# Synthetic Studies of Meloscine and Related Alkaloids

by

Hanmo Zhang

BS, Xiangya School of Medicine, 2006

Submitted to the Graduate Faculty of

the Dietrich School of Arts and Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2013

UNIVERSITY OF PITTSBURGH

DIETRICH SCHOOL OF ARTS AND SCIENCES

This thesis was presented

by

Hanmo Zhang

It was defended on

Feburary 28, 2013

and approved by

Paul E. Floreancig, Professor, Department of Chemistry

Craig S. Wilcox, Professor, Department of Chemistry

Billy W. Day, Professor, Departmental of Pharmaceutical Sciences

Thesis Director: Dennis P. Curran, Distinguished Service Professor of Chemistry and Bayer Professor, Department of Chemistry

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Hanmo Zhang, PhD

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The first section of this dissertation describes the discovery and studies of new radical desulfonylation reactions. These reactions allow convenient access to structurally diverse imines under mild conditions. We have examined several related desulfonylation reactions, and the results of this investigation support the general mechanism that we initially proposed.

The second section details the synthesis of (±)-epimeloscine, (±)-meloscine, and analogs. The invention of a novel, cascade radical annulation of divinylcyclopropanes enables expedient synthesis of (±)-epimeloscine and (±)-meloscine, and analogs. Preliminary studies on a chirality transfer approach towards (+)-meloscine are discussed. This approach delivered only moderate chirality transfer, however, a new cascade cope/ene reaction was discovered along the way.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| Ac | acetyl |
| AIBN | azobisisobutyronitrile |
| Bpin | 4,4,5,5-tetramethyl-1,3,2-dioxaborolane |
| Bn | benzyl |
| Boc | *tert*-butyloxycarbonyl |
| BuLi | *n*-butyllithium |
| Bz | benzoyl |
| COSY | correlation spectroscopy |
| Cy | cyclohexyl |
| DCC | dicyclohexylcarbodiimide |
| DIBAL-H | diisobutylaluminium hydride |
| DMAP | 4-dimethylaminopyridine |
| EDCI | 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| ESI | electrospray ionization |
| equiv | equivalent(s) |
| HATU | 2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate |
| HMQC | heteronuclear multiple quantum coherence |
| HPLC | high performance liquid chromatography |

| | |
|---|---|
| HRMS | high resolution mass spectroscopy |
| IR | infrared spectroscopy |
| KHMDS | potassium bis(trimethylsilyl)amide |
| LDA | lithium diisopropylamide |
| NaHMDS | sodium bis(trimethylsilyl)amide |
| NHC | N-heterocyclic carbene |
| NMR | nuclear magnetic resonance |
| NOSEY | nuclear Overhauser effect spectroscopy |
| Nu | nucleophile |
| PG | protecting group |
| RCM | ring closing metathesis |
| TBAF | tetrabutylammonium fluoride |
| TBDPS | *tert*-butyldiphenylsilyl |
| TBS | *tert*-butyldimethylsilyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| Ts | *p*-toluenesulfonyl |
| TS | transition state |

# PREFACE

I would like to take this opportunity to thank a group of incredible people whom I have met at Pitt and WVU. First and foremost, I would like to express my sincere gratitude to Prof. Dennis Curran for his support over the past five and half years, both professionally and financially. It has been my privilege to study the exciting radical chemistry under his mentorship. His brilliance, respectable personality, and relentless pursuit of innovation have made my educational experience in his group both intellectually stimulating and enjoyable. I am extremely grateful for the freedom that he has granted for me to conduct my research, as well as his help in improving my writing skills. It is under his mentorship that my passion and confidence in chemical research have started growing rapidly. And I will always owe a lot to him for that.

I am also grateful to my thesis committee members Profs. Paul Floreancig, Craig Wilcox, and Billy Day, for their time and valuable suggestions on my comprehensive exam, research proposal, and thesis writing. Special thank to Prof. Floreancig for his superb teaching of my physical organic and spectroscopy courses. Prof. Xinyu Liu is greatly acknowledged for guiding me through the proposal wiriting.

I have had a great time working with so many people in the Curran group over the years. I am grateful to Dr. Dave Guthrie for his beautiful work on tandem radical cyclization, which laid the foundation for my thesis work. Many thanks to my excellent lab partner Ben Hay, who

has made critical contribution to several projects related to my thesis work. Daniel Bolt, Tome Allen, and Brittany Kulscar are acknowledged for their contribution to my thesis and related work. I would also like to extend my gratitude to Drs. Wei Zhu and Jesse Sabatini with whom I have had short periods of apprenticeship. I have been really fortunate to work with and befriend these two passionate, experienced, and knowledgeable postdocs. My thanks go to all Curran group members, past and current, for their help and friendship. I cherish the friendship that I have had here and wish them all the best.

I would like to thank Dr. Damodaran Krishnan and Sage Bowser for maintaining our excellent NMR facilities. I am also grateful to Drs. John Williams and Bhaskar Godugu for directing the superb mass-spec facilities. Dr. Steve Geib is greatly acknowledged for solving my crystallography samples that are important to the success of my thesis work.

I am indebted to Prof. George O'Doherty for providing me with a great opportunity to study chemistry in his group when I first came to the U.S. My experience working with him has been both challenging and rewarding. I greatly appreciate his help and support during, and even after my brief stay at WVU. Prof. Xiaodong Michael Shi is greatly acknowledged for his help and encouragement during my stay at WVU.

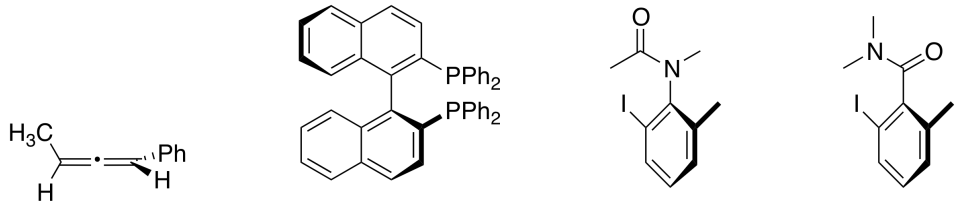
My thesis work would be impossible without the unconditional love, trust, and support of my parents, Jianjun Zhang and Ning Ouyang. They have always encouraged me to pursue true knowledge and career paths that I am really passionate about. In graduate school, I have been extremely fortunate to meet my girfriend, Shan Chen, who has been a source of endless love over the past five years. Her constant support has provided me with the greatest courage to overcome every challenge in my research and in my life. I have enormous gratitude and heartfelt thanks to my parents and Shan for everything they have done for me, and this thesis is dedicated to them.

# 1.0 STUDIES OF N-SULFONYL RADICAL ELIMINATION REACTIONS

## 1.1 INTRODUCTION

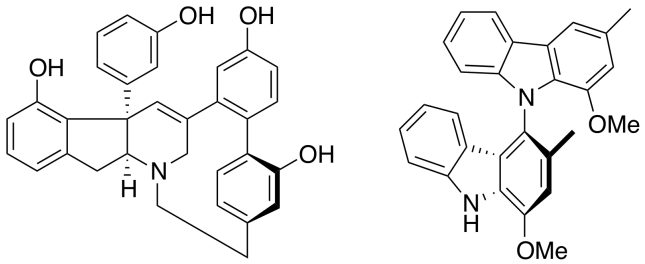
### 1.1.1 Axially Chiral Anilides

Eliel defines axial chirality as chirality stemming from four substituents held in a non-planar arrangement around an axis, such that the molecule is not superimposable to its mirror image.[1] Axial chirality arises from the restriction of free rotation about this axis or bond. Axially chiral compounds undergo isomerization when provided with enough energy to overcome the barrier of bond rotation. Representative classes of axially chiral compounds include allenes (**1.1**),[2] biaryl compounds (**1.2**),[3] anilides (**1.3**) and benzamides (**1.4**)[4] with substituents at the *ortho* positions of aryl rings (**Figure 1**). These compounds play important roles in organic synthesis and are often medicinally relevant.[5] For example, one of the most well known axially chiral compounds, BINAP **1.2**,[6] is extensively used in academia and industry as transition metal ligand for asymmetric synthesis. Several complex natural products that contain elements of axial chirality, including murrastifoline F[7] and haouamine A,[8] were also discovered and synthesized recently **(Figure 2)**.




(*M*)-**1.1** (*S*)-BINAP, **1.2** **1.3** **1.4**

**Figure 1** Representative Axially Chiral Compounds

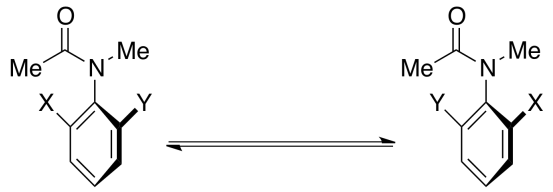



Haouamine A Murrastifoline F

**Figure 2** Structures of Haouamine A and Murrastifoline F

Axial chirality is often present in *ortho*-substituted anilides, as shown in **Figure 3**. In compounds like **1.5**, the steric hindrance of *ortho*-substituents X and Y prevents the coplanar arrangement of the aromatic ring with the amide group. For example, the early crystal structure of *N*-methyacetanilide (where X = Y = H) showed that the amide and aryl planes were arranged nearly perpendicular to each other in the solid state.[9] Therefore, the *N*-aryl bond becomes an axis of chirality when X and Y are different. If the other substituents on the amide do not have any stereogenic centers, then such anilides consist of a pair of enantiomers that can interconvert by rotation of the *N*-aryl bond. A high enough barrier of the *N*-aryl bond allows an anilide to be separated as two rotational isomers, or atropisomers. Oki defined atropisomers as interconvertible conformers with a longer half-life than 1000 s at a given temperature.[10]

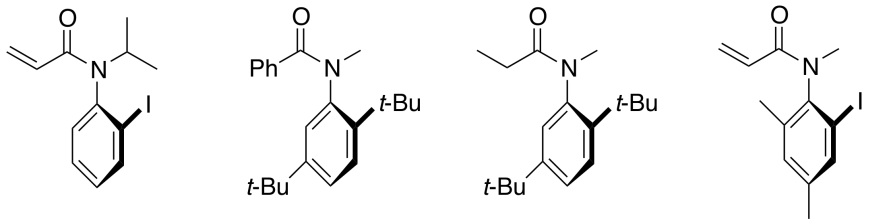
According to this definition, the separation of atropisomeric anilides at 300 K requires a rotational barrier higher than 22.3 kcal/mol for the *N*-aryl bond.




**1.5a** **1.5b**

**Figure 3** A Twisted Anilide

Sizes of substituents on the amide nitrogen atom and aryl ring significantly affect the rotational barriers of *N*-aryl bonds, as illustrated in **Figure 4**.[11] When one *ortho* substituent is hydrogen and the other is iodine, in the case of *N*-isopropyl acrylamide **1.6**, the barrier of *N*-aryl rotation is 22.8 kcal/mol. The presence of a bulky *t*-Bu group at the *ortho*-position provides a significantly boost of the *N*-aryl rotational barrier, as shown in the cases of *N*-methyl substituted amides **1.7** and **1.8**. When the *ortho* hydrogen substituent of 2-iodoanilide **1.6** is replaced with a methyl group, shown in the case of *N*-methyl acrylamide **1.9**, the *N*-aryl rotational barrier is also dramatically increased. In comparison of with propionamides such as **1.8**, benzoyl anilides such as **1.7** tend to have lower barriers. It is likely that aryl groups twist out of planarity with the amide group, reducing the steric repulsion with *ortho*-substituents in the rotation transition state.[11]




**1.6**
22.8 kcal/mol
$t_{1/2}$ at 25 °C =
49 min

**1.7**
26.4 kcal/mol
$t_{1/2}$ at 25 °C =
15 days

**1.8**
29.6 kcal/mol
$t_{1/2}$ at 25 °C =
9 years

**1.9**
30.8 kcal/mol
$t_{1/2}$ at 25 °C =
69 years

**Figure 4** Rotational Barriers of Selected Axially Chiral Anilides

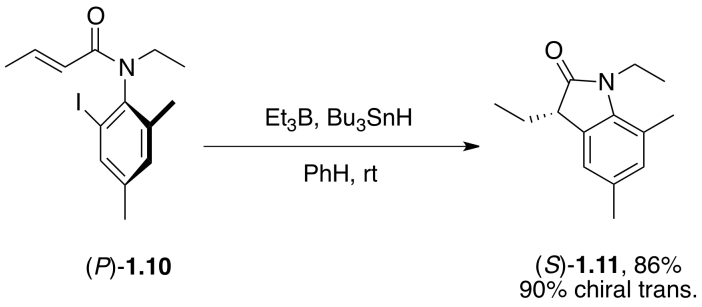
The enantioselective preparation of axially chiral anilides is challenging. Uemura,[4c, 12] Curran,[13] Taguchi,[14] and Maruoka[15] reported enantioselective syntheses of axially chiral anilides, but the scope of substrates is limited. Currently the most general method for preparation of axially chiral anilides is resolution of racemates by semi-preparative chiral HPLC. The Chiralcel OD column and the (*S,S*)-Whelk O1 column are especially efficient for such resolutions.[16]

### 1.1.2 Chirality Transfer and Radical Cyclizations of Axially Chiral Anilides

"Memory of chirality" occurs when the reaction of a chiral starting material results in a chiral product, despite proceeding through a configurationally labile intermediate containing no other permanent chiral features.[17] Chirality transfer is a subset of "memory of chirality". By definition, transfer of chirality requires destruction of the original chiral element with concomitant formation of a new one elsewhere. [18] Common examples of chirality transfer include $S_N2'$ nucleophilic displacements and sigmatropic rearrangements. The efficiency of chirality transfer is calculated by dividing the proportion of the major enantiomer in the product by the proportion

of the major enantiomer in the starting material. This is a measurement of the percentage of the configurationally labile intermediate reacted that conserves its memory of chirality.

Like an enantiopure compound with stereocenters, an axially chiral anilide may also serve as a valuable chiral substrate for enantioselective synthesis, provided that the chirality transfer is high and reliable. In 1999, the Curran group first disclosed chirality transfer in intramolecular radical cyclizations of axially chiral anilides[19] (**Scheme 1.1**). In a typical example, $Et_3B/Bu_3SnH$ induced radical cyclization of atropisomer (*P*)-**1.10** smoothly proceeded to form dihydroindole (*S*)-**1.11** in 86% yield and with 90% chirality transfer. The scope of this reaction is broad, and anionic and organometallic versions were also developed.[20]




**Scheme 1.1** Radical Cyclization of an Axially Chiral Anilide with Chirality Transfer

A mechanistic scheme for the chirality transfer in the above reaction is shown in **Figure 5**. Two features are key to the excellent chirality transfer of this reaction. First, the radical cyclization (**1.12a→1.13a**) is considerably faster than the *N*-aryl rotation (**1.12a→1.12b**), even though the initially formed aryl radical species **1.12a** has a lower rotational barrier than the aryl iodide (*P*)-**1.10**. Second, the cyclization is face-selective and only occurs to the back face of the alkene, presumably because the radical is also in the back.

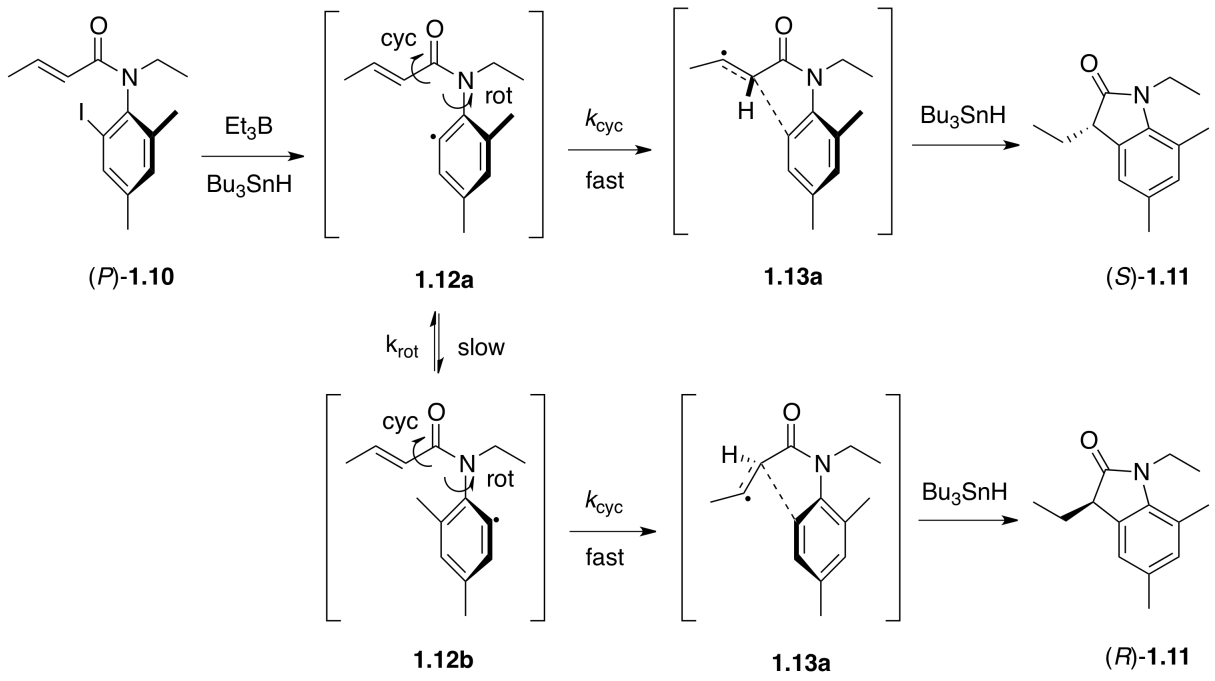
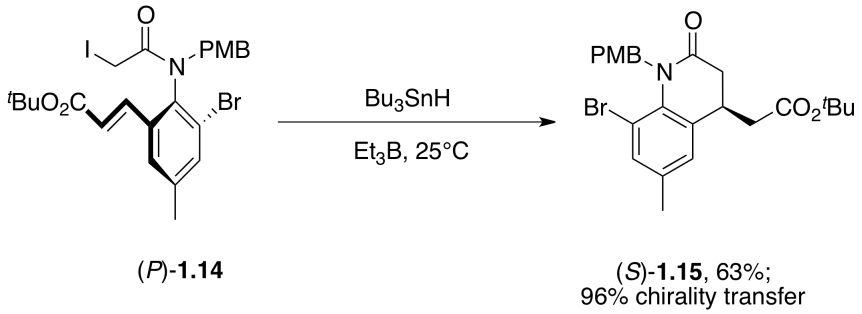



**Figure 5** A Mechanistic Scheme for the Chirality Transfer in the Radical Cyclization of (*P*)-**1.10**

In **Figure 5**, chirality transfer was realized in radical cyclizations through a face-selective addition of the intermediate aryl radical to the olefin acceptor on the amide side chain. Recently, Curran and Guthrie developed 6-*exo-trig* radical cyclizations with excellent chirality transfer (**Scheme 1.2**).[21] These reactions were termed "reverse" cyclizations because the positions of the radical precursors and acceptors were reversed to prior substrates like **1.10** (**Figure 5**). In a typical example of a single *6-exo-trig* cyclization, treatment of atropisomer (*P*)-**1.14** with $Et_3B$ and $Bu_3SnH$ generated 4-disubstituted dihydroquinoline-2-one (*S*)-**1.15** in 63% yield and with 96% chirality transfer.




(*P*)-**1.14**

(*S*)-**1.15**, 63%;
96% chirality transfer

**Scheme 1.2** A "Reverse-Type" 6-*Exo*-*Trig* Radical Cyclization

A variety of mono- and disubstituted dihydroquinoline-2-ones were synthesized via this methodology, with excellent enantioselectivity and diastereoselectivity. Importantly, dihydroquinoline-2-ones are a class of medicinally useful compounds, but they had rarely been synthesized enantioselectively before.[22]

**Figure 6** illustrates the mechanistic origin for chirality transfer. In the ground state of the initially formed radical **1.16**, the radical SOMO orbitals are orthogonal to the alkene LUMO orbitals. Thus the cyclization requires coordinated rotation of the *N*-aryl bond, the aryl-alkenyl bond and CO-$CH_2$• bond, as indicated, to reach a twisted transition state TS-**1.17**. Finally, TS-**1.17** progresses to the cyclized product (*S*)-**1.15**. Compared to aryl radical **1.12a**, which has only one substituent *ortho* to the amide group (**Figure 5**), amidoyl radical **1.16** has a considerably higher rotational barrier of *N*-aryl bond due to the presence of two *ortho* substituents. So the *N*-aryl bond of **1.16** will not rotate 180° to reach the transition state (not shown) that ultimately leads to the enantiomeric (minor) product. Conformationally, this transition state may also be accessed by rotating the aryl-alkenyl bond of **1.16** about 180°. However, this possibility is excluded because such rotation requires the C=C bond to eclipse with the *N*-aryl bond.

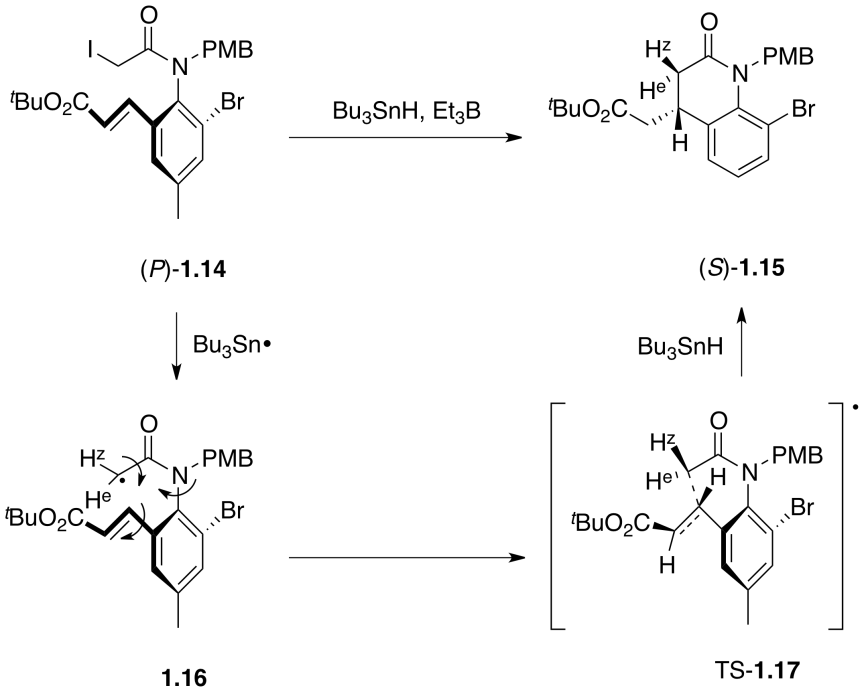
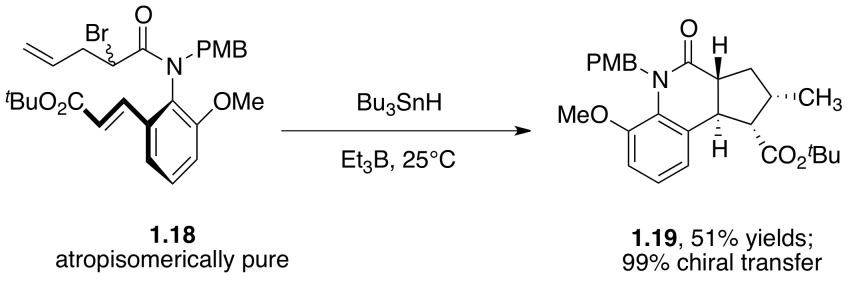



**Figure 6** A Model for the Chirality Transfer in the Cyclization of (*P*)-**1.14**

To culminate this work, an efficient tandem 6-*exo-trig*/5-*exo-trig* cyclization reaction was demonstrated (**Scheme 1.3**). Atropisomerically pure substrate **1.18** was prepared by chiral HPLC resolution of its racemic variant, and subsequent flash chromatography separation of **1.18** yielded two diastereomers (not shown). Each isomer was treated with $Bu_3SnH$ and $Et_3B$ under syringe pump conditions. In both cases, highly substituted 6,6,5-tricyclic product **1.19** was isolated as single isomer in 51% yield, with 99% chirality transfer.




**Scheme 1.3** Tandem 6-*Exo-Trig*/5-*Exo-Trig* Radical Cyclization of An 2-Alkenylanilide

**Figure 7** depictes models for the above cyclizations. The model for the first cyclization (chirality transfer step) is similar to the one described in Scheme **1.4**. The allyl group orients *s-cis* to the carbonyl group in TS-**1.21**, so *trans*-ring fused product **1.22** is favored. The diastereoselectivity of the second cyclization was explained by a chair-like transition state TS-**1.23** with the ester substituent placed at an equatorial position, according to the Beckwith-Houk model.[23]

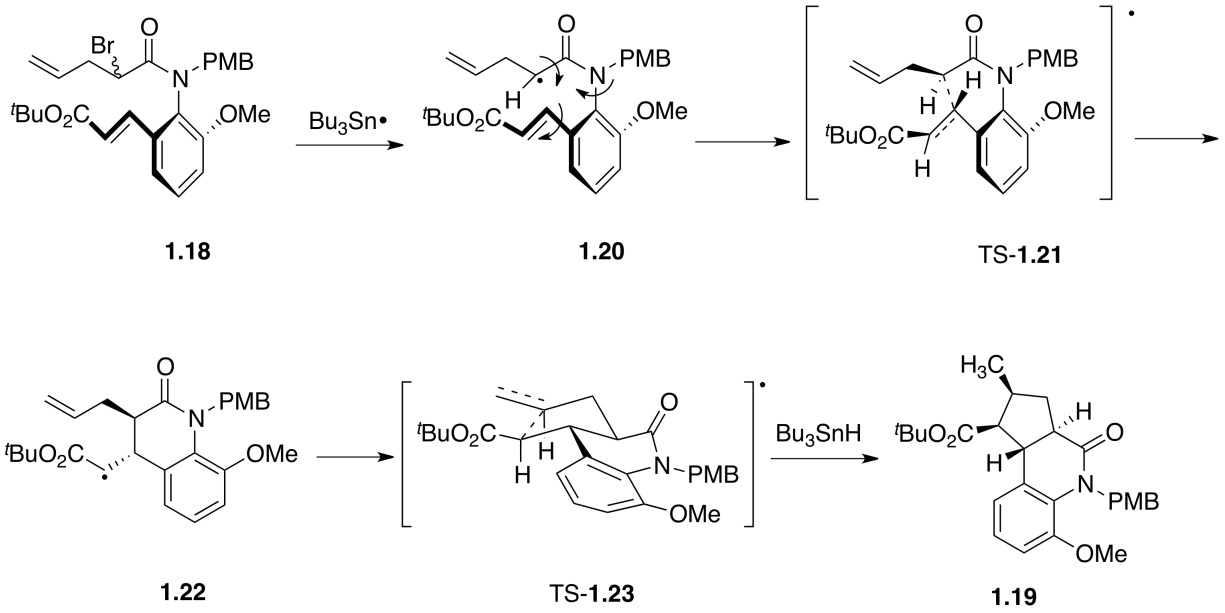



**Figure 7** A Transition-State Model for the Tandem Cyclization of **1.18**

The tandem 6-*exo-trig*/5-*exo-trig* radical cyclization is a potentially powerful tool to quickly access complex ring systems in natural products such as meloscine (**Chapter 2.1**). Moreover, the reliable chirality transfer in radical cyclizations of axially chiral amides suggested a fundamentally new way to establish the absolute configuration in heterocycles containing dihydroquinoline-2-one moieties.

### 1.1.3 Radical β-Elimination of Sulfonyl Groups

A radical that has a sulfonyl group at the β-position can undergo a facile elimination reaction, ejecting a sulfonyl radical with the formation of a double bond.[24] The radical β-sulfonyl elimination reaction has often been applied in combination with other reaction processes. For example, the intermolecular radical addition/elimination sequence has proved synthetically useful.[25]

Three typical modes of radical sulfonyl elimination reactions are shown in **Figure 8**. Most commonly, radical sulfonyl elimination proceeds on substrates that have both the sulfonyl group and the radical placed on adjacent carbons atoms.[26,46,47] For example, treatment of β-sulfonyl thioester **1.28** with $Bu_3SnH$ provided alkene **1.30** in 61% yield, presumably via elimination of β-sulfone radical **1.29**. Another well-documented class of sulfonyl radical elimination reactions involves amido radicals with sulfonyl groups on the adjacent carbons. These reactions give imines, oximes, and hydrozones, depending on the *N*-substitution pattern of the precursors.[27] For example, irradiation of a mixture of cyclohexyl iodide, α-sulfonyl oxime ether **1.31** and hexabutylditin afforded cyclohexyl-substituted oxime ether **1.33** in 91% yield.[43] It was proposed that addition of cyclohexyl radical to **1.31** gives amino radical **1.32**, which releases a phenylsulfonyl radical to form oxime ether **1.33**. Alternatively, β-sulfonyl radical elimination reactions may occur on nitrogen centers and produce imine products.

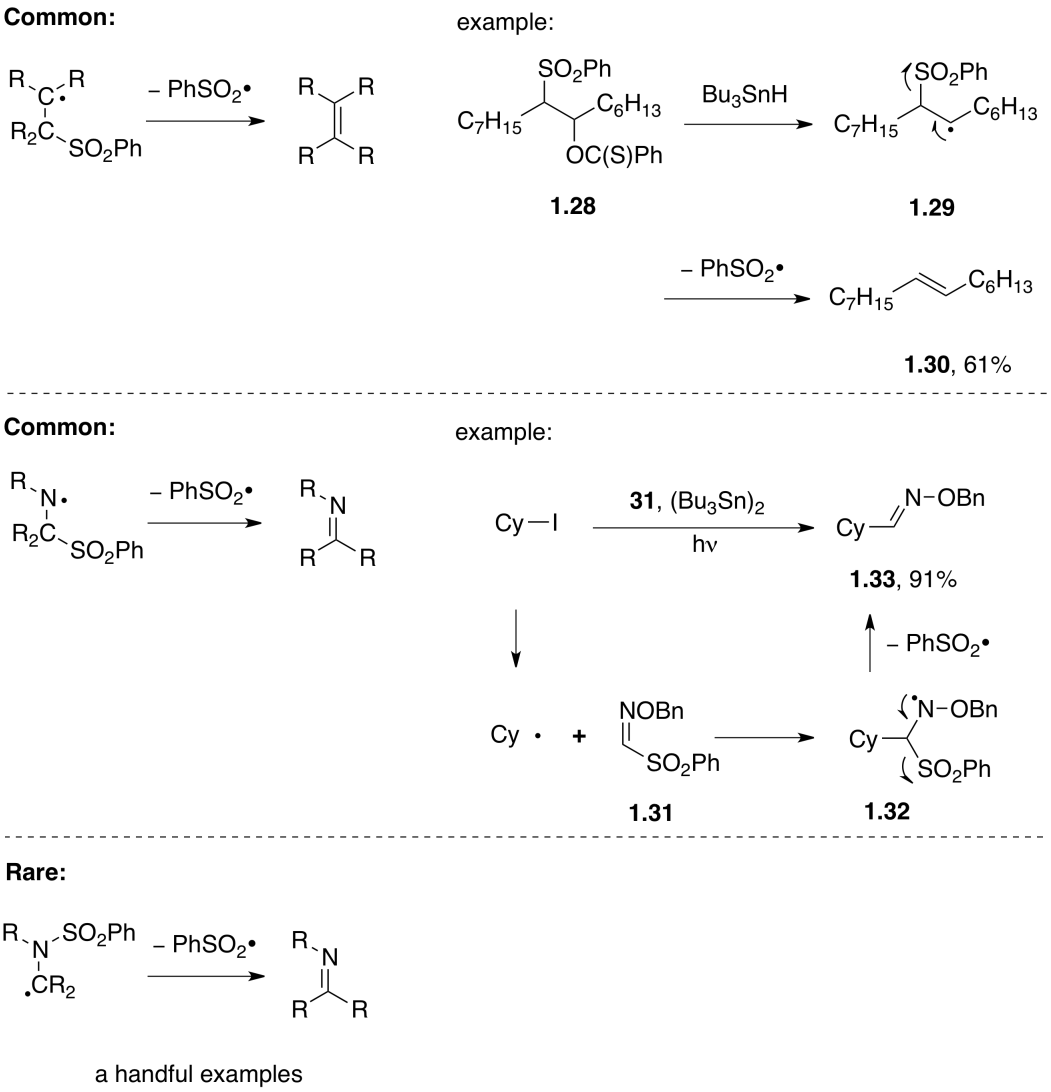
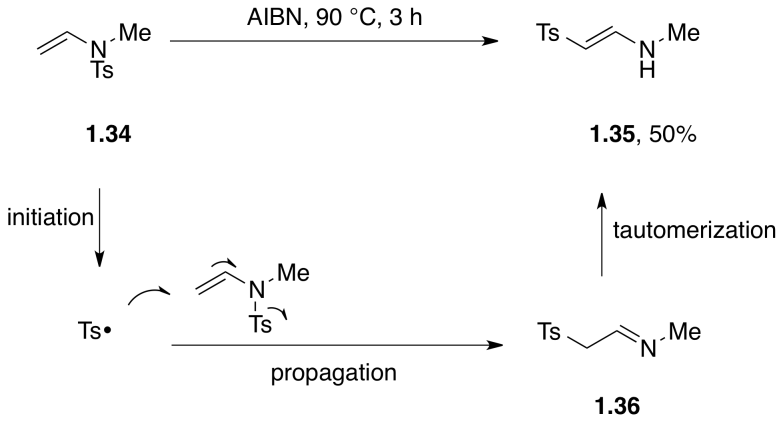



**Figure 8** Representative Classes of Radical β-Sulfonyl Elimination Reactions

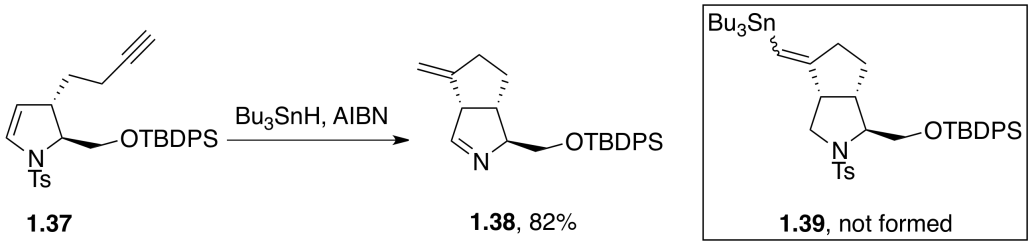
The third mode of sulfonyl radical elimination reactions, which features "reverse" position of the radical on C and the sulfonyl group on N, is much less common. In 1958, Stacey, Sauer, and McKusick reported examples of vinylsulfonamide isomerization that could be promoted by either irradiation or AIBN initiation (**Scheme 1.4**).[28] In a typical reaction, vinylsulfone **1.34** was isolated in 50% yield after heating a solution of AIBN and vinylsulfonamide **1.35** at 90 °C for 3 h. Mechanistic studies suggested the radical chain character

of these reactions. It was proposed that homolytic cleavage of the N-S bond initiates the chain process, producing a tosyl radical that adds to another molecule of **1.34**. Imine **1.36** is formed, along with concomitant release of a new tosyl radical that propagates the reaction. Finally, **1.36** quickly tautomerizes in an ionic fashion to form enamine **1.35**. In 1974, Hertler studied the scope of this reaction, and his experimental results supported the radical chain mechanism.[29]



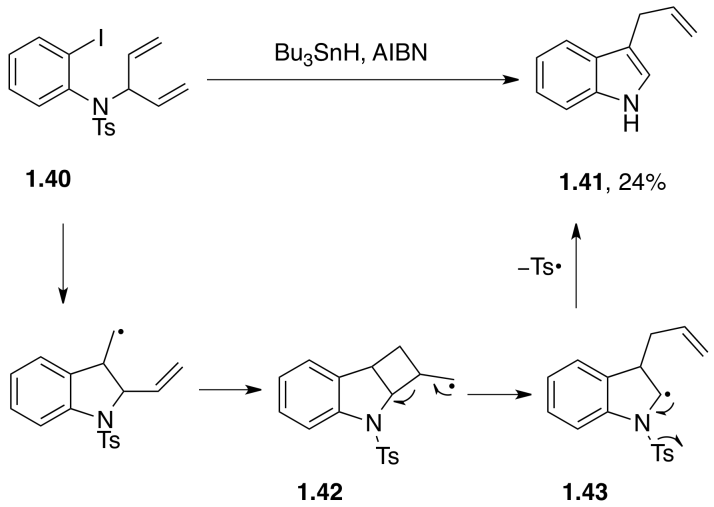

**Scheme 1.4** Radical Induced Vinylsulfonamide Rearrangement

Following the initial discovery of vinylsulfonamide isomerization, several research groups occasionally encountered possible radical *N*-sulfonyl elimination reactions. In an effort to construct the bicyclic scaffold of α-kainic acid, Cossy conducted radical cyclization of enamide **1.37** bearing an alkyne side chain (**Scheme 1.5**).[30] However, the expected tin-addition/cyclization sulfonamide product **1.39** was not formed. Instead, bicylic imine product **1.38** was obtained in 82% yield.



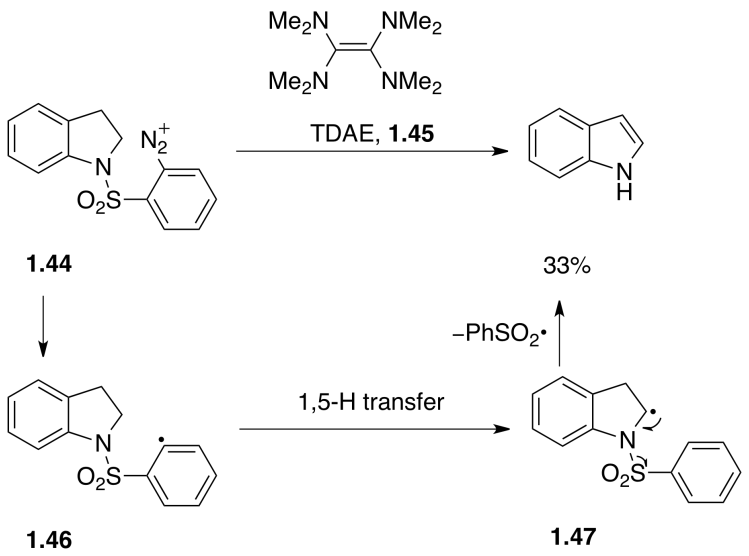

**Scheme 1.5** An Unexpected *N*-Desulfonylation Reaction Reported by Cossy

In 2001, Murphy reported an interesting cascade radical cyclization of *N*-2-iodophenyl-*N*-1,4-pentadienyl-3-sulfonamide **1.40** that gave desulfonylated 3-allylindole **1.41** in 24% yield.[31] According to Murphy's proposed mechanism, initial 5-exo-trig cyclization of **1.40**, followed by a subsequent 4-exo-trig cyclization, generates tricyclic primary radical **1.42**. This radical then rearranges to form α-amino radical species **1.43**, which then undergoes sequential β-sulfonyl radical elimination/tautomerization to produce **1.41** (**Scheme 1.6**).



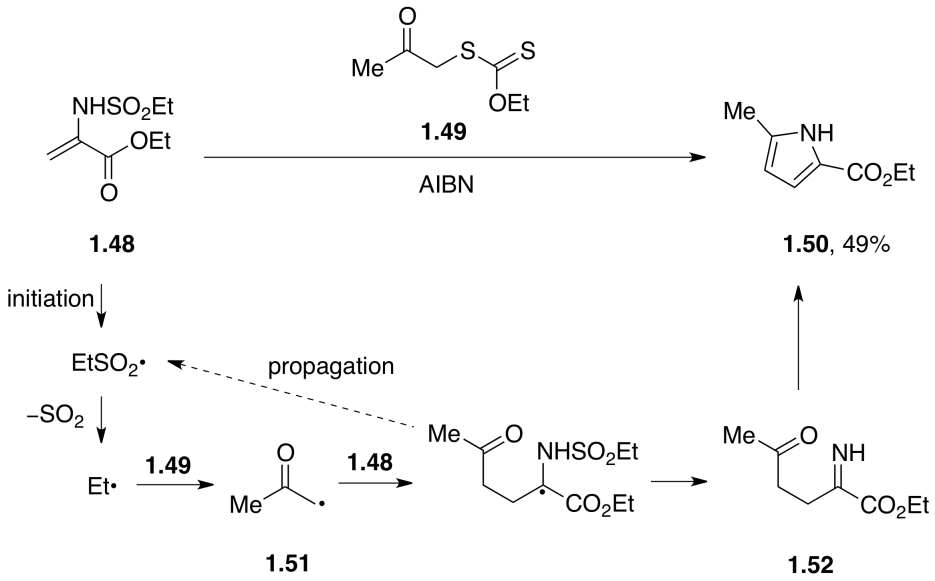

**Scheme 1.6** An Unexpected *N*-Desulfonylation Reaction Reported by Murphy

In another interesting example presented by Murphy, submission of *ortho*-diazophenylsulfonamide **1.44** to tetrakis(dimethylamino)ethylene (TDAE) **1.45** generated indole in 33% yield.[32] Murphy proposed that diazonium salt **1.44** is reduced by TDAE to form aryl radical **1.46**. Radical translocation of **1.46** provides α-amino radical species **1.47** that ejects a sulfonyl radical to form 3*H*-indole, which readily tautomerizes to provide 1*H*-indole (**Scheme 1.7**).



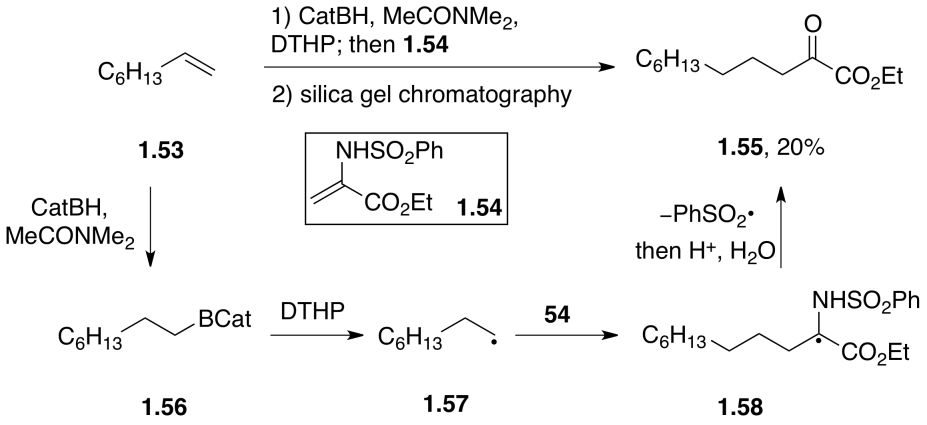

**Scheme 1.7** Dehydrogenation of a Dihydroindole via *N*-Desulfonylation

More recently, Zard discovered a novel approach to substituted pyrroles via *N*-sulfonyl elimination.[33] As shown in **Scheme 1.8**, heating a mixture of AIBN, vinylsulfonamide **1.48**, and xanthate **1.49** provided pyrrole **1.50** in 54% yield. The initiation of this reaction is thought to involve the generation of an ethyl radical that abstracted the xanthate group of **1.49** to give α-keto radical species **1.51**. Addition of radical **1.51** to vinylsulfonamide **1.48** produces imine **1.52**, releasing a sulfonyl radical that propagates the chain reaction. Spontaneous condensation of **1.52** affords pyrrole **1.50**.



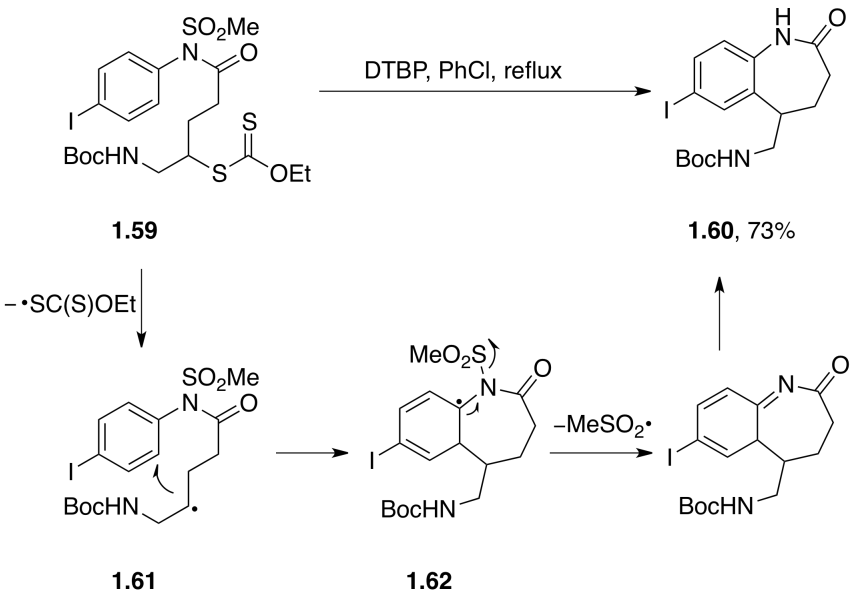

**Scheme 1.8** Zard's Pyrrole Synthesis via *N*-Desulfonylation

A related process was disclosed by Renaud (**Scheme 1.9**).[34] In a typical reaction, addition of vinylsulfonamide **1.54** and di-*tert*-butylhyponitrite (DTHP) to a premixed solution of alkene **1.53** and catecolborane furnished alkylated pyruvate **1.55** in 20% yield. Mechanistically, Renaud suggested that DTHP initiation of *in situ* generated alkylborane **1.56** provides alkyl radical **1.57** that adds to vinylsulfonamide **1.54**. Sulfonyl elimination of the resulting α-amino radical species **1.58**, followed by hydrolysis of the resulting iminoester upon silica gel chromatography, provides pyruvate **1.55**.



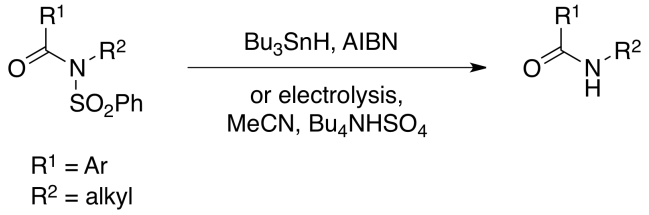

**Scheme 1.9** Renaud's Pyruvate Synthesis via *N*-Desulfonylation

Most recently, Zard reported a creative synthetic method for making benzazepinones using an unexpected *N*-sulfonyl elimination reaction. As shown in **Scheme 1.10**, reaction of sulfonamide **1.59** with di-*tert*-butylperoxide initiator (DTBP) in refluxing chlorobenzene affords benzazepinone **1.60** in 73% yield. Zard proposed that loss of a xanthate group of **1.59** generates secondary radical **1.61**, which cyclizes to the phenyl ring to form aryl radical **1.62** bearing a 7-membered ring. Subsequent elimination of a methanesulfonyl radical, followed by rearomatization, produces benzazepinone **1.60**.




**Scheme 1.10** Zard's Benzazepinone Synthesis via Radical Cyclization/*N*-Desulfonylation

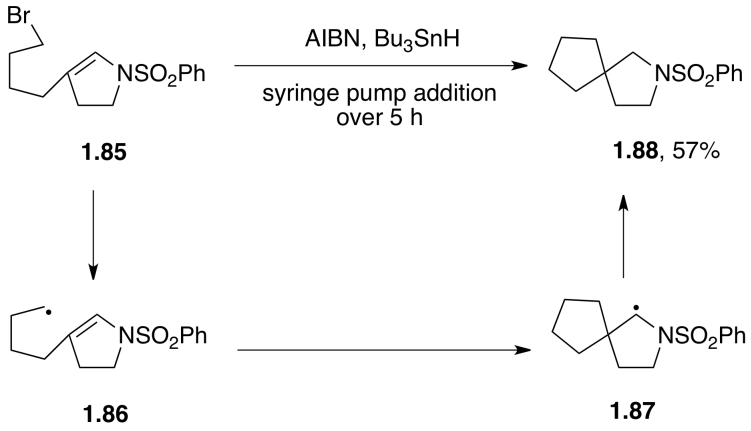
Aside from aforementioned examples of *N*-desulfonylation that involve carbon-carbon bond forming events, direct removal of sulfonyl groups from certain types of amides have been achieved using tin hydride and electrochemistry (**Scheme 1.11**).[35] In addition, scattered examples of photo-induced, homolytic *N*-sulfonyl bond cleavage have been reported.[36]




**Scheme 1.11** Radical and Electrochemical Cleavage of Amide Sulfonyl Groups

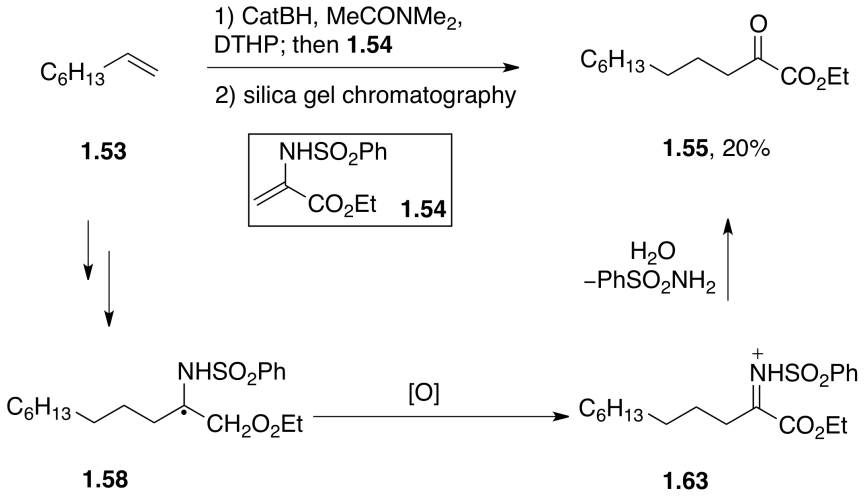
While carbon-centered, α-sulfonamido radicals can undergo facile elimination of sulfonyl radicals, as shown in above examples, different reactivities of these radicals have been observed. For example, the Somfai group reported that cyclization of **1.85** under syringe pump condition afforded sulfonamide **1.88** in 57% yield (**Scheme 1.12**).[37] Mechanistically, 5-*exo*-*trig*

cyclization of initially formed primary radical **1.86** to the enamide moiety produces intermediate α-amino radical **1.87**, which is reduced by tin hydride to form sulfonamide product **1.88**.




**Scheme 1.12** Somfai's Cyclization Experiment

The interesting precedents listed above illustrate the synthetic potential of *N*-sulfonyl elimination under radical conditions, combined with other processes, to provide facile access to heterocycles that are structurally novel and biologically relevant. However, neither the scope nor mechanism of radical *N*-sulfonyl elimination has yet to be systematically studied. Even though indirect evidence for the formation of defonylated imine products has been shown, in most cases they were not isolated. It was suggested that they either tautomerize into corresponding enamines or hydrolyze to generate ketones. Nonetheless, some of these products may form by other ways (**Scheme 1.13**). In Renaud's reaction (**Scheme 1.9**), for example, oxidation of electron-rich radical **1.58** may provide iminium ion **1.63** that can be converted to ketone **1.55** via hydrolysis. Only Cossy actually isolated the imine product, however, she proposed a mechanism that does not involve β-sulfonyl radical elimination.[30]



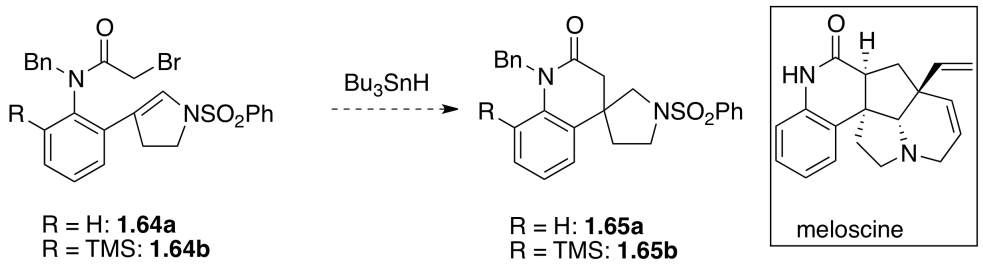

**Scheme 1.13** An Alternative Reaction Pathway of α-Amino Radical **1.58**

In the course of our synthetic studies of meloscine alkaloids, we discovered an unexpected, imine-forming radical desulfonylation reaction. In **Chapter 1.2**, we report our studies on the scope and mechanism of this reaction.

## 1.2 RESULTS AND DISCUSSION

### 1.2.1 Discovery of an Imine-Forming, Radical *N*-Desulfonylation Reaction

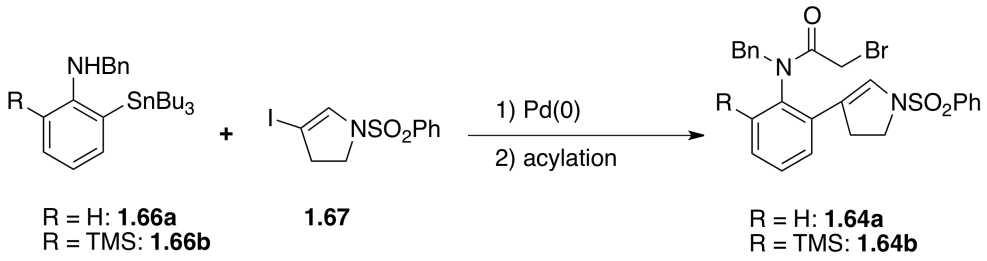
To probe the viability of a tandem radical 6-*exo*-*trig*/5-*exo*-*trig* cyclization strategy in the synthesis of meloscine alkaloids, we designed model compounds **1.64a** and **1.64b** for testing the first 6-*exo*-*trig* cyclization (**Scheme 1.14**). The electron-withdrawing benzenesulfonyl group was chosen as the enamine protecting group, because electron transfer side reactions are a potential risk for radical cyclizations of electron-rich enamines.[38]




**Scheme 1.14** A Model System for Testing the Radical Cyclization Strategy in the Synthesis of Meloscine

## 1) Synthesis of Model Substrates

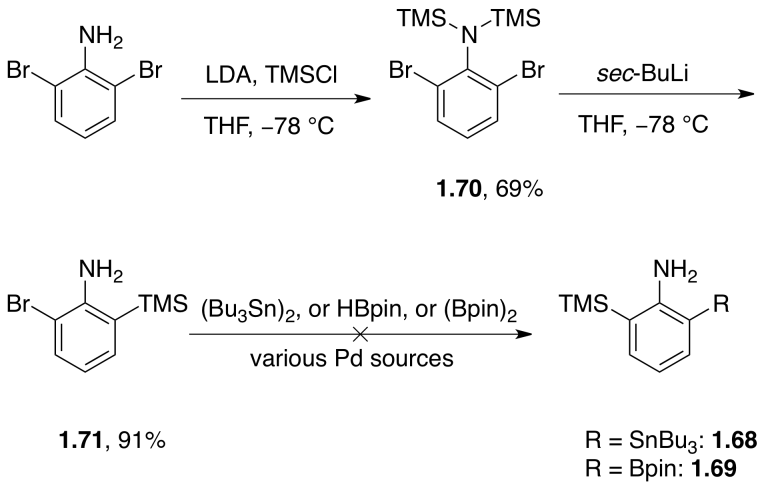
There are only few reported syntheses of 3-aryl-$\delta_2$-pyrroline systems similar to **1.64a**.[39] Strong basic conditions were used for several transformations in these syntheses. Considering the sensitivity of the *ortho*-TMS functionality of substrate **1.64b**, we planned to develop a unified approach toward **1.64a** and **1.64b** without using any harsh conditions. Initial attempts at Suzuki coupling[40] or α-arylation of sulfonamide[41] routes were unfruitful. However, synthesis of substrate **1.64a** was achieved by Stille coupling of arylstannane **1.66a** and vinyl iodide **1.67** (**Scheme 1.15**).




**Scheme 1.15** A Stille-Coupling Approach towards **1.64a** and **1.64b**

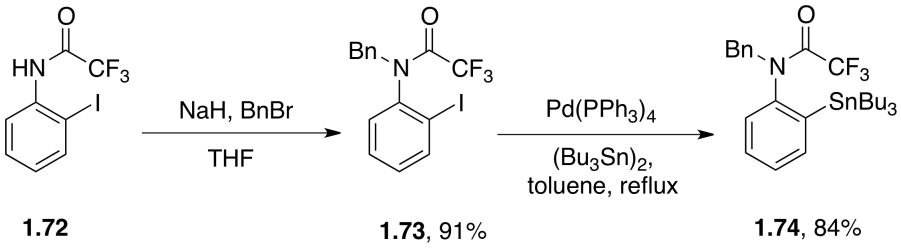
An attempted synthesis of arylstannane **1.68** and its boronate analog **1.69** is shown in **Scheme 1.16**. Deprotonation of commercially available 2,6-dibromoaniline with LDA, followed by addition of TMSCl, produced *bis*-TMS protected aniline **1.70** in 69% yield. Lithium-bromide

exchange of **1.70**, followed by a silyl migration and hydrolysis of the remaining *N*-TMS group,[42] provided *ortho*-TMS-substituted aniline **1.71** in 91% yield. However, reactions of **1.71** with hexabutylditin, pinacolborane, or pinacolato diborane, using several typical catalytic systems, failed to produce arylstannane **1.66b** or arylboronate **1.68**.



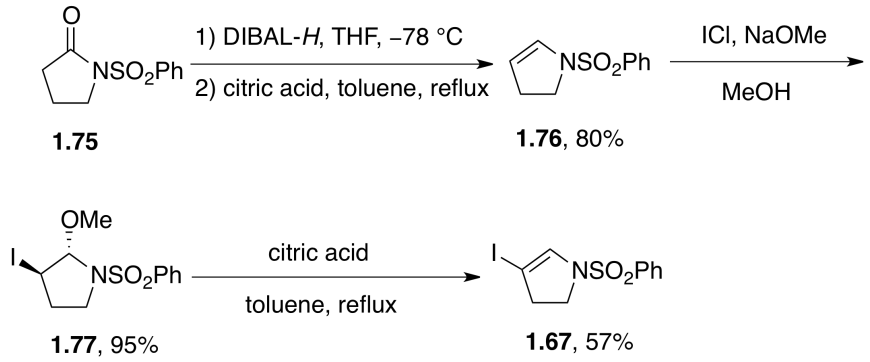

**Scheme 1.16** Attempted Synthesis of Arylstannane **1.68** and Arylboronic Ester **1.69**

Arylstannane **1.74** was synthesized in a two-step sequence (**Scheme 1.17**). Deprotonation of known trifluoroacetamide **1.72** with NaH, followed by addition of benzyl bromide, provided 2-iodoanilide **1.73** in 91% yield. Subsequently, palladium-catalyzed cross-coupling of **1.73** with hexabutylditin in refluxing toluene gave arylstannane **1.74** in 84% yield.[43]



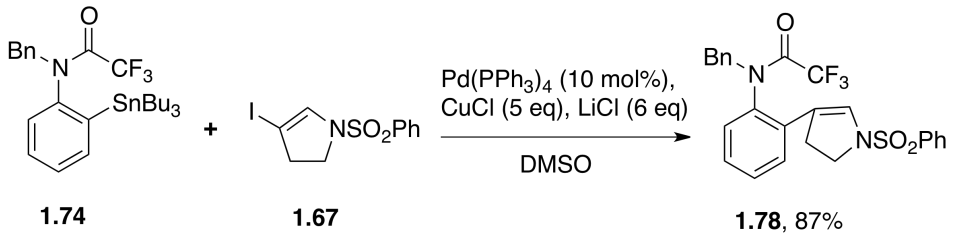

**Scheme 1.17** Synthesis of Arylstannane **1.74**

The preparation of the vinyl iodide **1.67** was accomplished in a four-step sequence (**Scheme 1.18**). DIBAL-*H* reduction of known sulfonamide **1.75**, followed by dehydration of the resulting crude hemiaminal with citric acid in refluxing toluene, afforded enesulfonamide **1.76** in 80% yield over two steps.[44] Enesulfonamide **1.76** reacted with iodine monochloride and sodium methoxide to provide crude alkyl iodide **1.77** in 95% yield.[45] This product was heated with 3 equiv of citric acid in refluxing toluene to eliminate methanol, furnishing the target vinyl iodide **1.67** in 57% yield.




**Scheme 1.18** Synthesis of Vinyl Iodide **1.67**

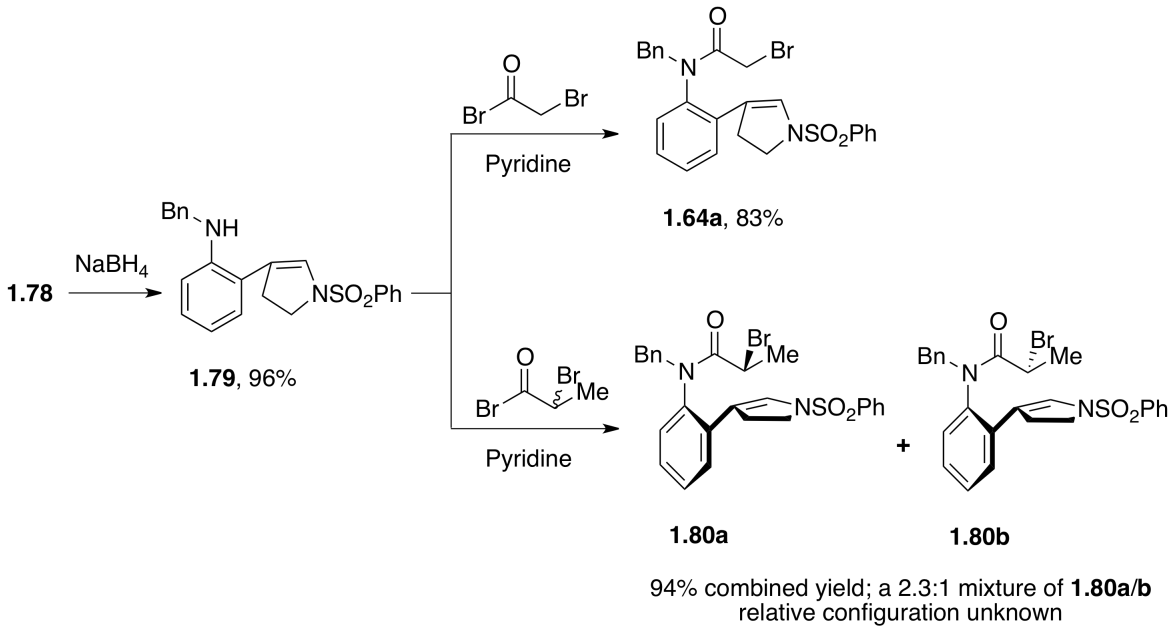
Next, we surveyed three typical conditions for Stille coupling of arylstannane **1.74** with vinyliodide **1.67**. Refluxing a solution of reactants and $Pd(PPh_3)_4$ in toluene[46] resulted in no desired product. After submission of the reactants to a mixture of $Pd_2(dba)_3{\cdot}CHCl_3$, $(2\text{-furyl})_3P$, and CuI (Farina-Liebeskind conditions),[47] coupling product **1.78** was formed in 25% yield with an appreciable amount of biaryl byproduct from **1.74**. Finally, the target product **1.78** was prepared in 87% yield on multi-gram scale by reacting the substrates with $Pd(PPh_3)_4$, LiCl, and CuCl, according to Corey's protocol (**Scheme 1.19**).[48]




**1.74** **1.67** **1.78**, 87%

**Scheme 1.19** Stille-Coupling of Arylstannane **1.74** and Vinyl Iodide **1.67**

Treatment of trifluoroacetamide **1.78** with $NaBH_4$ produced aniline **1.79** in 96% yield. Subsequent acylation of **1.79** with bromoacetyl bromide in the presence of pyridine furnished α-bromoamide **1.64a** in 83% yield (**Scheme 1.20**). Similarly, treatment of aniline **1.79** with *rac*-2-bromo-propionyl bromide provided precursor **1.80** in 94% yield (**Scheme 2.7**). In principle, anilide **1.80** consists a maximum of four possible diastereomers, because it contains two axes of chirality as well as a stereogenic center. However, only two diastereomers **1.80a** and **1.80b** were observed by NMR, suggesting that one of the aforementioned axes of chirality, likely the aryl-dihydropyrrole bond, rotates fast relative to the NMR time scale. Most of aromatic signals of **1.80a** and **1.80b** overlapped on $^1$H NMR spectrum, but the other signals separated into two sets, which were integrated in a 2.3:1 ratio. The two diastereomers were observed as a single spot on TLC. However, the separation of **1.80a** and **1.80b** should not be important to the cyclization reaction, since we expected both diastereomers to give the same product as in **Scheme 1.3**.



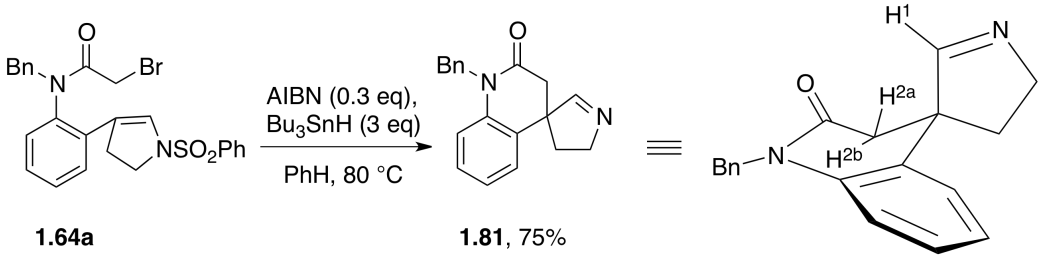

**Scheme 1.20** Synthesis of Cyclization Precursors **1.64a** and **1.80**

## 2) Discovery of β-Sulfonyl Elimination Reactions

With precursors **1.64a** and **1.80** in hand, we set out to study the radical 6-*exo*-*trig* cyclization reactions. Based on Somfai's results (**Scheme 1.12**), we anticipated sulfonamide products of the reaction to be formed in this reaction. However, the reaction took an unexpected course.

In a typical experiment, AIBN and $Bu_3SnH$ were mixed with a 0.01 M solution of substrate **1.64a** in refluxing benzene **(Scheme 1.21)**. After 30 min, the solvent was removed, and the residue was partitioned between acetonitrile and hexane to remove most of the tin byproduct into the hexane layer. After column chromatography purification of the acetonitrile extract, a single major product was isolated in 75% yield whose structure was assigned as tricyclic imine **1.81**. Based on $^1H$ and $^{13}C$ NMR spectroscopy, several features were indicative of the spiroimine structure: 1) benzenesulfonyl signals were absent in the $^1H$ NMR spectrum; 2) a singlet at δ 7.51

ppm ($H^1$) on the $^1H$ NMR spectrum, as well as a carbon signal at 167.8 ppm, suggested the presence of an imine; and 3) mutually coupled doublets of two geminal protons at δ 2.97 ppm and 2.67 ppm ($H^{2a}$ and $H^{2b}$) were observed. This $CH_2$ group is isolated between the quaternary center and the lactam carbonyl in a spiro structure. In addition, the molecular weight of **1.81** is determined to be 290.1414 by HRMS (EI), and this was in line with a calculated molecular weight of 290.1419 $[M]^+$.




**1.64a** **1.81**, 75%

**Scheme 1.21** Unexpected Formation of Desulfonylated Imine **1.64a**

A proposed mechanism for the formation of imine **1.81** is outlined in **Figure 9**. Initially formed amidoyl radical **1.82** cyclizes to the dihydropyrrole alkene, generating β-sulfonyl radical **1.83**. Instead of reacting with tin hydride to give sulfonamide **1.65a**, **1.83** eliminates a benzenesulfonyl radical to give imine **1.81**. The released benzenesulfonyl radical abstracts a hydrogen atom from a second molecule of $Bu_3SnH$ to form benzenesulfinic acid and a new tin radical that possibly propagates the chain reaction. Aldimines are in general easy to hydrolyze, but the presence of an adjacent quaternary center in **1.81** presumably stabilizes the imine functionality. In addition, this quarternary center prevents the formation of the enamine tautomer.

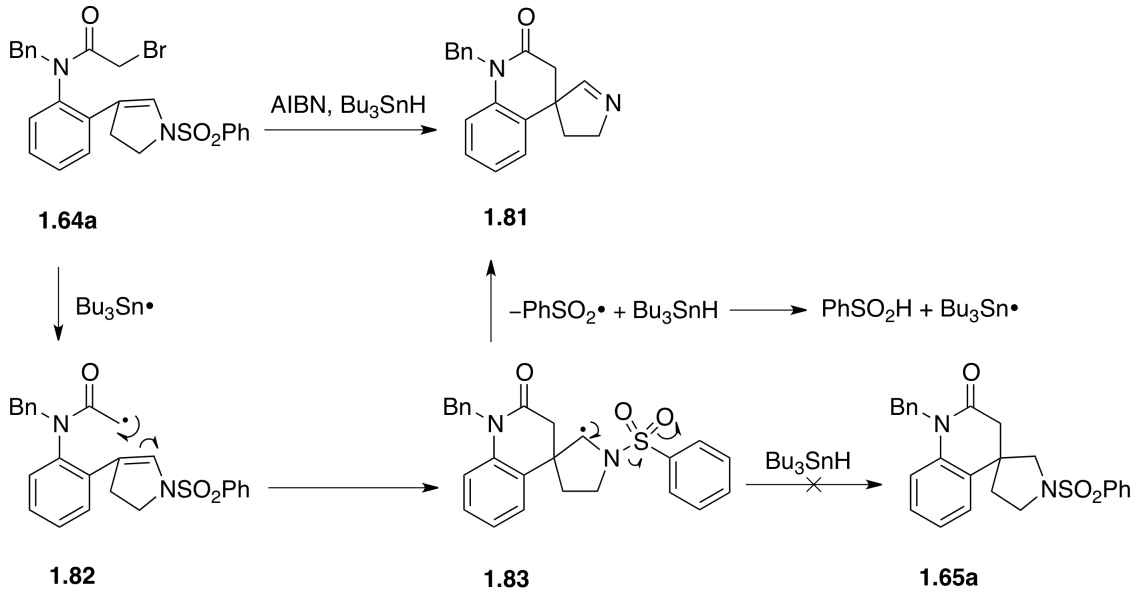
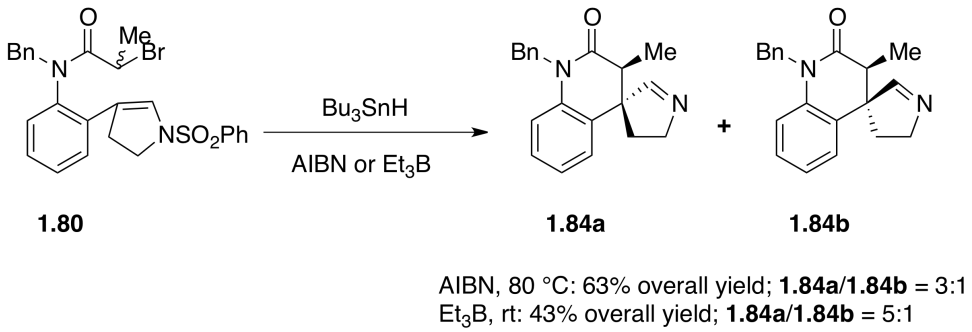



**Figure 9** Proposed Mechanism for the Formation of Imine **1.81**

To study the diastereoselectivity of the radical cyclization, we subjected substrate **1.80** to the same reaction condition as described above ($Bu_3SnH$, 80 °C; **Scheme 1.22**). The solvent was evaporated and the crude product was determined to be a pair of diastereomers in a 3:1 ratio, based on $^1H$ NMR analysis. Column chromatography provided less polar **1.84a** in 50% yield and more polar **1.84b** in 13% yield. In another experiment, $Bu_3SnH$ and $Et_3B$[21] were added to a 0.01 M solution of substrate **1.80** in benzene, and the mixture was stirred at room temperature for 30 min. The crude product was determined to be a 5:1 mixture of **1.84a** and **1.84b**. These products were collected together in one fraction and the combined yield was 43%.




**Scheme 1.22** Radical Cycliation of **1.80** with $Bu_3SnH$ at Different Temperatures

We performed NOESY experiments on both diastereomers to determine the relative stereochemistry of **1.84a** and **1.84**. Strong $H^1/H^2$ and $H^{3b}$/methyl cross-peaks together with a weak $H^1$/methyl cross-peak were observed in the spectrum of major isomer **1.84a** (**Figure 10**). A strong $H^1$/methyl cross-peak and a weak $H^1/H^2$ cross-peak were observed on the spectrum of minor isomer **1.84b**. In addition, the $H^{3b}$/methyl cross-peak, as shown in the spectrum of **1.84a**, was not found in the spectrum of **1.84b**. Therefore, the methyl group should be *anti* to the imine group in **1.84a**. This stereochemical assignment was later unambiguously confirmed by X-ray crystallography of stereoisomer **1.84a**.

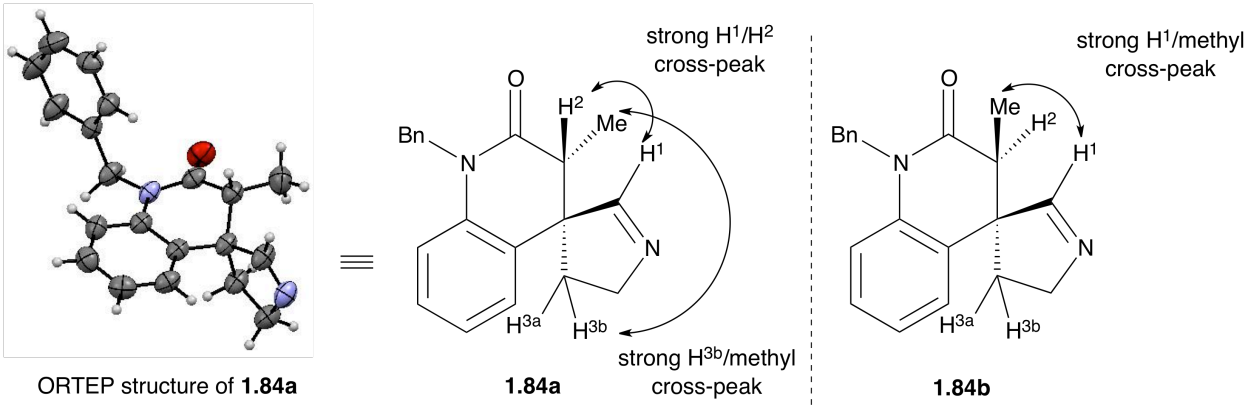


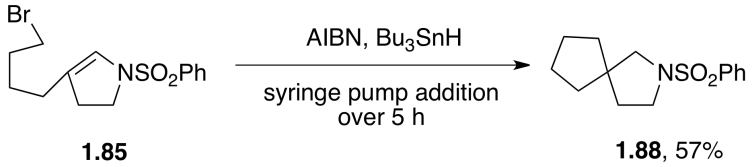

**Figure 10** Stereochemical Assignment of **1.84a** and **1.84b** by NOESY and X-Ray Crystallography

In summary, the first radical 6-*exo*-*trig* cyclization smoothly proceeded on the model systems, and byproducts of 7-*endo*-*trig* cyclization or premature reduction were not detected. In addition, an interesting radical, imine-forming β-sulfonyl elimination reaction was discovered.

### 1.2.2 Scope and Limitations of the Radical *N*-Sulfonyl Elimination Reaction

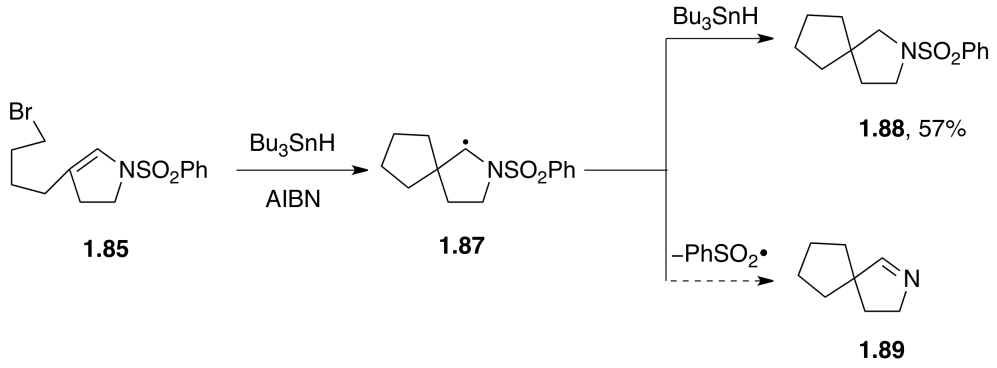
#### 1) 3-Alkyl Substituted 2,3-Dihydropyrroles

To test the generality of the β-sulfonyl elimination reaction, we decided to study cyclization behaviors of *N*-sulfonyl dihydropyrrole **1.85** (**Scheme 1.23**),[37a] a substrate similar to **1.64a** (**Scheme 1.21**). The Somfai group reported that cyclization of **1.85** under syringe pump condition afforded reduced spirosulfonamide **1.88** in 57% yield.



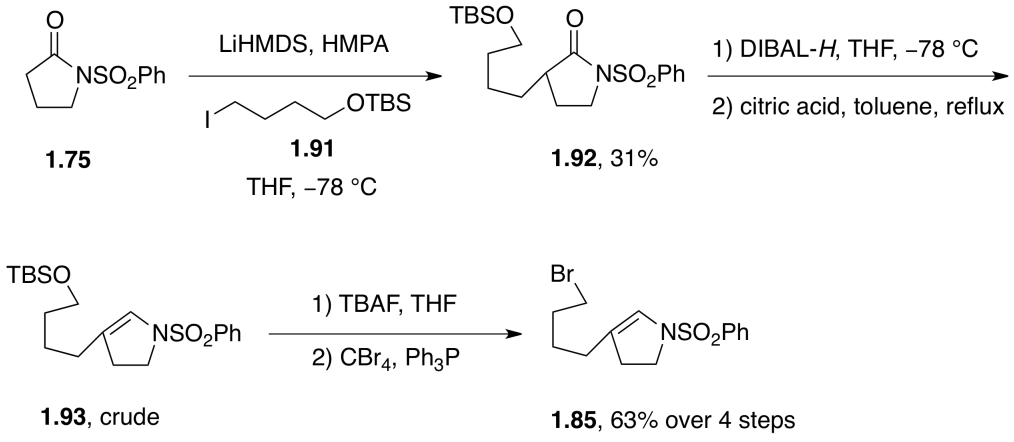

**Scheme 1.23** Cyclization of **1.85**

Mechanistically, Somfai suggested that 5-*exo*-*trig* radical cyclization of dihydropyrrole **1.85** produces intermediate α-amino radical **1.87**, which is reduced by tin hydride to form sulfonamide product **1.88**. We have shown that similar α-amino radicals generated after 6-*exo*-*trig* cyclizations can eliminate benzenesulfonyl radical to form imines (**Section 1.2.1**). Therefore, even though spirosulfonamide **1.88** was isolated as the single major product of Somfai's reaction, we wondered whether imine product **1.89** could be produced along with **1.88** under tin hydride treatment (**Scheme 1.24**).



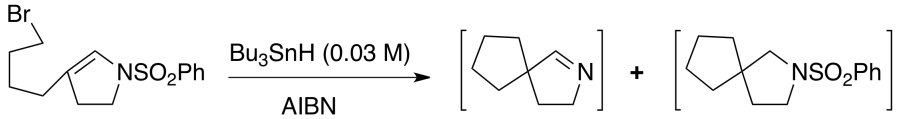

**Scheme 1.24** Possible Reaction Pathways of Radical **1.87**

To test this idea, we synthesized Somfai's substrate **1.85** in five steps from sulfonamide **1.75**, according to his procedures (**Scheme 1.25**). Under Oppolzer's conditions,[49] sulfonamide **1.75** was alkylated with unactivated alkyl iodide **1.91** to provide **1.92** in 31% yield. DIBAL-*H* reduction of **1.92**, followed by acidic dehydration of the resulting crude hemiaminal, afforded crude enamide **1.93**. Deprotection of silylether **1.93** with TBAF generated the corresponding crude alcohol, which was subsequently subjected to triphenylphosphine and carbon tetrabromide to furnish the target bromide substrate **1.85** in 63% yield over four steps. Spectroscopic data of **1.85** matched with Somfai's,[37a] and yields of all the intermediates were comparable to reported ones.




**Scheme 1.25** Synthesis of Somfai's Substrate **1.85**

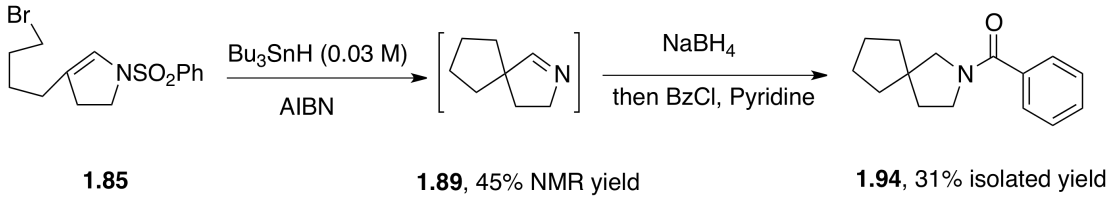
The hypothesized *N*-desulfonylation of **1.85** was quickly supported by a cyclization experiment conducted under the condition of a fixed tributyltin hydride concentration (**Scheme 1.26**). A mixture of AIBN, $Bu_3SnH$ (0.03 M), and bromide substrate **1.85** in benzene was refluxed for 30 min. A characteristic *N*-$CH_2$ peak of known bicyclic imine **1.89**, shown as a triplet of doublets at δ 3.86 ppm, was found in the crude product. Notably, a similar signal at 4.02 ppm that represents the *N*-$CH_2$ group of tricyclic imine **1.84a** was also observed by $^1H$ NMR (**Section 1.2.1**). We calculated a 57% NMR yield of **1.89** by integrating this *N*-$CH_2$ peak against the aromatic peak of 1,3,5-trimethoxybenzene as an internal standard. In addition, key signals of the reported sulfonamide product **1.88**, namely the *N*-$C_{(a)}H_2$ peak shown as a singlet at 3.09 ppm and the *N*-$C_{(b)}H_2$ peak shown as a triplet at 3.33 ppm, were detected in the crude product. The NMR yield of **1.88** was calculated to be 23%.




**1.85** **1.89**, 57% NMR yield **1.88**, 23% NMR yield

**Scheme 1.26** Cyclization of **1.85** with a Fixed Concentration of $Bu_3SnH$

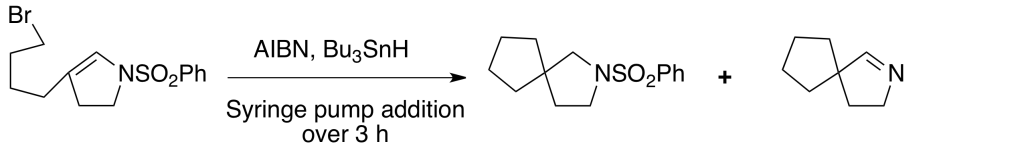
It was difficult to isolate imine **1.89** due to the contamination of alkylstannane byproducts. We addressed this issue by *in situ* functionalization (**Scheme 1.27**). The cyclization reaction of dihydropyrrole **1.85** with tin hydride was repeated, and the crude reaction mixture containing **1.89** was sequentially treated with $NaBH_4$ and benzoyl chloride. The resulting crude benzamide **1.94** was isolated in 31% yield after flash chromatography.




**1.85** **1.89**, 45% NMR yield **1.94**, 31% isolated yield

**Scheme 1.27** Conversion of *In Situ* Generated Imine **1.89** to Benzamide **1.94**

Next, we repeated Somfai's experiment under syringe pump conditions (**Scheme 1.28**). A solution of AIBN (0.2 eq.) and $Bu_3SnH$ (1.5 eq.) in benzene was added via syringe pump to a solution of **1.85** (0.06 M) and AIBN in refluxing benzene over a period of 3 h. Full conversion of the starting material was achieved. Based on $^1H$ NMR analysis, the crude product was a mixture of imine **1.89** and sulfonamide **1.88**, in a 2.5:1 ratio, along with some unidentifiable byproducts. Careful purification of the crude product afforded the target sulfonamide product **1.88** in 15% yield. Thus we partially reproduced Somfai's experiment despite that the formation of imine was also observed.

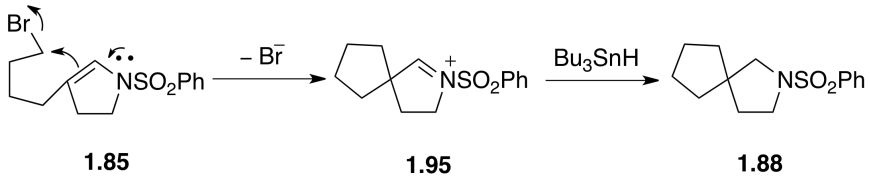



**1.85** **1.88**,15% isolated yield **1.89**, yield not calculated

1 : 2.5

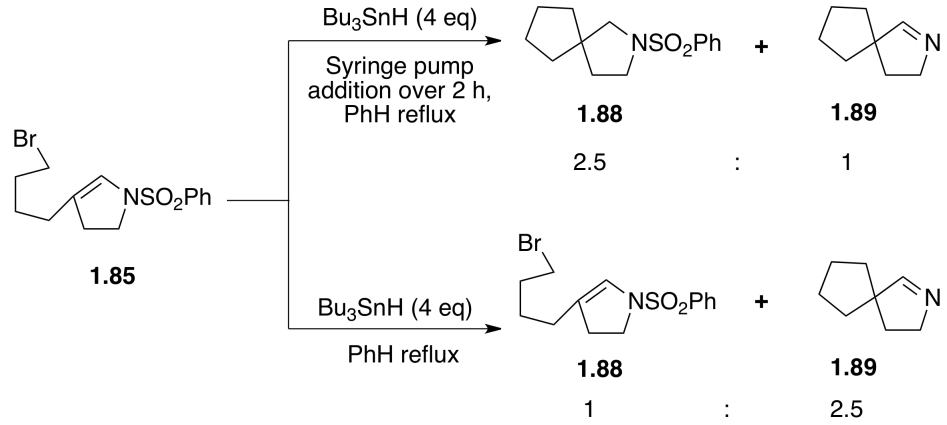
**Scheme 1.28** Cyclization of **1.85** under the Syringe Pump Conditions

In addition to Somfai's radical mechanism for the formation of sulfonamide **1.88**, we considered that ionic pathways might be possible because a bromide on a primary carbon is a good leaving group (**Scheme 1.29**).




**Scheme 1.29** An Ionic Pathway for the Formation of Spirosulfonamide **1.88**

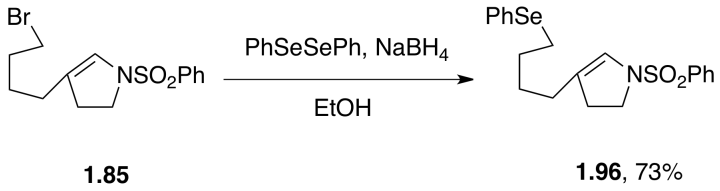
To differentiate ionic and radical pathways, we first conducted two control experiments without AIBN initiation (**Scheme 1.30**). In the first experiment, 4 equiv of $Bu_3SnH$ was added via syringe pump to a 0.01 M solution of bromide **1.85** in refluxing benzene over a period of 2 h. Complete conversion of the starting material was observed, judged by $^1H$ NMR analysis of the crude product, and a 2.5:1 mixture of spirosulfonamide **1.88** and imine **1.89** was observed. In the second experiment, 4 equiv of $Bu_3SnH$ was added to a 0.01 M solution of bromide **1.85** in refluxing benzene in one portion. After 12 h, a 2.5:1 mixture of imine **1.89** and unconsumed bromide **1.85** was observed by $^1H$ NMR. The results of these two experiments suggested that bromide **1.85** likely underwent self-initiation in the absence of AIBN.




**Scheme 1.30** Cyclization of **1.85** in the Absence of AIBN

Next, we decided to prepare phenylselenide **1.96** (**Scheme 1.31**). Bromides and phenylselenides have comparable reactivities toward tin hydride, but unlike bromide,

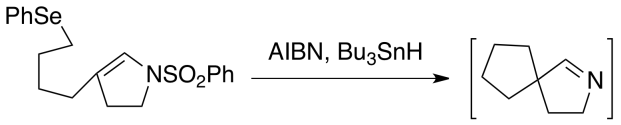
phenylselenide is not a good leaving group in $S_N2$ reactions. Therefore, treatment of a solution of bromide **1.85** with an *in situ* prepared solution of phenylselenide anion in EtOH provided phenylselenide substrate **1.96** in 73% yield.[50]




**1.85** **1.96**, 73%

**Scheme 1.31** Synthesis of Phenylselenide **1.96**

Phenylselenide substrate **1.96** was cyclized under the conditions of fixed tin hydride concentration in the same manner of bromide **1.85** (**Scheme 1.32**). Evaporation of the solvent provided a crude product that contained imine **1.89** and unidentifiable byproducts, based on $^1$H NMR analysis. No spirosulfonamide product **1.88** was detected, and the NMR yield of imine **1.89** was calculated to be 60%.

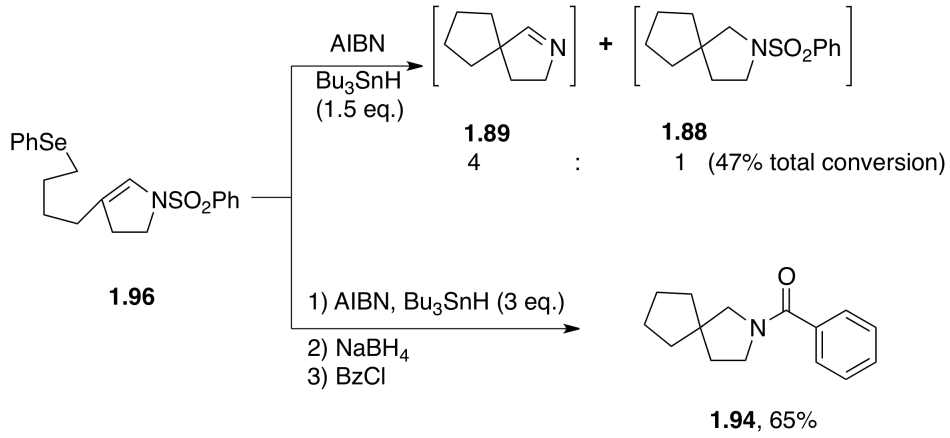



**1.96** **1.89**, 60% NMR yield

**Scheme 1.32** Cyclization of **1.96** under the Fixed Concentration Conditions

Similar results were obtained using the syringe pump conditions (**Scheme 1.33**). The use of a double-syringe pump ensured that this experiment was conducted in the same fashion as the cyclization of bromide substrate **1.85**. Based on $^1$H NMR analysis, a 4:1 mixture of imine **1.89** and spirosulfonamide **1.88** was formed, along with 53% of unconsumed starting material. In another experiment, full conversion of the phenylselenide substrate **1.94** was achieved using 3

equiv of $Bu_3SnH$, and the crude imine product **1.89** was converted to benzamide **1.94** in an overall yield of 65%.




**Scheme 1.33** Cyclization of **1.96** under the Syringe Pump Conditions

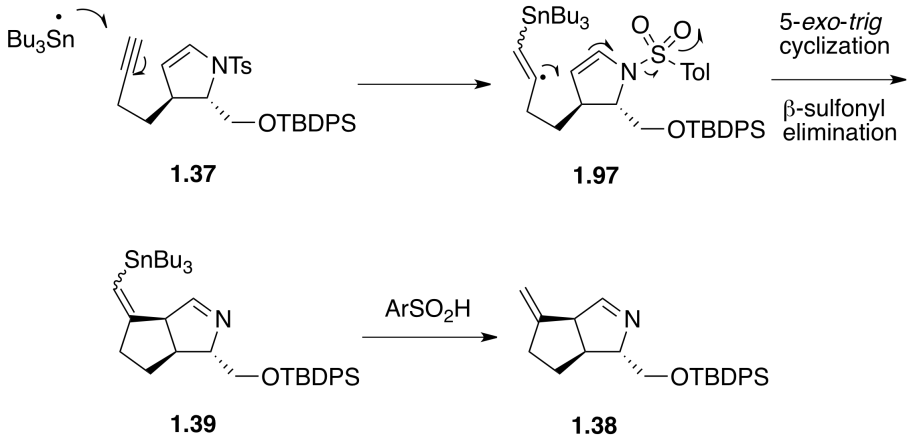
In summary, we studied the cyclization behaviors of bromide **1.85** and phenylselenide **1.94** under both syringe pump conditions and the conditions of fixed tin hydride concentration. Under both conditions, cyclization of bromide **1.85** generated spiroimine **1.89** as the major product, along with an appreciable amount of spirosulfonamide product **1.88**. Cyclization of phenylselenide **1.94** gave predominantly imine product **1.89** under both conditions. Even though the origin of the difference between our results and Somfai's remained unclear, our studies of Somfai's system broadened the current scope of the radical *N*-desulfonylation reaction.

## 2) 4,5-Disubstituted 2,3-Dihydropyrrole Substrate and Mechanistic Evidence on the β-Scission of an α-Sulfonamidoyl Radical

Having demonstrated the utility of radical *N*-desulfonylation to produce spirocyclic imines, we sought to extent this method to the synthesis of fused-bicyclic imines. We were

especially interested in a radical cyclization reaction reported by Cossy, as illustrated in **Section 1.1.3** (**Scheme 1.5)**. Reaction of enamide **1.37** with $Et_3B$ and $Bu_3SnH$ provided imine **1.38** in 82% yield. Two possible mechanisms for the formation of **1.38** were considered by Cossy (**Figure 11**). In the β-elimination mechanism, the addition of tributyltin radical to the alkyne of **1.37** generates vinyl radical **1.97**, which undergoes a 5-*exo*-*trig* cyclization followed by β-sulfonyl elimination to form imine **1.39**. Finally, destannylation of this intermediate provides **1.38**, possibly upon purification of the reaction mixture on silica gel. In the sulfonyl abstraction mechanism, tributyltin radical attacks the tosyl group of **1.37** to form intermediate α-aminyl radical **1.98**. Then a 5-*exo*-*dig* cyclization takes place and produces vinyl radical **1.99**, which is reduced by tin hydride to give **1.38**.

**β-Elimination mechanism:**




**Sulfonyl abstraction mechanism:**

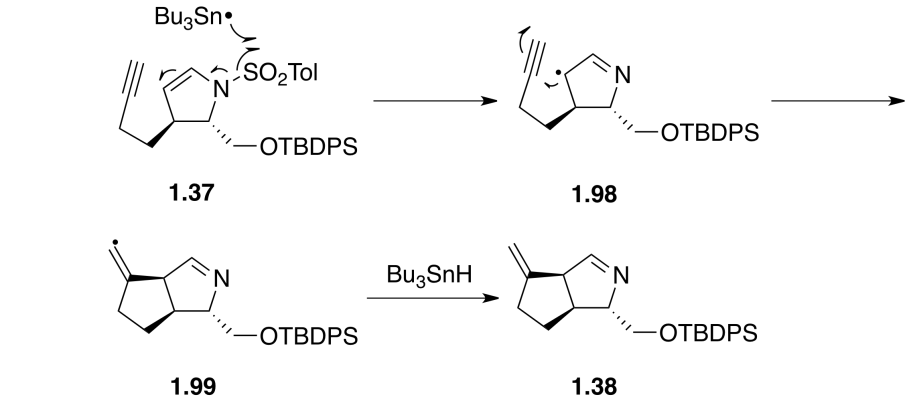
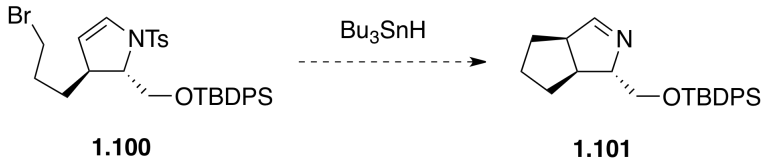



**Figure 11** Two Possible Mechanisms for the Formation of Imine **1.38**

Cossy suggested that the sulfonyl abstraction mechanism was more likely because the vinylstannane intermediate **1.39** proposed in the first mechanism was not detected in the crude product before column chromatography purification. In other words, even though an imine product was formed, the authors concluded that β-elimination of sulfonyl radical was not involved. Based on our previous discoveries of *N*-desulfonylation reactions, however, the "reversed" mechanism seemed unlikely.

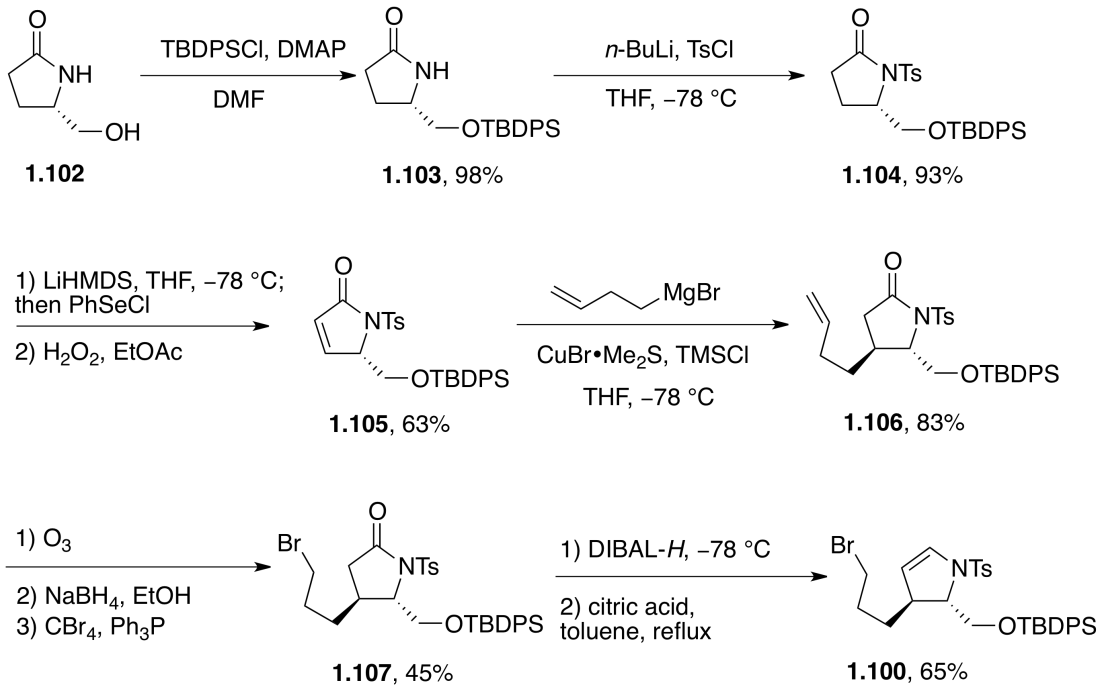
To understand the mechanism and to expand the scope of the reaction, we designed dihydropyrrole substrate **1.100** with a bromide in place of the alkyne on the 4-alkyl chain (**Scheme 1.34**). The expected product of cyclization in the β-elimination pathway is imine **1.101**. However, the cyclization will not occur if the reaction proceeds through the sulfonyl abstraction mechanism, because the bromide is not a radical acceptor.




**1.100** **1.101**

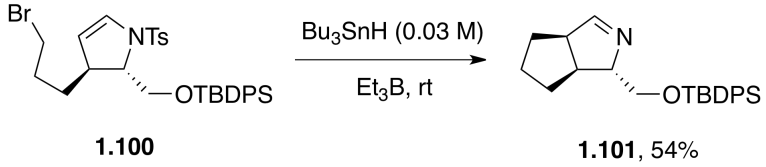
**Scheme 1.34** Bromide Substrate **1.100** and Expected Cyclization Product **1.101**

**Scheme 1.35** illustrates a ten-step synthesis of substrate **1.100**. Commercial hydrolactam **1.102** was protected as TBDPS ether **1.103** in 98% yield. Deprotonation of **1.103** with *n*-BuLi, followed by addition of tosyl chloride, provided tosylimide **1.104** in 93% yield. Phenyselenylation of compound **1.104**, followed by oxidation of the resulting phenylselenide with $H_2O_2$, afforded enamide **1.105** in 63% yield over two steps. Conjugate addition of homoallyl cuprate to this product in the presence of TMSCl gave **1.106** in 83% yield. Sequential ozonolysis, $NaBH_4$ reduction, and Appel reaction provided bromide **1.107** with an overall yield of 45% over three steps. Finally, reduction/dehydration reactions of **1.107** provided target dihydropyrrole **1.100** in 65% yield over two steps.



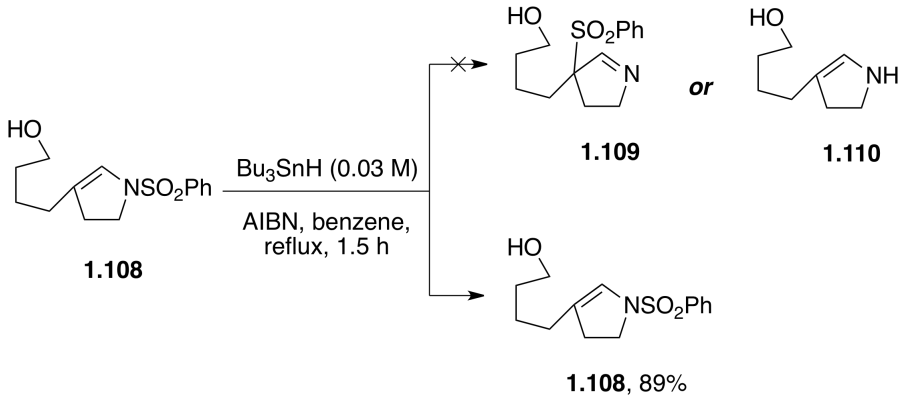

**Scheme 1.35** Synthesis of Bromide Substrate **1.100**

Next, we conducted the key cyclization experiment under conditions that were similar to Cossy's (**Scheme 1.36**). Treatment of bromide **1.100** with $Et_3B$ and $Bu_3SnH$ (0.03 M) at room temperature afforded target imine product **1.101** in 54% yield. Neither the cyzliation/hydrogen abstraction product nor the premature reduction product was detected by TLC or $^1H$ NMR. This example further expanded the scope of the radical cyclization/β-sulfonyl elimination reaction. In addition, Cossy's direct *N*-*S* scission hypothesis was invalidated since alkylbromides did not behave as radical acceptors (**Figure 11**).




**Scheme 1.36** Formation of Imine **1.101**

To further support our conclusions, we designed a simple control experiment in which primary alcohol **1.108**, an intermediate towards Somfai's substrate **1.85**, was subjected to the standard AIBN/$Bu_3SnH$ conditions (**Scheme 1.37**). We found neither the isomerization product **1.109** nor the directly desulfonylated product **1.110** in the crude reaction mixture. Instead, alcohol **1.108** was recovered in 89% yield after flash chromatography. These results suggest that direct *N*-*S* bond cleavage of **1.108** and structurally similar dihydropyrroles should be a negligible process under typical conditions for radical cyclization.




**Scheme 1.37** Attempted Isomerization of Enesulfonamide **1.108**

### 3) Indole Substrates

Radical cyclizations of indoles that occur on the 3-position are interesting processes in that aromaticity of substrates is disrupted with the formation of carbon-centered α-amino radicals. In addition, such processes generate 3,3'-spiroindole products that are often regarded as "privileged" structures in medicinal chemistry. Despite of their potential value, only a handful of examples of these reactions have been reported. In these examples, the initially formed α-amino radicals after radical cyclization abstracted hydrogen from $Bu_3SnH$ to form 2,3-dihydroindoles.[51]Shown in **Figure 12** are two typical examples. Fang reported that treatment of

3-bromobutyl-substituted indole **1.111** with $Bu_3SnH$ afforded spiro-dihydroindole **1.112** in 81% yield.[51a] As one of the key steps in Nicolaou's synthesis of (–)-aspidophytine,[51b] radical cyclization of xanthate **1.113** under standard AIBN/$Bu_3SnH$ conditions produced pentacycle **1.114** in 58% yield.

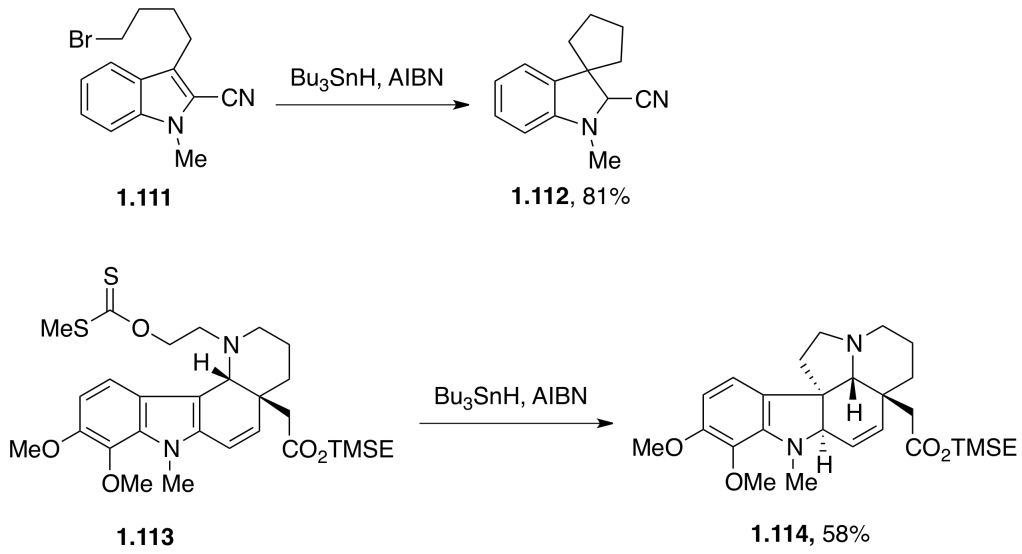



**Figure 12** Two Examples of 3,3'-Spiroindole Synthesis by Radical Cyclization

In 2005, Stevens reported an interesting example of spiroindole synthesis via halogen atom transfer radical cyclization (**Figure 13**).[52] In the presence of TMEDA and CuCl, radical cyclization of trichloroacetamide **1.115** produced 2-chlorinated spiroindole **1.118** in 64% yield. The authors noted that prolonged reaction time led to the formation of imine product **1.119**. Nonetheless, the experimental details and mechanism for the formation of **1.119** were not discussed. Given our discovery of radical *N*-sulfonyl cleavage in 2,3-dihydropyrrole systems, we expect that the initially generated α-amino radical **1.117**, in the absence of copper, will expel a sulfonyl radical to give imine product **1.119**.

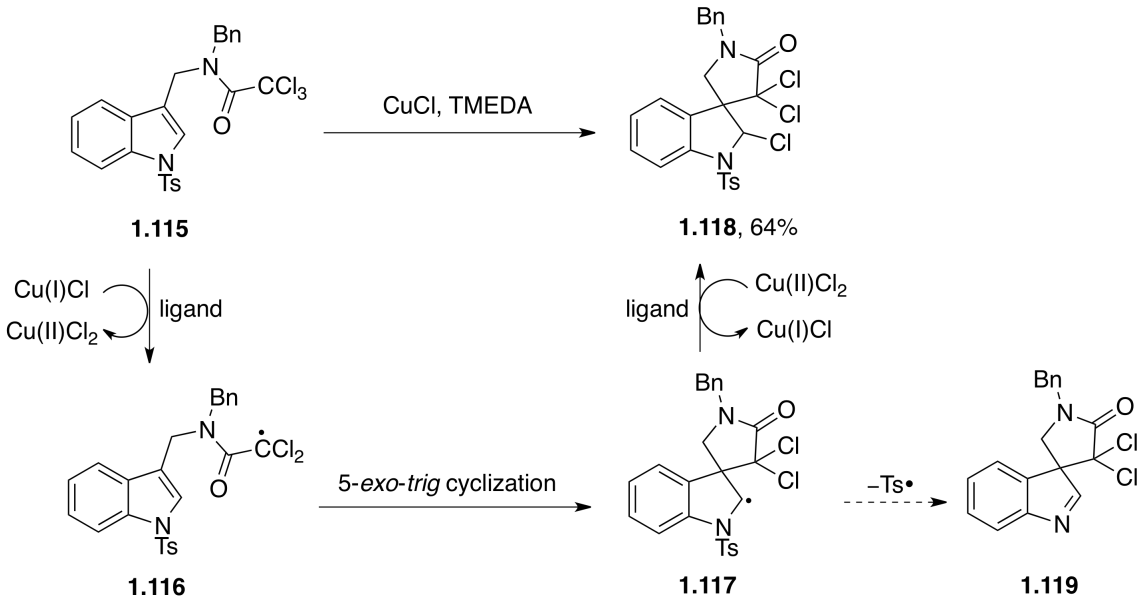
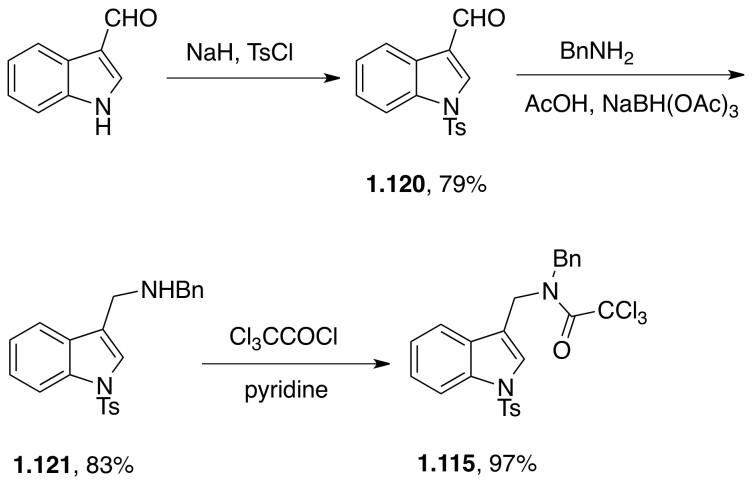


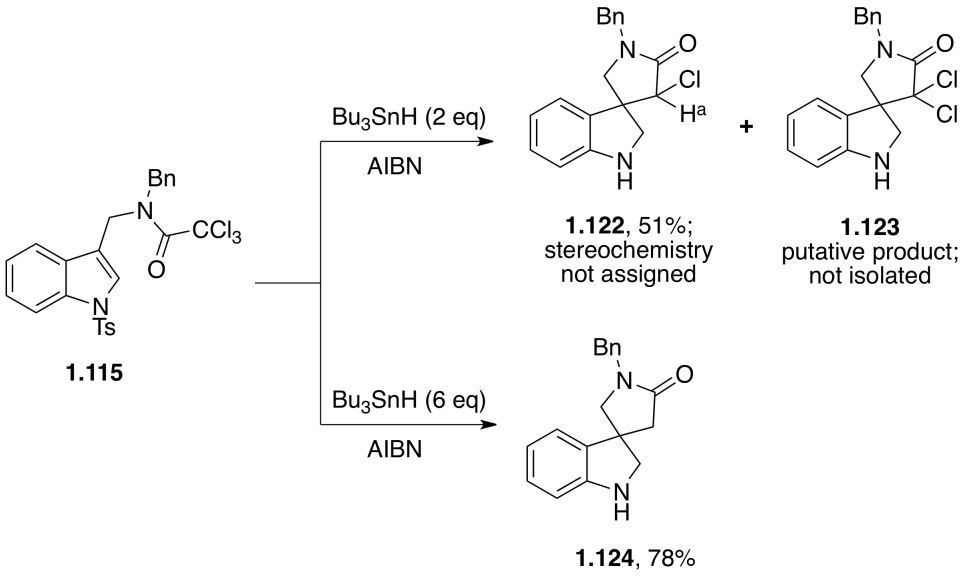

**Figure 13** Cyclization of **1.115** and Hypothesized Formation of Imine **1.119** from Radical **1.117**

To test the hypothesis, we prepared substrate **1.115** in a three-step sequence, according to Stevens' procedures (**Scheme 1.38**). Deprotonation of commercially available indole-3-carbaldehyde with NaH, followed by addition of TsCl, afforded sulfonylation product **1.120** in 87% yield. Reductive amination of **1.120** with benzylamine, $NaBH(OAc)_3$, and acetic acid provided secondary amine product **1.121** in 83% yield. Finally, this compound was acylated with trichloroacetyl chloride to give target substrate **1.115** in 97% yield.




**Scheme 1.38** Synthesis of Trichloroacetamide **1.115**

In initial experiments, a mixed solution of AIBN and $Bu_3SnH$ (2~6 equiv) in benzene was added slowly via syringe pump to a solution of **1.115** in refluxing benzene. However, only complex mixtures were generated. We then conducted the reaction under fixed concentration conditions. AIBN and 2 equiv of $Bu_3SnH$ were mixed with a 0.01 M solution of **1.115** in refluxing benzene (**Scheme 1.39**). After 0.5 h, a mixture of two new products was observed by TLC. Whereas it was difficult to get a clean sample of the minor, less polar product by column chromatography, the major, more polar product **1.122** was carefully isolated as a single diasteroeomer in 51% yield. The 2D structure of **1.122** was solved based on several key features of the $^1H$ NMR spectrum, including: 1) a sharp singlet at 4.45 ppm denoting $H^a$, and 2) the absence of both sulfonyl and imine signals.

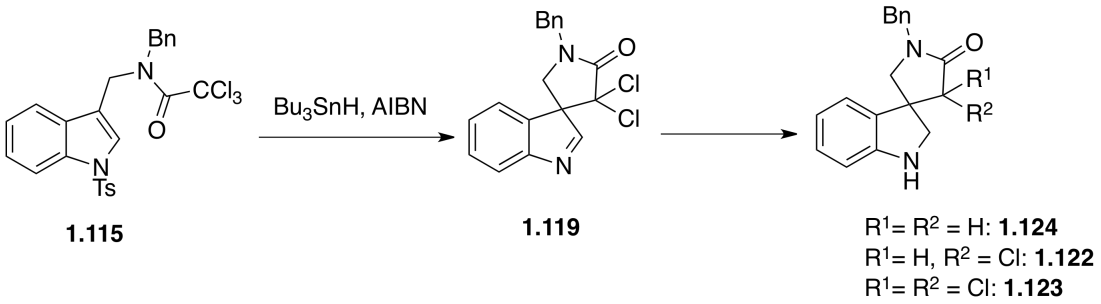



**Scheme 1.39** Radical Cyclization of **1.115** to Provide Desulfonylated Spiroindoles

Next, we decided to synthesize the fully reduced product **1.124** that could be easily characterized. Six equivalents of $Bu_3SnH$ was used to achieve full conversion of the starting material (**Scheme 1.39**). After column chromatography, dihydro-spiroindole **1.124** was obtained as a single major product in 78% yield. Several key signals in the $^1H$ NMR spectrum of **1.124** are characteristic, including: 1) four sets of methylene protons at 4.64~2.62 ppm, 2) a free aliphatic N-H signal at 3.74 ppm, and 3) the absence of both sulfonyl and imine protons. The structural assignment of **1.124** was also confirmed by $^{13}C$ NMR, IR, and HRMS.

These results offered solid evidence for our hypothesis regarding the sulfonyl radical elimination of α-amino radical species **1.117** (**Figure 13**). We concluded that the initially formed dichloroimine product **1.119** could be further reduced by $Bu_3SnH$ to provide dihydroindoles **1.122** or **1.124**, or possibly dichloro product **1.123** (not isolated), depending on the stoichiometry of $Bu_3SnH$ that was used (**Scheme 1.39**). Whereas reduction of dichloromethylene group is believed to occur via a radical mechanism, the mechanism for $Bu_3SnH$-mediated imine reduction

is unclear. Compared to imine **1.81** that is stable towards the $Bu_3SnH$ conditions (**Section 1.2.1**), the electron-withdrawing groups of **1.119** are closer to the imine group.




**1.115** **1.119**

$R^1 = R^2 = H$: **1.124**
$R^1 = H$, $R^2 = Cl$: **1.122**
$R^1 = R^2 = Cl$: **1.123**

**Scheme 1.40** *In Situ* Reduction of Dichloroimine **1.119**

Encouraged by our studies of Stevens' system, we decided to extend the *N*-desulfonylation chemistry to indoles bearing an additional aryl ring. Very reactive radical species, such as alkyl and trichloromethyl radicals, have shown effective in breaking the indole aromaticity. It is also worth mentioning that our preliminary studies have shown that α-amidoyl radicals lack of such reactivities. Therefore, we chose precursors **115** and **116** bearing aryl iodide moieties that would provide reactive aryl radicals **117** and **118** (**Scheme 2.27**). Spiro-bisindoles **119** and **120** were the expected products of the radical cyclization reactions.

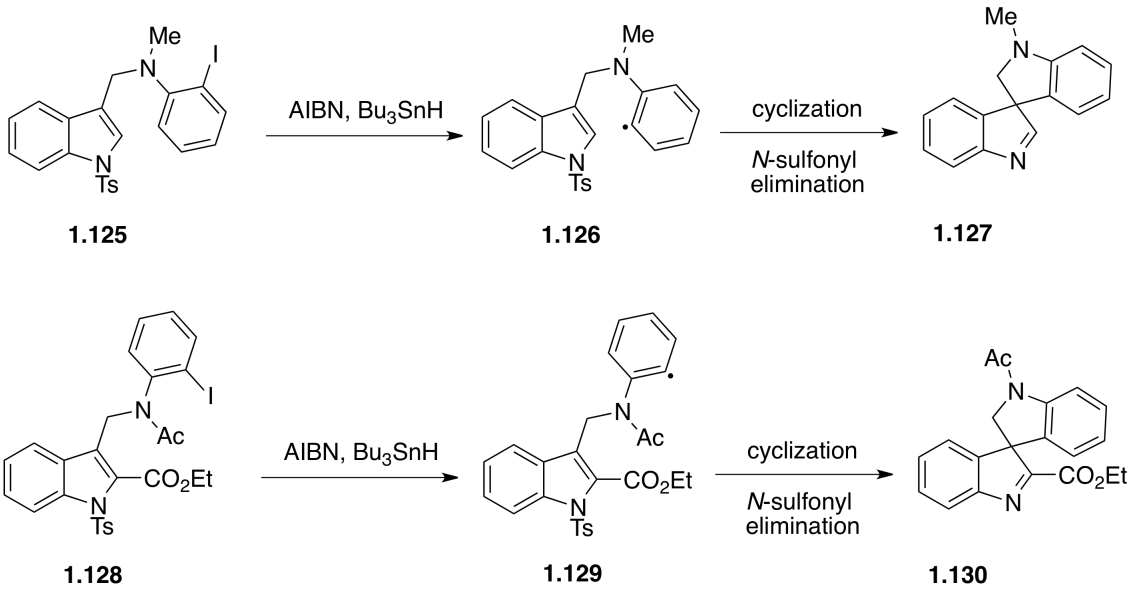
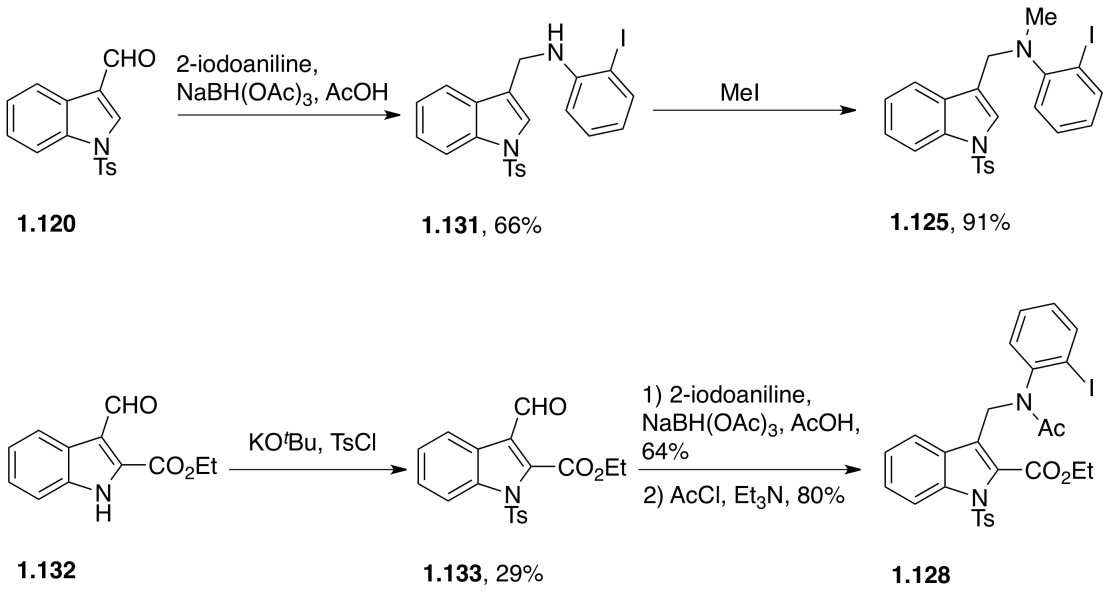


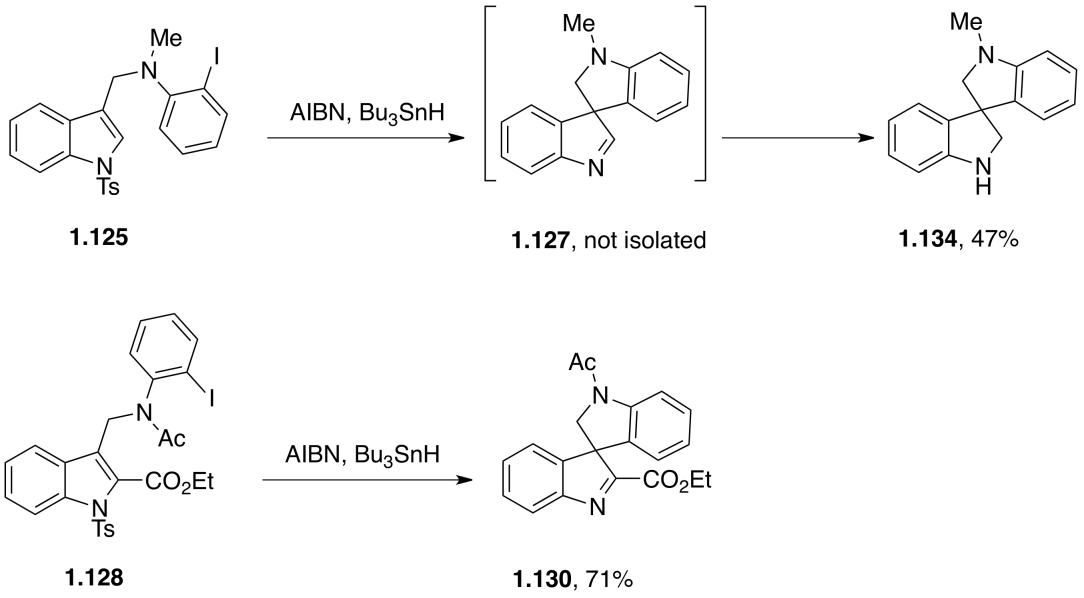

**Figure 14** Proposed *N*-Desulfonylation Reactions Triggered by Cyclization of Aryl Radicals

Indoles **1.125** and **1.128** were conveniently synthesized via reductive amination (**Scheme 1.41**). Reductive amination of 1-tosyl-1*H*-indole-3-carbaldehyde **1.120** in the presence of 2-iodoaniline, acetic acid, and $NaBH(OAc)_3$ gave secondary aniline **1.131** in 66% yield, which was subsequently methylated to provide target precursor **1.125** in 91% yield. Commercially available ethyl 3-formyl-1*H*-indole-2-carboxylate **1.132** was tosylated to form indole **1.133** in 29% yield. Reductive amination of this product in the manner of **1.131** provided corresponding secondary aniline in 64% yield, which was then acylated with acetyl chloride to furnish **1.128** in 80% yield.




**Scheme 1.41** Synthesis of Aryl Iodides **1.125** and **1.128**

As we expected, cyclization of indole precursor **1.125** under the fixed tin-hydride-concentration condition provided desulfonylated dihydroindole product **1.134** in 47% yield after column chromatography (**Scheme 1.42**). Two and half equiv of tin hydride was required to achieve full conversion of the starting matarial, and the formation of imine **1.127** was not observed under this condition. We believe that the initially formed imine **1.127** was quickly reduced by $Bu_3SnH$ in a similar manner of **1.119** (**Scheme 1.40**). In another experiment, radical cylcization of precursor **1.128** produced desulfonylated, yet not fully reduced product **1.130** in 71% yield.

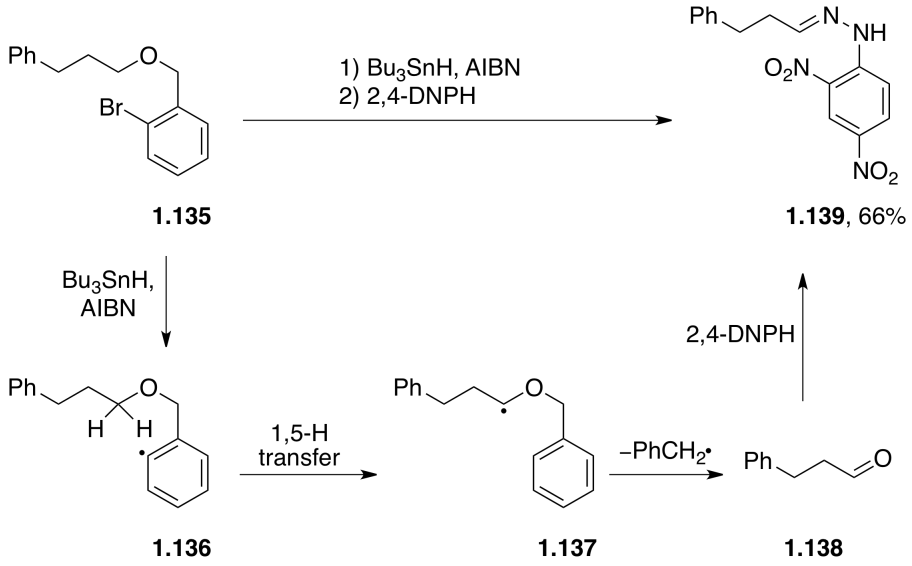



**Scheme 1.42** *N*-Desulfonylation of **1.125** and **1.128**

## 4) 2-Iodobenzenesulfonyl as a Protecting/Radical Translocating Group for 1,2,3,4-Tetrahydroquinoline

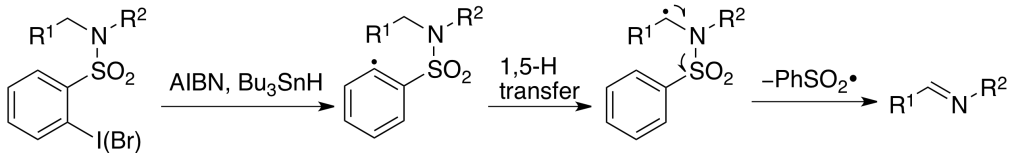
Protecting groups are frequently used in organic synthesis to allow selective elaboration of one or several particular functional groups within complex settings. In most cases, protecting groups do not participate in desired bond-forming processes and need to be removed separately. In this regard, protecting/radical translocating (PRT) groups are attractive because they not only serve as traditional protecting groups, but selectively activate a remote functionality for a bond-forming process.[53] For example, Curran demonstrated that treatment of *o*-bromobenzyl ether **1.135** with $Bu_3SnH$ provided 3-phenylpropanal **1.138**, which was trapped with 2,4-dinitrophenyl hydrazine (2,4-DNPH) to provide hydrazone **1.139** in 66% yield over two steps (**Scheme 1.43**).[53b] It was proposed that initially generated aryl radical **1.136** underwent 1,5-hydrogen transfer to produce tertiary alkyl radical **1.137** that afforded **1.138** via β-elimination. In this case,

the *o*-bromobenzyl group serves as a self-oxidizing protecting group that can be removed under reductive conditions.




**Scheme 1.43** *o*-Bromobenzyl as a Self-Oxidizing PRT Group for Alcohols

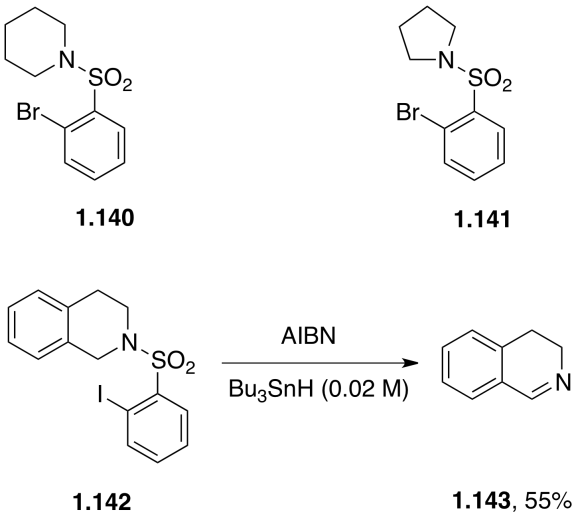
We envisioned an interesting merger of the radical *N*-desulfonylation chemistry with the concept of self-oxidizing PRT group (**Scheme 1.44**). As a bonus, the protecting group is simultaneously removed after the bond-forming process. 2-Iodo- and 2-bromo-benzenesulfonyl groups were selected to integrate with standard sulfonyl protecting groups for amines.




**Scheme 1.44** 2-Iodo(bromo)benzenesulfonyl a Self-Oxidizing PRT Group for Amines

Several sulfonamide precursors were synthesized and subjected to $Bu_3SnH$ conditions (**Scheme 1.45**). Only directly reduced products were detected in the reactions of simple pyrroline and piperidine derivatives (**1.140** and **1.141**). Finally, a mixture of AIBN, $Bu_3SnH$ (0.02 M), and

1,2,3,4-tetrahydroquinoline precursor **1.142** was refluxed for 30 min. To our delight, 3,4-dihydroquinoline **1.143** was isolated in 55% yield after column chromatography.




**Scheme 1.45** Substrates for Testing 2-Iodo(bromo)benzenesulfonyl as a PRT Group

The above results suggest that a radical stabilizing group next to the α-sulfonamidoyl group is required for successful 1,5-hydrogen transfer/desulfonylation process. Further investigation of this reaction is currently undergoing in the Curran lab.

## 1.3 CONCLUSIONS

We discovered a tandem radical cyclization/*N*-sulfonyl elimination reaction in the course of synthetic studies of meloscine. Several classes of spiro- and fused-imine products were accessed via this reaction, as demonstrated by eight representative examples. We carefully studied two related cyclization reactions reported by Somfai and Cossy. We partially reproduced Somfai's results and more importantly, proved the formation of an unreported spiroimine as the major product under fixed tin hydride concentration conditions. For Cossy's reaction, we were able to

exclude the direct radical cleavage of *N*-*S* bond as a mechanism for imine formation. Instead, the imine forms by sulfonyl radical elimination. Finally, the radical desulfonylation reaction was extended to tetrahydroisoquinoline system. We illustrated that 2-iodobenzenesulfonyl acts as a protecting/radical translocating (PRT) group for tetrahydroquinoline. This reaction features a neutral condition for deprotection of *N*-sulfonyl group, with concomitant activation of a C-H bond of tetrahydroquinoline.

## 1.4 EXPERIMENTALS

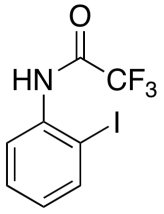
**General Information:** Chemicals and solvents were purchased from commercial suppliers and used as received, except as follows. Dichloromethane, THF, ether, and toluene were dried by passing through an activated alumina column. All reactions were carried out under an inert atmosphere of dry argon, unless otherwise indicated.

All reactions were followed by TLC or $^{1}$H NMR spectroscopy. TLC visualizations were performed by illumination with a UV lamp (254 nm) or staining with a phosphomolybdic acid solution in ethanol and heating. All flash chromatography was performed with 230-400 mesh silica gel purchased from Sorbent Technoloies as the stationary phase.

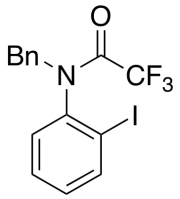
$^{1}$H NMR spectra were recorded on a Bruker Avance instruments at 300, 400 and 500 MHz with deuterated chloroform as solvent, unless otherwise indicated. $^{13}$C NMR spectra were measured on Bruker Avance instruments at 75, 100, 125, 150, 175 MHz. The chemical shifts in spectra were measured in parts per million (ppm) on the delta (δ) scale relative to the resonance of the solvent peak ($CDCl_3$: $^{1}$H = 7.27 ppm, $^{13}$C = 77.0 ppm). Unless otherwise noted, NMR spectra were recorded at 293 K.

IR spectra were recorded on a Nicolet Avatar 360 FTIR spectrometer and ran as thin films on sodium chloride plates. Mass spectra were obtained on Fisons Autospec high-resolution magnetic sector mass spectrometer or a Micromass Q-Tof Ultima mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter using a 1 dm cell length. All quoted optical rotation values are corrected for 100% ee samples, and have the units (deg $cm^2$ $g^{-1}$).

Ethyl 3-formyl-1*H*-indole-2-carboxylate **1.132** and 2-Iodobenzenesulfonyl chloride were purchased from Ryan Scientific, Inc. Compounds **1.140** and **1.141** were prepared by known procedures, and the spectral data matched the reported ones.[54]

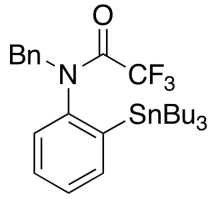



**2,2,2-Trifluoro-*N*-(2-iodophenyl)acetamide (1.72)**: $Et_3N$ (7.1 mL, 51.3 mmol) was added to a solution of 2-iodoaniline (10.2 g, 46.7 mmol) in THF (60 mL) at −15 °C, followed by dropwise addition of trifluoroacetic anhydride (7.1 mL, 51.3 mmol). The reaction mixture was stirred at −15 °C for 30 min and then at room temperature for 2 h. The reaction was quenched with water and the aqueous layer was extracted with $Et_2O$. The combined organic layers were washed with brine, dried over $NaSO_4$, and concentrated *in vacuo*. The residue was passed through a pad of silica gel (1:10 EtOAc/hexanes) to provide the title compound (14.0 g, 95%) as a white solid: $^1$H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.23 (dd, $J$ = 8.1 Hz, 1.2 Hz, 1H), 7.85 (dd, $J$ = 8.1, $J$ = 1.2 Hz, 1H), 7.42 (dt, $J$ = 7.8 Hz, 1.2 Hz, 1H), 6.98 (dt, $J$ = 7.8 Hz, 1.2 Hz, 1H). Above spectral data are consistent with reported ones.[55]

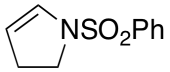



***N*-Benzyl-2,2,2-trifluoro-*N*-(2-iodophenyl)acetamide (1.73)**: A solution of trifluoroacetamide **1.72** (3.0 g, 9.52 mmol) in DMF (10 mL) was added dropwise to a suspension of NaH (11.43 mmol) in DMF (25 mL) at 0 °C. After 30 min, a solution of BnBr (1.36 mL, 11.43 mmol) in DMF (10 mL) was added dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 h. The reaction was quenched with a saturated aqueous $NH_4Cl$ solution and the aqueous layer was extracted with $Et_2O$. The combined organic layers were

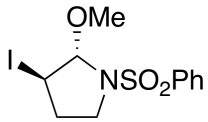
washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 1:50 EtOAc/hexanes) to provide the title compound (3.5 g, 91%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.33-7.17 (m, 6H), 7.09 (dt, *J* = 7.8 Hz, 1.5 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 5.74 (d, *J* = 14.1 Hz, 1H), 4.04 (d, *J* = 14.1 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 156.9 (q, $J_{CF}$ = 35.2 Hz), 140.1, 134.8, 131.4, 131.3, 130.7, 129.7, 128.7, 128.6, 128.3, 116.1 (q, $J_{CF}$ = 287.2 Hz), 99.4, 53.8; HRMS (TOF ES) calcd for $C_{15}H_{11}NOF_3NaI$ $[M+Na]^+$: 427.9735, found: 427.9705.




***N*-Benzyl-2,2,2-trifluoro-*N*-(2-(tributylstannyl)phenyl)acetamide (1.74)**: $Pd(PPh_3)_4$ (143 mg, 0.12 mmol) and hexabutylditin (3.7 mL, 7.4 mmol) were added to a solution of aryliodide **1.73** (1.0 g, 2.5 mmol) in toluene (20 mL), and the reaction mixture was refluxed for 24 h. The solvent was evaporated and the crude product was purified by flash chromatography (silica gel, 1:50 EtOAc/hexanes) to provide the title compound (1.2 g, 84%) as a light green oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.33-7.27 (m, 4H), 7.15-7.10 (m, 3H), 6.51 (d, *J* = 7.5 Hz, 1H), 5.75 (d, *J* = 13.5 Hz, 1H), 3.83 (d, *J* = 13.5 Hz, 1H), 1.59-1.47 (m, 6H), 1.34 (m, 6H), 1.10 (m, 6H), 0.90 (t, *J* = 7.2 Hz, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) 156.9 (q, $J_{CF}$ = 35.0 Hz), 144.4, 142.5, 138.1, 135.1, 130.1, 129.7, 128.5, 128.3, 128.23, 128.21, 116.5 (q, $J_{CF}$ = 287.0 Hz), 55.4, 29.0 (t, $J_{CSn}$ = 10.0 Hz), 27.3 (t, $J_{CSn}$ = 31.0 Hz), 13.6, 10.3 (t, $J_{CSn}$ = 170.0 Hz); FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 2957, 2926, 2854, 1693, 1465, 1437, 1205, 1176, 1154; HRMS (EI) calcd for $C_{23}H_{29}NOF_3Sn$ $[M-C_4H_9]^+$: 508.1219, found: 508.1229.

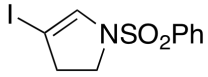



**1-(Phenylsulfonyl)-2,3-dihydro-1*H*-pyrrole (1.76)**: A DIBAL-*H* solution (1 M in hexane, 39 mL) was added dropwise to a solution of sulfonamide **1.75** (5.8 g, 26 mmol) in THF (250 mL) −78 °C. After 1 h, the reaction mixture was diluted with $Et_2O$ (200 mL) and a saturated aqueous potassium-sodium tartrate solution (400 mL) was added. The mixture was stirred for 12 h. The aqueous layer was extracted with $Et_2O$, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude hemiaminal product was dissolved in toluene (150 mL). Citric acid (5.4 g, 26 mmol) was added and the reaction mixture was stirred at 80 °C for 4 h. The reaction mixture was cooled to room temperature and a saturated aqueous $NaHCO_3$ solution was carefully added. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 1:4 EtOAc/hexanes) to provide the title compound (4.3 g, 80%) as a white solid: mp 114-115°C; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.8 Hz, 2H), 7.61-7.50 (m, 3H), 6.38 (td, *J* = 4.2 Hz, 2.1 Hz, 1H), 5.12 (td, *J* = 4.2 Hz, 2.7 Hz, 1H), 3.50 (t, *J* = 9.0 Hz, 2H), 2.48 (tt, *J* = 9.0 Hz, 2.4 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 135.8, 133.01, 130.52, 129.08, 127.67, 111.56, 47.23, 29.06; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 3094, 2989, 2940, 2878, 1613, 1468, 1446, 1169, 1114, 1090, 1065; HRMS (EI) calcd for $C_{10}H_{11}NO_2S$ $[M]^+$: 209.0510, found: 209.0510.



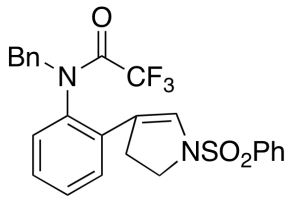

***trans*-3-Iodo-2-methoxy-1-(phenylsulfonyl)pyrrolidine (1.77)**: Sodium methoxide (5.8 g, 107 mmol) was added to a solution of enamide **1.76** (11.2 g, 53.5 mmol) in MeOH (200 mL),

followed by dropwise addition of a solution of ICl (1 M in $CH_2Cl_2$, 54 mL). After 30 min, the reaction was quenched with a saturated aqueous $NaS_2O_3$ solution. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was washed with mixed hexane/$Et_2O$ (4:1) to provide the title compound (18.7 g, 95%) as a yellow solid: mp 80-81 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 6.9 Hz, 2H), 7.61-7.50 (m, 3H), 5.22 (s, 1H), 4.17 (d, *J* = 4.8 Hz, 1H), 3.52 (dt, *J* = 8.7 Hz, 1.2 Hz, 1H), 3.48 (s, 3H), 3.44-3.36 (m, 1H) 2.58 (dddd, *J* = 13.8 Hz, 10.8 Hz, 8.1 Hz, 5.7 Hz, 1H), 2.07 (dd, *J* = 13.8 Hz, 5.7 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 137.7, 133.0, 129.0, 128.1, 98.5, 56.1, 46.3, 34.3, 25.3; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 2937, 1446, 1349, 1288, 1207, 1164, 1098, 1014; HRMS (TOF ES) calcd for $C_{11}H_{14}NO_3NaSI$ $[M+Na]^+$: 389.9637, found: 389.9627.



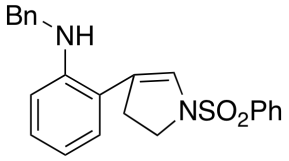

**4-Iodo-1-(phenylsulfonyl)-2,3-dihydro-1*H*-pyrrole (1.67)**: Citric acid (2.60 g, 12.4 mmol) was added to a solution of **1.77** (7.08 g, 20.22 mmol) in toluene (240 mL) and the reaction mixture was refluxed for 6 h. The reaction mixture was cooled to room temperature and a saturated aqueous $NaHCO_3$ solution was carefully added. The aqueous layer was extracted with $Et_2O$, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 1:5 EtOAc/hexanes) to provide the title compound (3.88 g, 57%) as a yellow solid: mp 106-107 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 7.8 Hz, 1.8 Hz, 2H), 7.63-7.53 (m, 3H), 6.57 (t, *J* = 2.1 Hz, 1H), 3.55 (t, *J* = 9.0 Hz, 2H), 2.70 (dt, *J* = 9.0 Hz, 2.1 Hz, 2H); $^{13}$C NMR (300 MHz, $CDCl_3$) δ 135.74, 135.47, 133.28, 129.31, 127.65, 70.52, 48.21, 39.61; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$)

3105, 3062, 2857, 1607, 1474, 1445, 1351, 1166, 1099; HRMS (TOF ES) calcd for $C_{10}H_{10}NO_2NaSI$ $[M+Na]^+$: 357.9375, found: 357.9355.

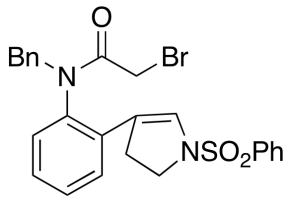



***N*-Benzyl-2,2,2-trifluoro-*N*-(2-(1-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)phenyl)acetamide (1.78)**: A Schlenck tube (100 mL) was charged with LiCl (1.14 g, 26.87 mmol) and flame-dried under vacuum. Upon cooling, CuCl (2.22 g, 22.34 mmol) and $Pd(PPh_3)_4$ (0.518 g, 0.448 mmol) were added and the mixture was degassed under vacuum with an Ar purge. Anhydrous DMSO (15 mL) was introduced, followed by a solution of arylstannane **1.74** (3.05 g, 5.37 mmol) in anhydrous DMSO (5 mL), and finally a vinyl iodide **1.67** (1.5 g, 4.48 mmol). The resulting mixture was degassed three times through freeze-pump-thaw processes, and stirred at room temperature for 30 min and then heated to 60 °C for 1.5 h. The reaction mixture was cooled, diluted with $Et_2O$, and washed with a 5% aqueous $NH_4OH$ solution (30 mL) and brine (150 mL). The aqueous layer was extracted with $Et_2O$, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 1:3 EtOAc/hexanes) to provide the title compound (1.90 g, 87%) as a yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, $J$ = 7.8 Hz, 1.5 Hz, 2H), 7.59-7.54 (m, 3H), 7.29 (t, $J$ = 6.3 Hz, 3H), 7.24 (dt, $J$ = 6.3 Hz, 1.5 Hz, 2H), 7.10 (dd, $J$ = 7.8 Hz, 1.5 Hz, 2H), 7.46 (dt, $J$ = 7.8 Hz, 1.5 Hz, 1H), 6.68 (t, $J$ = 1.5 Hz, 1H), 6.57 (d, $J$ = 7.8 Hz, 1H), 5.53 (d, $J$ = 13.5 Hz, 1H), 3.79-3.70 (m, 2H), 3.56 (app q, $J$ = 9.3 Hz, 1H), 2.85 (t, $J$ = 9.3 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 157.10 (q, $J_{CF}$ = 35.2 Hz), 135.49, 134.63, 133.35,

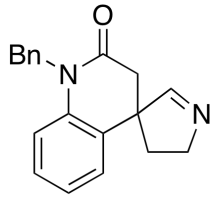
132.01, 131.04, 129.62, 129.53, 129.41, 129.19, 128.63, 128.39, 128.33, 127.61, 127.08, 120.43, 116.20 (q, $J_{CF}$ = 287.2 Hz) 53.41, 47.18, 32.03; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 3066, 2939, 1692, 1613, 1493, 1447, 1358, 1207, 1168, 1093, 1047; HRMS (TOF ES) calcd for $C_{25}H_{21}N_2O_3F_3NaS$ $[M+Na]^+$: 509.1123, found: 509.1147.



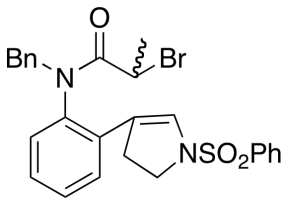

***N*-Benzyl-2-(1-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)aniline (1.79)**: $NaBH_4$ (16 mg, 0.432 mmol) was added in two portions to a solution of trifluoroacetamide **1.78** (30 mg, 0.062 mmol) in EtOH (1 mL). The reaction mixture was stirred at room temperature for 3 h. After the solvent was evaporated, the residue was purified by flash chromatography (silica gel, 1:3 EtOAc/hexanes) to provide the title compound (23 mg, 96%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.61-7.58 (m, 2H), 7.53-7.29 (m, 8H), 7.13 (dt, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.24 (dt, *J* = 6.3 Hz, 1.5 Hz, 2H), 7.10 (dd, *J* = 7.8 Hz, 1.5 Hz, 2H), 7.46 (dt, *J* = 7.5 Hz, 1.5 Hz, 1H), 6.96 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 6.83 (t, *J* = 1.8 Hz, 1H), 6.72 (dt, *J* = 7.5 Hz, 1.2 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 4.30 (s, 2H), 4.07 (brs, 1H), 3.58 (t, J = 9 Hz, 1H), 2.84 (dt, *J* = 9 Hz, 1.5, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 145.34, 139.03, 135.09, 132.98, 129.07, 128.90, 128.39, 127.73, 127.70, 127.53, 127.36, 127.07, 122.67, 119.91, 117.63, 111.16, 46.86, 46.80, 32.85; IR (thin film, $CH_2Cl_2$, $cm^{-1}$) 3340, 3031, 2923, 2853, 1596, 1500, 1448, 1349, 1164, 1090, 1043, 749, 704; HRMS (EI) calcd for $C_{23}H_{22}N_2O_2S$ $[M]^+$: 390.1402, found: 390.1408.




***N*-Benzyl-2-bromo-*N*-(2-(1-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)phenyl)acetamide (1.64a)**: Pyridine (10 μL, 0.128 mmol) and bromoacetyl bromide (7 μL, 0.077 mmol) were successively added to a solution of aniline **1.79** (25 mg, 0.064 mmol) in $CH_2Cl_2$ (1 mL). After 10 min, the reaction mixture was quenched with a saturated aqueous $NH_4Cl$ solution, and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 1:2.5 EtOAc/hexanes) to provide the title compound (27 mg, 83%) as a viscous, colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.86-7.83 (m, 2H), 7.61-7.54 (m, 3H), 7.31-7.19 (m, 5H), 7.15-7.11 (m, 2H), 7.06 (td, *J* = 7.8 Hz, 1.5 Hz, 1H), 6.71 (s, 1H), 6.67 (dd, *J* = 7.8 Hz, 0.9 Hz, 1H), 5.55 (d, *J* = 13.8 Hz, 1H), 3.73 (d, *J* = 13.8 Hz, 1H), 3.75-3.68 (m, 1H), 3.52 (app q, *J* = 9.3 Hz, 1H), 3.46 (d, *J* = 16.8 Hz, 1H), 3.42 (d, *J* = 16.8 Hz, 1H), 2.83 (t, *J* = 9 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.3, 137.2, 136.1, 135.5, 133.4, 131.8, 130.6, 129.5, 129.4, 129.3, 129.2, 128.5, 128.4, 127.9, 127.7, 120.0, 52.0, 47.1, 32.0, 27.5; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 3062, 1662, 1356, 1167; HRMS (TOF ES) calcd for $C_{25}H_{23}N_2O_3NaSBr$ $[M+Na]^+$: 533.0510, found: 533.0506.

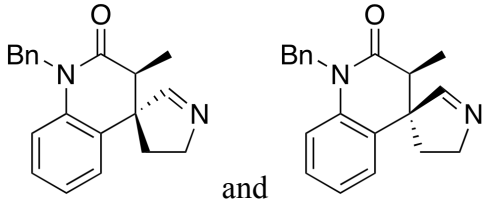



**1'-Benzyl-4,5-dihydro-1'*H*-spiro[pyrrole-3,4'-quinolin]-2'(3'*H*)-one (1.81)**: A mixture of bromoacetamide **1.64a** (12 mg, 0.023 mmol), $Bu_3SnH$ (18 μL, 0.069 mmol), and AIBN (1 mg) in benzene (2.5 mL) was refluxed for 30 min. The solvent was evaporated, and the residue was partitioned between hexane (5 mL) and acetonitrile (5 mL) to remove most of the tin residue. The acetonitrile layer was concentrated *in vacuo*, and the crude product was purified by flash chromatography (silica gel, 2:1 EtOAc/hexanes) to provide the title compound (5 mg, 75%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.34-7.15 (m, 6H), 7.04-6.95 (m, 3H), 5.35 (d, *J* = 16.2 Hz, 1H), 5.10 (d, *J* = 16.2 Hz, 1H), 4.08 (m, 2H), 2.97 (d, *J* = 15.6 Hz, 1H), 2.67 (d, *J* = 15.4 Hz, 1H), 2.22 (dt, *J* = 13.2 Hz, 6.6 Hz, 1H), 1.89 (dt, *J* = 13.2 Hz, 6.6 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) 168.7, 167.8, 138.7, 136.6, 129.2, 128.8, 128.4, 127.3, 126.5, 125.0, 123.6, 116.4, 61.1, 54.8, 46.1, 39.5, 35.9; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 3033, 2960, 2867, 1676, 1625, 1600, 1495, 1455, 1379, 1324, 1284, 1223, 1192; HRMS (EI) calcd for $C_{19}H_{18}N_2O$ $[M]^+$: 290.1419, found: 290.1414.




***N*-Benzyl-2-bromo-*N*-(2-(1-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)phenyl)propanamide (1.80)**: Aniline **1.79** (200 mg, 0.513 mmol) was acylated in the manner of **1.64a** and purified by flash chromatography (silica gel, 1:2.5 EtOAc/hexanes) to provide the

title compound (252 mg, 94%) as a colorless oil, in a 2.3:1 ratio of two inseparable diastereomers. $^1$H NMR (300 MHz, $CDCl_3$) δ major isomer: 6.60 (t, *J* = 1.5 Hz, 1H), 5.56 (d, *J* = 13.8 Hz, 1H), 3.90 (q, *J* = 3.6 Hz, 1H), 2.80 (td, *J* = 9.3 Hz, 1.8 Hz, 1H), 1.49 (*J* = 6.6 Hz, 3H); minor isomer: 6.43 (d, *J* = 7.5 Hz, 1H), 5.45 (d, *J* = 13.8 Hz, 1H), 4.24 (q, *J* = 3.6 Hz, 1H), 2.91 (td, *J* = 9.3 Hz, 1.8 Hz, 1H), 1.69 (d, *J* = 6.6 Hz, 3H); overlapping signals: 7.86-7.83 (m, 2H), 7.59-7.55 (m, 3H), 7.35-7.05 (m, 8H), 6.87-6.84 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 169.8, 169.7, 137.0, 136.9, 136.3, 136.1, 136.0, 135.8, 133.4, 133.2, 132.2, 131.9, 130.5, 130.0, 129.5, 129.4, 129.3, 129.1, 129.0, 128.5, 128.4, 128.3, 128.2, 127.8, 127.7, 127.5, 120.0, 119.9, 51.8, 51.7, 47.4, 47.2, 39.6, 39.2, 32.2, 32.0, 22.5, 21.6; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 3063, 1741, 1664, 1447, 1358, 1167, 1093, 1070; HRMS (EI) calcd for $C_{26}H_{25}N_2O_3SBr$ $[M]^+$: 524.0769, found: 524.0761.

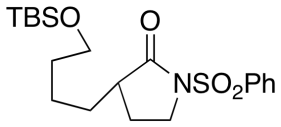



**(3*R**,3'*R**)-1'-Benzyl-3'-methyl-4,5-dihydro-1'*H*-spiro[pyrrole-3,4'-quinolin]-2'(3'*H*)-one (1.84a)** and **(3*R**,3'*S**)-1'-Benzyl-3'-methyl-4,5-dihydro-1'*H*-spiro[pyrrole-3,4'-quinolin]-2'(3'*H*)-one (1.84b)**:

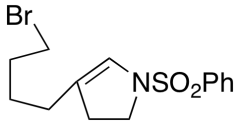
**AIBN initiation at 80 °C**. Compound **1.80** (126 mg, 0.24 mmol) was subjected to the condition described for cyclization of compound **1.81**. Purification of the crude product by flash chromatography (silica gel, 2:1 EtOAc/hexanes) provided two diastereomers **1.84a** and **1.84b**. The less polar diastereomer, **1.84a**, was isolated (36 mg, 50%) as a colorless oil, which was crystallized from vapor diffusion of EtOAc/hexanes: mp 117-118 °C; $^1$H NMR (300 MHz,

$CDCl_3$) δ 7.46 (t, *J* = 2.4 Hz, 1H), 7.33-7.15 (m, 6H), 7.00 (td, *J* = 7.5 Hz, 1.2 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.92 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 5.31 (d, *J* = 16.2 Hz, 1H), 5.10 (d, *J* = 16.2 Hz, 1H), 4.03 (td, *J* = 6.9 Hz, 2.4 Hz, 2H), 3.03 (q, *J* = 6.9 Hz, 1H), 2.16 (app dt, *J* = 13.8 Hz, 6.9 Hz, 1H), 1.70 (app dt, *J* = 13.8 Hz, 6.9 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.8, 168.4, 138.3, 136.9, 130.9, 128.8, 128.3, 127.2, 126.6, 124.6, 123.4, 116.3, 62.2, 59.2, 46.5, 40.7, 30.3, 10.4; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 3032, 2940, 2868, 1677, 1625, 1600, 1494, 1455, 1378, 1325, 1259, 1215; HRMS (EI) cald for $C_{20}H_{20}N_2O$, 304.1576 $[M]^+$, found: 304.1580. The more polar diastereomer, **1.84b**, was isolated (9 mg, 13%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.34-7.15 (m, 6H), 7.05-6.94 (m, 3H), 5.39 (d, *J* = 16.2 Hz, 1H), 5.00 (d, *J* = 16.2 Hz, 1H), 4.08-4.02 (m, 2H), 2.81 (q, *J* = 7.2 Hz, 1H), 2.21 (app dt, *J* = 13.8 Hz, 6.9 Hz, 1H), 1.86 (app dt, *J* = 13.8 Hz, 6.9 Hz, 1H), 1.28 (d, *J* = 7.2 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 171.7, 167.8, 138.0, 136.8, 128.8, 128.3, 128.1, 127.2, 126.4, 125.9, 123.7, 116.0, 60.8, 58.5, 46.0, 44.6, 36.8, 13.2; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 2933, 1674, 1600, 1495, 1455, 1382, 1319, 1276, 1228; HRMS (TOF ES) calcd for $C_{20}H_{20}N_2ONa$ $[M+Na]^+$: 327.1473, found: 327.1451. A sample of **1.84a** for X-ray crystallography analysis was prepared by vapor diffusion crystallization method. A dram glass vial (2 mL) was charged with a solution of imine **1.84a** (3 mg) in EtOAc (0.2 mL), and this vial was placed in a 150 mL beaker containing hexane (5 mL). After 48 h, a small crystal precipitated at the bottom of the vial.

**$Et_3B$ initiation at room temperature**. A mixture of compound **1.80** (60 mg, 0.12 mmol), tributyltin hydride (150 μL, 0.56 mmol), and $Et_3B$ (123 μL, 0.14 mmol) in benzene (11 mL) was stirred for 30 min. The solvent was evaporated and the crude product was purified by flash chromatography to provide a 5:1 mixture of **1.84a** and **1.84b** (15 mg, 43% combined yield).




**3-(4-(*tert*-Butyldimethylsilyloxy)butyl)-1-(phenylsulfonyl)pyrrolidin-2-one (1.92)**: A LiHMDS solution (1 M in THF, 13.9 mL) was added dropwise to a solution of sulfonamide **1.75** (2.6 g, 11.5 mmol) in THF (20 mL) −78 °C, and the mixture was stirred for 30 min. A solution of alkyl iodide **1.91** (9 mL, 34.6 mmol) in HMPA (6 mL) was added in one portion at −78 °C, and the reaction mixture was stirred at this temperature for 12 h. The reaction was quenched with water and the aqueous layer was extract with $Et_2O$. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 1:5 EtOAc/hexanes) to provide the title compound (1.5 g, 31%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 8.05-8.02 (m, 2H), 7.64-7.61 (m, 1H), 7.56-7.51 (m, 3H), 3.95 (ddd, *J* = 9.9 Hz, 8.7 Hz, 2.7 Hz, 1H), 3.69 (appt dt, *J* = 9.6 Hz, 6.9 Hz, 1H), 3.55 (t, *J* = 6.3 Hz, 1H), 2.46-2.36 (m, 1H), 2.28-2.18 (m, 1H), 1.77-1.70 (m, 2H), 1.49-1.41 (m, 2H), 1.37-1.27 (m, 2H), 0.86 (s, 9H), 0.01 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 175.3, 138.1, 134.0, 129.0, 128.0, 63.7, 45.5, 43.2, 32.4, 29.9, 25.9, 25.0, 23.2, 18.3, -5.3; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 2931, 2858, 1737, 1362, 1228, 1254, 1172, 1102; HRMS (TOF ES) calcd for $C_{20}H_{33}NO_4NaSiS$ $[M+Na]^+$: 434.1797, found: 434.1806.




**4-(4-Bromobutyl)-1-(phenylsulfonyl)-2,3-dihydro-1*H*-pyrrole (1.85)**:

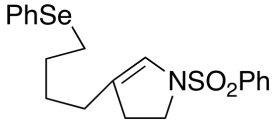
A solution of DIBAL-*H* (1 M in hexane, 25.3 mL) was added dropwise to a solution of sulfonamide **1.92** (1.3 g, 3.16 mmol) in THF (15 mL) at −78 °C. The reaction mixture was

stirred at this temperature for 2 h. It was diluted with $Et_2O$ and quenched with a saturated aqueous potassium-sodium tartrate solution. The mixture was stirred overnight. The aqueous layer was extracted with $Et_2O$ and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude hemiaminal product was dissolved in toluene (25 mL). Citric acid (663 mg, 3.16 mmol) was added and the reaction mixture was stirred at 80 °C for 4 h. The reaction mixture was cooled to room temperature and a saturated aqueous $NaHCO_3$ solution was carefully added. The aqueous layer was extracted with $Et_2O$ and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude ene-sulfonamide **1.93**: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.76 (m, 2H), 7.61-7.49 (m, 3H), 6.08 (s, 1H), 3.57 (t, *J* = 6.0 Hz, 2H), 3.50 (t, *J* = 8.7 Hz, 2H), 2.32 (*J* = 8.7 Hz, 2H), 2.00 (*J* = 6.0 Hz, 2H), 1.42-1.36 (m, 4H), 0.89 (s, 9H), 0.03 (s, 6H).

Crude ene-sulfonamide **1.93** was dissolved in THF (40 mL), and a TBAF solution (1 M in THF, 4 mL) was added at 0 °C. After 2 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution, and the aqueous layer was extracted with $Et_2O$. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was passed through a short pad of silica gel (silica gel, 1:2 EtOAc/hexanes) to afford the crude alcohol intermediate: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.79-7.75 (m, 2H), 7.62-7.49 (m, 3H), 6.08 (t, *J* = 1.5 Hz, 1H), 3.61 (q, *J* = 5.7 Hz, 2H), 3.49 (t, *J* = 9.0 Hz, 2H), 2.32 (t, *J* = 9.0 Hz, 2H), 2.00 (t, *J* = 7.5 Hz, 2H), 1.53-1.39 (m, 4H). The above spectral data were identical to those reported.[37a]

The crude alcohol intermediate was dissolved in $CH_2Cl_2$ (4 mL), followed by addition of $CBr_4$ (156 mg, 0.47 mmol) and $Ph_3P$ (128 mg, 0.49 mmol) at 0 °C. The reaction was quenched with water after 2 h. The aqueous layer was extract with $Et_2O$, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was

purified by flash chromatography (silica gel, 1:5 EtOAc/hexanes) to provide the title compound (105 mg, 61% over 4 steps) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.76 (m, 2H), 7.63-7.50 (m, 3H), 6.10 (t, *J* = 1.2 Hz, 1H), 3.50 (t, *J* = 9.0 Hz, 2H), 3.36 (t, *J* = 6.6 Hz, 2H), 2.33 (t, *J* = 9.0 Hz, 2H), 2.02 (t, *J* = 7.5 Hz, 2H), 1.76 (quintet, *J* = 7.5 Hz, 2H), 1.50 (quintet, *J* = 7.5 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) 135.7, 132.9, 129.0, 127.7, 126.5, 124.6, 47.6, 33.4, 32.1, 32.0, 27.3, 25.8; HRMS (TOF ES) calcd for $C_{14}H_{19}NO_2SBr$ $[M]^+$: 344.0306, found: 344.0320. The above spectral data were identical to those reported.[37a]



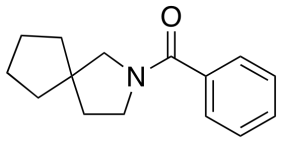

**4-(4-(Phenylselanyl)butyl)-1-(phenylsulfonyl)-2,3-dihydro-1*H*-pyrrole (1.96)**: $NaBH_4$ (19 mg, 0.5 mmol) was added in one portion to a solution of diphenyl diselenide (52 mg, 0.17 mmol) in EtOH (3 mL), and the mixture was stirred for 30 min. A solution of bromide **1.85** (115 mg, 0.33 mmol) in EtOH (2 mL) was added and the reaction mixture was stirred for 12 h. The solvent was evaporated and the crude product was purified by flash chromatography (silica gel, 1:5 EtOAc/hexanes) to provide the title compound (102 mg, 73%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.2 Hz, 2H), 7.59-7.45 (m, 5H), 7.26-7.24 (m, 3H), 6.06 (s, 1H), 3.48 (t, *J* = 9.0 Hz, 2H), 2.87 (t, *J* = 7.2 Hz, 2H), 2.89 (t, *J* = 8.7 Hz, 2H), 1.98 (t, *J* = 7.2 Hz, 2H), 1.62 (quintet, *J* = 7.2 Hz, 2H), 1.46 (quintet, *J* = 7.2 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 135.8, 132.8, 132.4, 130.4, 129.1, 129.0, 127.7, 126.9, 126.8, 124.4, 47.6, 32.1, 29.5, 27.6, 27.5, 27.4; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 3060, 2930, 2855, 1579, 1476, 1445, 1351, 1166, 1092; HRMS (TOF ES) calcd for $C_{20}H_{23}NO_2NaSSe$ $[M+Na]^+$: 444.0512, found: 444.0497.

**General Procedures for the cyclization of bromide 1.85 and phenylselenide 1.96 under fixed tin-hydride concentration conditions**:

In a sealed tube, alkyl bromide **1.85** (0.1 mmol) or phenylselenide **1.96** (0.1 mmol) was mixed with AIBN (0.03 mmol) and $Bu_3SnH$ (0.3~0.6 mmol) in benzene (10 mL). The mixture was heated at 80°C for 30 min. The solvent was evaporated and 1,3,5-trimethyoxybenzene (0.1 mmol) was added as the internal standard for calculating the NMR yields of known spiro-imine **1.89**[56] and spiro-sulfonamide **1.88**.[37a]

**General Procedures for the cyclization of bromide 60 and phenylselenide 64 under syringe pump conditions:**

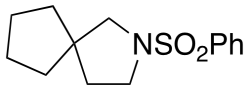
A solution of AIBN (0.03 mmol) and $Bu_3SnH$ (0.22~0.45 mmol) in benzene (2.5 mL) was added to a refluxing solution of alkyl bromide **1.85** (0.15 mmol) or phenylselenide **1.96** (0.15 mmol) in benzene (2.5 mL) via syringe pump over a period of 3 h. The solvent was evaporated and 1,3,5-trimethyoxybenzene (0.1 mmol) was added as the internal standard for calculating the NMR yields of known spiro-imine **1.89**[56] and spiro-sulfonamide **1.88**.[37a]




**Phenyl(2-azaspiro[4.4]nonan-2-yl)methanone (1.94)**: Cyclization of phenylselenide **1.96** (57 mg, 0.14 mmol) under abovementioned syringe pump condition afforded crude spiro-imine **1.89**. It was dissolved in EtOH (1.5 mL), and $NaBH_4$ (5 mg, 0.14 mmol) was added in one portion. After 1 h, the reaction mixture was diluted with $Et_2O$ and washed with a saturated aqueous

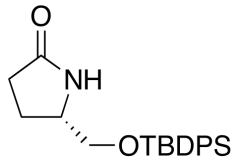
$NaHCO_3$ solution. The aqueous layer was extracted with $Et_2O$ and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*.

The resulting crude amine product was dissolved in $CH_2Cl_2$ (2 mL), followed by dropwise addition of pyridine (50 μL, 0.61 mmol) and benzoyl chloride (50 μL, 0.43 mmol). The reaction mixture was stirred for 3 h before it was diluted with $CH_2Cl_2$ and quenched with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extract with $CH_2Cl_2$, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 1:2 EtOAc/hexanes) to provide the title compound (18 mg, 59%) as a colorless oil, in a 1.2:1 ratio of rotamers: $^1$H NMR (300 MHz, $CDCl_3$) δ major rotamer: 3.69 (t, $J$ = 6.9 Hz, 2H), 3.25 (s, 2H), 1.84 (t, $J$ = 6.9 Hz, 2H); minor rotamer: 3.48 (t, $J$ = 6.9 Hz, 2H), 3.49 (s, 2H), 1.79 (t, $J$ = 6.9 Hz, 2H); overlapping signals: 7.54-7.51 (m, 2H), 7.49-7.37 (m, 3H), 1.70-1.48 (m, 8H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.0, 169.7, 137.1, 137.0, 129.7, 128.2, 127.1, 127.0, 60.8, 57.4, 50.1, 49.1, 48.3, 45.7, 38.0, 36.7, 36.5, 36.2, 24.8, 24.6; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 2950, 2864, 1630, 1576, 1447, 1416; HRMS (EI) cald for $C_{15}H_{19}NO$, 229.1467 $[M]^+$, found: 229.1458.

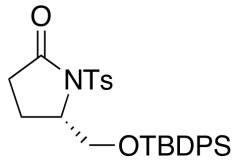



**2-(Phenylsulfonyl)-2-azaspiro[4.4]nonane (1.88)**: Cyclization of bromide **1.85** under abovementioned fixed tin hydride concentration condition afforded a 2:1 mixture of spiro-imine **1.89**/spiro-sulfonamide **1.88**. The mixture was then subjected to flash chromatography (1:5 EtOAc/hexanes) to afford the title compound (15%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.86-7.83 (m, 2H), 7.60-7.52 (m, 3H), 3.33 (t, $J$ = 7.2 Hz, 2H), 3.09 (s, 2H), 1.65 (t, $J$ = 7.2 Hz, 2H), 1.59-1.55 (m, 4H), 1.36-1.32 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 137.2, 132.5,

129.0, 127.4, 58.7, 49.9, 47.4, 37.4, 36.4, 24.5. The above spectral data were identical to those reported.[37a]

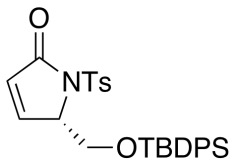



**(*S*)-5-((tert-Butyldiphenylsilyloxy)methyl)pyrrolidin-2-one (1.103)**: TBDPSCl (5.73 g, 20.85 mmol) and imidazole (2.95 g, 43.43 mmol) were added to a solution of hydrolactam **1.102** (2 g, 17.37 mmol) in DMF (20 mL). The reaction mixture was stirred at room temperature for 12 h. It was diluted with $Et_2O$ and successively washed with a 10% citric acid solution, a saturated aqueous $NaHCO_3$ solution and water. The organic fraction was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 1:1 EtOAc/hexanes) to provide the title compound (6.02 g, 98%) as a light yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.65-7.62 (m, 4H), 7.45-7.37 (m, 6H), 5.80 (brs, 1H), 3.85-3.76 (m, 1H), 3.62 (dd, *J* = 10.2 Hz, 3.9 Hz, 1H), 3.50 (dd, *J* = 10.2 Hz, 7.8 Hz, 1H), 2.34 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 2.32 (d, *J* = 7.5 Hz, 1H), 2.14 (td, *J* = 12.9 Hz, 7.8 Hz, 1H), 1.77-1.65 (m, 1H), 1.05 (s, 9H). The above spectral data were identical to those reported.[30]



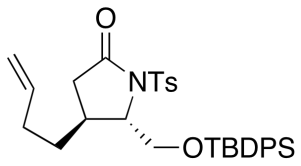

**(*S*)-5-((*tert*-Butyldiphenylsilyloxy)methyl)-1-tosylpyrrolidin-2-one (1.104)**:

A LiHMDS solution (1 M in THF, 17.8 mL) was added dropwise to a solution of amide **1.103** (6 g, 16.97 mmol) in THF (60 mL) at −78 °C, and the mixture was stirred at this temperature for 10 min. A solution of tosyl chloride (3.88 g, 20.37 mmol) in THF (10 mL) was added dropwise at −78 °C. The reaction mixture was slowly warmed to room temperature and then stirred for 1 h. The reaction was quenched with a saturated aqueous $NH_4Cl$ solution, and the aqueous layer was extract with $Et_2O$. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 1:5 EtOAc/hexanes) to provide the title compound (8.01 g, 93%) as a viscous, colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.1 Hz, 2H), 7.60-7.56 (m, 4H), 7.49-7.36 (m, 6H), 7.24 (d, *J* = 8.1 Hz, 2H), 4.46-4.42 (m, 1H), 4.01 (dd, *J* = 10.8 Hz, 4.2 Hz, 1H), 3.81 (dd, *J* = 10.8 Hz, 2.4 Hz, 1H), 2.68 (appt td, *J* = 17.4 Hz, 10.2 Hz, 1H), 2.40 (s, 3H), 2.37-2.14 (2H), 2.04-2.00 (m, 1H), 1.01 (s, 9H). The above spectral data were identical to those reported.[30]



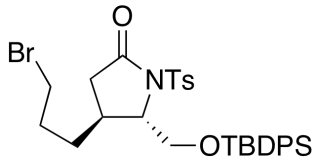

**(*S*)-5-((*tert*-Butyldiphenylsilyloxy)methyl)-1-tosyl-1*H*-pyrrol-2(5*H*)-one (1.105)**: A solution of sulfonamide **1.104** (1.02 g, 1.97 mmol) in THF (4 mL) was added dropwise to a solution of LiHMDS (2.17 mmol) in THF (6 mL) at −78 °C. After30 min, a solution of PhSeBr (558 mg, 2.36 mmol) in THF (4 mL) was added dropwise at −78 °C. The reaction mixture was stirred at -78°C for 30 min and then at room temperature for 1 h. The reaction was quenched with a saturated aqueous $NH_4Cl$ solution, and the aqueous layer was extracted with $Et_2O$. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was passed through a pad of silicagel (silica gel, 1:4 EtOAc/hexanes) to give the crude

phenylselenide product as an inseparable mixture of diastereomers: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.8 Hz, 2H), 7.52-7.14 (m, 17H), 4.23-4.00 (m, 3H), 3.83-3.71 (m, 1H), 2.44-2.28 (m, 4H), 2.20-2.05 (m, 1H), 0.98 (s, 9H). The crude phenylselenide product was dissolved in EtOAc (25 mL) and cooled to 0°C. A 30% $H_2O_2$ solution (1.2 mL) was added in one portion and the reaction mixture was warmed to room temperature. After 30 min, the reaction mixture was diluted with $Et_2O$ and successively washed with water, brine and a saturated aqueous $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (1:3 EtOAc/hexanes) to give the title compound (1.31 g, 63%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.58-7.54 (m, 4H), 7.46-7.36 (m, 6H), 7.26-7.22 (m, 2H), 7.08 (dd, *J* = 6.0 Hz, 1.8 Hz, 1H), 6.02 (dd, *J* = 6.0 Hz, 1.5 Hz, 1H), 4.80-4.76 (m, 1H), 4.22 (dd, *J* = 10.2 Hz, 3.3 Hz, 1H), 3.99 (dd, *J* = 10.2 Hz, 6.3 Hz, 1H), 2.39 (s, 3H), 0.97 (s, 9H). The above spectral data were identical to those reported.[30]



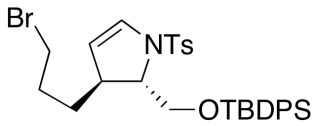

**(4*S*,5*S*)-4-(But-3-enyl)-5-((*tert*-butyldiphenylsilyloxy)methyl)-1-tosylpyrrolidin-2-one (1.106)**: A solution of but-3-enylmagnesium bromide (0.5 M in THF, 13 mL) was added dropwise to a solution of CuBr•$Me_2S$ (134 mg, 0.65 mmol) in THF (2 mL) at −78 °C, and the mixture was stirred at this temperature for 10 min. TMSCl (275 μL) was added to the resulting organocuprate solution at −78 °C, followed by addition of a solution of enamide **1.105** in THF (5 mL). The reaction mixture was stirred at -78°C for 2 h, and then a saturated aqueous $NH_4Cl$ solution was added. The aqueous layer was extracted with $Et_2O$, and the combined organic layers

were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by chromatography (silica gel, 1:4 EtOAc/hexanes) to give the title compound (510 mg, 83%) as a colorless oil: $[\alpha]_D^{23}$ −18.5 (*c* 8.0 mg/mL, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 6.6 Hz, 1.8 Hz, 2H), 7.61-7.57 (m, 4H), 7.46-7.36 (m, 6H), 7.26-7.23 (m, 2H), 5.68 (tdd, *J* = 16.5 Hz, 10.5 Hz, 6.6 Hz, 1H), 4.98-4.92 (m, 2H), 4.06-4.04 (m, 1H), 3.94 (dd, *J* = 10.5 Hz, 4.8 Hz, 1H), 3.87 (dd, *J* = 10.5 Hz, 2.7 Hz, 1H), 2.79 (dd, *J* = 17.4 Hz, 8.7 Hz, 1H), 2.40 (s, 3H), 2.24 (appt q, *J* = 8.1 Hz, 1H), 2.03-1.95 (m, 3H), 1.42-1.22 (m, 2H), 1.01 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 173.6, 144.9, 137.1, 135.8, 135.7, 135.6, 132.8, 132.5, 130.0, 129.5, 128.1, 127.9, 127.8, 115.6, 66.0, 65.3, 37.7, 34.1, 33.9, 30.6, 26.8, 21.7, 19.2; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 3071, 2931, 2858, 1738, 1596, 1424, 1360, 1170, 1111; HRMS (TOF ES) cald for $C_{32}H_{39}NO_4NaSiS$, 584.2267 $[M+Na]^+$, found: 584.2239.



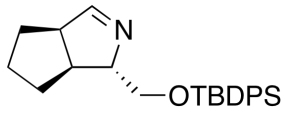

**(4*S*,5*S*)-4-(3-Bromopropyl)-5-((*tert*-butyldiphenylsilyloxy)methyl)-1-tosylpyrrolidin-2-one (1.107)**: Ozone was bubbled to a solution of alkene **1.106** (220 mg, 0.39 mmol) in $CH_2Cl_2$/MeOH (1:1, 8 mL) at −78 °C over a period of 30 min. $Me_2S$ (1 mL) was added at −78 °C and the reaction mixture was stirred for 4 h. The reaction mixture was purged with Ar before the solvent was evaporated. The crude aldehyde product was dissolved in MeOH (3 mL). $NaBH_4$ (10 mg, 0.27 mmol) was added in one portion and the reaction mixture was stirred for 2 h. The solvent was evaporated, and the residue was diluted with $Et_2O$ and washed with a saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was passed through a short pad of silica gel (silica gel, 1:1 EtOAc/hexanes) to provide

crude alcohol product, which was then dissolved in $CH_2Cl_2$ (2 mL). $CBr_4$ (85 mg, 0.26 mmol) and $Ph_3P$ (71 mg, 0.27 mmol) were added, and the reaction mixture was stirred for 2 h. The crude product was purified by flash chromatography (silica gel, 1:4 EtOAC/hexanes) to provide the title compound (90 mg, 45%) as a colorless oil: $[\alpha]_D^{23}$ −18.3 (*c* 8.3 mg/mL, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 6.9 Hz, 1.5 Hz, 2H), 7.62-7.58 (m, 4H), 7.47-7.38 (m, 6H), 7.28-7.25 (m, 2H), 4.04-4.02 (m, 1H), 3.94 (dd, *J* = 10.2 Hz, 5.1 Hz, 1H), 3.88 (dd, *J* = 10.5 Hz, 2.7 Hz, 1H), 3.32-3.27 (m, 2H), 2.80 (dd, *J* = 17.7 Hz, 8.4 Hz, 1H), 2.40 (s, 3H), 2.21 (app q, *J* = 7.8 Hz, 1H), 1.98 (dd, *J* = 17.7 Hz, 1.2 Hz, 1H), 1.76 (quintet, *J* = 7.2 Hz, 2H), 1.47-1.32 (m, 2H), 1.03 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 173.1, 145.0, 135.6, 135.5, 132.7, 132.4, 130.0, 129.5, 128.1, 127.9, 127.8, 65.8, 65.2, 37.5, 33.9, 33.2, 32.7, 29.5, 26.8, 21.6, 19.1; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 3070, 2932, 2858, 1736, 1428, 1361, 1170, 1112; HRMS (TOF ES) cald for $C_{31}H_{38}NO_4NaSiSBr$, 650.1372 $[M+Na]^+$, found: 650.1344.




**(2*S*,3*S*)-3-(3-bromopropyl)-2-((*tert*-butyldiphenylsilyloxy)methyl)-1-tosyl-2,3-dihydro-1*H*-pyrrole (1.100)**: A DIBAL-*H* solution (1 M in hexane, 0.32 mL) was added dropwise to a solution of sulfonamide **1.107** (100 mg, 0.16 mmol) in THF (2 ml) at −78 °C. After 1 h, the reaction mixture was diluted with $Et_2O$ and a saturated aqueous potassium-sodium tartrate solution was added. The mixture was stirred for 12 h. The aqueous layer was extracted with $Et_2O$, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude hemiaminal was dissolved in toluene (5 mL), and citric acid (34 mg, 0.16 mmol) was added. After refluxing for 3 h, the reaction mixture was cooled to room

temperature and a saturated aqueous $NaHCO_3$ solution was carefully added. The aqueous layer was extract with $Et_2O$, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 1:6 EtOAc/hexanes) to provide the title compound (65 mg, 65%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.70-7.65 (m, 4H), 7.56 (d, *J* = 7.8 Hz, 2H), 7.49-7.39 (m, 6H), 7.32-7.27 (m, 2H), 6.30 (d, *J* = 3.9 Hz, 1H), 5.05 (t, *J* = 3 Hz, 1H), 3.93 (dd, *J* = 9.9 Hz, 3.9 Hz, 1 H), 3.71 (dd, *J* = 9.9 Hz, 8.4 Hz, 1 H), 3.31 (ddd, *J* = 7.8 Hz, 3.9 Hz, 3.9 Hz, 1H), 3.09 (t, *J* = 6.6 Hz, 2H), 2.78 (m, 1 H), 2.43 (s, 3H), 1.49-1.35 (m, 2H), 1.07 (s, 9H), 0.89-0.79 (m, 1H), 0.71-0.60 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 143.9, 135.7, 135.6, 133.5, 133.2, 133.0, 129.8, 129.6, 128.3, 127.8, 127.7, 127.6, 115.5, 65.6, 65.2, 45.7, 34.2, 33.3, 29.3, 26.9, 21.6, 19.3; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 3070, 2931, 2858, 1470, 1429, 1355, 1166, 1110; HRMS (TOF ES) cald for $C_{31}H_{38}NO_3NaSiSBr$, 634.1423 $[M+Na]^+$, found: 634.1401.

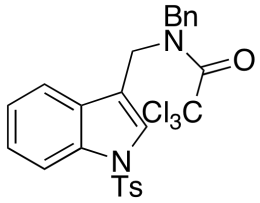



**(1*S*,3a*R*,6a*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-1,3a,4,5,6,6a-hexahydrocyclopenta[c]pyrrole (1.101)**: $Bu_3SnH$ (71 μL, 0.26 mmol) and $Et_3B$ (1 M in hexane, 35 μL) were added to a solution of enamide **1.100** (54 mg, 0.088 mmol) in benzene (9 mL), and the reaction mixture was stirred for 30 min. The solvent was evaporated and the crude product was purified by flash chromatography (silica gel, 1:4 EtOAc/hexanes) to provide the title compound (18 mg, 55%) as a colorless oil: $[\alpha]_D^{23}$ +97.7 (*c* 3.0 mg/mL, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.70-7.66 (m, 4H), 7.44-7.37 (m, 6H), 3.91-3.85 (m, 2H), 3.73-3.69 (m, 1H), 3.36 (t, *J* = 8.1 Hz, 1H), 2.67 (tt, *J* = 8.1 Hz, 2.7 Hz, 1H), 1.74-1.46 (m, 5H), 1.32-1.23 (m, 1H),

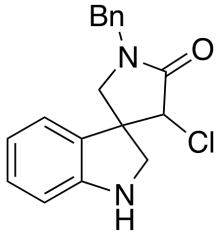
1.05 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.2, 135.7, 135.6, 133.8, 133.6, 129.6, 129.5, 127.7, 127.6, 83.4, 66.4, 55.4, 41.9, 34.2, 29.1, 26.8, 24.9, 19.3; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 2933, 2860, 1625, 1470, 1427, 1112, 1028; HRMS (TOF ES) cald for $C_{24}H_{32}NOSi$, 378.2253 $[M+H]^+$, found: 378.2270.

**Attempted isomerization of alcohol 100:**

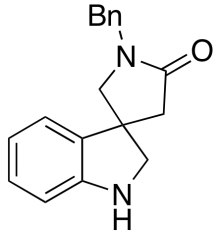
A mixture of alcohol **1.108** (5.6 mg, 0.020 mmol), AIBN (1.0 mg, 0.006 mmol), and $Bu_3SnH$ (16 μL, 0.060 mmol) in benzene (1.5 mL) was heated at 80 °C for 1 h. The solvent was evaporated, and the residue was purified by flash chromatography (silica gel, 1:2 EtOAc/hexanes) to provide recovered **1.108** (5 mg, 89%) as a colorless oil.




***N*-Benzyl-2,2,2-trichloro-*N*-((1-tosyl-1*H*-indol-3-yl)methyl)acetamide (1.115)**: The title compound was prepared as a mixture of 2.5:1 rotamers: $^1$H NMR (300 MHz, $CDCl_3$) δ major rotamer: 4.87 (s, 2H), 4.73 (s, 2H); minor rotamer: 4.99 (s, 2H), 4.66 (s, 2H); overlapping signals: 8.04 (d, $J$ = 7.8 Hz, 1H), 7.78 (d, $J$ = 7.8 Hz, 2H), 7.45-7.12 (m, 10H), 2.37 (s, 3H). The above spectral data were identical to those reported.[52]

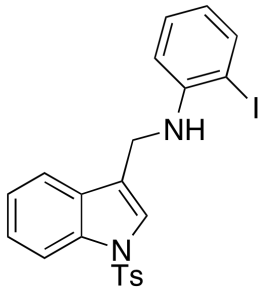



**1'-Benzyl-4'-chlorospiro[indoline-3,3'-pyrrolidin]-5'-one (1.122)**: A mixture of tin hydride (110 μL, 0.411 mmol), AIBN (17 mg, 0.102 mmol), and trichloroacetamide **1.115** (110 mg, 0.205 mmol) in benzene (10 mL) was refluxed for 30 min. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, 30% EtOAc/hexanes) to provide the title compound (33 mg, 51%) as a colorless oil: $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 7.18-7.10 (m, 2H), 6.74 (td, *J* = 7.5 Hz, 1.0 Hz, 1H), 6.68 (d, *J* = 7.5 Hz, 1H), 4.63 (d, *J* = 14.4 Hz, 1H), 4.53 (d, *J* = 14.4 Hz, 1H), 4.45 (s, 1H), 3.77 (brs, 1H), 3.75 (d, *J* = 10.2 Hz, 1H), 3.63 (d, *J* = 9.6 Hz, 1H), 3.48 (d, *J* = 9.6 Hz, 1H), 3.25 (d, *J* = 10.2 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 169.3, 151.6, 135.4, 129.5, 128.9, 128.3, 128.1, 126.6, 125.6, 118.8, 110.1, 61.5, 58.6, 55.0, 52.2, 47.2; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 3334, 3030, 2922, 2856, 1701, 1607, 1486, 1465, 1257, 742; HRMS (TOF ES) cald for $C_{18}H_{17}N_2ONaCl$, 335.0927 $[M+Na]^+$, found: 335.0916.



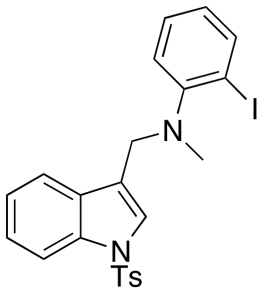

**1'-Benzylspiro[indoline-3,3'-pyrrolidin]-5'-one (1.124)**: A mixture of tin hydride (150 μL, 0.560 mmol), AIBN (4 mg, 0.023 mmol), and trichloroacetamide **1.115** (50 mg, 0.093 mmol) in benzene (10 mL) was refluxed for 30 min. The solvent was evaporated and the residue was

purified by flash chromatography (silica gel, 75% EtOAc/hexanes) to provide the title compound (20 mg, 78%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.75 (t, *J* = 7.8 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 4.62 (d, *J* = 14.4 Hz, 1H), 4.41 (d, *J* = 14.4 Hz, 1H), 3.75 (brs, 1H), 3.50 (d, *J* = 14.4 Hz, 1H), 3.48 (d, *J* = 14.4 Hz, 1H), 3.39 (d, *J* = 13.8 Hz, 1H), 3.36 (d, *J* = 13.8 Hz, 1H), 2.87 (d, *J* = 16.8 Hz, 1H), 2.65 (d, *J* = 16.8 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 173.0, 150.7, 136.2, 132.5, 128.8, 128.6, 128.3, 127.8, 122.1, 119.3, 110.0, 60.6, 58.3, 46.7, 45.8, 44.0; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 3336, 2920, 2855, 1680, 1608, 1488, 1256, 745, 702; HRMS (TOF ES) cald for $C_{18}H_{18}N_2ONa$, 301.1317 $[M+Na]^+$, found: 301.1304.



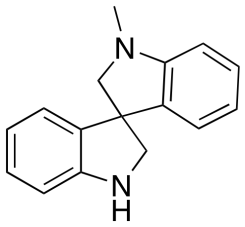

**2-Iodo-*N*-((1-tosyl-1*H*-indol-3-yl)methyl)aniline (1.131)**: 2-Iodoaniline (241 mg, 1.10 mmol), acetic acid (60 mg, 1.00 mmol), and sodium triacetoxyborohydride (637 mg, 3.00 mmol) were added to a stirred solution of 1-tosyl-1*H*-indole-3-carbaldehyde **1.120** (300 mg, 1.00 mmol) in 1,2-dichloroethane (8 mL). After 12 h, the reaction was quenched with a saturated $NaHCO_3$ solution and the aqueous layer was extracted with 1,2-dichloroethane. The combined organic layer was washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 15% EtOAc/hexanes) to give the title compound (330 mg, 66%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.1 Hz, 1H), 7.73-7.69 (m, 3H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.51 (s, 1H), 7.36 (td, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.27 (m,

1H), 7.22-7.14 (m, 3H), 6.58 (dd, *J* = 8.1 Hz, 1.2 Hz, 1H), 6.50 (td, *J* = 7.5 Hz, 1.2 Hz, 1H), 4.54-4.47 (m, 3H), 2.35 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 146.9, 145.0, 139.1, 135.6, 135.1, 129.9, 129.6, 126.9, 125.1, 124.2, 123.4, 119.9, 119.6, 119.2, 114.0, 111.1, 85.6, 40.2, 21.6; FTIR (thin film, $CH_2Cl_2$, cm$^{-1}$) 3394, 3061, 2921, 1589, 1502, 1448, 1367, 1277, 1173, 1121, 1005, 970, 810, 744; HRMS (EI) cald for $C_{22}H_{19}N_2O_2SI$, 502.0212 $[M]^+$, found: 502.0198.

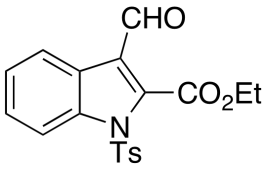



**2-Iodo-*N*-methyl-*N*-((1-tosyl-1*H*-indol-3-yl)methyl)aniline (1.125)**: A NaHMDS solution (450 μL, 1M in THF) was added dropwise to a solution of aniline **1.131** (150 mg, 0.30 mmol) in THF (5 mL) at −78 °C. After 30 min, iodomethane (46 μL, 0.75 mmol) was added dropwise at this temperature. The reaction mixture was then stirred at room temperature for 12h. A saturated aqueous $NaHCO_3$ solution was added, and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 20% EtOAc/hexanes) to afford the title compound (140 mg, 91%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.1 Hz, 1H), 7.88 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 2H), 7.60-7.54 (m, 2H), 7.32-7.17 (m, 5H), 7.02 (dd, *J* = 8.1 Hz, 1.2 Hz, 1H), 6.80 (t, *J* = 7.8 Hz, 1H), 4.24 (s, 2H), 2.67 (s, 3H), 2.33 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 153.8, 144.8, 140.3, 135.4, 135.3, 130.6, 129.9, 129.1, 126.8, 125.7, 125.4, 124.8, 123.1, 122.2, 120.6, 119.5, 113.7, 98.6, 51.7, 42.4, 21.7; FTIR (thin film, $CH_2Cl_2$, cm$^{-1}$) 3053, 2947, 1596, 1470, 1446, 1367, 1173, 1119,

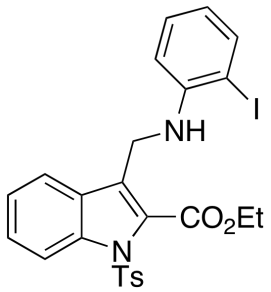
1093, 978, 812, 747, 702; HRMS (TOF ES) cald for $C_{23}H_{22}N_2O_2SI$, 517.0447 $[M+H]^+$, found: 517.0460.



**1-Methyl-3,3'-spirobi[indoline] (1.134)**: A mixture of aryl iodide **1.125** (70 mg, 0.136 mmol), tributyltin hydride (91 μL, 0.340 mmol) and AIBN (7 mg, 0.040 mmol) in benzene (13 mL) was refluxed for 20 min. TLC suggested the starting material was not completely consumed. Tin hydride (163 μL, 0.610 mmol) was added in two portions with a catalytic amount of AIBN. After 20 min, the solvent was evaporated, and the residue was purified by flash chromatography (silica gel, 20% EtOAc/hexanes) to provide the title compound (15 mg, 47%) as a colorless oil: $^1$H NMR (600 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.8 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.77-6.72 (m, 3H), 6.60 (d, *J* = 7.8 Hz, 1H), 3.78 (d, *J* = 9.0 Hz, 1H), 3.63 (d, *J* = 9.0 Hz, 1H), 3.62 (d, *J* = 9.0 Hz, 1H), 3.27 (d, *J* = 9.0 Hz, 1H), 2.82 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 153.1, 151.4, 135.3, 134.1, 128.4, 128.2, 124.1, 123.6, 119.3, 118.6, 109.7, 107.5, 68.9, 60.3, 54.5, 36.1; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 3374, 3046, 2949, 2853, 2805, 1606, 1487, 1463, 1295, 1252, 1151, 1121, 1021, 745; HRMS (EI) cald for $C_{16}H_{16}N_2$, 236.1313 $[M]^+$, found: 236.1313.

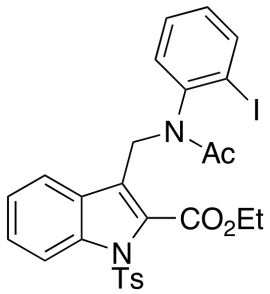


**Ethyl 3-formyl-1-tosyl-1*H*-indole-2-carboxylate (1.133)**: Ethyl 3-formyl-1*H*-indole-2-carboxylate **1.132** (150 mg, 0.69 mmol) and tosyl chloride (197 mg, 1.04 mmol) were added to a stirred suspension of $Cs_2CO_3$ (675 mg, 2.07 mmol) in DMF (4 mL). After 30 min, the reaction was quenched with a saturated aqueous $NH_4Cl$ solution, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 15% EtOAc/hexanes) to afford the title compound (75 mg, 29%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 8.02-7.98 (m, 3H), 7.46 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.38 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.61 (q, *J* = 7.2 Hz, 2H), 2.39 (s, 3H), 1.50 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 185.3, 161.1, 146.4, 139.3, 135.3, 134.4, 130.2, 127.9, 127.8, 127.4, 125.7, 125.3, 123.1, 120.9, 114.2, 63.7, 21.9, 14.2; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 2924, 2360, 1734, 1680, 1545, 1380, 1321, 1268, 1206, 1179, 1141, 1111, 1086, 1015, 986, 817, 749; HRMS (TOF ES) cald for $C_{19}H_{17}NO_5NaS$, 394.0725 $[M+Na]^+$, found: 394.0699.



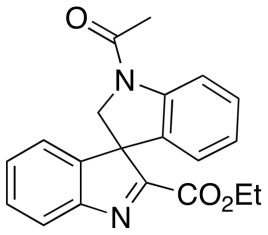

**Ethyl 3-((2-iodophenylamino)methyl)-1-tosyl-1*H*-indole-2-carboxylate (1.90)**: A mixture of aldehyde **1.133** (66 mg, 0.178 mmol), 2-iodoaniline (43 mg, 0.195 mmol), anhydrous $MgSO_4$ (64 mg, 0.533 mmol), and pyridinium *p*-toluenesulfonate (13 mg, 0.053 mmol) in $CH_2Cl_2$ (2 mL) was stirred for 12 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution, and

the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude imine was dissolved in EtOH (3 mL), and $NaBH_4$ (20 mg, 0.533 mmol) was added in one portion. After 3 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 15% EtOAc/Hexane) to afford the title compound (65 mg, 64%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 7.81 (m, 2H), 7.67 (m, 2H), 7.43 (td, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.30 (m, 1H), 7.21 (m, 3H), 6.72 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 6.49 (td, *J* = 7.5 Hz, 1.5 Hz, 1H), 4.53 (s, 1H), 4.48 (q, *J* = 7.0 Hz, 1H), 2.34 (s, 3H), 1.39 (t, *J* = 7.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 162.4, 146.8, 145.1, 139.1, 136.8, 134.4, 129.7, 129.6, 129.5, 128.9, 127.2, 126.9, 124.4, 124.3, 120.8, 119.3, 115.5, 110.9, 85.5, 62.6, 39.0, 21.6, 14.0; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 3395, 2982, 1724, 1590, 1503, 1451, 1371, 1312, 1266, 1177, 1006, 814, 746; HRMS (EI) cald for $C_{25}H_{23}N_2O_4SI$, 574.0423 $[M]^+$, found: 574.0408.



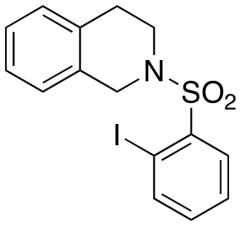

**Ethyl 3-((*N*-(2-iodophenyl)acetamido)methyl)-1-tosyl-1*H*-indole-2-carboxylate (1.128)**: DMAP (4 mg, 0.03 mmol), pyridine (19 μL, 0.23 mmol), and acetyl chloride (8 μL, 0.11 mmol) were added to a stirred solution of **1.90** (33 mg, 0.057 mmol) in $CH_2Cl_2$ (2 mL) at 0 °C. The reaction mixture was then stirred at room temperature for 12 h. It was diluted with $CH_2Cl_2$ and a

saturated aqueous $NaHCO_3$ solution was added. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 25% EtOAc/hexanes) to afford the title compound (29 mg, 80%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.0 Hz, 1H), 7.91 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.30-7.27 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.10 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.02 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 6.40 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H), 5.74 (d, *J* = 14.4 Hz, 1H), 4.52 (d, *J* = 14.4 Hz, 1H), 4.17-4.01 (m, 2H), 2.35 (s, 3H), 1.78 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ major rotamer: 62.3, 21.6, 13.9; minor rotamer: 60.4, 21.1, 14.2; overlapping signals: 169.9, 161.4, 145.0, 143.0, 140.1, 136.5, 134.5, 131.3, 130.6, 130.0, 129.6, 129.5, 129.0, 127.3, 126.9, 124.6, 122.6, 121.9, 115.1, 100.0, 39.4, 22.8; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 2982, 1723, 1664, 1469, 1372, 1313, 1267, 1177, 1017, 762; HRMS (TOF ES) cald for $C_{27}H_{25}N_2O_5NaSI$, 639.0427 $[M+Na]^+$, found: 639.0479.



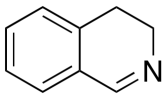

**Ethyl 1'-acetylspiro[indole-3,3'-indoline]-2-carboxylate (1.130)**: In a sealed tube, a mixture of tin hydride (28 μL, 0.105 mmol), AIBN (1 mg, 0.006 mmol), and aryl iodide **1.128** (13 mg, 0.021 mmol) in benzene (2 mL) was refluxed for 30 min. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, 60% EtOAc/hexanes) to provide the title compound (5 mg, 71%) as a colorless oil, in a 5:1 ratio of rotamers: $^1$H NMR (400 MHz,

$CDCl_3$) δ major rotamer: 4.73 (d, *J* = 12.0 Hz, 1H), 2.28 (s, 3H); minor rotamer: 4.80 (d, *J* = 12.0 Hz, 1H), 2.59 (s, 3H); overlapping signals: 8.36 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.32-7.27 (m, 2 H), 6.89 (t, *J* = 7.6 Hz, 1H), 6.42 (d, *J* = 7.6 Hz, 1H), 4.31-4.29 (m, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.3, 168.2, 160.7, 152.6, 145.2, 144.2, 129.8, 129.5, 128.9, 124.0, 123.9, 122.7, 122.3, 118.1, 64.2, 62.3, 55.4, 24.4. 14.0; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$) 2923, 1722, 1665, 1593, 1482, 1402, 1339, 1267, 1146, 1106, 1021, 754; HRMS (TOF ES) cald for $C_{20}H_{18}N_2O_3Na$, 357.1215 $[M+Na]^+$, found: 357.1239.




**2-(2-iodophenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline** (**1.142**): A solution of 2-iodo-benzenesulfonyl chloride (100 mg, 0.33 mmol) in $CH_2Cl_2$ (1 mL) was added to a mixture of piperidine (36 μL, 0.36 mmol), triethylamine (70 μL, 0.50 mmol), and DMAP (4 mg, 0.033 mmol) in $CH_2Cl_2$ at 0 °C. After 30 min, the reaction was quenched with a saturated aqueous $NH_4Cl$ solution, and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layer was dried with $MgSO_4$, concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 40% EtOAc/hexanes) to afford the title compound (103 mg, 89%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 8.09 (dd, *J* = 7.2 Hz, 1.2 Hz, 1H), 7.52 (td, *J* = 7.5 Hz, 1.2 Hz, 1H), 7.23-7.06 (m, 5H), 4.53 (s, 2H), 3.61 (t, *J* = 6.0 Hz, 1H), 2.95 (t, *J* = 6.0 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 143.1, 140.9, 133.5, 133.4, 131.9, 129.0, 128.3, 126.8, 126.4, 126.3, 92.8, 46.9, 43.2, 28.8; FTIR (thin film, $CH_2Cl_2$, $cm^{-1}$)

3053, 2947, 1596, 1470, 1446, 1367, 1173, 1119, 1093, 1015, 978, 747; HRMS (TOF ES) cald for $C_{15}H_{14}NO_2NaSI$, 421.9688 $[M+Na]^+$, found: 421.9654.




**3,4-Dihydroisoquinoline** (**1.143**): A mixture of sulfonamide **1.142** (56 mg, 0.14 mmol), AIBN (7 mg, 0.042 mmol), and $Bu_3SnH$ (75 μL, 0.28 mmol) in benzene (13 mL) was refluxed for 30 min. The solvent was evaporated, and the residue was purified by flash chromatography (silica gel, 10% MeOH/$CH_2Cl_2$) provided the title compound (10 mg, 54%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 8.35 (brs, 1H), 7.40-7.26 (m, 3H), 7.17 (d, $J$ = 7.2 Hz, 1H), 3.79 (td, $J$ = 7.5 Hz, 2.1 Hz, 2H), 2.77 (t, $J$ = 7.8 Hz, 1H). The above spectral data were identical to those reported.[57]

# 2.0 TOTAL SYNTHESES OF (±)-EPIMELOSCINE, (±)-MELOSCINE, AND ANALOGS

## 2.1 INTRODUCTION

Dr. David Guthrie recently demonstrated that slow addition of $Bu_3SnH$ and $Et_3B$ to anilide **1.18** leads to tricycle **1.19** in 51% yield.[21] The ring system in this tricycle resembles the A/B/C ring system of several typical *Melodinus* alkaloids, including meloscine **2.1**, epimeloscine **2.2**, and scandine **2.3** (**Scheme 2.1**). This tandem reaction served as a starting point for our synthetic studies on meloscine alkaloids.

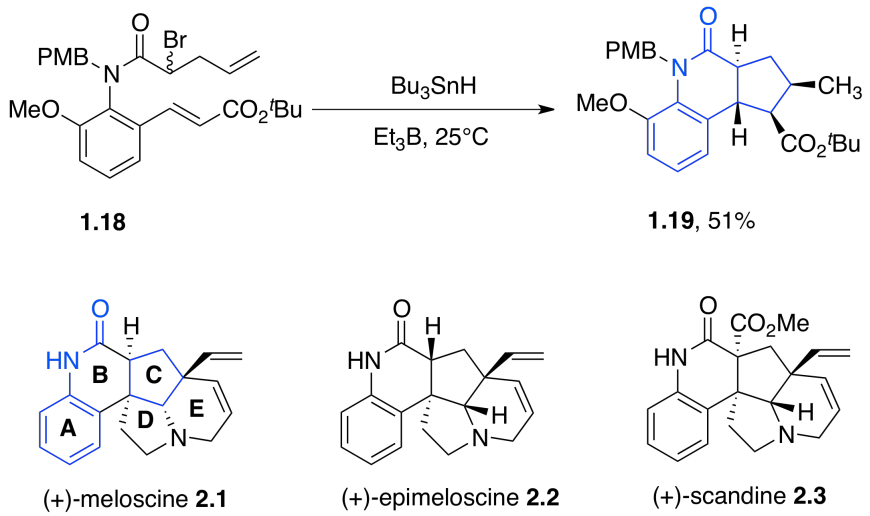
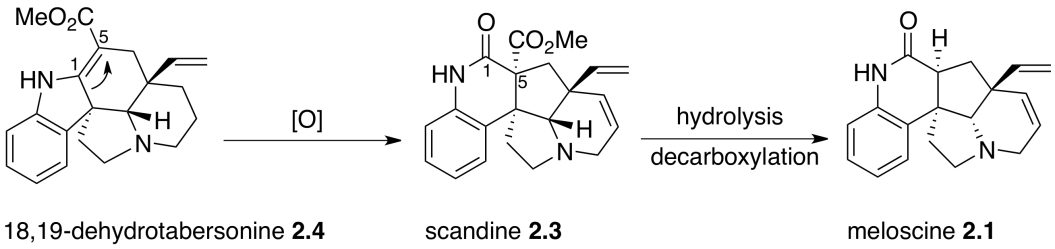



**Figure 15** A Tandem Radical Cyclization Reaction That Generates the A,B,C Ring System of Meloscine and Related Alkaloids

### 2.1.1 Structures and Biosynthesis of Meloscine Alkaloids

Meloscine **2.1**, a representative member of *Melodinus* alkaloids, was isolated from the New Caledonian plant *Melodinus Scandens Forst* in 1969.[58] The structures of meloscine and related alkaloids epimeloscine and scandine were later established with the aid of NMR spectroscopic and X-ray crystallographic techniques. The structural uniqueness of these alkaloids is represented by the existence of a dihydroquilolin-2-one moiety (rings A/B) within the monoterpenoid *Aspidosperma* alkaloid skeleton.

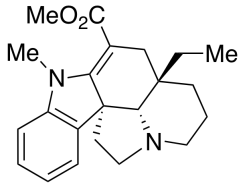
Early biosynthetic studies suggested that meloscine derives from hydrolysis and decarboxylation of scandine **2.3**. In turn, scandine **2.3** could arise from oxidative rearrangement of *Aspidosperma* alkaloid 18,19-dehydrotabersonine **2.4** (**Scheme 2.1**).[58] In the 80s, Levy and Palmisano successfully realized the skeletal rearrangement of *Aspidosperma* to *Melodinus* alkaloids by achieving a partial synthesis of meloscine and scandine starting from 18,19-dehydrotabersonine.[59,60] The rearrangment yields were low, but these results solidified the early biosynthetic hypothesis.



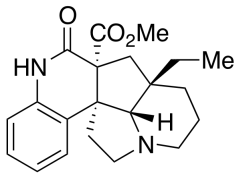

**Scheme 2.1** Proposed Biosynthesis of Scandine and Meloscine

Extracts of some *Melodinus* species are traditional Chinese folk medicines to treat meningitis and rheumatic heart disease.[61] However, the biological activities of meloscine alkaloids remain unknown, even though they were isolated more than 40 years ago.

Vincadifformine **2.5**, a putative biosynthetic precursor of tetrahydroscandine **2.6**,[62] shows moderate cytotoxic activities against several cancer cell lines (**Figure 16**).[63]




vincadifformine **2.5**




tetrahydroscandine **2.6**

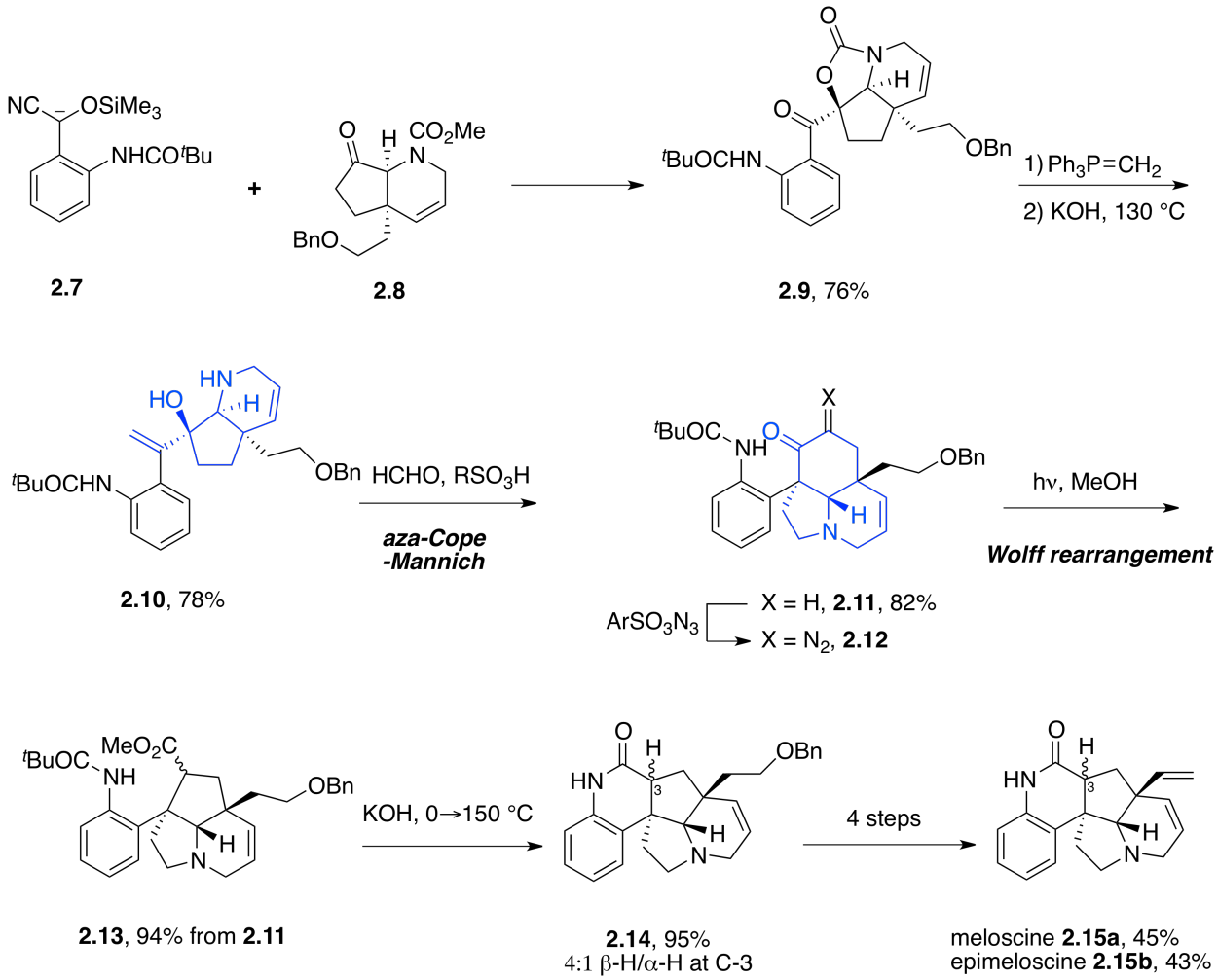
**Figure 16** Structures of Vincadifformine and Tetrahydroscandine

### 2.1.2 Previous Synthetic Studies on Meloscine Alkaloids

Meloscine alkaloids are interesting synthetic targets because of their intriguing structures. In particular, their highly functionalized cyclopentane C ring has four stereocenters, two (meloscine) or three (scandine) of which being quaternary centers. The fusion of this ring with a dihydroquinoline-2-one moiety (rings A/B) poses a significant synthetic challenge (**Figure 15**).

In 1989, Overman published the first total synthesis of (±)-meloscine and (±)-epimeloscine that features a classic cascade aza-Cope-Mannich sequence.[64] **Scheme 2.2** outlines several key transformations of this synthesis. Nucleophilic addition of enolate **2.7** to bicyclic ketone **2.8**, which was prepared in 12 steps from 2-oxocyclopentaneacetate, produced cyclic carbamate **2.9** in 78% yield. Wittig reaction of **2.9** followed by hydrolysis generated complex styrene **2.10** in 78% yield over two steps. This intermediate underwent the key aza-Cope-Mannich cascade to afford tricyclic ketone **2.11** in 83% yield. Subsequent Wolff rearrangement of the C ring and a late-stage lactamization ultimately forged the pentacycle **2.14** as a 4:1 mixture of diastereomers, which were separated by flash chromatography. The major

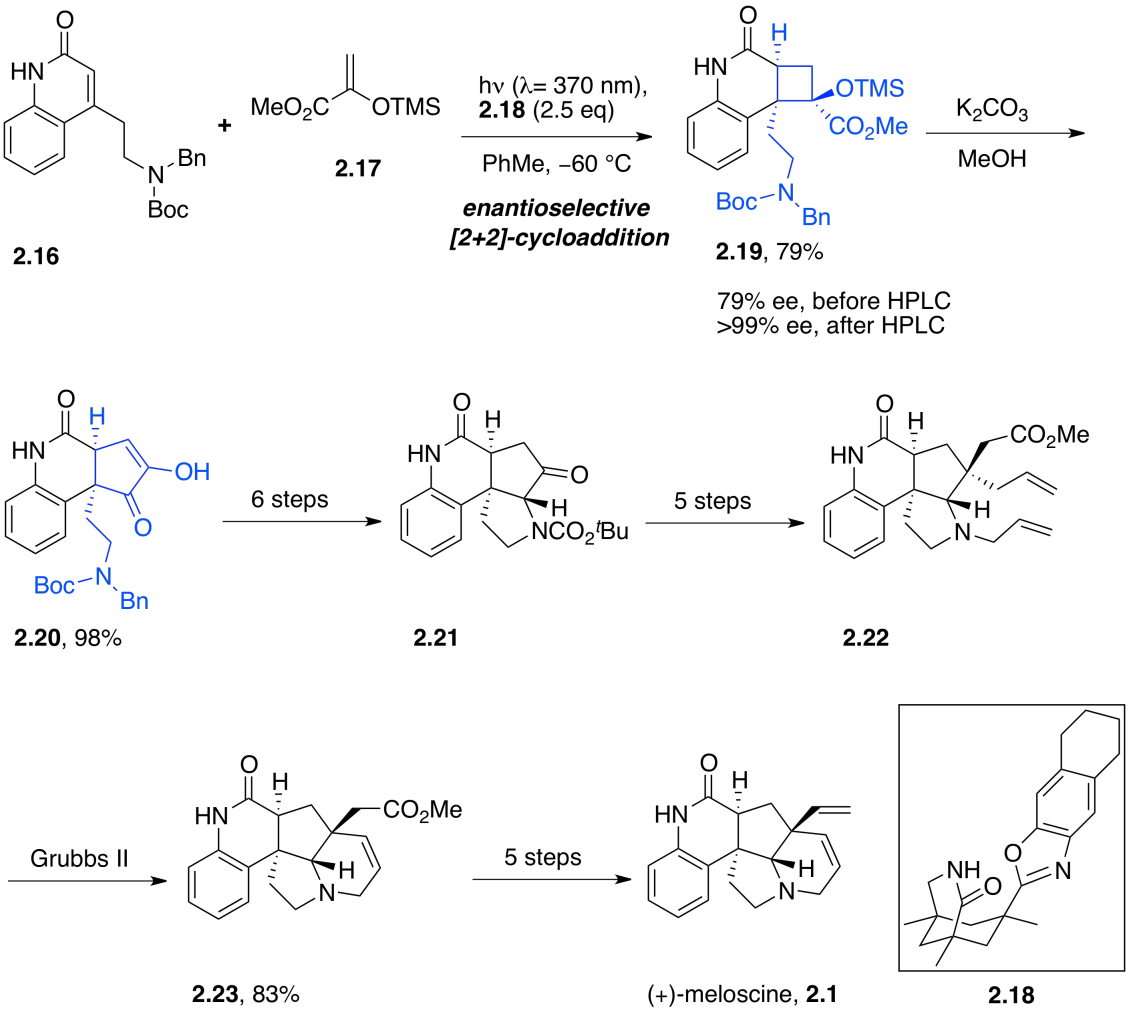
diastereomer was elaborated over 4 steps to produce (±)-meloscine **2.15a**. (±)-Epimeloscine **2.15b** was obtained along the way from the minor diastereomer.




**Scheme 2.2** Summary of Overman's Synthesis of (±)-Meloscine and (±)-Epimeloscine

In 2008, Bach reported an enantioselective synthesis of (+)-meloscine (**Scheme 2.3**).[65] This elegant synthesis highlighted several novel transformations including: 1) a highly enantioselective [2+2] cycloaddition of quinolone **2.16** with enol-ether **2.17**, and 2) a subsequent ring expansion of the cycloaddition product **2.19**. These two reactions set up the A,B,C ring system in **2.20** with the desired absolute stereochemistry. Diketone **2.20** was then converted into

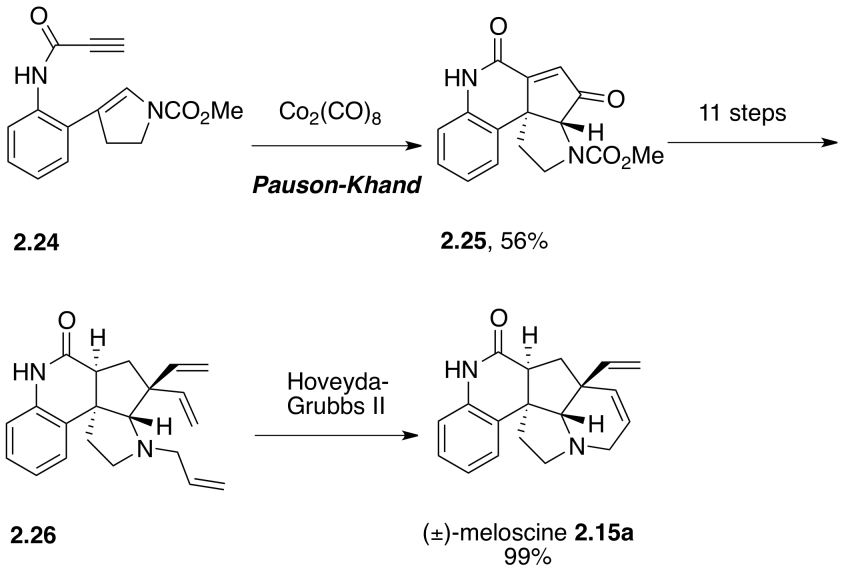
tetracyclic intermediate **2.21** by reductive amination. Further elaboration of **2.21** provided diene **2.22**, which underwent RCM to form the E ring of (+)-meloscine **2.1**.




**Scheme 2.3** Summary of Bach's Synthesis of (+)-Meloscine

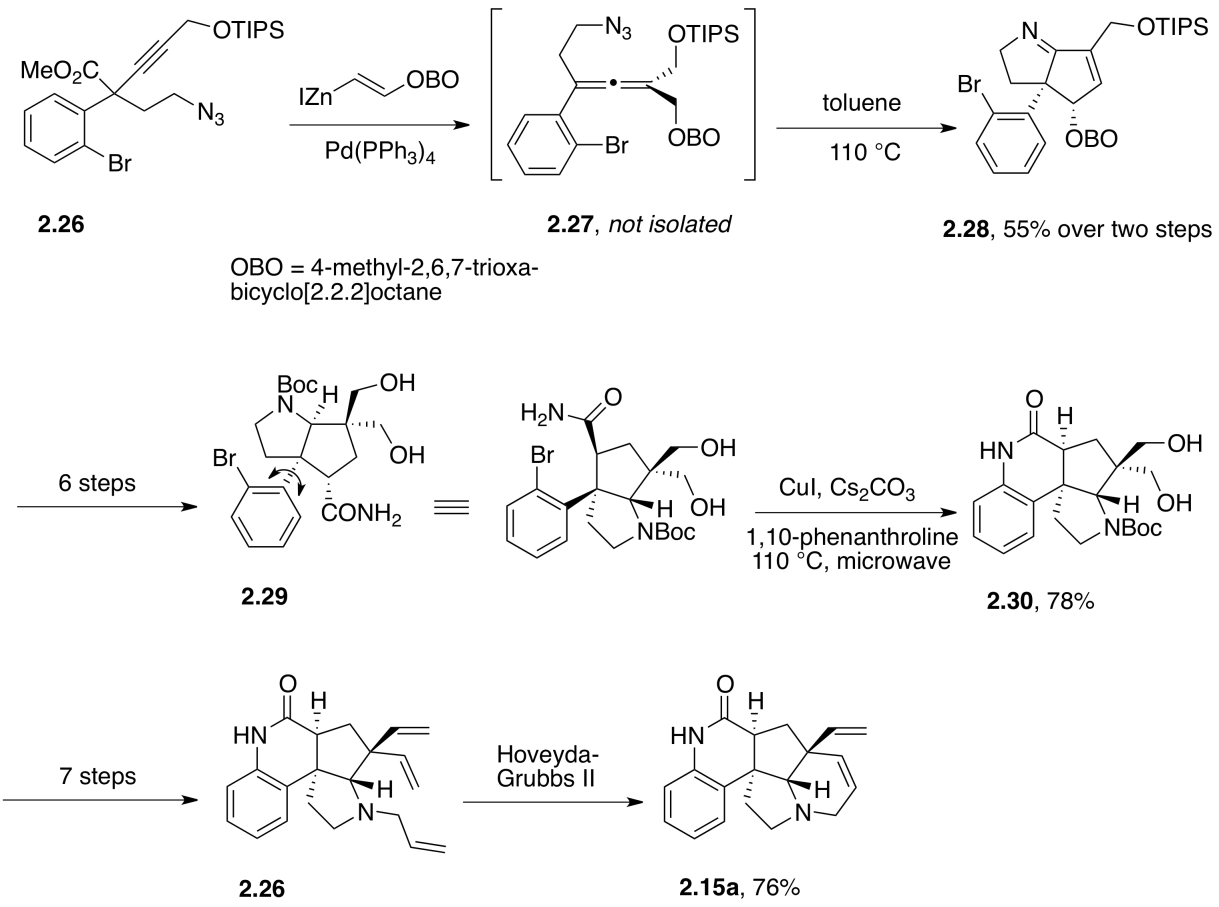
In a synthesis of (±)-meloscine that appeareared during our work, Mukai efficiently constructed the A,B,C,D ring system via an intramolecular Pauson-Khand reaction of propiolamide **2.24**.[66] The E ring was then installed by a RCM reaction of symmetrical triene **2.25** with complete stereocontrol (**Scheme 2.4**). Although the Bach and Mukai syntheses are very

different, they share a general feature. That is, they efficiently make the A,B,C,D ring system, but then use more than ten steps to make ring E.



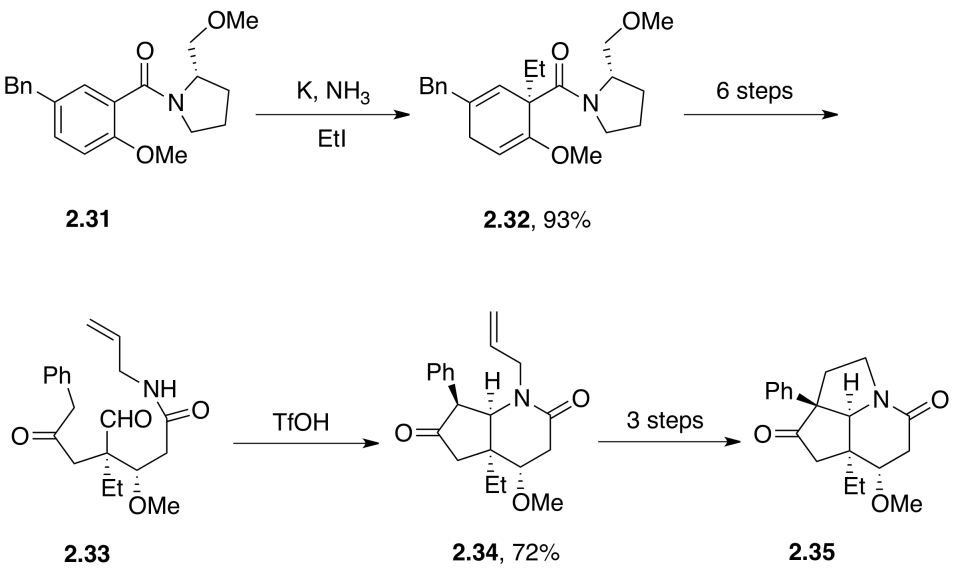

**Scheme 2.4** Summary of Mukai's Synthesis of (±)-Meloscine

Most recently, the Feldman group reported a total synthesis of (±)-meloscine by using the allene-azide-cycloaddition chemistry (**Scheme 2.5**).[67] One of the pivotal steps was the thermolysis of *in situ* generated allene **2.27**, which led to bicyclic imine **2.28** in 55% yield. The lactam ring of tetracycle **2.30** was later formed via microwave assisted Goldberg-type coupling of aryl bromide **2.29**. Finally, ring-closing metathesis of triene **2.26** in the manner of Mukai's synthesis completed the molecule. Prior to the publication of Mukai's synthesis, we independently designed and executed a similar RCM reaction for our synthesis of (±)-epimeloscine and (±)-meloscine.



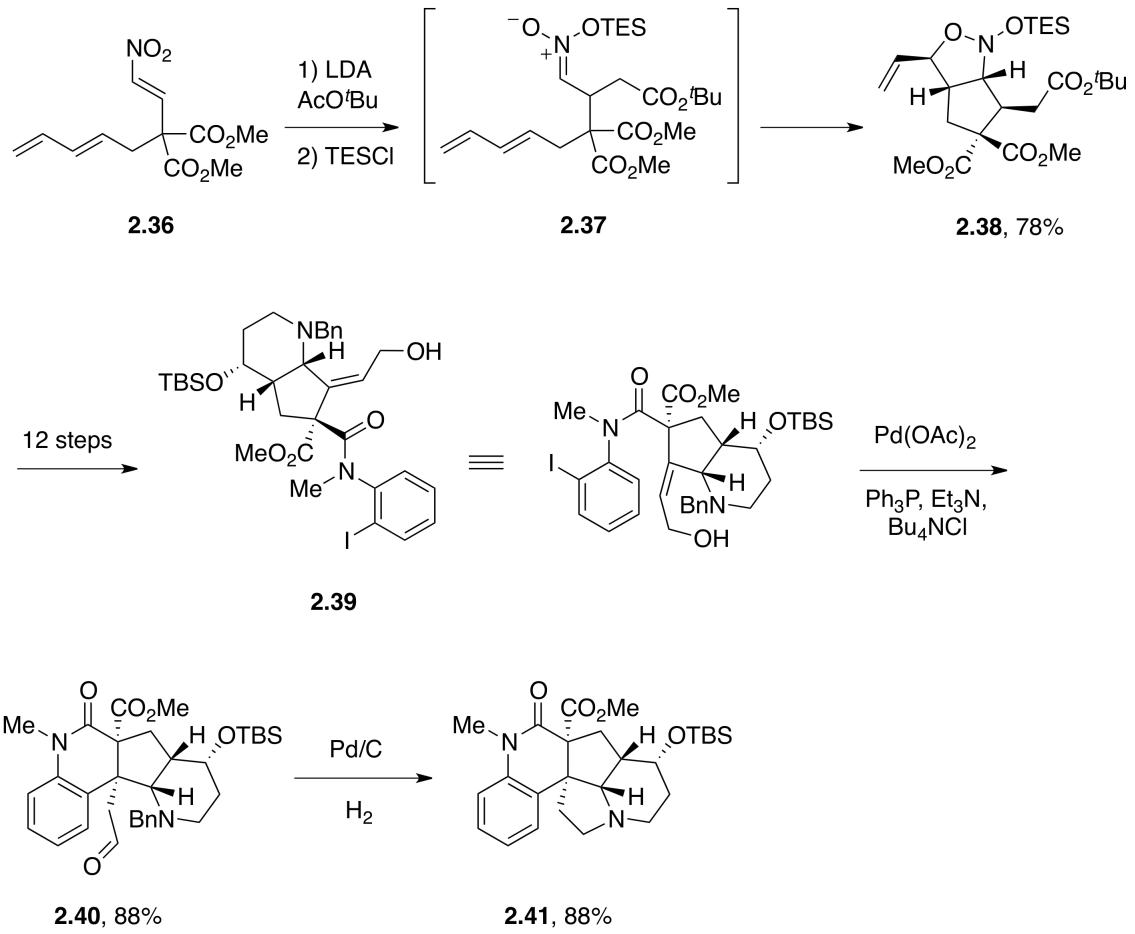

**Scheme 2.5** Summary of Feldman's Synthesis of (±)-Meloscine

In addition to these total syntheses, several interesting synthetic routes have been developed to construct the melodan core.[68] In 1999, Schultz reported an asymmetric route to the B,C,D core structure of scandine based on a tandem intramolecular Mannich/aldol reaction (**Scheme 2.6**).[68b] Reductive alkylation of enentioenriched aromatic amide **2.31** forged 1,4-hexadiene **2.32** in 93% yield, with the establishment of an essential stereogenic quaternary center. Stereochemical relay during the ensuing 6 transformations gave acyclic precursor **2.33**. Subsequently, a tandem Mannich/Aldol reaction smoothly converted acyclic precursor **2.33** to bicyclic amide **2.34** in 72% yield, which was elaborated into tricyclic compound **2.35** over 3 steps.



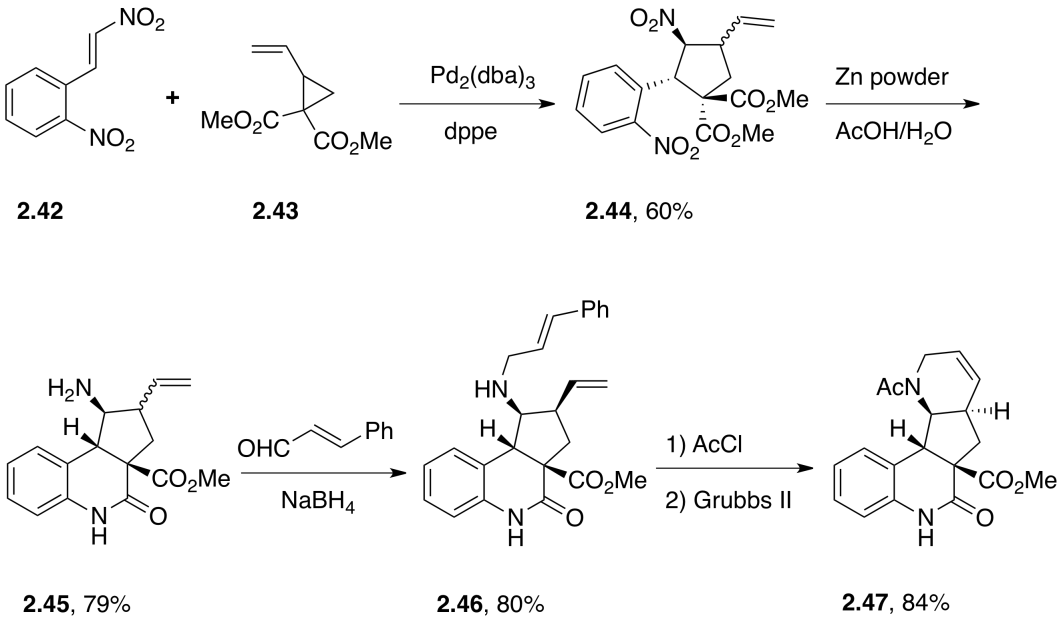

**Scheme 2.6** Schultz's Synthesis of a Tricyclic Core of Scandine

In 2003, Denmark reported an elegant synthesis of the pentacyclic core of scandine by using a tandem conjugate addition/cycloaddition reaction (**Scheme 2.7**).[68a] In the key reaction, conjugate addition of *tert*-butyl acetate enolate to nitroalkene **2.36**, followed by quenching with TESCl, produced **2.37**. This intermediate then underwent intramolecular [3+2] cycloaddition to give silyl nitroso acetal **2.38** in 78% yield. This product was converted to *ortho*-iodoanilide **2.39** in 12 steps. Intramolecular Heck reaction of **2.39** generated the lactam ring (B ring), providing tetracycle **2.40** in 88% yield. The pyrrolidine ring (D ring) was subsequently furnished by a reductive amination of **2.40**, giving pentacycle **2.41** in 88% yield.




**Scheme 2.7** Denmark's Synthesis of a Pentacyclic Core of Scandine

Most recently, an innovative approach towards the core structure of scandine was disclosed by Stoltz (**Scheme 2.8**).[68c] Palladium-catalyzed [3+2] addition of vinylcyclopropane **2.43** and β,2-dinitrostyrene **2.42** rapidly assembled the highly substituted cyclopentane ring of **2.44**. This dinitro-intermediate was reduced by zinc powder to give tricyclic amine **2.45** in 79% yield, which underwent reductive amination with cinnamyl aldehyde to produce diene **2.46** in 80% yield. This product was first protected with acetyl group and then treated with Grubbs II catalyst, affording tetracycle **2.47** in 84% yield.



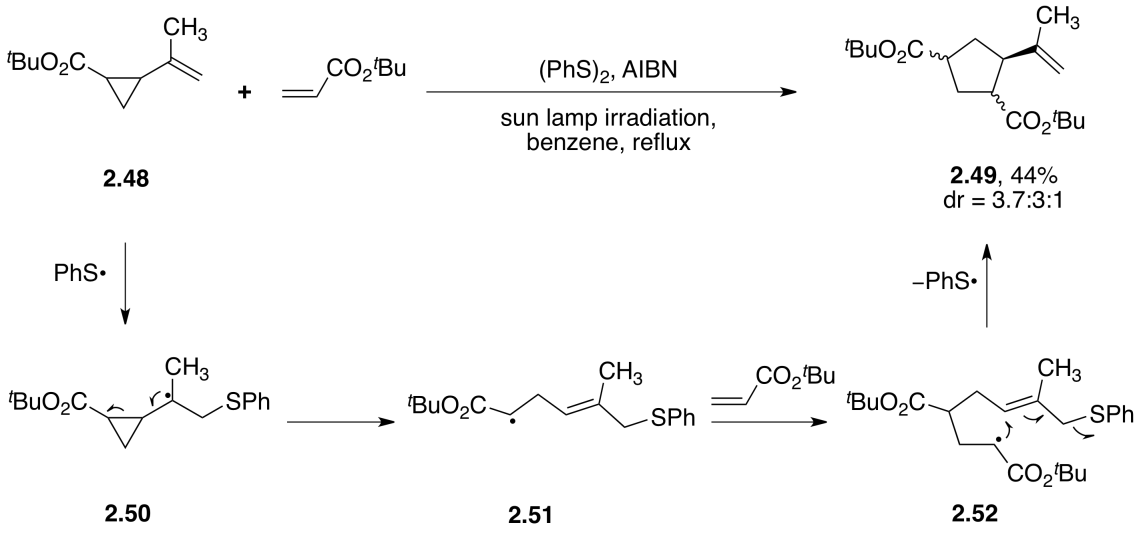

**Scheme 2.8** Stoltz's Synthesis of a Tetracyclic Core of Scandine

### 2.1.3 Radical [3+2] Annulation Reaction of Vinylcyclopropanes and Alkenes

Vinylcyclopropanes (VCPs) are an important class of building blocks in organic synthesis. The inherent ring strain of VCPs, as well as their bent HOMO that tends to conjugate with the double bond,[69] enable rich chemistry of VCPs.[70] The remarkable reactivities of VCPs can be illustrated by a variety of rearrangement,[70b, 71] cycloaddition,[72] and annulation reactions[73] mediated by transition-metals, thermolysis, and external free radical sources. From the standpoint of atom- and step-economy,[74] cycloaddition of a VCP with a synthon containing a multiple bond represents a powerful approach towards five-membered carbocycles and heterocycles. For example, a cyclopentane can be accessed via [3+2] cycloaddition of a VCP and an alkene. Nonetheless, there are only scattered examples of transition-metal-catalyzed [3+2] cycloaddition of VCPs and two-carbon synthons,[70a, 72a, 75] despite of the extensive documentation of the [5+2] counterpart.[70a, 72c, d, 76] The reported, transition-metal catalyzed [3+2]-cycloaddition

methodologies have a relatively limited substrate scope.[72a, 75c, d] In addition, thermal activation of such process remains unexplored.

Radical mediated, formal [3+2] vinylcyclopropane cycloaddition, on the other hand, has offered great opportunities on the synthesis of highly substituted cyclopentanes.[73] In 1986, Feldman reported remarkable examples of thiol- or selenyl-radical mediated annulation reaction of vinylcyclopropanes and dioxygen to give dioxolanes.[77] Following this seminal work, Feldman and Oshima reported related annulation reactions between vinylcyclopropanes and two-carbon synthons.[73, 78] For example, treatment of vinylcyclopropane **2.48** and *tert*-butyl acrylate with diphenyl disulfide and AIBN under irradiation condition produced a diastereomeric mixture of cyclopentane **2.49** in a combined yield of 44% (**Scheme 2.9**).[73a]

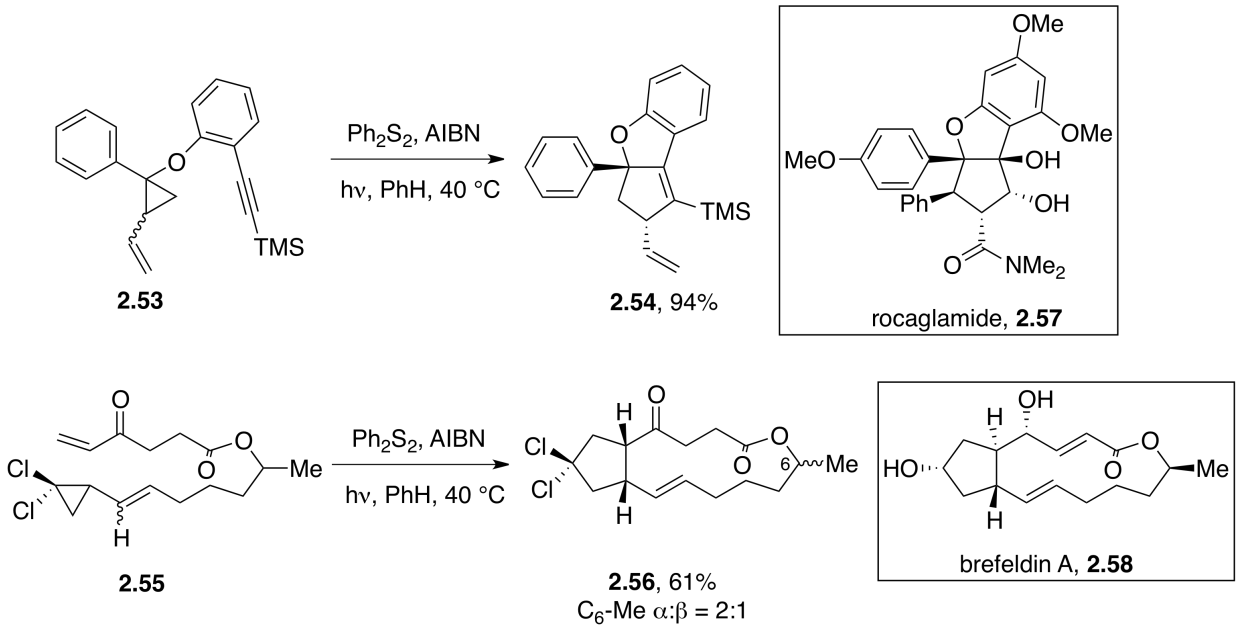



**Scheme 2.9** Radical [3+2] Annulation of a Vinylcyclopropane and an Alkene

Mechanistically, addition of phenylthiol radical to vinylcyclopropane **2.48** generates **2.50**, which undergoes irreversible β-scission to give a new radical **2.51** that is stabilized by the adjacent ester group. Addition of this radical to *tert*-butyl acrylate produces radical **2.52** that

cyclizes to provide a new radical (not shown). This radical collapses to form cyclopentane **2.49** and regenerates a phenylthiol radical.

The application of radical [3+2] vinylcyclopropane annulation to natural product total synthesis is a promising but underdeveloped area. In 1991, Feldman reported model studies of (±)-rocaglamide **2.57** via an intramolecular, radical [3+2] annulation of vinylcyclopropane-yne **2.53** (**Scheme 2.10**).[79] A few years later, Feldman demonstrated the utility of this methodology in the synthesis of brefeldin scaffold **2.56**, in which a vinylcyclopentane motif was embedded in a macrocyclic structure.[80] As far as we know, no natural product has yet been synthesized by radical [3+2] vinylcyclopropane annulation.




**Scheme 2.10** Feldman's Syntheses of the Core Structures of (±)-Rocaglamide and (±)-Brefeldin A

## 2.2 TOTAL SYNTHESIS OF (±)-EPIMELOSCINE AND (±)-MELOSCINE

### 2.2.1 Synthesis Plan

Our retrosynthetic analysis for meloscine is outlined in **Figure 17**. We plan to close the E ring by using a diastereotopic group-selective RCM reaction on tetracyclic triene intermediate **2.59** in the final step. Presumably, the ring closure will be biased towards the α-vinyl group of the cyclopentane ring (**C**), which is closer to the *N*-allyl group than the β-vinyl group. Both Mukai and Feldman independently devised a very similar, late-stage RCM strategy in their syntheses of (±)-meloscine,[66-67] and Mukai published his synthesis soon after we completed the synthesis of (±)-epimeloscine and (±)-meloscine.[66]

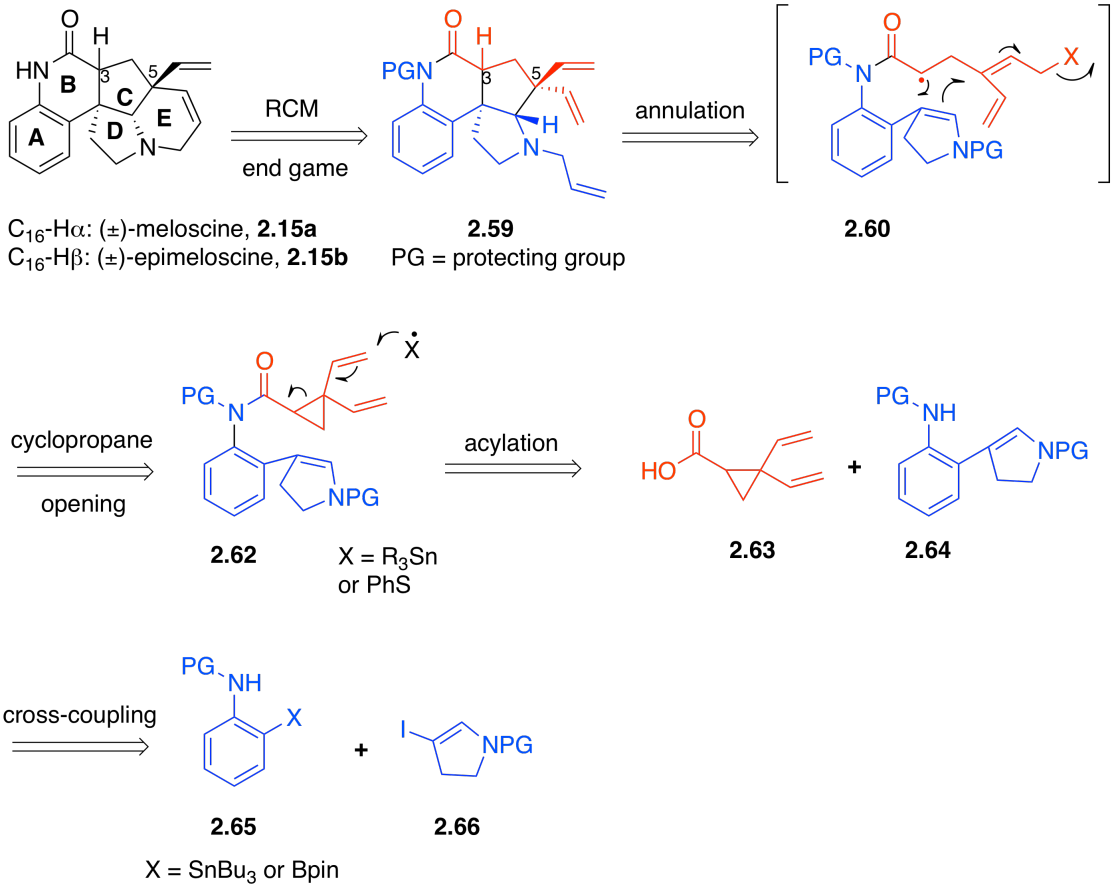



**Figure 17** Retrosynthetic Analysis of (±)-Meloscine

Recognizing the problem of late introduction of the vinyl group at C-5 quaternary carbon in both Bach's and Mukai's syntheses, we envisioned that a cascade radical annulation of a divinylcyclopropane **2.62** will forge the B,C of the A,B,C,D rings with the requisite geminal vinyl groups in a single step. In the design, we propose that a trialklytin or thiol radical will first attack one of the two vinyl groups on the cyclopropane ring with rapid ring opening, releasing the ring strain to form intermediate α-amidoyl radical **2.60**.[80] Subsequent tandem 6-*exo-trig*/5-*exo-trig* cyclization followed by β-scission of the tributyltin/thiol radical will generate target divinylcyclopentane **2.59**. The stereochemical outcome of the tandem cyclization will be dictated by the first 6-*exo-trig* cyclization because the second 5-*exo-trig* cyclization must generate a *cis*-

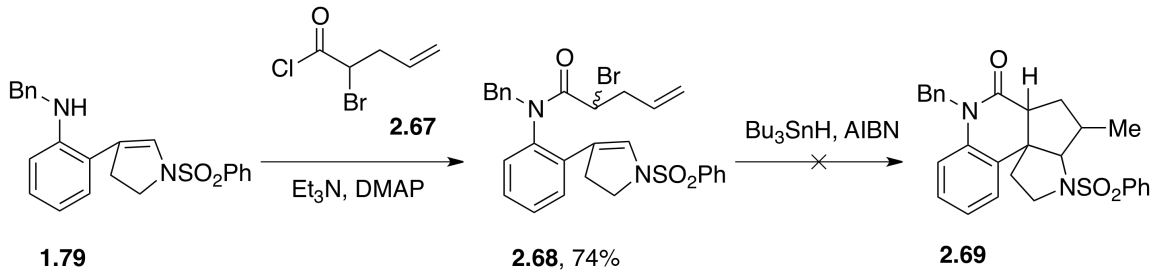
fused [5,5] ring system.[23a] The diastereoselectivity of the 6-*exo*-*trig* cyclization is uncertain because a new quaternary stereogenic center at the junction of B/C rings is formed. However, both stereoisomers are interesting because one of them is the core structure of meloscine and the other is the core structure of *epi*-meloscine. Even though there are no examples of radical reactions of 1,1'-divinylcyclopropanes, precedents of radical [3+2] annulation of monovinylcyclopropanes[73, 79] and our studies on radical cyclization of *ortho*-alkenyl anilides[21] support the viability of this approach.

Annulation precursor **2.62** will be formed by amide coupling of divinylcyclopropinoic acid **2.63** with aniline **2.64**. Previous syntheses of 3-aryl-$\delta_2$-pyrrolines like **2.64** are limited to substrates with carbamate groups on the dihydropyrrole nitrogen.[39] To synthesize sulfonamide analogs of **2.64** that served our studies of *N*-sulfonyl elimination, we discovered a Stille-coupling route that requires arylstannane **1.67** and vinyl iodide **1.74** (**Section 1.2.1**, **Scheme 1.19**). Therefore, we anticipate that aniline **2.64** will be provided by cross-coupling of arylstannane or arylboronic ester **2.65** with vinyl iodide **2.66**.

The synthesis and reactivity of 1,1'-divinylcyclopropanes remain unexplored, despite of extensive synthetic studies on the mono-vinyl and 1,2-divinyl counterparts.[70-71, 81] To our knowledge, thermal isomerization to vinylcyclopentene is the only known reaction of 1,1'-divinylcyclopropane.[82] We foresaw two challenges for the synthesis of divinylcyclopropane **2.63**. First, we were concerned about the thermodynamic stability of **2.63** and related intermediates because thermal rearrangements of vinylcyclopropanes are well documented.[70b, 71, 81b] Second, it is difficult to directly incorporate the geminal vinyl groups onto the cyclopropane ring by cyclopropanation reactions. In **Section 2.2.3**, we describe our discoveries of a scalable route towards building block **2.63**.

### 2.2.2 Construction of a Tetracyclic Core of (±)-Epimeloscine

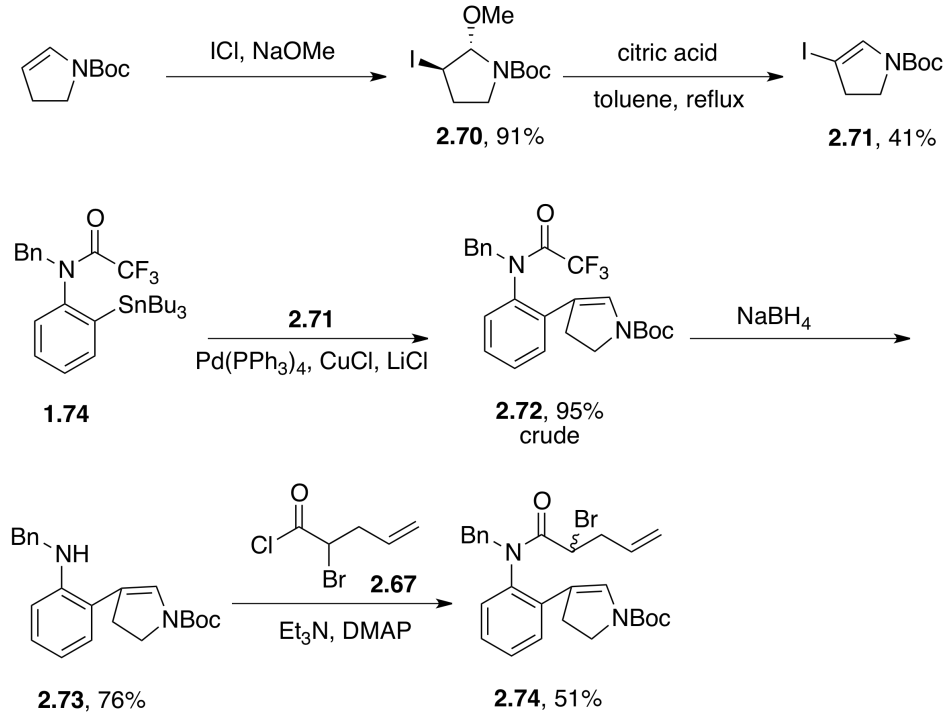
Having validated the feasibility of the first 6-*exo*-*trig* radical cyclization in our proposed cascade annulation event (**Scheme 1.21**), we set out to study the tandem cyclization of a model substrate **2.68** that would provide tetracycle **2.69**, a simplified A,B,C,D ring system of meloscine alkaloids. **Scheme 2.11** illustrates the synthesis of tandem precursor **2.68**. *N*-Benzyl aniline **1.79** was synthesized by Stille coupling, as described in **Section 1.2.1**. Racemic 2-bromo-4-butenoic acid was prepared according to known procedures.[83] Reaction of this acid with oxalyl chloride generated acid chloride **2.67**, which was added to a solution of **1.79** and $Et_3N$ in $CH_2Cl_2$, producing amide **2.68** 74% yield. This product is a 1.5:1 mixture of inseparable diastereomers because it has both an axis of chirality (the *N*-Ar bond) and a stereogenic center. Reaction of **2.68** with AIBN and $Bu_3SnH$ only produced a complex mixture without any major product identifiable by TLC or $^1H$ NMR.




**Scheme 2.11** Attempted Tandem Cyclization of Sulfonamide **2.68**

As mentioned earlier, an electron-withdrawing protective group is preferred, so we synthesized *N*-Boc protected precursor **2.74** in a similar manner of its sulfonamide analog **2.69** (**Scheme 2.12**). A mixture of sodium methoxide and commercially available *N*-Boc-2,3-dihydropyrrole was treated with iodine monochloride to provide hemiaminal ether **2.70** in 91% yield. This product was then heated with 3 equiv of citric acid in refluxing toluene to afford vinyl

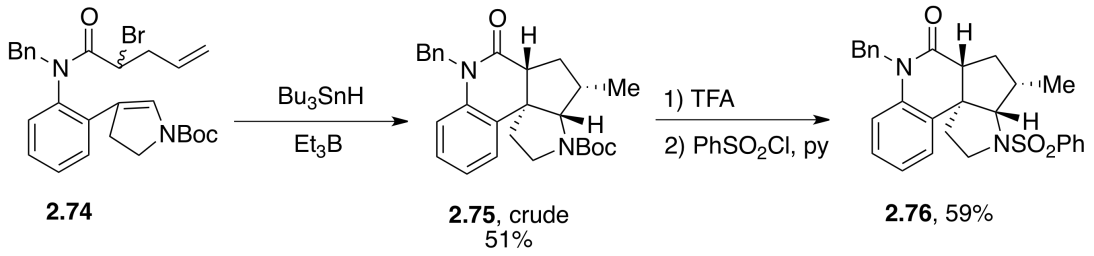
iodide **2.71** in 41% yield. Under Corey's conditions,[48] Stille-coupling of vinyl iodide **2.71** with arylstannane **1.74** at room temperature furnished bicyclic heterocycle **2.72** in 95% yield. Reductive cleavage of the trifluoroacetyl group with $NaBH_4$ generated aniline **2.73** in 76% yield. Finally, acylation of **2.73** with *in situ* prepared acid chloride **2.67** produced target precursor **2.74** in 51% yield. The $^1H$ NMR spectrum of **2.74** was even more complicated than that of *N*-sulfonyl precursor **2.68** due to the existence of carbamate rotamers. Despite the complex NMR spectrum, **2.74** was pure by TLC, and its structural assignment was supported by HRMS.




**Scheme 2.12** Synthesis of Carbamate Precursor **2.74** of the Tandem Radical Cyclization

Substrate **2.74** was reacted with $Et_3B$ and $Bu_3SnH$, and tetracyclic product **2.75** was isolated as a single stereoisomer in 51% yield after column chromatography (**Scheme 2.13**). We did not observe appreciable amounts of UV-active side products by TLC analysis. The molecular weight of **2.75** is determined to be 432.2422 by HRMS (EI), and this was in line with the

calculated molecular weight of 432.2413 $[M]^+$. Even though the $^1H$ NMR spectrum of **2.75** was complicated by minor impurities in the upfield region, the proposed structure was evidenced by the absence of vinyl protons in the $^1H$ NMR spectrum, as well as a distinct doublet at δ 1.04 ppm attributed to the methyl signal on the cyclopentane ring. Aside from these features, most of $^1H$ NMR signals come in pairs, presumably due to the presence of *N*-Boc rotamers.




**2.74** **2.75**, crude 51% **2.76**, 59%

**Scheme 2.13** Cyclization of **2.74** and Conversion of Carbamate **2.75** to Sulfonamide Analog **2.76**

To remove the complications caused by the *N*-Boc group, carbamate **2.75** was treated with TFA, and the resulting crude amine was protected with $PhSO_2Cl$ to provide sulfonamide **2.76** in 59% yield over two steps. The complete structure of this compound was unambiguously solved with the aid of 1D and 2D NMR spectroscopy, HRMS, and single crystal crystallography. As shown in the ORTEP structure (**Figure 18**), the first 6-*exo*-*trig* cyclization generated the stereochemistry of B/C ring fusion of epimeloscine **2.15b**. The C/D ring fusion is *cis*, as predicted. Moreover, the second 5-*exo*-*trig* cyclization forged the cyclopentane ring with a methyl group *syn* to the pyrrolidine ring, as predicted by the Beckwith-Houk model.[23b, 84] In the proposed synthesis of meloscine, however, this stereochemical outcome is a minor point because of the presence of two symmetrical vinyl groups. This successful model of tandem cyclization encouraged us to undertake the synthesis of meloscine alkaloids.

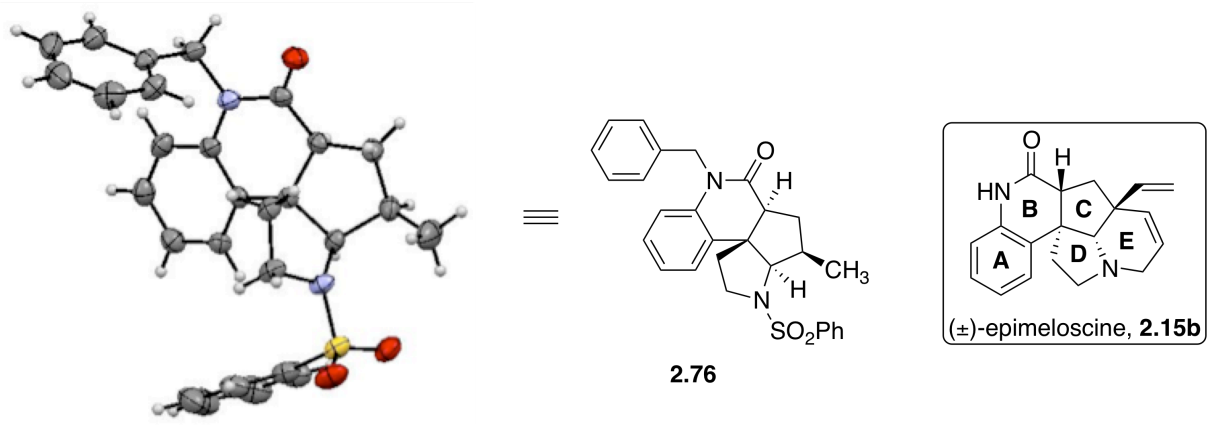



**Figure 18** ORTEP Structure of Tetracyclic Sulfonamide **2.76**

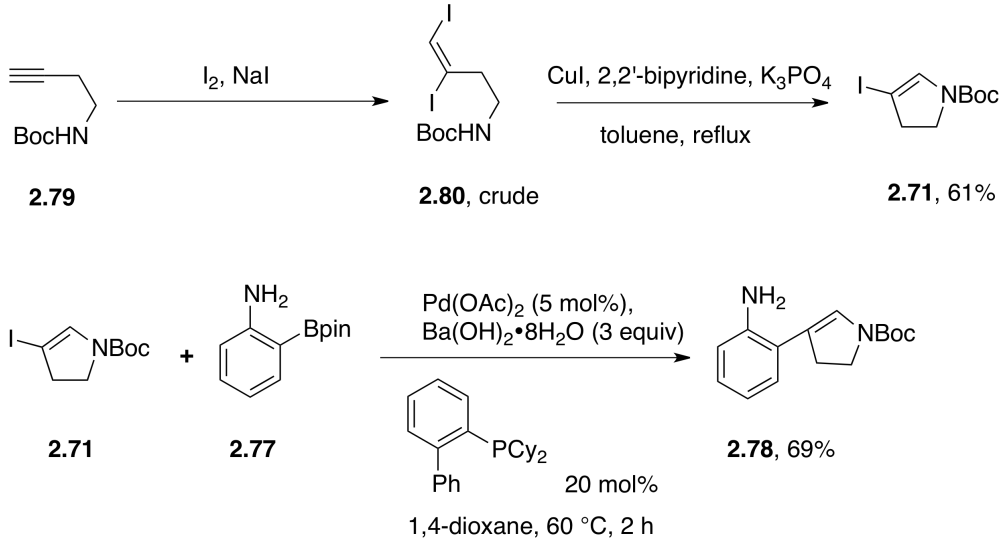
### 2.2.3 Synthesis of the Dihydropyrrole Fragment

The Stille-coupling route was successfully applied to the synthesis of sulfonamide **1.78**, as shown in **Section 1.2.1**. Nonetheless, this synthesis involves the use of a toxic arylstannane **1.74** that required three steps of preparation from 2-iodoaniline. To avoid the use of stannane reagents and to shorten the synthetic sequence, we decided to study the Suzuki-coupling reaction[85] between vinyl iodide **2.71** and commercially available boronic ester **2.77** (**Scheme 2.14**).


**Scheme 2.14** A Suzuki Coupling Route to Bicyclic Carbamate **2.78**

Vinyl iodide **2.71** was originally synthesized via an iodination-demethanolation process from commercially available 2,3-dihydropyrrole (**Scheme 2.12**). However, this process gave only 35% overall yield despite its expediency. In addition, we observed a tendency of diminishing yield upon scale-up. To develop a scalable approach to this key building block, we

looked into a copper-catalyzed 5-*endo*-cyclization reaction that was developed by Jiang.[86] Thus, crude diiodide **2.80** was conveniently prepared by treatment of known but-3-yn-1-ylcarbamate **2.79**[87] with NaI and $I_2$, according to Jiang's procedures (**Scheme 2.15**). Next, cyclization of **2.80** in the presence of CuI, 2,2'-bipyridyl, and $K_3PO_4$ in refluxing toluene furnished the target vinyl iodide **2.71** in 61% overall yield.



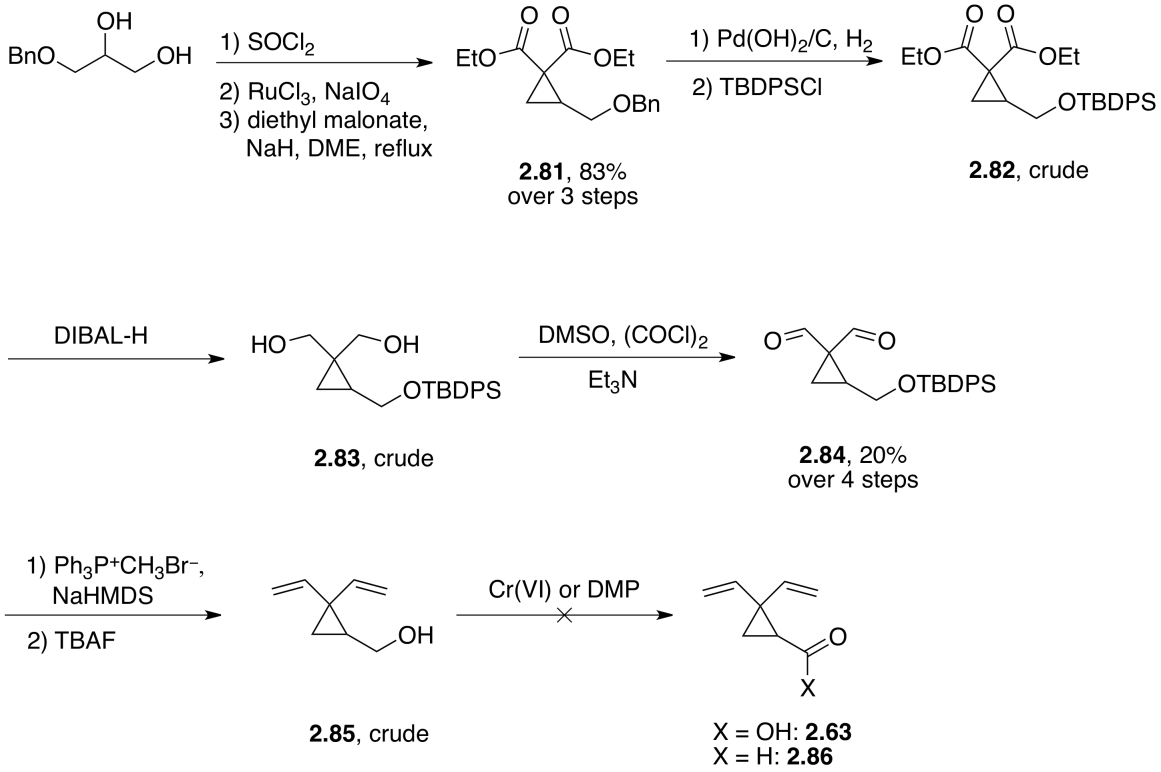

**Scheme 2.15** Improved Synthesis of **2.71** and Suzuki Coupling of **2.71** and **2.77**

There are only a handful of precedents for Suzuki coupling between amino-substituted aryl-boronic ester **2.77** and β-haloenamides.[88] We tested several typical conditions for the Suzuki-coupling reaction between vinyl iodide **2.71** and **2.77**. Heating a mixture of **2.71**, **2.77**, $Pd(PBu_3)_2$ and KO$^t$Bu at 80 °C in *tert*-butanol did not give target product **2.78**. Instead, the target coupling product **2.78** could be obtained in 14% yield when reacting a mixture of **2.71**, **2.77**, $Pd(dppf)_2Cl_2$, and $Na_2CO_3$ in DMF. Replacing $Na_2CO_3$ with $Tl_2CO_3$ increased the yield to 30%. Pleasingly, the use of 5 mol% of $Pd(OAc)_2$, 3 equiv of barium hydroxide octahydrate, and 20 mol% of (2-dicyclohexylphosphino)biaryl ligand further improved the yield of **2.78** to 69%.[88d] This optimized reaction, in combined with the improved synthesis of vinyl iodide **2.71**, enabled a

four-step, multi-gram scale synthesis of aniline **2.78** from commercially available 1-amino-4-butyne (**Chapter 2.5**). Only two column chromatography purifications were required. Aside from its efficiency, this modular process based on cross-coupling underpinned later studies on the divergent synthesis of meloscine analogs (**Chapter 2.3**).

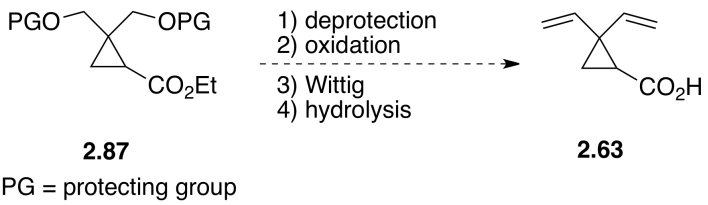
### 2.2.4 Synthesis of the Divinylcyclopropane Fragment

The initially attempted route towards divinylcyclopropane acid **2.63** relied on redox manipulation of known diester **2.81**, which was synthesized in three steps from commercially available 3-benzyloxy-1,2-propanediol (**Scheme 2.16**).[89] Hydrogenolysis of **2.81** with 5% (w/w) of $Pd(OH)_2/C$ in ethanol removed the benzyl group to generate crude alcohol **2.82**. Reaction of this product with TBDPSCl afforded the corresponding silylether, which was then reduced with 6 equiv of DIBAL-H to generate crude diol **2.83**. Swern oxidation of this product afforded dialdehyde **2.84** in 20% yield over 4 steps. Treatment of **2.84** with methyltriphenylphosphonium bromide and NaHMDS gave corresponding crude diene, which reacted with TBAF to generate crude, volatile divinyl alcohol **2.85**. However, the use of several oxidative reagents, including chromium (VI) compounds and Dess-Martin periodinane (DMP),[90] failed to provide acid **2.63** or aldehyde **2.86** in useful yield.



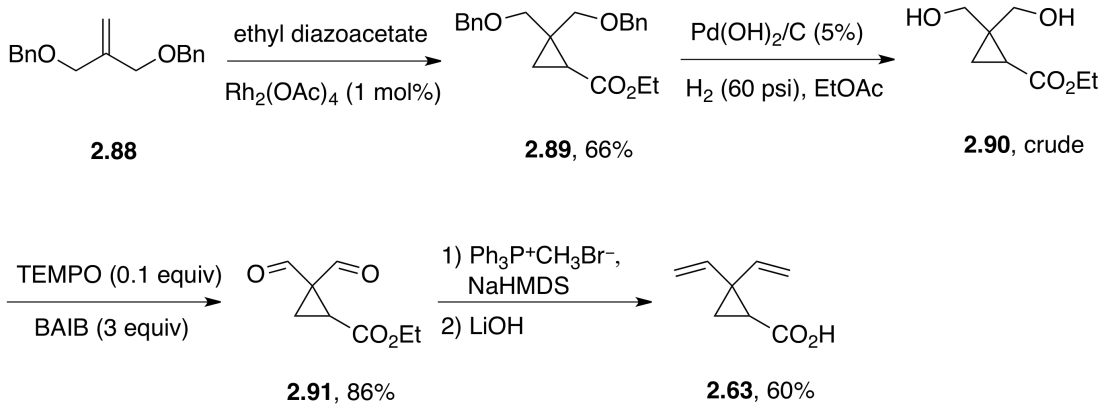

**Scheme 2.16** Attempted Synthesis of Divinylcyclopropane **2.63** from Known Cyclopropane **2.81**

To circumvent late-stage oxidation in the presence of vinyl groups, we chose to synthesize cyclopropane **2.87** because its protected hydroxyl groups could be elaborated into geminal vinyl groups (**Scheme 2.17**). However, preliminary studies suggested that when TBS was used as the protecting group for **2.87**, lactonization occurred under both basic and acidic desilylation conditions. To avoid the use of acid and base in the deprotection reaction of **2.87**, we chose benzyl as the protecting group for **2.87** because it can be removed under neutral hydrogenolysis conditions.




**Scheme 2.17** Proposed Synthesis of **2.63** from Protected Diol **2.87**

**Scheme 2.18** shows the application of this strategy to a successful synthesis of divinylcyclopropane acid **2.63**. Slow addition of ethyl diazoacetate to a mixture of known *bis*-benzyl ether **2.88**[91] and of rhodium acetate dimer (1 mol%) gave cyclopropane **2.89** in 69% yield. Both benzyl groups were removed by using 4% (w/w) $Pd(OH)_2/C$ under 60 psi $H_2$ without any detectable lactone formation. Ethanol was initially used as the solvent for the hydrogenolysis. Because it was difficult to remove ethanol from crude diol **2.90**, a large excess of oxidant (4.5–7 equiv) was required to achieve high conversion of **2.90** in the subsequent oxidation reaction. Ethyl acetate was found a better solvent for the hydrogenolysis reaction because, unlike ethanol, residual ethyl acetate does not impede the next oxidation reaction. Subsequently, crude diol **2.90** was treated with 0.1 equiv of TEMPO and 3 equiv of iodobenzene diacetate (BAIB) to generate dialdehyde **2.91** in 86% yield over two steps. This product was then added to a pre-mixed solution of methyltriphenylphosphonium bromide and KHMDS, providing the corresponding divinylcyclopropane ester. Hydrolysis of this product with LiOH furnished the target acid **2.63** in 60% yield over two steps. Multigram-scale synthesis of **2.63** has been realized by this route, which requires only five reactions and three flash chromatography purifications. We were also pleased to find that divinylcyclopropane **2.63** was stable to prolonged storage at –20°C.




**Scheme 2.18** Five-Step Synthesis of Divinylcyclopropane Fragment **2.63**

### 2.2.5 The Cascade Radical Annulation Reaction

Amide bonds have restricted rotation due to their partial double-bond character.[92] In many cases, E/Z rotamers of an amide can be observed by NMR spectroscopy, or even isolated under bench conditions. According to the Curtin-Hammett Principle,[93] divergent reaction pathways can be expected for amide E/Z rotamers when the ongoing reactions are faster than the interconversion between E/Z rotamers. This type of kinetics is especially prevalent in radical reactions because they are generally very fast. Therefore, adoption of correct amide conformation is crucial to the success of intramolecular radical reactions.

To this end, we initially chose *N*-benzyl-protected anilide **2.92** as the annulation precursor. Its ground-state conformation is expected to be predominantly the *E*-rotamer **2.92a**,[11, 94] which is pre-disposed to undergo the annulation reaction (**Figure 19**).[95] Fast cyclopropane ring-opening of **2.92a** generates α-amidoyl radical **2.94a** which leads to the target tetracycle **2.96** by fast radical annulation (productive pathway). Likewise, cyclopropane ring-opening of the disfavored *Z*-rotamer **2.92b** forms α-amidoyl radical **2.92b**, which will not be positioned for the annulation (unproductive pathway). Because the interconversion between radicals **2.92a** and

**2.92b** is slow due to hindered rotation of amide bond, the reaction outcome is ultimately dictated by the ground-state distribution of rotamers **2.92a** and **2.92b**. In this case, the productive reaction pathway is predominant. In contrast, secondary-anilide **2.93** will adopt *Z*-conformation **2.93b**,[11, 94] and the unproductive pathway that does not lead to **2.97** is predominant.

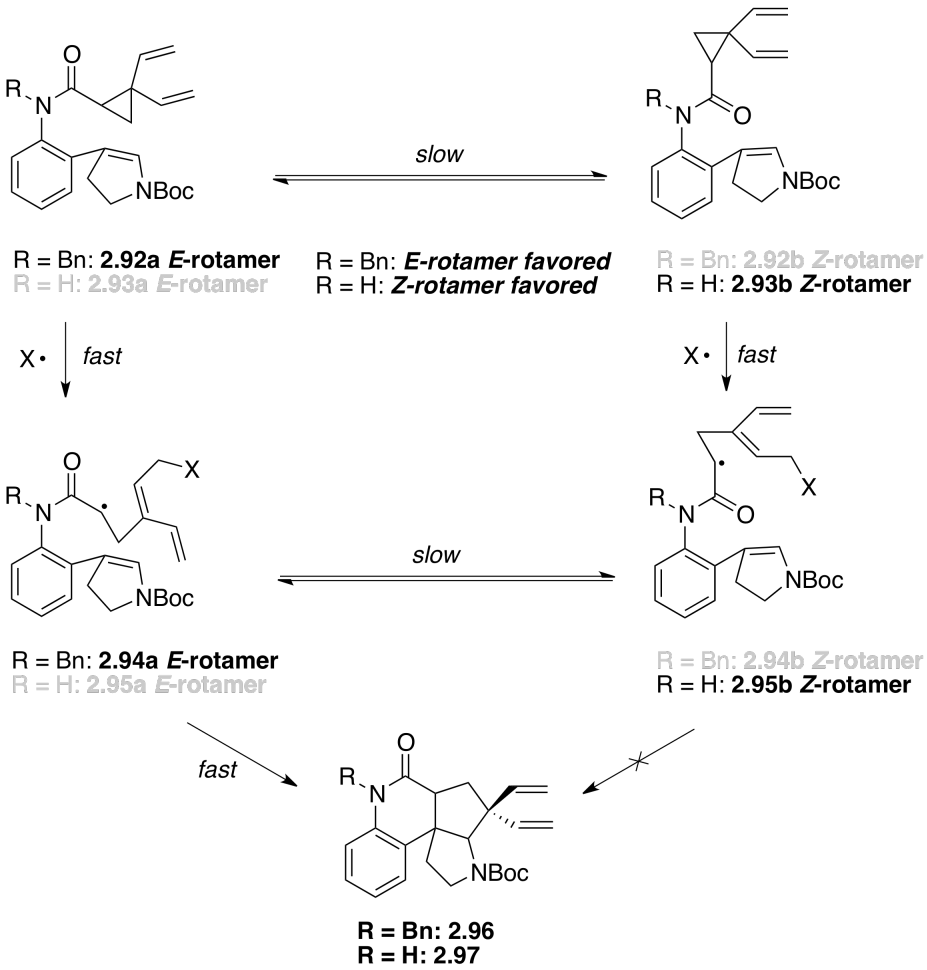
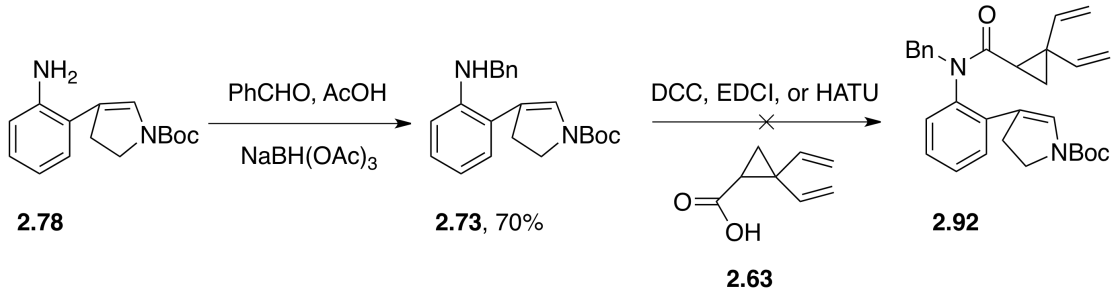



**Figure 19** Reaction Kenetics of Anilides **2.92** and **2.93** under Radical Conditions

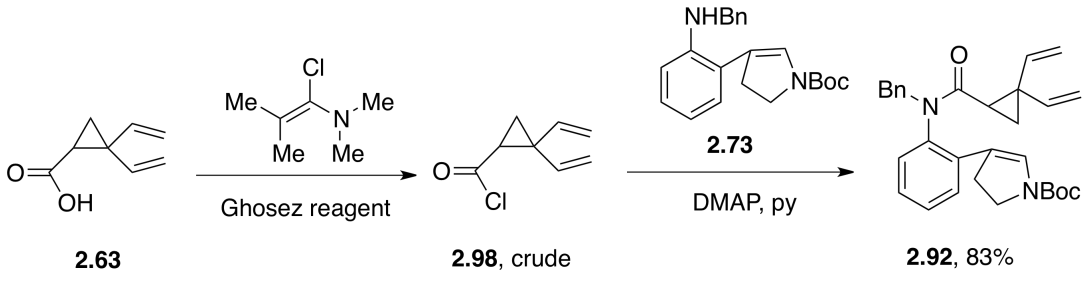
The synthesis of tertiary amide **2.92** required *N*-benzyl aniline **2.73**. This fragment was prepared in 70% yield by reductive amination of **2.78** with benzaldehyde, $NaBH(OAc)_3$, and acetic acid (**Scheme 2.19**).[96] Next, we surveyed several coupling reagents for the amide coupling

reaction of anilinde **2.73** with acid **2.63**. Unfortunately, the use of DCC, EDCI, or HATU failed to generate target amide **2.92**, presumably due to the low nucleophicity of aniline partner **2.73**.




**Scheme 2.19** Attempted Coupling of **2.73** and **2.63**

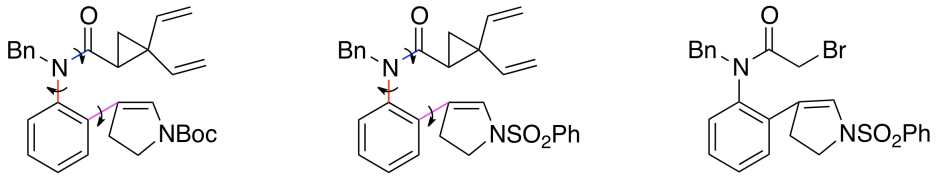
We then turned to conditions that involved activation of acid **2.63** to the corresponding acid chloride **2.98** (**Scheme 2.20**). Reaction of **2.63** with oxalyl chloride gave crude acid chloride **2.98**, which was added to a pre-mixed solution of DMAP, pyridine, and aniline **2.73**. An unknown, polar side-product was isolated by flash chromatography, and target coupling product **2.92** was not detected by TLC or NMR. In another experiment, acid **2.63** reacted with Ghosez reagent (1-chloro-*N*,*N*,2-trimethyl-1-propenylamine)[97] to produce crude acid chloride **2.98**. This product was then transferred to a pre-mixed solution of pyridine, DMAP, and aniline **2.73**. To our delight, amide product **2.92** was isolated in 83% yield after flash chromatography.




**Scheme 2.20** Synthesis of **2.92** by Coupling of **2.73** and Acid Chloride **2.98**

The molecular weight of **2.92** was determined to be 493.2488 by HRMS (EI), and this is in line with the calculated molecular weight of 493.2467 $[M+Na]^+$. In addition, the co-existence of signals of two diastereotopic vinyl groups and dihydropyrrole supported the structural assignment of amide **2.92**.

Like the *N*-Boc-protected model compound **2.74** (**Scheme 2.12**), the existence of multiple rotamers substantially complicated the interpretation of the $^1H$ and $^{13}C$ NMR spectra of **2.92**. To remove the complication caused by the *N*-Boc rotamers, sulfonamide analog **bh.124-38** was prepared and characterized by Mr. E. Ben Hay (**Figure 20**). The presence of only two sets of NMR signals suggested that either of the amide, *N*-aryl, or aryl-vinyl bonds of **bh.124-38** has a reasonably high rotational barrier. We were mostly concerned about whether the doubled signals of **bh.124-38** should be attributed to the amide rotamers because, as stated earlier, the groud-state amide geometry is critical to the ensuing annulation reaction. This concern was eliminated after re-examining the NMR spectra of structurally similar amide **1.64a** that shows only one set of signals. Based on our previous studies of *o*rtho-alkenyl anilides,[20a, 83] we tentatively attributed the doubled NMR signals of **bh.124-38** to the slow rotation of its *N*-aryl bond. By analogy, this conclusion also applies to carbamate **2.92**.



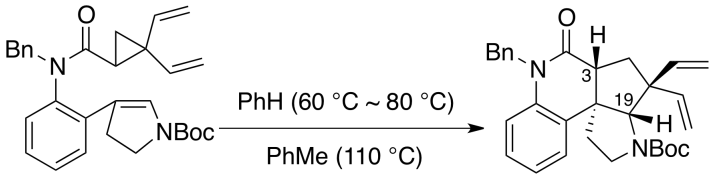

**2.92** **bh.124-38** **1.64a**

**Figure 20** Structures of **2.92** and Its Sulfonamides Analogs **bh.124-38** and **1.64a**

Confident about our structural assignment of amide **2.92**, we examined the pivotal cascade annulation reaction under a series of conditions (**Table 1**). Reactions of **2.92** with

PhSSPh,[73a] *N*-heterocyclic carbene boronodithiolate,[98] $CCl_4$ or TTMSS[99]/AIBN in refluxing benzene or toluene, did not provide a detectable amount of tetracycle **2.96** (entries 1–4). Formation of only a trace amount of **2.96** was observed using tosylcyanide and AIBN (entry 5). Nonetheless, we were excited to find that **2.96** could be obtained in 24% yield by refluxing a solution of substrate **2.92**, AIBN, and $Bu_3SnH$ (0.02 M) in benzene (entry 6). Slow addition of $Bu_3SnH$/AIBN by syringe pump boosted the yield to 41% (entry 7). We then reasoned that a higher temperature would accelerate the interconverion of *E*/*Z* rotamers of precursor **2.92**, thereby further increasing the conversion of **2.92** to **2.96**. Indeed, slow addition of $Bu_3SnH$/AIBN to a refluxing solution of **2.92** in toluene gave **2.96** in 55% yield as a single diastereomer (entry 8). Slow addition of PhSH/AIBN to a refluxing solution of **2.92** in toluene also yielded the target product, but in far lower yield of 22% (entry 9).

**Table 1** Screening of Conditions for the Radical Annulation of **2.92**




**2.92** **2.96**

| entry | conditions | yield |
|---|---|---|
| 1 | PhSSPh, hν, 60 °C | nd. |
| 2 | NHC-$BH(SPh)_2$, hν, 60 °C | nd. |
| 3 | $CCl_4$/$(PhCOO)_2$, slow addition, 110 °C | nd. |
| 4 | TTMSS/AIBN, slow addition, 80 °C | nd. |
| 5 | TsCN/AIBN, slow addition, 80 °C | trace |
| 6 | $Bu_3SnH$/AIBN, 80 °C | 24% |
| 7 | $Bu_3SnH$/AIBN, slow adition, 80 °C | 41% |
| **8** | **$Bu_3SnH$/AIBN, slow adition, 110 °C** | **55%** |
| 9 | PhSH/AIBN, 80 °C | 22% |

The existence of multiple *N*-Boc rotamers once again complicated the $^{1}$H NMR analysis of tetracycle **2.96**. Nonetheless, the assigned structure of **2.96** was supported by several distinctive signals, including: 1) singlets at 4.52 ppm (minor rotamer) and 4.36 ppm (major rotamer) attributed to the $C_{19}H$ adjacent to the *N*-Boc group, and 2) a pair of dd signals at 3.03 ppm (major rotamer) and 2.97 ppm (minor rotamer) attributed to the $C_3H$ adjacent to the amide carbonyl. In addition, HRMS and $^{13}$C NMR results of **2.96** were in line with the proposed structure.

The stereochemistry of **2.96** was unknown at this stage, but was quickly established by a three-step conversion to (±)-*N*-benzyl-epimeloscine **2.100** (**Chapter 2.2.6**). We proposed a transition-state model that accounts for the stereochemical outcome of the annulation reaction (**Figure 21**). Tin radical-mediated ring-opening of DVCP **2.92** produces interconverting radicals **2.Aa** and **2.Ab**, which undergo the first 6-*exo*-*trig* cyclization through transition states **2.Ba** and **2.Bb**. Subsequent 5-*exo*-*trig* cyclization, followed by β-elimination of the tin radical, affords annulated products **2.96** and *epi*-**2.96**. Studies of related systems suggested that the interconversion between **2.Aa** and **2.Ab** is fast compared to the ensuing 6-*exo*-*trig* cyclization.[83] Therefore, the stereochemical outcome of the 6-*exo*-*trig* cyclization is dictated by the relative stability of transition states **2.Ba** and **2.Bb**. Compared to **2.Ba** that leads to tetracycle **2.96**, transition state **2.Bb** is substantially less favored due to the steric repulsion between the large alkyl group R and the dihydropyrrole radical acceptor. Thus, tetracycle *epi*-**2.96** should form as a minor product and, in this case, was not detected.

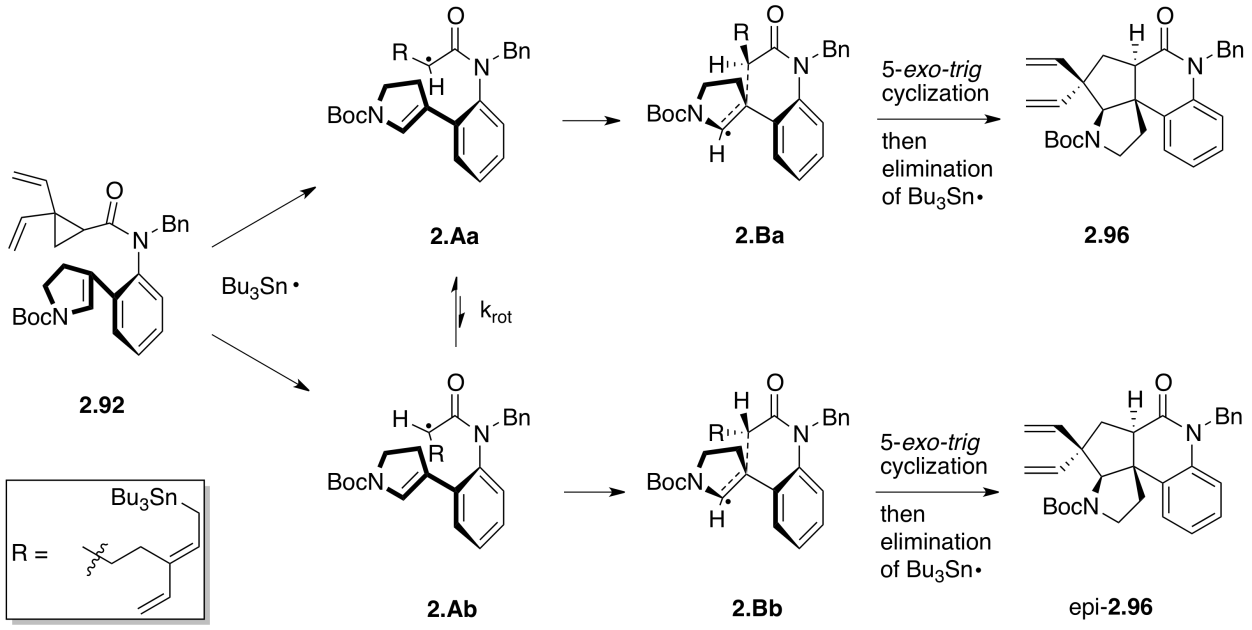
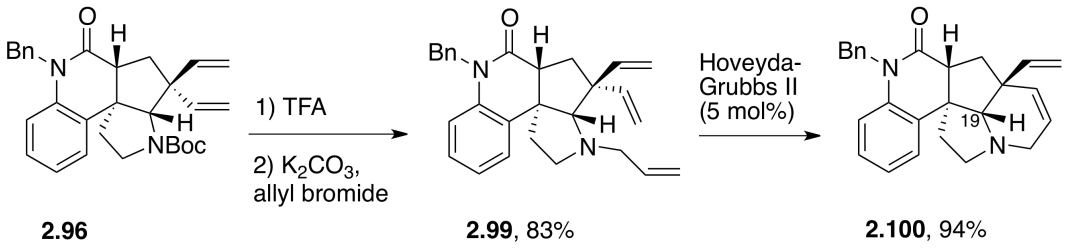



**Figure 21** Proposed Stereochemical Model for the Key Annulation Reaction of **2.92**

### 2.2.6 Completion of the Synthesis

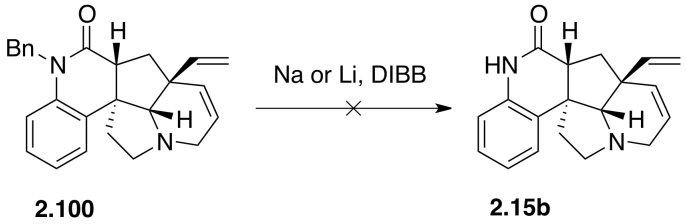
The completion of the synthesis requires installation of *N*-allyl functionality that is necessary for the final ring-closing metathesis. The Boc group of tetracycle **2.96** was removed with a dilute TFA solution in DCM, and allyl bromide was added to the resulting crude amine to provide allylamine **2.99** in 83% yield. Subsequent RCM reaction smoothly proceeded with 5 mol% of the second-generation Hoveyda-Grubbs catalyst,[100] providing benzyl-protected pentacycle **2.100** as the sole product in 94% yield (**Scheme 2.25**).




**Scheme 2.21** Synthesis of *N*-Benzyl-Epimeloscine from Tetracycle **2.96**

The 2D structure of **2.100** was then validated by techniques of HMRS, $^{1}H/^{13}C$ NMR, and $^{1}H$-$^{1}H$ COSY. Although its stereochemistry could not be unambiguously assigned, we found that **2.100** bore considerable spectral resemblance to epimeloscine **2.15b** in terms of chemical shifts. For example, the $C_{19}HN$ groups of both **2.100** and epimeloscine **2.15b** show as singlets at about 4 ppm in $^{1}H$ NMR spectra, whereas the chemical shift of the corresponding singlet in meloscine **2.15a** is 3.52 ppm.[101]

Limited options were available for the removal of the amide benzyl group because harsh conditions are required.[102] Considering the instability of the terminal vinyl groups towards hydrogenolysis conditions, we elected to use single-electron reducing reagents for the final debenzylation reaction of **2.100**.[103] Disappointingly, pilot reactions using sodium or lithium metal with naphthalene or di-*tert*-butylbiphenyl (DBB) only resulted in the formation of complex mixtures (**Scheme 2.22**).

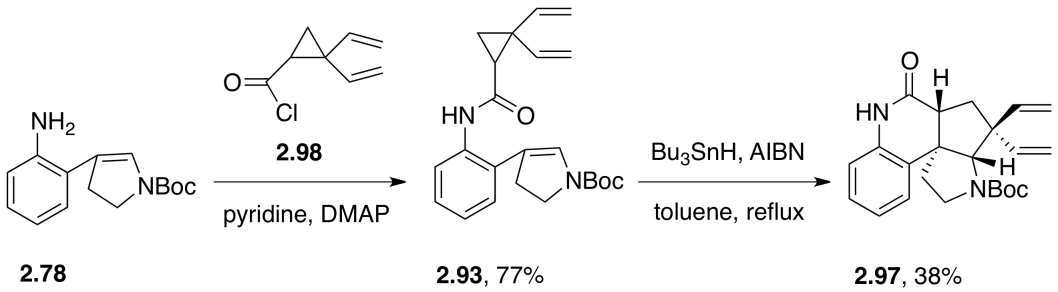



**2.100** **2.15b**

**Scheme 2.22** Unsuccessful Debenzylation of **2.100**

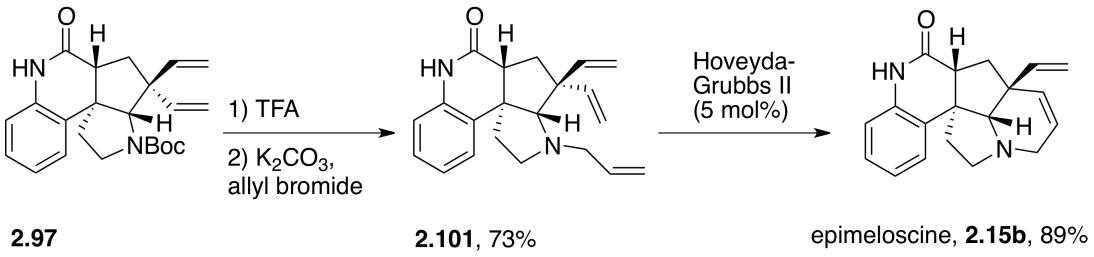
To circumvent the protecting-group manipulation, we decided to attempt the annulation of unprotected amide **2.93** (**Scheme 2.23**). The aforementioned risk of this approach could possibly be outweighed by its step-economy. Thus, secondary anilide precursor **2.93** was easily prepared in 77% yield by acylation of **2.78** with *in situ* prepared acid chloride **2.98**. Gratifyingly, syringe pump addition of $Bu_3SnH$/AIBN to a refluxing solution of **2.93** in toluene provided the

target tetracycle **2.97**, although in low yields ranging from 22% to 38%. This reaction was tested on several different scales (56 mg, 115 mg, 180 mg, and 250 mg), and the best yield (38%) was obtained from a 56 mg scale experiment. Again, the stereochemistry of **2.97** was not immediately established, but was later confirmed by elaboration of **2.97** into (±)-epimeloscine **2.15b** in three steps.



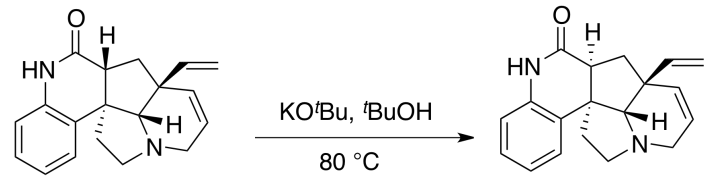

**Scheme 2.23** Synthesis of Tetracycle **2.97** by Radical Annulation of **2.93**

Conversion of tetracycle **2.97** to (±)-epimeloscine **2.15b** was accomplished in the manner of **2.100**. The Boc group of **2.97** was removed by TFA, and the resulting crude amine was allylated to provide the triene **2.101** over two steps in 73% yield. Finally, RCM of this product furnished (±)-epimeloscine **2.15b** as the sole product in 89% yield. $^{1}H$ and $^{13}C$ NMR data of the synthetic sample were identical to those reported.[101] Its structure was also confirmed by HRMS data.




**Scheme 2.24** Completion of the Synthesis of (±)-Epimeloscine

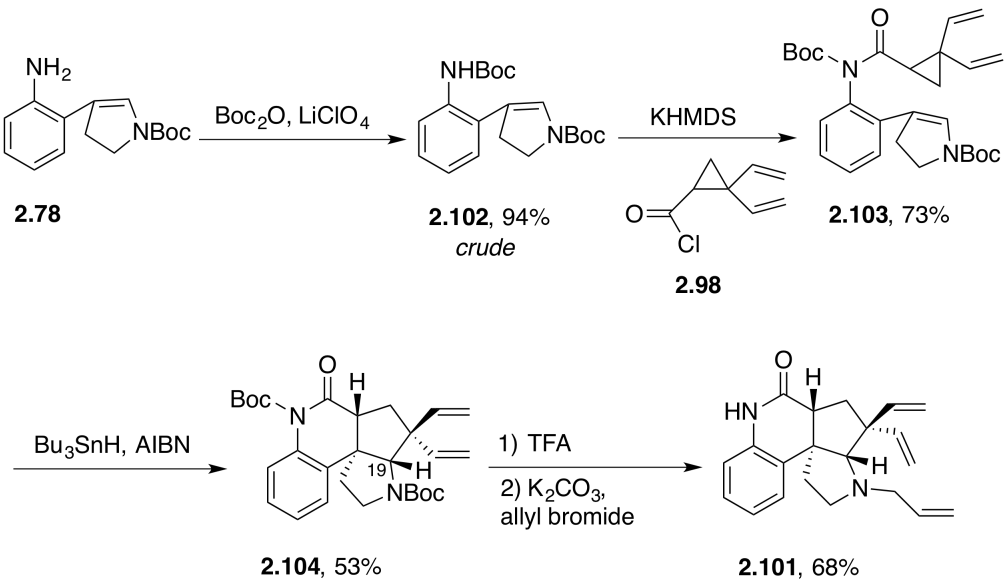
Bernauer demonstrated that epimeloscine undergoes epimerization under basic conditions to provide meloscine exclusively.[101] We repeated this reaction by heating (±)-epimeloscine **2.15b** with two equiv of KO$^t$Bu in *tert*-butanol and obtained (±)-meloscine **2.15a** in 86% yield (**Scheme 2.25**). The $^1$H and $^{13}$C NMR data of synthetic meloscine **2.15a** were consistent with those reported previously.[65-66]




epimeloscine, **2.15b** meloscine, **2.15a**, 86%

**Scheme 2.25** Epimerization of Epimeloscine to Meloscine

The main problem with the synthesis described above is the low-yielding radical annulation of secondary anilide **2.93**. To address this issue, we decided to protect the amide *N*-H with a removable group, which would ensure a favorable amide conformation for the annulation reaction (**Scheme 2.26**).[11, 94] Thus, treatment of **2.78** with $Boc_2O$ and catalytic $LiClO_4$ afforded *bis*-carbamate **2.102** in 94% yield.[104] Deprotonation of **2.102** with KHMDS, followed by quenching the resulting anion with acid chloride **2.98**, furnished *bis*-carbamate **2.103** in 73% yield. Now, annulation of key precursor **2.103** under the syringe pump conditions gave tetracycle **2.104** in 53% yield. This is better than the yield for the annulation of secondary anilide **2.93**, and importantly, the yield of **2.104** is also reproducible.




**Scheme 2.26** Improved Synthesis of Epimeloscine by Annulation of *Bis*-Carbamate **2.103**

The $^{1}$H NMR spectrum of **2.104** was very similar to that of tetracycle **2.97** in terms of chemical shift and peak splitting pattern. In particular, two singlets at 4.47 ppm and 4.32 ppm represents the diagnostic $C_{19}H$ signal of *bis*-carbamate **2.104**, and the corresponding signal of **2.97** is shown as two singlets at 4.50 ppm and 4.35 ppm. This spectral feature, coupled with a two-step conversion of **2.104** into allylamine **2.101**, confirmed the stereochemical assignment of tetracycle **2.104**. Treatment of **2.104** with dilute TFA removed both Boc groups, and the resulting crude amine reacted with allyl bromide to furnish **2.101** in 68% yield over two steps.

To summarize, we have developed an efficient total synthesis of (±)-epimeloscine and (±)-meloscine based on a novel, radical annulation of a divinylcyclopropane.[105] Annulation of N-benzyl amide substrate **2.92** afforded target tetracycle **2.96** in 55% yield, which was readily converted to *N*-benzyl epimeloscine. However, the benzyl group could not be removed. To address this issue, we chose secondary anilide **2.93** that annulated to provide target tetracycle **2.97** in low yields (22~38%). Elaboration of this product quickly furnished (±)-epimeloscine and

(±)-meloscine. This route delivered 18 mg of (±)-epimeloscine and 4 mg of (±)-meloscine. To improve the efficiency of the key radical annulation reaction, we replaced secondary anilide **2.93** with *N*-Boc protected tertiary amide **2.103**, which annulated to give target tetracycle **2.104** in 52% yield. This product can be elaborated in the same manner of **2.97** to form (±)-epimeloscine and (±)-meloscine.

## 2.3 SYNTHESIS OF MELOSCINE ANALOGS

From the standpoint of diversity-oriented-synthesis, the small family of meloscine alkaloids represents a poorly populated "chemistry space",[106] where the structure/property relationships are yet to be established. This fact could be partially attributed to the insufficient supplies of meloscine alkaloids and their structural analogs, from either natural or synthetic sources.[64-66, 101, 107] Given our development of an efficient synthesis meloscine and epimeloscine,[105] we initiated a synthetic program to produce meloscine derivatives with new scaffolds. First we aimed to prepare a small library via late-stage functionalization of either epimeloscine or advanced intermediates that were used in our original total synthesis.

**Figure 20** outlines four groups of meloscine analogs that we planned to synthesize: 1) lactam and sulfonamide E-ring analogs **2.105a** and **2.106a** that will be made from tetracyclic intermediate **2.96**; 2) six- and seven-membered D-ring analogs **2.109a** and **2.110a** that will be constructed from vinyl iodides **2.107** and **2.108**; 3) vinyl-side-chain analogs **2.111** that will be accessed by cross-metathesis or hydroboration reactions of *N*-benzyl epimeloscine **2.100**; and 4) analogs with different amide substituents **2.112**.

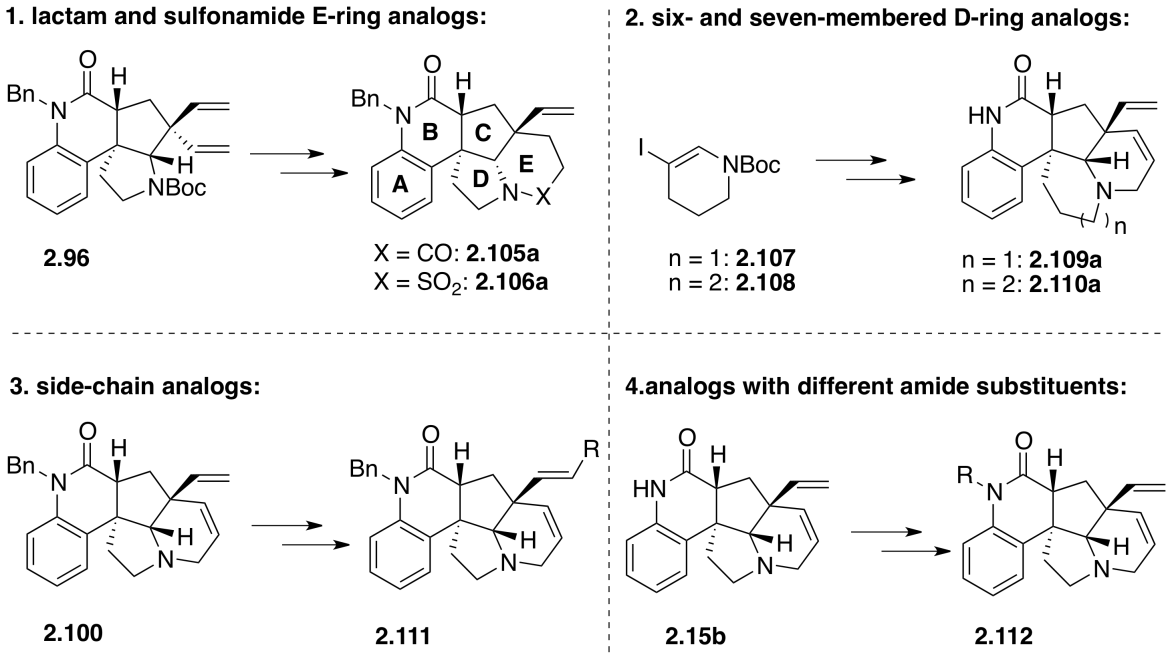
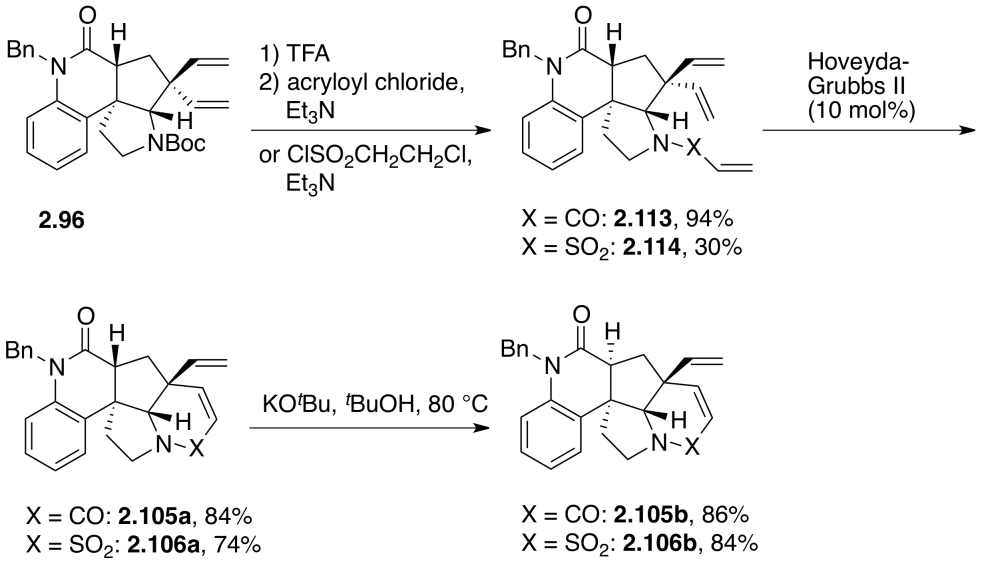



**Figure 22** Synthesis Plan for the Meloscine Analogs

### 2.3.1 Synthesis of E-Ring Analogs

The synthesis of lactam analog **2.105a** and sulfonamide analog **2.106a** was illustrated in **Scheme 2.27**. Tetracycle **2.96** was deprotected with dilute TFA, and the resulting crude amine intermediate was acylated with acryloyl chloride to give acrylamide **2.113** in 92% yield. In parallel, sequential treatment of above-mentioned crude amine with $Et_3N$ and $ClSO_2CH_2CH_2Cl$ chloride provided sulfonamide **2.114** in 30% yield.[108] Now, RCM reaction of acrylamide **2.113** with 10 mol% of second generation Hoveyda-Grubbs catalyst, produced *N*-benzyl-16-oxo-epimeloscine **2.105a** in 84% yield. RCM of vinylsulfonamide **2.114** in the same manner furnished analog **2.106a** in 74% yield. Interestingly, both analogs **2.105a** and **2.106a** underwent smooth epimerization with KO$^t$Bu in *tert*-butanol at 80 °C, providing new analogs **2.105b** and **2.106b** in 86% and 84% yield respectively.

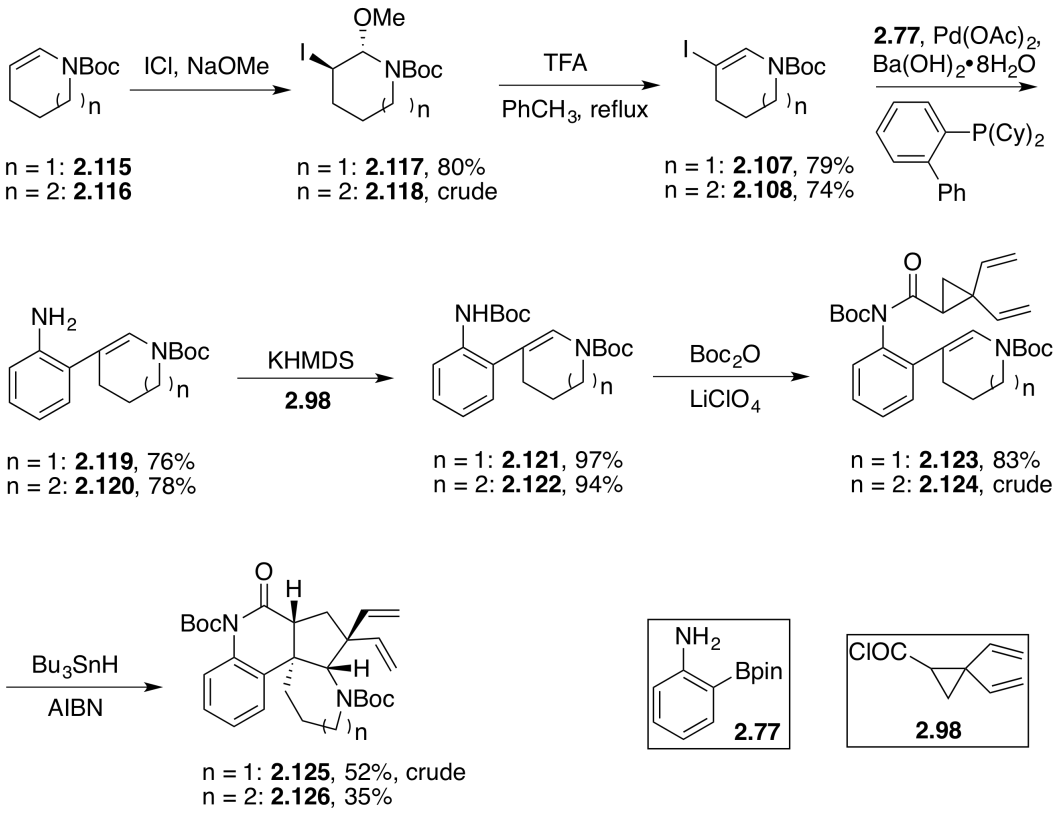



**Scheme 2.27** Synthesis of E-Ring Analogs of Meloscine

### 2.3.2 Synthesis of D-Ring Analogs

We then synthesized analogs with different sized D-rings. The flexibility of the Suzuki-coupling strategy allowed facile introduction of D-ring analogs from commercially available ene-carbamates **2.115** and **2.116** (**Scheme 2.28**). *N*-Boc-3,4-dihydro-2*H*-pyridine **2.115** was converted to vinyl iodide **2.107** in two steps using Sulikowski's procedures.[109] Treatment of **2.115** with iodine monochloride and sodium methoxide gave hemiaminal ether **2.117** in 97% yield. This product was then heated with 5 mol% TFA in refluxing toluene to afford known vinyl iodide **2.107** in 79% yield. Suzuki coupling of **2.107** with boronic acid ester **2.77** in the manner of **2.78** provided aniline **2.119** in 82% yield. Subsequent *N*-Boc protection in the manner of **2.102** generated *bis*-carbamate **2.121** in 97% yield, which was then acylated with acid chloride **2.98** in the manner of **2.103** to afford precursor **2.123** for the key radical annulation. Gratifyingly, slow addition of $Bu_3SnH$ and AIBN to a refluxing solution of **2.123** furnished the

target tetracycle **2.125** in 44% yield, along with minor, inseparable impurities. In parallel, tetracycle **2.126** was made from seven-memered ene-carbamate **2.116** by the same route and with comparable yields.




**Scheme 2.28** Synthesis of Tetracycles **2.125** and **2.126**

The assigned structure of **2.125** is supported by $^{1}$H NMR and HRMS analyses, however, the presence of minor, inseparable impurities complicates the $^{13}$C NMR spectrum. The diagnostic $C_{19}H$ signal of **2.125** is shown as two singlets at 4.79 ppm and 4.63 ppm in the $^{1}$H NMR spectrum, which are more downfield than the corresponding signals of five-membered D-ring analog **2.104** (**Scheme 2.26**). To confirm the structural assignment of **2.125**, we removed both Boc groups with dilute TFA. Flash chromatography purification of the crude product provided free amine **2.127** in 80% yield, which was fully characterized by $^{1}$H and $^{13}$C NMR, COSY, and

HRMS. The "epimeloscine-type" B/C ring fusion of **2.127** was unambiguously established by this X-ray crystallography analysis (**Figure 21**).

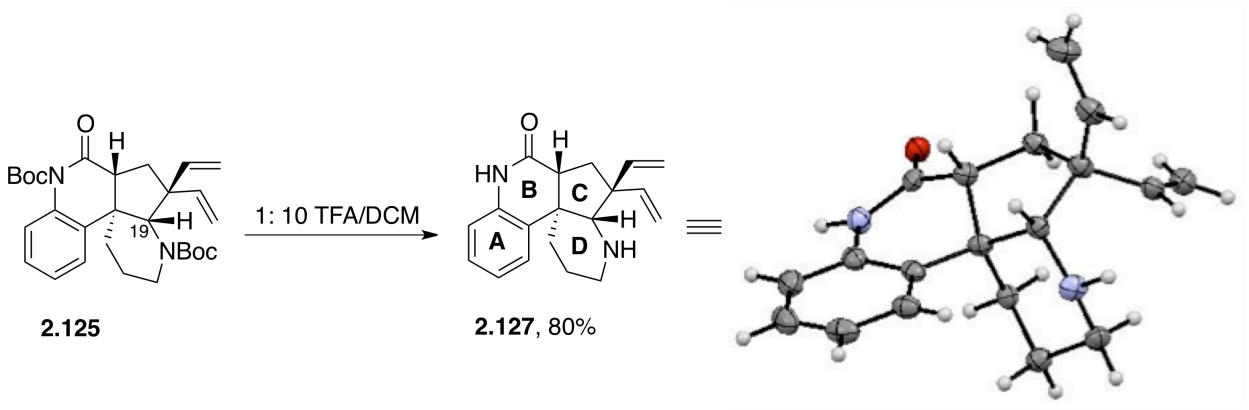
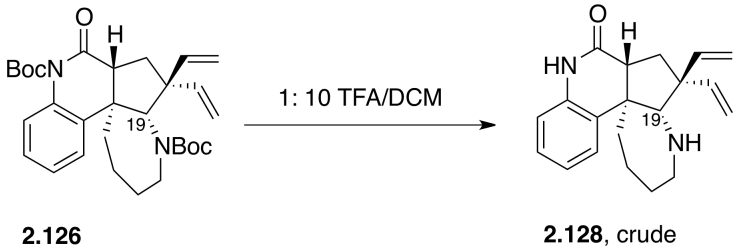



**Figure 23** Deprotection of *Bis*-Carbamate **2.125** and ORTEP Structure of **2.127**

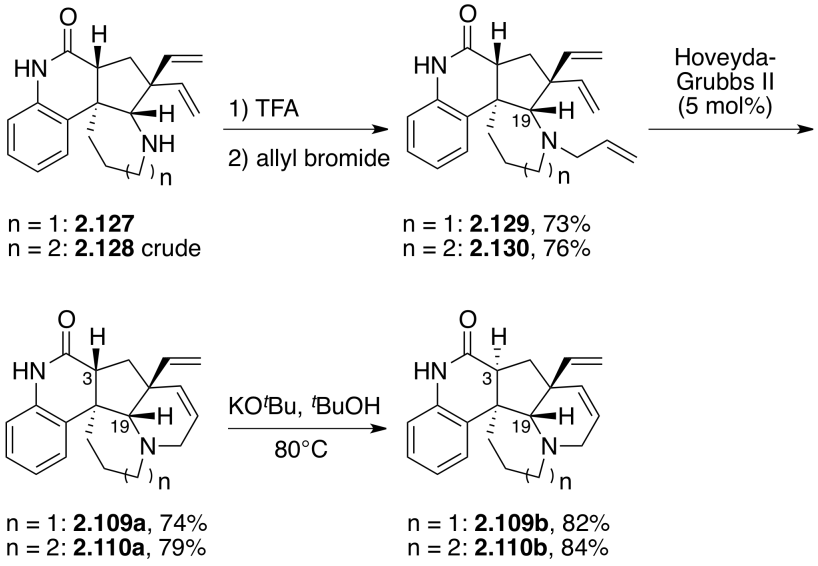
The assigned 2-D structure of seven-membered D-ring analog **2.126** is supported by $^{1}H/^{13}C$ NMR and HRMS analysis. In the $^{1}H$ NMR spectrum, the $C_{11}H$ signal overlaps with the terminal vinyl protons. This signal is even more downfield than the corresponding signal of six-membered D-ring analog **2.125**. We also made free amine derivative **2.128** in the manner of **2.127 (Scheme 2.29)**. Even though amine **2.128** was not purified by flash chromatography, the $C_{11}H$ signal is easily distinguishable by $^{1}H$ NMR, shown as a singlet at 3.53 ppm. This chemical shift is very close to that of the corresponding $C_{19}H$ in **2.127**, and therefore we assigned "epimeloscine-type" stereochemistry of **2.128** based on analogy. This assignment is also supported by the analogy between the $^{1}H$ NMR spectra of allylamine derivatives **2.129** and **2.130** (**Scheme 2.30**).




**2.126** **2.128**, crude

**Scheme 2.29** Deprotection of Bis-Carbamate **2.126**

The synthesis of target analogs **2.109a** and **2.109b** was then completed via sequential *N*-Boc deprotection, allylation, and RCM, in the manner of **2.104** (**Scheme 2.30**). Allylation of amines **2.113** with an excess amount of allyl bromide (5–10 equiv) at 50 °C provided triene **2.129** in 73% yield. RCM of this product with 5 mol% of Hoveyda-Grubbs II catalyst furnished target pentacycle **2.109a** in 74% yield. Applying the same reaction sequence on crude amine **2.128** produced seven-membered D-ring analog **2.110a** in similar efficiency. Finally, epimerization of pentacycles **2.109a** and **2.110a** smoothly proceeded with 2 equiv of KO$^t$Bu in *tert*-butanol, providing **2.109b** and **2.110b** in 82% and 84% yield, respectively.




n = 1: **2.127**
n = 2: **2.128** crude

n = 1: **2.129**, 73%
n = 2: **2.130**, 76%

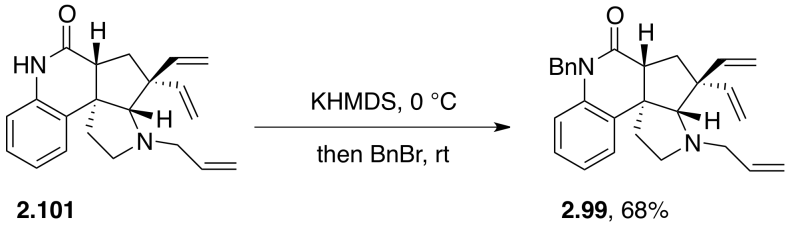
n = 1: **2.109a**, 74%
n = 2: **2.110a**, 79%

n = 1: **2.109b**, 82%
n = 2: **2.110b**, 84%

**Scheme 2.30** Completion of the Synthesis of Six- and Seven-Membered D-Ring Analogs

The diagnostic $C_{19}H$ signal of six-membered D-ring analog **2.109a** is shown as a singlet at 3.53 ppm in $^1H$ NMR spectrum, and the chemical shift of the corresponding singlet of **2.109b** is much more upfield, at 2.93 ppm. This pattern is in-line with the $^1H$ NMR spectra of epimeloscine/meloscine pair. Surprisingly, the chemical shift of the $C_{19}H$ singlet in the $^1H$ NMR spectrum of seven-membered D-ring analog **2.110a** is about 0.5 ppm more downfield than that of the corresponding signal of **2.110b**.

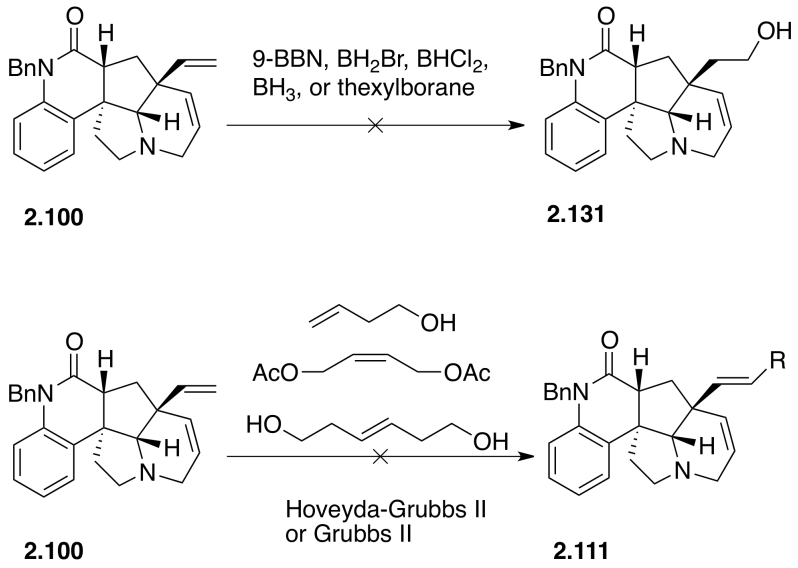
Next, we planned to synthesize meloscine analogs through a traditional-medicinal-chemistry based approach. In particular, we envisioned that direct functionalization of the amide moiety, or the terminal vinyl group of meloscines, would quickly provide an array of interesting compounds (**Figure 20**). We first examined the possibility of direct benzylation of the amide group. Initial experiments of benzylating epimeloscine with NaH and BnBr were not successful. However, we found that benzylation of secondary anilide **2.101** with KHMDS and BnBr gave **2.99** in 68% yield (**Scheme 2.36**).




**2.101** **2.99**, 68%

**Scheme 2.31** *N*-Benzylation of **2.101** to Produce **2.99**

We found it difficult to functionalize the terminal alkene moiety of *N*-benzyl epimeloscine **2.100** under either cross-metathesis[110] or hydroboration[111] conditions (**Scheme 2.32**). In most cases, the attempted reactions either provided no conversion of the starting material, or resulted in the formation of complex mixtures. A potential problem associated with these reactions could be the local steric hindrance of the substrate.




**Scheme 2.32** Attempted Functionalization of the Terminal Vinyl Group of **2.100**

In conclusion, we have synthesized lactam and sulfonamide E-ring analogs of meloscine from tetracycle **2.96**. In addition, we have demonstrated the generality of the radical [3+2]-annulation reaction of divinylcyclopropane-enamides that enables facile preparation of six- and seven-membered D-ring analogs.

## 2.4 PRELIMINARY STUDIES ON THE MEMORY-OF-CHIRALITY APPROACH TOWARDS (+)-MELOSCINE

### 2.4.1 Radical Annulation of Enantio-enriched Divinylcyclopropane Anilides

Our next goal was to test an enantioselective variant of the current racemic synthesis of meloscine alkaloids. In the racemic synthesis, three out of four required stereocenters were constructed by the cascade radical annulation reaction, while the group-selective RCM reaction

forged the final one.[105] We elected to establish the absolute chemistry of (+)-meloscine by an asymmetric radical cascade reaction. However, the lack of an obvious chiral element in the radical annulation precursors poses a major challenge for this strategy. In the racemic synthesis, the only stereocenter present in **2.104** is eventually destroyed during the annulation reaction.

The design of a memory-of-chirality (MOC) reaction could be a potentially appealing solution to this challenge. In a typical MOC reaction, a stereogenic center of the starting material is first destroyed, and a "conformationally chiral" reactive intermediate is generated.[112] This reactive intermediate does not readily racemize and is quickly consumed by the subsequent reaction with high stereoselectivity.[17b, 19, 20b, 110, 112-113] A typical example of asymmetric radical reaction via MOC is shown in **Figure 22**. Irradiation of solution of enantiopure *N*-hydroxypyridine-2-thione ester **2.132** and thiophenol in toluene gives tetrahydropyran (*S*)-**2.134** in 92% yield with 86% ee.[112e] Mechanistically, decarboxylation of **2.132** generates radical **2.133a** that is stereoselectively captured by PhSH, an efficient hydrogen donor. Slow ring flip of **2.133a** generates enantiomeric radical **2.133b**, which is reduced by PhSH to produce (*R*)-**2.134** as the minor product.

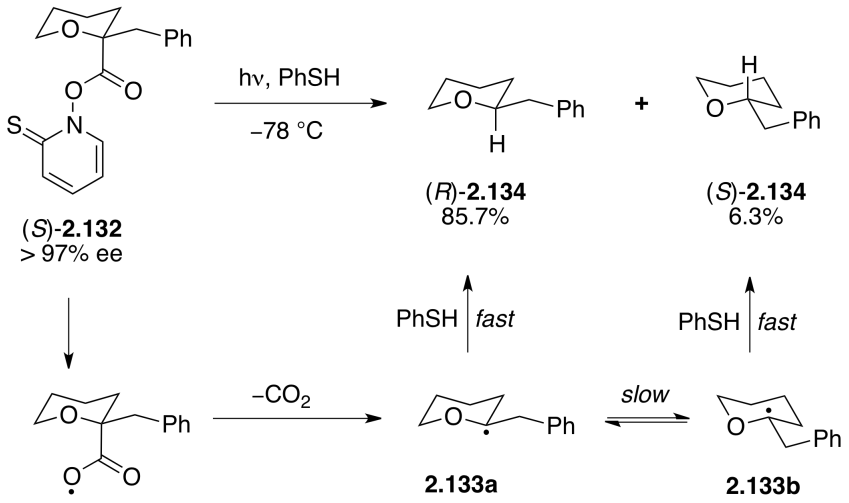



**Figure 24** Radical Reduction of Enantio-Pure **2.132** with Memory of Chirality

We decided to test whether a memory-of-chrality (MOC) approach would enable the production of enantio-enriched product **2.137** via stereoselective cyclization of enantiomerically pure substrate **2.135** (**Figure 23**). In principle, cyclization of dynamically chiral radical **2.136** would afford target MOC product **2.137**, given that the interconversion of **2.136** to *ent*-**2.136** was slower than the ensuing radical cyclization. On the other hand, if the interconversion of **2.136** to *ent*-**2.136** is much faster than the cyclization, then *rac*-**2.137** will be generated.

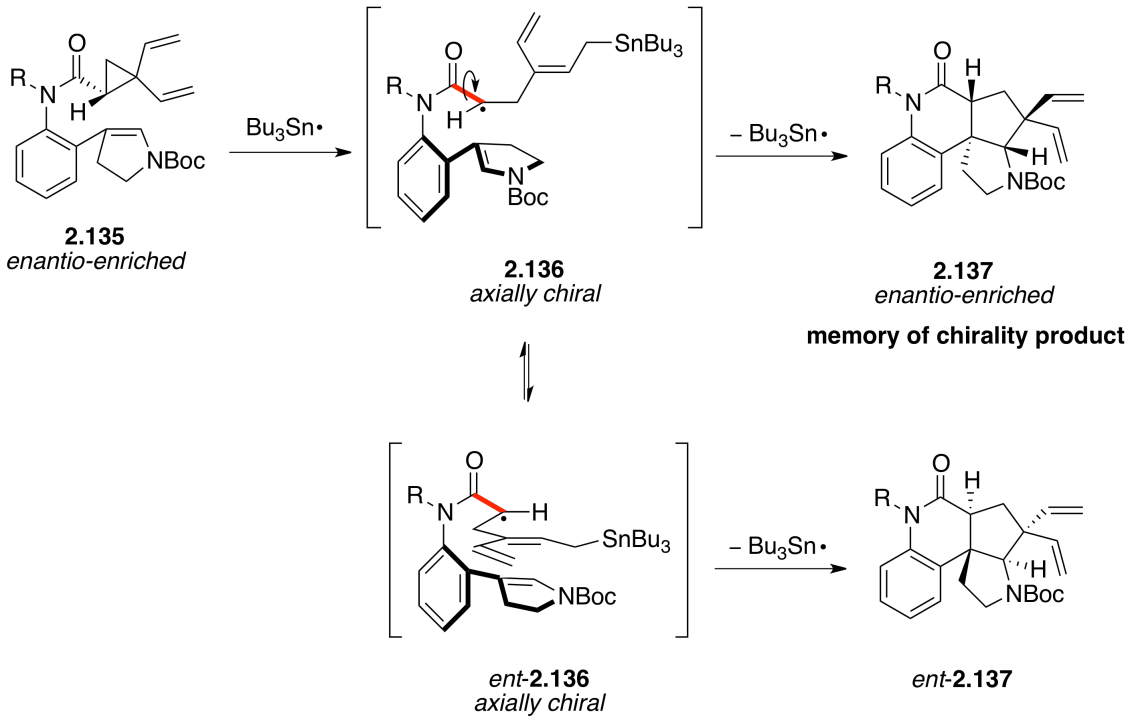
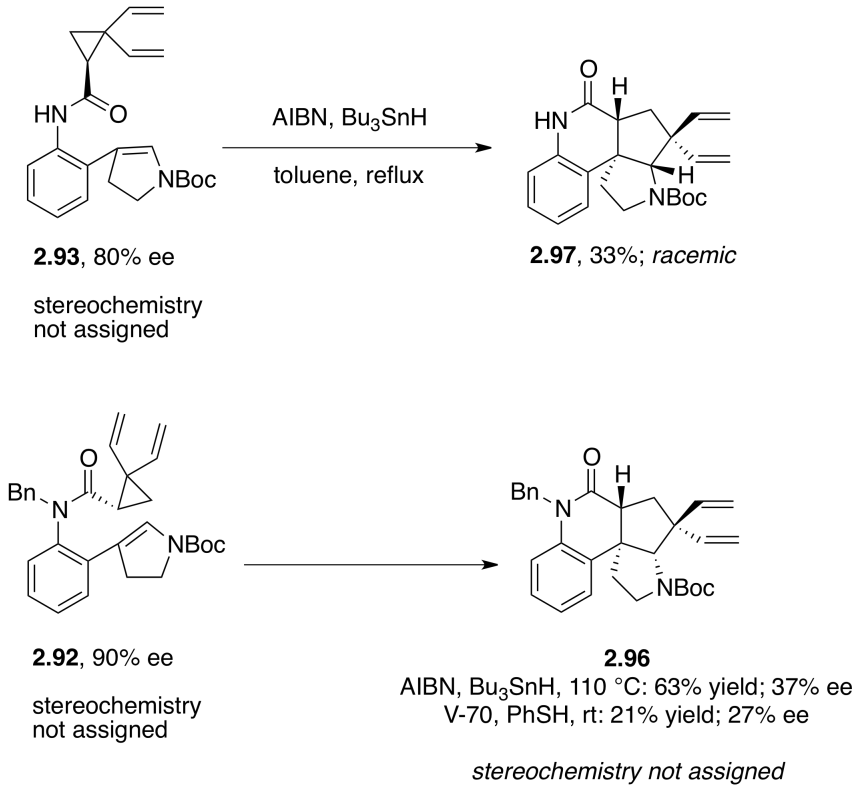



**Figure 25** Proposed Radical Annulation of Enantio-Enriched Divinylcyclopropane **2.135** with MOC

Before undertaking the enantioselective synthesis of annulation precursors, we conducted several proof-of-concept experiments (**Scheme 2.33**). Racemic secondary anilide **2.93** was resolved by chiral HPLC (*S*,*S*-Whelk O1 column) to give enantiomers **2.93a** (the first eluting enantiomer, FEE) and **2.93b** (the second eluting enantiomer, SEE) with greater than 80% ee.

Similarly, resolution of *N*-benzyl-substituted anilide **2.92** provided enantiomers **2.92a** (FEE) and **2.92b** (SEE) with greater than 90% ee. Subjection of both **2.93a** and **2.93b** to the standard AIBN/$Bu_3SnH$ condition, however, produced only racemic tetracycle **2.97** in 33% yield. Nonetheless, we were able to obtain target annulation product **2.96** with moderate degree of enantiomeric excess (37%) from *N*-benzyl substituted precursors **2.92a** and **2.92b**. To probe the temperature effect, we subsequently performed the same reaction with PhSH and V-70 initiatior at room temperature. Disappointingly, the reaction provided **2.96** in 21% yield, with even slightly lower ee (27%).




**Scheme 2.33** Pilot Experiments for Testing the MOC Strategy in the Synthesis of (+)-Meloscine

In conclusion, the above pilot experiments show that annulation of enantio-enriched secondary anilide **2.93** gives only racemic tetracyclic product **2.97**. Nonetheless, annulation of

enantio-enriched tertiary anilide **2.92** affords target tetracycle **2.96** with partial memory of chirality. These results will serve as the basis for the design of new divinylcyclopropane annulation reactions with improved memory of chirality.

### 2.4.2 Discovery of a Tandem Cope/Ene Reation of a Phenyl-Substituted Divinylcyclopropane

Encouraged by the initial MOC experiments that offered partial chirality transfer, we decided to investigate other substrates that contained an additional substituent on the cyclopropane ring. Diallylamide **2.138** was chosen as the initial target (**Figure 24**). We speculated that ring-opening of enantio-pure **2.138** could generate dynamically chiral tertiary radical **2.139** that might be less prone towards racemization than a secondary radical counterpart.

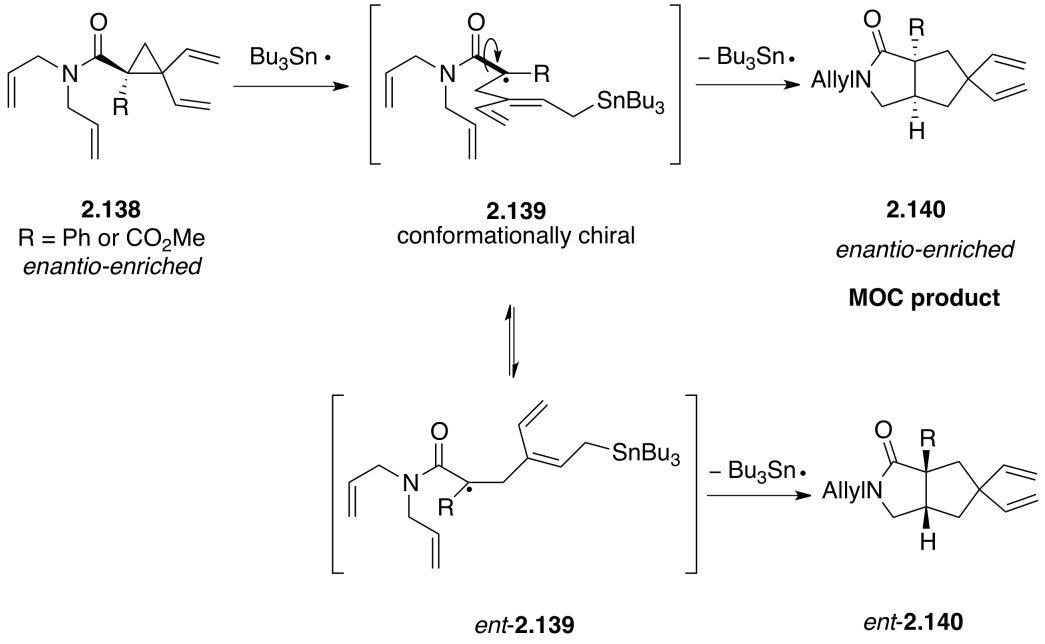



**Figure 26** The Design of New Divinylcyclopropane Substrates for Testing MOC in the Radical Annulation

The retrosynthesis of diallylamide **2.138** is shown in **Figure 25**. The amide bond of **2.138** will be constructed by coupling of diallylamine and acid **2.141**. We envision that a copper-catalyzed $S_N2'$ replacement of allylic phosphate intermediate **2.142** will allow rapid assembly of the divinyl moiety of cyclopropane **2.141**. In turn, methylene-cyclopropane **2.142** will be prepared by Rh-catalyzed cyclopropanation of known allenic phosphate **2.143**.

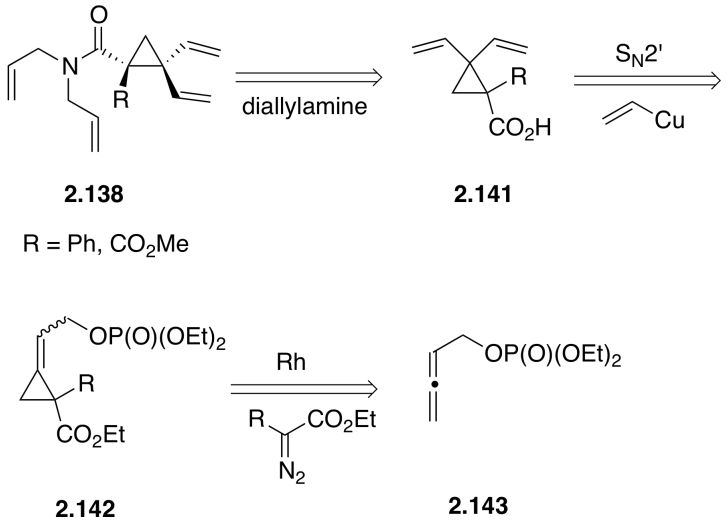
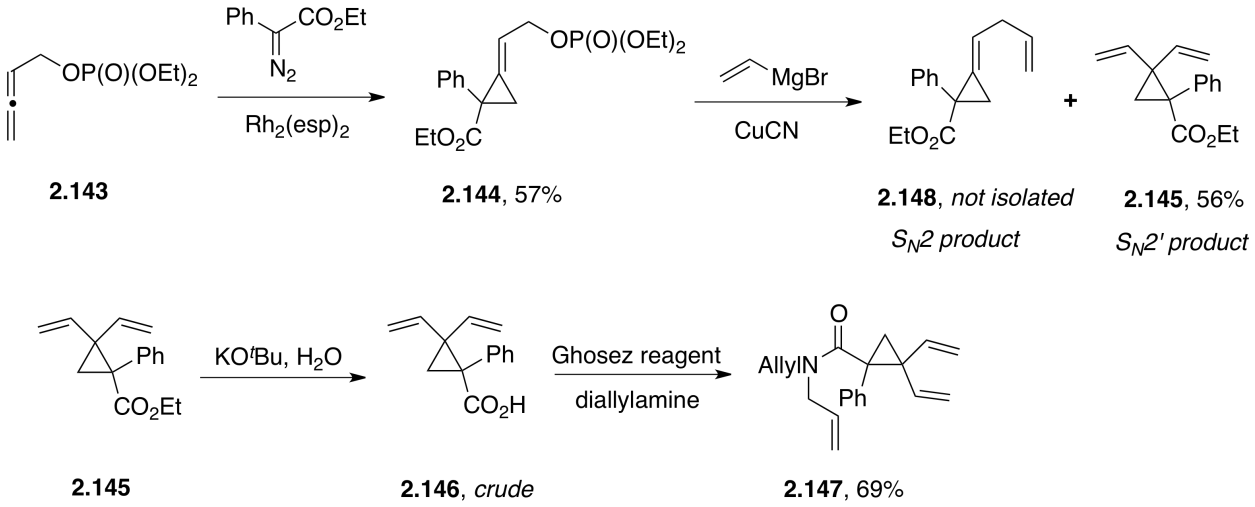



**Figure 27** Retrosynthesis of Diallylamide **2.138**

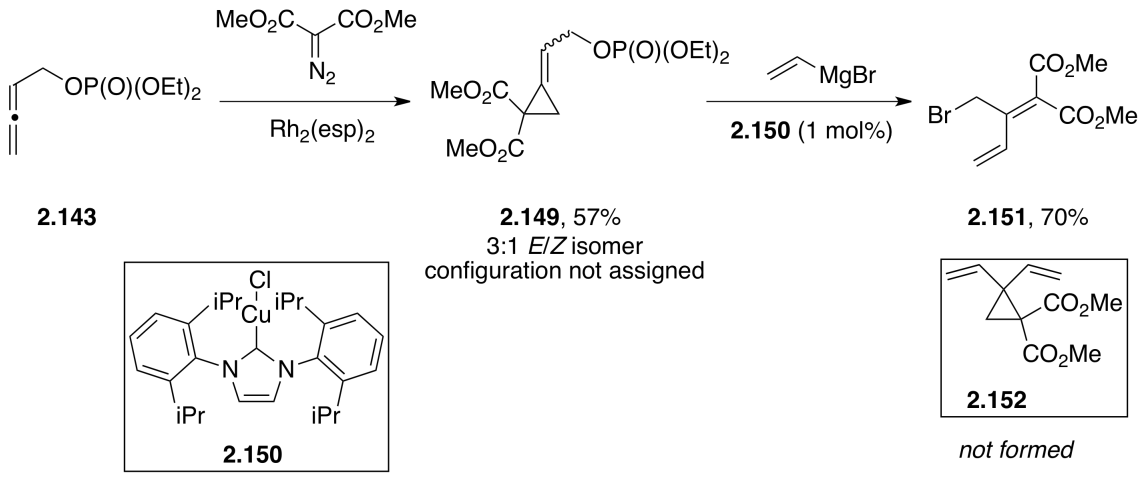
**Scheme 2.40** illustrates the successful execution of this route for the synthesis of phenyl-substituted substrate **2.147**. Ethyl phenyldiazoacetate was added to a refluxing solution of known allenic phosphate **2.143**[114] and $Rh_2(esp)_2$ catalyst[115] (0.2 mol%) in DCM, providing methylene-cyclopropane **2.144** in 57% yield. This product was slowly added to a pre-mixed solution of copper cyanide (20 mol%) and vinylmagnesium bromide (3 equiv). Gratifyingly, the target $S_N2'$ product **2.145** was obtained in 56% yield after careful chromatography purification. The regio-selectivity ($S_N2'$:$S_N2$) of the cuprate substitution was determined to be 3:1, according to $^1H$ NMR analysis of the crude product. Treatment of **2.145** with KOH gave no hydrolyzed product **2.146** at room temperature, and elevated temperature (50 °C) was required for the completion of the

hydrolysis reaction. However, an unidentifiable side-product was formed under this condition, and it is inseparable from target acid **2.146** by flash chromatography. We then optimized the hydrolysis reaction using Gassman's procedures.[116] Reaction of a mixture of **2.145**, KO$^t$Bu, and $H_2O$ at room temperature afforded crude acid **2.146** without the formation of aforementioned side-product. This product was treated with Ghosez reagent to generate corresponding acid chloride, which was subsequently added to diallylamine to form amide **2.147** in 69% yield.




**Scheme 2.34** Four-Step Synthesis of Diallylamide **2.147**

This route was also applied to the attempted synthesis of divinylcyclopropane diester **2.152** (**Scheme 2.35**). $Rh_2(esp)_2$-Catalyzed cyclopropanation of allenic phosphate **2.143** with dimethyl diazomalonate in the manner of **2.144** provided methylene-cyclopropane **2.149** as 3:1 mixture of E/Z isomers in 57% yield. Unfortunately, subjection of this product to a premixed solution of CuCN and vinylmagnesium bromide only produced a complex mixture. Treatment of methylene-cyclopropane **2.144** with a premixed solution of NHC-CuCl complex **2.150**[117] (1 mol%) and vinylmagnesium bromide (1.5 equiv), however, furnished ring-opened diene **2.151** as the sole product in 70% yield.




**Scheme 2.35** Attempted Synthesis of **2.152** by $S_N2'$ Vinylation of **2.149**

The structural assignment of the ring-opened diene **2.151** is supported $^{1}H/^{13}C$ NMR and HRMS analyses. Given the known, magnesium-halide mediated ring-opening of related cyclopropene diesters,[118] we proposed a tandem ring-opening/δ-elimination mechanism for the formation of **2.151** (**Figure 26**).

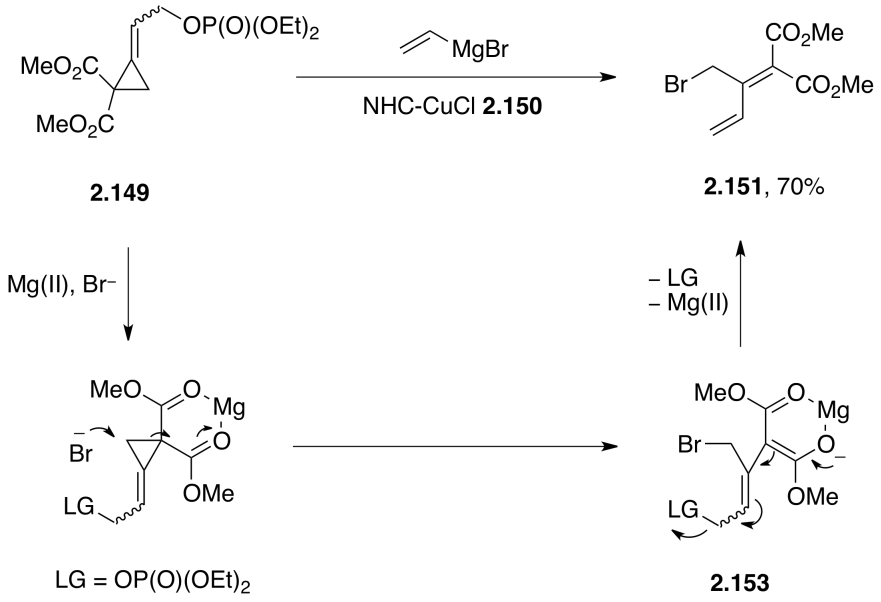
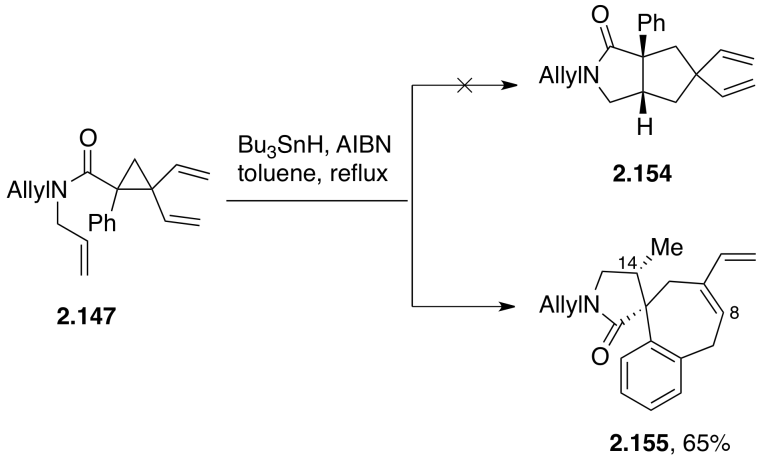



**Figure 28** Proposed Mechanism for the Formation of **2.151**

Before conducting MOC experiments that required chiral resolution of diallylamide **2.147**, we decided to obtain a racemic sample of the expected annulation product **2.154**. Thus, AIBN and $Bu_3SnH$ were slowly added via syringe pump to a solution of **2.147** in refluxing toluene. To our surprise, target bicycle **2.154** was not detected. Instead, a tricyclic benzo-annulene **2.155** was isolated as the sole product in 65% yield. The structural assignment of **2.134** is supported by several spectral features in the $^1H$ NMR spectrum: 1) the presence of only seven vinyl protons suggesting that two vinyl groups of diallylamide **2.147** are incorporated in the skeleton of **2.155**; 2) a doublet at 0.62 ppm attributed to the methyl group on $C_{14}$; and 3) a triplet of triplet at 6.07 ppm attributed to the $C_8$ vinyl proton. In addition, the structure of **2.155** was fully assigned by HRMS, $^{13}C$, DEPT-135, COSY, and HMQC NMR analysis.




**Scheme 2.36** Formation of Unexpected Tricycle **2.155**

**Figure 27** shows our mechanistic hypothesis of this reaction. Given the known, thermal-induced 1,2-divinyl-cyclopropane/cycloheptadiene rearrangement,[71b] we speculated that a similar process provided the benzo-annulene fragment of **2.155**. Presumably, the γ-lactam ring of **2.155** was generated via a subsequent intramolecular Alder-ene reaction. Based on this mechanism, the stereoselectivity of this cascade reaction originates from: 1) a boat-like transition-state that is

required for the Cope rearrangement; and 2) the arrangement of one allyl group and Ha that is required for the subsequent ene-reaction (shown in intermediate **2.161**). To test this hypothesis, a sample of diallylamide **2.147** in $CDCl_3$ was placed in an oil bath at 40 °C. After 36 h, a 3:2 mixture of **2.147** and tricycle **2.155** was observed by $^1H$ NMR. Complete conversion of **2.147** to **2.155** was observed after heating a solution of **2.147** in refluxing toluene for 3 h. These results showed that this reaction is thermal driven.

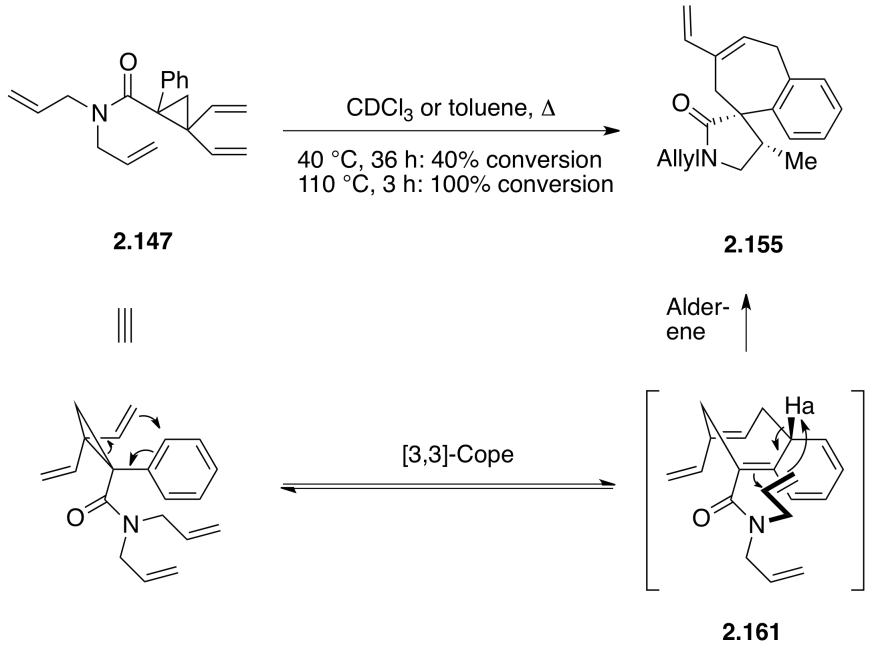
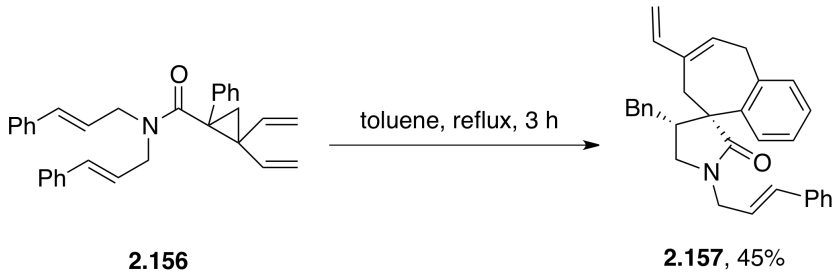



**Figure 29** Proposed Mechanism for the Formation of Tricycle **2.155**

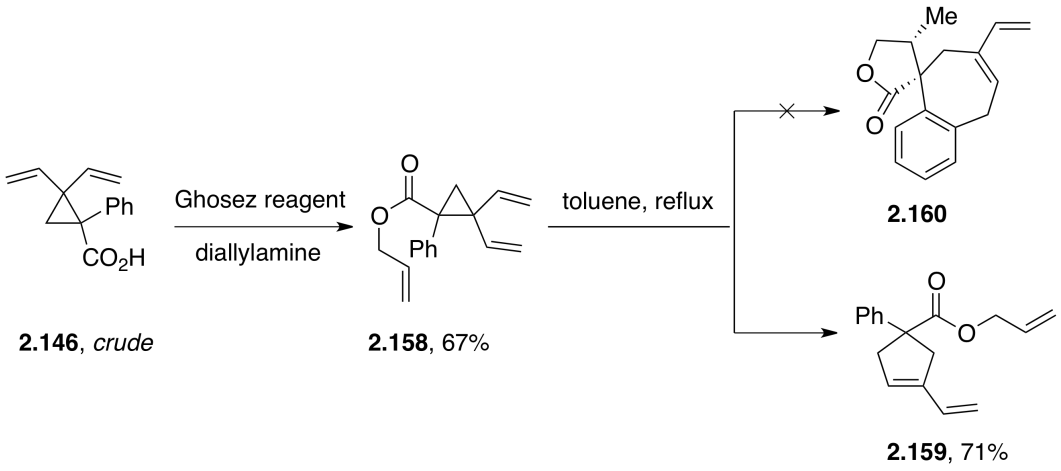
As a second test of this new reaction, we prepared *bis*-cinnamylamide analog **2.156** and conducted a thermal experiment (**Scheme 2.37**). The expected tricycle **2.157** was carefully isolated in 45% yield from several unidentified byproducts.




**2.156** **2.157**, 45%

**Scheme 2.37** Tandem Cope/Ene Reaction of *Bis*-cinnamylamide **2.156**

We also made ester substrate **2.158** for testing the tandem Cope/Ene reaction (**Scheme 2.38**). However, vinyl cyclopentene **2.159** was obtained in 73% yield after refluxing a solution of **2.158** in toluene for 3 h. The expected tricycle **2.160** was not detected by TLC or $^{1}$H NMR. Further studies on the scope and limitations of the new tandem Ene/Cope reaction are currently undertaken by Mr. E. Ben Hay.




**2.146**, *crude* **2.158**, 67% **2.160** **2.159**, 71%

**Scheme 2.38** Thermal Rearrangement of Divinylcyclopropane Ester **2.158**

## 2.5 CONCLUSIONS

The tandem 6-*exo*-*trig*/5-*exo*-*trig* radical cyclization methodology of *ortho*-alkenyl anilides has been extended to the synthesis of pentacyclic meloscine alkaloids. Based on this methodology, we have developed a novel cascade radical annulation reaction of a divinylcyclopropane, which enabled an expedient synthesis of (±)-epimeloscine and (±)-meloscine. Our synthesis provides (±)-epimeloscine in a longest linear sequence of 10 steps and in about 6% yield. Another key transformation of our synthesis is a group-selective RCM reaction that, in combination with the cascade radical reaction, dramatically facilitates the construction of the allylic quaternary center. In addition, the facile, five-step synthesis of divinylcycloprionic acid **2.63** provides opportunities to broaden the scope and utility of the new annulation reaction.

A divergent synthesis of meloscine analogs has been achieved via late-stage functionalization of epimeloscine and its derivatives. We made lactam and sulfonamide E-ring analogs as well as expanded D-ring analogs. In all cases, the cascade annulation produced the $C_{16}$-epi isomers, which could later be epimerized. This work sets the stage for the preparation of new libraries of meloscine analogs.

To develop an enantioselective synthesis of (+)-meloscine, we conducted preliminary studies on a MOC-based approach. Partial chiral transfer was observed in the radical annulation reaction of an enantio-enriched tertiary amide, while annulation of an enantio-enriched secondary amide analog gave only racemic product. A redesigned model compound for MOC studies was efficiently synthesized using a copper-catalyzed $S_N2'$-displacement reaction. However, this substrate did not undergo the expected radical annulation reaction. Instead, it rearranged through an unexpected, thermal-driven Cope/ene pathway to provide a tricyclic

benzo-annulene. We anticipate this reaction to provide quick access to an array of unusual spiro/fused tricycles.

## 2.6 EXPERIMENTALS

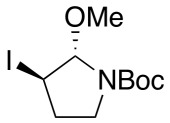
**General Information:** Chemicals and solvents were purchased from commercial suppliers and used as received, except as follows. Dichloromethane, THF, ether, and toluene were dried by passing through an activated alumina column, unless otherwise indiciated. All reactions were carried out under an inert atmosphere of dry argon unless otherwise indicated.

All reactions were followed by TLC or $^{1}$H NMR spectroscopy. TLC visualizations were performed by illumination with a UV lamp (254 nm), in combined with staining with a solution of phosphomolybdic acid in ethanol, or a solution of anisaldehyde in ethanol, and heating. All flash chromatography was performed with 230-400 mesh silica gel purchased from Sorbent Technoloies as the stationary phase, or by CombiFlash system (Teledyne ISCO).

$^{1}$H NMR spectra were recorded on Bruker Avance instruments at 300, 400, 500, 600 and 700 MHz with deuterated chloroform as solvent, unless otherwise indicated. $^{13}$C NMR spectra were measured on Bruker Avance instruments at 75, 100, 125, and 150 MHz. The chemical shifts in spectra were measured in parts per million (ppm) on the delta (δ) scale relative to the resonance of the solvent peak ($CDCl_3$: $^{1}$H = 7.27 ppm, $^{13}$C = 77.0 ppm). Unless otherwise noted, NMR spectra were recorded at 293 K.

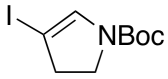
IR spectra were recorded on a Nicolet Avatar 360 FTIR spectrometer and ran as thin films on sodium chloride plates. Mass spectra were obtained on Fisons Autospec high-resolution magnetic sector mass spectrometer or a Micromass Q-Tof Ultima mass spectrometer.

*N*-Boc-2,3-dihydropyrrole, *N*-Boc-2,3-dihydro-2*H*-pyridine **2.115**, and *N*-Boc-2,3,4,5-tetrahydroazepine **2.108** were purchased from Sigma-Aldrich. Vinyl iodide **2.107** was prepared in two steps from **2.115** using known procedures.[45] Arylboronic ester **2.77** was purchased from Boron Molecular Inc. Carbamate **2.79** was prepared in one step from 1-amino-3-butyne (purchased from Sigma-Aldrich) using known procedures.[87] *Bis*-benzyl ether **2.88** was prepared in one step from 2-methylene-1,3-propenediol (purchased from Sigma-Aldrich) using known procedures.[91] Allenic phosphate **2.143** was prepared in one step from 2,3-butadien-1-ol (purchased from Sigma-Aldrich) using known procedures.[114] Ethyl phenyldiazoacetate[119] and dimethyl diazomalonate[120] were prepared in one step using known procedures.




***trans-tert*-Butyl 3-iodo-2-methoxypyrrolidine-1-carboxylate (2.70)**: Sodium methoxide (1.82 g, 33.68 mmol) was added to a stirred solution of *N*-Boc-2,3-dihydropyrrole (3.01 g, 16.84 mmol) in MeOH (60 mL). An ICl solution (1 M in $CH_2Cl_2$, 18.5 mL) was added dropwise, and the mixture was stirred for 30 min after the completion of addition. The reaction was quenched with a saturated aqueous $Na_2S_2O_3$ solution, and the aqueous layer was extracted with $Et_2O$. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 15% EtOAc/hexanes) to provide the title compound (5.01 g, 91%) as a colorless oil, in a nearly 1:1 ratio of *N*-Boc rotamers: $^1$H NMR (300 MHz, $CDCl_3$) δ 5.37, 5.24 (s, 1H, rotamers), 4.22 (d, $J$ = 4.8 Hz, 1H), 3.71-3.55 (m, 1H), 3.50-3.46 (m, 1H), 3.41, 3.62 (s, 3H, rotamers), 2.50-2.47 (m, 1H), 2.16-2.09 (m, 1H), 1.50 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 155.1, 154.4, 96.4, 96.2, 80.6, 80.3, 56.2,

55.9, 44.9, 44.3, 33.8, 32.9, 28.4, 27.0, 26.2; FTIR (thin film, $CHCl_3$) 2976, 1706, 1478, 1384, 1343, 1164, 1116, 1075 $cm^{-1}$; HRMS (EI) cald for $C_{10}H_{18}NO_3NaI$, *m/z* 350.0229 $[M+Na]^+$, found: 350.0239.




***tert*-Butyl 4-iodo-2,3-dihydro-1*H*-pyrrole-1-carboxylate (2.71)**: A solution of **2.70** (3.64 g, 11.13 mmol) and citric acid (7.0 g, 33.39 mmol) in toluene (100 mL) was refluxed for 6 h in a 250 mL flask fitted with a Dean-Stark trap. The mixture was cooled to room temperature and the solid was filtered off. The filtrate was washed with a saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 7% EtOAc/hexanes) to provide the title compound (1.37 g, 42%) as a colorless oil: $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.77, 6.64 (rotamers, s, 1H), 3.80-3.73 (m, 2H), 2.87-2.81 (m, 2H), 1.47 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 151.0, 150.4, 135.8, 80.9, 80.7, 66.2, 46.5, 45.9, 39.8, 38.7, 28.3; FTIR (thin film, $CHCl_3$) 2975, 2930, 1703, 1611, 1477, 1454, 1396, 1244, 1173, 1128 $cm^{-1}$; HRMS (TOF ES) cald for $C_9H_{14}NO_3INa$, *m/z* 317.9991 $[M+Na]^+$, found: 318.0002.

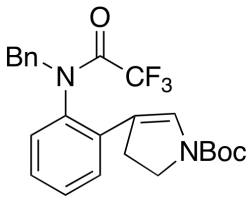
**Large-scale preparation of vinyl iodide 2.71 from 4-amino-1-butyne**:

***N*-Boc protection of 4-amino-1-butyne**: $Boc_2O$ (9.39 g, 42.98 mmol) was added to a solution of 4-amino-1-butyne (2.70 g, 39.07 mmol) in diethyl ether (ACS reagent grade; 150 mL) at −78 °C, and the reaction mixture was stirred at this temperature for 2 h. A saturated aqueous $NaHCO_3$ solution was added, and the biphasic mixture was stirred vigorously at room temperature for 10 min. The aqueous layer was extracted by diethyl ether, and the combined

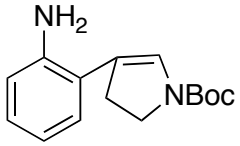
organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude carbamate **2.79** (6.6 g) was directly used for the next reaction.

**Diiodination of alkyne 2.79**: NaI (17.57 g, 117.20 mmol) and $I_2$ (11.90, 46.88 mmol) were added sequentially to a stirred solution of *tert*-butyl but-3-yn-1-ylcarbamate **2.79**[87] (6.6 g, 39.07 mmol) in dichloromethane (150 mL). The reaction mixture was stirred in dark for 12 h, before a saturated aqueous solution of $Na_2S_2O_3$ was added. After vigorously stirred for 10 min, the biphasic mixture was transferred into a separatory funnel. The aqueous layer was extracted with dichloromethane, and the combined organic layers was dried over $MgSO_4$, and concentrated *in vacuo*. The crude diiodide product **2.80** (15.5 g) appeared as an yellow oil, as a 6:1 mixture of *N*-Boc rotamers, and was directly subjected to the next reaction without purification: $^1$H NMR (400 MHz) δ 6.99 (s, 1H), 4.65 (brs, 1H, major rotamer), 4.40 (brs, 1H, minor rotamer), 3.38-3.34 (m, 2H), 2.76 (t, $J$ = 6.5 Hz, 2H), 1.46 (s, 9H).

**Copper-mediated 5-*endo-trig* cyclization of diiodide 2.80**: The crude diiodide **2.80** (8.20 g, 19.39 mmol; based on a hypothetical 100% yield of the diiodonation reaction) was dissolved in toluene (300 mL), followed by addition of $K_3PO_4$ (12.35 g, 58.17 mmol), 2,2'-bipyridyl (3.03 g, 19.39 mmol), CuI (1.85 g, 9.70 mmol), and water (0.3 mL). The reaction mixture was refluxed for 48 h, before it was cooled to room temerature and filtered through a pad of celite. The solvent was removed by rotary evaporation, and the residue was loaded on a pad of silica gel (diameter = 2.5 in, height = 3 in). The desired cyclic vinyl iodide **2.71** (3.50 g, 61% over two steps; with >90% purity) was separated from 2,2'-bipyridyl ligand with an eluent of 30% $Et_2O$/hexanes (~600 mL).

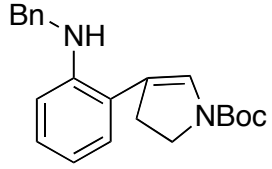



***tert*-Butyl 4-(2-(*N*-benzyl-2,2,2-trifluoroacetamido)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carboxylate (2.72)**: Vinyl iodide **2.71** (1.20 g, 4.07 mmol) was coupled with arylstannane **1.74** (2.77 g, 4.88 mmol) in the manner of sulfonamide analog **1.78**. After aqueous workup and ether extraction, the combined organic layer was concentrated *in vacuo*. The residue was passed through a short pad of silica gel (hexanes→1:5 EtOAc/hexanes) to provide the title compound (1.74 g, 95%) as a colorless oil, in an unidentified ratio of rotamers: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.32-6.82 (m, 9H), 6.62-6.59 (m, 1H), 5.63-5.51 (m, 1H), 4.04-3.98 (m, 1H), 3.86-3.76 (m, 2H), 3.11-3.00 (m, 1H), 2.95-2.82 (m, 1H), 1.53 (s, 9H). HRMS (EI) cald for $C_{24}H_{25}N_2O_3F_3$, 446.1817 $[M]^+$, found: 446.1814. This product was contaminated with minor, inseparable impurities, and was directly subjected to the subsequent *N*-trifluoroacetyl deprotection reaction without further purification.



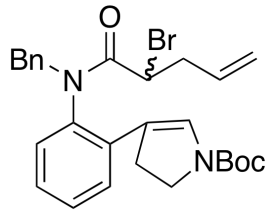

***tert*-Butyl 4-(2-aminophenyl)-2,3-dihydro-1*H*-pyrrole-1-carboxylate (2.78)**: 2-aminophenyl pinacolboronate (3.60 g, 16.44 mmol), barium hydroxide octahydrate (11.00 g, 34.86 mmol), and 2-(dicyclohexylphosphino)biphenyl (815 mg, 2.32 mmol) were added to a solution of vinyl iodide **20** (3.43 g, 11.62 mmol) in dioxane (ACS-reagent grade; 60 mL). Palladium acetate (130 mg, 0.58 mmol) was then added, and the reaction mixture was stirred at 80 °C for 3 h. The reaction mixture was partitioned in ethyl acetate and water, and the aqueous layer was extracted

with EtOAc. The combined organic layers was then washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 25% EtOAc/hexane) to provide the title compound (2.5 g, 83%) as a red oil (with inseparable Pd impurities; 3:1 rotamer ratio): $^1$H NMR (400 MHz, $CD_3CN$) δ major rotamer: 6.98 (td, $J$ = 7.2 Hz, 1.2 Hz, 1H); minor rotamer: 6.91 (brs, 1H); overlapping resonances: 7.03 (d, $J$ = 7.6 Hz, 1H), 6.73 (d, $J$ = 8.0 Hz, 1H), 6.69 (t, $J$ = 7.2 Hz, 1H), 4.18 (brs, 2H), 3.76 (m, 2H), 3.02-2.97 (m, 2H), 1.48 (s, 9H). Above spectral data were identical to those reported.[39c]

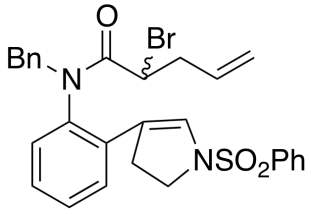



***tert*-Butyl 4-(2-(benzylamino)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carboxylate (2.73)**: A mixture of aniline **2.78** (245 mg, 0.941 mmol), benzaldehyde (115 μL, 1.04 mmol), acetic acid (54 μL, 0.94 mmol), and sodium triacetoxyborohydride (800 mg, 3.76 mmol) in 1,2-dichloroethane (ACS-reagent grade; 6 mL) was stirred at room temperature for 5 h. The reaction was quenched with an aqueous NaOH solution (1 M), and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 15% EtOAc/hexane) to provide the title compound (241 mg, 73%) as a colorless oil, in a 1.5:1 ratio of rotamers: $^1$H NMR (300 MHz, $CDCl_3$) δ major rotamer: 4.38 (brs, 1H), 1.44 (s, 9H); minor rotamer: 4.64 (brs, 1H), 1.46 (s, 9H); overlapping resonances: 7.41-7.29 (m, 5H), 7.16-6.95 (m, 3H), 6.80-6.59 (2H), 4.34 (s, 2H), 3.83 (t, $J$ = 9.0 Hz, 2H), 3.08-2.98 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 151.4, 145.4, 139.4, 139.2, 128.7, 127.7, 127.6, 127.4, 127.0, 121.2, 121.0, 118.4, 117.7, 117.2, 111.0, 80.4, 48.9, 48.3, 44.8, 44.2, 33.1, 31.8, 28.4; FTIR (thin film, $CHCl_3$)

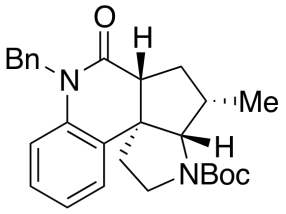
3029, 2975, 2929, 1700, 1598, 1504, 1452, 1408, 1364, 1269, 1170, 1117, 745 $cm^{-1}$; HRMS (TOF ES) cald for $C_{22}H_{27}N_2O_2$, *m/z* 351.2073 $[M]^+$, found: 351.2084. In another experiment, the title product was obtained in 76% yield by reductive cleavage of trifluoroacetamide **2.72** in the manner of sulfonamide analog **1.79** (**Chapter 1.4**).




***tert*-Butyl 4-(2-(*N*-benzyl-2-bromopent-4-enamido)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carboxylate** (**2.74**): Oxalyl chloride (14 μL, 0.16 mmol) and a drop of DMF were successively added to a stirred solution of acid **2.67** (29 mg, 0.16 mmol) in $CH_2Cl_2$ (1 mL). The mixture was warmed to room temperature and stirred for 2 h. This mixture containing the crude acid chloride was transferred dropwise to a stirred solution of aniline **2.73** (20 mg, 0.057 mmol) and $Et_3N$ (16 μL, 0.114 mmol) in $CH_2Cl_2$ (2 mL) at 0 °C. After 1 h, the reaction was quenched with a saturated aqueous $NH_4Cl$ solution, and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography (1:3 EtOAc/hexane) to provide the title compound (26 mg, 74%) as a colorless oil, in a mixture of multiple rotamers (see attached $^1H$ and $^{13}C$ NMR spectra). FTIR (thin film, $CHCl_3$) 3064, 2978, 2931, 1701, 1667, 1406, 1256, 1166, 735; HRMS (EI) cald for $C_{27}H_{31}N_2O_3Br$, 510.1518 $[M]^+$, found: 510.1508.

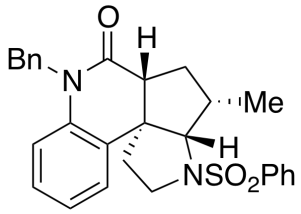



***N*-Benzyl-2-bromo-*N*-(2-(1-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)phenyl)pent-4-enamide (2.68)**: Acylation of enesulfonamide **1.79** (25 mg, 0.064 mmol) with acid **2.67** (29 mg, 0.16 mmol) in the manner of **62** gave the title compound (26 mg, 74%) as a white film, in a mixture of diastereomers (see attached $^1$H NMR spectrum).




**(3a*S*,4*S*,5a*R*,11b*R*)-*tert*-Butyl 7-benzyl-4-methyl-6-oxo-3a,4,5,5a,6,7-hexahydro-1*H*-pyrrolo[3',2':2,3]cyclopenta[1,2-*c*]quinoline-3(2*H*)-carboxylate** (**2.75**): A mixture of dihydropyrrole **2.74** (50 mg, 0.098 mmol), triethylborane (1 M in hexane, 49 μL), and $Bu_3SnH$ (52 μL, 0.196 mmol) in benzene (10 mL) was stirred at room temperature for 1 h. The solvent was evaporated, and the residue was purified by flash chromatography (silica gel, 20% EtOAc/hexanes) to provide the title compound (22 mg, 52%) as a colorless oil, in a 1:1 mixture of rotamers: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.30-6.96 (m, 9H), 5.35 (d, *J* = 15.9 Hz, 1H), 5.34 (d, *J* = 15.9 Hz, 1H), 4.99 (d, *J* = 15.9 Hz, 1H), 4.58 (d, *J* = 9.3 Hz, 1H), 4.44 (d, *J* = 9.0 Hz, 1H), 3.53-3.28 (m, 2H), 2.90-2.79 (m, 1H), 2.54-2.39 (m, 1H), 2.29 (dd, *J* = 13.2 Hz, 6.6 Hz, 1H), 2.26 (dd, *J* = 13.2 Hz, 6.6 Hz, 1H), 2.13-1.99 (m, 1H), 1.80-1.67 (m, 1H), 1.60-1.45 (m, 1H), 1.54 (s, 9H), 1.50 (s, 9H), 1.05 (d, *J* = 6.9 Hz, 3H); HRMS (EI) cald for $C_{27}H_{32}N_2O_3$, *m/z* 432.2413 $[M]^+$, found: 432.2422. This product was contaminated with minor, inseparable

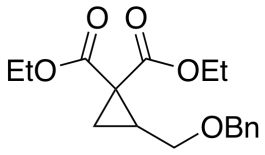
impurities, and was submitted to the subsequent *N*-Boc deprotection reaction without further purification.



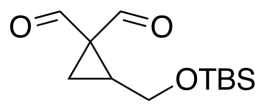

**(3a*S*,4*S*,5a*R*,11b*R*)-7-Benzyl-4-methyl-3-(phenylsulfonyl)-2,3,3a,4,5,5a-hexahydro-1*H*-pyrrolo[3',2':2,3]cyclopenta[1,2-*c*]quinolin-6(7*H*)-one (2.76)**: Crude carbamate **2.75** (22 mg, 0.051 mmol) was stirred in a mixed solvent of dichloromethane/TFA (6:1, 3 mL). The solvent was evaporated after 2 h, and the residue was redissolved in dichloromethane and washed with an aqueous NaOH solution (1 M). The organic layer was dried over $MgSO_4$, and the volume was reduced to 2 mL. Triethylamine (21 μL, 0.153 mmol) and benzenesulfonyl chloride (20 μL, 0.153 mmol) were added sequentially, and the reaction mixture was stirred for 3 h. The solvent was evaporated, and the crude product was partitioned between acetonitrile and hexanes. The acetonitrile layer was concentrated *in vacuo*, and the residue was purified by flash chromatography (silica gel, 30% EtOAc/hexanes) to provide the title compound (10 mg, 59%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 8.01-7.99 (m, 2H), 7.75 (tt, *J* = 7.2 Hz, 1.2 Hz, 1H), 7.67-7.63 (m, 2H), 7.30-7.26 (m, 2H), 7.23-7.18 (m, 3H), 7.02 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.42 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 5.58 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 5.23 (d, *J* = 16.0 Hz, 1H), 4.99 (d, *J* = 16.0 Hz, 1H), 4.33 (d, *J* = 9.2 Hz, 1H), 3.55 (t, *J* = 8.4 Hz, 1H), 3.07 (ddd, *J* = 15.2 Hz, 9.2 Hz, 6.0 Hz, 1H), 2.76 (q, *J* = 6.4 Hz, 1H), 2.49-2.40 (m, 1H), 2.25 (ddd, *J* = 13.6 Hz, 7.2 Hz, 6.4 Hz, 1H), 2.10 (td, *J* = 12.4 Hz, 7.6 Hz, 1H), 1.76 (q, *J* = 12.4 Hz, 1H), 1.40 (dd, *J* = 12.4 Hz, 6.4 Hz, 1H), 1.32 (d, *J* = 6.8 Hz, 3H); $^{13}$C NMR (100 HMz,

$CDCl_3$) δ 170.6, 139.0, 137.8, 137.0, 134.4, 133.0, 129.5, 128.7, 128.0, 127.5, 127.3, 127.0, 122.8, 122.7, 116.6, 66.5, 55.5, 47.7, 47.0, 46.0, 37.0, 31.8, 31.1, 17.1; FTIR (thin film, $CHCl_3$) 2957, 2926, 2870, 1684, 1453, 1385, 1348, 1164, 1096, 756, 727; HRMS (TOF ES) cald for $C_{28}H_{29}N_2O_3S$, *m/z* 473.1899 $[M+H]^+$, found: 473.1885.

A sample for X-ray crystallography analysis was prepared by vapor diffusion crystallization technique. A dram glass vial (2 mL) was charged with a solution of sulfonamide **65** (2 mg) in benzene (0.5 mL), and this vial was placed in a 150 mL beaker containing hexane (5 mL). After 48 h, a small crystal precipitated at the bottom of the vial.




**Diethyl 2-((benzyloxy)methyl)cyclopropane-1,1-dicarboxylate** (**2.81**): The title compound was prepared according to Burgess's procedures[89] (83% over two steps), except that the product was purified by flash chromatography (silica gel, 15% EtOAc/hexanes): $^1$H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H), 4.49 (s, 2H), 4.26-4.09 (m, 4H), 3.55 (dd, *J* = 10.4 Hz, 6.0 Hz, 1H), 3.50 (dd, *J* = 10.4 Hz, 6.0 Hz, 1H), 2.30-2.22 (m, 1H), 1.55 (dd, *J* = 7.6 Hz, 4.8 Hz, 1H), 1.44 (dd, *J* = 10.2 Hz, 4.4 Hz, 1H), 1.31-1.23 (m, 6H). The above spectral data were identical to those reported.[89]




**2-(((*tert*-Butyldimethylsilyl)oxy)methyl)cyclopropane-1,1-dicarbaldehyde** (**2.83**):

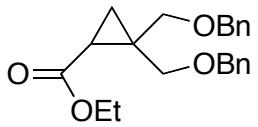
**Synthesis of silylether 2.82**:[89] A flask was sequentially charged with $Pd(OH)_2$/C catalyst

(340 mg) and a solution of benzyl ether **2.81** (6.80 g, 22.20 mmol) in MeOH (80 mL), under a stream of Ar. The flask was then fitted with a $H_2$ balloon, and the reaction mixture was then stirred at room temperature for 12 h. It was filtered through a short pad of celite, and the filtrate was concentrated *in vacuo*. The resulting crude alcohol was dissolved in DMF (50 mL). TBDPSCl (7.02 g, 25.53 mmol) and imidazole (3.62 g, 53.18 mmol) were added, and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with diethyl ether and sequentially washed with a 10% aqueous citric acid solution, a saturated $NaHCO_3$ solution, and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was quickly passed through a pad of silica gel (0~10% EtOAc/hexanes), and the eluent was concentrated *in vacuo*, providing **2.82** (7.26 g) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.74-7.63 (m, 4H), 7.44-7.36 (m, 6H), 4.29-4.06 (m, 4H), 3.75 (s, 1H), 3.73 (s, 1H), 2.22-2.12 (m, 1H), 1.51 (dd, *J* = 7.5 Hz, 4.5 Hz, 1H), 1.36 (dd, *J* = 9.3 Hz, 4.5 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.04 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.2, 167.9, 135.6, 134.8, 133.5, 133.4, 129.7, 127.7, 61.8, 61.5, 61.4, 32.9, 29.4, 26.7, 26.6, 19.2, 18.5, 14.1, 14.0. This product was directly used for the next step without further purification.

**DIBAL-H Reduction of 2.82**: Diester **2.82** (6.80 g, 14.96 mmol) was dissolved in THF (80 mL). A DIBAL-H solution (1 M in hexanes, 89.7 mL, 89.74 mmol) was slowly added via a syringe pump at −78 °C. After 1 h, the reaction mixture was stirred at 0 °C for 3 h, before it was diluted with diethyl ether and treated with a saturated aqueous potassium sodium tartrate solution. The aqueous layer was extracted with diethyl ether, and the combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was passed through a short pad of silica gel (EtOAc) to provide crude diol **2.83** (3.10 g) as a colorless oil: $^1$H NMR (400 MHz,

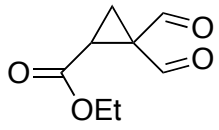
$CDCl_3$) δ 7.75-7.67 (m, 4H), 7.47-7.40 (m, 6H), 4.16 (t, *J* = 12.0 Hz, 1H), 3.76-3.69 (m, 2H), 3.57-3.52 (m, 2H), 3.39 (t, *J* = 11.6 Hz, 1H), 2.59 (m, 1H), 1.60 (m, 1H), 1.29-1.22 (m, 1H), 1.07 (s, 9H), 0.65 (dd, *J* = 8.4 Hz, 5.2 Hz, 1H), 0.36 (t, *J* = 5.2 Hz, 1H). This product was directly used for the next step without further purification.

**Oxidation of the 2.83**: A solution of DMSO (3.22 mL, 45.34 mmol) in dichloromethane (10 mL) was slowly added to a solution of oxalyl chloride (2.60 mL, 30.23 mmol) in dichloromethane (50 mL) at −78 °C, followed by dropwise addition of a solution of the crude diol **2.83** (2.80 g, 7.56 mmol). After 15 min, triethylamine (10.5 mL, 75.56 mmol) was added dropwise, and the reaction mixture was stirred at 0 °C for 30 min. $H_2O$ was added to quench the reaction, and the aqueous layer was extracted with dichloromethane. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 10% EtOAc/hexanes) to afford the title compound **2.84** (1.30 g, 20% over four steps) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 9.98 (s, 1H), 7.65-7.61 (m, 4H), 7.48-7.39 (m, 6H), 4.06 (dd, *J* = 12.0 Hz, 4.4 Hz, 1H), 3.67 (dd, *J* = 12.0 Hz, 8.4 Hz, 1H), 2.38 (ddd, *J* = 13.2 Hz, 8.4 Hz, 4.8 Hz, 1H), 1.91 (dd, *J* = 4.4 Hz, 3.6 Hz, 1H), 1.84 (q, *J* = 4.4 Hz, 1H), 1.04 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 197.4, 196.7, 135.6, 135.5, 133.0, 132.9, 130.0, 127.9, 60.4, 44.9, 40.3, 26.8, 23.0, 19.1; FTIR (thin film, $CHCl_3$) 3071, 2932, 2858, 1705, 1427, 1110, 823, 741, 702; HRMS (TOF ES) cald for $C_{22}H_{27}O_3Si$, *m/z* 367.1729 $[M+H]^+$, found: 367.1740.




**Ethyl 2,2-bis(benzyloxymethyl)cyclopropanecarboxylate (2.89)**: A solution of ethyl

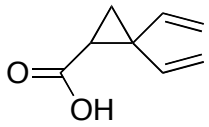
diazoacetate (566 mg, 4.47 mmol) in dichloromethane (2 mL) was added via syringe pump to a mixture of **2.88** (1.02 g, 3.73 mmol) and rhodium (II) acetate dimmer (16 mg, 0.037 mmol) in refluxing dichloromethane (3 mL) over a period of 5 h. After the addition was complete, the reaction mixture was refluxed for 12 h. The solvent was evaporated, and the residue was purified by flash chromatography (silica gel, 15% EtOAc/hexanes) to provide the title compound (870 mg, 66%) as a colorless oil: $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (m, 10H), 4.53 (d, *J* = 12.8 Hz, 1H), 4.50 (d, *J* = 12.8 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.43 (d, *J* = 12.0 Hz, 1H), 4.16-4.07 (m, 2H), 3.89 (d, *J* = 10.0 Hz, 1H), 3.75 (d, *J* = 9.6 Hz, 1H), 3.59 (d, *J* = 10.0 Hz, 1H), 3.30 (d, *J* = 9.6 Hz, 1H), 1.78 (dd, *J* = 8.0 Hz, 6.0 Hz, 1H), 1.27 (t, *J* = 5.6 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 1H), 1.13 (dd, *J* = 8.0 Hz, 4.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.0, 138.6, 138.3, 128.4, 128.3, 127.7, 127.6, 127.5, 127.4, 73.0, 72.9, 72.7, 68.3, 60.6, 30.8, 22.2, 16.7, 14.3; FTIR (thin film, $CHCl_3$) 3063, 3030, 2980, 2861, 1724, 1496, 1453, 1407, 1366, 1384, 1300, 1217, 1179, 1097, 1027, 738 cm$^{-1}$; HRMS (TOF ES) cald for $C_{24}H_{25}O_4$, *m/z* 377.1753 $[M]^+$, found: 377.1759.




**Ethyl 2,2-diformylcyclopropanecarboxylate (2.91)**: $Pd(OH)_2$/C catalyst (200 mg) was added under a flush of argon to a solution of *bis*-benzyl ether **2.89** (5.13 g, 14.47 mmol) in EtOAc (ACS-reagent grade; 80 mL). The reaction mixture was stirred under 60 psi of $H_2$ for 12 h. The catalyst was filtered off, and the filtrate was concentrated *in vacuo*.

The crude diol **2.90** was dissolved in dichloromethane (80 mL). Iodobenzene diacetate (14.03 g, 46.7 mmol) and TEMPO (226 mg, 1.45 mmol) were added, and the reaction mixture

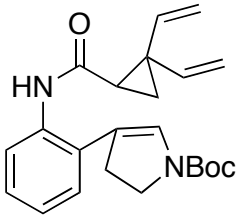
was stirred at room temperature for 12 h. The reaction was first quenched with a saturated aqueous $Na_2S_2O_3$ solution to remove excess of iodobenzene diacetate, and was then treated with $NaHCO_3$ power to remove acetic acid. The aqueous layer was extracted with dichloromethane, and the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated by rotary evaporation (water aspirator; the water bath temperature was kept below 20 °C). The crude product was purified by flash chromatography (silica gel, 20% EtOAc/hexanes) to provide the title compound (2.12 g, 86%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 10.30 (s, 1H), 9.64 (s, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 2.78 (t, *J* = 8.1 Hz, 1H), 2.28 (dd, *J* = 7.5 Hz, 4.5 Hz, 1H), 2.02 (dd, *J* = 8.4 Hz, 4.5 Hz, 1H), 1.30 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 196.8, 195.7, 168.4, 62.3, 44.2, 38.9, 23.0, 14.2; FTIR (thin film, $CHCl_3$) 2985, 2873, 1725, 1711, 1381, 1247, 1192, 1006 cm$^{-1}$; HRMS (TOF ES) cald for $C_8H_{10}O_4Na$, *m/z* 193.0477 $[M+Na]^+$, found: 193.0502.




**2,2-Divinylcyclopropanecarboxylic acid (2.63)**: A NaHMDS solution (1 M in THF, 32.1 mL) was added dropwise to a stirred solution of methyl triphenylphosphonium bromide (13.2 g, 37.0 mmol) in THF (70 mL) at −78 °C. The reaction mixture was stirred at this temperature for 1 h, then a solution of dialdehyde **2.91** (2.1 g, 12.3 mmol) in THF (15 mL) was added dropwise. The reaction mixture was warmed to 0 °C and stirred for 2 h. The reaction was quenched with a saturated aqueous $NH_4Cl$ solution, and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated by rotary evaporation (water aspirator; the water bath temperature was kept below 20 °C). The residue was

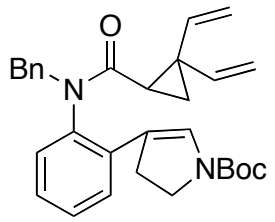
quickly passed through a short pad of silica gel (5% EtOAc/hexanes) to remove the polar phosphine oxide byproduct. The collected eluent was then concentrated by rotary evaporation (water aspirator; the water bath temperature was kept below 20 °C).

The crude divinyl ester was dissolved in a 1:1:1 mixture of THF/$H_2O$/MeOH (90 mL). Lithium hydroxide monohydrate (592 mg, 24.7 mmol) was added, and the reaction mixture was stirred at room temperature for 5 h. The mixture was diluted with $H_2O$ (50 mL) and acidified with 3 M HCl until pH = 3. The mixture was extracted with dichloromethane, and the combined organic layer was dried over $MgSO_4$ and concentrated by rotary evaporation (water aspirator; the water bath temperature was kept below 23 °C). The crude product (light yellow oil) could be directly used for the subsequent amide coupling reactions. To get an analytically pure sample, flash chromatography purification (silica gel, 50% EtOAc/hexanes) was performed to provide the title compound (1.02 g, 60%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 5.96 (dd, *J* = 16.8 Hz, 10.4 Hz, 1H), 5.95 (dd, *J* = 16.8 Hz, 10.4 Hz, 1H), 5.22 (dd, *J* = 10.0 Hz, 1.2 Hz, 1H), 5.21 (dd, *J* = 17.2 Hz, 1.2 Hz, 1H), 5.14 (dd, *J* = 10.8 Hz, 1.2 Hz, 1H), 5.13 (dd, *J* = 16.8 Hz, 1.2 Hz, 1H), 2.00 (dd, *J* = 8.0 Hz, 6.4 Hz, 1H), 1.63 (dd, *J* = 6.4 Hz, 4.8 Hz, 1H), 1.44 (dd, *J* = 8.0 Hz, 4.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 177.1, 138.9, 135.3, 117.4, 115.3, 35.8, 28.8, 20.0; FTIR (thin film, $CHCl_3$) 3089, 2703, 1700, 1636, 1433, 1276, 1238, 1217, 991, 914, 853 cm$^{-1}$; HRMS (TOF ES) cald for $C_8H_{10}O_2K$, *m/z* 177.0318 $[M+K]^+$, found: 177.0315.

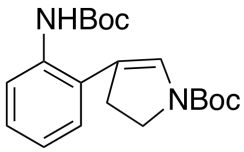



***tert*-Butyl 4-(2-(2,2-divinylcyclopropanecarboxamido)phenyl)-2,3-dihydro-1*H*-pyrrole-1-**

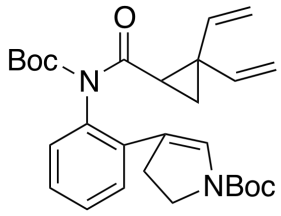
**carboxylate (2.93)**: The Ghosez reagent (76 μL, 0.576 mmol) was added to a solution of acid **2.63** (80 mg, 0.576 mmol) in dichloromethane (2 mL), and the mixture was stirred at room temperature for 2 h. The resulting crude acid chloride solution was added dropwise to a mixture containing aniline **2.78** (100 mg, 0.384 mmol), pyridine (94 μL, 1.15 mmol), and DMAP (5 mg, 0.038 mmol) in dichloromethane (3 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 5 h. It was diluted with dichloromethane and then washed with a 0.5M NaOH solution (to remove the excess of acid **2.63** that may co-elute with the product) and a saturated $CuSO_4$ solution. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 30% EtOAc/hexanes) to provide the title compound (113 mg, 77%) as a colorless oil, in a 1.6:1 mixture of *N*-Boc rotamers: $^1$H NMR (400 MHz, $CDCl_3$) δ major rotamer: 7.92 (brs, 1H), 7.09 (t, *J* = 8.4 Hz, 1H), 6.22 (d, *J* = 6.0 Hz, 1H), 6.11 (dd, *J* = 17.2 Hz, 10.4 Hz, 1H), 5.63 (dd, *J* = 17.2 Hz, 10.4 Hz, 1H), 3.74-3.70 (m, 1H), 1.83 (dd, *J* = 10.8 Hz, 4.8 Hz, 1H), 1.46 (s, 9H); minor rotamer: 8.14 (brs, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.62 (d, *J* = 7.6 Hz, 1H), 5.96 (dd, *J* = 17.2 Hz, 10.4 Hz, 1H), 5.95 (dd, *J* = 17.2 Hz, 10.4 Hz, 1H), 1.63 (dd, *J* = 10.8 Hz, 4.8 Hz, 1H), 1.48 (s, 9H); overlapping resonances: 7.24-7.17 (m, 2H), 5.31-5.02 (m, 4H), 4.04-3.70 (m, 2H), 2.90-2.76 (m, 1H), 2.18-2.13 (m, 1H), 2.07-1.95 (m, 1H), 1.38-1.32 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.4, 152.0, 151.4, 139.4, 135.8, 134.5, 128.4, 128.3, 127.6, 127.4, 124.7, 122.9, 117.5, 116.8, 114.7, 80.9, 80.6, 45.3, 44.8, 34.6, 33.0, 32.5, 32.2, 31.9, 28.4, 18.5, 18.3; FTIR (thin film, $CHCl_3$) 3265, 2977, 1700, 1576, 1522, 1451, 1409, 1255, 1170, 1127, 905, 754 $cm^{-1}$; HRMS (TOF ES) cald for $C_{23}H_{28}N_2O_3Na$, *m/z* 403.1998 $[M+Na]^+$, found: 403.1988.



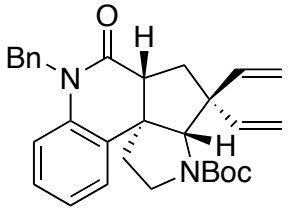

***tert*-Butyl 4-(2-(*N*-benzyl-2,2-divinylcyclopropanecarboxamido)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carboxylate (2.92)**: Benzylaniline **2.73** (100 mg, 0.285 mmol) was acylated in the same manner as **2.93**, and the crude product was purified by flash chromatography (silica gel, 20% EtOAc/hexanes) to provide the title compound (112 mg, 83%) as a colorless oil, that was a mixture of multiple rotamers (see attached $^{1}$H NMR and $^{13}$C NMR spectra): FTIR (thin film, $CHCl_3$) 3084, 3063, 2977, 2929, 1703, 1654, 1616, 1450, 1405, 1365, 1282, 1256, 1169, 1128, 1001, 906, 753 cm$^{-1}$; HRMS (TOF ES) cald for $C_{30}H_{34}N_2O_3Na$, *m/z* 493.2467 $[M+Na]^+$, found: 493.2488.




***tert*-Butyl 4-(2-((*tert*-butoxycarbonyl)amino)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carboxylate (2.102)**: A mixture of free aniline 2.78 (510 mg, 1.96 mmol), $LiClO_4$ (42 mg, 0.39 mmol), and $Boc_2O$ (869 mg, 3.92 mmol) in dichloromethane (25 mL) was stirred at room temperature for 12 h. The remaining solid in the reaction mixture was filtered off, and the solvent was evaporated. The residue was purified by flash chromatography (silica gel, 15% EtOAc/hexanes) to provide the title compound (664 mg, 94%) as a brown oil, with a small amount of inseparable impurities (see attached $^{1}$H NMR spectrum).

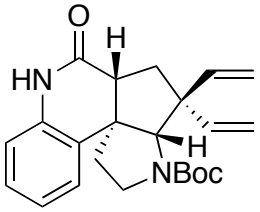



***tert*-Butyl 4-(2-(*N*-(*tert*-butoxycarbonyl)-2,2-divinylcyclopropanecarboxamido)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carboxylate (2.103)**: The Ghosez reagent (80 μL, 0.608 mmol) was added to a solution of acid **2.63** (84 mg, 0.608 mmol) in toluene (2 mL), and the mixture was stirred at room temperature for 2 h. A KHMDS solution (0.5 M in toluene, 0.97 mL) was slowly added to a solution of **2.102** (172 mg, 0.406 mmol) in THF (5 mL) at 0 °C. After 30 min, a fresh solution of acid chloride **2.98** (0.608 mmol, in 2 mL of toluene), prepared from acid **2.63** and Ghosez reagent, was slowly added. The reaction mixture was then stirred at room temperature for 12 h, before it was partitioned between $H_2O$ and diethyl ether. The aqueous layer was extracted with diethyl ether, and the combined organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 15% EtOAc/hexanes) to provide the title compound (152 mg, 70%) as a colorless oil, that was a mixture of multiple rotamers (see attached $^1$H NMR and $^{13}$C NMR spectra): FTIR (thin film, $CHCl_3$) 2977, 2931, 1732, 1700, 1451, 1408, 1368, 1299, 1253, 1156, 1128, 896, 757; HRMS (TOF ES) cald for $C_{28}H_{36}N_2O_5Na$, *m/z* 503.2522 $[M+Na]^+$, found: 503.2519.



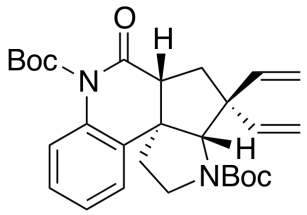

**(3a*S**,5a*R**,11b*R**)-*tert*-Butyl 7-benzyl-6-oxo-4,4-divinyl-3a,4,5,5a,6,7-hexahydro-1*H*-pyrrolo[3′,2′:2,3]cyclopenta[1,2-*c*]quinoline-3(2*H*)-carboxylate (2.96)**: A solution of AIBN (9

mg, 0.054 mmol) and $Bu_3SnH$ (57 μL, 0.217 mmol) in toluene (3 mL) was added via syringe pump to a solution of divinylcyclopropane **2.92** (51 mg, 0.108 mmol) in refluxing toluene (9 mL) over a period of 4 h. The reaction mixture was cooled to room temperature, and the solvent was evaporated. The residue was purified by flash chromatography (silica gel, 15% EtOAc/hexanes) to provide the title compound (28 mg, 55%) as a colorless oil, in a 1.5:1 mixture of rotamers: $^1$H NMR (500 MHz, $CDCl_3$) δ major rotamer: 4.36 (s, 1H), 2.97 (dd, *J* = 12.0 Hz, 6.0 Hz, 1H), 1.54 (s, 9H); minor rotamer: 4.52 (s, 1H), 3.03 (dd, *J* = 12.0 Hz, 6.0 Hz, 1H), 1.51 (s, 9H); overlapping resonance: 7.34-7.16 (m, 6H), 7.02-6.95 (m, 3H), 6.15-5.90 (m, 2H), 5.39-5.34 (m, 1H), 5.24-4.99 (m, 5H), 3.52-3.30 (m, 2H), 2.45-2.36 (m, 1H), 2.32-2.27 (m, 1H), 2.21-2.15 (m, 1H), 1.61 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.1, 170.8, 154.4, 154.1, 144.4, 143.6, 140.8, 140.6, 139.1, 137.1, 135.1, 134.9, 128.8, 127.8, 127.7, 127.3, 126.8, 123.3, 123.0, 122.7, 116.7, 114.1, 113.4, 112.1, 112.0, 80.5, 79.8, 71.8, 71.5, 54.6, 54.4, 54.0, 53.4, 46.2, 45.8, 45.7, 45.4, 45.2, 31.5, 31.3, 30.6, 30.5, 28.6, 28.5; FTIR (thin film, $CHCl_3$) 2974, 2924, 1690, 1490, 1455, 1392, 1159, 1110, 914, 754 cm$^{-1}$; HRMS (TOF ES) cald for $C_{30}H_{34}N_2O_3Na$, *m/z* 493.2467 $[M+Na]^+$, found: 493.2494.



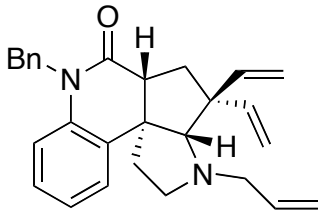

**(3a*S**,5a*R**,11b*R**)-*tert*-Butyl 6-oxo-4,4-divinyl-3a,4,5,5a,6,7-hexahydro-1*H*-pyrrolo[3′,2′:2,3]cyclopenta[1,2-*c*]quinoline-3(2*H*)-carboxylate (2.97)**: Annulation of **2.93** (56 mg, 0.147 mmol) in the manner of **2.96**, followed by flash chromatography purification (silica gel, 30% EtOAc/$CH_2Cl_2$), provided the title compound (21 mg, 38%) as a colorless oil, in

a 1.5:1 mixture of rotamers: $^1$H NMR (600 MHz, $CDCl_3$) δ major rotamer: 6.97 (d, *J* = 7.2 Hz, 1H), 6.01 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H), 5.91 (dd, *J* = 17.2 Hz, 10.8 Hz, 1H), 4.35 (s, 1H), 2.87 (dd, *J* = 12.0 Hz, 6.8 Hz, 1H), 1.54 (s, 9H); minor rotamer: 6.11 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H), 5.97 (dd, *J* = 17.2 Hz, 10.8 Hz, 1H), 5.20 (d, *J* = 17.6 Hz, 1H), 4.50 (s, 1H), 2.93 (dd, *J* = 12.0 Hz, 6.8 Hz, 1H), 1.51 (s, 9H); overlapping resonances: 7.25-7.22 (m, 1H), 7.07-7.03 (m, 2H), 6.88 (d, *J* = 7.6 Hz, 1H), 5.14-5.06 (m, 4H), 3.52-3.28 (m, 2H), 2.38-2.12 (m, 3H), 1.59 (dd, *J* = 12.4 Hz, 6.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.8, 171.6, 154.5, 154.1, 144.2, 143.5, 140.7, 140.6, 136.4, 133.1, 132.9, 128.0, 127.8, 123.5, 123.3, 123.1, 116.3, 116.2, 114.2, 113.5, 112.1, 112.0, 80.5, 79.8, 71.4, 71.0, 55.1, 54.6, 54.1, 54.0, 45.5, 45.4, 45.3, 45.1, 31.6, 30.6, 30.3, 29.6, 28.6, 28.5; FTIR (thin film, $CHCl_3$) 3241, 3083, 2960, 2927, 1690, 1610, 1589, 1477, 1393, 1301, 1250, 1171, 1111, 915, 756 cm$^{-1}$; HRMS (TOF ES) cald for $C_{23}H_{29}N_2O_3$, *m/z* 381.2178 $[M+H]^+$, found: 381.2181.




**(3a*R*,5a*R*,11b*R*)-Di-*tert*-butyl 6-oxo-4,4-divinyl-4,5,5a,6-tetrahydro-1*H*-pyrrolo[3',2':2,3]cyclopenta[1,2-*c*]quinoline-3,7(2*H*,3a*H*)-dicarboxylate (2.104)**: *Bis*-carbamate **2.103** (104 mg, 0.216 mmol) was annulated in the manner of **2.96**, and the crude product was partitioned between acetonitrile and hexanes to remove most of the tin residue. The acetonitrile layer was concentrated, and the crude product was purified by flash chromatography (silica gel, 15% EtOAc/hexanes) to provide the title compound (55 mg, 53%) as a colorless oil, in a 1.5:1 mixture of rotamers: $^1$H NMR (400 MHz, $CDCl_3$) δ major rotamer: 6.00 (dd, *J* = 17.6

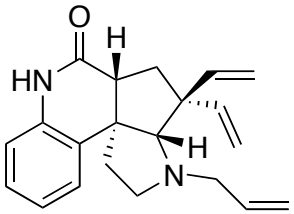
Hz, 10.8 Hz, 1H), 5.91 (dd, *J* = 17.2 Hz, 10.8 Hz, 1H), 4.32 (s, 1H), 2.87 (dd, *J* = 12.4 Hz, 8.0 Hz, 1H), 2.33 (t, *J* = 13.2 Hz, 1H), 1.54 (s, 9H); minor rotamer: 6.09 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H), 5.95 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H), 4.47 (s, 1H), 2.92 (dd, *J* = 12.4 Hz, 8.0 Hz, 1H), 2.37 (t, *J* = 13.2 Hz, 1H), 1.51 (s, 9H); overlapping signals: 7.29-7.25 (m, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.06-6.97 (m, 2H), 5.17-5.04 (m, 4H), 3.55-3.34 (m, 2H), 2.23-2.13 (m, 2H), 1.70-1.65 (m, 1H), 1.62 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.8, 169.5, 154.5, 154.0, 152.0, 151.9, 144.2, 143.4, 140.6, 140.5, 136.7, 135.0, 134.8, 127.7, 127.6, 124.7, 123.1, 122.8, 119.1, 119.0, 114.2, 113.5, 112.0, 85.2, 85.1, 80.5, 79.9, 77.6, 71.8, 71.5, 54.9, 54.5, 54.0, 53.9, 46.6, 46.4, 45.4, 45.3, 31.6, 30.6, 28.6, 28.5, 28.0, 27.8, 23.5, 22.7; FTIR (thin film, $CHCl_3$) 2976, 2928, 1698, 1454, 1392, 1368, 1249, 1150; HRMS (TOF ES) cald for $C_{28}H_{36}N_2O_5Na$, *m/z* 503.2522 $[M+Na]^+$, found: 503.2540.




**(3a*S**,5a*R**,11b*R**)-3-Allyl-7-benzyl-4,4-divinyl-2,3,3a,4,5,5a-hexahydro-1*H*-pyrrolo[3′,2′:2,3]cyclopenta[1,2-*c*]quinoline-6(7*H*)-one (2.99)**: Carbamate **2.96** (33 mg, 0.07 mmol) was dissolved in 15:1 $CH_2Cl_2$/TFA (3 mL), and the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated and the residue was re-dissolved in dichloromethane. This solution was washed with a 1 M NaOH solution, dried over $MgSO_4$, and concentrated *in vacuo*.

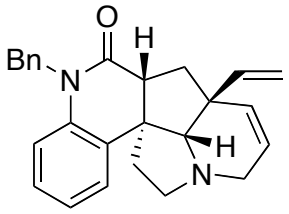
The crude amine product was dissolved in acetonitrile (1 mL), followed by addition of $K_2CO_3$ (10 mg, 0.140 mmol) and allyl bromide (8 μL, 0.091 mmol). The reaction mixture was

stirred at room temperature for 12 h. The reaction was quenched with water, and the mixture was extracted with dichloromethane. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 10% EtOAc/hexanes) to provide the title compound (24 mg, 83%) a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.33-7.24 (m, 5H), 7.15 (td, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.10 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.02-6.99 (m, 2H), 6.27 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H), 5.97 (dddd, *J* = 17.6 Hz, 10.8 Hz, 6.8 Hz, 5.2 Hz, 1H), 5.78 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H), 5.39 (d, *J* = 16.0 Hz, 1H), 5.24 (dd, *J* = 17.2 Hz, 1.2 Hz, 1H), 5.15 (d, *J* = 10.8 Hz, 1H), 5.12 (d, *J* = 10.8 Hz, 1H), 5.11 (dd, , *J* = 10.8 Hz, 1.6 Hz, 1H), 5.04 (dd, *J* = 17.6 Hz, 1.6 Hz, 1H), 5.03 (d, *J* = 17.6 Hz, 1H), 4.95 (d, *J* = 16.0 Hz, 1H), 3.52 (m, 1H), 3.51 (s, 1H), 3.20 (dd, *J* = 13.2 Hz, 8.0 Hz, 1H), 2.97 (dd, *J* = 8.8 Hz, 6.4 Hz, 1H), 2.91 (dd, *J* = 12.8 Hz, 6.4 Hz, 1H), 2.35 (ddd, *J* = 13.6 Hz, 8.8 Hz, 4.8 Hz, 1H), 2.23 (t, *J* = 12.8 Hz, 1H), 2.11 (dd, *J* = 12.0 Hz, 6.4 Hz, 1H), 2.05 (dd, *J* = 12.8 Hz, 4.8 Hz, 1H), 1.35 (dd, *J* = 12.0 Hz, 4.8 Hz, 1H); $^{13}$C NMR (100 HMz, $CDCl_3$) δ 171.8, 143.8, 142.8, 139.6, 137.5, 137.4, 135.9, 128.7, 127.2, 127.1, 126.9, 123.6, 122.5, 117.0, 116.7, 114.2, 113.2, 74.8, 58.4, 55.3, 54.5, 50.9, 47.5, 46.3, 34.0, 32.7; FTIR (thin film, $CHCl_3$) 3077, 2970, 2795, 1687, 1601, 1454, 1387, 1210, 916, 753, 730 $cm^{-1}$; HRMS (TOF ES) cald for $C_{28}H_{31}N_2O$, *m/z* 411.2436 $[M+H]^+$, found: 411.2407.



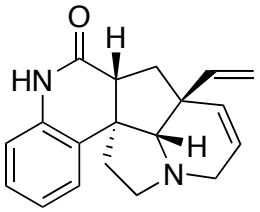

**(3a*S**,5a*R**,11b*R**)-3-Allyl-4,4-divinyl-2,3,3a,4,5,5a-hexahydro-1*H*-pyrrolo[3′,2′:2,3]cyclopenta[1,2-*c*]quinoline-6(7*H*)-one (2.101)**: *N*-Boc deprotection and

allylation of carbamate **2.97** (13 mg, 0.034 mmol) in the manner of **2.99** provided the title compound (8 mg, 73%) a colorless oil after flash chromatography purification (silica gel, 15% EtOAc/hexanes). Alternatively, the title compound could be obtained in similar yields via *N*-Boc deprotection and allylation of *bis*-carbamate **2.104** in the manner of **2.99**: $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.20 (td, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.12 (d, *J* = 6.5 Hz, 1H), 7.03 (td, *J* = 7.5 Hz, 1.0 Hz, 1H), 6.85 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 6.26 (dd, *J* = 17.5 Hz, 10.5 Hz, 1H), 5.97 (dddd, *J* = 17.5 Hz, 10.5 Hz, 7.0 Hz, 6.0 Hz, 1H), 5.77 (dd, *J* = 17.5 Hz, 10.5 Hz, 1H), 5.25 (dd, *J* = 17.5 Hz, 1.5 Hz, 1H), 5.15 (d, *J* = 10.5 Hz, 1H), 5.11 (d, *J* = 11.0 Hz, 1H), 5.10 (dd, *J* = 10.5 Hz, 1.5 Hz, 1H), 5.04 (dd, *J* = 17.5 Hz, 1.5 Hz, 1H), 5.02 (d, *J* = 17.5 Hz, 1H), 3.52 (dd, *J* = 13.5 Hz, 5.5 Hz, 1H), 3.49 (s, 1H), 3.21 (dd, *J* = 13.5 Hz, 7.5 Hz, 1H), 2.98 (dd, *J* = 8.5 Hz, 6.0 Hz, 1H), 2.82 (dd, *J* = 13.0 Hz, 5.5 Hz, 1H), 2.38 (ddd, *J* = 14.0 Hz, 9.0 Hz, 5.0 Hz, 1H), 2.17 (t, *J* = 13.0 Hz), 2.09 (td, *J* = 12.0 Hz, 6.5 Hz, 1H), 1.45 (dd, *J* = 12.0 Hz, 5.0 Hz, 1H); $^{13}$C NMR (100 HMz, $CDCl_3$) δ 172.4, 143.7, 142.7, 136.8, 135.9, 135.6, 127.3, 124.0, 122.6, 117.0, 116.3, 114.2, 113.3, 74.4, 58.4, 55.9, 54.6, 50.7, 47.2, 34.2, 31.8; FTIR (thin film, $CHCl_3$) 3223, 3079, 2971, 2917, 2795, 1687, 1473, 1395, 1295, 1246, 916, 752 $cm^{-1}$; HRMS (TOF ES) cald for $C_{21}H_{25}N_2O$, *m/z* 321.1967 $[M+H]^+$, found: 321.1964.



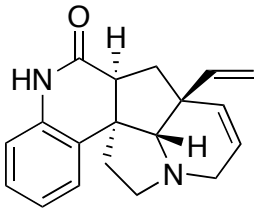

**(6b*R**,6b$^{1}$*S**,12a*S**,13a*S**)-2-Benzyl-12a-vinyl-2,6b$^{1}$,7,8,10,12a,13,13a-octahydro-1*H*-indolizino[1′,8′:2,3,4]cyclopenta[1,2-*c*]quinolin-1-one (2.100)**: Hoveyda-Grubbs II catalyst (2 mg, 0.004 mmol) was added to a solution of triene **2.99** (16 mg, 0.039 mmol) in toluene (5 mL),

and the reaction mixture was heated at 60 °C for 5 h. The solvent was evaporated, and the residue was purified by flash chromatography (silica gel, 50% EtOAc/$CH_2Cl_2$) to afford the title compound as a yellow oil (14 mg, 94%): $^1$H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.33-7.29 (m, 2H), 7.25-7.23 (m, 3H), 7.11 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.02 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 6.94 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 5.84 (dd, *J* = 10.0 Hz, 2.0 Hz, 1H), 5.75 (dd, *J* = 17.2 Hz, 10.4 Hz, 1H), 5.72 (ddd, *J* = 10.4 Hz, 5.2 Hz, 1.6 Hz, 1H), 5.36 (d, *J* = 16.0 Hz, 1H), 5.03 (d, *J* = 17.2 Hz, 1H), 5.00 (d, *J* = 10.4 Hz, 1H), 4.98 (d, *J* = 16.0 Hz, 1H), 3.96 (s, 1H), 3.64 (dt, *J* = 17.6 Hz, 2.0 Hz, 1H), 3.28 (dd, *J* = 17.6 Hz, 5.6 Hz, 1H), 3.11-3.02 (m, 2H), 2.94 (t, *J* = 8.8 Hz, 1H), 2.26 (dd, *J* = 12.4 Hz, 5.6 Hz, 1H), 2.15 (ddd, *J* = 13.2 Hz, 8.0 Hz, 1.2 Hz, 1H), 1.82 (dd, *J* = 17.2 Hz, 13.2 Hz, 1H), 1.81 (t, *J* = 12.8 Hz, 1H); $^{13}$C NMR (100 HMz, $CDCl_3$) δ 171.8, 144.8, 139.2, 138.1, 137.3, 131.3, 128.7, 127.1, 127.0, 126.7, 123.5, 122.5, 121.1, 116.6, 112.4, 72.2, 54.9, 52.1, 48.4, 46.2, 46.0, 45.0, 35.5, 35.0; FTIR (thin film, $CHCl_3$) 3024, 2925, 2842, 1684, 1601, 1455, 1389, 1212, 754, 730 cm$^{-1}$; HRMS (TOF ES) cald for $C_{26}H_{27}N_2O$, *m/z* 383.2123 $[M+H]^+$, found: 383.2146.



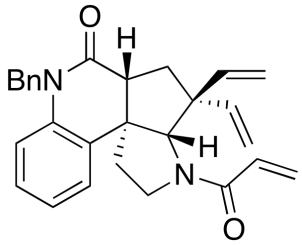

**(6b*R**,6b$^1$*S**,12a*S**,13a*S**)-12a-Vinyl-2,6b$^1$,7,8,10,12a,13,13a-octahydro-1*H*-indolizino[1′,8′:2,3,4]cyclopenta[1,2-*c*]quinolin-1-one, (±)-epimeloscine (2.15b)**: Ring-closing metathesis of triene **2.101** (16 mg, 0.05 mmol) in the manner of **2.100**, followed by flash chromatography purification (silica gel, 5% MeOH/$CH_2Cl_2$), afforded the title compound as a yellow oil. Further purification by HPLC ($C_{18}$ column, 70:30 $CH_3CN/H_2O$) provided (±)-

epimeloscine (13 mg, 89%) as an off-white solid: mp 172-175 °C; $^1$H NMR (700 MHz, $CDCl_3$) δ 7.38 (brs, 1H), 7.36 (d, *J* = 7.0 Hz, 1H), 7.17 (td, *J* = 7.0 Hz, 1.4 Hz, 1H), 7.05 (t, *J* = 7.0 Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 5.82 (dd, *J* = 10.5 Hz, 2.8 Hz, 1H), 5.73 (dd, *J* = 17.5 Hz, 10.5 Hz, 1H), 5.72 (ddd, *J* = 10.5 Hz, 5.6 Hz, 1.4 Hz, 1H), 5.03 (d, *J* = 16.8 Hz, 1H), 5.00 (d, *J* = 10.5 Hz, 1H), 3.94 (s, 1H), 3.64 (dt, *J* = 17.5 Hz, 2.1 Hz, 1H), 3.28 (dd, *J* = 17.5 Hz, 4.9 Hz, 1H), 3.04 (dd, *J* = 17.6 Hz, 9.1 Hz, 1H), 2.99 (dd, *J* = 13.3 Hz, 5.6 Hz, 1H), 2.94 (t, *J* = 9.1 Hz, 1H), 2.21 (dd, *J* = 13.6 Hz, 6.3 Hz, 1H), 2.18 (dd, *J* = 13.6 Hz, 6.3 Hz, 1H), 1.84 (ddd, *J* = 14.0 Hz, 10.5 Hz, 9.1 Hz, 1H), 1.74 (t, *J* = 13.3 Hz, 1H); $^{13}$C NMR (150 HMz, $CDCl_3$) δ 172.6, 144.5, 136.5, 136.0, 131.1, 127.0, 123.6, 122.7, 121.1, 116.1, 112.4, 71.6, 55.4, 51.9, 48.0, 45.9, 45.0, 35.6, 34.0; FTIR (thin film, $CHCl_3$) 3212, 3079, 2923, 2843, 1686, 1609, 1588, 1475, 1396, 1300, 1253, 1152, 1108, 916, 755, 733 cm$^{-1}$; HRMS (TOF ES) cald for $C_{19}H_{20}N_2O$, *m/z* 293.1654 $[M+H]^+$, found: 293.1658.



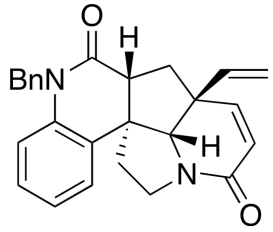

**(6b*R**,6b$^1$*S**,12a*S**,13a*R**)-12a-Vinyl-2,6b$^1$,7,8,10,12a,13,13a-octahydro-1*H*-indolizino[1′,8′:2,3,4]cyclopenta[1,2-*c*]quinolin-1-one, (±)-meloscine (2.15a)**: Potassium *tert*-butoxide (5 mg, 0.041 mmol) was added to a solution of (±)-epimeloscine **2.15b** (6 mg, 0.021 mmol) in *tert*-butanol (2 mL), and the reaction mixture was heated at 80 °C for 12 h. The solvent was evaporated and the residue was dissolved in a minimum amount of methanol. Flash chromatography purification (silica gel, 7% MeOH/$CH_2Cl_2$) provided the title compound (5 mg, 83%) as an off-white solid: mp 206-210 °C; $^1$H NMR (700 MHz, $CDCl_3$) δ 7.89 (brs, 1H), 7.40

(d, *J* = 7.7 Hz, 1H), 7.16 (t, *J* = 7.0 Hz, 1H), 7.06 (t, *J* = 7.7 Hz, 1H), 6.69 (d, *J* = 7.7 Hz, 1H), 6.02 (m, 1H), 5.73 (d, *J* = 9.1 Hz, 1H), 5.55 (dd, *J* = 17.5 Hz, 10.5 Hz, 1H), 4.92 (d, *J* = 16.8 Hz, 1H), 4.80 (d, *J* = 10.5 Hz, 1H), 3.52 (s, 1H), 3.31 (dd, *J* = 16.1 Hz, 5.6 Hz, 1H), 3.20 (dd, *J* = 15.4 Hz, 7.7 Hz, 1H), 3.15 (d, *J* = 16.1 Hz, 1H), 2.97 (t, *J* = 9.1 Hz, 1H), 2.89 (dd, *J* = 11.9 Hz, 7.7 Hz, 1H), 2.32 (dd, *J* = 13.3 Hz, 7.7 Hz, 1H), 2.18 (dd, *J* = 13.6 Hz, 9.8 Hz, 1H), 2.12 (dt, *J* = 11.2 Hz, 5.6 Hz, 1H), 1.97 (dt, *J* = 13.3 Hz, 7.0 Hz, 1H); $^{13}$C NMR (100 HMz, $CDCl_3$) δ 171.6, 143.1, 135.0, 132.6, 127.9, 127.7, 127.0, 124.0, 115.3, 112.7, 82.3, 56.9, 53.0, 50.8, 48.0, 46.7, 43.4, 42.1; FTIR (thin film, $CHCl_3$) 3200, 3058, 2920, 1672, 1593, 1492, 1386, 1244, 754 $cm^{-1}$; HRMS (TOF ES) cald for $C_{19}H_{20}N_2O$, *m/z* 293.1654 $[M+H]^+$, found: 293.1657.



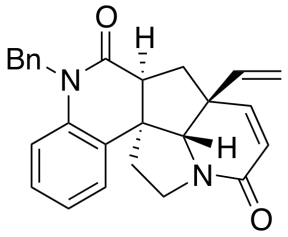

**(3a*S*,5a*R*,11b*R*)-3-Acryloyl-7-benzyl-4,4-divinyl-2,3,3a,4,5,5a-hexahydro-1*H*-pyrrolo[3',2':2,3]cyclopenta[1,2-*c*]quinolin-6(7*H*)-one (2.113)**: Carbamate **2.96** (27 mg, 0.057 mmol) was dissolved a mixed dichloromethane/TFA (10:1, 2 mL). The reaction mixture was stirred at room temperature for 4 h, before the sovent was evaporated. The residue was redissolved in dichloromethane and washed with an aqueous NaOH solution (1 M). The solution was dried over $MgSO_4$ and the volumn was reduced to 2 mL. Pyridine (19 μL, 0.23 mmol) and acryloyl chloride (19 μL, 0.114 mmol) were added at 0 °C. The reaction mixture was then stirred at room temperature for 2 h. It was diluted with dichloromethane, washed with an aqueous $CuSO_4$ solution, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 30% EtOAc/dichloromethane) to provide the title compound (23 mg,

94%) as a colorless oil, in a 2:1 mixture of amide rotamers: $^{1}$H NMR (400 MHz, $CDCl_3$) δ major rotamer: 6.21 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H), 5.89 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H), 4.86 (s, 1H), 3.09 (dd, *J* = 12.0 Hz, 6.4 Hz, 1H), 2.48 (t, *J* = 13.2 Hz, 1H); minor rotamer: 6.08 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H), 5.85 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H), 4.55 (s, 1H), 3.07 (dd, *J* = 12.0 Hz, 6.4 Hz, 1H), 2.59 (t, *J* = 13.2 Hz, 1H); overlapping resonance: 7.34-7.16 (m, 6H), 7.05-6.92 (m, 3H), 6.52-6.49 (m, 2H), 5.79-5.75 (m, 1H), 5.39-5.00 (m, 6H), 3.71-3.51 (m, 2H), 2.36-2.18 (m, 2H), 1.65-1.60 (m, 1H); $^{13}$C NMR (100 HMz, $CDCl_3$) δ 170.9, 170.4, 164.8, 164.6, 144.2, 143.4, 140.5, 139.4, 139.1, 137.9, 137.0, 136.9, 134.5, 134.4, 129.1, 128.8, 128.7, 128.2, 128.1, 127.9, 127.8, 127.4, 127.3, 126.9, 126.8, 125.3, 123.5, 123.4, 122.9, 122.5, 116.9, 116.8, 115.8, 113.5, 113.2, 112.2, 72.0, 71.5, 55.3, 54.6, 53.9, 52.8, 46.3, 46.2, 45.8, 45.7, 45.6, 45.5, 33.2, 31.6, 30.2, 21.5; HRMS (TOF ES) cald for $C_{28}H_{29}N_2O_2$, *m/z* 425.2229 $[M+H]^+$, found: 425.2213.



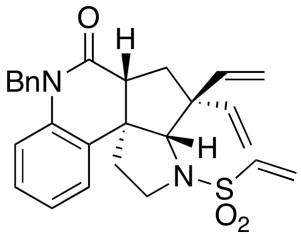

**(6b*R*,6b$^{1}$*S*,12a*S*,13a*R*)-2-Benzyl-12a-vinyl-6b$^{1}$,7,8,12a,13,13a-hexahydro-1*H*-indolizino[1',8':2,3,4]cyclopenta[1,2-*c*]quinoline-1,10(2*H*)-dione (2.105a)**: Acrylamide **2.113** (12 mg, 0.028 mmol) was dissolved in toluene (5 mL), and Hoveyda-Grubbs II catalyst (2 mg, 0.0028 mmol) was added. The reaction mixture was stirred at 80 °C for 8 h, and another portion of Hoveyda-Grubbs II catalyst (2 mg, 0.0028 mmol) was added. After 4 h, the solvent was evaporated, and the residue was purified by flash chromatography (silica gel, 5% MeOH/dichloromethane, with 0.5% $Et_3N$) to provide the title compound (9 mg, 80%) as a light brown oil: $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.34-7.31 (m, 2H), 7.26-7.19 (m, 5H), 7.09 (d, *J* = 7.5

Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.30 (d, *J* = 10.0 Hz, 1H), 5.94 (d, *J* = 10.0 Hz, 1H), 5.80 (dd, *J* = 17.5 Hz, 10.5 Hz, 1H), 5.33 (d, *J* = 16.0 Hz, 1H), 5.25 (d, *J* = 11.0 Hz, 1H), 5.14 (d, *J* = 17.5 Hz, 1H), 5.00 (d, *J* = 17.0 Hz, 1H), 4.60 (s, 1H), 4.31 (dd, *J* = 12.0 Hz, 7.0 Hz, 1H), 3.07 (dd, *J* = 13.0 Hz, 5.0 Hz, 1H), 2.96 (td, *J* = 12.5 Hz, 5.0 Hz, 1H), 2.24 (dd, *J* = 12.5 Hz, 5.0 Hz, 1H), 2.07 (t, *J* = 12.5 Hz, 1H), 1.89 (td, *J* = 12.5 Hz, 7.0 Hz, 1H), 1.50 (dd, *J* = 12.0 Hz, 5.0 Hz, 1H); $^{13}$C NMR (100 HMz, $CDCl_3$) δ 170.0, 160.7, 142.7, 141.3, 139.7, 137.0, 136.0, 128.8, 127.7, 127.4, 127.0, 123.1, 122.1, 121.8, 117.4, 117.3, 66.3, 55.8, 48.3, 48.2, 46.3, 43.6, 36.2, 34.1; FTIR (thin film, $CHCl_3$) 2928, 1686, 1663, 1603, 1453, 1391, 1255, 753, 733; HRMS (TOF ES) cald for $C_{26}H_{25}N_2O_2$, *m/z* 397.1916 $[M+H]^+$, found: 397.1909.



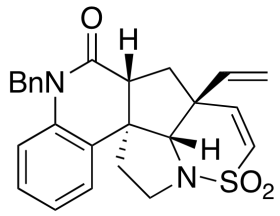

**(6b*R*,6b$^1$*S*,12a*S*,13a*S*)-2-Benzyl-12a-vinyl-6b$^1$,7,8,12a,13,13a-hexahydro-1*H*-indolizino[1',8':2,3,4]cyclopenta[1,2-*c*]quinoline-1,10(2*H*)-dione (2.105b)**: Epimerization of *N*-Bn-10-oxoepimeloscine **2.105a** (2.5 mg, 0.0063 mmol) by potassium *tert*-butoxide (1.4 mg, 0.013 mmol) in the manner of meloscine **2.15b**, followed by flash chromatography purification (silica gel, with 0.5% $Et_3N$, 7% MeOH/dichloromethane), provided the title compound (1.8 mg, 72%) as a thin film: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.35-7.30 (m, 4H), 7.22-7.16 (m, 3H), 7.08 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 6.94 (dd, *J* = 8.0 Hz, 0.8 Hz, 1H), 6.35 (d, *J* = 9.6 Hz, 1H), 5.96 (d, *J* = 9.6 Hz, 1H), 5.49 (d, *J* = 17.6 Hz, 1H), 5.46 (dd, *J* = 17.2 Hz, 10.4 Hz, 1H), 4.94 (d, *J* = 17.6 Hz, 2H), 4.91 (d, *J* = 10.6 Hz, 1H), 4.48 (s, 1H), 4.06 (dt, *J* = 12.8 Hz, 8.4 Hz, 1H), 3.68 (ddd, *J* = 13.6 Hz, 10.4 Hz, 3.6 Hz, 1H), 3.22 (t, *J* = 10.0 Hz, 1H), 2.55 (dd, *J* = 13.6 Hz, 9.6 Hz, 1H),

2.39 (ddd, *J* = 13.2 Hz, 8.8 Hz, 4.0 Hz, 1H), 2.27 (dd, *J* = 13.6 Hz, 10.8 Hz, 1H), 2.07 (ddd, *J* = 13.6 Hz, 10.4 Hz, 8.0 Hz, 1H); $^{13}$C NMR (150 HMz, $CDCl_3$) δ 169.3, 162.0, 143.6, 143.2, 138.2, 136.7, 128.9, 128.7, 127.3, 127.0, 126.3, 124.8, 123.8, 122.4, 116.2, 115.2, 57.3, 49.3, 47.5, 46.1, 45.4, 43.7, 36.3, 29.7; FTIR (thin film, $CHCl_3$) 2924, 1666, 1601, 1497, 1456, 1384, 1322, 923, 756, 730; HRMS (TOF ES) cald for $C_{26}H_{25}N_2O_2$, *m/z* 397.1916 $[M+H]^+$, found: 397.1935.

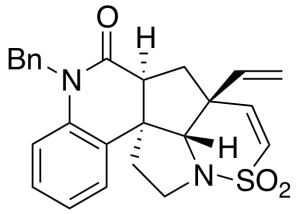



**(3a*S*,5a*R*,11b*R*)-7-Benzyl-4,4-divinyl-3-(vinylsulfonyl)-2,3,3a,4,5,5a-hexahydro-1*H*-pyrrolo[3',2':2,3]cyclopenta[1,2-*c*]quinolin-6(7*H*)-one** (**2.114**): Carbamate **2.96** (31 mg, 0.065 mmol) was dissolved a mixed dichloromethane/TFA (10:1, 2 mL). The reaction mixture was stirred at room temperature for 4 h, before the sovent was evaporated. The residue was redissolved in dichloromethane and washed with an aqueous NaOH solution (1 M). The solution was dried over $MgSO_4$, and the volumn was reduced to 2 mL. Collidine (43 μL, 0.324 mmol) and 2-chloroethane- sulfonyl chloride (14 μL, 0.129 mmol) were added at 0 °C. The reaction mixture was then stirred at room temperature for 12 h. It was diluted with dichloromethane, washed with an aqueous $NH_4Cl$ solution, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 50% EtOAc/dichloromethane) to provide the title compound (8 mg, 27%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.33-7.17 (m, 7H), 7.07-7.02 (m, 2H), 6.64 (dd, *J* = 16.8 Hz, 10.0 Hz, 1H), 6.35 (d, *J* = 16.8 Hz, 1H), 6.14 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H), 6.05 (d, *J* = 10.0 Hz, 1H), 5.96 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H), 5.35 (d, *J* = 16.0 Hz, 1H), 5.21-5.11 (m, 4H), 4.99 (s, *J* = 16.0 Hz, 1H), 4.63 (s, 1H), 3.33-

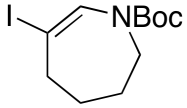
3.29 (m, 2H), 3.00 (dd, *J* = 12.4 Hz, 6.4 Hz, 1H), 2.39-2.20 (m, 3H), 1.63-1.56 (m, 1H); $^{13}$C NMR (100 HMz, $CDCl_3$) δ 170.7, 143.2, 141.4, 139.0, 136.9, 135.2, 134.6, 128.8, 128.0, 127.8, 127.4, 126.9, 123.4, 123.0, 116.9, 113.8, 113.2, 72.5, 54.7, 54.5, 46.6, 46.3, 46.0, 32.3, 31.0; FTIR (thin film, $CHCl_3$) 3061, 2925, 1684, 1603, 1492, 1455, 1385, 1346, 1213, 1149, 1029, 980, 920, 735; HRMS (TOF ES) cald for $C_{27}H_{29}N_2O_3S$, *m/z* 461.1899 $[M+H]^+$, found: 461.1879.



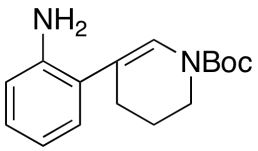

**(6b*R*,6b$^1$*S*,11a*S*,12a*R*)-2-Benzyl-11a-vinyl-6b$^1$,7,8,11a,12,12a-hexahydro-9-thia-2,8a-diazabenzo[*c*]cyclopenta[*ef*]fluoren-1(2*H*)-one 9,9-dioxide (2.106a)**: Ring-closing metathesis of vinylsulfonamide **2.114** (8 mg, 0.017 mmol) in the manner of **2.105a**, followed by flash chromatography purification (silica gel, with 0.5% $Et_3N$, 2% MeOH/dichloromethane), provided the title compound (6 mg, 84%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.2 Hz, 1H), 7.35-7.31 (m, 2H), 7.27-7.20 (m, 4H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 10.8 Hz, 1H), 6.39 (d, *J* = 10.8 Hz, 1H), 5.85 (dd, *J* = 17.2 Hz, 10.4 Hz, 1H), 5.34 (m, 2H), 5.28 (d, *J* = 10.4 Hz, 1H), 5.03 (d, *J* = 16.0 Hz, 1H), 4.76 (s, 1H), 3.65 (td, *J* = 9.6 Hz, 4.8 Hz, 1H), 3.35 (q, *J* = 9.6 Hz, 1H), 3.16 (dd, *J* = 13.2 Hz, 5.6 Hz, 1H), 2.50 (dd, *J* = 13.2 Hz, 6.0 Hz, 1H), 2.23 (ddd, *J* = 13.6 Hz, 8.8 Hz, 4.8 Hz, 1H), 2.05 (t, *J* = 13.2 Hz, 1H), 1.85 (dt, *J* = 13.2 Hz, 8.0 Hz, 1H); $^{13}$C NMR (100 HMz, $CDCl_3$) δ 169.8, 143.0, 140.6, 138.7, 136.8, 134.9, 128.8, 127.4, 126.8, 124.0, 123.5, 122.9, 117.0, 116.5; FTIR (thin film, $CHCl_3$) 3059, 2921, 1683, 1602, 1492, 1455, 1390, 1339, 1158, 758, 734; HRMS (TOF ES) cald for $C_{25}H_{25}N_2O_3S$, *m/z* 433.1586 $[M+H]^+$, found: 433.1606.




**(6b*R*,6b$^1$*S*,11a*S*,12a*S*)-2-Benzyl-11a-vinyl-6b$^1$,7,8,11a,12,12a-hexahydro-9-thia-2,8a-diazabenzo[*c*]cyclopenta[*ef*]fluoren-1(2*H*)-one 9,9-dioxide (2.106b)**: Epimerization of sulfonamide **2.105a** (3.5 mg, 0.0081 mmol) by potassium *tert*-butoxide (1.8 mg, 0.016 mmol) in the manner of meloscine **2.15a**, followed by flash chromatography purification (silica gel, with 0.5% $Et_3N$, 3% MeOH/dichloromethane), provided the title compound (3.0 mg, 86%) as a thin film: $^1$H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.27-7.25 (m, 1H), 7.19-7.16 (m, 3H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 10.8 Hz, 1H), 6.35 (d, *J* = 10.8 Hz, 1H), 5.96 (dd, *J* = 17.4 Hz, 10.2 Hz, 1H), 5.48 (d, *J* = 16.2 Hz, 1H), 5.10 (d, *J* = 10.2 Hz, 1H), 5.06 (d, *J* = 16.8 Hz, 1H), 4.99 (d, *J* = 17.4 Hz, 1H), 4.76 (s, 1H), 3.82 (dd, *J* = 9.6 Hz, 7.2 Hz, 1H), 3.31 (ddd, *J* = 12.0 Hz, 10.2 Hz, 5.4 Hz, 1H), 2.97 (dd, *J* = 12.6 Hz, 6.6 Hz, 1H), 2.32 (t, *J* = 12.6 Hz, 1H), 2.28 (dd, *J* = 12.6 Hz, 6.6 Hz, 1H), 2.16 (dd, *J* = 13.2 Hz, 5.4 Hz, 1H), 2.06 (td, *J* = 12.6 Hz, 7.2 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.4, 144.8, 140.9, 137.0, 136.3, 129.0, 128.9, 128.8, 127.5, 127.4, 126.2, 126.1, 124.4, 116.0, 115.9, 80.2, 58.5, 50.1, 48.5, 47.6, 46.0, 42.3, 37.7; FTIR (thin film, $CHCl_3$) 2955, 2918, 2851, 1666, 1600, 1498, 1454, 1386, 1337, 1162; HRMS (TOF ES) cald for $C_{25}H_{25}N_2O_3S$, *m/z* 433.1586 $[M+H]^+$, found: 433.1599.

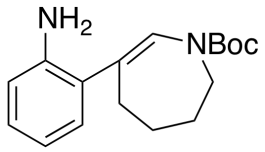


***tert*-Butyl 6-iodo-2,3,4,5-tetrahydro-1*H*-azepine-1-carboxylate (2.108)**: Sodium methoxide (0.55 g, 10.10 mmol) was added to a stirred solution of *tert*-butyl 2,3,4,5-tetrahydro-1*H*-azepine-1-carboxylate (1.0 g, 5.10 mmol) in MeOH (20 mL). An ICl solution (1 M in $CH_2Cl_2$, 5.60 mL) was added dropwise, and the mixture was stirred for 30 min after the completion of addition. The reaction was quenched with a saturated aqueous $Na_2S_2O_3$ solution, and the aqueous layer was extracted with $Et_2O$. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude 1-methoxy-2-iodo-tetrahydroazepine product was dissolved in toluene (75 mL), and the solution was heated at 130 °C. TFA (30 μL) was then added in one portion, and the reaction mixture was heated at this temperature for 10 min, during which time the colorless reaction mixture turned dark red. The reaction mixture was cooled to room temperature and neutralized with triethylamine (the reaction mixture turned yellow). The solvent was evaporated, and the residue was purified by flash chromatography (silica gel, 10% EtOAc/hexanes) to provide the title compound (1.1 g, 73%) as a colorless oil, in a 2:1 ratio of *N*-Boc rotamers: $^1$H NMR (500 MHz, $CDCl_3$) δ major rotamer: 6.96 (s, 1H); minor rotamer: 7.10 (s, 1H); overlapping resonance: 3.66 (m, 2H), 2.77-2.75 (m, 2H), 1.78-1.74 (m, 4H), 1.48 (s, 9H); FTIR (thin film, $CHCl_3$) 2976, 2932, 1706, 1628, 1390, 1348, 1250, 1161, 976; HRMS (TOF ES) cald for $C_{11}H_{19}NO_2I$, *m/z* 324.0461 $[M]^+$, found: 324.0469. This product was contaminated with minor, inseparable impurities, and was submitted to the subsequent Suzuki-coupling reaction without further purification.

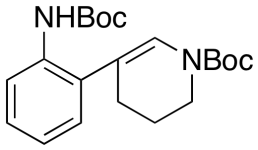



***tert*-Butyl 5-(2-aminophenyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (2.119)**: Suzuki

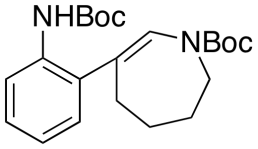
coupling of vinyl iodide **2.107** (1.02 g, 3.20 mmol) and 2-aminophenyl pinacolboronate **2.77** (0.86 g, 3.90 mmol) in the manner of **2.78**, followed by flash chromatography purification (silica gel, 30% EtOAc/hexanes), afforded the title compound (brown oil, 0.67 g, 76%) as a mixture of *N*-Boc rotamers: $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.09-7.05 (m, 2H), 6.90 (s, 1H), 6.77-6.73 (m, 2H), 3.81 (brs, 2H), 3.65 (m, 2H), 2.33 (t, *J* = 6.5 Hz, 2H), 1.49 (s, 9H); $^{13}$C NMR (125 HMz, $CDCl_3$) δ 152.8, 152.4, 143.9, 143.8, 129.8, 129.6, 127.8, 127.7, 124.9, 124.5, 118.5, 115.9, 115.5, 115.2, 80.9, 80.7, 42.4, 41.3, 28.4, 26.2, 25.9, 22.1, 22.0; FTIR (thin film, $CHCl_3$) 3450, 3361, 2976, 2932, 1697, 1650, 1615, 1493, 1452, 1390, 1367, 1311, 1253, 1162, 1116, 749; HRMS (TOF ES) cald for $C_{16}H_{23}N_2O_2$, *m/z* 275.1760 $[M+H]^+$, found: 275.1747.



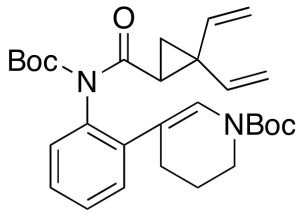

***tert*-Butyl 6-(2-aminophenyl)-2,3,4,5-tetrahydro-1*H*-azepine-1-carboxylate (2.120)**: Suzuki coupling of vinyl iodide **2.108** (1.05 g, 3.25 mmol) and 2-aminophenyl pinacolboronate **2.77** (0.86 g, 3.90 mmol) in the manner of **2.78**, followed by flash chromatography purification (silica gel, 30% EtOAc/hexanes), afforded the title compound (0.73 g, 78%) as a brown oil, in a 1:1 mixture of *N*-Boc rotamers: $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.07-7.02 (m, 2H), 6.75-6.71 (m, 2H), 6.55 (m, 1H), 3.74 (t, *J* = 6.0 Hz, 2H), 2.49 (m, 2H), 1.85 (m, 4H), 1.49 (s, 9H); $^{13}$C NMR (125 HMz, $CDCl_3$) δ 153.9, 143.2, 130.7, 129.6, 129.1, 127.9, 126.7, 118.5, 115.6, 80.6, 46.9, 31.9, 28.4, 28.3, 25.0; FTIR (thin film, $CHCl_3$) 3462, 3361, 2976, 2931, 2860, 1697, 1647, 1616, 1493, 1452, 1393, 1367, 1306, 1241, 1161, 1117, 749; HRMS (TOF ES) cald for $C_{17}H_{25}N_2O_2$, *m/z* 289.1916 $[M+H]^+$, found: 289.1925.



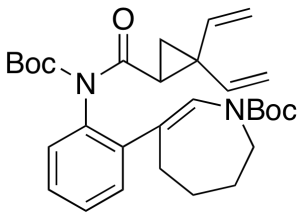

***tert*-Butyl 5-(2-(tert-butoxycarbonylamino)phenyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (2.121)**: A mixture of $LiClO_4$ (7 mg, 0.068 mmol), free aniline **2.119** (94 mg, 0.34 mmol), and $Boc_2O$ (82 mg, 0.38 mmol) in DCM (3 mL) was stirred at room temperature for 12 h. The solvent was evaporated, and the residue was purified by flash chromatography (silica gel, 15% EtOAc/hexanes) to give the title compound (123 mg, 97%) as a colorless oil, that was a mixture of multiple rotamers (see attached $^1$H NMR and $^{13}$C NMR spectra): FTIR (thin film, $CHCl_3$) 3418, 2977, 2932, 1704, 1650, 1514, 1447, 1386, 1367, 1312, 1252, 1159, 754; HRMS (TOF ES) cald for $C_{21}H_{30}N_2O_4Na$, *m/z* 397.2103 $[M+Na]^+$, found: 397.2097.




***tert*-Butyl 6-(2-(*tert*-butoxycarbonylamino)phenyl)-2,3,4,5-tetrahydro-1*H*-azepine-1-carboxylate (2.122)**: *N*-Boc protection of aniline **2.120** (100 mg, 0.35 mmol) in the manner of **2.121**, followed by flash chromatography (silica gel, 15% EtOAc/hexanes), provided the title compound (125 mg, 93%) as a colorless oil, that was a mixture of multiple rotamers (see attached $^1$H NMR and $^{13}$C NMR spectra): FTIR (thin film, $CHCl_3$) 3414, 2977, 2931, 1703, 1513, 1481, 1448, 1389, 1367, 1246, 1160, 753; HRMS (TOF ES) cald for $C_{22}H_{33}N_2O_4$, *m/z* 389.2440 $[M+H]^+$, found: 389.2459.

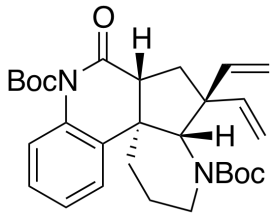



***tert*-Butyl 5-(2-(*N*-(*tert*-butoxycarbonyl)-2,2-divinylcyclopropanecarboxamido) phenyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (2.123)**: Acid chloride **2.98** (0.22 mmol in 2 mL of toluene) was prepared from acid **2.63** (30 mg, 0.22 mmol) and Ghosez reagent (29 μL, 0.22 mmol). In a separate fask, a NaHMDS solution (1 M in THF, 131 μL) was added dropwise to a solution of **2.121** (41 mg, 0.11 mmol) in THF (2 mL) at −78 °C. After 30 min, the abovementioned acid chloride solution was added dropwise at this temperature. The reaction mixture was slowly warmed to room temperature and stirred for 1 h. TLC analysis confirmed the completion of the reaction (the starting material and the product have the same Rf value, but show different colors unpon staining with *p*-anisaldehyde). The reaction was quenched with water, and the mixture was extracted with diethyl ether. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 15% EtOAc/hexanes) to provide the title compound (24 mg, 83%) a colorless oil, in a mixture of multiple rotamers (see attached $^{1}H$ and $^{13}C$ NMR spectra): FTIR (thin film, $CHCl_3$) 3086, 2978, 2933, 1733, 1702, 1649, 1386, 1298, 1254, 1160, 1119, 895, 759; HRMS (TOF ES) cald for $C_{29}H_{38}N_2O_5Na$, *m/z* 517.2678 $[M+Na]^+$, found: 517.2673.



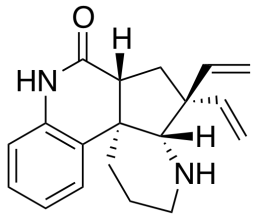

***tert*-Butyl 6-(2-(*N*-(*tert*-butoxycarbonyl)-2,2-divinylcyclopropanecarboxamido) phenyl)-**

**2,3,4,5-tetrahydro-1*H*-azepine-1-carboxylate (2.124)**: Acylation of (62 mg, 0.16 mmol) was in the manner of, followed by flash chromatography (silica gel, 15% EtOAc/hexanes), provided the title compound (51 mg, 63%) as a colorless oil, in a mixture of multiple rotamers (see attached $^{1}H$ and $^{13}C$ NMR spectra): FTIR (thin film, $CHCl_3$) 2978, 2932, 1733, 1701, 1647, 1391, 1368, 1300, 1251, 1158, 757; HRMS (TOF ES) cald for $C_{30}H_{40}N_2O_5Na$, *m/z* 531.2835 $[M+Na]^+$, found: 531.2816. This product was contaminated with minor, inseparable impurities.




**(4a*S*,6a*R*,12b*R*)-Di-*tert*-butyl 7-oxo-5,5-divinyl-2,3,5,6,6a,7-hexahydropyrido[3',2':2,3]cyclopenta[1,2-*c*]quinoline-4,8(1*H*,4a*H*)-dicarboxylate (2.125)**: A solution of AIBN (4 mg, 0.026 mmol) and $Bu_3SnH$ (1 M in cyclohexane, 129 μL, 0.129 mmol) in toluene (3 mL) was added via syringe pump to a solution of **2.123** (32 mg, 0.065 mmol) in refluxing toluene (8 mL) over a period of 4 h. The reaction mixture was cooled to room temperature, and the solvent was evaporated. The residue was partitioned between acetonitrile and hexanes. The acetonitrile layer was washed with hexanes and then concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 15% EtOAc/hexanes) to provide the title compound **105** (15 mg, 52%, contaminated with minor, inseparable impurities) as a colorless oil, in a 2:1 mixture of *N*-Boc rotamers: $^{1}H$ NMR (400 MHz, $CDCl_3$) δ major rotamer: 7.10 (t, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.09 (dd, *J* = 17.2 Hz, 10.2 Hz, 1H), 5.92 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H), 5.25 (d, *J* = 17.2 Hz, 1H), 5.22 (d, *J* = 10.4 Hz, 1H), 4.94 (d, *J* = 17.2 Hz, 1H), 4.89 (d, *J* = 10.4 Hz, 1H), 4.63 (s, 1H), 4.20-4.16 (m, 1H), 2.52 (t, *J* = 12.8 Hz,

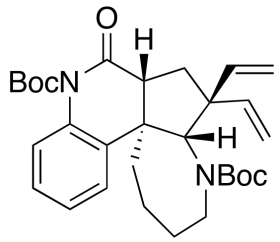
1H), 2.06 (dd, *J* = 13.2 Hz, 6.0 Hz, 1H), 1.52 (s, 9H); minor rotamer: 7.09 (t, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 7.2 Hz, 1H), 6.28 (dd, *J* = 17.2 Hz, 10.2 Hz, 1H), 5.89 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H), 5.19 (d, *J* = 17.2 Hz, 1H), 5.15 (d, *J* = 10.8 Hz, 1H), 4.79 (s, 1H), 4.02-3.98 (m, 1H), 2.42 (t, *J* = 12.8 Hz, 1H), 2.20 (dd, *J* = 13.2 Hz, 6.0 Hz, 1H), 1.52 (s, 9H); overlapping resonance: 7.28-7.22 (m, 1H), 7.21-7.15 (m, 1H), 2.94-2.81 (m, 2H), 1.62 (s, 9H), 1.59-1.54 (m, 3H); FTIR (thin film, $CHCl_3$) 2978, 2934, 1733, 1694, 1392, 1368, 1278, 1253, 1151, 915, 848, 758. This product was directly subjected to the next reaction without further purification.




**(4a*S*,6a*R*,12b*R*)-5,5-divinyl-1,2,3,4,4a,5,6,6a-octahydropyrido[3',2':2,3]cyclopenta[1,2-*c*]quinolin-7(8*H*)-one (127)**: Crude biscarbamate **125** (15 mg) was dissolved in a mixed solvent of dichloromethane/TFA (10:1, 3 mL), and the reaction mixture was stirred at room temperature for 4 h. The solvent was evaporated, and the residue was purified by flash chromatography (silica gel, 40% EtOAc/dichloromethane) to provide the title compound (7 mg, 35% over 2 steps) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 8.19 (brs, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.20 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.07 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.32 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H), 5.88 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H), 5.24 (d, *J* = 16.8 Hz, 1H), 5.21 (d, *J* = 10.4 Hz, 1H), 4.98 (d, *J* = 16.4 Hz, 1H), 4.94 (d, *J* = 10.4 Hz, 1H), 3.64 (s, 1H), 2.94 (td, *J* = 11.6 Hz, 4.0 Hz, 1H), 2.86-2.83 (m, 1H), 2.75 (dd, *J* = 12.8 Hz, 6.4 Hz, 1H), 2.48 (t, *J* = 13.2 Hz, 1H), 2.12 (dd, *J* = 12.4 Hz, 6.4 Hz, 1H), 1.59 (td, *J* = 11.6 Hz, 4.0 Hz, 1H), 1.52-1.47 (m, 1H), 1.45-1.35 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.1, 146.1, 142.6, 136.6, 134.5, 127.2,

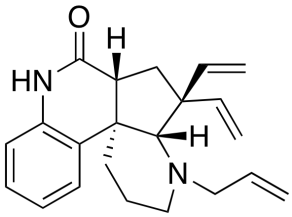
126.4, 122.8, 116.2, 113.7, 110.4, 67.2, 54.2, 47.2, 44.1, 41.8, 30.7, 25.0, 20.4; FTIR (thin film, $CHCl_3$) 3218, 3079, 2934, 2859, 1682, 1475, 1396, 1304, 1254, 912, 758, 735; HRMS (TOF ES) cald for $C_{19}H_{23}N_2O$, *m/z* 295.1810 $[M+H]^+$, found: 295.1805.

A sample for X-ray crystallography analysis was prepared by slow evaporation crystallization technique. A test tube (13 mL) was charged with a solution of amine **127** (2 mg) in ethyl acetate (3 mL). After 72 h, a small crystal was found on the wall of this tube.



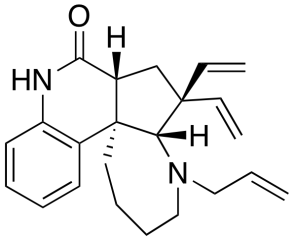

**(5a*S*,7a*R*,13b*R*)-Di-*tert*-butyl 8-oxo-6,6-divinyl-3,4,6,7,7a,8-hexahydro-1*H*-azepino[3',2':2,3]cyclopenta[1,2-*c*]quinoline-5,9(2*H*,5a*H*)-dicarboxylate (2.126)**: Radical annulation of divinylcyclopropane **2.124** (41 mg, 0.081 mmol) in the manner of **2.125**, followed by flash chromatography purification (silica gel, 15% EtOAc/hexanes), provided the title compound (15 mg, 36%) as a colorless oil, in a 1:1 mixture of *N*-Boc rotamers: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.40-7.35 (m, 1H), 7.28-7.22 (m, 1H), 7.15-7.11 (m, 1H), 7.02, 6.97 (d, *J* = 8.0 Hz, 1H), 5.94, 5.88 (dd, *J* = 17.5 Hz, 10.5 Hz, 1H), 5.85, 5.80 (dd, *J* = 17.5 Hz, 10.5 Hz, 1H), 5.39-4.92 (m, 3H), 3.93, 3.65 (d, *J* = 15.0 Hz, 1H), 3.14, 3.12 (d, *J* = 15.0 Hz, 1H), 2.87, 2.84 (dd, *J* = 8.0 Hz, 5.0 Hz, 1H), 2.45, 2.39 (t, *J* = 13.0 Hz, 1H), 2.12, 2.08 (dd, *J* = 8.0 Hz, 5.0 Hz, 1H), 1.92-1.80 (m, 2H), 1.63 (m, 9H), 1.57-1.56 (m, 9H), 1.59-1.41 (m, 3H), 0.90 (m, 1H); $^{13}$C NMR (125 HMz, $CDCl_3$) δ 169.9, 169.8, 156.0, 155.3, 152.2, 152.0, 146.1, 146.0, 141.8, 141.2, 137.1, 136.7, 136.4, 136.2, 127.3, 127.1, 126.1, 125.3, 124.6, 124.1, 119.3, 119.0, 113.6, 113.1, 112.1, 110.9, 85.0, 84.9, 80.7, 80.0, 68.3, 66.5, 54.3, 53.8, 51.6, 51.1, 48.8, 48.7, 43.3, 42.5, 30.5,

28.6, 28.5, 27.8, 25.9, 25.5, 25.3, 24.6, 23.5, 18.5, 18.1; FTIR (thin film, $CHCl_3$) 2976, 2929, 1688, 1421, 1368, 1278, 1249, 1149; HRMS (TOF ES) cald for $C_{30}H_{40}N_2O_5Na$, *m/z* 531.2835 $[M+Na]^+$, found: 531.2854.

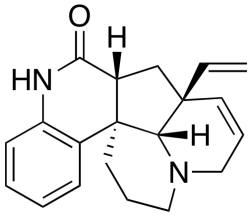



**(4a*S*,6a*R*,12b*R*)-4-Allyl-5,5-divinyl-1,2,3,4,4a,5,6,6a-octahydropyrido[3',2':2,3]cyclopenta[1,2-*c*]quinolin-7(8*H*)-one (2.129)**: Free amine **2.127** (15 mg, 0.030 mmol) was dissolved in $CH_3CN$ (5 mL), followed by addition of $K_2CO_3$ (25 mg, 0.182 mmol) and allyl bromide (13 μL, 0.182 mmol). The reaction mixture was stirred at 45 °C for 12 h. The reaction mixture was diluted with dichloromethane (20 mL), washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 50% EtOAc/hexane) to afford the title compound (8 mg, 80%) as a light yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.0 Hz, 1H), 7.51 (brs, 1H), 7.18 (td, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.45 (dd, *J* = 17.5 Hz, 10.5 Hz, 1H), 6.11 (dd, *J* = 17.5 Hz, 10.5 Hz, 1H), 5.95-5.87 (m, 1H), 5.31-5.14 (m, 4H), 4.98 (d, *J* = 17.5 Hz, 1H), 4.93 (d, *J* = 10.5 Hz, 1H), 3.71 (dd, *J* = 14.5 Hz, 5.5 Hz, 1H), 3.63 (s, 1H), 3.51 (dd, *J* = 14.5 Hz, 7.0 Hz, 1H), 3.11-3.06 (m, 1H), 2.76 (dd, *J* = 12.5 Hz, 6.0 Hz, 1H), 2.76 (m, 1H), 2.55 (t, *J* = 13.0 Hz, 1H), 2.00 (dd, *J* = 13.5 Hz, 6.5 Hz, 1H), 1.72-1.65 (m, 1H), 1.46-1.42 (m, 3H); $^{13}$C NMR (125 HMz, $CDCl_3$) δ 171.8, 147.2, 143.3, 136.9, 136.5, 134.6, 127.1, 126.7, 122.7, 116.4, 115.8, 113.3, 109.9, 73.9, 57.7, 55.7, 47.0, 45.6, 44.8, 30.8, 24.1, 21.0; FTIR (thin film, $CHCl_3$) 3236, 3080, 2922, 2851, 1684, 1474, 1393, 1302, 1253, 914, 758; HRMS (TOF ES) cald

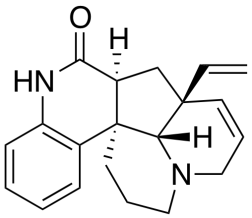
for $C_{22}H_{27}N_2O$, *m/z* 335.2123 $[M+H]^+$, found: 335.2127.




**(5a*S*,7a*R*,13b*R*)-5-Allyl-6,6-divinyl-2,3,4,5,5a,6,7,7a-octahydro-1*H*-azepino[3',2':2,3]cyclopenta[1,2-*c*]quinolin-8(9*H*)-one (2.130)**: *N*-Boc deprotection of *bis*-carbamate **2.126** (23 mg, 0.045 mmol) in the manner of **2.127** provided crude amine **2.128** (mg,) as a colorless oil. This product was then allylated in the manner of **2.129**, and the title compound (12 mg, 76%) was isolated as a light yellow oil after flash chromatography purification (silica gel, 50% EtOAc/hexane): $^1$H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.2 Hz, 1H), 7.44 (brs, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.43 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H), 6.02 (dd, *J* = 17.2 Hz, 10.4 Hz, 1H), 5.99 (m, 1H), 5.26-5.14 (m, 4H), 4.98 (d, *J* = 17.2 Hz, 1H), 4.90 (d, *J* = 10.8 Hz, 1H), 3.72 (m, 1H), 3.69 (s, 1H), 3.61 (dd, *J* = 10.4 Hz, 6.4 Hz, 1H), 3.37 (t, *J* = 12.4 Hz, 1H), 2.81 (dd, *J* = 13.2 Hz, 6.0 Hz, 1H), 2.51 (t, *J* = 13.2 Hz, 1H), 2.00 (dd, *J* = 12.8 Hz, 6.0 Hz, 1H), 1.90 (t, *J* = 12.8 Hz, 1H), 1.47-0.86 (m, 5H); $^{13}$C NMR (100 HMz, $CDCl_3$) δ 172.3, 147.8, 143.2, 137.6, 136.3, 134.3, 127.2, 126.6, 122.8, 116.5, 116.0, 112.4, 109.9, 79.3, 61.8, 54.4, 50.8, 48.2, 47.0, 30.0, 27.4, 25.2, 21.0; FTIR (thin film, $CHCl_3$) 3239, 3081, 2925, 2861, 1682, 1472, 1401, 759; HRMS (TOF ES) cald for $C_{23}H_{29}N_2O$, *m/z* 349.2280 $[M+H]^+$, found: 349.2276.

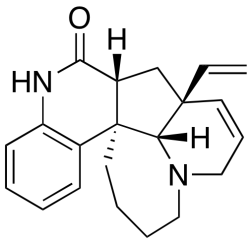



**(6b*R*,6b$^1$*S*,13a*S*,14a*R*)-13a-Vinyl-6b$^1$,7,8,9,11,13a,14,14a-octahydroquinolizino[1',9':2,3,4]cyclopenta[1,2-*c*]quinolin-1(2*H*)-one (2.109a)**: Hoveyda-Grubbs II catalyst (1 mg, 0.0018 mmol) was added to a solution of triene **2.129** (6 mg, 0.018 mmol) in toluene (4 mL). The reaction mixture was heated at 80 °C for 12 h. The solvent was evaporated, and the residue was purified by flash chromatography (silica gel, 5% MeOH/dichloromethane, with 0.5% $Et_3N$) to provide the title compound (6 mg, 73%) as a white, amorphous powder: $^1$H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.2 Hz, 1H), 7.38 (brs, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 5.95-5.92 (m, 1H), 5.87 (d, *J* = 9.6 Hz, 1H), 5.69 (dd, *J* = 17.4 Hz, 10.8 Hz, 1H), 4.99 (d, *J* = 17.4 Hz, 1H), 4.89 (d, *J* = 10.8 Hz, 1H), 3.56 (s, 1H), 3.22-3.16 (m, 2H), 2.92 (dd, *J* = 12.6 Hz, 4.8 Hz, 1H), 2.78 (td, *J* = 10.2 Hz, 4.8 Hz, 1H), 2.64-2.62 (m, 1H), 2.21 (dd, *J* = 12.6 Hz, 4.8 Hz, 1H), 2.04 (t, *J* = 12.6 Hz, 1H), 1.57-1.39 (m, 4H); $^{13}$C NMR (175 MHz, $CDCl_3$) δ 171.9, 144.8, 136.5, 135.1, 133.0, 127.2, 125.6, 122.9, 116.3, 110.7, 68.9, 51.1, 49.2, 48.4, 47.5, 45.7, 31.3, 25.5, 19.5; FTIR (thin film, $CHCl_3$) 3411, 2927, 1684, 1474, 1399, 1302, 758, 726; HRMS (TOF ES) cald for $C_{20}H_{23}N_2O$, *m/z* 307.1810 $[M+H]^+$, found: 307.1809.



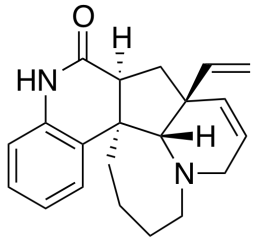

**(6b*R*,6b$^1$*S*,13a*S*,14a*S*)-13a-Vinyl-6b$^1$,7,8,9,11,13a,14,14a-**

**octahydroquinolizino[1',9':2,3,4]cyclopenta[1,2-*c*]quinolin-1(2*H*)-one (2.109b)**: Epimerization of pentacycle **89** (4.6 mg, 0.015 mmol) by potassium *tert*-butoxide (3.0 mg, 0.030 mmol) in the manner of meloscine **2.15a**, followed by flash chromatography purification (silica gel, 3% MeOH/dichloromethane, with 0.5% $Et_3N$), provided the title compound (4.0 mg, 87%) as an amporphous powder: $^1$H NMR (700 MHz, $CDCl_3$) δ 7.51 (brs, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 6.98 (t, *J* = 7.7 Hz, 1H), 6.65 (d, *J* = 7.7 Hz, 1H), 5.79 (dd, *J* = 9.1 Hz, 5.6 Hz, 1H), 5.36 (d, *J* = 9.8 Hz, 1H), 5.20 (dd, *J* = 17.5 Hz, 10.5 Hz, 1H), 4.66 (d, *J* = 17.5 Hz, 1H), 4.46 (d, *J* = 11.2 Hz, 1H), 3.70 (t, *J* = 9.8 Hz, 1H), 3.14 (dd, *J* = 16.1 Hz, 5.6 Hz, 1H), 2.95 (s, 1H), 2.92 (d, *J* = 11.2 Hz, 1H), 2.82 (d, *J* = 16.1 Hz, 1H), 2.46 (dd, *J* = 14.0 Hz, 11.9 Hz, 1H), 2.28 (t, *J* = 11.9 Hz, 1H), 2.05 (dd, *J* = 14.0 Hz, 9.1 Hz, 1H), 1.95-1.93 (m, 2H); $^{13}$C NMR (175 MHz, $CDCl_3$) δ 171.6, 143.2, 135.0, 132.4, 127.9, 127.7, 127.6, 127.1, 123.9, 115.2, 112.7, 82.5, 56.8, 53.0, 51.0, 48.1, 46.9, 43.4, 42.2, 31.0; FTIR (thin film, $CHCl_3$) 3420, 1649, 1387, 1159; HRMS (TOF ES) cald for $C_{20}H_{23}N_2O$, *m/z* 307.1810 $[M+H]^+$, found: 307.1807.



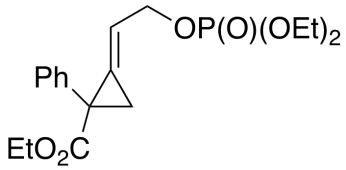

**(6b*R*,6b$^1$*S*,13a*S*,14a*R*)-13a-Vinyl-2,6b$^1$,7,8,9,10,11,13a,14,14a-decahydro-1*H*-2,10a-diazabenzo[*c*]cyclohepta[*ef*]fluoren-1-one (2.110a)**: Ring-closing metathesis of triene **2.130** (11 mg, 0.032 mmol) in the manner of **2.109a**, followed by flash chromatography purification (silica gel, 4% MeOH/dichloromethane, with 0.5% $Et_3N$) to provide the title compound (8 mg, 79%) as a white, amorphous powder: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.5 Hz, 1H), 7.61 (s, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 5.94-5.90

(m, 1H), 5.69 (dd, *J* = 17.5 Hz, 10.5 Hz, 1H), 5.65 (d, *J* = 17.5 Hz, 1H), 5.02 (d, *J* = 17.5 Hz, 1H), 4.97 (d, *J* = 10.5 Hz, 1H), 3.58 (s, 1H), 3.18 (m, 2H), 3.15 (dd, *J* = 11.5 Hz, 7.0 Hz, 1H), 3.01 (t, *J* = 13.0 Hz, 1H), 2.80 (d, *J* = 14.0 Hz, 1H), 2.23 (t, *J* = 13.0 Hz, 1H), 2.08 (t, *J* = 6.0 Hz, 1H), 1.75 (dd, *J* = 7.0 Hz, 6.0 Hz, 1H), 1.47-1.44 (m, 2H), 0.91-0.83 (m, 1H); $^{13}$C NMR (175 MHz, $CDCl_3$) δ 172.6, 145.4, 136.9, 135.3, 131.6, 127.1, 126.9, 124.8, 122.4, 117.0, 112.4, 73.8, 58.0, 54.7, 53.0, 51.7, 50.9, 30.9, 29.6, 26.8, 24.5; FTIR (thin film, $CHCl_3$) 3391, 2989, 2927, 1685, 1474, 1401, 1158, 805, 756, 728; HRMS (TOF ES) cald for $C_{21}H_{25}N_2O$, *m/z* 321.1967 $[M+H]^+$, found: 321.1973.

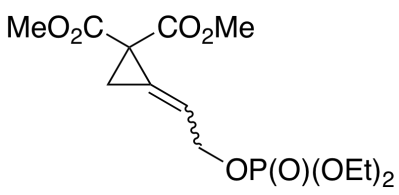



**(6b*R*,6b$^1$*S*,13a*S*,14a*S*)-13a-Vinyl-2,6b$^1$,7,8,9,10,11,13a,14,14a-decahydro-1*H*-2,10a-diazabenzo[*c*]cyclohepta[*ef*]fluoren-1-one (2.110b)**: Epimerization of pentacycle **2.110a** (4.0 mg, 0.012 mmol) by potassium *tert*-butoxide (2.8 mg, 0.025 mmol) in the manner of meloscine **2.15b**, followed by flash chromatography purification (silica gel, 3% MeOH/dichloromethane, with 0.5% $Et_3N$), provided the title compound (3.5 mg, 88%) as an amporphous powder: $^1$H NMR (700 MHz, $CDCl_3$) δ 8.03 (brs, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 6.09 (dd, *J* = 9.8 Hz, 4.2 Hz, 1H), 5.79 (dd, *J* = 16.8 Hz, 10.5 Hz, 1H), 5.51 (d, *J* = 10.5 Hz, 1H), 4.97 (d, *J* = 16.8 Hz, 1H), 4.94 (d, *J* = 9.8 Hz, 1H), 4.01 (s, 1H), 3.86 (d, *J* = 17.5 Hz, 1H), 3.46 (d, *J* = 14.7 Hz, 1H), 3.14-3.10 (m, 2H), 2.82 (dd, *J* = 13.3 Hz, 4.9 Hz, 1H), 2.10-2.07 (m, 1H), 1.80 (dd, *J* = 13.3 Hz, 4.9 Hz, 1H), 1.76 (d, *J* = 13.3 Hz, 1H), 1.70-1.66 (m, 2H), 1.60 (m, 1H), 1.50 (m, 2H); 171.8, 144.7, 134.9, 130.1, 129.5,

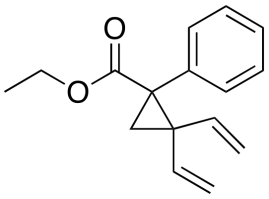
128.5, 127.4, 126.7, 122.8, 116.1, 112.9, 75.2, 57.4, 57.0, 52.2, 49.3, 44.7, 40.0, 36.5, 27.0, 23.3; FTIR (thin film, $CHCl_3$) 3400, 2925, 1674, 1481, 1395, 1157; HRMS (TOF ES) cald for $C_{21}H_{25}N_2O$, *m/z* 321.1967 $[M+H]^+$, found: 321.1977.




**Ethyl 2-(2-(diethoxyphosphoryloxy)ethylidene)-1-phenylcyclopropane-carboxylate (2.144)**: A solution of ethyl diazophenylacetate (1.30 g, 6.79 mmol) in dichloromethane (3 mL) was added dropwise to a solution of allenic phosphate **2.143** (1.00 g, 4.85 mmol) and $Rh_2(esp)_2$ (11 mg, 0.015 mmol) in dichloromethane (10 mL). The reaction mixture was refluxed for 2 h, before the solvent was evaporated. The residue was purified by flash chromatography (silica gel, 70% EtOAc/hexanes) to provide the title compound (1.25 g, 70%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39-7.30 (m, 5H), 6.35 (tt, *J* = 6.4 Hz, 2.4 Hz, 1H), 4.76 (t, *J* = 7.6 Hz, 2H), 4.18-4.06 (m, 6H), 2.49 (d, *J* = 9.2 Hz, 1H), 1.79 (d, *J* = 9.2 Hz, 1H), 1.39-1.30 (m, 6H), 1.21 (t, *J* = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.3, 137.4, 131.5, 129.1, 128.2, 127.5, 114.8 (d, $J_{C\text{-}P}$ = 6.7 Hz), 66.6 (d, $J_{C\text{-}P}$ = 5.4 Hz), 63.9 (d, $J_{C\text{-}P}$ = 5.7 Hz), 63.8 (d, $J_{C\text{-}P}$ = 5.7 Hz), 61.5, 32.1, 19.2, 16.1 (d, $J_{C\text{-}P}$ = 6.7 Hz), 14.1; FTIR (thin film, $CHCl_3$) 3085, 3060, 2981, 2904, 1723, 1637, 1447, 1366, 1296, 1241, 1196, 1061, 1027, 933, 914 $cm^{-1}$; HRMS (TOF ES) cald for $C_{18}H_{25}O_6NaP$, *m/z* 391.1286 $[M+Na]^+$, found: 391.1266.

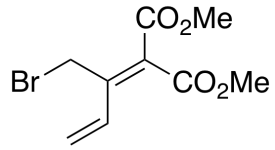


**Dimethyl 2-(2-((diethoxyphosphoryl)oxy)ethylidene)cyclopropane-1,1-dicarboxylate (2.149)**: Cyclopropanation of allenic phosphate **2.143** (220 mg, 1.07 mmol) with dimethyl diazomalonate (272 mg, 1.71 mmol) in the manner of **2.144**, followed by flash chromatography purification (silica gel, 100% EtOAc), provided the title compound (240 mg, 67%) as a colorless oil, in a 3:1 mixture of inseparable *E/Z* isomers: $^{1}$H NMR (500 MHz, $CDCl_3$) δ major isomer (configuration not assigned): 6.18 (tt, $J$ = 6.0 Hz, 3.0 Hz, 1H), 4.71 (ddt, $J$ = 8.5 Hz, 6.0 Hz, 2.0 Hz, 2H), 4.10 (q, $J$ = 7.5 Hz, 4H), 3.74 (s, 6H), 2.25-2.24 (m, 2H), 1.34 (t, $J$ = 7.0 Hz, 3H), 1.33 (t, $J$ = 7.0 Hz, 3H); minor isomer: 6.10 (tt, $J$ = 6.0 Hz, 2.5 Hz, 1H), 4.68 (ddt, $J$ = 8.5 Hz, 6.0 Hz, 2.0 Hz, 2H), 4.12 (q, $J$ = 7.5 Hz, 4H), 3.75 (s, 6H), 2.23-2.22 (m, 2H), 1.33 (t, $J$ = 7.0 Hz, 3H), 1.32 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ major isomer: 167.7, 126.1, 115.8 (d, $J_{C\text{-}P}$ = 7.1 Hz), 65.9 (d, $J_{C\text{-}P}$ = 5.1 Hz), 63.9 (d, $J_{C\text{-}P}$ = 5.6 Hz), 52.9, 31.3, 17.7, 16.1 (d, $J_{C\text{-}P}$ = 6.5 Hz); minor isomer: 167.6, 125.9, 115.9 (d, $J_{C\text{-}P}$ = 7.1 Hz), 65.8 (d, $J_{C\text{-}P}$ = 5.1 Hz), 63.8 (d, $J_{C\text{-}P}$ = 5.6 Hz), 53.0, 31.6, 17.6, 16.0 (d, $J_{C\text{-}P}$ = 6.5 Hz); FTIR (thin film, $CHCl_3$) 2987, 2957, 1736, 1439, 1314, 1269, 1110, 1029, 884, 822; HRMS (TOF ES) cald for $C_{13}H_{21}O_8NaP$, *m/z* 359.0872 $[M+Na]^+$, found: 359.0883.



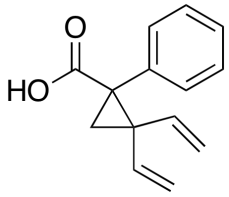

**Ethyl 1-phenyl-2,2-divinylcyclopropanecarboxylate (2.145)**: A vinylmagnesium bromide solution (1 M in THF, 9.45 mL) was added to a suspension of CuCN (56 mg, 0.630 mmol) in THF (20 mL) at 0 °C. After 15 min, the reaction mixture was cooled to −78 °C, and a solution of methylene-cyclopropane **2.144** (1.16g, 3.15 mmol) in THF (5 mL) was added via syringe pump

over a period of 20 min. The reaction mixture was stirred at this temperature for 2 h, before a saturated aqeous $NH_4Cl$ solution was added to quench the reaction. The mixture was extracted with diethylether, and the combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue that contains a 1.6:1 mixture of $S_N2'/S_N2$ regioisomers (judged by $^1H$ NMR analysis) was purified by flash chromatography (silica gel, 10% $Et_2O$/hexanes) to afford the title compound (400 mg, 52%) as a colorless oil: $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.39-7.38 (m, 2H), 7.31-7.25 (m, 3H), 6.04 (dd, *J* = 17.0 Hz, 10.5 Hz, 1H), 5.29-5.20 (m, 3H), 4.98 (d, *J* = 17.0 Hz, 1H), 4.91 (d, *J* = 10.5 Hz, 1H), 4.13-4.06 (m, 1H), 4.03-3.96 (m, 1H), 2.27 (d, *J* = 5.0 Hz, 1H), 1.62 (d, *J* = 5.0 Hz, 1H), 1.17 (t, *J* = 7.0 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 170.1, 138.3, 136.2, 135.2, 131.5, 127.8, 127.3, 117.6, 115.3, 61.1, 43.5, 38.0, 21.7, 14.2; FTIR (thin film, $CHCl_3$) 3085, 3060, 2982, 1723, 1631, 1447, 1366, 1293, 1241, 1195, 1108, 1064, 1029, 993, 915 $cm^{-1}$; HRMS (TOF ES) cald for $C_{16}H_{19}O_2$, *m/z* 243.1385 $[M+H]^+$, found: 243.1392.

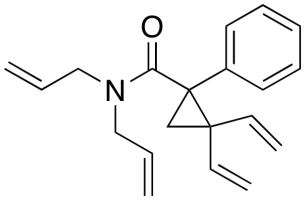



**Dimethyl 2-(1-bromobut-3-en-2-ylidene)malonate (2.151)**: A dipp-NHC-CuCl solution (0.1 M in diethyl ether, 52 μL) was prepared according to literature procedures, except that the filtration step was skipped. This solution was diluted with diethyl ether (5 mL), and vinyl-magnesium bromide solution (1 M in THF, 0.78 mL) was added slowly at 0 °C. After 15 min, a solution of methylene-cyclopropane **2.149** (174 mg, 0.517 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 1.5 h, before it was quenched with a saturated aqueous $NH_4Cl$ solution. The mixture was extracted with diethylether, and the combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel,

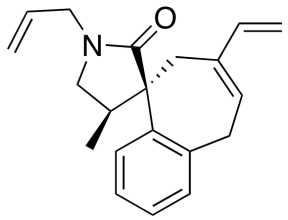
20% $Et_2O$/hexanes) to afford the title compound (40 mg, 70%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 6.68 (dd, *J* = 17.2 Hz, 10.8 Hz, 1H), 5.92 (d, *J* = 17.6 Hz, 1H), 5.68 (d, *J* = 10.2 Hz, 1H), 4.55 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 165.6, 164.2, 147.4, 131.6, 126.4, 124.0, 52.7, 52.6, 22.9; FTIR (thin film, $CHCl_3$) 2956, 1789, 1730, 1437, 1252, 1136, 1058, 736; HRMS (TOF ES) cald for $C_9H_{11}O_4Br$, *m/z* 261.9841 $[M]^+$, found: 261.9825.



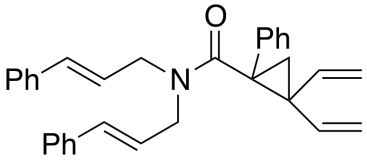

**1-Phenyl-2,2-divinylcyclopropanecarboxylic acid (2.146)**: A solution of ester **2.145** (360 mg, 1.48 mmol) in diether ether (2 mL) was added to pre-mixed KO$^t$Bu (1.41 g, 12.60 mmol)/$H_2O$ (75 μL, 4.15 mmol) in diethylether (20 mL). The reaction mixture was stirred at room temperature for 12 h, and another portion of KO$^t$Bu (0.71 g, 6.30 mmol) was added. After 4 h, the reaction mixture was diluted with water and washed with dichloromethane. 6 N HCl was added dropwise until the PH reached 3, and the aqueous solution was extracted with dichloromethane. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude acid (310 mg, 77%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5H), 6.07 (dd, *J* = 17.2 Hz, 10.4 Hz, 1H), 5.30 (dd, *J* = 17.2 Hz, 10.4 Hz, 1H), 5.29 (d, *J* = 10.8 Hz, 1H), 5.24 (d, *J* = 17.6 Hz, 1H), 4.98 (d, *J* = 17.2 Hz, 1H), 4.92 (d, *J* = 10.8 Hz, 1H), 2.26 (d, *J* = 5.2 Hz, 1H), 1.69 (d, *J* = 5.2 Hz, 1H). This product was directly subjected to the subsequent amide coupling reactions without further purification.



***N*,*N*-Diallyl-1-phenyl-2,2-divinylcyclopropanecarboxamide (2.147)**: Ghosez reagent (72 μL, 0.541 mmol) was added to a solution of crude acid **2.146** (116 mg, 0.541 mmol) in dichloromethane (2 mL), and the reaction mixture was stirred at room temperature for 2 h. The resulting acid chloride solution was added dropwise to a stirred mixture of diallylamine (133 μL, 1.083 mmol) and pyridine (177 μL, 2.166 mmol) in dichloromethane (5 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with dichloromethane and poured into a saturated aqueous $CuSO_4$ solution. The organic layer was collected, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 10% EtOAc/hexanes) to provide the title compound (110 mg, 70%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.2 Hz, 2H), 7.33-7.25 (m, 3H), 6.16 (dd, *J* = 17.2 Hz, 10.4 Hz, 1H), 5.62 (ddt, *J* = 17.2 Hz, 10.8 Hz, 5.6 Hz, 1H), 5.52 (dd, *J* = 17.2 Hz, 10.8 Hz, 1H), 5.35 (ddt, *J* = 17.2 Hz, 10.8 Hz, 5.6 Hz, 1H), 5.19-4.92 (m, 8H), 4.25 (dd, *J* = 16.0 Hz, 4.8 Hz, 1H), 4.03 (dd, *J* = 16.0 Hz, 4.8 Hz, 1H), 3.87 (dd, *J* = 16.0 Hz, 5.6 Hz, 1H), 3.67 (dd, *J* = 14.8 Hz, 6.0 Hz, 1H), 1.97 (d, *J* = 5.6 Hz, 1H), 1.76 (d, *J* = 5.6 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 169.8, 138.6, 137.8, 136.6, 133.3, 132.8, 129.7, 128.3, 127.1, 117.8, 116.9, 115.7, 114.7, 49.3, 46.5, 42.9, 37.5, 21.7; FTIR (thin film, $CHCl_3$) 3082, 3010, 2983, 2922, 1637, 1637, 1451, 1410, 1245, 1209, 993, 920 cm$^{-1}$; HRMS (TOF ES) cald for $C_{20}H_{23}NONa$, *m/z* 316.1677 $[M+Na]^+$, found: 316.1664.

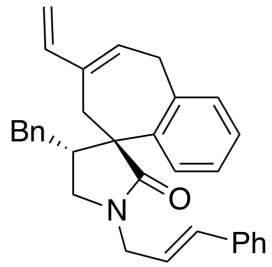


**(3'*R*,4'*R*)-1'-Allyl-4'-methyl-7-vinyl-6,9-dihydrospiro[benzo[7]annulene-5,3'-pyrrolidin]-2'-one (2.155)**: A solution of diallylamide **2.147** (48 mg, 0.162 mmol) was dissolved in toluene and heated at 110 °C for 3 h. The solvent was evaporated, and the residue was purified by flash chromatography (silica gel, 20% EtOAc/hexanes) to provide the title compound (31 mg, 65%) as a colorless oil: $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.17-7.09 (m, 4H), 6.46 (dd, *J* = 17.5 Hz, 11.0 Hz, 1H), 6.07 (tt, *J* = 6.0 Hz, 1.0 Hz, 1H), 5.87 (ddt, *J* = 17.0 Hz, 10.0 Hz, 6.5 Hz, 1H), 5.31 (dq, *J* = 17.0 Hz, 1.5 Hz, 1H), 5.29 (dq, *J* = 10.0 Hz, 1.5 Hz, 1H), 5.22 (d, *J* = 17.0 Hz, 1H), 5.02 (d, *J* = 11.0 Hz, 1H), 4.11 (ddt, *J* = 15.0 Hz, 6.5 Hz, 1.5 Hz, 1H), 4.01 (ddt, *J* = 15.0 Hz, 6.5 Hz, 1.5 Hz, 1H), 3.83 (dd, *J* = 17.5 Hz, 6.5 Hz, 1H), 3.48 (m, 1H), 3.47 (dd, *J* = 10.0 Hz, 8.0 Hz, 1H), 3.22 (dd, *J* = 15.5 Hz, 1.0 Hz, 1H), 2.98 (dd, *J* = 10.0 Hz, 6.0 Hz, 1H), 2.69 (ddq, *J* = 8.0 Hz, 7.0 Hz, 6.0 Hz, 1H), 2.59 (d, *J* = 16.0 Hz, 1H), 0.62 (d, *J* = 7.0 Hz, 3H); $^{13}$C NMR (125 HMz, $CDCl_3$) δ 177.8, 140.3, 138.2, 137.6, 137.5, 132.4, 130.9, 130.2, 129.2, 126.8, 126.4, 118.6, 111.2, 54.1, 51.6, 45.6, 35.8, 35.7, 33.9, 16.7; FTIR (thin film, $CHCl_3$) 2926, 1683, 1438, 1263, 992, 927, 760 cm$^{-1}$; HRMS (TOF ES) cald for $C_{20}H_{24}NO$, *m/z* 294.1858 $[M+H]^+$, found: 294.1848.



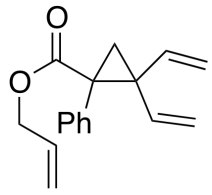
***N*,*N*-Dicinnamyl-1-phenyl-2,2-divinylcyclopropanecarboxamide (2.156)**: Acylation of *bis*-cinnamyl amine (99 mg, 0.367 mmol) with crude acid **2.146** (50 mg, 0.198 mmol) in the manner

of **2.147**, followed by flash chromatography purification (silica gel, 10% EtOAc/hexanes), provided the title compound (64 mg, 72%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.54-7.52 (m, 2H), 7.39-7.22 (m, 13H), 6.35 (d, *J* = 16.0 Hz, 1H), 6.31 (d, *J* = 16.0 Hz, 1H), 6.23 (dd, *J* = 17.0 Hz, 10.5 Hz, 1H), 6.06 (dt, *J* = 16.0 Hz, 6.0 Hz, 1H), 5.65 (dt, *J* = 16.0 Hz, 6.0 Hz, 1H), 5.60 (dd, *J* = 17.0 Hz, 10.5 Hz, 1H), 5.24 (dd, *J* = 10.5 Hz, 1.0 Hz, 1H), 5.18 (dd, *J* = 17.0 Hz, 1.0 Hz, 1H), 5.07 (dd, *J* = 17.0 Hz, 1.0 Hz, 1H), 5.04 (dd, *J* = 10.5 Hz, 1.0 Hz, 1H), 4.44 (dd, *J* = 16.5 Hz, 5.5 Hz, 1H), 4.23 (dd, *J* = 16.5 Hz, 5.5 Hz, 1H), 4.11 (dd, *J* = 16.5 Hz, 6.0 Hz, 1H), 3.91 (dd, *J* = 15.0 Hz, 6.5 Hz, 1H), 2.07 (d, *J* = 5.5 Hz, 1H), 1.81 (d, *J* = 5.5 Hz, 1H); $^{13}$C NMR (125 HMz, $CDCl_3$) δ 169.9, 138.5, 137.8, 136.8, 136.7, 136.3, 132.8, 132.5, 129.9, 128.7, 128.6, 128.5, 128.4, 127.8, 127.5, 127.2, 126.3, 124.7, 124.4, 115.8, 114.9, 48.9, 46.2, 43.2, 37.6, 22.1; FTIR (thin film, $CHCl_3$) 3082, 3058, 3026, 2922, 1635, 1600, 1495, 1450, 1414, 1360, 968, 912, 735 cm$^{-1}$; HRMS (TOF ES) cald for $C_{32}H_{32}NO$, *m/z* 446.2484 $[M+H]^+$, found: 446.2505.



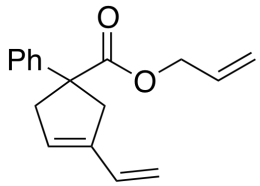

**(3'*R*,4'*R*)-4'-Benzyl-1'-cinnamyl-7-vinyl-6,9-dihydrospiro[benzo[7]annulene-5,3'-pyrrolidin]-2'-one (2.157)**: A solution of *bis*-cinnamylamide **2.156** (18 mg, 0.040 mmol) in toluene (1.5 mL) was heated at 110 °C in a sealed tube, for a period of 3 h. The reaction mixture was directly purified by flash chromatography (silica gel, 20% EtOAc/hexanes) to provide the title compound (8 mg, 44%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 7.19-7.10 (m, 7H), 6.98 (d, *J* = 7.0 Hz, 2H), 6.59 (dd, *J* = 17.5 Hz, 11.0 Hz), 6.58 (d, *J* = 16.0

Hz, 1H), 6.21 (dt, *J* = 16.0 Hz, 7.0 Hz, 1H), 6.18 (m, 1H), 5.35 (d, *J* = 17.5 Hz, 1H), 5.16 (d, *J* = 10.5 Hz, 1H), 4.25 (ddd, *J* = 15.0 Hz, 7.0 Hz, 1.0 Hz, 1H), 4.09 (ddd, *J* = 15.0 Hz, 7.0 Hz, 1.0 Hz, 1H), 4.02 (dd, *J* = 17.0 Hz, 5.5 Hz, 1H), 3.47 (dd, *J* = 17.0 Hz, 7.0 Hz, 1H), 3.42 (d, *J* = 15.5 Hz, 1H), 3.16 (dd, *J* = 10.0 Hz, 8.0 Hz, 1H), 3.11 (dd, *J* = 10.0 Hz, 7.5 Hz, 1H), 2.83 (dtd, *J* = 15.5 Hz, 8.0 Hz, 4.0 Hz, 1H), 2.70 (d, *J* = 15.0 Hz, 1H), 2.47 (dd, *J* = 14.0 Hz, 4.0 Hz, 1H), 1.79 (dd, *J* = 14.0 Hz, 12.0 Hz, 1H); $^{13}$C NMR (125 HMz, $CDCl_3$) δ 177.9, 140.2, 139.7, 138.3, 138.2, 137.2, 136.4, 134.1, 131.3, 131.2, 129.1, 128.8, 128.7, 128.4, 128.0, 127.0, 126.6, 126.5, 126.2, 123.4, 112.0, 53.0, 49.6, 45.2, 43.7, 37.9, 35.7, 33.9; FTIR (thin film, $CHCl_3$) 3026, 2940, 1684, 1493, 1447, 1262, 968, 736 cm$^{-1}$; HRMS (TOF ES) cald for $C_{32}H_{32}NO$, *m/z* 446.2484 $[M+H]^+$, found: 446.2490.




**Allyl 1-phenyl-2,2-divinylcyclopropanecarboxylate (2.158)**: Ghosez reagent (12 μL, 0.093 mmol) was added to a solution of crude acid **2.146** (20 mg, 0.093 mmol) in dichloromethane (1 mL), and the reaction mixture was stirred at room temperature for 2 h. The resulting acid chloride solution was added drowpise to a mixture of allyl alcohol (13 μL, 0.187 mmol), pyridine (23 μL, 0.28 mmol), and DMAP (2 mg, 0.019 mmol) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The solvent was evaporated, and the residue was purified by flash chromatography (silica gel, 5% EtOAc/hexanes) to provide the title compound (16 mg, 67%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.41-7.26 (m, 5H), 6.06 (dd, *J* = 17.0 Hz, 10.5 Hz, 1H), 5.82 (ddt, *J* = 17.0 Hz, 11.0 Hz, 5.5 Hz, 1H), 5.30 (dd,

*J* = 17.0 Hz, 10.5 Hz, 1H), 5.28 (d, *J* = 10.5 Hz, 1H), 5.23 (dd, *J* = 17.0 Hz, 1.0 Hz, 1H), 5.17 (dd, *J* = 17.0 Hz, 1.0 Hz, 1H), 5.14 (dd, *J* = 10.5 Hz, 1.0 Hz, 1H), 5.00 (dd, *J* = 17.0 Hz, 1.0 Hz, 1H), 4.93 (dd, *J* = 10.5 Hz, 1.0 Hz, 1H), 4.54 (ddt, *J* = 13.5 Hz, 5.5 Hz, 1.5 Hz, 1H), 4.47 (ddt, *J* = 13.5 Hz, 5.5 Hz, 1.5 Hz, 1H), 2.31 (d, *J* = 5.5 Hz, 1H), 1.65 (d, *J* = 5.5 Hz, 1H); $^{13}$C NMR (125 HMz, $CDCl_3$) δ 169.8, 138.2, 136.1, 135.1, 132.2, 131.6, 127.9, 127.3, 117.8, 117.6, 115.5, 65.7, 43.4, 38.3, 22.0; FTIR (thin film, $CHCl_3$) 3085, 2928, 1724, 1447, 1241, 1189, 992, 921; HRMS (TOF ES) cald for $C_{17}H_{19}O_2$, *m/z* 255.1385 $[M+H]^+$, found: 255.1388.




**Allyl 1-phenyl-3-vinylcyclopent-3-enecarboxylate (2.159)**: A solution of divinylcyclopropane **2.158** (5.5 mg, 0.026 mmol) was dissolved in toluene and heated at 110 °C for 3 h. The title compound has the same Rf value as **2.158**. The solvent was evaporated, and the residue was purified by flash chromatography (silica gel, 5% EtOAc/hexanes) to provide the title compound (4 mg, 73%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.36-7.25 (m, 5H), 6.53 (dd, *J* = 17.0 Hz, 10.5 Hz, 1H), 5.81 (ddt, *J* = 17.0 Hz, 10.5 Hz, 5.5 Hz, 1H), 5.73 (brs, 1H), 5.19 (d, *J* = 17.5 Hz, 1H), 5.15-5.11 (m, 3H), 4.57 (d, *J* = 5.0 Hz, 2H), 3.56 (d, *J* = 15.5 Hz, 1H), 3.54 (d, *J* = 16.0 Hz, 1H), 2.89 (d, *J* = 15.0 Hz, 1H), 2.87 (d, *J* = 16.5 Hz, 1H); $^{13}$C NMR (125 HMz, $CDCl_3$) δ 175.5, 143.6, 141.4, 133.0, 132.0, 128.4, 128.2, 126.9, 126.5, 117.6, 114.7, 65.6, 58.2, 43.2, 41.1; FTIR (thin film, $CHCl_3$) 3086, 2927, 2853, 1729, 1495, 1446, 1262, 1219, 1163, 988, 906; HRMS (TOF ES) cald for $C_{17}H_{19}O_2$, *m/z* 255.1385 $[M+H]^+$, found: 255.1375.

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