Gold Approach to Polycyclic Indole Alkaloids and Chemical Probes for Histone Demethylases

by

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This thesis entitled:
Gold Approach to Polycyclic Indole Alkaloids and Chemical Probes for Histone Demethylases
written by Wenqing Xu
has been approved for the Department of Chemistry and Biochemistry

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Xiang Wang

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Tarek Sammakia

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Xu, Wenqing (Ph.D., Chemistry and Biochemistry)

Gold Approach to Polycyclic Indole Alkaloids and Chemical Probes for Histone Demethylases

Thesis directed by Assistant Professor Xiang Wang

My research contains two divisions:

The first one is to develop novel synthetic methods for polycyclic indole alkaloids, such as strictamine. As one of the constituents of Rhazya alkaloids, strictamine was first isolated from the flower of Alstonis scholaris, which has been used as folk medicine in India, by H. K. Schnoes, etc in 1966, while the absolute structure was resolved with the aid of X-ray crystallography in 1977. The densely fused pentacyclic skeleton of the indole alkaloid has attracted considerable interest and posed great challenge to organic chemists. Since its isolation, several groups have reported their synthetic studies, but no total synthesis is completed. In 2013 we succeeded in constructing the bridged skeleton under the catalysis of gold complex and further studies of strictamine is in progress.

The second one is focused on the development of chemical probes for jumonji C domain-containing histone demethylases (JHDMs). As one of the most important epigenetic modifications, histone methylation is closely associated with heritable changes without altering DNA sequence. Based on the enzymatic mechanisms, histone demethylases can be categorized into two classes: flavin adenine dinucleotide (FAD)-dependent monoamine oxidases (LSD1 and 2) and JHDMs. Compared to LSDs, JHDMs have a much broader substrate scope and can modify lysine residues at all methylation states. In 2011, our group reported the discovery of methylstat as the first cell-active selective small-molecule inhibitor of JHDMs. Based on the structure of methylstat, we designed and synthesized a series of fluorescent probes for quantitative analysis of JHDMs in fluorescence polarization (FP) assays. Also, a library of over 100 compounds was prepared. Their binding affinities to JHDM1A were evaluated in FP assays and structure-activity relationship (SAR) was further studies.

Dedicated to My Parents

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Finally, thanks to my parents, without whom I couldn't have done these.

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List of Acronyms and Abbreviations

Ac	acetyl
AIBN	2,2'-azo-bis-isobutyronitrile
aq	aqueous
Ar	aryl (substituted aromatic ring)
atm	1 atmosphere = 10^5 Pa (pressure)
BBN(9-BBN)	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*t*-butoxycarbonyl
bp (b.p.)	boiling point
Bz	benzoyl
Bu	*n*-butyl
Cbz	benzyloxycarbonyl
CSA	camphorsulfonic acid
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAP	*N*,*N*-4-dimethylaminopyridine
DMDO	dimethyl dioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DNA	deoxyribonucleic acid

dr (d.r.)	diastereomeric ratio
Et	ethyl
FP	fluorescent polarization
HRMS (ESI)	high-resolution electrospray ionisation mass spectrometry
IBX	*o*-iodoxybenzoic acid
LA (L.A.)	Lewis acid
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
Ns (4-Ns)	4-nitrobenzenesulfonyl
Nuc	nucleophile
Ph	phenyl
Pr	propyl
RCM	ring-closing metathesis
TBAF	tetra-*n*-butylammonium fluoride
TBS	*t*-butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TMS	trimethylsilyl
Tol	*p*-tolyl

Chapter 1

Monoterpene Indole Alkaloids

1.1 Introduction

Monoterpene indole alkaloids are one class of indole alkaloids, which contain structural moiety of indole and are prevant in plants and fungi (Figure 1.1). These natural products possess a range of complex chemical structures and exhibit diverse biological activities.[1] Ajmalicine is an antihypertensive drug used in the treatment of high blood pressure. [1] Vindoline is the synthetic precursor of the anticancer drugs, vinblastine and vincristine. Strychnine is highly toxic and used as pesticide.[1] Based on preliminary study, aspidophylline A can reverse drug resistance in drug-resistant KB cells.[2] Pseudoakuammigine has exhibited in *vivo* anti-inflammatory and analgesic activities.[3] The antagonism displayed by corymine at the glycine repeptor have been reported.[4]

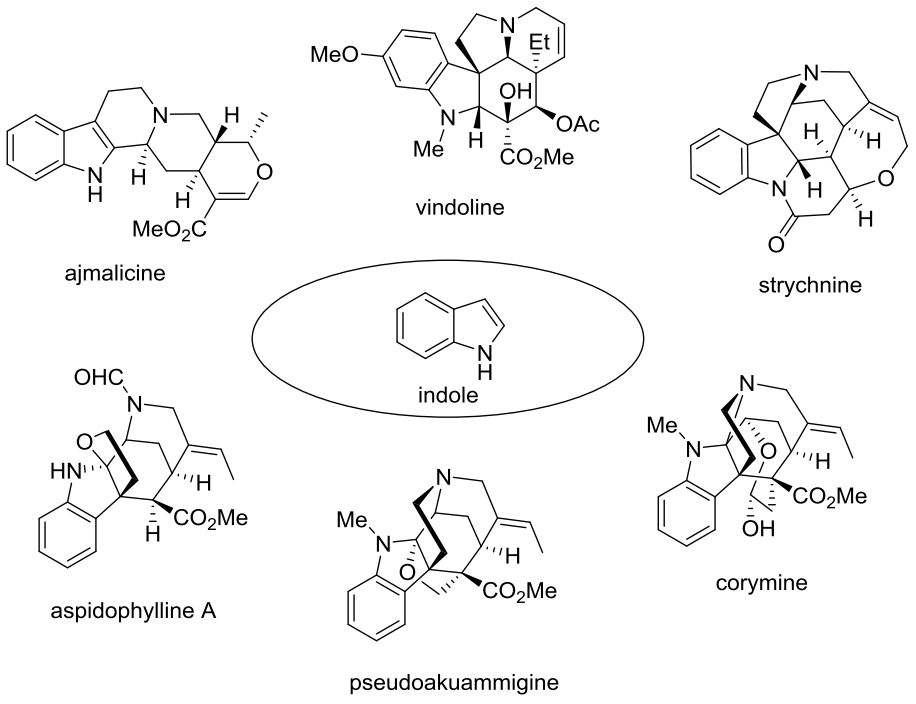
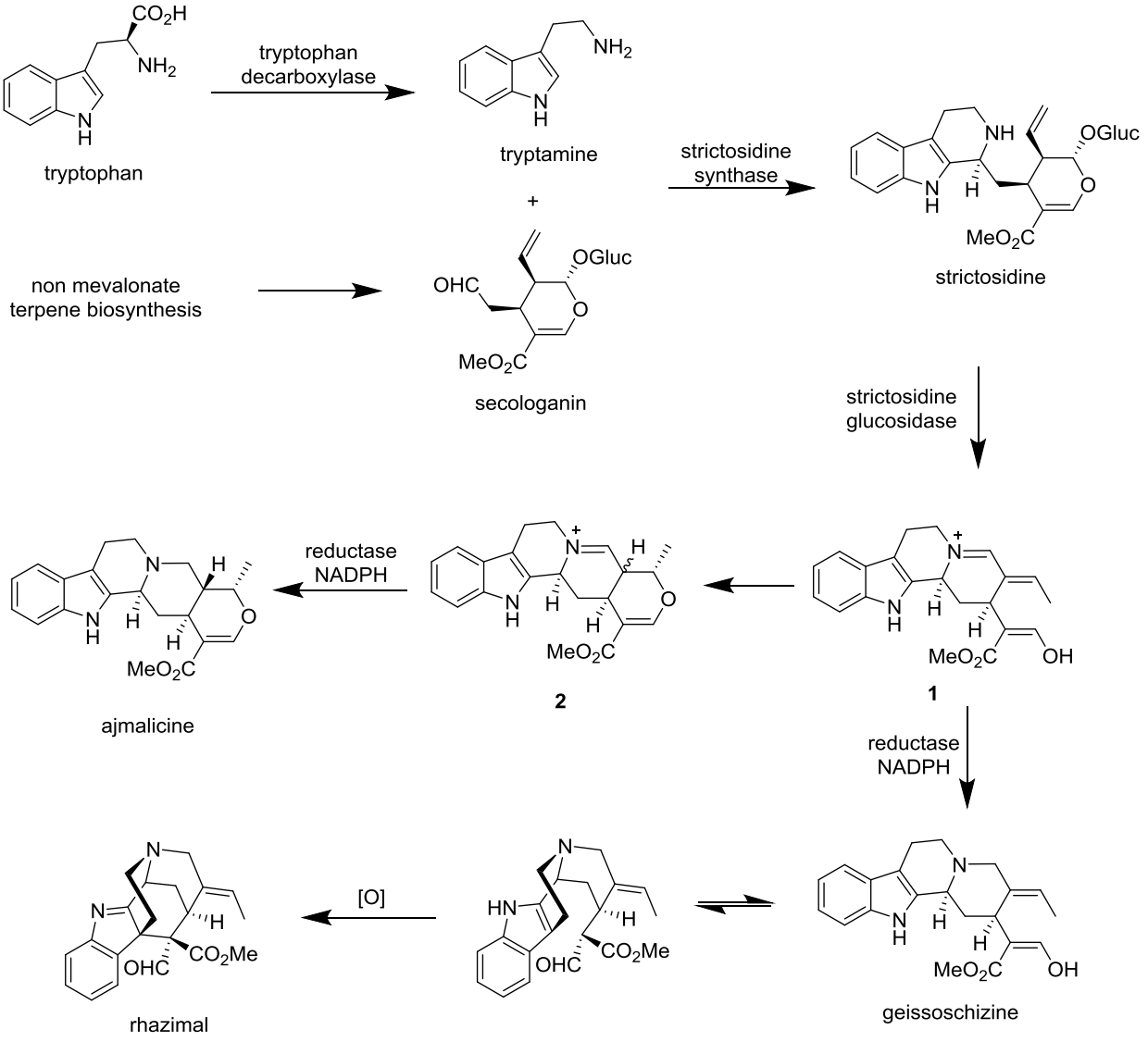


Figure 1.1 Representative Monoterpene Indole Alkaloids

1.2 Biosynthesis

All monoterpene indole alkaloids are derived from tryptophan and the iridoid terpene secologanin (Scheme 1.1).[5] Tryptophan decarboxylase converts tryptophan to tryptamine and secologanin is derived from non-mevalonate through terpene biosythesis.[6]



Scheme 1.1 Biosyntheses of Monoterpene Indole Alkaloids

In the presence of strictosidine synthase, tryptamine and secologanine are converted into strictosidine,[7] which is rearranged into **1** after deglucosylation catalyzed by strictosidine

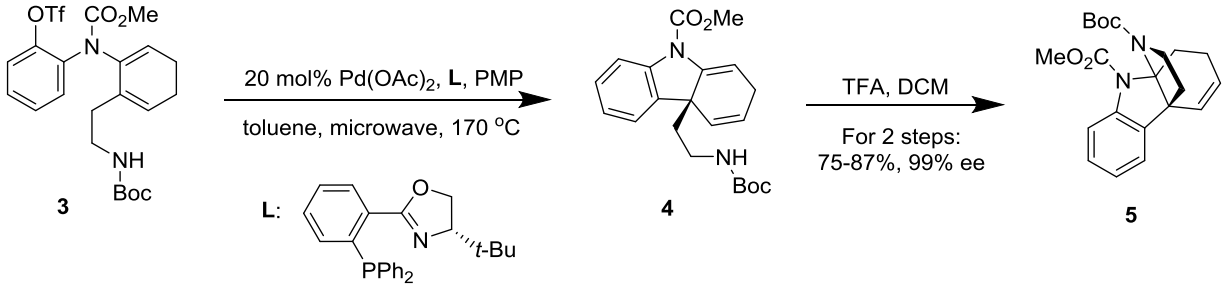
glucosidase.[8] Intramolecular conjugate addition of **1** gives **2** and the following NADPH-catalyzed reduction affords ajmalicine.[9] Geissoschizine is obtained from reduction of **1** catalyzed by NADPH reductase. The cyclization of geissoschizine leads to the formation of rhazimal,[10] but the mechanism is still unkown.[11] Rhazimal represents the central building block, from which many monoterpenoids, such as pseudoakuammigine, aspidophylline A and strictamine, can be accessed.

1.3 Reported Approaches to Polycyclic Indole Alkaloids and Application to Total Syntheses of Monoterpene Indole Alkaloids

The biological activities of monoterpene indole alkaloids and their complex polycyclic indoline scaffolds have attracted considerable attention of synthetic research groups. Until now, many synthetic methods and strategies have been developed. The syntheses of strychnos family, especially strychnine, have been investigated extensively since 1954.[12] Thus, only the recent methodologies and application to total syntheses are described here.

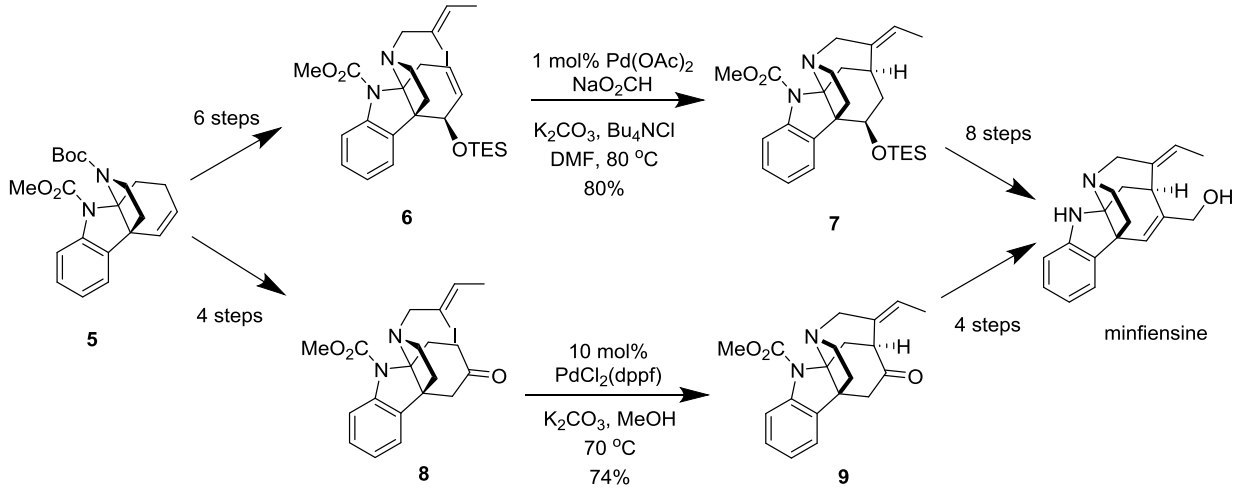
1.3.1 Heck Cyclization Approach

In 2005, Overman and co-workers reported the development of an efficient catalytic enantioselective synthesis of 3,4-dihydro-9a,4a-(iminoethano)-9*H*-carbazole **5** (Scheme 1.2) by combining a palladium-catalyzed asymmetric Heck cyclization of **3** into **4** with an intramolecular iminium ion cyclization of **4** into **5**. The intermediate **5** was utilized to accomplish the first total synthesis of minfiensine.[13]



Scheme 1.2 Asymmetric Intramolecular Heck Cyclization

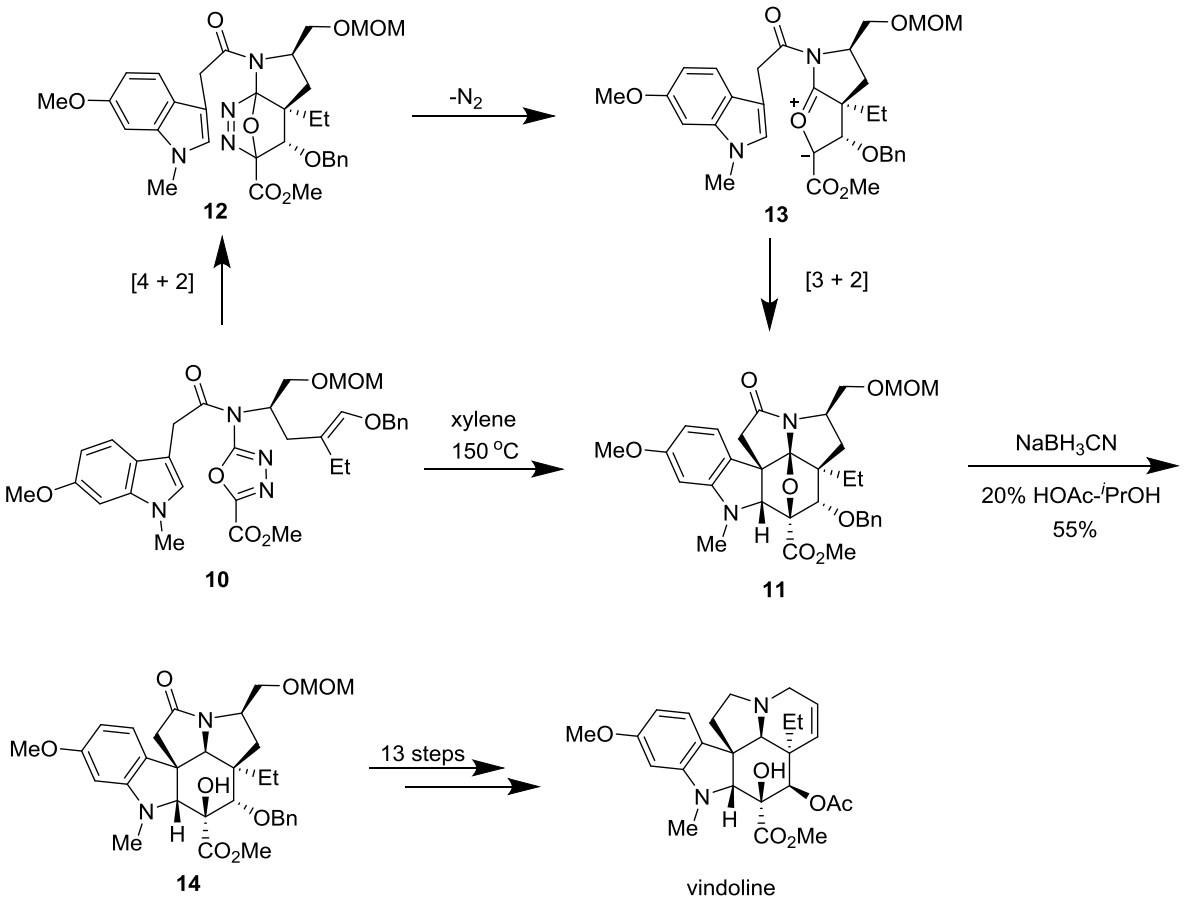
Compound **6** (Scheme 1.3), prepared from **5** in 6 steps, was subjected to palladium-catalyzed reductive cyclization to give **7** in 80% yield and minfiensine was obtained upon 8 steps of modification of **7**(Scheme 1.3).[13] The synthetic route was further optimized and ketone **8** was synthesized from **5** in 4 steps. **8** was cyclized under palladium-catalyzed intramolecular α-vinylation of ketone to afford **9** in 74% yield. Another 4 steps of modification completed the synthesis of minfiensine.[14]



Scheme 1.3 Total Syntheses of Minfiensine by the Overman Group

1.3.2 Tandem [4 + 2]/[3 + 2] Cycloaddition Approach

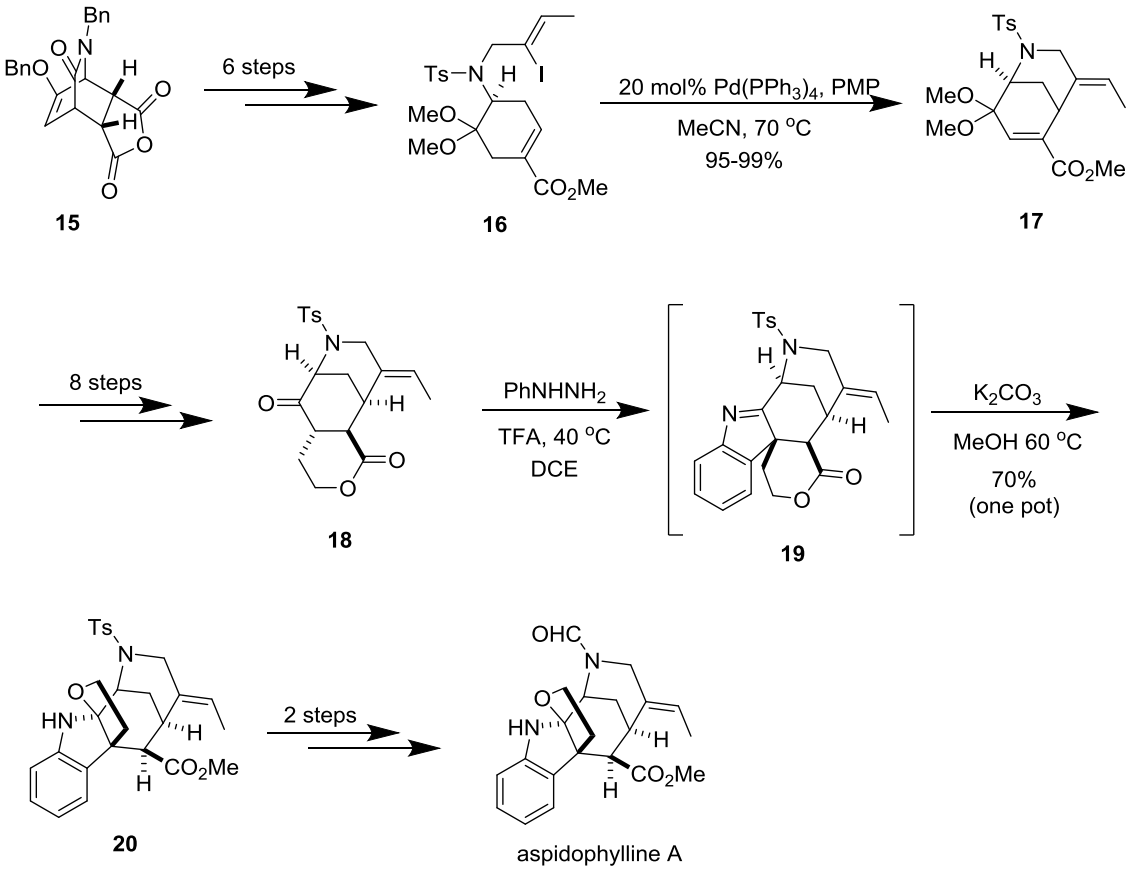
In 2009 Boger and co-workers reported a concise total synthesis of vindoline featuring a tandem intramolecular [4 + 2]/[3 + 2] cycloaddition cascade of a 1,3,4-oxadiazole **10** (Scheme 1.4).[15] Facial selective Diels-Alder reaction gave intermediate **12** and exclusion of nitrogen afforded dipole **13**, which underwent an intramolecular [3 + 2] cyclization to furnish **11**. Three rings and four C-C bonds were formed central to the characteristic pentacyclic ring system with six stereocenters. Reduction under acidic condition gave **14** in 55% over 2 steps and the enantioselective synthesis of vindoline was completed in another 13 steps from **14**.



Scheme 1.4 Total Syntheses of Vindoline by the Boger Group

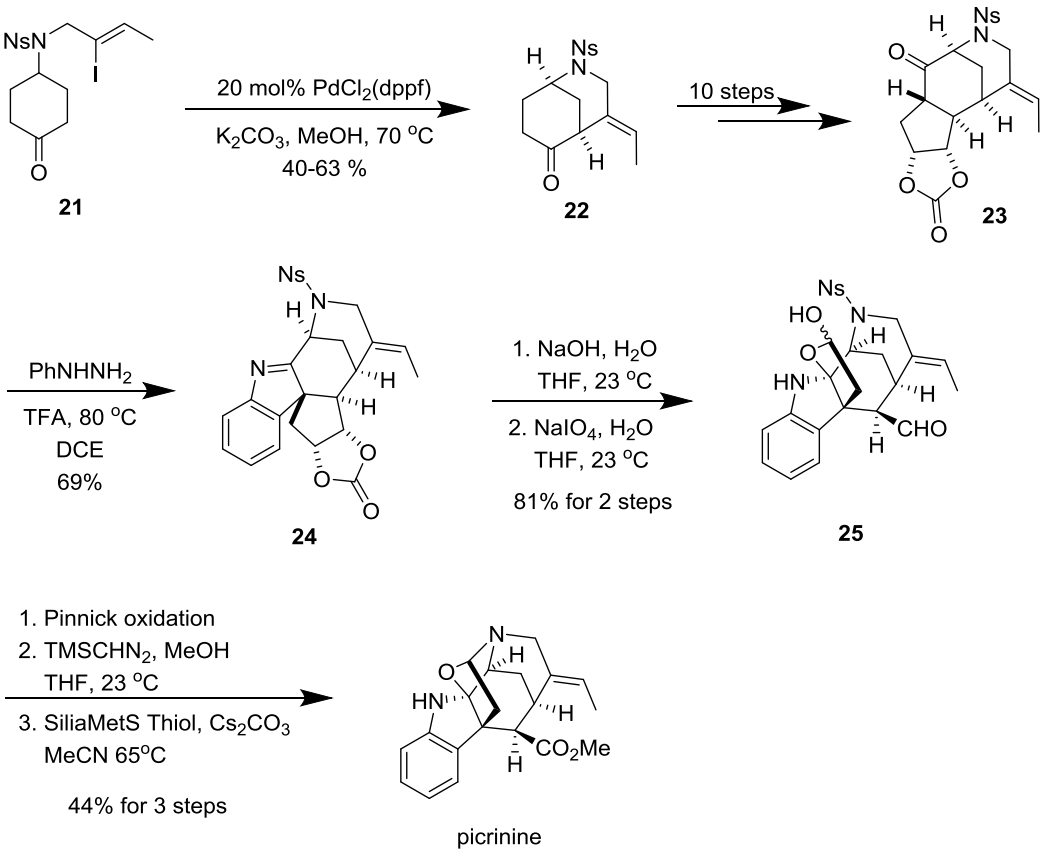
1.3.3 Interrupted Fischer Indolization

In 2011, Garg and co-workers reported the first total synthesis of aspidophylline A (Scheme 1.5).[16] The substrate **16** was treated with Pd(0) under Vanderwal's conditions to afford bicycle **17** in near quantitative yield. After 8 steps, **17** was converted into ketone **18**, which was subjected to Fischer indolization condition to give indolenine **19** and methanolysis of the lactone under basic condition followed by cyclization afforded the pentacycle **20** in 70% yield in one pot. Removal of tosyl group and formylation of the resulting amine furnished aspidophylline A.



Scheme 1.5 Total Synthesis of Aspidophylline A by the Garg Group

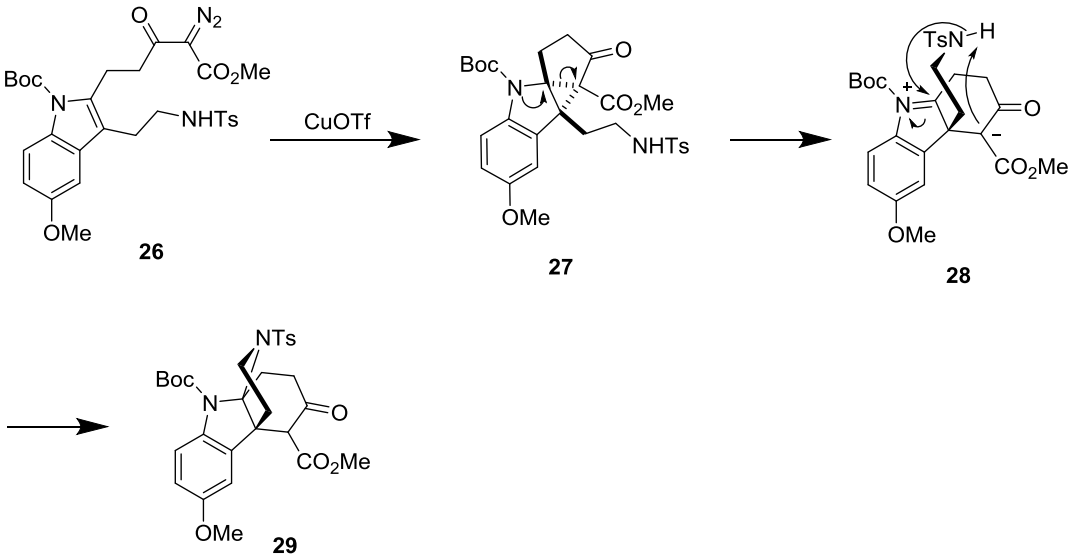
The interrupted Fischer indolization has also been applied to the synnthesis of picrinine by Garg group (Scheme 1.6).[17] Treatment of **21** with $PdCl_2$(dppf) under basic condition furnished bicycle **22** via Pd-catalyzed enolate cyclization. **22** was converted to ketone **23** in another 10 steps. **23** was treated with phenylhydrazine under Fischer indolization condition afforded the indoleneine **24** in 69% yield. **24** was converted to **25** in 81% in 2 steps. Oxidation, esterifaction, deprotection of nosyl group and proximity-driven cyclization completed the synthesis of picrinine.



Scheme 1.6 Total Synthesis of Picrinine by the Garg Group

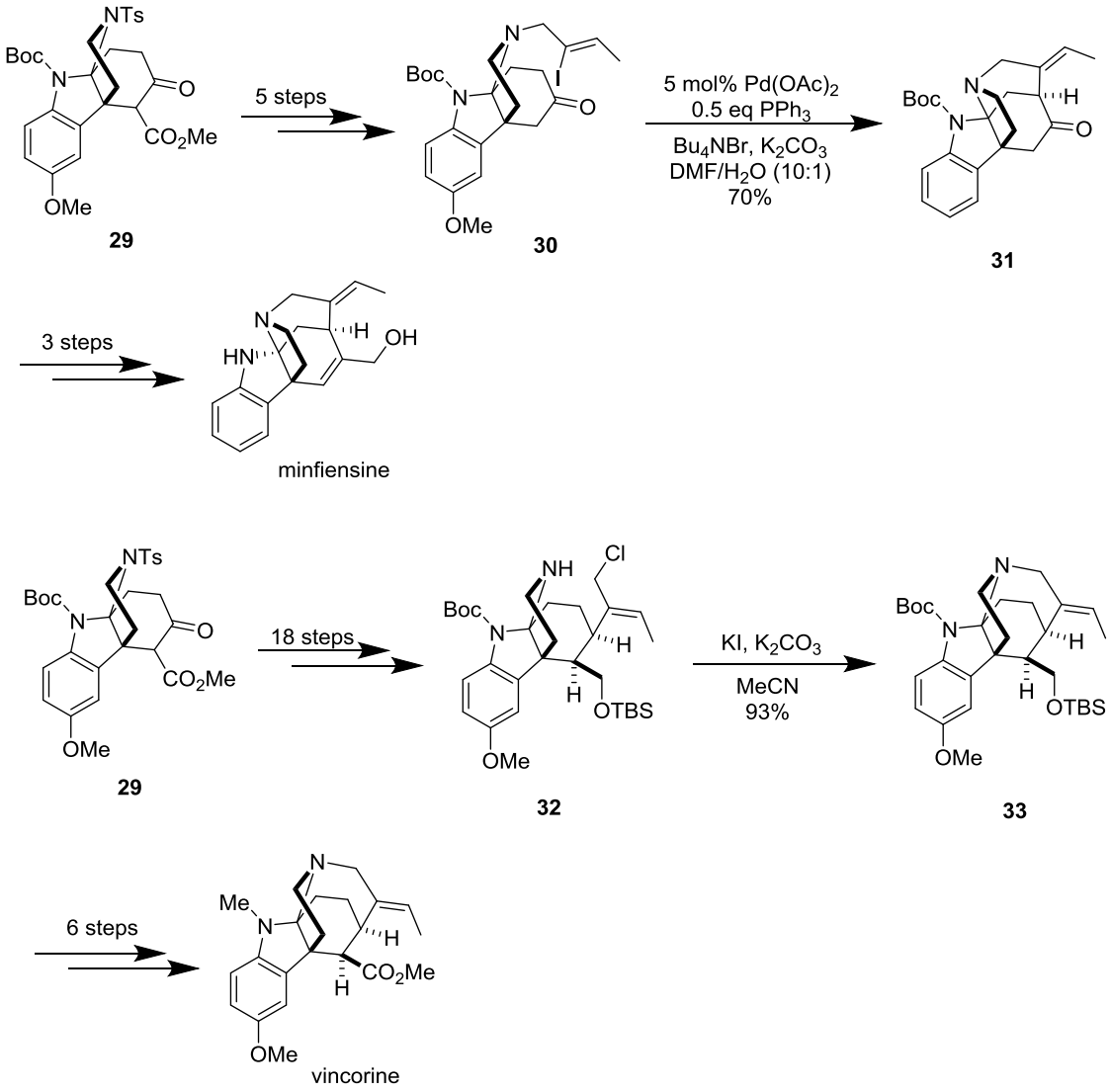
1.3.4 Cyclopropanation Strategy

In 2008, Qin and co-workers reported a cascade reaction for asssembly of tetracyclic framework (Scheme 1.7).[18] Under the catalysis of CuOTf, the diazo ester **26** formed cyclopropane intermediate **27**, which was prone to collapse to generate indolenium cation **28**. **28** was captured intramolecularly by the nitrogen of sulfonamide to afford the tetracyclic compound **29**.



Scheme 1.7 Cyclopropanation Strategy

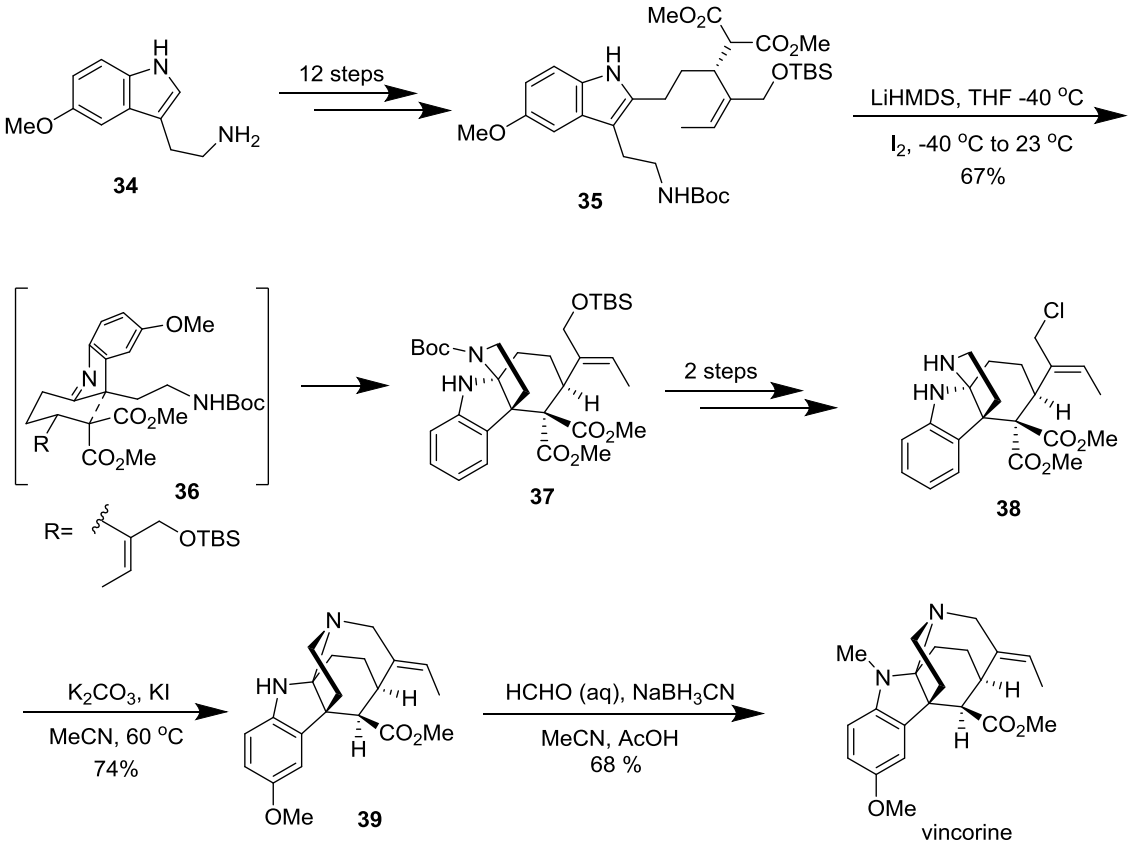
This cyclopropanation approach has been applied to the syntheses of minfiensine[18] and vincorine[19] by Qin and co-workers (Scheme 1.8). The tetracycle **30** prepared from β-ketoester **29** in 5 steps, was cyclized under palladium-catalyzed intramolecular α-vinylation of ketone to afford the pentacyclic compound **31**, which furnished minfiensine over 3 steps.[18] For the synthesis of vincorine, the tetracycle **32** was prepared from β-ketoester **29** over 18 steps and subsequent intramolecular alkylation furnished **33** in 93% yield. The first racemic synthesis of vincorine was achieved over another 6 steps.[19]



Scheme 1.8 Total Syntheses of Minfiensine and Vincorine by the Qin Group

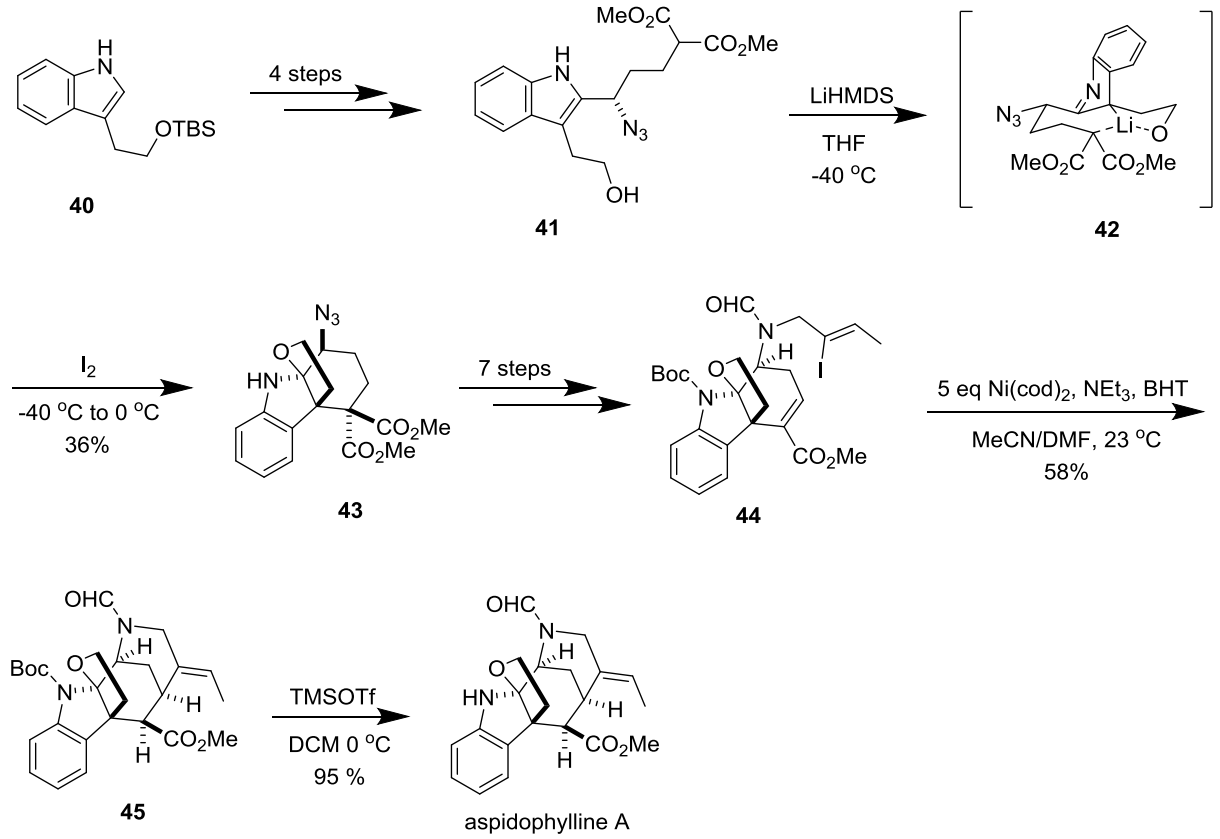
1.3.5 Oxidative Anion Coupling

In 2012, Ma and co-workers reported an asymmetric total synthesis of (-)-vincorine featuring an intramolecular oxidative coupling reaction.[20] Substrate **35** (Scheme 1.9) was prepared from 5-methoxytryptamine **34** in 12 steps. Under the treatment of LiHMDS and iodine, **35** was efficiently and diastereoselectively cyclized into the tetracyle **37** through intermediate **36** based on the proposed mechanism. The compound **38** was obtained from **37** in 2 steps and then subjected to intramolecular alkylation condition to afford the pentacycle **39** in 74% yield. Reductive amination completed the total synthesis of vincorine.



Scheme 1.9 Total Synthesis of Vincorine by the Ma Group

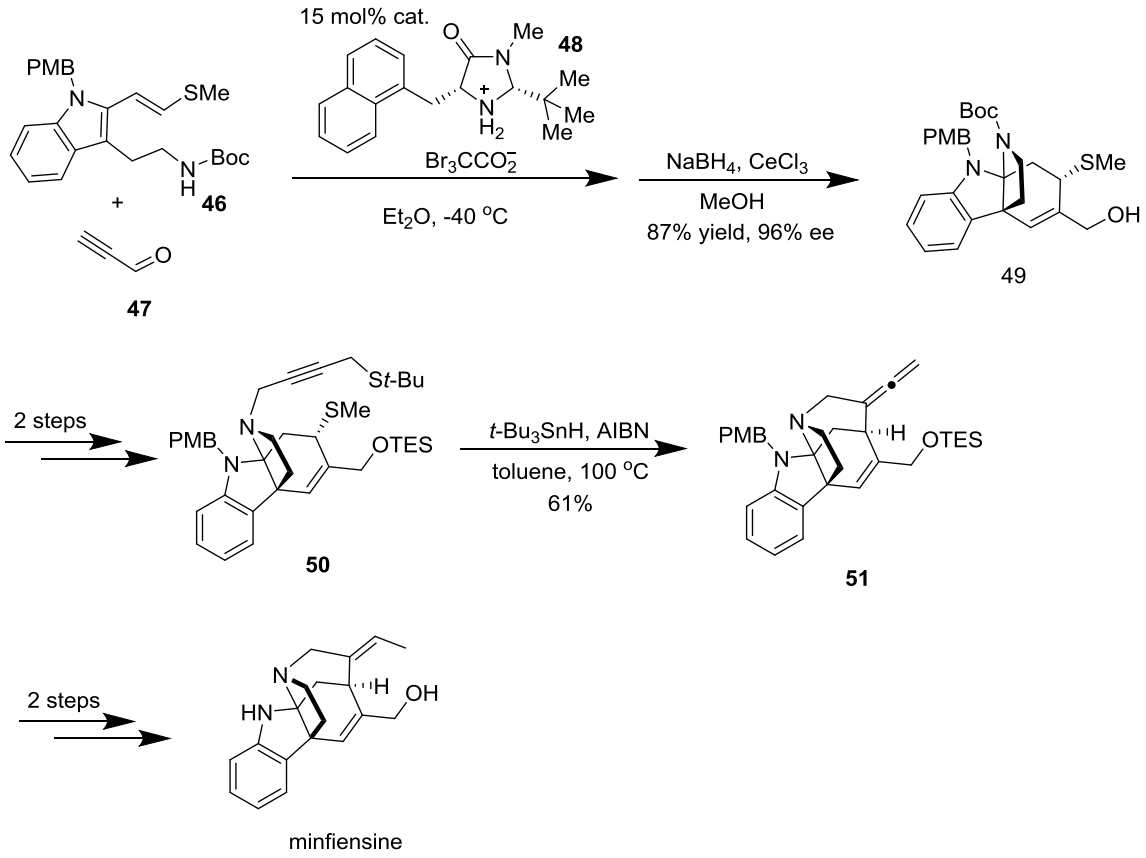
The oxidative coupling has also been applied to synthesis of aspidophylline A as shown in Scheme 1.10.[21] The indole **41** prepared from **40** in 4 steps, was treated with LiHMDS to give **42** based on the proposed mechanism and oxidation with iodine afforded the tetracycle **43** in 36% yield. **43** was modified into cyclization precursor **44** in 7 steps. $Ni(cod)_2$-mediated reductive cyclization of **44** furnished the tetracyclic indoline motif **45** in 58% yield. Deprotection of Boc completed the synthesis of aspidophylline A.



Scheme 1.10 Total Synthesis of Aspidophylline by the Ma Group

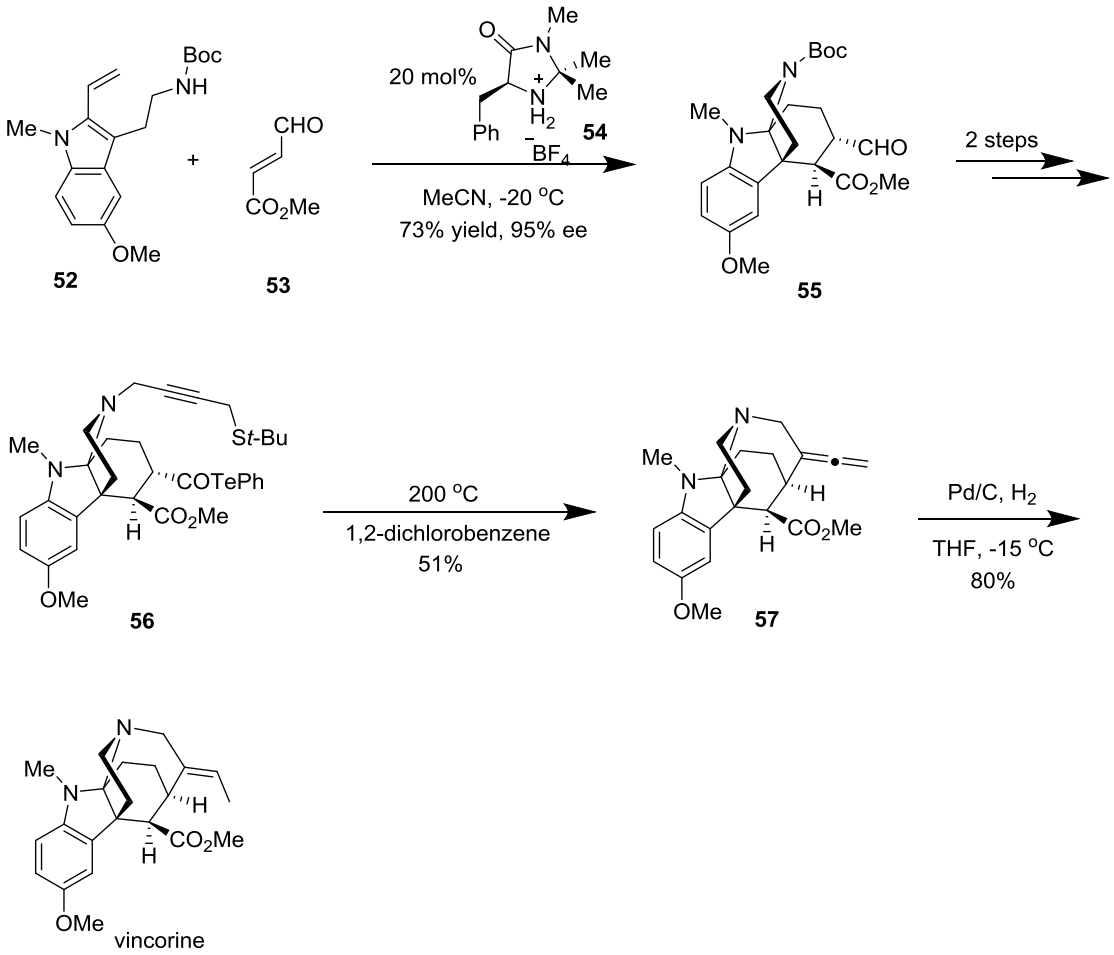
1.3.6 Diels-Alder/Amine Cyclization Approach

In 2009, MacMillan and co-workers reported the Diels-Alder/cyclization cascade reaction.[22] Subjection of 2-vinylindole **46** (Scheme 1.11) to propynal **47** in the presence of imidazolidinone catalyst **48** at -40 °C over 24 h and following reduction produced the tetracycle **49** in 87% yield with 96% enantiomeric excess. Further deprotection and alkylation afforded the final cyclization precursor **50**, which underwent radical reaction to furnish allene **51** in 61% yield. The allene **51** was efficiently converted into minfiensine in another 2 steps and the enantioselective synthesis of minfiensine was accomplished in overall 9 steps.



Scheme 1.11 Enantioselective Synthesis of Minfiensine by the MacMillan Group

In 2013, MacMillan and co-workers accomplished a concise and enantioselective total synthesis of vincorine, featuring an enantioselective organocatalytic Diels-Alder/iminium cyclization cascade sequence (Scheme 1.12).[23] Tetracycle **55** was obtained from the diene **52** and the dienophile **53** in 73% yield and 95% enantiomeric excess. The enclosure of the 7-member ring of allene **57** by a single electron-mediated cyclization event initiated from an acyl telluride precursor **56** was achieved in 51% yield. Hydrogenation of **57** completed the enantioselective synthesis of vincorine.



Scheme 1.12 Enantioselective Synthesis of Vincorine by the MacMillan Group

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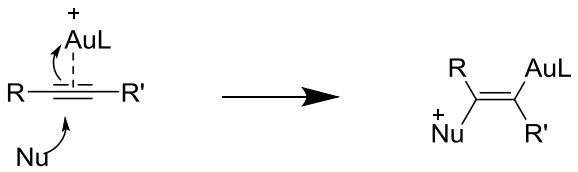
Chapter 2

Au(I)-Catalyzed Tandem Cyclization Approach to Tetracyclic Indolines

2.1 Gold Catalysis

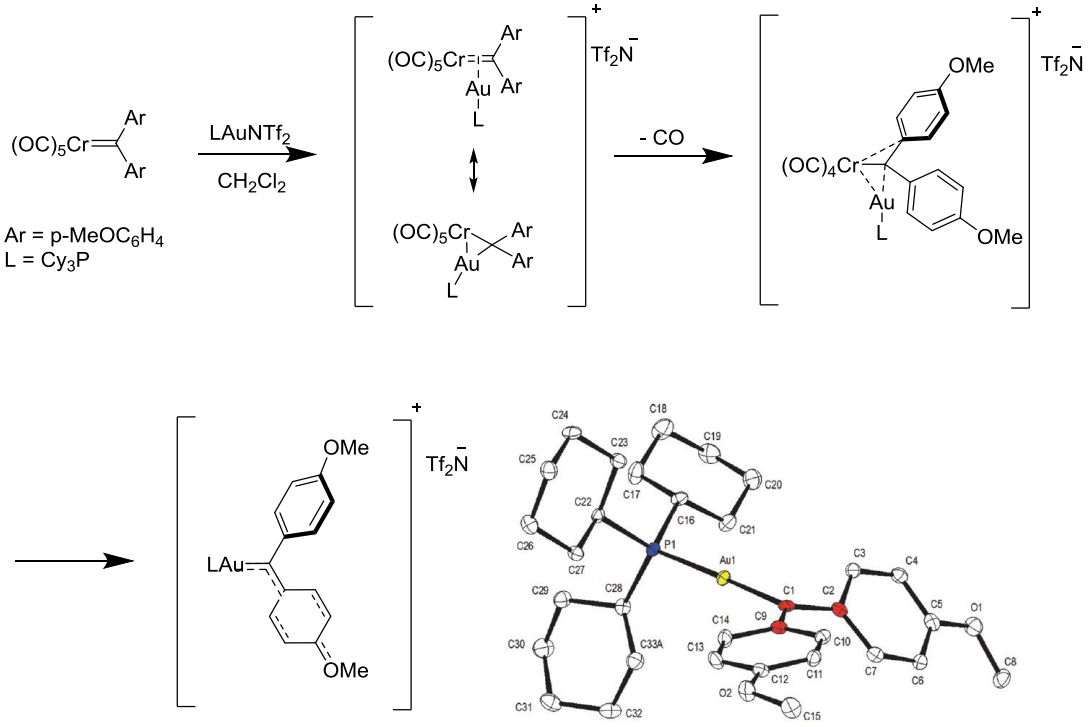
Gold catalysis has attracted considerable interest from organic chemists since the beginning of the 21st century.[1] The soft Lewis acidic nature of gold allows selective activation of unsaturated carbon-carbon bonds. For Au(I), it predominantly forms linear two-coordinate complexes. Abstraction of a coordinating halide or an alkyl group (such as Me) by treatment with silver salt or Brønsted acid is therefore required to provide a free coordination site for the ligand, which is generally a phosphine or *N*-heterocyclic carbene ligand. The generated Au(I) cation is a soft Lewis acid and prefers to bind to a soft Lewis base, such as π-system, instead of oxygen which is a relatively harder Lewis base. Consequently, air and moisture stability of gold catalysts adds to their practicality in organic synthesis. The *anti*-addition of the nucleophile to the activated π-system with respect to Au(I) also provides a simplified chemical interaction among catalyst, binding site and nucleophile (Scheme 2.1). The reactivity of gold catalysts can be fine-tuned with various ligands and counterions.[2]



Scheme 2.1 Au(I)-Catalyzed Nucleophilic Addition to Alkyne

It is undisputed that many gold-catalyzed transformations proceed via carbenoid intermediates, but the nature of the Au–C bonds, either Au=C carbenes or Au-stabilized carbocations, has been debated.[3] In 2014, Fürstner and co-workers isolated the gold carbenoid

species $[Cy_3PAuCAr_2]^+ NTf_2^-$ (Ar = *p*-$MeOC_6H_4$-) in crystalline form from a formal gold-for-chromium transmetalation (Scheme 2.2).[4] The bond lengths (Au–C1, 2.039(5) Å; C1–C9, 1.429(7) Å; C1–C2, 1.455(6) Å) suggests that gold carbenoids are better described as gold carbocations. This result is also consistent with previously reported data.[5] Thus, all the carbenoids reported in the literature are drawn as gold carbocations herein.



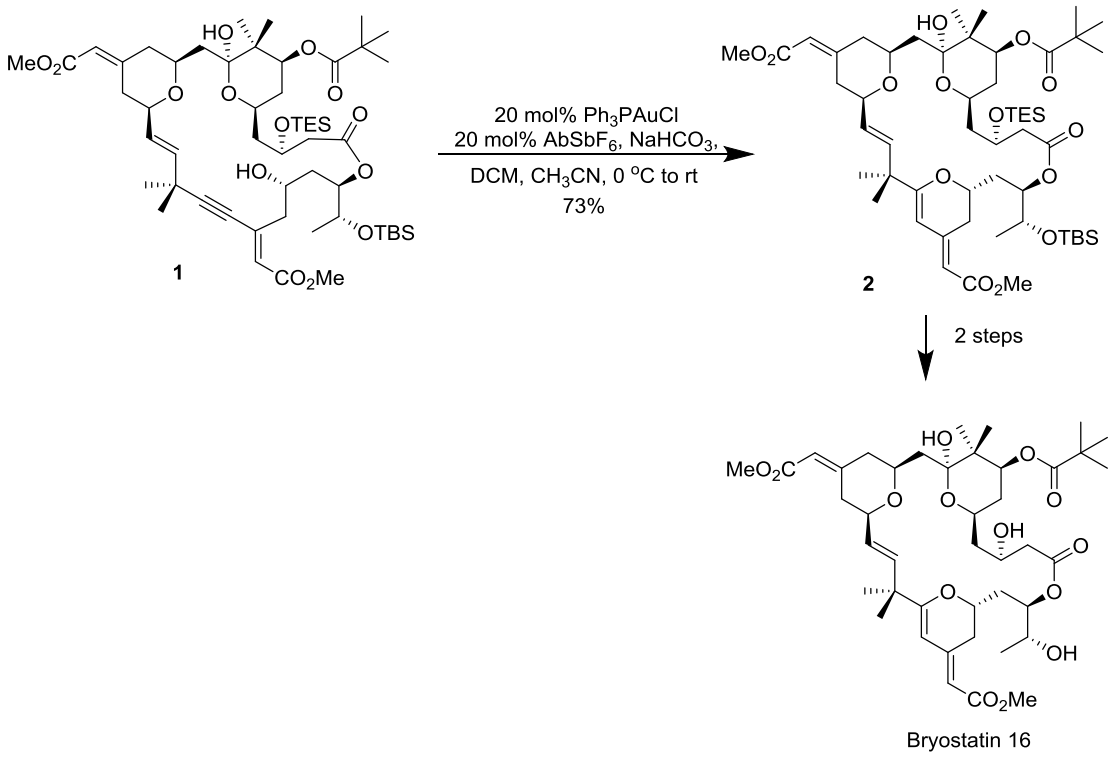
Scheme 2.2 Gold-for-Chromium Transmetalation and the Structure of Isolated Gold Carbenoid

Gold-catalyzed cyclization reactions of alkynyl substrates have been well documented and some have been applied to construct complex ring systems for natural product syntheses.[1] Various nucleophiles, such as O, N, alkenes and aromatic systems, have been explored for nucleophilic addition to alkynes under the catalysis of Au(I) or Au(III) catalysts.

2.1.1 Oxygen Nucleophiles

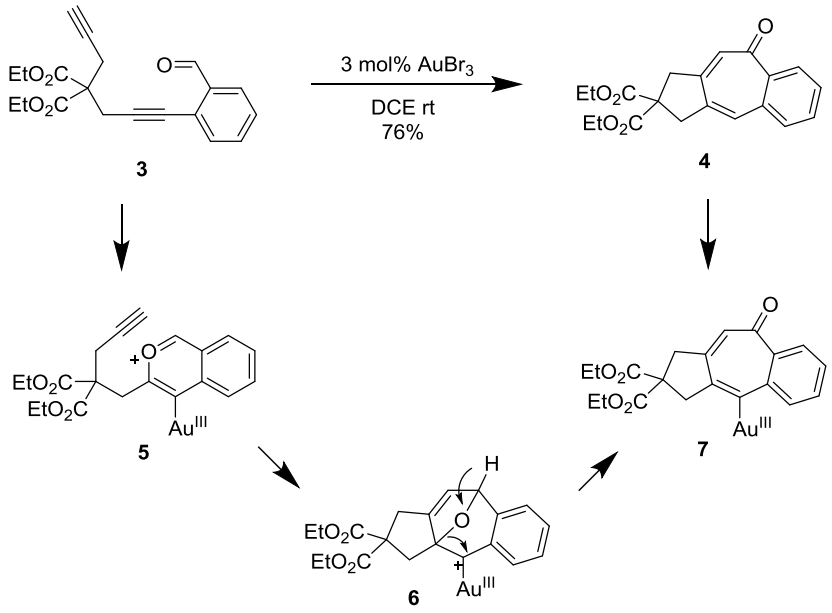
In 2008, the total synthesis of Bryostatin 16 was completed by Trost and co-workers.[6] One of the key steps of the synthesis, the late-stage cyclization of **1** (Scheme 2.3) catalyzed by

Au(I), furnished the closure of the dihydropyran of **2**. The reaction conditions tolerated a variety of functional groups, including several alkene groups. As the product **2** is highly sensitive to acid, the selective 6-*endo-dig* cyclization was accomplished in buffered solution under the catalysis of $Ph_3PAuSbF_6$ in 73% yield.



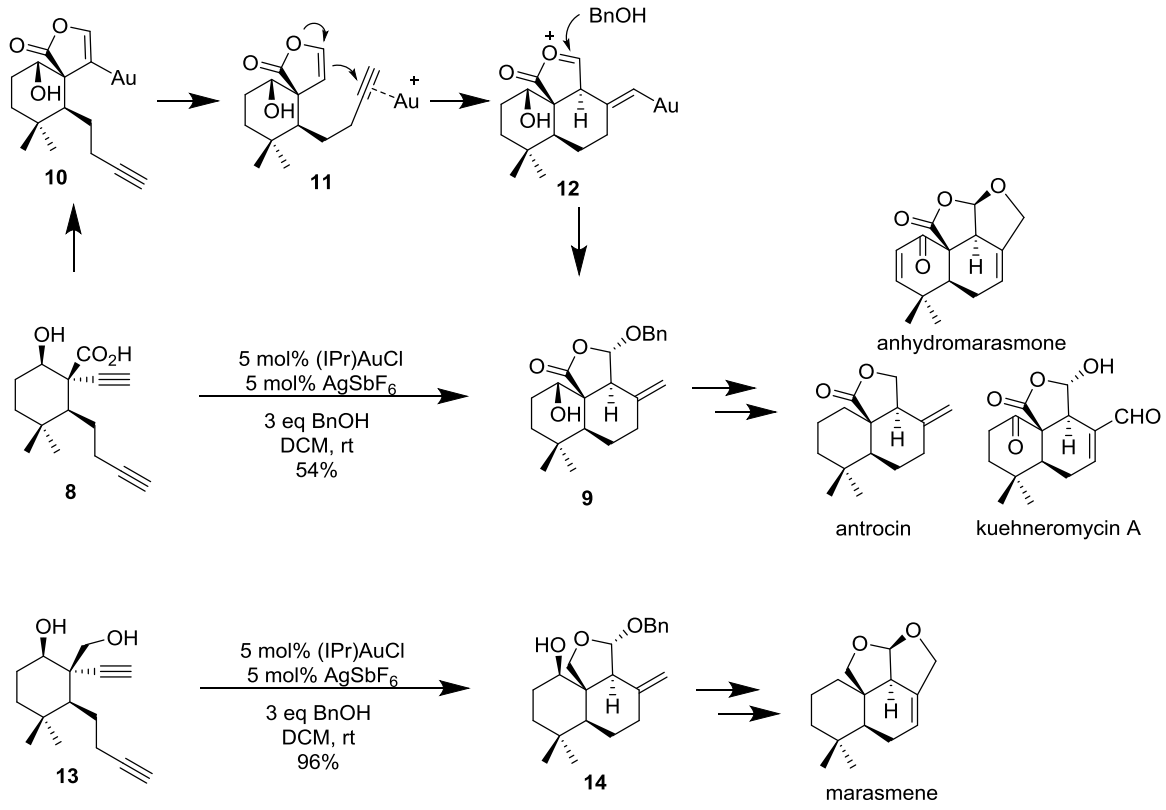
Scheme 2.3 Synthesis of Bryostatin 16

In 2005, Oh and co-workers developed a methodology to construct tricyclic ketone **4** through Au(III)-catalyzed cycloisomerization of diynal **3** (Scheme 2.4).[7] Nucleophilic addition of aldehyde to gold-activated internal alkyne gave the pyrylium ion intermediate **5**, which delivered seven-membered cyclic ketone **6** through an intramolecular 1,3-dipolar cycloaddition. A sequential fragmentation and protodeauration afforded the tricyclic product **4** in 76% yield.



Scheme 2.4 Synthesis of Tricyclic Ketone

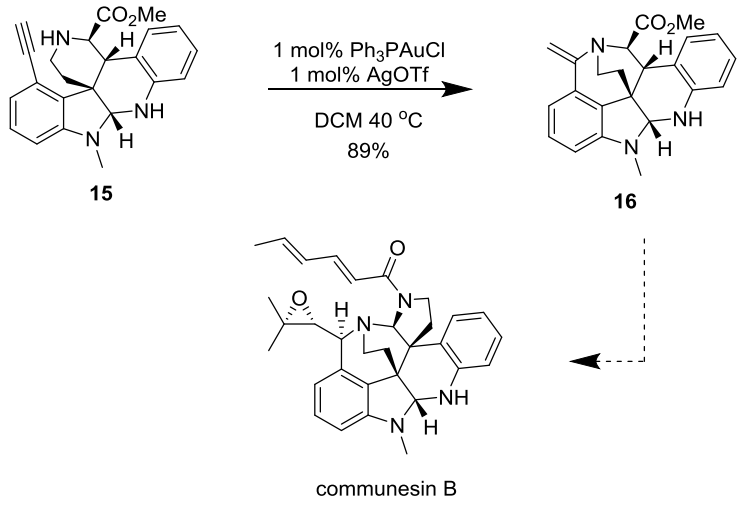
In 2011, Yang and co-workers developed a gold-catalyzed tandem cyclization of 1,7-diynes (Scheme 2.5).[8] Carboxylic acid **8** underwent nucleophilic attack to the neigboring gold-activated alkyne to form enol **11**, which acted as a nucleophile to attack the second activated alkyne to give intermediate **12**. Addition of BnOH and protonation provided the fused product **9** in 54% yield. This methodology can be applied to the syntheses of kuehneromycin A, anhydromarasmone and antrocin. The carboxylic acid of **8** can be replaced by alcohol of **13**, which was applied to synthesis of marasmene.



Scheme 2.5 Tandem Cyclization of 1,7-diyne

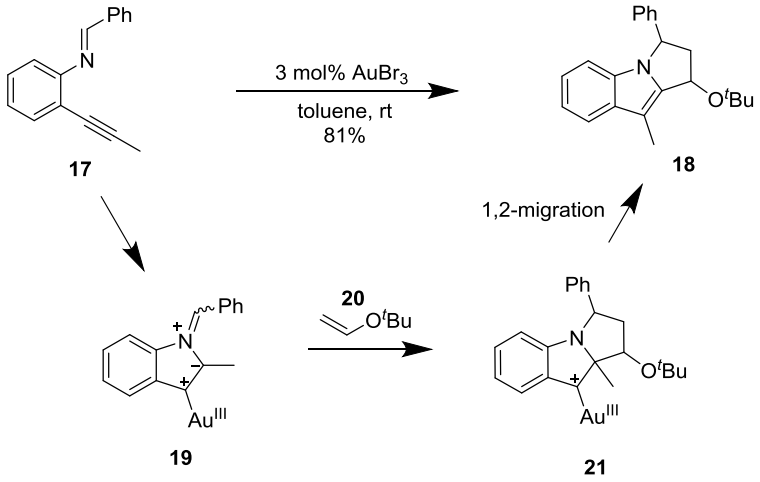
2.1.2 Nitrogen Nucleophiles

Funk and co-workers reported the intramolecular hydroamination of alkyne **15** (Scheme 2.6), which was applied to the synthetic study of communesin B.[9] Under the catalysis of $Ph_3PAuOTf$, the alkyne **15** underwent 7-*exo*-*dig* ring closure to provide highly strained enamine **16**, which gave the core carbocyclic skeleton of communesin B.



Scheme 2.6 Au(I)-Catalyzed Hydroamination

Iwasawa and co-workers reported a Au(III)-catalyzed [3 + 2] cycloaddition reaction (Scheme 2.7).[10] Nucleophilic addition of imine to gold-activated alkyne generated the gold carbenoid intermediate **19**, which underwent 1,3-dipolar cycloaddition to afford the tricyclic indole **18** in 81% yield.

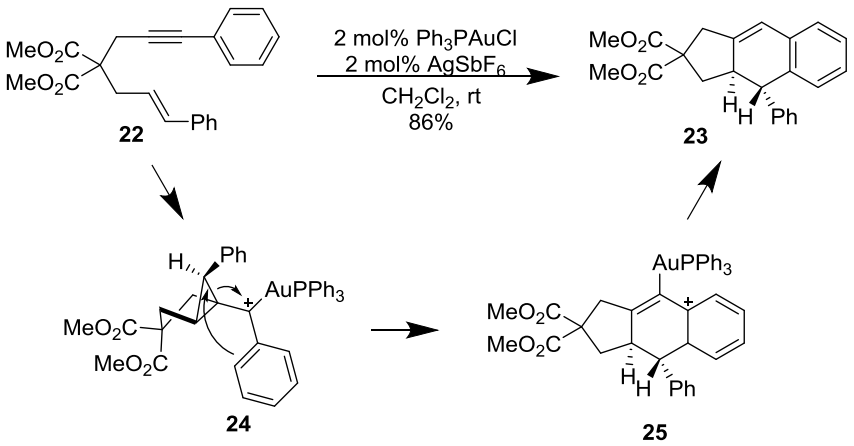


Scheme 2.7 Au(III)-Catalyzed [3+2] Cycloaddition Reaction

2.1.3 Alkenes as Nucleophiles (Enyne Cyclization)

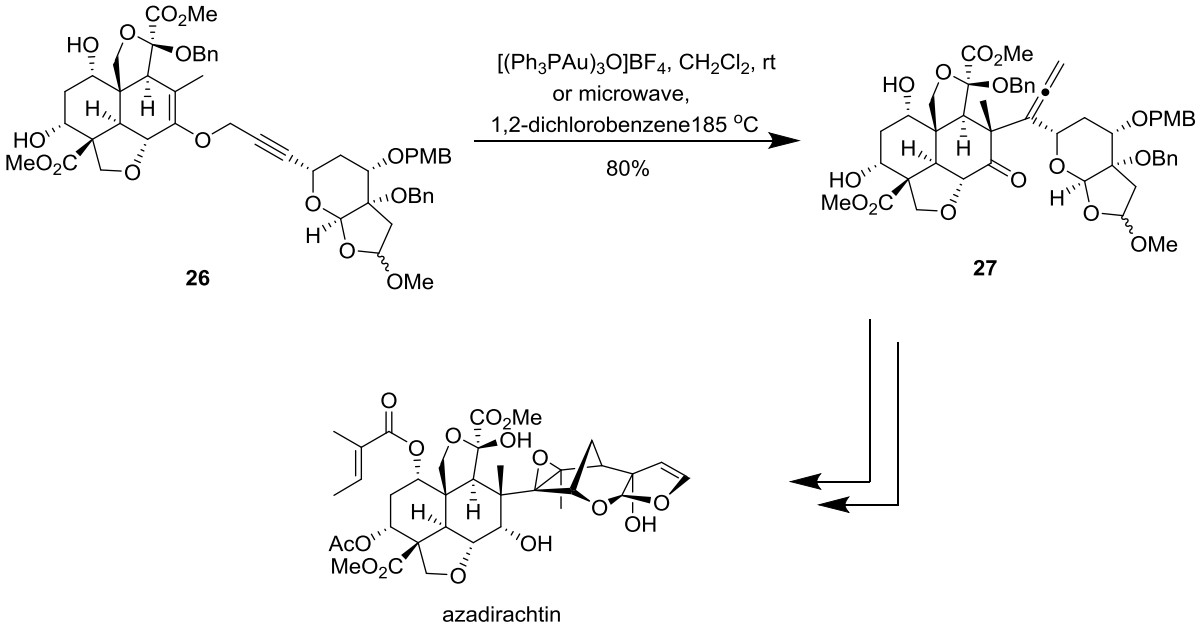
Echavarren and co-workers reported the Au(I)-catalyzed 1,6-enyne cyclization (Scheme 2.8).[11] Enyne **22** undwent 5-*exo-dig* cyclization and the generated cyclopropyl gold carbenoid **24**

was converted to **25** by a Nazarov-type cyclization. Aromatization and deauration furnished the tricyclic product **23** in 86% yield.



Scheme 2.8 Au(I)-Catalyzed 1,6-Enyne Cyclization

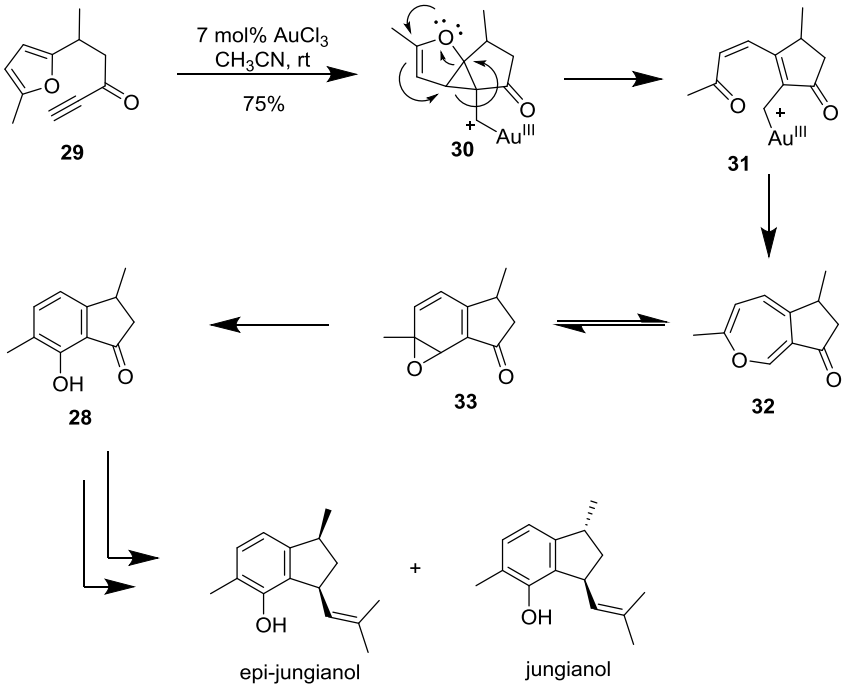
Ley and co-workers published the total synthesis of azadirachtin A after 22-years of synthetic effort (Scheme 2.9).[12] One of the key steps is the Au(I)-catalyzed Claisen rearrangement, which allowed the formation of allene **27** under mild conditions in 80% yield.



Scheme 2.9 Au(I)-Catalyzed Claisen Rearrangement

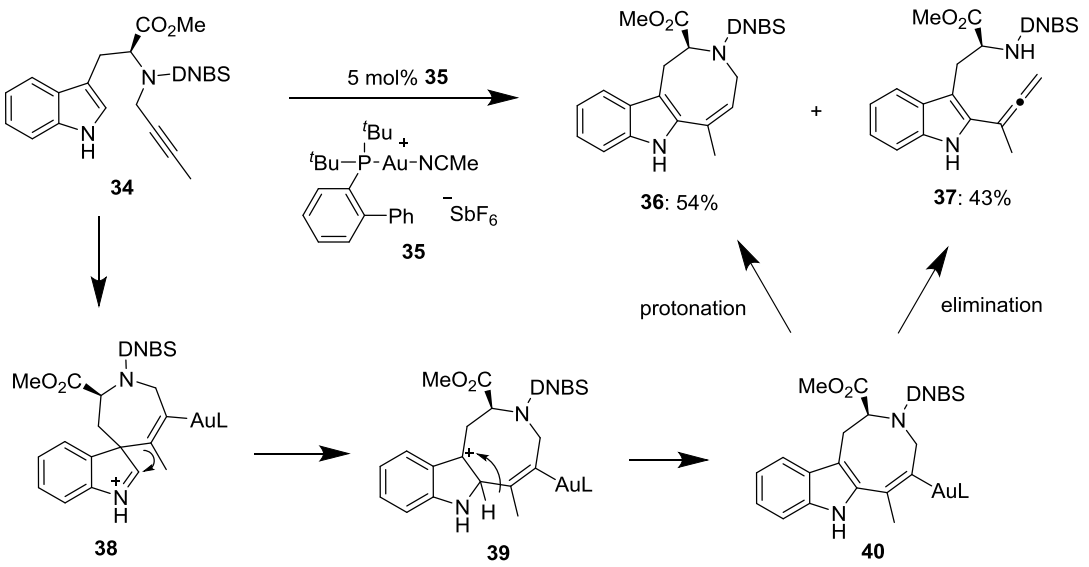
2.1.4 Aromatic Systems as Nucleophiles

Hashmi and co-workers reported a Au(III)-catalyzed synthesis of phenol **28** (Scheme 2.10) bearing a phenolic hydroxyl group *ortho*- to the ring-junction in 2000.[13] The cascade reaction started from the nucleophilic addition of the furan ring to gold-coordinated alkyne of ketone **29** to give the cyclopropyl intermediate **30**, which rearranged to form ring-opened intermediate **31**. Further cyclization and deauration provided the oxepine intermediate **32** and its arene oxide tautomer **33**, which underwent an epoxide ring opening and aromatized into phenol in 75% yield. This methodology was applied to syntheses of jungianol and *epi*-jungianol.



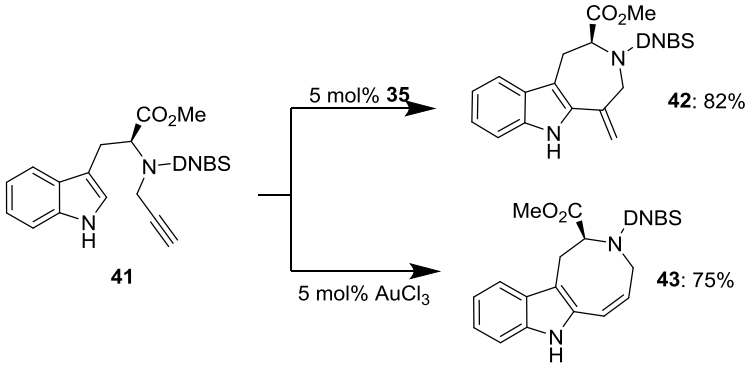
Scheme 2.10 Au(III)-Catalyzed Formation of Substituted Phenol

Echavaren and co-workers developed a method to access indoloazocines under gold catalysis (Scheme 2.11, 2.12).[14] Tryptophan derivative **34** (Scheme 2.11) was treated with Au(I) catalyst **35**, which provided a tricyclic indole **36** and an allene **37**. Initial 7-*endo*-*dig* cyclization gave iminium intermediate **38**, which rearranged into **39**. Rearomatization followed by protonation or elimination afforded indoloazocine **36** in 54% yield and allene **37** in 43% yield.



Scheme 2.11 Au(I)-Catalyzed Formation of Indoloazocines

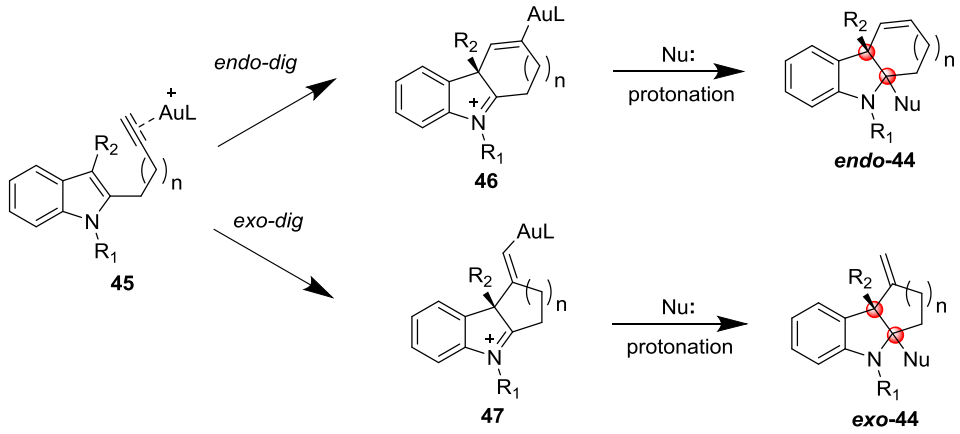
For the terminal alkyne **41** (Scheme 2.11), cyclization through a 7-*exo*-*dig* pathway afforded cyclized product **42** under the treatment of catalyst **35**. In contrast, $AuCl_3$-catalyzed cyclization preferred to proceed through 8-*endo*-*dig* cyclization to give product **43**.



Scheme 2.12 Various Cyclization Under Au(I)/(III) Catalysts

2.2 Proposed Approach to Polycyclic Indoline Alkaloids

To construct the skeleton of naturally occurring indoline alkaloids shown in Chapter 1, we envisioned a novel and potentially general approach to polycyclic indolines **44** bearing two stereocenters by using noble metal catalyst as shown in Scheme 2.13.[15] A gold or platinum catalyst would selectively activate the terminal alkyne of alkynylindole **45** and promote either *endo*- or *exo*-cyclization. The resulting iminium ions **46** and **47** would then be susceptible to nucleophilic attack, which was expected to provide highly functionalized indolines **44** after protonation of the vinylmetal species.

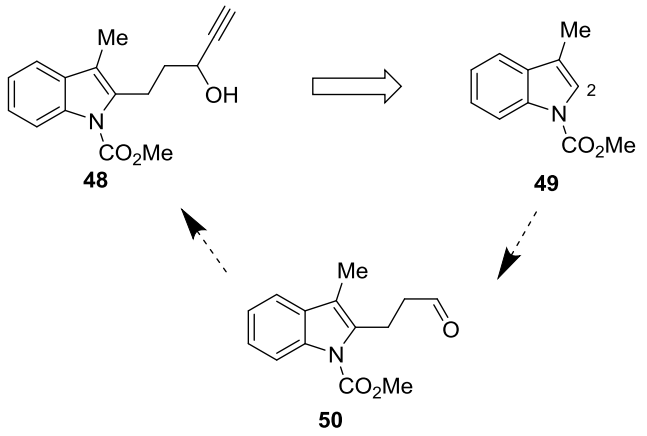


Scheme 2.13 Proposed Approach

2.3 Tandem Cyclization of Alkynylindole

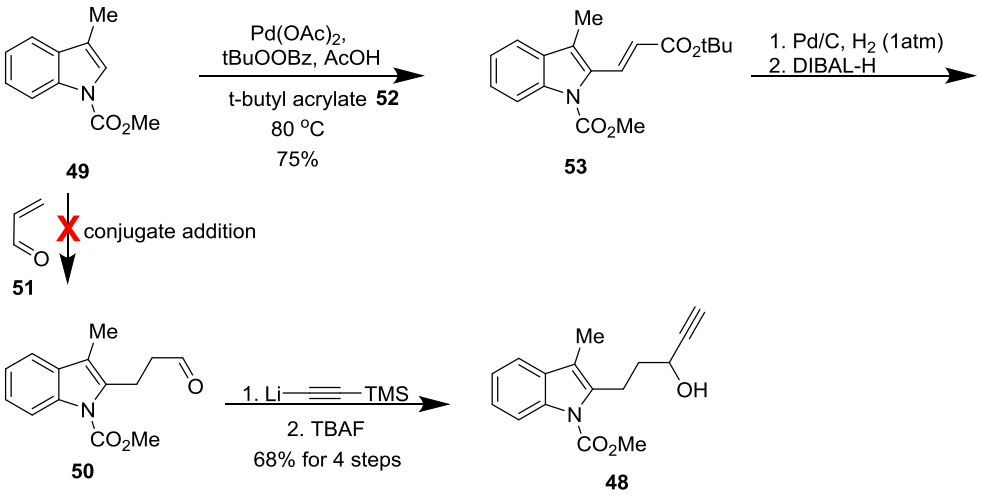
2.3.1 Substrate Preparation

Alkynylindole **48** (Scheme 2.14) was chosen as the substrate to test the proposed cyclization shown in Scheme 2.13. It contains a secondary alcohol, which may serve as an internal nucleophile in a second step of cyclization. Commerically available indole **49** was used to prepare alkynylindole **48**. The major challenge in this route is the formation of C-C bond at C2 of indole **49** to give aldehyde **50**.



Scheme 2.14 Designed Route for Synthesizing Alkynylindole **48**

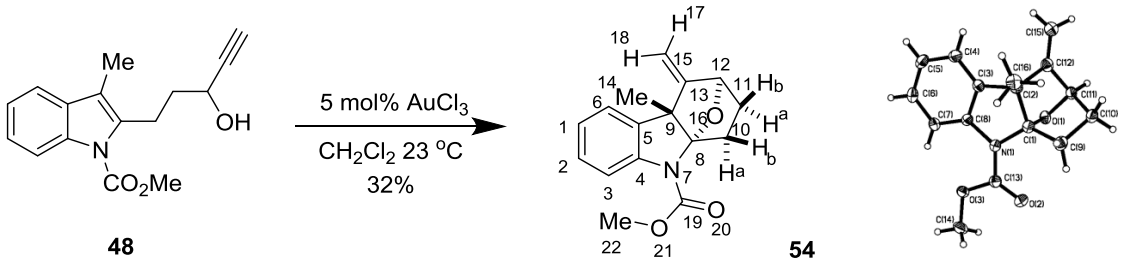
To prepare aldehyde **50** from indole **49**, various Lewis acids were screened for conjugate addition of indole **49** to acrolein **51**, *t*-buyl acrylate **52** and other electrophiles (Scheme 2.15).[16] Decomposition occurred or less than 10% yield of product **50** was obtained. Following the procedure of reported oxidative heck reactions,[17] compound **53** was obtained in 75% yield under the catalysis of $Pd(OAc)_2$ using *t*-butyl peroxybenzoate as the oxidant in acetic acid at 80 ^oC. Pd-catalyzed hydrogenation and DIBAL-H reduction gave the desired aldehyde **50**, which was subjected to nucleophilic addition of alkyne under basic condition. TBAF-mediated desilylation afforded alkynylindole **48** in 68% yield over 4 linear steps (Scheme 2.15).



Scheme 2.15 Synthesis of Alkynylindole **48**

2.3.2 Au(III)-Catalyzed Tandem Cyclization of Alkynylindole

Initially, alkynylindole **48** was subjected to 5 mol% of $AuCl_3$ in dichloromethane at room temperature and 32% yield of compound **54** was isolated (Scheme 2.16).



Scheme 2.16 Tandem Cyclization of **48** into **54**

Its structure was assigned based on a series of 1D and 2D NMR studies (Table 2.1) and further confirmed by X-ray crystallographic analysis (Scheme 2.16).

Table 2.1 Hydrogens (Hs) and Their Coupled Atoms in 2D NMR Experiments

Hs	Coupled Atoms			
	COSY	NOESY	HSQC	HMBC
H_1	H_2, H_6	H_2, H_6	C_1	C_3, C_5
H_2	H_1, H_3	H_1, H_3	C_2	C_6
H_3	H_2	H_2	C_3	n/a
H_6	H_1	H_1, H_{18}	C_6	C_2, C_4
H_{10a}	H_{10b}, H_{11a}, H_{11b}	H_{10b}, H_{11a}, H_{11b}	C_{10}	C_9, C_{11}, C_{13}
H_{10b}	H_{10a}, H_{11a}, H_{11b}	H_{10a}, H_{11a}, H_{11b}, H_{14}	C_{10}	C_9, C_{12}
H_{11a}	H_{10a}, H_{10b}, H_{11b}	H_{10a}, H_{10b}, H_{11b}, H_{12}	C_{11}	C_8, C_{12}
H_{11b}	H_{10a}, H_{10b}, H_{11a}	H_{10a}, H_{10b}, H_{11a}, H_{12}, H_{14}	C_{11}	C_8, C_{13}
H_{12}	H_{11a}	H_{11a}, H_{11b}	C_{12}	C_9, C_{10}, C_{13}
H_{14}	n/a	H_{10b}, H_{11b}	C_{14}	C_5, C_9, C_{13}
H_{17}	H_{12}, H_{18}	H_{12}, H_{18}	C_{15}	C_5, C_8, C_9, C_{11}, C_{12}, C_{14}, C_{15}
H_{18}	H_{12}, H_{17}	H_6, H_{17}	C_{15}	C_5, C_8, C_9, C_{12}, C_{15}
H_{22}	n/a	n/a	C_{22}	C_{22}

2.3.3 Optimization of the Gold-Catalyzed Tandem Cyclization

Several catalysts were investigated for the tandem cyclization reaction shown in Scheme 2.15 (Table 2.2). Platinum(II) chloride and triflic acid were also capable of promoting this reaction (Table 2.2, entries 2 and 3); however, significant decomposition of the substrate **48** was observed in these conditions. Attempts to use different Lewis acids, such as $AgSbF_6$, and Brønsted acid, *p*-toluenesulfonic acid, failed to provide any desired product (Table 2.2, entries 4 and 5). Ph_3PAuCl-promoted process required higher temperature, longer reaction time, but provided a slightly better yield of **54** than with $AuCl_3$ (Table 2.2, entry 1 versus 6). Good to high yields of the isolated products were obtained (67-83%; Table 2.2, entries 7-9) by using cationic Au(I) species generated from gold catalysts and silver salts. Based on the screening results of various couterions, hexafluoroantimonate was found to be the optimal counterion providing the product **54** in 83% yield (Table 2.2, entry 9).

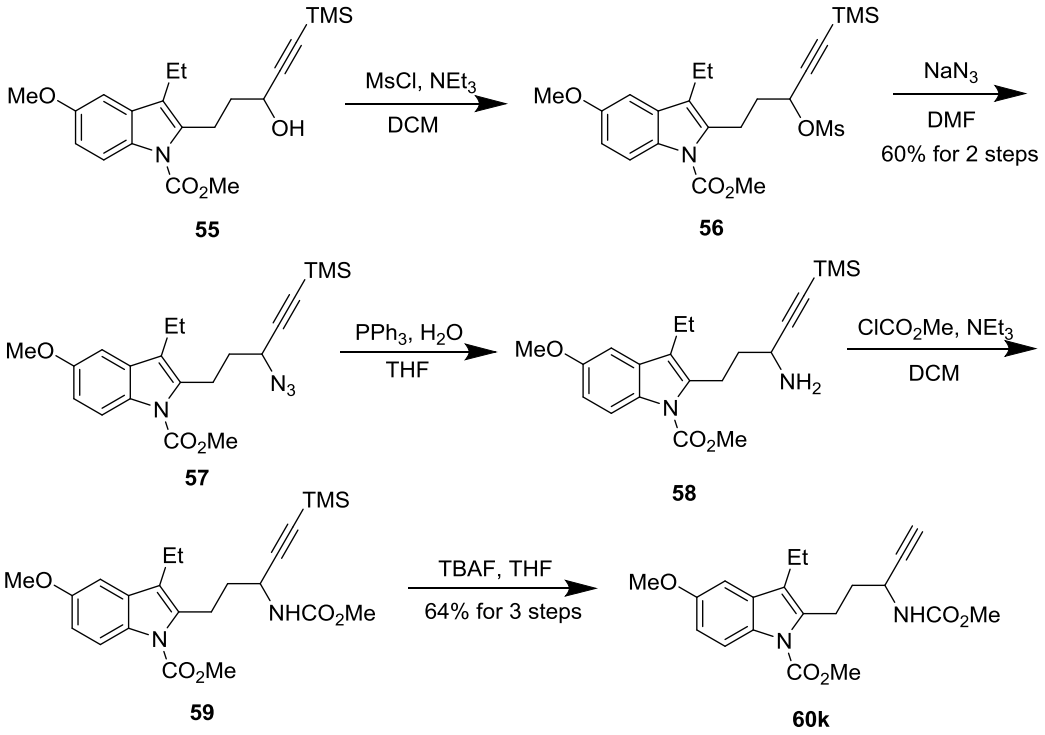
Table 2.2 Optimization of the Gold-Catalyzed Tandem Cyclization

Entry	Catalyst/Additive[a]	Time (h)	Temp (^oC)	Consumption of **48** (%)[b]	Yield[c] of **54** (%)
1	$AuCl_3$	0.5	23	100	32
2	$PtCl_2$	12	80	50	14[d]
3	TfOH	12	23	70	35
4	$AgSbF_6$	12	23	0	0
5	TsOH	12	23	0	0
6	Ph_3PAuCl	12	80	80	55[e]
7	$Ph_3PAuCl/AgBF_4$	1	23	100	78
8	Ph_3PAuCl/AgOTf	1	23	100	67
9	$Ph_3PAuCl/AgSbF_6$	1	23	100	83

[a] 5 mol%. [b] Consumption of **48** was calculated by the integration of H-NMR spectra. [c] Average isolated yield of at least of two runs. [d] In toluene. [e] In acetonitrile.

2.3.4 Substrate Scope of the Au(I)-Catalyzed Tandem Cyclization

A variety of alkynylindoles **60a-j** were prepared and the syntheses were the same as shown in Scheme 2.14. For **60k-n**, a representative synthetic route was described in Scheme 2.17. Propargyl alcohol **55** was mesylated under basic conditions, and S_N2 reaction afforded azide **56** in 60% yield for 2 steps. Under Staudinger reduction conditions, azide **56** was reduced into primary amine **58**, which was converted into methyl carbamate **59**. TBAF-mediated desilylation gave alkynylindole **60m** in 64% yield for 3 steps (Scheme 2.17).

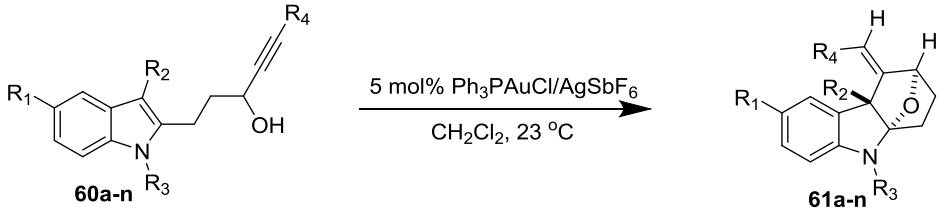


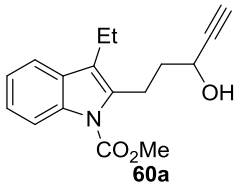
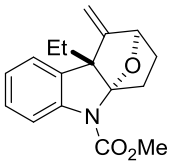
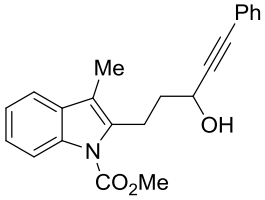
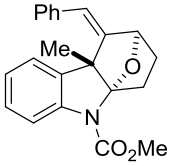
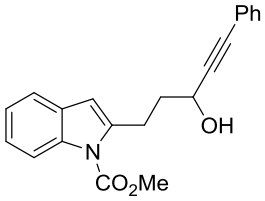
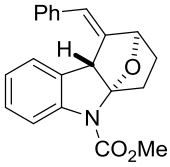
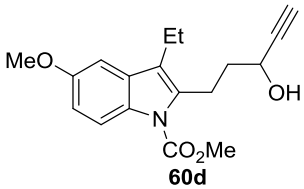
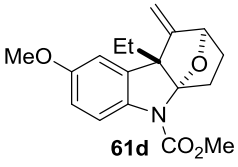
Scheme 2.17 Representative Preparation of **60k**

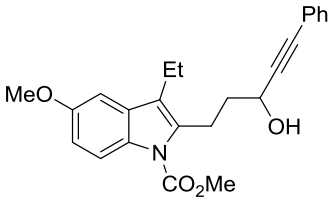
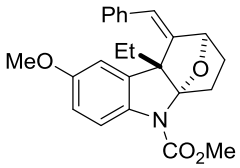
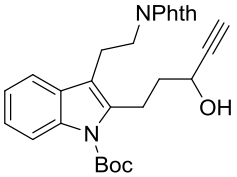
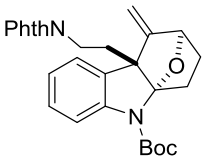
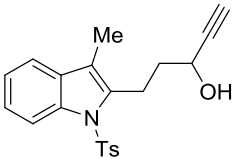
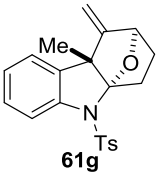
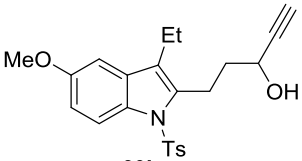
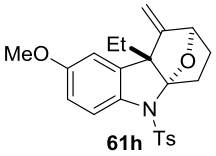
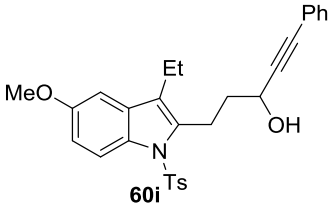
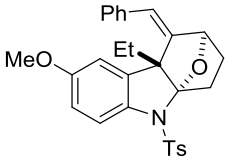
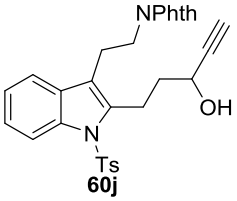
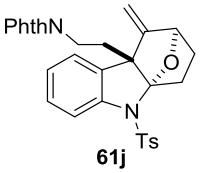
The alkynylindoles **60a-k** were subjected to the optimized Au(I)-catalyzed cyclization conditions. The reactions proceeded very well in all cases as shown in Table 2.3. No other regioisomers or diastereomers were identified from the reaction mixtures. Indoles possessing substitution at C3 and C5, including tryptamine derivatives (Table 2.3, entries 6 and 10), were generally well tolerated. The indole nitrogen requires an electron-withdrawing group, such as a methoxycarbonyl, Boc, or tosyl group, to provide the desired products. The N^{in}-Me or N^{in}-H substrates failed to cyclize under the standard reaction conditions and provided a complex

mixture of products at higher temperature. Phenyl-substituted alkynes (Table 2.3, entries 2, 3, 5, and 9) required longer reaction time and provided slightly lower yields of the desired products. The olefin geometry of the products was determined to be *E* by 1D NOE studies, which is consistent with literature reports on several other gold-catalyzed cyclizations.[18]

Table 2.3 Substrate Scope – *O* as Nucleophile

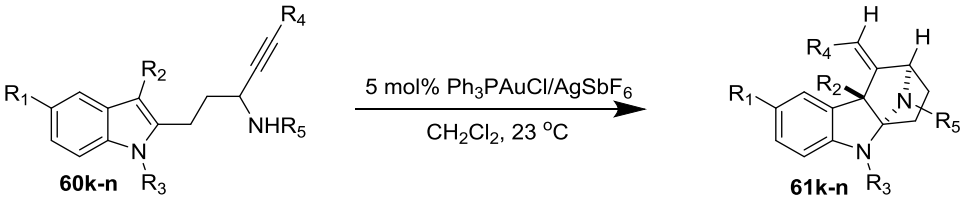


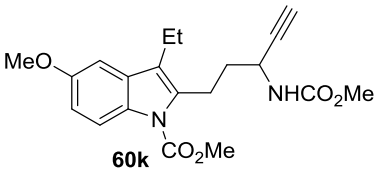
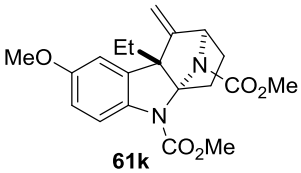
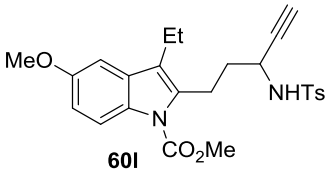
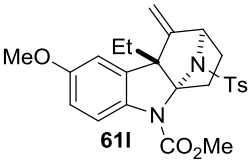
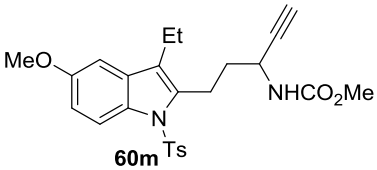
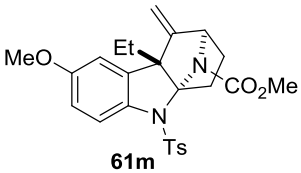
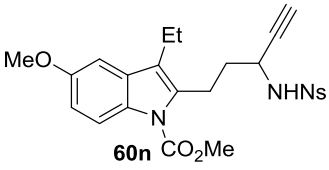
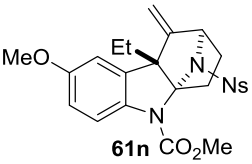
Entry	Alkynlindole	Product	Yield (%)
1	 **60a**	 **61a**	83
2	 **60b**	 **61b**	65
3	 **60c**	 **61c**	67
4	 **60d**	 **61d**	85

5	 **60e**	 **61e**	75
6	 **60f**	 **61f**	84
7	 **60g**	 **61g**	85
8	 **60h**	 **61h**	88
9	 **60i**	 **61i**	64
10	 **60j**	 **61j**	82

These tandem cyclization reactions are not limited to alcohol nucleophiles. Sulfonamides or carbamates also served as nucleophiles in the second cyclization reaction and afforded the tetracyclic indolines with good yields and selectivity. (Table 2.4, entries 1-4).

Table 2.4 Substrate Scope – *N* as Nucleophile

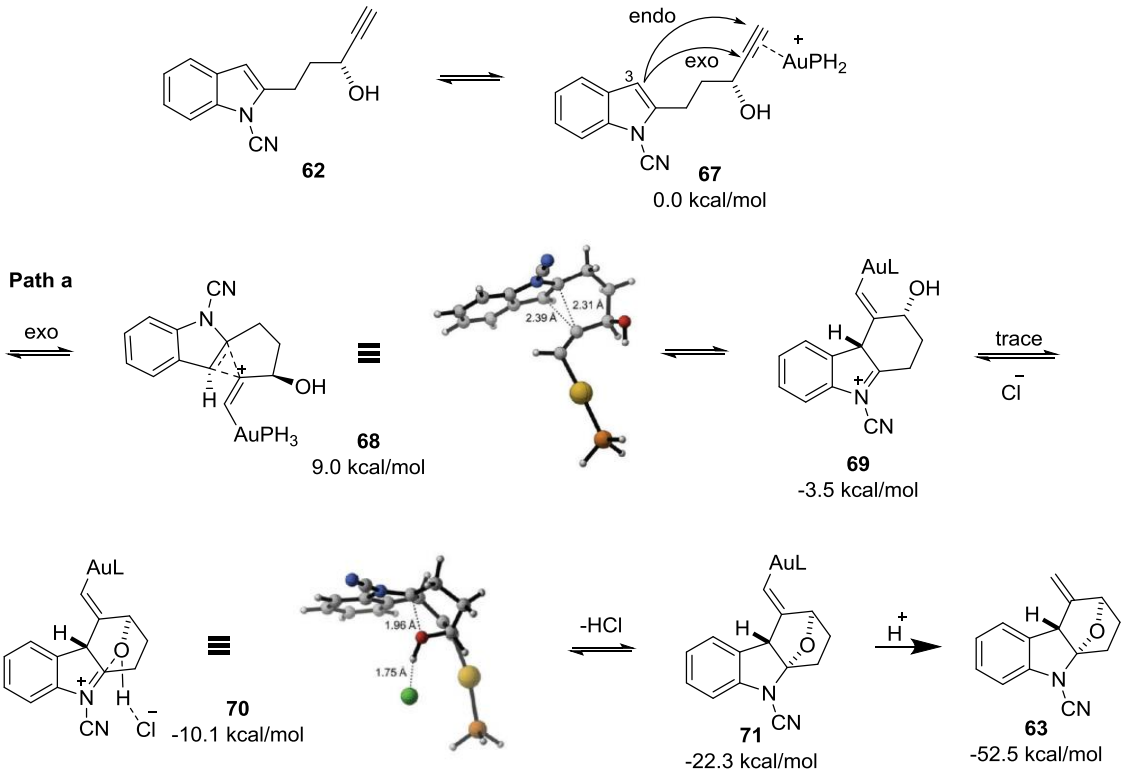


Entry	Alkynylindole	Product	Yield (%)
1			78
2			75
3			79
4			70

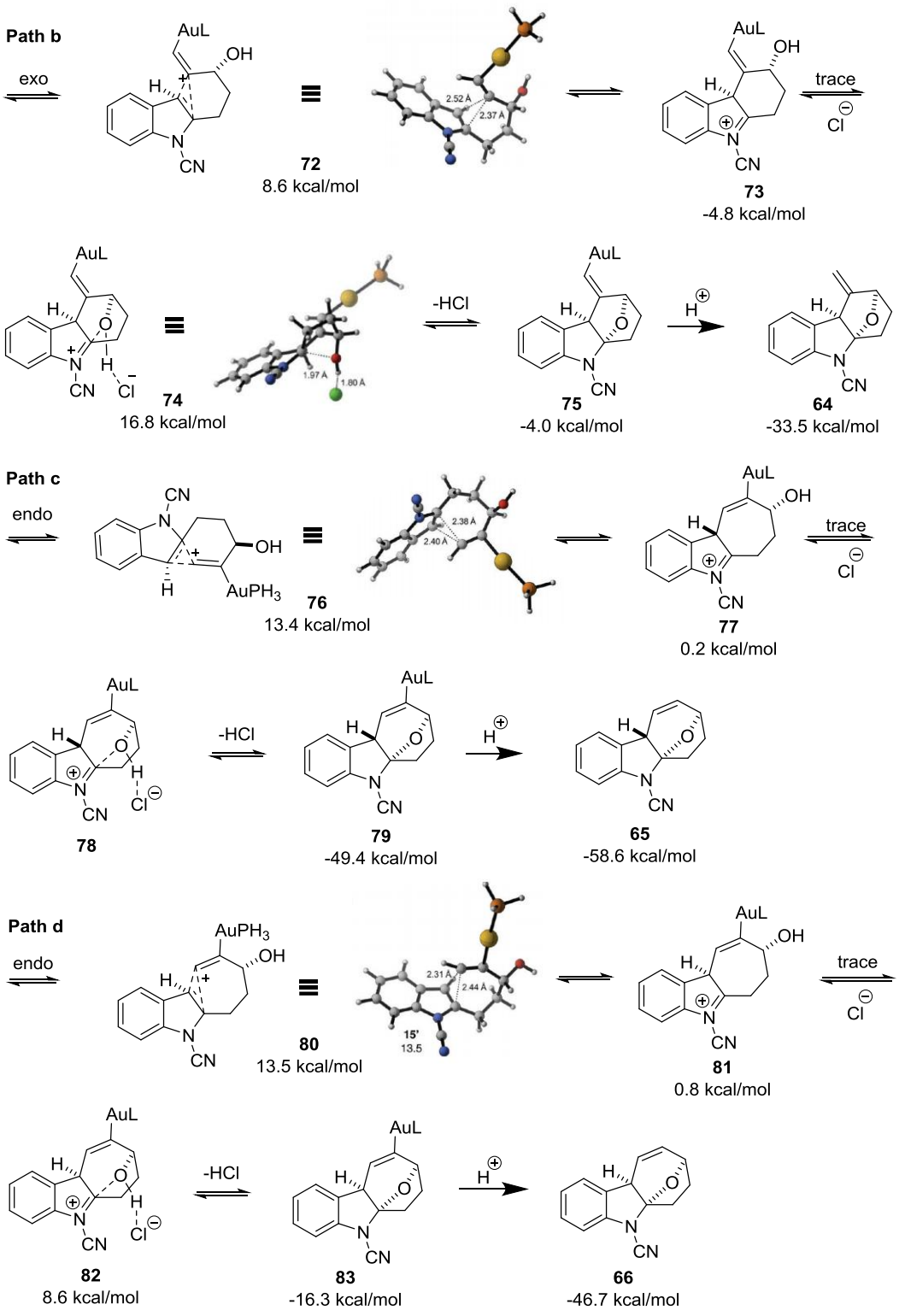
2.4 Mechanistic Study

The mechanism of cyclization was investigated in silico in collaboration with Prof. K. N. Houk.[19] All calculations were based on the model reaction of substrate **62** under the catalysis of $AuPH_3^+$ in dichloromethane (Scheme 2.18). The alkyne **62** is coordinated by Au(I) catalyst to form the complex **67**. For the following nucleophilic attack of C3 of indole **67** at activated alkyne, regioselectivity can give rise to four different intermediates **68**, **72**, **76** and **80** in paths a-c. Nucleophiles undergo intramolecular addition to the iminium ions generated in situ and final

processes of deprotonation/protonation afford the polycyclic products **63, 64, 65** and **66**. Since compound **63** is the sole product based on the previous experimental result, discrimination of the other three paths is studied by calculating the free energy diagram for all four paths.



Scheme 2.18 Cyclization Paths-continued on the next page



Scheme 2.18 Cyclization Paths

The free energy diagram (Figure 2.1) shows that *exo* transition structures **68** and **72** are lower in energy than the *endo* transition structures **76** and **80** by about 4 to 5 kcal/mol. Also, the *exo* intermediates formed, **69** and **73**, are lower in energy than the *endo* intermediates, **77** and **81**. Intermediate **73** would form ether-bridged species **75** through transition structure **74**. The barrier from **73** to **75** is 21.6 kcal/mol, while the barrier from **73** back to starting material, **67**, is only 13.4 kcal/mol, so **73** will revert back to **67**. However, **69** forms the ether-bridged species **71** with no barrier and the final protonation is exothermic. These data provide an explation for the preference of path a to form product **63** instead of **64**, **65** and **66**.

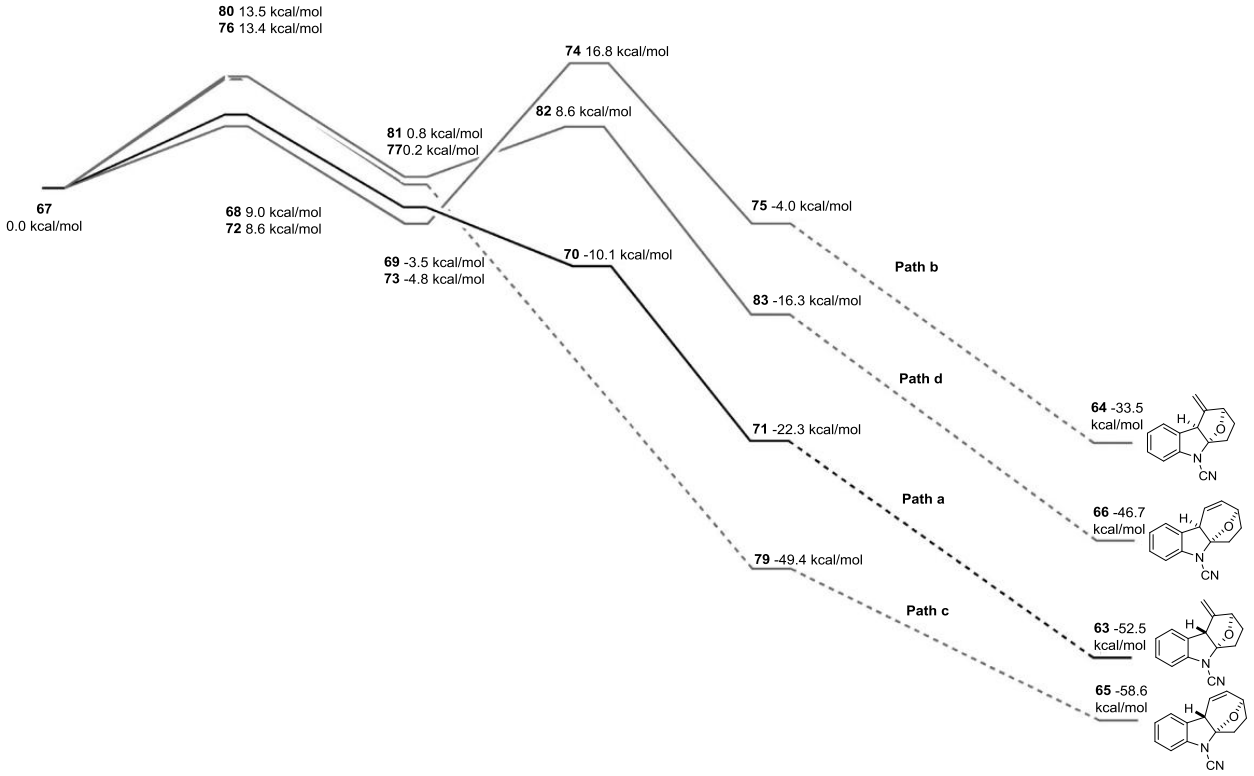


Figure 2.1 Free Energy Diagram

2.5 Application to Construction of Fused Indoline Skeleton

The fused indoline skeleton **84** is found to be the core motif of many akuammiline alkaloids (Figure 2.2).[20] We set out to investigate the application of the Au(I)-catalyzed tandem cyclization described above to the construction of fused indoline **84**.

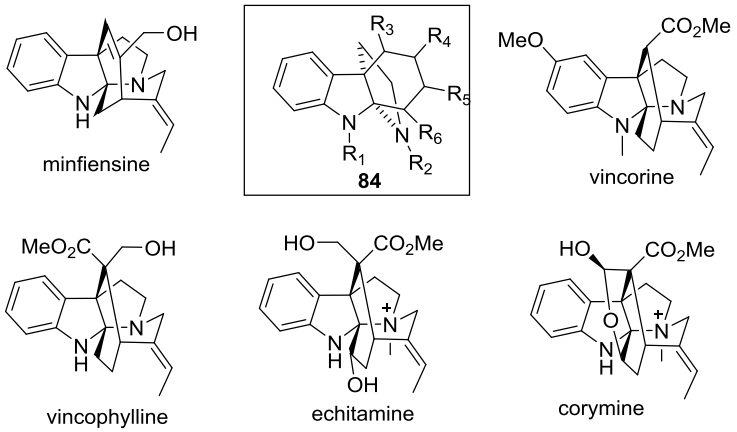
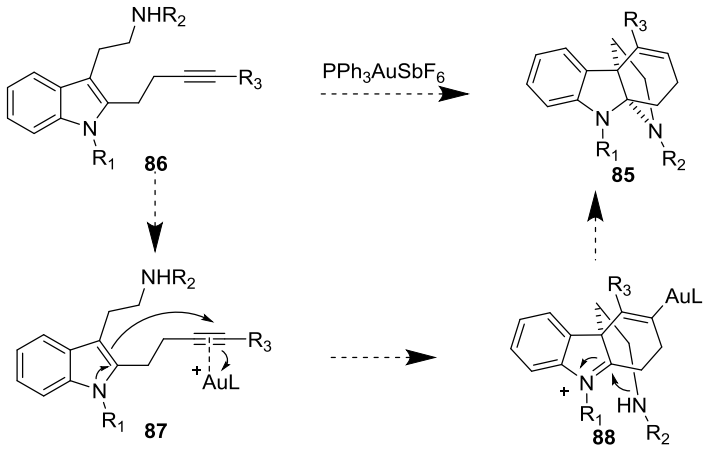


Figure 2.2 Core Motif of Akuammiline Alkaloids

85 was envisioned to be formed from alkynylindole **86** under Au(I) catalysis (Scheme 2.19). Nucleophilic attack of indole at gold-activated alkyne **87** was anticipated to generate the iminium intermediate **88** which could undergo intramolecular addition to afford the tetracycle **85**.

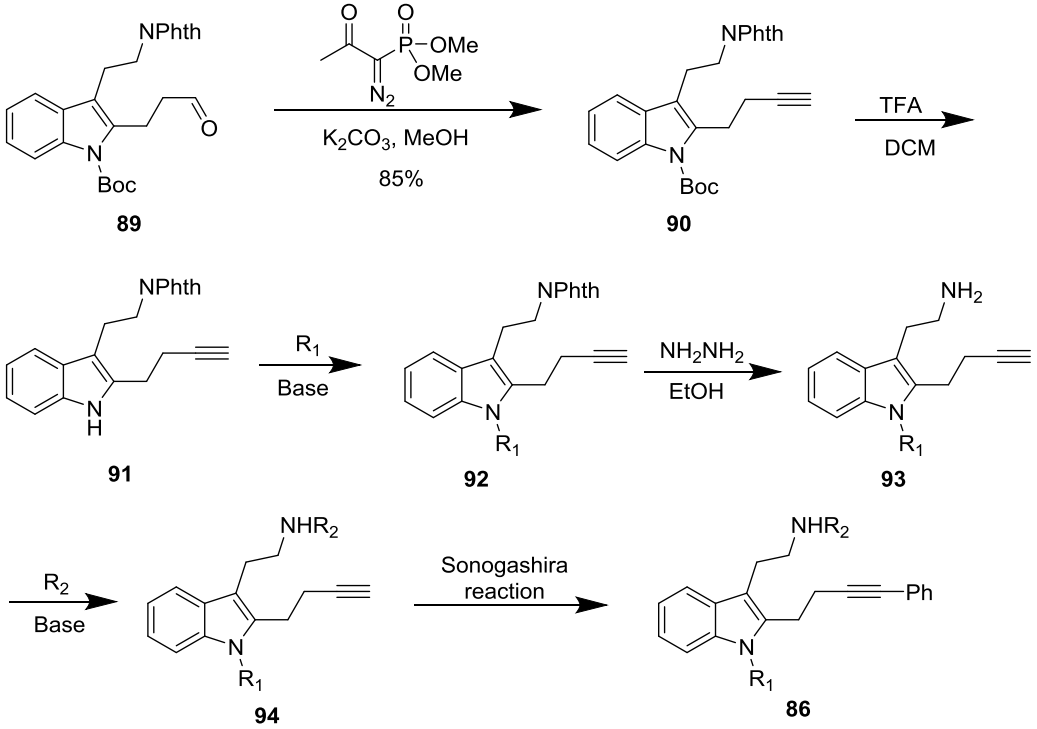


Scheme 2.19 Proposed Au(I)-Catalyzed Tandem Cyclization

2.5.1 Substrate Preparation

Alkynylindole **86** (Scheme 2.20) was synthesized from the aldehyde **89**, which was prepared as shown in Scheme 2.14. Seyferth-Gilbert homologation[21] transformed the aldehyde **89** into alkyne **90**, which was deprotected in acidic condition to give indole **91**. Installation of R_1

under basic condition, deprotection of phthalimide (Phth) and installation of R_2 to primary amine **93** afforded alkynylindole **94**. Sonogashira reaction condition[22] gave internal alkynylindole **86**.

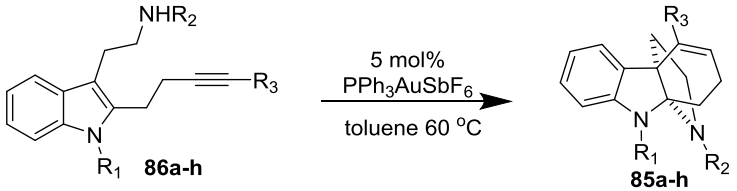


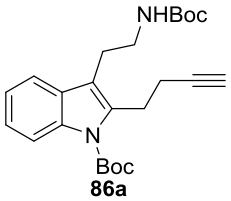
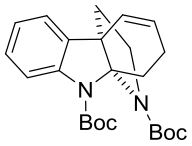
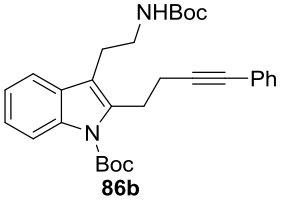
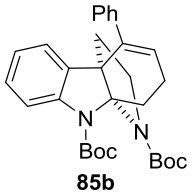
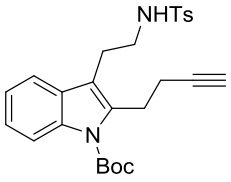
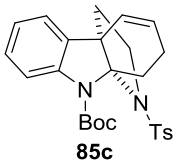
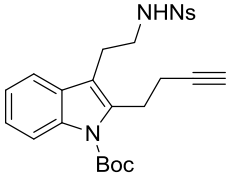
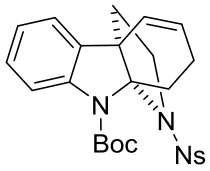
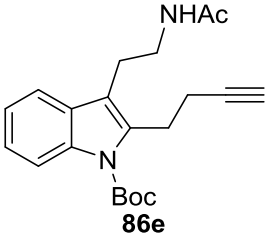
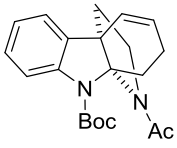
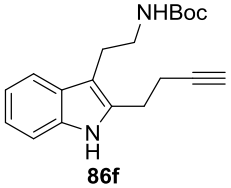
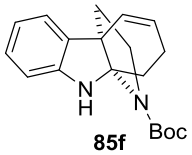
Scheme 2.20 Preparation of Alkynylindole **86**

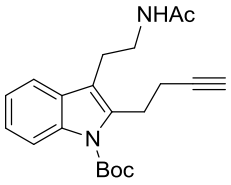
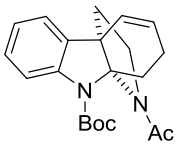
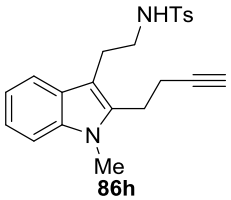
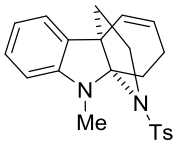
2.5.2 Au(I)-Catalyzed Tandem Cyclization

For all substrates tested (Table 2.5), the reactions went to completion within 2 h and afforded the core structures of the akuammiline alkaloids (Figure 2.2) in good yields (75-88%); no 5-*exo-dig* products were detected in all cases. In addition to carbamates and sulfonamides, secondary amides (Table 2.5, entries 5 and 7) also served as nucleophiles in the second cyclization steps. Interestingly, the N^{in}-H and N^{in}-Me substrates also participate in this tandem cyclization reaction and provide tetracyclic indolines **85** cleanly (Table 2.5, entries 6-8).

Table 2.5 Scope of Au(I)-Catalyzed Tandem Cyclization

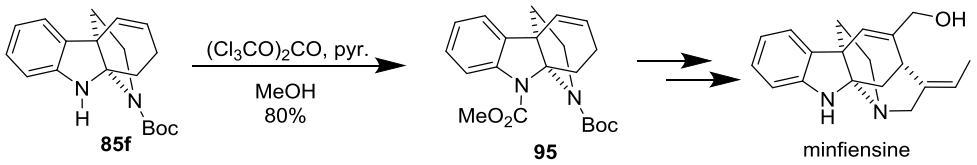


Entry	Alkynylindole	Product	Yield (%)
1	 **86a**	 **85a**	75
2	 **86b**	 **85b**	84
3	 **86c**	 **85c**	81
4	 **86d**	 **85d**	88
5	 **86e**	 **85e**	80
6	 **86f**	 **85f**	87

7	 **86g**	 **85g**	83
8	 **86h**	 **85h**	86

2.5.3 Formal Synthesis of Minfiensine

For the indoline **85f**, the aniline was converted to a methyl carbamate when treated with triphosgene followed by quenching with anhydrous methanol (Scheme 2.21). The resulting compound **95** is a key intermediate in Overman's total synthesis of the akuammiline alkaloid minfiensine.[23]



Scheme 2.21 Formal Synthesis of Minfiensine

2.6 Conclusion

In summary, a novel approach to the construction of tetracyclic indolines using stereoselective cationic Au(I)-catalyzed tandem cyclization reactions was developed. This approach allows rapid assembly of two rings and two stereocenters including a quaternary carbon center in a single step with a wide substrate scope and tolerance of functional groups. A formal synthesis of the akuammiline alkaloid minfiensine was also completed. Furthermore, this

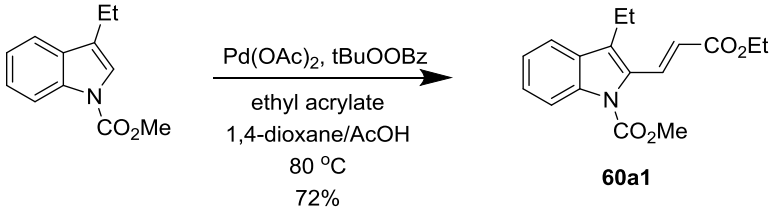
methodology has been applied to synthesis of a small-molecule library and diverse skeletons have been constructed, some of which exhibited excellent antibiotic activity.[24]

2.7 Experimental

Unless otherwise noted, reagents were obtained commercially and used without further purification. CH_2Cl_2 was distilled from CaH_2 under a nitrogen atmosphere. THF was distilled from sodium-benzophenone under a nitrogen atmosphere. Toluene was distilled from sodium under a nitrogen atmosphere. Thin-layer chromatography (TLC) analysis of reaction mixtures was performed on Dynamicadsorbents silica gel F-254 TLC plates. Flash chromatography was carried out on Zeoprep 60 ECO silica gel. ^1H and ^{13}C NMR spectra were recorded with Varian INOVA 400, 500 and Bruker Avance-III 300 spectrometers. Mass spectral and analytical data were obtained via the PE SCIEX/ABI API QSTAR Pulsar i Hybrid LC/MS/MS, Applied Biosystems operated by the Central Analytical Laboratory, University of Colorado at Boulder. Infrared (IR) spectra were recorded on a Thermo Nicolet Avatar 370 FT-IR spectrometer. Melting point (mp) determinations were performed by using a Thomas Hoover capillary melting point apparatus and are uncorrected. High performance liquid chromatography (HPLC) analyses of chiral compounds were performed using a ChiralCel OD column (250 x 4.6 mm) and ChiralPak IA column (250 x 4.6 mm). Compounds were detected by monitoring UV absorbance at 254 nm. Optical rotations were determined on a JASCO 1030 polarimeter at 25 ℃.

General preparation of alkynylindoles and characterization data

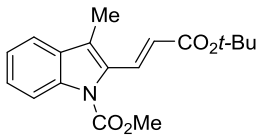
(*E*)-Methyl 2-(3-ethoxy-3-oxoprop-1-enyl)-3-ethyl-1H-indole-1-carboxylate (60a1)



60a1

To a solution of the indole substrate **60a1** (1.02 g, 5.0 mmol) in 1, 4-dioxane/AcOH (3:1, v:v, 10.0 mL) was added $Pd(OAc)_2$ (23 mg, 0.10 mmol), tert-butyl benzoyl peroxide (1.3 g, 6.5 mmol) and ethyl acrylate (2.9 mL, 20.0 mmol). The resulting mixture was heated to 80 ℃ under N_2 atmosphere for 24 h before it was cooled to room temperature., diluted with ethyl acetate, and filtered through a pad of celite. The filtrate was washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude oil, which was purified by column chromatography (hexanes/ethyl acetate = 30:1) to afford desired product **60a1** (1.10 g, 3.6 mmol) as a white solid in 72% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.3 Hz, 1H), 8.06 (d, *J* = 16.1 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.62 – 7.56 (m, 1H), 7.31–7.27 (m, 1H), 6.11 (d, *J* = 16.1 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.05 (s, 3H), 2.84 (q, *J* = 7.6 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.6 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 166.92, 152.55, 136.54, 135.87, 131.00, 129.89, 127.31, 126.16, 123.43, 120.49, 119.73, 115.92, 60.84, 54.09, 18.31, 15.21, 14.56.
m.p. 65 – 66 ℃.
IR (neat, cm^{-1}): ν 2967, 1740, 1713, 1629, 1455, 1441, 1359, 1176, 1037.
HRMS (ESI) m/z calcd for $C_{17}H_{19}NNaO_4^+$: 324.1206, Found: 324.1196.



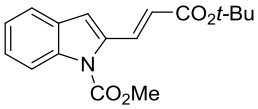
(*E*)-Methyl 2-(3-tert-butoxy-3-oxoprop-1-enyl)-3-methyl-1H-indole-1-carboxylate (53)
A colorless oil was obtained in 75% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 16.0 Hz, 1H), 7.59 – 7.52 (m, 1H), 7.39 – 7.34 (m, 1H), 7.32 – 7.27 (m, 1H), 6.03 (d, *J* = 16.0 Hz, 1H), 4.05 (s, 3H), 2.38 (s, 3H), 1.56 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.18, 152.39, 136.19, 134.88, 131.59, 130.70, 126.02, 123.30, 123.23, 120.68, 119.52, 115.71, 80.69, 53.93, 28.38, 10.78.

IR (neat, cm^{-1}): ν 3359, 3053, 2977, 1698, 1626, 1455, 1145, 1065, 1025.

HRMS (ESI) m/z Calcd for $C_{18}H_{21}NNaO_4^+$: 338.1362, Found 338.1372.



(*E*)-Methyl 2-(3-*tert*-butoxy-3-oxoprop-1-enyl)-1H-indole-1-carboxylate (60c1)

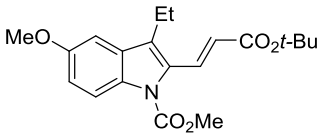
A colorless oil was obtained in 71% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (dd, *J* = 15.8 Hz, 0.9 Hz, 1H), 8.13 (dd, *J* = 8.5 Hz, 0.9 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.35 (ddd, *J* = 8.5 Hz, 7.2 Hz, 1.3 Hz, 1H), 7.30 – 7.26 (m, 1H), 6.97 (s, 1H), 6.34 (d, *J* = 15.8 Hz, 1H), 4.09 (s, 3H), 1.54 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.82, 152.08, 137.31, 136.11, 134.63, 128.81, 125.66, 123.57, 121.73, 121.10, 115.82, 110.41, 80.55, 53.94, 28.23.

IR (neat, cm^{-1}): ν 2977, 1715, 1625, 1440, 1368, 1160, 1121, 1072.

HRMS (ESI) m/z Calcd for $C_{17}H_{19}NNaO_4^+$: 324.1206, Found 324.1192.



(*E*)-Methyl 2-(3-*tert*-butoxy-3-oxoprop-1-enyl)-3-ethyl-5-methoxy-1H-indole-1-carboxylate (60d1)

A white solid was obtained in 78% yield by following general procedure.

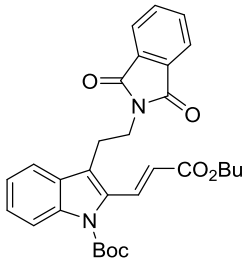
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.5 Hz, 1H), 7.96 (d, *J* = 16.1 Hz, 1H), 7.00 – 6.94 (m, 2H), 6.02 (d, *J* = 16.1 Hz, 1H), 4.03 (s, 3H), 3.88 (s, 3H), 2.80 (q, *J* = 7.6 Hz, 2H), 1.55 (s, 9H), 1.30 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.19, 156.29, 152.39, 134.82, 131.74, 131.13, 130.72, 126.61, 122.27, 116.74, 114.55, 101.88, 80.75, 55.84, 53.89, 28.39, 18.28, 15.00.

m.p. 116–118 ℃;

IR (neat, cm^{-1}): ν 2971, 2934, 1737, 1705, 1625, 1479, 1366, 1144, 1025.

HRMS (ESI) m/z Calcd for $C_{20}H_{25}NNaO_5$ $[M+Na]^+$: 382.1624, Found 382.1623.



(*E*)-*tert*-Butyl 2-(3-butoxy-3-oxoprop-1-enyl)-3-(2-(1, 3-dioxoisoindolin-2-yl)ethyl)-1H-indole-1-carboxylate (60f1)

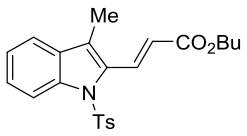
A colorless oil was obtained in 73% yield by following general procedure.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.3 Hz, 1H), 7.97 (d, *J* = 16.2 Hz, 1H), 7.89 – 7.83 (m, 2H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.73 – 7.68 (m, 2H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.31 – 7.26 (m, 1H), 6.35 (d, *J* = 16.2 Hz, 1H), 4.25 (t, *J* = 6.7 Hz, 2H), 4.09 – 3.88 (m, 2H), 3.24 – 3.09 (m, 2H), 1.76 – 1.70 (m, 2H), 1.66 (s, 9H), 1.53 – 1.44 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.09, 166.75, 150.09, 136.58, 135.86, 134.04, 132.35, 132.16, 129.48, 126.02, 123.34, 120.65, 119.77, 119.37, 115.69, 84.72, 64.61, 37.74, 30.90, 28.26, 24.34, 19.29, 13.95.

IR (neat, cm^{-1}): ν 2959, 1771, 1715, 1632, 1455, 1361, 1287, 1166, 1107.

HRMS (ESI) m/z Calcd for $C_{30}H_{32}N_2NaO_6^+$: 539.2125, Found 539.2172.



(*E*)-Butyl 3-(3-methyl-1-(4-methylbenzene-sulfonyl)-1H-indol-2-yl)acrylate (60g1)

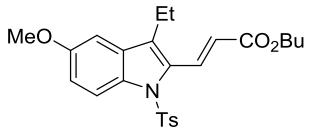
A colorless oil was obtained in 70% yield by following general procedure.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 – 8.21 (m, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.41 – 7.37 (m, 1H), 7.30 – 7.26 (m, 1H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.11 (d, *J* = 16.1 Hz, 1H), 4.27 (t, *J* = 6.7 Hz, 2H), 2.30 – 2.32 (m, 6H), 1.75 (dt, *J* = 14.6 Hz, 6.8 Hz, 2H), 1.52 – 1.43 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.62, 145.00, 137.20, 135.00, 134.64, 131.83, 131.49, 129.74, 126.77, 126.56, 124.15, 123.43, 122.55, 119.93, 115.49, 64.83, 30.88, 21.66, 19.36, 13.94, 11.04.

IR (neat, cm^{-1}): ν 2959, 1712, 1628, 1450, 1372, 1311, 1175, 1133.

HRMS (ESI) m/z Calcd for $C_{23}H_{25}NNaO_4S^+$: 434.1396, Found 434.1401.



(*E*)-Butyl 3-(3-ethyl-5-methoxy-1-(4-methylbenzenesulfonyl)-1H-indol-2-yl)acrylate (60h1)

A white solid was obtained in 76% yield by following general procedure.

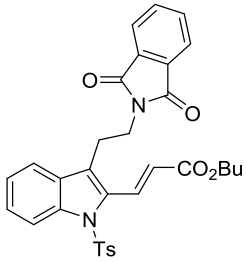
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 16.1 Hz, 1H), 8.10 (d, *J* = 9.1 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.98 (dd, *J* = 9.1 Hz , 2.5 Hz, 1H), 6.85 (d, *J* = 2.5 Hz, 1H), 6.10 (d, *J* = 16.1 Hz, 1H), 4.26 (t, *J* = 6.8 Hz, 2H), 3.84 (s, 3H), 2.71 (q, *J* = 7.6 Hz, 2H), 2.30 (s, 3H), 1.74 (dt, *J* = 14.6 Hz, 6.8 Hz, 2H), 1.53 – 1.41 (m, 2H), 1.16 (t, *J* = 7.6 Hz, 3H), 0.99 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.71, 157.05, 144.89, 134.70, 134.64, 132.28, 131.93, 130.09, 129.65, 126.83, 121.72, 116.92, 115.20, 102.21, 64.93, 55.83, 30.94, 21.74, 19.42, 18.52, 14.66, 14.01.

m.p. 146–147 ℃.

IR (neat, cm^{-1}): ν 2954, 1713, 1630, 1450, 1311, 1176, 1163.

HRMS (ESI) m/z Calcd for $C_{25}H_{29}NNaO_5S^+$ 478.1659, Found 478.1664.



(*E*)-Butyl 3-(3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1-(4-methylbenzene-sulfonyl)-1Hindol-2-yl)acrylate (60j1)

A white solid was obtained in 76% yield by following general procedure.

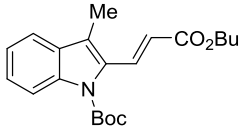
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 16.2 Hz, 1H), 7.87 – 7.78 (m, 2H), 7.75 – 7.69 (m, 2H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.40 – 7.34 (m, 1H), 7.32 – 7.26 (m, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.38 (d, *J* = 16.2 Hz, 1H), 4.28 (t, *J* = 6.8 Hz, 2H), 3.84 – 3.79 (m, 2H), 3.14 – 3.06 (m, 2H), 2.32 (s, 3H), 1.76 (dt, *J* = 14.6 Hz, 6.8 Hz, 2H), 1.59 – 1.40 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$):) δ 168.11, 166.37, 145.16, 137.27, 135.05, 134.21, 133.78, 133.01, 132.14, 130.48, 129.86, 126.87, 126.66, 124.46, 123.49, 123.02, 122.71, 119.89, 115.59, 64.95, 37.42, 30.93, 24.55, 21.78, 19.39, 14.05.

m.p. 149–151 ℃.

IR (neat, cm^{-1}): ν = 2959, 2873, 1771, 1713, 1632, 1449, 1174, 1090.

HRMS (ESI) m/z Calcd for $C_{32}H_{30}N_2NaO_6S^+$: 593.1717, Found 593.1733.



(*E*)-*Tert*-butyl 2-(3-butoxy-3-oxoprop-1-enyl)-3-methyl-1H-indole-1-carboxylate

A white solid was obtained in 72% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 – 8.13 (m, 1H), 8.08 (dd, *J* = 16.1 Hz, 0.7 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.36 (ddd, *J* = 8.4 Hz, 7.2 Hz, 1.3 Hz, 1H), 7.31 – 7.25 (m, 1H), 6.10 (d, *J* = 16.1 Hz, 1H), 4.23 (t, *J* = 6.7 Hz, 2H), 2.39 (s, 3H), 1.78 – 1.67 (m, 2H), 1.67 (s, 9H), 1.52 – 1.38 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).

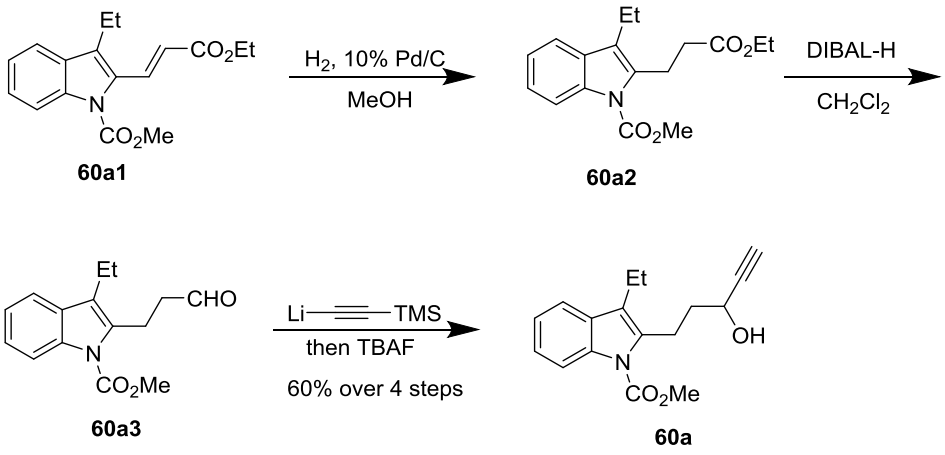
^{13}C NMR (101 MHz, $CDCl_3$):) δ 167.06, 150.36, 136.77, 136.61, 131.41, 130.51, 126.01, 123.04, 120.56, 120.30, 119.50, 115.66, 84.50, 64.62, 30.96, 28.35, 19.38, 13.95, 10.73.

m.p. 45–46 ℃.

IR (neat, cm^{-1}): ν = 2959, 2931, 2872, 1731, 1630, 1455, 1354, 1331, 1283, 1145, 1065.

HRMS (ESI) m/z Calcd for $C_{21}H_{27}NNaO_4^+$: 380.1832, Found 380.1832.

General preparation of alkynylindole substrates for Au(I)-catalyzed cycliczation and characterization data



Methyl 2-(3-hydroxypent-4-ynyl)-3-methyl-1H-indole-1-carboxylate (60a)

To a solution of conjugate ester (1.1 g, 3.6 mmol) in anhydrous methanol (10.0 mL) was added 10% Pd/C (110 mg). The resulting mixture was stirred under hydrogen atmosphere (56 psi) for 1 h before it was filtrated through a short pad of silica gel to afford reduced ester, which was used for the next step without further purification.

The ester was dissolved in anhydrous dichloromethane and the solution was cooled to -78 ℃ before the addition of the solution of DIBAL-H (1.0 M in hexane, 4.3 mL, 4.3 mmol) dropwise. The reaction mixture was stirred for 2 h at -78 ℃ before it was treated with saturated aqueous solution of Rochelle salt (10.0 mL) at -78 ℃. After being stirred for 1 h at r.t., the layers were separated. The aqueous layer was extracted with ether, and the combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give aldehyde as a yellow oil, which was used for the next step without further purification.

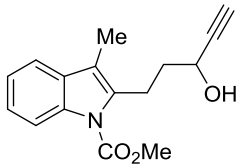
A solution of *n*-BuLi (1.6 M in hexanes, 4.5 mL, 7.2 mmol) was added to a solution of trimethylsilylacetylene (1.06 mL, 7.5 mmol) in anhydrous THF (20.0 mL) at -78 ℃. The resulting mixture was stirred for 30 min before the addition of the solution of aldehyde in anhydrous THF (3.0 mL) dropwise. The reaction mixture was stirred for 1 hour at the same temperature before it was quenched with water, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford a yellow oil, which was then dissolved in anhydrous THF (10.0 mL) and cooled to 0 ℃. Tetrabutylammonium fluoride (1.0 M in THF, 3.6 mL, 3.6 mmol) was added dropwise to the above solution, and the resulting mixture was stirred for 10 min at 0 ℃. After the reaction was terminated by the addition of water (20.0 mL), the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to produce a crude oil, which was purified by column chromatography (hexanes/ethyl acetate = 5:1) to afford alkynylindole (616 mg, 2.16 mmol) as a colorless oil in 60% yield over 4 steps.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (dd, *J* = 7.1 Hz, 2.1 Hz, 1H), 7.48 (dd, *J* = 6.5 Hz, 2.5 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.26 – 7.21 (m, 1H), 4.46 (td, *J* = 6.1 Hz, 2.9 Hz, 1H), 4.05 (s, 3H), 3.20 (m, 2H), 2.71 (q, *J* = 7.6 Hz, 2H), 2.53 – 2.49 (d, *J* = 4.0 Hz,1H), 2.23 (d, *J* = 5.5 Hz, 1H), 2.05 (dt, *J* = 10.8 Hz, 6.6 Hz, 2H), 1.22 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 152.76, 135.88, 135.40, 130.02, 123.98, 122.97, 122.11, 118.45, 115.95, 84.84, 73.22, 61.78, 53.69, 37.90, 22.28, 17.38, 15.13.

IR (neat, cm^{-1}): ν 3288, 2963, 1731, 1458, 1442, 1360, 1330, 1216, 1136.

HRMS (ESI) m/z calcd for $C_{17}H_{20}NO_3^+$: 286.1437, Found: 286.1441.



Methyl 2-(3-hydroxypent-4-ynyl)-3-methyl-1H-indole-1-carboxylate 48

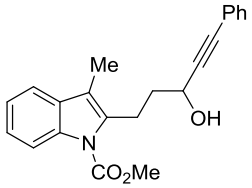
A colorless oil was obtained in 68% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$):) δ 8.06 – 8.02 (m, 1H), 7.46 – 7.42 (m, 1H), 7.32 – 7.23 (m, 1H), 7.27 – 7.21 (m, 1H), 4.42 (qd, *J* = 6.2 Hz, 2.0 Hz, 1H), 4.05 (s, 3H), 3.25 – 3.20 (m, 2H), 2.50 (d, *J* = 2.0 Hz, 1H), 2.23 (s, 3H), 2.09 – 2.00 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 152.60, 135.68, 135.55, 130.83, 123.95, 122.90, 118.21, 115.70, 115.67, 84.92, 73.07, 61.49, 53.56, 37.31, 22.33, 8.73.

IR (neat, cm^{-1}): ν 3435, 3288, 2955, 2864, 1732, 1459, 1379, 1254, 1221, 1136, 1057.

HRMS (ESI) m/z Calcd for $C_{16}H_{17}NNaO_3^+$: 294.1101, Found 294.1094.



Methyl 2-(3-hydroxy-5-phenylpent-4-ynyl)-3-methyl-1H-indole-1-carboxylate (60b)

A white solid was obtained in 70% yield by following general procedure.

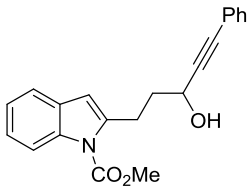
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.30 – 9.27 (m, 1H), 8.07 – 8.02 (m, 1H), 7.47 – 7.43 (m, 2H), 7.42 – 7.37 (m, 3H), 7.29 – 7.26 (m, 1H), 7.26 – 7.24 (m, 1H), 4.64 (q, *J* = 6.2 Hz, 1H), 4.05 (s, 3H), 3.28 (td, *J* = 8.8 Hz, 4.0 Hz, 2H), 2.26 (s, 3H), 2.13 (dd, *J* = 12.0 Hz, 8.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 152.75, 135.94, 135.70, 131.83, 130.99, 128.56, 128.46, 124.07, 123.00, 122.74, 118.34, 115.83, 115.80, 90.08, 85.15, 62.37, 53.66, 37.66, 22.59, 8.91.

m.p. 91–92 ℃.

IR (neat, cm^{-1}): ν 3435, 3051, 2954, 2863, 1732, 1459, 1354, 1220, 1135, 756.

HRMS (ESI) m/z Calcd for $C_{22}H_{21}NNaO_3^+$: 370.1414, Found 370.1426.



Methyl 2-(3-hydroxy-5-phenylpent-4-ynyl)-1H-indole-1-carboxylate (60c)

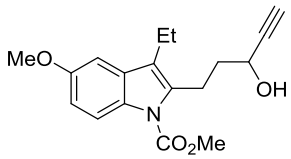
A colorless oil was obtained in 58% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.1 Hz, 1H), 7.47 (d, *J* = 7.1 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.35 – 7.31 (m, 3H), 7.30 – 7.26 (m, 1H), 7.26 – 7.19 (m, 1H), 6.46 (s, 1H), 4.71 (q, *J* = 6.1 Hz, 1H), 4.06 (s, 3H), 3.30 – 3.24 (m, 2H), 2.26 – 2.19 (m, 2H), 2.11 (d, *J* = 5.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 152.72, 141.09, 136.61, 131.89, 129.56, 128.66, 128.50, 123.89, 123.27, 122.68, 120.11, 115.87, 108.66, 89.87, 85.42, 62.44, 53.80, 37.18, 25.86.

IR (neat, cm^{-1}): ν 3434, 2954, 2853, 1739, 1456, 1332, 1214, 1059.

HRMS (ESI) m/z Calcd for $C_{21}H_{19}NNaO_3^+$ 356.1257, Found 356.1252.



Methyl 3-ethyl-2-(3-hydroxypent-4-ynyl)-5-methoxy-1H-indole-1-carboxylate (60d)

A white solid was obtained in 72% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 9.0 Hz, 1H), 6.93 (d, *J* = 2.6 Hz, 1H), 6.86 (dd, *J* = 9.0 Hz, 2.6 Hz, 1H), 4.45 (m, 1H), 4.03 (s, 3H), 3.87 (s, 3H), 3.18 (td, *J* = 8.0 Hz, 4.0 Hz, 2H),

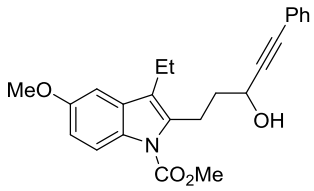
2.68 (q, *J* = 7.6 Hz, 2H), 2.50 (d, *J* = 2.1 Hz, 1H), 2.04 (t, *J* = 8.0 Hz, 2H), 1.21 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.09, 152.61, 136.24, 130.94, 130.43, 121.95, 116.73, 111.88, 101.56, 84.85, 73.19, 61.76, 55.89, 53.61, 37.85, 22.34, 17.37, 15.00.

m.p. 69–70 ℃.

IR (neat, cm^{-1}): ν 3451, 3284, 2961, 1731, 1608, 1478, 1442, 1364, 1262, 1131.

HRMS (ESI) m/z Calcd for $C_{18}H_{21}NNaO_4^+$: 338.1362, Found 338.1364.



Methyl 3-ethyl-2-(3-hydroxy-5-phenylpent-4-ynyl)-5-methoxy-1H-indole-1-carboxylate (60e)

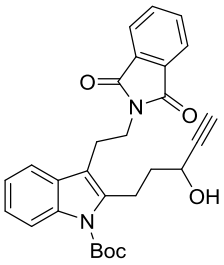
A colorless oil was obtained in 74% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$):) δ 7.94 (d, *J* = 9.0 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.34 – 7.28 (m, 3H), 6.93 (d, *J* = 2.6 Hz, 1H), 6.86 (dd, *J* = 9.0 Hz, 2.6 Hz, 1H), 4.69 (t, *J* = 5.5 Hz, 1H), 4.02 (s, 3H), 3.87 (s, 3H), 3.31 – 3.21 (m, 2H), 2.71 (q, *J* = 7.6 Hz, 2H), 2.13 (m, 2H), 1.23 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.09, 152.61, 136.40, 131.80, 130.96, 130.49, 128.53, 128.44, 122.75, 121.91, 116.73, 111.86, 101.55, 90.07, 85.12, 62.44, 55.88, 53.57, 38.11, 22.57, 17.41, 14.99.

IR (neat, cm^{-1}): ν 3442, 2956, 1731, 1454, 1333, 1221, 1067.

HRMS (ESI) m/z Calcd for $C_{24}H_{25}NNaO_4^+$: 414.1676, Found 414.1667.



***Tert*-butyl 3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-2-(3-hydroxypent-4-ynyl)-1H-indole-1-carboxylate (60f)**

A white solid was obtained in 65% yield by following general procedure.

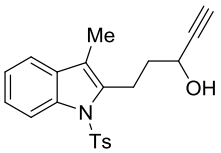
m.p. 140–141 ℃;

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 – 8.04 (m, 1H), 7.88 – 7.84 (m, 2H), 7.76 – 7.71 (m, 2H), 7.68 (dt, *J* = 7.9 Hz, 3.1 Hz, 1H), 7.26 – 7.21 (m, 2H), 4.52 – 4.42 (m, 1H), 3.98 – 3.81 (m, 2H), 3.35 – 3.20 (m, 2H), 3.06 (t, *J* = 8.3 Hz, 2H), 2.91 (d, *J* = 6.1 Hz, 1H), 2.50 (d, *J* = 2.1 Hz, 1H), 2.28 – 2.10 (m, 2H), 1.70 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.95, 142.71, 141.91, 137.62, 132.89, 129.31, 128.08, 127.96, 126.94, 125.83, 123.79, 121.69, 118.14, 90.00, 82.26, 58.02, 48.51, 33.08, 31.33, 29.91, 28.39, 23.64, 21.61.

IR (neat, cm^{-1}): ν 3466, 3287, 2930, 2359, 1770, 1712, 1457, 1365, 1328, 1161.

HRMS (ESI) m/z Calcd for $C_{28}H_{29}N_2O_5^+$: 473.2086, Found 473.2088.



5-(3-Methyl-1-(4-methylbenzene-sulfonyl)-1H-indol-2-yl)pent-1-yn-3-ol (60g)

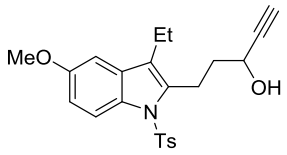
A colorless oil was obtained in 72% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J* =8.0 Hz, 1H), 7.56 (d, *J* = 8.2 Hz,, 2H), 7.37 (d, *J* =8.0 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 4.43 (m, 1H), 3.17 (td, *J* = 7.2 Hz, 3.0 Hz, 2H), 2.50 (d, *J* = 2.1 Hz, 1H), 2.31 (s, 3H), 2.22 – 2.10 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.75, 136.84, 135.93, 135.83, 131.60, 129.93, 126.41, 124.53, 123.71, 118.70, 117.98, 115.35, 84.72, 73.30, 61.65, 38.16, 22.20, 21.75, 9.16.

IR (neat, cm^{-1}): ν 3291, 2924, 1453, 1360, 1232, 1170, 1042.

HRMS (ESI) m/z Calcd for $C_{21}H_{22}NO_3S^+$: 368.1315, Found 368.1317.



5-(3-Ethyl-5-methoxy-1-(4-methylbenzene-sulfonyl)-1H-indol-2-yl)pent-1-yn-3-ol (60h)

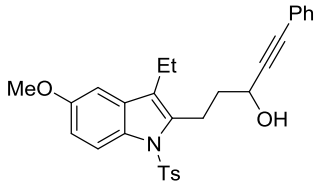
A colorless oil was obtained in 71% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (dd, *J* = 9.0 Hz, 0.4 Hz, 1H), 7.51(d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.87 (dd, *J* = 9.0 Hz, 2.6 Hz, 1H), 6.83 (d, *J* = 2.2 Hz, 1H), 4.47 (td, *J* = 6.3 Hz, 2.1 Hz, 1H), 3.83 (s, 3H), 3.22 – 3.04 (m, 2H), 2.60 (m, 2H), 2.51 (d, *J* = 2.1 Hz, 1H), 2.30 (s, 3H), 2.16 (td, *J* = 7.8 Hz, 6.4 Hz, 2H), 1.13 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.71, 144.60, 136.47, 135.61, 131.86, 131.62, 129.80, 126.31, 124.48, 116.47, 112.40, 101.85, 84.68, 73.28, 61.73, 55.83, 38.71, 22.28, 21.70, 17.66, 14.77.

IR (neat, cm^{-1}): ν 3289, 2966, 1598, 1447, 1359, 1214, 1175, 1036.

HRMS (ESI) m/z Calcd for $C_{23}H_{25}NNaO_4S^+$: 434.1397, Found 434.1400.



5-(3-Ethyl-5-methoxy-1-(4-methylbenzene-sulfonyl)-1H-indol-2-yl)-1-phenylpent-1-yn-3-ol (60i)

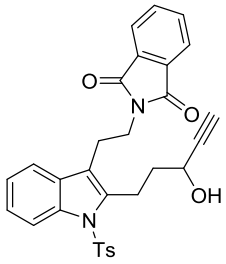
A colorless oil was obtained in 77% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$):) δ 8.07 (d, *J* = 9.0 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.47 – 7.41 (m, 2H), 7.34 – 7.29 (m, 3H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.87 (dd, *J* = 9.0 Hz, 2.6 Hz, 1H), 6.84 – 6.80 (m, 1H), 4.69 (t, *J* = 6.2 Hz, 1H), 3.83 (s, 3H), 3.27 – 3.10 (m, 2H), 2.62 (q, *J* = 7.6 Hz, 2H), 2.30 (s, 3H), 2.28 – 2.16 (m, 2H), 1.17 – 1.10 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.73, 144.57, 136.64, 135.75, 131.89, 131.69, 129.81, 128.58, 128.47, 126.35, 124.39, 122.79, 116.50, 112.39, 101.85, 89.87, 85.25, 62.49, 55.84, 38.97, 22.49, 21.72, 17.73, 14.79.

IR (neat, cm^{-1}): ν 3345, 3027, 2942, 2876, 1603, 1496, 1453, 1046, 747.

HRMS (ESI) m/z Calcd for $C_{29}H_{29}NNaO_4S^+$: 510.1509, Found 510.1514.



2-(2-(2-(3-Hydroxypent-4-ynyl)-1-(4-methylbenzene-sulfonyl)-1H-indol-3-yl)ethyl)-isoindoline-1,3-dione (60j)

A colorless oil was obtained in 69% yield by following general procedure.

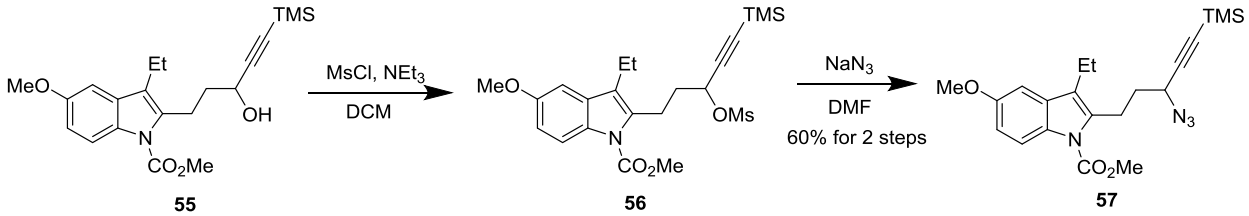
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 – 8.15 (m, 1H), 7.89 – 7.78 (m, 2H), 7.77 – 7.70 (m, 2H), 7.65 – 7.60 (m, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.33 – 7.23 (m, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.50 (tdd, *J* = 6.8 Hz, 4.6 Hz, 2.1 Hz, 1H), 3.88 – 3.78 (m, 2H), 3.31 – 3.13 (m, 2H), 3.03 – 2.97 (m, 2H), 2.53 (d, *J* = 2.1 Hz,1H), 2.33 (s, 3H), 2.28 – 2.11 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.46, 144.89, 137.56, 136.85, 1315.98, 134.33, 132.19, 130.28, 130.02, 126.45, 124.73, 123.97, 123.58, 118.81, 118.01, 115.36, 84.71, 73.26, 61.53, 39.00, 37.77, 29.92, 23.89, 22.21, 21.79.

IR (neat, cm^{-1}): ν 3349, 2963, 1713, 1596, 1447, 1358, 1218, 1180.

HRMS (ESI) m/z Calcd for $C_{30}H_{27}N_2O_5S^+$: 527.1635, Found 527.1637.

General preparation of alkynylindoles containing nitrogen nucleophiles and characterization data



Methyl 2-(3-azido-5-(trimethylsilyl)pent-4-ynyl)-3-ethyl-5-methoxy-1H-indole-1-carboxylate (57)

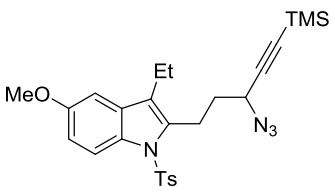
A solution of alcohol (1.94 g, 5.0 mmol) in anhydrous dichloromethane (10.0 mL) was cooled to -20 ℃ before triethylamine (1.70 mL, 12.0 mmol) was added dropwise. The mixture was stirred at -20 ℃ for 10 min; then tosyl chloride (0.47 mL, 6.0 mmol) was added over a period of 10 min. The resulting mixture was stirred at 0 ℃ for 2 h before quenched with saturated aqueous $NaHCO_3$ (10.0 mL) and extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered through a pad of celite, and the solvent was removed in vacuo to yield crude mesylate. A mixture of mesylate and sodium azide (0.98 g, 15.0 mmol) in anhydrous DMF (20.0 mL) was stirred at RT for 12 h. After removal of DMF in vacuo, water was added to the reaction solution and the mixture was extracted with ethyl acetate. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a crude oil, which was purified by column chromatography (hexanes/ethyl acetate = 20:1) to afford azide (1.24 g, 3.0 mmol) as a yellowish oil in 60% yield (2 steps):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 9.0 Hz, 1H), 6.93 (d, *J* = 2.6 Hz, 1H), 6.87 (dd, *J* = 9.0 Hz, 2.6 Hz, 1H), 4.18 – 4.12 (m, 1H), 4.03 (s, 3H), 3.87 (s, 3H), 3.21 – 3.08 (m, 2H), 2.68 (q, *J* = 7.6 Hz, 2H), 2.00 (q, *J* = 7.4 Hz, 2H), 1.22 (t, *J* = 7.6 Hz, 3H), 0.22 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.13, 152.39, 135.55, 130.83, 130.52, 122.11, 116.73, 112.03, 112.01, 101.56, 100.48, 92.73, , 55.88, 55.86, 53.53, 53.24, 35.51, 23.13, 17.38, 15.00, 0.05.

IR (neat, cm^{-1}): ν 2961, 2106, 1732, 1478, 1442, 1363, 1262, 1217, 1131, 845.

HRMS (ESI) m/z Calcd for $C_{21}H_{28}N_4NaO_3Si^+$: 435.1823, Found 435.1840.



2-(3-Azido-5-(trimethylsilyl)pent-4-ynyl)-3-ethyl-5-methoxy-1-tosyl-1H-indole (60m1)

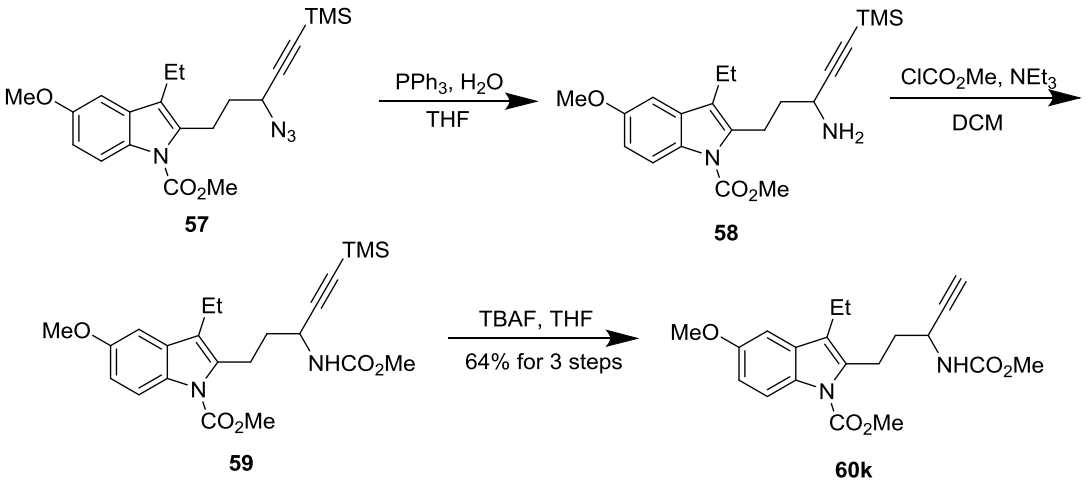
A yellowish oil was obtained in 56% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 9.0 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.85 (dd, *J* = 9.0 Hz, 2.6 Hz, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 4.12 (t, *J* = 6.7 Hz, 1H), 3.81 (s, 3H), 3.14 – 2.99 (m, 2H), 2.58 (q, *J* = 7.6 Hz, 2H), 2.29 (s, 3H), 2.15 – 2.05 (m, 2H), 1.11 (t, *J* = 7.6 Hz, 3H), 0.20 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.75, 144.59, 135.87, 135.67, 131.77, 131.66, 129.80, 126.33, 124.68, 116.51, 112.53, 101.87, 100.37, 92.70, 55.83, 55.81, 53.16, 36.26, 29.90, 23.03, 21.72, 17.68, 14.78, 0.07.

IR (neat, cm^{-1}): ν 2964, 2106, 1599, 1475, 1362, 1216, 1035, 744.

HRMS (ESI) m/z Calcd for $C_{26}H_{32}N_4NaO_3SSi^+$: 531.1857, Found 531.1843.



Methyl 3-ethyl-5-methoxy-2-(3-(methoxycarbonylamino)pent-4-ynyl)-1H-indole-1-carboxylate (60k)

To the solution of the azide in anhydrous THF (10.0 mL) at room temperature was added triphenylphosphine (0.87 g, 3.3 mmol) and water (0.54 mL, 30.0 mmol). The resulting mixture was heated to 55 ℃ for 1.5 h before it was cooled to room temperature and concentrated in vacuo. The crude amine was then dissolved in anhydorus dichloromethane (10.0 mL) and cooled to 0 ℃. To the cooled solution triethylamine (1.65 mL, 6.0 mmol) was added followed by the addition of methyl chloroformate (0.25 mL, 3.2 mmol). The resulting solution was stirred at

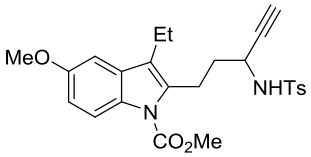
room temperature for 3 h before quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, and the solvents were removed in vacuo to give the crude, which was used for the next step without further purification. Tetrabutylammonium fluoride (1.0 M in THF, 3.0 mL, 3.0 mmol) was added to a solution of the crude in THF (3.0 mL) at 0 ℃, and the resulting mixture was stirred for 10 min at 0 ℃. After the reaction was terminated by the addition of water, the organic layer was extracted with ethyl acetate. The combined organic parts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude oil, which was purified by column chromatography (hexanes/ethyl acetate = 3:1) to afford propargyl carbamate (715 mg, 1.92 mmol) as a colorless oil in 64% yield over 3 steps.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 9.0 Hz, 1H), 6.94 (d, *J* = 2.5 Hz, 1H), 6.88 (dd, *J* = 9.0 Hz, 2.5 Hz, 1H), 5.25-5.15 (br, 1H), 4.60-4.50 (br, 1H), 4.05 (s, 3H), 3.88 (s, 3H), 3.72 (s, 3H), 3.17 – 3.04 (m, 2H), 2.67 (q, *J* = 7.6 Hz, 2H), 2.37 (d, *J* = 2.3 Hz, 1H), 2.04 – 1.94 (m, 2H), 1.22 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.38, 156.13, 152.48, 135.86, 130.89, 130.43, 121.89, 116.75, 111.98, 101.55, 83.23, 77.43, 71.58, 55.90, 55.88, 53.60, 52.53, 43.31, 35.78, 23.10, 17.40, 15.07.

IR (neat, cm^{-1}): ν 3295, 2964, 1731, 1723, 1522, 1475, 1361, 1242.

HRMS (ESI) m/z Calcd for $C_{20}H_{25}N_2O_5^+$: 373.1758, Found 373.1759.



Methyl 3-ethyl-5-methoxy-2-(3-(4-methylphenylsulfonamido)pent-4-ynyl)-1H-indole -1-carboxylate (60l)

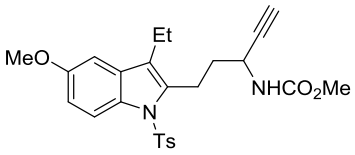
A colorless oil was obtained in 69% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 9.0 Hz, 1H), 7.77 (d, *J* = 6.4 Hz, 2H), 7.27 (d, *J* = 6.4 Hz, 2H), 6.92 (d, *J* = 2.6 Hz,1H), 6.86 (dd, *J* = 9.0 Hz, 2.6 Hz, 1H), 5.09 (d, *J* = 8.2 Hz, 1H), 4.15 (qd, *J* = 6.7 Hz, 2.3 Hz, 1H), 4.02 (s, 3H), 3.87 (s, 3H), 3.17 – 3.00 (m, 2H), 2.62 (q, *J* = 7.6 Hz, 2H), 2.41 (s, 3H), 2.15 (d, *J* = 2.3 Hz, 1H), 1.99 – 1.96 (m, 2H), 1.17 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.07, 152.39, 143.60, 137.36, 135.45, 130.77, 130.39, 129.62, 127.49, 121.97, 116.71, 111.99, 101.52, 81.86, 72.88, 55.85, 53.63, 45.38, 36.45, 22.87, 21.68, 17.32, 15.00.

IR (neat, cm^{-1}): ν 3274, 2961, 2929, 1731, 1607, 1478, 1442, 1332, 1161, 1090.

HRMS (ESI) m/z Calcd for $C_{25}H_{28}N_2NaO_5S^+$: 491.1611, Found 491.1614.



Methyl 5-(3-ethyl-5-methoxy-1-(4-methylbenzene-sulfoyl)-1H-indol-2-yl)pent-1-yn-3-ylcarbamate (60m)

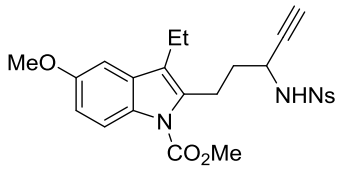
A colorless oil was obtained in 52% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 9.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.87 (dd, *J* = 9.0 Hz, 2.5 Hz, 1H), 6.83 (d, *J* = 2.5 Hz, 1H), 5.18 (d, *J* = 7.2 Hz, 1H), 4.55 – 4.45 (br, 1H), 3.83 (s, 3H), 3.72 (s, 3H), 3.10 – 2.96 (m, 2H), 2.57 (q, *J* = 7.6 Hz, 2H), 2.34 (d, *J* = 2.3 Hz, 1H), 2.31 (s, 3H), 2.19 – 2.06 (m, 2H), 1.12 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.74, 156.50, 144.64, 135.98, 135.74, 131.72, 131.63, 129.84, 126.29, 124.36, 116.39, 112.54, 101.88, 83.18, 71.57, 55.82, 52.55, 43.24, 36.61, 23.11, 21.69, 17.68, 14.81.

IR (neat, cm^{-1}): ν 3294, 2965, 1723, 1599, 1520, 1475, 1360, 1246, 1163, 1047.

HRMS (ESI) m/z Calcd for $C_{25}H_{28}N_2NaO_5S^+$: 491.1611, Found 491.1599.



Methyl 3-ethyl-5-methoxy-2-(3-(2-nitrophenylsulfonamido)pent-4-ynyl)-1H-indole-1-carboxylate (60n)

A colorless oil was obtained in 65% yield by following general procedure.

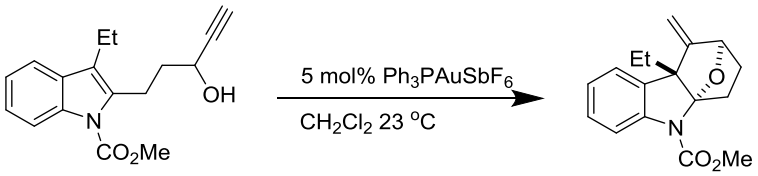
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 – 8.15 (m, 1H), 7.95 – 7.92 (m, 2H), 7.78 – 7.70 (m, 2H), 6.94 (d, *J* = 2.3 Hz, 1H), 6.89 (dd, *J* = 9.0 Hz, 2.6 Hz, 1H), 5.96 – 5.85 (br, 1H), 4.35 – 4.24 (br, 1H), 4.06 (s, 3H), 3.89 (s, 3H), 3.29 – 3.08 (m, 2H), 2.67 (q, *J* = 7.6 Hz, 2H), 2.11 – 2.02 (m, 3H), 1.21 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.06, 152.33, 147.92, 135.16, 134.18, 133.84, 132.91, 131.66, 130.72, 130.37, 125.50, 122.08, 116.71, 112.07, 112.04, 101.48, 80.97, 73.40, 55.80, 53.65, 46.09, 36.26, 22.95, 17.34, 15.04.

IR (neat, cm^{-1}): ν 3286, 2962, 2932, 1728, 1608, 1541, 1478, 1363, 1170, 1132.

HRMS (ESI) m/z Calcd for $C_{24}H_{26}N_3O_7S^+$: 500.1486, Found 500.1473.

General procedure of Au(I)-catalyzed tandem cyclization reaction



60a **61a**

The catalyst solution was prepared by addition of Ph_3PAuCl (2.5 mg, 0.005 mmol) to a suspension of $AgSbF_6$ (1.7 mg, 0.005 mmol) in anhydrous dichloromethane (0.50 mL) at room temperature. The suspension was stirred for 20 min at room temperature under Argon atmosphere. The resulting catalyst solution was then added to a solution of substrate (28.5 mg, 0.10 mmol) in anhydrous dichloromethane (0.50 mL) dropwise at room temperature. The

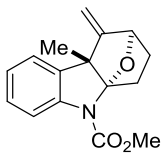
resulting mixture was kept stirring at room temperature until TLC showed that there was no starting material left (about 1 h). The reaction mixture was then filtered through a short pad of silica gel. The filtrate was concentrated in vacuo, and purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to afford tetracyclic indoline (23.7 mg, 0.083 mmol) as a colorless oil in 83% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.6 Hz, 1H), 7.26 – 7.21 (m, 2H), 7.07 (td, *J* = 7.5 Hz, 1.0 Hz, 1H), 5.10 (d, *J* = 0.7 Hz, 1H), 5.01 (s, 1H), 4.59 (d, *J* = 6.1 Hz, 1H), 3.91 (s, 3H), 3.06 – 3.03 (m, 1H), 2.27 (tdd, *J* = 12.4 Hz, 6.1 Hz, 3.5 Hz, 1H), 2.10 (ddd, *J* = 12.4 Hz, 9.0 Hz, 3.5 Hz, 1H), 1.90 (dq, *J* = 15.2 Hz, 7.6 Hz, 1H), 1.79 (ddd, *J* = 12.2 Hz, 9.1 Hz, 5.5 Hz, 1H), 1.72 – 1.60 (m, 1H), 0.60 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.21, 154.02, 133.34, 128.04, 123.93, 123.29, 115.94, 105.62, 102.47, 77.15, 60.11, 53.09, 33.23, 30.82, 29.93, 23.54, 8.90.

IR (neat, cm^{-1}): ν 2957, 2923, 1720, 1458, 1442, 1360, 1242, 1132.

HRMS (ESI) m/z Calcd for $C_{17}H_{20}NO_3^+$: 286.1437, Found 286.1443.



Methyl 9-methyl-10-methylidene-14-oxa-2-azatetracyclo[9.2.1.0 ^{1,9}.0 ^{3,8}]tetradeca-3,5,7-triene-2-carboxylate (48)

A white solid was obtained in 83% yield by following general procedure.

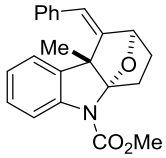
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.2 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.19 (td, *J* = 8.2 Hz, 1.3 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 5.10 (s, 1H), 5.00 (s, 1H), 4.57 (t, *J* = 11.8 Hz, 1H), 3.89 (s, 3H), 2.99 (td, *J* = 12.1 Hz, 5.0 Hz, 1H), 2.23 (tdd, *J* = 12.4 Hz, 6.1 Hz, 3.6 Hz, 1H), 2.09 (ddd, *J* = 12.4 Hz, 9.0 Hz, 3.6 Hz, 1H), 1.76 (ddd, *J* = 12.3 Hz, 9.0 Hz, 5.4 Hz, 1H), 1.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.91, 154.36, 141.66, 136.09, 127.94, 123.96, 122.88, 116.20, 106.05, 102.42, 77.28, 56.86, 53.11, 30.62, 26.25, 23.40.

m.p. 105–106 ℃.

IR (neat, cm^{-1}): ν 2956, 2924, 1720, 1479, 1440, 1361, 1316, 1240, 1101.

HRMS (ESI) m/z Calcd for $C_{16}H_{17}NNaO_3^+$: 294.1101, Found 294.1090.



Methyl (10*E*)-9-methyl-10-(phenylmethylidene)-14-oxa-2-azatetracyclo[9.2.1.0 ^{1,9}.0 ^{3,8}]tetradeca-3,5,7-triene-2-carboxylate (61b)

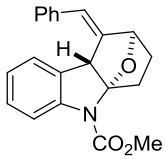
A colorless oil was obtained in 65% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.2 Hz, 1H), 7.44 – 7.33 (m, 5H), 7.15 – 7.08 (m, 1H), 6.79 (td, *J* = 7.5 Hz, 1.0, 1H), 6.59 (dd, *J* = 7.6 Hz, 0.9 Hz, 1H), 5.96 (d, *J* = 4.9 Hz, 1H), 4.55 (dd, *J* = 6.3 Hz, 5.0 Hz, 1H), 3.93 (s, 3H), 3.38 – 3.29 (m, 1H), 2.52 – 2.37 (m, 1H), 2.37 – 2.29 (m, 1H), 2.04 (ddd, *J* = 11.7 Hz, 9.2 Hz, 2.7 Hz, 1H), 1.48 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.37, 143.06, 139.55, 134.45, 129.07, 128.09, 128.36, 128.09, 126.66, 124.34, 123.28, 115.48, 102.66, 72.79, 52.52, 33.82, 30.02, 26.17, 23.24.

IR (neat, cm^{-1}): ν 3581, 2923, 1715, 1463, 1360, 1236.

HRMS (ESI): m/z: Calcd for $C_{22}H_{21}NNaO_3^+$: 370.1414, Found 370.1409.



Methyl (10*E*)-10-(phenylmethylidene)-14-oxa-2-azatetracyclo[9.2.1.0^{1,9}.0^{3,8}]tetradeca-3,5,7-triene-2-carboxylate (61c)

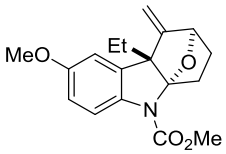
A colorless oil was obtained in 67% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.6 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.45 – 7.36 (m, 3H), 7.14 (t, *J* = 7.9 Hz, 1H), 6.75 (td, *J* = 7.9 Hz, 5.0 Hz, 1H), 6.50 (d, *J* = 7.5 Hz, 1H), 6.41 (dd, *J* = 4.7 Hz, 1.9 Hz, 1H), 4.74 – 4.61 (m, 1H), 4.11 – 4.14 (m, 1H), 3.94 (s, 3H), 3.42 (t, *J* = 11.9 Hz, 1H), 2.37 (ddd, *J* = 11.5 Hz, 7.0 Hz, 4.4 Hz, 1H), 2.12 (td, *J* = 9.2 Hz, 4.6 Hz, 1H), 2.00 (dt, *J* = 12.6 Hz, 8.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.28, 142.97, 139.46, 134.36, 130.91, 129.48, 128.98, 128.36, 128.00, 126.57, 124.25, 123.19, 115.39, 99.91, 72.70, 52.43, 33.73, 29.93, 14.30.

IR (neat, cm^{-1}): ν 3608, 3583, 2924, 1714, 1477, 1358, 1259.

HRMS (ESI) m/z Calcd for $C_{21}H_{19}NNaO_3^+$: 356.1257, Found 356.1250.



Methyl 9-ethyl-6-methoxy-10-methylidene-14-oxa-2-azatetracyclo[9.2.1.0^{1,9}.0^{3,8}]tetradeca-3,5,7-triene-2-carboxylate (61d)

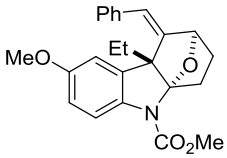
A colorless oil was obtained in 85% yield by following general procedure.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.9 Hz, 1H), 7.42 – 7.28 (m, 5H), 6.67 (dd, *J* = 8.9 Hz, 2.7 Hz, 1H), 6.18 (d, *J* = 2.7 Hz, 1H), 5.94 (d, *J* = 5.0 Hz, 1H), 4.53 – 4.49 (m, 1H), 3.90 (s, 3H), 3.56 (s, 3H), 3.36 (t, *J* = 10.7 Hz, 1H), 2.41 – 2.29 (m, 3H), 2.03 (dt, *J* = 11.5 Hz, 7.1 Hz, 2H), 1.95 (dt, *J* = 15.9 Hz, 7.9 Hz, 1H), 1.89 (dd, *J* = 14.1 Hz, 7.5 Hz, 1H), 0.54 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 157.12, 156.57, 153.92, 136.74, 134.82, 116.49, 112.24, 110.00, 109.97, 105.87, 102.49, 102.45, 77.10, 60.16, 55.87, 52.96, 33.11, 30.79, 23.59, 8.88.

IR (neat, cm^{-1}): ν 2964, 1720, 1484, 1367, 1114, 1087, 1025, 1065.

HRMS (ESI) m/z Calcd for $C_{18}H_{21}NNaO_4^+$: 338.1362, Found 338.1353.



Methyl (10E)-9-ethyl-6-methoxy-10-(phenylmethylidene)-14-oxa-2-azatetracyclo [9.2.1.0^{1,9}.0^{3,8}]tetradeca-3,5,7-triene-2-carboxylate (61e)

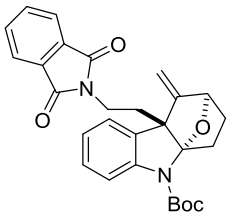
A colorless oil was obtained in 75% yield by following general procedure.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.2 Hz, 1H), 7.42 – 7.28 (m, 5H), 6.67 (dd, *J* = 8.2 Hz, 2.7 Hz, 1H), 6.18 (t, *J* = 2.7 Hz, 1H), 5.94 (d, *J* = 5.0 Hz, 1H), 4.53 – 4.49 (m, 1H), 3.90 (s, 3H), 3.56 (s, 3H), 3.36 (t, *J* = 10.7 Hz, 1H), 2.41 – 2.29 (m, 2H), 2.03 (dt, *J* = 11.5 Hz, 7.1 Hz, 1H), 1.95 (dt, *J* = 15.9 Hz, 7.9 Hz, 1H), 1.89 (dd, *J* = 14.1 Hz, 7.5 Hz, 1H), 0.54 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.99, 154.20, 141.31, 140.55, 136.66, 132.98, 130.78, 127.98, 127.68, 115.88, 112.67, 110.84, 102.73, 71.23, 56.60, 55.63, 52.86, 33.38, 31.41, 30.00, 23.31, 9.42.

IR (neat, cm^{-1}): ν 2925, 1713, 1481, 1362, 1272, 1100, 1045.

HRMS (ESI) m/z Calcd for $C_{24}H_{26}NO_4^+$: 392.1856, Found 392.1854.



tert-Butyl 9-[2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)ethyl]-10-methylidene-14-oxa-2-azatetracyclo[9.2.1.0^{1,9}.0^{3,8}]tetradeca-3,5,7-triene-2-carboxylate (61f)

A white solid was obtained in 84% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 – 7.76 (m, 3H), 7.72 – 7.65 (m, 2H), 7.36 (dd, *J* = 7.5 Hz, 1.0 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.11 (td, *J* = 8.0 Hz, 2.6 Hz, 1H), 5.10 (s, 1H), 5.01 (s, 1H),

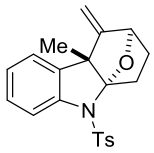
4.59 (d, *J* = 6.0 Hz, 1H), 3.45 (td, *J* = 12.9 Hz, 4.1 Hz, 1H), 3.20 (td, *J* = 12.6 Hz, 5.5 Hz, 1H), 3.10 (ddd, *J* = 13.5 Hz, 12.1 Hz, 5.2 Hz, 1H), 2.44 (ddd, *J* = 12.4 Hz, 9.0 Hz, 3.4 Hz, 1H), 2.34 – 2.19 (m, 1H), 1.99 – 1.87 (m, 1H), 1.79 (ddd, *J* = 12.3 Hz, 9.1 Hz, 5.6 Hz, 1H), 1.63 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.11, 156.65, 152.32, 143.06, 134.14, 132.18, 132.03, 128.47, 124.12, 123.32, 123.24, 116.26, 105.51, 102.78, 82.85, 58.44, 38.39, 33.93, 30.86, 29.90, 28.59, 23.63.

m.p. 165–167 ℃.

IR (neat, cm^{-1}): ν 2978, 1772, 1713, 1477, 1398.95, 1368, 1247, 1161, 1075.

HRMS (ESI) m/z Calcd for $C_{28}H_{29}N_2O_5^+$: 473.2071, Found 473.2086.



9-Methyl-2-(4-methylbenzenesulfonyl)-10-methylidene-14-oxa-2-azatetracyclo [9.2.1.0^{1,9}.0^{3,8}]tetradeca-3,5,7-triene (61g)

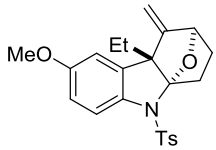
A colorless oil was obtained in 85% yield by following general procedure.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 – 7.89 (m, 2H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.24 – 7.21 (m, 2H), 7.18 – 7.14 (m, 1H), 7.05 – 6.99 (m, 1H), 5.07 (s, 1H), 4.98 (s, 1H), 4.56 (d, *J* = 6.0 Hz, 1H), 3.04 – 2.93 (m, 1H), 2.36 (s, 3H), 2.20 (ddd, *J* = 15.7 Hz, 8.9 Hz, 3.6 Hz, 2H), 1.78 – 1.70 (m, 1H), 1.23 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.36, 144.26, 141.37, 136.65, 136.15, 129.64, 128.08, 127.97, 124.22, 123.29, 114.95, 107.58, 102.61, 77.34, 57.66, 30.39, 25.55, 24.05, 21.79.

IR (neat, cm^{-1}): ν 2924, 1475, 1458, 1360, 1163, 1094, 1025.

HRMS (ESI) m/z Calcd for $C_{21}H_{22}NO_3S^+$: 368.1315, Found 368.1318.



9-Ethyl-6-methoxy-2-(4-methylbenzenesulfonyl)-10-methylidene-14-oxa-2-azatetracyclo

[9.2.1.0^{1,9}.0^{3,8}]tetradeca-3,5,7-triene (61h)

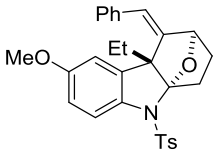
A colorless oil was obtained in 88% yield by following general procedure.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 – 7.90 (m, 2H), 7.43 (d, *J* = 8.9 Hz, 1H), 7.25 – 7.21 (m, 2H), 6.75 (d, *J* = 2.6 Hz, 1H), 6.70 (dd, *J* = 8.9 Hz, 2.7 Hz, 1H), 5.02 (s, 1H), 4.95 (s, 1H), 4.53 (d, *J* = 5.8 Hz, 1H), 3.74 (s, 3H), 3.06 – 2.93 (m, 1H), 2.36 (s, 3H), 2.25 – 2.17 (m, 2H), 1.83 (dq, *J* = 15.2 Hz, 7.6 Hz, 1H), 1.77 – 1.70 (m, 1H), 1.67 – 1.58 (m, 1H), 0.66 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.63, 156.55, 144.06, 136.83, 136.34, 134.70, 129.56, 129.55, 129.53, 128.20, 128.19, 128.17, 114.71, 112.34, 110.63, 107.49, 102.62, 77.29, 60.95, 55.88, 32.82, 30.41, 24.28, 21.76, 8.74.

IR (neat, cm^{-1}): ν 2934, 1475, 1456, 1359, 1162, 1099, 1027.

HRMS (ESI) m/z Calcd for $C_{23}H_{25}NNaO_4S^+$: 434.1397, Found 434.1402.



(10*E*)-9-ethyl-6-methoxy-2-(4-methylbenzenesulfonyl)-10-(phenylmethylidene)-14-oxa-2-azatetracyclo[9.2.1.0^{1,9}.0^{3,8}]tetradeca-3,5,7-triene (61i)

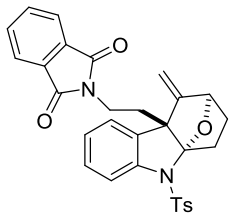
A colorless oil was obtained in 64% yield by following general procedure.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 – 8.02 (m, 2H),7.53 (d, *J* = 8.1 Hz, 1H), 7.41 – 7.25 (m,5H),), 6.67 (dd, *J* = 8.1 Hz, 2.5 Hz, 1H), 6.15 (t, *J* = 2.5 Hz, 1H), 5.92 (d, *J* = 5.0 Hz, 1H), 4.52 – 4.43 (m, 1H), 3.56 (s, 3H), 3.36 (t, *J* = 10.8 Hz, 1H), 2.42 – 2.26 (m, 2H), 2.23 (s, 3H), 2.04 (dt, *J* = 11.5 Hz, 7.2 Hz, 2H), 1.95 (dt, *J* = 15.9 Hz, 7.6 Hz, 1H), 1.89 (dd, *J* = 14.2 Hz, 7.6 Hz, 1H), 0.54 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.92, 141.24, 140.48, 136.59, 132.91, 130.71, 127.82, 127.61,126.51, 124.23, 115.81, 112.60, 110.77, 102.66, 71.16, 56.53, 55.56, 52.79, 33.31, 31.34, 29.93, 23.24 , 21.78, 9.35.

IR (neat, cm^{-1}): ν 2941, 1472, 1456, 1364, 1160, 1099.

HRMS (ESI) m/z Calcd for $C_{29}H_{29}NNaO_4S^+$: 510.1509, Found 510.1503.



2-{2-[2-(4-methylbenzenesulfonyl)-10-methylidene-14-oxa-2-azatetracyclo[9.2.1.0^{1,9}.0^{3,8}] tetradeca-3,5,7-trien-9-yl]ethyl}-2,3-dihydro-1H-isoindole-1,3-dione (61j)

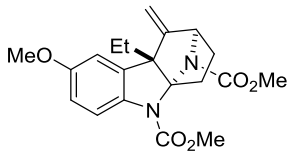
A colorless oil was obtained in 82% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.4 Hz, 2H), 7.79 (m, 2H), 7.69 (m, 2H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.32 (dd, *J* = 7.5 Hz, 0.9 Hz, 1H), 7.26 – 7.20 (m, 1H), 7.11 (td, *J* = 7.5 Hz, 1.0 Hz, 1H), 5.06 (s, 1H), 4.98 (s, 1H), 4.57 (d, *J* = 5.9 Hz, 1H), 3.57 – 3.45 (m, 1H), 3.15 (dd, *J* = 12.9 Hz, 5.7 Hz, 1H), 2.60 (td, *J* = 9.2 Hz, 4.5 Hz, 1H), 2.35 – 2.26 (m, 4H), 2.17 (td, *J* = 13.1 Hz, 4.9 Hz, 1H), 1.98 – 1.89 (m, 1H), 1.84 – 1.73 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.03, 155.80, 144.36, 142.27, 136.50, 134.17, 132.20, 131.89, 129.68, 128.67, 128.32, 124.62, 123.79, 123.37, 114.50, 106.94, 103.14, 59.44, 38.29, 33.61, 30.51, 29.93, 24.28, 21.77.

IR (neat, cm^{-1}): ν 2924, 1772, 1713, 1458, 1399, 1365, 1164, 1090, 1038.

HRMS (ESI) m/z Calcd for $C_{30}H_{27}N_2O_5S^+$: 527.1635, Found 527.1636.



2,14-Dimethyl 9-ethyl-6-methoxy-10-methylidene-2,14-diazatetracyclo[9.2.1.0^{1,9}.0^{3,8}] tetradeca-3,5,7-triene-2,14-dicarboxylate (61k)

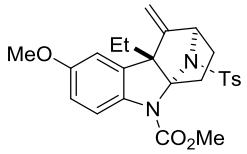
A colorless oil was obtained in 78% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.3 Hz, 1H), 6.92 (d, *J* = 2.6 Hz, 1H), 6.79 (dd, *J* = 8.3 Hz, 2.6 Hz, 1H), 5.95 – 6.45 (br, 1H), 5.27 (s, 1H), 5.16 (s, 1H), 4.75 – 4.83 (br, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.69 (s, 3H), 3.00 – 2.85 (m, 1H), 2.01-2.04 (m, 1H), 1.82 (t, *J* = 7.4 Hz, 2H), 0.78 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.65, 155.93, 153.08, 146.44, 144.36, 135.08, 134.42, 116.23, 112.32, 111.87, 108.23, 105.31, 55.85, 53.32, 53.04, 52.46, 48.78, 35.19, 32.60, 29.91, 8.59.

IR (neat, cm^{-1}): ν 3095, 1720, 1442, 1432, 1261, 1105, 1129.

HRMS (ESI) m/z Calcd for $C_{20}H_{25}N_2O_5^+$: 373.1758, Found 373.1752.



Methyl 9-ethyl-6-methoxy-14-(4-methylbenzenesulfonyl)-10-methylidene-2,14-diazatetracyclo[9.2.1.0^{1,9}.0^{3,8}]tetradeca-3,5,7-triene-2-carboxylate (61l)

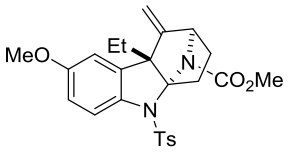
A colorless oil was obtained in 75% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (m, 3H), 7.28 – 7.21 (m, 2H), 6.74 (dd, *J* = 8.9 Hz, 2.7 Hz, 1H), 6.70 (d, *J* = 2.6 Hz, 1H), 5.92 (s, 1H), 5.20 (s, 1H), 5.10 (d, *J* = 1.2 Hz, 1H), 4.59 (d, *J* = 9.0 Hz, 1H), 4.33 (dd, *J* = 15.1 Hz, 6.2 Hz, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 2.65 (ddd, *J* = 17.1 Hz, 6.4 Hz, 3.2 Hz, 1H), 2.41 (s, 3H), 2.14 (dt, *J* = 17.1 Hz, 6.0 Hz, 1H), 1.79 – 1.68 (m, 1H), 1.66 – 1.57 (m, 1H), 0.62 (q, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.99, 153.01, 145.45, 144.24, 143.58, 138.12, 134.81, 134.53, 129.84, 127.23, 116.14, 111.99, 111.49, 111.15, 105.17, 60.63, 55.86, 53.06, 52.67, 52.04, 35.90, 32.74, 29.92, 29.59, 21.77, 21.29, 14.42, 8.60.

IR (neat, cm^{-1}): ν 3274, 2923, 1713, 1481.71, 1275, 1158, 1093, 1035.

HRMS (ESI) m/z Calcd for $C_{25}H_{29}N_2O_5S^+$: 469.1792, Found 469.1778.



Methyl 9-ethyl-6-methoxy-2-(4-methylbenzenesulfonyl)-10-methylidene-2,14-diazatetracyclo[9.2.1.0^{1,9}.0^{3,8}]tetradeca-3,5,7-triene-14-carboxylate (61m)

A white solid was obtained in 79% yield by following general procedure.

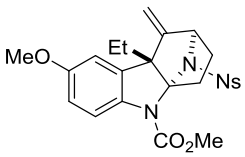
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.8 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.51 – 7.44 (m, 1H), 7.19 (d, *J* = 8.1 Hz, 1H), 6.80– 6.82 (m, 2H), 6.01 (dd, *J* = 5.3 Hz , 3.3 Hz, 1H), 5.11 (s, 1H), 5.05 (s, 1H), 4.70 – 4.53 (m, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 2.85 (ddd, *J* = 17.7 Hz, 7.2 Hz, 3.3 Hz, 1H), 2.35 (s, 3H), 2.11 (dt, *J* = 17.7 Hz, 6.0 Hz, 1H), 1.35 – 1.27 (m, 1H), 0.60 – 0.53 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.70, 156.56, 145.58, 144.80, 144.61, 135.49, 134.76, 134.63, 129.63, 129.39, 127.46, 116.93, 112.72, 112.05, 108.84, 108.27, 55.83, 54.01, 52.46, 48.54, 34.26, 32.71, 29.93, 21.77, 8.28.

m.p. 129–130 ℃.

IR (neat, cm^{-1}): ν 2924, 1724, 1525, 1476, 1363, 1252, 1171, 1088, 1037.

HRMS (ESI) m/z Calcd for $C_{25}H_{28}N_2NaO_5S^+$: 491.1611, Found 491.1598.



Methyl 9-ethyl-6-methoxy-10-methylidene-14-(4-nitrobenzenesulfonyl)-2,14-diazatetracyclo[9.2.1.0^{1,9}.0^{3,8}]tetradeca-3,5,7-triene-2-carboxylate (61n)

A colorless oil was obtained in 70% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (dd, *J* = 7.8 Hz, 1.4 Hz, 1H), 7.70 (td, *J* = 7.6 Hz, 1.5 Hz, 1H), 7.62 (td, *J* = 7.7 Hz, 1.4 Hz, 2H), 7.56 (dd, *J* = 7.9 Hz, 1.4 Hz, 1H), 6.65 (dd, *J* = 8.9 Hz, 2.7 Hz, 1H), 6.15 (m, 2H), 5.79 (d, *J* = 9.5 Hz, 1H), 5.32 (s, 1H), 5.18 (s, 1H), 4.55 (dt, *J* = 9.2

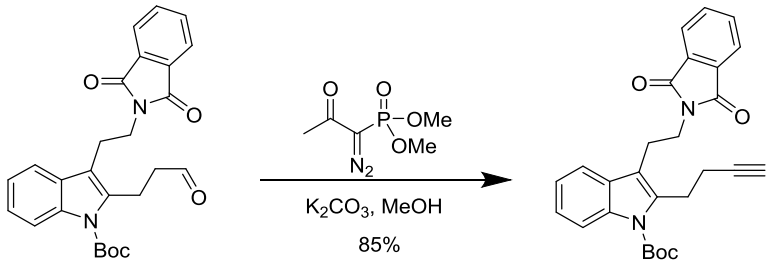
Hz, 4.5 Hz, 1H), 3.92 (s, 3H), 3.74 (s, 3H), 2.65 (ddd, *J* = 16.6 Hz, 4.9 Hz, 3.1 Hz, 1H), 2.44 (ddd, *J* = 16.6 Hz, 7.1 Hz, 4.4 Hz, 1H), 1.71 (dq, *J* = 14.7 Hz, 7.3 Hz, 2H), 1.61 – 1.44 (m, 1H), 0.66 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.70, 152.94, 147.44, 145.25, 144.76, 135.02, 134.98, 134.63, 133.32, 132.56, 131.25, 125.67, 115.99, 113.80, 111.20, 109.87, 104.89, 60.63, 55.60, 54.88, 53.16, 51.46, 38.10, 29.93, 14.42, 8.91.

IR (neat, cm^{-1}): ν 2923, 2852, 1714, 1539, 148, 1363, 1275, 1165.

HRMS (ESI) m/z Calcd for $C_{24}H_{26}N_3O_7S^+$: 500.1486, Found 500.1481.

General preparation of alkynylindoles and characterization data



***tert*-Butyl 2-(but-3-ynyl)-3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1H-indole-1-carboxylate (90)**

To a solution of aldehyde (4.46 g. 10 mmol) in anhydrous MeOH (20 mL) was added a solution of Ohira-Bestmann Reagent (4.80 g, 25 mmol) in MeOH (5 mL) and K_2CO_3 (4.15 g, 30 mmol) at 0 ℃. The resulting mixture was stirred at room temperature for 3 h before quenched with an aqueous solution of NH_4Cl. The aqueous phase was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give an oil. Purification by column chromatography (hexanes/ethyl acetate = 3:1) afforded alkyne (3.76 g, 8.5 mmol) as a white solid in 85% yield.

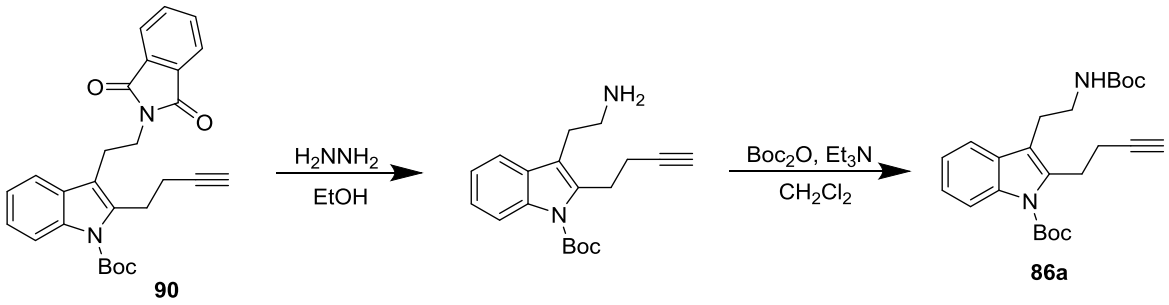
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 – 8.07 (m, 1H), 7.89 – 7.82 (m, 2H), 7.73 – 7.68 (m, 3H), 7.26 – 7.20 (m, 2H), 3.96 – 3.85 (m, 2H), 3.32 (t, *J* = 7.3 Hz, 2H), 3.17 – 3.04 (m, 2H), 2.59 (td, *J* = 7.3 Hz, 2.6 Hz, 2H), 1.99 (t, *J* = 2.6 Hz, 1H), 1.69 (s, 9H).

^{13}C NMR (101 MHz, $CDCl^3$) δ 168.43, 150.52, 136.14, 136.09, 134.23, 134.16, 132.33, 129.56, 124.23, 123.44, 122.99, 118.58, 116.39, 115.96, 84.19, 83.70, 69.59, 38.09, 28.43, 26.25, 23.78, 19.62.

m.p. 183–184 ℃.

IR (neat, cm^{-1}): ν = 3305, 2930, 1769, 1712, 1457, 1363, 1165, 1107.

HRMS (ESI) m/z Calcd for $C_{27}H_{26}N_2NaO_4^+$: 465.1785, Found 465.1779.



***tert*-Butyl 2-(but-3-ynyl)-3-(2-(tert-butoxycarbonylamino)ethyl)-1H-indole-1-carboxylate (86a)**

To a solution of phthalimide (3.76 g, 8.5 mmol) in absolute EtOH (20 mL) was added anhydrous hydrazine (3.0 mL, 85 mmol). The resulting mixture was heated to 60 ℃ for 1 h before it was cooled to room temperature, filtered through a pad of celite. The filtrate was concentrated in vacuo to give 7a-2 as colorless oil, which was used in the next step without purification. To a solution of amine in anhydrous dichloromethane was added triethylamine (2.4 mL, 17.0 mmol) and Boc_2O (2.3 g, 10.2 mmol) at 0 ℃. The resulting mixture was stirred at room temperature for 3 h before an aqueous solution of NH_4Cl was added. The aqueous phase was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give an oil. Purification by column chromatography

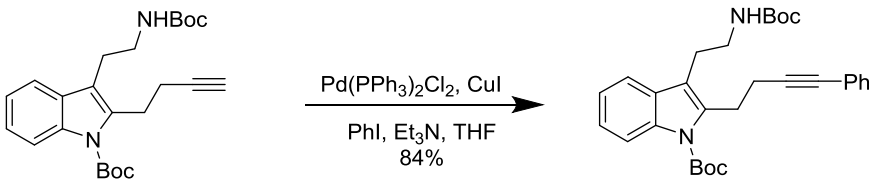
(hexanes/ethyl acetate = 5:1) afforded alkynylindole (2.84 g, 6.9 mmol) as a colorless oil in 81% yield over 2 steps.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.32 – 7.18 (m, 2H), 4.70 – 4.50 (br, 1H), 3.38 (d, *J* = 5.8 Hz, 2H), 3.24 (t, *J* = 7.4 Hz, 2H), 2.92 (t, *J* = 6.8 Hz, 2H), 2.53 (td, *J* = 7.4 Hz, 2.6 Hz, 2H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.69 (s, 9H), 1.44 (s, 9H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.04, 150.51, 136.15, 136.05, 129.75, 124.20, 122.85, 118.62, 117.11, 115.91, 84.17, 83.75, 79.42, 69.49, 40.74, 28.61, 28.42, 26.25, 24.99, 19.62.

IR (neat, cm^{-1}): ν 2976, 2927, 1725, 1367, 1164, 1133.

HRMS (ESI) m/z Calcd for $C_{24}H_{33}N_2O_4^+$: 413.2435, Found 413.2441.



86a **86b**

***tert*-Butyl 3-(2-(tert-butoxycarbonylamino)ethyl)-2-(4-phenylbut-3-ynyl)-1H-indole-1-carboxylate (86b)**

A solution of alkyne (144 mg, 0.35 mmol) and iodobenzene (195 mg, 0.53 mmol) in THF (2 mL) was frozen with liquid nitrogen and thoroughly degassed under high vacuum. $Pd(PPh_3)_2Cl_2$ (28 mg, 0.04 mmol) was added and the resulting suspension was degassed in the same way. Freshly purified copper(I) iodide (16 mg, 0.08 mmol) was added and degassing was repeated. Previously degassed triethylamine (0.5 mL, 3.5 mmol) was added and the mixture was heated at 70 ℃ for 2 h. The reaction was allowed to cool to room temperature, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with ethyl acetate. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give brown foam, which was purified by

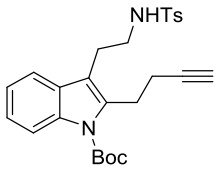
column chromatography (hexanes/ethyl acetate = 10:1) to afford desired product (140 mg, 0.29 mmol) as a colorless oil in 84% yield:

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 7.4 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.27 – 7.16 (m, 5H), 4.68 – 4.45 (br, 1H), 3.50 – 3.27 (m, 4H), 2.97 (t, *J* = 6.8 Hz, 2H), 2.75 (t, *J* = 7.4 Hz, 2H), 1.71 (s, 9H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.05, 150.57, 136.28, 136.20, 131.65, 129.81, 128.39, 127.82, 124.18, 123.89, 122.86, 118.58, 117.13, 115.92, 89.43, 84.17, 81.65, 79.40, 40.75, 28.60, 28.44, 26.51, 24.97, 20.67.

IR (neat, cm^{-1}): ν 2974, 2928, 1708, 1476, 1382, 1172.

HRMS (ESI): Calcd for $C_{30}H_{36}N_2NaO_4^+$: 511.2567, Found 511.2559.



***tert*-Butyl 2-(but-3-ynyl)-3-(2-(4-methylphenylsulfonamido)ethyl)-1H-indole-1-carboxylate (86c)**

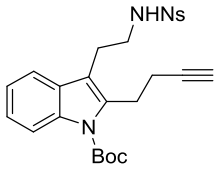
A colorless oil was obtained in 88% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.3 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.35 – 7.21 (m, 3H), 7.17 (t, *J* = 7.4 Hz, 1H), 4.51 (t, *J* = 6.3 Hz, 1H), 3.24 (q, *J* = 6.9 Hz, 2H), 3.18 (t, *J* = 7.2 Hz, 2H), 2.92 (t, *J* = 7.1 Hz, 2H), 2.49 (td, *J* = 7.2 Hz, 2.6 Hz, 2H), 2.40 (s, 3H), 1.90 (t, *J* = 2.6 Hz, 1H), 1.69 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.42, 143.63, 136.98, 136.41, 136.18, 129.87, 129.25, 127.25, 124.37, 122.98, 118.25, 116.08, 115.88, 84.44, 83.71, 69.72, 43.14, 28.46, 26.12, 25.07, 21.78, 19.51.

IR (neat, cm^{-1}): ν 3291, 2927, 1727, 1457, 1325, 1158.

HRMS (ESI) m/z Calcd for $C_{26}H_{30}N_2NaO_4S^+$: 489.1819, Found 489.1800.



***tert*-Butyl 2-(but-3-ynyl)-3-(2-(2-nitrophenylsulfonamido)ethyl)-1H-indole-1-carboxylate (86d)**

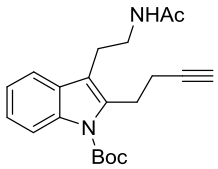
A colorless oil was obtained in 80% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.3 Hz, 1H), 7.98 – 7.93 (m, 1H), 7.73 – 7.69 (m, 1H), 7.58 (pd, *J* = 7.5 Hz, 1.7 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.16 – 7.09 (m, 1H), 5.38 (t, *J* = 5.8 Hz, 1H), 3.42 (dd, *J* = 13.1 Hz, 7.1 Hz, 2H), 3.18 (t, *J* = 7.2 Hz, 2H), 2.98 (t, *J* = 7.2 Hz, 2H), 2.48 (td, *J* = 7.2 Hz, 2.6 Hz, 2H), 1.91 (t, *J* = 2.6 Hz, 1H), 1.68 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.27, 147.65, 136.50, 136.12, 133.74, 133.56, 132.84, 130.83, 129.01, 125.49, 124.29, 122.90, 118.08, 116.11, 115.58, 84.46, 83.58, 69.68, 43.77, 29.90, 28.41, 26.15, 25.12, 19.54.

IR (neat, cm^{-1}): ν 3294, 2927, 1726, 1540, 1457, 1394, 1164.

HRMS (ESI) m/z Calcd for $C_{25}H_{27}N_3NaO_6S^+$: 520.1513, Found 520.1531.



***tert*-Butyl 2-(but-3-yn-1-yl)-3-(2-acetamidoethyl)-1H-indole-1-carboxylate (86e)**

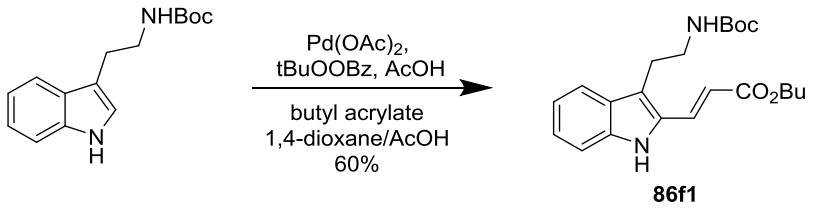
A colorless oil was obtained in 74% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 7.4 Hz, 1H), 7.56 – 7.51 (m, 1H), 7.33 – 7.26 (m, 1H), 7.26 – 7.20 (m, 1H), 5.65 – 5.56 (br, 1H), 3.52 (q, *J* = 6.8 Hz, 2H), 3.25 (t, *J* = 7.3 Hz, 2H), 2.94 (t, *J* = 7.0 Hz, 2H), 2.54 (td, *J* = 7.3 Hz, 2.6 Hz, 2H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.93 (s, 3H), 1.70 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.35, 150.52, 136.14, 136.05, 129.81, 124.32, 122.97, 118.52, 117.12, 116.01, 110.84, 84.31, 83.70, 69.60, 39.95, 28.45, 26.16, 24.46, 23.58, 19.63.

IR (neat, cm^{-1}): ν 3290, 2922, 2851, 1726, 1650, 1457, 1341, 1163.

HRMS (ESI): m/z: Calcd for $C_{21}H_{26}N_2NaO_3^+$: 377.1835, Found 377.1817.



86f1

(*E*)-Butyl 3-(3-(2-(*tert*-butoxycarbonylamino)ethyl)-1H-indol-2-yl)acrylate (86f1)

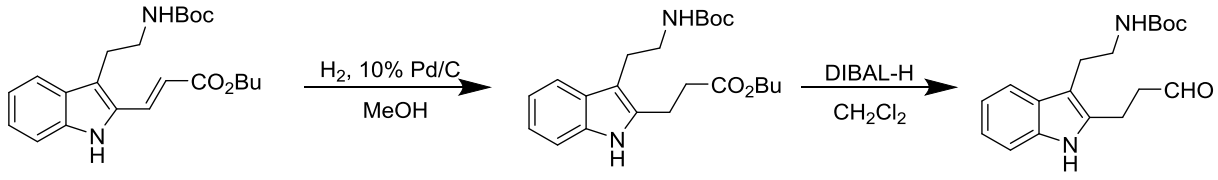
A colorless oil was obtained in 60% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 – 8.35 (br, 1H), 7.75 (d, *J* = 15.9 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.20 (d, *J* = 15.9 Hz, 1H), 4.65 – 4.52 (br, 1H), 4.22 (t, *J* = 6.6 Hz, 2H), 3.43 – 3.35 (m, 2H), 3.10 – 3.06 (m, 2H), 1.86 – 1.55 (m, 2H), 1.51 – 1.40 (m, 9H), 0.97 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.63, 156.13, 137.76, 132.06, 130.90, 128.48, 125.10, 120.14, 119.63, 114.97, 111.37, 79.40, 64.69, 41.66, 30.92, 28.57, 28.29, 25.03, 19.32, 19.22, 13.92.

IR (neat, cm-1): ν 3339, 2961, 1693, 1613, 1513, 1455, 1251, 1171, 1069, 739.

HRMS (ESI) Calcd for $C_{22}H_{31}N_2O_4^+$: 387.2278, Found 387.2289.



86f1 86f2

***tert*-Butyl 2-(2-(3-oxopropyl)-1H-indol-3-yl)ethylcarbamate (86f2)**

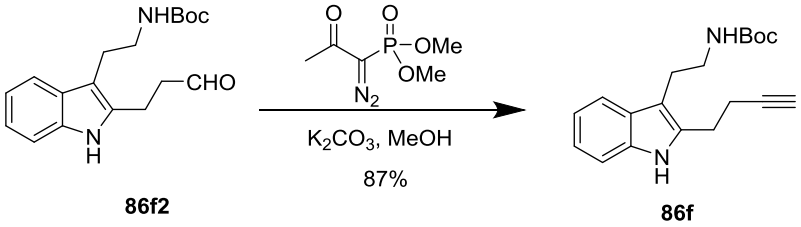
A colorless oil was obtained in 82% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (s, 1H), 8.40 – 8.31 (br, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.19 – 7.12 (m, 1H), 7.10 – 7.02 (m, 1H), 4.60 – 4.50 (br, 1H), 3.37 (dd, *J* = 12.6 Hz, 6.2 Hz, 2H), 3.12 – 2.97 (m, 2H), 2.94 – 2.86 (m, 4H), 1.43 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.34, 202.31, 156.13, 135.48, 134.99, 128.11, 121.43, 119.21, 118.20, 110.73, 108.43, 79.19, 44.27, 41.22, 28.50, 24.74, 18.08.

IR (neat, cm^{-1}): ν 3402, 3055, 2976, 2931, 2727, 1689, 1513, 1462, 1366, 1169, 741.

HRMS (ESI) Calcd for $C_{18}H_{25}N_2O_3^+$: 317.1860, Found 317.1867.



86f2 **86f**

***tert*-Butyl 2-(2-(but-3-ynyl)-1H-indol-3-yl)ethylcarbamate (86f)**

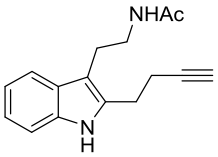
A colorless oil was obtained in 87 % yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.20 – 7.13 (m, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 4.70 – 4.56 (br, 1H), 3.38 (d, *J* = 6.4 Hz, 2H), 2.98 (t, *J* = 6.8 Hz, 2H), 2.91 (t, *J* = 6.6 Hz, 2H), 2.55 (td, *J* = 6.8 Hz, 2.6 Hz, 2H), 2.13 (t, *J* = 2.6 Hz, 1H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.14, 135.67, 135.00, 128.18, 121.77, 119.52, 118.54, 110.79, 109.19, 84.10, 79.29, 70.31, 41.20, 28.63, 25.00, 24.81, 19.47.

IR (neat, cm^{-1}): ν 3403, 3303, 2975, 2931, 1689, 1511, 1462, 1250, 1166.

HRMS (ESI) Calcd for $C_{19}H_{25}N_2O_2^+$: 313.1911, Found 313.1911.



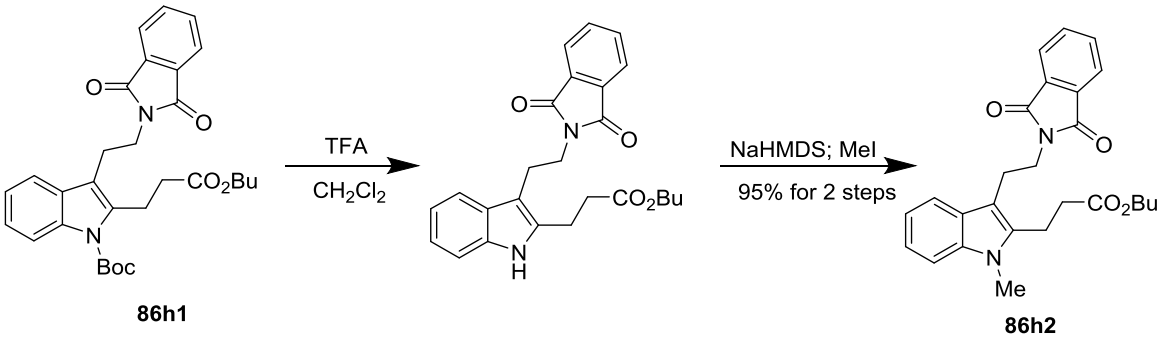
***N*-(2-(2-(But-3-ynyl)-1H-indol-3-yl)ethyl)acetamide (86g)**

A colorless oil was obtained in 84 % yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 – 8.31 (br, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.17 (t, J = 7.2 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 5.75 – 5.62 (br, 1H), 3.53 (dd, J = 12.9 Hz, 6.4 Hz, 2H), 3.04 – 2.87 (m, 4H), 2.55 (td, J = 6.9 Hz, 2.6 Hz, 2H), 2.11 (t, J = 2.5 Hz, 1H), 1.93 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.13, 135.67, 135.02, 128.22, 121.94, 119.75, 118.33, 110.95, 108.95, 83.99, 70.48, 40.61, 29.92, 24.93, 24.18, 23.37, 19.46.

HRMS (ESI) m/z Calcd for $C_{16}H_{19}N_2O^+$: 255.1492, Found 255.1480.



Butyl 3-(3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1-methyl-1H-indol-2-yl)propanoate (86h2)

To a solution of substrate (1.56 g, 3.0 mmol) in anhydrous dichloromethane (10 mL) was added trifluoroacetic acid (2.3 mL, 30.0 mmol). The resulting mixture was stirred at room temperature for 2 h before the solvents were removed in vacuo to give an oil, which was dissolved in anhydrous DMF (10 mL) and cooled to -50 ℃. A solution of NaHMDS (2.0 M in THF, 1.6 mL, 3.2 mmol) was added to the above solution. After 30 min, iodomethane (0.37 mL, 6.0 mmol) was added in one portion and the resulting mixture was slowly warmed to room temperature and

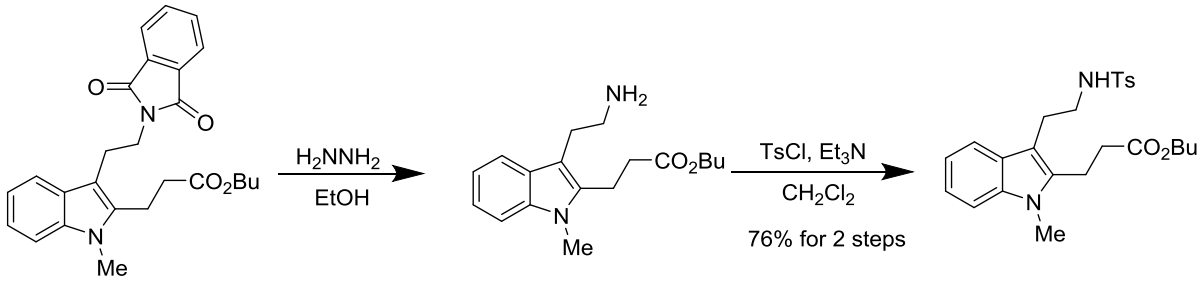
stirred for 2 h before it was quenched with water, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford a yellow oil, which was purified by column chromatography (hexanes/ethyl acetate = 10:1) to afford N-methyl indole (1.23 g, 2.85 mmol) as a colorless oil in 95% yield over 2 steps.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 – 7.86 (m, 2H), 7.77 – 7.76 (m, 3H), 7.31 (d, *J* = 5.8 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.16 – 7.11 (m, 1H), 4.15 (t, *J* = 6.7 Hz, 2H), 4.00 – 3.88 (m, 2H), 3.76 (s, 3H), 3.28 – 3.20 (m, 2H), 3.20 – 3.12 (m, 2H), 2.77 – 2.63 (m, 2H), 1.64 (dt, *J* = 14.6 Hz, 7.0 Hz, 2H), 1.46 – 1.34 (m, 2H), 0.99 – 0.92 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.61, 168.48, 136.99, 135.98, 134.03, 132.40, 127.66, 123.33, 121.39, 119.42, 118.54, 109.04, 108.14, 64.85, 38.91, 34.75, 30.78, 29.92, 29.87, 24.02, 20.03, 19.29, 13.91.

IR (neat, cm^{-1}): ν 2957, 1770, 1712, 1470, 1396, 1258, 1171, 1024.

HRMS (ESI) m/z Calcd for $C_{26}H_{28}N_2NaO_4^+$: 455.1914, Found 455.1934.



86h2 **86h3**

4-Methyl-*N*-(2-(1-methyl-2-(3-oxopropyl)-1H-indol-3-yl)ethyl)benzenesulfonamide (86h3)

To a solution of phthalimide (1.23 g, 2.85 mmol) in absolute EtOH (5 mL) was added anhydrous hydrazine (1.0 mL, 28.5 mmol). The resulting mixture was heated to 60 ℃ for 1 h before it was cooled to room temperature, filtered through a pad of celite. The filtrate was concentrated in vacuo to give amine as a crude oil, which was used in the next step without purification. To a solution of crude amine in anhydrous dichloromethane was added triethylamine (0.8 mL, 5.7 mmol) and TsCl (0.77 g, 3.42mmol) at 0 ℃. The resulting mixture was stirred at room

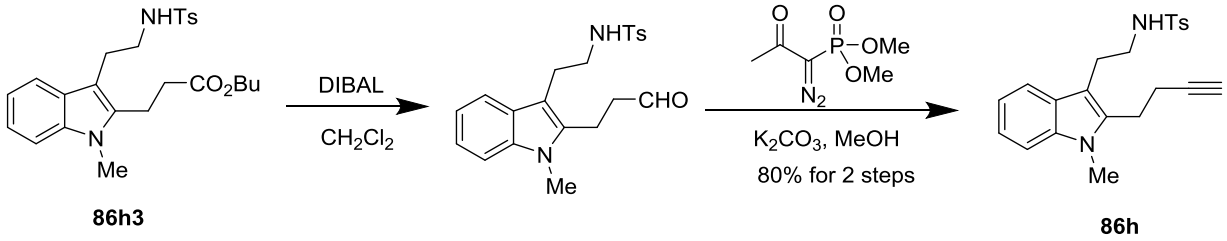
temperature for 10 h before quenched with an aqueous solution of NH_4Cl. The aqueous phase was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give an oil, which was purified by column chromatography (hexanes/ethyl acetate=5:1) to afford sulfonamide (1.05 g, 2.3 mmol) as a colorless oil in 81% yield over 2 steps.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 6.6 Hz, 2H), 7.21 – 7.15 (m, 2H), 7.07 – 7.00 (m, 1H), 4.45 (t, *J* = 6.2 Hz, 1H), 4.07 (t, *J* = 6.7 Hz, 2H), 3.67 (s, 3H), 3.21 (q, *J* = 6.7 Hz, 2H), 3.08 – 3.03 (m, 2H), 2.95 (t, *J* = 6.8 Hz, 2H), 2.56 – 2.50 (m, 2H), 2.40 (s, 3H), 1.62 – 1.53 (m, 2H), 1.32 (dt, *J* = 14.7 Hz, 7.5 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.44, 143.12, 136.91, 136.13, 129.72, 129.57, 127.14, 127.03, 121.30, 119.21, 118.06, 109.00, 107.36, 64.73, 43.58, 34.39, 30.59, 29.73, 29.67, 24.97, 21.53, 21.50, 19.74, 19.11, 13.75.

IR (neat, cm^{-1}): ν 3290, 2958, 2872, 1731, 1471, 1330, 1160.

HRMS (ESI): m/z: Calcd for $C_{25}H_{33}N_2O_4S^+$: 457.2156, Found 457.2144.



86h3 **86h**

***N*-(2-(2-(But-3-ynyl)-1-methyl-1H-indol-3-yl)ethyl)-4-methylbenzenesulfonamide (86h)**

Ester (1.05 g, 2.3 mmol) was dissolved in anhydrous dichloromethane and the solution was cooled to -78 ℃ before the addition of the solution of DIBAL-H (1.0 M in hexane, 2.76 mL, 2.76 mmol) dropwise. The reaction mixture was stirred for 1 h at -78 ℃ before it was treated with saturated aqueous solution of Rochelle salt (5.0 mL) at -78 ℃. After being stirred at room temperature for 1 h, the layers were separated. The aqueous layer was extracted with ether, and

the combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to produce aldehyde as a yellow oil, which was used for the next step without further purification. To a solution of aldehyde in anhydrous MeOH (5 mL) was added a solution of Ohira-Bestmann Reagent (1.03 g, 5.75 mmol) in MeOH (5 mL) and K_2CO_3 (0.96 g, 6.9 mmol) at 0 ℃. The resulting mixture was stirred at room temperature for 3 h before quenched with an aqueous solution of NH_4Cl. The aqueous phase was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give an oil, which was purified by column chromatography (hexanes/ethyl acetate = 5:1) to afford alkyne (0.70 g, 1.8 mmol) as a white solid in 80% yield over 2 steps:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 – 7.59 (m, 2H), 7.37 – 7.32 (m, 1H), 7.27 – 7.20 (m, 3H), 7.17 (ddd, *J* = 8.2 Hz, 7.0 Hz, 1.1 Hz, 1H), 7.02 (ddd, *J* = 8.0 Hz, 7.0 Hz, 1.1 Hz, 1H), 4.35 (t, *J* = 6.1 Hz, 1H), 3.68 (s, 3H), 3.23 (q, *J* = 6.7 Hz, 2H), 3.02 – 2.91 (m, 4H), 2.48 – 2.34 (m, 5H), 1.96 (t, *J* = 2.7 Hz, 1H).

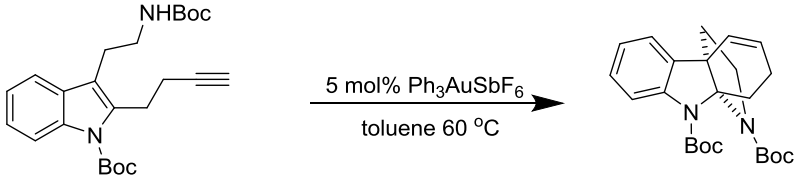
^{13}C NMR (101 MHz, $CDCl_3$) δ 143.41, 137.04, 136.90, 136.28, 129.78, 127.19, 127.16, 121.54, 119.39, 118.25, 109.20, 107.59, 82.96, 69.98, 43.63, 30.05, 30.00, 25.18, 23.64, 21.70, 21.67, 19.60.

m.p. 160–161 ℃.

IR (neat, cm^{-1}): ν 3287, 2924, 1471, 1324.49, 1158, 1093.

HRMS (ESI) m/z Calcd for $C_{22}H_{24}N_2NaO_2S^+$: 403.1450 , Found 403.1461.

Au(I)-catalyzed tandem cyclization for the synthesis of akuammilines



86a **85a**

The catalyst solution was first prepared by addition of Ph_3PAuCl (2.5 mg, 0.005 mmol) to a suspension of $AgSbF_6$ (1.7 mg, 0.005 mmol) in anhydrous toluene (0.50 mL) at room

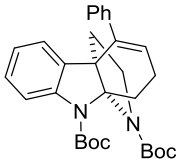
temperature. The suspension was stirred for 20 min at room temperature under Argon atmosphere. The resulting catalyst solution was then added to a solution of substrate (41.2 mg, 0.10 mmol) in anhydrous toluene (0.50 mL) dropwise at room temperature. The resulting mixture was heated at 60 ℃ until TLC showed that there was no starting material left (about 1-2 h). The reaction mixture was cooled to room temperature, filtered through a short pad of silica gel. The filtrate was concentrated in vacuo, and purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to afford cyclized product (23.7 mg, 0.083 mmol) as a colorless oil in 75% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.23 – 7.12 (m, 2H), 7.00 (t, *J* =7.3 Hz, 1H), 5.74 – 5.70 (m, 1H), 5.60 (d, *J* = 10.0 Hz, 1H), 3.53 (t, *J* = 9.1 Hz, 2H), 3.00 (dt, *J* = 17.3 Hz, 8.7 Hz, 1H), 2.25 (dd, *J* = 13.1 Hz, 5.9 Hz, 2H), 2.16 – 2.11 (m, 1H), 2.07 – 1.97 (m, 2H), 1.57 (s, 9H), 1.45 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.29, 134.20, 128.15, 128.12, 126.40, 123.17, 122.27, 118.03, 117.95, 117.88, 117.81, 117.61, 87.70, 81.31, 76.75, 56.61, 56.57, 46.27, 33.93, 29.91, 29.58, 29.54, 29.41, 28.76, 28.63, 28.50, 27.99, 27.93, 27.88, 23.21, 22.91.

IR (neat, cm^{-1}): ν 2973, 2927, 1708, 1477, 1376, 1172, 1144.

HRMS (ESI) m/z calcd for $C_{24}H_{32}N_2NaO_4^+$: 435.2254 , Found: 435.2266.



8,16-Di-*tert*-butyl 13-phenyl-8,16-diazatetracyclo[7.4.3.0^{1,9}.0^{2,7}]hexadeca-2,4,6,12-tetraene-8,16-dicarboxylate (85b)

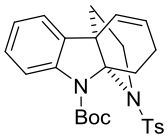
A colorless oil was obtained in 84% yield by following general procedure.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 – 7.21 (m, 3H), 7.14 – 7.05 (m, 1H), 6.97 – 6.92 (m, 2H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.20 (d, *J* = 6.7 Hz, 1H), 5.60 (d, *J* = 3.9 Hz, 1H), 3.82 – 3.78 (m, 1H),

3.65 – 3.55 (m, 1H), 2.92 – 2.82 (m, 1H), 2.47 (dd, *J* = 12.3 Hz, 6.1 Hz, 2H), 2.35 (td, *J* = 12.0 Hz, 8.3 Hz, 1H), 2.26 (d, *J* = 18.5 Hz, 1H), 1.92 – 1.83 (m, 1H), 1.63 (s, 9H), 1.43 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.76, 141.17, 139.40, 131.52, 130.41, 129.94, 129.65, 128.10, 127.74, 126.98, 124.67, 122.36, 118.14, 110.31, 88.28, 81.30, 46.12, 33.21, 30.04, 28.89, 28.75, 24.00.

HRMS (ESI) m/z Calcd for $C_{30}H_{36}N_2NaO_4^+$: 511.2567, Found 511.2577.



***tert*-Butyl 16-(4-methylbenzenesulfonyl)-8,16-diazatetracyclo[7.4.3.0^{1,9}.0^{2,7}]hexadeca-2,4,6,12-tetraene-8-carboxylate (85c)**

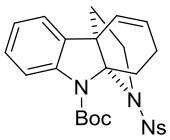
A colorless oil was obtained in 81% yield by following general procedure.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (d, *J* =8.3 Hz, 2H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.09 – 7.04 (m, 1H), 6.98 (td, *J* = 7.8 Hz, 1.5 Hz, 1H), 6.93 (dt, *J* = 7.4 Hz, 3.7 Hz, 1H), 5.70 – 5.62 (m, 1H), 5.49 (dt, *J* = 9.9 Hz, 1.9 Hz, 1H), 3.83 – 3.71 (m, 2H), 2.92 (dd, *J* = 16.2 Hz, 10.2 Hz, 1H), 2.42 – 2.31 (m, 4H), 2.26 – 2.15 (m, 1H), 2.15 – 2.08 (m, 2H), 2.01 – 1.87 (m, 1H), 1.61 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.70, 141.90, 137.62, 132.88, 129.29, 128.07, 127.96, 127.03, 126.94, 125.83, 123.79, 121.69, 118.14, 89.99, 82.26, 58.02, 48.55, 48.49, 33.07, 31.40, 31.36, 31.30, 29.91, 28.38, 23.63, 21.60.

IR (neat, cm^{-1}): ν 2924, 1697, 1477, 1365, 1161, 1098, 1043.

HRMS (ESI) m/z Calcd for $C_{26}H_{30}N_2NaO_4S^+$: 489.1819, Found 489.1823



***tert*-Butyl 16-(4-nitrobenzenesulfonyl)-8,16-diazatetracyclo[7.4.3.0^{1,9}.0^{2,7}]hexadeca-2,4,6,12-tetraene-8-carboxylate (85d)**

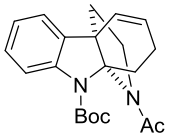
A colorless oil was obtained in 88% yield by following general procedure.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.62 (dd, *J* = 11.4 Hz, 3.8 Hz, 1H), 7.60 – 7.49 (m, 3H), 7.20 (ddd, *J* = 7.3 Hz, 4.3 Hz, 2.8 Hz, 2H), 7.07 (t, *J* = 7.4 Hz, 1H), 5.70 – 5.65 (m, 1H), 5.55 (d, *J* = 10.0 Hz, 1H), 3.93 – 3.82 (m, 1H), 3.66 (d, *J* = 13.8 Hz, 1H), 3.14 (m, 1H), 2.46 (dd, *J* = 12.7 Hz, 5.7 Hz, 1H), 2.24 (td, *J* = 12.1 Hz, 8.2 Hz, 1H), 2.11 – 2.07 (m, 2H), 1.95 – 1.86 (m, 1H), 1.56 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.97, 148.34, 141.89, 135.06, 133.19, 133.11, 131.74, 131.15, 128.67, 128.35, 125.74, 124.12, 122.29, 117.99, 90.61, 82.65, 58.54, 49.55, 32.80, 31.80, 29.91, 28.38, 28.26, 23.41, 22.87, 14.35.

IR (neat, cm^{-1}): ν 2925, 1711, 1544, 1366, 1164, 1035.

HRMS (ESI) m/z Calcd for $C_{25}H_{27}N_3NaO_6S^+$: 520.1513, Found 520.1517.



***tert*-Butyl 16-acetyl-8,16-diazatetracyclo[7.4.3.0^{1,9}.0^{2,7}]hexadeca-2,4,6,12-tetraene-8-carboxylate (85e)**

A colorless oil was obtained in 80% yield by following general procedure.

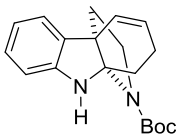
^{1}H NMR (400 MHz, C_6D_6, 60 ℃): δ 8.41 – 8.11 (m, 1H), 7.10 – 7.01 (m, 1H), 6.92 – 6.79 (m, 2H), 5.55 – 5.41 (m, 1H), 5.36 (d, *J* = 10.1 Hz, 1H), 3.69 (d, *J* = 14.3 Hz, 1H), 2.80 – 2.56 (m, 2H), 2.34 (t, *J* = 14.4 Hz, 1H), 1.87 (dd, *J* = 12.3 Hz, 7.4 Hz, 2H), 1.63 – 1.52 (m, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.31, 143.17, 134.44, 134.30, 132.88, 132.20, 129.50, 129.39, 128.61, 128.34, 128.02, 126.41, 124.88, 124.63, 123.06, 122.37, 122.10, 119.44, 117.47, 88.15,

81.56, 55.88, 47.23, 46.05, 33.84, 31.68, 29.92, 29.20, 28.47, 28.13, 27.68, 24.71, 23.39, 23.25, 22.67.

IR (neat, cm^{-1}): ν 2927, 1698, 1664, 1477, 1404, 1364, 1167.

HRMS (ESI) m/z Calcd for $C_{21}H_{26}N_2NaO_3^+$: 377.1835, Found 377.1846.



***tert*-Butyl 8,16-diazatetracyclo[7.4.3.0^{1,9}.0^{2,7}]hexadeca-2,4,6,12-tetraene-16-carboxylate (85f)**

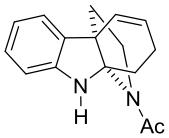
A colorless oil was obtained in 87% yield by following general procedure.

^{1}H NMR (400 MHz, Toluene-d8, 95°C) δ 6.90 – 6.82 (m, 2H), 6.62 (t, *J* = 7.4 Hz, 1H), 6.35 (d, *J* = 7.6 Hz, 1H), 5.58 – 5.45 (m, 3H), 3.37 (s, 1H), 3.37 (t, *J* = 8.2 Hz, 1H), 3.10 – 3.02 (m, 1H), 2.80 – 2.68 (br, 1H), 2.23 (ddd, *J* = 16.3 Hz, 11.1 Hz, 5.1 Hz, 1H), 2.03 (ddd, *J* = 12.4 Hz, 6.8 Hz, 2.2 Hz, 1H), 1.88 – 1.61 (m, 4H), 1.37 (s, 9H).

^{13}C NMR (101 MHz, CD_3OD) δ 155.72, 155.68, 150.35, 149.86, 133.85, 133.59, 131.21, 131.20, 129.33, 126.66, 126.58, 124.05, 123.95, 123.92, 120.21, 120.19, 111.14, 111.02, 87.28, 86.91, 82.09, 80.97, 58.22, 57.08, 47.43, 47.38, 47.28, 35.33, 34.89, 30.28, 30.25, 29.30, 29.26, 29.03, 28.90, 23.78.

IR (neat, cm^{-1}): ν 3377, 2972, 2927, 1681, 1609, 1365, 1254, 1169, 951.

HRMS (ESI) m/z Calcd for $C_{19}H_{25}N_2O_2^+$: 313.1911, Found 313.1917.



1-{8,16-diazatetracyclo[7.4.3.0^{1,9}.0^{2,7}]hexadeca-2,4,6,12-tetraen-16-yl}ethan-1-one (85g)

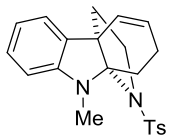
A colorless oil was obtained in 83% yield by following general procedure.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 – 7.03 (m, 2H), 6.75 (dd, *J* = 7.4, 6.5 Hz, 1H), 6.62 (d, *J* = 7.7, 1H), 5.79 (s, 1H), 5.76 – 5.59 (m, 2H), 3.59 (t, *J* = 8.5 Hz, 1H), 3.29 – 3.17 (m, 1H), 2.92 (dd, *J* = 13.6 Hz, 3.2 Hz, 1H), 2.45 (dd, *J* = 12.7 Hz, 5.5 Hz, 1H), 2.41 – 2.26 (m, 2H), 2.23 – 2.11 (m, 1H), 1.97 (s, 3H), 1.78 – 1.67 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.56, 149.24, 131.90, 129.60, 128.58, 126.37, 123.04, 119.17, 110.61, 87.38, 55.46, 47.58, 34.49, 29.92, 27.70, 27.66, 23.91, 22.87.

IR (neat, cm^{-1}): ν 3387, 2924, 1660, 1457, 1401, 1311, 1127 cm-1;

HRMS (ESI) m/z Calcd for $C_{16}H_{19}N_2O^+$: 255.1492 , Found 255.1483.



8-methyl-16-(4-methylbenzenesulfonyl)-8,16-diazatetracyclo[7.4.3.0^{1,9}.0^{2,7}]hexadeca-2,4,6,12-tetraene (85h)

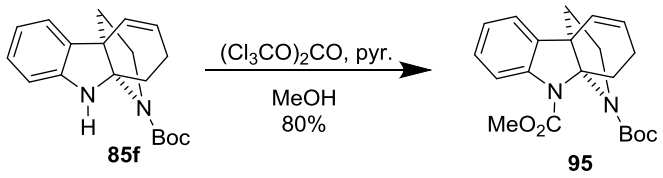
A colorless oil was obtained in 86% yield by following general procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 – 7.59 (m, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.12 (td, *J* = 7.7 Hz, 1.3Hz, 1H), 7.02 (dd, *J* = 7.2 Hz, 0.9 Hz, 1H), 6.69 (td, *J* = 7.4 Hz, 0.9 Hz, 1H), 6.36 (d, *J* = 7.8 Hz, 1H), 5.73 – 5.61 (m, 2H), 3.49 (td, *J* = 7.7 Hz, 3.8 Hz, 1H), 3.15 (d, *J* = 6.5 Hz, 1H), 3.01 (s, 3H), 3.00 – 2.92 (m, 1H), 2.38 (s, 3H), 2.36 – 2.29 (m, 1H), 2.10 – 1.95 (m, 4H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.45, 142.89, 138.22, 131.22, 129.54, 129.49, 128.80, 127.02, 125.28, 122.00, 118.05, 106.57, 93.71, 57.62, 48.10, 34.80, 29.73, 29.70, 28.18, 22.65, 21.64, 21.62.

IR (neat, cm^{-1}): ν 2923, 1605, 1491, 1332, 1153, 1094, 920.

HRMS (ESI) m/z Calcd for $C_{22}H_{24}N_2NaO_2S^+$: 403.1450, Found 403.1464.



To a solution of the substrate **85f** (31 mg, 0.1 mmol) in anhydrous dichloromethane (0.5 mL) was added pyridine (40 μL, 0.5 mmol) and a solution of triphosgene (89 mg, 0.3 mmol) in dichloromethane (0.2 mL) at -10 ℃. The reaction was slowly warmed to room temperature and stirred for 30 min. MeOH (40 μL, 1 mmol) was added to the above solution and the reaction was stirred for another 2 h before the solvents were removed in vacuo to give a crude oil, which was purified by column chromatography (petroleum ether/ethyl acetate=10:1) to produce **95** (29.6 mg, 0.08 mmol) as a colorless oil in 80% yield.

^{1}H NMR (400 MHz, C_6D_6, 60 ℃): δ 8.16 (d, *J* = 7.6 Hz, 1H), 7.12 – 7.05 (m, 1H), 6.97 – 6.83 (m, 2H), 5.59 – 5.51 (m, 1H), 5.47 (d, *J* = 10.0 Hz, 1H), 3.64 (s, 3H), 3.50 – 3.47 (m, 1H), 3.18 – 2.98 (m, 2H), 2.42 – 2.35 (m, 1H), 2.15 – 1.95 (m, 1H), 2.06 – 1.96 (m, 1H), 1.90 – 1.78 (m, 1H), 1.74 – 1.63 (m, 1H), 1.42 (s, 9H).

^{13}C NMR (101 MHz, C_6D_6, 60 ℃): δ 154.54, 153.76, 142.55, 135.21, 129.01, 128.89, 128.27, 127.04, 123.63, 122.61, 117.82, 89.34, 79.72, 56.92, 52.35, 52.29, 47.13, 35.35, 28.94, 28.73, 23.53.

IR (neat, cm^{-1}): ν 2927, 1708, 1479, 1439, 1378, 1242, 1169, 752.

HRMS (ESI) m/z calcd for $C_{21}H_{27}N_2O_4^+$:371.1965 , Found: 371.1958.

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Chapter 3

Construction of Bridged Tetracyclic Indolenine Skeleton through Gold Carbene-Catalyzed Desilylative Cyclization

3.1 Background of Bridged Tetracyclic Indolenine Alkaloids

Bridged tetracyclic indolenine skeletons **1** (Figure 3.1) are prevalent core motifs in several families of indole alkaloids,[1] many of which possess interesting biological activities. (*E*)-16-formyl-5α-methoxy-strictamine,[2] scholarisin VII,[2] perakine N_4-oxide,[3] raucaffrinoline N_4-oxide,[3] and vinorine N_4-oxide[3] exhibit significant cytotoxic and anti-inflammatory activity. Strictamine[4] was reported to inhibit herpes simplex virus (HSV) and adenovirus (ADV).[5]

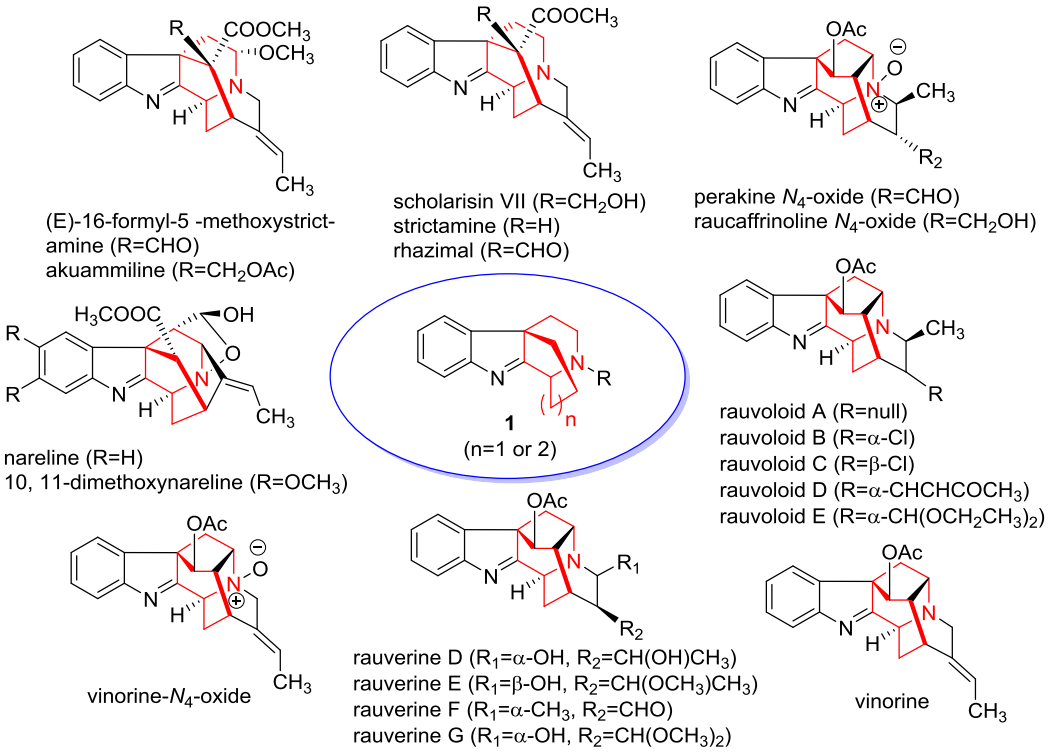
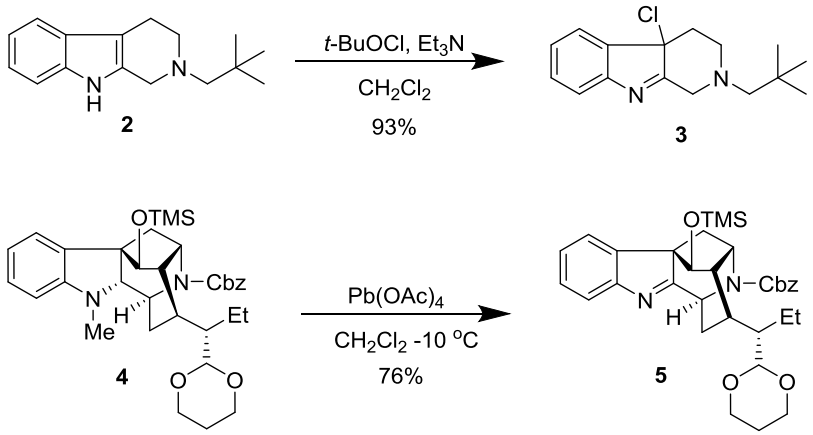


Figure 3.1 Representative Bridged Indolenine-Containing Natural Products

3.2 Reported Methodology of Construction of Indolenine Skeleton

3.2.1 Oxidation of Indole or Indoline Derivative

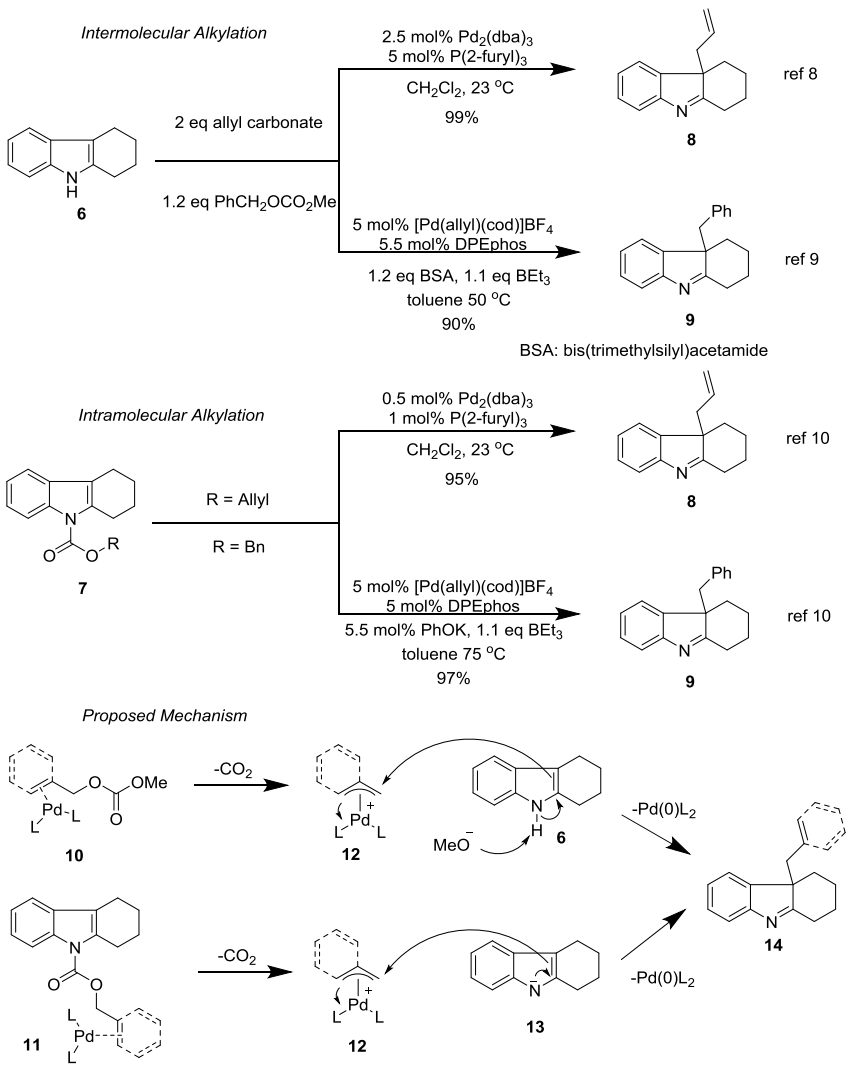
As shown in Scheme 3.1, oxidation of substituted indole **2** with *t*-BuOCl afforded 3-chloro-indolenine **3** in 93% yield.[6] For indoline derivative **4**, indolenine **5** was obtained in 76% yield when treated with $Pb(OAc)_4$.[7]



Scheme 3.1 Formation of Indolenine by Oxidation

3.2.2 Palladium-Catalyzed Allylation or Benzylation

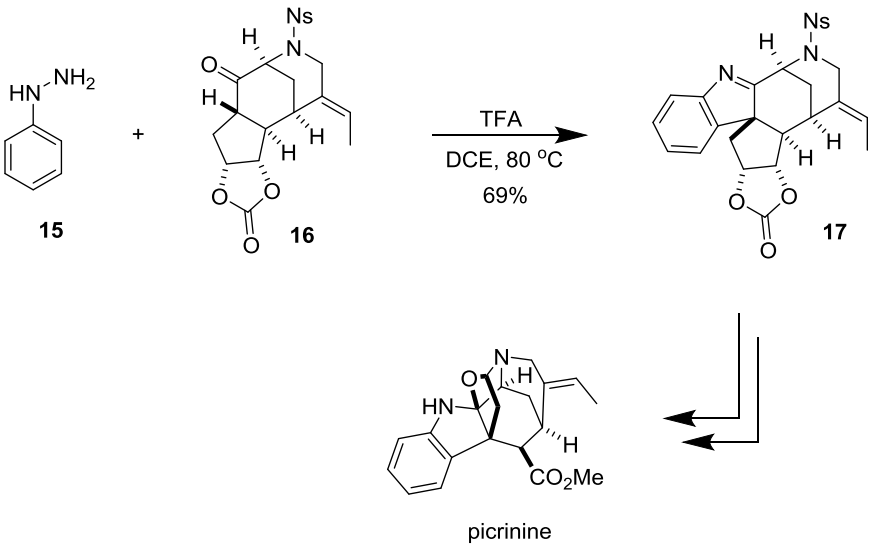
Rawal and co-workers reported the palladium-catalyzed decarboxylative C3-allylations and -benzylations of indoles **6**, **7** to indolenines **8**, **9** respectively (Scheme 3.2).[8,9,10] For both intermolecular and intramolecular benzylation reactions, boron Lewis acids, such as triethylborane, were added to accelerate the disruption of aromaticity in the formation of the corresponding η^3-palladium complexes **12**.[9,10]



Scheme 3.2 Pd-Catalyzed Decarboxylative Allylation and Benzylation

3.2.3 Interrupted Fischer Indolization

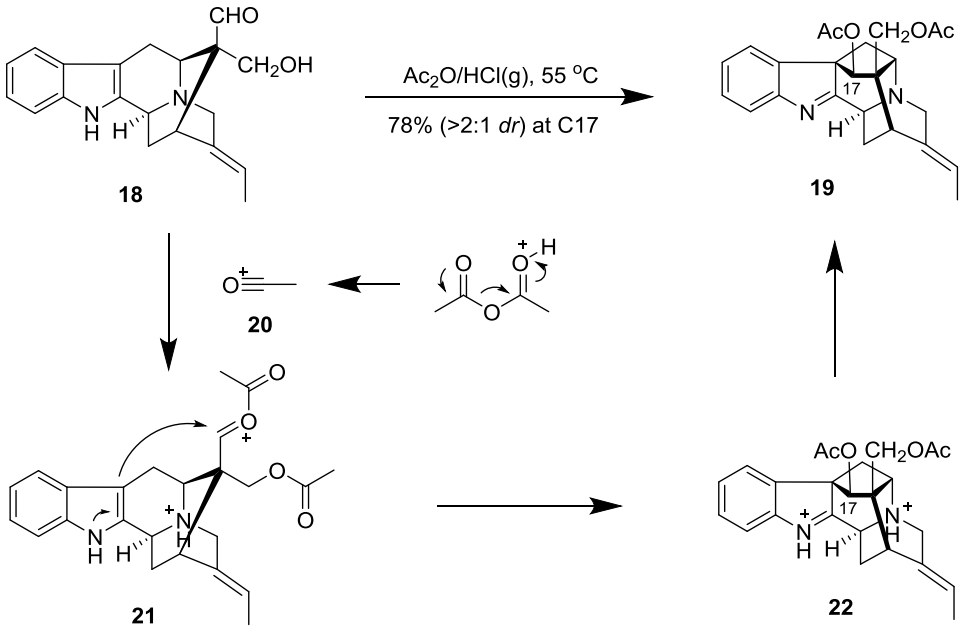
Garg and co-workers reported the first total synthesis of picrinine in 2014.[11] One of the key steps is the formation of indolenine intermediate **17** (Scheme 3.3) through interrupted Fischer indolization of hydrazine **15** and ketone **16** under acidic condition.



Scheme 3.3 Interrupted Fischer Indolization Applied to Total Synthesis of Picrinine

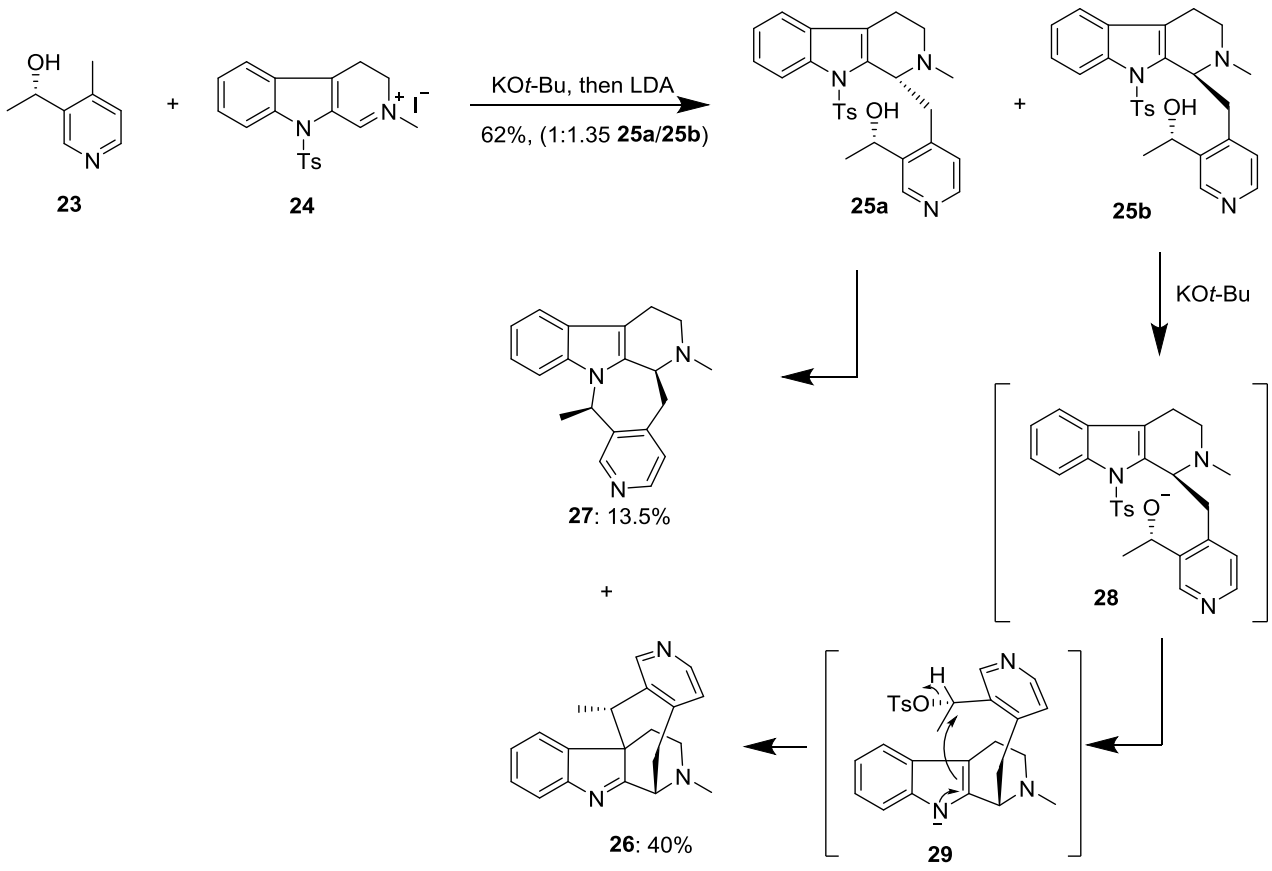
3.2.4 Others

The intramolecular cyclization of compound **18** occurred in the presence of Ac_2O and HCl (g) to give indolenine **19** in 78% yield with >2:1 diastereomeric ratio at C17 (Scheme 3.4).[12] Activation of the aldehyde moiety of **18** by acylium ion **20**, which was generated from Ac_2O and HCl (g), facilitated the nucleophilic addition process afforded the cyclized product **19** after aqueous workup.



Scheme 3.4 Intramolecular Cyclization under Acidic Condition

Bridged indolenine **26** was synthesized by intramolecular cyclization of **25b**, which was prepared from base-mediated coupling of **23** and **24** (Scheme 3.5).[13] During the cyclization process, tosyl group was migrated from *N* of indole to *O* in the presence of of KO*t*-Bu and the following substitution reaction afforded the cyclized indolenine **26**.



Scheme 3.5 Preparation of Indolenine by Base-Mediated Cyclization

For all these reported methods, either limited reagents, tedious steps of substrate preparation or harsh reaction conditions limit their applications to complex molecular syntheses. Thus, the development of new strategies for the convenient construction of bridged indolenine skeleton is in great demand.

3.3 Initial Attempt to Construct Bridged Tetracyclic Indolenine

We started the study of construction of bridged tetracyclic indolenine from the cyclization reactions of alkynylindoles **30-32** under the catalysis of Au(I) cation (Figure 3.2).

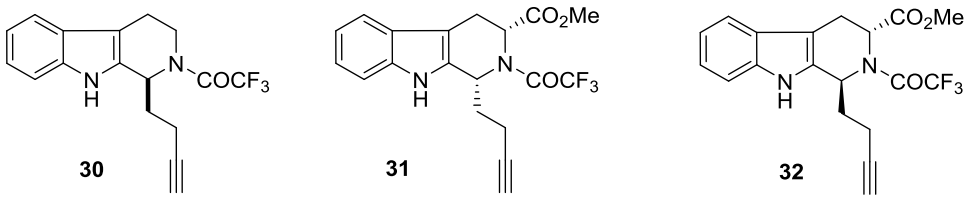
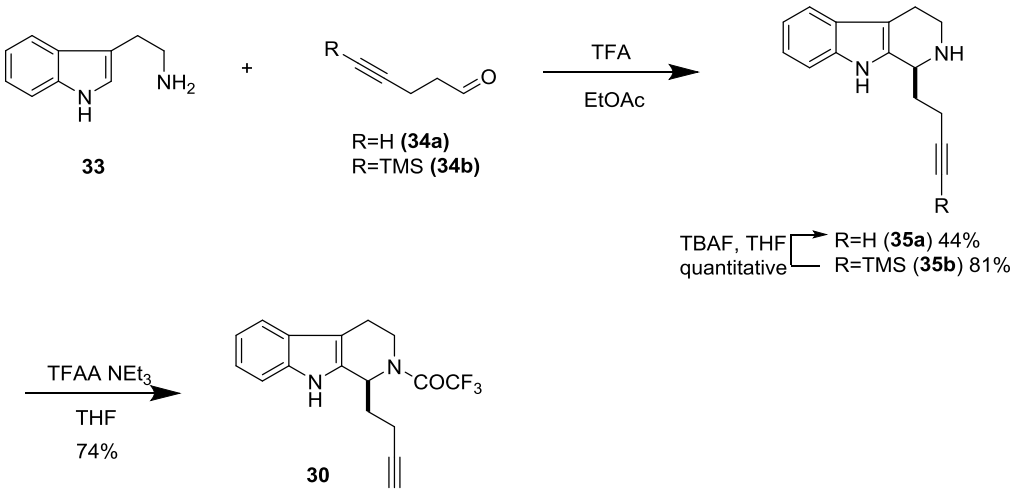


Figure 3.2 Alkynylindoles

3.3.1 Substrate Preparation

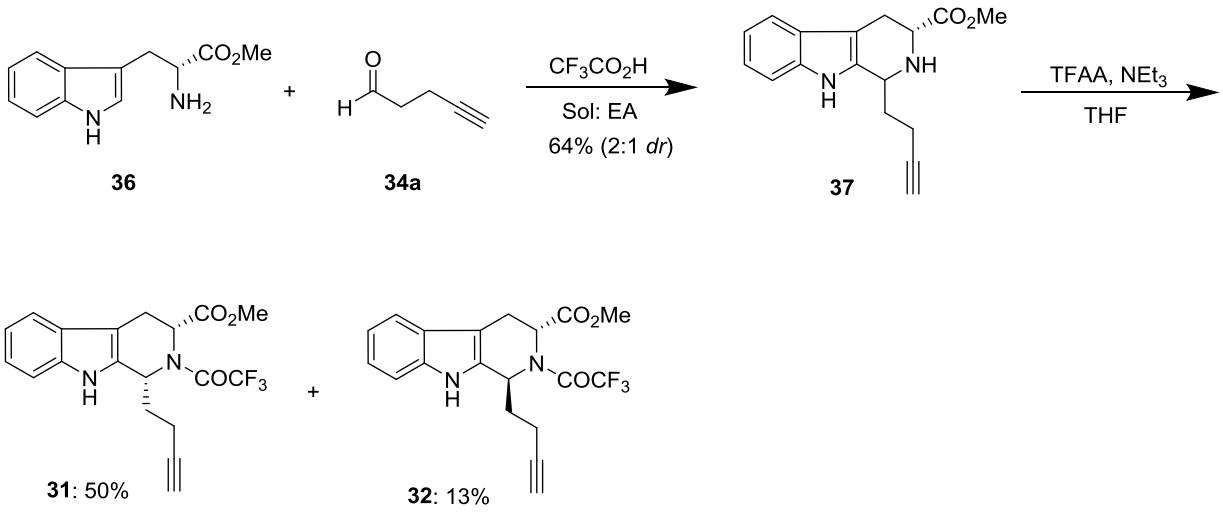
The synthesis of alkynylindole **30** (Scheme 3.6) was initiated by condensation of tryptamine **33** and aldehyde **34a**, and trifluoroacetic acid-mediated Pictet-Spengler reaction afforded the tetrahydrocarboline **35a** in 44% yield.[14] We reasoned that the low yield was due to poor solubility of tryptamine **33** in ethyl acetate and lability of the alkynal **34a** under acidic condition. Thus, aldehyde **34a** was replaced by silylated alkynal **34b**. In the presence of trifluoroacetic acid, **34b** reacted with tryptamine **33** in ethyl acetate to afford cyclized amine **35b** in 81% yield. Removal of TMS by TBAF was quantitative. Acylation of the secondary amine **35b** with TFAA in the presence of NEt_3 afforded **30** in 74% yield.



Scheme 3.6 Preparation of **30**

To prepare **31** and **32**, D-tryptophan methyl ester **36** was condensed with aldehyde **34a** under acidic condition, and Pictet-Spengler cyclization of the imine generated in situ afforded the

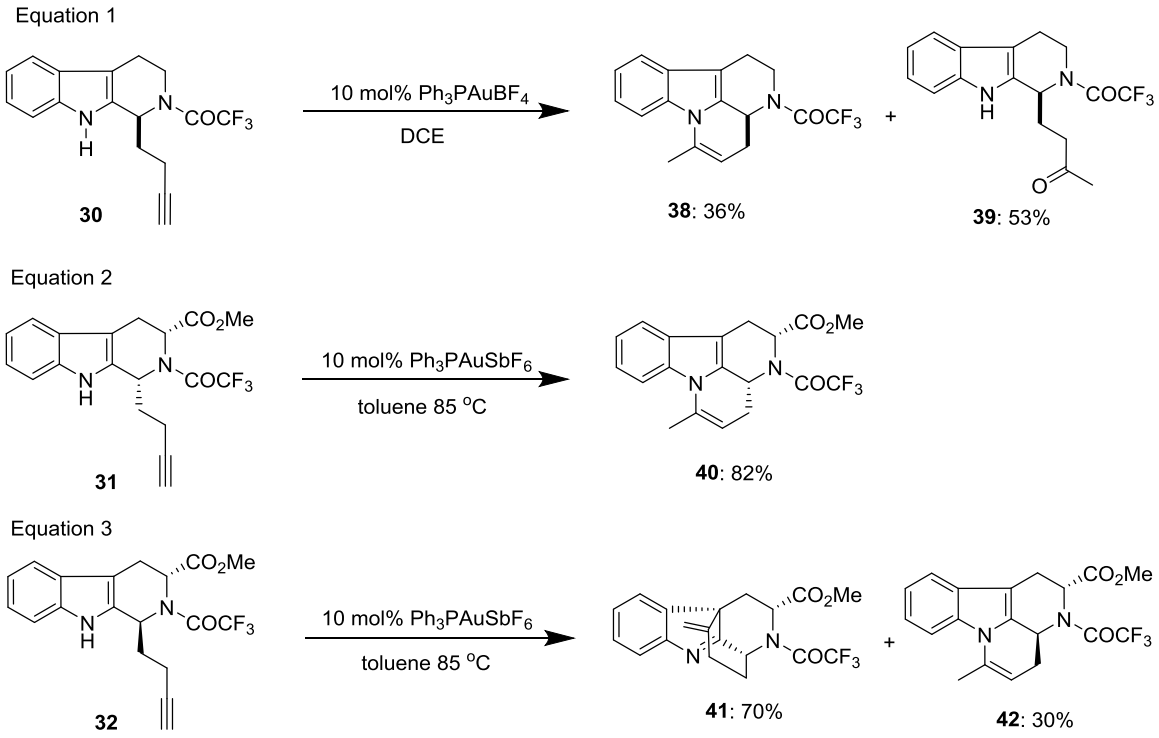
tetrahydrocarboline **37** in 64% yield with 2:1 diastereoselectivity (Scheme 3.7). These two diastereomers cannot be separated by flash chromatography due to their similar polarity. Acylation of **37** with TFAA in the presence of NEt_3 gave *cis*-tetrahydrocarboline **31** in 50% isolated yield and *trans*-tetrahydrocarboline **32** in 13% isolated yield.



Scheme 3.7 Preparation of **31**, **32**

3.3.2 Gold-Catalyzed Cyclization

Tetrahydrocarboline **30** was subjected to 10 mol% Ph_3PAuBF_4 in DCE at room temperature. Enamine **38** and ketone **39** were obtained in 36% and 53% yields respectively (Equation 1, Scheme 3.8). However, no desired indolenine was formed. When diastereomers **31**, **32** were subjected to 10 mol% $Ph_3PAuSbF_6$ in toluene, no reaction occurred at room temperature. When the temperature of both reactions was increased to 85 ^oC, *cis*-tetrahydrocarboline **31** was converted to enamine **40** in 82% yield (Equation 2, Scheme 3.8) while *trans* **32** yielded bridged indolenine **41** and enamine **42** in 70% and 30% yields respectively (Equation 3, Scheme 3.8).



Scheme 3.8 Initial Results of Attempted Cyclization Reactions

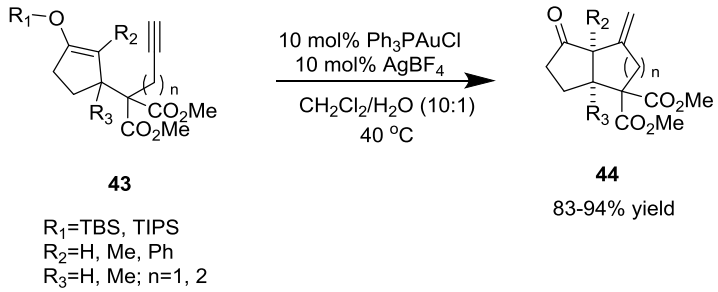
3.4 Construction of Bridged Tetracyclic Indolenine through Gold-Catalyzed Desilylative Cyclization

3.4.1 Background of Metal-Catalyzed Desilylative Cyclization of Acetylenic Silyl Enol Ether

The transition metal-catalyzed desilylative cyclization through nueclophilic addition of silyl enol ether to alkyne is a powerful method for the construction of carbocyclic compounds.[15] Until now, various metal catalysts, such as mercuary, palladium, tungsten, rhodium, rhenium, platinum, silver and gold, have been reported. Especially for gold catalysts, the soft Lewis acidic nature allows conversion of acetylenic silyl enol ethers into rigid frameworks under mild conditions in the presence of silyl scavengers.

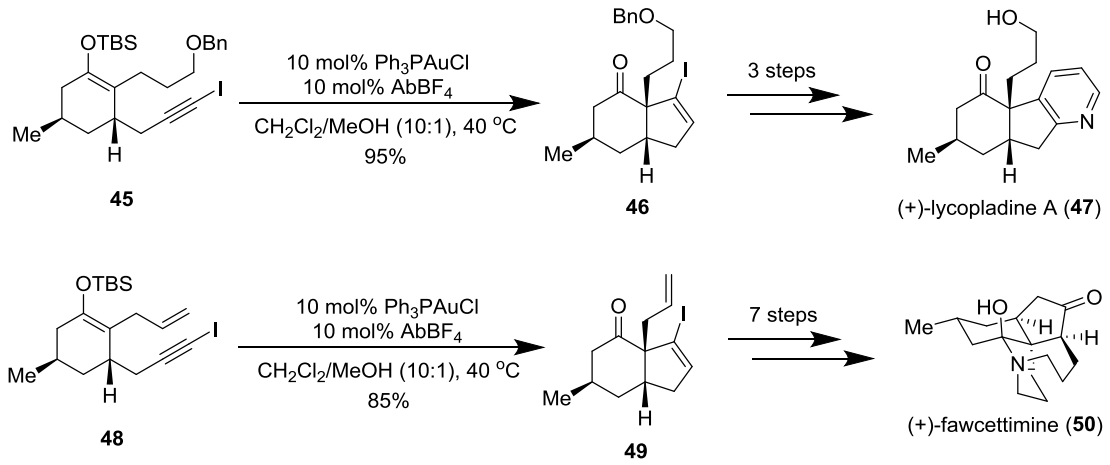
Toste and co-workers reported a Au(I)-catalyzed cyclization of silyl enol ethers (Scheme 3.9).[16] In the presence of water or MeOH as silyl scavengers, enynes **43** were cyclized to compounds **44** in 83-94% yield under Ph_3PAuBF_4 catalysis in DCM at 40 ^oC. TBS and TIPS

enol ethers were used as "frozen enol equivalents". Both 5 and 6-member rings were formed under mild conditions.



Scheme 3.9 Au(I)-Catalyzed Desilylative Cyclization

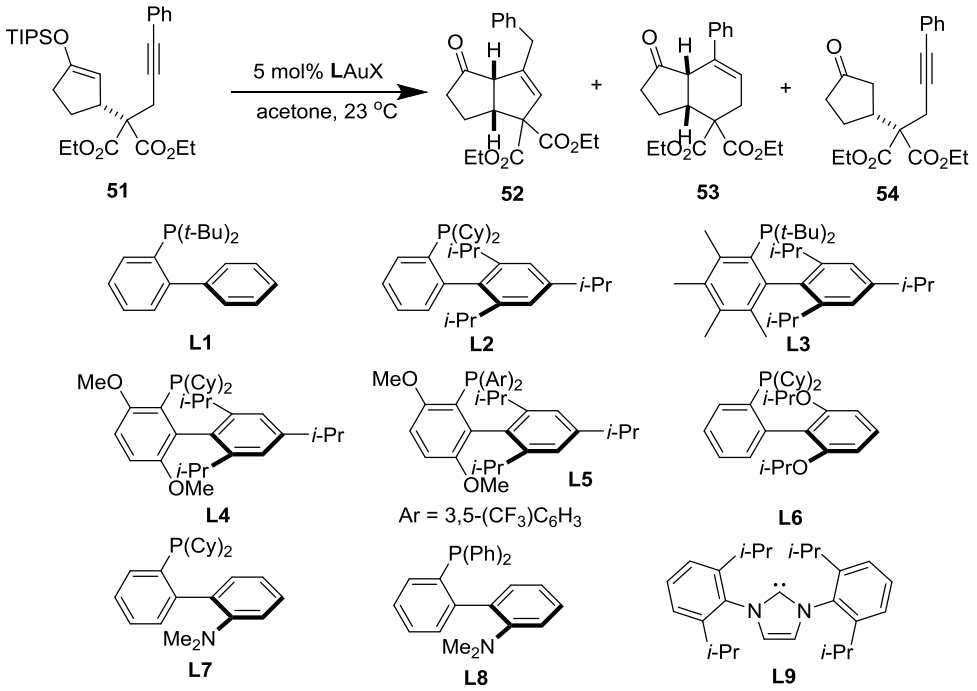
This methodology has been applied to the total synthesis of (+)-lycopladine A **47**[16] and (+)-fawcettimine **50**[17] (Scheme 3.10). Isolated from *Lycopodium* complantum, **47** shows modest but selective cytotoxicity against murine lymphoma L1210 cells.[18] Iodoacetylene **45** underwent Au(I)-catalyzed 5-*endo-dig* cyclization to give **46** in 95% yield and further modifications in 3 steps furnished the total synthesis of (+)-lycopladine A (**47**). The terminal alkene moiety of enyne **48** was tolerated in the desilylative cycliation of **48** to compound **49**, which was efficiently converted to (+)-fawcettimine **50** over 7 steps.



Scheme 3.10 Total Syntheses of (+)-lycopladine A and (+)-fawcettimine

Barriault and co-workers reported a Au(I)-catalyzed synthesis of fused carbocycles **52**, **53** (Table 3.1).[19] The regioselectivity can be modulated by the steric and electronic properties of Au(I) complexs. 5-*exo-dig* process was most favored for [**L9**AuNCMe]SbF_6-catalyzed cyclization while 6-*endo-dig* process for [**L3**AuNCMe]SbF_6 catalysis.

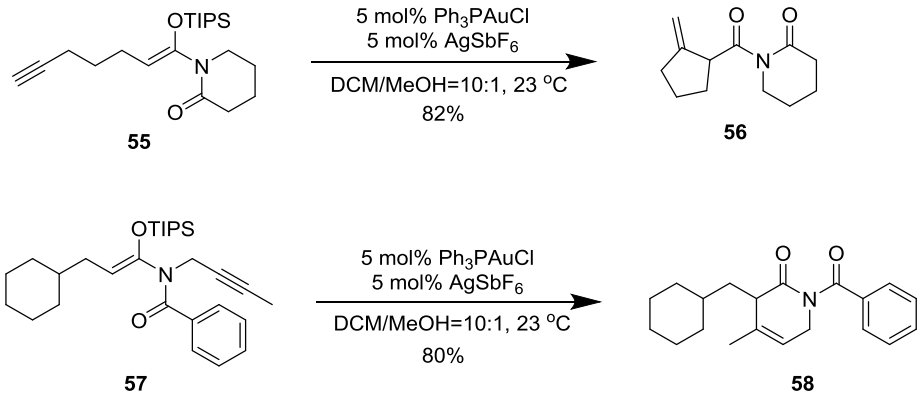
Table 3.1 Au(I)-Catalyzed Cyclization Reactions



Entry	LAuX	Ratio (**52**/**53**/**54**)	Yield (%)
1	$Ph_3PAuSbF_6$	22:3:75	87
2	$Ph_3PAuBF4$	43:15:58	92
3	$Et_3PAuSbF_6$	66:9:25	93
4	$(4\text{-}CF_3C_6H_4)_3PAuBF_4$	50:15:35	93
5	[**L1**AuNCMe]SbF_6	64:36:0	87
6	[**L2**AuNCMe]SbF_6	37:63:0	89
7	[**L3**AuNCMe]SbF_6	29:71:0	82
8	[**L4**AuNCMe]SbF_6	38:62:0	86

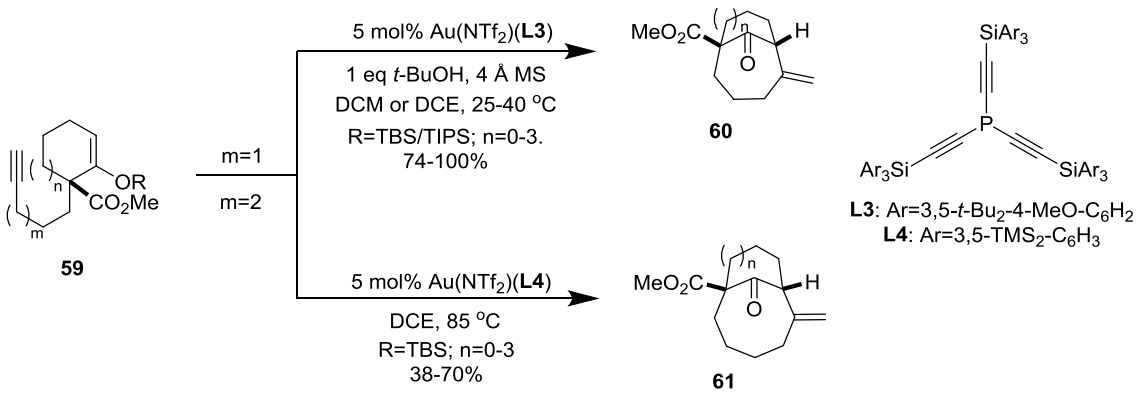
9	[**L5**AuNCMe]SbF_6	54:46:0	72
10	[**L6**AuNCMe]SbF_6	71:29:0	78
11	[**L7**AuNCMe]SbF_6	58:42:0	84
12	[**L8**AuNCMe]SbF_6	62:38:0	90
13	[**L9**AuNCMe]SbF_6	95:5:0	91

Shen and co-workers reported Au(I)-catalyzed cyclization reactions of silyl ketene amides **55** and **57** (Scheme 3.11).[20] Both 5-*exo-dig* and 6-*endo-dig* processes were observed for desilylative cyclizations in the presence of MeOH as a silyl scavenger.



Scheme 3.11 Au(I)-Catalyzed Cyclizations of Silyl Ketene Amides

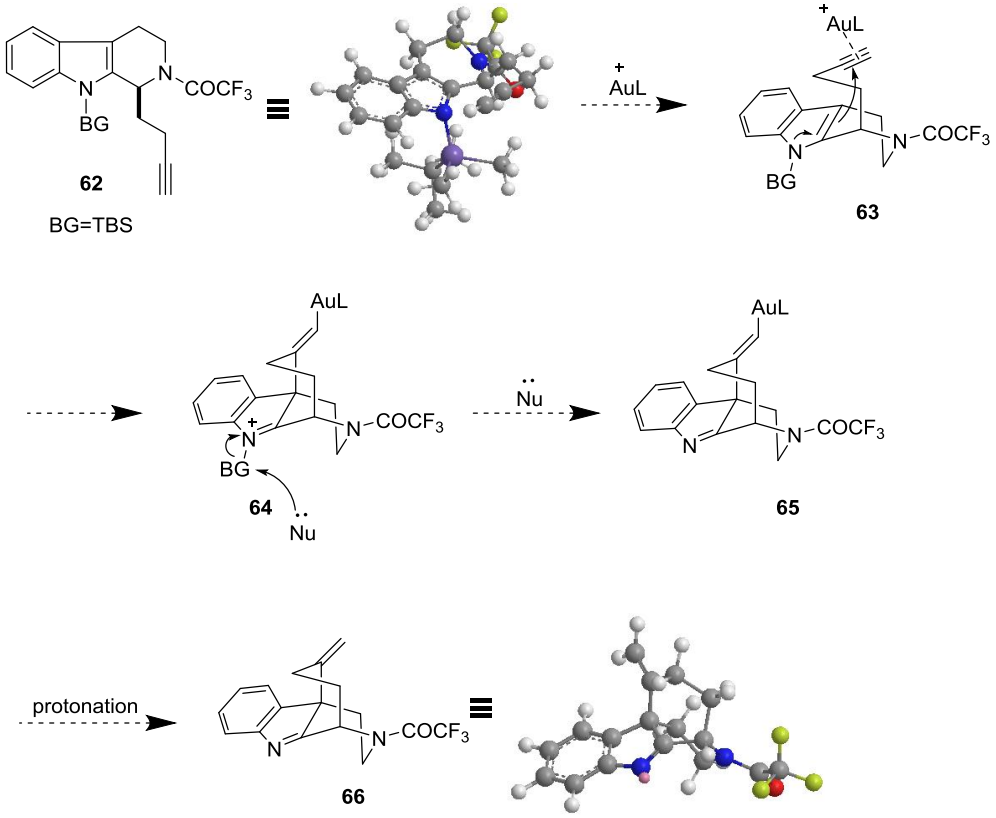
Sawamura and co-workers reported the construction of highly strained methylenecycloheptane and methylenecyclooctane frameworks through cyclizations of acetylenic silyl enol ethers catalyzed by triethynylphosphine (**L3**, **L4**)-coordinated gold complexs (Scheme 3.12).[21] *t*-BuOH was used as the silyl scavenger and additon of 4 Å MS minimized the side reaction.



Scheme 3.12 Au(I)-Catalyzed Formation of Bridged Cycloheptanes and Cyclooctanes

3.4.2 Proposed Approach

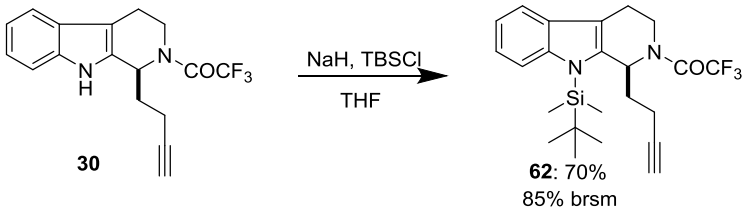
Based on our initial study of construction of indolenine and the reported gold-catalyzed desilylative reactions, we proposed an approach to the bridged indolenine **66** under the catalysis of noble metal catalysts (Scheme 3.13). Installation of a blocking group (BG) was anticipated to minimize the formation of C-N product. TBS (*t*-butyldimethylsilyl) group was chosen considering its bulkiness and feasible cleavage with alcohol. Based on the results of MM2 energy minimization calculation, the alkynyl chain of alkynylindole **62** was found to be at pseudoaxial position. Upon activation by catalyst (gold or platinum), **62** might be cyclized to intermediate **64**, which would undergo removal of blocking group of N^{in} and proto-deauration to give the tetracyclic indolenine **66**.



Scheme 3.13 Proposed Approach to Indolenine **66**

3.4.3 Preparation of *N*-silyl Indole Substrate

As shown in Scheme 3.14, TBS was installed on the *N* of indole under basic condition in 70% yield (85% based on recovery of starting material). Other bases, such as NaHMDS, LiHDMS and LDA, gave lower conversions and yields.



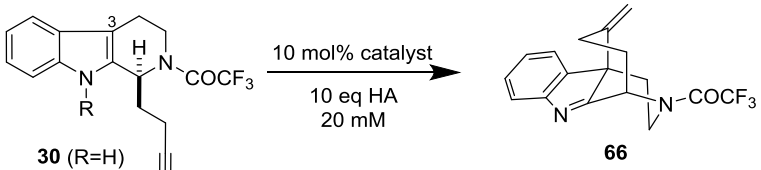
Scheme 3.14 Preparation of *N*-silyl Substrate

3.4.4 Gold-Catalyzed Desilylative Approach to Tetracyclic Indolenine

Catalyst Screening

N-TBS indole **62** was tested for cyclization using various catalysts in the presence of methanol as silyl scavenger (Table 3.2).

Table 3.2 Screening of Au-Catalyzed Desilylative Cyclization



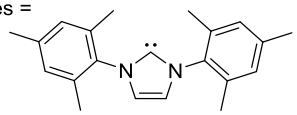
30 (R=H)
62 (R=TBS)
67 (R=TES)

66

Entry	R	Catalyst	HA	Solvent	Temp ^{o}C	Consumption of Substrate (%)	Yield[a] (%)
1	H	Ph_3PAuBF_4	MeOH	DCE	25	100	0
2	TBS	$AuCl_3$	MeOH	DCE	95	51	6
3	TBS	$PtCl_2$	MeOH	DCE	95	37	0
4[b]	TBS	$(Ph_3PAu)_3OBF_4$	MeOH	DCE	95	45	25
5[c]	TBS	$Ph_3PAuNTf_2$	MeOH	DCE	95	100	0
6[d]	TBS	$Ph_3PAuNTf_2$	*i*-PrOH	DCE	95	97	0
7	TBS	$IMesAuBF_4$[e]	MeOH	DCE	95	52	27
8	**TBS**	**$IPrAuBF_4$[f]**	**MeOH**	**DCE**	**95**	**82**	**67**
9	TBS	IPrAuCl	MeOH	DCE	95	13	0
10	TBS	IPrAuOTf	MeOH	DCE	95	100	0
11	TBS	$IPrAuSbF_6$	MeOH	DCE	95	43	7
12	TBS	$IPrAuBF_4$	*i*-PrOH	DCE	95	64	20
13	TBS	$IPrAuBF_4$	EtOH	DCE	95	60	35
14	TBS	$IPrAuBF_4$	H2O	DCE	95	63	27
15	TBS	$IPrAuBF_4$	4-NO_2-PhOH	DCE	95	60	22
16	TES	$IPrAuBF_4$	MeOH	DCE	95	100	12

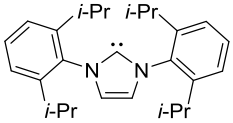
[a] 1 eq DMAP was added as internal standard before taking NMR. Converstion and yield were calculated based on NMR integration.
[b] 5 mol% catalyst was used.
[c] 40% **38**, 25% **39**.
[d] 13% **38**, 44% **39**.
[e]

IMes =



[f]

IPr =



After stirring at 95 ^{o}C in DCE for 12 h, 6% yield of desired indolenine **66** (entry 2) was obtained under the catalysis of $AuCl_3$ and 49% of starting material **62** remained unreacted. $PtCl_2$ catalysis led to partial decompostion and no product **66** was found (entry 3). When trigoldoxonium salt was used, 25% yield of **66** was obtained (entry 4). C-N cyclization product **38** and ketone **39**, instead of desired indolenine **66**, were generated under the catalysis of $Ph_3PAuNTf_2$ (entry 5). Probably silyl group was removed first and either nucleophilic addition of *N*-indole or methanol to alkyne under the catalysis of gold gave rise to the side products **38** and **39**. Replacement of MeOH with *i*-PrOH made no difference to the results (entry 6). Various other phosphine-gold catalysts were screened but none gave satisfactory results.

Gold carbene comlexes have been reported to show unique steric and electronic attributes compared to phosphine ligands.[22] IMes and IPr ligands were invesitgated for the proposed desilylative cyclization. $IMesAuBF_4$ gave 52% consumption of starting material and 27% yield of product **66** (entry 7). The other gold-carbene catalyst, IPrAuBF4, afforded 67% yield and 82% yield based on recovered starting material (entry 8). Compared to IPrAuCl, IMesAuCl is more hydroscopic and the moisture might be involved into the reaction which could give rise to a lower yield (entry 7 versus 8).

Counterions Screening

Without $AgBF_4$, IPrAuCl itself did not catalyze the formation of indolenine and only 13% decomposition occurred at 95 ^{o}C in the presence of MeOH (entry 9), which underlined the

crucial role of silver salt. Counterions OTf^- and SbF_6^- gave little desired product **66**, which might be due to the weak stability of gold cations under reaction conditions (entries 10 and 11). Of all these couterions, BF_4^- afforded the best result (entry 8).

Silyl Scavenger Screening

When MeOH was replaced by bulky *i*-PrOH as the silyl scavenger, conversion of substrate **62** and yield of product **66** were significantly lower than those of MeOH (entry 12 versus 8). EtOH afforded 58% yield based on recovery of 40% unconsumed s.m. (entry 13). Lower yield and lower conversion were obtained in the presence of water which could be rationarized by the water-induced decomposition and precipitation of gold-carbene catalyst (entry 14 versus 8). Acidic 4-nitro-phenol gave similar results as *i*-PrOH (entry 15).

Silyl Group Screening

TBS group was proved to be stable under gold cabene-catalyzed reaction condition (entry 9), and complete conversion of substrate **62** was very difficult (enttry 8). Extended reaction time ensured the consumption of all the starting material **62**, but the yield of indolenine **69** decreased slightly to 60%. Labile *N*-TES indole **67** was tested for the cyclization. No reaction occurred at room temperature. At 95 ^oC, **66** was obtained in only 12% yield and no starting material was recovered (entyr 16 versus 8).

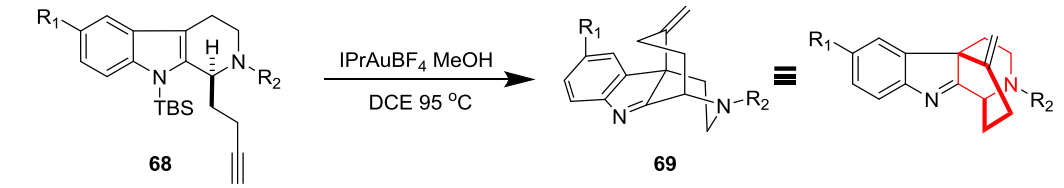
Based on all these experimental data, TBS was found to be the optimal blocking group, which is stable under the reaction condition and can be efficiently removed by the silyl scavenger MeOH during the process of cyclization under the catalysis of $IPrAuBF_4$ in DCE at 95 ^oC (entry 8).

3.4.5 Substrate Scope

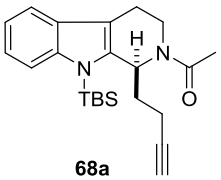
With the optimized reaction condition in hand, we set out to explore the scope of this desilylative cyclization. Substrates **68** (Table 3.3A) and **70** (Table 3.3B) bearing different substitutions on the benzene (R_1), protecting groups (R_2) and lengths of alkynyl chain, are to be tested. The expected cyclized products **69** and **71** shares the skeleton of natural products shown in Figure 3.1. The preparation of substrates **68** and **70** is similar to that of **62** as described in Scheme 3.14. The syntheses are in progress and the cyclization will be investigated in the near future.

Table 3.3 Gold Carbene-Catalyzed Desilylative Cyclization

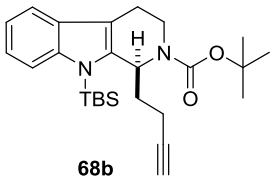
A



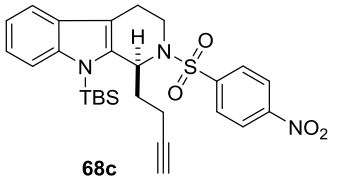
68 **69**



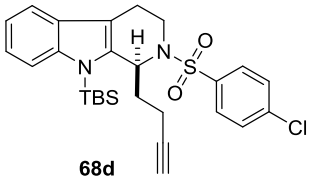
68a



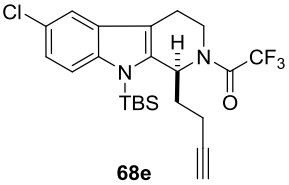
68b



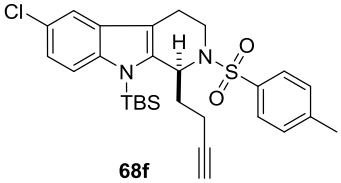
68c



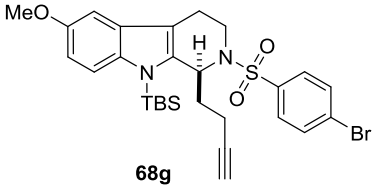
68d



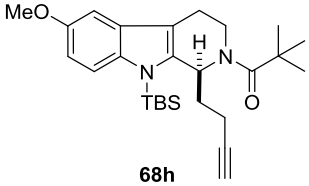
68e



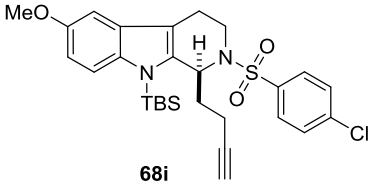
68f



68g

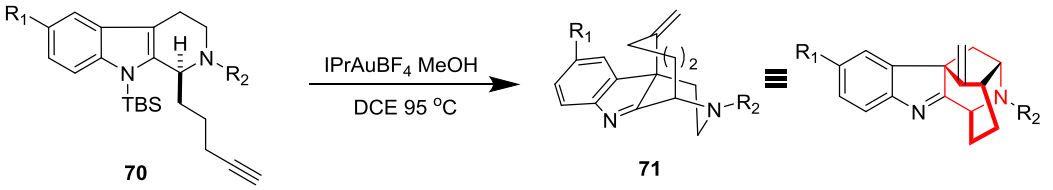


68h

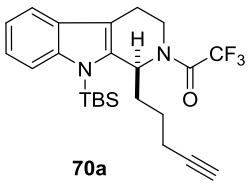


68i

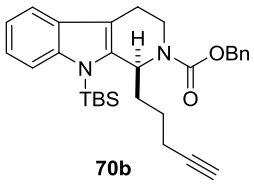
B



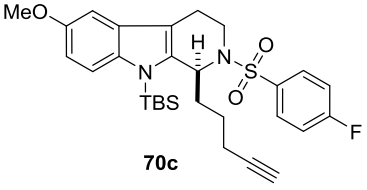
70 **71**



70a



70b

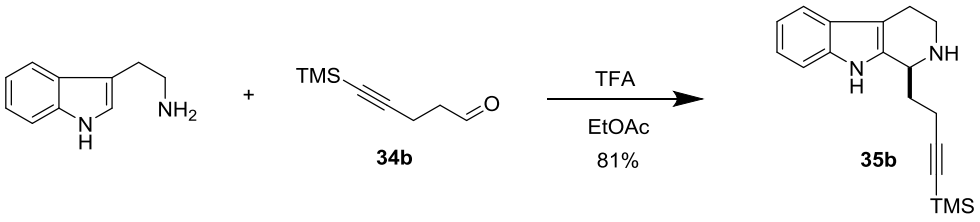


70c

3.5 Experimental

Unless otherwise noted, reagents were obtained commercially and used without further purification. CH_2Cl_2 was distilled from CaH_2 under a nitrogen atmosphere. THF was distilled from sodium-benzophenone under a nitrogen atmosphere. Toluene was distilled from sodium under a nitrogen atmosphere. Thin-layer chromatography (TLC) analysis of reaction mixtures was performed on Dynamicadsorbents silica gel F-254 TLC plates. Flash chromatography was carried out on Zeoprep 60 ECO silica gel. ^{1}H and ^{13}C NMR spectra were recorded with Varian INOVA 400, 500 and Bruker Avance-III 300 spectrometers. Mass spectral and analytical data were obtained via the PE SCIEX/ABI API QSTAR Pulsar i Hybrid LC/MS/MS, Applied Biosystems operated by the Central Analytical Laboratory, University of Colorado at Boulder. Infrared (IR) spectra were recorded on a Thermo Nicolet Avatar 370 FT-IR spectrometer. Melting point (mp) determinations were performed by using a Thomas Hoover capillary melting point apparatus and are uncorrected. High performance liquid chromatography (HPLC) analyses of chiral compounds were performed using a ChiralCel OD column (250 x 4.6 mm) and ChiralPak IA column (250 x 4.6 mm). Compounds were detected by monitoring UV absorbance at 254 nm. Optical rotations were determined on a JASCO 1030 polarimeter at 25 ℃.

1-(4-(Trimethylsilyl)but-3-ynyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (35b)



General Procedure of Pictet-Spenger Reaction: To tryptamine (2 g, 12.48 mmol) in dry EtOAc (25 mL) at 0 ^{o}C was added aldehyde **34b** (0.96 g, 6.24 mmol) followed by slow addition of TFA (1.49 mL, 24.97 mmol). Another portion of aldehyde (2.89 g, 18.73 mmol) was added within 3 h through syringe pump. The resulting mixture was stirred at 25 ^{o}C for 12 h before cooled to 0 ^{o}C.

The solution was basified with 2 M NaOH (13 mL). The aqueous layer was extracted with DCM (50 ml×3). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (20:1 DCM/MeOH) provided the pure product **35b** (3 g, 81 %) as a yellowish solid.

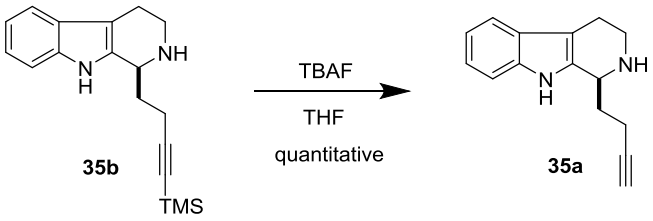
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (s, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.32 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.20 – 7.14 (m, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 4.37 – 4.30 (m, 1H), 4.14 (s, 1H), 3.33 (dt, *J* = 12.9, 5.4 Hz, 1H), 3.12 (ddd, *J* = 12.6, 6.8, 5.4 Hz, 1H), 2.86 – 2.72 (m, 2H), 2.57 – 2.40 (m, 2H), 2.09 (dtd, *J* = 14.3, 7.2, 4.9 Hz, 1H), 2.00 (dt, *J* = 14.0, 6.9 Hz, 1H), 0.19 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 135.79, 134.95, 127.29, 121.67, 119.37, 118.12, 110.97, 108.81, 106.86, 86.31, 51.50, 41.60, 33.06, 22.28, 16.77, 0.23.

IR (neat, cm^{-1}): 3287, 2957, 2171, 1678, 1454, 1251, 1143, 842.

HRMS (ESI) m/z calcd for $C_{18}H_{24}N_2SiH^+$: 297.1782, found: 297.1787.

1-(But-3-ynyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (35a)



General Procedure of Desilylation by TBAF: To substrate **35b** (3 g, 10.12 mmol) in THF (33 mL) at 0 ^oC was added 1 M TBAF (12 mL, 12 mmol). The reaction solution was warmed to 25 ^oC and stirred at 25 ^oC for 1 h before quenched with water (15 mL). The aqueous layer was extracted EtOAc (40 mL×3), dried over Na_2SO_4, decanted and concentrated. Purification by flash chromatography (20:1 DCM/MeOH) provided the pure product **35a** (2.27 g, 100 %) as a yellow oil.

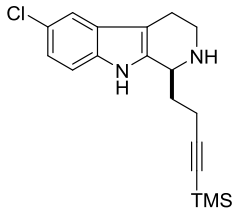
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.16 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 7.13 – 7.07 (m, 1H), 4.24 (dd, *J* = 9.1, 4.2 Hz, 1H), 3.28 (dt, *J* = 13.0, 5.3 Hz, 1H), 3.08 (ddd, *J* = 12.8, 6.8, 5.4 Hz, 1H), 2.81 – 2.65 (m, 2H), 2.58 – 2.37 (m, 2H), 2.11 – 2.02 (m, 1H), 2.06 (t, *J* = 2.6 Hz, 1H), 1.98 – 1.86 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 135.77, 135.64, 127.45, 121.59, 119.36, 118.14, 110.94, 109.10, 84.20, 69.74, 51.12, 41.63, 33.35, 22.71, 15.27.

IR (neat, cm^{-1}): 3291, 3058, 2928, 2116, 1685, 1441, 1197, 1130.

HRMS (ESI) m/z calcd for $C_{15}H_{16}N_2H^+$: 225.1387, found: 225.1394.

6-Chloro-1-(4-(trimethylsilyl)but-3-ynyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (68e.1)



Prepared by the same procedure as compound **35b.** Purification by flash chromatography (20:1 DCM/MeOH) provided the title product (0.16 g, 31%) as a yellowish oil.

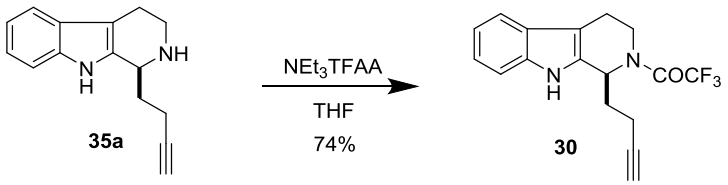
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.23 – 7.17 (m, 1H), 7.09 (dd, *J* = 8.5, 2.0 Hz, 1H), 4.25 – 4.16 (m, 1H), 3.26 (dt, *J* = 13.1, 5.3 Hz, 1H), 3.06 (ddd, *J* = 12.7, 6.6, 5.5 Hz, 1H), 2.69 (tdd, *J* = 5.2, 3.2, 1.6 Hz, 2H), 2.59 – 2.38 (m, 2H), 2.04 (dtd, *J* = 14.6, 7.3, 4.7 Hz, 1H), 2.04 – 1.83 (br, 1H), 1.98 – 1.83 (m, 1H), 0.17 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 137.00, 134.03, 128.50, 124.85, 121.62, 117.60, 111.76, 108.81, 106.68, 86.37, 51.37, 41.52, 33.13, 22.37, 16.76, 0.16.

IR (neat, cm^{-1}): 2956, 2177, 1443, 1311, 1251, 842, 756.

HRMS (ESI) m/z calcd for $C_{18}H_{23}ClN_2SiH^+$: 331.1392, found: 331.1392.

1-(1-(But-3-ynyl)-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2,2,2-trifluoroethanone (30)



The substrate **35a** (0.138 g, 0.46 mmol) was dissolved in THF (4.5 mL) and the resulting reaction solution was cooled to -78 ^{o}C. TEA (0.39 mL, 2.77 mmol) and TFAA (0.19 mL, 1.38 mmol) were added. After stirring at -78 ^{o}C for 2 h, the reaction solution was diluted with EtOAc (50 mL), warmed to 25 ^{o}C, then washed with saturated NH_4Cl (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (10:1 Hexanes/EtOAc) provided the pure product **30** (0.11 g, 74 %) as a white solid.

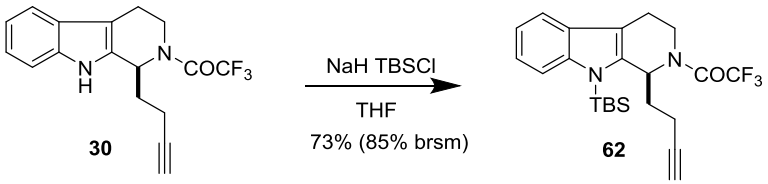
^{1}H NMR (500 MHz, $CDCl_3$; mixure of two rotamers of 10:1 ratio) δ 8.07 (s, 1H), 7.48 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 7.16 – 7.10 (m, 1H), 5.85 (t, *J* = 7.3 Hz, 1H), 4.33 – 4.17 (m, 1H), 3.60 (ddd, *J* = 13.9, 11.8, 4.4 Hz, 1H), 3.02 – 2.92 (m, 1H), 2.88 (ddd, *J* = 15.7, 4.5, 1.5 Hz, 1H), 2.50 (dtd, *J* = 17.3, 6.7, 2.7 Hz, 1H), 2.40 (dtd, *J* = 17.3, 7.5, 2.7 Hz, 1H), 2.23- 2.09 (m, 1 H), 2.16 (t, *J* = 2.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$; mixure of two rotamers of 10:1 ratio) δ 156.91, 136.21, 131.72, 126.28, 122.40, 119.85, 118.23, 116.16, 111.32, 107.48, 82.99, 70.00, 50.84, 40.70, 32.59, 22.25, 15.72.

IR (neat, cm^{-1}): 3330, 3272, 1676, 1454, 1274, 1179, 1140.

HRMS (ESI) m/z calcd for $C_{17}H_{15}F_3N_2OH^+$: 321.1210, found: 321.1211.

1-(1-(But-3-ynyl)-9-(tert-butyldimethylsilyl)-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2,2,2-trifluoroethanone (62)



To NaH (2.32 g, 58.1 mmol, 60 % in mineral oil) in THF (240 mL) at 0 ^{o}C was slowly added the solution of substrate **30** (15.5 g, 48.4 mmol) in THF (60 mL). The reaction mixture was stirred at 25 ^{o}C for 30 min before cooled to 0 ^{o}C. The solution of TBSCl (8.75 g, 58.1 mmol) in THF (60 mL) was slowly added. The mixture was warmed to 25 ^{o}C and stirred for 12 h before quenched with water (50 mL). The aqueous layer was extracted with EtOAc (150 mL×3), washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (10:1, then 10:1 Hexanes/EtOAc) provided the pure product **62** (15.25 g, 73 %) as a white solid and unreacted starting material **30** (2.16 g, 14 %) as a yellowish solid.

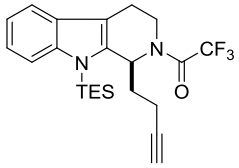
^{1}H NMR (500 MHz, $CDCl_3$; mixure of two rotamers of 17:1 ratio) δ 7.61 – 7.52 (m, 1H), 7.42 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.18 – 7.09 (m, 2H), 6.03 (dd, *J* = 11.4, 2.3 Hz, 1H), 4.20 (dd, *J* = 14.7, 6.4 Hz, 1H), 3.70 (ddd, *J* = 14.3, 11.9, 5.2 Hz, 1H), 3.02 (ddd, *J* = 15.3, 11.9, 6.4 Hz, 1H), 2.90 (dd, *J* = 15.5, 5.3 Hz, 1H), 2.34 (dtd, *J* = 13.3, 10.4, 9.6, 3.3 Hz, 1H), 2.30 – 2.20 (m, 2H), 2.16 – 2.04 (m, 1H), 1.98 (t, *J* = 2.5 Hz, 1H), 0.84 (s, 9H), 0.82 (s, 3H), 0.69 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$; mixure of two rotamers of 17:1 ratio) δ 156.65, 142.48, 139.00, 129.76, 121.98, 120.31, 117.91, 116.56, 115.08, 110.98, 82.54, 69.35, 51.25, 38.35, 33.31, 27.34, 22.20, 20.98, 15.38, -0.39, -0.67.

IR (neat, cm^{-1}): 3270, 2933, 1683, 1452, 1199, 1140, 812.

HRMS (ESI) m/z calcd for $C_{23}H_{29}F_3N_2OSiH^+$: 435.2074, found: 435.2074.

1-(1-(But-3-ynyl)-9-(triethylsilyl)-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)-2,2,2-trifluoroethanone (67)



Prepared by the same procedure as compound **62**. Purification by flash chromatography (1:1 hexanes/EtOAc) provided the title product **67** (0.14 g, 66%) as a colorless oil.

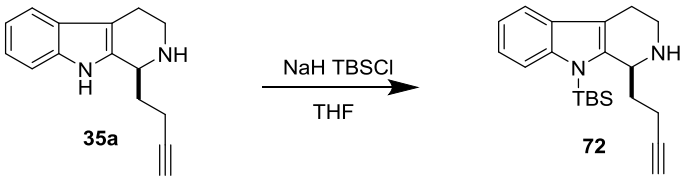
^{1}H NMR (400 MHz, $CDCl_3$; mixure of two rotamers of 6.7:1 ratio): δ 7.55 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.23 – 7.11 (m, 2H), 5.99 (dd, *J* = 11.2, 3.2 Hz, 1H), 4.21 (dd, *J* = 14.7, 6.0 Hz, 1H), 3.70 – 3.58 (m, 1H), 3.01 (ddd, *J* = 17.8, 12.0, 6.1 Hz, 1H), 2.89 (dd, *J* = 15.6, 4.9 Hz, 1H), 2.44 – 2.25 (m, 2H), 2.15 (dtdd, *J* = 23.3, 16.8, 12.8, 7.8 Hz, 2H), 2.02 (q, *J* = 2.2 Hz, 1H), 1,32 – 1.08 (m, 6H), 1.04 – 0.95 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$; mixure of two rotamers of 6.7:1 ratio): δ 156.74, 141.36, 138.39, 129.56, 121.83, 120.09, 118.02, 113.69, 110.15, 82.50, 69.23, 50.93, 38.61, 33.66, 22.29, 15.32, 7.02, 5.04.

IR (neat, cm^{-1}): 3283, 2963, 1678, 1454, 1177, 1141, 1000.

HRMS (ESI) m/z calcd for $C_{23}H_{29}F_3N_2OSiLi^+$: 441.2157, found: 441.2163.

1-(But-3-ynyl)-9-(tert-butyldimethylsilyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (72)



Prepared by the same procedure as compound **62**. Purification by flash chromatography (30:1 DCM/MeOH) provided the title product **72** (3 g, 60%) as a yellowish oil.

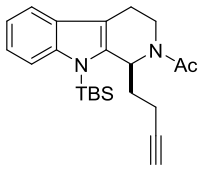
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 – 7.53 (m, 1H), 7.47 – 7.39 (m, 1H), 7.14 – 7.06 (m, 2H), 4.21 (dd, *J* = 10.7, 3.7 Hz, 1H), 3.22 – 3.05 (m, 2H), 2.82 (ddd, *J* = 17.1, 10.2, 7.3 Hz, 1H), 2.72 (ddd, *J* = 15.9, 5.4, 2.1 Hz, 1H), 2.47 (dddd, *J* = 17.0, 14.3, 10.4, 7.6 Hz, 2H), 2.02 (t, *J* = 2.7 Hz, 1H), 1.97 (dtd, *J* = 14.6, 9.4, 8.7, 3.4 Hz, 2H), 0.86 (s, 9H), 0.78 (s, 3H), 0.64 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.69, 142.07, 130.86, 121.14, 119.66, 117.58, 114.71, 112.12, 84.02, 69.09, 51.47, 36.48, 32.28, 27.45, 22.71, 20.97, 15.56, -0.11, -0.47.

IR (neat, cm^{-1}): 3296, 2926, 2114, 1454, 1255, 1147.

HRMS (ESI) m/z calcd for $C_{21}H_{30}N_2SiH^+$: 339.2251, found: 339.2255.

1-(1-(But-3-ynyl)-9-(tert-butyldimethylsilyl)-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)ethanone (68a)



Prepared by the same procedure as compound **30**. Purification by flash chromatography (5:1 hexanes/EtOAc) provided the title product **68a** (0.17 g, 72%) as a yellowish oil.

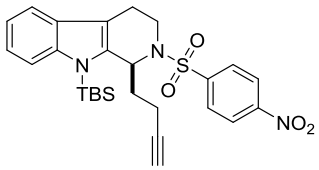
^{1}H NMR (400 MHz, $CDCl_3$; mixure of two rotamers of 3:1 ratio): δ 7.64 – 7.52 (m, 1H), 7.45 – 7.36 (m, 1H), 7.16 – 7.07 (m, 2H), 6.11 (dd, *J* = 11.6, 2.7 Hz, 1H), 4.02 – 3.89 (m, 1H), 3.61 (ddd, *J* = 14.2, 11.6, 5.3 Hz, 1H), 3.05 – 2.87 (m, 1H), 2.83 (ddd, *J* = 15.5, 5.3, 1.5 Hz, 1H), 2.43 – 2.23 (m, 2H), 2.21 (s, 3H), 2.19 – 1.97 (m, 2H), 1.96 (t, *J* = 2.6 Hz, 1H), 0.91 (s, 3H), 0.84 (s, 9H), 0.69 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$; mixure of two rotamers of 3:1 ratio): δ 169.69, 142.31, 141.04, 129.99, 121.41, 119.92, 117.58, 114.95, 111.13, 83.67, 68.43, 48.69, 38.85, 33.71, 27.36, 21.89, 21.84, 20.90, 15.52, -0.36, -0.71.

IR (neat, cm^{-1}): 3237, 2929, 1635, 1425, 1235, 1151, 1026.

HRMS (ESI) m/z calcd for $C_{23}H_{32}N_2OSiH^+$: 381.2357, found: 381.2353.

1-(But-3-ynyl)-9-(tert-butyldimethylsilyl)-2-(4-nitrophenylsulfonyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (68c)



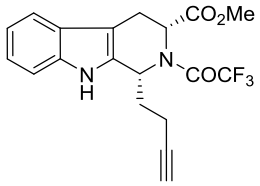
Prepared by the same procedure as compound **30**. Purification by flash chromatography (3:4 hexanes/DCM) provided the title product **68c** (0.13 g, 60%) as a yellowish solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.9 Hz, 2H), 7.90 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.11 (ddd, *J* = 8.3, 7.1, 1.4 Hz, 1H), 7.04 (t, *J* = 7.4 Hz, 1H), 5.36 (dd, *J* = 11.7, 2.9 Hz, 1H), 4.16 – 4.02 (m, 1H), 3.50 (ddd, *J* = 15.0, 11.0, 6.7 Hz, 1H), 2.68 – 2.53 (m, 2H), 2.46 (dddd, *J* = 16.7, 8.2, 4.8, 2.6 Hz, 1H), 2.32 (dtd, *J* = 16.9, 7.9, 2.6 Hz, 1H), 2.25 – 2.14 (m, 1H), 2.04 (t, *J* = 2.6 Hz, 1H), 2.04 – 1.96 (m, 1H), 0.92 (s, 9H), 0.83 (s, 3H), 0.72 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.56, 146.22, 141.64, 138.96, 129.57, 127.97, 123.82, 121.96, 120.11, 117.61, 115.03, 110.93, 82.76, 69.75, 53.57, 37.39, 33.85, 27.68, 20.85, 19.99, 15.57, -0.57, -0.77.

IR (neat, cm^{-1}): 3304, 2939, 1525, 1452, 1348, 1164, 1095.

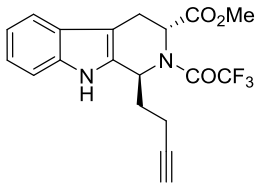
Methyl (1*R*,3*R*)-1-(but-3-yn-1-yl)-2-(trifluoroacetyl)-1H,2H,3H,4H,9H-pyrido[3,4-b]indole-3-carboxylate (31)



Prepared by the same procedure as compound **30**. Purification by flash chromatography (6:1 hexanes/EtOAc) provided the title product **31** (0.119 g, 50%) as a yellowish solid.

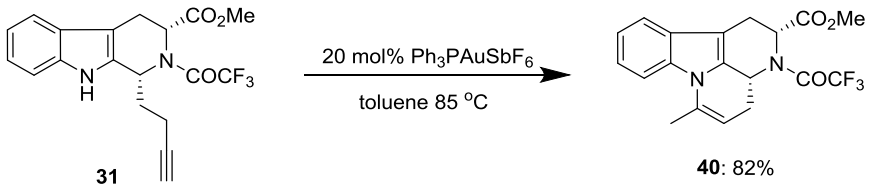
^{1}H NMR (500 MHz, Chloroform-d) δ 8.55 (s, 1H), 7.55 – 7.50 (m, 1H), 7.37 – 7.32 (m, 1H), 7.24 – 7.19 (m, 1H), 7.14 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H), 5.56 (t, *J* = 6.1 Hz, 1H), 5.12 (dd, *J* = 6.4, 1.5 Hz, 1H), 3.78 (s, 1H), 3.68 (s, 3H), 3.63 (dd, *J* = 15.9, 1.5 Hz, 1H), 3.10 (ddd, *J* = 15.8, 6.4, 2.0 Hz, 1H), 2.81 – 2.72 (m, 1H), 2.57 (dtd, *J* = 17.2, 6.0, 2.7 Hz, 1H), 2.34 – 2.26 (m, 1H), 2.25 (t, *J* = 2.7 Hz, 1H).

Methyl (1*S*,3*R*)-1-(but-3-yn-1-yl)-2-(trifluoroacetyl)-1H,2H,3H,4H,9H-pyrido[3,4-b]indole-3-carboxylate (32)



Prepared by the same procedure as compound **30**. Purification by flash chromatography (5:1 hexanes/EtOAc) provided the title product **32** (0.031 g, 13%) as a yellowish solid.

^{1}H NMR (400 MHz, Chloroform-d) δ 8.56 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.17 – 7.11 (m, 1H), 5.56 (t, *J* = 6.1 Hz, 1H), 5.12 (dd, *J* = 6.4, 1.5 Hz, 1H), 3.78 (s, 1H), 3.69 (s, 3H), 3.63 (dd, *J* = 15.9, 1.5 Hz, 1H), 3.11 (ddd, *J* = 15.9, 6.4, 2.0 Hz, 1H), 2.85 – 2.71 (m, 1H), 2.57 (dtd, *J* = 17.2, 6.1, 2.9 Hz, 1H), 2.34 – 2.27 (m, 1H), 2.25 (t, *J* = 2.6 Hz, 1H).

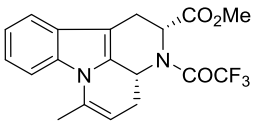


31 **40**: 82%

Representative Procedure of gold-catalyzed cyclization: Mixture of PPh_3AuCl (2.6 mg, 5 μmol) and $AgSbF_6$ (1.8 mg, 5 μmol) in 0.5 mL DCM was stirred for 5 min. The solution was added to

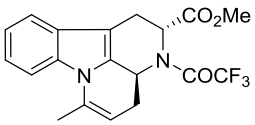
the alkynylindole **31** (10 mg, 26 μmol) in 3 mL toluene. Then the reaction solution was heated to 85 ^{o}C and stirred at 85 ^{o}C for 4 h. The reaction was cooled to room temperature and the solution was filtered through a plug of silca gel, then concentrated. Purification by flash chromatography (15:1, hexanes/EtOAc) afforded **40** (8 mg, 82% yield) as a colorless oil.

Methyl (5*R*,7*R*)-2-methyl-6-(trifluoroacetyl)-1,6-diazatetracyclo[7.6.1.0^{5,16}.0^{10,15}]hexadeca-2,9(16),10,12,14-pentaene-7-carboxylate (40)



^{1}H NMR (500 MHz, Chloroform-d): δ 7.66 (d, *J* = 8.6 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.19 (ddd, *J* = 8.5, 7.1, 1.4 Hz, 1H), 7.16 – 7.11 (m, 1H), 5.24 – 5.14 (m, 1H), 5.10 (dd, *J* = 5.6, 1.8 Hz, 1H), 5.05 (dd, *J* = 6.7, 1.6 Hz, 1H), 3.66 (dd, *J* = 15.7, 1.9 Hz, 1H), 3.60 (s, 3H), 3.10 (ddd, *J* = 15.7, 5.5, 2.2 Hz, 1H), 3.06 – 2.95 (m, 1H), 2.52 (s, 3H), 2.57 – 2.47 (m, 1H).

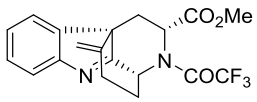
Methyl (5*S*,7*R*)-2-methyl-6-(trifluoroacetyl)-1,6-diazatetracyclo[7.6.1.0^{5,16}.0^{10,15}]hexadeca-2,9(16),10,12,14-pentaene-7-carboxylate (42)



Prepared by the same procedure as compound **40**. Purification by flash chromatography (15:1 hexanes/EtOAc) provided the title product **42** (0.17 g, 72%) as a yellowish oil.

^{1}H NMR (500 MHz, Chloroform-d) δ 7.64 (d, *J* = 8.3 Hz, 1H), 7.51 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.22 – 7.18 (m, 1H), 7.17 – 7.13 (m, 1H), 5.12 (s, 1H), 5.06 (d, *J* = 7.5 Hz, 1H), 4.99 (d, *J* = 12.8 Hz, 1H), 3.71 (s, 3H), 3.58 (t, *J* = 11.8 Hz, 2H), 3.24 (ddd, *J* = 15.9, 6.0, 2.5 Hz, 1H), 2.51 (t, *J* = 1.9 Hz, 3H), 2.04 (d, *J* = 12.6 Hz, 1H).

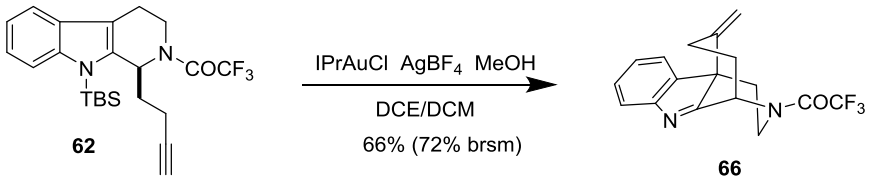
Methyl (1*R*,10*S*,12*R*)-14-methylidene-11-(trifluoroacetyl)-8,11-diazatetracyclo[8.3.3.0^{1,9}.0^{2,7}] hexadeca-2,4,6,8-tetraene-12-carboxylate (41)



Prepared by the same procedure as compound **40**. Purification by flash chromatography (5:1 hexanes/EtOAc) provided the title product **41** (0.17 g, 72%) as a yellowish oil.

^{1}H NMR (500 MHz, Chloroform-d) δ 7.67 (dt, *J* = 7.8, 0.8 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.41 (td, *J* = 7.6, 1.4 Hz, 1H), 7.36 (td, *J* = 7.4, 1.2 Hz, 1H), 5.34 (s, 1H), 4.75 – 4.73 (m, 1H), 4.72 (d, *J* = 1.5 Hz, 1H), 4.71 (d, *J* = 1.6 Hz, 1H), 3.44 (s, 3H), 3.01 (dd, *J* = 14.6, 1.5 Hz, 1H), 2.87 – 2.79 (m, 1H), 2.74 (dd, *J* = 14.6, 6.3 Hz, 1H), 2.65 (ddd, *J* = 13.4, 10.6, 5.0 Hz, 1H), 2.33 (ddd, *J* = 14.9, 5.0, 1.7 Hz, 1H), 1.71 (tdd, *J* = 13.7, 5.0, 2.4 Hz, 1H).

2,2,2-Trifluoro-1-{14-methylidene-8,11-diazatetracyclo[8.3.3.0^{1,9}.0^{2,7}]hexadeca-2,4,6,8-tetraen-11-yl}ethan-1-one (66)



To 100 mL sealed tube were added IPrAuCl (0.114 g, 0.18 mmol) and $AgBF_4$ (36 mg, 0.18 mmol) followed by DCM (1.5 mL). and the resulting mixture was stirred for 5 min. The solution of substrate **62** (1 g, 2.30 mmol) in DCE (11.5 mL) was added followed by methanol (1.87 mL, 46 mmol). The reaction solution was stirred at 95 ^oC for 12 h before cooled to 25 ^oC. The mixture was filtered through a short plug of silica gel and the solution was concentrated. Purification by flash chromatography (50:1, then 7:1 Hexanes/EtOAc) provided the pure product

66 (486 mg, 66 %) as a white solid and unreacted starting material **62** (80 mg, 8 %) as a white solid.

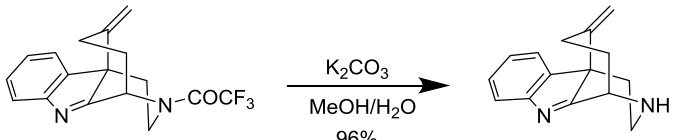
^{1}H NMR (500 MHz, $CDCl_3$; mixure of two rotamers of 4:1 ratio) δ 7.72 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.34 (td, *J* = 7.5, 1.1 Hz, 1H), 5.45 (t, *J* = 3.1 Hz, 1H), 4.89 (s, 1H), 4.86 (s, 1H), 3.98 – 3.84 (m, 1H), 3.13 (ddd, *J* = 13.8, 10.4, 4.9 Hz, 1H), 2.80 – 2.63 (m, 2H), 2.59 (ddd, *J* = 13.9, 10.5, 4.9 Hz, 1H), 2.38 – 2.24 (m, 1H), 2.09 (dt, *J* = 14.1, 4.9 Hz, 1H), 1.91 – 1.82 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$; mixure of two rotamers of 4:1 ratio) δ 181.53, 156.21, 154.77, 147.25, 142.34, 128.39, 125.95, 124.08, 121.91, 116.36, 110.96, 59.90, 54.18, 41.98, 35.11, 31.49, 27.64.

IR (neat, cm^{-1}): 2952, 1691, 1626, 1447, 1378, 1208, 1141, 909.

HRMS (ESI) m/z calcd for $C_{17}H_{15}F_3N_2OH^+$: 321.1210, found: 321.1199.

14-Methylidene-8,11-diazatetracyclo[8.3.3.0^{1,9}.0^{2,7}]hexadeca-2,4,6,8-tetraene (73)



To substrate **66** (40 mg, 0.13 mmol) in MeOH/H_2O (1.2 mL, 1:1) was added K_2CO_3 (80 mg, 0.58 mmol). After stirring at 25 ^oC for 12 h, the solvent was evaporated and water was added. The aqueous layer was extracted with chloroform (10 ml×3) and the combined organic phases were dried over Na_2SO_4, decanted and concentated. Purification by flash chromatography (12:1 DCM/MeOH) provided the pure product **73** (27 mg, 96 %) as a yellowish solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.7 Hz, 1H), 7.49 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.37 (td, *J* = 7.6, 1.3 Hz, 1H), 7.26 – 7.22 (m, 1H), 5.13 (s, 1H), 5.00 (s, 1H), 4.22 (dd, *J* = 6.3, 3.3 Hz,

1H), 3.35 (ddd, *J* = 14.2, 12.2, 3.7 Hz, 1H), 2.77 (ddd, *J* = 14.4, 5.7, 2.0 Hz, 1H), 2.74 – 2.67 (m, 1H), 2.67 – 2.62 (m, 1H), 2.28 – 2.18 (m, 2H), 2.24 – 2.18 (br, 1H), 2.07 (dtt, *J* = 15.2, 7.5, 1.4 Hz, 1H), 1.60 (td, *J* = 12.6, 5.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 188.08, 155.01, 149.05, 143.57, 127.89, 125.03, 123.24, 121.11, 111.25, 59.40, 51.79, 46.88, 39.07, 31.78, 31.63.

IR (neat, cm^{-1}): 3263, 2929, 1678, 1594, 1434, 1184, 1121, 897.

HRMS (ESI) m/z calcd for $C_{15}H_{16}N_2H^+$: 225.1387, found: 225.1390.

3.6 References

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Chapter 4

Studies Towards the Total Synthesis of Strictamine: Application of Gold Carbene-Catalyzed Desilylative Cyclization

4.1 Background of Strictamine

Strictamine **1** (Figure 4.1) was isolated from *Rhazya stricta* in 1966 by Biemann, Chatterjee and co-workers.[1] Its structure was determined by ultrviolet absorbance, infrared bands, NMR and mass spectroscopy. Subsequent experiments confirmed the skeletone of strictamine and it was found to undergo rearrangement to akuammicine under treatment of strong base, such as KO^{t}Bu. In 1976, strictamine **1** and strictalamine were isolated by Ahmad and the absolute configuration was resolved by X-ray crystallography (Figure 4.1).[2]

In 2014, strictamine **1** was reported to exhibit inhibitory activity against herpes simplex virus (HSV) and adenovirus (ADV) with EC50 value of 0.36 μg/ml for HSV and 0.28 μg/ml for ADV.[3]

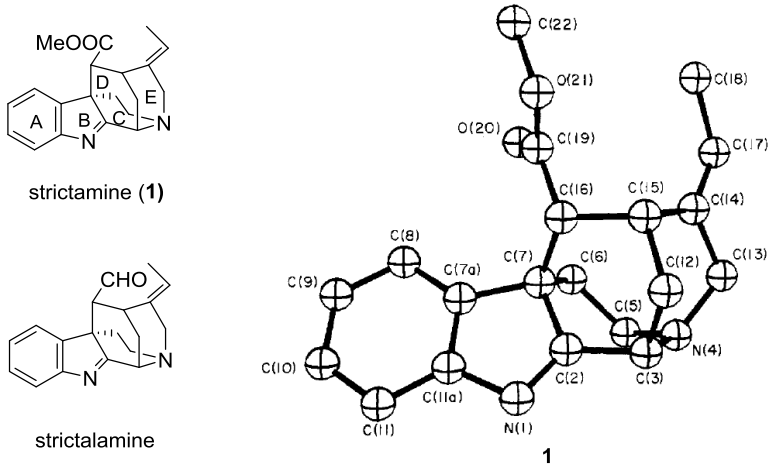


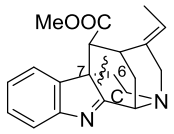
Figure 4.1 Structures of Strictamine **1** and Strictalamine

4.2 Previous Attempted Syntheses of Strictamine

Until now, the densely fused pentacyclic skeleton and related bioactivity of strictamine (**1**) have attracted considerable interest from organic synthetic groups.

4.2.1 Synthetic Study Reported by the Bosch Group

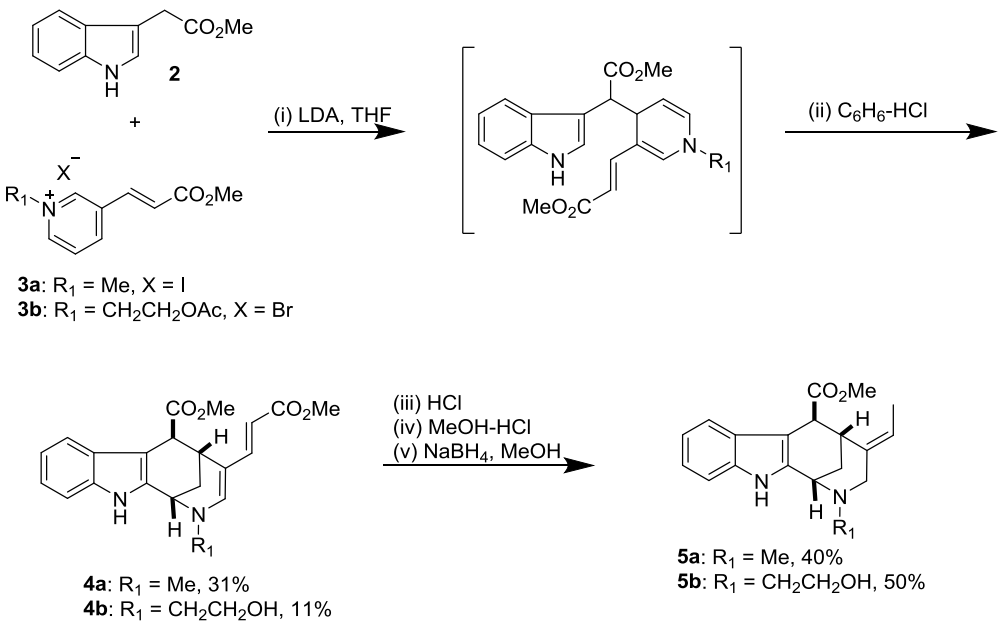
In 1988 and 1996, synthetic efforts to form ring C of strictamine **1** (Figure 4.2) were reported by the Bosch group.[4, 5]



1

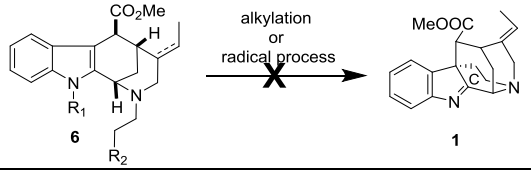
Figure 4.2 Synthetic Strategy of Strictamine by the Bosch Group

The tandem nucleophilic addition of enolate of ester **2** (Scheme 4.1) to a pyridinium salt **3** was applied to the synthesis of bridged indole alkaloids. After several steps of functional group transformation, key intermediate **5** was prepared before attempting the closure of the six-member ring.[4]



Scheme 4.1 Preparation of Tetracycle

Upon minor modification from compound **5**, compound **6** (Scheme 4.2) was subjected to various cyclization conditions. No desired product **1** was found. Instead, C-N bond was formed intramolecularly or intermolecularly. Further study afforded either dealkylated indole or C-R_2 bond-cleaved product of tetracycle **6**.[5]

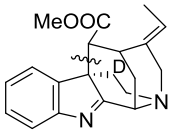


R_1 & R_2	Results
R_1 = H	No **1** was formed.
R_1 = Me, CO_2Me; R_2 = SePh, SOPh, $(SMe)_2$.	No **1** was formed. C-R_2 bond was cleaved.

Scheme 4.2 Results of Attempted Cyclization

4.2.2 Synthetic study reported by the Cook group

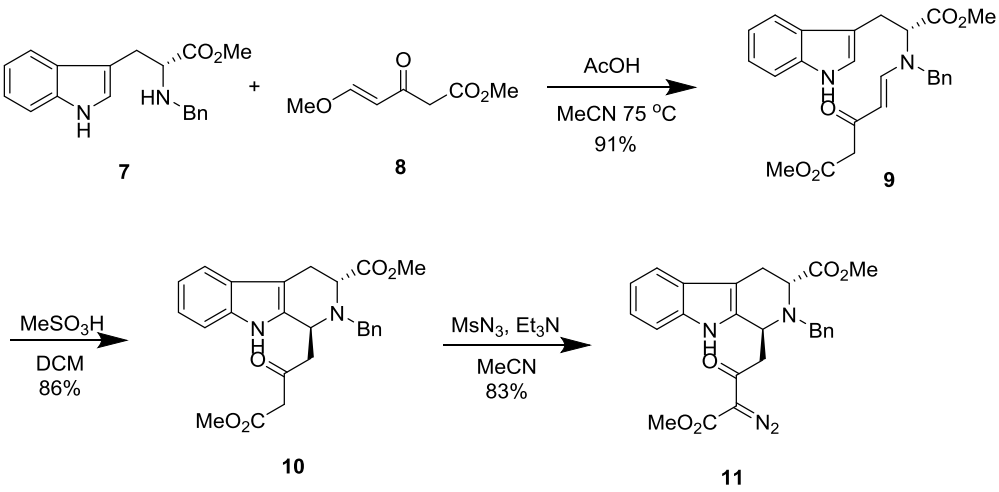
In 2012, the Cook group reported their strategy of rhodium-catalyzed cyclization of diazonium salt to construct ring D of strictamine **1** (Figure 4.3).[6]



1

Figure 4.3 Synthetic Strategy of Strictamine by the Cook Group

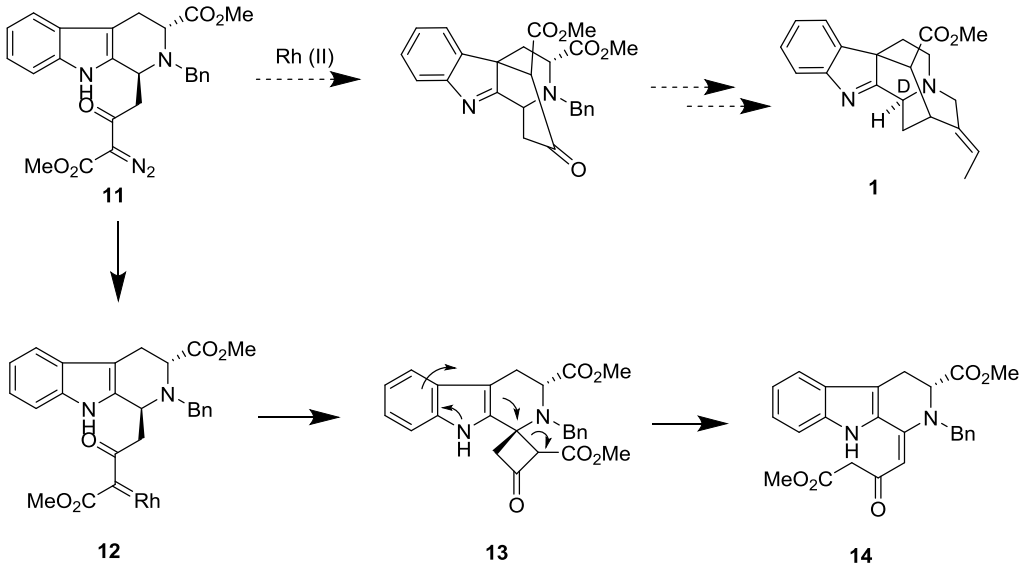
Condensation of D-(+)-N^b-benzyltryptophan methyl ester **7** (Scheme 4.3) and readily accessible Michael acceptor **8** furnished enaminone, which was subjected to acid-mediated cyclization condition to afford the β-keto ester **10**. Under standard diazo transfer condition, the α-diazo β-keto ester **11** was prepared from compound **10**.



7 **8** **9** **10** **11**

Scheme 4.3 Synthesis of Diazonium Salt

Under the catalysis of $Rh_2(OAc)_4$, diazo compound **11** (Scheme 4.4) was converted into enone **14** through cyclization and ring-opening of cyclobutanone **13** in 75% yield.



Scheme 4.4 Attempted Rh(II)-Catalyzed Cyclization of Diazonium Salt

4.2.3 Synthetic Study Reported by the Tokuyama Group

In 2013, the Tokuyama group reported their strategy of constructing ring D by rearrangement of lactone and forming ring E by ring-closing olefin metathesis (RCM) of diene (Figure 4.4).[7]

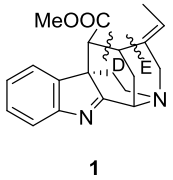
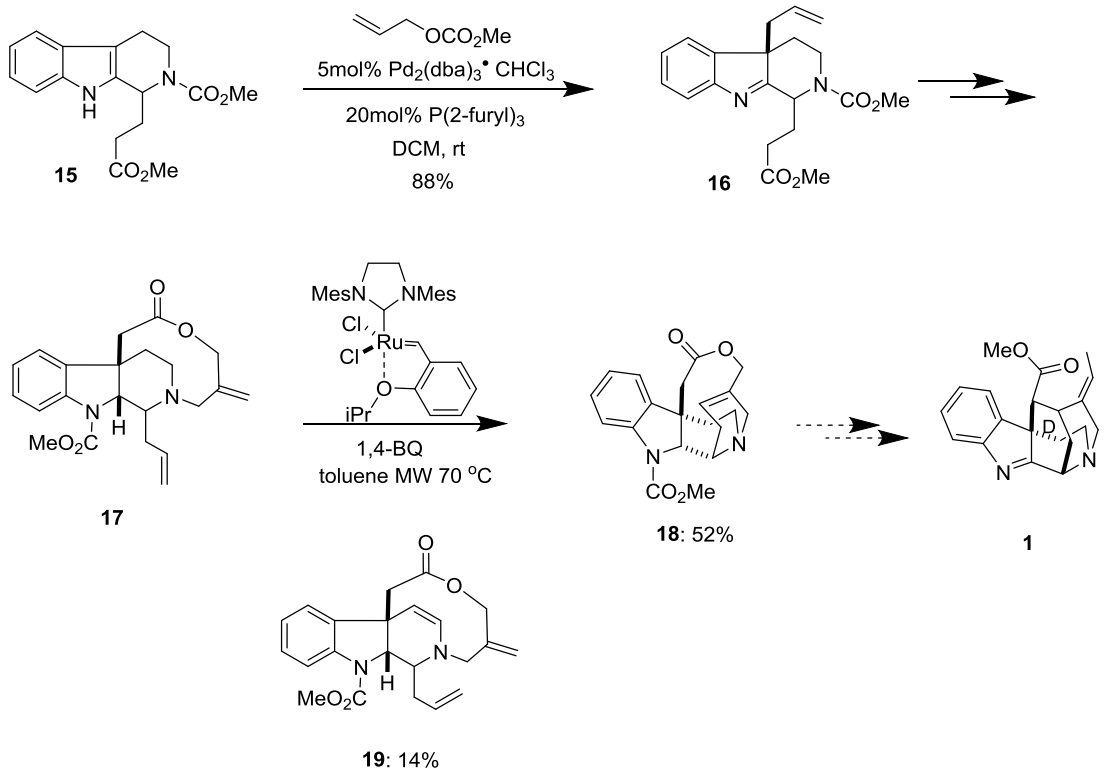


Figure 4.4 Synthetic Strategy of Strictamine by the Tokuyama Group

Starting from the literature-known tetrahydro-β-carboline derivative **15** (Scheme 4.5), the quaternary carbon center of indolenine **16** was constructed by the palladium-catalyzed allylation. After several steps of modification, diene **17** was subject to RCM condition. Desired cyclized product **18** was formed in 16% yield and several side products were identified as isomerzied alkene and oxidized enamine **19** from tertiary amine. Extensive optimization gave

rise to 52% yield under microwave irradiation. For the rearrangement of lactone **18** to construct ring D, no further progress has not been published until now.



Scheme 4.5 Tokuyama's Synthetic Route

3.2.4 Synthetic Study Reported by the Zhu Group

In 2013, the Zhu group exploited their designed approach of intramolecular oxidative coupling of a dianion to construct rind D of strictamine **1** (Figure 4.5). [8]

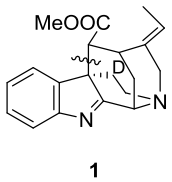
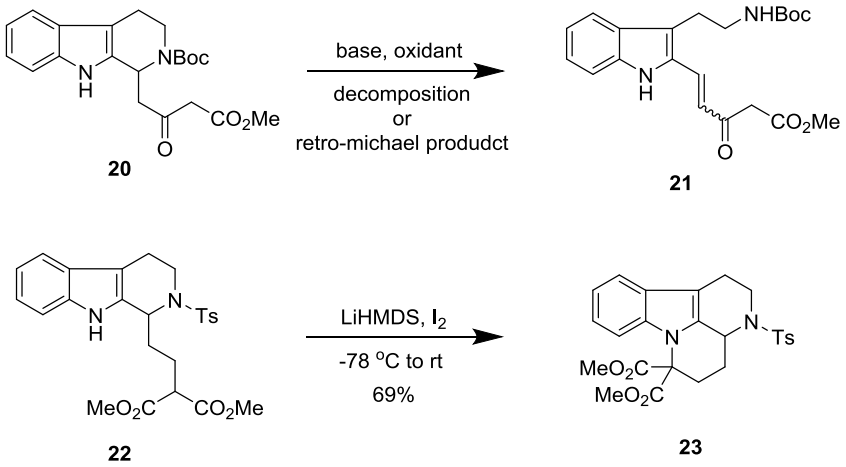


Figure 4.5 Synthetic Strategy of Strictamine by the Zhu Group

Tetrahydocarboline **20** was treated with various bases and oxidants to give no desired product (Scheme 4.6). Instead, degradation was observed and a small amount of retro-Michael reaction product **21** was isolated. Elongated dimethyl malonate derivative **22** was cyclization into tetracyle **23** after deprotonation with LiHMDS at – 78 ℃ followed by oxidation by iodine at room temperature. Based on their rationalization, the failure of formation of desired C-C bond is due to the ring strain within the bridged ring system of **1**.

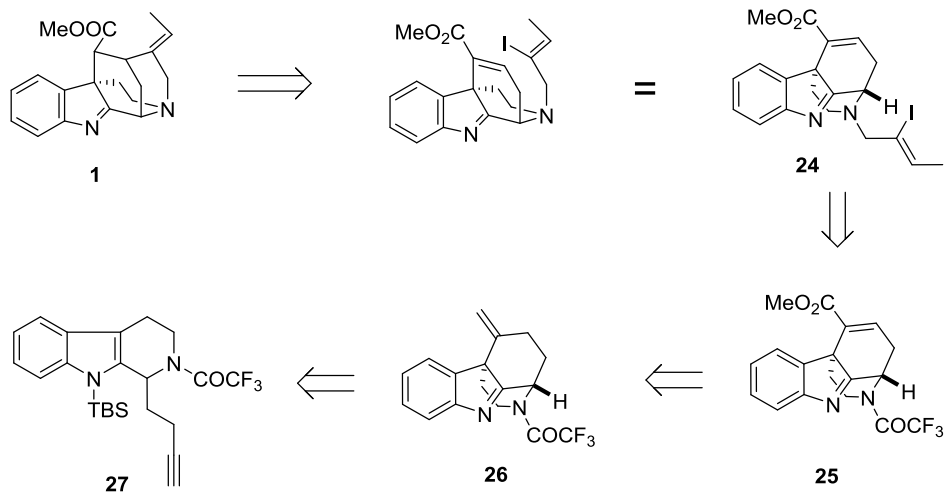


Scheme 4.6 Attempted Oxidative Cyclization

4.3 Retrosynthetic Analysis of Strictamine

Until now, several synthetic studies have been published as described as above, but no total synthesis of strictamine has been reported or accomplished. Due to the challenging rigid skeleton, interesting bioactivity and biogenetic relationship with many bioactive alkaloids[3], such as 17-nor-excelsinidine and akuammicine[9], we are motivated to work on the synthesis of strictamine.

Retrosynthetically, strictamine **1** was envisioned to arise from a transition metal-catalyzed reductive intramolecular cyclization of **24** (Scheme 4.7),[10] which would be obtained from compound **25** by deprotection and alkylation. Ester **25** may be prepared from oxidation of the indolene **26.**



Scheme 4.7 Our Retrosynthetic Analysis

4.4 Synthetic Study of Strictamine

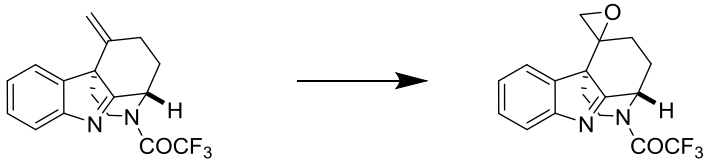
Following the procedure described in the previous chapter, silylated tetrahydrocarboline **27** underwent a gold-catalyzed desilylative cyclization using MeOH as TBS scavenger to give indolenine **26** in 66% isolated yield in 6.7 g scale (70% based on recovered starting material).

Converting the *exo* alkene of compound **26** to conjugated ester **25** while keeping the imine intact proved to be difficult. Riley oxidation with SeO_2 gave no reaction at room temperature and decomposition occurred at 60 ^{o}C.[11] Various boron reagents, such as BH_3•SMe_2, 9-BBN and catecholborane, were exploited for Brown reaction.[12] However, the imine moiety was reduced at the same time as hydroboration of alkene moiety. To achieve the oxidation without destroying the imine moiety, mild and efficient transformation conditions were investigated.

Epoxidation of alkene has been widely applied in organic synthesis especially complex natural product synthesis.[13] Exposed to Lewis acid or Brønsted acid, epoxides can be isomerized into allylic alcohol or aldehyde,[14] which may be converted into conjugated ester **25**.

After screening various oxidants, dimethyldioxirane (DMDO) was found to be efficient and selective for epoxidation of **26** into epoxides **28** (Table 4.1). At room temperature, oxidation by mCPBA led to decomposition of starting material (entry 1). Methyl trifluoromethyl dioxirane[15] (entry 2) gave lower yield of epoxides than in situ generated DMDO (entry 4). Although dioxirane generated from tetrahydrothiopyran-4-one-1,1-dioxide[16] (entry 3) afforded reasonable yield considering recovery of starting material **26**, the diasteroselective ratio (d.r.) was unsatisfactory (entry 4). Thus, distilled DMDO was chosen and lower temperature was tested. Yield remained unchanged while d.r. increased to 4.6:1 from 2.7:1 when the reaction was carried out at 0 ^{o}C (entry 5). Even lower temperature (-20 ^{o}C) afforded 79% yield with 7:1 ratio of distereoselectivity. Indeed, oxidation of the imine moiety was not ceased but slower when DCM was used as co-solvent with acetone (entries 5, 7; 6, 8). The optimized epoxidation condition, carried out in co-solvents of acetone and DCM using distilled DMDO as the oxidant, gave 90% yield with 7:1 d.r. based on recovery of starting material (entry 8). The two epoxides can be separated by flash chromatography on silica gel, but the stereochemistry cannot be assigned due to the absence of long-distance nOe signal. Thus, the major isomer is labeled as compound **28a** and the minor as compound **28b**.

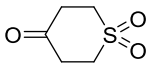
Table 4.1 Screening for Epoxidation



Entry	Reagents	Solvents	Temperature ^{o}C	Converstion %	Yield % (**28a** : **28b**)
1	mCPBA	DCM	23	100	decomposition
2	oxone ketone **I** [a] $NaHCO_3$	MeCN/0.4 mM Na_2EDTA	23	73	23
3	oxone ketone **II** [b] $NaHCO_3$	MeCN/0.4 mM Na_2EDTA	23	68	54 (1:1)
4	oxone $NaHCO_3$	Acetone/H_2O	23	100	70 (2.7:1)
5	DMDO (distilled)	Acetone	0	100	70 (4.6:1)
6	DMDO (distilled)	Acetone	-20	97	79 (7:1)
7	DMDO (distilled)	Acetone/DCM (1:1)	0	100	80 (5:1)
8	DMDO (distilled)	Acetone/DCM (1:1)	-20	87	78 (7:1)

[a] ketone I:

[b] ketone II:



Based on the result of MM2 energy minimization calculation, the conformation of indolenine **26** is shown in Figure 4.6. Epoxidation could proceed in path a and b. Due to the

interaction between DMDO and the hydrogens around olefin, path a is preferred and epoxide **28a** should be the major product.

With epoxides in hand, isomerization of epoxides was investigated. Initial study showed the major epoxide **28a** was isomered into allylic alcohol and aldehyde, while aldehyde was the only product of the minor epoxide **28b**. As the result of MM2 energy minimization calculation shown in Figure 4.6, the conformation of **28a** allowed both C2 and C3 β-elimination processes to afford allylic alcohol **29** and aldehyde **30**. For conformation of **28b**, only C3 β-elimination process was allowed to give aldehyde **30**.

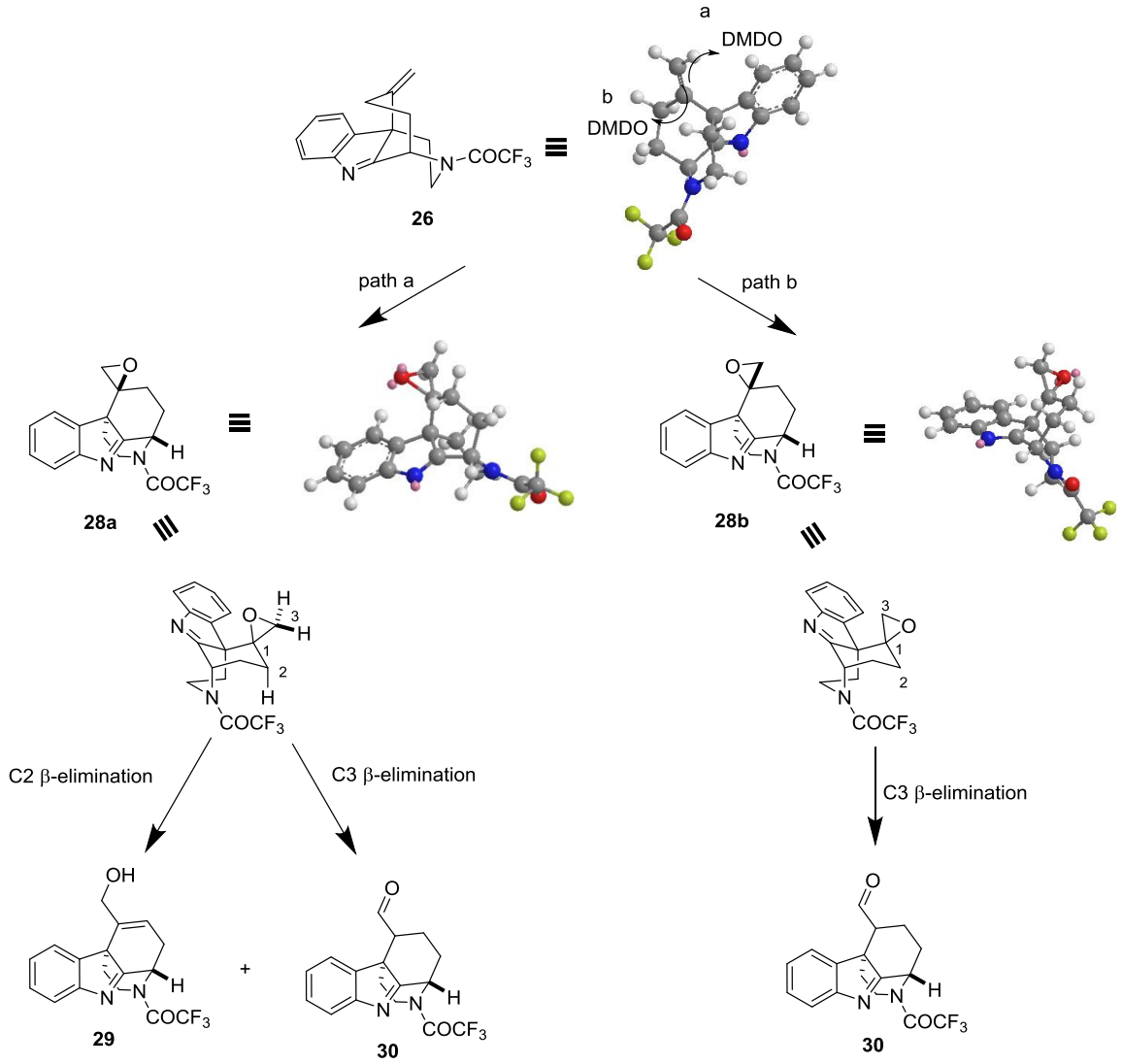
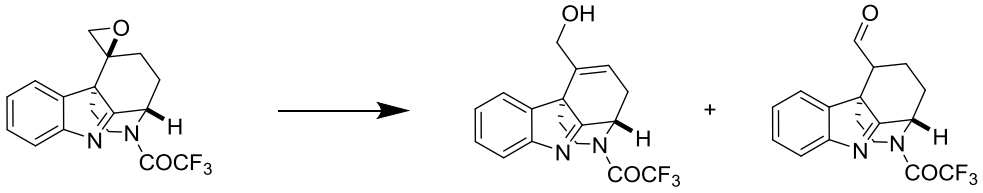


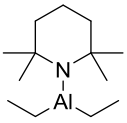
Figure 4.6 Formation and Isomerization of Epoxides

Compared to aldehyde, allylic alcohol is preferred since it can be easiluy oxidized into α,β-unsaturated ester. Thus, various conditions were screened for isomerization of epoxide **28b** into allylic alcohol as shown in Table 4.2. Treated with diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP), [17] CSA[18] or TMSI,[19] epoxide was decomposed or converted into messy mixture. $Al(O^iPr)_3$[20] was found to reduce the imine moiety before inducing isomerization. Allylic alcohol was obtained in 15% yield with aldehyde in 41% yield in the presence of TBSOTf and DBU after workup with TBAF.

Table 4.2 Reagent Screening for Isomerization of Epoxide



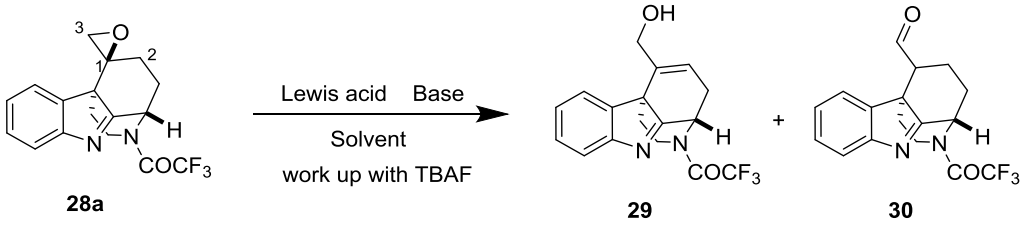
28a **29** **30**

Reagent	Solvent	Temperature ^oC	Result
	Toluene	0	Decomposition
CSA	MeCN/DMSO	25	messy mixture was isolated
TMSI, DBU	MeCN	75	messy mixture was isolated
$Al(O$*i*$-Pr)_3$	Toluene	100	imine was reduced before isomerization
DBU, TBSOTf (workup with TBAF)	DCM	-78 to 25	15% **28a** 15% **29** 41% **30**

The reaction was further optimized as shown in Table 4.3. Replacement of TBSOTf with TMSOTf improved the yield of allylic alcohol **29** from 15% into 33% and all starting

material **28a** was consumed probably due to the less bulky environment (entry 1, 2). Solvent screening gave no better result (entry 2-5). Co-solvent of toluene afforded slightly better yield, but it exihibited no preference in selectivity (entry 7). For hexanes, poor solubility of the complex of TMSOTf and DBU might be used for elucidating the decrease of yield (entry 6). Other than DBU, different bases, such as NEt_3 (entry 8), gave rise to decomposition, while addition of 2,6-lutidine made no difference (entry 9). In the end, the optimized isomerization condition afforded 40% allylic alcohol and 40% aldehyde in the presence of TMSOTf and DBU (entry 7). Bulky environment surrounding the epoxide **28a** gives rise to no selectivity of C2 and C3 β-elimination (Figure 4.6), which probably explains 1:1 ratio of isomerized products **29** and **30**.

Table 4.3 Optimization of Epoxide Isomerization



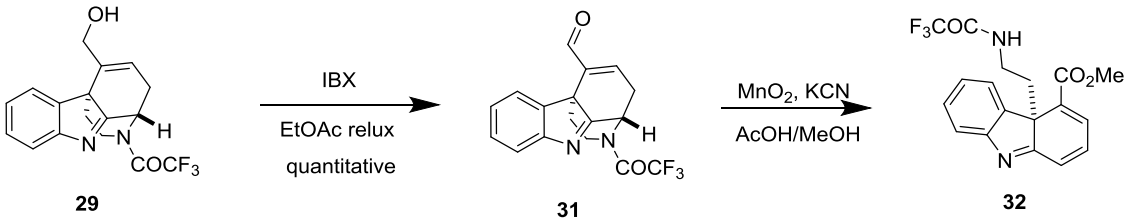
28a **29** **30**

Entry	Lewis acid	Base	Solvent	Conversion %	Yield % **29** : **30**
1	TBSOTf	DBU	DCM	85	15 : 41
2	TMSOTf	DBU	DCM	100	33: 35
3	TMSOTf	DBU	Toluene	100	0 : 0
4	TMSOTf	DBU	MTBE	100	0 : 0
5	TMSOTf	DBU	DCE	100	29 : 27
6	TMSOTf	DBU	DCM/hexanes (1:1)	100	25 : 20
7	TMSOTf	DBU	DCM/toluene (1:1)	100	40 : 40
8	TMSOTf	DBU 2,6-lutidine	DCM/toluene (1:1)	100	40 : 40
9	TMSOTf	Net_3	DCM/toluene (1:1)	100	0 :0

[a] 10 eq DBU and 9 eq TMSOTf was added to epoxide in soln at -78 ^{o}C, then slowly warmed to rt stirred for overnight before general workup. After that, TBAF was added to the crude in THF for desilylation.
[b] 5 eq DBU and 4 eq 2,6-lutidine were used.

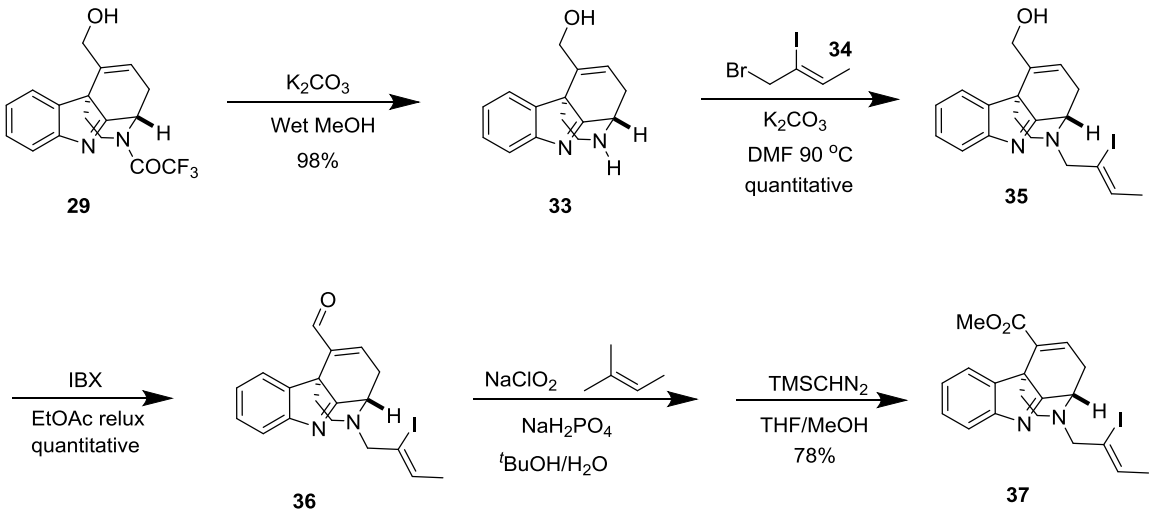
For aldehyde **30** isomerized from epoxide **28a**, various conditions were tested for converstion of aldehyde into α,β-unsaturated aldehyde. IBX oxidation in DMSO/toluene led to decomposition of starting material;[21] silyl enol ether of **30** was subjected to a Saegusa condition using $Pd(OAc)_2$ as the oxidant in acetonitrile to afford messy mixture.[22] Preparation of α-selenide of aldehyde **30** turned out to be inefficient (<10% yield) while decomposition occurred under harsh condition.[23]

Subsequently, allylic alcohol **29** was quantitatively oxidized into aldehyde **30** by IBX in ethyl acetate under reflux.[24] Further oxidation into ester with MnO_2[25] in the presence of KCN, MeOH and acetic acid afforded ring-opened alkene **32** (Scheme 4.8). It can be rationalized in terms of releasing the internal strain of the bridged ring system.



Scheme 4.8 Ring Opening Under Acidic Oxidative Condition.

The synthetic sequence was altered then (Scheme 4.9). Indolenine **29** was deprotected with K_2CO_3 in wet methanol. Following alkylation with vinyl bromide **34** afforded allylic alcohol **35**. After oxidation by IBX, Pinnick oxidation and esterification with trimethylsilyldiazomethane, compound **35** was converted to cyclization precursor **37** of strictamine **1**.

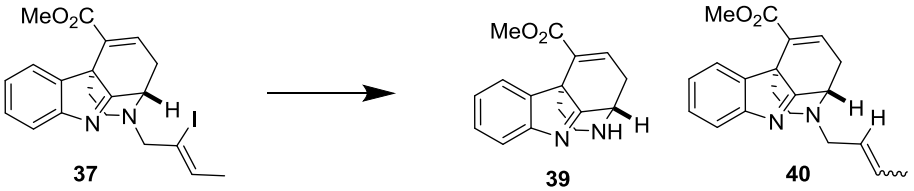


Scheme 4.9 Prepration of Precursor of Strictamine

4.5 Attempted Cyclization

Various conditions were exploited for cyclization of compound **37** (Table 4.4). Reductive Pd-catalyzed cyclization[28] afforded deallylated product **39**. Radical cyclization condition[29] reduced the vinyl iodide into alkene **40**. Conjugate addition[30] and $Ni(COD)_2$-mediated reductive cyclization[31] led to decomposition.

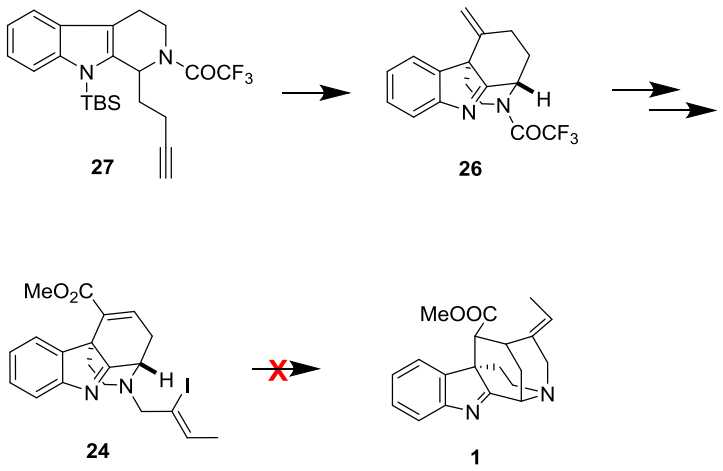
Table 4.4 Attempted Cyclization



Entry	Reaction condition	Results
1	Pd_2dba_3, NaOCOH; DMF 85 ^oC	deallylated product **40** was found; no product or sm existed.
2	AIBN, Bu_3SnH; toluene, 80 ^oC	reduced compound **39** was found; no product or sm existed.
3	*t*-BuLi, THF, -78 ^oC, then 23 ^oC	no rxn occurred at -78 ^oC, then warmed to 23 ^oC, decomposition occurred.
4	$Ni(COD)_2$, NEt_3; MeCN/DMF, 60 ^oC	no rxn occurred at 23 ^oC. At 60 ^oC, decomposition occurred.

4.6 Conclusion

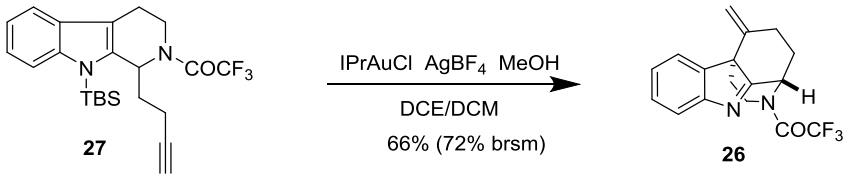
Our strategy (Scheme 4.10) utilized the gold-catalyzed desilylative cyclization of TBS-protected indole substrate **27** to construct the tetracyclic indolenine **26**, which was further modified into precursor **24** of final cyclization. Unfortunately, either transition metal-catalyzed reductive reaction condition or radical process didn't afford the desired strictamine **1**. Further investigation of cyclization is in progress.



Scheme 4.10 Our Route of Synthetic Study of Stricatmine.

4.7 Experimental

2,2,2-Trifluoro-1-{14-methylidene-8,11-diazatetracyclo[8.3.3.$0^{1,9}$.$0^{2,7}$]hexadeca-2,4,6,8-tetraen-11-yl}ethan-1-one (26)



1 gram-scale preparation of desilylative cyclized product **26**: To 100 mL sealed tube were added IPrAuCl (0.114 g, 0.18 mmol) and $AgBF_4$ (36 mg, 0.18 mmol) followed by DCM (1.5 mL). and the resulting mixture was stirred for 5 min. The solution of substrate **26** (1 g, 2.30 mmol) in DCE (11.5 mL) was added followed by methanol (1.87 mL, 46 mmol). The reaction solution was stirred at 95 ^{o}C for 12 h before cooled to 25 ^{o}C. The mixture was filtered through a short plug of silica gel and the solution was concentrated. Purification by flash chromatography (50:1, then 7:1 Hexanes/EtOAc) provided the pure product **27** (486 mg, 66 %) as a white solid and unreacted starting material **26** (80 mg, 8 %) as a white solid.

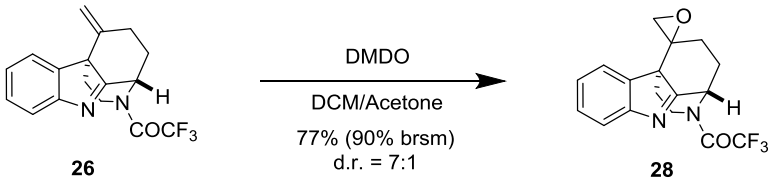
^{1}H NMR (500 MHz, $CDCl_3$; mixure of two rotamers of 4:1 ratio) δ 7.72 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.34 (td, *J* = 7.5, 1.1 Hz, 1H), 5.45 (t, *J* = 3.1 Hz, 1H), 4.89 (s, 1H), 4.86 (s, 1H), 3.98 – 3.84 (m, 1H), 3.13 (ddd, *J* = 13.8, 10.4, 4.9 Hz, 1H), 2.80 – 2.63 (m, 2H), 2.59 (ddd, *J* = 13.9, 10.5, 4.9 Hz, 1H), 2.38 – 2.24 (m, 1H), 2.09 (dt, *J* = 14.1, 4.9 Hz, 1H), 1.91 – 1.82 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$; mixure of two rotamers of 4:1 ratio) δ 181.53, 156.21, 154.77, 147.25, 142.34, 128.39, 125.95, 124.08, 121.91, 116.36, 110.96, 59.90, 54.18, 41.98, 35.11, 31.49, 27.64.

IR (neat, cm^{-1}): 2952, 1691, 1626, 1447, 1378, 1208, 1141, 909.

HRMS (ESI) m/z calcd for $C_{17}H_{15}F_3N_2OH^+$: 321.1210, found: 321.1199.

1-{8',16'-diazaspiro[oxirane-2,13'-tetracyclo[8.3.3.0^{1,9}.0^{2,7}]hexadecane]-2',4',6',8'-tetraen-16'-yl}-2,2,2-trifluoroethan-1-one (28)



To a 250 ml round bottom flask were loaded substrate **26** (0.5 g, 1.56 mmol) and DCM (71 mL). The solution was cooled to -20 ^{o}C before addition of the solution of DMDO (71 mL, 0.033 M in acetone). The reaction solution was stirred at -20 ^{o}C for 12 h before concentration. Purification by flash chromatography (10:1, then 5:1 Hexanes/EtOAc) provided the pure major epoxide **28a** (337 mg, 64 %) as a yellowish solid, minor epoxide **28b** (49 mg, 9 %) and unreacted starting material **26** (71 mg, 14 %) as a yellowish solid.

Major isomer 28a

^{1}H NMR (500 MHz, $CDCl_3$; mixure of two rotamers of 10:1 ratio) δ 7.71 – 7.68 (m, 1H), 7.42 (td, *J* = 7.7, 1.3 Hz, 1H), 7.39 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.28 – 7.24 (m, 1H), 5.35 (t, J = 3.0 Hz, 1H), 4.00 (dd, *J* = 14.0, 5.0 Hz, 1H), 3.00 (td, *J* = 12.7, 4.2 Hz, 1H), 2.96 – 2.91 (m, 1H), 2.89 – 2.83 (m, 1H), 2.57 – 2.45 (m, 1H), 2.34 (d, *J* = 4.7 Hz, 1H), 2.16 – 2.10 (m, 1H), 2.08 (dd, *J* = 4.7, 1.9 Hz, 1H), 1.71 (tdd, *J* = 14.1, 4.9, 2.7 Hz, 1H), 1.39 (ddd, *J* = 14.5, 5.0, 2.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$; mixure of two rotamers of 10:1 ratio) δ 180.17, 156.46, 155.34, 141.09, 128.88, 126.54, 123.22, 121.93, 116.02, 64.21, 57.23, 54.55, 52.34, 42.52, 30.94, 27.33, 25.90.

IR (neat, cm^{-1}): 2967, 1687, 1447, 1276, 1141.

HRMS (ESI) m/z calcd for $C_{17}H_{15}F_3N_2O_2H^+$: 337.1159, found: 337.1156.

Minor isomer 28b

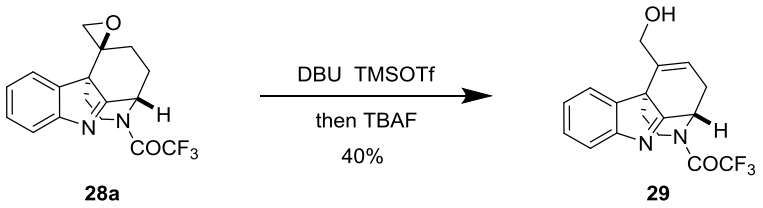
^{1}H NMR (500 MHz, $CDCl_3$; mixure of two rotamers of 10:1 ratio) δ 7.69 (d, *J* = 7.8 Hz, 1H), 7.42 (td, *J* = 7.6, 1.3 Hz, 1H), 7.31 – 7.28 (m, 1H), 7.26 – 7.22 (m, 1H), 5.37 (t, *J* = 3.0 Hz, 1H), 3.98 (d, *J* = 14.0 Hz, 1H), 3.03 – 2.94 (m, 1H), 2.97 (d, *J* = 4.3 Hz, 1H), 2.89 – 2.81 (m, 1H), 2.76 – 2.64 (m, 1H), 2.69 (d, *J* = 4.2 Hz, 1H), 2.60 (dd, *J* = 14.6, 5.1 Hz, 1H), 2.23 (ddd, *J* = 14.4, 4.6, 2.6 Hz, 1H), 2.06 (tdd, *J* = 11.8, 10.9, 5.3, 2.7 Hz, 1H), 1.32 (ddd, *J* = 15.2, 5.2, 1.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$; mixure of two rotamers of 10:1 ratio) δ 181.11, 156.47, 156.14, 140.25, 129.10, 125.90, 122.31, 121.84, 116.10, 63.53, 57.44, 55.63, 49.77, 42.75, 31.66, 28.30, 25.75.

IR (neat, cm^{-1}): 2933, 1689, 1445, 1384, 1208, 1138.

HRMS (ESI) m/z calcd for $C_{17}H_{15}F_3N_2O_2H^+$: 337.1159, found: 337.1156.

2,2,2-trifluoro-1-[14-(hydroxymethyl)-8,11-diazatetracyclo[8.3.3.0^{1,9}.0^{2,7}]hexadeca-2,4,6,8,14-pentaen-11-yl]ethan-1-one (29)



28a **29**

To a stirred solution of epoxide **28a** (350 mg, 1.04 mmol) in DCM/toluene (12 mL, 1:1) at -78 ^{o}C was added DBU (0.63 mL, 4.22 mmol) followed by dropwise addition of TMSOTf (0.96 mL, 5.28 mmol) over 5 min under argon atmosphere. The reaction was slowly to warm to 25 ^{o}C. After 12 h, the reaction was quenched with water (5 mL) and the aqueous layer was extracted with diethyl ether (15 mL×3). The combined organic phases were washed with saturated NH_4Cl (5 mL), brine (5 mL), dried over Na_2SO_4, decanted and concentrated. The crude was dissolved in THF (5 mL) at 0 ^{o}C, follwed by addition of 1 M TBAF in THF (1.06 mL, 1.06 mmol). The solution was stirred at 0 ^{o}C for 10 min before quenched with saturated NH_4Cl (5 mL). The aqueous layer was extracted with EtOAc (15 mL×3), then the combined organic phases were washed with saturated $NaHCO_3$ (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (1:1 Hexanes/EtOAc) provided the pure product **29** (0.14 g, 40 %) as a yellowish oil.

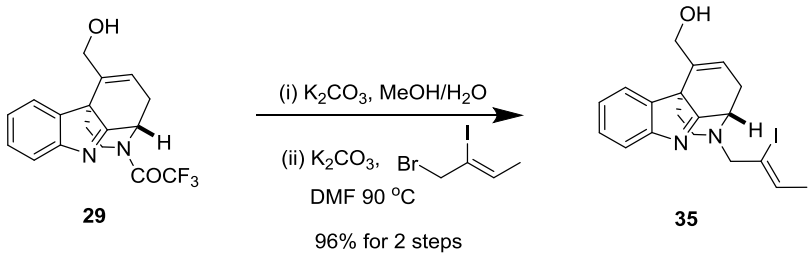
^{1}H NMR (500 MHz, $CDCl_3$; mixure of two rotamers of 1.3:1 ratio) δ 7.74 – 7.70 (m, 2H), 7.44 (td, *J* = 7.6, 1.3 Hz, 1H), 7.34 – 7.29 (m, 1H), 6.07 (d, *J* = 3.7 Hz, 1H), 5.91 (d, *J* = 5.9 Hz, 1H), 4.43 – 4.33 (m, 1H), 4.22 (dd, *J* = 13.3, 3.0 Hz, 1H), 3.97 (d, *J* = 13.2 Hz, 1H), 3.81 (td, *J* = 13.5, 3.2 Hz, 1H), 2.95 (t, *J* = 19.8 Hz, 1H), 2.78 (d, *J* = 19.7 Hz, 1H), 2.75 – 2.66 (m, 1H), 1.55 – 1.37 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$; mixure of two rotamers of 1.3:1 ratio) 181.15, 155.90, 154.86, 139.10, 135.64, 128.80, 126.14, 125.38, 124.58, 121.44, 116.21, 64.85, 56.05, 49.67, 39.01, 36.12, 35.68.

IR (neat, cm^{-1}): 3300, 3028, 1685, 1445, 1136, 1017.

HRMS (ESI) m/z calcd for $C_{17}H_{15}F_3N_2O_2H^+$: 337.1159, found: 337.1152.

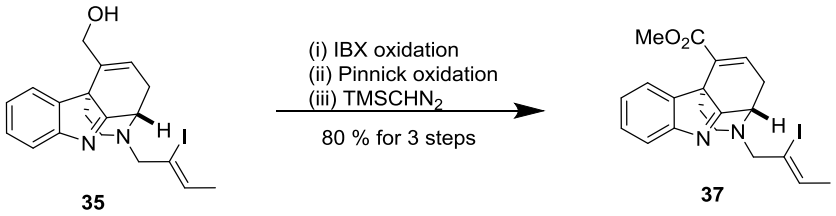
{11-[(2Z)-2-iodobut-2-en-1-yl]-8,11-diazatetracyclo[8.3.3.0^{1,9}.0^{2,7}]hexadeca-2,4,6,8,14-pentaen-14-yl}methanol (35)



To substrate **29** (15 mg, 45 μmol) in MeOH/H_2O (0.4 mL, 1:1) was added K_2CO_3 (30 mg, 0.22 mmol). After stirring at 25 °C for 1 h, the solvent was evaporated under rotavap before chloroform was added to the solid. The slurry was filtered through celite and concentrated. Mixture of the yellowish crude oil, bromide (22 mg, 83 μmol) and K_2CO_3 (29 mg, 0.21 mmol) in DMF (0.55 mL) was stirred at 90 °C for 12 h before concentration. The crude was dissolved in EtOAc (25 mL), washed with water (5 mL), brine (5 mL), dried over Na_2SO_4, decanted and concentrated. Purification by flash chromatography (3:2 Hexanes/EtOAc) provided the pure product **30** (18 mg, 96% for 2 steps) as a yellowish oil.

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.88 (d, *J* = 7.7 Hz, 1H), 7.63 – 7.57 (m, 1H), 7.21 (td, *J* = 7.6, 1.3 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 5.62 (q, *J* = 6.4 Hz, 1H), 5.49 – 5.43 (m, 1H), 3.92 (d, *J* = 6.7 Hz, 2H), 3.57 (d, *J* = 13.4 Hz, 1H), 3.24 (d, *J* = 14.0 Hz, 1H), 3.02 (td, *J* = 13.3, 3.1 Hz, 1H), 2.97 – 2.90 (m, 1H), 2.50 – 2.42 (m, 1H), 2.34 – 2.27 (m, 1H), 2.27 – 2.17 (m, 1H), 2.13 (d, *J* = 13.0 Hz, 1H), 1.62 (d, *J* = 6.3 Hz, 3H), 1.34 (td, *J* = 12.9, 4.3 Hz, 1H).
^{13}C NMR (101 MHz, Benzene-d_6) δ 184.46, 156.60, 141.07, 135.00, 132.21, 128.11, 126.01, 124.71, 124.23, 121.26, 109.31, 65.09, 64.80, 56.39, 54.88, 42.74, 36.64, 33.46, 21.35.

methyl 11-[(2Z)-2-iodobut-2-en-1-yl]-8,11-diazatetracyclo[8.3.3.0^{1,9}.0^{2,7}]hexadeca-2,4,6,8,14-pentaene-14-carboxylate (37)



To substrate **35** (58 mg , 0.139 mmol) in reagent-grade EtOAc (2 mL) was added IBX (0.2 g). The reaction mixture was stirred at 80 ^{o}C for 2 h before concentration. Mixture of hexanes and EtOAc (2:1) was added to the crude and the slurry was filtered through a short plug of silica gel. The solution was concentrated to give 58 mg pure product as a yellowish oil without further purification. The yellowish oil was dissolved in MeCN/^{t}BuOH (5.4 mL, 1:1), then to the solution were added NaH_2PO_4 monohydrate (96 mg, 0.69 mmol), 2-methyl-2-butene (0.74 mL, 6.93 mmol) and $NaClO_2$ (75 mg, 0.83 mmol) in water (1.8 mL). The mixture was stirred at 25 ^{o}C for 4 h before cooled to 0 ^{o}C. 10 % $Na_2S_2O_3$ (0.83 mL) was added and the mixture was stirred at 25 ^{o}C for 5 min before concentration. The solid was dissolved in DCM/MeOH (10:1) and the slurry was filtered through a short plug of silica gel. After concentration, the crude acid was dissolved in toluene/MeOH (1:1) before cooled to 0 ^{o}C. The solution of trimethyldilyldiazomethane solution in THF (0.28 mL, 2 M) was added dropwise. The solution was allowed to warm to 25 ^{o}C and stirred for 12 h before concentration. Purification by flash chromatography (6:1 Hexanes/EtOAc) provided the pure product **37** (50 mg, 80 % for 3 steps) as a yellowish oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.5 Hz, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.42 – 7.35 (m, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 3.5 Hz, 1H), 5.89 (q, *J* = 6.3 Hz, 1H), 3.95 (d, *J* = 6.2 Hz, 1H), 3.76 (s, 3H), 3.39 (d, *J* = 14.0 Hz, 1H), 3.23 (d, *J* = 14.0 Hz, 1H), 3.06 (t, *J* = 13.8 Hz, 1H), 2.99 – 2.85 (m, 1H), 2.78 (ddd, *J* = 20.6, 6.4, 3.0 Hz, 1H), 2.73 – 2.60 (m, 2H), 1.79 (d, *J* = 6.3 Hz, 3H), 1.57 (td, *J* = 12.9, 4.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 183.00, 165.76, 155.96, 141.12, 140.09, 132.92, 129.73, 128.35, 126.27, 125.49, 120.78, 108.49, 65.06, 55.22, 54.72, 51.68, 43.13, 35.83, 33.86, 21.76.

IR (neat, cm^{-1}): 2948, 1715,1438, 1283, 1229, 1065, 914.

HRMS (ESI) m/z calcd for $C_{20}H_{21}IN_2O_2H^{+}$: 449.0721, found: 449.0719.

4.8 Reference

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Chapter 5

Quantitative Analysis of Histone Demethylase Probes Using Fluorescence Polarization

5.1 Background

Methylation of histone proteins is one of the most important epigenetic modifications.[1] These reversible modifications recruit effector proteins and trigger a wide range of cellular events, including regulation of gene expression, proliferation, and differentiation. Histone methylations are closely regulated by histone methyltransferases and histone demethylases. Since 2004, two families of enzymes have been reported to exhibit demethylation activities: flavin adenine dinucleotide (FAD)-dependent monoamine oxidases (LSD1 and 2) and jumonji C domain-containing histone demethylases (JHDMs).[2] Compared with LSDs, JHDMs have a much broader substrate scope and can modify lysine residues at all methylation states.

Expression of JHDMs plays critical roles in both development and diseases such as cancer and mental retardation.[3] Overproduction of 2-hydroxy-glutarate, a natural JHDM inhibitor, due to mutation of isocitrate dehydrogenases, has been identified in multiple cancers.[4] This development has led to numerous efforts to develop chemical probes targeting JHDMs. Several classes of α-ketoglutarate (αKG) mimics have been developed to inhibit JHDM activity[5] because all JHDMs use αKG as a cofactor. In addition, a substrate-mimicking small molecule was recently reported to selectively inhibit H3K9-demethylase KIAA1718.[6] Our group recently discovered a selective, cell-permeable, small-molecule inhibitor methylstat (**1**, Figure 5.1), which was designed as a bivalent substrate-cofactor conjugate.[7] Its corresponding acid, **2** (Figure 5.1), selectively inhibits JHDMs in vitro. This bivalent strategy has also proven successful in two very recent reports on JMJD2 class-selective peptidic inhibitors.[8]

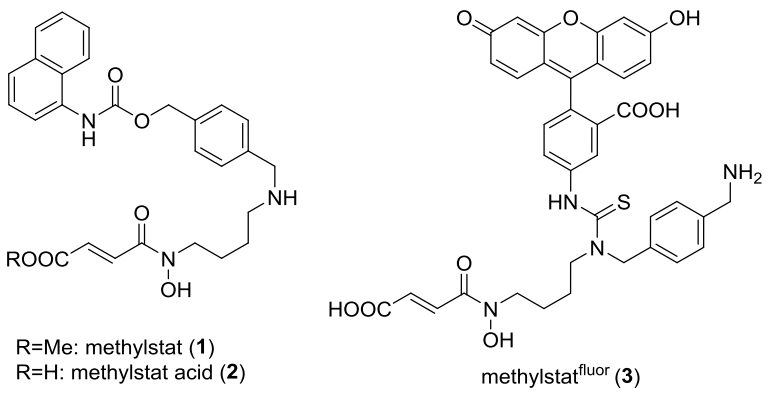


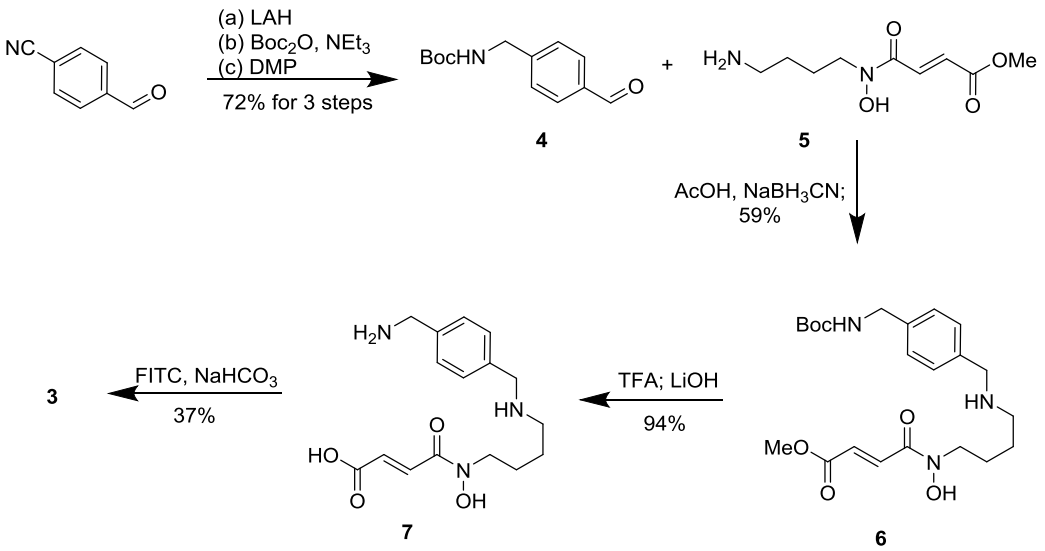
Figure 5.1 Structure of Methylstat (**1**), Methylstat Acid (**2**) and Its Fluorescent Analogue Methylstat^{fluor} (**3**)

Although several classes of JHDM inhibitors have been discovered, determining the selectivity of these inhibitors against various JHDM classes remains a major challenge. This is mainly due to the lack of a uniform biochemical assay for various JHDM isoforms. Most established JHDM biochemical assays are enzyme inhibition assays.[5a,9] Because of the self-destructive nature of JHDMs under biochemical reaction conditions,[10] these assays typically require optimization for different JHDM isoforms. In addition, they do not allow for accurate measurement of the dissociation constants of the JHDM probes. Thus, the IC_{50} values derived from these assays cannot be compared directly. Thus, we are motivated to design a fluorescent JHDM probe, **3** (Scheme 5.1), and develop a fluorescence polarization (FP)-based binding assay. This assay will allow us not only to quantitatively measure the dissociation constants of several JHDM probes but also to validate the inhibitory mechanism of methylstat.

5.2 Synthesis of Methylstat^{fluor}

The synthesis of fluorophore **3** was started from conversion of commercially available 4-cyanobenzaldehyde to aldehyde **4** (Scheme 5.1),[11] which then underwent a reductive amination with amine **5**[7] to afford secondary amine **6**. The tertbutoxycarbonyl (Boc) protecting group of **6**

was then removed by trifluoroacetic acid (TFA) and ester was hydrolyzed under basic conditions. The resulting diamine **7** was then treated with fluorescein isothiocyanate (FITC) to afford **3** as the major product.



Scheme 5.1 Synthesis of Fluorophore **3**

5.3 Application of Methylstat^{fluor}(3) as A Probe to Fluorescence Polarization Binding and Competition Assays

*Binding of **3** to Various JHDMs*

Since fluorophore **3** closely resembles the structure of methylstat acid **2**, and it has favorable fluorescent properties for use in a variety of instruments, we envisioned that it could be used as a tracer in a fluorescence polarization binding assay. Three cloned JHDM enzymes (JHDM1A, JMJD2A, and JMJD3) were tested for their binding ability to **3**;. These three demethylases were chosen because of their differing substrate specificity.[13] Members of the Wang lab (Xuang Dong and Jessica Podoll) thus set out to develop and optimize an FP binding assay to determine the affinity of fluorophore **3** to these three JHDMs. The initial binding experiment was adapted from an FP binding procedure reported previously.[13] Preliminary

results indicated that only the binding of JHDM1A and **3** reached saturation at the concentration of 5 nM **3** in assay (Figure 5.2); therefore, JHDM1A was used for assay optimization.

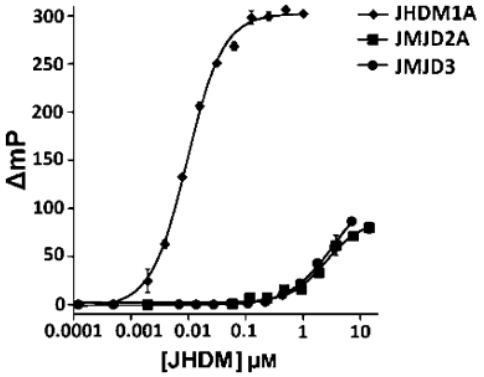


Figure 5.2 Assessment of Binding of fluorophore **3** to JHDM1A, JMJD2A, and JMJD3

Optimized FP Assay

Optimization of the FP assay included optimizing the assay buffer and addition of metal ions, which was carried out by Xuang Dong and Jessica Podoll. The assay buffer was adapted from previous reports on JHDM enzyme activity assays. As for addition of metal ions (Figure 5.3A), Fe^{2+} and Ni^{2+} afforded best binding affinity (K_d: 8.2 nM for Fe^{2+}, 9.3 nM for Ni^{2+}). Although binding was quantifiable using of Fe^{2+} (sodium ascorbate was added),[2,7] P_{max} was found to be increased by at least 200 mP by using Ni^{2+} instead of Fe^{2+} (Figure 5.3A). Besides, binding of fluorophore **3** to JHDM1A in the presence of Ni^{2+} was highly stable over time (Figure 5.3B). Once binding reached equilibrium (approximately 4 hours), signals stayed stable over the course of at least 20 hours.

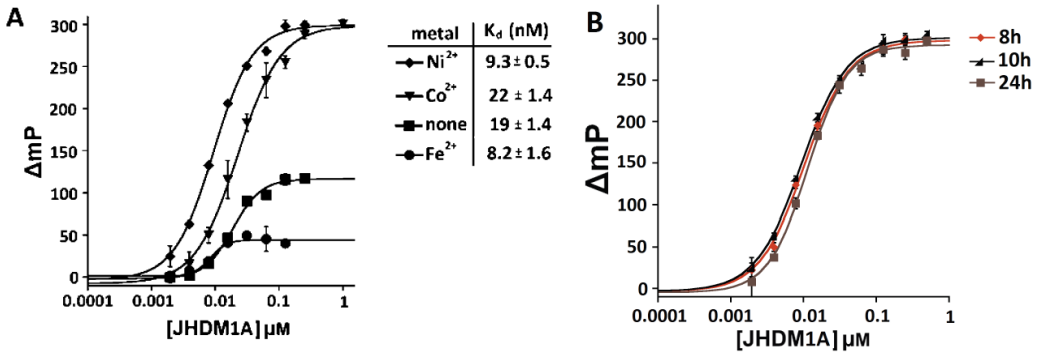


Figure 5.3 Optimization of Binding of fluorophore **3** to JHDM1A in the presence of Ni^{2+}: (A) addition of various metal ions. (B) Stablized FP signals over the course of at least 20 hours

Quantification of Binding Affinity of JHDM ligands to JHDM1A

With optimized FP assay in hand, Xuang Dong and Jessica Podoll performed a competition assay using **3** as a tracer in order to confirm its binding at the JHDM active site and to quantify the binding affinity of known JHDM ligands: methylstat acid **2**, αKG, *N*-oxalylglycine (NOG, an αKG mimic), 2,3-Pyridinedicarboxylic Acid (PDCA) and H3K36me2.[5a,14] The results (Figure 5.4) showed that all of the above molecules can displace **3** from JHDM1A. Methylstat acid **2** was proved to be a competitive JHDMs inhibitor with IC_{50} value of 135 nM and K_i value of 11.3 nM.

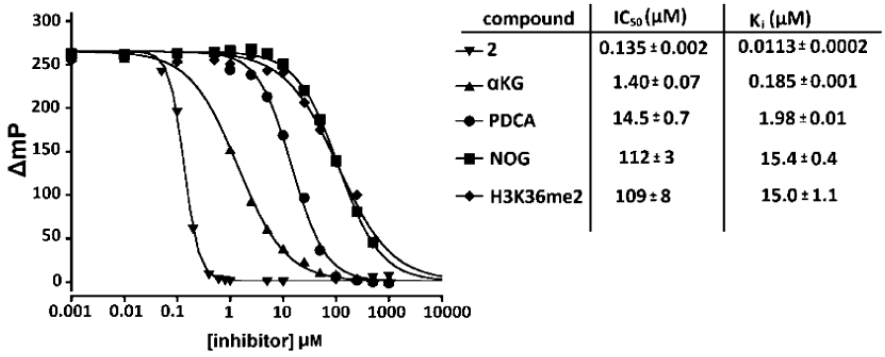


Figure 5.4 Determination of IC_{50} and K_i values for known JHDM probes using our FP competition assay

This competition assay also allowed quantification of the binding affinities of multiple JHDM active site binding molecules including αKG, for which a K_d has never previously been reported due to its role in JHDM catalysis. Since this FP-binding and competition assays were able to elucidate binding affinity constants, it may identify specific binders of a JHDM isoform. Further expansion of our FP binding assay to other JHDM isoforms may be extremely useful for assessing the specificities as well as the inhibitory mechanism of various JHDM probes.

Application to High-Throughput Screening

The FP competition assay was also reformatted by Xuan Dong for high-throughput screening (HTS) using methylstat acid **2** (100 μM in DMSO) and DMSO as positive and negative controls respectively (Figure 5.5). The *Z′*-score,[15] a characteristic parameter for the quality of the assay without intervention of test compounds, was calculated to be 0.78, indicating the this assay is suitable for HTS of JHDM active site binders and could be used to screen small molecule libraries for novel JHDM inhibitors in the future.

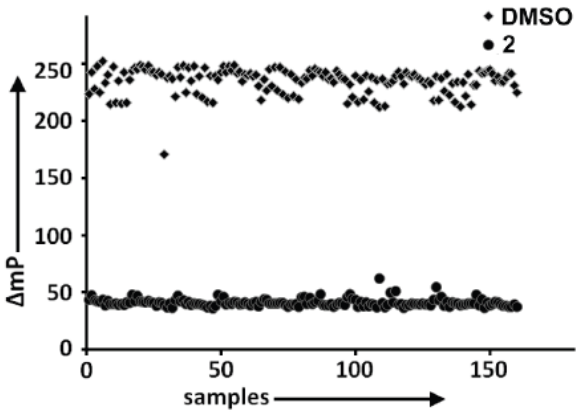


Figure 5.5 Application of Fluorophore **3** to High-Throughput Screening of JHDM inhibitors

5.4 Conclusion

A fluorescent analog **3** of methylstat was designed and synthesized and used to develop novel FP-based binding and competition assays for JHDM1A. By adjusting catalytic assay

conditions, highly stable binding assay conditions were developed that have allowed quantification of **3** to JHDM1A as well as known JHDM inhibitors and native substrates. Additionally, the FP assay allowed development of a highly robust and miniaturized assay appropriate for high-throughput screening of large compound libraries (Z': 0.78).

5.5 Outlook

Recently, fluorescent probe **8** was synthesized and used to perform FP binding assay with JMJD2A. The K_d of this interaction is 85 nM. This probe might be used for the FP competition assay using JMJD2A to determine the K_i values for known JHDM active site binders including , PDCA and αKG (Figure 5.6).

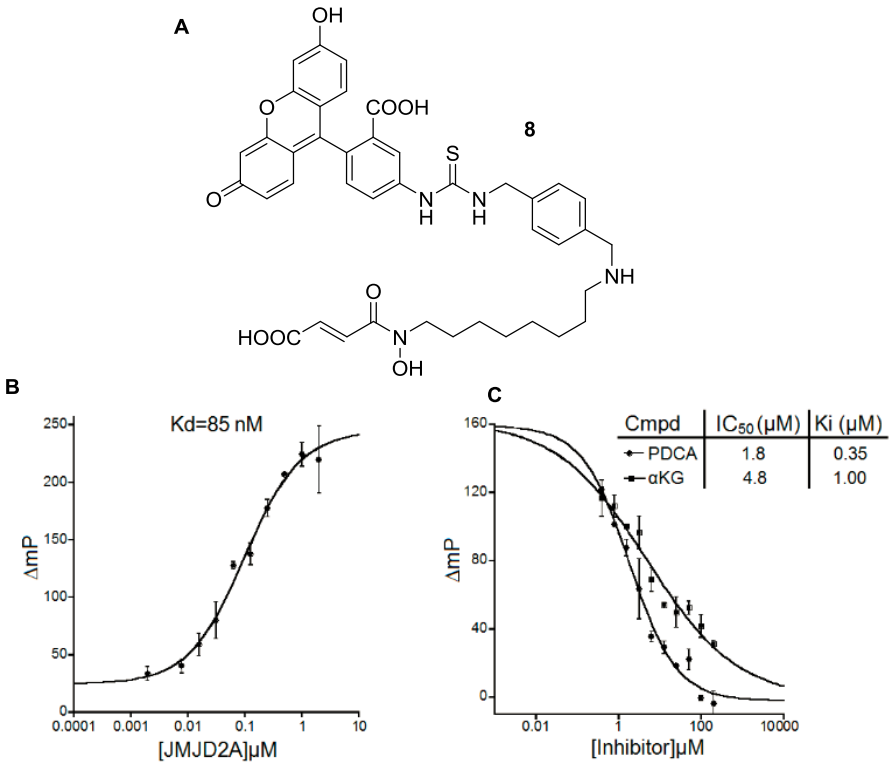
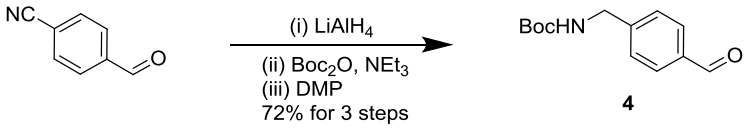


Figure 5.6 (A) Structure of fluorophore **8** (B) Binding of **8** to JMJD2A. (C) FP competition assay for determination of IC_{50} and K_i values for known probes

5.6 Experimental

Unless otherwise noted, reagents were obtained commercially and used without further purification. Solvents were dried using standard procedures. TLC analysis of reaction mixtures was performed on Dynamic adsorbents gel F- silica 254 TLC plates. Flash chromatography was carried out on Zeoprep 60 ECO silica gel. ^{1}H and ^{13}C NMR spectra were recorded with Varian INOVA 400, 500 and VXRs-300 spectrometers. Mass spectral and analytical data were obtained via the PE SCIEX/ABI API QSTAR Pulsar iHybrid LC/MS/MS. Infrared (IR) spectra were recorded on a Thermo Nicolet Avatar 370 FT-IR spectrometer. The purity was determined by Agilent Technologies 6120 Quadrupole LC/MS with 1260 Series HPLC System from the integration of the area under the UV absorption curve at λ = 254 or 210 nm signals. The system was eluted at 0.5 ml/min with a gradient water/acetonitrile in 0.1% formic acid: 0-5min, linear gradient of 5-95% acetonitrile + 0.1% formic acid; 5-7 min, 95% acetonitrile + 0.1% formic acid; 7-7.25 min, linear gradient of 95-5% acetonitrile + 0.1% formic acid; 7.25-8.5 min, 5% acetonitrile + 0.1% formic acid.

t-Butyl 4-formylbenzylcarbamate (4)

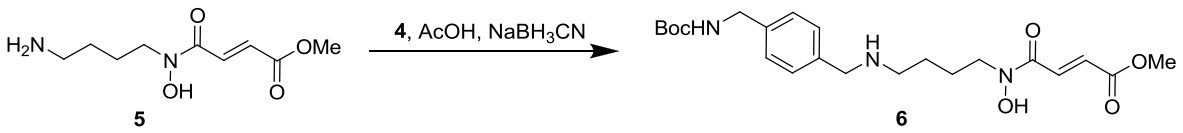


4

A solution of 4-cyanobenzaldehyde (0.086 g, 0.66 mmol) in 4 mL THF was added dropwise to the solution of $LiAlH_4$ (1 M in THF, 1.65 mL) at 0 ^{o}C under N_2. The light yellow-green solution was stirred at 0 ^{o}C for 3 h and refluxed under N_2 for 12 h. After cooling down to room temp, MeOH (0.35 mL) was added to the suspension to quench the reaction. The suspension generated

foams while being stirred and cooled in an ice-bath. When no more bubble formation was observed, NaOH (2 M, 2.1 ml) solution was added into the suspension. The solution became colorless while white precipitate was observed. The solution was concentrated *in vacuo* and the residue was suction filtered. The solid was repeatedly washed with ethyl acetate. The filtrate was combined and washed with water. The organic phase was separated, dried over sodium sulfate and concentrated to give 0.08 g white solid. The solid was dissolved in 0.8 mL THF and triethylamine (0.089 mL, 0.64 mmol) was added followed by the addition of di-*t*-butyl dicarbonate (0.14 g, 0.64 mmol) in 0.8 mL dry THF dropwise. The reaction solution was stirred at room temp for 12 h before concentration on a rotavap. The residue was dissolved in 50 mL ethyl acetate. The solution was sequentially washed with 2 M HCl, saturated $NaHCO_3$ and brine, and then dried over sodium sulfate. Filtration and solvent evaporation yielded 0.14 g white powder. The powder was dissolved in 3 mL CH_2Cl_2 and the solution was cooled to 0 ^oC, to which was added Dess-Martin periodinane (0.310 g, 0.71 mmol). The resulting mixture was stirred at 0 ^oC for 30 min before addition of 5 mL hexanes. The white precipitate was filtered through silica gel and concentrated *in vacuo*. The residue was purified over silica gel using hexanes : ethyl acetate = 4 : 1 as eluent to give **4** (0.112 g, 72%) as a white solid. Data is consistent with that reported in the literature.[18]

(*E*)-Methyl 4-((4-(4-((*tert*-butoxycarbonylamino)methyl)benzylamino)butyl)(hydroxy)amino)-4-oxobut-2-enoate (5)



To the mixture of aldehyde **4** (0.094 g, 0.4 mmol) and amine **5** (0.079 g, 0.37 mmol) in 3.6 mL methanol at 0 ^{o}C was added acetic acid (0.062 mL, 1.1 mmol). After 30 min, sodium cyanoborohydride (0.12 g, 1.82 mmol) was added at 0 ^{o}C and the resulting mixture was stirred at 25 ^{o}C for 12 h before concentration. Water was added and aqueous layer was extracted with ethyl acetate 3 times. The combined organic phases were washed with saturated $NaHCO_3$ and brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified over silica gel using CH_2Cl_2 : MeOH = 10 : 1 as eluent to give **6** (0.094 g, 59%) as a yellowish oil.

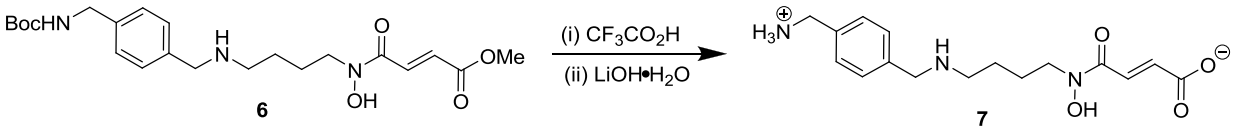
^{1}H-NMR (CD_3OD, 500 MHz): δ = 7.65 (d, *J*=15.7 Hz, 1H), 7.43 (d, *J*=8.1 Hz, 2H), 7.37 (d, *J*=8.1 Hz, 2H), 6.75 (d, *J*=15.7 Hz, 1H), 4.25 (s, 2H), 4.16 (s, 2H), 3.80 (s, 3H), 3.76 (t, *J*=6.3 Hz, 2H), 3.11 – 3.01 (m, 2H), 1.85 – 1.64 (m, 4H), 1.44 (s, 9H).

^{13}C-NMR (CD_3OD, 75 MHz): δ = 167.14, 165.64, 158.23, 142.39, 133.70, 131.69, 131.00, 130.90, 128.67, 80.26, 52.86, 51.98, 48.48, 48.10, 44.46, 28.78, 24.52, 24.12.

IR (neat, cm^{-1}): 3382, 2974, 2337, 2173, 1699, 1520, 1274, 943, 812.

HRMS (ESI) (*m/z*) $[M+H]^+$ 436.2419 (calcd for $C_{22}H_{34}N_3O_6$: 436.2443).

(*E*)-4-((4-(4-(Aminomethyl)benzylamino)butyl)(hydroxy)amino)-4-oxobut-2-enoic acid (6)



To compound **6** (0.023 g, 0.34 mmol) in 0.2 mL CH_2Cl_2 at 0 ^{o}C was added 0.1 mL trifluoroacetic acid. The reaction solution was stirred at 0 ^{o}C for 0.5 h before concentration *in vacuo*. The oil

was dissolved in 0.5 mL THF, to which was added the solution of LiOH monohydrate (0.022 g, 0.53 mmol) in 0.5 mL water. The resulting mixture was stirred at 25 ^{o}C for 2 h. The solution was cooled to 0 ^{o}C and HCl in dioxane (4 M, 0.11 mL) was added. After 5 min, the solvents were removed *in vacuo*. The residue was purified over silica gel using MeOH : H_2O = 3 : 1 as eluent to give **7** (0.016 g, 94%) as a white solid.

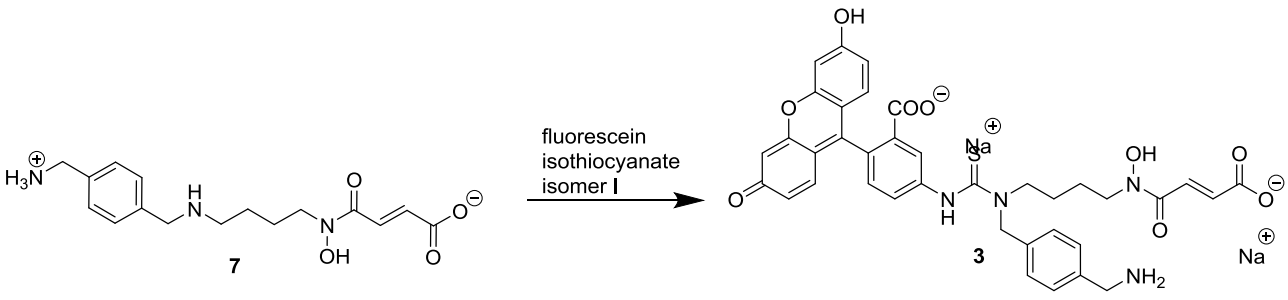
^{1}H NMR (CD_3OD, 400 MHz) δ = 7.40 (s, 4H), 7.24 (d, *J*=15.7 Hz, 1H), 6.76 (d, *J*=15.7 Hz, 1H), 3.98 (s, 2H), 3.87 (s, 2H), 3.69 (t, *J*=6.2 Hz, 2H), 2.74 (t, *J*=7.1 Hz, 2H), 1.79 – 1.68 (m, 2H), 1.67 – 1.55 (m, 2H).

^{13}C NMR (CD_3OD, 75 MHz) δ = 173.96, 167.64, 140.35, 138.84, 137.91, 130.61, 129.71, 128.51, 53.36, 45.21, 26.48, 25.34.

IR (neat, cm^{-1}): 3354, 2970, 2976, 1454, 1380, 1160, 1127, 951, 812.

HRMS (ESI) (*m/z*) $[M+H]^+$ 322.1794 (calcd for $C_{16}H_{24}N_3O_4$: 322.1762).

Sodium (*E*)-4-((4-(4-((3-(3-carboxy-4-(6-hydroxy-3-oxo-3*H*-xanthen-9-yl)phenyl)thioureido)methyl)benzylamino)butyl)(hydroxy)amino)-4-oxobut-2-enoate (3)



To the mixture of fluorescein isothiocyanate isomer I (0.01 g, 0.025 mmol) and amine **7** (0.016 g, 0.05 mmol) in 0.2 mL THF was added 0.2 mL sat $NaHCO_3$ at 0 ^{o}C The solution was warmed

to 25 ^{o}C and stirred for 12 h. NaOH (2 M, 0.12 mL) solution was added and the mixture was stirred at 25 ^{o}C for 5 min before concentration. The residue was purified over silica gel using $CHCl_3$: MeOH : H_2O = 6 : 4 : 0.5 as eluent to give **3** (0.007 g, 37%) as an orange solid.

^{1}H NMR (CD_3OD, 300 MHz) δ = 7.73 (s, 1H), 7.67 (dd, *J*=8.3 Hz, 2.1 Hz, 1H), 7.43 (s, 4H), 7.26 (d, *J*=16.0 Hz, 1H), 7.21 – 7.12 (m, 3H), 6.74 (d, *J*=15.6 Hz, 1H), 6.62 – 6.53 (m, 4H), 5.20 (s, 2H), 4.05 (s, 2H), 3.86 (s, 2H), 3.73 (t, *J*=5.4 Hz, 2H), 1.88 – 1.61 (m, 4H).

^{13}C NMR (CD_3OD, 75 MHz) δ = 183.57, 179.92, 173.95, 173.50, 167.98, 159.86, 143.15, 141.25, 140.74, 139.39, 134.80, 132.79, 132.19, 130.56, 130.35, 129.14, 128.88, 128.28, 128.21, 123.07, 114.46, 104.31, 55.35, 51.89, 44.41, 25.54, 24.94.

IR (neat, cm^{-1}): 3387, 3240, 2615, 2361, 1576, 1388, 1458, 1204, 1102, 910.

HRMS (ESI) (*m/z*) $[M]^-$ 709.1956 (calcd for $C_{37}H_{33}N_4O_9S$: 709.1975).

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