (q, *J* = 6.4 Hz, 2H), 2.52 – 2.32 (m, 5H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 163.72, 161.76, 143.83, 137.03, 136.77, 129.96, 128.60, 128.54, 127.20, 115.61, 115.44, 83.44, 82.69, 63.95, 41.88, 21.70, 20.37;

^{19}F NMR (470 MHz, Chloroform-*d*) δ -114.98.

2.93g
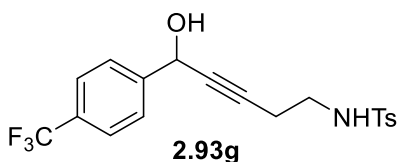
141 mg, 71% yield, while solid;

IR (neat): *v* =3283, 1619, 1507, 1417, 1324, 1157, 1123, 1066, 814, 661, 551 cm^{-1};

HRMS (ESI), calcd for $C_{19}H_{18}F_3NO_3SNa$ [M+Na]$^+$ 420.0858, found 420.0786 m/z;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.77 – 7.68 (m, 2H), 7.58 (m, 4H), 7.29 – 7.23 (m, 3H), 5.62 (t, *J* = 6.4 Hz, 1H), 5.54 – 5.36 (m, 1H), 3.37 (d, *J* = 5.5 Hz, 1H), 3.10 (q, *J* = 6.3 Hz, 2H), 2.50 – 2.35 (m, 5H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 144.74, 143.94, 136.92, 130.50, 130.24, 129.98, 127.16, 126.98, 125.63, 125.60, 125.57, 125.54, 125.29, 123.13, 83.81, 82.31, 77.40, 63.88, 41.84, 21.65, 20.34;

^{19}F NMR (470 MHz, Chloroform-*d*) δ -63.56.

**2.93h**
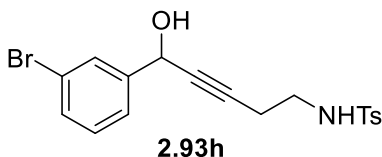
134 mg, 66% yield, light yellow oil;

IR (neat): v =3286, 1595, 1427, 1322, 1157, 1093, 814, 662, 550 cm^{-1};

HRMS (ESI), calcd for $C_{18}H_{18}BrNO_3SNa$ [M+Na]$^+$ 430.0089, found 430.0099 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.78 – 7.72 (m, 2H), 7.63 (t, J = 1.9 Hz, 1H), 7.48 – 7.38 (m, 2H), 7.32 – 7.27 (m, 2H), 7.23 (t, J = 7.8 Hz, 1H), 5.38 (dt, J = 5.8, 2.0 Hz, 1H), 5.08 (t, J = 6.4 Hz, 1H), 3.12 (q, J = 6.4 Hz, 2H), 2.66 (d, J = 5.8 Hz, 1H), 2.48 – 2.32 (m, 5H), 1.63 (s, 1H);

^{13}C NMR (125 MHz, Chloroform-d) δ 143.88, 143.05, 137.06, 131.53, 130.36, 130.01, 129.75, 127.23, 125.31, 122.78, 83.76, 82.30, 63.96, 41.86, 21.74, 20.43.

2.93i
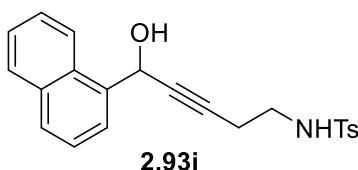
147 mg, 49% yield, colorless oil;

IR (neat): v =3285, 1597, 1412, 1326, 1157, 1093, 782, 661, 550 cm^{-1};

HRMS (ESI), calcd for $C_{22}H_2NO_3SNa$ [M+Na]$^+$ 402.1141, found 402.1066 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.92 – 7.82 (m, 2H), 7.76 (dt, J = 7.0, 1.0 Hz, 1H), 7.68 – 7.62 (m, 2H), 7.55 (dddd, J = 24.4, 8.1, 6.8, 1.4 Hz, 2H), 7.47 (dd, J = 8.2, 7.1 Hz, 1H), 7.25 – 7.20 (m, 2H), 6.06 (dt, J = 5.5, 2.1 Hz, 1H), 4.84 (t, J = 6.4 Hz, 1H), 3.11 (q, J = 6.4 Hz, 2H), 2.50 – 2.41 (m, 3H), 2.39 (s, 3H);

^{13}C NMR (125 MHz, Chloroform-d) δ 143.73, 137.11, 135.91, 134.21, 130.54, 129.92, 129.52, 129.03, 127.19, 126.72, 126.16, 125.44, 124.54, 123.93, 83.86, 82.67, 63.13, 41.90, 21.69, 20.43.

OH
|
Ph―⟨C≡C⟩―NHTs

2.93j
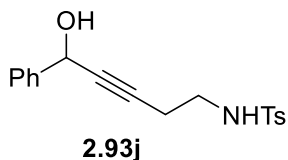
116 mg, 70% yield, colorless oil;

IR (neat): v =3300, 1453, 1324, 1157, 817, 662, 550 cm^{-1};

HRMS (ESI), calcd for $C_{18}H_{19}NO_3SNa$ [M+Na]$^+$ 366.1141, found 366.1105 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.77 – 7.68 (m, 2H), 7.51 – 7.46 (m, 2H), 7.40 – 7.30 (m, 3H), 7.28 (d, J = 8.0 Hz, 2H), 5.41 (s, 1H), 5.00 (t, J = 6.4 Hz, 1H), 3.12 (q, J = 6.5 Hz, 2H), 2.49 – 2.38 (m, 6H);

^{13}C NMR (125 MHz, Chloroform-d) δ 143.75, 140.84, 137.07, 129.93, 128.80, 128.54, 127.21, 126.64, 83.19, 82.83, 64.74, 41.87, 21.68, 20.36.

OH

2.93l
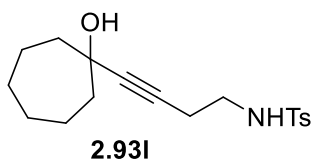
124 mg, 74% yield, white solid;

IR (neat): v =3290, 1598, 1445, 1325, 1157, 1094, 1025, 814, 664, 551 cm^{-1};

HRMS (ESI), calcd for $C_{18}H_{25}NO_3SNa$ [M+Na]$^+$ 358.1454, found 358.1405 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.78 – 7.72 (m, 2H), 7.31 – 7.26 (m, 2H), 5.51 (t, J = 6.3 Hz, 1H), 3.05 (q, J = 6.5 Hz, 2H), 2.63 (s, 1H), 2.40 (s, 3H), 2.33 (t, J = 6.6 Hz, 2H), 1.97 – 1.82 (m, 2H), 1.75 (m, 2H), 1.65 – 1.31 (m, 9H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 143.59, 137.22, 129.86, 127.15, 87.70, 79.50, 77.42, 71.81, 43.16, 42.09, 28.11, 22.27, 21.64, 20.13.

2.93m
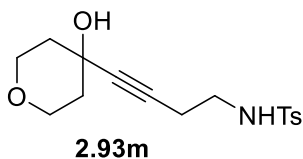
52.3 mg, 32% yield, white solid;

IR (neat): *v* =3280, 1598, 1424, 1327, 1156, 1092, 815, 663, 550 cm^{-1};

HRMS (ESI), calcd for C$_{16}$H$_{21}$NO$_4$SNa [M+Na]$^+$ 346.1090, found 346.1049 m/z;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.80 – 7.71 (m, 2H), 7.34 – 7.27 (m, 2H), 5.59 (t, *J* = 6.3 Hz, 1H), 3.83 (dt, *J* = 11.7, 4.2 Hz, 2H), 3.55 (ddd, *J* = 11.8, 9.0, 3.0 Hz, 2H), 3.14 (s, 1H), 3.08 (q, *J* = 6.3 Hz, 2H), 2.41 (s, 3H), 2.37 (t, *J* = 6.5 Hz, 2H), 1.83 (dddd, *J* = 13.0, 5.0, 3.1, 1.5 Hz, 2H), 1.73 (ddd, *J* = 13.0, 9.0, 3.9 Hz, 2H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 143.79, 137.09, 129.95, 127.14, 85.43, 81.23, 77.40, 65.70, 64.91, 42.02, 40.00, 21.67, 20.17.

2.93n
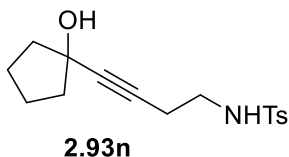
95 mg, 62% yield, white solid;

IR (neat): *v* =3281, 1598, 1436, 1324, 1157, 1093, 993, 814, 662, 550 cm^{-1};

HRMS (ESI), calcd for C$_{16}$H$_{21}$NO$_3$SNa [M+Na]$^+$ 330.1141, found 330.1099 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.79 – 7.73 (m, 2H), 7.31 – 7.27 (m, 2H), 5.52 (t, J = 6.3 Hz, 1H), 3.05 (q, J = 6.5 Hz, 2H), 2.58 (s, 1H), 2.40 (s, 3H), 2.32 (t, J = 6.5 Hz, 2H), 1.91 – 1.71 (m, 6H), 1.65 (m, 2H);

^{13}C NMR (125 MHz, Chloroform-d) δ 143.61, 137.15, 129.86, 127.16, 86.74, 79.24, 77.40, 74.42, 42.43, 42.01, 23.47, 21.64, 20.16.

2.93o
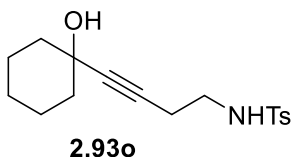
37 mg, 31% yield, white solid;

IR (neat): v =3277, 1597, 1448, 1328, 1158, 1094, 963, 814, 662, 552 cm^{-1};

HRMS (ESI), calcd for $C_{17}H_{23}NO_3SNa$ [M+Na]$^+$ 344.1297, found 344.1228 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.76 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 5.26 (t, J = 6.3 Hz, 1H), 3.08 (q, J = 6.5 Hz, 2H), 2.42 (s, 3H), 2.36 (t, J = 6.5 Hz, 2H), 1.81 (m, 2H), 1.69 – 1.58 (m, 2H), 1.57 – 1.37 (m, 6H), 1.22 (m, 1H);

^{13}C NMR (125 MHz, Chloroform-d) δ 143.69, 137.22, 129.92, 127.20, 86.71, 80.31, 68.76, 42.11, 40.08, 25.28, 23.45, 21.69, 20.15.

2.93p
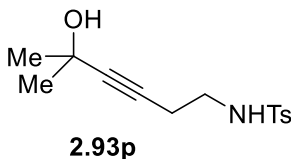
48.4 mg, 59%, white solid;

IR (neat): v =3285, 1598, 1432, 1324, 1157, 1093, 815, 664, 551 cm^{-1};

HRMS (ESI), calcd for C$_{14}$H$_{19}$NO$_3$SNa [M+Na]$^+$ 304.0984, found 304.0950 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.82 – 7.71 (m, 2H), 7.30 (d, J = 8.0 Hz, 2H), 5.32 (t, J = 6.4 Hz, 1H), 3.07 (q, J = 6.4 Hz, 2H), 2.42 (s, 3H), 2.38 – 2.21 (m, 3H), 1.45 (d, J = 1.1 Hz, 6H);

^{13}C NMR (125 MHz, Chloroform-d) δ 143.72, 137.21, 129.93, 127.21, 87.79, 78.34, 65.23, 42.00, 31.63, 21.69, 20.09.

2.93q
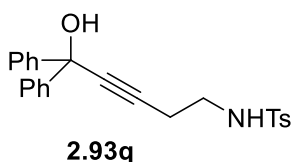
125 mg, 62% yield, colorless oil;

IR (neat): v =3284, 1597, 1449, 1324, 1157, 1093, 814, 754, 700, 662, 550 cm^{-1};

HRMS (ESI), calcd for C$_{24}$H$_{23}$NO$_3$SNa [M+Na]$^+$ 428.1297, found 428.1320 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.75 – 7.64 (m, 2H), 7.60 – 7.49 (m, 4H), 7.36 – 7.29 (m, 4H), 7.29 – 7.22 (m, 5H), 4.93 (t, J = 6.4 Hz, 1H), 3.13 (q, J = 6.5 Hz, 2H), 2.99 (s, 1H), 2.49 (t, J = 6.5 Hz, 2H), 2.41 (s, 3H);

^{13}C NMR (125 MHz, Chloroform-d) δ 145.15, 143.74, 137.08, 129.95, 128.45, 127.88, 127.21, 126.07, 85.93, 83.85, 74.49, 41.96, 21.71, 20.44.

2.93r
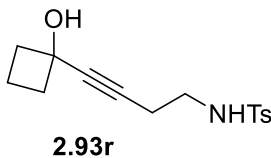
49.7 mg, 34% yield, colorless oil;

IR (neat): v =3282, 1770, 1598, 1423, 1325, 1157, 1093, 815, 661, 551 cm^{-1};

HRMS (ESI), calcd for $C_{15}H_{19}NO_3SNa$ [M+Na]$^+$ 316.0984, found 314.0950 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.80 – 7.68 (m, 2H), 7.35 – 7.26 (m, 2H), 5.33 (t, J = 6.4 Hz, 1H), 3.08 (q, J = 6.4 Hz, 2H), 2.85 (s, 1H), 2.42 (s, 3H), 2.37 (t, J = 6.5 Hz, 2H), 2.34 – 2.27 (m, 2H), 2.20 (qd, J = 9.3, 2.8 Hz, 2H), 1.84 – 1.66 (m, 3H);

^{13}C NMR (125 MHz, Chloroform-d) δ 143.72, 137.16, 129.93, 127.21, 86.52, 79.71, 67.93, 42.02, 38.65, 21.69, 20.27, 13.00.

2.93s
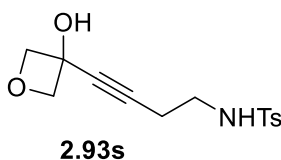
82.4 mg, 56% yield, colorless oil;

IR (neat): v =3283, 1597, 1422, 1323, 1154, 1092, 973, 815, 662, 550 cm^{-1};

HRMS (ESI), calcd for $C_{14}H_{17}NO_4SNa$ [M+Na]$^+$ 318.0777, found 318.0752 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.85 – 7.68 (m, 2H), 7.41 – 7.29 (m, 2H), 5.16 (t, J = 6.4 Hz, 1H), 4.73 (dd, J = 6.5, 0.9 Hz, 2H), 4.66 (dd, J = 6.5, 0.9 Hz, 2H), 3.12 (q, J = 6.4 Hz, 2H), 3.04 (s, 1H), 2.54 – 2.33 (m, 5H);

^{13}C NMR (125 MHz, Chloroform-d) δ 144.01, 137.01, 130.06, 127.23, 84.70, 83.13, 82.41, 67.18, 41.81, 21.75, 20.43.

2.93t
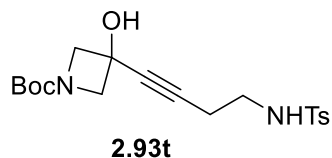
129 mg, 65% yield, white solid;

IR (neat): v =3281, 1825, 1676, 1421, 1330, 1252, 1158, 1095, 815, 663, 551 cm^{-1};

HRMS (ESI), calcd for $C_{19}H_{23}N_2O_5SNa$ [M+Na]$^+$ 417.1461, found 417.1402 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.83 – 7.70 (m, 2H), 7.40 – 7.29 (m, 2H), 5.52 (s, 1H), 4.08 (dd, J = 9.0, 1.0 Hz, 2H), 3.97 (dd, J = 9.0, 1.0 Hz, 2H), 3.79 (s, 1H), 3.09 (q, J = 6.4 Hz, 2H), 2.43 (s, 3H), 2.40 (t, J = 6.3 Hz, 2H), 1.42 (s, 9H);

^{13}C NMR (125 MHz, Chloroform-d) δ 156.43, 143.92, 137.00, 130.03, 127.20, 83.16, 82.64, 80.19, 62.09, 41.80, 28.53, 21.72, 20.37.

General procedure of preparation of 2.93c, e, k :
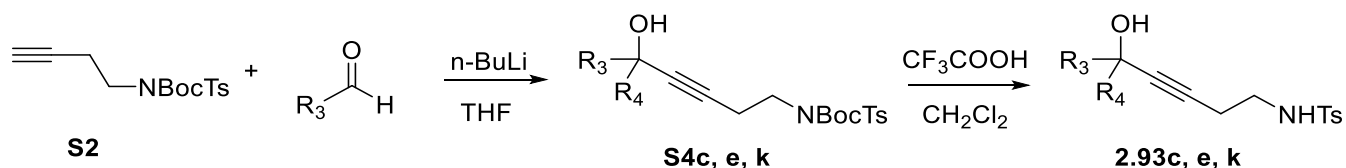
Step1:

To a stirred solution of **S2** (323 mg, 1.0 mmol) in dry THF (10 mL), a 2.5 M solution of n-BuLi (0.40 mL, 1.0 mmol) in Hexane was added dropwise at -78 ˚C over 10 mins under argon atmosphere. The reaction mixture was allowed to react at the same temperature and stirred for 1 h. Corresponding aldehyde (1.5 mmol) was dissolved in 10 mL THF added at -78 ˚C over 10 mins. The mixture was allowed to warm up to room temperature and react for an additional 1 h. The

reaction was quenched by saturated NH$_4$Cl solution (10 mL) and extracted by EtOAc for 3 times. The organic layer was washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (hexane/ethyl acetate = 5/1) to give **S4c, e, k**.

Step2:

To a stirred solution of **S4** (0.50 mmol) in dry CH$_2$Cl$_2$ (5 mL), 1.0 mL CF$_3$COOH was added dropwise at 0 ˚C over 10 mins under argon atmosphere. The reaction mixture was allowed to warm up to room temperature and react for additional 3 h. The solvent was removed under reduced pressure and dissolved in EtOAc (5 mL). The organic layer was washed with saturated NaHCO$_3$ solution one time, brine and dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (hexane/ethyl acetate = 3/2) to give **2.93c, e, k**.

S4c
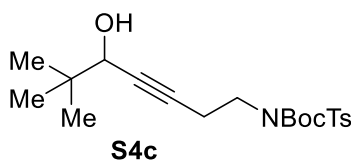
367 mg, 87% yield, colorless oil;

IR (neat): v =3545, 1729, 1597, 1354, 1158, 1090, 674 cm^{-1};

HRMS (ESI), calcd for C$_{21}$H$_{32}$NO$_5$S [M+H]$^+$ 410.2002, found 410.1994 m/z;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.85 – 7.70 (m, 2H), 7.36 – 7.28 (m, 2H), 4.07 – 3.92 (m, 3H), 2.78 – 2.65 (m, 2H), 2.44 (s, 3H), 1.95 (d, *J* = 5.9 Hz, 1H), 1.33 (s, 9H), 0.97 (s, 9H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 150.95, 144.43, 137.50, 129.47, 127.98, 84.80, 82.43, 82.40, 71.68, 45.60, 35.91, 28.05, 25.48, 21.81, 20.29.

2.93c
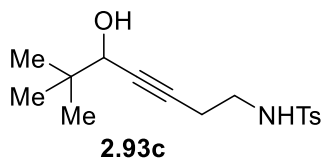
28.6 mg, 18%, colorless oil;

IR (neat): v =3280, 1598, 1324, 1158, 1094, 814, 662, 574 cm^{-1};

HRMS (ESI), calcd for $C_{16}H_{23}NO_3SNa$ [M+Na]$^+$ 332.1297, found 332.1272 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.82 – 7.68 (m, 2H), 7.36 – 7.28 (m, 2H), 5.14 (s, 1H), 3.94 (t, J = 2.0 Hz, 1H), 3.09 (q, J = 6.5 Hz, 2H), 2.42 (s, 3H), 2.37 (td, J = 6.6, 2.0 Hz, 2H), 2.04 (s, 1H), 0.93 (s, 9H);

^{13}C NMR (125 MHz, Chloroform-d) δ 143.75, 137.13, 129.95, 127.23, 82.60, 81.95, 71.52, 42.09, 35.88, 25.45, 21.69, 20.20.

S4e
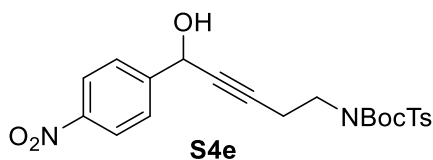
321 mg, 68%, colorless oil;

IR (neat): v =3509, 1729, 1522, 1346, 1155, 672 cm^{-1};

HRMS (ESI), calcd for $C_{23}H_{27}N_2O_7S$ [M+H]$^+$ 475.1540, found 475.1536 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 8.28 – 8.15 (m, 2H), 7.79 – 7.74 (m, 2H), 7.74 – 7.68 (m, 2H), 7.33 – 7.28 (m, 2H), 5.53 (s, 1H), 4.05 (t, J = 6.7 Hz, 2H), 3.02 (s, 1H), 2.74 (td, J = 6.7, 2.1 Hz, 2H), 2.44 (s, 3H), 1.31 (s, 9H);

¹³C NMR (125 MHz, Chloroform-*d*) δ 150.87, 148.07, 147.79, 144.63, 137.35, 129.51, 127.93, 127.60, 123.86, 85.06, 84.95, 81.89, 63.77, 45.36, 28.02, 21.80, 20.22.

2.93e
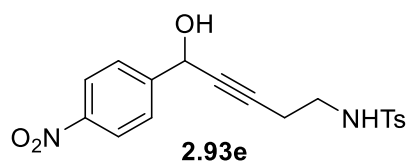
166 mg, 89% yield, colorless oil;

IR (neat): v =3280, 1591, 1519, 1345, 1157 cm^{-1};

HRMS (ESI), calcd for $C_{18}H_{18}N_2O_5SNa$ [M+Na]$^+$ 397.0835, found 397.0816 m/z;

¹H NMR (500 MHz, Chloroform-*d*) δ 8.23 – 8.13 (m, 2H), 7.74 (m, 2H), 7.70 – 7.60 (m, 2H), 7.34 – 7.26 (m, 2H), 5.51 (d, *J* = 2.1 Hz, 1H), 5.22 (s, 1H), 3.13 (q, *J* = 6.4 Hz, 2H), 2.50 – 2.35 (m, 5H);

¹³C NMR (125 MHz, Chloroform-*d*) δ 147.73, 144.04, 136.97, 130.03, 128.88, 127.46, 127.20, 124.40, 123.91, 84.38, 81.91, 63.65, 41.81, 21.73, 20.49.

S4k
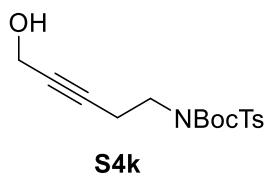
123 mg, 35%, white solid;

IR (neat): v =3529, 1727, 1351, 1291, 1155, 1090, 814, 673, 583 cm^{-1};

HRMS (ESI), calcd for $C_{17}H_{24}NO_5S$ [M+H]$^+$ 354.1376, found 354.1329 m/z;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.86 – 7.75 (m, 2H), 7.40 – 7.29 (m, 2H), 4.23 (t, *J* = 2.2 Hz, 2H), 4.00 (dd, *J* = 7.4, 6.8 Hz, 2H), 2.77 – 2.62 (m, 2H), 2.44 (s, 3H), 1.69 (s, 2H), 1.34 (s, 9H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 150.91, 144.47, 137.45, 129.47, 128.02, 84.79, 82.80, 81.05, 51.49, 45.52, 28.04, 21.81, 20.32.

2.93k
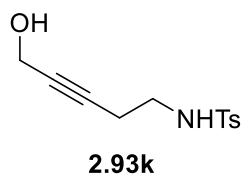
41.1 mg, 33%, colorless oil;

IR (neat): *v* =3277, 1597, 1429, 1323, 1157, 1093, 816, 662, 549 cm^{-1};

HRMS (ESI), calcd for C$_{12}$H$_{15}$NO$_3$SNa [M+Na]$^+$ 276.0668 found 276.0623 m/z;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.83 – 7.68 (m, 2H), 7.38 – 7.28 (m, 2H), 5.46 (t, *J* = 6.6 Hz, 1H), 4.20 (t, *J* = 2.1 Hz, 2H), 3.08 (q, *J* = 6.2 Hz, 2H), 2.42 (s, 3H), 2.36 (tt, *J* = 6.4, 2.2 Hz, 3H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 143.77, 137.07, 129.95, 127.21, 82.22, 81.18, 51.16, 41.92, 21.70, 20.27.

Preparation of 2.93a' :

S3 + **2.93a'**
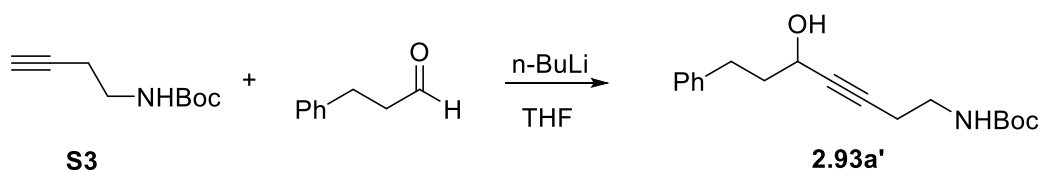
To a stirred solution of **S3** (85 mg, 0.50 mmol) in dry THF (5 mL), a 2.5 M solution of n-BuLi (0.39 mL, 0.98 mmol) in Hexane was added dropwise at -78 ˚C over 10 mins under argon atmosphere. The reaction mixture was allowed to react at the same temperature and stirred for an 1 h. 3-Phenylpropanal (200 mg, 1.5 mmol) was added at -78 ˚C over 10 mins. The mixture was allowed to warm up to room temperature and react for additional 1 h. The reaction was quenched by saturated NH_4Cl solution (5 mL) and extracted by EtOAc for 3 times. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (hexane/ethyl acetate = 3/1) to give a clear, colorless oil.

2.93a'
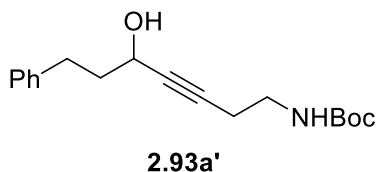
94 mg, 62% yield, colorless oil;

IR (neat): v =3355, 1690, 1514, 1251, 1169, 1060, 699 cm^{-1};

HRMS (ESI), calcd for $C_{18}H_{25}NO_3Na$ [M+Na]$^+$ 326.1732, found 326.1717 m/z;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.32 – 7.25 (m, 2H), 7.24 – 7.16 (m, 3H), 4.82 (s, 1H), 4.44 – 4.27 (m, 1H), 3.28 (q, *J* = 6.4 Hz, 2H), 2.78 (t, *J* = 7.8 Hz, 2H), 2.42 (td, *J* = 6.5, 2.0 Hz, 2H), 2.15 – 1.85 (m, 3H), 1.44 (s, 9H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 155.96, 141.49, 128.66, 128.61, 126.15, 83.12, 82.77, 79.72, 62.06, 39.65, 31.64, 28.58, 20.53.

Preparation of 2.100a, b：
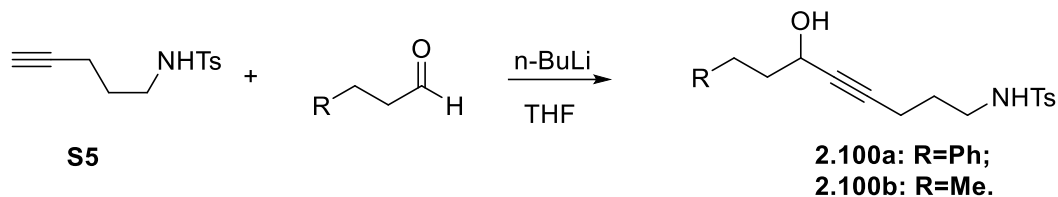
To a stirred solution of **S5** (237 mg, 1.0 mmol) in dry THF (10 mL), a 2.5 M solution of n-BuLi (0.80 mL, 2.0 mmol) in Hexane was added dropwise at -78 ˚C over 10 mins under argon atmosphere. The reaction mixture was allowed to react at the same temperature and stirred for an 1 h. Corresponding aldehyde (3.0 mmol) was dissolved in 10 mL THF and added at -78 ˚C over 10 mins. The mixture was allowed to warm up to room temperature and react for additional 1 h. The reaction was quenched by saturated NH$_4$Cl solution (10 mL) and extracted by EtOAc for 3 times. The organic layer was washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (hexane/ethyl acetate = 3/2) to give **2.100a, b.**

2.100a
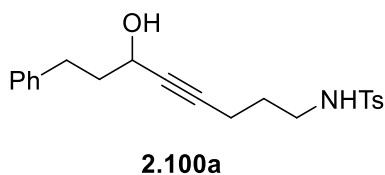
332 mg, 89% yield, colorless oil;

IR (neat): v =3277, 1599, 1453, 1321, 1154, 1093, 814, 669, 661, 549 cm^{-1};

HRMS (ESI), calcd for C$_{21}$H$_{25}$NO$_3$SNa [M+Na]$^+$ 394.1451, found 394.1378 m/z;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.83 – 7.63 (m, 2H), 7.31 – 7.25 (m, 4H), 7.21 – 7.16 (m, 3H), 5.14 (t, *J* = 6.3 Hz, 1H), 4.44 – 4.26 (m, 1H), 3.05 (q, *J* = 6.6 Hz, 2H), 2.74 (t, *J* = 7.9 Hz,

2H), 2.43 (d, *J* = 5.3 Hz, 1H), 2.39 (s, 3H), 2.26 (td, *J* = 6.8, 2.0 Hz, 2H), 2.05 – 1.88 (m, 2H), 1.67 (p, *J* = 6.7 Hz, 2H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 143.57, 141.53, 136.98, 129.86, 128.61, 128.53, 127.19, 126.05, 84.21, 82.60, 61.93, 42.28, 39.59, 31.58, 28.29, 21.64, 16.14.

2.100b
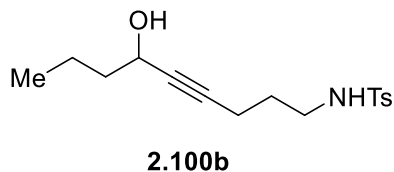
296 mg, 76% yield, colorless oil;

IR (neat): *v* =3280, 1598, 1431, 1322, 1155, 1093, 1019, 814, 661, 550 cm^{-1};

HRMS (ESI), calcd for C$_{16}$H$_{23}$NO$_3$SNa [M+Na]$^+$ 332.1297, found 332.1211 m/z;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.81 – 7.65 (m, 2H), 7.35 – 7.20 (m, 2H), 5.29 (t, *J* = 6.3 Hz, 1H), 4.42 – 4.16 (m, 1H), 3.02 (q, *J* = 6.6 Hz, 2H), 2.40 (s, 4H), 2.22 (td, *J* = 6.8, 2.0 Hz, 2H), 1.75 – 1.48 (m, 4H), 1.48 – 1.32 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 143.49, 137.00, 129.82, 127.18, 83.67, 82.86, 77.33 (d, *J* = 32.1 Hz), 76.95, 62.35, 42.24, 40.19, 28.28, 21.62, 18.58, 16.09, 13.86.

III. Palladium-Catalyzed carbonylation

General procedure of preparation of 2.94a-t and 2.101a, b :

Pd(MeCN)$_2$Cl$_2$ (2.6 mg, 0.01 mmol), AgOTf (5.2 mg, 0.02 mmol) and ligand **G** (3.6 mg, 0.01 mmol) were dissolved in dry MeCN (2 mL) and allowed to react for 1 h under argon atmosphere. DDQ (34.1 mg, 0.15 mmol) and **2.93 a-t** and **2.100a, b** (0.1 mmol) were added and filled by CO balloon. The mixture was allowed to react at room temperature and the reaction was

monitored by TLC plate until no starting material left. The solvent was removed under reduced pressure and dissolved in CHCl$_3$ (1 mL). The crude product in CHCl$_3$ was purified by flash column chromatography (CHCl$_3$ and then hexane/ethyl acetate = 5/1) to give **2.94a-t** and **2.101a,b**.

2.94a
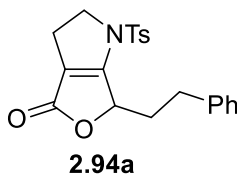
38.3 mg, 90% yield, white solid;

IR (neat): v =1755, 1651, 1405, 1363, 1167, 671, 576, 544 cm^{-1};

HRMS (ESI), calcd for C$_{21}$H$_{22}$NO$_4$S [M+H]$^+$ 384.1270, found 384.1308 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.62 – 7.54 (m, 2H), 7.36 – 7.28 (m, 4H), 7.27 – 7.19 (m, 3H), 5.16 (m, 1H), 4.23 (td, J = 10.8, 6.5 Hz, 1H), 4.00 (td, J = 10.8, 8.0 Hz, 1H), 2.83 (m, 2H), 2.74 – 2.53 (m, 3H), 2.45 (s, 3H), 2.25 – 2.06 (m, 1H);

^{13}C NMR (125 MHz, Chloroform-d) δ 171.92, 167.24, 145.74, 140.28, 132.97, 130.55, 128.84, 128.62, 127.59, 126.37, 116.52, 77.01, 57.27, 34.17, 30.83, 22.85, 21.82.

2.94b
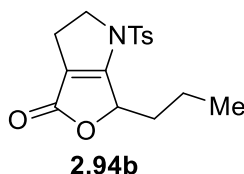
29.1 mg, 91% yield, white solid;

IR (neat): v =1755, 1848, 1407, 1362, 1168, 671, 575 cm^{-1};

HRMS (ESI), calcd for C$_{16}$H$_{20}$NO$_4$S [M+H]$^+$ 322.1114, found 322/1165 m/z;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.75 – 7.61 (m, 2H), 7.47 – 7.32 (m, 2H), 5.31 – 5.09 (m, 1H), 4.30 (td, *J* = 10.9, 6.5 Hz, 1H), 4.03 (td, *J* = 10.8, 7.7 Hz, 1H), 2.77 – 2.55 (m, 2H), 2.47 (s, 3H), 2.30 – 2.14 (m, 1H), 1.87 – 1.67 (m, 1H), 1.53 – 1.43 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, Chloroform-*d*) δ 172.19, 167.39, 145.77, 132.98, 130.56, 127.67, 116.51, 78.01, 57.16, 35.05, 29.84, 22.91, 21.84, 18.02, 13.72.

2.94c
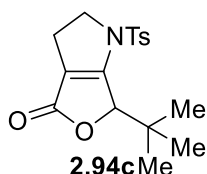
31.1 mg, 93% yield, colorless oil;

IR (neat): *v* =1760, 1653, 1364, 1167, 979, 677, 576 cm^{-1};

HRMS (ESI), calcd for C$_{17}$H$_{22}$NO$_4$S [M+H]$^+$ 336.1270, found 336.1257 m/z;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.73 – 7.60 (m, 2H), 7.42 – 7.31 (m, 2H), 5.08 (dd, *J* = 2.5, 1.1 Hz, 1H), 4.27 (dt, *J* = 12.6, 10.4 Hz, 1H), 4.15 (ddd, *J* = 12.6, 9.4, 3.1 Hz, 1H), 2.46 (s, 3H), 2.36 (dddd, *J* = 15.6, 10.3, 3.1, 1.1 Hz, 1H), 2.07 (dddd, *J* = 15.6, 10.4, 9.4, 2.5 Hz, 1H), 1.09 (s, 9H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 171.78, 167.29, 145.76, 132.69, 130.49, 127.84, 124.65, 86.23, 58.23, 36.51, 26.06, 23.13, 21.86.

2.94d
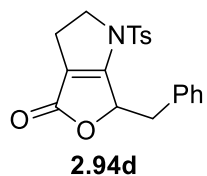
33.7 mg, 91% yield, white solid;

IR (neat): v =1758, 1653, 1362, 1166, 1031, 671, 577 cm^{-1};

HRMS (ESI), calcd for $C_{20}H_{20}NO_4S$ [M+H]$^+$ 370.1114, found 370.1098 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.73 – 7.66 (m, 2H), 7.38 (d, J = 8.1 Hz, 2H), 7.32 – 7.25 (m, 4H), 7.23 (tt, J = 5.6, 1.9 Hz, 1H), 5.40 (m, 1H), 4.20 (td, J = 10.9, 6.1 Hz, 1H), 3.90 (td, J = 10.7, 7.9 Hz, 1H), 3.52 (dd, J = 14.3, 3.4 Hz, 1H), 3.22 (dd, J = 14.3, 5.8 Hz, 1H), 2.50 – 2.40 (m, 4H), 2.35 (m, 1H);

^{13}C NMR (125 MHz, Chloroform-d) δ 170.66, 166.79, 145.84, 134.61, 132.74, 130.60, 129.97, 128.45, 127.70, 127.36, 117.78, 77.92, 56.94, 38.84, 22.76, 21.83.

2.94e
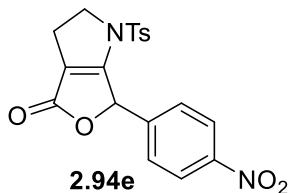
20.5 mg, 51% yield, light yellow solid;

IR (neat): v =1759, 1649, 1522, 1347, 1166, 1101, 975, 669, 577 cm^{-1};

HRMS (ESI), calcd for $C_{19}H_{17}N_2O_6S$ [M+H]$^+$ 401.0808, found 401.0790 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 8.33 – 8.15 (m, 2H), 7.67 – 7.53 (m, 2H), 7.25 – 7.19 (m, 4H), 6.23 (t, J = 1.8 Hz, 1H), 4.42 – 4.27 (m, 1H), 4.27 – 4.15 (m, 1H), 2.87 (m, 2H), 2.42 (s, 3H);

^{13}C NMR (125 MHz, Chloroform-d) δ 170.85, 166.40, 148.84, 145.90, 140.54, 133.43, 130.38, 129.41, 127.28, 124.14, 115.61, 57.14, 23.29, 21.83.

2.94f
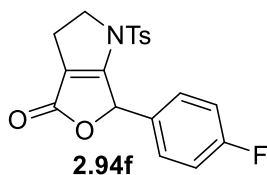
30.9 mg, 83% yield, white solid;

IR (neat): v =1759, 1650, 1410, 1324, 1165, 1113, 1066, 975, 673, 577, 542 cm^{-1};

HRMS (ESI), calcd for $C_{19}H_{17}FNO_4S$ [M+H]$^+$ 374.0863, found 374.0913 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.37 – 7.31 (m, 2H), 7.21 – 7.15 (m, 2H), 7.12 – 7.05 (m, 4H), 6.13 (t, J = 1.7 Hz, 1H), 4.40 (td, J = 10.8, 6.8 Hz, 1H), 4.15 (ddd, J = 11.3, 10.4, 7.5 Hz, 1H), 2.99 – 2.75 (m, 2H), 2.40 (s, 3H);

^{13}C NMR (125 MHz, Chloroform-d) δ 171.21, 167.01, 164.63, 162.65, 145.37, 133.83, 130.43, 130.36, 130.15, 129.50, 127.25, 116.11, 115.94, 114.66, 78.10, 56.94, 23.14, 21.76;

^{19}F NMR (470 MHz, Chloroform-d) δ -112.27.

2.94g
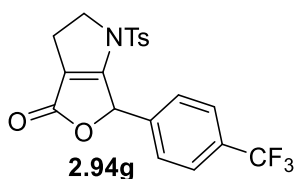
28.8 mg, 68% yield, white solid;

IR (neat): v =1756, 1650, 1510, 1408, 1361, 1167, 1105, 971, 670, 574 cm^{-1};

HRMS (ESI), calcd for $C_{20}H_{17}F_3NO_4S$ [M+H]$^+$ 424.0831, found 424.0872 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.71 – 7.60 (m, 2H), 7.53 – 7.46 (m, 2H), 7.16 – 7.09 (m, 2H), 7.06 – 7.00 (m, 2H), 6.19 (t, J = 1.6 Hz, 1H), 4.42 (td, J = 10.8, 6.8 Hz, 1H), 4.17 (ddd, J = 11.3, 10.5, 7.6 Hz, 1H), 3.00 – 2.75 (m, 2H), 2.38 (s, 3H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 171.02, 166.80, 145.50, 137.50, 133.74, 132.17, 131.91, 130.14, 128.96, 127.09, 126.00, 125.97, 125.94, 125.01, 122.84, 114.74, 77.83, 57.03, 29.86, 23.18, 21.73;

^{19}F NMR (470 MHz, Chloroform-*d*) δ -63.86.

2.94h
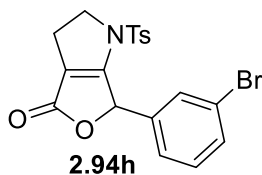
37.8 mg, 87% yield, colorless oil;

IR (neat): v =1758, 1647, 1361, 1167, 1107, 974, 669, 576 cm^{-1};

HRMS (ESI), calcd for C$_{19}$H$_{17}$BrNO$_4$S [M+H]$^+$ 424.0062, found 424.0040 m/z;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.57 (ddd, *J* = 7.9, 2.0, 1.2 Hz, 1H), 7.40 – 7.33 (m, 2H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.21 – 7.15 (m, 2H), 7.11 – 7.04 (m, 2H), 6.09 (t, *J* = 1.7 Hz, 1H), 4.42 (td, *J* = 10.7, 6.9 Hz, 1H), 4.17 (ddd, *J* = 11.2, 10.4, 7.7 Hz, 1H), 2.97 – 2.75 (m, 2H), 2.40 (s, 4H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 170.83, 166.84, 145.39, 135.74, 133.72, 132.98, 130.86, 130.60, 130.22, 127.74, 127.18, 122.99, 114.75, 77.91, 56.99, 23.14, 21.77.

2.94i
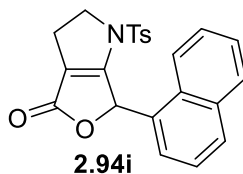
13.3 mg, 33% yield, colorless oil;

IR (neat): v =1755, 1650, 1411, 1361, 1167, 1036, 958, 671, 576 cm^{-1};

HRMS (ESI), calcd for $C_{23}H_{20}NO_4S$ $[M+H]^+$ 406.1114, found 406.1110 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 8.28 – 8.17 (m, 1H), 7.93 (ddt, J = 7.7, 5.3, 0.9 Hz, 2H), 7.62 (ddd, J = 8.5, 6.8, 1.5 Hz, 1H), 7.56 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 7.36 (dd, J = 8.2, 7.1 Hz, 1H), 7.31 – 7.20 (m, 2H), 7.10 (s, 4H), 6.97 (t, J = 1.8 Hz, 1H), 4.51 (td, J = 10.7, 7.4 Hz, 1H), 4.44 – 4.22 (m, 1H), 2.95 (m, 2H), 2.37 (s, 3H);

^{13}C NMR (125 MHz, Chloroform-d) δ 171.11, 167.09, 145.22, 134.09, 133.90, 131.96, 130.67, 130.04, 129.77, 128.96, 127.41, 127.35, 126.51, 125.96, 125.16, 123.35, 116.06, 75.48, 57.15, 23.38, 21.77.

2.94j
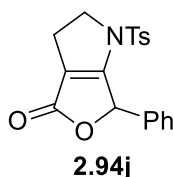
18.7 mg, 53% yield, white solid;

IR (neat): v =1754, 1646, 1410, 1360, 1167, 1104, 969, 670, 576 cm^{-1};

HRMS (ESI), calcd for $C_{19}H_{18}NO_4S$ $[M+H]^+$ 356.0957, found 356.0963 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.49 – 7.43 (m, 1H), 7.43 – 7.38 (m, 2H), 7.38 – 7.33 (m, 2H), 7.11 (d, J = 8.1 Hz, 2H), 7.01 – 6.95 (m, 2H), 6.15 (t, J = 1.6 Hz, 1H), 4.42 (td, J = 10.8, 6.6 Hz, 1H), 4.11 (ddd, J = 11.3, 10.4, 7.6 Hz, 1H), 3.02 – 2.75 (m, 2H), 2.37 (s, 3H);

^{13}C NMR (125 MHz, Chloroform-d) δ 171.25, 167.17, 144.95, 133.70, 133.35, 129.91, 129.72, 128.90, 128.38, 127.19, 114.16, 78.76, 56.67, 22.97, 21.58.
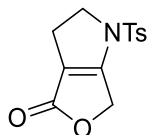
2.94k

13.7 mg, 49% yield, colorless oil;

IR (neat): v =1757, 1653, 1424, 1361, 1166, 1108, 986, 671, 576, 544 cm^{-1};

HRMS (ESI), calcd for $C_{13}H_{14}NO_4S$ [M+H]$^+$ 280.0641, found 280.0612 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.77 – 7.65 (m, 2H), 7.46 – 7.37 (m, 2H), 5.01 (t, J = 2.0 Hz, 2H), 4.18 (dd, J = 9.5, 8.5 Hz, 2H), 2.85 – 2.69 (m, 2H), 2.47 (s, 3H).

^{13}C NMR (125 MHz, Chloroform-d) δ 170.04, 167.75, 145.89, 133.14, 130.67, 127.57, 114.26, 65.67, 56.67, 23.43, 21.88.
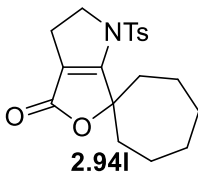
2.94l

33.8 mg, 94% yield, colorless oil;

IR (neat): v =1751, 1639, 1360, 1167, 670, 577, 544 cm^{-1};

HRMS (ESI), calcd for $C_{19}H_{24}NO_4S$ [M+H]$^+$ 362.1427, found 362.1399 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.77 – 7.71 (m, 2H), 7.42 – 7.33 (m, 2H), 4.27 – 4.04 (m, 2H), 2.65 (dd, J = 9.8, 8.7 Hz, 2H), 2.53 (ddd, J = 13.9, 10.9, 2.2 Hz, 2H), 2.46 (s, 3H), 1.97 – 1.80 (m, 4H), 1.80 – 1.67 (m, 5H), 1.67 – 1.47 (m, 3H), 1.42 (m, 1H);

^{13}C NMR (125 MHz, Chloroform-d) δ 176.07, 166.89, 145.31, 133.86, 130.26, 127.64, 113.55, 87.77, 57.48, 36.83, 26.92, 22.64, 21.78, 21.68.

2.94m
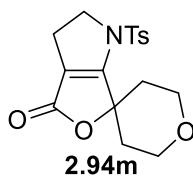
24.6 mg, 71% yield, white solid;

IR (neat): v =1751, 1637, 1395, 1359, 1165, 1055, 670, 581, 544 cm^{-1};

HRMS (ESI), calcd for $C_{17}H_{20}NO_5S$ [M+H]$^+$ 350.1063, found 350.1029 m/z;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.76 – 7.64 (m, 2H), 7.46 – 7.34 (m, 2H), 4.19 (dd, *J* = 9.9, 8.7 Hz, 2H), 4.02 – 3.92 (m, 2H), 3.90 – 3.79 (m, 2H), 2.92 – 2.79 (m, 2H), 2.69 (dd, *J* = 9.9, 8.7 Hz, 2H), 2.47 (s, 3H), 1.61 – 1.50 (m, 2H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 173.39, 165.97, 145.50, 133.65, 130.36, 127.55, 115.64, 82.13, 63.72, 57.55, 33.37, 21.90, 21.69.

2.94n
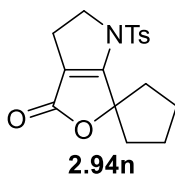
28.1 mg, 84% yield, white solid;

IR (neat): v =1751, 1639, 1398, 1360, 1168, 1067, 978, 669, 580, 544 cm^{-1};

HRMS (ESI), calcd for $C_{17}H_{20}NO_4S$ [M+H]$^+$ 334.1114, found 334.1082 m/z;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.75 – 7.69 (m, 2H), 7.43 – 7.34 (m, 2H), 4.19 (dd, *J* = 9.8, 8.6 Hz, 2H), 2.69 (dd, *J* = 9.8, 8.7 Hz, 2H), 2.65 – 2.54 (m, 2H), 2.47 (s, 3H), 2.03 – 1.84 (m, 6H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 172.04, 166.61, 145.49, 134.00, 130.47, 127.63, 116.09, 92.55, 57.53, 37.15, 25.00, 22.24, 21.84.

2.94o
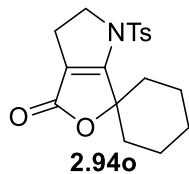
30.3 mg, 87% yield, white solid;

IR (neat): v =1746, 1637, 1392, 1360, 1167, 1089, 1066, 670, 578, 544 cm^{-1};

HRMS (ESI), calcd for $C_{18}H_{22}NO_4S$ [M+H]$^+$ 348.1270, found 348.1230 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.78 – 7.67 (m, 2H), 7.45 – 7.34 (m, 2H), 4.22 – 4.06 (m, 2H), 2.65 (dd, J = 9.8, 8.7 Hz, 2H), 2.55 – 2.40 (m, 5H), 1.82 – 1.63 (m, 7H), 1.45 – 1.23 (m, 1H);

^{13}C NMR (125 MHz, Chloroform-d) δ 175.03, 166.83, 145.44, 133.88, 130.42, 127.70, 115.37, 85.24, 57.68, 33.41, 24.22, 22.07, 22.00, 21.82.

2.94p
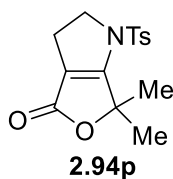
30.0 mg, 98% yield, white solid;

IR (neat): v =1752, 1641, 1396, 1357, 1164, 1091, 671, 568, 544 cm^{-1};

HRMS (ESI), calcd for $C_{15}H_{18}NO_4S$ [M+H]$^+$ 308.0957, found 308.0969 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.78 – 7.63 (m, 2H), 7.46 – 7.31 (m, 2H), 4.27 – 4.07 (m, 2H), 2.75 – 2.60 (m, 2H), 2.46 (s, 3H), 1.78 (s, 6H);

^{13}C NMR (125 MHz, Chloroform-d) δ 174.81, 166.42, 145.53, 133.78, 130.44, 127.74, 114.79, 83.14, 57.48, 25.36, 22.11, 21.82.

2.94q
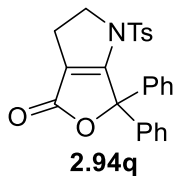
16.4 mg, 38% yield, colorless oil;

IR (neat): v =1757, 1636, 1391, 1365, 1092, 559, 578 cm^{-1};

HRMS (ESI), calcd for $C_{25}H_{22}NO_4S$ [M+H]$^+$ 432.1270, found 432.1238 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.53 – 7.48 (m, 4H), 7.48 – 7.38 (m, 6H), 7.03 (d, J = 8.0 Hz, 2H), 6.69 – 6.48 (m, 2H), 4.30 (dd, J = 9.9, 8.8 Hz, 2H), 2.83 (dd, J = 9.8, 8.8 Hz, 2H), 2.36 (s, 3H);

^{13}C NMR (125 MHz, Chloroform-d) δ 172.00, 166.59, 145.03, 136.96, 133.04, 129.90, 129.65, 129.18, 128.22, 127.90, 116.24, 89.91, 57.50, 22.16, 21.72.

2.94r
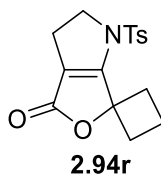
27.7 mg, 87% yield, white solid;

IR (neat): v =1751, 1634, 1400, 1359, 1258, 1163, 1089, 1053, 670, 579, 543 cm^{-1};

HRMS (ESI), calcd for $C_{16}H_{18}NO_4S$ [M+H]$^+$ 320.0957, found 320.0955 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.81 – 7.70 (m, 2H), 7.48 – 7.33 (m, 2H), 4.17 (dd, J = 9.7, 8.7 Hz, 2H), 3.35 – 3.04 (m, 2H), 2.64 (dd, J = 9.8, 8.7 Hz, 2H), 2.55 – 2.39 (m, 5H), 2.39 – 2.18 (m, 1H), 2.18 – 1.94 (m, 1H).

^{13}C NMR (125 MHz, Chloroform-d) δ 170.67, 166.36, 145.50, 133.94, 130.51, 127.57, 116.28, 85.60, 57.48, 32.29, 22.23, 21.83, 14.85;

2.94s
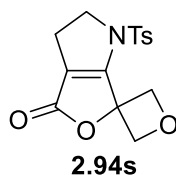
31.9 mg, 99% yield, white solid;

IR (neat): v =1765, 1637, 1411, 1361, 1167, 1091, 671, 581 cm^{-1};

HRMS (ESI), calcd for C$_{15}$H$_{16}$NO$_5$S [M+H]$^+$ 322.0750, found 322.0743 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.86 – 7.71 (m, 2H), 7.48 – 7.34 (m, 2H), 5.37 (dd, J = 7.3, 1.1 Hz, 2H), 4.93 (dd, J = 7.3, 1.2 Hz, 2H), 4.37 – 4.19 (m, 2H), 2.80 – 2.65 (m, 2H), 2.47 (s, 3H);

^{13}C NMR (125 MHz, Chloroform-d) δ 166.59, 164.96, 145.93, 133.90, 130.61, 127.68, 116.89, 82.06, 78.05, 57.58, 22.34, 21.86.

2.94t
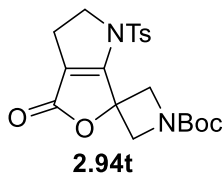
30.0 mg, 71% yield, white solid;

IR (neat): v =1769, 1704, 1416, 1366, 1166, 1053, 671 cm^{-1};

HRMS (ESI), calcd for C$_{20}$H$_{25}$N$_2$O$_6$S [M+H]$^+$ 421.1434, found 431.1374 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.88 – 7.73 (m, 2H), 7.46 – 7.36 (m, 2H), 4.71 (dd, J = 48.1, 9.8 Hz, 2H), 4.47 – 4.10 (m, 4H), 2.89 – 2.65 (m, 2H), 2.48 (s, 3H), 1.47 (s, 9H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 168.15, 165.25, 156.63, 145.90, 133.98, 130.66, 127.77, 116.08, 80.57, 77.28, 59.40, 57.97, 57.42, 28.49, 22.46, 21.88.

2.101a
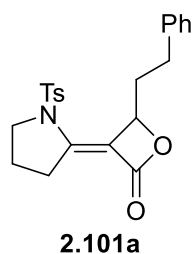
15.2 mg, 40% yield, white solid;

IR (neat): *v* =1784, 1692, 1363, 1205, 1165, 1086, 813, 671, 589, 544 cm^{-1};

HRMS (ESI), calcd for $C_{22}H_{24}NO_4S$ [M+H]$^+$ 398.1427, found 398.1356 m/z;

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.65 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.27 – 7.23 (m, 2H), 7.22 – 7.15 (m, 1H), 5.34 (d, *J* = 7.9 Hz, 1H), 3.71 (ddd, *J* = 9.9, 7.4, 4.1 Hz, 1H), 3.37 (ddd, *J* = 10.0, 8.6, 7.0 Hz, 1H), 3.05 (ddd, *J* = 16.6, 7.2, 4.3 Hz, 1H), 2.99 – 2.72 (m, 2H), 2.65 (dddd, *J* = 14.5, 10.1, 6.3, 2.4 Hz, 1H), 2.59 – 2.48 (m, 1H), 2.45 (s, 3H), 2.24 – 2.07 (m, 1H), 1.88 – 1.70 (m, 2H);

^{13}C NMR (125 MHz, Chloroform-*d*) δ 166.13, 145.49, 143.82, 141.35, 133.96, 130.34, 128.70, 128.53, 127.34, 126.05, 112.94, 80.38, 51.97, 34.10, 32.33, 31.07, 21.85.

2.101b
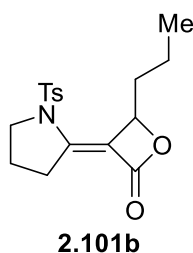
6.0 mg, 18% yield, colorless oil;

IR (neat): v =1713, 1327, 1159, 1094, 815, 664, 550 cm^{-1};

HRMS (ESI), calcd for C$_{17}$H$_{22}$NO$_4$S [M+H]$^+$ 336.1270, found 336.1236 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.76 – 7.63 (m, 2H), 7.43 – 7.33 (m, 2H), 5.41 – 5.24 (m, 1H), 3.85 – 3.69 (m, 1H), 3.37 (ddd, J = 9.9, 8.8, 6.8 Hz, 1H), 3.11 (ddd, J = 16.5, 7.3, 4.0 Hz, 1H), 2.59 – 2.37 (m, 5H), 2.37 – 2.22 (m, 1H), 1.97 – 1.63 (m, 4H), 1.60 – 1.47 (m, 3H), 0.98 (t, J = 7.4 Hz, 3H);

^{13}C NMR (125 MHz, Chloroform-d) δ 166.33, 145.48, 143.46, 133.94, 130.35, 127.41, 113.79, 81.25, 51.93, 34.79, 32.28, 21.98, 21.86, 18.44, 13.99.

Preparation of 2.92 :

2.92 are prepared according to the previously reported procedures. [78]

2.92
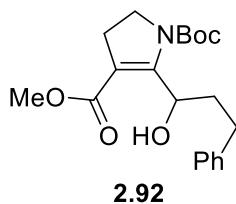
8.6 mg, 24% yield, colorless oil;

IR (neat): v =1715, 1681, 1453, 1403, 1308, 1251, 1158 cm^{-1};

HRMS (ESI), calcd for C$_{20}$H$_{28}$NO$_5$ [M+H]$^+$ 475.1540, found 475.1536 m/z;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.26 (m, 2H), 7.23 – 7.11 (m, 3H), 5.77 (d, J = 12.1 Hz, 1H), 5.64 (m, 1H), 3.77 (m, 1H), 3.71 – 3.61 (m, 4H), 3.01 – 2.89 (m, 1H), 2.80 – 2.66 (m, 2H), 2.61 (m, 1H), 1.50 (s, 9H);

^{13}C NMR (125 MHz, Chloroform-d) δ 166.77, 157.54, 153.01, 142.34, 128.65, 128.38, 125.83, 110.85, 82.71, 66.08, 51.70, 48.23, 36.67, 32.42, 28.40, 27.51.

Total Syntheses of Bisdehydroneostemoninine and Bisdehydrostemoninine by Catalytic Carbonylative Spirolactonization

Kaiqing Ma[+], Xianglin Yin[+], and Mingji Dai*

Abstract: The first total syntheses of the stemona alkaloids bisdehydroneostemoninine and bisdehydrostemoninine in rac-emic forms have been achieved. The synthetic strategy features a novel palladium-catalyzed carbonylative spirolactonization of a hydroxycyclopropanol to rapidly construct the oxaspir-olactone moiety. It also features a Lewis acid promoted tandem Friedel–Crafts cyclization and lactonization to form the 5-7-5 tricyclic core of the target stemona alkaloids.

The *Stemonaceae* plants have been widely used in Chinese and Japanese traditional medicines for their antitussive effect and insecticidal activity. They are rich sources of complex bioactive natural products, especially alkaloids. So far, over 150 stemona alkaloids have been isolated from these plants.[1] These alkaloids are categorized into eight different groups and most of them feature a characteristic pyrrolo[1,2-*a*]aze-pine nucleus. Our recent interest in oxaspirolactone syn-thesis[2] and the stemofoline group[3] brought our attention to the stemoamide group because many of its members, such as bisdehydroneostemoninine (**1a**, Figure 1 A), (iso)bisdehy-drostemoninine (**1b** and **1c**),[4] stemoninines A and B (**1d** and **1e**),[5] tuberstemoamide (**1f**),[6] sessilifoliamide A (**1g**),[7] (dihydro)stemoninine (**1h** and **1i**),[8] and stemoenonine (**1j**),[9] contain an oxaspirolactone moiety. Despite the recent efforts toward the total syntheses of stemona alkaloids,[10] only a few members of the stemoamide group have been synthesized. While there are over 20 total syntheses of the simplest member stemoamide (**1l**, Figure 1 B),[11] total syntheses of the more complex ones are very rare. Notably, Williams and co-workers reported the first total synthesis of stemonine (**1m**) in 2003[12] and Chida, Sato and co-workers developed a unified approach to synthesize both **1m** and saxorumamide (**1n**) from **1l** in 2017.[13] So far, there have been no reported total syntheses of these oxaspirolactone-containing stemona alka-loids (**1a–k**). The existence of an acid-sensitive oxaspirolac-tone moiety generates a significant synthetic challenge in its installation as well as the control of the stereochemistry at the

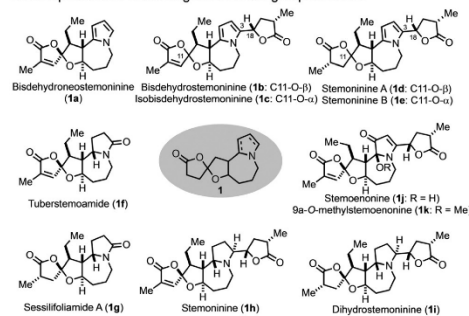[*] Dr. K. Ma,[+] X. Yin,[+] Prof. M. Dai
      Department of Chemistry, Center for Cancer Research,
      and Institute for Drug Discovery, Purdue University
      West Lafayette, Indiana 47907 (USA)
      E-mail: mjdai@purdue.edu
      Dr. K. Ma[+]
      Modern Research Center for Traditional Chinese Medicine
      of Shanxi University, Taiyuan 03006, Shanxi (China)
  [+] These authors contributed equally to this work.
  📄 Supporting information and the ORCID identification number(s) for
  🆔 the author(s) of this article can be found under:
      https://doi.org/10.1002/anie.201809114.

A. Oxaspirolactone-containing stemoamide group members

B. Previously synthesized stemoamide group members
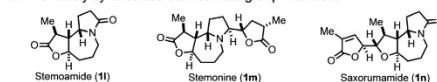
Figure 1. Selected stemoamide group stemona alkaloids.

spirocenter (C11). Additionally, several of these natural products (**1a–e**) contain an aromatic pyrrole ring and the others (**1f–k**) have either a pyrrolidine (**1h** and **1i**) or oxidized derivatives thereof (**1f, 1g, 1j,** and **1k**). For the cases of **1b**, **1c**, **1d**, and **1e**, a γ-butyrolactone is appended to the pyrrole ring at the C3 position, and renders the C18 stereocenter labile for epimerization. Therefore, extra cau-tion is necessary to avoid scrambling the corresponding stereochemistries. These structural features drastically increase the structural complexity of the targets and enhance difficulties in conquering their total syntheses. Additionally, the relative stereochemistry of **1b** was unambiguously established by X-ray crystallography.

We recently developed a palladium-catalyzed carbon-ylative spirolactonization of hydroxycyclopropanols to syn-thesize oxaspirolactones in one step (**3**→**5**, Scheme 1 A).[2] The starting hydroxycyclopropanols are readily available by a Kulinkovich reaction of the corresponding lactones (**2**→**3**). Recognizing the oxaspirolactone moiety of the aforemen-tioned stemona alkaloids, we wondered about the possibility of using the palladium-catalyzed carbonylative spirolactoni-zation to convert the intermediate **8** into oxaspirolactone **9** (Scheme 1 B). The latter would serve as a key intermediate toward some of the target stemona alkaloids such as **1a** and **1b**. The cyclopropanol **8** could be derived from the tricyclic lactone **7** by an α-ethylation and Kulinkovich reaction. To quickly access **7**, and inspired by the pioneering work of the

106

A. Our reported Pd-catalyzed carbonylative spirolactonization

B. Synthetic design

Scheme 1. Synthetic plan featuring carbonylative cyclizations.

groups of Yang[14] and Widenhoefer,[15] we envisioned a palladium-catalyzed oxidative tandem cyclization and carbonylative lactonization to convert the allylic alcohol **6** into **7**. Additionally, in the long term, we wished to use **1a** to access the related non-pyrrole-containing natural products (cf. **1f–i**) by identifying or developing new methods to convert the pyrrole into either the corresponding pyrrolidines or γ-butyrolactams. Herein, we report the first total syntheses of **1a** and **1b** in their racemic forms.

Our synthesis commenced with the commercially available starting materials **10** and **11**, which were readily converted into the pyrrole **12** by a modified Clauson–Kaas reaction[16] and Weinreb amide formation. Vinyl Grignard nucleophilic addition followed by Luche reduction of the resulting enone gave **6** in 67% yield. We then started to explore different oxidative carbonylation reaction conditions to transform **6** into **7** in one step. Unfortunately, all the

Scheme 2. Total syntheses of bisdehydroneostemoninine (**1a**) and bisdehydrostemoninine (**1b**): BQ = benzoquinone, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DCE = 1,2-dichloroethane, HMPA = hexamethylphosphoramide, LDA = lithium diisopropylamide, LiHMDS = lithium bis(trimethylsilyl)amide, pyr. = pyridine, rt = room temperature, THF = tetrahydrofuran, tol. = toluene.

107

reaction conditions we investigated failed to deliver **7**. Some of them gave a cyclized product where a carbon–carbon bond was formed between the pyrrole ring and the allylic carbon atom to build a six-membered ring (see the Supporting Information). Thus, we developed a two-step detour to realize the synthesis of **7** from **6**. Cross-metathesis of **6** and methyl acrylate with the Grubbs second-generation catalyst afforded the α,β-unsaturated ester **13** in 91% yield.[17] We then used a boron trifluoride etherate promoted tandem Friedel–Crafts cyclization and lactonization to build the azepine ring as well as the fused γ-butyrolactone ring.[18] The reaction took place smoothly to give tricyclic lactone in 79% yield as a 2.6:1 mixture of separable diastereomers favoring the desired product **7**, which has a *trans* ring junction. Upon the treatment of **7** with LDA and EtI in a mixed solvent of HMPA and THF, α-ethylation occurred to provide a 1.3:1 mixture of **14** and **15** in 86% yield. While the reaction slightly favors the undesired product **14**, it was readily epimerized to the desired **15** with K_2CO_3 as base in MeOH. In addition to comprehensive NMR analysis, the relative stereochemistry of both **7** and **14** was confirmed by X-ray crystallography.[19]

With **15** in hand, the next step was to convert it into **8** using the Kulinkovich reaction. We first explored the standard and modified Kulinkovich reaction conditions[20] such as EtMgBr, Ti(O*i*Pr)₄, THF or MeMgBr, EtMgBr, Ti(O*i*Pr)₄, THF or Cp₂ZrCl₂, EtMgBr, Ti(O*i*Pr)₄, THF, but none of them gave **8** in synthetically useful yield. We also investigated the possibility of employing a Dreiding–Schmidt reaction between lactone **15** and methyl 2-(bromomethyl)acrylate to install the oxaspirolactone moiety with an *exo* methylene group.[21] Again, the strategy was not fruitful. These failures are presumably due to the steric hindrance around the lactone moiety. We then noted a remarkable cyclopropanol synthesis from a sterically hindered ester in Corey's isoedunol total synthesis,[22] where ClTi(O*i*Pr)₃ was used instead of the commonly used Ti(O*i*Pr)₄. The replacement of one bulky isopropoxide group with a chloride group significantly reduced the steric hindrance and increased the electrophilic property of the titanium center and made it possible for sterically challenging substrates. We then investigated Corey's Kulinkovich protocol and were delighted to see the formation of **8** in 63% yield. The palladium-catalyzed carbonylative spirolactonization of **8** was less problematic. With 10 mol% of the Waymouth catalyst [Pd(neoc)(OAc)]₂(OTf)₂ in stock, the corresponding oxaspirolactone product was obtained in 60% yield as a 2.3:1 mixture of stereoisomers favoring the desired **9a**. The undesired epimer was isomerized to **9a** with TFA in CH₂Cl₂ at ambient temperature in 75% yield plus 15% of starting material recovery (see the Supporting Information). We later found out that the use of freshly prepared Waymouth catalyst provided **9a** from **8** as a single isomer in 54% yield. It was speculated that the freshly prepared Waymouth catalyst may be able to promote an in situ epimerization process. With **9a** in hand, the Eschenmoser protocol was used to install an α-*exo*-methylene group and provide the compound **17**. Ru₃-(CO)₁₂-catalyzed isomerization of the *exo*-methylene to an endocyclic double bond completed the first total synthesis of bisdehydroneostemoninine (**1a**) in its racemic form.[23] Notably, **1a** was produced in an overall 68% yield from **9a** with

only one column purification. The structure of synthetic **1a** was unambiguously confirmed by X-ray crystallography.[19] While **1b** and **1c**, and **1d** and **1e** (Figure 1) exist as a pair of epimers in nature, the C11-epimer of **1a** has not been reported so far. Since we also accessed the C11-epimer of **9a** in the carbonylative spirolactonization step, we advanced it to the C11-epimer of **1a** using the same Eschenmoser protocol and double-bond isomerization procedure (see the Supporting Information).

Next was the conversion of **1a** into bisdehydrostemoninine (**1b**) by installing the γ-butyrolactone at C3. There are several challenges involved in its installation. First, the oxaspirolactone moiety of **1a** is acid sensitive. Therefore, the subsequent steps must entail mild reaction conditions. Second, the two chiral centers of the γ-butyrolactone moiety are remote from the rest of the chiral centers. It is difficult to use the existing stereocenters to control the newly formed ones. Third, as noted before, the C18 stereocenter, once introduced, is prone to epimerization. With these potential problems in mind, we first used a modified Vilsmeier–Haack reaction[24] to introduce an aldehyde group at C3 and the product **18** was obtained in 75% yield. The reaction between **18** and the organozinc reagent derived from **19** gave the 1,2-addition adduct in 83% yield,[25] but as we expected, a 1:1 mixture of the diastereomers **20** and **22** were produced. Since **20** and **22** can be separated by flash column chromatography, we decided to use **20** for the total synthesis of **1b** and **22** for creation of bisdehydrostemoninine analogues for future biological evaluations. While the lactonization did not take place under the 1,2-addition reaction conditions, it occurred smoothly with K_2CO_3 in *t*BuOH to afford **21** in 76% yield.[26] As we expected, once the lactone ring is formed, the C18 stereocenter of **21** becomes very labile. Partial epimerization occurred even on triethylamine-pretreated silica gel. It also caused a problem for the subsequent hydrogenation step to reduce the *exo*-methylene group. After many trials, we learned that the use of a benzene-pyridine (1:1) mixed solvent was the key for the *exo*-methylene reduction and bisdehydrostemoninine (**1b**) was produced in 86% yield with 9:1 diastereoselectivity.[27] Notably, no column purification is needed from **20** to **1b**. Following the same protocol, **22** was converted into **24**, an analogue of **1b**. The structures of **21**, **23**, **24**, and synthetic bisdehydrostemoninine (**1b**) were unambiguously confirmed by X-ray crystallography.[19]

In summary, we completed the first total syntheses of the stemona alkaloids bisdehydroneostemoninine (**1a**) and bisdehydrostemoninine (**1b**) using a palladium-catalyzed carbonylative spirolactonization as the key step to constructing the oxaspirolactone moiety. We are currently adopting this approach to synthesize other related stemona alkaloids as well as their analogues for biological profiling and target identification.

Acknowledgements

108

[1] For reviews: a) R. A. Pilli, M. C. F. de Oliveira, *Nat. Prod. Rep.* **2000**, *17*, 117–127; b) R. A. Pilli, G. B. Rosso, M. C. F. de Oliveira, *Nat. Prod. Rep.* **2010**, *27*, 1908–1937; c) H. Greger, *Planta Med.* **2006**, *72*, 99–113.

[2] D. C. Davis, K. L. Walker, C. Hu, R. N. Zare, R. M. Waymouth, M. Dai, *J. Am. Chem. Soc.* **2016**, *138*, 10693–10699.

[3] X. Yin, H. Mohammad, H. E. Eldesouky, A. Abdelkhalek, M. N. Seleem, M. Dai, *Chem. Commun.* **2017**, *53*, 7238–7241.

[4] L.-G. Lin, Q. X. Zhong, T. Y. Cheng, C. P. Tang, C.-Q. Ke, G. Lin, Y. Ye, *J. Nat. Prod.* **2006**, *69*, 1051–1054.

[5] P. Wang, A. L. Liu, Z. H. Li, G. H. Du, H. L. Qin, *J. Asian Nat. Prod. Res.* **2008**, *10*, 311–314.

[6] W. H. Lin, L. Ma, M. S. Cai, R. A. Barnes, *Phytochemistry* **1994**, *36*, 1333–1335.

[7] D. Kakuta, Y. Hitotsuyanagi, N. Matsuura, H. Fukaya, K. Takeya, *Tetrahedron* **2003**, *59*, 7779–7786.

[8] D. Cheng, J. Guo, T. T. Chu, *J. Nat. Prod.* **1988**, *51*, 202–211.

[9] L.-G. Lin, K. M. Li, C.-P. Tang, C.-Q. Ke, J. A. Rudd, G. Lin, Y. Ye, *J. Nat. Prod.* **2008**, *71*, 1107–1110.

[10] For reviews: a) R. A. Pilli, G. B. Rosso, M. C. F. de Oliveira in *The Alkaloids, Vol. 62* (Ed.: G. A. Cordell), Elsevier, New York, **2005**, pp. 77–173; b) R. Alibés, M. Figueredo, *Eur. J. Org. Chem.* **2009**, 2421–2435. For recent examples: c) C. K. G. Gerlinger, S. Krüger, T. Gaich, *Chem. Eur. J.* **2018**, *24*, 3994–3997; d) S. Fujita, K. Nishikawa, T. Iwata, T. Tomiyama, H. Ikenaga, K. Matsumoto, M. Shindo, *Chem. Eur. J.* **2018**, *24*, 1539–1543; e) A. Varela, L. K. B. Garve, D. Leonori, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2017**, *56*, 2127–2131; *Angew. Chem.* **2017**, *129*, 2159–2163; f) Y. Nakayama, Y. Maeda, M. Kotatsu, R. Sekiya, M. Ichiki, T. Sato, N. Chida, *Chem. Eur. J.* **2016**, *22*, 3300–3303; g) P. Q. Huang, S. Y. Huang, L. H. Gao, Z. Y. Mao, Z. Chang, A. E. Wang, *Chem. Commun.* **2015**, *51*, 4576–4578; h) E. Ideue, J. Shimokawa, T. Fukuyama, *Org. Lett.* **2015**, *17*, 4964–4967; i) J. Fu, H. Shen, Y. Chang, C. Li, J. Gong, Z. Yang, *Chem. Eur. J.* **2015**, *21*, 12881–12888; j) C. Fang, C. S. Shanahan, D. H. Paull, S. F. Martin, *Angew. Chem. Int. Ed.* **2012**, *51*, 10596–10599; *Angew. Chem.* **2012**, *124*, 10748–10751; k) Y. Wang, L. Zhu, Y.

Zhang, R. Hong, *Angew. Chem. Int. Ed.* **2011**, *50*, 2787–2790; *Angew. Chem.* **2011**, *123*, 2839–2842; l) Z. H. Chen, J. M. Tian, Z. M. Chen, Y. Q. Tu, *Chem. Asian J.* **2012**, *7*, 2199–2202; m) Z.-H. Chen, Z.-M. Chen, Y.-Q. Zhang, Y.-Q. Tu, F.-M. Zhang, *J. Org. Chem.* **2011**, *76*, 10173–10186; n) K. J. Frankowski, V. Setola, J. M. Evans, B. Neuenswander, B. L. Roth, J. Aubé, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 6727–6732; o) M. Brüggemann, A. I. McDonald, L. E. Overman, M. D. Rosen, L. Schwink, J. P. Scott, *J. Am. Chem. Soc.* **2003**, *125*, 15284–15285.

[11] For a review: G. A. Brito, R. V. Pirovani, *Org. Prep. Proced. Int.* **2018**, *50*, 245–259.

[12] D. R. Williams, K. Shamim, J. P. Reddy, G. S. Amato, S. M. Shaw, *Org. Lett.* **2003**, *5*, 3361–3364.

[13] M. Yoritate, Y. Takahashi, H. Tajima, C. Ogihara, T. Yokoyama, Y. Soda, T. Oishi, T. Sato, N. Chida, *J. Am. Chem. Soc.* **2017**, *139*, 18386–18391.

[14] S. Li, F. Li, J. Gong, Z. Yang, *Org. Lett.* **2015**, *17*, 1240–1243.

[15] a) C. Liu, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2004**, *126*, 10250–10251; b) C. Liu, R. A. Widenhoefer, *Chem. Eur. J.* **2006**, *12*, 2371–2382.

[16] B. S. Gourlay, P. P. Molesworth, J. H. Ryan, J. A. Smith, *Tetrahedron Lett.* **2006**, *47*, 799–801.

[17] B. Schmidt, S. Hauke, *Org. Biomol. Chem.* **2013**, *11*, 4194–4206.

[18] a) M. G. Banwell, D. A. S. Beck, J. A. Smith, *Org. Biomol. Chem.* **2004**, *2*, 157–159; b) N. A. Paras, D. W. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370–4371; c) R. W. Bates, S. Sridhar, *J. Org. Chem.* **2011**, *76*, 5026–5035.

[19] CCDC 1859471, 1859473, 1859474, 1859476, 1859477, 1859475, and 1859478 (**7**, **14**, **1a**, **21**, **1b**, **23** and **24**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[20] a) O. G. Kulinkovich, *Chem. Rev.* **2003**, *103*, 2597–2632; b) I. Haym, M. A. Brimble, *Org. Biomol. Chem.* **2012**, *10*, 7649–7665.

[21] a) Y.-A. Zhang, Q. Liu, C. Wang, Y. Jia, *Org. Lett.* **2013**, *15*, 3662–3665. b) E. Öhler, K. Reininger, U. Schmidt, *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 457; *Angew. Chem.* **1970**, *82*, 444; c) A. Löffler, R. J. Pratt, H. P. Rüesch, A. S. Dreiding, *Helv. Chem. Acta.* **1970**, *53*, 383–403.

[22] a) J. S. Kingsbury, E. J. Corey, *J. Am. Chem. Soc.* **2005**, *127*, 13813–13815; b) E. J. Corey, S. A. Rao, M. C. Noe, *J. Am. Chem. Soc.* **1994**, *116*, 9345–9346.

[23] E. Yoneda, S.-W. Zhang, D.-Y. Zhou, K. Onitsuka, S. Takahashi, *J. Org. Chem.* **2003**, *68*, 8571–8576.

[24] A. I. Mikhaleva, A. V. Ivanov, E. V. S. Tseva, I. A. Ushakov, A. M. V. Tsov, B. A. Trofimov, *Synthesis* **2009**, 587–590.

[25] K. Miura, D. Wang, A. Hosomi, *J. Am. Chem. Soc.* **2005**, *127*, 9366–9367.

[26] W. Chen, Q. Yang, T. Zhou, Q. Tian, G. Zhang, *Org. Lett.* **2015**, *17*, 5236–5239.

[27] D. A. Horne, B. Fugmann, K. Yakushijin, G. Buchi, *J. Org. Chem.* **1993**, *58*, 62–64.

109

ChemComm

COMMUNICATION

Check for updates

Rapid synthesis of bicyclic lactones *via* palladium-catalyzed aminocarbonylative lactonizations†

Xianglin Yin,[a] Haroon Mohammad,[b] Hassan E. Eldesouky,[b] Ahmed Abdelkhalek,[b] Mohamed N. Seleem*[bc] and Mingji Dai [ID] *[ac]

A novel and efficient palladium-catalyzed aminocarbonylative lactonization of amino propargylic alcohols has been developed to provide rapid access to various bicyclic lactones especially dihydropyrrole-fused furanones, which are novel structures and have not been explored in biological and medicinal settings. This method can also be used to access β-lactone products such as 16. Preliminary biological evaluations revealed that compounds 13h and 13s demonstrated promising activity against *Clostridium difficile* and compounds 13h, 13k, 13s, and 16b showed activity against several important fungal pathogens.

Our recent efforts[1–3] in developing tandem palladium-catalyzed carbonylation reactions[4–8] for complex natural product synthesis have resulted in a novel method to synthesize oxaspirolactones from hydroxyl cyclopropanol starting materials (Fig. 1A).[2] We envisioned that this new synthetic capability could be potentially used to synthesize oxaspirolactone 5, an important precursor for the total syntheses of stemofoline alkaloids (*cf.* 4).[9–14] We proposed a tandem process to prepare 5 from 7 *via* a tandem Mannich reaction and ketalization. Compound 7 could be derived from hydroxyl cyclopropanol 8 *via* the palladium-catalyzed carbonylative oxaspirolactonization we have developed. Compound 8 could be synthesized from dihydropyrrole-fused furanone 10. In order to quickly access 10, we envisioned another palladium-catalyzed amino-carbonylative lactonization of amino propargylic alcohol 11. Surprisingly, there was no documented synthesis of dihydropyrrole-fused furanone (*cf.* 10), which turned out to be a novel scaffold. Their potential biological activities and use in medicinal
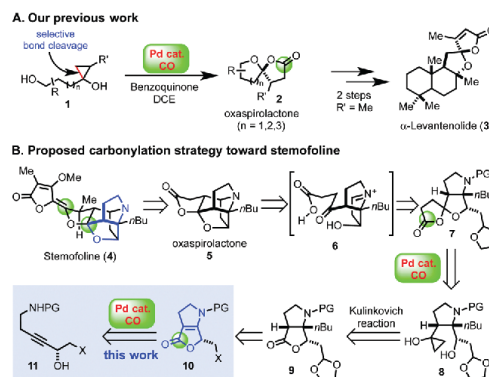
Fig. 1 Background and research design.

chemistry remain unknown. Therefore, we decided to develop and generalize the proposed palladium-catalyzed aminocarbonylative lactonizations to provide expedient avenues toward dihydropyrrole-fused furanones.

Significant advances have been made in the area of metal-catalyzed carbonylation of alkynes.[15] In 1979, Murray and Norton reported an elegant palladium-catalyzed carbonylation of homo-propargylic alcohols to synthesize α-methylene γ-lactones.[16,17] Since then, many palladium-catalyzed cyclocarbonylations of alkynes have been reported. Notably, Alper and co-workers reported carbonylative syntheses of 2(5*H*)-furanones from propargylic alcohols;[18–20] Yang,[21–25] Akita,[26] Gabriele[27–29] and others[30–34] have reported oxy or amino-palladation-alkoxycarbonylation of alkynes to synthesize various heterocycles. Despite these progresses, the intramolecular aminopalladation-carbonylative lactonization of amino propargylic alcohols of type 11 to synthesize dihydropyrrole-fused furanones (*cf.* 10) has not been reported. Herein, we describe elements of our recent efforts in developing such transformations to rapidly construct dihydropyrrole-fused furanones, which would not only facilitate total syntheses of complex natural products such as

[a] *Department of Chemistry and Center for Cancer Research, Purdue University, West Lafayette, Indiana, 47907, USA. E-mail: mjdai@purdue.edu; Tel: +1-765-496-7898*

[b] *Department of Comparative Pathobiology, Purdue University College of Veterinary Medicine, West Lafayette, IN 47907, USA. E-mail: mseleem@purdue.edu; Tel: +1-765-494-0763*

[c] *Purdue Institute for Drug Discovery and Institute for Inflammation, Immunology, and Infectious Diseases, West Lafayette, IN 47907, USA*

110

Table 1 Reaction condition optimizations

Entry	Reaction conditions (equiv.)	Yield^a (%)
1	PdCl$_2$ (0.1), **A** (0.1), BQ (1.5), PG = Ts	0
2	Pd(tfa)$_2$ (0.1), **A** (0.1), BQ (1.5), PG = Ts	63
3	Pd(tfa)$_2$ (0.1), **B** (0.1), BQ (1.5), PG = Ts	58
4	Pd(tfa)$_2$ (0.1), **C** (0.1), BQ (1.5), PG = Ts	63
5	Pd(tfa)$_2$ (0.1), **D** (0.1), BQ (1.5), PG = Ts	58
6	Pd(tfa)$_2$ (0.1), **E** (0.1), BQ (1.5), PG = Ts	53
7	Pd(tfa)$_2$ (0.1), **Xantphos** (0.1), BQ (1.5), PG = Ts	Trace
8	Pd(tfa)$_2$ (0.1), **F** (0.1), BQ (1.5), PG = Ts	33
9	PdCl$_2$(MeCN)$_2$ (0.1), **E** (0.1), BQ (1.5), PG = Ts	0
10	Pd(tfa)$_2$ (0.1), **C** (0.2), BQ (1.5), PG = Ts	41
11	Pd(tfa)$_2$ (0.1), **C** (0.1), BQ (3.0), PG = Ts	51
12	Pd(tfa)$_2$ (0.1), **C** (0.1), BQ (1.0), PG = Ts	61
13	Pd(tfa)$_2$ (0.1), **C** (0.1), BQ (1.0), PG = Ts, Cs$_2$CO$_3$ (1.0)	0
14	Pd(tfa)$_2$ (0.1), **C** (0.1), BQ (1.5), PG = Ts, CO (7 atm)	31
15	PdCl$_2$(MeCN)$_2$ (0.1)/AgOTf (0.2), **C** (0.1), BQ (1.5), PG = Ts	72
16	PdCl$_2$(MeCN)$_2$ (0.1)/AgOTf (0.2), **G** (0.1), BQ (1.5), PG = Ts	81
17	PdCl$_2$(MeCN)$_2$ (0.1)/AgOTf (0.2), **H** (0.1), BQ (1.5), PG = Ts	42
18	[Pd(neoc)(OAc)]$_2$(OTf)$_2$ (0.1), BQ (1.5), PG = Ts	69
19	PdCl$_2$(MeCN)$_2$ (0.1)/AgOTf (0.2), **G** (0.1), CuCl$_2$ (1.5), PG = Ts	0
20	**PdCl$_2$(MeCN)$_2$ (0.1)/AgOTf (0.2), G (0.1), DDQ (1.5), PG = Ts**	**90**
21	PdCl$_2$(MeCN)$_2$ (0.1)/AgOTf (0.2), **G** (0.1), DDQ (1.5), PG = Boc	0
22	Pd(tfa)$_2$ (0.1), BQ (1.5), PG = Boc, MeOH	24^b

^{a} Isolated yield. ^{b} Yield of **14** with MeOH as the solvent.

the stemofoline alkaloids, but also provide novel molecules for therapeutic development.

Our investigation started with model substrate **12a** (Table 1), which was readily prepared *via* 1,2-addition of acetylide to hydrocinnamaldehyde (see the ESI†). When the commonly used carbonylation catalyst PdCl$_2$ was used in combination with 2,2-bipyridine ligand **A**, no desired product **13a** was obtained. We hypothesized that a more cationic and electron-deficient palladium catalyst should function better to activate the triple bond for the aminopalladation step than the neutral PdCl$_2$ catalyst. Thus, Pd(tfa)$_2$ was explored next. To our delight, the desired product **13a** was produced in 63% yield with *p*-benzoquinone (BQ, 1.5 equiv.) as an oxidant and MeCN as a solvent. We then investigated the effect of different ligands and several bipyridine and 1,10-phenanthroline-based ligands (entries 3–6) were evaluated. These ligands are either the same as ligand **A** or slightly less effective, but are much more effective than BOX-ligand **F** (entry 8). Bidentate phosphine ligand Xantphos (entry 7) turned off the reaction almost completely and only a trace amount of **13a** was obtained. We further found that a 1 : 2 ratio of

the palladium catalyst and the ligand is not as good as 1 : 1. Increasing the amount of BQ from 1.5 equiv. to 3.0 equiv. (entry 11) made the reaction messier with 51% yield of the desired product, and decreasing the amount to 1.0 equiv. slightly reduced the reaction yield (61%, entry 12). Adding a base such as Cs$_2$CO$_3$ was detrimental (entry 13) and increasing the carbon monoxide pressure to 7 atm showed an inhibitory effect (entry 14). To further improve the reaction yield, we explored the more electron deficient Pd(OTf)$_2$ (0.1 equiv.) complex generated from a combination of PdCl$_2$(MeCN)$_2$ and AgOTf (1 : 2 ratio). The yield did increase to 72% (entry 15). Ligand **G** (entry 16, 81% yield) was found to be superior to ligand **C** (entry 4) and ligand **H** (entry 16). [Pd(neoc)(OAc)]$_2$(OTf)$_2$, a cationic dimeric palladium complex developed by the Waymouth lab[35] also worked for this transformation but with reduced reaction yield. While CuCl$_2$ as an oxidant was deleterious, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) increased the yield to 90% (entry 20). Interesting, when the nitrogen-protecting group was changed to Boc (**12a′**), even the optimized reaction conditions did not give any desired product **13a′** (entry 21). When MeOH
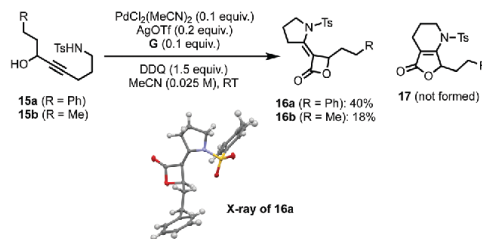
111

Table 2 Substrate scope

Fig. 2 Formation of β-lactone product.

carbon added between the nitrogen nucleophile and the triple bond, in addition to the expected 6-*endo-dig* amino-palladation, a 5-*exo-dig* amino-palladation becomes a potential competing pathway. If the latter occurs, we would be expecting a strained β-lactone product (*cf.* **16**). Interestingly, under the optimal reaction conditions for the formation of 5,5-fused furanones, no fused product **17** was identified in the reaction mixture, instead β-lactone product **16** was produced in 40% (R = Ph) or 18% (R = Me) yield.[37] The structure and double bond geometry of **16a** were unambiguously validated by X-ray analysis (Fig. 2).[36]

Mechanistically, as shown in Fig. 3, after ligand exchange, a hydroxyl group-directed activation of the alkyne with the Pd(II) catalyst would trigger a 5-*endo-dig anti*-aminopalladation to form the dihydropyrrole ring and produce vinyl-palladium species **19** from **18**. Carbon monoxide migratory insertion followed by lactonization would lead to product **13** and a Pd(0) catalyst. The latter would be oxidized to a Pd(II) catalyst by DDQ to continue the next catalytic cycle. For the formation of **16**, a 5-*exo-dig anti*-aminopalladation overrides a 6-*endo-dig* amino-palladation. The *trans* double bond geometry of **16** supported the *anti*-aminopalladation process over a *syn*-aminopalladation process.

Due to the structural novelty of the aminocarbonylative lactonization products, we evaluated them against several important bacterial, yeast and mold pathogens (see the ESI†). Our preliminary results showed that compounds **13h** and **13s** exhibited promising activity against toxigenic strains of *Clostridium difficile* with 128 μM and 64 μM minimum inhibitory concentration (MIC) values. Interestingly, these two compounds did not show side effects on the beneficial intestinal microflora and were nontoxic to Caco-2 cell lines up to 256 μM. Compounds **13h**, **13k**, **13s**, and **16b**

was used as the solvent with Pd(tfa)₂ as the catalyst and BQ as the oxidant, product **14** was produced in 24% yield (entry 22), which indicates that with the Boc-protected substrate, the aminopalladation and alkoxycarbonylation steps could take place, but not the lactonization step. These results suggest that the formation of the furanone ring is the problematic step presumably due to pseudo-A_{(1,3)} interaction between the Boc group and the alkyl side chain.

With optimized reaction conditions established, the substrate scope of this new aminocarbonylative lactonization method was assessed (Table 2). A variety of hydropyrrole-fused furanones can be prepared. In general, for secondary propargylic alcohols with an alkyl substituent, the reaction yield is excellent (*cf.* **13a**–**d**). The yield for secondary propargylic alcohols with an aryl substituent dropped slightly (*cf.* **13f**–**h**) or significantly (*cf.* **13e**, **13i**–**j**) presumably due to the ease of oxidizing the secondary alcohol to a ketone and other undesired reaction pathways. A primary propargylic alcohol substrate gave modest yield of the desired hydropyrrole-fused furanone product (*cf.* **13k**). Notably, sterically hindered tertiary alcohols (**13i**–**t**) are excellent substrates and high yields were obtained except for the case of **13q**. Tricyclic products **13l**–**o** and **13r**–**t** containing a spirocyclic ring system were produced in excellent yields. The structure of **13o** was unambiguously confirmed by X-ray analysis.[36] Due to the mild reaction conditions, functional groups such as sulfonamide, Boc-carbamate, bromide, and nitro group are well tolerated. The reaction can also be conducted on a gram-scale (**13p**).

We then prepared substrate **15** and wondered the possibility of forming a 5,6-fused furanone product (*cf.* **17**, Fig. 2). With one
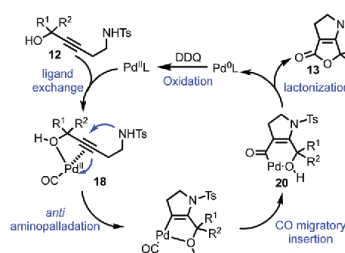

Fig. 3 Proposed catalytic cycle.

112

showed activity against several important fungal pathogens including strains of *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Cryptococcus gattii*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Aspergillus niger*, and *Aspergillus brasiliensis* with 64–128 µM MIC values.

In summary, we have developed an efficient palladium-catalyzed aminocarbonylative lactonization to synthesize various novel dihydropyrrole-fused furanones. This method can also be used to access β-lactone product such as **16**, another novel scaffold with potential biological functions. Our preliminary biological evaluations have identified several compounds including **13h**, **13k**, **13s**, and **16b** with promising antibacterial and antifungal activity. We are currently using this new synthetic capability to facilitate total syntheses of complex natural products as well as preparing analogues of the antibacterial and antifungal lead compounds to improve potency and physicochemical properties for new therapeutic development.

Notes and references

1 Y. Bai, X. Shen, Y. Li and M. J. Dai, *J. Am. Chem. Soc.*, 2016, **138**, 10838–10841.
2 D. C. Davis, K. L. Walker, C. Hu, R. N. Zare, R. M. Waymouth and M. J. Dai, *J. Am. Chem. Soc.*, 2016, **138**, 10693–10699.
3 Y. Bai, D. C. Davis and M. J. Dai, *Angew. Chem., Int. Ed.*, 2014, **53**, 6519–6522.
4 Y. Bai, D. C. Davis and M. J. Dai, *J. Org. Chem.*, 2017, **82**, 2319–2328.
5 X.-F. Wu, H. Neumann and M. Beller, *Chem. Rev.*, 2013, **113**, 1–35.
6 P. H. Gehrtz, V. Hirschbeck, B. Ciszek and I. Fleischer, *Synthesis*, 2016, 1573–1596.
7 K. Gabor, *Chem. Rev.*, 2001, **101**, 3435–3456.
8 C. F. J. Barnard, *Organometallics*, 2008, **27**, 5402–5422.
9 R. A. Pilli, G. B. Rosso and M. C. F. de Oliveira, *Nat. Prod. Rep.*, 2010, **27**, 1908–1937.
10 A. S. Kende, T. L. Smalley Jr. and H. Huang, *J. Am. Chem. Soc.*, 1999, **121**, 7431–7432.
11 M. Brüggemann, A. I. McDonald, L. E. Overman, M. D. Rosen, L. Schwink and J. P. Scott, *J. Am. Chem. Soc.*, 2003, **125**, 15284–15285.
12 C. Fang, C. S. Shanahan, D. H. Paull and S. F. Martin, *Angew. Chem., Int. Ed.*, 2012, **51**, 10596–10599.
13 E. Ideue, J. Shimokawa and T. Fukuyama, *Org. Lett.*, 2015, **17**, 4964–4967.
14 P.-Q. Qiang, S.-Y. Huang, L.-H. Gao, Z.-Y. Mao, Z. Chang and A.-E. Wang, *Chem. Commun.*, 2015, **51**, 4576–4578.
15 For a review: S. Quintero-Duque, K. M. Dyballa and I. Fleischer, *Tetrahedron Lett.*, 2015, **56**, 2634–2650.
16 T. F. Murray and J. R. Norton, *J. Am. Chem. Soc.*, 1979, **101**, 4107–4119.
17 T. F. Murray, E. G. Samsel, V. Varma and J. R. Norton, *J. Am. Chem. Soc.*, 1979, **103**, 7520–7528.
18 B. E. Ali and H. Alper, *J. Org. Chem.*, 1991, **56**, 5357–5360.
19 W.-Y. Yu and H. Alper, *J. Org. Chem.*, 1993, **58**, 5684–5687.
20 W.-J. Xiao and H. Alper, *J. Org. Chem.*, 1997, **62**, 3422–3423.
21 Y. Nan, H. Miao and Z. Yang, *Org. Lett.*, 2000, **2**, 297–299.
22 Y. Hu and Z. Yang, *Org. Lett.*, 2001, **3**, 1387–1390.
23 Y. Liao, M. Reitman, Y. Zhang, R. Fathi and Z. Yang, *Org. Lett.*, 2002, **4**, 2607–2609.
24 Y. Hu, Y. Zhang, Z. Yang and R. Fathi, *J. Org. Chem.*, 2002, **67**, 2365–2368.
25 Y. Liao, J. Smith, R. Fathi and Z. Yang, *Org. Lett.*, 2005, **7**, 2707–2709.
26 K. Kato, S. Motodate, T. Mochida, T. Kobayashi and H. Akita, *Angew. Chem., Int. Ed.*, 2009, **48**, 3326–3328.
27 B. Gabriele, R. Mancuso, V. Maltese, L. Veltri and G. Salerno, *J. Org. Chem.*, 2012, **77**, 8657–8668.
28 B. Gabriele, L. Veltri, R. Mancuso, G. Salerno and M. Costa, *Eur. J. Org. Chem.*, 2012, 2549–2559.
29 B. Gabriele, G. Salerno, P. Plastina, M. Costa and A. Crispini, *Adv. Synth. Catal.*, 2004, **346**, 351–358.
30 A. Ogawa, H. Kuniyasu, N. Sonoda and T. Hirao, *J. Org. Chem.*, 1997, **62**, 8361–8365.
31 Y. Tamaru, M. Hojo and Z.-I. Yoshida, *J. Org. Chem.*, 1991, **56**, 1099–1105.
32 J.-H. Li, S. Tang and Y.-X. Xie, *J. Org. Chem.*, 2005, **70**, 477–479.
33 C. Copéret, T. Sugihara, G. Wu, I. Shimoyama and E.-I. Negishi, *J. Am. Chem. Soc.*, 1995, **117**, 3422–3431.
34 L. Zhao and X. Lu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4343–4345.
35 N. R. Conley, L. A. Labios, D. M. Pearson, C. C. L. McCrory and R. M. Waymouth, *Organometallics*, 2007, **26**, 5447–5453.
36 CCDC 1540287 and 1540288 contain the supplementary crystallographic data for compounds **13o** and **16a**, respectively.
37 S. Ma, B. Wu and S. Zhao, *Org. Lett.*, 2003, **5**, 4429–4432.

113

REFERENCES

1. Chung, H-S.; Hon, P-M. G.; Lin, P.; But, P-H.; Dong, H. *Planta Med*. **2003**, *69*, 914-920.

2. Lin, L-G.; Zhong, Q-X.; Cheng, T-Y. Tang, C-P.; Ke,C-Q.; Lin, G.; Ye, Y. *J. Nat. Prod*. **2006**, *69*, 1051-1054.

3. Pilli, R. A.; de Oliveira, M. C. F. *Nat. Prod. Rep*. **2000**, *17*, 117-127.

4. Pilli, R. A.; Rosso, G. B. M.; de Oliveira; C. F. *Nat. Prod. Rep*. **2010**, *27*, 1908-1937.

5. Greger, H. *Planta Med.* **2006**, *72*, 99-113.

6. Lin, L.-G.; Zhong, Q. X.; Cheng, T.Y.; Tang, C.P.; Ke,C.-Q.; Lin, G.; Ye, Y. *J. Nat. Prod.* **2006**,*69*,1051-1054.

7. Wang, P.; Liu, A.L.; Li, Z. H.; Du, G. H.; Qin, H. L.; *J. Asian. Nat. Prod. Res*. **2008**, *10*, 311-314.

8. Lin, W. H.; Ma, L.; Cai, M. S.; Barnes, R. A. *Phytochemistry* **1994**, *36*, 1333-1335.

9. Kakuta, D.; Hitotsuyanagi, Y.; Matsuura, N.; Fukaya, H.; Takeya, K. *Tetrahedron* **2003**, *59*, 7779-7786.

10. Cheng, D.; Guo, J.; Chu, T.T. *J. Nat.Prod.* **1988**, *51*, 202-211.

11. Lin, L.-G.; Li, K. M.; Tang, C.-P. Ke, C.-Q.; Rudd, J. A.; Lin, G.; Ye, Y. *J. Nat. Prod.* **2008**, *71*, 1107-1110.

12. Williams, D. R.; Reddy, J. P. Amato, G. S. *Tetrahedron Lett.* 1994, 35, 6417-6420.

13. Kohno, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn*. **1996**, *69*, 2063-2070.

14. Kinoshita, A.; Mori, M. *Heterocycles* 1997, 46, 287-299.

15. Jacobi, P. A. Lee, K.; *J. Am. Chem. Soc*. **1997**, *119*, 3409-3410.

16. Gurjar, M. K.; Reddy, D. S. *Tetrahedron Lett.* **2002**, *43*, 295-298.

17. Sibi, M. P.; Subramanian, T. *Synlett* **2004**, *7*, 1211-1214.

18. Yoritate, M.; Takahashi, Y.; Tajima, H.; Ogihara, C.; Yokayama, T.; Soda, Y.; Oishi, T.; Sato, T.; Chida, N. *J. Am.Chem. Soc.* **2017**, *139*, 18386-18391.

19. Hou, Y.; Shi, T.; Yang, Y.; Fan, X.; Chen, J.; Gao, F.; Wang, Z. *Org. Lett.* **2019**, *21*, 2952-2956.

20. Bogliotti, N.; Dalko, P. I.; Cossy, J. *Synlett* **2005**, 349-351.

21. Bogliotti, N.; Dalko, P. I.; Cossy, J. *J. Org. Chem.* **2006**, *71*, 9528-9531.

22. Bogliotti, N.; Dalko, P. I.; Cossy, J. *Synlett* **2006**, *16*, 2664-2666.

23. Muňoz-Bascon, J.; Hernandez-Cervantes, C.; Padial, N. M.; Á lvarez-Corral, M.; Rosales, A.; Rodríguez-García, I.; Oltra, J. E. *Chem.-Eur. J.* **2014**, *20*, 801-810.

24. Torssell, S.; Wanngren, E.; Somfai, P. *J. Org. Chem.* **2007**, *72*, 4246-4249.

25. Brito, G. A.; Sarotti, A. M.; Wipf, P.; Pilli, R. A. *Tetrahedron Lett.* **2015**, *56*, 6664−6668.

26. Davis, D. C.; Walker, K. L.; Hu, C.; Zare, R. N.; Waymouth, R. M.; Dai, M. J. *J. Am. Chem. Soc.* **2016**, *138*, 10693-10699.

27. Ma, K.; Yin, X.; Dai, M. J. *Angew. Chem. Int. Ed.* **2018**, *57*, 15209-15212.

28. Gourlay, B. S.; Molesworth, P.P.; Ryan, J. H.; Smith, J. A. *Tetrahedron Lett.* **2006**, *47*, 799-801.

29. Schmidt, B.; Hauke, S.; *Org. Biomol. Chem.* **2013**, *11*, 4194-4206.

30. Banwell, M. G.; Beck, D. A. S.; Smith, J. A. *Org. Biomol. Chem.* **2004**, *2*, 157-159.

31. Paras, N. A. MacMillan, D. W. *J. Am. Chem. Soc.* **2001**, *123*, 4370-4371.

32. Bates, R. W.; Sridhar, S. *J. Org.Chem.***2011**, *76*, 5026-5035.

33. Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597-2632.

34. Haym, I. Brimble, M. A. Org. *Biomol. Chem.* **2012**, *10*, 7649-7665.

35. Kingsbury, J. S. Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 13813-13815.

36. Corey, E. J.; Rao, S. A.; Noe, M. C. *J. Am. Chem. Soc.***1994**, *116*, 9345-9346

37. Yoneda, E.; Zhang, S.-W. Zhou, D.-Y.; Onitsuka, Takahashi, K. S. *J. Org. Chem.* **2003**, *68*, 8571-8576.

38. Mikhaleva, A. I.; Ivanov, A. V.; Tseva, E.V.S.; Ushakov, I. A.; Tsov, A. M. V.; Trofimov, B. A. *Synthesis* **2009**, 587-590.

39. Miura, K. Wang, D. Hosomi, A. *J. Am. Chem. Soc.* **2005**, *127*, 9366–9367.

40. Chen, W.; Yang, Q.; Zhou, T.; Tian, Q.; Zhang, G. *Org. Lett.* **2015**, *17*, 5236-5239.

41. Horne, D. A.; Fugmann, B.; Yakushijin, K.; Buchi, G. *J. Org. Chem.* **1993**, *58*, 62–64.

42. Trost, B. M. Zhang, Y. *Chem. Eur. J.* **2011**, *17*, 2916–2922.

43. Hinman, R. L. Bauman, C. P. *J. Org. Chem.* **1964**, *29*, 1206–1215.

44. van Deurzen, M. P. J. F.; van Rantwijk, R. A.; Sheldon, J. *Mol. Catal. B: Enzym.* **1996**, *2*, 33–42.

45. Perez, D. I. Grau, M. M. Arends,I. W.; Hollmann, F. *Chem. Commun.* **2009**, 6848-6850.

46. Krieg, T.; Hüttmann, S. Mangold, K.-M.; Schrader, J.; Holtmann, D. *Green Chem.* **2011**, *13*, 2686-2689.

47. Kungumathilagam, D.; Karunakaran, K. *Pol. J. Chem. Technol.* **2013**, *15*, 107–111.

48. Vazquez, E.; Payack, J. F. *Tetrahedron Lett.* **2004**, *45*, 6549–6550.

49. Alamgir, M. P.; Mitchell, S. R. Bowyer, P. K.; Kumar, N.; Black, D. S. *Tetrahedron* **2008**, *64*, 7136–7142.

50. Bouchikhi, F.; Anizon, F.; Moreau, P. *Eur. J. Med. Chem.* **2008**, *43*, 755–762.

51. Jiang, X.; Zheng, C.; Lei, L.; Lin, K.; Yu, K. *Eur. J. Org. Chem.* **2018**, 1437–1442.

52. Irie, H.; Masaki, N.; Ohno, R.; Osaki, K.; Taga, T.; Uyeo, S. *J. Chem. Soc., Chem. Commun.* **1970**, 1066.

53. Kende, A. S. Smalley, T. L. Jr.; Huang, H. *J. Am. Chem. Soc.* **1999**, *121*, 7431-7432.

54. Bruggemann, M.; McDonald, A. I.; Overman, L. E.; Rosen,M. D; Schwink, L.; Scott, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 15283-15285.

55. Huang, P-Q.; Huang, S-Y.; Gao, L-H.; Mao, Z-Y.; Chang, Z.; Wang, A-E. *Chem. Commun.* **2015**, *51*, 4576.

56. Shanahan, C. S.; Fang, C.; Paull, D. H.; Martin, S. F. *Tetrahedron* **2013**, *69*, 7592-7607.

57. Murray, T. F.; Norton, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 4107–4119.

58. Murray, T. F.; Samsel, E. G. Varma, V.; Norton, J. R.; *J. Am. Chem. Soc.* **1979**, *103*, 7520-7528.

59. Ali, B. E.; Alper, H. *J. Org. Chem.* **1991**, *56*, 5357–5360.

60. Yu, W.-Y.; Alper, H. *J. Org. Chem.* **1993**, *58*, 5684–5687.

61. Xiao, W.-J.; Alper, H. *J. Org. Chem.* **1997**, *62*, 3422–3423.

62. Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 297–299.

63. Liao, Y.; Reitman, M.; Zhang, Y.; Fathi, R.; Yang, Z. *Org. Lett.* **2002**, *4*, 2607–2609.

64. Hu, Y.; Yang, Z. *Org. Lett.* **2001**, *3*, 1387–1390.

65. Liao, Y.; Reitman, M.; Zhang, Y.; Fathi, R.; Yang, Z. *Org. Lett.* **2002**, *4*, 2607–2609.

66. Zhao, L.; Lu, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4343–4345.

67. Li, J.-H.; Tang, S.; Xie, Y.-X. *J. Org. Chem.* **2005**, *70*, 477–479.

68. Kato, K.; Motodate, S.; Mochida, T.; Kobayashi, T.; Akita, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 3326–3328.

69. Tamaru, Y.; Hojo, M.; Yoshida, Z.-I. *J. Org. Chem.* **1991**, *56*, 1099–1105.

70. Coperet, C.; Sugihara, T.; Wu, G.; Shimoyama, I.; Negishi, E.-I. *J. Am. Chem. Soc.* **1995**, *117*, 3422–3431.

71. Ogawa, A.; Kuniyasu, H.; Sonoda, N.; Hirao, T. *J. Org. Chem.* **1997**, *62*, 8361–8365.

72. Hu, Y.; Zhang, Y.; Yang, Z.; Fathi, R. *J. Org. Chem.* **2002**, *67*, 2365–2368.

73. Gabriele, B.; Mancuso, R.; Maltese, V.; Veltri, L.; Salerno, G. *J. Org. Chem.* **2012**, *77*, 8657–8668.

74. Conley, N. R.; Labios, L. A.; Pearson, D. M.; McCrory, C. C. L.; Waymouth,R. M. *Organometallics* **2007**, *26*, 5447–5453.

75. Wang, X.; Yao, Z.; Dong, S.; Wei, F.; Wang, H.; Xu, Z. *Org. Lett.*, **2013**, *15*, 2234

76. Teichert, J. F.; Zhang, S., Zijl, A. W.; Slaa, J. W.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2010**, *12*, 4658.

77. Tran, G.; Pardo, D. G.; Tsuchiya, T.; Hillebrand, S.; Vors, J-P.; Sossy, J. *Org. Lett.* **2015**, *17*, 3414

78. Shen, R.; Kusakabe, T.; Takahashi, K.; Kato, K. *Org. Biomol. Chem.* **2014**, *12*, 4602.